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STOCHASTIC RESONANCES IN ACTIVE TRANSPORT IN BIOLOGICAL MEMBRANES* **

A. Fuliński

M. Smoluchowski Institute of Physics, Jagellonian University
Reymonta 4, 30-059 Kraków, Poland
e-mail: `fulinski@jetta.if.uj.edu.pl`; `http://zfs.if.uj.edu.pl`

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It is shown that experimental data (D.-S. Liu, R.D. Astumian, T.Y. Tsong, *J. Biol. Chem.* **265**, 7260 (1990)) on active transport of Na^+ in human erythrocytes (catalyzed by Na^+-K^+-ATPase) under the influence of external ac electric fields can be interpreted as the evidence of stochastic resonance between the external ac field and the fluctuations of the membrane potential (energy barrier of the process): the signal-to-noise ratio J/γ_i, where J is the ionic current (signal), γ_i — the intensity of intrinsic fluctuations (noise), exhibits strong maximum as the function of γ_i. The model calculations show that in the considered system one can expect the appearance of *(i)* inverse stochastic resonance, and of *(ii)* aperiodic stochastic resonance: *(i)* the ratio J/ψ_a *vs* intensity of external ac field ψ_a exhibits maximum in the presence of barrier fluctuations; *(ii)* the external periodic ac field can be replaced by the external random ac field (dichotomous Markovian noise in our calculations) of strength γ_e and inverse correlation time Λ_e, and the ratio J/γ_e vs. γ_e also exhibits a distinct maximum in the presence of internal fluctuations of the membrane potential. Note that the superposition of two Markovian dichotomous noises (internal fluctuations and external ac field) is equivalent to non-Markovian barrier fluctuations.

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1. Introduction

In last years a growing attention is paid to the kinetics of transitions over a fluctuating barrier [1]. Various physical, chemical, *etc.* processes, as well as various types of fluctuations were discussed in literature. The fluctuating

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barrier problem seems to be of interest especially for the kinetics of biophysical and biochemical enzymatic processes, which are governed by big protein molecules, undergoing complicated structural (conformational) transitions during their work. These structural changes are easily influenced by the random or regular changes in their environment, leading to the changes in the barrier height for the processes catalyzed by these proteins.

Random fluctuations and periodic oscillations of various physical parameters are common to the environment of biomolecules, especially in the vicinity of cell membranes. Membrane proteins (enzymes) play very important roles in mediating signal transduction, in transporting material to and from the living cells, *etc.*, and frequently function as free energy transductors in synthesizing some chemicals or in transporting ions against a free energy gradients. In carrying such functions, the protein undergoes a cycle of conformational transitions between different states which may have very different charge distributions. The action of such a molecule will thus be influenced strongly by membrane electrical potential: (*i*) the electric fields are greatly magnified in the lipid membrane, and (*ii*) the membrane prevents the enzyme from rotating freely and thus following the field.

Therefore membrane proteins can sense the fluctuations of electric fields, generated either by externally imposed ac fields, or by fluctuations of ionic concentrations, both thermal and resulting from the action of ion channels [2]. The membrane electric potential plays in such situations the role of activation energy (potential barrier), and it was shown that, when a membrane enzyme is electroconformationally coupled to an ac field (either regular or random), it can transduce energy from that field to force the catalyzed process to go against free energy gradient [3–6].

In our former paper [7] we have shown that the assumption of random fluctuations of the membrane potential is sufficient to explain existing experimental data on active ionic flow through cell membranes (catalyzed by ATPases) under the influence of external ac electric fields, which exhibit a distinct maximum of the flow (increase of flow about two- three times) for some range of frequencies [6, 8–10]. The feasibility of the fit implies that the experimental result (peak of $J(\omega)$ at $\omega_{\max}$) can be interpreted as the resonance between internal fluctuations and external oscillating field.

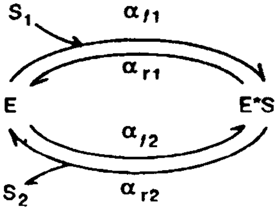
The enhancement of the action of the external regular field by stochastic field resembles the well-known effect of stochastic resonance [11–13], the phenomenon of an increase of the response of the system to the deterministic forcing by an increase in the input noise, occuring in systems subjected to both periodic and random driving. The most popular characteristics of this effect being commonly in use is the peak in the signal-to-noise ratio (SNR) as a function of the input noise strength, although the physics of this phenomenon is the transfer of energy into some physical process from the stochastic field (*noise*) with the assistance of the regular field (*pumping, signal*). The idea of SR was introduced for the first time as a plausible explanation, based on numerical simulations, of the recurrence of ice ages [11], and later discussed in many aspects, both purely theoretical and in application to several specific physical systems. SR is presently one of most popular subjects in the theory of stochastic processes, and the relevant literature is vast [12–14].

