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PHANTOM AND COMPUTATIONAL
STUDIES TOWARDS THE CLINICAL
TRANSLATION OF GAS IN SCATTERING
MEDIA ABSORPTION SPECTROSCOPY
INTO NEONATAL RESPIRATORY CARE

Thesis presented by
Andrea Liliana Pacheco Tobo
ORCID: 0000-0002-1856-4731

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University College Cork
Physics Department

Head of Department: John McInerney
Supervisor: Stefan Andersson-Engels
Co-supervisor: Eugene Dempsey
Research advisor: Konstantin Grygoryev

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PHANTOM AND COMPUTATIONAL STUDIES TOWARDS THE CLINICAL TRANSLATION
OF GAS IN SCATTERING MEDIA ABSORPTION SPECTROSCOPY INTO NEONATAL
RESPIRATORY CARE

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Biophotonics, Tyndall National Institute
Department of Physics
University College Cork, UCC
Ireland

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Papers

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Andrea Liliana Pacheco Tobo

Every summit is within reach, if one just keep climbing, still the
best part is to stop to breath and enjoy the sunsets

ABSTRACT

Everything except vacuum is heterogeneous to some extent. Even media that we consider homogeneous (such as pure gases and water) can be taken apart into individual heterogeneities (such as atoms and molecules), which can be distinguished with a *sufficiently fine probe*.

Absorption spectroscopy was extensively used by Robert Bunsen and Gustav Kirchhoff in the 1860's to separate, identify and measure various chemical substances. They defined a line of research, where traces of elements were just detectable with the aid of specialized instruments like the spectroscope, and since then, the absorption lines have been subject of experimental and theoretical developments.

Today, we know that the nature of the absorption lines can be described by quantum mechanical changes induced in the atoms or molecules, and with the advances in light sources and sensing technologies, absorption spectroscopy has become a tremendously useful tool with a wide range of applications.

The studies presented in this thesis are related to gas absorption spectroscopy, in particular, a technique called GASMAS, which stands for “*GAs in Scattering Media Absorption Spectroscopy*”. This spectroscopy technique was introduced in Lund University in 2001 by S. Svanberg's group, to study the spectral features of gases inside porous or hollowed scattering media, combining laser spectroscopy with sensitive modulation techniques. Unlike solids and liquids, which have a smooth absorption and scattering wavelength dependence ($1 - 10$ nm), gases exhibit sharp absorptive features (10^{-4} nm). This difference between the absorption spectra of solid state matter and gases, is the cornerstone of this technique. In a typical GASMAS measurement, the laser wavelength is scanned across at least one of the absorption lines of the gas of interest. The small gas absorption signal (embedded in the scattered spectrum from the bulk material) is then filtered from the detected signal, making it possible to retrieve the gas concentrations and study their diffusion dynamics using the principles of the Beer-Lambert law. Although there is evidence of the potential of GASMAS to sense oxygen and water vapour in human cavities, such as the ear, nasal sinuses, lungs, intestines and hip bone, one of the most promising clinical applications could be the lung function assessment in neonates. The focus of this thesis is to investigate the potential of translating GASMAS into such an application, combining a computational and experimental approach. Most of the work was done in a collaboration between Biophotonics@Tyndall, the Infant Centre (hosted at the Cork University Maternity Hospital-UCC) and the Swedish industry partner, GPX Medical who have built a pioneering GASMAS instrument, suitable for clinical use. The motivation behind this collaborative work, is to assist clinicians in the monitoring of lung function in premature newborns, as their lungs lack structural and biochemical maturation, which can result in respiratory failure.

Currently, the use of GASMAS is limited to observational studies with healthy babies. Thus, the improvement and optimization of the technology depends on feasibility tests with tissue-like models. Phantoms mimicking the geometry and optical properties of the main thoracic organs, were created to study the influence of source detector positioning and chest physiognomy in the GASMAS signals. A functional phantom resembling the anatomy, temperature and humidity of the respiratory zone, was also developed to investigate the potential of GASMAS technique in measuring changes in inflated volume.

The optimization of source-detector configurations over the thorax is one of the challenges in the clinical translation of GASMAS. It is crucial to define the optimal probe positioning, to obtain the highest possible signal reaching the detector, which also carries information of the gas absorption in lung tissue. Computational studies are then used to simulate the light transport in accurate anthropomorphic models, which contributes with the understanding of near infra-red interaction with the thorax, and most of all, to find the probe locations for which the detection of gas absorption is feasible, and enhance the data acquisition in future clinical studies.

This document includes the theoretical background of GASMAS, the basics of respiratory physiology, and the current methods for clinical monitoring and diagnostics of lung pathologies in neonates. The following two chapters, show how the developed phantom and computational models enable the recreation of different clinical scenarios, suitable for GASMAS studies. The main contribute is the identification of the minimum requirements necessary to further improve and advance towards a GASMAS bedside clinical device, that can potentially be used, for lung function assessment and monitoring in neonatal respiratory health.

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals in the text.

I Translation of Gas Spectroscopy into the Clinic, a Promising Tool for Non-Invasive Diagnostics in Respiratory Health Care of Neonates

A. Pacheco, E. Dempsey, and S. Andersson-Engels.

American Journal of Biomedical Science and Research **9**, 251–253 (2020).

II Solid phantom recipe for diffuse optics in biophotonics applications: a step towards anatomically correct 3D tissue phantoms

S. Konugolu, A. Pacheco, P. Martella, H. Li, P. Lanka, A. Pifferi and S. Andersson-Engels.

Biomedical Optics Express **10**, 2090–2100 (2019).

III Anthropomorphic optical phantom of the neonatal thorax: a key tool for pulmonary studies in preterm infants

A. Pacheco, H. Li, M. Chakravarty, S. Konugolu, and S. Andersson-Engels.

Journal of Biomedical Optics **25**, 115001-1– 115001-11 (2020).

IV Lung tissue phantom mimicking pulmonary optical properties, relative humidity, and temperature: a tool to analyze the changes in oxygen gas absorption for different inflated volumes

Andrea Pacheco, Konstantin Grygoryev, Walter Messina, and Stefan Andersson-Engels.

Journal of Biomedical Optics **27**, 074707-1–074707-10 (2021).

V Laser absorption spectroscopy measurements of different pulmonary oxygen concentrations in transmittance and remittance geometry – phantom study

Andrea Pacheco, Jean Matias , Konstantin Grygoryev , Martin Hansson , Stefan Andersson-Engels.

Journal of Biophotonics **Draft to be submitted**, April 2022.

VI Near Infrared Light Propagation Modeling of Infant Lung with Light Source Placed Inside Intubated Airway

A. Pacheco, E. Krite Svanberg, E. Dempsey, and S. Andersson-Engels.

Proc. Biophotonics Congress **CF3B.4**, (2018).

VII Simulation of near-infrared light propagation through the thorax of a neonate: addressing the optimisation of source and detector positions for measuring lung oxygen content in preterm infants

A. Pacheco, E. Krite Svanberg, E. Dempsey, and S. Andersson-Engels.

Proc. SPIE **11190**, 111901C1–111901C6 (2019).

VIII Numerical investigation of the influence of the source and detector position for optical measurement of lung volume and oxygen content in preterm infants

Andrea Pacheco, Baptiste Jayet, Emilie Krite Svanberg, Hamid Dehghani, Eugene Dempsey, Stefan Andersson-Engels.

Journal of Biophotonics **15:e202200041**, March 25 2022.

IX Gas in scattering media absorption spectroscopy as a potential tool in neonatal respiratory care

Jurate Panaviene, Andrea Pacheco, Christoph E. Schwarz, Konstantin Grygoryev, Stefan Andersson-Engels and Eugene Dempsey.

Pediatric Research doi: **10.1038/s41390-022-02110-y**, May 23 2022.

ABBREVIATIONS

2D	Two dimensional
3D	Three dimensional
A-a	alveolar to arterial O_2 gradient
ABG	Arterial blood gas test
Al_2O_3	Aluminium oxide
ARDS	Acute respiratory distress syndrome
BPD	Bronchopulmonary dysplasia
CLD	Chronic lung disease
CO_2	Carbon dioxide
CPAP	Continuous positive airway pressure
CT	Computed tomography
DICOM	Digital Imaging and Communications in Medicine
ECMO	Extra corporeal membrane oxygenation
EIT	Electrical impedance tomography
ERV	Expiratory Reserve Volume
ET	Endotracheal
FiO_2	Fraction of inspired oxygen
FDPM	Frequency Domain Photon Migration
FMLSI	Frequency Modulated Light Scattering Interferometry
FRC	Functional Residual Capacity
GA	Gestational age
GASMAS	Gas in scattering media absorption spectroscopy
H_2O	Water
IC	Inspiratory Capacity
IRV	Inspiratory Reserve Volume
J	Joule (unit of energy)
Kg	Kilogram
laser	Light amplification by stimulated emission of radiation
MAS	Meconium aspiration syndrome
MRI	Magnetic resonance imaging
MTOF	Mean time-of-flight
N_2	Nitrogen
NICU	Neonatal intensive care unit
NIV	Non-invasive ventilation
n_m	Refraction index of the medium
n_p	Refraction index of the particle
n_r	Reduced refraction index

NRDS	Newborn Respiratory distress syndrome
O_2	Oxygen
p	Partial pressure
P	Pressure
$PaCO_2$	partial pressure of carbon dioxide
PEEP	Positive end-expiratory pressure
P_{atm}	Atmospheric pressure at sea level
PAO_2	alveolar pressure
PaO_2	arterial pressure
PH_2O	partial pressure of water vapour
PHD	Photon Hitting Density
Q	Blood perfusion
RDS	Respiratory distress syndrome
RH	Relative humidity
RQ	respiratory quotient
RTE	Radiative function equation
RV	Residual Volume
SDGs	Sustainable Development Goals
SiO_2	Silica
T	Temperature
TDLAS	Tunable diode laser absorption spectroscopy
TiO_2	Titanium dioxide
TLC	Total Lung Capacity
TOF	Time-of-flight
TOFS	Time-of-flight spectroscopy
TTN	Transient tachypnea of the newborn
TV	Tidal Volume
US	Ultrasonography
V	Volume
VC	Vital Capacity
V_{ent}	Ventilation
VBG	venous blood gas test
WMS	Wavelength modulation spectroscopy
x	Size parameter of a sphere
X	Scattering efficiency
ϵ	Permittivity
λ	Wavelength
μ	Permeability
μ_a	Absorption coefficient
μ_s	Scattering coefficient

TECHNICAL BACKGROUND

1.1 The quantum nature of matter

Matter is composed of atoms which combine into molecules and exist in specific quantum states. Since molecules can vibrate and rotate, the internal energy of a molecule is quantized and is stored in electronic, vibrational and rotational modes (Fig. 1.1).

$$E_{tot} = E_{elec} + E_{vib} + E_{rot}. \quad (1.1)$$

E_{elec} describes changes in the electronic state, which corresponds to the transition of an electron bound to an atom or to a molecule from a lower to a higher energy orbital. E_{vib} is related to molecular vibrations, which result from the excitation of atoms within the molecule into periodic and oscillating motion (Fig. 1.2). And E_{rot} is associated with the rotational excitation, namely the rigid rotation of polar molecules as a result of the torque exerted on them by electromagnetic waves (Fig. 1.3) [1].

The energies associated with electronic, vibrational and rotational states lie in different ranges¹ and can therefore be studied separately. The quantized internal energies lead to discrete energy shifts when molecules change quantum states. Vibrational transitions occur between different vibrational levels of the same electronic state and, rotational transitions occur mostly between rotational levels of the same vibrational state. The spectra for vibrational and rotational transitions of molecules are typically in the infra-red and microwave regions respectively [2].

Spectroscopy is the study of interactions between the electromagnetic radiation and matter (solid, liquids and gases). Fig. 1.4 shows the Jablonski diagram of light-matter interactions in the singlet state. The response of matter to excitation at different wavelengths, can be used to characterize its structure and composition. Photon absorption occurs when the interaction between electromagnetic radiation and matter is resonant. As such, the incidence of electromagnetic radiation over matter, brings the molecules into an electronic, vibrational or rotational excited state. The de-excitation process is called radiative if involves the emission of a photon, such transition can be elastic (the energy of the absorbed and emitted photon is the same), or inelastic (the energy of the absorbed photon is different to the energy of the emitted photon). Hence, the energy transitions from equation (1.1) are directly correlated with the energy of emitted or absorbed photons.

The energy of the photon (emitted or absorbed) in such transitions is equal to the difference in energy between the upper and lower energy

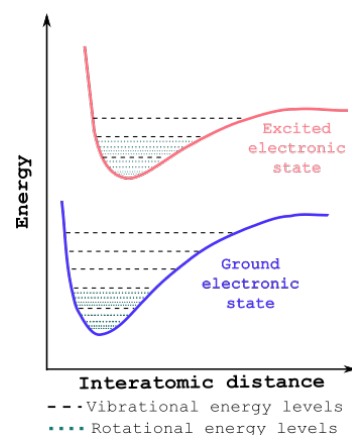


Figure 1.1. Molecular spectra of a diatomic molecule

¹ Electronic transitions are of the order of 1eV, vibrational transitions 10⁻²eV and rotational transitions are of order 10⁻³eV.

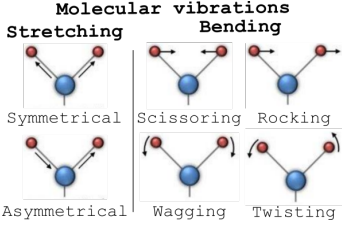


Figure 1.2. Vibrational modes of a diatomic molecule [3].

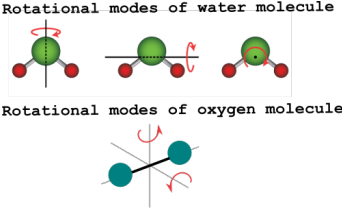


Figure 1.3. Rotational modes of H_2O (top) and O_2 (bottom) molecules.

levels $\Delta E = E_{up} - E_{low} = h\nu$, where $h = 6.63 \times 10^{-34} Js$ is Planck's constant, and ν is the frequency of light.

Extending equation (1.1), the change in energy of the molecule is given by

$$\Delta E = \Delta E_{elec} + \Delta E_{vib} + \Delta E_{rot} = h\nu, \quad (1.2)$$

being the sum of the individual changes in electronic, vibrational and rotational energy.

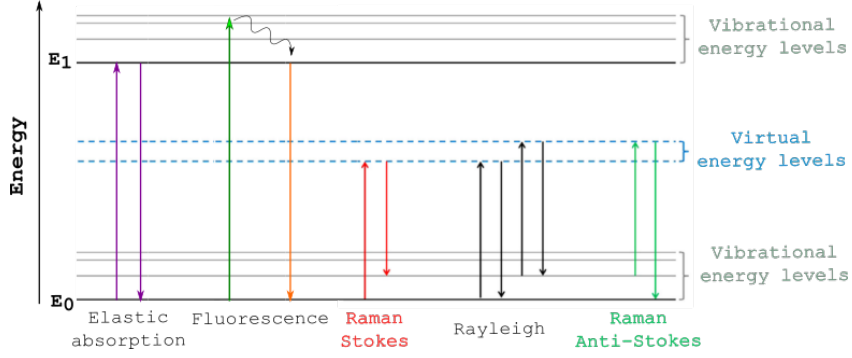


Figure 1.4. Jablonski diagram of energy transitions involved in absorption and scattering. In elastic absorption, the energy of absorbed and emitted photon is the same. Fluorescence occurs when the energy of absorbed and emitted photons are different. In Rayleigh scattering, the incident and scattering photon have the same energy (elastic process). And, in Raman scattering, the scattered photon is of lower (Stokes) or greater (Anti-Stokes) energy than the incident photon (inelastic process).

Non-resonant interactions occur when the energy of the incoming radiation does not match a transition energy of the system. In this case, photons are not absorbed but scattered, meaning that they interact with the molecules, inducing a short-lived transition to a virtual energy state, while changing the direction of propagation. These interaction can be elastic (Rayleigh scattering: for which no energy transfer occurs between the incident radiation and the system) or inelastic (Raman scattering: in which the wavelength of the scattered photon is different to the energy of the incident photon) [4].

1.2 Gas spectroscopy

Gas spectroscopy refers to the study of the emission and absorption lines that appear when the gaseous molecules change quantum states from higher to lower energy or vice-versa.

A *line* is a part of the spectrum that correspond to transitions between quantum states. A group of individual lines, with common upper and lower vibrational quantum numbers, form a *vibrational band* and several vibrational bands comprise an electronic system (see the structure of the electronic levels in Fig. 1.6). The Fig. 1.5(a) shows an O_2 absorption line, which corresponds to the vibrational band plot below. The line position (λ_0) and spacing ($\Delta\lambda$) parameters carry molecular information, such as the internuclear spacing and bond angles. The absorbance and linewidth ($\delta\lambda$) are related to the molecule composition, temperature (T) and pressure (P) [5].

Tunable diode laser absorption spectroscopy (TDLAS), is a typical absorption spectroscopy technique which includes a tunable diode laser

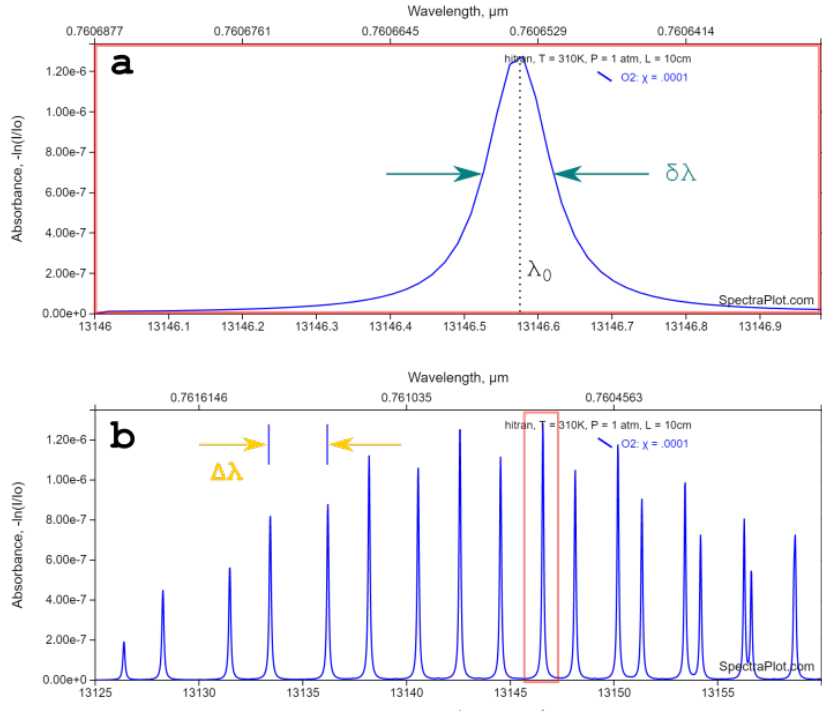


Figure 1.5. O₂ absorption spectra. **a)** shows the zoomed plot of a single line at position λ_0 and signal linewidth $\delta\lambda$, which correspond to the line enclosed in red in **b)** the respective vibrational band. Data taken from spectraplot [6].

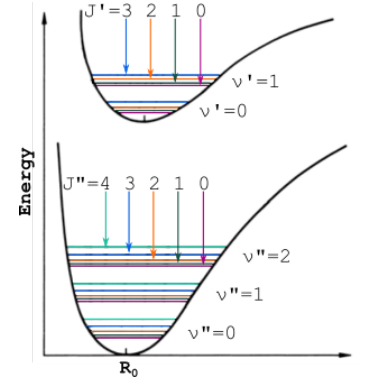


Figure 1.6. General structure of the vibrational levels of a diatomic molecule, composed of vibrational states (indicated by ν), and rotational levels (Indicated by J). In this case ν_0'' , ν_1'' , and ν_2'' represent vibrational bands of the ground electronic state, and the J'' the respective rotational bands. In a similar fashion, ν_0' and ν_1' represent vibrational bands of the first excited electronic state, and the J' their rotational bands.

source, a gas cavity with known length and a photo-detector. Fig. 1.7 shows the TDLAS set up and illustrates its principles. A laser beam with intensity I_0 , and emission wavelength (λ) is scanned over the line positions (λ_0) of the target gas, by ramping the driving current of the diode laser.² When it matches an absorption line of the gas ($\lambda = \lambda_0$), light is attenuated. After passing through the gas, light of intensity I reaches a photo-detector in order to obtain the absorption spectrum.

² The injection current of the laser is increased as function of time, producing a concomitant change in the emission wavelength of the laser diode.

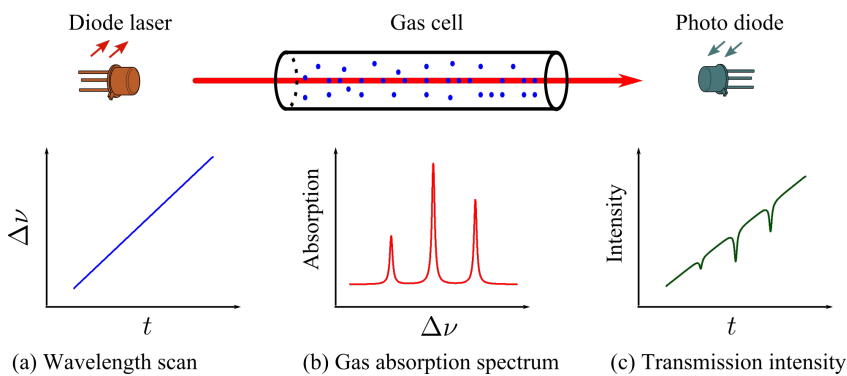


Figure 1.7. Schematic diagram of tunable diode laser spectroscopy (TDLAS). **a)** The optical frequency of the diode laser is linearly scanned across the gas absorption lines; **b)** Absorption spectrum of the gas in the gas cell; **c)** Detected gas intensity with gas absorption imprints. Diagram taken from [7].

The **Beer-Lambert law** is the governing law for absorption spec-

troscopy. It describes the relationship between the incident (I_0) and transmitted (I) light intensities, and is given by

$$T_\lambda = \left(\frac{I}{I_0} \right)_\lambda = \exp(-k_\lambda L). \quad (1.3)$$

T_λ is the fractional transmission at wavelength λ , k_λ is the spectral absorption coefficient [cm^{-1}], and L is the absorption path length [cm]. The spectral absorption coefficient for a single, spectrally isolated transition is given by

$$k_\lambda = S \times \Phi(\lambda) \times P_i, \quad (1.4)$$

where S is the ‘strength’ of the transition [$\text{cm}^{-2}\text{atm}^{-1}$], Φ is the ‘line shape function’ [cm], and P_i is the partial pressure of the absorbing species [atm].

³ The Beer-Lambert law is also used to describe the absorption of solid state materials (liquids and solids). In such cases the absorption coefficient is noted by μ_a [cm^{-1}].

The Beer-Lambert law³ can also be expressed in terms of the absorption cross section ($\sigma_\lambda[\text{cm}^2]$)⁴ and gas (or substance) concentration ($N[\text{cm}^{-3}]$) by

$$I = I_0 \exp(-\sigma_\lambda N L). \quad (1.5)$$

If there are more than one substance in the gas sample, the total absorption cross section coefficient corresponds to the sum of all substance coefficients and the previous equation becomes

$$I = I_0 \exp \left(\sum_i -\sigma_{i\lambda} N_i L \right). \quad (1.6)$$

By measuring the light attenuation, the concentration of an specific substance can be calculated if σ_λ and L are known. In some cases the species composition can be differentiated due to their unique quantum nature, i.e. absorption imprints.

1.3 Highlights of tissue optics

Light interacts in different ways with human tissue. Geometric optics describes the macroscopic phenomena most of us are familiar with, such as the formation of shadows, prescription of glasses or our reflection on a mirror. In all these cases, the system size is greater than the wavelength of light.

On the other hand, physical optics describes phenomena in which the approximation of geometrical optics is not valid because the system’s size is comparable with the wavelength of light. This section is dedicated to the light-tissue interactions that can take place within the body.

1.3.1 Tissue composition

In general, human tissue is made up of water, lipids, proteins, carbohydrates, nucleic acids and minerals. An organ is a group of tissues, whose structure and function depend on the relative amounts and composition of its main constituents. The relevant tissues in the work related to this thesis are: *skin*, which includes dermis, epidermis and connective tissue; *fat*, composed of a protein matrix which supports cells with the function of lipid storage; *blood*, mainly water mixed with proteins and electrolytes; *muscle*, made of contractile cells, blood vessels and lipids; *bone*, with various tissue types known as cartilage, cortical bone, spongiosa, red and yellow marrow; *trachea*, major airway that contains rings of cartilage muscle and connective tissue; and *lung*, mainly made

of blood circulating vessels and parenchyma (substance involved with gas exchange including alveoli and bronchioles) [8].

The distinctive colour of each tissue type (yellowish or brownish for fat, beige for bone, red for blood, etc) is an effect of the *chromophores*, a part of the molecule that absorbs photons with certain energy ($E_{\text{photon}} = h\nu$ where $\nu = 1/\lambda$) and transmits or reflects other wavelengths.⁵

Fig. 1.8 shows the relative sizes of the main constituents of human tissue. By selecting specific wavelengths it is possible to interrogate biological systems and acquire information about its constituents and functionality at subcellular, cellular, tissue and organ levels [9].

⁵ The scattering and absorption of light in subsurface tissue layers gives skin its color and soft appearance, as such, different skin colours imply the presence of different chromophores.

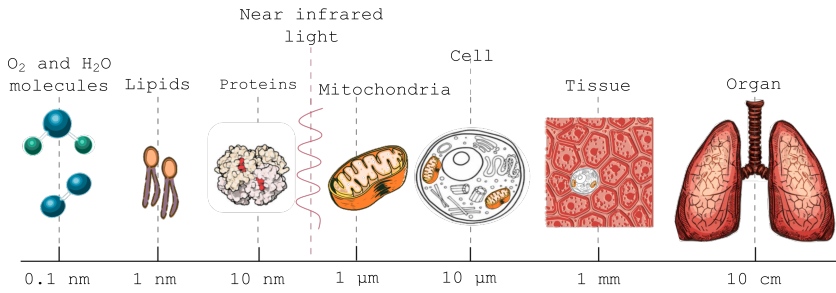


Figure 1.8. Relative size of oxygen and water vapour molecules, and the main constituents of human tissue.

1.3.2 Light-tissue interactions

As mentioned in Section 1.1, the possible interaction events of light with tissue depend on the atomic structure of the specimen under study. *Absorption* and *scattering* are the most recurrent interactions between light and tissue [10].

A photon is absorbed when the incoming radiation energy is transferred to atoms and molecules resulting in a higher energy level. As the energetic levels in matter are quantized, photons will be absorbed only if their frequencies match the transition between two energetic states of an specific chromophore. The absorption of tissue is characterized by an absorption coefficient μ_a [cm^{-1}]; in a purely absorbing medium, the attenuation of a beam of light traveling a distance L within the medium, can be described using equation (1.5), with the spectral absorption coefficient $k_\lambda = \mu_a$

$$I(L) = I_0 \exp(-\mu_a L), \quad (1.7)$$

where μ_a is defined as the reciprocal of the absorption distance (L_a) for which light of intensity $I(L = 0) = I_0$ is attenuated to $\approx 0.37I_0$.

When the incident photons do not match the transition energy of atoms and molecules, the light is scattered, which means that the incident light wave changes its features (polarization and intensity), after interacting with tissue constituents of different shapes, sizes and refractive index, such as blood vessels and all diverse types of cells. The emerging scattered light carries information about the tissue structure and cellular composition. Scattering is characterized by a scattering coefficient μ_s

$[cm^{-1}]$; in purely scattering media, collimated light is also attenuated according to the exponential law of equation (1.5)

$$I(L) = I_0 \exp(-\mu_s L), \quad (1.8)$$

where μ_s is defined as the reciprocal of the scattering distance (L_s) for which light of intensity $I(L=0) = I_0$ is attenuated to $\approx 0.37I_0$.

Light absorption and scattering occur in biological tissue simultaneously. The scattering properties are related to its morphology and the absorption properties to its biochemistry.⁶ The total light attenuation is therefore in accordance with the Beer-Lambert law (equation (1.5)):

$$I(L) = I_0 \exp(-\mu_t L), \quad (1.9)$$

where $I(L)$ is the transmitted intensity measured with a remote photodetector with a small aperture $[\frac{W}{cm^2}]$ and $\mu_t = \mu_a + \mu_s$.

Fig. 1.9 pictures the different light-tissue interactions. Such interactions are complex given that the constituents of tissue are multi-layered, multi-component and optically inhomogeneous [12].

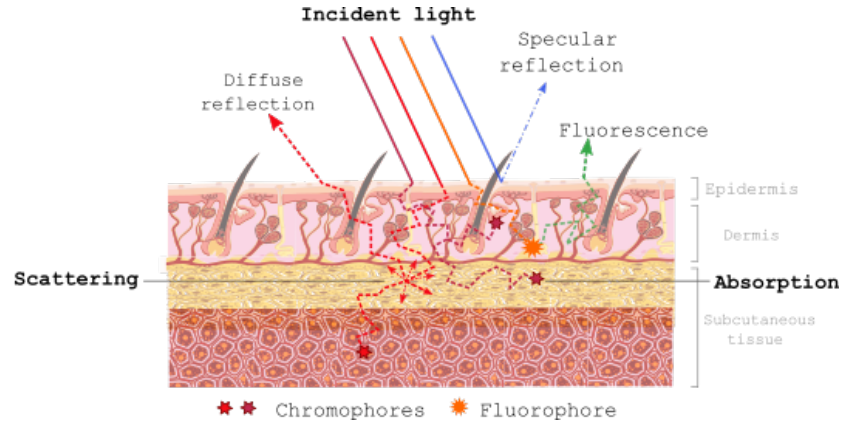


Figure 1.9. Schematic representation of light-tissue interactions.

In *specular reflection* the tissue surface components (such as the thin oily layer covering the fine-scale roughness of skin) are smaller than the wavelength of incident light, which is partially reflected at a definite angle following Snell's law.⁷ The amount of reflected light, depends upon the different refraction indexes of air and tissue, and is described by the Fresnel equations [1]. Any light not directly reflected on the tissue surface, enters the subsurface layers. The different layers absorb and scatter light differently. *Diffuse reflectance*⁸ occurs when the incident light undergoes multiple scattering events in the medium, to the extent that it becomes randomized in direction [13]. *Fluorescence* is a radiative relaxation, which involves photon emission following non-radiative internal conversion down to the lowest vibrational state of the excited electronic state. This transition is inelastic, and due to energy lost during de-excitation, the emitted photon has a longer wavelength than the incident light.

The combined absorption of the tissue constituents define how far light can penetrate into tissue for a specific wavelength. Light travels through thin tissue layers, like the ear or finger.

Penetration depth is a measure of how deep light can penetrate into the

⁶ Scattering is expected to occur from cells, organelles, and proteins. Mammalian cells vary in size between 1.5 to 10 μm radius, therefore, it is expected that tissue scattering centres vary in size from small particles such as proteins to larger particles like cells (see figure Fig. 1.8) [11].

⁷ *Snell's law* states that the ratio of the sines of the angles of incidence and refraction is equivalent to the reciprocal of the ratio of the indexes of refraction $\frac{\sin(\theta_1)}{\sin(\theta_2)} = \frac{n_2}{n_1}$. In the case of reflection, $n_1 = n_2$ and $\sin(\theta_1) = \sin(\theta_2)$.

⁸ *Diffuse transmission* can be observed in living humans and animals, when light passes through thin tissue layers as the finger or the ear. In other cases (non-visible to the naked eye), light is diffusely transmitted through several centimetres of tissue, as is the case of optical mammography.

tissue and is defined as the depth at which the intensity of radiation inside the medium falls to $\frac{1}{e}$ of its original value [10]. The attenuation of a laser beam of intensity I_0 in biological tissue at depth $L > \frac{1}{\mu_{eff}}$ is described by the following equation:

$$I(L) \approx I_0 b_s \exp(-\mu_{eff} L), \quad (1.10)$$

where b_s accounts for additional irradiation of upper layers of a tissue, due to multiple backscattering and specular reflection on the tissue surrounding, and

$$\mu_{eff} = [3\mu_a(\mu_a + \mu'_s)]^{1/2}, \quad (1.11)$$

is related to photon diffusion, the reader can look at section 4.2 to find information about the derivation of equation (1.11). μ'_s is the reduced scattering coefficient⁹ which is used to classify tissues as **absorption-dominated** for $\mu_a \geq \mu'_s$ or **scattering-dominated** medium for $\mu_a \ll \mu'_s$.

⁹ μ'_s is a lumped property incorporating the scattering coefficient μ_s and the anisotropy factor g ; g is a measure of the directionality of elastic light scattering and is defined as the average cosine $\langle \cos(\theta) \rangle$ of the scattering angle θ . The closer g is to unity, the more probable it will be for a photon to be scattered in the forward direction.

In physics of small particles, the term scattering is used to describe changes in an electromagnetic field due to localized obstacles in the medium (with different refractive index) through which it travels (see chapter 3). In tissue optics, the term scattering refers to the transfer of energy from an incoming wave into an scattered wave resulting from the passage of light through biological tissue, and undergoing multiple scattering events. The scattering interactions frequently encountered in biomedical optics are:

- *Rayleigh scattering*: elastic scattering of light by dielectric particles much smaller than the incident wavelength;
- *Mie scattering*: elastic scattering of light by dielectric particles, valid for any particle size; and
- *Raman scattering*: inelastic scattering resulting in a Stokes or anti-Stokes shift (see figure Fig. 1.4)

Fig. 1.10 shows the absorption spectra for the main constituents (chromophores) of biological tissue, namely fat, blood and water. The shadowed region between 650 nm and 950 nm is known as the *first therapeutic optical window* where light has its maximum depth of penetration in tissue. The dashed-dot line and the dashed lines sit on the O_2 and H_2O vibrational bands at 760, 820 and 935 nm, which are relevant to the experimental and computational research presented in this thesis.

The spectroscopic fingerprint of each molecule or tissue type can be used to distinguish from other surrounding molecules (or tissues). Given that the optical properties of tissue are dependent on its constituents, the generic constituent properties can be mixed to mimic any tissue type, at a certain wavelength λ which will be described by μ_a and μ'_s using [14]:

$$\mu_a = \sum C_V \mu_{a,c}, \quad (1.12)$$

where C_V and $\mu_{a,c}$ are the volume fraction and absorption coefficient of each constituent for λ , respectively, and

$$\mu'_s = \mu'_{s,\lambda_1} \left(f \left(\frac{\lambda}{\lambda_1} \right)^{-4} + (1-f) \left(\frac{\lambda}{\lambda_1} \right)^{-b_{Mie}} \right), \quad (1.13)$$

where λ_1 is the normalization wavelength, μ'_{s,λ_1} is the reduced scattering coefficient at λ_1 , f is the fraction of scattering at λ_1 due to

¹⁰ b_{Mie} characterize the size of the scatterers similar to the wavelength of the incident light [13].

Rayleigh scattering, $(1 - f)$ is the fraction of scattering at λ_1 due to Mie scattering and b_{Mie} is the power for Mie scattering.¹⁰

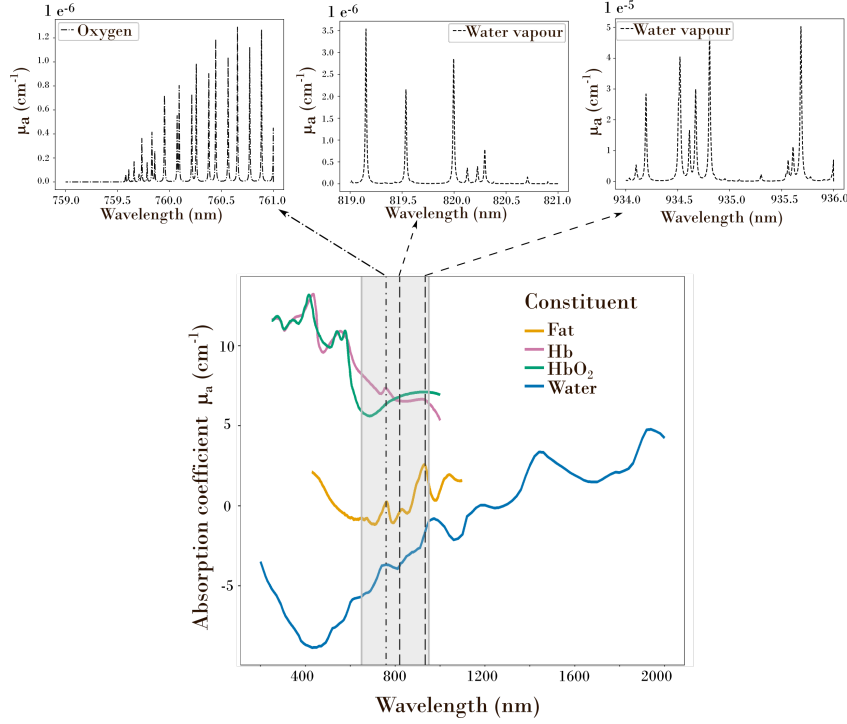


Figure 1.10. Absorption coefficient spectra for the main constituents of biological tissue, fat, deoxy-haemoglobin (Hb), oxy-haemoglobin (HbO₂) and water. The shaded area corresponds to the first optical window. The dashed-dot line, shows the absorption spectra of molecular O₂ at 760 nm and the dashed lines the water vapour absorption spectra at 820 nm and 935 nm.

The understanding of how light penetrates in tissue and interacts with the molecules via absorption and scattering, is key to diagnostics and therapeutic applications.

1.4 Gas in scattering media absorption spectroscopy

Gas in scattering media absorption spectroscopy, known as GASMAS, was introduced by Sune Svanberg's group in 2001, with the aim to study the spectral features of gases embedded in porous or hollowed scattering media, by using diode laser spectroscopy combined with sensitive modulation techniques [15]. The main difference between GASMAS and TDLAS technique is that the samples under study are turbid materials with air cavities, where light has diffused completely before reaching the detector. This technique has been used in the last two decades, mainly for sensing O₂, H₂O and N₂ gases in a wide range of samples and environments such as food (eggs, fruits and vegetables) [16, 17], food packaging [18], porous materials (pharmaceutical tablets, wood, foams and ceramics) [19–22] and air cavities in the human body (ear, nasal sinuses, lungs, intestines and hip bone)[23–27].

The absorption and scattering properties of solids and liquids have a smooth wavelength dependence (as can be seen in Fig. 1.10). In contrast, gases exhibit sharp absorptive features (as shown in Fig. 1.5).

This difference between the absorption spectra of solid state matter and gases, is the corner stone of GASMAS technique.¹¹ By scanning the laser wavelength across at least one of the absorption lines of the gas of interest, and filtering the small gas absorption signal embedded in the scattered signal from the bulk material, one is able to retrieve the gas concentrations and study its diffusion dynamics.

¹¹ The absorption lines of O_2 and H_2O vapour are typically in the order of 0.001 nm [28], which can be distinguish from the absorption imprint of human tissue which is in the 10 nm range [14].

To exploit GASMAS technique, the wavelengths have to be carefully chosen to guarantee that the light from the source will interact with the gas content cavities after or during undergoing diffusion by the bulk material. The technique is also limited to the availability of laser sources which match the absorption lines of the gases under study. Since diffuse light is detected during GASMAS measurements, the source and detector can be set in remittance and/or transmittance geometry, and the source-detector separation will be limited by those configurations for which light carrying the gas imprint is reaching the detector. In remittance geometry some of the detected photons will not interact with the gas within the sample, generating an attenuated light signal without any gas absorption feature as can be seen in figure Fig. 1.11.

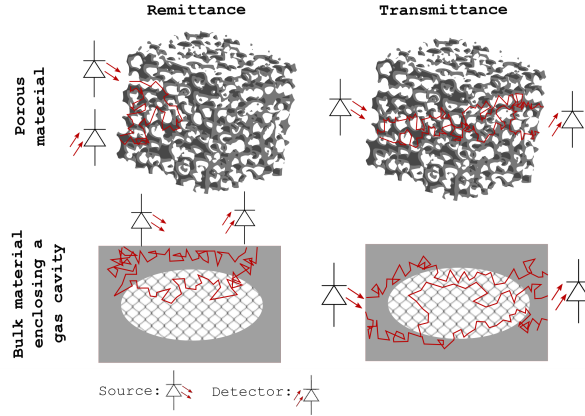


Figure 1.11. Diagram of two different GASMAS samples and source-detector configurations.

According to equation 1.5, the gas absorption imprint depends on the product of gas concentration and path length, and the path length must be determined independently to obtain the gas concentration, or vice versa. One of the main challenges in GASMAS spectroscopy for applications related to the human body, is that the gas absorption path length is unknown, given that upon interaction with the bulk material (meaning the organs surrounding the gas content cavities) the light is completely diffused before reaching the detector.

The concept of *equivalent path length* (L_{eq}) was introduced in the first GASMAS publication [15], and it corresponds to the distance that light needs to pass through a reference gas, to undergo an equivalent absorption as when interacting with the gas inside the sample

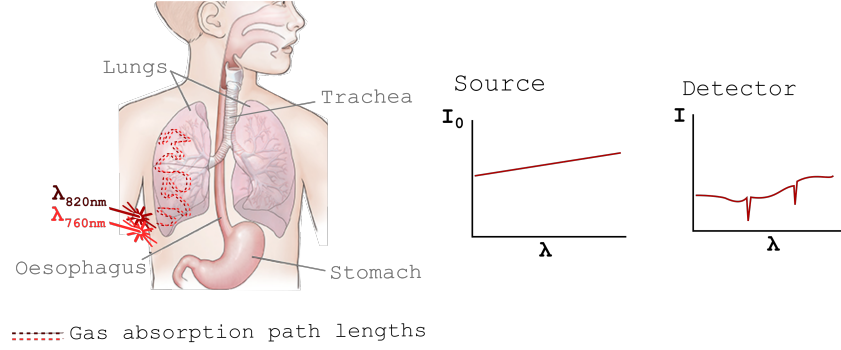
$$L_{eq} = L_{ref} \frac{S_{sam}}{S_{ref}}, \quad (1.14)$$

here L_{ref} and S_{ref} correspond to the absorption path length and absorption signal of the reference gas, and S_{sam} to the absorption signal

of the sample. The relation between L_{eq} and the actual absorption path length within the sample (L_{gas}) is given by

$$L_{eq} = L_{gas} \frac{C_{gas}}{C_{ref}}, \quad (1.15)$$

and $L_{eq} = L_{gas}$ is satisfied if the gas concentration in the sample (C_{gas}) is equal to the concentration of the reference (C_{ref}). Which means that if the gas inside the sample is under the same temperature (T), pressure (P) and buffer gas as the reference, L_{eq} would correspond to the distance light has travelled within the sample.



GASMAS principle

1. Signal acquisition: H_2O vapour (Known μ_a) O_2 (Unknown μ_a and L)
 $I(\lambda) = I_0(\lambda) \exp(\mu_a L)$ $I(\lambda) = I_0(\lambda) \exp(\mu_a L)$
2. Assumption: $L \sim L$
3. Estimation of O_2 concentration: $\mu_a = 1/L \log\{I_0(\lambda) - I(\lambda)\}$

Figure 1.12. Principle of GASMAS application to estimate O_2 concentration in the lungs of newborns. A dual wavelength diffuse laser source (λ_{820} and λ_{760}) is placed over the thorax. As light travels deep in tissue, is attenuated due to absorption and scattering. when the light interacts with the gases in the lung, spectrally sharp absorption signals are detected. The H_2O vapour signal is used to estimate the light absorption path length, which is used to estimate the O_2 concentration.

Mei et al. have studied three different approaches to obtain the actual gas absorption path length of light propagating through heavy scattering media [22]:

- *Path length calibration:* Involves the simultaneous monitoring of a second gas with known concentration. Human cavities, such as the nasal sinuses and the lungs, have 100% relative humidity (RH) due to the presence of water (H_2O) vapour. The saturated concentration of H_2O vapour, depends on ambient T and P according to the Arden-Buck equation which states that the partial pressure of saturated H_2O vapour in moist air (p) with defined T and P is given by [29]:

$$p = [1.0007 + (3.46 \times 10^{-6} P)] \times 6.1121 \exp \left[\frac{17.502T}{240.97 + T} \right]. \quad (1.16)$$

Therefore, in cases where the gas under study (e.g. oxygen (O_2)) and H_2O vapour are present in the same cavity, the concentration

of the last can be calculated for known T and P , and the path length for a H_2O vapour can be calculated, using the absorption signal at a resonant wavelength. If the wavelengths used to perform gas spectroscopy of both gases are spectrally close (i.e. both have similar scattering cross-sections), the path lengths can be assumed to be the same for both gases,¹² in order to retrieve the concentration of the target gas.

This approach was used for the work relevant to this thesis, which is focused on preliminary studies towards the clinical translation of GASMAS technology to sense the absorption imprints of O_2 (760 nm) and H_2O vapour (820 nm) in the lungs of newborn infants. In this case, H_2O vapour is used to perform path length calibration and then retrieve molecular O_2 concentration, as shown in figure Fig. 1.12.

- *Measurement of the optical path length with other methods:*¹³ The mean optical path length can be obtained by means of time of flight spectroscopy (TOFS)[30], frequency modulated light scattering interferometry (FMLSI) [31], and frequency domain photon migration (FDPM)[32]. Once the path length is obtained, the gas concentration can be assessed using the light intensities from the source and the detector acquired with the GASMAS system and equation 1.5.

¹² This is only an approximation in view of Mie and Rayleigh scattering theory, for certain samples large differences can occur.

¹³ This method is mainly used with highly porous materials as the calculated path length includes the path lengths of the gas cavities (pores) and the bulk material.

TOFS consists on delivering a short light pulse to the diffuse media under study, the time dispersion of the source is then studied by a highly sensitive detector and fast electronics, to retrieve μ_a and μ'_s . Apart from the pulsed light source and the sensitive detectors, the main challenge in TOFS systems is to detect the picosecond scale time dispersion, which is beyond the detection limit of normal electronics.

FMLSI studies light propagation in diffuse media by using a coherent tunable continuous-wave laser diode. In principle, interference signals are generated from optical waves with different frequencies, and the amplitude of the detected signal depends on the phase changes due to different travelling paths. The scattered light can be resolved by mechanically changing the path length of the reference arm. The disadvantage of this method is that it only allows for measurements in transmittance geometry, limiting the applications.

FDPM utilizes intensity-modulated continuous light sources (typically in the 100 MHz range), and measures the phase shift in light intensity through the scattering media. By evaluating the phase shift and modulation depth variations the optical properties can be obtained. Thus, FDPM avoids the need of sophisticated pulsed sources and detection electronics required for TOFS. The advantage of employing FDPM is that the same laser diode can be used as a source for GASMAS.

The main disadvantage of estimating the optical path length with methods different to GASMAS, is that the path length measured with TOFS, FMLSI and/or FDPM includes both, the path length through the gas (L_{gas}) and through the matrix material (L_{matrix})

$$L_{measured} = L_{gas} + n_{matrix}L_{matrix} \quad (1.17)$$

where n_{matrix} is the refracting index of the matrix material. Thus, this approach is valid only for gas content materials with high porosity and weak scattering, which will give a good approximated value for the gas absorption path length.

- *Path length independent calculation of the gas concentration:* The concentration of species within a gas mixture can be determined simultaneously, by analysing their impact on the shape of the normalized gas absorption line of a reference gas. This is possible because the normalized absorption line only depends on the intermolecular collisions of its own nature and buffer¹⁴ gas molecules, which is defined by the gas mixture and concentrations. This enables the retrieval of gas concentration without knowing the path length, by analysing the gas absorption line shape [33].

¹⁴ Other gases present in the mixture inside the pores or cavities under study.

Many of the articles cited in this thesis correspond to GASMAS studies where a 935 nm laser diode source was used to scan the absorption bands of H_2O vapour. However, most of the studies and bench top measurements I carried out throughout the last years, are based in the assumption of using a 820 nm source instead, as the absorption and scattering features (and consequently the path length approximation) of the main chromophores of biological tissue, are closer for 760 and 820 nm (see Fig. 1.10).

MEDICAL BACKGROUND

2.1 Respiratory physiology

The respiratory system consists of conducting and respiratory airways, as can be seen in Fig. 2.1. The conducting airways lack alveoli and take no part in gas exchange, they constitute the anatomic dead space whose function is to conduct, clean, warm and moisten the air to 37°C and 100% RH. The respiratory airways make up most of the lung and is the region where gas exchange occurs. It is composed of the respiratory bronchioles (which have scarce alveoli on the walls) and the alveolar ducts which are completely lined by millions of alveoli (~ 0.3 mm in diameter each). The stability of the alveoli relies on the presence of surfactant (see Section 2.1.1) [34].

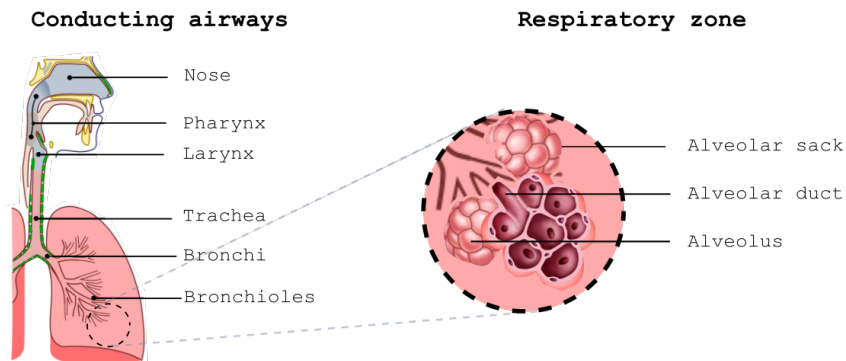


Figure 2.1. Diagram of the conducting airways and the respiratory zone.

The pressure in the alveoli is usually close to atmospheric pressure, they are surrounded by the blood-gas interface and blood capillaries to accomplish the main function of the lung, *gas exchange*. 30 % of the air passing mouth and nose rests in the anatomic dead space, the remaining fraction represents the amount of fresh inspired air available for gas exchange (*alveolar ventilation*). *Diffusion* is the mechanism used by the alveolar wall to take oxygen (O_2) from the airways and transfer it to the venous blood and collect carbon dioxide (CO_2) from the blood vessels back into the lung, to be exhaled [35].

Respiration, either natural or artificial, is a cyclical process of inspiration or expiration. The ability to maintain an appropriate lung volume throughout the breathing cycle is essential for gas exchange and survival.

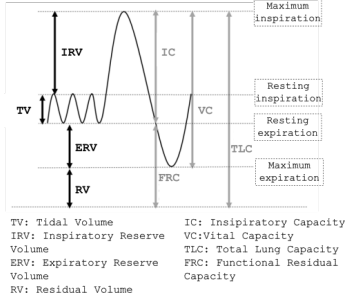


Figure 2.2. Lung volumes [36] (black arrows) and capacities (grey arrows) from a spirometer output.

In humans, diffusion does not fulfil the cellular metabolic requirements, and gas exchange is enhanced by gas convection mechanisms which move air back and forth through the conductive airways and the respiratory zone. The volume of gas in the lung is constantly changing during the respiratory cycle (figure Fig. 2.2). These respiratory volumes are classified as:

- *Tidal Volume (TV)*: Amount of gas that can be inhaled or exhaled during a respiratory cycle (normal breathing).
- *Inspiratory Reserve Volume (IRV)*: Is the maximum amount of gas that can be inhaled beyond the peak of TV (deep breathing).
- *Expiratory Reserve Volume (ERV)*: Volume of gas that can be exhaled by force beyond exhalation of the normal TV.
- *Residual Volume (RV)*: Volume of gas which remains in the lung after maximal expiration.

Lung capacity tests are performed to evaluate lung function and diagnose restrictive or obstructive conditions, where the lungs cannot expand fully, or present a narrowing of the airways preventing the patient from breathing out the volume that counts for normal breathing. The lung capacities are:

Functional residual capacity (FRC) corresponds to the volume of gas that remains in the lung and airways after a normal tidal expiration (volume of gas in the lung when the lung is at rest).

$$FRC = RV + ERV. \quad (2.1)$$

A normal FRC is important to determine optimum lung mechanics and alveolar gas exchange.

Inspiratory capacity (IC) is the maximum volume of gas that can be inhaled after resting respiratory state.

$$IC = IRV + TV. \quad (2.2)$$

Total lung capacity (TLC) is the maximum volume of gas that the lungs can hold after maximum inspiration.

$$TLC = TV + IRV + ERV + RV. \quad (2.3)$$

Vital capacity (VC) is the exhaled gas volume, after maximal inspiration. It reflects the inspiratory and expiratory muscle strength.

$$VC = TV + IRV + ERV. \quad (2.4)$$

TV and VC are measured with a spirometer. TLC, FRC and RV can also be measured using the spirometer with an additional helium dilution (gas washout) or with the body plethysmograph (see Section 2.4).

The lung exhibits regional differences in ventilation depending on the subject's position, in general the ventilation per unit volume tend to be greatest near the lowermost lung, decreasing progressively towards the top.

Balance of forces

The chest wall, composed of bones, muscle and connective tissue of the thorax, has elastic properties. Therefore, when forces are applied to the chest wall it will resist to the movement, to come back to resting volume. Throughout the breathing process, the chest wall is at a smaller volume than the one it will occupy in an unstressed state. Thus, the chest wall tends to “spring outwards” to resume equilibrium. Lungs, are also elastic and in a living organism, they are always stretched above the equilibrium position and exert a collapsing force. To inflate the lung, an opposite force must be applied to overcome the inherent elastic recoil of lung tissue. When the force is removed, the lung will recoil expelling the gas.

Chest wall and lungs affect their movement via the pleural space exerting forces in opposite directions. The resting volume of the chest wall is between 75 % to 80 % of the TLC. Volumes below this level require a pressure to compress the chest wall; and volumes above this level require an expansion force. When the lung volume corresponds to the FRC, the inward (deflating) force of the lungs is balanced by the outward (inflating) force of the chest wall.

Lung compliance is a measure of the lungs capability to stretch and expand with increasing transmural pressure, or resistance to recoil towards its resting volume and is defined as:

$$Compliance = \frac{\Delta Volume}{\Delta Pressure} = \frac{\Delta V}{\Delta P}. \quad (2.5)$$

A high compliance is related to a reduced elastic recoil of the lung and a low compliance to stiffness or scarring of lung tissue.

2.1.1 In-utero development of lung tissue

During gestation, lung development occurs in the following five main stages pictured in Fig. 2.3[37, 38]:

- * *Embryonic*, at 3 weeks Gestational age (GA): Development of the lung buds in fusion together with the oesophago-tracheal ridges.
- * *Pseudoglandular*, 5 - 17 weeks GA: Formation of the conducting airways made of primary lung lobes (three on the right and two on the left) and terminal bronchioles. The primitive respiratory tree structure is too immature to support gas exchange. Further growth occurs by elongation and widening of existing airways.
- * *Canalicular*, 16 - 25 weeks GA: The respiratory region of the lung is formed. The terminal bronchioles subdivide into respiratory bronchioles and alveolar ducts. Vascularization and angiogenesis also starts at this stage. Differentiation of type I pneumocytes (gas exchange will occur across these primary structural cells of the alveoli) and lamellar bodies in type II cells, which are the sites for surfactant¹ storage, prior to its release into the alveolar space.
- * *Terminal saccular*, 24 weeks GA until term: Development of the lymphatic network, decrease in interstitial tissue and thinning of the alveolar walls. Towards the end of this stage, the foetal lung can support gas exchange in pre-term born neonates. If the maturation of surfactant synthesis and secretion is weak, the alveoli are unstable, and the lung cannot maintain them open, resulting in an ineffective gas exchange due to lung collapse.

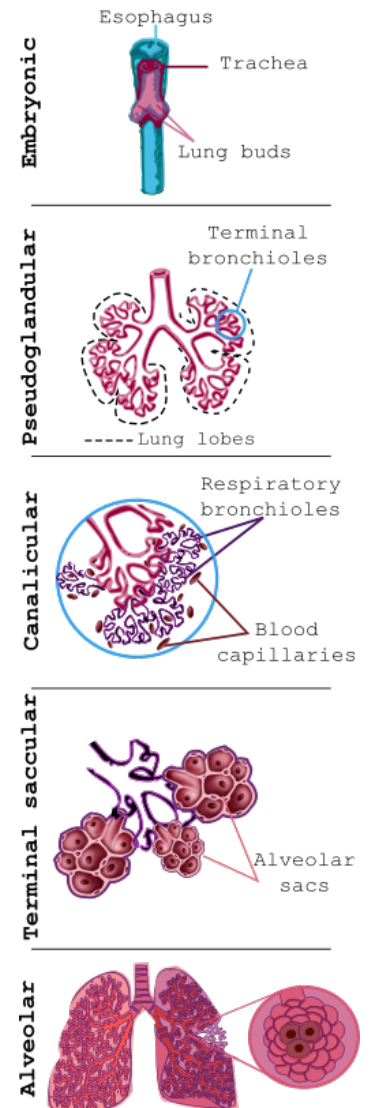


Figure 2.3. Main stages of in-utero lung development.

¹ Surfactant is a compound rich of phospholipids and hydrophobic proteins, produced by Type II cells, and secreted into the alveolar space, necessary for alveolar stability. It decreases the surface tension within the alveoli and prevents their collapse during exhalation. Hence, the stability of the lung correlates with the number of lamellar bodies at birth.

The saccular stage follows and lasts until birth, the growth of pulmonary parenchyma, the thinning of connective tissue between air spaces and the further maturation of surfactant are the most important steps towards life.

* *Alveolar*: At birth, the lung is functional but structurally immature, given that the alveolar units of the adult lung are scarce or missing. The alveolarization occurs after birth. In humans, more than 90% of all alveoli are created after birth, forming the majority of the gas exchange surface. At this stage saccules (air-containing spaces) continue to mature until their geometry achieve “adult” configuration, in which the alveoli:

- are connected to alveolar ducts lined with type I cells (in contact with pulmonary capillaries);
- contain surfactant produced by type II cells;
- and, have pores of Kohn connecting them to adjacent alveoli.

Functional maturity is reached with approximately 300 million alveoli in the lung (8 years after birth).

The pulmonary arterial system has a similar development to the airways. In the cannalicular stage, the arteries in the conducting airways (pre-acinar region) are formed. The formation of muscle tissue of intra-acinar arteries is completed during the childhood ² .

² There is not absolute agreement among the authors about the timing of each stage, in fact, the gestational maturity of the lung varies among fetuses.

2.1.2 Gas exchange and hypoxaemia

An appropriate matching between ventilation (V_{ent}) and blood perfusion (Q) is the foundation of adequate gas exchange which is the cornerstone to bring O_2 to the cells. This requires adequate ventilation of the alveoli, and a functional blood circulation in close proximity to those air cavities. V_{ent} and Q of the lung are adjusted under normal conditions, a V_{ent}/Q mismatch results in *hypoxaemia* (low O_2 concentration in the blood) and increase of CO_2 which impairs the cellular respiration.

Newborns are prone to hypoxaemia because they have a small intra-vascular O_2 reserve, their FRC approaches airway closing volume where atelectasis (complete or partial collapse of lung tissue which occurs when the alveoli are deflated or filled with alveolar fluid instead of air) can develop, and their metabolic demand exhausts any intra-vascular or alveolar O_2 .

Pre-term born infants have a higher susceptibility for hypoxaemia due to apnoea³ (produced by an immature respiratory drive) and lung collapse at the end of expiration (due to compliant chest walls).

The *alveolar to arterial O_2 gradient* (A-a Gradient, equation 2.6) measures the difference between the O_2 concentration in the alveoli (gaseous O_2) and arterial system (diluted O_2 in blood) [39]

$$\text{A-a Gradient} = PAO_2 - PaO_2, \quad (2.6)$$

here, PAO_2 and PaO_2 correspond to the alveolar and arterial O_2 pressures. PaO_2 can be measured with an arterial blood gas test (ABG). PAO_2 is estimated using the *alveolar gas equation*:

$$PAO_2 = (Patm - PH_2O)FiO_2 - \frac{PaCO_2}{RQ}, \quad (2.7)$$

where $Patm$ is the atmospheric pressure at sea level, PH_2O is the partial pressure of water vapour, FiO_2 is the fraction of inspired oxygen, $PaCO_2$ is the partial pressure of carbon dioxide, and RQ is the

³ Absence of respiratory effort for more than 20 seconds, or if cessation of breathing lasts more than 10 seconds and is accompanied by bradycardia and/or desaturation.

respiratory quotient (volume of carbon dioxide released over the volume of oxygen absorbed during respiration). An ideal system where all the alveolar oxygen is transferred to the pulmonary arteries would result in an A-a Gradient = 0. Nevertheless, there is a physiological mismatch between V_{ent} and Q which induces natural changes in the A-a Gradient.

