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Zeeman–Stark Modeling of the RF EMF Interaction With Ligand Binding

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The influence of radiofrequency electromagnetic exposure on ligand binding to hydrophobic receptor proteins is a plausible early event of the interaction mechanism. A comprehensive quantum Zeeman–Stark model has been developed which takes into account the energy losses of the ligand ion due to its collisions inside the receptor crevice, the attracting nonlinear endogenous force due to the potential energy of the ion in the binding site, the out of equilibrium state of the ligand–receptor system due to the basal cell metabolism, and the thermal noise. The biophysical ''output'' is the change of the ligand binding probability that, in some instances, may be affected by a suitable low intensity exogenous electromagnetic ''input'' exposure, e.g., if the depth of the potential energy well of a putative receptor protein matches the energy of the radiofrequency photon. These results point toward both the possibility of the electromagnetic control of biochemical processes and the need for a new database of safety standards. Bioelectromagnetics 21:312–324, 2000.

Key words: receptor; protein; electromagnetic exposure; mechanism of interaction

INTRODUCTION

The reported biological effects of low intensity nonionizing electromagnetic fields (EMF) on living systems lead to two application areas. One is related to therapeutic, diagnostic, and biological applications. The second area concerns the updating of the database for EMF safety standards, eventually going beyond the current mechanistic assumption that is based on the disruption of metabolism due to the electromagnetic (EM) power deposition in biological tissues, e.g., if the specific absorption rate, (SAR) is above 4 W kg^{-1} at radiofrequencies (RF). In this paper, low intensity exposure means EMF below the current safety standards (see for example CENELEC, [1995a, b]).

Admittedly some of the experimental evidence, scattered in the scientific literature, concerning the biological effects of low intensity EM exposure are not considered reproducible and there is a lack of both understanding and consensus about the underlying interaction mechanisms [Astumian et al., 1995; Bach Anderson et al., 1995]. As a consequence there is a need for guidelines to design optimal experimental conditions, to develop theories that would be able to fit experimental data and to predict the bioeffects to be experimentally ascertained. Therefore, irrespective of the fact that some available results have already generated clinical applications, e.g., EMF therapies of recalcitrant bone fractures, the bioelectromagnetics data are not reliable enough to be included in the database for use in the future, for updating the current safety standards.

In attempting to elucidate the missing mechanisms, if any, most researchers have concentrated their experimental and theorical efforts on the early steps of the EM interaction at the molecular level. One of the most interesting biochemical processes is the binding of light ligands (e.g., metal ions, like Ca^{++}) to receptor proteins. Some classical and quantum biophysical models, applicable to various extents to ion binding, have been developed, ranging from DC to microwaves. In this paper, we deal with the quantum mechanical based ones only. Among the quantum models proposed in the literature [Bianco and Chiabrera, 1992; Bianco et al., 1993a, 1997; Blackman et al., 1995; Chiabrera

†It is with profound sadness that his co-authors acknowledge the passing of their dear friend and colleague, Alessandro Chiabrera, who died on November 8, 1999.

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et al., 1991, 1992a, 1995b; Engstrom, 1996; Lednev, 1991, 1994; Moggia et al., 1993], the Zeeman–Stark (Z–S) model is by far the most comprehensive. It has been conceived to capture the essential features of the EM interaction with the binding process, avoiding all the details of the complete molecular dynamics simulation [D'Inzeo et al., 1995; Karplus, 1984; Weinstein and Mehler, 1994] of the ligand ion–receptor protein system under EM exposure.

The purpose of this paper is to describe the most recent developments of the aforesaid quantum Z–S model and to offer some plausible predictive examples of its application in the case of RF sinusoidal EM exposure, because of its increasing and pervasive presence [Bach Anderson et al., 1995; Li and Qiu, 1986; Wickelgren, 1996].

LIGAND BINDING TO A RECEPTOR PROTEIN

Before analyzing in detail the Z–S model of the binding process, it is worthwhile to give a brief qualitative description of the process itself, which should help to link the theory to the experiments. The current view is that a ligand controls receptor function through the absolute requirement for bound ligand in modulating the conformation of the protein and in creating its active conformation. The docking ligand completes the hydrophobic core of the active conformation of the receptor and directs the alignment of its secondary structure elements, critical for its biochemical function.

The case we discuss concerns an ensemble of idealized identical proteins of the cell membrane, each one equipped with a single type of isotropic binding site attracting a ligand ion, e.g., a cation of charge Q (C) and mass M (kg). The ligand adsorption/desorption is a reversible process. An empty crevice of a receptor attracts a free ligand in its endogenous potential energy well while a bound ligand desorbs because of thermal collisions.

Each receptor site can be occupied by one ligand only, with probability *P*. We assume that the ligand ion is bound (adsorbed) if its distance from the receptor center is less than a critical distance R_c [m]. Otherwise the ion is unbound (desorbed) and the site is empty. A practical range for R_c is 0.5-5 nm. In practice, the changes of *P* due to EM exposure can be considered, per se, a reasonable effect that is sufficient to assess the potential biological effectiveness of the EMF. Note that by definition, $0 \leq P \leq 1$; changes in *P* due to exogenous EMF exposure should be viewed with respect to the unperturbed value of *P*, that is the value in absence of any exogenous exposure. These changes offer the experimentalist the chance to make an educated guess about the susceptibility of the ligand–receptor system under consideration to the various parameters which characterize the EMF. In fact, once the values of *P* are theoretically evaluated under and in absence of an exogenous EM exposure, they can be used for the analysis of real binding experiments in vitro, e.g., desorption rates, which are an indirect measure of *P* [Lauffenburger and Linderman, 1993; Wyman et al., 1990]. From the modeling point of view the ligand ion and the receptor protein constitute the system to be analyzed, the exogenous EM exposure is the input signal to the system, and the consequent changes of *P* is the output.

THE STATE OF THE SCIENCE OF THE ZEEMAN–STARK QUANTUM MODEL

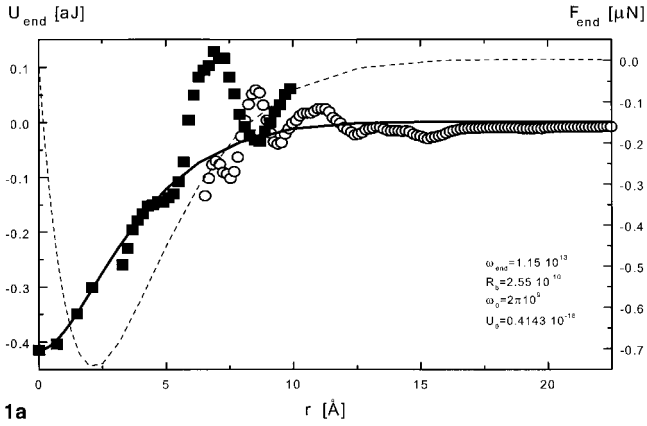
General Properties

A quite general approach to the study of ligand binding to a receptor under EM exposure from DC to microwaves is based on quantum modeling of the process (Z–S model). The first goal is to find the expected value of the so called reduced density operator ρ [Abragam, 1961; Cohen-Tannoudji et al., 1977; Landau and Lifschitz, 1966; Sargent et al., 1974; Shore, 1990; Ter Haar, 1961] which describes the ion motion in the endogenous attracting potential energy well $U_{end}(\mathbf{r})$[J] in presence of exogenous EM potentials, i.e., a scalar potential ϕ [V] and a vector potential $\mathbf{A}$ [Tm]. The exogenous electric field is given by $\mathbf{E}[\mathrm{Vm}^{-1}] = -\nabla\phi - \partial\mathbf{A}/\partial t$ and the magnetic inductor is given by $\mathbf{B}[\mathrm{T}] = \nabla\wedge\mathbf{A}$, where ∇ is the nabla operator.

