Collective Properties of the Exactly Solvable Model of Ion-Channel Assemblies in a Biological Cell Membrane

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The behaviour of a system of ion channels formed across the cell membrane is presented. The infinite number of channels with an infinite coupling is introduced first as a reference point for the detailed derivation of the thermal-equilibrium probability distribution and the classification of the phase transitions. Fluctuations in a finite system are discussed next. We propose a new, step-like model of the ion channel switching, for which we provide the analytical results. The relation of this model to experiment is also provided. Finally, the master equation for the finite channel-number membrane is analysed numerically with the help of an exact-diagonalization technique. In particular, the decay-time of a metastable solution is estimated. The results do not agree with those obtained perturbationally, the difference is explained by the proposed frozen-diffusion approach.

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1. Introduction

All living cells are effectively separated from the environment by the lipids that constitute the cell membrane. The lipid bilayer formation and its dynamics have been recently objects of an intensive molecular dynamics studies [1]. However, ions such as sodium Na\(^+\) or potassium K\(^+\) can interact with proteins in the cell membrane that transport the ions across the membrane. Ion channels are one of the three types of proteins involved in the ion transport; the others are the pumps and the carriers. Approximately, an equal portion of the ionic current passes through each of these routes [2].

Classic experiments using the patch clamp technique showed an interesting stochastic behaviour of the ion channels that is controlled by the voltage across the membrane [3]. For example, this behaviour is crucial for the phenomena of neural excitability [4]. The fractal model of ion channel kinetics was formulated [5] and widely discussed in relation to the Markov
model [6]. Recently, Kramers’ diffusion theory has been considered as an alternative to those models [7]. One should also mention a significant improvement in the data analysis [8] namely, a new method was developed for the identification of deterministic structure in the time series, such as obtained from the patch clamp experiments, and successfully applied to the hearth disease and the epilepsy research.

In all above experimental and theoretical analyses, the kinetics of the single ion-channel was investigated. In this paper we discuss collective effects in both infinite-size system (Sec. 3), and realistic system (Sec. 4-6) of a few-hundred coupled ion channels along the cell membrane. We discuss the so-called step-like empirical model of the ion-channel switching affected by the voltage across the membrane that is based on that proposed by Hodgkin and Huxley [4], but is much simpler and approximately rationalises the experimental data for the potassium and the sodium channels [9].

2. Model and the physical system

In this section we discuss a simple model of ion channel switching and apply it to the system of \( m \)-channels across the membrane (see Fig. 1).

The ion channels are formed by specific membrane proteins which undergo a spontaneous, voltage-sensing conformational transitions between the open and the closed states [10]. Hereinafter, we will concentrate on isolated assembly of \( m \) ion channels of one type, i.e. potassium \( \text{K}^+ \). Let us suppose the simplest 2-state Markov model of the single channel switching (this is not a strict supposition, because such a model is equivalent to the \( m+1 \) -state Markov model of the whole membrane, cf. Sec. 4). In this model such a channel is characterised by two microscopic parameters determined by the voltage \( V_m \) across the membrane: the inverse average open- and closed times (\( \lambda_{\text{open}} = \lambda_{\text{open}}(V_m) \), and \( \lambda_{\text{closed}} = \lambda_{\text{closed}}(V_m) \), respectively). Physically, parameters \( \lambda_{\text{open}} \) and \( \lambda_{\text{closed}} \) are measured indirectly in a time series obtained from patch clamp experiment for single channel [3], whereas \( V_m \) is the driving parameter controlled in such an experiment. Subsequently, the expectation value of the fraction of opened channels \( \langle n_{\text{open}} \rangle \) obey the two-state, “open-closing” dynamics [4]:

\[
\frac{d}{dt} \langle n_{\text{open}} \rangle = \lambda_{\text{open}}(1 - \langle n_{\text{open}} \rangle) - \lambda_{\text{closed}} \langle n_{\text{open}} \rangle.
\]

For the sake of convenience, one can define the decay constant \( \lambda = \lambda_{\text{open}} + \lambda_{\text{closed}} \) (that provides natural timescale of the processes), and the probability of single channel open \( p_{\text{open}} = \lambda_{\text{open}} / \lambda \), which allow us to rewrite eq. (1) in form:

\[
\frac{1}{\lambda} \frac{d}{dt} \langle n_{\text{open}} \rangle = p_{\text{open}} - \langle n_{\text{open}} \rangle.
\]
In further considerations, parameter $\lambda = \lambda(V_m)$ is regarded as constant, and used to define the dimensionless time:

$$\tau = \lambda t.$$ (3)

One can verify this approximation for a broad range of voltage across the membrane $V_m$ by looking at the experimental data (see Table 1). With this simplification, only one microscopic parameter $p_{\text{open}}(V_m)$ remains.

Our starting assumptions, concerning the electrical properties of the membrane (see Fig. 1), are as follows: (i) the conductance of the membrane is directly proportional to the number of open channels, i.e. its resistivity

![Fig. 1. The patch clamp experiment version for a $m$-channel membrane and the corresponding electric circuit. The membrane parameters are: $I_p$ - the constant current of the ionic pumps, $R_G$ - the resistivity for the ionic diffusion across the membrane, $C$ - the membrane capacity, and $R_m$ - the $m$-channel system resistivity when all the channels open. For further considerations we suppose, that the system is connected to the external voltage $V$ and resistivity $R$. Below: the effective circuit for long-timescale processes in the membrane ($t \gg R_G C$). The effective external voltage $V_{\text{eff}}$ and resistivity $R_{\text{eff}}$ are defined in the main text.](image)
Table 1. Microscopic parameters of single potassium channel from human ocular epithelial cells (after Twohig, Ref. [9]).

