Review Article

QUANTITATIVE EVALUATIONS OF MECHANISMS OF RADIOFREQUENCY INTERACTIONS WITH BIOLOGICAL MOLECULES AND PROCESSES

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Abstract—**The complexity of interactions of electromagnetic fields up to 10^{12} Hz with the ions, atoms, and molecules of biological systems has given rise to a large number of established and proposed biophysical mechanisms applicable over a wide range of time and distance scales, field amplitudes, frequencies, and waveforms. This review focuses on the physical principles that guide quantitative assessment of mechanisms applicable for exposures at or below the level of endogenous electric fields associated with development, wound healing, and excitation of muscles and the nervous system (generally, 1 to 10^2 V m^{-1}), with emphasis on conditions where temperature increases are insignificant ($\ll$1 K). Experiment and theory demonstrate possible demodulation at membrane barriers for frequencies $\leq$10 MHz, but not at higher frequencies. Although signal levels somewhat below system noise can be detected, signal-to-noise ratios substantially less than 0.1 cannot be overcome by cooperativity, signal averaging, coherent detection, or by nonlinear dynamical systems. Sensory systems and possible effects on biological magnetite suggest paradigms for extreme sensitivity at lower frequencies, but there are no known radiofrequency (RF) analogues. At the molecular level, vibrational modes are so overdamped by water molecules that excitation of molecular modes below the far infrared cannot occur. Two RF mechanisms plausibly may affect biological matter under common exposure conditions. For frequencies below approximately 150 MHz, shifts in the rate of chemical reactions can be mediated by radical pairs and, at all frequencies, dielectric and resistive heating can raise temperature and increase the entropy of the affected biological system.**
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INTRODUCTION

THIS PAPER evaluates interactions of electromagnetic fields with biological materials from the perspective of the direct effects of electric and magnetic fields on the ions, atoms, and molecules of biological systems. This perspective requires attention to the time and distance scales appropriate for specific mechanisms in addition to amplitude, frequency, and other field properties. So far as possible, we estimate thresholds for effects from basic principles rather than attempting to determine if a particular combination of field magnitude, frequency, and modulation appears to satisfy criteria for a physiologically meaningful biophysical interaction. Our approach is quantitative and focused on fundamental physical mechanisms. An emphasis on fundamental interactions allows consideration of the effects of exogenous fields in context with effects of endogenous fields caused by natural activity of the heart and other muscles, the brain, and other parts of the nervous system.

To explain experimental observations of effects with radiofrequency (RF) fields at low amplitudes, a variety of mechanisms has been suggested for amplification by physical, chemical and biological means. For example, we discuss mechanisms that utilize coherence, resonance, signal averaging, and the non-uniformity of fields in inhomogeneous dielectric structures and at dielectric discontinuities. Nonlinear mechanisms have been proposed to address modulation-dependent effects. Although the time average of any oscillatory field is zero, nonlinear systems respond to the second or higher powers of the field.

Although we attempt to be comprehensive, the very large number of suggested physical mechanisms for RF effects requires that some be mentioned only by entries in a table. Some of the mechanisms listed are well known and readers can consult the cited papers, but others are not much more than general suggestions that have not been developed to the point where they can be evaluated quantitatively. Although we adopt a broad scope, we do

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not treat electrostimulation, a recognized and established effect used as the basis for protective standards at frequencies below 100 kHz. Reilly provides a complete discussion of this subject and summarizes stimulation effects in Table 11.7 of Reilly (1998).

We set the stage for quantitative discussions of proposed mechanisms for RF bioeffects by noting that electric and magnetic forces are fundamental to the arrangements of electrons and atomic nuclei that determine chemical structures. Correspondingly, all chemical and biochemical changes occur though electric and magnetic interactions affecting charged particles. In this sense, all biological processes ultimately could be viewed as events mediated by changes in the local electric fields associated with chemical structure.

Although this paper is guided—and simplified—by an interest in biological effects for fields in the gigahertz range, we consider mechanisms involving at least 12 orders of magnitude in frequency, from quasi-static to over 10^{12} Hz. These various mechanisms can contribute to our understanding of RF effects because the time scale for many biochemical changes is so rapid that even fields in the gigahertz range are essentially stationary during a chemical transition occurring on the sub-nanosecond time scale. However, chemical change occurs over such a wide range of characteristic times that a 1 GHz electromagnetic field that might be treated as quasi-static for one type of biochemical event would be rapidly varying for another. For example, catalyzed reactions occur on the nanosecond to picosecond scale (Gilch et al. 1998; Pilet et al. 2004; Schramm 2005; Clore and Schwieters 2006) but synthesis and folding of macromolecules can take several seconds or even much longer (Martin and Schmid 2003).

For oscillatory fields of any frequency, linear responses average to zero over one period, but for nonlinear responses, such as a hypothetical alteration in the rate of a rapid chemical reaction, mechanisms of an RF field with a period in the nanosecond range might not differ from those at lower frequencies.

This emphasis on the fundamental role of electric and magnetic forces in relation to chemical and structural time scales suggests that the endogenous quasi-static electric fields associated with development and wound healing provide suitable quantitative benchmarks for analysis of mechanisms of biological effects by RF electromagnetic fields. Subsequently, this paper takes note of the biogenic fields of the heart, bone, nervous system, and other tissues, and considers the sensitivity of sensory systems that have evolved to detect electric and magnetic fields. The remainder of the paper considers numerous biophysical mechanisms that are either proven or proposed. Many readers already will be familiar with the most common mechanisms, which therefore are treated briefly, allowing more detailed consideration of several proposed mechanisms, some of which can only be tabulated and discussed briefly.

NATURALLY OCCURRING FIELDS AND SENSORY SYSTEMS

This section addresses naturally occurring endogenous macroscopic fields all of which fall below the RF range. These macroscopic fields govern, or are generated by, vital biological processes such as embryonic development, bone growth, and wound healing. We examine these fields to determine whether RF energy can interfere directly and whether nonlinear demodulation of RF fields can change physiological functions operating at frequencies far below RF. Thus, the magnitudes of the endogenous fields discussed in this section, the background electrical noise, and the ability of the biological system to demodulate RF fields, discussed later, are key factors in evaluating the effects of external fields.

Endogenous fields

Experimental techniques have been developed to measure the quasi-static fields associated with development, wound healing, and other time-varying endogenous fields of living systems (Jaffe and Nuccitelli 1974). These naturally occurring fields provide an approximate yardstick for physiological changes in tissues and their underlying molecular and biochemical processes by externally applied fields, including RF energy.

Experimental data obtained from vertebrate and invertebrate species ranging from dinoflagellates to humans demonstrate that steady ionic currents over a range from a few to 100 μA cm^{-2} flow in normally developing tissue and at the sites of tissue amputation (Nuccitelli 1992, 2003). The dc (or slowly varying) fields that apparently play a role in embryonic development and wound healing have been measured to be in the range from about 10 to 150 V m^{-1} (Nuccitelli 2003). In particular, the electric fields in epidermal and corneal tissues healing from experimentally created wounds were measured at 40 and 150 V m^{-1}, respectively, and right-left asymmetry in developing frog and chick embryos was accompanied by an even smaller field of 10 to 20 V m^{-1} (Nuccitelli 2003). The range of physiological steady state electric fields was estimated to lie within the range 1 to 200 V m^{-1} based on a body of literature showing that single cells and cells in a variety of developing and repairing tissues are guided and oriented by imposed electric fields in this range (reviewed by Nuccitelli 1992). The Nuccitelli review cited effects on cell motility for a variety of cells,

including cells of the immune system, developing nervous system, bone, skin, and even protozoa, and effects on growth axis orientation in developing organisms ranging from fungi to mammals.

Hart and Gandhi (1998) measured and calculated cardiac-induced endogenous fields in three low-frequency bands fields from 0 to 100 Hz. They found tissue field strengths that ranged from tenths of a volt per meter in the heart to millivolts per meter at a distance from the heart. Reilly (1998) calculated the minimum in-situ electric field across the membrane that would be equivalent to thermal noise to be about 2 V m^{-1} for a spherical cell and much less, 0.08 V m^{-1}, for an elongated cell (length of 150 μm and radius of 25 μm), and noted that the example would only apply to frequencies below a few kilohertz.

In addition, the nervous system produces electric fields as a result of neuronal activity in the brain, spinal cord, and peripheral nerves; myogenic fields arise from excitable tissue of the heart, diaphragm, gut, and other muscle tissue; and pancreatic beta-cells also are electrically excitable.

Bone-generated electric currents and the associated electric fields have been the focus of research on their role in normal growth and injury repair. Tissues have been exposed using a wide variety of irradiation parameters and many different types of applicators. For example, physiological effects have been reported for electric fields of 1, 100, and 1,000 V m^{-1} in a number of experimental designs where tissue was exposed to pulsed magnetic fields over regions that typically were over one centimeter in radius (Pilla 2007). These electric field strengths are not greatly dissimilar from those cited by Nuccitelli (1992). Somewhat stronger electric field strengths were derived from studies of strain-produced fields on small bone samples. Observed potentials of 3 V across a 1.3 mm bone slice would indicate an electric field strength of 2 kV m^{-1} (Salzstein and Pollack 1986). The apparent overlap between the physiological range of 1 to 200 V m^{-1} reported for a variety of biological systems and the applied fields used clinically to treat non-union fractures supports the idea that endogenous fields play a role in the healing of bone fractures.

It is also important to note that exogenous fields must be on the order of these endogenous fields to affect these normal functions or any associated functions. Nuccitelli (2003) suggested that a level of 0.1 V m^{-1} would have no effect on a biological system. However, active neuronal circuits studied in vitro in brain slices respond to extremely low frequency (ELF) electric fields at about this level. In contrast, effects on individual neurons required a considerably greater field strength. Experimental studies discussed in the later section "Physical Principles Governing RF Mechanisms" showed that neuronal circuit oscillations were affected in some preparations by an in-situ 50 Hz electric field strength as low as 0.2 V m^{-1} (root mean square, rms). Biological mechanisms involving electric induction of ELF fields at these frequencies are not relevant for exposures to unmodulated RF fields because biological structures capable of supporting induction at RFs are not known to exist. Induction of ELF amplitude-modulated RF fields would be of interest if there were a demodulation mechanism that produced ELF electric signals of sufficient magnitude, but no such demodulation mechanism has been reported for frequencies above approximately 10 MHz, as discussed below. For this reason, RF fields above several megahertz cannot couple to the biological systems that respond to endogenous DC or ELF fields by mechanisms involving electrical potential changes at the plasma membrane.

Emission spectrum of endogenous fields

The existence of endogenous fields naturally leads to the question of emissions by these fields. The emission spectrum of large living organisms has complex features at ELFs (<3 kHz) due to endogenous signals generated by the heart, the central nervous system, and other organs (Guyton 1976a and c; Nunez 1981; Hart and Gandhi 1998). In humans, the low-frequency spectral power density of these signals is dominated by the electric field from the heart QRS pulse that has a maximum value of 0.4 to 0.6 V m^{-1} in the torso (Hart and Gandhi 1998) and about 15 mV m^{-1} in the brain, with average values that are approximately one-fifth to one-tenth as great.

The spectrum of living tissue above a few megahertz has the characteristics of a black body at $\approx$300 K and lacks any sharp peaks in emission or absorption. Exceptions to this generality for absorption appear as various relaxation processes, including the prominent broad relaxation of water in biological tissues that is centered near 25 GHz at body temperature (Foster and Schwan 1996). The peak emission frequency lies in the infrared at a wavelength of 10^{-5} m. In the RF-microwave spectrum, living tissue and its DNA (Bigio et al. 1993) absorb RF signals as a broadband receiver (without sharp selectivity). The energy is entirely converted to random molecular motion as in a Planckian black body. However, the discussion that follows on specialized sensory systems is stimulated by the fact that structural and biomolecular adaptations found in living systems support functions that are not evident from the gross dielectric properties of tissue. For that reason, conclusions based on material properties alone can be misleading. For example, rhodopsin molecules are tuned photodetectors whose spectroscopic properties can be measured and related to

molecular structure (Jasaitis et al. 2007), but those properties and the phenomenon of vision are not evident from the dielectric properties of the eye and retinal tissue. Similarly, the electric and magnetic field sensitivity of some organisms is not grossly evident, but requires examination of specific anatomical and biophysical structures as in the electrosensory organ of elasmobranch fish (Montgomery and Bodznick 1999), magnetic compass of certain invertebrates (Phillips et al. 2002), and bird navigation using magnetic cues (Wiltschko et al. 2006).

Features of electromagnetic field-sensing systems

Organisms at all stages of evolutionary development (invertebrates to humans) have electromagnetic field-sensing systems that detect heat and light, often with extraordinary sensitivity as indicated just above and in topics found in this section and the following subsections. In some species, quasi-static and low-frequency electric and magnetic fields are detected for use in orientation, navigation, defense, and prey detection. The mechanisms of these sensory systems merit discussion because high sensitivities to specific electric, magnetic and electromagnetic fields exemplify the extraordinary sensory capabilities of biological systems developed through evolutionary forces. In general, sensitive sensory systems exploit a cascade of signal detecting structures and signal processing by the nervous system to utilize environmental signals as stimuli necessary for survival (Torre et al. 1995; Adair et al. 1998). At the cellular level, the underlying biophysical mechanisms are framed in terms of altered cell membrane potentials and altered neuronal firing rates, which provide a classical perspective for cell participation in the extracellular electrical environment. Subsequent cellular events in electrosensory organs do not appear in the published literature, but are likely to involve second messengers cascades as in other sensory modalities such as mechanotransduction, chemical transduction, and phototransduction (Torre et al. 1995; Hudspeth et al. 2000; Takeuchi and Kurahashi 2005).

This evolutionary argument suggests that if sensory physiology is to be a guide for RF sensitivity, one would want to inspect existing sensory modalities for an opportunity where RF energy might inadvertently be transduced by a system developed for another type of energy. Vision, thermo-sensing, taste, and touch do not offer obvious opportunities for incidental RF sensitivity, but microwave hearing provides an example where the sensitivity of the hearing system to small pressure waves permits detection of such a wave when it is induced by an RF pulse (Foster and Finch 1974; Chou et al. 1975, 1976, 1982; Elder and Chou 2003).

Extraordinary amplitude sensitivity for organs that detect light, heat and molecules. Detection of low levels of light occurs through a physico-chemical (structural) change in the photochemical rhodopsin. In the eye, a single photon of incident light can cause a measurable hyperpolarization (1 mV) of a rod cell (Darnell et al. 1986). Rod cell signals are integrated by retinal ganglion cells, each of which is stimulated by up to 600 rod cells (Guyton 1976b) whose axons merge to form the optic nerve. The rods have a sensitivity of about 2×10^{-8} W m^{-2} in humans and an even lower threshold of stimulation in some nocturnal animals.

Energy in forms much less energetic than light quanta can also be detected in biological systems by thermo-sensitive molecules that can respond to small temperature changes, including temperature increases caused by absorption of RF electromagnetic energy in body tissues. Although a receptor for innocuous temperatures that are not elevated far above body temperature has not been identified, a variety of sensory cells respond in stepwise fashion upon elevation of tissue temperature (Peier et al. 2002). Sensitivity to temperature change depends not only on the temperature gradient but also on the particular sensory area, indicating that there is spatial summation of the thermal stimulus. The human skin can detect a rapid change of 0.01 K if the entire body is affected simultaneously (Guyton 1976b).

At the extremes of signal detection, such as detection by a sensory cell of one or a few light photons or similarly scant numbers of receptor-binding ligands, there are physical limits based on the counting of sparse, discrete, events that set the system noise floor independent of the details of chemical kinetics and cooperativity among receptor elements (Bialek and Setayeshgar 2005).

Electric field sensing in marine organisms. Elasmobranch fish exhibit sensitivity to low-frequency ($<$10 Hz) electric fields of the order of 0.5 μV m^{-1} (Kalmijn 1982), which corresponds to a potential of the order of 2.5×10^{-8} V across the sensory epithelium of the electrosensory organ, the Ampulla of Lorenzini (Kalmijn 2000). The mechanism of these electrosensors is still being investigated. Kalmijn (2000) has introduced the hypothesis of electrically excitable ion channels amplifying the input signal from the sensory canals in a stable positive feed-back loop. The summation of inputs to the afferent nerve fibers from approximately 10,000 cells in each of 1,000 ampullae has been advanced as the explanation of this unique electric field sensitivity (Petracchi and Cercignani 1998; Kalmijn 2000).

Heiligenberg and colleagues studied the jamming avoidance behavior of electric fish whereby one fish can shift the frequency of its own electrical pulse generator—

necessary for its active electrical imaging sense—in order to avoid interference from another nearby electric fish that might be emitting a similar pulse train (Heiligenberg et al. 1991; Heiligenberg 1991). The complex behavior exhibited by electric fish is achieved by the sensitivity and specificity with which they can detect weak electric fields using integration of outputs from numerous sensory neurons, a distributed system for neural processing of these sensory signals, and higher order processing in the brain.

These two examples of specialized fish behaviors illustrate a general observation that biological systems can achieve great sensitivity, often at theoretical limits, by developing highly specialized sensory systems under evolutionary stress. In the absence of specialized cells, tissues, and the techniques employed by these fish and other organisms (spatial amplification, signal summation and signal averaging, and phase discrimination in brain structures), biological systems are not inherently sensitive to weak external stimuli. For example, biological cells themselves are not sensitive to sound waves. Hearing requires the mechanical structures of the ear, a specialized neuromechanical transducer found in the cochlea, and extensive brain processing of a great number of nerve signals. It bears noting that because coherent RF fields of significant magnitude were introduced into the environment only a short time ago, there has not been enough time for evolutionary forces to develop specialized sensors for RF field detection even if such detection were somehow advantageous to survival.

Magnetic field sensing in bacterial, avian, and mammalian species. There are three basic mechanisms for magnetic field sensing (Tenforde 1989; Lohmann and Johnsen 2000; Johnsen and Lohmann 2005):

1. Faraday induction and Lorentz forces (up to about 10 Hz). Faraday induction in tissues has not been shown to play a role in sensing magnetic fields in tissues of terrestrial animals for which the small size of any current loops suggests field detection is unlikely. However, electrosensitive marine animals may be able to sense induced ELF electric fields because they are surrounded by a conducting medium, that is, seawater (Johnsen and Lohmann 2005);
2. A magnetite-based receptor could be broadly tuned in the 0.5–10 GHz range. An array of 10^6 or more single domain particles of magnetite could be sensitive to static magnetic fields as low as 1–10 nT (Phillips and Deutschlander 1997) (see section below, "Magnetic dipole interactions in biological magnetite," for further discussion of magnetite). Studies of animal behavior indicated sensitivity of vertebrates to static magnetic fields of 0.50–10 μT, comparable to the geomagnetic field strength (Phillips and Deutschlander 1997); and
3. Biochemical reaction yields can be changed by both static and RF magnetic fields that alter the number of spin-coupled radical pairs that recombine. Several distinct mechanisms exist to explain radical pair recombination effects that occur with static and RF magnetic fields over the range from millitesla to microtesla levels. Radical pair mechanisms depend on the magnetic properties of the nuclei comprising the spin-coupled radical pair (Timmel et al. 1998) and do not apply generally in radical pair chemistry because not all molecules have nuclei with suitable magnetic moments.

