# TIME-RESOLVED TRANSILLUMINATION AND OPTICAL TOMOGRAPHY

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## ABSTRACT

In response to an invitation by the editor-in-chief, I would like to present the current status of time-domain imaging. With exciting new photon diffusion techniques being developed in the frequency domain and promising optical coherence tomography, time-resolved transillumination is in constant evolution and the subject of passionate discussions during the numerous conferences dedicated to this subject. The purpose of time-resolved optical tomography is to provide noninvasive, high-resolution imaging of the interior of living bodies by the use of nonionizing radiation. Moreover, the use of visible to near-infrared wavelength yields metabolic information. Breast cancer screening is the primary potential application for time-resolved imaging. Neurology and tissue characterization are also possible fields of applications. Time-resolved transillumination and optical tomography should not only improve diagnoses, but the welfare of the patient. As no overview of this technique has yet been presented to my knowledge, this paper briefly describes the various methods enabling time-resolved transillumination and optical tomography. The advantages and disadvantages of these methods, as well as the clinical challenges they face are discussed. Although an analytic and computable model of light transport through tissues is essential for a meaningful interpretation of the transillumination process, this paper will not dwell on the mathematics of photon propagation.

**Key Words** contrast; diaphanography; image quality; optical tomography; resolution; time-of-flight; tissue optics.

## 1 INTRODUCTION

Viewing hidden lesions or abnormalities in the interior of living bodies is the objective of noninvasive medical imaging. Various techniques to do this are available, such as radiography, magnetic resonance imaging (MRI), positron-emission tomography (PET), or echography. Each of these techniques has advantages for a specific diagnostic process and drawbacks that limit their use as a continuous, noninvasive, and nondestructive monitoring system for living organisms.

Besides the classical diagnosis of broken bones, radiography has found applications in diagnosis of coronary and blood vessel lesions or diseases (angiography), breast cancer screening (mammography), or tomography (scanner). However, x-rays are known as ionizing radiation, so that their use for continuous monitoring or frequent screening is not recommended. Particularly adapted to the diagnosis of lesions in soft tissues, MRI is a powerful imaging technology that makes it possible to study tissue metabolism quantitatively (measurements of adenosine triphosphate, ATP), but it is necessary to use a contrast agent, its sensitivity is somewhat low, and the technique is expensive. PET has found numerous applications in neurology by precisely locating brain functional areas, but similarly to MRI, a contrast agent is necessary and PET images suffer from poor spatial resolution. Ultrasound is a benign form of imaging and echography has found numerous applications in blood flow and heart function measurements, breast cancer screening, and gynecology. A precise characterization of tissues in certain cases is, however, difficult because of the similarity of mechanical properties of different tissues. Thus the most competitive and flexible technique remains conventional x-ray radiography, yielding micrometric resolution at a relatively low cost.

Transillumination, or diaphanography,[1–5] is a convenient alternative to radiography. It provides full images of body content and metabolic information with nonionizing radiation in the visible to near infrared (NIR) range. The ideal use of diaphanography is the direct differentiation of neoplastic from normal tissues, but also the diagnosis of other tissue abnormalities, such as dysplastic tissues, cysts, lymph gland metastases or inflammations. Furthermore, a tissue characterization based on spectroscopic signature should improve a diagnosis by giving information on metabolism. The direct consequences are a reduction in the patient's physical and emotional trauma, and a reduction of health costs because the technique can be performed on an

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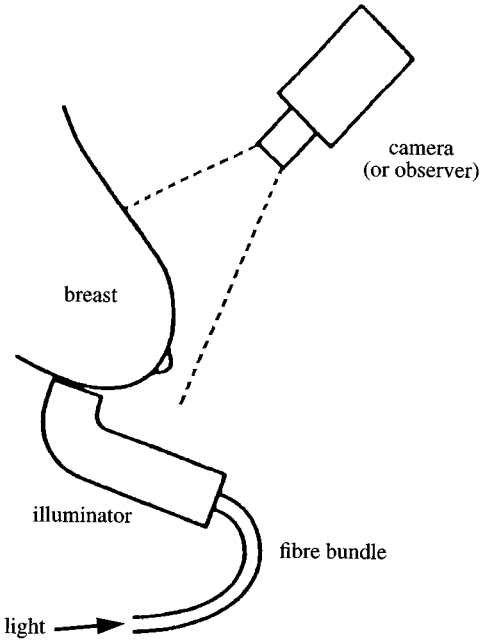


**Fig. 1** Conventional diaphanography setup.

outpatient basis and eliminates histology and the need for a surgical environment.

