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OPTICAL COHERENCE TOMOGRAPHY IN ONCOLOGICAL IMAGING*

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Abstract. The Optical Coherence Tomography (OCT) is an emerging imaging technique with applications in medicine and biomedical optics. OCT is capable of analyzing internal localized microstructures and obtaining high-resolution cross-sectional images by backscattered light echo analyze. With resolutions of 1-15 μm, one or two orders of magnitude finer than conventional ultrasound, the OCT is improving the small body imaging techniques.

The OCT is mostly a near infrared based analysis technique. The design of OCT systems is based on a *Michelson interferometer* coupled with a low coherence light source. One arm of the interferometer emits a directed beam scanning the sample. OCT imaging engines usually employ time domain detection using a reference delay arm in order to perform the interferometry. The development of high speed diffraction grating scanners enabled OCT systems to achieve imaging speeds of several thousand axial scans per second and also video rate imaging. A generic OCT system uses a circulator to collect phase interference signals. By subtracting the signals, the desired interference signal adds and excess noise from the light source gets cancelled. This configuration is nominated as dual balanced detection and is used in coherent optical communications systems.

Considering its ability to in vivo analyze and its capacity to obtaining cross-sectional images, the OCT system can be implemented as a tool used to improve the surgical gesture during tumor removal surgeries. In order to obtain the best results, the OCT needs to be improved with a simple spectroscopic device.

Key words: optical coherence tomography, medical imaging, oncology.

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1. INTRODUCTION

Cancer is acknowledged worldwide as one of the leading diseases with respect to the total number of fatalities. The high percentages of fatalities recorded for cancer are mostly caused by late diagnosis. Up to this day the techniques used to diagnose cancer are the Alpha-fetoprotein (AFP) blood test [1], biopsy and various medical imaging tests. In terms of resolution, Magnetic Resonance Imaging (MRI), Computer Tomographies (CT) and Positron Emission Tomographies-Computed Tomographies (PET-CT) techniques are vastly used because of their capacity to image large portions of the body, but speaking of imaging techniques capable of imaging small body parts we can relate mostly to Ultrasound Imaging (US) and recently, the Optical Coherence Tomography (OCT) started to be acknowledged as a medical imaging technique.

The development of OCT started from the need for in-vivo ocular eye measurements. Taking the white light interferometry as a starting point, multiple investigations were performed by various groups [13, 14] in order to obtain a complete image of the biological tissue of the human eye. Fercher *et al.* [15] was the first to depict in vivo images of the human eye fundus whose recording was based on light interferometric depth scans, back in 1990. His work was continued by Naohiro Tanno [16, 17] and finalized in 1991 by Huang *et al.* [6] who succeeded in recording in vitro images of the human peripapillary region of the retina and also of the coronary arteries. After his work, OCT with micrometer resolution and cross-sectional imaging capabilities became a prominent biomedical tissue-imaging technique. Even if Huang *et al.* have proven that the OCT may be used for applications other than in ophthalmology, this technique was considered to be particularly suited for ophthalmologic applications. Up until recent the OCT wasn't taken into consideration for other tissue imaging applications that require micrometer resolution, especially because its poor penetration, which is in the order of a few millimeters [18]. Since the introduction of fiber optics the OCT became a suitable tool for morphological tissue imaging [7], taking into consideration that the other imaging techniques available, Magnetic Resonance Imaging and Medical Ultrasonography are not suited due to lacks in image resolution.

Generally, a tomographic technique is based on the cross-sectional reconstruction of the sample image using its projections. Considering the fact that the theoretical base for this method was early established, its implementation in medicine was slow and a great number of configurations were proposed, each differing with the properties of the various radiations used [11]. This is why the signification of the term tomography lost its restrictions and it's currently being used whenever 2D data recorded from 3D objects in order to obtain a slice image of the internal analyzed sample. Nowadays in tomography, three basic principles used by two tomographic techniques exist. More precisely straight ray tomography,

diffraction tomography or time-resolved tomography can be used in Diffuse Optical Tomography (DOT) or Optical Diffraction Tomography (ODT) to obtain an optic tomography [12]. The OCT uses the physical principles of ODT.

