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Ultrashort electromagnetic pulses are being increasingly produced by modern high power microwave and laser devices. These ultrashort pulses can produce electromagnetic transients in tissue that prompt safety questions concerning the possible exposure of living beings to ultra-short electromagnetic pulses. The existence of electromagnetic transients may permit meaningful advances in medical therapy and imaging. Electromagnetic transients, potential medical applications, and anticipated research avenues relevant to occupational health and safety issues are discussed.

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Ultrashort Electromagnetic Signals: Biophysical Questions, Safety Issues, and Medical Opportunities

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Ultrashort electromagnetic pulses are being increasingly produced by modern high power microwave and laser devices. These ultrashort pulses can produce electromagnetic transients in tissue that prompt safety questions concerning the possible exposure of living beings to ultrashort electromagnetic pulses. The existence of electromagnetic transients may permit meaningful advances in medical therapy and imaging. Electromagnetic transients, potential medical applications, and anticipated research avenues relevant to occupational health and safety issues are discussed.

ENGINEERING AND physical science have produced several devices that radiate ultrashort electromagnetic signals. These are high power microwave devices that produce electromagnetic pulses with pulse widths of just a few nanoseconds (a nanosecond is 10^{-9} seconds); pulse electric field amplitudes may exceed 100,000 volts per meter (V/m). Some lasers produce electromagnetic pulses with pulse widths of just a few femtoseconds (fs) (1 fs is 10^{-15} s); associated electric field amplitudes can exceed 1,000,000 V/m. These signals raise occupational health issues, and it is not clear whether existing safety guidelines apply. These occupational safety issues have stimulated scientific inquiry into the mechanisms of interaction between short pulse electromagnetic signals and living tissue. Signal-tissue interaction has kindled scientific curiosity along many fronts creating several opportunities for medical and technological spinoffs.

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This article describes how ultrashort electromagnetic signals propagate in human tissue, with emphasis on pulses at microwave frequencies. Some details of signal-tissue interaction are presented as they relate to tissue damage mechanisms. We discuss the use of ultrashort signals for tissue imaging, bioenvironmental monitoring and localized tissue hyperthermia. In the summary we chart future research directions and concepts in this exciting new domain of radiation biology and medicine.

Before starting the description of how ultrashort electromagnetic signals propagate in living tissue, it might help to describe what these signals are like in air. In air, these signals are bursts of electromagnetic energy emerging from the radiating device. These bursts or localized packets of energy are characterized by a direction of motion symbolized by the vector $\vec{k}$ (Fig. 1). When one is at a relatively great distance from a radiating source or antenna (that is, when one is in the so-called far field which is frequently a distance that is five times or more the diameter of the antenna), one will find the electric ($\vec{E}$) and magnetic ($\vec{H}$) vector fields at right angles to one another and each at right angles to the direction of motion of the pulse (Fig. 1). When the $\vec{E}$ and $\vec{H}$ vectors do not rotate around the direction of propagation, one has a linearly polarized pulse. In certain instances the $\vec{E}$ and $\vec{H}$ vectors may rotate around the direction of propagation $\vec{k}$ providing an additional level of complexity. Close to a radiating source, the right-angled structure of the $\vec{E}$, $\vec{H}$, $\vec{k}$ system usually breaks down and the electric and magnetic vectors are not perpendicular to each other nor to the direction of pulse propagation. This breakdown in the right-angled structure also frequently occurs when a pulse enters a material such as living tissue. In air, the electromagnetic pulse moves at the speed of light (usually symbolized as c). However, slower speeds often occur in tissue where the speeds may be one eighth the speed of light. In the

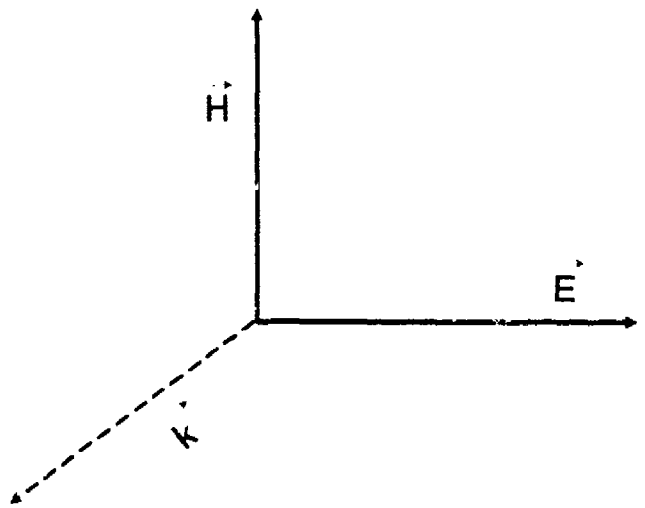

Fig. 1. The electric ($\vec{E}$), magnetic ($\vec{H}$) and propagation ($\vec{k}$) vectors in free space.

above description, we have not defined what we mean by an electric or magnetic vector or force. These definitions may be inferred from the following discussion of pulse-tissue interactions.

