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Review paper

Non-ionizing, laser radiation in Theranostics: The need for dosimetry and the role of Medical Physics

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ABSTRACT

The discovery of coherent laser light in 1960 shifted and expanded the biomedical applications of radiation to the non-ionizing part of the electromagnetic spectrum. As in the case of ionizing radiation, but considering the laser specific features, the effective, safe and ethically acceptable use of biomedical laser technology requires interdisciplinary collaboration between physicists, engineers and physicians. This should extend at the research, preclinical and clinical level, inspiring at this time the dynamic discipline of Medical Physics in new areas.

With this work we aim to introduce the interested reader in the need of dosimetry in medical applications of laser radiation, as this field is still unexplored. After some necessary definitions, we give a brief review of the basic biophysical mechanisms of coherent light-matter interactions. The manuscript focuses on biomedical laser applications in diagnosis and therapy (i.e. in Theranostics). From the vast field of laser theranostic applications we have chosen some experimental and theoretical results – examples of quantification of the laser effect, particularly relevant to soft and hard tissue laser ablation, laser induced photodiagnosis and photodynamic therapy of cancer. These topics intend to highlight the important role of Medical Physicists in the optimization of well-established laser based clinical procedures and mainly emerge the necessity of the relevant dosimetry for each application. Finally, we hope that this effort is going to give food for thought and highlight the importance of deep knowledge of the physics behind some everyday medical applications.

1. Some introductory remarks

Among the 20th century Physics' achievements, lasers provide an extremely wide range of applications. They were almost immediately employed after the report for the first laser (ruby laser) realization by Maiman in 1960. During this approximately 60 years' time period, both research developments and applications of laser radiation are impressive, particularly in Medicine (in all areas: diagnosis, treatment and biomedical research and technology).

Definitely, if the 20th century was characterized by the dominance of ionizing radiation, the discoveries of Physics and Technology of Lasers and Photonics in the 21st century shifted and expanded the biomedical applications of Physics to the non-ionizing radiation part of the electromagnetic radiation spectrum. Most importantly, they inspire the discipline of Medical Physics that is and must further be a dynamic and constantly growing field of Applied Physics, embracing its novelties.

It is worth stressing that the first applications of laser radiation in medicine, as early as 1961 – one year after the laser discovery, were governed by the clinical experience of physicians. Nevertheless, today, it is easy to understand that the effective, safe and ethically acceptable use of biomedical laser technology requires interdisciplinary collaboration between physicists, engineers and physicians at the research, preclinical and clinical level. Good training and continued collaboration between the different scientists' specialties is needed to optimize the exploitation of the important properties of the laser light [1].

However, even at the time of preparation of this overview, we came across lack in literature of new or even updated dosimetry protocols regarding medical applications of non-ionizing light. Therefore, we planned to highlight the need for dosimetry and the role of Medical Physics. Regarding the laser dosimetry, the interdependence of the parameters under consideration (physical parameters of the laser beam and of the biological target) and the measuring devices and methods, results in very complicated procedures.

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2. Laser radiation: definition, properties, and biomedical applications

The term laser is an acronym, which stands for Light Amplification by Stimulated Emission of Radiation – LASER. Laser light has three characteristic properties, which differentiate it from ambient, natural light. Laser irradiation is monochromatic, coherent, and collimated. Consequently, laser-based techniques have high spectral, spatial and temporal resolution. Another interesting property of laser sources is the possibility of light emission in continuous wave (cw lasers) that has a constant power output during the whole operation time, or in pulsed mode (pulsed lasers) emitting light periodically with no light between pulses. Clinical laser applications span a range of wavelengths from 193 nm, ultraviolet (UV) excimer laser, to 10.6 μm, infrared (IR) CO_2 laser. In our days, all light-based technologies applied to life sciences and medicine form an emerging multidisciplinary research area, named Biophotonics [2]. Biophotonics is the combination of the Greek syllables "bios" standing for life and "phos" standing for light. Biophotonics' achievements and ongoing research efforts in both early diagnosis and imaging, as well as in novel human treatment options, have revolutionized the biomedical cosmos. The link between thera(peutics) and diag(nostics) led to the development of a new field, entitled "Theranostics", which became very exciting for scientists after the first reports during the last decade [3–5].

Certainly, the biomedical applications of lasers are constantly growing and cover an ever wider range of areas. Nevertheless, it is true that many of the first spectacular declarations for a "revolution" in surgery through the use of non-contact "laser scalpel", have not justified all the predictions and the initial enthusiasm of scientists for the medical applications, especially in cases of general surgery. During this time, however, important new biomedical applications have emerged, precisely because of the existence of lasers and their unique properties! For example, in the field of Dermatology lasers have become particularly popular as they allow treatments that were not possible with the use of other biomedical technologies. Definitely, hemangioma therapy, port wine stain and tattoo removal were impracticable before the onset of the laser. In Ophthalmology, diagnosis and treatment of retina diseases (e.g. diabetic retinopathy) are possible exclusively with non-invasive laser light. In Ophthalmology also, by applying laser technologies the myopia correction became one of the most effective and rapidly developing eye operations for the general population. Let's not forget that the action of laser radiation, from the beginning of laser development, was easier to be applied in ophthalmic structures, as eye is the physiological optical instrument that is customized by nature to accept and focus electromagnetic waves – photons.

The future offers a wider use of lasers, likely to involve less invasive and more specific targeting, potentially to a cellular level. A dream for the biophotonic applications in diagnosis of human diseases is the so called "optical biopsy". The term "optical biopsy" is frequently used for optical spectroscopy methods, like the laser induced fluorescence technique or optical coherence tomography, applied to characterize a tissue. A generally accepted definition for optical biopsy is: the *in situ* imaging of tissue microstructure with a resolution approaching that of histology, but without the need for tissue excision and processing. Laser light based therapies have the advantage of being non-invasive or semi-invasive loco-regional procedures, with site specificity and non-toxic application, permitting to be given as repetitive treatment protocols. Laser medicine is a rapidly growing field of both research and applications. Nevertheless, we point out that lasers are not a panacea for some medical fields. Furthermore, laser therapy will not be chosen if more conventional methods are available, as well experienced physicians feel that it is easier and safer to perform them, instead of the laser based ones. However, we repeat that there are medical applications for which the use of lasers is perhaps the only solution. To give just one example of the unique laser accomplishments in medicine, we mention the need to deal with anticoagulated patients requiring surgical procedures, without changes in their anticoagulation regime that is associated with an increased risk of thromboembolism. For instance, the hemostatic properties of high-power lasers could be helpful during oral soft tissue surgeries in anticoagulated patients [6]. Three decades ago, several research and clinical efforts worldwide were addressed to face the problem of hemophilia patients needed to undergo a surgery, using lasers and their hemostatic properties. At that time, Santos-Dias [7] among others concluded that CO_2 laser surgery for hemophiliacs has a confirmed place in laser technology, "provided the standard precautions are taken and facilities are available". Unfortunately, the majority of laser applications are still based on empirical protocols and the physicians' experience, while in some cases there are complications and adverse effects described. Consequently, one reason for some medical groups to abandon the laser based methods is the fear of efficacy and efficiency failure.

As a result, with this work we aim to defend the necessity of radiation dosimetry and eventually treatment planning in the biomedical applications of lasers. Moreover, representative examples are used to

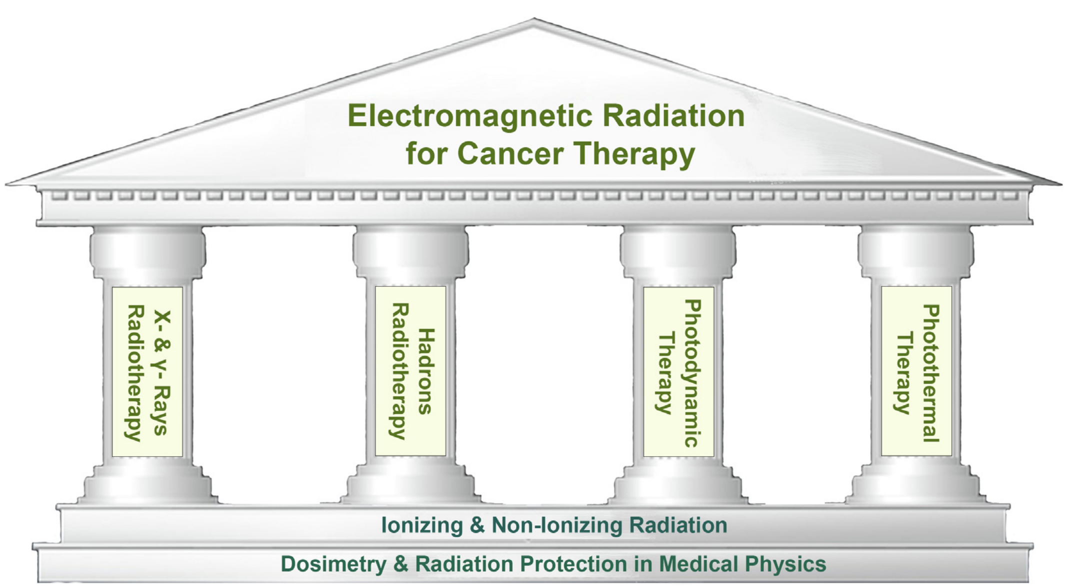

Fig. 1. The main pillars of cancer radiation therapy and Medical Physics scientific contribution.

demonstrate the above, justifying the involvement of the modern Medical Physics scientific contributions in the biomedical applications of laser and laser-like light, especially – but not exclusively – in cancer radiation therapy (see Fig. 1 for an illustration of the main pillars of cancer radiation therapy and Medical Physics scientific contribution).

