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Mechanisms of Electromagnetic Interaction with Cellular Systems*

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The question of how electromagnetic fields – static or low to high frequency – interact with biological systems is of great interest. The current discussion among biologists, chemists, and physicists emphasizes aspects of experimental verification and of defining microscopic and macroscopic mechanisms. Both aspects are reviewed here. We emphasize that in certain situations *nonthermal* interactions of electromagnetic fields occur with cellular systems.

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During the past decade, the study of interactions of nonionizing electromagnetic waves with whole organisms, but specifically with well-characterized cellular model systems in vitro, has received increased recognition: A growing number of experimental findings has been reported each year (for review, see [1–7]), and hypothetic mechanisms which might be involved in mediating these effects have emerged [2–8]. Furthermore, the public interest has grown for investigating possible health effects from electromagnetic fields (EMFs) generated, for example, by 50/60-Hz high-voltage transmission lines, video display terminals, or clinical NMR-imaging procedures. Particular concern came from epidemiological findings which correlate the exposure of humans to weak magnetic fields in the home with an elevated risk for developing certain leukemias and other cancers [9–12]. These results may suggest that nonionizing EMFs have an as yet unrecognized potential for modifying human physiology, but they cannot prove a causal relationship. We believe that not epidemiological surveys will decide the basic questions, but rather careful cellular studies together with efforts to understand the fundamental mechanisms of electromagnetic interaction with living systems.

The purpose of this article is therefore to give an overview of selected and recent experimental results, and also survey new theoretical attempts to explain nonthermal actions of EMFs on cellular systems.

The Experimental Evidence

Laboratory experiments to investigate the biological effects of relatively weak EMFs have been performed for some decades. But only in recent years have the experiments reached a level of sophistication which allowed a convincing demonstration of some nonthermal field phenomena at the cell, tissue, and whole orga-

nism levels. Note, however, that one has to remain critical of work which has not been independently validated.

Evidence at the cell level comes from observations of (1) changes in cellular Ca^{2+} regulation, for example, in normal human lymphocytes [13, 15], murine lymphocytes [16, 17], and in the lymphoid tumor cell lines HL-60 [18] and EL-4 [17], (2) changes in ornithine decarboxylase enzyme activity in CCRF-CEM T-lymphoblastoid and other cell types [19], (3) altered Na^+/K^+-ATPase activity in erythrocytes and microsomal preparations [20, 21], (4) stimulation of RNA synthesis in HL-60 and CCRF-CEM cells [22, 23] and changes in specific RNA-transcript levels in HL-60 cells [24], (5) altered DNA synthetic activity or cell cycle times in lymphocytes [25–29], fibroblasts [30], and yeast cells [31], (6) altered protein synthetic activity or differentiation of field-exposed fibroblasts [32, 33], and (7) field-triggered responses in neuronal cells [34–36]. At the tissue level, EMF effects on Ca^{2+} efflux from chick brain were most extensively studied [37–41]. In most of these studies the possibility that purely thermal effects can cause the effects was excluded either by the performance of control experiments at elevated temperatures, the observation of a sharp frequency dependence or a nonlinear intensity dependence, or by theoretical estimates of EMF-induced heating in the exposed samples. Therefore, *non-thermal* interaction mechanisms must be involved.

Evidence at the whole organism level includes (1) stimulation of healing of non-union bone fractures in humans (for reviews, see [42, 43]), (2) modification of immunological parameters such as blood or spleen leukocyte counts [44–46] and inflammatory responses in rats and mice [47, 48], and (3) suppression of the nighttime production of melatonin, a pineal hormone known to be involved in the control of reproductive cycles in seasonal breeders and to have oncostatic potential (e.g., [49]). This latter EMF effect has also been demonstrated by weak magnetic-field exposure of isolated pineal glands in organ culture [50].

The above list of in-vitro and in-vivo effects is by no means exhaustive but demonstrates the diversity and the possible significance of the present evidence. Furthermore, there are well-established behavioral effects due to the magnetic sensitivity of certain organisms: for example, small changes in the earth's magnetic field can influence the behavior of animal species from fish to birds [51].

Finally, there is now a growing awareness that the induction of EMF effects can depend on a variety of biological and physical boundary conditions. For example, the intensity or frequency of the applied field (e.g., [20–22, 25, 31, 32, 37–40]), the geomagnetic field (e.g., [15, 41]), and the biological status of the exposed cell system itself (e.g., [13, 16, 26, 27]) have all been demonstrated as critical in inducing specific effects. The detailed characterization of these conditions and their careful experimental verification need to be key concerns of future experimenters in order to provide reliable data which can be used for the development and testing of theory. Two examples of experiments will be described in some detail. The first experiment is a study in which the field exposure parameters (viz. intensity and frequency) were varied. The second experiment emphasizes the importance of biological parameters in the induction of EMF effects.

