

ON THE BALL AND CHAIN MODEL  
BY SIMPLE AND HYPERBOLIC DIFFUSION  
— AN ANALYTICAL APPROACH\*

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Ball and chain model of inactivation process of some of the ion channels is resolved by means of diffusion (hyperbolic and parabolic operators). Polypeptide ball — a part of the channel's protein that is responsible for inactivation, is treated as a Brownian particle tethered on polypeptide chain. First passage time of the ball is calculated and compared with experimental data. It is shown that diffusion provides an insight into the mechanism of inactivation process in agreement with experimental data.

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### 1. Ion channels permeability

Ion channels play crucial role in the process of conduction of electrical impulses (particularly, in nerve and muscle cells). They permeate selectively sodium and potassium ions and allow to polarize/depolarize neuron's membrane — creating thus a traveling impulse.

Channels are integral proteins immersed in the cell's lipid bilayer, which itself has usually poor ionic permeation. Channel's third order structure creates a transmembrane “pore” — a passage for ions. Voltage clamp technique developed by Marmont, Hodgkin, Huxley and Katz in late forties, allows to investigate channel's ionic permeabilities by measurement of ionic currents through the membrane, when transmembrane potential is held constant [1, 2]. Further introduction of, so called, “patch clamp” allows to perform measurements even on a single ionic channel [3].

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As comes out from experiments, permeability of channels fluctuates in time and is determined by varying structure of the channel. Modulation of permeability (modulation of ionic flux) is called gating. Gating may be driven by different stimuli like chemical species, or variation of electric field [3].

Gating by electric field is the basic phenomenon that allows the nerve impulses to flow. It is widely accepted that voltage gated ion channels have a voltage sensor located at their S4 segment. Part of the protein that builds the sensor is usually rich with arginine and lysine, and is able to move under the external, electrostatic field, changing the whole conformation of channel, thus making it impermeable for ions. Interesting fact is, that even if channel is subjected to the constant, positive transmembrane voltage that keeps it open, its permeability decreases after short time (channel inactivates). It is than clear that the voltage gating is not the only one mechanism of gating present in ion channels [5].

## 2. Ball and chain model of inactivation

Explanation of inactivation phenomenon was given by Armstrong and Benzanilla, who proposed, so called, “*ball and chain model*”, confirmed by experiments and measurements described in [4, 6]. According to the model, part of a channel’s protein (in case of potassium *Shaker* channel which was extensively investigated — its first twenty aminoacids) acts like a ball, tethered on the polypeptide chain. When the channel is closed, ball remains in ceaseless motion, limited by the length of the chain. When channel opens, ball may struck and bind to the active site of a channel — blocking its pore and causing inactivation. It is worthy to realize, that the opening and closing of a voltage-gated channel is a voltage stimulated process. When channel is open, the inactivation takes place due to the ball’s random walk of diffusional nature.

In this approach to the formulation of the model, we have assumed:

- reduction to one spatial dimension,
- position of the ball, at the moment of opening of the channel, is given between 0 and  $L$ , where  $L$  is the length of the polypeptide chain,
- every collision with the channel’s inlet is effective — once the ball strikes the channel it blocks it,
- length of the chain generates the length of the region at which the ball may wander; chain has no any other influence on the ball’s movement.

It may be therefore concluded, that the model does not describe the quasi-periodic behavior of the ionic channel, but the process of its inactivation.

### 3. Diffusional approach to the ball and chain model — survival probability and first passage time

Application of diffusion to the ball and chain concept becomes clear when we realize, that ball which inactivates the channel behaves like the Brownian particle. Its ceaseless motion originates from the frequent collisions with comparatively small molecules of surroundings, and is limited by the chain linking it to the channel. In our approach to the ball and chain model, we do not attempt to track the trajectory of inactivating ball. Instead, we describe its position in terms of probabilities using following differential equations: (link between differential equations we use, and the random walk of Brownian particle, is given in [10])

- **Parabolic equation of diffusion**

Although it implies the infinite speed of propagation, what is hardly acceptable from the physical view point, the parabolic equation produces results, that are intuitive and easy to interpret. For long times, its “parabolic defect” (*i.e.* infinite speed of density propagation) has no significance.