In this paper we are going to examine the model [3, 4, 7] describing the active ionic flow through cell membranes under the influence of external ac electric fields, and in the presence of random fluctuations of the membrane potential from the point of view of stochastic resonance. One of the aims is the search of effects which can be measured experimentally and therefore can substantiate the interpretation of the behaviour of transmembrane ionic flows in terms of stochastic resonance.

2. The model

As in [7], we consider the active transport of ions across membrane under the action of external ac field, and under the influence of spontaneous fluctuations of the membrane potential. We shall use the Astumian and Robertson (A–R) model [3, 4], constructed for the description of the effect of an ac electric field on the action and efficiency of the membrane proteins.

The A–R model describes the collection of identical protein molecules (enzymes E) in a planar bilayer membrane, each oriented in the same way, and each able to exist in two electrically distinct conformational states. Protein–protein interactions are assumed to be negligible. The overall enzyme cycle describing the whole catalyzed process is, schematically:



(2.1)

or, in short,

$$A \overset{E}{\rightleftarrows} B \tag{2.1a}$$

where E and E* represent different conformations of the enzyme. S_1 and S_2 may represent either two different chemical species (catalyzed production of the product S_2 from the substrate S_1), or the same species outside and inside the biological cell (active transport through the membrane). Each pathway may consist of several intermediate stages; also E and [E*S] may represent several different states in internal equlibrium.

A good measure of the rate and direction of the catalyzed process are the currents j_1, j_2 describing the instantaneous flows in the upper and lower pathways of the overall process, *i.e.*, the instantaneous rates of binding of S_1 and of S_2 to the enzyme E:

$$j_j = \alpha_{fj} S_j E - \alpha_{rj}[E^\star S] = (\alpha_{fj} S_j + \alpha_{rj})E - \alpha_{rj}\,, \tag{2.2}$$

where E, $[E^\star S]$ are the probabilities for the enzyme to be in the state E, [E*S], respectively ($E + [E^\star S] = 1$), S_1, S_2 represent the concentrations of the substances S_1, S_2, and $\alpha_{k,j}$ ($j = 1,2$, $k = f,r$) are the effective rate coefficients in different pathways. Sign of currents j_j is chosen for convenience: net transition $S_1 \to S_2$ will correspond to $j_1 > 0$, *etc.* The kinetic equation describing this process, *i.e.* the equation of change for the probability E reads:

$$\dot{E} = -j_1 - j_2 = -\sum_{j=1,2} \left[(\alpha_{fj} S_j + \alpha_{rj})E - \alpha_{rj}\right]. \tag{2.3}$$

From our present point of view, the most important feature of the chemical reactions of this type is the dependence of the rate coefficients $\alpha_{k,j}$ on the membrane potential ψ:

$$\alpha_{k,j} = \alpha^o_{k,j} e^{-D_{k,j}\psi}, \quad D_{k,j} = d_{k,j}\,\Delta x_j/RT\,, \tag{2.4}$$

where Δx_j is the effective charge transported across the membrane in the j-th pathway, ψ is the electrical potential difference across membrane, α^o are the rate coefficients for $\psi = 0$, $d_{f,j} = \delta_j$, $d_{r,j} = -(1 - \delta_j)$, and δ_j denote the apportionement constants, which split up the total effects of $\Delta x_j \psi$ between the forward and reverse process.

We shall consider the situation when the concentrations S_1, S_2 are held constant [9] (stationary condition). The electric field ψ across membrane is assumed to be composed of internal and external parts:

$$\psi = \psi_i + \psi_e\,, \tag{2.5}$$

ψ_i is fluctuating randomly around some average (static) value:

$$\psi_i = \psi_s + \gamma_i \xi_i(t)\,, \tag{2.6}$$

ψ_e is decomposed into static and alternating parts, and the latter is taken either in the simple sinusoidal form, or as the random dichotomous process, or both:

$$\psi_e = \psi_0 + \psi_a \cos(\omega t) + \gamma_e \xi_e(t)\,. \tag{2.7}$$

As previously, we shall approximate the stochastic parts by the dichotomous noise (DN), but in contrast to [7], we shall consider Markovian asymmetric DNs. Note that the linear combination of two Markovian DNs is equivalent to one non-Markovian four-state stochastic process. Therefore some of the results presented below can be interpreted also as the effect of non-Markovian barrier fluctuations.

