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INTERACTIONS

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### Abbreviations

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CTLM</td>
<td>Computed Tomography Laser Mammography</td>
</tr>
<tr>
<td>NIR</td>
<td>Near Infra-Red</td>
</tr>
<tr>
<td>MCSLTT</td>
<td>Monte Carlo Simulation of Light Transport in Tissue</td>
</tr>
<tr>
<td>SA</td>
<td>sclerotic adenosis</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>FNAC</td>
<td>Fine Needle Aspiration Cytology</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single Photon Emission Computed Tomography</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>FDG</td>
<td>[fluorine-18] fluoro-2-deoxy-D-glucose</td>
</tr>
<tr>
<td>FES</td>
<td>16[F-18] fluoroestradiol</td>
</tr>
<tr>
<td>OCT</td>
<td>Optical Coherence Tomography</td>
</tr>
<tr>
<td>LASER</td>
<td>Light Amplification by Stimulated Emission of Radiation</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>CW</td>
<td>continuous-wave</td>
</tr>
<tr>
<td>FWHM</td>
<td>Full Width at Half Maximum</td>
</tr>
<tr>
<td>PDT</td>
<td>Photodynamic Therapy</td>
</tr>
<tr>
<td>YAG</td>
<td>Yttrium Aluminum Garnet</td>
</tr>
<tr>
<td>LITT</td>
<td>Laser Induced Interstitial Thermotherapy</td>
</tr>
<tr>
<td>MOI</td>
<td>Medical Optical Imaging</td>
</tr>
<tr>
<td>TPSF</td>
<td>Temporal Point Spread Function</td>
</tr>
<tr>
<td>CC</td>
<td>cranio-caudal</td>
</tr>
<tr>
<td>ML</td>
<td>medio-lateral</td>
</tr>
<tr>
<td>NOHD</td>
<td>Nominal Ocular Hazard Distance</td>
</tr>
<tr>
<td>PRS</td>
<td>Physician’s Review Station</td>
</tr>
<tr>
<td>EC</td>
<td>endothelial cells</td>
</tr>
<tr>
<td>MMP</td>
<td>matrix metalloproteinases</td>
</tr>
<tr>
<td>PDF</td>
<td>Probability Density Function</td>
</tr>
<tr>
<td>CDF</td>
<td>Cumulative Distribution Function</td>
</tr>
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</table>
A.1 Introduction

A.1.1 The problem

Breast cancer is the prime factor of women mortality in the developed countries. 75,000 women die every year of breast cancer in Europe alone. And many more have to suffer the procedure of screening and possible surgical biopsy. During the recent years however, many techniques have been developed and applied, whereas many more are in experimental stage. X-ray mammography, perhaps the most widely used of cancer diagnostic tests, has its problems, which range from false-positive results to missed lesions. While it still remains the frontline diagnostic technique in the fight against breast cancer, it may soon have help. Regardless of the publicized problems with x-ray mammography, from false positives to missed lesions and the risk of carcinogenesis, the technique still provides the most-readyly-available front-line imaging option to aid clinicians in breast-cancer diagnosis. There is no question, even among the technique's naysayers, that the widespread implementation of x-ray mammography that began in the 1980s has been a contributing factor in the steady decline in deaths from breast cancer.

But, mammography, whether conventional or digital, has been thoroughly documented as missing between 25% and 40% of breast cancers. The miss rate is even higher for women with dense breasts, which constitute 40% of the female population, whereas the sensitivity of the mammographic technique is very low, ranging from 24.5% to 37%. And mammography has additional drawbacks. Of every 100 cases deemed “positive” and, therefore, resulting in biopsy, between 60% and 80% are actually negative or benign. A huge number of women undergo these biopsies that would not be necessary if a more accurate imaging procedure was used; they are subjected to the mental trauma of being told they may have breast cancer and the subsequent agony of awaiting biopsy results. These unnecessary biopsies also add significant costs to the healthcare system.

The principal reason for the low sensitivity of mammography is that it only images anatomic detail and provides no functional information. Functional information is essential for early and accurate diagnosis of breast cancer and can be expected to significantly reduce the number of unnecessary biopsies. The special properties of light could help optical imaging "see" what other diagnostic methods, including conventional x-ray mammography, may miss. The CT Laser Mammography (CTLM) system, that utilizes patented continuous wave laser technology and computer algorithms to create 3-D and tomographic sections of the breast, combines morphologic and functional information that could change the current diagnostic and clinical management of breast cancer by detecting angiogenesis, the very first visible sign of breast cancer growth. Angiogenesis is the process by which new blood vessels are formed in response to a chemical signal emitted out by a collection of cancer cells. Without angiogenesis, tumors cannot grow larger than 1 mm to 2 mm and cannot metastasize throughout the body. Therefore, detecting angiogenesis is one of the most important ways functional information can be utilized to diagnose cancer at an early stage. CTLM has the potential to determine whether a mass seen on mammography is benign or malignant and – because the volume of the angiogenesis is usually considerably larger than the tumor tissue itself – to detect tumors that are invisible on mammography[1].

When applying laser light to biological tissue, the occurrence of a variety of
interaction mechanisms is multiple. This diversity is due to specific tissue characteristics as well as laser parameters. Laser radiations induce biological damage in tissues via photochemical, photothermal, and photomechanical interactions. The aim of this thesis was the investigation of the photothermal phenomena induced in breast tissue during its irradiation with the NIR light emitted from the laser source of the CTLM unit. In order to do that, we used the MCLTT (Monte Carlo Simulation of Light Transport in Tissue) code, which is a useful tool in diagnostic as well as therapeutic laser applications, in the study of laser-tissue interactions and the results occurring during these interactions. The particular code measures quantities such as the total reflected light, the total transmitted light, and the total heat absorbed [2]. The use of the specific Monte Carlo simulation model leads us to the quantification of the photothermal phenomena inside the breast tissue as well as the quantification of the influence of several parameters on breast’s temperature, when being irradiated with laser beams.

A.1.2 Thesis originality

The originality of this thesis can be focused on the use of MCLTT (Monte Carlo Simulation of Light Transport in Tissue) code in the study of the thermal interactions that occur during an alternative breast imaging technique, the Computed Tomography Laser Mammography method. These effects were studied extensively and the emerging results led to useful conclusions about the possible “thermal” danger that might occur.

A.1.3 Thesis layout

Before proceeding to the reading of this thesis it would be useful to take a look at the different parts, which it comprises of. In section A.2 a short description of the breast’s physiology is presented, as well as the most important and most frequently diagnosed breast disorders. Furthermore, a historical review of breast imaging was attempted, whereas the current status of breast imaging methods was demonstrated. Due to the fact that the technique that this thesis studies utilizes laser light, section A.3 presents the basic principles of lasers, whereas in section A.4 a detailed description of the light-matter effects and the interaction mechanisms that can be observed, are exhibited. Section A.5 provides a full description of the CTLM unit, its design and theoretical background and also attempts a comparison with conventional x-ray mammography. The theoretical part ends with section A.6, which includes an introduction to Monte Carlo simulation and to random numbers.

Section B, which is titled “Materials and Methods” presents the Monte Carlo simulation code MCLTT (Monte Carlo Simulation of Light Transport in Tissue) that was used for the study of thermal effects on breast tissue during the CTLM imaging procedure.

In section C, the occurring from the MCLTT (Monte Carlo Simulation of Light Transport in Tissue) code results are demonstrated. Specifically, in section C.1 the effects of input power on temperature rise, on total heat and on photon distribution, as
well as the effect of breast thickness on temperature rise on glandular tissue are presented and commented, whereas in section C.2 the effects of the same parameters on skin are also presented and discussed.

The final section, D includes a discussion on the results that have arose with the use of the MCSLTT (Monte Carlo Simulation of Light Transport in Tissue) code, followed by suggestions on further efforts that could be attempted as a future work.
Chapter A

Introduction – Theoretical part

A.2 Breast cancer and detection

A.2.1 Female Breast physiology and anatomy

A.2.1.1 Breast composition

A.2.1.2 Inflammatory disorders of the breast

A.2.1.3 Hyperplastic lesions

A.2.1.4 Breast lumps

A.2.1.5 Breast cancer

A.2.2 Historical review

A.2.3 Present status of diagnosis

A.2.3.1 X-ray Imaging

A.2.3.2 X-ray Mammography

A.2.3.3 Ultrasound Imaging

A.2.3.4 Magnetic Resonance Imaging

A.2.3.5 Triple Examination

A.2.3.6 Radioisotope Imaging

A.2.3.7 Nuclear Medicine Breast Imaging Techniques

A.2.3.8 Optical Tomography

A.2.3.9 Optical Coherence Tomography
A.2. Breast cancer and detection

After skin cancer, breast cancer is the most frequently diagnosed cancer in women and appears to be one of the most popular "diseases" targeted by optical imaging researchers—or perhaps the reason is simply that the breast is easily accessible compared to other body parts. 75,000 women die every year of breast cancer in Europe alone. And many more have to suffer the procedure of screening and possible surgical biopsy. Thus, the need for a reliable, accurate and cost effective technique is imperative.

A.2.1 Female Breast physiology and anatomy

A.2.1.1 Breast composition

The breast is a mass of glandular, fatty and fibrous tissues positioned over the pectoral muscles of the chest wall and attached to the skin by fibrous strands called Cooper’s ligaments. The mammary glands are modified eccrine glands of the skin located on the anterior chest wall whose ductal and lobular units extend far into the adjacent subcutaneous fat. The gland itself is segmentally divided into 15 to 20 distinct glandular units, or lobes, each of which has a ductal orifice at the apex of the nipple. Prior to puberty, a mammary gland consists of little more than a complex system of ductal structures, a configuration that persists in the male breast throughout life. At puberty, the glands in the female progressively enlarge. The amount of fibrofatty elements increases, the ducts elongate, and small areolar buds form, but full maturation is not attained until pregnancy [3].

The adult mammary gland is situated principally between the superficial and deep layers of the superficial pectoral fascia of the anterior chest wall, extending roughly from the second to the sixth or seventh anterior intercostal space. The cephalocaudal dimensions is 10 to 12 cm on the average, and the gland generally has a maximum thickness of 3 to 5 cm. The fatty layer overlying the parenchyma of the breast makes a variable contribution to the mass of the breast and fluctuates with total body fat.

The structure, size, form and function of the breast tissue result from an intricate combination of hormone signals and ratios that permit epithelial cells to produce and secrete milk for the nourishment and sustenance of infants. Apart from the overt changes occurring at puberty, pregnancy, lactation and menopause, more subtle changes also occur within the normal menstrual cycle; as a result of hormonal disturbances, which probably underlie various disorders of the breast, especially fibroadenosis, but might also play some role in the pathogenesis of more serious conditions such as breast tumours. Likewise, the male breast normally remains rudimentary unless breast enlargement; which may also result from the use of certain drugs [3].
Most clinically significant breast disorders occur as lumps. It is thus of vital importance to identify those, which are malignant tumours so that the patient may be treated promptly. Several screening programs nowadays use radiological techniques (mammography) to identify early suspicious breast lesions, which are then subject to excision biopsy in the hope that removal of early-stage malignancy will prevent metastasis[4].

**A.2.1.2 Inflammatory disorders of the breast**

Infections of the breast are uncommon and mainly occur during lactation. The organisms (usually Staphylococcus aureus) gain access through cracks and fissures in the nipple and areola. Without early antibiotic therapy the resulting bacterial mastitis is often followed by the development of a breast abscess, which may require surgical drainage. More commonly, localized areas of the inflammation of the breast follow trauma, which may be of sufficient severity to produce necrosis of mammary adipose tissue, a condition known as fat necrosis (Figure 2.2). Following a typical initial acute inflammatory response, the continuing presence of necrotic adipose tissue excites a chronic inflammatory cell infiltrate, in which lipophages (macrophages containing lipid) and plasma cells may be present in large numbers. Fibrous proliferation at the margins of the damaged area produces a hard, often irregular, breast lump, which may resemble a breast carcinoma on palpation.
A.2.1.3 Hyperplastic lesions

The term hyperplastic lesion implies a benign condition of the breast and includes adenosis, ductal and lobular hyperplasia, papillary lesions, radial scar and fibrous change (fibrosis). These conditions are common in the breasts of mature women, increasing in frequency and severity towards the menopause. They are characterized by proliferative changes affecting components of the mammary unit (lobule, ducts and supporting stroma) probably in response to subtle disturbances of the hormone levels, particularly oestrogen. Unequal growth of epithelial and stromal elements gives rise to a variety of solid and cystic nodules within the breast, which are clinically important, as they must be distinguished from malignancy. The basic lesion is illustrated in Figure 3 and common variants shown in Figure 2.4.

In essence, the changes of fibroadenosis are the result of various different patterns of distortion and overgrowth of the functional breast unit, including ducts, lobules and supporting fibrous stroma. The epithelial components show hyperplastic overgrowth (adenosis) and the fibrous tissue increases (fibrosis).

The micrograph of Figure 2.3 shows the histological appearances of a typical lesion of fibroadenosis. There is hyperplasia of the breast acinar tissue in the lobules (adenosis) to produce islands of dark staining epithelium A. A prominent feature is fibrosis F surrounding the areas of adenosis. A frequent feature is marked dilatation of the ducts, to produce cystic lesions C lined by flattened ductular epithelium. The epithelium in areas of adenosis often develops strongly eosinophilic cytoplasm and comes to resemble the epithelium in apocrine sweat glands. This is termed apocrine metaplasia and is shown in the top of the micrograph M. Several variants of the fibroadenosis, which are commonly encountered and produce histological patterns, which can be confused with carcinomas, are illustrated in Figure 2.4.
Figure 2.3: Fibroadenosis-typical lesion

The hyperplastic overgrowth of epithelium and stroma in fibroadenosis may preferentially affect one tissue component, giving rise to patterns, which can superficially resemble carcinoma. Two of the more common variants of fibroadenosis are illustrated in these micrographs. Sometimes marked epithelial overgrowth results in the cystically dilated ducts C being filled by papillary ingrowths from the wall, a condition known as duct papillomatosis shown in micrograph (a). Solitary duct papillomas of similar appearance may occlude the larger mammary and nipple ducts. Note the areas of adenosis A and fibrosis F, which continue more usual components of fibroadenosis.

The changes, which may occur in the mammary lobules in fibroadenosis, are essentially those of hyperplastic proliferation of lobular acini (adenosis) and of the terminal part of the mammary duct within the lobule (terminal duct hyperplasia). In some variants, there is proliferation of the specialized hormone responsive lobular stromal elements, splitting the acini apart and compressing them into elongated strips. The change, known as sclerotic adenosis SA, is seen in micrograph (b). The importance of this condition is that it may be difficult to distinguish histologically from some invasive patterns of carcinoma, particularly in frozen sections of breast biopsies. Sclerotic lesions smaller than 1 cm are called radial scars. They have lost the lobulocentric configuration of sclerotic adenosis and are characterized by a central fibro-elastic core with a stellate arrangement of radiating tubular structures. The cellular, connective tissue around the ducts causes much distortion, but careful examination will demonstrate the two-cell structure of benign lesions. Micrograph (b) also illustrates apocrine metaplasia M. Some areas of fibroadenosis occasionally contain ill-defined nodules, which are histologically identical to benign fibroadenoma.

At one extreme, fibroadenosis may show only replacement of mammary adipose tissue by dense fibrous tissue, with the only epithelial component being dilated mammary ducts. This is particularly seen in women after the menopause and is described as mammary fibrosis with duct ectasia [4].
The only other benign tumour of much clinical significance is the benign Intraduct papilloma (Figure 2.6), usually occurring as a solitary lesion in one of the larger mammary ducts. Histologically similar papillary lesions may also be multifocal, occupying some of the ectatic (dilated) as a component of some patterns of fibroadenosis. Here the lesion is known as duct papillomatosis and probably represents hormone induced hyperplasia rather than a true neoplasm.
A.2.1.4 Breast lumps

The most common benign neoplasm of the breast is the fibroadenoma (Figure 2.6), a localized proliferation of breast ducts and stroma. Such lesions occur most frequently in isolated form in women aged 25-35 (‘breast mice’), but nodules of histologically identical tissue may also be a component of fibroadenosis. Fibroadenoma may therefore be a form of hormone dependent nodular hyperplasia rather than a true benign tumor. It is usually considered to be a benign tumor but may well represent a nodular form of benign mammary hyperplasia (fibroadenosis). It is well circumscribed by a condensation of connective tissue and is composed of both epithelial and fibrous stromal components. The epithelial components form glandular structures lined by mammary duct type epithelium, whilst the stromal component is a loose, cellular form of fibrous tissue F. In very large masses, the stroma may be myxomatous [4].

Two patterns of growth are seen, often in the same lesion. In the pericanalicular pattern P, the epithelial component takes the form of rounded ducts, which remain small and undistorted, with the stroma arranged round them in a roughly symmetrical and regular manner. By contrast, in the intracanalicular pattern I, the ducts appear elongated but actually represent sections cut through flattened spaces compressed by the stromal component, which appears to proliferate in an irregular nodular manner. In general, this latter pattern is more prominent in the larger fibroadenoma. In both patterns of fibroadenoma, hormonal changes such as those occurring during pregnancy and lactation may induce marked proliferation of the epithelial component.

A.2.1.5 Breast cancer

Malignant tumours of the female breast are extremely common, with a peak incidence in the decade before the menopause. Most are adenocarcinomas arising from the epithelium of either the mammary lobules (lobular carcinoma) or the mammary ducts (ductal carcinoma). The range of histological appearances is illustrated in figure 2.7. In some cases the development of invasive breast cancer may be preceded by carcinoma in situ in which the malignant cells proliferate.
within the mammary ducts or lobules but do not breach the basement membrane (intraduct or intralobular carcinoma). In addition to the main groups of lobular and ductal carcinoma there is a small group of special breast carcinomas, which are associated with distinct clinical and pathological features, often with a good prognosis. Examples are tubular carcinoma and medullary carcinoma. Carcinoma of the breast does occur in males but is extremely uncommon.

Figure 2.7: Carcinoma of the breast: a) intraduct carcinoma, b) lobular carcinoma in situ, c) invasive ductal carcinoma and d) invasive lobular carcinoma

In non-invasive intraduct carcinoma, tumor cells fill and distend the ducts. In micrograph (a), note a small duct filled with tumor T surrounded by normal acini A. The tumour cells are large and pale staining with large nuclei. There may be evidence of increased mitotic activity. Sometimes, duct distension is marked and the tumor cells at the center undergo necrosis (comedo pattern). Note that there is no infiltration into surrounding stroma S and that the epithelial basement membrane is not breached. Infiltration eventually supervenes with development of an invasive ductal carcinoma. As shown in micrograph (c), cords of tumor cells T then spread out from their ductal origin into the surrounding fibrous stroma S.

In non-invasive lobular carcinoma in situ as shown in micrograph (b), the normal lobular mammary architecture is maintained but the mammary lobules are increased in size as a result of proliferation of lobular epithelial cells with the cytological characteristics of malignancy. The cells fill and expand the acini of the mammary lobule, but the basement membrane remains intact and the general architecture of the lobule thus remains undisturbed.

In invasive lobular carcinoma as shown in micrograph (d), the tumor cells T breach the basement membranes of the acini and spill out into the surrounding stroma S, where they infiltrate into the fibro-adipose breast tissue, often in narrow cords and rows of cells described as ‘Indian file’ pattern of invasion. Lobular carcinoma has a high risk of bilateral breast involvement [4].
A.2.2 Historical review

The idea of medical imaging appeared for the first time many years ago and has become one of the most important aspects for the development of medicine. Both in diagnosis and prognosis the contribution of tomography has been of catalytic importance. It has helped greatly to the understanding of the function of human organs and has given solutions to problems that used to demand surgical operations in order to assess both the disease and therapy processes.

The basic experimental setup consists of the source of radiation, the target and the detector. Since many years tomography is a separate scientific field exploiting many physical and computational methods in order to develop techniques suitable for non-invasive imaging. Nowadays the use of on-line imaging systems is possible, which monitor the function of vital organs and blood flow. However, the development of a system that could be used from the patient, such as a monitoring device for the glucose level in the blood for diabetics, without blood extraction would have been a breakthrough. This has been the ultimate goal of scientific research.

