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Prospect for feedback guided surgery with ultra-short pulsed laser light

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The controlled cutting of tissue with laser light is a natural technology to combine with automated stereotaxic surgery. A central challenge is to cut hard tissue, such as bone, without inducing damage to juxtaposed soft tissue, such as nerve and dura. We review past work that demonstrates the feasibility of such control through the use of ultrafast laser light to both cut and generate optical feedback signals via second harmonic generation and laser induced plasma spectra.

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The anatomy of animals consists of a variety of distinct tissue types that may be directly juxtaposed to each other. Hard tissue constitutes bone in vertebrates and chitin in insects, while soft tissue constitutes skin, muscle, connective tissue, and nerve. The ability to surgically operate on hard tissue structures without inflicting damage to surrounding soft structures, such as removing bone while not affecting underlying nerve, is especially important for *in vivo* neurophysiological studies.

In vivo imaging of neuronal activity [1] or blood flow [2] in the brain with resolution near the optical diffraction limit typically requires mechanical thinning [3–5] or removal [6,7] of a portion of the skull to gain optical access to the brain. The realization of a craniotomy or thinned-skull preparation requires fine surgical skill and is typically performed with a hand-held dental drill. The outcome of the procedure can vary widely from surgeon to surgeon. This influences the physiology of the underlying brain, including the potential for inflammation [8], disturbed vasodynamics [9], and cortical spreading depression [10]. Craniotomies often stand as the rate-limiting step in biomedical research that enables the use of sophisticated optical tools to image structures deep within the cortex [11,12] of mouse models of brain function, in which structural or functional fluorescent indicators are expressed in specific cell types [13] (Figure 1A). A similar set of concerns exists for gaining optical access to the spinal cord [14].

Paths to automation of animal surgery are motivated by computer numerical control machine tools as a mechanism to guide a cutting tool to form craniotomies [15]. We consider the literature in support of ultra-short pulses, that is, of order 100 fs, of laser light, as a tool for surgical cutting [16–23] (Figure 1B). We then ask: (1) How can ultra-short pulses be incorporated with range-finding to provide constant control of the cutting path? (2) How can ultra-short pulses be combined with optical spectroscopy to provide feedback on the type of tissue being cut? (3) What are the prospects for an integrated surgical and diagnostic approach that can cut quickly and accurately, while minimizing collateral damage to neighboring tissue that must be preserved? This would allow plasma-mediated cutting to merge with robotic surgical techniques [24].

The physics of plasma-mediated ablation for cutting tissue

Plasma-mediated ablation with pulsed laser excitation builds on the concept of local excitation of molecules through nonlinear absorption, yet uses energy densities that are high enough to tear molecules apart rather than just drive electronic transitions that lead to fluorescent relaxation [25•]. Energy fluence, defined as the energy per unit area in the pulse, is a natural metric to describe the extent of material damage produced by a short laser pulse focused to a spot. As an example, a 10-nJ, 100-fs pulse that is focused to an 1-μm^2 area yields a fluence of 1 J/cm^2 (Figure 2) or an intensity of 10 TW/cm^2. This is equivalent to an electric field of $\sim 10^8$ V/cm or $\sim$1 V/Å, which approaches the $\sim$10 V/Å Coulomb field seen by valence electrons in atoms and molecules and leads to significant electron tunneling that frees bound electrons from their molecular orbitals to form a plasma [26].

The plasma grows as the free electrons seed an impact ionization cascade that involves acceleration of the electrons by inverse-Bremsstrahlung absorption, in which an electron absorbs photons while colliding with molecules [27]. After several absorption events, the free electrons

