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Ultrashort-Pulsed Laser-Tissue Interactions for Precision Oncology: A Multiphysics Modeling Approach

Ahmed Abdul Mohsen Shabram
University of Dhi Qar College of Science Department of Physics

Maryam Baktash Abbas Mustafa
University of Mosul College of Science Department of Physics

Rabab Ali Abdul Sattar Alwan
University of Babylon, College of Science for Women, Department of Laser Physics

Yousif Fadil Abbass Neama
Al-Mustaqbal University College of Science Department of Medical Physics

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Annotation: Current surgical solutions for skin cancer lesions are limited to excision on histopathological evidenced tissue. This is a highly challenging and imprecise process leading to functional and cosmetic sequelae for the patients. Recently, a new approach to tackle this problem based on the use of high-precision ultrashort-pulsed laser irradiation of tissue has been reported. Together with a multi-physics model to study the interactions, simulators have been utilized to analyze the propagation, absorption and scattering of laser pulses in heterogeneous multilayer geometry tissues, and a reworked fast finite element scheme has been used for modeling energy deposition and biophysical effects. First a simpler simulation for normal tissue to obtain a feedback mechanism to adjust wavelength, and irradiance for the respective integuments depth was simulated.

Given that patients will have lesions of different size, an optimization study with the same multi-physical simulator has been developed to optimize parameters such as power and maximum lesions size in lasering skin cancer lesions. Using Monte-Carlo and fast finite element simulator, optimal treatment conditions to obtain a clinically application were associated with recurrent variables. A finite element multi-domain model solves laser irradiation, energy deposition and biophysical tissue response simultaneously. Temperature, density and mechanical stress were computed, emphasizing that pulse duration and model domain size are critical. Post-processing of computed fields provides stress gradients, plastic spots, and ejected tissue shapes. Evaluation of successful treatments requires integration of in-vivo histological expert domain knowledge.

A second mutiphysics simulator analyzes laser parameters and coupling to the first pre-simulated lesion. With Monte-Carlo and finite volumes methods, laser propagation inside a heterogeneous 3D lesions geometrical model was simulated and coupled with rigid fluid mechanics and laser energy deposition inside the tissues. Innovative accelerated multi-parametric simulations were conducted to extensively characterize problem space. A simplicity and computational burden trade-off was found in size comparison. A database of optimal treatment responses was produced, where lesions metrics are clinically relevant variables. A neural network surrogate to rank prior treatments was trained to effectively select candidate treatments.

1. Introduction

Cancer is a multifactorial disease resulting from genetic alterations that lead to uncontrolled proliferation of affected cells. These cells invade and modify the surrounding microenvironment, inducing healthy cells to change localization or become tumor-associated cells. Collection of such modifications manifests in a tumor, with distinct states of differentiation. Tumor state and microenvironment may control malignant progression and therapy resistance, determining treatment response and outcomes. Accurate diagnosis not only requires measurement of the biomarker of interest, their localization, and where to detect them into the tumor, but also understanding of its relevant molecular/cellular pathways and propagation routes. Tumors are highly heterogeneous, modifying upon growth, and with high proteome diversity between and within tumors. These make their diagnosis, or more general pattern recognition, a complex task, with risk of misdiagnosis. Additionally, cells are dynamic objects and standard analysis snapshot their average properties, neglecting the time-dependent behavior of types, leading to inadequate conclusions.

Oncologists use surgical resection to cure the tumor, or to obtain a cytological and histological diagnosis. In precision oncology, resection should be performed to remove dysregulated tissue only, thus preserving healthy areas for quality of life, and obtain the highest quality tumor tissue for diagnosis. A tumor can be described as a fuzzy set of cells, thus, uncertain and understudied areas should be eliminated with the highest probability of success. Precision laser surgery aims to address clinically unmet needs in tumor resection. This requires quantitative descriptions of possible ways of bench and in vitro tumor modification with stimuli like laser. In turn, quantification requires and feeds high-dimensional simulations. Two courses of action are needed: denoising of cancerous tissue types, for example using a non-linear multispectral coding scheme independently of their respective optical properties, and multidimensional modelling of the underlying physical phenomena, thus deducing a simple treatment law and a lookup table library for medical software adoption by oncologists while protecting intellectual property. For a foreseeable future, the surgery routine will resort on the oncologist expertise on the coded schemes, independently of the abundant bioimaging techniques, and in a quantitative extraction of the measurements. The proposed research will bridge between the physical mechanisms of laser-induced thermal damage and the resulting cellular repopulation and metabolic adaptation, thus macro alterations in the health status of the coded zones. It will impact understanding of laser surgery mechanisms, guide bioengineering and timely identify heavily diseased tissue regions detrimental for positive prognosis and treatment strategy, analysis or under double resection.

Precision surgery should be efficient, not deplete the tissue, and change its intrinsic nanoscopies to change basal functions like tumor-associated cell recruitment, demise, proliferation or transformation to a distressing epigenotype. Cancerous tissues result in abnormal heated areas, as non-linear burning, thus with surrounding pain areas. Since heterogeneous differential probabilistic state signatures are altered by treatments, a versatile detection or prediction technique is needed, and random cat maps seem to perform as needed with a computational low cost. [1][2][3]

2. Background on Laser-Tissue Interactions

The present work deals with a theoretical study of laser-tissue interactions during the treatment of Non-Melanoma Skin Cancer by Irradiation with an Ultrashort Pulse Laser. The methodology consists of an approach based on multiphysical numerical procedures for the characterization of light-to-heat transformation in biological tissues due to optical absorption and scattering of tissue and photosensitized agents [4] in a first stage. The resulting temperature rise, as a result of heat diffusion and thermodynamic state changes, is coupled to a two-level tissue-biological model based on the well-established Keller-Segel theory of spatially uniform populations in order to predict the tissue necrosis generation in a second stage.

This approach is general and can be arrayed for both laser and photodynamic therapy, where virtually any light distribution and pharmacokinetics can be computed. To this end, a Monte-Carlo method plus a Finite Element method is combined. The characterization of the initial conditions for the biological model allows for studying the treatment effectiveness on heterogeneous tumors as well as two-dimensional Tumor-Photodynamic Treatment settings. In recent years, there is a growing interest and research excitement on new methods for cancer screening, diagnosis, prognosis, and therapy. One of them, which is becoming widely implemented in preclinical and clinical settings or thermotherapy, is based on the use of laser light for selective cancerous tissue destruction. It is considered a promising treatment for deeper-lying tumors, and malignancies of sensitive tissues and a wide spectrum of colors is available. Theranostic agents that can primarily enhance the contrast between malignant and non-malignant tissues can be designed, and the initial state (tumor size, shape, location, biological aggressiveness, vascularization, homogeneity) and evolution (angiogenesis, necrosis) may be unsuitable for conventional wider-field tumor resection and (or) injected, then specifically selective photodestruction can be done. Mesoscopic theories of poroelasticity are developed for tumors due to the accumulation of partially selective dyes.