Even from the 19th century medical doctors together with scientific groups tried to combine the function of internal organs with external visual symptoms. The goal was the immediate diagnosis without invading the patient’s body with an operation. The most successful method to date is histological analysis, even though it requires the excision of small biopsy tissue samples. The first to attempt an optical biopsy were the Victorian medical doctors, who tried to perform mammography with candlelight. Unfortunately the results were disappointing because of the excessive scattering that the light underwent so that any information useful for imaging the interior of the breast was lost.

A.2.3 Present status of Diagnosis

A.2.3.1 X-ray Imaging

During the recent years however, many techniques have been developed and applied, whereas many more are in experimental stage. They are based on the exploitation of different radiations that can be transmitted through tissue and image the shadow of inner organs and bones. The most commonly used are X-rays, which are applied to the detection of bone fractions, dental lesions and breast tumor imaging (mammography). X-ray imaging is so clear because of the small wavelength (~0.01 nm) of the radiation, which cancels the extensive scattering. The scattering of radiation becomes stronger as the wavelength approaches the dimensions of the components of tissue (typically in the range of nm –μm). Thus, X-rays penetrate deep into the tissue in contrast with highly scattered visible (400 – 800 nm) radiation. The produced image is the 2D projection of the attenuating properties of tissue along the path of the detected X-rays. The principal interactions that cause the attenuation are photoelectric absorption and inelastic scattering. The drawback however of the use of X-rays is introduced by the small wavelength, which is associated with very high energies (~100 KeV for X-rays), which can highly damage the tissue by ionization, breaking of DNA molecules and carcinogenesis. This limits the exposures a patient can undergo during his/her life. Moreover, these energies are much higher than the
molecular energy levels, thus making impossible the determination of chemical composition. Finally, X-rays present many difficulties since they cannot be manipulated with conventional optics [5].

Conventional radiographic imaging provides no depth information, as the 3D body structure is projected onto a 2D image. Another limitation mentioned above is the low soft tissue contrast, which is particularly important in many imaging schemes. X-rays computed tomography imaging is the development that gave the answer to these limitations. It produces thin 2D sections of the body, approximately 1 mm in thickness. Sub-millimeter spatial resolution with good discrimination between tissues (better than 1% attenuation change) can be achieved. The data acquisition is performed with a rotating fan beam X-ray source, which scans along the patient and a series of detectors. The image is then reconstructed from the 2D body slices [5].

A.2.3.2 X-ray Mammography

Mammography has an indispensable role in the detection of breast cancer. Many cancers can be discovered at a smaller size by mammography than by physical examination alone. It is an essential complement to the physical examination for the complete evaluation of symptomatic adults and for the screening of asymptomatic women at risk for breast cancer or for those who have undergone treatment for breast cancer. It has also helped to demonstrate the natural history of breast cancer. Mammography is used to direct the aspiration or core needle biopsy of non palpable lesions and to localise such lesions for surgical excision. Specimen radiographs serve to confirm that the appropriate site was removed for diagnosis [5].

The inability of this technique to differentiate between different types of soft tissue, introduces serious drawbacks since an interventional surgical biopsy would be required. This lack of specificity subjects a large number of women with benign breast diseases to unnecessary biopsy. And this is a very serious disadvantage taking into account that the cost of the performed biopsies is higher than the cost of the mammograms themselves. Furthermore, more effort should be directed towards an increasing compliance of the women to X-ray mammography, since even though inherently limited it is the only modality capable of decreasing mortality as much as 30% [5].

A.2.3.3 Ultrasound Imaging

Ultrasound is often a valuable complement to physical examination and mammography. It is non-invasive and involves no radiation exposure. At present, ultrasound is used for the evaluation of breast lesions and, in some cases, for guiding aspiration. Two techniques for examination of the breast are in use. One involves the use of a hand-held real-time scanner, where direct contact is made between the scanner and the skin of the breast, and a lubricant is used to eliminate the air-tissue interface, resulting in a two-dimensional, grey scale image. The second technique is a dedicated, whole-breast, computed ultrasonic examination that uses multiple step images.
In diagnostic ultrasound imaging, high frequency pulses of acoustic energy are emitted into the patients’ body where they experience reflection at boundaries between tissues of different characteristic impedance. From the measurement of time delay and intensity of the reflected pulses (echoes), an image indicating tissue interfaces can be reconstructed. Ultrasound imaging is considered to involve negligible risk, provided that the incident intensities are sufficiently small. The comparable long wavelengths of ultrasounds (>cm) minimize scattering and on the same time are harmless for humans. Unfortunately this sets the limit of the resolution to the centimeter range. Moreover as for X-rays they are not absorbed by the molecules, thus giving no information concerning the composition of tissue [6].

A.2.3.4 Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI), also referred as Nuclear Magnetic Resonance Imaging (NMR), is a means for the detection and diagnosis of breast lesions. It does not involve the exposure of patients to ionizing radiation, but the method is cumbersome and expensive. The image is produced by energy released from the motion of atoms subjected to a powerful magnetic field. The patient is placed inside a strong magnetic field, which is usually generated by large bore super conducting magnets. The resolution can go below the millimetre scale and many attempts are made to overcome that limit. Further advantages of MRI are the very low risk imposed to the patient and the complete non-invasive nature of the technique. With MRI, cysts are easily distinguished from solid tumors, and masses as small as 2mm in diameter can be detected. However, microcalcifications are not well visualized with MRI, and the morphologic character of cancers do not readily distinguish them from benign masses. The main drawback of MRI however is the extremely high cost of the devise and especially of the super conducting magnets that are necessary for the strong magnetic field, the large size of the equipment and the requirement for the patient to stay still in the magnet for up to about half an hour, as well as the problems associated with the presence of high magnetic fields [6].

A.2.3.5 Triple Examination

The combination of Fine Needle Aspiration Cytology (FNAC), mammography and physical examination – often referred to as “triple diagnosis” – may be more reliable than cytology alone. When the results of all three are indicative of cancer, open biopsies confirm cancer in 99.4% of cases. Conversely, when the results of all three suggest a benign lesion, cancer is found in only 0.4% of cases. Some physicians feel that observation is justified if the results of all three tests are negative for cancer. Impressions are not uniform, however, and concurrence is not regularly obtained. When the results of either physical examination or mammography suggest cancer, a negative result on FNAC is not reliable. The probabilities of cancer being present when varying results are obtained from these three modalities are shown in Table 1.
The data were obtained from one institution. Results tend to vary between institutions and should be determined in each case [4].

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td>Probability of cancer in patients with palpable breast masses according to results of “Triple Diagnosis”</td>
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<table>
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<tr>
<th>Result on FNAC, Probability of cancer (%)</th>
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<tr>
<td>Benign</td>
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<tr>
<td><strong>Result on Physical Examination</strong></td>
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<tr>
<td><strong>Benign</strong></td>
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<td>Results on Mammography:</td>
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<tr>
<td>Benign</td>
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<td><strong>Result on Physical Examination</strong></td>
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<td>Suspicious or Positive</td>
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<tr>
<td>Results on Mammography:</td>
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<td>Benign</td>
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<tr>
<td>Suspicious</td>
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### A.2.3.6 Radioisotope Imaging

Radioisotope imaging is fundamentally different from the previously introduced imaging modalities in that the radiation originates from inside the body. Radioisotope tagged compounds in tracer quantities are injected into the patients’ body where they decay and produce detectable photons. Hence it is possible to obtain images of the distribution of the radionuclide. Through the suitable choice of a labeled agent its distribution can be made representative of physiological function, such as blood flow, blood volume and various metabolic processes. Radioisotope imaging modalities are Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET).

In SPECT a single –ray is emitted per nuclear decay. A gamma camera, fitted with a parallel-hole collimator, rotates around the patient and records 1D projections of the radioactivity. A large number of such data sets allow the reconstruction (using a filtered back-projection similar to X-rays Computer Tomography) of a 2D cross-sectional image of the radiopharmaceutical distribution inside the body. Combining opposite projections helps to take into account the photon absorption
within the body. SPECT provides functional images with improved contrast at the expense of spatial resolution, as compared to planar radioisotope imaging. The question of a relatively cheap and fast imaging technique remains while the need for such a system becomes ever more essential [4].

A.2.3.7 Nuclear Medicine Breast Imaging Techniques

Nuclear medicine breast imaging techniques with use of single-gamma (scintimammography) or dual-gamma (positron-emitting PET) radiotracers are being considered as complementary modalities to conventional mammography for breast cancer diagnosis and characterisation, for evaluation of metastases, and as an aid in the selection of appropriate therapies.

Nuclear medicine imaging is a way of obtaining functional or metabolic information that could potentially decrease the number of unnecessary biopsies performed and may also act as an adjunct imaging modality for patients with radiodense breasts.

With future developments, it will most likely be of clinical value in cases where conventional imaging gives indeterminate or conflicting results. Success in imaging of small lesions will depend in part on the development of dedicated imaging devices. Future developments will enable pre- or intraoperative localisation, functional characterisation of breast lesions, and patient follow-up during and after therapy.

Technetium-99m sestamibi and Technetium-99m tetrafosfamin are used in scintimammography. Scintimammography has excellent sensitivity for tumours larger than about 1 cm; but it does have difficulty detecting smaller, non palpable or medially located lesions. For scintimammography to be accepted as a method that reliably detects small lesions, future developments in producing high-resolution, dedicated gamma cameras is crucial.

Other applications of scintimammography under study, include the detection of multidrug resistance in breast tumours, stereotaxic prebiopsy localisation of occult breast lesions and detection of axillary lymph node involvement in breast cancer. Positron emission tomography (PET) of the breast is based primarily on assessment either of the glucose metabolic rate via 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG) or of oestrogen- or progesterone-receptor density with 16[F-18]fluoroestradiol (FES).

Breast cancers aggressively accumulate the radiotracer FDG relative to the surrounding tissue. This has been studied in the past decade and as with scintimammography, lesions smaller than 1cm are typically not detected. FDG PET has been evaluated for the staging of recurrent breast cancer and detection of metastases.

Tumour oestrogen- or progesterone-receptor density is known to be a prognostic factor in patients with breast cancer and can be an important indicator of the potential efficacy of hormone replacement therapies. Approximately two-thirds of breast cancers are oestrogen receptor positive. Tumour uptake level of the radiolabeled oestrogen ligand FES has been shown to correlate strongly with estrogen-receptor content. Furthermore, FES has demonstrated promise as a way of identifying and evaluating the estrogen-receptor content of metastatic tumors of the axillary and mediastinal lymph node chain.
As is the case for scintimammography, future improvements in PET of breast cancer will include the development of dedicated image acquisition systems to enable detection of smaller lesions [5], [6].

### A.2.3.8 Optical Tomography

Optical tomography, which uses laser radiation, appears advantageous over the previous methods. The technique is based on the use of non-ionizing radiation (wavelengths in the visible and near infrared-NIR region), minimizing the effects on the tissue and if the intensity delivered is limited to the maximum permissible exposure of 2 mW/mm² (which corresponds to the solar constant), the only effect is thermal heating. Furthermore, if the wavelength chosen is between 600 and 900 nm (where the absorption is minimum), the thermal effects are also minimized. Moreover, since the energies in the visible range correspond to the energy gaps of the molecular transitions, spectroscopic information could also be obtained. This makes possible the imaging of the blood substance in the tissue, which is important for the monitoring of the function of vital organs. Moreover, optical imaging gives the potential of discriminating between different types of soft tissue (major advantage over X-ray imaging), as well as the possibility to derive functional information from quantitative measurements of chromophore concentrations [6].

However, the main drawback of using visible radiation for breast imaging is the extensive scattering that the photons undergo inside tissue which occurs due to the fact that the dimensions of the typical scatterers are the same as the wavelength. In order to overcome this drawback, a variety of techniques have been used so as to detect objects hidden in turbid media. Enhancement of the early part of the propagating pulse via non-linear techniques or time gating imaging has been used in order to discriminate between the photons that can carry information from the diffusively scattered ones. These are the photons that are transmitted ballistically through the medium and arrive first on the detector. The temporal spreading of a short light pulse as it propagates through the scattering medium might provide further information about the optical coefficients of the medium. A different approach, namely “the inverse problem”, which is based on the detection of the entire transmitted radiation and on the application of mathematical models in order to calculate characteristic parameters and reconstruct the medium that the photons have transmitted through, is used for imaging of discontinuities buried in turbid media [6].

### A.2.3.9 Optical Coherence Tomography

Optical Coherence Tomography (OCT), is an example of a successful clinical diagnostic application of near infrared light imaging technology, which overcomes the scattering problem of conventional optical tomography. It is based on
the use of short coherence length light to record depth resolved images using an interferometer. Depth information is obtained by optical ranging. Low coherence length light is directed into an interferometer (Michelson), one arm of which consists of a mirror on an adjustable stage and the other is used to direct the light onto the sample surface and collect the diffused reflected light. When the difference between the lengths of the two arms is less than the coherence length of the light, then a fringe pattern will be observed at the output. Thus by scanning the length of the reference arm and recording the mirror positions for which interference fringes are obtained, it is possible to determine the depth from which the light in the sample arm was reflected. The amplitude of the detected fringes depends on the amount of the absorption along the line-of-sight in the sample arm. By transversely scanning the line-of-sight of the sample arm through two dimensions, it is possible to build-up a depth-resolved absorption distribution. Thus a three dimensional image can be constructed. The depth resolution is limited to the coherence length. The time-of-flight or time gating technique may employ either broadband incoherent white light or ultra-short coherent optical pulses [6].
Chapter A

Introduction – Theoretical part

A.3. Lasers in Medicine
A.3.1 Characteristics of laser sources
A.3.1.1 Lasers
A.3.1.2 Light-Matter Interaction Processes
A.3.1.3 Components of a typical laser system
A.3.2 Thermodynamic equilibrium & population inversion
A.3.3 Properties of laser radiation
A.3.4 Laser applications
A.3. Lasers in Medicine

A.3.1 Characteristics of laser sources

A.3.1.1 Lasers

The word **LASER** stands for *Light Amplification by Stimulated Emission of Radiation* just to imply not only the distinctiveness of the creation of this light but also its special characteristics which are attributed to the way of its formation. It was invented in 1958 by Charles Townes and Arthur Schawlow of Bell Laboratories, based on Einstein’s idea of the “particle-wave duality” more than 30 years earlier.

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![Electromagnetic Radiation Spectrum](image)

*Figure 3.1: Electromagnetic Radiation Spectrum*

The term **LASER** is used to indicate both the apparatus that produces the light and the radiation itself. The simplest descriptive definition of **LASER** one could give, is that it is a layout, an apparatus that converts energy of different forms (electrical, chemical, electromagnetic, e.t.c.) into electromagnetic radiation that exhibits defined characteristics (monochromaticity, directionality, coherence, brightness). This radiation can be emitted in a visible or non-visible area of the electromagnetic spectrum, e.g. Ultraviolet (UV), Infrared (IR) [7], [8].

A.3.1.2 Light-Matter Interaction Processes

In 1917 Einstein, in an effort to explain radiation density that is emitted from a blackbody, he described the three processes through which the interaction of radiation with the atom occurs.
- Spontaneous emission of radiation
- Absorption, and
- Stimulated emission of radiation.

**Spontaneous emission of radiation**

It is the process during which a population of $N_2$ atoms of the $E_2$ state decay spontaneously to the state $E_1$ by emitting photons of energy $\hbar \nu = E_2 - E_1$.

![Figure 3.2: Spontaneous emission of radiation in a two level system](image)

If the population density in the excited state $E_2$ of a two level system is $N_2$, the decay to state $E_1$ is given by:

$$\frac{dN_2}{dt} = -A_{21}N_2,$$

where $A_{21}$ is the Einstein’s coefficient for spontaneous emission and is also referred as the probability of spontaneous emission. The solution of equation (3.1) is:

$$N_2(t) = N_2(t=0)e^{-A_{21}t},$$

where $N_2(t=0)$ is the original population $N_2$ of the level 2 at $t=0$. After time $t = \tau = \frac{1}{A_{21}}$, the population $N_2(\tau)$ will be reduced to $\frac{1}{e}$ of the original population. The time $\tau$ is also called the lifetime of the excited state $E_2$. During the exponential reduction in the population of level 2, the population of level 1 is exponentially increasing, according to:

$$N_1(t) = 1 - N_2(t=0)e^{-A_{21}t},$$

provided that $N_1(t) + N_2(t) = 1$ every time. Since the probability is constant over time, an ensemble of excited atoms or molecules will decay exponentially. The spontaneous emission intensity will be given by:

$$I_{sp}(t) = I_0e^{-t/\tau}.\quad (3.4)$$
Absorption

Absorption is the process in which a photon from the incident field is absorbed by an atom or molecule of the material, which is then driven to an excited state. The energy $E = h\nu$ of the photon corresponds to the energy difference of the two states (resonance condition) and is then converted into other forms of energy. The rate at which this process is taking place depends on the concentration of the absorbing atoms or molecules and the incident field. If $W(\nu)$ is the energy density per frequency interval, $B_{12}$ is the Einstein’s coefficient of absorption and $N_1$, $N_2$ the populations in the ground and excited state of a two level atomic system respectively we obtain:

$$\frac{dN_2}{dt} = B_{12}N_1W(\nu) = -\frac{dN_1}{dt}. \quad (3.5)$$

![Figure 3.3: Absorption of radiation in a two level system](image)

However, the absorption of light is a complicated quantum process. A description in the microscopic level would require the use of quantum electrodynamics. The description that follows will account for the macroscopic effect of the absorption of light in matter, which is the attenuation of the number of photons transmitted through a given material.

In linear optics the incremental decrease of the intensity is proportional to the intensity itself:

$$dI(z) = -\mu_n I(z), \quad (3.6)$$

where $\mu_n$ is the absorption coefficient measured in $mm^{-1}$. Integration of this equation leads to the well known Lambert-Beer law:
\[ I = I_0 e^{-\mu L}, \quad (3.7) \]

where \( I_0 \) is the incident and \( I \) is the transmitted intensity and \( L \) is the width of the material that photons have to travel through. For the determination of absorption the incident intensity \( I_0 \) and the transmitted intensity \( I \) have to be measured. Then the transmission \( T \) can be calculated by:

\[ T = \frac{I}{I_0}, \quad (3.8) \]

and thus the absorption coefficient can be determined as \( \mu_a = \frac{\ln(T)}{L} \). The inverse of the absorption coefficient gives the mean free path between two absorption events or absorption length \( l_a \) measured in mm. In terms of the particle density \( \rho \) and absorption cross section \( \sigma_{abs} \), \( \mu_a = \rho \sigma_{abs} \). The absorption coefficient is related to the imaginary part of the complex refractive index \( n_{complex} = n_{real} + i n_{imag} \), by:

\[ \mu_a = \frac{4\pi}{\lambda} n_{imag}. \quad (3.9) \]

The absorption coefficient depends on the wavelength for the different chromophores comprising biological tissue. The absorption of water dominates the IR (Infra-Red) region of the spectrum and the macromolecules and pigments dominate over the visible and UV regions. However, since the absorption of both water and macromolecules is minimized over the NIR region, a therapeutic window is opened between roughly 600 nm and 1200 nm, which is also referred to as “biological window”. In this spectral range the radiation penetrates deeper in biological tissue and it is in these wavelengths that all the attempts for optical imaging inside tissue have been performed.

**Stimulated emission of radiation**

The process of stimulated emission is the inverse of absorption. The atom or molecule that lies on an excited state is forced to return back to the ground state by emitting a photon and thus giving its energy \( h\nu \) to the field. The stimulatively emitted photon has the same frequency, phase and polarization and propagates in the same direction as the photon that induced the transition. The rate of the stimulated emission depends on the density of atoms or molecules and the strength of the stimulating field:

\[ \frac{dN_2}{dt} = -B_{21}N_2W(\nu) = - \frac{dN_1}{dt}. \quad (3.10) \]
From the basic electromagnetic theory arises the following relationship of the Einstein’s coefficients:

\[ A_{21} = \frac{8\pi\hbar n^2 n_g v^3 B_{21}}{c^3} = \frac{8\pi\hbar n^2 n_g v^3 B_{12}}, \]  
(3.11)

where \( n \) accounts for all the allowed values of the field energy and \( n_g \) for the group refractive index of the material.

