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Title	Agile optical confocal microscopy instrument architectures for high flexibility imaging
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Publication date	2004-07-13
Original Citation	Riza, N. A. and Bokhari, A. (2004) 'Agile optical confocal microscopy instrument architectures for high flexibility imaging', Proceedings of SPIE 5324, Three-Dimensional and Multidimensional Microscopy: Image Acquisition and Processing XI, 13 July 2004, (12 pp). doi: 10.1117/12.529073
Type of publication	Conference item
Link to publisher's version	10.1117/12.529073
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Agile optical confocal microscopy instrument architectures for high flexibility imaging

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ABSTRACT

Ideally, a no-moving parts fast and agile scanning confocal microscope system is required that can produce true real-time 3-D scans with precision and repeatability. In this paper, such agile optical confocal microsopy designs are proposed that enable high speed precise non-invasive 3-D imaging. These compact confocal microscopes can provide real-time pin-point focussed imaging to enable confocal slices in-vivo, thus greatly reducing motion artifacts. These microscopes can be modified into interferometric microscopes for phase contrast imaging. The proposed microscopes can also greatly improve confocal fluorescence imaging as needed for cancer detection. An ultracompact confocal probe tip connected to a single ultra-thin fiber is another design option allowing flexibility for usage in tight cavities.

Keywords: Confocal Microscopy, Fiber-optics, Instrument, 3-D Imaging

1. INTRODUCTION

Today, real-time confocal image formation is possible using a fast polygon scanner for 15.734 KHz line scanning and slower 60 Hz galvonometric scanner for y-axis (across lines) scan. Nevertheless, for implementation of axial scan these confocal microscopes use mechanical motion of the sample or the objective lens to get the different slices of the 3-D sample. Because biomedical applications work with ultra-small micron level depth resolutions over typically 500 microns total thickness, this implies generating up-to 500 axial slices, a very challenging task. Hence today's confocal microscopes use very costly precision translation stages to enable the axial imaging of the sample. Depending on the size of the objective or sample housing, axial data acquisition can become a slow process leading to limitations when the sample contains fast temporal effects such as flow patterns and neuronal or cellular activity. Ideally, a no-moving parts fast and agile scanning confocal microscope system is required that can produce true real-time 3-D scans with precision and repeatability.

In this paper, such agile optical confocal microsopy designs are proposed that enable high speed precise non-invasive 3-D imaging. These compact confocal microscopes can provide real-time pin-point focussed imaging to enable confocal slices in-vivo, thus greatly reducing motion artifacts. These microscopes can be modified into interferometric microscopes for phase contrast imaging. The proposed microscopes can also greatly improve confocal fluorescence imaging as needed for cancer detection. An ultracompact confocal probe tip connected to a single ultra-thin fiber is another design option allowing flexibility for usage in tight cavities.

In recent years, optical technology has shown great promise for in-vivo tomography and systems using both low coherence and high coherence light have been built and tested. One such example is Optical coherence tomography (OCT) systems relying on using small coherence relatively broadband (e.g., >10 % instantaneous bandwidth) light to

accomplish high resolution (1-100 microns) depth direction image slices from a test sample such as a tissue.[1-5] Here, the coherence gating effect is used to separate the coherent back scattered photons from the in-coherent photons to enable axial or depth direction imaging.

Another very important class of 3-D optical imaging instrument is the confocal optical microscope [6-8] that has been built using high temporal coherence laser light to form direct detection and interferometric 3-D imagers. In particular, confocal microscopy has the additional capability to enable and implement 3-D fluorescence imaging (that involves incoherent light generation) critical in applications linked to cancer detection. Today, real-time or video rate confocal image formation is possible using a fast polygon scanner for 15.734 KHz line scanning and slower 60 Hz galvonometric scanner for y-axis (across lines) scan.[9] Nevertheless, for implementation of axial scan these confocal microscopes use mechanical motion of the sample or the objective lens to get the different slices of the 3-D sample. Because biomedical applications work with ultra-small micron level depth resolutions over typically 500 microns total thickness, this implies generating up-to 500 axial slices, a very challenging task. Hence today's confocal microscopes use very costly precision translation stages to enable the axial imaging of the sample. Depending on the size of the objective or sample housing, axial data acquisition can become a slow process (due to mechanical inertia) leading to limitations when the sample contains fast temporal effects such as flow patterns and neuronal or cellular activity. Ideally, a no-moving parts fast and agile axial scanning confocal microscope system is required that can produce true real-time 3-D scans with precision and repeatability.

