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Statistical Analysis of $^{11}\text{CO}_2$ Contamination Correction in ^{11}C -Acetate PET Imaging Studies

Tao Lan

**Thesis submitted for the degree of
Doctor of Philosophy**



**NATIONAL UNIVERSITY OF IRELAND, CORK
SCHOOL OF MATHEMATICAL SCIENCES**

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A handwritten signature in black ink that reads "TAO LAN". The letters are cursive and connected, with a horizontal line drawn underneath the entire signature.

Tao Lan

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Abstract

Positron Emission Tomography (PET) is a noninvasive imaging modality widely used in cancer management and medical research. It supports diagnosis, prognosis, treatment monitoring, and clinical decisions by tracking radiotracers labeled with positron-emitting isotopes. Tracer choice depends on the biological process of interest, such as tumor metabolism, cell proliferation, or blood flow. The most common tracer is fluorodeoxyglucose ($[^{18}\text{F}]\text{FDG}$), which accumulates in tissues with high glucose metabolism (e.g., brain, heart, and many tumors), and is used for cancer detection, staging, and treatment monitoring, as well as neurological and cardiac assessment. Another key tracer is ^{11}C -acetate, involved in cell membrane synthesis and oxidative metabolism. It complements FDG, especially in tissues with low or variable glucose uptake. However, its oxidative metabolism generates $^{11}\text{CO}_2$, which is indistinguishable from the PET measured signal. The main goal of this thesis is to develop a statistical model to estimate and correct the contribution of metabolically produced $^{11}\text{CO}_2$ in ^{11}C -acetate PET imaging. The model is constructed using non-parametric residue mapping (NPRM) and the extended semi-parametric residue mapping (SPRM), based on a dynamic PET dataset acquired with $^{11}\text{CO}_2$ - ^{11}C -acetate dual injection. The correction performance is evaluated at the voxel and region-of-interest (ROI) levels. Furthermore, this thesis explores the feasibility of performing $^{11}\text{CO}_2$ contamination correction using only ^{11}C -acetate PET data, without requiring a separate $^{11}\text{CO}_2$ scan. Promising results are presented to demonstrate the potential of this approach.

Chapter 1

Thesis Introduction and Overview

1.1 Introduction

Medical imaging is considered one of the most common diagnostic tools in modern healthcare [Kasban et al., 2015]. Over the past decade, it has undergone revolutionary advancements aimed at faster development, increased accuracy, and reduced invasiveness [Angenent et al., 2006]. The primary goal of medical imaging is to provide a comprehensive understanding of both the anatomical structure (e.g., X-ray, computed tomography (CT), magnetic resonance imaging (MRI)) and physiological function (e.g., positron emission tomography (PET), single photon emission computed tomography (SPECT)) of the human body in vivo. Molecular imaging, a distinct branch of medical imaging that primarily includes PET and SPECT, is significantly transforming how researchers and clinicians visualize and investigate complex biochemical processes [James and Gambhir, 2012]. Among these two modalities, PET offers distinct advantages due to its higher spatial resolution and the availability of radiotracers with shorter

half-lives [Rahmim and Zaidi, 2008]. Thus, PET has emerged as a cornerstone in oncology, offering a quantitative imaging modality critical for tumor diagnosis, therapeutic planning, and longitudinal response assessment. PET detects photon pairs resulting from positron annihilation events emitted by positron-emitting isotopes labeled onto specific radiotracers. These detections are used to generate static or dynamic images that reflect the spatial and temporal distribution of the radiotracer within the subject through an image reconstruction process. Four positron-emitting isotopes are used more frequently than others in PET imaging: fluorine-18 (^{18}F), carbon-11 (^{11}C), nitrogen-13 (^{13}N), and oxygen-15 (^{15}O). These isotopes are particularly suitable because they can be readily substituted into biologically relevant molecules without significantly altering their chemical properties [Schlyer, 2004]. As a ^{18}F -labeled tracer and a glucose analogue, ^{18}F -fluorodeoxyglucose (^{18}F -FDG) is the most widely used ^{18}F -labeled radiotracer due to its relatively long half-life (109.8 minutes) and its versatility in targeting various metabolic processes, particularly in oncologic, cardiac, and neurologic imaging applications [Kapoor et al., 2025, Hoh, 2007]. In FDG, the ^{18}F atom replaces a hydroxy, resulting in a different behavior compared to natural glucose [Barrio et al., 2020]. Carbon is a fundamental biological building block found in naturally occurring biomolecules, including amino acids, glucose, fatty acids, and carbon dioxide. As a result, radiolabeling with carbon isotopes offers a valuable opportunity to explore key biological processes relevant to cancer [Shields et al., 1992]. However, many ^{11}C -labeled tracers are involved in multiple metabolic pathways, leading to the production of other labeled, naturally occurring molecules, such as $^{11}\text{CO}_2$ —which can complicate the interpretation of PET imaging data. Examples include ^{11}C -acetate [Spence et al., 1998], ^{11}C -thymidine [Shields et al., 1992], and ^{11}C -glucose [Spence et al., 1998].

^{11}C -acetate is involved in two key metabolic pathways: cellular respiration and membrane biosynthesis [Grassi et al., 2012]. Due to its dual metabolic role, ^{11}C -acetate serves as a valuable complement to FDG in PET imaging, particularly in tissues or tumor types where glucose metabolism is low or variable. However, $^{11}\text{CO}_2$ is produced as a by-product of cellular respiration during ^{11}C -acetate PET imaging, and PET measures only the total radioactivity within tissues, without distinguishing the chemical form of the radiolabeled species [Shields et al., 1992]. Since CO_2 is cleared relatively slowly from the body [AS et al., 1964, Baker et al., 1954], correcting for the radioactive signal contamination from $^{11}\text{CO}_2$ is essential for accurate interpretation of ^{11}C -acetate PET data.

In this thesis, we present a statistical approach to estimate and correct $^{11}\text{CO}_2$ contamination from $^{11}\text{CO}_2$ - ^{11}C -acetate dual-injection PET imaging data. The correction model is developed using non-parametric residue mapping (NPRM) and semi-parametric residue mapping (SPRM), enabling the generation of corrected kinetic information. In addition, we explore the potential to estimate $^{11}\text{CO}_2$ contamination using only single-injection ^{11}C -acetate PET data, combining model-based and machine learning tools. The goal of this thesis is to evaluate whether it is possible to develop more efficient methods to account for the contaminating effects of CO_2 metabolism when using ^{11}C -labeled tracers. While the focus is on the ^{11}C -acetate tracer, the proposed methodology can also be applied to a broader range of scenarios involving other ^{11}C -labeled tracers.

1.2 Main Contributions

The main contributions of this thesis are as follows:

- An overview of the physics foundation and the radiotracer of PET.
- An overview of kinetic analysis of dynamic PET imaging, including the basic equation to model tissue time activity curve(TAC), the arterial input function(AIF) models, and several kinetic models of dynamic PET data.
- Non-parametric Residue Mapping (NPRM) Technique
 - A non-parametric residue mapping procedure is proposed to generate parametric imaging. The uncertainties in parametric imaging are assessed with an image-domain bootstrap model.
 - The variation of kinetic parametric estimation under different levels of noise is assessed with a simulation study with NPRM.
- $^{11}\text{CO}_2$ Correction in ^{11}C -acetate PET Imaging
 - The main metabolic pathways of ^{11}C -acetate is summarized.
 - The semi-parametric residue mapping(SPRM), based on NPRM, is proposed and used in the metabolic contamination correction model.
 - A generalized metabolic contamination correction model is proposed and examined. This is demonstrated using a $^{11}\text{CO}_2$ - ^{11}C -acetate dual-injection dynamic PET dataset.
 - A novel approach is proposed and evaluated for modeling the metabolite arterial input function and for estimating either sample-based or population-scaled metabolite arterial input functions.
 - A series of metabolic contamination correction methods (involving a combination of model-based and machine learning tools)

that do not require a separate C-11 labeled CO₂ PET study are proposed and examined.

1.3 Thesis Structure

Chapter 2 outlines the physics and development of PET imaging, explaining the principles of key elements in PET imaging, including positron annihilation, data acquisition with essential corrections, and reconstruction methods such as filtered back-projection (FBP) and iterative algorithms. Key radiotracers, such as FDG and acetate, are discussed along with their metabolic pathways and clinical applications. PET quantitation approaches are also reviewed.

Chapter 3 introduces kinetic models for dynamic PET data, including graphical analyses (Patlak plot and Logan plot), spectral analysis, compartmental models, and non-parametric residue mapping (NPRM). NPRM is emphasized for its flexibility in modeling tissue residue functions without predefined assumptions. An image-domain bootstrap technique is presented to assess the uncertainties of kinetic parametric maps. A simulation study is also proposed to evaluate the noise sensitivity of NPRM. The chapter concludes with a straightforward comparative analysis of the NPRM and two compartmental models, demonstrating the NPRM's superiority in fitting tissue activity curves under specific scenarios.

Chapter 4 addresses metabolic contamination from ¹¹CO₂ in ¹¹C-acetate PET imaging. A ¹¹CO₂-¹¹C-acetate dual injection protocol is combined with the semi-parametric residue mapping (SPRM) to separate signals. Results are demonstrated using corrected parametric maps and time-activity curves for

both tumor and normal brain regions. The method's feasibility is validated, but clinical practicality remains limited by procedural complexity.

Chapter 5 explores and examines methods for correcting CO₂ contamination without the need for dedicated CO₂ scans. These methods involve machine learning predictions, expanding the NPRM models, and valuable approaches to estimate CO₂ kinetic information. Convolution-based methods show higher reliability, though machine learning exhibits potential despite current accuracy limitations. The chapter underscores the potential to accurately estimate CO₂ contamination with a statistical model.

Chapter 6 introduces a model for estimating the CO₂ arterial input function in the absence of direct blood sampling. This model is combined with several CO₂ correction methods—introduced in the previous chapter—that do not require separate CO₂ scans and is applied to a prostate cancer dataset, yielding promising results. These findings motivate further investigation of the correction model across different organs and tissues, suggesting the potential for developing a unified correction framework applicable throughout the human body.

Chapter 7 provides a comprehensive summary of this thesis by synthesizing contributions. Limitations of current methods and potential future developments are discussed.

Chapter 2

Positron Emission Tomography

Positron emission tomography (PET) is a type of nuclear medical imaging modality that utilizes the positrons (β^+) emitted from radionuclides injected into the body. The positron travels very shortly to collide with an electron, leading to matter-antimatter annihilation, which creates two γ -photons with an energy of 511 keV each, traveling in opposite directions [Haidekker, 2013]. The γ photons are collected by detectors and processed with an image reconstruction algorithm to produce image data, unlike other modalities, which can evaluate biological functions and in a non-invasive manner [Wacholtz, 2011]. These characteristics enable PET scanning to play a vital role in oncology, cardiology, and neurology. In this chapter, we will provide a brief introduction to PET, including its development history, physics principles, and quantification of PET imaging.

2.1 Development of PET Scanners

The development of PET scanners over 70 years (1950 to 2020) has seen significant contributions from numerous exceptional physicists, chemists, biologists, and mathematicians/statisticians, greatly advancing this tech-

nology [Rich, 1997, Nutt, 2002, Wacholtz, 2011, Jones and Townsend, 2017, Vandenberghe et al., 2020]. The history of PET scanner development is reviewed here in a timeline series.

1950-1960: From Concept to Prototype The first medical application for positron was reported in 1951 with two independent papers [Sweet, 1951, Wrenn Jr et al., 1951]. Two years later, Brownell and Sweet utilized a pair of sodium iodide detectors to locate brain tumors [Sweet, 1953]. Kuhl and Edwards were pioneers in the early 1960s, being among the first to explore image reconstruction algorithms for single photon tomography [Kuhl and Edwards, 1963].

1970s: Beginning of Modern PET The development of modern PET began in 1973 with two pioneering systems: the first ring tomograph by Robertson at Brookhaven National Laboratory [Robertson et al., 1972] and the Positron Emission Transaxial Tomograph (PETT I) by Michael E. Phelps at Washington University. Both systems faced critical limitations in image reconstruction due to sparse angular sampling and the absence of attenuation correction [Nutt, 2002]. Later that year, PETT II—a collaborative effort between Washington University and EG&G ORTEC—achieved functional imaging of blood flow and metabolism in animals [Phelps et al., 1975, Ter-Pogossian et al., 1975]. The term “transaxial” was subsequently dropped, simplifying the name to PET. In 1974, Phelps and Ed Hoffman led the development of PET III. This first human-capable tomograph produced foundational images of human blood flow, oxygen/glucose metabolism, and bone scans using filtered backprojection algorithms [Phelps et al., 1976, Hoffman et al., 1976, Chesler, 1971, Chesler, 1973]. Building on this success, the first commercial PET scanner,

the ECAT II (derived from PET III), was deployed at UCLA, marking the transition of PET to clinical utility [Nutt, 2002].

Another key factor in PET scanner development is the utilization of new materials as detectors, which determines sensitivity, image resolution, count rate capability, and other factors. A crystal known as bismuth-germanate(BGO) was first studied for its luminescence [Weber and Monchamp, 1973] and later used in PET by Cho and Farukhi [Cho and Farukhi, 1977] and Derenzo [Derenzo, 1981]. BGO is better than NaI (Tl), which was the only choice in the mid-1970s as a PET scanner detector because BGO is very dense and has a high effective atomic number [Nutt, 2002]. The most commonly used PET scanning tracer, [^{18}F]Fluoro-2-deoxy-2-D-glucose, also known as FDG, was first synthesized by the joint effort of Sokoloff and Martin Reivich [Sokoloff et al., 1977] and Wolf and Fowler's group [Ido et al., 1978]. The first PET imaging with FDG was performed on an ECAT II instrument by Phelps et al. [Phelps et al., 1979, Reivich et al., 1979].

1980-1990s: Advancements in Research and Clinical Performance

During this period, the rapid progressions in PET scanners in both research and clinical sectors are the result of discoveries and improved designs, including new detector design, improved detector material, better image reconstruction algorithms, and a larger commercialization environment.

The 1980s marked pivotal advancements in PET detector technology. Scanditronix pioneered a dual-crystal tomograph in 1984, combining bismuth germanate (BGO) and gadolinium orthosilicate (GSO) with a shared photomultiplier [Eriksson et al., 1984]. Building on this, Casey and Nutt intro-

duced the block detector—a modular design integrating four photomultipliers with an 8×4 BGO crystal array—enabling cost-effective, high-resolution PET imaging [Casey and Nutt, 1986, Casey et al., 1988, Nutt, 2002].

The 1990s saw the emergence of lutetium oxyorthosilicate (LSO), a scintillator superior to BGO due to its higher light yield, enhanced spatial/energy resolution, and faster timing resolution [Melcher, 1990]. Cherry et al. at UCLA developed the first LSO-based PET scanner in 1997 [Cherry et al., 1997]. LSO's rapid decay kinetics enabled time-of-flight (TOF) PET, which localizes annihilation events by measuring photon arrival time differences, significantly improving image quality and quantitative accuracy [Jones and Townsend, 2017].

An iterative image reconstruction algorithm, based on the maximum-likelihood expectation maximization (ML-EM) proposed by Dempster et al. [Dempster et al., 1977], was applied to PET by Shepp and Vardi [Shepp and Vardi, 1982] and Lange and Carson [Lange et al., 1984]. Moreover, an accelerated version of ML-EM, ordered subset EM (OSEM), was published by Hudson and Larkin [Hudson and Larkin, 1994], making it a practical alternative to the FBP algorithm [Jones and Townsend, 2017]. The OSEM algorithm provides a good foundation to many of today's popular algorithms that incorporate different techniques, including AWOSEM, (OP)-OSEM, and 3D-OP-OSEM [Comtat et al., 1998, Michel et al., 1998, Liu et al., 2001, Comtat et al., 2004].

Ever since the deployment of the first commercial PET scanner, various organizations and companies have made significant efforts to integrate this technique into the clinical sector. In 1986, the first Radiopharmaceutical De-

livery System (RDS112), an 11 MeV and negative-ion proton cyclotron, was delivered to the University of Wisconsin. The RDS was capable to produce ^{18}F , ^{11}C gases, ^{15}O water, ^{15}O gases and $^{13}\text{NH}_3$ [Satyamurthy et al., 1999]. Later, the first automated chemistry module for synthesizing PET, which required molecular probes, was built [Padgett et al., 1989]. Today, a typical PET radiopharmacy site requires only three people to safely and responsibly produce and locally distribute FDG. This technology enables the automated production of PET molecular probes electronically, forming the foundational technology for PET radiopharmacies to support PET clinical services and research [Nutt, 2002]. In the late 1980s and early 1990s, Siemens and General Electric entered the PET scanner industry. The entry of these two large imaging companies into PET indicates that this technology is ready for clinical applications [Nutt, 2002]. In 1991, Phelps presented the first whole-body PET imaging using a multi-bed protocol [Dahlbom et al., 1992]. The first success in whole-body PET imaging greatly expands PET's role in oncology and neurology and also stimulates further research interest in long axial PET imaging [Jones and Townsend, 2017, Vandenberghe et al., 2020].

2000s: Fusion Imaging with PET Fusing different imaging modalities for a combination of anatomic and functional images has raised interest even as far back as the 1960s [Jones and Townsend, 2017]. Two major fusion options are PET/CT and PET/MR.

A transformative milestone emerged in 1991 when Townsend and Nutt proposed integrating PET and x-ray computed tomography (CT) into a single hybrid system [Jones and Townsend, 2017]. This innovation addressed two critical limitations of stand-alone PET: patient motion artifacts and the need for external attenuation correction. By leveraging CT-derived attenuation

maps, PET/CT systems enable the precise alignment of metabolic (PET) and anatomical (CT) data, streamlining workflows.

The first clinical prototype, developed in 1998 at the University of Pittsburgh Medical Center, demonstrated superior diagnostic accuracy over sequential PET and CT scans [Beyer et al., 2000]. These results catalyzed commercial development, with GE and Siemens launching dedicated PET/CT systems by the early 2000s. By 2004, PET-only scanners were obsolete, reflecting the dominance of PET/CT; today, over 5,000 systems operate globally, underscoring its clinical indispensability [Jones and Townsend, 2017].

Due to the advantages of MR over CT, including better soft tissue contrast, no radiation dose, and the possibility of motion correction, considerable interest arose in the fusion of PET and MR around the mid-1990s. However, the photodetectors used in PET do not function near a magnetic field. A new semiconductor photodetector, APD, was used in the first PET detector ring that cooperates with a 3T clinical MR. Despite the advantages mentioned above, most interest in PET/MR remains in research studies rather than clinical applications.

2010-2020s: Long Axial Field of View PET Scanner The field of view (FOV) from a conventional PET system is generally about 15-30cm and is suitable for one organ imaging at a time. With a multiple-bed protocol, a whole-body scan can be obtained using a conventional PET scanner; however, this process is time-consuming. Since 2019, long axial field of view (LAFOV) PET scanners - the uEXPLORER from United Imaging Healthcare & UV Davis [Badawi et al., 2019], the PennPET Explorer from University of Pennsylvania [Karp et al., 2020], and the Biograph Vision Quadra from Siemens Healthineers [Prenosil et al., 2022] have brought total body

PET imaging into both research and clinical areas. These state-of-the-art scanners show superior performance than conventional PET scanners ($10\text{--}40\times$ higher sensitivity) and provide a revolutionary way of PET imaging that holds many possibilities which could benefit both research (e.g., development of new tracers and drugs and more sophisticated kinetic models) and clinical (e.g., shorter scanning time and lower tracer dosage) areas [Jones and Townsend, 2017, Vandenberghe et al., 2020].

2.2 Radiotracer

A radiotracer is a set of specialized radioactive compounds that are essential for PET imaging. The synthesis of radiotracers involves integrating positron-emitting radioisotopes into biologically active molecules. These labeled molecules then get administered into the body to qualitatively or quantitatively measure biomarkers (e.g., enzymes and transporters) and biochemical processes (e.g., energy metabolism and DNA synthesis) in a non-invasive manner [Schlyer, 2004, Lau et al., 2020]. The most frequently used radioisotopes in PET are fluorine-18 (^{18}F), Carbon-11 (^{11}C), Oxygen-15 (^{15}O) and Nitrogen-13 (^{13}N). These radioisotopes are selected not only because their decay mode is mainly β^+ decay, but also because they can be incorporated into biomolecules without significantly altering their biological behavior. As the most commonly used radionuclides for PET [Schlyer, 2004], ^{11}C and ^{18}F will be introduced with more details as follows.

^{18}F labeled Tracer

^{18}F labeled tracer plays an important role for diagnostic PET imaging because of the relatively long half-life time ($T_{1/2} = 109.8\text{min}$) [Coenen et al., 2010], which could allow longer synthesis and distribution time and make ^{18}F la-

Table 2.1: Commonly used radiotracers in clinical PET that are approved by the US Food and Drug Administration(FDA) or the European Medicines Agency(EMA) [Lau et al., 2020]

Radioisotope	Half-life(min)	Decay mode	Radiotracer	Biological Process/Target
^{18}F	109.8	$97\%\beta^+3\%\text{EC}$	$[^{18}\text{F}]\text{FDG}$	Glucose Metabolism
			$[^{18}\text{F}]\text{NaF}$	Bone Remodeling
			$[^{18}\text{F}]\text{FMISO}$	Hypoxia
			$[^{18}\text{F}]\text{Choline}$	Phospholipid Synthesis
			$[^{18}\text{F}]\text{FLT}$	DNA Replication
^{11}C	20.4	$100\%\beta^+$	$[^{11}\text{C}]\text{Acetate}$	Acetyl-CoA Synthetase
			$[^{11}\text{C}]\text{Thymidine}$	DNA Replication
			$[^{11}\text{C}]\text{Methionine}$	Amino Acid Transport
			$[^{11}\text{C}]\text{Choline}$	Phospholipid Synthesis
^{15}O	2.03	$100\%\beta^+$	$[^{15}\text{O}]\text{H}_2\text{O}$	
^{13}N	9.97	$100\%\beta^+$	$[^{13}\text{N}]\text{Ammonia}$	

FMISO: fluoromisonidazole; FLT: fluorothymidine

beled tracer more available in clinical application. ^{18}F atom often substitutes for a hydroxy group when tagging it to a molecule [Schlyer, 2004]. Because of the electronic properties of fluorine, it is necessary to evaluate new ^{18}F labeled compounds to make sure it does not significantly alter the biological behavior of the molecule [Krohn et al., 2005].

Though there are many well-developed ^{18}F labeled tracers as shown in Table 2.1, Fluorodeoxyglucose($[^{18}\text{F}]\text{FDG}$) is still the most widely used PET radiotracer in both clinical and research areas and the gold standard of PET radiopharmaceuticals [Wacholtz, 2011, Lau et al., 2020]. $\text{FDG}(\text{C}_6\text{H}_{11}^{18}\text{FO}_5)$ is an analog of glucose($\text{C}_6\text{H}_{12}\text{O}_6$) where one hydroxyl group is replaced with a ^{18}F atom [Kobayashi et al., 2012]. This difference makes FDG only share part of the glucose metabolism pathway. FDG enters tissue via glucose transporter on the membrane, then gets phosphorylated by the hexokinase enzyme to give FDG-6-phosphate. Because of the ^{18}F atom replacement, FDG-6-phosphate cannot get further metabolized and gets trapped and accumulated in tissue [Miller et al., 2008]. The FDG and glucose metabolism process is illustrated in Figure 2.1

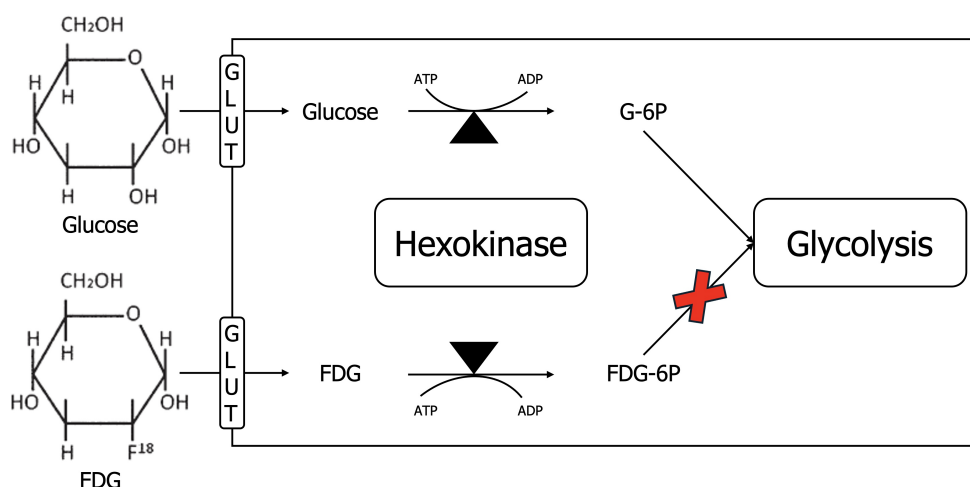


Figure 2.1: FDG and glucose metabolism process [Kobayashi et al., 2012]. GLUT:glucose transporter; ATP:adenosine triphosphate; ADP:adenosine diphosphate; 6P:6-phosphate.

Given that numerous pathological states are associated with changes in glucose regulation, PET scans utilizing FDG as a tracer can be employed for therapy monitoring, tumor staging, assessing myocardial energy turnover, and diagnosing various diseases at multiple stages. This versatility, on the other hand, brings many limitations to FDG, including difficulties in distinguishing inflammation from tumor, no assignment to specific tumor origins, and only limited delineation when the tumor is embedded in tissue with high energy consumption (brain, muscles, and bladder) [Wadsak and Mitterhauser, 2010, Kobayashi et al., 2012, Shibata et al., 2009, Barrio et al., 2020, Evan et al., 2011]. Thus, despite the popularity of FDG in PET imaging, pairing it with other tracers that target more specific diseases or pathways could enhance the reliability of FDG PET imaging.

Another important ^{18}F -labeled tracer is ^{18}F -choline. Choline plays an essential role in the synthesis of phosphatidylcholine, a major

constituent of cell membranes, via the Kennedy pathway through phosphorylation by choline kinase [Kwee et al., 2007a]. Elevated cellular proliferation and membrane synthesis are hallmark features of tumors; consequently, choline metabolism has been recognized as a pivotal biomarker for cancer diagnosis and treatment monitoring [Moestue et al., 2010, Yao et al., 2023, Kwee and Lim, 2016]. ^{18}F -choline, an analog of natural choline, exhibits comparable uptake kinetics to its endogenous counterpart [DeGrado et al., 2001], making it a practical alternative in clinical settings lacking on-site cyclotron infrastructure.

In hepatocellular carcinoma (HCC), ^{18}F -choline uptake (SUV_{max}) has shown strong correlations with histopathological features, liver fibrosis indices, and inflammatory activity [Kwee et al., 2018]. This tracer also demonstrates utility in detecting HCC and other hepatic pathologies, including chronic liver disease [Kwee et al., 2015, Talbot et al., 2010, Talbot et al., 2006]. Beyond hepatic applications, ^{18}F -choline has proven effective in delineating prostate tumors [Kwee et al., 2005, Kwee et al., 2006] and select brain malignancies [DeGrado et al., 2001, Kwee et al., 2007b].

However, it is critical to acknowledge the limitations of ^{18}F -choline PET imaging. Diagnostic specificity may be compromised by false-positive uptake in inflammatory processes (e.g., prostatitis) or benign hypermetabolic conditions, necessitating complementary diagnostic evaluation [Calabria et al., 2014].

[¹¹C] labeled Tracer

[¹¹C] atom can be directly substituted into molecules for [¹²C] atom without altering the mechanism of a molecule. Due to its slightly longer half-life ($T_{1/2} = 20.4$ minutes) and the availability of various radio-labeling synthesis methods, numerous tracers labeled with [¹¹C] have been developed to address the limitations of FDG [Goud et al., 2021, Schlyer, 2004].

[¹¹C]Acetate has the same manner as natural acetate, as [¹¹C] atom only replaces a regular C atom in the acetate molecule [Phelps et al., 1985]. After entering cells, acetate is metabolized into acetyl-CoA, and further metabolism of acetyl-CoA differs in different cells [Grassi et al., 2012]. In myocardial tissue, acetyl-CoA is mainly metabolized to CO₂ via the tricarboxylic acid cycle(TCA) [Randle et al., 1970]. In contrast, in tumor cells, acetyl-CoA is primarily employed to build cell membrane fatty acids due to overexpression of the enzyme fatty acid synthesis in tumor cells [Swinnen et al., 2000, Swinnen et al., 2003]. For its versatile mechanism, [¹¹C]Acetate PET imaging has already been used in cardiology, tumor staging, and therapy control of prostate cancer [Grassi et al., 2012, Pike et al., 1982, Dimitrakopoulou-Strauss and Strauss, 2003] and outperformed FDG in specific areas such as detection of lymph node metastases [Evan et al., 2011] and predicting myocardial functional recovery [Rubin et al., 1996].

However, as a [¹¹C]-labeled radiotracer metabolized through the TCA cycle, [¹¹C]acetate suffers from ¹¹CO₂ contamination. PET imaging measures the total radioactivity in tissue and cannot distinguish a specific type of molecule to which the radioisotope is associated. Thus, when interpreting PET imag-

ing with [^{11}C] labeled tracer, it is vital to understand the metabolism of the tracer that is being used and take into account that the PET measurements may also contain metabolized molecules labeled with the radioisotope. In [^{11}C]Acetate PET imaging, $^{11}\text{CO}_2$ will be metabolized in various tissues over the body and transported through blood and finally be captured in PET measurement. [Shields et al., 1992, Vander Borgh et al., 1994]. Significant efforts have been made to address this contamination issue. For instance, Lewis et al. utilized late-time imaging data to obtain more accurate measurements of fatty acid synthesis [Lewis et al., 2014] and Muzi et al. used a combined two-compartmental model coupled with dual-injection dynamic PET imaging of CO_2 and Acetate to eliminate contamination with CO_2 kinetic parameters [Muzi et al., 2011].

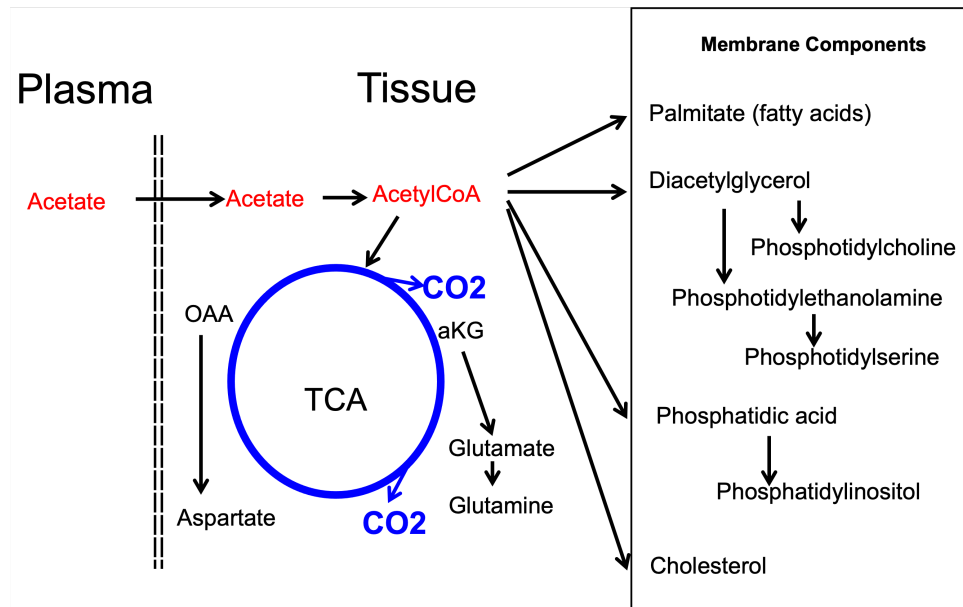


Figure 2.2: Acetate metabolism process in the human body. aKG: α -Ketoglutaric acid; OAA: Oxaloacetic acid; TCA: tricarboxylic acid.