First Experimental Example: Frequency- and Intensity-Dependent Cellular Response to Microwave Radiation

Eighteen years ago, Soviet authors reported biological influences of millimeter microwaves [52], and stimulated elaborate investigations of microwave actions on yeast (*Saccharomyces cerevisiae*). In the first experimental phase, the growth behavior of suspension cultures was analyzed monitoring visible light extinction [53]. It was found that continuous low-intensity (< 10 mW/cm^2) microwave irradiation altered the growth characteristics of the cells in strong dependence on the applied frequency in a 200-MHz wide band near 42 GHz. The growth rate of irradiated cultures either stayed constant or was considerably enhanced or reduced (up to 20 %). Especially, a spectral fine structure with a half-width of the order 10 MHz was observed around distinct frequencies. These sharp reaction resonances ($\Delta f/f \approx 10^{-4}$) were confirmed in subsequent experimental series with improved frequency stability [31]. However, a lack of full reproducibility suggested the need for refined intensity control and for experiments with single cells.

Subsequent work was carried out with single yeast cells synchronized in G_1-phase and observed with a scanning light microscope during microwave exposure over three growth cycles. The images of the observed cell microcolonies were collected at distinct intervals and digitally processed to reveal differences in growth kinetics of irradiated and control cells [71].

Action spectra near 41 700 MHz were recently taken at substantially reduced mean power densities, namely, 1 μW/cm^2, 1 nW/cm^2, and 5 pW/cm^2. These values correspond to a mean electric field of 1.9 V/m, 61 mV/m, and 4.3 mV/m, and a mean specific absorption rate of 40 mW/kg, 0.04 mW/kg, and 0.2 μW/kg, respectively. The frequency was stabilized within 0.1 MHz.

Figure 1 shows the resulting normalized growth rate vs. frequency at the intensity of 1 μW/cm^2 and demonstrates the existence of microwave effects on yeast cell

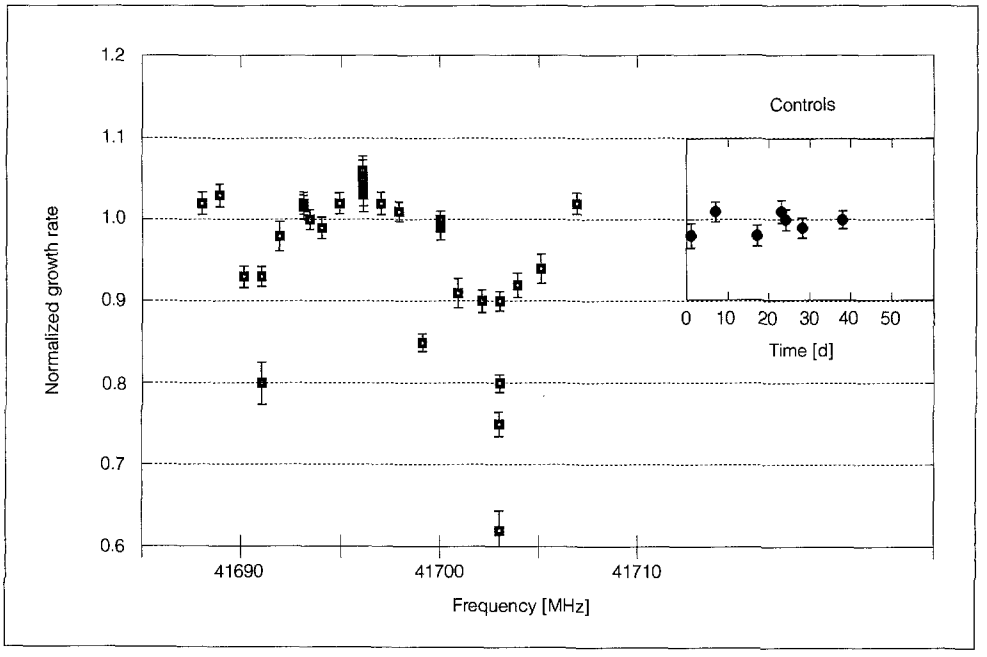

Fig. 1. Normalized growth rate of yeast cells obtained by averaging over individually determined cell cycle times, vs. irradiation frequency. The intensity was 1 μW/cm^2, square-wave modulated at 8 kHz. The corresponding control values (no irradiation) vary within ± 3 % only

growth at very low power densities. Growth rate values are found significantly outside the scatter of the control runs (± 3 %). The effects again show a strong dependence on frequency in a resonant-like fashion. The frequency of maximum field effect agrees well with the one determined in the former study with suspension cultures [31, 71]. The two other tested intensities showed a similar frequency dependence.
Altogether, we find a sharp resonant response repeatedly in distinctly different experimental arrangements and, furthermore, we find the effects even at drastically reduced intensity.