The OCT technique borrows its principle from Ultrasound Imaging. As stated by its name, the Ultrasound Imaging uses ultrasounds to obtain images of the studied samples. In this kind of imaging technique, called straight ray reflection, the transit times of various types of waves are measured and used alongside with depth positions of reflecting sites in the studied sample. For Ultrasound Imaging the propagating waves travel slowly enough so that transit times can be measured using purely electronic means. In optics, including here the OCT, techniques such as photon density waves, femtosecond impulses and coherence techniques need to be used [10]. The OCT technique uses the reflected straight rays to scan in vivo samples. Considering their basic principles, Ultrasound Imaging and OCT are largely considered to be two analogous imaging or tomographic techniques [2]. Both imaging techniques, due to their use of sound and light, are characterized by noncontact and a strongly noninvasive character capable of providing the user with high-resolution images.

2. INFORMATION CONTENT OF OPTICAL COHERENCE TOMOGRAPHY

The OCT is thought to be an emerging imaging technique with applications in medicine and biomedical optics being capable of analyzing internal localized microstructures and obtaining high-resolution cross-sectional images by backscattered light echo analyze [3]. With resolutions of 1-15 μm, one or two orders of magnitude finer than conventional ultrasound, the OCT represents a solid candidate for improving the small body imaging techniques. By providing also cross-sectional imaging at a cellular level, the OCT is considered to be a promising technique, capable of imaging successfully the limit healthy/tumoral tissue for oncology and medical imaging.

2.1. THE OPTICAL COHERENCE TOMOGRAPHY TECHNIQUE

The OCT is capable of recording cross-sectional images of the sample through the use of magnitude and echo time delay measurements of the backscattered light. Firstly used by Huang *et al.* for ophthalmological and cardiac imaging [6], the OCT is mostly a near infrared based analysis technique. Usually the design of OCT systems, depicted in Figure 1, is based on a Michelson interferometer. For this system, a low coherence light source is coupled into the interferometer [5]. The coupler is assumed to split the incident optical power in an unbalanced manner, usually 80% to sample and 20% to reference [20, 21]. The light exiting the reference arm is incident upon a delay and returned to the

computational device through the same arm. The light exiting the sample arm is incident upon a scanning device capable of focusing the beam on the studied sample and scan it in one or two lateral directions as commanded by the computational device. The backscattered light returning from the studied sample is redirected through the sample arm into the same coupler system where it is mixed with the returning reference light and the combined light is made to interfere on the surface of a photodetector, usually a charged couple device (CCD). The electronic signals detected by the CCD are processed by the computational device into A-scans, which represent the depth resolved reflectivity profile of the sample at the focal spot of the sample beam at a fixed lateral position. As the sample beam steps its scanning position across the studied sample, multiple A-scans are recorded and assembled by the computational device into a cross-sectional 2D image of the studied sample. This image is generally known as a B-scan. Various combinations of multi-dimensional lateral scans and A-scans recordings are possible to obtain images as a function of time of the same studied sample, termed as M-scans; B-scans with lateral rather than depth priority, 3D OCT volume datasets and image from OCT signal averaging in various combinations of dimensions.

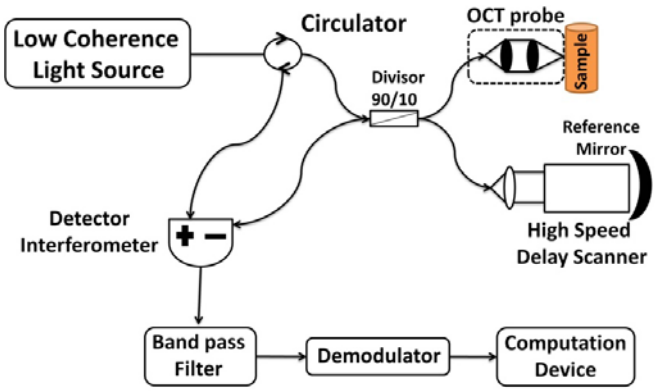

Fig. 1 – Fiber optic Michelson interferometer based OCT system.