- **Hyperbolic equation of diffusion**

This equation implies the finite speed of propagation — it is the generalization on short times of parabolic diffusion equation [8]. We postulate, that this equation should provide a richer description for the ball and chain problem than the parabolic one. This becomes clear by realizing, that the movement of the inactivating ball shall indicate a correlation in the certain directions of motion, and thus posses a non-Markovian character. These correlations may have different contributions. The most obvious is the inertia of the wandering ball, and local electromagnetic fields. Another important source of the correlation in the ball’s motion is the relaxation of stresses in the aminoacid chain that links the ball to the channel. This will facilitate the ball’s movement in the direction that minimizes the overall chain stress.

Thus the non-Markovian, correlated random walk, that stays behind the hyperbolic diffusion, should resemble the nature of ball’s movement more accurately. This approach also provides more characteristic quantities describing the process (diffusion constant  $D$  and the average correlation time  $\tau$ ).

To stay in agreement with model’s assumptions the initial and boundary conditions have to be imposed as specified in Fig. 1:

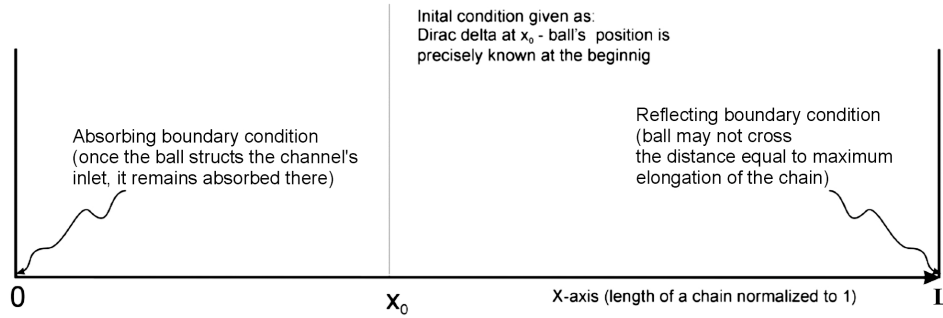


Fig. 1. Initial and boundary conditions for the ball and chain model.

Diffusional approach to ball and chain model, allows to estimate the probability density distribution of the ball's position as a function of time and space. Based on that the following quantities, easily comparable with electrophysiological data, may be derived:

- **Survival probability** defined as:

$$S(t) = \int_0^L f(x, t) dx \quad (1)$$

which indicates the probability that the ball is still in region  $x \in (0, L)$  (where  $L$  is the length of the polypeptide chain), and therefore, that the channel remains open (survives at its opened state); plot of  $S$  vs time shows the shape of relation of average ionic trans-channel current vs time, when the channel is open and inactivates;

- **First passage time** defined as:

$$F(t) = \frac{d(1 - S(t))}{dt} = -\frac{d(S(t))}{dt} \quad (2)$$

which is the probability density distribution for times of channel's closure. The above formula may be justified by noting that  $1 - S(t)$  indicates the probability if the time  $t$  was bigger or equal to the time that ball needed to reach the channel's inlet. Therefore  $1 - S(t)$  is the cumulative distribution for so called first passage time. To get its probability density distribution,  $1 - S(t)$  has to be differentiated with respect to time.

Important parameter in the diffusional approach is the length of the chain, denoted by  $L$ . Its value is estimated on the basis of aminoacid sequence of the chain. According to [11] it is equal to  $2.1 \times 10^{-8}$  [m].

#### 4. Formulation of the problems, methods of solution

The ball and chain model was resolved by parabolic and hyperbolic equations of diffusion. As noted earlier, hyperbolicity shows its importance in short times, as it implies the finite speed of propagation. For sufficiently long times, parabolic and hyperbolic approaches produce the same results.

