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Biophotonics in Healthcare: Advancements in Light-Based Imaging and Therapy

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Annotation: Biophotonics—a rapidly expanding field of light-based technology—provides powerful advances in light-based science, medicine, biology, environmental monitoring, national defense, and automation. It includes—as a broad definition—the interactions and applications of macro, micro, and nano-scale photons with biosystems and, importantly, incorporates advanced biophotonics methods to address critical light-tissue interaction issues for the advancement of physical, chemical, and biological measurements in prevention, diagnosis, and treatment of health disorders

For example, biophotonic-based laboratory tests can detect diseases at earlier stages, thereby permitting easier and more effective healing. To fulfill Van Leeuwenhoek's pioneering idea of investigating processes in-vivo, modern biophotonics has benefited from advanced light sources, detectors, and new approaches of interaction of light with biological tissues. Innovations in biophotonics have already provided (1) numerous transformative light-based imaging and therapy tools currently affecting the way healthcare is delivered; (2) many powerful lab-on-a-chip platforms for point-of-care detection of biomarkers to monitor diseases and customize drug delivery; and (3) new lighting technology tools to study the effects of light on circadian rhythm and overall health.

The light-based injection and treatment of malignant tissues based on immunotherapy opens a new paradigm in oncology with the powerful side effect without affecting normal tissues.

1. Introduction to Biophotonics

Welcome to the IEEE JOURNAL OF SELECTED TOPICS IN QUANTUM ELECTRONICS Special Issue on Biophotonics—Part 1! In the papers included in this issue, you will be introduced to the latest developments in biophotonics, one of the most extensively growing areas in biomedical technology [1]. Today, clinical prospects in biophotonics are vast and exciting. Biophotonics provides a broad potential in biomedical technology with clinical applications ranging from minimally invasive diagnostics and therapeutics to the further development of novel nanobiotechnologies and nanobiomaterials. Considered as a bridge between the life and physical sciences, the biophotonics field introduces a wide range of attractive opportunities for interdisciplinary research between physicists and life scientists.

One of the most widely used biomedical technologies today is advanced biophotonics imaging, microscopy, and sensing, mainly based on nonionizing radiation. Nonionizing radiation applies a broad part of the electromagnetic spectrum (wavelength range between 200 nm and over 10 m), permitting a new generation of sophisticated methods for noninvasive or minimally invasive sensing and imaging of tissues and other complex organic structures in vivo with a high spatial resolution. Instead of ionizing x-ray techniques or aggressive MRI methods, low-energy nonionizing radiation-based biophotonics modalities represent safe alternatives for patients and medical staff. Over the last decade and even earlier, biophotonic techniques developed as non- or minimally invasive approaches to be a potential alternative to conventional medical methods for diagnostics, monitoring, and therapeutics of diseases, drug discovery, and environmental detection of bioterrorism agents. A wide variety of biophotonic techniques, devices and systems have been developed, offering a non-contact, effective, fast, and often pain-free way for sensing and monitoring a lot of biomedical quantities. Due to the benefits, many new devices, instruments and tools based on biophotonics technology are already in the mainstream, providing a new level of early disease diagnosis, patient acceptance, and comfort; more and more are in the phase of clinical trials or pre-market approval, and even more are in continuous development and coming to the market.

2. Fundamentals of Light Interaction with Biological Tissues

Fundamental knowledge of optical properties of biological tissues is critical for the understanding of laser-tissue interactions and the design of laser-based diagnostic and therapeutic medical devices. A concise review covers basic information on biological tissue composition and morphology. Optical parameters characterizing light propagation through tissues are introduced including the absorption and scattering coefficients, the anisotropy of scattering, and others. The most important optical properties of some particular biological tissues are described such as the eye and skin. The new effects and modalities of advanced biophotonics imaging and sensing using light interaction with tissue background are highlighted as well. Biophotonics is one of the most rapidly growing areas in modern technological and biomedical advances. This multidisciplinary field includes a variety of physical, chemical, and other life sciences, as well as engineering. The development of biophotonic sensors and techniques is rapidly expanding, highlighting the continuing interest of this field. Furthermore, new opportunities are emerging from the synthesis of interdisciplinary research aimed at developing novel biophotonic technologies. Biophotonic technologies provide advanced techniques in quantum electronics, nonlinear and ultra-fast photonics, lasers, and electro-optics applicable in the life sciences, and clinical medicine as well as for bio/nano-technology materials and systems.

Quantitative, noninvasive biophotonic techniques are of special interest in clinical practice owing to their potential for application not only to in vitro but also in vivo studies. Broadband, low-coherence photon-migration and autocorrelation techniques are the most beneficial approaches to the analysis of highly scattering biological tissues; those commonly meet endoscopic demands. Nonionizing biophotonic techniques provide minimally invasive tissue sensing and imaging in vivo. Because of a very high spatial resolution obtaining significantly higher than the diffraction limit, they are dominating in the analytical work for tissue diagnostics, imaging, microscopy, and sensing concerning health and medical areas. Bioimpedance, endocavity, and photoacoustic imaging biophotonic modalities are also widely used in clinical practice. Biophotonics for minimally-invasive applications is developing in the direction of quantification, multimodal combination, and computer 3D reconstructions as well [1]. [2][3][4]

3. Light-Based Imaging Techniques

Biophotonics has revolutionized a variety of biomedical fields over the last decade by providing high-resolution light-based techniques. Biophotonics utilizes various optical imaging technologies to visualize and detect biological objects and mortal diseases with light. In clinical terms, it’s important to develop biophotonics applications that can offer new methods to monitor the growth, aggressiveness, and response to therapy of malignant diseases, such as autopsy, biopsy, mastectomy, and cystoscopy. Biophotonic technology can eliminate these frequently invasive diagnosis and surgeries, although traditional light-based technique has a limit to apply in clinical detection studies. A variety of light-based imaging systems have been developed that can provide remarkably penetration depth to living tissue [5]. This article summarizes recent efforts and progress in biophotonics for fluorescence with time-domain and spectral-domain techniques by focusing on emerging clinical applications, as well as providing a perspective for biophotonics technologies.

