Review

Principles of Lasers and Biophotonic Effects

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ABSTRACT

In this review, we discuss how, due to a variety of different interactions between laser radiation and biological tissue, the laser has become an established instrument in most medical fields. Depending on the interaction time and the effective power density, three types of laser tissue interaction can be distinguished: photochemical effects, photothermal effects, and photomechanical and photoionizing effects. After a description of the physical mechanisms, the typical parameters, and the medical applications of these effects, a review of the laser types used in medicine is given. For percutaneous laser disc decompression (PLDD), lasers in the near-infrared region (Nd:YAG, Ho:YAG, and diode lasers) and with visible green radiation (frequency doubled Nd:YAG, called “KTP laser”) were reported to be effective.

INTRODUCTION

Among the first laser applications were material processing such as cutting, drilling, and welding, as well as the use in medicine. The prerequisite for the medical laser application is the accordance of technical possibilities with medical requirements.

The basic process of light amplification by stimulated emission of radiation—giving the laser its name—is taking place in a long, narrow column of material, which is excited by an external source of energy (e.g., light, electricity, chemical reaction). Placing this laser medium between two mirrors (into an optical resonator) intensifies the interaction between the electromagnetic field and the excited material by orders of magnitude. Making one of the mirrors partly transparent allows the resulting laser beam to exit the resonator. This laser radiation displays three important characteristics: it is coherent (i.e., all the wave trains are exactly in phase, in time as well as in space), well collimated (i.e., the radiation beam is almost parallel), and monochromatic (i.e., all photons have the same wavelength, frequency, and energy). By using different lasing media, laser systems emitting light of different wavelengths can be designed beginning in the ultraviolet region at about 200 nm and reaching into the infrared up to a wavelength of 10 µm. In the region of wavelengths between 300 nm and 2.2 µm, it is possible to transmit laser light in very thin but still mechanically robust quartz glass fibers (core diameter 0.2–0.6 mm) on the basis of successive total internal reflection. This permits use in endoscopic techniques.

Laser systems differ also with regard to duration and power of the emitted laser radiation. In continuous wave lasers (cw-mode) with power outputs of up to 10^3 W, the lasing medium is excited continuously. With pulsed lasers, excitation is effected in a single pulse or in on-line pulses (free-running mode). Peak powers of 10^5 W can be developed for a duration of 10 ms to 100 µsec. Storing the excitation energy and releasing it suddenly (q-switch mode or mode-locking) leads to a peak power increase of up to 10^10 to 10^12 W, and a pulse duration of 100 nsec to 10 psec.

BIOPHYSICAL CONSIDERATIONS

In order to determine the interaction between laser light and biological tissues quantitatively, the physical parameters of the biological object must be related to the parameters of the laser light. The degree and extent of the effect depend on the properties of the tissue, which are determined by the structure, water content, and blood circulation, that is, absorption, scattering, reflection, thermal conductivity, heat capacity and density, as well as on the parameters of the laser beam, that is, its power density, energy content, and wavelength (Fig. 1).

Depending on the duration of the laser irradiation on the tissue (interaction time), on the one hand, and the laser irradiance...
at the surface or in the interaction volume (effective power density), on the other hand, three types of laser tissue interaction are distinguished (Fig. 2):

- Photochemical effects (10 sec–1000 sec; 10^{-3}–1 W/cm^2)
- Photothermal effects (1 msec–100 sec; 1–10^6 W/cm^2)
- Photomechanical and photoionizing effects (10 psec–100 nsec; 10^8–10^{12} W/cm^2)

The photochemical and photothermal processes can be achieved with quasi-continuous wave irradiations. The photoablativ and photomechanical processes are induced with short pulses in the high-power regions.

