Active Transport in Biological Membranes and Stochastic Resonances

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The role of intrinsic fluctuations of the membrane electric potential (barrier height) in the active transport of ions through cell membranes is examined. Experimental data [D.-S. Liu *et al.*, J. Biol. Chem. **265**, 7260 (1990)] on active transport of Na^+ in human erythrocytes under the influence of ac electric fields can be interpreted as the evidence of stochastic resonance between the external field and the fluctuations of the membrane potential. The calculations show that in the considered system one can expect also the appearance of aperiodic stochastic resonance. [S0031-9007(97)04653-X]

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The impact of intrinsic noise (spontaneous fluctuations) on biophysical and biochemical processes has been widely discussed in current literature (cf. [1–3], and references therein). However, as Simonotto *et al.* wrote in their most recent paper [1(c)], *though tantalizing, this idea* (that internal noise may serve a useful role) *remains undemonstrated in any biological experiment.*

Most of the papers cited above discuss collective behavior of ensembles of neurons (brain, neuronal networks) [1]. In turn, neuronal conductance is built of the orchestrated action of a multitude of ionic channels and ionic pumps. Internal noise in collective behavior of ensembles of ion channels is discussed in [2]. In this Letter we are going to show how to link the intrinsic noise with the measured behavior of ionic pumps. The aim is to supply an example of indirect evidence of the active presence of intrinsic fluctuations in biophysical processes and to propose experimental verification of this effect [4].

Among various biophysical processes, of utmost vital importance is the trafficking of two cations: Na^+ and K^+, between the cell interior and the environment [5]. Lipid bilayer, which forms the basic structure of all cellular membranes, is impermeable for electrolytes, and gradients across the plasma membrane are built and maintained by the operation of ATP-driven ion pumping while their dissipation proceeds via specific ion channels.

Both these types of transport depend on—among other factors—membrane electric potential (which plays the role of barrier height), and can be stimulated by both dc and ac external fields. Channel currents under stimulation exhibit strongly irregular character mostly of the dichotomous type (open-closed channel, [5,6]). Active current under stimulation by ac electric field exhibits distinct maximum both as the function of frequency and of voltage [7,8].

Intrinsic fluctuations may also play some role in the membrane enzymatic processes [3]. In our former paper [9] we have shown that the existing experimental data [7(a)] on active transport of Na^+ in human erythrocytes (catalyzed by Na^+-K^+-ATP-ase) under the influence of external ac electric fields can be interpreted in terms of the transfer of energy from the stochastic field (fluctuations of membrane potential) to the enzymatic system. This result can be interpreted [10] as the stochastic resonance (SR) between external periodic ac field of frequency ω and the intrinsic fluctuations ("noise") of the membrane potential. Figure 1 presents the ratio of the current J to noise intensity γ_i (signal-to-noise ratio, SNR) vs γ_i for a few values of ω [12].

SR is the phenomenon of an increase of the response of the system to the deterministic forcing by an increase of the noise. The most popular characteristic of this effect commonly in use is the peak in SNR vs 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*). SR is currently one of the most popular subjects in the theory of stochastic processes, and the relevant literature is vast [15,16].

The results shown in Fig. 1 look like typical SR. However, there are no experimental data which can be compared directly with these in Fig. 1. The intensity of intrinsic noise at constant temperature is also constant, so that adjusting the intrinsic noise directly seems to be difficult [1(a)]. On the other hand, the fluctuations of

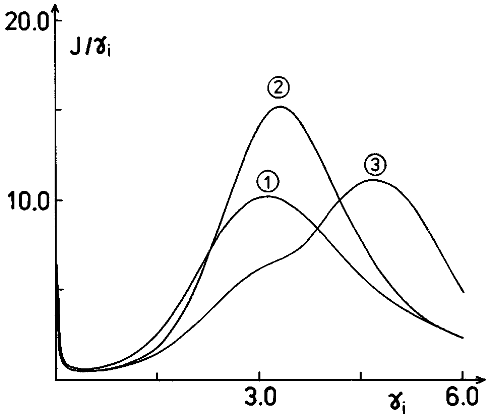

FIG. 1. Signal-to-noise ratio vs intrinsic noise intensity for the model of Ref. [9]; (1) $\omega = 10^3$, (2) $\omega = 10^4$, and (3) $\omega = 10^6$ Hz [11].