All the above considerations were made with the assumption that the energy density of the field follows the blackbody radiation theory and the fact that the multiplicity factors of all the involved states are equal. However, when dealing with a real laser system we have to account for the fact that the gain medium emits a narrow band of frequencies or a lineshape \( \gamma(v) \) with a certain width \( \Delta v \). Thus, the *stimulated emission cross section* can be calculated as:

\[ \sigma_{em}(v) = A_{21} \frac{\lambda^2}{8\pi n^2} \gamma(v). \]  
(3.12)

The amplification of the intensity of the field travelling inside a cavity is given by:

\[ \frac{dI_v}{dz} = g(v)I_v, \]  
(3.13)

where \( g(v) = \sigma_{em}(v) \left( N_2 - \frac{g_2}{g_1} N_1 \right) \) is the gain coefficient of the lasing medium. The condition for positive gain and amplification is \( N_2 > (g_2/g_1)N_1 \), the well known *population inversion* condition.

Taking all these into account the basic coupled lasing equations, which describe the rate of the energy density of the field travelling inside the cavity and the rate of the number of molecules of each state, can be derived:

\[ \frac{dW_{em}}{dt} = -DW + \sigma_{em} cN_1 W_{em} + \frac{N_1}{\tau_{sp}}, \]  
(3.14)
\[
\frac{dN_1}{dt} = R - \sigma_{em} c N_1 W_{em} \frac{N_1}{\tau_{sp}},
\]

where D is a factor that accounts for all the losses of energy that are caused by the cavity and R is the pumping rate that produces the population inversion [9].

### A.3.1.3 Components of a typical laser system

A conventional laser system consists of the following components:

- **Lasing active medium**
- **Optical feedback or Optical cavity**
- **Output mechanism of electromagnetic radiation**
- **Pumping source**

![Figure 3.5: A simple laser system](image)

**Lasing active medium**

The active medium of a laser consists of a volume of atoms or molecules that can be excited in a state of inverted population (non-thermodynamic equilibrium) and with the aid of stimulated emission of radiation can emit radiation. The active medium of a laser can be in every form of matter: solid, liquid, gas or plasma, electrically neutral or ionized. The combination of the active medium and the optical cavity is what defines the wavelength on which a laser can emit. The emission wavelength is imposed by the possible transitions among the energy levels of the active medium.

**Optical cavity**

The feedback mechanism allows a part of the produced inside the active medium, coherent, laser radiation to remain in it. Usually, the feedback mechanism consists of two straight mirrors (between which lies the active medium), so as the radiation can
be reflected from one to another passing through the active medium. This arrangement is called optical cavity. Most of the times, the one mirror is 100% reflective, whereas the second is partially reflective (from 10 to 99% depending on the laser type). The part of radiation that escapes the partially reflective mirror comprises laser radiation. The feedback allows photons to pass through the optical cavity many times and to multiply, that is to amplify laser radiation. Due to the geometry of the optical cavity, only the photons travelling on the optical axis “survive” and amplify, resulting in the directionality of the laser radiation beam. Generally, the role of the optical cavity is to support the oscillation modes of laser radiation, on which the laser’s energy is imploded.

**Output mechanism of electromagnetic radiation**

The output beam mechanism consists of a partially reflective mirror, as mentioned before. The part of the beam that is not reflected by this mirror inside the active medium, exits the optical cavity of the laser. In continuous-wave (CW) lasers, the larger part of radiation is reflected by the partially reflective mirror and remains inside the cavity while only a small part exits. On the contrary, in some pulsed lasers, the larger part of produced radiation, at a particular moment exits the cavity in the form of a pulse.

**Pumping source**

Finally, the pumping mechanism is the energy source of the system, so as to achieve the necessary for laser action population inversion. There are different ways to achieve that:

- Optical pumping (Excitation with photons)
- Electrical gas excitation
- Excitation through atom striking
- Chemical excitation
- Excitation with electric current

**A.3.2 Thermodynamic equilibrium & population inversion**

The thermodynamic equilibrium between two bodies of different temperatures that are in contact or close one to another, is achieved when these two bodies obtain the same temperature with the aid of thermal conduction, thermal transport and radiation. In the case where the bodies are in vacuum and not in contact, the only process that can lead them to a state of thermodynamic equilibrium is radiation. It is then necessary that one of the bodies emit and the other one absorb radiation. The restoration of thermodynamic equilibrium will occur when the two bodies obtain the
same temperature $T$. In this case, the ratio of the atom population with electrons in the energy levels 2 and 1 (with energies $E_2$ and $E_1$ respectively) is determined by the temperature $T$, according to Boltzmann’s relationship:

$$\frac{N_2}{N_1} = \frac{g_2}{g_1} e^{-\frac{(E_2 - E_1)}{kT}} = \frac{g_2}{g_1} e^{-\frac{\Delta E}{kT}},$$  \hspace{1cm} (3.15)$$

where $g_2, g_1$ and $E_2, E_1$ ($E_2 > E_1$) are the statistical weights and the energies of the states 2 and 1 respectively, and $K = 1.38 \times 10^{23}$ Joule/°K is Boltzmann’s constant.

The natural meaning of equation (3.15) is extremely important, since it allows the calculation of the population ratio as a function of temperature $T$ (for given $\Delta E$), or the calculation of temperature $T$ if the ratio $\frac{N_2}{N_1}$ is known or countable in a way. In the following figure, we can see the populations of different energy levels, when the system is in a state of thermodynamic equilibrium. Of course, the lower energy states have larger populations.

![Figure 3.6: Distribution of a system’s populations in thermodynamic equilibrium](image)

One of the characteristics of the thermodynamic equilibrium existence is that Boltzmann’s relationship stands for every pair of populations $N_1 > N_2 > N_3$. In exceptional cases, though, if a system is provided with energy, it is possible that higher energy levels will appear larger populations than those of lower energy levels, in addition to Boltzmann’s equation. This is the case of inversed populations, which is far away from thermodynamic equilibrium and comprises the capable and necessary condition for laser action. The process to achieve the excitation of the electrons of the atoms to higher energy levels is called pumping, and specifically if it is performed with the use of optical radiation, it is called optical pumping [7],[8].
Figure 3.7: Distribution of the system’s populations:
i) in thermodynamic equilibrium, and
ii) in inversed populations state

A.3.3 Properties of laser radiation

Usually, when people talk about lasers and properties of the light that they emit, they refer to monochromaticity, directionality, brightness and coherence.

Monochromaticity

If natural or artificial white light passes through a prism, we know we can have its resolution on a white paper, in different colours-wavelengths of the visible spectrum (red, orange, yellow, green, blue and violet). If the experiment is repeated with a laser beam, only one colour will be observed on the paper, the one of the incident on the prism beam. If instead of a prism, a monochromator of great resolution ability was used, the distribution of the intensity of laser light as a function of its wavelength would be measurable. The monochromaticity of laser radiation or equally the bandwidth is characterized by Full Width at Half Maximum (FWHM). The narrower the distribution, the more monochromatic the radiation will be. Of course, there is a limit to the narrowness of the distribution [8].

Figure 3.8: Radiation bandwidth
**Directionality**

In addition to other light sources, the radiation emitted from a laser is propagating towards a particular direction, with a small angular dispersion to the propagating direction, meaning that laser radiation appears directionality.

![Diagram of directionality of a laser beam](Figure 3.9: Directionality of a laser beam)

The variation angle defines the directionality of a laser beam. In fact, the beam’s directionality is higher if the variation angle is small. The type of the optical resonator, the quality of the cavity mirrors, as well as the way of laser pumping determine the extend of directionality of the laser beam. The value of the angle \( \theta \) (expressed in mrad) is used to quantify the property of directionality. Since the variation of a typical laser beam is in the mrad order of magnitude, the beam is practically parallel and can propagate in large distances appearing small attenuation (due to the angular dispersion) of the energy transporting.

Generally, the directionality of a laser beam is directly related to the transport and deposition of electromagnetic energy far from the source. For example, the attenuation of the emitted energy from a glow lamp is reducing, according to the law of \( \frac{1}{r^2} \), showing that the measured energy depends on the square of the distance. On the contrary, in the case of a laser, the electromagnetic energy transported from the beam does not depend on the distance (in a first approach) [9].

**Brightness**

The brightness of the radiation emitted from the different types of laser systems is extremely high and can be compared (or even surpass) to the brightness of the sun. This is why the appropriate precautions must be taken and laser sources should never be observed directly. The Brightness is expressed in radiant power per unit lightened surface, per unit solid angle and, per unit optical frequency \( W/m^2srHz \). Especially for lasers, the amount of radiant energy that is transported from a laser beam is measured in Joule. The radiant power \( P \), that expresses the amount of energy the beam transports per unit time, is measured in watt. The power of laser radiation that
illuminates a surface over this surface, is called power density or irradiance $I$ and is measured in $\text{w/cm}^2$.

For CW lasers, the radiant power is of great importance. For pulsed lasers, however, the significant magnitudes are: the energy per pulse (J), the temporal duration per pulse (sec) and, the laser operation frequency (Hz) [9].

**Coherence**

Laser radiation has an extra characteristic that is relevant to the degree of interrelation among phase, magnitude and, frequency of the source emitted waves. This property, coherence, is not as obvious as the others. In simple words, coherence is the state in which the fluctuations of the relevant phases and magnitudes of the elementary electric dipoles that emit laser radiation are as small as possible, given a limit imposed by uncertainty principle. According to quantum field theory, the field of laser radiation is in the state called coherent state. So as to characterize fully laser beams, there is discrimination between temporal and spatial coherence. The first one relates to monochromaticity, while the second to directionality and the relevant position of waves in space.

**Temporal coherence**

Let’s imagine a wave, emitted by a light point source that has a bandwidth $\Delta\lambda$ and with the assistance of a light beam separator we divide it, which means we have two new waves. The temporal coherence is referred to the relationship between the relevant phases of the two waves along their spread direction, in two different points. These waves have perfect temporal coherence when their relevant phase at a time is the same with their relevant phase after time $\Delta t$ and after having covered a distance $l_c$ (in time $\Delta t = \frac{l_c}{c}$). The distance $l_c$ is called coherent length and is given by:

$$l_c = \lambda \left( \frac{\lambda}{\Delta\lambda} \right) = \frac{\lambda^2}{\Delta\lambda},$$

where $\Delta\lambda$ is the bandwidth of radiation and $\lambda$ the wavelength. Obviously, the wavelengths of emitted radiation remain the same, since $\Delta\lambda \ll \lambda$. The temporal coherence is also called longitudinal coherence due to the fact that it relates to the longitudinal modes propagation of the laser radiation.

**Spatial or Transverse coherence**

Let’s imagine two light sources or two parts of the same light source that abstain distance $s$ and let’s call $r$ the distance from the observation point.
If the confluence of the waves appears coherence elements in different points $a$ and $b$ of space that are in distance $r$ from the source (or the sources), then we have *Spatial or Transverse coherence* and is characterized by the *transverse coherence length* $l_h$:

\[ l_h = \frac{r\lambda}{s} \]  \hspace{1cm} (3.17)

The spatial coherence is related to the transverse longitudinal modes of laser radiation inside the optical cavity and states how relatively shifted can two sources or two parts of a source at a perpendicular plane to the direction of observation be and how coherent phenomena can still be observed [9].

### A.3.4 Laser applications

Lasers can be implemented into a variety of applications ranging from industrial to medical and market fields. Some of the concepts have already been forwarded, since the field exhibits an increasing interest among, both researchers and marketing people. Applications can be seen in:

- Physics (harmonic formation, stimulated scattering, temporal analysis measurements, spectroscopy, e.t.c.)
- Chemistry (uses for diagnostic causes, creation of non-reversed chemical alteration, photochemistry, e.t.c.)
- Material processing
- Optical communications
- Thermonuclear fusion
- Military applications
- Register and processing of information
- Distance measurements

The most important applications of lasers, however, focus on:

- Biology (fluorescence caused in the DNA from minor time laser pulses, coordinative Ramman scattering for biomolecule studies, photon correlation spectroscopy for information uptake, photolysis method with picosecond
brilliance for studying the dynamic behaviour of biomolecules in the excited state)

- Medicine (great applications in surgery, diagnosis, treatment (i.e. PDT)) [8]

This thesis deals with the diagnostic applications of lasers and particularly with a breast imaging technique that is called Computed Tomography Laser Mammography (CTLM) and will be unfolded in a following chapter.
Chapter A

Introduction – Theoretical part

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A.4. Light–matter effects and interaction mechanisms

A.4.1 Maxwell’s equations

The interaction of light with matter can be described by the well-known Maxwell’s equations:

\[ \nabla \cdot D = \rho \quad \text{(Gauss’s Law)} \]  \hspace{1cm} (4.1)

\[ \nabla \cdot B = 0 \]  \hspace{1cm} (4.2)

\[ \nabla \times E = -\frac{\partial B}{\partial t} \quad \text{(Faraday’s Law)} \]  \hspace{1cm} (4.3)

\[ \nabla \times H = J + \frac{\partial D}{\partial t} \quad \text{(Ampere – Maxwell’s Law)} \]  \hspace{1cm} (4.4)

where,

\[ D = \varepsilon_0 E + P \]

\[ H = \frac{1}{\mu_0} B - M. \]

The interaction of the light electric field with the charges of the material (electrons and ions) can be described by the combination of the wave equation and the time dependent Schrödinger equation:

\[ \nabla^2 E - \frac{1}{c^2} \frac{\partial^2 E}{\partial t^2} - \frac{\partial}{\partial t} (\nabla \cdot E) = \mu_0 \frac{\partial^2 P}{\partial t^2}, \quad \text{(wave equation - the magnetic component (4.5) can be usually neglected)} \]

\[ H(r,t)\Psi(r,t) = i \frac{\hbar}{2\pi} \frac{\partial \Psi(r,t)}{\partial t}, \quad \text{(time dependent Schrödinger equation)} \]  \hspace{1cm} (4.6)

The Hamilton operator \( H \) represents the total energy of the light-matter system and the wave function \( \Psi \) the quantum state of this system [10].
A.4.2 Light and Matter

When matter is exposed to light basic phenomena occur, due to the fact that it can act on electromagnetic radiation in manifold ways. When a light beam is incident on a slice of matter, three effects exist which may interfere with its undisturbed propagation:

- reflection and refraction,
- absorption,
- scattering.

Reflection and refraction are strongly related to each other by Fresnel’s laws. However, in medical laser applications, refraction plays a significant role only in the irradiation of transparent media like corneal tissue. In opaque media, usually the effect of refraction is difficult to measure due to the significant presence of the effects of absorption and scattering.

Only non-reflected and non-absorbed or forward scattered photons are transmitted by the slice and contribute to the intensity detected behind the slice. The ratio of the transmitted and incident intensities is called transmittance. The type of material and the incident wavelength determines which of the effects (reflection, absorption or scattering) is primarily dominant. In particular, wavelength is an extremely important parameter since it defines the index of refraction as well as the absorption and scattering coefficients. The index of refraction is governing the overall reflectivity of the target and only in regions of high absorption it strongly depends on the wavelength. On the other hand, the scattering coefficient can scale inversely with the fourth power of wavelength [11], [12].
A.4.2.1 Reflection and Refraction

Reflection is defined as the returning of electromagnetic radiation by surfaces upon which it is incident. Generally, a reflecting surface is the physical boundary between two materials of different indices of refraction such as air and tissue. The simple law of reflection requires the wave normals of the incident and reflected beams and the normal of the reflecting surface to lie within one plane being called the plane of incidence. It also states that the reflection angle $\theta'$ equals the angle of incidence $\theta$ as shown in Figure 4.2 and expressed by

$$\theta' = \theta$$

(4.2.1)

The angles $\theta$ and $\theta'$ are measured between the surface normal and the incident and reflected beams, respectively. The surface itself is assumed to be smooth, with surface irregularities being small compared to the wavelength of radiation. This results in so called specular reflection.

In contrast, i.e. when the roughness of the reflecting surface is comparable or even larger than the wavelength of radiation, diffuse reflection occurs. Then, several beams are being reflected which do not necessarily lie within the plane of incidence, and Equation (4.2.1) no longer applies. Diffuse reflection is a common phenomenon of all tissues, since none of them is provided with highly polished surfaces such as optical mirrors. Only in special cases such as wet tissue surfaces might specular reflection surpass diffuse reflection [11], [12].

![Figure 4.2.1: Geometry of specular Reflection and Refraction](image)

Refraction usually occurs, when the reflecting surface separates two media of different indices of refraction. It originates from a change in speed of the light wave. The simple mathematical relation governing refraction is known as Snell’s law:
\[
\frac{\sin \theta}{\sin \theta''} = \frac{\nu}{\nu'},
\]

(4.2.2)

where \( \theta'' \) is the angle of refraction, and \( \nu, \nu' \) are the speeds of light in the media before and after the reflecting surface, respectively. Since the corresponding indices of refraction are defined by

\[
n = \frac{c}{\nu},
\]

(4.2.3)

\[
n' = \frac{c}{\nu'},
\]

where \( c \) denotes the speed of light in vacuum, Equation (4.2.2) turns into

\[
n \sin \theta = n' \sin \theta'' .
\]

(4.2.4)

Only for \( \sin \theta > n'/n \) can Equation (4.2.4) not be fulfilled, meaning that refraction will not occur. This event is also referred to as total reflection.

The reflectivity of a surface is a measure of the amount of reflected radiation. It is defined as the ratio of reflected and incident electric field amplitudes. The reflectance is the ratio of the corresponding intensities and is thus equal to the square of the reflectivity. Reflectivity and reflectance depend on the angle of incidence, the polarization of radiation, and the indices of refraction of the materials forming the boundary surface. Relations for reflectivity and refraction are commonly known as Fresnel’s laws, which are given by:

\[
\frac{E_{r'}}{E_s} = -\frac{\sin(\theta - \theta'')}{\sin(\theta + \theta'')} 
\]

(4.2.5)

\[
\frac{E_{p'}}{E_p} = \frac{\tan(\theta - \theta'')}{\tan(\theta + \theta'')} 
\]

(4.2.6)

\[
\frac{E_{r'}}{E_s} = \frac{2\sin\theta''\cos\theta}{\sin(\theta + \theta'')} 
\]

(4.2.7)

\[
\frac{E_{p'}}{E_p} = \frac{2\sin\theta''\cos\theta}{\sin(\theta + \theta'')\cos(\theta - \theta'')} 
\]

(4.2.8)

where \( E, E' \) and \( E'' \) are amplitudes of the electric field vectors of the incident, reflected and refracted light, respectively. The subscripts “s” and “p” denote the two planes of oscillation with “s” being perpendicular to the plane of incidence and “p” being parallel.

Further interaction of incident light with the slice of matter is limited to the refracted beam. One might expect that the intensity of the refracted beam would be complementary to the reflected one so that the addition of both would give the
incident intensity. However, this is not correct, because intensity is defined as the power per unit area, and the cross-section of the refracted beam is different from that of the incident and reflected beams except at normal incidence. It is only the total energy in these beams that is conserved. The reflectances in either plane are given by:

\[
R_s = \left( \frac{E_s'}{E_s} \right)^2,
\]

\[
R_p = \left( \frac{E_p'}{E_p} \right)^2
\]

\textit{A.4.2.2 Absorption}

During absorption, the intensity of an incident electromagnetic wave is attenuated in passing through a medium. The absorbance of a medium is defined as the ratio of absorbed and incident intensities. Absorption is due to a partial conversion of light energy into heat motion or certain vibrations of molecules of the absorbing material. A perfectly transparent medium permits the passage of light without any absorption, i.e. the total radiant energy entering into and emerging from such a medium is the same. Among biological tissues, cornea and lens can be considered as being highly transparent for visible light. In contrast, media in which incident radiation is reduced practically to zero are called opaque.

The terms “transparent” and “opaque” are relative, since they certainly are wavelength-dependent. Cornea and lens, for instance, mainly consist of water which shows a strong absorption at wavelengths in the infra-red spectrum. Hence, these tissues appear opaque in this spectral region. Actually, no medium is known to be either transparent or opaque to all wavelengths of the electromagnetic spectrum.

