

MMF — Mobile Manufacturers Forum

Mechanisms for Interactions of Radiofrequency Energy with Biological Systems: Principal Conclusions from a Seminar held in Washington, DC

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This report was prepared by Asher R. Sheppard, Mays L. Swicord, Sakari Lang, and Frank Gollnick and reviewed by the meeting participants to whom we are grateful for corrections and advice.

Purposes

A group of scientists with backgrounds almost exclusively in the areas of biophysics and physics met in Washington, D.C. on May 22-23, 2001 to evaluate mechanisms for interactions of radiofrequency (RF) energy with biological systems. Discussions ranged over models applicable from molecular to tissue dimensions, with little emphasis on biological models and no intention to evaluate the accuracy of experimental results from biological studies that have driven theoretical developments. Attention was given both to existing and possible new mechanistic approaches. Conclusions were drawn about the physical feasibility of various mechanisms that give quantitative limits on sensitivity to RF and gaps in understanding and published research. Although it was understood that the ultimate application would be to phenomena that might occur at the frequencies, waveforms, and field strengths characteristic of cellular telephony (handset and base station emissions), the direction of discussions was to evaluate mechanisms for conceptual plausibility and suggest topics for additional research. Recommendations were sought where theoretical analysis or biophysical experimentation could yield quantitative information on plausible mechanisms.

Participants

The 15 participants were: Dean Astumian (Department of Physics, University of Maine), Quirino Balzano (after 4 PM, 22 May) (Consultant), Howard Bassen (23 May only) (Electrophysics Branch, US Food and Drug Administration), Frank Barnes (Department of Electrical

Engineering and Computer Science, University of Colorado), Ferdinando Bersani (Dipartimento Di Fisica, Universita Di Bologna), Chris Davis (Department of Electrical Engineering University of Maryland), Larry Dworsky (Florida Research Laboratories, Motorola, Inc.), Roland Glaser (Institut für Biologie u. Experimentelle Biophysik Humboldt-Universität zu Berlin), Frank Gollnick (Forschungsgemeinschaft Funk e.V. [FGF]), Sakari Lang (Nokia Research Center), William F. Pickard (Department of Electrical Engineering, Washington University), Earl Prohofsky (Physics Department, Purdue University), Asher Sheppard (Asher Sheppard Consulting), Mays Swicord (Florida Research Laboratories, Motorola, Inc.), James Weaver (Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology).

Introductory Remarks

Mays Swicord began the meeting with an overview of the current MMF research program. He stated that the purpose of the meeting was to identify biophysical mechanisms that are plausible and testable by theoretical methods (calculations) and biophysical experiments, and to distinguish these from mechanisms that are not. For plausible mechanisms, it is important to specify the electromagnetic field conditions required for a biophysically significant interaction. The group was asked to indicate where calculations or biophysical experimentation are needed to fill gaps in understanding and in the published literature. Biological experiments conducted in the absence of guidance from biophysical theory are, at this stage of scientific development, unlikely to advance the science of RF bioeffects. A participant remarked that biochemical change is required in order that there be a biological effect, and that in principle a plausible mechanism is one that produces an observable chemical change. Subsequent comments noted the fact that the experiments such as those showing effects of modulated RF energy on “calcium efflux” gave evidence for a chemical change with no demonstrated biochemical or biological sequelae, and that chemical changes can occur without necessarily being harmful to an organism. The example of hearing near the lower threshold was presented as evidence that although biochemical changes occur, it could be very difficult to identify them before a complex mechanism is well understood.

Summaries of Topical Discussions

The meeting was organized around five topics, shown as I through V below. Discussions sometimes crossed topical areas, although this summary categorizes ideas more neatly.

During the meeting, several topics were highlighted as especially worthy of follow-up study. These “do-ables” are shown below in italics and in Table 2.