##### 4.1. The parabolic diffusion

The following IBVs<sup>1</sup> problem was posed

$$-D \frac{\partial^2 f(x, t)}{\partial x^2} + \frac{\partial f(x, t)}{\partial t} = 0, \quad x \in (0, L), \quad t \in (0, +\infty), \quad (3)$$

$$f(x, t = 0) = \delta(x - x_0), \quad (4)$$

$$f(x, t)|_{x=0} = 0, \quad (5)$$

$$\left. \frac{\partial f(x, t)}{\partial x} \right|_{x=L} = 0, \quad (6)$$

where  $f(x, t)$  is the probability density distribution of the ball's position in time,  $D$  is the diffusion constant,  $L$  denotes the length of the chain. Definition of absorbing and reflecting boundary is obvious, and does not require comment.

The problem was solved by two methods: the separation of variables and by the method of reflection and superposition. Moreover, results were confirmed by numerical solution (standard Crank–Nicholson scheme), and some simple random walk simulations (results from random walk are also presented in ([11]).

Solution of equation (3) with conditions (4)–(6) obtained by the separation of variables has the following form

$$\begin{aligned} f(x, t) = \frac{1}{2\sqrt{\pi Dt}} \sum_{m=0}^{\infty} & \left[ (-1)^m e^{\left( \frac{-(x-x_0+2mL)^2}{4Dt} \right)} + (-1)^m e^{\left( \frac{-(-x-x_0+(2m+2)L)^2}{4Dt} \right)} \right. \\ & \left. + (-1)^{m+1} e^{\left( \frac{-(x+x_0+2mL)^2}{4Dt} \right)} + (-1)^{m+1} e^{\left( \frac{-(-x+x_0+(2m+2)L)^2}{4Dt} \right)} \right]. \quad (7) \end{aligned}$$

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<sup>1</sup> IBVs stands for the *initial-boundary values* problem. This acronym is commonly used in the theory of differential equations, and means that for a specific problem with the differential equation, initial and boundary conditions were specified.

While the solution obtained through reflection and superposition reads

$$f(x, t) = \sum_{n=0}^{\infty} \left[ \frac{2}{L} \sin \left[ \frac{(2n+1)\pi}{2L} x_0 \right] \sin \left[ \frac{(2n+1)\pi}{2L} x \right] \right. \\ \left. \times \exp \left[ - \left[ \frac{(2n+1)}{2L} \right]^2 Dt \right] \right]. \quad (8)$$

Series (7) shows fast convergence for short times (only a few terms are needed to get satisfactory result), while series (8) shows excellent convergence for long times. As a matter of fact the solutions (7) and (8) can be obtained following suggestions given by Crank, many years ago [7].

Numerical solutions with Dirac delta as the initial condition, might have stability troubles at early times, when delta's "peak" is sharp. To avoid this, we initially used at early time stages analytical solution for corresponding Cauchy problem (given in [7]), and once boundaries became important, we switched to pure numerical scheme.

#### 4.2. The hyperbolic diffusion

In this case the following IBVs problem is posed

$$\tau \frac{\partial^2 f(x, t)}{\partial t^2} - D \frac{\partial^2 f(x, t)}{\partial x^2} + \frac{\partial f(x, t)}{\partial t} = 0, \quad x \in (0, L), \quad t \in (0, +\infty), \\ f(x, t=0) = \delta(x - x_0), \quad \left. \frac{\partial f(x, t)}{\partial t} \right|_{t=0} = 0, \quad (9)$$

$$2\tau \left. \frac{\partial f(x, t)}{\partial t} \right|_{x=0} = 2\tau v \left. \frac{\partial f(x, t)}{\partial x} \right|_{x=0} - f(0, t), \quad (10)$$

$$\left. \frac{\partial f(x, t)}{\partial x} \right|_{x=L} = 0, \quad (11)$$

where  $D$  stands for the diffusion coefficient,  $\tau$  for the correlation time,  $v$  for the mean speed of the inactivating ball, and  $L$  for the length of the chain.

It the case of hyperbolic equation, formulation of absorbing and reflecting boundary condition requires some comments.

