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Integrative Applications of General and Medical Physics With Laser Technologies in Precision Diagnostics and Therapy

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Annotation: Non-invasive biomedical research and diagnostics enabled by innovative compact lasers. For over half a century, laser technology has undergone a technological revolution. These technologies, particularly semiconductor lasers, are employed in a myriad of fields. Optical medical diagnostics, one of the emerging areas of laser application, are on the forefront of application around the world. Optical methods of non- or minimally invasive bio-tissue investigation offer significant advantages over alternative methods, including rapid real-time measurement, non-invasiveness and high resolution. These advantages demonstrate the growing success of such techniques. Will outline the recent status of laser technology applied in the biomedical field, focusing on various available approaches, particularly utilising compact semiconductor lasers. Will further consider the advancement and integration of several complimentary biophotonic techniques into single multimodal devices. Will demonstrate the easy and convenient operation of the device as well as the possibility to automatically process the collected data and determine tissue pathological status. Based on own studies, will also cover the simultaneous collection of physiological data with the aid of a multifunctional diagnostics system, concentrating on the optimisation of the new technology toward a clinical application. Such data is invaluable for developing algorithms capable of delivering consistent, reliable and meaningful diagnostic information, which can ultimately be employed for the early diagnosis of disease conditions.

Lasers are used today more and more in therapy and diagnostics. In diagnostics, they are used additional to other procedures like metabolic monitoring resp. for optical imaging. Main topic of medical applications therapy, in which laser is sometimes a surgical instrument sometimes a central, alone standing therapeutic procedure. But it is forgotten that laser is light, a special light, but the biological reactions are in general not different from normal light. This is important to prevent disappointments on the other to use the experience of photobiology and light therapy. In medicine, laser is used since his invention mostly destructive but nature uses light since billion of years mainly constructive. So lasers are used not only for cutting and removal on surfaces the application is more complex. This is caused by a continuous technical development of laser systems and accessories, like endoscops, but more important is the better knowledge about laser-tissue-interaction. The field of application is broad, there are daily new indications but other are replaced by the development of other techniques. The indications are from plastic surgery over the congenital and vascular diseases to open surgical organ and tumor resections. Very important is laser in endoscopic surgery and in interstitial laser coagulation. But in contrast to thermal procedures, the indication for photo dynamic therapy are dysplasias and virus-induced tumors.

1. Introduction to Medical Physics

The success of medical physics depends on the ability to work at the interface between fundamental scientific disciplines and clinical practice. In recent years, as available medical modalities have considerably increased, an important aspect of the physicist's role is the effective choice and implementation of these modalities. Traditional diagnostic X-ray imaging systems, both mammographic and general-purpose, share the same basic technology but differ considerably in particulars. Consequently, the ability to address such differences becomes crucially important in more complex modalities such as computed tomography and nuclear medicine cameras. While medical physicists' responsibilities relate to classically stable X-ray and gamma-ray modalities, new developments arise in laser technologies. These technologies are also attractive because of the present massive momentum for the clinical translation of experimental diagnostic and therapeutic procedures. This review discusses, with a few notable examples, an integrative application of the earliest laser technologies in medicine: laser-induced fluorescence spectroscopy in early dermatological diagnostics and therapy and other new optical technologies.

Lasers have revolutionized a number of diagnostic and therapeutic modalities in medicine and are increasingly finding applications in clinical practice. However, many new systems and techniques, including promising compact laser technologies for in vivo or ex vivo use in diagnosis and therapy, are mostly as yet limited to research settings. The future challenge regarding the integration of this new laser technology with medical imaging is to keep them separate and complementary, but the most demanding efforts will be needed in combining them. Historical time is a crucial player in the observation of implausible technological developments. It took over half a century for the development of X-ray radiography from fundamental understanding to commonly applied medical diagnostics, and about the same time for medical-computed tomography. The remarkable early-21st-century development of laser technologies for medical applications raises prospects for greatly accelerated development to improvised kitchen appliances of biophotonics technologies for diagnostic and therapeutic applications. [1][2][3][4]

2. Fundamentals of Laser Technologies

Laser-technology-based systems are employed in precision medicine for diagnostic detection of diseases and therapy of malignant tumors. Medical lasers are employed in laser medicine applications in industrially developed countries. Research of basic processes in laser technology, such as phenomena that occur in laser media advancement of laser medicine, laser diagnostics, laser surgery, dermatology, eye treatment, cosmetic medical aid and other fields of medicine. The basic principles of laser action on biological tissues are considered along with laser application in medicine. Analytical description of laser action on biological tissues providing background for innovative development of laser medical systems in forward-looking medical aid. Biomedical applications of laser technologies, such as detection of diseases and therapy of malignant tumors, are discussed. At present, laser technologies are widely used in clinical medicine for diagnosis and treatment of various pathological conditions. Medical lasers mainly include solid-state lasers, CO2 lasers, semiconductor lasers and dye lasers. These lasers have stimulated development of laser systems for new applications such as laser diagnostics of precancerous lesions and malignant tumors in the surface layers of the skin and mucous tissues as well as the treatment of these pathological states. Various medical laser technologies for disease diagnosis and therapy are, at present, widely used in clinical medicine. Marx first predicted the laser action in 1916. After more than 30 years, laser technologies entered both scientific research and high-tech applications, which had stimulated rapid development of various fields of optics. The first laser of continuous fields appeared in 1960. The first laser device was employed. This technological breakthrough initiated the laser revolution. 60 million lasers for laser technologies, based on solid-state, gas, dye and fiber lasers are used in an ever widening variety of applications. Basics of laser technology are discussed. It is shown that the basic laser approach consists in nonlinear amplification of photons due to stimulated emission in gain media. This approach is based on Planck-Kirchhoff-Boltzmann theory of thermal radiation. Extension of this laser approach to amplification of matter waves in optical lattices is discussed. It is shown that the consideration of laser.Q and gain media on the same footing provides an understanding of gain and Q switching of lasers and laser jets. Advantages of the new approach include standard study of laser action in spectral and temporal domains, on quantum and semiclassical levels as well as with understanding of complexity of laser systems and their states

[5].

