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The importance of physics to progress in medical treatment

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Physics in therapy is as diverse as it is substantial. In this review, we highlight the role of physics—occasionally transitioning into engineering—through discussion of several established and emerging treatments. We specifically address minimal access surgery, ultrasound, photonics, and interventional MRI, identifying areas in which complementarity is being exploited. We also discuss some of the fundamental physical principles involved in the application of each treatment to medical practice.

Introduction

Technologies used in the treatment of patients with life-threatening disorders can be categorised as facilitative, enabling, additive, or disruptive.[1] Facilitative technologies improve the efficiency of a procedure and reduce its difficulty (eg, robot-assisted surgery). Enabling technologies make possible therapeutic interventions that would otherwise be impossible or very difficult (eg, radiofrequency and microwave devices for in-situ ablation). Additive technologies bring sophistication and precision to surgical and interventional manipulations (eg, augmented reality systems) and might replace existing systems as the technology develops. Initially, additive technologies are very expensive and thus, their use is restricted to major centres. The term disruptive was coined by Christensen[2] to describe new technologies that change the way we work and do things (eg, minimal access surgery). In this review we aim to show the importance of the physics and engineering that underpins the established and emerging technologies within these categories.

Although engineering and physics have contributed to advances in therapy in many ways, we will focus only on selected themes as examples of the importance of current and emerging technological developments for progress in modern health care.

Physics and engineering for minimal access surgery

Minimal access surgery emerged in the early 1980s when the technologies—based on photonics—developed, permitting operations to be done from images. Minimal access surgery ushered in a new era of technology-dependent interventions designed to reduce trauma to patients undergoing operations. In the history of surgery, it is difficult to think of any surgical advance that had such a large effect on surgical health-care delivery, or caused such controversy, problems and, initially, major concerns about patient safety. Yet within two decades of its introduction, minimal access surgery altered surgical practice well beyond the expectations of the early European pioneers. Thus, based on robust level 1 clinical evidence (evidence based on several randomised controlled trials or a meta-analysis) and level 2 clinical evidence (evidence based on one large randomised controlled trial), minimal access surgery is now the gold standard for many common surgical operations (table 1). In retrospect, this development should be categorised as disruptive, because it has altered the way surgeons operate: in the latter half of the 20th century it would have been difficult to predict that surgeons would be undertaking major operations for cancer without opening the abdomen or chest of patients.

The two key technologies that made the introduction of minimal access surgery possible were the rod-lens telescope and the charge-coupled device camera. Other important components include fibreoptic light guides, light sources, master-slave manipulators, and image display systems.

Rigid rod-lens telescope

This seminal development is owed to Harold Horace Hopkins, whose substantive contributions include the rod-lens telescope, coherent fibreoptics, the fibrescope (precursor of the flexible endoscope), the optical zoom lens, and laser disc and compact disc optics.

Before Hopkins' invention of the rod-lens system, rigid endoscopes, based on the Nitze cystoscope (figure 1A), had been used almost unchanged for more than 150 years. Rigid endoscopes had weak distal illumination, with a small light bulb, and incorporated a series of small relay lenses supported on rings that were often misaligned because of difficulties in assembly. These telescopes transmitted light very poorly and yielded a dark, inferior image such that they were of little clinical value, and useless for surgery. Hopkins' solution was to use self-aligning glass rods with concave ends, which

Key messages

- Progress in the physical sciences (physics and engineering) substantially affects the life sciences, especially the progress of medical care.
- Closer collaboration is needed between the two research sectors through a new paradigm of interface science by which multidisciplinary teams from both sectors work closely in a shared research environment to stimulate progress in science and technology and their clinical translation for the benefit of society.
- The experience of the Institute for Medical Science and Technology (Dundee, UK) has shown the benefits of this approach and perhaps shows the need for reappraisal of departmentalised PhD studentships to meet the rapidly changing requirements of collective research and development.

could be made to fit with great precision inside the endoscope sheath (figure 1B).[3,4] Light is transmitted from a powerful external halogen light source to the tip of the telescope by bundles of glass fibre. The translation of this ground-breaking development into clinical practice owes much to the partnership between Hopkins and Karl Storz and his company. Karl Storz manufactured the first rod-lens telescope in 1967.

Charge-coupled device cameras

Boyle and Smith developed the charge-coupled device,[5] for which they were awarded the Nobel Prize in Physics in 2009. Initially, the charge-coupled device was intended to be a shift register, a type of memory device. Tompsett and colleagues[6,7] subsequently showed that a charge-coupled device could also accumulate charge via the photoelectric effect, thereby creating images. The introduction of the charge-coupled device ushered in a new era of miniature high-resolution cameras, which replaced all existing imaging systems.