A substance is said to show general absorption if it reduces the intensity of all wavelengths in the considered spectrum by a similar fraction. In the case of visible light, such substances will thus appear grey to our eye. Selective absorption, on the other hand, is the absorption of certain wavelengths in preference to others. The existence of colors actually originates from selective absorption. Usually, body colors and surface colors are distinguished. Body color is generated by light which penetrates a certain distance into a substance. By backscattering, it is then deviated and escapes backwards from the surface but only after being partially absorbed at selected wavelengths. In contrast, surface color originates from reflection at the surface itself. It mainly depends on the reflectances which are related to the wavelength of incident radiation.

The ability of a medium to absorb electromagnetic radiation depends on a number of factors, mainly the electronic constitution of its atoms and molecules, the wavelength of radiation, the thickness of the absorbing layer and internal parameters such as the temperature or concentration of absorbing agents. Two laws are frequently applied which describe the effect of either thickness or concentration on absorption,
respectively. They are commonly called Lambert’s law and Beer’s law, and are expressed by

\[ I(z) = I_o e^{-\mu a z} \]  
\[ I(z) = I_o e^{-k' cc} \]

where \( z \) denotes the optical axis, \( I(z) \) is the intensity at a distance \( z \), \( I_o \) is the incident intensity, \( \mu_a \) is the absorption coefficient of the medium, \( c \) is the concentration of absorbing agents, and \( k' \) depends on internal parameters other than concentration. Since both laws describe the same behavior of absorption, they are also known as Lambert – Beer’s law. From Equation (4.2.11) we can obtain

\[ z = \frac{1}{\mu_a} \ln \frac{I_o}{I(z)} . \]  

The inverse of the absorption coefficient \( \mu_a \) is also referred to as absorption length \( L \), i.e.

\[ L = \frac{1}{\mu_a} . \]  

The absorption length measures the distance \( z \) in which the intensity \( I(z) \) has dropped to \( 1/e \) of its incident value \( I_o \).

In biological tissues, absorption is mainly caused by either water molecules or macromolecules such as proteins and pigments. Whereas absorption in the IR region of the spectrum can be primarily attributed to water molecules, proteins as well as pigments mainly absorb in the UV and visible range of the spectrum. Proteins, in particular, have an absorption peak at approximately 280 nm.

Two elementary biological absorbers are melanin and hemoglobin (HbO₂). Melanin is the basic pigment of skin and is by far the most important epidermal chromophore. Its absorption coefficient monotonically increases across the visible spectrum toward the UV. Hemoglobin is predominant in vascularized tissue. It has relative absorption peaks around 280nm, 420nm, 540nm and 580nm, and then, exhibits a cut-off at approximately 600nm. Since neither macromolecules nor water strongly absorb in the near IR, a “therapeutic window” is delineated between roughly 600nm and 1200nm. In this spectral range, radiation penetrates biological tissues at a lower loss, thus enabling treatment of deeper tissue structures and it is in these wavelengths that all the attempts for optical imaging inside tissue have been performed [11], [12].
A.4.2.3 Scattering

When elastically bound charged particles are exposed to electromagnetic waves, the particles are set into motion by the electric field. If the frequency of the wave equals the natural frequency of free vibrations of a particle, resonance occurs being accompanied by a considerable amount of absorption. Scattering, on the other hand, takes place at frequencies not corresponding to those natural frequencies of particles. This resulting oscillation is determined by forced vibration. In general, this vibration will have the same frequency and direction as that of the electric force in the incident wave. Its amplitude, however, is much smaller than in the case of resonance. Also, the phase of the force vibration differs from the incident wave, causing photons to slow down when penetrating into a denser medium. Hence, scattering can be regarded as the basic origin of dispersion.

Scattering is the process during which the propagation direction of an electromagnetic wave, which is incident on a particle, is altered. It takes place when the light electric field induces dipoles upon incident on the medium, which re-emit the light in the plane perpendicular to the dipole (figure 4). Interpretation of scattering can be made in terms of the ratio between the wavelength of the incident light $k = 2\pi n/\lambda$ and the size of the scattering particle $a$. $k$ is the wavenumber, $\lambda$ the wavelength and $n$ the refractive index of the medium in which the field is travelling. The difference of the refractive indices of the medium and the scattering particle is also very important. Elastic and inelastic scattering are distinguished, depending on whether part of the incident photon energy is converted during the process of scattering. When $ka << 1$ the interaction is called Rayleigh scattering and when $ka \approx 1$ it is called Mie scattering. Both processes are elastic, meaning that the energy of the photons is conserved. However, there are other scattering processes in which the energy and frequency of photons are changed (inelastic scattering), such as Raman and Brillouin scattering [11], [12].
Figure 4.2.3: Schematic representation of scattering by a localized object.

**Single scattering**

A special kind of elastic scattering is *Rayleigh scattering*. Its only restriction is that the scattering particles are smaller than the wavelength of incident radiation \((ka \ll 1)\). In Figure 4.2.4, a simple geometry of Rayleigh scattering is shown. A plane electromagnetic wave is incident on a thin scattering medium with a total thickness \(L\). At a particular time, the electric field of the incident wave can be expressed by:

\[
E(z) = E_0 e^{ikz},
\]

(4.2.15)

where \(E_0\) is the amplitude of the incident electric field, \(k\) is the amount of the propagation vector, and \(z\) denotes the optical axis. In a first approximation, we assume that the wave reaching some point \(P\) on the optical axis will essentially be the original wave, plus a small contribution due to scattering. The loss in intensity due to scattering is described by a similar relation as absorption, i.e.

\[
I(z) = I_0 e^{-\mu_s z},
\]

(4.2.16)

where \(\mu_s\) is the scattering coefficient. Differentiation of Equation (4.2.16) with respect to \(z\) leads to

\[
dI = -\mu_s I dz.
\]

(4.2.17)

Figure 4.2.4: Geometry of Rayleigh scattering
The angular distribution of the scattered energy is governed by the incoherent scattering from the dipole scatterers and depends on the state of polarization of the incident wave. The total scattering cross section for Rayleigh scattering is given by:

$$\sigma_R = \frac{8}{3} \left[ \frac{\pi (n^2 - 1)}{N \lambda^2} \right]^2 \propto \frac{1}{\lambda^4}$$  \hspace{1cm} (4.2.18)

where \( n \) is the refractive index of the scatterer, \( N \) the concentration of scattering particles and \( \lambda \) the wavelength of the incident light. The above formula is the well known Rayleigh law, which describes very accurately the scattering of light in the atmosphere, which is responsible for the colours of the sunset and blue sky since blue light is scattered more effectively than red. A typical value of this cross section of the air with density of \( 2.5 \times 10^{19} \text{ cm}^{-3} \) at 500 nm is \( \sigma_R = 6.91 \times 10^{-28} \text{ cm}^2 \).

On the other hand when the particle’s size is comparable with the wavelength of the incident light field (\( ka \approx 1 \)) Mie scattering occurs. These particles can be aerosols or other fine particles in the air or colloids in a solution. The scattering intensity and angular distribution is a complicated function of the particle size, distributions and complex refractive indices. The problem can be solved only by a formal solution of the Maxwell’s equations, which can be applied only for certain simple symmetric shapes such as a sphere or a cylinder. However, the scattering cross section of Mie scattering shows a weaker dependence on wavelength than for Rayleigh scattering:

$$\sigma_{Mie} \propto \frac{1}{\lambda^x}$$  \hspace{1cm} (4.2.19)

where \( x \) could be \( 0.4 \leq x \leq 1.6 \). Moreover, Mie scattering takes place preferably in the forward direction, whereas Rayleigh scattering is proportional to \( (1 + \cos^2(\theta)) \) i.e. forward and backward directions are the same [11], [12].

**Multiple scattering**

However, when a macroscopic medium is studied, the total scattering of the radiation should be accounted for, which is the effect of multiple scattering events cause by an ensemble of scattering centers on the propagating light field. In that case a macroscopic optical parameter can be defined. This parameter is the scattering coefficient \( \mu_s \) measured in \( \text{mm}^{-1} \). Then the attenuation of the light intensity is defined from:

$$I(z) = I_o e^{-\mu_s L}$$  \hspace{1cm} (4.2.20)

where \( I_o \) is the incident and \( I \) is the transmitted intensity and \( L \) is the width of the material that photons have to travel through. From the scattering coefficient the scattering mean free path (measured in mm) between two scattering events can be defined as:
\[
I_s = \frac{1}{\mu_s} .
\]  
(4.2.21)

However, since in multiple scattering materials many random scattering events take place, it is important to define a probability function \( p(\theta) \) of a photon to be scattered at an angle \( \theta \). If \( p(\theta) \) does not depend on the angle then the scattering is \textit{isotropic}. Otherwise, \textit{anisotropic scattering} occurs. A measure of the anisotropy of scattering is given by the \textit{anisotropy factor} \( g \), where \( g = 1 \) denoted purely forward, \( g = -1 \) purely backward and \( g = 0 \) isotropic scattering. By definition \( g \) represents the average of the cosine of the scattering angle \( \theta \):

\[
g = \langle \cos \theta \rangle = \frac{\int_{4\pi} p(\theta) \cos \theta \sin \theta d\theta d\phi}{\int_{4\pi} p(\theta) \sin \theta d\theta d\phi}
\]  
(4.2.22)

In very complex media such as biological tissue (as discussed in the following section) the scattering coefficient is usually determined coupled to the anisotropy factor as the \textit{reduced scattering coefficient} \( \mu'_s \), defined as:

\[
\mu'_s = (1 - g)\mu_s
\]  
(4.2.23)

The probability function \( p(\theta) \), which is also called phase function, is normalized by:

\[
\frac{1}{4\pi} \int_{4\pi} p(\theta) \sin \theta d\theta d\phi = 1
\]  
(4.2.24)

Several theoretical phase functions \( p(\theta) \) have been proposed, but the most commonly used and the most accurate for describing light transport in tissue is the \textit{Henyey - Greenstein} function, which was first used for the description of light scattering in galaxies:

\[
p(\theta) = \frac{1 - g^2}{(1 + g^2 - 2g \cos \theta)^{3/2}}
\]  
(4.2.25)

\textbf{Scattering in biological tissue}

Biological tissue is one of the most complicated materials combining both absorption and multiple scattering. In such media a total \textit{attenuation coefficient} \( \mu = \mu_s + \mu_a \) can be defined to account for both processes. The behaviour of tissue cannot be accurately explained either with Rayleigh nor Mie scattering and thus only macroscopic description can be made as illustrated in the following sections. The scattering inside biological tissue is due to the microscopic components that it consists of such as cells, intracellular organelles or collagen fibers. In figure 4.2.5 the relative
size of these scattering components compared with the wavelength of the light is depicted [14].

![Figure 4.2.5: Schematic representation of the relative sizes of the scattering components of biological tissue and the corresponding scattering mechanism.](image)

**A.4.3 Turbid media**

In most tissues, both absorption and scattering are present simultaneously. Such media are called *turbid media*. In turbid material light is scattered and absorbed due to the inhomogeneities and absorption characteristics of the medium. Their total attenuation coefficient can be expressed by:

\[
\mu_t = \mu_a + \mu_s
\]

A mathematical description of the propagation and scattering characteristics of light can be made using two different approaches: analytical theory and transport theory. *Analytical theory*, which is the most fundamental approach although mathematically complexed, starts with the Maxwell’s equations takes into account the statistical nature of the medium and considers the statistical moments of the wave. On the other hand, *transport theory*, which has been used extensively, deals directly with the transport of power through turbid media and is applicable to a large number of practical problems but lacks the rigor of analytical theory [14], [15].
A.4.4 Photon Transport Theory

The fundamental quantity in transport theory is called the radiance $J(r,s)$ and is expressed in units of $Wcm^{-2}sr^{-1}$. It denotes the power flux density in a specific direction $s$ within a unit solid angle $d\omega$. The governing differential equation for radiance is called the radiative transport equation and is given by:

$$\frac{dJ(r,s)}{ds} = -\mu_s J(r,s) + \frac{\mu_t}{4\pi} \int p(s,s') J(r,s') d\omega'$$ \hspace{1cm} (4.4.1)

where $p(s,s')$ is the phase function of a photon to be scattered from direction $s'$ into $s$, $ds$ is an infinitesimal path length, and $d\omega'$ is the elementary solid angle about the direction $s'$. If scattering is symmetric about the optical axis, we may set $p(s,s') = p(\theta)$ with $\theta$ being the scattering angle. However, in experimental measurements of optical properties, the observable quantity is the intensity ($Wcm^{-2}$) which is derived from radiance by integration over the solid angle:

$$I(r) = \int_{4\pi} J(r,s) d\omega.$$ \hspace{1cm} (4.4.2)

On the other hand, radiance can be expressed in terms of intensity by:

$$J(r,s) = I(r) \delta(\omega - \omega_s),$$ \hspace{1cm} (4.4.3)

where $\delta(\omega - \omega_s)$ is a solid angle delta function pointing into the direction given by $s$.

When a laser beam is incident on a turbid medium, the radiance inside the medium can be divided into a coherent and a diffuse component according to the following relation $J = J_c + J_d$.

The coherent radiance is reduced by attenuation due to absorption and scattering of the direct beam and can thus be calculated by:

$$\frac{dJ_c}{ds} = -\mu_s J_c,$$

with solution $J_c = I_0 \delta(\omega - \omega_s) e^{-d}$, where $I_0$ is the incident intensity and $d$ is the optical depth defined by $d = \int_0^\prime \mu ds'$.

The main drawback of the transport theory is the evaluation of the diffuse radiance, since scattered photons do not follow a determined path. Therefore, adequate approximations and statistical approaches for the solution must be chosen, depending on whether absorption or scattering is the dominant process of attenuation. Some of these approaches are First-Order Scattering for $J_c >> J_d$ and Kubelka-Munk Theory for $J_c << J_d$ (analytically) or Monte Carlo Simulation (numerically). However, the most general applicable approach for scattering dominating over absorption is the Diffusion Approximation [14], [15].
**A.4.5 Diffusion Approximation**

When a laser beam enters a medium, the radiance can be expressed as a sum of a coherent and a diffuse component. If the medium is mostly scattering, the diffuse radiance tends to be almost isotropic and the diffuse radiance has a broad angular spread. Therefore, the diffuse radiance can be expended in a series of spherical harmonics. The two first terms of the expansion constitute the diffusion approximation:

\[
J_d = \sum_{n=0}^{\infty} J_n = \frac{1}{4\pi} (I_d + 3F_d \cdot s + \ldots) \quad (4.5.1)
\]

where \( I_d \) is the diffuse intensity and \( F_d \) is the vector flux determined by:

\[
F_d(r) = \int_{4\pi} J_d(r,s) \cdot s \, d\omega. \quad (4.5.2)
\]

The diffuse intensity then satisfies the following diffusion equation:

\[
\frac{n}{c} \frac{\partial I_d(r)}{\partial t} - D \nabla^2 I_d(r) + \mu_t I_d(r) = S(r) \quad (4.5.3)
\]

where \( n \) is the refractive index of the medium, \( c \) the speed of light, \( S(r) \) is the photon source and \( D \) is the diffusion coefficient defined by:

\[
D = \frac{1}{3[\mu_a + (1-g)\mu_t]} \quad (4.5.4)
\]

The diffusion of light inside a turbid medium can be described by an effective attenuation coefficient \( \mu_{\text{eff}} \) given by:

\[
L_{\text{eff}}^{-1} = \mu_{\text{eff}} = \sqrt{3} \mu_a (\mu_a + \mu_t (1-g)) \quad (4.5.5)
\]

and thus the diffusion approximation states that:

\[
I = I_c + I_d = A e^{-\mu_c z} + B e^{-\mu_{\text{eff}} z} \quad (4.5.6)
\]

where \( A + B = I_0 \).

When an optical beam enters a turbid medium, the first-order scattering is dominant near the surface and as the observation point moves into the medium second-order and higher-order scattering increases. The diffusion solution is an approximation representing the limiting case where the multiple scattering is dominant. It is therefore clear that near the surface (or for very thin media) the diffusion solution may not be applicable [14], [15].
A.4.6 Optical Tissue Properties Measurement

Generally, the measurement of optical tissue properties is performed with the assistance of several methods, which focus on different quantities such as transmitted, reflected, and scattered intensities. The absorbance itself is difficult to determine, since photons absorbed by the tissue cannot be used anymore for detection. Therefore, the absorbed intensity is usually obtained when subtracting transmitted, reflected and scattered intensities from the incident intensity. Depending on the experimental method, either only the total attenuation coefficient or the coefficients of both absorption and scattering can be evaluated. If the angular dependence of the scattered intensity is measured by rotating the corresponding detector, the coefficient of anisotropy can be obtained, as well.

Biological tissue is something very inhomogeneous and fragile. The inhomogeneity makes it difficult to transfer experimental data from one sample to another. Usually, it is taken into account by applying generous error bars. However, optical properties determined in vitro may differ extremely from those valid in vivo, due to several reasons. Firstly, alive tissue does not have the same morphologic structure as excised tissue, with the typical example of corneal tissue that turns into a turbid material within a few hours after dissection. Secondly, alterations are induced by unavoidable deformation and handling of the tissue such as drying, freezing or just soaking in saline. Dehydration especially leads to a gross effect on the optical properties of tissue [16], [17].
A.4.7 Interaction Mechanisms

When applying laser light to biological tissue, the occurrence of a variety of interaction mechanisms is multiple. This diversity is due to specific tissue characteristics as well as laser parameters. Most important among optical tissue properties are the coefficients of reflection, absorption and scattering, which determine the total transmission of the tissue at a certain wavelength. On the other hand, parameters such as the wavelength, the exposure time, the applied energy, the focal spot size, the energy density and the power density are determined by the laser radiation itself.

Currently, five categories of interaction types are being classified:

- Photochemical interactions
- Thermal interactions
- Photoablation
- Plasma-induced ablation
- Photodisruption.

Laser radiations induce biological damage in tissues via photochemical, photothermal, and photomechanical interactions. The type of response depends on the optical and thermal properties of the tissue, wavelength, laser power density, and pulse duration. The optical absorption spectra of tissue chromophores are shown in Figure 4.7.

![Figure 4.7](image.png)

*Figure 4.7: UV is absorbed primarily by "colourless" structural macromolecules and nucleic acids, visible light is absorbed by hemoglobin and melanin, and IR is absorbed by tissue water and calcified substances.*

The average power density within the irradiated region of the tissue is inversely proportional to the optical penetration depth. The latter parameter is designated as $d_{op}$ in this chapter to distinguish it from the thermal penetration depth $d_{th}$. The spectra in Figure 4.7 shows that both UV and IR laser radiations are strongly absorbed by tissues. However, there is a significant difference in the physical mechanisms. IR lasers heat and ablate tissue by macroscopic thermal and photomechanical effects, while the basic interactions for UV lasers are initiated by photoionization and
photodissociation of the constituent molecules. High values of $d_{op}$ are desirable for applications requiring deep light penetration such as hyperthermia and coagulation. The Nd: YAG laser is especially useful for coagulation because the 1064 nm emission lies in a "window" between the strong absorptions of hemoglobin and tissue water. Small values of $d_{op}$ are useful for controlled vaporization and ablation as provided by carbon dioxide and Excimer surgical lasers. The pulsed erbium-YAG laser is approved in the U.S. for dental applications. The 2.94 μm IR emission is strongly absorbed by hydroxyapatite, the predominant crystal structure in dentin and enamel. In recent work the pulsed 9.6 μm carbon dioxide laser is being tested for dental applications [11], [12], [13].

![Figure 4.7.1: Power density versus interaction time for a variety of medical applications.](image)

Interestingly, these two quantities span many orders of magnitude but their product (the light fluence), varies over a much smaller range. This emphasizes the point that it is the rate of energy absorption that determines the nature of the light-tissue interaction.

**A.4.7.1 Photochemical Interaction**

Light can induce chemical effects and reactions with macromolecules or tissues. This fact, which has been observed empirically, has comprised the basis for the study
of photochemical interactions. In the field of medical laser physics, photochemical interaction mechanisms play a significant role during Photodynamic Therapy (PDT). Frequently, biostimulation is also attributed to photochemical interactions, although this is not scientifically ascertained.

Photochemical interactions take place at very low densities (typically $1 \text{ W/cm}^2$) and long exposure times ranging from second to continuous wave. Careful selection of laser parameters yields a radiation distribution inside the tissue that is determined by scattering. In most cases, wavelengths in the visible range are used because of their efficiency and their high optical penetration depths.

