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Spatial distribution of ion channel activity in biological membranes: the role of noise

P. Babinec*, M. Babincová

Department of Biophysics and Chemical Physics, Comenius University, Mlynská dolina F1, 842 48 Bratislava, Slovakia

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Abstract

A new approach is proposed to model a collective ion channel dynamics. We have assumed that ion channels create a two-component spatio-temporal interaction field. Every channel at its current spatial location in membrane contributes permanently to this field with its state (open or closed) and coupling strength to other channels. This field is described by a reaction–diffusion equation, the transition of ion channel from closed to open state (and vice versa) is described by a master equation, and migration of channels in membrane is described by a set of Langevin equations coupled by the interaction field. Within this model, we have investigated critical conditions for spatial distribution of ion channel activity. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Ion channels; Collective phenomena; Nonlinear dynamics; Noise

1. Introduction

Voltage-gated ion channels are proteins responsible for the generation of electrical signals in nerve and other excitable cells. They work by selectively conducting ionic currents through impermeable membranes [1]. Generally, the channels can switch between different conformational states, which are conducting (open) or nonconducting (closed), with voltage-dependent rates of transition. One consequence of the voltage-dependent transition rates is the intrinsic noise an ensemble of channels generates, which may lead to nontrivial dynamics. The suggestion that the noise may be a source of order rather than disorder, and that a biological organism makes use of energy-driven fluctuations for the purpose of signal and free-energy transduction was put forward almost 10 years ago by Astumian et al. [2]. In a recent study [3], the fluorescence of a rat neurons stained with the voltage-sensitive dye were optically excited in synchrony with electric stimulation of the cell, and recorded with a high spatial resolution. During an action potential, the fluorescence patterns exhibited clusters of different sizes corresponding to a non-homogeneous distribution of electric field across the membrane. To gain insight into this and related problems, we have in this study further developed our model of ion channel collective dynamics [4].

2. Stochastic model of channel state change and migration

Let us consider a two-dimensional spatial system with the total area A, with N ion channels. Each of them can be in one of two opposite states (open and closed), denoted as $\theta_i = \pm 1$; $i = 1,\ldots,N$. Here, θ_i is considered as a channel parameter, representing an *internal degree of freedom*. Within a stochastic approach, the probability $p_i(\theta_i,t)$ to find the channel i with the state θ_i, changes in the course of time due to the following master equation:

$$\frac{\mathrm{d}}{\mathrm{d}t}p_i(\theta_i,t) = \sum_{\theta_i'} w(\theta_i \mid \theta_i')p_i(\theta_i',t) - p_i(\theta_i,t)\sum_{\theta_i'} w(\theta_i' \mid \theta_i). \qquad (1)$$

Here, $w(\theta_i' | \theta_i)$ means the transition rate to change the state θ_i into one of the possible states, θ_i', during the next time step, with $w(\theta_i|\theta_i) = 0$. In the considered case, there are only two possibilities, either $\theta_i = +1 \rightarrow \theta_i' = -1$, or $\theta_i = -1 \rightarrow \theta_i' = +1$. We will start with a simple assumption that the change of states depends on the "impact factor" I_i, and a noise intensity quantified by a "*generalized temperature*" T

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[*] Corresponding author. Fax: +42-12-6541-2305.
E-mail address: babinec@fmph.uniba.sk (P. Babinec).

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(more precisely, we should write $k_{\mathrm{B}}T$ for the noise intensity, but for simplicity we have put Boltzmann constant $k_{\mathrm{B}} = 1$). At the thermal equilibrium, the generalized temperature is identical with the ordinary Boltzmann temperature, but in biomembranes may be significant additional stochastic fields of various origins, therefore the generalized temperature may be significantly higher than ordinary temperature. This excess of noise may lead, e.g. to the increase of signal-to-noise ratio, which is known as stochastic resonance effect [5].

A possible ansatz for the transition rate reads:

$$w(\theta_i' \,|\theta_i) = \eta \, \exp\{I_i/T\}. \tag{2}$$

Here, η[1/s] defines the time scale of the transitions.