Present evidence indicates that both the magnetite and radical pair mechanisms are utilized among various vertebrates, including bird species (Mouritsen and Ritz 2005; Wiltschko and Wiltschko 2005). The magnetite and radical pair mechanisms for the avian magnetic compass differ in their responses to oscillatory fields. Behavioral and theoretical studies indicate that certain birds navigate using a radical pair mechanism sensitive to small changes in the geomagnetic field of approximately 50 μT. The altered reaction rates underlying radical pair magnetoreception in birds may be sensed visually through effects on retinal photochemistry (specifically, cryptophores) and possibly neuronal transmitters in the avian retina (Ritz et al. 2000; Timmel and Henbest 2004; Ritz et al. 2004). A broadband magnetic field (0.1 to 10 MHz) at the remarkably low level of 0.085 μT, approximately 0.2% the geomagnetic field strength, was sufficient to disrupt orienting behavior attributed to a radical pair mechanism in birds (Ritz et al. 2004). Resonances with energy levels split by the hyperfine interaction might occur for frequencies of up to approximately 100 MHz (Timmel and Henbest 2004; Ritz et al. 2004) in contrast to the more broadly tuned magnetite-based receptor.

Additional comments on electromagnetic field sensing. The foregoing examples of sensory systems sensitive to EMFs often involve specialized receptors tissues and organs such that the extraordinary sensitivity to electromagnetic energy is not constrained by simplistic appearances about the signal-to-noise ratio (S/N) because sensitivity is achieved through an array of parallel sensors and a cascade of organs that integrate the effects on individual receptors over space or time or both. See for example a discussion of the shark's electric sense by Fields (2007).

This brief overview of sensory systems that detect weak electric, magnetic and electromagnetic fields illustrates the sensitivity and specificity of organs developed under evolutionary pressure in order to enhance survival, especially along the predator-prey axis and for migration. Although sensory systems exist in the low-frequency region and for the infrared and optical regions, there is no evidence of comparable sensors that developed to obtain an evolutionary advantage using RF energy. The reason is clear. The RF spectrum lacks natural significant coherent sources and was essentially featureless until the advent of modern sources of electromagnetic fields. As a matter of economy for species pursuing means to gain survival advantages, the absence of naturally occurring RF coherent electromagnetic signals strongly suggests that biological systems did not develop means to detect RF because they would have been useless. Nonetheless, the radical pair mechanism illustrates a case where an RF magnetic field can disrupt orienting behavior and, in principle, might affect other biochemical processes.

PHYSICAL PRINCIPLES GOVERNING RF MECHANISMS

There are well-established basic physical principles that must be considered when proposing any mechanism of interaction with a biological system. If a proposed mechanism challenging fundamental principles were supported by convincing experimental data, the impact would be revolutionary and lead to a major effort in theoretical and experimental research.

First principles require that interactions of RF electromagnetic energy with matter by any mechanism whatsoever will ultimately result in heat from dissipation of that energy. The dissipated RF increases the average energy level of the random molecular agitation within the absorbing body resulting in a temperature increase that may be readily evident as, for example, in microwave cooking, or too slight to be measurable as, for example, in many common exposures occurring several wavelengths from an antenna fed at a typical average input power (1–1,000 W). The thermal effects of RF energy have been examined in considerable detail for exposures in various technological and laboratory applications over a wide part of the spectrum (Johnson and Guy 1972; Elder and Cahill 1984; Durney et al. 1986; Stuchly et al. 1986; Kuster and Balzano 1992; Bernardi et al. 2000; Dimbylow 2002; Bernardi et al. 2003; IEEE 2005). Thermalization is not the focus of interest for effects and mechanisms that occur when the temperature increase is insufficient to change biochemical reactions and the biological processes they serve. Effects and mechanisms of this sort have been called *athermal* and *non-thermal*. There is no firm basis to distinguish these terms, both of which are widely understood to involve temperature changes of <1 K. Some uses would restrict *non-thermal* to designate mechanisms where temperature changes are too small to measure reliably (e.g., <0.01 K), are in the range of thermal fluctuations (thermal noise) and thereby too small to alter biochemical reactions, and perhaps additionally for laboratory exposure levels, low enough that temperatures can be kept stable with aggressive methods of cooling (Sheppard 1998). The conduct and evaluation of experimental work requires careful attention to the manner in which RF heat is transferred from the biological test system regardless of descriptive labels such as *athermal* and *non-thermal.* Because it can be difficult to thoroughly assess temperature effects in many biological experiments, the possible application of any of the athermal mechanisms to be described below needs consideration for a particular biological study only after ruling out heat effects.

Mechanistic alternatives to thermalization that may be called upon to explain observations concerning RF fields too weak to act through heating must consider such weak forces and low quantum energies that they naturally lead to suggestions for resonance phenomena of one kind or another. Mechanical, electrical and atomic systems offer many examples where resonance with internal modes can, over time, concentrate energy from an external oscillatory driving force resulting in a greatly amplified response at the driving frequency. A suspension bridge driven into galloping motion by marching soldiers, an inductor and capacitor tuned to an alternating current, and the emission and absorption spectroscopic features of atoms and molecules are well-known examples that have served as paradigms for possible resonant behavior in biological systems exposed to RF energy. As in the foregoing examples, RF resonance would require a system responsive at and tuned to the RF frequency, internal losses that are small with respect to the driving force, and a driving signal strong enough to overcome intrinsic noise. Although we focus on physical mechanisms, the same principles can be extended to biochemical resonances and complex sensory systems of living systems where, as in the example of hearing, mechanical, neuronal, and brain structures perform as amplifying subsystems.

Prohofsky (2004) summarized the nature of resonant absorption of electromagnetic energy in biological molecules in this way: “The absorption of electromagnetic energy by matter always depends upon mechanical motion of charged matter, such as the orbital motions of electrons in atoms or molecules, which must be resonant with X-rays or light; or the vibrational and spinning motions of relatively massive chemical groups that can

absorb energy in the infrared and RF regions. Most molecular spectroscopy is conducted in the range above 10–100 cm^{-1} (300 GHz–3 THz) because below these frequencies one usually sees only a continuum in absorption rather than line spectra characteristic of isolated resonant vibrational motion."

Exceptions exist where electromagnetic resonances occur at lower frequencies (e.g., the ammonia maser at 24 GHz) and acoustic modes can, in principle, exist at any frequency. Electromagnetic coupling to acoustic modes is discussed below.

The sections below review proposed mechanisms of interaction, several of which involve forms of resonance, in light of physical concepts from signal theory, thermodynamics, quantum mechanics, and dielectric theory in order to identify the conditions of frequency and amplitude for a response to RF energy, thereby setting limits on the RF fields that would plausibly elicit a response from a biological system.

Influence of dielectric loss in water on the RF properties of ions and charged molecular structures

The interaction of ions and charged molecular structures with electric fields results in motion of a magnitude that depends on the strength and frequency of the field and the inertia of the charged object. Ideally, small charged particles, such as monopolar ions, would be able to respond at frequencies greater than 10^{12} Hz (in the infrared), but the association of ions with water molecules (solvation) means that the dielectric properties of water, with its large dipole moment, are dominant in biological solutions.

At low frequencies, water molecules are able to rotate freely in an oscillating electric field with little energy loss. As the frequency of the electric field is increased above approximately 10^8 Hz, the rotational inertia of the molecules ("dielectric friction") begins to inhibit rotation, causing energy absorbed from the field to be dissipated by collisions or nearest neighbor interactions in the medium. The dielectric relaxation of pure water at 310 K is centered at approximately 25 GHz, but the rotational response of water dipoles to an electromagnetic field extends over a very broad range. The upper response frequency is set by intermolecular forces that produce a rotational time constant of a few picoseconds. Frequencies greater than several terahertz produce an insignificant response of the water molecule such that the dielectric constant at infinite frequency (ε'_∞) becomes frequency independent. The frequency-independent value ε'_∞ is 1.8, which reflects internal molecular motion and not dipole rotation (Hasted 1973).

Proteins bear charged groups located at sites specific to the atomic arrangements of the molecule. Like isolated ions, these groups are associated with (bound to) water, which strongly influences the dielectric behavior of molecular structures. For this reason, the dielectric properties of biological tissues depend on and vary with water content. Relaxation of various large molecules causes additional variation with frequency. This subject has been extensively reviewed by Foster and Schwan (1996), at length by others (Cole 1972; Grant et al. 1978; Schanne and Ruiz-Ceretti 1978; Pethig 1979), and recently by Despa (2005). Despa and Berry (2007) have described water's role in long-range attractive forces between hydrophobic molecules and the role of hydrophobic attraction in protein folding and self-assembly, and the relaxation of proton magnetic resonances.

Direct electric field effects on ion transport at the plasma membrane

The practical limits for direct field effects on ion transport across a plasma membrane are set by shot noise, averaging time, and ion transit rate. The upper bound for dynamical effects on ionic transport through a transmembrane channel protein is ~10 MHz (Pickard and Barsoum 1981), reflecting the shortest time ($\sim 10^{-7}$ s) in which an ion can be translocated a distance of approximately 10^{-8} m across the membrane (Pickard and Rosenbaum 1978).

S/N considerations

The superposition principle indicates that the net field affecting a linear biological system is the sum of endogenous and applied fields, with possible new components for nonlinear systems (see further discussion below). Consequently, applied fields much smaller than naturally occurring fields in the same frequency band can produce only a small perturbation in ongoing processes. The external applied signal must have an amplitude of the order of magnitude of the endogenous fields in order to have an effect, but if it is much smaller, for example, one-tenth of the physiological field amplitude in the same frequency band, the addition of the external field can only perturb the amplitude slightly and introduce a small amount of phase-modulation. Another consideration is that, based on existing experimental observations, there is no evidence that changes in tissue fields are physiologically significant unless their magnitude is comparable to the endogenous fields arising in electrically excitable tissues. Naturally occurring physiological fields are not constant in amplitude or phase but vary in response to an ever-changing physiological and environmental milieu. Because physiological fields generated by muscles (including the heart) and the nervous system (including the brain) are summations of discrete electrical pulses from a large number of electrically active cells,

they are not harmonically pure. Their spectrum is continuous and generally confined to parts of the ELF and very low frequency (VLF) regions. From signal detection theory, such endogenous fields are the source of a band of electrical noise that determines whether a specific low-frequency external sinusoidal field has sufficient amplitude for detection. (Signals with non-sinusoidal phase progression pose additional problems to a detector, as is evident from the theoretically infinite Fourier spectrum of a step function.) The foregoing fundamental considerations indicate that an RF carrier amplitude modulated by a low-frequency signal could be expected to produce a biological effect only if the demodulated baseband signals are approximately of the order of the magnitude of the endogenous fields (see section immediately below and section titled "Demodulated field strengths are very weak" for additional discussion of demodulation).

S/N considerations for detection of exogenous fields. Natural systems and man-made electronic devices can enhance signal detection by assembling a large number of detectors to achieve spatial summation (for example, with a large telescope mirror or lens or by the rod cells of the retina) and by temporal summation that can involve various forms of signal averaging and amplification, as discussed below.

We briefly consider results from experiments with mammalian brain tissue to illustrate the general principle. The membrane potential at the cell bodies of individual hippocampal neurons was observed to change by an average of 0.18 mV per V m^{-1} (rms) in an applied steady electric field, and declined exponentially with increasing frequency (Deans et al. 2007). Compared to those at 0 Hz, potentials at 50–60 Hz were attenuated by a factor of $\approx$0.4. The principle that a cellular ensemble fashioned into a neuronal circuit is more sensitive than individual neurons was demonstrated by the low threshold for effects in tissue exposed to 50 Hz fields. Field levels as low as 0.18 V m^{-1} (rms) affected circuit oscillatory behavior in a threshold manner. This field strength corresponds to a membrane potential change at a neuronal cell body of just $\approx$0.07 mV, which is below the membrane noise level of an individual cell (Deans et al. 2007).

Other research showed that neuronal systems of modest size can exhibit collective network properties as a result of weak pairwise correlations between neurons of a large population (Schneidman et al. 2006). Model calculations and experimental data on neuronal firing rates indicated that for large interconnected systems, focusing solely on interactions with a single element is not sufficient to describe system properties. Correlation analyses of groups of retinal ganglion cells showed that weak pairwise correlations were sufficient to exhibit collective properties in the spike trains of a system of fewer than 15 neurons.

S/N in thermodynamics. The S/N can be used to understand RF energy absorption in view of fundamental thermodynamic factors. Any interaction that occurs between incident RF energy and a single biological molecule, a living cell, or an entire organism is a physical event in which the RF field changes the energy states of atoms or molecules. All such transfers or transformations of energy absorbed from the RF field obey thermodynamics laws. The kinetic energy associated with random motions of atoms and molecules results in background electromagnetic noise that, depending on context, is called blackbody radiation or Johnson noise (Wannier 1966). Biological systems have additional noise sources (Vaughan and Weaver 2005). In order to affect molecular function, incoming RF energy must either "pump" existing vibrational, rotational, or electronic modes of resonant absorption, or affect non-resonant energy absorption processes in a way that overcomes the molecular level noise resulting from fluctuating temperature, concentration, mechanical stress, and background electric fields (Vaughan and Weaver 2005).

The distinction between resonant and non-resonant absorption is critical to many discussions of effects of weak RF fields. Resonant absorption, for example a photon-driven transition between electronic states, occurs when the signal is in a narrow bandwidth B for which the relevant noise energy is confined to the same bandwidth, and thereby reduced by the factor B (and by $B^{1/2}$ for the field strength). In contrast, a non-resonant effect such as an increase in temperature for the entire thermodynamic system occurs against the background of thermodynamic noise over an unlimited spectrum. For this reason, nearly all proposed mechanisms for effects of weak (non-thermal) RF fields concern pumping energy into resonant modes for which the in-band noise level is very much reduced from the system-wide noise level. The exceptions involve speculations about regions or entities somehow isolated from the overall thermodynamic system and thereby able to absorb energy selectively and have a lower noise level.

In the RF band, the spectrum of noise arising from random particle motions is featureless, having no outstanding or dominant frequency components. For a system at equilibrium, the noise can be represented by the Rayleigh-Jeans law (Wannier 1966; Illinger 1982), which is a limiting case of Planck's law and suitable for a blackbody at biological temperatures ($\approx 3 \times 10^2$ K). On

a prima facie basis, any exogenous signal has to overcome this in-band background signal if there is to be a plausible interference with ongoing biological processes. A S/N of <0.1 is considered a conservative threshold for RF to be effective in changing a biochemical process (Vaughan and Weaver 2005).

S/N analysis for electrostriction. Adair (2003) made calculations using dimensional analysis indicating the impossibility of overcoming thermal noise with an RF electric field strength of 200 V m^{-1}. He showed that a direct field effect on a proton moving in a water-like medium would have a S/N of about 2×10^{-13}. For a field acting to switch a system from a lower to a high energy state with no significant energy lost to dissipative processes (for example, representing a transmembrane ionophore), Adair estimated a S/N of 5.5×10^{-9}. For the case of electrostrictive forces on an object the size of a large molecule (characteristic volume of about 10^{-21} m^3) the S/N = 10^{-7}. However, for a cell of 10 μm radius, electrostrictive forces can result in a S/N of 0.3, but the effect will be masked by other dc forces. Direct forces on ions, molecular switches, and electrostriction are dissipative, producing energy proportional to the square of the electric field strength. Adair noted that electrostrictive forces are not oscillatory and should be compared to other steady forces, for example, gravitational forces and body movement.

Time averaging. Time averaging is a powerful tool to extract a coherent signal from random background noise. Because white noise of constant spectral power density N_0 over a large band is incoherent [it has the autocorrelation function $R(\tau) = N_0\delta(\tau)$, where $\delta(\tau)$ is the delta function] (Davenport and Root 1958), in theory, a low-level purely harmonic signal can be extracted from white noise if it is possible to limit the noise to a narrow spectrum surrounding the signal frequency to be detected, perform a time averaging or autocorrelation operation (e.g., using an electronic instrument) over the narrow band, and detect the coherent signal. Various instruments and computer-based simulations function as band-limited time-averaging resonant detectors as do the basilar membrane and associated elements of the auditory system (Guyton 1976b). For a coherent harmonic signal, the time-averaging function increases in value over the averaging time while the noise tends to zero over the same interval (Davenport and Root 1958). For an averaging period P, the S/N improves as $P^{1/2}$, indicating that under ideal circumstances it may take a very long time to detect the desired coherent signal if the initial S/N is low (weak harmonic signal). Phase jitter of the harmonic signal and inability to limit the noise bandwidth degrade signal averaging.

Stochastic resonance is the phenomenon whereby a nonlinear system achieves a better S/N by addition of a moderate amount of noise (Gammaitoni et al. 1998). Stochastic resonance was demonstrated to improve sensory performance in crayfish mechanoreceptors (Douglass et al. 1993) and signal transduction in ion channels (Bezrukov and Vodyanoy 1995). The characteristic signature of stochastic resonance is a peak in a plot of S/N vs. noise. For crayfish mechanoreceptors and other physiological systems, the improvement in S/N can be by as much as one order of magnitude. Adair (1996b) noted that signals very much weaker than the system noise level will be ineffective regardless of the existence of stochastic resonance, which improves signal detection only for signals closer to the noise level.

Direct electric field effects on molecular reactions and molecular structure

In principle, RF energy could affect molecular processes (e.g., chemical binding at ion transport channels, receptor sites, enzymes and other proteins) through an accumulation of small molecular or dynamical changes or by perturbation of reaction rates. As an example of the field strengths required, Apollonio et al. (2006) used ab initio computational methods to obtain molecular potentials for the binding/unbinding of CO to the active site of the heme group. The model showed that 10^8 V m^{-1} was the lowest local field strength that could affect the binding and unbinding energy barriers. Thus, it would require an unattainably strong exogenous electric field to directly perturb the energy surface at the active site. Other research focused on the complementary perspective provided by the fields associated with changes in molecular structure. Electric fields of 10^8 to 10^9 V m^{-1} were associated with functionally significant changes in structure of the enzyme aldose reductase (Suydam et al. 2006). Those field strengths are consistent with the estimate easily obtained by assuming a covalent bond of 1 eV in which one or more electrons are shared over an interaction length of 10^{-9} m. Suydam et al. (2006) also observed the variations in local electric field strength that result from thermally-driven fluctuations in protein structure. The fluctuation-driven electric field distribution was much broader than the shift in average electric field strength associated with experimentally-induced alterations in molecular structure. This distribution of field strengths illustrates the important point that in the inverse situation of applying an electric field in order to affect molecular structure the applied field would be embedded in a background of fluctuations measured experimentally as having a width of tens of wavenumbers (hundreds of gigahertz) in the case of aldose reductase (Suydam et al. 2006). Therefore, even if local fields of approximately

10^9 V m^{-1} could be applied, they would be not be distinguished from a broad distribution of electric fields of similar strength arising from fluctuations in molecular structure. In this manner, thermal energy sets a limit for the lowest effective local electric field strength at approximately 10^9 V m^{-1}.