Pulse-Tissue Interactions

When a pulse strikes and enters a material such as tissue, a complex sequence of events, not fully understood at this time, is set in motion. It is critical to note that, as an electromagnetic field strikes and moves through a material, it exerts a mechanical force ($\vec{F}$) on the charged particles in the material. This force is given by the fundamental Lorentz equation written below:

$$\vec{F} = q\vec{E} + \frac{q}{\mu}\frac{\vec{v}}{c} \times \vec{H} \qquad \text{Eq. 1}$$

In Eq. 1, q is the charge on the exposed particle. Again, $\vec{E}$ is the electric field vector at the charged particle. The symbol μ is the permeability of the material to magnetic fields, $\vec{v}$ is the velocity of the charged particle, and, as before, $\vec{H}$ is the magnetic field. In this equation, the "X" symbol does not represent ordinary multiplication, rather this symbol represents vector multiplication. This "vector product" produces a third vector ($\vec{P}$) that is at right angles to the two vectors whose product is being taken, and the length of $\vec{P}$ (symbolized $|\vec{P}|$) is given by the expression:

$$|\vec{P}| = |\vec{v}|\,|\vec{H}|\sin\theta \qquad \text{Eq. 2}$$

where θ is the angle between the two vectors being vector multiplied. Putting the Lorentz equation together with the definition of vector multiplication, the following can be inferred. When an electromagnetic pulse strikes a material, charged particles in the material will tend to move in the direction of the electric vector $\vec{E}$. However, if that charge is moving, it will experience an additional force perpendicular to its own velocity and the magnetic vector $\vec{H}$. The interaction of the electric and magnetic fields will, in general, tend to curve the path of the charged entity. In tissue, there are many charged entities; for example: most, if not all, membranes carry charges at their surfaces in association with transmembrane potentials, and proteins have dissociated ionic sites as does DNA. Finally, potassium, sodium, chloride, calcium, and magnesium ions among others all exist in tissue and, thus, are subject to the forces associated with the Lorentz equation.

By generating charge movement and, thus, mechanical force within the tissue, the electromagnetic pulsed field deposits mechanical energy in the medium. But not all forces generated in the medium stay in the medium as mechanical forces because a second fundamental physical factor is operative. The second fundamental physical factor to remember is the fact that accelerating charged bodies themselves become sources of radiating electromagnetic fields.

To sum up, when an electromagnetic pulse strikes human tissue or similar material, charged entities are moved by the passing pulse; these displaced particles, having absorbed energy from the electromagnetic pulse, in turn, radiate a portion of that energy as a propagating electromagnetic field. This very complex and dynamic interaction is modeled well by a set of equations known as Maxwell's equations. This set of equations describes pulse propagation quite accurately, even in complex media such as tissue.

Consider the pulse shown in Fig. 2. This pulse, in air, is a square wave modulated sinusoid; the modulated sinusoid has a frequency of 10^{10} cycles/s (or 10 gigahertz). Fig. 3 shows what this pulse looks like after it has passed through 1 cm of pure water, the major component of tissue. The shape of the pulse is somewhat unexpected, yet this is the prediction of Maxwell's equations and qualitatively fits what has been, in fact, observed in the laboratory (16). The propagated pulse is slightly broader than is the pulse in air but, most prominently, the fundamental sinusoidal structure has been altered by the presence of large leading and trailing edge transients. These transients are called Brillouin precursors and are named after the mathematical physicist who first postulated their existence (4). These transients represent radiation from the initial and terminal transient movements of charged particles in the water as the pulse first strikes and then leaves the local region in the