*Transillumination*, a term describing any method for viewing the interior of an object by shining light through it (Fig. 1), has been used as a diagnostic aid since the mid-1800s in inflammatory diseases of the sinuses or for differentiating between solid tumors of the testis and hydroceles. Later, diaphanography was one of the first diagnostic aids used to detect and diagnose various breast lesions. Cutler[2] started to evaluate breast lesions in 1929 after observations on breast specimens and suggested the possibility of establishing some points of difference between tumors of different density (Fig. 2). Interest in this method rapidly decreased, however, because of the poor spatial resolution of the technique, and the method was replaced by mammography. Today, diaphanography is occasionally used as a complementary examination before biopsy. Other applications of transillumination cover the broad field of oximetry, where the current metabolic status of a patient or an organ is monitored by real-time measurements of oxygen saturation.[6–9] Similarly, brain lesions can be detected by shining a light through the skull and observing the distribution of blood within the brain, thus detecting and localizing oxygen insufficiency, hemorrhages, or blood clots.[10–14]

The fundamental problem encountered in dc imaging or imaging that is not time resolved is the strong blurring of the images caused by light scatter within tissues. As a result, a host of authors have developed and investigated various time-resolved imaging techniques. By reducing the contribution of multiple scattered light, the resolution and the contrast of the obtained images is improved. Thus spatial filtering,[15] confocal configuration,[16,17] streak cameras,[18–27] Kerr gating,[28–31] photon counting,[32–34] and ultrafast photodetectors,[35–37] holography,[38–45] Raman amplification,[46–48] optical parametric amplification (OPA),[49,50] and finally heterodyne detection[51–53] have yielded numerous interesting results on imaging capability and image quality improvement. Generally these techniques have been targeted at breast cancer detection.

## 2 Application Fields

The characterization of biological tissues is one of the challenges of modern medicine. Therefore, a time-dependent light propagation method that would lead to the eventual differentiation and characterization of tissues would provide useful information for the diagnosis of pathologies and in physiology.

Another promising field where time-resolved optical tomography could be applied is neurology. Blood flow in the brain is an indicator of the cere-

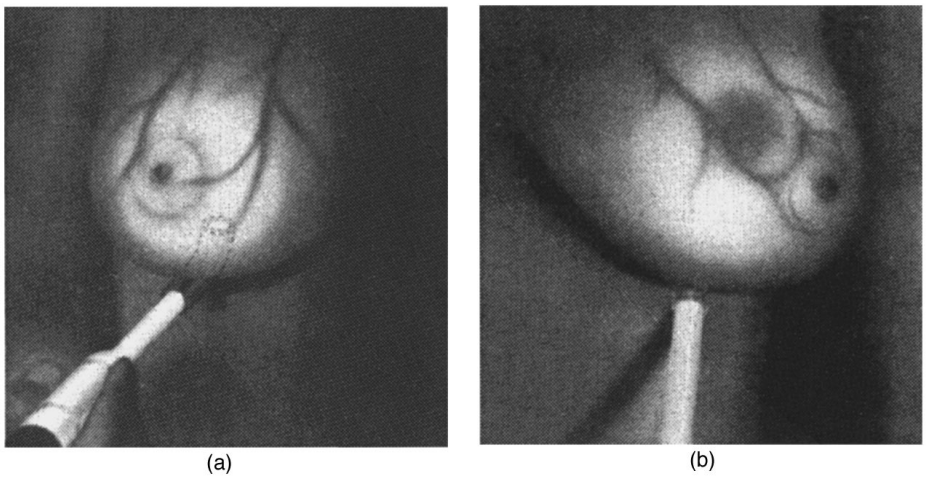


**Fig. 2** Diaphanography of a right healthy breast (a) and a left breast displaying a dense tumor (b).[2]

bral activity of brain regions, and can vary from one region to another. Therefore, measurements providing tomograms of brain activity with NIR radiation would offer a useful tool to neurologists and significantly improve the detection of brain dysfunctions or lesions. Congenital brain lesions often originate from hemorrhage, hypoxemia due to blood supply deficiency, or blood clots in arteries or veins of the brain. Systematic screening of neonates or even premature infants would prevent irreversible processes in brain and nervous functions. Such tomographic measurements would also improve the early detection of strokes, fast-growing tumors (due to an increased vascularization), degeneration of the brain (senility, dementia praecox), and Alzheimer disease. They could be used to detect cognitive difficulty (memory, vigilance, perception) related to such psychic disorders as depression, schizophrenia, or even drug addiction. Furthermore, therapy could be controlled and evaluated continuously.

The major concern, however, of time-resolved transillumination is breast cancer detection. In 1991, one woman out of ten developed breast cancer, and one-fourth of the diseased patients died.[54–56] While 76.6% of breast cancer patients survive 5 years after surgery, only 63% are alive 10 or more years later. Indeed, breast cancer is the leading cause of mortality for women aged 35 to 50. The continuous climb in the incidence of breast cancer and the fast-growing process of breast carcinomas[57] requires a systematic and regular screening of women 40 and older. For the last 10 years, screening produced a 70% early detection rate for breast cancer in women 50 and older with a detection rate above 98%.[56,58–61] However, breast cancer also strikes 3% of women under 35 and in 90% of the registered cases it is lethal because of late detection.[62] Therefore, a regular screening of younger patients 35 and below is necessary. Moreover, the use of x-rays in mammography is suspected to induce 0.2% of the breast cancers.[62–64] A regular mammographic screening in younger patients is thus unacceptable. Mammography has also inherent shortcomings in the diagnosis of benign breast lesions. A bad contrast between tissues is sometimes observed. The neoplasms most often overlooked by mammography are embedded in dysplastic tissue of a high radiodensity that prevents radiographic visualization of the tumor. Diaphanography is not affected by dysplastic tissue in its ability to detect tumors. Furthermore, by the time microcalcifications of 100 $\mu$m or more, which reveal the presence of a tumor on a mammogram, are detected, the surrounding lesion can have grown to several millimeters. Diaphanography should help in the early detection of the tumor before the formation of the microcalcifications, in the preclinical stage. Although mammography is the best screening tool, giving an image resolution and contrast that enables a precise and reliable diagnosis, novel techniques, such as time-resolved transillumination and optical tomography, have to be considered in order to bypass the drawbacks of mammography and provide better differentiation and early detection.