A similar conclusion comes from recent molecular dynamics calculations that showed changes in the secondary structure of lysozyme in a frequency- and field strength-dependent manner at a specified constant temperature of 298 K (English and Mooney 2007). Structural effects appeared for local electric field strengths in the range 1–5 $\times$ 10^9 V m^{-1} at frequencies of 50 to 500 GHz. This non-thermal mechanism for protein denaturation was attributed to interactions with the overall protein molecular dipole moment with further influences due to sidechain interactions with solvent (water) molecules. The degree of denaturation would have required temperatures of 400–500 K if it had been produced by heating. It is worth emphasizing that these electric fields could be introduced into the model to explore effects on molecular structure although there are no technological or laboratory devices that could achieve such extreme field strengths at these frequencies. Moreover, even at the most sensitive frequencies, the required field strength exceeds the field strengths used for supra-electroporation by more than an order of magnitude.

Small quantum energy

Ionizing radiation is defined by its ability to remove electrons from atoms and break chemical bonds. In contrast, RF energy is nonionizing because the energy that might be localized at a chemical bond is much too weak for a direct effect. The RF photon energy for a frequency of 1 GHz is 4.0 $\times$ 10^{-4} kJ mol^{-1}, which is much smaller than the thermal energy at body temperature (310 K) of 2.6 kJ mol^{-1}. Only resonant absorption (i.e., a mechanism with a very large Q-factor) or multiple photon processes at a molecular site could overcome unfavorable energy ratios of the order of 6,500, as in this example.

Multiple photon processes

The question arises as to whether absorption of multiple RF photons in the GHz range can excite low-lying absorption modes in biological molecules such as the mode at 184 GHz ($\approx$6 cm^{-1}) calculated for myoglobin by Rai and colleagues (Rai et al. 2003[§]; Prohofsky 2004). In principle, multiple photon processes could upshift incident energy to a region where resonant interactions are known to occur. In general, multiphoton absorption requires very intense incident photon beams so that there can be an appreciable probability that successive photons arrive rapidly enough to excite successive virtual energy states during their lifetimes. Examples of multiphoton absorption use laser sources to achieve conditions necessary for absorption of two or more photons. Simultaneous absorption of m photons becomes more and more unlikely as m increases because the transition probability P_m for an m-order process must be less than the m-th power of P_{ij}, the transition probability for one photon, i.e., $P_m < (P_{ij})^m$ (Pantell and Puthoff 1969). Because P_{ij} itself is <1, multiphoton probabilities for high order processes are exceptionally low, that is, undetectable, and can be ignored. For example, a highly improbable 18th order transition is required to shift frequency from $\approx$10 GHz to 184 GHz, the frequency where Rai and colleagues (Rai et al. 2003[§]; Prohofsky 2004) predicted an unusually low-lying mode in the myoglobin molecule. In contrast, most molecular vibrational modes are in the range above 20 cm^{-1} reflecting the fact that molecular spectroscopy typically is conducted in the range of 10 to 100 cm^{-1} (300 to 3,000 GHz). In a calculation of multiphoton events, Pickard and Moros (2001) assumed a specific absorption rate (SAR) of 100 W kg^{-1}, which exceeds exposures permitted by safety standards and is likely to heat tissue by several degrees, but the probability of observable multiphoton absorption effects was indistinguishable from zero.

Water damping limits mode excitation

Molecules, molecular subgroups, and atoms have freedom to move in translational and rotational modes that in principle could absorb RF energy. Although continuum models (Adair 2002) provide a broadly applicable perspective, the complexity of large molecules requires a more detailed look at vibrational modes within a molecule, particularly because energy absorbed by specific molecular structures can lead to structural changes that are significant for biochemical reactions. For example, in the case of an enzyme, such structural change could affect physiological functions of a living system (Prohofsky 2004). As suggested above in noting the featureless nature of RF spectra below several hundred gigahertz, the frequency range over which intramolecular electromagnetic absorption occurs is determined by the strengths and orientation of chemical bonds and the viscosity of the immediate environment. Like overdamped macroscopic objects, atoms and molecules cannot follow an imposed oscillatory force when frictional forces exceed the driving force. In such cases, despite the possibility of resonant energy absorption in the absence

[§] Rai BK, Prohofsky EW, Durbin SM. Protein control of heme binding dynamics in myoglobin from Green-function analysis of heme and globin normal mode coupling. Unpublished report, Department of Physics, Purdue University, W. Lafayette, IN; 2003.

of damping, oscillatory modes cannot appear in damped systems.

Ignoring damping, calculations show that a roughly spherical protein with a structure representative of myoglobin and other compact proteins has its lowest resonant vibrational mode at a frequency of approximately 720 GHz and a protein of similar size but an elongated shape could be resonant to as low as 182 GHz (Prohofsky 2004). For an extended flexible structure such as DNA, acoustic mode vibrations at much lower frequencies are possible, but the lowest electromagnetic coupling is at 240 GHz. Prohofsky (2004) also discussed a vibrational mode unique to a molecule like myoglobin in which the large heme group resonates at the relatively low frequency of 184 GHz because of rotational freedom within a pocket of surrounding protein that effectively isolates the heme group from viscous damping by water outside the pocket (Rai et al. 2003[§]; Prohofsky 2004). Moreover, both acoustic modes, where compression waves flow along a linear structure, and transverse waves are overdamped by water for frequencies below ≈300 GHz. The same damping forces also prevent intermolecular movements of an entire molecule ("bulk modes") (Prohofsky 2004).

Water provides a frequency-dependent molecular viscosity that is strongly overdamping (damping factor ≈1) for frequencies above approximately 10 GHz, which is consistent with a relaxation time of 39 ps (and corresponding frequency of 4 GHz). At frequencies below several gigahertz, damping falls toward zero because water has become unified with the molecular structure and they move as a unit. However, this unit is far too massive to exhibit resonant behavior.

In summary, detailed calculations for typical molecular structures show that, disregarding damping, compact molecules have their lowest intramolecular vibrational modes at frequencies no lower than approximately 2×10^{11} Hz and that acoustic modes can exist in long flexible molecules at arbitrarily low frequencies. However, overdamping by water precludes energy absorption by all modes for frequencies up to the far infrared. A conventional lower bound for molecular absorption spectroscopy is approximately 3×10^{11} Hz (Prohofsky 2004).

Field enhancement due to structural focusing and dielectric discontinuities

At RFs, the electric and the magnetic fields of the incident wave can be "focused" on specific parts of an organized structure, which experience energy densities higher than those of the incident signal. This event is entirely described by the geometry and dielectric properties of tissue, as for example in studies of layered tissues (Barber et al. 1979). A site-specific amplification factor can be defined as the ratio of the absorbed power averaged over the whole exposed tissue mass to the absorbed power at the site. For exposure of the whole human body (E-polarization, grounded standing man) at its resonant frequency of approximately 35 MHz, the enhancement factor for absorbed power (peak/average rates of energy absorption) is of the order of 10–100 (Guy et al. 1984; Stuchly et al. 1986; Dimbylow 2002; Bernardi et al. 2003). In view of the interaction of morphology, body orientation in the field, frequency, and tissue characteristics, amplification factors may fall outside this range.

To evaluate variations in field strengths and power absorption at the tissue level, Gowrishankar and Weaver (2003) modeled the microanatomy of a tissue in order to estimate enhancements in transmembrane electric field strength and power absorption as a function of frequency. The computer-based model simulated a portion of tissue anatomy involving several hundred cells arranged to resemble the irregular orientations and neighbor-to-neighbor placements of cells. Each cell was represented by lumped elements with frequency-dependent dielectric and conductivity constants for the cell membrane, cytosol, and extracellular space. For frequencies from about 0.1 to 10 GHz they found that the nonuniformity in transmembrane electric field strength did not exceed a factor of 10. Graphical data suggested that at 1 GHz the rate of energy absorption (SAR) varied by less than a factor of 3 over the model tissue.

The degree to which biological tissue can form a dielectric lens that could focus and enhance the electric field at cellular or subcellular levels can be assessed quantitatively in order to determine if locally increased field strength could cause a localized temperature increase ("microthermal effect"). Qualitatively, it can be expected that diffraction would preclude significant focusing of RF fields over microscopic dimensions and that the relative transparency of biological matter to RF over very short distances would preclude concentrated energy absorption. Focusing, that is, refraction that concentrates the energy in an electromagnetic wave, is described by the intensity function $I(\upsilon)$, which for of a lens of diameter $2a$ and focal length F is $[2J_1(\upsilon)/\upsilon]^2 I_0$, where $\upsilon = 2\pi(a/F)(r/\lambda)$, r is the distance from the focal axis, λ is the wavelength, $J_1(\upsilon)$ is the Bessel function of order 1, and I_0 is the initial intensity (Born and Wolf 1975). A minimum spot size (focus) for a plane wave incident on a lens of focal length F can be readily calculated from the following considerations. The field strength falls to 1/e of its value when $\upsilon = 2\pi\,(a/F)(r/\lambda) = 3.3$; a good lens has a focal ratio $a/F \sim 1$ and $r \sim \lambda/2$. For the non-planar wave fronts found in many practical circumstances, it is appropriate to consider a Gaussian distribution, which

produces a larger diffraction-limited spot diameter, $r \sim 2\lambda$ (Siegman 1971), and therefore much less energy concentration. Because the smallest focal spot has a radius of the order of a wavelength, a field at a few gigahertz, for which the wavelength in biological material is of the order of 10^{-2} m, can at best be focused to an area that is vastly larger than a typical cell (radius of 10^{-5} m). Thus dielectric focusing could do no better than to focus gigahertz energy over an area of roughly one million such cells.

For a perspective on energy absorption at cellular and subcellular dimensions, it is instructive to note that cells and similar-sized objects are so thin with respect to wavelength that they have no appreciable effect on an electromagnetic wave as it propagates through (e.g., Stratton 1941). The reflection coefficient approaches zero and the transmission coefficient approaches one for thicknesses that are small relative to the wavelength ($<0.1\lambda$). Obviously, energy absorption within a single layer of cells is nearly zero. Of course, for bulk material with a thickness along the propagation direction that approaches one wavelength, integration of this minuscule absorption over many cell-sized layers gives the net energy absorption that characterizes passage of the wave through tissue.

Although energy absorption and heating at the cellular level are trivial in the perspective just discussed, there remain interesting questions about the electric fields and rates of energy absorption for subcellular elements. A number of theoretical papers have addressed the non-uniformity of electric fields at subcellular and molecular dimensions (Liu and Cleary 1995; Kotnik and Miklavcic 2000a, 2000b; Simeonova and Gimsa 2006). Despite significant model-related differences in the numerical values for regional dielectric properties and in qualitative appearances of the data, the various approaches had some overall similarities. All cell models showed that the electric field strength and energy absorption differed significantly among the plasma membrane, cytosol, and extracellular space, and that fields and power dissipation can differ by orders of magnitude when comparisons are made at certain frequencies or between models. Quantitative results depended on the models and the fact that some key dielectric properties are not well established experimentally over the 7 log units in frequency over which the modeled dielectric dispersions occur (Kotnik and Miklavcic 2000b; Simeonova and Gimsa 2006).

Kotnick and Miklavcic (2000b) calculated approximately 5-fold membrane electric field strength enhancements in the 1–10 GHz range for a model incorporating dispersive properties for each cell region. When membrane conductivity was taken into account, power dissipation within the membrane for this frequency range was significantly greater than in earlier models. Membrane dissipation exceeded dissipation in both the cytoplasm and extracellular space for frequencies below about 20 GHz. However, dissipation in the membrane fell below that in the intracellular and extracellular compartments at frequencies above approximately 20 GHz. Simeonova and Gimsa (2006) developed a similar model with greater detail for the lipid head groups of the membrane inner and outer surfaces and for the adjacent bound water. In a comparison of energy absorption averaged over the membrane for their model and one closely resembling the model used by Kotnik and Miklavcic (2000b), Simeonova and Gimsa (2006) found that the peak power absorption in the membrane was approximately 10-fold greater than for a model of a homogenous membrane. This was attributed to the greater contributions to the membrane average that resulted from explicit treatment of absorption by the lipid headgroups and bound water.

As will be discussed below, thermal diffusion precludes creation of significant temperature differentials regardless of relatively high energy absorption in a subcellular element. This is emphasized by work by Liu and Cleary (1995) who estimated that the thermal time constant for a 0.5 nm layer of bound water was 2×10^{-12} s, leading to their conclusion that there would be no granularity in microwave heating at the subcellular level.

Thermal diffusion

Even though some degree of focusing may occur, thermal diffusion precludes significant temperature differentials over cellular dimensions. Consider a simplified model for thermal diffusion where the rate of heat flow from a point source is given by $T = [Q/8\ (\pi\kappa t)^{3/2}] \exp(-r^2/4\kappa t)$, with T the temperature, t the time after the source is turned on, Q the quantity of heat, κ the diffusivity, and r the distance from the source (Carslaw and Jaeger 1959). The above equation leads to the relationship $r^2 = 6\ \kappa t$ between the time and distance at which T reaches a local maximum. In one microwave cycle ($t \sim 10^{-9}$ s), a point source of energy would raise the temperature over a mean radius of about 30 nm, less than 0.1% of typical cellular dimensions. A useful form for r^2 follows from noting that κ is related to the thermal conductivity Γ by $\kappa = \Gamma/\rho c$, where ρ is the mass density, c is the heat capacity ($c = Q\ m^{-1}\Delta T^{-1}$), and Q is the energy absorbed by mass m over time t. For a mass m (in grams) the SAR is Q/tm. Thus r^2 can be expressed as $6\Gamma\Delta T/\rho$. As an example, for a SAR of 10 W kg^{-1} and a density of 1.0 g cm^{-3} at equilibrium, ΔT across a 30 μm cell is $\sim 2.5 \times 10^{-12}$ K, undoubtedly an insignificant temperature gradient even if one such small region of a cell acted as a point source of heat. As this example

shows, microthermal effects caused by temperature differences between points separated by subcellular dimensions are not plausible consequences of exposures at RF. Furthermore, for a radius of 0.6 cm, ΔT is still only 0.1 K, indicating that even for a relatively high SAR, biologically significant temperature gradients would not occur over this dimension and certainly not over the much smaller dimensions of anatomical, cellular, and subcellular features.

Foster and Glaser (2007) conducted similar calculations for the maximum temperature increase and thermal response time of a sphere subject to microwave heating at a rate of 10 W kg^{-1} and surrounded by unheated media. They showed that a significant temperature rise does not occur in spherical structures smaller than a few mm. For example, a sphere of 10 μm radius with the material properties of water will reach an equilibrium temperature of only 10^{-6} K when surrounded by material of like properties. However, for a single very intense pulse (1.8 MW kg^{-1}, 1 ms) with whole body average SAR, SAR_{avg} = 2 W kg^{-1}, temperature can increase by 0.4 K (Laurence et al. 2003). Such extreme exposures do not occur in the environment.

ESTABLISHED MECHANISMS OF RF INTERACTIONS WITH BIOLOGICAL SYSTEMS

Mechanisms can be classified as established and proposed (that is, unproven or not established). Among established mechanisms are those discussed below. Table 1 indicates the plausibility of established and proposed mechanisms that are discussed here and in the next section, respectively. Table 2 lists salient features of the established mechanisms discussed below and their regimes of application.

Dielectric relaxation, ohmic loss, and heating

Some molecules have a permanent dipole moment due to the separation of positive and negative charge even in the absence of an external field. When placed in an external electric field $\vec{E}$ the interaction energy **U** of a permanent dipole $\vec{M}$ is given by $U = -\vec{M} \cdot \vec{E}$, and the force $\vec{F}$ on this dipole is given by the gradient of the energy,

$$\vec{F} = \nabla(\vec{M} \cdot \vec{E}). \quad (1)$$

In a uniform field, the translational forces on the positive and negative charges of the dipole cancel, leaving only a torque $\vec{N} = \vec{M} \times \vec{E}$ that tends to rotate the dipole around an axis that is mutually perpendicular to the dipole axis and field direction. For alternating electric fields, the changing field polarity causes oscillation of the dipole, which gives rise to the two major phenomena found in materials with dipolar molecules in RF fields: dielectric dispersion and dielectric loss. Dielectric dispersion, which appears as a change in the relative dielectric constant with frequency, is a result of changing ability of the dipole to rotate in phase with the driving field. Dielectric loss, which appears as heating of the material, occurs because rotational motion of molecular dipoles is hindered by interactions with neighboring molecules. In addition, there are conduction losses due to collision of mobile charges. RF heating per unit volume at frequency υ is given by $E^2\varepsilon''$), where ε'' is the loss (i.e., the imaginary part of the complex dielectric constant $\varepsilon^* = \varepsilon' - j\varepsilon''$) (Foster and Schwan 1996). This well-studied mechanism is the basis for dielectric heating in bulk materials and for most acknowledged biological effects.

The extensive literature on the theory and experimental data for the dielectric behavior of water, tissues, cells, and cell suspensions has been reviewed by several authors (Cole 1972; Hasted 1973; Grant et al. 1978; Pethig 1979; Foster and Schwan 1996). For our purposes, it is sufficient to note that dielectric properties change gradually over orders of magnitude in frequency and without the occurrence of narrow resonances. The permanent dipoles of water and biological material do not absorb energy resonantly into internal modes and therefore the oscillatory molecular motion is not tuned to a particular modal frequency. However, polarization (corresponding to ε') and dielectric loss (corresponding to ε'') are frequency dependent. Consequently, the temporal response of molecules to the applied oscillating field follows an exponential relationship that is characterized by a decay time constant of 5.84×10^{-11} s (17.1 GHz) for liquid water at 20°C (Hasted 1973). Unlike pure water, biological materials have additional dielectric mechanisms involving charges at the cell membrane, proteins, and charge interfaces. Each of these mechanisms is most effective in a different frequency range and follows its own exponential decay law, giving rise to three main overlapping relaxation processes labeled α, β, and γ. The process characterized by the α relaxation can increase the low-frequency permittivity by as much as 10^6 times, but is strongly attenuated above a few hundred hertz (a typical relaxation frequency is 100 Hz). The β relaxation disappears above a few megahertz, and the γ relaxation, which is essentially the relaxation process of water, has a relaxation center frequency of approximately 25 GHz at 310 K and persists to frequencies above 100 GHz (Foster and Schwan 1996). In summary, several relaxation processes of biological materials extend over more than 11 orders of magnitude in frequency and affect permittivity by a factor of as much as 10^6, but have more modest effects on conductivity (roughly over a 10^2–10^3 range) (Foster and Schwan 1996).

Table 1. Plausibility of fundamental mechanisms of interaction with electromagnetic fields.