Based on these discussions, the field of biomedical optics can undergo a significant paradigm shift if it is simultaneously possible in real-time to provide biologically vital information on a depth direction image slice by slice basis in combination with a spatial point-by-point transverse basis. In addition, the new instrument's precision and repeatability in the depth direction can provide a rapid and reliable means to quickly access and study the appropriate parts of the sample without resorting to a full axial direction scan with enormous amounts of unwanted data for later processing. Thus, a smart agile z-scan confocal microscope is awaited in the biomedical community.

The purpose of this paper is to introduce a smart agile z-scan confocal microscopy probe system for biomedical applications that for the first time, to the best of our knowledge, can provide the mentioned revolutionary paradigm shift in biological sample z-scan data acquisition via its unique no-moving parts precise and repeatable z-scanning method. The proposed optical innovation can be applied across various prior-art confocal microscope designs using an ultracompact agile z-scanning optic for operation with generic in-vivo confocal probes for any disease and organ with both internal and external operating conditions. With the suggested z-scan confocal optic, one can expect in real-time, a thousand depth or axial scan image slices produced via a thousand agile focal point optic, leading to an unprecedented biological database for further electronic processing via software. Because the instrument's basic smart design involves the unique yet simple and easy to incorporate or deploy z-scan smart optic, these next generation confocal microscopes can be generic, compact, and fast, with use in a wide variety of commercial applications such as but not limited to stimulated neuron imaging, blood flow measurements, intracavity imaging, cancer tumor detection,[10] retinal imaging,[11] skin mapping, and diabetes diagnostics.

Much research and development has taken place on electronically programmable optical beam control devices. The proposed concept on confocal microscopy is based on our prior research expertise in the mentioned optical beamforming devices, in particular, liquid crystal (LC) based devices. For example, LC-based optical devices have been developed for applications that include antenna controls,[12] data retrieval,[13] fiber telecommunications switching,[14] and 3-D scanning.[15-16] More recently, demonstrations of fast switching LC-based optical scanner technology has taken place for long range (> 1 km) infrared (IR) laser communications.[17] In contrast to laser communications, the focus of this paper is to propose an agile z-scan confocal optical microscopy probe for biomedical applications where short sample depth optical beam access (e.g., < 1 mm) and microscopic transverse zones (e.g., < 1 mm x 1 mm) are required. In addition, both visible spectrum and NIR instrument designs have to be realized for the biomedical arena. Hence, for the first time, agile LC thin lens scan optics will be combined with classic confocal microscopy optics designed specifically for the biomedical arena to realize true 3-D confocal fast real-time imaging.[18] Previously, non-mechanical means for axial scanning have been suggested such as using a broadband source and a highly chromatic objective lens[19-21] or the use of adaptive mirror switching to calculate the axial height via a genetic algorithm.[22] In general, adaptive optics have been used to correct for off-axis aberrations in an x-y optical scanning confocal microscope.[23]

2. PRINCIPLES OF THE AGILE Z-SCAN CONFOCAL OPTICAL MICROSCOPE

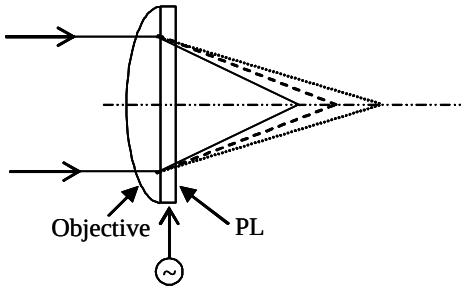


Fig.1 Operation of the smart lens optic that is critical for realization of the precision variable focal length optics used to enable agile z-scans in confocal microscopes. The smart optic consists of a fixed focal length objective cascaded with an electrically programmable thin lens PL.

Fig.1 shows the principles of the smart optic used to realize the proposed agile z-scan confocal optical microscope. Recall that confocal microscopy generally works with precise (e.g., 1 micron) z-axis scans over a short (e.g., 100 microns) distance. Hence, in traditional confocal microscopy, the sample or objective lens is moved by say 100 microns in one micron steps. In this paper is proposed the use of a variable focus objective optic for confocal microscopy. The principles of this smart optics is shown in Fig.1 and the optic consists of a fixed focal length objective cascaded with an electrically programmable thin lens called PL. In effect, the combination lens system via the "thin lens formula" gives a combined power that is the sum of the powers in Diopters of the two lenses. A Diopter is given by the inverse of the lens focal length in meters. If the focal length of the objective lens is known, which is the case for confocal microscopes, given a desired change in combined focal length, the required power of the programmable thin lens can be calculated. The thin-lens combination principle when applied with a strong focus power microscope objective lens is the key idea proposed in this paper. Liquid Crystal (LC) and Deformable Mirror (DM) technologies are key thin lens technologies that can achieve the proposed goals.