I – RF-produced Temperature Gradients

In most contexts, “microwave heating” refers to an elevation of the mean temperature of the body as a whole or regionally, or a mean temperature measured in an experimental vessel. Because of the strong temperature sensitivity of the biochemical reactions inherent in biological systems, temperature changes are accepted as a plausible mechanism for biological effects. In contrast, the meeting considered changes in temperature over short intervals in time and distance. The context for the discussions of temperature gradients was intervals of less than 1 ms (and in cases <10 ns) and dimensions as small as those of protein molecules (<0.1 μm) or as large as tissues regions (tens to thousands of cells). It is well known that temperature reaches equilibrium in small volumes very rapidly so that localized temperature elevations that might occur with pulsed and amplitude-modulated waveforms could influence biochemical systems only for a brief time but nonetheless introduce biochemically, and perhaps biologically significant changes.

The participants recognized a need for theoretical analyses of temporal and spatial gradients in temperature and energy at ultrastructural (nanometer), microscopic (micrometer), and macroscopic (sub-millimeter) levels. The analyses, which preferably would be presented mathematically in functional form (rather than only as numerical results), would determine the magnitude and duration of gradients in SAR and temperature. Such gradients would be developed using models that take into account discontinuous dielectric properties to represent protein moieties in lipid or aqueous environments, cells of various sizes and shapes (“complex geometries”), and tissues composed of diverse biological materials. The results would be estimates of the limiting values for exposure variables and parameters at which there could be

plausible effects attributable to temperature gradients occurring without gross heating, i.e., in the non-thermal regime.

Based on conflicting comments, it would be valuable to establish the conditions under which periodic changes in temperature, particularly changes of 1°C or less, can serve as a stimulus affecting ongoing biochemical processes. How might periodic temperature changes differ from normal variations in temperature of the order of 1°C that occur daily with changing activity and environmental conditions? Although thermal equilibrium is achieved too quickly to establish meaningful temperature differences across the cell membrane, at the molecular level, energy resident in a protein over a span of nanoseconds might affect protein function. The feasibility of effects at the molecular level would have to be evaluated with recognition that internal vibrational modes rapidly transfer energy within a molecule. For low frequencies, this process occurs at approximately the speed of sound. Two suggestions for possible experimental research were to invent very fast responding, highly temperature sensitive dyes for biophysical studies and secondly, to use laser interferometry to detect the density change associated with a temperature change.

These specific topics concerning thermal gradients were listed for further investigation:

- ★ *Examine ΔT at microscopic and molecular (e.g., protein molecule) levels*
- ★ *Examine ΔT over short times (10^{-8} s) in the case of pulsed signals or for processes occurring over the period of a sinusoidal signal (e.g., about one nanosecond for frequencies near 1 GHz).*
- ★ *Examine ΔT at the millimeter scale, especially for application to in vitro studies.*
- ★ *Given that the occurrence of a biochemical change does not necessarily predict a biological change, investigate the biophysical and biochemical features that could determine when the temperature gradients discussed above might affect biological systems.*

The above calculations require explicit reference to energy, power, temperature, and thermal time constants.

II – RF Interactions at Cellular Level

The plausibility of a model for RF interactions affecting ion channel flux rates (Apollonio et al., 1998) was not apparent from the information available during discussions and could not be resolved. In part, this was because the physical basis for a transmembrane potential of the order of one microvolt was not clear. The model considers a transmembrane voltage of this magnitude as the initial physical change, although such a signal is less than naturally occurring membrane noise levels (DeFelice, 1981). The remainder of the model involved analysis of established biophysical models in which ion channel open/closed probabilities are treated as a Markov process and the functional role of ion channels in cells was evaluated. However, these elements of the model did not address the central mechanistic issues of the meeting and therefore these aspects were not useful in assessing the model as a description of a plausible mechanism for molecular effects of RF energy.

A model (Chiabrera et al., 2000) for RF effects on ligand (e.g., Ca^{2+}) binding to cell receptor proteins was discussed. As was the case for the forgoing model, it was not possible to understand how the initial RF interaction might occur. It appeared that this model postulated an RF effect on ligand binding and then treated the complex consequences in detail. It also was not possible during discussions to clarify the mechanism whereby ligand dynamics would be changed during exposures to pulsed and modulated fields, although such a dynamical effect is presented as a central feature of the model. However, a participant suggested that there are experimental methods that could directly test for changes in binding site dynamics proposed in the Chiabrera model.