During PDT, spectrally adapted chromophores (photosensitizers) are injected into the body and with the use of monochromatic irradiation, selective photochemical reactions are then triggered, resulting in certain biological transformation. Laser irradiation causes resonant excitation and the photosensitizer performs several simultaneous or sequential decays that result in intramolecular transfer reactions. Finally, highly cytotoxic reactants are released causing an irreversible oxidation of essential cell structures. The main idea of photochemical treatment is to use a chromophore receptor acting as a catalyst. Its excited states are able to store energy transferred from resonant absorption and their deactivation leads to toxic compounds leaving the photosensitizer in its original state (photosensitized oxidation) [11], [12], [13].

### Photochemical Interaction

<table>
<thead>
<tr>
<th>Main idea</th>
<th>using a photosensitizer acting as a catalyst (only in photodynamic therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observations</td>
<td>no macroscopic observations</td>
</tr>
<tr>
<td>Typical Lasers</td>
<td>red dye lasers, diode lasers</td>
</tr>
<tr>
<td>Typical pulse durations</td>
<td>$1\text{s...CW}$</td>
</tr>
<tr>
<td>Typical power densities</td>
<td>$0.01...50 \text{ W/cm}^2$</td>
</tr>
<tr>
<td>Special applications</td>
<td>photodynamic therapy, biostimulation</td>
</tr>
</tbody>
</table>

#### A.4.7.2 Thermal interaction

The term thermal interaction includes a large group of interaction types, where the increase in local temperature is the significant parameter change. Thermal effects can be induced by either CW or pulsed laser radiation. In general, thermal effects tend
to be non-specific. However, different effects like coagulation, vaporization, carbonization and melting can be distinguished, depending on the duration and peak value of the tissue temperature achieved.

Temperature is the governing parameter of all thermal laser-tissue interactions. At the microscopic level, thermal effects have their origin in bulk absorption occurring in molecular vibration-rotation bands which are followed by a non-radiative decay. The reaction with a target molecule $A$ can be considered as a two-step process. First, absorption of a photon with an energy $h\nu$ promotes the molecule to an excited state $A'$, and second, inelastic collisions with some partner $M$ of the surrounding medium lead to a deactivation of $A'$ and a simultaneous increase in the kinetic energy of $M$. Therefore, microscopically, the temperature rise originates from the transfer of photon energy to kinetic energy.

Absorption: $A + h\nu \rightarrow A'$

Deactivation: $A' + M(E_{\text{kin}}) \rightarrow A + M(E_{\text{kin}} + \Delta E_{\text{kin}})$

The large number of accessible vibrational states of most biomolecules, facilitates the effect of absorption. Moreover, the channels that are available for deactivation and thermal decay are also numerous, due to the fact that typical energies of laser photons (Er:YAG laser: $0.35\, eV$, Nd:YAG laser: $1.2\, eV$, ArF laser: $6.4\, eV$) exceed by far the kinetic energy of a molecule at room temperature which is only about $0.025\, eV$. Thus, both steps are highly efficient, as long as the duration of laser exposure is selected properly.

The spatial extend and degree of tissue damage mainly depend on magnitude, exposure time and placement of the heat deposited inside the tissue. However, the laser energy deposited is not only a function of laser parameters (wavelength, power density, exposure time, spot size and repetition rate) but depends also strongly on optical tissue properties (absorption and scattering coefficients). Specifically, thermal tissue properties, such as heat capacity and thermal conductivity are of major significance.

In biological tissue, the effect of absorption, which is governed by Lambert’s law, takes place primarily due to the presence of free water molecules, proteins, pigments, and other macromolecules. The absorption coefficient highly depends on the wavelength of the incident laser radiation. In thermal interactions, absorption by water molecules (which are important constituents of most tissues) plays an extremely important role. In the visible range, the absorption coefficient of water is extremely small. Absorption in tissue in this section of the spectrum and in the UV is high, depending on the relative content of macromolecules such as melanin and hemoglobin. On the other hand, in the IR range of the spectrum, water molecules are the dominant absorbers, since their absorption coefficient increases then by several orders of magnitude.

The basic parameters that govern thermal effects are summarized in the following Figure 4.7.2. Heat generation is determined by laser parameters and optical tissue properties (irradiance, exposure time and the absorption coefficient, which is a function of the laser wavelength). Heat transport is characterized by thermal tissue properties such as heat conductivity and heat capacity. Finally, heat effects, depend on the type of tissue and the temperature achieved inside the tissue.
We consider a Gaussian-shaped laser beam that irradiates a slab of tissue exposed in air. To make things simple, a cylindrical geometry is chosen, with \( z \) denoting the optical axis and \( r \) the distance from this axis. The amplitude of the electric field and the corresponding intensity are given by the following equations:

\[
E(r,z,t) = E_0 \exp\left(-\frac{r^2}{\omega^2} - \frac{\mu_u z}{2}\right) \exp\left(-\frac{4t^2}{r^2}\right),
\]

\[
I(r,z,t) = I_0 \exp\left(-\frac{2r^2}{\omega^2} - \mu_u z\right) \exp\left(-\frac{8t^2}{r^2}\right),
\]

where \( E_0 \) and \( I_0 \) are the incident values of the electric field and intensity, respectively, \( \omega \) is the beam waist, \( \mu_u \) is the absorption coefficient and \( r \) is the pulse duration. The incident values \( E_0 \) and \( I_0 \) are related to each other by the basic electrodynamic equation

\[
I_0 = \frac{1}{2} \varepsilon_0 c E_0^2,
\]

where \( \varepsilon_0 \) is the dielectric constant, and \( c \) is the speed of light. In a first approximation scattering inside the tissue is neglected.
Heat generation

During laser exposure, heat is generated inside the tissue. The light absorbed in the tissue, results in the deposition of heat in it. For a light flux in the \( z \)-direction in a non-scattering medium, the local deposition per unit area and time in a thickness \( \Delta z \) \((W/cm^2)\) is given by:

\[
S(r,z,t) = \frac{I(r,z,t) - I(r,z + \Delta z,t)}{\Delta z}.
\]

(4.7.2.3)

And as \( \Delta z \) approaches zero,

\[
S(r,z,t) = -\frac{\partial I(r,z,t)}{\partial z}
\]

Under all circumstances, heat deposition is determined by

\[
S(r,z,t) = \mu_a I(r,z,t).
\]

(4.7.2.4)

The heat source \( S(r,z,t) \) inside the exposed tissue is a function of the absorption coefficient \( \mu_a \), which is wavelength-dependent and the local intensity. If phase transitions (vaporization, melting) or tissue alterations (coagulation, carbonization) do not occur, an alteration in heat content \( dQ \) induces a linear change in temperature \( dT \) according to a basic role of thermodynamics

\[
dQ = mc dT,
\]

(4.7.2.5)

where \( m \) is the tissue mass, and \( c \) is the specific heat capacity expressed in units of \( kJ \cdot kg^{-1} \cdot K^{-1} \).

Heat transport

The relationship between temperature and heat content for a closed physical system is given by:

\[
dQ = mc dT.
\]

However, in real laser-tissue interactions, another aspect must be taken into consideration, losses of heat. They are based on either heat conduction, heat convection, or heat radiation. For most types of laser applications, the latter two are neglected due to their insignificance. A typical example of heat convection in tissue is heat transfer due to blood flow. However, heat convection can be neglected in a first approximation, due to the low perfusivity of most tissues. Only during long exposures and in special cases, such as Laser Induced Interstitial Thermotherapy (LITT) does it play a significant role and should be considered by adding a negative heat loss \( S_{loss} \) to the source term \( S \). Stefan-Boltzmann’s law describes heat radiation and states that the radiated power is related to the fourth power of temperature. In
most laser-tissue interactions, moderate temperatures are achieved, so heat radiation
can often be neglected.

Heat conduction, though, is a significant heat loss term and is the primary
mechanism by which heat is transferred to unexposed tissue structures. The heat flow
\( \dot{Q} \) is proportional to the temperature gradient according to the general diffusion
equation

\[
\dot{Q} = -k \nabla T ,
\]

where the constant \( k \) is called heat conductivity and is expressed in units of \( \text{Wm}^{-1}\text{K}^{-1} \).

The general heat conduction equation is derived from the equation of continuity
(which describes the temporal change in heat content per unit volume) with the
combination of the previous equations and is expressed by:

\[
\begin{align*}
T &= \kappa \Delta T , & \text{homogeneous heat conduction equation} \\
T &= \kappa \Delta T + \frac{1}{\rho c} S , & \text{inhomogeneous heat conduction equation}
\end{align*}
\]

where \( \kappa \) is the temperature conductivity and \( \Delta \) is the Laplace operator.

The spatial extend of heat transfer is described by the time-dependent thermal
penetration depth, which is the distance in which the temperature has decreased to
\( 1/e \) of its peak value.

\[
z_{\text{therm}}(t) = \sqrt{4\kappa t} .
\]

For thermal decomposition of tissues and in order to minimize thermal damage to
adjacent structures, the duration of the laser pulse must be modulated. This leads to
the minimum possible necrosis. The parameter that defines all the above is thermal
relaxation time \( \tau_{\text{therm}} \)

\[
L = \sqrt{4\kappa \tau_{\text{therm}}} ,
\]

where \( L \) is the optical penetration depth mentioned previously. During thermal
decomposition, \( \tau_{\text{therm}} \) becomes very important, since it measures the thermal
susceptibility of the tissue.

**Heat effects**

Thermal interaction deals with biologic effects related to different temperatures
inside the tissue, which can be manifold depending on the type of tissue and laser
parameters chosen. The first mechanism by which tissue is thermally affected can be
attributed to conformational changes of molecules. The term hyperthermia ranging
from approximately 42°–50°C, includes these effects as well as bond destruction
and membrane alterations. If hyperthermia lasts for several minutes, an important
percentage of the tissue will undergo necrosis. Beyond $50^\circ C$, a measurable reduction in enzyme activity is observed, resulting in a reduced energy transfer within the cell and immobility of the cell. Furthermore, certain repair mechanisms of the cell are disabled. Thus, the fraction of surviving cells is further reduced.

At $60^\circ C$, denaturation of proteins and collagen occurs which leads to coagulation of tissue and necrosis of cells. The corresponding macroscopic response is visible paling of the tissue. Several treatment techniques (i.e. LITT) aim at temperatures just above $60^\circ C$. At even higher temperatures (> $80^\circ C$), the membrane permeability is drastically increased, resulting in the destruction of the otherwise maintained equilibrium of chemical concentrations.

At $100^\circ C$, water molecules contained in most tissues start to vaporize. The large vaporization heat of water (2253 kJ/kg), is advantageous since the vapor generated carries away excess heat and helps to prevent any further increase in the temperature of adjacent tissue. The large volume increase during this phase transition, results in the formation of gas bubbles which induce mechanical ruptures and thermal decomposition of tissue fragments.

The increase in temperature proceeds only if all water molecules are vaporized and laser exposure still continues. At temperatures exceeding $150^\circ C$, carbonization takes place. This effect is observable by the blackening of adjacent tissue and the escape of smoke. In order to avoid carbonization, the tissue is usually cooled with either water or gas. Beyond $300^\circ C$, melting can occur, depending on the target material [11], [12], [13].

<table>
<thead>
<tr>
<th>Thermal Interaction</th>
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<tbody>
<tr>
<td><strong>Main idea:</strong></td>
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<tr>
<td><strong>Observations:</strong></td>
</tr>
<tr>
<td><strong>Typical Lasers:</strong></td>
</tr>
<tr>
<td><strong>Typical pulse durations:</strong></td>
</tr>
<tr>
<td><strong>Typical power densities:</strong></td>
</tr>
<tr>
<td><strong>Special applications:</strong></td>
</tr>
</tbody>
</table>

**A.4.7.3 Photoablation**

Photoablation is a kind of UV light-induced ablation that concerns the removal of tissue without the appearance of thermal damage. It was firstly identified as ablati...
photodecomposition, denoting that material could be decomposed when exposed to high intense laser irradiation. At pulse durations in the range of nanoseconds, the typical threshold values of power densities for this type of interaction are \(10^7 - 10^8 W/cm^2\). The ablation depth, which is the depth of tissue removal per pulse, is determined by the pulse energy up to a certain saturation limit. The spatial parameters of the laser beam define the geometry of the ablation pattern. The technique appears high precision of the etching process, excellent predictability and above all, lack of thermal damage to adjacent tissue. Nowadays, photoablation is used in refracting corneal surgery, where the refractive power of the cornea is altered in myopia, hyperopia or astigmatism.

Photoablation will take place as long as the following inequality is satisfied:

\[
I_0 e^{-\mu_\alpha z} \geq I_{ph},
\]

(4.7.3.1)

where \(I_0\) is the incident laser intensity, \(\mu_\alpha\) the absorption coefficient of the tissue, \(z\) the optical axis and \(I_{ph}\) is the threshold intensity for photoablation. The ablation depth \(d\), the depth at which \(I(z) = I_{ph}\), should then be

\[
d = \frac{1}{\mu_\alpha} \ln \frac{I_0}{I_{ph}}.
\]

(4.7.3.2)

A second threshold \(I_{pl}\), which is the threshold of plasma generation, determines the saturation of the ablation depth per pulse. The generation of a high electric field at high power densities, results in the absorption of the larger part of the succeeding laser radiation by the plasma ignited, thereby heating it up and leading to additional thermal effects [11], [12], [13].

<table>
<thead>
<tr>
<th>Photoablation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main idea</strong> :</td>
</tr>
<tr>
<td><strong>Observations</strong> :</td>
</tr>
<tr>
<td><strong>Typical Lasers</strong> :</td>
</tr>
<tr>
<td><strong>Typical pulse durations</strong> :</td>
</tr>
<tr>
<td><strong>Typical power densities</strong> :</td>
</tr>
<tr>
<td><strong>Special applications</strong> :</td>
</tr>
</tbody>
</table>
A.4.7.4 Plasma-Induced Ablation

When applying power densities that exceed \(10^{11} \text{W/cm}^2\) in solids and fluids or \(10^{14} \text{W/cm}^2\) in air, \emph{optical breakdown} occurs and results in a bright plasma spark. The term optical breakdown emphasizes that UV, visible and IR light are strongly absorbed by the plasma. The \emph{plasma-induced ablation} concerns very clean and well defined removal of tissue without evidence of thermal or mechanical damage, if the appropriate laser parameters are chosen. This kind of ablation is primarily caused by plasma ionization itself, and its most important parameter is the local electric field strength \(E\) that determines when optical breakdown is achieved. The electric field strength is related to the local power density \(I\) by the basic electrodynamic equation

\[
I(r, z, t) = \frac{1}{2} \varepsilon_0 c E^2, \quad (4.7.4.1)
\]

where \(\varepsilon_0\) is the dielectric constant, and \(c\) is the speed of light. The typical threshold intensities of optical breakdown for picosecond pulses are \(10^{11} \text{W/cm}^2\), whereas the corresponding electric field amounts to approximately \(10^7 \text{V/cm}\), which is comparable to the intramolecular Coulomb electric fields and provides the necessary conditions for plasma ionization. \emph{Plasma-induced ablation} is described by Maxwell’s equations -which have been given previously- of electrodynamics relating the electric and magnetic field strengths \(E\) and \(H\) to the electromagnetic inductions \(D\) and \(B\), respectively.

The interaction type of \emph{plasma-induced ablation} can also be used for diagnostic purposes. With the assistance of a spectroscopic analysis of the induced plasma spark, the free electron density and the temperature of the plasma can be evaluated. Thus, information on the chemical consistency of the target could be obtained, allowing consumptions about the state of health of the tissue volume under investigation [11], [12], [13].

### Plasma-Induced Ablation

<table>
<thead>
<tr>
<th>Main idea</th>
<th>ablation by ionizing plasma formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observations</td>
<td>very clean ablation, associated with audible report and bluish plasma sparking</td>
</tr>
<tr>
<td>Typical Lasers</td>
<td>Nd:YAG, Nd:YLF, Ti:Sapphire</td>
</tr>
<tr>
<td>Typical pulse durations</td>
<td>100fs…500ps</td>
</tr>
<tr>
<td>Typical power densities</td>
<td>(10^{11}…10^{13} \text{ W/cm}^2)</td>
</tr>
<tr>
<td>Special applications</td>
<td>refracting corneal surgery, caries therapy</td>
</tr>
</tbody>
</table>
A.4.7.5 Photodisruption

Generally, photodisruption may be regarded as a multi-cause mechanical effect starting with optical breakdown. Optical breakdown is associated with the physical effects of plasma formation and shock wave generation. Additionally, if the optical breakdown takes place inside soft tissues or fluids, cavitation which occurs when focusing the laser beam not on the surface of a tissue but into the tissue, and jet formation may be observed. The four effects (plasma formation, shock wave generation, cavitation, jet formation), take place at a different time scale. During plasma-induced ablation and at higher pulse energies, shock waves and other mechanical side effects become more important since they are capable of determining the global effect upon the tissue. This is due to the fact that mechanical effects have a linear relationship with the absorbed energy. Therefore, since the effect appears mechanical impact, the most appropriate term to use is disruption.

During photodisruption, the tissue is split by mechanical forces. The effects of shock wave and cavitation propagate into adjacent tissue, limiting the localization of the zone to interact. For pulse durations in the range of nanoseconds, the spatial extend of the mechanical effects is already of the order of millimeters even at the very threshold of breakdown. For nanosecond pulses, plasma-induced ablation is not observed, due to the fact that the threshold energy density of optical breakdown is higher compared to picosecond pulses and the pressure gradient balances with plasma energy. For nanosecond pulses, optical breakdown is associated with shock wave formation. Disruptive forces can damage the adjacent tissue, so these effects are undesired. For picosecond or femtosecond pulses, high peak intensities are generated with considerably lower pulse energies and disruptive effects as well as optical breakdown may still be observed, despite the significantly reducing plasma energy. Both interaction mechanisms, plasma-induced ablation and photodisruption, are based on plasma generation, making the discrimination of the two processes difficult.

As mentioned before, the four effects (plasma formation, shock wave generation, cavitation, jet formation), take place at a different time scale. Plasma formation begins during the laser pulse and lasts for a few nanoseconds, which is the time needed for the diffusion of free electrons into the surrounding medium. Shock wave generation is related to the expansion of the plasma, begins during plasma formation, and propagates into adjacent tissue, leaving the focal volume and slowing down to an acoustic wave after 30-50ns. Cavitation, at last, is a macroscopic effect that begins 50-150ns after the laser pulse, with the process of vaporization being the cause of the time delay. The cavitation bubble performs several oscillations of expansion and collapses within a period of a few hundred microseconds. During the collapse, the pressure inside the bubble increases, so each rebound of the cavitation bubble is followed by another shock wave. Thus, if the bubble is generated in the vicinity of a solid boundary, jet formation can be induced by every collapse [11], [12], [13].
# Photodisruption

<table>
<thead>
<tr>
<th>Main idea :</th>
<th>fragmentation and cutting of tissue by mechanical forces</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observations :</td>
<td>plasma sparking, generation of shock waves cavitation, jet formation</td>
</tr>
<tr>
<td>Typical Lasers :</td>
<td>solid state lasers, e.g. Nd:YAG, Nd:YLF, Ti:Sapphire</td>
</tr>
<tr>
<td>Typical pulse durations:</td>
<td>100fs...10ns</td>
</tr>
<tr>
<td>Typical power densities :</td>
<td>$10^{11}...10^{16} \ \text{W/cm}^2$</td>
</tr>
<tr>
<td>Special applications :</td>
<td>lens fragmentation, lithotripsy</td>
</tr>
</tbody>
</table>
Chapter A

Introduction – Theoretical part

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A.5 Computed Tomography Laser Mammography (CTLM)

A.5.1 Introduction in Optical Breast Imaging

The field of biomedical optics, the use of light in medicine, has seen rapid growth over the last decade. The development of non-invasive medical optical imaging (MOI) modalities using harmless near infrared (NIR) light, is a major goal of biomedical optics research. Arguably, the most interesting application of MOI is breast imaging, with the potential to provide a safer and possibly more effective alternative to x-ray mammography [19].

