THREE DIMENSIONAL BALL AND CHAIN PROBLEM BY THE HYPERBOLIC RANDOM WALK*

Przemysław Borys†, Zbigniew J. Grzywna

Department of Physical Chemistry and Technology of Polymers
Section of Physics and Applied Mathematics
Silesian University of Technology
Ks. M. Strzody 9, 44-100 Gliwice, Poland

Larry S. Liebovitch

Center for Complex Systems Florida Atlantic University
Boca Raton, FL 33431, USA

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A first passage time distribution (FPTD) based on 3-D hyperbolic diffusion addressed to the "ball and chain" model, is presented. The resulting shape of FPTD with respect to time is shown. The possibility for comparison with experimental data is also provided.

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1. Introduction

The ball and chain problem refers to inactivation process of a potassium channel [1]. The potassium channel consists of a pore formed by four peptide units [2]. At the N-ends of each unit there are four peptide chains that end with hydrophobic sequence which forms a sort of a "ball" [3].

In the open potassium channel the balls can freely move in the surrounding, and it may happen that they hit the channels pore, binding to it and blocking the ion conduction. This is called an N-type inactivation, or ball and chain inactivation [3].

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† pborys@mer.chemia.polsl.gliwice.pl

Natural approach to modelling of this sort of process involves diffusion as the main kinetic mechanism associated with the motion of the ball. This corresponds, on a molecular level to a random walk picture of the moving ball (Brownian particle) [4–6]. (Extensions include fractional diffusion modelling [7]).

When taking into account constraints to the motion in the ball and chain system together with interaction of charged amino acid groups, and ionic gradients, it can be expected that the motion of a ball will reveal some correlation characterized, in average, by time τ. This leads to a correlated random walk problem, and in result, among other effects, to the hyperbolic diffusion equation for the probability density [8–10], *i.e.*

$$\frac{\partial p}{\partial t} + \tau \frac{\partial^2 p}{\partial t^2} = D\nabla^2 p\,, \tag{1}$$

where τ is the correlation time and D, the diffusion constant. It can be easily seen, that going with τ to zero, we can recover a simple parabolic diffusion equation. This idea is supported by literature [10], where through Sirovich's method we can see that long time behavior of densities, obeying equation (1), is diffusive.

The nature of correlations can also be analyzed based on the self similarity of ionic current. The ball and chain must receive inertial correlations of order m/γ, where γ is the damping coefficient and m the mass of ball or chain. Due to the strength of the local electrostatic fields the "native" mass becomes an "effective" one, presumably, orders of magnitude larger. As it was shown elsewhere [11], ionic current shows self similarity in time, *i.e.* there are bursts within bursts within bursts of openings and closings. It gives an opportunity to explain the "local character" of an effective correlation time of the randomly walking ball. Closer to the channel's throat smaller the ratio of average ball distance from the throat to the ball's fluctuations, and smaller the "effective mass" of a ball.

In this paper we investigate the ball and chain problem and formulate the initial and boundary conditions for the diffusion. We also justify the possibility of an analysis of 1-D diffusion modelling. We preform a correlated random walk simulation for the hyperbolic diffusion problem, and show the possibility of obtaining the FPTD curve under such conditions. We also inspect its properties, and search for the possible distinguishing effects compared to a simple parabolic diffusion model (*i.e.* the influence of correlation time on the shape of the curve).

2. Posing the ball and chain problem

The ball and chain problem can be formulated in terms of a transport operator — $\hat{L}$:

$$\hat{L}p(\vec{r},t) = 0\,. \tag{2}$$

The operator may be of various form. For example, it can be a simple diffusion operator

$$\hat{L} = \frac{\partial}{\partial t} - D\nabla^2 \tag{3}$$

or, it can be the damped wave (hyperbolic diffusion) operator

$$\hat{L} = \frac{\partial}{\partial t} + \tau\frac{\partial^2}{\partial t^2} - D\nabla^2\,. \tag{4}$$

The operator acts in a domain

$$|r| \in (0, r_{\max}) \tag{5}$$

with initial and boundary conditions

$$p(\vec{r},0) = \alpha(\vec{r})\,, \tag{6}$$

$$\frac{\partial p(\vec{r},0)}{\partial t} = \beta(\vec{r})\,, \tag{7}$$

$$f_B\left(p(0,t), \frac{\partial^2 p(0,t)}{\partial x^2}, \frac{\partial^2 p(0,x)}{\partial t^2}\right) = 0\,, \tag{8}$$

$$\mathrm{Flux}(\vec{r}_{\max},t) = 0\,. \tag{9}$$

The initial conditions are given in terms of some functions. $\alpha(\vec{r})$ and $\beta(\vec{r})$ which will be determined in the next section.