3. Fluctuations

The stochastic parts are described by independent Markovian asymmetric dichotomous noises :

$$\xi_m(t) \in \{\Delta_{m,1}, -\Delta_{m,2}\}, \quad \langle \xi_m(t)\rangle = 0, \quad \langle \xi_m(t)\xi_n(t')\rangle = \delta_{m,n} e^{-\Lambda_m |t-t'|}, \quad m = i, e, \tag{3.1}$$

with $\Lambda_m = 1/\tau_{cm}$, τ_c being the noise correlation times, and with

$$\Delta_{m,1}\Delta_{m,2} \equiv \Delta_m^2, \quad \Delta_{m,1} - \Delta_{m,2} = \Delta_m^0, \quad \xi_m^2(t) = \Delta_m^2 + \Delta_m^0 \xi_m(t). \tag{3.2}$$

In the following we shall absorb intensity of the noises (measured by Δ_m^2) in the parameters γ_m, *i.e.*, we put formally $\Delta_m^2 = 1$.

Due to the last relation (3.2) (which is characteristic for any dichotomous noise), any function of $\xi(t)$ can be evaluated in a simple way. Especially,

$$\begin{aligned}\alpha_{k,j} = \tilde{\alpha}^o_{k,j} e^{-D_{k,j}\psi_e(t)}[F_i(\gamma_i D_{k,j}) &- \xi_i(t) G_i(\gamma_i D_{k,j})][F_e(\gamma_e D_{k,j}) \\ &- \xi_e(t) G_e(\gamma_e D_{k,j})],\end{aligned} \tag{3.3}$$

where $\tilde{\alpha}^o_{k,j} = \alpha^o_{k,j} \exp(-D_{k,j}\psi_s)$, and

$$G_m(x) = \frac{e^{\gamma_m \Delta_{m,2} x} - e^{-\gamma_m \Delta_{m,1} x}}{\Delta_{m,1} + \Delta_{m,2}}, \quad F_m(x) = e^{-\gamma_m \Delta_{m,1} x} - \Delta_{m,1} G_m(x). \tag{3.4}$$

The kinetic equation (2) thus reads:

$$\begin{aligned}\dot{E} &= [-a_{cc} + a_{cs}\xi_i(t) + a_{sc}\xi_e(t) - a_{ss}\xi_i(t)\xi_e(t)]E \\ &\quad + b_{cc} - b_{cs}\xi_i(t) - b_{sc}\xi_e(t) + b_{ss}\xi_i(t)\xi_e(t),\end{aligned} \tag{3.5}$$

where the coefficients are built of the functions (3.4). When $\psi_a \neq 0$ these coefficients are time-dependent.

4. Solution of kinetic equation

We follow here the method described in Ref. [7]: the kinetic equation (3.5) is averaged over the stochastic process (processes), and the Shapiro–Loginov theorem [15] is used for the evaluation of time derivatives of correlation functions appearing in the result of averaging. In effect, we get the set of four averaged kinetic equations:

$$\dot{\boldsymbol{W}}(t) = -\mathcal{P}(t)\cdot\boldsymbol{x}(t) + \boldsymbol{y}(t) \tag{4.1}$$

$$\mathcal{P}=\begin{pmatrix} a_{cc} & -a_{cs} & -a_{sc} & a_{ss} \\ -a_{cs} & \Lambda_i + a_{cc} - a_{cs}\Delta_i^0 & a_{ss} & -a_{sc} \\ -a_{sc} & a_{ss} & \Lambda_e + a_{cc} - a_{sc}\Delta_e^0 & -a_{cs} \\ a_{ss} & -a_{sc} + a_{cs}\Delta_i^0 & -a_{cs} + a_{sc}\Delta_e^0 & \Lambda_i + \Lambda_e + a_{cc} - a_{cs}\Delta_i^0 - a_{sc}\Delta_e^0 \end{pmatrix} \tag{4.2}$$

$$\boldsymbol{W}(t) = \begin{pmatrix} \langle E(t)\rangle \\ \langle E(t)\xi_i(t)\rangle \\ \langle E(t)\xi_e(t)\rangle \\ \langle E(t)\xi_i(t)\xi_e(t)\rangle \end{pmatrix}, \quad \mathbf{y(t)} = \begin{pmatrix} b_{cc} \\ -b_{cs} \\ -b_{sc} \\ b_{ss} \end{pmatrix}. \tag{4.3}$$

