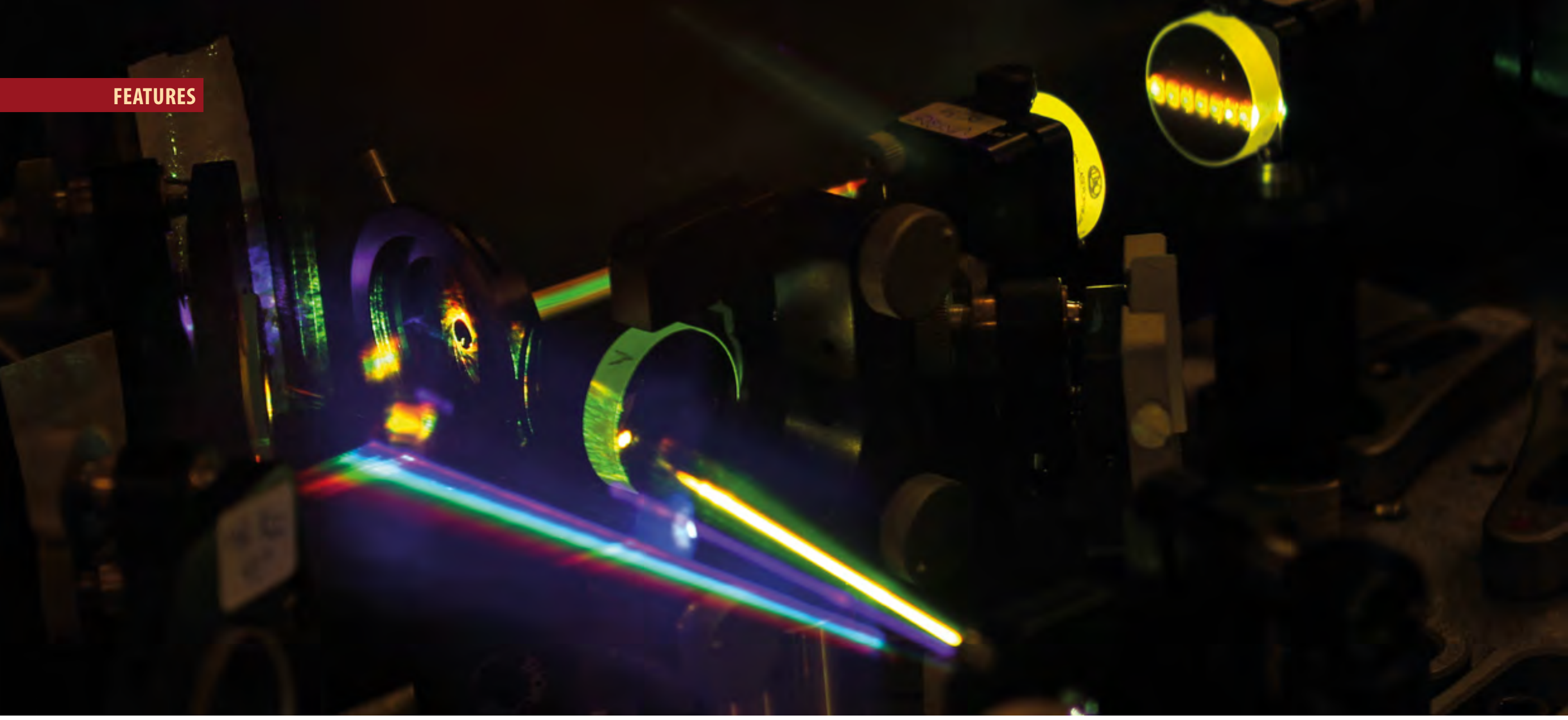

LASERS FOR HEALTH

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Thanks to its spatial and temporal coherence properties, laser light lends itself to a wealth of biomedical applications. We review the use of lasers in medical sciences, from microscopy for understanding the origin of diseases, to diagnostics for enhancing the accuracy of therapies to surgery of almost any organ of the human body.

Light for life

Light is intimately linked to life. Many bio-organisms have developed sophisticated molecular machineries to interact with light and exploit it for their functions. In photosynthesis, plants absorb solar energy in light-harvesting complexes and use it to drive charge separation and ultimately convert it into chemical energy [1]. The vision system of higher organisms is based on phototransduction triggered by the isomerization of the retinal chromophore within visual (opsin) proteins [2]. Some animals have learned to generate and manipulate light for improved survival and reproduction. Examples are fireflies and jellyfish which exploit chemical reactions in luciferin compounds to generate bioluminescence, which is used to attract preys, repel predators or to communicate. Other animals, such as peacocks and butterflies, use photonic crystal structures to generate bright color patterns [3].

Light is also intimately linked to medicine, since almost every component of the electromagnetic spectrum can be used for diagnostic and therapeutic purposes [4]. For example, radio waves are employed for magnetic resonance imaging (MRI), infrared and visible light finds application to microscopy and laser surgery, ultraviolet (UV) light is used for eye refractive surgery and for virus and bacteria disinfection, X-rays are employed for computed tomography (CT) and gamma rays for positron emission tomography (PET) and radiotherapy. We will here focus on the medical application of lasers, sources of coherent electromagnetic waves in the optical range of frequencies.