The physiological causes of hypoxaemia are high altitude, hypo-ventilation, diffusion limitation, shunt and ventilation-perfusion mismatch.

High altitude

The atmospheric pressure at sea level is 100 KPa ($\sim 1\text{ atm}$), which corresponds to the sum of the partial pressures of the constituent gases.⁴ As the partial pressure of water vapour at 37°C is 6.3 KPa ($\sim 0.062\text{ atm}$) and oxygen is 21% of dry air, the inspired O_2 pressure at sea level is $0.21 \times (100 - 6.3)\text{ KPa} = 19.6\text{ KPa}$. Both, atmospheric pressure and inspired O_2 pressure decrease with altitude (roughly 50% at 5500 m and 70% at 8900 m), this fall in the driving pressure for O_2 from alveolar gas into arterial blood, is insufficient to fully oxygenate the blood as it passes through the pulmonary capillaries. In this case the A-a Gradient is normal and the body response is hyperventilation [40].

⁴ Mainly oxygen, nitrogen and water vapour.

Hypo-ventilation

Hypo-ventilation occurs when the minute ventilation (given by the respiratory rate $\times TV$) goes down causing an abnormally low alveolar ventilation.⁵ The major consequence of hypo-ventilation is an increase of alveolar CO_2 which in turn, reduces the amount of molecular O_2 that can be held in the alveoli. Equation 2.7 shows that an increase in $PaCO_2$ will lower the PAO_2 . A decrease in PAO_2 results in a lower PaO_2 , therefore the A-a Gradient remains steady despite the reduction of alveolar and arterial oxygenation. Patients with hypo-ventilation will respond to supplementary O_2 therapy.

⁵ Hypo-ventilation can happen when the patient breaths at a low rate or with low TV .

Diffusion limitation

The alveolar O_2 turns into arterial O_2 after diffuse passing through a one cell layer thick epithelium (which is the epithelium of the lung), followed by a single cell layer thick of endothelium which leads to the pulmonary artery. A blockage in the area between the alveolar sack and the artery may cause a diffusion abnormality. This can be seen in infiltrated diseases of the lung, specially during exercising, or with pulmonary oedema. In this case, the A-a Gradient increases and a patient with hypoxia due to diffusion limitation will respond to 100 % O_2 administration.

Shunt

Shunting refers to blood that enters the arterial system without passing through ventilated alveoli. In this case, the A-a Gradient increases and a patient with hypoxaemia due to shunt will not respond to 100 % O_2 administration.

An example of shunt is surfactant deficiency in the newborn, where hyaline membranes formed on the alveoli, impairing gas exchange, and preventing the gaseous O_2 from diffusing through epithelium and endothelium cells.

Ventilation/perfusion inequality

V_{ent} and Q occur simultaneously in each pulmonary unit, and the V_{ent}/Q ratio determines the gas exchange of each alveolar unit.

The mismatch of V_{ent} and Q in different regions of the lung, impairs the uptake of O_2 and elimination of CO_2 , in other words, a less efficient lung with uneven ventilation and blood flow affect the overall gas exchange of the lung.⁶ Since the respiratory exchange ratio is not constant, the equation 2.7 is not applicable in this case. Alveoli with high V_{ent}/Q ratio, increase the O_2 concentration of effluent blood at a lower rate, compared to the low blood oxygenation caused by alveoli with a low V_{ent}/Q ratio.

In this case, the A-a Gradient increases and the patient with hypoxaemia resulting from V/Q inequality, will respond to 100 % O_2 administration.

Some of the causes of V_{ent}/Q inequality are fibrosis, asthma, pulmonary embolism and pneumonia.

⁶ Gas exchange refers to the ability to take up O_2 and take out CO_2 .

2.2 Lung pathologies in neonates

Pre-term births compromise the functionality of the lung given that the pulmonary structure of the neonates is immature. The transition from foetus to infant involves the complex adaptation of the lung at birth as a gas exchange organ, and newborns with surfactant deficiency are not fully equipped to deal with this transition. Hypoxic pulmonary vasoconstriction is a natural response of the lung to prevent localized V_{ent}/Q mismatch (it reduces blood flow to hypo-ventilated regions of the lung). As the O_2 levels in the alveoli decrease, resistance of muscular arteries increase, causing shunting of blood into ventilated areas, and a progressive enlargement of lung areas with atelectasis eventually results into V_{ent}/Q inequality.

A diseased neonatal lung can present simultaneous atelectasis in different regions and the situation can be more challenging if localized infection is present where inflammatory mediators inhibit vasoconstriction. Hyperinflation occurs when the gas is trapped in the lung above tidal levels and is a symptom of obstructive conditions such as bronchitis. Many pre-term infants have difficulty in clearing lung fluids, which reduces pulmonary compliance and impairs ventilation.

A description of the main pulmonary diseases present among pre-term neonates is presented below.

2.2.1 Respiratory Distress Syndrome

Neonatal respiratory distress syndrome (RDS) [41] is one of the major causes of mortality and morbidity among infants. As mentioned in Section 2.1.2, a proper matching of ventilation and perfusion results in optimum gas exchange. Besides the mechanical action of blocking the airways, a surfactant deficiency occurs through inactivation carried out by the proteins. FRC is reduced in a surfactant deficient lung, due to the displacement of the intrapulmonary gas volume by vascular congestion, interstitial oedema, and proteinaceous exudation.

Decrease in lung compliance is one of the indicators of RDS, it is the result of a reduction in the number of ventilated terminal airspaces, over-distension in ventilated airspaces (which increases the recoil pressure) and changes in the viscoelastic properties of the lung. The dead space in lungs of infants with RDS makes up a larger proportion of the

TV, to compensate for this, infants breath faster.

Transient tachypnea of the newborn (TTN) is caused by the delay in the clearance of foetal lung fluid after birth, which leads to ineffective gas exchange and is one of the main causes of RDS [42].

2.2.2 Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is characterized by surfactant catabolism and diffuse lung inflammation which increases alveolar capillary permeability and reduces aerated lung tissue, leading to lung dysfunction. Clinical criteria are acute onset; hypoxaemia; decreased lung compliance requiring positive pressure to recruit the alveoli; increase of the respiratory dead space; respiratory failure not fully explained by lung oedema due to heart failure; and diffuse bilateral opacities with loss of aeration on chest radiographs [43, 44].

2.2.3 Air leaks

Pulmonary air leaks are caused by alveolar overdistention associated with high transpulmonary pressure swings, air trapping, and uneven ventilation, which results in rupture of the alveolar bases. The following pathologies are related to air leaking [45]:

- Pneumopericardium: Air in the pericardial cavity.
- Pneumomediastinum: Air present in the space in the chest between the two lungs.
- Pneumoperitoneum: Air or gas in the abdominal cavity, which usually results from perforation of the gut.
- Pneumothorax: air ruptures into the pleural space between the chest wall and the lung.
- Interstitial emphysema: air in the pulmonary interstitium (support tissue within the lung including alveolar epithelium, pulmonary parenchyma, and interlobular or subpleural loose connective tissue).
- Emphysema: air in the extra-thoracic areas like the neck.

2.2.4 Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) also known as chronic lung disease (CLD), is a major cause of long-term lung dysfunction. BPD develops in premature infants exposed to mechanical ventilation and O_2 supplementation, and is defined as O_2 dependence for at least 28 days after birth. It affects infants born before the terminal saccular gestational stage (see Section 2.1.1). It is characterized by injuries occurring in the canicular and saccular phases of lung development, which disrupt its subsequent alveolarization and vascularization. A reduction in the cross-sectional area of the pulmonary vascular bed, increases the pulmonary vascular resistance, which leads to onset of pulmonary arterial hypertension. BPD make infants susceptible to lower respiratory tract disease, and promotes airflow obstruction in adulthood. School-age children with a history of BPD have lower VC and higher RV compared to a control group born at term. This is a consequence of airway obstruction, and alveolar hyperinflation. A lung with hyper-inflated areas can be easily distended, therefore it has a high compliance [46].

2.2.5 Pneumonia

Invasion of lung tissue by pathogenic micro-organisms which leads to infection. These organisms are acquired from the maternal genital tract or the nursery. Premature birth increases the susceptibility to pneumonia, but it also can happen to term infants.

2.2.6 Meconium aspiration

⁷ Foetal bowel content. The word derives from the Greek *mekonion*, meaning poppy juice or opium).

The meconium⁷ aspiration syndrome (MAS) is a common cause of neonatal RDS. It results from the aspiration of meconium-stained amniotic fluid into foetal or neonatal lungs.

Other not so well known aspiration syndromes include aspiration of amniotic fluid, gastric contents, and blood.

2.3 Treatment of lung pathologies in neonates

As mentioned in Section 2.1.2, an adequate gas exchange is key to prevent hypoxemia. There must be sustained effective ventilation to replenish O_2 and enable the diffusion of O_2 and CO_2 across the alveolar wall. Also, an appropriate FRC must be established after birth to maintain an optimal V/Q ratio. Despite the fact that many of these treatments save lives, postnatal interventions such as resuscitation manoeuvres, O_2 administration and mechanical ventilation increase the risk of lung damage.

The following mechanisms are used in the intensive care unit (ICU) to aid neonates with respiratory dysfunction, by administering O_2 , and inducing both bronchodilatation and/or pulmonary vasodilatation.

2.3.1 O_2 administration

When the infant requires an increase in the inspired O_2 concentration $\leq 25\%$, it can be achieved by administering O_2 rich gas into the incubator. If the O_2 requirement is $> 25\%$ a head-box or a nasal cannula is used, to deliver humidified O_2 gas. The oxygen concentration is monitored continuously using a gas analyser close to the neonate's mouth. The nasal cannula⁸ is mostly used to deliver supplementary O_2 , the advantage over the headbox is that it facilitates the access to the infant, who in turn has greater mobility. Nasal cannula gas flow, causes changes in respiration due to the generation of positive and expiratory pressures.

⁸ Double cannula which is inserted 2-3 cm into one nostril.

Very premature infants have extremely thin skin, therefore, O_2 can be also absorbed cutaneously if the baby is nursed in 95 % O_2 rather than air [45].

2.3.2 Mechanical ventilation

The aim of mechanical ventilation is to provide respiratory support of neonates with lung disease and achieve adequate gas exchange. It can be an invasive procedure (implying full endotracheal (ET) intubation of the neonate) or non-invasive (using systems to deliver O_2 and air alternative to intubation). The major reasons to use mechanical ventilation support are poor gas exchange, increased work of breathing, apnoea, and the need for surfactant-replacement therapy.

Ventilation control is critical as one of the major causes of lung damage is over-inflation, which in turn, reduces the surfactant efficacy, and is a primary risk factor for neonates to develop BPD. Allowing lungs to collapse at the end of expiration can also lead to lung damage, because higher pressures are necessary to open atelectatic alveoli compared

to the pressure used to inflate already opened alveoli. The complications of mechanical ventilation include volutrauma, extrapulmonary air leak syndroms, traumatic injury to large airways, and ET tube complications. Uncontrolled increase in pressure (such as that exerted during positive pressure resuscitation), can lead to high TV and over-distension, causing epithelial injury [47]. Among the available ventilation strategies, patient-triggered ventilation is preferred over machine triggered forms. Volume-targeted ventilation modes have shown to be more beneficial in providing lung protection, compared to the pressure control modes. The key to protect the neonatal lung during mechanical ventilation is to *optimize lung volume*, and limit excessive lung expansion, with appropriate pressure and short inspiration time [48].

Continuous positive airways pressure

Continuous positive airway pressure (CPAP) is the simplest mode of respiratory assistance. It can be administrated by different interfaces (nasal and face masks, nasal pillows and helmets) without the hazards associated with intubation. The ventilation is lead by the infant's own respiratory drive, and the device delivers oxygen helping to keep the airway pressure at a higher level than atmospheric pressure during the whole respiratory cycle. CPAP maintains adequate FRC and lung compliance, prevents atelectasis, and improves gas exchange do to the recruitment of previously collapsed alveoli [49].

Non-invasive ventilation

Non-invasive ventilation (NIV), is a form of respiratory assistance which avoids airway invasion, by conducting pressurized gas from a positive pressure ventilator to the airways, via oronasal or nasal masks. NIV provides higher level of respiratory support than CPAP, the infant's spontaneous breaths can be assisted by patient-triggered or machine-triggered modes with time-cycled inflations [50].

Positive end-expiratory pressure

Positive end-expiratory pressure (PEEP) is one of the usual ventilator settings chosen when mechanical ventilation is initiated. In this mode, the alveolar pressure is kept above the existing atmospheric pressure at the end of expiration. The application of PEEP is done during expiration, to maintain the alveolar units opened, generating a recruitment of new lung units and over-distension of already opened alveoli. Consequently, it increases the FRC and improves arterial oxygenation [51].

PEEP protects the alveoli from injury during the phasic opening and closing of atelectatic units producing hypoxaemia [52].

2.3.3 Extra corporeal membrane oxygenation

Extra corporeal membrane oxygenation (ECMO) consists on pumping blood out of the body into an oxygenator machine which has blood and gas compartments separated by membranes which facilitate CO_2 (removal) and O_2 diffusion; the oxygenated blood is warmed and returned into the body at a rate compatible with venous return. ECMO is used when the lungs or heart are not able to support the needs of the body. There are two forms of ECMO; veno-arterial, in which blood is taken from the right jugular vein and returned via the right common carotid artery, and veno-venous, in which blood is taken from the right jugular vein and returned through the femoral vein[45].

⁹ Surfactant can be animal-derived or synthetic. Animal-derived surfactants are modified or purified from porcine or bovine lungs and contain surfactant protein B (SP-B) which enhances the absorption of phospholipid at the air-water interface, is involved in the formation of tubular myelin and has anti-inflammatory properties.

Synthetic surfactants contain 21-amino acid peptide, which mimics SP-B activity.

2.3.4 Surfactant therapy

Surfactant ⁹ replacement therapy, consist of the administration of exogenous surfactant via ET tube or nebulization. Studies indicate that surfactant administration reduce the incidence of pneumothorax, pulmonary interstitial emphysema and improve survival without BPD; which suggest that lung injury is mitigated after surfactant replacement. Surfactant therapy has been essential in the prevention and treatment of RDS in pre-term neonates. Large doses may be required to counterbalance surfactant inactivation, and removal of material from the lungs to treat MAS.

The delivery of surfactant results in a rapid improvement in lung volume, FRC and compliance. Therefore, expeditious changes in the mechanical ventilator settings are necessary to minimize lung injury and air leakage. Despite the increase in survival rates in pre-term newborns, the use of surfactant have also resulted in chronic lung disease [53].

2.3.5 Antenatal corticosteroids

The administration of corticosteroids such as dexamethasone or betamethasone, promotes foetal lung maturation in pregnant women at risk of pre-term birth. The corticosteroids induce the production of surfactant proteins and lipid synthesis, and alter pre-term responses to oxidative stress. Randomized trials demonstrated that antenatal corticosteroids reduce the incidence of RDS, acute lung disease and neonatal death. On the other hand the use of antenatal corticosteroids may increase the risk of developing BPD [54].

2.4 Diagnostic tools

2.4.1 Apgar scoring

This test is named after Dr. Virginia Apgar, who designed the first standardized method for evaluating a newborn's transition to life outside the womb [55]. When the head and feet of the infant are both visible (after delivery), five signs, namely heart rate, respiratory effort, muscle tone, reflex response and skin color, are observed and given 0, 1 or 2 points. The total points are then totalled to get the newborn's score.

The *Heart rate* is evaluated with the stethoscope:

- If there is no heartbeat, the infant scores 0 for heart rate.
- If heart rate is less than 100 beats per minute, the infant scores 1 for heart rate.
- If heart rate is greater than 100 beats per minute, the infant scores 2 for heart rate.

Breathing effort:

- If the infant is not breathing, the respiratory score is 0.
- If the respirations are slow or irregular, the infant scores 1 for respiratory effort.
- If the infant cries well, the respiratory score is 2.

Muscle tone:

- If muscles are loose and floppy, the infant scores 0 for muscle tone.
- If there is some muscle tone, the infant scores 1.

- If there is active motion, the infant scores 2 for muscle tone.

Reflex response:

- If there is no reaction, the infant scores 0 for reflex response.
- If there is grimacing, the infant scores 1 for reflex response.
- If there is grimacing and a cough, sneeze, or vigorous cry, the infant scores 2 for reflex response.

Skin color:

- If the skin color is pale blue, the infant scores 0 for skin color.
- If the body is pink and the extremities are blue, the infant scores 1 for color.
- If the entire body is pink, the infant scores 2 for skin color.

The test is performed on newborns at 1 and 5 minutes after birth as a guide to the need for resuscitation. The 1-minute score determines how well the newborn tolerated the birthing process, and the 5-minute score advises how well he/she is doing outside the mother's womb. The Apgar score does not reflect oxygenation itself, but it has been demonstrated that infants with low O_2 levels and highly acidic blood had low Apgar score.

2.4.2 Lung imaging

Lung functional tests are an indirect method to diagnose lung disease, and are not suitable for localized detection of structural changes in tissue. Complementary diagnostic studies are useful to define the severity of lung disease, and the location of significant airway lesions. Accurate diagnosis requires detailed clinical history, physical examination, and laboratory examination.

Chest imaging¹⁰ has gained importance in paediatric pulmonology as a diagnostic and monitoring tool in the past decade.

Chest radiography

Chest radiography is the most widely available imaging modality commonly used to assess the status of pulmonary and cardiac systems in neonates. This imaging technique uses ionizing radiation projected on the chest of the neonate. The different structural composition and densities of the thoracic tissues cause differential absorption, and the X-ray beam passing through the body is captured by a detector, generating a two dimensional (2D) snapshot of the chest. The standard chest radiograph consists of an anteroposterior projection, lateral views may be required to localize pathologies related to adjacent structures. The identification of the different pathologies mentioned in Section 2.2 may require a thorough evaluation and clinico-radiological correlation [57].

Computed tomography

Computed tomography (CT scanning) employs an ionizing radiation source and a set of rotatory detectors which generate 2D images in the axial, coronal, and sagittal planes. These images are further processed to create a three dimensional (3D) image of the different chest tissue types. CT provides more information than conventional chest radiography; therefore, it is considered "gold standard" technique for lung

¹⁰ DICOM stands for *Digital Imaging and Communications in Medicine*, and is the standard for medical images and related information. It defines the formats for medical images that can be exchanged with the data and quality necessary for clinical use. DICOM is implemented in almost every X-ray, CT, MRI and ultrasound device [56].

¹¹ The sievert (Sv) is a derived unit of ionizing radiation dose in the International System of Units, and is used to measure the health effect of ionizing radiation on the human body. $1Sv = 1J.Kg^{-1}$ representing the equivalent biological effect of the deposit of a joule of radiation energy in a kilogram of human tissue.

imaging and is normally used in critically ill neonates. Dynamic lung CT with respiratory gating has proven to be effective in the evaluation of FRC and tidal volumes in animal models [58].

Studies conducted by Greenberg have shown that dynamic CT at low radiation dose (2 mSv) can be used for treatment monitoring and diagnostics in patients with persistent respiratory distress [59].¹¹ However, repeated exposure to ionizing radiation represents a risk to patient safety if used for routine assessment of paediatric lung disease.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) provides 3D, high-resolution imaging without ionizing radiation. MRI scanners use magnetic field gradients and radio-waves to image the organs in the body. The MRI of neonatal lung is challenging due to the anatomy of the infants, the low-proton density of lung tissue, the continuous motion during respiration and the large content of air, which results in low MRI signal intensity. The latest advance in fast acquisition techniques are closing the image-quality gap between CT and MRI [60].

Ultrasound

Ultrasound (US) imaging techniques use high frequency sound waves to create a sonogram of different structures inside the body; based on the fact, that each tissue type has a distinctive acoustic impedance. US is limited in healthy aerated lungs, since there is not interference of the acoustic wave in air. The large change in acoustic impedance occurs at the pleura-lung interface which generates horizontal artefacts in the US scan in a healthy lung. When air content decreases, a characteristic acoustic mismatch occurs, generating different lines to those of a healthy lung. The thickness, orientation and spacing between these lines, help to identify pulmonary pathologies. Lung US is performed in a supine, lateral or prone position, and each hemithorax is divided into anterior, lateral, and posterior regions. Longitudinal and transverse scans are performed in all areas. US is a non-invasive, low cost and easy to operate tool which can be repeatedly used at the bedside [61].

2.4.3 Assessment of pulmonary volume

The assessment of pulmonary volume is important to evaluate growth and development of the lungs. FRC is the only static lung volume that can be assessed in non cooperative infants. The measurements of FRC are useful to evaluate the lung condition and treatment efficacy of infants with respiratory disease, because it is a function of lung size, structure and mechanical properties.

Gas dilution/washout

The FRC is measured in infants in supine position during behaviourally determined quiet sleep. A trace gas (inert and insoluble in blood) of known concentration C_1 is administered via respiratory mask. It stays in the alveoli as it is not absorbed into the blood, and dilutes into the lung mixing with the air contained within it. When the infant is breathing with tidal respiration, the gas valve is turned and the infant begins to breath in and out from a container of known volume (V_1) reducing the trace gas concentration until reaching a new steady state of C_2 and $V_2 = V_{\text{container}} + V_{\text{lung}}$. This final concentration is sampled from the mask using a mass spectrometer or a flow meter and the FRC is calculated from $FRC = V_2 - V_1$ [35, 62].

The nitrogen (N_2) washout technique is the most commonly used. This test makes use of the fact that 79% of the air is N_2 , and O_2 is the only gas that is exchanged from the lungs to the blood. Therefore, the amount of exhaled N_2 is the same as the amount inhaled. In this case, the infant breaths 100% O_2 and the N_2 in the lungs will be gradually replaced by O_2 as the infant exhales N_2 and replaces it with O_2 [63].

Gas dilution methods have the limitation that just the lung alveoli with good communication with the central airways are measured. In cases where the lung units do not communicate with the central airways, plethysmography is used instead.

Plethysmography

This technique uses Boyle's law¹² to measure changes in lung volume and airways resistance by enclosing the infant in supine position inside a rigid, airtight container with known $V_{container}$ and $P_{container}$. The tidal flow and volume are recorded from a flow-meter linked to the face cuff through which the infant breaths. The airway opening is occluded while the infant is breathing, as a natural response, the infant makes respiratory efforts compressing and decompressing the thoracic gas and the $P_{airways}$ measured at the airway opening reflects changes in alveolar pressure. The $P_{container}$ changes due to the chest expansion and contraction during breathing efforts and is measured simultaneously. Knowing $V_{container}$, $P_{container}$ and $P_{airways}$ the total V_{thorax} and FRC can be calculated[64].

¹² The Boyle's law ($PV = k$) relates the compression and expansion of a gas at constant temperature. It states that the product of pressure (P) and volume (V) is a constant (k) in isothermal state. The law can also be expressed as $P_1 * V_1 = P_2 * V_2$ to compare the same gas under two sets of conditions.

Previously, plethysmography was used together with the N_2 washout method to assess lung volume, alveolar ventilation and the efficiency of ventilation in critically ill infants[65]. It has been used recently in full term healthy neonates to determine neonatal body composition, and is perceived as a viable method for close monitoring of growth in infants. However, these techniques are not available on the cot side, and factors like body moisture and temperature, objects attached to infants, body movements, and thoracic gas predictions affects the the accuracy of the systems [66, 67].

Electrical impedance tomography

Electrical impedance tomography (EIT) is a non-ionizing, non-invasive imaging technique, increasingly utilized to detect changes in regional lung aeration in patients under mechanical ventilation. In this case, electrodes are placed in the perimeter of the back and chest of the patient to get the distribution signals of electrical conductivity, permittivity and impedance (or resistance) and its alterations through time. These signals are then processed to get morphological information used to build two dimensional images, and reconstruct a tomographic model of the organs in the thorax. The impedance changes are linearly related to air volume, and consequently with variations in lung volume. The low rate of image analysis EIT can be used for intra-individual and not inter-individual quantitative monitoring of regional ventilation and lung volume in infants, this is due to the fact that EIT gives information about the regional ventilation (and not absolute ventilation) which depends on body and head position, ventilator pattern, acid base status, oximetry, transcutaneous CO_2 , and lung mechanics (minute volume, tidal volume, resistance, etc) which are unique to each patient. The main disadvantage is the poor image resolution and operational limitations related to the proper placement of electrodes around the thorax [68].



Figure 2.4. Pulse oximetry is a light based test that measures the oxygen saturation in blood, which is the fraction of O_2 -saturated haemoglobin relative to total haemoglobin in blood.

Pressure and ventilation measurements with the mechanical ventilator

In patients with tracheal intubation, air flow and P are measured directly at the proximal end of the ET tube, or at the inspiratory and expiratory ports of the ventilator. Modern monitors allow separate measurements of the gas volume delivered by the ventilator and the volume due to spontaneous breathing and measurement of air flow and TV by integration of the air flow. Any modification of the original ventilator circuit (change of tubes or humidifier) may affect these measurements [69].

2.5 GASMAS as a potential tool for monitoring of lung function in neonates

In the past two decades, GASMAS has been used in industry for quality control and characterization of wood, food packaging, ceramics and pharmaceutical tablets [7, 18, 19, 21]. Further studies are addressing the clinical translation of this technology in a wide range of applications, such as the assessment of inflammation and infection in para-nasal sinus cavities [24, 70, 71], diagnosis of otitis [23], and early prediction of osteonecrosis [27].

The application of interest for the work developed in this thesis is the monitoring of molecular O_2 and H_2O vapour in the lungs of new-born infants [26, 72]. These studies have focused on neonates (and not in adults) as the thickness of the protective organs surrounding their lungs is within the limits of penetration depth of near infrared (NIR) light [73, 74]. The use of GASMAS for lung function assessment in adults is limited due to the technological state of art. However, the ongoing development of highly sensitive detectors, laser sources and techniques to deliver light into the body might enable the clinical translation of this technique beyond the neonatal care. It is important to note that the concentration of molecular O_2 in the lung is related to the diluted O_2 in blood, which can be measured by means of pulse oximetry (Fig. 2.4), but is not the same quantity.

The prototypes built for this application are designed to illuminate the thoracic walls of the infant in remittance geometry, with a diffuse dual light source (operating at 760 nm and 820/935 nm to match the absorption lines of O_2 and H_2O vapour respectively) and a photo-detector placed over the thorax. The scattered light reaching the detector, carries the absorption signals of H_2O vapour and O_2 . H_2O is used as reference gas, as mentioned in section 1.4, its concentration can be determined by means of equation 1.16 and using the Beer-Lambert law (equation 1.5). Then, the approximated gas absorption path length of both gases is calculated, in order to retrieve the molecular O_2 concentration [25, 26, 72].

The first GASMAS studies which aimed to assess gas content in the lungs of a full-term newborn with 4 kg weight were done in 2012. In this case, the source was placed in the armpit area and the detector below the collar bone. Even though a dual diode laser source operating at 760 nm and 935 nm (4 mW output power, each) was used, only H_2O vapour absorption imprint was obtained in the lungs, and the authors considered it could be possible to obtain signals for both gases with smaller neonates.

Then, the same GASMAS set up was used for a feasibility study with three full-term infants weighing 4 – 5 kg, for different source-detector configurations at the back, chest and side of the torso [26]. The geometry that worked the best for all subjects, was with the source under the right

collar bone and the detector through the ribcage, just below the right armpit. Despite the fact that O_2 absorption was not detectable for any of the subjects, the authors envisioned that with pre-term subjects (who are the target population for this GASMAS application), a larger fraction of the light would pass through the lung, and a higher light intensity will reach the detector, given the much thinner tissue protecting the lungs in the thorax. All factors which may enable good absorption signal for both O_2 and H_2O vapour.

Three years later, another study with 29 healthy newborn full-term infants with birth weight between 2.9 – 3.9 kg was conducted [25]. In this case the 760 nm diode laser had 30 mW power and 60% of the overall O_2 absorption measurements were successful.

Recent phantom and animal studies suggest that the quality of the measured gas absorption imprint could improve by allocating the probes in transmittance geometry. This could be achieved by placing the light source inside the breathing or naso-gastric feeding tubes, in the trachea or oesophagus of already intubated infants, and the detector on the skin over the thorax [75–77]. The phantom and computational studies of Paper V, Paper VI, Paper VII and Paper VIII reassure this rationale and together with the outcomes of Paper IV, show that GASMAS could potentially be used to monitor volume changes in the lung, which extends the possible applications of this technology in respiratory treatment and diagnostics.

With the work presented in this thesis, the potential of GASMAS to aid clinical staff in assessing lung function in neonates is explored. The following table, shows a comparison between the existing monitoring and diagnosis techniques, and the ideal GASMAS bedside device.

Diagnostics tool	Imaging	Volume assessment	Continuous use	Alveolar composition
Radiography	✓	x	x	x
CT	✓	Post-processing	x	x
MRI	✓	Post-processing	x	x
US	✓	x	x	x
Gas dilution	x	✓	x	x
Plethysmography	x	✓	x	x
EIT	✓	✓	✓	x
Ventilator	x	✓	✓	x
GASMAS	x	✓	✓	✓

Table 1: Characteristics of tools used for lung function assessment.

GASMAS is a non imaging technique, which could be used to obtain complementary information to the existing screening modalities (i.e radiography, CT, MRI, EIT and/or US) and those used to measure respiratory volumes and lung capacity tests. It has the advantage of being non-invasive and light based, which allows its use for continuous monitoring. On the other hand, its unique capability of quantifying the alveolar gas composition in real time, would enable the localization of under ventilated lung sections, monitoring of the patient response to surfactant administration, and ventilation therapy, and assist clinicians in ET placement, as stated in Paper I.



Figure 2.5. Picture taken the first day of NIOMI study. From right to left Jurate Panaviene (research nurse), Eugene Dempsey (neonatologist and principal investigator), myself and the first baby who take place in NIOMI study together with her parents.

EIT and US would be the best modalities to combine with GASMAS, both have the advantage of being non-invasive, bedside, radiation-free techniques which do not need cooperation from the patient. Since one of the main advantages of a GASMAS system is the possibility to assess continuously the lung function, EIT would be a better technique, as it is capable of assessing spatial lung inhomogeneities and changes in lung ventilation in a neonate under assisted ventilation or undergoing surfactant therapy. GASMAS and EIT need to place probes in contact with the skin, therefore, a prototype which can deliver or detect light in combination with the EIT electrodes could be evaluated.

2.5.1 Non-invasive lung oxygen monitoring in term infants: NIOMI-observational study

The Biophotonics@tyndall group acquired in October 2021 the NEOLA-alpha 2 (Fig. 2.6), a GASMAS system built by GPX Medical, specifically designed to measure directly H_2O vapour and O_2 signals from the lungs of full-term infants. The system uses a laser diode source at 935 nm to match the absorption lines of H_2O vapour, the detected signal at this wavelength is used to estimate the absorption path length inside the lung (assuming 100% RH and $37^\circ C$). The signal from a second laser at 764 nm is used to estimate the O_2 concentration by means of the *path length calibration* approach described in section 1.4.

NEOLA stands for “Neonatal Lung Analyser”, the system has source and detector probes adapted for measurements on the torso. The light is guided through a 400 μm core diameter fiber to the diffuser, which also contains a reference detector for signal monitoring and noise reduction. The detector consists of a photodiode and a pre-amplifier connected to the signal sampling and data processing unit. The current of the lasing diode is linearly ramped, resulting in a wavelength tuning across the specific absorption lines of O_2 and H_2O vapour. The system drives the two lasers in a time-multiplexed fashion at a scanning frequency of 279 Hz. The signal is sampled and averaged over several sampling periods, before being further processed. Upon evaluation of the averaged detected signal, the absorption of the gas is identified and the O_2 concentration estimated.

In order to remove absorption offsets, the optics box (where the light of the two laser diodes is combined with collimating lenses, a beam splitter and a focussing lens which guides the light into the fiber) is purged with N_2 gas.

The electronics, optics and lasers are assembled in the medical cart. The source and detector probes are accessed from a side of the cart. The system has a user interface that allows for data acquisition and control settings.

The NEOLA-alpha 2 was used to conduct the measurements in the NIOMI study, at the INFANT centre in the Cork University Maternity Hospital. The aim of this **observational study** was to test the NEOLA-alpha 2 in a group of 100 full-term healthy infants, during the first and second days of life. This study is significant, given that the most common techniques to monitor lung function in neonates (see Table 1), cannot measure gas concentration directly nor lung volumes continuously. And the successful development of GASMAS technique would lead to faster detection of lung dysfunction, diagnosis and ultimately treatment. Paper IX shows a comparison between GASMAS and the light-based devices currently used in the neonatal ward and discuss the possible clinical benefits of GASMAS technology in optimizing the management of neonates during the cardiorespiratory

transition in the delivery room, assessing surfactant deficiency, and optimizing endotracheal tube positioning.

The outcomes from previous feasibility studies with full-term neonates and the work presented in this thesis (specifically from papers Paper V and Paper VIII), helped to establish the objectives of NIOMI study and prepare the respective measurement protocol. The goal of this study is to answer the following questions:

- Can this GASMAS system detect O_2 absorption signals in the lungs of healthy, full term infants?
- Can this system measure the oxygen concentration? (As the target group are healthy full-term infants, it is expected to obtain estimations of O_2 concentration close to 21%)
- What is the repeatability among consecutive GASMAS measurements of O_2 concentration, when source and detector are kept in the same position?
- Is there an optimal source-detector configuration (position of the probes over the torso) for which the GASMAS measurements are consistent and present an acceptable signal to noise ratio?

The analysis of the data collected throughout NIOMI study, will be the base to further develop the clinical adaptation of GASMAS-based systems. Not just regarding the optimization of gas absorption signals and probe placement, but also to have an impression of the user experience while handling the equipment. The probes of the NEOLA-alpha 2 were handled by qualified clinical staff during the measurements with the neonates, and research staff from Bophotonics@tyndall was assisting any technical issues and taking part in data analysis.



Figure 2.6. NEOLA-alpha 2, clinical research system for GASMAS measurements in lungs of newborns. The area of the diffuse light source is 1 cm^2 with maximum output powers of 25 mW at 764 nm and 8 mW at 935 nm. The detector consists of a photodiode with a sensitive area of $1 \times 1 \text{ cm}$. Both probes are attached to the infant's skin with a double sided medical tape.

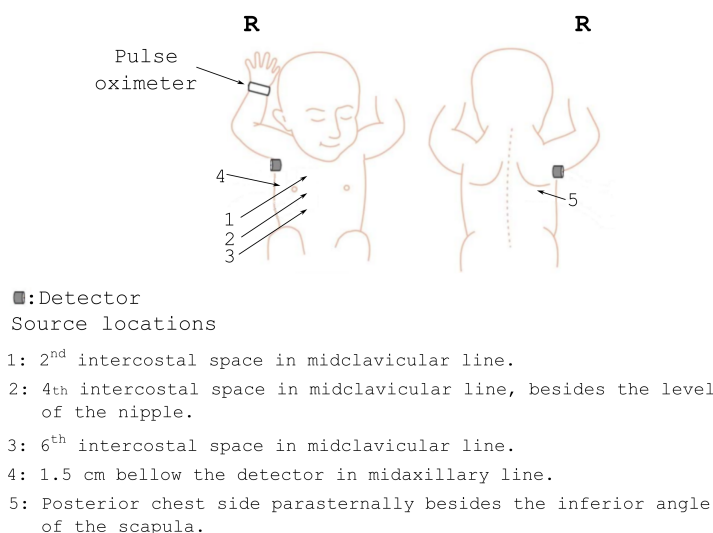


Figure 2.7. Diagram of source detector configurations used to acquire the data in NIOMI observational study.

The recruitment process of the infants who took part in NIOMI study, involved approaching the parents of the newborn in the postnatal ward, giving a description of NIOMI study and the principles of GASMAS technique. For the cases where parents agreed to participate in the study, the following protocol was conducted for each measurement

session:

Study subject: Newborn accompanied by his/her parent.

Location: Monitoring room on postnatal ward.

Procedure: GASMAS measurements were recorded with the detector placed underneath the right armpit, and the diffuse light source was placed in 5 different positions over the chest (Four in the front and one in the back as shown in figure Fig. 2.7). The same procedure was followed on the left side of the torso if parents agreed to continue with the measurements. The peripheral O_2 saturation was measured with a pulse oximeter during the whole session.

Duration: A total of 10 measurements on both sides of the torso, 2 minutes each. The total session was completed maximum within 30 minutes.

NOTE: Another session took place the next day if the neonate was cooperative and the parents agreed to do so.

Clinical data such as gestational age, birth weight, Apgar scores and mode of delivery were documented to be used throughout the data analysis. The measured absorption spectra from O_2 and H_2O vapour were saved for post-processing and development, to improve the evaluation algorithms. The target of 100 recruited patients was reached in May 2022. Researchers from INFANT centre, Tyndall and GPX Medical are working on a comprehensive data analysis, and designing the follow up clinical studies based on the results.

OPTICAL PHANTOMS

Optical phantoms are liquid, solid or gelatinous materials with absorbing and scattering properties which mimic the light distribution in living tissue. They are mainly used to test and validate optical spectroscopy, imaging and therapeutic systems, for quality control and optimization of existing devices, and to compare the performance between different optical apparatuses and techniques.

The primary factors taken into account to design a tissue phantom are the absorption (μ_a) and reduced scattering (μ'_s) coefficients of the materials. To understand the role of the particles size, shape and composition in the macroscopic optical properties of tissue, I outline in the section below the physical principles behind light extinction.

3.1 Physical basis for scattering and absorption

ⁱ The scattering of light by any media is related to the heterogeneity of that media.¹ The underlying physics of scattering is the same for all systems, *matter is composed of discrete electric charges (electrons and protons)*. An electron, a molecule or a particle represents an obstacle for an incident electromagnetic wave (light). Upon interaction, the electric charges in the obstacle will be set into oscillatory motion by the incident wave, and part of it will be *scattered* by the obstacle, re-radiating electromagnetic energy. In addition, the excited elementary charges may transform part of the incident electromagnetic energy into other forms (thermal energy, for example) in a process called *absorption*.²

The treatment of absorption and scattering of light by small particles is a fundamental problem of electrodynamics: *Given a particle of specific size, shape and optical properties that is illuminated by an arbitrary polarized, monochromatic wave, determine the electromagnetic field inside and outside the particle*. As any arbitrary field can be decomposed into its Fourier components (which are plane waves), the solution for the scattering-absorption problem can be obtained by superposition, regardless the illumination.

The electric and magnetic fields inside the particle can be denoted by $\mathbf{E}_1$ and $\mathbf{H}_1$ respectively. The fields in the surrounding medium ($\mathbf{E}_2$, $\mathbf{H}_2$) correspond to the superposition of the incident ($\mathbf{E}_i$, $\mathbf{H}_i$) and scattered ($\mathbf{E}_s$, $\mathbf{H}_s$) fields, as pictured in figure Fig. 3.1.

¹ Heterogeneity in the molecular scale, as is the case of gases or in the scale of aggregation of many molecules, as is the case of biological tissue.

² *Scattering* and *absorption* are mutually independent processes, which occur simultaneously.

ⁱThis section was written based on the books from Craig F. Bohren and Donald R. Huffman [78], H.C. van de Hulst [79] and Caroline Boudoux [1].

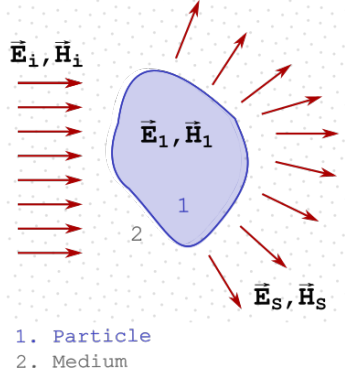


Figure 3.1. The incident field ($\mathbf{E}_i$, $\mathbf{H}_i$), rises a field ($\mathbf{E}_1$, $\mathbf{H}_1$) inside the particle and a scattered field ($\mathbf{E}_s$, $\mathbf{H}_s$) in the medium surrounding the particle.

Therefore:

$$\mathbf{E}_2 = \mathbf{E}_i + \mathbf{E}_s \quad \mathbf{H}_2 = \mathbf{H}_i + \mathbf{H}_s,$$

where

$$\mathbf{E}_i = \mathbf{E}_0 e^{(i\mathbf{k} \cdot \mathbf{x} - i\omega t)} \quad \mathbf{H}_i = \mathbf{H}_0 e^{(i\mathbf{k} \cdot \mathbf{x} - i\omega t)},$$

and $\mathbf{k}$ is the wave vector appropriate to the surrounding medium. Both fields must satisfy the Maxwell equations

$$\nabla \cdot \mathbf{E} = 0 \quad (3.1)$$

$$\nabla \cdot \mathbf{H} = 0 \quad (3.2)$$

$$\nabla \times \mathbf{E} = i\omega\mu\mathbf{H} \quad (3.3)$$

$$\nabla \times \mathbf{H} = -i\omega\epsilon\mathbf{E} \quad (3.4)$$

at all points where the permeability (μ) and the permittivity (ϵ) are continuous. The curl of equations (3.3) and (3.4) is

$$\nabla \times (\nabla \times \mathbf{E}) = i\omega\mu\nabla \times \mathbf{H} = \omega^2\epsilon\mu\mathbf{E}$$

$$\nabla \times (\nabla \times \mathbf{H}) = -i\omega\epsilon\nabla \times \mathbf{E} = \omega^2\epsilon\mu\mathbf{H}$$

and using the vector identity $\nabla \times (\nabla \times \mathbf{A}) = \nabla(\nabla \cdot \mathbf{A}) - \nabla \cdot (\nabla \mathbf{A})$ one obtains

$$\nabla^2 \mathbf{E} + \omega^2\epsilon\mu\mathbf{E} = 0, \quad \nabla^2 \mathbf{H} + \omega^2\epsilon\mu\mathbf{H} = 0 \quad (3.5)$$

Re-writing $k^2 = \omega^2\epsilon\mu$, the last two equations get the form:

$$\nabla^2 \mathbf{E} + k^2 \mathbf{E} = 0, \quad \nabla^2 \mathbf{H} + k^2 \mathbf{H} = 0 \quad (3.6)$$

given that $\nabla^2 \mathbf{A} = \nabla \cdot (\nabla \mathbf{A})$, $\mathbf{E}$ and $\mathbf{H}$ satisfy the Helmholtz equation.³

$$\nabla^2 \Psi + k^2 \Psi = 0. \quad (3.7)$$

The Mie scattering theory, models the elastic scattering of light by homogeneous spheres, of all sizes and refractive indexes, under illumination of any wavelength, which is treated by the formal solution of Maxwell's equations with the appropriate boundary conditions. In order to avoid discontinuities at the boundaries between the spheres and the surrounding medium, it is imposed that:

$$(\mathbf{E}_i + \mathbf{E}_s - \mathbf{E}_1) \times \mathbf{r} = \mathbf{0}, \quad (\mathbf{H}_i + \mathbf{H}_s - \mathbf{H}_1) \times \mathbf{r} = \mathbf{0}, \quad (3.8)$$

and in addition to these boundary conditions, the solution needs also to satisfy equation (3.7).

The calculation algorithm to define how the observable quantities vary with the size and optical properties of the sphere, and the nature of the surrounding medium, is done in detail by Bohren and Huffman [78], and utilize two parameters:

³ Any vector field with zero divergence that satisfy the vector wave equation is an admissible electric field, and the associated magnetic field is related to the curl of the electric field through equation (3.4) (The reader can find a complete mathematical treatment for isotropic dielectric spheres and cylinders in [78]):

- The size of the sphere's circumference normalized by the free-space wavelength of the incident light (x), denoted as

$$x = \frac{2\pi a n_m}{\lambda}, \quad (3.9)$$

where a is the radius, λ is the free-space wavelength and n_m corresponds to the refractive index of the medium, and

- the relative refractive index n_r which is the ratio of the particle refraction index n_p to the one of the medium

$$n_r = \frac{n_p}{n_m}. \quad (3.10)$$

The scattering coefficients are found using the boundary conditions for all components of $\mathbf{E}$ and $\mathbf{H}$, and can be written in terms of, x , n_r and the Ricatti-Bessel⁴ functions as:

$$a_n = \frac{n_r \zeta(n_r x) \zeta'_n(x) - \zeta_n(x) \zeta'_n(n_r x)}{n_r \zeta_n(n_r x) \xi'_n(x) - \xi_n(x) \zeta'_n(n_r x)}, \quad (3.11)$$

$$b_n = \frac{\zeta_n(n_r x) \zeta'_n(x) - n_r \zeta_n(x) \zeta'_n(n_r x)}{\zeta_n(n_r x) \xi'_n(x) - n_r \xi_n(x) \zeta'_n(n_r x)}. \quad (3.12)$$

The electrostatics approximation leads to the solution of the scattering efficiency of the particles of size x based on the average of the scattering efficiencies of a small sphere

$$Q_{abs} = 4xIm \frac{\epsilon_1 - \epsilon_m}{\epsilon_1 + 2\epsilon_m}, \quad Q_{sca} = \frac{8}{3}x^4 \left| \frac{\epsilon_1 - \epsilon_m}{\epsilon_1 + 2\epsilon_m} \right|^2, \quad (3.13)$$

where ϵ_1 and ϵ_m are the permittivities of the sphere and the surrounding medium, respectively. The scattering cross sectional σ_s area is calculated as $x\pi a^2$, and the scattering coefficient μ_s is calculated as $\rho_s \sigma_s$ where ρ_s is the density of scatterers. The angular dependence of the scattering is also computed to obtain the anisotropy g factor and the reduced scattering coefficient $\mu'_s = \mu_s(1 - g)$.

If $\left(\frac{\epsilon_1 - \epsilon_m}{\epsilon_1 + 2\epsilon_m} \right)$ is a weak function of wavelength, then, for sufficiently small particles the Rayleigh scattering approximation is valid:

$$Q_{abs} \propto \frac{1}{\lambda}, \quad Q_{sca} \propto \frac{1}{\lambda^4}. \quad (3.14)$$

This approximation, is used to describe the scattered wave from particles much smaller than the wavelength of light. Which means, with a radius $a \ll \frac{\lambda}{2\pi}$, small enough to consider the external electromagnetic field homogeneous throughout the particle.

It is worth to highlight, if simplifying assumptions are made that the scattering centers in tissue are homogeneous dielectric spheres, and that the electromagnetic field incident on each sphere is a plane wave, Mie theory can be used to predict the wavelength dependence of scattering [80].

Light extinction in biological tissue

Scattering and absorption remove energy of a light beam interacting with biological tissue, and as a consequence the beam is attenuated. This

⁴ The Ricatti-Bessel functions are defined as:

- $\zeta_n(\rho) = \rho j_n(\rho)$
- $\xi_n(\rho) = \rho h_n^{(1)}(\rho)$

The reader can refer to [78] for a complete mathematical derivation.

attenuation is called *extinction* and can be seen when we place a hand in front of a candle. Whether scattering or absorption is mainly responsible for this extinction cannot be judged from this observation alone.

$$\textit{Extinction} = \textit{Scattering} + \textit{Absorption},$$

therefore, light extinction depends on the chemical composition of the particles, their shape, size and orientation, the surrounding media, their density, the polarization state, and frequency of the incident beam.

Tissue absorption is dominated by proteins, and the membranous structures of the tissue cells are major source of scattering of NIR light (see figure Fig. 1.8). These scatterers include, the mitochondria, nuclei, endoplasmic reticulum and the cell itself, covering a range of sizes in the $0.1 - 10 \mu\text{m}$ range. The Mie scattering for spheres with comparable diameter of the tissue cells, has been applied to estimate their scattering contribution to specific wavelengths, using a relative refraction index $n_r = \frac{1.46}{1.35}$, and showing how the Mie theory for spheres mimics the absolute value and wavelength dependence of the macroscopic scattering of tissue [81]. In the same way, spherical particles with similar size distribution to the scatterers in biological tissue, can be used to reproduce the phase function, μ'_s and μ_a of biological tissue, at a given wavelength [82].

3.2 Documentation of optical properties

The values for μ_a and μ'_s used in bench top and computational studies in this thesis, were sourced in the literature as referenced in Paper **III**, Paper **VII** and Paper **VIII**.

Optical properties, vary from tissue to tissue, from person to person and even from time to time. However, the estimation of absorption and scattering of a generic tissue is a tool to guide the preparation of therapeutic protocols, interpret tomographic signals for diagnosis, and design biomedical devices. These generic tissues can be constructed by specifying the concentration of absorbing chromophores and by estimating the Mie scattering in tissue. Thus, any tissue can be characterized by defining the concentration of the main chromophores, namely oxygen-haemoglobin, deoxy-haemoglobin, bilirubin, beta carotene and melanine, together with fat content, the average blood volume fraction, and water content. Depending on the wavelength some chromophores become less or more relevant. Most of the information to compute μ_a and μ'_s was obtained from the review by Steve Jacques [14], in this excellent publication, the author guides the reader through the process of formulating reduced scattering and absorption of a tissue at any given wavelength.

Generic tissues were used in all the studies of this thesis, it allowed to adequately mimic any real organ and generate predictable spectra for absorption and scattering at the wavelengths of interest (760, 820 and 934 nm). This constitutes a first step in testing GASMAS clinical prototypes to guide the clinical translation, but data with real patients should be stored and properly analysed to obtain clinical validation. Even though, all efforts were made to be as accurate as possible, new phantoms should be created to target specific populations, for example the optical properties of skin used in this thesis correspond to dermis. Which was made under the assumption that most of the clinical measurements would be performed in Ireland, with a Caucasian-dominant population that generally has low levels of melanin. The creation of a comprehensive data base with the optical properties of tissue in neonates would contribute

enormously in the development of light-based technologies for paediatric healthcare.

3.3 Phantom fabrication

The materials used to mimic the optical properties of biological tissue, usually consist of a suspension of particles in an homogeneous solid or liquid matrix. The selection of the matrix material is defined by the application, by the choice of scatters and absorbers, and their stability in that medium. The use of appropriate amounts of scatterers and absorbers, enables to produce a tissue-like object or *phantom*, matching the desired values of μ'_s and μ_a , and allowing for spectral fitting. For small scale (< 1 mm) applications it is important to match $\mu_a(\lambda)$ and $g(\lambda)$ coefficients. Over larger distances (more than 5 scattering lengths), matching the so called transport scattering coefficient ($\mu'_s = (1 - g)\mu_s$) is enough [83].

The phantom matrix options used to hold scatterers and absorbers are aqueous suspension, gelatin or agar, polyacrylamide gel, polyester or epoxy resin, polyurethane resin, and room-temperature-vulcanized silicone. The main choices for scattering agents are lipids⁵ (such as Intralipid or milk), polymer microspheres, titanium dioxide (TiO_2) or aluminium oxide (Al_2O_3) powders, and quartz glass spheres. And, the choices for absorbers are whole blood, ink and molecular dyes. Pogue and Patterson wrote a comprehensive review of tissue simulating phantoms, where they summarize the strengths and limitations of the different matrix options, their lifetimes, and compatibility with the available scattering and absorbing agents [84].

⁵ The benefit of lipid microparticles is that they are biologically similar to the bilipid membrane of cells and organelles, which is believed to cause scattering in tissue.

It is important to note that most of the existing phantom recipes, match the optical properties at a single wavelength. In these cases, the use of the recipe is limited, and if another phantom is required to perform experiments at a different wavelength, the whole characterization process and recipe standardization has to be repeated. On the other hand, suspensions made with biologically compatible components such as lipids, whole blood, agar, or hydro-gels, have short life times, and in order to use them over days, the storage and mixing process must be consistent, and carefully conducted to guarantee repeatability and homogeneity in the phantom optical properties [85].

Aiming to produce a solid, long lasting phantom recipe, covering most of wavelengths of the tissue optical window, and mimicking a wide range of optical properties ($\mu_a = 0.1 - 1 \text{ cm}^{-1}$ and $\mu'_s = 5 - 25 \text{ cm}^{-1}$), the work described in Paper II was done. Silicon (PlatSil SiliGlass) was chosen as phantom matrix as it is transparent and do not become turbid or yellowish on curing.⁶ The silicone was mixed with silica (SiO_2) microspheres with comparable size to the main scatters in tissue ($9 - 13 \text{ }\mu\text{m}$), and a SiliGlass compatible black ink (absorption agent) in different concentrations. The recipe provides a step by step protocol to fine-tune the components, in order to obtain the optical properties required for the intended application in a broad wavelength range ($600 - 1100 \text{ nm}$), the recipe cannot be used for wavelengths outside this spectrum, as such values were not characterized in this study.

⁶ Curing refers to the hardening process that the silicon experiences.

The largest challenge in fabricating a silicone phantom is to obtain a homogeneous distribution of scatterers and absorbers without aggregates, sedimentation or air bubbles. To avoid this problem we implemented the phantom preparation method proposed by C. Maughan



Figure 3.2. Resin 3D printed models of main organs, used to make the negative moulds of the anthropomorphic phantom from Paper III.

and P. Munro [86], which involves magnetic stirring, sonicating and placing the A and B Siliglass parts in a vacuum chamber, prior to solidification. An extra step was added in our mixing protocol, to break manually the big clusters of SiO_2 microspheres formed upon contact with the part B of Siliglass (see Fig 1 in Paper II). A phantom matrix with 24 slabs was created, using 4 different absorber concentrations matched with 6 scattering combinations. Each slab was characterized using a time-domain diffuse optical spectrometer [87], in collaboration with Professor Pifferi's group from the Physics Department in Politecnico di Milano. Finally, a table with the linearity parameters (slope and intercept) of the phantom matrix was presented, to enable the user to fabricate phantoms with optical properties relevant to human tissue.

P. Naglic et al. revised the recipe protocol, and conducted the optical characterization of phantoms, that were prepared following the work proposed in Paper II, in the spectral range from 475 to 925 nm [88]. They showed that the refractive index of these phantoms is not affected by the inclusion of SiO_2 microspheres and black ink, and that μ_a exhibits linear dependency on the ink concentration. They also found that the ink particles contribute to the phantom μ'_s , and sums up to 1 cm^{-1} at the lower end of the investigated spectral range. Finally, the authors concluded that given that the ink and microspheres were not fully characterized by the manufacturers, the optical properties are likely subject to inter-batch variability, and suggested to be cautious and verify the μ_a and μ'_s values of the prepared phantoms.

3.4 Phantoms manufactured for the clinical translation of GASMAS into neonatal respiratory health care

As the development of GASMAS as a tool for respiratory assessment continues to advance, the need for complex human-like tissue phantoms is growing. Ideally, the phantoms designed for this application, should resemble the tissue morphology of the organs in the thorax, and allow gas exchange in the pulmonary cavity, making sure there is no gas pockets elsewhere. These features are essential to recreate the clinical scenario of a neonatal thorax, and investigate the changes in the gas absorption signal for different source-detector configurations.

Larsson et. al built a phantom for this purpose [89], developing a 3D-printed nylon model with 4 void shells resembling the geometry of heart, bone, lung, and skin (together with subcutaneous fat). Once each shell was filled with liquid phantom,⁷ a set of measurements was performed with a GASMAS device scanning H_2O vapour and O_2 absorption lines around 935 and 760 nm, in order to find the best positions to place the source and detector for an infant with 1700 g weight.

The presence of nylon material in the boundary between liquid phantoms, is a drawback of this model, because its high scattering ($\mu'_s = 46.5 \text{ cm}^{-1}$) biases the light propagation through the thorax. On the other hand, the use of liquid phantoms becomes challenging, due to the layered 3D structure of the human body and the fact that water-based suspensions remain homogeneous for a period of hours [84], making it difficult to conduct repeatable measurements over days, while keeping the homogeneity of the optical properties. Additionally, the GASMAS studies were performed on a phantom with optical properties at a single wavelength, yielding no indication of the light extinction for each of the operation wavelengths used in GASMAS prototypes.

⁷ The matrix of the liquid phantom was water, mixed with Intralipid (scatterers) and indian ink (absorber) in different proportions to customize the optical properties of relevant tissues (fat, muscle and heart) at 760 nm, the bone was made of solid white nylon resin.

The same group used an improved model, with smoother nylon surfaces, which included a sponge material in the pulmonary cavity [76]. In this case, the shells were filled (and the sponge was impregnated) with liquid phantom matching optical properties of heart, muscle, fat and lung at 764 and 820 nm. The authors found the values of mean absorption path length and transmitted intensity at 764 nm, to be lower in comparison with the values obtained for the phantom with void lung cavity at 760 nm. As a new approach, the authors made two measurement sets, to obtain gas absorption signals for light delivered internally (through an optical fiber placed in the phantom's trachea), and on the chest (placing a diffuse light source under the phantom's armpit), with an identical set of detectors placed on the phantom's thorax. They found larger interaction of light with the gas in the lung for internal light administration, which resulted in larger gas absorption path lengths and higher signal to noise ratios compared to dermal light administration.

The aforementioned models could be further improved. Therefore, we designed a solid anthropomorphic thoracic phantom, made with silicone with homogeneous optical properties for the different organs, and a pulmonary cavity which could be filled with gases. In this case, the high scattering associated with nylon was avoided and there was not need to rely on the repeatability and homogeneity of liquid phantom preparations. I developed a detailed protocol (published in Paper III) to produce a long-lasting, multi-structure phantom of a neonate's thorax.⁸ The anatomic geometry of heart, lungs, bones, muscle, fat, and skin was obtained from a neonatal CT scan by means of NIRFAST software (see Fig. 3.3).⁹

⁸ This protocol can be implemented to reproduce any 3D geometry and optical properties of any DICOM file of human or animal organs.

⁹ A detailed explanation of the segmentation process and NIRFAST software can be found in section 4.4.

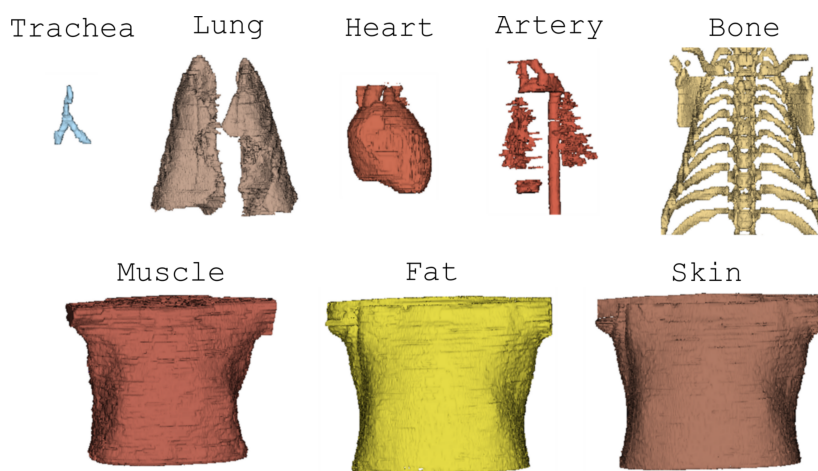


Figure 3.3. Image of segmented organs from a DICOM image stack of the thoracic CT scan of a full term neonate.

The 3D models printed in resin from Fig. 3.2, were used to create negative rubber moulds and the entire thorax was built by placing all phantom organs inside the muscle structure, the relevant optical properties were customized by mixing specific ratios of ink and SiO_2 microspheres, according to the phantom recipe published in Paper II. The pulmonary cavity was achieved by moulding initially the lung with solid coconut oil, once the external organs (made of Siliglass) were cured, the coconut oil was melted and extracted from the phantom. The feasibility of conducting GASMAS bench top studies on this phantom for dermal and internal illumination was proven.

