LIGAND BINDING UNDER RF EM EXPOSURE

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1. Abstract

The influence of electromagnetic exposure on ligand binding to receptor proteins is a putative early event of the interaction mechanism leading to biological effects. The most recent development of the quantum Zeeman-Stark model is reviewed, addressing the following points: losses due to the collisions of the ligand ion inside the hydrophobic binding crevice and thermal noise; evaluation of the attracting endogenous force of the binding site from the protein data base; out of equilibrium state of the ligand-receptor system due to the basal cell metabolism.

The biochemical output is the change of the ligand binding probability due to low intensity electromagnetic exposure at radio frequencies.

2. Introduction

The scientific interest in the biological effects induced by the exposure of living systems to an electromagnetic field (e.m.f.) is related to biomedical applications and to a new database for safety standards of non-ionizing e.m.f., going beyond the current mechanistic assumption, based on the electromagnetic (e.m.) power deposition in biological tissues (Specific Absorption Rate, S.A.R. [W kg^{-1}]), in order to incorporate the experimental evidence of the biological effects of the e.m. exposure (see, for example [4, 6, 9, 12, 21, 22, 25, 31, 32, 63-65, 67-69, 73, 82, 84, 86, 90, 91, 98, 101-106, 108, 110, 112, 116, 120]). Therefore there is the need of clarifying the underlying interaction mechanisms [2, 3, 5, 24, 25, 36, 52, 70, 71, 78, 121, 122] and the of improving the reproducibility and the quality of the experiments [49]. Toward this goal most researchers have concentrated their experimental and theoretical efforts on the early steps of the e.m. interaction, at the molecular level [9, 33, 61-63, 66-70, 73, 83, 84, 86-91, 93, 107-110, 116].

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In this respect, one of the most widely studied biochemical processes is the binding of light ligands (e.g. metal ions, like Ca^{++}) to receptor proteins. Two general theoretical models of ion binding are available in the literature: the classical Langevin-Lorentz (L-L) model [14, 15, 17, 35-37, 42, 43, 48, 53, 56, 57, 66, 87, 88, 96, 97] and the quantum Zeeman-Stark (Z-S) model [15-17, 20, 23, 41, 44, 48, 52, 59, 83, 94]. They are simplified in such a way as to retain the essential features of the e.m. interaction with the binding process and to neglect all the details of the complete molecular dynamics simulation of the ion-protein system [54, 76].

The purpose of this paper is to review the state of the science concerning the aforesaid quantum Z-S model and to offer a predictive example of its application to radio frequency (r.f.) sinusoidal e.m. exposures [7, 20, 48, 50, 124].

The e.m.f. intensities considered in this paper are low, i.e., intensities below the current safety standard based on thermal effects [28, 29].

3. Ligand Binding to a Receptor Protein

Before analysing in detail the Z-S model, it is worthwhile to review the simplest possible description of the binding process, that could be linked to experimental data [10, 11, 72, 81, 99, 111, 113-115, 118, 126, 128].

The example we discuss concerns an idealized protein of the cell membrane, with a single type of binding site attracting a ligand ion. The cell is considered as a sphere of radius R_0 [m] and therefore area $4\pi R_0^2$ [m^2].

The number of receptor proteins embedded in the cell membrane is S. Their binding sites are located, for example, on the extracellular side of the cell membrane. Each receptor site can be occupied by one ligand only, or it is empty. Letting P_B be the probability for a receptor to be occupied and L [m^{-3}] the concentration of the ligands near the cell surface, the simplest first order mass-action law which gives the time course of P_B is:

$$dP_B/dt \approx K^+ L(1 - P_B) - K^- P_B \tag{1}$$

where K^- [s^{-1}] and K^+ [s^{-1} m^{-3}] are, respectively, the so-called dissociation and association rate "constants" in SI units.

In biochemistry L is measured in [M^{-1}] and K^+ in measured in [min^{-1} M^{-1}], where 1 $M = N_A / (1\ dm^3) = 6\ 10^{26}\ m^{-3}$, being N_A the Avogadro's constant.

In general, K^- and K^+ depend not only on the endogenous attractive force exerted by the binding site on the ligand, but they may depend also on the exogenous e.m. exposure, i.e., on the electric field vector $\vec{E}$ [Vm^{-1}] and the magnetic induction vector $\vec{B}$ [T]. Therefore, strictly speaking, K^- and K^+ may depend on time, via the time dependence of $\vec{E}$ and $\vec{B}$.