| Membrane potential $V_m$ [mV] | Ave. open time $1/\lambda_{open}$ [ms] | Ave. closed time $1/\lambda_{closed}$ [ms] | Time unit $1/\lambda$ [ms] | Prob. of open chan. $p_{open}$ |
|-----------------------------|---------------------------------------|------------------------------------------|----------------------------|-----------------------------|
| -20                         | 14.57                                 | 1.58                                     | 1.425                      | 0.098                       |
| -30                         | 11.84                                 | 2.04                                     | 1.740                      | 0.147                       |
| -40                         | 5.18                                  | 3.62                                     | 2.131                      | 0.411                       |
| -50                         | 5.42                                  | 5.42                                     | 2.710                      | 0.500                       |
| -60                         | 3.94                                  | 8.06                                     | 2.646                      | 0.672                       |
| -70                         | 2.72                                  | 15.46                                    | 2.313                      | 0.850                       |
| -80                         | 1.77                                  | 39.37                                    | 1.694                      | 0.957                       |
| -90                         | 1.71                                  | 60.32                                    | 1.663                      | 0.973                       |

is equal to $R_m/n_{open}$, where $R_m$ is the resistivity when all the channels are open, (ii) the total current of the ionic pumps $I_p$ is constant, (iii) the voltage-induced ionic diffusion across the membrane is described by the linear resistivity $R_G$, (iv) the relevant time-scale is that of long-time processes $t \gg R_G C$, where $C$ is the membrane capacity, and (v) whole the system (i)-(iv) is coupled to the constant voltage $V$ source with internal resistivity $R$.

After introducing all above suppositions, a direct application of the Kirchhoff’s laws to the electric circuit shown in Fig. 1 proves its equivalence to the effective circuit, which contains only an assembly of switching channels coupled to the external voltage $V_{eff}$ and the resistivity $R_{eff}$:

$$V_{eff} = \frac{V - RI_p}{1 - R/R_G}; \quad R_{eff} = \frac{R}{1 - R/R_G}.$$  \hfill (4)

The calculation of the relation between the voltage across the membrane $V_m$ and the fraction of open channels $n_{open}$ for the effective electric circuit is straightforward and yields

$$V_m = \frac{V_{eff}}{1 + n_{open}R_{eff}/R_m}.$$  \hfill (5)

This allows us to consider the probability of a single channel open as a function $p_{open} = p_{open}(n_{open})$, since $V_m$ is a function of $n_{open}$ (5). Moreover, instead of applying phenomenological models of single channel switching $p_{open}(V_m)$, such that proposed by Hodgkin and Huxley [4], we can now consider indirectly a model function $p_{open}(n_{open})$, describing the assembly of coupled ion channels themselves.
Namely, for a qualitative analysis of the membrane, one can select any model function \( p_{\text{open}}(n_{\text{open}}) \) that retains principal properties of physical system, such as negative feedback (which means that channel remains closed for high polarising voltage \( V_m \) and open for low, see [9]), and have convenient analytical properties. In Sec. 4-6 we apply the step-like function

\[
p_{\text{open}}(n_{\text{open}}) = \left( 1 + e^{B(n_0 - n_{\text{open}})} \right)^{-1},
\]

where \( B \) and \( n_0 \) are adjustable parameters, which allow us to perform some integrations analytically. A brief comparison of the model of channel switching defined by the function (6) with some of available experimental data [9] are provided in Fig. 2. Strictly speaking, the relation inverse to (5) permitted us to write the probability of channel open as a function of voltage again, i.e.

\[
p_{\text{open}}(V_m) = \left( 1 + e^{A + V_0/V_m} \right)^{-1},
\]

where \( A = B(n_0 + R_m/R_{\text{eff}}) \) and \( V_0 = -BV_{\text{eff}}R_m/R_{\text{eff}} \) are empirical parameters, constant for a particular type of ion channel (i.e. potassium channel for human ocular epithelial cells, see Fig. 2). Empirical parameters \( A \) and \( V_0 \) provides the relation between model parameters \( B, n_0 \) and the physical driving parameters \( V_{\text{eff}}, R_m/R_{\text{eff}} \) (see Fig. 1):

\[
V_{\text{eff}} = \frac{V_0}{Bn_0 - A}, \quad R_m/R_{\text{eff}} = A/B - n_0.
\]

![Fig. 2. Comparison between the step-like model of ion channel switching for the fitted empirical parameters \( A = -3.85 \pm 0.78 \) and \( V_0 = -142 \pm 30 \) mV (see main text for a detailed description) and the experimental data for human ocular epithelial cells listed in Table 1.](image-url)
In effect, the selection of the probability of channel open in the form (6) constitutes the step-like model, which, as we just shown, rationalises the experimental data of Ref. [9].

3. Deterministic system: long-range coupled infinite membrane

In this section we consider the limiting case of the membrane with infinite number of channels \((m \to \infty)\), and far from a critical point [11]. For such a system one can suppose that the probability distribution is narrow and, subsequently, the fraction of open channels \(n_{\text{open}}\) is close to its average value \(n_{\text{open}} \approx \langle n_{\text{open}} \rangle\). With this assumption (which will be verified in the next section), we can write down an approximate version of Eq. (2) as follows

\[
\frac{d}{d\tau} n_{\text{open}} = p_{\text{open}}(n_{\text{open}}) - n_{\text{open}},
\]

(9)

where \(\tau\) is a dimensionless time (3). Equation (9) becomes exact in limit \(m \to \infty\) (except in the case when the system undergoes the 2-nd order phase transition), as a mean-field solution of the systems with the infinite coupling [11].