3. Precision Diagnostics: An Overview

With the rapid advancement of laser technologies, the application potential of lasers in biomedical research and diagnostics are rapidly expanding as well. The technology, uniqueness, and versatility of lasers dominate traditional imaging modalities in imaging biomedical phenomena. Laser-based measurements are with high temporal (up to femtoseconds) and spectral (up to 0.001 nm accuracy) resolutions. Compact laser systems can be built using huge variety of optoelectronic components such as lasers diodes, modulators, detectors, etc. These compact systems can be interfaced with portable electronics, laptops, and tablets accessible to the wider biomedical community. A wide variety of spectral domain methods are developed in the optical wavelength range. Time-resolved measurements are actively used in measurements beyond the optical range, in particular in terahertz measurements of tissue biopsies. The broadening application scope brings new challenges for engineers and scientists. Technical limitations of existing technologies contribute to them. Application limitations of lap top-based systems in a routine clinical use, decrease of measuring speed by increasing the size of optical probes are highlighted.

“Laser” is derived from the abbreviation of Ligh Amplification by Stimulated Emission of Radiation. Chu in the early 1960s expanded Einstein’s theory of stimulated emission and showed that laser basis, Coherent Electro-Magnetic Radiation (CEMR), can be produced. CEMR has a number of special properties, including spectral purity, spatial coherence, and storage in a laser cavity [5]. These properties have led to the fast expansion of laser systems and their applications in the range of laser technologies, with a relatively slow response in medicine in a broader aspect, and particularly in laser biomedicine investigations. The laser applications were initially fast grounded in basic univesities as laser spectroelectrochemistry/homogeneous/enzyme/fluorescence/linear variable imaging methods for biosample monitoring and analysis in a population or high-throughput analysis of biosamples.

4. Role of General Physics in Medical Applications

Medical physics is essential in medical treatment and diagnosis. In medicine, mainly particle physics is applied, and therefore, knowledge of the atomic nucleus is essential. This knowledge in medicine is necessary concerning treatment and due to the use of radioactivity in. It is important to reduce the usage of non-ionizing radiation for treating and diagnostics indications in rehabilitation medicine as well. General physics is a main stream for medical physics, and a macro- and micro understanding of the physical phenomena is hence investigated foundations of modern physics are basics of instrumentation, detector devices are basic knowledges too. Medical physics is closely linked with medical engineering: In addition with the working principles, important are knowledge about calculation methods as well, especially in constructing Monte Carlo code. In this context, applications to planar imaging (e.g. SPECT, PET) and tomographic imaging (e.g. CT, MRI) are investigated as examples on the instrumentation side, whereas calculation methods for treatment planning and radiation transport simulation code are discussed as examples of methods [6]. Detection, transport, interaction, and detection of x-/g-Ray or particle are investigated, as well as medical application of fast neutrons, focused X-ray beams, and nonlinear optics to molecule imaging. Laser are used today more and more in therapy and diagnostics. In diagnostics they are used for optical imaging. Main topic of medical applications therapy, in which Laser is sometimes a surgical instrument. It is important to use the experience of photobiology and light therapy. In medicine laser is used since his invention 40 years ago mostly destructive but nature uses light mainly constructive [5]. Lasers are used not only for cutting and removal on surfaces. The application is more complex due to a continuous technical development of laser-systems and accessories. The indications are from plastic surgery over congenital and vascular diseases to open surgical organ and tumor resections. Very important is laser in endoscopic surgery and in interstitial lasercoagulation. The indications for photo dynamic therapy are dysplasias and virus-induced tumors. The experiences by the photodynamic therapy and the better understanding of biochemical metabolic processes open the field of indications for this therapeutic principle also for benign chronic diseases.

5. Laser Interaction with Biological Tissues

Lasers are used today more and more in therapy and diagnostics. In diagnostics, lasers are applied for metabolic monitoring by means of (non)invasive Raman, fluorescence or photoacoustic spectroscopy as well as optical imaging methods like optical coherence tomography (OCT) or single-photon emission computed tomography/single-photon emission computed tomography with transaxial scanning (SPECT/SPECT). A broad range of lasers is in diagnostic use in medicine, covering nearly any laser technology [5].

The main topic of medical applications is therapy, where lasers are employed sometimes as a surgical instrument (incision, excision, vaporisation, coagulation, etc.), but sometimes as a central therapeutic procedure (focused dosage of energy for stimulation, heating, photodynamical reaction etc.). The misconception often exists that medical lasers represent a special technology whose biological reactions significantly differ from those of normal light. However, this is not the case; by nature, ‘only’ ordinary black body light was present, hence for that there are mechanisms of light-tissue interaction and, thereby, tolerance windows (such as selectivity, penetration depth, reaction time) [7]. The reason for using lasers in medicine is the generation of electromagnetic radiation in a monochromatic, intense and temporally bundled (coherent) manner, combined with intact energy delivery systems.

The application of the then still novel laser technology in medicine began in the early 1960s with the pioneering works of T. E. M. (Ted) Maiman on ruby as laser medium, A. L. P. (Al) Schawlow on CO2 lasers and F. A. (Frank) P. H. N. (Nels) deBrubaker on the first endoscopic intervention with Nd: YAG lasers. The ensuing technology spread worldwide at an astonishingly fast pace, furthered by a broad general publicity due to fanciful experiments. The available laser sources and delivery systems developed in kind, frequency, intensity and miniaturization, broadening the range of applications. However, under the critical sight of 38 years of application, it can be concluded that the initial overestimations of some effects intuitively drawn from laws of physics did not happen, but on the other hand, the then fantasized out of reach applications, e.g., thermal tissue welding, endoscopic retraction of mucosal folds, selectivity for absorption band curing with non-invasive visible light, extensive photodynamic therapy (PDT) indications etc., became a reality.