At this point we need to clarify that, although the optimal use of lasers in Theranostics offers several advantages, there are also risks such as eye and skin burns, fire, inhalation of toxic fumes and electrical shocks, which are not related to laser dosimetry but to laser safety in general. As a consequence, safety for patients and health care personnel depends on the safe and effective use/supervision of lasers by a qualified expert, the Laser Safety Officer (LSO) or Medical Laser Safety Officer (MLSO). The LSO/MLSO, who is responsible for directing the safe use of lasers and ensuring compliance with laser hazard standards and controls, could also have a Medical Physicist's license. In this optimal case, he/she would have not only the necessary knowledge of laser safety but also of important medical physics aspects.

3. Laser – Tissue interactions and photobiological mechanisms

A special demand for better understanding of the basic biophysical mechanisms of light propagation into biological media and the prediction of laser-tissue interactions is of great importance for the optimization of effective and safe clinical laser applications. This is more evident if one considers the increasing use of lasers in biomedical research and clinical praxis, as well as the increasing number of available laser light wavelengths.

It is worth pointing out that when laser light enters into tissue the penetration depth is limited, compared to that of ionizing radiation, which can penetrate the whole human body. Visible photons have energy of a few eV, while X-rays are 10^4–10^7 times more energetic [8]. Therefore, photons of the optical part of electromagnetic spectrum have very limited penetration depth and their applications in both diagnosis and therapy impose specific configurations in the set-up of light source and light guidance, patient and detector or target positions. In this point, we shall give a very short reference on laser-based diagnosis, because some dosimetry protocols or laser interventions monitoring procedures are based on similar to imaging laser spectroscopy techniques.

We must emphasize that the introduction of laser and laser like (i.e. Light-emitting Diode – LED) radiation in the biomedical imaging diagnosis arena, established the so called Biophotonics field and the relevant imaging techniques. These are stand-alone or could be additional to other well established conventional ones, like Magnetic Resonance Imaging (MRI), Ultrasounds (US), Positron Emission Tomography (PET) and Computerized Tomography (CT). Biophotonic imaging could not replace them, although in some applications results in better resolution. For example, optical coherence tomography (OCT), which has 3–10 μm resolution (one or two orders of magnitude better resolution than US), approaches the resolution of histopathology and have gained the name of "optical biopsy" [9]. The basic phenomena in laser – tissue interactions, either for diagnosis or for therapy, are related to light propagation into tissue and the relevant optical properties of the biological structure. If an incoming photon carries energy that matches the gap between two energy levels in a molecule (or a chromophore) it can be absorbed. A chromophore is a molecule absorbing visible light resulting in a "colored" compound (from the Greek word chroma = color). Here we will extend the definition to molecules absorbing in the entire optical spectrum (e.g. near-UV, visible (VIS) and near-IR region), including in chromophores even the colorless water, a component that predominates in soft tissues. The conversion of the photon energy of the incident laser radiation in other energy forms, leads to the manifestation of primary and secondary photobiological effects, which are the basis of the wide range of laser biomedical applications, such as surgery, therapy and diagnosis. Depending on the end result of photonic energy conversion in another energy form, we can differentiate between three major photobiological effects: photochemical effects, photothermal effects and photomechanical effects.

3.1. Photochemical effects

Photochemical processes result from molecular photo-excitation, following absorption of one or more photons. Laser radiation in the VIS or UV range of the electromagnetic spectrum is absorbed by natural or "exogenous" chromophores – biomolecules of the tissues and induces electronic excitation with subsequent photo-biochemical effects. A molecule of biological importance can be raised from a ground electronic to an excited state. From there a variety of chemical reactions are possible, such as the generation of free radicals and reactive oxygen species (ROS). The main applications, based on photochemical mechanism of laser-tissue interaction, are photodynamic therapy (PDT) of tumors, biostimulation for wound healing in the so called low level laser therapy (LLLT), photodiagnosis and photo-detection.

Apart from the above mentioned applications, an interesting photochemical effect is the so called photo-chemical ablation or photodisruption. It is theorized that when short-pulsed lasers are used with UV wavelength emission, the high energies of the UV photons cause organic molecular bonds in biological tissue to simply breakup, without any local heating. This process is called "photo-chemical ablation" and results in clean-cut incision. The thermal component is relatively small and the zone of a possible thermal interaction is limited in the incision wall. Therefore, the photo-chemical ablation mechanism in biomedical interventions is considered as a "cold" cutting mechanism, very important especially in delicate surgery. This mechanism is applied, among other medical specialties, in Ophthalmology for myopia correction with lasers, i.e. in the so called refractive surgery.

3.2. Photothermal effects

When VIS or IR photons traveling into a tissue are absorbed by biomolecules – tissue constituents, the conversion of their energy could generate heat (thermal energy). In relation to the amount of heat deposition, several photobiological effects can occur, which transform the temperature increase to reversible or irreversible alterations in tissue structure [10]. All these phenomena are characterized by the so called "photothermal mechanism". Depending on biological target's optical and thermal properties, the typical thermal events associated with the photothermal mechanism of tissue damage include: hyperthermia at $\leq 43\,^{\circ}C$, photocoagulation (protein denaturation and disordering, contraction of collagen, hemostasis) at $60^{\circ} - 80\,^{\circ}C$, photothermal ablation (water surface evaporation and tissue dehydration, subsurface explosive vaporization, explosive expansion of superheated fluid) at $100\,^{\circ}C$, carbonization at approximately 150–300 °C and pyrolysis and vaporization of solid tissue matrix at temperatures $> 400\,^{\circ}C$.

Every step of the photothermal effects gained several biomedical applications. To name a few examples, hyperthermia is used in cancer radiotherapy and in physiotherapy, photocoagulation was the first laser medical application, just one year after the laser discovery (in 1961, in diabetic retinopathy) and photothermal ablation is the basis of the noncontact laser "scalpel" in surgery. However, an uncontrolled photothermal mechanism could create undesirable secondary effects, as shown schematically in Fig. 2. In the scheme a Gaussian laser beam is shown that hits a tissue surface and creates a photo-thermally induced ablation crater, corresponding to tissue ejection for surgical incision. This process occurs at temperatures about 100 °C and, in these conditions, the tissular/cellular water evaporates within a relatively short time, ejecting cells and other constituting elements. On the other hand, at the borders of the ablated area, one can observe a necrotic zone (tissue carbonization) and a coagulated area, as temperature decreases continuously from the injured to the healthy tissues. As it is logically expected, the secondary thermal effects and the relevant non-excised tissue alterations are usually undesirable, especially in surgical

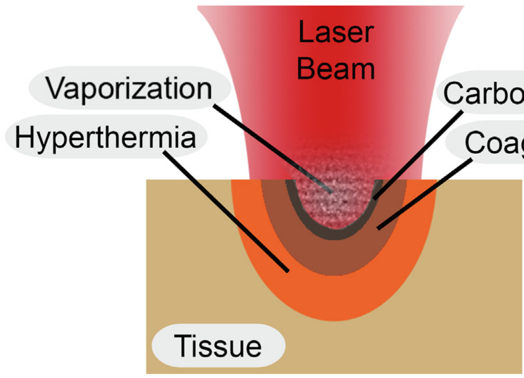

Fig. 2. Schematic representation of photothermal effects on the impact of a nearly Gaussian laser beam incident on a soft tissue simulator (sizes are arbitrary).

incisions where high precision is needed. This is especially true for brain surgery, where the damage to surrounding healthy tissues must be minimized.