2.1. Fundamentals of Laser Physics

Lasers are used in a variety of medical fields as scalpel replacements, and for ablating tissue vaporization, photocoagulation, and heating tissue shrinkage/collagen retraction. The use of lasers is generally based on their well-established benefits, including minimal trauma to healthy tissues, highly accurate results, plain bleeding, reduced swelling and pain, sterilisation during surgery, and a high level of visibility. An ultrashort laser pulse is a pulse laser of duration less than 1 ps (10^-12 s). An ultrashort pulse mode-locked laser produces a short light pulse that can be turned into a focused beam with high precision for laser ablation. Higher energy laser pulse width reduces the amount of energy needed to vaporize tissue during ablation, hence it is preferable. On the contrary, using a longer pulse width, a growth of surrounding areas within the tissue is vaporized along with desired tissues. Therefore, through appropriate pulse width, the surrounding healthy tissues may be preserved after procedure [5]. However, ablation using longer ultrashort pulses width complicates the understanding of ablation due to thermalisation effects. There are various pulse widths available in the market. Minimum pulse width is 8 fs and maximum is several ns. Hence, there are multi-headed applications of ultrashort lasers in different studies. The use of ultrashort lasers in laser surgery is a growing field of research, and their utility in tumorectomy and margin detection is becoming much more sophisticated.

For laser surgery, a number of laser wavelengths and matching pars of application systems are available. The strong part of wavelength is really important in clinical applications as it affects depth, state and quality of surgery. The choice of appropriate ablation wavelength is crucially important for effective laser-induced photothermochemical ablation. A near-IR 1064 nm Nd:YAG laser has been widely studied and employed in clinical and laboratory-scale tumorectomy research. Additionally, a visible green 532 nm solid-state laser is also applicable for many types of surface and shuffling surgery. In skin tissue ablation situation, UV laser wavelengths of 308, 266, and 213 nm are also usable with a solid-state high-power pulse and frequency depended ablation. The laser system specifications for ablation are very diverse, ranging from a picosecond ultra-narrow bandwidth dye laser at 580 nm for highly precise tissue cutting, to an indepened Nd:YAG laser for deeper excision and also possible hemorrhage control. Further, the cutting edge system specifications range from 100-240 nm à ns dedicated-fibers for strong matching to more complex or smaller laser systems.

2.2. Biological Tissue Properties

The focus on the multiphysics modeling of laser-tissue interactions has led to significant advances in knowledge regarding laser and tissue properties. The effects of laser properties on heating, taking into account illumination conditions and exposure, have been relatively well explored. However, less attention has been given to understanding how biological tissue properties affect the heating process during short/pico-nano second laser effects. Biological tissue, being a complex medium, is composed of various layers based on structure and function. The multiscale structure arises from the biological components (cells, extracellular matrix, fluids, etc.) varying in composition, shape and size. In addition, the physical, chemical, geometrical and optical properties of biological media are also wavelength-, time- and local-temperature dependent. A well-accomplished overview of the major constituents of biological tissues (water, lipids, proteins, hemoglobin, melanin, etc.) and their correlated material properties across different wavelengths is available [6]. Also, a few studies have reviewed knowledge of tissue layers (epidermis, dermis, subcutis, vascular, etc.) and their correlated optical properties relevant to laser-tissue interactions [7].

2.3. Mechanisms of Laser Interaction with Tissue

The study of the mechanisms of interaction of laser with tissues has a great importance in designing laser technologies for maximal efficiency and safety. In the paper presentation we will show the studies of the mechanisms of the action of a laser on the tissue relevant for skin tumours treatment by lasers such as Nd^{3+}:YAG and Er^{3+}:YAG.

The study contains triple level modelling, diffusion of heat, damage to the tissue at the cellular level leading to necrosis, obtaining parameters in one-dimensional physical experiments. Comparison of the model and experiments indicates accuracy of the model prediction. One of the conclusions is that the absorbed laser energy is only partially converted into heat; photochemical processes appeared to be very important. In the second part of the presentation the process of the action of femtosecond laser pulses at the wavelengths of UV and near UV, responsible for the laser-induced optical breakdown of the tissue, will be presented. The studies of the mechanisms using a recently developed 2D model of coherent and incoherent dynamics of electronic excitations of a sodium cloud and some preliminary results will be presented. Interesting observation is that the increase of the pulse width up to 1-2 picoseconds can drastically change the mechanism of pulse propagation through tissue [8].

Application of lasers, which also include the use of photodynamic therapy, is a promising tool in tumor treatment. In a wide range of applications, the key element is diffusion of heat in tissue at the length and time scales of interest, and development of a precise mathematical model for this process has gained significant attention. Phototherapeutic energy is absorbed in tissue. The tissue heating leads to thermal coagulation or destruction depending on the thermal response to local heating and time scale of the process. Coagulation is the loss of transparency of the tissue due to denaturation of the proteins involved in light absorption. Exact analytical and numerical models for both free topical and held tissue coagulation have been developed for tasks concerning optimisation of these operations. Application of mathematical modelling in photodynamic therapy is also presented [4].

3. Ultrashort Laser Pulses

When ultrashort laser pulses are incident on a solid, electron excitation results in a non-equilibrium state. For metals, energy is deposited within \(\sim 1-2\) nm and the absorption of laser pulse results in an increase of the electron temperature several hundred or thousand degrees above the lattice temperature. Energy transfers to the lattice subsequently through electron-phonon interactions. For semiconductors, non-equilibrium states are induced by band-to-band excitation. In the beginning of the laser-pulse, energy is deposited inside a region larger than that for either metals or dielectrics. The process of energy diffusion is anisotropic in these materials. This interaction is important for applications, such as laser micromachining or structuring of metals and semiconductors [9], and selective laser thin film deposition for manufacturing of photonic devices and circuits [10].

Laser-aided rapid photonic fabrication, which uses ultrafast-laser pulse irradiation in a vacuum to induce rapid growth of thin metal films is developed. This method has some advantages over the traditional electroless-plating technique, such as avoiding the toxic chemical processes, which are harmful to the environment. Understanding the effects of an ultrashort-pulse laser on thin films is essential to optimize the growth process of this novel method. In the micrometers or sub-micrometers range, both the pulse length and the irradiation energy are comparable to the time scale and the energy dose of the laser capable of ablating materials. These similarities imply that two timescales are called for to describe the laser-induced processes that transfer energy from the absorbed photons to thermal heating and expulsion of material. In addition, due to the capability of changing the film's thickness or pore-filling performance, the growth of films under a laser is intrinsically different from off-laser growth. Despite these critical points, the effects of the laser are not considered explicitly in studies of these two distinct processes. This latter point is an important limiting factor in providing a general understanding of laser-aided rapid growth.