For all the models of ion channel switching [9], qualitatively similar to that defined by (6), eq. (9) could have from one to three stationary solutions \(n_{\text{open}}(\tau) = n_*\), that obey the relation (cf. Fig. 3)

\[
p_{\text{open}}(n_*) = n_*.
\]

(10)

For each of these solutions, one can consider its stability against small fluctuations \(n_{\text{open}} = n_* + \delta n\), by making a proper linearization of the relation

![Fig. 3. Stable and unstable stationary solutions \(n_* = p_{\text{open}}(n_*)\) of the dynamical equation for the infinite membrane (see main text). The step-like model of ion channel switching is applied.](image-url)
(10):
\[ p_{\text{open}} (n_{\text{open}}) = p_{\text{open}} (n_* + \delta n) = n_* + p'_* \delta n + \mathcal{O} (\delta n^2), \]  
(11)

where \( p'_* \) is the first derivative of the probability as a function of the fraction of open channels: \( p'_* = p'_{\text{open}} (n_*) \). The equation (11), after substituting to the dynamical eq. (9) provides us with an approximate result (for \( \delta n \ll 1 \)):

\[ \delta n(\tau) = \delta n(0) e^{-(1-p'_*) \tau}. \]  
(12)

This result simply means, that the first derivative of the probability \( p'_* \) in the stationary point \( n_* \) defined by the relation (10), allows us to identify stable (for \( p'_* < 1 \)) and unstable (for \( p'_* < 1 \)) stationary solutions of the dynamical eq. (9) (see Fig. 3). The threshold value \( p'_* = 1 \) will be shown to correspond with the critical point in terms of 2-nd order phase transition in the next section.

The approach presented above provides us two equivalent stable solutions (see Fig. 3). In the next section we will start the considerations for finite number of channels \( m \), and will verify (in Sec. 5) one of these stable points to be actually metastable, with a finite decay time growing exponentially with \( m \).

4. Stationary probability distribution for a finite membrane

Let us consider the finite, \( m \) ion channel cell membrane, and the evolution of its probability distribution \( P = \{ P_k \} \), (where \( k = 0, \ldots, m \) is the number of open channels, and the normalization condition \( \sum_k P_k = 1 \) is satisfied) in time. All the probability flows between \( k \)-th point and two neighbouring points are shown symbolically on Fig. 4.

In the limit of the stationary probability distribution \( P^{(0)} = \{ P_k^{(0)} \} \) one can write down the detailed-balance equation between \( k-1 \) and \( k \) points (cf. Fig. 4) in the form

\[ (m-k+1)p_{k-1}P_{k-1}^{(0)} - k(1-p_k)P_k^{(0)} = 0 \]  
(13)

for each \( k = 1, \ldots, m \), where \( p_k \) is the probability of open channel when \( k \) channels are open, \( p_k = p_{\text{open}}(k/m) \) (see Sec. 2). For non-zero probability distribution (this seems to be natural supposition for physical systems and will be verified a posteriori) one can rewrite Eq. (13) in the form

\[ P_k^{(0)} = \frac{m-k+1}{k} \frac{p_{k-1}}{1-p_k} P_{k-1}^{(0)}, \]  
(14)

for \( k = 1, \ldots, m \), that determines the stationary probability distribution \( P^{(0)} = \{ P_k^{(0)} \} \) except of the multiplicative constant \( P_0^{(0)} \), which has to be
adjusted to conserve normalization \( \sum_{k} P_k^{(0)} = 1 \). Eq. (14) provides the powerful tool for estimating numerically the stationary probability distribution for \( m \)-channel system with given model of ion channel switching \( p_{\text{open}}(n) \). Moreover, in Appendix A, using Eq. (14), we discuss small fluctuations around the stationary solutions (10) for a general model \( p_{\text{open}}(n) \).

The numerical results, presented in Fig. 5, as well as an approximate formula for small fluctuations (A.8), derived in App. A, suggest the approximate analytical way of solving detail balance equations for large \( m \). In this limit, one can look for universal function \( f(k/m) \), such that

\[
P_0(n) = e^{m(f(n)+C_m)}.
\] (15)

In Eq. (15) we define a *quasi-continuous* variables: fraction of open channels \( n = k/m \), and the stationary probability distribution function \( P_0(n) \), defined by relation \( P_k^{(0)} = P_0(k/m)\Delta n \), where \( \Delta n = 1/m \). \( C_m \) is an adjustable parameter, so that function \( P_0(n) \) (15) satisfy the normalization condition \( \int_{0}^{1} dn P_0(n) = 1 \). One can roughly estimate the value of \( C_m \) by making Gaussian approximation around the global maximum of \( f \): \( f(n) \approx f_{\text{max}} - f''_{\text{max}}(n - n_{\text{max}})^2/2 \), obtaining:

\[
C_m = -f_{\text{max}} + \frac{1}{2} \ln \frac{m}{n_{\text{max}}} + O(1/m).
\] (16)

**Fig. 4.** Time evolution of the probability distribution for finite \( m \)-channel membrane toward the stationary state \( \{P_k^{(0)}\} \). Index \( k = 0, \ldots, m \) is the number of open channels, the amounts of probability flowing between each pair of the points in the dimensionless time interval \( \Delta \tau \) are shown. The coefficients \( u_k \), \( v_k \) and \( p_k \) in probability flows are defined above.
Then, making an expansion

\[ mf(n - \Delta n) = m \left[ f(n) - \frac{df}{dn} \Delta n + \mathcal{O} \left( \Delta n^2 \right) \right] = mf(n) - \frac{df}{dn} + \mathcal{O}(1/m), \]

and substituting it into the detail-balance equations (14), we obtain:

\[ e^{-\frac{df}{dn}} = \frac{n}{1-n} \frac{1 - p_{\text{open}}(n)}{p_{\text{open}}(n)} + \mathcal{O}(1/m). \]

(18)