The purpose of this paper is to outline a procedure, based on the aforesaid Z-S model, for evaluating the changes of K^- and K^+ due to the e.m.f.. Hence, the theory can be linked by means of equation (1) to binding experiments, i.e., to the measurement of the total number of bound ligands (i.e., SP_B), once L and S are known.

The model assumes, as a further simplification, that the binding crevice of the protein is isotropic, and that the ligand ion is a point charge Q [C] and mass M [kg], without any magnetic property. The site is occupied if the ion is inside a sphere of radius R_C [m], whose centre coincides with the binding crevice centre, chosen as origin of the coordinates.

It is clear, from equation (1), that in order to fully predict the influence of the e.m.f. on P_B during any binding experiment, one should be able to evaluate K^- and K^+ from first principles.

This can be obtained by means of a "gedanken" experiment performed by choosing a special value for L, say L_P, such that the corresponding value P, assumed by P_B when $L = L_P$, can be theoretically computed.

The peculiar concentration value L_P of L is chosen in such a way that there is always just one ligand interacting with one site, which is occupied with probability $P_B = P$ or is empty with probability $(1-P)$. In order to clarify the issue, one could consider the S receptors as uniformly distributed on the surface $4\pi R_0^2$ of the spherical cell membrane.

The next step is the practical evaluation of L_P which can be obtained from the computation of the average R_P [m] of the ion displacement given by:

$$\lim_{t\to\infty} < \vec{r}(t)\cdot\vec{r}(t) > = (R_P)^2 \tag{2}$$

where <...> means expectation value of the "observable" argument, i.e., the observable ensemble average.

Typically, such a limit always exists, because of the attracting endogenous force of the site. In order to be consistent with the conceptual framework developed in this section, one can conclude, by assuming a conservative radius $2R_P$ that inside the volume $(4/3)\pi(2R_P)^3$ centred around each site there should always be just one ligand ion (bound or unbound), so that one can directly assume that

$$L_P \approx 3(1-P) / [4\pi(2R_P)^3] \tag{3}$$

The modelling approach discussed in the next section allows the theoretical evaluation of $P(t)$, i.e., the value of P_B in the case $L = L_P$ under e.m. exposure. Consequently, for the introductory purposes of this section, one can assume that P and R_P (i.e., L_P), can be theoretically evaluated.

A way of evaluating K^- is to perform another "gedanken" experiment, i.e., releasing at time t=0 the ion at the crevice centre with some initial velocity $\vec{v}_{bm}$ [ms^{-1}] and

computing both its displacement $\vec{r}(t)$ [m] and the time t^- needed to reach the binding distance R_C in the mean square sense :

$$< \vec{r}(t^-) \cdot \vec{r}(t^-) >= (R_C)^2 < (R_P)^2 \tag{4}$$

Once t^- is computed from equation (4) it offers an estimate of the value of K^- according to the following relationship

$$K^- \approx 1/t^- \tag{5}$$

In conclusion, knowing P , L_P and R_P, one gets

$$K^+ = (K^-P + dP/dt) / [L_P(1 - P)] \approx (K^-P + dP/dt) (4/3)\pi(2R_P)^3 / (1 - P)^2 \tag{6}$$

so that the value of P_B corresponding to general value L can be obtained by substituting equation (6) in equation (1):

$$dP_B/dt \approx [(K^-P + dP/dt) / (1 - P)] (L/L_P) (1 - P_B) - K^-P_B \tag{7}$$

If the microscopic process is slow enough to average the time variations of P due to the e.m. exposure, then $dP/dt \approx 0$ and the corresponding term can be dropped out from equation (6, 7).

In general, once the values of P, K^-, L_P, i.e., R_P are theoretically evaluated with and without exogenous exposure, equation (7) can be applied to the analysis of a real binding experiment.

If it is $dP_B/dt \approx 0$, e.g. in a steady state experiment, so that both time derivatives can be neglected in equation (7), we obtain

$$P_B = P\{L(4\pi/3)(2R_P)^3/[1+PL(4\pi/3)(2R_P)^3-P^2]\} \tag{8}$$

In practice, the changes of P due to the e.m. exposure can be already considered, per se, a reasonable assessment of the potential biological effectiveness of the e.m.f.. These changes are sufficient to offer the experimentalist the possibility of an educated guess about the susceptibility of the ligand-receptor under consideration of the various parameters which characterize the e.m.f..