Second Experimental Example: Extremely Low-Frequency Magnetic Field Effects on Ca^{2+}-Mediated Signal Transduction Events in Lymphocytes

At least 11 different research groups have reported nonthermal, extremely low-frequency (ELF; < 300 Hz) EMF effects on cells of the immune system (e.g., lymphocytes) including effects on Ca^{2+} regulation and RNA and DNA synthesis (for review see [54]). Recent results of ELF exposure experiments on Ca^{2+} transduction in lymphocytes will be summarized here [16]. In these experiments the effect of a (nonthermal) 22-mT, 60-Hz sinusoidal magnetic field (exposure for 60 min at E_{max} = 100 mV/m) on Ca^{2+} transport across the cell membrane of rat thymic lymphocytes was assessed by measuring the radioactive isotope $^{45}Ca^{2+}$ as a tracer. It was found that after the addition of the mitogenic plant lectin concanavalin A (Con A), an activator of the membrane-mediated signal transduction cascade in these cells, the field stimulated the $^{45}Ca^{2+}$ uptake on the average by 170 % ($p < 0.01$) in comparison to isothermal, nonexposed control cells (Fig. 2). In contrast, when resting, nonactivated rat thymic lymphocytes were exposed to an identical magnetic field for 60 min, $^{45}Ca^{2+}$ uptake was *not* affected by the applied magnetic field (Fig. 3).
However, when a 6.5-mT, 3-Hz square-wave magnetic field (E_{max} = 16 mV/m) was used in similar experiments, $^{45}Ca^{2+}$ uptake by mitogen-treated lymphocytes was reduced by 45 % on the average; again, no effect of the field was seen with resting cells [55]. These latter findings are in agreement with earlier results that 6.0-mT, 3-Hz square-wave magnetic fields reduced $^{45}Ca^{2+}$ uptake by mitogen-treated, but not by resting lymphocytes, by approximately 70 % [13, 14]. The results demonstrate that cellular signal transduction pathways can be measurably influenced by nonthermal ELF field intensities. Additionally, these findings also show that *biological parameters* (i.e., the activation status) can be as important as physical EMF exposure parameters (i.e., intensity, frequency) in triggering field effects.

Proposed Mechanisms of Electromagnetic Interaction

Here, we describe some physical and biological concepts which we think can contribute to explaining how nonthermal electromagnetic intensities can induce bio-

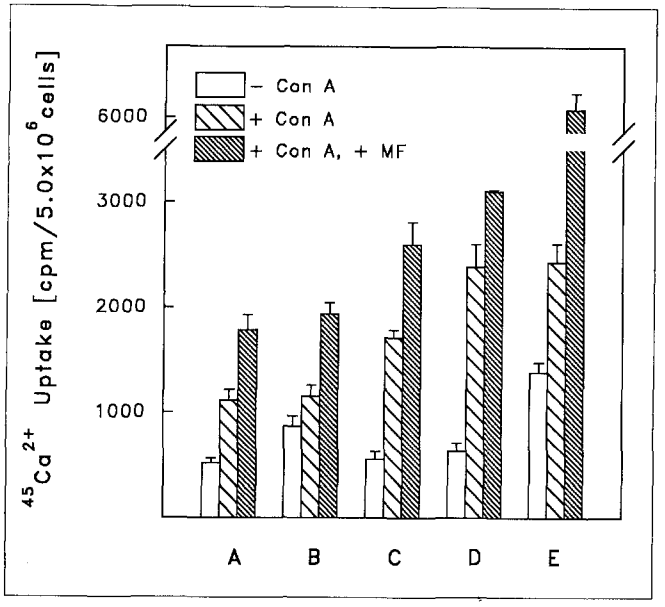

Fig. 2. Nonthermal 60-Hz magnetic field effect on concanavalin (Con A)-induced $^{45}C^{2+}$ uptake in rat thymic lymphocytes. – *Con A*, cells not activated by Con A; + *Con A*, cells in the presence of Con A; + *MF*, cells exposed to a sinusoidal 22-mT, 60-Hz magnetic field (E_{max} = 10 mV/m) for 60 min. *A – E*, denote cell preparations from five different animals. The results are expressed as means ± SD. Analysis of the pooled data demonstrates a 60-Hz field effect (n = 5) by the paired t-test: $p < 0.01$. Adapted from [16]