Various setups exist for the OCT, in the case of Time-Domain OCT (TDOCT), the low coherence light source depicted in Fig. 1 is a broadband and a continuous-wave. The reference arm delay is scanned repetitively in length and the required signal processing consists of detecting the envelope of the detected fringe burst pattern corresponding to interference between the reference arm light and each successive scattering site in the sample. Fourier-Domain OCT system (FDOCT) setups represent a class of OCTs subdivided in Spectral-Domain (or spectrometer based OCT, SDOCT) and Swept-Source OCT (SSOCT). For the SDOCT, the source is represented by a continuous-wave and a broadband, the reference arm's length is fixed at a position that corresponds to the studied sample and the spectral interference pattern between the reference and the sample lights is

firstly being dispersed by a spectrometer and collected simultaneously by a CCD. For the case of SSOCT, the reference arm is also fixed and the light source allows instantaneous linewidth but is swept in wavelength and the spectral interference pattern is detected on a photoreceiver as a function of time. In FDOCT the spectral interference pattern encodes in its frequency the entire depth-resolved structure of the sample at the focal spot's position and A-scans may be recovered using an inverse Fourier transform.

2.2. LATERAL RESOLUTION IN OPTICAL COHERENCE TOMOGRAPHY SYSTEMS

Some previous analyses described the lateral resolution and axial field of view of OCT systems as depicted in Fig. 1 as the spot size and depth of focus of an assumed Gaussian profile sample arm beam [22–24]. This represents a reasonable approach, however it is more correct to treat the OCT's sample arm as a reflection-mode scanning confocal microscope, in which the aperture is represented by the singlemode optical fiber used for both studied sample's illumination and information collection. Confocal microscopes that use fiber optics for delivery and detection have previously been described by the literature [25–27]. In the case of singlemode fiber optics used by the OCT systems the mathematical expressions for lateral and axial detected intensity are similar to those for an ideal confocal microscope. It is well described how and why the confocal microscopes possess an improved lateral resolution over conventional black-field microscopes and this has been passed to OCT units as well. A short and comprehensive summary of the results characterizing the quantities in lateral and axial directions are presented in Fig. 2. The optical system is presumed to be cylindrically symmetric and so only one lateral dimension is described.

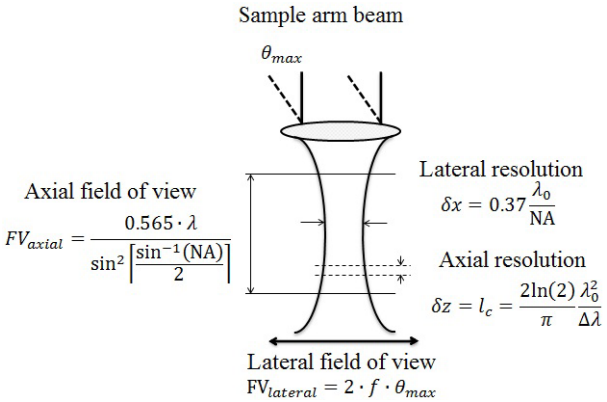

Fig. 2 – Schematic view over the sample arm of a general OCT system. Formulas depicted are assumed for axial field of view FVaxial and lateral resolution δ_x (quantities dominated by confocal geometrical optics), axial resolution δ_y (limited by the low-coherence interferometer) and lateral field of view FVlateral (for a simple scanning system).

Only one lateral dimension will be described, assuming that the optical system is cylindrically symmetric.

An expression for the detected intensity from a reflector point in an ideal reflection confocal microscope's focal plane given as a function of lateral position is given by:

$$I(v) = \left(\frac{2J_1(v)}{v}\right)^4, \tag{1}$$

where $J_1(v)$ is a Bressel function and v is the normalized lateral range parameter defined by $v=2\pi x\sin(\alpha)/\lambda_0$. In the previous expression x represents the lateral distance from the optical axis, α represents half of the angular optical aperture subtended by the objective, while λ_0 represents the center wavelength of the light source. Assuming the objective is ideal, its numerical aperture is given by $NA=\sin(\alpha)$. If the equation 1 expresses the lateral point-spread function of an OCT system at the position of its focal plane and this function is characterized by its lateral resolution δx, than the lateral resolution can be expressed by

$$\delta x = 0.37\frac{\lambda_0}{\sin(\alpha)} = 0.37\frac{\lambda_0}{NA}. \tag{2}$$

Considering the fact that the FO of an OCT unit depends upon the details of the employed lateral scanning system, a simple scanning system employing the means to rotate the sample arm may be needed in order to ensure a maximum one-sided scan angle θ_{max}, in which case the lateral field of view will be given by $FV=2f\theta_{max}$.

