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Relevance of quantum mechanics on some aspects of ion channel function

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Abstract

Mathematical modeling of ionic diffusion along K ion channels indicates that such diffusion is oscillatory, at the weak non-Markovian limit. This finding leads us to derive a Schrödinger–Langevin equation for this kind of system within the framework of stochastic quantization. The Planck’s constant is shown to be relevant to the Lagrangian action at the level of a single ion channel. This sheds new light on the issue of applicability of quantum formalism to ion channel dynamics and to the physical constraints of the selectivity filter.

Keywords

Ion channel; Potassium; Stochastic mechanics; Schrödinger-Langevin equation

1. Introduction

Ion channels are transmembrane protein structures that selectively allow given ion species to travel across the cell membrane. Zhou et al. [1] demonstrate that the channel protein transiently stabilize three K^+ states, two within the selectivity filter and one within the water basket towards the intracellular side of the selectivity filter. Experimental evidence indicates that the selectivity filter is devoid of water molecules other than single water molecule between K ions [2]. By contrast, the basket is water molecule rich. We propose a Generalized Langevin Equation (GLE) that combines Markovian and non-Markovian processes at different time scales to describe the dynamics of ionic flow in K ion channels. This approach affords the development of an algorithm that describes oscillatory ionic diffusion along the selectivity filter. The resulting oscillatory functional behavior, with exponential decay, is obtained at the weak non-Markovian limit with two distinct time scales. They correspond to the processes of ionic diffusion and ionic drift. This oscillatory motion can be viewed as a time reversible stochastic process where the oscillatory time scale is very small compared to the diffusional time scale. The non-Markovian behavior, having a memory kernel associated with the frictional forces is

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due to the shear viscosity of water in the basket, considered as glue-like compared with ordinary water, due to the change in length scale [3]. Indeed, it is found in the recent experiments that the viscosity of water increases when the inner lining of nano-cavity is hydrophilic as well as hydrophobic [4]. However, the viscosity increases dramatically in case of hydrophilic surface. As a result of this spatial arrangements of water molecules, at the selectivity filter, ion movement may be considered a time reversible Markovian while at the water basket, it would behave in a non-Markovian regime.

Recent developments concerning quantum processes [5] demonstrate that there exists time reversible Markov process corresponding to Schrödinger's equation (at least in the non-relativistic domain) known as stochastic or Nelson's mechanics. Here, the diffusion constant has been shown to be related to Planck's constant. This framework has been extended [6–9] to address the dissipative forces i.e. velocity dependent forces in terms of quantum dynamics. Following Nelson's framework, a non-linear Schrödinger–Langevin equation has been derived for dissipative forces where the diffusion constant has been assumed to be related to Planck's constant. Recently, Bernroider and Roy [10] estimated the Lagrangian action at the level of a single ion channel using dimensional arguments. By considering empirically established conduction properties, the action is shown to be of the order of Planck's constant. This finding lead us to construct a non-linear Schrödinger–Langevin equation corresponding to this admixture of Markovian and non-Markovian processes for K ion channel dynamics. Moreover, the existence of a time reversible Markovian process associated with K ions in the selectivity filter at a relatively shorter time scale sheds new light on the applicability of quantum theory in the biological domain, at least in case of K ion channel.

The present Note will discuss: results on oscillatory ion flow in Section 2, stochastic quantization for dissipative forces in Section 3, the Schrödinger–Langevin equation approach to ion channel permeability in Section 4 and finally, conclusions and implications in Section 5.

2. Oscillatory ionic sequences

The generalized Langevin equation [11] for $n = N$ interacting ions is given by

$$\dot{v}_i = - \int_{t_0}^t dt' \Theta(q, t - t') v(t') - V'(q) + f_i + dW, \quad i=1, \dots, N \quad (1)$$

where W and f are random and systematic forces acting on the ions and

$$\langle W(t) \rangle = 0$$

and

$$\langle W(t_1)W(t_2) \rangle = \min(t_1, t_2).$$

The Wiener process W is the 3-dimensional Gaussian process of which first moment is zero vector and second moment is a diagonal matrix whose element is minimum time between two Wiener processes. The memory kernel $\Theta(q, t - t')$ describes the generalized viscosity.

Brownian motion triggers a Wiener process that distinguishes the SDE (Stochastic Differential Equation) from the ODE (Ordinary Differential Equation), so the term associated to the random force is referred to as the diffusion term.