Eq. (18) in turn, provides the approximate differential equation for function \( f(n) \) (exact in the limit \( m \to \infty \)):

\[ \frac{df}{dn} = \ln \left( \frac{1 - n}{n} \frac{p_{\text{open}}(n)}{1 - p_{\text{open}}(n)} \right). \]

(19)

Fig. 5. Exact numerical solutions of the detailed-balance equations for different \( m \) compared with an analytical solution of corresponding differential equation for \( m \to \infty \) (see main text). The quasi-continuous probability distribution function is defined as \( P(n) = mP_k \), where \( n = k/m \). Above: symmetric step-like model of ion channel switching \((B = 5, n_0 = 0.5)\), below: an asymmetric case \((B = 5, n_0 = 0.49)\).
In particular, when looking for extrema of the function \( f(n) \) (the condition \( df/dn = 0 \)), which are equivalent to the extrema of the stationary probability distribution function \( P_0(n) \) (15), Eq. (19) reduces to the condition for stationary solutions of the deterministic equation of motion (9) \( n^* = p_{\text{open}}(n^*) \) (see Sec. 3). This provides the link between these two approaches.

Eq. (19) can be solved analytically for the step-like model of ion channel switching \( p_{\text{open}}(n) \) defined by Fermi-Dirac function (6):

\[
f(n) = -n \ln n - (1 - n) \ln(1 - n) + \frac{B}{2} (n - n_0)^2.
\]  

(20)

Plots of the function (20) for sample parameters \( B \) and \( n_0 \) are shown in Fig. 6. According to the formal correspondence of Eq. (15) with the prob-

Fig. 6. Free energy per channel in the step-like model of ion channel switching for different parameters \( B \) and \( n_0 \). Top panel: 2-nd order phase transition for symmetric case \((n_0 = 0.5)\) and varying \( B \). Bottom: the phase transition for fixed \( B = 5 \) and varying \( n_0 \) (note the presence of the secondary minimum on the left, corresponding to a metastable state).
ability distribution for Gibbs canonical ensemble [11]

\[ P_k = \frac{Z_k}{\sum_k Z_k} = e^{-\mathcal{F}(n,B,n_0)/\Theta}, \quad (21) \]

where \( Z_k \) is the sum of states above all \( \binom{m}{k} \) configurations for given number of open channels \( k \), \( \Theta \) is the reduced temperature, and \( \mathcal{F}(n,B,n_0) \) is the free energy of the system with given fraction of open channels \( n \), one can formally define the mean-field Ginzburg-Landau [11] free energy functional for \( m \to \infty \) limit (and subsequently \( n \approx \langle n \rangle \)):

\[ \mathcal{F}(n,B,n_0) = -mf(n). \quad (22) \]

Here we will concentrate only on the isothermal ensemble (\( \Theta = 1 \)), [12]. The definition (21) allows us to identify the candidates for 1-st and 2-nd order phase transitions (cf. Fig.6) in terms of Ginzburg-Landau theory [11]. However, when the parameter \( B \) is constant and \( n_0 \) varies, the configurational entropy of the system \( S_{\text{conf}} = \ln \binom{m}{k} \) does not change when the fraction of open channels \( n \) switch between two equivalent minima at the point \( n = 0.5 \), so this process also has to be considered as the 2-nd order phase transitions within the Ehrenfest classification scheme. The remarkable feature of this case is possible existence of a metastable state (cf. Fig.6), that motivated us to study the dynamics of the system in the next section.

5. Dynamics of the probability distribution via an exact diagonalization

In this section we derive the system of dynamical equations (the master equation), which describe time evolution of the probability distribution of the number of open channels for the \( m \)-channel membrane. We will also present results obtained when solving this system by using the numerical exact diagonalization technique. These results are substantial for further considerations, i.e. they are used to justify the approximate approach proposed in Sec. 6 for large systems.

Let us consider a discrete probability distribution for the \( m \)-channel membrane \( (P_k) \), where \( k = 0, \ldots, m \) is the number of open channels, and the normalization condition \( \sum_k P_k = 1 \) is satisfied (see Sec. 4). Taking into account probability flows between the \( k \)-th point and its two neighbours \( k - 1, k + 1 \) (see Fig. 4) one can write down the system of linear, ordinary differential equations:

\[ \frac{d}{d\tau} P_k = -\sum_{l=0}^{m} A_{kl} P_l, \quad (23) \]
where matrix \([A_{kl}]\) has a tridiagonal form

\[
A_{kl} = (u_k + v_k)\delta_{kl} - u_{k+1}\delta_{k+1,l} - v_{k-1}\delta_{k-1,l},
\]

\(\delta_{kl}\) is the Kronecker delta, \(u_k = k(1 - p_k)\), \(v_k = (m - k)p_k\) (see also Fig. 4), and the probabilities \(p_k = p_{\text{open}}(k/m)\) are given by the model of ion channel switching (cf. Sec. 2).

The system (23) can be simplified by the rescaling \(L_k = P_k/\alpha_k\), where coefficients \((\alpha_k)\) are defined for \(k = 1, \ldots, m\) by the recursive formula:

\[
\alpha_k = \sqrt{\frac{v_{k-1}}{u_k}} = \left(\frac{m - k + 1}{k} \frac{p_{k-1}}{p_k}\right)^{1/2},
\]

and \(\alpha_0\) remains a free multiplicative parameter. However, comparing the formula (24) and the detailed balance Eq. (14), one can choose \(\alpha_k = \sqrt{P_k^{(0)}}\) for \(k = 0, \ldots, m\) (cf. Sec. 4), and adjust \(\alpha_0\) appropriately. That form will be suitable for e.g. perturbation approach (see Sec. 6). In terms of variables \((L_k)\), the linear system (23) takes the form:

\[
\frac{d}{d\tau} L_k = -\sum_{l=0}^{m} B_{kl} L_l,
\]

where \([B_{kl}]\) is the symmetric, tridiagonal matrix with diagonal elements \(B_{kk} = u_k + v_k\), and off-diagonal \(B_{k-1,k} = -\alpha_k u_k/\alpha_{k-1} = -\sqrt{v_{k-1}u_k}\). For particular model of ion channel switching, in our case the step-like model (6), the matrix \([B_{kl}]\) can be diagonalized with standard numerical packages [13], up to \(m \approx 1000\). Presented technique allows us to examine time intervals as long as \(\tau \approx 10^{10}\) (3), unreachable by an indirect numerical methods of solving of the system (23) (e.g. with Runge-Kutta method). These features have substantial meaning for searching metastable states for a large system that will be discussed further in this section.