Optical imaging techniques for imaging the breast have been evaluated beginning with Dr. M. Cutler’s article in 1929 describing a simple breast transillumination system. A cooled light source was used to transilluminate the breast in a darkened room, and the unaided eye viewed the breast and was able to differentiate between normal and pathological breast tissue. In 1980, Ohlsson reported on his experiences with a more sophisticated form of breast transillumination called diaphanography, and employed a 35mm camera that used near infrared sensitive film to photograph the breast transilluminated by a high intensity strobe lamp contained within the light source. Over the years, the technique was improved by researchers that used more sensitive optical detectors and NIR light sources with greater transmission through the breast. However, the highly scattering optical properties of breast tissues severely blurred the transmission images obtained with this technique [20].

Technological advances in recent years, specifically pulsed lasers and ultra-fast detectors, have revived interest in medical optical imaging. The ability to illuminate the breast with picosecond pulses of NIR laser light and measure the temporal distribution of transmitted photons, known as the temporal point spread function (TPSF), enables investigation of time-resolved approaches to medical optical imaging. Phantom studies have indicated that measuring the TPSF and using only the photons arriving earliest at a detector (time-gating technique) can improve the image spatial resolution to about 1cm, but also provide a poor signal-to-noise ratio [19].

An alternative to transmission images of the breast is to acquire optical images in a similar fashion to x-ray computed tomography (CT). The specific technique generally uses a modified back-projection algorithm that is proportional to x-ray CT, but incorporates the physics of NIR diffusion in the breast. Back-projected slices yield the spatial variation in attenuation of the NIR light within the breast. A more sophisticated approach to reconstruct slice images uses a complex iterative inversion technique to predict TPSFs, or some characteristic of them, via a finite element forward model based on diffusion theory. This approach is theoretically more sound and enables the attenuation of NIR light to be de-coupled into an absorption image and a scattering image of the breast.

Several universities and a growing number of companies are actively pursuing medical optical imaging with time-resolved methods. Some have chosen to pursue similar ideas in the frequency domain, which greatly reduces the complexity and expense of the imaging device. At present, however, the frequency domain systems acquire less information content than time-resolved systems.
Mammography is currently the primary imaging technique in the detection of breast cancer. The technology of mammography has developed to the point that extremely sharp, detailed pictures can be obtained if the breast is tightly compressed, a rather painful and undignified procedure. These pictures, in the hands of an expert radiologist, will reveal whether any abnormality is present in only approximately 70 out of 100 cases. This means that up to 30 out of 100 cancers are “missed” on the first set of mammograms. This occurs most frequently in breasts that are very dense. Many of these missed lesions will subsequently be picked up by other imaging techniques or by follow-up mammography. However, it is very important to note that the mammogram, no matter how good its quality, does not contain all of the necessary information for many radiologists, no matter how expert, to say whether the abnormality detected is a cancer, requiring surgery, or a benign lesion, which can simply be followed by imaging. Therefore, in order to avoid missing a cancer, the mammographer advises biopsy on many lesions which later turn out to be benign (up to 80%). Thousands of women sustain great emotional and/or physical trauma, removal of breast tissue, and considerable expense only to prove that the mammographic finding was a “false positive.” The high percentage of false positive biopsies also presents a substantial cost to the health care system. Reducing false positive biopsies, therefore, can have a favourable effect on managing breast cancer detection and staging [19].

Mammography is far from perfect, and a range of techniques may serve in a supporting role to this omnipresent but notoriously fallible breast cancer screening tool. One of the newest on the scene is CT laser mammography (CTLM), a computed tomographic laser light-based scanner for the breast, which is able to detect greater blood flow that is a sign of cancer, with a radiation free energy source. The Computed Tomography Laser Mammography (CTLM®) system, which has been developed by Imaging Diagnostic Systems, Inc., uses lasers to image the breast in a non-invasive procedure. Unlike x-ray mammography, CTLM images blood hemoglobin and the process of neoangiogenesis or new vessel formation which is often associated with breast cancer. The CT Laser Mammography (CTLM®) system is intended for use as an adjunct to mammography in patients who have indeterminate mammographic findings, particularly in dense breasts. It is not intended for use in cases with clear mammographic or non-mammographic indications for biopsy. This device provides the radiologist with additional information to decide whether a biopsy is necessary [21].

The CT Laser Mammography (CTLM®) system appears certain benefits, which make the need for its use imperative. Primarily, the technique is performed with the use of non-ionizing NIR light, unlike mammography that utilizes ionizing radiation (x-ray). As mentioned before, the system complements conventional mammography, helping the elimination of unnecessary biopsies. Moreover, the system works well with dense breasts. Furthermore, it is non-invasive neither painful (since there is no breast compression), so as to ease the patient to be examined. Another advantage is its operational easiness as well as its operational inexpensiveness. Finally, the CT Laser Mammography (CTLM®) system appears a high throughput.

The CTLM functions somewhat like a conventional CT scanner in that an energy source, a near-infrared (NIR) laser, scans the breast; a computer reconstructs cross-sectional images based on measured optical data. The measured optical values are
directly related to the optical effective transport coefficient of the breast tissue. Like CT, the images may be viewed as single slices or as 3D volumes [21].

**A.5.3 Optical Computed Tomography Design**

The design of the scanner places the patient prone on a scanning table, with the breast to be examined extending through the tabletop into the scanning area. The Scanning Bed is 737mm (29") tall for easy patient access and includes a cushioned pad for patient comfort. The enclosure of the Scanning Bed is of fiberglass material supported by a metal frame. Interchangeable rings (4 centering rings) are provided to accommodate the range of breast sizes, up to 20cm, normally encountered, and to generally center the breast in the scanning chamber. There is no breast contact, i.e. the breast is not compressed, and no optical matching fluid is used. The diameter of the laser source beam illuminating the breast is 3mm ±20% through the scanning well. The average power delivered to the patient does not exceed 500mW. The wavelength is nominally 808 nanometers. Polarization is random [21].

The current design uses two rows of 84 silicon photo-diodes arranged in a circular arc around the breast. One row of the NIR-sensitive detectors is fitted with optical filters to remove the laser excitation wavelength when fluorescence imaging is used. Each detector is fitted with an optical collimator to define its field of view. The breast is illuminated in a horizontal plane mid-way between the first and last detectors by a pencil beam of NIR light from a laser source on the gantry. A complete rotation of the gantry rotates the laser source and the detectors 360° around the breast. During rotation, the detectors measure the light transmitted through the breast from the pencil beam. Simultaneously, CCD cameras on the gantry view the pencil beam on the breast surface in order to measure the boundary shape of the breast. Once rotation is completed, the gantry can be moved vertically to another horizontal plane (slice) of the breast. During a typical scan, CTLM system starts at the chest wall and acquires successive slices as the gantry is lowered down the breast in increments of a few millimeters (typically 4mm). The direction of the orbit is reversed from clock-wise to counter-clock-wise for each data acquisition to prevent excessive twisting of the electronic cables. The scanner acquires data from a 200mm diameter by 200mm tall right cylindrical field of view. Depending on the breast size, as many as 50 slice-planes of data are acquired to cover a maximum vertical distance at 20cm. A bilateral breast examination requires about 15 minutes and the acquired data is fed to an image reconstruction algorithm [21].

![Figure 5.3.1: Breast in scanning position](image)
After the row data has been processed to compensate for hardware-induced variations, a data reconstruction algorithm is applied to create the slice-plane image. There are two main approaches to reconstructing images of the breast from optical CT data. A modified back-projection algorithm in which the effects of optical absorption and scattering are taken into account, and an iterative inversion algorithm that takes advantage of finite-element modelling as well as standard algebraic reconstruction methods. The modified back-projection reconstruction technique, reconstructs a single slice of data in typically 75 seconds using a 700 MHz CPU. Due to its computational intensity, the iterative reconstruction scheme may take from several minutes to several hours to reconstruct a slice, depending upon which reconstruction options are selected. Both techniques may be extended to include tree-dimensional data and effects at the expense of increased reconstruction times [21].

Figure 5.2.3: This is the standard four view image presented on the reading console: the coronal, sagittal, and axial views and the three dimensional image. The white lines indicate intense angiogenesis in an invasive ductal cancer.
The individual slice-plane images can be directly displayed as individual coronal views of the breast. A volumetric reconstruction technique is applied to the array of slice-plane images to allow simultaneous display of axial and sagittal optical images, i.e., equivalent to cranio-caudal (CC) medio-lateral (ML) projections routinely seen with mammography. However, instead of single axial and sagittal projections, a series of sequential axial and sagittal projections are provided. These projections are used to examine the features seen in mammography films by positioning the axial and sagittal views to better visualize the suspect area. A bilateral axial and sagittal display is also provided. This feature emulates the common practice of placing left and right CC and ML mammography films on a film display box. The displayed optical coronal, axial, and sagittal views are available for printing on an external printer. CTLM images can be displayed as CT sections or as true 3D images, rotatable in space [21].

![Figure 5.2.4: Both pictures present the same case in different projections. The first one displays the Maximum Intensity Projection (MIP) where the arrowheads mark a large volume of angiogenesis and the short arrows indicate normal “tubular” veins, whereas in the second the morphology of the angiogenesis is better demonstrated.](image)

The Computed Tomography Laser Mammography scanner appears to have certain characteristics:

- **Nominal Ocular Hazard Distance (NOHD)**
  \[ \text{NOHD} = \frac{((2.5 \times 4 \times \text{Po} / \pi \times \text{EMPE})^{1/2} - a)}{\varphi} = 69 \text{ meters} \]

- **Positioning accuracy**
  The orbit position is accurate to better than ±0.1%, relative to the start flag.

- **Rotational speed constancy**
  The orbit speed variations do not exceed ±3% over the orbit time range of 12 – 45 seconds.
• **Elevation accuracy**  
The elevator position accuracy is better than ±0.5mm.

• **Laser Stability**  
For the duration of 1 slice (45 seconds max), the laser output power varies no more than ±0.2% peak-to-peak.

• **Perimeter Accuracy**  
The measured perimeter lies within ±0.5 millimeters of a fitted circle, measured with a centered 110mm diameter, circular IntraLipid-filled phantom.

The CTLM system also appears certain electrical characteristics:

• **Earthing**  
All devices that receive hazardous voltage with accessible metal parts have less than 0.1 Ohms of resistance between the accessible metal part and the earth ground at the supply connection.

• **Residual Power**  
A voltage of 60V is not available at the source of the unit 1 sec after the disconnection from the mains.

• **Isolation**  
The surfaces of the unit that are intended to come in contact with the patient are isolated from the power circuits such that a potential of 1500Vdc is applied between the two points and a breakdown of the insulation does not occur.

• **Leakage Current**  
The maximum normal condition leakage current does not exceed 500 microamperes. The maximum single fault leakage current does not exceed 1 mA.

• **Operator Console**  
The Operator Console requires a 220VAC line source (198VAC - 250VAC) at 50/60 Hz with a capacity of 20 Amps.

• **System**  
The system typically draws 5 Amps at 220VAC, 60 Hz. The heat dissipation is 1100 Watts or 3760 BTUs/hour.

All the information received during the examination is being registered in the operator’s console, which includes the system PC (a Pentium 4 personal computer running the Windows 2000 operating system and CTLM system software that includes 1GB of memory, dual 120GB mirrored disk drives for data storage and a 256MB video card), a 21” LCD video monitor for image review, a writable DVD-R drive for image archive and an optical mouse and keyboard for operator interaction. An uninterruptible power supply for immunity to power surges and drawer space for storage are also included. An optional image printer can connect to the Operator’s Console or to the Physician’s Review Station. The Operator’s Console is 53” x 33” (1345mm x 840mm), weighs 390 lbs (180 kg), and is made of fiberglass.

The CTLM system operates in a temperature range of +18ºC to +27ºC, a relative humidity of 30% to 75%, and an atmospheric pressure of 700hPa to 1060hPa.
(altitudes of sea level to 10,000 feet), as long as the dew point does not exceed the laser operating temperature of 19°C.

The Physician’s Review Station (PRS) is an accessory to the CTLM system that allows simultaneous image review and archiving while scanning. The PRS supports the full display functionality of the CTLM system. It can be used to archive images and to reformat images into axial, sagittal, and 3D projections. The PRS can perform any image metrics supported by the CTLM display software for the scan in progress. The PRS consists of a PC, a 21” LCD video monitor for image review and an uninterruptible power supply for immunity to power surges and dropouts. The PC is a 3.4GHz Pentium 4 personal computer running the Windows 2000 operating system and the CTLM image analysis software. It includes 1GB of memory, a 120GB disk drive, a CDRW to capture images, and a 256MB video card. The Physician’s Review Station connects to the Operator’s Console via a private 100Mbit Ethernet link.

The printer used is the Horizon® Ci, which is an intelligent desktop dry film imager that produces superior diagnostic-quality medical films as well as colour and grayscale paper images quickly, conveniently and affordably. The imager is compatible with many industry-standard protocols including DICOM and Windows network printing. High-speed image processing, networking and spooling are standard [21].

A.5.4 Theory of Computed Tomography Laser Scanning

All cancers must develop a blood supply of their own in order to survive. In fact, a cancer can not grow beyond 2.0 mm in size without this new blood supply, which is developed through the process of angiogenesis, an important natural process occurring in the body, both in health and in disease, which concerns the growth of new blood vessels. The process of angiogenesis occurs as an orderly series of events. Diseased or injured tissues produce and release angiogenic growth factors (proteins) that diffuse into the nearby tissues. The angiogenic growth factors bind to specific receptors located on the endothelial cells (EC) of nearby pre-existing blood vessels and once growth factors bind to their receptors, the endothelial cells become activated. Thus, signals are sent from the cell's surface to the nucleus. The endothelial cell's machinery begins to produce new molecules including enzymes, which dissolve tiny holes in the sheath-like covering (basement membrane) surrounding all existing blood vessels. The endothelial cells begin to divide (proliferate), and they migrate out through the dissolved holes of the existing vessel towards the diseased tissue (tumor). Specialized molecules called adhesion molecules, or integrins (avb3, avb5) serve as grappling hooks to help pull the sprouting new blood vessel sprout forward. Additional enzymes (matrix metalloproteinases or MMP) are produced to dissolve the tissue in front of the sprouting vessel tip in order to accommodate it. As the vessel extends, the tissue is remolded around the vessel. Sprouting endothelial cells roll up to form a blood vessel tube. Individual blood vessel tubes connect to form blood vessel loops that can circulate blood. Finally, newly formed blood vessel tubes are stabilized by specialized muscle cells (smooth muscle cells, pericytes) that provide structural support. Blood flow then begins [19], [20].
The CTLM system images the angiogenic blood supply by detecting the presence of increased hemoglobin in the imaging field. Since the area of angiogenesis is much larger than the tumor itself, tumors which are invisible or barely visible on the mammogram can be detected. Images are not as sharp and crisp as seen on CT or mammography, but have the character of Nuclear Medicine results because the process of angiogenesis is diffuse. CTLM is, therefore, a ‘functional’ imaging modality with the potential to perform molecular imaging. At the particular wavelength chosen (Fig. 3), blood absorbs most of the light, providing excellent 3D and tomographic images of the entire breast from the chest wall to the nipple. If there is a cancer present, an area of angiogenesis will be seen, which will be invariably much larger, and therefore easier to see, than the original lesion on the mammogram. In fact, a tumor which is only 3.0 mm in size on the mammogram will usually have an area of angiogenesis which is 4 to 6 cm in size on CTLM studies [21], [22].

![Absorption of light (vertical axis) in hemoglobin, water, and fat, at various wavelengths (horizontal axis). CTLM uses a wavelength of 808 nm, the point at which both oxy and deoxyhemoglobin absorb the near infrared light but water and fat absorb virtually none.](image)

**A.5.5 Image Quality**

Phantoms with optical properties similar to breast tissue have been manufactured to help the development of CTLM system. In-vitro studies of imaging phantoms provide objective performance quantifications. Primarily, the image’s **Object Detectability**, since the CTLM system clearly resolves a 2.0 ±0.2 mm spherical opaque inclusion suspended in a 110mm diameter circular phantom of standard IntraLipid solution, with the inclusion 20mm (radially) from the bucket wall. Furthermore, the image acquired appears an excellent **Field Uniformity**, as the CTLM clearly resolves a 3.0 ± 0.2mm spherical opaque inclusion suspended in a 110 x 80mm elliptical phantom of standard IntraLipid solution, with the inclusion 10mm (radially) from the bucket wall at the 12:00, 3:00, 6:00 and 9:00 positions [21].
A.5.6 Computed Tomography Laser Mammography – Conventional Mammography comparison

As mentioned previously, breast cancer is worldwide the most frequent cancer in women. At present, the most important breast imaging technique is x-ray mammography which has been shown to be effective in reducing breast cancer mortality. Nevertheless, mammography has some characteristic difficulties such as the compromise between low breast dose and high image quality along with the achievement of high sensitivity and specificity. The above special requirements lead to the continuing effort to optimize the mammographic technique and develop new modalities in breast imaging such as the Computed Tomography Laser Mammography (CTLM). When it comes to the comparison of the two methods, mammography dominates due to its efficacy proved over the years. Yet, the CTLM system could be evaluated, either when used alone or as an adjunct to conventional mammography. Primarily, the energy source used in CTLM is a laser diode beam instead of x-rays used in a mammographic examination. This fact makes CTLM a great imaging tool for patients that have to undergo the process of breast imaging as often as needed, since it does not expose the patient to ionizing radiation. Moreover, the CT Laser Mammography technique is a non-invasive procedure and requires no breast compression unlike mammography which can be considered as rather painful. Furthermore, the CTLM system performs imaging of the blood flow and visualization of the tumour angiogenesis. In addition, conventional mammography detects and evaluates breast abnormalities. Finally, the Computed Tomography Laser Mammography images through implants and dense breast tissue easily, unlike mammography which has difficulty penetrating very dense tissue. All the above and the fact that fusion with conventional mammography and breast MRI can be performed, makes CTLM a useful tool in breast imaging [21],[23].
Chapter A

Introduction – Theoretical part

A.6 Monte Carlo simulation

A.6.1 Introduction to Monte Carlo methods

A.6.2 Fundamental theory of random numbers
A.6 Monte Carlo simulation

A.6.1 Introduction to Monte Carlo methods

The “term” Monte Carlo was introduced during World War II by Von Neumann and Ulam, as a code word for the work done at Los Alamos and was named after the city Monte Carlo of Monaco which was a center for gambling. Ulam’s interest in poker, gave him the idea of using statistical simulation -applied to games of chance- to the problems related to the atomic bomb. Monte Carlo refers to a technique that simulates physical processes using a stochastic model. The Monte Carlo method is a statistical simulation, defined as a method that uses sequences of random or pseudorandom numbers so as to perform the simulation. In recent years, the method has received the credit that deserves and has been recognized as a numerical technique that can be used to complex applications. Nowadays, the Monte Carlo methods have numerous applications in stochastic, but also deterministic problems.

In many physical systems, the Monte Carlo method is directly used and does not demand the differential equations that describe the system, but only the Probability Density Functions (PDFs). Once the PDFs are known, the Monte Carlo simulation can proceed by random sampling from the PDFs. Many simulations are then performed (multiple “trials” or “histories”) and the desired result is taken as an average over the number of observations (which may be a single observation or perhaps millions of observations). In many practical applications, one can predict the statistical error (the “variance”) in this average result, and hence an estimate of the number of Monte Carlo trials that are needed to achieve a given error. If \( f(x) \) is the Probability Density Function (PDF), then:

\[
f(x) \geq 0 \quad \text{for all} \quad x \in \mathbb{R}
\]

\[
\int_{-\infty}^{\infty} f(x) \, dx = 1
\]

\[
P(a < X < b) = \int_{a}^{b} f(x) \, dx
\]

where \( X \) is the continuous variable, defined over the set of real numbers \( \mathbb{R} \). In many cases, however, the Cumulative Distribution Function (CDF) is used. If \( F(x) \) is the Cumulative Distribution Function (CDF), then:

\[
F(x) = P(X \leq x) = \int_{-\infty}^{x} f(t) \, dt
\]

where \( X \) is the continuous random variable with density function \( f(x) \). The Monte Carlo method is basically a technique for sampling the probability functions PDF and CDF based on random number sequences, generated by computers.

The Monte Carlo simulation process is described in the following diagram. The physical (or mathematical system) must be described by a set of probability density functions PDF and a source of random numbers uniformly distributed on the unit interval must be available. Thus, a prescription for sampling from the specified PDFs, assuming the availability of random numbers on the unit interval, must be given. The
outcomes must be accumulated into overall tallies or scores for the quantities of interest. Furthermore, an estimate of the statistical error (variance) as a function of the number of trials and other quantities must be determined. Finally, methods for reducing the variance in the estimated solution to reduce the computational time for Monte Carlo simulation must be applied.