Biophotonic technologies in the short-wave infrared (SWIR, 1000–2000 nm) region have shown great promise for visualization of malignant diseases because of the advantages of low tissue attenuation, weak body autofluorescence, and reduced scattering. In this report, SWIR fluorescence bioimaging and microscopy using rare-earth neodymium (Nd3+) polymeric nanoparticles excitation upconversion its far-red emission are performed. The method of utilizing various wavelengths to differentiate two emission centers in multicomponent NaYF4 UCNP up to 4 mm imaging depth in simple-tissue phantoms. Additionally, cytotoxicity and the immune reaction of the PPSyl-Nd/Er/Tm UCNP are evaluated to demonstrate that the medically certified agent material has low toxicity [6]. Ran is a small molecule, renal clearable SWIR-emissive organic fluorophore emitting at 1350 nm, is utilized to visualize real-time lymphatic drainage. SWIR-based video-rate imaging microscopy employing a single multimode fiber is applied to visualize lymphatic flow and real-time lymph node drainage.

Cherenkov luminescence imaging (CLI) for superficial mapping of cancer has emerged as a low-cost and easy-to-implement alternative to charged-particle imaging used in preclinical studies. However, the limited depths of BL penetration have hindered the translation of these developments into clinically useful devices, as most previous efforts rely on photomultiplier tubes that have poor sensitivity and need cooling. A miniaturized high-sensitivity time-gated imaging system based on a low-noise ultra-fast-gated camera that is capable of detecting BL from positron radionuclides through a biophotonic approach. The wide spectral response and time-gating capability of the camera allow a simple photon counting that discriminates the prompt-gamma signal from positron radionuclides, which are typically used for CLI and preclinical image-guided surgery. Feasibility experiments in phantoms and mice demonstrate that the camera can measure the output of both commercially available clinical radionuclides and those widely used in preclinical studies, enabling the longitudinal imaging of pharmacokinetics of pairing agents. Such advancement aids in the optimization of PC amplified CLI, opens new avenues for concurrent acquisition of BL and Cerenkov radiation, and holds the potential to facilitate the rapidly growing field of theranostics. [7][8][9]

3.1. Fluorescence Microscopy

Fluorescence microscopy is a fast-growing discipline. With the advent of new fluorescent proteins, dyes, and improvements in microscope sensitivities, cell biologists are able to glean more information than ever from their samples. In many biological applications—including immunocytochemistry, RNAi-mediated knockdown of protein expression, and protein trafficking studies—fluorescence microscopy is the only practical method of examination. Before plunging into the world of high sensitivity CCDs and bright 10 watt LEDs, however, it is important to understand the basic components of a fluorescence microscope and the principles that govern image formation. A few of the more important details relevant to a fluorescence novice are presented here.

But first, the basics. Specimens, whether living or fixed, are incubated with heavy metal ions or organic molecules which have the property of converting invisible ultraviolet light into highly visible blue, green or red light. The bright colors from black, light-absorbing specimens such as bacteria, yeasts, mammalian cells are much easier to see and identify than their unstained, unilluminated state. The colors from a well-stained specimen contrast to the black color of embedding resins. It should come as no surprise, then, that many of us find it easier to photograph colored, fluorescent specimens than their colorless cousins. Fluorescence allows for simple and specific labeling of proteins or organelles. There are more than 500 anti-bodies directed against different epitopes of proteins of a simple eukaryote like S. cereviseae. Biochemistry allows to produce peptides and proteins with given properties but this requires a lot of upstream work. Many fluorescent dyes and fluorescent proteins are commercially available. Transgenic S. cer. yeast strains used in genome wide screenings are available, but they are time-consuming to make.

Fluorescence is very useful for a wide range of biological applications; however, these experiments are best done on a core facility with a professional full time operator. Paying the initial setup fee at the facility allows for proper training. However, some data sets can be collected in the laboratory on the fluorescence microscopes available. The advantages and limitations of the main techniques discussed here will allow for informed choices to be made. These techniques have been the ones most commonly used throughout the research experience. Both immunofluorescence and FISH should work well on any microscope that has the capability of imaging by widefield fluorescence. The highest resolution of 60X has been sufficient for most immunofluorescence labeling. For thicker samples, it is desirable to use the 60X (1.4 N.A.) objective. Higher resolution can be obtained by deconvolution software. But the best images will be obtained on the confocal microscope. Also consider that the deconvolution of the images can result in a final image that is less bright than the original raw data. There are many decisions that need to be made before performing an experiment—proceed through these steps. [10][11][12]

3.2. Optical Coherence Tomography (OCT)

Optical coherence tomography (OCT) is an imaging modality that images and provides cross-sectional information of tissue ultrastructure. The development of OCT has greatly expanded its applications in the fields of healthcare and health sciences. One key foreshadowing time had been concerns about the possible effects of the use of increasing amounts of imaging. The four use-cases discussed are general-purpose diagnostics, biomolecule tracking, in-silico physiological modeling and in-silico drug optimization. OCT has evolved greatly over the years, providing increased resolution, imaging speeds, and imaging modalities. OCT’s use in many different fields and by many scientific methodologists has been greatly expanded; additionally, it has ventured to more non-traditional fields such as manufacturing and forensic science. Along with the development of new systems, novel courses of action have been pursued including the operation of OCT systems on balloons and satellites [13].

OCT is an imaging technique that enables high resolution, cross-sectional imaging of biological tissues. It is based on low coherence interferometry of light backscattered from biological tissues being imaged. The main feature of OCT is its ability to produce images at cellular level resolution—meaning that at this resolution level OCT can detect features within various biological tissues such as skin or blood vessels. Another key feature of OCT is its outstanding capability to image through tissue layering; in other words, the dynamics within or underneath any biological tissue layer can be observed. OCT is already widely used in clinical applications, particularly in ophthalmology. The ongoing effort and current challenges in developing new algorithms to increase the capabilities of OCT will be addressed. A number of research directions for enhancing OCT will be examined. The design of various multimodal OCT systems enables the enhancement of OCT imaging and can improve understanding of different tissue features. The emerging use of nanoparticles combined with the special parametric monitoring capability of OCT will be discussed. This capability enables the measurement of an additional parameter—a back scattering radiation-pattern from within the sample—which can reveal the dynamics of the nanoparticles becoming sedimented [14]. This discussion will provide an overview of OCT and its most positive aspects, such as its noninvasiveness, high imaging resolution, speed, and safety. The potential of using multiple beam paths and scanning platforms for the in vivo investigation of the human body in a minimally invasive procedure is also emphasized. [15][16][17]