In the absence of external periodic field ($\psi_a = 0$) these coefficients are time-independent and the stationary solution is trivial:

$$\boldsymbol{W}_\infty = \mathcal{P}^{-1}\cdot\boldsymbol{y}\,. \tag{4.4}$$

For $\psi_a \neq 0$ the coefficients are periodic in time. In this case we approximate the periodic field by M rectangular impulses [7,16] (in practice, $M = 50$ gives very good accuracy):

$$\psi_{ac}(t) = \psi_m \quad \text{for} \quad t_{n,m} < t < t_{n,m+1}, \quad t_{n,m} = n\Delta + m\tau, \quad \tau = \Delta/M,$$

solve Eq. (4.1) between impulses, and sew together the solutions by the stroboscopic mapping:

$$\boldsymbol{W}_{n,m+1} = \mathcal{A}_m\cdot\boldsymbol{W}_{n,m} + \boldsymbol{X}_m\,, \quad \boldsymbol{W}_{n+1,1} = \mathcal{H}\,\boldsymbol{W}_{n,1} + \boldsymbol{Y}, \tag{4.5}$$

with

$$\mathcal{A}_m = e^{-\mathcal{P}_m\tau} = \mathcal{R}_m^{-1}\cdot e^{-\mathcal{L}_m\tau}\cdot\mathcal{R}_m\,, \quad \boldsymbol{X}_m = (\mathcal{I} - \mathcal{A}_m)\cdot\boldsymbol{y}_m\,,$$

$\mathcal{I}$ being the identity matrix, $\mathcal{L}$ – the diagonal matrix of eigenvalues ζ_i of the matrix $\mathcal{P}$, $\mathcal{R}\cdot\mathcal{P}\cdot\mathcal{R}^{-1} = \mathcal{L}$, and

$$\mathcal{H} = \prod_{m=1}^{M}\mathcal{A}_m, \quad \boldsymbol{Y} = \boldsymbol{X}_M + \sum_{l=1}^{M-1}\Big(\prod_{j=l}^{M-1}\mathcal{A}_{j+1}\Big)\boldsymbol{X}_l\,.$$

The asymptotic ($n \to \infty$) solution of the mappings (4.5) reads

$$\boldsymbol{W}_1^\infty = (\mathcal{I} - \mathcal{H})^{-1}\boldsymbol{Y} .$$

These formulae enable the calculation of the asymptotic values J of the current j_1^∞, Eq. (2.2), averaged over noise, and over period of the ac field, which is the measurable quantity:

$$J = \frac{1}{\Delta} \int\limits_{n\Delta}^{n\Delta+\Delta} \langle j_1(t) \rangle dt , \tag{4.6}$$

In [7] the formula (4.6) was fitted successfully (the fit is shown in Fig.3 below) to the existing experimental data on active flow of Na^+ ions through plasma membrane of human erythrocytes (catalysed by [Na,K]-ATPase) under the influence of an external ac electric field [9,6], for symmetric Markovian DN. Only intrinsic fluctuations $\xi_i(t)$ of the membrane potential were considered there.

5. Stochastic resonance

In [7] we have mentioned that the success of the fit shows that the experimental result (peak of $J_1(\omega)$ at $\omega_{\max}$) can be interpreted as the resonance between internal fluctuations and external oscillating field, especially because *(i)* the location of the peak (*i.e.*, the value of $\omega_{\max}$) depends mainly on the correlation time Λ_i^{-1} and on the intensity γ_i of the noise: increase of Λ_i or γ_i results in the increase of $\omega_{\max}$, *(ii)* the considered model cannot be fitted to the experimental data in the absence of the noise. We shall now prove that indeed this is the stochastic resonance, and we shall examine numerically this effect in more detail.

In numerical calculations we shall use the the values of the parameters of the model found in [7]. These are:
$\tilde{\alpha}_{f1}^o S_1 = 270$, $\tilde{\alpha}_{f2}^o S_2 = 5.4$, $\tilde{\alpha}_{r1}^o = 4.0$, $\tilde{\alpha}_{r2}^o = 0.11$, $\Delta x_1/RT = 3.48$, $\Delta x_2/RT = 5.24$, $\delta_1 = 0.499$, $\delta_2 = 0.500$.

For the symmetric Markovian DN (normalized to unity), the best-fit fluctuation parameters were: $\gamma_i/\psi_a = 5.15$, $\Lambda_i = 1300\ \mathrm{s}^{-1}$ (and $\gamma_e \equiv 0$).

In this section we shall examine the dependence of the stochastic resonance effect on various parameters describing different types of barrier fluctuations.