## 3 LIGHT TRANSPORT THROUGH TISSUES

The propagation of light through biological tissues is a subject of growing interest in many medical applications, particularly in laser medicine. For theoretical reasons, biological tissues are generally considered turbid media. Light is transmitted with varying degrees of scattering and absorption. In the visible to NIR range, scattering dominates because of the inhomogeneities of tissues and cellular structures, and particle sizes on the order of an optical wavelength. Scattering occurs at such discrete locations as the interfaces between cells; in the components of the cells;[65] in solutes such as glucose, mannitol, or sucrose in body fluids; or along neurons when electrical impulses are transmitted.[66,67] Absorption also occurs at discrete locations where chromophores, such as hemoglobin (in the red cells), myoglobin (in the muscle cells), cytochrome (in the mitochondria), or chromatin (in the nuclei), are present. These pigments have a particular absorption spectrum that allows them to be differentiated and for the three first-named chromophores, there is also a difference between the reduced and oxidized state that is generally used for a metabolic state signature.[68,69]

The three fundamental optical interaction coefficients characterizing a turbid medium are the *absorption coefficient* $\Sigma_a$, the *scattering coefficient* $\Sigma_s$ and the single scattering *phase function* $p(\vec{s},\vec{s}')$. The absorption and scattering coefficients, within the confines of radiative transfer theory, represent the probability per infinitesimal path length for a photon to be absorbed or scattered. The phase function describes the angular dependence of each scattering event. Two other parameters encountered, derived from the fundamental interaction coefficients, are the average cosine of scattering or anisotropy parameter $g$ and the reduced scattering coefficient $\Sigma_s'=\Sigma_s \cdot (1-g)$. All these parameters describe accurately how light propagates through tissues. To obtain the optical characteristics, one has to convert measured quantities into parameters according to a particular theory of light transport in tissues (see Refs. 70 and 71 for a complete review of the optical properties of tissues).

It is therefore essential to discuss a theoretical model to understand the process of light transport through turbid media. Many models that predict light distribution within tissues have been developed.[72,73] The most commonly used models refer to the diffusion approximation of the radiative transfer theory[74,75] or Monte-Carlo simulation.[76,77] In radiative transfer theory, the diffuse photon fluence rate $U(\vec{r},t)$ should satisfy the time-dependent diffusion equation where $S(\vec{r},t)$ is the source term and $c_n$ the speed of light in the tissue [Eq. (1)].

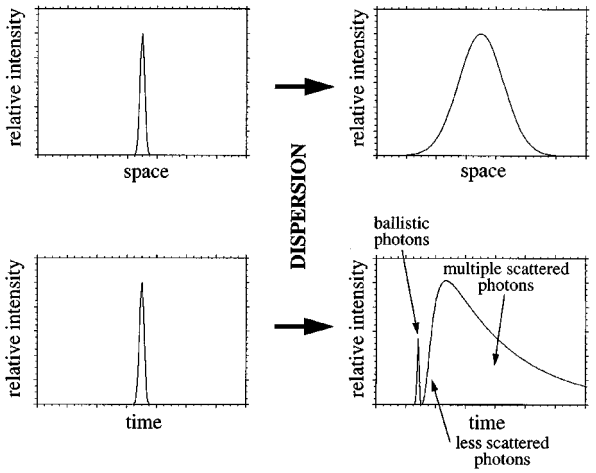


**Fig. 3** Schematic diagram of the spatial and temporal dispersion observed on short light pulses propagating through turbid media.

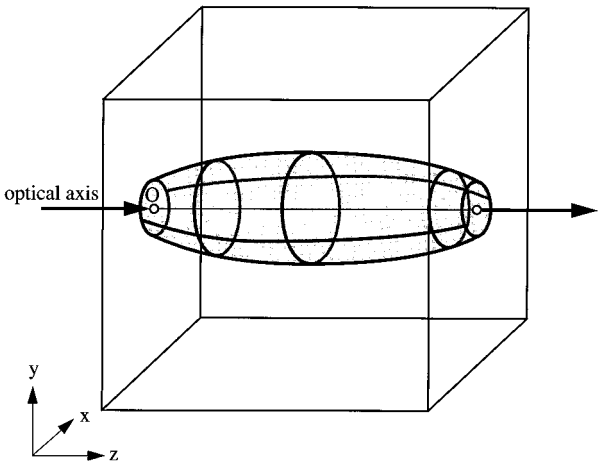


**Fig. 4** Schematic representation of a 3-D turbid medium into which photons are released at the origin in an incidence normal to the input surface. The cigar-shaped volume contains all the possible paths of photons within a given time $t_{int}$ and each section of the volume represents the expected resolution.