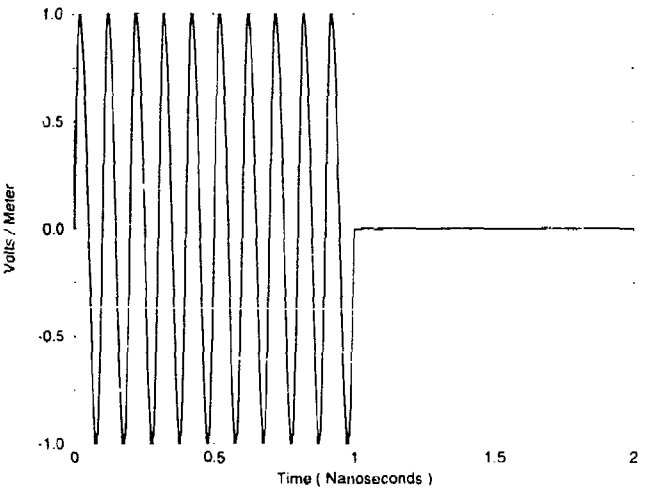

Fig. 2. An example of an ultrashort electromagnetic pulse.

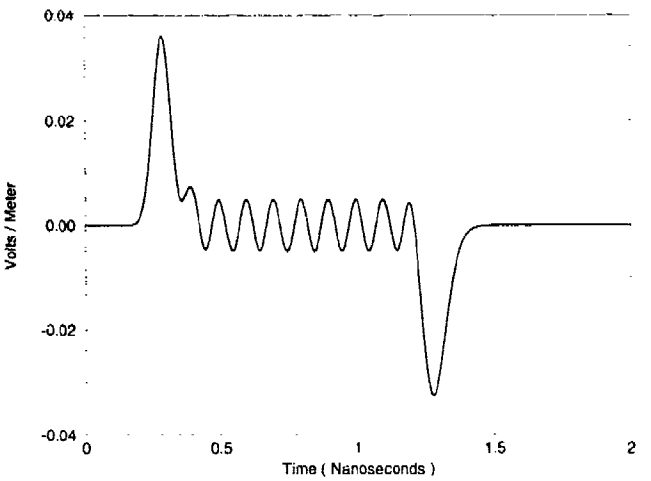

Fig. 3. The pulse of Fig. 2 after passage through 1 cm of pure water.

medium. The charged entities in pure water that are reacting to the field are the small charge separations in each water molecule associated with the 108° chemical hydrogen-oxygen-hydrogen bond. When a water-based tissue is stimulated by a pulse with higher frequencies, additional transients called Sommerfeld precursors are expected (20). These transients are illustrated in Fig. 4, representing the case of a pulse identical in shape with that of Fig. 2, but involving a base frequency in the optical spectrum (10^{14} to 10^{16} cycles per second). The Sommerfeld precursors reflect radiation from the outer shell electrons of molecules in the tissue.

The precursors described above were first postulated in 1914 in classic articles by Sommerfield and Brillouin (4,20). The mathematical analysis of that era left out some terms; therefore, the amplitude of the Brillouin precursor was thought to be quite small compared to what is seen in Fig. 3 and 4. Sommerfeld and Brillouin precursors were first seen experimentally in a waveguide structure by Pleshko and Palocz, but this experimental work did not discern the error in the available mathematical treatment because of the special material used as a propagation medium (16). The mathematical research of Oughstun and Sherman, using a refined version of the approximation used by Sommerfeld and Brillouin, clarified the proper relative magnitude of the Brillouin precursor, and independent computations at Armstrong Laboratory, employing the complete equations with no approximating forms, confirmed the advance of Oughstun and Sherman (2,10,14,15,19). Having established this phenomenological description of ultrashort pulse propagation, potential tissue damage mechanisms may now be considered.

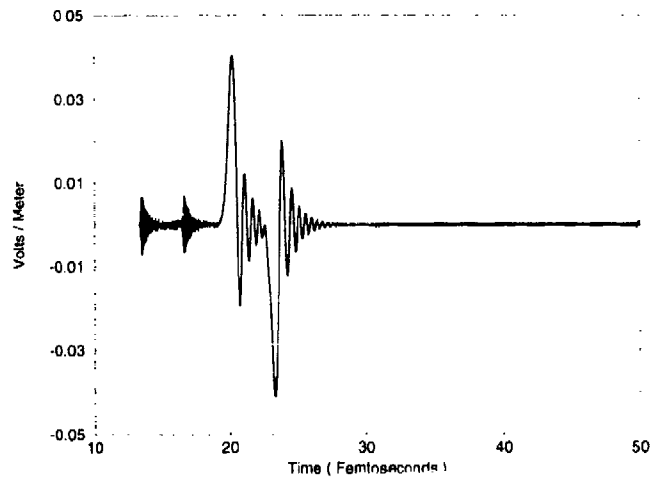

Fig. 4. A transmitted pulse induced by an incident signal as shown in Fig. 2, but at optical frequencies and just micrometers into the medium.

