

Non-Markovian noise mediated through anomalous diffusion within ion channels

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It is evident from a wide range of experimental findings that ion channel gating is inherently stochastic. The issue of “memory effects” (diffusional retardation due to local changes in water viscosity) in ionic flow has been recently addressed using Brownian dynamics simulations. The results presented indicate such memory effects are negligible, unless the diffusional barrier is much higher than that of free solute. In this paper using differential stochastic methods we conclude that the Markovian property of exponential dwell times gives rise to a high barrier, resulting in diffusional memory effects that cannot be ignored in determining ionic flow through channels. We have addressed this question using a generalized Langevin equation that contains a combination of Markovian and non-Markovian processes with different time scales. This approach afforded the development of an algorithm that describes an oscillatory ionic diffusional sequence. The resulting oscillatory function behavior, with exponential decay, was obtained at the weak non-Markovian limit with two distinct time scales corresponding to the processes of ionic diffusion and drift. This will be analyzed further in future studies using molecular dynamics simulations. We propose that the rise of time scales and memory effects is related to differences of shear viscosity in the cytoplasm and extracellular matrix.

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I. INTRODUCTION

Ion channels are transmembrane proteins that include a pore-forming subunit that allows ions to flow between the extracellular and intracellular and interior of a cell. The open or closed condition of such channels may be gated by either the transmembrane electric field, via a dipole moment sensitive moiety, or via ligand interactions with “chemical sensing” moieties in the channel proteins. Ion channel pores present a narrow cross section (100 Å) and define a path of low dielectric constant across the membrane. When open, the channel pore presents a rather specific ion selectivity filter where the lines of the electric field tend to be confined to the high dielectric interior of the pore. This paper addresses the problem of pore selectivity.

The continuity requirement for the orthogonal component of the electric displacement field between the interior of a channel and membrane is given by $\epsilon_w \mathbf{E}_w^n = \epsilon_p \mathbf{E}_m^n$. Since the lipid membrane has a dielectric constant $\epsilon_p \approx 2$, while the dielectric constant of water is $\epsilon \approx 80$, it becomes evident that the orthogonal component of the electric field at the membrane pore boundary must be very close to zero. Indeed, there is only a very slight penetration of the electric field into the interior of the phospholipid membrane. The situation, therefore, is very similar to the expulsion of the magnetic field by a superconductor. As an example, in a channel with a 3 Å radius and a channel of length $L=25$ Å, the barrier is about $6k_B T$. Although it is quite large, it should allow ionic conductivity. This is not too different from such conditions

where water filled nanopores are introduced into silicon oxide films, polymer membranes, etc. [1,2].

Methods ranging from molecular dynamics (MD) and Brownian dynamics (BD) (which treat water implicitly as a uniform dielectric continuum) to the mean-field Poisson-Nernst Planck equation (PNP) (which treats both the ions and water implicitly as a uniform dielectric continuum) have been used to simulate the characteristics of ion channel phenomena. While MD simulations are clearly the most accurate, they are computationally very intensive [3]. Brownian dynamics are significantly faster than MD, but because of the dielectric discontinuities across the various interfaces, a new solution of the Poisson equation is required for each configuration of the ionic-pore profiles during permeation. The simplest approach to study the ionic conduction is based on the PNP theory [4,5]. This combines the continuity equation with the Poisson equation and Ohm’s and Fick’s laws. PNP is intrinsically mean field and is, therefore, bound to fail when ionic correlations become important.

For narrow channels, the cylindrical geometry, combined with the field confinement, results in a pseudo one-dimensional potential of very long range [6]. Under these conditions the correlational effects dominate, and the mean-field approximation fails [7]. Indeed, a recent comparison between the BD and the PNP showed that the PNP breaks down when the pore radius is smaller than about two debye lengths [8,9]. At the moment, therefore, for narrow pores it appears that a semicontinuum (implicit solvent) BD simulation is best compromised between computational load and accuracy [10–12]. If the interaction potential between the ions inside the channel were known, the simulation could proceed orders of magnitude faster.

Note that though BD simulations of ion channels have yielded suitable results, these studies have been confined to the use of the Langevin equation with Markovian random

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forces. The Markovian approximation is justified when the Brownian particles are much heavier than the solvent molecules, a condition that obviously is not satisfied for ions in water. Correlations are important and can be taken into account using the generalized Langevin equation (GLE) [13]. In a recent paper these issues have been discussed in the context of memory effect and were found to be negligible in bulk simulations [14]. However, when ions have to cross energy barriers, the memory effects via the GLE become quite significant. This means that interesting physics of ion channels are concentrated in the pore region where the stochasticity of gating phenomena is a crucial parameter. We argue here, that while Einstein's relation $\sigma = nq^2D/kT$ indicates that ionic conductivity exhibits a simple dependence on Δt and may be employed in the BD simulations at lower field strength, such a simple relation disappears in a higher field strength. Indeed, as mentioned before, the stochastic nature of the potential energy barrier being defined by $V(z, i) = V_i \exp(-z^2/2d^2)$, where V_i is the random variable associated with the barrier height and d is its width, implies a stochastic contribution to the barrier height. Thus, contrary to the recent survey [14], memory effects will be important in a variety of cases depending on the random effects of the potential barrier.