3.3. Photoacoustic Imaging

Photoacoustic imaging (PAI) is a hybrid imaging modality that combines the advantages of the contrast offered by optical imaging and the high resolution in deep tissues by ultrasound imaging. PAI is a promising modality that has shown significant potential in a variety of preclinical and clinical imaging and sensing applications in the last two decades. Various commercial preclinical PA imaging systems can deliver quantitative functional and molecular information with high spatial resolution down to 30 μm. They are primarily used in characterizing cancer, brain, cardiovascular, and other diseases. In the clinical domain, several research groups have reported various PA imaging systems for endoscopy, oral, breast, and prostate imaging. Most of these systems employ Nd: YAG lasers to generate photoacoustic signals. However, the clinical translation of PAI has been limited due to the requirement of bulky and expensive pulsed lasers for excitation. In order to accelerate the clinical translation of PAI and explore its potential for resource-limited settings, it is critical to develop portable and affordable light sources that will enable the pollution of PAI probes and systems with wider accessibility. In the following, inexpensive light sources for PA imaging will be discussed, including their working and implementation principles and light source performance for different imaging applications. Additionally, important preclinical and clinical applications that have been demonstrated using affordable light sources will be reviewed. The primary focus will be on laser diodes and light-emitting diodes. As an additional focus, recent advances with laser diodes and cavitation sensors will be additionally highlighted. PAI is based on the detection of ultrasound waves generated from tissue in response to the absorption of optical energy. The initiated waves can be detected by ultrasound transducers and converted into images. The main advantage of PAI is that it provides functional and structural information at deeper depths of tissue compared to pure optical imaging. Broadband ultrasonic transducers are commonly used for PAI in research and clinical settings. The early PA-based tissue imaging systems generally employed Q-switched Nd: YAG lasers. With advancements in technology and for safer clinical translation, flash lamps, optical parametric oscillators, seeded preamplified optical parametric oscillators, OPO-based light sources, large-area arc lamps, and more recently, LEDs and laser diodes with center-wavelength from 590 to 1310 nm were used. In contrast to conventional bulky and expensive pulsed lasers, continuous or quasi-continuous light sources are an economic and easier alternative. LED arrays and commercial hand-wands have been reported with a spherical design of 2–5 cm diameter integrating 16 to 20 LED modules. On the market, various ready-to-use LED sources are available and consist of 8–16 LED modules. C-shaped LED arrays with 6 or 7 modules were implemented and have shown potential for PAI instrumentation. Advancements in PAI system development have been observed in the last decade. Recent works have reported a portable and robust PAI system where LED light sources were built into the structure of an ultrasound transducer. Such a design simplifies setup time and provides better co-localization between optical and ultrasound imaging modalities. Moreover, a waterless hand-held imaging probe with an integrated LED light source has been shown. Three PAI light sources, i.e., laser diodes, LEDs, and spark-based sources, were employed together with different detection methods. The high versatility of the proposed setup was demonstrated in a murine model. TA and DT were performed on human volunteers. Despite such a positive result, DL PAI still faces considerable challenges before being translated into clinics. [18][19][20]

3.4. Multiphoton Microscopy

In the last few decades, science and technology in the healthcare sector has gone through a revolution, promising novel diagnostic and therapeutic techniques and special focus on the use of light. A constant and impressive growth in knowledge has deepened many of the phenomena occurring inside living organisms. This provides a clearer understanding and opens up many possibilities for innovative applications. At the same time technological progress has been remarkable, often following parallel tracks. Development of new therapeutic possibilities is now supported by a broader vision of biophysical processes, unveiling answers that in some cases were waiting decades to be discovered.

In a broader sense, Biophotonics may be defined as the science and technology of the generation, action and application of photons for the life sciences and biomedicine. It embraces the most typical uses of light for life science applications: Investigative and therapeutic uses of optical imaging for visualisation purposes, also extending to in situ studies in live cells and tissues at high relative spatial resolution; Investigative and therapeutic uses of a well-defined range of electromagnetic radiation in all forms of delivery, extending but not limited to laser use; Spectroscopic diagnostic applications of optics, extending from the UV to beyond the IR; The controlled and investigated use of optical radiation in the illumination or control of non-living materials with a view to understanding, e.g. as in drug interaction and optical tweezers. This definition goes beyond the use of light in a commonly intended medical sense and takes into account broader trends and new or emerging applications. Modern optics has the power of acting, manipulating and controlling living matter in manners that were unthinkable several years ago [21].

Moreover, the potential of Biophotonics goes well beyond the simple sum of its parts, thanks to the diversity of the scientific areas involved, creating a list of possible and potential new and surprising applications, as in the case of biophotonics at the nanoscale. The trend of “label-free bio-imaging” is also a result of new and amazing development in the field of laser sources and in novel optical detection approaches. Additionally, a new generation of powerful super-resolution confocal microscopy systems are already commercially available and represent a great opportunity for an extensive range of cell biology applications. Another relevant equipment regarding the nano-biotechnology application will include near-field scanning optical microscopy that, coupled with high resolution topographic analysis, will allow fluorescent correlated high resolution images to be acquired. This new equipment will provide observation of living cells at the protein molecular level and will be used to study single protein complex interactions. Astrochemistry represents an Earth-compatible and non-invasive way to explore the Universe. Stimulated by extraterrestrial applications there are also unexpected and useful applications that can be turned back to the Earth like water and air quality monitoring, or non-invasive food analysis. [22][23][24]

4. Therapeutic Applications of Biophotonics

In early years, optical biophotonics applications were mainly focused on noninvasive diagnostics with laser light studied in exterior channels such as skin, body fluids, and exhaled breath. Technological progress in the last decades has initiated the transformation of various modes of biophotonics light penetration into the next step biosee-through surgery. Since the observation of autofluorescence of tumor tissues, researches in the early age were developed and later on attracted to portable fiber-based technology. However, the early history was based on the visible and ultraviolet light illumination and monitoring mainly concentrating on fluorescence excitation-emission.