4. The State of the Science for the Zeeman-Stark Quantum Model

The most general approach to the study of ligand binding to a receptor under e.m. exposure is based on quantum modelling of the process (Z-S model). Adopting a scheme similar to the classical one, the problem is to find the so called reduced density

operator ρ [1, 20, 51, 80, 117, 119] which describes the ion motion in the attracting (isotropic) potential energy well $U_{end}(r)$ [J], in presence of exogenous e.m. potentials, i.e., a scalar potential ϕ [V] and a vector potential $\vec{A}$ [T m] such that $\vec{E} = -\nabla\phi - \partial\vec{A}/\partial t$ and $\vec{B} = \nabla \wedge \vec{A}$.

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

$$U_{end}(r) \approx -\xi_B/r + \left\{\xi_B/R_B - U_0 + \xi_B/r + \left(\xi_B/2R_B^2 - U_0/R_B\right)r + \right.$$
$$\left. + \left(M\omega_{end}^2/2 - U_0/2R_B^2 + \xi_B/6R_B^3\right)r^2\right\}\exp(-r/R_B) \qquad (9)$$

to the available data of the protein of interest, as obtained from the Brookhaven Protein Data Bank.

The energy ($-U_0$) is the depth of the potential energy well at the centre of the binding crevice ($\vec{r} = 0$), whereas $R_B > R_C$ is related to the protein size. For small values of $\vec{r}$, the above expression gives:

$$-\nabla U_{end} = Q\vec{E}_{end} \approx -M\omega_{end}^2\vec{r} \qquad (r << R_B) \qquad (10)$$

which is coincident with the typical "linear" endogenous attractive force (spring like) used by most authors [15, 43, 47, 54, 56, 66]. The nabla operator is ∇. Therefore ($M\omega_{end}^2$) plays the role of the spring constant.
For large value of r, the above expression gives:

$$-\nabla U_{end} = Q\vec{E}_{end} \approx -\xi_B\vec{r}/r^3 \qquad (r >> R_B) \qquad (11)$$

which is the typical "coulombic" endogenous attractive force originally used in the Z-S model.

The time evolution of ρ must obey the following relationship:

$$\partial\rho/\partial t = \left(-j/\hbar\right)\left[H_{end} + H_{bm} + H_1, \rho\right] - \left(j\beta/2\hbar\right)\sum_{i=1}^{3}\left[r_i, \Theta_i\rho + \rho\Theta_i\right] +$$
$$- \left(\beta K_B T M/\hbar^2\right)\sum_{i=1}^{3}\left[r_i, \left[r_i, \rho\right]\right] \qquad (12)$$

where r_1=x, r_2=y and r_3=z.

The Hamiltonian $H_{end} = -\left(\hbar^2/2M\right)\nabla^2 + U_{end}$ refers to the ion motion in the potential energy U_{end}. The Hamiltonian H_{bm}, takes into account the contributions of the

endogenous basal force $\vec{F}_{bm} = -\nabla H_{bm}$, which emulates the effects of the basal metabolism of the living cell on the ion receptor system [19, 20, 45, 48, 50]. The need of such a force is consistent with the exponential macroscopic evidence that across the membrane of any living cell it exists an excess voltage drop sustained by the biochemically driven ion pumps. The related excess electric field is $\vec{E}_{bm} = \vec{F}_{bm} / Q$.

We assume for simplicity sake that the spatial force is spatially uniform and constant in time.

The Hamiltonian H_1 takes into account the contribution of ϕ and $\vec{A}$. We adopt the gauge condition $\nabla \cdot \vec{A} = 0$ so that $H_1 \approx j\hbar\gamma\vec{A} \cdot \nabla$, where $\gamma = Q/M$. A typical assumption is that $\vec{A}$ is small enough so that the term proportional to $\vec{A} \cdot \vec{A}$ in H_1 can be neglected. The commutator [S,R] means, by definition, SR-RS.

Care must be paid in fitting the above parameters to the protein data. A common practice is to evaluate, from the protein data bank, the endogenous electric potential $\phi_{end} = U_{end}/Q$ [V] generated by the surrounding atoms (the contribution of the protein embedding medium should be included if necessary) inside the binding crevice, in a static conformation [75].