At the reflecting boundary condition, we demand to have flux equal to zero. In case of hyperbolic diffusion the flux is given by the following relation:

$$J_{\text{hip}}(x, t) = -D \frac{\partial f(x, t)}{\partial x} - \tau \frac{\partial J_{\text{hip}}(x, t)}{\partial t}. \quad (12)$$

Since at  $x = L$ ,  $J(L, t) = 0$  for all  $t$ , its time derivative is also zero. Therefore (12) reduces effectively to the form given in the formulation of the problem.

The absorbing boundary condition for hyperbolic operator is totally different in comparison with that used in parabolic diffusion. Posing  $f(x, t)|_{x=0} = 0$  in hyperbolic case, causes the solution to take the negative values, which is unacceptable, since probability density must be positive definite. Correct formulation of absorbing boundary may be justified by considering correlated random walk from which hyperbolic equation of diffusion may be derived.

In this derivation, one usually considers a particle moving to the left or right, for which, we may define the following probabilities:

- $\alpha(x, t)$  which is the probability that at time  $t$  and position  $x$ , we may find particle that arrived there from left;
- $\beta(x, t)$  which is the probability that at time  $t$  and position  $x$ , we may find particle that arrived there from right;

Discretizing time and space, we make particle to move at jumps (of length  $\delta$  and time  $T$ ). After each jump, particle may change its direction of motion (with probability  $q$ ) or keep it (with probability  $p$ ). Since particle may not stand still,  $p + q = 1$ .

Evolution of  $\alpha(x, t)$  and  $\beta(x, t)$  may be described by the following set of equations:

$$\alpha(x, t + T) = p\alpha(x - \delta, t) + q\beta(x - \delta, t), \quad (13)$$

$$\beta(x, t + T) = p\beta(x + \delta, t) + q\alpha(x + \delta, t). \quad (14)$$

In our boundary condition, there is no particle, that arrived there from the left side (from position  $x - \delta$ ), therefore  $\alpha(x, t + T)$  is equal to zero. Further,  $\alpha(x + \delta, t)$  has to be also equal to zero, since at point  $x + \delta$  there is no particle that arrived there from the left (because particle can not escape from absorbing boundary condition). Therefore the above set of equations reduces to:

$$\beta(x, t + T) = p\beta(x + \delta, t). \quad (15)$$

Expanding  $\beta(x, t + T)$  and  $\beta(x + \delta, t)$  into the Taylor series, with  $p = 1 - \lambda T$ , where  $\lambda$  is the rate of reversal of direction of particle's movement we get:

$$\beta(x, t) + \frac{\partial \beta(x, t)}{\partial t} T = \beta(x, t) + \delta \frac{\partial \beta(x, t)}{\partial x} - \lambda T \beta(x, t) - \lambda T \delta \frac{\partial \beta(x, t)}{\partial x}. \quad (16)$$

In the limit, when  $T \rightarrow 0$  and  $\delta \rightarrow 0$ , such that  $\delta/T \rightarrow v$ , where  $v$  is the finite speed of a particle, (16) reduces to:

$$\frac{\partial \beta(x, t)}{\partial t} = \frac{\partial \beta(x, t)}{\partial x} v - \lambda \beta(x, t). \quad (17)$$

Since, as mentioned previously, at the absorbing boundary only the particle that travels to the left is present, we have  $\beta(x, t) = f(x, t)|_{x=0}$ . Moreover, from the derivation of hyperbolic equation we have:  $\lambda = \frac{1}{2\tau}$ , where  $\tau$  is the correlation time (the mean time after which particle will reverse its direction of motion). Rewriting (17) we get:

$$2\tau \frac{\partial f(x, t)}{\partial t} \Big|_{x=0} = 2\tau v \frac{\partial f(x, t)}{\partial x} \Big|_{x=0} - f(0, t) \quad (18)$$

which is the absorbing boundary condition posed at the formulation of the problem. It is worth to notice, that at the limit, when  $\tau \rightarrow 0$ , which means that all the correlation in the motion is lost, (18) tends, as it should, to (5).