**Photochemical effects**

With extremely long interaction times and low-power densities, photochemical transformation occurs by absorption of light with no primary heating of the tissue. The most prominent example for photochemical effects is photosensitized oxidation. The combined use of laser light and...
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Injected photosensitizers, for example, porphyrins, initiate a cytotoxic process. Most of the tissue is destroyed after excitation of the photosensitizer by laser light. The stimulated sensitizer undergoes a series of intramolecular chemical reactions that lead to the oxidation of various cellular components. The fact that the residence time of some photosensitizers in pathologic tumor tissue is longer than in healthy tissue permits selective tumor eradication. In photodynamic therapy (PDT), use is made of argon-pumped dye lasers (1 W at 630 nm, cw) or diode lasers (e.g., 10 W at 633 nm). Synthetic porphyrins such as hematoporphyrin derivates (HPD) have significant side effects, especially a sensitize time of some weeks. With the use of second generation photosensitizers, mainly 5-aminolaevulinic acid (5-ALA), such side effects do not occur.

The residence of injected photosensitizers in tumor tissue is also used for diagnostic purposes. When irradiated with ultraviolet light, fluorescence occurs and even a carcinoma in situ can be visualized. The fluorescence endoscopy for the detection of superficial carcinoma of the bladder and esophageus tumors is state of the art.

Biostimulation mainly for wound healing or pain relief with stimulation of microcirculatory effects also belong to this field. Systematic studies have not yet given reasonable explanations for the clinically observed improvements. Use is made of HeNe lasers (1–5 mW at 633 nm) and GaAs laser diodes (5 mW at 850 nm).

Photothermal effects

With decreasing interaction time and power density, the transition to photothermally induced effects begins. The main surgical applications for lasers are based on the conversion of laser light into heat. This thermal effect is broadly applied in surgery for tissue removal, cutting, and tissue coagulation with sealing of vessels and lymphatics, and for tissue welding in reconstructive surgery. The course of the thermal denaturation of tissue can be described approximately as follows. Both the structure and the function of living cells are determined, to large extent, by a wide variety of proteins. These macromolecules have a highly ordered structure that is stable at body temperature. If the temperature is increased locally to about 50°C or more, a certain percentage of the molecules passes into an energy-activated state, from which an irreversible transition into the denaturated state takes place. When this happens, the protein molecule loses its spatial arrangement and, consequently, its ability to function in the cell. Depending on the nature of the irradiated tissue, individual thermolabile enzymes may play a leading role in the tissue reaction. Then there is a delayed tissue necrosis, although little or no structural damage to the tissue can be seen immediately after the irradiation.

The optical and thermal properties of the tissue as well as the laser beam geometry and energy of the incident light influence the degree and extent of the thermal action. The most important optical parameter is the wavelength-dependent absorption of biological molecules. Since the building blocks of living systems, amino acids, proteins, and nucleic acids, despite their great variety, are made up of only a few basic elements, some fundamental rules can be formulated for the absorption of optical radiation. The main absorption of biological molecules occurs within the range of wavelength shorter than about 280 nm (ultraviolet). The far more molecule-specific vibrational and rotational absorption bands are all in the range of wavelengths longer than 1 µm (infrared). Visible laser radiation is hardly absorbed by biological material. One of the most important exceptions to this rule is the hemoglobin in the red blood corpuscles and melanin, which is stored as a pigment in the skin and also in large quantities in the pigment epithelium of the retina. A strong absorption in the green spectrum occurs in both substances. The high water content (60~80%) of most tissue leads to an extensive absorption of infrared radiation and thus to a very efficient energy transfer and heating of the tissue when irradiated with lasers of these wavelengths (e.g., Er:YAG or CO2 laser).

In addition to absorption, scattering must be considered as a further optical tissue parameter. Tissue is a highly structured medium, so that directed optical radiation is completely altered in its spatial distribution due to reflection, refraction, and diffraction. This scattering effect is mainly relevant when the absorption is weak.

The thermal properties of tissue—the heat capacity and conductivity—can be taken in the first approximation to be the same as those of water. However, estimation of the spread of the energy by thermal conductivity is often very difficult when tissue layers of strongly differing structure and complicated geometry are involved, such as the stomach wall, the retina, and the bladder wall, or when blood vessels give rise to a very non-homogeneous removal of energy due to the usually irregular blood flow.