The formal solution of the system (23) is given by the linear combination:

\[
P_k(\tau) = \alpha_k \sum_{l=0}^{m} c_l L_k^{(l)} e^{-\omega_l \tau},
\]

where \(\omega_l\) are the eigenvalues of \([B_{kl}]\) in ascending order \(\omega_0 \leq \ldots \leq \omega_m\), \(\{L^{(l)}\}\) are the corresponding, orthonormal eigenvectors, \(L^{(l)} = \{L_k^{(l)}\}, k, l = 0, \ldots, m\) (so that \(\sum_k L_k^{(l)} L_k^{(n)} = \delta_{ln}\)), and coefficients \(c_l\) are defined by decomposition of the initial probability distribution \(\{P_k(\tau = 0)\}\) in the basis \(\{L^{(l)}\}\):

\[
c_l = \sum_{k=0}^{m} L_k^{(l)} P_k(0)/\alpha_k.
\]
One can find the lowest eigenvalue of the matrix \([B_{kl}]\) to be equal \(\omega_0 = 0\), by substituting \(L^{(0)}_k = \sqrt{P^{(0)}_k}\), for \(k = 0, \ldots, m\), where \(P^{(0)} = \{P^{(0)}_k\}\) is the stationary probability distribution obtained in Sec. 4 from detailed-balance equation (13). In other words, the solution (26) of the system (23) relaxes to the stationary distribution \(\{P^{(0)}_k\}\), for \(\tau \to \infty\). In all the numerical analysis below, we examine the details of this relaxation, particularly we search the possible metastable state associated with the secondary maximum of the stationary probability distribution \(\{P^{(0)}_k\}\) (see Fig. 5).

We have applied the step-like model of ion channel switching (6) in symmetric \((B = 5, n_0 = 0.5)\) as well as asymmetric \((B = 5, n_0 = 0.49)\) case. The initial state \((P_k(0))\) was chosen to be the 50% mixture of the stationary probability distribution \((P^{(0)}_k)\) and 50% of narrow-peaked distribution, concentrated in secondary maximum of the stationary distribution (see Fig. 5). Two characteristics periods have been identified in the time evolution of \(m = 400\) channels membrane, in both symmetric and asymmetric case: (i) a fast diffusion from the initial conditions to metastable solution (see Fig. 7), and (ii) a slow relaxation to the stationary solution. Both of these features are shown in Fig. 7. Our quantitative observations for the membranes with different numbers of channels \(m\) can be briefly reported as follows: the time of diffusion (i) was found to be approximately constant for \(m = 100 \div 400\), whereas the life time of the metastable solution (ii) grows rapidly with \(m\). Moreover, for large systems, the shape of the probability distribution remains exactly constant for a long period of time, i.e. \(\tau = 10^2 \div 10^4\) for \(m = 400\), that correspond to the real time approx. 0.2 \(\div\) 20 s (see Table 1).

According to these results, one can expect a broad window in the spectrum of eigenvalues \((\omega_k)\) of the dynamical system (23). Spectra presented in Fig. 9 confirm clearly this hypothesis, for both the symmetric and the asymmetric cases. Moreover, first excited-state eigenvalue \(\omega_1\) increases exponentially with the number of channels \(m\), (except of the numerical round-off errors, which become significant for \(\omega_1 < 10^{-12}\)), whereas all the other excited-state eigenvalues lie in approximately constant (for different \(m\) band bordered by the eigenvalues \(\omega_2\) and \(\omega_m\). This simple picture proves, that for the \(m\)-s of order few hundreds and larger, the dynamics of the probability distribution \((P_k)\) is completely determined by first eigenvalue \(\omega_1\) and associated eigenvector \(P^{(1)} = (P^{(1)}_k)\), for times longer than \(\tau \approx 100\) (that correspond to the real time approx. 0.2 s).

A further numerical evidence for this statement is provided with Table 2, as well as Fig. 10. and 11. Let us define the trapping times \(T_{(\omega)}\) and \(T_{Sh}\) as a position of the last inflection points (before the system reaches
Table 2. Brief comparison of the decay-time defined by first excited eigenvalue $1/\omega_1$ with trapping times $T_{(n)}$ and $T_{Sh}$ (see Fig. 10 and 11 for definitions). Sample results for symmetric ($B = 5$, $n_0 = 0.5$) and asymmetric ($B = 5$, $n_0 = 0.49$) step-like models of ion channel switching are provided.

| $n_0$ | $m$ | $-\log \omega_1$ | $\log T_{(n)}$ | $\log T_{Sh}$ |
|-------|-----|-------------------|-----------------|---------------|
| 0.5   | 100 | 2.748             | 2.540           | 2.392         |
|       | 200 | 4.293             | 4.106           | 3.968         |
|       | 400 | 7.397             | 7.230           | 7.091         |
| 0.49  | 100 | 2.364             | 2.195           | 2.110         |
|       | 200 | 3.236             | 3.057           | 2.948         |
|       | 400 | 4.942             | 4.768           | 4.653         |