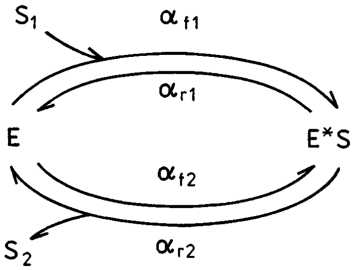

FIG. 2. Enzyme cycle of A-R model [3,13,14].

the local membrane potential in the vicinity of an ionic pump are caused by, among other reasons, the stochastic activity of ionic channels nearby [17]. In turn, the random opening/closing of passive ionic channels is stimulated by external electric fields, either ac or dc [5,6]. Therefore the increase of the field intensity V_e should result in the increase of the random currents from ionic channels, i.e., of the intrinsic noise ξ_i. We shall now argue that experimental data on $J(V_e)$ [7(a)] can be interpreted along these lines.

The shape of $J(\omega)$ can be fitted to an approximate solution of a more involved, four-state model [8] without fluctuations. However, this model predicts monotonic dependence of J vs intensity V_e and therefore is not able to explain the experimental shape of $J(V_e)$ [8(b)]. These data can be reproduced by our model [9] (cf. [12]) under one additional assumption: that the intensity γ_i of internal noise is a function of V_e, e.g., of the type

$$\gamma_i = \gamma_0 + \gamma_1 f(\psi_{\mathrm{ac}}), \tag{1}$$

where γ_0 represents spontaneous intrinsic fluctuations, γ_1 represents induced ones, and $\psi_{\mathrm{ac}} \sim V_e$ [11]. Good fit is found for $\gamma_i = 1 + 4.15\sqrt{\psi_{\mathrm{ac}}}$. The result [11] is shown in Fig. 3. Three types of dependence of J on ψ_{ac} are shown: $R = J$ (∘), $R = J/\gamma_i$ (*), and $R = J/\psi_{\mathrm{ac}}$ (×).

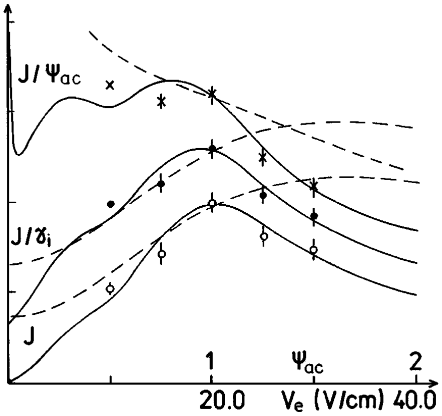

FIG. 3. Comparison of experimental data [7(a)] on $J(V_e)$ with the model [9] (cf. text for details). Dashed lines: $\gamma_i = 5.15$; full lines: $\gamma_i = 1 + 4.15\sqrt{\psi_{\mathrm{ac}}}$ (similar results have been obtained for $\gamma_i = 3.15 + 2\psi_{\mathrm{ac}}$). Bars denote standard deviation. To enable better comparison of variants, the curves are normalized at the peak and shifted upwards with respect to each other [11].

It is seen that the first two fit better than the third, which seems to support the SR interpretation of these results.