We have integrated Eq. (1) numerically using the Euler scheme. In Eq. (1) the frictional force depends on the previous velocities through the integral over the kernel $\Theta(q, t - t')$, which is quantified by the fluctuation dissipation theorem as

$$\langle W_i(t') W_j(t) \rangle = \beta k T \Theta(q, t - t') \delta_{ij},$$

where $\beta = \frac{6\pi\eta a}{m}$ for an ion with mass m and with spherical shape of radius a , η being the coefficient of viscosity of the surrounding water, k and T are Boltzmann constant and the absolute temperature, respectively.

Here, we attempt to construct a classical description of the invariant measures of 2D Navier Stokes equation including the Stochastic effects. The existence of an invariant measure may be used to represent the asymptotic behavior of the system. If this invariant measure is unique, there is the possibility that the law of the process solution will converge to it. Therefore, when this holds true, this unique invariant measure describes the equilibrium to which the system tends. In fact, a unique invariant measure has been constructed by Li and Wagner [12] and the convergence has been shown when the 2D Navier–Stokes equations are perturbed by a white noise (not degenerate in space) with no limitations on phase space modes. In general, without constraints on the Reynolds number, the deterministic Navier–Stokes equations have many stationary solutions. However, while there is no information about the long time behavior of such deterministic processes, they can be viewed as invariant measures for the Navier–Stokes equations without the noise. Based on their findings, our result indicates that, given a sufficiently distributed random perturbation noise, just one invariant measure exists. The noise effect results in the generation of mixed system dynamics, allowing a unique asymptotic behavior.

At low flow rates, the diffusion term introduces the fluctuation into the ensemble averaged stress tensor, which appears as unwanted noise which severely limits our ability to calculate low flow rate viscosity, where the signal to noise ratio becomes very small. However, it can be reduced by variance reduction method. In the case of simple shear flow, the velocity field is time dependent, along with the dependence on shear rate and the fluctuating viscosity. At the inception of shear flow, the system is initially at equilibrium and the stress tensor vanishes. For time $t \geq 0$, a constant shear rate is applied and the stresses grow until they reach their steady state values, where the elongation rate is indeed time dependent. Note that, as we make no approximations here, in regards to the relative strength of the solvent molecules in comparison to the ions, and consequently no simplification can be made. The crux here is our assumption that the memory kernel $\Theta(q, t - t')$ can be written as

$$\Theta(q, t - t') = a_0 \delta(t - t') + \frac{a_1}{\tau_1} e^{-\frac{|t-t'|}{\tau_1}} - \frac{a_2}{\tau_2} e^{-\frac{|t-t'|}{\tau_2}} \quad (2)$$

where, τ_1 and τ_2 denote the characteristic time scales.

Eq. (2) contains both Markovian and non-Markovian contributions that allows a continuous change from Markovian to non-Markovian dynamics and enables identification of both the

terms. The non-Markovian process has two time scales whose contributions are dominated by the parameters a_1, a_2 respectively. It is clear from the form of kernel that in the limit of weak non Markovian process ($a_{1,2} \ll a_0$),

$$\langle v_i(t_0)v_j(t) \rangle = kT e^{(-a_0 t)} \quad (3)$$

with a relaxation time constant a_0^{-1} which can be determined from experiments using the Einstein relation. Similarly, in the limit of weak non-Markovian noise, the spectral density can be evaluated as

$$S(\omega) = \frac{2kT\omega^2}{(1+\tau_1^2\omega^2)(1+\tau_2^2\omega^2)} \quad (4)$$

with ω as the frequency. This produced the spectrum limits for $\tau_{1,2} \rightarrow 0$ which give us color noise combination.

