ON THE POSSIBLE METHODS FOR THE MATHEMATICAL DESCRIPTION OF THE BALL AND CHAIN MODEL OF ION CHANNEL INACTIVATION

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Abstract: Ion channels are large transmembrane proteins that are able to conduct small inorganic ions. They are characterized by high selectivity and the ability to gate, i.e. to modify their conductance in response to different stimuli. One of the types of gating follows the ball and chain model, according to which a part of the channel’s protein forms a ball connected with the intracellular side of the channel by a polypeptide chain. The ball is able to modify the conductance of the channel by properly binding to and plugging the channel pore. In this study, the polypeptide ball is treated as a Brownian particle, the movements of which are limited by the length of the chain. The probability density of the ball’s position is resolved by different diffusional operators – parabolic (including the case with drift), hyperbolic, and fractional. We show how those different approaches shed light on different aspects of the movement. We also comment on some features of the survival probabilities (which are ready to be compared with electrophysiological measurements) for issues based on the above operators.

Key words: Voltage-gated ion channel, N-inactivation, Hyperbolic diffusion, Subdiffusion
INTRODUCTION

The controlled transport of ions across biological membranes is a process of primary importance for every living cell. Cell volume regulation, hormonal secretion and the creation and propagation of neural impulses are all based on the controlled transport of ions. Due to its structure, the cellular membrane itself is unable to provide sufficient fluxes of ions or their proper modulation. To fulfill these purposes, the membrane is equipped with specialized proteins called ionic channels. Channels belong to the class of integral membrane proteins. Their shape is usually tubular, with an empty (water-filled) interior that creates a passage for ions. A single channel protein may be composed of a few hundreds of amino acids, which translates to a mass of the order of 10 to 100 kDa, and a length (measured along the pore) up to 10 nm. The abundance of ion channels in the cellular membrane varies greatly depending on the cell type. It may even reach 1000 (channels/μm²) [1].

The superfamily of ionic channels is very broad, coded by at least 143 genes in the human genome [2]. This diversity is even larger due to the possibility of alternative splicing [3]. The whole superfamily of ionic channels is subdivided into families using the criterion of ion-type selectivity: channels belonging to a given family are only permeable to one type of ion.

One important property of ionic channels is called gating. Gating is the phenomenon of modulation of ionic flux (channel permeability) in response to different types of stimuli, including the binding of a given chemical species, and changes in the transmembrane potential or in the membrane tension. Gating occurs through proper, reversible conformational changes induced by the action of stimuli that lead to the closing/plugging of the channel pore.

This study was mostly inspired by earlier experimental and theoretical studies [3-5] on a special type of gating, called fast or N-type inactivation. It occurs in voltage-gated sodium and potassium channels. The material presented here is an extension of the diffusional approach to the inactivation described in [6].

FAST INACTIVATION OF VOLTAGE-GATED SODIUM AND POTASSIUM CHANNELS

Voltage-gated channels have the ability to open or close in response to changes in the transmembrane potential. The details of the mechanism of voltage gating may be found in [7]. For sodium and potassium voltage-gated channels, it was observed that once the positive transmembrane potential opens the channel, the current of ions rapidly decreases (within a ms time scale), even when the potential is held constant [8]. Thus, shortly after opening, the channel falls into a non-conductive state in a process called fast or N-type inactivation [8]. This is illustrated in Fig. 1.
Extensive experimental studies on fast inactivation were conducted by Armstrong and Benzanilla for sodium channels [9, 10], and by Hoschi et al. in [11] and Zagotta et al. [12] for potassium channels. Based on these papers, and the structural studies on the inactivation gates of sodium [12] and potassium [13] channels, the following features of inactivation emerge.