A typical first order approximation for $U_{end}(\mathbf{r})$ can be obtained by fitting the parameters U_0[J], ω_{end}[Hz], ξ[Jm] of the isotropic relationship

$$U_{end}(r) \approx -\frac{\xi}{r} + \left\{\frac{\xi}{R_0} - U_0 + \frac{\xi}{r} + \left(\frac{\xi}{2R_0^2} - \frac{U_0}{R_0}\right)r + \left[\frac{M\omega_{end}^2}{2} - \frac{U_0}{2R_0^2} + \frac{\xi}{6R_0^3}\right]r^2\right\}\exp\left(-\frac{r}{R_0}\right) \quad (1)$$

to the available characteristic data of the protein of interest, as obtainable, for example, from the Brookhaven Protein Data Bank (Fig. 1). The fitting procedure is summarized in the caption of Figure 1. The energy $(-U_0)$ is the classical finite depth of the potential energy well at the center of the binding crevice $(r \to 0)$, whereas R_0[m] is a dimensional parameter, whose order of magnitude corresponds to the distance where the attracting force $(-dU_{end}/dr)$ is



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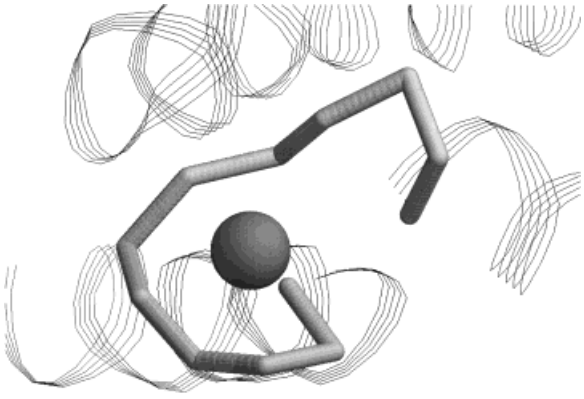

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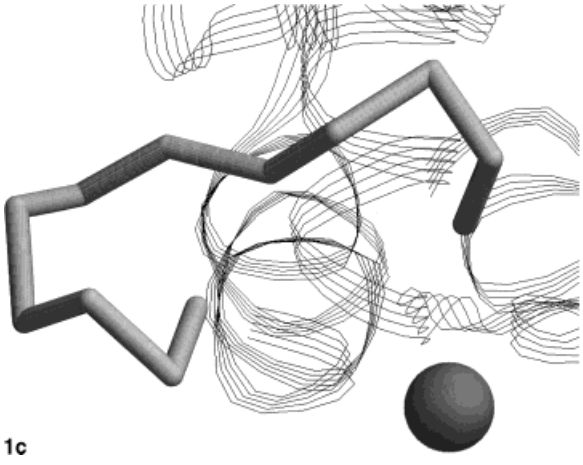

1c

Fig. 1. Plot of the isotropic approximation given by Eq. (1) of the endogenous potential energy U_{end} (continuous line) and of the corresponding attractive force $F_{end} = -dU_{end}/dr$ (dashed line) for a ligand cation at distance r from the binding center (**1a**). The distance where F_{end} attains its minimum value is related to R_0. The squares are an example of data obtained from the Brookhaven Protein Bank for one Ca^{++} binding site of calmodulin, corresponding to the site conformation when the ligand is bound (**1b**). These data must be fitted by Eq. (1) for $\mathbf{r} \to 0$ (see Eq. (2)). The open circles correspond to the site conformation occuring when the ligand is almost desorbed (**1c**). They must be fitted by Eq. (1) for $\mathbf{r} \gg R_0$ (see Eq. (3)). The fitting has been obtained choosing $\xi = 5 \times 10^{-34}$ Jm, $U_0 = 0.41$ aJ, $\omega_{end} = 11$ THz, $R_0 = 2.6$ Å.

maximal. As pointed out in the previous section, the docking/sailing ligand displaces the protein atoms, inducing a reaction field which acts on the ligand ion itself [Karplus, 1984]. Such rearrangements of the protein atoms are extremely fast with respect to the ion movement [D'Inzeo et al., 1995; Karplus, 1984]. Therefore the expression (1) incorporates the effects of the "instantaneous" rearrangements of the protein atoms when the ligand ion is at the position r. These induced small structural transitions generate the protein conformation change which allow the subsequent biochemical steps to occur.

For small values of r, the above expression becomes coincident with the harmonic oscillator approximation

$$U_{end} \cong -U_0 + (1/2)M\omega_{end}^2 r^2; \quad -\nabla U_{end} \cong -M\omega_{end}^2 \mathbf{r} \quad (r \ll R_0) \qquad (2)$$

which is, classically speaking, coincident with the typical "linear" endogenous attracting force (spring like) often used in the literature, where $(M\omega_{end}^2)$ is the elastic constant. For large values of r, the above expression (1) gives:

$$U_{end} \cong -\xi/r; \nabla U_{end} \cong -\xi \mathbf{r}/r^3 \quad (r \gg R_0) \qquad (3)$$

which is a typical "coulombic" endogenous attracting force, originally adopted in the Z–S model [Bianco and Chiabrera, 1992; Bianco et al., 1993b].

The attracting force $\mathbf{F}_{end} = -\nabla U_{end}$ as obtained from Eq. (1) is shown in Figure 1. It is evident that Eq. (1) allows a more satisfactory fit of realistic data as obtained from the Protein Bank with respect to the approximation offered by Eq. (2) or Eq. (3). Admittedly, the fitting of the ξ parameter is not constrained that much by the available protein data of Figure 1. On the other hand, our choice of the value of ξ is not inconsistent with these data. Our objective is to explore if a receptor protein characterized by a set of plausible parameter values as those of Figure 1 is susceptible to low intensity RF EM exposure.

The time evolution of ρ must obey the following relationship [Abragam, 1961; Bianco et al., 1997; Chiabrera et al., 1993, 1995b; Shore, 1990]:

$$\partial\rho/\partial t = (-j/\hbar)[H_{end} + H_{bm}, \rho - \rho_0] - \sum_S [T_S, [T_S, \rho - \rho_0]] - (j/\hbar)[H_1, \rho] \qquad (4)$$

where t [s] is the time variable and $\hbar$ [JS] is the Planck's constant divided by 2π. The Hamiltonian

$H_{end}[J] = -(\hbar/2M)\nabla^2 + U_{end}$ refers to the ion motion in the potential energy U_{end} given by Eq. (1). The Hamiltonian H_{bm} [J] takes into account the living state of the cell, via the contribution of the metabolic driving force $-(\nabla H_{bm}) = \mathbf{F}_{bm}$, assumed spatially uniform for sake of simplicity. It accounts for the effects of the basal metabolism of any living cell, which biochemically induces a steady excess voltage drop across the cell membrane [Bianco, 1995; Bianco et al., 1997; Chiabrera et al., 1994a, 1995a, 1996; Tuvia et al., 1997; Weinans and Pendergast, 1996]. In other words such a metabolic force is consistent with the experimental macroscopic evidence that across the membrane of any living cells there exists the aforesaid excess voltage drop (typically less than 100 mV, internal negative), sustained by the biochemically driven ion pumps [Tuvia et al., 1997; Weinans and Pendergast, 1996]. In other words, the metabolic driving force F_{bm} simply mimics the local effects of the aforesaid membrane voltage drop at the receptor site, and both go to zero if the cell metabolism ceases. The above statements can be summarized saying that, in absence of any exogenous exposure, the basal metabolism per se causes a macroscopic average steady ion velocity $\mathbf{v}_{bm}$ [ms^{-1}], which classically speaking, can be related to the metabolic driving force by the relationship, $\mathbf{v}_{bm} \cong \mathbf{F}_{bm}/(\beta M)$. The coefficient β [Hz] is the Langevin collision frequency of the ion in the binding cleft. This relationship holds almost true at $\mathbf{r} = 0$, i.e., at the bottom of the potential energy well (Eq. (1)), and it is true for large values of $\mathbf{r}$. We reiterate that, at thermal equilibrium, $\mathbf{v}_{bm} = \mathbf{F}_{bm} = 0$.