Similar way of deriving the absorbing boundary for hyperbolic diffusion equation is given in [13] and in [14].

The hyperbolic ball and chain problem, such as formulated above, was solved with application of two auxiliary problems (19) and (20), that are shown below, and some rules of symmetry illustrated in Fig. 2

$$\left\{ \begin{array}{l} \tau \frac{\partial^2 f_1(x, t)}{\partial t^2} - D \frac{\partial^2 f_1(x, t)}{\partial x^2} + \frac{\partial f_1(x, t)}{\partial t} = 0, \quad x \in (0, 2L), \quad t \in (0, +\infty), \\ f_1(x, t = 0) = \delta(x - x_0), \quad \frac{\partial f_1(x, t)}{\partial t} \Big|_{t=0} = 0, \\ 2\tau \frac{\partial f_1(x, t)}{\partial t} \Big|_{x=0} = 2\tau v \frac{\partial f_1(x, t)}{\partial x} \Big|_{x=0} - f_1(0, t), \\ 2\tau \frac{\partial f_1(x, t)}{\partial t} \Big|_{x=2L} = 2\tau v \frac{\partial f_1(x, t)}{\partial x} \Big|_{x=2L} - f_1(2L, t), \end{array} \right. \quad (19)$$

$$\left\{ \begin{array}{l} \tau \frac{\partial^2 f_2(x, t)}{\partial t^2} - D \frac{\partial^2 f_2(x, t)}{\partial x^2} + \frac{\partial f_2(x, t)}{\partial t} = 0, \quad x \in (0, 2L), \quad t \in (0, +\infty), \\ f_2(x, t = 0) = \delta(x - 2L + x_0), \quad \frac{\partial f_2(x, t)}{\partial t} \Big|_{t=0} = 0, \\ f_1(x, t = 0) = \delta(x - x_0), \quad \frac{\partial f_1(x, t)}{\partial t} \Big|_{t=0} = 0, \\ 2\tau \frac{\partial f_2(x, t)}{\partial t} \Big|_{x=0} = 2\tau v \frac{\partial f_2(x, t)}{\partial x} \Big|_{x=0} - f_2(0, t), \\ 2\tau \frac{\partial f_2(x, t)}{\partial t} \Big|_{x=2L} = 2\tau v \frac{\partial f_2(x, t)}{\partial x} \Big|_{x=2L} - f_2(2L, t), \end{array} \right. \quad (20)$$

where the detailed analytical form of  $f_1(t, x)$  and  $f_2(x, t)$  is given in [14]. Fig. (2a) shows the evolution of solution  $f_1(x, t)$ , *i.e.* problem (19), while (2b) shows the same for  $f_2(x, t)$ , *i.e.* problem (20). In both cases, the domain of spatial variable  $x$  belongs to the region  $(0, 2L)$ . It may be noticed, that problems (19) and (20) are symmetric with respect to the line positioned at