5.1. Mechanisms of Laser-Tissue Interaction

The term “laser” is an abbreviation of “Light Amplification by Stimulated Emission of Radiation”. When describing lasers, the terms “wavelength”, “energy emission (pulse width)”, “delivery system” and “operating mode” are essential parameters to evaluate its use. A particular laser wavelength will interact specifically with the target tissue based on its absorption spectra, whilst energy emission will determine its effect. There are three fundamental delivery systems: fibre, hollow waveguide, and bare optics. The most thorough mode of operation is the continuous wave mode, whereby sheets, ribbons or other examples of laser light can be produced [7]. Since the introduction of the first continuous wave laser in 1960, lasers have been developed with wavelengths extending between the vacuum ultraviolet (193 nm) to the microwave region (106 GHz). These lasers operate based on the ionization of gases, solid-state arrangements, chemical compounds, semiconductor junctions, or photo-pumped gases or dyes to produce the laser light. The controlled application of laser wavelengths to interact with matter has resulted in a wide range of clinical laser applications for oral and dental tissues (hard and soft tissues) in a variety of standard modes, including vaporization, cutting, whitening, coagulation, and fluorescence.

Dental Lasers: Laser Development and Applications

The term “laser” refers to a device that generates and amplifies light through a process of stimulated emission of radiation. Lasers have been classified as Continuous Wave (CW) or Pulsed Operation (PO) based on the type of energy output. There are four types of laser operation: gas, dye, solid-state, and semiconductor lasers. The review outlined how wavelengths of lasers are absorbed by targets, how geometries of lasers are applied to oral tissues, and how power levels of lasers are operated on tissue surfaces. The review presented dental hard tissue caries removal and hard tissue conditioning using ; 800-900 nm lowpower semiconductor laser light (< 100 mW) for dentin bonding; 1480 nm solid-state laser for noncutting and nonvaporizing smooth sensate dentin cavity margin; and 980 nm high power solid-state laser for non-invasive anterior dentin sealing.

5.2. Safety Considerations in Laser Applications

Laser technology has made an impact across a broad range of disciplines, including industrial processing, medicine, and computer science. In medicine, the focus has typically been on applications in therapy. Noninvasive diagnostics and imaging using laser sources have grown rapidly in the past two decades. Most recent developments center on the use of two-photon excited fluorescence for high-resolution cellular imaging and on optical coherence tomography, an interferometric imaging technique that penetrates tissue to depths on the order of 1 mm with 10 to 20 M resolution. Current research is directed at enhancing contrast in angiography and viewing transparent structures such as the cornea [8]. As laser technology has matured, the number of medical laser procedures has exploded. Contrary to popular belief, lasers in medicine were not born in the 1990s as a result of a scientific and industrial revolution. The origins of the medical laser date back over 40 years to the invention of the ruby laser [5]. Though about 70% of today's laser procedures are performed in dermatology, laser use in other medical, surgical, and diagnostic fields is increasing rapidly. Most, if not all, surgical and therapeutic lasers are also extensively used for diagnostic purposes. For these reasons, it is important to understand processes and concepts associated with the interaction of laser light with tissue, to become familiar with the basic physical principles behind lasers and the invention of specific laser systems, and to acquire a general understanding of the anatomy and physiology of the human body. As medical lasers strive for niche applications in specific fields, new proprietary proprietary laser wavelengths, systems, or techniques are being continuously invented and marketed by laser companies. An overview of the many different kinds of lasers and of the many different applications of lasers in medicine necessitates a separate book with over a dozen contributors.

6. Applications of Lasers in Diagnostics

Lasers are deployed in diagnostics as a basis for laser safety standards for the man-made environment [5]. Interactions of lasers with biological tissues and laser-induced effects on healthy and cancerous cells are critical in the provision of clinical applications for diagnostics in optical imaging techniques, showing the safety class limitations for selectable laser source parameters, operating modes, mainly CW and Laser-Diode mode-locked, and accessories. Laser safety setups for the relevant wavelengths are included such as visible or near-IR w.r.t. 1.06 µm, using average and pulse power density and energy density. Moreover, the interaction of lasers with biological tissues in histology and its classification considering imaging techniques by the processing of the analytical diameter of the lasers’ source. In addition to encoded laser image signatures on tissues, laser-tissue interaction modeling results are presented and finally, the significance of computational modeling in laser diagnostics in medicine is illustrated.

Non-invasive biomedical research and diagnostics enabled by innovative compact lasers have arisen in response to the demands of the future. For over half a century, laser technology has undergone a technological revolution. Inventors of the laser and renowned visionaries also underestimated societal impact. Today, laser and optoelectronic technologies are employed in a myriad of fields: space exploration, environment monitoring, metrology and testing, industrial and manufacturing applications, and medicine, biology, and astronomy [9]. Optical medical diagnostics, one of the emerging areas of laser application, are on the forefront of application around the world. Optical methods of non- or minimally invasive bio-tissue investigation offer significant advantages over alternative methods, including rapid real-time measurement, non-invasiveness, and high resolution. The integration of several optoelectronic methods into more complex systems with greater diagnostic capabilities is particularly relevant. Initially, lasers, which were bulky and expensive, were used in medical research with very limited success or were used mainly for therapy on tissues with a high water content. The need to connect sources and detectors required non-flexible system assembly and raster scanning, which considerably complicated lots of conventional applications.

6.1. Optical Coherence Tomography

Optical coherence tomography (OCT) is akin to ultrasound imaging in that it targets sub-surface structures. However, instead of reflection measurements of short ultrasonic pulses, low coherence interferometry is applied to infrared light [10]. Analogous to the echo time delay measurement in ultrasonics, OCT measurements of the backreflection intensity are based on correlation techniques in which the backscattered light signal is compared with a reference light signal. The latter is split off the light source and sent down a fixed path length. A few hundred microns below the surface, the backscattering light from the surface will move into the coherent area and registration will occur. Repeatedly scanning the low coherence light spot on the surface provides an image of depth profiling. The dimensional dependence of Gaussian beam propagation in a homogeneous medium results in a spatial coherence limit for tomographic imaging. For image sampling, a resolution element of at least 2x the coherence length of the light source is necessary. Reflection power density is measured at 512 sampling positions.