2.3 The Physics of PET

PET imaging relies fundamentally on β^+ decay, a nuclear process in which a proton (p) within a radioactive tracer isotope transforms into a neutron (n), emitting a positron (β^+) and a neutrino (ν) (Equation 2.1). The emitted positron travels a short distance before annihilating with an electron (e^-), producing two 511 keV gamma photons propagating in opposite directions (180° apart). A coincidence event is registered when detectors identify these paired photons along a line of response (LOR) within a narrow time window. These events form the raw PET data, with spatial localization inferred from the intersection of LORs [Schmitz et al., 2005, Bailey et al., 2005].

$$p \rightarrow n + \beta^+ + \nu \quad (2.1)$$

All the registered coincidences are the PET raw measures data, which are converted into a sinogram. To get a sinogram, the x and y coordinates of the LOR are converted into the corresponding LOR angle ϕ and offset from the center of the scanner r as indicated in Figure 2.4. Their relationship is given by:

$$r = x \cos \phi + y \sin \phi \quad (2.2)$$

A sinogram is a 2D raw data structure in PET where each row corresponds to parallel lines of response (LORs) at a fixed angular orientation ϕ , and each column represents the radial displacement r from the scanner's central axis. During acquisition, detected coincidence events are mapped to their corresponding LORs, incrementing the count in the sinogram bin indexed by (ϕ, r) . The final sinogram thus encodes the total coincidence counts along each LOR over the acquisition period. Each sinogram captures data from a single transaxial slice; tomographic reconstruction in-

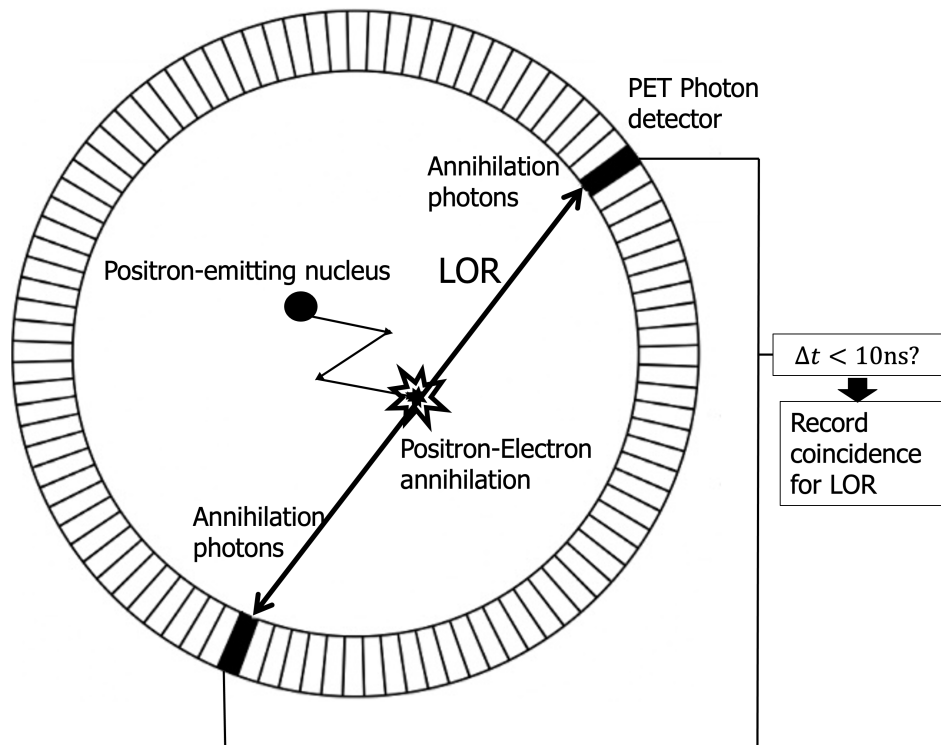


Figure 2.3: A general principle of PET scanner: radioactive isotope decay, positron emission, and scatter in tissue, annihilate with an electron and produce two gamma rays, coincidence detected and registered if the time frame is small enough [Schmitz et al., 2005].

tegrates multiple sinograms across slices to generate volumetric projections [Cherry et al., 2006, Saha and Gopal, 2005].

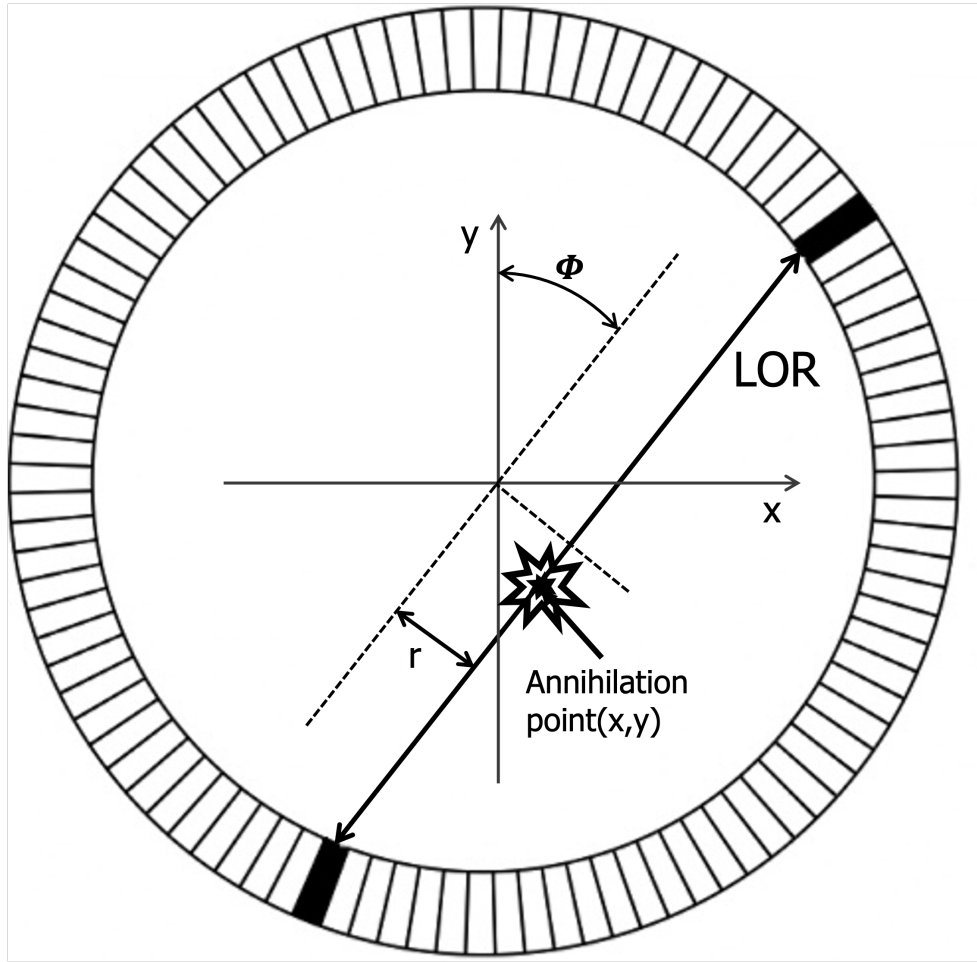


Figure 2.4: The relationship between the (x, y) coordinates system and (r, ϕ) coordinates system of the annihilation point [Cherry et al., 2006, Saha and Gopal, 2005].

2.3.1 Data Correction

When the raw data is acquired after a PET scanning procedure, certain corrections must be applied before image reconstruction.

Normalization Normalization is to average out the physical variation of tens of thousands of detectors in modern PET scanners. A normalization factor F_i for each pair of detectors and the corresponding LORs is calculated regularly, either by performing a scan over a 511 keV photon source or by the computer software provided by the scanner's vendor. The normalization

factor is then applied to the measured data as follows:

$$C_{norm,i} = C_i \times F_i \quad (2.3)$$

where $C_{norm,i}$ is the normalized counts in the i th LOR, C_i is the measured counts in the i th LOR and F_i is the normalization factor of the i th LOR [Saha and Gopal, 2005].

Attenuation Correction When the 511 keV annihilation photons travel through the body to hit the PET detector, it is possible that the photons are attenuated when they penetrate different tissues or organs. Similar to normalization, an attenuation correction factor needed to be applied to each LOR count value in the sinogram. The attenuation correction factor for LOR connecting detector i and j , a_{ij} , can be given by

$$a_{ij} = \exp(\mu D_{ij}) = \frac{I(0)}{I(D_{ij})} \quad (2.4)$$

where μ is the attenuation coefficient, which depends on the type of tissue, D_{ij} is the tissue thickness for the corresponding LOR, and $I(0)$ is a blank scan measurement which can be taken daily to correct the scanning on that day. $I(D_{ij})$ is the scan data from the LOR connecting detector i and j , which can be obtained via either an additional transmission scan with a rod or point source of positron emitter attached to the scanner gantry or the CT transmission scan in a PET/CT scanner [Cherry et al., 2006, Saha and Gopal, 2005].

Random and Scatter Correction Among all the registered coincidences, not all coincidences come from the assigned LOR as described in Figure 2.5. Random coincidences happen when a pair of detectors detects two 511 keV

photons from two separate annihilation locations within the time window. It will add artifacts to the background and lower the image contrast. Using a detector with a shorter time window could reduce the number of random events. Scatter coincidences happen when an annihilation photon undergoes Compton scattering while travelling through tissue and changes its direction, but without much loss of energy [EJ, 1986]. Since the reduction of energy of random coincidences annihilation photon is too small to be distinguished by detectors, it is difficult to correct for it from true coincidences. One possible correction method is to take coincidences outside the field of view where no true coincidences are expected. By subtracting both random and scatter coincidences in the field of view, an accurate coincidence count can be generated [Saha and Gopal, 2005].

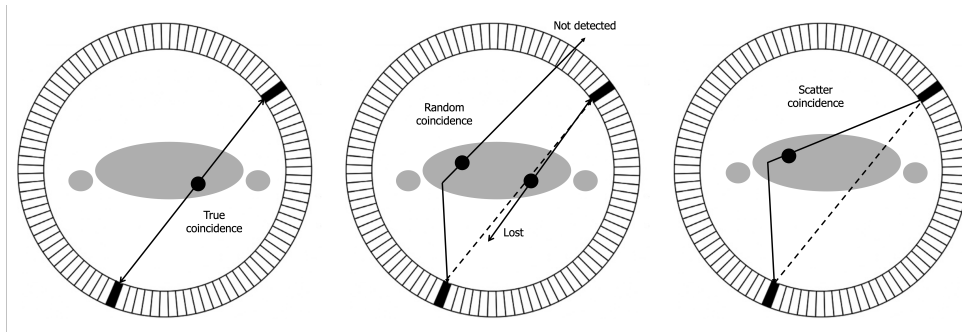


Figure 2.5: Types of coincidences. From left to right: True coincidence, random coincidence, and scattered coincidence [Schmitz et al., 2005].

Decay Correction As a result of radioactive decay, the number of radio-tracer atoms capable of triggering coincidences decreases over time, resulting in a reduction in the number of detected coincidences. The decay process follows an exponential model, where the rate of decay is proportional to the remaining quantity of the isotope. Assuming A_0 is the total activity at time $t = 0$, then the activity A_t at time t can be given as:

$$A_t = A_0 e^{-\lambda t} \quad (2.5)$$

Where λ is the decay constant that depends on the half-life of the particular radioactive nuclide. The half-life($t_{1/2}$) of a radionuclide is defined as the amount of time required for half of the radioactive atoms in a sample to decay, which is unique for every radionuclide, and λ can be expressed as

$$\lambda = \frac{\ln 2}{t_{1/2}} \quad (2.6)$$

Suppose y_t is the raw count data over a time bin with duration Δ_t , the decay-corrected activity z_t over the same time bin can be given by

$$z_t = \frac{y_t}{f_t}; \quad f_t = \Delta_t e^{-\lambda t} \quad (2.7)$$

2.3.2 Image Reconstruction

The acquired PET projection data stored in the sinogram are reconstructed with mathematical algorithms to obtain the image of the administered radiotracer distribution over the field of view. Many efforts have been made in the development of PET image reconstruction algorithms over the past five decades. The two widely used image reconstruction algorithms today are filtered backprojection (FBP) and iterative reconstruction. The former is an analytic approach that typically generates images by solving an explicit formula, while the latter relies on iterative estimation and algorithm convergence to generate reconstructed images. Both methods will be introduced in this section.

Filtered Backprojection (FBP) Filtered Backprojection is an analytic image reconstruction algorithm that assumes PET data is noise-free and reconstructs the image based on the measured counts. A simple backprojection algorithm averages the counts across all pixels along LORs, which

can only generate an approximation of the actual image with a blurring issue [Cherry et al., 2006, Saha and Gopal, 2005, Tong et al., 2010]. To address the blurring issue, the direct Fourier transform was introduced to reconstruct the activity distribution image using the central slice theorem, which connects the projection data and the activity distribution [Tong et al., 2010, Kak and Slaney, 2001]. The Fourier transform is applied to each row in the sinogram (i.e., with respect to the distance offset from the center for all angles), and the inverse Fourier transform is then used to reconstruct the image [Cherry et al., 2006]. This algorithm involves interpolating the offset distance, as the detectors are not point detectors and have a finite density. Thus, the interpolation error decides the reconstructed image quality [Tong et al., 2010]. The filtered backprojection applies a filter function to the Fourier transform of the sinogram data before backprojection. The implementation of FBP is as follows:

1. Fourier transform of the first row in the sinogram
2. Multiply it by a filter function
3. Take the inverse Fourier transform
4. Backprojection to image domain
5. Repeat 1-4 for remaining rows in the sinogram

The primary purpose of the filter function is to reduce high-frequency noise; however, it also reduces the spatial resolution of the reconstructed images. Different filter functions should be chosen based on the trade-off between reconstructed image signal-to-noise ratio and spatial resolution [Cherry et al., 2006, Saha and Gopal, 2005]. While FBP is fast and easy to implement, it has some limitations. It assumes noise-free data, which is

not possible in the clinical environment, and it cannot model some physical degrading factors in a PET scanner, such as intercrystal scatter, positron range, and non-collinearity [Cherry et al., 2006, Tong et al., 2010].

Iterative Reconstruction An alternative image reconstruction approach is iterative reconstruction, which not only models the image data but also accounts for the statistical noise inherent in the acquisition process, as well as various physical effects that FBP cannot capture. The general structure of iterative reconstruction is shown in Figure 2.6. It starts with an initial guess of the image estimation (usually a blank or a uniform gray-scale image). The projection estimation is calculated by forward projection from the image estimation. The projection estimation and measurement from the PET scanner are then compared to check specific criteria. If the requirements are met, the final reconstructed image can be obtained by backprojecting the estimated projection. Otherwise, the current image estimation is updated based on the difference between the projection estimation and the measurement to generate a new image estimation for the next iteration. The iteration will be repeated until the criteria are satisfied [Schmitz et al., 2005, Saha and Gopal, 2005, Tong et al., 2010]. Two key components in iterative reconstruction are the choice of the optimization criterion and the algorithm used to update the current image estimate. The most widely used criterion (also known as the cost function) is the maximum-likelihood (ML) estimation function. By maximizing the function, it produces a projection that is 'most likely' to be the same as the measured projection. The expectation-maximization algorithm offers an efficient approach to finding ML estimation and, therefore, can be used to update the image estimation [Cherry et al., 2006, Saha and Gopal, 2005, Tong et al., 2010]. One major problem of iterative reconstruction is its computationally inten-

sive nature. Each iteration involves a backprojection and a sophisticated forward projection, as it needs to model the probability that each pixel will be detected on all LORs. The time required for one iteration is roughly equivalent to a full FBP, and it typically takes 30-100 iterations to reach convergence and reconstruct the image [Cherry et al., 2006]. A faster version of ML-EM is introduced to address the time-consuming problem. The Ordered Subsets Expectation Maximization (OSEM) algorithm uses only a subset of projection angles at each iteration to accelerate convergence, approximately by a factor equal to the number of subsets, while maintaining comparable reconstructed image quality [Saha and Gopal, 2005, Tong et al., 2010]. The advantage of iterative reconstruction is that it offers a better signal-to-noise ratio at a given spatial resolution compared to FBP. But it also has a noisy image due to the ill-conditioning problem. Additional stopping rules can be used to terminate the iterations before convergence, thereby reducing the amount of noise at the expense of increasing bias [Tong et al., 2010, Shepp and Vardi, 1982].

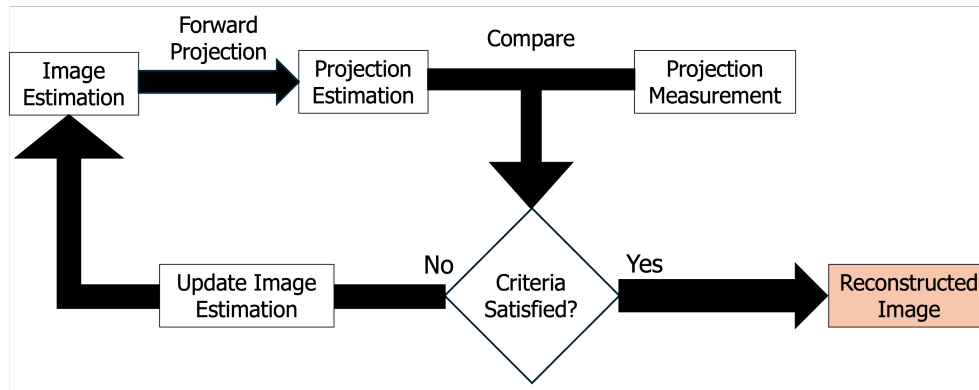


Figure 2.6: The general structure of iterative image reconstruction algorithm [Schmitz et al., 2005, Saha and Gopal, 2005, Tong et al., 2010]

2.4 Quantitation of PET Imaging

In clinical routine, PET images are typically assessed visually or with simple indices. However, the potential of PET can be further explored and utilized through quantitative analysis in disease diagnosis, assessment of treatment response, and management of therapy [Tomasi et al., 2012]. The PET quantification analysis models usually use the PET measurements data from the scanner (tracer concentration in tissues) and arterial input function (tracer concentration in plasma acquired during the PET scanning) as inputs, and the outputs are summarized by a set of tracer kinetic parameters that reveal the underlying metabolic processes involving the injected radio-tracer [Bertoldo et al., 2014, Veronese et al., 2016]. Several well-developed and widely used semi-quantitative and quantitative PET models are employed in both clinical and research studies, with various application assumptions and kinetic information, as summarized in Figure 2.7. In this section, we will introduce some semi-quantitative indices and multiple methods for acquiring the arterial input function (AIF). The full models will be introduced in the next chapter.

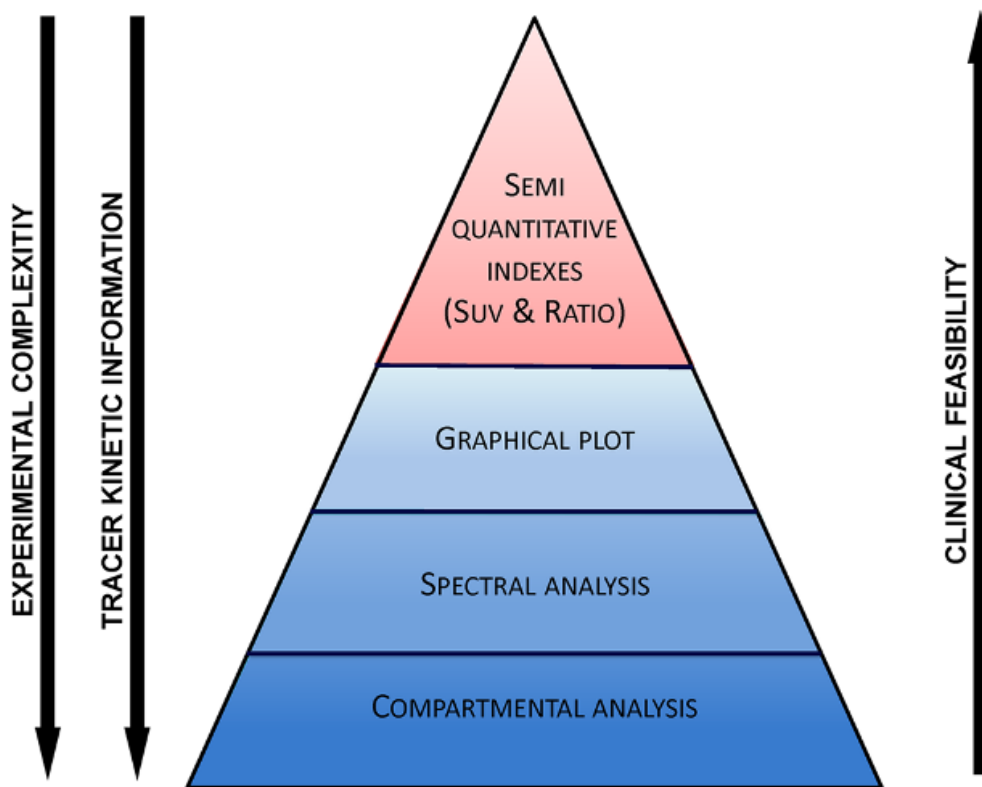


Figure 2.7: A Hierarchical summary of major PET quantitation approaches [Bertoldo et al., 2014]

2.4.1 Static and Dynamic PET Scans

Typically, there are two types of PET scanning as shown in Figure 2.8. A static PET scan is made by a single-frame acquisition at a given time after the radiotracer administration, usually 10-60 minutes, depending on the half-life of the radiotracer isotope and the biochemical process in which the radiotracer is involved [Veronese et al., 2016]. This approach is widely adopted in clinical practice due to its practicality, cost-effectiveness, streamlined patient workflows, and high throughput [Bertoldo et al., 2014]. However, static PET imaging can only provide a 'screenshot' of the tracer distribution and hence limits the amount of information obtained from a single PET scan. It will considerably reduce the versatility of PET imaging, especially in more accurate diagnostic, prognostic, and treatment response

assessments [Zaidi and Karakatsanis, 2017]. In this setting, PET quantitation is usually represented by standardized uptake value (SUV) or ratio methods, which will be introduced later.

Dynamic PET imaging involves the spatiotemporal acquisition of PET data, resulting in 4D datasets (3D in space and 1D in time). It is typically coupled with arterial blood sampling during the scanning process, which is necessary for kinetic modeling. The 4D PET dynamic data are commonly used in research studies employing various kinetic modeling approaches to derive physiological parameters that summarize the different characteristics of the tracer distribution within a region of interest or across the field of view, thereby generating a parametric image. Compared to static PET imaging, dynamic PET imaging requires much longer scanning time and invasive arterial blood sampling, which are the main reasons that dynamic PET is limited in clinical routine [Bertoldo et al., 2014, Zaidi and Karakatsanis, 2017, Burger et al., 2011].

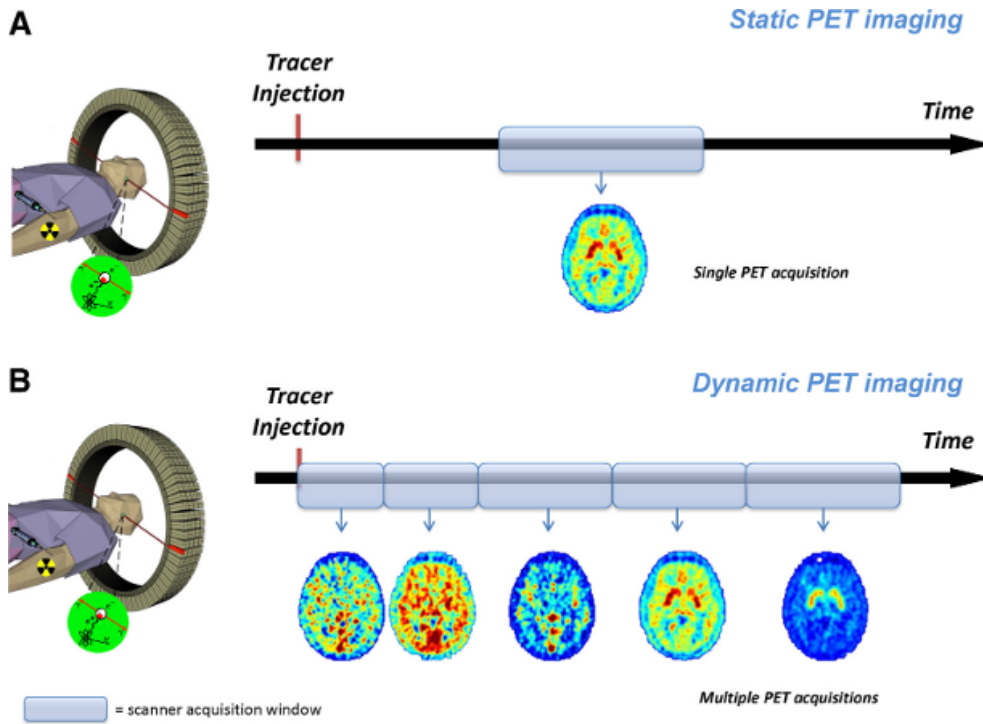


Figure 2.8: Two types of PET imaging (A:static; B:dynamic) [Bertoldo et al., 2014]

2.4.2 ROI Versus Voxel-Level Analysis

PET quantitation data analysis can be performed either with region of interest (ROI) data or voxel-level data to obtain a set of summary kinetic parameters over the ROI or parametric images, respectively. ROI analysis yields more robust results, as it averages the voxel data within the ROI and significantly reduces the noise level [Bertoldo et al., 2014]. But it will introduce some biases in certain instances, such as a small lesion in the ROI that may be invisible in ROI analysis [Bertoldo et al., 2014]. Voxel-level analysis is an alternative approach to ROI analysis. It can generate parametric images and can reveal the heterogeneity of tumors [Muzi et al., 2012]. However, the time-activity curve from a voxel could be dominated by noise, which can affect the voxel-level result. The selection of models and noise suppression should be carefully considered [Wang et al., 2022]. Regardless of whether

data are analyzed at the voxel level or aggregated into ROIs, several factors can compromise the accuracy of kinetic parameter estimates. These include motion artifacts due to patient movement [Bowen et al., 2012], inaccuracies introduced by the partial volume effect [Erlandsson et al., 2012], and contamination from adjacent tissue activity (spillover).

2.4.3 Semi-Quantitative Index

Standardized Uptake Value Standardized uptake value (SUV) was first proposed as a semi-quantitative index in oncological studies [Kubota et al., 1985] and now it stands as the most commonly adopted semi-quantitative index for PET quantification in clinical settings [Boellaard, 2009]. The SUV is defined as the radiotracer concentration within a region or voxel of interest, normalized by the injected dose and a patient-specific normalization factor (NF) that accounts for body weight and composition.

$$\text{SUV} = \frac{\text{radiotracer concentration}}{\frac{\text{injected dose}}{\text{NF}}} \quad (2.8)$$

The radiotracer concentration is determined by PET scanner measurements taken over a brief acquisition period—typically between 5 and 15 minutes—following a fixed uptake duration after tracer injection (commonly 30 or 60 minutes post-administration). The injected dose represents the total amount of radiotracer administered. NF is commonly based on body weight or body surface area [Bertoldo et al., 2014, Thie, 2004]. Due to the simplicity (simple calculation and no need for arterial sampling) and versatility (can be used with a variety of radiotracers), SUV has been widely applied in clinical oncology diagnosis and tu-

mor staging in lung [Hickeson et al., 2002], breast [Ulaner et al., 2013], ovarian [Rockall et al., 2014], and esophageal [Pan et al., 2009]. However, SUV has an inconsistency problem, either due to the scanner [Boellaard, 2009, Reuzé et al., 2018] or the patient [Hatt et al., 2017]. It is necessary to validate SUV reproducibility given a particular tracer and a system [Bertoldo et al., 2014, Tomasi et al., 2012]. Additionally, SUV can only quantify the tracer uptake but does not reflect any physiological or pharmacological processes.

Ratio methods Another semi-quantitative index can be obtained by calculating the ratio of tracer concentration in different regions or tissues. Volume distribution V_d equals the ratio between tracer concentration in tissue and tracer concentration in plasma in a true equilibrium situation [Bertoldo et al., 2014, Carson et al., 1993]. Although achieving true equilibrium is challenging in clinical settings, a stable tissue-to-plasma concentration ratio can still emerge over time. When using a reversible tracer (the tracer will not be fixed or trapped in a specific metabolic process), the estimation is the apparent volume distribution, V_{app} , where $V_{app} > V_d$. The difference is influenced by both the rate at which the tracer is cleared from the plasma and the specific kinetic properties of the local tissue [Lehtiö et al., 2003]. The ratio method is also applicable for estimating the binding potential BP_{ND} in receptor imaging studies. In this context, BP_{ND} is defined as the ratio of tracer concentration in the target tissue to that in a reference region devoid of specific receptor binding. The BP_{ND} estimated from the ratio method is highly correlated with the BP_{ND} estimated from more complicated compartmental modeling [Bertoldo et al., 2014, Farde et al., 1989, Ito et al., 1998].

2.4.4 Arterial Input Function (AIF)

Dynamic PET analysis requires knowledge of the tracer's arterial plasma concentration during the PET imaging time, which serves as the arterial input function (AIF). Typically, the AIF can be obtained from direct blood sampling, population-based function, a time-activity curve from the blood pool image, or a model-based function. This section will briefly review all four approaches.

Blood Sampling Arterial catheterization, performed during dynamic PET imaging to obtain arterial blood samples, has long been regarded as the gold standard for the input function in tracer kinetic modeling [Graham and Lewellen, 1993]. Nonetheless, its routine use in clinical settings is limited due to several drawbacks: it increases patient discomfort, introduces additional radiation exposure, and incurs higher costs associated with processing multiple blood samples [Feng et al., 2020]. There are efforts to eliminate invasive blood sampling in PET quantification. Some studies, including those involving the quantification of cerebral blood flow, use models that do not require a blood fraction term and are therefore suitable for blind estimation approaches [Di Bella et al., 1999, Feng et al., 2020]. Other approaches focus on reducing the number of blood samples while maintaining acceptable quantification results [Bentourkia et al., 1999, Kato et al., 1984].

Population-Based Input Function (PBIF) The population-based approach assumes that individuals who have the same injection protocol share one set of physiological characteristics. This type of input function is typically constructed by averaging and scaling multiple input functions derived from direct blood sampling. Then the input function for each

individual is adjusted based on the population-based input function and a few blood samples from the individual [Gu, 2023]. This approach can only minimize, but not eliminate, the need for blood sampling to one or two samples per patient [Feng et al., 2020]. Also, this approach needs to adapt and validate for different tracers, and only a few tracer tracers have been validated for this approach, such as ^{18}F -FDG [Vriens et al., 2009], ^{18}F -NaF [Hirata et al., 2005], ^{11}C -(R)-rolipram [Zanotti-Fregonara et al., 2012].

Image-Derived Input Function (IDIF) Image-derived input functions (IDIFs) are extracted from dynamic PET data by imaging blood pools within the field of view, such as the cardiac chamber, descending aorta, or carotid artery [Iida et al., 1998, Ohtake et al., 1991, Germano et al., 1992, Chen et al., 1998, Rajeswaran et al., 1992]. Fast frame acquisition (1–2 minutes post-injection) is critical to capture the arterial input function's peak [Feng et al., 2020]. However, IDIFs require corrections for spillover and partial volume effects to ensure quantitative accuracy [Mourik et al., 2008, Zhou et al., 2012]. Additionally, extended scan durations may be necessary to simultaneously image blood pools and target tissues across different fields of view. A key limitation of this approach is its restriction to tracers without metabolites, such as ^{18}F -FDG [Bertoldo et al., 2014, Feng et al., 2020].

Model-Based Input Function (MBIF) The model-based input function (MBIF) is introduced to obtain a continuous and noise-free input function with mathematical descriptions from either clinically sampled blood samples, image-derived signals, or a combination of both [Gu and Wu, 2023]. The widely used models, such as Feng's AIF model [Feng et al., 1993], tri-exponential model [Parsey et al., 2000], and

convoluted models [Tonietto et al., 2015], are capable of capturing some significant characteristics of the AIF. However, they fall short in capturing the full complexity of the AIF and often do not adequately accommodate variations in injection protocols [Tonietto et al., 2015]. An alternative approach, based on a Markov chain with time-steps directly connected to the beats of the heart, is developed to simulate an eight-state blood flow that carries tracer atoms, showing good agreement between the model-estimated AIF and arterially sampled data [Huang and O’Sullivan, 2014]. Some more recently developed novel approaches such as the population-based projection model(PBPM) from Xiu et al. [Xiu et al., 2022] that combines population profiling and dynamic blood pool imaging and the model developed by Finbarr O’Sullivan [O’Sullivan, 2023] that represent the AIF in terms of the whole-body impulse to the injection profile are capable to model AIF with higher accuracy and allow varying injection protocols with different image quality.