2.3. AXIAL RANGING IN OPTICAL COHERENCE TOMOGRAPHY

The reason that OCT is not considered to be a microscopy mode is that the predominant axial component of image formation derives from a ranging measurement performed using low-coherence interferometry (LCI). If we consider a classic Michelson interferometer depicted in Fig. 3 illuminated by a polychromatic plane wave whose electric field can be expressed as

$$E_i = s(k,\omega)e^{i(kz-\omega t)}, \tag{3}$$

where $s(k,\omega)$ is the electric field amplitude as a function of the wavenumber $k=2\pi/\lambda$ and the angular frequency $\omega=2\pi\nu$, which are respectively the spatial and temporal frequencies of each spectral component of the field having the wavelength λ. The index of refraction $n(\lambda)$ and the speed of light in dispersive media ($c/n(\lambda)=\lambda\nu$) couple the wavelength λ and the frequency ν, because this index is wavelength dependent in dispersive media. For this case, the coupler is assumed to have a wavelength independent, or achromatic, power splitting ratio of minimum 0.5 (although most OCT systems use a splitting ratio of 0.8 –sample– to 0.2 –

reference–). The reference mirror is assumed to have the electric field reflectivity r_R while the reflectivity's power is expressed by $R_R=|r_R|^2$, also the distance between the coupler and the mirror is expressed as z_R.

The studied sample is characterized by its depth-dependent electric field reflectivity profile along the sample axis $r_S(z_S)$, where z_S represents the pathlength of the sample arm. The sample axis expression, $r_S(z_S)$, is considered to be continuous, but can also be complex. Assuming a series of N discrete, real function reflections of the form $r_S(z_S) = \sum_{n=1}^{N} r_{Sn}\delta(z_S - z_{Sn})$ where each reflection is characterized by its reflectivity (r_{Sn}) and pathlength from the coupler to sample (z_{Sn}). The power reflectivity of each reflector is given by the magnitude squared of the electric field reflectivity, $R_{Sn}=|r_{Sn}|^2$. Here, the mathematical reconstruction of the $\sqrt{R_S(z_S)}$ function using noninvasive interferometric measurements represents the main goal of the LCI in OCT.

Using the above, the electric field passing through the coupler after returning from the sample arm can be expressed using the following formula

$$E_S = \frac{E_i}{\sqrt{2}}\left[r_S(z_S) \otimes e^{i2kz_S}\right], \tag{4}$$

where $\otimes$ represents the operation of convolution, and the factor 2 in the exponential kernel accounts for the round trip of the wave [20–22].

For the case of discrete reflections, which are very usual considering the nature of the disperse media represented by the human body, the fields incident on the coupler after returning from the reference mirror and the sample are expressed by:

$$E_R = \frac{E_i}{\sqrt{2}} r_R e^{i2kz_R}, \tag{5}$$

$$E_S = \frac{E_i}{\sqrt{2}} \sum_{n=1}^{N} r_{Sn} e^{i2kz_n}. \tag{6}$$

The powers corresponding to these waves are significantly lower as compared to the initial waves, due to various physical effects, and passing through the coupler they interfere at the square-law detector, which generates a photocurrent proportional to the square of the fields' sum incident upon it. This photocurrent is expressed by the following formula:

$$I_D(k,\omega) = \frac{\rho}{2}\langle|E_R + E_S|^2\rangle = \frac{\rho}{2}\langle(E_R + E_S)(E_R + E_S)^*\rangle, \tag{7}$$

where ρ represents the responsivity of the detector (units A/W), the factor 2 reflects the second pass of each field and the angular brackets denote integration over the response time of the detector.