Mechanism	Plausibility[a]	Comments
Dielectric relaxation & ohmic loss	Established	The basis of RF heating
Elevated temperature	Established for SAR $> \sim 10^0$ W kg^{-1}	Field threshold depends on exposure conditions and temperature sensitivity of the test biological system; further discussion is not needed
Temporal and spatial gradients in temperature	Over macroscopic dimensions, but not at cellular and subcellular dimensions	Direct changes in ion fluxes require very large fields at frequencies $< \sim 10^7$ Hz; no indirect mechanisms found
Cellular electrochemistry	Implausible	
Direct field effect on cell membrane potential and ion fluxes	Established for $\Delta V_{membrane} > \sim 10^{-4}$ V	Membrane potential and potential-dependent ion fluxes are of fundamental significance for excitation-contraction coupling, signaling in excitable and inexcitable cells, development, neuroendocrine function, and wound healing
Nonlinear ion transport producing signal rectification and demodulation	Established for $f < \approx 10^7$ Hz, $\Delta V_{membrane}$ above membrane noise	Demonstrated with nonbiological resins and accepted as mechanism for large permittivity of biological cells at ELF
Counterion polarization	Established for $f < \approx 10^4$ Hz	
Kinematic effect on ion velocity or flux	Implausible	Forces are minute and high collision rate with milieu would greatly overdamp any dynamical changes
Direct field effect on molecular structure	Implausible	Occurs only for field strengths at molecular sites that are comparable to electric fields of chemical bonds, which exceed strong environmental field strengths by $\approx 10^6$ times
Molecular resonances	Occurs for frequencies in the far infrared	Molecular motions below $f > 10^{11}$ Hz are overdamped; vibrational modes exist above $\approx$150 GHz
Non-resonant effects on chemical kinetics	Implausible	Without resonant interactions, energy density is far too low
Cooperative interactions; nonlinear dynamics	Implausible	Cooperative modes for energy exchange exist in far infrared, but are overdamped below 10^{11} Hz
Magnetic dipole interactions with molecular subgroups	Implausible	Motions are overdamped below $\approx 10^{11}$ Hz
Ferrimagnetic resonance	Implausible	Magnetite
Magnetic field effect on radical pair recombination rates	Established for limited number of molecules	Effects above $\approx 10^8$ Hz are unlikely, but may occur for molecules with exceptionally large magnetic moments (corresponding to large hyperfine shifts)

[a] Plausibility that interactions occur at environmental field strengths and relevant frequencies without temperature elevation (for nonthermal exposures).

The loss processes deposit heat by transformation of electromagnetic energy to thermal energy for all field strengths. Experiments conducted across species and frequencies found that temperature increases of about 1°C, sufficient to disrupt animal learned behavior, required SAR_{avg} of approximately 4 W kg^{-1} (Table 1 of Elder 1994; D'Andrea et al. 2003). This temperature rise occurred in animals that were not provided additional cooling. The actual temperature rise for a given RF exposure will depend on the environmental conditions and the ability of the animal to thermoregulate (Adair 1996a; Adair and Black 2003).

Electric dipole interaction

Unlike fields of uniform amplitude, an electric field amplitude with a spatial gradient can exert a translational force on a permanent dipole (Stratton 1941). The force on the center of gravity of a dipolar molecule of moment $\boldsymbol{M}$ in presence of a non-uniform electric field $\boldsymbol{E}$ is given by eqn (1), which in Cartesian coordinates becomes $F_x = \boldsymbol{M} \cdot \partial \boldsymbol{E}/\partial x$; $F_z = \boldsymbol{M} \cdot \partial \boldsymbol{E}/\partial z$.

To simplify the theory, we consider a transverse magnetic (TM) wave of angular frequency $\omega = 2\pi\nu$ propagating along the x-axis and aligned with a dipole moment also along the x-direction. The electric field $\boldsymbol{E} = \boldsymbol{x}_0 \, Ee^{-j(k_x x - \omega t)}$ has a gradient $\partial \boldsymbol{E}/\partial x = -jk_x \boldsymbol{E}$, where k_x is the circular wavenumber, resulting in a periodic force on the dipole of $F_x = -jk_x MEe^{-j(k_x x - \omega t)}$. Obviously, the time average for such an alternating force is zero and there is no net displacement of the dipole.

Nonetheless, if the field strength is high enough to impart a substantial amount of kinetic energy to the dipole,

Table 2. Physical thresholds or limiting properties for specific mechanisms of interaction.

Mechanism and cascade of sequelae	Key references	Physical limits or thresholds	Comments
Increased temperature → changed biochemical reaction rates → altered biochemical and physiological processes (observed in vivo and in vitro); → thermoregulatory responses in animals; → altered animal behavior; possible cell death, tissue damage, and burns	Weaver et al. 1999; Adair 2003; Kerbacher et al. 1990; Barnes 1989; de Lorge 1984; Elder 1994; Adair and Black 2003; D'Andrea et al. 2003; Szasz et al. 2003	$>10^2$ V m^{-1}	- Established physical, biochemical, biological, and physiological mechanisms - The rotation of water molecule dipoles in an applied electric provides the major loss mechanism that leads to heating over a boad frequency range centered near 25 GHz (4×10^{-11} s)
Thermoelastic expansion → "*microwave hearing*"	Elder and Chou 2003	2.4 MHz–10 GHz; 40 mJ cm^{-2} per pulse	- Established biophysical and physiological mechanisms. - Requires pulsed high intensity RF
Enhanced fields and energy absorption at dielectric boundaries at tissues, cell membranes (and other structures with dielectric discontinuities)	Barber et al. 1979; Guy et al. 1984; Stuchly et al. 1986; Dimbylow 2002; Bernardi et al. 2003; Gowrishankar and Weaver 2003; Kotnik and Miklavcic 2000a; Kotnik and Miklavcic 2000b; Simeonova and Gimsa 2006; Liu and Cleary 1995	- SAR enhancement 10–100-fold at whole body resonance - Dielectric lensing is diffraction limited to $r \sim 2\lambda$ or $\sim 10^{-2}$ m for $f \approx 10^9$ Hz - Peak power enchancement at cellular dielectric discontinuities (membranes) of ~10-fold - Thermal diffusion limits temperature increase to negligible amount ($\approx$ 0 K)	- Established physical principles, demonstrated at gross anatomical scale; plausible models for microscopic scale
Enhanced RF absorption and localized heating for ferrimagnetic resonance in biological magnetite at microscopic dimensions	Adair 2002; Kirschvink 1996	Negligible temperature increase ($<5 \times 10^{-4}$ K) at 10^2 W m^{-2}	On microscopic scale, magnetoacoustic process is overdamped and rapidly thermalized
Chemical reactions rates altered in correspondence to temperature pulses from heating by pulsed RF energy	Frauenfelder and Wolynes 1985; Cha et al. 1989	τ of reaction $< T$, RF period Pulse duration $< \tau$ thermal relaxation	For reactions faster than an RF period, pulsed RF could modulate reaction rates if the pulses are short compared to the thermal relaxation time. This speculative comment by the authors has not been evaluated by theory or experiment
Cell size and shape affect coupling to external currents with enhanced sensitivity for cells with long processes (e.g., axons, dendrites) and for active neuronal circuits in brain tissue	Reilly 1998; Jack et al. 1975; Gowrishankar and Weaver 2003; Weaver et al. 1998; Jefferys 1981; Jefferys et al. 2003; Deans et al. 2007; Saunders and Jefferys 2007	Estimated that ongoing synaptic activity may be altered by static fields and physiological effects suggest sensitivity to sinusoidal fields below ~20 Hz at field strengths $>5 \times 10^{-2}$ V m^{-1}; Individual long cells may respond at $>10^{-2}$ V m^{-1}; Threshold for effects on a neuronal circuit (phase-locked shifts in circuit activity) seen at >2.1 V m^{-1}; at 50 Hz, 0.35 V m^{-1} affected spike rates and corresponding somatic potential changes are $<10^{-4}$ V.	Ephaptic coupling between neurons that are part of a neuronal circuit renders the circuit highly sensitive to external perturbation
Altered molecular transport through ion channels	Astumian and Robertson 1989; Schatz and Dobberstein 1996	Calculated limit of 2.6×10^3 V m^{-1}, but there is no experimental information on sensitivity to external fields	This mechanism was suggested on the basis of membrane potential control of protein translocation

(*Continued*)

Table 2. Continued.

Mechanism and cascade of sequelae	Key references	Physical limits or thresholds	Comments
Resonant absorption in microscopic and molecular structures (acoustic resonance; intramolecular electron currents)	Prohofsky 2004	Generally, $>3 \times 10^{11}$ Hz, but exceptional resonances occur as low 184 GHz. Damping by water molecules has a dominant relaxation time of 39 ps (corresponding to 4 GHz); molecular motions are strongly overdamped for $f > 10$ GHz	
Altered protein conformation (tertiary and quartenary protein structure)	Eyster and Prohofsky 1977; Balabin and Onuchic 2000	Generally, limited to $f > 10^{12}$ Hz Electron tunneling can occur at lower frequencies, e.g., 24 GHz for the NH_3 maser; electron tunneling pathways in biomolecules are very sensitive to small temperature changes	
Change in biochemical rate or molecular structure → Free radical formation	Woodward et al. 2001; Timmel et al. 1998; Weaver et al. 2000	Generally $f < 100$ MHz, but exceptionally large hyperfine constants could be resonant above 1 GHz	Weaver et al. (2000) estimated sensitivity to ΔB (static field) $\sim 10^{-7}$ to 10^{-6} T in modeling possible sensory detector
Intermolecular electric dipole-dipole interactions	Adair 2003; Fröhlich 1968	Lower frequency limit $\approx 1.5 \times 10^{11}$ Hz	
Absorption in water bound at cell surfaces	Simeonova and Gimsa 2006		
Torque on electric or magnetic dipoles at cellular or molecular dimensions; e.g., electrorotation	Maier 1997; Becker et al. 1995; Georgieva et al. 1998; Gimsa 2001	Electrorotation: Order $>10^1$ to 10^8 Hz and $E \ll 10^2$ V m^{-1}	
Dielectrophoresis	Pohl 1951; Pohl 1978; Gimsa 2001	Frequencies from static to 10^9 Hz and large field gradients, e.g., near needle points	
Magnetic orientation of reactants	Pilla et al. 1997	Lower limit B $\sim 10^{-7}$ to 10^{-6} T at ELF	Hypothetical magnetic orientation of bound water associated with receptor molecules
Nonlinear responses of biological systems	Balzano and Sheppard 2003; Balzano et al. 2008	For incident frequency ω_c, nonlinear response produces a signal at $2\omega_c$, $3\omega_c$ and higher frequencies; amplitude modulation results in sideband generation Demodulated ELF signal $<3 \times 10^{-3}$ V m^{-1} for 100 V m^{-1} input	
Coherent long-range intermolecular interactions; nonlinear dynamics	Adair 2003; Kaiser 1996	Lower limit at $f \approx 1.5 \times 10^{11}$ Hz (Adair 2003) or as low as 8×10^9 Hz (see text)	
Cooperativity among charged structures	Changeux et al. 1967; Fröhlich 1968; Grodsky 1976; Thompson et al. 2000; Duke and Bray 1999; Pickard and Moros 2001; Adair 2003	Cooperative coupling of entire cell surface required for S/N $\sim$1, but collisional damping prevents coherence for more than $\sim 10^{-11}$ s, indicating lower limit at $\sim$8 GHz	See item on "Amplification by biochemical function, structure and cascades" for examples of other forms of cooperativity
Stochastic resonance	Astumian et al. 1995; Astumian et al. 1997; Weaver et al. 1998	Signal averaging over time T improves S/N as $T^{1/2}$; stochastic resonance can achieve as much as 10-fold improvement in S/N	Unless initial physiological signal is comparable to noise, neither signal averaging nor stochastic resonance can improve S/N sufficiently. Any demodulated components would be far too weak for adequate amplification by these means
Amplification by biochemical function, structure and cascades	Goldbeter et al. 2001; Goldbeter 2002; Gonze et al. 2002; Bray and Duke 2004; Yifrach 2004; Gonze and Goldbeter 2006	Dynamical behavior of oscillatory systems (both stochastic and genetically regulated aspects) determine physiological functioning	- Down-regulation of genes by cooperative protein bindings stabilizes circadian rhythm (Gonze et al. 2002; Goldbeter 2002)
		Degree of cooperativity set and bounded by molecular and multi-unit interactions	- Hill coefficients (index of degree of cooperativity) for voltage-gated membrane channel proteins < 2 (Yifrach 2004). K-channel voltage sensitivity is due to charge-field interactions and energetics of the channel protein; requires changes in membrane electric field (order 10^6 V m^{-1})

then this type of interaction might be of further interest. To establish an amplitude for which gradient field effects on a permanent dipole could be biologically relevant, we compute the values of E and $k_x E$ that can impart the arbitrarily chosen energy of $k_B T/100$ to a water molecule over a half period $P/2$, where ν is the mean molecular velocity, and k_B the Boltzmann constant. Note that the strong polarizability of water and its low mass provide an extreme case in comparison with most molecules.

For a first example, we choose a model in which the field gradient is related to the propagation of a wave in a dielectric medium. Note that there is no cutoff for the upper frequency for this mechanism, but the relaxation of ε_r would increase the required field strength. The simple dynamic equations are

$$mv = j\int_0^{P/2} Mk_x\, Ee^{jwt}\, dt = 2EMk_x/\omega, \qquad (2)$$

and

$$\tfrac{1}{2}mv^2 = k_B T/100. \qquad (3)$$

From eqns (2) and (3) we have $E = (\tilde{c}/10M)\,[mk_B T/(2\varepsilon_r)]^{1/2}$, with $\tilde{c}$ the free space velocity of light, ε_r the relative dielectric constant (≈80) and $T = 310$ K. For water, where $M = 1.84$ Debye (where 1 Debye $= 3.356 \times 10^{-30}$ C m), we find the required field strength is $E = 4 \times 10^{12}$ V m^{-1} and its gradient at 1 GHz, $\partial E/\partial x = 2\pi\sqrt{\varepsilon_r}/\lambda\ E$, is approximately 7×10^{15} V m^{-2}, where λ is the wavelength in the medium. It is evident that the required field strength is orders of magnitude beyond practical levels.

In view of the very large field strength just calculated, we consider the more extreme field gradient produced near the tip of a very sharply rounded cone (needle) in order to estimate how much less field strength is required for the same energy transfer to the dipole. The fields near the tip of a conductive cone of semi-aperture θ_c (the angle measured within the cone from its axis to the surface) have their source in an axially symmetric charge distribution on the tip. The solution of the static potential equation in spherical coordinates (Stratton 1941) yields the following expression for the radial component of the electric field:

$$E_r(r,\theta) = E_0 r^{-1}\, j_\nu(r)\, P_\nu(\cos\theta), \qquad (4)$$

where $P_\nu(\cos\theta)$ is a Legendre function of the first kind, ν is the first root of the equation $P_\nu[\cos(180-\theta_c)] = 0$, r is the radial distance measured in a spherical coordinate system with origin at the tip of the cone, θ and φ are the usual angular coordinates, $j_\nu(r)$ is a spherical Bessel function of non-integer order ν, and E_0 is the field amplitude, which is found by applying Gauss's law.

We consider a sharply pointed cone with $\theta_c = 5°$, which yields the value $\nu \sim 0.16$ (Balzano and Dowling 1974). In the proximity of the conical tip, $j_\nu(r) \approx r^\nu/\sqrt{r} = 1/r^{1/2-\nu}$ so the radial field can be expressed as:

$$E_r(r,\theta) = E_0 \frac{1}{r^{3/2-\nu}} P_\nu(\cos\theta). \qquad (5)$$

As all charges at the tip are contained on the surface of the cone within a small distance a from the surface that we will set at 10^{-2} m, Gauss's law yields:

$$E_0 \frac{a^2}{a^{3/2-\nu}} \int_0^{2\pi}\int_0^{180-\theta_c} P_\nu(\cos\theta)\sin\theta d\theta d\phi = \frac{Q}{\varepsilon},$$

$$\text{giving } E_0 = \frac{a^{\nu+1/2}\, Q}{4\pi\, 0.83\, \varepsilon},$$

where $\varepsilon = \varepsilon_r\varepsilon_0$ is the dielectric constant of the medium surrounding the conductive cone ($\varepsilon_0 = [36\pi]^{-1} \times 10^{-9}$ F m^{-1}), and Q is the total charge on the tip of the needle.

The field and its gradient diverge near the tip of the cone where $r \to 0$, as seen from eqn (4). Setting the maximum value of the energy imparted to a molecule of dipole moment M in the direction of the conical axis equal to the same ad hoc energy increment as before,

$$\tfrac{1}{2}mv^2 = k_B T/100 = \int_b^{b+d} M\frac{\partial E_r}{\partial r}\, dr$$

$$\approx -\int_b^{b+d} ME_0 \frac{3/2-\nu}{r^{5/2-\nu}}\, dr = \frac{M}{b^{3/2-\nu}} E_0\left[1 - \frac{b^{3/2-\nu}}{(b+d)^{3/2-\nu}}\right],$$

where b is the radius of curvature of the tip of the cone and d is the mean free path of the molecule in the surrounding medium (water).

For this model with $b = 10^{-6}$ m, $d = 10^{-10}$ m, and keeping other parameters as in the previous model, we determine that the required charge $Q \approx 5.4 \times 10^{-5}$ C, the field strength close to the needle is $E_r(b, 0) = 5.3 \times 10^{10}$ V m^{-1}, and the field gradient $\partial E_r/\partial r = 7.8 \times 10^{24}$ V m^{-2}. In order to compare the two models, the interaction energy at the tip is summed over time $P/2$ as before. During interval $P/2$ (5×10^{-10} s), there are approximately 1.2×10^3 collisions, for a collision interval of 4×10^{-13} s (Hille 2001). For simplicity in getting an extreme estimate, we ignore dynamic influences such as the effects of collisions on dipole orientation and position near the tip that would reduce average energy imparted between collisions and would therefore require still greater field strengths to impart the criterion energy increment. Although E_r for the needle is approximately 75 times lower than E in the first

model, the same total energy is given the molecule by the gradient field acting over $P/2$. This calculation emphasizes that even for extreme field gradients an impractically large field strength in the medium is needed to impart a minimal amount of energy ($k_B T/100$) to polar molecules.

Forces on induced dipoles; dielectrophoresis in non-uniform (gradient) electric fields

A dipole moment is induced when the positive and negative charge distributions of a body with overall charge neutrality are slightly separated by electrostatic forces. If a uniform field alternates in direction, the equal and opposite dipole moments induced during each half-cycle result in no net translation of the body, just as for a permanent dipole. However, in a gradient field the force on induced dipoles has the same direction for both field orientations, giving rise to a translation of the body known as dielectrophoresis (Pohl 1951, 1978). The force on the center of gravity of an induced dipole $\boldsymbol{M}(\omega)$ located in an electric field $\boldsymbol{E}$ of angular frequency ω with a non-vanishing gradient is given by $\boldsymbol{F}(\omega) = \mathrm{Re}\{[\boldsymbol{M}(\omega)\cdot\nabla]\boldsymbol{E}\}$. For a spherical distribution of radius a and dielectric constant ε_p located in a medium of dielectric constant ε_m, the induced dipole moment is $\boldsymbol{M} = 4\pi\varepsilon_m f(\varepsilon_p^*, \varepsilon_m^*)a^3\,\boldsymbol{E}$, where f, the Clausius-Mosotti factor, expresses the dependence of polarization forces on the dielectric constants, $f(\varepsilon_p^*, \varepsilon_m^*) = (\varepsilon_p^* - \varepsilon_m^*)/(\varepsilon_p^* + \varepsilon_m^*)$. It is obvious from the numerator that the dielectric constants of the medium and particle must be different for a non-zero net dielectrophoretic force.

Pearl-chain formation in uniform electric fields

The alignment of micrometer sized particles in the presence of a uniform DC or alternating electric fields occurs because of forces on the induced dipoles. Particles with a surface charge distribution will tend to align along an applied oscillating field because the oscillatory movement of charge along the surface allows alignment for both directions of the field. For sufficiently strong fields, linear strands of particles form after a brief delay. Formation of these strands, which are known as pearl-chains, is a well-studied phenomenon that has been observed at frequencies from 0 to 100 MHz for both continuous wave (CW) and pulsed fields (Schwan and Sher 1969; Hu and Barnes 1975; Takashima and Schwan 1985). Pearl-chain formation is an established non-thermal effect with a field strength threshold that depends on particle size, but the required field strengths are strong enough that significant heating also occurs. Pearl-chains form only above a threshold electric field that is inversely proportional to a power of the particle radius ($\sim R^{-1.5}$). Takashima and Schwan (1985) studied the threshold electric field as a function of frequency for particles with mean diameters of 2.2×10^{-6} m. Their results indicated thresholds of $\approx$2 kV m^{-1} at 500 Hz and $\approx$10 kV m^{-1} at 100 kHz.