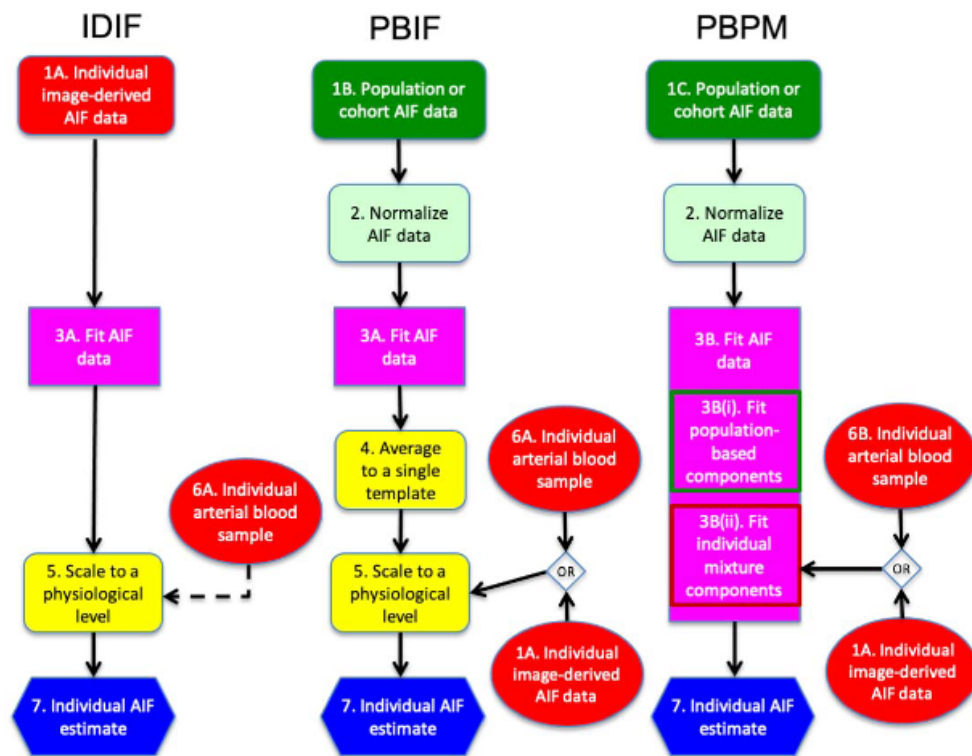


Figure 2.9: Flowchart of typical IDIF and PBIF, alongside the PBPM model(a version of MBIF) [Xiu et al., 2022].

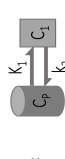
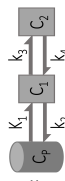
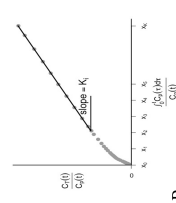
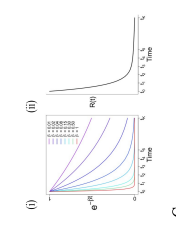
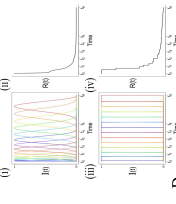
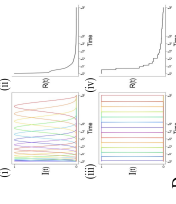
Chapter 3

PET Kinetic modeling

3.1 Outline

In this chapter, we provide an overview of different kinetic models that can deliver some or all sets of kinetic parameters related to the injected radio-tracer and the physiological process in which it is involved. We will begin with the indicator-dilution method, as described by Meier and Zierler [Meier and Zierler, 1954]. Then we will go through graphical analysis (Patlak plot [Patlak et al., 1983] and Logan plot [Logan et al., 1990]), the spectral analysis [Cunningham and Jones, 1993], different compartmental models [Kety et al., 1948, Mintun et al., 1984, Sokoloff et al., 1977, Phelps et al., 1979, Huang et al., 1980]. We also introduce the non-parametric residue mapping method as a more flexible and versatile kinetic model. A summary of these kinetic models is presented in Table 3.1.

Table 3.1: A summary of major PET kinetic models [Gu and Wu, 2023]

Kinetic Model	Compartmental Model	Patlak Plot	Spectral Analysis	Non-parametric Analysis
Graphical Representation	1C:  2C:  A			
				
Formula	1C: $\frac{dC_1(t)}{dt} = K_1 C_p(t) - k_2 C_1(t)$ 2C: $\begin{cases} \frac{dC_1}{dt} = K_1 C_p(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t) \\ \frac{dC_2}{dt} = k_3 C_1(t) - k_4 C_2(t) \end{cases}$ $\frac{C_T(t)}{C_p(t)} = K_1 \int_0^t \frac{C_p(\tau) d\tau}{C_p(t)} + C, t \geq t^*$ $C_T(t) = \sum_{j=0}^J \alpha_j g_j(t), \alpha_j \geq 0$ $C_T(t) = \sum_{j=0}^J \alpha_j f_j(t), \alpha_j \geq 0$			
Residue Form	1C: $R(t) = K_1 e^{-k_2 t}$ 2C: $R(t) = K_1(\pi_1 e^{-\theta_1 t} + \pi_2 e^{-\theta_2 t})$	$R(t) = K_i, t \geq t^*$	$R(t) = \sum_{j=0}^J \alpha_j e^{-\beta_j t}$	$R(t) = \sum_{j=1}^J \alpha_j I_j(t)$
Kinetic Parameters	All	Only K_i	All	All
Computation	Nonlinear Least Square or Maximum Likelihood	Ordinary Least Square	Non-negative Least Square	Quadratic Programming

A: One (1C) and two compartmental (2C) models. C_p is the plasma compartment; C_1 and C_2 are tissue compartments.

B: Patlak plot.

C: Spectral Analysis. (i) exponential distribution for different values of β ; (ii) the typical residue estimated by spectral analysis.

D: Non-parametric Analysis. (i) general form of B-spline basis elements; (ii) the typical residue estimated by B-spline function; (iii) general form of piece-wise elements; (iv) the typical residue estimated by piece-wise function.

$$\text{Notations: } \begin{cases} \pi_1 = \frac{k_4 - \theta_1 + k_3}{\theta_2 - \theta_1}, \pi_2 = \frac{\theta_2 - k_4 - k_3}{\theta_2 - \theta_1} \\ \theta_1 = \frac{k_2 + k_3 + k_4 - \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2 k_4}}{2} \\ \theta_2 = \frac{k_2 + k_3 + k_4 + \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2 k_4}}{2} \end{cases} \quad \begin{aligned} g_j(t) &= C_p(t) \otimes e^{-\beta_j t} & f_j(t) &= C_p(t) \otimes I_j(t), I \text{ represents basis function (B-spline or piece-wise form)} \end{aligned}$$

3.2 Indicator-Dilution Method

The indicator-dilution method was first introduced by Stewart [Stewart, 1897]. It was then developed to measure cardiac output [Hamilton et al., 1932], the volume of blood in the heart and lungs [Stewart, 1921], and the volume of a vascular bed [Hamilton et al., 1932]. Meier and Zierler first demonstrated that dynamic PET data are suitable for analysis using the indicator-dilution method [Meier and Zierler, 1954]. This method assumes that the radiotracer-tissue interaction follows a linear and time-invariant behavior, allowing the vascular system to be modeled as a linear time-invariant (LTI) system (see Appendix B.1 for details). Then, the measured voxel time-activity curve (TAC) $C_T(t)$ can be expressed as a convolution between the arterial input function (AIF) $C_p(t)$ and the tissue residue or impulse response function $R(t)$.

$$C_T(t) = \int_0^t R(t-s)C_p(s)ds = R(t) \otimes C_p(t) \quad (3.1)$$

Where the tissue residue function $R(t)$ is a necessarily monotonic decreasing function that would give the number of remaining radiotracers in the tissue as a function of time if all radiotracers were introduced instantaneously into the body [O’Sullivan et al., 2014]. Several kinetic models can be used to estimate this function, and many kinetic parameters can be derived from it.

With an adjustment for the fractional blood volume (V_b) and the delay (Δ) from AIF [Gu et al., 2021a], the basic equation of dynamic PET data become

3.2

$$C_T(t) = V_b C_p(t - \Delta) + (1 - V_b) \int_0^t R(t - s) C_p(s - \Delta) ds \quad (3.2)$$

3.3 Graphical Analysis

By transforming the dynamic PET scanning data, we can generate a series of data with a linear trend, where the slope is designed to be an estimator of the parameter of interest. This graphical analysis uses the equilibrium status of the injected tracer in the system after a certain amount of time after tracer injection [Bertoldo et al., 2014]. Thus, graphical analysis requires only a few late frames of dynamic scanning, and the parameter of interest can be computed using ordinary least squares, which is fast and easy to implement. Therefore, it is suitable for voxel-level application and generates the parametric map [Tomasi et al., 2012]. However, only a reduced set of parameters (K_i for the Patlak plot and V_d for the Logan plot) can be obtained with each plot, and no other information regarding the kinetics of the tracer can be accessed by graphical analysis. The two primary graphical analyses are the Patlak plot [Patlak et al., 1983] and the Logan plot [Logan et al., 1990], which are designed for irreversible and reversible tracers, respectively. An illustrated example is shown in Figure 3.1

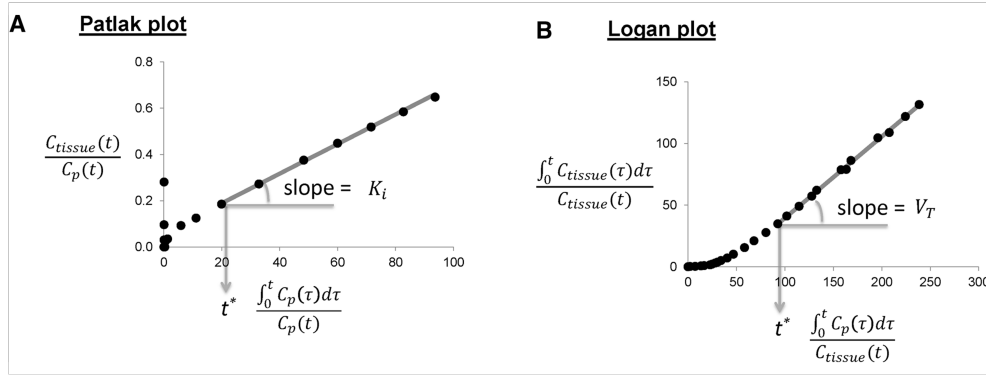


Figure 3.1: An example of Patlak plot (A) and Logan plot (B). The slope of the data after equilibration time t^* becomes constant and represents the estimated parameter K_i for the Patlak plot and V_d for the Logan plot [Bertoldo et al., 2014].

Patlak Plot Patlak plot was originally developed for quantification of FDG PET studies and is suitable for irreversible tracers. The Patlak plot returns K_i , the uptake rate constant in tissue after equilibrium. The Patlak plot is given by the expression [Patlak et al., 1983]:

$$\frac{C_T(t)}{C_p(t)} = K_i \frac{\int_0^t C_p(\tau) d\tau}{C_p(t)} + C, \quad t > t^* \quad (3.3)$$

Where $C_T(t)$ is tracer concentration in tissue measured by dynamic PET scanner, $C_p(t)$ is the tracer concentration in plasma from AIF, and C is a constant. When the system reaches the equilibrium state (after t^*), K_i can be estimated using ordinary least squares (OLS) as the slope of the Patlak plot. The Patlak plot is based on two assumptions: (i) the presence of an irreversible compartment for the tracer; (ii) after a certain amount of time t^* , all reversible systems are equilibrated with plasma [Bertoldo et al., 2014]. So, it is critical to choose an appropriate t^* for an acceptable estimation of K_i [Choi et al., 1991].

Logan Plot Logan plot is designed for the reversible tracer, where V_d can

be estimated from the slope of the transformed data given by this expression [Logan et al., 1990]:

$$\frac{\int_0^t C_T(\tau) d\tau}{C_T(t)} = V_d \frac{\int_0^t C_p(\tau) d\tau}{C_T(t)} + C, \quad t > t^* \quad (3.4)$$

Similarly to the Patlak plot, the choice of t^* is also vital for the Logan plot. The V_d estimated from the Logan plot tends to be underestimated as the estimation can be affected by the noise in the data. Several attempts have been made to improve the analysis of the Logan plot, either by using a more complicated estimation algorithm or rearranging the Logan plot equation [Bertoldo et al., 2014, Slifstein and Laruelle, 2001].

3.4 Spectral Analysis (SA)

Spectral Analysis (SA) models the dynamic PET data $C_T(t)$ as the convolution between the AIF $C_p(t)$ and $M+1$ distinct exponential terms [Cunningham and Jones, 1993].

$$C_T(t) = \sum_{j=1}^M \alpha_j C_p(t) \otimes e^{-\beta_j t} \quad (3.5)$$

And the residue function is

$$R(t) = \sum_{j=1}^M \alpha_j e^{-\beta_j t} \quad (3.6)$$

where α_j and β_j are assumed to be non-negative. β_j are pre-defined to cover a range of different events of the tracer in the tissue, while the amplitudes α_j are unknown and estimated from the data [Veronese et al., 2016, Cunningham and Jones, 1993, Turkheimer et al., 1994]. The SA model can provide a 'kinetic spectrum' that represents the different func-

tional processes of the involved tracer and identifies the number and type of compartments needed for modeling [Cunningham and Jones, 1993, Bertoldo et al., 2014]. SA is also capable of estimating kinetic parameters, including influx rate constant K_1 , K_i , and K_d [Tomasi et al., 2012, Veronese et al., 2016].

$$K_1 = \sum_{j=0}^M \alpha_j; \quad K_i = \lim_{t \rightarrow \infty} \sum_{j=0}^M \alpha_j e^{-\beta_j t}; \quad V_d = \sum_{j=1}^M \frac{\alpha_j}{\beta_j} \quad (3.7)$$

The main advantage of SA is its versatility, as it can be applied to both reversible and irreversible tracers, as well as homogeneous and heterogeneous tissues [Schmidt, 1999]. It also makes SA widely applicable from preclinical data to research studies involving brain neuroreceptors, heart, breast cancer, and gastrointestinal cancer [Bertoldo et al., 2014]. But it is sensitive to noise in the data, and many efforts have been made to improve SA [Gunn et al., 2002]. The two most widely used SA alternatives to reduce the effect of noisy data are rank-shaping spectral analysis (RSSA) [Turkheimer et al., 2003] and spectral analysis with iterative filter (SAIF) [Veronese et al., 2010], which are designed for reversible and irreversible tracers, respectively.

3.5 Compartmental modeling

Compartmental models form the mathematical foundation for quantifying tracer kinetics in dynamic PET imaging. Initially developed for brain PET studies, these models have since been adapted to diverse biological systems, including skeletal muscle [Bertoldo et al., 2001] and breast cancer [Kenny et al., 2005]. The two primary variants—the one-tissue and two-tissue compartmental models (Fig. 3.2)—enable absolute quantification of

physiological parameters such as perfusion (K_1), metabolic flux (K_i), and distribution volume (V_d) [Bertoldo et al., 2014, Cobelli and Carson, 2019]. Each compartment is defined as a kinetically homogeneous, well-mixed entity governed by a set of first-order differential equations. These equations are solved via non-linear least-squares optimization to estimate kinetic parameters from time-activity curves [Cobelli et al., 2007, Bertoldo et al., 2014]. The following sections detail the structural and functional distinctions between one-tissue and two-tissue compartmental models.

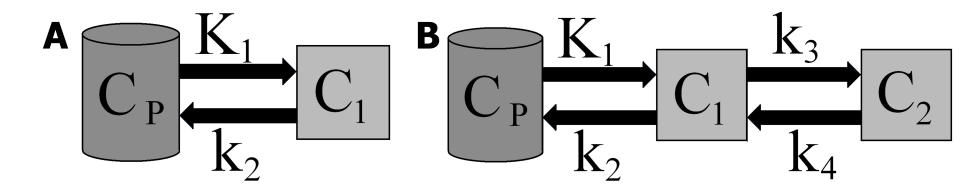


Figure 3.2: One tissue (A) and two tissue (B) compartmental models. C_1 and C_2 are tissue compartments and C_P represent the plasma compartment. Each arrow indicates the flux of material from one compartment to another, resulting from transport, chemical transformation, or both [Hawe et al., 2012].

One tissue compartmental (1C) model One tissue compartmental model was developed for quantitative assessment of blood perfusion with two rate constants (K_1 in $\text{ml}/\text{min}/\text{cm}^3$ and k_2 in min^{-1}) [Kety et al., 1948]. The model is given by a differential equation, as shown in equation 3.8.

$$\frac{dC_1(t)}{dt} = K_1 C_p(t) - k_2 C_1(t) \quad (3.8)$$

Assuming $C_p(t)$ is known, this equation can be solved for $C_1(t)$ using the integrating factor [Trench, 2013]. The detailed derivations are given in Appendix B.2.

$$C_1(t) = K_1 \int_0^t e^{-k_2(t-s)} C_p(s) ds \quad (3.9)$$

With equation 3.1, the residue function of the 1C model can be obtained as

$$R(t) = K_1 e^{-k_2 t} \quad (3.10)$$

Two-Tissue Compartmental (2C) Model Two tissue reversible compartmental (2Cr) model is initially designed for receptor ligand binding studies with four rate constants (K_1 in ml/min/cm³, k_2 , k_3 , and k_4 in min⁻¹) [Mintun et al., 1984]. When $k_4 = 0$, the model becomes the two-tissue irreversible compartmental (2Ci) model with three rate constants. It is most widely used for the quantitation of the metabolic rate of glucose with FDG [Sokoloff et al., 1977, Phelps et al., 1979, Huang et al., 1980]. A coupled system of differential equations can represent the model as

$$\begin{cases} \frac{dC_p}{dt} = k_2 C_1(t) - K_1 C_p(t) \\ \frac{dC_1}{dt} = K_1 C_p(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t) \\ \frac{dC_2}{dt} = k_3 C_1(t) - k_4 C_2(t) \end{cases} \quad (3.11)$$

Similarly to the 1C model, C_p is assumed to be known, and the equations are solved for C_1 and C_2 with the Laplace transform [Trench, 2013] in equation 3.12. Full details of the solution can be found in the Appendix B.3.

$$C_T(t) = C_1(t) + C_2(t) = K_1(\phi_1 e^{-\theta_1 t} + \phi_2 e^{-\theta_2 t}) \otimes C_p(t) \quad (3.12)$$

where

$$\begin{cases} \phi_1 = \frac{k_4 - \theta_1 + k_3}{\theta_2 - \theta_1}, \phi_2 = \frac{\theta_2 - k_4 - k_3}{\theta_2 - \theta_1} \\ \theta_1 = \frac{k_2 + k_3 + k_4 - \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2 k_4}}{2}, \theta_2 = \frac{k_2 + k_3 + k_4 + \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2 k_4}}{2} \end{cases} \quad (3.13)$$

and based on equation 3.1 the residue function can be expressed as

$$R(t) = K_1(\phi_1 e^{-\theta_1 t} + \phi_2 e^{-\theta_2 t}) \quad (3.14)$$

The assumption of compartmental models is homogeneity of each compartment, instant mixing within each compartment, and compartments follow the law of mass action [Hawe, 2016]. Compartmental modeling can describe the mechanisms of system functioning [Bertoldo et al., 2014]. Still, it is not practical to incorporate into clinical routine, as it requires fully dynamic scanning, arterial blood samples, and high computational time. The selection of different compartmental models is also critical because each compartmental model is generally adopted in conjunction with a specific type of tracer and target tissue or organ. For example, the 1C model is more widely used for ^{15}O -H $_2$ O studies, the 2Cr model is used for ^{11}C -raclopride, and 2Ci is the most commonly used for ^{18}F -FDG studies. Studies and applications of different tracers may require additional modifications based on the purpose of the studies.

3.6 Non-Parametric Residue Mapping (NPRM)

3.6.1 Residue Representation

In non-parametric residue mapping(NPRM), the residue function $R(t)$ in equation 3.1 can be expressed in terms of the travel-time density of injected radiotracer, h ,

$$R(t) = \alpha(1 - \int_0^t h(s)ds) \quad (3.15)$$

with $\alpha > 0$ and $\int_0^\infty h(s)ds \leq 0$. Note that α is a positive scaling pa-

parameter and $h(s)$ is not a proper probability distribution, as some tracer may be retained by the tissue within the observation window, resulting in effectively infinite transit times. Typical parametric models, such as compartmental models and spectral analysis, assume that the travel-time density function follows an exponential form. However, the exponential travel-time density function may not accurately represent the actual density function, as it is not necessarily a monotonic decreasing function. Non-parametric approaches approximate the travel-time density using a collection of basis functions. The basis function can be a cubic B-spline function([O'sullivan et al., 2009, Chen et al., 2019], a piece-wise constant function([Hawe et al., 2012, O'Sullivan et al., 2014] or piece-wise linear basis functions as introduced below. This approach provides more flexibility in the estimation process. We consider flexible residue function estimators of the form.

$$h(s) \approx \sum_{m=1}^M h_m B_m(s) ds \quad (3.16)$$

where the scanning time window, denoted $[0, T_e]$, is partitioned using $0 = \tau_0 < \dots < \tau_M = T_e$ and B_m is a linear function supported on the interval $[\tau_{m-1}, \tau_m)$. The model implies a linear form for the tissue concentration in equation 3.1

$$C(t|\theta) = \sum_{m=1}^M \theta_m X_m(t - \Delta_m) = X(t - \Delta)' \theta \quad (3.17)$$

where $X(t - \Delta) = (X_1(t - \Delta_1), \dots, X_M(t - \Delta_M))$ and $X_m(t - \Delta_m) = R_m \otimes C_p[t - \Delta_m]$. The delays $\Delta = (\Delta_1, \dots, \Delta_M)$ capture the differences in the time of arrival of the tracer to various regions within the field of view. The coefficients $\theta = (\theta_1, \dots, \theta_M)$ must be non-negative. The basis elements $X_m(t - \Delta_m)$, also referred to as sub-TACs, are chosen through a basis se-

lection procedure. This procedure utilizes cross-validation-guided backward elimination to identify a relatively small subset (K) of basis elements from a finely sampled set (M). The positive linear combinations of the selected basis elements are intended to provide an adequate fit to a reduced dataset D_s , which is derived from a recursive hierarchical clustering of the measured PET data. The selected basis elements are defined to include time activity curves corresponding to the AIF pattern and the integral of the AIF pattern to model a spike residue and a constant residue, respectively. The voxel-level time activity curve data (z_{it}) can be well-approximated by a positive linear combination of the selected basis.

$$z_{it} = \sum_{k=1}^K \hat{\theta}_{ik} X_k(t) \quad (3.18)$$

Given PET-measured values of tracer concentration, $z_t \approx C(t)$, the unknown coefficients (θ) can be estimated by minimizing the weighted residual sums of squares

$$WRSS(\theta) = \sum_t w_t [z_t - X(t)' \theta]^2 \quad (3.19)$$

This optimization problem for θ can be solved by quadratic programming with non-negative constraints.

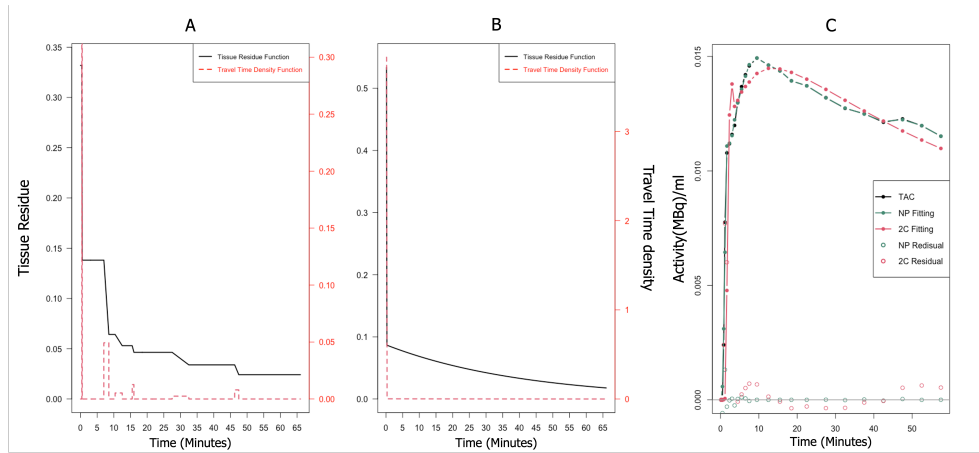


Figure 3.3: An example of tissue residue function(solid black) and corresponding travel time density function(dash red) from NPRM(A) and 2C model(B). The corresponding model fitting is shown in C, where the ROI TAC is in black, the NPRM fitting is in green, and the 2C model fitting is in red. The residuals for both models are shown in the same colour as empty dots.

3.6.2 Residue Decomposition and Kinetics Mapping

The residue function $R(t)$ can be expressed as a sum of three components, vascular component $R_B(t)$, in-distribution component $R_D(t)$, and extracted component $R_E(t)$ [O’Sullivan et al., 2014].

$$R(t) = R_B(t) + R_D(t) + R_E(t) \quad 0 \leq t \leq T_E \quad (3.20)$$

These three components are defined over intervals separated by two critical time points T_B and T_E , where $0 < T_B < T_E$. T_B represents the upper bound for the travel time of tracer atoms within large vessels. A value of $T_B = 15$ seconds is generally considered physiologically reasonable. T_E represents the end time of the PET scanning time frame. The relationship can be summarized as

$$\begin{aligned}
R_E(t) &= R(T_E) \quad 0 \leq t \leq T_E \\
R_B(t) &= \begin{cases} R(t) - R(T_B) & 0 \leq t \leq T_B \\ 0 & t > T_B \end{cases} \\
R_D(t) &= R(t) - R_B(t) - R_E(t) \quad 0 \leq t \leq T_E
\end{aligned}$$

The key physiological parameters - blood volume(V_b), in-distribution volume(V_d), in-distribution flow(K_d), apparent flux(K_i) and overall flow(K_1) - can be summarized as follows

$$\begin{aligned}
V_b &= \int_0^{T_B} R_B(t) dt; \quad V_d = \int_0^{T_D} R_D(t) dt; \\
K_d &= R_D(0); \quad K_i = R_E(0); \quad K_1 = K_d + K_i
\end{aligned} \tag{3.21}$$

The tracer extraction is measured as K_i/K_1 , and the mean transit time(MTT) is measured as the ratio of volume to flow according to the central volume theorem [Meier and Zierler, 1954]. Accounting for a delay factor(Δ), MTT can be measured as $MTT = V_d/K_d + \Delta$.

The voxel-level non-parametric residue mapping method is employed to generate parametric maps for each physiological parameter. A recursive hierarchical clustering model is used to partition the PET-measured image data into a set of N segments. These N segments are then modeled using NPRM through a cross-validation-guided backward elimination procedure to identify a reduced set of S segments. The mean time activity curves of these S segments are expected to form a positive linear combination that approximates the voxel-level time activity curve data. A more comprehensive intro-

duction to this method can be found in [Gu et al., 2021a]. Based on equation 3.18, the residue function of voxel i can be measured as

$$R(t, i) = \sum_{k=1}^K \hat{\theta}_{ik} R_k(t) \quad (3.22)$$

Where $R_k(t)$ is the residue function of the selected basis. The parametric images of kinetic parameters can be estimated with equation 3.21 from the voxel level of the residue function.

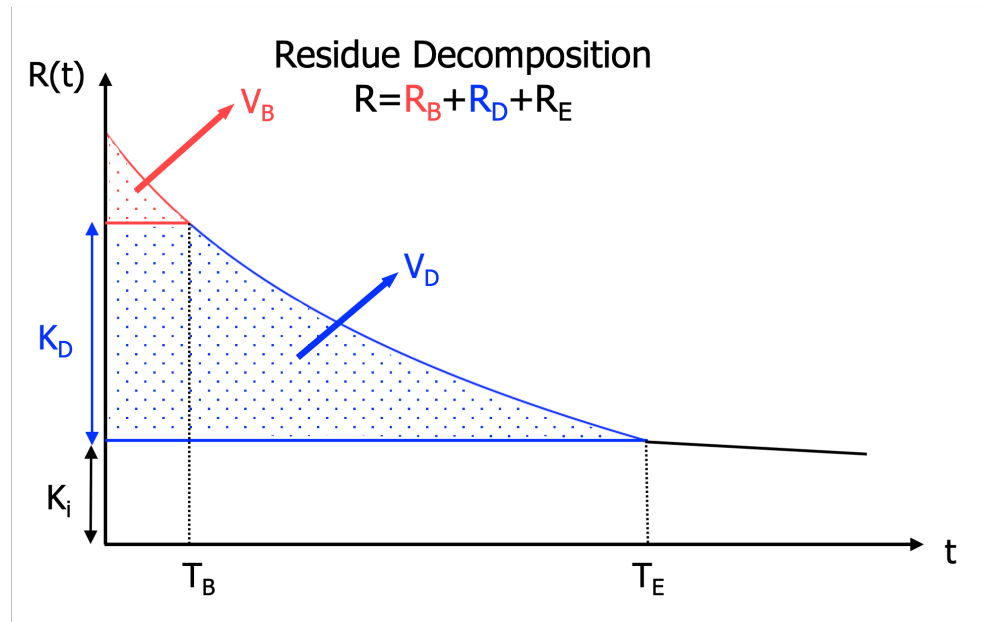


Figure 3.4: Decomposition of residue function(R) into vascular(R_B), in-distribution(R_D) and extracted(R_E) components. Blood volume(V_b), distribution volume(V_d), distribution flow(K_d) and flux(K_i) are defined as indicated [Wu et al., 2024].

3.7 Parameters Uncertainty Evaluation with Bootstrapping

3.7.1 General Bootstrap

The bootstrap is a resampling technique in statistical analysis that was first introduced by Efron [Efron, 1992]. It is a data-based simulation method for statistical inference that can be used to evaluate the sampling distribution of a statistic, estimate the bias and variance of a computed summary statistic, and formally assess associated hypotheses [Gu, 2023]. A flowchart of the general bootstrap is presented in Figure 3.5. Two widely used bootstrap techniques are briefly introduced as follows.

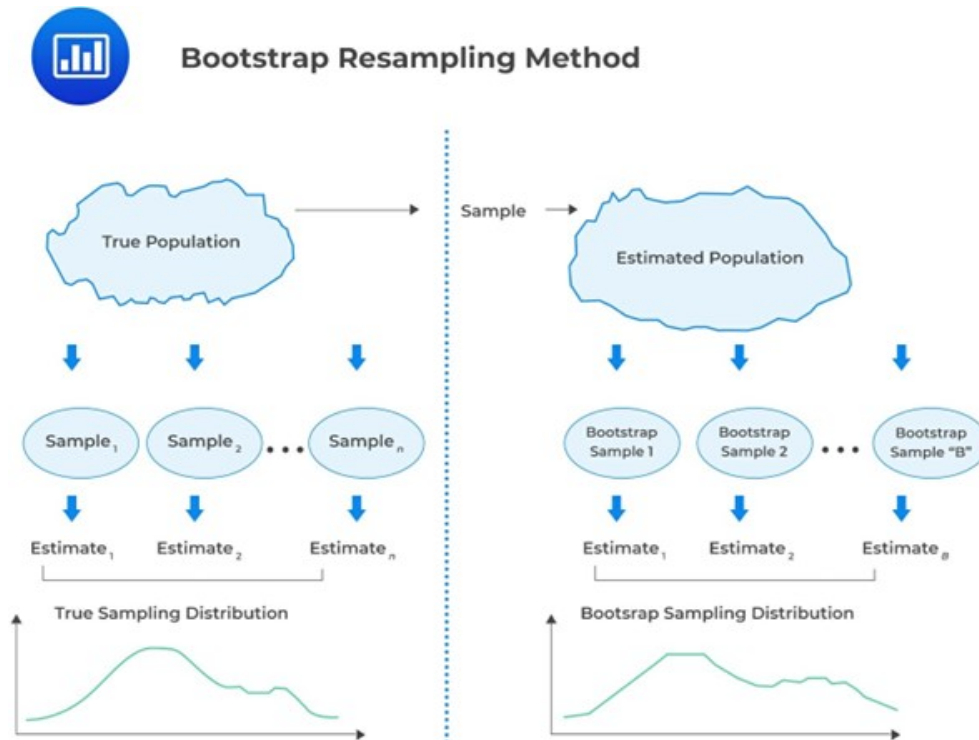


Figure 3.5: A general process of bootstrap [Kajal, 2024]

Non-Parametric Bootstrap Suppose $\mathbf{x} = (x_1, \dots, x_n)$ is an observed random sample from a unknown distribution. θ is a parameter of interest and $\hat{\theta}$

is an estimator of θ . The non-parametric bootstrap estimate of the distribution of $\hat{\theta}$ is obtained as follows [Rizzo, 2019].