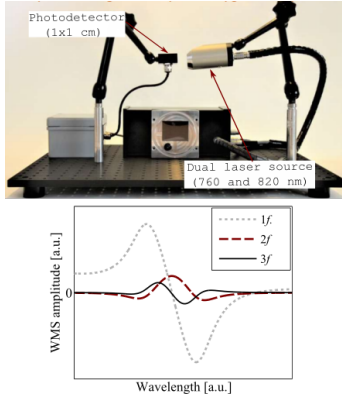


Figure 3.4. Top: GASMAS benchtop system built by GASPOROX AB (*MicroLab Dual O₂/H₂O*). The laser source is designed to scan across absorption lines of O₂ (760 nm) and H₂O vapour (820 nm). After interaction with the sample, the scattered light is collected by a photo-detector and the system performs wave modulation spectroscopy (WMS) to increase the detection sensitivity of the gas absorption signals. **Bottom:** Typical appearance of the first three WMS curves. The characteristic output of this instrument is the amplitude signal obtained by WMS for the second harmonic component 2f (here in red)[90]. WMS consists in modulating the laser wavelength in a sinusoidal manner, when the source wavelength is close to resonance with the gas absorption line, the detected intensity also fluctuates and its modulation can be found with a lock-in amplifier. WMS quasi zero background signals and has the advantage that the lock-in amplifier is only sensitive to modulations around the chosen frequency, thus noise with frequencies above or below will be cancelled.

3.5 Mimicking the alveolar structure and composition of lung tissue

The anthropomorphic phantoms produced by Larsson et. al and by our group (Paper III) are useful to evaluate the best source-detector configurations. However, they lack of alveolar-like structure within the lung cavities, together with the absence of pulmonary environment (RH and T). As GASMAS strength is to sense the gas in lung tissue, mimicking the anatomy of the respiratory zone, was the next natural step in building phantoms to exploit this technique. As shown in chapter 2, the respiratory airways are composed of millions of air pockets called alveoli which are responsible for gas exchange and cellular oxygenation. In the process of breathing, the volume of air we inspire (or expire) is a parameter of clinical importance because it helps to identify obstructive respiratory pathologies.

In Paper IV we published the design of a simplified model of lung tissue which recreates inflated alveoli embedded in lung phantom. It was built using a capillary structure with analogous size of alveolar units. While empty capillaries mimic the alveoli, the remaining were filled with liquid lung phantom to recreate the scattering and absorption that light undergoes when traversing lung tissue. The capillary array was placed inside a custom-made chamber to maintain the phantom at pulmonary RH and T (100% and 37 °C respectively), recreating the clinical scenario for accurate operation of a GASMAS based system.

The phantom was then used to make GASMAS measurements with the *MicroLab Dual O₂/H₂O* (see figure Fig. 3.4) probing the feasibility of detecting volume changes with GASMAS technique. This was a significant contribution since, most of the previous studies addressing the clinical translation of GASMAS into respiratory healthcare, only reported on sensing the absorption imprint of O₂ and H₂O vapour to quantify gas concentrations [25, 26, 72, 76, 89].

E.K Svanberg et al. observed changes in transmission of O₂ and H₂O vapour signals, associated with respiration in mechanically ventilated piglets [77], and mentioned ‘...GASMAS method appeared to be sensitive enough to detect inspiration and expiration changes to each breath’. However, there has not been done any experiment, focused on measuring quantified changes of gas volume using a GASMAS device. Hence, the finding reported in Paper IV stated a new possible application of GASMAS for respiratory treatment and diagnostics.

3.6 GASMAS measurements in solid anthropomorphic phantoms

Even though Paper III refers to a protocol to build an optical phantom with optical properties at 760 nm, three sets of phantoms (six in total) were manufactured for the two different geometries, obtained from segmentation of 2 anonymized CT scans (illustrated in Fig. 3.5), each geometry was made with optical properties at 760, 820 and 935 nm. These phantoms were manufactured with the aim to study the variations in GASMAS signals associated with different geometries, wavelengths and gas content in the pulmonary cavity.

The four phantoms from figure Fig. 3.6 were used to conduct the measurements used to obtain the results shown in detailed in the draft of Paper V. In this study, 30 source-detector configurations were used to acquire gas absorption signals, the detector was placed at 8 positions in front of the thorax and 6 on the back. While the light source was placed

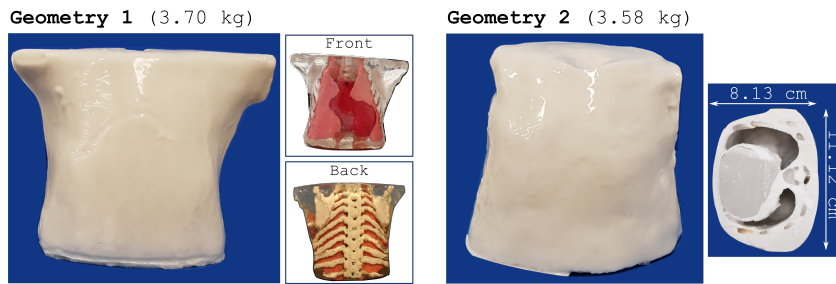


Figure 3.5. Picture of the two phantom geometries used for the studies in this thesis. A transparent model with geometry 1 was also created for visualization of the inner structure of the different organs. And a phantom with geometry 2, was sliced to show the lung cavity which facilitates gas exchange.

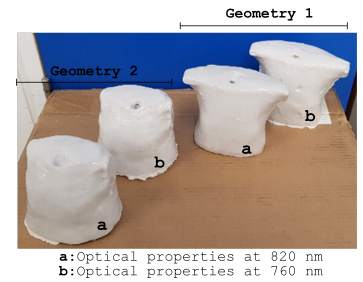


Figure 3.6. Set of phantoms used to perform the GASMAS measurements of paper WRITE HERE. The geometry of the main organs (muscle, bone, heart and lung) was obtained from two anonymized neonatal CT scans.

in the region under the armpits (dermal light administration) or inside the trachea (internal light administration), to resemble gas spectroscopy in remittance and transmittance geometry, respectively.

Each of the phantoms had an empty lung cavity which was filled with humidified gas of four different O_2 concentrations (21%, 30%, 50% and 100%). A total of 32 data sets were collected, as gas absorption signals were collected for each phantom, filled with the different gases, using both dermal and internal light administration.

The experimental protocol followed for each measurement set, includes 3 main steps (as can be seen in the diagram of Figure 2 in Paper V):

- Transit of the gas from the supply through a humidifier, to guarantee 100% RH, which is key to make a correct estimation of the concentration of H_2O vapour in the gas, and therefore influences the calculation of path length.
- Calibration of the gas using a gas spectroscopy cell made by GAS-POROX AB. The cell has a humidity-meter and a dual laser diode source as the NEOLA system. Given that the length of the cell is known, the estimation of the gas concentration by means of the Beer-Lambert law is straight forward.
- Input of gas in the phantom cavity, followed by the placement of probes over (or inside) the phantom, and data acquisition. A black mask is placed around the dermal source and detector (see figure 3 in Paper V), to avoid straight light detection during data acquisition.

We present in this manuscript the best source-detector configurations to obtain reliable gas absorption signals for both geometries, and plot the calculated values of O_2 concentration for each batch of gas with every phantom using the GASMAS technique. Less variations in the signals were obtained with the phantoms of geometry 2, most likely due to the fact that they correspond to a smaller infant and still enough light reaches the detector after being attenuated by the thoracic organs. The gas concentrations calculated with signals obtained with the phantoms with optical properties at 820 nm, exhibit more variations compared to those at 760 nm, this could be because the laser diode output at the latter wavelength almost doubles in power.

These results are of help to design and prepare further clinical studies and complement the results published by Larsson et al. who studied

the differences in signal with internal and dermal light sources, at four locations in the back and front of a 3-dimensional nylon thorax phantom. The phantom consisted of four hollowed compartments with the boundary structure of skin, subcutaneous fat, lung and heart, designed to be filled with liquid optical phantom; and the gas cavity was filled with room air [76]. The study from Paper **V** presents GASMAS measurements in 32 source-detector configurations (16 with internal and 16 with dermal light administration), using 4 different kinds of gas to fill the pulmonary cavity. Therefore it provides a comprehensive mapping of the thoracic cavity, and information about the GASMAS signal dependence of the O_2 gas concentration inside the pulmonary cavity. The implementation of new, more accurate phantom models for similar studies, mimicking all possible clinical scenarios, would contribute to the testing of existing clinical prototypes to identify technical and conceptual pitfalls which may hinder the prompt clinical translation of GASMAS systems.

COMPUTATIONAL MODELLING OF LIGHT PROPAGATION IN NEONATAL THORAX

The advances in modelling light propagation in tissue have been driven by the development of optical tomography¹ along the past three decades. The light propagation is governed by the presence of scatterers and absorbers in tissue, therefore in optical tomographic imaging, the aim is to provide the spatial distribution of tissue's μ'_s and μ_a and the related physiological parameters by probing the tissue with light, and measuring the transmitted light distribution on the tissue's surface. The measured signals, are then used in a transport-model-based image reconstruction algorithm, to solve the intrinsic optical properties of the tissue at the applied wavelengths, or to estimate the functional information such as the chromophores content for multi-wavelength measurements [13].

¹ Also known as *Diffuse optical tomography* or *NIR tomography* because the transport of NIR light in tissue becomes isotropic, over distances greater than few scattering lengths, and is well described by photon diffusion.

The radiative transfer equation (RTE) and the diffusion approximation, are used in biomedical optics to make an estimation of the path of photons interacting with biological tissue. The principles of these tools are described in the following sections. A thorough development of the theoretical and mathematical basis can be found in the review written by Durduran et al. [91].

4.1 Radiative transfer equation

The light propagation is most accurately expressed by the RTE, which describes the transformation of energy from the photons propagating within biological tissue.

To account for the direction of the energy flow ($\hat{\mathbf{e}}_s$), new terms are defined below [1]:

- *Radiance*, $L(\mathbf{r}, \hat{\mathbf{e}}_s, t)$ [$W/m^2 sr$], a quantity used to describe the propagation of electromagnetic energy, and represents the radiant power, per unit solid angle, about unit vector $\hat{\mathbf{e}}_s$. Hence, the *radiant power* dP [W] transported across unit area dA in the direction $\hat{\mathbf{e}}_s$ within a unit solid angle $d\Omega$ and at position $\mathbf{r}$ is given by:

$$dP = L(\mathbf{r}, \hat{\mathbf{e}}_s, t)(\hat{\mathbf{e}}_s \cdot \hat{\mathbf{e}}_n)dAd\Omega, \quad (4.1)$$

where $\hat{\mathbf{e}}_s = (\sin\theta\cos\phi, \sin\theta\sin\phi, \cos\theta)$.

- *Current density*, $\mathbf{J}(\mathbf{r}, t)$ [W/m^2] describes the energy flow per unit area per unit time, and is obtained by integrating the radiance over all directions of propagation:

$$\mathbf{J}(\mathbf{r}, t) = \int_{4\pi} \hat{\mathbf{e}}_s L(\mathbf{r}, \hat{\mathbf{e}}_s, t) d\Omega. \quad (4.2)$$

- *Fluence rate*, $\Phi(\mathbf{r}, t)$ [W/m^2] is defined as the total power per area moving radially outward from an infinitesimally small volume element, and it is obtained by integrating the radiance over all directions of propagation:

$$\Phi(\mathbf{r}, t) = \int_{4\pi} L(\mathbf{r}, \hat{\mathbf{e}}_s, t) d\Omega. \quad (4.3)$$

- *Fluence*, $F(\mathbf{r})$ [J/m^2] is the time-integrated fluence rate, which corresponds to the energy radiating from an infinitesimally small volume element per unit area:

$$F(\mathbf{r}) = \int \Phi(\mathbf{r}, t) dt. \quad (4.4)$$

The RTE describes the variation of radiant power during photon propagation through an infinitesimal small volume element $dV = dA ds$, which is expressed as:

$$dP = \frac{\partial L(\mathbf{r}, \hat{\mathbf{e}}_s, t)}{\partial s} dV d\Omega = \frac{1}{v} \frac{\partial L(\mathbf{r}, \hat{\mathbf{e}}_s, t)}{\partial t} dV d\Omega, \quad (4.5)$$

where v is the speed of light in a medium of refractive index n . Any variations in the radiant power, are due to photon extinction ($dP_{a/s}$), multiple scattering (dP_s), the presence of a source within dV (dP_S) and, beam divergence or convergence due to illumination optics ($dP_{c/d}$). The expression associated to each of them is described next.

Photon extinction due to scattering and absorption

Along the path ds , photons can be absorbed or scattered out of the infinitesimal volume dV , causing a variation of radiant power $dP_{a/s}$:

$$dP_{a/s} = -(\mu_a + \mu_s) ds L(\mathbf{r}, \hat{\mathbf{e}}_s, t) dA d\Omega = -\mu_t L(\mathbf{r}, \hat{\mathbf{e}}_s, t) dV d\Omega, \quad (4.6)$$

where the negative sign represents losses through photon extinction, and $\mu_t = (\mu_a + \mu_s) ds$ corresponds to the probability of an interaction occurring.

Gains in radiant power due to multiple scattering

There is a gain in radiant power from photons scattered into dV and redirected into $\hat{\mathbf{e}}_s$. The probability for scattering to occur within dV is proportional to the number of scatterers within the volume element given by $N dV \sigma_s$, where N is the number density of scatterers and σ_s is the scattering cross-section. The probability of photons being redirected to $\hat{\mathbf{e}}_s$, given by the phase function $\Phi(\hat{\mathbf{e}}_{s'} \cdot \hat{\mathbf{e}}_s)$, is also included into the mathematical expression, as follows:

$$dP_s = N dV \left(\int_{4\pi} \sigma_s \Phi(\hat{\mathbf{e}}_{s'} \cdot \hat{\mathbf{e}}_s) L(\mathbf{r}, \hat{\mathbf{e}}_{s'}, t) d\Omega' \right) d\Omega, \quad (4.7)$$

where the integration is performed for all photon directions $\hat{\mathbf{e}}_{s'}$. If σ_s within dV is constant, this term can be taken out of the integral and

$$dP_s = \mu_s \left(\int_{4\pi} \Phi(\hat{\mathbf{e}}_{s'} \cdot \hat{\mathbf{e}}_s) L(\mathbf{r}, \hat{\mathbf{e}}_{s'}, t) d\Omega' \right) dV d\Omega, \quad (4.8)$$

given that $N \sigma_s = \mu_s$.

Source contribution to the radiant power

This term is associated with the source S [$W/(m^3 sr)$] at position $\mathbf{r}$, oriented along $\hat{\mathbf{e}}_s$, and is described by:

$$dP_S = S(\mathbf{r}, \hat{\mathbf{e}}_s, t) dV d\Omega. \quad (4.9)$$

The contribution associated with an isotropic² source, takes the form:

$$S_{isotropic}(\mathbf{r}, \hat{\mathbf{e}}_s, t) = \frac{S(\mathbf{r}, t)}{4\pi}. \quad (4.10)$$

² A source which radiant power has the same value when measured in all different directions. Under some considerations a fiber optic can be considered isotropic.

Variations in radiant power caused by beam convergence or divergence

The optics used to bring photons into the volume element dV , can increase or decrease the radiant power depending on the convergent or divergent nature of the beam:

$$dP_{c/d} = \pm \nabla \cdot [L(\mathbf{r}, \hat{\mathbf{e}}_s, t) \hat{\mathbf{e}}_s] dV d\Omega, \quad (4.11)$$

where $\nabla \cdot$ is the divergence operator and the sign describes whether the beam is divergent (+) or convergent (-).

Combining all possible losses and gains on the left of the equation 4.5, the expression for the radiance in each infinitesimal volume element within the sample is obtained:

$$\begin{aligned} \frac{1}{v} \frac{\partial L(\mathbf{r}, \hat{\mathbf{e}}_s, t)}{\partial t} = & -\mu_t L(\mathbf{r}, \hat{\mathbf{e}}_s, t) + S(\mathbf{r}, \hat{\mathbf{e}}_s, t) \\ & + \mu_s \left(\int_{4\pi} \Phi(\hat{\mathbf{e}}_{s'} \cdot \hat{\mathbf{e}}_s) L(\mathbf{r}, \hat{\mathbf{e}}_{s'}, t) d\Omega' \right) \\ & \pm \nabla \cdot [L(\mathbf{r}, \hat{\mathbf{e}}_s, t) \hat{\mathbf{e}}_s]. \end{aligned} \quad (4.12)$$

This equation can only be solved numerically for very simple cases. To obtain analytical solutions, the spherical harmonics are used to express the radiance ($L(\mathbf{r}, \hat{\mathbf{e}}_s, t)$) in terms of fluence rate (equation 4.3) and current density (equation 4.2):

$$L(\mathbf{r}, \hat{\mathbf{e}}_s, t) = \frac{1}{4\pi} \Phi(\mathbf{r}, t) + \frac{3}{4\pi} \mathbf{J}(\mathbf{r}, t) \cdot \hat{\mathbf{e}}_s, \quad (4.13)$$

this solution is inserted into the RTE equation, to simplify it into the Fick's law which leads to the diffusion equation. The diffusion approximation can be used to describe light transport, under the following assumptions:

- Source isotropy.
- Slow temporal photon flux variations.
- Rotational symmetry.
- The photon propagation occurs far from the source, after multiple scattering events. Any distance beyond the so called mean transport free path ($MFP = 1/[\mu_a + \mu_s(1 - g)]$) from the source will satisfy this condition.
- Photons should undergo many scattering events before being absorbed. Usually $\mu'_s/\mu_a > 10$ is used as benchmark for photon diffusion in tissue, which also guarantees the radiance to be nearly isotropic ($\Phi \gg |\mathbf{J}|$).
- The photons are far from boundaries between regions of differing optical properties such as the air/tissue surface, and also from strongly absorbing objects (where $\mu'_s/\mu_a \ll 10$).

4.2 Diffusion equation

The transport of light in tissue can be treated as a concentration of optical energy that diffuses down a concentration gradient. The photons scattered by interaction with biological tissue, lose their directionality. Hence, diffusion theory can be used to describe light propagation in these media, as the resulting radiant energy does not have a preferential direction to travel [92].³

Inserting the expression for radiance in equation 4.13 into the RTE, multiplying both sides by $\hat{\mathbf{e}}_s$, solving the integral over 4π and assuming an isotropic source, yields:

$$\frac{1}{v} \frac{\partial \mathbf{J}(\mathbf{r}, t)}{\partial t} + (\mu_a + \mu'_s) \mathbf{J}(\mathbf{r}, t) + \frac{1}{3} \nabla \Phi(\mathbf{r}, t) = 0. \quad (4.14)$$

Considering that the temporal variation of the current density is slow, the term $\frac{\partial \mathbf{J}(\mathbf{r}, t)}{\partial t}$ can be neglected in comparison to $(\mu_a + \mu'_s) \mathbf{J}(\mathbf{r}, t)$ and the last expression will be reduced to the Fick's law for diffusion:⁴

$$\nabla \Phi(\mathbf{r}, t) = -3(\mu_a + \mu'_s) \mathbf{J}(\mathbf{r}, t), \quad (4.15)$$

which can be re-written

$$\mathbf{J}(\mathbf{r}, t) = -D \nabla \Phi(\mathbf{r}, t), \quad (4.16)$$

where D corresponds to the *diffusion coefficient* $D = \frac{1}{3(\mu_a + \mu'_s)}$.⁵

Equation 4.16 allows to write the RTE for an isotropic source ($S_{isotropic}(\mathbf{r}, t)$), which only depends on the fluence rate ($\Phi(\mathbf{r}, t)$), known as the *diffusion equation*:

$$\frac{1}{v} \frac{\partial \Phi(\mathbf{r}, t)}{\partial t} + \mu_a \Phi(\mathbf{r}, t) - D \nabla^2 \Phi(\mathbf{r}, t) = S_{isotropic}(\mathbf{r}, t). \quad (4.17)$$

The use of the Fick's law has two consequences relevant to tissue optics. First, there is continuity of $\Phi(\mathbf{r}, t)$ across any boundary, even when there is a difference in optical properties on each side of the boundary. Second, photons do not accumulate on a boundary surface, as flux incident on a boundary equals the flux leaving the boundary.

The diffusion approximation can be used to evaluate the radiance distribution within biological tissue illuminated with different sources such as continuous illumination (point or extended source), time pulsed illumination; and modulated illumination (amplitude or spatially modulated); with the source and detection systems either in reflection or transmission geometries. A complete derivation for the solutions in each case can be found in [13].

4.3 Photon hitting density

In biological tissues, the light scattering is characterized by the MFP (previously mentioned in section 4.1) which is considered to be much smaller than the size of the system. Since coherence of scattered light is lost after multiple scattering events that are longer than the MFP, the path of a scattered photon can be described as a random walk with step size MFP.

The photon hitting density (PHD) is a photon measurement density function, which describes the expected local time spent by photons when migrating from source to detector. In other words, it is an expression of the deviation of photons from the direct path connecting the source and the detector. At extremely early times, the PHD is concentrated

³ In the NIR, a distance of one *MFP* corresponds to less than 1 or 2 mm, therefore diffusion theory is useful to study light transport over several millimetres or more.

⁴ The fluence rate ($\Phi(\mathbf{r}, t)$) can be seen as a measure of concentration of radiant energy, and the diffusion of light as the movement of photons down concentration gradients.

⁵ D is used to define the effective attenuation coefficient $\mu_{eff} = (\mu_a/D)^{1/2} = 3(\mu_a(\mu_a + \mu'_s))^{1/2}$, used to define the penetration depth of light, mentioned in section 1.3 (equation 1.10).

on the straight path connecting the source and detector, this represent the dominant contribution from nearly ballistic photons. At later times, photons that underwent multiple scattering contribute non-linear paths to the PHD, thus the PHD maps, exhibit the so called “banana shaped” as seen in Fig. 4.1. The calculations of the PHD models was reported by Schotland et al. in [93].

An explanation in depth of photon-measurement density functions and they derivation from the Green’s function of diffusion equation, and on the basis of the finite-element model for light propagation in tissue, can be found in the articles written by Arrige [94, 95].

4.4 Near Infra-red Fluorescence and Spectral Tomography (NIRFAST): Software package used to simulate light propagation in biological tissue

The simulation of light propagation and recovery of optical properties, can be seen as the two general classes of problems in the theory of the interaction of an electromagnetic wave with a small particle (figure Fig. 4.2), stated by Boren and Huffman in [78]:

The *direct problem*: Given a system with particles of known shape, size and composition, which is illuminated by a beam of specific irradiance, polarization and frequency, determine the field inside and outside the system.

The *inverse problem*: By a suitable analysis of the scattered field, describe the particle or particles that are responsible for the scattering.

Fortunately, there are tools like NIRFAST, a MATLAB-based software which facilitates the combination of NIR tomography measurements with pre-defined tissue geometries from standard clinical imaging systems. NIRFAST also allows users to import standard DICOM images, to do segmentation and meshing of the organs of interest, either for simulation of light propagation (forward model) or recovery of optical properties (inverse model). A basic description of these models is presented next. And a detailed numerical implementation of this methods can be found in the article written by Dehghani et al. [96].

Forward model

The forward model refers to the calculation of the fluence rate on the tissue surface given a particular spatial distribution of optical properties.

Solutions to the diffusion problem can be accomplished analytically or numerically. They can be derived from the time-domain diffusion equation (see equation 4.17) where each term on the left is a loss of photons, and the term in the right corresponds to the light source. Or it can also be solved using the frequency domain version given by:

$$-\nabla \cdot D\nabla\Phi(\mathbf{r},\omega) + \left(\mu_a + \frac{i\omega}{v}\right)\Phi(\mathbf{r},\omega) = S_{isotropic}(\mathbf{r},t). \quad (4.18)$$

For the air-tissue boundary, the fluence at the edge of the tissue exits but does not return, and the fluence leaving the external boundary is equal to the fluence rate at the boundary weighted by a factor that accounts for the internal reflection of light back into the tissue. This relationship is described by:

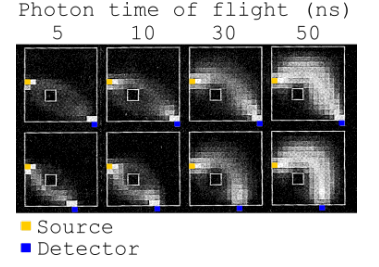


Figure 4.1. Photon hitting density maps for two different source-detector configurations, taken from [93]. Each column represents a different time of flight for the photons, and each map is scaled to its own maximum value.

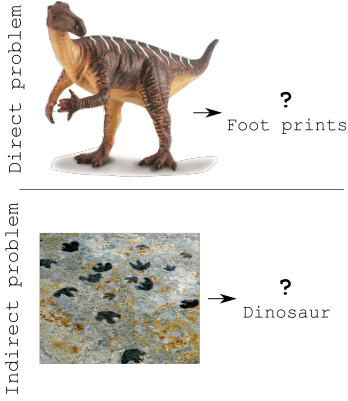


Figure 4.2. Direct problem: Describe the footprints of a given dinosaur (top). Inverse problem: Describe a dinosaur from the footprints (bottom).

$$\Phi(\zeta, \omega) + 2A\hat{\mathbf{e}}_n \cdot D(\zeta)\nabla\Phi(\zeta, \omega) = 0, \quad (4.19)$$

where ζ represents a point on the external boundary, $\hat{\mathbf{e}}_n$ is the outward pointing normal and A depends upon the relative refractive index mismatch between the tissue domain and air.

When the refraction index is homogeneous, the fine element discretization of a volume, can be obtained by subdividing the domain into elements joined at vertex nodes. This corresponds to the implementation of the finite element method (FEM) approach to solve partial differential equations, which consists on solving the equation as integrated on arbitrary discrete elements, called basis functions φ_i , which map pieces of the entire domain between discrete points, called nodes. In the FEM formalism, the frequency domain solution $\phi(r, \omega)$ can be discretize onto the basis functions multiplied by weighting coefficients $\phi = \sum_{j=1}^N \Phi_j \varphi_j$ where Φ is the discrete fluence rate at each node j with weight φ , which are linear mapping functions. The discrete values of the fluence are determined as part of the solution process, given simple fixed weight functions.

Inverse model

This model corresponds to the problem of predicting the optical properties at each FEM node within the domain, given some measure of the fluence from the tissue surface. In this case, regions to be recovered could be the entire tissue (assumed to be homogeneous), layers of tissue, locally embedded regions within the bulk or recovery of properties at every point in the tissue [92]. NIRFAST uses the modified-Tikhonov minimization function given by:

$$\chi^2 = \left\{ \sum_{i=1}^{NM} (\Phi_i^M - \Phi_i^C)^2 + \gamma \sum_{j=1}^{NN} (\mu_j - \mu_0)^2 \right\}_{\mu}^{min}, \quad (4.20)$$

where Φ^M represents the fluence at the tissue surface and the calculated data using the forward solver are represented by Φ^C , NM is the number of measurements obtained with the imaging device, NN is the number of FEM nodes (the unknowns) and $\gamma = \sigma_{\Phi^M}^2 / \sigma_{\Phi^C}^2$ is the Tikhonov regularization parameter defined as the ratio of the variances of the measurement data and optical properties. μ_0 is an initial estimate of the optical properties or an a priori distribution, which may be available.

The minimization with respect to μ of equation 4.20, involves setting all the first-order derivative to zero and ignoring higher order terms (The reader can refer to [96] to see a detailed derivation of the mathematical procedure that leads to equations 4.21 and 4.22). The first-order condition leads to:

$$\left(\frac{\partial \Phi^C}{\partial \mu} \right)^T (\Phi^M - \Phi^C) - \gamma(\mu - \mu_0) = 0. \quad (4.21)$$

The derivative matrix $(\frac{\partial \Phi^C}{\partial \mu})$ is the Jacobian matrix $\mathbf{J}$ also known as the weight or sensitivity matrix, which defines the relationship between changes in boundary data Φ^C , resulting from small changes in the optical properties; and the exponent (T) indicates the transpose of the matrix. Using this linear approximation of the problem, and solving it as iterative scheme gives:

$$(\mathbf{J}^T \mathbf{J} + \gamma \mathbf{I}) \delta \mu = \mathbf{J}^T \delta \Phi - \gamma(\mu_i - \mu_0), \quad (4.22)$$

where $\delta\mu$ corresponds to the update for the optical properties, $\delta\Phi$ is the data-model misfit at the current iteration, and $\mathbf{I}$ is the identity matrix.

The structure of the Jacobian matrix, which involves diffusion coefficient (D) and absorption (μ_a) derivatives can be found in [96]. This matrix is solved to obtain the optical properties and the chromophore concentrations are calculated using a least square fit to the Beer's law (equation 1.7). Similarly, an empirical approximation to Mie scattering theory given by [80]

$$\mu'_s = a\lambda^{-b}, \quad (4.23)$$

is used to evaluate the model parameters scatter amplitude (a) and scatter power (b), and estimate the reduced scattering (μ'_s).⁶

Fig. 4.3 shows two flow charts with the specific commands used in NIRFAST to solve the forward model and simulate light propagation in a given volume with known μ_a and μ'_s , or to solve the inverse model and recover the optical properties from a set of diffuse optical measurements.

⁶ The scatter amplitude a and the scattering power b depend on the scattering center size and the number density, and may reflect variations in tissue composition and structural densities. Typically, large scatterers have lower a and b values and vice-versa.

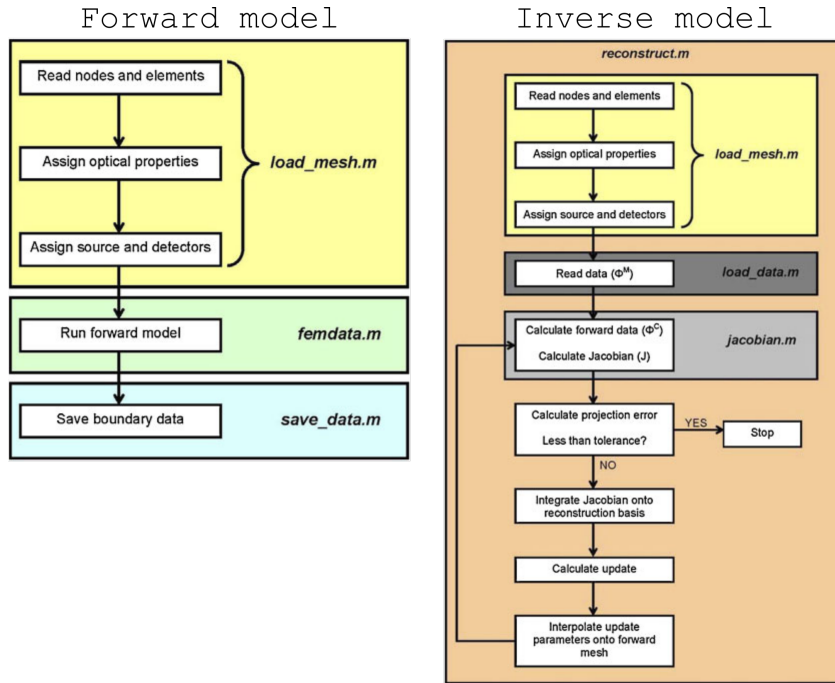


Figure 4.3. Flow charts with the sequence and commands used in NIRFAST for a generalized forward model (left), and a generalized image reconstruction problem (right). Taken from [96].

4.5 Mesh creation

Accurate diffusion modelling in optical tomography requires a 3D geometry, given that the photons scatter in all directions. NIRFAST includes segmentation and mesh creation tools which allow to create 3D fine-element meshes from medical images. A comprehensive description of these segmentation and mesh creation procedure is given by Jermyn et al. in [97].

NIRFAST allow for inputs of DICOM formats for medical images, therefore, it can be used for imaging modalities such as CT, MRI and

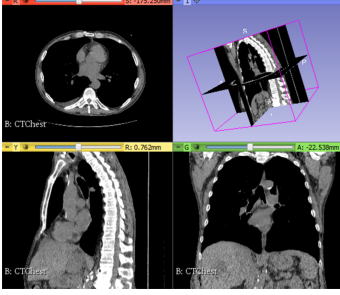


Figure 4.4. Screen shot of the NIRFAST interface where the DICOM images from a thoracic CT scan were loaded.

US, described in chapter 2. The general process to create the mesh in NIRFAST has the following steps:

- (i) The DICOM images are imported into the segmentation interface (see Fig. 4.4).
- (ii) The automatic segmentation modules are used for identification of tissue types and regions as accurately as possible.
- (iii) Manual touch-up of the regions segmented in the previous step, in order to fix any remaining issues like stray pixels or holes.
- (iv) Provide the segmentation as input to the meshing routine, which creates a 3D tetrahedral mesh from the 2D DICOM image stack, in a single run. The user can set the element size, quality and approximation error of the mesh.

The resulting mesh is a 3D volume consisting of several non-overlapping regions, which preserve the structural boundaries of segmented tissues. The mesh allows the utilization of structural prior information in diffuse optical imaging, and is suitable for finite element analysis.

4.6 Simulation of light propagation in a neonatal thorax

Light undergoes a strong attenuation due to the scattering and absorption in the different organs of the thorax. When source and detector are placed over the thorax (remittance geometry), light is attenuated before reaching the alveoli in the lungs and also on the way back to the detector, resulting in faint gas signals. Emilie Krite Svanberg, proposed in her doctoral thesis [75], to use internal illumination via the nasogastric or endotracheal tubes, while placing the detectors over the thorax (transmittance geometry), to increase the amount of light propagating through lung tissue and reduce the light attenuation by different thoracic organs (i.e. heart, bone, muscle, fat and skin).

The differences between internal and dermal light administration, were studied by doing GASMAS measurements in phantom and animal models. Larsson et al. measured the gas absorption signals in a thoracic phantom, with dermal and internal light administration. The light source was placed at the anatomical position of armpit, trachea and oesophagus, and 8 detectors were placed over the thorax (4 on the front and 4 on the back) [76].⁷ The results showed a larger gas absorption path length and higher detected signals (both in the front and back of the phantom) for internal sources, in comparison to dermal light administration. The authors mentioned that the detector placement is less critical with light delivered internally, and the source placement in the oesophagus was preferable instead of the trachea, as this last exhibited larger variation between signals detected at different positions.

Svanberg et al. measured O_2 and H_2O vapour absorption signals in 5 mechanically ventilated piglets, using the same GASMAS device [77]. Two source-detector configurations were studied with a detector placed in the right axillary line (2 cm below the foreleg), and the source either in the oesophagus (21 cm from the snout) or in the midclavicular line on the right side of the thorax with at least 3 cm distance to the detector. Measurements with the internal light source showed a detected absorption signal one order of magnitude larger compared with the dermal illumination. The absorption of H_2O vapour was not always

⁷ The system used in this study was developed by GPX Medical, two diode lasers emitting light with wavelengths centred at 763.8 nm and 820.0 nm were time multiplexed and scanned, at a frequency of 1 KHz over the O_2 and H_2O vapour absorption bands. In this system, the light from the two lasers was superimposed using a dichroic mirror, and then coupled into a 400 μm diameter optical fiber. The illumination tip was customized to deliver diffuse light in the transmittance and remittance configurations.

detected when using the dermal source, and since the evaluation of O_2 concentration depends on getting absorption signal of both gases (see Fig. 1.12), the estimation of oxygen content was not possible for all the piglets. On the other hand, signal from both gases was always detected with the internal illumination, and the authors highlighted the agreement between the evaluated O_2 concentrations and the fractional inspired O_2 concentration, which suggested that GASMAS could be sensitive enough to detect inspiration and expiration changes to each breath.

These results could be improved upon detailed answer to the following questions:

- What portion of the delivered light interacts with lung tissue?
- What is the gain in signal quality by placing the source in the trachea or naso-gastric feeding tube?
- Is it possible to optimize the source and detector configuration to get a high amount of light reaching the detector which also includes the gas absorption imprint?

The simulation of light propagation in the thorax is key to understand the factors that influence the quality of gas absorption signal, and contribute in answering these questions.

Modelling of light transport can be done analytically, but only for simple and dominantly homogeneous geometries. Therefore, NIRFAST software is an ideal tool to model the light propagation in the thorax of a neonate by means of the numerical methods, in geometries relevant to the clinical translation of GASMAS into respiratory health care.

Liao et al. did computational studies, aiming to better understand the light transport in the complicated geometry of the human thorax, and how the positioning of the probes could affect the measurement of O_2 concentration. The authors built a 3D mesh by segmentation of CT images, and placed landmarks representing different source-detector configurations over the skin resembling remittance geometry. Then, they modelled the light propagation at 760 nm using the diffusion approximation, and solving the light fluence rate (Φ) for each node of the mesh. The Φ values were then used to compute the *PHD* for 187 source-detector pairs mapping the thorax, and to estimate the fractional signal yielded by the gas absorption in the lung. The authors showed that there is a trade-off between the light transmission from source to detector and the magnitude of gas absorption. Due to the fact that more light is detected if the source and detector are close, while the fraction of light having passed through the lung is larger with the detector further from the light injection point. Finally, the authors concluded that to get the most reliable signal, source and detector should be placed in the front and side of the lung.

To further investigate the effects of placing an internal source and complement the studies reported above, two computational models with two sets of anonymized CT scans, described in Paper VI, Paper VII and Paper VIII were created, following the process described in section 4.5.⁸ The Fig. 4.5 shows the segmentation of one of the CT scan slices and the respective mesh, which was used in the work related to this thesis.⁹

Paper VI corresponds to the proceeding of an oral presentation in the Biomedical optics congress 2018. A set of five detectors was placed over the mid and upper lobes of the right lung, to analyse the differences

⁸ The data from the 3D mesh of the thorax of a neonate are openly available at the public repository doi.org/10.5281/zenodo.4916862.

⁹ This segmentation and meshing process was used to acquire the geometry of the thoracic organs for the elaboration of the anthropomorphic phantoms of chapter 3.

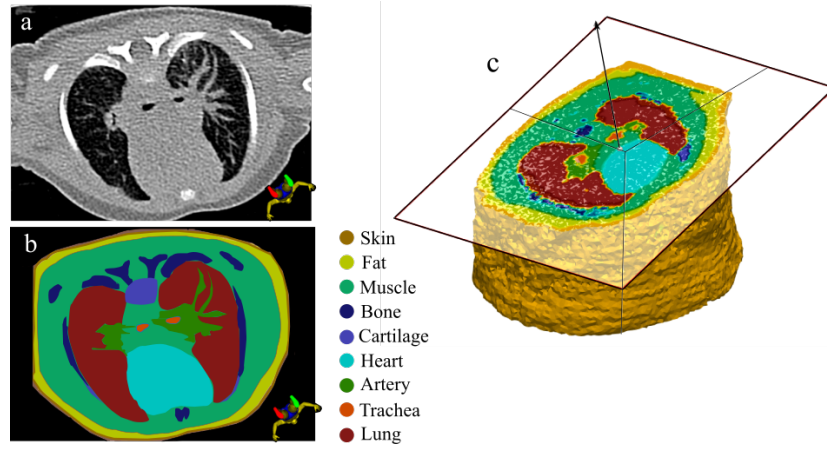


Figure 4.5. Original CT slice of neonatal thorax (a), segmentation of the different tissue types (b), and 3D mesh of the thorax, sliced for visualization of all internal regions.

in the detected signal with internal illumination from the trachea and a dermal source placed over the right middle lung lobe as shown in Fig. 4.6.



Figure 4.6. Coronal slice and volume render from CT scan of the thorax of a 3.7 kg infant. The corresponding mesh was used to study the two source-detector configurations in Paper VI, one delivering light inside the trachea, and another one delivering light from a dermal source, the set of detectors was the same in both cases.

The Matlab interface of NIRFAST was used to assign optical properties at 760 nm to lung, heart, bone, muscle, fat and skin, in this case, μ_a and μ'_s of lung tissue were set the same for trachea (see **Table 1** in Paper VII)¹⁰. Then, the forward model was solved for the two different geometries, and the detected intensities for each detector was plot in Fig. 4.7. The simulation showed that when the light is delivered internally, the detected signal would be stronger, which was expected as light is less scattered and absorbed by tissue surrounding the lungs. One advantage of this configuration is that light is “forced” to diffuse through lung tissue, before reaching the detector increasing the probabilities to carry a gas absorption imprint.

In these simulations, the presence of gas inside lung tissue was neglected. Consequently, to have an idea of the change in signal that could arise from the interaction of light with the gas, the absorption of lung tissue was increased by 10^{-4} cm^{-1} and the forward model was solved

¹⁰ The reader can refer to section 3.2 for information about the approach used to assign μ_a and μ'_s to each organ.

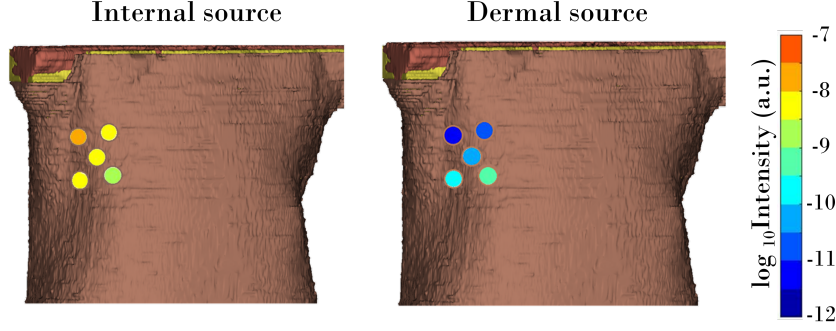


Figure 4.7. Plot of the intensity values of light reaching each detector, when the light source is placed inside the trachea (left) and over the skin close to the right middle lung lobe (right).

for the internal illumination again. Fig. 4.8 shows the ratio between the intensity values in each detector before (I) and after (I') increasing μ_a in lung tissue. The detector with the lowest detected intensity for the internal source in Fig. 4.7 presents the higher I/I' ratio. This means that higher gas absorption imprints will be detected for geometries where light have a longer path length, confirming the trade off between gas absorption imprint and detected intensity stated in [98]. The longer (deeper) the interaction of light with tissue, the higher number of scattering and absorption events will be experienced by photons. A high scattering increases, the gas absorption imprint in the detected photons. The light attenuation in GASMAS, with the technology available today, is very high and the source and detector needs to be placed strategically on the thorax to prevent the total absorption of photons which will result in null signal.

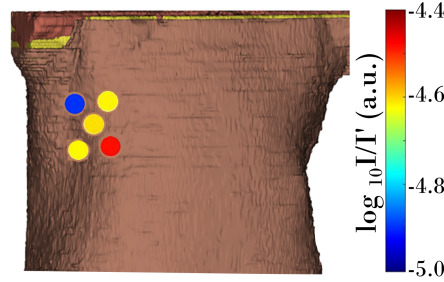


Figure 4.8. Ratio of detected intensity before (I) and after (I') increasing $\mu'_a = \mu_a + 10^{-4} \text{ cm}^{-1}$ in lung tissue.

Changes in fluence rate for different positions in the lung were studied, placing the source inside the trachea and a set of 4 detectors between the lung-muscle boundary for the same sagittal plane (Fig. 2 Paper VI). The forward model was solved showing that the fluence rate (Φ) diminish as the source-detector distance increase. In the clinical scenario, the O_2 concentration in a healthy lung might remain constant, thus, GASMAS signals for different source-detector configurations would give different values for gas absorption path length (which is calculated from the H_2O absorption, as explained in section 1.4) but the estimated O_2 concentration for each, should be similar. Which leads to the question: Do changes in path length correlate with the inflated pulmonary volume?

¹¹ The simulations of Paper VI were limited to 10 source-detector configurations, 5 in transmittance and 5 in remittance geometry. In Paper VII a mesh of detectors surrounding the thorax was preferred, to include all possible positions for which a strong enough signal could be detected.

The work presented as an oral presentation in Photonics Asia 2019 (Paper VII), aimed to answer the previous question. A mesh with the same geometry of Paper VI was used in this study, with different source-detector configurations.¹¹ In this case, the cartilage and pulmonary arteries were included in the segmentation, and a set of 68 landmarks (see Fig 2 Paper VII) were placed as detectors around the thorax to map the changes in intensity for different locations with internal illumination from the trachea and dermal illumination with a source under the armpit. In order to study if different inflated lung volumes will generate relevant changes in the detected signal, two lung models were implemented. One recreated “inhalation” in which lung μ_a and μ'_s were assigned to the complete segmented volume from the CT scan, whereas for the “exhalation” model, the lung was sub-segmented in two parts, the inner part maintained pulmonary μ_a and μ'_s and muscle optical properties were given to the external edge of the lung sub-segment.

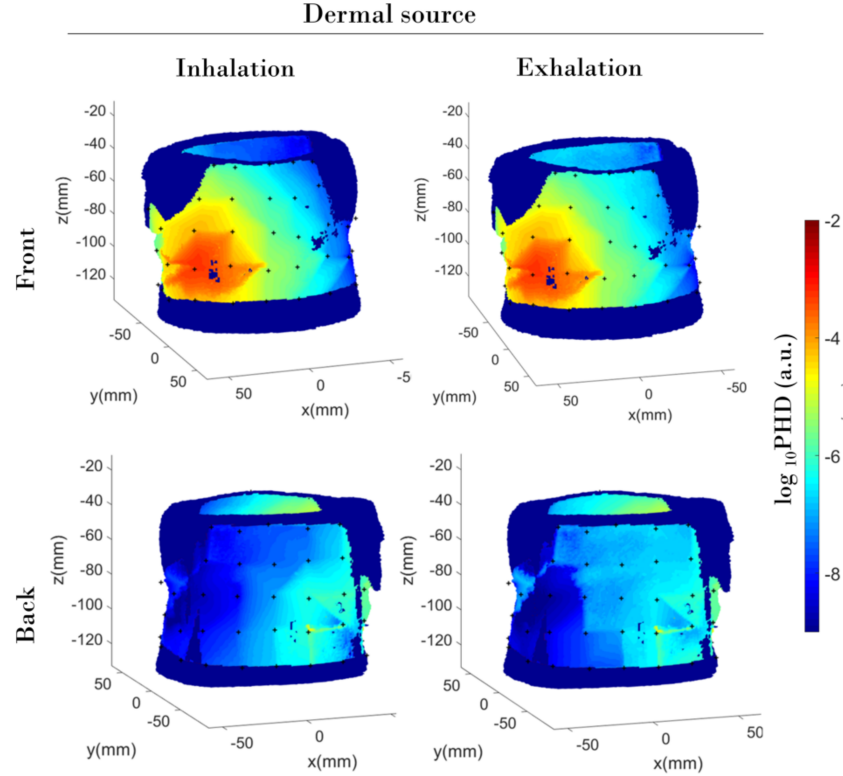


Figure 4.9. Logarithmic plots of the interpolated PHD values in the front (first row) and back (second row) of the thorax, for inhalation (first column) and exhalation models in remittance geometry.

The light intensity reaching each detector is proportional to the PHD, which can be calculated by solving Φ_s for all nodes in the mesh (x, y, z) with the light injection point in the source (s), followed by the calculation of the Φ_d assuming that the light injection point is now located in the position of the detector (d), and then multiplying both values [98]:

$$PHD_{s,d}(x, y, z) = \Phi_s(x, y, z) \cdot \Phi_d(x, y, z). \quad (4.24)$$

The PHD was calculated for the tracheal and dermal sources and the two pulmonary volumes. Fig. 4.9 and Fig. 4.10 show the interpolated

values of the PHD for the full detector set, for dermal and internal illumination, respectively. The PHD for the dermal source in Fig. 4.9 does not exhibit relevant changes between “inhalation” and “exhalation”. This might be due to the fact that light is attenuated by organs surrounding the lung, reducing the amount of photons interacting with lung tissue before reaching the detectors. On the contrary, Fig. 4.10 shows that when light interacts with a fully inflated lung (“inhalation”), the PHD is lower compared to the case of a reduced inflated volume (“exhalation”).

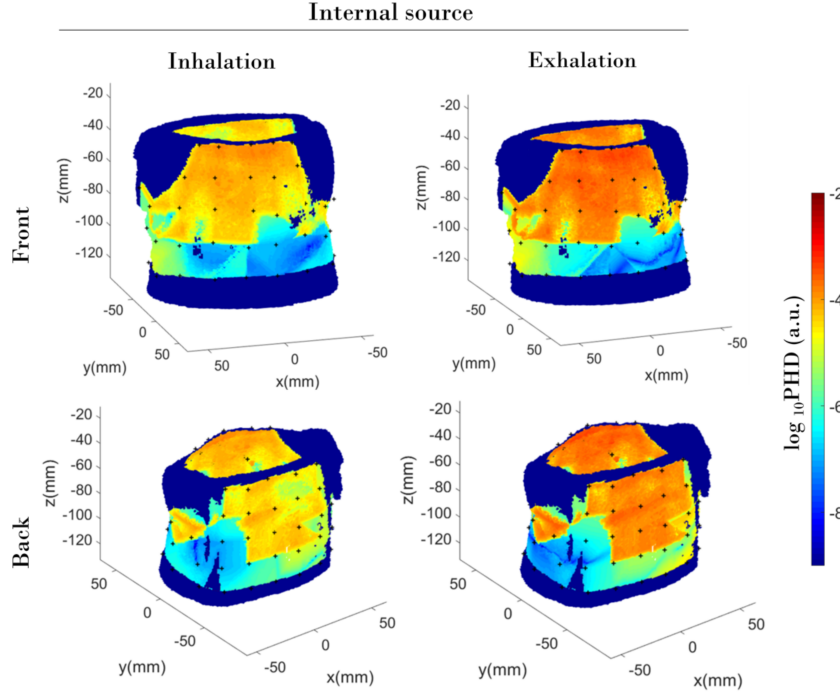


Figure 4.10. Logarithmic plots of the interpolated PHD values in the front (first row) and back (second row) of the thorax, for inhalation (first column) and exhalation models in transmittance geometry.

The changes in signal for both inflated volumes suggest that GASMAS could potentially be used to quantify inflated pulmonary volumes when the source is placed in the trachea, which in turn could be correlated with the alveolar composition of lung tissue. However, these studies lacked of an estimation of the amount of the detected signal that accounted for interaction with the lung.

The findings from Paper **VI** and Paper **VII** are part of an integral study which was concluded with the recently published Paper **VIII**. In this article, the lung was sub segmented in three different volumes, inspiratory reserve volume (IRV= 206 ml), inspiratory lung volume (IV= 195 ml) and residual lung volume (RV= 137 ml). The forward model was solved for two computational thoraxes with optical properties at 760 nm and 820 nm, for dermal illumination with the source placed under the armpit, and internal illumination with an intratracheal source. As part of the analysis, the concept of *GASMAS sensitivity* (σ) was included. It corresponds to the ratio between the sum of all PHD for nodal points allocated within the lung and the sum of all PHD for all the nodal points in the mesh.

$$\sigma = \frac{\sum_{lung} \Phi_s(x, y, z) \cdot \Phi_d(x, y, z)}{\sum_{mesh} \Phi_s(x, y, z) \cdot \Phi_d(x, y, z)}. \quad (4.25)$$

This quantity leads to the evaluation of source-detector configurations which are more likely to output a gas absorption signal. The discussion includes argumentation to explain why the light at 820 nm is less likely to reach lung tissue in remittance geometry, which is consistent with the measurements made by Svanberg et al. in mechanically ventilated piglets [77], and the results from the phantom studies of Paper **V**. It also shows evidence of the potential of GASMAS technique to monitor changes in pulmonary volumes during respiration. And shows that the placement of an intratracheal source is linked to less light attenuation before reaching the detectors, and could improve the lung function assessment as it distributes evenly in both lungs.

PERSPECTIVES

GASMAS is a promising tool for continuous monitoring and diagnostics of lung function in neonates. The NIOMI study has been a great starting point to collect significant data with infants. Most likely, the outcome of this study will define the next step in enhancing the clinical prototype. Robust probes are needed,¹ the power of the laser diodes and the data processing have place for further optimization, as well as the source-detector configurations. However, there is no doubt that the strong collaborative work between clinical, academy and industry parties will hasten the process to reach the clinical applicability.

One of the main outcomes from the phantom and computational studies of this thesis, was to probe the feasibility of detecting gas volume changes with the GASMAS technique, stating a new possible application for GASMAS respiratory treatment and diagnostics. The data analysis from the NIOMI study might help to determine the best source detector configurations to get gas absorption signals in infants. New clinical protocols can be implemented, for those source-detector geometries, to make continuous measurements, and track the changes in path length linked to lung inflated volumes during respiration.

The developed tools for the simulation of light propagation in the thorax can be further exploited to evaluate the changes in signal associated with the movement of the endotracheal source, and evaluation of source placement into the oesophagus.² Furthermore, the forward model could be solved for each of the 68 dermal land marks in the computational model, to define the regions over the thorax for which, there is a high photon hitting density and sensitivity, valuable parameters to decide the probe locations to use in further clinical trials. As 935 nm is one of the wavelengths which could potentially be used to match absorption of H_2O vapour, the implementation of optical properties for the organs at this wavelength could also be done and compared with the results discussed in this thesis.³

The phantom studies are becoming critical in advancing the GASMAS technique. The next generation should include physiological parameters, other than just accurate organ geometry and optical properties of biological tissue. The implementation of physiological parameters such as temperature, pressure, and a soft thoracic structure which allows for air volume changes in the lung, would be ideal to narrow the gap between the real clinical scenario and bench top studies.

The Fig. 5.1 summarizes the main factors for which a clinical GASMAS device would be favourable in respiratory surveillance of neonates.

¹ When half of the target population was recruited (50 infants) for NIOMI study, the light source detached from the optical fibre twice.

² This will be also associated with the development of a miniature diffuse source to be placed inside the ET or naso-gastric tubes.

³ Out of the scope of this clinical application of GASMAS. The computational model of the thorax, plotting and data analysis functions used in these simulations, are available in open repositories. Researchers working in diffuse optical tomography or different studies for similar anatomical geometries can benefit of it. In this way we are saving to the community, the burden of long segmentation/mesh creation hours, and also give place to the creation of improved algorithms based on our scripts.

GASMAS could potentially be used during O_2 and surfactant administration, and give objective feedback about the neonate's response to the treatment. It should be used together with the existent imaging tools, to provide exhaustive information which could aid to clinical decision making.

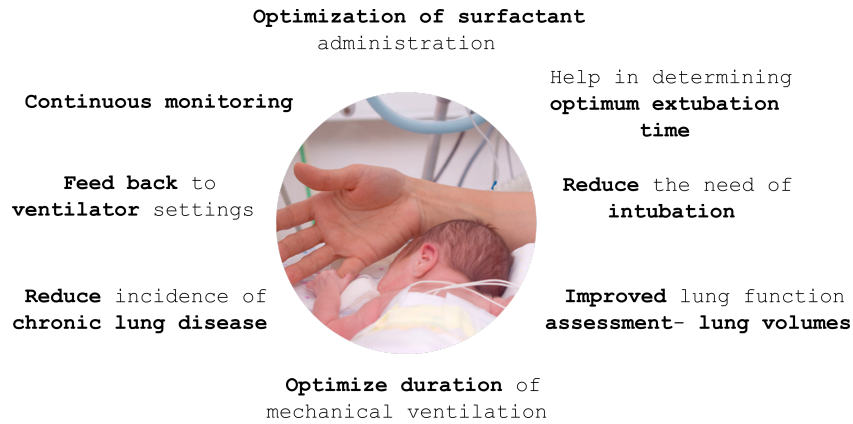


Figure 5.1. Benefits of the clinical translation of GASMAS into respiratory health care of neonates. Picture taken with the permission of Tommys org.

Recently, a group of researchers performed phantom studies with a 2 kg chicken broiler filled with 6 cm of house hold sponges, and a piece of polystyrene foam surrounded by pork slabs [99]. With the aim to see the effect of absorption in time-resolved recordings done with both samples, using a high energy pulsed laser and a detector in transmittance geometry.⁴ Even though, the authors did not find a clear differential absorption effect, nor a significant broadening of the temporal curve, they propose the use of laser diode pumped solid state amplifiers to boost the laser output of the current GASMAS prototypes, and explore its applicability in large children or adult patients.

The use of sponge material or polystyrene to mimic the pulmonary tissue has the advantage of introducing light scattering, which is much more realistic compared to the phantoms with hollowed cavities. However, the lung structure is much more dense and flexible than sponge or polystyrene materials, letting room for improvement in this aspect. On the other hand, the chicken and pork slabs do not match the optical properties of human tissue, therefore the use of a generic tissue phantom would be more accurate. The authors used TOFS to estimate the light absorption path length, as mention in Section 1, this approach does not allow to differentiate the path of light in the gas from its trajectory in the bulk material, thus, it is not possible to make an absolute estimation of air volume or oxygen concentration, rather a relative inter-patient assessment which could complicate the integration of GASMAS with the ventilator systems to give a back-end feedback during therapies. However, this last issue could be resolved by training the system with data from different geometries of bulk material and gas cavities.

The ability of monitoring continuous changes in pulmonary air volume and oxygenation, would improve the medical treatment of patients with respiratory failure, ranging from pre-term newborn and adults. Another possible solution would be the use of the emerging photonics integrated circuits, which allow for miniaturization of laser based devices. A miniature GASMAS probe, could be combined with the existing pulmonary endoscopes and enable GASMAS measurements

⁴ High laser intensity in repetitive pulses would allow the signal photons to be better distinguished from the background noise.

in adults. Adult patients may suffer from respiratory issues, such as, pneumonia, chronic obstructive pulmonary disease, lung fibrosis, etc. Thus, a GASMAS system could measure changes in air volume and O_2 concentration and so be used for prompt detection and monitoring of treatment/disease progression in grown up patients.

COMMENTS ON THE PAPERS

I Translation of Gas Spectroscopy into the Clinic, a Promising Tool for Non-Invasive Diagnostics in Respiratory Health Care of Neonates

This perspective article highlights the potential advantages of translating GASMAS into clinical devices for early detection of Respiratory Distress Syndrome (RDS) and the assessment of respiratory health in neonates.

I wrote the manuscript. *E. Dempsey* and *S. Andersson-Engels* were involved in the discussion, conceptualization and edition of the manuscript.

II Solid phantom recipe for diffuse optics in biophotonics applications: a step towards anatomically correct 3D tissue phantoms

The article presents a detailed recipe to produce long lasting, silicone phantoms to mimic the optical properties of human tissue in the span of absorption $0.1 < \mu_a < 1\text{cm}^{-1}$ and reduced scattering $5 < \mu'_s < 25\text{cm}^{-1}$. This publication is relevant given that in contrast to most of the phantom recipes available in literature, we provided a protocol which can be used to produced phantoms with an extensive choice to tune absorption and scattering of most of organs of interest for biomedical applications, and in a wide spectral range within the first tissue optical window 600 – 1100 nm.

I proposed to work in the fabrication of long lasting tissue phantoms, led and participate in the literature review, protocol preparation, production of the phantom matrix and contributed to the data analysis and manuscript preparation.

S. Konugolu participated in characterization of optical properties and data analysis, and wrote the manuscript.

P. Martella contributed in the preparation of the phantom matrix.

H. Li contributed in the protocol and phantom preparation.

P. Lanka contributed in characterization of optical properties and data analysis, and

A. Pifferi and *S. Andersson-Engels* were involved in supervision and project management.

This publication was one of the top 20 downloaded articles on tissue optics and spectroscopy from Biomedical Optics Express during 2017-2019. And was awarded third place in the “Tyndall postgraduate best publication of the year 2019”.

III Anthropomorphic optical phantom of the neonatal thorax: a key tool for pulmonary studies in preterm infants

The article presents the protocol to produce a multi-structure anthropomorphic optical phantom of the thorax of a neonate, which contains an empty pulmonary cavity to enable GASMAS studies. The protocol developed to build this phantom can be used together with the silicon phantom recipe of Paper **II**, to reproduce the geometry and optical properties of any human or animal tissue in the cm scale.

The planning of this work was discussed with all co-authors, to solve the need of a robust solid phantom to perform GASMAS measurements over months, resembling the clinical scenario.

I led and participated in the CT segmentation to extract the organ structures, mould elaboration and phantom assembling. I also wrote the manuscript.

H. Li smoothed the .stl files of organ models, 3D printed the resin structures and participated in protocol standardization.

M. Chakravarty participated in CT segmentation, phantom moulding and assembling, and

S. Konugolu and *S. Andersson-Engels* were involved in supervision and project management.

S. Konugolu and *S. Andersson-Engels* started a company called BioPixS, which mission is to create standards in the field of Biophotonics through innovative phantoms that mimic tissue optical properties and geometry. I am one of the co-inventors of the UCC trade secret (ID: 20-010) with which the company was created.

IV Lung tissue phantom mimicking pulmonary optical properties, relative humidity, and temperature: a tool to analyze the changes in oxygen gas absorption for different inflated volumes

The article presents the elaboration of a lung phantom which recreates the tissue in the respiratory zone of the lung (alveolar sacks filled of air, surrounded by absorbing and scattering material). The phantom was then used to demonstrate the feasibility of measuring volume changes with a GASMAS device.

The planning of this work was discussed with all co-authors.

I participated in the phantom elaboration, performed experimental measurements and data analysis, and led the manuscript writing.