- Fast inactivation is mediated by the intracellular part of the ionic channel, referred to as the inactivating gate.
- Once the channel has been opened by the positive transmembrane voltage, the gate may bind to its receptor, located on the channel pore inlet, and plug its pore, thereby causing inactivation.
- The inactivating gate of the potassium channel is formed by its N-endings; it has two domains, namely the ball (20 amino acids) and the polypeptide chain (40 amino acids) on which it is tethered [11]. Excision of the ball prevents inactivation, and mutations in the region of the ball make inactivation less effective.
- The inactivating gate of the sodium channel is formed by the intracellular linker between channel domains III and IV. The linker looks like a hinged lid and is able to swing and block the channel inlet, causing inactivation. It contains the IFM motif that binds to the receptor on the channel inlet.

The fast inactivation of a sodium or potassium channel as described above is termed inactivation via the ball and chain mechanism.
THE PHYSICAL FORMULATION OF THE BALL AND CHAIN MODEL

The usual modeling of an ionic channel’s state transitions (including inactivation) works on the assumption that any transition is a Markov process. This essentially reduces the modeling to the estimation of rate constants for a set of coupled chemical reactions [14, 15]. This type of modeling does have advantages, but also suffers from some serious drawbacks, like the difficulty in relating the rate parameters to the physical features of the channel or its surroundings. Moreover, in some cases, the kinetics of the processes occurring in ionic channels exhibits a dependence upon previous states (like the recovery of a sodium channel from slow inactivation), and consequently has a rather non-Markovian character.

An alternative approach to the modeling of the inactivation of a voltage-gated ionic channel via the ball and chain mechanism may be found in [5, 6, 16, 17]. All these studies take as a starting point the hypothesis that the inactivation rate is controlled by the diffusion of an inactivating gate in the region, restricted by the length of its tether.

The aim of this paper is to provide new possibilities for the diffusional modeling of the ball and chain inactivation by capturing diffusion-accompanying effects like a crowded surrounding or the existence of an external force field.

As stated previously, the basic observation that leads to the diffusional description of inactivation is that the inactivating part of a channel (the ball in case of potassium, the lid in case of sodium) undergoes restricted Brownian motion due to its perpetual collisions with surrounding molecules.

In our approach, we used the continuous description in terms of the probability density functions, the dynamics of which is governed by various diffusional operators. The general setup of the problem for all the operators used is this study is shown in Fig. 2.

![Fig. 2. The general setup of the ball and chain for the diffusional approach. L is the length of the chain in the potassium channel or the length of the lid in the sodium channel.](image)

As emerges from Fig. 2, we reduced the problem of inactivation to one dimension. This may be done due to the symmetry of movements of the inactivating ball and the inactivating lid. Moreover, we sought a solution with the initial position of the inactivating particle given exactly, as the solution to
such a problem, given homogenous boundary conditions, is easily generalized to other initial conditions (since Green’s function applies for all).

As shown in Fig. 2, the space for a random walking inactivating particle is restricted to the region (0, L) with the reflecting boundary imposed in x = L. This formulation mimics the limitations imposed by the length L of a tether (i.e. length of the chain or the length of the lid). The absorbing boundary condition at x = 0 mimics the binding place of the inactivating particle and states that once the particle collides with the channel, it irreversibly binds to its surface.

In conclusion, the models presented in this paper do not describe the quasi-periodic behavior of the channel, only its inactivation, i.e. its transition from the open to the inactivated state.

THE TRANS-CHANNEL CURRENT AND THE SURVIVAL PROBABILITY OF ITS OPEN STATE

The standard electrophysiological technique used to investigate the kinetics of the inactivation of an ion channel is the patch clamp method. The basis of this is the formation of a tight seal (a so-called gigaseal) between the measuring electrode and the patch of membrane. The tight seal allows the detection of small currents originating from a single channel that are of the order of pA. In certain modes, the patch clamp allows the measurement of currents flowing through a larger group of channels or even through the channels from a whole cell (whole-cell patch clamp). It is worth mentioning that under the assumption that channels inactivate independently of each other, and that during the measurement they are subject to uniform conditions, the measurements from a group of channels may be understood as the average of repeated measurements over a single channel [18].