As we have said in the Introduction, the standard measure of SR being commonly in use is the appearance of the peak in the signal-to-noise ratio (SNR) vs. input noise strength. The directly measurable quantity, which can be used as the outcoming signal, is obviously the current J, Eq. (4.6): in the

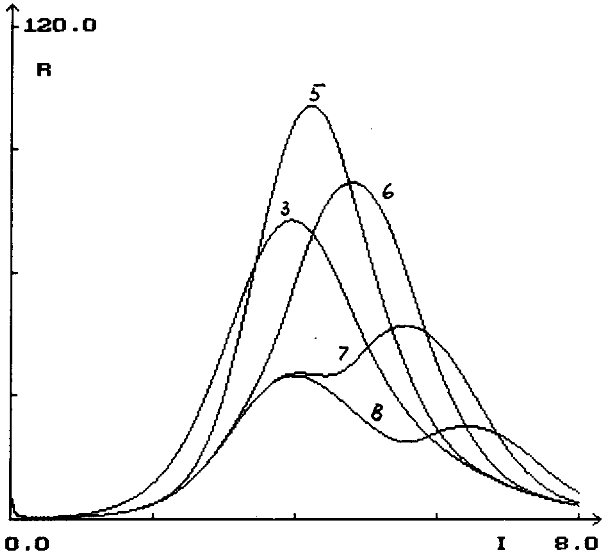


Fig. 1. Standard stochastic resonance: $R = J/\gamma_i$, $I = \gamma_i$, $\Lambda_i = 10^4$, $\psi_{ac} = 1$, dependence on frequency of driving periodic field $\omega = 10^n$ (curves are labeled by n), $\gamma_e = 0$.

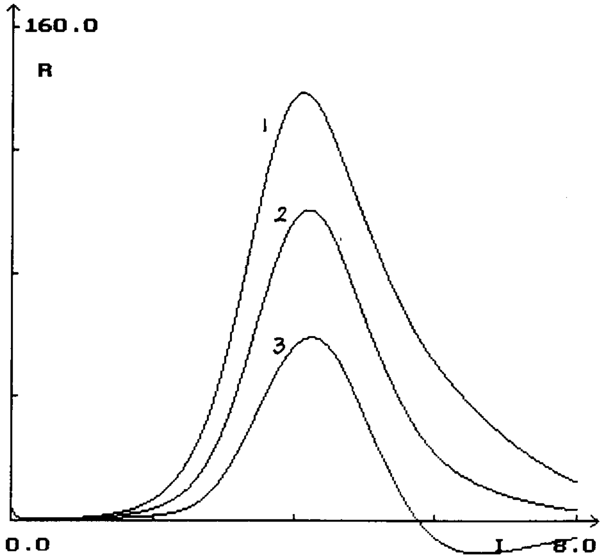


Fig. 2. As in Fig.1: dependence on the asymmetry of stochastic field: (1) $\Delta_i^0 = 0.005$, (2) $\Delta_i^0 = 0.0$, (3) $\Delta_i^0 = -0.005$.

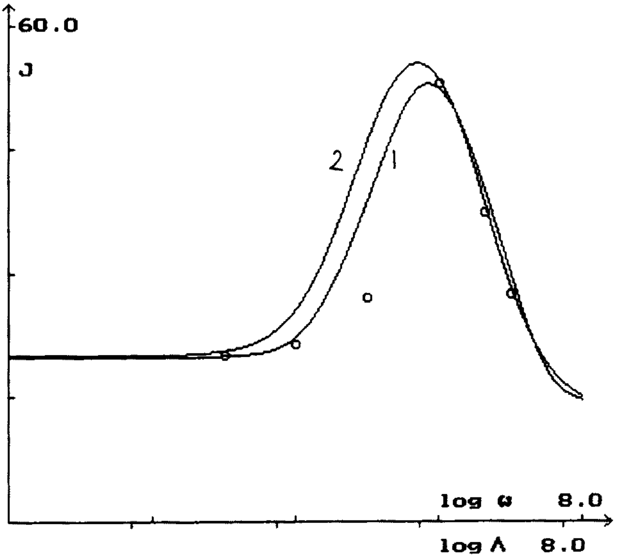


Fig. 3. Equivalence of stochastic and periodic driving ac fields: (1) periodic driving: $J(\omega)$ for $\psi_1 = 1$, $\gamma_e = 0$, (fit to experimental data [9]); (2) stochastic driving: $J(A_e)$ for $\gamma_e = 0.9$, $\psi_1 = 0$. $\Delta_0 = 0$, $\gamma_i = 5.15$, $A_i = 1300$. ○ denote experimental data [6, 7, 9].

absence of driving ac field the current is very low and negative, whereas in the presence of ac field current changes direction and increases in magnitude. The presence of stochastic field results in additional increase of current. The measure of the intensity I of the noise (of barrier fluctuations) ξ_m is the parameter γ_m. Figs. 1 and 2 show the SNR $R = J/\gamma_i$ vs. $I = \gamma_i$ in dependence on the frequency ω of the periodic ac field, and on the asymmetry Δ_i^0 of intrinsic fluctuations, in the absence of external stochastic ac field ($\gamma_e = 0$). The dependence of ratio of current to the noise intensity on the noise intensity shows the maximum characteristic for SR.