Now we shall consider the existence of glue-like viscous properties [3,4] which are quite different from the water dynamics outside the channel. Doyle et al. [2] justified the existence of one water molecule only between the two K ions in the selectivity filter studying the strong electron density peak in the experimental map. Recently, Saparov and Pohl [13] claimed that the two ions in selectivity filter does not leave enough room to accommodate a vaporized water molecule (within the framework of water-vapor oscillation hypothesis). In fact, it is now known that the distance between two such water molecules exceeds the filter length [13]. The selectivity filter is about 12 Å long, whereas the remainder of the pore is wider and has a hydrophobic lining [2], contains water molecules. Thus, given that the selectivity filter is almost devoid of water and that the water in the basket is glue-like, we propose that such change in length scale at the interface gives rise to shear viscosity and hence to non-Markovian processes with memory. Further more, recent experiments suggest [4] that the viscosity of water becomes even more glue-like in hydrophilic nanoscale constraints, and that a hydrophobic surface resulting in a milder constraint [14]. This gives us the possibility to add a simple viscous term to our simulation. The most challenging aspect of simulation of ion channels has been the implementation of particle coupling and boundary conditions. In Brownian Dynamic (BD) simulations it is particularly difficult to maintain the correct particle concentrations and behavior that occur under extreme conditions in channel simulations. Here we use a simple algorithm in order to solve, the GLE.

We can use the second order Runge–Kutta method by discretizing the above GLE and approximating the potential as $\int_t^{t+\Delta t} V(x(s))ds = V(x(t)\Delta t)$. We need n Gaussian random numbers to be picked at each step for the algorithm. Integrations of noise can be simulated by linear combinations of 3 normal Gaussian random numbers. The matrix elements of the coefficients are evaluated by the auto and cross-correlations of the noise integrations. We have used a set of algorithms that allow a comparison between the time scales of diffusion and shift performed along a selectivity filter in a model K-channel. The model describes two time scales for atomic ionic movement along the channel's length. This results in an oscillatory flow in the selectivity filter where the velocity autocorrelation exhibit an exponential decay. The Brownian simulation for GLE has been performed by subdividing the charge of the particle and increasing the number of particles by the same factor. We have obtained the velocity distributions corresponding to different limits of the processes and is explicit that oscillations dominate at the limit of weak non-Markovian process.

The time evolution of the kernel makes it clear that a phase transition of the shear viscosity within the channels may give an important clue as regards the rise of memory effects and the evolution of flip flop motion within ionic channels. It is apparent from the above analysis that using different time scales results oscillatory behavior within selectivity filter. Since this can occur at the weak non-Markovian limit (defined above), this oscillatory behavior can be described in terms of a time-reversible stochastic process. The diffusion co-efficient for stochastic process is related to the action relevant to the scale of the occurrence of this process. It is important to estimate the action relevant at the scale of ionic diffusion.

2.1. Appropriate action at the level of ion channel

It is well known from Dimensional analysis that the mechanical action can be written as

$$[\text{action}] = [\text{mass}] \cdot [\text{length}]^2 \cdot [\text{time}]^{-1}.$$

The action can also be expressed in terms of energy, mass and length. Hodgkin and Huxley [15] discussed two type of processes i.e. permeation of ions and gating associated with the abrupt changes in resting transmembrane electric field. The recent observations of Mackinnon et al. [1] clearly indicated that it is possible to have data at the level of atomic resolution down to 0.2 nm Bragg spacing. It is clear that the channels can pass at least 1 pA current corresponding to 10^8 monovalent ions per second. 3×10^{-26} kg mass is involved in the process of single charge transfer extending up to the range of 4×10^{-9} m and time of 10^{-8} s. From such observation it is possible to estimate the numerical order of the action [10] using the above formulas as

$$A = 0.48 \times 10^{-34} L\hbar.$$

Thus, the ion permeation process occurs at the scale where the relevant action is Planck action. Our simulation results indicate that at certain time scales, one can associate a time reversible stochastic process with the oscillatory ionic sequence where the relevant parameter is the Planck action. Thus at this scale, the diffusion coefficient can be related to Planck's constant and physical realization of Nelson process is possible at least in the biological domain. The process associated with GLE is an admixture of Markov and non-Markov processes. The dissipative force arises due to the viscosity of glue like water in the channel. It gives rise to a possibility of describing this velocity dependent dissipative force using the stochastic quantization introduced by Nelson [5]. Before going into details, let us briefly discuss the procedure of describing the velocity dependent force using the tools of stochastic mechanics.