Besides the role of tissue absorptivity, the role of selecting the photon energy or power fluence value is demanding for surgical applications. Energy fluence, F, is defined as the total energy delivered by a laser source on a target area (I) during an exposure time T_{exp}:

$$F(J/cm^2) = I(W/cm^2)\cdot T_{exp}(s) \tag{1}$$

Definitely, the role of laser energy or power fluence, instead of the simple laser output energy per pulse or power (in cw operation) is crucial for the start of laser dosimetry and the obtained result. For example, when using a CO_2 laser scalpel the surgeon has to decide whether he applies a laser beam in focused or defocused mode for either tissue excision or hemostasis respectively, as shown in Fig. 3. The reader should have in mind that with the advantage of laser directionality there is the simultaneously possibility to focus or defocus a laser beam using a lens. This can be used to vary accordingly the intensity of the laser. With a tightly focused beam, a deep excision is achieved, while with a defocused beam the power density decreases, resulting in a value below the threshold of vaporization and tissue is only coagulated (for example for hemostasis) [11].

Apart from the intentionally controlled laser focusing-defocusing, there are circumstances where the focus of laser beam is incorrectly estimated. For example, as shown in Fig. 4a, when a visible laser is used as aiming beam in non-visible lasers applications (e.g. IR CO_2 surgical laser, UV excimer lasers), the focal points of the two coaxial lasers are different. More precisely, in a medical CO_2 laser system (λ = 10.6 μm) with a He-Ne laser (λ = 632.8 nm) as a targeting beam, we irradiate the biological target with two wavelengths that are far apart from each other and, consequently, the index of refraction of the optics in the beam manipulation system (e.g. lenses of surgical microscope) significantly differs for these two lasers. As a result the He -Ne beam is focused closer to the optics than the CO_2 laser beam (see Fig. 4a) and special precautions are needed to resolve the dosimetry problems raised, as by using special diffractive optics, permitting focusing in the same point (see Fig. 4b) [12].

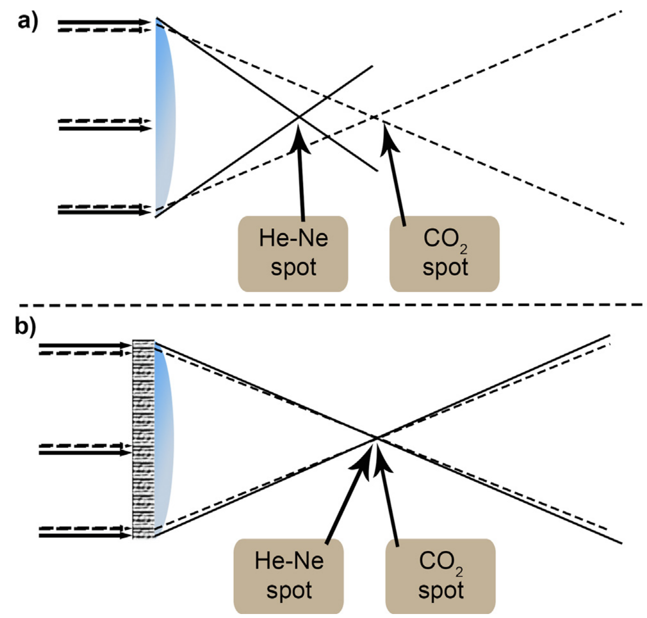

Fig. 4. (a) With conventional lens, the He-Ne beam is focused closer to the optics than CO_2 laser beam. (b) By adding a single diffractive surface on the lens, the focus of He-Ne beam will coincide with that of invisible CO_2 beam (modified after [12]).

Without using special optics in the case of double laser beams or without careful evaluation of the focusing distance in single beam applications, the fluence calculation could be either over- or under-estimated. To give an example, we designed an experiment to critically test the influence of laser beam defocusing (see Fig. 5) in a clinically important ablation parameter, namely the ablation rate. As shown in Fig. 5, the ablation rate versus laser energy fluence for a hydrated dental tissue, after Er:YAG laser irradiation with a focused and a

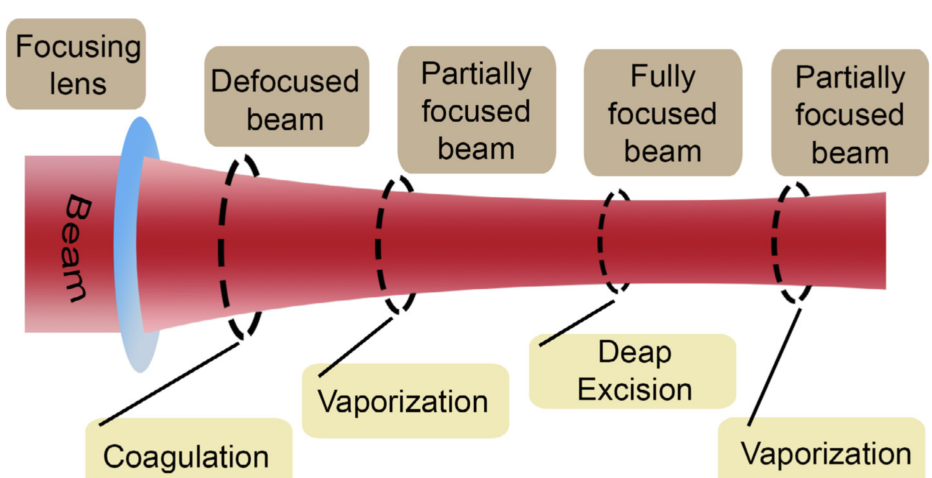

Fig. 3. Schematic representation of different photothermal effects depending on a defocused (coagulation), partially focused (vaporization), or tightly focused (excision) CO_2 laser beam (modified after [11]).

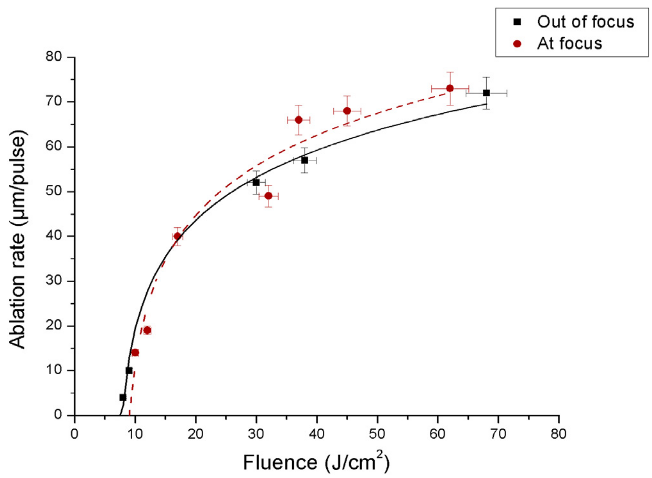

Fig. 5. Ablation rate versus laser energy fluence for a hydrated dental tissue after Er:YAG laser irradiation, with a focused and a defocused laser beam. Error bars not shown are smaller than the symbol.

slightly defocused laser beam, proves the expected differences, i.e. higher rate in focus.

3.3. Photomechanical effects

During the photomechanical interaction process, the incident high-power pulsed laser radiation is absorbed by certain biomolecules and causes photo-ionization and molecular breakdown in a "cold" manner. Strong electromagnetic laser radiation is achieved *via* high optical intensities reached in pulses generated either by a Q-switched laser (with nanosecond pulse duration) or by a mode-locked laser, amplified in a regenerative amplifier (for pulse duration of picoseconds or femtoseconds). Photo-ionization, either by thermionic electron emission or by multiphoton ionization, generates electron avalanche, i.e. plasma, which is expanded by simultaneous generation of hydrodynamic acoustic and shock waves, causing disruption of molecular bonds and ablation. This leads to a photomechanical damage mechanism, schematically illustrated in Fig. 6. The power density required for the above phenomenon is in the order of 10^{10} W/cm^2, easily achievable by ultrashort pulsed lasers. Clinical applications based on the photomechanical effect are found in photorefractive eye surgery, endoscopic laser lithotripsy, certain types of surgery and more.

4. Biomedical laser applications and the involvement of dosimetry

As we mentioned earlier, the first applications of laser radiation in medicine were governed by the clinical and experimental experience of physicians. This connection remains challenging and invaluable, given the complexity of the biophysical mechanisms involved. However, a number of post-operative complications recorded, in combination with the lack of understanding the fundamental mechanisms that govern laser-tissue interactions, could explain some degree of dissatisfaction and the delay between the invention of the laser and its successful clinical applications. To overcome this, within the last twenty years, a better understanding of light propagation into turbid media has been attained, providing tools for the precise prediction of laser-tissue interactions and for the optimization of clinical laser applications, with collaboration of physicians and physicists. For example, in laser surgery, to treat the problems concerning the interaction mechanism(s) during laser ablation, the interdisciplinary approach could answer the logically born question: what laser type, emission wavelength, interaction time and energy fluence is the best?