The metabolic driving force $\mathbf{F}_{bm}$ is of paramount importance in explaining how low intensity exposure can affect biological processes. In fact, the power necessary to sustain the changes induced by the exogenous EMF can be provided by the cell basal metabolism, i.e., by $\mathbf{F}_{bm}$, via $\mathbf{v}_{bm}$. The EM average power transferred by the exogenous EMF to the ion is not directly related to the observed bioeffect, as it is in the case of the thermal effects, i.e., of the induced tissue heating considered by the current safety standards [CENELEC, 1995a, b]. What mainly matters is the waveform of the EMF, which affects the ligand dynamics. The role of the exogenous EM power is limited to the detectability of the low intensity signal at the first interaction step, above the thermal noise.

We point out that $H_{bm} \cong -\mathbf{F}_{bm} \cdot \mathbf{r}$ ($\mathbf{F}_{bm}$ being assumed as constant) induces a Stark effect in Eq. (4). The Hamiltonian H_1 [J] takes into account the contributions of ϕ and $\mathbf{A}$. We adopt the gauge condition $\nabla \cdot \mathbf{A} = 0$ so that $H_1 \cong j\hbar\,(Q/M)\mathbf{A} \cdot \nabla + Q\phi$. It provides the Zeeman effect in Eq. (4). A typical assumption is that $\mathbf{A}$ is small enough so that the term proportional to $\mathbf{A} \cdot \mathbf{A}$ in H_1 can be neglected [Cohen-Tannoudji et al., 1977]. The commutator [P,R] in Eq. (4) means, by definition, PR-RP. The sum of double commutators of the lifetimes operators T_s in Eq. (4) takes into account the interaction of the ion–protein sytem with the thermal bath and is discussed below [Chiabrera et al., 1993]. The density operator ρ_0 is the value of ρ in the basal steady state which occurs when $H_1 = 0$, so that it provides also the boundary condition $\rho(0) = \rho_0$ at the onset ($t = 0$) of the exogenous EMF. We stress the influence of $\mathbf{F}_{bm}$, i.e., of $\mathbf{v}_{bm}$ also on the value of ρ_0 as discussed in [Bianco et al., 1997; Chiabrera et al., 1995b]; see also Eqs. (16,17) below.

The solution of Eq. (4) can be obtained by choosing a complete base of orthonormal functions $\psi_n(x, y, z)$. We use the eigenfunctions of the hydrogenoid Hamiltonian ($H_{end} - U_{end} - \xi/r$), which formally refers to the idealized ion motion in the coulombic potential energy ($-\xi/r$) [Bianco and Chiabrera, 1992]. The corresponding eigenvalues are ε_n [J]. Therefore ρ and, in general, any linear operator R can be represented, in the aforesaid base, by a matrix, whose elements are $R_{mn} = \int \Psi_m^* R \Psi_n dx dy dz$, where * means complex conjugate and the integration is performed over the whole space. Hence, Eq. (4) can be interpreted in terms of the corresponding matrices. Of course, any base of orthonormal functions is suitable. The hydrogenoid set is a convenient one to use as it is available in an analytical form. Therefore we can evaluate in a closed form the matrix elements R_{mn} of all the operators used in the paper. In particular, the choice of U_{end} as a combination of the exponential $\exp(-r/R_o)$ and integer powers r^n allows the closed form computation of its matrix elements in the hydrogenoid base. So doing, we resort to the numerical computation only for the time evolution of ρ.

The five eigenfunctions corresponding to the smallest eigenvalues ε_n of the hydrogenoid Hamiltonian are the most important ones because they are adequate for evaluating $P(t)$, whereas it is assumed that the contribution of the others can be neglected [Bianco et al., 1997; Moggia et al., 1993]. This assumption is based on two factors, one motiviated by physical considerations and the other by a practical one. Physically, the five eingenfunctions are those which are not negligible in the finite region of interest ($0 \le r \le R_B$), while they become rather small for $r > R_B$. This region of interest is the one where the absolute value of the potential energy $U_{end}(r)$ is relatively large and where the binding probability P(t) is to be computed. On the contrary the additional but neglected eigenfunctions oscillate and are rather small in the finite region of interest ($0 \le r \le R_B$), and they become appreciable only outside ($r > R_B$). Thus, it

is not unreasonable to expect that the error induced by neglecting the higher eigenfunctions is relatively small with respect to the overall solution, nor does it impact on the overall validity of the proposed model. From a practical point of view, it is extremely difficult to use additional eigenfunctions in our computation. In particular, the next truncation alone ($n = 14$) implies an extreme additional computational overhead. This is because the use of n eigenfunctions implies the evaluation of the time course of $n(n+1)/2$ independent entries of the $n \times n$ density matrix, ρ. Therefore, for $n = 5$, fifteen matrix entries are evaluated (the case carried out in this study), while for $n = 14$ we would have to evaluate 105 matrix entries, a task beyond our computing capabilities.

Thus, and in consideration of the above, we adopt the so called n-state formalism of quantum mechanics [Shore, 1990], letting $n = 5$. The ground eigenvalue is

$$\varepsilon_1 = -(M\xi^2)/(2\hbar) = -4\hbar\omega_0/3 \qquad (5)$$

The angular frequency ω_0 is a characteristic parameter of a binding site, because $(\hbar\omega_0)$ is the energy to be supplied in order to induce the ion transition from the ground energy level ε_1 to the first excited energy level $\varepsilon_2 = \varepsilon_3 = \varepsilon_4 = \varepsilon_5$. From a quantum point of view, what matters is the value of ξ. In terms of characterization of the receptor crevice, ω_0 is equivalent to ξ, so that from now on we shall consider ω_0 instead of ξ. In quasi classical terms, $(\hbar\omega_0)$ is a quantum measure of the depth of the binding potential energy well, as opposed to the aforesaid classical depth U_0. The other four eigenvalues are degenerate, that is

$$\varepsilon_2 = \varepsilon_3 = \varepsilon_4 = \varepsilon_5 = -\hbar\,\omega_0/3 \qquad (6)$$

These values correspond to the asymptotic values shown in Figure 2. In this example H_{end} and the hydrogenoid Hamiltonian have the same eigenvalues if $U_0 > 10\hbar\omega_0$.