Within a simplified approach, every channel can be ascribed a single parameter, the "strength", s_i. Furthermore, an ion channel distance d_{ij} may be defined, which measures the distance between each two channels (i,j) in a *biomembrane space*, which does not necessarily coincide with the physical space. It is assumed that the impact factor between two channels decreases with the distance in a nonlinear manner. The above assumptions are included in the following ansatz:

$$I_i = -\theta_i \sum_{j=1,\, j\neq i}^{N} s_j \theta_j / d_{ij}^n \; + e\theta_i, \tag{3}$$

$n > 0$ is a model constant and e is the external influence, which may be regarded as a global preference towards one of the states. The long-range coupling between ion channels arises from membrane-mediated direct energy interactions [6], and also from global capacitative coupling [7]. As a basic element of our theory, a scalar *spatio-temporal interaction field* $h_\theta(\mathbf{r},t)$ is used. Every channel contributes permanently to this field with its state θ_i and with its strength s_i at its current spatial location $\mathbf{r}_i$. The interaction generated this way has a certain life time $1/\beta$[s], further, it can spread throughout the system by a diffusion-like process, where D_h [m^2/s] represents the diffusion constant for interaction exchange. We have to take into account that there are two different states in the system, hence the interaction field should also consist of two components.

The spatio-temporal change of the interaction field can be summarized in the following equation:

$$\begin{aligned}\frac{\partial}{\partial t} h_\theta(\mathbf{r},t) = \sum_{i=1}^{N} s_i \; \delta_{\theta,\theta_i} \; \delta(\mathbf{r}-\mathbf{r}_i) - \beta h_\theta(\mathbf{r},t) \\ + D_h \Delta h_\theta(\mathbf{r},t).\end{aligned} \tag{4}$$

Here, δ_{θ,θ_i} is the Kronecker Delta, indicating that the channels contribute only to the field component which matches their state θ_i. $\delta(\mathbf{r}-\mathbf{r}_i)$ means Dirac's Delta function used for continuous variables, which indicates that the channels contribute to the field only at their current position, $\mathbf{r}_i$.

The interaction field $h_\theta(\mathbf{r},t)$ influences the channel i as follows: at a certain location $\mathbf{r}_i$, the channel in the state $\theta_i = +1$ is affected by two kinds of interaction; the interaction resulting from channels which are in the same state, $h_{\theta=+1}(\mathbf{r}_i,t)$, and the interaction resulting from the channels with the opposite states $h_{\theta=-1}(\mathbf{r}_i,t)$. The diffusion constant D_h determines how fast the interaction spreads, and the decay rate β determines, how long a generated interaction will exist.

For the change of states, we can generalize the transition probability, Eq. (2), by replacing the impact factor I_i with the influence of the local interaction field. A possible ansatz reads:

$$\begin{aligned} w(\theta_i' \mid \theta_i) &= \eta \, \exp\{[h_{\theta'}(\mathbf{r}_i,t) - h_\theta(\mathbf{r}_i,t)]/T\} \\ w(\theta_i \mid \theta_i) &= 0 \end{aligned} \tag{5}$$

As in Eq. (2), the probability to change state θ_i is rather small, if the local field $h_\theta(\mathbf{r}_i,t)$, which is related to the support of state θ_i, overcomes the local influence of the opposite state. This effect, however, is scaled again by the generalized temperature T, which is a measure for the randomness in channel interaction. Note that this temperature is measured in units of the interaction field.

The complete dynamics of the ensemble of ion channels can be formulated in terms of the canonical N-particle distribution function

$$P(\underline{\theta},\underline{r},t) = P(\theta_1,\mathbf{r}_1,\ldots,\theta_N,\mathbf{r}_N,t), \tag{6}$$

which gives the probability to find the N channels with the states $\theta_1,\ldots,\theta_N$ in the vicinity of $\mathbf{r}_1,\ldots,\mathbf{r}_N$ on the biomembrane surface A at time t. Considering both state changes and movement of the channels, the master equation for $P(\underline{\theta},\underline{r},t)$ reads:

$$\begin{aligned}\frac{\partial}{\partial t} P(\underline{\theta},\underline{r},t) = \sum_{\underline{\theta}' \neq \underline{\theta}} \Big[& w(\underline{\theta} \mid \underline{\theta}')P(\underline{\theta}',\underline{r},t) \\ & - w(\underline{\theta} \mid \underline{\theta}')P(\underline{\theta},\underline{r},t)\Big] \\ & - \sum_{i=1}^{N} \big[\nabla_i(\alpha \nabla_i h_\theta(\mathbf{r},t) P(\underline{\theta},\underline{r},t)) \\ & - D_n \Delta_i P(\underline{r},\underline{\theta},t)\big].\end{aligned} \tag{7}$$

The first line of the right-hand side of master describes the "gain" and "loss" of channels (with the coordinates $\mathbf{r}_1,\ldots,\mathbf{r}_N$) due to state changes, where $w(\theta|\theta')$ means any possible transition within the state distribution θ', which leads to the assumed distribution $\underline{\theta}$. The second line describes the change of the probability density due to the motion of the channels on the surface. Eq. (7) together with Eqs. (4) and (5) forms a complete description of our system.