The first boundary condition (*i.e.* Eq. (8)) describes the absorbing boundary at the channels pore end. The second condition (*i.e.* Eq. (9)) represents the reflection of the ball when it elongates the chain to maximum value. The absorbing condition is not specified simply as $p(0,t) = 0$ (which is true for simple diffusion) for it leads in hyperbolic diffusion problem to a negative reflected wave. In hyperbolic diffusion, the condition can be deduced from the correlated random walk framework to be [12]

$$\frac{\partial^2 p(0,t)}{\partial t^2} = \left(\frac{D}{\tau}\right)^2 \frac{\partial^2 p(0,t)}{\partial x^2}\,. \tag{10}$$

3. Specifying initial conditions

The process of specifying the initial data is of crucial importance (see Fig. 1, Fig. 2).

If we assume that no point in the space can be distinguished, then each position in the volume of half of a sphere $V = 2/3\pi r_{\max}^3$ (where $r_{\max}$ is the length of the chain) is equally possible. If so, then the probability to find the ball at the radius $r \in (0, r)$ equals

$$F(r) = \frac{2/3\pi r^3}{2/3\pi r_{\max}^3} = \frac{r^3}{r_{\max}^3}\,, \tag{11}$$

i.e. the (cumulative) distribution function, that changes with r from 0 to 1, as r goes from 0 to $r_{\max}$. As we can see the probability density function $f = dF/dr$ is simply a parabola. Thus, our initial distribution $\alpha(\vec{r})$ is also a parabola, of the form

$$\alpha(r) = f(r) = \frac{3r^2}{r_{\max}^3} \tag{12}$$

which can be seen in Fig. 2.

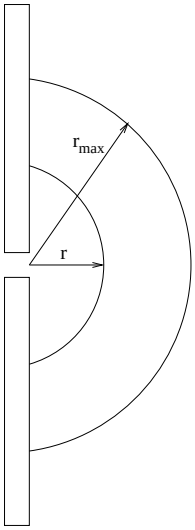

Fig. 1. The volumes associated with various distances from the channels end.

The initial condition $\beta(\vec{r})$ should be constructed from $\alpha(\vec{r})$, after taking into account that each initial condition generates a spherical wave, propagating with constant velocity. Thus, the new value of density after $t + dt$ will be equal to the average value of densities at radius $|r_1| = vdt$ from the considered point. Estimating this value by averaging a square around a

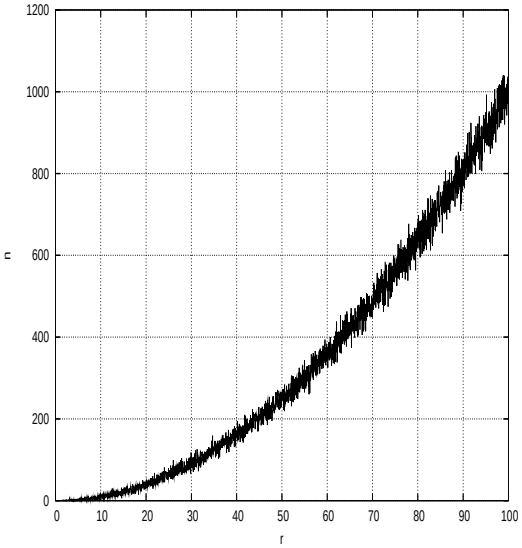

Fig. 2. The histogram of the initial distribution for the ball and chain problem when uniform distribution of initial density in the space is assumed. Number of particles $N = 10^6$. r stands for the radius from the pore center.

specified point, we see that the contributions along the circumference have the same value and we can reduce the problem to average contributions from $\alpha(r - vdt)$ and $\alpha(r + vdt)$ which gives for $t \to 0$:

$$p(r,t) = \tfrac{1}{2}\left[\alpha(r - vt) + \alpha(r + vt)\right], \tag{13}$$

$$\beta = \frac{dp(r,0)}{dt} = -v\frac{d\alpha}{dr} + v\frac{d\alpha}{dr} = 0\,. \tag{14}$$

This is not surprising and states that for short times nothing happens to the initial distribution (which additionally is quite uniform in the considered case).