Konstantin Grygoryev designed and built the controlled environment chamber, designed figures and wrote part of the manuscript.

Walter Messina designed and 3D printed the capillary holder, designed figures and wrote part of the manuscript, and

S. Andersson-Engels edited the manuscript and was involved with supervision and project management.

This publication had awakened the enthusiasm of the optics and photonics community about the viabilities and potential applications of gas spectroscopy into respiratory health care, catching the attention of researchers around the world about the technologies we are advancing in Cork. This is evidenced in the fact that our article was flagged for promotion upon publication by the SPIE Senior Editor Renae Keep, who wrote ‘Lung model proves viability of spectroscopy technique’. It was also featured in OPTICSPHOTONICS NEWS magazine by Karen Kwon with ‘Spectroscopy Could Improve Lung-Health Measurement’; and in the Analytical Scientist with ‘The Phantom Lung’ written by Lauren Robertson.

This article was selected for the “Tyndall postgraduate best publication of the year” 2021 award.

V Laser absorption spectroscopy measurements of different pulmonary oxygen concentrations in transmittance and remittance geometry – phantom study

In this article we present the results from GASMAS bench top measurements, conducted in a set of two phantom pairs with different anatomic geometries recovered from CT thoracic scans of neonates weighing 3.7 kg and 3.6 kg. All the phantoms had a pulmonary cavity which was flushed with humid gas with 21%, 30%, 50% and 100% oxygen concentration, and gas absorption signals were acquired for 30 different source-detector configurations resembling transmittance (using a tracheal source) and remittance geometries.

I was involved in the conceptualization, investigation and bench top measurements. I led the discussions with the co-authors and wrote the manuscript.

Jean Matias was involved in conceptualization and data analysis.

Konstantin Grygoryev and *Martin Hansson* were involved in building the experimental set up, and

Stefan Andersson-Engels was involved in writing-review and editing, supervision and project management.

VI Near Infrared Light Propagation Modeling of Infant Lung with Light Source Placed Inside Intubated Airway

In this conference we presented a simulation of the changes in detected intensity for different source-detector configurations in transmittance geometries. All authors contributed to the planning of this study.

I performed the simulations, made the slides for the oral presentation and wrote the manuscript.

E. Krite Svanberg and *E. Dempsey* were involved in conceptualization, and

S. Andersson-Engels was involved in manuscript-review and editing, supervision and project management.

VII Simulation of near-infrared light propagation through the thorax of a neonate: addressing the optimisation of source and detector positions for measuring lung oxygen content in preterm infants

In this conference, we presented the simulation of changes in photon hitting density produced by two different lung volumes during respiration with an intra-tracheal source and detectors placed over the torso in transmittance geometry, and with a dermal source over the mid-lung lobe in remittance geometry.

I took part in preparatory discussions with the co-authors, executed the simulations in NIRFAST and data analysis, prepared the slides for the oral presentation and wrote the manuscript.

E. Krite Svanberg and *E. Dempsey* were involved in conceptualization, and

S. Andersson-Engels was involved in writing-review and editing, supervision and project management.

VIII Numerical investigation of the influence of the source and detector position for optical measurement of lung volume and oxygen content in preterm infants

In this article we present the anthropomorphic computational model of the thorax of a neonate with nine main organs. It is used to model the light transport for two main source-detectors configurations, while mimicking 3 main respiratory lung volumes. The photon hitting density and sensitivity maps obtain for each configuration, suggest that GASMAS can be used to assess continuously pulmonary volumes, and highlights the benefits of placing an internal light source.

I was involved in the conceptualization, investigation, CT segmentation and mesh creation, led the discussions with the co-authors and wrote the manuscript.

Baptiste Jayet was involved in conceptualization, investigation and data visualization (plots).

Emilie Krite Svanberg, *Hamid Dehghani*, *Eugene Dempsey* and *Stefan Andersson-Engels* were involved in conceptualization, reviewing and edition of the manuscript, and

S. Andersson-Engels was involved in writing-review and editing, supervision and project management.

IX Gas in scattering media absorption spectroscopy as a potential tool in neonatal respiratory care

In this article we present GASMAS as a novel optical technique to measure oxygen concentrations in the lung, summarize the current light-based technique for lung function assessment; and highlight the potential clinical use of GASMAS in paediatric care.

I was involved in the conceptualization, and literature review. I wrote the supplementary material and design the respective graphics.

Jurate Panavienė lead the discussions among authors and wrote most of the paper.

Konstantin Grygoryev was involved in conceptualization, investigation and graphics.

Christoph E. Schwarz, *Stefan Andersson-Engels* and *Eugene Dempsey* were involved in conceptualization, reviewing and edition of the manuscript, and

Eugene Dempsey was involved in writing-review and editing, supervision and project management.

ACKNOWLEDGEMENTS

It would clearly not have been possible to perform this work without cooperation, and I would therefore like to thank a number of people.

First, I would like to thank my supervisors Stefan Andersson-Engels and Eugene Dempsy for the insightful discussions and guidance.

There are also a number of actual or former group members who have all my gratitude. **Big thanks** to: *Haiyang*, for the motivation at the beginning of my PhD, for being an inspiration, always pursuing excellence and enjoying the process; *Kasia*, for all the presentation and writing tips, there is not doubt that your guidance and advice was behind all the poster competition prizes; *Jacque*, for having the patience to read all my manuscripts and help me to communicate in a foreign language; *Baptist*, for the fruitful discussions and all the effort put into making very pretty plots; *Jean* (my Python master), for your support in defeating my coding fears and teaching me the cool stuff to manage large data files; *Kon*, for always giving a good advice and having a solution to my technical issues; *Walter*, for making possible and improving the models I had in my head, and for the good laugh in long working days; *Hui Hui*, for making of the lab space an organized place to work, best lab manager ever!; *Simon*, for your support in the activities of the student chapter and the yummy birthday cakes (here I feel in conflict as Baptist, Kasia and Jacque are also excellent bakers!); *Piero*, *Monisha*, *Jane* and *Laura*, it was a big pleasure to work with you during your internships at Tyndall, I hope you have learnt with me as much as I learnt with all of you, your scientific skills and hard work nature will take you far; *Patrick Lundin* for introducing me to the bench top GASMAS prototype and for being always willing to answer my doubts; *Jim* and *Denis* for your assistance and support during the phantom measurements in Lund.

Deepest thanks to the members of the *Tyndall UCC student chapter*, it was an honour to fund such an active association conformed of brilliant minds, I wish you success in every project ahead. *Alessandra* and *Kevin* the journey of the organization of IONS Ireland conference would not be the same without you, what a great team!

Luiza, it has been a blessing to share with you the Famelab journey all the way to the Irish final, not just because I defeated my fear of talking in public, but for what I am sure will be a life-long friendship. *Ursula*, *Alida* and *Sinead*, thanks for the support throughout all the STEM activities in the past years, your spirit in sharing science is contagious!

I also want to express my appreciation to the IPIC centre, the Physics Department at University College Cork, the INFANT center, GASPOROX and GPX Medical for an outstanding collaboration throughout the last years. I know that this is just the beginning of many

studies which will bring GASMAS to the clinic.

Throughout this experience I have met excellent professionals pursuing to advance optics and photonics in a wide range of applications, Tyndall is a center with a great social environment which I highly appreciated, many of the ideas developed in this thesis were born during a coffee break or lunch with researchers from different backgrounds. Thanks to everyone who was up for a cup of coffee, for sharing the good moments in and outside Tyndall and for the good craic!

A group of people (while I don't know who they are) deserve special thanks. These are all the referees of our published papers. This job is essential!, thank you so much for the thorough revision of the work this thesis is based on, your questions, comments and suggestions made possible the best version of each paper.

And last, but not least, I want to thank my family and friends for always believing in me (even if I had doubts from time to time). *Marco* your support in finishing this thesis means so much to me, thanks for encouraging me to always run the extra mile.

REFERENCES

- [1] C. Boudoux, *Fundamentals of Biomedical Optics* (2016).
- [2] A. Beiser, *Concepts of modern physics* (McGraw-Hill, Boston, 2003), 6th ed ed.
- [3] M. Mutsaers, *Zika vector control: Near infrared spectroscopy predicting Wolbachia infection in post-mortem Aedes aegypti*, Ph.D. thesis (2018).
- [4] K. J. I. Ember, M. A. Hoeve, S. L. McAughtrie, M. S. Bergholt, B. J. Dwyer, M. M. Stevens, K. Faulds, S. J. Forbes, and C. J. Campbell, “Raman spectroscopy and regenerative medicine: a review,” *npj Regenerative Medicine* 2, 12 (2017).
URL <http://www.nature.com/articles/s41536-017-0014-3>
- [5] R. K. Hanson, R. M. Spearrin, and C. S. Goldenstein, *Spectroscopy and Optical Diagnostics for Gases* (Springer International Publishing, Cham, 2016).
URL <http://link.springer.com/10.1007/978-3-319-23252-2>
- [6] C. S. Goldenstein, V. A. Miller, R. Mitchell Spearrin, and C. L. Strand, “SpectraPlot.com: Integrated spectroscopic modeling of atomic and molecular gases,” *Journal of Quantitative Spectroscopy and Radiative Transfer* 200, 249–257 (2017).
URL <https://linkinghub.elsevier.com/retrieve/pii/S0022407317302996>
- [7] L. Mei, *Light propagation and gas absorption studies in turbid media using tunable diode laser techniques* (2014), oCLC: 1064989331.
- [8] H. Q. Woodard and D. R. White, “The composition of body tissues.” *The British journal of radiology* 59, 1209–1218 (1986).
- [9] L. Marcu, S. A. Boppart, M. R. Hutchinson, J. Popp, and B. C. Wilson, “Biophotonics: the big picture,” *Journal of Biomedical Optics* 23, 1 (2017).
URL <https://www.spiedigitallibrary.org/journals/journal-of-biomedical-optics/volume-23/issue-02/021103/Biophotonics-the-big-picture/10.1117/1.JBO.23.2.021103.full>
- [10] A. Douplik, G. Saiko, I. Schelkanova, and V. Tuchin, “The response of tissue to laser light,” in “Lasers for Medical Applications,” pp. 47–109 (Elsevier, 2013).
URL <https://linkinghub.elsevier.com/retrieve/pii/B9780857092373500035>
- [11] G. C. Salzman, “Light Scattering Analysis of Single Cells,” in “Cell Analysis: Volume 1,” (N. Catsimpooolas, ed.), pp. 111–143 (Springer US, Boston, MA, 1982).
URL https://doi.org/10.1007/978-1-4684-4097-3_5

- [12] G. Keiser, "Light-Tissue Interactions," in "Biophotonics," pp. 147–196 (Springer Singapore, Singapore, 2016).
URL http://link.springer.com/10.1007/978-981-10-0945-7_6
- [13] N. Ramanujam, C. Pitris, and D. A. Boas, "Handbook of Biomedical Optics," *BIOMEDICAL OPTICS* p. 817.
- [14] S. L. Jacques, "Optical properties of biological tissues: a review," *Physics in Medicine and Biology* 58, R37–R61 (2013).
URL <https://iopscience.iop.org/article/10.1088/0031-9155/58/11/R37>
- [15] M. Sjöholm, G. Somesfalean, J. Alnis, S. Andersson-Engels, and S. Svanberg, "Analysis of gas dispersed in scattering media," *Optics Letters* 26, 16 (2001).
URL <https://www.osapublishing.org/abstract.cfm?URI=ol-26-1-16>
- [16] W. Li, H. Lin, H. Zhang, K. Svanberg, and S. Svanberg, "Detection of free oxygen and water vapor in fertilized and unfertilized eggs by diode laser spectroscopy-Exploration of diagnostics possibilities," *Journal of Biophotonics* 11, e201700154 (2018).
URL <https://onlinelibrary.wiley.com/doi/10.1002/jbio.201700154>
- [17] J. Huang, H. Zhang, H. Lin, T. Li, L. Mei, K. Svanberg, and S. Svanberg, "Gas exchange in fruits related to skin condition and fruit ripening studied with diode laser spectroscopy," *Journal of Biomedical Optics* 21, 127007 (2016).
URL <http://biomedicaloptics.spiedigitallibrary.org/article.aspx?doi=10.1117/1.JBO.21.12.127007>
- [18] P. Lundin, L. Cocola, M. Lewander, A. Olsson, and S. Svanberg, "Non-intrusive headspace gas measurements by laser spectroscopy – Performance validation by a reference sensor," *Journal of Food Engineering* 111, 612–617 (2012).
URL <https://linkinghub.elsevier.com/retrieve/pii/S0260877412001409>
- [19] T. Svensson, L. Persson, M. Andersson, S. Svanberg, S. Andersson-Engels, J. Johansson, and S. Folestad, "Noninvasive Characterization of Pharmaceutical Solids by Diode Laser Oxygen Spectroscopy," *Applied Spectroscopy* 61, 784–786 (2007).
- [20] T. Svensson, E. Alerstam, J. Johansson, and S. Andersson-Engels, "Optical porosimetry and investigations of the porosity experienced by light interacting with porous media," *Optics Letters* 35, 1740 (2010).
URL <https://www.osapublishing.org/abstract.cfm?URI=ol-35-11-1740>
- [21] J. Alnis, B. Anderson, M. Sjöholm, G. Somesfalean, and S. Svanberg, "Laser spectroscopy of free molecular oxygen dispersed in wood materials," *Applied Physics B* 77, 691–695 (2003).
- [22] L. Mei, G. Somesfalean, and S. Svanberg, "Pathlength Determination for Gas in Scattering Media Absorption Spectroscopy," *Sensors* 14, 3871–3890 (2014).
URL <http://www.mdpi.com/1424-8220/14/3/3871>

- [23] L. Hu, W. Li, H. Lin, Y. Li, H. Zhang, K. Svanberg, and S. Svanberg, "Towards an optical diagnostic system for otitis media using a combination of otoscopy and spectroscopy," *J. Biophotonics* p. 10 (2019).
- [24] J. Huang, H. Zhang, T. Li, H. Lin, K. Svanberg, and S. Svanberg, "Assessment of human sinus cavity air volume using tunable diode laser spectroscopy, with application to sinusitis diagnostics," *Journal of Biophotonics* 8, 985–992 (2015).
URL <http://doi.wiley.com/10.1002/jbio.201500110>
- [25] E. K. Svanberg, P. Lundin, M. Larsson, J. Åkeson, K. Svanberg, S. Svanberg, S. Andersson-Engels, and V. Fellman, "Diode laser spectroscopy for noninvasive monitoring of oxygen in the lungs of newborn infants," *Pediatric Research* 79, 621–628 (2016).
URL <http://www.nature.com/articles/pr2015267>
- [26] P. Lundin, E. K. Svanberg, L. Cocola, M. L. Xu, G. Somesfalean, S. Andersson-Engels, J. Jahr, V. Fellman, K. Svanberg, and S. Svanberg, "Noninvasive monitoring of gas in the lungs and intestines of newborn infants using diode lasers: feasibility study," *Journal of Biomedical Optics* 18, 127005 (2013).
URL <http://biomedicaloptics.spiedigitallibrary.org/article.aspx?doi=10.1117/1.JBO.18.12.127005>
- [27] D. Chen, W. Li, W. He, H. Zhang, Q. Zhang, H. Lin, S. Svanberg, K. Svanberg, and P. Chen, "Laser-based gas absorption spectroscopy in decaying hip bone: water vapor as a predictor of osteonecrosis," *Journal of Biomedical Optics* 24, 1 (2019).
URL <https://www.spiedigitallibrary.org/journals/journal-of-biomedical-optics/volume-24/issue-06/065001/Laser-based-gas-absorption-spectroscopy-in-decaying-hip-bone/10.1117/1.JBO.24.6.065001.full>
- [28] I. Gordon, L. Rothman, C. Hill, R. Kochanov, Y. Tan, P. Bernath, M. Birk, V. Boudon, A. Campargue, K. Chance, B. Drouin, J.-M. Flaud, R. Gamache, J. Hodges, D. Jacquemart, V. Perevalov, A. Perrin, K. Shine, M.-A. Smith, J. Tennyson, G. Toon, H. Tran, V. Tyuterev, A. Barbe, A. Császár, V. Devi, T. Furtenbacher, J. Harrison, J.-M. Hartmann, A. Jolly, T. Johnson, T. Karman, I. Kleiner, A. Kyuberis, J. Loos, O. Lyulin, S. Massie, S. Mikhailenko, N. Moazzen-Ahmadi, H. Müller, O. Naumenko, A. Nikitin, O. Polyansky, M. Rey, M. Rotger, S. Sharpe, K. Sung, E. Starikova, S. Tashkun, J. V. Auwera, G. Wagner, J. Wilzewski, P. Wcisło, S. Yu, and E. Zak, "The HITRAN2016 molecular spectroscopic database," *Journal of Quantitative Spectroscopy and Radiative Transfer* 203, 3–69 (2017).
URL <https://linkinghub.elsevier.com/retrieve/pii/S0022407317301073>
- [29] A. L. Buck, "New Equations for Computing Vapor Pressure and Enhancement Factor," *Journal of Applied Meteorology* 20, 1527–1532 (1981).
URL [/brokenurl#10.1175/1520-0450\(1981\)020<1527:NEFCVP>2.0.CO;2](https://doi.org/10.1175/1520-0450(1981)020<1527:NEFCVP>2.0.CO;2)
- [30] G. Somesfalean, M. Sjöholm, J. Alnis, C. a. Klinteberg, S. Andersson-Engels, and S. Svanberg, "Concentration measurement of gas embedded in scattering media by employing absorption and time-resolved laser spectroscopy," *Applied Optics* 41, 3538 (2002).

- URL <https://www.osapublishing.org/abstract.cfm?URI=ao-41-18-3538>
- [31] L. Mei, H. Jayaweera, P. Lundin, S. Svanberg, and G. Somesfalean, "Gas spectroscopy and optical path-length assessment in scattering media using a frequency-modulated continuous-wave diode laser," *Optics Letters* 36, 3036 (2011).
URL <https://www.osapublishing.org/abstract.cfm?URI=ol-36-16-3036>
- [32] L. Mei, G. Somesfalean, and S. Svanberg, "Light propagation in porous ceramics: porosity and optical property studies using tunable diode laser spectroscopy," *Applied Physics A* 114, 393–400 (2014).
URL <https://doi.org/10.1007/s00339-013-8137-x>
- [33] P. Lundin, L. Mei, S. Andersson-Engels, and S. Svanberg, "Laser spectroscopic gas concentration measurements in situations with unknown optical path length enabled by absorption line shape analysis," *Applied Physics Letters* 103, 034105 (2013).
URL <http://aip.scitation.org/doi/10.1063/1.4813860>
- [34] M. Ochs, J. R. Nyengaard, A. Jung, L. Knudsen, M. Voigt, T. Wahlers, J. Richter, and H. J. G. Gundersen, "The Number of Alveoli in the Human Lung," *American Journal of Respiratory and Critical Care Medicine* 169, 120–124 (2004).
URL <http://www.atsjournals.org/doi/abs/10.1164/rccm.200308-11070C>
- [35] R. M. Schwartzstein and M. J. Parker, *Respiratory Physiology: A Clinical Approach* (Philadelphia : Lippincott Williams & Wilkins, 2006).
- [36] M. F. Lutfi, "The physiological basis and clinical significance of lung volume measurements," *Multidisciplinary Respiratory Medicine* 12, 3 (2017).
URL <http://mrmjournal.biomedcentral.com/articles/10.1186/s40248-017-0084-5>
- [37] D. Warburton, A. El-Hashash, G. Carraro, C. Tiozzo, F. Sala, O. Rogers, S. D. Langhe, P. J. Kemp, D. Riccardi, J. Torday, S. Bellusci, W. Shi, S. R. Lubkin, and E. Jesudason, "Lung Organogenesis," in "Current Topics in Developmental Biology," , vol. 90pp. 73–158 (Elsevier, 2010).
URL <https://linkinghub.elsevier.com/retrieve/pii/S0070215310900033>
- [38] P. H. Burri, "Fetal and Postnatal Development of the Lung," p. 15.
- [39] P. J. Hantzidiamantis and E. Amaro, "Physiology, Alveolar to Arterial Oxygen Gradient." (2021).
URL <https://www.ncbi.nlm.nih.gov/books/NBK545153/>
- [40] A. J. Peacock, "ABC of oxygen: Oxygen at high altitude," *BMJ* 317, 1063–1066 (1998).
URL <https://www.bmj.com/lookup/doi/10.1136/bmj.317.7165.1063>
- [41] S. B. Ainsworth, "Pathophysiology of Neonatal Respiratory Distress Syndrome: Implications for Early Treatment Strategies," *Treatments in Respiratory Medicine* 4, 423–437 (2005).
URL <http://link.springer.com/10.2165/00151829-200504060-00006>

-
- [42] L. Guglani, S. Lakshminrusimha, and R. M. Ryan, “Transient Tachypnea of the Newborn,” p. 7.
 - [43] D. De Luca, A. H. van Kaam, D. G. Tingay, S. E. Courtney, O. Danhaive, V. P. Carnielli, L. J. Zimmermann, M. C. J. Kneyber, P. Tissieres, J. Brierley, G. Conti, J. J. Pillow, and P. C. Rimensberger, “The Montreux definition of neonatal ARDS: biological and clinical background behind the description of a new entity,” *The Lancet Respiratory Medicine* 5, 657–666 (2017).
URL <https://linkinghub.elsevier.com/retrieve/pii/S221326001730214X>
 - [44] E. Fan, D. Brodie, and A. S. Slutsky, “Acute Respiratory Distress Syndrome: Advances in Diagnosis and Treatment,” *JAMA* 319, 698 (2018).
URL <https://jamanetwork.com/journals/jama/fullarticle/2673154>
 - [45] A. Greenough and A. D. Milner, (Eds.) *Neonatal respiratory disorders* (Arnold ; Distributed in the U.S.A. by Oxford University Press, London : New York, 2003), 2nd ed ed.
 - [46] D. El Mazloum, L. Moschino, S. Bozzetto, and E. Baraldi, “Chronic Lung Disease of Prematurity: Long-Term Respiratory Outcome,” *Neonatology* 105, 352–356 (2014).
URL <https://www.karger.com/Article/FullText/360651>
 - [47] J. D. Miller and W. A. Carlo, “Pulmonary Complications of Mechanical Ventilation in Neonates,” *Clinics in Perinatology* 35, 273–281 (2008).
URL <https://linkinghub.elsevier.com/retrieve/pii/S0095510807000851>
 - [48] M. K. Brown and R. M. DiBlasi, “Mechanical Ventilation of the Premature Neonate,” *Respiratory Care* 56, 1298–1313 (2011).
URL <http://rc.rcjournal.com/cgi/doi/10.4187/respcare.01429>
 - [49] F. Mojoli and A. Braschi, *Respiratory support with continuous positive airways pressure*, vol. 1 (Oxford University Press, 2016).
URL <http://oxfordmedicine.com/view/10.1093/med/9780199600830.001.0001/med-9780199600830-chapter-89>
 - [50] G. Spoletini and N. S.Hill, *Oxford textbook of critical care* (Oxford university press, Oxford, 2016), 2nd ed ed.
 - [51] D. Chiumello, G. Chidini, E. Calderini, A. Colombo, F. Crimella, and M. Brioni, “Respiratory mechanics and lung stress/strain in children with acute respiratory distress syndrome,” *Annals of intensive care* 6, 11–11 (2016).
URL <https://pubmed.ncbi.nlm.nih.gov/26847436>
 - [52] I. Martin-Loeches and A. Artigas, *Respiratory support with positive end-expiratory pressure*, vol. 1 (Oxford University Press, 2016).
URL <http://oxfordmedicine.com/view/10.1093/med/9780199600830.001.0001/med-9780199600830-chapter-94>
 - [53] R. A. Polin, W. A. Carlo, and COMMITTEE ON FETUS AND NEWBORN, “Surfactant Replacement Therapy for Preterm and Term Neonates With Respiratory Distress,” *Pediatrics* 133, 156–163 (2014).
URL <http://pediatrics.aappublications.org/lookup/doi/10.1542/peds.2013-3443>

- [54] S. G. Kallapur and A. H. Jobe, "Chapter 2 - Perinatal Events and Their Influence on Lung Development and Injury," in "The Newborn Lung (Third Edition)," (E. Bancalari, ed.), pp. 31–64 (Elsevier, Philadelphia, 2019).
URL <https://www.sciencedirect.com/science/article/pii/B9780323546058000027>
- [55] V. Apgar, "The Newborn (APGAR) Scoring System: Reflections and Advice," *Pediatric Clinics of North America* 13, 645–650 (1966).
URL <https://linkinghub.elsevier.com/retrieve/pii/S0031395516318740>
- [56] W. D. Bidgood, S. C. Horii, F. W. Prior, and D. E. V. Syckle, "Understanding and Using DICOM, the Data Interchange Standard for Biomedical Imaging," 4, 14 (1997).
- [57] S. N. Jain, T. Modi, and R. U. Varma, "Decoding the neonatal chest radiograph: An insight into neonatal respiratory distress," *Indian Journal of Radiology and Imaging* 30, 482–492 (2020).
URL http://www.thieme-connect.de/DOI/DOI?10.4103/ijri.IJRI_281_20
- [58] T. Elgeti, H. Proquitté, N. E. Rogalla, J. Mews, R. Wauer, B. Hamm, G. Schmalisch, and P. Rogalla, "Dynamic Computed Tomography of the Neonatal Lung: Volume Calculations and Validation in an Animal Model," *Investigative Radiology* 40, 761–765 (2005).
URL <https://journals.lww.com/00004424-200512000-00003>
- [59] S. B. Greenberg, "Dynamic Pulmonary CT of Children," *American Journal of Roentgenology* 199, 435–440 (2012).
URL <http://www.ajronline.org/doi/abs/10.2214/AJR.11.8014>
- [60] H. A. Tiddens, W. Kuo, M. van Straten, and P. Ciet, "Paediatric lung imaging: the times they are a-changin'," *European Respiratory Review* 27, 170097 (2018).
URL <http://err.ersjournals.com/lookup/doi/10.1183/16000617.0097-2017>
- [61] H.-Y. Liang, X.-W. Liang, Z.-Y. Chen, X.-H. Tan, H.-H. Yang, J.-Y. Liao, K. Cai, and J.-S. Yu, "Ultrasound in neonatal lung disease," *Quantitative Imaging in Medicine and Surgery* 8, 535–546 (2018).
URL <http://qims.amegroups.com/article/view/19924/19944>
- [62] J. Pillow, H. Ljungberg, G. Hülkamp, and J. Stocks, "Functional residual capacity measurements in healthy infants: ultrasonic flow meter versus a mass spectrometer," *European Respiratory Journal* 23, 763 (2004).
URL <http://erj.ersjournals.com/content/23/5/763.abstract>
- [63] M. Morris, P. Gustafsson, R. Tepper, M. Gappa, and J. Stocks, "The bias flow nitrogen washout technique for measuring the functional residual capacity in infants," *European Respiratory Journal* 17, 529 (2001).
URL <http://erj.ersjournals.com/content/17/3/529.abstract>
- [64] J. Stocks, S. Godfrey, C. Beardsmore, E. Bar-Yishay, and R. Castile, "Plethysmographic measurements of lung volume and airway resistance," *European Respiratory Journal* 17, 302–312 (2001).
URL <http://erj.ersjournals.com/content/17/2/302>

- [65] K. E. Edberg, K. Sandberg, A. Silberberg, B. A. Sjöqvist, B. Ekström-Jodal, and O. Hjalmarson, "A Plethysmographic Method for Assessment of Lung Function in Mechanically Ventilated Very Low Birth Weight Infants," *Pediatric Research* 30, 501–501 (1991).
URL <https://doi.org/10.1203/00006450-199111000-00020>
- [66] C. Wiechers, S. Kirchhof, C. Maas, C. F. Poets, and A. R. Franz, "Neonatal body composition by air displacement plethysmography in healthy term singletons: a systematic review," *BMC Pediatrics* 19, 489 (2019).
URL <https://bmcpediatr.biomedcentral.com/articles/10.1186/s12887-019-1867-y>
- [67] H. Mazahery, P. R. von Hurst, C. J. D. McKinlay, B. E. Cormack, and C. A. Conlon, "Air displacement plethysmography (pea pod) in full-term and pre-term infants: a comprehensive review of accuracy, reproducibility, and practical challenges," *Maternal Health, Neonatology and Perinatology* 4, 12 (2018).
URL <https://mhnpjournal.biomedcentral.com/articles/10.1186/s40748-018-0079-z>
- [68] I. Chatziioannidis, T. Samaras, and N. Nikolaidis, "Electrical Impedance Tomography: a new study method for neonatal Respiratory Distress Syndrome?" *Hippokratia* 15, 211–215 (2011), publisher: LITHOGRAPHIA Antoniadis I.-Psarras Th. G.P.
URL <https://pubmed.ncbi.nlm.nih.gov/22435017>
- [69] G. Schmalisch, "Basic principles of respiratory function monitoring in ventilated newborns: A review," *Paediatric Respiratory Reviews* 20, 76–82 (2016).
URL <https://linkinghub.elsevier.com/retrieve/pii/S1526054216000348>
- [70] L. Persson, K. Svanberg, and S. Svanberg, "On the potential of human sinus cavity diagnostics using diode laser gas spectroscopy," *Applied Physics B* 82, 313–317 (2006).
URL <http://link.springer.com/10.1007/s00340-005-1968-1>
- [71] M. Lewander, Z. Guan, K. Svanberg, and T. Svensson, "Clinical system for non-invasive in situ monitoring of gases in the human paranasal sinuses," p. 15 (2009).
- [72] M. Lewander, A. Bruzelius, S. Svanberg, K. Svanberg, and V. Fellman, "Nonintrusive gas monitoring in neonatal lungs using diode laser spectroscopy: feasibility study," *Journal of Biomedical Optics* 16, 127002 (2011).
URL <http://biomedicaloptics.spiedigitallibrary.org/article.aspx?doi=10.1117/1.3663211>
- [73] T. A. Henderson and L. Morries, "Near-infrared photonic energy penetration: can infrared phototherapy effectively reach the human brain?" *Neuropsychiatric Disease and Treatment* p. 2191 (2015).
URL <http://www.dovepress.com/near-infrared-photonic-energy-penetration-can-infrared-pho>
- [74] T. Terboven, G. Leonhard, L. Wessel, T. Viergutz, M. Rudolph, M. Schöler, M. Weis, and H. Haubenreisser, "Chest wall thickness and depth to vital structures in paediatric patients – implications for prehospital needle decompression of tension pneumothorax," *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 27, 45 (2019).
URL <https://sjtrem.biomedcentral.com/articles/10.1186/s13049-019-0623-5>

- [75] E. K. Svanberg, *Non-invasive optical monitoring of free and bound oxygen in humans.*, PhD Thesis, Lund University (2016).
- [76] J. Larsson, D. Leander, M. Lewander Xu, V. Fellman, J. Bood, and E. Krite Svanberg, "Comparison of dermal vs internal light administration in human lungs using the TDLAS-GASMAS technique—Phantom studies," *Journal of Biophotonics* 12 (2019).
URL <https://onlinelibrary.wiley.com/doi/abs/10.1002/jbio.201800350>
- [77] E. K. Svanberg, J. Larsson, M. Rasmussen, M. Larsson, D. Leander, S. Bergsten, J. Bood, G. Greisen, and V. Fellman, "Changes in pulmonary oxygen content are detectable with laser absorption spectroscopy: proof of concept in newborn piglets," *Pediatric Research* (2020).
URL <http://www.nature.com/articles/s41390-020-0971-x>
- [78] C. F. Bohren and D. R. Huffman, *Absorption and scattering of light by small particles* (John Wiley & Sons, 2008).
- [79] H. C. Hulst and H. C. van de Hulst, *Light scattering by small particles* (Courier Corporation, 1981).
- [80] J. R. Mourant, T. Fuselier, J. Boyer, T. M. Johnson, and I. J. Bigio, "Predictions and measurements of scattering and absorption over broad wavelength ranges in tissue phantoms," *Applied Optics* 36, 949 (1997).
URL <https://opg.optica.org/abstract.cfm?URI=ao-36-4-949>
- [81] S. Jacques, "Origins of tissue optical properties in the UVA, visible, and NIR regions," *Adv Opt Imaging Photon Migration* 2 (1996).
- [82] D. Passos, J. C. Hebden, P. N. Pinto, and R. Guerra, "Tissue phantom for optical diagnostics based on a suspension of microspheres with a fractal size distribution," *Journal of Biomedical Optics* 10, 064036 (2005).
URL <http://biomedicaloptics.spiedigitallibrary.org/article.aspx?doi=10.1117/1.2139971>
- [83] T. J. Farrell, M. S. Patterson, and B. Wilson, "A diffusion theory model of spatially resolved, steady-state diffuse reflectance for the noninvasive determination of tissue optical properties in vivo." *Medical physics* 19, 879–888 (1992), place: United States.
- [84] B. W. Pogue and M. S. Patterson, "Review of tissue simulating phantoms for optical spectroscopy, imaging and dosimetry," *Journal of Biomedical Optics* 11, 041102 (2006).
URL <http://biomedicaloptics.spiedigitallibrary.org/article.aspx?doi=10.1117/1.2335429>
- [85] P. D. Ninni, F. Martelli, and G. Zaccanti, "Intralipid: towards a diffusive reference standard for optical tissue phantoms." *Physics in medicine and biology* 56, N21–28 (2011), place: England.
- [86] C. J. Maughan Jones and P. R. T. Munro, "Development of a reliable and reproducible phantom manufacturing method using silica microspheres in silicone," *Journal of Biomedical Optics* 22, 1 (2017).
URL <https://www.spiedigitallibrary.org/journals/journal-of-biomedical-optics/volume-22/issue-09/095004/Development-of-a-reliable-and-reproducible-phantom-manufacturing-method-using-10.1117/1.JBO.22.9.095004.full>

- [87] S. Konugolu Venkata Sekar, A. Dalla Mora, I. Bargigia, E. Marti-nenghi, C. Lindner, P. Farzam, M. Pagliazzi, T. Durduran, P. Taroni, A. Pifferi, and A. Farina, “Broadband (600–1350 nm) Time-Resolved Diffuse Optical Spectrometer for Clinical Use,” *IEEE Journal of Selected Topics in Quantum Electronics* 22, 406–414 (2016). URL <http://ieeexplore.ieee.org/document/7349112/>
- [88] P. Naglič, Y. Zelinskyi, L. Rogelj, J. Stergar, M. Milanič, J. Novak, B. Kumperščak, and M. Bürmen, “Optical properties of PlatSil SiliGlass tissue-mimicking phantoms,” *Biomedical Optics Express* 11, 3753 (2020). URL <https://opg.optica.org/abstract.cfm?URI=boe-11-7-3753>
- [89] J. Larsson, P. Liao, P. Lundin, E. Krite Svanberg, J. Swartling, M. Lewander Xu, J. Bood, and S. Andersson-Engels, “Development of a 3-dimensional tissue lung phantom of a preterm infant for optical measurements of oxygen-Laser-detector position considerations,” *J. Biophotonics* 11, e201700097 (2018). URL <http://doi.wiley.com/10.1002/jbio.201700097>
- [90] P. Lundin, *Laser Sensing for Quality Control and Classification – Applications for the Food Industry, Ecology and Medicine*, Doctoral Thesis, Lund University (2014).
- [91] T. Durduran, R. Choe, W. B. Baker, and A. G. Yodh, “Diffuse optics for tissue monitoring and tomography,” *Reports on Progress in Physics* 73, 076701 (2010). URL <https://iopscience.iop.org/article/10.1088/0034-4885/73/7/076701>
- [92] S. L. Jacques and B. W. Pogue, “Tutorial on diffuse light transport,” *Journal of Biomedical Optics* 13, 041302 (2008). URL <http://biomedicaloptics.spiedigitallibrary.org/article.aspx?doi=10.1117/1.2967535>
- [93] J. C. Schotland, J. C. Haselgrove, and J. S. Leigh, “Photon hitting density,” *Applied Optics* 32, 448 (1993). URL <https://opg.optica.org/abstract.cfm?URI=ao-32-4-448>
- [94] S. R. Arridge, “Photon-measurement density functions Part I: Analytical forms,” *Applied Optics* 34, 7395 (1995). URL <https://www.osapublishing.org/abstract.cfm?URI=ao-34-31-7395>
- [95] S. R. Arridge and M. Schweiger, “Photon-measurement density functions Part 2: Finite-element-method calculations,” *Applied Optics* 34, 8026 (1995). URL <https://opg.optica.org/abstract.cfm?URI=ao-34-34-8026>
- [96] H. Dehghani, M. E. Eames, P. K. Yalavarthy, S. C. Davis, S. Srinivasan, C. M. Carpenter, B. W. Pogue, and K. D. Paulsen, “Near infrared optical tomography using NIRFAST: Algorithm for numerical model and image reconstruction,” *Communications in Numerical Methods in Engineering* 25, 711–732 (2009). URL <http://doi.wiley.com/10.1002/cnm.1162>
- [97] M. Jermyn, H. Ghadyani, M. A. Mastanduno, W. Turner, S. C. Davis, H. Dehghani, and B. W. Pogue, “Fast segmentation and high-quality three-dimensional volume mesh creation from medical images for diffuse optical tomography,” *Journal of Biomedical*

- Optics* 18, 086007 (2013).
URL <http://biomedicaloptics.spiedigitallibrary.org/article.aspx?doi=10.1117/1.JBO.18.8.086007>
- [98] P. Liao, J. Larsson, E. Krite Svanberg, P. Lundin, J. Swartling, M. Lewander Xu, J. Bood, and S. Andersson-Engels, “Computer simulation analysis of source-detector position for percutaneously measured O₂-gas signal in a three-dimensional preterm infant lung,” *Journal of Biophotonics* 11, e201800023 (2018).
URL <https://onlinelibrary.wiley.com/doi/10.1002/jbio.201800023>
- [99] Y. Lin, P. Lundin, E. Krite Svanberg, K. Svanberg, S. Svanberg, and A. Sahlberg, “Gas in scattering media absorption spectroscopy on small and large scales: Toward the extension of lung spectroscopic monitoring to adults,” *Translational Biophotonics* 3 (2021).
URL <https://onlinelibrary.wiley.com/doi/10.1002/tbio.202100003>

PAPERS

Translation of Gas Spectroscopy into the Clinic, a Promising Tool for Non-Invasive Diagnostics in Respiratory Health Care of Neonates

A. Pacheco, E. Dempsey, and S. Andersson-Engels.

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Perspective

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Translation of Gas Spectroscopy into the Clinic, a Promising Tool for Non-Invasive Diagnostics in Respiratory Health Care of Neonates

Andrea Pacheco^{1,2*}, Eugene Dempsey³ and Stefan Andersson-Engels^{1,2}

¹Department of Physics, University College Cork, Ireland

²IPIC, Tyndall National Institute, Ireland

³Cork University Maternity Hospital Wilton, Cork, Ireland

*Corresponding author: Andrea Pacheco, IPIC Tyndall National Institute, Lee Maltings Complex Dyke Parade, Cork, T12 R5CP, Ireland.

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Abstract

Respiratory Distress Syndrome (RDS) is the leading cause of death among preterm infants worldwide. The latest improvements made in tackling RDS are focused on less invasive surfactant therapy and non-invasive ventilation. As a consequence of the more advanced and intensive respiratory support, there is an increase in the prevalence of infants with chronic lung disease. The current first line techniques used to monitor at risk infants with respiratory distress are pulse oximetry, chest radiography (X-ray) and blood gas analysis with X-ray imaging being the main diagnostic tool used. However, ionized radiation can be harmful for the infant and exposure should be kept to the minimum requirement.

Translation of the gas spectroscopy to the clinic could provide additional information about alveolar composition and make the step forward in objective medical assessment for RDS in neonates. Lack of direct, non-invasive method of measuring the oxygen concentration in the lung instead of oxygen saturation in blood, precludes understanding of underlying cause of the RDS and real time monitoring of the response of neonates under treatment. Gas spectroscopy has proven successful in quantifying gas content inside cavities surrounded by solids or liquids, and thus may be used to assess the oxygen content in the lungs of a neonate. This non-invasive light-based technology opens a new range of tools for lung function assessment, as it can be used to map continuously the oxygen presence and the changes in the volume of the lungs during respiration. Its superior specificity makes it a good candidate for the early diagnosis of respiratory distress. In addition, it could also be integrated to existing equipment to help optimize respiratory support during treatment.

Keywords: Respiratory distress; Neonatal healthcare; Non-invasive; Gas spectroscopy

Abbreviations: RDS: Respiratory Distress Syndrome; CLD: Chronic Lung Disease; MRI: Magnetic Resonance Imaging; GASMAS: Gas in Scattering Media Absorption Spectroscopy; IR: Infrared; CPAP: Continuous Positive Airway Pressure; CT: Computed Tomography

Introduction

The motivation for this article is that each year an estimated of 15 million infants are born preterm (before 37 completed weeks of gestation) [1]. 95 % of neonates at 24 weeks gestational age and 80% of infants born at 28 weeks have respiratory distress syndrome (RDS) [2]. RDS in neonates is due to a deficiency of surfactant, which is a protein produced by the cell lining in the alveoli of the foetus, which reduces the surface tension of pulmonary fluids and contributes to the elasticity of the lungs. It is detectable from approximately week 23 onward and enables the platform for gas exchange [3]. The deficiency of surfactant results in reduced lung

compliance increased respiratory effort and increased likelihood of alveolar collapse [4]. RDS-specific interventions, therapies and advanced care technologies including administration of antenatal corticosteroids, surfactant, alternative modes of non-invasive ventilation and ventilatory strategies such as high-frequency oscillatory ventilation have reduced the neonatal mortality rate over the past two decades [5]. However, mechanical ventilation can have a bad effect on a lung that is developing or in the process of repairing. The longer mechanical ventilation is administered, the more likely is for the infant to develop chronic lung dysfunction (CLD).



Although current research is aiming for less invasive and more targeted diagnostics and treatment techniques [6], the main tool is X-ray imaging such as chest radiograph or rarely volumetric computed tomography (CT) with the drawback of radiation burden [7]. Alternative non harmful diagnostic tools are magnetic resonance imaging (MRI) and ultrasound imaging. The image quality of MRI can be affected by heartbeat and respiration motion and there is still on-going work to fully achieve lung imaging comparable to CT [8]. Lung ultrasound imaging has been proven to be of good use for bedside differential diagnosis of RDS in new-borns [9,10].

While the above-mentioned imaging techniques enable the localization of gas filled cavities in the body, none of them make it possible for the quantification of alveolar gas composition in real time. Gas in Scattering Media Absorption Spectroscopy (GASMAS) is a non-invasive optical technique which can be used to measure continuously oxygen concentration and inflated volume locally in the lung [11]. The clinical applications of this novel technology are currently being explored and this article provides insights into the potential improvements that could rise from translating GASMAS as a rapid non- radiographic bedside detection of alveolar oxygen gas for neonatal respiratory health care.

Principles of GASMAS technique

Optical spectroscopy is widely used to provide information on different gas species [12]. GASMAS refers to the regime where the absorbing gas is inside a highly scattering media and relies on the difference between the absorptive imprints between solid-state materials and free gas. The absorption spectrum of free oxygen inside the alveoli is 10,000 times narrower than those of blood, and other surrounding tissues of the thoracic cavity. The deepest penetration of light in human tissue corresponds to wavelengths between 650 nm and 1.4 microns. Since molecular oxygen has a wide range of absorption lines around 760 nm and water vapor has numerous lines around 820 and 980 nm, the selection of light sources for clinical applications of GASMAS in respiratory health care are restricted to these wavelengths [13].

Previous feasibility studies demonstrated that gas sensing in the lung can be achieved by sending low-intensity laser light through the thoracic wall and detecting the emerging light with a photodetector, which reveals the absorption imprints of oxygen and water vapor [14]. The Beer-Lambert law is used to assess the gas concentration. In scattering media, the path length is not well defined; hence two wavelengths are necessary to tune across the absorption lines of water vapor and molecular oxygen simultaneously. By making the assumption that optical properties are the same for the two wavelengths, the absorption signal from oxygen is normalized by the water vapor one and then the absolute concentration of oxygen is calculated [15].

Potential clinical application of GASMAS

In the transition from intrauterine environment to air, immediately after birth, the neonate fills the airways down to the alveolar level with air to start breathing and gas exchange. Preterm neonates are born with lungs still in prenatal stages. The lack of surfactant results in increase respiratory effort to expand the lung which has weak alveoli due to RDS. By enabling the localization of regions in the lung with poorly inflated alveoli, GASMAS technology could be a key support for clinicians in the diagnostics and quantification of surfactant deficiency. The probes could be placed over the thorax for long hours and track the administration of exogenous surfactant as well as the treatment response of the patient. This could result in optimized timing of rescue doses of surfactant and prevention of alveolar collapse.

Recent efforts have assessed minimally invasive surfactant administration to provide surfactant without intubation and thus avoiding mechanical ventilation [16]. The results of such studies are promising. GASMAS technology may have a very important additional role to play in optimizing surfactant administration, mechanical ventilation techniques, endotracheal tube placement if required, and an additional tool to enhance extubating thresholds and strategies to prevent reintubation. Chronic Lung Dysfunction (CLD) usually evolves in preterm infants from their RDS. It is a consequence of the improved survival of new borns and the most relevant specific condition that adversely affects postnatal lung development. Risk factors for CLD are mechanical ventilation, fluid overload and hyperoxia [17]. Inflammation is an indication that CLD will develop. GASMAS technology is also capable of measuring inflated volume in the lung and can potentially quantify inflammatory changes within the lungs of preterm infants. This would present a huge step in the optimization of clinical care, since chest radiography, the gold standard for diagnosis, might not always correlate with the clinical severity in CLD [7]. Postnatal infections, including sepsis and pneumonia are also risk factors for CLD where lung injury is thought to be mediated by inflammation [18]. Further studies could determine if infection of lung tissue has a gaseous biological marker. If so, GASMAS technology could optimize antibiotics administration.

Conclusion

The last advances in laser, photodetector and software technology make it possible to design a bedside GASMAS device with compact source and detector probes, capable of measuring oxygen concentration and lung volume in real time. The probes can be placed in remittance geometry for different positions over the thorax, allowing the mapping of alveolar performance over the different lung lobes. A bedside clinical device combining imaging features from ultrasound and the quantification gas composition and inflated volume of the lung offered by GASMAS has the potential

to achieve a thorough lung function assessment of new-borns and help in the diagnosis of underlying respiratory conditions, diminishing the need of X-ray imaging. GASMAS technology may have a very important role to play in optimizing respiratory support for preterm infants and potentially decrease the incidence of CLD.

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Conflict of Interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Reference

1. (2018) World Health Organization.
2. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, et al. (2017) European Consensus Guidelines on the Management of Respiratory Distress Syndrome-2016 Update. *Neonatology* 111(17): 107-125.
3. Joshi S, Kotecha S (2007) Lung Growth and Development. *Early Human Development* 83: 789-794.
4. Gallacher DJ, Hart K and Kotecha S (2016) Common respiratory conditions of the newborn. *Breathe* 12(1): 30-42.
5. Kamath BD, Macguire ER, McClure EM, Goldenberg RL, Jobe (2011) Neonatal Mortality from Respiratory Distress Syndrome: Lessons for Low-Resource Countries. *Pediatrics* 127(6): 1139-1146.
6. Dyer J (2019) Neonatal Respiratory Distress Syndrome: Tackling A Worldwide Problem. *P&T* 44(1): 12-14.
7. Rossi U, Owens C (2005) The radiology of chronic lung disease in children. *Arch Dis Child* 90(6): 601-607.
8. Hahn AD, Higano NS, Walkup LL, Thomen RP, Cao X, et al. (2017) Pulmonary MRI of neonates in the intensive care unit using 3D ultrashort echo time and a small foot-print MRI system. *J Magn Reson Imaging* 45(2): 463-471.
9. Liang H, Liang X, Chen Z, Tan X, Yang H, et al. (2018) Ultrasound in neonatal lung disease. *Quant Imaging Med Surg* 8(5): 535-546.
10. Vergine M, Copetti R, Brusa G, Cattarossi L (2014) Lung Ultrasound Accuracy in Respiratory Distress Syndrome and Transient Tachypnea of the Newborn. *Neonatology* 106(2): 87-93.
11. Svanberg EK, Lundin P, Larsson M, Åkeson J, Svanberg K, et al. (2016) Diode laser spectroscopy for noninvasive monitoring of oxygen in the lungs of newborn infants. *Pediatric Research* 79(4): 621-628.
12. Rothman LS, Gordon IE, Babikov Y, Barbe A, Benner DC, et al. (2013) The HITRAN 2012 molecular spectroscopic database. *JQSRT* 130: 4-50.
13. Svanberg S (2013) Gas in scattering media absorption spectroscopy - from basic studies to biomedical applications. *Laser Photonics Rev* 7(5): 779-796.
14. Lewander M, Bruzelius A, Svanberg S, Svanberg K, Fellman V (2011) Noninvasive Gas Monitoring in Neonatal Lungs Using Diode Laser Spectroscopy: Feasibility Study. *J Biomed Opt* 16(12): 127002.
15. Persson L, Lewander M, Andersson M, Svanberg K, Svanberg S (2008) Simultaneous detection of molecular oxygen and water vapor in the tissue optical window using tunable diode laser spectroscopy. *Applied Optics* 47(12): 2028-2034.
16. Aguar M, Nuñez A, Cubells E, Cernada M, Dargaville PA, et al. (2014) Administration of Surfactant Using Less Invasive Techniques as a Part of a Non-Aggressive Paradigm Towards Preterm Infants. *Early Hum Dev* 90(2): S57-59.
17. Bhandari V (2010) Hyperoxia-derived lung damage in preterm infants. *Semin Fetal Neonatal Med* 15(4): 223-229.
18. Van Marter LJ, Dammann O, Allred EN, Leviton A, Pagano M, et al. (2002) Chorioamnionitis, Mechanical Ventilation, and Postnatal Sepsis as Modulators of Chronic Lung Disease in Preterm Infants. *J Pediatr* 140(2): 171-176.

**Solid phantom recipe for diffuse optics in
biophotonics applications: a step towards
anatomically correct 3D tissue phantoms**

S. Konugolu, A. Pacheco, P. Martella, H. Li, P. Lanka, A. Pifferi and
S. Andersson-Engels.

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Solid phantom recipe for diffuse optics in biophotonics applications: a step towards anatomically correct 3D tissue phantoms

SANATHANA KONUGOLU VENKATA SEKAR,^{1,7,*} ANDREA PACHECO,^{1,2,7}
PIERLUIGI MARTELLA,^{1,3} HAIYANG LI,^{1,4} PRANAV LANKA,⁵ ANTONIO
PIFFERI,^{5,6} AND STEFAN ANDERSSON-ENGELS^{1,2}

¹Biophotonics@Tyndall, IPIC, Tyndall National Institute, Lee Maltings, Dyke Parade, Cork, Ireland

²Department of Physics, University College Cork, College Road, Cork, T12 K8AF, Ireland

³Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Pavia, Italy

⁴School of Mechanical Engineering and Automation, Northeastern University, China

⁵Dipartimento di Fisica, Politecnico di Milano, Milano, Italy

⁶Consiglio Nazionale delle Ricerche, Istituto di Fotonica e Nanotecnologie, Milano, Italy

⁷These authors contributed equally to this research.

*sanathana.konugolu@tyndall.ie.

Abstract: We present a tissue mimicking optical phantom recipe to create robust well tested solid phantoms. The recipe consists of black silicone pigment (absorber), silica microspheres (scatterer) and silicone rubber (SiliGlass, bulk material). The phantom recipe was characterized over a broadband spectrum (600-1100 nm) for a wide range of optical properties (absorption $0.1-1 \text{ cm}^{-1}$, reduced scattering $5-25 \text{ cm}^{-1}$) that are relevant to human organs. The results of linearity show a proper scaling of optical properties as well as the absence of coupling between the absorber and scatterer at different concentrations. A reproducibility of 4% among different preparations was obtained, with a similar grade of spatial homogeneity. Finally, a 3D non-scattering mock-up phantom of an infant torso made with the same recipe bulk material (SiliGlass) was presented to project the futuristic aspect of our work that is 3D printing human organs of biomedical relevance.

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1. Introduction

Tissue-mimicking optical phantoms play a crucial role in characterization, optimization, routine calibration and validation of biophotonics systems [1–3]. The phantoms can be made both in solid or liquid forms, however, solid phantoms have some advantages such as long shelf life, can be molded to realistic organ shapes, stable optical properties (absorption- μ_a , reduced scattering- μ'_s), and easy handling for routine instrument validation. In general, a phantom consists of three main components: bulk material (water, epoxy resin, silicone, agar), absorber (India ink, printer toner, black silicone), and scatterer (intralipid, titanium oxide, aluminum oxide, silica microspheres) [4–8]. The advent of silicone rubber has enabled the phantoms to mimic not only optical but also mechanical properties to some extent [7,9]. Importantly, the advancement of 3D printing technology has enabled the printing of realistic human organs from X-ray CT scans [10]. The recent work of Larsson *et al.* showed a 3D phantom of the upper body of an infant which includes lung, heart, bones, and muscles. This work used a liquid phantom recipe to obtain realistic optical properties [11]. Taking this technology to solid phantoms was achieved by Dempsey *et al.* who created a 3D printed brain phantom [12]. The recent work of Kennedy *et al.* used a room temperature vulcanizing silicone rubber as a bulk material and a special absorber to mimic optical properties of water and lipid absorption [13]. A recent review of tissue-mimicking optical phantoms can be found in Ref [8].

Multiple phantom recipes are thus found in literature, indicating remaining challenges to find a phantom material that is ideal for a wide range of needs in biophotonics. Possible limiting factors for the acceptance of some of the published phantom recipes include that the recipe does not provide a detailed manufacturing procedure or a systematic study of phantom behavior over a wide range of absorber and scatterer concentrations. In addition, liquid phantoms are cumbersome to handle especially for realistic tissue geometries and typically have a short shelf life. An example of a phantom developed for a specific purpose is given by Maughan Jones *et al.* They proposed an improved method for phantom manufacturing using silica microsphere as a scatterer for OCT applications. This phantom was thereby characterized at a single wavelength only [4]. Similarly, multiple groups have proposed various manufacturing procedures, some proposed complex methods to ensure absorber and scatterer uniformity [14,15], while some simpler recipes are also available [9,13,16]. Yet, all of these methods lack one of the following aspects:

- i) A detailed protocol for the procedure of phantom manufacturing and the phantom recipe.
- ii) A characterization of the behavior of the phantom over a wide range of absorber and scatterer concentrations relevant to the tissue optical properties.
- iii) A broadband (600-1100 nm) optical characterization of the phantoms.
- iv) Characterization of the phantoms in terms of reproducibility, shelf life, and homogeneity.

The first (i) point takes care of robust manufacturing procedure, whereas the second point ensures the phantoms have linear optical behavior over the entire range of absorber and scatterer concentrations. Point (iii) makes sure that point (ii) was tested over a broad wavelength range, while (iv) ensures the phantoms are optically reproducible and homogeneous over the entire phantom volume. In addition, thorough consideration of phantom ingredients is important in order to facilitate the best possible properties. These points form the building block to provide a well-tested, robust solid phantom that could be manufactured by any group interested in optical properties relevant to human organs.

In our opinion there is still a need for a recipe for a good 3D tissue-mimicking phantom that is robust and tested over the wide range of optical properties covering most of the human organs, preferably characterized over the entire therapeutic wavelength range to benefit the wide community in biophotonics. The aim of this work was to fulfill this need. The study was designed to cover optical properties (absorption $0.1\text{--}1\text{ cm}^{-1}$, reduced scattering $5\text{--}25\text{ cm}^{-1}$) relevant to various organs of the human body. The optical characterization was performed using photon time-of-flight diffuse optical spectrometer (pTOFS) which has been validated in various phantom and clinical studies [17]. Time domain measurements can inherently disentangle absorption and scattering properties, providing reliable results of both absorption and scattering properties of the phantoms [18–21]. To the best of our knowledge, this was the first study that covers all the above-mentioned challenges to provide an integrated recipe solution that could provide 3D solid phantoms in biomedical optics. To emphasize the cause, a realistic anatomically correct 3D phantom of an infant's torso was provided in the results section.

2. Materials and methods

2.1 Phantom recipe

A detailed description of the phantom ingredients, the method to make the phantoms, and the concentration of absorber and scatterer for different optical properties are shown in Fig. 1. The bulk material of the phantom was made of SiliGlass which is a transparent silicone rubber procured from MBFibreglass (PlatSil SiliGlass). SiliGlass is a two-component cured room-temperature-vulcanizing (RTV) silicone. It consists of two liquid parts, part A (base material) and part B (hardener). When the two parts are mixed together in a 1:1 ratio, the

mixture cures to a solid at room temperature within 1 hour. Compared to other silicone based rubbers, SiliGlass is a clear medium instead of becoming bluish or turbid on curing. The scattering contribution from the silicone matrix needs to be negligible for better control of scattering properties in the produced phantoms. Also, low scattering regions, such as the cerebrospinal fluid (CSF) in the human head can be accurately modeled. The absorber employed was black silicone pigment (Polycraft Black Silicone Pigment) compatible with silicone and silica microspheres (440345, Sigma-Aldrich) were used to obtain the desired reduced scattering. The pure absorber was highly absorbing hence it was diluted in Part A (silicone base) at a ratio of (2272:1), here onwards whenever the absorber is mentioned it is the diluted (2272:1) stock solution of black silicone pigment in Part A.

The phantom preparation includes two parallel processes. One part comprises of mixing part A of the SiliGlass and the absorber (stock solution). The absorption properties of the phantoms were tuned by changing the quantity of absorber (stock solution) and part A with their total sum kept at constant value (75 g). The second process constitutes mixing part B of the SiliGlass with the microspheres. Both processes follow a similar procedure as shown in Fig. 1. Process B includes an extra step where the silica microspheres were disaggregated manually for 15 minutes with a spatula prior to the mixing with a magnetic stirrer (two magnetic beads (25x8 mm), speed-5, VWR VMS-C7). In general, both processes start with magnetic stirring for 15 minutes followed by ultrasonication (power-5, VWR USC500THD, 45 kHz) for 15 minutes. The entire preparation of the phantoms produced in this study was carried out at a controlled temperature (21° C) to avoid temperature-related reactions and extensive bubbling in the vacuum chamber employed for degassing. Following the bubble removal in a vacuum, both parts were mixed together and stirred manually for 5 minutes to ensure uniformity of the phantom mixture. The final step was to pour the mixture in the phantom cast, which for the characterization was a 3D printed cylinder with large diameter (10 cm). Subsequent measurements were performed in transmittance geometry. Therefore, the phantoms were made with large diameter (10 cm) to avoid boundary effects and granting use of a slab model [22]. The thickness of the phantoms was 18 mm. This value was chosen as a good compromise between the validity of the Diffusion equation and the signal level over the entire spectrum. A previous study on the validity of the Diffusion equation for time-resolved measurements at different source detector distances is reported in reference [23]. In total 24 phantoms were created with a matrix combination of 6 absorption values and 4 reduced scattering values as shown in Fig. 1. For a convention we used small alphabets (a, b, c, d, e, f) for the absorption series and capital letters (A, B, C, D) for the scattering series. The exact values of the absorber (stock solution) and scatterer percentage concentrations used for the entire phantom matrix are tabulated in the table of Fig. 1.