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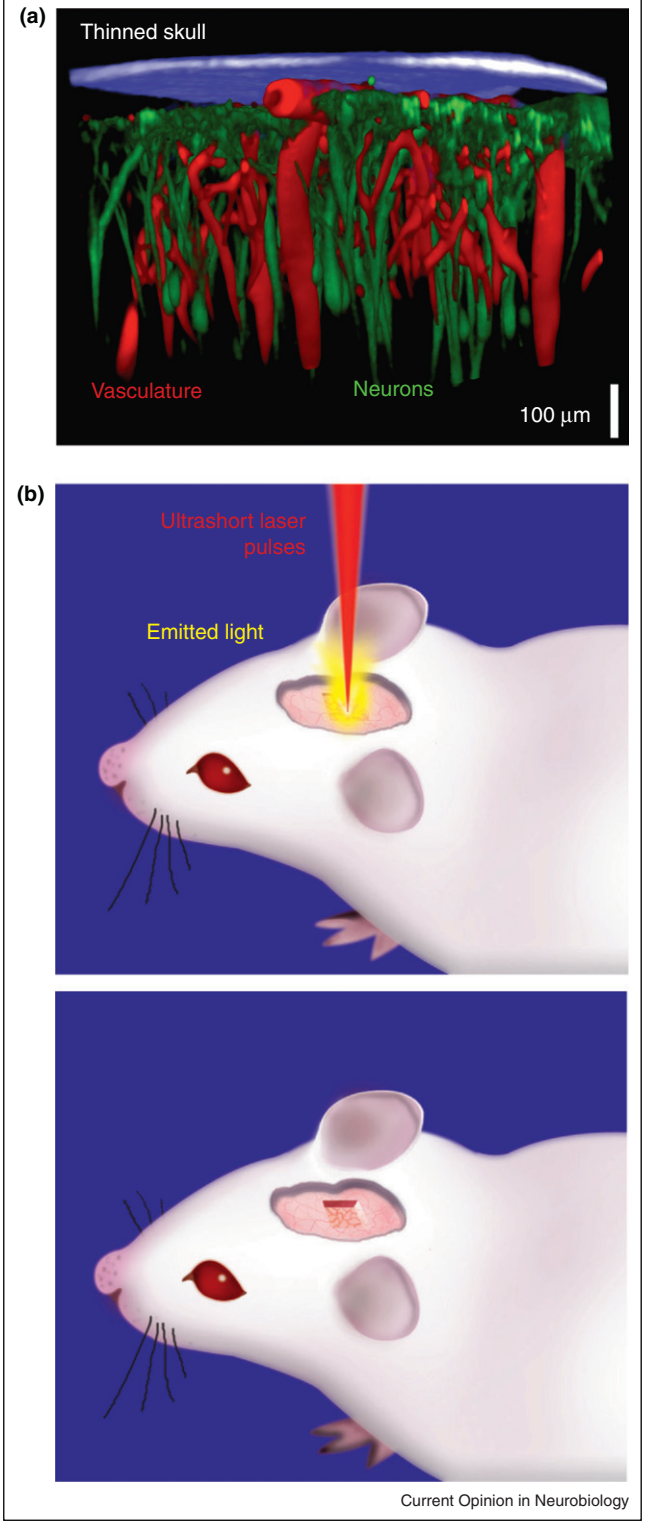
Figure 1



Cranial window to image brain function. **(A)** Maximal projection of a stack of images taken through a transcranial, thinned skull preparation. The skull was imaged with second harmonic generation (blue), the vasculature by two-photon laser scanning microscopy of blood plasma stained with the dye Texas red conjugated to dextran (70 kDa) (red), and the pyramidal neurons of layer 5b were imaged via their endogenous expression of green fluorescent protein (green). Adapted from [4]. **(B)** Idealized schematic of the use of pulsed laser light to reliably cut away bone and form a craniotomy or thinned-skull preparation.

achieve sufficiently high kinetic energy to ionize another molecule by impact ionization. This cascade, along with the continued generation of photoelectrons, leads to exponential growth of a micrometer-sized plasma bubble. Eventually the plasma becomes dense and limits the penetration of the incident light to a skin depth of only tens of nanometers. The restricted penetration depth provides axial localization of the plasma that is far better than the focal depth of the incident light.

The termination of the laser pulse is followed by recombination of the free electrons with the positively ionized molecules at the focus (Figure 3A). This occurs on the picosecond time scale of electron collisions at typical electron densities and leads to a transfer of energy from the electrons to the material on a time scale that is short compared to the ~100 ps acoustic relaxation time in the material. The result is a dramatic pressure increase within the excitation volume that can produce a rupture of the material and form a cavitation bubble. The bubble constitutes the region of ablation. The expansion of the cavitation bubble is associated with an acoustic shockwave that propagates into the surrounding tissue [28] and has the potentially deleterious effect of spreading damage into the sample.