Charge-coupled devices and, more recently, complementary metal-oxide-semiconductor chips, are used either at the distal end of an endoscope, forming digital or optoelectronic endoscopes, or in a lightweight camera coupled to a Hopkins' rod-lens system with output via a camera control unit to an external image display. Both charge-coupled device and complementary metal-oxide-semiconductor chips are pixelated metal oxide semiconductors with an epitaxial layer of silicon as the photodetector. Signal charge accumulates in each pixel proportional to the intensity of illumination. When exposure is complete, the charge-coupled device transfers each pixel's charge packet sequentially, as a shift register,[8] to a common output device, which converts the charge into a voltage and sends the voltage to the display. In a complementary metal-oxide-semiconductor sensor, the conversion of charge to voltage occurs in each active pixel sensor.[9] Complementary metal-oxide-semiconductor chips have the advantages of high integration and functionality, small size, and low power consumption, which are particularly suited to wireless capsule endoscopy, introduced in the 1990s.[10]

The images from the first charge-coupled device cameras were black and white, which is of limited clinical and surgical use. Single-chip colour charge-coupled device cameras use a Bayer mask, which lies over the silicon epitaxial layer and provides each square of four pixels with four filters, one red, one blue, and two green. Better colour separation and luminance is obtained by cameras equipped with three charge-coupled devices and a dichroic beam prism, which splits the image into its red, green, and blue components with each of the three charge-coupled devices configured to respond to one colour. The three-chip camera is used in minimal access surgery because of its better colour rendering and higher light sensitivity for a particular aperture size compared with single-chip cameras.

	Routine use (gold standard)	Level 2 or 3 evidence of patient benefit
Cholecystectomy	✓	
Inguinal and incisional hernia repair	✓	
Anti-reflux surgery	✓	
Heller's cardiomyotomy	✓	
Adrenalectomy	✓	
Splenectomy	✓	
Radical prostatectomy	✓	
Live related donor nephrectomy	✓	
Left hepatic resection	✓	
Thyroidectomy		✓
Resection for gastric and oesophageal cancers		✓
Resection for colorectal cancers		✓
Resection for inflammatory bowel disease		✓
Resection for colonic diverticulitis		✓
Distal pancreatic resection		✓
Major urological operations (pyeloplasty, radical nephrectomy)		✓
Major thoracoscopic operations (pulmonary lobectomy, thymectomy)		✓

Table 1: **Operations done with the minimal access surgery**

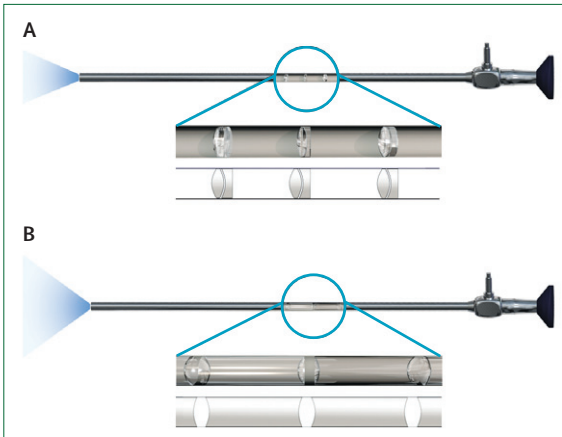

Figure 1: **Comparison of Nitze telescope with Hopkins' rod-lens telescope**
The Nitze cystoscope (A), and the Hopkins' rod-lens based endoscope (B), which has superior and more robust, optical capability (increased illumination, field, and depth of view).

Image display systems

Image display systems have progressed from cathode ray tubes to liquid crystal display and plasma screens, and, more recently, to displays based on organic light-emitting diodes.

Cathode ray tubes have high colour fidelity and contrast, and a wide viewing angle, but their weight, bulk, and the flicker that degrades the fixation and refixation movements of the human eye[11] have led to them being superseded. The merits of liquid crystal displays for minimal access

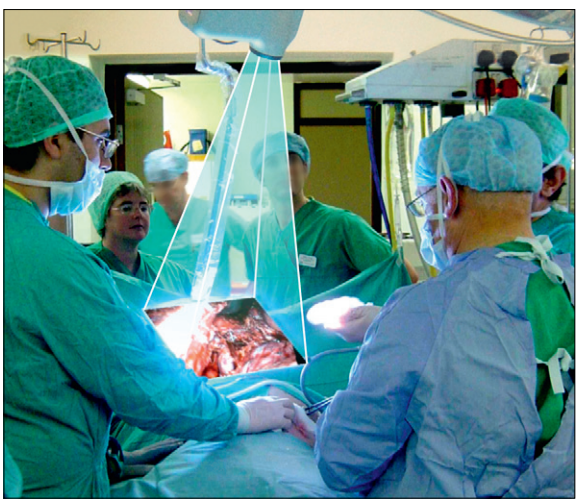

Figure 2: **Operation for radical (curative) removal of gastric cancer**
A projection image display system is being used instead of a conventional monitor. The image is projected onto a sterile screen on the anterior chest wall of the patient. Organic light-emitting diodes are likely to be used for such projection displays in the future.

surgery are their light weight and lack of bulk such that they can be mounted to the ceiling and easily positioned for the surgeon to view.[12] The only drawback is a restricted viewing angle. In a liquid crystal display screen, each pixel consists of a layer of liquid crystal molecules aligned between two transparent electrodes (eg, indium tin oxide), and two polarising filters with perpendicular axes of transmission. By controlling the voltage applied across the liquid crystal layer in each pixel, light is allowed to pass through in varying amounts to provide different shades of grey. In colour liquid crystal displays, each pixel is divided into three cells (subpixels) coloured red, green, and blue by colour filters.