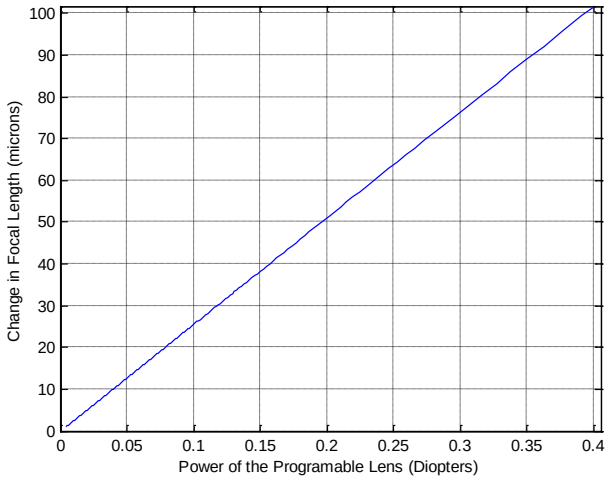


Fig.2 showing the change in focal length of the smart agile confocal optic in Fig.1 versus the electrically programmed power in Diopters of the thin lens. The plot assumes a 16 mm focal length objective lens.

Fig.2 assumes a 16 mm focal length objective and calculates the Dioptric power of the thin lens required to enable a change in the proposed combined two lens system focal length from 16 mm to 15.9 mm, a change in -100 microns. The interesting result of this analysis is that only a weak thin lens of a maximum 0.4 Diopters (or a focal length of 2.5 m) is required to form the programmable thin lens such as required for the agile confocal microscope.

Prior work in LC lenses show that LC lenses can be electronically programmed to form variable focal length lenses. Much of the work on LC lenses has focused on enabling high Dioptric power LC lenses for applications such as fiber-optic switching and optical data reading. This paper on the contrary takes advantage of the so called limitation of LC lenses, namely, their weak Dioptric power. Specifically, because in the confocal microscopy application where such fine z-scan control is required over very short distances, the exact need is for a weak lens as shown by the smart-optic z-scan design in Fig.1. Hence, this paper proposes the use of the smart z-scan optic as the new objective lens in all prior and to be proposed confocal microscopy systems.

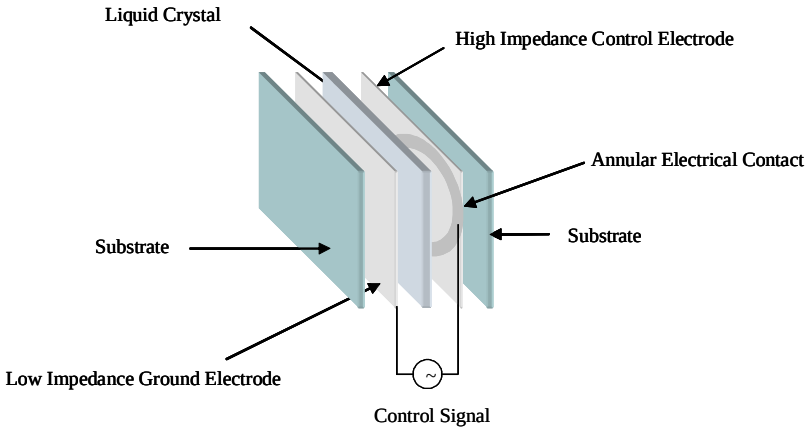


Fig.3 Sample LC lens design used to realize the agile PL lens.

Today, LC lens designs such as being tested at Nuonics (see Fig.3; Lens design by TU Delft.) have many useful properties that make them ideal for use in the proposed smart-optic. First, LC cells by nature are thin cells where the entire LC lens cell thickness is under 2 mm. Second, because the cells use thin (e.g. 50 micron) LC layer, the power to run these devices runs into nano-Watts. Next, LC cells can be fabricated with large apertures, such as between 1 to 3 cm, matching the fixed objectives in confocal microscopes. Finally, for real-time z-scan operations, one 2-D image slice is produced every 1/30 seconds (or 1/60 seconds with line interlacing). Hence the LC lens device requires electronic resetting at a tens of milliseconds rate that is compatible with high birefringence nematic LC materials. Note that the devices in Fig.3 operate with linearly polarized light. In case light of an un-known polarization is used, two LC devices with crossed nematic directors can be used in cascade to make a polarization independent electronically programmable lens.

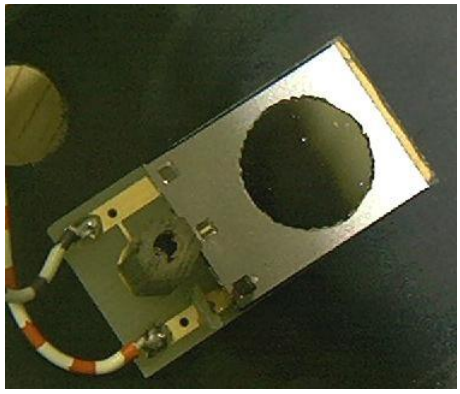


Fig.4 Shown is a deformable mirror (DM) based electrically programmable lens. Device fabricated at TU Delft-Holland.