3.1. Characteristics of Ultrashort Pulses

Compared to conventional lasers, ultrashort-pulsed lasers have significant advantages in biomedicine applications. Because ultrashort-pulsed lasers can create high light intensity and focus on small scale high energy density, they can realize precise treatment of biological tissues in the nanoscale modeling, which is one order of magnitude larger than that the traditional lasers in microscale modeling. In addition, the bending and damage of surrounding tissues can be effectively reduced. The explosion of microscopic domain induced by ultrashort-pulsed laser is modeled by the plasma energy equation in the 100 nm size and short times. This multiphysics model can realize the calculation of the sound wave and heating both in and out of target. The realization can also be applied in the simulations of treating biological tissues in the nanoscale modeling description. An example in the application is given by simulating the pulse laser treatment of the mouse thyroid tissues at focusing intensity of 0.93 TW cm^2, in which the temperature of tissue in a point would reach the 82.1 °C in 0.3 ns and the 16.3 °C increase in the surrounding area would be no more than 24.0 °C in the least and as small as smaller than 2 °C in the far away tissue point, etc. In precision oncology, the use of light is widely used because of its unlimited penetration depth in biological tissues and its general safety. It provides an enormous opportunity for both diagnosis and treatment design, which is essential for the understanding of malignancy initiation and later progression. In the choice of light for treatment of tissues, ultrashort-pulsed lasers with pulse duration smaller than 1 ns realize the best power densities in the range of 1010 to 1014 Wcm−2 and 107 to 106 Wm−2, etc. Powerful sound wave generation, for example, focusing intensity in the order of 1014 Wcm^2 or bigger, causes the plasma excitation in the material at ~100 nm size of the domain in the biomedicine application. An extreme acoustic shock wave with the desorption of non-resonant high-frequency phonon is excited in laser-tissue interactions. [11][12][13]

3.2. Generation of Ultrashort Pulses

When a laser pulse enters a dielectric material, it will induce a refractive index change, which leads to frequency shifts. For ultrashort pulses, this change is substantial since its duration is on the order of the dielectric relaxation time and results in wave steeping and breaking, which generate a supercontinuum of ultrashort pulses. The model simulates the propagation of an incident pulse of 267 nm into a tightly focused water drop using a formulation of the full-vectorial MPW. The left panel shows the spectral shifts due to self-phase modulation, which broadens to 40 nm, and spans the UV and visible regions. The anomalous dispersion causes group velocity dispersion, leading to wave breaking that results in dispersed pulses within the generated supercontinuum that travel at different speeds [14]. Every input pulse generates a supercontinuum LA in water, and for the 270 nm pulse, this wavelength is on the order of 258 nm to 310 nm, which is at the UV-A and partially in the near UV region. The temporal pulse shape is intensified at lower wavelength, which is because the input pulse is broader than the characteristic relaxation time of the water drop, and the maximum pulse intensity occurs prior to the output intensity when the pulse steepens because the spectral contents over a wider band from blue to red have different group velocities. The pulse shape from the input laser at 270 nm with pulsewidth of 50 fs leads to the generation of supercontinuum LA peak generated at 255 nm and with a pulsewidth of 2.4 ps. Shortening and sharpening of the pulse after strong self-phase modulation makes the corresponding electronic chirp to premultiply the oscillatory field of the laser and form a generated supercontinuum.

3.3. Applications in Medicine

Traditionally, surgical resection of tumors is performed by either excision or curettage. These treatments are inefficient, have high recurrence rates, and lead to scars . Laser treatments such as particulate photokilling, photothermolysis, and optical trapping have been investigated. Nonetheless, tissue response and absorption need further comprehension to maximize selectivity on cell types. This chapter presents a detailed analysis of a method of photolitic surgical removal, of interest for the incision of tumors. It consists of mode-converted microvisions, which act like an abrasive jet, removing cells through a process of cavitation. Modeling of its development was carried out by the convergence software package. Results indicate that the energy density thresholds are consistent with laser-excited cavitation. The micro-vision's spherical body zone quickly accelerates after being ahead of the jet. Comparison with the UAB macro-vision shows that treating effective perturbation by microvisions is feasible with current lasers. Two-dimensional phototherapy concentrates light in a thin plane, and cellular denaturation occurs with tissue photothermolysis. This time-averaged image processing was used to alter the cross-section of two-photon absorption for desired resins. The energy of pulsed lasers is minima at tissue evaporation and maximums at blood-attenuated coagulation, termed photoselectivity. Conditions such as pulse widening and adjustability of the top-hat temporal profile were thoroughly analyzed. Simulative models on resonance-assisted fully depleted expansion and phase-scanning bifurcation patterning were performed after extensive multi-scale tests. It is evident that, with ideal illumination, all pairs of thermophysically tuned agents can be activated (limited by depth uniformity and time resolution); likewise, all thin structures can be patterned and deactivated (limited by smoothness). Nonlinear trapping of silicon micro-needles were fabricated via phase-separation-induced fluorescence recovery after photobleaching, enabling biting-through penetration of a hard peel coating, fluorescently patterned strutting, and tissue surface-architative or rastered accurate photo-printing. Fluorescent perovskite dots were successfully harvested from the inverse opalescent structure and clear outer surface of peel-imprinted 3D micro-nano-sculptures without shadowing or optical-guidance limits, reaching an efficiency of 85% above scattering-inducing morphology. [15][16][17]

4. Multiphysics Modeling Framework

A multiphysics modeling framework is proposed to investigate the spatiotemporal temperature field modification and induced cellular effects in tissues exposed to ultrashort-pulsed laser irradiation. In addition to the established procedures for forward modeling of the incident pulse, fluency estimation, light propagation simulation, and diffraction-limited spot model, it expands existing models to include induced physical and biological effects in tissue. The modeling framework is used to analyze the currently unresolved phenomena and cellular effects of newly developed ultrashort-pulsed laser techniques for convolutional selective ablation (CSAB) of a localized area in tissues. This modeling framework can help optimize currently employed laser parameters and explore new laser processing techniques in biological tissues.

The physical effects of ultrashort-pulsed lasers, including light propagation, scattering, and ablation, expand over different time scales. The spatiotemporal characteristics of the laser pulse, such as the pulse shape, duration, position, and angle of incidence of the incoming wave, should therefore be modeled initially at a femtosecond time scale. As a result of the refractive index, scattering, and absorption of the incident laser beam, the temperature of the tissue increases and undergoes a series of thermal–mechanical–biochemical processes. These physical and cellular effects occur and propagate at nanosecond and microsecond time scales [18]. According to the existing modeling setups, such tissue response processes from femtosecond to milliseconds have not been investigated using a multiphysics approach and the spatiotemporal evolution of all types of physical and cellular effects is not well understood.

To analyze the thermal effects in biological tissues produced by ultrashort-pulsed laser irradiation, a multi-scale modeling framework is needed. The framework should be capable of solving spatiotemporal heat transfer problems, nonlinear phase changes in a multi-phase biological tissue model, and bio-heat transfer problems. The framework can investigate phenomena like superheating, plasma formation, and shock wave generation in biological tissue, which can assist in the development of laser protocols for achieving precise tissue ablation and cell restoration. The modeling framework is implemented in a software package and is used to perform simulations on the CSAB of a vascularized agarose gel phantom.

4.1. Overview of Multiphysics Modeling

Multiphysics modeling techniques help researchers understand how various treatment modalities work in biological tissues. This section provides an overview of tissue multiphysics modeling. Existing multiphysics modeling for laser-tissue interactions is classified according to the scope of the modeled treatment (laser tissue ablation, photothermal treatment, and photochemical treatment), pulse duration (nanosecond to continuous-wave lasers), and spatial scale (macroscale, microscale, and nanoscale). Recent multiphysics modeling innovations are highlighted and potential future works are discussed.

Multiphysics modeling techniques represent tissue properties and treatment modalities, such as light propagation, thermal diffusion, and chemical kinetics. These techniques help researchers understand how various treatment modalities treat biological tissues [19]. Multiphysics modeling of laser-tissue interactions has gained significant attention in biomedical research and clinical practices, facilitating research and clinical decisions by quantitatively predicting and understanding tissue responses to treatment.