Optical coherence tomography (OCT) is a three-dimensional, structural, cross-sectional imaging modality. Although it integrates ultra-high speed and high spatial resolution multi-dimensional imaging, its use has not been widely extended for telepathology or robotic surgery applications [11]. Tele- or remote operations is targeted at intra-and post-operation management of patients, especially patients of outlying areas of health care. Robotic surgery has been adopted to overcome the limitations of conventional surgical therapy for various organs. Integration of these two techniques is actively studied to provide surgeons with enhanced usability, accessibility, and affordability. Multimodal imaging systems are proposed for vision-guided tele- and robotic surgery. Utilization of optical coherence tomography (OCT) offers novel assistance capability of low-coherence backscattering measure where target sites are of small blood vessels to reduce damage of surrounding tissue. This view contrasts with that of conventional visual and photoacoustic imaging where site targets are biomarker point targets to visualize or quantify image contrast-enhanced appearance.

6.2. Laser-Induced Fluorescence

The most general application of mineral lasers in biology and medicine is in the field of diagnostics. There, the special characteristics of laser excitation are used to detect either specific molecules or non-defined molecules with specific spectral properties to give information about metabolic conditions in living tissue. The condition of living tissues directly correlates to the fluorescent parameters of certain metabolites. Health, disease, tumor transformation - already at the beginning of differences were detected by laser-induced fluorescence techniques. Non-invasively, early detection of disturbed metabolic conditions or altitude changes in a tumor is possible. A laser application may be used with one laser and a single detection system or by a laser scanning microscope, where the same scanner is used for excitation and detection [9]. More than 15 years ago the laser-induced fluorescence of porphyrins was observed under endoscopic, natural light and laser light excitation in tissue culture. Only LIF techniques with laser spectroscopic sorting of tissue with e.g. normal, pathological, confusing fluorescence properties were able to provide groups comparable to that of histology [5]. After the first experimental proof using light-producing devices, these optical techniques were wished to be used commercially. Disadvantages concerned the bulkiness, on-line use for therapy not only for diagnostics. Noisy, cheap, stable sources of fluorescence excitations are better usable in the diagnostic field. The aim may be the diagnostics of tissue not vegetation at first sightings in spectral images or video. The use of laser sources like for fluorescence diagnostics - as both side narrow band lasers is a potentially new idea. Laser sources with a stable and narrow band line width enhance resolution. In the field of early dermatoscopy, the same narrow line - LIF output from the dye lasers - might be achieved by the right choice of raw dye or by a non-saturable grating with 5 - 15 nm.

6.3. Endoscopic Laser Techniques

Endoscopic laser techniques are becoming more widespread in the medical field due to their advantages over other medical laser applications. Many techniques are used in endoscopy, including photocoagulation for hemostasis, tissue vaporization, tissue dissection, vascular occlusion, and biofilm removal. In general, therapeutic endoscopes are rigid optical systems incorporating laser fibers without laser aiming or feedback control systems. Thus, treatment quality is not guaranteed and may be affected by the conditions of the treatment. Many efforts have been made to overcome the limitations of such rigid endoscopes. The presented techniques involving laser imaging feedback or precise laser aiming systems may be valid solutions but require noncompact optical elements and are very cost intensive. Moreover, with such systems, it is difficult to provide not only the optical channel for imaging but also a compact, deployable system for laser delivery. Consequently, these kinds of systems are limited to research laboratories and not available in the clinic. Inversely, a new compact device providing laser delivery capability to a standard commercial endoscope is presented by adopting the same fiber-bundle technology used in laser imaging feedback [12].

As a first step in advancing forward, a miniaturized endoscopic image-guided laser treatment system based on imaging feedback for a standard commercial endoscope was presented. Since the tactic of compact and deployable design is employed, it will be advantageous not only for its own feedback control but also for other simplified approaches. The demonstrated proof-of-principle point targeting application is still valid in the treatment of several kinds of benign lesions after careful preprocessing with a conventional narrowing endoscope. Conventional devices are generally simple and compact, but their applications are limited primarily to large organs with standard wider lumens, such as the pharynx and colon. On the other hand, the fiber-bundle-based system may be applicable for narrowing organs with compact endoscopes where conventional devices are not applicable.

7. Laser Technologies in Cancer Therapy

Laser technology is a completely new powerful device developed for diagnosis and treatment in medicine. Usually, lasers are produced in a laboratory where this research takes place. Nevertheless, they must be reliably and practically applied in a hospital, which requires special consideration. Laser technology has now reached a level where it can be broadly applied, e.g., new types of lasers that do not require a big facility (sometimes called table-top lasers) can be easily transported. This means even diagnostic laser tests can be performed in the field, or on-the-spot measurement could be performed. Treatment using lasers is uncomplicated and safe since everything is computerized and pre-set. However, a well-educated physicist or technician must be there to supervise the treatment consistently [13].

Laser treatment in medicine can be broadly applied, like surgery, coagulation, vaporization, peeling, drilling, and wound hemostasis. Special triggers are also introduced to these procedures, such as hemophilia or auto-genetic traits. Ancillary devices must be developed considering the nature of the procedure, such as catheters in the case of endoscopy, and lung or heart surgery must be performed with careful consideration of the physiological factors. Numerous ancillary devices could also be developed for precision treatment [5].

Since the establishment of the laser, applications in theaters and in vivo pathological studies have been very fruitful, but there have been very few substantial developments in experimental research. Integration of laser scanning optical microscopy or laser scanning two-photon diaphragm microscopy requires consideration of the aberration of the lenses/nosepieces because they seriously distort the image, especially for thick specimens. The high-speed image processing adjustment for range compensation is needed again for focusing depth displaying. The employment of a high-speed Z-stage is also required for dynamic measurement. Continuous recording of temperature and oxygen-dissolved ratio is a necessity for free-moving animals.