As stated in [6], the diffusional approach to the ball and chain produces a quantity that is directly comparable with the electrophysiological measurements of an averaged, inactivating current. This quantity is the survival probability, defined as:

$$SP(t) = \int_0^L p(x,t)dx$$  \hspace{1cm} (1)

where \(p(x,t)\) is the probability density function of the position of the inactivating gate. The survival probability is the time-dependent probability that the inactivating particle survives in the region (0, L), i.e. that at any given time (counting from the moment of opening), the channel remains open. If the survival probability is rescaled as

$$I(t) = SP(t) \cdot I_{\text{max}} = \int_0^L p(x,t)dx \cdot I_{\text{max}}$$  \hspace{1cm} (2)

where \(I_{\text{max}}\) is the current flowing through the open channel (or through a group of open channels), it gives the time course of the averaged patch clamp...
measurement on a single channel (or a single measurement simultaneously capturing the current from a sufficiently large group of channels).

**THE APPROACH TO THE BALL AND CHAIN WITH DIFFERENT DIFFUSIONAL OPERATORS**

Diffusion in the cellular medium is a complicated process. It is often accompanied by various side-phenomena, including the external force fields of the different sources that may act on a randomly walking particle, or the effects of the level of crowding in the surroundings in which the particle wanders. The nature of those effects may also vary over time due to the living processes occurring in the cell.

As can be seen from [6], having only a time series of a current from electrophysiological measurements, it is impossible to recognize the one true mechanism that produces the output, especially since the quality of data fitting is important, but not an ultimate criterion in testing the model’s validity. The same property of the considered system may also manifest itself in different ways, depending on the approach. The example is the description of the correlated random walk in terms of hyperbolic diffusion and Fickian diffusion, with the diffusion coefficient being the function of the dependent variable [19]. In this paper, we present several possible models for voltage-gated channel inactivation. Each of the employed diffusional operators indicates a different feature of the inactivating particle’s behavior. The parabolic equation models the simple diffusion of the ball, the hyperbolic equation is more accurate for short periods and includes the finite speed of the motion of the ball, the Smoluchowski equation includes the external forces acting on the ball, and the subdiffusion equation includes the motion of the ball through an environment crowded with obstacles.

Of the presented approaches, the standard Fickian and hyperbolic ones have already been subjected to the data fitting [6]. They concurred well with the measurements, and yielded the expected diffusion coefficients. However, the hyperbolic approach showed an unexpectedly high correlation time, indicating that the correlation may not only be inertia originated.

Diffusion in the external potential (the Smoluchowski approach) is the current subject of comparison with the experimental data from the channels, where the electrostatic field seems to have an easily distinguishable influence on the inactivation [3-4].

**THE PARABOLIC EQUATION OF DIFFUSION**

The standard approach with Fick’s second law is an easy and illustrative way to visualize the idea of diffusional modeling of the ball and chain. Thus, the following problem is posed:
where $D$ is the diffusion coefficient of the ball’s probability density, $x_0$ is its initial position, and $L$ is the length of the chain (or lid). $p(x,t)$ is the probability density function of the ball’s position.

The imposed boundary conditions are:

- $p(x,t)|_{x=0} = 0$ — absorbing b.c., to mimic the irreversible binding of the inactivating particle to its receptor on the surface of the channel;

- $\frac{\partial p(x,t)}{\partial x}|_{x=L} = 0$ — reflecting b.c., to limit the available space for a random walker.

The formulated problem is well tractable both numerically (standard Crank-Nicolson scheme) and analytically through the method of separation of variables. Following [21], the analytical solution takes the well-known form:

$$p(x,t) = \sum_{m=0}^{\infty} \frac{2}{L} \sin \left( \frac{(2m+1)\pi}{2L} x \right) \sin \left( \frac{(2m+1)\pi}{2L} x_0 \right) \exp \left(- \left( \frac{(2m+1)\pi}{2L} \right)^2 \cdot D \cdot t \right)$$

The survival probability is easily obtained by integration. Fig. 3 shows how the survival probability depends upon $D$.