3. Critical conditions for spatial separation of ion channel activity

Starting with the canonical N-particle distribution function, $P(\underline{\theta},\underline{r},t)$, Eq. (7), the spatio-temporal density of channels with state θ can be obtained as follows:

$$n_\theta(\mathbf{r},t) = \int \sum_{i=1}^{N} \delta_{\theta,\theta_i}\ \delta(\mathbf{r}-\mathbf{r}_i) \times P(\theta_1,\mathbf{r}_1\ldots,\theta_N,\mathbf{r}_N,t)\ d\mathbf{r}_1\ldots d\mathbf{r}_N. \tag{8}$$

Integrating Eq. (7) according to Eq. (8) and neglecting higher order correlations, we obtain, using the transition rates from Eq. (5), the following reaction–diffusion equation for $n_\theta(\mathbf{r},t)$

$$\frac{\partial}{\partial t} n_\theta(\mathbf{r},t) = -\nabla\left[n_\theta(\mathbf{r},t)\alpha\nabla h_\theta(\mathbf{r},t)\right] + D_n\Delta n_\theta(\mathbf{r},t) - \sum_{\underline{\theta}'\neq\underline{\theta}}[w(\theta'\mid\theta)n_\theta(\mathbf{r},t) + w(\theta\mid\theta')n_{\theta'}(\mathbf{r},t)]. \tag{9}$$

With $\theta=\{+1,-1\}$, Eq. (9) is a set of two reaction–diffusion equations, coupled both via $n_\theta(\mathbf{r},t)$ and $h_\theta(\mathbf{r},t)$. Inserting the densities $n_\theta(\mathbf{r},t)$ and neglecting any external preferences, Eq. (4) for the spatial interaction field can be transformed into the linear deterministic equation:

$$\frac{\partial}{\partial t} h_\theta(\mathbf{r},t) = s n_\theta(\mathbf{r},t) - \beta h_\theta(\mathbf{r},t) + D_h\Delta h_\theta(\mathbf{r},t). \tag{10}$$

The solutions for the spatio-temporal distributions of channels and states are now determined by the four coupled equations, Eqs. (9) and (10). For our further discussion, we assume again that the spatio-temporal interaction field relaxes faster than the related distribution of channels into a quasi-stationary equilibrium. From Eq. (10), we find with $(\partial/\partial t)h_\theta(\mathbf{r},t)=0$ and $D_h=0$:

$$h_\theta(\mathbf{r},t) = \frac{s}{\beta} n_\theta(\mathbf{r},t), \tag{11}$$

which can now be inserted into Eq. (9), thus reducing the set of coupled equations to two equations.

The homogeneous solution for $n_\theta(\mathbf{r},t)$ is given by the mean densities:

$$\bar{n}_\theta = \langle n_\theta(\mathbf{r},t)\rangle = \frac{\bar{n}}{2}. \tag{12}$$

Under certain conditions however, the homogeneous state becomes unstable and a spatial separation of ion channel activity occurs. In order to investigate these critical conditions, we allow small fluctuations around the homogeneous state $\bar{n}_\theta$:

$$n_\theta(\mathbf{r},t) = \bar{n}_\theta + \delta n_\theta; \quad \left|\frac{\delta n_\theta}{\bar{n}_\theta}\right| \ll 1. \tag{13}$$

Inserting Eq. (13) into Eq. (9), a linearization gives:

$$\frac{\partial \delta n_\theta}{\partial t} = \left[D_n - \frac{\alpha s \bar{n}}{2\beta}\right]\Delta\delta n_\theta + \left[\frac{\eta\ s\ \bar{n}}{\beta T} - \eta\right](\delta n_\theta - \delta n_{-\theta}). \tag{14}$$

With the ansatz

$$\delta n_\theta \sim \exp(\lambda t + i\mathbf{k}\mathbf{r}) \tag{15}$$

we find the dispersion relation $\lambda(\mathbf{k})$ for inhomogeneous fluctuations with wave vector $\mathbf{k}$:

$$\lambda_1(\mathbf{k}) = -k^2 C + 2B; \lambda_2(\mathbf{k}) = -k^2 C \tag{16}$$

$$B = \frac{\eta\ s\ \bar{n}}{\beta T} - \eta; \ C = D_n - \frac{\alpha s \bar{n}}{2\beta}.$$