Fig. 7. Evolution of the initial probability distribution for $m = 400$ channels membrane (see main text for details) to the metastable solution, obtained from the numerical exact diagonalization technique. The stationary solution for $\tau \to \infty$ is also presented. The quasi-continuous probability distribution function is defined as $P(n) = mP_k$, where $n = k/m$. Top panel: symmetric step-like model of ion channel switching with $n_0 = 0.5$ and $B = 5$. Bottom: an asymmetric case with $n_0 = 0.49$ and $B = 5$. 
an equilibrium) of average fraction of open channels \( \langle n \rangle \) and the Shannon entropy \( S_{Sh} \), respectively (see Fig. 10 and 11 for details). By looking at Table 2, one can find the trapping times \( T_{\langle n \rangle} \) and \( T_{Sh} \) to be in the same order as corresponding decay times defined by first excited eigenvalue \( 1/\omega_1 \), i.e. \( T_{Sh} \approx 10^{-0.3}/\omega_1 \approx 1/2\omega_1 \), where the factor \( 1/2 \) could be simple explained by representing the probability distribution in the form: 

\[ P(n) = P_0(n) + \delta(n), \]

and calculating the Shannon entropy in this manner:

\[
S_{Sh} = \int dnP(n) \ln P(n) = S_0 - \frac{1}{2} \int dn \frac{\delta^2}{P_0(n)} + O(\delta^3) \approx S_0 + \text{const} \ e^{-2\omega_1 \tau},
\]

where approximation works for \( \tau \gg 1/\omega_2 \) and \( S_0 \) is the value of Shannon entropy for the stationary distribution \( P_0(n) \). One remarkable feature of the Shannon entropy \( S_{Sh} \) for the membrane is that its value for the stationary

![Fig. 8. The metastable probability distribution for \( m = 400 \) channels membrane obtained from numerical exact diagonalization technique, (datapoints does not change visibly in given time intervals) and its relaxation to the stationary solution for \( \tau \to \infty \) (also presented). The quasi-continuous probability distribution function is defined as \( P(n) = mP_k \), where \( n = k/m \). Above: symmetric step-like model of ion channel switching \( (B = 5, n_0 = 0.5) \), below: an asymmetric case \( (B = 5, n_0 = 0.49) \).]
distribution is not always maximal, for same cases entropy $S_{Sh}$ can decrease as a function of time (see e.g. Fig. 11). This is caused by the fact, that we are studying a dissipative system, connected to the environment (see Sec. 2), whereas only the total entropy of the system together with its environment grows in time, not necessarily the fractional entropy of the membrane (i.e. Shanon entropy).

Observations discussed in this section, particularly the simple structure of the eigenvalue spectrum (presented on Fig. 9), gave us the motivation for some approximate approach for the first-excited eigenvalue $\omega_1$, that is discussed in the next section.

Fig. 9. Spectrum of eigenvalues obtained from the numerical exact diagonalization approach, as a function of the number of channels $m$. The first ($\omega_1$), the second ($\omega_2$) and the last ($\omega_m$) excited eigenvalues are shown, all the others are lying between $\omega_2$ and $\omega_m$ (except from $\omega_0 = 0$). To make interpretation in terms of decay time easier, $-\log \omega_k$ are presented. Above: symmetric step-like model of ion channel switching ($B = 5$, $n_0 = 0.5$), below: an asymmetric case ($B = 5$, $n_0 = 0.49$).
6. Perturbative analysis and discussion

Let us consider the membrane with large number of channels \( m = 200 \div 1000 \), e.g.) and a metastable solution for the fraction of open channels \( n_M \) clearly separated from the stable \( n_S \) (in other words: secondary and primary maximum of the stationary probability distribution, see i.e. Fig. 5.) by an unstable point \( n_U \) (and corresponding minimum of the stationary probability distribution, see Fig. 5, e.g.). For this case, according to the broad window in the spectrum of eigenvalues found in Sec. 5. (see Fig. 9.), the distribution function \( P(n) \) relax nearly independently in sections \( n < n_S \) and \( n > n_S \) after a time defined by second excited eigenvalue \( \sim 1/\omega_2 \), and then, after a time of order \( \sim 1/\omega_1 \) (where \( \omega_1 \) is first excited eigenvalue) the probability start to flow through the unstable point \( n_U \), what let the distribution function \( P(n) \) to relax to the stationary solution \( P_0(n) \), see Fig. 7-8. Motivated by this brief summary of the results presented in Sec. 5.,

![Graph](image)

Fig. 10. Average fraction of open channels \( \langle n \rangle = \int dnnP(n) \), as a function of time for membranes with \( m = 100 \div 400 \) channels with symmetric \( (B = 5, n_0 = 0.5, \text{above}) \) and asymmetric \( (B = 5, n_0 = 0.49, \text{below}) \) step-like model of ion channel switching. The quasi-continuous probability distribution function is defined as \( P(n) = mP_k \), where \( n = k/m \). The last inflection points on these plots define trapping times \( T(\langle n \rangle) \), collected in Table 2.
we discuss now perturbative approach in terms of weak coupling at the point \( n_U \).