$$\frac{1}{c_n}\frac{\partial}{\partial t}U(\vec{r},t)-\frac{1}{3(\Sigma_a+\Sigma_s(1-g))}\nabla^2 U(\vec{r},t)+\Sigma_a U(\vec{r},t)=S(\vec{r},t). \quad (1)$$

Although an analytical solution does not exist for the general case, some are solutions provided for particular geometries and happen to fit experimental measurements. The fluence rate can then be accurately calculated for biological tissues where $\Sigma_a \ll \Sigma_s$. In Monte-Carlo simulations, each photon is considered independently and its trajectory, modified by scattering and absorption events, is computed. Thus, following the random path of a very large number of photons to reduce statistical discrepancy, the fluence rate can be computed with accuracy also.

### 3.1 LIGHT DISPERSION

As a light pulse propagates through a turbid medium, it undergoes both temporal and spatial dispersion (Fig. 3). Plotting the time dispersion of the output intensity, the transmitted photons can be classified in three categories: the *ballistic* or coherent photons, propagating straight; the *less scattered* or partially coherent photons, undergoing only a few scattering events; and the *multiple scattered* photons. Ballistic photons are mainly observed in tissuelike phantoms made out of suspensions of microspheres, or fatty droplets such as milk or Intralipid. However, in real biological tissues, it is mostly impossible to observe a ballistic transmission, due to both discrete steps and continuous variations in the dielectric constant of tissues.[22,26,32] The less scattered photons are also called the *snake* photons, which is from my point of view somewhat confusing; therefore I prefer to speak about the *less scattered* photons. The multiple scattered photons are responsible for the spatial dispersion. This is the source of image blurring and resolution deterioration. Since the distinction between the less and multiple scattered photons is somewhat unclear, one can assume that the less scattered photons are those necessary to create an informative unblurred image.

Actually, the intensity measured over a very small period of time, or integration time, after the first-arriving photons emerge from the sample will depend on the absorption and scattering properties[25,78] of the cigar-shaped volume of medium surrounding the optical axis (Fig. 4). This volume contains all the possible paths that could be taken by the detected light during the selected integration time. The size of each transversal section of this volume represents the spatial resolution of the final image as a function of the position of an object along the optical axis. If the period of time is constrained, the volume gets narrower, and the spatial resolution increases. To improve the resolution obtained with dc imaging, one has to discriminate the first-arriving photons from the pack of multiple scattered photons by using an adequate filter to get the narrowest possible volume. These first-arriving photons enclose the less scattered ones.

### 3.2 MECHANISM RESPONSIBLE FOR THE IMAGE

The formation of the image provided by time-resolved transillumination is mainly due to the differential transmittance of radiation in different tissues.[79,80] The tissue architecture as well as the shape and content of each cell strongly influence the transmittance of light. Biological tissues are usually composed of a dense assembly of cells which are in general several microns in diameter. Moreover, the spectroscopic study of hemoglobin shows that blood has absorption peaks in the red and NIR region so that a strongly perfused part of the body should appear as a shadow, and other relatively more translucent tissues, such as bone,

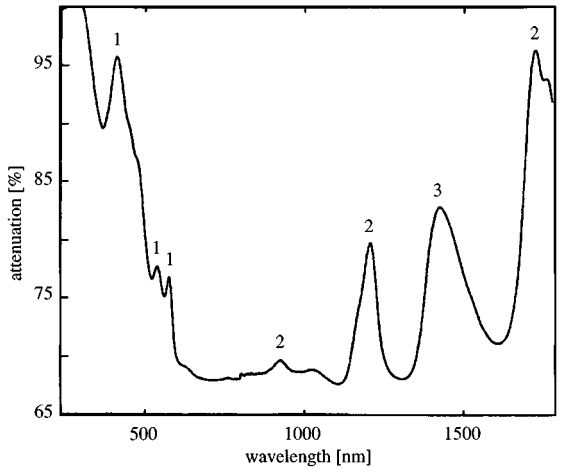


**Fig. 5** Attenuation spectrum through a 3-mm-thick slab of breast tissue[81] with the contribution of hemoglobin (1), fat (2), and water (3).