4. On the probabilities to move to various values of radius r

If we know the relative probabilities of increasing and decreasing the distance of a ball from the channels pore, we would be able to formulate the problem for simple diffusion of it in terms of a random walk in r coordinate (the angular position of spherical coordinates does not matter for the considerations of channel blocking).

Let us take a look at the situation in Fig. 3. We can see that if a particle is found at some radius r, and performs a jump in some direction (where no direction is distinguished), then the probability to jump toward channel

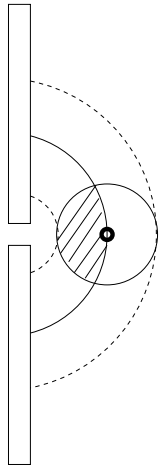

Fig. 3. The possibility of bias in the random walk due to unequal probabilities of going toward and outward of channels pore.

pore (the dashed area) is smaller than that of jumping outward. This is directly connected to the volume $dV = 2\pi r^2 dr$ associated to both sides of the sphere at radius r (the regions separated by a dashed line in Fig. 3). Because of that, a ball jumping from r has larger number of destinations at $r + dr$ than at $r - dr$.

Comparing two adjacent volumes, separated by dr, we see that $dV(r + dr) - dV(r) = 4\pi(r + dr)^2 dr - 4\pi r^2 dr = 8\pi r dr^2 + 4\pi dr^3$. Thus, having the maximum value for $r = r_{\max}$ the bias is limited to the order of dr^2. In diffusive modelling, such bias does not influence the dynamics. Only terms of order dr could do this [10, 13, 14].

These considerations lead to a conclusion that the ball and chain problem can be modeled by an unbiased diffusion in r direction with equal probabilities for increasing and decreasing the radius. This is an important result.

5. Hyperbolic equation

If we allow the ball to wander in the chosen direction for a longer time than dt, for example for time τ, we end up with hyperbolic diffusion equation (see Eq. (1)).

The behavior of the solutions to this equation for short and long time regimes is known from the literature [10]. For short times the decorrelation effects are not visible and the solution behaves like a traveling wave (ballistic motion). Then, after some transient time, the correlation in the motion is getting lost and the solution turns into the diffusive behavior [10].

The ballistic motion out of each point of initial condition (the initial condition is the probability to find the ball in a given point of space when the process starts) corresponds to generation of a spherical wave. If the wave starts at large radius r from the channel pore, the probability to hit the pore is proportional to the weighted average

$$p \sim \int_0^{\pi} \frac{A \sin \alpha}{2\pi r^2} \cos \alpha d\alpha \sim \frac{A}{2\pi r^2}\,, \tag{15}$$

where A is the sub-area of the sphere of radius r, occupied by the pore and α is the angle between channel's wall and the radius r. $\cos \alpha$ is the weight, which scales like the perimeter of the circle that can face the pore at radius r and angle α from the pore.

If r is sufficiently large, parameter A can be viewed constant, since the piece of sphere that is expanded on it tends to be flat (see Fig. 4). Thus, the probability of being directed to the pore center, depending on radius, is chosen to be

$$p \sim \frac{A}{2\pi r^2}\,. \tag{16}$$

This approximation becomes disturbed in the near of the pore where it is difficult to form a sphere around initial condition that would not reach too

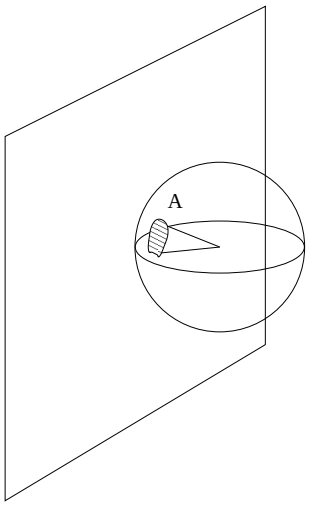

Fig. 4. The directions, that allow to end the travel of the ball by closing the pore. The dashed area is the area occupied by the pore, the sphere center is the initial condition of the ball, and the sphere area represents the possible initial directions of motion. The cone represents directions, ending in the pore.

deep into the pore and besides the assumption that area A lies on the sphere is obviously violated. Additionally the initial condition for the density in a small distance r from the pore is not parabolic (because the pore is not a point structure).