Another alternative for the LC weak lens is a deformable mirror-based lens, as shown in Fig.4. The advantage of the DM is that it is intrinsically broadband in operations and is polarization independent. It should be pointed out that although LC lenses are wavelength sensitive, many confocal microscopes operate for a given laser wavelength or a narrow

wavelength band. Moreover, since the LC lenses operate in weak lensing modes, the wavelength dependence of the net birefringence and phase shift is minimized to produce minimal focal position errors. An important point to note with the proposed weak lens designs is their non-pixelation nature, thus eliminating pixelation diffraction and fill factor effects. Because both LC and DM weak lenses can be made as single large aperture devices, the optical quality of the objective lens imaging optics in the confocal microscope can be preserved, a must for high fidelity 3-D imaging. In particular, LC devices are flat glass plate high optical quality devices that can be placed in tight contact with the objective optics to form overall high beam quality z-scan confocal microscopy optics. Another LC device that can be used for the proposed application is the Hamamatsu optically addressed LC spatial light modulator (SLM).

3. DESIGNS OF THE AGILE Z-SCAN CONFOCAL OPTICAL MICROSCOPE

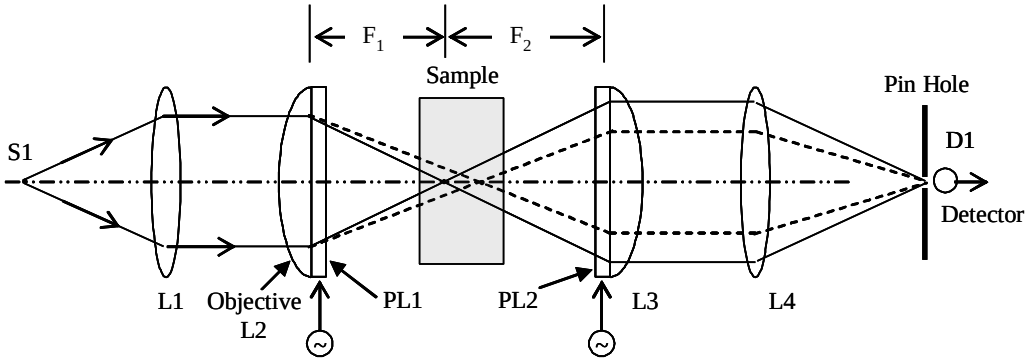


Fig.5 shows the basic transmissive agile z-scan confocal microscope.

There are various designs possible for the Nuonics Agile z-scan confocal microscope. This section highlights some of these designs operating with various probing conditions and optical hardware. Fig.5 shows the basic transmissive agile z-scan confocal microscope where two agile lens units in cascade are used to track the focal plane in the sample. Hence, when PL1's focal length decreases, PL2's focal length increases to maintain the point sampling and point detection condition.