Displacement of membrane-associated ions in an RF field

When ions near the surface of a plasma membrane are subjected to an alternating RF electric field, the forces in the direction perpendicular to the membrane are non-isotropic. Charges on the membrane form an immobile charged sheet in contrast to mobile counterions in the region within approximately 5×10^{-9} m of the external membrane face that create a diffuse electrical double-layer (Pethig 1979). Moreover, ELF dielectric studies indicate that ions of the counterion layer are constrained to move in a plane parallel to the membrane surface, giving rise to a large dielectric increment at frequencies below several kilohertz (O'Konski 1960; Schwarz 1962; Einolf and Carstensen 1971). Ideally, counterions would have no velocity components perpendicular to the membrane, although ion exchange with the outer ionic milieu is possible. In principle this charge barrier might asymmetrically modify the mobility of ions in the counterion region adjacent to the membrane, resulting in a nonlinear response. The question then arises whether an RF electric field acting on mobile counterions of the double-layer can modulate the separation between the fixed and mobile surfaces of the double-layer, thereby influencing proteins at the membrane surface. Counterions are bound to membrane charges in potential wells with a relatively low barrier height of only a few times kT, for example, 3.4 kT in a model for K^+ ions (Pethig 1979). This weak interaction energy indicates relatively weak coulombic forces between counterions and surface charges. However, as noted previously, RF energies are $\ll$kT and could not perturb the counterions significantly.

Other speculations about effects of RF electric fields on mobile species face similar considerations concerning available RF energy and the resultant dynamical effects. For example, it can be speculated that ions and other charged particles near the membrane surface might have their densities altered with consequent influences on collision rates at the entrance to membrane ionophores, or that chemical reactions might be affected by alterations in collision rates of charged ligands and the substrate, or that reactions sensitive to steric arrangement might be affected by establishment of preferred field-directed motions, or that the RF energy imparted to reactants might change reaction kinetics. However, as just noted, the energy supplied by any practical RF field to ions near the membrane is insufficient to significantly perturb thermally driven motions or the forces applied by

endogenous fields that are at least several orders of magnitude greater, consistent with RF energies $\ll$kT.

Effects of very strong electric fields

Exogenous fields that exceed or are on the order of endogenous fields can be expected to cause effects. For example, conventional electroporation employs pulses of 100 μs or longer with peak field strengths between 10 and 100 kV m^{-1} (Gowrishankar et al. 2006) to induce pores in the cell membrane. Electroporating pulses were initially developed for gene transfer, but now are used for delivery of a large variety of molecules, including drugs, dyes, tracers, antibodies, and oligonucleotides (Gehl 2003). Supra-electroporation employs much shorter and more intense pulses (1 to 30 MV m^{-1} and 1 μs or less) and apparently affects nuclear membranes and organelles within the cell (Gowrishankar et al. 2006). Conventional electroporation pulse currents tend to flow around the cell in the low conductivity extracellular medium but supra-electroporation pulses are short compared to the charging time of the outer membrane and thus penetrate the cell. Research on the use of supra-electroporation as a treatment for cancer is now underway. Tumor regression has been observed after short treatments (Nuccitelli et al. 2006) with effects observed on apoptosis and other cell functions (Beebe et al. 2002; White et al. 2004).

Electroporation and other phenomena raise questions about possible effects from RF pulses of comparable high magnitude and short duration. The well established phenomenon of microwave hearing involves short RF pulses in the frequency range of 2.4–10,000 MHz inducing pressure waves in the head that typically are detected by the auditory system as clicks or a buzz (Elder and Chou 2003). In the transduction of heat to a pressure wave, microwave hearing is just a specialized case of an effect of heating, albeit one that involves an extremely small temperature change of, for example, $<10^{-6}$ K for one typical set of conditions (Guy et al. 1975). The threshold for RF-induced hearing of pulsed electromagnetic energy was determined by Guy and colleagues (1975) to be related to the energy density with a threshold of about 40 mJ cm^{-2} per pulse and the additional requirement that the subject could hear acoustic waves above about 5 kHz (also see Table 2, "Thermoeleastic expansion"). Intense fields at frequencies up to the 90 GHz band are now being employed in devices designed for crowd control (electromagnetic antipersonnel devices) (Murphy et al. 2003). There are reports, including one by Doyle et al. (2006), suggesting that there may be non-thermal explanations for some observed effects with very intense pulsed fields (9.6 GHz, 2 μs pulses, 740 kW g^{-1}). These two "non-thermal" effects of RF pulses illustrate that even for special circumstances where strong fields are applied but bulk temperature does not rise significantly, the underlying transient thermal event (thermoacoustic expansion), or an as yet unexplained effect on neurons, requires fields that greatly exceed endogenous levels.

Gowrishankar et al. (2006) modeled membranes and organelles exposed to conventional and supraelectroporating pulses. Membrane charging time-intensity relationships set lower limits for the field amplitudes sufficient to cause pore formation or other structural responses. It is questionable whether RF fields could be used to cause effects similar to those of the intense DC pulses used in electroporation and supra-electroporation because an RF field would need to remain in one direction ($\approx$½ cycle) long enough to effectively charge the cell or organelle surface, thereby requiring frequencies likely to lie below approximately 10 MHz, although further investigation is needed to establish a minimum period. However, because extremely large field strengths are required, electroporation does not provide information useful at environmental level field strengths that are at least several hundred times weaker.

Effects of exogenous fields through nonlinearities

In principle, nonlinear processes such as rectification can transduce RF signals modulated at low frequency into the frequency range where physiological systems operate. Nearly all uses of RF energy involve modulated fields rather than CW fields. For example, typical wireless communications protocols for cellular telephone systems combine pulse-, frequency-, and phase-modulation, and high power CW amplifiers may have unintentional amplitude modulation derived from power supply ripple. Demodulation by nonlinear electronic circuits is essential to almost all wireless communications. Some form of demodulation is implied by biological effects that have been reported to depend on fields that were pulsed, sinusoidally amplitude-modulated, and modulated with a combination of frequency-, amplitude-, and phase-modulations (for review, NCRP 2003). The following sections explore the possibilities for demodulation in biological tissues and in biological molecules from several perspectives that allow quantitative estimates for the magnitude of a demodulated signal.

Nonlinearity generates harmonic frequencies and demodulation. A generalized nonlinear response (*NL*) to an incident electric field E of frequency ν can be expressed as a Taylor series, $NL\ (|E|) = a_1|E| + a_2|E|^2 + a_3|E|^3 +$ higher order powers of $|E|$, where a_1, a_2, and a_3 are constants characteristic, for example, of the tissue nonlinearity (Balzano 2002). For example, for a molecular ensemble *NL* ($|E|$) could represent polarization. As

this expansion implies, a nonlinear RF absorption process would have two effects. First, for an RF carrier [$|E| = A \sin(\omega_c t)$] a nonlinear response in a medium would necessarily create harmonics at $2\omega_c$, $3\omega_c$, etc., and a static, dissipative term (Balzano and Sheppard 2003). Second, for amplitude-modulated carriers [i.e., $|E| = A f(t) \sin(\omega_c t)$, where f represents an arbitrary modulating waveform], nonlinear interactions would generate demodulated components that would affect a biological system at the modulation (baseband) frequencies. These two fundamental properties underlie all experimental efforts to identify demodulation in biological systems.

Demodulation at the plasma membrane is frequency-limited. Assuming that an endogenous electric field occurring in a tissue or organ is physiologically significant (rather than epiphenomenal), a plausible benchmark for effects is that the exogenous field should introduce a dc bias or low-frequency field that is of the same order of magnitude as the in-situ physiological electric field. For exposures to a modulated RF field, an effect on cell membrane potential requires rectification of a sufficiently strong carrier wave by an efficient mechanism. Biophysical theory (Pickard and Rosenbaum 1978) and experiments in plant cells (Barsoum and Pickard 1982) showed that in the absence of heating, nonlinear behavior at cell membranes does not occur above approximately 10 MHz. These findings should apply to animal cells too, as was demonstrated by experimental data from human subjects tested for nerve stimulation thresholds as a function of frequency (Silny 2007). A single pulse of up to 100 ms duration was used over a range of RFs to determine whether there would be a response to modulated signals at each frequency. Unlike lower frequencies, at 10 MHz the required amplitude of the RF electric field was so large that the pain threshold was reached before being able to observe nerve stimulation indicative of demodulation (Silny 2007).

Nonlinear responses not directly affecting transmembrane potential. It is possible that nonlinear effects at the cell membrane would not be reflected in the foregoing tests of changes in membrane polarization. In this context, information carried on an incident electromagnetic wave might act through an electric field effect on the charge structure of biological matter. For example, because the charge distribution within a cell membrane ion channel can mimic a potential barrier within the channel (Stoykov et al. 2004), an effect on the intrachannel charge distribution is among the possible means for nonlinear transduction in biological systems without a change in transmembrane potential. Similarly, biopolymers have free electrons that exhibit semiconductor characteristics (Pethig 1979), suggesting that they may be able to rectify RF signals and demodulate amplitude-modulated RF carriers. However, the mere existence of nonlinearities of these kinds at a molecular level or in bulk matter is not sufficient for a biological response. For that to occur, any demodulated signal acting at the molecular or bulk levels would have to be large enough to affect a biochemical or biophysical process that is sensitive to the demodulated potential, thereby causing a physiological change. There is at this time no evidence for biochemical effects that demonstrate an underlying nonlinear response to RF fields.

Demodulated field strengths are very weak. The magnitude of a demodulated electric field generated by a nonlinear mechanism can be estimated from fundamental relationships of physical electronics that show that the down conversion of the envelope of an RF carrier by its nature must attenuate the amplitude of the modulating signal. For an ideal hypothetical lossless detection process where the reverse biased nonlinear device acts as a lossless capacitor C, the attenuation of I, the current across the energy gap at a material discontinuity, is inversely proportional to the angular frequency ω ($=2\pi\nu$) of the signal, that is, the gap voltage $V(\omega) = I/j\omega C$. Consequently, in the example of a 900 MHz carrier amplitude-modulated at 16 Hz, a perfect square law detector would attenuate the signal power at baseband in the proportion 16/900,000,000, or by about 77 dB, simply because of the lesser energy associated with slow variation of the field amplitude compared to variation at the carrier rate (Balzano and Sheppard 2003). An attenuation of 90–100 dB is more likely because of leakage losses across the hypothesized potential barrier in living tissue. For attenuation of this order, a 10^{-3} W (1 mW) RF carrier 100% amplitude-modulated at 16 Hz can be expected to yield a demodulated signal power of no more than 10^{-12} W at the 16 Hz baseband frequency.

A recent experiment obtained measurements showing that the ELF electric field detected by a nonlinear material from an incident ELF amplitude-modulated RF electric field of 100 V m^{-1} would be no more than approximately 3×10^{-3} V m^{-1} in the ELF band (Balzano et al. 2008). Consequently, the voltage across a 10^{-8} m thick membrane could be no more than 3×10^{-11} V. This astonishingly small signal is approximately 10^7 times (140 dB) smaller than the low-frequency membrane voltage noise that limits physiologically significant events in excitable cells (Jacobson et al. 2005; Billimoria et al. 2006; Kole et al. 2006) and would be equally far below the cell membrane voltage noise of 10^{-6} V Hz$^{-1/2}$ observed by Roa and Pickard (1976) in the band from 1 Hz to 10^4 Hz. These fundamental considerations show

that for any practical exposure the demodulated ELF signal that may exist across the membrane would be irretrievably lost in membrane noise.

Nonlinearity of the radical pair mechanism. Looking beyond effects at potential barriers, we note that not all nonlinear mechanisms depend on electric field interactions with charges on molecules, cells and membranes. The nature of magnetic field interactions with certain atoms of spin-correlated radical pairs leads to magnetic resonances with RF fields that have been demonstrated for frequencies of up to approximately 100 MHz (Timmel and Henbest 2004) and may occur in the low gigahertz region for nuclei with very strong hyperfine couplings, such as phosphorus-based radicals (Timmel et al. 1998; Henbest et al. 2004). It remains to be shown if demodulation could occur via the radical pair mechanism through low-frequency alterations in biochemical reaction rates.

PROPOSED MECHANISMS OF RF INTERACTIONS WITH BIOLOGICAL SYSTEMS

We define as "proposed" a number of RF interaction mechanisms that have not yet gained acceptance through rigorous experiments. Often such mechanisms were developed to explain particular experimental observations, but we also include as "proposed" applications of established mechanisms for which no biological effects have been shown.

Microthermal effects and "hot spots"

Our review of molecular absorption mechanisms (detailed in the previous section) emphasizes that all energy is rapidly thermalized and not selectively stored in any single mode. There has, however, been speculative interest in rapid, localized temperature gradients that might lead to "microthermal effects" at "hot spots." Neither term is apt because, as emphasized above, rapid thermal diffusion precludes significant increases in temperature at cellular, sub-cellular, and molecular dimensions. As a result, from a microthermal perspective (i.e., at dimensions of a cell and smaller), even in the extreme hypothetical case of selective heating over dimensions of a cell, the minuscule temperature increase of $\ll 10^{-3}$ K would reach equilibrium in less than one millisecond, far too small an increase over far too short a time to affect physiology or biochemistry (Foster and Glaser 2007).

The term "hot spots" also is used in models of cellular and subcellular dielectric properties where it refers to regions of increased electric field strength and energy absorption, but not to a temperature increase.

"Microthermal" may also be used to refer to effects occurring although the temperature change is very small (e.g., $\ll 10^{-3}$ K). At threshold for the microwave hearing phenomenon, temperature changes of 5×10^{-6} K are calculated to occur upon the absorption of pulsed RF energy in tissue that launches thermoelastic shock waves (Elder and Chou 2003). Otherwise, the effects produced by the mechanisms reviewed above require energy inputs sufficient to elevate temperature of the body core or some localized tissue by a physiologically significant amount, typically given as 0.1 to 1 K or more. A change by several degrees is needed for effects challenging the human body's capacity for thermoregulation or to cause cell and tissue injury or death (Tables C.3 and C.4 of IEEE 2005). However, for some sensory systems, changes of as little as 0.01 K can be significant.

Interatomic molecular resonances

The interatomic potential energy surface of the four atoms forming an ammonia molecule (NH_3) permits tunneling that causes transitions between configurations at the relatively low frequency of 24 GHz at room temperature. Prohofsky (2004) noted that this process is limited to small molecules because a greater number of atoms splits the near degeneracy of molecular energy levels that is required for tunneling. Resonance-based conformational transitions in large helical molecules (including DNA) occur at initial frequencies somewhat below 10^{12} Hz (Eyster and Prohofsky 1977; Prohofsky 2004).

Electron tunneling

Electron transfer reactions are key features in biochemical pathways for metabolism and photochemistry (Daizadeh et al. 1997). Most electron transfer reactions in biological systems involve separations on the order of 5×10^{-10} to 2×10^{-9} m with the result that electron tunneling weakly couples the donor and acceptor sites (Balabin and Onuchic 2000). Electron tunneling between donor and acceptor sites in proteins can proceed via a few or multiple transfer pathways with major differences in the electron transfer rate for reactions involving multiple pathways. Electron transfer rates are high for simple pathways and for multiple pathways that interfere constructively and orders of magnitude slower for destructively interfering pathways. Destructive interference can be significantly reduced by vibrational motions of the atomic nuclei (so-called dynamical amplification) and by changes in protein conformation, with the greatest increase in tunneling rates occurring for protein conformations far from equilibrium.

Electron tunneling also may occur for a group of similar tunneling pathways that constitute a tube. Tunneling via tubes can be strongly influenced by changes in the spatial relationship of donor and acceptor sites according to protein conformation and nuclear dynamics,

neither of which is perturbed by the low photon energy of RF signals. However, electron tunneling can be strongly influenced if the RF energy absorption rate is high enough to cause a temperature increase within complex molecular structures, e.g., proteins. In this case atomic and molecular agitation can increase tunneling rates by opening tubes with constructively interfering pathways or relieving the destructive interference in other tubes. SAR levels in excess of 100 W kg^{-1} are necessary to affect protein conformation (Webb 1980; Bohr and Bohr 2000).

Radical pair mechanism

As discussed above, spin-correlated interactions between radical pairs provide mechanisms for a compass in birds and possibly other animals (Wiltschko and Wiltschko 2005) and additionally allow for the possibility of RF effects on a variety of biological reactions involving pairs of radicals. The mechanisms that underlie magnetic effects on free radical reaction rates depend on quantum mechanical resonances at magnetic nuclei of certain molecules rather than a magnetic interaction generally applicable to radicals formed from biological molecules. As quantum mechanical magnetic resonances, they also are sensitive to the relative orientation of the static and oscillatory magnetic fields. The plane wave RF power densities that disrupted bird orientation can be estimated from the experiments reported by Ritz et al. (2004) in which a 0.085 μT magnetic field over the 0.1–10 MHz band and a 0.47 μT field at 7 MHz had a similar disruptive effect. For these RF magnetic fields, the respective free space plane wave power densities were 1.7 W m^{-2} and 53 W m^{-2}, but these do not represent minimum effective field strengths, which were not determined. In a similar experiment, a 485 nT magnetic field (1% of the local geomagnetic field intensity) with a frequency of 1.315 MHz was selected to match the energy level splitting at the Larmor frequency for a free radical in the geomagnetic field at the experimental site (Thalau et al. 2005). As in the test with a 7 MHz field, bird orientation was disrupted if the RF field was oriented at an angle to the geomagnetic field vector, but not for a parallel orientation. The several experiments mentioned here are consistent with a resonance mechanism in which the RF energy couples energy levels of radical pairs in a photosensitive molecule. Recent research points to a role for blue-sensitive cryptophores in the retina of migratory songbirds that have remarkably long-lived radical pairs ($\gg$1 ms) (Brown 2003), but much remains to be explained about the radical pairs involved (Efimova and Hore 2008), the related photochemical reactions, and the affected biological pathways in relation to behaviors observed in migratory and non-migratory birds (Wiltschko et al. 2007).

Magnetic field effects on a photochemical reaction yield in solution have been observed at discrete frequencies in the range 1 to 80 MHz using a 300 μT RF magnetic field (Woodward et al. 2001; Timmel and Henbest 2004). These experiments were done with no static magnetic field component, which allowed isolation of effects on each member of the radical pair. The molecular hyperfine coupling constant sets the limit for energy level splitting of a radical pair causing RF resonance effects to be limited to frequencies below approximately 100 MHz, although resonances in most molecules occur between 0.1 to 10 MHz (Ritz et al. 2004). Unusually large hyperfine coupling constants associated with strongly magnetic nuclei could lead to effects above 100 MHz (Woodward et al. 2001). Although Zmýslony et al. (2004) reported an increase in oxygen free radical production for cells exposed to a 930 MHz field, they did not attribute it to the radical pair mechanism because of the requirement for an unreasonably large hyperfine coupling strength for resonance at that frequency. A speculation that a phosphorus-associated radical pair could have hyperfine couplings strong enough to support resonance at 1–2 GHz (Timmel et al. 1998) suggests a hyperfine coupling strength very much greater than those known from studies of a large variety of biological molecules (Grissom 1995; Cintolesi et al. 2003; Ritz et al. 2004).