The most significant dynamic aspects of the memory effects can best be visualized using recent development in atomic force microscopy [15] that suggests that capillary water condensation increases short term memory due to shearing elastic frictional forces. This indicates that there is a crucial change in the elastic response of the forces between water molecules at nanoscale that leads to a different viscosity than in the ionic channels. This viscosity difference is thus the key element that gives rise to memory effects. Such an assertion requires a serious investigation of how the shear response behavior may be coupled to the stochastic dynamics. In this context, it should be noted that diffusion governed by Brownian motion is an efficient transport mechanism for short time and length scales. Even a highly organized system, such as a living cell, relies on the random Brownian motion of its constituents to fulfill complex functions. A Brownian particle will rapidly explore a heterogeneous environment that in turn strongly alters its trajectory. Thus, detailed information about the environment can be gained by analyzing the particle's trajectory. It is well known that the non-negligible fluid's inertia leads to hydrodynamic memory effects [16] resulting in a characteristic long-time tail of $t^{-3/2}$ in the velocity correlations of the particle's motion. The viscosity of the PE solution is recently calculated [17–22] as a function of the concentration and hydrodynamic memory effects present in such solutions. We find that memory is lost above the critical concentration C^* , which corresponds to the point where neighboring polymer coils start to overlap and form a transient mesh where fluid dynamics is dominated by viscous terms rather than inertial ones. Above this point the mesh surrounding the Brownian particle increases its effective mass and therefore the characteristic power law of the velocity correlations vanishes. In this paper we construct a GLE model including non-Markovian processes using a white noise and a linear combination of colored noises, in the sense of the Ornstein-Uhlenbeck process. Our model in-

cludes an evolutionary memory and the mixing processes that generate oscillations within the pore. For purely Markovian or purely non-Markovian processes the time dependence is monotonic, thus, it is clear that the oscillations are the result of the competitive interactions between the Markovian and non-Markovian subprocesses. The non-Markovian nature of the noise affects both the time dependent and stationary properties of the driven stochastic processes. We also initiate a brief discussion on the physical origin of non-Markovian processes. The time dependent processes are characterized by distinct time scales. A discussion of the time scales for the diffusive process will be followed by a description of our model and the specific algorithm for the mixture of the Markovian and non-Markovian processes.

II. POTASSIUM CHANNELS

The structure of the KcsA channel is strikingly consistent with the classical views of a very selective, fast-conducting, multi-ion pore. The pore comprises a wide, nonpolar aqueous cavity on the intracellular side, leading up, on the extracellular side to a narrow pore that is 12 Å long and lined exclusively by main chain carbonyl oxygens. Formed by the residues corresponding to the signature sequence *TTVGYG*, common to all K⁺ channels, this region of the pore acts as a selectivity filter by allowing only the passage of nearly dehydrated K⁺ ions across the cell membrane. The x-ray crystallographic structure unambiguously demonstrated that the K⁺ ions entering the selectivity filter have to lose nearly all their hydration shell and must be directly coordinated by backbone carbonyl oxygens. Specifically, the K⁺ ion in the selectivity filter is surrounded by two groups of four oxygen atoms, just as in water. These oxygen atoms are held in place by the protein, and are in the backbone carbonyl oxygens of the selectivity filter loops of the four surrounding filter subunits. In this manner, the filter is constrained in an optimal geometry so that a dehydrated K⁺ ion fits with proper coordination, but the Na⁺ ions are too small for proper coordination, in accordance with the snug-fit mechanism proposed by Bezanilla and Armstrong [23]. This simple and appealing structural mechanism has been widely adopted to explain the selectivity of the K⁺ channel. Indeed, a rigid K⁺ pore cannot close down around a Na⁺ ion, and so presents a much higher energy than diffusion in water. Indeed, for structural reasons, the selectivity filter cannot constrict sufficiently to bring more than two of the carbonyls within good bonding distance of the Na⁺ and as a result, the energy of the Na⁺ in the pore is very high compared with its energy in water [24].

This implies a significant structural inability to deform and adapt: the energetic cost upon collapsing to cradle a Na⁺ (a structural distortion of about 0.38 Å) must give rise to a significant energy penalty (much larger than $k_B T$ assuming the existence of molecular forces opposing a subangstrom distortion is tantamount to postulating structural rigidity). Furthermore, the geometry of such a rigid pore must be very precisely suited for K⁺ because it would be unable to adapt small perturbations without paying a significant energy price (much larger than $k_B T$). Therefore, precisions in structural rigidity and geometric precision are two underlying micro-