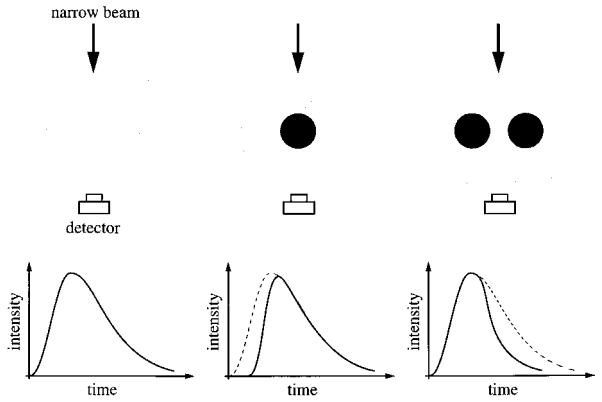


**Fig. 6** Schematic representation of the time distribution disturbance as a function of the position of an absorbing object in the sample.

adipose tissue or skin, should look brighter. For breast tissues (which are principally composed of adipose and fibrous tissues), there is a window between 700 and 1100 nm where the lowest percentage of light is absorbed (Fig. 5). A cancerous lesion, however, is suspected to contain more blood than the surrounding tissues. It should be then easily differentiated from the surrounding tissues, which are normally perfused. Furthermore, the cancerous cells are known to have a larger nucleus than normal cells. This nucleus contains chromatin, a chromophore responsible for light absorption.

If light-absorbing lesions are present in tissues, the transmitted signal is modified as a function of the position of the lesion (Fig. 6). Compared with the time distribution obtained without inhomogeneities, the presence of one opaque object on the optical axis will delay the output signal and an image is only formed by multiple scattered photons.[24,33] When there are two objects on either side of the axis, the output signal decays abruptly. Indeed, it appears that the ballistic and less scattered photons are mainly affected by central absorption, whereas multiple scattered photons are influenced by peripheral absorption.[33] Therefore, by using information carried by narrow regions of the output signal, time-resolved imaging enables a better detection of a lesion through improved resolution and contrast.

## 4 AVAILABLE TECHNIQUES

Time-resolved transillumination and optical tomography are obtained through the detection of the ballistic photons, if any, and the less scattered photons over a very short period of time. From the pioneering experiments combining Raman amplification and Kerr gating to obtain tomographic views of a bovine heart *in vitro*,[30] to the latest investigations on *in vivo* images of compressed breasts with a streak camera,[25] a host of authors have proposed various techniques for time-resolved transillumination and optical tomography. These methods could be classified as (1) direct or ballistic methods, based on time-of-flight selection; and (2) indirect methods, based on such intrinsic properties of light as coherence or polarization. The indirect methods select the first arriving photons "naturally." Published results pertains to the evaluation of resolution and improving contrast by gating the detected signal, or the feasibility of a proposed technique to obtain images of objects in turbid media with improved resolution. Generally, the studies are aimed primarily at detection of breast cancer and secondarily at localization of lesions. The detection of a lesion is achieved by recording a 2-D image with sufficient contrast, while localization needs ranging, or more views and tomographic reconstruction to obtain the 3-D images, by which the size, shape and position of the object can be determined. Detection is a simple task, whereas the accuracy of localization depends on how exact the information about absorption and scattering is in the sample, particularly for ranging.

### 4.1 BALLISTIC METHODS

The typical experimental setup for ballistic measurements consist of a pulsed femto- or picosecond laser source combined with an ultrafast photodetector (Fig. 7). Generally the narrow beam or confocal configuration is used to further hinder multiple scattered photons from reaching the detector. The sample is placed on a *X-Y* translation stage to be able to record 2-D images by scanning. The measurement procedure is completed by sampling the intensity of each pixel as a function of time, to obtain a time-space intensity mapping. The image is finally numerically reconstructed by attributing to each pixel the intensity measured over the selected integration time (Fig. 8).

The use of narrow beam scanning[16] or confocal configuration,[17] as well as spatial filtering[15] with

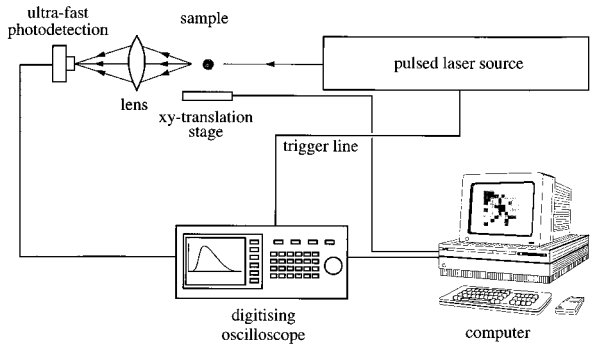


**Fig. 7** Typical experimental setup for time-of-flight measurements with an ultrafast photodiode.

small apertures in the back Fourier plane of the optics has been proposed to obtain a simple first-arriving light filter without the use of expensive ultra-fast detectors. Although part of the multiple scattered photons are discarded, the selectivity for the ballistic and less scattered photons is not good enough for a sufficient improvement of the resolution. Therefore, the addition of fast detection is necessary. The most versatile and widely used device is the streak camera.[18–27] The use of photon counters[32–34] or ultrafast photodiodes[36,37] has also been proposed. Although these methods have provided numerous promising experimental results, one of their drawbacks is the time-consuming scanning of the sample needed to obtain 2-D images. This is overcome by using an ultrafast Kerr gate, which was once proposed to photograph light in flight.[28,29] Instead of processing the image on a computer, a direct 2-D recording is made by allowing only the ballistic and less scattered photons to pass through the Kerr gate.[30,31] Although the method makes time-resolved imaging possible, the wavelength used to transilluminate the sample is generally in the green region (second harmonic generation of an infrared pump laser), which is strongly absorbed by tissues. This prevents its use in clinical situations, where a thickness of at least 40 to 50 mm for a compressed breast is common.