1. For each bootstrap replicate, index $b = 1, \dots, B$:
 - (a) Generate sample $\mathbf{x}^{*(b)} = x_1^*, \dots, x_n^*$ by sampling with replacement from the observed sample $\mathbf{x}$.
 - (b) Compute the b^{th} replicate $\hat{\theta}^{(b)}$ from the b^{th} bootstrap sample.
2. The bootstrap estimate of $F_{\hat{\theta}}(\cdot)$ is the empirical distribution of the replicates $\hat{\theta}^{(1)}, \dots, \hat{\theta}^{(B)}$

Parametric(Model-Based) Bootstrap The parametric bootstrap assumes a relationship between at least two groups of data that can be described by a statistical model. The parameter of interest is then estimated based on this model. Here, an example of a linear model from [Gu et al., 2019] is used for better demonstration. The process is also summarized in Figure 3.6.

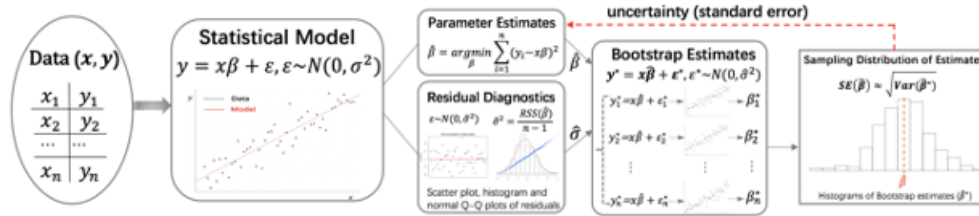


Figure 3.6: A summary of model-based bootstrap in simple linear model [Gu et al., 2019]

Suppose there is a linear relationship between the predictor variable $\mathbf{x}$ and response variable $\mathbf{y}$ as follows

$$\mathbf{y} = \mathbf{x}\beta + \epsilon, \epsilon \sim N(0, \sigma^2) \quad (3.23)$$

Where ϵ is a sequence of independent, distributed random variables following a standard normal distribution. The linear coefficient $\hat{\beta}$ can be estimated

with ordinary least square(OLS) and $\hat{\sigma}$ can be estimated with residual sum of squares(RSS) as follows

$$\hat{\sigma}^2 = \frac{\text{RSS}(\hat{\beta})}{n - p} \quad (3.24)$$

where n is the sample size and p is the number of coefficient which is 1 in this example. We can simulate $\mathbf{y}^*$ with such model fittings:

$$\mathbf{y}^* = \mathbf{x}\hat{\beta} + \epsilon^*, \epsilon^* \sim N(0, \hat{\sigma}^2) \quad (3.25)$$

The empirical distribution of $\hat{\beta}$ can be obtained from the model fitting of $\mathbf{y}^*$ and $\mathbf{x}$.

3.7.2 Bootstrap in PET

With the growing use of PET in both clinical and research settings, considerable efforts have been made to evaluate the uncertainty of PET results arising from analytic approaches in the reconstruction process [Huesman, 1977, Maitra and O'sullivan, 1998, Ibaraki et al., 2014, Qi and Leahy, 2000]. Haynor and Woods [Haynor and Woods, 1989] described the potential of applying bootstrap methods in this context. Most contributions involving the application of bootstrap to PET data have focused on the sinogram data or projection domain, as variations of Haynor and Woods' work [Lartizien et al., 2010, Kucharczak et al., 2018]. Huang et al propose an image domain bootstrap scheme for PET data [Huang et al., 2019]. This method is based on a subordinate Gaussian structure with the Gaussian copula form [Joe, 2014]. It can capture the Poisson-like nature of the PET data. It uses a parametric Gamma model to represent the marginal distributions of voxel-level data and a spatial autoregressive(SAR) model

to represent covariance patterns. The method used in this thesis employs a standard non-parametric 3D spectral density estimation approach, which involves smoothing a raw 3D periodogram to determine the spatial covariance structure of 3D PET data [O’Sullivan et al., 2021]. This method has been compared to the list-mode data resampling bootstrap method proposed by Haynor and Woods, and its performance has been validated through simulation studies [O’Sullivan et al., 2021]. This method has also been applied to various datasets, including data with a long axial field of view [Wu et al., 2024, Gu et al., 2021b]. A schematic is shown in Figure 3.7, and a general introduction of this method is as follows.

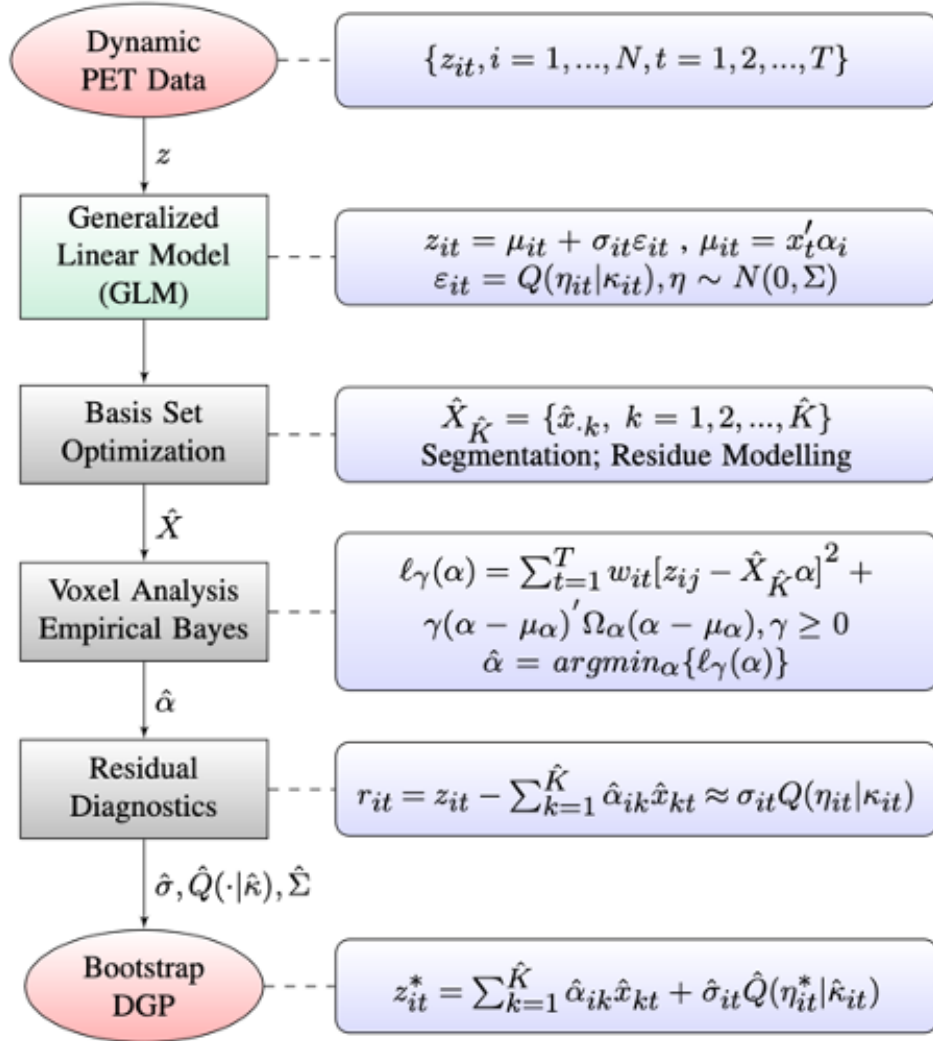


Figure 3.7: Graphical representation of the generalized linear model (GLM) used to define the data generation process (DGP) for PET image-domain bootstrapping [Gu, 2023].

The dynamic PET data is represented by an $N \times T$ array as $\{z_{it}, i = 1, \dots, N, t = 1, \dots, T\}$, where N is the total number of voxels and T is the number of time frames. A general linear model (GLM) is used to represent the dynamic PET data as a combination of systematic and stochastic components. The GLM can be specified by the following system of equations.

$$\begin{aligned}
z_{it} &= \mu_{it} + \sigma_{it}\epsilon_{it}; \quad \epsilon_{it} = Q(\eta_{it}|k_{it}) \text{ with } \eta \sim N(0, \Sigma) \\
\mu_{it} &= x_t' \alpha_i; \quad k_{it} = \frac{\mu_{it}}{\sigma_{it}}; \quad \sigma_{it} = \sigma_i \phi_t; \quad \sum_{t=1}^T \phi_t^2 = T \\
\Sigma &= \Gamma \Lambda^2 \Gamma; \quad \Gamma = \mathcal{F}_N \otimes I_T
\end{aligned} \tag{3.26}$$

Where μ_{it} is the systematic component, which models the mean of the voxel-level time activity curve(TAC) as a linear combination of a series of TAC shape basis functions that are defined by segmentation of the full voxel-level data. x_t is the vector of sampled basis function at time t and α_i is an unknown coefficient. μ_{it} and σ_{it} is are the true mean and standard deviation of z_{it} and σ_{it} is a product of spatial (σ_i) and temporal (ϕ_t) factors. The quantile function, $Q(\eta_{it}|k_{it})$, is strictly monotone for any fixed value of k_{it} , which is the inverse coefficient of variation [O’Sullivan et al., 2021]. The underlying Gaussian process, η , is assumed to be stationary. The Fourier matrix $\mathcal{F}_N$ and a T-dimensional identity matrix I_T are used to ensure that the underlying Gaussian process is spatially stationary. And Λ , a diagonal matrix with elements $\lambda = \{\lambda_i, i = 1, \dots, N\}$, corresponds to the temporal components of the Gaussian process. With the estimated unknown in equation 3.26 (details of estimation process are described in [O’Sullivan et al., 2021]), the bootstrap simulated data, z_{it}^* , can be expressed as

$$z_{it}^* = \hat{x}_t' \hat{\alpha}_i + \hat{\sigma}_{it} \hat{Q}(\eta_{it}^* | \hat{k}_{it}) \tag{3.27}$$

where $\eta_{it}^* = \mathcal{F}_N^t(\hat{\lambda}^{1/2} \xi_{it}^*)$ with $\xi_{it}^* \sim N(0, 1)$. Repeating this process N_B times will give image domain bootstrap samples, $\mathcal{B} = \{z^b, b = 1, \dots, N_B\}$ where z^b is the b th realization of z^* in equation 3.27. Then, each bootstrap-simulated dataset is processed using the same kinetic models as the original

dataset. This could lead to a bootstrap sample of the kinetic parameters $\mathcal{K}_B = \{\theta^b, b = 1, \dots, N_B\}$ where θ^b is the bootstrap realization of the kinetic parameters from the original data [Gu, 2023]. With the empirical distribution of mapped kinetic parameters, we will be able to evaluate the uncertainty of each parameter on the voxel level.

3.8 Illustration of NPRM with Acetate Data From a Brain Tumor Study

In this section, we will illustrate the NPRM with an acetate dataset from a brain tumor study. This particular dataset has been reported in [Muzi et al., 2011]. This dynamic PET dataset consists of $128 \times 128 \times 35$ voxels and $T = 24$ time frames of acquisition. The data was collected over 60 minutes with the following acquisition sequence(number of frames $\times$ durations): $4 \times 20s, 4 \times 40s, 4 \times 60s, 4 \times 180s, 8 \times 300s$. The AIF in this study was collected during the PET scanning period, as shown in Figure 3.8. The data was first corrected for metabolic contamination using the scheme described in [Muzi et al., 2011, Wells et al., 2002]. However, instead of compartmental models, this correction was performed using NPRM. Full details of this correction will be discussed in Chapter 4.

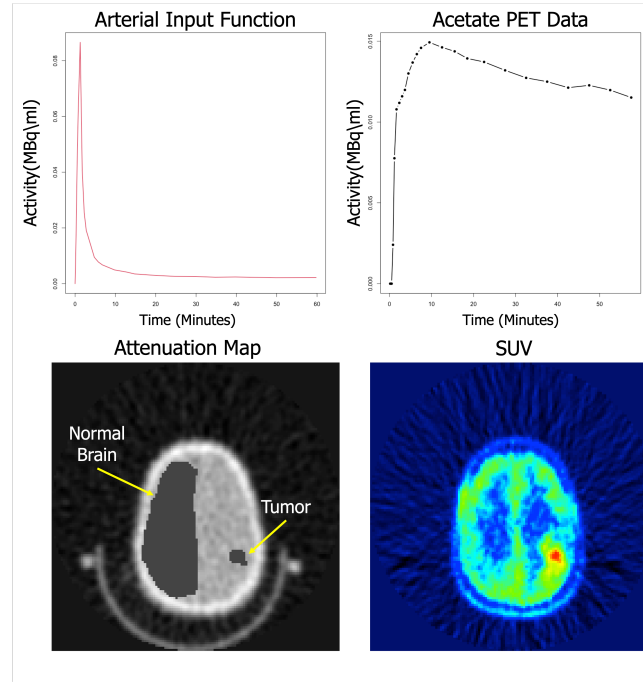


Figure 3.8: A example of AIF function(top left) and CO_2 contamination corrected tumor TAC(top right). The corresponding attenuation map(bottom left) and SUV image(bottom right) indicate the region of the tumor area and the normal brain area.

The analysis provides voxel-level mapping of acetate flux(K_i), distribution flow(K_d), and distribution volumes(V_d) and associated standard error(SE) from the PET bootstrapping technique described in section 3.7.2. These three parameters were chosen as they may reflect the volume of ^{11}C metabolites involved in the tissue or tumor metabolism. The relationship between these parameters and tumor characteristics has been documented in [Muzy et al., 2011, Van den Hoff et al., 1996, Schiepers et al., 2008]. These maps are shown in the coronal plane in Figure 3.10. These three parameters in the tumor region(1009 voxels) and the normal brain region(a combination of white and gray matter, 3890 voxels) are compared in Figure 3.9. All three parameters successfully highlight the tumor region, with their distributions significantly differing between the tumor and normal brain regions (p-values for all three parameters are less than 10^{-16}).

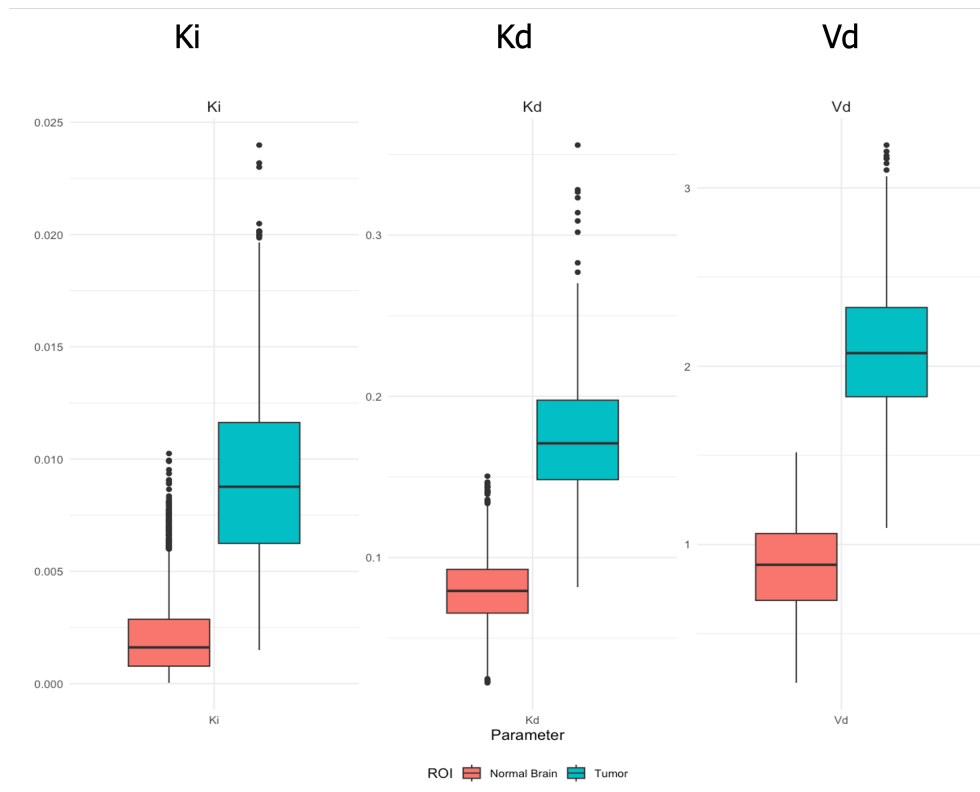


Figure 3.9: Differences of K_i , K_d and V_d in tumor region and normal brain region

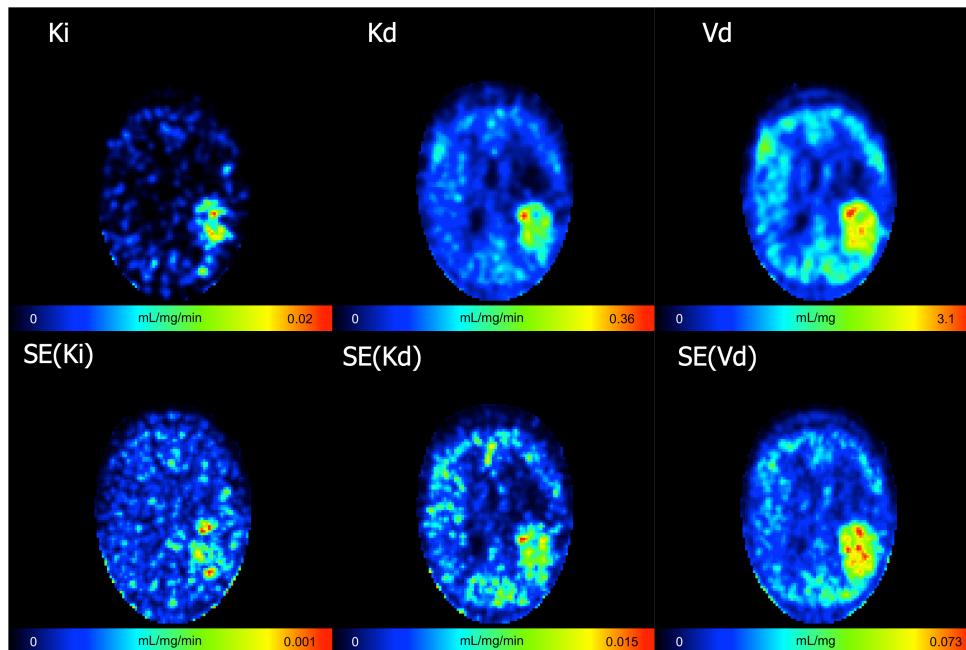


Figure 3.10: Parametric images of K_i , K_d and V_d and the associated SE maps. SEs are based on the SD of each parameter from 25 bootstrap replications.

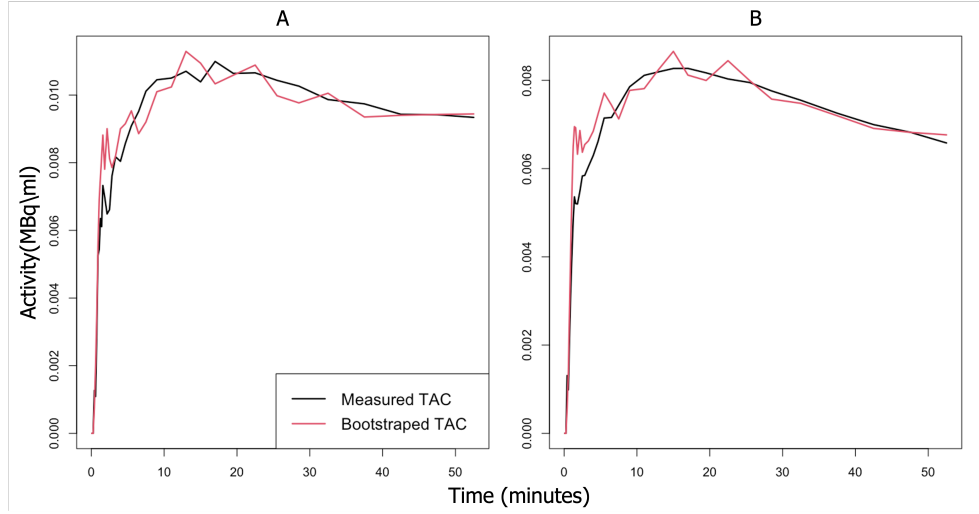


Figure 3.11: An example of measured(black) and bootstrapped(red) TAC in tumor(A) and normal brain(B) ROI

3.8.1 Numerical Experiment

A numerical experiment was conducted to test the variability of the parameters estimated by NPRM using data with varying noise levels. Because the detection of coincidence in a PET scanner is essentially a counting process, the detected annihilation coincidence follows a Poisson distribution. Many studies have demonstrated that the raw count data in a given time frame is deemed to have Poisson statistics [Huesman, 1984, Mou et al., 2017, Wu et al., 2024]. Thus the expected value and variance of y_t and z_t in equation 2.7 can be summarized as

$$E(y_t) = c_t f_t; \quad Var(y_t) \approx \alpha E(y_t) = \alpha c_t f_t \quad (3.28)$$

$$E(z_t) = c_t; \quad Var(z_t) = \frac{Var(y_t)}{f_t^2} \approx \frac{\alpha c_t}{f_t} \quad (3.29)$$

In the data simulation process, the simulation data z_t^* can be generated as

$$z_t^* = c_t + A\sigma w_t^{-1/2}\epsilon_t; \quad \epsilon \sim N(0, 1) \quad (3.30)$$

$$\sigma^2 = \frac{\sum_{t=1}^T (z_t - c_t)^2 w_t}{N}; \quad w_t = \frac{f_t}{c_t + 0.01\bar{c}_t} \quad (3.31)$$

where c_t is the best fit to z_t from NPRM, N is the number of voxel, σ represents ROI level of noise and w_t represents Poisson characteristic of PET raw data, with $0.01\bar{c}_t$ added to avoid zero in the denominator. $A = \{0.01, 0.05, 0.1, 0.2, 0.5, 1, 2, 4, 8, 15, 30\}$ controls the noise level. $A = 1$ represents a reasonable ROI level of noise.

Twelve PET acetate datasets were modeled using NPRM, with four ROIs defined for each dataset: tumor, white matter, gray matter, and normal brain (a combination of white and gray matter). Tumor cases are divided into two groups, hot tumor cases and cold tumor cases, based on the K_i value. Four cases, representing hot tumor, cold tumor, white matter, and gray matter, are selected as the true sources in the simulation studies. The ROI kinetic parameters and parametric images with SUV of the chosen true sources are shown in Table 3.2 and Figure 3.14. The σ value in Table 3.2 represents the average value among all cases in the four ROIs and reflects the fitting errors adjusted for scanning time bin, voxel value, decay, and fitting value in equation 3.31. A summary of fitting errors is presented in Figure 3.13. The fitting among the four ROIs shows a similar bias but differs in variance. Cold tumor and white matter have higher variance than hot tumor and gray matter, corresponding to the σ values in Table 3.2.

Table 3.2: Kinetic parameters and σ values from True Source of Simulation

Case	V_d	K_d	K_i	σ
Hot Tumor	0.319	0.086	0.022	0.0009
Cold Tumor	0.522	0.034	0.012	0.0022
Normal White Matter	0.088	0.040	0.004	0.0020
Normal Grey Matter	0.163	0.045	0.004	0.0009

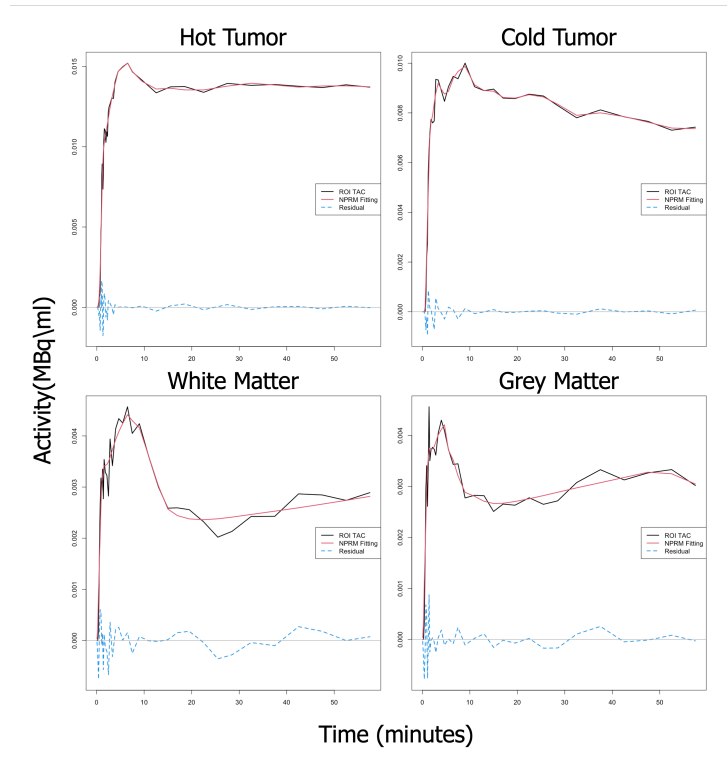


Figure 3.12: NPRM fitting of the four chosen ROIs as the true source in simulation

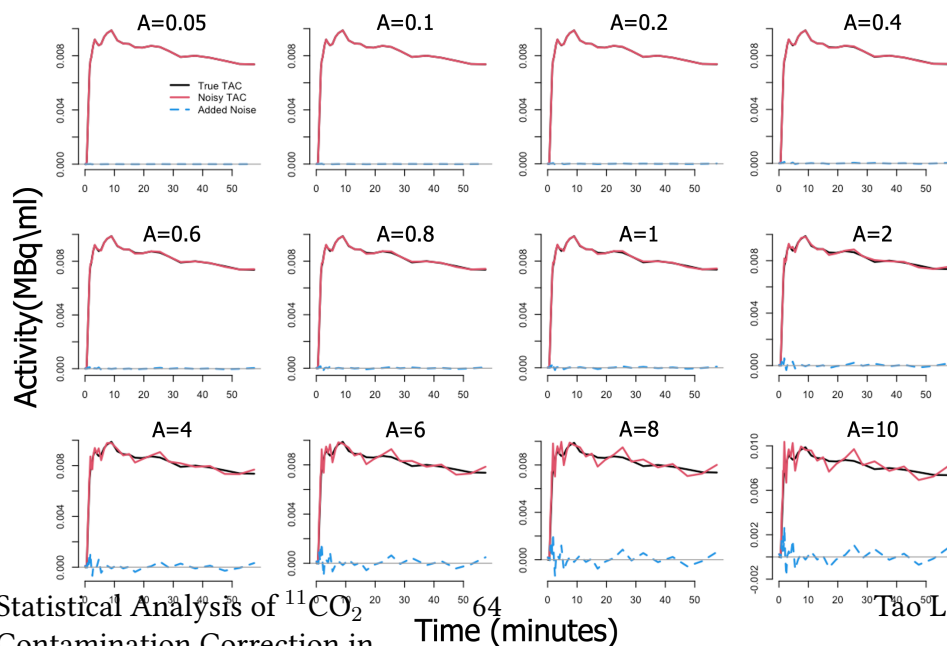


Figure 3.15: An illustration of noise level in simulation

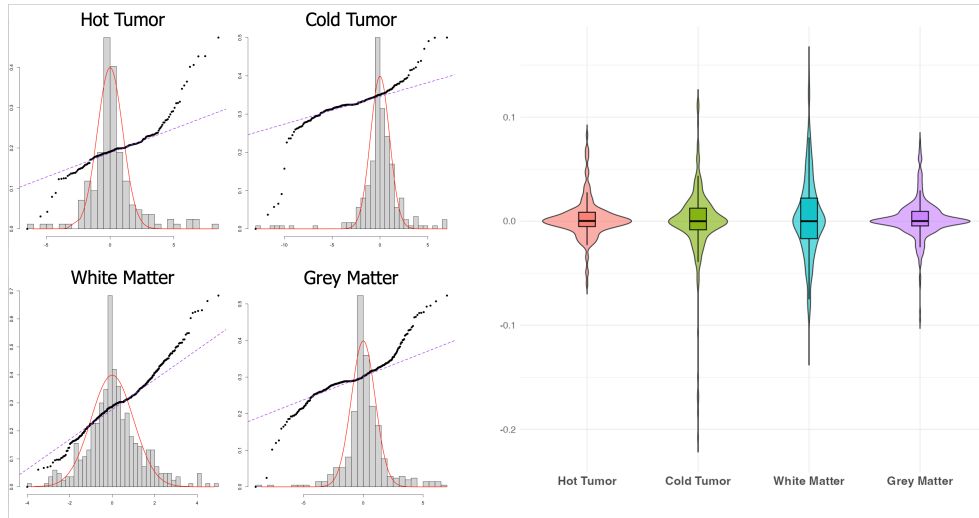


Figure 3.13: NPRM ROI scaled residual distributions for hot tumor, cold tumor, white matter, and gray matter are presented with a direct comparison. The red curves represent density curves from a standard normal distribution, while the black lines indicate normal Q-Q lines with purple dashed diagonal lines as references. The comparison of the four raw residual distributions is shown on the right-hand side, with hot tumor (red), cold tumor (green), white matter (blue), and gray matter (purple).

Each ROI dataset was replicated 500 times with varying levels of noise. An illustrative example of the noise level is shown in Figure 3.15. The resulting noisy TACs were analyzed using NPRM, and the accuracy of the parameter estimates was evaluated. Parameter estimation results are summarized as root mean square error (RMSE) and raw errors as presented in Figure 3.16 and Figure 3.17. The relationship between parameter RMSE and noise level is predominantly linear, particularly in the lower noise range, reflecting the linear nature of the model. The studies focusing on the lower noise range have more realistic implications because the data used in this study were collected in the early 2000s, and PET image resolution has significantly improved since then. The raw parameter estimates also suggest an approximately linear relationship between noise level and both estimation bias and variance. The RMSE patterns for K_i and V_d are similar, with the RMSE for cold tumor increasing rapidly with noise level, while the RMSE for white

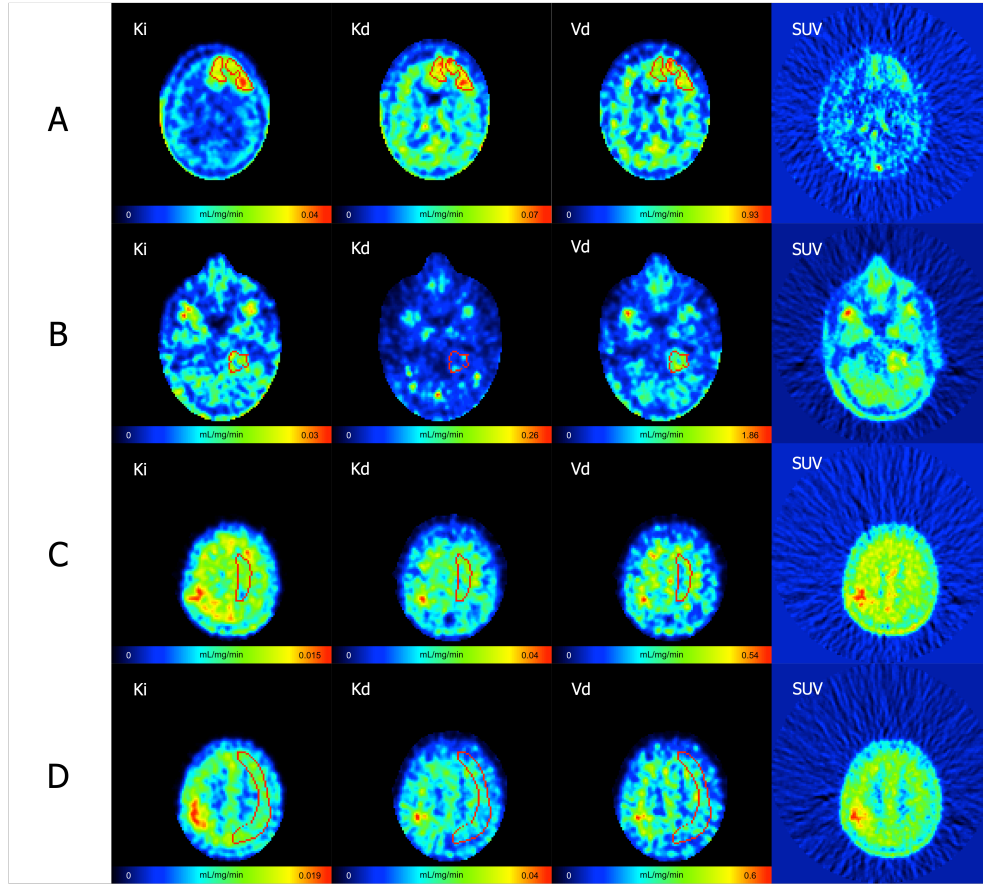


Figure 3.14: SUV and True parametric images for K_i , K_d , and V_d are presented with regions of interest delineated by red lines. Each row represents a different region: Row A: Hot tumor; Row B: Cold tumor; Row C: Normal white matter; Row D: Normal gray matter.

and grey matter show a more gradual increase. In contrast, the RMSE for the hot tumor exhibits only a slight increase as the noise level rises. However, the RMSE pattern for K_d is different: the RMSE for the hot tumor increases rapidly with noise level. This discrepancy could be because K_d is measured as a single value of the residue function, leading to a different behavior compared to K_i and V_d .