Based on the Pickard and Rosenbaum (1978) model, direct rectification of RF fields at the cell membrane results from non-linearities affecting ion movement across the cell membrane. Rectification of this sort is limited to low megahertz frequencies of the carrier wave because of the time required for ions to move a significant distance. In principle, there is no sharp threshold inasmuch as high field strengths and long integration times could produce rectified transmembrane voltages of arbitrarily small magnitude. *Calculations are needed to refine thresholds in field strength, carrier frequency, and pulse parameters for direct effects on membrane potential. Calculations also are needed to determine whether multi-cell structures enhance rectification over the limits derived for isolated cells.* The ion transit mechanism is

plausible in a range below a few megahertz and has been confirmed by experiments in algal (plant) cells. However, it appeared unlikely to be important at field strengths commonly found in the environment for the gigahertz range frequencies used in cellular telephony.

It would be useful to conduct experiments using physical measurement methods to investigate cell non-linearities at low-gigahertz frequencies. One such method would make direct measurements of harmonic frequencies generated by non-linear processes occurring in biological cells. Very small amounts of energy radiated at harmonic frequencies might be detectable with sensitive antennas, low-noise receiver technology, and a high Q cavity.

Recent papers by (Kotnik and Miklavcic, 2000a; Kotnik and Miklavcic, 2000b) extend the well-known Schwan equation for transmembrane potential of a spherical cell located in an external electric field. Their work takes into account field enhancement at dielectric discontinuities, such as at the interfaces between the cell plasma membrane and the cytoplasm, and between the membrane and extracellular medium. *The implications of the Kotnik and Miklavčič model for differential energy deposition and heat fluxes at the scale of the cell membrane ($\sim 10^{-8}m$) and over brief time intervals requires theoretical research to determine the exposure levels at which there might be temperature effects significant for biological systems. This work should allow evaluation of potential relevance for the conditions of exposure to wireless communications devices.*

Ions of the counterion layer adjacent to the outer cell membrane surface were discussed because of interest in the possibility that surface polarization of these ions might be significant for a system meeting certain sensitivity criteria. Although the α -dispersion is generally viewed as a broad low frequency phenomenon that can be related to a surface current according to theoretical treatments such as those by Schwarz (1962) and O'Konski (1960), counterion polarization does not have a sharp cutoff frequency and might be of interest at low gigahertz frequencies. One such circumstance might occur if a biological system (e.g., a protein) were teetering between two nearly equal energy states and the population of states could be altered by polarization energy. Another circumstance where polarization might be significant arises in processes such as cell aggregation and protein aggregation, although these are multi-step processes and therefore may

not show a net response to a weak perturbation. The assembly of colloidal particles into long fibers is an example of a multi-step process. In this case, interaction energies are well below kT (e.g., 0.1 kT), but are effective because the system lies at an unstable point on the potential energy surface (saddle point). Greatest sensitivity to weak perturbations may arise in the case of an influence on proofreading, such as occurs in transcription of DNA, or in an analogous process. Because a very large number of steps are involved in an irreversible process, small changes in the probability of correct function (e.g., error correction) may bias the outcome of the process. In this way, small changes in probability might result in a very large effective amplification factor. *It was recommended that calculations be made to estimate quantitative limits on mechanisms related to ion polarization and proofreading type molecular systems. An approach to the latter process could be a theoretical analysis to estimate the number of steps and the magnitude of effects on each step.* A specific calculation that was suggested would estimate electrophoretic forces ($\mu \cdot E$) on a molecular entity (enzyme) that assists in DNA transcription.

Discussions on interactions at the cellular level frequently emphasized that *theoretical examinations should not be limited to effects on a single cell held in isolation, but should consider multi-cell structures and, where applicable, analysis at the ultra-structural level of the inhomogeneity of dielectric properties.* The three dimensionality of real biological structures stands as a warning for the limitations of research conducted in vitro with cells in isolation or arranged in layers.