Fig. 3. The survival probability plots for different (as per the legend) values of $D$. $L = 1$, $x_0 = 0.3$. The results are intuitive: for a higher diffusion coefficient, the inactivation goes faster.
THE HYPERBOLIC EQUATION OF DIFFUSION

This equation (also used to describe a propagating damped wave) is the generalization of the parabolic diffusion equation for short periods. Its derivation from the persistent random walk was originally presented in [22] and is also described in [23]. In contrast to the parabolic diffusion, this operator introduces a finite speed of propagation of an impulse. For longer periods, however, both operators produce the same results. The problem posed with the hyperbolic operator takes the form:

\[ \begin{align*} 
  &x \in (0, L), \quad t \in (0, +\infty) \\
  &\frac{\partial p}{\partial t} + \frac{\tau}{2} \frac{\partial^2 p}{\partial t^2} - D \frac{\partial^3 p}{\partial x^3} = 0 \\
  &p(x, t) \big|_{x=0} = \delta(x - x_0) \\
  &\frac{\partial p(x, t)}{\partial t} \big|_{t=0} = 0 \\
  &2\tau \frac{\partial p(x, t)}{\partial t} \big|_{t=0} = 2\tau \cdot \nu \frac{\partial p(x, t)}{\partial x} \big|_{t=0} - p(x, t) \big|_{t=0}, \quad \frac{\partial p(x, t)}{\partial x} \big|_{x=0} = 0
\end{align*} \tag{5} \]

where \( D \) stands for the diffusion coefficient, and \( \tau \) indicates the correlation time, which may be interpreted in the framework of the random walk as the average time after which the particle changes the direction of its motion. The velocity \( v \) of a traveling impulse is defined as:

\[ v = \frac{D}{\sqrt{\tau}} \tag{6} \]

For \( \lim_{\tau \to 0^+} \), the correlation in motion is lost, and set (5) reduces to set (3) with the infinite speed of propagation that emerges from equation (6).

The second initial condition is necessary to pose the hyperbolic problem well, since the operator contains a time derivative of the second order. The absorbing boundary condition for the hyperbolic diffusion takes a rather non-standard form. Its detailed derivation (from the random walk) may be found in [6] and [24]. The derivation of an analytical solution of (5) in terms of the hyperbolic Bessel functions may also be found in [6] and [24]. For this operator, the correlation time plays a crucial role (see Fig. 4).

For increasing \( \tau \), the survival probability falls less rapidly, as the velocity of propagation decreases. For higher values of \( \tau \), the hyperbolic diffusion equation manifests its wave nature, by the contribution of the wave of probability reflected from the right boundary. This may be observed for \( \tau = 0.1 \) as a small “cusp” for \( t = 0.5 \).
THE SMOLUCHOWSKI EQUATION

The inactivating lid of the sodium channel effectively has nine positively charged amino acids [25], while the inactivating ball of the potassium channel carries two positively charged amino acids [26]. Under some conditions, the electrostatic interactions between the charged inactivating particle and the interior of the channel have a visible impact on the rate of inactivation [26]. Therefore, in the diffusional approach to the ball and chain, the electrostatic interaction should also be included via the phenomenon of drift. The simplest way to incorporate the external potential field is via the Smoluchowski equation, which describes the diffusion in the linear potential. The ball and chain problem posed with the Smoluchowski equation takes the following form:

\[
\begin{aligned}
 x \in (0, L), \ t \in (0, +\infty) \\
 \frac{\partial p(x,t)}{\partial t} &= -c \frac{\partial p(x,t)}{\partial x} + D \frac{\partial^2 p(x,t)}{\partial x^2} \\
 p(x,t)\big|_{x=0} &= \delta(x-x_0) \\
 p(x,t)\big|_{x=L} &= 0, \quad -D \frac{\partial p(x,t)}{\partial x}\bigg|_{x=L} + c \cdot p(x,t)\bigg|_{x=L} = 0
\end{aligned}
\]  