Figure 6.1: A simplified block diagram of the Monte Carlo process

A.6.2 Fundamental theory of random numbers

For the implementation of a Monte Carlo simulation process, the first and major part is an infinite sequence of random numbers. A random number is a particular value of a continuous variable uniformly distributed on the unit interval which, together with others of its kind, satisfies certain conditions. A high quality random number sequence is a long stream of numbers with the characteristic that the occurrence of each number in the sequence is unpredictable. Although databases of real random numbers can be found their use is limited due to the large size, which makes the simulation process very slow. Thus, mathematical algorithms for the generation of “pseudorandom numbers” have been introduced. The outputs of pseudorandom numbers generators are not random; they only approximate some of the properties of random numbers. Careful mathematical analysis is required to ensure that the generated numbers are sufficiently “random”.

By far the most popular random number generators in use today are special cases of the following scheme, introduced by D.H. Lehmer (1951). For the implementation of this scheme, four “magic numbers” are selected:

\[ m, \text{ the modulus}; \]
\[ a, \text{ the multiplier}; \]
\[ c, \text{ the increment}; \]
\[ X_0, \text{ the starting value}; \]

Given a modulus \( m \), a multiplier \( a \) and a starting value – “seed” \( X_0 \), the desired sequence of random numbers \( X_n \) is then obtained by setting:
\[ X_{n+1} = (aX_n + c) \mod m \]  
(6.1)

This is called a linear congruential sequence.

Before a random number generator can be regarded as acceptable, its output must pass certain standard randomness tests (Frequency Test, Serial Test, Gap Test, Poker Test, Serial Correlation Test etc), which check very carefully the statistical properties of uniformity and independence. The length of the period of a random number generator must be long enough to avoid repetitions in the sequence of numbers used during the simulation process, as otherwise correlations can be produced. There are simulations however, where the set of independent numbers needed might exceed the repetition period of the generator being used. When the generator is “well behaved”, even if the sequence of numbers is used more than once, the probability of having more than one particle history starting in the same position of the sequence of random numbers is practically negligible. This means that when the end of the sequence is reached it will be started again during some of the sampling procedures used along the simulation.

The selection of a random value of a specific quantity, from a continuous probability density function is realized in Monte Carlo simulation through sampling methods, which are namely: the inversion method and the rejection method. In the code utilized in this study both methods were used.
Chapter B

Materials and Methods

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B. Materials and Methods

B.1 Laser simulation

When laser light passes through biological tissue, absorption and scattering phenomena take place for every photon travelling into the tissue and forming a path that can be determined with the aid of statistics by calculating probabilities of scattering and absorption. The MCSLTT (Monte Carlo Simulation of Light Transport in Tissue) code is a useful tool, in diagnostic laser applications as well as in the study of laser-tissue interactions and the results occurring during these interactions. The particular code measures as well quantities such as the total reflected light, the total transmitted light, and the total heat absorbed. The code is interactive and was tested at the NEA Data Bank on a PC with 3GHz INTEL Pentium 4 running WINDOWS XP Professional with programming language LabVIEW.

B.1.2 Monte Carlo simulation of laser beams propagation in biological tissue

In a radiative transport problem, the Monte Carlo method consists of recording photons histories as they are scattered and absorbed. Generally, precise modelling of the propagation of light in turbid media such as the biological tissues has remained as a fundamental challenge. Investigation of light propagation in these materials requires that both the absorption and the scattering of the light be considered. Among different approaches, the radiative transport theory has served as the foundation for many theoretical investigations, in which the radiation field of light is analyzed in terms of the radiance on the basis of energy conservation, and the light interaction with the medium is described through absorption and scattering processes. Except for only a few cases of simple geometry for which analytical solutions can be obtained, various approximations and numerical methods have been used to solve the radiative transfer problems with practical boundary conditions. On the other hand, the principle of the radiative transfer theory can be equally served by use of statistical methods in which the light distribution is treated as a collection of classical particles, i.e., the photons with no direct characterizations of phase and polarization. The interaction of the photons with a turbid medium can then be studied with a random-walk model of Monte Carlo simulation. Over the past decade, the Monte Carlo simulation has been given considerable attention in the studies of interaction between visible or near-infrared light and the turbid media of the biological tissues. This is mostly because of its potential to offer nearly exact solutions for three-dimensional 3-D problems of light propagation based on the radiative transfer theory with virtually any boundary conditions. Therefore it has significant advantages over approximate methods such as the diffusion approximation of the radiative transport equation and the more approximate Kubelka–Munk two-flux theory in obtaining a complete understanding of light distribution. In the past, the heavy demand of computation time of the Monte Carlo simulation to reduce statistical errors has impeded wide application of the method. With the recent advent of low-cost personal computers with high computation power, it appears that the potential of Monte Carlo method can now be fully appreciated [24], [25], [26].
Solution of a general problem of radiation dosimetry in biological materials yields two distinctly different types of results. The first result provides the spatial distribution of energy deposition of the radiation in the medium due to absorption; it is often needed in cases such as the modelling of photodynamic therapy. The second result furnishes the spatial distribution of the radiation energy, inside or through the tissue, which supplies important information on the availability of radiation for either diagnostic or therapeutic purposes.

Figure 1.1: Flowchart for the variable stepsize Monte Carlo technique.

The Monte Carlo method for modelling light transport in tissue can be summarized in the above flowchart. The Monte Carlo method begins by launching a photon into the tissue. If a collimated beam normally incident on a slab is simulated then the photon’s initial direction is chosen downwards into the tissue. If a diffuse irradiance is simulated, then the photon’s direction is chosen randomly from all possible directions in the downward hemisphere. The coordinates of the photon are usually identical for all photons. This allows convolution techniques to be used to determine fluence rates from a wide variety of beam shapes. Usually only one photon follows each pathway, and at each step the photon may be either absorbed or scattered. If a packet of photons followed each pathway then some portion of the packet would be absorbed at each step. The size of this packet is called the weight \( w \) of the photon. Its initial weight is set to unity [25].

The simplest Monte Carlo method propagates each photon with small, fixed incremental stepsizes. The fixed stepsize \( \Delta s \) must be small relative to the average
mean free pathlength of a photon in the tissue, which is the reciprocal of the total attenuation coefficient:

$$
\Delta s \ll \frac{1}{\mu_t} = \frac{1}{\mu_a + \mu_s},
$$

(1.2.1)

where $\mu_t$, $\mu_a$, and $\mu_s$ are the total attenuation, the absorption, and the scattering coefficients respectively. If the stepsize is too small the photon will rarely interact with the tissue and the Monte Carlo method will be inefficient, conversely if the stepsize is too large then the distance travelled by a photon is a poor approximation to that of a real photon.

A much more efficient method chooses a different stepsize for each photon step. The probability density function for the stepsize follows Beer’s law (i.e. it is more likely for a photon to travel a short distance than a long distance and the probability is proportional to $e^{-\mu_s \Delta s}$.) A function of a random variable ($\xi$) uniformly distributed between zero and one which yields a random variable with this distribution is:

$$
\Delta s = -\ln \xi \frac{\mu_t}{\mu_s}.
$$

(1.2.2)

The stepsize found represents the distance that a photon will travel before interacting (through absorption or scattering) with the tissue.

A photon is uniquely described by three spatial coordinates for the position and two directional angles for the direction of travel. For simplicity, the photon’s spatial position is described with three Cartesian coordinates and the direction of travel with three direction cosines. The required formulas for propagation are simple, and the angle variables describing photon direction do not change unless the photon’s direction changes. The direction cosines are specified by taking the cosine of the angle that the photon’s direction makes with each axis. These are specified by $\mu_x$, $\mu_y$, and $\mu_z$ corresponding to each of the x, y, and z-axes respectively. For a photon located at $(x, y, z)$ travelling a distance $\Delta s$ in the direction $(\mu_x, \mu_y, \mu_z)$, the new coordinates $(x’, y’, z’)$ are given by:

$$
x’ = x + \mu_x \Delta s
$$

$$
y’ = y + \mu_y \Delta s
$$

$$
z’ = z + \mu_z \Delta s
$$

(1.2.3)

Once launched, the photon is moved a distance $\Delta s$ where it may be scattered, absorbed, propagated undisturbed, internally reflected, or transmitted out of the tissue. The photon is repeatedly moved until it either escapes from or is absorbed by the tissue. If the photon escapes from the tissue, the reflection or transmission of the photon is recorded. If the photon is absorbed, the position of the absorption is recorded. This process is repeated until the desired number of photons has been propagated. The recorded reflection, transmission, and absorption profiles will approach true values (for a tissue with the specified optical properties) as the number of photons propagated approaches infinity [25].
Reflection

The possibility of internal reflection occurs when the photon is propagated across a boundary into a region with a different index of refraction. The probability that the photon will be internally reflected is determined by the Fresnel reflection coefficient:

\[ R(\theta_i) = \frac{1}{2} \left[ \frac{\sin^2(\theta_i - \theta_t)}{\sin^2(\theta_i + \theta_t)} + \frac{\tan^2(\theta_i - \theta_t)}{\tan^2(\theta_i + \theta_t)} \right], \quad (1.2.4) \]

where \( \theta_i = \cos^{-1} \mu_z \) is the angle of incidence on the boundary and the angle of transmission \( \theta_t \) is given by Snell’s law \( n_i \sin \theta_i = n_t \sin \theta_t \), where \( n_i \) and \( n_t \) are the indices of refraction of the medium from which the photon is incident and transmitted, respectively. A random number \( \xi \) uniformly distributed between zero and one is used to decide whether the photon is reflected or transmitted. If \( \xi < R(\theta_i) \) then the photon is internally reflected, otherwise the photon exits the tissue and the event is recorded as backscattered light (when the photon exits the top) or transmitted light (when it exits the bottom). If the photon is internally reflected, then the position and direction of the photon are adjusted accordingly. For a slab geometry, infinite in the x and y directions with a thickness \( t \) in the z-direction, the internally reflected photon position \((x'', y'', z'')\) is obtained by changing only the z-component of the photon coordinates:

\[
(x'', y'', z'') = \begin{cases} 
(x, y, -z), & \text{if } z < 0 \\
(x, y, 2t - z), & \text{if } z > t
\end{cases}
\]

The new photon direction \((\mu_x', \mu_y', \mu_z')\) is

\[
(\mu_x', \mu_y', \mu_z') = (\mu_x, \mu_y, -\mu_z),
\]

where both \( \mu_x, \mu_y \) remain unchanged.

Absorption

The technique of implicit capture assigns a weight to each photon as it enters tissue. After each propagation step, the photon packet is split into two parts—a fraction is absorbed and the rest is scattered. The fraction of the packet that is absorbed is:

\[
\text{fraction absorbed} = \frac{\mu_a}{\mu_a + \mu_s} = 1 - \frac{\mu_s}{\mu_a + \mu_s} = 1 - a,
\]

(1.2.7)
where \( a \) is the single particle albedo. Consequently, the new photon weight \( w' \) is given by \( w' = aw \), which represents the fraction of the packet that is scattered on this step. An absorption event requires that both the location and the amount of light absorbed be recorded. For example, the appropriate element of the absorption matrix is incremented by \((1 - a)w\). The number of bins in the absorption matrix is determined by the spatial resolution desired. Increasing the number of entries increases the spatial resolution, but also increases the absorption uncertainty in each element (because fewer absorption events will take place in each element and the error is inversely proportional to the square root of the number of absorption events). The fluence rate is obtained by dividing the final value of each matrix element by the equivalent spatial volume of the element, the absorption coefficient, the total number of photons propagated, and the initial weight of each photon [25].

**Scattering**

A normalized phase function describes the probability density function for the azimuthal and longitudinal angles for a photon when it is scattered. If the phase function has no azimuthal dependence, then the azimuthal angle \( \phi \) is uniformly distributed between 0 and \( 2\pi \), and may be generated by multiplying a pseudo-random number \( \xi \) uniformly distributed over the interval zero to one by \( 2\pi \) (i.e. \( \phi = 2\pi \xi \)). The azimuthal angle \( \theta \) for an isotropic distribution is given by:

\[
\cos \theta = 2\xi - 1 .
\] (1.2.8)

Since scattering in tissue is characterized by the Henyey-Greenstein phase function, the generating function for the Henyey-Greenstein phase function is:

\[
\cos \theta = \frac{1}{2g} \left[ 1 + g^2 - \left[ \frac{1 - g^2}{1 - g + 2g\xi} \right]^2 \right] .
\] (1.2.9)

If scattering is isotropic (\( g = 0 \)) then equation (6.2.8) should be used. If a photon is scattered at an angle \((\theta, \phi)\) from the direction \((\mu_x, \mu_y, \mu_z)\) in which it is travelling, then the new direction \((\mu_x', \mu_y', \mu_z')\) is specified by:

\[
\mu_x' = \sin \theta \left( \mu_x \cos \phi - \mu_y \sin \phi \right) + \mu_z \cos \theta
\]

\[
\mu_y' = -\sin \theta \left( \mu_y \cos \phi - \mu_x \sin \phi \right) + \mu_z \cos \theta
\] (1.2.10)

\[
\mu_z' = -\sin \theta \cos \phi \sqrt{1 - \mu_z^2} + \mu_z \cos \theta .
\]
If the angle is too close to the normal (say $|\mu_z| > 0.99999$), the following formulas should be used

\[
\begin{align*}
\mu_z' &= \sin \theta \cos \phi \\
\mu_y' &= \sin \theta \sin \phi \\
\mu_z' &= \frac{\mu_z}{|\mu_z|} \cos \phi
\end{align*}
\]

(1.2.11)

For the specific study, 90 simulation runs were performed, with a simulation time of 30 seconds for each one utilizing a Pentium 4 dual core PC, $5 \cdot 10^3$ photons were utilized for each simulation, which are considered statistically enough for the simulations performed. Parameters such as the thickness of the medium and the input laser power were considered for two kinds of irradiating media, skin and breast tissue, in order to examine the heat deposition, as well as to extract information about the photon paths inside the medium (maximum depth, backscattering, etc) [25].

### B.2 Irradiated media

The \textit{MCSSLTT (Monte Carlo Simulation of Light Transport in Tissue)} code was utilized in the study of the absorption and scattering phenomena that take place inside the irradiated media, glandular and skin breast tissue [2]. As mentioned in the section A.2, the anatomy of the adult female breast consists of 12 - 20 conical lobes. The base of a lobe lies on top of the pectoral muscles and ribs, and its apex is at the areola and nipple. Lobular (glandular) and ductal tissue lie within each lobe supported by intralobular connective tissue and adipose tissue. There is also extralobular connective tissue which binds the lobes together as well as extralobular adipose tissue. The irradiated media includes the skin which is consisted of adipose tissue and the breast tissue which is consisted of 50% glandular and 50% adipose tissue.
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C. Results and Discussion

The CTLM unit, as mentioned in the introduction, is a breast imaging method that is performed without the use of ionizing radiation since its energy source is a laser diode beam. Therefore, the effects observed on the breast tissue during the specific imaging process are mostly thermal. Heat generation is an undesirable effect in optical diagnosis because tissue damage occurs at relatively low temperatures. The purpose of this thesis was the study of thermal effects on glandular and skin tissue of the breast with the aid of Monte Carlo simulation. The MCSLTT (Monte Carlo Simulation of Light Transport in Tissue) code that was utilized, provided us with graphics (which were performed with the aid of Microsoft Excel) appearing the temperature rise (°C) as a function of the depth that the laser light penetrates inside the tissue as well as valuable informations concerning quantities such as the total heat, the maximum photon depth when using different input powers and different medium thicknesses [2].

C.1 Effects on glandular tissue

C.1.1 Effect of input power on temperature rise

When the laser beam irradiates the medium, the temperature rises proportionally to the input power applied but in different amounts depending on the depth that penetrates. In particular, when the laser light reaches the surface (0.00cm thickness) the temperature rises from 0 (input power: 0 W/cm²) to 285 °C for the maximum input power (100 W/cm²) applied (figure 1a, 1b, 1c, 1d, 1e). In addition, as the NIR laser light penetrates into the breast tissue, i.e. 0.15cm, the elevation of the temperature still occurs but in lower maximum values (the maximum temperature rise, 3.7°C, is observed for a 2.00cm thick medium and for 100 W/cm² input power (figure 1.a’). These results are in agreement with the theoretical ones that occur from the heat conduction equation that was quoted in the introduction, since the heat transported into the tissue is reversely proportional to the penetration depth. Because optical energy is converted into radiant heat by near-infrared irradiation of the skin, the temperature heat effect appears and blood flow increases without causing a marked increase in the surface skin temperature except for high input powers. For the input power that the Computed Tomography Laser Mammography (CTLM) system works, the elevation in temperature for the glandular breast tissue was within bearable values (from 1.4°C at the surface to 0.01°C at 1.5mm depth) [28], [29].
Figure 1: The effect of input power on temperature rise is presented in the above diagrams for medium thicknesses 0.00cm (surface) and 0.15cm
**C.1.1.1 Effect of input power on total heat**

The total heat is a quantity given by the simulation code in every measurement and represents the average temperature rise that occurs in the irradiated medium. The observation of the graphics of the total heat as a function of input power revealed some fluctuations in the total heat of the tissue, particularly for the low input powers applied, which is obvious in all five diagrams. This is due to the fact that the input power is directly related to the depth that the photons reach inside the glandular breast tissue, resulting in small maximum photon depths and small temperature rises for the low input powers applied. The fluctuations observed at those input powers can also be attributed to the fact that the photons do not travel in a straight line, but are scattered again and again before they reach their final destination. Yet, these fluctuations are not to be considered as important since they varied from 5% to 9% especially for low input powers (0.1 – 5 W/cm²) and for all medium thicknesses, as we can see in all five diagrams. Furthermore, for breast thicknesses up to 8.00cm the highest input power applied (100 W/cm²) resulted in a total heat of about 0.47 cal, in addition to the 10.00cm breast thickness where the highest input power (100 W/cm²) resulted in a total heat of 0.457cal. It is important to denote that the increase in the input powers applied, affect mostly the path that the photons will follow and the depth that they reach. This is why the deviations observed during all the measurements are not important, so we can conclude that the total heat does not contribute burdensomely in the procedure (causing erythema, burn, etc). In the Computed tomography Laser Mammography (CTLM) method, the input power applied (0.5 W/cm²) resulted in an average value of the total heat 0.465cal [28], [29].

---

**a. Thickness of medium: 2.00cm**

![Graph showing total heat vs. input power for medium thickness of 2.00cm]

**b. Thickness of medium: 4.00cm**

![Graph showing total heat vs. input power for medium thickness of 4.00cm]
c. Thickness of medium: 6.00cm

d. Thickness of medium: 8.00cm

e. Thickness of medium: 10.00cm

Figure 1.1: The effect of input power on total heat for various medium thicknesses

C.1.2 Effect of input power on photon distribution

The photons emitted from the laser energy source travel inside the tissue and depending on the different wavelengths or – in other words- depending on the different energies or input powers applied and the medium, reach certain maximum depths. As we can clearly observe from the data extracted from the Monte Carlo simulation code and the performing graphics, the maximum photon depth for low input power and for all medium thicknesses varies from 0.15cm to 0.25cm whereas for high input powers the maximum photon depth variation occurs between 0.25cm and 0.30cm. It is important to say that for the different medium thicknesses used, the different input powers applied influenced the maximum photon depth causing fluctuations in its value (from 0.13cm to 0.39cm). We can also denote that for the input power range used in the CTLM method, the maximum depth that the photons travel inside the breast tissue has an average value of 0.30cm, whereas the occurring temperature rise in this input power lies among 1.4°C at the surface and 0.01°C at 0.15cm depth. Biological tissue is one of the most complicated materials combining both absorption and multiple scattering. Depending on the angle $\theta$ of the photon’s scattering direction, the probability function $p(\theta)$ defines whether the scattering is isotropic or anisotropic. Given that the beam irradiating the breast tissue is highly
penetrating, the photons are forward-directed (anisotropic). This fact is in absolute agreement with the simulation results where no back-scattering was observed [28], [29].