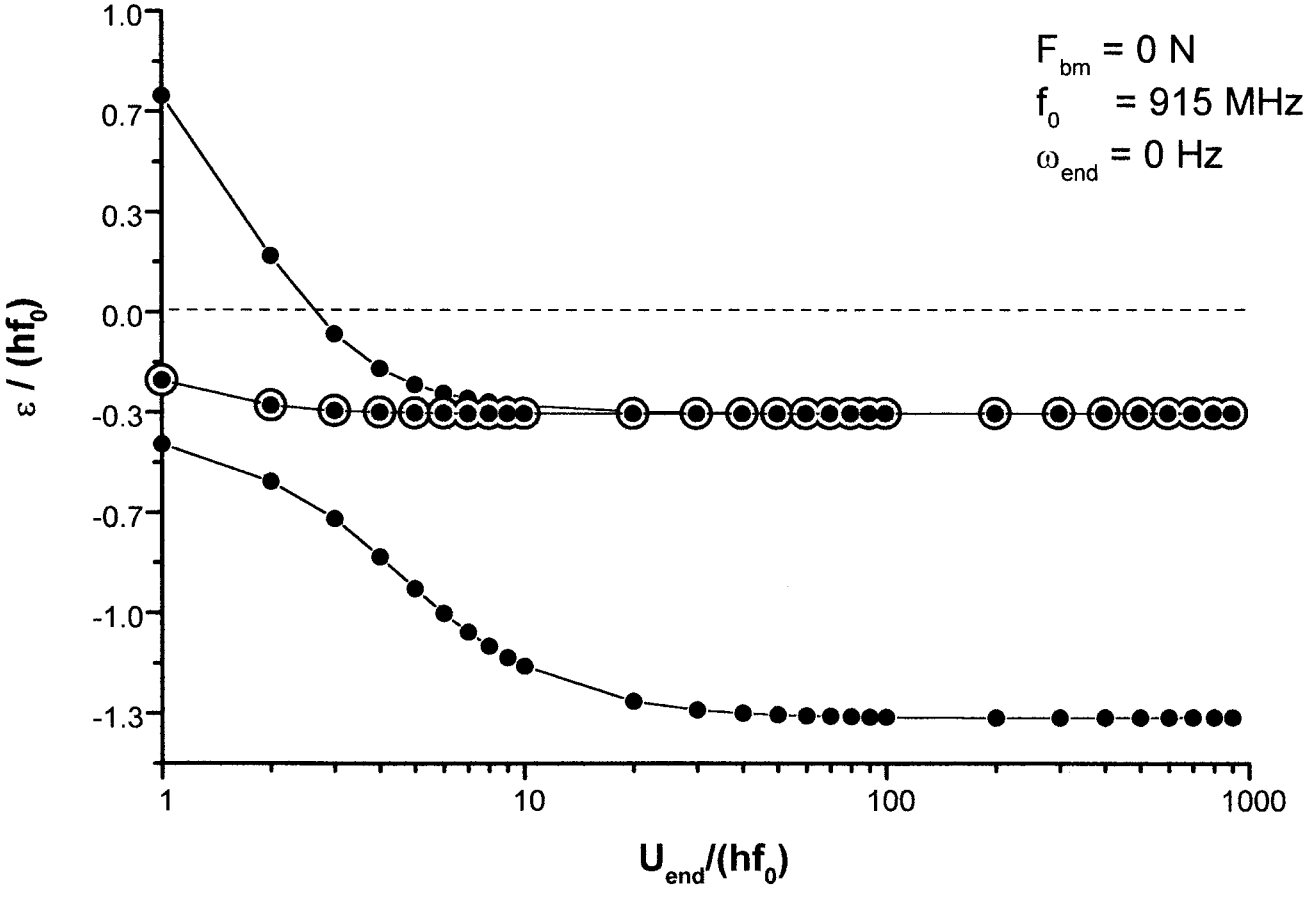

Fig. 2. Eigenvalues ε of H_{end} vs. U_0. The bottom curve corresponds to the first (ground) level. The encircled dots correspond to the next three degenerate levels. The uppermost curve corresponds to the fifth level. The eigenvalues become coincident with the hydrogenoid eigenvalues if $U_0 > 10\,\hbar\omega_0$ and if $\omega_{end} < (1/\xi)[3U_0^3/(4M)]^{1/2}$.

The use of a finite number of eigenfunctions, corresponding to the lowest energy eigenvalues implies some limitations on the applicability of theory [Bianco et al., 1997], which will be discussed later in the following application paragraph. The matrix expression of the summation of the double commutators on the right hand side of Eq. (4) is given in [Chiabrera et al., 1993]. The elements of the matrix contain suitable lifetimes $\theta_{mn}[s], \tau_{mn}[s]$, which are the quantum-mechanical counterparts of the classical Langevin collision frequency β of the ion [Shore, 1990]. The lifetimes allow the system to relax to steady state when the exogenous field is reduced to zero. The off-diagonal elements (m, n) of the summation of the double commutators are

$$(\rho_{mn} - \rho_{0,mn})/\tau_{mn}(m \neq n), \tag{7}$$

and the resulting diagonal terms (m, m) are

$$\sum_{n}[(\rho_{mm} - \rho_{0,mm}) - (\rho_{nn} - \rho_{0,nn})]/\theta_{mn} \tag{8}$$

The lifetimes obey the conditions [Chiabrera et al., 1993]

$$\theta_{mn} = \theta_{mn} > \tau_{mn} = \tau_{mn} > 0, \quad \text{for every } m \neq n \tag{9}$$

The integration of Eq. (4) leads to the evaluation of the matrix components $\rho_{mn}(t)$ so that the observed value R of any linear operator R corresponding to a dynamical variable can be computed from the trace expression

$$R = \mathrm{Tr}(R\rho). \tag{10}$$

The Z–S model is applicable in any frequency range, from DC to microwaves. It suffices to provide the related scalar and vector potentials ϕ and $\mathbf{A}$. At low frequencies numerical problems may arise because the integration time step must be smaller than $1/\omega_0$ and $1/\omega_{end}$, e.g., tens of picoseconds or less, a value that is dictated by the protein data. On the other hand the numerical integration of Eq. (4) must be carried out for thousands of EM signal periods. Such a task is affordable at RF but it requires very large computational resources at extremely low frequencies.

Relationship to Previous Models

Equation (4) can model the ion dynamics in various situations, depending on the choice of H_{end} and H_{bm}, so that a comparison with other published models is possible. By letting $H_{bm} = 0$, postulating a putative excited energy level (eigenvalue of an unspecified Hamiltonian H_{end}) above the ground level, and evaluating the contribution of the Zeeman component in H_1 due to the vector potential only, the ion parametric resonance model (IPR) [Lednev, 1991; 1994], based on an earlier atomic spectroscopy theory, could be obtained. This model has been re-evaluated by Blackman et al., [1995; Blanchard and Blackman, 1994, 1995; Lednev, 1995; Liboff, 1995; Blanchard et al., 1995] but this approach is rather heuristic because it is not related to the integration of Eq. (4). Instead, it is based on the direct computation of the probability transition (based on the Schrödinger equation) of the ion between the energy levels obtained by the Zeeman splitting of the putative excited level. The departure and arrival states of the ion (before and after transition) are assumed to be perfectly known (pure states). The implicit underlying hypothesis [Blackman et al., 1995; Blanchard and Blackman, 1994, 1995; Blanchard et al., 1995; Lednev, 1991, 1994, 1995; Liboff, 1995] is that all the T_s are zero, i.e., the lifetimes are extremely (∞) long. Such a hypothesis is per se inconsistent, because the ion–protein system is in contact with a thermal bath. The ion dynamics are in fact characterized by a statistical mixture of states, and must therefore be described by the density operator. Furthermore, the IPR model does not provide any relaxation mechanism from the excited state to the ground state. A phenomenological approach has been adopted by Engstrom [1996], where an extended IPR model includes an excitation and de-excitation probability due to noise.