To check the hypothesis stated above, we propose to perform further measurements similar to those of Refs. [7], with stochastic external driving. To this aim, consider as previously [9] the Astumian and Robertson (A-R) model [3,13,14] with inclusion of internal and external stochastic fields. The A-R model, constructed for the description of the effect of an ac electric field on the action and efficiency of the membrane proteins, 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 shown in Fig. 2, and its kinetic equation reads

$$\dot{E} = -j_1 - j_2 = -\sum_{\sigma=1,2} [(\alpha_{f\sigma} S_\sigma + \alpha_{r\sigma})E - \alpha_{r\sigma}]. \tag{2}$$

E, $[E^\star S]$ are the probabilities for the enzyme to be in the state E, $[E^\star S]$, respectively, $(E + [E^\star S] = 1)$, S_1, S_2 represent the concentrations of the substances S_1, S_2 (e.g., Na^+ inside and outside the cell), and $\alpha_{\phi,\sigma}$ $(\sigma = 1, 2,\ \phi = f, r)$ are the effective rate coefficients in different pathways.

The most important feature of the chemical reactions of this type is the dependence of the rate coefficients $\alpha_{\phi\sigma}$ on the membrane potential ψ:

$$\alpha_{\phi\sigma} = \alpha^o_{\phi\sigma} e^{-D_{\phi\sigma}\psi}, \qquad D_{\phi\sigma} = d_{\phi\sigma}\Delta x_\sigma / RT, \tag{3}$$

where Δx_σ is the effective charge transported across the membrane in the σth pathway, ψ is the electrical potential difference across membrane, α^o are rate coefficients for $\psi = 0$, $d_{f,i} = \delta_\sigma$, $d_{r,\sigma} = -(1 - \delta_\sigma)$ are the apportionment constants which split up the total effects of $\Delta x_i \psi$ between the forward and reverse process. In principle, this model results from the reduction of several elementary processes (cf. [14]); therefore these quantities are to be treated as effective parameters.

The membrane potential is composed of static part ψ_0, intrinsic fluctuations $\xi_i(t)$, and external stochastic ac field $\xi_e(t)$ of dichotomous character:

$$\psi(t) = \psi_0 + \gamma_i \xi_i(t) + \gamma_e \xi_e(t), \tag{4}$$

$$\xi_l(t) \in \{\Delta_{1l}, -\Delta_{2l}\}, \qquad \langle \xi_l(t) \xi_m(t') \rangle = \delta_{l,m} e^{-\Lambda_l |t-t'|}, \tag{5}$$

$$\begin{gathered} \Delta_{1l} - \Delta_{2l} = \Delta_{0l}, \qquad \Delta_{1l} + \Delta_{2l} \equiv D_l, \\ \Delta_{1l}\Delta_{2l} \equiv \Delta_l^2, \end{gathered} \tag{6}$$

$$\begin{gathered} \langle \xi_1(t) \rangle = 0, \qquad \xi_l^2(t) = \Delta_l^2 + \Delta_{0l}\xi_l(t), \\ l, m = e, i, \end{gathered} \tag{7}$$

with $1/\Lambda_l$ being the noise correlation time. The intrinsic noise is assumed to be the same as that fitted above [9]; therefore it is symmetrical, $\Delta_{0i} = 0$.

Because of relations (7), any function of $\eta(t)$ can be evaluated in a simple way:

$$\begin{gathered} \alpha_{\sigma,k} = [\alpha^{ec}_{\sigma,k} + \xi_e(t)\alpha^{es}_{\sigma,k}][\alpha^{ic}_{\sigma,k} + \xi_i(t)\alpha^{is}_{\sigma,k}], \\ \alpha^{l,\beta}_{\sigma,k} = \tilde{\alpha}_{\sigma,k} \exp(z_{\sigma,k}\psi_e) f^{l,\beta}_{\sigma,k}, \\ (\beta = c,s)\tilde{\alpha}_{\sigma,r} = \alpha^o_{\sigma,r}, \quad \tilde{\alpha}_{\sigma,f} = \alpha^o_{\sigma,f} S_\sigma, \\ f^{l,s}_{\sigma,k} = D_l^{-1}(e^{\gamma_l z_{\sigma,k}\Delta_{1l}} - e^{-\gamma_l z_{\sigma,k}\Delta_{2l}}), \\ f^{l,c}_{\sigma,k} = D_1^{-1}(\Delta_{2l} e^{\gamma_l z_{\sigma,k}\Delta_{1l}} + \Delta_{1l} e^{-\gamma_l z_{\sigma,k}\Delta_{2l}}). \end{gathered} \tag{8}$$