Organic light-emitting diodes have emissive and conductive layers, a substrate, and anode and cathode terminals. The layers are made of organic polymers that conduct electricity[13] discovered by Alan Heeger, Alan MacDiarmid, and Hideki Shirakawa, for which they received the Nobel Prize in Chemistry in 2000. Organic light-emitting diodes are deposited in arrays onto a flat carrier with patterning technologies. The resulting matrix of pixels emit light of different colours. Organic light-emitting diodes offer better brightness, contrast, viewing angle, and range of colours than do liquid crystal diplays because organic light-emitting diode pixels emit light directly. Televisions based on organic light-emitting diodes have been produced commercially.

For minimal access surgery, transparent organic light-emitting diode screens could be stacked to produce 3D images with much greater contrast ratios and viewing angles than existing products. Organic light-emitting diodes might also allow the introduction of so-called gaze-down frontal viewing with the image of the operating field projected on top of the patient. This image display configuration has been shown to be optimal for minimal access surgery, because it improves efficiency and reduces technical manipulation errors.[14] Currently, the only way in which a gaze-down display can be used for minimal access surgery is by projection of the image from the charge-coupled devices camera onto a sterile screen placed on the patient's chest (figure 2).

Master-slave manipulators for minimal access surgery

Master-slave manipulators, although frequently referred to as surgical robots, are not engineered for independent activity but are totally controlled by the surgeon. Through a computer interface, master-slave manipulators reproduce the exact hand manipulations of the surgeon sitting at an operating console, which might be a few metres away or thousands of miles.

The advantages of master-slave manipulators compared with direct hand-operated minimal access surgery include the increased degrees of freedom (n=7), because of an internal wrist joint, greatly enhanced precision of movement from motion scaling by the computer interface, and abolition of tremor. Thus, the maximum benefit of master-slave manipulators is seen in operations requiring complex tasks for which precision of surgical manipulation is essential for safety and within an anatomically constrained operating field, such as for intracorporeal suturing.

Master-slave manipulators are exemplified by the da Vinci system (Intuitive Surgical, Sunnyvale, CA, USA).[15] The latest model, Si HD, has four manipulator arms, enhanced 3D high-definition imaging, and an optional dual-console for training and to enable cooperation of two surgeons during a procedure. High-definition imaging provides more than 2 million pixels, approximately four times better than the best non-high-definition television systems. Problems with the da Vinci system include absence of tactile feedback and high cost of equipment, contract maintenance, and consumables because each end effector has limited use.

Robotic-assisted surgery with the da Vinci system is especially useful in major advanced operations requiring complex tasks, such as intracorporeal anastomosis of small vessels and tubular structures and in regions of the abdomen where space is restricted (eg, radical prostatectomy, curative resections for rectal cancer, fallopian tube surgery for sterility).

Ultrasound and photonics

Although photonics (based on electromagnetic radiation) and ultrasound (based on mechanical radiation) are physically very different, they have many analogous physical properties, especially in their use in medicine. The frequency, or related wavelength, of optical or ultrasonic radiation often determines its use in medical technology. Resolution—the smallest distance between two objects that can be distinguished in an image—is usually expressed as the diffraction limit, which is

proportional to wavelength. Because the speed of the wave is constant in a particular medium, we can infer that high frequencies, hence short wavelengths, yield high resolution images. However, when a wave is strongly absorbed and scattered, which is what imaging depends on, the depth of penetration of the wave decreases with increasing frequency. Thus, generation of an image with both optics and ultrasound entails a trade-off between resolution and depth of penetration.

For therapeutic applications, light and ultrasound are often focused, concentrating the energy in a defined volume, to localise or target the therapy. As a consequence of the wave-like nature of electromagnetic and mechanical radiation, a fundamental physical constraint exists for how strongly either can be focused, known as the diffraction limit. In optics this limit can be circumvented by making use of non-linear effects such as two-photon absorption, which requires very high intensities, such as those available with ultrashort pulsed lasers. High intensity ultrasound can also lead to non-linearity, in which effects do not scale proportionally with intensity.

Ultrasound in therapy

Ultrasound at frequencies close to audible sound (in the range of several tens of kHz), is widely used to assist surgical procedures such as cutting and can also be used to disrupt tissue—for example during liposuction. In this report, however, we address applications in which the ultrasound itself has a therapeutic effect, potentially mediated by encapsulated drugs, but without mediation by a surgical tool. Such applications use high frequency ultrasound, in the range of several hundred kHz up to several MHz.

The use of ultrasound for therapeutic heating was first suggested in Germany in the early 1930s and first used for cancer in 1944,[16] just 2 years after the first reported medical diagnostic use. Diagnostic ultrasound provides non-invasive imaging with non-ionising radiation in real time at the point of care, including for anaesthesia, cardiology, and surgery outside of radiology departments. Conventional systems operate at frequencies of 3–20 MHz, with low beam intensity and spatial resolution corresponding to ultrasonic wavelengths of 0·5–75 μm. Functional imaging by Doppler ultrasound, elastography, or molecular imaging with contrast agents complements anatomical imaging.[17]

The key difference between diagnostic and therapeutic ultrasound is the higher intensity of therapeutic ultrasound. Increased intensity has two main effects: increased temperature and cavitation. Increased temperature results from viscous absorption, with the duration of application of ultrasound an important factor. Ultrasound to alter temperature has varied applications, from small increases (eg, to 42°C in targeted drug delivery), to rapid, large increases (eg, to more than 56°C for targeted cell necrosis). Cavitation is a process in which small gaseous inclusions in the negative pressure phases of applied ultrasound expand to form bubbles of several μm or more.[18] Inertial cavitation, so called because the inertia of the liquid acts to close the void after a single oscillation, involves expansion then rapid implosion, radiating energy throughout the tissue. Non-inertial cavitation is repeated, potentially stable, expansion and contraction of bubbles affected by ultrasound.