The special nature of plasma-mediated ablation with ultra-short pulses

The minimum value of the fluence necessary to cause ablation depends on the width of the laser pulse and is lowest for ultra-short laser pulses [29–31] (Figure 3B), where the threshold level of order 1 J/cm^2. In practice, fluences of 10–100 J/cm^2 have been used for the ablation of a number of hard tissues, beginning with pioneering work on cuticle [32], followed by the cutting of dental enamel [33], dentine [34] and, of direct relevance, bone [35–37] (Figure 3C). The precision of plasma-mediated ablation of hard tissue was demonstrated by cutting microscopic features in bone [38] (Figure 3D).

A crucial issue for the use of plasma-mediated ablation in surgery is the magnitude and extent of the rise in temperature of the volume that surrounds the ablation region. The literature is equivocal on this point. Theoretical calculations point to a rise in temperature that decays in less than a micrometer from the site of the plasma bubble [39]. Yet direct measurements of the rise in temperature yield values that range from one-tenth to ten degrees at distances of tens to hundreds of micrometers from the site of ablation [40–42]. As a practical matter, microscopic ablations have been

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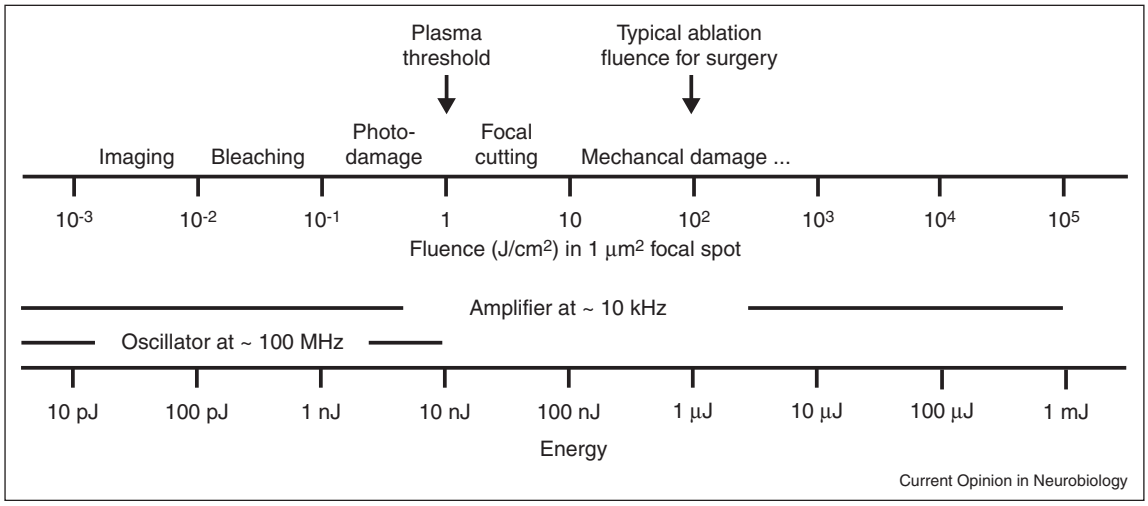
Figure 2



Scales in optical-assisted plasma-mediated ablation. A typical state-of-the-art amplified Ti:Sapphire system produces a 10 kHz train of 100 μJ, 100-fs pulses, to achieve a peak power of 1 GW at an average power of 1 W.

achieved for the cutting of fine subcellular processes [43–48], as well as the cutting of corneal tissue [49,50] and the manipulation of fine vascular processes [51–53]. Histological analyses of brain tissue ablated with a strongly focused beam show that the damage is confined to within a micrometer of the ablated surface [54] (Figure 3E). *In toto*, these data support the utility of plasma-mediated ablation with ultra-short laser pulses as a precision surgical tool.

Second harmonic generation for range-finding but not tissue identification

Automated surgery requires a means to detect the surface of the skull or other hard tissue as well as to map the local shape of the surface. Range-finding based on interferometric techniques is common, yet range-finding can also be performed by harmonic generation with the ultra-short laser pulses [55•].