A more specific approach has been adopted in [Bianco and Chiabrera, 1992; Bianco et al., 1993a, b; Chiabrera et al., 1991, 1992a], where $H_{bm} = 0$ but H_{end} has been modeled by means of the endogenous attracting potential ($-\xi/r$) of the coulombic type, which emulates in a crude fashion a binding site. Furthermore, the contribution of finite lifetimes has also been taken into account. The exogenous Hamiltonian has been evaluated in the case of a TEM exposure at RF [Bianco et al., 1993a]. The binding probability P of the ligand ion has been computed, in the presence and in the absence of exogenous exposure. By doing so, resonance effects are possible, but the change in binding probability is negligible if the intensity of the EM exposure is low. On the other hand, in absence of the exogenous exposure, the

aforesaid condition $H_{bm}=0$ [Bianco and Chiabrera, 1992; Bianco et al., 1993a, b; Chiabrera et al., 1991, 1992a] corresponds to thermal equilibrium, i.e., $\rho_0=\rho_{th}$, where ρ_{th} is the thermodynamic equilibrium value of ρ, as given by Eq. (16) below. In other words, letting $\rho_0=\rho_{th}$ in Eq. (4), the effect of any low intensity exposure becomes negligible, as compared with thermal noise. A similar result occurs in the case of classical modeling [Chiabrera et al., 1992b]. As already discussed, such a simplifying condition is not reasonable for living systems which are by definition out of equilibrium [Chiabrera et al., 1994a].

This is the key point which was previously discussed [Bianco et al., 1997; Chiabrera et al., 1995b, 1996], i.e., letting $H_{bm}\neq 0$. In this way we were able to grasp the most important aspect of the interaction mechanism, demonstrating that the effects of low intensity RF exposure on $\rho_{mn}(t)$ are enhanced by H_{bm}, i.e., by $-\nabla H_{bm}\cong M\beta\mathbf{v}_{bm}$.

Application of the Z–S Model to RF Exposure

In this paper we evaluate, as a representative output of the ion–protein system, the ion binding probability $P(t)$, with $H_{bm}\neq 0$. Such a probability is the classical expected value of a random variable which assumes the value 1 inside the sphere of radius R_c and the value 0 outside. In the quantum language, $P(t)$ is merely the observed value of a linear operator P, actually a mathematical function, defined as $P=1$ inside the aforesaid sphere and $P=0$ outside.

The elements of its matrix are given by:

$$P_{mn}=\int \Psi_m^{*}\Psi_n dxdydz \tag{11}$$

where the integration domain is the sphere $r\leq R_c$. The hydrogenoid eigenfunctions not considered in the 5-state approximation used in this paper are almost negligible [Landau and Lifschitz, 1966] for $r<6\hbar^2/(\xi M)$, i.e., if $R_c<3[3\hbar/(2M\omega_0)]^{1/2}$. For example, letting $R_c=1$ nm, it must be $\omega_0<210^{10}$ Hz (shallow potential energy wells).

In practice, the solution of Eq. (4) with the initial condition $\rho(0)=\rho_0$ gives the system transient behavior, actually ρ_{mn}, corresponding to the onset of the EM exogenous exposure H_1 at $t=0$ [Bianco et al., 1997; Chiabrera et al., 1995b, 1996]. Then, the time evolution of the components $P_{mn}(t)$ can be computed and $P(t)$ evaluated from the trace of (ρP), as previously stated in Eq. (10). In most cases it is more interesting to evaluate its behavior for large values of t, when the effect of the initial state becomes negligible. We define:

$$P_{as}(t)=P(t)\big|_{t\ large} \tag{12}$$

In the case of periodic exposure also P_{as} is periodic, so that it can be evaluated by its average value

$$\langle P_{as}\rangle=\frac{1}{T_c}\int P_{as}dt \tag{13}$$

when $T_c[s]$ is the period and the integration domain is $(t, t+T_c)$ for large values of t. The value of $\langle P_{as}\rangle$ can be compared with the initial value $P(0)$ in absence of any exposure:

$$P(0)=Tr(P\rho_0) \tag{14}$$

The quantity $[P(0)-\langle P_{as}\rangle]/P(0)$ is the relative excess change of probability due to the EM exposure, and it is assumed to be a measure of its biological effectiveness.

The results depend on the values of the lifetimes parameters θ_{mn} and τ_{mn}which enter the matrix representation of the summation of the double commutators $\sum_s[T_s,[T_s,(\rho-\rho_0)]]$ in Eq. (4). The lifetimes are related to the loss of energy of the ion–protein system, when it is out of thermodynamic equilibrium, because of its interactions with the thermal bath. They are the quantum mechanical counterparts of the collision frequency β [Chiabrera et al., 1994b] of the ion with the water molecules and the protein molecules, so that their orders of magnitude, say θ and τ, are linked by the following relationship [Bianco, 1994]:

$$\theta>\tau\cong 1/\beta \tag{15}$$

For all the numerical simulations performed in this paper we assume for sake of simplicity $\tau_{mn}\cong\tau=1/\beta$ and $\theta_{mn}\cong\theta=5/\beta$ for every $m\neq n$. For the hydrophobic crevices considered in this paper, β can be as low as 10^4 Hz [Chiabrera et al., 1994b].

The expression of ρ_0 given in [Bianco et al., 1997; Chiabrera et al., 1995b] as function of $\mathbf{F}_{bm}$, reduces to the thermodynamic equilibrium relationship ρ_{th} when $\mathbf{F}_{bm}=0$:

$$\begin{aligned}\rho_{th}&=\{\exp[-(\mathbf{p}.\mathbf{p}/(2M+U_{end}))/(K_BT)]\}/Z_{th}\\&=\{\exp[-H_{end}/(K_BT)]\}/Z_{th}\end{aligned} \tag{16}$$

which corresponds to the Boltzmann distribution, where $\mathbf{p} = j\hbar\nabla$, $K_B[JK^{-1}]$ is the Boltzman's constant and T [K] is the temperature. The denominator Z_{th} is the trace of the corresponding operator at the numerator of Eq. (16) so that the trace of ρ_{th} is equal to 1, as it must be. The role of $\mathbf{F}_{bm} \neq 0$ can be better appreciated if one formally lets $U_{end} = 0$ in the quoted expression of ρ_0. Within this limit one obtains

$$\lim_{U_{end}\to 0} \rho_0 = \{\exp[-(\mathbf{p} - \mathbf{F}_{bm}/\beta) \cdot (\mathbf{p} - \mathbf{F}_{bm}/\beta)/(K_B T)]\}/Z_0 \quad (17)$$

which does not obey the Boltzmann statistics, but instead implies a net flow with a classical mean velocity $\mathbf{v}_{bm} \approx \mathbf{F}_{bm}/(\beta M)$. The operator $\rho_{bm} = \rho_0 - \rho_{th}$ indicates how far from thermodynamic equilibrium the ion–protein system is maintained by basal metabolism, i.e., by $\mathbf{v}_{bm}$. The endogenous Hamiltonian H_{end} provides the nonlinearity which transduces the power supplied by the metabolic sources via $\mathbf{v}_{bm}$, i.e., $\mathbf{F}_{bm}$ into the time-varying power necessary to affect the temporal evolution of the state variables induced by the low intensity EM input signal.