Potential Tissue Damage Mechanisms

In this section and the remaining portions of the article, the emphasis will be on ultrashort pulses describable using frequencies from 100,000 hertz (Hz) to 10^{11} Hz (1 Hz is 1 cycle/s). Long pulses with fast onset and/or offset times also give rise to transients or precursors and, thus, are also included in the following. The reader familiar with occupational or environmental medicine and with nonionizing radiation hazards may recall that guidelines have been published limiting human exposure to nonionizing radiation. A recently promulgated exposure standard is IEEE C95.1-1991 published by the Institute of Electrical and Electronics Engineers on 27 April 1992 (9). This standard covers pulses with durations less than 100 ms and frequencies in the range from 10^5 to 30×10^{10} Hz which would include a pulse such as that shown in Fig. 2. However, IEEE C95.1-1991 was developed from biomedical data on pulses whose onset and offset times (or rise and fall times) were much slower than those shown in Fig. 2; the standard does not embody the precursor phenomenon. Thus, in practical terms, the sharp, ultrafast category of pulses being discussed here are not covered by IEEE C95.1-1991 nor by any other formal guideline known to us; therefore, the issue of potential tissue damage mechanisms becomes particularly relevant for this category of electromagnetic events. Until the issue of tissue damage mechanisms associated to pulses that cause precursors is fully studied, the authors recommend zero human exposure to such unique precursor and gendering pulses.

With the above medical assessment as a prelude, four potential tissue damage mechanisms are outlined: molecular conformation changes, alterations in chemical reaction rates, membrane effects, and thermal damage. This list is not exhaustive, but is presented as a tentative starting point for scientific thought and deliberation.

Molecular Conformation Changes

During the passage of an action potential, the nerve membrane potential shifts from approximately −70 mV to +50 mV. Because the membrane is approximately 100 Angstroms (A) thick (1 A is 10^{-10} m), this voltage change represents a shift from −7,000 kilovolts per meter (kV/m) to +5,000 kV/m—a very large field strength change in the neighborhood of the cell membrane. In 1972, Neumann and Katchalsky wondered whether these short high peak voltage transient fields could alter the conformation of large macromolecules and, thus, possibly provide a mechanism for memory in the central nervous system (11). These authors ob-

served that very short pulses (about 10 μs in duration) with peak amplitudes around 2,000 kV/m could cause partial strand unwinding in polynucleotides. The polynucleotides have charged ionic surface sites. These sites attract free ions (such as potassium, sodium, and chloride ions) in the macromolecule environment to form the so-called electrical double layer. Neumann and Katchalsky postulated that the strand unwinding results from the perturbation of the macromolecule-double layer structure by the imposed electromagnetic pulse. Further research is indicated to define the threshold voltage and pulse repetition rate at which such conformation changes occur.

A second indication of the importance of macromolecular conformation change in considering tissue damage mechanisms for very short electromagnetic pulses is the fascinating recent research on pulse gel electrophoresis of DNA (7,18). Low peak amplitude pulses (350 V/m) applied for 1–10 s significantly alter the pattern of motion of DNA suspended in a gel matrix. The mechanism is a complex interaction between the large charged molecule, the impressed electromagnetic field and the pore structure of the gel containing the DNA. Study of electromagnetic thresholds for induced DNA mobility and biomedical consequences might become a promising research direction.

Alterations in Chemical Reaction Rates

In the above description of pulse propagation in a medium like tissue, field-induced movement of the tissue components was described along with reradiation from accelerated charges in the tissue. When one realizes that molecular motion and electron (charge) exchange are fundamental to the determination of chemical reaction dynamics, one may infer that ultrashort high peak voltage electromagnetic pulses could interfere with biomolecular chemical reactions. Indeed, it is a derived result of thermodynamics that chemical equilibrium constants will be shifted in a continuous wave electromagnetic field. In fact, Chen, Heinsohn, and Mulay (6) show through mathematical analysis and experimentation that a continuous wave electromagnetic field will change the chemical equilibrium constant K, in the absence of a field, to the equilibrium constant K_e, in the presence of an electromagnetic field, in accordance with the equation:

$$\ln(K_e/K) = w_1|E|^2 + w_2|H|^2 \qquad \text{Eq. 3}$$

In the above equation w_1 and w_2 are weighing parameters that are inversely proportional to the absolute temperature, and directly related to the dielectric constants and magnetic molecular susceptibilities of the chemical reactants and products (6).