Instead periodic ac field, stochastic driving can be used. Fig.3 shows the equivalence of stochastic and periodic driving ac fields: — curve 1 presents the fit [7] of the model including intrinsic fluctuations (symmetric dichotomous noise $\xi_i(t)$ with parameters quoted above), driven by periodic ac field of variable frequency ω, to experimental data (circles) mentioned above. Curve 2 shows the behaviour of the same model driven by random external field (in this case the symmetric dichotomous random signal ξ_e) with $\gamma_e = 0.9$, and variable inverse correlation time A_e. The scaling of A_e *vs* ω is $A = 0.4\omega$ and is chosen in order to obtain the coincidence of peaks. These results show that suitably chosen random and periodic external fields produce very similar "resonance" between external field and intrinsic fluctuations.

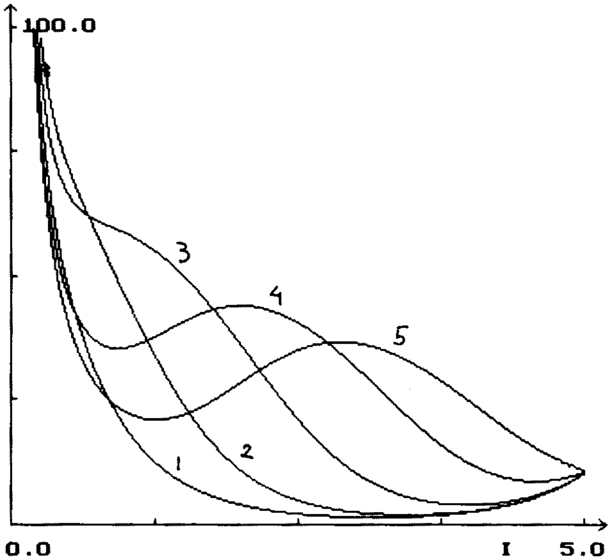


Fig. 4. Aperiodic stochastic resonance, $R = J/\gamma_e$, $I = \gamma_e$, $\psi_{ac} = 0$, $\gamma_i = 5.15$, $\Lambda_i = 1300$, dependence on the inverse correlation time Λ_e of external stochastic field: (1) $\Lambda_e = 10^7$, (2) $\Lambda_e = 10^6$, (3) $\Lambda_e = 10^5$, (4) $\Lambda_e = 10^4$, (5) $\Lambda_e = 10^3$. $\Delta_0 = 0$.

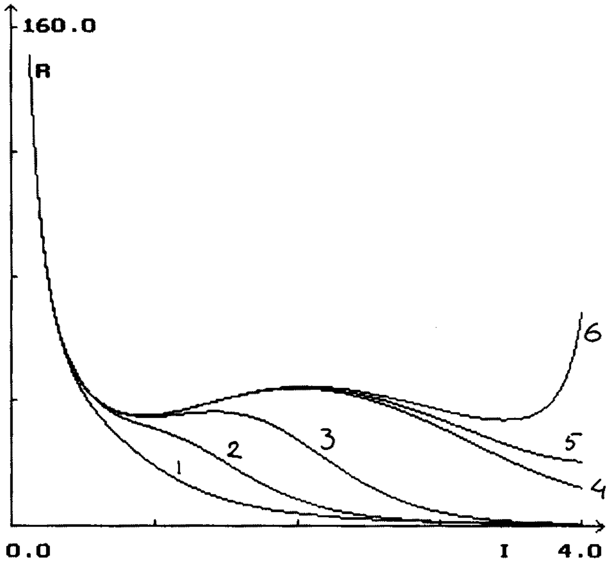


Fig. 5. As in Fig. 4 – dependence on the asymmetry of external stochastic field: (1) $\Delta_e^0 = -10^{-2}$, (2) $\Delta_e^0 = -10^{-3}$. (3) $\Delta_e^0 = -10^{-4}$, (4) $\Delta_e^0 = 0$, (7) $\Delta_e^0 = 10^{-6}$, (8) $\Delta_e^0 = 2 \cdot 10^{-6}$. $\Lambda_e = 10^4$.