### 4.2 INDIRECT METHODS

Another way to obtain direct images is offered by indirect methods. These are either based on holography, on Raman amplification, or on OPA. It has been demonstrated that holography is an effective way to remove the multiple scattered photons from the detected signal. The multiple scattered photons are totally incoherent relative to the reference pulse, so that they do not contribute to the formation of the hologram. The integration time is set by the reference pulse, which is generally identical to the incident pulse on the sample. By using the basic method of light in flight[82,83] in the so-called chronocoherent imaging (CCI) configuration,[44,45] holograms of the first-arriving light can be recorded on a conventional film or plate. A classical Mach–Zehnder interferometer (Fig. 9) also fulfills the requirement for time-resolved imaging.[38–43] The holograms are recorded on a CCD (charge coupled device) camera and reconstructed numerically.[84] The use of a CCD camera overcomes the problems encountered with classical hologram recording on plates or films, such as lack of sensitivity and, for time-resolved transilluminations, a long exposure time. Moreover the background noise is numerically removed and images are averaged over a large number of frames to reduce the speckle noise. Indeed, the natural instability of living objects is a great advantage for holographic time-resolved imaging. The effectiveness of hologram averaging depends on the speckle decorrelation between successive images. When the exposure time is reduced, the speckle pattern obtained is stationary, so that with a time interval between two exposures longer than the correlation time of speckle, the speckle pat-

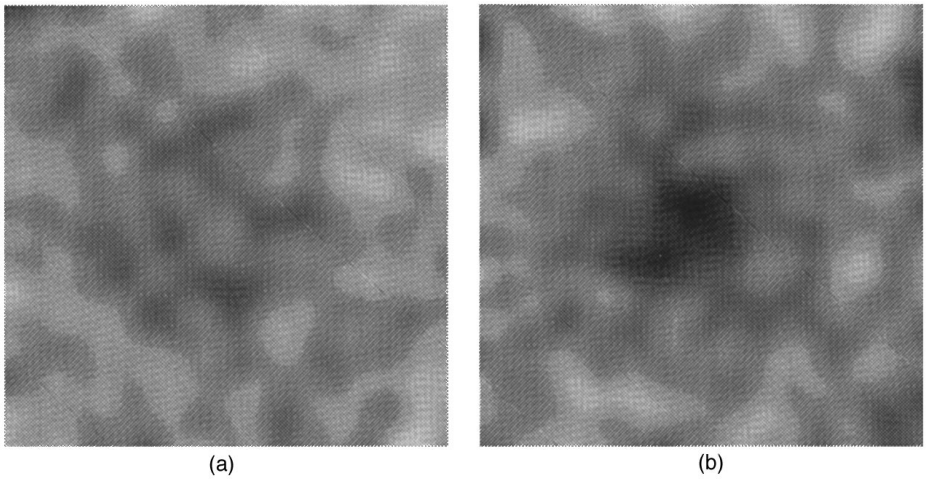


**Fig. 8** Reconstructed image of a 5-mm cancerous lesion in a 20-mm-thick sample of breast tissue,[37] dc-image (a) and image with 40 ps integration time (b).

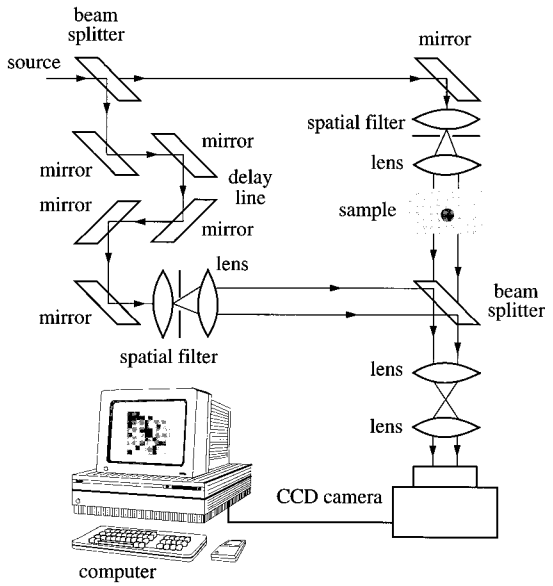


**Fig. 9** Schematic representation of the experimental setup for time-resolved optical tomography with the Mach–Zehnder interferometer.[42]