As the main intention of this work is to emphasize the potential difficulties and complications arising from either under- or over-estimation of laser dosimetry, we have chosen to present some experimental and theoretical examples. These demonstrate the quantification of the laser effect to evoke a basic feeling for using certain dosimetry protocols, in some significant biomedical Theranostics applications. As this is a vast field, we selected some applications for which we have previous experience in the level of basic and pre-clinical research and that are particularly relevant to laser ablation in surgical interventions and to laser propagation in tissues, during either laser spectroscopy or PDT.

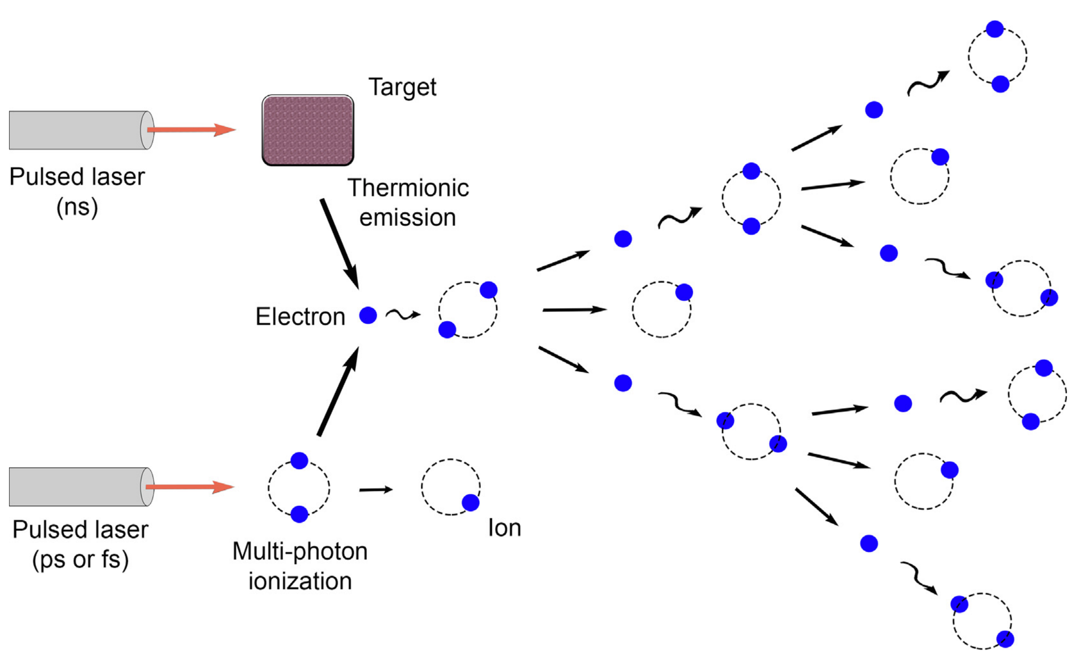

Fig. 6. Schematic representation of the photomechanical interaction mechanism. Short and ultrashort laser pulses, incident on a target, start photo-ionization of the target either by thermionic electron emission or by multiphoton absorption, generating electron avalanche which results in plasma formation.

4.1. Biomedical laser applications in surgical interventions – Efforts for dosimetry of laser ablation

The photothermal ablation interaction, which is the basic mechanism of laser cutting involved in the laser surgical interventions, is not yet totally understood and therefore, the development of a dosimetry model is still a difficult task, despite the fact that several theoretical models have been developed to predict the ablation rates and the crater quality. The basis for laser ablation dosimetry is the simple theoretical model of photon absorption, the well-known exponential attenuation law (Beer – Lambert law):

$$F_x = F_0 \cdot e^{-\alpha x} \tag{2}$$

where F_x and F_0 are the laser energy fluence per pulse (J/cm^2) at a depth x in the tissue and at the surface correspondingly, and α is the absorption coefficient of the tissue.

The photo-ablation effect only happens if the absorbed energy fluence is equal or greater than the threshold laser energy fluence, F_{th} (J/cm^2). The ablation depth per pulse, d, is (according to Eq. (2)):

$$d = (1/\alpha) \cdot \ln(F_0/F_{th}), \tag{3}$$

The logarithmic dependence of the ablation depth on the pulsed laser fluence is well known for laser ablation of biological tissues and tissue simulators. As a consequence of this model, any attempt for laser ablation dosimetry (i.e. to predict the penetration depth, the ablation rate, the temperature distribution and the thermal damage zone) is strongly dependent on the estimation of target's absorption coefficient. As the predominant component of soft tissues is water, the majority of laser ablation dosimetry efforts have been based on the water absorption spectrum, assuming that tissue optical properties are dominated by water absorption. Fortunately, hydroxyapatite, the major component of hard tissues (bones and dental tissues), absorbs preferentially in mid-IR, facilitating the modeling of mid-IR ablation for both soft and hard tissues, only for this spectral area.

In the last decade, significant advances have been made in the development of theoretical models to predict laser light energy deposition and ablation rates in biological tissues. These models are used to guide experimental work rather than clinical studies, and the appropriate dosimetry of laser ablation in surgical interventions is still under question. Parallel to biomedical applications, lasers entered and conquered other technological fields, as the polymer micromachining for photolithography and microelectronics. In literature, many experimental and computational simulation models have been developed in order to study the interaction between short pulsed laser radiation and polymers [13–15] and to elucidate the ablation mechanism(s) for other applications. Since several biocompatible polymers are used as biomedical implants, biosensors and tissue simulators/phantoms, the majority of experimental and theoretical studies for laser ablation dosimetry were first performed on polymers (considered as homogeneous tissue simulators), before the efforts on animal or human tissues [13–15].

A comprehensive and extended review of the mechanisms of pulsed laser ablation of biological tissues was published by Vogel and Venugopalan in 2003 [16], covering the fundamental mechanisms involved in pulsed laser tissue ablation. Remember that photobiological effects depend on both the physical parameters of the laser beam (e.g. time of interaction or pulse width, laser emission wavelength) and the physical tissue properties (e.g. absorption coefficient, scattering coefficient, thermal conductivity and thermal relaxation time). Ten years ago, we reported some experimental and theoretical results on Polymethyl methacrylate (PMMA) laser ablation, using two different solid-state pulsed lasers, emitting at the same visible wavelength (λ = 532 nm) but with different pulse widths, namely at ps and ns pulse duration, respectively [17]. The laser ablation mechanism was examined separately in each case and a mathematical model was developed. Due to its biocompatibility with human tissues, PMMA is widely used not only as tissue phantom but also in various medical applications, such as bone cement for fixation of prosthetics to bone [18]. In Ophthalmology, PMMA is a very important biocompatible polymer, used as ophthalmic tissue simulator (e.g. cornea) and for fabrication of intraocular lenses. Obviously, PMMA is transparent in the visible range of the spectrum while it absorbs in mid-IR. As a single photon of visible light does not has enough energy to excite an electron from the valence to the conduction band, in a transparent material, multiple photons are required for excitation. With this assumption, the experimental data of ablation rate versus laser fluence in the article of Spyratou et al. [17] were in excellent agreement with the theoretically simulated curve, based on a two-photon absorption model (according to Sauerbrey and Pettit model [19]), for PMMA at λ = 532 nm and t_p = 100 ps, while for the same wavelength but for t_p = 6 ns pulse width a thermo-elastic photomechanical mechanism was considered (Paltauf and Dyer model, [20]). The role of the pulse width is also important in a pure photothermal mechanism of laser-tissue interactions. However, thermal tissue ablation could be considered by the combined action of evaporation, ejection of liquid and elastic deformation of the region of radiation impact, mathematically simulated by expanded thermo-mechanical models.

Due to the complexity of the photothermal ablation mechanism, several important parameters, such as the already mentioned pulse width and tissue absorptivity should be considered. As a rule, which simplifies mathematical modeling, it is supposed that the optical properties of the tissues are dominated by water absorption (especially for soft tissues), but experimental data on various tissue models deviate sometimes from this hypothesis. Obviously, in relatively water free tissues, such as bone or dental tissues, the photothermal mechanism of the IR laser ablation cannot be attributed exclusively to water absorption characteristics.