Therapeutic ultrasound shares problems with diagnostic ultrasound, such as the hyperechogenicity of bone and gas, resulting in inaccessible regions. Additionally, physical contact is required between the surface of the skin and the ultrasound source (the transducer). This contact is usually achieved with water or gel; in therapeutic ultrasound, care must be taken to avoid cavitation in this medium to prevent disruption of the beam. Table 2 summarises established and emerging therapeutic uses of ultrasound. The earliest reports of therapeutic ultrasound relate to physical therapy;[19] although widely practised, evidence for the clinical efficacy of physiotherapy is weak.[20]

Therapeutic high-intensity focused ultrasound, also known as focused ultrasound surgery, is used primarily for non-invasive thermal ablation of solid tumours. Ultrasound offers two advantages compared with microwave and radiofrequency techniques.[21] Low absorption with ultrasound allows deep penetration with low attenuation of the beam. Furthermore, the ability to configure the transducer with large dimensions of the ultrasound source relative to the wavelength (ie, a ratio of dimension to wavelength of roughly 50–100), allows precise focusing.

Basic high-intensity focused ultrasound can be achieved with a very simple transducer incorporating a single concave spherical bowl of piezoelectric material (a substance that deforms mechanically when a voltage is applied across it and vice versa—ie, acquires a charge when deformed mechanically) connected to signal generation and power amplification instruments. This arrangement provides a fixed focal point and an operating frequency of 1 MHz that will generate a characteristic

	Clinical	Experimental	Developmental
Physiotherapy	✓		
Prostate cancer ablation	✓	✓	
Uterine fibroid ablation	✓	✓	
Pain palliation of bone metastases		✓	
Palliative ablation of pancreatic cancer		✓	
Deep brain ablation for neuropathic pain		✓	
Breast cancer ablation		✓	✓
Liver and kidney cancer ablation		✓	✓
Targeted drug delivery			✓

Experimental is those applications still in the experimental stage. Developmental is those applications being translated into clinical practice.

Table 2: **Uses of therapeutic ultrasound**

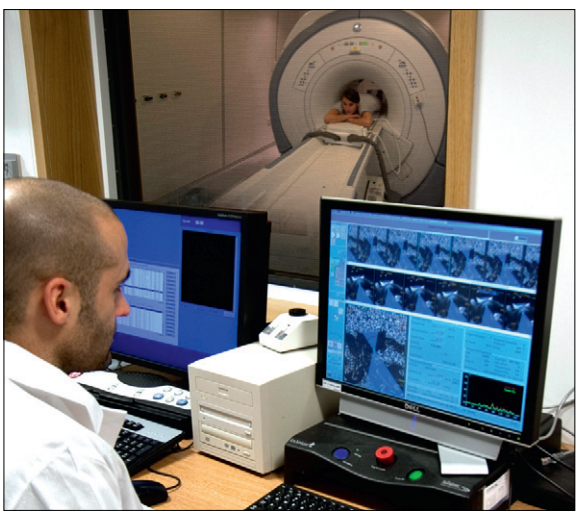

Figure 3: **Magnetic resonance-guided focused ultrasound administration with computer control includes software interfacing between MRI imaging and thermometry for guidance, and sonication delivery**

See Online for appendix

ellipsoidal lesion of 1–3 mm diameter and 10–15 mm length in tissue (appendix). Intensity at the focus is typically 1–10 kWcm², causing hyperthermia in 1–10 s, which leads to tissue ablation and avoids effects of thermal conduction and perfusion. However, such an approach requires mechanical motion of the transducer to cause volumetric ablation of lesions. Therefore, clinical high-intensity focused ultrasound systems often use a transducer consisting of an array of many elements, each controlled individually. Such electronic control allows very rapid alteration of the beam but does not shorten the overall time for ablation of the lesion, which is a key parameter for high-intensity focused ultrasound and all ablative therapies.

Three main types of high-intensity focused ultrasound array have been developed: an annular array, which consists of 10–20 rings arranged on the surface of a bowl; a sector array, made as an annular array and typically divided into eight sectors; and a matrix array, with hundreds or thousands of tessellated elements. An annular array can move the focus electronically only along its axis and requires cumbersome mechanical motion for changes in other directions. A sector array also allows a small amount of electronically controlled movement around the axis, and a matrix array allows full control of the beam throughout a volume of tissue dependent on the size of the aperture and penetration depth of the array. High-intensity focused ultrasound arrays have been developed to operate at frequencies from 250 kHz (wavelength roughly 6 mm) for transcranial applications to more than 3 MHz (wavelength more than 0·5 mm) for prostate treatment.