Lasers and medicine

The invention of the ruby laser by Theodor Maiman in 1960 immediately triggered a variety of medical applications. Differently from natural light sources, lasers emit light at specific wavelengths, tunable from the infrared to the UV, and with a high degree of spatial coherence; in addition, mode-locked lasers generate ultrashort light pulses, with picosecond to femtosecond duration [5]. These properties allow to concentrate large amounts of electromagnetic energy into small volumes, resulting in precise tissue ablation. Early examples of laser therapies were photocoagulation in the retina, destruction of skin lesions and removal of cardiovascular plaque. Nowadays, laser applications in medicine can be broadly classified in three categories: i) microscopy, for studying fundamental biological processes and understanding the cellular mechanisms leading to the development of diseases; ii) optical diagnosis, for real-time visualization of tissues and cells, also in the operating room and inside the body thanks to endoscopic probes; iii) laser surgery and light-activated therapies.

Optical microscopy

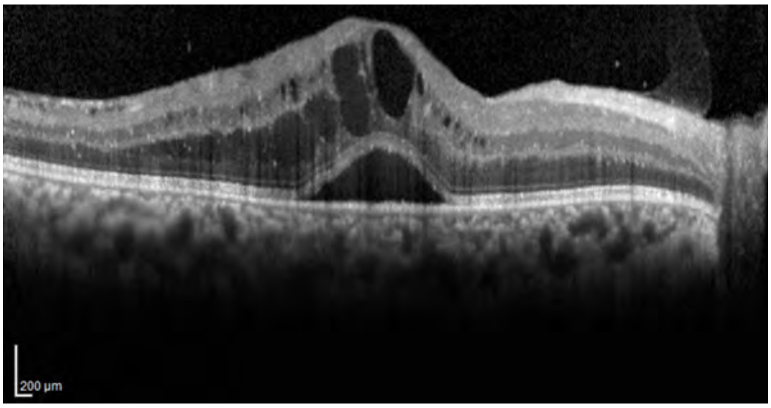
The birth of modern biology goes hand in hand with the invention of the optical microscope. In 1655 the English physicist Robert Hooke used one of the first compound optical microscopes to observe thin cork slices and coined the word "cells", likening their structure to that of cubicles in monasteries. Since then, optical microscopy has gone a long way in imaging the composition of living cells and tissues and studying their dynamical evolution. With respect to other imaging techniques such as MRI, it has the advantage of high spatial resolution; with respect to electron microscopy, it has the advantage of being non-destructive, enabling to operate on living samples. While there are many imaging modalities, the most used, due to its sensitivity, is fluorescence, using either exogenous (such as dyes and quantum dots) or endogenous (such as fluorescent proteins) chromophores [6].

The resolution of optical microscopy is set by diffraction of light and, according to Abbe's limit, is of the order of half of the wavelength of light (or 200-300 nm in the visible range). Recently, super-resolution microscopy techniques such as stimulated emission depletion (STED) [7] and photoactivated localization microscopy (PALM) [8] enabled to overcome the diffraction limit by almost an order of magnitude and to understand biological function at the molecular level.

Lasers for diagnostics

Coherent vibrational microscopies, such as stimulated Raman scattering (SRS), enable to determine the chemical composition of cells and tissues in a label-free and non-destructive way [9]. The current gold standard of tumor diagnosis in histopathology is the century old H&E technique, which requires staining the tissue slices with the hematoxylin and eosin dyes, followed by visual inspection by the histopathologist. SRS promises to improve the diagnostic accuracy by measuring the vibrational response of unstained samples (virtual histopathology) [10] and providing not only morphological but also biochemical information (spectral histopathology).

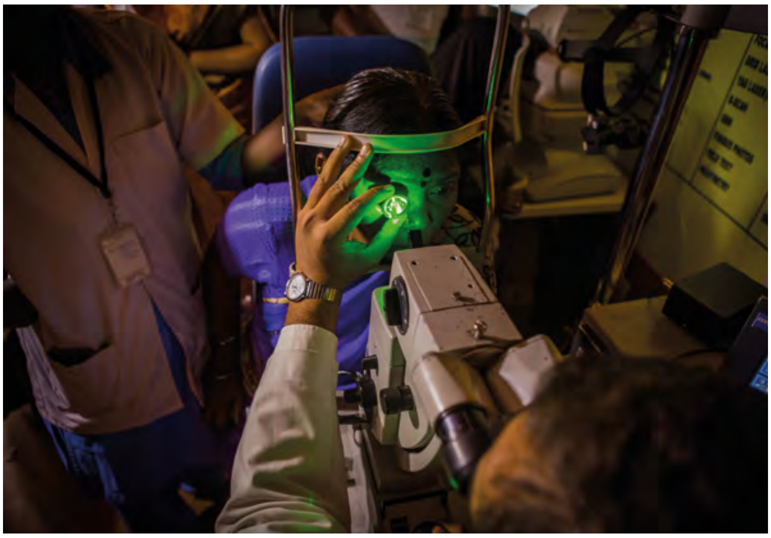
Many laser-based optical imaging techniques have been developed which are non-invasive and with high spatial resolution, employing a multiplicity of contrast mechanisms. They are used both in diagnosis and in therapy to enhance the precision of surgical interventions, enabling to distinguish between healthy and diseased tissue with • • •