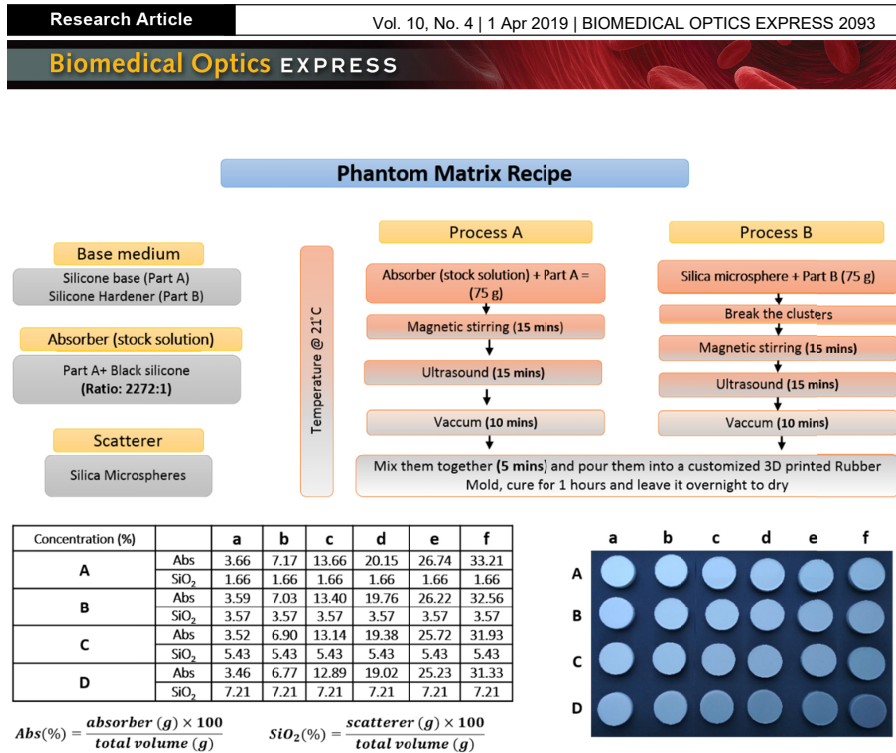


Fig. 1. The key ingredients (top left), the phantom recipe with detailed manufacturing procedure (top right), a picture of the phantom matrix (bottom right) produced and their respective absorber (stock solution) and scatterer percentage concentrations (bottom left).

2.2 Instrumentation, measurement protocol, data analysis

A time-domain diffuse optical spectrometer was used for the characterization of the phantoms. The spectrometer is described in detail elsewhere [17] and briefly described here. The setup consists of a pulsed supercontinuum laser (SC450, Fianium, UK) coupled to a Pellin Broca prism for wavelength selection. Light between 600 and 1100 nm was wavelength-scanned by rotating the prism and coupled into a 50 μ m fiber. Depending on the wavelength, the bandwidth of the laser was varying between 2 - 6 nm. The fiber coupled light was injected into the tissue phantom. The diffused light from the phantom was collected in transmittance geometry using a fiber (core 1 mm, 0.39 NA) set on the opposite side of the phantom on the very same axis. The light transmitted to the other end of the fibre was focused on a silicon photomultiplier (SiPM) [24]. The instrument used in the present study was built by Politecnico di Milano and was a lab version of the portable system described in Ref [17]. The system has since previously been characterized, tested, validated and employed in various phantom design, tissue chromophore characterization and clinical studies [22,25–27]. The use of well-validated time-domain instrument adds reliability to the phantom recipe as it inherently disentangles absorption and reduced scattering, thus avoiding coupling between optical properties.

The measurements of the tissue phantoms were conducted in transmission geometry. The source-detector distance of the phantom was thereby 18 mm. The measurements were repeated 3 times of 1.0 s acquisition for each wavelength over the entire broadband range (600-1100 nm) at steps of 20 nm. All phantoms were measured in the same session to minimize instrument error and the instrument response function (IRF) was taken before and after the measurement session.

The acquired temporal curves were summed over repetitions and were analyzed using the semi-infinite slab model of the diffusion equation with extrapolated boundary conditions [28], [29]. The theoretical curves were convolved with the IRF and a nonlinear Levenberg-

Marquardt algorithm was used for residual minimization between the theoretical and experimental data to extract optical properties (μ_a , μ'_s). The curve fitting was performed from 80% of the rising edge to 1% of the falling edge of the acquired temporal curves. A home-made fully automated software was used to automatize the entire fitting procedure over the broadband range for 24 phantoms.

3. Results and discussion

The various results presented in this work followed a protocol similar to the MEDPHOT protocol, well-established and agreed by 21 European laboratories for assessment of time domain diffuse optical instrument performance [1]. This rigorous protocol enabled the phantom recipe to be tested for various parameters like linearity, optical properties coupling, reproducibility and homogeneity. The obtained optical properties of the phantoms are shown in Fig. 2(a) for the absorption series, and Fig. 2(b) for the scattering series of the entire phantom matrix. The optical properties were extracted by the time domain instrument using the method discussed in the previous section. The coefficient of variation (CV) which is defined as the ratio of standard deviation to mean was used to determine the dispersion in the estimated optical properties. The CV of the absorption series was found to be less than 4% which was the expected CV of the time domain instrument used in this study and also partially due to the change in total volume of the phantom due to changing volume of the added scatterers within each series. The silicone peaks at 910 nm and 1020 nm are evident from all absorption spectra. Figure 2(b) shows the reduced scattering coefficient for different scattering series. As expected, the reduced scattering values decrease with increasing wavelength. A slight increase in scattering spectrum at 900 nm was observed which could be caused by some residual absorption-to-scattering coupling due to the model related to the absorption change at 900 nm or to the increased bandwidth effect [22,30] caused by the wider laser bandwidth. The CV of all scattering series was found to be less than 4%.

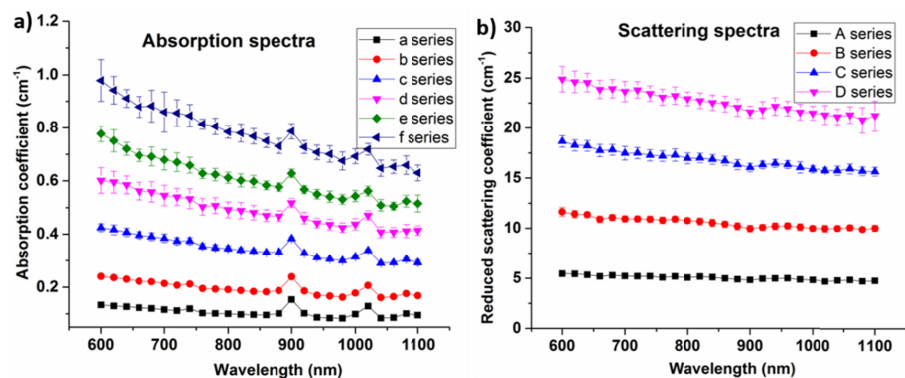


Fig. 2. a) Average absorption spectra of all the scattering phantoms with fixed absorption, and b) average reduced scattering spectra of all the absorption phantoms with fixed reduced scattering coefficients. The error bar represents the standard deviation of the spectra in a series.

As mentioned in the introduction, one of the novelties of this work is to provide a phantom recipe that is well tested for its linear behavior over the wide range of absorber and scatter concentrations. Figure 3a plots the change in absorption for different concentrations of absorber solution at 820 nm. The absorption scales linearly with increasing absorber concentration. The same plot was repeated for reduced scattering at different scatter concentrations (Fig. 3b) at 820 nm. There was a linear change in optical properties with changing concentration of absorber or scatterer within the limits of the instrument's CV. The 820 nm was chosen for two reasons: this wavelength lies around the mid-point of the range of

observed wavelengths and is one of the key wavelengths in gas in scattering media absorption spectroscopy (GASMAS) technique. GASMAS has been an emerging non-invasive technique to monitor gas concentration in human cavities like sinus, lung, etc [31,33]. One of our main projects for the tissue phantoms developed is to develop a method to measure oxygen in the lung of 3D printed infant phantom using GASMAS [11], [34]. The reference gas, water vapor, has an absorption line at 820 nm, which prompted us to choose this wavelength. In conjunction with the linearity plot at 820 nm (Fig. 3(a), 3(b)), a table containing linearity parameters (slope, y-intercept) for each series over the broadband range is presented (Table 1). This enables the user to fabricate optical phantoms with well characterized deterministic optical properties. The slope and intercept values are characterized over a limited range of optical properties (absorption 0.1-1 cm^{-1} , reduced scattering 5-25 cm^{-1}) relevant to human tissues and caution should be used for values beyond this range that were not characterized in this study. Using Table 1, for a given series, users can compute:

$$\text{Expected absorption coefficient}(\mu_a) = \text{slope} * \text{Absorber}(\%) + \text{intercept}$$

$$\text{Expected reduced scattering coefficient}(\mu_s') = \text{slope} * \text{Scatter}(\%) + \text{intercept}$$

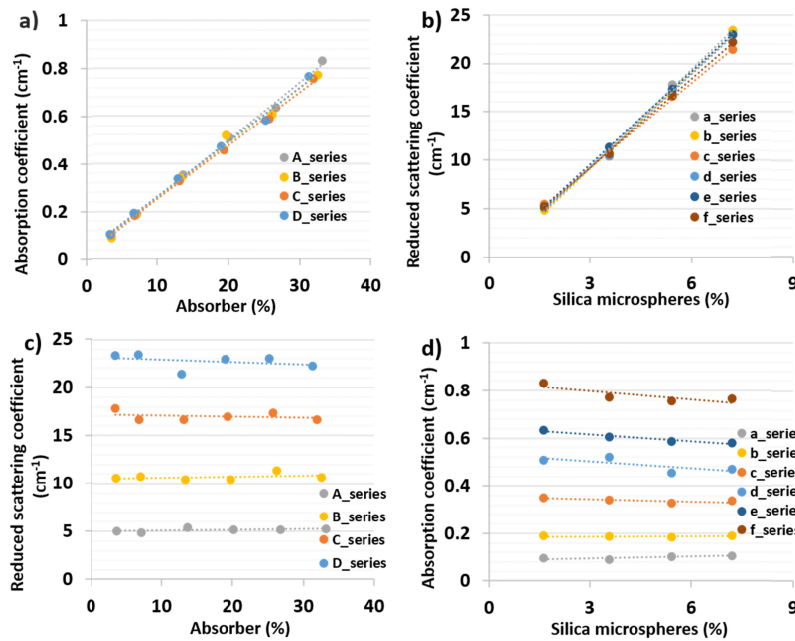


Fig. 3. Results of linearity tests at 820 nm a) absorption linearity as a function of added absorber b) scattering linearity as a function of added scatterers c) scattering properties of phantoms for different amount of absorber d) absorption properties of phantoms for different amount of added scatterers.

Table 1. Linearity parameters (slope and intercept) of phantom matrix over the broadband range (600-1100 nm)

Wavelength λ (nm)	Parameters	Absorption Linearity				Reduced scattering Linearity					
		A	B	C	D	a	b	c	d	e	f
600	slope	0.031	0.028	0.029	0.027	3.70	3.72	3.30	3.44	3.79	3.22
	intercept	0.015	0.041	0.025	0.056	-1.26	-1.57	0.15	-0.53	-0.93	0.47
700	slope	0.028	0.026	0.024	0.024	3.54	3.53	3.11	3.43	3.43	3.01
	intercept	0.016	0.033	0.042	0.053	-1.23	-1.37	0.28	-1.00	-0.56	0.31
800	slope	0.024	0.024	0.023	0.024	3.36	3.34	2.97	3.30	3.26	3.15
	intercept	0.018	0.026	0.029	0.032	-0.81	-1.04	0.33	-0.79	-0.31	-0.37
820	slope	0.024	0.023	0.022	0.023	3.36	3.33	2.93	3.23	3.22	3.08
	intercept	0.011	0.024	0.026	0.033	-0.82	-0.96	0.41	-0.53	-0.15	-0.05
900	slope	0.022	0.021	0.021	0.022	3.05	3.10	2.86	3.16	3.14	2.97
	intercept	0.075	0.094	0.087	0.090	-0.49	-0.77	0.09	-0.93	-0.48	-0.40
1000	slope	0.021	0.019	0.020	0.021	3.06	3.09	2.80	3.02	3.18	2.96
	intercept	0.020	0.041	0.038	0.044	-0.56	-0.87	0.30	-0.47	-0.66	-0.37
1100	slope	0.019	0.018	0.018	0.019	3.02	3.11	2.62	3.01	3.33	2.76
	intercept	0.023	0.044	0.045	0.046	-0.50	-1.02	0.76	-0.43	-1.07	0.12

Figure 3(c), 3(d) illustrate the dependency of reduced scattering coefficient on absorber concentration and vice versa. The straight lines observed in these plots confirm the absence of any chemical reaction between the scatterer and absorber. The slight coupling of absorption to scatterer concentration observed in Fig. 3(d) (especially for the f-series) relates to the change in total volume of the phantom due to increasing scatterer concentration and may be partly due to no longer fulfilling the assumptions of the diffusion approximation for high absorption ($\mu_a \approx 0.8 \text{ cm}^{-1}$) and low reduced scattering ($\mu_s' \approx 5 \text{ cm}^{-1}$).

A key feature of a robust recipe is to ensure that the outcome is insensitive to irrelevant parameters like the person who made the phantom, the day it was produced, the batch of raw material used, etc. To this end, a reproducibility test was conducted by manufacturing four phantoms (series code: cB) on different days by different people using a different batch of bulk material. Figure 4(a), 4(b) show the absorption and reduced scattering spectra, respectively, of the same phantom (series code: cB) produced under different conditions. Though the CV was found to be slightly higher in the shorter wavelengths, the overall CV of around 4% reaffirms the robustness of the recipe. Finally, a test to confirm the homogeneity of the phantom (series code: cB) was carried out by measuring optical properties at different points on the same phantom surface. Five points on the phantom surface were chosen, one in the middle and four points were around the midpoint of the phantom top surface (Fig. 4(c) and 4(d)). Similar to the reproducibility test, the CV of the homogeneity test was well below 4%, which confirms the homogenous nature of the sample. A long term stability of the phantom was performed by measuring phantom (cB) 3 times in the last 5 months and the results showed that the phantom were fairly stable with a CV close to 5% with more variation in the short wavelength range.

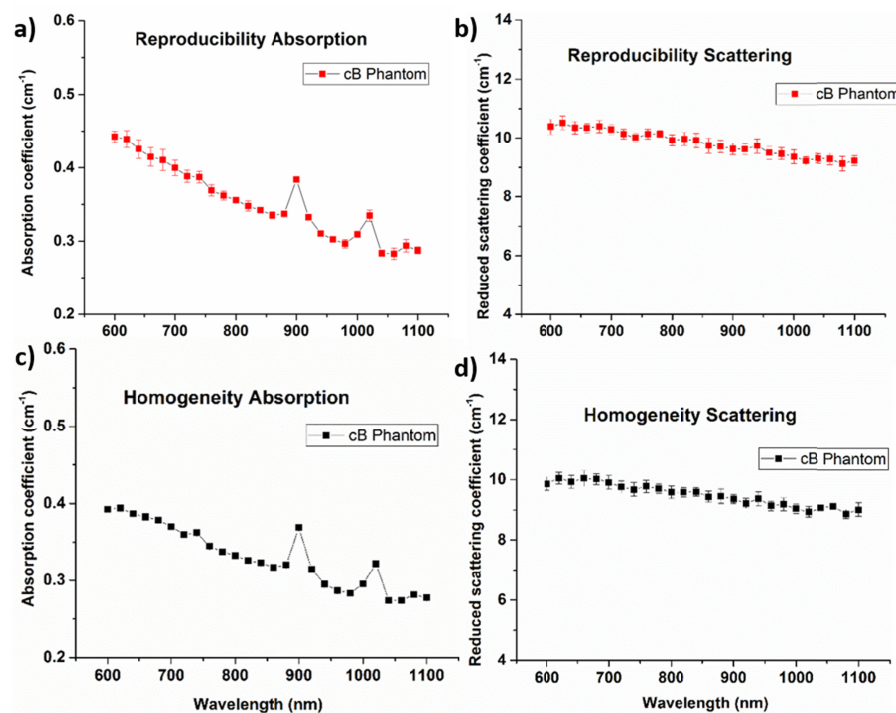


Fig. 4. Reproducibility test a) absorption reproducibility, b) reduced scattering coefficient reproducibility of the cB phantom. Homogeneity test results of absorption (c) and reduced scattering (d) both tests were found to have CV less than 4%.

As mentioned in the introduction, one of the key aspects of this study was to provide a robust phantom recipe that can be used to make realistic 3D phantoms of biomedical importance. For example, the present recipe can be used to match all optical properties of various main organs of an infant torso (heart, muscle, lung, bone, fat and skin). An anatomically correct 3D phantom with multiple structures can be built by placing individual organs inside out as shown in the Fig. 5. A CAD design of the phantoms was obtained by segmenting an anonymized DICOM image of computed tomography (CT) scan of a newborn infant with consent from the parents and hospital. The forms of the segmented individual organs in the infant (heart, lung, trachea, thoracic cage, muscles) were cast in resin using the 3D printer (Formlabs Form 2). These forms were subsequently employed to create negative molds of organs which were then used to produce anatomically correct organs in SiliGlass. The fabrication method ensures that no air gaps were present in our phantom assemble, the phantoms were assembled into torso negative mold and liquid phantom mixture was poured to bind them with perfect contact thus simulating an ideal human body conditions. Figure 5 shows the mockup transparent sample that emphasizes the vision that we want to achieve, to make 3D printed phantoms with realistic optical properties.



Fig. 5. Non-scattering anatomically correct 3D mock-up SiliGlass phantom made using CT scans of a newborn infant.

4. Conclusion

We have presented a robust, broadband (600–1100 nm) characterized, well-tested, and documented phantom recipe. To the best of our knowledge, this is the first study that tackles simultaneously the multiple issues of robust recipe, optical properties, and wavelength range relevant to human organs. The linearity, reproducibility, and homogeneity tests ensured the reliable nature of the phantom recipe. All the tested variables were found to have a CV of less than 4% which is the inherent CV of the time-domain system and a long term stability of CV of 5% was observed. With the technological advancement in 3D printing, we foresee this recipe could play a crucial role in the future of realistic biomedical 3D optical phantoms [11,31].

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Disclosures

The authors declare that there are no conflicts of interest related to this article.

References

1. A. Pifferi, A. Torricelli, A. Bassi, P. Taroni, R. Cubeddu, H. Wabnitz, D. Grosenick, M. Möller, R. Macdonald, J. Swartling, T. Svensson, S. Andersson-Engels, R. L. van Veen, H. J. Sterenborg, J. M. Tualle, H. L. Nghiem, S. Avrillier, M. Whelan, and H. Stamm, "Performance assessment of photon migration instruments: the MEDPHOT protocol," *Appl. Opt.* **44**(11), 2104–2114 (2005).
2. J. Swartling, J. S. Dam, and S. Andersson-Engels, "Comparison of spatially and temporally resolved diffuse-reflectance measurement systems for determination of biomedical optical properties," *Appl. Opt.* **42**(22), 4612–4620 (2003).

3. H. Wabnitz, D. R. Taubert, M. Mazurenka, O. Steinkellner, A. Jelzow, R. Macdonald, D. Milej, P. Sawosz, M. Kacprzak, A. Liebert, R. Cooper, J. Hebden, A. Pifferi, A. Farina, I. Bargigia, D. Contini, M. Caffini, L. Zucchelli, L. Spinelli, R. Cubeddu, and A. Torricelli, "Performance assessment of time-domain optical brain imagers, part I: basic instrumental performance protocol," *J. Biomed. Opt.* **19**(8), 086010 (2014).
4. C. Maughan Jones and P. R. T. Munro, "Development of a reliable and reproducible phantom manufacturing method using silica microspheres in silicone," *J. Biomed. Opt.* **22**(9), 1–5 (2017).
5. A. Pifferi, A. Torricelli, R. Cubeddu, G. Quarto, R. Re, S. K. Sekar, L. Spinelli, A. Farina, F. Martelli, and H. Wabnitz, "Mechanically switchable solid inhomogeneous phantom for performance tests in diffuse imaging and spectroscopy," *J. Biomed. Opt.* **20**(12), 121304 (2015).
6. R. Cubeddu, A. Pifferi, P. Taroni, A. Torricelli, and G. Valentini, "A solid tissue phantom for photon migration studies," *Phys. Med. Biol.* **42**(10), 1971–1979 (1997).
7. G. C. Beck, N. Akgün, A. Rück, and R. Steiner, "Design and characterisation of a tissue phantom system for optical diagnostics," *Lasers Med. Sci.* **13**(3), 160–171 (1998).
8. B. W. Pogue and M. S. Patterson, "Review of tissue simulating phantoms for optical spectroscopy, imaging and dosimetry," *J. Biomed. Opt.* **11**(4), 041102 (2006).
9. R. Bays, G. Wagnières, D. Robert, J. F. Theumann, A. Vitkin, J. F. Savary, P. Monnier, and H. van den Bergh, "Three-dimensional optical phantom and its application in photodynamic therapy," *Lasers Surg. Med.* **21**(3), 227–234 (1997).
10. J. Wang, J. Coburn, C. P. Liang, N. Woolsey, J. C. Ramella-Roman, Y. Chen, and T. J. Pfeifer, "Three-dimensional printing of tissue phantoms for biophotonic imaging," *Opt. Lett.* **39**(10), 3010–3013 (2014).
11. J. Larsson, P. Liao, P. Lundin, E. Krite Svanberg, J. Swartling, M. Lewander Xu, J. Bood, and S. Andersson-Engels, "Development of a 3-dimensional tissue lung phantom of a preterm infant for optical measurements of oxygen-Laser-detector position considerations," *J. Biophotonics* **11**(3), 1–8 (2018).
12. L. A. Dempsey, M. Persad, S. Powell, D. Chitnis, and J. C. Hebden, "Geometrically complex 3D-printed phantoms for diffuse optical imaging," *Biomed. Opt. Express* **8**(3), 1754–1762 (2017).
13. G. T. Kennedy, G. R. Lentsch, B. Trieu, A. Ponticorvo, R. B. Saager, and A. J. Durkin, "Solid tissue simulating phantoms having absorption at 970 nm for diffuse optics," *J. Biomed. Opt.* **22**(7), 076013 (2017).
14. C. E. Bisailon, G. Lamouche, R. Maciejko, M. Dufour, and J. P. Monchalin, "Deformable and durable phantoms with controlled density of scatterers," *Phys. Med. Biol.* **53**(13), N237–N247 (2008).
15. M. Firbank, M. Oda, and D. T. Delpy, "An improved design for a stable and reproducible phantom material for use in near-infrared spectroscopy and imaging," *Phys. Med. Biol.* **40**(5), 955–961 (1995).
16. D. Y. Diao, L. Tchivaleva, G. Dhadwal, H. Lui, D. I. McLean, and T. K. Lee, "Durable rough skin phantoms for optical modeling," *Phys. Med. Biol.* **59**(2), 485–492 (2014).
17. S. Konugolu Venkata Sekar, A. Dalla Mora, I. Bargigia, E. Martinenghi, C. Lindner, P. Farzam, M. Pagliazzi, T. Durduran, P. Taroni, A. Pifferi, and A. Farina, "Broadband (600–1350 nm) Time Resolved Diffuse Optical Spectrometer for Clinical Use," *IEEE J. Sel. Top. Quantum Electron.* **22**(3), 7100609 (2015).
18. T. Svensson, E. Alerstam, D. Khoptyar, J. Johansson, S. Folestad, and S. Andersson-Engels, "Near-infrared photon time-of-flight spectroscopy of turbid materials up to 1400 nm," *Rev. Sci. Instrum.* **80**(6), 063105 (2009).
19. D. Khoptyar, A. A. Subash, S. Johansson, M. Saleem, A. Sparén, J. Johansson, and S. Andersson-Engels, "Broadband photon time-of-flight spectroscopy of pharmaceuticals and highly scattering plastics in the VIS and close NIR spectral ranges," *Opt. Express* **21**(18), 20941–20953 (2013).
20. A. Pifferi, A. Torricelli, P. Taroni, D. Comelli, A. Bassi, and R. Cubeddu, "Fully automated time domain spectrometer for the absorption and scattering characterization of diffusive media," *Rev. Sci. Instrum.* **78**(5), 053103 (2007).
21. E. Alerstam, T. Svensson, S. Andersson-Engels, L. Spinelli, D. Contini, A. Dalla Mora, A. Tosi, F. Zappa, and A. Pifferi, "Single-fiber diffuse optical time-of-flight spectroscopy," *Opt. Lett.* **37**(14), 2877–2879 (2012).
22. S. Konugolu Venkata Sekar, A. Farina, A. Dalla Mora, C. Lindner, M. Pagliazzi, M. Mora, G. Aranda, H. Dehghani, T. Durduran, P. Taroni, and A. Pifferi, "Broadband (550–1350 nm) diffuse optical characterization of thyroid chromophores," *Sci. Rep.* **8**(1), 10015 (2018).
23. R. Cubeddu, A. Pifferi, P. Taroni, A. Torricelli, and G. Valentini, "Experimental test of theoretical models for time-resolved reflectance," *Med. Phys.* **23**(9), 1625–1633 (1996).
24. A. D. Mora, E. Martinenghi, D. Contini, A. Tosi, G. Boso, T. Durduran, S. Arridge, F. Martelli, A. Farina, A. Torricelli, and A. Pifferi, "Fast silicon photomultiplier improves signal harvesting and reduces complexity in time-domain diffuse optics," *Opt. Express* **23**(11), 13937–13946 (2015).
25. S. Konugolu Venkata Sekar, A. Farina, E. Martinenghi, A. Dalla Mora, P. Taroni, A. Pifferi, T. Durduran, M. Pagliazzi, C. Lindner, P. Farzam, M. Mora, M. Squarcia, and A. Urbano-Ispizua, "Broadband time-resolved diffuse optical spectrometer for clinical diagnostics: characterization and in-vivo measurements in the 600–1350 nm spectral range," *Proc. SPIE* **9538**, 95380R (2015).
26. S. Konugolu Venkata Sekar, J. S. Beh, A. Farina, A. Dalla Mora, A. Pifferi, and P. Taroni, "Broadband diffuse optical characterization of elastin for biomedical applications," *Biophys. Chem.* **229**, 130–134 (2017).
27. L. Di Sieno, N. G. Boetti, A. Dalla Mora, D. Pugliese, A. Farina, S. Konugolu Venkata Sekar, E. Ceci-Ginistrelli, D. Janner, A. Pifferi, and D. Milanese, "Towards the use of bioresorbable fibers in time-domain diffuse optics," *J. Biophotonics* **11**(1), 1–12 (2018).
28. D. Contini, F. Martelli, and G. Zaccanti, "Photon migration through a turbid slab described by a model based on diffusion approximation. I. Comparison with Monte Carlo results," *Appl. Opt.* **36**(19), 4587–4599 (1997).

29. R. C. Haskell, L. O. Svaasand, T. T. Tsay, T. C. Feng, M. S. McAdams, and B. J. Tromberg, "Boundary conditions for the diffusion equation in radiative transfer," *J. Opt. Soc. Am. A* **11**(10), 2727–2741 (1994).
30. A. Farina, A. Bassi, A. Pifferi, P. Taroni, D. Comelli, L. Spinelli, and R. Cubeddu, "Bandpass effects in time-resolved diffuse spectroscopy," *Appl. Spectrosc.* **63**(1), 48–56 (2009).
31. E. K. Svanberg, P. Lundin, M. Larsson, J. Åkeson, K. Svanberg, S. Svanberg, S. Andersson-Engels, and V. Fellman, "Diode laser spectroscopy for noninvasive monitoring of oxygen in the lungs of newborn infants," *Pediatr. Res.* **79**(4), 621–628 (2016).
32. L. Mei, G. Somesfalean, and S. Svanberg, "Pathlength determination for gas in scattering media absorption spectroscopy," *Sensors (Basel)* **14**(3), 3871–3890 (2014).
33. P. Lundin, E. K. Svanberg, L. Cocola, M. Lewander Xu, G. Somesfalean, S. Andersson-Engels, J. Jahr, V. Fellman, K. Svanberg, and S. Svanberg, "Noninvasive monitoring of gas in the lungs and intestines of newborn infants using diode lasers: feasibility study," *J. Biomed. Opt.* **18**(12), 127005 (2013).
34. P. Liao, J. Larsson, E. Krite Svanberg, P. Lundin, J. Swartling, M. Lewander Xu, J. Bood, and S. Andersson-Engels, "Computer simulation analysis of source-detector position for percutaneously measured O₂ -gas signal in a three-dimensional preterm infant lung," *J. Biophotonics* **11**(11), e201800023 (2018).

PAPER III

Anthropomorphic optical phantom of the neonatal thorax: a key tool for pulmonary studies in preterm infants

A. Pacheco, H. Li, M. Chakravarty, S. Konugolu, and
S. Andersson-Engels.

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Anthropomorphic optical phantom of the neonatal thorax: a key tool for pulmonary studies in preterm infants

Andrea Pacheco^{Ⓜ, a, b, *}, Haiyang Li^{Ⓜ, a}, Monisha Chakravarty,^a
Sanathana Konugolu Venkata Sekar^{Ⓜ, a} and Stefan Andersson-Engels^{Ⓜ, a, b}

^aTyndall National Institute, Biophotonics@Tyndall, Irish Photonic Integration Centre,
Lee Maltings, Dyke Parade, Cork, Ireland

^bUniversity College Cork, Department of Physics, College Road, Cork, Ireland

Abstract

Significance: Gas in scattering media absorption spectroscopy (GSMAS) is a technique for gas sensing in cavities surrounded by scattering materials. GSMAS could be translated to the clinic to monitor lung function continuously and noninvasively in neonates. Accurate tissue phantoms are essential to assess the strengths and limitations of gas spectroscopy in gas-containing cavities in the human body.

Aim: The aim is to develop a detailed protocol to produce a long-lasting, multistructure tissue phantom of the thorax of a neonate. The phantom mimics the geometry and the optical properties of the main organs of the thorax and has an empty pulmonary cavity that facilitates GSMAS monitoring of gas content.

Approach: The anatomic geometry of heart, lungs, bones, muscle, fat, and skin was obtained from a neonatal computed tomography scan. Once segmented, organs were 3D printed and used to create negative rubber molds. The entire thorax was built in phantom material (silicone as matrix, black ink as absorber, and silica microspheres as scatters) by placing all phantom organs inside the muscle structure. Our phantom recipe was customized by mixing specific ratios of ink and spheres to match the optical properties of the different organs that were considered to be homogeneous.

Results: An anthropomorphic thorax phantom with the desired optical properties (μ_a and μ_s') at 760 nm was built and used to obtain “transdermal” GSMAS measurements of oxygen content within the lung cavity.

Conclusion: A protocol to build a robust optical phantom of the thorax of a neonate was used to conduct benchtop studies. This recipe can be implemented to reproduce the geometry and optical properties of any human or animal tissue.

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Keywords: anthropomorphic optical phantom; gas spectroscopy; absorption; scattering; diffusive media.

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1 Introduction

Over the last decade, the feasibility of the clinical translation of gas in scattering media absorption spectroscopy (GSMAS) to measure the existence and concentration of gas in the human body has been pursued.¹ There are various biomedical applications for this technique, such as detection of water vapor in necrotic femoral heads,^{2,3} molecular oxygen and water vapor within the maxillary and frontal sinuses,⁴ water vapor in the intestines of neonates, and air content in the

*Address all correspondence to Andrea Pacheco, andrea.pacheco@tyndall.ie

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lungs of infants using near-infrared (NIR) spectroscopy.⁵⁻⁸ The assessment of air content in the lungs of neonates has drawn attention in the NIR spectroscopy field due to the nature of lung tissue encompassing the air-filled alveoli.

Tissue-simulating phantoms are typically used for standardization, quality control, calibration, and validation of system performance.⁹ Studies of optical tissue phantoms that closely resemble a real clinical situation are an essential step in developing novel optical technologies,^{10,11} especially for vulnerable patients such as preterm neonates. The geometry of the phantom and materials that mimics the absorption and scattering properties of human tissue are chosen according to the intended use. To accurately characterize clinical devices in biophotonics, there is a need to develop anthropomorphic phantoms that mimic both optical properties and morphological features of human organs.¹²⁻¹⁴ 3D printing techniques have been used to replicate complex anatomic structures, such as human breast.¹⁵ However, reduced scattering and absorption properties of 3D-printed phantoms are, so far, restricted to the mixing compatibility of the printing material with scattering particles and ink. Most of the 3D printers just print one material at a time, making it impossible to obtain a phantom with diverse optical properties in a single cross section.

Molding tissue layers with accurate optical properties of interest in diffuse optics has been achieved.¹⁶ However, in cases such as GASMAS studies where the focus is on respiratory health care of neonates, the phantoms must mimic properties of the main thoracic organs and facilitate gas exchange inside the lungs. This issue was solved by Larsson et al.¹⁷ who built a 3D optical phantom of the thorax of a preterm infant. The model consists of void white nylon shells ($\mu_a = 0.02 \text{ cm}^{-1}$ and $\mu_s' = 46.5 \text{ cm}^{-1}$) in the shape of skin, bone, and heart, which are filled with liquid optical phantom materials of the corresponding organs. Another void shell filled with gas has the geometry of the lungs. In this thoracic model, the high scattering of the nylon interfaces biases the propagation of light along the different organs. Typically, Intralipid-based tissue phantoms are employed. These phantoms are stable as long as the Intralipid is diluted with either purified water, demineralized water, or distilled water.¹⁸ However, liquid phantom preparations remain homogeneous for a period of hours.⁹ To reuse the solutions over many days, the storage and mixing process must be consistent and carefully conducted to ensure repeatability and homogeneity in the phantom optical properties.

We present, to the best of our knowledge, the first solid long-lasting anthropomorphic thoracic phantom with specifically defined homogeneous optical properties for different tissue structures and a pulmonary cavity that can be filled with various gas compositions. This phantom is key in the validation studies to address the clinical translation of GASMAS technology. The 3D printing and molding method presented here is, however, not limited to anthropomorphic phantoms for GASMAS measurements but is general and could be translated to mimic any part of the human body for diverse optical imaging and sensing techniques.

2 Methods

Figure 1 illustrates the workflow to construct the anthropomorphic optical phantom for the validation of the GASMAS technique, which can be used to assess the lung function in preterm

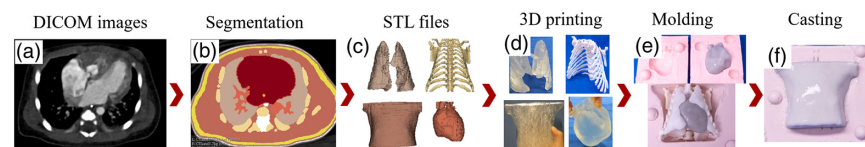


Fig. 1 Workflow to build an anthropomorphic thorax phantom with optical properties of relevant organs and empty pulmonary cavity. (a) A stack of DICOM images from a CT scan of a neonate was used for (b) segmentations of all organ types. (c) Files for 3-D printing were created for each organ by segmenting the CT image stack. (d) These files were then 3-D printed to produce resin structures. (e) Silglass mixed with silica microspheres and ink was molded to create a phantom with the specific homogenous optical properties of each organ. (f) Finally, organs were assembled to create the anthropomorphic optical phantom of the thorax of the neonate.

neonates. This procedure is applicable to any tissue volume containing several structures with various optical properties by implementing the appropriate modifications. An optical phantom of a thorax of a 3.7-kg neonate was used as an example in this paper.

Briefly, anthropomorphic computer models of the relevant organs within the thorax were created after segmenting the organs in a computed tomography (CT) scan. All geometries were 3-D printed in resin. Afterward, rubber molds of the heart, lungs, and muscle were made.

The recipe for the silicone phantoms (heart, muscle, skin, and fat) was prepared assuming the optical properties of each organ to be homogeneous. Scatters and absorbers were uniformly mixed within the silicone matrix and the characteristic μ_a and μ_s' were assigned based on the values available for each organ in literature. A solid silicone phantom with the optical properties of the heart was cast using the heart mold. This was cast along with the lungs and trachea models, which were made of coconut oil instead of silicone. The coconut oil has a liquid form when heated above 24°C; it was melted and poured in the molds. The molds containing the coconut oil were placed inside the refrigerator at 5°C for solidification. The solid structure with the pulmonary geometry enabled the correct placement of the innermost structure of the neonatal thorax (the heart), surrounded by the lungs connected to the main branches of the trachea. The parts were assembled according to the anatomy of the neonate by placing the resin bone structure around the lungs and incorporating the silicon phantom with the muscle optical properties to embed the above-mentioned organs.

Finally, two additional layers of the phantom, which match the optical properties of fat and skin, respectively, were added on top of the muscle phantom. The void pulmonary cavity required for the intended measurements was achieved by draining the coconut oil from the lungs and the main branches of the trachea. This empty chamber with the geometry of the trachea connected to the lungs can be filled with different gases for further GASMAS studies.

2.1 Segmentation: Acquisition of Organ Structure

The realistic geometry of the main organs in the thorax was achieved by segmenting Digital Imaging and Communications in Medicine (DICOM) images from a pseudoanonymized full-term female neonate (weight 3.7 kg). The segmentation was conducted by employing the NIRFAST software package, which enables the visualization of different organs recovered from overlaid 3-D standard medical images.¹⁹ The clinical indication for the CT scan was a heart dysfunction. There were 255 slices in the image for a body length of 22.3 cm. This means a z-resolution of 0.87 mm. The lateral resolution was similar. Motion artifacts were not observed in the scan, giving an accurate anatomical map of the body. The main thoracic organs (lung, trachea, muscle, bone, heart, fat, and skin) were shaded with different colors, slice by slice, until the whole geometry of each organ was color coded, as seen in Fig. 2. A computer 3-D stereo lithography (STL) file was created for each organ. The STL file for each organ was imported into Autodesk MESHMIXER software to enable smoothing. Since the files were created from a scan with coarse spatial resolution, the smoothing improved the file's resemblance to real organs.²⁰ The same software was used to increase the size of the trachea (to facilitate the removal of coconut oil content in the lung cavity) and to stitch the different segments of bone to print vertebrae, ribs, and shoulder blades as a singular structure.

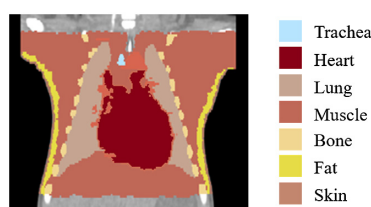


Fig. 2 Segmentation of a DICOM image from a pseudoanonymized CT scan of a neonate, where the main organs (lungs, heart, muscle, bone, fat, and skin) have been identified and color coded.

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Fig. 3 3D-printed resin structures of the organs in a neonate's thorax to be used for molding, except for the bones (in white)- which were included in the phantom.

2.2 3D Printing and Molding

The smoothed STL files of the lungs, trachea, heart, muscle, and bone were 3D printed to scale with Form 2 (commercial 3D printer from Formlabs), as shown in Fig. 3. The printer operates with a violet light curing technique using a 405-nm laser to cure the resin layer by layer with an axial resolution of 25 μm . The biggest volume that can be printed with this printer model is $145 \times 145 \times 175 \text{ mm}^3$. The dimensions of the thorax used in this study are below this limit, but for other applications, the build volume of the 3D printer can pose a constraint.

The bone structure was 3D printed in white resin from the company Formlabs. This material was characterized using a broadband time-resolved diffuse optical spectrometer, which was designed and validated to measure absorption and scattering spectra of highly diffusive media over 600 to 1350 nm.²¹ The measured absorption and reduced scattering coefficients of the resin were $\mu_a = 0.02 \text{ cm}^{-1}$ and $\mu'_s = 34.3 \text{ cm}^{-1}$, respectively; these values differ from the bone optical properties published in literature $\mu_a = 0.01 \text{ cm}^{-1}$ and $\mu'_s = 9.3 \text{ cm}^{-1}$.²² Despite these discrepancy, the bone structure was used as printed to facilitate the building of the complex thorax phantom, as it is used to keep in place the inner phantom organs.

The 3D-printed resin structures of lungs, trachea, heart, and muscle were used to create negative casting molds with Mold MaxTM 30, a two-part silicone rubber compound manufactured by Smooth-On, Inc.

For the construction of the molds, square cardboard containers were constructed according to the dimensions of the lungs, trachea, muscle, and heart. The mold was made in two parts so that the cast could be removed later. For all the aforementioned resin organs, a 1-cm-thick support made of sponge was placed on the bottom of the respective box. The resin structures were daubed by a layer of Vaseline and placed on top of the sponge. The two compounds of the rubber (silicone and hardener in a 100:10 ratio) were mixed homogeneously and poured inside the containers to cover half of the volume of the organ structures. Spherical objects were also daubed with Vaseline and fixed on the surface of the liquid rubber to cast a lock system on the edge of the rubber mold, which guaranteed that the two parts of each mold will bind and remain fixed during casting.

The containers were placed in a vacuum degassing chamber for 15 min to eliminate any entrapped air in the pourable Mold MaxTM rubber. The molds were then allowed to cure overnight (minimum 16 h) at room temperature. Afterward, the spherical objects were removed and a layer of Vaseline was spread over the cured rubber surfaces. A new mix of liquid rubber was poured on top until each of the resin structures was covered. Again, the rubber was allowed to cure overnight until the cardboard containers could be safely removed, and the two parts of each mold were pulled apart. The molding forms for casting were then completed.

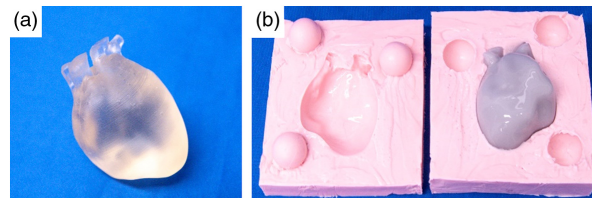
To cast the different organ phantoms, a funnel was inserted through an x-shape incision made on the upper side of the molds. The preparation of the cast was done using a phantom recipe, which uses PlatSil SiliGlass as the matrix, silica microspheres as scatters, and ink as absorbers (Table 2). In the preparation of the recipe, cylindrical slabs of identical phantom material were produced to allow characterization of the optical properties through time-of-flight

Table 1 The aimed optical properties taken from the literature at 760 nm for the different phantoms to be embodied in the thorax model.

Organ	μ_a (cm ⁻¹)	μ'_s (cm ⁻¹)
Heart ²²	0.11	4.45
Muscle ^{22,24}	0.20	12.8
Fat ²⁵	0.07	13.2
Skin (dermis) ^{22,26}	0.03	24.8
Bone ²²	0.10	9.3

Table 2 Cast volumes and quantities of scatters and absorbers used in the preparation of each organ in the phantom thorax to match the optical properties of Table 1.

Organ	Volume (± 0.05 ml)	Ink solution (± 0.05 ml)	Silica microspheres (± 0.05 g)
Heart	111.4	13.14	2.16
Muscle	608.6	43.89	30.22
Fat	53.5	5.49	5.27
Skin (dermis)	31.5	0.95	6.12
Lungs and trachea (cast with coconut oil)	195.7	—	—

**Fig. 4** (a) 3D-printed resin heart structure. (b) Molded heart phantom with realistic optical properties defined in Table 1 (gray), sitting in the respective rubber negative cast (pink).

measurements.²³ Table 1 provides the values of the aimed absorption and reduced scattering coefficients of each organ phantom for this study.

Table 2 shows the volumes of the cast organs and the respective quantities of scatters and absorbers used for the preparation of each phantom recipe.

Figure 4 shows an example of the 3D-printed resin structure for the heart (a) followed by the respective negative cast (in pink) containing a molded silicone phantom (b). The lock system created with the three spherical inclusions is clearly seen.

2.3 Thorax Reconstruction and Void Pulmonary Cavity

The complete thorax phantom was constructed by placing all the organs according to the structure of the thorax. The inner organs (heart and lung) were supported by the bone structure as can be seen in Fig. 5(a). After casting the silicone phantom with the muscle optical properties, all

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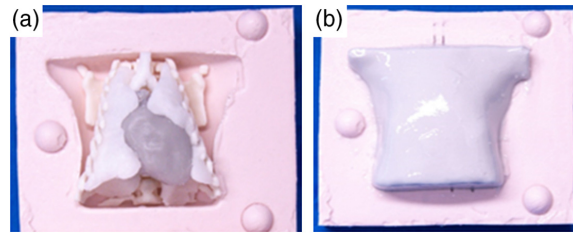


Fig. 5 (a) Phantom bone, heart, lungs, and trachea placed in the lower side of the muscle mold before the mold was closed and filled with phantom material mimicking muscle tissue. (b) The same mold after curing the muscle phantom material, where all tissues are assembled.

assembled organs fit together [Fig. 5(b)]. This is a great advantage because the path of the light inside the phantom would not be affected by the presence of boundary material among organs, solving one of the problems present in nylon phantoms.¹⁷ A phantom designed for GASMAS studies should ideally have no air pockets besides the air content cavity under study. In the case of the thoracic model, air should be present only in the pulmonary cavity. Dead space is avoided when manufacturing the phantom. Therefore, it is also a benefit for our application to ensure there are no gases outside the lung cavity within the phantom, to recreate the clinical scenario of gas presence only in the lungs of neonates.

To build the pulmonary cavity, the lungs and trachea were molded with coconut oil. After the silicone with muscle optical properties was cured, the phantom was heated above 24°C to melt the oil. The oil keeping the geometry of the trachea and lungs was poured out of a 5-mm hole pierced from the upper surface of the phantom reaching into the trachea, and the cavity was washed multiple times with acetone to remove any residual oil. This left inside the phantom an empty cavity with the correct pulmonary geometry form in which the gas composition can be measured using GASMAS technology. Two layers with fat and skin optical properties were poured over the cast muscle phantom to mimic the outer tissues of the thorax.

2.4 GASMAS Measurements for Phantom Validation

GASMAS is a nonimaging technique used to sense gas enclosed in a bulk scattering media. It exploits the differences in the features of absorption spectra between gases and condensed matter (liquid and solid) such as the width of the absorption bands, which are many orders of magnitude broader for condensed matter compared to gases, typically in the order of 10 nm for tissue versus 0.001 nm for gases. In a typical GASMAS measurement, the walls of the bulk material are illuminated and the light scatters into the gas cavity. Photons scattered back from the gas cavity are sensed with a photodetector placed over the bulk surface either in remittance or transmission geometry.¹

The absorption signal from the gas is identified from the detected light intensity and the Beer–Lambert law is used to calculate the concentration of the gas. The Beer–Lambert law states that the intensity of the light (I), propagating through a gas with concentration (c) and along an optical path length (l), decays in an exponential way. The strength of the absorption also depends on the absorption cross section of the gas (ϵ), which is specific for each gas and the transition chosen for the absorption measurement.

$$I = I_0 e^{-\epsilon c l}.$$

In cases where the aim is to measure the gas concentration and the optical path length is unknown, a dual-laser source system is used to interrogate a reference gas (present in the same cavity) with known concentration. This can be done only if the wavelengths used to interrogate each of the gases are close enough to assume that the path lengths are the same.²⁷

MicroLab Dual O₂/H₂O is a GASMAS benchtop system produced by GASPOROX AB. This system has two diode lasers that sense oxygen (760 nm) and water vapor (820 nm). The wavelengths were chosen to be spectrally close so the absorption lines have a similar

distribution of the light, and the absorption signal from water vapor can be used for normalization. Water vapor is used as a reference gas. Its concentration at a given temperature is calculated using the Arden Buck equation for a given temperature.²⁸ Consequently, a value for the path length is obtained and used to estimate the oxygen concentration.

When measuring with the MicroLab Dual, both laser wavelengths are scanned across the absorption lines of oxygen (760 nm) and water vapor (820 nm) by alternating the respective currents. A light intensity dip is detected due to the absorption of the gas molecules present between the light source and the detector. The detection is improved using wave modulation spectroscopy (WMS), which generates as output the characteristic WMS amplitude signal in a GASMAS experimental set up.⁵

3 Results

We present an anthropomorphic phantom with the structure of the thorax of a neonate. The multiple organs were made of homogeneous phantom material, considering that each organ constitutes a single tissue type. In this case, we are not taking into account the presence of multiple structures in any human body organ, such as arteries, collagen, etc. The obtained optical properties of the different organs at 760 nm of the phantom built for this study are listed in Table 3. The measurements of the recipe were performed with three repetitions and the coefficient of variation (CV) was found to be less than 3%.²³ The white resin used to 3D print the bone structure was 50 times less absorptive and 3 times more scattering than human bone. The rigid bone structure is needed to keep the phantom organs in place when curing the muscle, which simplifies the thorax building process and avoids the need for additional support structures.

The presence and concentration of molecular oxygen inside a reference box and the phantom was measured with MicroLab Dual O₂/H₂O.

The dashed plot in Fig. 6(c) corresponds to the oxygen absorption imprint of the gas inside a 3-cm-width hollowed reference box in transmission geometry [Fig. 6(a)]. A signal with a similar characteristic absorption peak of oxygen was also obtained using the anthropomorphic phantom in remittance geometry [Fig. 6(b)]. The thicknesses of the thorax wall (between the skin layer and lung cavity) where the source and detector are placed are 6.4 and 19.3 mm, respectively. The plots of gas absorption correspond to the room oxygen present inside the box and phantom cavity. Transparent ultrasound gel was placed between the box and phantom surfaces and the probes (light source and detector) to ensure that the measured oxygen absorption signal corresponded to the gas inside the cavities.

A set of 10 measurements was taken with the reference box in transmission geometry (22.5°C) and with the phantom in remittance geometry (23.2°C), giving average oxygen concentrations of 19.2 % and 18.8%, with standard deviations of 0.01 and 0.03, respectively. Hence, we demonstrate the potential use of these realistic phantoms for quality control and validation of the GASMAS technique.

Table 3 Optical properties of the organs at 760 nm embodied in the realistic thorax phantom. (The CV of these values is <3%.)

Organ	μ_a (cm ⁻¹)	μ'_s (cm ⁻¹)
Heart	0.110 ± 0.003	4.45 ± 0.09
Muscle	0.200 ± 0.005	12.8 ± 0.3
Fat	0.070 ± 0.002	13.2 ± 0.3
Skin (dermis)	0.030 ± 0.001	24.8 ± 0.5
Bone (white resin)	0.020 ± 0.001	34.3 ± 1.4

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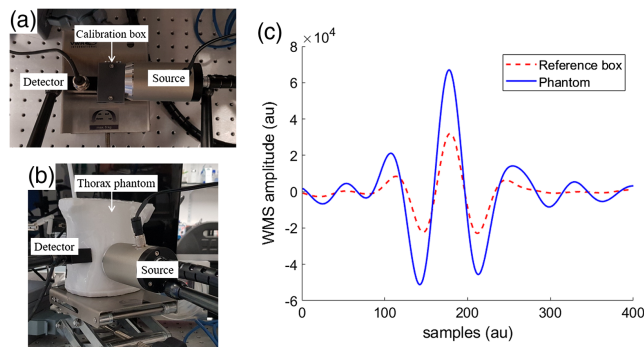


Fig. 6 (a) MicroLab Dual O₂/H₂O system with light source and detector placed on both sides of a reference box in transmission geometry. (b) MicroLab Dual O₂/H₂O system with light source and detector placed over the thorax of the realistic phantom in remittance geometry used to sense the absorption signal of oxygen. (c) WMS amplitude signals produced by the absorption of molecular oxygen inside a reference box and the optical thorax phantom in transmittance and remittance geometry, respectively.

4 Discussion and Conclusion

A protocol to build an anthropomorphic phantom of the thorax of a neonate is presented. The phantom includes the geometrical structures of heart, muscle, fat, and skin together with the respective realistic homogeneous optical properties. If a different wavelength is chosen to perform future studies, a phantom recipe with different concentrations of scatters and absorbers can be prepared to cast another thorax phantom matching the optical properties of biological tissue at that wavelength. The geometry can be replicated reusing the organ molds from this study.

The multiple fine structures present in each organ, such as arteries and blood vessels, are not included. Each phantom organ is built with homogeneous optical properties.

The mismatch of optical properties of human bone and those of the bone structure of the phantom could be solved using a different 3D-printing material suitable for customized optical properties. One can also use a mold and cast the bone structure with the aimed optical properties with a material that is mechanically harder than SiliGlass, so the bone structure can still be used to keep the inner organs in place during the casting of the muscle tissue structure.

The experimental studies performed with this phantom resemble a simplified model of light propagation through the thorax of a neonate with gas absorption in the pulmonary cavity. The feasibility to conduct phantom studies with the MicroLab Dual O₂/H₂O GASMAS benchtop system has been proven, raising the possibility to perform transdermal spectroscopy measurements of oxygen concentration inside the lung cavity of the phantom in a controlled environment. To the best of our knowledge, there is not an easy way to produce a phantom that accurately mimics simultaneously the absorption and scattering properties of human tissue at more than one wavelength. To perform further studies with the MicroLab Dual O₂/H₂O GASMAS system, which operates with a dual source at 760 and 820 nm, we propose to build two geometrically identical phantoms, each with the optical properties matching the tissue at one of these wavelengths. Such studies constitute an important step in developing a lung function-monitoring technique for a vulnerable group of patients in the need for better tools in respiratory health care.

Further studies involving the injection of oxygen gas mixed with nitrogen and carbon dioxide in different concentrations inside the pulmonary cavity would be key to define the limitations of GASMAS technology in the development of a bedside clinical device for lung function assessment in neonates.

This recipe can be implemented to reproduce the 3D geometry and optical properties of any DICOM image file with multiple volumes from human or animal organ. As mentioned in Sec. 2.2, the only constraint is the maximum volume of the 3D printer, which is used to produce the solid physical models of the organs of interest. Even though PlatSil SiliGlass was chosen as

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the matrix for the phantom material in this study, other suitable phantom materials such as Sylgard might produce similar results as long as the pertinent changes are made with the curing requirements of the material.²⁹

The present work opens a wide range of possibilities for complementary validation and standardization of diverse optical imaging systems and sensing techniques prior to prototyping of systems for clinical translation. Such phantoms may also be used to reduce some preclinical and clinical studies in the development of new photonics-based instruments or techniques.

Disclosures

Three authors (Andrea Pacheco, Haiyang Li, and Monisha Chakravarty) certify that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this paper. Sanathana Konugolu Venkata Sekar and Stefan Andersson-Engels are both engaged in the spin-off company BioPixS founded 2020.

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References

1. S. Svanberg, "Gas in scattering media absorption spectroscopy—from basic studies to biomedical applications," *Laser Photonics Rev.* **7**(5), 779–796 (2013).
2. H. Lin et al., "Diagnostics of femoral head status in humans using laser spectroscopy—in vitro studies," *J. Biophotonics* **10**, 1356–1364 (2017).
3. D. Chen et al., "Laser-based gas absorption spectroscopy in decaying hip bone: water vapor as a predictor of osteonecrosis," *J. Biomed. Opt.* **24**(6), 1–6 (2019).
4. L. A. Persson et al., "Gas monitoring in human sinuses using tunable diode laser spectroscopy," *J. Biomed. Opt.* **12**(5), 054001 (2007).
5. P. Lundin et al., "Noninvasive monitoring of gas in the lungs and intestines of newborn infants using diode lasers: feasibility study," *J. Biomed. Opt.* **18**(12), 127005 (2013).
6. E. K. Svanberg et al., "Diode laser spectroscopy for noninvasive monitoring of oxygen in the lungs of newborn infants," *Pediatr. Res.* **79**(4), 621–628 (2016).
7. P. Lundin et al., "Non-invasive gas monitoring in newborn infants using diode laser absorption spectroscopy: a case study," *Proc. SPIE* **8229**, 822903 (2012).
8. M. Lewander et al., "Nonintrusive gas monitoring in neonatal lungs using diode laser spectroscopy: feasibility study," *J. Biomed. Opt.* **16**(12), 127002 (2011).
9. B. W. Pogue and M. S. Patterson, "Review of tissue simulating phantoms for optical spectroscopy, imaging and dosimetry," *J. Biomed. Opt.* **11**(4), 041102 (2006).
10. Q. Zhang and H. Jiang, "Three-dimensional diffuse optical imaging of hand joints: system description and phantom studies," *Opt. Lasers Eng.* **43**, 1237–1251 (2005).
11. A. Godavarty et al., "Diagnostic imaging of breast cancer using fluorescence-enhanced optical tomography: phantom studies," *J. Biomed. Opt.* **9**(3), 488–496 (2004).
12. L. A. Dempsey et al., "Geometrically complex 3D-printed phantoms for diffuse optical imaging," *Biomed. Opt. Express* **8**(3), 1754–1762 (2017).
13. Y. Liu et al., "Biomimetic 3D-printed neurovascular phantoms for near-infrared fluorescence imaging," *Biomed. Opt. Express* **9**(6), 2810–2824 (2018).
14. P. Diep et al., "Three-dimensional printed optical phantoms with customized absorption and scattering properties," *Biomed. Opt. Express* **6**(11), 4212–4220 (2015).
15. N. Kiarashi et al., "Development of realistic physical breast phantoms matched to virtual breast phantoms based on human subject data," *Med. Phys.* **42**, 4116 (2015).

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16. V. O. Korhonen et al., "Light propagation in NIR spectroscopy of the human brain," *IEEE J. Sel. Top. Quantum Electron.* **20**(2), 289–298 (2014).
17. J. Larsson et al., "Development of a 3-dimensional tissue lung phantom of a preterm infant for optical measurements of oxygen—laser-detector position considerations," *J. Biophotonics* **11**, e201700097 (2018).
18. P. Di Ninni et al., "Intralipid: towards a diffusive reference standard for optical tissue phantoms," *Phys. Med. Biol.* **56**, N21–N28 (2011).
19. H. Dehghani et al., "Near infrared optical tomography using NIRFAST: algorithm for numerical model and image reconstruction," *Int. J. Numer. Methods Biomed. Eng.* **25**(6), 711–732 (2009).
20. T. M. Bücking et al., "From medical imaging data to 3D printed anatomical models," *PLoS One* **12**(5), e0178540 (2017).
21. S. K. V. Sekar et al., "Broadband (600–1350 nm) time-resolved diffuse optical spectrometer for clinical use," *IEEE J. Sel. Top. Quantum Electron.* **22**(3), 406–414 (2016).
22. S. L. Jacques, "Optical properties of biological tissues: a review," *Phys. Med. Biol.* **58**(11), R37–R61 (2013).
23. S. K. V. Sekar et al., "Solid phantom recipe for diffuse optics in biophotonics applications: a step towards anatomically correct 3D tissue phantoms," *Biomed. Opt. Express* **10**(4), 2090–2100 (2019).
24. R. Re et al., "Time domain near infrared spectroscopy device for monitoring muscle oxidative metabolism: custom probe and *in vivo* applications," *Sensors* **18**(1), 264 (2018).
25. R. L. P. van Veen et al., "Determination of VIS-NIR absorption coefficients of mammalian fat, with time- and spatially resolved diffuse reflectance and transmission spectroscopy," in *Biomed. Top. Meeting*, Optical Society of America, Miami Beach, Florida (2004).
26. N. Choudhury, R. Samatham, and S. L. Jacques, "Linking visual appearance of skin to the underlying optical properties using multispectral imaging," *Proc. SPIE* **7548**, 75480G (2010).
27. S. Svanberg, "Gas in scattering media absorption spectroscopy," *Proc. SPIE* **7142**, 714202 (2008).
28. A. L. Buck, "New equations for computing vapor pressure and enhancement factor," *J. Appl. Meteor.* **20**, 1527–1532 (1981).
29. C.-É. Bisaillon, M. L. Dufour, and G. Lamouche, "Artery phantoms for intravascular optical coherence tomography: healthy arteries," *Biomed. Opt. Express* **2**(9), 2599–2613 (2011).

Andrea Pacheco is PhD student of the Biophotonics team at Tyndall National Institute (Cork, Ireland). She received her BS and MS degrees in physics from the Universidad Nacional de Colombia (Bogota) in 2013 and 2016, respectively. Her current research interests include optical phantoms for diffuse optics, gas spectroscopy, applied optics, and clinical translation of photonics-based technologies. She is an active member of SPIE and OSA, and cofounder of the Tyndall and University College Cork OSA/SPIE student chapter.

Haiyang Li was a post-doctoral researcher in the Biophotonics team at Tyndall National Institute, Cork, Ireland, from 2017 to 2018, after earning his PhD in electrical engineering from the University College Cork. Currently, he is an associate professor in the School of Mechanical Engineering and Automation at Northeastern University, China. His research interests include synthesis, modeling, and optimization and control of compliant mechanisms and robots.

Monisha Chakravarty is a medical student at the University College Cork. She received her BSc degree in biomedical science from the University College Cork/Cork Institute of Technology in 2018. She joined the Biophotonics team at Tyndall National Institute, under the guidance of Professor Andersson Engels and Andrea Pacheco, to gain experience in the field of photonics and its uses with medicine. Her current research interests include bile acid receptors and their link to cardiovascular disease.

Sanathana Konugolu Venkata Sekar is a researcher in BioPhotonics@Tyndall, and also CEO and cofounder of the BioPixS-Biophotonics Standards company. He got his PhD in biophotonics from Politecnico di Milano, Milan, Italy. His current area of research and interests are

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upconverting nanoparticles for deep tissue imaging and optogenetics applications, gas in scattering media absorption spectroscopy for infant lung vitals monitoring, TDDOS, Raman spectroscopy, probes, and entrepreneurial activities in biophotonics. He is the vice-chair at OSA TG, organizer, seasonal moderator, and rapporteur at international panel/conferences.