III – Interactions at the molecular/chemical level

Resonant mechanisms in the vibrational motions of molecules have been studied because such resonances would be a means to store RF energy at the molecular level. Molecular resonances appear as a “softening” of vibrational modes with an attendant reduction in mode frequency and increase in vibrational amplitude. However, theory and experiment led to the conclusion that although resonances occur at frequencies where the quantum energy is thousands of times greater than for a 1 GHz quantum, they are absent at microwave frequencies. For example, hydrogen bond modes as low as 63.2 cm^{-1} have been identified theoretically in a DNA polymer (Saxena and Van Zandt, 1994), and a low-lying molecular vibrational mode has been observed experimentally in a yeast ribonucleotide reductase at 85 cm^{-1} (Bar et al., 2001), an energy that is

still approximately 2500 times greater than the energy quantum of 0.033 cm^{-1} at 1 GHz. This lower frequency limit for resonant absorption corresponds to relaxation times in the picosecond range. Strong damping of molecular motions by water molecules appears to preclude pumping energy into resonant modes in the gigahertz range. Changes in molecular conformation also can be analyzed from the perspective of vibrational modes, which are the "soft modes" for the particular conformation changes. An example of such a mechanism may be the phase transition reported in β -lactose exposed to 400 W/kg. Damping at lower power levels once again indicates that no significant energy is likely to be absorbed, or build up, in such modes. In summary, it would require un-damped resonant absorption at microwave frequencies for any of the effects of radiation described above to occur.

Kapitza Resistance is a factor that has to be taken into account in calculations of thermal transport and build up of locally higher temperature. Kapitza resistance is a property of phonon propagation at the interface between disparate materials that is essentially an impedance mismatch for acoustic waves. Kapitza resistance has so far been overlooked in modeling microwave interactions, and can conceivably lead to higher local temperatures. This effect is unlikely to have an influence that exceeds a factor of the order of two. It was asked if there might be a phenomenon at microwave frequencies that creates anomalously low viscous damping in analogy to the low viscous damping of a golf ball created by turbulence at its dimpled surface—although this analogy was not meant to suggest actual turbulence affecting biological molecules. In response, one participant noted that that this mechanism had not been ruled out explicitly, but was vague and difficult to imagine.

Another approach to low-frequency (gigahertz range) molecular energy absorption considered caged ions, such as calcium ions bound in certain biological enzymes, or possibly in a large protein such as a membrane ion channel. *Calculational studies are needed in order to assess quantitatively if significant energy absorption by caged ions could occur despite the presumed effects of strong damping.*

Another perspective was provided by the question, "Why can't biological systems store energy as do phosphofluorescent molecules?" A response is that the light energy used to pump

fluorescent molecules is greater than thermal noise (“kT”) and therefore it is possible to isolate the energy in energy levels that are isolated from rapid relaxation. This answer suggested a cascade or two-quantum model for microwave effects in which the primary energy source is from chemical or light energy and microwave energy is stored together with the higher energies. *Such perturbation of an ongoing enzymatic reaction by microwave energy is an example of a mechanism that requires two photons, two phonons, or joint interaction of a photon and phonon. The plausibility of multi-particle interactions should be investigated further.* However, it seemed to some participants implausible that chemical energy could be sufficient to excite long-lived states and, in general, events requiring coincident interactions are expected to occur with low probability. The Woodward-Hoffman symmetry rules that govern photonic interactions in organic chemistry also appear to be a strong constraint against a photon-phonon transition. Moreover, microwave energy falls into the continuum part of the vibrational spectrum so that the environment would be characterized by a large specific heat, whereas narrow resonant interactions are characterized by a small specific heat. Overall, the mechanisms suggested during these discussions did not appear highly plausible, but further investigation is warranted.

The following simple model assumes that thermal energy kT in a vibrational mode is of the same magnitude as the energy absorbed in a volume of biological material exposed to microwave energy at a specific absorption rate S over an integration time Δt. The relationship among these quantities and the mass density ρ for a cubic volume l^3 , where the edge length is l , is,

$$S \rho \Delta t l^3 = kT, \quad \text{or } l = (kT/S\rho\Delta t)^{1/3} \sim 7 \text{ nm},$$

indicating that for a 1 s integration time, and an SAR of 10 W/kg, a mass density of 10^3 kg/m^3 , and $kT = 4 \times 10^{-21} \text{ J}$, the require structure would have a linear dimension comparable to cell membrane thickness in order to absorb the energy. In view of the great number of modes in such a large volume, it seemed highly unlikely that this energy could be condensed into a single mode that would cause a chemical change.