In optics, many approaches using straight rays including here the time resolved techniques neglect the physical phenomena of diffraction. Hence these structures are not comparable to a wavelength or smaller. Even so, through the use

of the Fourier diffraction theorem [19] and a short analysis of diffraction tomography

2.4. TISSUE PENETRATION OF OPTICAL COHERENCE TOMOGRAPHY

The tissue penetration is considered to be one of the OCT's biggest disadvantages, as due to the physical effects encountered at and after the light/tissue interface the power of the beam is significantly decreased.

In order to be successfully implemented in oncological imaging, the OCT needs to be capable of biological tissue imaging at depths reached by Ultrasound Imaging. But the biological tissue provides a rather turbid media that necessitates the use of special techniques in order to reach reasonable depths. The main problem raised by OCT's penetration is that the intensity distribution of the objects "seen" by the light wave is significantly disturbed because the photons are deviated from their straight trajectory.

A series of physical phenomenas are responsible for this scattering and all of them are caused by various inhomogeneities such as cell membranes or intracellular structures. This scattering is caused by a relative refractive index mismatch at the boundaries between these structures, one example can be given by the interface between the cell membrane and the extracellular fluid existing in the human body.

Figure 3 depicts a generalized cell (Marieb, 1995) representing mostly the basic components found in many human cells, but of no one cell type in particular. Human cells may vary greatly in size or form, can take sizes from approximately 4 μm to cells as long as a meter in length. However, all human cells consist of these three main components: the nucleus, the membrane, and the cytoplasm. The outer boundary of the cell or its membrane is made up of a phospholipid bilayer, and in terms of dimensions it has approximately 8 nm in thickness, with numerous proteins embedded in it. The cell's cytoplasm represents the intracellular matrix contained within the outer boundary. It is composed of cytosol, a water-based fluid within which the other constituents are suspended, the organelles, each of which have a special function in the cell mechanism, and non-functioning units known as inclusions, which include lipid droplets in fat cells and melanin granules in certain skin cells. The human cells receive their energy supply from organelles called mitochondria, the number of which reflects a cell's need for energy. The mitochondria, approximately 1–4 μm by 0.3–0.5 μm in size (Palade, 1972), are surrounded by a double layer of membrane similar to the outer cell membrane. The nucleus is the largest organelle in the cell and constitutes its control centre. The size of the nucleus varies with cell type, with an average diameter in the order of 5 μm (Marieb, 1995). The nucleus, like the mitochondria, is surrounded by a double-layered phospholipid membrane.

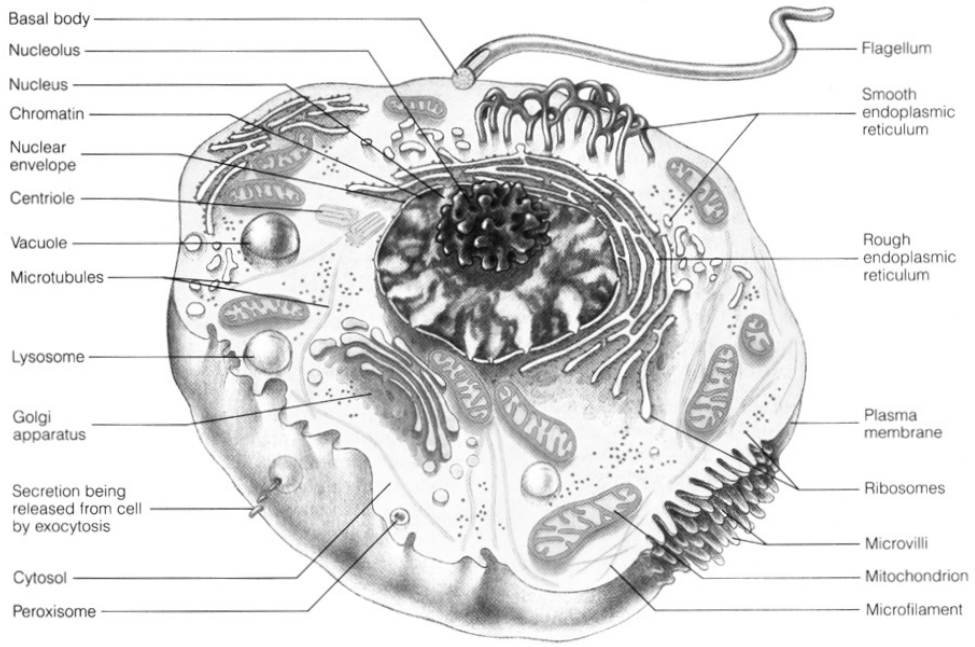

Fig. 3 – A generalized human cell (Marieb, 1995).