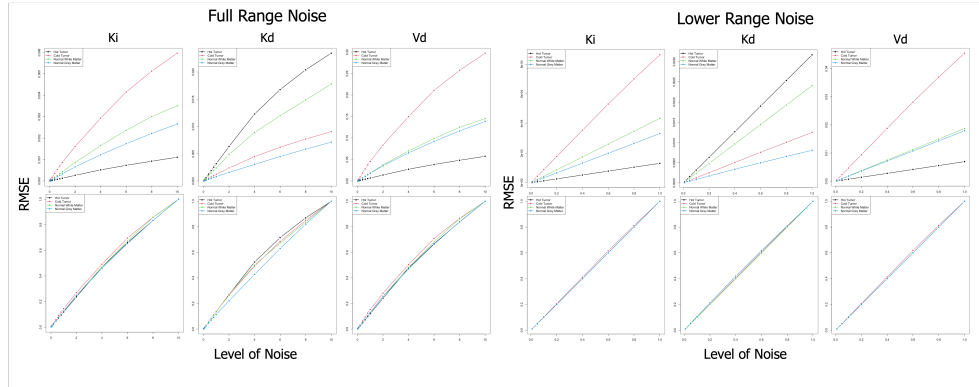


Figure 3.16: Relationship between the RMSE of estimation errors of K_i , K_d , and V_d with different noise levels simulation. The left-hand side plots show the results for the full noise range (0–10), while the right-hand side plots display the results for the lower noise range (0–1). The first row illustrates the raw estimation errors, whereas the second row presents the errors scaled to their respective maximum values.

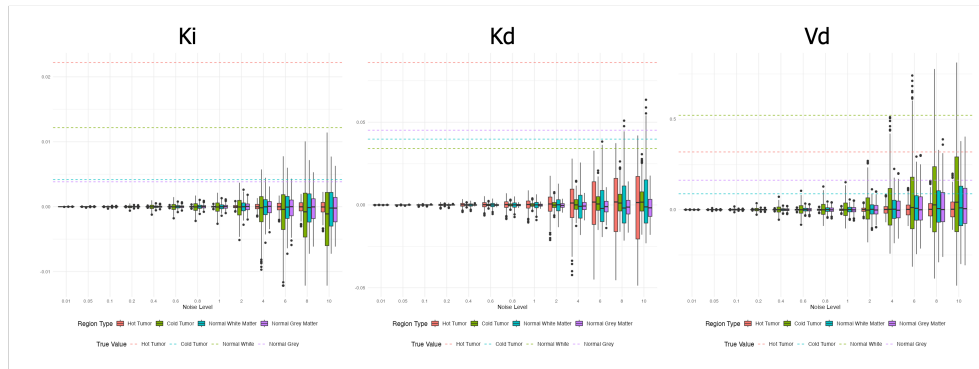


Figure 3.17: The distribution of estimation errors of K_i , K_d and V_d at different levels of noise simulation

3.9 Discussion

In this chapter, we introduce several PET kinetic models, with a primary focus on NPRM. This method is capable of modeling the whole process of dynamic PET imaging data while requiring minimal assumptions. A simple model performance with the NPRM and Two-Tissue Compartmental Model is summarized in Figure 3.18. The same selection of 12 acetate PET datasets with four ROIs in Section 3.8.1 is also modeled with the 2C Model. The model performance of the NPRM and 2C models is presented as the

weighted residual sum of squares (WRSS) of TACs and the difference in the estimation of three parameters: K_i , K_d , and V_d . The estimates of K_i and V_d show high similarity between the two models (correlation parameters are 0.94 for K_i and 0.93 for V_d), whereas K_d demonstrates a weaker relationship (correlation is 0.77). NPRM outperforms the 2C model in WRSS over all four ROIs in our example dataset. A larger dataset is necessary to draw more robust conclusions; however, the results presented here suggest that NPRM can provide a better fit to the data in certain situations, potentially benefiting PET bootstrapping applications. With more robust and thorough validation, NPRM has the potential to serve as a viable supplementary kinetic model alongside the 2C model.

All ^{11}C -acetate PET data used and presented in this chapter are corrected for their metabolites - $^{11}\text{CO}_2$. It is achieved using prior full $^{11}\text{CO}_2$ PET imaging data and additional AIF data, as outlined in the scheme that will be fully introduced in Chapter 4.

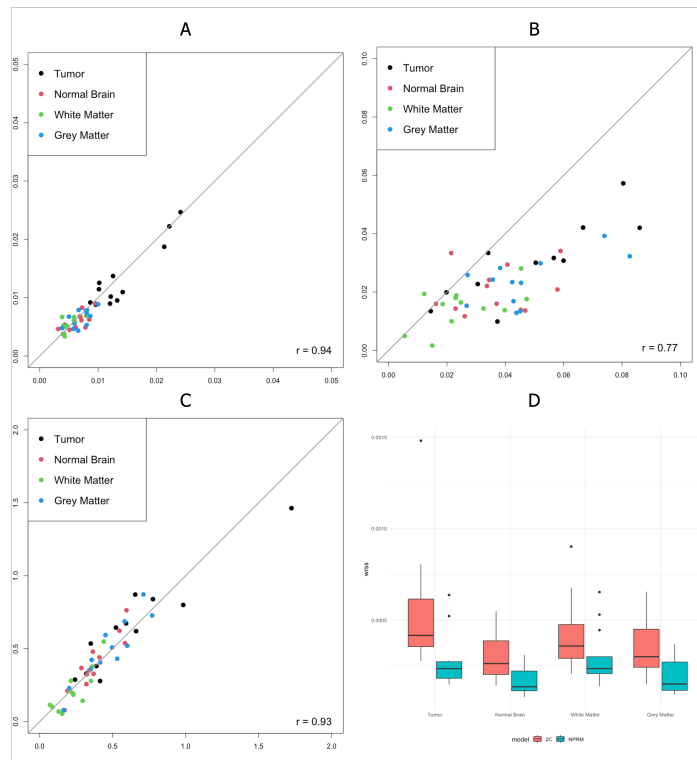


Figure 3.18: Summary of model performance of NPRM and 2C model. A, B, C: relationship between NPRM estimated and 2C model estimated K_i (A), K_d (B), and V_d (C) with correlation parameter in the bottom right corner. D: WRSS comparison of NPRM and 2C model over four ROIs.

Chapter 4

$^{11}\text{CO}_2$ Contamination

Correction of ^{11}C Acetate PET using Dual Injection Protocol

4.1 Introduction

Many ^{11}C labeled PET tracers, including glucose, amino acids [Shields et al., 1992], thymidine [Wells et al., 2002], and acetate [Muzi et al., 2011], generate $^{11}\text{CO}_2$ as a primary metabolites which contaminate the target PET signal as PET can not distinguish the radioactive signal from different molecules. In this thesis, we will mainly focus on the correction in ^{11}C Acetate PET data. To be utilized, acetate needed to be converted to acetyl-CoA(acetyl coenzyme A) by two types of enzymes, and the generated acetyl-CoA by different enzymes in different tissues will be mainly utilized in different metabolic pathways [Moffett et al., 2020b]. The majority of acetyl-CoA generated in heart, skeletal muscle, and brown adipose tissue will enter the citric acid cycle for energy production, ultimately being converted into CO_2 via oxidation [Pessentheiner et al., 2013]. In

contrast, the acetyl-CoA generated in tissue under different levels of physiological stress has a more diverse functionality, including histone acetylation, cytoplasmic metabolism, and lipid synthesis [Moffett et al., 2020b]. In tumor tissue, usually under hypoxia or nutrient deprivation, the level of acetate uptake and metabolism increases for membrane lipid synthesis and acts as a metabolic substrate [Kamphorst et al., 2014, Schug et al., 2015, Gao et al., 2016, Yun et al., 2009]. Thus, although acetate PET imaging can effectively differentiate between tumor and normal tissue, it may still be contaminated by ^{11}C -labeled CO_2 originating from other tissues and transported into the PET field of view via blood flow. In this chapter, we will review the combined multi-compartmental model from [Muzi et al., 2011] and generalize it with NPRM and the extended semi-parametric residue mapping (SPRM) to address the $^{11}\text{CO}_2$ signal contamination issue in ^{11}C acetate PET imaging data. The model will be illustrated with a collection of CO_2 -acetate dual-injection brain tumor PET data in both voxel and ROI level analysis.

4.1.1 The CO_2 -Acetate Dual Injection data

The data used in this chapter is a collection of 12 patients with brain tumors who were imaged dynamically with $^{11}\text{CO}_2$ for 60 minutes, followed by ^{11}C acetate for 60 minutes with arterial blood sampling for both studies. The $^{11}\text{CO}_2$ activity in blood was measured by acidification of the acetate study blood samples under argon gas. All data were acquired on a GE-Advance scanner with an imaging volume of $N = 128 \times 128 \times 35$, and other information is presented in Table 4.1. Four ROIs (tumor, normal brain, white matter, and gray matter) are chosen for each case.

With dual injection data, the PET measured data during the acetate study, C_T^{TA} , is expressed as

$$\begin{aligned} C_T^{TA} &\approx C_T^{PA} + C_T^{C1} + C_T^{CA} \\ &= R_A \otimes C_P^A[t] + R_C \otimes C_P^{C1}[t] + R_C \otimes C_P^{CA}[t] \end{aligned} \quad (4.1)$$

Here, C_T^{PA} represents the pure acetate signal, our target for analysis. The residual signal from prior CO_2 injections is denoted as C_T^{C1} , while C_T^{CA} accounts for acetate-generated CO_2 during the acetate study. The residue functions of acetate and CO_2 are R_A and R_C , respectively. Additionally, C_P^A refers to the acetate input function, while C_P^{C1} and C_P^{CA} are the CO_2 input functions from the CO_2 and acetate studies, respectively.

We assume that the arterial blood information, C_P^A , C_P^{C1} , and C_P^{CA} , is available. Thus, the focus is on developing methods to estimate R_C , enabling kinetic analysis of the corrected PET measurement to be performed in a standard manner using C_P^A as the arterial input function.

$$C_T^{PA} \approx C_T^{TA} - C_T^{C1} + C_T^{CA} \quad (4.2)$$

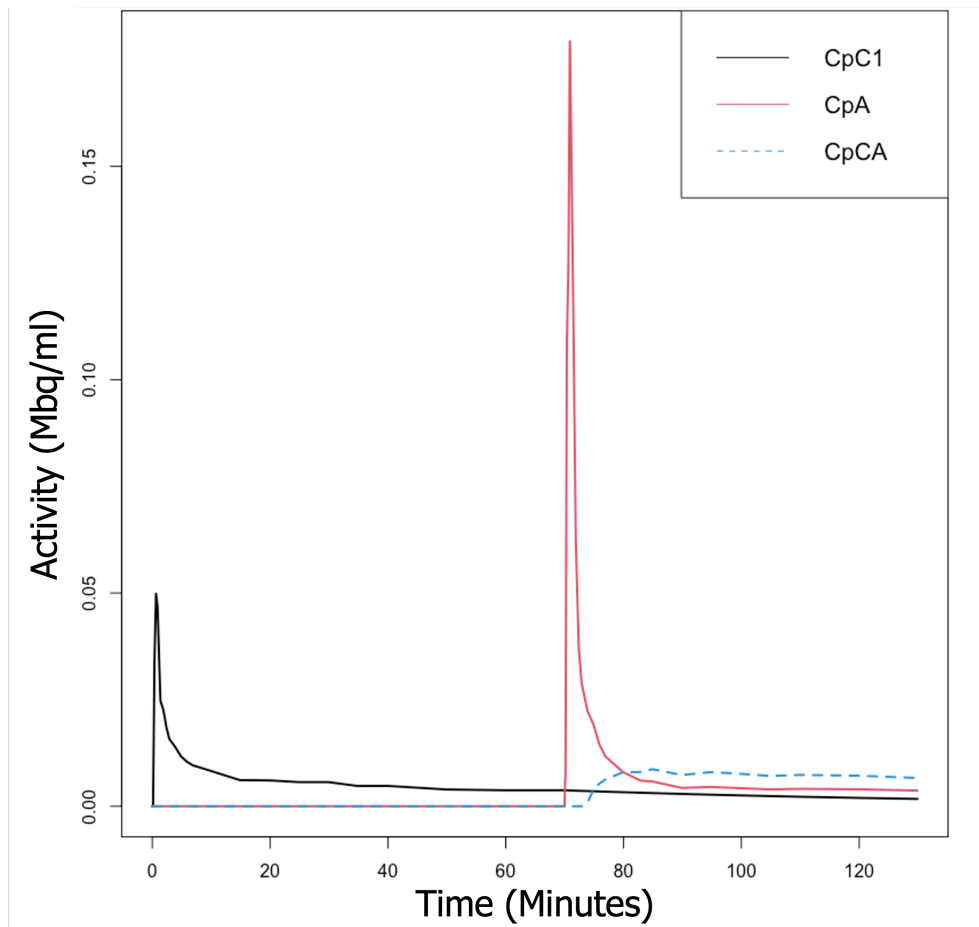


Figure 4.1: An illustrated arterial blood data example. The black line is the activity of $^{11}\text{CO}_2$, the red line is the activity of ^{11}C -acetate, and the blue dotted line is the activity of $^{11}\text{CO}_2$ produced by the metabolism of ^{11}C -acetate. All activity data is decay-corrected corresponding to the time.

Table 4.1: Basic Information of CO_2 -Acetate Dual Injection data

Case	Tumor Grade	Imaging Time Frames	Acetate Acquisition Sequence	Time gap Between Two Imaging
1	4	24(CO_2)+ 24(Acetate)	$4 \times 20s, 4 \times 40s, 4 \times 60s, 4 \times 180s,$ $8 \times 300s$	13.5 mins
2	3	24(CO_2)+ 24(Acetate)	$4 \times 20s, 4 \times 40s, 4 \times 60s, 4 \times 180s,$ $8 \times 300s$	15.5 mins
3	2	35(CO_2)+ 35(Acetate)	$10 \times 10s, 4 \times 20s, 3 \times 40s, 3 \times 60s,$ $5 \times 120s, 4 \times 180s, 6 \times 300s$	15 mins
4	2	35(CO_2)+ 35(Acetate)	$10 \times 10s, 4 \times 20s, 3 \times 40s, 3 \times 60s,$ $5 \times 120s, 4 \times 180s, 6 \times 300s$	7 mins
5	2	35(CO_2)+ 34(Acetate)	$10 \times 10s, 4 \times 20s, 3 \times 40s, 3 \times 60s,$ $5 \times 120s, 4 \times 180s, 5 \times 300s$	17 mins
6	3	35(CO_2)+ 35(Acetate)	$10 \times 10s, 4 \times 20s, 3 \times 40s, 3 \times 60s,$ $5 \times 120s, 4 \times 180s, 6 \times 300s$	13.1 mins
7	2	35(CO_2)+ 35(Acetate)	$10 \times 10s, 4 \times 20s, 3 \times 40s, 3 \times 60s,$ $5 \times 120s, 4 \times 180s, 6 \times 300s$	16 mins
8	4	35(CO_2)+ 35(Acetate)	$10 \times 10s, 4 \times 20s, 3 \times 40s, 3 \times 60s,$ $5 \times 120s, 4 \times 180s, 6 \times 300s$	11.5 mins
9	3	35(CO_2)+ 35(Acetate)	$10 \times 10s, 4 \times 20s, 3 \times 40s, 3 \times 60s,$ $5 \times 120s, 4 \times 180s, 6 \times 300s$	19 mins
10	2	45(CO_2)+ 45(Acetate)	$18 \times 5s, 7 \times 10s, 4 \times 20s, 4 \times 60s,$ $4 \times 180s, 8 \times 300s$	14.5 mins
11	4	45(CO_2)+ 45(Acetate)	$18 \times 5s, 7 \times 10s, 4 \times 20s, 4 \times 60s,$ $4 \times 180s, 8 \times 300s$	14 mins
12	2	45(CO_2)+ 45(Acetate)	$18 \times 5s, 7 \times 10s, 4 \times 20s, 4 \times 60s,$ $4 \times 180s, 8 \times 300s$	35 mins

Note: Time gap is measured from the end of CO_2 imaging to the start of acetate imaging

4.2 Method

4.2.1 $^{11}\text{CO}_2$ Contamination Correction Method

There are two main ways to correct or avoid $^{11}\text{CO}_2$ contamination in ^{11}C acetate PET imaging. Lewis et al. [Lewis et al., 2014] found that the late imaging data(at least 30 minutes after injection) have less TCA cycle metabolites and bicarbonate, therefore the dominant signal comes from membrane lipid that utilizes labeled acetate. But it will lose a significant amount of early information due to the short half-life of ^{11}C (20.4 minutes). The other way is to estimate the $^{11}\text{CO}_2$ contamination signals with the information from a prior $^{11}\text{CO}_2$ PET imaging with a combined multi-compartmental model [Muzi et al., 2011, Schiepers et al., 2008, Wells et al., 2002] as shown in Figure 4.2 as an example.

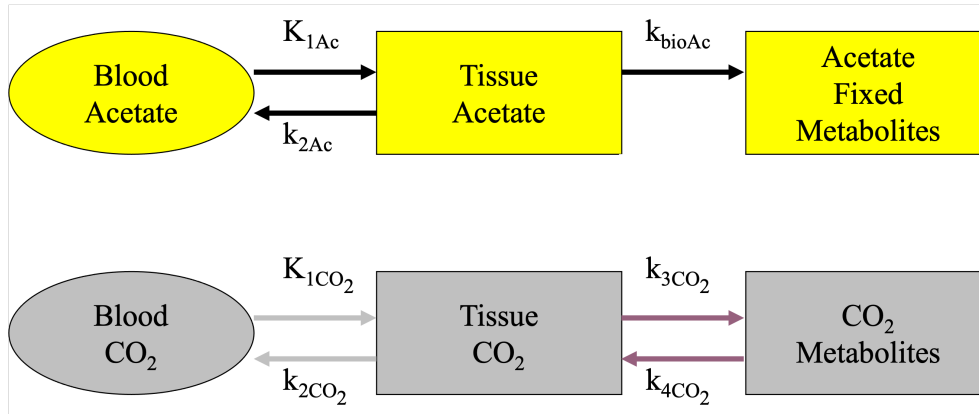


Figure 4.2: The combined multi-compartmental model applied to a dual injection of $^{11}\text{CO}_2$ followed by ^{11}C acetate [Muzi et al., 2011].

The combined multi-compartmental model defines two two-compartmental models for CO_2 and acetate. R_A and R_C in equation 4.1 are assumed to have exponential forms as follows

$$R_A = a_1 e^{-\phi t} + a_2 \quad (4.3)$$

$$R_C = b_1 e^{-\phi_{b1} t} + b_2 e^{-\phi_{b2} t} \quad (4.4)$$

where $a_2 = \frac{K_{1Ac} * k_{bioAc}}{k_{2Ac} + k_{bioAc}}$, which is also refereed as acetate biosynthetic flux K_{iAcM} . The model involves a two-step estimation process. The parameters related to CO_2 are initially determined using only the CO_2 imaging data and its corresponding input functions. Once these values are estimated, they are kept constant. Subsequently, the acetate-specific parameters K_1 and V_d (where $V_{dAc} = \frac{K_{1Ac}}{k_{2Ac} + k_{bio} + k_{eng}}$), along with k_{bio} and k_{eng} , are calculated based on the acetate input functions. The flux rate into membrane intermediates k_{bio} can be compared to the flux rate into energy metabolism intermediates k_{eng} , for which $^{11}\text{CO}_2$ is an end product. This model successfully separates the $^{11}\text{CO}_2$ signal from the ^{11}C acetate signal by mathematical modeling. In this chapter, we adapt the NPRM to this model to achieve the same objective with improved accuracy. It will be illustrated with the same CO_2 -acetate dual injection dataset used by Muzi in [Muzi et al., 2011].

4.2.2 Correction Model with NPRM and Semi-parametric Residue Mapping (SPRM)

In this section, we incorporate the NPRM and semi-parametric residue mapping (SPRM) into the CO_2 contamination correction model. SPRM is introduced as a variation of NPRM where the travel-time density function consists of a combination of piecewise linear basis functions and an exponential form basis function to add the ability to be extrapolated. Assuming that the travel-time density function is partitioned into M pieces over the scanning

window, the exponential basis is added as the last basis with an unknown rate parameter, ϕ ,

$$B_M(s|\phi) = \begin{cases} \phi e^{-\phi(s-\tau_{M-1})} & , s \geq \tau_{M-1} \\ 0 & , \text{otherwise} \end{cases} \quad (4.5)$$

This model implies a semi-linear version of equation 3.17

$$C_T(t|\theta, \phi) = \sum_{m=1}^M \theta_m X_m(t - \Delta_m) = X(t - \Delta|\phi)' \theta \quad (4.6)$$

where $X(t - \Delta|\phi) = (X_1(t - \Delta_1), \dots, X_{M-1}(t - \Delta_{M-1}), X_M(t - \Delta_M|\phi))$ and $X_m(t) = R_m \otimes C_p[t]$ with $R_m(t) = 1 - \int_0^t B_m(s)ds$. It is sufficient to determine the non-negative scale coefficients $(\theta_1, \dots, \theta_M)$ in equation ???. Similar to NPRM, the unknown coefficients (ϕ, θ, Δ) can be estimated by minimizing the weighted residual sum of squares between the PET-measured values z_t and the modeled TAC:

$$WRSS(\theta, \phi, \Delta) = \sum_t w_t [z_t - X(t - \Delta|\phi)' \theta]^2 \quad (4.7)$$

with fixed ϕ and Δ , the optimization problem for θ can be solved with quadratic programming. The optimization for ϕ and Δ uses a grid search. With the incorporation of NPRM and SPRM, equation 4.1 can be expressed in a semi-linear form

$$\begin{aligned} C_T^{TA} &\approx C_T^{PA} + C_T^{C1} + C_T^{CA} \\ &= X_A(t - \Delta_A)\theta_A + X_{C1}(t - \Delta_{C1}|\phi)\theta_{C1} + X_{CA}(t - \Delta_{CA}|\phi)\theta_{CA} \end{aligned} \quad (4.8)$$

where delays Δ and exponential basis coefficient ϕ is the nonlinear part. In this form, only the CO_2 residue function is estimated with SPRM, while the

acetate residue function is still estimated with NPRM.

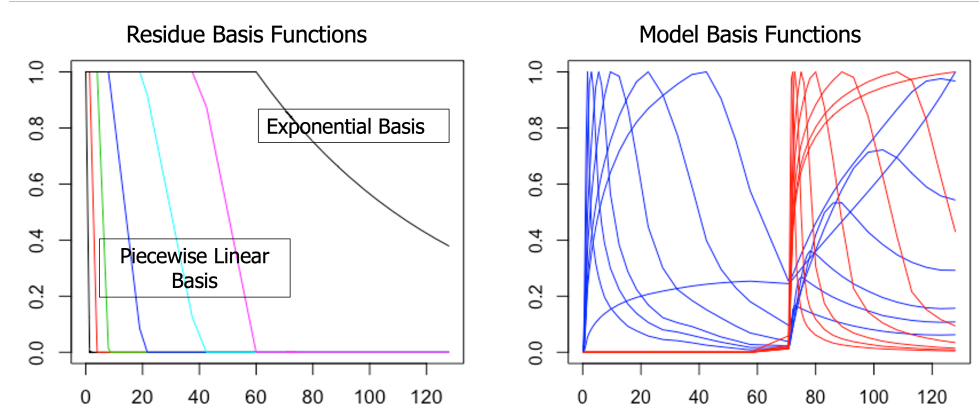


Figure 4.3: An illustrated example of scaled residue basis functions of SPRM and model basis functions with CO_2 -acetate dual injection data. The model basis functions represent X_A , X_{C1} , and X_{CA} in equation 4.8, where blue basis functions are related to the CO_2 signal and red basis functions are related to the acetate signal.

The exponential form basis is practical due to the inherent smoothness of the late-time PET data curve. Thus, we need to choose a suitable value for τ_{M-1} , where the PET dynamic data after τ_{M-1} are sufficiently smooth for an exponential curve. The choice of τ_{M-1} is primarily influenced by the fitting of CO_2 TACs. The main goal is to achieve the same level of Weighted Residual Sum of Squares (WRSS) as NPRM. A preliminary experiment has been conducted as shown in Figure 4.4 where $\tau_{M-1} = 24$, $\tau_{M-1} = 36$, $\tau_{M-1} = 48$ could all achieve similar level of WRSS as NPRM. It motivates the exploration to shorten the CO_2 scanning time and, therefore, shorten the overall length of the dual tracer study.

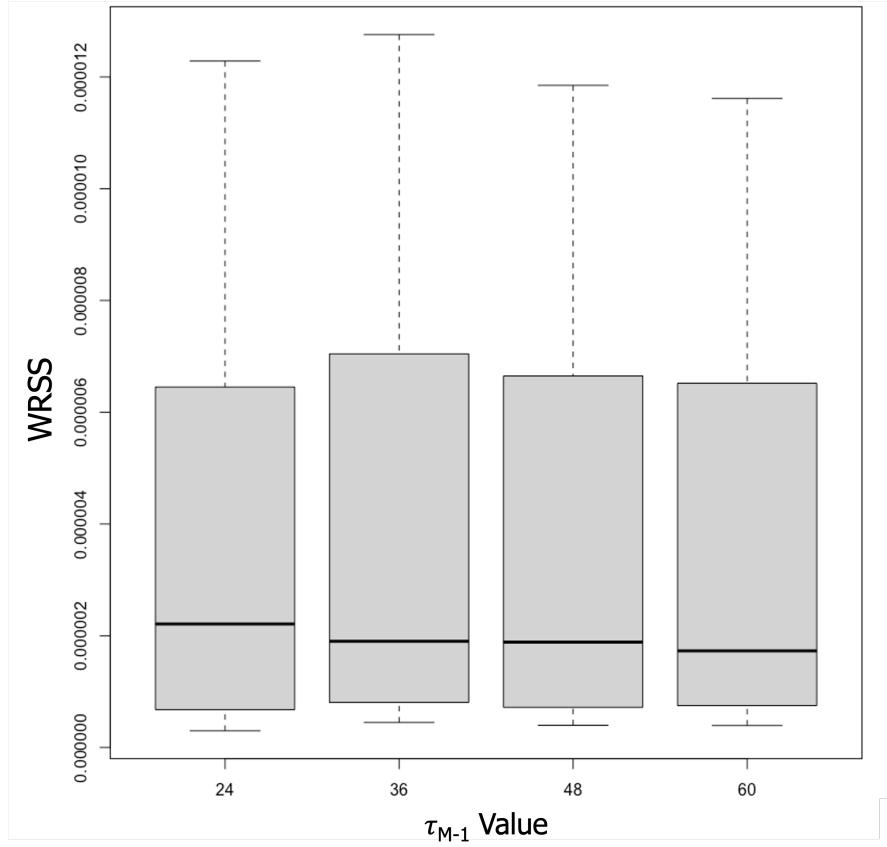


Figure 4.4: Weighted Residual Sum of Squares value of 12 CO_2 studies with different τ_{M-1} value. $\tau_{M-1} = 60$ means NPRM model.

4.3 Application to the Acetate Brain Data Studies

In this section, we present the correction results on the CO_2 –acetate dual injection dataset, including both ROI-level and voxel-level analyses. We explore the relationship between corrected and uncorrected acetate key kinetic parameters. Additionally, we use the corrected and uncorrected tumor region K_i values to evaluate their ability to differentiate between low-grade and high-grade tumors.

Voxel-level NPRM was performed on both uncorrected and corrected

acetate PET data using the same AIF. An example of the comparison of corrected and uncorrected parametric images is presented in Figure 4.5. After correction, K_i is most affected on the parametric images, but still highlights the tumor region. While the corrections to K_d and V_d are less pronounced, the tumor region and periphery area of the brain are also successfully highlighted in the corrected parametric images. However, the uncorrected parametric images can also highlight the tumor region to a similar extent.

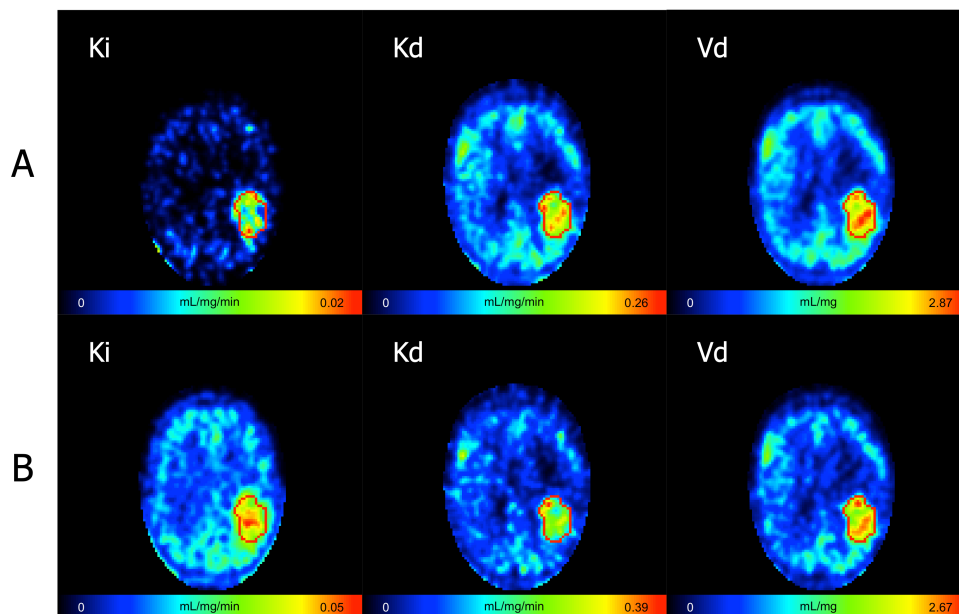


Figure 4.5: An example of corrected(A) and uncorrected (B) parametric images of K_i , K_d and V_d . Tumor regions are highlighted in red lines.

The correction on tumor and normal brain TAC is presented in Figure 4.6. While the correction in the normal brain region is greater than that in the tumor region when compared to the uncorrected TAC, the absolute value of the correction is similar within each case. This could indicate that the amount of acetate used for energy production in both the tumor and normal regions is at a similar level, and the higher uptake of acetate in the tumor re-

gion is primarily utilized for membrane synthesis. The relationship between corrected and uncorrected K_i , K_d , and V_d in the tumor region is shown in Figure 4.7. There is a strong linear relationship between corrected and uncorrected K_i ($r = 0.93$) and V_d ($r = 0.98$). Parameters for high-grade and low-grade tumors are presented as red and blue points, respectively. High-grade tumors exhibit higher upper limits across both corrected and uncorrected parameters while sharing similar lower limits with low-grade tumors. Both corrected and uncorrected acetate K_i are used to differentiate low from high-grade tumors in Figure 4.8. Both corrected and uncorrected K_i can roughly differentiate low and high tumor grades with similar p-value (0.065 for corrected K_i and 0.076 for uncorrected K_i).