(7)

where \(D\) stands for the diffusion constant, and \(c\) is a drift coefficient. The boundary condition is posed in \(x = L\), and comes from the definition of flux, which reads:
The procedure for the analytical solution begins with the substitution (Fürth substitution) of the original \( p(x,t) \) with:

\[
P(x,t) = p^*(x,t) \cdot \exp\left(\frac{c}{2D} x - \frac{c^2}{4D} t\right)
\]  

(9)

After this substitution, the problem is reduced to an ordinary diffusion, supplemented by absorbing- and Robin-type boundary conditions:

\[
\begin{aligned}
\frac{\partial p^*(x,t)}{\partial t} &= D \frac{\partial^2 p^*(x,t)}{\partial x^2} \\
p^*(x,t) \bigg|_{t=0} &= \delta(x - x_0) \cdot \exp\left(-\frac{c}{2D}\right) \\
p^*(x,t) \bigg|_{x=L} &= 0, \quad \frac{\partial p^*(x,t)}{\partial x} \bigg|_{x=L} = 0
\end{aligned}
\]  

(10)

Following [21], the solution to this auxiliary problem may be found in the form:

\[
p^*(x,t) = \sum_{n=0}^{\infty} \frac{\beta_n^2 + H^2}{L(\beta_n^2 + H^2) + H^2} \sin(\beta_n \cdot x_0) \exp(-H \cdot x_0) \sin(\beta_n \cdot x) \cdot \exp(-\beta_n^2 \cdot D \cdot t)
\]  

(11)

where \( H = \frac{c}{2D} \cdot \beta_n \) are the positive roots of the following transcendental equation:

\[
\beta_n \cot(\beta_n L) + H = 0
\]  

(12)

Having \( p^*(x,t), p(x,t) \) is easily found with (9). Unfortunately, this method only works for negative values of \( c \). When positive \( c \) is taken, the Robin boundary condition forces the solution of an auxiliary problem to take negative values, which are unacceptable as probabilities. A rough justification of this may be provided by noting that the positive \( c \) induces a positive value for the slope of \( p(x,t) \) at the boundary. In effect, \( p^*(x,t) \) fulfills this requirement by taking the negative values.

Thus, for the treatment of cases with positive \( c \), we are left with some numerical solvers. For the diffusion-dominated problems, the standard Crank-Nicolson scheme with upwind finite differences works well for sufficiently small time and position increments. According to the literature, for the drift-dominated problems, other methods should be used, preferably those belonging to the finite-volume class, like the Quick scheme [27].
Fig. 5. The dependence of the survival probability \(S_P(t)\) on the drift coefficient \(c\) for the diffusion coefficient \(D = 1\), \(L = 1\), \(x_0 = 0.3\).

Fig. 5 shows the \(S_P(t)\) obtained by the integration of (9) with the applied (11). An increase in the drift directed into the channel causes the survival probability to fall more rapidly.

**SUBDIFFUSION**

The cytoplasm of a living cell is a fluid structured in many length scales [28]. At the range of \(\mu\)m, organelles (mitochondria, Golgi apparatus) may be found. The endoplasmatic reticulum imposes its structure at the length scale of 100 nm. Refining the length scale, one may still find floating molecules of sugars, fats, and proteins, which constitute around 40% of the cytoplasm volume [29], providing a crowding environment at the level of nanometers.