In the modern age, other illumination modalities such as Raman and fluorescence have greatly developed owing to the broad availability of near-infrared lasers to compose the so-called biophotonics. There are several inherent advantages of the biophotonics in comparison to the well-established imaging techniques in surgical guiding. The lack of ionizing radiation eliminates the need for special infrastructural installation to reach an imaging target. It is portable hence, the technology can be installed directly on an operating microscope, implement it as the hand-held system, or buy the portable unit, which can be easily moved on to all surgical rooms. Optical imaging is high-speed-to-quality, i.e., it provides high-resolution information quickly in real time. Hence, imaging results can be immediately used for surgical decision making and significantly shortening the surgical time. To date, several clinical studies on the application of handheld fiber-based technologies to image brain, breast, pituitary, and lung and other cancers have been conducted.

In this clinical report, the focus will be addressed on the intraoperative biophotonic imaging systems, in which the surgical channel operating modes are composed by utilizing reflectance, fluorescence, and Raman light generated information to guide the surgical procedures. Following a brief introduction to the intraoperative imaging modalities, their engineering aspects including optical detection hardware and acquisition software are described. Then, clinical images are demonstrated to provide guidance information to achieve image-guided surgical resection in image-guided transoral robotic surgery. At the end, the potential clinical impacts of the biophotonic imaging systems on image-guided interventions are discussed via comparison studies of the results before and after surgical procedures. [25][26][27]

4.1. Photodynamic Therapy

Interaction of light with matter is central to the investigation of the nature of dyes. Today, we can say methods for tanning dyes or pigments on textiles, paper, or related materials. Contemporarily, this supports the use of laser radiation. The fact that significantly lower exposures to this type of radiation than the solar radiation cause precisely the intended effect on the surface of the skin, i.e., browning. This process is based on the interaction of visible light with dyes. The energy absorption by a dye molecule occurs when the quantity of photon energy matches the type of dye energy level width. This leads to electronic transition from the so-called ground (S0) electronic state to one of higher energy states (Sn) [28]. There are many different quantum states between the ground and the excited state. Depending on the probability of nonradiative or radiative transitions, the adhered energy can be released with different kinetics, fluorescence, phosphorescence, or heat. As a result of an electronic transition, changes are occurring in the molecular structure. It is necessary to acquire in a very short time (transitional time tens of picoseconds or less), which results in the so-called primary photophysical process. It may consist of different changes, i.e., vibrational relaxation, energy transfer, isomer conversion, or the separation of various types of free radicals [29]. Since energy absorption occurs frequently in a specific part of the molecule, all these changes are restrained in a distance of 1-50 nm in the proximity of each other (the so-called recoiling wall), when the dye concentration in air is equal to 10-3 M.

4.2. Laser Surgery

The unique capability of in vivo fluorescence spectroscopy to register and analyse many lifelong maintained endogenous fluorescent substances (autofluorophores) in tissues and organs can be seen as a specific niche of the technique in broader medical application [30]. The focal point for this research has been to develop new techniques and apparatuses to determine in a non-destructive and rapid way the content of intrinsic fluorescent substances in human bodies such as normal organs and tissues, and the pathological changes of them. This would open the possibility to improve the diagnostic and therapeutical tools by providing advanced means for treatment and surgery of different human diseases. It has been known for many years that the luminescence of biological tissues exhibits several characteristic features: it has a broad band emission, the exciting light is of shorter wavelength than radiation, the luminescence maximum is in UV-to-blue range, and the luminescence of one tissue arises at different wavelengths when illuminated by different wavelengths of exciting light. This is the basis of the fluorescence of biological tissues and this fluorescence is used in present diagnostics to examine the wellness of patient tissues. In the beginning of 1980s, instruments have been developed making it possible to register fluorescence signals and transmit them into a spectrometer. Thereby, it now became possible to find the fluoroprobe in the system where samples consist of several organic and inorganic compounds. Much like autofluorescence, Raman spectroscopy also allows for non-invasive measurement without the need for exogenous labels. Thus, optical methods of bio-tissue investigation can be used as navigation and guidance towards diseased areas on a macroscopic level. Bio-imaging and spectroscopy can be automated with robotic means and made compatible with different types of surgical tools. With the expected advances in miniaturisation of bio-photonic technologies it can be foreseen that during some decades biomedical lasers and fibereds will be one of the most important means for medical image management.

4.3. Light-Activated Drug Delivery

Light-activated drug delivery systems have been pursued as a targeted approach for treating diseases in recent years. Using light as an external trigger can allow the controlled release of drugs within the controlled-in space and time of the pathological region, minimizing off-target toxicity [31]. Phototoxicity as well as certain light wavelengths in the UVB and UVC range can cause cellular damage (DNA mutations) which is a leading factor in melanoma, while UVA is also a significant cause of pre-mutation DNA damage that induces photochemical reactions and can promote free radical formation that accelerates skin aging through molecular degradation.

Skin cancers, melanoma and non-melanoma, belong to the top five most commonly diagnosed cancers in Europe in 2018 and have been classified by the World Health Organization as a global epidemic, with an estimate of 71.943 deaths in Europe in 2018, in which it is an estimate of 22.255 patients that will die because of melanoma. An effective way to address negative issues related to UVA stress in the clinical field is the development of formulations that are designed to protect the skin and mitigate the damaging effects by converting part of the absorbed energy into non-emissive photons that can initiate defensive photoprotective reactions. Efficient UV glucose releasing formulation and UVA-triggered glucose release is expected to be developed into a skin protective drug delivery system, which is an important step to provide protection against UV irradiation.

5. Current Advancements in Biophotonics Technology

Welcome to the Special Issue on Biophotonics—Part 1! In this issue you will be introduced to the latest developments in one of the most extensively growing areas in biomedical technology, biophotonics. There are clinical prospects in biophotonics that include applications ranging from minimally invasive diagnostics and therapeutics to development of novel nanobiotechnologies and nanobiomaterials. Biophotonics is a relatively new but rapidly growing branch of research in healthcare, based on the development of advanced photonic methods for diagnostics, therapeutic and monitoring applications. The need for alternative innovative techniques, providing improved results, has led to the development of biophotonics-based tools. Next to classical optics-based healthcare techniques, biophotonics combines the fields of optics and laser photonics directly with life science and medicine, introducing thus opportunities for interdisciplinary research between physicists and life scientists. Not only are techniques of quantum electronics, lasers, fiber optics, and electro-optics in more extensive application in this area, but most devices and systems primarily developed for application in quantum electronics also have advanced applications and increased demand in the field of life sciences and medicine. Advanced biophotonic imaging, microscopy, and sensing techniques are widely used due to their advanced features. Biophotonics is based on the use and processing of light, nonionizing radiation, enabling minimally invasive tissue sensing and imaging in vivo with a high spatial resolution. As a result, a number of different biophotonic-based techniques and tools have been developed for medical and diagnostic purposes. These techniques can be implemented for different types of optical characterization of biological tissues, cells, and various labels and contrast agents that have been intensively added to them.