In order to penetrate deep into the tissue, the light transmitted has to pass through a large number of human cells that vary in size or function. It is at this interface that the light looses very much of its intensity, and the physical processes responsible for this are the absorption of light by the biological tissues encountered, the refraction of light due to various reflexions caused by the biological tissue and also the diffraction encountered in the human body by the transmitted light.

However, some of the photons succeed in their path and are not being scattered. They continue to propagate along straight lines and are known as "ballistic photons". As the light passes deeper into the tissue, the number of unscattered photons drops exponentially until the multiply scattered photons will overwhelm the so called ballistic signal. In most biological mediums, the ballistic photons are further consumed by absorption. When only the ballistic light is used for tissue imaging, assuming that the broadband swept source is characterized by a 800 nm wavelength, Hee *et al.* [28] have estimated that the ballistic signal will drop below the shot noise after approximately 36 mean free paths (mfp) in the tissue. Hee *et al.* have calculated that this corresponds to a mean penetration into biological tissue of maximum 4 mm, as the mfp is about 100 μm. Considering that the goal is the implementation of OCT in oncological imaging to replace ultrasound imaging, this mean penetration in biological tissue can be considered to be a strong disadvantage.

Currently, fiber optics are considered to be employed as a way of overcoming this disadvantage [7]. The fiber optics represent also the channels used by the OCT to transmit and receive the light to and from the biological tissue. The thought of using them in order to improve OCT's penetration was considered somehow natural.

The main disadvantage in the implementation of fiber optics is that the OCT will lose its noninvasive character. It has to be further discussed and decided whether its great resolution can justify the loss of its noninvasivity.

3. CURRENT APPLICATIONS AND PERSPECTIVES

Despite its low penetration, OCT is currently being used in ophthalmology, to study the eye. Considering the properties of the human eye, OCT's low penetration isn't considered to be an issue for ophthalmological use. Also, latest studies indicate its use in neuro-ophtalmology [8] and also in dentistry [9], here to probe and study teeth.

Considering its principle and current applications it is supposed that the OCT isn't far from being adapted to other medical applications.

Currently the OCT represents a strong and performant imaging technique that promises much more applications as compared to those already employed, not only in biomedical research but also in medicine, because it allows in situ visualization of pathological structures without the need of excision and specimen processing. This technique represents in fact a noninvasive optical biopsy allowing the operator the ability to visualize the tissue's morphology in real time, and taking these into consideration it can be used for a large range of applications. Looking past its use in ophthalmology, where its being used to supply valuable structural and quantitative information that isn't available through other types of exams, the OCT can be adapted to be used on a range of instruments, such as endoscopes, catheters or laparoscopes, through this allowing the user to obtain coherent images of the internal organs. Also, the continuous development of this imaging mode in the field of cardiology may represent a huge impact factor on mortality and morbidity among inflammatory cardiac pathologies.

Returning to our primary focus, oncology, the OCT's application in detecting the neoplasmic changes represents one of the most intensively debated investigation areas, and although it represents a domain where the OCT hasn't been implemented yet, it is seen as having a bright future and a huge potential impact on improving diagnostic techniques on cancerous tumors.

Looking through the fundamental research point of view, the OCT has a large range of fields where it can be used. Various themes target various materials, biological tissue engineering and biological imaging over small dimension animals.

Recent advances in Fourier domain detection in OCT field have had a significant impact, allowing the augmentation in imaging recording speeds. These

significantly improved imaging speeds allow an improved in situ 3D data collection and also the use of a mediation technique over the signal in order to obtain an improved measuring sensitivity [3, 4].

These progresses and also the continuous innovation from the international researchers community that are interested in the OCT systems promise to allow newer applications in fundamental research but also in clinical medicine.

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