Taking into account the probability flows between point \( k_U - 1 \) and \( k_U \), where \( k_U \equiv mn_U \) (see Fig 4), we obtain the equation expressing total balance of the probability in the system in the form

\[
\frac{d}{d\tau} \int_0^{n_U} P(n, \tau)dn = n_U(1 - n_U)\Delta_U(\tau),
\]

where \( \Delta_U \) is defined as a difference \( \Delta_U \equiv P(n_U) - P(n_U - \Delta n) \), \( \Delta n = 1/m \) and \( \tau \) is an dimensionless time (3). Whereas the eq. (29) has a general character, for further discussion the integral \( \int_0^{n_U} P(n)dn \) and difference \( \Delta_U \) need to be approximated for \( \tau \gg 1/\omega_2 \). To establish such an approximation, one can define the decomposition of the stationary probability distribution

![Graph](image)

**Fig. 11.** Shanon entropy per channel \( S_{Sh}/m \), where \( S_{Sh} = \int dn P(n) \ln P(n) \), as a function of time for membranes with \( m = 100 \div 400 \) channels with symmetric \((B = 5, n_0 = 0.5, \text{above})\) and asymmetric \((B = 5, n_0 = 0.49, \text{below})\) step-like model of ion channel switching. The quasi-continuous probability distribution function is defined as \( P(n) = mP_k \), where \( n = k/m \). Last inflection points on these plots define trapping times \( T_{Sh} \), gathered Table 2.
\[ P_0 = P_L + P_R, \]

where

\[
P_L(n) = \begin{cases} P_0(n) & \text{for } n < n_U \\ 0 & \text{elsewhere} \end{cases}, \quad P_R(n) = \begin{cases} P_0(n) & \text{for } n \geq n_U \\ 0 & \text{elsewhere} \end{cases}.
\]

The representation (30) and a brief discussion of the exact-diagonalization results, presented at the beginning of this section, brought us to an ansatz:

\[
P_\eta(n, \tau) = P_0(n) + \eta(\tau) [P_L(n) - c_R P_R(n)],
\]

where \( \eta(\tau) \) is a function of time, that we expect to behave as \( \eta \sim \exp(-\omega_1 \tau) \) for \( \tau \gg 1/\omega_2 \), and \( c_R \) is the coefficient defined to save the normalization

\[
f_0^1 P(n,1)dn = 1, \quad c_R \equiv P_L/(1 - P_L),
\]

where \( P_L = f_0^{n_U} P_0(n)dn \). After substituting (31) to the eq. (29), one can write the differential equation for the function \( \eta(\tau) \):

\[
\frac{d\eta}{d\tau} = -\frac{n_U(1-n_U)}{P_U(1-P_U)} P_U \eta,
\]

where \( P_U \) is the value of the stationary probability distribution function in point \( n_U \), \( P_U \equiv P_0(n_U) \). The solution of the eq. (32) is the simple exponential decay \( \eta(\tau) = \eta(0) \exp(-\omega_\eta \tau) \), where the decay constant

\[
\omega_\eta = \frac{n_U(1-n_U)}{P_L(1-P_L)} P_U
\]

is an approximation of first excited eigenvalue \( \omega_1 \). This approximation is essentially equivalent to the first-order perturbation correction to the \( \omega_1 \), if we consider the connection in point \( n_U \) as a perturbation.

Moreover, one can consider the stationary probability distribution in the limit form, for large \( m \) (15), and make the Gaussian approximation to calculate all the integrals. The practical formula, obtained in this manner

\[
\omega_\eta = -m(f_M - f_U) \log e + \frac{1}{2} \log m + \mathcal{O}(1),
\]

where \( f_M \) and \( f_U \) are values of the function \( f(n) \) (see Sec. 4) in point \( n_M \) and \( n_U \), respectively, can be compared indirectly with numerical exact-diagonalization results. Although the coefficient in the linear part of the eq. (34) \( (f_M - f_U) \log e \approx 0.01557 \) and \( 0.00857 \) for symmetric \( (B = 5, \ n_0 = 0.5) \) and asymmetric \( (B = 5, \ n_0 = 0.49) \) Fermi-Dirac model of the ion channel switching, approximately agree with corresponding numerical values obtained from exact-diagonalization (see Fig. 9), the term \( \log m/2 \) simply does not exists in numerics. This clear contradiction seems to be the immanent disadvantage of the perturbation approach to our system, that
simply produce too large value of the step $\Delta U$ in eq. (29). Moreover, it cannot be repaired in any perturbation scheme, because, what was shown numerically, the second perturbation correction to the first excited eigenvalue $\omega_1$ produce nonphysical negative results.

To avoid the problem mentioned above, one can derive the diffusion equation for $n \approx n_U$:

$$\frac{\partial P}{\partial t} = \frac{n_U(1-n_U)}{m} \frac{\partial^2 P}{\partial n^2},$$

(35)

find its Green function

$$G(n, \tau) = \sqrt{\frac{m}{4\pi n_U(1-n_U)}} \exp \left[ -\frac{mn^2}{4\pi n_U(1-n_U)} \right],$$

(36)

to take the ansatz (31) as the initial condition for the eq. (35) and frozen it after a time $\tau_{\text{diff}}$:

$$P_{\eta}^{\text{froze}}(n, \tau_{\text{diff}}) = \int dn' G(n-n', \tau_{\text{diff}}) P_{\eta}(n', \tau).$$

(37)

Then, the value of the step $\Delta U$ in eq. (29) is multiplied by factor $2G(0, \tau_{\text{diff}})\Delta n$, where $G(0, \tau_{\text{diff}})$ is the value of Green’s function (36) at point $n = 0$ and $\Delta n = 1/m$. That brought us to the new approximation of first excited eigenvalue

$$\omega_{\eta}^{\text{froze}} = \frac{2n_U(1-n_U)}{P_L(1-P_L)} G(0, \tau_{\text{diff}}) P_U \Delta n = \sqrt{\frac{n_U(1-n_U)}{\pi m \tau_{\text{diff}}}} \frac{P_U}{P_L(1-P_L)}.$$

(38)

The factor $\sqrt{1/m}$ appeared in eq. (38) cancel the logarithmic term in (34).