In recent times, the dynamic optical properties of tissue chromophores are considered, to fully understand tissue ablation. During the laser ablation procedure, the modifications inside tissue due to water loss involve variations of optical properties as well. Dehydration is important on tissue exposed to air, when the laser irradiation is sufficiently prolonged. Water has been postulated to be a major contributor to the mid-IR laser energy absorption. The investigation of the role of tissue hydration during laser ablation demonstrated higher ablation efficiency of hydrated dental tissue compared with the dehydrated samples, as shown in Fig. 7. In this graph, the ablation rate versus laser energy fluence for hydrated and dehydrated dental tissues, after mid-IR Er:YAG (λ = 2.94 μm) laser ablation, was recorded experimentally. In the graph, the full curves are the theoretical simulation according to a

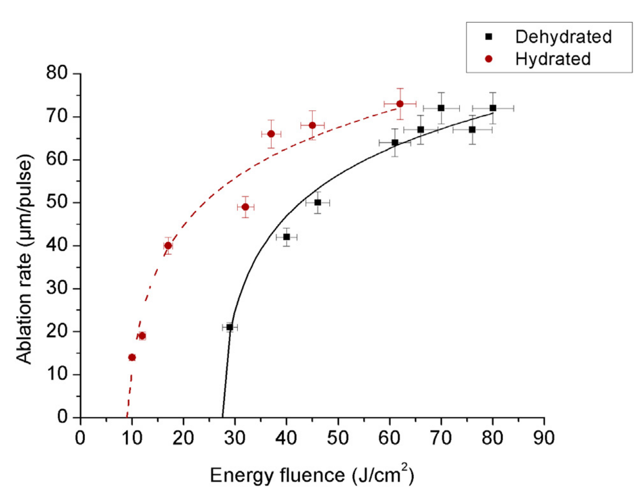

Fig. 7. Ablation rate versus laser energy fluence for hydrated and dehydrated dental tissues after Er:YAG laser ablation in the free-running mode (pulse duration 80 μs).

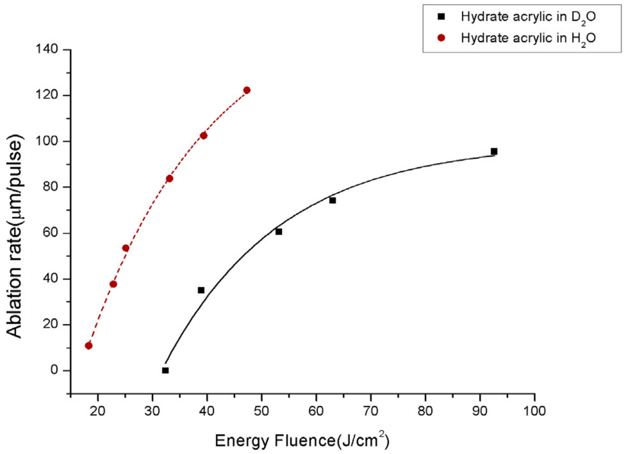

Fig. 8. The role of water in mid-IR laser ablation of hydrophilic acrylic intraocular lenses (IOLs) in two different cases: IOLs immersed in H_2O and IOLs in which the liquid phase changed from H_2O to D_2O.

photo-thermal mechanism, fitting well the experimental data.

One way to investigate the role of water in laser ablation is to change the liquid phase of tissue phantoms from H_2O to D_2O, because at mid-IR (namely at λ = 2.9 μm) the optical properties of H_2O and D_2O (heavy water) strongly differ [21]. Ten years ago we investigated experimentally the role of tissue hydration during laser ablation by the deuteration technique. An Er:YAG laser (λ = 2.94 μm) was used for ablation of hydrophilic acrylic intraocular lenses, with different H_2O and D_2O concentrations, expecting that the corresponding tissue phantoms will exhibit different ablation properties, if the water environment significantly contributes to the absorption mechanism at laser ablation regime. This was verified, both experimentally and theoretically, by the deuteration technique. The hydrophilic acrylic lenses with the higher concentration of H_2O gave the most satisfactory results regarding ablation efficiency [17]. The experimental data were successfully fitted using a mathematical model, based on a pure photothermal mechanism for soft intraocular lens ablation with mid-IR laser [17]. Some quantitative results are also illustrated in this work, in Fig. 8. Hence, it is obvious that knowledge about the changes in optical properties is needed for planning safer and more accurate laser treatments.

Even from the few mentioned reports we can notice that the laser ablation mechanism of polymers and tissues is a complex process that cannot be described by a simple mathematical model or a dosimetry protocol. Although a complete theoretical simulation is very difficult or un-realistic to be performed in general surgery, a successful mathematical model of the ablation behavior is definitely valuable in any laser dosimetry of modern photorefractive procedure and delicate surgery intervention. Thus, the profound understanding of the variety of laser-target interactions offers a toolkit for controlled, predictable and precise local action for delicate vision correction applications in Ophthalmology. After a careful search in literature for refractive surgery specialty, as well as after personal discussions with myopia correction laser specialists, we ascertained that the relevant laser manufacturers usually create their own algorithms that are proprietary. To do so they take into account some aspects for ablation depth as a function of incident laser fluence. However, some deviations of Lambert-Beer's law can result in discrepancies between real and expected post-surgical outcome of corneal refractive surgery [22]. Today, the Munnerlyn approximated formula is also used to estimate ablation depth (in microns) per diopter of refractive change that is equal to the square of the optical ablation zone measured in millimeters, divided by three [23]. Definitely, the cornea reshaping with lasers is a delicate procedure and even the environmental conditions in the operating room, e.g. the atmospheric pressure and the relative humidity at the time of surgery, will cause alterations in the end result [24], as we mentioned in this paragraph for the role of hydration in the ablation rate. Finally, each doctor has to improve the pre-alleged dosimetry (Munnerlyn formula approximation or manufacturer's software) based on his/her real practical experience, to reduce clinically significant errors.

Apart from the quantitative aspects of the ablation behavior, regarding ablation rates and efficiency, surface quality of tissue and tissue simulators are also a prerequisite in laser treatment. To give an example, we will discuss a relatively "negative" experimental result from laser ablation of biocompatible polymers.

In our previous studies we performed preliminary Intraocular Lens (IOL) surface structuring experiments on commercially available hydrophobic acrylic IOLs, using the 3rd harmonic of the Nd: YAG laser (λ = 355 nm, pulse duration 7 ns and photon energy of ~3.5 eV). The morphology of the ablated IOL surface, examined with a scanning electron microscope (SEM), revealed craters with asteroid cross-section and intense cavitation phenomena (see Fig. 9b).

In an effort to explain the morphology of these craters, one can consider the probability that their structure may be due to two reasons. The first concerns the mechanism of interaction of the beam with the specific polymeric material. It is supposed that the excess energy of

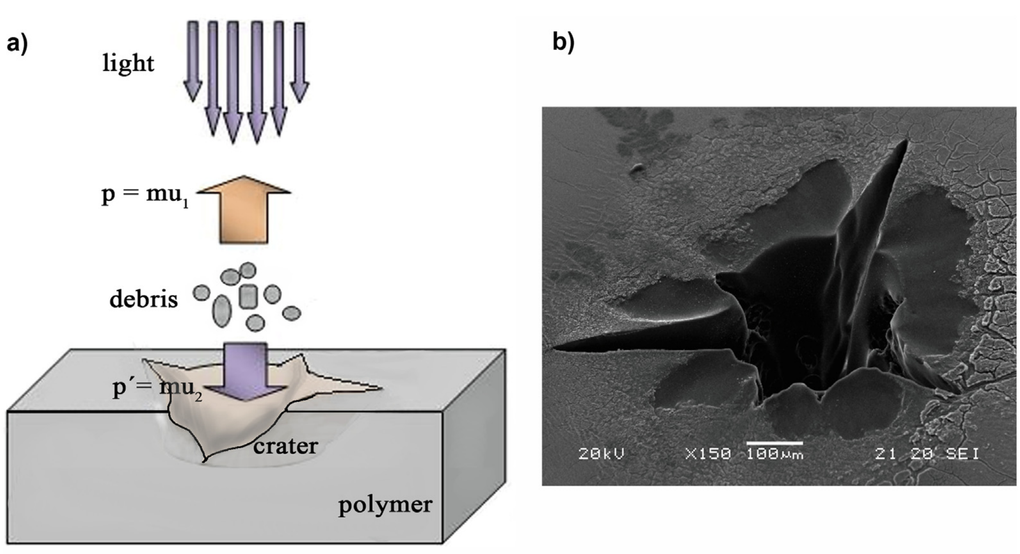

Fig. 9. (a) Schematic representation of the photomechanical action of a laser beam interacting with a polymer surface. Light's momentum results in debris creation and propagation of mechanical waves that can generate cracking on the material. (b) SEM image of an intraocular lens (Alcon MA30BA − 23D), irradiated with Nd:YAG laser (λ = 355 nm, f = 10 Hz, F = 5.3 J/cm^2, 600 pulses).