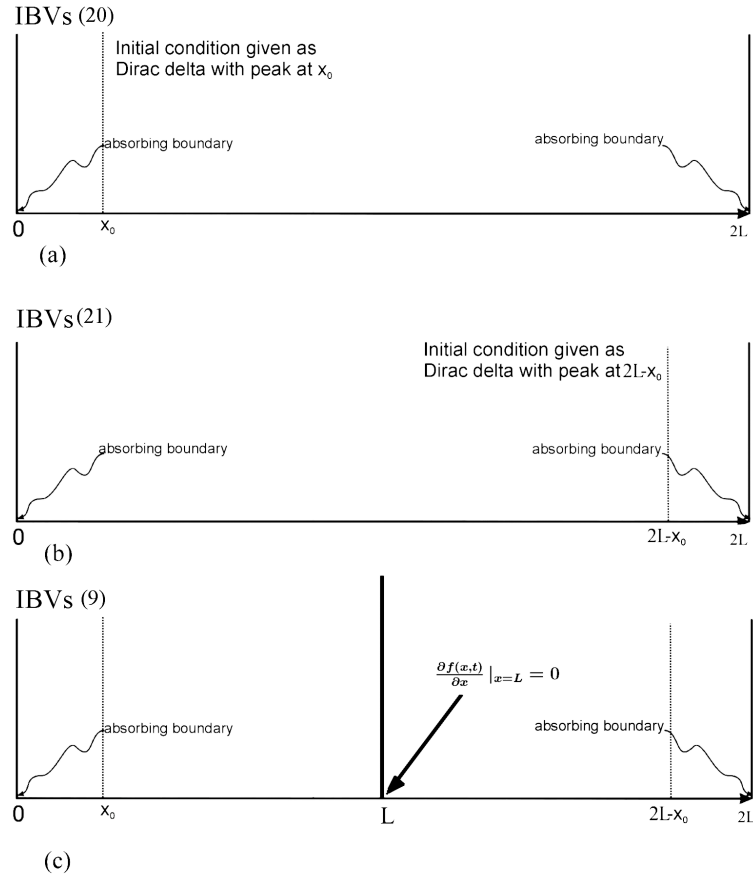


Fig. 2. An idea of the construction of solution (22) for hyperbolic ball and chain problem.

$x = L$ . Because of this symmetry, the following equality holds:

$$\frac{\partial f_1(x,t)}{\partial x} \Big|_{x=L} = - \frac{\partial f_2(x,t)}{\partial x} \Big|_{x=L}. \quad (21)$$

If we define the function  $f(x,t)$  as

$$f(x,t) = f_1(x,t) + f_2(x,t) \quad (22)$$

we may notice, that

$$\frac{\partial f(x,t)}{\partial x} \Big|_{x=L} = 0. \quad (23)$$

Thus the  $f(x, t)$  reads:

- is the solution of a linear hyperbolic diffusion equation, for it is the sum of two solutions of that equation,
- reproduces the initial condition of the ball and chain problem, because the second Dirac delta peak from (20) is outside the region  $(0, L)$  at  $t = 0$ ,
- keeps the absorbing boundary condition at  $x = 0$ , since both  $f_1(x, t)$  and  $f_2(x, t)$  also keep it,
- keeps the reflecting boundary condition at  $x = L$ , as shown above.

Therefore,  $f(x, t)$ , defined in (22), is the solution of the hyperbolic ball and chain problem, resulting from equations (19) and (20), respectively. Details concerning the derivation of  $f_1(x, t)$  and  $f_2(x, t)$  together with their analytical formulas may be found in [14].

## 5. Comparison with experimental data

Our theoretical results can be compared with electrophysiological data<sup>2</sup>. Experimental data were sampled with the time resolution equal to 0.1 [ms] and the whole experiment was 25 [s] long. During whole measurement channel was activated and deactivated many times, thus we were able to find mean experimental first passage time of inactivating ball.

Based on solution of parabolic equation, with aid of definitions (1), (2), theoretical first passage time was found. Fig. 3 shows the first passage time calculated from experiment, with the corresponding first passage time obtained theoretically, from the parabolic diffusion equation. For initial position  $x_0 = 0.4L$  ( $84 \times 10^{-10}$  [m]) with diffusion coefficient  $D = 1.2 \times 10^{-9}$  [cm<sup>2</sup>/s] theoretical curve was best fitted to experimental data.

In Fig. 4 the experimental first passage time is compared with the one calculated from the hyperbolic diffusion approach. Theoretical curve was fitted to experimental data, for the same initial position of the ball ( $x_0 = 0.4L$ ) as in the case of parabolic fitting. For diffusion coefficient  $D = 1.3 \times 10^{-9}$  [cm<sup>2</sup>/s] and the “effective” correlation time  $\tau = 2 \times 10^{-5}$  [s] we get the best agreement. Please note, that  $\tau$  and  $D$  were estimated from experimental data based on nonlinear regression. This is definitely a nonunique way of getting the numerical values of these parameters.