6. The first passage time distribution for short times-estimation and numerical verification

For short times we consider the density front to move as a traveling wave. The amount of density, that gets into the channel pore at time t equals the fraction of the density initially placed at a distance vt from the channel pore (v represents the density front velocity), which traveled in the proper direction. This means that it is proportional to the product of two probabilities (12), (16):

$$\mathrm{FPTD}(t) \sim (vt)^2 \, \frac{A}{2\pi(vt)^2} \, . \tag{17}$$

One should note that this equation is limited by construction to the time $vt < r_{\max}$ (because for higher radius the density of initial condition does not grow anymore and reflections enter to the considerations).

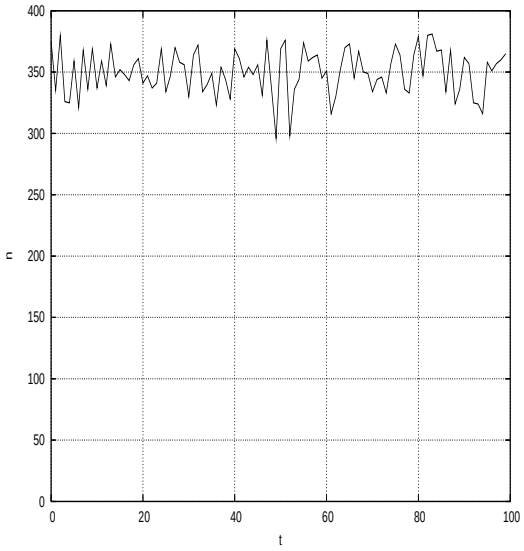

Fig. 5. The flatness of the FPT histogram curve shown by enlarging the correlation time to $\tau = 100$, where pore radius has 10 length units, the space step and time step equals 1 and, number of test particles $n = 10^6$, number of simulation repeats $n_r = 15$, maximum distance of the ball from the pore $R_{\max} = 100$.

The prediction shows that the first passage time distribution should be a flat line. The numerical calculations confirm this for a wide range of times after the experiment beginning. This can be seen in Fig. 5, where large correlation time was used. On the other hand on Fig. 6 we can see the influence of correlation time on the shape of the curve.

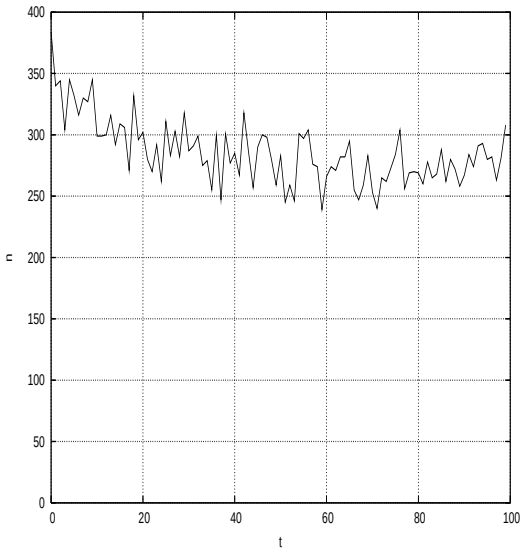

Fig. 6. The histogram done in the same circumstances as in Fig. 5 with the exception of using $\tau = 10$ instead of $\tau = 100$. The chart starts at the same value and then drops down after correlation time.

This shape is not expected in biological charts. In biology we would expect first passage time curve to grow from zero to some maximum, and then decay slowly [12].