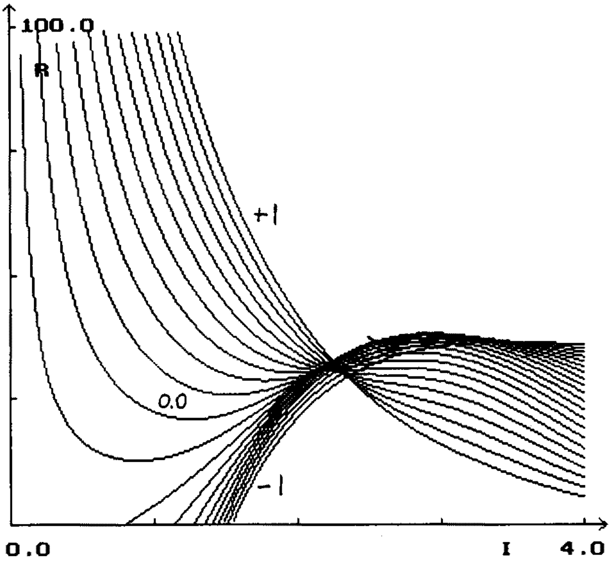


Fig. 6. As in Fig. 4 – dependence on external static field: $\psi_0 = 1.0, 0.9, \ldots - 0.9, -1.0$; $\Lambda_e = 10^4$, $\Delta_0 = 0$.

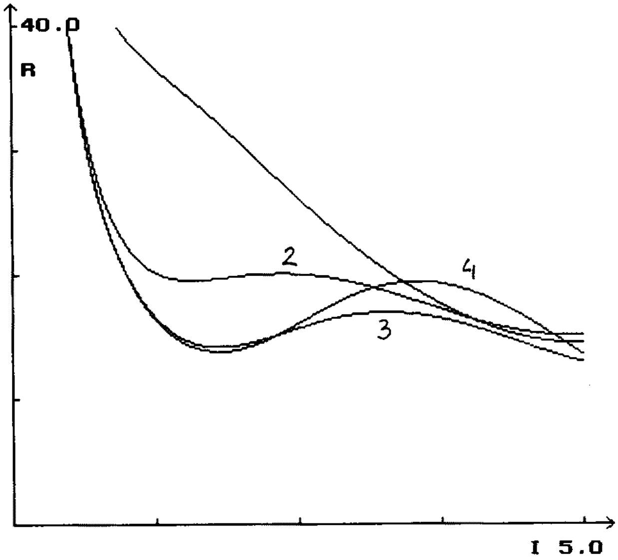


Fig. 7. Inverse stochastic resonance, $R = J/\psi_a$, $I = \psi_a$, one symmetric Markovian noise $\gamma_i = 5.15$, $\Lambda_i = 1300$, $\gamma_e = 0$, dependence on external periodic field: (1) $\omega = 10^5$, (2) $\omega = 10^4$, (3) $\omega = 10^3$, (4) $\omega = 1$.

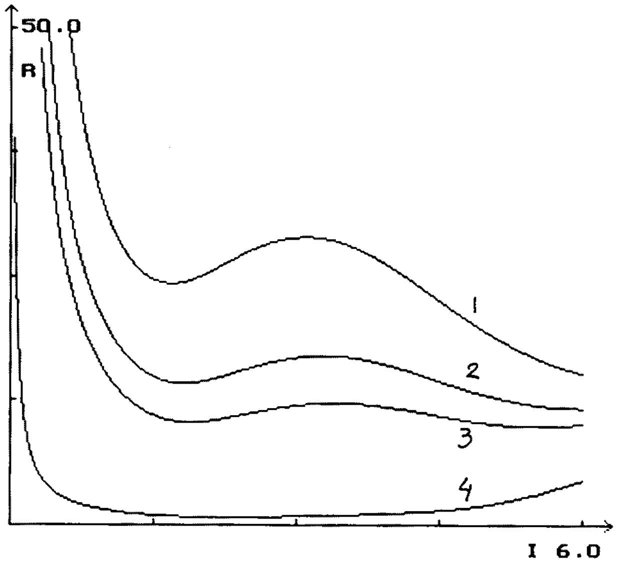


Fig. 8. As in Fig. 7 – $\gamma_i = 5.15$, $\omega = 10^3$, (1) $\Lambda_i = 2000$, (2) $\Lambda_i = 1300$, (3) $\Lambda_i = 1000$, (4) $\Lambda_i = 100$.