Second harmonic generation is a nonlinear process that produces coherent photons with twice the frequency of the incident laser pulses when the intensity of applied laser pulses is sufficiently high [56,57]. The strength of the signal depends on the molecular structure of the material. It must be asymmetric, in the sense that opposing molecules do not point in opposite directions, and have a high second-order electric susceptibility. Many tissues, including bone [58,59] (Figure 4A) as well as connective tissue [60] (Figure 4B), and nervous tissue [61] (Figure 4C) meet these criteria. *In vivo* second harmonic imaging is particularly useful for feedback guided surgery since it depends only on intrinsic properties of the sample and does not require external dyes to image [58,62,63].

The second harmonic signal is diffraction limited and thus provides high spatial resolution as the beam is scanned through the sample. For scattering media, such as both hard and soft tissues, backscattered second harmonic signal from the surface and from the inside of the sample can be used for measuring the thickness of the sample [64–66]. The focus of the beam is scanned from above the surface of the sample and down along the z-axis [55•] (Figure 4D). The second harmonic signal will rise towards its maximum value as the focus enters the sample. It then drops in amplitude as the focus moves further into the sample where optical aberrations distort the focus of the beam and both incident and second harmonic photons are lost to scattering [55•,67–71] (Figure 4E). The thickness of the sample can be determined from the intensity profile up to the depth that the second harmonic signal is undetectable; the maximum measurable thickness is likely to be less than 1 mm in analogy with the imaging depth of two photon laser scanning microscopy [72,73].

Laser induced plasma spectroscopy for tissue identification

Second harmonic generation enables the non-disruptive determination of surface location and curvature and sample thickness, yet the signal is not unique to the type of tissue. The complementary technique of laser induced plasma spectroscopy [74,75,76•] may be used to distinguish hard from soft tissue. Here, the light emitted from the ablation region (Figure 3A), which corresponds to the recombination spectra of ionized atoms and molecules, is analyzed with a spectrometer to resolve the atomic composition of the material (Figure 5A). The laser induced plasma spectrum can be used to distinguish among different biological samples based on their chemical composition [77–80]. In

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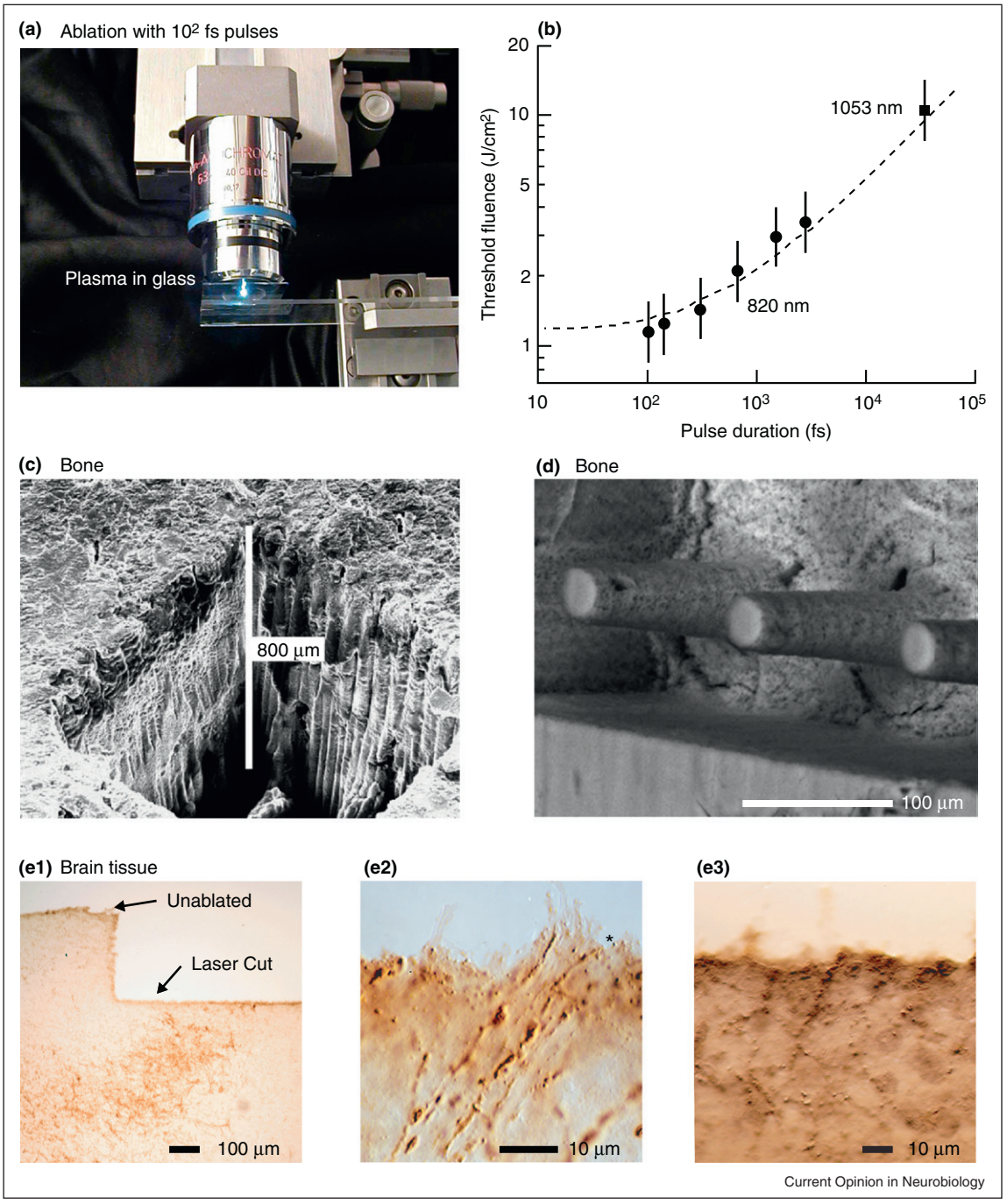
Figure 3