It is important to note that despite the great number of biochemical reactions involving free radicals, several restrictive conditions make RF magnetic field effects on biochemistry uncommon. In addition to the frequency constraints based on hyperfine coupling strength, radical pair interactions are restricted by the necessity for creation of spin-correlated radical pairs that remain in close proximity, radical lifetimes long enough to be affected by an oscillatory magnetic field, relaxation processes slow enough to allow adequate radical lifetime, and static magnetic fields of appropriate field strength (Timmel et al. 1998). Timmel and colleagues concluded that one radical pair mechanism, the "Low Field Effect," could in principle change reaction yields by 10 to 40% for radical pairs in general, subject to the conditions of sufficiently long lifetime and slow spin relaxation.

In summary, behavioral effects attributed to changes in a photochemical reaction have been observed in avians with magnetic fields at frequencies below 10 MHz (Ritz et al. 2004) and effects on photochemical reactions in solution have been observed at frequencies up to approximately 80 MHz (Woodward et al. 2001; Timmel and Henbest 2004). These observations and associated theoretical work establish the principle that magnetic fields

can affect selected reactions involving spin-correlated radical pairs. However, requirements on free radical lifetimes, spatial localization, relaxation processes, and hyperfine coupling constants indicate that static and RF magnetic field effects on the radical pair mechanism are not a general feature of biological chemistry above 10 MHz and especially above approximately 100 MHz.

Raman and Brillouin effects

There are several spectroscopic methods to determine the presence of resonant absorption modes in gases, solids, and liquids. Raman and Brillouin scattering have been used for investigating resonant modes in biological structures that were first observed in the 1960's and recognized as the result of modulation of the dielectric constant by vibrational modes in the media (Pantell and Puthoff 1969). The Raman effect (Raman and Krishnan 1928; Landsberg and Mandelstam 1928) is associated with excitation of optical modes and can also occur in resonance with electronic transitions of a molecule, whereas the Brillouin effect (Pantell and Puthoff 1969) excites acoustic modes and thus the shifts are smaller, on the order of several gigahertz. The Raman and Brillouin effects are the results of inelastic interactions of electromagnetic photons (usually in the infrared region) with phonons that produce frequency shifts of the scattered light corresponding to molecular velocity (Brillouin) and molecular vibration and rotation (Raman). However, these interactions cannot occur in the RF spectrum, especially below about 100 GHz, because molecules are hindered from the necessary motions by strong damping forces from water. A further consideration is that the intensity of Raman scattering is very low as most light is scattered by the Mie and Rayleigh collision processes and this low intensity signal often is masked by fluorescence.

Webb and Booth (1971) used Raman spectroscopic techniques and reported differences in the millimeter-wave absorption of normal and tumor cells. Several other experiments led by Webb yielded similar results (Webb and Stoneham 1977; Webb et al. 1977; Webb 1980). Furia and Gandhi (1984) attempted to reproduce the experiment of Webb et al. (1977) using *B. megaterium,* but found no Raman lines of biological origin. Cooper and Amer (1983) suggested that the time variations in the spectra observed by Webb et al. (1977) were due to clumping of the synchronous cells which produced changes in the total light scattered (Mie scattering from clumped cells) and were not due to specific frequency components. The experimental effects reported by Webb and colleagues are inconsistent with theoretical considerations. Resonant interactions cannot occur in the RF spectrum, especially below about 100 GHz, because of strong damping forces from water.

Coherent detection by many oscillators

It is possible that a group of N oscillators could be excited in a coherent and uniform fashion. In analogy with an antenna array, one type of coherent detection would achieve a total detected power that is N times larger than the power received by each oscillator in the group. In a biological context, such a mechanism would require coupling of electromagnetic energy between individual oscillators of a region in order that there could be integration over the region of the energy captured by each oscillator. The net coherent interaction would be dependent only on the nature of the coupling among oscillators and the extent of the coherent area or volume.

Fröhlich (1968) postulated the existence of coherent states in biological matter in a model where vibrational energy (i.e., longitudinal motions) in the infrared (10^{11} to 10^{12} Hz) drives dipole-dipole coupling in several candidate systems. Fröhlich (1968) suggested that oscillating dipoles may exist within cell membranes, as a feature of the vibrational modes of bonds in macromolecules, among non-localized electrons of a biological cell, and perhaps elsewhere. If the input RF energy is great enough, a region defined by coherence among its long-range electric dipoles can behave as a single mode, just as in the case of Bose-Einstein condensation. Consequently, the stored RF energy would not be thermalized, but, persisting in the form of coherent vibrational energy, would be available for physiologically significant molecular changes. Fröhlich (1968) recognized that the input energy would have to overcome losses such as those from collisions with molecules of water, but did not estimate their magnitude.

The collision rate for water molecules of several terahertz, as calculated from kinetic theory models (Hille 2001) and supported by experiments on liquid and frozen water (Hasted 1973; Hille 2001), sets a limiting frequency of approximately 10^{12} Hz for coherent driving of water and molecules bound to water. For coherence to occur at frequencies below $\approx 10^{12}$ Hz it would be necessary to postulate a feature to keep the coupled oscillators isolated from buffeting by frequent collisions. The limiting frequency can be estimated in more detail from the following considerations for phase randomization of initially coherent molecules (for example, coupled molecules arrayed near each other on the cell membrane). A phase coherence time constant τ_{coh} can be calculated from v_s, the velocity of sound in biological matter of density ρ, the size of the coherent region, and its characteristics as a resonator. Coherent exchanges between molecules in a cell layer of thickness d are

limited by the lowest frequency for mechanical resonances, which is roughly given by $\nu = v_s\, d^{-1}$. For $d = 10$ nm, similar to the thickness of a plasma membrane, and $v_s = 1{,}500$ m s^{-1}, $\nu \approx 1.5 \times 10^{11}$ Hz (Adair 2003). The coherence time constant at angular frequency ω can be determined from the system quality factor Q (energy stored/energy dissipated in one cycle) as $\tau_{coh} = Q\ \omega^{-1}$ (Adair 2003). To gain perspective on the effect of system Q, note that a relatively high Q of approximately 8,000 can be achieved in a high quality RF resonant cavity (Balzano et al. 2008) with the consequence that the coherence time constant in this case would be of the order of 10^{-8} s, corresponding to a remarkably low frequency limit of the order of 16 MHz. However, there is no basis to expect that such a high Q occurs in a biological system, and a more realistic Q for oscillators in a water-rich environment is ≈0.2 (Adair 2002). This latter Q yields a coherence time constant of about 2×10^{-11} s and a lower frequency limit of about 8 GHz. Therefore, phase randomization would prevent a coherent response among the oscillators of a coupled system exposed to a weak driving force at frequencies below about 8 GHz.

Coherence is of interest because for a system of N dipole oscillators the total coherently absorbed RF energy ("signal") grows proportional to N, while incoherent energy from thermal agitation ("noise") is proportional to $N^{1/2}$, such that the system S/N is increased by a factor of $N^{1/2}$ (Adair 2003). The RF energy at a frequency f of 3 GHz is smaller than thermal energy by the ratio $hf\,[(3/2)k_BT]^{-1} = 3.2 \times 10^{-4}$. Consequently, a coherent system of $N \approx 10^7$ elements is required for the signal energy to be comparable to the thermal energy. A relaxed requirement for a signal only 10% of thermal noise would need 10^5 coherently coupled elements. In order to gauge the likelihood that sufficient coupling could occur in a cell, note that the surface of a 10^{-5} m cell contains roughly 10^7 molecules, assuming an average mass of 10^3 D and a density of 3×10^2 kg m^{-3}. This indicates that almost the entire cell surface would have to act coherently in order to achieve a S/N of order one. Adair (2003) noted that dipole-dipole coupling is a resonance process with a very narrow intrinsic line width that precludes coherent energy absorption by a large number of independent elements unless each is tuned sharply. However, the damping forces from collisions with water and other molecules broaden resonance line widths by a factor of 10^3 while rapidly (within 10^{-11} s) attenuating any oscillatory motions of the dipole. In summary, coherent mechanisms in biological cells would require coupling among many, if not all, molecules at the membrane surface, but still could not avoid destruction by damping forces, nor last long enough to play any role for a driving force (RF field) in the range below about 10^{12}–10^{13} Hz.

Magnetic dipole interactions in biological magnetite

Because moving charges generate a magnetic field, a rotating body of charge q and mass m creates an intrinsic magnetic moment $\boldsymbol{M} = g\ q\ (2m)^{-1}\ \boldsymbol{S}$, where g is the gyromagnetic ratio and $\boldsymbol{S}$ is the intrinsic spin of the particle. For example, atomic nuclei have a magnetic moment that results from the spin of the protons and neutrons. The alignment of magnetic moments in a structure can lead to the formation of magnetic materials, including magnetite, Fe_3O_4. Kirschvink (1996) noted that magnetite might reside in most biological materials even though concentrations may be very small. He further noted that magnetite is an excellent absorber of microwave energy through interaction with the magnetic field (ferromagnetic resonance) and that the resulting absorbed energy is initially converted into acoustic vibrations. Kirschvink (1996) proposed that this magnetoacoustic process might lead to biological effects despite the negligible temperature increase of 5×10^{-4} K that would occur with absorption of the energy from a 10^2 W m^{-2} RF field. Adair (2002) also addressed resonant microwave energy absorption in magnetite with the conclusion that any motions from magnetoacoustic effects would be overdamped and rapidly thermalized by the surrounding viscous medium and confirmed that this absorbed energy produced only the negligible temperature increase in a magnetosome just mentioned.

Anomalous energy diffusion via normal modes

Spatial localizations ("hot spots") of vibrational energy in the chain dynamics, that is, in its normal modes, are necessary for anomalous diffusion and the resulting charge entrapment (Kalosakas et al. 2005). The temporal nature of protein normal modes is indicated by lifetimes that range from about 1–10 ps (Yu and Leitner 2003a). The mean square diffusive displacement of kinetic energy $<R^2>$ in a protein varies with time as $<R^2> \propto t^{2\nu}$. For normal diffusion $\nu = ½$, whereas for subdiffusive processes $\nu < ½$.

Anomalous energy subdiffusion occurs in cytochrome-c, myoglobin, and green fluorescent protein (Yu and Leitner 2003a) where vibrational energy flow exhibits anomalous subdiffusion as a consequence of trapping of energy by spatially localized normal modes. Protein hydration has little effect on anomalous diffusive energy transport, that is, ν is changed little (Enright et al. 2006). Anomalous subdiffusion is more likely in molecular chains that have a broad distribution of vibrational energy transfer times. A broad distribution of overlapping modes increases the likelihood of long-lasting trapping of vibrational energy

as it flows through a chain structure characterized by spatially localized normal modes.

Alteration of subdiffusion of normal vibrational modes in proteins would require either direct pumping in the frequency band above 300 GHz (Prohofsky 2004) or heating by more than 50 K above baseline (Yu and Leitner 2003b). Typical heating by RF energy could create a small temperature increase ($\leq$1 K) above baseline, but the incremental increase in vibrational energy of the protein normal modes would be distributed uniformly without creating the "hot spots" over atomic dimensions of 10^{-10} m that are necessary to alter the diffusion of vibrational wave packets.

Because diffusion processes are not direct interactions between an electric or magnetic field and protein structure but are consequences of energy fluxes related to heating, field amplitude is only indirectly involved and does not set a threshold distinct from temperature.

Population inversion and masers

There have been suggestions (e.g., Shashlov 1994) that a biological system exposed to microwaves might act as a maser and thereby amplify a weak signal into one strong enough to affect biological molecules. The acronym maser stands for "microwave amplification by stimulated emission of radiation." (This acronym was later changed to extend its meaning to include lasers, which operate at light frequencies, by substituting "molecular" for "microwave"). A classical form of the maser uses ammonia vapor that has an excitable transition in the microwave frequency range. To achieve maser action the gas is enclosed in a resonant cavity and exposed to microwave energy sufficiently intense that it can pump the excited molecular energy states to be more highly populated than the ground state, creating a population inversion. The numerous excited states can be stimulated to emit energy, thereby allowing amplified coherent emission because only one frequency resonates in the cavity. Confinement of energy in the cavity permits positive feedback that appears as amplifier gain. One surface of the cavity is partially transmitting so that a small part of the energy can be extracted. This classical version of the maser is not applicable in a biological context for frequencies in the low gigahertz region. First, biological molecules do not have energy level spacings that yield transitions in the range below a few hundred GHz. Second, a classical maser requires a well-tuned resonant cavity that does not exist in biological systems. There are, however, situations where stimulated emission occurs without a cavity. For example, superradiant emission is observed astronomically for rarified gases occupying vast dimensions in space (Weisberg et al. 2005) and comparable conditions for cavityless stimulated emission can be obtained in the laboratory (Kimberg et al. 2006). It is important to note that the amplification provided by a maser requires an energy supply greater than the extracted energy in order to populate an upper energy level and establish a population inversion. The output microwave signal contains less energy than the total energy supplied. Moreover, any suitable energy levels are, however, in thermal equilibrium and therefore would require pumping with energy greater than kT. In summary, this speculative idea has severe limitations that make it inapplicable to biological systems.

Non-equilibrium dynamical effects

In the last 40 years there has been substantial progress in the solution of nonlinear ordinary differential equations (Sachdev 1997). Nonlinear algorithms have found application to practically all branches of science, including biology (Scott 2003). The concepts of externally driven nonlinear oscillators make excellent models for biological cyclic events at the cellular level such as nitrogen uptake fluxes in yeasts (van Riel and Sontag 2006) and G-protein modulation (Nauroschat and an der Heiden 1997). Kaiser (1996) has applied nonlinear mathematical models to the mechanisms of interaction of RF energy with biological cells in an attempt to explain some experimental evidence that weak electromagnetic fields influence intracellular signal transduction pathways (Walleczek and Budinger 1992).

Although the nonlinear biological models have all the features of insensitivity to external noise and extreme sensitivity to frequency and amplitude of external or internal stimuli (Kaiser 1996), they do not explain the initial transduction event whereby an incident electromagnetic signal initiates the biochemical events so well described in terms of nonlinear equations. These biochemical events may produce electrical oscillations because they involve the motion of charged particles (for example, Ca^{2+}), but there is no model showing that such oscillations are actually triggered by a weak external electromagnetic signal.

Effects on the net transfer of ions across a cell membrane in an ELF electric field as low as 5 V m^{-1} (Walleczek et al. 1993) are consistent with other reported ELF effects on cells and with observations of endogenous steady fields associated with ion fluxes during embryogenesis and wound healing, which create extracellular fields $\geq$1 V m^{-1} (Nuccitelli 1992). In view of these approximate lower limits for ELF and quasi-static electric fields, it is difficult to conceive how ELF amplitude modulation of an RF carrier can cause similar effects because of the extreme attenuation of at least 90 to 100 dB suggested by recent measurements of cells in solution as discussed above.

Nonlinear molecular energy transfer (solitons)

Solitons are non-dispersive, non-dissipative, pulse-like waves that can be transmitted in optical materials (fiber optics), water (waves in oceans and canals), and happen to be solutions to equations applicable in elementary particle physics. The ability of solitons to propagate through a nonlinear medium with no attenuation stimulated theoretical models to evaluate whether energy in alpha-helical proteins propagates via solitons (Christiansen and Scott 1990; Kerr and Lomdahl 1990).

In Davydov's model, nonlinear properties of hydrogen bonding would allow launching of longitudinal pressure waves in a protein structure (Davydov 1982). Unlike linear molecular stretching modes of structural C=O bonds, soliton modes would propagate without loss. This model requires strong coupling between the C=O stretching vibration and the displacement of the hydrogen-bonded chain of the peptide groups. If the coupling is not sufficiently strong, a soliton is not supported. The vibrational energy of the amide group, necessary to trigger a nonlinear coupling with the peptide groups, 0.2 eV, cannot be excited by a single RF photon. Only an RF pulse of large amplitude could conceivably cause such a series of events.

Because energy of the order of kT at the amide-I group is needed to launch a soliton, RF fields could not couple energy sufficient to excite a soliton, making either emission or absorption of an RF photon unobservable (Davydov 1982; Scott 2003). Lawrence and Adey (1982) suggested that solitons might underlie signal transmission through the plasma membrane if binding of a hormone, antigen, or ligand at the membrane created a soliton that would supply energy for secondary cell messaging inside the cell. These authors further suggested that biological responses to weak ELF and RF signals could be explained in terms of modulation of solitonic energy transfer. In order to overcome the effects of damping forces that would prevent achieving the vibrational amplitudes needed to launch a soliton, it is necessary to postulate the coherent excitation of vibrational modes that could lead to the large amplitudes needed for soliton generation. However, calculations indicate that damping forces preclude establishing solitary wave excitation by incident RF fields (Prohofsky 2004).

Changes in integral membrane proteins by external electric fields

Astumian and Robertson (1989) postulated that external alternating electric fields can significantly perturb membrane potential with resulting effects on integral membrane protein transport rates. The significance of altered transport rates is evident from the numerous biochemically active entities transported across the plasma membrane such as ions, water, glucose and other metabolic factors, and proteins (including neurotransmitters and certain hormones). Biologically important secondary effects of transport include activation of protein kinases and other membrane-bound enzymes. The authors' model considered transporter effects caused indirectly by chemical equilibrium shifts occurring at applied field strengths of $E_{ext} = 2.6$ kV m^{-1}, which the authors emphasized is several thousand times weaker than the transmembrane electric field strength itself. The plausibility of effects at 2.6 kV m^{-1} is readily understood from the large membrane potential amplification factor for frequencies below 1 MHz, where a cell of diameter D can be a voltage divider that produces a transmembrane potential drop of as much as 1.5 E_{ext} D at the poles that are defined by the field direction (Foster and Schwan 1996). As an illustration, this relation gives a maximum cell membrane potential change of $\approx 4 \times 10^{-2}$ V for a cell 10^{-5} m in diameter located in the field, with the potential change decreasing progressively at cell surface locations away from the poles to a value of zero at the equator. This potential is comparable to typical static cell membrane potentials ($\approx 10^{-1}$ V) and represents considerable spatial amplification by the cell (by a factor of 3,000 in this example) of the potential drop of 1.3×10^{-5} V that occurs across an isolated 5 nm barrier, a thickness typical of the plasma membrane. This illustrative example is consistent with low-frequency amplification factors calculated by Gowrishankar and Weaver (2003) using a lattice model to represent cells located in a tissue. In the only experiment cited by Astumian and Robertson (1989), applied external fields that were on the order of 10^6 to 10^7 V m^{-1} shifted the average absorption spectrum of bacteriorhodopsin membranes (Tsuji et al. 1988), supporting previous statements that biochemical responses require externally applied fields large enough to create in-situ fields greater than endogenous fields, or at least of comparable magnitude.

CONCLUSION

An examination of all generally accepted and proposed mechanisms open to quantitative analysis shows that in the frequency range from several megahertz to a few hundred gigahertz, the focus of this paper, the principal mechanism for biological effects, and the only well-established mechanism, is the heating of tissues by dielectric and resistive loss.