scopic consequences. However, there are fundamental problems with the common view. Proteins, like most biological macromolecular assemblies, are soft materials displaying significant structural flexibility [25]. Despite some uncertainties, the B factors of the KcsA channel indicate that the rms fluctuations of the atoms lining the selectivity filter are on the order of 0.75–1.0 Å. This is in general agreement with numerous independent MD simulations of KcsA. The magnitude of atomic thermal fluctuations is fundamentally related to the intrinsic flexibility of a protein, i.e., how it responds structurally to external perturbations. These considerations suggest that, at room temperature, the flexible fluctuating channel should distort easily to cradle Na^+ with little energetic cost, as is seen in MD simulations with Na^+ in KcsA. The flexibility of the pore is further highlighted by the experimental observation that K^+ is needed for the overall stability of the channel structure [26,27]. Therefore, even ion channel proteins appear to be inherently too flexible to satisfy the requirement of the traditional snug-fit mechanism. Furthermore, structural flexibility is absolutely essential for ion conduction since in some places the diameter of the pore in the x-ray structure of KcsA is too narrow to allow the passage of a water molecule or a K^+ ion. In the electric circuit equivalent model the channel proteins thereby play the role of field-effect transistors, with a voltage imposed across the cell membrane “gating” the transfer of ion bound charges through the membrane. Two different aspects characterize channel function: ion-selective permeation and gating, i.e., control of access of ions to the permeation pathway. We will base the subsequent concept on potassium channels, employing the crystal structure of the KcsA and KvAP channels at a resolution ranging from 1.9×10^{-10} m to 3.2×10^{-10} m, as revealed by the work of MacKinnon’s group [28,29]. The channel structure is basically conserved among all potassium channels with some differences relating to gating characteristics rather than ionic selectivity. In the open gate configuration the protein selects the permeation of K^+ ions against other ions in the selectivity filter and can still allow ion permeation rates near the diffusion limit. In the view of Hodgkin-Huxley (HH)-type models of membrane potentials, K^+ permeation stabilizes the membrane potential, resetting it from firing threshold values to resting conditions.

The atomic level reconstruction of parts of the channel and accompanying MD simulations at the 10–12 s resolution have changed the picture of ion permeation: the channel protein can transiently stabilize three K^+ states, two within the permeation pathway and one within the “water cavity” located towards the intracellular side of the permeation path. The essential feature behind the channel structure relating to the present work is provided by the closed gate (low- K^+ permeation pore state) in accordance to the original crystallographic image, whereas in the open gate state (with the cavity exposed to the high intracellular K^+ concentration) the interior of the protein represents an almost barrierless pathway for selected ion flow. By contrast, the closed gate state represents a stable ion-protein conformation.

More recently, the development of computational approaches based on sophisticated all atom molecular dynamics simulations [30] offers a virtual route for testing various ideas about the molecular mechanism of ion selectivity. One

of our goals with this work, in addition to reviewing the recent results from modern computations, will be to provide a model based on the relation of non-Markovian processes linked with a proposal of a different viscosity of water inside and outside the channels to address the pore selectivity problem.

III. GATING KINETICS AND THE ROLE OF DIFFUSION

The equation describing diffusive motion in a one-dimensional (1D) potential of mean force (pmf) is given by the Smoluchowski equation as

$$\dot{p}(z,t) = - \frac{\delta}{\delta z} \left[- \frac{V'(z,i)}{R(z)} p - \frac{kT}{R(z)} \frac{\delta}{\delta z} p \right], \quad (1)$$

where p is the probability density of the gating particle, $V(z,i)$ is the random pmf, and $R(z)$ is the friction coefficient. The equation mainly states the local probability conservation corresponding to the processes of drift and diffusion. Drift motion occurs in the presence of a pmf gradient producing a directed displacement of the probability distribution to a region of local energy minimum. Diffusive motion allows activated transitions over energy barriers to take place. In the equilibrium state drift and diffusion balance each other through the Boltzmann distribution. Well-defined states happen only for local minima in the energy landscape. To satisfy the Markovian property of exponential dwell times activation barriers must be sufficiently high. Thus, in accordance to the previous analysis, the role of the GLE becomes inevitable and there arises the need to understand the dynamics of ion channels through the GLE by extending the process to be an admixture of both Markovian and non-Markovian processes. Experimentally, large bandwidth recordings of the initial transient current may measure drift phenomena after a rapid voltage jump. Giant patch recordings of K^+ channels provide evidence for the existence of an early fast component of gating currents. Apart from these variables there is another slow physiological time scale that is determined by the dwell time within the above states that can be measured by the detection of fluctuations in the gating current with shot noise features.

Equation (1) is of the form of a Fokker-Planck (FP) equation as

$$\frac{\partial p}{\partial t} = Fp, \quad (2)$$

where $F = -\frac{\delta}{\delta z} A(z) + \frac{1}{2} \frac{\delta^2}{\delta z^2} B(z)$ and A, B are the operators constructed from Eq. (1). The energy term $U(z)$ is constructed from the spurious drift term and the pmf as

$$U(z) = V(z) + kT \ln R(z). \quad (3)$$

The basic method used to obtain the probability density and the correlation functions is associated by solving Eq. (2). The methodology lies in discretizing the equation as

$$\begin{aligned} \frac{d}{dt}p(i\Delta z) &= a_{i-1}p((i-1)\Delta z) + b_{i+1}p((i+1)\Delta z) - a_i p(i\Delta z) \\ &+ b_i p(i\Delta z). \end{aligned} \quad (4)$$

Monte Carlo simulations [31] may be performed with a single barrier model, by placing two harmonic wells side by side separated by a $6k_B T$ barrier. The analysis showed that two transition rates can be obtained. With the full range of time scales taken into account the single barrier model combines features from both, harmonic well and discrete two state models.