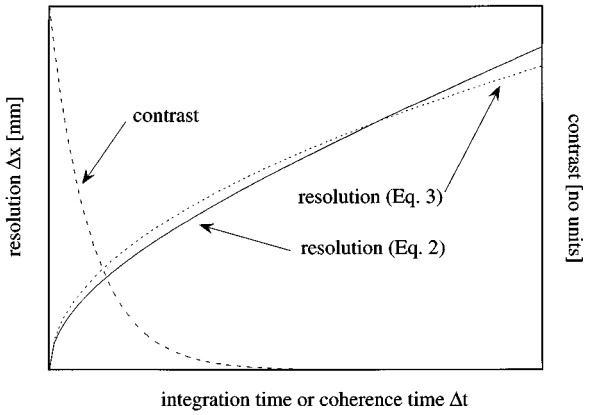


**Fig. 10** Schematic plot of the resolution $\Delta x$ [from Eq. (2) and Eq. (3)] and the contrast as a function of the integration time or the coherence time $\Delta t$.

tern vanishes by averaging. Another effective indirect method is optical heterodyne detection called coherent detection imaging (CDI).[51–53] Since a heterodyne system is both a sensitive receiver and a directive antenna, it yields high spatial resolution as well as high angular selectivity for the formation of images by ranging. The main drawback of holography and heterodyne detection is the loss of coherence as a result of strong scattering. Experiments have been performed in biological tissues with a limited thickness of about 10 mm. This is far from common clinical conditions. For larger parts of the body, the whole object wave would have completely lost its phase relative to a reference wave. Therefore, holography and heterodyne detection are confined to less scattering tissues or thin parts of the body.

All the aforementioned ballistic and indirect methods for time-resolved imaging suffer from the very low detected intensity. Actually, the signal-to-noise ratio (SNR) decreases as the number of photons is constrained and the improvement in image quality is overcome by the noise. Therefore, an image is formed by averaging numerous successive exposures to reduce the statistical noise. To overcome this problem, Raman amplification[46–48] and OPA[49–50] have been proposed to reduce exposure time. The output signal is amplified over a very short period of time, so that gains on the order of $10^6$ are achieved during the integration time set by a reference pump pulse. Full 2-D images can be obtained with a single shot. However, the main drawback of signal amplification (as well as optical heterodyne detection) is the high angular selectivity, so that in practice only ballistic photons can be detected. Therefore, in clinical use, where ballistic transmission is barely observed, the technique does not offer a profitable time-resolved imaging technique.

## 5 RESOLUTION AND SNR

For clinical purposes, time-resolved imaging has to improve the resolution of conventional diaphanography. The resolution of dc images has been estimated at about 15 to 20 mm for a compressed breast. Indeed, by reducing the integration time, the resolution and contrast of the images obtained by time-resolved transillumination are improved (Fig. 10).

Furthermore, it has been shown that the position of an heterogeneity in the sample influences the resolution and the contrast.[24,31] It appears that the worst case is a lesion located in the central plane of the sample (Fig. 4). Therefore, the resolution $\Delta x$ of a time-resolved imaging system is referred to an object located in the central plane.

Theoretical studies based on the diffusion approximation, Monte-Carlo simulations, or random path models, have shown that the curve describing the resolution $\Delta x$ as a function of the integration time $\Delta t$ and sample thickness $z_{\max}$ follows square root behavior [Eq. (2)].[20,37,85]

$$\Delta x = \frac{2}{3} \cdot \frac{(c_n \cdot \Delta t + z_{\max})}{2.0} [1 - z_{\max}{}^2 / (c_n \cdot \Delta t + z_{\max})^2]^{1/2}. \quad (2)$$

Similar curve shapes have been obtained using holography, and instead of the integration time, the resolution is plotted as a function of the coherence time of the reference pulse [Eq. (3)].[40]

$$\Delta x = 1.95 \cdot \sqrt{c_n \cdot \Delta t \cdot z_{\max}}\,. \quad (3)$$

These theoretical predictions have been confirmed by experimental results on phantoms and tissues.

Although the resolution and the contrast improve when the integration time is constrained, the SNR decreases strongly due to noise augmentation. This noise is basically composed of anatomical or structural noise and photon or quantum noise. The anatomical noise arises from the smaller inhomogeneities in the sample. Since the integration time is constrained, these inhomogeneities yield sharper contours on the image and could mask a lesion while the photon noise is principally responsible for the SNR deterioration. Indeed, the number of photons detected is insufficient to create an informative image.[86] Considering the light attenuation of a 50-mm breast or an infant's head, the average transmitted intensity is 6 to 10 orders of magnitude weaker than the incident one. To achieve time-resolved imaging, less than 1% of this transmitted light has to be detected.[25] To improve the SNR value, one would try to increase the input intensity or peak power of each pulse, but dosimetry sets the limits for the application of reasonable energy to human tissues without damage. The ANSI Z136.1-1986 indicates that no damage will occur to skin from a 1-ms duration, 694.3-nm pulse with 0.2 J/cm$^2$ energy or from a 1-ms duration, 1064-nm pulse with 1.0 J/cm$^2$ energy. Since the usual wavelengths for tissue transillumination are in the NIR range, the absorption can be considered as low, so that an estimated 0.8 J/cm$^2$ can be selected as a safe limit. It is also possible to combine measured temporal distributions with analytical results from the diffusion approximation of the radiative transfer theory.[23] By numerically solving the analytical time dispersion, a curve fit on the experimental time distribution is obtained, and the optical parameters of the tissue are determined. The analytical result is considered a high SNR representation of the measured data (the analytical model is supposedly free from noise). This method, however, does not improve the resolution and the contrast for very small integration time due to the difficulty of fitting a theoretical curve on noisy measured time distributions. Since the noise appears to be difficult to bypass, it appears necessary to introduce the noise component in evaluating the imaging performance of time-resolved transillumination and optical tomography.