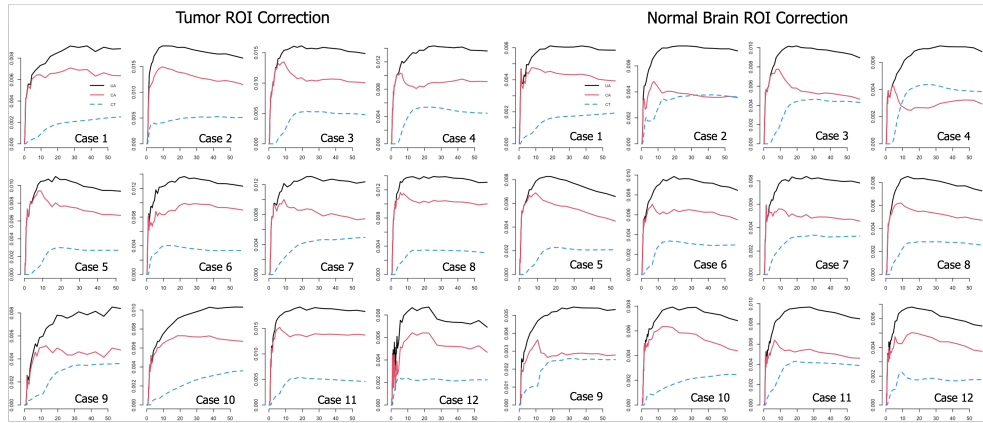


Figure 4.6: CO_2 correction on tumor and normal ROI TAC over all 12 cases. Black solid line(UA) is uncorrected acetate TAC, red solid line(CA) is corrected acetate TAC, and blue dotted line(CT) is the estimated CO_2 contamination TAC.

4. $^{11}\text{CO}_2$ Contamination Correction of ^{11}C Acetate PET using Dual Injection Protocol

4.3 Application to the Acetate Brain Data Studies

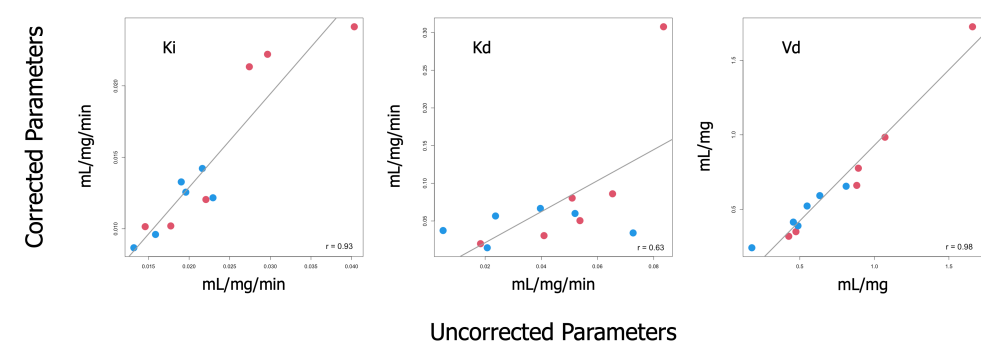


Figure 4.7: Relationship between uncorrected and corrected K_i , K_d and V_d . Best-fit linear regression is shown as a solid grey line. Red points mean high-grade tumors, and blue points mean low-grade tumors.

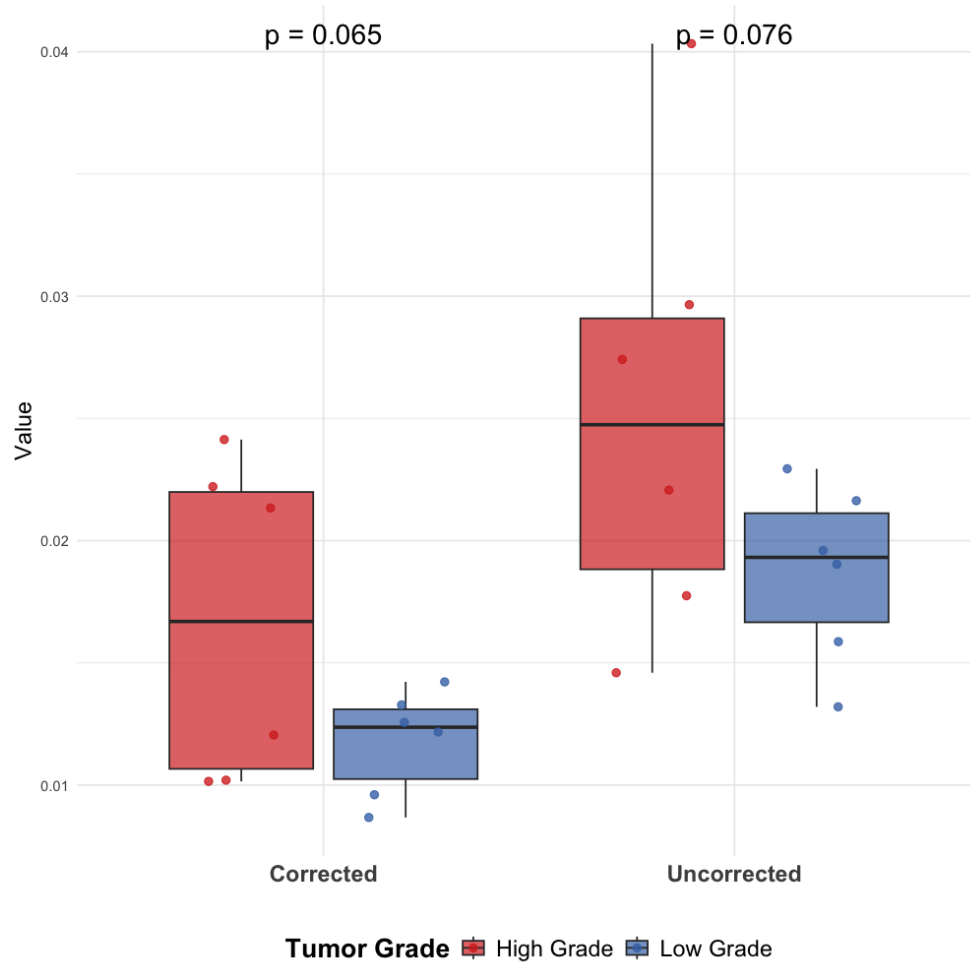


Figure 4.8: Use corrected and uncorrected acetate K_i to differentiate low and high grade tumors with p-value.

4.4 Discussion

In this chapter, we adapt the $^{11}\text{CO}_2$ contamination correction method for ^{11}C -acetate PET imaging using SPRM and $^{11}\text{CO}_2$ - ^{11}C -acetate dual injection dynamic PET data. This method has already been applied and reviewed in ^{11}C -thymidine (TdR) PET imaging studies [Wells et al., 2002]. It has the potential to be extended to other PET tracers where the labeled molecule follows more than one main pathway. Both voxel-level and ROI-based corrections are presented in this chapter with illustrative examples. The parametric images of K_i , K_d , and V_d from both corrected and uncorrected cases demonstrate the ability to distinguish tumor regions from normal brain areas. Additionally, both corrected and uncorrected K_i exhibit a similar ability to differentiate between low-grade and high-grade tumors.

The selection of hyperparameter τ_{M-1} in SPRM would benefit from more specific numerical studies. The average peak time from the 12 CO_2 studies is 1.58 minutes. Therefore, it is feasible to set $\tau_{M-1} \leq 10$. Furthermore, these findings suggest that a shorter CO_2 scanning duration may still provide sufficient information for correction, yielding results comparable to those obtained from the full 60-minute CO_2 scan. This has the potential to significantly reduce dual-injection scanning time without compromising accuracy, thereby enhancing the feasibility of implementing this protocol in clinical settings. The correction methods introduced in this chapter can also be extended to other PET tracers that are affected by metabolite contamination, such as ^{18}F -fluorobetaine in ^{18}F -fluorocholine PET imaging [Rubí et al., 2024, Roivainen et al., 2000]. Furthermore, Equation 4.1 is readily adaptable to multi-tracer PET imaging, which may offer improved

modeling accuracy [Gu et al., 2021a].

However, the correction method discussed in this chapter still relies on dual-injection PET data and additional arterial blood sampling procedures, which may not always be practical in routine clinical workflows and could increase patient discomfort. Therefore, there is a need to investigate alternative correction strategies that require less data and are more suitable for clinical application. The analysis of the acetate-generated CO_2 input function and the CO_2 residue function, along with their combined use to enable correction without dual-injection data, is discussed in the following two chapters.

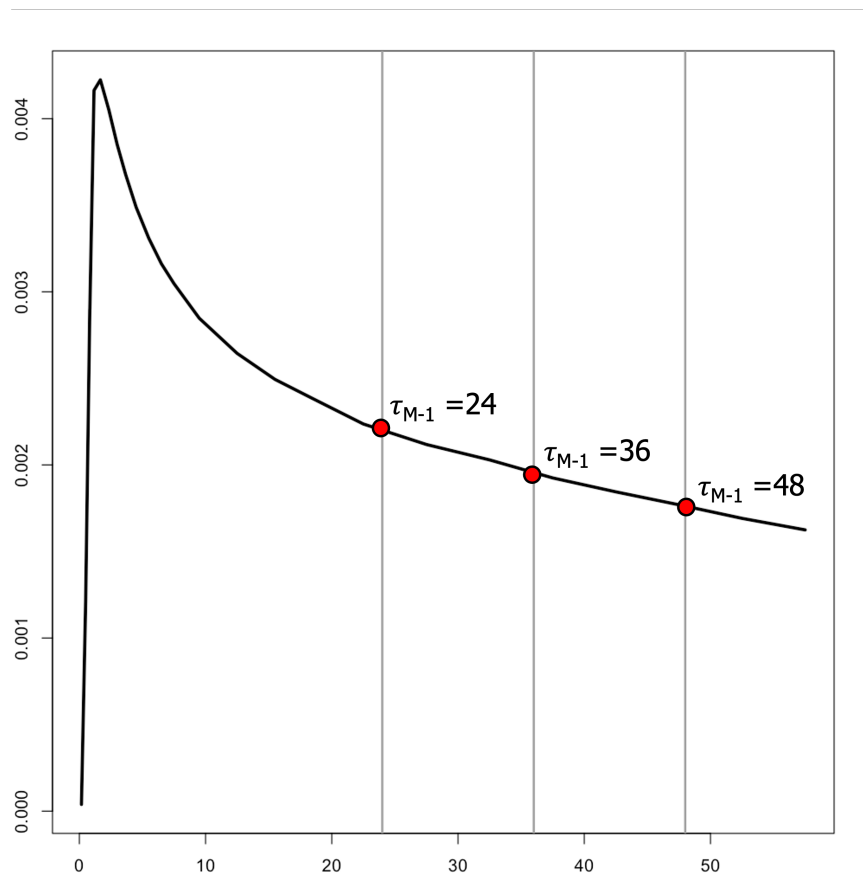


Figure 4.9: An example of CO_2 TAC with tested site of τ_{M-1}

Chapter 5

CO₂ Contamination Correction of ¹¹C-Acetate PET without any ¹¹CO₂ PET scanning

5.1 Introduction

In this chapter, we explore several methods to correct the metabolic CO₂ contamination signals in ¹¹C-acetate PET imaging when prior CO₂ PET imaging is not available. These correction methods are tested and validated with the CO₂-acetate dual injection data in section 4.1.1.

The correction methods are divided into three categories based on the use of the acetate-generated CO₂ input function and on how the CO₂ residue function information is determined. The first category (direct prediction) does not require any CO₂ information and uses machine learning models to directly construct an empirical relationship between the corrected and uncorrected acetate kinetic parameters. The second category (augmented modeling) assumes that the CO₂ contamination TACs are simple enough to

be modeled as Patlak elements [Patlak and Blasberg, 1985]. Two additional basis functions, derived from the acetate-generated CO₂ input function, are included in the NPRM models. Therefore, this correction method requires only the CO₂ input function. The third category (convolution) uses both the acetate-generated CO₂ input function and the CO₂ residue function. The CO₂ contamination TACs are estimated as the convolution of these two functions, as shown in Equation 4.1.

In the absence of actual CO₂ PET imaging data, we developed a model to reconstruct the CO₂ residue function using CO₂ kinetic parameters. These kinetic parameters are estimated from the uncorrected acetate kinetic parameters through machine learning models. We also developed a model to estimate the acetate-generated CO₂ input function with the total arterial activity course of acetate. The model can build a population-based CO₂ input function adjusted with a set of sparsely sampled CO₂ input data or population data. The full details of this model will be discussed in the next chapter. The relationship between the three categories of correction methods and their corresponding sources of CO₂ information is summarized in Figure 5.7.

5.2 Methods

In this section, we will introduce the details of the CO₂ kinetics reconstruction scheme, augmented modeling with NPRM, and machine learning model selection for corrected acetate kinetic parameters and CO₂ kinetic parameters.

5.2.1 modeling of CO₂ Residue Function

Based on the residue decomposition described in Section 3.6.2, we developed a method to roughly reconstruct the residue function using three components, as illustrated in Figure 5.1. The first component, R_B , is represented as a triangle with an area equal to V_b . The other two components, R_D and R_E , are step exponential curves starting at T_B and T_E , respectively, with different rate parameters, ϕ_D and ϕ_E . Consequently, the reconstructed residue function, $R_r(t)$, can be expressed as follows:

$$R_r(t) = \begin{cases} at + b & , 0 \leq t \leq T_B \\ K_d e^{-\phi_D t} & , T_B < t \leq T_E \\ K_i e^{-\phi_E t} & , t > T_E \end{cases} \quad (5.1)$$

where $a = \frac{\frac{2V_B}{T_B} + K_1}{-T_B}$, $b = \frac{2V_B}{T_B} + K_1$ and $\phi_E = \phi$ in equation 4.5. ϕ_D can be solved using grid search with $\frac{K_D}{\phi_D}(1 - e^{-\phi_D(T_E - T_B)}) = V_D - T_B K_D$. An illustrative example is shown in Figure 5.2. The primary differences between the true residue function and the reconstructed residue function occur at the transition points of the piecewise linear function and the initial point of the residue function. The former arises due to the inherent differences between piecewise linear functions and exponential functions. The latter may introduce scaling issues in the calculation of the corrected TAC, which we address by incorporating a scaling step based on the true corrected TAC data.

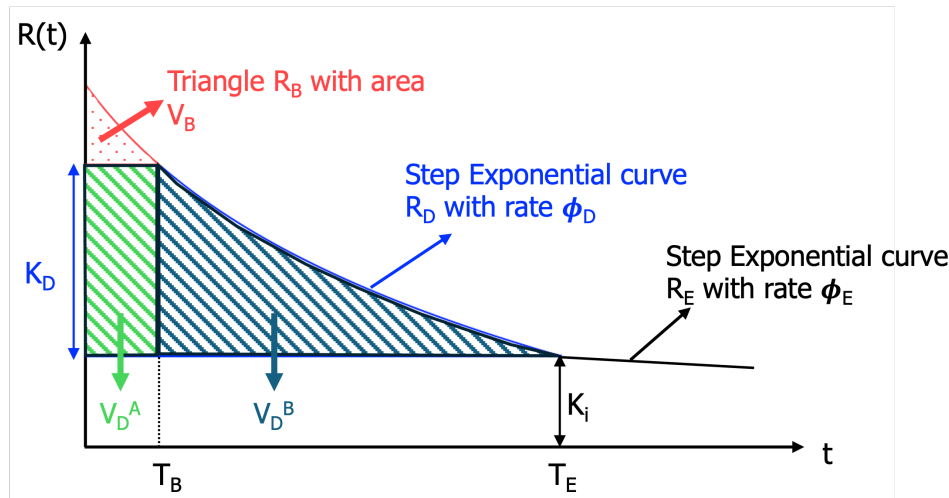


Figure 5.1: An illustration of the residue function reconstructed from kinetic parameters

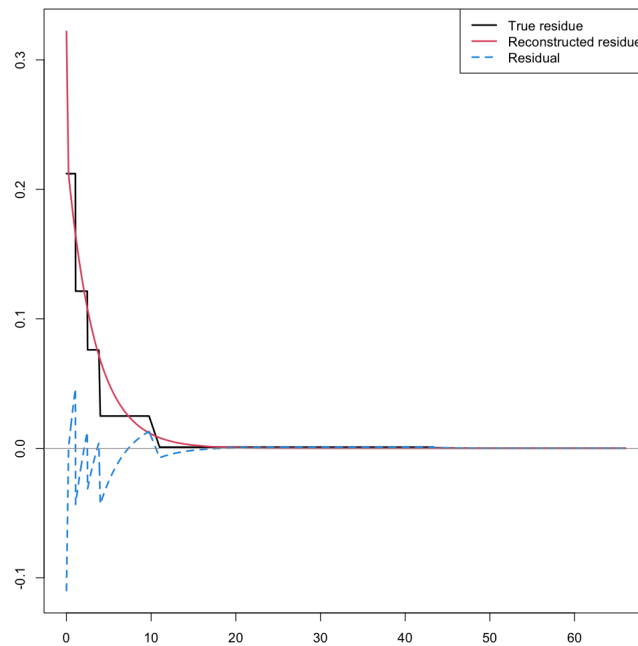


Figure 5.2: An illustrative example of residue function remonstration

5.2.2 Augmented modeling with NPRM

When the acetate-generated CO₂ input function is available—either from sampled data during the PET imaging process or estimated using equation 6.1—an alternative approach to evaluating the correction TAC can be

employed, aside from the convolution between the acetate-generated CO₂ input function and the CO₂ residue function. In NPRM, the PET-measured TAC can be expressed as a linear combination of basis elements, as shown in equation 3.17. We extend this model for acetate PET data as follows:

$$C^{Ac}(t|\theta) \approx \sum_{m=1}^M \theta_m X_m(t) + \theta_{m+1} X_{m+1}(t) + \theta_{m+2} X_{m+2}(t) \quad (5.2)$$

where

$$\theta_{m+1} X_{m+1}(t) = R_{m+1} \otimes C_P^{CA}[t]$$

represents a spike residue function, and

$$\theta_{m+2} X_{m+2}(t) = R_{m+2} \otimes \int_0^t C_P^{CA}[t]$$

corresponds to a constant residue function modeled with the integral of the AIF, commonly known as Patlak elements [Patlak and Blasberg, 1985].

The linear combination of these two basis elements provides an approximate estimation of the correction TAC. Consequently, the corrected fitting and kinetic parameters can be estimated using only the first M basis elements. The correction TAC in Figure 4.6 was modeled using only the two basis elements mentioned earlier, with results displayed in Figure 5.3. Due to the model's simplicity, the fitted correction TAC exhibits substantial deviation from the target TAC in the tumor ROI of cases 2, 3, and 11, and in the normal brain ROI of case 6, with residual sum of squares (RSS) values exceeding 10^{-5} . In contrast, the fitting in the normal brain ROI of cases 7 and 10 shows closer agreement, with RSS values on the order of 10^{-7} , indicating that the model can approximate correction TACs in specific scenarios without necessitating high complexity or computational cost.

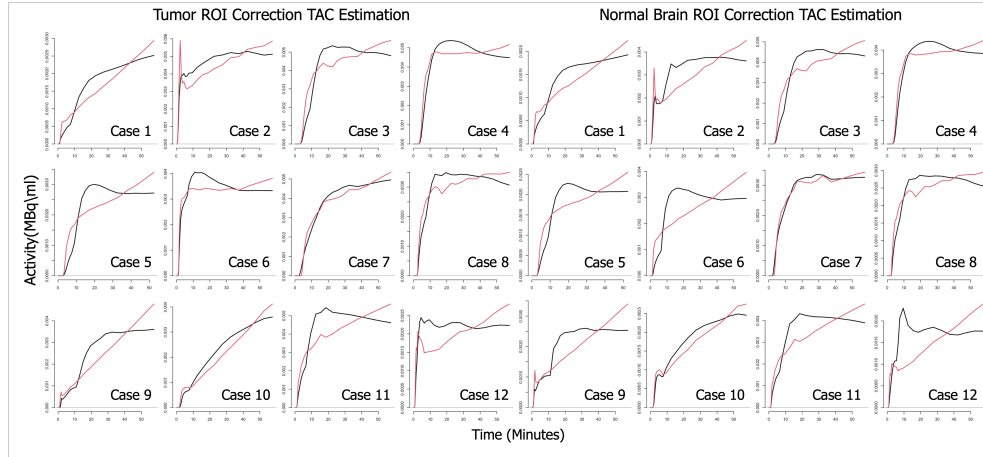


Figure 5.3: Tumor and normal brain region correction TAC estimation with acetate-generated CO₂ input function basis. Black lines are the correction amount estimated using dual injection data, and red lines are the estimated correction amount with augmented NPRM.

5.2.3 Kinetic Parameter Mapping with Machine Learning Models

Machine learning techniques have been widely applied to PET imaging studies even before the emergence of ChatGPT in 2022, as evidenced by 1,108 results on PubMed when searching for "machine learning PET imaging" up to the end of 2022. These techniques can be utilized throughout the entire PET imaging process, from image correction [Dong et al., 2020, Shi et al., 2021] and denoising [Daveau et al., 2022, Lu et al., 2019] during image acquisition to disease prognosis and monitoring [Onozato et al., 2023, Zhong et al., 2023], as well as diagnostic support [Song et al., 2021, Etminani et al., 2022] in the analysis and clinical application phase.

In our studies, in order to model the correction without a prior CO₂ PET imaging, the CO₂ kinetic parameters are modeled with various machine learning models using uncorrected acetate kinetic parameters. We have

also tried to directly model the corrected acetate kinetic parameters with the uncorrected acetate kinetic parameters. For each modeled parameter, five different models(robust regression, regularized regression, multivariate adaptive regression, eXtreme Gradient Boosting, and random forest) were trained with 10-fold cross-validation and a special leave-one-out cross-validation (LOOCV). The model with the smallest test prediction error and best residual performance was selected as the prediction model for that parameter. To increase the number of data points, 50 sub-TACs from each case were used to estimate a set of kinetics parameters, which come from the non-parametric mapping procedures used in section 3.6.2. A summary of the machine learning framework is shown in Figure 5.6.

The test prediction error rates for corrected acetate kinetic parameters and CO₂ kinetic parameters are summarized in Figure 5.4 and Figure 5.5, respectively. Note that these errors are the aggregated cross-validation test error from the LOOCV scheme. The error rates for each parameter, e_i , are calculated as

$$e^i = 100 \times \frac{\beta_t^i - \beta_p^i}{\bar{\beta}_t}$$

For $i \in \{V_b, V_d, K_1, K_d, K_i\}$, where β_t represents the true parameter values, and β_p denotes the predicted values obtained from the selected machine learning models. The mean value of the true parameters is used as the denominator to prevent division by zero or near-zero values.

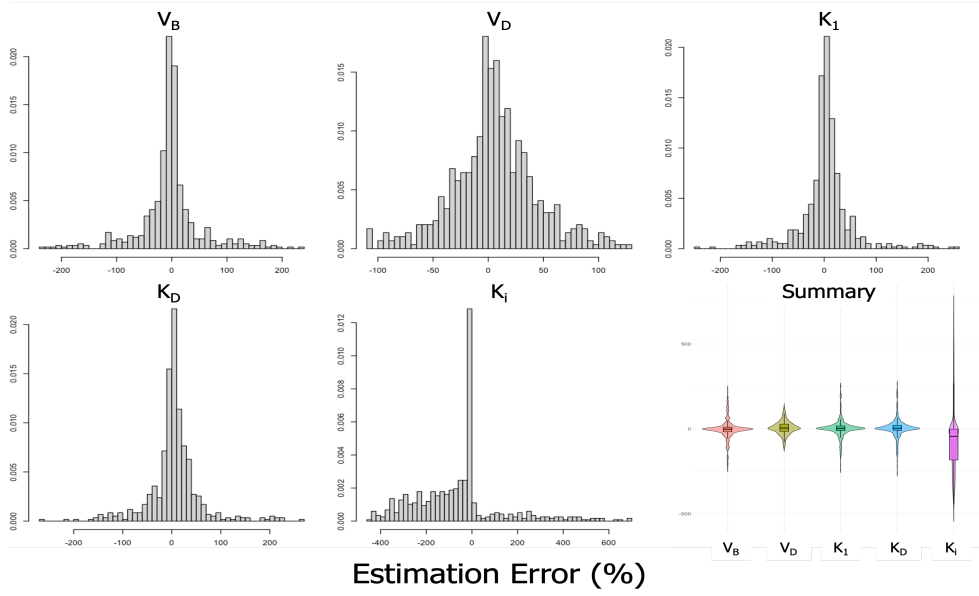


Figure 5.4: Test prediction error rate of corrected acetate kinetic parameters using only the uncorrected acetate kinetic parameters.

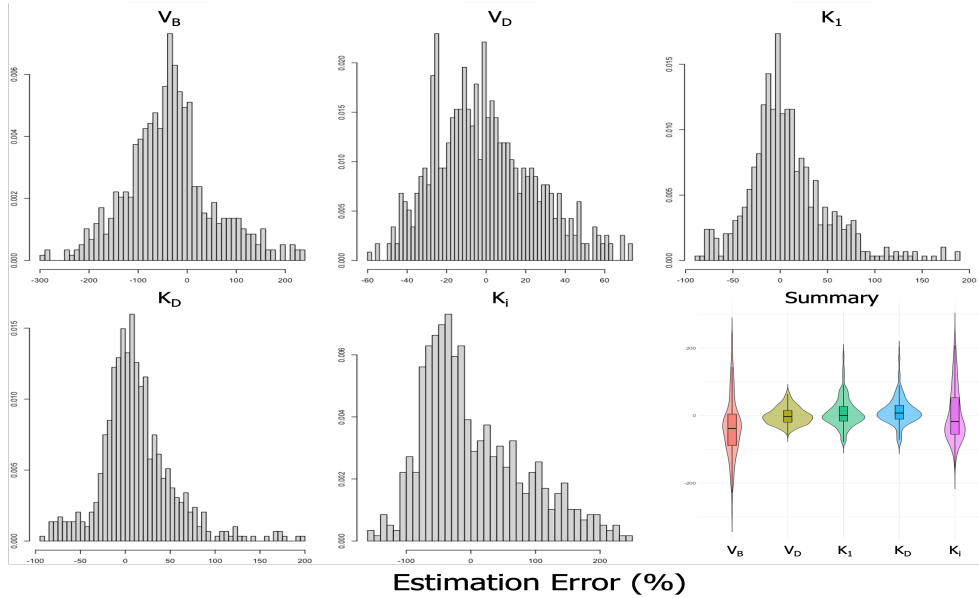


Figure 5.5: Test prediction error rate of CO₂ kinetic parameters using only the uncorrected acetate kinetic parameters.

When predicting corrected acetate kinetic parameters, the error rates are primarily normally distributed within $[-100\%, 100\%]$, except for K_i , which exhibits a slight right skew. Unlike other parameters, most predicted K_i values

tend to be overestimated. The prediction errors for CO₂ kinetic parameters are more dispersed but slightly lower compared to those of the corrected acetate kinetic parameters. However, the error rates for both cases remain too high for practical application, particularly in a clinical setting. This could be attributed to the limited model selection and dataset size. The five candidate models were chosen to account for both linear and non-linear relationships, but a broader range of models could be explored. Despite incorporating 50 sub-TACs per case instead of relying on a few ROIs, the dataset remains limited to only 12 cases, resulting in a total of 600 data points, still insufficient for robust machine-learning applications.

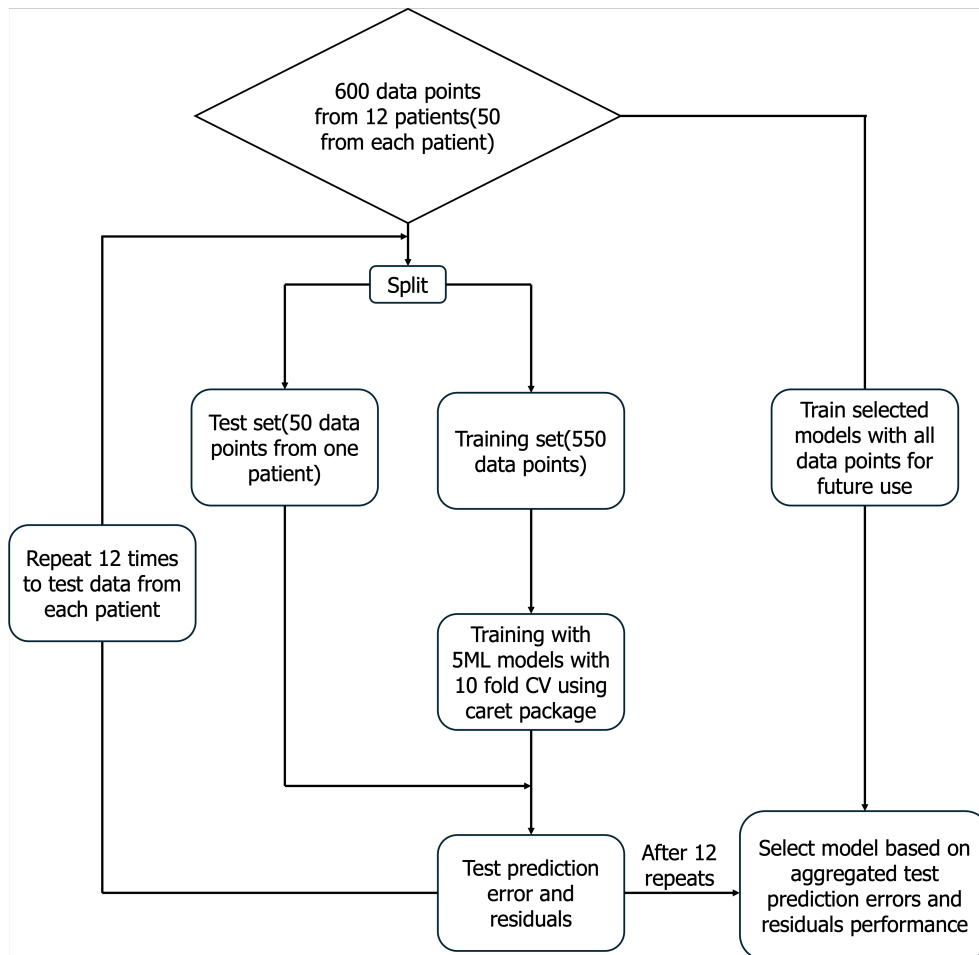


Figure 5.6: A flowchart of the machine learning training and validation framework

5.2.4 Summary of Methods to be Evaluated

With the mentioned models and schemes, the correction methods to be evaluated here are as follows:

(1) **Use no CO₂ information:**

(1.1) **Direct Prediction(DP):** Directly predict corrected acetate kinetic parameters from uncorrected acetate kinetic parameters with selected machine learning models.

(2) **Use only acetate-generated CO₂ input function:**

(2.1) **Full Augment(FA):** Correction by incorporating two additional basis elements derived from the fully sampled acetate-generated CO₂ input function in NPRM.

(2.2) **Sparse Augment(SA):** Correction by incorporating two additional basis elements derived from the sparsely sampled data scaled population acetate-generated CO₂ input function in NPRM.

(2.3) **Population Augment(PA):** Correction by incorporating two additional basis elements derived from the population data, scaled population acetate-generated CO₂ input function in NPRM.

(3) **Use both acetate-generated CO₂ input function and CO₂ residue function:**

(3.1) **Full Convolution(FC):** Correction using the convolution between an estimated CO₂ residue function (reconstructed from predicted CO₂ kinetic parameters from machine learning models) and the fully sampled acetate-generated CO₂ input function.

(3.1) **Sparse Convolution(SC)**: Correction using the convolution between an estimated CO₂ residue function (reconstructed from predicted CO₂ kinetic parameters from machine learning models) and the sparsely sampled data scaled population acetate-generated CO₂ input function.

(3.3) **Population Convolution(PC)**: Correction using the convolution between an estimated CO₂ residue function (reconstructed from predicted CO₂ kinetic parameters from machine learning models) and the population data scaled population acetate-generated CO₂ input function.