Recently, new minimally invasive biophotonic techniques have also been developed as potential alternatives to conventional medical methods for diagnostics, monitoring and therapeutics of diseases, drug discovery, proteomics, and environmental detection of biological agents. That is because the complexity of techniques is replaced with a simple effect model. These techniques provide a noncontact, effective, fast and painless way for sensing and monitoring various biomedical quantities and have found already many different biophotonic device implementations for different care applications. However rapid progress in this area, initiating from recent years, has led to very effective improvements of biophotonics technology and resulted in devices that could be used for precise biomedical applications and for which other important segments of treatment were developed. This is particularly the result of the newly enabled technical features, where rudimentary bulk spectroscopy developed into very advanced systems composed primarily of fiber sensing elements, sophisticated delivery and detection accessories and miniature electronic solutions. Biophotonic technology is chosen as an alternative biotechnique to predetermined techniques for cultivation and usage of bacterial cellulose fibers. The potential of these materials in medicine, food and packaging domains and needs for a very thorough understanding of their parametric qualities are today’s technological market trends.

Biophotonics, which cross-pollinates the traditionally distinct segments of physics and biology, brings together the most precise diagnostic methods of lightwaves and their extremely small targets. Moreover, new information. Potential market considerations, but also strategical community planning must now involve the modern technological impact for biophotonic solutions. Increments in novel biophotonics technology with the onset start in nanophotonics research as well as follow-up years confirmation that devising technology is well suited to modern trends in nanotechnology, so that is taken as a challenge for development of future new multifunctional medical applications. With the whole area of drug therapy becoming encapsulated. [32][33][34]

5.1. Nanotechnology in Biophotonics

Biophotonics—a fusion of biology and photonics—is an emerging array of products in the health discipline. By way of conventional Euclidean optics, biomedical photosensor and treatment devices could replace handling pesticides, serve water quality determination, and enable the monitoring and post mortem research. New biophotonics studies could be discovered through bibliometric analyses based on the retrieval and analysis of the papers appeared in the indexed journals since 2006. Future studies would have a chance to focus on emerging aspects, products and applications in biophotonics discipline and therefore helpful for the extension of optical technology to other application fields of natural sciences.

A previously prepared multiple scattering diffusion model that includes the resonance enhancement effect is employed. We describe the model in the first section and the imaging experiments on biological samples composed of a suspension of absorbing grains. A brief summary of the experiment is presented in the following section and the modeling of the experiments in the following section. We find from the experimental and theoretical studies that the enhanced resolution imaging of biological samples made of a suspension of absorbing particles is composed of an enhancement effect for better imaging results and a differential effect for filtering of the complex spatial distribution of the grains. Both of the effects for imaging of tissues are limited to low scattering parameter values. Possible applications of these results are presented.

5.2. Wearable Biophotonic Devices

In the world of healthcare advances, light-based technologies are pretty much on fire. In fact, so many innovative approaches are lighting up the biophotonics universe that a vital role in ensuring patients have top-tier care can easily be played by working practitioners. With a range of possible ultrasounds, instruments that shave energy use, and tactile imaging, there is quite a bit the up-to-date caregiver can accomplish simply by keeping an eye on what's new.

It is often said that the human body has its own light—a faint emission in the visible, ultraviolet, and near-infrared wavelength ranges that can be detected both as visible biophotons and as coherent radiation. Over tens of years, this phenomenon has been validated, concluded to be a product of the physics underlying metabolic reactions, and applied in various interesting and promising techniques. Today, a research ecosystem has been built between cells, tissues, and organs to investigate biofields and biophotonics perspectives and it is rapidly advancing the field of biophotonics. Because biophotonics couples nanophotonics, semiconductor quantum dots, and photonic materials to the perspective of biophotonics, it is believed that a comprehensive status including perspectives on basis, body, and technique will be helpful to understand the current status and potential of biophotonics. Five areas are covered: the broad landscape of biofields to unify perspectives, the historical journey of biophotonics, mechanisms, measurements, and various applications.

Biophotonics have shown great promise for therapeutic interventions between cells, tissues, and organs. It is noted that conventional therapies, such as irradiation to the brain or a malignant tissue, a common strategy for cancer treatment but this radiation is not accurate and often kills healthy tissues in the progress. The strategies suggested engage a number of advanced light diffusion and distribution solutions to develop new systems better fit to conditions in individual biological systems, demonstrating sensitivity to the Inverse Problem and a predictive power to experimental design. [35][32][36]

5.3. Artificial Intelligence in Imaging

Artificial intelligence (AI) techniques have significant potential to enable effective, robust and automated image phenotyping including identification of subtle patterns. There are two main tasks based on AI approaches using imaging: Detection and Classification. AI-based detection searches the image space to find regions of interest based on patterns and features. Early and effective screening for lung cancer while the lesions are still at the curable stage is crucial, especially given that the 5-year survival rate for lung cancer is generally < 20%. Screening includes the identification of patients with radiographically abnormal findings and further evaluation using Low-Dose Computed Tomography (LDCT). In addition to reducing search time, DL can identify non-solid nodules and nodules < 6 mm in diameter, which are generally missed on LDCT scan reading. There is a spectrum of tumor histologies from benign to malignant that can be identified by AI-based classification approaches using image features. Comparison of AI and human performance in the analysis of seven histology features showed cross-validated AUCs ranging from 0.847 to 0.900, which indicated the potential of AI as a cancer diagnostic tool. The extraction of minable information from images gives way to the field of radiomics. Radiomics analysis has the potential to be utilized as a noninvasive at baseline technique for the accurate characterization of tumors with respect to NEUROblastoma RISK (B-NER) to improve diagnosis, risk stratification and treatment monitoring. A good correlation between RCC and radiomic features is expected, as a high degree of heterogeneity suggestive of a more aggressive and metastatic behavior can be associated with unfavorable prognostic factors. Efforts have thus been made to predict patient survival and to distinguish between CDK4/6-resistant cancer cell lines by combining preclinical three-dimensional (3-D) models with high-throughput quantification of drug response via deep neural network (DNN). A comprehensive summary of AI-based techniques, with a special focus on oncological PET and PET/CT imaging, for different detection, classification, and prediction and prognosis tasks in medical imaging, is thus presented [37]. Artificial intelligence (AI) has attracted considerable attention during the last few years. With the introduction of deep learning algorithms, research focusing on multimodality medical imaging has increased exponentially. These algorithms exhibited tremendous potential to effectively learn from data and correctly interpret the data. AI is gaining momentum in medicine, owing to effective handling of the data overflow, management of rare diseases, and the possibility of being perfectly up-to-date with minor modifications. In the case of the latter, the RSNA's annual meeting emphasized the importance of ML- and DL-based products in radiology. AI and DL approaches can clearly be considered as competitive for PET and SPECT imaging. The applications of AI in radiomics demonstrated that AI based on first-order texture analysis that involves the histogram and derived variables notably overfits the incoherent signal of 18F-FDG PET. Moreover, radiomics derived from nonvolumetric images results in features that weakly correlate with the biologically relevant scale. AI effectively contributes to certain areas in nuclear medicine [38].