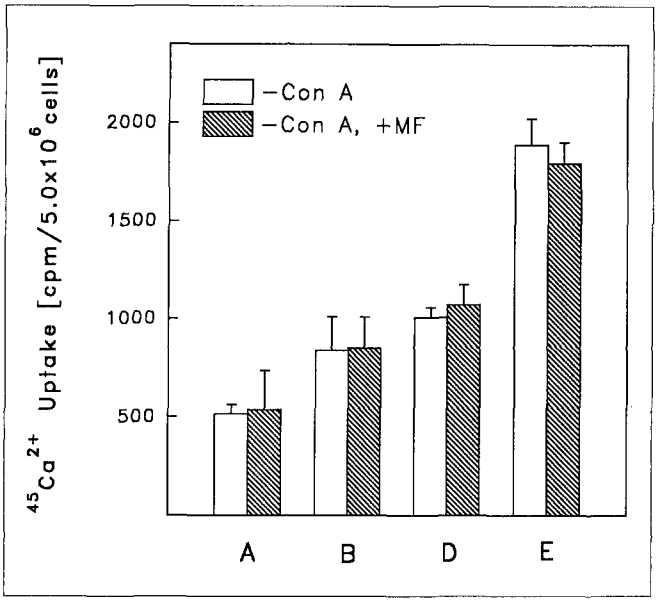

Fig. 3. Experimental results on $^{45}Ca^{2+}$ uptake in nonactivated rat thymic lymphocytes. No effect of the 22-mT, 60-Hz sinusoidal magnetic field is observed after 60-min exposure

logical effects. We will not review the earlier proposed hypotheses, for example, of Liboff [56], Lednev [57], Blank [58], or the recent calculations by Weaver and Astumian [8]. Rather, we present ideas which have not received widespread attention by the scientific community. We consider mechanisms of electromagnetic interactions based on (1) the chemistry of transient radical pair and triplet molecules, (2) the physics and chemistry of nonlinear dynamic processes, and (3) the biology (physics and chemistry included) of cellular signal transduction. These mechanisms, alone or in combination, can offer theoretically feasible interaction pathways by which relatively weak EMFs could influence cellular function.

One apparently fundamental theoretical constraint in explaining any field effect is the requirement that the primary interaction generates an excitation with energy greater than the average thermal energy (kT) inherent in any system. Some of the reported cellular effects indeed require unbelievably small field strengths. This apparent contradiction can be resolved by considering the existence of nonthermal and nonlinear states. We point out how these nonthermal and nonlinear states relax the kT argument which is tailored to thermal systems (described by equilibrium thermodynamics), and how they make nonthermal effects of electromagnetic fields plausible.

Spin-Mediated Electromagnetic Effects in Chemistry

Many chemical reactions involve molecules with one or more unpaired electrons. These so-called radicals and triplet molecules have in common a non-zero electron spin. The orientation of this spin can be influenced by an electromagnetic field, or more precisely, by a stationary or alternating magnetic field component. When such a molecule plays a decisive role in a (bio-)chemical reaction chain, the reaction yield can be affected by unexpectedly weak DC or AC magnetic fields ("magneto-chemistry", "radical-pair mechanism") and also, by weak resonant microwaves ("triplet mechanism").

These spin-related mechanisms are in contrast to the kT constraint just mentioned. A seemingly general statement forbids direct quantum steps as primary microscopic mechanisms of DC to high-frequency electromagnetic field effects in biology and general condensed-phase chemistry, by the following arguments: Only at very high frequencies, infrared and above, does the photon quantum energy suffice to ionize atoms or to dissociate molecules. Below the mid-infrared frequency of f = 6 THz the photon energy hf is smaller than the thermal energy kT = 1/40 eV (at room temperature), which is the average energy in every molecular degree of freedom; then a photon absorption cannot significantly increase, e.g., a vibrational amplitude. In addition, all vibrational degrees of freedom of a molecule or a larger complex are strongly

coupled so that any photon-induced nonequilibria relax in a few ps; this not only limits any effect, but also prevents any enhancement by sequential absorption of photons.
The solution of the discrepancy is (1) that the spin-related degrees of freedom are rather weakly coupled to the others, e.g., the vibrations, so that orders-of-magnitude longer lifetimes result, and (2) that radical pairs and triplet molecules are spin-polarized *in statu nascendi*. Both properties together mean that the spin is not randomly oriented but has a preferred direction for a significant time immediately following the creation of the molecule. In other words, triplet and radical states of reacting systems can be nonthermally populated. It is this inherently nonthermal preparation of these molecules in the biological process that makes them susceptible to otherwise necessarily ineffective electromagnetic interaction. Two examples will be discussed.