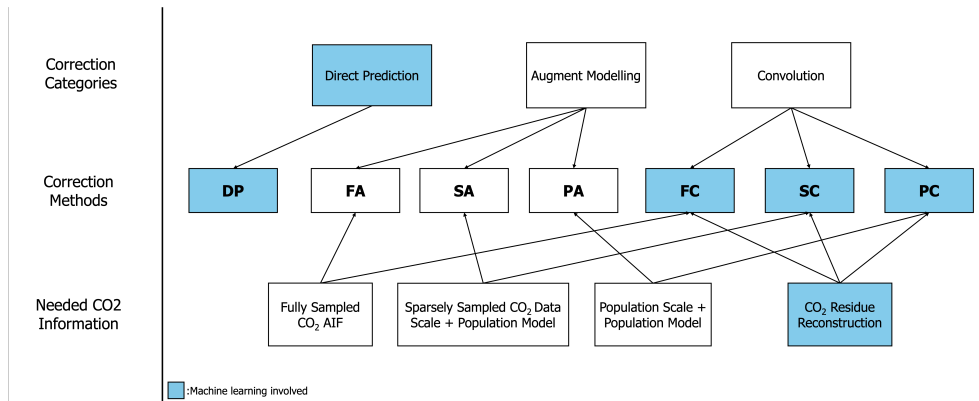


Figure 5.7: The summary of acetate-generated CO₂ correction methods. The top row is three categories of correction methods, the middle row is the correction methods, and the bottom row is the availability of CO₂ information. Names of correction methods are the combination of categories and the source of CO₂ AIF. Connection lines indicate the category and needed CO₂ information for each correction method. Blue boxes mean machine learning is involved.

5.3 Results

We treat the data and corrected acetate kinetic parameters from Chapter 4 as the ground truth and evaluate the performance of different correction methods with the estimation error of five kinetic parameters(V_b , V_d , K_1 , K_d ,

and K_i). A total of 48 PET ROI datasets will be used in the evaluation for each method. A reference estimation error is also presented for comparison. The reference group represents the level of estimation error under a similar level of noise and is estimated through a simulation study discussed in section 3.8.1. The distribution of estimation errors, along with median and median absolute deviation (MAD) values, is shown in Figure 5.8 and Table 5.1.

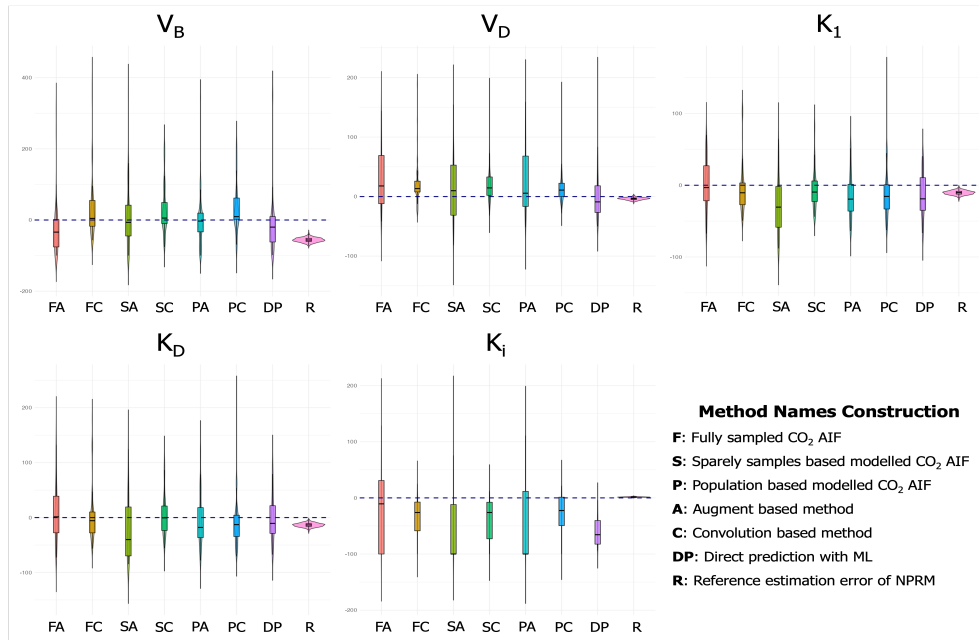


Figure 5.8: Estimation error rate of corrected acetate kinetic parameters from different methods. Names of each method are explained in the right corner according to the method's summary in section 5.2.4. Median and median absolute deviation(MAD) of each parameter across all methods are summarized in Table 5.1.

Table 5.1: Median and median absolute deviation(MAD) shown as median $\pm$ MAD of each correction method among the five kinetic parameters in Figure 5.8.

Method	V_b (mL/g)	V_d (mL/g)	K_1 (mL/min/g)	K_d (mL/min/g)	K_i (mL/min/100g)
FA	-34.01 $\pm$ 39.24	17.82 $\pm$ 31.60	-3.21 $\pm$ 23.44	1.36 $\pm$ 35.35	-10.62 $\pm$ 68.81
FC	4.50 $\pm$ 38.73	13.35 $\pm$ 7.04	-10.51 $\pm$ 14.33	-5.69 $\pm$ 20.33	-26.10 $\pm$ 20.44
SA	-6.62 $\pm$ 47.47	9.83 $\pm$ 43.78	-30.51 $\pm$ 29.18	-40.09 $\pm$ 35.26	-100.00 $\pm$ 0.00
SC	5.48 $\pm$ 23.33	14.55 $\pm$ 15.85	-9.49 $\pm$ 14.50	-0.48 $\pm$ 23.16	-26.04 $\pm$ 26.23
PA	-3.04 $\pm$ 27.08	5.62 $\pm$ 32.48	-19.37 $\pm$ 18.56	-17.99 $\pm$ 28.14	-100.00 $\pm$ 0.00
PC	9.47 $\pm$ 23.70	10.88 $\pm$ 11.33	-15.57 $\pm$ 16.57	-12.79 $\pm$ 20.58	-22.54 $\pm$ 24.01
DP	-19.96 $\pm$ 35.76	-8.95 $\pm$ 22.90	-18.94 $\pm$ 20.56	-10.54 $\pm$ 26.53	-65.57 $\pm$ 22.19
R	-56.24 $\pm$ 4.41	-3.54 $\pm$ 1.36	-10.32 $\pm$ 2.00	-13.42 $\pm$ 2.50	-1.50 $\pm$ 0.38

The analysis of parameter estimation errors reveals several critical insights. First, the reference (R) estimation error exhibits markedly lower variance (quantified by MAD) across all parameters compared to correction methods. For instance, in V_B , R achieves an MAD of 4.41, whereas other methods show MAD values as high as 47.47 (SA). This underscores R's superior precision despite its higher median bias in certain parameters. For V_B , the reference method (R) demonstrates the largest median bias (-56.24), exceeding all correction methods in absolute value. Population Augment (PA) achieves the lowest absolute median bias (-3.04) for this parameter. In V_D , a directional contrast emerges: most correction methods (e.g., FA: 17.82, FC: 13.35) exhibit positive median biases, while R and Direct Prediction (DP) show negative biases (-3.54 and -8.95 , respectively). In K_1 , Full Augment (FA) outperforms R with a median bias of -3.21 (vs. R: -10.32), whereas Full Convolution (FC: -10.51) and Sparse Convolution (SC: -9.49)

underperform relative to R. For K_D , FA excels with a near-zero median bias (1.36 vs. R: -13.42), while Sparse Augment (SA) shows the worst performance (-40.09). The K_i estimates highlight extreme anomalies: SA and PA yield a fixed median error of -100% (MAD = 0), likely due to methodological constraints. Convolution-based methods (FC, SC, PC) and DP exhibit more stable biases (medians: -22.54 to -26.10), though still substantially higher than R's minimal bias (-1.50 ± 0.38).

Augment-based methods (FA, SA, PA) display inconsistent bias magnitudes across parameters. For example, FA's V_B bias (-34.01) is the largest among all methods, while PA achieves the smallest (-3.04). Conversely, convolution-based methods (FC, SC, PC) demonstrate greater stability in both bias and variance. Direct Prediction (DP) performs competitively in V_B , V_D , K_1 , and K_D , but its K_i bias (-65.57) is notably higher than other methods. Notably, SA and PA's -100% median error in K_i suggests further investigation is needed for augment-based methods. Convolution-based corrections consistently balance bias and variance, whereas augment-based methods trade stability for parameter-specific accuracy.

5.4 Discussion

This chapter introduces several ¹¹CO₂ signal contamination correction methods for ¹¹C-acetate PET studies that do not require prior ¹¹CO₂ PET data. These methods are developed and validated using the ¹¹CO₂-¹¹C acetate dual-injection PET dataset and its corresponding 'true' corrected kinetics, as described in Chapter 4. One of the main motivations of this chapter, introduced in section 6.1, is to address the challenge that the acetate-generated CO₂ input function is required for all correction methods

except for the direct prediction using machine learning models.

Based on the results in Figure 5.8 and Figure 5.9, convolution-based methods appear more reliable than others, even though they involve two additional estimation steps that can introduce errors. These methods effectively reflect differences in estimation accuracy between using a fully sampled CO₂ AIF, a modeled CO₂ AIF from sparsely sampled data, and a modeled CO₂ AIF using population mean values, in terms of bias and variance of the estimated kinetic parameters.

In contrast, augmentation-based correction methods show unexpected performance. For example, the estimation error for V_b using a population-based modeled CO₂ AIF is smaller than that using a fully sampled CO₂ AIF. These methods also perform poorly in estimating K_i , a critical kinetic parameter. One possible explanation is that the Patlak elements may not sufficiently capture the CO₂ contamination TACs. The fitting results in Figure 5.3 also suggest room for improvement. A more restrictive or sophisticated weighting scheme could be incorporated into the NPRM when introducing the contamination AIF. This may help improve the accuracy of the parameter estimation.

The machine learning-based correction method remains under-explored but holds strong potential. Leave-one-out cross-validation (LOOCV) has been employed to reduce overfitting; however, the risk of validation bias still exists. It is therefore essential to clearly distinguish between the datasets used for model training and those reserved for testing or validation. One potential solution is the development of correction models that are applicable across different tissues and organs within the same patient, or

across groups of patients who share similar physiological characteristics. More advanced feature selection strategies could help tailor the prediction models to individual kinetic parameters. Machine learning models for parametric image prediction have been extensively studied in several works [Wang et al., 2023, Huang et al., 2022, Li et al., 2023, Wu et al., 2019], with the main focus on extracting reliable kinetic information from reduced imaging data. Given the physiological link between acetate and CO₂ in the human body, machine learning-based voxel-level correction offers significant opportunities for further research and application.

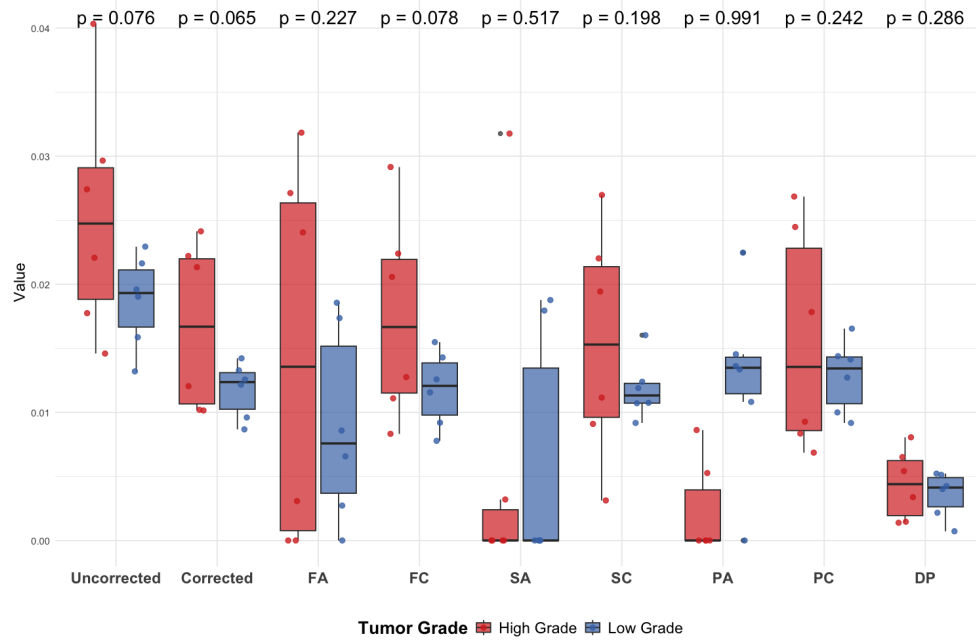


Figure 5.9: Use uncorrected and different method corrected K_i to differentiate tumor grade with p-value above for each group. The uncorrected and corrected groups are from Figure 4.8.

In general, this chapter explores the possible solution to ¹¹CO₂ signal contamination for ¹¹C-acetate PET studies when a ¹¹CO₂-¹¹C acetate dual-injection PET imaging is not available. Three methods that use population-based CO₂ information and machine learning models will be tested in the

next chapter with a prostate cancer bone metastases dataset, where the CO₂ imaging profile is not available.

Chapter 6

Illustration of Correction on Prostate Cancer Dataset without any $^{11}\text{CO}_2$ Scanning or any Blood Sampling

All methods introduced in the Chapter 5 are implemented and validated using CO_2 -acetate dual-injection PET data, where corrected kinetic parameters serve as the ground truth for model evaluation. The promising results motivate further investigation of the correction method, which does not rely on any patient-specific CO_2 information. In this chapter, we will discuss the modeling of the acetate-generated CO_2 input function using the total arterial activity course of acetate. We will also validate the acetate-generated CO_2 AIF model with the CO_2 -acetate dual injection PET data used in chapter 4 and chapter 5. Then we will apply three metabolite correction methods that do not require any prior CO_2 PET data, direct prediction, population-convolution, and augment with population-predicted acetate-generated CO_2 input function (population-augment), to an acetate PET prostate cancer bone

metastases dataset without any $^{11}\text{CO}_2$ input and kinetic information.

6.1 Reducing the Need for Blood Sampling and Metabolite Analysis

Blood sampling requirements for full kinetic analysis of dynamic PET data can be difficult to implement routinely in a clinical setting. As a result, it is most common to conduct studies with minimal reliance on direct blood sampling. A variety of approaches have been proposed in the literature to recover an arterial blood time course from an image-identified blood pool ROI within the scanner's field of view—see, for example, [O'Sullivan, 2023] for a recent review. When the blood pool ROI is affected by spillover, metabolic contamination, or dispersion effects, recovering the correct arterial input function (AIF) becomes more challenging. However, with the aid of some supplementary direct blood sampling, these challenges may be mitigated. The population-based technique described by [O'Sullivan, 2023] focuses on extracting the AIF for the injected tracer. Their analysis shows promising results for AIF recovery from image data for several tracers, including ^{11}C -labeled CO_2 and acetate. Validation was performed using the Brain Acetate dataset, which is also utilized in this thesis. In the context of ^{11}C -acetate imaging, it is essential to recover not only the arterial time-activity curve for the unmetabolized acetate signal (C_p^A), but also the arterial time-activity curve of the acetate-generated CO_2 metabolite (C_p^{CA}), which is the dominant labeled species in the blood. As discussed in Chapters 3 and 4, both curves are required for accurate quantitative kinetic analysis of the acetate time-activity data.

This section presents a short study investigating the feasibility of modeling the acetate-generated CO_2 arterial signal based on the total arterial blood signal in ^{11}C -acetate PET imaging.

6.1.1 Models for the CO_2 Metabolite of Acetate in the Arterial Blood

The whole-body metabolism of acetate has been reported by [Moffett et al., 2020b, Moffett et al., 2020a]. Since the metabolic $^{11}\text{CO}_2$ generated from ^{11}C -acetate originates from various parts of the human body, we adopt Finbarr’s AIF modeling technique [O’Sullivan, 2023] and assume that the indicator-dilution method [Meier and Zierler, 1954] is suitable for this scenario. Specifically, the metabolic $^{11}\text{CO}_2$ activity, C_P^{CA} , can be modeled as the convolution of the measured total ^{11}C activity in blood, C_p , with an unknown, non-negative impulse response function. Given this, a non-parametric residue mapping representation seems sufficient to estimate the impulse response function.

$$C_P^{CA} = \int_0^t R(t-s)C_P(s)ds = \sum_{m=1}^M \beta_m R_m \otimes C_P(t) \quad (6.1)$$

Where R_m denotes piecewise linear residue basis elements defined over a set of time knots. The time knots are chosen based on the sampling time points of the arterial blood data. β_m is the associated non-negative residue basis coefficient. The modeled CO_2 AIF can then be scaled and shifted with as few as two CO_2 blood samples, as discussed in [O’Sullivan, 2023].

In the absence of available CO_2 blood samples, the basis elements can be defined over a set of time knots derived from population sampling data acquired using the same tracer. A population impulse response function is then

estimated using the average residue basis coefficients from this dataset. The resulting population modeled CO_2 AIF is subsequently scaled and shifted based on the population mean to generate a population acetate-generated CO_2 AIF. The feasibility of this modeling and population estimation will be tested in the next section.

6.1.2 Application to Brain Data

In this section, we use the acetate-generated CO_2 AIF model to approximate the fully sampled CO_2 AIF gathered as part of the CO_2 -acetate dual injection brain studies. In addition to the population mean value, we also incorporate sparsely sampled CO_2 blood data to scale and shift the population modeled CO_2 AIF. This approach allows us to assess the estimation accuracy with only a few additional acidification steps.

6. Illustration of Correction on Prostate Cancer Dataset without any $^{11}\text{CO}_2$ Scanning or any Blood Sampling

6.1 Reducing the Need for Blood Sampling and Metabolite Analysis

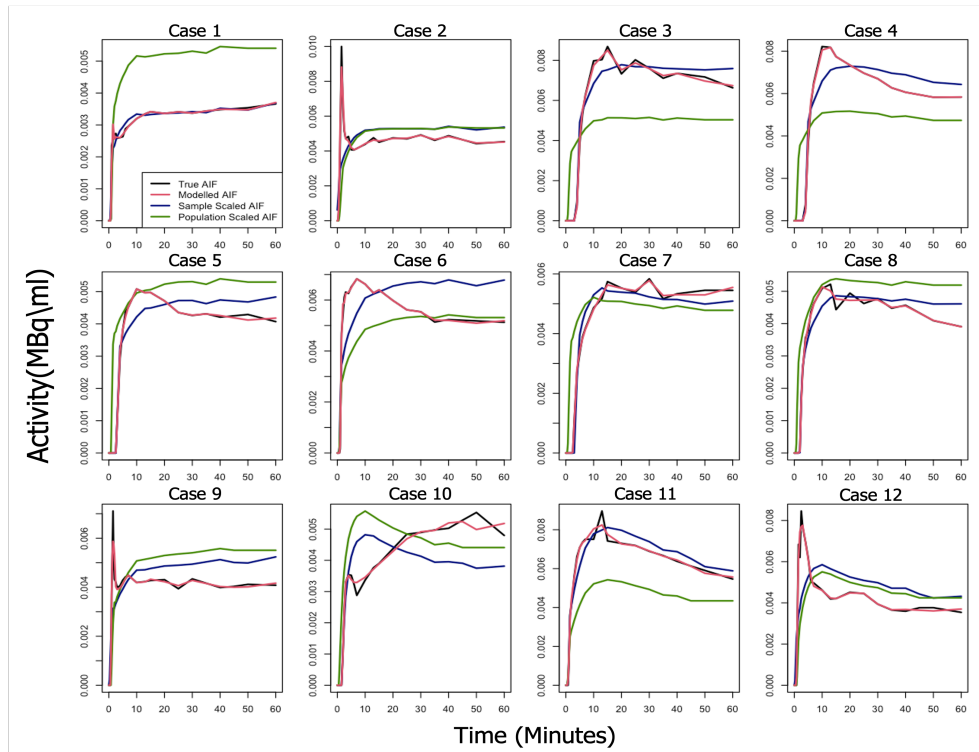


Figure 6.1: The modeling of acetate-generated CO_2 AIF using 12 brain tumor dataset. The black lines are the true CO_2 AIF. The red lines are the modeled CO_2 AIF with case-specific residue basis coefficients. While the blue and green lines are modeled AIF with population mean residue basis coefficients and scaled with sparsely sampled CO_2 blood data and population mean data, respectively.

Figure 6.1 summarizes the CO_2 AIF modeling results across the 12 cases in the brain dataset. The red lines represent the best fits obtained using Equation 6.1, and the results are promising, validating the feasibility of the CO_2 AIF model. The blue and green lines show the population average CO_2 AIF scaled using sparsely sampled CO_2 blood data and the population mean CO_2 blood data, respectively, representing scenarios with limited or no CO_2 blood information. When estimating each case, that case was excluded from the population group to ensure a more accurate population-based estimation.

The population AIF scaled using sampled blood data consistently outperforms the version scaled with population mean values in terms of over-

all scaling, particularly in cases 1, 3, 4, and 11, as expected. Notably, the population-scaled CO_2 AIFs in cases 3, 4, and 5 exhibit apparent deviations from the true AIF during the early phase, which could impact the estimation of delay in subsequent kinetic analyses. These findings highlight the importance of blood sampling in modeling the acetate-generated CO_2 AIF. Since the scaling process involves only two parameters—overall scale and temporal shift—even as few as two blood samples can significantly improve CO_2 AIF estimation. Nevertheless, even with a relatively small population group of 12 datasets, some population-scaled CO_2 AIFs show good agreement with the true AIF, as seen in case 7. This suggests that further investigation into metabolite AIF modeling based on total arterial activity curves is warranted.

6.2 The Prostate Cancer Bone Metastases Dataset

The dataset comprises 12 ^{11}C -acetate PET scans from 8 patients diagnosed with prostate cancer and presenting with more than three bone metastases. The scans cover regions with prominent and easily identifiable lesions, typically in the chest and abdominal areas. Eleven of these scans are paired with corresponding FDG PET scans acquired over the same anatomical regions. All PET images were obtained both before and 6 to 12 weeks after systemic therapy. These PET images were acquired on a GE Advance PET tomograph with an imaging volume of $N = 128 \times 128 \times 35$ with a dynamic sequence: 16×5 seconds, 7×10 seconds, 5×30 seconds, 5×60 seconds, 5×180 seconds and 1×300 seconds. No arterial blood samples were acquired during the imaging process. Further details about this dataset can be found in [Evan et al., 2011], where it was originally reported to evaluate

both qualitative and quantitative changes in acetate uptake before therapy,
as well as alterations in uptake in response to systemic treatment.

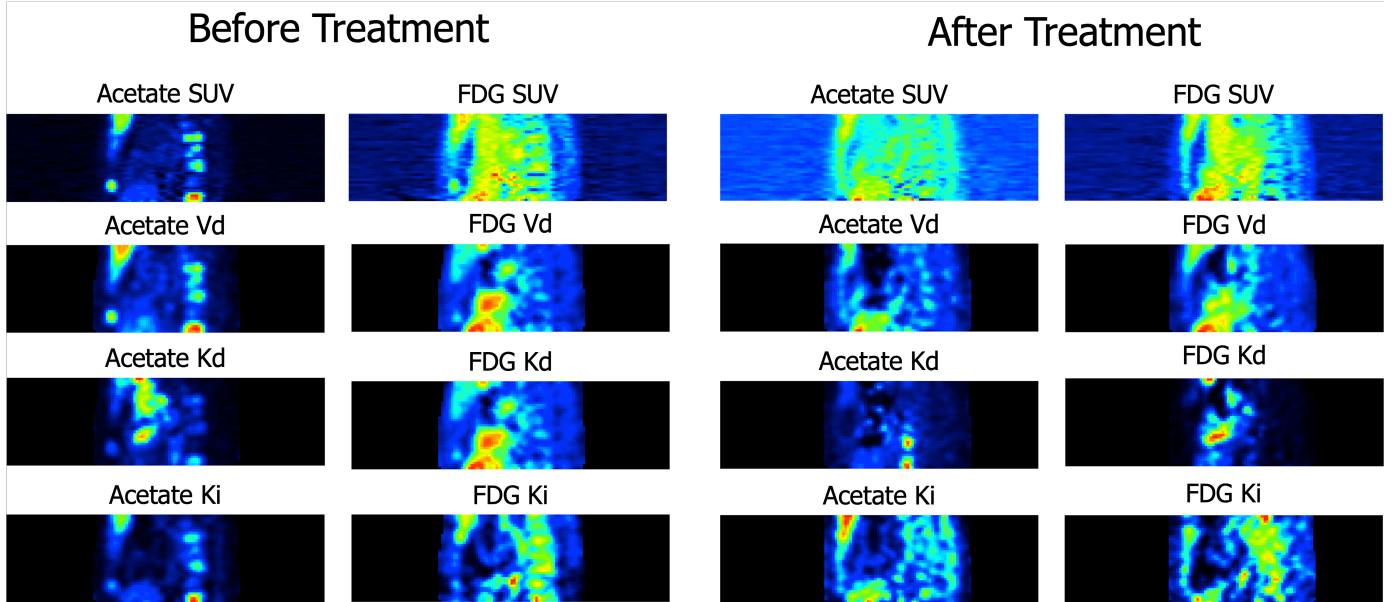


Figure 6.2: Response to androgen deprivation therapy according to [Evan et al., 2011]. This patient underwent acetate and FDG PET imaging before and after a 12-week-long therapy. His pain resolved, and his PSA level dropped significantly after the therapy. The SUV, V_d , K_d , and K_i map of this patient from his before-therapy imaging(1 and 2 columns) and after-therapy imaging(3 and 4 columns) are shown here. Only acetate SUV, acetate V_d , and acetate K_i show significant changes in bone metastases in response to the therapy.

We will use this dataset to assess the feasibility of applying the correction methods to diverse anatomical regions within the human body. The AIFs were extracted using the methodology in [O’Sullivan, 2023] over the descending aorta or common iliac artery ROIs. Additional ROIs are defined for key organs: lung, myocardium, bone marrow, liver, spleen, and kidney. All acetate and FDG PET data are analyzed using the NPRM model with the derived AIFs, both at the voxel level and ROI level. A comparison of responses to therapy is presented in Figure 6.2. FDG SUV, V_d , K_d , and K_i fail to identify the bone metastases before treatment, preventing meaning-

ful assessment of therapeutic response. In contrast, acetate SUV, V_d , and K_i successfully highlight the bone metastases before treatment and demonstrate significant changes in the affected areas following therapy. Figure 6.3 displays representative maximum intensity projection (MIP) maps of V_d , K_d , and K_i derived from FDG and acetate PET studies in a post-treatment case. Key kinetic parameters across different ROIs for both tracers are summarized in Tables 6.1 among all before and after treatment studies. The number of ROIs varies across cases due to differences in scanning coverage. Notably, regions such as the kidney, bladder, and pelvic cavity were identified in only one case.

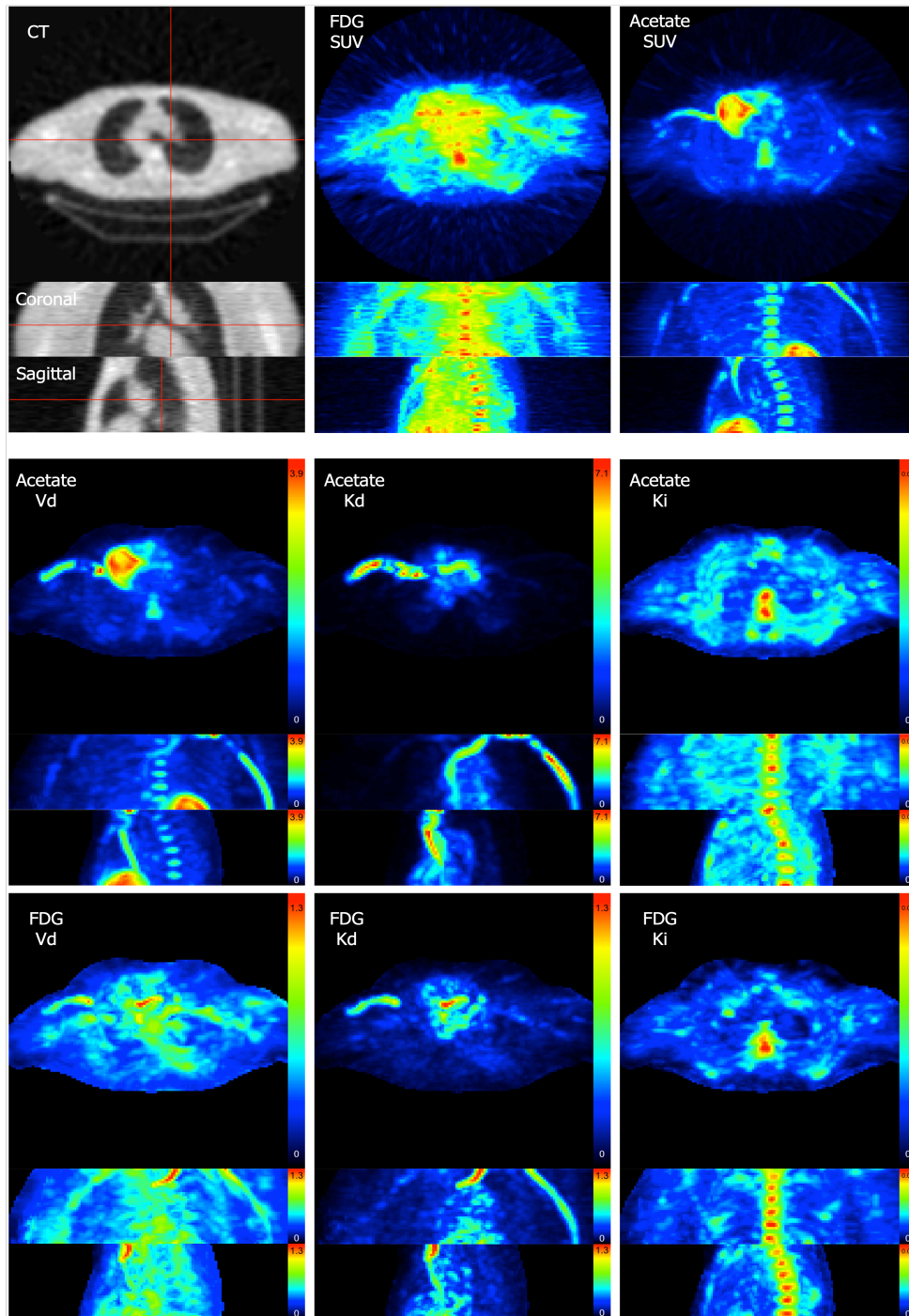


Figure 6.3: MIP maps of uncorrected V_d , K_d and K_i from a acetate and FDG PET chest studies. The top row shows CT images for selected sections and MIP maps of FDG SUV and acetate SUV.

Table 6.1: Acetate and FDG kinetics parameters on the prostate cancer bone metastases dataset (mean $\pm$ standard deviation) over different ROIs.

Tracer	ROIs	V_b (mL/g)	V_d (mL/g)	K_1 (mL/min/g)	K_d (mL/min/g)	K_i (mL/min/100g)
Acetate	Marrow(n=11)	0.03 ± 0.02	0.71 ± 0.39	0.20 ± 0.13	0.17 ± 0.13	2.84 ± 1.07
	Lung(n=10)	0.10 ± 0.08	0.43 ± 0.23	0.26 ± 0.20	0.24 ± 0.20	1.29 ± 0.72
	Myocardium(n=10)	0.26 ± 0.20	2.90 ± 0.79	0.63 ± 0.30	0.63 ± 0.31	0.13 ± 0.34
	Liver(n=6)	0.17 ± 0.22	1.52 ± 0.93	0.33 ± 0.17	0.26 ± 0.16	6.62 ± 2.52
	Spleen(n=6)	0.14 ± 0.14	2.65 ± 1.33	0.71 ± 0.44	0.65 ± 0.43	6.75 ± 3.13
	Kidney(n=1)	0.14	1.17	0.32	0.31	0.71
	Bladder(n=1)	0.001	0.33	0.13	0.12	1.31
	Pelvic cavity(n=1)	0.02	1.39	0.40	0.35	4.91
FDG	Marrow(n=11)	0.07 ± 0.12	0.36 ± 0.16	0.21 ± 0.09	0.21 ± 0.09	0.40 ± 0.21
	Lung(n=10)	0.24 ± 0.11	0.05 ± 0.05	0.06 ± 0.10	0.06 ± 0.10	0.07 ± 0.07
	Myocardium(n=10)	0.46 ± 0.30	0.35 ± 0.29	0.38 ± 0.57	0.37 ± 0.57	0.93 ± 0.89
	Liver(n=6)	0.07 ± 0.06	4.04 ± 0.23	0.90 ± 0.31	0.90 ± 0.31	0.22 ± 0.20
	Spleen(n=6)	0.35 ± 0.41	0.40 ± 0.49	0.98 ± 1.31	0.98 ± 1.31	0.21 ± 0.13
	Kidney(n=1)	0.45	2.22	0.30	0.30	0.29
	Bladder(n=1)	0.01	0.33	0.13	0.13	0.20
	Pelvic cavity(n=1)	0.04	0.72	0.51	0.50	0.84

6.3 Application of Correction Methods on Prostate Cancer Dataset

Corrections are applied to both the ROI and voxel-level analyses. Kinetic parameters from different methods over different ROIs are summarized in Table 6.2. Based on the results from the prostate cancer dataset, most

parameters decrease after correction with all three methods, especially V_d in the marrow and K_i in the liver and bladder. PA correction tends to aggressively reduce both the magnitude and variability of K_i across all included ROIs while introducing only minor changes to other parameters. Notably, it reduces K_i in the myocardium, kidney, bladder, and pelvic cavity to zero. Although there is only one sample in the last three ROIs, the 10 samples in the myocardium suggest systematic constraints in PA. Similar to PA, DP reduces K_i across all ROIs with the largest overall decrease. It also reduces the variability of some parameters (e.g., the standard deviation of spleen K_d drops from 0.43 to 0.23). In contrast, PC results in the smallest correction and remains closest to the uncorrected parameters across all five parameters and eight ROIs. Different ROIs respond differently to the correction methods. K_1 in the myocardium is particularly sensitive to the different correction approaches, while K_i in the liver and spleen is reduced by more than 90% in both PA and DP corrections.