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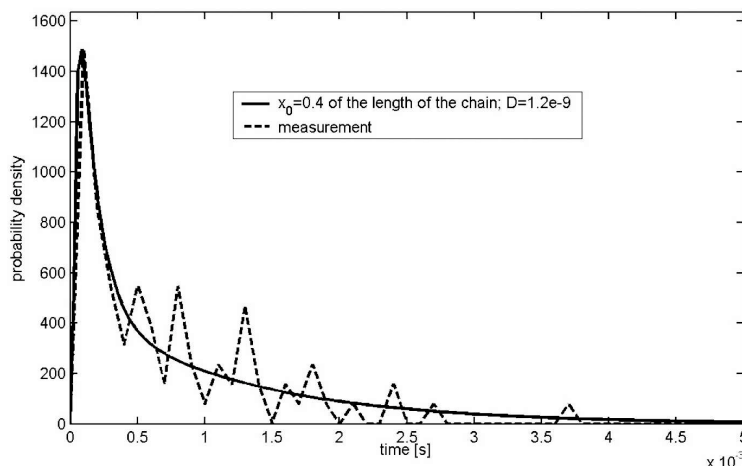


Fig. 3. Experimental (adult locust muscle  $K^+$  channels) and theoretical (parabolic diffusion) first passage time.

Our estimated average correlation time  $\tau$  may be compared with data presented in [16] and [17], where the correlation times for ions that crosses the channel were found to be of the order of femtoseconds ( $10^{-14}$  [s]). Taking into account the differences in masses between a single ion (say potassium or sodium ion) and the inactivating ball, it appears that the approximate correlation time for the ball should be at the scale of  $10^{-12}$  [s] (since the ball is about one hundred times heavier), what seems to stand against our results. This discrepancy may be explained by stating that there have to be some other factors, different than inertia, that increase the tendency of conserving the direction of ball's motion *i.e.* creating, so called, “effective mass”. One of the most prominent factor is the chain that links the ball to the channel. It not just increases the inertia of the whole moving system, but also adds the effect of the chain relaxation to its preferable conformations — promoting thus the conservation of movement at certain direction. We also think, that the electrostatic forces that drives the chain relaxation, together with the interactions between ball and the crowded surroundings in which it is diffusing, might be strong enough to make the effective correlation time  $\tau$  of the estimated order.

To sum up, the value of  $\tau = 2 \times 10^{-5}$  [s] results not only from the inertia of the aminoacid ball, but also from all the external influences, mainly the electrostatic fields, that supports the correlated ball's movement. As may be seen for the long times, the hyperbolic first passage time behaves similarly to parabolic one. Noticeable difference is observed for short times.

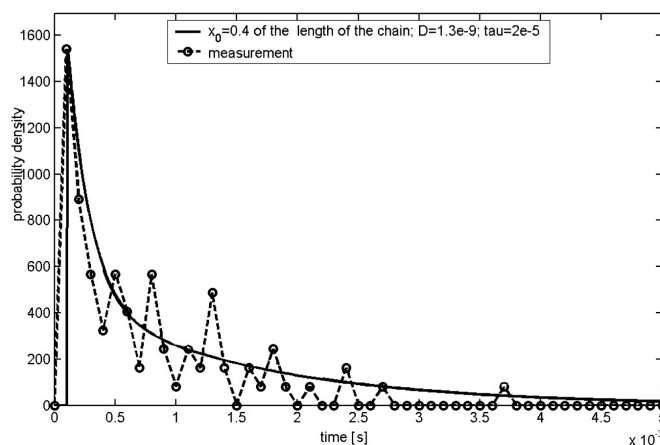


Fig. 4. Experimental (adult locust muscle  $K^+$  channels) and theoretical (hyperbolic diffusion) first passage time.

Hyperbolic first passage time predicts that the probability of blocking the channel at the time  $t \in (0, x_0/\sqrt{D/\tau})$  is equal to zero due to the finite speed of the ball which is defined as  $v = \sqrt{D/\tau}$ . As may be seen in Fig. 4, too low resolution of experimental data gave no possibility to verify if such a “lag” appears also in the measurements (experimental points were denoted with circles).