The decay is obviously also included in the hyperbolic model (*i.e.* in the random walk simulation in the end all of the test particles hit the pore and stop their motion (Fig. 7)), but the initial lack of probability for short times in first passage time distribution is not present in hyperbolic modelling. Does this mean the model is useless? No, because we can construct the experiment in such way that we obtain the desired shape of the FPTD curve.

To achieve this, we need to assume that the initial condition forbids the ball to stay in the near of the pore. This could be expected if the recovery from inactivation ejects the ball from the pore to some distance (for example due to tensions in the chain or electrostatic interactions; the mechanism is still not fully understood [17]). Then obviously, because the density from initial condition requires some time to get to the pore, we obtain an expected shape of FPTD curve (Fig. 8).

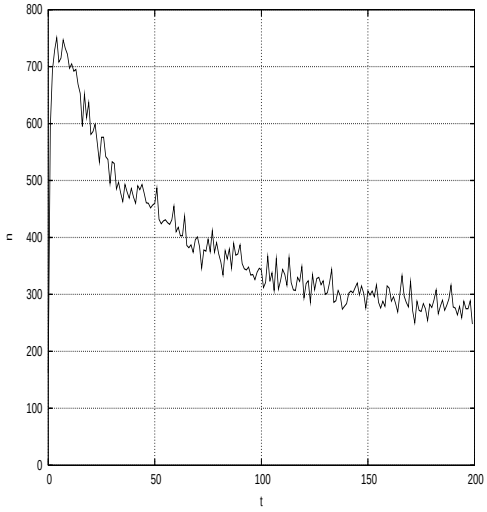

Fig. 7. The decay of FPT histogram curve forced by enlarging the pore radius to 50 units in the simulation, where space step and time step equals 1 and $\tau = 1.5$, number of test particles $n = 10^6$, number of simulation repeats $n_r = 2$, the repulsion from the pore in initial condition $R = 2$, maximum distance of the ball from the pore $R_{\max} = 100$.

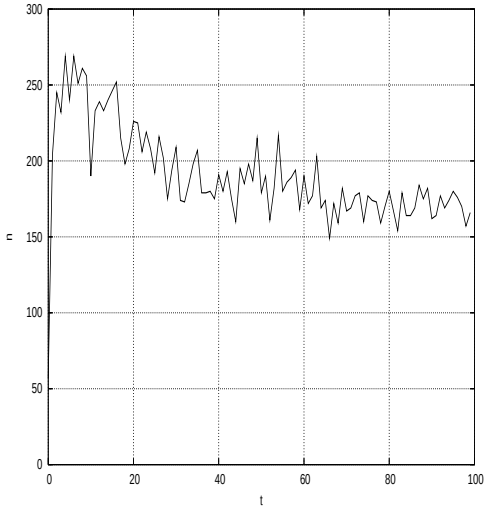

Fig. 8. A FPT histogram curve, that is similar to biological curves. The pore radius in the simulation was set to 10 units, where space step and time step equals 1 and $\tau = 1.5$, number of test particles $n = 10^6$, number of simulation repeats $n_r = 15$, the repulsion from the pore in initial condition equals $R = 2$, maximum distance of the ball from the pore $R_{\max} = 100$.

7. The possible dependence of correlation time on the length of the chain

The correlation time τ can possibly depend on the length of the chain inspected in the problem. A schematic illustration of this idea is put in Fig. 9. We can see that depending on the type of motion in the area of the chain residues, the undisturbed travel can take distances that scale like n or n^2 with the length of the chain. Because the velocity of motion is fixed in this model, we can say that the freely traveled distance $L \sim v\tau \sim \tau$, and hence we can get the scaling of τ for the mentioned types of motion.

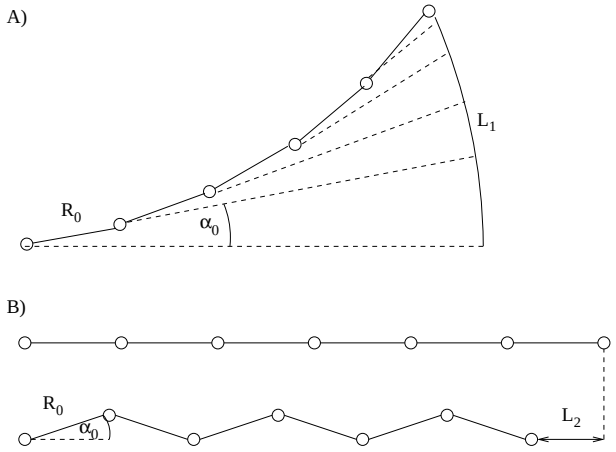

Fig. 9. The scaling of freely traveled distance with the length of the chain. In case (A) the scaling is proportional to $L \sim (n\alpha_0)(nR_0)$, and in case (B) it is proportional to $L \sim nR_0$.