laser pulses that have broken the material's molecular bonds is converted into thermal-kinetic energy of the excised fragments. The fragments have momentum **p** = m·**u** (where m is the ejected material mass, **u** is the fragment velocity) and their recoil from the interior of the crater causes mechanical waves, as shown graphically in Fig. 9a. Expansion of these waves leads to the creation of cracks that impart a characteristic asteroid shape to the craters. Obviously, any alteration or material debris deposition on polymer surface is a discarded effect, as a potential source of visible light scattering and/or a cause for cell attachment and clouding of implanted IOLs, in the case of the *in situ* laser intervention. The second reason could be a totally unwanted situation, in which the ablation crater is reflected an inhomogeneous, non-Gaussian laser beam profile. Obviously, the deep understanding of the real cause for the described bad-quality result is crucial for resolving the problem. Medical Physicists and not Physicians could check firstly the laser beam's profile, according to manufacturer instructions, to exclude the second possible reason for irregular polymer ablated surface.

4.2. Biomedical laser applications in Theranostics – Efforts for dosimetry of light propagation

The interaction of the coherent electromagnetic radiation with human tissues results to scattering, absorption and fluorescence, providing secondary emission of photon signals which can be helpful in the detection process. As a consequence, the laser based optical diagnostic methods are used to enable earlier, non-invasive and possibly repeatable detection and monitoring of human cancer and other diseases.

Modeling light transport into tissues is crucial to the profound understanding of laser-tissue interactions. Speaking about "*laser-tissue interactions*" it is important to emphasize that we refer to the real meaning of the word "interaction". Specifically, in diagnostic applications we monitor mostly the influence of tissue on light beam propagation (e.g. absorption, reflection, scattering), while in therapy the important issue is the effect of light beam on tissue integrity (e.g. photothermal, photochemical or photomechanical damage).

Definitely, the heterogeneity in depth distribution of different chromophores influences the spatial distribution of the laser beam. This must be considered seriously for any effective laser-based therapeutic procedure, where there is critical dependency on the delivery of sufficient light to the target volume for inducing the desired effect. Experimental measurements of the spectroscopic behavior of the tissue and the mathematical prediction of laser energy deposition can provide the clinician with the necessary information to customize the treatment parameters and thus to optimize the efficacy of laser therapy [25].

Since photons move through tissue in zigzag paths, in contrast to the straight-line routes taken by X-rays, biophotonic imaging (e.g. laser induced fluorescence spectroscopy, optical coherence tomography) involves the difficult task of reconstructing an image from highly scattered photons. A simplified measurement of light transmission, like one through a homogeneous clear sample of thickness × to calculate the absorption coefficient and concentration (as illustrated in Fig. 10a), introduces several errors because light can travel from source to detector through many different multiple scattering paths in a tissue (as illustrated in Fig. 10b). Therefore, instead of the simple exponential law of light transmission through a homogeneous tissue sample of thickness x, according to Beer-Lambert law, a more sophisticated mathematical approximation is needed.

An effective and relatively simple mathematical approach, for non-invasive tissue optical research, is that of the Monte Carlo (MC) simulation. The MC technique is a very flexible method for simulating light propagation into tissue, i.e. to trace optical rays propagating in complex inhomogeneous, randomly scattering and absorbing media as human tissue. The simulation is based on the random walks that photons make as they travel through tissue, which are chosen by statistically sampling the probability distributions for step size and angular deflection per scattering event. After propagating many photons, the net distribution of all the photon paths yields an accurate approximation to reality [26,27].

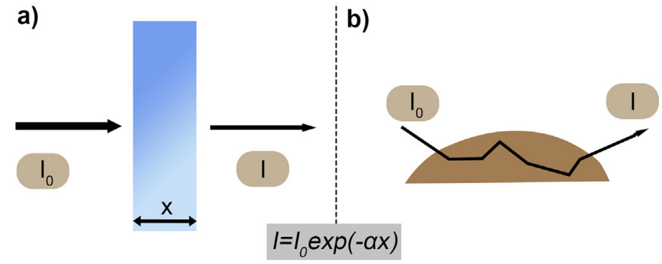

Fig. 10. (a) The intensity of coherent light transmission through a homogeneous clear slab of thickness x, according to Beer-Lambert law (I_0 and I are the intensity at the surface and distance x respectively, α is the absorption coefficient). (b) The intensity of coherent light transmission through an inhomogeneous tissue sample, after multiple scattering paths in the tissue.

Over the past decades, MC simulation has been successfully introduced for research and development in Medical Radiation Physics dosimetry, although its introduction into clinical practice delayed because of the prolonged calculation time required (the interested reader could obtain a compact 'primer' on different approaches to MC radiation treatment planning in the brief overview of Spezi and Lewis [28]). In 90′s, a customized approach for photons in the UV-VIS-IR part of the electromagnetic spectrum was introduced in Biomedical Optics, originally for counting the fluence rate distribution in biological tissue. The aim was to estimate laser radiation dose [26] or to compute tissue optical microscopic coefficients, when macroscopic properties have been measured, to help in PDT dosimetry [29]. Currently, this approach has become a primary tool for a number of diagnostic and monitoring applications in Biomedical Optics, in addition to laser dosimetry protocols. For example, MC technique has been used for simulation of skin optical and near-IR spectroscopic behavior, incorporated with computational model of human skin [30,31]. During the first era of applying MC algorithms in Biophotonics, the main limitation for translation of research to clinical applications was the requirement of large computation power. In our days, this problem becomes less important thanks to the modern developments in computers.

In the last two decades we have tried to evaluate the utility of MC modeling for measuring the light intensity distribution in skin samples with a pulsed UV (nitrogen laser, λ = 337 nm) and a cw VIS laser source (He-Ne laser, λ = 633 nm) [25]. In that effort we presented the simulation results of the spatial light distribution within a five-layer model of human skin tissue and the contribution of endogenous fluorophores to the detected signal. More specifically, the influence of varied hemoglobin and melanin distribution was studied. The distribution of continuous and pulsed laser light absorbed density was also considered in relation to the temperature dynamics in UV and visible laser irradiated skin, influencing a laser-induced fluorescence (LIF) or PDT application [32,33]. As a consequence, in order to avoid tissue destruction from unwanted thermal injuries, a proper energy density should be taken into consideration, as well as appropriate pulse duration (exposure time) and thermal relaxation time of the tissue. Selective photothermolysis could serve as an example, where choosing the appropriate wavelength, appropriate energy density and the appropriate pulse duration, the target dye can be thermally destroyed without damaging the surrounding tissue [34,35].

Non-invasive diagnosis is required in many treatments, like those concerning deeper skin- tissues (e.g., angiomas), where the use of UV photons is not appropriate due to the high absorption of melanin in this region. On the other hand, absorption of melanin is limited at longer wavelengths where light can penetrate into tissue selectively, depending on the pigments under study. Therefore, deeper radiation penetration, without the risk of epidermal injury is preferable e.g. use of longer wavelengths [34,35]. In that region radiation absorption by the chromophores melanin and hemoglobin is limited, even though melanin absorption is greater than that of hemoglobin [36]. Thus, tissues located deeper than the penetration depth of visible radiation are not approached. This problem cannot be solved simply by increasing beam's energy or energy density since thermal side effects will occur.

As a result, research and development efforts for dosimetry of light propagation in biomedical laser applications are in progress in both experimental and computational fields, aiming to their entrance to clinical practice. For example, in a 2018 study the development of a monitoring system was reported, based on an integrating sphere, in order to study the temperature-dependent changes in optical properties of a lipid emulsion [37]. In that study MC simulations were performed to observe the difference in light propagation within a tissue, using the measured optical properties.

4.3. Biomedical laser applications in phototherapy – Efforts for dosimetry in photodynamic therapy

Let's recall that lasers are used in the medical field for the cure of various pathological conditions or as palliative treatment options. The two major fields of their non-surgical therapeutic applications are photothermal therapy (PTT) and photodynamic therapy (PDT).