## 6. Calculation of the diffusion coefficient of the ball

Knowing the diffusion coefficient for a single aminoacid in water, we are able to estimate value of diffusion coefficient for inactivating ball, taking the corrections due to size and mass of the ball.

Diffusion coefficient for a single aminoacid rest is of the order of  $10^{-5}$  [cm<sup>2</sup>/s] (as given in [11]). An inactivating ball is characterized by different diffusion coefficient, since it has larger mass (what influences average velocity) and different area (and thus different collisions frequency with the molecules of surroundings) comparing to aminoacid rest.

Microscopically, diffusion coefficient for an inactivating ball, is equal to:

$$D = v \delta, \quad (24)$$

where  $\delta$  is mean free path, and  $v$  is the average velocity of the ball. Mean free path may be defined as:

$$\delta = \frac{v}{k}, \quad (25)$$

where  $k$  is the frequency of collisions with the molecules of surroundings. Therefore, reformulating (24) we get:

$$D = \frac{v^2}{k}. \quad (26)$$

Frequency of collisions  $k$  is linearly proportional to the surface area of the ball, that scales with ball's mass as follows:

$$k \propto \text{area} \propto \text{mass}^{2/3}. \quad (27)$$

Average velocity of the ball, denoted as  $v$ , scales with ball's mass as:

$$v \propto m^{-1/2} \quad (28)$$

(providing that the kinetic energy does not change). Concluding, we have the diffusion coefficient, that scales with the mass of the ball as:

$$D \propto m^{-5/3}. \quad (29)$$

Having the diffusion coefficient for aminoacid rest and knowing that ball consists of 20 aminoacids, we get the estimated diffusion coefficient of inactivating ball:

$$D_{\text{ball}} = D_0 \times 20^{-5/3} = 6.7 \times 10^{-8} [\text{cm}^2/\text{s}]. \quad (30)$$

The value of calculated diffusion coefficient however close to those obtained on the basis of parabolic and hyperbolic models, differs from them in the noticeable extent (about twice). The reasons for that could be as follows:

- In the calculations of diffusion coefficient, perfect, spherical shape of the inactivating ball was assumed. Differences in molar masses of aminoacids constituting the ball were neglected.
- Value of diffusion coefficient for which the parabolic and hyperbolic first passage time was fitted to experimental data is only approximate, because of rough shape of experimental curve (insufficient amount of experimental data).

## 7. Concluding remarks

Application of diffusion in ball and chain model is well justified. Diffusion arises from the physical and statistical properties of the inactivating ball and gives results, that stay in agreement with measurements. Value of diffusion coefficients calculated in (30) is in reasonable agreement with that obtained from the hyperbolic and parabolic models.

To provide more accurate results, longer measurement series would be of great value. It would result in smoother experimental first passage time, that would give more accurate diffusion coefficient for the ball.

Based just on the currently available, experimental data, it is not possible to decide whether the parabolic or hyperbolic approach is more appropriate in the modeling of the behavior of an inactivating ball. Time scale at which the parabolic and hyperbolic approaches produces different results is still beyond the capability of experiment. It might be however possible to extract the shorter time scales from the currently available data, basing on their self-similar nature [18]. Adjusting the hyperbolic model to the data with higher time resolution, will surely bring some corrections to the average correlation time  $\tau$ , allowing thus for more precise justification of the sources of correlation in the motion of the inactivating ball.

Yet, basing on another properties of the measured ionic current, we may attempt to choose the hyperbolic approach as the better one. As it was stated in [19] current produced by the adult locust muscle  $K^+$  channels has the non-Markovian character. Since the hyperbolic diffusion is the non-Markovian process, it seems right to choose it as a proper tool in this situation.

Of course, the hyperbolic equation is not the only possible choice to describe the correlated, non-Markovian motion of the aminoacid ball. One may employ the standard diffusion or Smoluchowski equations with functional coefficients as well. If successful, this will only proof that the phenomenon of inactivation could have a couple of nonunique analytical descriptions equally good, and being able to enlight the process from different view points, not only from the fitting data one.

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