Within the approximations of the five-state Z–S model, the contribution of H_{bm} becomes important with respect to H_{end} if [Bianco et al., 1997; Chiabrera et al., 1995b]:

$$F_{bm} > 10^{-2} M^2 \xi^3/\hbar^4 \quad (18)$$

This inequality is obtained comparing the matrix components of the two Hamiltonians. On the other hand, ρ_0 appreciably differs from ρ_{th} if [Bianco et al., 1997; Chiabrera et al., 1995b]:

$$F_{bm} > 3(2\pi) M \xi \beta/\hbar \quad (19)$$

Both conditions (Eqs. (18) and (19)) are compatible with an acceptable order of magnitude of F_{bm} (where F_{bm} is the modulus of the vector, $\mathbf{F_{bm}}$) if plausible low values of $\xi = [8\hbar^3\omega_0/(3M)]^{1/2}$ (shallow endogenous potential wells) and of β (hydrophobic clefts) are allowed [Bianco et al., 1997; Chiabrera et al., 1994b]. Adopting the electronic jargon, we conclude that reasonable values of $\mathbf{F}_{bm}$ can bias the ion–protein system far enough from thermodynamic equilibrium, at an operating point of the nonlinear $-\nabla H_{end} = -\nabla U_{end} = \mathbf{F}_{end}(\mathbf{r})$ characteristic where the system may be potentially able to detect small EM input signals. The system takes advantage of the power supply provided by the basal metabolism of the cell via $\mathbf{F}_{bm}$, much like a transistor using its power supply to amplify the (''small'') time-varying signal applied to its input gate.

We pointed out previously [Chiabrera et al., 1992b; Kaufman et al., 1990] that any bioelectromagnetic model must include the effects of thermal noise. In quantum dynamical terms, the density operator is the correct tool for handling the interactions with the thermal bath. Then, the first task to be accomplished is the evaluation of the output $P(0)$ when the exogenous EM exposure is absent in Eq. (4), i.e., $H_1 = 0$, so that thermal noise is the only input acting on the system. The second task is the evaluation of the output $P(t)$ when the exogenous EM exposure is active. Noise is always present. The third task is to compare, in relative terms, the outputs obtained in the two situations. Any conclusion about the effectiveness of the EM exposure on the ion–protein system must be drawn only from such a comparison.

As an example, we consider an application of the Z–S model to the EMF produced by mobile telecommunications equipment [Bach-Anderson et al., 1995; Li and Qiu, 1995] at RF. In this case, the exogenous EM input to the ion–protein system is described by $\mathbf{A}(x,y,z,t)$ and ϕ (x,y,z,t), and is classically known. It is adequate to consider a linearly polarized TEM wave [Bianco et al., 1993a, 1997; Chiabrera et al., 1995b] which can be described in terms of $\mathbf{A}$ only, letting $\phi = 0$. A reasonable approximation is to consider the RF carrier alone, at $f_c[Hz] = \omega_c/(2\pi)$, propagating along the y axis in a biological medium, whose average conductivity is $\sigma[Sm^{-1}]$, whose electric permittivity is $\varepsilon_0\varepsilon_r[Fm^{-1}]$ and whose magnetic permeability is $\mu_0[Hm^{-1}]$. As usual, ε_0 stands for the permittivity of vacuum. The permeability is assumed to be coincident with the vacuum one, μ_0 because we are dealing with either dia- or para-magnetic media. The vector potential is

$$\mathbf{A}_{rf} \cong \sqrt{\frac{2\rho_m S}{\sigma}} \left\{ \frac{\exp(-\alpha_c y)}{\omega_c} \cos[\omega_c(t - y/v_c)] \right\} \mathbf{i}_x \quad (20)$$

where S [W kg^{-1}] is the local SAR at $y = 0^+$, and $\rho_m[kg\,m^{-3}]$ is the local tissue density and $\mathbf{i}_x$ is the unit vector in the x direction. The expressions for the attenuation coefficient

$$\alpha_c = \frac{\sigma}{\sqrt{2}} \left\{ \frac{\varepsilon_0}{\mu_0} \left[\frac{\sigma}{\omega_c \varepsilon_0} + \left(\varepsilon_r^2 + \frac{\sigma^2}{\omega_c^2 \varepsilon_0^2} \right)^{1/2} \right] \right\}^{-1/2} \quad (21)$$

and the phase velocity

$$v_c = \sqrt{2}\left\{\varepsilon_0\mu_0\left[\frac{\sigma}{\omega_c\varepsilon_0} + \left(\varepsilon_r^2 + \frac{\sigma^2}{\omega_c^2\varepsilon_0^2}\right)^{1/2}\right]\right\}^{-1/2} \quad (22)$$

are the standard ones of electromagnetics.

We choose an ideal hydrophobic putative protein characterized by $R_c = 1\,\text{nm}$ and, as a paramount example, we consider the case $\omega_0 \cong 2\pi f_c$, so that the incoming photons match, in energy, the depth $(r\omega_0)$ of the ligand potential energy well.

RESULTS

We consider the case of a TEM wave, incoming from the half space $y < 0$ (in practice, air) which penetrates into the lossy semi-infinite medium $(\sigma = 1\,\text{Sm}^{-1}, \varepsilon_r = 80$ and $\rho_m = 10^3\text{kg}\,\text{m}^{-3})$, which fills the half space $y > 0$. The carrier frequency considered is $f_c = 915\,\text{MHz}$ (i.e., in the range of interest for cellular telephones [Bach-Andersen et al., 1995]. The putative process under consideration is the binding of a Ca^{++} ion to a putative receptor protein located at $x = z = 0$, and $y = 0+$. The EM sinusoidal exposure is switched on at $t = 0$. In these conditions, after the initial transient, the binding probability $P(t)$ reaches an asymptotic behavior $P_{as}(t)$ which is almost constant (see Fig. 3) and differs from $P(0)$. The asymptotic waveform $P_{as}(t)$ is shown in Figure 4 for two different exposure intensities. Therefore, it is convenient to consider the time average of P_{as}, i.e., $< P_{as} >$, which is constant as already anticipated, and to plot $[P(0) - < P_{as} >]/P(0)$ vs. the incident power density (IPD [W m^{-2}]) or vs. the SAR, as a measure of the biological effectiveness of the RF exposure.

A typical result is shown in Figures 5 and 6. It is apparent that, if $\mathbf{F}_{bm}$ goes to zero (so that $\rho(0) = \rho_{th}$), there is no practical effect, irrespective of the level of the incident EM power. If $\mathbf{F}_{bm}$ is increased, the effect on the binding probability of the TEM exposure becomes significant, at IPD (or SAR) values which are below the current safety standards. This result proves that a low-intensity RF exposure can affect an elementary biological process.