After the initial clinical studies with high-intensity focused ultrasound,[21] further developments enhanced the efficacy of the technique and integrated the system with high performance MRI and ultrasound imaging systems for planning of treatment and real time guidance (figure 3, appendix).

For intraoperative ultrasound guidance of high-intensity focused ultrasound, the imaging transducer is usually inserted centrally within the high-intensity focused ultrasound transducer, and coplanar to it. However, high-intensity focused ultrasound lesions are usually invisible to conventional ultrasound imaging, although techniques such as elastography have some potential to address this issue[22] and ultrasound temperature measurement is being developed. A major advantage of MRI guidance is that it offers accurate direct temperature measurement for monitoring and control combined with an adequate 3D spatial resolution and update rate.[23] However, the cost of an MRI system is substantial, the high-intensity focused ultrasound system must be engineered to be compatible with MRI, and patient access constraints are exacerbated by the long duration of high-intensity focused ultrasound treatments.

One advantage of high intensity focused ultrasound is the sharply defined lesion, with minimal collateral damage to surrounding normal tissues. The focal intensity used in high-intensity focused ultrasound also makes inertial cavitation likely. This effect was previously considered a disadvantage but is now being investigated as part of direct cell lysis[24] and to speed up hyperthermic necrosis by enhancement of absorption.

Clinical developments have been affected by various regulatory approaches for certification and adoption of new techniques in different parts of the world. China has more than one indigenous high intensity focused ultrasound system manufacturer and has done procedures on the largest number of patients, now exceeding 10 000. A possible order in which to consider clinical trials and approval is first for symptom relief of benign disorders (eg, uterine fibroids, benign prostatic hyperplasia, and neurosurgical treatment of chronic neuropathic pain); second, for palliative care in malignant disease (eg, bone metastases and pancreatic cancer); and, third as primary treatment of solid cancers.

The blood–brain barrier prevents effective delivery of therapeutic and imaging agents to the brain by restricting transport from the vascular system. After other studies in ultrasound-enhanced drug delivery,[25] transcranial ultrasound was identified as an alternative to tailored pharmaceuticals or direct infusion of hyperosmotic solutions into the vasculature. However, direct induction of hyperthermia or cavitation has not been reliably shown to cause disruption of the blood–brain barrier without producing lesions or necrosis. Thus, research has focused on the use of microbubbles activated by high-intensity focused ultrasound. This approach allows the intensity of ultrasound to be greatly reduced, decreasing the risk of collateral damage. However, the underlying physics is highly complex, including radiation force effects, microstreaming, and inertial cavitation, and still needs to be elucidated in vivo.[26]

Blood–brain barrier disruption is a type of ultrasound-mediated targeted drug delivery. A similar technique is possible for other clinical applications based on cell sonoporation to enhance cellular uptake. An alternative, potentially complementary, approach is to encapsulate the drug in a microbubble (with a gas core and drug release through mechanical rupturing of the microbubble), liposome (with the drug filling the core and thermal release), or polymer nanocarriers (appendix). Ultrasound is then used to trigger release of the drug adjacent to the site of treatment.[27] The inclusion of ligands on the carrier can further enhance targeting. However, further development is needed to increase retention in circulation, drug loading, and targeting.

Photonics in therapy

Light is so central to therapy that its role is often taken for granted. Fundamentally, all surgical and interventional procedures involve some form of visual guidance. Therefore, the outcome of the procedure is partly dictated by the quality of the visual input the operator receives. Light's role can be as basic as the lighting in the operating room, as sophisticated as optical coherence tomography, or simply the visual display used to present information obtained with a different imaging modality such as ultrasound.

Light can also have an active role in therapy by enabling new therapeutic approaches, such as photodynamic therapy. Table 3 summarises the contribution of photonics to medicine. Photonics can be applied to image guidance or direct delivery of a therapeutic effect, similar to therapeutic ultrasound. We concentrate on the use of light to deliver a therapeutic effect.

2010 was the 50th anniversary of the invention of the laser, a device that has led to many important technological advances.[28] Lasers are highly versatile, with a large range of controllable parameters including wavelength, determining penetration depth and permitting selective absorption by specific tissues; pulse length, allowing tuning between thermal and ablative tissue functions; power, allowing choice of diagnosis or therapeutic doses; and beam shape, allowing control of the depth of penetration and volume of tissue affected. All these parameters have equivalents in ultrasound. Other important parameters of lasers include polarisation and coherence. A laser has a high degree of spatial coherence allowing a very small focal volume to be produced, which allows non-linear interactions between light and material that could not be achieved before the development of modern lasers that can produce short pulses.

Interactions between the laser and the tissue determine the mechanism of a therapeutic modality, and can be categorised into four types: photoablative (or photomechanical), photothermal, photochemical, and photobiostimulation. Photoablative procedures use nanosecond or shorter pulses at very high intensities, capable of causing optical breakdown on absorption to form plasmas—ie, ionised regions of high free-electron density. A shockwave, travelling at supersonic speeds, is generated as the plasma expands, which can result in the mechanical rupture of the tissue. Photothermal applications involve direct absorption of optical energy to induce highly localised heating. This effect is sometimes mediated by nanoparticles, which act as photosensitisers that can be conjugated to pathological cells for enhanced targeting. Photochemical interactions mainly refer to photodynamic therapy. Photobiostimulation uses lasers as a source of illumination but only the beam intensity is relevant because collimation and polarisation are lost within a few millimetres of penetration into tissue. Photobiostimulation can also be thought of as the response of cells or tissue to the chemical, thermal, or mechanical interaction of the light with the tissue.