In so-called frozen diffusion approach, presented above, the diffusion time $\tau_{\text{diff}}$ is an free parameter, adjusted to agree with constants in formula for $\log \omega_1$ obtained from exact diagonalization. Although the frozen diffusion approach produce the results agreeable with the numerics, the physical reasons for introducing parameter $\tau_{\text{diff}}$ are not clear at this stage; the problem needs a further study, possibly with utilising the Real-Space Renormalization Group Technique.

**Summary**

We derived the detail-balance equations for stationary probability distribution of the number of open ion channels in the cell membrane. This equation was used to compare the extrema of the stationary probability distribution for large $m$-channel system with corresponding stationary solutions of the deterministic dynamical equation for $m \to \infty$, and to discuss the fluctuation around them for finite $m$. 
The so-called step-like model of ion channel switching, based on that studied by Hodgkin and Huxley [4], was briefly discussed in relation to the experimental data, applied to obtain an analytical solution of the detail-balance equation, qualitative discussion of the two classes of phase transitions in the system, and numerical exact-diagonalization calculations of the decay time of the metastable state of the system. The exact diagonalization results were shown to disagree with the first-order perturbations. Moreover, the perturbation scheme produces unphysical results in the second order. This contradiction shows essentially a non-perturbative character of coupled ion-channel system. The proposed frozen diffusion approach, with an additional adjustable parameter, was shown to explain the exact diagonalization results.

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Appendix A

Fluctuations around the stationary points obtained from the detailed-balance approach

In this appendix, we present the approximate derivation of the small fluctuations of the number of open channels around the stationary points for general model of ion channel switching. Let us apply the detailed balance
equation (13) to calculate the ratio of the probability distribution $P_{k-\Delta}/P_k$ for points in distance $\Delta$:

$$\frac{P_{k-\Delta}}{P_k} = \prod_{j=0}^{\Delta-1} \frac{P_{k-j-1}}{P_{k-j}} = \prod_{j=0}^{\Delta-1} \frac{k-j}{m-k+j+1} \frac{1-p_{k-j}}{p_{k-j-1}},$$

(A.1)

where probability of open channel $p_k \equiv p_{\text{open}}(k/m)$. For $\Delta/m << 1$ (small fluctuations), which supposition would be verified a posteriori, one can approximate the probabilities in eq. (A.1)

$$p_{k-j} \approx p_k - j p_k' = p_k(1 - \alpha j),$$

where $p_k' = p_{\text{open}}(j/m)/m$, and

$$\alpha = \frac{p_k'}{p_k} = \frac{1}{m} \frac{p_{\text{open}}(k/m)}{p_{\text{open}}(k/m)} \ll 1;$$

(A.2)

and analogically

$$1 - p_{k-j} \approx 1 - p_k(1 - \alpha j) = (1 - p_k)(1 + \beta j),$$

where:

$$\beta = \alpha \frac{p_k}{1 - p_k} = \frac{p_k'}{1 - p_k} \ll 1.$$ 

(A.3)

Subsequently, eq. (A.1) can be rewrite in the approximate form:

$$\frac{P_{k-\Delta}}{P_k} \approx \frac{k!}{(k-\Delta)!} \frac{(m-k)!}{(m-k+\Delta)!} \left( \frac{1-p_k}{p_k} \right)^{\Delta} \times \Pi_{\Delta},$$

(A.4)

where $\Pi_{\Delta}$ is the non-binomial factor in ratio $P_{k-\Delta}/P_k$:

$$\Pi_{\Delta} = \prod_{j=0}^{\Delta-1} \frac{1 + \beta j}{1 - \alpha (j+1)} \approx \prod_{j=0}^{\Delta-1} [1 + (\alpha + \beta) j] \approx e^{(\alpha + \beta) \Delta^2/2},$$

(A.5)

where we skipped the terms of order $\Delta/m$.

Furthermore, for stationary point $p_k = k/m \equiv n_*$ (see Sec. 3). So that, using Stirling approximation $\ln k! \approx k \ln k - k$, one can obtain from eq. (A.4):

$$\ln \frac{P_{k-\Delta}}{P_k} \approx -\frac{\Delta^2}{2mn_* (1 - n_*)} + \ln \Pi_{\Delta}.$$ 

After substituting eq. (A.5) and, subsequently (A.2) and (A.3), we finally obtain:

$$\ln \frac{P_{k-\Delta}}{P_k} \approx -\frac{1 - p_k'}{2mn_* (1 - n_*)} \Delta^2,$$

(A.6)
where $p'_s \equiv p'_{\text{open}}(n_*)$. Eq. (A.6) let us read the mean-square fluctuation of the fraction of open channels $\delta n \equiv \Delta/m$ around the stationary point $n_*:\$

$$\langle (\delta n)^2 \rangle = \frac{1}{m} \frac{n_*(1-n_*)}{1-p'_s}, \quad \text{(A.7)}$$

that confirms our starting supposition $\Delta/m << 1$ for large $m$. Moreover, eq. (A.7) let us to identify the value $p'_s = 1$, previously distinguishing between types of stationary solutions (see Sec. 3.), with critical point in terms of 2-nd order phase transitions, for which $\delta n \to \infty$. Additionally, for quasi-continuous probability distribution function $P(n)$, defined by the relation $P_k = P(n) \Delta n$ (cf. Sec. 4.) one can write (for $n \approx n_*):$

$$P(n) = P(n_*) \exp \left[ -m \frac{1 - p'_s}{n_*(1-n_*)} (n - n_*)^2 \right], \quad \text{(A.8)}$$

what clearly identifies stable and unstable solutions of the relation $n_* = p_{\text{open}}(n_*)$ with, respectively maxima and minima of the probability distribution. Eq. (A.8) motivates the ansatz $P \sim e^{m f(n)}$ in Sec. 4.