For a non-spherical entity, induced dipole moments might sum to produce a net dipole moment. A large dipole moment of this sort localized to a molecular site could interact with applied fields.

Although randomly arranged permanent dipoles will average to a net dipole moment of zero, it was stated that induced dipole moments, such as the London dispersion force (a quantum mechanical interaction arising from mutual induction between neighboring atoms and molecules), would not. In this connection, there was discussion of phenomena such as protein migration lymphocytes in the capping process and the intermolecular forces between serum proteins that underlie rouleau formation (stacking) in erythrocytes as examples of apparent long-range forces with biological significance for which the mechanisms are not well understood.

In general, at the molecular level any conceivable mechanism for a localized interaction is likely to fail unless the time between collisions is long compared to binding time, transit time, or another temporal aspect of the fundamental interaction. Similarly, a participant stated that it is not possible to have sharp resonances without being in the ballistic regime (such as for conduction electrons in a metal where collisions are elastic and damping is not a major factor). *Research was recommended to assess whether ballistic transmission can occur in membrane channel proteins.*

A number of published papers presented detailed analyses of the forgoing topics.

IV - Many-body interactions (Cooperativity; Coherence; Non-linear Dynamics and Stochastic Resonance)

Non-linear dynamics provides a heuristic for sensitive responses in complex systems, but does not address the nature of the primary direct interaction between a RF field and a biological system. Therefore, research on that primary interaction would not require application of principles derived from non-linear dynamics.

Stochastic resonance, which can enhance the sensitivity of other mechanisms, could not alter effective signal-to-noise ratios by a very large factor and therefore was not thought to play an important role in any microwave mechanisms.

The Fröhlich model for long-range coherence between electric dipoles on cell membrane surfaces is implausible because it did not indicate how such coherence could be maintained in the face of collisional damping, which principally involves water molecules. These collisions would critically overdamp any such interactions. A recent paper considered the destructive effect of damping by water on any large vibrational mode and evaluated the resonance energy of Fröhlich's proposal (Adair, 2001). He concluded that coherent, long-range cooperative interactions are not plausible.

On the other hand, in the absence of strong damping, synchronization of coupled oscillatory systems is possible and it would be useful to calculate in detail the conditions under which synchronized systems occur in living tissues. *Because strong dipole interactions are critically damped, it would be useful to calculate the field strength at which a large synchronous system can act coherently despite damping.*

V – Magnetic dipole interactions

(Kirschvink, 1996) suggested that small amounts of biological magnetite could absorb sufficient energy through the mechanism of ferromagnetic resonance to produce localized heating in the region surrounding a magnetosome, but Kirschvink recognized that the absorbed power is too small to cause a significant temperature rise. Kirschvink (1996) estimated that the increase in whole cell temperature for a cell exposed to 10 mW/cm^2 in the microwave region is only $\leq 10^{-4} \text{ }^\circ\text{C}$. Another factor limiting heating at magnetosomes is that the insulating layer that surrounds magnetosomes greatly reduces induced eddy currents in the surrounding region, a factor that was ignored in a recent published paper (Dobson et al., 2000). The small magnitude of temperature increases due to localized magnetosome heating led to a conclusion that mechanisms involving magnetite heating were implausible.

The close relationship between chemical change and biological change is apparent from considerations of the radical pair mechanism. Magnetic field effects on chemical reaction rates occur because radical pair recombination rates are altered by static magnetic fields of the order of 100 mT or greater (Steiner and Ulrich, 1989). However, a calculation of the effects of

perturbations by time-varying magnetic fields indicates possible influences on biological chemistry for magnetic flux densities approaching 3 μT (Grissom, 1995), p 9). *Calculations are needed to set limits on the applicability at radiofrequencies of the radical pair mechanism that describes free radical production in static magnetic fields.*

Summary of General Conclusions

For exposures to RF energy from sources in the general environment and from use of mobile telephone devices, the only clearly plausible mechanisms for RF interactions with biological systems involve heating. Theoretical analyses are needed to evaluate certain other proposed mechanisms in order to determine their range of applicability. Biophysical or biochemical experiments to confirm specific proposed mechanisms may or may not be required, depending upon the outcome of calculations that estimate the field strengths and frequencies at which effects are likely to appear.