As in [9], Eq. (2) is averaged over ξ_i and/or ξ_e, and the Shapiro-Loginov theorem [18] is used for the evaluation of the resulting equations for correlation functions:

$$\dot{\mathbf{W}} = -\mathcal{A} \cdot \mathbf{W} + \mathbf{y} \tag{9}$$

$$\mathcal{A} = \begin{pmatrix} a_{cc} & a_{cs} & a_{sc} & a_{ss} \\ a_{cs} & \Lambda_i + a_{cc} & a_{ss} & a_{sc} \\ a_{sc} & a_{ss} & \Lambda_e + \tilde{a}_{cc} & a_{cs} \\ a_{ss} & a_{sc} & \tilde{a}_{cs} & \Lambda_i + \Lambda_e + \tilde{a}_{cc} \end{pmatrix} \tag{10}$$

$$\mathbf{W}(t) = \begin{pmatrix} \langle E(t) \rangle \\ \langle E(t)\xi_i(t) \rangle \\ \langle E(t)\xi_e(t) \rangle \\ \langle E(t)\xi_i(t)\xi_e(t) \rangle \end{pmatrix}, \qquad \mathbf{y}(t) = \begin{pmatrix} b_{cc} \\ b_{cs} \\ b_{sc} \\ b_{ss} \end{pmatrix}, \tag{11}$$

$$\begin{gathered} a^\sigma_{\beta\nu} = \sum_k b^{\sigma,k}_{\beta\nu}, \qquad b^{\sigma k}_{\beta\nu} = \alpha^{e\beta}_{\sigma,k}\alpha^{i\nu}_{\sigma,k}, \\ a_{\beta\nu} = a^1_{\beta\nu} + a^2_{\beta\nu}, \\ b_{\beta\nu} = b^{1r}_{\beta\nu} + b^{2r}_{\beta\nu}, \qquad \tilde{a}_{c\beta} = a_{c\beta} - a_{cs}\Delta_{0e}, \\ \beta, \nu = c, s. \end{gathered}$$

In the absence of external periodic ac field the stationary solution of the kinetic equation (9) reads

$$\mathbf{W}_\infty = \mathcal{A}^{-1} \cdot \mathbf{y}, \tag{12}$$

and the stationary current is

$$\begin{aligned} J &= \lim_{t\to\infty} \langle j_1(t) \rangle \\ &= a^1_{cc} W_{1\infty} + a^1_{cs} W_{2\infty} + a^1_{sc} W_{3\infty} + a^1_{ss} W_{4\infty} - b^{1r}_{cc}. \end{aligned} \tag{13}$$

In numerical calculations the values of the parameters of the model found in [9] have been used. These are $\tilde{\alpha}_{f1} = 270$, $\tilde{\alpha}_{f2} = 5.4$, $\tilde{\alpha}_{r1} = 4.0$, $\tilde{\alpha}_{r2} = 0.11$, $\Delta x_1/RT = 3.48$, $\Delta x_2/RT = 5.24$, $\delta_1 = 0.499$, $\delta_2 = 0.500$, $\gamma_i/\psi^o_{\text{ac}} = 5.15$ ([11]), $\Lambda_i = 1300\ \text{s}^{-1}$.

Figure 4 shows the equivalence of stochastic and periodic driving: dashed curve presents the fit [9] of the model including intrinsic fluctuations driven by periodic ac field of variable frequency ω, to experimental data (circles) [7(a)]. Curves 1 and 2 show the behavior of the same model driven by random external field (in this case the symmetric dichotomous random signal ξ_e) with variable Λ_e.

