Derivation of Poisson and Nernst-Planck equations in a bath and channel from a molecular model

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Permeation of ions from one electrolytic solution to another, through a protein channel, is a biological process of considerable importance. Permeation occurs on a time scale of micro- to milliseconds, far longer than the femtosecond time scales of atomic motion. Direct simulations of atomic dynamics are not yet possible for such long-time scales; thus, averaging is unavoidable. The question is what and how to average. In this paper, we average a Langevin model of ionic motion in a bulk solution and protein channel. The main result is a coupled system of averaged Poisson and Nernst-Planck equations (CPNP) involving conditional and unconditional charge densities and conditional potentials. The resulting NP equations contain the averaged force on a single ion, which is the sum of two components. The first component is the gradient of a conditional electric potential that is the solution of Poisson's equation with conditional and permanent charge densities and boundary conditions of the applied voltage. The second component is the self-induced force on an ion due to surface charges induced only by that ion at dielectric interfaces. The ion induces surface polarization charge that exerts a significant force on the ion itself, not present in earlier PNP equations. The proposed CPNP system is not complete, however, because the electric potential satisfies Poisson's equation with *conditional* charge densities, conditioned on the location of an ion, while the NP equations contain unconditional densities. The conditional densities are closely related to the well-studied pair-correlation functions of equilibrium statistical mechanics. We examine a specific closure relation, which on the one hand replaces the conditional charge densities by the unconditional ones in the Poisson equation, and on the other hand replaces the self-induced force in the NP equation by an effective self-induced force. This effective self-induced force is nearly zero in the baths but is approximately equal to the self-induced force in and near the channel. The charge densities in the NP equations are interpreted as time averages over long times of the motion of a quasiparticle that diffuses with the same diffusion coefficient as that of a real ion, but is driven by the averaged force. In this way, continuum equations with averaged charge densities and mean-fields can be used to describe permeation through a protein channel.

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I. INTRODUCTION

The Poisson-Nernst-Planck (PNP) equations have been used for the description of macroscopic properties of electrochemical systems, usually without current flow, and also for the description of currents in semiconductor devices [1,2]. These equations have been also quite successfully applied to the description of ionic currents in protein channels of biological membranes [3–6]. The state variables in the PNP equations are the electrostatic potential and the charge densities of the different ionic species. The PNP equations are usually derived from conservation laws of a continuum formulation [2].

The application of the PNP equations inside narrow channels that can contain only a small number of ions at a time, or in channels where the ions are arranged in a single file, raises interesting conceptual and mathematical problems. For example, what is the meaning of concentration in such a context? The PNP equations predict quite accurately the current-voltage response of narrow channels over a wide range of salt concentrations in the bath. However, many phenomena, usually associated with single filing of ions, are missed by the PNP system [3]. The record of current vs time of a single channel in patch clamp and bilayer experiments [7] ranges from noisy to very noisy, depending on the type of channel. Although this noise is not captured by the PNP system at all, still the average net currents predicted by PNP in an open channel are quite accurately reproduced in several channels of known structure [6].

The partial success and partial failure of the PNP system poses the question why? Which results of the PNP model can be accepted and which cannot? The purpose of this paper is to partially answer these questions by deriving the PNP equations from a molecular model of ionic motion in both a bath and a channel. As discussed below, the resulting (exact) PNP equations differ from the standard ones used so far.

The point of departure for our derivation is the classical view that ionic motion in solution is governed by electrostatic forces and thermal fluctuations of the solvent [8]. The fluctuations give rise to the diffusive motion of ions in the bath as well as inside the channel. The prediction of macroscopic properties of ionic solutions from the microscopic Brownian motion of their components raises interesting

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mathematical issues illustrated here with a primitive Langevin model of ionic motion. In this model the electrostatic forces acting on the diffusing ions consist of the Coulombic interactions between the ions, the permanent charges, such as charges on molecules immersed in the solution, induced surface charges on dielectric boundaries, and the effects of an external field. Our simple model of ionic motion assumes that the fluctuating force exerted on an ion by the solvent can be represented as friction and a zero-mean Gaussian stationary force (noise) satisfying Einstein's (generalized) fluctuation-dissipation principle, and that noises acting on different ions, are independent of each other.

Our derivation follows traditional methods of statistical physics, where continuum equations for densities are derived from microscopic laws governing the motion of individual particles (see Ref. [9] and the more recent Ref. [10]). The case at hand differs from the standard models in that the force term in the equations of motion is governed by a separate Poisson equation. The assumptions on the independence of the noises in the Langevin equations and on the representation of the solvent as a dielectric constant in Poisson's equation need further examination in concentrated solutions and in multiply occupied protein channels. For other theories of multiply occupied narrow channels see Ref. [7] and references therein, and the more recent paper [11].