Plasma-mediated ablation of biological tissue with ultra-short laser pulses. **(A)** Emitted light from the plasma bubble in glass melted by 100-fs pulses whose fluence is well above threshold. Adapted from [105]. **(B)** Plot of minimum fluence for ablation as a function of pulse width. The short 100 fs pulses have the minimum fluence. Adapted from [30]. **(C)** Scanning electron micrograph of a porcine long bone cut in air. Adapted from [37]. (**D**) Scanning electron micrograph of patterned bone cut in air. Adapted from [38]. **(E1)** Bright-field image of immunostained surface of fresh brain tissue from rat, cut under saline. After completion of the optical ablation, the tissue was fixed, frozen, physically sectioned at a thickness of 25 µm, immunostained with anti-tyrosine hydroxylase, and visualized with diaminobenzadine precipitation. The brown regions correspond to immunostained axons and cell bodies. **(E2)** Tissue similar to that in panel G but imaged at high magnification to illustrate the cutting of individual axons (*). **(E3)** Immunoreactivity near an optically cut surface in unfixed neuronal tissue.

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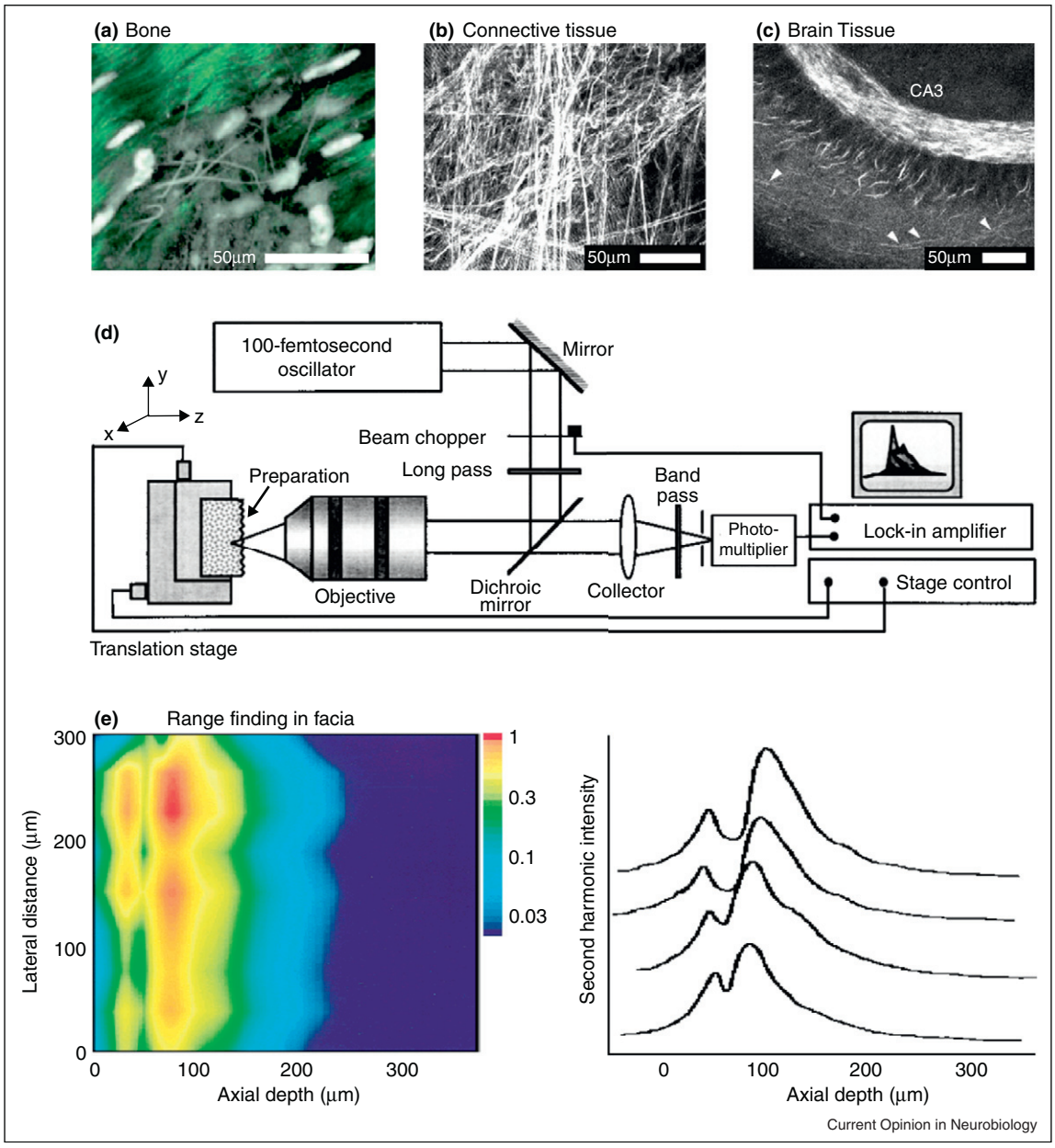
Figure 4