One of the properties of the Markov process is that it satisfies the Fokker-Planck equation or the Smoluchowski-Chapman-Kolmogorov equation [32]. The degree of non-Markovianity can be associated with the deviation from this equation. In fact, the Fokker-Planck equation can be obtained as an approximation to the generalized master equation [33]. Using the Kramers-Moyal expansion, one writes the equation as

$$\frac{\partial p(y,t)}{\partial t} = \sum_{\nu} \frac{(-1)^{\nu}}{\nu!} \left(\frac{\partial}{\partial y} \right)^{\nu} a_{\nu}(y) P. \quad (5)$$

This is normally identical with the above master equation. One obtains the Fokker-Planck equation as an approximation to this equation (Kramers-Moyal expansion) if all the terms after $\nu > 2$ are negligible. Kolmogorov took $a_{\nu} = 0$ for $\nu > 2$. In general, this is not true for physical systems [34]. Considering the higher order terms, the integral measure (mean square characteristics) of non-Markovianity can be written as [35]

$$G = G(\tau, T) = \left[\frac{1}{T} \frac{1}{M^2} \sum_{m,n}^M \int_{\tau}^{\tau+T} dt D_{m,n}^2(t, \tau) \right]^{1/2}, \quad (6)$$

where $D_{m,n}^2(t, \tau)$ is the degree of non-Markovianity, T is the range of time t , and τ is the shift in the master equation.

IV. DYNAMICAL SIMULATIONS

As mentioned in the last section, formulating the structure-function relationships in biological ion channels has gained a new impetus with the determination of the KcsA potassium channel structure. Most of the theoretical efforts in modeling the KcsA channel so far have focused on MD simulations of potassium ions in the channel. These studies provide valuable information on the selectivity mechanism and the energetics of ion permeation in the channel, but do not make predictions about the quantity that can be directly measured experimentally, namely, the conductance. A recent 100-ns MD simulation, [36] calculated the conductance of a simplified channel in somewhat extreme conditions (1 M solution with a 1.1-V applied potential). This gives hope that it may be possible to determine conductance of biological channels from MD studies. Currently, however, typical MD simulations of biological channels can be typically tuned for no more than 10 ns, which is too short to estimate the channel conductance, or even to explore the dynamics of a single conduction event. However, this is not

a new problem, and permeation models of lower resolution such as BD and PNP equations have long been addressed in the literature [37]. The latter approach has recently been shown to be invalid in a narrow pore environment because it neglects the self-energy of ions.

The determination of the structure of the KcsA K^+ channel represents an extraordinary opportunity for understanding biological ion channels at the atomic level. In principle, MD simulations based on detailed atomic models can complement the experimental data and help to characterize the microscopic factors that ultimately determine the permeation of ions through KcsA. A number of MD studies [38–42], broadly aimed at analyzing the dynamical motions of water molecules and ions in the KcsA channel, have now been reported. The potential functions that were used to calculate the microscopic interatomic forces and that predict the dynamical trajectory have been generated. In particular, the atomic partial charges and the Lennard-Jones radii, which are at the heart of the potential function, varied widely. Furthermore, some include all atoms (AMBER and CHARMM PARAM22), whereas others are extended-atom models that treat only the polar hydrogen atoms that are able to form hydrogen bonds explicitly (CHARMM PARAM19 and GROMOS). How these differences affect the results of MD calculations is an important concern for future investigation.

For meaningful theoretical studies of permeation, it is necessary to have a potential energy function that provides a realistic and accurate representation of the microscopic interactions. In practice, this presents a difficult challenge. The permeation process through KcsA involves the partial dehydration of a K^+ ion, followed by the translocation through the interior of a narrow pore that is 12 Å long, and is lined by backbone carbonyl oxygens, which act as a selectivity filter [43]. Thus, the conductance and selectivity of the KcsA channel results from a delicate balance of very strong microscopic interactions, the large energetic loss of dehydration being roughly compensated by coordination with main chain carbonyl oxygens. Gas phase experiments on model systems provide the most direct information concerning the individual microscopic interactions [44]. High-level quantum-mechanical *ab initio* calculations can also be used to supplement the (often scarce) information available from experiments [45]. Of particular interest is the interaction of ions with a single water molecule, or with a single isolated *N*-methylacetamide (NMA) molecule, an excellent model of the backbone carbonyl of proteins. Despite the considerable uncertainty in the experimental data and the *ab initio* calculations, both clearly indicate that the interaction of cations with a single NMA is substantially larger than with a single water molecule. The binding enthalpy of K^+ with a water molecule is 17.9 kcal/mol, whereas it is roughly 25–30 kcal/mol with NMA. The interactions are even larger in the case of Na^+ . This trend is generally reproduced by all the potential functions, with the exception of GROMOS [46]. In this case, the interaction of K^+ and Na^+ with a single NMA molecule is actually smaller than the interaction with a single water molecule. Our analysis has thereby relied on BD simulations with some assumptions overlaid.