To grasp the features of a crowd when modeling diffusion in the cellular interior, the subdiffusive approach has been used [30, 31]. The subdiffusion equation may be derived on the basis of a continuous time random walk, with a long-tailed probability density of waiting times, behaving in the limit of large \(t\) as

\[
(1 + \alpha \tau) \propto t^{1+\alpha} \quad [32].
\]

On the basis of a continuous time random walk analogy, it is clear how the subdiffusion handles the crowded surroundings. It simply provides the description of a random walker that may get stuck in a place with a diverging characteristic (mean) waiting time. The characteristic feature of subdiffusion is the power law scaling of the mean square displacement of a random walker, i.e. \(\langle x^2(t) \rangle \propto t^\alpha\), where \(\alpha\) is a parameter that takes the values \(\alpha \in (0,1)\) and determines the strength of the subdiffusive regime. For low values of \(\alpha\), the subdiffusive effects are dominant, while for \(\alpha = 1\), Fickian diffusion is recovered.
We applied the subdiffusive approach to the ball and chain model of inactivation. Following the approach of [32, 33], we posed the following problem:

\[
\begin{aligned}
x \in (0, L) \quad t \in (0, +\infty) \\
\frac{\partial p(x, t)}{\partial t} &= \frac{1}{\alpha} D_t^{1-\alpha} \left[ K_\alpha \frac{\partial}{\partial x} \int_0^t p(x, t') \, dt' \right] \\
p(x, t) \big|_{t=0} &= \delta(x - x_0) \\
p(x, t) \big|_{x=0, x=L} &= 0
\end{aligned}
\]  

(13)

where \( K_\alpha \) is the generalized diffusion constant, and \( _0 D_t^{1-\alpha} \) denotes Reimann-Liouville fractional differentiation of the order \( 1 - \alpha \), thus:

\[
_0 D_t^{1-\alpha} p(x, t) = \frac{1}{\Gamma(\alpha)} \frac{\partial}{\partial t} \int_0^t (t-t')^{\alpha-1} p(x, t') \, dt'
\]

(14)

where \( \Gamma(\alpha) \) is the gamma function (factorial generalized to real and imaginary numbers).

As seen in (14), because of the integration, the fractional derivative in a Riemann-Liouville sense is no longer a local property of a function. This implies that the dynamics of the probability density function of a system undergoing subdiffusion depends on all its previous values, i.e. on the history of the system. The strength of this dependence is dictated by the parameter \( \alpha \). For \( \alpha = 1 \), the denominator under the integral in formula (14) equals 1, and the standard Fickian diffusion is recovered. For low values of \( \alpha \), the subdiffusive regime dominates.

The solution of problem (13) can be readily obtained through separation ansatz, as shown in [33]. The solution takes the following form:

\[
p(x, t) = \sum_{n=0}^{\infty} \frac{2}{L} \sin \left( \frac{(2m+1)\pi}{2L} x_0 \right) \sin \left( \frac{(2m+1)\pi}{2L} x \right) \cdot E_\alpha \left( -\left( \frac{(2m+1)\pi}{2L} \right)^2 D \cdot t^\alpha \right)
\]

(15)

where \( E_\alpha \) denotes the Mittag-Leffler (generalized exponential) function. For \( \alpha = 1 \), equation (15) reduces to the solution of (3), as the Mittag-Leffler function reduces to the standard exponential function, which may be proven by a series expansion [33].

\[
E_\alpha(x) = \sum_{n=0}^{\infty} \frac{(x)^n}{\Gamma(1+\alpha \cdot n)} \Rightarrow E_1(x) = \sum_{n=0}^{\infty} \frac{(x)^n}{\Gamma(1+n)} = \sum_{n=0}^{\infty} \frac{(x)^n}{n!} = \exp(n)
\]

(16)

The solution to problem (13) can be alternatively obtained using the subordination method. However, for the problem with a finite spatial domain,
the solution along the separation ansatz is more convenient – it demands less computational efforts, and provides a formula, that is easily reducible the to the Brownian case.