In order to explain some experimental observations, hypothetical mechanisms have been advanced to refine models beyond simple thermalization of RF energy to include selective absorption by oscillatory modes of biomolecular structures. Detailed analysis of proposed molecular mechanisms showed that damping by water

imposes strict limitations on vibrational or rotational modes and precludes a direct RF pumping of such modes.

Other proposed mechanisms involve energy that is far weaker than thermal background and, even considering various circumstances for amplification, could not overcome the influence of thermal noise. Most quantum mechanical mechanisms also are coupled to the thermal bath and subject to this same limitation. Thus, there is no mechanistic path whereby RF energy can be directly imparted to selected oscillatory modes of the biomolecular system.

Other hypothetical mechanisms imply storage of energy at one molecular location in order to achieve a sufficiently strong signal to overcome the electromagnetic noise generated by the random molecular motion at about 300 K. Such mechanisms would require a Q of the order of 10^3 or higher. However, a volume with such a sharply tuned response requires a precision cavity of particular dimensions that would be detuned by just a few cubic millimeters of water. Thus a small biological structure with a Q of sufficient magnitude is implausible.

Concentration of RF energy density at biologically or physically sensitive locations can occur but only to a limited and insignificant degree. For example, structure and dielectric properties can act as a lens to focus RF fields at specific locations, but lensing over subcentimeter dimensions is greatly limited by the relatively long wavelength at RF. Even if energy could be concentrated, heat conduction and convection would not permit steep temperature gradients or significant local temperature rise in living tissue.

All mechanisms where an RF field directly interacts with charges and dipoles, including translational, dielectrophoretic and other ponderomotive forces, and other effects that require field strengths in excess of system noise, greatly exceed the weak field regime in which there is no detectable heating. Even if there were a mechanism that generated a signal that could be detected by a biological system in the absence of heating sufficient to affect temperature-sensitive chemical reactions, a putative RF signal could not overcome the background noise created by oscillations and collisions involving the various molecular oscillators of living tissue.

Some hypotheses invoke the existence of nonlinear processes whereby part of the incident RF energy is either up- or down-converted into bands where there are ongoing metabolically supported oscillations. Normal physiological functions would be affected if the converted RF energy could alter ongoing metabolic oscillators. Experimental observations and quantitative analysis have shown demodulation of nonlinear signals can occur below about 10 MHz and thereby introduce non-thermal effects at the modulation frequency. However, even without considering demodulation efficiency, the maximum theoretical power that can be demodulated is minuscule, for example, $\approx$1 pW at 16 Hz from an incident field of 100 V m^{-1} at 900 MHz. Experimental evidence suggests an even greater gap of at least 140 dB between a demodulated field and benchmark levels set by endogenous fields in the ELF band. Therefore, energy sufficient to destructively heat a sample (and far exceeding limits imposed by RF safety standards) would be needed to obtain a down-converted electric field strength of biological significance using an ELF-modulated incident RF field.

RF energy below thermal levels can affect radical pair-dependent chemistry with possible biological consequences. This unique phenomenon reflects the quantum mechanical nature of energy level splitting via the hyperfine interaction for certain nuclei of a radical pair. However, magnetic resonance in the gigahertz regime requires a nucleus with an exceptionally large hyperfine coupling constant, indicating that effects on free radical reaction rates are unlikely to be a general feature of biochemistry.

In summary, the consequences of low-level RF energy and thermalizing RF energy are similar because each only increases the entropy (the state of molecular disorder) of the biological system without coupling to specific modes in molecules, cells, and tissues. For this reason, we find no guidance for experimental research predicated on the existence of such couplings at non-thermal exposure levels and no encouragement for theoretical research on non-thermal mechanisms with the possible exception of biochemical changes based on spin-coupled radical pairs.

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REFERENCES

Adair ER. Thermoregulation in the presence of microwave fields. In: Polk C, ed. Handbook of biological effects of electromagnetic fields. Boca Raton, FL: CRC Press; 1996a: 403–433.

Adair RK. Didactic discussion of stochastic resonance effects and weak signals. Bioelectromagnetics 17:242–245; 1996b.
Adair RK. Vibrational resonances in biological systems at microwave frequencies. Biophys J 82:1147–1152; 2002.
Adair RK. Biophysical limits on athermal effects of RF and microwave radiation. Bioelectromagnetics 24:39–48; 2003.
Adair ER, Black DR. Thermoregulatory responses to RF energy absorption. Bioelectromagnetics Suppl 6:S17–S38; 2003.
Adair RK, Astumian RD, Weaver JC. Detection of weak electric fields by sharks, rays, and skates. Chaos 8:576–587; 1998.
Apollonio F, D'Abramo M, Liberti M, Amadei A, Di Nola A, D'Inzeo G. Myoglobin as a case study for molecular simulations in the presence of a microwave electromagnetic field. Piscataway, NJ: Institute of Electronics and Electrical Engineers, Inc; Microwave Symposium Digest, 2006 IEEE MTT-S International; 2006: 1746–1749.
Astumian RD, Robertson B. Nonlinear effect of an oscillating electric field on membrane proteins. J Chem Phys 91:4891–4901; 1989.
Astumian RD, Weaver JC, Adair RK. Rectification and signal averaging of weak electric fields by biological cells. Proc Natl Acad Sci USA 92:3740–3743; 1995.
Astumian RD, Adair RK, Weaver JC. Stochastic resonance at the single-cell level. Nature 388:632–633; 1997.
Balabin IA, Onuchic JN. Dynamically controlled protein tunneling paths in photosynthetic reaction centers. Science 290:114–117; 2000.
Balzano Q. Proposed test for detection of nonlinear responses in biological preparations exposed to RF energy. Bioelectromagnetics 23:278–287; 2002.
Balzano Q, Dowling T. Mutual coupling analysis of arrays of apertures on cones. IEEE AP-22:92–97; 1974.
Balzano Q, Sheppard AR. RF nonlinear interactions in living cells—I: Nonequilibrium thermodynamic theory. Bioelectromagnetics 24:473–482; 2003.
Balzano Q, Hodzic V, Gammon RW, Davis CC. A doubly resonant cavity for detection of RF demodulation by living cells. Bioelectromagnetics 29:81–91; 2008.
Barber PW, Gandhi OP, Hagmann MJ, Chatterjee I. Electromagnetic absorption in a multilayered model of man. IEEE Transactions on Biomedical Engineering BME-26:400–405; 1979.
Barnes FS. Radio-microwave interactions with biological materials. Health Phys 56:759–766; 1989.
Barsoum YH, Pickard WF. Radio-frequency rectification in electrogenic and nonelectrogenic cells of Chara and Nitella. J Membrane Biol 65:81–87; 1982.
Becker FF, Wang XB, Huang Y, Pethig R, Vykoukal J, Gascoyne PR. Separation of human breast cancer cells from blood by differential dielectric affinity. Proc Natl Acad Sci USA 92:860–864; 1995.
Beebe SJ, Fox PM, Rec LJ, Somers K, Stark RH, Schoenbach KH. Nanosecond pulsed electric field (nsPEF) effects on cells and tissues: apoptosis induction and tumor growth inhibition. IEEE Trans Plasma Sci 30:286–292; 2002.
Bernardi P, Cavagnaro M, Pisa S, Piuzzi E. Specific absorption rate and temperature increases in the head of a cellular-phone user. IEEE MTT 48:1118–1126; 2000.
Bernardi P, Cavagnaro M, Pisa S, Piuzzi E. Specific absorption rate and temperature elevation in a subject exposed in the far-field of radio-frequency sources operating in the 10–900-MHz range. IEEE Trans Biomed Eng 50:295–304; 2003.
Bezrukov SM, Vodyanoy I. Noise-induced enhancement of signal transduction across voltage-dependent ion channels. Nature 378:362–364; 1995.
Bialek W, Setayeshgar S. Physical limits to biochemical signaling. Proc Natl Acad Sci USA 102:10040–10045; 2005.
Bigio IJ, Gosnell TR, Mukherjee P, Safer JD. Microwave absorption spectroscopy of DNA. Biopolymers 33:147–150; 1993.
Billimoria CP, DiCaprio RA, Birmingham JT, Abbott LF, Marder E. Neuromodulation of spike-timing precision in sensory neurons. J Neurosci 26:5910–5919; 2006.
Bohr H, Bohr J. Microwave-enhanced folding and denaturation of globular proteins. Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Topics 61:4310–4314; 2000.
Born M, Wolf E. Principles of optics. Oxford: Pergamon Press; 1975.
Bray D, Duke T. Conformational spread: the propagation of allosteric states in large multiprotein complexes. Annu Rev Biophys Biomol Struct 33:53–73; 2004.
Brown BR. Neurophysiology: sensing temperature without ion channels. Nature 421:494–495; 2003.
Carslaw HS, Jaeger JC. Conduction of heat in solids. London: Oxford University Press, Inc.; 1959.
Cha Y, Murray CJ, Klinman JP. Hydrogen tunneling in enzyme reactions. Science 243:1325–1330; 1989.
Changeux J-P, Thíery J, Tung Y, Kittel C. On the cooperativity of biological membranes. Proc Natl Acad Sci USA 57:335–341; 1967.
Chou C-K, Galambos R, Guy AW, Lovely RH. Cochlear microphonics generated by microwave pulses. J Microwave Power 10:361–367; 1975.
Chou C-K, Guy AW, Galambos R. Auditory perception of radio-frequency electromagnetic fields. J Acoust Soc Am 71:1321–1334; 1982.
Chou CK, Guy AW, Galambos R. Microwave-induced cochlear microphonics in cats. J Microw Power 11:171–173; 1976.
Christiansen PL, Scott AC. Davydov's soliton revisited: self-trapping of vibrational energy in protein. New York: Plenum Press; 1990.
Cintolesi F, Ritz T, Kay CWM, Timmel C, Hore P. Anisotropic recombination of an immobilized photoinduced radical pair in a 50 microT magnetic field: a model avian photomagnetoreceptor. Chem Phys 294:385–399; 2003.
Clore GM, Schwieters CD. Concordance of residual dipolar couplings, backbone order parameters and crystallographic B-factors for a small alpha/beta protein: a unified picture of high probability, fast atomic motions in proteins. J Mol Biol 355:879–886; 2006.
Cole KS. Membranes, ions, and impulses: a chapter of classical biophysics. Berkeley, CA: University of California Press; 1972.
Cooper MS, Amer NM. The absence of coherent vibrations in the Raman spectra of living cells. Phys Letters 98A:138–142; 1983.
D'Andrea JA, Adair ER, de Lorge JO. Behavioral and cognitive effects of microwave exposure. Bioelectromagnetics Suppl 6:S39–S62; 2003.
Daizadeh I, Medvedev ES, Stuchebrukhov AA. Effect of protein dynamics on biological electron transfer. Proc Natl Acad Sci USA 94:3703–3708; 1997.
Darnell J, Lodish H, Baltimore D. Nerve cells and the electrical properties of cell membranes. In: Molecular cell biology. New York: Scientific American Books; 1986: 760–764.

Davenport WB, Root WL. An introduction to the theory of random signals and noise. New York: McGraw Hill Book Company; 1958.

Davydov AS. Solitons in α-spiral protein molecules. In: Biology and quantum mechanics. Elmsford, NY: Pergamon Press; 1982.

Deans JK, Powell AD, Jefferys JG. Sensitivity of coherent oscillations in rat hippocampus to AC electric fields. J Physiol 583(Pt 2):555–565; 2007.

de Lorge JO. Operant behavior and colonic temperature of Macaca mulatta exposed to radiofrequency fields at and above resonant frequencies. Bioelectromagnetics 5:233–246; 1984.

Despa F. Biological water its vital role in macromolecular structure and function. Ann NY Acad Sci 1066:1–11; 2005.

Despa F, Berry RS. The origin of long-range attraction between hydrophobes in water. Biophys J 92:373–378; 2007.

Dimbylow PJ. Fine resolution calculations of SAR in the human body for frequencies up to 3 GHz. Phys Med Biol 47:2835–2846; 2002.

Douglass JK, Wilkens L, Pantazelou E, Moss F. Noise enhancement of information transfer in crayfish mechanoreceptors by stochastic resonance. Nature 365:337–340; 1993.

Doyle J, Stuck B, Murphy MR, Pakhomov AG. Suppression of synaptic transmission in hippocampus by extremely-high power microwave pulses synchronized with neuronal excitation. In: Ayrapetyan SN, Markov MS, eds. Bioelectromagnetics: current concepts. Dordrecht, Netherlands: Springer Verlag; 2006: 123–133.

Duke TA, Bray D. Heightened sensitivity of a lattice of membrane receptors. Proc Natl Acad Sci USA 96:10104–10108; 1999.

Durney CH, Massoudi H, Iskander MF. Radiofrequency radiation dosimetry handbook. Brooks Air Force Base, TX: USAF School of Aerospace Medicine; 1986.

Efimova O, Hore PJ. Role of exchange and dipolar interactions in the radical pair model of the avian magnetic compass. Biophys J 94:1565–1574; 2008.

Einolf CW Jr, Carstensen EL. Low-frequency dielectric dispersion in suspensions of ion-exchange resins. J Chem Phys 75:1091–1099; 1971.

Elder JA. Thermal, cumulative, and life span effects and cancer in mammals exposed to radiofrequency radiation. In: Carpenter DO, Ayrapetyan S, eds. Biological effects of electric and magnetic fields. San Diego, CA: Academic Press; 1994: 279–295.

Elder JA, Cahill DF. Biological effects of radiofrequency radiation. Research Triangle Park: United States Environmental Protection Agency; 1984.

Elder JA, Chou CK. Auditory response to pulsed radiofrequency energy. Bioelectromagnetics Suppl 6:S162–S173; 2003.

English NJ, Mooney DA. Denaturation of hen egg white lysozyme in electromagnetic fields: a molecular dynamics study. J Chem Phys 126:091105-1–091105-4; 2007.

Enright MB, Yu X, Leitner DM. Hydration dependence of the mass fractal dimension and anomalous diffusion of vibrational energy in proteins. Physical Rev E (Statistical, Nonlinear, and Soft Matter Phys) 73:051905–051909; 2006.

Eyster JM, Prohofsky EW. On the B to A conformation change of the double helix. Biopolymers 16:965–982; 1977.

Fields RD. The shark's electric sense. Sci Am 297:74–81; 2007.

Foster KR, Finch ED. Microwave hearing: evidence for thermoacoustic auditory stimulation by pulsed microwaves. Sci 185:256–258; 1974.

Foster KR, Glaser R. Thermal mechanisms of interaction of radiofrequency energy with biological systems with relevance to exposure guidelines. Health Phys 92:609–620; 2007.

Foster KR, Schwan HP. Dielectric properties of tissues. In: Polk C, eds. Handbook of biological effects of electromagnetic fields. Boca Raton, FL: CRC Press; 1996: 25–102.

Frauenfelder H, Wolynes PG. Rate theories and puzzles of hemeprotein kinetics. Science 229:337–345; 1985.

Fröhlich H. Long-range coherence and energy storage in biological systems. International J Quantum Chem II:641–649; 1968.

Furia L, Gandhi OP. Absence of biologically related Raman lines in cultures of *Bacillus megaterium*. Phys Letters 102A:380–382; 1984.

Gammaitoni L, Hänggi P, Jung P, Marchesoni F. Stochastic resonance. Reviews Modern Phys 70:223–287; 1998.

Gehl J. Electroporation: theory and methods, perspectives for drug delivery, gene therapy and research. Acta Physiologica Scandinavica 177:437; 2003.

Georgieva R, Neu B, Shilov VM, Knippel E, Budde A, Latza R, Donath E, Kiesewetter H, Baumler H. Low frequency electrorotation of fixed red blood cells. Biophys J 74:2114–2120; 1998.

Gilch P, Pollinger-Dammer F, Musewald C, Michel-Beyerle ME, Steiner UE. Magnetic field effect on picosecond electron transfer. Science 281:982–984; 1998.

Gimsa J. A comprehensive approach to electro-orientation, electrodeformation, dielectrophoresis, and electrorotation of ellipsoidal particles and biological cells. Bioelectrochem 54:23–31; 2001.

Goldbeter A. Computational approaches to cellular rhythms. Nature 420:238–245; 2002.

Goldbeter A, Gonze D, Houart G, Leloup JC, Halloy J, Dupont G. From simple to complex oscillatory behavior in metabolic and genetic control networks. Chaos 11:247–260; 2001.

Gonze D, Goldbeter A. Circadian rhythms and molecular noise. Chaos 16:026110-1–026110-11; 2006.

Gonze D, Halloy J, Goldbeter A. Robustness of circadian rhythms with respect to molecular noise. PNAS 99:673–678; 2002.

Gowrishankar TR, Weaver JC. An approach to electrical modeling of single and multiple cells. Proc Natl Acad Sci USA 100:3203–3208; 2003.

Gowrishankar TR, Vasilkoski Z, Esser AT, Smith KC, Weaver JC. Microdosimetry for conventional and supra-electroporation in cells with organelles. Biochem Biophysical Res Comm 341:1266–1276; 2006.

Grant EH, Sheppard RJ, South GP. Dielectric behaviour of biological molecules in solution. Oxford: Clarendon Press; 1978.

Grissom CB. Magnetic field effects in biology: a survey of possible mechanisms with emphasis on radical-pair recombination. Chem Reviews 95:3–24; 1995.

Grodsky IT. Neuronal membrane: a physical synthesis. Mathematical Biosciences 28:191–219; 1976.

Guy AW, Chou CK, Lin JC, Christensen D. Microwave-induced acoustic effects in mammalian auditory systems and physical materials. Ann NY Acad Sci 247:194–218; 1975.

Guy AW, Chou C-K, Neuhaus B. Average SAR and SAR distributions in man exposed to 450-MHz radiofrequency radiation. IEEE Trans Microwave Theory and Tech 32:752–763; 1984.

Guyton AC. Electroencephalogram. In: Textbook of medical physiology. Philadelphia: W.B. Saunders Company; 1976a: 734–736.

Guyton AC. The eye. II. Receptor function of the retina. In: Textbook of medical physiology. Philadelphia: W.B. Saunders Company; 1976b: 804.

Guyton AC. The normal electrocardiogram. In: Textbook of medical physiology. Philadelphia: W.B. Saunders Company; 1976c: 190–196.

Hart RA, Gandhi OP. Comparison of cardiac-induced endogenous fields and power frequency induced exogenous fields in an anatomical model of the human body. Phys Med Biol 43:3083–3099; 1998.

Hasted JB. Aqueous dielectrics. London: Chapman and Hall; 1973.

Heiligenberg W. Neural nets in electric fish. Cambridge, MA: The MIT Press; 1991.

Heiligenberg W, Keller CH, Metzner W, Kawasaki M. Structure and function of neurons in the complex of the nucleus electrosensorius of the gymnotiform fish Eigenmannia: detection and processing of electric signals in social communication. J Comp Physiol A 169:151–164; 1991.

Henbest KB, Kukura P, Rodgers CT, Hore PJ, Timmel CR. Radio frequency magnetic field effects on a radical recombination reaction: a diagnostic test for the radical pair mechanism. J Am Chem Soc 126:8102–8103; 2004.

Hille B. Ion channels of excitable membranes. Sunderland, MA: Sinauer Associates, Inc.; 2001.

Hu CJ, Barnes FS. A simplified theory of pearl chain effects. Radiat Environ Biophys 12:71–76; 1975.