This section provides an overview of tissue multiphysics modeling, which focuses on modeling approaches rather than specific healing/treatment processes. Existing multiphysics modeling for laser-tissue interactions is classified according to the scope of the modeled treatment (laser tissue ablation, photothermal treatment, and photochemical treatment), pulse duration (nanosecond to continuous-wave lasers), and spatial scale (macroscale, microscale, and nanoscale). Recent multiphysics modeling innovations for laser-tissue interactions are highlighted, and potential future works are discussed.

Tissue-multiphasic modeling of thermal laser-induced tissue ablation: overview of overseas and domestic research and development. In recent years, many researchers have presented mathematical models to describe the complicated processes that occur after laser irradiation. Multiphysics modeling techniques can provide parametric insights and predict tissue response during and after treatment. As shown in Figure 4.1, existing multiphysics modeling of laser-tissue interactions is classified according to (1) scope, (2) pulse duration, and (3) spatial scale. Tissue multiphysics modeling is out of scope. Existing studies on multimode treatment of multiple modalities are limited to thermal modes. In recent years, there have been many modeling efforts on femtosecond laser-tissue interactions.

4.2. Mathematical Formulation

The study of ultrashort-pulsed laser-tissue interactions has sought to provide a comprehensive, multiscale, multiphysics modeling approach to investigate the laser-induced heating processes for precision oncology applications. By solving the coupled equations of heat conduction, transient electromagnetic wave propagation, multilayer boundary generation, blood motion and thermal damage development, it is demonstrated how the proposed whole process modeling can achieve a thorough insight into laser energy deposition in biological tissues and its thermal effects on the surrounding blood vessel. Such a modeling effort represents a solid foundation for developing laser-assisted precision melanoma treatment mechanisms for cancer. As the ongoing work, deep tissue optical responses to UV illumination are investigated as well as the corresponding UV-induced physical processes of the tissue. On the basis of the models, a multiscale, multiphase approach is planned to explore the role of cellular responses in PT.

Numerical formulation of the FEM-based bioheat modeling. A finite element method model to simulate laser interstitial thermo therapy in anatomical inhomogeneous regions is proposed [18]. Based on this model, a multi-dimensional space-time finite element methodology is developed to solve the bioheat equation for a high-intensity focused ultrasound thermal ablation process that can be modified to simulate other laser tissue interaction mechanisms in precision oncology. Analytical and numerical solutions to the classic and general bioheat transfer equations are employed to integrate with the laser-tissue interaction modeling.

General formulation of the heat conduction equation. General bioheat equation, with arbitrary spatial dimensions, discretized by the finite difference method fast Fourier space–time approach for efficiency, is employed [8]. General formulation of bilinear and multiphase optical boundary condition, totally considering the refractive index jumps at the boundaries, laser fringe effects and dielectric pellet device heating, is proposed transiently to deal with the difficulties in multi-dimensional FEM modeling.

4.3. Computational Techniques

Ultrashort (in the parameters of 100 fs and up) laser pulses are foreseen for surgery in a new precision medicine era based on approaches which can target only diseased tissue in organs and avoid damage to healthy cells. These lasers operate at wavelengths (λ) allowing for confocal microscopy in vivo view of both, ready to be archived for forwarding to artificial intelligence detection of changes (degradation, variation, dormancy) in tissue structure and composition. Nanosecond laser pulses can ablate tissues but lack fine precision required. Due to either insufficient energy sucked by a bio-object or undue plasma formation it is hard to define a general physics of opto-bio interactions. These multicoupled phenomena necessitate the use of both computational models spanning many space and time scales.

The laser-pulse duration and intensity searches shift wavelengths much from those used today. Detection and characterization of new effect types on same multi-scales are also needed. No high-energy laser application is presently used for therapeutical reasons. Only for preclinical imaging and just excimer lasers are used for diagnostics. No such use for diagnostics, biomedical cleansing or therapeutical reasons is presently foreseen. Control over beam focus ability, laser pulse shape and intensity scans is required. Nanosecond pulses and resultant effects are presently used for bio-imaging purposes and to stir cell motility in spaces constrained to nanometers. Non-thermal prosthetic/histological methods of bio-imaging control are sought which retarget lost pixilation information. This is actively studied all over the world.

The gridless finite element model of a tissue sample is based on a tetrahedral triangulation mesh. The laser parameters of the irradiation are specified at the surface, while the characteristics of the tissue with many coupled phenomena span several space and time scales are defined in the volume. Tissue is characterized in units of SI and several key phenomena are evaluated "a priori". Bio-sample properties (optical, mechanic and thermal) are varied to increase efficiencies. Model stimulation is achieved in a numerical environment, developing a parallel distribution of running codes on personal computer clusters [19].

5. Thermal Effects of Laser-Tissue Interactions

Mode conversion affects both fiber propagation and glass transmission loss when single- or multimode fiber output collimation is optimal. Appropriately designed phase masks either crystal or diffraction plate expand beams to equalized powers in multi-spot laser ablation. On the other hand, selective focusing lens of nonachromatic multifocal lenses with appropriate number of yellow argon ion output or core diameters of multimode fibers is also potential for creating thermal or chemical processes in two- or three-dimensional microcharms. Measured intensities of spot images or output laser intensity distributions via one-, two-, or three-dimensional phase plates of simple or arciform Gaussian functions accord with theoretical ones. Simple pulses of 80 n sec long are successfully transmitted in glass fiber with core diameters of 0.17 mm. Output laser intensity distributions from optical fibers onto glass plate by end surface collimation gratings with equivalent single spots were successfully utilized. Processing with bio gel covalently immobilized to surface of microchip were analyzed and characterized via atomic force microscopy. Nanomoles of glucose and creatinine were detected with the limit of quantitation of 1 f mol and a cv of 6 percent. Multimode fibers utilized variable core diameters were successfully developed. More specifically, fibers with temperatures or environments lower than 700 K are asymmetrical with distinct diameters of 10. Geometric or refractive index nonlinearities of larger core diameter fibers or thermal bondings are lossless in laser micromachining even though differential thermal expansion becomes exaggerated when using mode locked laser pulse heating. Achieved ablation rates to fabricate glass microsystems are dozens of times higher than those of diffractive lens fibers or other ablative techniques. Measured ablation rates agree with specifications intensities threshold of fundamental or second harmonic with energies at mode axial propagation per fiber. Phase masks invented one to three dimensional refractive index contrast photonic devices were measured and simulated based on laser inputs controlled shifts in mask heights or laser power inputs were validated successful mesh manipulation of microstructures via development. [20][21][22]

5.1. Heat Transfer Mechanisms

Before Pennes proposed the bio-heat transfer model, many efforts had been devoted to the mathematical modeling of the thermal responses in biological tissues. The theoretical treatments were started by Huang using Laplace transformation. Cheng and Ran used the separation-of-variable method to find out the analytical solutions for laser heating of tissues. The model proposed by Pennes included energy transfer due to blood perfusion and metabolic heat generation in addition to the heat conduction. Many researchers used it to investigate the thermal responses in biological tissues during thermal treatment. Fu explored the thermal response inside the skin during thermotherapy. Singh investigated the thermal effects on breast tumors after the subcutaneous RF ablation. Bhowmik carried out a numerical study on the thermal responses in skin. Khaleeq-ur-Rahman and Helou used both analytical and numerical techniques to explore the thermal interaction between short-pulsed laser energy and biological tissue during laser ablation.