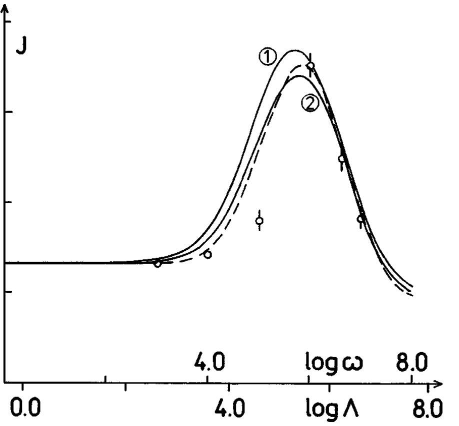

FIG. 4. Equivalence of periodic (dashed line) and stochastic (full lines) driving. o: experimental data [7(a),8]; bars denote standard deviation. $\gamma_i = 5.15$, $\Lambda_i = 1300$; (1) $\gamma_e = 0.9$, (2) $\gamma_e = 0.8$. The scaling $\Lambda = 0.4\omega$ is chosen in order to obtain the coincidence of peaks [11].

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 $I = \gamma_e$ (Fig. 5). These maxima can be interpreted as the *aperiodic stochastic resonance* (ASR) [16], being here the resonance between intrinsic and externally induced random fluctuations of the membrane potential.

The results presented in Figs. 3 and 4 give the indirect evidence of the constructive role of intrinsic noise in one of fundamental biophysical processes, viz. active ionic transport. This evidence can be verified by further measurements along the lines suggested in Figs. 1 and

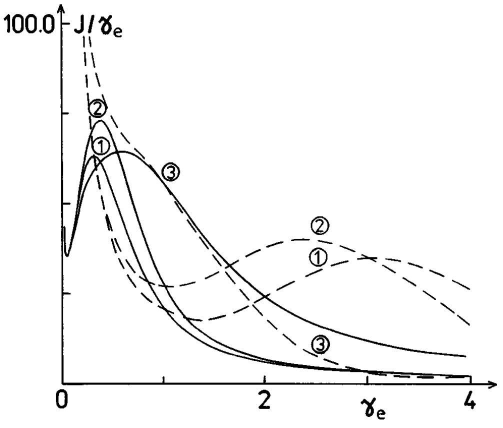

FIG. 5. Aperiodic stochastic resonance. Dashed lines: $\gamma_i = 5.15$; full lines: $\gamma_i = 1 + 4.15\sqrt{\psi_{\text{ac}}}$. Differences between full and dashed lines may serve for experimental verification of induction of intrinsic noise. $\Lambda_i = 1300$; (1) $\Lambda_e = 400$, (2) $\Lambda_e = 4000$, and (3) $\Lambda_e = 400\,000$ [11].

5, by repeating experiments of Ref. [7] with external ac field of dichotomous character [19]. Such a field, with required characteristics (intensity, correlation time, asymmetry), is easy to construct experimentally, and has more variable parameters than a periodic ac field. The hyphothesis of the dependence of the intensity of intrinsic fluctuations of the membrane potential on the intensity of external electric fields via the induction of the activity of ionic channels can be checked by the use of the *ligand and voltage sensitivity* of the latter: the equilibrium between "open" and "closed" states can be perturbed by transmembrane voltage (dc field) and/or the presence of specific chemical substances [5]. Another check is possible by experimental setup excluding from the picture the influence of channels (and other ionic pumps), e.g., by immersing a single ATP-ase in an artificial membrane.

Dependence of ASR on asymmetry of an external stochastic ac field and on a dc external field is not discussed here for the lack of space. However such dependence also can be used in the experimental check of conjectures formulated in this Letter.

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[12] In these calculations the model of Ref. [9] was used—it consists of Fig. 2 and Eqs. (2)–(13) below with membrane potential $\psi(t)$ given by $\psi(t) = \psi_0 + \psi_{\mathrm{ac}} \cos(\omega t) + \gamma_i \xi_i(t)$ instead of Eq. (4), therefore with $W_3 \equiv 0 \equiv W_4$, and with $\mathcal{A} = \mathcal{A}(t)$. The details of solution of kinetic equations for this case are given in Refs. [10,13].

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