Figure 7 clarifies that the EM exposure becomes effective when the carrier frequency is equal to $f_0 = \omega_0/2\pi$, so that the energy of the EM photon $(\hbar 2\pi f_c)$ matches the depth of the attracting potential

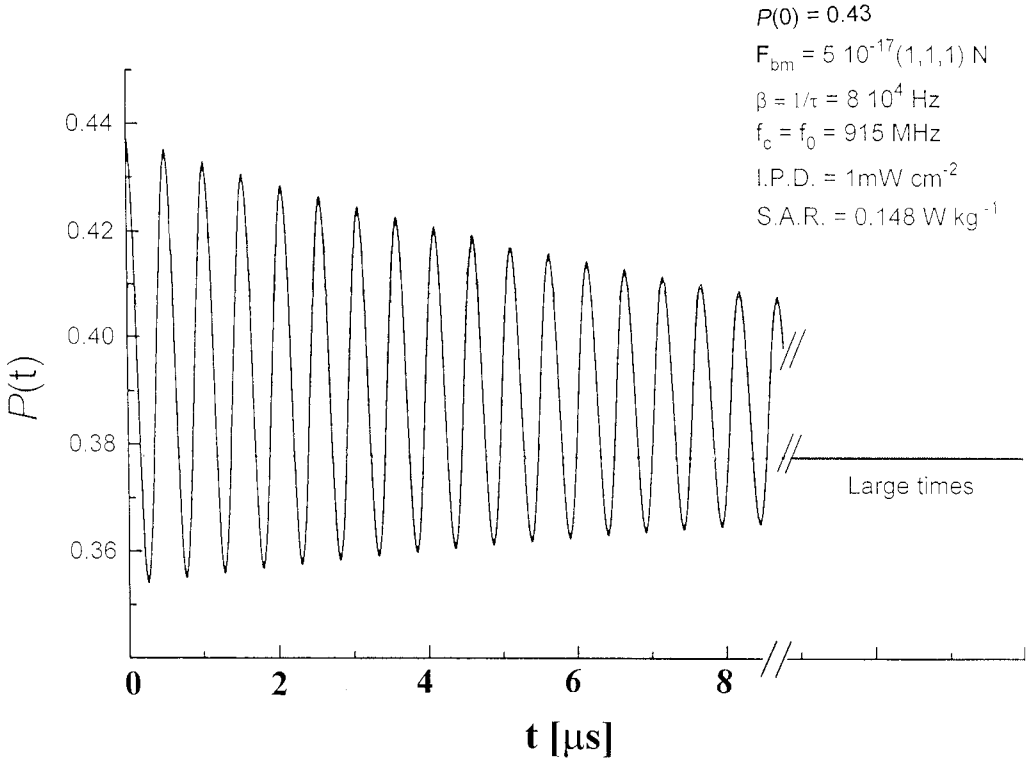

Fig. 3. Time evolution of the binding probability $P(t)$. For longer times it becomes periodic, with small time variations superimposed to a constant value (0.378) different from $P(0) = 0.437$. The cartesian components of F_{bm} are equal to $5\,10^{-17}$ N. The RF exposure is IPD $= 1\,\text{mW}\,\text{cm}^{-2}$ (SAR $= 0.148\,\text{W}\,\text{kg}^{-1}$).

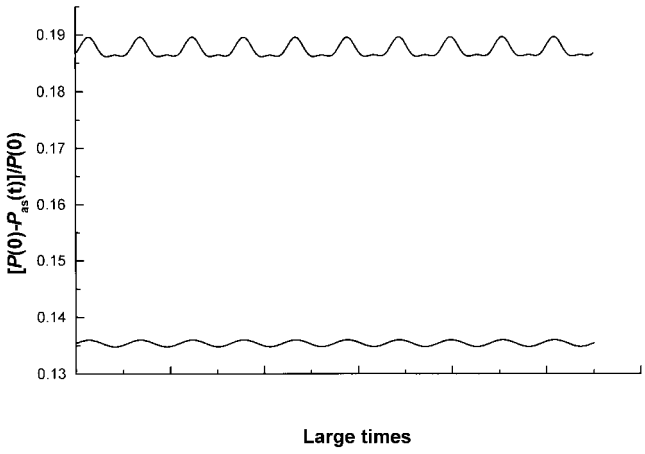

Fig. 4. Enlarged view of the asymptotic behavior $P_{as}(t)$ (bottom curve) of $P(t)$ in relation to Figure 3. The top curve shows $P_{as}(t)$ for a ten-fold exposure power intensity. It is evident the nonlinearity of the response as the exposure intensity is increased.

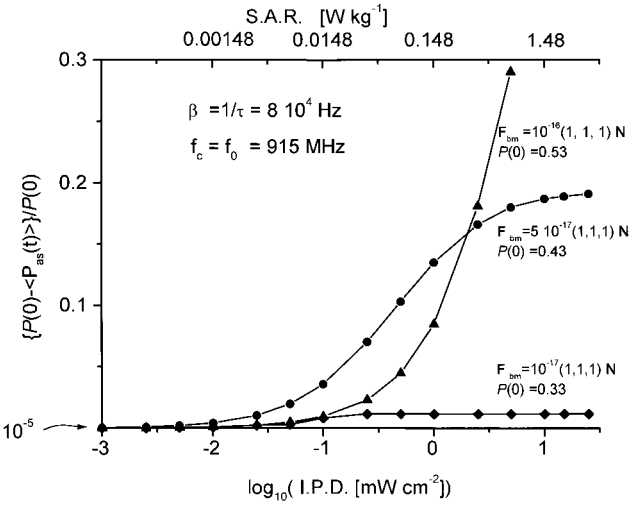

Fig. 5. Relative excess change of the binding probability vs. the exposure intensity, at different values of $\mathbf{F}_{bm}$, having identical cartesian components in each case, respectively equal to 10^{-17} N (diamonds), 5×10^{-17} N (circles), 10^{-16}N (triangles). The corresponding values of P(0) are, respectively, 0.33, 0.437, 0.53.

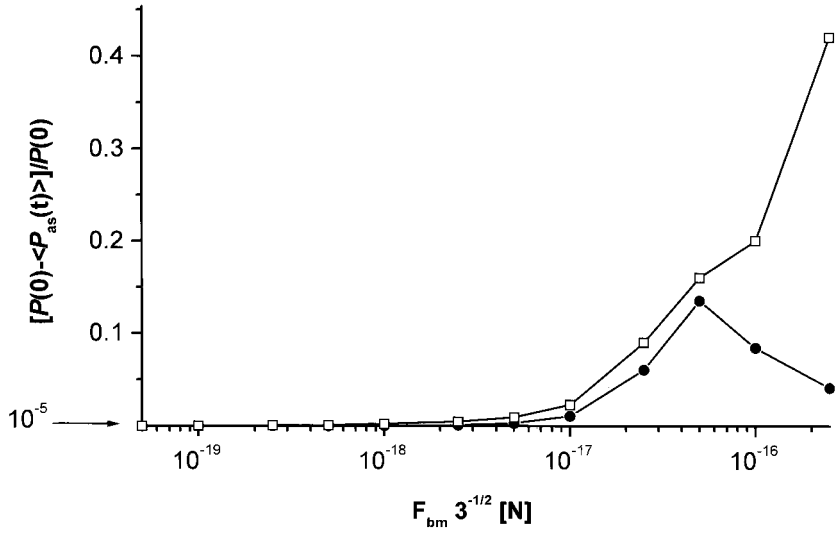

Fig. 6. Relative excess change of the binding probability vs. the modulus of $\mathbf{F}_{bm}$, whose cartesian components are identical, at different exposure intensities, respectively equal to 1 mW cm^{-2} (SAR = 0.148 W kg^{-1}) (full circles), 10 mW cm^{-2} (SAR = 1.486 W kg^{-1}) (open squares).

energy well ($\hbar\omega_0$). Two other resonances occur at the Stark shifts above and below f_0, due to $\mathbf{F}_{bm}$. A change of $\mathbf{F}_{bm}$ (dashed line in Figure 7) enhances these Stark effects. Finally, Figure 8 shows that, keeping $\mathbf{F}_{bm}$ constant, the Stark resonances do not change in frequency, but they are enhanced if the intensity of the EM exposure is increased.