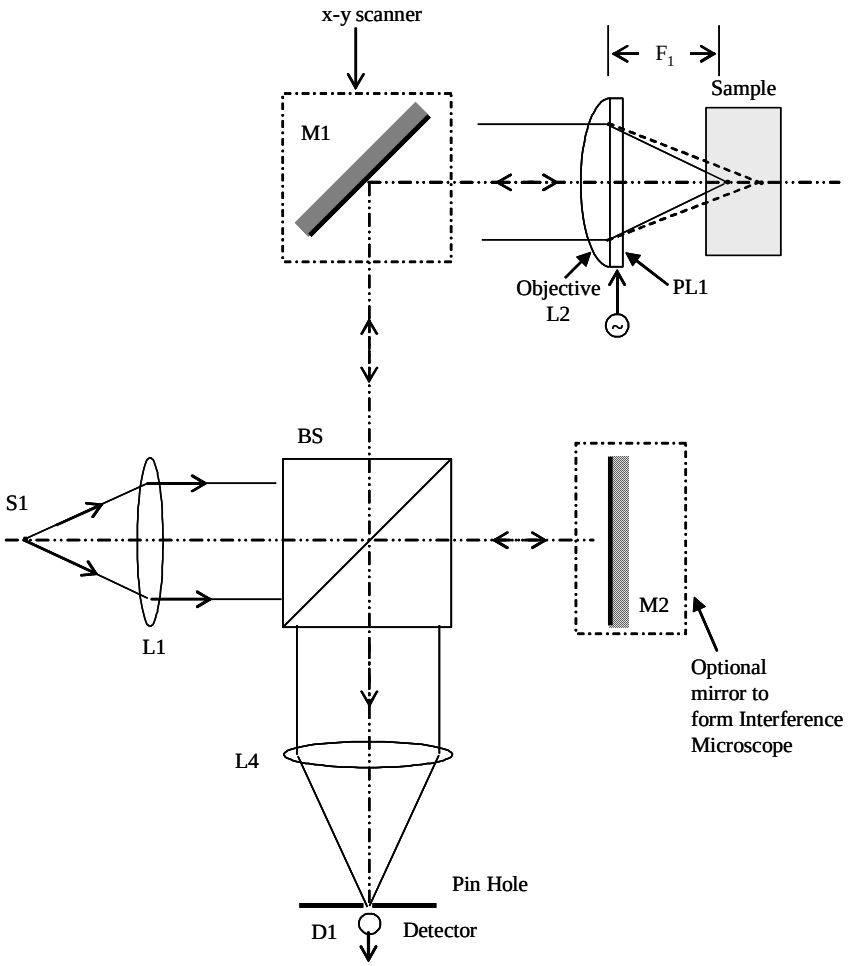


Fig.6 shows the basic reflective agile x/y and z-scan confocal microscope. BS: Beam Splitter; S1: Point source; L's: Spherical lenses; M: Mirrors.

Fig.6 shows the basic reflective agile x-y-z-scan confocal microscope that uses one PL agile lens unit. X-Y scanning is done by a two axis mirror, although any other x-y scan hardware can be used. The set-up shows an optional mirror M2 that can be inserted to form an interferometric confocal microscope such as for phase-based imaging.

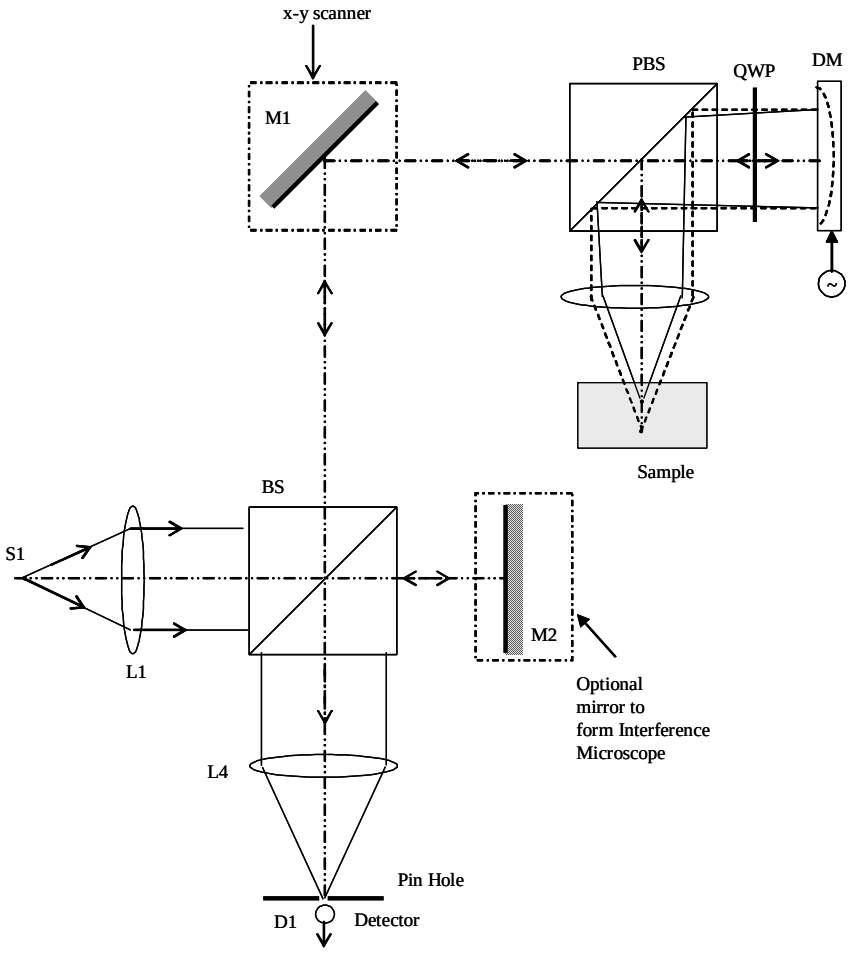


Fig.7 shows a reflective agile x-y-z-scan confocal microscope deploying a Deformable mirror to form a reflective agile lens unit. QWP: Quarter-wave plate; PBS: Polarizing BS.

Fig.7 shows a reflective agile x-y-z-scan confocal microscope similar to Fig.6 except that the Fig.7 microscope uses a PL agile lens unit based on an electrically controlled deformable mirror DM. This design gives a large optical bandwidth of operation versus an LC lens-based microscope.