In reality, when the ligand ion is approaching the binding site, the electric field due to its charge displaces the protein atoms in a very fast time scale, so that the actual ϕ_{end} to be used takes into account the "instantaneous" rearrangement of the protein atoms corresponding to the actual ion position [26, 27, 95]. The reaction field resulting from such displacement lowers the actual value of the endogenous force which attracts the ion toward the crevice centre, so that ω_{end} can assume values which could be orders of magnitude lower than those computed by assuming the protein atom in static position.

A procedure for obtaining these more realistic values of ω_{end}, without performing a detailed molecular dynamics simulation of the protein, is outlined in [26, 27, 95].

A rather effective and simpler approach is to obtain, from the protein data bank the value of ϕ_{end} in presence and absence of the ligand.

The schematic diagrams of figures. 1 and 2 offer a clear example of the different conformations assumed by a binding site of calmodulin in presence and in absence of Ca^{++}.

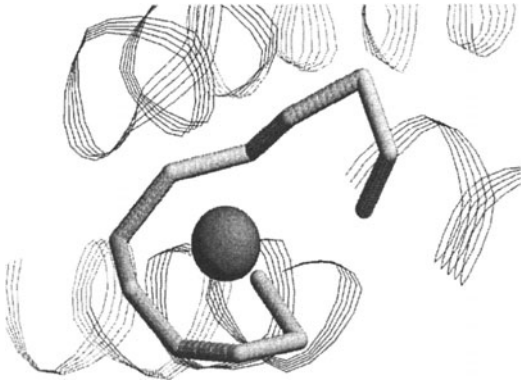

Figure 1. Backbone of one binding site of calmodulin, with bound ligand (Ca^{++}) (Brookhaven Protein Data Bank).

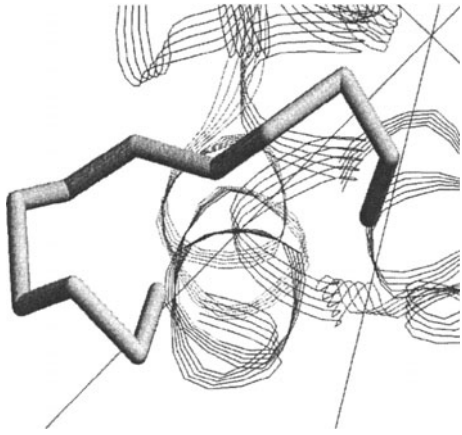

Figure 2. Backbone of one binding site of calmodulin, without bound ligand (Ca^{++}) (Brookhaven Protein Data Bank).

From the first set of values we can obtain U_0 and ω_{end} in the limit $r << R_B$. From the second set of values we obtain ξ_B in the limit $r >> R_B$. From both sets we obtain an estimate of R_B. A typical result is shown in Figure 3 for the same site sketched in Figures. 1 and 2.

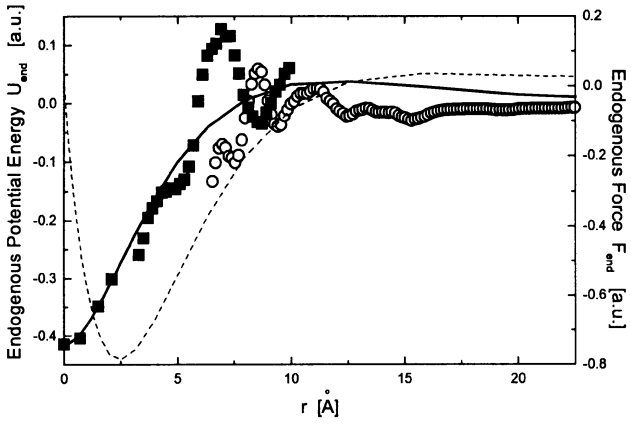

Figure 3. Example of the endogenous potential energy for Ca^{++} in one of the four binding sites of calmodulin, as obtained from the Brookhaven Protein Data Bank. The continuous curve has been obtained by fitting equation(9) to the protein data. The squares refer to the situation in which the ion is at the centre of the receptor site (see fig.1), the circles to the situation in which the ion is outside it (see fig.2). The dashed curve is the attractive endogenous force $-dU_{end}/dr$

The parameter β [Hz] is the classical Langevin's collision frequency of the ion in the binding crevice [18, 30].