BD simulations were first proposed as a way to study ion channels by Cooper and Jan [47]. The early simulations in-

volved 1D studies of schematic channels, but its extension to the three dimensions (3D), necessary for realistic modeling, has not been achieved until recently. The difficulty lies in the calculation of the forces on ions at each time step, typically found from the solution of Poisson's equation, which is computationally very intensive if implemented numerically. Thus, the first 3D BD simulations were performed [48,49] using a torus-shaped channel, for which analytical solutions of Poisson's equation are available. For a channel with an arbitrary shape, this problem was finally resolved by storing the potential and electric field values in a set of lookup tables, and interpolating the required values during simulations from the table entries [50–52]. Recently, questions have arisen about the methods of implementing the boundaries in BD simulations of ion channels. Another issue, distinct from that of boundaries, is the accurate representation of the forces on ions in the channel interior. In our simulations, viscosity is a mean-field parameter that plays a crucial role in determining the velocity profiles in the diffusion BD model that affords us distinct time scales for the profiles. Limits to our model accuracy are given by the fact that, as channel conductance has an exponential dependence on energy barriers, so calculated conductance values could be very sensitive to errors. A second concern is that in our treatment the self-energy of the ion is ignored.

The above discussion makes it clear that some simplifying assumptions are required. In the approach described in this section, it is assumed that the protein structure is held fixed and the water molecules are replaced by a continuum. With these assumptions, the 3D movement of ion i can be described by the following simple equation:

$$m \frac{dv}{dt} = m_i f_i v_i + F_R(t) + q_i E_i, \quad (7)$$

where m_i , v_i , q_i , and f_i are the mass, velocity, charge, and frictional coefficient on the i th ion, respectively. F_R is a random thermal force representing the effects of collisions with the water and channel wall. E_i is the total electrical field on the ion, including the partial charges in the protein, all the other ions in the system, and the induced charges from the variation in the dielectric constant at the boundaries between the protein, water, and lipid.

Although one could always add other short-range specific force terms, this would, in effect, be adding an empirical term that did not arise directly from the known protein structure. The solution for this approach proceeds as in the above MD method. The channel boundaries are defined, all the ions in the channel and attached bulk reservoirs are positioned, and then, for each ion i , it is integrated in discrete time steps (Brownian dynamics). Because the dynamics of the water and protein are no longer included and relatively long time steps can be taken for the ion motion, this approach is many orders of magnitude faster than the exact MD approach (see below for a specific example).

The ability to account accurately for the interaction between ions in the channel system is one of the most difficult and critical aspects of modeling ion channels. In the absence of such interactions, the channel conductance will vary linearly with the ion concentration. A major advantage of this

BD approach is that it allows a direct simulation of this ion-ion interaction. At each step in the dynamics, the position of all the ions in the channel system are determined and their interaction energy is calculated for each time step. One difficulty with this approach is that, because of the induced charges at the membrane and channel water interface, the calculation of the electrostatic energy at each step requires an involved, time-consuming calculation. Our approach (see below) is to operate with a nonequivalent role of viscosity in the outer and inner pore of the channels to modulate the conductance and thereby see how the Poisson-Boltzmann equation leads to a mean-field dynamics with distinct time scales.

The next simplifying approximation is to keep Eq. (7), but replace the exact expression by a mean-field approximation E_i that represents a sort of average over all the possible positions of the other ions in the system. This E is calculated using Poisson's equation. This combination of random thermal motion of the ion combined with a Poisson solution for E is referred to as the PNP solution. The modified 3D steady state Nernst-Planck equation is given by

$$0 = \nabla \cdot [\nabla c_i(x) + \beta \nabla V_i(x) c_i(x)], \quad (8)$$

$$V_i(x) = U(x) + z_i e \varphi(x), \quad (9)$$

where $U(x)$ is the potential due to nonelectrostatic forces, φ is the electrostatic potential, z_i is the valence of the i th ion, and e is the electron charge.

V. VARIABLE VISCOSITY AND NON-MARKOVIAN PROCESSES

Channels gating kinetics have been assumed to exist in a finite number of discrete states, where the transition rate constant among the states is independent of time, which can be defined as a time-homogeneous Markov chain model. The evidence, however, is clear for these cases where ionic channel current has been empirically demonstrated to be non-Markovian [32]. It is also well known that the spontaneous fluctuations in the conformation of proteins involve many different processes that occur over many different time scales [55,56]. As we constructed our model taking into account the large barrier height derived from our analysis in the preceding section, and the conclusions made in [54], it follows that memory effects cannot be ignored and we use GLE by taking into account an admixture of non-Markovian and Markovian processes. The generalization to the PNP model requiring that the non-Markovian process be included results in two time scales to take into account the distinct features of the diffusion and drift processes in ion channels. So in this case the generalized Langevin equation [57] for $n=N$ interacting ions is given by

$$\begin{aligned} \dot{v}_i = - \int_{t_0}^t dt' \Theta(q, t-t') v(t') - V'(q) + f_i + dW, \\ i = 1, \dots, N, \end{aligned} \quad (10)$$