Perhaps the best known photoablative procedure is laser-assisted in situ keratomileusis in which non-thermal ablation of tissue allows re-shaping of the cornea, directly correcting for refractive aberrations in the eye.[29] Such a procedure is possible only because of the ability to deliver very high peak powers in short pulses. Laser-assisted in-situ keratomileusis has very high accuracy, yet the precision of laser surgery can be even greater. For example, surgery at the subcellular scale is possible using short pulse (<10 ns) lasers, allowing individual chromosomes or sections of chromosomes within a cell to be ablated or cut selectively[30] without otherwise damaging the cell, including its membrane.

Laser lithotripsy[31] is a clinically effective technique widely used to fragment urinary calculi by delivering pulsed energy to a stone in the bladder or the ureter through an endoscope inserted through the urethra. Advantages compared with the traditional technique of extracorporeal shockwave lithotripsy include increased precision and

	Guidance	Therapy	Clinical	Developmental
Conventional optics (eg, endoscopes, operating room lighting)	✓		✓	
Fluorescence imaging, including multiphoton	✓		✓	✓
Spectroscopy (eg, Raman, diffuse scattering)	✓			✓
Optical coherence tomography (eg, ophthalmology)	✓			✓
Optical clearing (eg, tissue index matching)	✓	✓		✓
Photodynamic therapy		✓		✓
Laser cutting and welding of tissue		✓	✓	✓
Optically induced hyperthermia		✓	✓	
Laser lithotripsy		✓	✓	
Laser-assisted in situ keratomileusis		✓	✓	
Phototherapy		✓	✓	
Corneal crosslinking		✓	✓	
Laser capsulotomy		✓	✓	
Photocoagulation		✓	✓	
Retinal prostheses		✓		✓

Table 3: **Photonics in medicine**

avoidance of overtreatment, because stone fragments are observed and treatment halted when disintegration to the requisite size has been achieved. Early clinical laser lithotripsy used the pulsed dye laser, with a wavelength of 504 nm and pulse length of the order of 10 μs, but this laser has been superseded by holmium yttrium–aluminium–garnet (YAG) devices, which have a wavelength of 2120 nm, and pulse lengths of roughly 500 μs. The fragmentation mechanisms of these lasers are different. The pulsed dye laser effect is photomechanical, with the optical fibre placed in direct contact with the stone and the energy absorbed producing a shockwave at or near the surface. The holmium YAG laser effect is predominantly photothermal, with energy directly absorbed by the stone through a vapour channel formed in the containing fluid, resulting in chemical decomposition of the calculus.[32]

The archetypal application of a photothermal tissue interaction is tissue welding, typically done with wavelengths of around 800 nm in conjunction with a protein-based solder. Unlike many applications in which heating is actively avoided, increased temperature is the mechanism by which welding is initiated. Photothermal interactions can also be desirable because of their cauterising effect on wounds.

Photodynamic therapy is a photochemical approach to palliation or eradication of some cancers and various benign disorders, such as age-related macular degeneration. Photodynamic therapy uses optical irradiation and a photosensitiser drug that together produce cytotoxic reactive molecular species.[33] The preferential uptake of the photodynamic therapy drug by cancer cells, combined with local delivery of illumination, results in a highly spatially targeted therapy. Argon and solid state lasers are effective and popular sources for photodynamic therapy because of their high irradiance and ease of coupling to fibreoptics for delivery. Other commercially available systems include non-laser incandescent sources such as xenon arc and metal halide lamps. Other advances include the use of organic light-emitting diode patches (appendix) allowing photodynamic therapy to be done more slowly, hence more comfortably, and with outpatients, substantially reducing the cost.

The low depth of penetration of light into tissue restricts photodynamic therapy to the treatment of superficial tumours. Another possibility is the use of two-photon absorption for the photoactivation of drugs.[33] Well established in microscopy,[34] two-photon processes involve the simultaneous absorption of two low energy photons to induce an excitation level equivalent to the absorption of a single high energy photon. The photoelectric effect, for which Albert Einstein was awarded the Nobel Prize in Physics in 1921, dictates that the energy of a photon is related to its wavelength, as described by

$$E_\gamma = \frac{hc}{\lambda}$$

where h is Planck's constant, E_γ is the energy of a photon, c is the speed of light, and λ is wavelength. Thus, in effect two-photon processes use two long wavelength photons to do the job of a single short wavelength photon. As longer wavelengths penetrate further into tissue, this technique could enable other types of cancers to be treated. The probability of two-photon absorption is proportional to the square of the intensity and the two-photon cross-section, meaning that photodynamic therapy takes place only where the light is tightly focused, potentially allowing photodynamic therapy in a small volume deep within tissue. Two-photon absorption requires very high peak power, but the advent of titanium sapphire femtosecond pulsed lasers of tuneable wavelength—most efficient at wavelength 800 nm and pulse time about 10 fs—makes the required intensity feasible and photosensitisers with large two-photon cross-sections are being developed.