Radical-Pair Mechanism

A radical is a molecule with an unpaired electron spin and thus has spin $s = 1/2$. Assume a pair of radicals produced as step n of a reaction chain, e.g., by dissociation of an electronically excited triplet molecule with $s = 1$. Both radicals will have parallel spin orientation until a spin-flipping event occurs, typically after a spin-lattice lifetime T_1 in the ns to ms region. Assume further that the overall reaction depends on whether the pair recombines during T_1 in the electronic ground state with $s = 0$. As this step is spin-forbidden unless both spins are antiparallel, it becomes clear that any spin reorientation achieved by an external field can influence the reaction yield (Fig. 4 a).
Many such radical-pair reactions are described in the literature (for review, see [59]), very few yet in biochemistry. The effective magnetic field strengths vary near 1 to 100 mT. Clearly, the finite lifetimes allow effects from DC to high-frequency fields, with weak frequency dependences at most (no resonances).

Triplet Mechanism

A triplet molecule has two unpaired electrons whose total spin $s = 1$ can be oriented along three directions in the molecule frame. The three states have slightly different energies, with difference frequencies in the microwave region. Owing to a relatively long lifetime these states are not overdamped. Therefore, the population of these states is a meaningful concept, and well-defined resonant microwave transitions can be viewed to pump the population from one to another state.

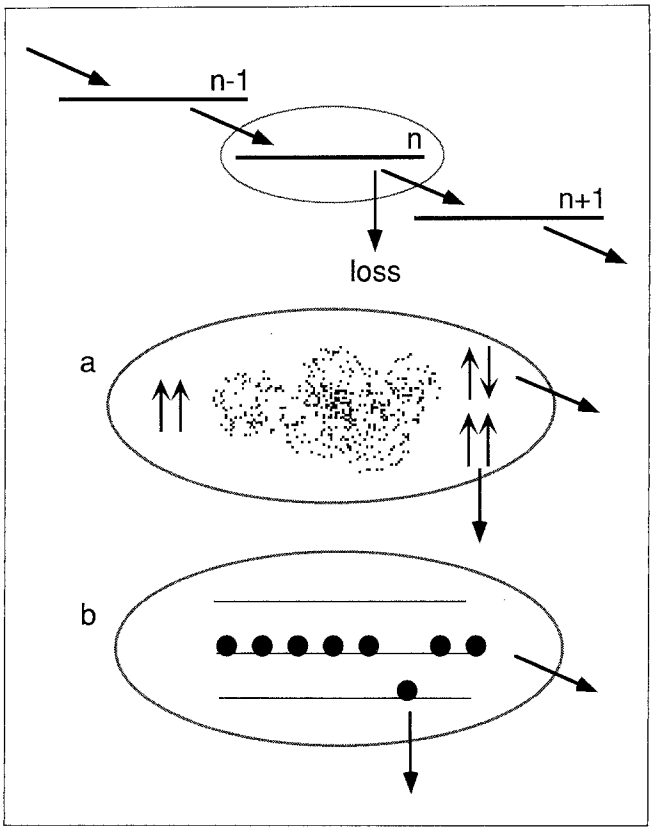

Fig. 4. Schematic illustration of two spin-dependent chemical reaction steps; a) radical pair mechanism, b) triplet mechanism

Assume a triplet molecule is produced as step n of a chemical reaction chain. In general, it will have a preferred spin orientation owing to some steric constraint or selection rule. This means that only one of the three spin substates is populated until the time T_1 when a spin-flipping event occurs (after this time the populations become thermalized, i.e., nearly equalized, and therefore resonant microwave transitions would not be able to change the populations). Assume further a substate-selective reaction of the triplet molecules to occur within T_1 that influences the overall reaction yield [59]. In this situation the action of resonant microwaves is to change the population of the substates and thus it influences the overall reaction yield (Fig. 4 b).
The effective field strength can be estimated by describing the microwave pumping with two-level rate equations [60]. As a result, the effect becomes saturated above a critical intensity that varies inversely with the relaxation time, with a value of 5 mW/cm^2 for a resonance width of 8 MHz and $T_1 = 1$ ms. Only few such reactions are yet described in the literature [59, 60].
Many resonant frequencies of triplet molecules have been published, mainly below $\approx$ 10 GHz, which constitutes an upper frequency limit of common electron

spin resonance spectrometers. Higher resonance frequencies have occasionally been noted but not been sought for systematically. Interestingly, molecules with a transition-metal ion complex such as hemoglobin have high resonances at several 100 GHz; an extension of spectroscopic methods to higher microwave and even far-infrared frequencies seem therefore attractive in view of the enzymatic function these molecules play in biochemistry.