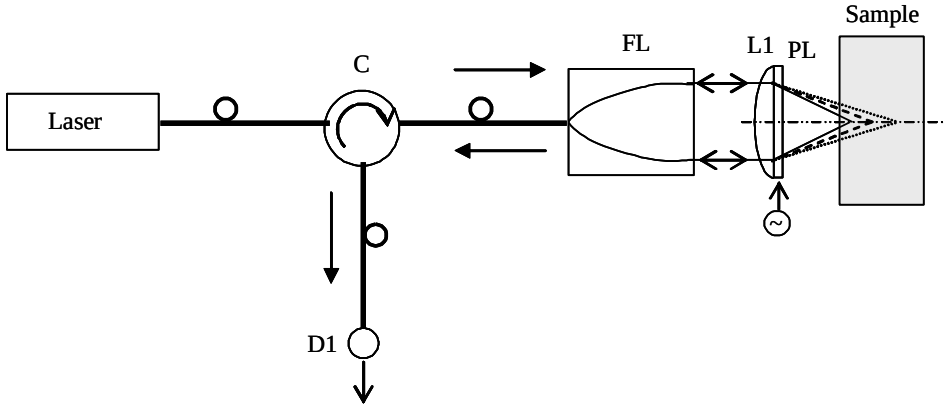


Fig.8 shows a reflective agile z-scan confocal microscope deploying a LC lens with ultra-compact fiber-optics to form a miniature z-scan imaging unit. FL: Fiber Lens (such as a microlens). L1: Objective lens.

Fig.8 shows a reflective agile z-scan confocal microscope that uses optical fibers to form a flexible and compact microscopic probe with z-scan imaging capability via an PL agile lens unit based on an electrically controlled LC lens. This design gives microscope motion and placement flexibility. The optical circulator C acts as a three port isolation device to separate the transmit and receive optical imaging signals.

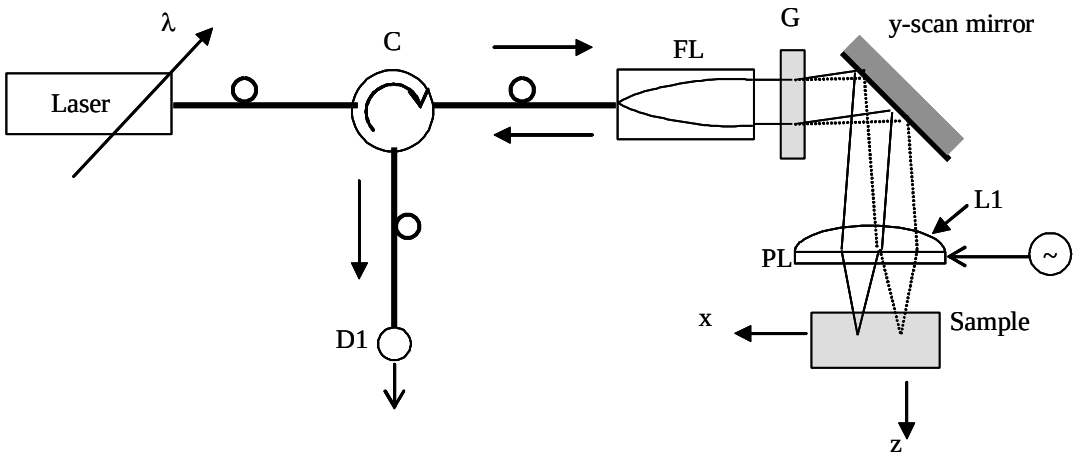


Fig.9 shows a novel reflective agile x-y-z-scan confocal microscope deploying ultra-compact fiber-optics to form a miniature 3-D scan imaging unit.

Fig.9 shows a reflective agile x-y-z-scan confocal microscope that is similar to the Fig.8 microscope except the Fig.9 system provides y-scan via a one-axis tilt micromirror and x-scan via wavelength scanning of the laser coupling with the grating G dispersive optics in the probe frontend.[24-32] The power of this microscope lies in its ultra-compact design to enable 3-D scan confocal microscopy. Again, an LC lens is used to form the agile z-scan unit.

The proposed agile thin-lens concept for the single fiber fed confocal microscope can be extended to a multi-fiber [33-34] design where two dimensional scanning is implemented via selection of optically active fibers. In this case, a 2-D N-element LC lens array can be used to match the N fibers with their N collimators and N objective lenses. Fiber selection can be done via a 1xN fiber-optic switch or a spatial light modulator such as a DMD. On the other hand, a multi-fiber cable (without fiber collimators) can be used as an input to a two lens imaging system, where the second lens, i.e., the microscope objective near the sample is sandwiched with the LC thin lens to enable motion of the focus plane or z-scan imaging. It is also possible to envison wavelength tuned-based scanning (like Fig.9) incorporated into these fiber bundle-based scanning confocal microscopes.