7.1. Photodynamic Therapy

Photodynamic therapy (PDT) is a therapeutic modality for specific malignant, non-malignant, and pre-malignant conditions. It has a virtually unlimited application area in the medical field due to its non-invasive or minimum invasive nature, cosmetic features, and significant destructive effect on cancer cells without remarkable damage to the surrounding viable tissues. PDT is a treatment approach that involves the use of a specific wavelength of light on the region which the target tissue is applied after an appropriate resolution period of a certain photosensitizing agent (PS) on the target tissues. The mechanism of actions depends on the generation of singlet oxygen (1O2) through the excitation of a particular PS, which transfers its excited energy to molecular oxygen (3O2) in the tumor tissues. The necrotic and/or apoptotic destruction of the tumor cells is induced by the cytotoxic singlet oxygen and other secondary molecules such as reactive oxygen species (ROS) [14]. Besides the direct action of singlet oxygen, there are also indirect effects such as damaging vascular structures, leading to anoxic regions in the tumor.

The very first PDT publications were revealed around 1900's. Von Tappeiner applied eosin to basal cell carcinomas topically, then visible light was applied to the region. In 1980's and 1990's, PhotoDerm-2300, WST-09, AlPc, etc. were developed as PDT agents. In 1995, Photofrin received FDA approval as a clinical application of PDT [15]. The efficacy of PDT mainly depends on the selectivity and efficiency of PS. Due to the weak absorption band of HpD on the visible wavelength region, the tunneling photofrin was later developed as a second generation PS with a strong and broad absorption band in the near infra-red (NIR) region. However, intense light is also required in order to induce a PDT effect for some tumor tissues. The limitations of the current PSs have been overcome by the design of more ideal PSs and advance technologies. Such second generation PSs were designed to be applied intra-vascularly by the application of nano-scale drug delivery systems, or with strongly attenuated light pulse lasers. The third generation PSs are integrated strategies that utilize targeting and delivery moieties, such as monoclonal antibodies and high-affinity ligands that can be attached to nanoparticles, liposomes, etc. Nowadays, the curative ability of PDT is still limited and under-theorized in the present medical field, and efforts in fundamental and applied sides are urgently needed.

7.2. Laser Ablation Techniques

Laser ablation is a well-studied method that allows the removal of both solid and liquid tissue depending on the parameters. In recent decades, it has become a popular technique for both basic and applied research, where the understanding and control of laser-tissue interaction phenomena are very important. An updated review is presented on the application of laser ablation and laser-assisted methods for precision tissue diagnostics and medical therapy. The theory of laser-tissue interaction and light propagation in biological tissues is presented as a basis for understanding the basic principles of laser technologies used in medicine. A focus is given to techniques based on laser thermal ablation, as well as to newer methods of laser-induced photochemical tissue processing. It is explained how the parameters associated with laser light, as well as those associated with the tissue, can be combined to tune the efficiency of tissue processing.

The concept of precision laser-assisted medicine is presented and explained as a trend for future improvement of medical robotics, including endoscope-based laser technologies and laser tissue interaction/diagnostics. A review of common laser-assisted techniques for tissue diagnostics and therapy is presented with an emphasis on handling and presentation as easy-to-read tables. Examples of recent trends in developing precision laser-assisted approaches for tissue research and processing are also included, from machine-learning-based biospecimen discrimination to imaging-guided and robotic laser therapy systems. Recent advances in laser-assisted molecular diagnostics and the coupling of molecular diagnostics to laser-assisted cancer treatment are also highlighted. Animal safety experiments revealing/confirming few effects and a precision treatment of single tumors within complicated/multitissue spatial models are also reviewed. Healthcare stakeholders and technical designers working on light/tissue interaction/micromorphology/medical devices are the target audience of this article. [16][17][18]

7.3. Brachytherapy with Laser Systems

Among various nanotechnologies, microbeam radio-therapy has shown a great future possibility. There are essential generative technologies such as fabrication of ultra-fine and high precision collimators, high resolution x-ray imaging systems, and development of synchrotron radiation beam players, which the present authors expect future inventions and innovations. Microbeam irradiation system based on laser plasma hard x-ray generation and scanning apparatus has been made to demonstrate a feasibility of using a compact hard x-ray generated by a table top laser system and multi-slit gold collimator mask designed by using micro fabrication technology. The various prototype systems and experimental investigations concerning to knowledge of de-facto damage threshold levels of microbeam x-ray irradiation have been studied and demonstrated using other nano/micro beam irradiations. Further works are needed to innovate and develop fabrication technologies. Results of the latest works on a prototype system for microbeam x-ray therapy are summarized [19]. Brachytherapy is among the oldest modalities for the treatment of solid malignancies within a multidisciplinary approach. In intracavitary or interstitial techniques, radioactive seeds are implanted closely to the tumor to deliver a high dose of irradiation, preserving the surrounding healthy tissue. The outstanding results of permanent seed implants in treating prostate cancer have set the stage for further applications, especially in combination with other treatment modalities. However, with the increase in life expectancy and an even increasing cancer incidence, there is a rising need for a more flexible brachytherapy technique with a precise and independent dose distribution. In so-called high-dose-rate (HDR) brachytherapy, the treatment is performed by the temporary positioning of high activity isotopes within the applied applicators where a high dose rate of up to 50 Gy/h is delivered. This time-resolved brachytherapy technique poses a variety of complex requirements to fulfill the need for safety, reliability, and accuracy. The implantation of a new exposure hole for the remote-controlled source change-out and the development of safety measures created the prerequisites for automated brachytherapy.

8. Integrative Approaches in Patient Care

The two overwhelming trends in contemporary biomedicine are the development of non- or minimally invasive biomedical research and diagnostics enabled by compact lasers, and optically transparent therapies based on percutaneous delivery of lasers, ultrasound and other energy sources. The first trend emerged more than half a century ago in response to the requirement of continuous and high-spatial resolution monitoring of physiological processes in living organisms. Several modalities of research were well established with the development of a range of transillumination methods to track propagation of laser beams injected into tissues. One of the most promising approaches incorporated multimodal imaging, which required the simultaneous use of several complementary modalities to probe a biological tissue under investigation with different contrasts, penetration depths, and imaging speeds. The other trend emerged relatively recently and evolved in response to the increasing demand for biocompatible and selective delivery of energy sources for phototherapy and hemostasis [9]. A wide variety of low-risk, gentle techniques have been developed and demonstrated to provide a minimally or non-invasive surgical replacement of conventional methods used in surgery, hemostasis, and tissue ablation.