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 3D Gaussian process of which the first moment is a zero vector and the second moment is a diagonal matrix whose element is the minimum time between two Wiener processes. The memory kernel $\Theta(q, t-t')$ describes the generalized viscosity. The Brownian motion triggers a Wiener process that distinguishes the SDE (stochastic differential equation) from the ODE (ordinary differential equation), so the second term is referred to as the diffusion term. We have integrated Eq. (1) numerically using the Euler scheme. In Eq. (8) 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 $\langle W_i(t')W_j(t) \rangle = \beta kT \Theta(q, t-t') \delta_{ij}$, where $\beta = \frac{6\pi a \eta}{m}$ for an ion with mass m and with a spherical shape of radius a , and η is the coefficient of viscosity of the surrounding water, k is the Boltzman constant, and T is the absolute temperature. In short, we are attempting to construct a classical description of the invariant measures of a 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, the process solution will converge to it and de facto, describes the equilibrium to which the system tends. It is already known that a unique invariant measure exists [58] and the convergence takes place when the 2D Navier-Stokes equations are perturbed by a time-white noise, not degenerate in space, but with no limitations on the way it affects the modes of the phase space. In general, without constraints on the Reynolds number, the deterministic Navier-Stokes equations have many stationary solutions. No information about the long-time behavior is directly related to them. They, in fact, may be taken as invariant measures for the Navier-Stokes equations without the noise.

Hence, our result means that, when a sufficiently distributed random perturbation is added, just one invariant measure exists. The effect of the noise is to combine the system allowing a unique asymptotic behavior. At low flow rate, the diffusion term introduces the fluctuation into the ensemble averaged stress tensor, which appears as unwanted *noise*. This noise severely limits our ability to calculate low flow rate viscosity, where the signal to noise ratio becomes very small. This undesirable noise can be reduced by a variance reduction method. In simple shear flow, the velocity field is time dependent along with the dependence on shear rate and the fluctuating viscosity. At 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, at which point the elongation rate is indeed time dependent.

It should also be mentioned here that we make no approximations about the relative strength of the solvent molecules in comparison to the ions, and consequently simplification cannot be made. The crux of the story, however, is that we assume that the memory kernel $\Theta(q, t-t')$ can be written as

$$\Theta(q, t-t') = a_0 \delta(t-t') + \frac{a_1}{\tau_1} e^{-(|t-t'|/\tau_1)} - \frac{a_2}{\tau_2} e^{-(|t-t'|/\tau_2)}, \quad (11)$$

that contains both Markovian and non-Markovian contributions. This fact 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 and a_2 , respectively. It is also clear from the form of the kernel that in the limit of the weak non-Markovian process ($a_{1,2} \ll a_0$)

$$\langle v_i(t_0)v_j(t) \rangle = kT e^{(-a_0 t)}, \quad (12)$$

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

$$S(\omega) = \frac{2k_B T \omega^2}{(1 + \tau_1^2 \omega^2)(1 + \tau_2^2 \omega^2)}. \quad (13)$$

Here it is worthwhile to point out that the power spectrum in the weak NM limit has a memoryless property in contrast to the $1/f$ flicker noise property characteristic of long tail correlations [59,60]. Our results at least do not contradict the fact as we expect that the weak limit of the NM process does indeed give rise to a Markovian process in the selectivity filter whereas the deviation from Markovianity occurs in the region containing the *water basket*. We obtain the spectrum limits for $\tau_{1,2} \rightarrow 0$, which give us a combination of the color noise.

Concerning the gluelike water viscosity in the channel lumen [61], this property makes the dynamics of such water quite different from that of external water. In addition, experimental characterization of the strong electron density peak by Doyle *et al.* [28] demonstrated that only one water molecule can be present between two K ions in the selectivity filter. Moreover, Saparov and Pohl [62] claimed that the two ions in the selectivity filter do not leave enough room to accommodate a vaporized water molecule (within the framework of the water-vapor oscillation hypothesis). In fact, it has been shown that the distance between two such water molecules exceeds the filter length [63]. While the selectivity filter is about 12 Å long, and thin, the remainder of the pore is wider and contains water molecules constrained within the hydrophobic lining of such a pore segment. In this situation, it is justifiable to consider the selectivity filter as almost devoid of water molecules. We propose that, with the exception of the selectivity filter, water attains gluelike viscosity within the channel pore. This change of property is due to the nanoscale physical restriction to water movement giving rise to shear viscosity and thus to non-Markovian water dynamics with memory. Experimental evidence further indicates that, in addition to the size restriction, the viscosity of water is further modified by the water avidity of the pore lining wall. In conditions where such lining is hydrophilic, viscosity is substantially increased, but decreases with hydrophobic lining [61]. In ionic channels the hydrophobic lining in the water basket serves, then, to maintain a certain degree of water mobility despite the gluelike properties of its bulk. This issue has been addressed by Siwy and Fulinski [35] who cited strong evidence supporting the importance of channel wall properties in the generation of flicker noise, i.e.,

