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PERSPECTIVE

Radiofrequency and microwave interactions between biomolecular systems

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Abstract The knowledge of mechanisms underlying interactions between biological systems, be they biomacromolecules or living cells, is crucial for understanding physiology, as well as for possible prevention, diagnostics and therapy of pathological states. Apart from known chemical and direct contact electrical signaling pathways, electromagnetic phenomena were proposed by some authors to mediate non-chemical interactions on both intracellular and intercellular levels. Here, we discuss perspectives in the research of nanoscale electromagnetic interactions between biosystems on radiofrequency and microwave wavelengths. Based on our analysis, the main perspectives are in (i) the micro and nanoscale characterization of both passive and active radiofrequency properties of biomacromolecules and cells, (ii) experimental determination of viscous damping of biomacromolecule structural vibrations and (iii) detailed analysis of energetic circumstances of electromagnetic interactions between oscillating polar biomacromolecules. Current cutting-edge nanotechnology and computational techniques start to enable such studies so we can expect new interesting insights into electromagnetic aspects of molecular biophysics of cell signaling.

Keywords Bioelectrodynamics · Biomolecules · Cell signaling · Electromagnetic field · Radiofrequency · Microwaves

1 Rationale for radiofrequency interactions in biosystems

Signaling within a cell and between cells is essential for the control of biological processes. Since it is well known that biological systems can take advantage of generation

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and perception of low-frequency ionic currents [1] and optical wavelength photons [2–4], it looks reasonable to ask whether cells or organisms have also developed an ability to use radiofrequency and microwave electromagnetic fields for communication/signaling purposes as several authors proposed [5–9]. Fields of the frequencies of 3 MHz up to approx. 300 GHz, which we term here, for the sake of brevity, by the definition of IEEE[1] only as *radiofrequency* electromagnetic fields, have quanta of energy much lower than the thermal energy per degree of freedom, $\mathrm{h}f \ll \mathrm{k}T/2$, where h is the Planck constant, f is the frequency, k is the Boltzmann's constant and T is the thermodynamic temperature. For this reason, many authors have disregarded radiofrequency fields to play a role in any kind of biological interactions because a single quantum interaction is indistinguishable from noise. Such argumentation is, however, too simplistic. Considering, for instance, a molecule with a dipole moment $p = 10^{-27}$ Cm, which is roughly the dipole moment of the tubulin protein [10], in the radiofrequency electric field of the intensity of about $E = 10^6$ V/m, which is realistic to expect on a nanometer scale around electrically polar vibrating molecules [11–13], we get interaction energy comparable to thermal energy per degree of freedom[2], $pE \approx \mathrm{k}T$. In order to promote a deeper discussion about physical possibility of electromagnetic interactions in biosystems on radio wavelengths, we try to clarify here what structures on which spatial scale can be involved in such interactions.

2 Substrate for biological radiofrequency activity

The central problem of biological radiofrequency interactions is *what* would generate the field and *how*. The quest to find the molecular substrate of radiofrequency activity in biosystems is delimited by the physical mechanisms enabling such an activity. A non-stationary electromagnetic field is generated by the agitation of an electric charge. The frequency of the generated field is the same as the frequency of the movement of the charge. Where in biosystems can the charge move with such frequencies and what drives its movement?

Electronic oscillations, i.e., oscillations of a free charge in a material, are only a speculative concept when talking about biological substrates, because the conductivity of biomolecules in this frequency range, though possible, is still only poorly explored and the mechanism driving such oscillations has not yet been proposed. Also high frequency oscillations of ions are not a probable model for biological radiofrequency activity because the mobility of ions is low among the discussed frequencies. The only remaining mechanisms are structural vibrations of electrically polar molecules or larger structures. Certain proteins manifest high electric dipole moments [14] which can therefore represent a good candidate for the sought-after substrate. The vibration modes of proteins themselves lie in the THz part of the spectrum [15], therefore beyond the frequency region of interest; however, we may consider larger polar biomacromolecular structures composed of proteins [12], for instance cytoskeletal filaments [11, 13], which are theoretically predicted to have vibration modes in the range from MHz to GHz [16, 17].

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[2] Such combination of dipole moment and electric intensities can be, in reality, achieved only for a limited number of physiological events. This fact is on the one hand limiting for the existence of radiofrequency signaling in biosystems as a generally widespread mechanism, but, on the other hand, it provides specificity necessary for meaningful interactions in cells.