▲ FIG. 1: OCT image of the retina of a patient affected by diabetic macular edema (both intraretinal and subfoveal subretinal fluid are present in the image). Image by Dr. Caterina Toma and prof. Stefano De Cillà

••• higher accuracy with respect to the naked eye. Fluorescence guided surgery uses the orally administered 5-aminolevulinic acid (ALA) which accumulates in the tumour tissues and is metabolically activated to form protoporphyrin IX, with intense red fluorescence. ALA assisted surgery allows a complete tumor resection with significantly improved outcome. Another successful imaging technique is optical coherence tomography (OCT), which exploits interference of low-coherence broadband light to obtain a 3D image of light back-scattered by a tissue with high spatial resolution (down to a few µm) at depth of up to several mm [11]. OCT has become a standard technique in ophthalmology, as it allows to obtain high resolution images of the retina morphology. It is the standard for diagnosis of pathologies such as glaucoma, diabetic retinopathy (see Fig. 1) and age-related macular degeneration. Time Domain Near-infrared Spectroscopy (TD-NIRS) uses the absorption and scattering of short (picosecond) laser pulses to measure the concentration and localization of various components of tissues, such as oxy- and deoxyhemoglobin, lipids and water. TD-NIRS allows non-invasive monitoring of tissue hemodynamics and oxidative metabolism, for studies of functional activation in our brain [12] and diagnosis of a variety of diseases.

▼ FIG. 2: Laser treatment being done inside a mobile eye van for a patient with diabetic retinopathy. by Rajesh Pandey. Copyright CC BY-NC-SA 2.0.



Lasers for surgery

With respect to the use of a scalpel, laser surgery has the advantage of being a non-contact technique and to enable high precision in tissue removal, limiting the damage to the adjacent tissue and, in some cases, cauterizing the surrounding vascular network. Among the factors that dictate the choice of the wavelength for laser surgery are the absorption coefficient of the tissue and the availability of optical fibers for endoscopic light transport. As tissues are made mostly of water, it is instructive to consider the water absorption coefficient, which peaks in the infrared around 3 µm, where Erbium lasers emit; however, no convenient optical fibers are available at this wavelength. A secondary maximum occurs around 2 µm, where Holmium lasers emit, a wavelength that can be easily guided by optical fibers. Light absorption is also very high in the UV range, where excimer lasers emit.

Lasers find numerous applications in dermatology, for permanent air removal, skin resurfacing resulting in facial rejuvenation and removal of tattoos or port wine stains. An application currently under development is laser lithotripsy for kidney stone fragmentation, using a Holmium laser coupled to an ureteroscope. Similarly, Holmium lasers are used for the treatment of benign prostatic hyperplasia, removing the excess tissue. Erbium lasers hold promise in dentistry for the ablation of hard (dentin and enamel) dental tissue, despite the complication caused by the lack of effective delivery fibers. Low intensity laser light in the red and near infrared is used for photobiomodulation, also known as low level laser therapy, to treat inflammation, chronic pain and sport injuries. The underlying mechanisms, still not fully understood, are related to light activation of the mitochondria in the cells.

Lasers find also numerous applications in ophthalmology, such as *e.g.* in the surgery of retinal detachment, of diabetic retinopathy (see Fig. 2) and of secondary cataract. An established application is refractive surgery for the correction of visual defects, by reshaping of the curvature of the cornea. In laser-assisted in situ keratomileusis (LASIK) a wavefront sensor first characterizes the curvature of the cornea. Subsequently, the corneal epithelium is cut creating a flap which is folded back by the surgeon to reveal the middle section of the cornea, the so-called stroma. At this point an UV excimer laser at 193 nm is used to ablate the stroma, precisely remodeling its curvature. Finally, the flap is folded back in place, and, after a short post-operative care, full visual acuity is recovered accompanied by a correction of the defect. Initially the flap was mechanically cut by a metal blade, but recently a femtosecond laser was found to give better outcomes [13]. With millions of surgeries performed and a very high degree of patient satisfaction, LASIK is an impressive example of how even sophisticated laser technologies have nowadays reached a level of maturity sufficient for their employment in mainstream applications.

Outlook

The future of applications of lasers to health looks bright. More and more sophisticated imaging techniques, both in vivo and ex vivo, can be used to improve the accuracy of the diagnostics and assist during treatment, allowing a personalized, precision medicine. On the other hand, technological progress has made even sophisticated systems, such as femtosecond lasers, robust and reliable enough to allow their use by non-experts in a medical environment. This considerably broadens the range of surgical applications for lasers. Finally, lasers can play an important role in nanomedicine, in which organic or inorganic nanoparticles are used to carry a drug cargo into the body [14]. Light-activated drug release will help to tailor the localization and the dose of the therapy to maximize its efficacy. ■

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