The temperature increase and temperature distribution in tissue exposed to laser radiation depend on the energy absorbed by the volume of tissue and on the thermal properties of the tissue. According to the temperature in the tissue, changes—such as discoloration, coagulation, shrinkage, carbonization, and vaporization—occur (Fig. 3). Up to a temperature of 45°C, no essential organic changes take place and there is no irreversible tissue damage. Between 45°C and 50°C, enzymatic changes occur and an edema develops. Heating to more than 60°C for more than a few seconds results in coagulation (i.e., a denaturation of the tissue protein). Between 90°C and 100°C, cellular protoplasm begins to vaporize. Following desiccation and shrinkage of the tissue, its temperature rises rapidly to several hundred degrees, whereupon it carbonizes, vaporizes, and burns. As a matter of fact, the process involved in the thermal interaction between laser radiation and biological tissue are highly complex. This makes it difficult to develop suitable interaction models that permit an approximation of at least qualitatively the optimal laser parameters for an intended and expected interaction. The choice of wavelength determines the depth of penetration according to the kind of tissue and thus influences the interaction between the different tissue reactions. Thus, a consideration of at least the wavelength-dependence of absorption and scattering in the tissue leads to a simple explanation of the various thermal effects of laser systems used in surgery.

Photomechanical and photoionizing effects

A power density exceeding 10^7 W/cm² causes non-linear effects. The high irradiance generates strong electric fields, which lead either to a breaking of the intracellular structures or to a dissociation or ionization of the tissue material involved. Thus, laser light is converted into kinetic energy.
The so-called photoablative effect occurs only with energy densities above a certain threshold. Below this threshold, the affected tissue volume determined by spot diameter and penetration depth is not removed spontaneously, but the absorbed energy is converted into heat, which results in linear thermal effects. With energy densities exceeding the threshold, the photoablation effect starts and increases. Far above the ablation threshold, the ablation rate is saturated due to the plasma shielding of the laser beam. Due to high absorption, the threshold of the energy density necessary for photoablation can be achieved in the ultraviolet region using excimer lasers (10^6 W/cm² with 10 nsec) and with solid-state lasers of wavelengths 2–3 µm in the mid-infrared region.

Photoablation is a combination of tissue evaporation and expulsion of liquified material by hydrodynamic mechanisms. The high intensity of the laser radiation evaporates tissue, and the arising pressure ejects the molten tissue material from the irradiated area. The extent of this process depends on the elastic properties of the tissue and on its viscosity. The laser energy is used particularly for phase transitions such as vaporization and liquification, as well as for the kinetic energy of the expelled tissue particles. Due to the small amount of remaining energy, only minimal thermal damage occurs at the margins. In short, photoablation is a thermal effect with almost no thermal injury. This process runs so quickly that thermal conductivity and thus thermal effects have almost no impact.

Keratotomy is one of the applications in ophthalmology with short-pulse lasers. Use of photodisruption is also made in ophthalmology in microsurgical interventions within the eye without any damage to the healthy anatomic structure (e.g., for the destruction of the membrane of the lens capsule).

For the laser-induced intracorporal shockwave lithotripsy photofragmentation using pulsed Ho:YAG lasers and q-switched Nd:YAG lasers (1064 nm) combined with frequency doubling (532 nm) is applied. The stones are gradually destroyed. Clinical applications to fragment kidney stones, ureterstones, gallstones, or sialolithes in patients have been performed. The endoscopic destruction of stones is carried out with thin fibers under endoscopic control.

Experimental treatments in orthopedics have been performed for minimal invasive surgery of joints. Also clinical results in vascular recanalization have been gained, which, however, are confined to wavelengths larger than 300 nm, because only for this range are fiber transmission systems available.

**TYPES OF LASERS**

**Solid-state lasers: ruby, Nd:YAG, Er:YAG, and Ho:YAG laser**

The historically absolutely first laser, invented in 1961 by Th. Maiman, was a solid-state ruby laser. In the past, the ruby laser had a lot of technical problems and drawbacks such as low efficiency or spatial intensity spikes that destroyed the fiber material. Modern flash-lamp-pumped ruby laser systems for medical applications are compact and reliable solid-state lasers operating in a pulsed mode with flexible silica fiber light delivery equipment. The red light of ruby lasers at a wavelength of 694 nm is only weakly absorbed by non-pigmented biological tissue, but selectively absorbed by structures with high melanin concentrations. This property has promoted the, at present, most important medical application of ruby laser light: rapid and gentle hair removal in the field of cosmetic surgery by thermal destruction of deep-lying hair follicles without damage to the surrounding skin.