3 How far can the biomacromolecular radiofrequency field reach?

After we have identified the possible substrate, we may at the very beginning rule out the possibility of radiofrequency interactions by means of far-field electromagnetic waves. It comes from the comparison of radio-wavelengths (1 mm $< \lambda <$ 100 m) with the size of cells or biomolecules (1 nm $< d <$ 100 μm) that the far field region of a radiofrequency antenna $r \gg 2\lambda$, λ being the wavelength of the electromagnetic radiation and r being the radial distance from the antenna, would be a distance of at least several millimeters from the generating structure for the highest frequency, $f = 300$ GHz, considered here. When considering the energy available in a cell (see Appendix), attenuation by the environment and propagation effects, the magnitude of the radiofrequency wave from any source in a cell would decrease under the level of noise in the far field and lose the ability to have any effect. The efficiency of radiation from such a small antenna, like a cell or a biomolecule, is also disputable.

Since we consider far-field interactions unrealistic, we may now discuss interactions in the near-field. The electromagnetic field in the near field region of an electrically short antenna[3], which is a volume within a radius of $r \ll \lambda$ from the field generator, manifests specific features, such as oscillations of energy from and back to the source and a different distance dependence of the electric field intensity than the far field region ($r \gg 2\lambda$). We consider the near field interactions of biomolecules on the nanoscale in this frequency region to be a perspective to follow in future research because the efficiency of power transmission between the sender and the receiver located within their near fields can be orders of magnitudes higher than in the case of the far field [18]. Such high efficiency of power transmission is not only because the sender and the receiver are simply closer to each other than in the far field situation, but because their fields are coupled and the governing equations are consequently different. Unlike in the optical region [19, 20], near field interactions between biomolecules on the nanoscale are poorly explored in radiofrequency and microwave regions. A lot of inspiration can be directly taken from the well-developed theory of near field power transfer between macroscopic antennas [21, 22] and near field physics in general [23].

To conclude this section, we may state that radiofrequency interactions are probable on sub-micron distances where the fields of these frequencies provide very efficient means of signaling, compared to, for instance, electrostatic interactions which are affected by Debye screening [24, 25].

4 Further open questions

Since the focus seems to be on near field radiofrequency interactions between polar biomolecules on the nanoscale, we may now identify open questions which point to future directions of research.

There is an ongoing debate about whether vibration modes of large biomolecular structures can be excited in a viscous environment in cells. The majority view is that such modes are overdamped [26–28]. However, direct spectroscopic evidence of the extent of damping is hard to deliver since the broadness of the observed absorption peaks which

[3] An electrically short antenna has dimensions much shorter than half of the wavelength it emits.

suggests overdamping can be also caused by high spectral density of modes. Actually, several experiments [29–31, 31, 32] and theoretical arguments [33–36] favor the possibility of underdamped vibrational modes of large biomolecular structures within the higher radiofrequency and THz regions. Prospective research lies in experimental quantification of damping of the radiofrequency vibrational modes using sophisticated spectroscopy techniques such as those exploiting high resolution Brillouin scattering [37], inelastic slow neutron scattering [38], nonlinear optical Kerr-effect pump-probe spectroscopy [32], extraordinary acoustic Raman spectroscopy [39, 40] and others.

When admitting the possibility of excitation, a key question to be solved is what mechanism could provide the energy to excite these modes over thermal equilibrium. There are several general proposals on the mechanisms of energy supply to polar vibration modes of biomolecules, but the mechanistic details have not yet been provided. In the case of cytoskeletal fibers composed of actin and tubulin (microfilaments and microtubules, respectively) which contain nucleotide hydrolyzing sites, free energy of ATP or GTP hydrolysis [41, 42] was proposed to excite collective vibration modes of those fibers, especially microtubules [43]. A great deal of energy is released from mitochondria during the respiration processes. Some authors suggest that a part of the "wasted" energy flux released from mitochondria could power the vibration modes of microtubules [44]. Endogenous nonthermal chemical electronic excitations take place in biological systems [2]. It is well known that electronic excited states can decay non-radiatively through vibrations under certain conditions [45, Ch. 5, p. 295] and therefore could be another channel for energy pumping into biomolecular vibration modes. Since these proposals are just conceptual, the prospective research of the considered energy supply processes lies in the quantification of their time scales and dissipation through mechanistic molecular dynamics and quantum chemical modelling.

5 Radiofrequency interactions

If we assume to have the substrate fed by the necessary energy, we may now discuss the interaction mechanisms of the generated field with its hypothetical receptor, because only this interaction can give deeper relevance to the discussed field. Interactions mediated by the electric component of the field reside in the generation of a force that acts on charged, polarized or polarizable objects. Such objects—be they ions, molecules or organelles—are then forced to move. Their motion can be linear translational, rotational or structural (a change of the shape) or a combination of these motions. The coupling of radiofrequency electromagnetic fields to vibration modes of electrically polar biomacromolecules is the subject of ongoing research and it will be interesting to relate it to the research of bio-nano-resonators [46].