In PTT the energy is transferred from the electromagnetic wave to the tissue which is then heated and thermally destroyed. The use of laser offers an alternative path from using radiofrequencies (RF), microwaves or high-intensity focused ultrasound (HIFU). Epigrammatically, the main problem when using RF or microwaves is the difficult focusing of their energy that results in temperature gradients, while in the HIFU case the thermal distribution is restricted [38]. On the contrary, two of the fundamental laser characteristics, namely coherence and monochromaticity, offer a more predictable and smooth temperature distribution. The dosimetry of PTT with lasers (laser-induced interstitial thermotherapy (LIIT)) is confined by the level of accuracy of the parameters used in photo-thermal distribution equations.

On the other hand, PDT is a non-invasive or minimally invasive treatment technique, based on the simultaneous action of the following three factors: i) photosensitizing agent (PS), able to photochemically eradicate malignant cells, ii) molecular oxygen ($^3O_2$), generating highly reactive singlet oxygen, and iii) non-thermal monochromatic light irradiation. The photo-generated singlet oxygen ($^1O_2$) (in Type II mechanism [39]) attacks cellular targets, causing destruction through direct cellular damage, vascular shutdown and activation of an immune response against targeted cells.

In PDT, the laser light is chosen to coincide with the maximum absorption wavelength of the photosensitizing agent molecules, usually in the red or near-IR part of the spectrum. The ideal light wavelength must give the proper photonic energy needed to photo-activate molecules for excitation and singlet oxygen production, as well as to ensure a good penetration of light in the tissue. These requirements impose the use of photons in the 600–850 nm region of the electromagnetic spectrum, since at wavelengths higher than 850–900 nm the photons might not have sufficient energy to produce $^1O_2$. On the contrary, the most energetic photons in UV – VIS region of the spectrum have lower penetration depth.

A review of the first twenty years of PDT was presented in 1998 by Dougherty et al. [40], receiving thousands of citations. Ten years later, in 2008, Wilson and Patterson published a comprehensive review paper [41], summarizing the status of PDT clinical applications with emphasis on the contributions of physics, biophysics and technology, and the challenges remaining in the optimization and adoption of this treatment modality. Recently, Kim et al. [42] and Zhang et al. [43], published two very interesting papers regarding the properties and the recent advances in the development of new PSs. Therefore, from the vast growth of the literature, it is more than obvious that PDT dosimetry is a rapidly expanding and propitious for studying field.

A very interesting and trouble-provoking issue is the complexity of PDT dosimetry of the three, simultaneously acting, essential components — light, photosensitizer and oxygen, in order to control and optimize the PDT efficacy. For example, an insufficient PS concentration in malignant tissue can lead to incomplete treatment of tumor, resulting in recurrence. On the contrary, PS overdose may cause significant damage to the healthy surroundings during the photodynamic treatment of the tumor [44].

Definitely, at least the first period of clinical PDT treatments was ruled worldwide by empirically prescribed dosimetry approaches. In an effort to develop a non-empirical monitoring method for PDT dosimetry, we measured in a preliminary work the absorption and laser induced fluorescence spectra in tissue phantoms, for identification and quantification of the concentration of the photosensitizer m-THPC [45]. By searching the relevant literature we can realize that still, in nowadays, the most recent and complete available protocol for guidelines in the dosimetry of PDT is the report No. 88, of the American Association of Physicists in Medicine (AAPM) [46], which also summarizes the relevant basic physical quantities and their definitions (at this point the interested reader may refer to AAPM report No. 57 for further information about physical quantities in medical applications of light [47]).

As mentioned above, the successful outcome of PDT is based on the concentration of the three key parameters, namely, [PS], [$^3O_2$] and singlet oxygen leading to cell death [$^1O_2$]$_{rx}$ (apparent reacted singlet oxygen). As an example we present Fig. 11, where the reader can see the spatial distribution of these parameters, presented for a radiation-induced fibrosarcoma (RIF) virtual case, studied in previous published work [48]. It was assumed that C3H mice were the carriers of RIF tumors and that they were subjected to PDT using Photofrin (for the values of the parameters used see Table 1 and for the problem's geometry see reference [48]). As it can be observed, [$^1O_2$]$_{rx}$ at the upper tumor layers is significantly higher than at deeper layers, and since cell death is inextricably correlated to [$^1O_2$]$_{rx}$ it is reasonable to assume that the necrotic effect will be more evident at that area. As a result, special attention should be paid when irradiating tumors with point source geometries, like the one used in the above mentioned study. The limited light penetration into tissue can be addressed by using other source geometries (i.e. line sources), larger spot sizes [49], and wavelengths in the infrared region of the electromagnetic spectrum, or a combination of the above.

The importance of adequate dosimetry in PDT can be understood from Fig. 12, where the different outcome of PDT is presented in three virtual cases, based on previous published work [48,50]. In the first case we studied a cylindrical structure representing rat skin tissue affected by RIF and treated with Photofrin – PDT. In the second case the same structure was assumed to have been affected by basal cell carcinoma (nBCC) and treated with ALA-PpIX – PDT. In the third case the same structure was representing a rat liver surface affected by metastatic cancer (i.e. colon adenocarcinoma) and treated by mTHPC - PDT (for the values of the parameters used see Table 1 and for the problems' geometry see reference [48]). In Fig. 12a the light fluence rate profile is plotted versus depth, at the axis of the light beam. The noticeable difference in light penetration is anticipated due to the different optical properties of the three geometries. It is interesting to notice that after the first few micrometers there are more similarities in light distribution between the nBCC and the colon adenocarcinoma metastasis, than between the two skin cancers. This is attributed to the combination of the optical properties and the photochemical parameters used for the former two types of malignances. Hence, knowledge of the values of cancerous and healthy tissues' optical properties is crucial in order to design trustworthy and personalized PDT. Fig. 12b presents the amount of minimum initial molecular oxygen [$^3O_2$]$_0$ needed in order to achieve a constant value of [$^1O_2$]$_{rx}$, for various oxygen supply rate (g_0) values. The differences in light distributions and in photochemical parameters

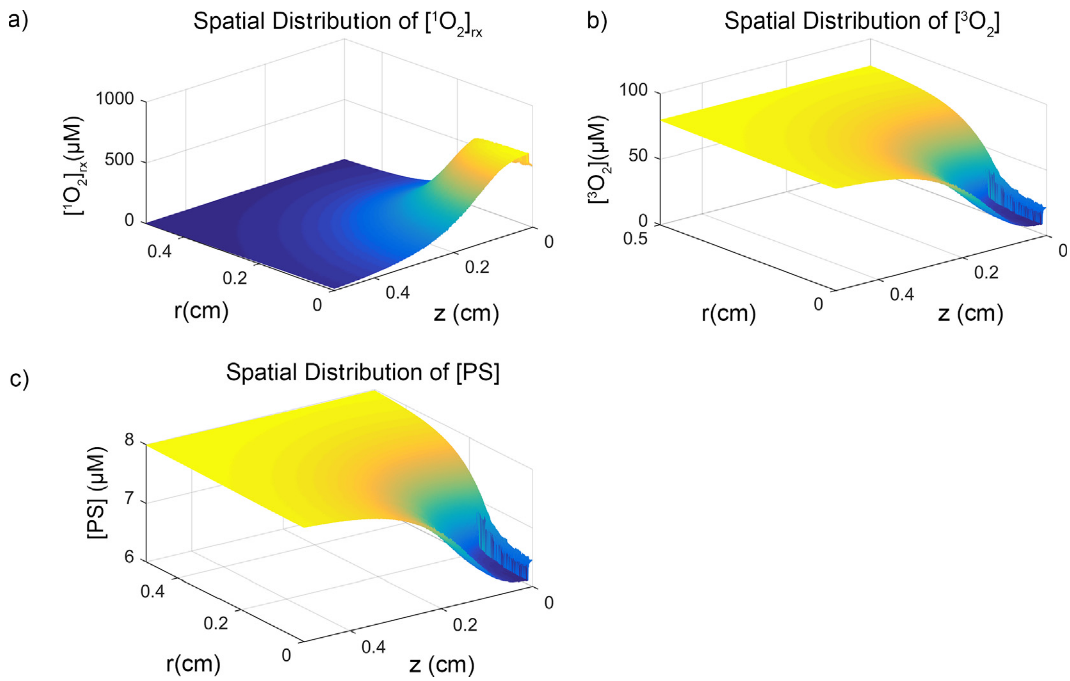

Fig. 11. Spatial distribution of the three key parameters for a RIF case. The production of singlet from molecular oxygen leads to photosensitizer's degradation.

of PSs have a distinguishable impact on the combination of the above parameters that has to be achieved in order to reach certain $[^1O_2]_{rx}$ values.