A practical issue is the value of β. It has been conclusively demonstrated that the binding crevice of some proteins can be hydrophobic, if the modulus of $-\nabla U_{end}$ is large and negative dielectrophoresis of the solvent (water) dipolar molecules occurs [38-40, 60, 74, 127]. The ligand ion experiences few collisions inside the crevice, where it moves in a Knudsen (ballistic) regime [8, 46]. Therefore β can assume local values which could be several order of magnitude smaller than in bulk water ($\beta_{water} \approx 0.5\ 10^{14}$ [Hz]). Small values of β, i.e. $\beta << \beta_{water}$, are a necessary prerequisite for possible bioeffects of low intensity e.m.f.. The value of the initial velocity mentioned in the previous section can be approximated by $\vec{v}_{bm} = \vec{F}_{bm}/\beta M$.

The operators Θ_i play the role of appropriate quantum analogues of the classical drag terms in the Fokker-Plank equation which gives the time evolution of the classical probability density of the ligand. Their physical meaning become apparent when the system relaxes to thermal equilibrium, in the limit of $(1/T) \to 0$ and $\vec{F}_{bm} = 0$, when Θ_i becomes coincident with the i-th momentum component of the ligand. The last term in equation (12), which is proportional to the product of the Boltzmann's constant K_B with T, is the quantum counterpart of the thermal (white) noise effects in the classical Fokker-Plank equation.

The novel result is that equation (12) takes into account all the various aspects of the interaction of the quantum system with the thermal bath, as a function of T and of one fitting parameter only, i.e. β, which has a classical physical meaning.
It is beyond the scope of this paper to further discuss this point. It is enough to clarify that the operators Θ_i are chosen in such a way that the steady state value ρ_0 assumed by ρ when $H_1=0$ is the same as given in [20]. Furthermore, equation (12) is consistent with the so-called Generalised Master Equation [51]. In this case, by using the secular approximation, one can retrieve the link among the drag operators Θ_i and the lifetimes introduced in [20, 44].

Once a complete set of suitable orthonormal basis functions $\psi_m(x,y,z)$ has been chosen, the integration of equation (12) leads to the evaluation of the reduced density matrix entries $\rho_{mn}(t)$ of ρ so that the observable expectation value R of any quantum operator R can be computed from the trace expression

$$R = \mathrm{Tr}\,(R\rho) \tag{13}$$

Note that we neglect from now on the notation <...> which is implicit in the trace expression above.

We evaluate, as a representative output of the ion protein system, the binding probability $P(t) = \mathrm{Tr}\,(P\rho)$, with $H_{bm}\neq 0$, as discussed in the previous section. The value of the quantum operator P, actually a function, is 1 inside the binding sphere, and 0 outside, so that the entries of its matrix representation are

$$P_{mn} = \int \psi_m^* \psi_n \, dx\, dy\, dz \tag{14}$$

where the integration domain is a binding sphere of radius $R_C \leq R_B$.

In practice, the solution of equation (12) with the boundary condition $\rho(0) = \rho_0$ gives the system transient behaviour $\rho(t)$, in terms of the matrix entries $\rho_{mn}(t)$, corresponding to the onset of the e.m. exogenous exposure H_1 at t = 0 [20, 48, 50]. Then, the time evolution of $\rho(t)$, can be obtained and $P(t)$ can be computed from equation (13) and finally introduced in equation (6, 7). Sometimes it is more interesting to compute the time average

$$P_{av} = (1/t) \int P(t)\, dt \tag{15}$$

where the integration domain is [0,t], and to compare its asymptotic value

$$P_{av,\infty} = \lim_{t\to\infty} P_{av} \tag{16}$$

with its value $P(0)$ in the absence of any exposure, being

$$P(0) = \mathrm{Tr}\,(P\rho_0) \tag{17}$$

The value of $(R_P)^2$ of equation (2) can be computed as $(R_P)^2 = \lim_{t\to\infty} \mathrm{Tr}\left[\vec{r}(t)\cdot\vec{r}(t)\rho\right]$.

The value of $t^- \approx 1/K^-$ of equation (4) can be computed from $\mathrm{Tr}\left[\vec{r}(t^-)\cdot\vec{r}(t^-)\right] = R_c^2$.

We pointed out previously [43, 47, 77, 96] that any bioelectromagnetic model must include thermal noise as input. Then, the first task to be accomplished is the evaluation of the output $P(t)$ when the exogenous e.m. exposure is absent in equation (12), i.e., $H_1 = 0$, so that noise is the only input acting on the system. The second task is the evaluation of the output $P(t)$ when the exogenous e.m. exposure is active, and noise is still present. The third task is to compare, in relative terms. the outputs obtained in the two situations. Any conclusion about the effectiveness of the e.m. exposure on the ion-protein system must be drawn only as consequence of such a comparison.