Stefan Andersson-Engels received his MSc degree in physics in 1985 and PhD in 1990 from Lund University. He was a postdoc at McMaster University in Canada 1990 to 1991 and became a full professor at Lund University in 1999. In 2016, he was recruited as the head of Biophotonics at Tyndall National Institute and is a deputy director of the IPIC Centre. His research interests include tissue optics and applications of light in biomedical diagnostics and treatments.

PAPER IV

Lung tissue phantom mimicking pulmonary optical properties, relative humidity, and temperature: a tool to analyze the changes in oxygen gas absorption for different inflated volumes

Andrea Pacheco, Konstantin Grygoryev, Walter Messina, and Stefan Andersson-Engels.

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Lung tissue phantom mimicking pulmonary optical properties, relative humidity, and temperature: a tool to analyze the changes in oxygen gas absorption for different inflated volumes

Andrea Pacheco^{a,b,*}, Konstantin Grygoryev,^a Walter Messina,^a
and Stefan Andersson-Engels^{a,b}

^aBiophotonics@Tyndall, IPIC, Tyndall National Institute, Lee Maltings,
Dyke Parade, Cork, Ireland

^bUniversity College Cork, Department of Physics, Cork, Ireland

Abstract

Significance: Gas in scattering media absorption spectroscopy (GASMAS) enables noninvasive gas sensing in the body. It is developing as a tool for diagnosis and monitoring of respiratory conditions in neonates. Phantom models with relevant features to the clinical translation of GASMAS technology are necessary to understand technical challenges and potential applications of this technique. State-of-the-art phantoms designed for this purpose have focused on the optical properties and anthropomorphic geometry of the thorax, contributing to the source–detector placement, design, and optimization. Lung phantom mimicking the alveolar anatomy has not been included in the existent models due to the inherent complexity of the tissue. We present a simplified model that recreates inflated alveoli embedded in lung phantom.

Aim: The goal of this study was to build a lung model with air-filled structures mimicking inflated alveoli surrounded by optical phantom with accurate optical properties ($\mu_a = 0.50 \text{ cm}^{-1}$ and $\mu'_s = 5.4 \text{ cm}^{-1}$) and physiological parameters [37°C and 100% relative humidity (RH)], and to control the air volume within the phantom to demonstrate the feasibility of GASMAS in sensing changes in pulmonary air volume.

Approach: The lung model was built using a capillary structure with analogous size to alveolar units. Part of the capillaries were filled with liquid lung optical phantom to recreate scattering and absorption, whereas empty capillaries mimicked air filled alveoli. The capillary array was placed inside a custom-made chamber that maintained pulmonary temperature and RH. The geometry of the chamber permitted the placement of the laser head and detector of a GASMAS bench top system (MicroLab Dual $\text{O}_2/\text{H}_2\text{O}$), to test the changes in volume of the lung model in transmittance geometry.

Results: The lung tissue model with air volume range from $6.89 \times 10^{-7} \text{ m}^3$ to $1.80 \times 10^{-3} \text{ m}^3$ was built. Two measurement sets, with 10 different capillary configurations each, were arranged to increase or decrease progressively (in steps of $3.93 \times 10^{-8} \text{ m}^3$) the air volume in the lung model. The respective GASMAS data acquisition was performed for both data sets. The maximum absorption signal was obtained for configurations with the highest number of air-filled capillaries and decreased progressively when the air spaces were replaced by capillaries filled with liquid optical phantom. Further studies are necessary to define the minimum and maximum volume of air that can be measured with GASMAS-based devices for different source–detector geometries.

Conclusions: The optical properties and the structure of tissue from the respiratory zone have been modeled using a simplified capillary array immersed in a controlled environment chamber at pulmonary temperature and RH. The feasibility of measuring volume changes with GASMAS technique has been proven, stating a new possible application of GASMAS technology in respiratory treatment and diagnostics.

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*Address all correspondence to Andrea Pacheco, andrea.pacheco@tyndall.ie

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Keywords: lung phantom; gas spectroscopy; inflated volume; alveolar structure.

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1 Introduction

The translation of light-based technologies into the clinic has been growing over the past decades. Biophotonics tools are starting to account for a larger proportion of next-generation diagnostic and therapeutic modalities, given that they provide information of tissue functionality and composition with minimal invasiveness. One of the major challenges in advancing biophotonics-based medical devices is transforming signals into useful information that can assist the clinicians in the treatment and diagnosis of diseases.¹ In this work, we contribute to the understanding of a potential application of an existent light-based technology for localized air volume assessment in lung tissue.

1.1 Respiratory Physiology and Clinical Relevance of Pulmonary Volumes

The respiratory system consists of conducting and respiratory airways (Fig. 1). The conducting airways lack alveoli and take no part in gas exchange. Their main function is to conduct, clean, heat up, and humidify the air to 37°C and 100% relative humidity (RH) as it reaches the alveolar sacks.² The respiratory airways make up most of the lung and is the region where gas exchange occurs, and it is composed by millions of alveoli (~0.3 mm in diameter each).³

The pulmonary gas volume is constantly changing during respiration. The four standard volumes corresponding to different degrees of inhalation or exhalation are classified as: tidal volume (amount of gas that can be inhaled or exhaled during a respiratory cycle; normal breathing); inspiratory reserve volume (the maximum amount of gas that can be inhaled beyond the normal tidal volume; deep breathing); expiratory reserve volume (volume of gas that can be exhaled by force beyond exhalation of the normal tidal volume); and residual volume (volume of gas that remains in the lung after maximal expiration). To assess and diagnose obstructive and restrictive pathologies, the measurement of respiratory volumes is of clinical importance.⁴

1.2 Gas in Scattering Media Absorption Spectroscopy

Gas in scattering media absorption spectroscopy (GSMAS) is a gas spectroscopy technique that uses tunable diode laser spectroscopy to measure the concentration of gases enclosed by diffuse media in a noninvasive way.⁵ The clinical applications of GSMAS include: assessment of infection in paranasal sinuses,⁶ diagnosis of otitis,⁷ early diagnosis of osteonecrosis,⁸ and monitoring of oxygen (O₂) and water vapor (H₂O) in the lungs of neonates.^{9–12} The studies advancing the clinical translation of GSMAS into respiratory healthcare have focused on

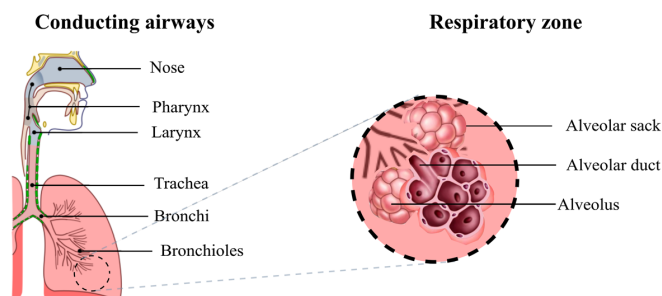


Fig. 1 Diagram of the respiratory airways. The conducting airways warm up and moisten the inhaled air, the gas exchange occurs in the respiratory zone where the alveoli are located.

neonates as the thickness of protective organs surrounding their lungs is within the limits of penetration depth for near-infrared light.^{13,14}

GASMAS exploits the fact that the absorption signal of gases is unique against the tissue background. The absorption bands of O₂ and H₂O are typically 0.001 nm,¹⁵ which can be distinguished from the absorption imprint of the organs around the lungs (both liquid and solid), which is generally in the 10 nm range.¹⁶ In clinical studies, the thoracic walls are illuminated with a diffuse source, and the scattered light reaching a photodetector is used to identify the absorption signal of molecular O₂, by means of the Beer–Lambert law equation, which states that the concentration of the gas c can be calculated from the absorbance (logarithm of the ratio of the source light intensity I_0 to detected intensity I) when the molar absorption $[e(\lambda)]$ and the gas absorption path length (l)¹⁷ are known:

$$I = I_0 e^{-ec l}. \quad (1)$$

In the case of gas assessment in the lung, the thorax is illuminated with two wavelengths chosen to minimize the absorption by tissue:¹² tunable diode lasers operating at 760 nm are typically selected to match the absorption bands of O₂, and 820 or 935 nm to match absorption of H₂O. The last is used as reference gas. Since temperature and RH of the lungs are well known, the concentration of H₂O is calculated using the ideal gas law, with the partial pressure computed by means of the Arden Buck equation, which states that the partial pressure of vapor saturation in moist air (e'_w) at ambient temperature T and pressure P is given as¹⁸

$$e'_w = [1.0007 + (3.46 \times 10^{-6} P)] \times 6.1121 \exp \left[\frac{17.502 T}{240.97 + T} \right]. \quad (2)$$

The Beer–Lambert law is applied to the H₂O absorption spectra to estimate l inside the lung. Consequently, the calculated value of l is input into Eq. (1) together with the absorption signal at 760 nm to estimate the O₂ concentration. This gas absorption path length approximation is valid for wavelengths that are spectrally close and interacting with identical media.¹⁹

The lung volume assessment is currently done using spirometry, flow volume curves, and/or plethysmography. However, these tests do not provide information of localized volume changes and patients are asked to make inspiratory and expiratory manoeuvres for volume assessment to be performed.²⁰ This represents a limitation in measuring the pulmonary volumes in neonates or patients under anesthesia. GASMAS can potentially solve such limitations given that the light absorbance depends on l , which is directly proportional to gas volume.

In this study, we prove the feasibility of measuring changes in gas volume using GASMAS technology. The absorption imprint of molecular O₂ was acquired using a pulmonary phantom model that includes air pockets mimicking the size, temperature, and RH of alveoli, surrounded by liquid phantom matching absorption and scattering of lung tissue.

2 Methods

2.1 Construction of Lung Tissue Phantom

The phantoms previously created to investigate the clinical application of GASMAS in neonatal respiratory healthcare had a hollow cavity with the outer geometry of the lung without the inner structure mimicking the alveolar anatomy.^{21,22} The phantom designed in this study recreated inflated alveoli surrounded by lung tissue.

The simplified pulmonary model required a three-dimensional (3D) rectangular holder ($0.025 \times 0.014 \times 0.035$ m), printed with clear resin (RS-F2-GPCL-04 Formlabs, Form 2) filled with a set of 229 glass capillaries (maximum amount of capillaries that fit in the holder forming a gridded array) of 0.25×10^{-3} m inner radius and 125×10^{-3} m length (SIGMA, batch Z114952). A fraction of the capillaries was filled with air (mimicking the alveoli) and the remaining capillaries were filled with liquid optical phantom of lung tissue ($\mu_a = 0.50 \text{ cm}^{-1}$ and $\mu'_s = 5.4 \text{ cm}^{-1}$, see Sec. 2.1).¹⁶ The number of capillaries filled with liquid phantom was altered and distributed randomly to reduce or increase the amount of air in the probed volume.

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To perform the measurements, the capillary array was enclosed in a controlled environment chamber (designed to fit the source and detector of a GASMAS bench top system), keeping the temperature and RH (see Sec. 1.1).

2.2 Preparation of Liquid Phantom with Optical Properties of Lung Tissue

The optical properties of lung tissue at 760 nm were assigned by filling the capillaries with liquid phantom. To produce 100 ml phantom, 8.5 ml of intralipid (SIGMA, Lot # MKCL8461) was mixed with 1.5 ml of stock ink-water solution (1% Winsor & Newton® black India ink diluted in 99 % distilled water) and 90 ml distilled water. The g -factor was defined by the scattering of intralipid $g = 0.6$,²³ and the optical properties were determined using the fiber optic probe system based on diffuse reflectance and diffuse spectroscopy from Ref. 24.

The capillary tubes used to mimic lung absorption and scattering were filled using capillary action. In some cases, air bubbles prevented the rising of the liquid in the tube, which was solved by gently tapping on the external side of the tube. The top end of the tubes was then sealed with starch-based modeling clay (Play-Doh) to prevent leakage during measurements.

The liquid phantom and air-filled capillaries were then randomly placed by hand into the holder to make up the capillary arrays for absorption measurements. The probed air volume was changed by varying the ratio of air-filled capillaries in the array (Sec. 3.2).

2.3 Chamber for Controlled Environment, Mimicking Lung Relative Humidity, and Temperature

Figure 2 shows the diagram of all the components used in the lung model. An enclosure with temperature and RH control was built using 12-mm thick acrylic sheets (Blarney Trading, Cork, Ireland). The overall dimensions of the enclosure were $0.28 \times 0.22 \times 0.20$ m ($L \times H \times W$). The temperature was controlled using a heater (50W, STEGO, Radionics Ireland) and a thermostat (Schneider Electric, Radionics Ireland) set to 37°C. To help maintain the temperature in the

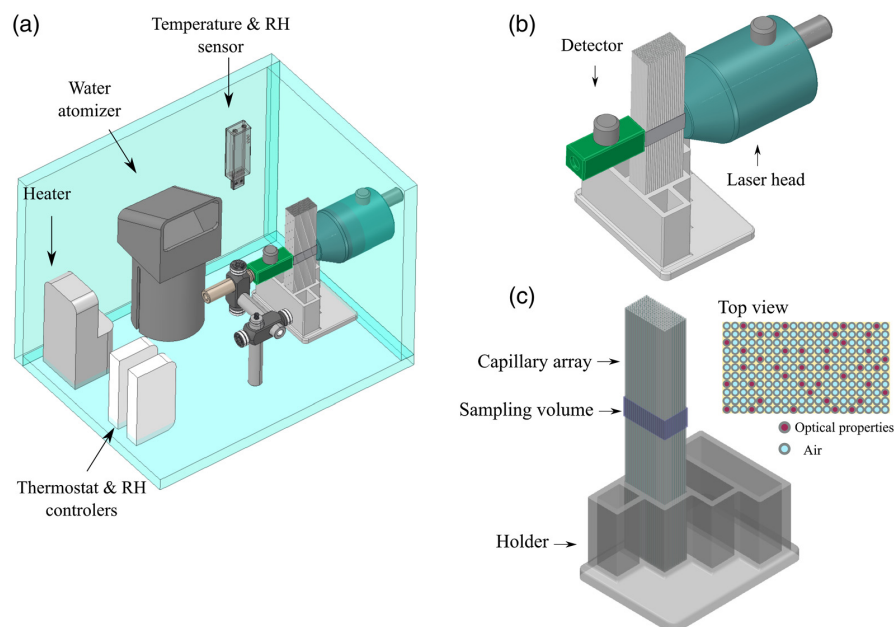


Fig. 2 (a) Diagram of the experimental set up designed to study the variations in GASMAS signal for different gas volumes in the lung tissue phantom. (b) Zoom in of source and detector placement in transmittance geometry. (c) The capillary array placed in the 3D printed holder, the sampling volume was defined by the size of light source and detector and the length of the capillary array.

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enclosure, the outer walls were covered with 0.3-m thick panels of expanded polystyrene foam. The RH was controlled via a generic fish tank water atomizer coupled to a humidity meter (Schneider Electric, Radionics Ireland) set to 90% RH (maximum range in the controller settings). The atomizer was placed inside a 200-ml Pyrex beaker filled with 50 ml of tap water. To prevent large drops of water being ejected from the beaker by the atomizer, an in-house 3D-printed catch lid was installed into the beaker. Both temperature and RH were monitored using a digital sensor (TSP01, ThorLabs). An opening was drilled in one of the walls of the enclosure for the dual laser head of the MicroLab Dual O₂/H₂O (see Sec. 3.1). The detector was mounted inside the enclosure on adjustable posts (RA90/M and TR75V/M, ThorLabs) and positioned directly in front of the source, to measure the gas content in the capillary array.

The capillary array was placed between the source and detector in transmission geometry. The long walls of the capillary array were masked with a black film, and the contact surfaces between the capillaries and the system source and detector were daubed with ultrasound gel, to prevent light absorption by the gas outside the capillary tubes.

3 GASMAS Measurements

3.1 MicroLab Dual O₂/H₂O

The GASMAS bench top system used in this study was MicroLab Dual O₂/H₂O (GASPOROX AB). The system was equipped with a dual diode laser source operating at 760 and 820 nm as well as a photodetector with 1×10^{-4} m² area. The values of temperature (taken with the Thorlabs probe) and room pressure (1.007 Atm) were input to the system prior to data acquisition.

One wall of the capillary array was illuminated using the 760- and 820-nm lasers. During the illumination, each laser scanned across the absorption lines of O₂ (760 nm) and H₂O (820 nm). The scattered light was collected by the detector placed on the opposite side of capillary array. The system employed wave modulation spectroscopy (WMS) to increase the detection sensitivity of O₂ and H₂O. To use this method, the detection band of each gas was modulated to higher frequencies (in the kilohertz range). Simultaneously, the laser wavelength was scanned across the gas absorption line, generating high harmonics of the absorption signal and suppressing the background noise. The characteristic output of this instrument was the amplitude signal obtained by WMS, which was used to detect the proportional light intensity dip for each wavelength.

3.2 Air Volumes to Test in the Pulmonary Phantom Model

The sampling air volume was defined by the dimensions of the diffuse light source and detector (0.01×0.005 m and 0.01×0.01 m, respectively) and the length of the capillary array (0.025 m) as shown in Fig. 2(c). The air volume between the capillaries (6.89×10^{-7} m³), constant to all measurements, was calculated by subtracting the total volume occupied by 229 capillaries (2.81×10^{-6} m³) from a cube with the dimensions of the analyzed volume (3.5×10^{-6} m³).

An alveolar unit holds $\sim 1.41 \times 10^{-8}$ m³ of air, assuming a spherical geometry. The air content of a single capillary in our model contained 1.96×10^{-9} m³ of air. The model could hold a maximum of 3.5×10^{-6} m³ of air within the sampling volume, analogous to a group of alveolar sacks with at least 250 inflated alveoli. The radius of the capillaries used in this study was in agreement with the physiological radius of an alveolar unit. Despite the cylindrical geometry, the air volumes were comparable with those of pulmonary tissue and the lung model made possible to recreate progressive changes in volume during respiration in a pulmonary section.

The test set 1 started with all the capillaries empty, and the absorption signal was measured 10 times. For each acquisition, the MicroLab Dual O₂/H₂O system averaged the absorption imprints from O₂ and H₂O over 10 s. The air content between source and detector was reduced by replacing (and allocating randomly by hand) 20 empty capillaries with those filled with liquid phantom, followed by the respective data acquisition. This process was repeated 10 times until a total of 200 capillaries were filled with lung tissue phantom and remaining 29 filled with air, as shown in Table 1. In the test set 2, the inverse process was done. It started with all capillaries

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Table 1 Air volumes in the capillary lung model conformed by 229 capillaries in total and a constant air space of $6.89 \times 10^{-7} \text{ m}^3$.

Test set 1: Air volume progressively reduced		Test set 2: Air volume progressively increased	
Capillaries filled with lung liquid phantom	Volume of air tested ($\times 10^{-6} \text{ m}^3$)	Capillaries filled with air	Volume of air tested ($\times 10^{-6} \text{ m}^3$)
0	1.14	0	0.69
20	1.10	20	0.73
40	1.06	40	0.77
60	1.02	60	0.81
80	0.99	80	0.85
100	0.94	100	0.89
120	0.90	120	0.93
140	0.86	140	0.97
160	0.83	160	1.00
180	0.77	180	1.04
200	0.75	200	1.08

filled with optical properties and a progressive increment in air volume of 20 capillaries at a time followed by the data acquisition. The process was repeated until a total of 200 empty and 29 capillaries filled with liquid phantom were placed in the holder.

4 Results and Discussion

The path length in GASMAS measurements correspond to the effective path that light travels inside the gas cavities where the absorption dominates over scattering. The surrounding bulk material (in this case the liquid phantom) attenuates the amount of light reaching the detector. The augmentation of liquid phantom-filled capillaries within the measurement sets increased the light diffusion within the phantom and at the same time reduced the number of gas cavities. The absorption path length in highly diffuse materials, such as biological tissue, is unknown. In this study, the gas concentration of H_2O was known, enabling the retrieval of the gas absorption path length (see Sec. 1.2), which was assumed to be the same for molecular O_2 .

The absorption signals acquired for the test set 1 are shown in Fig. 3(a), the dashed line corresponds to the capillary array with 100 units filled with optical phantom and 129 with air. The observed level of absorption resembled a condition where the air volume was larger than the maximum capacity of the sampling volume. For this reason, the measurements from that configuration were omitted from data analysis as shown in Fig. 3(b). The absorption signals from the second test set are plotted in Fig. 3(c).

According to Eq. (1), the absorptivity increases proportionally to the gas absorption path length, this is corroborated by the signals plotted in Figs. 3(b) and 3(c), which exhibit highest absorption for the arrays with maximum air volume, followed by a decrease in the absorption signal as the capillaries filled with optical phantom reduced the air volume. The O_2 concentration calculated during the first test set was 26.3% (SD = 2.3%) compared with 25.4% (SD = 2.9%) from the second test set.

The peak values of the absorption signals for sets 1 and 2 are plotted as a function of the number of capillaries filled with optical phantom in Fig. 4(a). As previously stated, the observed decreasing absorption peak trend was in agreement with decreasing volume of oxygen versus the gas absorption path lengths. The light transmission for the configurations that included a number

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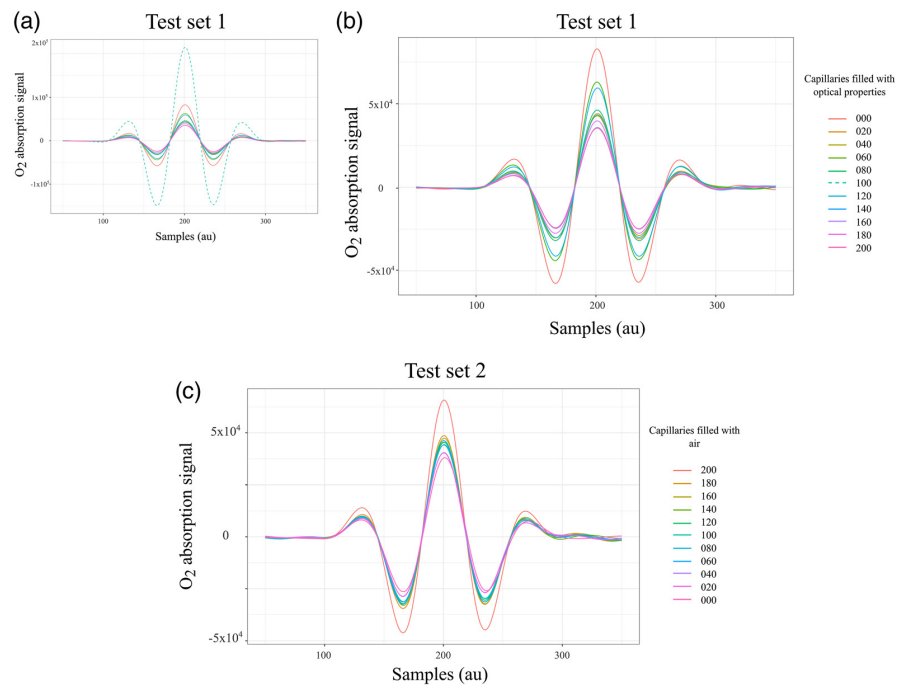


Fig. 3 WMS amplitude signals that correspond to the absorption of molecular oxygen tested in the lung model in transmittance geometry. (a) Complete test set 1, the acquisition started with all capillaries filled with air followed by a progressive reduction of air volume. The dashed line exhibits higher absorption compared with the absorption of the maximum sampling volume, therefore these data were removed in (b) for the analysis. (c) Signals from test set 2, the acquisition started with all capillaries filled with optical properties followed by a progressive increase of air volume.

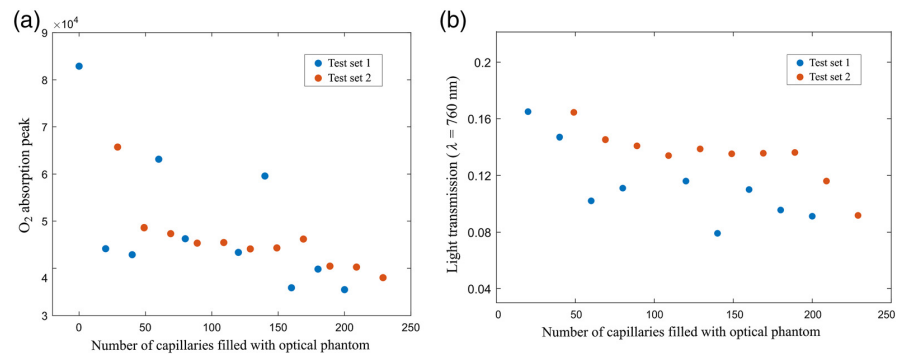


Fig. 4 (a) Peak values of the WMS absorption signals of molecular oxygen as a function of the number of capillaries filled with liquid phantom; and (b) light transmission values for the capillary arrays with optical phantom.

of capillaries filled with liquid phantom was plotted in Fig. 4(b). The light transmission decreased as the population of capillaries with optical properties grew. It is likely that this reduction in measured intensity also contributed to an error in absorption values. In this model, air volume and alveolar geometry were well defined, whereas in the human lung the air content and the geometry of the alveolar sacks change. A detailed understanding of variations in the light transmission could be linked to physiological values of alveolar inflation or deflation during

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respiration. The increment (or reduction) of air volume in the model was made in steps of 20 capillaries for each data acquisition set. The test set 1 exhibited higher variation in the absorption signals compared to the test set 2. This difference was likely related to the stability of temperature and RH during data acquisition. GASMAS requires a high humidity to estimate accurately the H_2O concentration. Ideally, RH should be 100%, but in this experiment, the RH was oscillating in the range of 90% to 94% due to condensation, and this variation also induced temperature changes between 36°C and 39°C during the data acquisition. Such fluctuations are not present in the human lung, because the body regulates the temperature to 37°C and the cooling effect associated with water condensation is nonexistent. The outlier data from test set 1 in Fig. 4(a) corresponded to 60 and 140 capillaries filled with phantom and exhibited poor light transmission as shown in Fig. 4(b).

This study was done using steady volumes for each data acquisition. A new version of the lung model with time dependence could be built, connecting the capillaries to a pumping system, to recreate tidal respiratory volumes.

The latest development in light sources and detectors could enable the implementation of GASMAS into pulmonary endoscopy, in a similar way as optical coherence tomography has become a complementary tool in bronchoscopy procedures.²⁵ GASMAS technology could be integrated into pulmonary endoscopes using optical fiber-based coupling. This has the potential to improve the patient-specific information content that will help the clinicians with lung obstruction assessment and track the patient's response to bronchodilators or hyperinflation-reducing therapies. The implementation of GASMAS technology in the clinic created the capability to locally assess the inflation of lung tissue, which is not possible with the existing diagnostic procedures such as spirometry and plethysmography.

5 Conclusion

A phantom with the optical properties and the structure of tissue from the respiratory zone has been modeled using a simplified capillary array immerse in a controlled environment chamber maintaining temperature and RH in the range of the human body.

The lung model enabled study of the changes in the GASMAS signals generated by the MicroLab Dual $\text{O}_2/\text{H}_2\text{O}$ system in transmittance geometry. The feasibility of sensing volume changes with GASMAS technique has been proven, stating a new possible application of GASMAS technology in respiratory treatment and diagnostics. This is a significant contribution since, to the best of our knowledge, previous studies addressing the clinical translation of GASMAS into respiratory healthcare reported on sensing the absorption imprint of H_2O and O_2 to quantify gas concentrations.

Disclosure

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this paper.

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Code, Data, and Materials Availability

The code and data used for this study are available upon request.

References

1. L. Marcu et al., "Biophotonics: the big picture," *J. Biomed. Opt.* **23**(2), 021103 (2017).

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2. R. Dery, "Humidity in anaesthesiology IV: determination of the alveolar humidity and temperature in the dog," *Can. Anaesth. Soc. J.* **18**(2), 145–51 (1971).
3. R. M. Schwartzstein and M. J. Parker, *Respiratory Physiology: A Clinical Approach*, Lippincott Williams & Wilkins, Philadelphia (2006).
4. M. F. Lutfi, "The physiological basis and clinical significance of lung volume measurements," *Multidiscip. Respir. Med.* **12**(1), 3 (2017).
5. S. Svanberg, "Gas in scattering media absorption spectroscopy: from basic studies to biomedical applications," *Laser Photonics Rev.* **7**(5), 779–796 (2013).
6. M. Lewander et al., "Clinical system for non-invasive in situ monitoring of gases in the human paranasal sinuses," *Opt. Express* **17**(13), 10849–10863 (2009).
7. L. Hu et al., "Towards an optical diagnostic system for otitis media using a combination of otoscopy and spectroscopy," *J. Biophotonics* **12**(6), e201800305 (2019).
8. D. Chen et al., "Laser-based gas absorption spectroscopy in decaying hip bone: water vapor as a predictor of osteonecrosis," *J. Biomed. Opt.* **24**(6), 065001 (2019).
9. M. Lewander et al., "Non-intrusive gas monitoring in neonatal lungs using diode laser spectroscopy: feasibility study," *J. Biomed. Opt.* **16**(12), 127002 (2011).
10. P. Lundin et al., "Non-invasive gas monitoring in newborn infants using diode laser absorption spectroscopy: a case study," *Proc. SPIE* **8229**, 822903 (2012).
11. P. Lundin et al., "Noninvasive monitoring of gas in the lungs and intestines of newborn infants using diode lasers: feasibility study," *J. Biomed. Opt.* **18**(12), 127005 (2013).
12. E. K. Svanberg et al., "Diode laser spectroscopy for noninvasive monitoring of oxygen in the lungs of newborn infants," *Pediatr. Res.* **79**(4), 621–628 (2016).
13. T. A. Henderson and L. Morries, "Near-infrared photonic energy penetration: can infrared phototherapy effectively reach the human brain?" *NDT* **2015**, 2191 (2015).
14. T. Terboven et al., "Chest wall thickness and depth to vital structures in paediatric patients: implications for prehospital needle decompression of tension pneumothorax," *Scand. J. Trauma Resusc. Emerg. Med.* **27**(1), 45 (2019).
15. I. E. Gordon et al., "The HITRAN2016 molecular spectroscopic database," *J. Quant. Spectrosc. Radiat. Transfer* **203**, 3–69 (2017).
16. S. L. Jacques, "Optical properties of biological tissues: a review," *Phys. Med. Biol.* **58**(11), R37–R61 (2013).
17. L. Mei, G. Somesfalean, and S. Svanberg, "Pathlength determination for gas in scattering media absorption spectroscopy," *Sensors* **14**(3), 3871–3890 (2014).
18. Arden L. Buck, "New equations for computing vapor pressure and enhancement factor," *J. Appl. Meteorol. Climatol.* **20**, 1527–1532 (1981).
19. A. Mallet et al., "Relating near-infrared light path-length modifications to the water content of scattering media in near-infrared spectroscopy: toward a new Bouguer–Beer–Lambert law," *Anal. Chem.* **93**(17), 6817–6823 (2021).
20. H. Ranu, M. Wilde, and B. Madden, "Pulmonary function tests," *Ulster Med. J.* **80**(2), 84–90 (2011).
21. J. Larsson et al., "Development of a 3-dimensional tissue lung phantom of a preterm infant for optical measurements of oxygen-laser-detector position considerations," *J. Biophotonics* **11**(3), e201700097 (2018).
22. A. Pacheco et al., "Anthropomorphic optical phantom of the neonatal thorax: a key tool for pulmonary studies in preterm infants," *J. Biomed. Opt.* **25**(11), 115001 (2020).
23. B. Aernouts et al., "Dependent scattering in Intralipid® phantoms in the 600–1850 nm range," *Opt. Express* **22**(5), 6086 (2014).
24. J. Gunther, H. Lu, and S. Andersson-Engels, "Combination of diffuse reflectance and transmittance spectroscopy to obtain optical properties of liquid phantoms," *Opt. Eng.* **59**(2), 024109 (2020).
25. M. J. Gora et al., "Endoscopic optical coherence tomography: technologies and clinical applications [Invited]," *Biomed. Opt. Express* **8**(5), 2405 (2017).

Andrea Pacheco is PhD student in biophotonics team at Tyndall National Institute, Cork, Ireland. She received her BS and MS degrees in physics from the Universidad Nacional de Colombia in 2013 and 2016, respectively. Her current research interests include optical

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phantoms for diffuse optics, gas spectroscopy, applied optics, and clinical translation of photonics-based technologies. She is an active member of SPIE and OSA and founder of the Tyndall and University College Cork OSA/SPIE student chapter.

Konstantin Grygoryev is a BioPhotonics researcher in Tyndall National Institute. He received his PhD in the field of microelectro mechanical systems from the University College Cork in 2013. He specializes in design, assembly, and programming of multispectral systems aimed at clinical measurements and surgical guidance. His current research interests are miniaturization of optical systems that can be used in a clinical setting under strong ambient illumination.

Walter Messina received his master's degree in biomedical engineering, from Polytechnic of Turin, Italy, and his PhD on micro- and nanobiosensor for biological and medical application from the University College Cork, Ireland. He is currently working in the BioPhotonics group at Tyndall National Institute, Cork, as a researcher on new photonics-based medical devices and as a part-time lecturer in the School of Chemistry at UCC.

Stefan Andersson-Engels received his MSc degree in physics in 1985 and PhD in 1990 from Lund University. He was a postdoc at McMaster University in Canada 1990 to 1991 and became a full professor at Lund University in 1999. In 2016, he was recruited as the head of biophotonics at Tyndall National Institute and is a deputy director of the IPIC Centre. His research interests include tissue optics and applications of light in biomedical diagnostics and treatments.

Laser absorption spectroscopy measurements of different pulmonary oxygen concentrations in transmittance and remittance geometry – phantom study

Andrea Pacheco, Jean Matias , Konstantin Grygoryev , Martin Hansson , Stefan Andersson-Engels.

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FULL ARTICLE (DRAFT)**Laser absorption spectroscopy measurements of different pulmonary oxygen concentrations in transmittance and remittance geometry – phantom study**Andrea Pacheco^{*,1,2} | Jean Matias^{1,2} | Konstantin Grygoryev¹ | Martin Hansson³ | Stefan Andersson-Engels^{1,2}¹ Biophotonics@Tyndall, IPIC, Tyndall National Institute, Cork, Ireland² Department of Physics, University College Cork, Cork, Ireland³ GPX Medical AB, Maskinvägen 1, SE-227 30 Lund, Sweden*** Correspondence**

Andrea Pacheco, Tyndall National Institute, Lee Maltings, Dyke Parade, T12R5CP Cork, Ireland

Email: andrea.pacheco@tyndall.ie

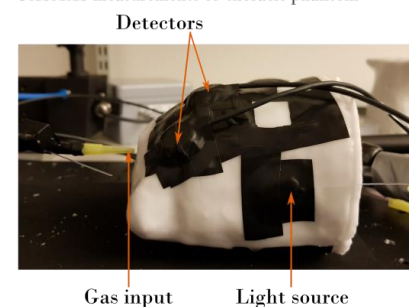
Anthropomorphic optical phantoms of neonatal thorax with two different geometries were used to acquire Gas in Scattering Media Absorption Spectroscopy (GSMAS) signals, for 30 source-detector configurations in transmittance and remittance geometry. The signals were used to estimate the oxygen concentration inside the lung cavity which was filled with humidified gas with 4 different oxygen concentrations varying

between 21% and 100%. The results show that internal light administration is more likely to give reliable GSMAS signals. In general, better signals were obtained with the set of phantoms recreating the smallest chest geometry. The values of path length and O₂ concentrations calculated with signals from the phantoms with optical properties at 820 nm, exhibit higher variations. The study shows that by moving the source and detector over the thorax, most of the lungs can potentially be assessed using GSMAS technique.

KEYWORDS

Computational model of a thorax; light transport; preterm infants; tuneable diode laser absorption spectroscopy.

GSMAS measurements of thoracic phantom

**1 | INTRODUCTION**

Approximately 1 million babies die every year due to complications of preterm birth^[1]. The lungs of neonates born before 37 completed weeks of pregnancy, may suffer from structural and biochemical immaturity, which together with surfactant deficiency (lack of phospholipid mixture that maintains alveolar stability) and incomplete vascularization, cause respiratory distress syndrome (RDS)^[2]. Despite the efforts to mitigate lung malfunction in neonates, RDS is still one of the major causes of mortality and morbidity among infants^[3]. Consequently, there is a compelling need to improve the diagnostic and treatment tools for lung disease in neonates.

The prevailing methods for diagnosis and monitoring of treatment response, are chest radiography and computer tomography (CT scanning). These techniques, use ionizing radiation projected on the torso of the neonate, and the repeated exposure to it, represents a risk to the neonate's safety if used for routine assessment of lung disease^[4]. Oxygen (O₂) administration is one of the mechanisms used in the intensive care unit to aid neonates with respiratory dysfunction, in this case, the delivered O₂ concentration varies between 30 % and 95 % depending of the need of the patient, and is measured by a gas analyser placed near the infant's mouth^[5].

Gas in scattering media absorption spectroscopy (GSMAS) is a tuneable diode laser spectroscopic technique developed for non-intrusive detection and monitoring of free gas enclosed

inside turbid media without extraction^[6]. GASMAS is a light-based non-imaging technique, which could be used to obtain complementary information to the existing screening modalities, namely radiography, CT, magnetic resonance imaging (MRI) and ultrasound. Feasibility studies have shown the potential of GASMAS to measure molecular oxygen (O₂) and water vapour (H₂O) gases in the lungs of neonates^[7-9]. Research efforts towards its clinical translation into neonatal respiratory health care, included animal studies^[10], computational modelling^[11] and phantom measurements^[12-15]. One of the main challenges is optimizing the source-detector configurations to acquire high signals and gain clinical acceptance.

Krite Svanberg et al. conducted GASMAS studies in five mechanically ventilated piglets, which were subject to stepwise increased and decreased fractions of inspired O₂ (in concentrations between 20 % and 97 %), atelectasis (partial or total lung collapse) and pneumothorax (air leakage between the lung and the chest wall). Light from a dual source (764 nm and 820 nm) was delivered externally on the skin, or internally with a source inside the oesophagus, and in both cases, the detector was placed over the skin. The results showed that H₂O vapour was only detectable with internal illumination, and specific light absorption patterns were identified in response to atelectasis and pneumothorax^[10].

Liao et al. simulated light transport at 760 nm for different source-detector pairs, placed over the chest of a computational model of neonatal thorax. The authors concluded that measurement geometries with the probes placed in front and in the region under the armpits, are favourable to obtain good gas absorption signals^[11].

With the aim to better understand the advantages and challenges of translating GASMAS in neonatal respiratory healthcare, different optical phantoms have been made. Larsson et al. developed a 3-dimensional nylon phantom, which consisted of 4 hollowed compartments with the boundary structure of skin, subcutaneous fat, lung and heart. Each of them, were designed to be filled with liquid phantom matching the respective tissue optical properties at 764 nm and 820 nm wavelength. Initially, GASMAS measurements were made without any absorbing or scattering material in the pulmonary cavity, and reliable O₂ and H₂O vapour absorption signals were found for source-detector separations up to 5 cm^[12]. In a follow up publication, the phantom included a structure with optical properties inside the lung, and GASMAS measurements were done to compare the differences in signal, when the probes were placed in remittance (source and detector over the chest) and transmittance (internal light source and detectors over the chest) geometries. The authors concluded that the internal light administration resulted in larger gas absorption, and higher signal to noise ratios, compared to dermal light administration^[13].

The Biophotonics@Tyndall group, created a lung tissue model which mimicked the alveolar structure, to demonstrate the potential of GASMAS technique to measure changes in inflated volume^[15].

In this article, we present the results from GASMAS measurements made with four solid anthropomorphic optical phantoms which resemble the thoracic organs of two neonates. A total of 30 source-detector geometries with detectors placed

in the front and back of the thorax were studied using four different gas mixtures. The main objectives of this study were to identify the best configurations to obtain good absorption signals of O₂ and H₂O vapour at 764 nm and 820 nm respectively, and to study the differences in GASMAS signal linked to changes in the O₂ concentration present inside the pulmonary cavity of the phantoms.

2 | METHODS

GASMAS principle

GASMAS technique is based on the difference between the absorption features of gases and solid state matter. Gases present sharp absorption lines (~0.001 nm width)^[16], enabling sensitive measurements of gas concentrations in the presence of a scattering solid-state media with much broader absorption features (~10 nm width)^[17]. In a typical GASMAS measurement targeting to sense O₂ and H₂O vapour content, a dual diffuse laser diode source illuminates the walls of the scattering object enclosing gas. Photons scattered from the gas pockets reach a photodetector and the absorption signal from the gas is identified. One of the lasers scans an absorption line of molecular oxygen (O₂) around 760 nm and the second scans an absorption line of water vapour (H₂O) around 820 nm or 934 nm. The wavelengths are spectrally close, which allows to make the assumption that the path length within the tissue for the light of both laser diodes, is approximately the same.

The concentration of H₂O vapour is calculated using the ideal gas law, and the partial pressure of vapour saturation in moist air (e'_w) at ambient temperature (T), and pressure (P), calculated by means of the Arden Buck equation^[18]:

$$e'_w = [1.0007 + (3.46 \times 10^{-6}P)] \times 6.1121 \exp[17.502 T/240.97 + T] \quad (2)$$

To use equation (2) the relative humidity (RH) of the gas has to be close to saturation. The absorption signal from H₂O vapour is then used to estimate the absorption path length by means of the Beer-Lambert law^[19]

$$I = I_0 e^{-\epsilon c l} \quad (1)$$

where I is the intensity of light at 820 nm reaching the detector, I_0 is the intensity of the light source, ϵ is the molar absorption of the gas, c the gas concentration and l the gas absorption path length. Consequently, the calculated value of path length is input in equation (1) to estimate the O₂ concentration, using the absorption signal of light at 760 nm.

GASMAS systems

Two GASMAS systems were used in this study: The gas calibration cell from GASPOROX which was included in the protocol to verify the values of O₂ and H₂O vapour concentration prior to the gas administration into the phantom. And the Neola system produced by GPX Medical, this system had a dual laser diode source cantered at 764 nm (22.1 mW) and 820nm (11.4 mW). Each wavelength was multiplexed and

scanned, at 1 kHz, over O_2 and H_2O vapour absorption bands by modulation of the injection current. The transmitted light was collected with a $10 \times 10 \text{ mm}^2$ photodiode.

Anthropomorphic phantoms

Two different thoracic phantom anatomies were used in this study. The organ geometry was recovered from anonymized computed tomography scans (CT) of pre-term neonates, with 3.7 kg and 3.6 kg of weight. The detailed description of the manufacturing protocol followed to obtain the phantoms used in this study, was published by Biophotonics@Tyndall in reference [14]. Briefly, each CT slice was segmented to distinguish seven different organs (skin, fat, muscle, bone, heart, trachea and lung). Computational models of heart, lung and muscle were 3D printed to create moulding casts to preserve the anatomic structure of the thorax. The moulds were filled with silicone mixed in different ratios with absorbers and scatters, in order to assign absorption and reduced scattering coefficients (μ_a and μ'_s) at 760 nm and 820 nm to the phantoms according to the values available in literature (see Table 1).

TABLE 1 Optical properties (absorption μ_a and reduced scattering μ'_s coefficients) at 760 nm and 820 nm assigned to the solid tissue phantoms in the thoracic models.

Tissue	760 nm		820 nm		Reference
	$\mu_a [\text{cm}^{-1}]$	$\mu'_s [\text{cm}^{-1}]$	$\mu_a [\text{cm}^{-1}]$	$\mu'_s [\text{cm}^{-1}]$	
Skin	0.031	24.82	0.027	22.76	[17,20]
Fat	0.128	13.85	0.069	13.24	[21]
Muscle	0.196	14.07	0.198	12.82	[17,22]
Bone	0.100	9.30	0.110	8.40	[17]
Heart	0.249	4.89	0.111	4.45	[17]

Each organ was considered optically homogeneous, and small structures usually present in tissue like veins or collagen, were not considered. All phantoms were made with an empty pulmonary cavity which facilitated gas exchange through a 5 mm tracheal hole which has two branches connected to the lungs, as can be seen in Figure 1.

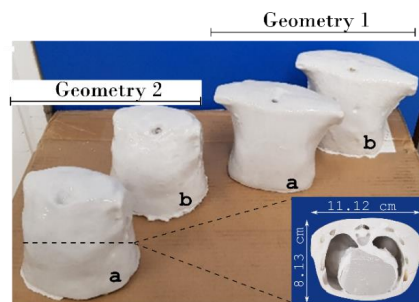


FIGURE 1. Phantoms used to perform the GASMAS measurements in this study. Geometries 1 and 2 correspond to the CT thoracic scans of 3.7 kg and 3.6 neonates, respectively. Phantoms labelled with “a” and “b” have absorption and scattering properties at 760 nm and 820 nm correspondingly. Every phantom had an empty pulmonary cavity as shown in the axial cut of the first phantom on the left.

2.1 | Experimental set up

The diagram of the protocol used in this study is shown in Figure 2. Gases with 21%, 30%, 50% and 100% O_2 concentration were humidified and delivered inside the pulmonary cavity of each phantom. The humid gas was assessed with the GASPOROX calibration cell prior to its delivery into the phantom, to verify the O_2 and H_2O concentrations of the gas exiting the humidifier. Once it was confirmed that the gas had a RH of 100% and the concentration was in agreement with the nominal percentage of the gas supply, the NEOLA source and detectors were fixed to the phantom to take the measurements for the remittance and transmittance geometries described in the following section.

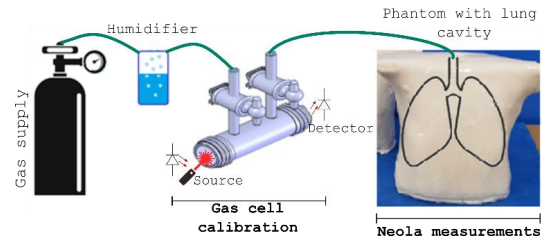


FIGURE 2. Diagram of the experimental protocol followed in this study. Gas with an specific O_2 concentration was humidified, then it pass through a calibration cell to verify 100 % RH and O_2 percentage prior to enter the pulmonary cavity of the phantom. Finally, NEOLA probes were fixed to the phantom for data acquisition.

2.2 | Measurement configurations

30 source detector configurations were included in this study. Figure 3 (a.) shows the 15 source-detector pairs in transmittance geometry with the source placed internally in the trachea and the detector over the thorax. Figure 3 (b.) corresponds to the 15 remittance geometries with source and detector placed over the phantom's skin, in this case the source was placed under the armpit on the right or left side of the phantom, depending on the detector positions, to avoid geometries for which the light should traverse the torso. This last scenario is clinically unavailable, given that the tissue will completely absorb and scatter the light, preventing the photons to reach the detector [23].

The black mask shown in Figure 3 (c.) was used in all measurements to prevent the detection of straight light (photons traveling from the source to the detector, without interaction with the gas enclosed in the pulmonary cavity). The detector position labelled with numbers 10 and 11 correspond to two consecutive measurements taken in the exact same position (as is the case of 14 and 15), which was made aiming to evaluate the reproducibility of the NEOLA system.

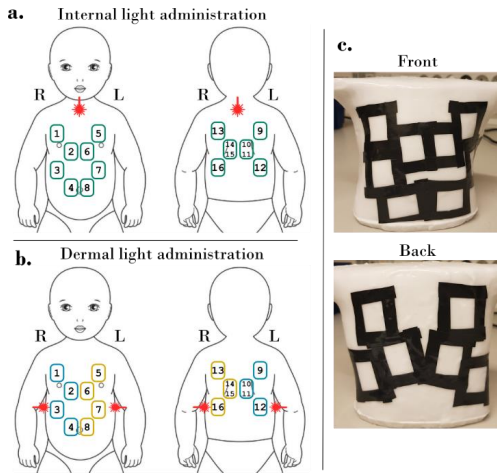


FIGURE 3. Diagram of the source-detector configurations used to measure gas content in the phantom's lung in **a.** transmittance and **b.** remittance geometries **c.** shows the black mask placed on the phantoms, to prevent straight light from the source reaching the detector.

3 | RESULTS AND DISCUSSION

The measurement protocol of **Figure 2** was used to acquire GASMAS measurements with all phantoms. 21 samples (O_2 and H_2O vapour absorption signals at 760 nm and 820 nm respectively) were taken for each of the 30 different source-detector configurations, administrating gas with 21%, 30%, 50% and 100% O_2 concentration.

GASMAS only measures the path length of light through the gas, therefore, this quantity will depend merely on the distance between the probes if the gas inside the phantom is maintained at constant RH, T and ambient P (parameters used to estimate the path length using the principle described in the methods section). Since the gas was humidified and maintained at the same room conditions during all the study, it was expected that the path length in all the 30 source-detector configurations, remained the same for each phantom pair with geometries 1 and 2, regardless the O_2 content in the gas. The path length was calculated for the 21 samples in each source-detector configuration, these values were averaged and plot in **Figure 4** for phantom geometries 1 and 2, when the light was administrated internally and over the skin. The measurement configurations for which the path length overlaps the most for the two phantoms with the same geometry, correspond to the source-detector combinations which may lead to the most

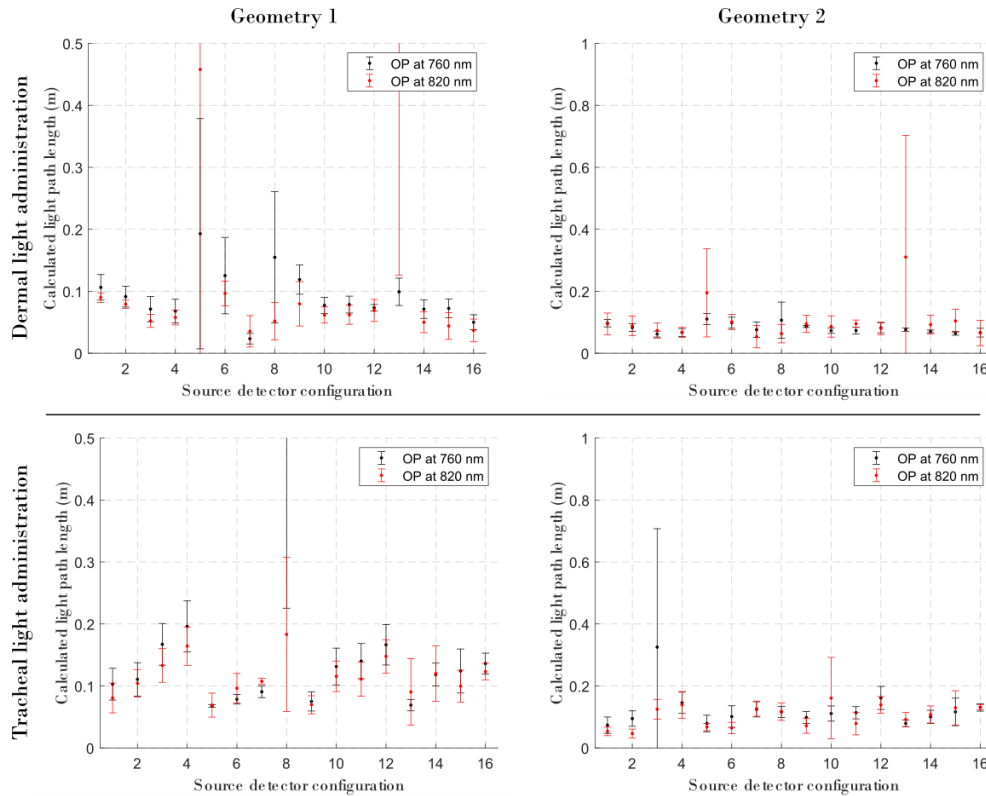


FIGURE 4. Calculated path length values of light through the gas cavity, for the two phantom geometries with source-detector probes resembling O_2 gas sampling in remittance and transmittance geometry.

reliable GASMAS signals. For example, in the case of geometry 1, configuration 12 and 2 showed to be the best for dermal and internal light administration, respectively. Whereas for geometry 2, configurations 4, 6 and 12 would work best for dermal light administration and 5 and 16 for internal illumination.

The plots showed less variation in path length values for geometry 2, which corresponds to a smaller thorax. Source-detector configurations 5 and 13 show high standard deviations, for dermal light administration in both phantoms. This was probably related with the light absorption of the heart, placed on the left of the phantoms.

The NEOLA system seem to have good repeatability for consecutive measurements, as path length values for the configuration pairs 10-11 and 14-15 are well correlated in all cases. This aspect should be further studied for more than one source-detector configuration.

Box plots of the calculated O_2 concentrations taken with the full set of phantoms, including all source-detector configurations are shown in **Figure 5**. The red lines in each box correspond to the median value, the lower and upper whiskers represent the median of the lower and upper half in each data set, and the top and bottom of the blue boxes show

the highest and lowest data points in the data excluding any outliers (red crosses). The nominal values of gas input for each measurement badge is represented by the dotted line.

Ideally, the same gas concentration, should be estimated for all the GASMAS samples at a specific gas badge. However, the estimated concentrations differ from the nominal values of O_2 percentage, exhibiting over-estimation in the case of 21% and 30%, and under-estimation for 50% and 100% O_2 supply. The phantoms with optical properties at 820 nm, show lower concentrations, and higher variation in their data sets, compared to their pairs with properties at 760 nm. This difference may be related with a higher light attenuation for the wavelength in resonance with the H_2O vapour molecules. The outliers may correspond to samples taken at source-detector configurations for which the light transmission was too low.

The phantom models used in this study lacked of a structure to mimic the absorption of scattering that light might undergo upon interaction with pulmonary tissue. In the real clinical scenario, the GASMAS signals may be further attenuated given the optical properties of lung ($\mu_{a760}=0.5 \text{ cm}^{-1}$, $\mu'_{s760}=5.4 \text{ cm}^{-1}$ and $\mu_{a820}=0.7 \text{ cm}^{-1}$, $\mu'_{s820}=4.9 \text{ cm}^{-1}$)^[17]. The placement of the endotracheal light source results in more reliable measurements for the phantom of geometry 1, which

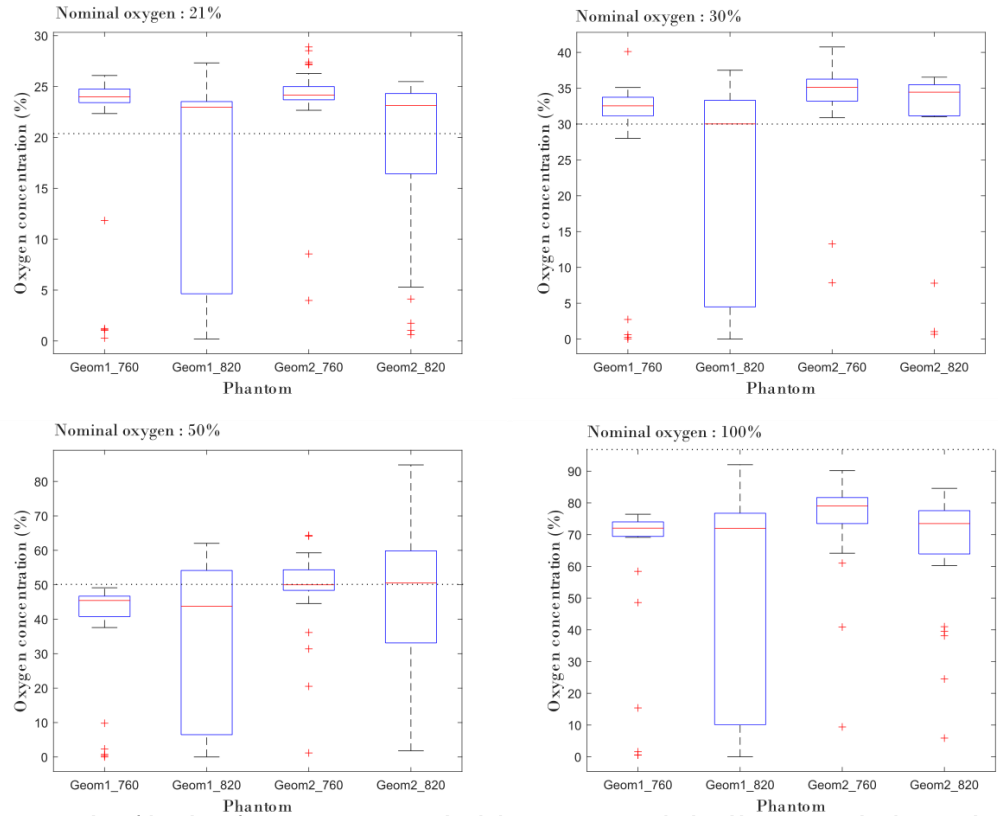


FIGURE 5. Plots of the values of O_2 concentration measured with the NEOLA system. The dotted lines correspond to the nominal values of O_2 content of the gas input in the phantom cavity.

shows at least 3 non-viable source-detector pairs when light is delivered over the thorax. The internal light administration assures light interaction with the gas inside the pulmonary cavity, as it necessarily has to go through before reaching the detectors over the torso. When source and detector are placed in remittance geometry, the light undergoes double attenuation by tissue surrounding the cavity.

The NEOLA system, shows to be sensitive enough to sense O₂ concentration changes among the different gas supply badges. However, it is necessary to investigate the possible sources of error that prevent the accurate estimation of O₂ concentration inside the phantoms.

Preterm infants are often intubated for breathing or feeding proposes. In those cases placing a light source in the trachea would be feasible. However, the main aim of GASMAS technology translated into respiratory healthcare, is a non-invasive assessment of lung function, and the endotracheal light source should be used just if the infant is already intubated. The localization of a Near Infra-Red light fiber inside the respiratory or feeding tube, could be prototyped and evaluated.

5 | CONCLUSION

GASMAS bench top measurements were conducted with a set of solid anthropomorphic phantoms with geometries obtained from two different neonatal chest CT scans. In each case, one of the phantoms had absorption and scattering at 760 nm, whereas the other at 820 nm. The phantoms had an empty pulmonary cavity which facilitated gas exchange. The cavity of every phantom was filled with humidified gas mixed with 21%, 30%, 50% and 100% O₂ concentration, while GASMAS measurements were conducted in remittance and transmittance geometry.

The results show the source-detector configurations which may lead to reliable O₂ and H₂O vapour absorption signals, together with those which may be avoided, due to high variation among consecutive samples for the same source-detector pair. The internal light administration would be preferable to obtain H₂O vapour absorption signals, which is critical to estimate the gas absorption path length inside the cavity and consequently for the correct calculation of O₂ concentration.

The results from this study may assist in optimizing the source-detector configurations to perform GASMAS measurements in the clinic, which could enable recordings of the oxygen levels in the lung. We have shown that by changing the position of source and detector over the torso, most of the lung can be assessed.

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AUTHOR CONTRIBUTIONS

A.P. was involved in conceptualization, investigation, bench top measurements and writing—original draft; J.M. was involved in conceptualization, investigation and writing—plots; K.G, A.P. and M.H. were involved in investigation—bench top set up, and K.G, M.H. and S. A. were involved in conceptualization, writing—review and editing and S. A. was involved in project management.

CONFLICT OF INTEREST

Martin Hansson works for GPX Medical, the company that developed and produced the NEOLA system used for this study, the other authors declare no financial or commercial conflict of interest.

DATA AVAILABILITY STATEMENT The data and scripts that support the findings of this study are openly available at the public repository ([Here we will include the repository's doi](#)).