Second harmonic generation from biological tissue using pulsed laser light at amplitudes below the threshold for ablation. **(A)** The signal from collagenous periosteum (green) and calcein-loaded osteoblast precursors (grayscale) in mouse long bone. Second harmonic light was measured in backscatter. Adapted from [58]. **(B)** Signal from connective and muscle tissue from an explanted leg muscle. Adapted from [60]. **(C)** The signal from the CA3 region *of hippocampus* shows individual axons that emanate from the pyramidal neurons (arrowheads). Adapted from [61]. **(D)** Schematic of the apparatus for range-finding with second harmonic generation. Adapted from [55•]. **(E)** A depth image of a fascia membrane attached to chicken muscle tissue formed from the intensity of the backscattered second harmonic signal; the logarithm of the signal is shown versus a lateral dimension and depth. The analog values of the depth profile are shown for four lateral positions on the right. Adapted from [55•].

particular, bone and other calcified tissue may be distinguished from soft tissue based on the strong calcium emission peaks [81•,82,83] (Figure 5B).

Feedback guided surgery must frequently be performed in an aqueous environment to protect living tissue. In this case, the laser induced plasma spectrum may be unresolved as a result of pressure broadening and shortened emission lifetimes [84,85]. A number of approaches have been implemented to overcome these complications. Of particular interest is the use of double-pulse excitation scheme [83,86–88]. Here, the incident ultra-short laser