The Nd:YAG laser is, at present, the most important solid-state laser. It covers a wide range of medical applications. The neodymium (Nd^{3+}) ion, implanted into a host crystal of yttrium aluminum garnet (YAG), is the source of radiation. These crystal rods have typical diameters of 3–7 mm and lengths of 90–150 mm. Inside the YAG crystals, the Nd^{3+} ions have a concentration of about 1.5 vol%. The laser-active transition is normally pumped with arc discharge lamps filled with noble gases (e.g., Kr or Xe). The pumping arrangement may be a double elliptic reflector made of a highly reflective, gold-coated material with the cylindrical Nd:YAG rod placed at the common focal line. Two arc discharge lamps are centered at the two other focal lines. The Nd:YAG laser may be operated in the continuous wave mode as well as in a pulsed mode. The commonly used wavelength is 1,064 µm in the near-infrared region. Because of its high penetration depth in tissue and the possibility of transmitting the laser light via optical wave guides, the Nd:YAG laser is applied in a multitude of endoscopic procedures in urology, pulmonology, and gastroenterology. Percuta-
neous laser disc decompression (PLDD) with this wavelength was found to be an effective method for the treatment of thoracic disc disorders with minimally invasive access.8,9 A much weaker emission line is situated at the wavelength 1,320 µm which is especially used for tumor resection in lung parenchyma.10

By placing nonlinear optical crystals in the beam path, higher harmonics of the 1,064-µm basic wavelength can be generated. The most commonly used material for frequency-doubling of Nd:YAG laser radiation is potassium titanium oxide phosphate (KTiOPo4, a.k.a. KTP), resulting in the emission of green light with a wavelength of 532 nm. These frequency-doubled Nd:YAG lasers were often called misleadingly “KTP lasers.” The use of these frequency-doubled systems for PLDD was studied in comparison to Ho:YAG lasers.11 No difference in outcome was identified with the wavelengths used.

Responsible for the laser process in erbium lasers are erbium ions (Er3+) in a solid-state matrix of yttrium aluminum garnet (YAG; wavelength 2.94 µm) or yttrium scandium gallium garnet (YSGG; wavelength 2.78 µm). For laser emission in this medically interesting 3-µm region, an erbium concentration of 30–50% is suitable. The relatively long lifetime of the lower laser level of Er3+ ions of about 2 μsec allows only pulsed operation of flash-lamp-pumped erbium lasers. Typical pulse durations of free-running systems are between 100 μsec and 1 msec. The laser output is characterized by short spikes (~1 μsec), especially at the beginning of the pulse. This spiking limits the maximum energy that can be produced in the optical resonator and transmitted via optical fibers without destruction of resonator components or the fiber material. On the other hand, the ablation of biological tissue is supported by intense short spikes, with their energy density reaching the ablation threshold. The pulse energies of modern medical erbium lasers vary between 10 and 3000 mJ, with repetition rates up to 50 Hz. The maximum average power is limited to about 30 W. The laser light is administered to the patient either by an articulated arm, or by zirconium fluoride or sapphire fiber.

The Er:YAG laser can work as a dental drill. By suitable application parameters and by cooling the surface of the tooth, cracks in the enamel can be avoided. The use of Er:YAG lasers in cosmetics and aesthetic surgery leads to smoothness of the skin and face lifting due to an edema reaction.

Experimental setups of holmium lasers with high-output powers have been known since the early 1970s, but were only working at very low temperature (e.g., cooled by liquid nitrogen). Compact, mobile holmium laser systems for medical applications became available in recent years.11 They can be operated around ambient temperatures in the pulsed mode if pumped by flash lamps or in the continuous mode if diode-pumped. The most efficient laser material proved to be CrTmHo:YAG—that is, laser-active holmium ions (Ho3+) with a concentration of about 0.5% AU (atomic units) in the host crystal, codoped with thulium ions (Tm3+, concentration about 6% AU) and chromium ions (Cr3+, concentration about 1% AU). Typical pulse durations of free-running systems are between 100 μsec and 1 msec. The laser output is also characterized by spiking, as described for the erbium lasers. The pulse energies of modern flash lamp-pumped medical holmium lasers vary between 0.2 and 3 J, with maximum repetition rates up to about 30 Hz, resulting in average powers of up to 45 W. Diode-pumped cw holmium lasers with output powers up to about 1 W are under investigation. The administration of the 2.1-µm wavelength radiation of holmium lasers to the patient is realized by standard waterless silica fibers with core diameters of 200–600 µm.