The effect of the magnetic field component should also be discussed. The magnetic component of even a weak radiofrequency field (magnetic induction $10 < B < 100$ μT) is supposed to act on cellular physiology through the effect on the spin biochemistry [47, 48]. Spin-correlated (quantum mechanically entagled [49]) radical pair chemical reactions must fulfil several conditions in order to be sensitive to a weak magnetic field [50]. Nevertheless, our expectations of the radiofrequency field between biosystems predict the intensity of the magnetic field component in the near field to be very weak since the source of the biological electromagnetic radiofrequency field is of an electrical character, namely electrically polar biomacromolecular vibration modes.

6 Concluding remarks

Since there are still some pieces of the puzzle missing, we conclude with a call for the verification of the open questions of the theories underlying biological radiofrequency interactions, namely (i) the micro and nanoscale characterization of both passive and active radiofrequency properties of biomacromolecules and cells, (ii) experimental determination of the damping of biomacromolecule structural vibrations and (iii) detailed analysis of energetic circumstances of resonant interactions between oscillating polar molecules.

We have shown that it is not realistic to expect radiofrequency fields to play a role in the interactions over the distances comparable with or larger than organelles and cells. From the historical point of view, a significant number of works (see Ref. [51] for review) on radiofrequency activity of cells were motivated by the search for a mechanism which could explain long range spatio-temporal organization of biological systems, including signaling and cell to cell interactions. However, recent views on biosystems explain their self-organization as an emergent phenomenon. It has been shown that cooperative behavior of an enormous number of a system's components can be achieved even when using very simple rules which are applied on a local scale just between neighboring components [52]. Also, the experimental effort to discover a radiofrequency electromagnetic field which would be detectable on the scale of individual cells has not yet been successful [53]. However, we argue here that radiofrequency interactions can be an important factor on a molecular scale where radiofrequency interactions between oscillating polar biomacromolecules, compared to other long-range molecular interactions (van der Waals, electrostatic), can have comparable energy and comparable, if not a larger, reach under certain conditions, even if this is still within the nanometer scale. Nevertheless, we have to admit that the understanding of radiofrequency molecular interactions is still very limited and more detailed research in this direction may, we believe, bring very interesting insight into molecular biophysics of cell signaling.

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Appendix

We can obtain a good insight into the limitations of relevance of the biological electromagnetic field by considering the physical limitations of the power on the the cellular level which may be channeled to such a field.

A simple way to estimate an upper boundary of cellular power production is via quantification of the total energy available in the cell considering the amount of common energy source, e.g. glucose, in the cell. Approximate glucose concentration in the cells is about 5 mM, i.e. $5 \cdot 10^{-14}$ mol/pL. Considering the standard enthalpy of the glucose oxidation of -2800 kJ/mol, the total energy released by complete oxidation of all glucose available in the cell would be 140 nJ/pL of cell volume. If this energy was released within the time $T = 1$ s, the corresponding generated power would be $P = E/T = 140$ nW/pL of the cell volume.

Of course, this is an upper power limit (given by physical constraint of energy availability) which is not reachable under physiological conditions. How much power is actually being consumed and produced by the cell under physiological conditions can be easily estimated either from direct calorimetric measurements [54, 55] or indirectly from consumption of oxygen [56] and consequent ATP production (about 2.5 ATP molecules / O_2 consumed). We can find from the data in the given references that a single cell operates with total power in the range of few units to hundreds of fW/pL of cell volume. Cell volumes span from few fL to hundreds of pL, which gives range of total power from 1 aW to 10 pW/cell. Obviously, this is just a time-averaged power.

Provided the energy is accumulated in some manner and released in short bursts, the efficient power within a small time scale may be higher by several orders of magnitude than the time-averaged power. One of the examples of such bursts is neuron firing, where the energy stored in the transmembrane potential and membrane capacitance is released though a burst of current flow. However, this is a very specific mechanism of burst like energy release and is not biologically general. In order to search for such accumulation/release mechanism, one would need to identify the magnitude of energy accumulation time T_1 and magnitude of release duration T_2. The ratio T_1/T_2 quantifies then the enhancement of released power over the average power enumerated earlier. Electromagnetic power is also distributed spectrally and spatially. Broad spectral distribution (such as that of thermal radiation) can be taken as a zero order estimate of spectral distribution of the cellular power, although some hypotheses about accumulation of energy at certain frequencies exist – see for instance the theory of H. Fröhlich [57]. Considering the spatial distribution of total power to be uniform and estimating that 0.1% of total cellular power is channeled to electromagnetic power generation, power densities at the cell surface integrated over the whole frequency spectrum may be of the order of 10^{-14} up to 10^{-10} W/cm^2 per single cell.

It is hard to estimate how much of the total power of the cell can and is actually used for generation of radiofrequency fields, since there are no confirmed generating mechanisms of cellular radiofrequency fields. In our earlier work [11], we roughly estimated that up to 10% of the total cellular power is supplied to vibrational systems (microtubules) predicted to be involved in generation of the radiofrequency electromagnetic field. We consider these estimates too optimistic based on our current understanding of the issue.

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