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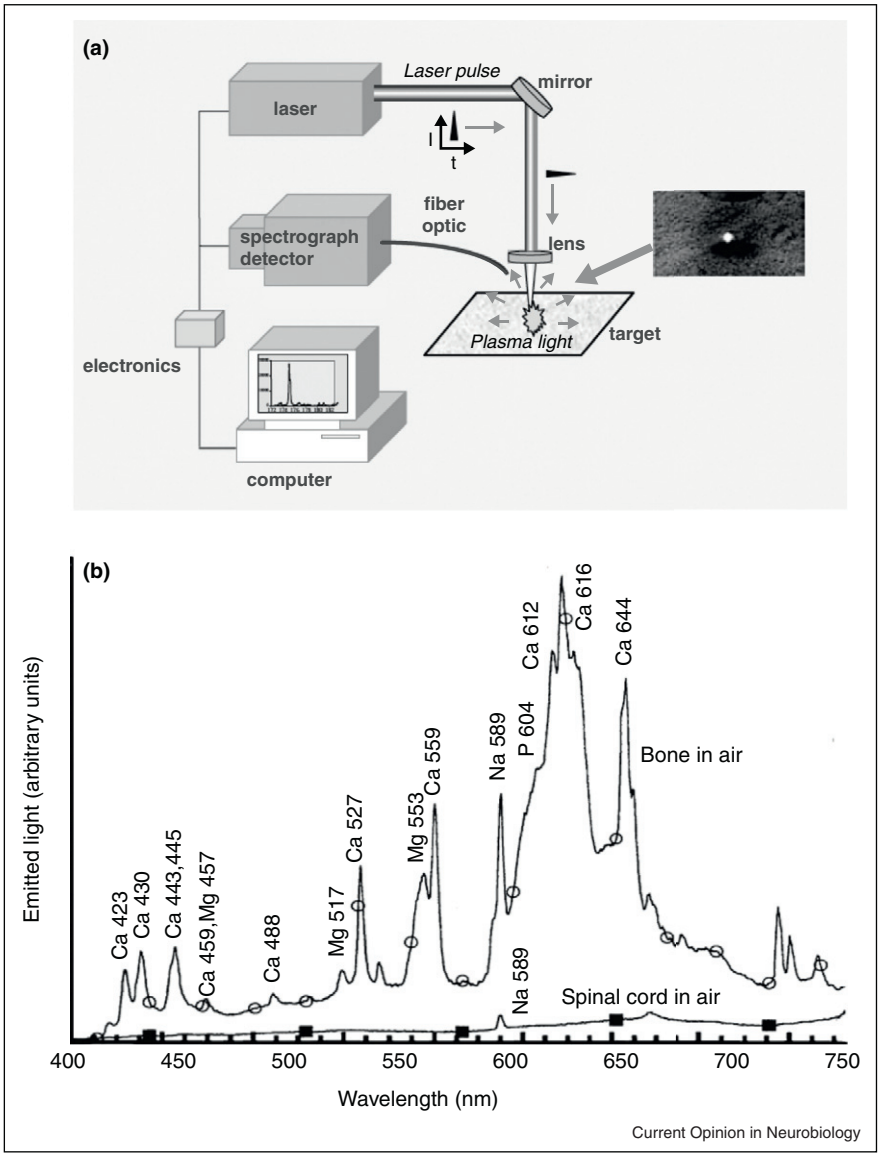
Figure 5



Laser induced plasma spectroscopy using ultra-short laser pulses in air. **(A)** Schematic of the process. Adapted from [75]. **(B)** The resultant emission spectrum for bone tissue versus spinal cord, a soft tissue. Adapter from [81•]. Note that soft tissue only has the sodium D line at 589 nm.

pulse is split, with both pulses focused on the same region of the sample but with one delayed by order of one nanosecond relative to the other [89,90]. The second pulse of light interacts with the plasma created by the first pulse and the emission spectrum has a greater signal-to-noise ratio than the spectrum after a single pulse. This improvement may relate to greater heating of the plasma, or the formation of an air-like expansion environment after the first pulse that minimizes pressure broadening of the plasma emission after the second pulse [86,91,92]. Further, temporal-gating of the collection of the spectra will isolate the signal from the initial broadband spectrum that is generated by nonlinear processes and initial pressure broadening at the center of the plasma bubble [76•,86,93–95]. Details aside, the existing literature supports the real-time identification of bone versus soft tissue via their optical emission spectrum on a pulse by pulse basis (Figure 5B) and forms the basis for control of the laser ablation beam.