REFERENCES

- [1] S. R. Walani, *Int J Gynecol Obstet* **2020**, *150*, 31–33.
- [2] T. J. M. Moss, *Proceedings of the Australian Physiological Society* **2005**, *36*, 23–28.
- [3] S. B. Ainsworth, *Treatments in Respiratory Medicine* **2005**, *4*, 423–437.
- [4] T. Olgar, E. Onal, D. Bor, N. Okumus, Y. Atalay, C. Turkyilmaz, E. Ergenekon, E. Koc, *Korean J Radiol* **2008**, *9*, 416.
- [5] B. Frey, F. Shann, *Arch Dis Child Fetal Neonatal Ed* **2003**, *88*, F84–88.
- [6] M. Sjöholm, G. Somesfalean, J. Alnis, S. Andersson-Engels, S. Svanberg, *Optics Letters* **2001**, *26*, 16–18.
- [7] M. Lewander, A. Bruzelius, S. Svanberg, K. Svanberg, V. Fellman, *Journal of Biomedical Optics* **2011**, *16*, 127002.
- [8] P. Lundin, E. K. Svanberg, L. Cocola, M. L. Xu, G. Somesfalean, S. Andersson-Engels, J. Jahr, V. Fellman, K. Svanberg, S. Svanberg, *J. Biomed. Opt.* **2013**, *18*, 127005.
- [9] E. K. Svanberg, *Pediatric Research* **n.d.**, *7*.
- [10] E. K. Svanberg, J. Larsson, M. Rasmussen, M. Larsson, D. Leander, S. Bergsten, J. Bood, G. Greisen, V. Fellman, *Pediatric Research* **2020**, DOI 10.1038/s41390-020-0971-x.
- [11] P. Liao, J. Larsson, E. K. Svanberg, P. Lundin, J. Swartling, M. L. Xu, J. Bood, S. Andersson-Engels, *J. Biophotonics* **2018**, *11*, 7.
- [12] J. Larsson, P. Liao, P. Lundin, E. Krite Svanberg, J. Swartling, M. Lewander Xu, J. Bood, S. Andersson-Engels, *J. Biophotonics* **2018**, *11*, e201700097.
- [13] J. Larsson, D. Leander, M. Lewander Xu, V. Fellman, J. Bood, E. Krite Svanberg, *J. Biophotonics* **2019**, *12*, DOI 10.1002/jbio.201800350.
- [14] A. Pacheco, H. Li, M. Chakravarty, S. K. V. Sekar, S. Andersson-Engels, *J. Biomed. Opt.* **2020**, *25*, DOI 10.1117/1.JBO.25.11.115001.
- [15] A. Pacheco, K. Grygoryev, W. Messina, S. Andersson-Engels, *J. Biomed. Opt.* **2021**, *27*, DOI 10.1117/1.JBO.27.7.074707.
- [16] I. E. Gordon, L. S. Rothman, C. Hill, R. V. Kochanov, Y. Tan, P. F. Bernath, M. Birk, V. Boudon, A. Campargue, K. V. Chance, B. J. Drouin, J.-M. Flaud, R. R. Gamache, J. T. Hodges, D. Jacquemart, V. I. Perevalov, A. Perrin, K. P. Shine, M.-A. H. Smith, J. Tennyson, G. C. Toon, H. Tran, V. G. Tyuterev, A. Barbe, A. G. Császár, V. M. Devi, T. Furtenbacher, J. J. Harrison, J.-M. Hartmann, A. Jolly, T. J. Johnson, T. Karman, I. Kleiner, A. A. Kyuberis, J. Loos, O. M. Lyulin, S. T. Massie, S. N. Mikhailenko, N. Moazzen-Ahmadi, H. S. P. Müller, O. V. Naumenko, A. V. Nikitin, O. L. Polyansky, M. Rey, M. Rotger, S. W. Sharpe, K. Sung, E. Starikova, S. A. Tashkun, J. V. Auwera, G. Wagner, J. Wilzewski, P. Wcisło, S. Yu, E. J. Zak, *Journal of Quantitative Spectroscopy and Radiative Transfer* **2017**, *203*, 3–69.
- [17] S. L. Jacques, *Phys. Med. Biol.* **2013**, *58*, R37–R61.
- [18] Arden L. Buck, *Journal of Applied Meteorology* **1981**, *20*, 1527–1532.

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- [19] D. F. Swinehart, *J. Chem. Educ.* **1962**, 39, 3.
- [20] N. Choudhury, R. Samatham, S. L. Jacques, in (Eds.: N. Kollias, B. Choi, H. Zeng, R.S. Malek, B.J. Wong, J.F.R. Ilgner, K.W. Gregory, G.J. Tearney, L. Marcu, H. Hirschberg, S.J. Madsen, A. Mandelis, A. Mahadevan-Jansen, E.D. Jansen), San Francisco, California, **2010**, p. 75480G.
- [21] R. L. P. van Veen, H. J. C. M. Sterenborg, A. Pifferi, A. Torricelli, R. Cubeddu, in *Biomedical Topical Meeting*, OSA, Miami Beach, Florida, **2004**, p. SF4.
- [22] R. Re, I. Pirovano, D. Contini, L. Spinelli, A. Torricelli, *Sensors* **2018**, 18, 264.
- [23] A. Pacheco, B. Jayet, E. Krite Svanberg, H. Dehghani, E. Dempsey, S. Andersson-Engels, *Journal of Biophotonics* **2022**, DOI 10.1002/jbio.202200041.
- [24] M. F. Lutfi, *Multidiscip Respir Med* **2017**, 12, 3.

PAPER VI

Near Infrared Light Propagation Modeling of Infant Lung with Light Source Placed Inside Intubated Airway

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Near Infrared Light Propagation Modeling of Infant Lung with Light Source Placed Inside Intubated Airway

Andrea Pacheco^{1,2}, Emilie Krite Svanberg³, Eugene Dempsey⁴ and Stefan Andersson-Engels^{1,2}

1. Biophotonics@Tyndall, IPIC, Tyndall National Institute, Lee Maltings, Dyke Parade, Cork, Ireland.

2. Department of Physics, University College Cork, Cork, Ireland.

3. Department of Clinical Sciences, Anesthesiology and Intensive Care Medicine, Skåne University Hospital, SE-221 85, Lund University, Lund, Sweden.

4. INFANT Center, Cork University Maternity Hospital Wilton, Cork, Ireland.
andrea.pacheco@tyndall.ie

Abstract: We simulate light propagation in 3D numerical model of infant thorax at 761 nm with light source placed inside the trachea and detectors over the skin between axilla and sternum.

OCIS codes: (170.1610) Clinical applications; (170.3880) Medical and biological imaging

1. Introduction

The clinical techniques such as X-ray and ultrasound imaging provide information about pulmonary function and gas filling in the lungs of infants but not about the alveolar composition. Gas in scattering media absorption spectroscopy (GASMAS) is a non-invasive method used to measure absolute lung oxygen volume and concentration. The feasibility of GASMAS has already been demonstrated by assessing lung gas content in infants [1, 2] The Biophotonics group at Tyndall is working on the clinical translation of GASMAS to improve the diagnosis accuracy and treatment monitoring of lung disease in new born.

Respiratory distress syndrome (RDS) is a common lung disease present in preterm infants [3]. A typical treatment of RDS involves surfactant administration via intubation [4]. The aim of this work is to study the improvement in lung function assessment that could arise of localizing a light source inside the trachea of an intubated infant and compare this results with previous modeling of light propagation with GASMAS technique where light source and detectors are placed over the skin [5].

2. Method

NIRFAST software [6] is used to construct a 3D numerical model of an infant's thorax and simulate light propagation with 761 nm wavelength in a specific set up where the light source is placed inside the infant's airway and detectors are allocated over the skin between the axilla and sternum (see Fig. 1).

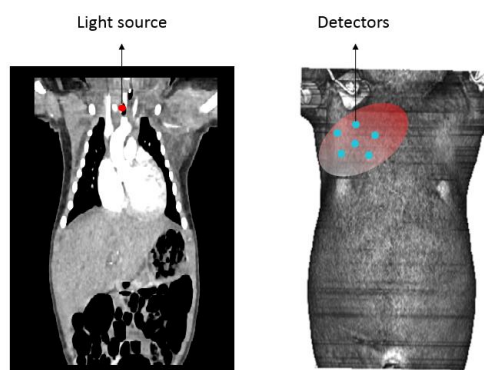


Fig. 1. Coronal slice and volume render from a full CT scan of thorax and abdomen area of a 3.7 kg infant with light source and detectors distribution illustrated.

After segmentation of each organ a set of meshes is created using Finite Element Method (FEM) to assign homogenous tissue optical properties of skin, bone, muscle, heart, arteries/veins and lung relevant for 761 nm wavelength. Once every organ has its respective absorption and scattering coefficients (μ_a and μ_s) the numerical model of the thorax is

used to measure the intensity reached by the detectors allocated over the skin in an array where different lung sections are sampled.

3. Simulation and preliminary results

The full thorax and abdomen CT of a 3.7 kg infant consist of 174 individual slices with a separation of 0.75 mm and a dimension of 512 x 512 pixels. The segmentation process used intensity thresholding in gray scale for each organ in the CT. A unique intensity for each volume is assigned. The segmented lungs can be seen in Fig. 2.c.

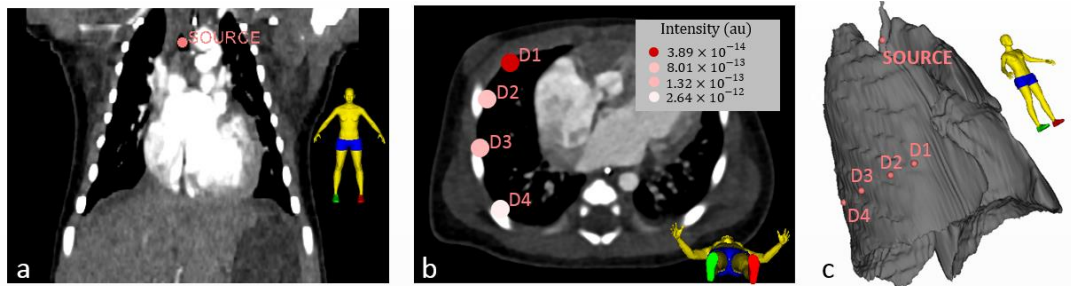


Fig. 2. Coronal and sagittal slices (a, b) and 3D lung model (c) from a CT scan of a 3.7 kg infant with light source placed inside the trachea and detectors (D1, D2, D3 and D4) over the external surface of the lung in the same sagittal plane.

The 3D numerical model of lungs was created with optical properties $\mu_a = 0.2 \text{ cm}^{-1}$ and $\mu_s = 10 \text{ cm}^{-1}$, a 761 nm light source was placed into the trachea (see Fig. 2) and a set of 4 detectors were placed in the external border of the right lung of a chosen sagittal plane.

In this case, scattering interactions are stronger than absorption and light propagation is executed with the forward model in NIRFAST. The strongest signal is detected in D4 (Fig. 2.b) which is closest to the light source. The detected intensity attenuates as long as light travels longer distances within the lung.

Currently we are working in arteries/veins, skin, bone, muscle and heart numerical models to have a realistic thorax geometry where light at 761 nm is scattered and absorbed by different kinds of tissue and to identify if there is an improvement in signal placing the light source inside the trachea compared to a set up where both light source and detectors are placed over the skin.

We will explore the optimal detector placement positions for accurate oxygen measurements for the clinical translation of GASMAS technique and model the novel idea of placing a light source inside the endotracheal tube to assess RDS treatment when the infant is intubated.

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4. References

- [1] P. Lundin, E. K. Svanberg, L. Cocola, M. L. Xu, G. Somesfalean, S. Andersson-Engels, J. Jahr, V. Fellman, K. Svanberg, and S. Svanberg, "Noninvasive monitoring of gas in the lungs and intestines of newborn infants using diode lasers: feasibility study," *Journal of Biomedical Optics*, vol. 18, no. 12, Dec, 2013.
- [2] E. K. Svanberg, P. Lundin, M. Larsson, J. Akesson, K. Svanberg, S. Svanberg, S. Andersson-Engels, and V. Fellman, "Diode laser spectroscopy for noninvasive monitoring of oxygen in the lungs of newborn infants," *Pediatr Res*, vol. 79, no. 4, pp. 621-8, Apr, 2016.
- [3] B. J. Stoll, N. I. Hansen, E. F. Bell, S. Shankaran, A. R. Laptook, M. C. Walsh, E. C. Hale, N. S. Newman, K. Schibler, W. A. Carlo, K. A. Kennedy, B. B. Poindexter, N. N. Finer, R. A. Ehrenkranz, S. Duara, P. J. Sanchez, T. M. O'Shea, R. N. Goldberg, K. P. Van Meurs, R. G. Faix, D. L. Phelps, I. D. Frantz, 3rd, K. L. Watterberg, S. Saha, A. Das, R. D. Higgins, H. Eunice Kennedy Shriver National Institute of Child, and N. Human Development Neonatal Research, "Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network," *Pediatrics*, vol. 126, no. 3, pp. 443-56, Sep, 2010.
- [4] T. P. Stevens, E. W. Harrington, M. Blennow, and R. F. Soll, "Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome," *Cochrane Database Syst Rev*, no. 4, pp. CD003063, Oct 17, 2007.
- [5] J. L. Peilang Liao, Emilie Krite Svanberg, Patrik Lundin, Johannes Swartling, Märta Lewander Xu, Joakim Bood and Stefan Andersson-Engels, "Source-detector position analysis of percutaneously measured O₂-gas signal in a 3D preterm infant lung computer simulation," *Paper under review*, 2017.
- [6] H. Dehghani, M. E. Eames, P. K. Yalavarthy, S. C. Davis, S. Srinivasan, C. M. Carpenter, B. W. Pogue, and K. D. Paulsen, "Near infrared optical tomography using NIRFAST: Algorithm for numerical model and image reconstruction," *International Journal for Numerical Methods in Biomedical Engineering*, vol. 25, no. 6, pp. 711-732, 2009.

PAPER VII

Simulation of near-infrared light propagation through the thorax of a neonate: addressing the optimisation of source and detector positions for measuring lung oxygen content in preterm infants

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Simulation of near-infrared light propagation through the thorax of a neonate: addressing the optimization of source and detector positions for measuring lung oxygen content in preterm infants

Andrea Pacheco^{*a, b}, Emilie Krite Svanberg^c, Eugene Dempsey^d, Stefan Andersson – Engels^{a, b}

^a Biophotonics@Tyndall, IPIC, Tyndall National Institute, Lee Maltings, Dyke Parade, Cork, Ireland.

^b Department of Physics, University College Cork, Cork, Ireland.

^c Department of Clinical Sciences, Anesthesiology and Intensive Care Medicine, Skåne University Hospital, SE-221 85, Lund University, Lund, Sweden.

^d INFANT Centre, Cork University Maternity Hospital Wilton, Cork, Ireland.

*andrea.pacheco@tyndall.ie

ABSTRACT

Gas in scattering media absorption spectroscopy shortly called GASMAS, is a tunable diode laser spectroscopic technique developed for the measurement of gas present in turbid media. The technique relies on the sharp and specific absorption lines of gases which enables sensitive measurements of gas concentrations in the presence of a scattering solid medium with much broader absorption features. The Biophotonics laboratory at Tyndall National Institute (Biophotonics@Tyndall) is currently exploring the clinical translation of GASMAS technology into the respiratory healthcare of neonates. In this study, we use computational tools to assess the potential gain in gas absorption signal. One of the challenges in the development of the GASMAS technique is to obtain a sufficiently good signal in the measurements, as the light attenuation is high in tissue and the lungs are interior organs. To have an estimation of the capabilities and limitations in this specific application of gas spectroscopy, we model the transmission of near infrared (NIR) light in tissue when a 760 nm source and a set of 68 detectors are placed in different locations over the thorax. We segmented the main organs of the thorax from anonymized DICOM images of a neonate. This is followed by the creation of 3D computational models to solve light propagation with the diffusion equation, and the modelling of light propagation through the thorax of an infant including optical properties of lung, heart, arteries, bone, muscle, trachea, fat and skin. Finally, we calculate a map of the optimal light source – detector configurations to obtain the highest signal from oxygen gas imprint in the lungs.

The use of computational tools such as NIRFAST Slicer 2.0 for investigation and further understanding of the advantages and limitations of the technology is fundamental. Such simulations enable the recreation of different clinical scenarios and identification of the minimum requirements necessary to further improve the application and develop a bedside clinical device that can potentially be used for continuous monitoring of lung function and control of ventilator settings. The potential capability of measuring non-invasively oxygen, water vapour and carbon dioxide in the lungs, would reduce the need for intubation and extracorporeal membrane oxygenation, as well as lower the incidences of chronic lung disease.

Keywords: GASMAS, multi structure tissue phantom.

1. INTRODUCTION

Preterm born infants often present respiratory distress syndrome (RDS) [1], due to immaturity of lung tissue and surfactant deficiency. The current clinical techniques for monitoring and diagnostics in the clinical course of lung dysfunction are pulmonary X-ray imaging and blood oximetry. Besides the fact that none of them provide information about the gas content

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in the lung and its concentration, there are many long term risks associated with early X-ray exposure of neonates [2]. Biophotonics@Tyndall is performing experimental and computational studies to evaluate the capability of GASMAS technology to measure continuously absolute lung oxygen volume and molecular concentration. This information could assist and improve the monitoring and assessment of respiratory healthcare in neonates [3].

GASMAS has previously been proposed to measure molecular oxygen in the sinus cavities, in the inner ear and in the lungs of infants [4, 5]. The feasibility of this technique in assessing oxygen and water vapor in pulmonary tissue was shown by Lewander et al [6]. The location of the source and detectors in different positions of the thorax is crucial in the detection of gas absorption signals from the different pulmonary lobes. Liao et al. suggest that geometries, where both source and detector are placed in front and on the side of the lung, are favorable to measure a good gas absorption signal from the lung [7]. In this work, we study the improvement in gas absorption signals that could arise from localizing a light source inside the trachea of an intubated infant. We also make a comparison with previous simulations of light propagation where light source and detectors are placed over the skin.

2. 3D COMPUTATIONAL MODEL FROM THE THORAX OF A NEONATE

DICOM images from an anonymized CT scan of a 3.58 kg infant born in gestational week 36 were used to construct the computational 3D model of the thorax with NIRFASTSlicer2.0 software [8].

2.1 SEGMENTATION

The anonymized CT scan was acquired after parental approval following the guidelines of the ethical approval ECM 4 (gg) 07/03/18 from the Clinical Research Ethics Committee of the Cork Teaching Hospitals and consist of 367 cross-sectional slices.

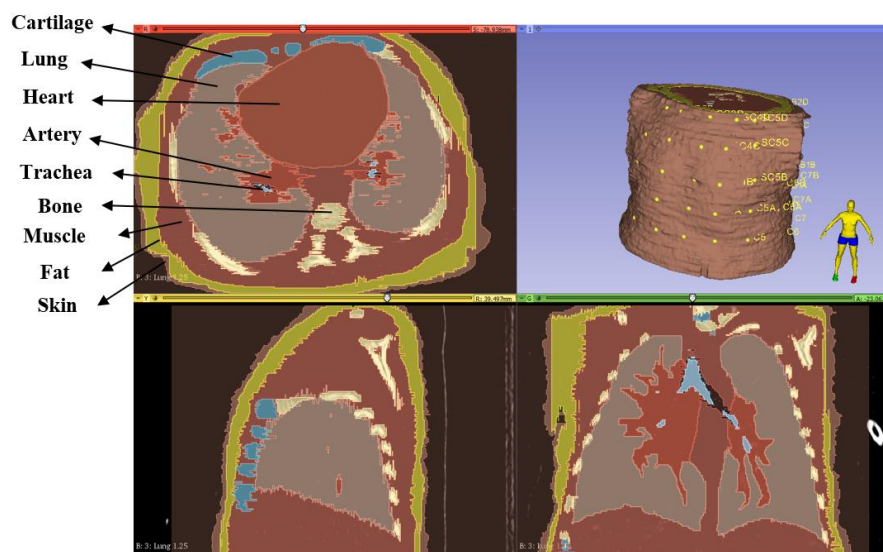


Figure 1: View of the segmented anonymized DICOM images from a CT scan of a neonate weighting 3.58 kg

In this process lung, heart, arteries, bone, muscle, trachea, fat and skin are stained with different colors slice by slice by direct drawing over the CT images until the whole geometry of each organ was recovered (Figure 1). The boundaries between organs were defined by differences in intensity levels of Housenfield Units (HU). The segment tool “Grow from seeds” was used to create complete segmentation and avoid empty spaces within the model.

2.2 MESH CREATION AND OPTICAL PROPERTIES

Once the organs of interest were segmented, a 3D mesh based on the Finite Element Method (FEM) with 229363 nodes and 1356069 elements of the thorax was generated. The mesh has 9 different regions from which each corresponds to a different segment. Each tissue type was considered to be optically homogeneous. Optical properties at 760 nm (wavelength at which oxygen gas is absorbing light) were taken from literature and values of absorption (μ_a) and scattering (μ_s) were assigned to each region. The trachea is composed of 90% muscle, therefore we assumed optical properties of trachea to be the same as muscle. The values of absorption and reduced scattering coefficients assigned to each tissue are listed in table 1.

Table 1: Optical properties for 760 nm wavelength assigned to segmented organs in the 3D computational model of the thorax of a neonate.

Tissue	μ_a [cm^{-1}]	μ_s [cm^{-1}]
Skin	0.031	24.82
Fat	0.128	13.85
Muscle	0.196	14.07
Bone	0.100	9.30
Cartilage	0.532	7.93
Heart	0.249	4.89
Artery	3.138	16.69
Trachea	0.196	14.07
Lung	0.505	5.37

3. MODELING OF LIGHT PROPAGATION IN HUMAN TISSUE

NIRFAST is used to solve the light transport equation in the FEM mesh of the thorax. In the simulation, two cases were evaluated one with a light source placed inside the trachea and another one with the light source over the skin close to the right armpit. In both configurations a set of 68 detectors were placed around the thorax. The different detector locations can be seen as yellow landmarks in figure 2.

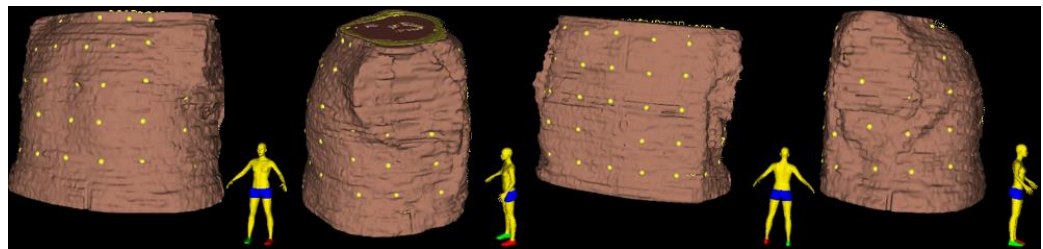


Figure 2: Position of the 68 detectors (yellow dots) placed over the skin around the thorax in the model of light propagation.

Once established the position of light source and detectors the forward model was solved, obtaining the light fluence rate for every element in the mesh, figure 3 shows the fluence rate for the elements that belong to lung region when light is injected under the armpit (cutaneous light source) and inside the trachea. The absorption of light due to the presence of oxygen inside the lung can be computed as the product of the fluence rate in lung tissue by the absorption of molecular oxygen gas. However, the gas absorption imprint is weak and will not change significantly the overall value of the fluence rate.

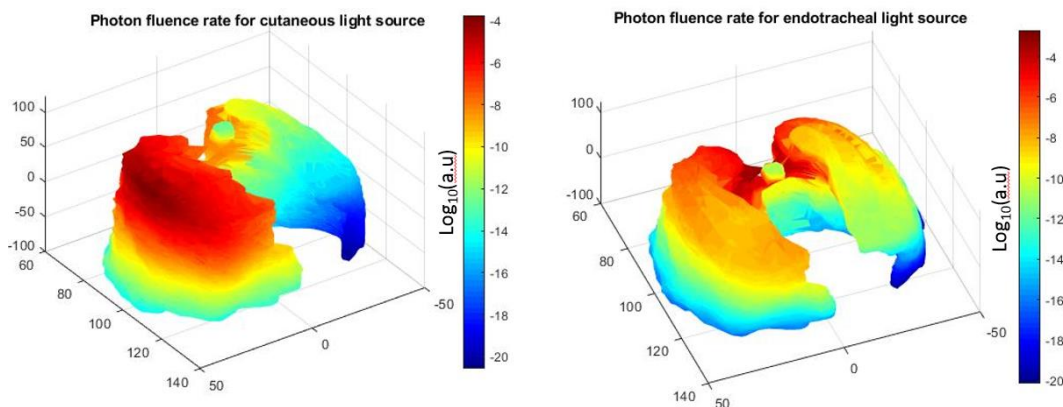


Figure 3: Light fluence rate in the lung with the cutaneous (left) and endotracheal (right) light source.

From the fluence plots in figure 3, we can conclude that there is gain in intensity signal when the light source is placed inside the trachea of the neonate. This finding is of high relevance in the clinical scenario. Preterm infants are often intubated either with a respiratory or a feeding tube, the localization of a Near Infra-Red light fiber inside the tube, could be prototyped and evaluated. On the other hand, the assessment of alveolar inflation in the upper lobe of both lungs would be better placing an endotracheal source do to the fact that light distributes evenly on both sides. Since the main aim of GASMAS technology translated into respiratory healthcare, is a non-invasive assessment of lung function, and endotracheal light source should be used just if the infant is already intubated.

The gas absorption signal is proportional to the photon hitting density (PHD). This is found by modeling the fluence rate for a mesh element in a position (x,y,z) with the light injection point in the source (S), followed by the calculation of the fluence rate assuming that the light injection point is now located in the position of the detector (D) and multiplying both values:

$$PHD_{S,D}(x,y,z) = \Phi_S(x,y,z) \cdot \Phi_D(x,y,z)$$

The total photon hitting density corresponds to the contribution from all elements of the mesh. The PHD was calculated for the case of the endotracheal light source when the lung tissue is fully inflated (inhalation) and when the inflated volume is reduced (exhalation) for each of the 68 detectors. Figure 4 shows the interpolated values of the photon hitting density on the full set of detectors. When light interacts with a smaller volume of inflated tissue, the signal intensity shows to be higher than in the case when the lung is fully inflated. This result shows that GASMAS measurements can potentially be used to quantify the inflated volume of the lung which could be correlated with the alveolar composition of pulmonary tissue.

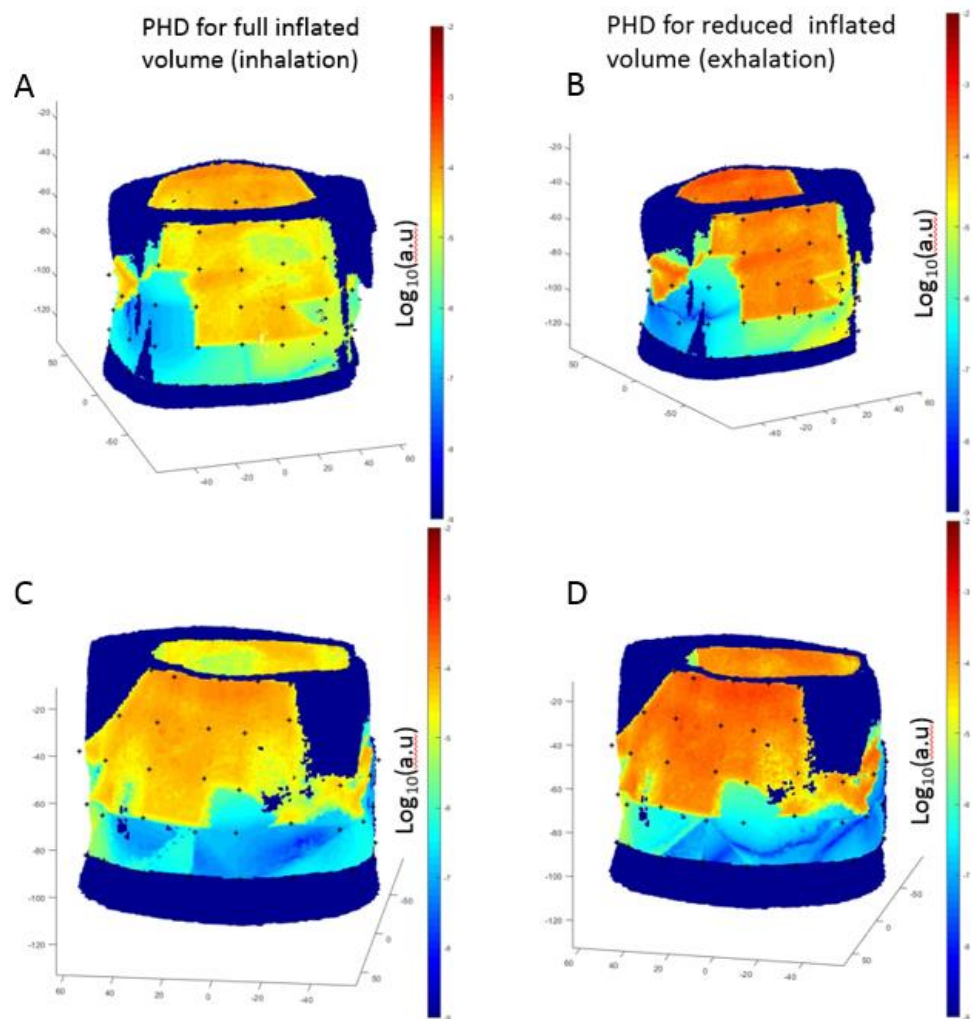


Figure 4: Photon hitting density plots for detectors on the front (A,B) and back (C,D) of the thorax for the maximum inflated volume of the lung (inhalation) and exhalation.

The development of the GASMAS technique has the potential to minimize critically mortality and morbidity in the severely ill group of preterm neonates. Computational models can be used to fast track and increase the potential of success of these studies.

REFERENCES

- [1] A. A. Fanaroff, B. J. Stoll, L. L. Wright, W. A. Carlo, R. A. Ehrenkranz, A. R. Stark, C. R. Bauer, E. F. Donovan, S. B. Korones, A. R. Laptook, J. A. Lemons, W. Oh, L.-A. Papile, S. Shankaran, D. K. Stevenson, J. E. Tyson, and W. K. Poole, "Trends in neonatal morbidity and mortality for very low birthweight infants," *American Journal of Obstetrics & Gynecology*, vol. 196, no. 2, pp. 147.e1-147.e8.
- [2] M. S. Linet, K. P. Kim, and P. Rajaraman, "Children's exposure to diagnostic medical radiation and cancer risk: epidemiologic and dosimetric considerations," *Pediatric radiology*, vol. 39 Suppl 1, no. Suppl 1, pp. S4-S26, 2009.
- [3] E. K. Svanberg, P. Lundin, M. Larsson, J. Akesson, K. Svanberg, S. Svanberg, S. Andersson-Engels, and V. Fellman, "Diode laser spectroscopy for noninvasive monitoring of oxygen in the lungs of newborn infants," *Pediatr Res*, vol. 79, no. 4, pp. 621-8, Apr, 2016.
- [4] L. A. Persson, Mats; Lewander, Märta; Svanberg, Katarina; Svanberg, Sune, "Gas monitoring in human sinuses using tunable diode laser spectroscopy," *Journal of Biomedical Optics*, vol. 12(5), no. [054001], 2007.
- [5] S. Svanberg, "Gas in scattering media absorption spectroscopy – from basic studies to biomedical applications," *Laser & Photonics Reviews*, vol. 7, no. 5, pp. 779-796, 2013.
- [6] M. Lewander, A. Bruzelius, S. Svanberg, K. Svanberg, and V. Fellman, "Nonintrusive gas monitoring in neonatal lungs using diode laser spectroscopy: feasibility study," *Journal of biomedical optics*, vol. 16, no. 12, pp. 127002-1270026, 2011.
- [7] J. L. Peilang Liao, Emilie Krite Svanberg, Patrik Lundin, Johannes Swartling, Märta Lewander Xu, Joakim Bood and Stefan Andersson-Engels, "Source-detector position analysis of percutaneously measured O₂-gas signal in a 3D preterm infant lung computer simulation," *Paper under review*, 2017.
- [8] H. Dehghani, M. E. Eames, P. K. Yalavarthy, S. C. Davis, S. Srinivasan, C. M. Carpenter, B. W. Pogue, and K. D. Paulsen, "Near infrared optical tomography using NIRFAST: Algorithm for numerical model and image reconstruction," *International Journal for Numerical Methods in Biomedical Engineering*, vol. 25, no. 6, pp. 711-732, 2009.

PAPER VIII

Numerical investigation of the influence of the source and detector position for optical measurement of lung volume and oxygen content in preterm infants

Andrea Pacheco, Baptiste Jayet, Emilie Krite Svanberg, Hamid Dehghani, Eugene Dempsey, Stefan Andersson-Engels.

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Numerical investigation of the influence of the source and detector position for optical measurement of lung volume and oxygen content in preterm infants

Andrea Pacheco^{1,2*} | Baptiste Jayet¹ | Emilie Krite Svanberg³ |
Hamid Dehghani⁴ | Eugene Dempsey⁵ | Stefan Andersson-Engels^{1,2}

¹Biophotonics@Tyndall, IPIC, Tyndall National Institute, Cork, Ireland

²Department of Physics, University College Cork, Cork, Ireland

³Department of Clinical Sciences, Paediatric Anaesthesiology and Intensive Care Medicine, Skåne University Hospital, Lund University, Lund, Sweden

⁴School of Computer Science, the University of Birmingham, Birmingham

⁵INFANT Centre, Cork University Maternity Hospital, University College Cork, Ireland

*Correspondence

Andrea Pacheco, Tyndall National Institute, Lee Maltings, Dyke Parade, T12R5CP Cork, Ireland.
Email: andrea.pacheco@tyndall.ie

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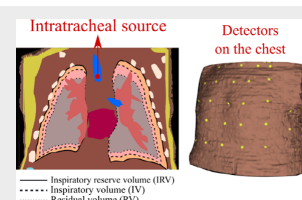
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Abstract

There is an urgent need for improved respiratory surveillance of preterm infants. Gas in scattering media absorption spectroscopy (GASMAS) is emerging as a potential clinical cutaneous monitoring tool of lung functions in neonates. A challenge in the clinical translation of GASMAS is to obtain sufficiently high signal-to-noise ratios in the measurements, since the light attenuation is high in human tissue. Previous GASMAS studies on piglets have shown higher signal quality with an internal source, as more light propagates through the lung and the loss due to scattering and absorption is less. In this article we simulated light propagation with an intratracheal and a dermal source, and investigated the signal quality and lung volume probed. The results suggest that GASMAS has the potential to measure respiratory volumes; and the sensitivity is higher for an intratracheal source which also enables to probe most of the lung.

KEYWORDS

computational model of a thorax, light transport, preterm infants, tuneable diode laser absorption spectroscopy



1 | INTRODUCTION

Prematurity is the leading cause of neonatal mortality worldwide. In 2010, the estimated mean preterm birth rate was between 12.3% and 18.1%, resulting in 14.9 million infants born before 37 weeks of gestation worldwide [1]. Premature birth can result in long-term

complications and the associated health-risks increase with lower gestational age [2].

The lungs of preterm infants lack both structural and biochemical maturation, which together with surfactant (lipoprotein decreasing surface tension in the alveoli) deficiency and incomplete vascularization can cause respiratory distress syndrome (RDS) [3]. RDS in turn

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results in respiratory failure manifested by a lack of oxygen and excess of carbon dioxide. The clinical criteria for RDS diagnosis include fast shallow breathing (tachypnea), blueish skin (cyanosis), chest retractions, flaring nostrils and expiratory grunting sounds [4]. Chest radiography shows a ground-glass appearance, air bronchograms and hypo-expansion of the lungs; pulse oximetry may show low level of oxygen and blood gas analysis an accumulation of carbon dioxide in the blood [5].

Antenatal administration of corticosteroids, nasal continuous positive airway pressure (NCPAP) and surfactant administration to preterm neonates reduce the severity of RDS and minimise further development of respiratory disease [5, 6]. These therapies alongside invasive mechanical ventilation aim to achieve optimal lung volumes. However, excessive inspiratory pressures represent a risk for baro-traumatic lung injury and long term problems such as chronic lung disease [7].

Gas in scattering media absorption spectroscopy (GASMAS) is a tuneable diode laser spectroscopic technique developed for noninvasive measurement of gas enclosed inside turbid media without extraction [8]. The technique relies on the sharp and specific absorption lines of gases, enabling sensitive measurements of gas concentrations in the presence of a scattering solid-state media with much broader absorption features [9, 10]. GASMAS has industrial applications including quality control and characterisation of wood, food packaging, ceramics and pharmaceutical tablets [11–15]; further studies are addressing its clinical translation for assessment of inflammation and infection in paranasal sinus cavities [16–18], otitis diagnosis [19] and early prediction of osteonecrosis [20]. The application of main relevance for the work in this article is the monitoring of oxygen (O_2) and water (H_2O) vapour in the lungs of new-born infants [21, 22]. GASMAS is a light-based technology, therefore, it is nonharmful and its clinical applications are contributing to the accomplishment of the UN third Sustainability Development Goal [23].

In a typical GASMAS measurement targeting to sense O_2 content in the lungs of a neonate, a dual wavelength diffuse laser source illuminates the walls of the chest. Light scattered from the inflated alveoli within the lung, reach a photodetector and the attenuated signal from the gas is identified. One of the lasers scans an absorption line of molecular O_2 around 760 nm and the second scans an absorption line of H_2O vapour around 820 or 934 nm. The wavelengths are spectrally close, and the path length within the tissue is assumed to be approximately the same. The vapour concentration is calculated using the ideal gas law and the Arden Buck equation [24], for known relative humidity and temperature (100%

and $\sim 37^\circ\text{C}$, respectively). The H_2O absorption signal is used to estimate the absorption path length by means of the Beer–Lambert law [25].

$$I = I_0 e^{-\epsilon c l} \quad (1)$$

where I is the intensity of light reaching the detector, I_0 is the intensity of the light source, ϵ is the molar absorption of the gas, c the gas concentration and l the gas absorption path length.

Consequently, the calculated value of l is input in Equation (1) to estimate the O_2 concentration, using the absorption signal of light at 760 nm.

Previous study focused in advancing GASMAS for O_2 gas sensing in the lungs of pre-term neonates included theoretical modelling [26], tissue phantom measurements [27–29], and feasibility studies with new-born piglets [30], and healthy full-term infants [22, 31, 32]. Most of these studies have been conducted noninvasively with both source and detector placed on the thorax wall. The results have suggested that stronger signal would be required to gain clinical acceptance.

The quality of the measured gas absorption signal could improve by utilising an internal light source. Severe RDS often need invasive mechanical ventilation, with a tube inserted in the trachea. Almost all preterm infants have a naso-gastric feeding tube, inserted in one nostril, located in the oesophagus and ending in the stomach. An internal light source approach, either through the endotracheal tube or the naso-gastric feeding tube, will potentially provide better signal quality, less light attenuation due to scattering and absorption, and a more robust signal [33].

Larsson et al. found that light administration with a fibre inside the trachea of a phantom model, gives larger gas absorption signals with higher signal-to-noise ratio compared with dermal sources [28]. Krite Svanberg et al. performed measurements in mechanically ventilated piglets with light sources placed in the oesophagus and on the skin, concluding that the detected gas absorption signal is one order of magnitude larger in comparison with measurements taken with a dermal light source [30]. Aiming to fully understand these results, and evaluate the pros and cons of placing an endotracheal and/or dermal source, we in this article, present simulations showing the gain in signal arising from the placement of a light source in the trachea of a computational model from a neonate's thorax. And, based on the results, we highlight the possibility to apply GASMAS technology to sense the changes in pulmonary volume during respiration.

The conducted studies are based on diffuse light modelling implemented with the software package NIRFAST [34]. The geometry of the thorax was recovered

TABLE 1 Optical properties (μ_a and μ_s') at 760 and 820 nm assigned to the 9 tissue types included in the computational thoracic models

Tissue	760 nm		820 nm		References
	μ_a (cm ⁻¹)	μ_s' (cm ⁻¹)	μ_a (cm ⁻¹)	μ_s' (cm ⁻¹)	
Skin	0.031	24.82	0.027	22.76	[10, 35]
Fat	0.128	13.85	0.069	13.24	[36]
Muscle	0.196	14.07	0.198	12.82	[10, 37]
Bone	0.100	9.30	0.110	8.40	[10]
Cartilage	0.532	7.93	0.544	8.46	[38]
Heart	0.249	4.89	0.111	4.45	[10]
Artery	3.138	16.69	4.906	15.87	[10]
Trachea	0.196	14.07	0.198	12.82	[10]
Lung	0.505	5.37	0.740	4.99	[10]

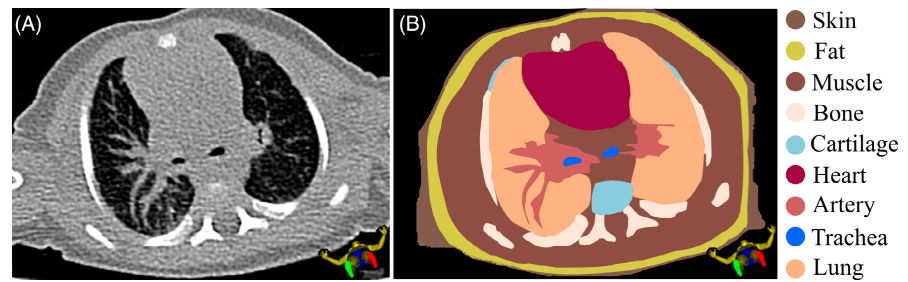


FIGURE 1 (A) Axial plane slice from anonymized CT scan of a 3.58 kg infant born in gestational week 36 and (B) equivalent segmented slice where each colour highlights a specific tissue (see legend to the right)

from a computed tomography scan (CT) of a pre-term neonate. Each CT slice was segmented to distinguish nine different organs (skin, fat, muscle, bone, cartilage, heart, artery, trachea and lung). A set of optical properties, absorption and reduced scattering coefficients (μ_a and μ_s'), were assigned to each organ, based on values available in literature (see Table 1). Finally, we modelled the intensity of light reaching detectors over the thorax with fixed endotracheal and dermal light sources; and evaluated how sensitive the signal would be to volume changes mimicking respiration.

2 | CONSTRUCTION OF THORACIC MODEL

2.1 | Anthropomorphic geometry

NIRFAST is a modelling and image reconstruction software, which uses Digital Imaging and Communications in Medicine (DICOM) images as input, to create computational models of biological tissue. These models preserve the anthropomorphic geometry of the segmented

organs and can be used to simulate near-infra-red (NIR) light propagation based on the finite element method (FEM) for a specific set of landmarks (source and detectors) defined by the user [39].

DICOM images from an anonymised CT scan of a 3.58 kg infant born in gestational week 36 were used to construct the computational 3D model of the thorax. The CT consisted of a stack of 367 cross sectional slices 0.625 mm thick. Each image had 512×512 pixels, with a pixel size of 0.356 mm in both directions. The CT scan was acquired after parental consent following the guidelines of the ethical approval ECM 4 (gg) 7 March 2018 from the Clinical Research Ethics Committee of the Cork Teaching Hospitals.

2.2 | Organ segmentation and creation of computational thorax

The 3D computational model of the thorax was constructed by means of NIRFAST, which allowed segmentation by direct drawing over the CT images. The organs conforming the computational thorax model were: skin,

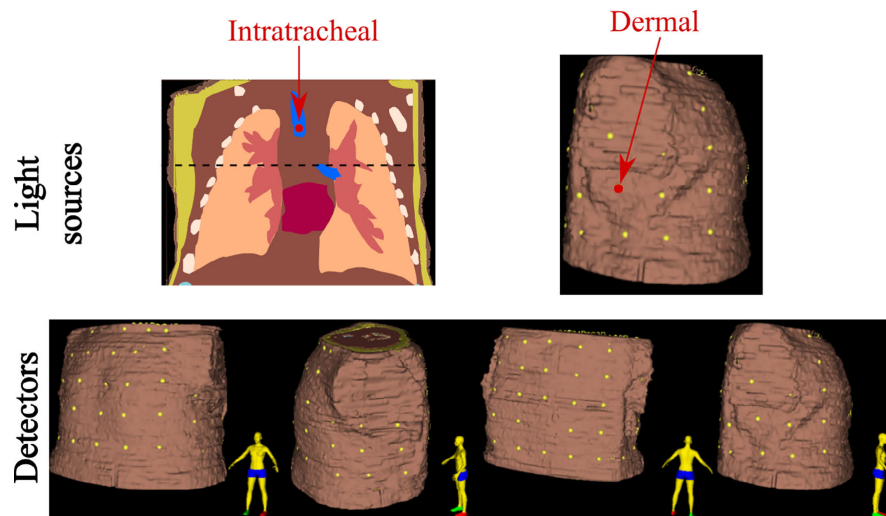


FIGURE 2 Positions of source and detector landmarks in the computational models. In transmittance geometry, the source was located inside the trachea and in remittance geometry under the right armpit. A set of the 68 dermal detectors (yellow dots) was located around the thorax to model NIR light propagation. The dashed line corresponds to the axial plane in Figure 1

fat, muscle, bone, cartilage, heart, artery, trachea (including the primary bronchi) and lung (Figure 1). For segmentation purposes a different label was assigned to each organ present in the CT stack. The boundaries between organs were defined by differences in intensity levels of Hounsfield Units (HU), a quantitative scale used to describe tissue radio-density [40]. The segmentation tool “Grow from seeds” was used to create complete segmentation and avoid empty spaces within the model.

Each organ was considered optically homogeneous; small structures usually present in tissue like veins, collagen, etc. were absent in this model. The values of absorption and reduced scattering were taken from literature [10, 34, 39, 40]. The optical properties of trachea, primary bronchi and muscle were considered to be the same, as muscle is one of the main constituents of trachea [41]. Since the latest GASMAS prototype combines two diode lasers operating at 760 and 820 nm [30], those wavelengths were chosen for this study (Table 1).

To have a deeper understanding of the interaction of NIR light injected from the trachea or armpit with the lung and the surrounding organs, a set of landmarks (points which define a position in space) was placed in the model to represent two configurations, one with an endotracheal light source (transmittance geometry) and one with a dermal source placed under the right armpit

(remittance geometry). A group of detectors distributed over the torso was used for both configurations, as can be seen in Figure 2.

The segmentation and the landmarks were provided as input to execute the standard meshing routine of NIRFAST [39].

A three-dimensional (3D) mesh of the thorax was created to model the diffusion of NIR light. The mesh had 1 356 069 tetrahedral elements, 229 363 nodes and 69 landmarks in total.

2.3 | Respiration model

Lung volume measurements are essential for diagnosis and surveillance of respiratory diseases [42]. To understand the variation in the GASMAS signal linked to pulmonary volume changes during respiration, three sub-segments of the lung were created, as a simplified model of inflation stages between inspiration and expiration (Figure 3). The inspiratory reserve lung volume (IRV = 206 ml) was modelled assigning lung optical properties to all segments; the inspiratory lung volume (IV = 195 ml) assigning muscle optical properties to the most exterior segment; and the residual lung volume (RV = 137 ml) assigning lung optical properties to the inner segment and muscle optical properties to the external segments.

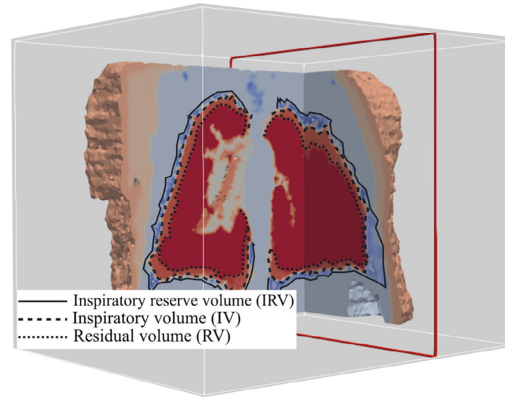


FIGURE 3 Computational model with lung sub-segments used to recreate the pulmonary volumes (IRV, IV and RV)

3 | MODELLING OF LIGHT PROPAGATION

3.1 | Forward model and photon hitting density

At the utilised wavelengths, scattering interactions dominate over absorption ($\mu_a \ll \mu_s$) and the detectors were placed far from the source, therefore, the diffusion equation approximation was used to solve the NIR light propagation [34]. This was achieved through the forward model of NIRFAST for both 760 and 820 nm.

The primary output from the forward model is the light fluence rate $\phi(x, y, z)$ at each nodal point of the mesh. The absorption of light due to the presence of molecular O_2 inside the alveoli can be computed, as the product of fluence rate in lung by the absorption of the gas. This absorption imprint of O_2 is about 10^{-4} weaker than that of the surrounding tissue and will not significantly change the value of fluence rate within the tissue [26].

The absorption imprint of the detected signal for any given position in the tissue is proportional to the photon hitting density (*PHD*) [43]. The *PHD* describes the expected path length spent by photons at any given position when travelling between source and detector. It thereby shows the probability of a change in optical properties at a certain position to affect the measured signal [44]. The *PHD* was found by solving the forward model to estimate ϕ_S for a mesh node in a location (x, y, z) with the light injection point in the source (*S*), followed by the calculation of ϕ_D assuming that the light injection point is now located in the position of the detector (*D*) and multiplying both values:

$$PHD_{SD}(x, y, z) = \phi_S(x, y, z) \cdot \phi_D(x, y, z) \quad (2)$$

The total photon hitting density (*TPHD*) corresponds to the contribution from all nodes (*n*) of the mesh. It is related to the total light intensity detected (see supplementary material), and does not provide information about the gas absorption in lung tissue.

$$TPHD_{SD} = \sum_{n_{\text{mesh}}} \phi_S(x, y, z) \cdot \phi_D(x, y, z) \quad (3)$$

Liao et al. introduced the concept of *sensitivity* (σ) for GASMAS measurements, as the ratio between the sum of the *PHD* for nodal points allocated within the lung and the *TPHD* [26]. Source-detector configurations with high sensitivity are more likely to output a high gas absorption signal as the path length of light within the lung is a larger fraction of the total path length.

$$\sigma = \frac{\sum n_{\text{lung}} \phi_S(x, y, z) \cdot \phi_D(x, y, z)}{\sum n_{\text{mesh}} \phi_S(x, y, z) \cdot \phi_D(x, y, z)} \quad (4)$$

TPHD and σ were calculated at two wavelengths for the three different lung volumes: IRV, IV and RV, for two different configurations, one with endotracheal source and 68 detectors on the torso and with a dermal source under the right armpit and 67 detectors.

4 | RESULTS AND DISCUSSION

The interpolated values of the fluence rate for each nodal point in the lung when light is injected inside the trachea and under the armpit (dermal light source) are shown in Figure 4. The dermal source was located under the armpit in agreement with the translational investigation article published by Krite Svanberg et al. who found this geometry to be the most favourable to obtain gas absorption signal for a set of 21 full term infants [31]. These geometries are analysed throughout this study.

The placement of the intratracheal light source results in a gain of two orders of magnitude ($\sim 1.6 \times 10^{-2}$) in light fluence rate in the lung. This means there will be more light interacting with the gas in the lung, while it tells little about how that absorption would be detectable at superficial locations around the thorax. To understand how placing an internal source could influence the detected signal in various positions over the torso, we revise next, the *TPHD* and σ for both configurations.

Equation 3 was computed for each of the 68 detectors with the source placed in the trachea of the computational model with optical properties at 760 and 820 nm. The interpolated values of *TPHD* were plotted for the

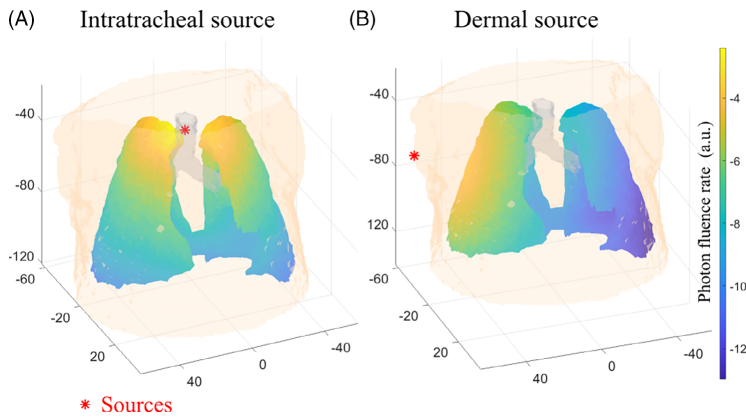


FIGURE 4 Logarithmic maps of light fluence rate for the computational model with optical properties at 760 nm with a tracheal (A) and a dermal (B) light source, which position is represented by a red asterisk

different respiratory volumes in Figure 5A. The same calculation was performed with the dermal source. In that case the number of detectors was 67 and the landmark located in the trachea was discarded prior to the data interpolation which can be seen in Figure 5B.

The maximum value of *TPHD* is obtained for the remittance configuration (dermal source placed under the armpit). Detectors close to the source will detect high light signals and will therefore have high *TPHD*. We discuss the combined requirement of high *TPHD* and σ below.

For the intratracheal light source, the *TPHD* increases in the respiration phase as the lung volume decreases. This is most likely related to the higher light attenuation of lung tissue compared with muscle, which was used to replace the perimeters of lung tissue in the simulations, for the inspiratory and reserve lung volumes. We see the same tendency for the dermal source but less accentuated, most likely because less of the detected light will pass through the lung tissue for this geometry.

Comparing the two wavelengths (760 and 820 nm), the values of *TPHD* for the intratracheal source simulations do not differ much, meaning that both wavelengths are attenuated similarly when transmitted through the tissue. This is ideal for the assumptions of similar path lengths in the lung tissue for the two wavelengths, made to estimate O_2 concentrations in the lung. In contrast, the light paths for the dermal source simulations are dominated by superficial tissue (skin, fat and muscle), and the light attenuation at 820 nm is lower for those tissues than at 760 nm, resulting in a higher *TPHD* for 820 nm compared with light at 760 nm.

To know how much of the light injected in the trachea and under the armpit would interact with the gas in the lung, σ was plotted for both configurations and all the pulmonary volumes in Figure 6. The regions of the

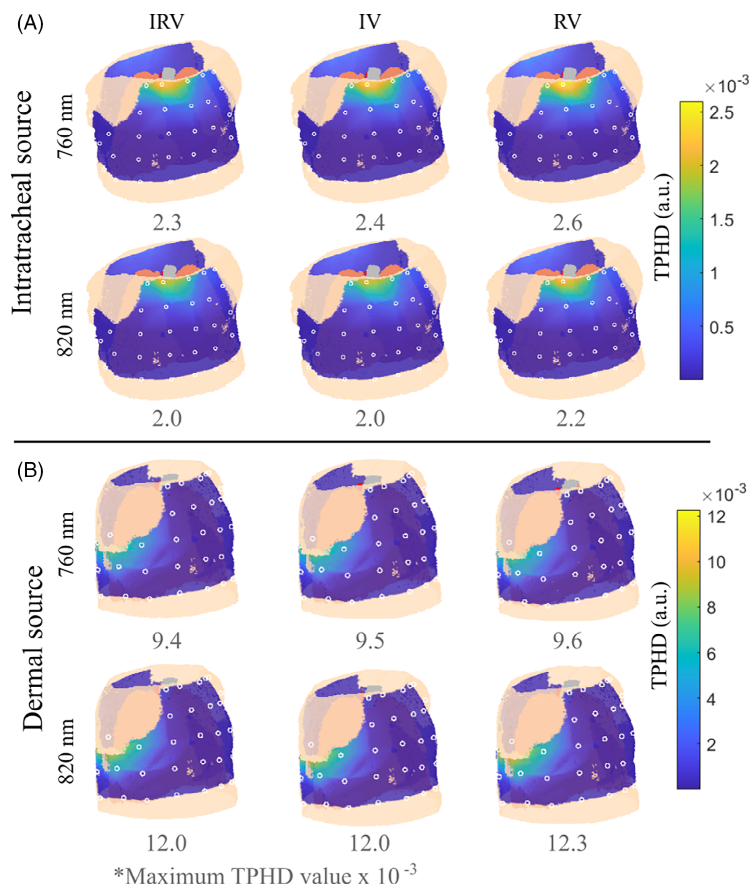
thorax with higher σ correspond to the configurations for which the light spent longer time interacting with lung tissue, which is correlated with higher gas absorption signals.

The σ maps for intratracheal source (Figure 6A) show that the percentage of the total path length spent in lung tissue is rather constant, independent on the detection configuration (slightly <1% of the total photon path is through lung tissue). A likely explanation is that the lung tissue is very close to the source and most of the path length is spent within the lung independently on the path the light takes through the tissue to reach the detectors. The pattern for the dermal source is very different (Figure 6B). For this configuration, the fraction of the path length spent in the lung tissue (deep into the body) is higher the further away from the source the detector is located. Comparing the two wavelengths, again σ differ more for the dermal than for the internal source, probably for same reason as discussed for the *TPHD*.

Figure 7A corresponds to transmittance geometry in which the source is placed in the trachea and the detectors over the thorax. In this case the light propagates towards the anterior (0° – 180°) and posterior (180° – 0°) sides of the thorax. The σ map overlaps at some angles with the *TPHD* lobes. This means it should be possible to obtain a position with both relatively high light transmission and gas sensitivity. Best detector position in this respect for this particular plane seems to be around 30° .

Figure 7B resembles the remittance geometry, in which the source (located under the armpit at 330°) and detectors are placed over the thoracic wall. In this case, the light undergoes attenuation by the external tissues (i.e. bone, muscle, fat and skin) as light goes from the source to the lung and on the way back to the detector. This plot shows how the σ distribution is strong when the *TPHD* value is low and vice versa, meaning it is

FIGURE 5 Interpolated TPHD for the respiratory volumes (IRV, IV and RV) at 760 and 820 nm with endotracheal (A) and dermal (B) light source with a set of detectors (circular markers) placed over the thorax. The numbers in grey indicate the maximum TPHD values within each case



unlikely to get both a strong light signal and sensitivity for the same source detector configuration. The optimal detection positions considering both sensitivity and light transmission is around 300° , corresponding to a measurable sensitivity and still a relatively high *TPHD*. This position relates well with the experimental findings reported in Ref [31].

The plots of Figure 7 are useful to identify optimum source-detector geometries. For example, the detectors shown in Table 2 will sense the highest signal carrying the absorption imprint of O_2 gas inside the lung, at this specific coronal plane. The values of *TPHD* and σ for intratracheal and dermal source for those detectors are specified below:

Table 2, show that light delivered internally is more likely to carry as absorption imprints, associated with high σ . The results show that GASMAS has the potential to quantify changes in lung volume, which could be correlated with the alveolar status of lung

tissue. And, it could be possible to perform continuous bedside measurement of pulmonary volumes in neonates. This represents an advantage compared with current methods such as radiography, gas dilution (requires the infant to remain quiet for at least 10 min) and plethysmography (not suitable for bedside measurements or assessment in very small infants) [45]. Electrical impedance tomography can be used to monitor changes in regional ventilation and lung volume in infants, but lacks of information about the alveolar gas content [46].