The aforementioned predictions of the expected resolution do not take into account the noise and the contrast changes observed as the integration times is reduced. Indeed, the consequent noise increase at short integration times compensates for the improvement of the resolution.[35] An optimum for the integration time has to be determined to obtain an informative image between a blurred dc image (integration time too long) and a noisy image (integration time too short). One can define the less scattered photons as those detected during that optimal time. It is then convenient to have a method for an objective quantitative evaluation of the quality of a time-resolved image to determine this optimum. By combining the variance $\sigma^2(\Delta t)$ of a Gaussian curve fitted on the measured line spread function (LSF), the noise pattern (Wiener spectrum) $W(\Delta t)$, the contrast $C(\Delta t)$, and a correcting constant $\gamma$, which is function of an estimated fixed value of the SNR for high detection probability, one can determine the resolution as the size $\Delta x$ of the smallest detectable object or image quality index (IQI).[37] This had been formerly proposed for the evaluation of mammography [Eq. (4)].[87,88]

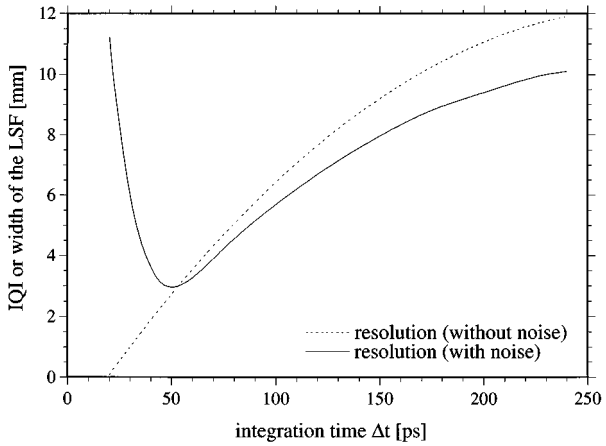


**Fig. 11** Comparison of the width of the LSF (dotted line) and the IQI (continuous line) as a function of the integration time $\Delta t$ for measurements through 20 mm of breast tissue.[37]

$$\Delta x \approx 2\left[\sigma^2(\Delta t) + \gamma \cdot \frac{\sqrt{W(\Delta t)}}{C(\Delta t)}\right]^{1/2}. \qquad (4)$$

As an illustration, the *in vitro* IQI of a 20-mm sample of breast tissue has been determined as a function of the integration time and compared with the width of the measured LSF. It appears that the IQI values approximate the width of the LSF for integration times above 50 ps, but a minimum value of 3 mm at 40 ps is observed and the IQI values increase again for integration times shorter than 30 ps (Fig. 11).[37] The LSF curve does not pass through the origin due to the uncertainty of the measurements. Actually, it is difficult to properly fit a Gaussian curve on the noisy LSF profile for short integration times. For thicker samples, the position of the minimal value of the IQI is shifted to higher integration times and resolution values. With *in vivo* compressed breasts (≈40 mm), the best measured resolution was about 10 mm for a 60 ps integration time,[25] which is within the theoretical predictions [Eq. (2)]. No informative images have been obtained with shorter integration times. Submillimetric resolution seems then to be hardly reachable under clinical conditions. Actually, the resolution limit is restricted by the input intensity, depending on the dosimetric requirements.

## 6 OUTLOOK

Recent progress in time-resolved transillumination and optical tomography has shown that spatial resolution as well as contrast are improved by detecting only the less scattered photons, while ballistic transmission can be barely observed under clinical conditions. The diversity of the techniques proposed to achieve time-resolved imaging is proof of scientists' eagerness to provide a high-resolution imaging device for the surgeon and the availability of affordable tools for that purpose. Unfortunately none of the proposed methods satisfies the clinical requirements for replacing conventional mammography. The drawbacks related to time-consuming scanning; long exposure time; incoherent transmission in thick parts of the body; high angular selectivity, which limits the detected intensity to the ballistic photons; and a mostly low detected intensity at short integration times, have to be overcome. Despite this doubtlessly pessimistic statement, the results obtained so far are encouraging. It is yet not established which experimental procedure will eventually find the most use in medicine. Experimental data on *in vivo* measurements have shown that ultrafast detection devices are not necessary in clinical conditions, where integration times in the tens of picoseconds are needed. Furthermore, it appears that time-resolved transillumination and optical tomography are limited to a certain optical thickness, hindering their use for imaging thick limbs or the chest. However, for a compressed breast, or an infant's head, the problem should find an acceptable solution. To evaluate the eventual practical benefit of time-resolved imaging, systematic clinical investigations are inevitable. Future investigations will also indicate which medical fields will profit most from time-resolved imaging.

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