References

- Adair RK. 2001. Vibrational resonances in biological systems at microwave frequencies. *Biophysical Journal*
- Apollonio F, D'Inzeo G, Tarricone L. 1998. Modelling of neuronal cells exposed to RF fields from mobile telecommunication equipment. *Bioelectrochemistry and Bioenergetics* 47:199-205.
- Bar G, Bennati M, Nguyen H, Ge J, Stubbe J, Griffin R. 2001. High-frequency (140-GHz) time domain EPR and ENDOR spectroscopy: the tyrosyl radical- Fe(II) cofactor in ribonucleotide reductase from yeast. *Journal of the American Chemical Society* 123:3569-3576.
- Chiabrera A, Bianco B, Moggia E, Kaufman JJ. 2000. Zeeman-stark modeling of the RF EMF interaction with ligand binding. *Bioelectromagnetics* 21:312-324.
- DeFelice, L. J. 1981. *Introduction to Membrane Noise*. New York: Plenum Press.
- Dobson J, St.Pierre T, Wieser HG, Fuller M. 2000. Changes in paroxysmal brainwave patterns of epileptics by weak-field magnetic stimulation. *Bioelectromagnetics* 21:94-99.
- Grissom CB. 1995. Magnetic field effects in biology: A survey of possible mechanisms with emphasis on radical-pair recombination. *Chemical Reviews* 95:3-24.
- Kirschvink JL. 1996. Microwave absorption by magnetite: a possible mechanism for coupling nonthermal levels of radiation to biological systems. *Bioelectromagnetics* 17:187-194.

- Kotnik T and Miklavcic D. 2000a. Second-Order model of membrane electric field induced by alternating external electric fields. *IEEE transactions on biomedical engineering* 47:1074-1081.
- Kotnik T and Miklavcic D. 2000b. Theoretical evaluation of the distributed power dissipation in biological cells exposed to electric fields. *Bioelectromagnetics* 21:385-394.
- O'Konski CT. 1960. Electric properties of macromolecules. V. Theory of ionic polarization in polyelectrolytes. *Journal of Physical Chemistry* 64:605-619.
- Saxena VK and Van Zandt LL. 1994. Local modes in a DNA polymer with hydrogen bond defect. *Biophysical Journal* 67:2448-2453.
- Schwarz G. 1962. A theory of the low-frequency dielectric dispersion of colloidal particles in electrolyte solutions. *Journal of Physical Chemistry* 66:2636-2642.
- Steiner UE and Ulrich T. 1989. Magnetic field effects in chemical kinetics and related phenomena. *Chemical Reviews* 89:51-147.

Table 1. Summary of discussions and conclusions on plausibility.

Mechanism	Plausibility	Other comments
Temporal and spatial temperature gradients	Possible	<p>Need for theoretical evaluation of temperature and energy gradients (temporal and spatial) at the microscopic (nano-scale) and macroscopic level.</p> <p>Determine whether such gradients can drive biochemical processes.</p> <p>Evaluate impact of Kapitza resistance.</p> <p>Consider temperature changes for times < 1 millisecond and complex geometries.</p>
Alteration of membrane potential	not plausible for brief exposures at low levels	Need to perform calculations to determine the thresholds.
Membrane rectification	Not generally plausible because small signals will result in insignificant non-linear responses.	<p>There is experimental evidence from biological studies to support the transit time model.</p> <p>Pickard suggests that rectification is not possible above a few MHz.)</p> <p>Need to (a) define theoretical lower limits of field strength for membrane interaction (b) theoretically investigate whether multiple-cell structures create situation for rectification or whether one can get a large oscillating or rectification change in membrane potential at frequencies above 10 MHz.</p> <p>Examine the possibility of conducting experiments that test for harmonic responses as a means of investigating existence of non-linearity in cell system.</p>
Polarization of structures or molecules	Not plausible for most cases	But there is a need to theoretically investigate whether small fields could affect a process that is teetering between two nearly equal energy states. Aggregation of cells or proteins is a possible example.
RF pumping & chemical kinetics.	Not plausible due to critical damping of any modes that may or may not exist.	<p>Need to theoretically examine:</p> <p>a) Isolated molecules (caged structures) to determine whether such isolation could exist and lead to realizable vibrational modes.</p> <p>b) The possibility and limitations of 2-photon, 2-phonon, or 1-photon plus 1-phonon interactions.</p> <p>c) The ballistic regime: Generally, a sharp resonance is not possible unless the time between collisions is long compared to binding or transit times, but ballistic transmission (as for ions in a channel) might be an exception. Therefore, need to (1) Calculate effective collision times and (2) determine whether ballistic transmission is realizable in biological systems</p>