CONCLUSIONS

We have analyzed the existence of a biophysical basis for assessing the effects of low-intensity RF fields on ligand adsorption/desorption to cell proteins, with specific emphasis on ion binding as a first interaction step. The ion binding to a receptor hydrophobic site is the process most widely studied, but a similar approach can be applied to ion transport through a protein channel by choosing a suitable dependence of the endogenous potential energy U_{end} on $\mathbf{r}$. We adopted and developed the Z–S quantum modeling of a ligand ion–receptor protein system.

Several topics that have been addressed in the paper can be revisited in quasi-classical terms, for the reader's convenience:

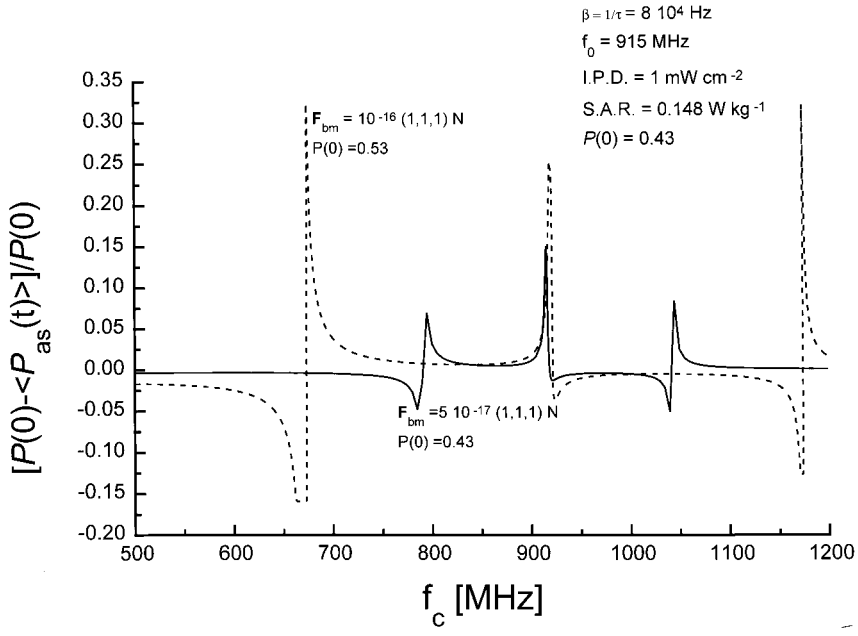

Fig. 7. Relative excess change of the binding probability vs. the carrier frequency at the same exposure intensity (1 mW cm^{-2} SAR = 0.148 W kg^{-1}), for two different $\mathbf{F}_{bm}$ with identical cartesian components equal to 5×10^{-17} N (continuous line) and 10^{-16} N (dotted line). The value of f_0 is 915 MHz.

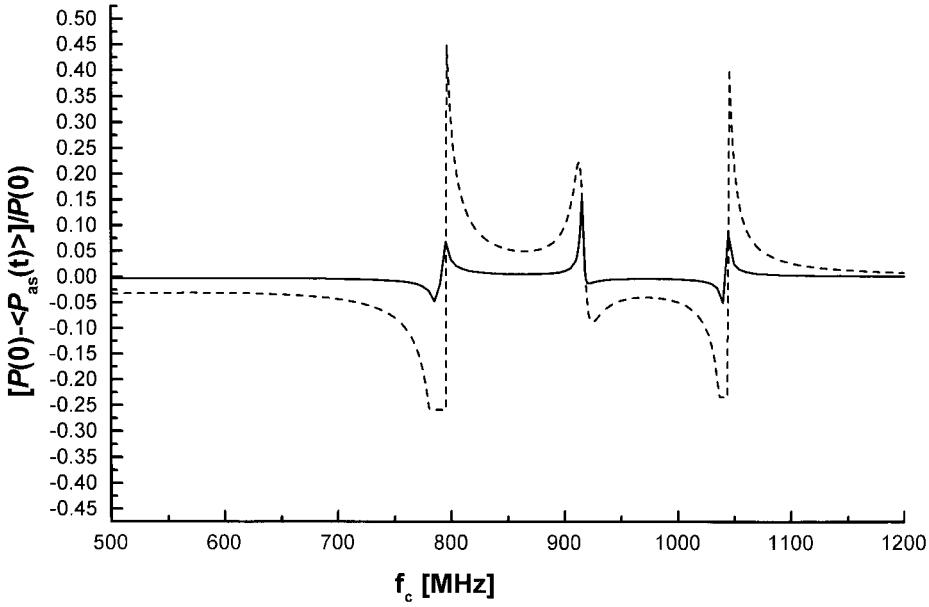

Fig. 8. Relative excess change of the binding probability vs. the carrier frequency at the same $\mathbf{F}_{bm}$, (having identical cartesian components equal to 5×10^{-17} N) at two different values of the exposure intensity, respectively, 1 mW cm^{-2} (SAR = 0.148 W kg^{-1}) and 10 mW cm^{-2} (SAR = 1.486 W kg^{-1}).

(1) The procedure for characterizing the endogenous attracting force inside the molecular structure, given by the Protein Data Bank, has been outlined. The reaction field induced on the protein by the ligand ion, which displaces the protein atoms while docking or sailing, is included in U_{end} by assuming that such a rearrangement of the protein atoms is extremely fast. The endogenous force $\mathbf{F}_{end} = -\nabla U_{end}$ provides a strong non-linearity in the state equations for the ion-protein system. The protein characteristic parameters which enter U_{end} are ω_0 (i.e., ξ), ω_{end}, U_0 and R_0.

(2) The Langevin ion collision frequency β in the hydrophobic crevice of the protein is much less than in bulk water so that viscous losses are small. The endogenous field at the protein boundaries is large enough and sufficiently nonuniform in space so that water molecules are rejected by the resulting dielectrophoretic force acting on their electric dipoles. Therefore, any protein with a hydrophobic crevice is a good candidate for hosting an effective interaction between low intensity exposure and a binding ion, because it can provide low values of β. As a consequence, the quantum counterparts of the classical collision frequency, i.e., the lifetimes θ and τ which enter the Z–S model, may assume large values, on the order of $1/\beta$.

(3) Basal metabolism maintains the cell out of thermodynamic equilibrium. At the molecular level, the metabolic activity sustains an average ion velocity, $\mathbf{v}_{bm}$. This amounts to say, classically, that a metabolic driving force $\mathbf{F}_{bm} \cong M\beta\mathbf{v}_{bm}$ contributes to the ion drift. A measurable indirect evidence of $\mathbf{F}_{bm}$ is a net voltage drop across the membrane of any living cell, in excess to the thermodynamic equilibrium. The force $\mathbf{F}_{bm}$ supplies power to the system. This power can be converted, via the nonlinearity provided by $\mathbf{U}_{end}$, into signaling power ''controlled'' by the low intensity EM exogenous field.

(4) Thermal noise must always be considered in any theoretical attempt to evaluate potential EM bioeffects. The density operator is the quantum description which inherently takes into account the statistical effects of the interaction with a thermal reservoir. The resulting noisy contribution to the ion–protein output can be taken into account in presence and in absence of EM exposure, whose effectiveness must be judged from the comparison of the expected values of the binding probability in the two situations.

The computer simulations, performed for a putative shallow binding site such that the depth of the corresponding quantum well is close to the RF photon energy of a sinusoidal carrier, prove that the low intensity EM exposure may affect the ion binding probability in a significant way. The mechanistic insight provided by the analysis outlined in this paper suggest novel possibilities for modulating the physiological function of receptor proteins by means of EM fields.

In conclusion, we have offered a plausible biophysical basis for potential biological effects of low-intensity EM exposure at RF, which could lead to novel clinical applications and should also be considered in the future by the safety standards regulators.

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