A gradual and seamless integration of these two trends far beyond their initial applications is foreseen, where compact lasers would be used not only for detailed and reliable understanding of a disease but also for the effective delivery of biocompatible optical neuromodulation or phototherapy. After properly targeted and complemented with machine learning methods, laser- and microlaser-based devices capable of wide range or simultaneous multi-faceted non- or minimally invasive research diagnostics would reach swarm level and provide real time biomarker tracing of health condition, elaboration of a therapy, and forensic analysis of streams in patient care [5].

8.1. Multidisciplinary Collaboration

The field of laser applications in medicine is rapidly expanding. Laser systems including sources, scanners/delivery systems, focusing optics and accessories for therapy and diagnostics are now available as CE approved certified devices. As there are still significant differences in regulations and certifications worldwide it will be discussed what an effective and safe Lasermed interaction means. The exciting aspects of laser application include the former so-called STAR approaches to Armenia, Integration of modern laser technologies with traditional cultures in Georgia and cultural heritage research in Ukraine, and general ideas about highly innovative approaches to the use of lasers in medicine. The keynote presentation deals with the special interdisciplinary aspect of boundary conditions which has yet to be established and harmonised at present, especially in countries where it does not yet exist [5].

The laser has established itself in medicine as a commonly used tool. For technical development, there are tight limits in miniaturized devices as well as in powerful solid-state lasers. Therefore, from the physicists' point of view, lasers mean applied physics and must be transferred in safe use. Since the early years of laser development, it has been known that on the one hand it does have a range of therapeutic options in medicine, on the other side it should be noted that lasers are complex, user-dependent devices and it has been demonstrated that misuses can cause unfavourable effects and even damaging results. There have been innumerable publications about safety and damage mechanisms, but there are still occasional cases of serious damage to skin or eyes. Not all laser producers supply basic information in laser safety standards and light-tissue interaction.

The participants are requested to present and discuss their significant experiences in this unexplored, multidisciplinary, and rather challenging area. The numerous applications of lasers in medicine are warranted by the wide variety of physical principles involved in different medical scenarios as therapeutic techniques increasingly known to the general practitioners, but much less by public and political views in terms of benefits/damage aspects. Examples of novel low-cost approaches to clinical applications are presented, paving the way towards the development of 'smart' devices capable of multispectral configurations for potential wider biomedical R&D utilization [9].

8.2. Patient-Centered Care Models

There is much discussion regarding patient-centered care models. The patient-centered care approach represents a more holistic and more empowering approach to both treatment and caring and health care in general [20]. Patient-centered care denotes more holism and empowerment than seen in person-centered care, itself a more holistic approach than patient-directed care. In the "patient-centered" model, which has rapidly gained traction, the model has requested and, in some places, mandated that health care users/patients be assisted to "take control of their lives" and, therefore, treatment/caring; i.e., personal health information are promoted/increased (and sometimes inappropriately mandated) to be accessible in various modes, formats, and avenues using updated technology. A "more personal" privacy-shared half-world is constructed to increase personal empowerment (to monitor illness, but even more, all aspects of wellness) [21]. It was hypothesized that such empowerment should be beneficial. The invalidation of that in the context of a patient with acute and continuous pain is considered a potential frontline of new directions of personalized medicine.

From another angle, "person-centered" care may even be more holistic than its predecessor. It promotes individualized care, while still asserting health care in a traditional system as the portion of personal care. It requests from care systems and specialists "to devote themselves to the whole person, rather than merely to an isolated body part or to an isolated medical condition". Instead of the "disease condition," "health and wellness," "whole person," "self-and-world," care for the individual becomes central. The question of true wellness arises; more likely, the "individual" as a whole, whether healthy or ill, may but may be incapable of living up to his/her or other detriments. A person going home is filled with pain, where it is a "security and habitation" to live in, which may deliver much "death" rather than "life." By implementation, personnel delegation or powerlessness in "care" decisions is warranted.

9. Advancements in Imaging Technologies

The increasing demand for accurate, portable, and cost-effective diagnostic devices has prompted extensive research in various disciplines, including laser technology, biophotonics, plasmonics, medical waveform generation, multi-metrology, and shorter and thinner non- or minimally-invasive probes. Compact lasers have drawn particular attention as they allow the performance of highly sensitive measurements and diagnostics in real-time mode due to their high-resolution spectrum. They are considered as one of the key tools for precision diagnostics of vital physiological parameters of various organic systems, including human beings [9]. For over half a century, laser technology has undergone a technological revolution. Optical medical diagnostics, one of the emerging areas of laser application, are on the forefront of application around the world. Various approaches in this research area vary widely, from relatively simple and "lighter" to advanced and extremely complicated. Irrespectively, the advancement of novel compact lasers and methodologies of their application are the underlying design of the future devices, as well as biomedical biophotonic research in general. Optical methods of non- or minimally invasive bio-tissue investigation offer significant advantages over alternative methods, including rapid real-time measurement, non-invasiveness, and high resolution. These advantages demonstrate the growing success of such techniques. Recently developed methodologies of spectral-based laser diagnostics of various tissues diversify the range of investigated tissues and broaden the fields of application. Hybrid approaches based on the combination of spectroscopic methods and a detailed analysis of the resulting high-dimensional data provide more consistent and reliable results. Such data are invaluable for developing algorithms capable of delivering consistent, reliable, and meaningful diagnostic information. Such capabilities can be also employed for the early diagnosis of disease conditions in individuals from around the world. The main targets of modern photonic research in biomedicine can be formulated as the development of effective and reliable approaches capable of non- and minimally-invasively discriminating healthy and diseased conditions at their earliest stage. Contemporary advances in imaging technologies, including those based on laser, allow the exploration of new application areas and play a significant role in the era of personalized medicine. Considerable advancement has been made in photo- and microwave-acoustic systems for imaging of bio-tissues and therapy guidance. A substantial number of high-power nanosecond and femtosecond sources based on solid state, fiber, and DLC technology offer unique capabilities in surgical applications of imaging, sensing, and therapeutic laser systems. [22][23][24]

9.1. MRI and Laser Applications

Magnetic resonance imaging (MRI) is an excellent medical imaging technique providing real-time and noninvasive information with respect to tissue morphology and physiological parameters. On the other hand, lasers have been used extensively in medicine for physical and thermal effecting tissue for therapeutic and diagnostic purposes. The combination of MRI and lasers is expected to lead to further breakthroughs in clinical medicine. Major applications include: MRI guidance of laser treatment and some smart combinations or several lasers to achieve imaging of tissue parameters and even treatment in operating room settings.