Thickness of medium: 2.00cm

![Graph](image1)

Thickness of medium: 4.00cm

![Graph](image2)

Thickness of medium: 6.00cm

![Graph](image3)

Thickness of medium: 8.00cm

![Graph](image4)

Thickness of medium: 10.00cm

![Graph](image5)

Figure 1.2: Effect of input power on maximum photon depth for various medium thicknesses

C.1.3 Effect of breast thickness on temperature rise

During the laser light – tissue interaction, the dominant effects are the thermal. A very important factor that could be examined whether it affects the temperature rise is the thickness of the medium irradiated. The MCSLTT code provided us with informations on the specific quantities and the graphics that have arisen from them are given below. For given input powers, the temperature rise remains almost stable at the surface, as well as, at 0.15cm depth. It is obvious that as the input power increases,
the temperature rise also increases both in the surface and in 0.15 cm depth of the medium (i.e. the maximum temperature rise (285°C) appears for the 100 W/cm² applied input power at the surface of the medium and at the 0.15 cm depth (10°C), whereas the minimum temperature rise (1.4°C) appears for the 0.5 W/cm² applied input power at the surface of the medium and at the 0.15 cm depth (0.01°C)). The final conclusion extracted from the following graphics is that the thickness of the medium does not affect the temperature rise and consequently does not contribute in the thermal effects occurring during the procedure [28], [29].
d. Input power: 40W/cm²

d'. Input power: 40W/cm²

e. Input power: 100W/cm²

e'. Input power: 100W/cm²

Figure 1.3: Effect of breast thickness on temperature rise for various input powers
Chapter C
Results and Discussion

C. Results and Discussion

C.2 Effects on skin
C.2.1 Effect of input power on temperature rise
C.2.1.1 Effect of input power on total heat
C.2.2 Effect of input power on photon distribution
C. Results and Discussion

C.2 Effects on skin

C.2.1 Effect of input power on temperature rise

As far the skin is concerned, for a given breast thickness (0.50cm) the effect of the input power on the temperature rise was also studied and the occurring results are to be considered predictable and in agreement with the theoretical ones. Analytically, the increase in the input power results in the increase of the temperature rise in the skin. The maximum temperature rise (60°C) is observed at the surface (0.00cm) and for the maximum input power (figure 2.1a) whereas at 0.10cm depth the maximum temperature rise reaches 35°C for the same input power (figure 2.1.b). The third graphic (2.1.c) appears a maximum temperature rise of 60°C for the maximum input power at 0.20cm depth. This result is not considered unpredictable, since the elevation of temperature is continuing to occur even in few millimeters depth below the skin. For the input power that the Computed Tomography Laser Mammography (CTLM) system works, the elevation in temperature for the skin was within bearable values (from 0.31°C at the surface to 0.17°C at 0.10cm depth), resulting in the assumption that the occurring thermal effects could not cause dangerous for the patient’s health phenomena, such as erythema, burn, etc [28], [29].

![Graph 2.1a: Depth: 0cm (surface) Thickness of medium: 0.5cm](image)

![Graph 2.1b: Depth: 0.10cm Thickness of medium: 0.5cm](image)

![Graph 2.1c: Depth: 0.20cm Thickness of medium: 0.5cm](image)

Figure 2.1: Effect of the input power on temperature rise for different depths (0.00-0.20cm)
C.2.1.1 Effect of input power on total heat

The total heat expresses the average temperature rise that is observed during the medium irradiation. When it comes to the skin, the graphic that occurred from the simulation code revealed interesting results. As we can see, for low input powers applied on the skin, the total heat fluctuated among the values 0.38cal and 0.397cal in a percentage 4.3%. The fluctuations eliminated as the input power increased, resulting in the decrease of the total heat as the input power increased. The decrease in the fluctuation observed in increasing input powers is due to the fact that the beam becomes more penetrating, resulting in the distribution of temperature in smaller depths as the photons travel inside the adipose tissue. Nevertheless, the variations in the total heat were not significant (from 0.38cal to 0.41cal) and the results revealed that for the input power applied during the CTLM method, the total heat developed does not contribute to any unwanted side effects for the patient (erythema, burn, etc.) [28], [29].

Thickness of medium: 0.5cm

![Total Heat vs Input power graph]

Figure 2.1.1: Effect of the input power on total heat for 0.5cm medium thickness

C.2.2 Effect of input power on photon distribution

When the NIR laser light irradiates the medium, it firstly contacts the skin. From that point further the photons are starting to propagate inside the tissue until their reach their maximum depth. With the aid of the MCSLTT code, the effect of the input power on the maximum depth that the photons reach was diagrammatized. It is obvious that for all the applied input powers (from 0.1 to 100 W/cm²) the maximum photon depth remained the same (0.50cm) and there was no back scattering, since the NIR laser beam is deeply penetrating and, therefore, the photons are forward-scattered (anisotropic). This is observed because the thickness of the medium is small, meaning that all the photons will penetrate the skin [28], [29].
As a conclusion, it should be mentioned that the temperature rise was studied (with the aid of the *MCSLTT* (*Monte Carlo Simulation of Light Transport in Tissue*) code) separately for the skin and breast tissue. In reality, however, this is not the case. Both breast tissue and skin form the mammary gland. The specific Monte Carlo code could not provide us with combinational data, but separately for each case (as was quoted previously). Yet, theoretical assumptions could be made. The combination of skin and breast tissue, when irradiated with the NIR laser light source of the Computed Tomography Laser Mammography (CTLM) system would result in the decrease in the temperature rise as the photons travel from the skin (0.00cm) to depths larger than 2.00cm. All these conclude to the assumption that the specific imaging technique even though it induces the presence of thermal effects, does not cause dangerous implications to the patient that has to undergo the imaging process.
Chapter D

Conclusions and future work

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D.1 Conclusions

Mammography is a breast imaging technique with very high standards as far as image quality is concerned. The requirements for visibility and accurate assessment of microcalcifications and breast lesions place very serious constraints upon equipment and techniques that are used in mammography. These constraints created the need for the development of alternative breast imaging techniques, such as the Computed Tomography Laser Mammography (CTLM) method. The technology is dependent on the differential absorption of the transmitted 808nm wavelength laser light by the relative concentrations of oxyhemoglobin and deoxyhemoglobin. The selected wavelength maximally detects the hemoglobin. The physical area of increased absorption is several folds greater than the tumour itself. Imaging is performed supine, with the uncompressed breast suspended. Images are collected in a manner similar to CT, with laser beam source diameter of 0.30cm. Object detectability in vitro has been reported at 0.20cm. Processed images are reconstructed into two or three dimensional displays onto a workstation and can be compared directly with mammography or fused with MR imaging [21].

Although the CTLM method is a rather new breast imaging technique, studies from diagnostic centers all over the world present it as a promising tool in the imaging of the breast either alone or as an adjunctive to conventional mammography. The purpose of this thesis was the study of the thermal effects induced during the CTLM technique of the NIR laser irradiation of the breast tissue. In order to do that, we utilized a Monte Carlo simulation code, the MCSLTT (Monte Carlo Simulation of Light Transport in Tissue) code, with the aid of which we simulated the photon propagation inside the breast tissue and the skin and we extracted graphics and results that concerned the parameters under investigation [2]. As mentioned in the previous section, the effects on breast tissue as well as skin were studied. The occurring results showed that the input power affected the temperature rise increasingly. Specifically, for all medium thicknesses, the temperature rise increased as the input power increased both in glandular and skin tissue. For the input power that the Computed Tomography Laser Mammography (CTLM) system works, the elevation in temperature for the glandular breast tissue was within bearable values (from 1.4°C at the surface to 0.01°C at 0.15cm depth), as well as for the skin (from 0.31°C at the surface to 0.17°C at 0.10cm depth), resulting in the assumption that the occurring thermal effects could not cause dangerous for the patient’s health phenomena, such as erythema, burn, etc. The same assumptions arose from the investigation of the effect of the input power on the total heat. The effect of the input power on the photon distribution was also studied and the results extracted showed small fluctuations for the different input powers used and for all the thicknesses, but the most important assumption was that for the input power range used in the CTLM method, the maximum depth that the photons travel inside the breast tissue appeared an average value of 0.30cm for the glandular breast tissue, whereas for the skin the maximum photon depth remained the same (0.50cm) and there was no back scattering. Finally, the effect of the breast thickness on the temperature rise was examined, showing that breast thickness does not affect the elevation of the temperature on the skin, whereas on glandular tissue, the temperature rise remains almost stable at the surface (1.4°C), as well as, at 0.15cm depth (0.01°C -0.05°C) for the input power used during the CTLM method, leading to the conclusion that the thickness of the medium does not affect the temperature rise and consequently does not contribute in the thermal effects occurring during the procedure. All these results conclude to the fact that the thermal
effects (in the form of temperature elevation) which appear during the CTLM technique, are not an inhibitory factor in the use of the particular method, given that the NIR irradiation of the breast tissue does not cause a marked increase in the temperature rise on skin and glandular tissue.

D.2 Future work

The incidence of breast cancer is growing steadily throughout the world. There is an urgent need for a simple, easily installed, inexpensive – but reliable – method of detecting breast cancer at an early stage that does not employ ionizing radiation or require the injection of contrast media, and has greater sensitivity and specificity than current mammographic techniques. In this thesis, we tried to present an alternative new breast imaging technique, the Computed Tomography Laser Mammography (CTLM) technique and with the aid of Monte Carlo simulation code, MCSLTT the (Monte Carlo Simulation of Light Transport in Tissue), we studied the thermal effects that occur during the procedure. As mentioned in the introduction part, when laser light is applied to biological tissue, a variety of interaction mechanisms is possible to occur. This is an aspect of future work, as far as the effects that can be observed during the CTLM method are concerned. The particular Monte Carlo simulation code (MCSLTT) provides us with information about the thermal effects on breast tissue. However, photochemical interactions, photoablation, plasma-induced ablation and photodisruption could as well be examined with the development of a new Monte Carlo simulation code, giving interesting results about the interaction mechanisms observed during the CTLM’ s laser beam irradiation of the breast tissue.
Abstract

Breast cancer is the prime factor of women mortality in the developed countries. During the recent years however, many techniques in breast imaging have been developed and applied, with X-ray mammography been perhaps the most widely used of cancer diagnostic tests. Nevertheless, X-ray mammography although still remains the frontline diagnostic technique in the fight against breast cancer and has been a contributing factor in the steady decline in deaths from breast cancer, it has certain drawbacks which range from false-positive results to missed lesions and the risk of carcinogenesis. Mammography, whether conventional or digital, has been thoroughly documented as missing between 25% and 40% of breast cancers, with a higher miss rate among women with dense breasts, which constitute 40% of the female population.

Because the mammogram is a projected image of superimposed breast structures, it is generally more difficult to detect cancer in a breast with a dense (i.e. lighter in appearance on a mammogram) pattern. As a result, mammography appears low sensitivity (ranging from 24.5% to 37%), especially in women with dense breasts. This is due to the fact that it only images anatomic detail and provides no functional information which is essential for early and accurate diagnosis of breast cancer and can be expected to significantly reduce the number of unnecessary biopsies. The special properties of light could help optical imaging "see" what other diagnostic methods, including conventional x-ray mammography, may miss. One of the newest techniques on the scene is CT laser mammography (CTLM), a computed tomographic laser light-based scanner for the breast, which is able to detect greater blood flow that is a sign of cancer, with a radiation free energy source. The Computed Tomography Laser Mammography (CTLM®) system uses laser to image the breast in a non-invasive procedure. Unlike x-ray mammography, CTLM images blood hemoglobin and the process of neoangiogenesis or new vessel formation which is often associated with breast cancer. The CTLM functions somewhat like a conventional CT scanner in that an energy source, a near-infrared (NIR) laser, scans the breast; a computer reconstructs cross-sectional images based on measured optical data. The measured optical values are directly related to the optical effective transport coefficient of the breast tissue. Like CT, the images may be viewed as single slices or as 3D volumes.

The Computed Tomography Laser Mammography method is a rather new breast imaging technique, yet studies from diagnostic centers all over the world present it as a promising tool in the imaging of the breast either alone or as an adjunctive to conventional mammography. When applying laser light to biological tissue, the occurrence of a variety of interaction mechanisms is multiple. This diversity is due to specific tissue characteristics as well as laser parameters. Laser radiations induce biological damage in tissues via photochemical, photothermal, and photomechanical interactions. During the CTLM technique of the NIR laser irradiation of the breast tissue, thermal effects take place, which were studied in this thesis with the aid of a Monte Carlo simulation code, the MCSLTT (Monte Carlo Simulation of Light Transport in Tissue) code. With the assistance of the MCSLTT code the simulation of the photon propagation inside the breast tissue and the skin was performed and graphics (appearing the temperature rise (°C) as a function of the depth that the laser light penetrates inside the tissue) and results that concerned the parameters under investigation (the total heat, the maximum photon depth when using different input powers and different medium thicknesses) were extracted. The combination of those results, led to the extraction of useful information and to the quantification of the
thermal effects induced on skin and breast tissue and to the quantification of the influence of several parameters on breast’s temperature, when being irradiated with laser beams. Photochemical interactions, photoablation, plasma-induced ablation and photodisruption could as well be examined with the development of a new Monte Carlo simulation code, giving interesting results about the interaction mechanisms observed during the CTLM’s laser beam irradiation of the breast tissue as an aspect of future work.
Περίληψη

Ο καρκίνος του μαστού αποτελεί τον πρωταρχικό παράγοντα θνησιμότητας των γυναικών στις ανεπισκευής χώρες. Κατά την διάρκεια των τελευταίων χρόνων, εντούτοις, άρκετες τεχνικές στην απεικόνιση του μαστού έχουν αναπτυχθεί και εφαρμοστεί, με την μαστογραφία ακτινών X να αποτελεί ίσως την πιο ευρέως χρησιμοποιούμενη από τις διαγνωστικές μεθόδους καρκίνου. Παρόλο που η μαστογραφία ακτινών X ακόμη παραμένει η κύρια διαγνωστική τεχνική στην μάζη κατά του καρκίνου του μαστού και αποτελεί έναν συνεισφέρον παράγοντα στην προβολική άνευρεσ στην επικίνδυνη διάνυσμα των οποιων που ισχύουν από πληθωρικά αποτελέσματα ως χαμένες αλλοίωσεις καθώς και το ρίσκο της κατανόησης. Εξετάζεται εκτενές τεκμηριωθεί τη μαστογραφία του τον τον τον την τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον τον 

Εφόσον η μαστογραφία αποτελεί μια προβολική απεικόνιση υπερτιθέμενων δομών μαστού είναι γενικά μικρά, δυσκολότερο να ανιχνευτεί καρκίνος σε έναν μαστό με πυκνή μορφή. Σαν αποτέλεσμα, η μαστογραφία παρουσιάζει χαμηλή ευαισθησία συμβατίκης μαστογραφίας ακτινών X στοιχείου μαστούς. Αυτό οφείλεται στο γεγονός ότι απεικονίζει μόνο ανατομική λεπτομέρεια και δεν παρέχει πληροφορίες που είναι απαραίτητες για την πρόβλεψη και ακριβή διάγνωση του καρκίνου του μαστού και αναμένεται να μειώσει σημαντικά τον αριθμό των μη απαραίτητων προστασίες. Ωστόσο, αποδεδειγμένες ιδιότητες του φωτοθεραπευτικού ροής μελέτες μπορούν να βοηθήσουν την απαραίτητη απεικόνιση να “δει” αυτά που οι άλλες διαγνωστικές μεθόδους, συμπεριλαμβανομένης και της συμβατικής μαστογραφίας ακτινών X, μπορεί να χάσουν. Μία από τις υπερτιθέμενως τεχνικές στο προσκήνιο, είναι η μαστογραφία laser με μεθόδους υπολογιστικής τομογραφίας (CTLM), ένας υπολογιστικός, τομογραφικός, βασιώνεται σε ακτινοβολία laser ανιχνευτής για τον μαστό, που μπορεί να ανιχνεύει μεγαλύτερη ροή αίματος (ή οποια αποτελεί ένδειξη του καρκίνου), χρησιμοποιώντας μία μη ιοντίζουσα πιθήνι ενέργειας. Το σύστημα CTLM χρησιμοποιεί laser για να απεικονίσει τον μαστό σε μία μη διήθητη διαδικασία. Αντίθετα με την μαστογραφία ακτινών X, το σύστημα CTLM απεικονίζει την εμπειρία του αίματος και την διαδικασία της νέας-αγχοποίησης ή της συμβατικής νέους συγκήρυξης που συχνά σχετίζεται με τον καρκίνο του μαστού. Το ΚΤΜ λειτουργεί σε έναν συμβατικός ανιχνευτής τομογραφίας ακτινοβολίας εφόσον η πιθήνι ενέργειας, ένα laser που εκπέμπει στο εγχύος υπέρθυρο ανιχνεύει τον μαστό και όταν υπολογιστικής εκχυτής συντελεστές μια ημέρα στην πύκνη οξείας του καρκίνου του μαστού. Οι μετρήσεις ιοντικής ροής μετρούν την επίπεδη υπολογιστικής τομογραφίας, οι οποίες μπορούν να απεικονιστούν σε ατομικές τμήματα ή ως τρισδιάστατο άγκουλο. 

Η μαστογραφία laser με μεθόδους υπολογιστικής τομογραφίας (CTLM) είναι μια σχετικά νέα τεχνική απεικόνισης του μαστού, παρόλο που αυτός διαδικαστικοί κέντροι από όλον τον κόσμο την παρουσιάζουμε ως μια πολλά υποσχόμενη μέθοδος στην απεικόνιση του μαστού είτε μόνη ή συνεπής στην επικέτη μαστογραφία. Κατά την εφαρμογή ακτινοβολίας η μαστογραφία laser με μεθόδους υπολογιστικής τομογραφίας laser σε βιολογικό ιστό, η εμφάνιση διαφόρων μηχανισμών αλληλεπίδρασης είναι πολλαπλή. Η ποικιλία αυτής οφείλεται στα ειδικά χαρακτηριστικά του ιστού καθώς και στις παραμέτρους του laser. Η ακτινοβολία laser προκαλεί βιολογική καταστροφή σε ιστών και φωτοχημικών, φωτοβερμίκων και
φωτομηχανικών αλληλεπιδράσεων. Κατά την διάρκεια της NIR laser ακτινοβολίας του μαστού της τεχνικής CTLM, θερμικά φαινόμενα λαμβάνουν χώρα, τα οποία μελετήθηκαν σε αυτή την διπλωματική εργασία με την βοήθεια ενός Monte Carlo κώδικα προσομοίωσης, του κώδικα MCSLTT (Monte Carlo Simulation of Light Transport in Tissue). Με την βοήθεια του συγκεκριμένου κώδικα πραγματοποιήθηκε η προσομοίωση της διάδοσης των φωτονίων εντός του ιστού και του δέρματος του μαστού και ελήφθησαν γραφικές που παρουσίαζαν την αύξηση της θερμοκρασίας (°C) ως συνάρτηση του βάθους που η ακτινοβολία laser φτάνει εντός του ιστού και αποτελέσματα που αφορούσαν τις παραμέτρους υπό διερεύνηση (συνολική θερμότητα, μέγιστο βάθος φωτονίων με χρήση διαφορετικών ισχυών εισόδου και διαφορετικών παχών μέσου). Ο συνδυασμός αυτών των αποτελεσμάτων οδήγησε σε χρήσιμες πληροφορίες και στην ποσοτικοποίηση των θερμικών φαινομένων στο δέρμα και στον ιστό του μαστού καθώς και στην ποσοτικοποίηση της επίδρασης αρκετών παραμέτρων στην θερμοκρασία του μαστού όταν αυτός ακτινοβολείται από δέσμε laser. Οι φωτοχημικές αλληλεπιδράσεις, η φωτοαποκόλληση, η αποκόλληση επαγόμενη από πλάσμα και η φωτοδιάσπαση θα μπορούσαν να μελετηθούν σε μία μελλοντική εργασία με την ανάπτυξη ενός νέου Monte Carlo κώδικα προσομοίωσης, οδηγώντας στην εξαγωγή συμπερασμάτων σχετικά με τους μηχανισμούς αλληλεπίδρασης κατά την διάρκεια της CTLM μεθόδου ακτινοβόλησης του μαστού.
References