Photoacoustics

Between photonics and ultrasonics lies photoacoustics, in which light can be used to produce ultrasound, and vice versa.[35] Photoacoustic imaging is developing rapidly and has a resolution and depth penetration intermediate between photonics and ultrasound. Photoacoustics can also be used for therapy. The therapeutic effect of optically induced cavitation nucleation around a nanoparticle contrast agent can be monitored or imaged with the acoustic signals produced by cavitation. Figure 4 shows an example of optoacoustics in vitro.

Because of the short wavelength of radiation compared with the size of features in tissue, optical imaging and therapy have very good resolution, but also suffer from substantial scattering at small depths within tissue. The much longer wavelengths of ultrasound mean that scattering is reduced and much greater depth penetration is possible. Photoacoustic approaches often aim to bridge this gap, combining the resolution of optics with the penetration of ultrasound.

Interventional and intraoperative MRI

Though able to produce images of greater resolution and interaction volumes of smaller size than any other modality, photonics is often limited by the rate at which light is scattered and absorbed by tissue. Ultrasound has much greater penetration but reduced resolution and contrast. MRI, however, has the best penetration of all, and better soft tissue contrast than do ultrasound imaging or radiography. MRI has huge potential as an imaging modality for therapy for vascular and percutaneous interventions and image-guided surgical procedures. Furthermore, MRI avoids the use of ionising radiation and iodine-based nephrotoxic contrast agents, which are used in radiological imaging.

MRI is based on a strong static magnetic field (net magnetisation 0·2–7 T) and alternating electromagnetic fields applied through gradient and radio frequency coils.

Acquisition of an image is based on the effects of resonance with the magnetic moment (spins) of hydrogen nuclei protons bound in water, lipid, and protein molecules.[36] Specific sequences of radio frequency pulses and millisecond switching of the spatially varying electromagnetic field gradients are used with specific times of echo for optimum received signal strength. Spin echo (SE) and fast gradient echo (GRE) sequences are used for image acquisition and image contrast can be weighted towards signals from water (T2) or lipids (T1) with options to suppress either signal.

Although MRI-guided biopsy was introduced in 1986,[37] the first clinical experiences of MRI-guided stent implantation were only reported in 2001.[38] Conventional metal-based devices and instruments such as stents, cannulae, and guidewires cause substantial image artifacts because of their electrical and magnetic properties.[39] One way to reduce artifacts and improve the visibility of devices and implants is to use non-conductive polymer composite materials and deliberately incorporate resonant electrical circuits tuned to the same oscillating frequency as the Larmor frequency of the MRI system[40] (eg, around 42 MHz for a magnetic field of 1 T) according to the equation

$$\omega_0 = \frac{1}{\sqrt{LC}}$$

where ω_0 is oscillating frequency, L is inductance, and C is capacitance. The resonant circuit, which consists of a coil and a capacitor, acts as an inductive coupling antenna for both electromagnetic energy in the radio frequency excitation pulse and energy emitted by proton relaxation. In MRI images acquired by GRE sequences with flip angle less than 60°, local enhancement of signal intensity occurs in the resonant circuit. This approach facilitates localisation, tracking, and guidance and improves imaging of implants, enabling detection of in-stent thrombosis and stenosis.[41]

Table 4 lists the various interventional and operative procedures for which MRI guidance is used. Intraoperative MRI was introduced by Jolesz and colleagues,[42] who used a 0·5 T vertical open magnet and by Lewin and colleagues,[43] who used a 0·2 T horizontal open magnet. Closed bore (as opposed to open MRI systems) MRI systems with 1·5 T[44] and 3 T field strengths[45] have been used since early 2000. High field magnets are preferred to low field magnets because of the better image quality, higher signal-to-noise ratio, improved contrast, and fast imaging capabilities for instrument guidance, diffusion, and perfusion imaging. With the commercial introduction of 125 cm length (instead of 165 cm) 1·5 T and 3 T magnets, with 70 cm bore instead of 60 cm, and patient transfer boards and ceiling-mounted moveable MRIs, intraoperative MRI has become a feasable option for modern operating rooms.

The main application of intraoperative MRI is in neurosurgery to enable total removal of operable cerebral tumours.[46] The introduction of MRI for the detection of early breast cancer and for cardiac imaging has enabled new MRI-guided procedures including breast biopsy. Image-guided treatment of structural heart diseases such as closure of septal defects, repair of heart valves,[47] and interventional treatment of arrhythmia,[48] benefit from simultaneous visualisation of the cardiac soft tissue and blood flow, avoiding the need for transoesophageal ultrasound.