MRI Guided Laser Interstitial Thermotherapy (LITT) is a promising, real-time, non-invasive treatment method for brain tumors. It combines the significant advantages of MR imaging and thermal laser techniques. Research in this area focuses on monitoring and modeling laser-induced temperature rises for treatment assessment, real-time modeling and compensatory control, and MR-monitoring of tissue properties. Nevertheless, MRI guided laser ablation is now used in clinical brain tumor treatment and is hoped to progress in more complex clinical treatment paradigms, like probing and re-routing pathways of functional tracts. Modern delivery systems, including fiber optic devices and robotic controllers, allow for flexible and precise positioning of laser sources.

On the therapeutic side it includes basic research with closed resonators to affect even the most minute physiological parameters with laser beams and biological processes with laser light pulse exposure in the form of laser shocks. Its application, however, targets adequate treatment effects on neoplasms and vascular malformations, but also include basic research regarding the slow photo-induced changes of living tissues. The appearance of opto-acoustic techniques made it possible to look, with several mm resolution, thousands of times quicker than traditional heated imaging techniques. An already successful application is foetal MRI, where MRI-guided foetoscopic laser therapy was used to treat twin-to-twin transfusion syndrome.

9.2. CT Imaging Enhancements with Lasers

X-ray Computed Tomography (CT) imaging enhancements with lasers have shown potential to improve diagnostic and therapeutic imaging for many biomedical applications. Digital or image processing is utilized for the CT image enhancement. Significant advancements have been realized in laser-based imaging approaches, particularly internal biomedical imaging and drug monitoring. Alternatively, an approach for a compact X-ray wavelength band (2–10 nm) laser to create X-ray free-electron-laser (XFEL)-like sources is discussed [9]. This recently predicted laser scheme can generate X-ray pulses adequate for highly coherent imaging, including complete phase contrast recovery with unprecedented spatial resolution. The capacity of Forest-Enhanced Coherent X-ray source is predicted using particle-in-cell simulations. Multiscale advances in nanotechnology hold great promise to advance biotechnological and medical research. Microbubbles (MB) of gas invite a variety of significant potential applications in biomedicine. For example, the use of ultrasound (US) and its microbubble (MB) contrast agents for imaging, non-invasive vascular imaging, drug delivery facilitation in tumours or bacterial biofilms, ablation of kidney stones, and therapeutic nerve regeneration after crush injuries in the factory that destroys optic nerves have been realized. In direct photosynthesis measurement applications, fluorescent MBs stabilized in aqueous solution have also been employed for fluorescence-based detection. The cost-effective development of opto- and photo-acoustic (PA) contrast agents for US with improved biocompatibility and effectiveness has gained great research attention in recent years.

Improvements in CT reconstruction using lasers have practical implications for in-tissue drug distribution monitoring diagnostics. Improvements in drug metabolite concentration estimation in tissues can be realized by applying laser-based CT image reconstruction approaches in conjunction with advanced spectral-spatial drug monitors. For example, fibrotic intratumoral drug distribution monitoring and treatment response evaluation can be enhanced. Improvements in premature drug release prevention in tissues have been realized by employing lasers in new drug formulation development. Further advances in 3D-printed and in-vivo biodegradable devices for pH-invasive drug sustained release in various tissues with dynamic laser-tailored release have been realized, avoiding uncontrolled drug concentration spikes or drops in tissues leading to side effects or treatment failure.

Laser-enhanced CT reconstruction may provide a new approach to transforming the biomedical observation domain from 2D to 3D. Digital or image processing is the conventional approach to improving biomedical CT images and has been extensively used in numerous fields. However, alternate laser-based CT imaging systems have been proposed to enhance the diagnostic and therapeutic imaging precision, capacity and efficiency, mitigate artifacts or distortion, and improve quality factors (Q-factors) in various applications. In the meantime, X-ray CT imaging with currently envisioned tunable small-sized compact laser-driven high-Q-factors continues to gain importance for enabling smaller and less expensive biomedically significant diagnostic imaging instruments with lower radiation dosages. At mid-IR and terahertz (THz; 0.3–30 THz) wavebands, the advent of compact quantum-cascade-laser (QCL)-based biomedically significant novel systems have already enabled TABLE I MC.-calibrated non-high-gain biomedical laser applications. [25][26][27]

10. Emerging Trends in Laser Research

Research on lasers has been an important and lively subject since their invention just over one quarter of a century ago. Today, it is my endeavor to speculate about the prospects of lasers over the next quarter-century. It is anticipated that imaging laser-based techniques will be used to detect things like chemical pollutants and land mines; lasers will be used to cut, drill, ablate, and weld objects in materials processing; and lasers will be used to diagnose and treat disorders in medicine. Further advances in lasers themselves, however, are likely to keep lasers at the center of the science for the indefinite future. Many laser colors will be available for a variety of purposes. New miniaturized lasers will be cheap and ubiquitous, allowing each person to use a laser as a key in a new, light-based secure identification protocol. Nanosecond and femtosecond laser pulses will be developed and employed by scientists in every field to probe phenomena that are currently inaccessible. Lasers will allow the collective motion of large numbers of atoms to be controlled for precision measurement and quantum computing, opening up new areas of basic and applied science.

The invisible frontier is varied and will see much action in the areas of frequency control and stabilization, optics, photonics, and nanotechnology. These devices will primarily be used with lasers for testing, short-distance communications, and displays in a multitude of products including televisions, radios, phones, computers, and cameras. Most optical devices will become cheaper and smaller over time. Lasers will be used in ever more innovative ways for things like achieving quantum communication, generating new states of focused light, and giving more and more people pictures of their children for the first time. Optical apertures will be expanded by orders of magnitude as planets across other solar systems are spotted through indirect means. This will help to refine models of Earth’s climate and lead to routine modeling of planetary atmospheres in astrobiology laboratories worldwide [28].