Voxel-level correction was performed only with the PA and PC methods, as the models used in DP were trained and validated with ROI data, making the results unreliable for voxel-level analysis. The MIP maps of uncorrected and corrected acetate V_d , K_d , and K_i are presented in Fig. 6.4. The corrections applied to V_d using PA and PC are similar, primarily removing vessel-like structures from the MIP maps while preserving details comparable to the uncorrected maps. In contrast, the corrections to K_d are more substantial with both methods. PA-corrected K_d exhibits a similar pattern to PA-corrected V_d , whereas PC-corrected K_d appears more diffused. The maximum value of K_d also changes significantly, decreasing from 7.1 in the uncorrected map to 0.9 in the PA-corrected map and 2.6 in the PC-corrected map. For K_i , the PA-corrected map lacks a clear structure, making it difficult to identify

meaningful patterns. In contrast, the PC-corrected K_i map closely resembles the uncorrected version but highlights the ribcage area. These differences in PA- and PC-corrected K_i align with the findings from the ROI analysis.

Table 6.2: Different methods corrected acetate kinetics parameters (mean $\pm$ standard deviation) over different ROIs. PA=population-augment, DP=direct and PC=population-convolution.

Method	ROIs	V_b (mL/g)	V_d (mL/g)	K_1 (mL/min/g)	K_d (mL/min/g)	K_i (mL/min/100g)
PA	Marrow(n=11)	0.04 $\pm$ 0.03	0.41 $\pm$ 0.31	0.20 $\pm$ 0.21	0.19 $\pm$ 0.21	0.31 $\pm$ 0.46
	Lung(n=10)	0.13 $\pm$ 0.15	0.20 $\pm$ 0.17	0.25 $\pm$ 0.26	0.25 $\pm$ 0.26	0.23 $\pm$ 0.32
	Myocardium(n=10)	0.27 $\pm$ 0.20	2.83 $\pm$ 0.87	0.76 $\pm$ 0.31	0.76 $\pm$ 0.31	0 $\pm$ 0
	Liver(n=6)	0.14 $\pm$ 0.26	0.58 $\pm$ 0.21	0.27 $\pm$ 0.20	0.27 $\pm$ 0.20	0.20 $\pm$ 0.35
	Spleen(n=6)	0.19 $\pm$ 0.20	1.01 $\pm$ 0.81	0.40 $\pm$ 0.32	0.40 $\pm$ 0.32	0.39 $\pm$ 0.86
	Kidney(n=1)	0.18	0.95	0.23	0.23	0
	Bladder(n=1)	0.01	0.09	0.08	0.08	0
	Pelvic cavity(n=1)	0.02	1.53	0.38	0.38	0
DP	Marrow(n=11)	0.04 $\pm$ 0.03	0.35 $\pm$ 0.20	0.15 $\pm$ 0.16	0.14 $\pm$ 0.14	0.20 $\pm$ 0.17
	Lung(n=10)	0.12 $\pm$ 0.14	0.19 $\pm$ 0.11	0.19 $\pm$ 0.19	0.18 $\pm$ 0.18	0.13 $\pm$ 0.15
	Myocardium(n=10)	0.26 $\pm$ 0.20	2.10 $\pm$ 0.62	0.59 $\pm$ 0.23	0.56 $\pm$ 0.22	0.55 $\pm$ 0.18
	Liver(n=6)	0.16 $\pm$ 0.24	0.58 $\pm$ 0.34	0.22 $\pm$ 0.15	0.21 $\pm$ 0.15	0.18 $\pm$ 0.18
	Spleen(n=6)	0.22 $\pm$ 0.21	1.05 $\pm$ 0.63	0.33 $\pm$ 0.25	0.32 $\pm$ 0.23	0.27 $\pm$ 0.29
	Kidney(n=1)	0.03	0.97	0.29	0.27	0.29
	Bladder(n=1)	0.01	0.10	0.06	0.06	0.003
	Pelvic cavity(n=1)	0.18	0.75	0.18	0.17	0.17
PC	Marrow(n=11)	0.04 $\pm$ 0.02	0.64 $\pm$ 0.30	0.22 $\pm$ 0.18	0.20 $\pm$ 0.18	2.25 $\pm$ 1.07
	Lung(n=10)	0.12 $\pm$ 0.13	0.33 $\pm$ 0.17	0.31 $\pm$ 0.30	0.30 $\pm$ 0.30	0.75 $\pm$ 0.52
	Myocardium(n=10)	0.13 $\pm$ 0.10	2.87 $\pm$ 0.79	0.93 $\pm$ 0.46	0.93 $\pm$ 0.46	0.06 $\pm$ 0.19
	Liver(n=6)	0.19 $\pm$ 0.22	1.47 $\pm$ 0.99	0.31 $\pm$ 0.17	0.25 $\pm$ 0.16	5.66 $\pm$ 2.30
	Spleen(n=6)	0.12 $\pm$ 0.12	2.59 $\pm$ 1.46	0.68 $\pm$ 0.48	0.62 $\pm$ 0.47	5.95 $\pm$ 3.27
	Kidney(n=1)	0.14	1.16	0.33	0.33	0.30
	Bladder(n=1)	0.01	0.24	0.15	0.15	0.66
	Pelvic cavity(n=1)	0.02	1.35	0.40	0.36	4.24

6. Illustration of Correction on Prostate Cancer Dataset without any $^{11}\text{CO}_2$ Scanning or any Blood Sampling

6.3 Application of Correction Methods on Prostate Cancer Dataset

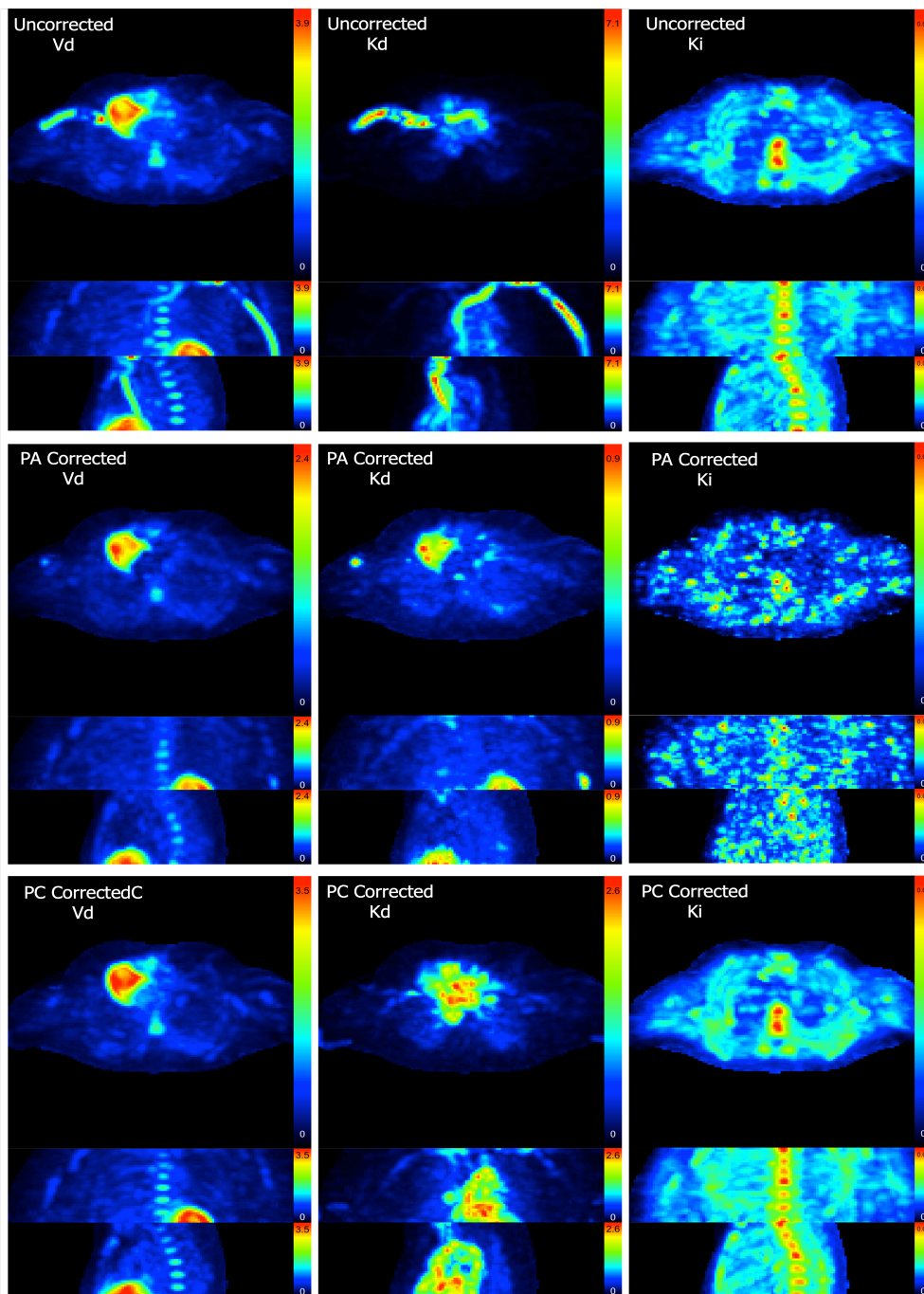


Figure 6.4: MIP maps of uncorrected and corrected V_d , K_d and K_i with two methods(PA=population-augment, PC=population-convolution) from the same case in Figure 6.3.

6.4 Discussion

In this chapter, we demonstrate the feasibility of the acetate-generated CO_2 AIF model and validate the potential to generate population-based metabolite CO_2 AIFs, which can be scaled using sparsely sampled CO_2 blood data to improve accuracy. This novel approach motivates the investigation into metabolite correction methods that do not require a separate metabolite PET scan, which are discussed in chapter 5. Three metabolite correction methods that do not rely on separate metabolite PET scans are also discussed in this chapter, using a prostate cancer bone metastases dataset comprising ^{11}C -acetate PET studies. Since no prior $^{11}\text{CO}_2$ scans are available for this dataset, it is not possible to obtain a definitive ‘ground truth’ for corrected kinetic profiles. Nonetheless, it is noteworthy that correction methods developed using brain tumor datasets have shown promising generalizability when applied to other anatomical regions. The models used in these correction methods were trained on brain tumor data. Ideally, correction strategies should be tailored to specific organs and tissue types, reflecting differences in metabolic behavior. However, the results presented in this chapter suggest that different organs and tissues may share common mechanisms underlying metabolite contamination. This raises the intriguing possibility of developing a unified correction approach applicable across various regions of the human body. Recent advances in long axial field-of-view (LAFOV) PET scanners offer a powerful platform for constructing and validating organ- or tissue-specific correction models. These scanners can capture multiple key organs and tissues simultaneously within a single dynamic imaging session, enabling the investigation of inter-organ relationships in metabolite behavior and correction strategies. Moreover, the inclusion of major blood vessels

within the field of view permits the study of labeled CO_2 transport dynamics throughout the body. The promising results presented in this chapter support further investigation into organ-specific and patient-specific correction methods, potentially enhancing the clinical utility and robustness of ^{11}C -acetate PET imaging.

Chapter 7

Discussion, Conclusions and Future Work

7.1 Discussion

The work in this thesis is inspired by the non-parametric residue mapping (NPRM) model [Hawe et al., 2012, O’Sullivan et al., 2014] and the multi-compartmental model for CO₂ contamination correction in ¹¹C-acetate PET imaging [Muzi et al., 2011]. We build upon the flexibility of NPRM by extending it with an exponential basis, resulting in a semi-parametric residue mapping model. This model forms the core of the proposed CO₂ contamination correction approach. Metabolic contamination correction in PET imaging with tracers that follow multiple metabolic pathways in the human body has received limited attention. The correction model developed in this thesis can be readily adapted to address contamination in PET studies involving tracers other than ¹¹C-acetate. Based on this approach, we develop several correction methods that require less data with the ¹¹CO₂-¹¹C acetate dual injection brain tumor data and apply them to a prostate cancer bone metastases dataset with ¹¹C acetate.

Chapters 2 and 3 review quantitative analysis and kinetic modeling for PET data. The summary of these kinetic models is presented in Table 3.1. Most of the kinetic models discussed are parametric models, which estimate one or more parameters using either ROI-level or voxel-level analysis. These parametric models typically rely on specific assumptions, and any violation of these assumptions may introduce additional bias into the estimates. In contrast, the NPRM model does not rely on such assumptions and offers greater flexibility than many commonly used models. NPRM also provides a unique advantage in assessing the uncertainty of estimated kinetic parameters through an image-domain bootstrapping technique. With slightly better weighted residual sum of squares (WRSS) performance than the widely used two-compartmental model (D in Figure 3.18), NPRM enables a more accurate representation of the data-generating process during bootstrapping and therefore yields more precise uncertainty estimates. The arterial input function(AIF) is an essential part of kinetic models. AIF can be derived from arterial blood samples, image-derived input function(IDIF), population-based input function(PBIF), or model-based input function. A general flowchart of IDIF, PBIF and population-based projection model(PBPM, a model-based input function) is summarized in Figure2.9.

Chapter 4 presents a $^{11}\text{CO}_2$ contamination correction method for ^{11}C -acetate PET imaging. This method generalizes the combined multi-compartmental model from [Muzi et al., 2011] and models the PET-measured signal as a combination of the ^{11}C -acetate signal and the $^{11}\text{CO}_2$ signal arising from ^{11}C -acetate metabolism. Both signals are analyzed using the Indicator-Dilution method developed by Meier and Zierler [Meier and Zierler, 1954], as reviewed in Section 3.2. The CO_2 residue function can be estimated

from prior CO₂ PET scans, and the CO₂ input function can be derived from arterial blood samples via acidification, with an example shown in Figure 4.1. A set of CO₂-acetate dual-injection PET studies is used to validate this correction method. To address the residual signal from the prior CO₂ imaging and enable the possibility of shortening the CO₂ scan duration, the semi-parametric residue mapping (SPRM) model is introduced as an extension of the NPRM model. Correction results from both ROI- and voxel-level analyses are shown in Figures 4.5 and 4.6. Based on the ROI analysis, the magnitude of correction varies between approximately 20% and 50% across normal and tumor brain regions. Furthermore, the corrected tumor K_i values show a slightly improved ability to differentiate between high-grade and low-grade tumors compared to uncorrected K_i , even with only 12 studies.

Chapter 5 develops several correction methods without requiring prior CO₂ PET scanning based on the findings from Chapter 4. These correction methods differ in their reliance on the acetate-generated CO₂ AIF and corresponding CO₂ kinetic information. A summary of the required CO₂ information for each method is presented in Figure 5.7. Machine learning models are employed either to predict the corrected acetate kinetic parameters directly or to estimate the associated CO₂ kinetic parameters, which are then used to reconstruct the CO₂ residue function. These correction methods are used to estimate a set of kinetic parameters, with the corresponding estimates obtained from CO₂-acetate dual-injection data in Chapter 4 treated as the 'ground truth' for error evaluation. The estimation errors from the various correction methods are summarized in Figure 5.8. Among the tested approaches, convolution-based methods demonstrate superior performance in terms of kinetic parameter estimation. Furthermore, the K_i values esti-

mated using the convolution-based approach achieve a comparable p-value for distinguishing high-grade from low-grade tumors, as shown in Figure 5.9.

Chapter 6 demonstrates the feasibility of modeling the acetate-generated CO₂ AIF. The proposed model is capable of generating a population-based CO₂ AIF while also offering the flexibility to improve estimation accuracy using as few as two CO₂ blood samples. The results, presented in Figure 6.1, are promising. This CO₂ AIF model, combined with other correction methods that do not rely on separate metabolite PET imaging data discussed in Chapter 5, is further applied to a prostate cancer bone metastases dataset, which includes only acetate and FDG PET scans. The corrected parametric maps example and different organ-based ROI kinetic parameter correction results are shown in Figure 6.4 and Table 6.2, respectively. Although no ground-truth corrected kinetics are available for comparison in this dataset, the correction methods developed from brain tumor data yield promising results when applied to prostate cancer bone metastases cases.

7.2 Conclusions

This thesis presents a statistical method for estimating and correcting CO₂ contamination in acetate PET imaging data. The method is based on non-parametric residue mapping (NPRM) and its extension, semi-parametric residue mapping (SPRM). These two approaches form the cornerstone of this work, enabling robust and flexible kinetic analysis. The correction method is validated using a CO₂-acetate dual-injection brain tumor dataset, demonstrating substantial correction at both the voxel and ROI levels. Several alternative correction strategies that do not require additional CO₂ scanning are also developed and tested on the same brain tumor dataset, and subsequently

applied to a prostate cancer bone metastases dataset. The promising results observed in this application highlight the potential for further research into metabolic contamination correction in PET imaging.

7.3 Future Work

7.3.1 Improvement on Correction Model

In pursuit of higher clinical patient throughput and improved patient comfort, obtaining comprehensive kinetic information from shorter PET scan durations has been a widely studied topic. Numerous studies have demonstrated that shorter scanning time PET studies can achieve comparable performance to full-duration scans in terms of image quality [Zhang et al., 2024], efficiency in image reconstruction [Hu et al., 2023], region and tumor detection [Weber et al., 2021, Nakajima et al., 2016, Schierz et al., 2013], and kinetic parameter estimation [Wu, 2024, Meng et al., 2023, Feng et al., 2021]. The extending nature of the semi-parametric residue mapping (SPRM) model offers the potential to estimate kinetic information from shorter scans with accuracy comparable to that of longer-duration studies. Furthermore, the choice of radiotracer and the specific clinical application are important factors that warrant further investigation.

Thus far, the machine learning models employed in this thesis have been limited to predicting ROI-level kinetic parameters using a relatively small dataset. However, it is essential to note that the prediction of voxel-level parametric maps using various machine learning and deep learning techniques has received growing attention in recent studies [Wang et al., 2023,

Huang et al., 2022, Li et al., 2023]. Therefore, it would be worthwhile to explore the potential of predicting corrected voxel-level parametric maps and ROI-level kinetic parameters using a broader range of machine learning models and architectures.

7.3.2 Application to other Contamination Affected Tracers

This thesis focuses specifically on metabolic contamination arising from ^{11}C -acetate. However, other radiotracers are also subject to similar types of metabolic contamination. Examples include ^{11}C -palmitate and the metabolite $^{11}\text{CO}_2$ for assessing myocardial fatty acid metabolism [Christensen et al., 2017, Coggan et al., 2009], ^{18}F -FDOPA and the metabolite ^{18}F -OMFD for imaging dopaminergic neurons [Somme et al., 2020, Xiao et al., 2019, Deep et al., 1997], and ^{18}F -FCH and the metabolite ^{18}F -fluorobetaine for imaging cell membrane synthesis [Rubí et al., 2024, Kwee et al., 2019, Villar et al., 2019]. With dual-injection PET imaging data involving the radiotracer and the labeled metabolic by-product, similar correction strategies could potentially be developed following the framework presented in this thesis.

7.3.3 Survival Analysis with Corrected Kinetic Parameters

Due to the limited survival data available in the dataset used in this thesis, only basic survival analyses have been conducted. However, the effectiveness of the correction methods on kinetic parameters should ideally be validated using more comprehensive survival analyses. Future work could involve comparing classification accuracy for tumor grade, tumor recurrence,

and key physiological indices using both corrected and uncorrected kinetic parameters. Furthermore, various classification models—such as Linear Discriminant Analysis (LDA), Quadratic Discriminant Analysis (QDA), and Support Vector Machines (SVM)—should be considered to explore the predictive potential of different kinetic parameters fully.

7.3.4 Improve Computational Efficiency

All the analyses in this thesis are conducted with R [R Core Team, 2023] on a 2018 MAC mini powered by an Intel Core 8700B processor clocked at 3.2 GHz with six cores and 16GB of DDR4 memory at 2667 MHz. A complete voxel-level segmentation and analysis of the PET dataset with the size of $128 \times 128 \times 35 \times 24$ with 25 bootstrap samples for uncertainty measurement will take around one hour and twenty minutes. Many of the tasks can be conducted independently, such as block-by-block segmentation and image-domain bootstrapping. Hence, there is a significant amount of potential to reduce the computation cost with some parallelization tools like the doParallel package in R [Corporation and Weston, 2022].

Appendix A

List of Conference Presentations by the Author

A.1 Conference Proceedings related to Chapter 3

1. M Muzi, T Lan, F O’Sullivan. “1- ^{11}C]Acetate Imaging of Membrane Biosynthesis in Glioma Patients”. *European Molecular Imaging Meeting (EMIM)*, Glasgow, UK, 19-22 March. 2019. [Poster Presentation]
2. T Lan, M Muzi, F O’Sullivan. “Mapping Kinetics in Brain Tumor PET Studies with C-11 Acetate-comparison between Parametric and Non-Parametric Methods”. *World Molecular Imaging Congress (WMIC)*, Montreal, Canada, 4-7 Sep. 2019. [Oral Presentation]

A.2 Conference Proceedings related to chapter 4

1. T Lan, M Muzi, F O'Sullivan. "Semi-parametric Residue Analysis of Dual-Injection PET Studies Illustrated by Brain Tumor Imaging with [^{11}C]-labeled CO₂ and Acetate", *IEEE NSS& MIC*, Manchester, UK, 26 Oct-2 Nov. 2019. [Poster Presentation]

Appendix B

Supplement Derivations

B.1 Linear time-invariant (LTI) System

Basic System A basic system is indicated by H that can take the input signal $x(t)$ and produce an output $y(t)$ as follows:

$$y(t) = H[x(t)] \tag{B.1}$$

Linear System A linear system should follow the two conditions:

- $H[ax(t)] = aH[x(t)]$ for all constants a and input signals $x(t)$
- $H[x_1(t) + x_2(t)] = H[x_1(t)] + H[x_2(t)]$ for all input signals $x_1(t)$ and $x_2(t)$

That means when an input to a given system is scaled or added by a value, the output of the system is scaled or added by the same amount.

Time-Invariant System A time-invariant system should satisfy this condition:

- $y(t - t_0) = H[x(t - t_0)]$ for all times t_0 and input signals $x(t)$

That means if the inputs were delayed by an amount of time, the behaviour of the system would not be changed, but would just be delayed by the same amount of time.

Linear Time-Invariant (LTI) System A linear time-invariant system(also known as LTI system) has both linear and time-invariant properties, that is

- $H[ax(t - t_0)] = aH[x(t - t_0)]$ for all constants a , input signals $x(t)$ and times t_0
- $H[x_1(t - t_1) + x_2(t - t_2)] = H[x_1(t - t_1)] + H[x_2(t - t_2)]$ for all input signals $x_1(t)$ and $x_2(t)$ and times t_1 and t_2

Suppose a delta function $\delta(t)$ (at sample number zero has value one and value zero at other samples) is the input signal. In that case, the output signal will be the impulse response function $h(t)$ as described in Figure B.1. Different systems will have different impulse response functions; therefore, the output signal $y(t)$ can be expressed as the convolution between the input signal $x(t)$ and the system impulse response function $h(t)$.

$$y(t) = x(t) \otimes h(t) \quad (\text{B.2})$$

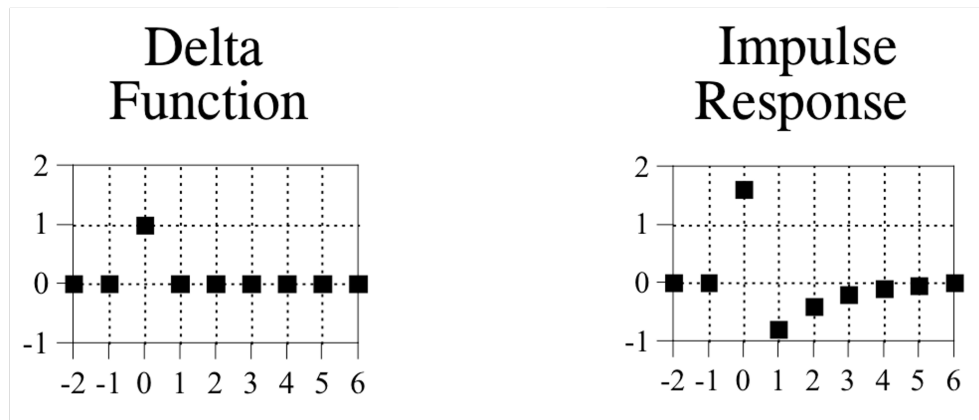


Figure B.1: Definition of delta function and an example of impulse response [Smith, 1997].

B.2 Solution of One Compartmental Model Ordinary Differential Equation

The equation 3.8 can be solved by multiplying both sides by $e^{k_2 t}$

$$\begin{aligned}
 \frac{dC_1(t)}{dt} &= K_1 C_p(t) - k_2 C_1(t) \\
 \Rightarrow \frac{dC_1(t)}{dt} + k_2 C_1(t) &= K_1 C_p(t) \\
 \Rightarrow e^{k_2 t} \frac{dC_1(t)}{dt} + e^{k_2 t} k_2 C_1(t) &= e^{k_2 t} K_1 C_p(t) \\
 \Rightarrow \frac{d(e^{k_2 t} C_1(t))}{dt} &= K_1 e^{k_2 t} C_p(t) \\
 \Rightarrow e^{k_2 t} C_1(t) &= K_1 \int_0^t e^{k_2 s} C_p(s) ds \\
 \Rightarrow C_1(t) &= K_1 \int_0^t e^{-k_2(t-s)} C_p(s) ds
 \end{aligned}$$

B.3 Solution of Two Compartmental Model Ordinary Differential Equation

Since $C_p(t)$ is assumed to be known, only equations involved C_1 and C_2 in equation 3.11

$$\begin{cases} \frac{dC_1}{dt} = K_1 C_p(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t) \\ \frac{dC_2}{dt} = k_3 C_1(t) - k_4 C_2(t) \end{cases} \quad (\text{B.3})$$

The coupled differential equation system can be solved using the Laplace transform as

$$\begin{cases} SC_1(S) = K_1 C_p(S) - (k_2 + k_3)C_1(S) + k_4 C_2(S) \\ SC_2(S) = k_3 C_1(S) - k_4 C_2(S) \end{cases} \quad (\text{B.4})$$

where $C_1(S)$, $C_2(S)$ and $C_p(S)$ are the Laplace transforms of $C_1(t)$, $C_2(t)$ and $C_p(t)$. We assume that the initial conditions in the tissue are zero; the set of equations can be solved as follows:

$$\begin{aligned} SC_2(S) &= k_3 C_1(S) - k_4 C_2(S) \Rightarrow C_2(S) = \frac{k_3 C_1(S)}{S + k_4} \\ SC_1(S) &= K_1 C_p(S) - (k_2 + k_3)C_1(S) + k_4 C_2(S) \\ &= K_1 C_p(S) - (k_2 + k_3)C_1(S) + k_4 \frac{k_3 C_1(S)}{S + k_4} \\ &\Rightarrow K_1 C_p(S) = (S + k_2 + k_3 - \frac{k_3 k_4}{S + k_4})C_1(S) \\ C_1(S) &= \frac{K_1(S + k_4)}{(S + k_2 + k_4)(S + k_4) - k_3 k_4} C_p(S) \\ &= \frac{K_1(S + k_4)}{S^2 + S(k_2 + k_3 + k_4) + k_2 k_4} C_p(S) \\ &= \frac{K_1(S + k_4)}{S^2 + S(\theta_1 + \theta_2) + \theta_1 \theta_2} C_p(S) \\ &= \frac{K_1(S + k_4)}{(S + \theta_1)(S + \theta_2)} C_p(S) \\ &= \frac{K_1}{\theta_2 - \theta_1} \left(\frac{k_4 - \theta_1}{S + \theta_1} + \frac{\theta_2 - k_4}{S + \theta_2} \right) C_p(S) \\ C_2(S) &= \frac{k_3 C_1(S)}{S + k_4} \\ &= \frac{K_1 k_3}{(S + \theta_1)(S + \theta_2)} C_p(S) \\ &= \frac{K_1 k_3}{\theta_2 - \theta_1} \left(\frac{1}{S + \theta_1} - \frac{1}{S + \theta_2} \right) C_p(S) \end{aligned}$$

where $\theta_1 = \frac{k_2 + k_3 + k_4 - \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2 k_4}}{2}$, $\theta_2 = \frac{k_2 + k_3 + k_4 + \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2 k_4}}{2}$,

$\theta_1 \theta_2 = k_2 k_4$ and $\theta_1 + \theta_2 = k_2 + k_3 + k_4$. Taking the inverse Laplace transform of $C_1(S)$ and $C_2(S)$ gives

$$\begin{cases} C_1(t) &= \frac{K_1}{\theta_2 - \theta_1} ((k_4 - \theta_1)e^{-\theta_1 t} + (\theta_2 - k_4)e^{-\theta_2 t}) \otimes C_p(t) \\ C_2(t) &= \frac{K_1 k_3}{\theta_2 - \theta_1} (e^{-\theta_1 t} - e^{-\theta_2 t}) \otimes C_p(t) \end{cases} \quad (\text{B.5})$$

Therefore, we have

$$C_T(t) = C_1(t) + C_2(t) = K_1(\phi_1 e^{-\theta_1 t} + \phi_2 e^{-\theta_2 t}) \otimes C_p(t) \quad (\text{B.6})$$

where $\phi_1 = \frac{k_4 - \theta_1 + k_3}{\theta_2 - \theta_1}$, $\phi_2 = \frac{\theta_2 - k_4 - k_3}{\theta_2 - \theta_1}$ and $\phi_1 + \phi_2 = 1$

Nomenclature

β^+	Positron
Δ	Delay
^{11}C	Carbon-11
^{13}N	Nitrogen-13
^{15}O	Oxygen-15
^{18}F	Fluorine-18
C_T	Tissue Activity
K_1	Overall Flow
K_b	Blood Flow
K_d	In-Distribution Flow
K_i	Flux
R	Residue Function
V_b	Blood Volume
V_d	In-Distribution Volume
1C	One Compartmental Model/Modeling

1D	One Dimension/Dimensional
2C	Two Compartmental Model/Modeling
2Ci	Two Irreversible Compartmental Model/Modeling
2Cr	Two Reversible Compartmental Model/Modeling
3D	Three Dimension/Dimensional
4D	Four Dimension/Dimensional
AIF	Arterial Input Function
CT	Computed Tomography
DGP	Data Generation Process
DNA	Deoxyribonucleic acid
EM	Expectation Maximization
FBP	Filtered Backprojection
FDG	Fluorodeoxyglucose
FDOPA	Fluorodopa
FLT	Fluorothymidine
FMISO	Fluoromisonidazole
FOV	Field of View
GE	General Electric
GLM	Generalized Linear Model
IDIF	Image-Derived Input Function

LAFOV Long Axial Field of View

MBIF Model-Based Input Function

ML Maximum Likelihood

MTT Mean Transit Time

NPRM Non-Parametric Residue Mapping

OLS Ordinary Least Square

OSEM Ordered Subset Expectation Maximization

PBIF Population-Based Input Function

PBPM Population-Based Projection Model

PET Positron Emission Tomography

RMSE Root Mean Square Error

ROI Region of Interest

RSS Residual Sum of Squares

SA Spectral Analysis

SD Standard Deviation

SE Standard Error

SUV Standardized Uptake Value

TAC Time Activity Curve

UCC University College Cork

WRSS Weighted Residual Sum of Squares

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