In the literature, some theoretical papers do not consider noise at all, and their authors perform the second task only in the absence of noise. These studies provide some information about the output dependence on the, e.m. parameters (e.g., frequency, amplitude, etc.) but nothing can be inferred concerning the effectiveness of the e.m. exposure [14, 23, 35, 56-58, 61, 62, 66, 83, 87-89, 92].

A further aspect is the possibility of stochastic resonance [13, 55, 79, 100, 109, 125], which was briefly reviewed in [47]. The ion-protein system retains all the necessary features for stochastic resonance so that one could expect that an optimal range of characteristic parameter values exist where the signal-to-noise ratio of the output is enhanced. The evaluation of the system state equation (12) does naturally include stochastic resonance, whose study does not require any inherently different model.

5. Bioeffect of RF Exposure

The improved Z-S model outlined in the previous section can be applied to analyse the bioeffects of the e.m.f. produced by mobile telecommunications equipment [7, 85] adopting the same approach outlined in [20]. In this case, the exogenous e.m. input to the ion-protein system is described by $\vec{A}(x,y,z,t)$ and $\phi(x,y,z,t)$ and is classically known. It is adequate to consider a linearly polarized TEM wave [16, 20, 48, 50] which can be described in terms of $\vec{A}$ only, letting $\phi = 0$. A reasonable approximation is to consider the r.f. carrier alone, at $f_c = \omega_c/2\pi$ [Hz], propagating in a biological medium, whose average conductivity is σ [S m^{-1}], whose electric permittivity is $\varepsilon_0\varepsilon_r$ [F m^{-1}] and whose magnetic permeability is μ_0 [H m^{-1}]. The vector potential is given by

$$A_{rf} \approx \sqrt{2\rho_t S/\sigma}\left(\exp(-\alpha_c y)/\omega_c\right)\cos\left[\omega_c(t - y/v_c)\right] \tag{18}$$

where S [W kg^{-1}] is the local S.A.R. and ρ_t [kg m^{-3}] is the local tissue density.

The attenuation coefficient is

$$\alpha_c = \left(\sigma/\sqrt{2}\right)\left[\left(\varepsilon_0/\mu_0\right)\left(\varepsilon_r + \sqrt{\varepsilon_r^2 + \sigma^2/\omega_c^2\varepsilon_0^2}\right)\right]^{-1/2} \tag{19}$$

and the phase velocity is

$$v_c = \left[\left(\varepsilon_0\mu_0/2\right)\left(\varepsilon_r + \sqrt{\varepsilon_r^2 + \sigma^2/\omega_c^2\varepsilon_0^2}\right)\right]^{-1/2} \tag{20}$$

The TEM wave is incident from the half space $y < 0$ (air) into the lossy semi-infinite medium (σ = 1 S m^{-1}, ε_r = 80 F m^{-1} and $\rho_t = 10^3$ kg m^{-3}), which fills the half space $y \geq 0$.

The carrier frequency is f_c = 915 MHz (i.e., in the range of interest for cellular telephones [7]). The putative process under consideration is the binding of Ca^{++} ion to a receptor protein located at x=z=0 and $y=0^+$. The e.m. sinusoidal exposure is switched on at $t=0^+$. Five Coulombic eingenfunctions have been used in the computer simulations. We choose an ideal putative protein characterized by $\omega_0 = 3\xi_B^2 M/8\hbar^3 \approx 2\pi f_c$, so that the e.m. photon matches, in energy, the depth of the ligand potential energy well.

In these conditions, after the initial transient, the binding probability $P(t)$ reaches an asymptotic behaviour $P_{as}(t)$ which is almost constant and differs from $P(0)$. Therefore it is convenient to consider the time average of P_{as}, i.e. $P_{av,\infty}$, which is constant, and to plot $[P(0) - P_{av,\infty}] / P(0)$ versus the incident power density I.P.D. [W m^{-2}] as a measure of the biological effectiveness of the r.f. exposure. A typical result is shown in fig. 4. It is apparent that if $\vec{F}_{bm} = -\nabla H_{bm}$ goes to zero (so that $\rho_0 = \rho_{th}$) there is no effect, irrespective of the level of the incident e.m. power. If $\vec{F}_{bm}$ is increased, the effect on the binding probability of the TEM exposure becomes significant, at power (or S.A.R.) values which are below the current safety standards. This result proves that low-intensity r.f. exposure can affect an elementary biological process in a living cell.