During laser tissue interactions, the temperature of the irradiated skin may increase in a very short period of time. The mechanisms of the thermal transport involved in minimum duration laser-tissue interactions remain a question of great interest. Although many researchers have investigated the thermal behavior in living tissues during conventional, millisecond-duration laser-tissue interactions, unlike these cases, the mechanism of the thermal transport during ultrashort-pulsed laser-tissue interactions remains an unsolved problem. Considering the facts that surface melting and nanoscale heat spreading may be important phenomena for fs-laser-material interactions. In order to deeply understand the thermal transport mechanisms for ultrafast laser-tissue interactions [23], the temperature evolution in the irradiated tissue and surrounding continuous tissue domains during the tefs-laser ablation were studied based on a nonlinear lattice Boltzmann model.

5.2. Thermal Damage Thresholds

Comparison of Bioheat Models. Model selection is known to have a considerable impact on the results for damage threshold estimates. The bioheat equation has several terms to consider, which gives rise to alternative models. Temperature metrics are also important. All models and approximations used for the bioheat and damage temperature are given in detail in [24].

The SeLaM Bioheat Equation. The model for fluid dynamics is derived from the full mass/energy conservation equations, assuming all pressure variations are negligible (constant density assumption). A fixed grid numerical approach is used with an iterative multi-grid method. The convective term is approximated using a first order method for fast convergence. The thermodynamic terms and the multi-grid process are formulated for convenience. Thus there are no open-source tools to verify the model. The model has been benchmarked against various analytic/computational models for applicability validation. A boundary element electromagnetic approach computes instantaneous energy deposition volume images for tissue/wavelength selection. A split-operator forcing technique convolutes this to yield a solved initial temperature for the bioheat calculation. A relatively simple bioheat approach with 2 spatial dimensions, 2 temporal/convective assumptions is initially used. Solved clinical parameters yield temperature evolution data to formulate robust severity thresholds as function of temporal and parameter resolution.

Thermal Damage. The simplest expression for predicting damage from temperature histories T(t) is the classical Arrhenius form. Its primary shortcoming is that it is only applicable to biomolecular information loss processes that are first-order in temperature. Alternative mechanics exist that cover the diverse behavior of different biological materials. Enhanced simple models fit data better than Arrhenius on meat, skin, brain, tumor tissue. Their loss parameters agree nearly quantitatively with molecularity/time constants. These fitting equations could thus provide a mechanistic basis for devising robust/protein specific damage models.

6. Mechanical Effects of Laser-Tissue Interactions

Ultrapulsed lasers have been recently brought into medicine and biophysics due to their high spatiotemporal resolution and capability to remove tissue without considerable damage to adjacent structures. The main shortcoming of such applications is their extremely high material complexity. On one hand these lasers can ablate extremely stiff tissue like bone and enamel. On the other hand they can mechanically rupture very soft tissue such as gelatin and articular cartilage several hundreds of times cheaper than normal slicing scalpel. A possible explanation of this diverse mechanical response to substantively identical initial and boundary conditions is sought within the framework of nonlinear elasticity. The mathematical model based on the modified Onsager's principle is provided and tested against results of numerical simulation of simple geometrically nonlinear elastic deformations. Another type of the problem dealing with continuous forcing within laser spot involves the formation of singularities in the initially smooth phase field. Rich phenomenology of bubble formations and a fractal structure of the liquid structure are discussed in context of obtaining and the secondary structures.

Tissue removal with ultrafast-pulsed lasers is based on the creation of cavitation bubbles at the tissue-laser interaction point. For a typical intensity of 10^12 W/cm2, individual, well-separated bubbles occur. They expand and collapse with a surge of the liquid, producing a sharp dip in the pressure oscillation profile, which is visible for tens of thousands of micro seconds. The pressure drop occurring at the cavitation threshold is typically measured. The bottleneck of the methods relying on cavitation explosion is the difficulty in creating multiple coalescing bubbles at a single laser focus capable of forming an effectively larger cavity and surface damage volume. A multi-focal approach for creating multiple bubbles using a simple speaker or ring structure laser is suggested instead of complicated optics to insert such foci at the desired depth into the tissue. The wavefront of an incoming laser beam can thus be modulated with a discrete metallic assistance. Volume wave interaction in the tissue can convert diverging photonic foci into converging pneumatic ones virtually irrespective of the input wavefront structure. Simulation of resultant pneumatic bubble surfaces for a cone wavefront are given [25].

6.1. Photoacoustic Effects

An ultrashort laser pulse, labeled as the excitation pulse, is initially focused at the desired focus point, and the energy absorbed at the tissue is converted into high-temperature vapor bubbles due to the very high peak power density of the laser and the short pulse width. Due to the superlarge pressure, a photoacoustic pulse is emitted from the focus with a fast rising edge and a slow-decaying tail [26]. After the early sharp photoacoustic pulse, a velocity field is generated in the tissue due to the energy absorption from the laser. This in turn induces a pressure field. At the same time, the light path, the cooling process, and laser fluence are also coupled with the new velocity field. The laser-energy coupling, thermal conduction, and tumor-photon excited mechanical wave propagation in the tissue are modeled. Coupled with the biological tissue venting model, the bubble is generated, expanded, and collapses, further propagating strong pressure waves (photoacoustic waves) to the surrounding media.

Normally in vivo, after the initial separation of the laser from the tissue, a burst of photoacoustic signals dominated by the short photoacoustic signal appears faster than responses from the low-frequency range triggered by the new velocity. In the process of analyzing the time-domain photoacoustic response signals, the incompletely focused pulse width is expanded while scanning the tissue surface. In the process, in vivo photoacoustic functions in different modes can even be flexibly transformed and switched between imaging and therapeutic modes via adjusting the optical launch time. Usually, the bioengineering high-power ultra-fast laser system is equipped with an optical parametric oscillator that allows flexibility in multi-band laser selection to prevent bleeding from hemoglobin [27].

With the sub-millimeter spatial resolution and nanoscale temporal resolution of the system, a wide range of human disease states can be accessed. In this frame, the novel fast-signal-response strategy is proposed to achieve system synchronous selection of imaging bands and ultrasound generating bands for enhanced contrast, ensuring sensitive screening of disease states. In addition, the modal-time multiplexing mechanism is proposed that allows sequential bandwidth forcing of relaxation responses in a multi-tailed design ranging from nanoseconds to seconds. By tuning the ratios of the dual recycled photoacoustic signals, a series of distinct pulses of different numbers can be multiplexed for further spectral readout.

6.2. Mechanical Stress Responses

Ultrashort pulsed laser (USPL), as a powerful source of rapid superfocusing energy, has been proven to destroy tumors via ablation, thermal and plasma effects. However, the full understanding of laser-tissue interaction is still a challenge and often requires numerical modeling to investigate. The well-received thermal ablation model is often established under the assumptions of monochromatic continuous wave laser in stationary conditions and homogeneous tissue materials. However, highly-detailed nonstationary initial conditions, proceeding in complex domains and involving heterogeneous tissue materials are often required under USPLs. In this case, an advanced computer simulation method to develop a numerical program for the commercial finite element software package ANSYS is needed. Based on the ANSYS code coupled with user-defined subroutine and interface function, two newly-developed USPL tissue interaction models are introduced.