The results of this paper are the derivation of a coupled system of NP equations for the charge densities and Poisson equations for averaged electric potentials, from a Langevin model of ionic motion. The force in the NP equations has two components, the gradient of an electric potential, and a self-induced force on an ion produced by surface charges induced by that ion at dielectric interfaces. The latter component in the NP equations seems to be new, although the existence of such a force has been considered in simulations [12]. The proposed PNP system, however, is not complete (i.e., ''closed''), since the electric potential depends on *conditional* charge densities, given the location of an ion, while the NP equations contain *un*conditional densities. Closure relations, mainly applied to equilibrium Poisson Boltzmann systems, have been the subject of extensive study in the literature [13,14,8,15], and references therein. The proposed theories are based on various physical and excluded volume assumptions, and sometimes lead to different results. Closure relations for nonequilibrium systems, e.g., for systems carrying a steady current, are still not known. In this paper we consider a closure relation for the particular case of an electrolytic solution in the presence of a dielectric interface. In this closure relation the conditional charge densities are replaced by the unconditional ones, and the self-induced force in the NP equation is replaced by an effective force.

Our derivation of PNP equations is essentially an averaging procedure of a finite but large discrete system. The charge densities in the NP equations are interpreted as time averages over long times of the number of particles per unit volume in the discrete system. This interpretation gives meaning to densities even in narrow channels that can contain at most one or two ions at a time. Although in the averaging procedure all microscopic phenomena in a narrow channel may be lost—including finite size of the ions, blocking, single filing, noise and so on [7]—still the average net flux is preserved. The average net flux is a measure of the biological function of most channels.

II. FORMULATION

We consider an electrostatically neutral binary solution confined in a finite volume, between electrodes and impenetrable hard walls. The two electrodes are connected to a feedback apparatus, external to our model, that maintains constant average voltage and concentrations at the electrodes. The feedback mechanism achieves this by removing and feeding back ions as current flows through the system. Thus, on average, the number of ions in the solution is constant. In reality, the voltage, concentrations, flux, and the number of ions are not constant but rather fluctuate in time. These fluctuations are caused by the random motion of the ions, the deterministic and random time delays of the feedback mechanisms, the finite precision of the measuring devices, and so on.

In this paper, we neglect these fluctuations and assume that the number of both positive and negative ions in the solution is constant at all times. In particular, we assume that the feedback mechanism is instantaneous, that is, when an ion reaches one electrode, it is immediately injected at the other electrode. Thus, the total flux of particles on the boundary of the system vanishes at all times. This approximation reduces the resolution of our analysis but is a reasonable representation of the typical experimental situation. These fluctuations are indeed negligible for an experimental system in which the electrodes are placed far away from the region of biological or chemical interest. Fluctuations are significant in computer simulations, in which the total number of ions is relatively small, and thus must be taken into account [31].

We consider a solution containing N positive and N negative ions. We denote the coordinates of a point by $\boldsymbol{x}=(x,y,z)$. We number the ions in the solution at time $t=0$ and denote the vectors of coordinates and velocity of the jth positive ion at time t by $\boldsymbol{x}_j^p(t)$ and $\dot{\boldsymbol{x}}_j^p(t)$, respectively, and those of the kth negative ion by $\boldsymbol{x}_k^n(t)$ and $\dot{\boldsymbol{x}}_k^n(t)$. The coordinate vector of all ions in the $6N$-dimensional configuration space is denoted $\tilde{\boldsymbol{x}}=(\boldsymbol{x}_1^p,\ldots,\boldsymbol{x}_N^p,\boldsymbol{x}_1^n,\ldots,\boldsymbol{x}_N^n)$, while in analogy, the vector of all velocities is denoted as $\dot{\tilde{\boldsymbol{x}}}$ or $\tilde{\boldsymbol{v}}$. For future reference, the vector of coordinates of all $2N-1$ ions, excluding the jth positive ion is denoted $\tilde{\boldsymbol{x}}_j^p$.

A. Equations of motion

Ionic solutions nearly always contain many more water molecules than ions, even when they are nearly saturated, at their solubility limit. For example, there are about 55 water molecules per ion in a 1 M salt solution, and at the biological concentration of 100 mM, there are about 550 water molecules per ion. Thus, the collective motion of only the ions (without the water) is a lower-dimensional projection of the joint motion of all water and salt molecules in the solution, that can be approximated by a system of generalized Lange-

vin equations [16]. These equations assume that the thermal motion of ions is due mainly to the thermal motion of the surrounding water molecules. There is of course another contribution to the diffusive motion of each ion, from its interactions with the other ions, as in an ionic plasma. This effect decreases as the solution becomes more dilute.