Nonlinear Dynamical Approach: the Influence of Weak External Fields on Periodic Processes

Nonlinear phenomena are abundant in the discipline of physics. Well-known examples are lasers and optical devices, nonlinear circuits, hydrodynamic and plasma instabilities. Nonlinear internal processes are necessary prerequisites for the creation, stabilization, and maintenance of specific states of order and function. The inherent nonlinearity allows for the occurrence of temporal, spatial, or spatiotemporal structures within the system. The most prominent examples for temporal structures are nonlinear oscillations, exhibiting a regular (periodic or quasiperiodic) or an irregular (deterministic chaotic) motion [61, 62]. Spatiotemporal structures include traveling pulses and nonlinear waves, spiral waves, and turbulent motion.
Nonlinear dynamics (nonlinear equations of motion) create these regular and irregular states via *self-organizing processes*. In addition, the systems are subject to an input of energy and/or matter. In general, all systems exhibiting self-organization are *open systems*, stabilized far from thermal equilibrium by energy fluxes. The systems' behavior and the transitions from one state to another one (bifurcations via instabilities) have to be discussed as *nonequilibrium phase transitions*. Consequently, at least those degrees of freedom which govern the specific nonlinear and nonequilibrium states must be partially decoupled from the rest of the system, which might well be in thermal equilibrium. This means that fast processes are required in order to prevent a thermalization of the input energy before the onset of certain processes or effects.
The creation and stabilization of specific states by both internal nonlinear processes and an external energy input, and their subsequent transitions to other states of order and function, by (even extremely weak) external influences are by no means a contradiction to thermodynamics. Regrettably, for example, the occurrence of nonlinear processes in chemistry, starting with the Lotka model and the Bray oscillations around 1920, was ignored and criticized for more than 50 years as being contrathermodynamic. Meanwhile many nonlinear chemical reactions are known which lead to oscillations, spatial pattern formation, and to spatiotemporal structures. Neither a new chemistry nor a new physics is required for their occurrence and understanding.
Nonlinear dynamics is now indispensable in all disciplines of science. It seems that in the next decade of nonlinear science increasing emphasis will be on phenomena in biological systems.

Biological Implications

Rhythmic phenomena are of fundamental importance for specific dynamic states of order and function in biology. The corresponding frequencies extend from the sub-Hz to the GHz region. The creation and stabilization of periodic states within biological units is based on nonlinear internal processes, including nonlinear dissipative processes in many cases. The latter processes are necessary for the onset of active or self-excited oscillations (limit cycles).
The interactions of the internal self-oscillating nonequilibrium states with external influences (e.g., electromagnetic fields) offer a variety of different motion and transitions between the dynamic states. Synchronization, sub- and superharmonic resonances, an extreme frequency and intensity sensitivity, very sharp resonances, continuous and discontinuous frequency and amplitude changes, etc. are some of the specific phenomena exhibited by driven nonlinear oscillators. The superposition of a static field (e.g., magnetic field) to the alternating one causes additional dramatic changes in the system's response; the behavior may completely change.
Nonlinear dynamics in general and the concept of external influences on actively oscillating states in particular offer a basis for both physical mechanisms and biological responses of weakly irradiated biosystems. Externally driven nonequilibrium states and transitions thus exhibit physical arguments for the occurrence of nonthermal effects in irradiated systems. Sharp resonances found in the yeast experiments and the field influence on Ca^{2+}-mediated signal transduction events are phenomena which have found a plausible explanation within our concepts. Several modeling approaches have been started.
As an example we briefly discuss the external influence on intracellular Ca^{2+} oscillations in nonexcitatory cells [63]. The cytosolic Ca^{2+} oscillations are described by a model which combines the intracellular steady Ca^{2+} efflux from a stimulus-sensitive calcium pool with an internal calcium-induced calcium release process [64]. If, in addition, a chemical stimulus is applied to the cell, a self-excited Ca^{2+} oscillation in the cell