4Pi confocal microscopy has been shown to be a very valuable technique leading to improved axial resolution confocal microscopy, in particular for fluorescent imaging.[35] 4Pi confocal microscopy relies on equal path length interference of two counter-propagating light waves launched via two opposing microscope objectives whose focal points must coincide in the same z-axis plane. From a practical point of view, this matching of focal points requires ultra-precise and costly motion controls for the two objective lenses. In addition, to generate constructive interference in the sample, both beams must be in phase and thus precise motion of a mirror is used to equalize paths modulo-2π.

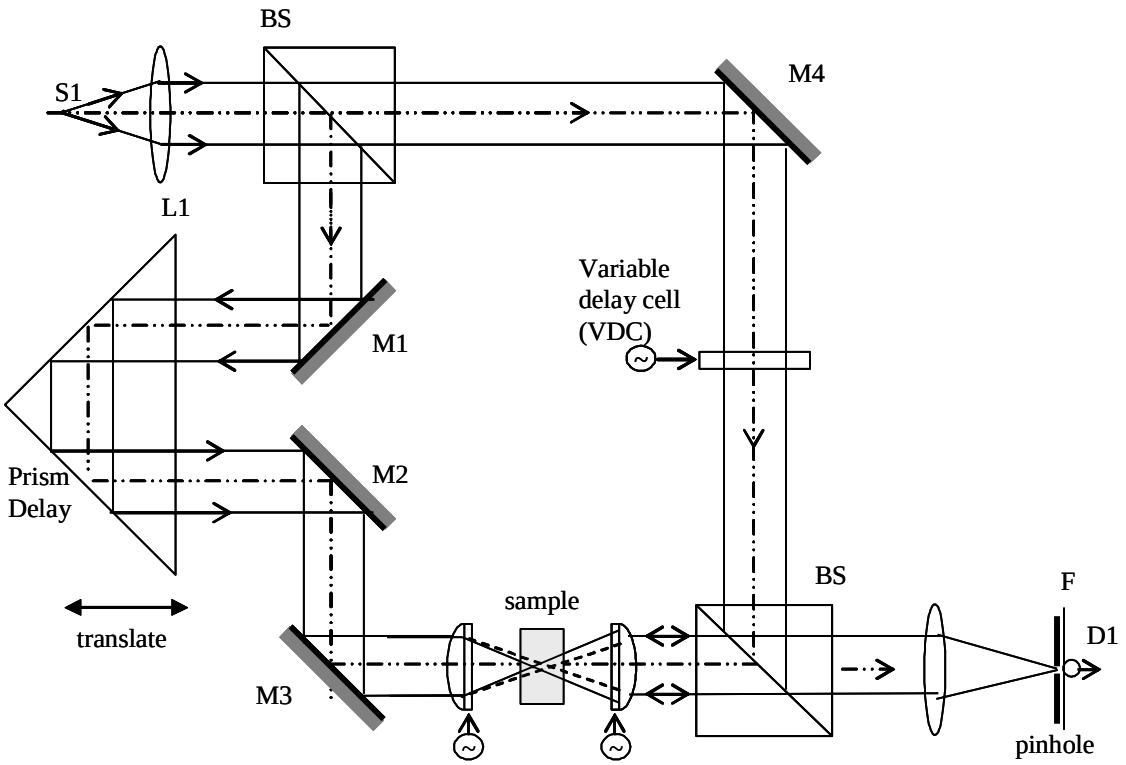


Fig.10 The proposed agile 4Pi confocal microscope that uses two agile lens units and one agile phase delay unit to form a precision, fast, no-moving parts z-scan microscope.

Fig.10 shows how the Nuonics agile z-scan unit can be deployed to implement 4Pi confocal microscopy using a freespace optics design. The Fig.10 design eliminates the need for both precise objective lens control and mirror motion. In effect, precise dual focal point positioning for both objectives is accomplished via the two LC lenses and the fine optical delay is implemented via a nematic LC phase cell called the Variable Delay Cell (VDC). Previously, Riza et.al. have proposed and used LC cells to form precise variable optical delay lines for antenna control applications.[36-37] Here, the same technology is adapted to form ultra-precise optical phase delays with 1/1000 of a wavelength precision in the near infrared and visible bands. Typically, a 10 micron thickness nematic LC cell can give 4Pi phase shift dynamic range at the mentioned wavelengths that are also appropriate for confocal microscopy. Note that these proposed 4Pi agile microscopes work with linearly polarized light when using nematic LC devices. Also note that a prism delay via mechanical translation is used to coarsely equalize the two light paths.