The generalized Langevin equations involve a friction memory kernel and correlated noise, satisfying a generalized fluctuation-dissipation principle [16]. The motion of ions in solution is strongly overdamped, and so the correlation time of the noise is much shorter than the characteristic diffusion time scale considered in this paper. On a sufficiently coarse time scale, much longer than the relaxation time of the solution, memory effects can be neglected [17]. Thus, our point of departure is the memoryless system of Langevin equations

$$\ddot{\boldsymbol{x}}_j^p + \gamma^p(\boldsymbol{x}_j^p)\dot{\boldsymbol{x}}_j^p = \frac{\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}})}{m^p} + \sqrt{\frac{2\gamma^p(\boldsymbol{x}_j^p)k_BT}{m^p}}\dot{\boldsymbol{w}}_j^p,$$

$$(j=1,2,\ldots,N), \tag{2.1}$$

$$\ddot{\boldsymbol{x}}_k^n + \gamma^n(\boldsymbol{x}_k^n)\dot{\boldsymbol{x}}_k^n = \frac{\boldsymbol{f}_k^n(\tilde{\boldsymbol{x}})}{m^n} + \sqrt{\frac{2\gamma^n(\boldsymbol{x}_k^n)k_BT}{m^n}}\dot{\boldsymbol{w}}_k^n,$$

$$(k=1,2,\ldots,N),$$

where a dot on a variable denotes differentiation with respect to time, $\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}})$ and $\boldsymbol{f}_k^n(\tilde{\boldsymbol{x}})$ denote the electrostatic forces acting on the jth positive ion and on the kth negative ion, respectively, $\gamma^c(\boldsymbol{x})$ is the location dependent friction coefficient per unit mass of the ionic species of type c ($c=p,n$), and $\dot{\boldsymbol{w}}_j^c$ are, by assumption, independent standard Gaussian white noises. The parameter k_B is Boltzmann's constant, T is the absolute temperature, and m^c is the effective mass of an ion of type c.

In addition we assume that positive and negative ions have radii a_p and a_n, respectively, and that there are hard wall potentials between ions, preventing oppositely charged ions from collapsing into each other.

The physical three-dimensional domain in which our system is confined, called Ω, is shown in Fig. 1. Its boundary $\partial\Omega$, consists of two parts. One is the electrodes, and the other one is impermeable walls. The $6N$-dimensional configuration space of the trajectories of all $2N$ particles in the Langevin system (2.1) is confined to the domain

$$\tilde{\Omega} = \bigtimes_{j=1}^{2N} \Omega_j,$$

where $\times$ denotes Cartesian product, and Ω_j is the three-dimensional physical domain of the jth particle, identical to Ω. The boundary of the domain $\tilde{\Omega}$ is

$$\partial\tilde{\Omega} = \bigcup_{j=1}^{2N} \Omega_1 \times \Omega_2 \times \cdots \times \Omega_{j-1} \times \partial\Omega_j \times \Omega_{j+1} \times \cdots \Omega_{2N},$$

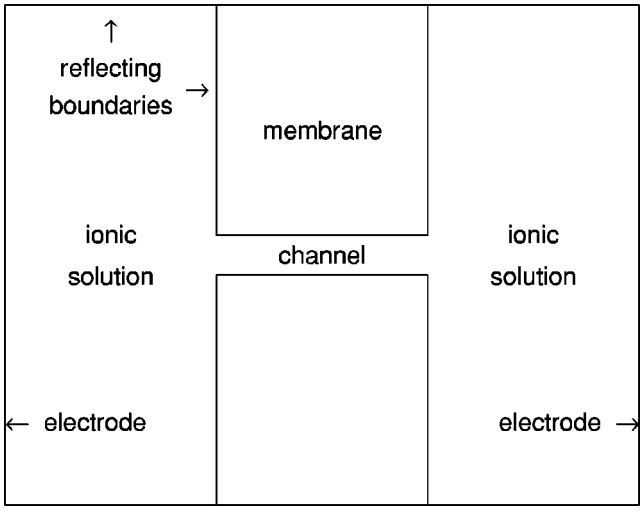

FIG. 1. A typical experimental setup. The region Ω consists of two baths separated by an impermeable membrane, with a possible channel embedded in it. The electrodes immersed in the two baths are connected to an external feedback mechanism (not shown in figure) that maintains a constant voltage difference between the electrodes, and constant concentrations in the baths.

which consists of all points in the $6N$-dimensional space, where at least one of the $2N$ components is on the boundary of the corresponding region Ω_j.

The boundary behavior of the random trajectories of the Langevin equations (2.1) reflects the physical boundary conditions imposed on the system at the boundary $\partial\Omega$. Every trajectory that reaches an electrode is instantaneously injected at the opposite one. Trajectories that reach other boundaries of the domain are reflected [3,18]. The fluctuations removed by this idealized electrode (voltage clamp) boundary condition will be studied elsewhere.