is stabilized. We have extended the model to include the influence of an externally applied ELF field. To describe field interaction mechanisms different processes are considered, e.g., active membrane oscillators, time-dependent Ca^{2+} transport through the membrane, regions of interacting dipoles in the membrane. Though the details of all our models are highly speculative, they incorporate a general idea: the coupling of the external field to a nonlinear membrane oscillator, which in turn is coupled directly or via a chemical pathway to the internal Ca^{2+} oscillator. The models consist of two coupled nonlinear oscillators, which are influenced by a chemical and an electromagnetic stimulus (Fig. 5). Depending on both the strength of the chemical signal and the frequency and intensity of the applied field, the Ca^{2+} oscillations display the whole bifurcation szenario of nonlinear oscillators. In Fig. 6 the Ca^{2+} oscillations are given for eight different excitation frequencies. Only resonant states are shown (5/1, 3/1, 3/2, 1/1, 1/2, 1/3, 1/4, 1/5 resonances; for more details, see [65, 66]).

The complex reaction mechanisms leading to the Ca^{2+} oscillations offer additional pathways for field-coupling mechanisms, especially in the high-frequency region. The individual reaction steps include intermediate steps where fast processes can directly interact with fields, for example, in the way discussed on p. 555. On the one hand, we have the possibility to combine the physical, chemical, and biological concepts, on the other hand, a close interaction between experiments and theoretical ideas is possible. Sophisticated experimental techniques, well-defined biological states, and modified and new theoretical concepts are all required in this promising interdisciplinary cooperation.

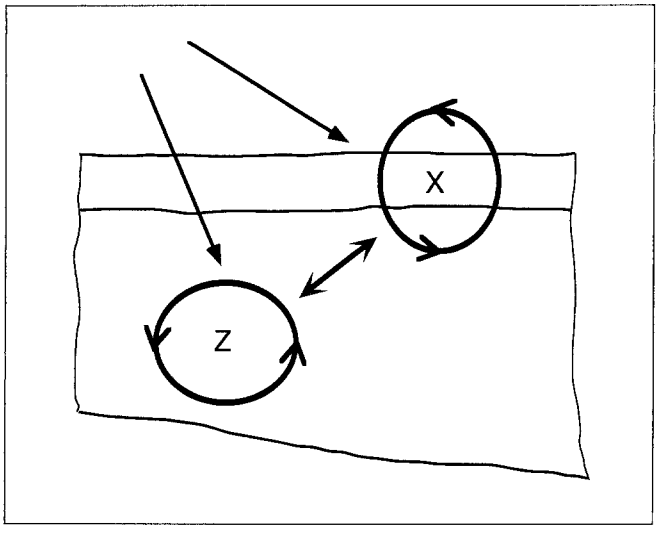

Fig. 5. Schematic illustration of the nonlinear Ca^{2+} oscillator model. Two coupled oscillators describe the Ca^{2+} concentrations X and Z, respectively, of the membrane and cytoplasma regions. Both oscillators are influenced by chemical and EMF stimuli