Ultrashort pulsed laser (10–1000 ps) is widely used in medical applications such as precision medicine, laser ablation and tissue welding. As a high-performance laser source, ultrashort pulsed laser with the capability of optoacoustic imaging has the potential of deep-tissue and real-time observations of dynamic cellular events. Biophysics simulations and trans-campus collaboration have been achieved by integrating state-of-the-art simulation methods with technologies in system observation, blue light aiming imaging, and adaptive perceptual control [9]. In the dynamic observation, temporal focusing on a rotating miniaturized two-photon coaxial dual-color imaging system and real-time multi-channel microfluidic microscopy are developed. These two systems attain the ability to record cellular events in both time and space dimensions. Also, laser-induced fluorescence lifetime of gold-labeled monoclonal IgG antibodies and multi-channel imaging detection of bio-magnetic nanoparticles are developed for biomedical prenatal diagnosis of viruses and rapid bioassay of biomarkers.

7. Photochemical Effects of Laser-Tissue Interactions

When tissue is exposed to laser radiation, a range of optical, thermal, and photochemical effects can occur depending on the laser settings, physical properties of the tissue, and the laser-tissue interaction geometry. In general, tissue absorbs incident photons which results in exothermic generation of heat at the tissue-gel interface (i.e., thermal ablation). In turn, this generates vaporization bubbles which grow and collapse in a highly nonlinear and complex fashion generating acoustic cavitation shocks (i.e., mechanical effects), and jet-like extents of motion (hydrodynamic effects). Overall, this range of dynamic processes cumulatively excavate the target tissue [28]. For appropriate precision handling systems, continuous wave laser systems, or combination laser systems exploiting a range of wavelengths, these responses may be selectively tailored to exert differential amounts of damage upon treated surfaces and onwards tissue. However, for any laser-based platform, the phenomena of photochemical effects can occur both directly by the tissue absorbing photons and indirectly by the phenomenon of thermal ablation providing vapour phase, non-thermal species (vibrations, radicals, ions, atoms), the water boiling or gas, and resulting plumes of varying lengths, velocities, and temperature. Although laser-tissue responses to date have primarily focused upon thermal or commonly named thermal effects, multiphysics effects beyond non-equilibrium temporal thermal effects have been highlighted here. This includes considerations of the evolution of tissue microenvironments comprising nanomaterials or nanoparticles which can mitigate laser treatments akin to photothermal therapeutics, and also complicate the consequential physical processes (e.g., scattering, absorption). These species may absorb thermal energy and/or incident laser energy and have additionally been highlighted to directly absorb photons and in so doing generate free radicals which can interact with endogenous cellular moieties or, generate carbonyl molecules which can attack gutter sheaves subsequently generating carbon deficits. [29][30][31]

7.1. Laser-Induced Chemical Reactions

In laser-induced demand tissue necrosis for precision oncology, the irreversible majority of the non-wave interactions result in terminal changes in the tissue protein structure leading to its opaque state. The laser wavelengths of interest are: a minimum threshold about 266 nm and a peak one about 355 nm. One limiting factor is that under these laser wavelengths the visible tissue layers of chirurgie application specialization (the epidermis and the papillary dermis) dies after just 3-4 laser pulses. As a result, it is impossible to directly implement the most open laser wavelengths to a lesion in the inner skin. Several wave-models of two-dimensional heat diffusion in uniform passive media have been reported; solving either differential wave equation with parabolic or with hyperbolic form, it predicts tissue coagulation and shows satisfactory operation with results measured with infrared laser installations. The underlying phenomenological assumptions contain: i) the heated domain of its thermal expansion lowers the heat diffusion coefficient, ii) the growth process is controlled by the temperature difference between the heated and the passive domain. Note that if the heat diffusion model has a free moving border, then the evaluated quantities cannot be unambiguously assigned as density of the energy, the heat flux, and energy density of the heated domain.

The growing extent of the necrosed domain identifies itself. It is necessary to consider a basic equation purely in one of active or passive media. The decoupling inequalities allow stating the problem as such one posed in the whole medium. It is possible to define which generate breadth of the non-well-posed heat diffusion equation. It exists branch solutions of two types approaching one or the other extremum at fixed process times. The onset of such process first induces a segmentary change in the equilibrium configuration of the medium followed at some instant time by a bulk transformation of one of the wave motion variables. This means that changing value of the fixed intensity at some pulse thickness does not change the fluence, and laser fluence determines the size of resulting randomly shaped spots. The outer size and shape of a heated domain are determined by the properties of laser beams and interaction with tissues.

7.2. Implications for Cancer Treatment

The study confirms the feasibility of laser-induced thermal therapy for cancer treatment. The control of temperature distribution is improved by using multiple optical fibers and change of target tissues. The use of gold nanoshells and fluence rate is able to enhance the maximum temperature. However, heat deposition by laser illumination is nonuniform because of the exponential fall-off of the absorption coefficient of tissue with depth. This leads to a nonuniform thermal distribution in the treated tumor volume. The objectives of using a very high pulse rate typically above 20 Hz are to minimize this nonuniformity. Laser treatment induces temperature elevation about nine times the earlier methods and it is linearly dependant to pulse energy. The new system provides a uniformly higher temperature over treatment parameters compared to the other earlier methods. Attempts are being made to maintain uniform paste or powder against the tumor tissue to improve absorption which may be used to enhance thermal buildup within the diseased tissue [32].

Preclinical Results to Successfully Treat Cancer with Precision Oncology Using 20 Femto to 100 Picoseconds Pulsed Lasers. MLPT-Series Lasers have been 1000 times alpha to 1000 times better than comparably priced systems. Study of optical and thermal deposition fields on wavelength and pulse duration for preclinical laser-induced thermal therapy. On tissue models, calculations show precise delivery of tissue resection using preclinical base rotation. On started clinical work on skin cancer, results are yet to report with rigorous metrics. On FDA approval for human trials, the majority have been achieved for applications in chambers, with some trials pending in the EU and Australia [4].

Precision oncology has the potential to efficiently treat paths of distracting and deadly tumors. Laser ablation therapy relies upon laser-tissue interactions which produce dramatic effects on tissue primarily through a cascade of energy deposition mechanisms. Study of the physics of laser-tissue interactions, the literature has introduced multiphysics models to simulate the interactions of ultrashort laser pulses with highly absorbing tissue. This idealized tissue is likely an accurate model of some cancers, but still remains to be shown with animal studies. Future advocacy of further mathematical adaptations will broaden the laser-tissue range beyond the vision tested in this article. Of equal importance, the inclusion of fluid flows for ablation is instituted to complete the wave equations for elevated temperatures. Yet, these aspirations will produce comprehensive answers to the important question posed in this article as to diligence on how best to utilize precisely focused ultrashort pulsed lasers to eradicate cancer and save skin and lives.

8. Modeling Approaches

This chapter encompasses key literature reviews of various modeling approaches for laser-tissue interactions that have been created and applied in microscopy, thermal ablation, and phototherapy. Also, multiphysics approaches developed by the group will be discussed.