It should be noted that in this study the light sources were placed in a fixed position and a different placement would alter the light distribution and to some extent the conclusions. However, these results are in agreement with the experimental studies performed in Bio-photonics@Tyndall in which the optical properties and structure of tissue from the respiratory zone were modelled in an optical phantom, that enabled benchtop

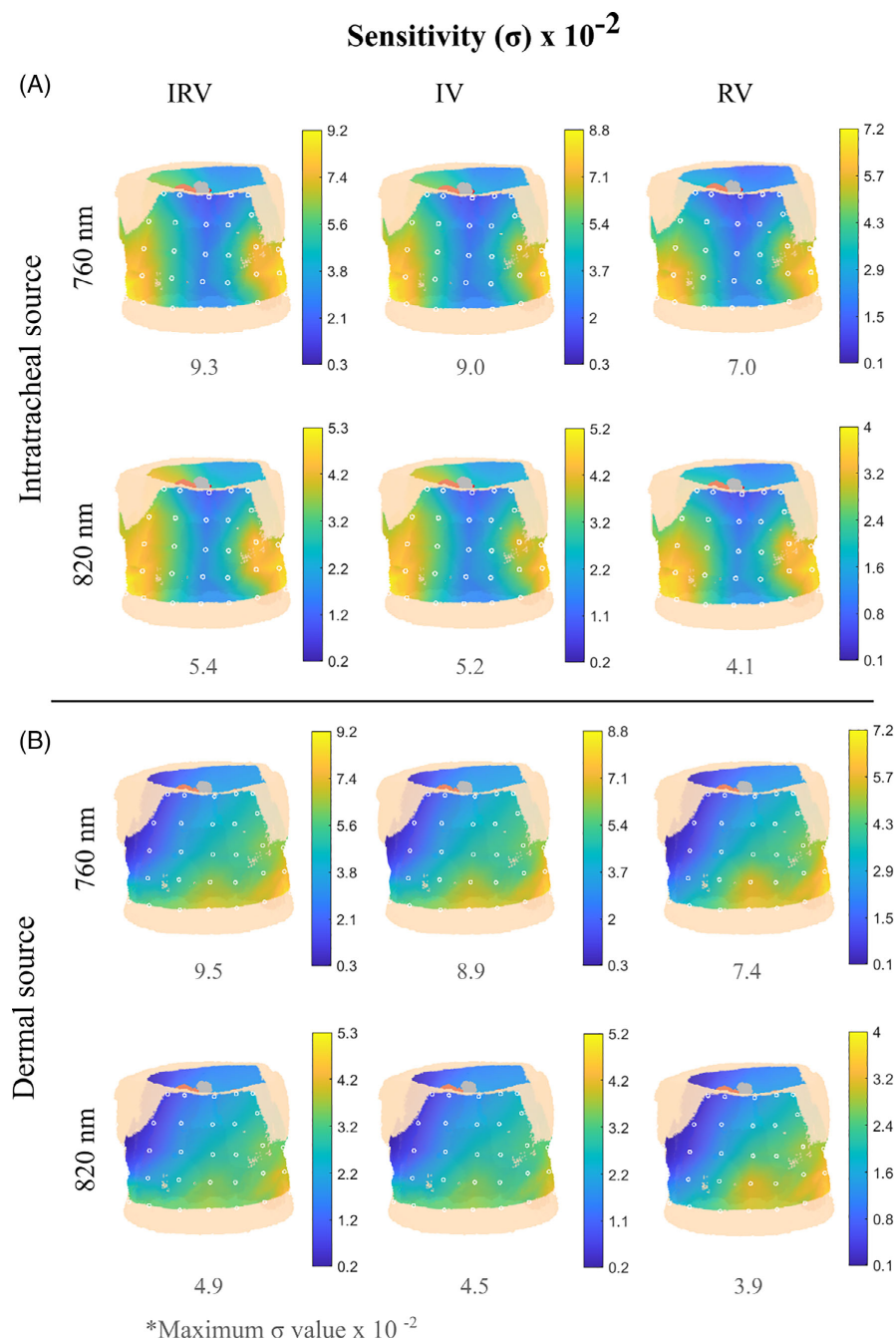


FIGURE 6 Sensitivity (σ) plots for the respiratory volumes (IRV, IV and RV) at 760 nm (top row) and 820 nm (bottom row) with endotracheal (A) and dermal (B) light source with a set of detectors (circular markers) placed over the thorax. The numbers in grey indicate the maximum σ values

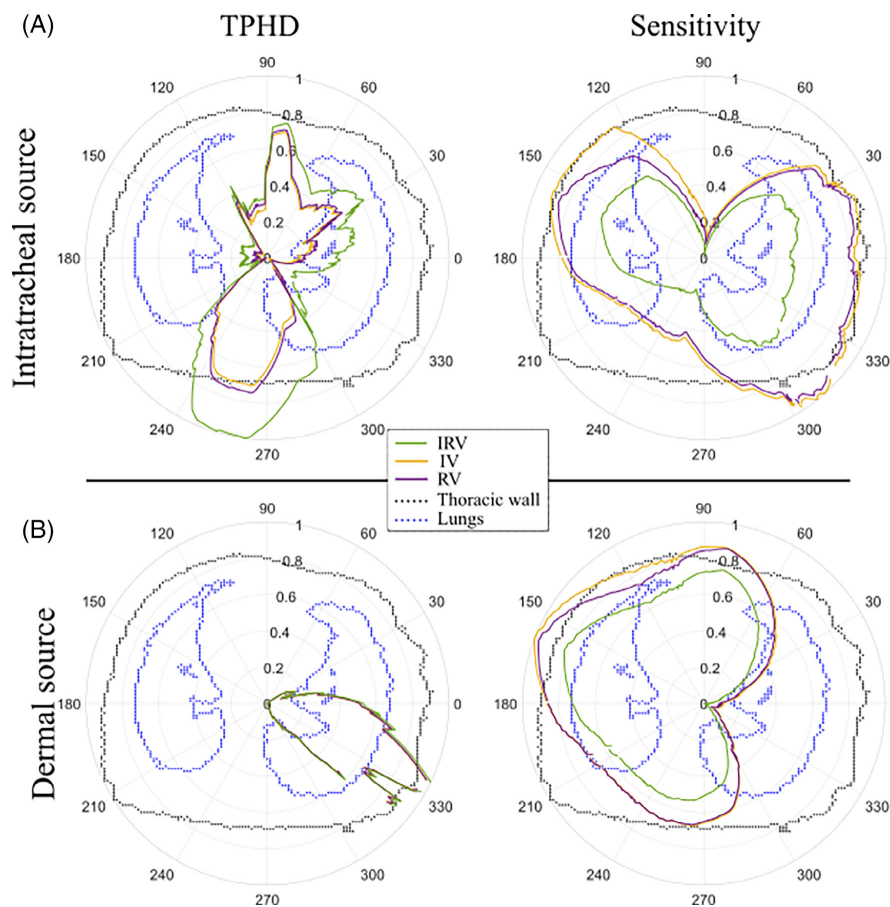


FIGURE 7 The normalised polar plot of the $TPHD$ and σ values for the intratracheal and dermal sources at 760 nm. The coronal plane (vertical plane dividing the body into anterior and posterior parts) is signed with the dashed line in Figure 2

measurements of changes in gas volume with a GASMAS system in transmittance geometry [47]. And the gain in detected signal carrying information of gas absorption (photons reaching the detector after interacting with lung tissue), associated with the placement of an endotracheal light source compared with the dermal source, is in agreement with the results from Krite Svanberg et al. who analysed O_2 and H_2O absorption signals in five mechanically ventilated piglets with a probe delivering light externally, on the skin and internally, through the oesophagus [30]. In the same study, the authors found a weak or non-existent H_2O vapour signal when using the dermal light source, and as a consequence, the determination of O_2 concentration was not achieved. The low σ for the dermal source at 820 nm exhibited in Figure 6B confirms that for this configuration, a small amount of light reaches the

lung and the associated GASMAS signal would be non-existent or low.

Preterm infants with severe RDS often need intubation for invasive mechanical ventilation due to respiratory failure. A naso-gastric tube is inserted in almost all preterm infants for feeding proposes. Placing a light source in the trachea or the oesophagus would be feasible, and it will still be “noninvasive”, since the light source would be placed in the trachea through an already existing tube. The stronger signals, would further allow to reduce the measurement times to permit recordings of the O_2 levels in the lung as a function of phase in the respiration cycle. However, the main aim of GASMAS translated into respiratory health-care, is a noninvasive assessment of lung function, and the internal light source should be used just if the infant is already intubated. The

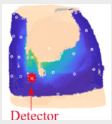
Source-detector configuration		Respiratory volume	TPHD × 10 ⁻⁴	σ × 10 ⁻²
	760	IRV	5.2	4.7
		IV	5.4	4.5
		RV	6.2	3.1
	820	IRV	4.0	3.2
		IV	4.2	3.1
		RV	5.0	2.1
	760	IRV	13	1.0
		IV	13	0.9
		RV	14	0.4
	820	IRV	14	0.6
		IV	15	0.5
		RV	16	0.2

TABLE 2 TPHD and σ values for the different respiratory volumes, with the best source detector configurations in Figure 7

localization of a near- infra-red light fibre inside the respiratory or potentially naso-gastric feeding tube, could be prototyped and evaluated.

The enhancement of sophisticated neonatal intensive care is increasing the viability of extremely preterm babies. However, prolonged intubation in low birthweight neonates is associated with risk of infection and higher morbidity [48]. The clinical translation of GASMAS technique can potentially be of help in aiding physicians to diagnose and continuously monitor the respiratory function of pre-term infants and their response to oxygen and surfactant administration [49]. As a noninvasive technique it also could develop as a tool to optimise time for extubation (withdrawal of the endotracheal tube) and contribute to the current need of improving new-born medical care [2].

5 | CONCLUSION

An anthropomorphic computational model of the thorax of a neonate with nine main organs (skin, fat, muscle, bone, cartilage, heart, artery, trachea and lung) was created. The model was used to simulate light propagation at 760 and 820 nm wavelength, for two different light-source detector configurations (remittance and transmittance geometries) during respiration.

The sensitivity maps showed that the placement of an endotracheal light source would improve the assessment of the pulmonary lobes, as light exhibits less attenuation and distributes evenly in the lung.

The variations in TPHD and σ associated to changes in pulmonary volume suggest that GASMAS can be used to assess continuously lung volumes during respiration.

The results from this study are in agreement with the experimental studies conducted by Krite Svanberg et al. in a group of mechanically ventilated piglets; our numerical model could be further used to analyse different source-detector configurations and assist in the planning of clinical protocols to advance the clinical translation of GASMAS as a complementary tool to improve the respiratory healthcare in neonates.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Andrea Pacheco was involved in conceptualization, investigation and writing—original draft; Baptiste Jayet was involved in conceptualization, investigation and writing—plots; Emilie Krite Svanberg, Hamid Dehghani, Eugene Dempsey and Stefan Andersson-Engels were involved in conceptualization, writing—review and editing and Stefan Andersson-Engels was involved in supervision and project management.

DATA AVAILABILITY STATEMENT

The data from the discrete 3D mesh of the thorax of the neonate are openly available at the public repository <https://doi.org/10.5281/zenodo.4916862>. The scripts that support the findings of this study are openly

available at the public repository <https://doi.org/10.5281/zenodo.5996855>.

ORCID

Andrea Pacheco  <https://orcid.org/0000-0002-1856-4731>

REFERENCES

- [1] S. Beck, D. Wojdyla, L. Say, A. Pilar Bertran, M. Meraldi, J. Harris Requejo, C. Rubens, R. Menon, P. Van Look, *Bull World Health Org* **2010**, *88*, 31.
- [2] H. Blencowe, S. Cousens, D. Chou, M. Oestergaard, L. Say, A.-B. Moller, M. Kinney, J. Lawn, *Reprod Health* **2013**, *10*, S2.
- [3] T. J. M. Moss, *Proc Aust Physiol Soc* **2005**, *36*, 23.
- [4] P. O. Kero, E. O. Mikinen, *Eur. J. Pediatr.* **1979**, *130*, 271.
- [5] C. L. Hermansen, A. Mahajan, L. G. Hospital, *Am. Fam. Physician* **2007**, *76*, 987.
- [6] R. Soll, C. J. Morley, *Cochrane Database of Systematic Reviews* (Ed.: *The Cochrane Collaboration*), John Wiley & Sons, Ltd, Chichester, UK **2001**, CD000510.
- [7] K. N. Farrow, P. Fliman, R. H. Steinhorn, *Semin. Perinatol.* **2005**, *29*, 8.
- [8] M. Sjöholm, G. Somesfalean, J. Alnis, S. Andersson-Engels, S. Svanberg, *Opt. Lett.* **2001**, *26*, 16.
- [9] I. E. Gordon, L. S. Rothman, C. Hill, R. V. Kochanov, Y. Tan, P. F. Bernath, M. Birk, V. Boudon, A. Campargue, K. V. Chance, B. J. Drouin, J.-M. Flaud, R. R. Gamache, J. T. Hodges, D. Jacquemart, V. I. Perevalov, A. Perrin, K. P. Shine, M.-A. H. Smith, J. Tennyson, G. C. Toon, H. Tran, V. G. Tyuterev, A. Barbe, A. G. Császár, V. M. Devi, T. Furtenbacher, J. J. Harrison, J.-M. Hartmann, A. Jolly, T. J. Johnson, T. Karman, I. Kleiner, A. A. Kyuberis, J. Loos, O. M. Lyulin, S. T. Massie, S. N. Mikhailenko, N. Moazzen-Ahmadi, H. S. P. Müller, O. V. Naumenko, A. V. Nikitin, O. L. Polyansky, M. Rey, M. Rotger, S. W. Sharpe, K. Sung, E. Starikova, S. A. Tashkun, J. V. Auwera, G. Wagner, J. Wilzewski, P. Wcisło, S. Yu, E. J. Zak, *J Quant Spectrosc Radiat Transf* **2017**, *203*, 3.
- [10] S. L. Jacques, *Phys. Med. Biol.* **2013**, *58*, R37.
- [11] J. Alnis, B. Anderson, M. Sjöholm, G. Somesfalean, S. Svanberg, *Appl Phys B* **2003**, *77*, 691.
- [12] T. Svensson, E. Alerstam, J. Johansson, S. Andersson-Engels, *Opt. Lett.* **2010**, *35*, 1740.
- [13] P. Lundin, L. Cocola, M. Lewander, A. Olsson, S. Svanberg, *J. Food Eng.* **2012**, *111*, 612.
- [14] T. Svensson, E. Adolfsson, M. Burresi, R. Savo, C. T. Xu, D. S. Wiersma, S. Svanberg, *Appl Phys B* **2013**, *110*, 147.
- [15] L. Mei, G. Somesfalean, S. Svanberg, *Sensors* **2014**, *14*, 3871.
- [16] M. Lewander, Z. Guan, K. Svanberg, S. Svanberg, T. Svensson, *Opt Express* **2009**, *17*, 10849.
- [17] L. Persson, K. Svanberg, S. Svanberg, *Appl Phys B* **2006**, *82*, 313.
- [18] J. Huang, H. Zhang, T. Li, H. Lin, K. Svanberg, S. Svanberg, *J. Biophotonics* **2015**, *8*, 985.
- [19] L. Hu, W. Li, H. Lin, Y. Li, H. Zhang, K. Svanberg, S. Svanberg, *J. Biophotonics* **2019**, *12*, e201800305.
- [20] D. Chen, W. Li, W. He, H. Zhang, Q. Zhang, H. Lin, S. Svanberg, K. Svanberg, P. Chen, *J. Biomed. Opt.* **2019**, *24*, 1.
- [21] M. Lewander, A. Bruzelius, S. Svanberg, K. Svanberg, V. Fellman, *J. Biomed. Opt.* **2011**, *16*, 127002.
- [22] P. Lundin, E. K. Svanberg, L. Cocola, M. L. Xu, G. Somesfalean, S. Andersson-Engels, J. Jahr, V. Fellman, K. Svanberg, S. Svanberg, *J. Biomed. Opt.* **2013**, *18*, 127005.
- [23] W. Rosa Ed., *A New Era in Global Health*, Springer Publishing Company, New York, NY **2017**.
- [24] A. L. Buck, *J. Appl. Meteorol.* **1981**, *20*, 1527.
- [25] D. F. Swinehart, *J. Chem. Educ.* **1962**, *39*, 3.
- [26] P. Liao, J. Larsson, E. K. Svanberg, P. Lundin, J. Swartling, M. L. Xu, J. Bood, S. Andersson-Engels, *J. Biophotonics* **2018**, *11*, 7.
- [27] J. Larsson, P. Liao, P. Lundin, E. Krite Svanberg, J. Swartling, M. Lewander Xu, J. Bood, S. Andersson-Engels, *J. Biophotonics* **2018**, *11*, e201700097.
- [28] J. Larsson, D. Leander, M. Lewander Xu, V. Fellman, J. Bood, E. Krite Svanberg, *J. Biophotonics* **2019**, *12*, e201800350. <https://doi.org/10.1002/jbio.201800350>.
- [29] A. Pacheco, H. Li, M. Chakravarty, S. K. V. Sekar, S. Andersson-Engels, *J. Biomed. Opt.* **2020**, *25*, 25. <https://doi.org/10.1117/1.JBO.25.11.115001>.
- [30] E. K. Svanberg, J. Larsson, M. Rasmussen, M. Larsson, D. Leander, S. Bergsten, J. Bood, G. Greisen, V. Fellman, *Pediatr. Res.* **2020**, *89*, 823. <https://doi.org/10.1038/s41390-020-0971-x>.
- [31] E. K. Svanberg, P. Lundin, M. Larsson, J. Åkeson, K. Svanberg, S. Svanberg, S. Andersson-Engels, V. Fellman, *Pediatr. Res.* **2016**, *79*, 621.
- [32] P. Lundin, E. K. Svanberg, L. Cocola, M. Lewander, S. Andersson-Engels, J. Jahr, V. Fellman, K. Svanberg, S. Svanberg, in *Proc. SPIE 8229, Optical Diagnostics and Sensing XII: Toward Point-of-Care Diagnostics; and Design and Performance Validation of Phantoms Used in Conjunction with Optical Measurement of Tissue IV* (Eds: R. J. Nordstrom, G. L. Coté), SPIE BiOS, San Francisco, CA **2012**, 822903. <https://doi.org/10.1117/12.907464>.
- [33] E. K. Svanberg, S. Svanberg, Device and technique for internal illumination for human gas monitoring., n.d., CN107923847A.
- [34] H. Dehghani, M. E. Eames, P. K. Yalavarthy, S. C. Davis, S. Srinivasan, C. M. Carpenter, B. W. Pogue, K. D. Paulsen, *Commun. Numer. Methods Eng.* **2009**, *25*, 711.
- [35] N. Choudhury, R. Samatham, S. L. Jacques, in *Proc. SPIE 7548, Photonic Therapeutics and Diagnostics VI*, 75480G, **2010**. <https://doi.org/10.1117/12.842648>.
- [36] R. L. P. van Veen, H. J. C. M. Sterenborg, A. Pifferi, A. Torricelli, R. Cubeddu, *Biomedical topical meeting, OSA*, Optica Publishing Group, Miami Beach, FL **2004**, p. SF4.
- [37] R. Re, I. Pirovano, D. Contini, L. Spinelli, A. Torricelli, *Sensors* **2018**, *18*, 264.
- [38] D. W. Ebert, C. Roberts, S. K. Farrar, W. M. Johnston, A. S. Litsky, A. L. Bertone, *J. Biomed. Opt.* **1998**, *3*, 326.
- [39] M. Jermyn, H. Ghadyani, M. A. Mastanduno, W. Turner, S. C. Davis, H. Dehghani, B. W. Pogue, *J. Biomed. Opt.* **2013**, *18*, 086007.
- [40] M. Mahesh, *Radiographics* **2002**, *22*, 14.
- [41] B. E. M. Brand-Saberi, T. Schäfer, *Thorac. Surg. Clin.* **2014**, *24*, 1.
- [42] M. F. Lutfi, *Multidiscip. Respir. Med.* **2017**, *12*, 3.
- [43] J. C. Schotland, J. C. Haselgrove, J. S. Leigh, *Appl. Optics* **1993**, *32*, 448.
- [44] S. R. Arridge, *Appl. Optics* **1995**, *34*, 7395.

- [45] G. Hülskamp, J. J. Pillow, J. Dinger, J. Stocks, *Pediatr. Pulmonol.* **2006**, *41*, 1.
- [46] I. Chatziioannidis, T. Samaras, N. Nikolaidis, *Hippokratia* **2011**, *15*, 211.
- [47] A. Pacheco, K. Grygoryev, W. Messina, S. Andersson-Engels, *J. Biomed. Opt.* **2021**, *27*, 27. <https://doi.org/10.1117/1.JBO.27.7.074707>.
- [48] D. Holleman-Duray, D. Kaupie, M. G. Weiss, *J. Perinatol.* **2007**, *27*, 776.
- [49] A. Pacheco, E. Dempsey, S. Andersson-Engels, *Asian J Basic Sci Res* **2020**, *9*, 251.

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PAPER IX

Gas in scattering media absorption spectroscopy as a potential tool in neonatal respiratory care

Jurate Panaviene, Andrea Pacheco, Christoph E. Schwarz, Konstantin Grygoryev, Stefan Andersson-Engels and Eugene Dempsey.

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REVIEW ARTICLE OPEN



Gas in scattering media absorption spectroscopy as a potential tool in neonatal respiratory care

Jurate Panaviene^{1,2,3} , Andrea Pacheco^{4,5}, Christoph E. Schwarz^{1,3,6}, Konstantin Grygoryev⁴, Stefan Andersson-Engels^{4,5} and Eugene M. Dempsey^{1,2,3}

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Gas in scattering media absorption spectroscopy (GSMAS) is a novel optical technology employing near-infrared light. It has a potential use in the medical setting as a monitoring and diagnostic tool by detecting molecular oxygen within gas pockets and thus may be a useful adjunct in respiratory monitoring. GSMAS has potential advantages over other monitoring devices currently used in clinical practice. It is a non-invasive, continuous, non-ionising technology and provides unique information about molecular oxygen content inside the lungs. GSMAS may have a future role in optimising respiratory management of neonates in different clinical scenarios such as monitoring cardiorespiratory transition in the delivery room, assessing surfactant deficiency, and optimising endotracheal tube positioning. This article aims to summarise current evidence exploring GSMAS application in a neonate, discuss possible clinical benefits, and compare with other devices that are currently used in neonatal care.

Pediatric Research; <https://doi.org/10.1038/s41390-022-02110-y>

IMPACT:

- This article presents a novel optical technique to measure lung oxygen concentrations that may have important clinical uses.
- This review summarises the current literature investigating the concept of optical lung oxygen measurement.
- Information from this review can guide researchers in future studies.

INTRODUCTION

Medical applications of laser light technology are an ever-expanding area, enabling the improvement of non-invasive diagnostic and treatment techniques in different areas of medicine. In particular, a technique such as gas in scattering media absorption spectroscopy (GSMAS) has the potential to become a beneficial respiratory monitoring tool in clinical practice. Initially, GSMAS has been employed in different commercial areas (e.g., food,^{1–4} pharmaceutical industries^{5–7}) helping to detect, measure and analyse gas trapped inside diffuse materials. More recent in vitro and in vivo studies evaluated the concept of non-invasive oxygen detection inside biological tissues like sinuses,^{8–13} middle ear,^{14,15} femoral bone¹⁶ and lungs. Different lung phantom models were used for GSMAS measurements, such as porcine lung samples,¹⁷ or produced by 3D printing nylon shells filled with tissue optical phantom material and air^{18,19} or structured sponge.²⁰ An in vivo study has demonstrated GSMAS effectiveness in detecting pneumothorax and lung collapse in ventilated piglets.²¹ Following feasibility studies involving infants,^{22,23} GSMAS have been identified as a potential respiratory monitoring tool that might play a role in neonatology, managing infants in delivery room and intensive care units, where quantitative, non-invasive bedside monitoring of sick newborn infants is essential.

Respiratory illness is the most common indication for admission to the neonatal unit.²⁴ Whilst up to 10% of term and late preterm

infants born between 34 and 40 weeks gestational age can have respiratory problems,²⁴ more than 80% of infants born before 28 weeks will require respiratory support.²⁵ Reasons include delayed clearance of foetal lung fluid or aspiration of meconium for term babies and surfactant deficiency for premature neonates,^{26,27} compromising oxygen diffusion, absorption and subsequently resulting in decreased blood oxygen levels.

Neonatal respiratory status is currently monitored using continuous pulse oximetry (PO), intermittent blood sampling, and X-ray imaging. These methods cannot measure oxygen concentration or lung volume directly and carry some short and long-term risks.^{28,29} Optical oxygen concentration measurements present a clinical and diagnostic advantage allowing fast and non-invasive detection of suboptimal oxygen concentrations within the lung, subsequently allowing prevention of potential respiratory complications.

Currently, there is no commercially available GSMAS-based monitoring/diagnostic method that could be used in clinical practice to assess real-time regional ventilation and oxygen content at the bedside on a continuous basis.

This review article aims to summarise current evidence exploring neonatal oxygen monitoring of the lungs, discuss possible clinical applications of a novel GSMAS-based device and compare with other devices/techniques that are currently used in neonatal units.

¹INFANT Research Centre, University College Cork, Cork, Ireland. ²Department of Neonatology, Cork University Maternity Hospital, Cork, Ireland. ³Department of Paediatrics and Child Health, University College Cork, Cork, Ireland. ⁴Biophotonics@Tyndall, Irish Photonic Integration Centre, Tyndall National Institute, University College Cork Lee Maltings, Dyke Parade, Cork, Ireland. ⁵Department of Physics, University College Cork, Cork, Ireland. ⁶Department of Neonatology, University Children's Hospital, Tübingen, Germany. [✉]email: jurate.panaviene@ucc.ie

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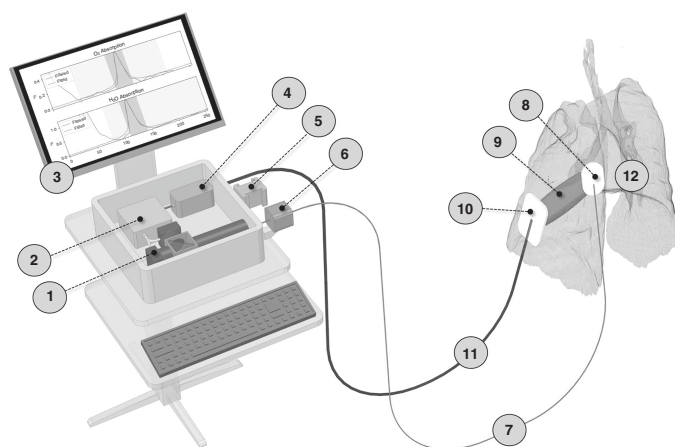


Fig. 1 Schematic drawing of the GASMAS-based lung analyser system. 1 – Dual laser source; 2 – Data acquisition and laser control module; 3 – PC; 4 – Signal pre-amplifier; 5 – Reference measurement cube; 6 – Fibre interference eliminator; 7 – Optical fibre; 8 – Light source probe (emitter); 9 – Diffuse light passing through the lung tissue; 10 – Photosensitive detector probe; 11 – Electric cable; 12 – Neonatal lung.

GAS IN SCATTERING MEDIA ABSORPTION SPECTROSCOPY

The most recurrent interactions between light and tissue are absorption and scattering (Supplementary 1 and 2). Characteristics of these interactions have been employed to develop optical technology called GASMAS. It is a technique, which measures the concentration of gas inside diffuse substances like biological tissue, relying on the difference between the absorption spectra of molecular gas and condensed matter (solids and liquids).³⁰ A usual absorption band of biological tissue is 10^1 nm broad versus 10^{-4} nm for gases. For a GASMAS measurement, a narrow-band diode laser at a specific wavelength is scanned across a characteristic gas absorption line to interrogate the material and gas pockets contained within.

The diffuse light emerging from this media carries the spectroscopic information about the gas that it passed through, which is recorded by a detector/sensor placed away from the light source. This information is used to calculate the gas concentration by means of the Beer–Lambert law, which states that the intensity of the emerging light (I), propagating through gas with concentration (c) and absorption cross-section (ϵ) along an optical path length (l), decays in an exponential way.

$$I = I_0 e^{-\epsilon c l}$$

In cases where the optical path length (l) of the gas is unknown, a dual diode laser source is used to interrogate a reference gas present in the same cavity (e.g., water vapour). The optical path length can be assumed equal for both gases if their absorption bands are spectrally close.

The novel clinical application of GASMAS technology is targeting the detection of molecular oxygen (O_2) and water (H_2O) vapour, common gases inside human body cavities, e.g., lung tissue. It uses a dual laser source with 760 and 935 nm to measure absorption signals from molecular O_2 and H_2O vapour, respectively. The concentration of H_2O vapour in a cavity with 100% relative humidity and known central body temperature (like a neonate's lung) can be calculated using the Arden Buck equation.^{31,32} Therefore, H_2O vapour is used as a reference gas to estimate the optical path length and calculate the O_2 concentration. Devices for the clinical application have the probe with integrated laser fibres attached to the skin as a light source and detector probe with the photosensitive area (Figs. 1 and 2).

OXYGEN MEASUREMENT USING GASMAS TECHNOLOGY IN CLINICAL SETTING

GASMAS applications in adult medicine

GASMAS have been applied in several feasibility studies to describe common adult diseases, like sinusitis, otitis media and osteonecrosis of femoral head. Sinusitis is an inflammatory condition resulting in a blockage of normal gas drainage and affecting the gas volume and content inside the sinus cavity due to mucosal swelling and production of secretions. The resulting blockage of normal gas drainage affects the gas volume inside the sinus cavity.

Persson et al. used two plastic plates simulating light transmission through sinuses. One plate acted as a human facial bone-muscle layer, and another plate like the base of the sinus cavity composed of mucous membranes and bone. By altering the thickness of the plates and the distance between them, it was possible to show that the O_2 absorption signal was proportional to the distance between plates and O_2 volume, thus allowing the detection of reduced gas content in cases of sinus pathology.⁸ Later Persson et al. demonstrated that GASMAS can be used to detect O_2 within the maxillary and frontal sinuses in 11 volunteers. No O_2 signal was detected where the volunteer was experiencing recurrent sinus issues. Also, the gas exchange process inside the sinus cavity has been investigated by flushing the sinuses with nitrogen, which cleared the cavity from O_2 . It has shown a 'real-time' O_2 signal drop, indicating normal gas drainage due to non-obstructed connections between air pockets.⁹ Frontal sinus H_2O signal repeatability analysis demonstrated that the recorded values remain consistent within one day or 6-day span with persistent right and left asymmetry.¹³ Further investigations have shown, that several gases (H_2O vapour and O_2) can be detected simultaneously.¹¹

Thirty-one patients with suspected mastoid sinus pathology underwent laser spectroscopy measurements and the results were compared with subsequently performed computer tomography (CT) scans. Correlation was found between sinus volume based on CT scan grading and H_2O vapour absorption imprints ($r^2 = 0.69$, 47% of variance related). Weak reproducibility has been demonstrated for H_2O vapour and molecular O_2 . Although, all cases with radiological signs of mastoid pathology were identified with laser spectroscopy.¹²

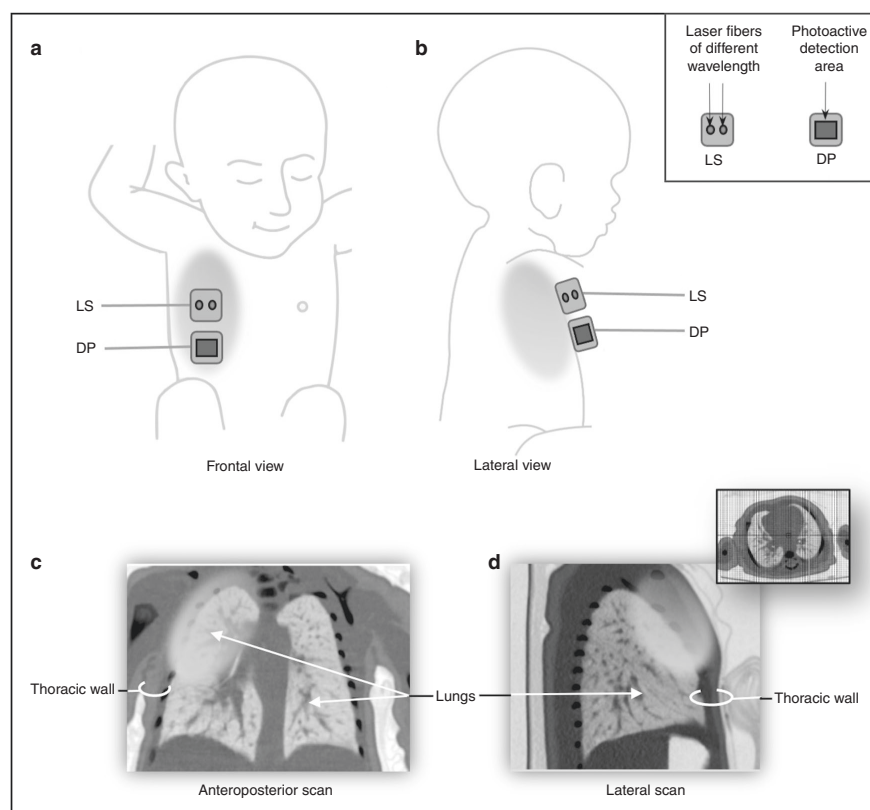


Fig. 2 GASMAS clinical application for neonatal lung oxygen detection and monitoring. **a, b** Skin placement of the probes overlying lung area. LS - light source probe, DP - detector probe. **c, d** Illustration of light distribution using thoracic CT images of a full-term 4-week-old newborn as an example. Parental consent to use images obtained. Pink-coloured areas represent the approximate extent of near-infrared light illumination used for GASMAS. Given the difficulties in predicting photon migration, the areas of light illumination are not necessarily the same as the areas of light detection.

Middle ear phantoms have been used to prove the concept of GASMAS ability to detect changes consistent with otitis media diagnosis when air volume behind eardrum reduces due to increment secretions. O_2 signal increases when flushing the phantom middle ear cavity with pure O_2 and stays stable over time. It decreases gradually when opening the orifice of the cavity and reduces when flushed with nitrogen, demonstrating the relation between the signal and O_2 concentration.^{14,15}

Chen et al. demonstrated the role of GASMAS in the early detection of osteonecrosis of the femoral head. Femoral head decay is associated with forming of air-filled pores replacing normal vessels, which can be detected using GASMAS. Eighteen hip samples obtained after routine joint replacement surgery were investigated. Eleven of them were affected by osteonecrosis. Comparing water vapour signals from normal bones and affected, a significant difference ($P < 0.05$) was found illustrating in vitro detection efficacy. In vivo studies using arthroscopy with integrated laser is to follow by this research group.¹⁶

Laser spectroscopy studies with infants

The first feasibility study performing lung measurements enrolled three healthy term-born babies. The study aimed to

investigate the quality of signal detected by probes placed in different locations on the chest and abdomen. Most of the O_2 and H_2O signal received by the detector probe was weak. Poor signal quality was likely related to the thickness of the probed tissue. Because the measurements were performed on older babies (weighing above 4 kg) with a thicker subcutaneous layer, the light was likely to be scattered and attenuated before reaching the detector. However, one position gave a clear absorption signal for H_2O vapour, with the laser source probe below the collar bone and detector just below the armpit. Few abdominal light source-detector positions were suitable to detect H_2O vapour. The probe separation and absorption signal quality relationship was demonstrated by computer simulations.^{33,34}

A subsequent study recruited 29 full-term healthy infants and obtained 390 lung optical measurements. The power of laser used for O_2 detection has increased significantly (30 mW), compared to previous studies. A total of 60% of all measurements revealed good quality signals ($SNR > 3$), and O_2 was detected at least once in each baby.²³ Nevertheless, investigators suggested the need for technical improvements for the future development of a clinical device.

GASMAS safety

The International Electrotechnical Commission and the American National Standards Institute have published a standard that outlines the safety of laser products. Laser light at the wavelengths and power level used for GASMAS falls under Class I category that is considered safe and presents no hazard to the eye or the skin under direct exposure. Laser light is coupled to the skin using a diffuser, which spreads the light over the larger surface area over the skin, reducing power density and maintaining skin and eye safety.

In previous animal and human models, the safety of the device hasn't been reported. This is particularly important when applying long-term monitoring of vulnerable populations such as newborn, especially preterm babies that have immature skin. This needs to be factored into future study designs.

OPTICAL LUNG MEASUREMENT VERSUS OTHER INSTRUMENTAL LUNG ASSESSMENT TECHNIQUES

Table 1 provides a comparative overview of the various technologies for lung evaluation available in the neonatal clinical setting.

Chest X-ray is the most common method of evaluating the lung status of newborns. Radiologic appearance of different neonatal lung pathologies can be non-specific³⁵ and is caused by different constituents remaining inside the alveoli: hyaline membrane, foetal lung fluid or meconium. Gaining more information about the optical features of lung constituents may lead to the development of light-based technologies to enable more specific differentiation.

Lung ultrasound provides the possibility to image air-filled or collapsed parts of the lungs and is now more often utilised in neonatal units.^{36–39} While there are defined diagnostic criteria available for differentiation of various neonatal respiratory pathologies⁴⁰ obtaining and interpreting these images requires training and a new skill set for the operators.

Lung CT greatly improves imaging of the pulmonary parenchymal and airway pathology and is considered as the gold standard for lung evaluation. Unfortunately, CT delivers significant concentrations of radiation compared to other radiological imaging techniques and has been found to be associated with increased risk for intracranial tumours.⁴¹ Furthermore, chest CT is resource and time intensive, requiring skilled personnel and effective patient immobilisation.⁴²

While magnetic resonance imaging is generally considered safer than CT, its uses for neonatal lung evaluation are predominantly restricted to research settings only as spatial resolution quality is inferior to CT. Moreover, patient sedation is often necessary to avoid movement artefacts. Unlike the described radiological technologies, GASMAS would allow continuous monitoring at the cot side with comparatively easy interpretation of the results. In addition, GASMAS enables the detection of O₂ at the molecular level and, with advancing technology, could also be used to analyse gas mixtures of O₂, nitric oxide, or carbon dioxide.⁴³

OPTICAL LUNG MEASUREMENT VERSUS OTHER OPTICAL OXYGEN MONITORING TECHNIQUES: PULSE OXIMETRY AND NEAR-INFRARED SPECTROSCOPY

Neonatologists are familiar with other optical devices used daily in the neonatal units such as PO⁴⁴ and near-infrared spectroscopy (NIRS). It is important to acknowledge the differences between PO, NIRS and GASMAS to understand how this new technology would add additional information about the overall O₂ status of a neonate and what information is still missing to validate GASMAS. The main technical differences between these optical devices are demonstrated in Supplementary Fig. S3.

Table 1. Comparison of GASMAS versus other oxygenation assessment and lung imaging methods used in clinical practice.

	Scanning time	Output	Ionising radiation	Bedside accessibility	Device cost ^a	Additional staff required	Skilled interpretation required	Motion sensitivity
GASMAS	Continuous	Numeric	No	Yes	Medium ^b	No	No	Unknown
Pulse Oximetry	Continuous	Numeric	No	Yes	Low	No	No	Yes
Chest X-ray	5 min	Images	Yes	Yes, if portable X-ray machine is available	High	Yes	Yes	Yes
Lung US	15–30 min	Images	No	Yes, if portable ultrasound machine is available	High	Yes	Yes	Yes
Lung CT	5 min	Images	Yes	Patient transfer required	Very high	Yes	Yes	Yes
Lung MRI	30–45 min	Images	No	Patient transfer required	Very high	Yes	Yes	Yes

GASMAS gas in scattering media absorption spectroscopy, US ultrasound, CT computer tomography, MRI magnetic resonance imaging.

^aGrouped by cost for hospital-grade device as follows: very high >500,000 EU; high >100,000 EU; medium >10,000 EU; low >1000 EU.

^bEstimated price of commercialised GASMAS device.

PO is used for continuous monitoring of the pulsatile haemoglobin bound O₂ saturation (SpO₂) signal that is a product of gas exchange at the alveolar level present in a peripheral vascular bed, while GASMAS targets free O₂ molecules inside the gas pockets of the alveoli before they diffuse through the pulmonary capillaries and bind to haemoglobin. The light source of PO is emitting red and near-infrared light at the wavelengths specific to the absorption of deoxygenated (HHb) and oxygenated haemoglobin (HbO₂). A single detector is positioned using diffuse transmittance geometry on the opposite side of the palm, wrist, feet, or ankle. Measurements obtained are dependent on pulsatile activity: light absorption changes with increasing blood volume present under the light emitter during systolic phase of cardiac cycle and reduces with diastole. As most of these rhythmic changes are associated with arterial vessel dilatation and constriction, PO is calculating arterial O₂ saturation, based on red and infrared light absorption ratio. If pulse signal is lost (e.g., due to probe displacement or in cases of non-pulsatile or bradycardic conditions), measurement of SpO₂ becomes unreliable.⁴⁵

NIRS is used to monitor regional tissue oxygenation status, most commonly assessing neonatal brain tissue, by placing the probe on the infant's forehead. It operates using the non-pulsatile, continuous wave (CW) signal within the same tissue optical window (Supplementary Fig. S2), penetrating brain tissue to a depth of 1–3 cm.⁴⁶ Unlike PO, NIRS values are based predominantly on venous HbO₂ saturation rather than arterial, because most of the haemoglobin is found within the venous compartment.⁴⁷

NIRS measurements can be achieved using three different modes: CW, frequency domain (FD) or time domain (TD).^{48,49} CW-NIRS uses a single emitter delivering steady light and two or more detectors with a specific distance. The photodetector is sensing the light coming back from the tissues after interacting with HbO₂ and HHb. Analysing the ratio between the intensity and frequency of diffusely reflected light it calculates the regional percentage of brain O₂ saturation (RStO₂).⁴⁶

TD-NIRS relies on the ability to measure the photon distribution of time-of-flight in a diffuse media, following the emission of pulsed light with a duration of tens of picoseconds. Analytical algorithms provide values of HbO₂, HHb, total amount of haemoglobin and RStO₂, by estimating the absorption coefficient at two or more wavelengths.⁵⁰

NIRS measurements incorporating FD use multiple emitter-detector pairs and estimate absolute values by evaluating phase shift and time-of-flight information.

GASMAS measurements are performed using two wavelength light sources specific to H₂O vapour and molecular O₂ absorption and a single detector. It is not targeting the absorption differences between HbO₂ and HHb, like PO and NIRS. The calculation of O₂ concentration using GASMAS is described in paragraph 2. While the distance between the emitter and detector as well as geometry (reflectance or transmittance) are well defined in PO and NIRS, there is a lack of studies confirming optimal probe placement for GASMAS measurements. Furthermore, optimal positioning on the chest is not well validated (Supplementary Table S1). Other factors that possibly would influence signal detection, like patient movement, cardiac contractility, breathing activity have not been investigated to date.

POTENTIAL CLINICAL APPLICATIONS OF GASMAS IN NEONATAL CARE

Cardiorespiratory transition monitoring in the delivery room

Current clinical practice to maintain optimal oxygenation of a preterm baby in the delivery room is based on SpO₂ and electrocardiogram derived heart rate values. Not reaching an SpO₂ of 80% at 5 min postnatally was found to be associated with adverse outcomes, including intraventricular haemorrhage.⁵¹ It has been shown that despite using SpO₂ and heart rate-driven O₂

titration strategies, many infants spend a significant portion of time outside of the targeted O₂ saturation range.^{52,53} Delayed availability of PO values,⁵⁴ inaccurate values in bradycardic situations and lack of information about the actual efficacy of lung ventilation and aeration contribute to this finding. Lung recruitment is the crucial first step of neonatal transition and resuscitation. There is no current standard monitoring method of lung ventilation in the delivery room. Tidal volume monitoring is feasible, but challenging^{55,56} and can be inaccurate, especially in high mask leak situations. Non-invasive lung O₂ monitoring using an optical device may provide 'real-time' information on lung ventilation, and subsequently optimise respiratory management during the dynamic situation soon after birth.

Endotracheal tube placement

Endotracheal (ET) intubation is a high skill requiring procedure performed by clinicians in the delivery room and the neonatal intensive care unit. The success rate of correct ET tube placement on the first attempt is 24% by paediatric trainees, 52% by fellows, 64% by neonatologists.⁵⁷ Chest radiography as well as clinical signs and exhaled carbon dioxide detector are commonly used to confirm the correct ET tube position. On the other hand, each monitoring modality has some limitations, for example, the end-tidal colorimeter may not change in colour if there is no cardiac output, but the ET tube is in the correct place; gastric secretions may cause the device to change colour, but the ET tube is in the oesophagus instead of trachea. While correct and prompt ET tube position confirmation is critical to avoid complications due to delayed effective ventilation, continuous non-invasive O₂ monitoring could be beneficial. Optical monitoring of O₂ content could reveal asymmetrical O₂ distribution within a chest suggesting ET tube tip located too deep in one of the main bronchi or no O₂ detected would prompt the clinician to consider a misplaced ET tube.

There are three techniques currently used to estimate the depth of ET tube insertion to ensure optimal midtracheal position. The first is based on the calculation of estimated distance from the lip to midtracheal location (in centimetres) using equation 6 + baby's weight (kg). Second, guided by a vocal cord mark present on the tube. And third, palpation of the ET tube tip at the suprasternal notch. The proportion of correctly positioned ET tubes was found to be similar using either of these techniques (suprasternal palpation 47%, weight 38–44%, vocal cord guide 40%). In all, 82–87% incorrectly positioned ET tubes were too low.^{58,59} This demonstrates the need for a more efficient method to detect the position of ET tubes in neonatal care.

It has been demonstrated that by simulating atelectasis of one lung because of ET tube malposition, GASMAS technology has the potential to detect the difference of gas content (reduced on the side of atelectasis) with suddenly dropping O₂ absorption value.²¹ Moreover, prompt technique could allow monitoring of ET position in cases when X-ray imaging is not available.

Surfactant therapy

Surfactant therapy plays an essential role predominantly in the management of premature babies with RDS that is affecting approximately 80% of babies born at 28 weeks' gestation.⁶⁰ RDS causes diffuse alveolar collapse and compromises O₂ delivery to the body. Multiple researchers are seeking to find an ideal standard of the best timing, dose, and methods of delivering surfactant treatment to maximise effect and minimise risks. GASMAS technology could help to detect early O₂ level changes inside the lungs to determine optimal timing of surfactant administration. Moreover, different methods of delivering surfactant could be investigated by continuous real-time monitoring. A previously reported study has demonstrated that GASMAS technology can detect gas volume change.¹³ Furthermore, it is known that equally diffused spread of surfactant inside proximal airways is essential for the therapy to be effective.⁶¹ While distribution depends on

multiple factors (instillation technique, speed, volume of preparation, ET tube position, ventilation strategy, gravity),⁶² continuous measurements of lung O₂ would be the first available and informative method to monitor the surfactant administration procedure and potentially optimise the treatment algorithms.

Patient positioning improving lung ventilation

Multiple adult and animal models have shown gravity-dependent lung inhomogeneity with gas exchange and ventilation/perfusion matching improving when treated in the prone position. In the presence of an abdominal distension, which is a common issue for neonates, the prone position has a positive effect on gas exchange as well.⁶³ Infants that require assisted ventilation are regularly repositioned to improve lung gas exchange. Studies comparing different neonatal positions have shown that arterial O₂ saturation increases if the ventilated baby is being nursed in a prone or prone alternant position ($P < 0.001$).^{64,65} While baby's body position has an impact on cardiopulmonary function,⁶⁵ it is still unclear when the position should be changed, how often and which positions should be chosen. More knowledge about the changes in lung inflation obtained from continuous optical monitoring is required to give us the answers to the above questions.

Bronchopulmonary dysplasia diagnostics

Bronchopulmonary dysplasia (BPD) is a long-term adverse outcome of preterm delivery and often requires prolonged ventilation support and O₂ therapy. Histopathological findings of BPD include alveolar simplification, dysmorphic capillaries, increased in vascular and airway smooth muscle cells, abnormal deposition of the extracellular components (e.g., elastin and collagen) and interstitial fluid accumulation.⁶⁶ All these changes cause alveolar collapse (atelectasis) and compensatory overexpansion, subsequently impairing gas exchange and causing dependency on respiratory support and O₂ therapy. BPD diagnosis has been evolving over time, initially based on histopathological findings, later relying on the duration of O₂ supplementation, the amount of O₂ required and most recently adding criteria of positive pressure ventilation support at ≥ 28 days post-natal age or at ≥ 36 weeks post-menstrual age.⁶⁷ GASMAS with multisite measurements could be used to measure lung volume and O₂ content to optimise diagnostic and management strategies for babies with BPD. To our knowledge, to date, no studies have reported the application of multiple light sources and detector probes and measuring signals simultaneously.

CONCLUSIONS

GASMAS-based devices have potential clinical use in neonatology, especially in the assessment and management of various respiratory conditions. Currently, only a few studies have assessed its feasibility in the neonatal population. More findings are available from studies performed with phantoms and will add important information on GASMAS applicability and required improvements in the future. Compared with other devices currently used in clinical practice for lung function monitoring, GASMAS has the advantages of bedside availability, continuous monitoring option, and unique information about molecular oxygen content inside the lung. Future research should aim to validate GASMAS measurements to prove reliability and precision.

REFERENCES

- Persson, L., Gao, H., Sjöholm, M. & Svanberg, S. Diode laser absorption spectroscopy for studies of gas exchange in fruits. *Opt. Lasers Eng.* **44**, 687–698 (2006).
- Tylewicz, U. et al. Gas in scattering media absorption spectroscopy (GASMAS) detected persistent vacuum in apple tissue after vacuum impregnation. *Food Biophys.* **7** (2012).

- Olawajolu, O. O., Bertling, I. & Magwaza, L. S. Non-destructive evaluation of avocado fruit maturity using near infrared spectroscopy and PLS regression models. *Sci. Horticulturae* **199**, 229–236 (2016).
- Li, W., Lin, H., Zhang, H., Svanberg, K. & Svanberg, S. Detection of free oxygen and water vapor in fertilized and unfertilized eggs by diode laser spectroscopy—exploration of diagnostics possibilities. *J. Biophotonics* **11** (2018).
- Svensson, T. et al. Noninvasive characterization of pharmaceutical solids by diode laser oxygen spectroscopy. *Appl. Spectrosc.* **61**, 784–786 (2007).
- Khoptyar, D. et al. Broadband photon time-of-flight spectroscopy of pharmaceuticals and highly scattering plastics in the VIS and close NIR spectral ranges. *Opt. Express* **21**, 20941–20953 (2013).
- Johansson, J. et al. Optical porosimetry by gas in scattering media absorption spectroscopy (GASMAS) applied to roller compaction ribbons. *Int. J. Pharm.* **592**, 120056 (2020).
- Persson, L., Svanberg, K. & Svanberg, S. On the potential of human sinus cavity diagnostics using diode laser gas spectroscopy. *Appl. Phys. B* **82**, 313–317 (2006).
- Persson, L., Andersson, M., Cassel-Engquist, M., Svanberg, K. & Svanberg, S. Gas monitoring in human sinuses using tunable diode laser spectroscopy. *J. Biomed. Opt.* **12**, 054001 (2007).
- Persson, L. et al. Non-invasive optical study of gas and its exchange in human maxillary sinuses. *Proc. SPIE* **6628** (2007).
- Persson, L., Lewander, M., Andersson, M., Svanberg, K. & Svanberg, S. Simultaneous detection of molecular oxygen and water vapor in the tissue optical window using tunable diode laser spectroscopy. *Appl. Opt.* **47**, 2028 (2008).
- Lindberg, S. et al. Method for studying gas composition in the human mastoid cavity by use of laser spectroscopy. *Ann. Otol. Rhinol. Laryngol.* **121**, 217–223 (2012).
- Huang, J. et al. Assessment of human sinus cavity air volume using tunable diode laser spectroscopy, with application to sinusitis diagnostics. *J. Biophotonics* **8**, 985–992 (2015).
- Hu, L. et al. Towards an optical diagnostic system for otitis media using a combination of otoscopy and spectroscopy. *J. Biophotonics* **12**, e201800305 (2019).
- Zhang, H., Huang, J., Li, T., Svanberg, S. & Svanberg, K. Optical detection of middle ear infection using spectroscopic techniques: phantom experiments. *J. Biomed. Opt.* **20**, 057001 (2015).
- Chen, D. et al. Laser-based gas absorption spectroscopy in decaying hip bone: water vapor as a predictor of osteonecrosis. *J. Biomed. Opt.* **24**, 1 (2019).
- Lewander, M., Bruzelius, A., Svanberg, S., Svanberg, K. & Fellman, V. Noninvasive gas monitoring in neonatal lungs using diode laser spectroscopy: feasibility study. *J. Biomed. Opt.* **16**, 127002 (2011).
- Larsson, J. et al. Development of a 3-dimensional tissue lung phantom of a preterm infant for optical measurements of oxygen-laser-detector position considerations. *J. Biophotonics* **11** (2018).
- Pacheco Toba, A. L., Li, H., Chakravarty, M., Konugolu Venkata Sekar, S. & Andersson-Engels, S. Anthropomorphic optical phantom of the neonatal thorax: a key tool for pulmonary studies in preterm infants. *J. Biomed. Opt.* **25**, 115001 (2020).
- Larsson, J. et al. Comparison of dermal vs internal light administration in human lungs using the TDLAS-GASMAS technique—Phantom Studies. *J. Biophotonics* **12**, e201800350 (2019).
- Svanberg, E. K. et al. Changes in pulmonary oxygen content are detectable with laser absorption spectroscopy: proof of concept in newborn piglets. *Pediatr. Res.* **89**, 823–829 (2021).
- Lundin, P. et al. Noninvasive monitoring of gas in the lungs and intestines of newborn infants using diode lasers: feasibility study. *J. Biomed. Opt.* **18**, 127005 (2013).
- Svanberg, E. K. et al. Diode laser spectroscopy for noninvasive monitoring of oxygen in the lungs of newborn infants. *Pediatr. Res.* **79**, 621–628 (2015).
- Hibbard, J. U. et al. Respiratory morbidity in late preterm births. *JAMA* **304**, 419–425 (2010).
- Dyer, J. Neonatal respiratory distress syndrome: tackling a worldwide problem. *PT* **44**, 12–14 (2019).
- Ainsworth, S. B. Pathophysiology of neonatal respiratory distress syndrome: implications for early treatment strategies. *Treat. Respir. Med.* **4**, 423–437 (2005).
- Guglani, L., Lakshminrusimha, S. & Ryan, R. M. Transient tachypnea of the newborn. *Pediatr. Rev.* **29**, e59–e65 (2008).
- Olgar, T. et al. Radiation exposure to premature infants in a neonatal intensive care unit in Turkey. *Korean J. Radio.* **9**, 416–419 (2008).
- Jakacka, N., Snarski, E. & Mekuria, S. Prevention of iatrogenic anemia in critical and neonatal care. *Adv. Clin. Exp. Med.* **25**, 191–197 (2016).
- Sjöholm, M., Somesfalean, G., Alnis, J., Andersson-Engels, S. & Svanberg, S. Analysis of gas dispersed in scattering media. *Opt. Lett.* **26**, 16–18 (2001).
- Buck, A. L. New equations for computing vapor pressure and enhancement factor. *J. Appl. Meteorol.* **20**, 1527–1532 (1981).
- Pacheco, A., Grygoryev, K., Messina, W. & Andersson-Engels, S. Lung tissue phantom mimicking pulmonary optical properties, relative humidity, and temperature: a tool to analyze the changes in oxygen gas absorption for different inflated volumes. *J. Biomed. Opt.* **27**, 074707 (2021).

33. Persson, L., Kristensson, E., Simonsson, L. & Svanberg, S. Monte Carlo simulations related to gas-based optical diagnosis of human sinusitis. *J. Biomed. Opt.* **12**, 054002 (2007).
34. Liao, P. et al. Computer simulation analysis of source-detector position for percutaneously measured O₂ gas signal in a three-dimensional preterm infant lung. *J. Biophotonics* **11**, e201800023 (2018).
35. Liszewski, M. C. & Lee, E. Y. Neonatal lung disorders: pattern recognition approach to diagnosis. *AJR Am. J. Roentgenol.* **210**, 964–975 (2018).
36. Perri, A. et al. Lung ultrasonography score versus chest X-ray score to predict surfactant administration in newborns with respiratory distress syndrome. *Pediatr. Pulmonol.* **53**, 1231–1236 (2018).
37. Kartikeswar, G. A. P., Parikh, T. B., Pandya, D. & Pandit, A. Ionizing radiation exposure in NICU. *Indian J. Pediatr.* **87**, 158–160 (2020).
38. Choi, G. et al. Development of quality-controlled low-dose protocols for radiography in the neonatal ICU using a new mobile digital radiography system. *AJR Am. J. Roentgenol.* **215**, 488–493 (2020).
39. Hong, J. Y., Han, K., Jung, J. H. & Kim, J. S. Association of exposure to diagnostic low-dose ionizing radiation with risk of cancer among youths in South Korea. *JAMA Netw. Open* **2**, e1910584 (2019).
40. Corsini, I., Parri, N., Ficial, B. & Dani, C. Lung ultrasound in the neonatal intensive care unit: review of the literature and future perspectives. *Pediatr. Pulmonol.* **55**, 1550–1562 (2020).
41. Meulepas, J. M. et al. Radiation exposure from pediatric CT scans and subsequent cancer risk in the Netherlands. *J. Natl Cancer Inst.* **111**, 256–263 (2019).
42. Semple, T., Akhtar, M. R. & Owens, C. M. Imaging bronchopulmonary dysplasia—a multimodality update. *Front Med (Lausanne)* **4**, 88 (2017).
43. Lundin, P., Mei, L., Andersson-Engels, S. & Svanberg, S. Laser spectroscopic gas concentration measurements in situations with unknown optical path length enabled by absorption line shape analysis. *Appl. Phys. Lett.* **103**, 034105 (2013).
44. Millikan, G. A. The oximeter, an instrument for measuring continuously the oxygen saturation of arterial blood in man. *Rev. Sci. Instrum.* **13**, 434–444 (1942).
45. Chan, E. D., Chan, M. M. & Chan, M. M. Pulse oximetry: understanding its basic principles facilitates appreciation of its limitations. *Respir. Med.* **107**, 789–799 (2013).
46. Bruns, N. et al. How to administer near-infrared spectroscopy in critically ill neonates, infants, and children. *J. Vis. Exp.* (2020).
47. Watzman, H. M. et al. Arterial and venous contributions to near-infrared cerebral oximetry. *Anesthesiology* **93**, 947–953 (2000).
48. Davies, D. J. et al. Frequency-domain vs continuous-wave near-infrared spectroscopy devices: a comparison of clinically viable monitors in controlled hypoxia. *J. Clin. Monit. Comput* **31**, 967–974 (2017).
49. van Essen, T. et al. Comparison of frequency-domain and continuous-wave near-infrared spectroscopy devices during the immediate transition. *BMC Pediatr.* **20**, 94 (2020).
50. Torricelli, A. et al. Time domain functional NIRS imaging for human brain mapping. *NeuroImage* **85**, 28–50 (2014).
51. Oei, J. L. et al. Outcomes of oxygen saturation targeting during delivery room stabilisation of preterm infants. *Arch. Dis. Child. Fetal Neonatal Ed.* **103**, F446–F454 (2018).
52. White, L. N. et al. Achievement of saturation targets in preterm infants <32 weeks' gestational age in the delivery room. *Arch. Dis. Child Fetal Neonatal Ed.* **102**, F423–F427 (2017).
53. Brouwer, E. et al. Physiological-based cord clamping in preterm infants using a new purpose-built resuscitation table: a feasibility study. *Arch. Dis. Child Fetal Neonatal Ed.* **104**, F396–F402 (2019).
54. Rabi, Y., Yee, W., Chen, S. Y. & Singhal, N. Oxygen saturation trends immediately after birth. *J. Pediatr.* **148**, 590–594 (2006).
55. te Pas, A. B. et al. Spontaneous breathing patterns of very preterm infants treated with continuous positive airway pressure at birth. *Pediatr. Res.* **64**, 281–285 (2008).
56. Schmolzer, G. M. et al. Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room. *Arch. Dis. Child Fetal Neonatal Ed.* **95**, F393–F397 (2010).
57. Foglia, E. E. et al. Neonatal intubation practice and outcomes: an international registry study. *Pediatrics* **143**, e20180902 (2019).
58. Gill, I. et al. Randomised trial of estimating oral endotracheal tube insertion depth in newborns using weight or vocal cord guide. *Arch. Dis. Child Fetal Neonatal Ed.* **103**, F312–F316 (2018).
59. Murphy, M. C., Donoghue, V. B. & O'Donnell, C. P. F. Randomised trial of estimating oral endotracheal tube insertion depth in newborns using suprasternal palpation of the tip or weight. *Arch. Dis. Child Fetal Neonatal Ed.* **105**, 196–200 (2020).
60. Sweet, D. G. et al. European consensus guidelines on the management of respiratory distress syndrome - 2019 update. *Neonatology* **115**, 432–450 (2019).
61. Tarawneh, A., Kaczmarek, J., Bottino, M. N. & Sant'anna, G. M. Severe airway obstruction during surfactant administration using a standardized protocol: a prospective, observational study. *J. Perinatol.* **32**, 270–275 (2012).
62. Nouraeyan, N., Lambrinakos-Raymond, A., Leone, M. & Sant'Anna, G. Surfactant administration in neonates: a review of delivery methods. *Can. J. Respir. Ther.* **50**, 91–95 (2014).
63. Mure, M. & Lindahl, S. G. Prone position improves gas exchange-but how? *Acta Anaesthesiol. Scand.* **45**, 150–159 (2001).
64. Rivas-Fernandez, M., Roque, I. F. M., Diez-Izquierdo, A., Escibano, J. & Balaguer, A. Infant position in neonates receiving mechanical ventilation. *Cochrane Database Syst. Rev.* **11**, CD003668 (2016).
65. Barsan Kaya, T., Aydemir, O. & Tekin, A. N. Prone versus supine position for regional cerebral tissue oxygenation in preterm neonates receiving noninvasive ventilation. *J. Matern. Fetal Neonatal Med.* **34**, 3127–3132 (2021).
66. Hilgendorff, A., Reiss, I., Ehrhardt, H., Eickelberg, O. & Alvira, C. M. Chronic lung disease in the preterm infant. Lessons learned from animal models. *Am. J. Respir. Cell Mol. Biol.* **50**, 233–245 (2014).
67. Ochiai, M. et al. A new scoring system for computed tomography of the chest for assessing the clinical status of bronchopulmonary dysplasia. *J. Pediatr.* **152**, 90–95 (2008).

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The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to Jurate Panaviene.

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