6. Clinical Applications and Case Studies

Welcome to the IEEE JOURNAL OF SELECTED TOPICS IN QUANTUM ELECTRONICS (JSTQE) Special Issue on Biophotonics—Part 1! The latest developments in biophotonics, one of the most extensively growing areas in biomedical technology, are presented. Many of the papers included in Part 1 of this special issue are dedicated to fundamental theoretical and experimental research and developments, while others are more focused on the design and analytical aspects of novel biophotonic devices, systems, and platforms. Clinical prospects in biophotonics are vast and exciting because of the versatility and noninvasive nature of optical methods. Biophotonic applications range from minimally invasive diagnostics and therapeutics to development of novel nanobiotechnologies and nanobiomaterials with broad applications in molecular and cell biology, biotechnology, and medicine. New advanced biophotonics imaging, microscopy, and sensing techniques remain at the forefront of the most widely used and rapidly growing biomedical technologies because of their advanced features, including very low noise and invasiveness, and compatibility with innovations such as "omics" science. Nonionizing radiation in the visible and near-UV spectrum ranges provides minimally invasive tissue sensing and imaging in vivo with high spatial resolution. "Laboratory-on-a-chip" principles have been utilized for designing novel biophotonic devices and systems to improve detection of pathological or normal conditions in biological tissues and cells. Assisted diagnosis of tissue diseases is possible with integration of biophotonics techniques with conventional medical methods. To avoid light scattering in biological tissues, low-dimensionally designed biophotonic systems have been investigated. Optical fibers, on the other hand, can be compatible with the applications of point and line in vivo sensing and imaging widely used in biomedical research [1]. An integrated biophotonic device has been developed with direct coupling of a multimode optical fiber and a gas discharge light source. Photoluminescence properties of biological tissues have been utilized for the analysis of some tumor changes in patients with bronchial cancer. Treatments of such diseases require surgical intervention, and complex biophotonic systems have been developed to accurately evaluate the extent of pathological conditions in biological tissues. Biochemical agents can enhance tumor or normal tissues fluorescent luminescence or scattering, improving assists diagnosis of tumors localized in skin, colon, or lungs. Compact biophotonic devices and systems have been designed as potential alternatives to conventional bulky medical methods with applications for diagnostics and therapeutics of diseases, drug discovery, proteomics, and environmental detection of biological agents [39]. Such devices can be attached to an optomechanical device or catheter that is easily applied to skin or mucosal surfaces. Recently, teams proposed applications of fiber-optic Raman endoscope probes for ex-vivo and in vivo studies for obtaining information about the biochemical properties of different tissue pathologies. Modern biophotonic technologies are advantageous and offer great promise for use in clinical practice, enabling detection of various pathological conditions of biological tissues, including those at the early stages of diseases. Therefore, various kinds of biophotonic devices and systems for in vivo and ex vivo studies of human tissues have been designed and developed. Such systems are based primarily on differences in the behavior of normal and pathological tissues and provide new, often unique optical contrast for biochemical, morphological, and functional analysis of tissues using a wide range of biophotonic techniques: light, Raman and fluorescence spectroscopies, microscopies, and imaging. Advanced development and analytical approaches go beyond simple proof of concept studies and offer a more comprehensive description of biophotonic devices, systems and platforms with emphasis on their working principles and the application of biophotonics for the design of novel technologies beyond the mainstream devices, systems, and modalities most commonly found in today's clinical environment. Considering the rapidly developing technology, biophotonic methods in the transition from "laboratory bench" towards more advanced, commercial and standardized platforms are also of interest.

6.1. Cancer Diagnosis and Treatment

Numerous challenges still exist in the proper detection, diagnosis, treatment, and monitoring of cancers for the personalized therapy. Current cancer therapies, such as surgery, radiation, and chemotherapy, have limitations, and malignant growths can develop ways to circumvent treatment sooner or later. For these reasons it becomes vital to detect malignancies before cells invade other tissues or metastases become established. In recent years, many advancements have been realized in development of non-invasively early detection methods. Several biophotonic methodologies have been presented to differentiate malignant tissues from non-malignant tissues using light originating from within the cells. reported that the elevated biophoton emissions from cancer patients have specific spectral profiles within the wavelength range between 200 and 900 nm. This work suggests that the cellular based ultra-weak biophoton emissions may be used as a biological marker for development of innovative detection methodologies in oncology.

The possibility that with the use of light, tissues may be imaged so that diagnosis may be made through means that do not involve the use of nuclear materials has the potential to greatly reduce the time necessary to reveal the existence of a cancer. However, biophotonic markers of cancer must first be characterized and then differentiated from the biophotonic activity due to normal cellular events. In the work by , a cosmologist resonance frequency model of cellular derived proteins was used for the first time as a means to define the potential biophotonic markers of malignancy. In this model, biophotonic interactions between proteins define the characteristic frequencies of the proteins as particular quasi-particle vibrations, expressing the electron energy from the sequence of their amino acids. The research also hypothesizes a locational association of proteins existing in such qua states with particular biophotonic oscillatory modes that fall within the light frequency range of 200 to 950 nm. Proteins that drive molecular pathways are anticipated to be locational and associated with peak frequencies in a particular range of light corresponding to UV-C. Such characteristic resonant signatures of biophotonic activity may be used as future biophotonic markers for cancers.