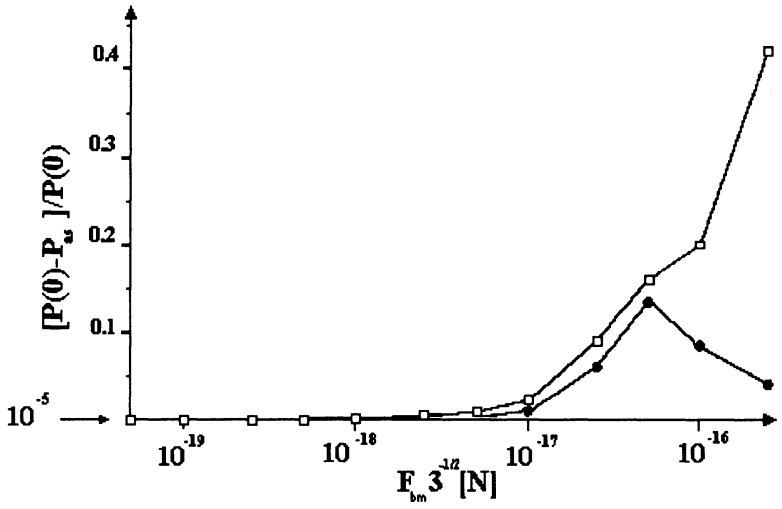

Figure 4. Relative excess change of the binding probability versus the modulus of $\vec{F}_{bm}$, assuming that $F_{bm,x}=F_{bm,y}=F_{bm,z}$. The exposure intensities are, respectively, 1 mW cm^{-2} (S.A.R. = 0.148 W kg^{-1}) (full circles) and 10 mW cm^{-2} (S.A.R. = 1.486 W kg^{-1}) (open squares). Some representative values of P(0) are 0.33 at $F_{bm,x,y,z}= 10^{-17}$ N, 0.43 at $F_{bm,x,y,z}= 5\ 10^{-17}$ N and 0.53 at $F_{bm,x,y,z}= 10^{-16}$ N.

6. Conclusions

We have laid down a biophysical basis for assessing the effects of low-intensity e.m. r.f fields on ligand binding to receptors, with specific emphasis on ion binding to a receptor protein as a first step of interaction.

Several topics have been analyzed by means of the quantum Z–S model:

1) The endogenous field inside a molecular structure has been characterized according to the protein database. The related endogenous force provides a strong nonlinearity in the state equations for the ion-protein system.

2) Any protein with a hydrophobic crevice is a putative candidate for hosting an effective interaction between low-intensity exposure and a binding ion, by providing low values of the classical collision frequency β, i.e., long quantum lifetimes.

3) Basal metabolism maintains the cell out of thermodynamic equilibrium [1, 2, 3]. At the molecular level, the metabolic activity maintains the ion-protein system itself out of thermodynamic equilibrium sustaining an excess ion velocity inside the binding crevice, and it supplies power to the system. This power can be converted, via the nonlinearity provided by the endogenous force, into signalling power "controlled" by the low-intensity e.m. exogenous field.

4) The contribution of thermal noise to the ion-protein binding probability has been taken into account in the presence and in the absence of e.m. exposure, whose effectiveness has been judged from the comparison of the two situations.

These results seem in contrast with those reported in [2, 3, 5] irrespective of the similar physical approach adopted. The differences can be better understood by resuming the electronic jargon.

The metabolic activity can *bias* the ion-protein system far enough from thermodynamic equilibrium, at an *operating point* of the nonlinear binding *characteristic* where the system may be potentially able to detect small e.m. signals. The system takes advantage of the *power supply* provided by the basal metabolism of the cell, much like transistor uses its power supply to amplify the time-varying signal applied to its input gate.

Therefore, in this paper we deal with a *transistor* analogy of processes in *living* cells ($\vec{E}_{bm} \neq 0$), whereas the approach developed in [5] deals with a *diode* analogy of processes in *dead* cells ($\vec{E}_{bm} = 0$). In fact, if the exogenous e.m. exposure is switched off, the systems considered in [3, 5] return to thermodynamic equilibrium, so that "it is difficult to make consistent biological effects with low fields strengths" in this case [5].

In conclusion, we have offered a plausible biophysical basis for potential effects of low-intensity e.m. fields.

7. References

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