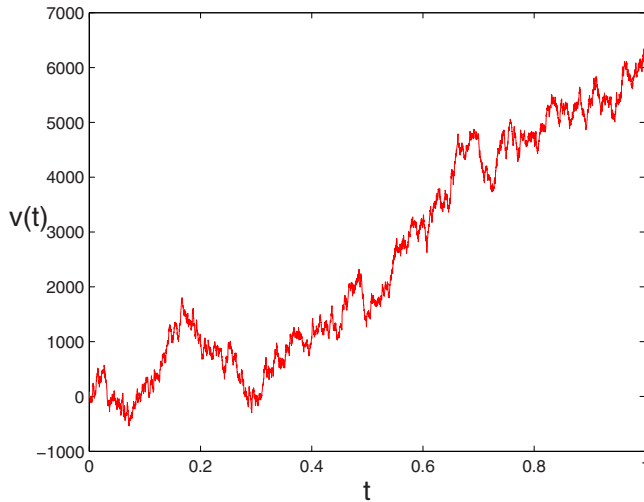


FIG. 1. (Color online) Velocity plots with no correlation.

$\frac{1}{f^\alpha}$ noise, as originally proposed by Bezrukov [64]. It should be noted that the power spectrum in the weak NM limit has a memoryless property in contrast to the $1/f$ flicker noise property characteristic of long tail correlations [59,60]. Our results do not contradict our expectations that at the weak NM limit, Markovian dynamics occur at the selectivity filter. This event will then give rise, by interactions with water dynamics in the water basket, to deviations in Markovianity generating a spectral limit for $\tau_{1,2} \rightarrow 0$, which generates the proposed combination of color noise. Here, from a purely physical perspective, we have added the viscous term to the simulations. We would also like to point out some results [65,66]. The most challenging aspect of the simulation of ion channels has been the implementation of particle coupling and boundary conditions. In BD simulations it is particularly difficult to maintain the correct particle concentrations and behavior that occur under extreme conditions such as that in channel simulations. Here we use a simple algorithm. The GLE can be written as a set of 3 LE's,

$$\ddot{z} = -a_0 V'(z) + \beta_1 + \beta_2,$$

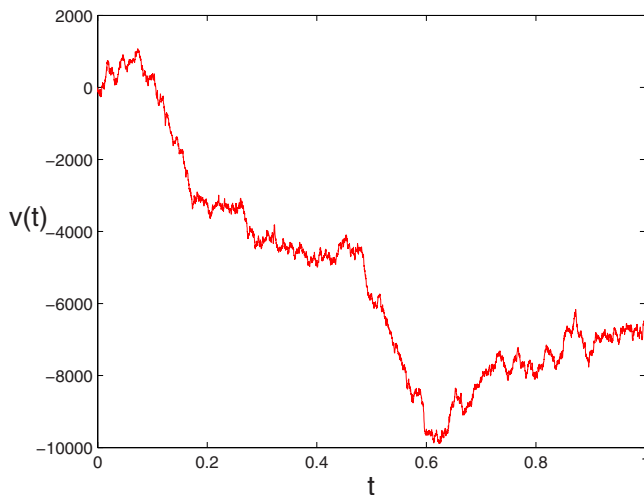


FIG. 2. (Color online) Velocity plots at length scales where the viscosity is weak.

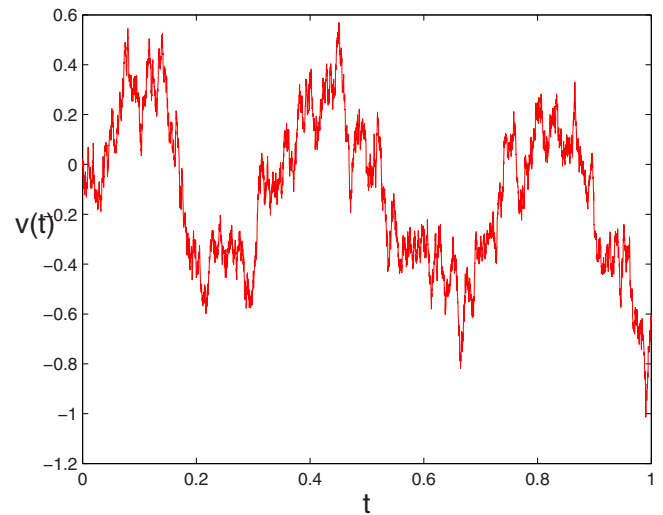


FIG. 3. (Color online) Velocity plots at length scales where the viscosity is dominant.

$$\dot{\beta}_{1,2} = -\frac{-\beta_{1,2}}{\tau_{1,2}} - \frac{a_{1,2}}{\tau_{1,2}} \dot{z} + r_i + f_i. \quad (14)$$

The distribution functions from our simulations are shown below, which show a specific correlation. In Fig. 1 we have plotted the velocity profile with no correlation.

The velocity profiles are shown in Fig. 2 for weak viscosity and for strong viscosity in Fig. 3 and for various time scales in Fig. 4.

When we did large iterations, the plot is shown in Fig. 5.