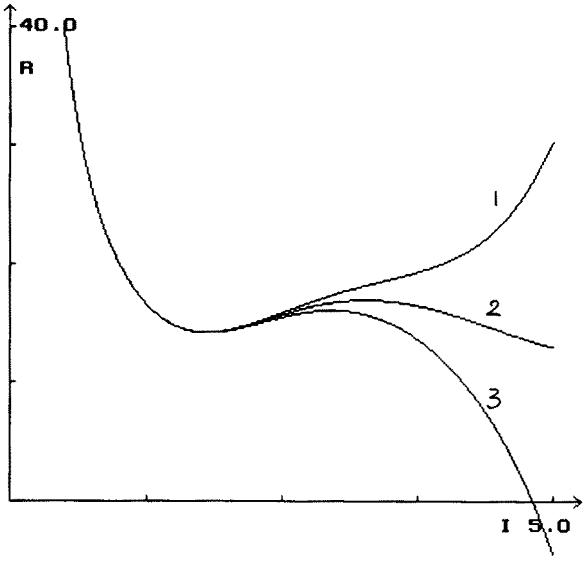


Fig. 9. As in Fig. 7 – asymmetric intrinsic noise: (1) $\Delta_i^0 = 10^{-6}$, (2) $\Delta_i^0 = 0.0$, (3) $\Delta_i^0 = -10^{-6}$; $\Lambda = 1300$.

The use of stochastic driving in the place of periodic one also leads to the appearance of distinct maxima in the plots of $R = J/\gamma_e$, with $I = \gamma_e$ (Figs. 4–6). These maxima can be interpreted as the *aperiodic stochastic resonance* (ASR) [13,14], being here the resonance between intrinsic and externally induced random fluctuations of the membrane potential. Figs. 4–6 show the dependence of ASR on parameters describing these fluctuations, and on the presence of external static field.

In the case discussed above the distinction between incoming signal and amplifying field is not so well-defined as in the case of standard SR — the roles of intrinsic and extrinsic fluctuations can be exchanged. This suggests the possibility of *inverse SR*: the search for maximum in the dependence of $R = J/\psi_a$ vs. $I = \psi_a$ in the presence of fluctuations. The results are shown in Figs. 7–9 for several combinations of the values of parameters describing periodic and stochastic fields. It is seen that indeed there is such inverse effect.

6. Final remarks

Although the A–R 2-state model (2.1)–(2.4) is the simplest model of the enzyme kinetics in cell membranes, it is fairly realistic. It explains the observed action of ac external field on the ionic current in the active ionic transport, especially the inversion of the direction and the increase of the magnitude of the active ionic transport. The original model [4,16] is not able to explain the frequency dependence of the current (of the presence of maximum of $J(\omega)$) in the experimental data, but the last effect can be reproduced by inclusion of random fluctuations of the membrane potential [7].

The results presented in this paper show that the effect of stimulation of biomembrane electric potential by external ac fields on the effectiveness of membrane ezymes — or at least on the active transport of Na^+ in human erythrocytes catalyzed by Na^+-K^+-ATPase [6,7,9] — can be interpreted as the stochastic resonance between the external ac field and the fluctuations of the membrane potential (energy barrier of the process): the dependence of signal-to-noise ratio on the intensity of intrinsic fluctuations (noise), exhibits strong maximum (Figs. 1, 2). Note that these fluctuations can be treated as the effective way of taking into account of many intermediate stages of the process (2.1) (configurations of the enzyme-reagent complex).

However, there is no simple controlled way of changing either the intensity γ_i of the intrinsic fluctuations of the membrane potential ("noise" in Figs. 1,2), nor their other characteristics. Therefore the results shown in Figs. 1,2 only suggest the possibility of the SR in transmembrane ionic transport. This deficiency can be remedied by the use of extrinsic random electric field inducing additional random fluctuations of the membrane potential. This in turn leads to the proposed above notions of *aperiodic stochastic resonance*, and *inverse stochastic resonance*. SR with aperiodic inputs was recently discussed by Collins *et al.* [14] (cf. also [13]). ASR and ISR effects can be used for the experimental verification of the presence, strength, and other characteristics of intrinsic fluctuations.

The drawback of the considered model seems to be its high sensitivity on asymmetry of the barrier fluctuations: for strong driving fields, *i.e.* for higher values of either γ_e or ψ_a the model becomes divergent even for very small values of the asymmetry parameter Δ_0 (cf. Figs. 5 and 9).

The noise intensities used in our calculations may seem to be rather high in comparison with the amplitude of the external periodic fields. However, as we have said in [7], the size of a biological cell is fairly small, and the size of one protein molecule is still much smaller, consequently the fluctuations of the number of ions in the immediate vicinity of an enzyme, even very small in macroscopic terms (of the order of thermal fluctuations), will appear big enough on the microscopic scale to cause fairly strong fluctuations in the electrical potential acting on this enzyme. Therefore it seems quite natural to expect that the random fluctuations in the enzyme potential barrier, caused by random fluctuations of ion numbers, can be bigger than the intensity of the regular changes in enzyme potential, caused by oscillations of the external driving field. More details can be found in the literature; extensive discussion is presented in Ref. [3].

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