Exposure of a chemical reacting system to a single sharp electromagnetic pulse or a rapid sequence of such pulses does not represent an equilibrium exposure; therefore, one should not expect that the above equilibrium thermodynamic equation should strictly hold. Were the equation to hold, an electric field intensity of approximately 1,000 V/m could engender a 1% change in equilibrium constant K. Research on transient electromagnetic field-induced chemical reaction rate changes might well be very useful and instructive.

Membrane Effects

It is well established that high peak field pulses can open small channels through cell membranes. The process is called electroporation and has been reported at peak fields between 400 and 600 kV/m (5,21). From the point of view of establishing health and safety guidelines and from the point of view of biophysical curiosity, it appears important to determine the threshold of this phenomenon and the fundamental mechanisms by which it occurs. Prior to the occurrence of electroporation, rapidly applied pulses modify the transmembrane potential of a living cell (5,21).

Thermal Damage

When a pulse moves through tissue, it causes charged components to move with the field. These orderly directed movements accelerate the collision rate of the charged molecules (or other components such as membranes) with structures in their environment. Thus, the field-directed mechanical energy imparted to the charged particles is subsequently passed to other structures, some of which may have no charge at all. These collisions of the driven particles with particles in their environment increase the total kinetic energy in the medium raising the temperature in the medium as a whole. Deposition of thermal energy in a tissue can offset homeostatic mechanisms in the organism and cause physiological stress; at high temperatures, deleterious phenomena such as protein denaturation can occur.

Experts in electrodynamics do not have a complete understanding of how electromagnetic field energy is converted into thermal energy. For example, charged molecular species have specific modes of motion to which they are constrained by their pattern of internal bonding. While synthetic DNA has been well studied, in general, molecular modes of motion have not been characterized, and it is not known in most cases which modes are stimulated by electromagnetic fields including pulsed fields (17,22). Also, it is not known whether molecular modes of motion can internally share energy absorbed from an electromagnetic field (such sharing would imply nonlinearity in the molecule as a mechanical structure). Furthermore, and perhaps most importantly, it is not known how much time the collision process takes to offload the electromagnetic energy a molecule has absorbed into one or more of its modes of motion. If the rate of energy removal from a target molecule is slower than its absorption from the electromagnetic field, in some sense significant heating of the individual molecule could occur during a radiation exposure with little gross change in the overall medium temperature causing highly localized damage (1). It would be interesting and possibly important to study the details of these thermal mechanisms.

Applications of Ultrashort Signals

While there is much to be done to assess the occupational health implications of ultrashort electromagnetic pulses, it is clear that positive applications of these sig-

nals are possible. For example, electroporation is being considered for cancer therapy (21). If a brief, intense, locally applied electromagnetic field can open pores in cancer cells, chemotherapeutic agents may more readily enter to destroy the cancer. If the electromagnetic field is applied differentially so that normal cells surrounding the tumor are not opened, it is possible that the cancer could be removed with reduced chemical side effects in the patient. Applying pulsed energy to thermalize tissue could also be useful because hyperthermalization itself has been found to complement the action of chemotherapeutic agents and ionizing radiation in cancer research efforts (8,12,13).

Ultrashort pulses may also lead to the development of new techniques for imaging tissue structures. The precursors formed by the passage of short pulses carry with them detailed information about the molecular dynamics and structure of the medium through which the pulse has passed. The precursors contain this information through the process of selective absorption and reradiation that was previously discussed. By studying pulse returns in detail one can infer, at least in some cases, the dielectric constant and conductivity of the medium at each point in the medium. This determination can permit a visual reconstruction of internal structures (3).

Soils, particularly those containing water, have electrical properties that are similar to those of tissue. It may be possible to assess the purity of ground water using propagated electromagnetic fields. Detailed dielectric maps of underground structures, to include waste deposits, may also be feasible.

Summary

Ultrashort electromagnetic pulses are an exciting new modality with which to explore biological tissue. Medical applications include hyperthermia, electroporosis, and imaging. At high peak power levels, one may expect occupational health hazards to ensue and radiation safety thresholds for these hazards must be determined. Four potential tissue damage mechanisms have been outlined including macromolecular conformation changes, chemical reaction effects, membrane alterations and temperature mediated adverse responses. Investigation of these four, and possibly other, mechanisms can be expected to open new horizons into which we can expand our biomedical technology.

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