6.2. Cardiovascular Imaging

Biophotonics aims to improve and validate the integration of optical imaging and biomedical applications for improved health care, being ideally suited for the imaging, diagnosis, and treatment of cardiovascular diseases. Multiphoton microscopy, spectral imaging, macroscopic imaging, and laser processing are the key techniques involved in biophotonics that pertain to cardiovascular diseases. This study focuses on the key innovations in the development of biophotonics in cardiovascular medicine. The applications of biophotonics imaging and therapy in cardiovascular diseases including atherosclerosis, coronary heart disease, restenosis after angioplasty, and heart failure are presented [40].

Many core technologies developing in the past 30 years contribute to the appearance and flourish of biophotonics, which are ideally suited for the imaging, diagnosis, and treatment of cardiovascular diseases. By inheriting from traditional optics, it is powerful in the use of fingerprint optical techniques such as fluorescence and Raman spectroscopy that can elicit optical signals from biological tissues and cells and has good capability for the subcellular level imaging. By combining optics with advanced developments in molecular and cell biology, it can provide powerful tools for genome visualization and diagnosis of early diseases at the molecular level, which is the main reason that biophotonics, especially the optical coherence tomography (OCT), become hot in this century's cardiovascular imaging community [41].

6.3. Neurological Applications

The research in this science domain was done out of general interest in biophotonics, a combination of different scientific fields: biology and photonics. There is already some advancement in biophotonics and its application in healthcare, but it is still a relatively new, relatively open, and very interesting scientific field. This review presents the research on relevant topics in the domain of biophotonics and the results obtained in research. Also, a clinical perspective on biophotonics and its potential applications in healthcare in the near future is also proposed.

The contents of this document include six chapters. The first is an introduction that puts the thesis in context in general and outlines the research areas covered. The following chapters describe research on procedural Pain in clinical practice, detection of cancerous tissues by laser Raman spectroscopy, multimodal imaging of living cells by CARS and fluorescence microscopy, simultaneous generation of THz radiation to image breast cancer tissues, and modeling of broadband pulses in tissues for biomedical applications. Each chapter was either published in a journal or presented and is planned to be submitted or to be presented in a reputed conference. [42]

Neurological disorders are diseases of the central and peripheral nervous systems such as Alzheimer’s disease, multiple sclerosis, arthritis, paralyzes and so on; or the care of any situation that affects the central nervous system to the disadvantage of the patient, such as headache, chronic pain, so on. However, the definition can run from the basic worrying of measuring the parabometer cone of a patient with a phaser to the state control of mental states via the imagining of the connectomes structure. It is a term that demonstrates the approach to the nervous system which is undertaken at a variety of levels and techniques, and there is up till now a demand for a science understanding.

7. Regulatory and Ethical Considerations

Biophotonics is gradually drawing widespread attentiveness and appearing in various subjects. Regulatory concern in biophotonics focuses on the care of safety in research and clinical applications on it basically. An observational analysis on fluorescence resonance energy transfer research and this optics indicates severe limitations in current applications in established optics [43]. Establishment of safety guidelines, proper staff training, and monitoring of ongoing research are considered crucial. One of the issues relates to biosafety compliance according to which assurance must be given that exposures to materials, products, or systems during diagnostic imaging; biophotonics therapy; or occupational exposure, and environmental exposure, are within accepted thresholds.

Ethical repercussions in biophotonics also cover a variety of aspects concerning research integrity and the health and rights of participants involved in it. Biophotonics, especially that of the most advanced type, affects not only light and human tissues but also ethical considerations.

An ethnographic approach is taken to investigatively review the far-reaching ethical and clinical consequences and suggest the need for patient awareness in biophotonics surgery. In biophotonics surgery, near infrared spectroscopy is used. Biophotonics is a new frontier area, which requires pre-marketing clinical studies to device safety. Minimally invasive biophotonic diagnostics is dealt with and consists of concerns over ethical validity, safety, and lack of accuracy in clinical trials. Systematic efforts for understanding the implications biophotonics exerts must grow in order to protect individual rights or health itself.

8. Future Directions in Biophotonics Research

Biophotonics is a fast-growing interdisciplinary field of research that integrates the principles of optical science and engineering to study biological issues. Typically, lasers, white light sources, fibre optics and parallel processing are utilised in biophotonics. In medicine, biophotonics has been extensively applied for the conversation of high-resolution optical images. Initiatives have been made to establish techniques that can provide diagnostic imaging information at various depth levels, from superficial organs to deeper structures in surgery and endoscopy. Biophotonics is also utilised in optoelectronic sensing techniques to monitor targeted treatment bio-physiological changes, image-guided surgery and imaging to observe skin diseases, microscopy, near-field imaging, and single-molecule detection. Eye diseases could be precisely monitored with miniaturized wearable photo-detectors. A photo-detector in the form of a glove was constructed to facilitate the measurement of knee-joint reflectance through near-infrared spectroscopy fiber-guide [43]. A bibliometric analysis was carried out to investigate the development of biophotonics as a new application, through the exploring of a large dataset comprising 1527 records, 480 journals and 47 categories. The results revealed a continuously rising level of interest in biophotonics research since 2015. On the word-map generated, spectral-domain optical coherence tomography appears to be the hot topic in this area. The field of neuroscience has gained increasing attention from biophotonics researchers, neuroscientists and photonic experts alike. FRET microscopy imaging has been successfully applied in the observation of live cell protein localisations within a brain slice. Machine learning techniques were employed on spectral data to successfully classify. Different flow deformability profiles obtained from platelet actuation were studied. To stimulate interest in multi-disciplinary academic discussion. A brief overview of biophotonics technology and its applications in neuroscience will be presented, along with some relevant technical and clinical publications. In combination with theoretical and ex vivo studies, this will also provide some insight into the potential for related in vivo research. That optic technology can play a role in the field of biology has long been clear, dating the concept back to the birth of instrumentation and observation in the 19th century. Optical microscopy and, more recently, highly advanced photo-detection methods, enabling observation at the cellular and molecular levels, is predicted to bring about dramatic developments in the area of biological research. Peripheral to this field, the entirely novel discipline of biophotonics has been emerging, bringing significant advances in current visualization technology. Systems combining optical and bio-chemical analysis have, for example, been developed to observe Ca^{2+} signals in neuronal circuits. The underlying ideas on which biophotonic technology research are based on are simplicity, cost-effectiveness, reliability, functionality and validity.