10.1. Nanotechnology in Laser Applications

Semiconductor lasers possess a number of advantageous characteristics such as compactness, robustness, efficiency, and low cost. Besides their distinct characteristics, compact lasers can offer unique wavelength ranges which, combined with appropriate biosensor platforms, can also be exploited for the development of a number of new bioengineering applications in clinical diagnostics and biomedical imaging. The application of lasers in these fields has led to the rapid growth of pre-clinical and clinical research with strong commercialization potential. Semiconductor quantum well laser, operating at room temperature, have a wavelength range of 700 nm to 5 um. Quantum dots operating at 6 um wavelength range have been demonstrated in the laboratory. To this end, the application of photonic devices based on semiconductor lasers, both in terms of biosensing and imaging, has the potential to lead to a strong impact on healthcare and the medical economy. To enhance light absorption, the nanostructures can be interfaced with laser light sources and integrated in photonic devices with detection methods based on SPAD for multiplex level of detection. The quantum dots can be surface functionalized, and confocal enhancement can be achieved with a number of designs, with the potential to interface them with detection devices for early detection in clinics.

Non-invasive/real-time biophotonics which is employed in clinical diagnostics, imaging, and therapeutic applications is a category of techniques that bias phenomena of light-tissue interactions for investigation of biological tissues via detection of spectroscopic, morphological, and dynamic information. Non-invasive/real-time laser-based biophotonic techniques including laser-induced fluorescence, diffuse reflectance, imaging/multiphoton microscopy are highlighted. It has become clear that invasive diagnostic techniques widely used in clinical practice are not consistent and practical for detecting cancer at early stage. Thus, more emphasis should be on the development of novel non-invasive techniques. In addition to being non-invasive, they are also fast and can be carried out in vivo and in real-time. Emerging biophotonic techniques guidance by lasers are reviewed.

Innovative laser technologies based on semiconductor quantum well and bismuth oxide have been demonstrated and will be applied in the pre-clinical studies on brain cancer. On-chip lasers have been designed to fit detection methods, and low cost, portable devices for laser control have been developed. Biocompatible and biocompatible laser can be utilized in photothermal therapy, photodynamic therapy, and nonspecific immunoassay for tumor marker detection. Lasers can also be applied in biomedicine towards 104 protein molecular weight order detection with phosphate signal readout and localized sensitization on upconversion particles. The diagnostic techniques using lasers can be expanded to new particles, new markers, and new readouts. [29][30][31]

10.2. Artificial Intelligence and Laser Diagnostics

Development of laser diagnostics for bio-tissues is the most rapidly growing field of optical medical diagnostics. Among many advantages, non- or minimally invasive high resolution optical techniques provide significantly better spatial resolution compared to magnetic resonance imaging, computed tomography and other hefty, bulky methods. Moreover, needle-based photonic probes allow clinical diagnostics of barely accessible tissues, thus complementing routine diagnostics of more accessible modalities. Miniaturisation of various optical techniques requires reconsideration of many objective parameters. Currently available diagnostic equipment is bulky, due to stringent photonic technology requirements. As it cannot be clinically applied, highly sensitive optical techniques are underutilized in medical routines. Compactisation of optical sources, detectors and electronics paving the way towards portable precision devices is reviewed [9]. Optical techniques are rapidly penetrating a biomedical field, bringing needs for further advancements and enhancements. One of the most promising approaches is integration and/or combination of biochemical and biophysical techniques, which expands the versatility, novelty, and dimension of biomedical investigations. Integrative devices are viewed, including non-invasive imaging, spectroscopic, and biochemical diagnostics of modern attractions and successful implementations are presented. Combining different techniques within a single portable device capable of relatable, parallel, or synchronised analyse of biomechanical, biomedical and biofluidic parameters is reviewed. Developed components, measuring, and data processing procedures, including an artificial intelligence-based algorithm enabling non-experienced users to obtain biomedical information are considered. Current achievements in compact and portable optoelectronic components development open the pathway towards the incorporation of a broad range of optical biomedical research and diagnostics on board of a single portable instrument. [32][33][34]

11. Conclusion

In this review is outlined the common integrative applications of general and medical physics with laser technologies in the fields of optoacoustics biomedical imaging, intrasurgical systemic monitoring of patients' individuality with laser, aeolian-laser technology for rapid, non-invasive diagnostics of intraocular fluid presence in assisting and guiding approached to in-depth microscopic observation of patient-eye vascularity for risk assessment of diabetic retinopathy, laser monitoring biofiability of antimicrobial cationic calcogenide-ultradispersed silica glasses film on-cornea-tufts of bacteria-filaments in at array of laser-pumped plane-ring-waveguides, development of laser-based optoacoustic technology for early diagnostics and explication of COVID-19, multiscale, hybrid functional-multi-focal model of the cornea and the eye-ball with application to retinal imaging diagnostics are simultaneously across integrative nano-micro-meso technological scales, laser-assistant optoacoustics, gravimetry-thermoacoustics-photoplanetry triplets for household and homecare meditation accessibility of aerial-turbulence-caustic flux for laser-aided noninvasive diagnostics of physiological act levels of transferring mediators in physiological norm and pathology. The given results could be useful in the study of early symptoms of diseases, enabling cancer-target drugs, biologically active tissue-scissors, up- and down-converting light beacons for biowave laser and magnet-therapies, reducing vitality postoperning times, updated-carry and developmental effective-national-education and for bridge projects. The potential use of laser-aided optoacoustics, photoplanetry, vibro-gravimetric and - thermoacoustic techniques in wide areas of medicine are discussed. To accommodate the nondestructiveness and non-invasiveness of laser diagnostic techniques, only the respective studies are taken into account. The traditional connect-vision diagnostics combine centenary experience of photo-film technologies with telemetric transmission. Quantitative fill-facility and depth-wise interactivity of cornea, eye-ball, retina biocomplex and systemic polygraphy enable precisions diagnostic of emergent working states and pre-pathology phases.

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