3. Stochastic quantization and dissipative forces

Stochastic mechanics provides a deeper understanding to treat velocity dependent forces in terms of quantum theory. Let us consider that the position of a particle $x(t)$ executes a stochastic process and the quantization rule is given by

$$E[dx(t)dx(t)] = 2D dt \quad (5)$$

with D as diffusion constant. Here

$$D = \frac{\hbar}{m};$$

$\hbar$ being the Planck's constant and m be the mass of the particle. $E(\cdot)$ indicates the conditional expectation values. The above stochastic process is a Markov process of the Weiner type. If the particle is subjected to a conservative force i.e.

$$F = - \frac{\partial}{\partial x} \varphi(x) \quad (6)$$

with $\varphi(x)$ as potential function in 1-D. Now the dynamical equations can be derived for the stochastic process in terms of current velocity $v(x, t)$ and the stochastic velocity $u(x, t)$,

$$F = m \left[\frac{\partial v}{\partial t} + \left(\frac{\partial v}{\partial x} v - \frac{\partial u}{\partial x} u + D \frac{\partial^2 u}{\partial x^2} \right) \right] \quad (7)$$

and

$$\frac{\partial u}{\partial t} + D \frac{\partial^2 v}{\partial x^2} + \frac{\partial v}{\partial x} u = 0. \quad (8)$$

Using the following complex function

$$\psi(x, t) = \exp(R(x, t)) e^{i \frac{S(x, t)}{2mD}} \quad (9)$$

and assuming

$$mv(x, t) = \frac{\partial S(x, t)}{\partial x} \quad (10)$$

one can show that $\psi(x, t)$ satisfies the Schrödinger equation

$$i\hbar \frac{\partial \psi(x, t)}{\partial t} = - \frac{\hbar^2}{2m} \frac{\partial^2 \psi(x, t)}{\partial x^2} + \varphi(x) \psi(x, t). \quad (11)$$

The function $R(x, t)$ is related to the density in $\rho = 2R(x, t)$. Using this approach Nelson proved that there exists a time reversible Markov process corresponding to Schrödinger's equation by assuming the diffusion constant as related to Planck's constant. This framework has been extended to incorporate the velocity dependent forces and hence for dissipative forces as mentioned by various authors [6–9]. From a physical point of view, this means that if the dynamic system interacts with its chaotic (thermal) environment, it is possible to extend the

above framework as introduced by Nelson. In classical paradigm, the dynamical behavior of an open system can be described by Langevin equation

$$m \dot{q} = -\beta \dot{q} - \nabla \varphi(q(t), t) + A(t),$$

$$q(t), q(t)^1, \dots, q(t)^n \quad (12)$$

be the reduced coordinate variables of the open system and $A(t)$ be a Gaussian white noise with mean 0 and variance

$$[A^i(t)A^j(t')] = 2D\delta^{ij}\delta(t-t')$$

and the diffusion coefficient

$$D = \beta kT.$$

k is the Boltzmann constant and T is the temperature of the thermal environment.

The quantum mechanical behavior of an open system can be derived by the quantum mechanical version of Langevin equation. Since there is no well defined procedure to construct a Lagrangian or Hamiltonian for any open system in general, it will be more attractive to use stochastic quantization as proposed by Nelson. Here, there is no need to start from Lagrangian or Hamiltonian but one can begin with Newtonian equation in a more generalized sense. The first basic assumption of stochastic quantization is the following: The quantum mechanical behavior of the coordinate variable $q(t)$ for open dynamical system can be represented by an n -dimensional diffusion process described by the following stochastic differential equation.

$$dq(t) = b(q(t), t)dt + dW(t) \quad (13)$$

where $b(q, t)$ is drift vector and $W(t)$ an n -dimensional Wiener process. $dW(t)$ is n -dimensional Wiener process with mean zero and variance

$$E[dW(t)dW(t)] = \frac{\hbar}{m} dt. \quad (14)$$

The probability density $\rho(q, t)$ satisfies Fokker–Planck equation.

The second basic assumption is that the Langevin equation can be expressed in terms of mean velocity and mean acceleration. After some algebraic calculations, one gets quantum mechanical wave equation for the open system:

$$i\hbar \frac{\partial \psi(q, t)}{\partial t} = \left[-\frac{\hbar^2}{2m} \nabla \cdot \nabla + V(q, t) - q \cdot A(t) + \frac{i\beta \hbar}{2m} \ln \frac{\psi^*(q, t)}{\psi(q, t)} \right] \psi(q, t) \quad (15)$$

where

$$\psi(q, t) = [\rho(q, t)]^{1/2} e^{iS(q, t)}.$$

Now we shall consider the GLE and the quantum mechanical wave equation for the velocity dependent forces considered in GLE.