Irradiation of RIF and nBCC tumors was applied using a 630 nm laser source and of Colon adenocarcinoma metastasis using a 652 nm laser source. In all cases the laser beam was assumed to be flat and with radius of 5 mm.

5. Summary and future perspectives

In summary, the purpose of this work was to highlight the existence of a synergy between the role of Medical Physicists in ionizing radiation and non-ionizing radiation medical applications, especially in determining the optimum radiation dosimetry that ensures the maximum treatment efficacy and safety. It is generally accepted that the 20th century was characterized by several paradigmatic changes and applications of ionizing radiation in both therapeutic and diagnostic clinical approaches, to achieve the best medical outcome for patients. In the 21st century, the broad range of biomedical applications of laser light, from the non-ionizing radiation part of the electromagnetic spectrum, is definitely interrelated to dosimetry, treatment predictive planning and diagnostic/monitoring assessment. Without doubt, the effective, safe

Table 1
Optical and photochemical parameters used for the virtual tumor models.[a]

Optical parameters			Photochemical parameters	
Layer	Parameter	Value	Parameter	Value
RIF tumor	μ_α	1.03 (cm^{-1})	ε[b]	0.0035 ($cm^{-1}\,\mu M^{-1}$)
	μ_s	269.2 (cm^{-1})	ε[c]	0.0030 ($cm^{-1}\,\mu M^{-1}$)
	g_f	0.95	ε[d]	0.0480 ($cm^{-1}\,\mu M^{-1}$)
	n	1.54	ξ[b,c]	$3.7{\cdot}10^{-3}$ ($cm^2\,mW^{-1}\,s^{-1}$)
			ξ[d]	$30.0{\cdot}10^{-3}$ ($cm^2\,mW^{-1}\,s^{-1}$)
nBCC tumor	μ_α	1.17 (cm^{-1})	σ[b]	$7.60{\cdot}10^{-5}$ (μM^{-1})
	μ_s	113.4 (cm^{-1})	σ[c]	$9.00{\cdot}10^{-5}$ (μM^{-1})
	g_f	0.80	σ[d]	$2.97{\cdot}10^{-5}$ (μM^{-1})
	n	1.40	β[b,c]	11.9 (μM)
			β[d]	8.7 (μM)
Colon adenocarcinoma metastasis	μ_a	1.40 (cm^{-1})	δ	33 (μM)
	μ_s	275.5 (cm^{-1})	g_0	1 ($\mu M\,s^{-1}$)
	g_f	0.95	$[^3O_2]_0$	70 (μM)
	n	1.36	$[^1O_2]_{rx,0}$	0
			$[S]_0$	7 (μM)
			φ [e]	100 (mW/cm^2)
			Total fluence [e]	90 (J/cm^2)

[a] Symbols: (μ_α) – absorption coefficient, (μ_s) – scattering coefficient, (g_f) – scattering anisotropy factor, (n) – refractive index, (ε) – extinction coefficient, (ξ) – specific oxygen consumption rate, (σ) – specific photobleaching ratio, (β) – oxygen quenching threshold, (δ) – low concentration correction, (φ) – fluence rate.
[b] For Photofrin.
[c] For ALA-PpIX.
[d] For mTHPC.
[e] At tissue's surface.

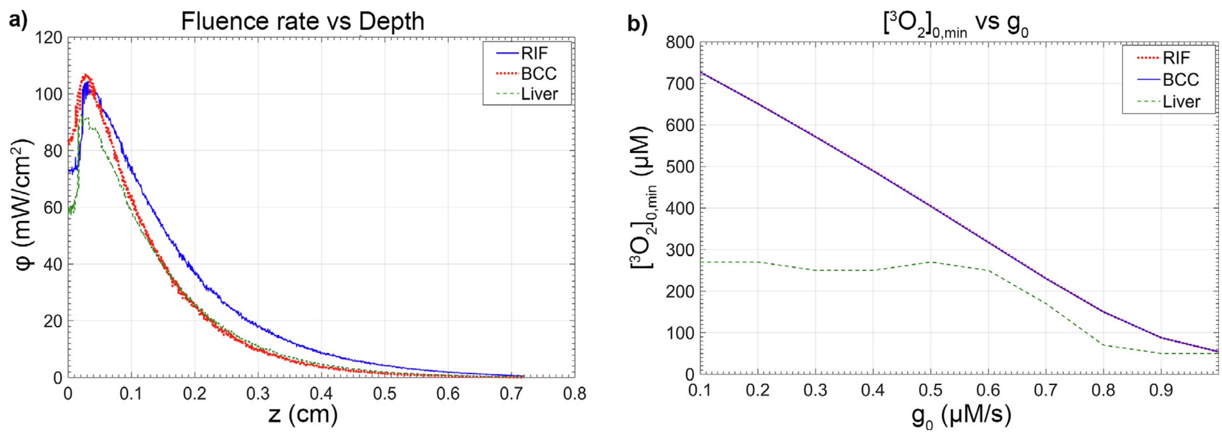

Fig. 12. (a) Light fluence rate profiles versus depth for RIF, nBCC and colon adenocarcinoma metastasis at liver surface. (b) Correlation between the minimum value of initial $[^3O_2]$ needed and oxygen supply rate (g_0), in order to achieve $[^1O_2]_{rx}$ = 0.8 mM.

and ethically acceptable use of laser technology in biology and medicine requires interdisciplinary collaboration between physicists, engineers and physicians at the research, preclinical and clinical level.

Particularly in cancer PDT and other diseases, the role of physicists in providing the basic tools and interpretations of dosimetry is well known. As stated in a recent comprehensive review of Pogue et al., "the goal of providing a complete computational framework for estimating dose has been a long desired ideology" [51]. Moreover, while bridging ionizing and non-ionizing radiation in cancer therapy we face the tendency to develop novel cancer treatment strategies, based specifically on dual mode therapeutical schemes. An example is applying ionizing radiation and biophotonic principles, using non-ionizing photons (e.g. PDT, PTT) [52].

Regarding the 21st century's achievements in laser physics and technology, we emphasize that the history of laser intensity achieved levels reflects the different laser-matter interaction periods. Furthermore, we currently face progress that generates new perspectives in laser-driven therapies. Since its advent, the laser has been mainly effective in acting on the level of chemical bonds in the electron-volt (eV) energy range. Over the past thirty years, studies conducted in the sub-relativistic and relativistic regimes [53] allowed a rapid six-orders-of-magnitude increase in available intensities. Moreover, taking into account that the visible laser-matter interaction is governed by the electron relativistic behavior we faced a plethora of novel effects [54], such as X-ray generation and ion and proton acceleration. The method of laser amplification invented in the mid-1980s by Strickland and Mourou [53] has enabled a new generation of table-top lasers that produce ultrashort pulses of extremely intense light (e.g. with pulse widths around 30 fs). These result in particle beam acceleration from the rear side of a laser-irradiated thin foil, based on the laser-matter interaction mechanisms (massive multiphoton ionization and plasma creation in the target) [55]. Potential applications include high-resolution medical imaging, inexpensive precision radiation therapy, nuclear fusion, and research in numerous subfields of physics. The recognition of the fascinating physics that governs these phenomena was crowned with the Nobel Prize in Physics 2018 that was awarded "for groundbreaking inventions in the field of laser physics" with one half to Arthur Ashkin "for the optical tweezers and their application to biological systems", the other half jointly to Gérard Mourou and Donna Strickland "for their method of generating high-intensity, ultra-short optical pulses" [56].

Closing this work, a question is naturally formed: What do we expect from the advances in Physics for the field of Medical Physics?

Certainly, any effort to answer this question results in enumeration of several fields. We suppose that the topics presented in our work have highlighted some of them and the role of Medical Physics in the optimization of laser-based biomedical procedures will emerge. Moreover, recent advances in laser physics and technology have a very interesting impact in Biomedical Physics: In Oncology the efforts in finding and curing cancer impose the bridging of ionizing radiation (where the role of Medical Physics is inevitable) with non-ionizing laser radiation (where the role of Medical Physics is gradually recognized). By generating highly penetrating radiation, such as X-rays or particle beams, laser-driven charged-particle accelerators may be used for cancer diagnosis and therapy. Although still a not trivial procedure, the treatment of cancer with laser-driven accelerated protons offers a significantly cheaper and relatively convenient route to generate proton beams instead of the very expensive conventional particle accelerators. This is a paradigm for which a well-trained Medical Physicist in both radiation physics and laser-matter interactions is needed for dosimetry, treatment planning and safety responsibilities.

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