One of the main technical problems with both intraoperative and percutaneous interventional MRI is achievement of reproducible, stable instrument position within the magnet during imaging. This difficulty has been solved with MRI-compatible robotics and guiding systems[49] exemplified by the pneumatically driven Innomotion robotic arm (Synthes Innomedic GmbH, Herxheim, Germany), which is made of polymers and ceramics and has been successfully used in clinical studies.[50]

Changes in temperature can be detected with MRI on the basis of the temperature sensitivity of proton relaxation. Proton resonance frequency uses rapid GRE

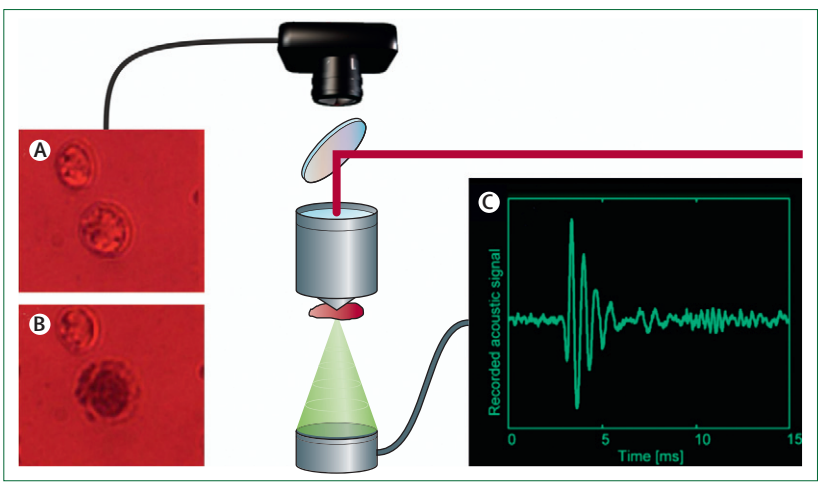

Figure 4: **In-vitro example of optoacoustics in therapy**
Nanoparticle-mediated, selective cell lysis with pulsed laser light monitored by ultrasound. Cells before irradiation (A). One cell irradiated with a single laser pulse (B), trypan blue staining shows cell damage. (C) An acoustic signal upon irradiation indicates that cavitation nucleation occurred when a nanoparticle was absorbed. For sufficiently intense laser pulses a cavitation response can result, which leads to highly selective cell damage. Data courtesy of Michael Kitz, Michael Jaeger, and Martin Frenz (University of Bern, Switzerland).

	Clinical	Experimental
Neuronavigation and intraoperative guidance	✓	
Biospy or resection of cerebral tumours (gliomas)	✓	
Endoscopic transphenoidal resection of pituitary macroadenomas	✓	
Biopsy of intra-abdominal organs and subclinical breast lesions	✓	
Angioplasty and stent placement for arterial stenoses	✓	
Closure of atrial septal defect		✓
Coronary sinus intubation		✓

Table 4: **Interventional MRI procedures**

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imaging.[51] After image processing, the MRI signal is associated with individual voxels (the volumetric equivalent of a pixel) each of which is given a greyscale value. Grey shade in anatomical images is proportional to the MRI signal magnitude, whereas their phase relates to the proton resonance frequency. Temperature change is then calculated from phase changes for each voxel obtained at different times with the equation

$$\Delta T = \frac{4\Delta\phi}{\gamma\alpha B_0 TE}$$

where ΔT is change in temperature, Δφ is phase difference, γ is the gyromagnetic ratio, TE is echo time, B_0 is net magnetisation, and α is temperature coefficient (about 0·01 parts per million per °C). Temperature changes can be mapped in real time, during thermal ablation by, for example, percutaneously inserted laser probes[52] or magnetic-resonance-guided focused ultrasound surgery.[53]

Focused ultrasound surgery guided by magnetic resonance has the potential to replace surgical resection for certain benign and malignant tumours (figure 3, appendix). Already approved in Europe, Japan, and the USA for the treatment of uterine fibroids, magnetic-resonance-guided focused ultrasound surgery is currently undergoing clinical trials for the treatment of breast,[54] pancreatic,[55] prostate, liver, and brain cancer[56] and for the palliation of pain in bone metastases.[57] Current research aims to target tumours with magnetic-resonance-guided focused ultrasound surgery to trigger drug release from encapsulated formulations (appendix) where treatment is needed, thus achieving lower systemic drug concentrations and reduced side-effects. Magnetic-resonance-guided focused ultrasound surgery is an excellent example of how multimodality physics applied to interdisciplinary science can provide a disruptive technology for more effective, and minimally invasive, therapies.

Conclusion

The capabilities of ultrasound and photonics are growing, both for guidance and direct delivery of therapy. Both will contribute to exciting future possibilities in minimal access surgery. Photonic and ultrasonic techniques can also be made compatible with MRI, with focused ultrasound surgery guided by magnetic resonance offering particular potential.

This report underscores the importance of physics as the basis of technologies used in the delivery of health care, which will only increase as diagnosis and treatment of life-threatening disorders become increasingly dependent on technologically. In this context, a change is needed in research and development to provide more structured integration between research in the physical and life sciences, hitherto overlooked in most countries, with any interactions being largely fortuitous. Increasingly, real progress in emerging techniques such as cell therapy and tissue engineering need a broad range of scientific expertise in multidisciplinary groups of life and medical scientists and practitioners, physical scientists and bioengineers. This need underpins the establishment of institutions such as the Institute for Medical Science and Technology (Dundee, UK), established in 2006, and the planned Francis Crick Institute, which aim to integrate these once disparate disciplines.

Contributors

AM and ZW wrote the report. SC and MPM wrote and revised the report. PP wrote and revised the report, and coordinated the figures. AC wrote, revised, and coordinated the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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