We can use the second order Runge-Kutta method by discretizing Eq. (14) 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 three normal Gaussian random numbers and the matrix elements of the coefficients are evaluated by the self- and cross correlations of the integrations of noise. Finally, it should be mentioned that some interesting results have been obtained by

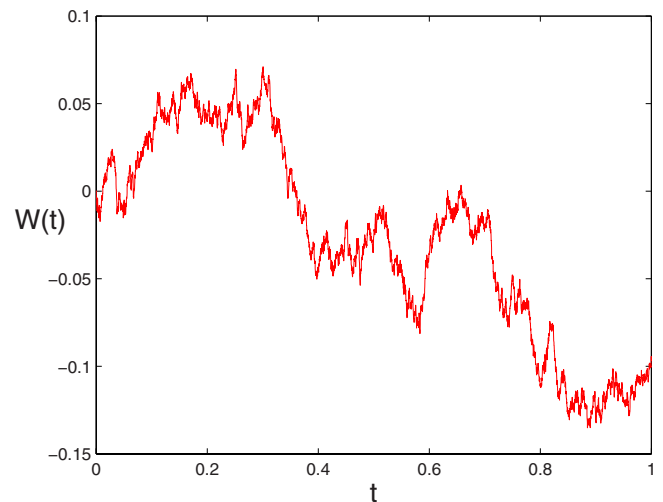


FIG. 4. (Color online) Plots of velocity profiles from simulations that indicate the role of viscosity at different time scales.

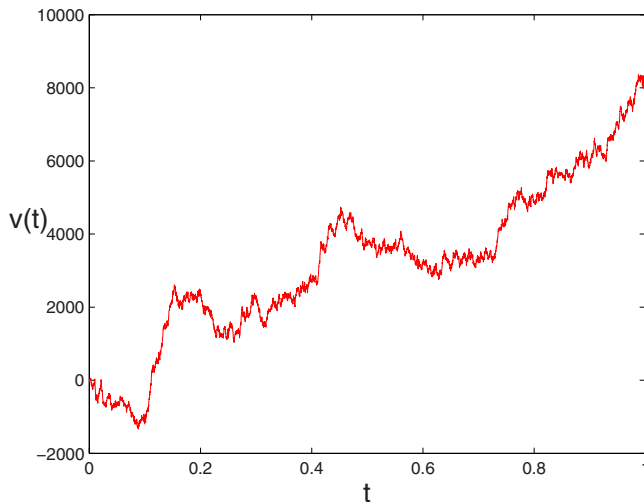


FIG. 5. (Color online) Velocity plots with no correlation up to 10 000 iterations.

considering a Gillespie algorithm in the context of BD simulation [53], which has not been considered here.

VI. DISCUSSION

We have applied a set of algorithms that allow a comparison between the time scales of diffusion and drift performed along a selectivity filter in a model K^+ channel. The model describes two time scales for atomic ionic movement along the filter's length. This results in an oscillatory flow where the velocity autocorrelations 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 it is explicit that oscillations dominate at the limit of the weak non-Markovian process (shown in Fig. 6).

We have shown here the results from a non-Markovian process that gives rise to a memory function along with the two time scales in the BD behavior and determined the standard deviations of the results.

The results of the simulations clearly show that the BD approach can be used to describe the Coulomb interaction and different time scales. It is also clear that the single barrier model with a threshold for the barrier plays an important role for charge transport through ion channels and advocates

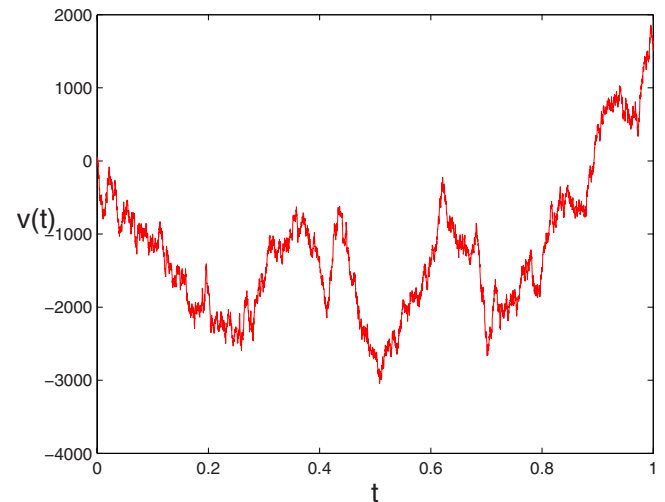


FIG. 6. (Color online) Velocity plots in the weak non-Markovian limit.

the use of particle based simulation models. But the most striking feature of the model is that it is possible to model both the memory effects of gating and the oscillatory behavior of flow by a GLE, which contains an admixture of Markovian and non-Markovian processes.

Both the admixture of the time evolution kernel and the viscosity terms and the correlation function make it clear that a phase transition of the shear viscosity within the channels may give an important clue to the rise of memory effects and the evolution of flip flop motion within the selectivity filter of potassium channels. The exact stochastic simulation using nonlinear 3D Navier needs to be shown. It is to be noted that water plays an important role in describing the dynamics of the ion channel. The water in the region of the channel containing a *water basket* behaves like glue with a larger viscosity than that outside the channel. However, the activity of water in the pore is supposed to be higher than that in the external solution even in the absence of a pressure difference. This is similar to the idea of expanded, stretched, viscous water, which is strongly hydrogen bonded and selects a K^+ ion [67].

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