Hudspeth AJ, Choe Y, Mehta AD, Martin P. Putting ion channels to work: mechanoelectrical transduction, adaptation, and amplification by hair cells. Proc Natl Acad Sci USA 97:11765–11772; 2000.

Illinger KH. Spectroscopic properties of in vivo biological systems: boson radiative equilibrium with steady-state nonequilibrium molecular systems. Bioelectromagnetics 3:9–16; 1982.

Institute of Electronics and Electrical Engineers, Inc. IEEE safety levels with respect to human exposure to radio frequency electromagnetic fields, 3 kHz to 300 GHz. Piscataway, NJ: IEEE; IEEE Std C95.1-2005; 2005.

Jack JJB, Noble D, Tsien RW. Electric current flow in excitable cells. London: Oxford University Press; 1975.

Jacobson GA, Diba K, Yaron-Jakoubovitch A, Oz Y, Koch C, Segev I, Yarom Y. Subthreshold voltage noise of rat neocortical pyramidal neurones. J Physiol 564:145–160; 2005.

Jaffe LF, Nuccitelli R. An ultrasensitive vibrating probe for measuring extracellular currents. J Cell Biol 63:614–628; 1974.

Jasaitis A, Johansson MP, Wikstrom M, Vos MH, Verkhovsky MI. Nanosecond electron tunneling between the hemes in cytochrome bo3. PNAS 104:20811–20814; 2007.

Jefferys JG. Influence of electric fields on the excitability of granule cells in guinea-pig hippocampal slices. J Physiol 319:143–152; 1981.

Jefferys JG, Deans J, Bikson M, Fox J. Effects of weak electric fields on the activity of neurons and neuronal networks. Radiat Prot Dosim 106:321–323; 2003.

Johnsen S, Lohmann KJ. The physics and neurobiology of magnetoreception. Nat Rev Neurosci 6:703–712; 2005.

Johnson CC, Guy AW. Nonionizing electromagnetic wave effects in biological materials and systems. Proceedings of the IEEE 60:692–718; 1972.

Kaiser F. External signals and internal oscillation dynamics: biophysical aspects and modelling approaches for interactions of weak electromagnetic fields at the cellular level. Bioelectrochem Bioenerg 41:3–18; 1996.

Kalmijn AJ. Electric and magnetic field detection in elasmobranch fishes. Science 218:916–918; 1982.

Kalmijn A. Detection and processing of electromagnetic and near-field acoustic signals in elasmobranch fishes. Philos Trans R Soc Lond B Biol Sci 355:1135–1141; 2000.

Kalosakas G, Ngai KL, Flach S. Breather-induced anomalous charge diffusion. Phys Rev E 71:061901-1–061901-7; 2005.

Kerbacher JJ, Meltz ML, Erwin DN. Influence of radiofrequency radiation on chromosome aberrations in CHO cells and its interaction with DNA-damaging agents. Radiat Research 123:311–319; 1990.

Kerr WC, Lomdahl PS. Quantum-mechanical derivation of the Davydov equations for multi-quanta states. In: Christiansen PL, Scott AC, eds. Davydov's soliton revisited: self-trapping of vibrational energy in protein. Proceedings of a NATO Advanced Research Workshop on Self-Trapping of Vibrational Energy in Protein, Thisted, Denmark. New York: Plenum Press; 1990: 23–30.

Kimberg V, Polyutov S, Gel'Mukhanov F, Agren H, Baev A, Zheng Q, He GS. Dynamics of cavityless lasing generated by ultrafast multiphoton excitation. Phys Rev A 74:033814; 2006.

Kirschvink JL. Microwave absorption by magnetite: a possible mechanism for coupling nonthermal levels of radiation to biological systems. Bioelectromagnetics 17:187–194; 1996.

Kole MHP, Hallermann S, Stuart GJ. Single I_h channels in pyramidal neuron dendrites: properties, distribution, and impact on action potential output. J Neurosci 26:1677–1687; 2006.

Kotnik T, Miklavcic D. Second-order model of membrane electric field induced by alternating external electric fields. IEEE Trans Biomed Engineering 47:1074–1081; 2000a.

Kotnik T, Miklavcic D. Theoretical evaluation of the distributed power dissipation in biological cells exposed to electric fields. Bioelectromagnetics 21:385–394; 2000b.

Kuster N, Balzano Q. Energy absorption mechanism by biological bodies in the near field of dipole antennas above 300 MHz. IEEE Trans Vehicular Technol 41:17–23; 1992.

Landsberg GS, Mandelstam LI. Eine neue Erscheinung bei der Lichtzerstreuung in Krystallen. Naturwissenschaften 16: 557–558; 1928.

Laurence JA, McKenzie DR, Foster KR. Application of the heat equation to the calculation of temperature rises from pulsed microwave exposure. J Theor Biol 222:403–405; 2003.

Lawrence AF, Adey WR. Nonlinear wave mechanisms in interactions between excitable tissue and electromagnetic fields. Neurol Research 4:115–153; 1982.

Liu LM, Cleary SF. Absorbed energy distribution from radiofrequency electromagnetic radiation in a mammalian cell model: effect of membrane-bound water. Bioelectromagnetics 16:160–171; 1995.

Lohmann KJ, Johnsen S. The neurobiology of magnetoreception in vertebrate animals. Trends Neurosci 23:153–159; 2000.

Maier H. Electrorotation of colloidal particles and cells depends on surface charge. Biophys J 73:1617–1626; 1997.

Martin A, Schmid FX. The folding mechanism of a two-domain protein: folding kinetics and domain docking of the gene-3 protein of phage fd. J Mol Biol 329:599–610; 2003.

Montgomery JC, Bodznick D. Signals and noise in the elasmobranch electrosensory system. J Exp Biol 202:1349–1355; 1999.

Mouritsen H, Ritz T. Magnetoreception and its use in bird navigation. Curr Opin Neurobiol 15:406–414; 2005.

Murphy MR, Merritt JH, Mason PA, D'Andrea JA, Blick DW, Scholl EW. Bioeffects research in support of the active denial system (ADS): a novel directed energy non-lethal weapon. In: Non-lethal capabilities facing emerging threats. Ettlingen, Germany: Fraunhofer Institut Chemische Technologie; 2003: 23.1–23.15.

National Council on Radiation Protection and Measurements. Biological effects of modulated radiofrequency fields. Bethesda, MD: NCRP; Scientific Committee 89-4; NCRP Commentary No. 18; 2003.

Nauroschat J, an der Heiden U. A theoretical approach to G-protein modulation of cellular responsiveness. J Math Biol 35:609–627; 1997.

Nuccitelli R. Endogenous ionic currents and DC electric fields in multicellular animal tissues. Bioelectromagnetics Suppl 1:147–157; 1992.

Nuccitelli R. Endogenous electric fields in embryos during development, regeneration and wound healing. Radiat Protect Dosim 106:375–383; 2003.

Nuccitelli R, Pliquett U, Chen X, Ford W, Swanson JR, Beebe SJ, Kolb JF, Schoenbach KH. Nanosecond pulsed electric fields cause melanomas to self-destruct. Biochem Biophys Res Comm 343:351–360; 2006.

Nunez PL. Electric fields of the brain. London: Oxford University Press; 1981.

O'Konski CT. Electric properties of macromolecules. V. Theory of ionic polarization in polyelectrolytes. J Physical Chem 64:605–619; 1960.

Pantell RH, Puthoff HE. Fundamentals of quantum electronics. New York: John Wiley and Sons; 1969.

Peier AM, Reeve AJ, Andersson DA, Moqrich A, Earley TJ, Hergarden AC, Story GM, Colley S, Hogenesch JB, McIntyre P, Bevan S, Patapoutian A. A heat-sensitive TRP channel expressed in keratinocytes. Science 296:2046–2049; 2002.

Pethig R. Dielectric and electronic properties of biological materials. Chichester, UK: John Wiley & Sons, Ltd; 1979.

Petracchi D, Cercignani G. A comment on the sensitivity of fish to low electric fields. Biophys J 75:2117–2120; 1998.

Phillips JB, Deutschlander ME. Magnetoreception in terrestrial vertebrates: implication for possible mechanisms of EMF interaction with biological systems. In: Stevens RG, Wilson BW, Anderson LE, eds. The melatonin hypothesis: breast cancer and the use of electric power. Columbus, OH: Battelle Press; 1997: 111–172.

Phillips JB, Freake MJ, Fischer JH, Borland C. Behavioral titration of a magnetic map coordinate. J Comp Physiol A Neuroethol Sens Neural Behav Physiol 188:157–160; 2002.

Pickard WF, Barsoum YH. Radio-frequency bioeffects at the membrane level: separation of thermal and athermal contributions in the Characeae. J Membr Biol 61:39–54; 1981.

Pickard WF, Moros EG. Energy deposition processes in biological tissue: nonthermal biohazards seem unlikely in the ultra-high frequency range. Bioelectromagnetics 22:97–105; 2001.

Pickard WF, Rosenbaum FJ. Biological effects of microwaves at the membrane level: two possible athermal electrophysiological mechanisms and a proposed experimental test. Mathematical Biosciences 39:235–253; 1978.

Pilet E, Jasaitis A, Liebl U, Vos MH. Electron transfer between hemes in mammalian cytochrome c oxidase. Proc Natl Acad Sci USA 101:16198–16203; 2004.

Pilla AA. Mechanisms and therapeutic applications of time-varying and static magnetic fields. In: Barnes FS, Greenebaum B, eds. Handbook of biological effects of electromagnetic fields: biological and medical aspects of electromagnetic fields. Boca Raton, FL: CRC Press, Taylor and Frances Group; 2007: 351–412.

Pilla AA, Muehsam DJ, Markov MS. A dynamical systems/larmor precession model for weak magnetic field bioeffects: ion binding and orientation of bound water molecules. Bioelectrochem Bioenerg 43:239–249; 1997.

Pohl HA. The motion and precipitation of suspensoids in divergent electric fields. J Applied Phys 22:869–871; 1951.

Pohl HA. Dielectrophoresis: the behavior of neutral matter in non-uniform electric fields. London: Cambridge University Press; 1978.

Prohofsky EW. RF absorption involving biological macromolecules. Bioelectromagnetics 25:441–451; 2004.

Raman CV, Krishnan RS. A new type of secondary radiation. Nature 121:501; 1928.

Reilly JP. Applied bioelectricity. New York: Springer-Verlag; 1998.

Ritz T, Adem S, Schulten K. A model for photoreceptor-based magnetoreception in birds. Biophys J 78:707–718; 2000.

Ritz T, Thalau P, Phillips JB, Wiltschko R, Wiltschko W. Resonance effects indicate a radical-pair mechanism for avian magnetic compass. Nature 429:177–180; 2004.

Roa RL, Pickard WF. The use of membrane electrical noise in the study of *Characean* electrophysiology. J Exp Bot 27:460–472; 1976.

Sachdev PL. A compendium on nonlinear ordinary differential equations. New York: John Wiley & Sons; 1997.

Salzstein RA, Pollack SR. Electromechanical potentials in cortical bone—II. Experimental analysis. J Biomechanics 20:271–280; 1986.

Saunders RD, Jefferys JG. A neurobiological basis for ELF guidelines. Health Phys 92:596–603; 2007.

Schanne OF, Ruiz-Ceretti E. Impedance measurements in biological cells. New York: John Wiley & Sons; 1978.

Schatz G, Dobberstein B. Common principles of protein translocation across membranes. Science 271:1519–1526; 1996.

Schneidman E, Berry MJ, Segev R, Bialek W. Weak pairwise correlations imply strongly correlated network states in a neural population. Nature 440:1007–1012; 2006.

Schramm VL. Enzymatic transition states and transition state analogues. Curr Opin Struct Biol 15:604–613; 2005.

Schwan H, Sher L. Alternating-current field-induced forces and their biological implications. J Electrochemical Society 116:22C--26C; 1969.

Schwarz G. A theory of the low-frequency dielectric dispersion of colloidal particles in electrolyte solutions. J Physical Chem 66:2636–2642; 1962.

Scott AC. Nonlinear science: emergence and dynamics of coherent structures. London: Oxford University Press; 2003.

Shashlov VA. On the mechanism of frequency-selective biological effects of EHF radiation and methods of their amplification. Radiophys Quantum Electronics 37:59–62; 1994.

Sheppard AR. Where does the energy go? Microwave energy absorption in biological objects on the microscopic and molecular scales. In: Carlo GL, eds. Wireless phones and

health: scientific progress. Norwell, MA: Kluwer Academic Publishers; 1998: 165–176.

Siegman AE. An introduction to lasers and masers. New York: McGraw-Hill; 1971.

Silny J. Demodulation in tissue, the relevant parameters and the implications for limiting exposure. Health Phys 92:604–608; 2007.

Simeonova M, Gimsa J. The influence of the molecular structure of lipid membranes on the electric field distribution and energy absorption. Bioelectromagnetics 27:652–666; 2006.

Stoykov NS, Jerome JW, Pierce LC, Taflove A. Computational modeling evidence of a nonthermal electromagnetic interaction mechanism with living cells: microwave nonlinearity in the cellular sodium ion channel. IEEE Trans Microwave Theory and Tech 52:2040–2045; 2004.

Stratton JA. Electromagnetic theory. New York: McGraw Hill Publishing Co.; 1941.

Stuchly SS, Stuchly MA, Kraszewski A, Hartsgrove G. Energy deposition in a model of man: frequency effects. IEEE Trans Biomed Eng 33:702–711; 1986.

Suydam IT, Snow CD, Pande VS, Boxer SG. Electric fields at the active site of an enzyme: direct comparison of experiment with theory. Science 313:200–204; 2006.

Szasz A, Vincze G, Szasz O, Szasz N. An energy analysis of extracellular hyperthermia. Electromagn Biol Med 22:103–115; 2003.

Takashima S, Schwan HP. Alignment of microscopic particles in electric fields and its biological implications. Biophys J 47:513–518; 1985.

Takeuchi H, Kurahashi T. Mechanism of signal amplification in the olfactory sensory cilia. J Neurosci 25:11084–11091; 2005.

Tenforde TS. Biological responses to static and time-varying magnetic fields. In: Lin JC, eds. Interaction of electromagnetic waves in biological systems. New York: Plenum; 1989: 83–107.

Thalau P, Ritz T, Stapput K, Wiltschko R, Wiltschko W. Magnetic compass orientation of migratory birds in the presence of a 1.315 MHz oscillating field. Naturwissenschaften 92:86–90; 2005.

Thompson CJ, Yang YS, Anderson V, Wood AW. A cooperative model for CA++ efflux windowing from cell membranes exposed to electromagnetic radiation. Bioelectromagnetics 21:455–464; 2000.

Timmel CR, Henbest KB. A study of spin chemistry in weak magnetic fields. Phil Trans R Soc Lond A 362:2573–2589; 2004.

Timmel CR, Till U, Brocklehurst B, McLauchlan KA, Hore PJ. Effects of weak magnetic fields on free radical recombination reactions. Molecular Phys 95:71–89; 1998.

Torre V, Ashmore JF, Lamb TD, Menini A. Transduction and adaptation in sensory receptor cells. J Neurosci 15:7757–7768; 1995.

Tsuji K, Müller SC, Hess B. Electric field induced conformational changes of bacteriorhodopsin in purple membrane films. II. Alternating field effects. Eur Biophys J 15:329–337; 1988.

van Riel NAW, Sontag ED. Parameter estimation in models combining signal transduction and metabolic pathways: the dependent input approach. IEE Proc Systems Biol 153:263–274; 2006.

Vaughan TE, Weaver JC. Molecular change signal-to-noise criteria for interpreting experiments involving exposure of biological systems to weakly interacting electromagnetic fields. Bioelectromagnetics 26:305–322; 2005.

Walleczek J, Budinger TF. Pulsed magnetic field effects on calcium signaling in lymphocytes: dependence on cell status and field intensity. FEBS Letters 314:351–355; 1992.

Walleczek J, Miller PL, Adey WR. Simultaneous dual-sample fluorimetric detection of real-time effects of ELF electromagnetic fields on cytosolic free calcium and divalent cation flux in human leukemic T-cells (Jurkat). In: Blank M, ed. Electricity and magnetism in biology and medicine. San Francisco: San Francisco Press, Inc.; 1993: 303–306.

Wannier GH. Statistical physics. New York: John Wiley and Sons, Inc.; 1966 [republished (1987) by Dover Publications, Inc., New York].

Weaver JC, Vaughan TE, Adair RK, Astumian RD. Theoretical limits on the threshold for the response of long cells to weak extremely low frequency electric fields due to ionic and molecular flux rectification. Biophys J 75:2251–2254; 1998.

Weaver JC, Vaughan TE, Martin GT. Biological effects due to weak electric and magnetic fields: the temperature variation threshold. Biophys J 76:3026–3030; 1999.

Weaver JC, Vaughan TE, Astumian RD. Biological sensing of small field differences by magnetically sensitive chemical reactions. Nature 405:707–709; 2000.

Webb SJ. Laser-Raman spectroscopy of living cells. Phys Reports 60:201–224; 1980.

Webb SJ, Booth AD. Microwave absorption by normal and tumor cells. Science 174:72–74; 1971.

Webb SJ, Stoneham ME. Resonances between 100 and 1000 GHz in active bacterial cells as seen by laser Raman spectroscopy. Phys Letters 60A:267–268; 1977.

Webb SJ, Stoneham ME, Fröhlich H. Evidence for non-thermal excitation of energy levels in active biological systems. Phys Letters 63A:407–408; 1977.

Weisberg JM, Johnston S, Koribalski B, Stanimirovic S. Discovery of pulsed OH maser emission stimulated by a pulsar. Science 309:106–110; 2005.

White JA, Blackmore PF, Schoenbach KH, Beebe SJ. Stimulation of capacitative calcium entry in HL-60 cells by nanosecond pulsed electric fields. J Biol Chem 279:22964–22972; 2004.

Wiltschko W, Wiltschko R. Magnetic orientation and magnetoreception in birds and other animals. J Comp Physiol A Neuroethol Sens Neural Behav Physiol 191:675–693; 2005.

Wiltschko W, Munro U, Ford H, Wiltschko R. Bird navigation: What type of information does the magnetite-based receptor provide? Proc R Soc B 273:2815–2820; 2006.

Wiltschko W, Freire R, Munro U, Ritz T, Rogers L, Thalau P, Wiltschko R. The magnetic compass of domestic chickens, Gallus gallus. J Exp Biol 210:2300–2310; 2007.

Woodward JR, Timmel CR, McLauchlan KA, Hore PJ. Radio frequency magnetic field effects on electron-hole recombination. Physical Review Letters 87:1–4; 2001.

Yifrach O. Hill coefficient for estimating the magnitude of cooperativity in gating transitions of voltage-dependent ion channels. Biophys J 87:822–830; 2004.

Yu X, Leitner DM. Anomalous diffusion of vibrational energy in proteins. J Chem Phys 119:12673–12679; 2003a.

Yu X, Leitner DM. Vibrational energy transfer and heat conduction in a protein. J Physical Chem B 107:1698–1707; 2003b.

Zmýslony M, Politanski P, Rajkowska E, Szymczak W, Jajte J. Acute exposure to 930 MHz CW electromagnetic radiation in vitro affects reactive oxygen species level in rat lymphocytes treated by iron ions. Bioelectromagnetics 25:324-328; 2004.

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