Magnetic dipole interactions	Not plausible.	Published calculations show that energy absorbed in magnetite is too small to cause significant temperature rise. No other effects in microwave range were identified as plausible. Magnetic fields effects on free radical formation should be theoretically evaluated.
Synchronization		Synchronized systems need to be theoretically examined to determine whether there may be an increased level of response in those systems that otherwise are implausible.
Electrophysiological		See "General Consideration" below.
General Consideration:		All work at the cellular level should consider multi-cell and ultra-structural analysis of inhomogeneous complex properties. 3-D structures imply limitations of in vitro studies.
Cooperative	Not plausible	No known way of coupling cooperative systems to RF energy.
Coherence	Not plausible	Critical damping would prevent appearance of any modes that might exist.

Table 2. Specific recommendations for research (“do-ables”)

1	<i>Theoretical analyses of temporal and spatial gradients in temperature and energy at ultrastructural (nanometer), microscopic (micrometer), and macroscopic (sub-millimeter) levels.</i>
2	<i>Theoretically establish the conditions under which small periodic changes in temperature (e.g., of order 0.1°C) can serve as a stimulus affecting ongoing biochemical processes.</i>
3	<i>Theoretically examine:</i> <ul style="list-style-type: none"> ★ <i>ΔT at microscopic and molecular (e.g., protein molecule) levels</i> ★ <i>ΔT over short times (10⁻⁸ s) in the case of pulsed signals or for processes occurring over the period of a sinusoidal signal (e.g., about one nanosecond for frequencies near 1 GHz).</i> ★ <i>ΔT at the millimeter scale, especially for application to in vitro studies.</i> ★ <i>the biophysical and biochemical features that could determine when the temperature gradients discussed above might affect biological systems, given that the occurrence of a biochemical change does not necessarily predict a biological change.</i>
4	<i>Refine thresholds in field strength, carrier frequency, and pulse parameters for direct effects on membrane potential. Calculations also are needed to determine whether multi-cell structures enhance rectification over the limits derived for isolated cells.</i>
5	<i>Conduct experiments using physical measurement methods to investigate cell non-linearities at low-gigahertz frequencies.</i>
6	<i>Theoretical research to determine the exposure levels at which there might be temperature effects significant for biological systems. Suggested by a model for differential energy deposition and heat fluxes for short times and at the scale of the cell membrane. This work should allow evaluation of potential relevance for the conditions of exposure to wireless communications devices.</i>
7	<i>It was recommended that calculations be made to estimate quantitative limits on mechanisms related to ion polarization and proofreading type molecular systems. An approach to the latter process could be a theoretical analysis to estimate the number of steps and the magnitude of effects on each step.</i>
8	<i>Theoretical examinations should not be limited to effects on a single cell held in isolation, but should consider multi-cell structures and, where applicable, analysis at the ultra-structural level of the inhomogeneity of dielectric properties.</i>
9	<i>Perturbation of an ongoing enzymatic reaction by microwave energy is an example of a mechanism that requires two photons, two phonons, or joint interaction of a photon and phonon. The plausibility of multi-particle interactions, interactions with caged ions and other structures possibly isolated from damping, and coherent responses of synchronous systems should be investigated further by theoretical methods.</i>
10	<i>Theoretically assess whether ballistic transmission can occur in membrane channel proteins.</i>