With the Ho:YAG laser, incisions in cartilage and bone can be produced with minimal minor secondary damage. Thus, the Ho:YAG laser is not only successful in the endoscopic and open ablation of tissue but also in arthroscopic or percutaneous orthopedics and the recanalization of vessels. Efficacious clinical outcomes have been reported following lumbar laser disc decompression using Ho:YAG laser systems.11

**Diode lasers**

Currently, diode lasers are finding more and more applications in medicine, as they display several advantages compared with other lasers. They are among the most efficient converters of electric energy into coherent radiation. Diode lasers employ semiconductor crystals as active media, which, after excitation, will emit coherent radiation in the VIS or IR region (typical medical diode lasers range between 630 and 980 nm), which can be easily transmitted via optical wave guides to the patient.

Diode lasers are frequently employed as diagnostic or therapeutic instruments, or as positioning tools for medical devices (MRT, CT). Diode lasers for use in diagnostics work at their lower output power range up to 1 W and are mainly utilized as devices to illuminate structures in biological tissues and/or to determine, as a laser-Doppler probe, the speed of moving particles (e.g., erythrocytes). They may also be used for fluorescence diagnostics and PDT. Following the recent development in high-power diode lasers (up to 50 W), many therapeutic laser configurations with outstanding features have become available. Various tissue reactions—such as hyperthermia, coagulation, and vaporization—can be induced.

For PLDD, diode lasers with wavelengths of 805 nm13 and 980 nm14 were studied. While at 805 nm an enhancement of absorption by injection of indocyanine green dye was found necessary, the wavelength of 980 nm proves to be an efficient tool for this application.

**CO₂ lasers**

The carbon dioxide (CO₂) laser is one of the most important lasers used in medicine. It is ideally suited for surgical applications, involving the cutting and vaporization of tissue. The CO₂ molecules are the laser-active part of a gas mixture, with a helium content of 60–80%, and the rest is N₂ and CO₂ at a ratio of about 5:1. The gas is stimulated (by DC discharge or RF fields) to emit useful coherent light with a wavelength range of 9–11 µm, localized within the infrared spectrum. The laser wavelength most often used is 10.6 µm, because it is the most intensive one.

The transmission of CO₂ laser light takes place mostly through articulated arms. For special applications, hollow-wave guides are employed. Articulated arms. For use in the medical field usually incorporate seven swivel joints, each with a laser mirror placed inside the joint at a 45° angle. In this way, the typical small beam parameter product (i.e., beam divergence multiplied by beam diameter) of gas lasers is conserved during transmission, resulting in smaller focal points at the distal handpiece compared to hollow-wave guides.

The 10.6-µm laser radiation is subject to a very high absorption, effected by the high water content of most tissues. Due to
Due to high absorption, the conversion of radiation to heat is confined in very small volumes, resulting in excellent efficiency in tissue cutting and vaporization typical for the CO₂ laser. Careful timing of irradiation (pulsed or scanned) permits cutting or ablation without thermal side effects, which is often used in cosmetic surgery for skin resurfacing.

**Argon and krypton ion lasers**

The argon laser is the best-known example of an ion laser having a noble gas as its active medium. The gas is contained at a pressure of about 0.5 mbar inside a plasma tube with an inner diameter of about 3 mm. The argon atoms are ionized by an electric discharge; the generated Ar⁺ ions are excited from a ground state into higher energy levels by an additional collision with an electron. A number of discrete wavelengths between 250 and 530 nm are available. The two most powerful lines are emitted at 488 nm in the blue and at 514.5 nm in the green (in each case, up to 15 W in output power).

The krypton ion laser works on the same principle, with the discharge tube being filled with the gas krypton instead of argon. The Kr⁺ ion laser also emits several wavelengths. Laser lines in the spectral range from 350 to 800 nm are available. The most intense lines are at 530.9 nm in the green, 568.2 nm in the yellow-green, and 676.4 nm in the red. The accessible power for a Kr⁺ ion laser is 5–10 W.