8.1. Integration with Other Modalities

Biophotonics and other imaging techniques can complement each other for a more comprehensive picture of the underlying biology in tissues, improve spatial resolution without missing any significant features, and enhance the sensitivity of the overall imaging technique with the combined signals. Moreover, the operation of one technique does not disturb most of the others, advantageous for imaging settings with predetermined order of performing the measurements. Fluorescence is a versatile technique with sensitivity to biochemical composition [44], while Raman spectroscopy and x-ray computed tomography are sensitive to molecular bond vibrations and electron density. Autofluorescence imaging contrasts the endogenous fluorescence of tissue in contrast to surface excitation Raman spectroscopy in which tissue is illuminated with large power lasers causing the generation of particularly wavenumber Raman spectra. Multi-excitation multispectral autofluorescence can cover multiple biomolecules, and x-ray tomography can image a much greater depth compared to the other imaging techniques. Light distribution models can improve the understanding of light propagation in tissue for the other imaging techniques. Light doses, optical filters, and lasers used for autofluorescence imaging can be adjusted based on the model. Biophotonic tissue can be used for validating software and simulations resulting from light distribution models, necessary for interpreting the optical images.

In the advances in light-based imaging modalities in healthcare article, few technologies are combined to form one imaging system with distinctive benefits; Dual excitation spectral autofluorescence and reflectance bimodal imaging setup of tissue in real time and at different wavelengths in the visible spectrum; Raman probe integrated into the Raman microscopy [5] head enabling 2D imaging as opposed to traditional point measurement. 8 spatially offset measurements can resolve a 2D map of the tissue optical properties, from which a scalable mathematical model can determine localized 3D tissue chromophore content. Bioptic (bovine) eye samples were imaged to validate the technology under different imaging configurations. A homogeneous tissue region (bovine fat) thickness calibration sample was also used for validation. Refractive index ratio and combined hemoglobin concentration, oxygen saturation and scattering coefficient maps of the lung neoplasia samples clearly show the contrast with healthy tissue. Moreover, the oxygen saturation level contrast between artery and vein species is shown in succinct samples. Fully assembled and tested first-generation system demonstrated that UBCM can be used for partial section cutting and imaging the tissue section surface, while reducing artefacts observed with traditional cutting techniques.

8.2. Personalized Medicine Approaches

In recent years, the term 'prosmetic' has been introduced. This term implies a 'halfway' type of novel medical intervention technique which includes promotion, prevention, protection, and prophylaxis integrated with minimally and/or noninvasive propaedeutic biophotonic techniques. New prosmetic approaches will be developed based on prosphotonics, conceptually extending the meaning of wellbeing to biophotonic wellbeing [1].

9. Challenges and Limitations

The very first case about biophotonics was settled as a descriptive word in 1998. The next year, what is now known as “bio-optics” was started as operative words in the field of science. From that time on, the application of light in the health care world became a subject of important consideration, and the idea it can cultivate into a momentous world focus point emerged. Currently, in a worldwide range, numerous resources conduct biophotonics; it is anticipated to improve in diversity and manner. For those reasons, the evolution of biophotonics technology scaled distinctly in the healthcare area, symbolizing tumors and their treatment. An unfortunate tumor is perceived as a paramount problem, leading to the development of huge numbers of investigation work aimed at that surprisingly widespread and frequently lethal disease. Visualizations and illustrations dealing with different types of biophotonics applications are anticipated to provide an undergraduate grasp on how unique this technology is. Regardless of all achievements, the development of biophotonics is in its original manner, and numerous issues are expected to be sought in the forthcoming future. The reality is, in less than two decades, a significant amount of achievements have turned biophotonics into one of the most game-changing and hopeful innovations for the development of science in various modes. It is anticipated that, besides investments in both public and private research work, biophotonics may cultivate an increasing wave of focus from scientific analysts globally, leading to exhaustive investigation to determine how best to use such promising technology in the health care world.

10. Conclusion

Introduction. Biophotonics developments in healthcare support the growing demand of people requiring longer, healthier, more active lives. Minimally invasive biophotonics imaging, sensing, and therapeutic techniques enable earlier diagnostics and more effective treatments of major diseases, reducing mortality rates and significantly lowering healthcare costs. These biophotonic technologies can also afford personalized and patient-friendly healthcare service at home. The objectives of the I Year Biophotonics in Healthcare (BH) Workshop are: to bring together the biophotonics researchers, medical practitioners, and industry representatives from EU and non-EU countries to discuss perspectives and strategies for future developments and applications of biophotonics in medicine, and to establish a new interdisciplinary and intersectoral network providing a solid foundation for expanding novel smart biophotonics devices, technologies, and approaches in healthcare and medical applications.

Measured light information, originating from biotissues, is usually inverse analyzed in terms of understood biochemical and biophysical models to assess quantitatively the tissue parameters or the biochemical constitution in an examined tissue or organ. For the visible and near-infrared spectral region, where biological tissues are relatively transparent, light scattering is the main mechanism of light propagation in the tissue. Near-infrared light interacts minimally with water molecules, so it allows for light penetration in biological tissues in the range of millimeters or even a few centimeters and can probe several centimeters thick tissues in fiber and compact array configurations. Biophotonic techniques are based on the analysis of applied light caused by the photons of endogenous molecules, either intrinsic chromophores or fluorophores, or exogenous biochemicals following their transport to the tissue of interest. Light penetration in turbid media is a few times of l∗s, where l* is the light transport mean free path of photons in the turbid medium, and s is the reduced scattering coefficient. For human brain tissues at λ = 785 nm, l* = 0.978 mm and s = 1.104 cm-1, thus, light penetrates up to a couple of centimeters from the tissue surface. Signal light remitted inside the tissue is detected by diode/fiber arrays of up to a few tens of detectors and is analyzed regarding the pathological information . Detected signals are further processed by the inverse analysis of a pertinent mathematical/physical model relating measured light absorption and/or scattering to desired tissue information, performed by means of advanced signal processing algorithms and software.

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