Because the total available number of possible modes of motion covers both cases, we cannot say that τ in general scales like n^2 or n. The scaling would be expected to be of some intermediate type, *i.e.* a fractal scaling.

8. Concluding remarks

We have investigated the ball and chain problem. We have formulated the initial and boundary values for the hyperbolic and parabolic diffusion models. We have shown that diffusion analysis can be preformed in one dimension. We have also shown that it is possible to obtain a FPTD curve from the hyperbolic diffusion framework. The framework predicts some properties for this type of model, *i.e.* that the ball should be ejected from the binding site in the recovery from inactivation, and that for the short time regime the distribution is expected to be flat.

After a longer time period, the regular diffusive regime enters, and the scaling obeys the diffusive FPT for long times, $\exp(-t/\tau_1)$ where $\tau_1 \sim n^2$, where n is the number of residues in the chain [4, 10, 15].

Interesting continuation of the work presented in this paper would be to compare the predictions with charts, found in biophysical measurements. In such measurements (whole cell voltage clamp), we usually have a chart of current, passing through potassium channels versus time [16]. This current is proportional to the number of open channels, and therefore to the probability that a channel is open at given time.

This chart has therefore the interpretation of survival probability that a channel remains open at time t. To obtain FPT distribution, we need to notice that this probability is a cumulative distribution of probability of closing the channel, *i.e.*

$$P_{\text{surv}} = 1 - \int_0^t \text{FPTD}(\tau) d\tau \,. \tag{18}$$

Using this equation it is possible to extract the FPTD from measurements, and to decide whether it is driven by a hyperbolic diffusion process (*i.e.* to compare the flatness of the curve in the region of the maximum and in the beginning of the tail-recall Fig. 5 and Fig. 6).

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REFERENCES

[1] C.M. Armstrong, *Physiol. Rev.* **61**, 644 (1981).

[2] D.A. Doyle, J.M. Cabral, R.A. Pfuetzner, B.T. Chait, R. MacKinnon, *Science* **280**, 69 (1998).

[3] G. Yellen, *Quarterly Rev. Biophys.* **31**, 239 (1998).

[4] L.S. Liebovitch, L.Y. Selector, R.P. Kline, *Biophys. J.* **63**, 1579 (1992).

[5] R.M.W. Collins, *American Journal of Undergraduate Research*, **3**, 27 (2004).

[6] I. Goychuk, P. Hanggi, *Proc. Natl. Acad. Sci.* **99**, 3552 (2002).

[7] I. Goychuk, P. Hanggi, *Phys. Rev.* **E70**, (2004).

[8] Z.J. Grzywna, J.K. Stolarczyk, *Acta Phys. Pol. B* **36**, 1595 (2005).

[9] Z.J. Grzywna, J. Luczka, *Acta Pharm. Jugosl.* **41**, 327 (1991).

[10] E. Zauderer, *Partial Differential Equations of Applied Mathematics*, Wiley, 1989.

[11] J.B. Bassigntwaighte, L.S. Liebovitch, *Fractal Physiology*, American Physiological Society, 1994.

[12] K. Malysiak, P. Borys, Z.J. Grzywna, *Acta Phys. Pol. B* **38** (2007), these proceedings.

[13] R. Metzler, J. Klafter, *Phys. Rep.* **339**, 1 (2000).

[14] R. Metzler, J. Klafter, *J. Phys. A* **37**, 161 (2004).

[15] J. Crank, *The Mathematics of Diffusion*, Clarendon Press, Oxford 1976.

[16] B. Hille, *Ionic Channels of Excitable Membranes*, Sinauer Associates, 2001.

[17] S.D. Demo, G. Yellen, *Neuron* **7**, 743 (1991).