4. Potassium channel and Schrödinger–Langevin equation

The Generalized Langevin Equation (GLE) used for the description of K ion channel is written as

$$m\ddot{q}(t) = -m \int_0^t \Theta(t-t') \dot{q}(t') dt' - \nabla q(t) + f_R(t) \quad (16)$$

where f_R be the random force and

$$\dot{q} = \frac{dq}{dt},$$

$$\Theta(t-t') = a_0 \delta(t-t') + \frac{a_1}{\tau_1} e^{-\frac{|t-t'|}{\tau_1}} - \frac{a_2}{\tau_2} e^{-\frac{|t-t'|}{\tau_2}}.$$

In the weak non-Markovian limit i.e.

$$a_1, a_2 \ll a_0, \quad \langle v_i(0)v_j(t) \rangle = kT \exp^{-a_0 t} \delta_{ij}. \quad (17)$$

Following the rule of stochastic quantization as described in the previous section, we get

$$i\hbar \frac{\partial \psi}{\partial t} = \frac{\hbar^2}{2m} \frac{\partial^2 \psi}{\partial x^2} + V\psi + \frac{a_0 \hbar}{2i} \ln \left[\frac{\psi(x, t)}{\psi^*(x, t)} \right] \psi(x, t) + \frac{\hbar}{2i} \left[\frac{a_1}{\tau_1} \int_0^t \exp^{-\frac{|t-t'|}{\tau_1}} dt' - \frac{a_2}{\tau_2} \int_0^t \exp^{-\frac{|t-t'|}{\tau_2}} dt' \right] \ln \frac{\psi(x, t')}{\psi^*(x, t')} \psi(x, t). \quad (18)$$

Let us discuss the different non-linear terms due to various physical situations. The first nonlinear term is associated with Markov process taking delta function in the memory kernel. The velocity correlation is given by

$$\langle v_i(0)v_j(t) \rangle = kT \exp^{-a_0 t} \delta_{ij}.$$

The first part of the second non-linear term contains a characteristic time scale τ_1 . Recent experimental observations [4] showed that water exhibits very different properties when it is confined to nano channels. Thus the velocity may be taken as almost constant throughout the integration and this part of the 2nd term can be written as

$$\left(\frac{a_1}{\tau_1} \int_0^t \exp^{-\frac{|t-t'|}{\tau_1}} dt' \right) S(x, t). \quad (19)$$

As the second part remains unchanged, the quantum mechanical wave equation can be written as

$$\begin{aligned} -\hbar \frac{\partial \psi}{\partial t} = & -\frac{\hbar^2}{2m} \frac{\partial^2 \psi}{\partial x^2} \\ & + V\psi + \frac{a_0 \hbar}{2i} \left[\ln \frac{\psi(x, t)}{\psi^*(x, t)} \right] \psi(x, t) \\ & + \frac{\hbar}{2i} \left[\left(\frac{a_1}{\tau_1} \int_0^t \exp^{-\frac{|t-t'|}{\tau_1}} dt' \right) \left(\ln \frac{\psi(x, t)}{\psi^*(x, t)} \right) - \frac{a_2}{\tau_2} \int_0^t \exp^{-\frac{|t-t'|}{\tau_2}} dt' \left(\ln \frac{\psi(x, t')}{\psi^*(x, t')} \right) \right] \psi(x, t). \end{aligned} \quad (20)$$

It seems evident, from channels characteristics, that the weak non-Markovian approximation may be valid for the selectivity filter. In this approximation $a_1, a_2 \ll a_0$ and hence the contribution from the second non-linear term will be negligible leading to oscillatory ionic sequence.

5. Possible implications

The oscillatory ionic dynamics in Kion channels is proposed to occur at the limit of the weak non-Markovian approximation associated with a time reversible Markov process, at the selectivity filter. This reversible stochastic process belongs to a different time scale to that governing diffusion across the rest of the channel, which is determined by the glue-like properties of water at the water basket. The framework of stochastic mechanics provides a model for such dissipative force in terms of quantum theory. That channel ionic permeation can be associated with non-linear Schrödinger equation which addresses the issue of de-coherence and time scale considerations. At this point it is worth mentioning that the Nelson process (the time reversible Markov process associated with Schrödinger equation) can, indeed, be considered an intermediate between quantum and classical time reversible processes, at least in the realm of ionic channel permeation.

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