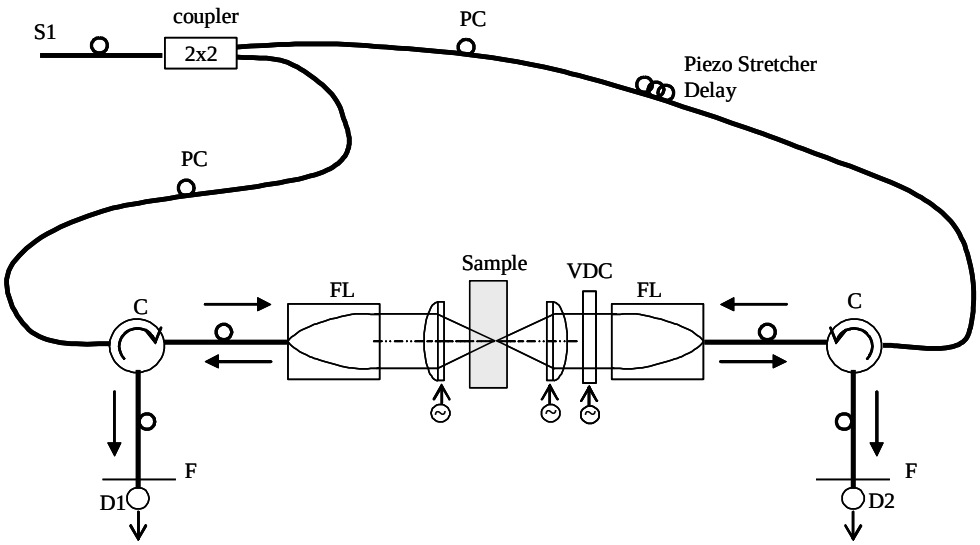


Fig.11 The fiber version of the proposed agile 4Pi confocal microscope that uses two agile lens units and one agile phase delay unit to form a precision, fast, no-moving parts z-scan microscope.

Fig.11 shows a fiber-based implementation of the proposed agile 4Pi microscope that uses two fiber Polarization Controllers (PCs), one piezo-fiber stretcher delay device for coase delay control, one nematic LC VDC for fine optical phase control, two fluorescence filters F, among other components described earlier. Note that this microscope has two output detection ports that can provide capabilities for advanced signal processing.

4. CONCLUSION

In conclusion, the basic features of the proposed agile z-scan confocal optical microscope are**:**

- High Speed
  The ability to switch objective lens focus control at video rates allows real-time generation of 2-D confocal image slices that combine to produce a full 3-D image map data. The agile z-scan features allows mapping of rapidly varying in time electrically/chemically triggered biological effects. In addition, Doppler effects can be sampled to examine sample temporal behavior. In short, super speed oversampling in the z-scan confocal direction is possible leading to highly accurate sampled data.
- Precision Focal Control
  The ability to precisely and smoothly control via an electrical signal the focal length of the PL lens allows smart probing of the biological sample for optimum optical spatial response. If needed, a given focal zone can be oversampled or jumped to produce the desired optical response from the biological sample. This feature is very useful for agile 4Pi confocal microscopy.
- No Moving Parts Z-scan Capability
  As an LC lens based agile objective lens confocal z-scan unit deploys no moving parts, confocal scanning at the probe tip is done without mechanically perturbing the sample, thus not launching any compression or expansion waves that can alter the real spatial nature of the microscopic biological bodies in the sample. Hence, the proposed Nuonics microscope forms a true non-invasive probe. In addition, no moving parts within the front-end microscope head improves instrument long term reliability. If the deformable mirror is used, the fact that a very weak lens is required also implies very small mechanical perturbation unlike prior art where the whole objective is moved or the complete sample is moved.
- Compact Low Power Consumption Packaging Options
  The proposed microscope allows fiber-optic designs that are effective for internal optical access applications such as intracavity and endoscopic applications where flexible and small probes are required. Because both the LC lens and DM lens are low power consumption devices, efficient probes can be realized.

- Amenable to both In-Coherent and Coherent Designs
  Both low cost incoherent detection and higher sensitivity coherent optical detection can be achieved with the basic proposed agile confocal microscope designs. This gives added flexibility to the biomedical user. In addition, agile 4Pi confocal microscopy can be realized.
- Amenable to Multi-Fiber Designs
  Multi-fiber cables can be used with the proposed agile z-scan designs to provide a 2-D scanning option.
- Amenable to Use of SLM Adaptive Optics for Aberration Correction
- Can use Thin Stack P-MOS [38] Scanner to realize 3-D No-Moving parts fast (microsec) Confocal Microscope.

Future work relates to the experimental verification of the proposed concepts.

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