For homogeneous fluctuations, we obtain from Eq. (16)

$$\lambda_1 = \frac{2\ \eta\ s\ \bar{n}}{\beta T} - 2\ \eta; \quad \lambda_2 = 0 \quad \text{for;}\ \mathbf{k}=0, \tag{17}$$

which means that the homogeneous system is marginally stable as long as $\lambda_1<0$, or $s\ \bar{n}/\beta T<1$. The condition $B=0$ defines a *critical generalized temperature*

$$T_1^{\mathrm{c}} = \frac{s\ \bar{n}}{\beta}. \tag{18}$$

For temperatures $T<T_1^{\mathrm{c}}$, the homogeneous state $n_\theta(\mathbf{r},t)=\bar{n}/2$, where channels of both states are equally distributed, becomes unstable and the spatial separation process occurs. This is in direct analogy to the phase transition obtained from the Ising model of a ferromagnet. Here, the state with $T>T_1^{\mathrm{c}}$ corresponds to the *paramagnetic* or disordered phase, while the state with $T<T_1^{\mathrm{c}}$ corresponds to *ferromagnetic* ordered phase.

The conditions of Eq. (17) denote a *homogeneous* stability condition. To obtain stability against inhomogeneous fluctuations of wave vector $\mathbf{k}$, the two conditions $\lambda_1(\mathbf{k})\leq 0$ and $\lambda_2(\mathbf{k})\leq 0$ have to be satisfied.

Taking into account the critical temperature T_1^{c}, Eq. (18), we can rewrite these conditions, Eq. (16), as follows:

$$\mathbf{k}^2(D_n - D_n^{\mathrm{c}}) - 2\eta\left(\frac{T_1^{\mathrm{c}}}{T} - 1\right) \geq 0 \tag{19}$$

$$\mathbf{k}^2(D_n - D_n^{\mathrm{c}}) \geq 0.$$

Here, a *critical diffusion* coefficient, D_n^{c} results from the condition $C=0$:

$$D_n^{\mathrm{c}} = \frac{\alpha}{2}\frac{s\bar{n}}{\beta}. \tag{20}$$

Hence, the condition $D_n>D_n^{\mathrm{c}}$ denotes a second stability condition. In order to explain its meaning, let us consider that the diffusion coefficient of the channels D_n, may be a function of the generalized temperature T. This is reasonable since the generalized temperature is a measure of randomness in channel interaction, and an increase of such a randomness leads to an increase of a random spatial migration. The simplest relation for a function $D_n(T)$ is the linear one, $D_n = \mu T$. By assuming this, we may rewrite Eq. (19) using a *second critical temperature*, T_2^{c} instead of a critical diffusion coefficient D_n^{c}:

$$\mathbf{k}^2 \mu (T - T_2^{\mathrm{c}}) - 2\eta \left(\frac{T_1^{\mathrm{c}}}{T} - 1 \right) \geq 0 \tag{21}$$

$$\mathbf{k}^2 \mu (T - T_2^{\mathrm{c}}) \geq 0.$$

The second critical temperature, T_2^{c}, reads as follows:

$$T_2^{\mathrm{c}} = \frac{\alpha}{2\mu} \frac{s\bar{n}}{\beta} = \frac{\alpha}{2\mu} T_1^{\mathrm{c}}. \tag{22}$$

The occurrence of two critical temperatures T_1^{c} and T_2^{c} allows a more detailed discussion of the stability conditions. Therefore, we have to consider two separate cases: (1) $T_1^{\mathrm{c}} > T_2^{\mathrm{c}}$ and (2) $T_1^{\mathrm{c}} < T_2^{\mathrm{c}}$. In the first case, $T_1^{\mathrm{c}} > T_2^{\mathrm{c}}$, we can discuss three ranges of the temperature T:

(i) For $T > T_1^{\mathrm{c}}$, both eigenvalues $\lambda_1(\mathbf{k})$ and $\lambda_2(\mathbf{k})$, Eq. (16), are nonpositive for all wave vectors, $\mathbf{k}$, and the homogenous solution $\bar{n}/2$ is *completely stable*.