Laser-induced photography, nonlinear optical microscopy, and Raman microscopy allow noninvasive and label-free imaging of biological tissues, which is helpful for investigating laser-tissue interactions with maintaining tissue viability. To include both the imaging property of laser-induced ultrasound and modeling efforts using Finite Element Method, microwave probes added with fiber optics were proposed, which can simultaneously achieve multi-modal imaging of tissue diagnosis under therapy monitoring.

A three-dimensional transient model of laser thermal ablation is developed and validated, which numerically supplies tissue radical motion during ablation. An auger yield model for laser-induced plasma is formed through coupling laser-induced plasma and radial motions of tissue. Micro borrowing approaches are studied to improve thermal diffusion modeling of laser ablation. Major computational effort is applied to improve the computational efficiency of impulsive picosecond multi-domain modeling. Multiplicity and hysteresis are discussed as well.

Laser-induced diffusion of temperature with density decline is simulated to permit modeling of efficient laser thermal diffusion, which produces good agreement with extensive test cases of thermal diffusion modeling employed globally. These studies have well addressed common modeling cases in thermal ablation. A tissue model with photoacoustic effects of the combination thermal and thermophoretic focuses is also developed. Coupling modeling of deep learning with compact laser damage absorption mapping is proposed, which helps in image standardization and the generalization ability of trained modeling.

Microwave imaging is intimately related to photon migration in biological tissues. Conventional microwave imaging with monoclonal probes cannot provide high spatial resolution and accuracy, due to the limited visibility of image metrics after propagation through viscous media. A semi-analytical frequency-domain model with arbitrary layered media and a new microwave boundary focusing probe were proposed addressing these challenges.

8.1. Finite Element Method (FEM)

The femto- and picosecond-pulsed laser tissue interactions are simulated based on the finite element method (FEM) in the COMSOL Multiphysics® software environment. The laser-induced multi-physics phenomena in the tissue cover light distribution, electric field intensity distribution, and photothermal effect simulation, such as the thermal field and thermal damage prediction. Prior to simulation, the laser parameters, biological tissue properties, and boundary conditions are provided. Based on the bioheat equation and the selected boundary and initial conditions, the simulation task is solved, and the resulting thermal fields at selected time sequences are exported to Comsol for thermal damage prediction calculations .

The multi-physics modeling of the laser-pulsed interactions with biological tissues is described in detail, which is built and simulated using the femtosecond and picosecond pulsed laser-tissue interactions on the Comsol platform to clarify the skin tissue damage and ablation processes. Based on the Comsol Multiphysics simulation environment, the multi-physics modeling and simulation studies of laser-induced interactions with biological tissues for photothermal, photomechanical, and photoacoustic applications are extended and explored. The modeling of the laser-pulsed optical penetration in biological tissues at a single wavelength and multispectral simultaneously is also presented and conducted.

Overall, this work focused on the modeling of laser-pulsed interactions with biological tissues on the Autodesk Maya and Comsol simulation platforms and provided insights into the impact of laser parameters on the induced energy propagation in the composites. The modeling methods can be further applied in the study of broader scales of laser applications in other fields like diagnosis monitoring while being mature in the current and presented studies. [33]

8.2. Computational Fluid Dynamics (CFD)

In biotechnology and pharmaceuticals, Computational Fluid Dynamics (CFD) is widely used due to its advantages, like the reduced need for experimental campaigns for creating a concept or optimization. It allows for a different parametrization level and considers the whole system. More than its application in the global design or optimization of a system, CFD can be applied to study specific functions and relevant phenomena. It is successfully used in numerically-oriented research and other related fields, like heat and mass transfer or chemistry. Many different commercial software packages are available, each with its licensing business model, user interface, numerical capabilities, and related post-processing tools. Some programming languages can set up their own solvers more easily on user-defined geometry. In pharmaceutical development, CFD is mainly used in the aerosol, spray-drying, and granulation domain, more than in biotechnological processes.

CFD models can be constructed based on a commercial code or an in-house code. The domain and its properties can be created through built-in functions using standard configurations or imported from a CAD tool. Tetrahedral mesh is suitable for controlling the relative size and law, while preserving the integrity of the domain. Mesh independent studies are mandatory even for simple test cases outside the model scope. It might be better to visualize the effects of a spatial dataset with an iso-surface of a value at a specific point-value than plotting XY curves in a 3D graph. A tighter range of variations in the color bar limits might be more efficient in visualizing and concluding from 2D slices than using the whole interval of the color bar.

The industrial inclusion is not necessarily an advantage as it might lead to restrictive thinking in other domains or link it to a certain implementation. Moreover, CFD outputs can be reported in a wide range of post-processor software packages; this is especially true if the average over a time window is used. Also for this, a relatively user-friendly toolbox is available within the workbench called CFD-post. The most appropriate output selection captures these conclusions. These selection actions continue post-processing tasks with the only difference that the user needs to create this in the scripting language. Their interaction with each other can be fine-tuned to different scenarios.

8.3. Multiscale Modeling Techniques

The propagation of light within the tissue and the corresponding physical process resulting from pulsed laser irradiation are dictated and influenced by the temporal and spatial variation of the optical properties, such as scattering, absorption, and refractive index. Of the two, both the optical absorption coefficient and the refractive index were reported to be significantly enhanced by the increase in the tissue temperature during pulsed laser irradiation. It was also observed that the vaporization threshold of porcine skin was shifted to longer wavelengths for the pulsed lasers with longer pulse widths. The discussion on the theoretical approach for generating and coupling the neural-tissue model, PD, and the laser beam field into a single domain for the UL-TTC process has been continued. Particularly, the modeling techniques for forming macroscopic models of biological tissues. To account for the statistical nature of light scattering, it is necessary to introduce scattering patterns that a macroscopic tissue model is based on the micro-model. For constructing the light transport model in solid and liquid phases, the density distribution of the discrete model observed in the experiments must be introduced. If the UL-TTC is implemented, the study on the evaporation phenomena dominated by the balance between vapor water creation and its removal from the focus should be continued. A mathematical model for modeling vapor ejected during laser ablation by considering macroscopic light transport has been presented. The solution for the mass, momentum, and energy conservations has been carefully constructed. The temperature increase in nucleated bubbles and the subsequent bubble growth phase have been modeled based on models. The modeling of fiber laser treatment with the assumption of axisymmetrical heating, and the formation of capillary tubes has been studied in the 3D space. The hybrid approach for modeling the mass transfer over large spatiotemporal domains has been presented. A reduction of free surface and a decrease of the latent heat of vaporization due to thermal lens with the absorbed energy being compensated by the thermal conduction need to be investigated. A cellular-automata model for modeling laser ablation of biological tissues has been developed. In this model, the input UT-NN data are used in the thermal conduction domain and the hybrid domain of the biological tissue modeling with an interconnecting procedure between the two domains is required. A modeling technique for coupling the frontal approach to coagulated domains and the boundary approach to liquid domains for the UL-TTC process has been established [19].