Feasibility

An initial demonstration of feedback controlled surgery involved a perfused and fixed mouse head [96]. Plasma-mediated ablation with ultra-short laser pulses was used to cut an opening in the skull. The position of the head was under computer control via a three-axis motorized

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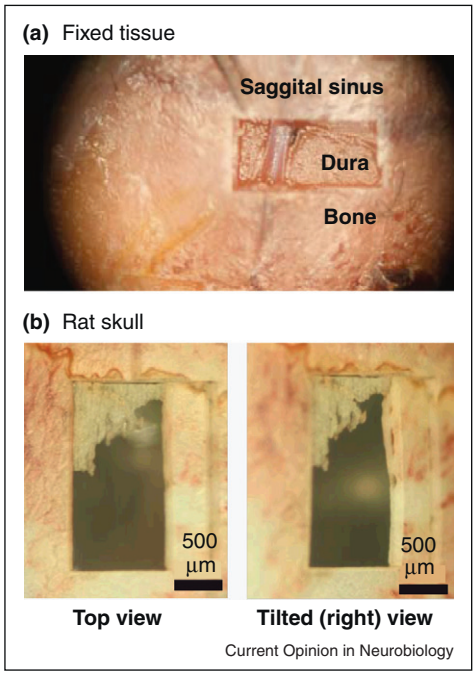
Figure 6



Preliminary results on plasma-mediated ablation of the rodent skull. **(A)** Data from a fixed but intact animal. The optically-cut window measures 2 mm by 1 mm. **(B)** The use of temporal focusing to achieve a greater depth profile with more efficient cutting. Adapted from [102•].

translation stage. The laser induced plasma spectrum was continuously monitored, with a scheme similar to that in Figure 5A, and was used to shutter the beam when regions of soft tissue were encountered. This led to a precision craniotomy that transversed the midline, a difficult manual procedure, without overt damage to the sagittal sinus (Figure 6A). Range-finding was not incorporated in this demonstration.

The depth of the ablated region depends on the numerical aperture of the objective and the energy of the incident laser pulses [30,31,54]. Higher energy will lead to deeper cuts. Thus the full power of the amplified laser source cannot be utilized to make shallow cuts with a single focus near the interface of bone and soft tissue. Two schemes that can make complete use of the output of the amplified laser source are cutting with multiple foci, as an extension of multi-focal imaging techniques in two-photon laser scanning microscopy [97–100], and temporal focusing [101,102•]. The latter scheme utilizes the spectral bandwidth of the laser pulse to decouple the axial and lateral spatial widths of the focus, so that one can construct shallow, pancake-shaped foci whose axial extent is at the diffraction limit but whose lateral extent is broad. This technique was used to ablate a variety of materials, including skull [102•] (Figure 6B).

How rapidly can cutting be achieved? The most powerful commercial amplified system, currently the Wyvern^{TM} 1000-30 Ti:Sapphire regenerative amplifier (Kapteyn-Murnane Laboratories, Inc., Boulder), produces 1.6 mJ pulses at 10 kHz. This implies an ablation rate of 1 mm^3 in 30 s for a single, temporally focused beam. The actual rate for removal of tissue can be faster if the ablation is designed to undercut the surface of the tissue. Lastly, temporal focusing may be further used to pattern as well as cut surfaces [103]; this may allow adhesives to stick more reliably to bone.

Epilog

No device currently exists that combines the cutting capability of plasma-mediated ablation, using ultra-short laser pulses to ensure negligible collateral tissue damage, with feedback control of the cutting process. The techniques reviewed here for range-finding and online tissue identification, all of which rely on the use of ultra-short pulses, can in principle be combined with plasma-mediated ablation to achieve a device for automated removal of bone juxtaposed with soft tissues. This forms the basis of a tool to further industrialize experimental physiology [104] through the automatic realization of craniotomies and thinned skull transcranial windows (Figure 1).

The challenges that abound for experimental studies in small animals are also present in numerous head and neck surgical procedures on human patients. Many surgical procedures with humans require thinning and removal of bone that overlies nerve and dura. As examples, these include procedures to decompress the optic, facial, or trigeminal nerve after tumor growth or traumatic injury as well as procedures to remove tumors from cranial regions that may be accessed through facial cavities, such as the *clivus*, a hollow that seats the pons, and the *sella turcica*, a hollow that seats the pituitary. Plasma-mediated ablation may prove to be useful for these tasks, where the relatively slow cutting rate of plasma-mediated ablation is offset by the precise feedback control.

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