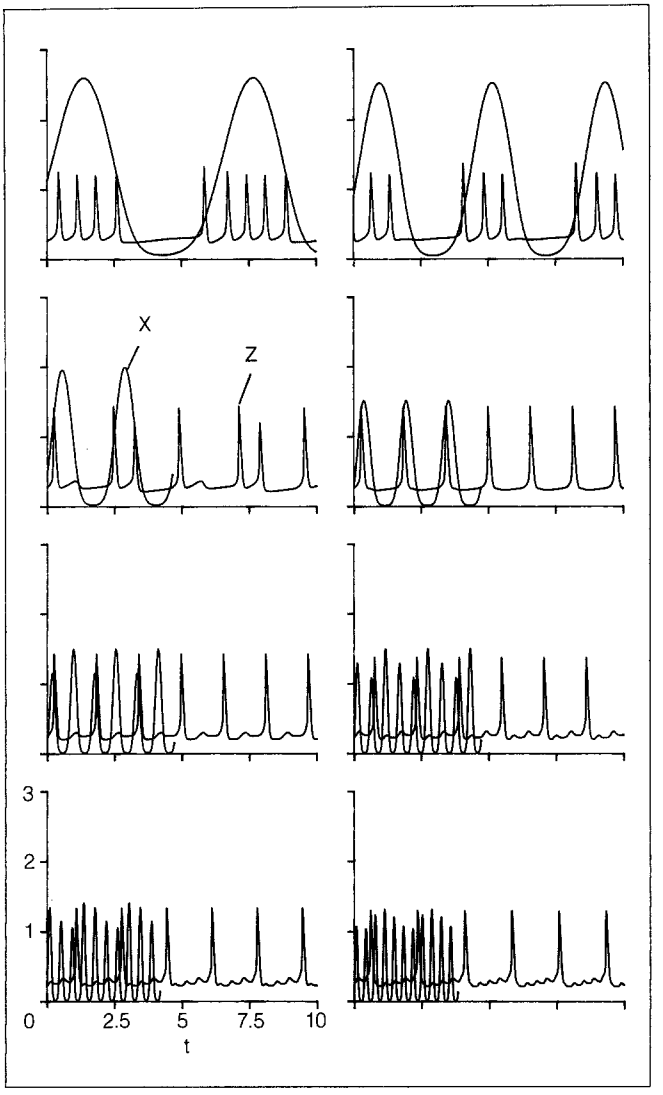

Fig. 6. Calculated membrane (X) and cytosolic (Z) Ca^{2+} concentrations vs. time for eight different EMF frequencies, increasing from top to bottom

Biological Signal Transduction and Amplification

We have outlined how nonthermal states and nonlinear dynamics can provide a basis for explaining critical aspects of low-level field phenomena. Now these physical concepts are extended into the biological complexity. The possible involvement of what appear to be distinctly biological qualities in EMF interactions will be discussed. In particular, the potential of cells to amplify weak external stimuli and thus the ability to actively enhance the signal-to-noise ratio of received low-energy signals is considered.

From early years on, probably because of the fact that signal-receiving and -transducing molecules operate at

the cell membranes, scientists have focused their attention on studying EMF interactions with the plasma membrane and membrane-mediated signal transduction processes [1, 2, 67]. In any such interaction the primary excitation localized, e.g., somewhere on the membrane, must be translated into some persistent biochemical change in order to generate a downstream cellular effect. The theory of how this can be described in general has just been outlined. The exact mechanisms in these interactions are, however, still speculative.

It is worthwhile to recall some well-established studies that demonstrate that there are mechanisms by which extremely weak physical or chemical stimuli can be detected by cells and subsequently are translated into meaningful biological responses. It is remarkable that in some cases the sensitivity reaches the basic physical limit (for an overview, see [68]). For example, the ability of (1) photoreceptors to detect single photons, (2) hair cells to sense tiny displacements in the order of only a few Å, or (3) cells of the olfactory system to sense only one or a few molecules is proof of the surprising ability of some specialized cell types to respond to extremely weak signal inputs in the presence of biological noise. This exquisite sensitivity involves highly specialized receptor structures which are functionally linked to sophisticated cellular signal transduction/amplification pathways. Molecular studies of membrane signaling processes have shown, for example, that the involved cells can use mechanisms such as intracellular second-messenger (e.g., Ca^{2+}, cAMP, cGMP) cascades, positive feedback, and nonlinear membrane channel-gating. In this manner the signal-to-noise ratio is actively improved [68]. It might well be that weak EMFs are received and processed by cells in a manner reminiscent of sensory transduction. Then the two distinct questions could guide future experimentation: (1) are there any primary biological receptors which may also act as primary EMF receptors? and (2) are there parts in the cellular transduction/amplification pathways which may be sensitive to EMFs, even in cells which are not considered specialized sensory cells (e.g., cells of the immune, nervous, or musculo-skeletal system)?

The answer can be yes for both questions, given that the reaction rates of a large number of chemical reactions are magnetic-field-dependent, as pointed out on p. 555. There is evidence that cytochrome-catalyzed reactions which involve transient radical pairs can be affected by weak magnetic fields in vitro [59]. This, together with the increasingly recognized importance of free-radical production, such as reactive oxygen or nitric oxide, in cellular regulation and signaling [69, 70], points towards a sensible EM interaction mechanism based, e.g., on spin-mediated field effects.

The general involvement of signal transduction/amplification processes was already described on p. 553 where the experiment demonstrates a strict dependence of a number of field effects on cellular signal transduction events (Fig. 2; [54] for an overview). Further experiments can identify these signal transduction and amplification steps in detail.

Conclusions

Neither the primary nor the consequential steps are known by which low-level EMFs can interact with biological systems. As for the primary interaction we suggest to investigate spin-polarized chemical steps. Any biophysical model would be limited if it did not take into account the possibility of cellular transduction or amplification mechanisms, since these can increase the sensitivity. This modeling must include the possibility of nonthermal states and nonlinear dynamics in order to account for the experimentally observed cellular effects. We hope that this review will encourage other physicists, chemists, and biologists to advance this highly interdisciplinary and innovative field of research.

Note added in proof: Specific radical-pair reactions of interest in our context are discussed in a recent publication [72].

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