(ii) For $T_1^{\mathrm{c}} > T > T_2^{\mathrm{c}}$ the eigenvalue $\lambda_2(\mathbf{k})$ is still nonpositive for all values of $\mathbf{k}$, but the eigenvalue $\lambda_1(\mathbf{k})$ is negative only for wave vectors that are larger than some critical value $\mathbf{k}^2 > \mathbf{k}_c^2$:

$$\mathbf{k}_{\mathrm{c}}^2 = \frac{2\eta}{\mu T} \frac{T_1^{\mathrm{c}} - T}{T - T_2^{\mathrm{c}}}. \tag{23}$$

This means that, in the given range of temperatures, the homogeneous solution $\bar{n}/2$ is *metastable* in an infinite system, because it is stable only against fluctuations with large wave numbers, i.e. against small-scale fluctuations. Large-scale fluctuations destroy the homogeneous state and result in a spatial separation process, i.e. instead of a homogenous distribution of states, channels with the same state form separated *spatial domains* which coexist.

(iii) For $T < T_2^{\mathrm{c}}$ both eigenvalues $\lambda_1(\mathbf{k})$ and $\lambda_2(\mathbf{k})$ are positive for all wave vectors $\mathbf{k}$, which means that the homogeneous solution $\bar{n}/2$ is completely unstable. On the other hand, systems with spatial dimension $L < 2\pi/k_c$ are stable in this region.

In the second case, $T_1^{\mathrm{c}} < T_2^{\mathrm{c}}$, which corresponds to $\alpha > 2\mu$, already small inhomogeneous fluctuations result in an instability of the homogenous state for $T < T_2^{\mathrm{c}}$, i.e. we have a direct transition from the completely stable to the completely unstable regime at the critical temperature $T = T_2^{\mathrm{c}}$.

In conclusion, we would like to note that our model of collective ion channel dynamics only sketches some basic features of structure formation in excitable biomembrane systems. There is no doubt, that in the real living cells, a more complex behavior among the ion channels occurs, and may depend on numerous influences beyond a quantitative description. One especially interesting direction of the further development is analysis of the possible orchestration of ion channel fluctuations by a cytoskeleton in a cooperative manner [8,9] in a squid's giant axons. The first step is to analyse subthreshold dynamics in periodically stimulated axons [10] in the framework of our model. Our next step would be the study of channels noise in neurons of the superficial medial entorhinal cortex, which are responsible for delivering information to the hippocampus via the perforant path. These neurons exhibit subthreshold oscillations in membrane potential at a frequency 8 Hz [11].

We hope that our model may give rise to further investigations in this exciting field of bioelectrochemistry.

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References

[1] B. Hille, Ionic Channels of Excitable Membranes, Sinauer Associates, Sunderland, 1992.

[2] R.D. Astumian, P.B. Chock, T.Y. Tsong, H.V. Westerhof, Effects of oscillations and energy-driven fluctuations on the dynamics of enzyme catalysis and free energy transduction, Phys. Rev. A 39 (1989) 6416–6435.

[3] P. Gogan, I. Schmiedel-Jakob, Y. Chitti, S. Tyč-Dumont, Fluorescence imaging of local membrane fields during the excitation of single neurons in culture, Biophys. J. 69 (1995) 299–310.

[4] P. Babinec, M. Babincová, Collective dynamics of ion channels in biological membranes, Gen. Physiol. Biophys. 15 (1996) 65–69.

[5] R.D. Astumian, J.C. Weaver, R.K. Adair, Rectification and signal averaging of weak electric fields by biological cells, Proc. Natl. Acad. Sci. U. S. A. 92 1995, pp. 3740–3743.

[6] U. Hianik, V.A. Buckin, B. Piknová, Can a single bacteriorhodopsin molecule change the structural state of one liposome? Gen. Physiol. Biophys. 13 (1994) 493–501.

[7] R.F. Fox, Y.N. Lu, Emergent collective behavior in large numbers of globally coupled independently stochastic ion channels, Phys. Rev. E 49 (1994) 3421–3431.

[8] Y. Hanyu, G. Matsumoto, Spatial long-range interactions in squid giant axons, Physica D 49 (1991) 198–213.

[9] W.D. Griggs, Y. Hanyu, G. Matsumoto, Cultured giant fiber lobe of squid expresses three distinct potassium channel activities in selective combinations, J. Membr. Biol. 152 (1996) 25–37.

[10] D.T. Kaplan, J.R. Clay, T. Manning, L. Glas, M.R. Guevara, A. Shrier, Subtreshold dynamics in periodically stimulated squid giant axons, Phys. Rev. Lett. 76 (1996) 4074–4077.

[11] J.A. White, R. Klink, A. Alonso, A.R. Kay, Noise from voltage-gated ion channels may influence neuronal dynamics in the entorhinal cortex, J. Neurophysiol. 80 (1998) 262–269.