Gas ion lasers are relatively expensive and comparatively vibration-sensitive, and the serviceable life of the laser tubes is 1000–10,000 operating hours. Their main fields of application are in ophthalmology, dermatology, and photodynamic therapy.

**Excimer lasers**

The excimer laser is a pulsed gas laser emitting in the UV-wavelength range from 157 to 351 nm. Its active medium is a mixture of a noble gas (argon, krypton, or xenon), a halogen (chlorine or fluorine), and a buffer gas (helium or neon). The various wavelengths emitted depend on the combination of the noble gas and the halogen, forming an instable noble gas halogenide with a lifetime of several nanoseconds during the excitation process. (The name excimer is derived from this excited dimer.) A typical excimer laser operates at a total pressure of the laser medium of 2–3 bar. An electric discharge between two electrodes of a length of approximately 1 m excites the noble gas halogen mixture. The typical pulse duration is in the region from 10 to several 100 nsec at a repetition rate of up to 1000 Hz, with the average power output being up to 200 W. The excimer laser emits a mixture of modes; consequently, it is a multimode laser with a uniform beam profile.

Due to high absorption, the threshold of the energy density necessary for photoablation can be achieved in the ultraviolet region using ArF, KrF, XeCl excimer lasers (10⁶ W/cm² with 10 nsec at 193, 249, and 308 nm). Typical medical applications are photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK) in ophthalmology as well as laser angioplasty.

**Dye lasers**

Dye lasers, in contrast to most other lasers, offer the possibility of shifting the output wavelength. The wavelength range for one dye is 50–100 nm. Employing presently available dyes, it is possible to cover the entire range from 400 to 900 nm. Two types of dye laser design can be distinguished: first, the pulsed systems with a dye-filled cuvette. The dye molecules are excited by a flash lamp arranged parallel to the cuvette. An ellipsoidal mirror surrounds the flash lamp and optic cell, focusing the light of the flash lamp onto the cuvette. To increase the service life of the dye, the content of the optical cell is pumped over and cooled. Second, continuous-wave dye lasers employ a so-called jet, where the dye molecules are pumped through a small flat nozzle and are excited as a free beam by a pumping laser (e.g., argon ion laser).

Flash lamp-pumped dye lasers have been employed in laser lithotripsy whereas cw systems have there main field of application in dermatology.

**Free electron lasers**

A free electron laser (FEL) generates tunable radiation with wavelengths ranging from microwaves over visible and ultraviolet light up to x-rays. It differs from conventional lasers in using a relativistic electron beam, harnessed by magnetic fields, as active medium, as opposed to the electrons bound to the atoms or molecules of material lasing media.

Collectively, FEL pulse durations range from quasi-continuous to sub-picoseconds, in some cases with complex superpulse structures. Any given FEL, however, has a more restricted set of operational parameters. FELs with high peak and high average power are enabling biophysical and biomedical investigations of infrared tissue ablation.

A mid-infrared FEL has been upgraded to meet the standards of a medical laser and is serving as a surgical tool in ophthalmology (corneal tissue), otolaryngology, and neurosurgery (e.g., tumor ablation), or generalized wound healing in consequence of photovasodilation. Other science research focused on spectroscopy studies of biological micromolecules, inactivation of pathogenic microorganisms or development of methods for the use of optical coherence tomography (OCT) imaging in diagnostic applications.

**CONCLUSION**

The history of laser applications in medicine starts almost with the invention of the laser itself. Forty years later, established treatment methods have been accepted by physicians and are widespread throughout the world. As today’s medical lasers represent designed solutions to identified problems, various complex tissue effects are used in laser medicine. Therefore, the basics of biomedical photonics are increasingly essential for the successful and safe application of these fascinating tools. Combined efforts of scientists, engineers, and experienced physicians will lead to superior new diagnostic and therapeutic methods, using the technical opportunities offered by advanced laser systems and accessories. To be a part of this evolution is extremely satisfying for any professional engaged in this vividly developing field.

**REFERENCES**


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