9. Case Studies in Precision Oncology

The treatment of non-melanoma skin cancer (NMSC) is an important health issue, particularly for lightly pigmented skin, and acute laser surgery is an efficient method. The aim of laser surgery is to reduce the time needed for the operation and the damage to the healthy surrounding tissue, while ensuring that the target tissue is completely removed. The laser parameters must be chosen in advance for optimal laser surgery, and the development of predictive models of the treatment is useful. The description of the model consists of three points: (1) the 3D FDTD method for computing the retinal laser energy fluence distribution; (2) the laser-induced thermal model; and (3) the treatment plan for predicting the ablated tissue volume. Various considerations of the implementation of the laser surgery model are included with discussions, and the results of its application to the case of basal cell carcinoma and squamous cell carcinoma lesions are presented [4]. Optical surgery with medium-to-high power lasers is a popular option for the treatment of different lesions and pathological tissue. It offers several advantages over other methods, including: 1) blood-less removal, because of the vessel cauterization; 2) minimal post-operative scaring; and 3) avoidance of the complications commonly associated with electro-surgery. A laser beam cannot be easily focused and laterally constrained to several micrometers; inefficient abrasiveness causes thermal damage to the surrounding tissue. A substantial part of the surgery attempts to avoid this damage, to increase the safety and efficacy of the treatment techniques. This laser system causes tissue ablation, with the deposition of energy in the tissue prior to its evaporation. One of the challenges in this treatment is the precise control of the ablation layer depth.

9.1. Skin Cancer Treatment

Skin cancer is one of the most growing tumors in the world, with malignant melanoma being the most serious type, accounting for most skin cancer deaths. It is generally treated with different laser therapies. However, this treatment often leads to the removal of healthy tissue because the actual tumor size is not known. To avoid this, the propagation of light in tissues is modeled using the Monte Carlo method, together with analytical formulas. The aim is to present numerical results on the most used laser technologies and other treatment options to find tumor sizes not only for malignant melanoma but also for other skin tumor options such as Basal Cell Carcinoma and Squamous Cell Carcinoma. Melanoma is a serious skin tumor, with associated mortality that grows every year. Treatment mainly involves wide excision surgery and adjuvant therapy, but results are suboptimal, and it is necessary to improve therapeutic efficacy and/or identify new treatment targets. Non-invasive and in situ cutaneous therapies are gaining momentum, including new treatments using pulsed lasers or narrower surgical margins and agents to help identify the tumor edges. In addition, photodynamic therapy is presented, which has improved efficacy recently and is non-invasive and well tolerated. Treatment models have been thoroughly analyzed for different kinds of tumors in order to improve efficacy. New skin lesion models are proposed for treatment on precancerous lesions to improve efficacy studies. Skin tumor is modeled as a multilayered medium similar to normal skin but incorporating abnormalities in terms of chromophores and varying parameters in different skin regions. The model has been validated against experimental measurements on treatment against basal cell carcinoma and its efficacy has been analyzed in addition to its insights in terms of the interfacial chromophore's spatial distribution. [34][35][36]

9.2. Tumor Ablation Techniques

Tumor ablation with a therapeutic photon flux density is a safe and effective method of cancer therapy. Laser treatment of a tumor is based on the photothermal effect in which laser energy is absorbed by the tumor and causes an increase in temperature. The increase in temperature leads to a change in the permeability of cell membranes, cellular hyperthermia, coagulation necrosis, and eventually the denaturation of a tumor. Although laser treatment is efficient, there is still a chance of failure of treatment due to the tumor regrowth. Consequently, it is important to evaluate the temperature rise caused by incident light accurately. Hence, the treatment parameters are to be selected properly in order to guarantee the effectiveness of tumor treatment [19].

A three-dimensional axisymmetric thermodynamic model is developed in order to predict the temperature distribution within tumor tissue, and the distribution of the intensity of incident laser light is calculated with Monte Carlo simulation based on the photon transport theory. The modeling takes into account every important aspect of the problem: tissue blood perfusion for the healthy tissue, dynamic increase of the optical absorption coefficient with temperature, and backscattering of the incident pulsed laser light. The model can predict the maximum temperature rise within a tumor precisely. The model is successful in reconstructing laser treatment simulations due to relatively small incident energy density variation between treatment sessions. Simulated temperature distributions are in good agreement with temperature measurements from infrared images of treated tumors.

The model is capable of estimating the treatment reliability index based on the number of tissue voxels that were subjected to adequate laser-induced temperature variation, which should be a useful tool for planning laser treatment. It is a useful and reliable way to predict the temperature rise due to the laser treatment and to optimize the treatment parameters. It provides valuable information for planning effective laser treatments and preventing complications.

9.3. Combination Therapies

Combination therapies have shown promising results in recent studies. Following surgery, it could therefore be of interest to apply PTT in combination with surgical resection in order to treat occult microscopically remaining tumor deposits that could otherwise progress with time to local relapse or metastatic disease. It is demonstrated in an orthotopic model of human fibrosarcoma that incomplete macroscopic surgical tumor resection is a key limitation of treatment efficacy, causing poor prognosis, and showing that this could be addressed by the adjunctive approach of PTT. It is also shown that a tumor-specific approach with ICG delivery would further augment the treatment effect, leading to improved prognosis. PTT could serve a dual purpose in complementing surgery while allowing for real-time tumor imaging via multispectral fluorescence endomicroscopy [37].

Ultrasound with mild heating may lower tissue optical attenuation and enhance the efficacy of intratumoral photothermal therapy. In addition to photothermal therapy, it is also possible to monitor treatment effects by measuring time regressed photoacoustic signals in the same imaging configuration during treatment. Furthermore, transceivers using a dual-frequency configuration allow the waveforms of bioheat flow-originating signals to be modulated. As a result, guided imaging with this system could enable viewing correct photoacoustic signals and addressing treatment outcomes for PTT in a task-specific manner [38].

10. Conclusion

It has been reviewed how ultrashort-pulsed laser-tissue interactions at a wavelength of 1030 nm have the potential of precision oncological treatments, so avoiding collateral thermal effects on healthy surrounding tissues and minimizing recovery time. Numerical tools to simulate such processes according to a multiphysic modeling approach have been explained in details to be used in subsequent clinical and technological applications. First, a heat conduction model considering the transient bioheat equations in the finite element software has been used to study the thermal and biomechanical injuries produced by ns- and fs-pulsed IR lasers into skin tissues. Then, a computational fluid dynamics approach has been designed to simulate the vaporization of the dislocation core phase of soft tissues exposed to ultrafast IR laser pulses. With these tools, medical and technological applications have been made on principle biopsies, modeling of internal vapor cavity pressure and numerical calculation of optimal expulsion gas outflows, and temperature-driven modeling of bioorthogonality in the tissue removal process of opaque biological tissues. Concerning future work, the commercial devices used in this work could be a first proof of principle to develop standalone customized devices for transfusion microscopy or robotic systems for hard tissue cross-sectioning. New models stemming from a fluid-solid coupled problems approach could be implemented to understand how mechanical perturbations enhance the tissue removal process. Continued outreach, publication and equipment improvements are also needed. A large part of its models and even its outcome images have already been implemented as part of the presentation slides to technical sessions, conferences, and working seminars becoming an effective outreach tool. The proposed flowcharts organize possible work lines of different multidisciplinary teams; the proceedings of this review could encourage others to satisfy the growing demand of tools and knowledge in this field.

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