From equation (15), the survival probability may be calculated according to the definition given in (1). Fig. 6 shows how the survival probability depends upon $\alpha$.

It can be observed that for short periods, the subdiffusive survival probability falls more rapidly, which may be supported by the analysis of the behavior of the mean square displacement. For longer periods, the more subdiffusive the case, the more slowly it falls.

It should also be noted that the value of the generalized diffusion constant $K_\alpha$ depends on $\alpha$. The exact dependence can be found using detailed knowledge about the system (the distribution of traps, the PDF of waiting times, etc.). Since the electrophysiological measurements do not bear such information, when comparing theory with experimental data, the $K_\alpha$ should be the subject of a data fitting. An example of an exact dependence of the generalized diffusion constant upon the subdiffusive regime strength may be found in [32], where the subdiffusion is derived from a continuous time random walk.

**SUMMARY**

The diffusional approach to the ball and chain model is well justified. It provides the link between the kinetics of fast inactivation and the structural features of the channel or its surroundings. As shown, the standard approach through simple Fickian diffusion may be enriched by the inclusion of some additional diffusion-accompanying effects, such as the presence of an external potential field or crowded surrounding, or correlation in the motion of the inactivating particle.
The survival probability curves for each of the cases considered show how the strength of those additional effects influences the inactivation dynamics. The presented approaches may be further generalized by the modification of the boundary conditions to account for the kinetics of the binding of the inactivating particle to its receptor. This is the subject of our current research.

The models proposed in this paper should be most effective when used for the comparative analysis of electrophysiological measurements under different external conditions. For example, we would use a simple diffusional approach to grasp the behavior of an inactivating channel with deletions or insertions in the chain, leading to its shortening or elongation. Such experiments were conducted in [11, 12], and were found to result in changes in the spatial domain length L. Modifications in the charge of the inactivating ball, and/or modifications in the charge density in the surroundings lead to changes in the ball’s drift, which can be modeled via the Smoluchowski equation. Such experiments were conducted in [26], where the role of long range electrostatics in the inactivation process was explicitly stated.

The effects of correlation in the ball’s random walk that could be emphasized by the hyperbolic diffusion operator should be easily matched in the measurements due to the characteristic cusps (Fig. 4), provided that the correlation is strong enough. In the registered time scales, a correlation of the ball’s motion may appear, for example due to the relaxation of stresses in the amino acid chain that links the ball to the channel. The correlation in the inactivating current in single channel measurements was studied in [43], and the hyperbolic equation we propose might be one of the tools to study the effects of correlation in the whole-cell measurements.

To the best of our knowledge, the subdiffusive behavior has yet to be the subject of an electrophysiological study in the context of N-inactivation, so the formulation of the model might be a good stimulator for experimental researchers to search for heavy tailed inactivating currents at a remarkable level of molecular crowd in the channel surroundings.

By fitting the proposed models to a single measurement, it is not always possible to distinguish which of the diffusion-accompanying effects appeared in the output. For example, the subdiffusive effects should be well recognized even from that single measurement (the long tail of the current). On the other hand, the distinction between the drift and drift-free cases may give rise to some difficulties. By raising the diffusion constant in the parabolic model, one may achieve very similar SP curves as for the Smoluchowski equation with a lower diffusion coefficient but with drift directed toward the channel. The interplay between drift strength and the diffusion coefficient within the Smoluchowski-based model may also yield a similar output, as illustrated by Fig. 7.
Fig. 7. A comparison of the SP(t) for the Smoluchowski equation (two set of parameters) and the parabolic diffusion equation.

To conclude, there is a family of analytical forms of solution which uniquely exists in the form of a graph. Thus, the solution is unique but may be presented in various forms, from either one operator or many. The choice of a diffusional operator for a certain case must be supported by additional knowledge on the system, and might depend on our subjective intention of how we want to emphasize its properties. The successful application of various approaches to one case proves that the phenomenon has a few analytical descriptions, highlighting its different features.

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