B. The electrostatic forces

As stated in the introduction, we assume that the electrolytic solution is a *fast bath*, namely, that the relaxation time of the solvent water is very fast so that the dielectric coefficient of the pure solvent is time independent. We also assume that the potential in the bath can be represented as the solution of Poisson's equation, and not of the time dependent Maxwell equations. The effects of displacement current and possible radiation will be examined elsewhere. The electrostatic force acting on an ion is then computed from the electrostatic potential $\phi(\boldsymbol{x})$, a solution of Poisson's equation

$$\Delta\phi(\boldsymbol{x}) = -\frac{1}{\varepsilon_0}\left[e\rho_{perm}(\boldsymbol{x}) + e\sum_j \delta(\boldsymbol{x}-\boldsymbol{x}_j^p) - e\sum_k \delta(\boldsymbol{x}-\boldsymbol{x}_k^n)\right] + \nabla\cdot\boldsymbol{P}(\boldsymbol{x}), \tag{2.2}$$

where $\rho_{perm}(\boldsymbol{x})$ is the permanent charge density, and $\boldsymbol{P}(\boldsymbol{x})$ is the polarization field, that describes the charge induced by the electric field in matter that otherwise would be charge neutral [19]. In an isotropic medium with linear response, the polarization field is connected to the local field by

$$\boldsymbol{P}(\boldsymbol{x}) = \chi\boldsymbol{E}(\boldsymbol{x}) = -\chi\nabla\phi(\boldsymbol{x}), \tag{2.3}$$

where $\chi(\boldsymbol{x})=\varepsilon(\boldsymbol{x})-1$ is the dielectric susceptibility of the medium [19]. Combining Eq. (2.3) and Eq. (2.2), we obtain the familiar form of Poisson's equation

$$\nabla\cdot\varepsilon(\boldsymbol{x})\nabla\phi(\boldsymbol{x})=-\frac{1}{\varepsilon_0}\left[e\rho_{perm}(\boldsymbol{x})+e\sum_j\ \delta(\boldsymbol{x}-\boldsymbol{x}_j^p)-e\sum_k\ \delta(\boldsymbol{x}-\boldsymbol{x}_k^n)\right].$$

In addition, the potential $\phi(\boldsymbol{x})$ satisfies boundary conditions on the electrodes and the standard continuity conditions of the electric displacement vector across surfaces of discontinuity of the dielectric coefficient [19].

The electrostatic force on the jth positive ion at position $\boldsymbol{x}_j^p$, denoted $\boldsymbol{f}_j^p$, is calculated from the potential $\phi(\boldsymbol{x})$ as follows:

$$\boldsymbol{f}_j^p=-e\nabla\left(\phi(\boldsymbol{x})-\frac{1}{4\pi\varepsilon_0\varepsilon(\boldsymbol{x}_j^p)}\frac{1}{|\boldsymbol{x}-\boldsymbol{x}_j^p|}\right)\Bigg|_{\boldsymbol{x}=\boldsymbol{x}_j^p}. \quad (2.4)$$

The last term on the right-hand side of Eq. (2.4) removes the singularity of the potential $\phi(\boldsymbol{x})$ at the location of the ion (see Appendix A for details).

This force, which in general depends on the coordinate vector $\tilde{\boldsymbol{x}}$ of all the charges in the system, can be decomposed into two components,

$$\boldsymbol{f}_j^p=\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}},P)+\boldsymbol{f}_D(\boldsymbol{x}_j^p). \quad (2.5)$$

The first component $\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}},P)$, includes the interaction forces of the jth positive ion with all other ions in the solution, the permanent charge, the charges on the electrodes that maintain a fixed applied voltage, and the surface charges induced by these charges. The second component $\boldsymbol{f}_D(\boldsymbol{x}_j^p)$, is a self-induced force produced by the surface charges induced at the dielectric interfaces by the ion at $\boldsymbol{x}_j^p$. If there are no dielectric interfaces, this induced force is zero. Note that this force component is proportional to the *square* of the ion's charge, regardless of its sign. For example, it is equal for monovalent anions and cations (see Appendix A for details).

While the first component depends on the locations of *all* charges in the system, the second component depends only on the location of the jth positive ion, and is independent of the location of all the other charges in the system, and in particular, of the applied voltage. The computation of this self-induced force component is described in Appendix A. The decomposition (2.5) of the total force into these two components, is particularly important in the averaging process described below.

The first component of the force $\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}},P)$, is obtained from the solution of Poisson's equation (2.2), with the charge of the jth positive ion removed from the right-hand side. We denote the resulting electric potential by $\phi_j^p(\boldsymbol{x},\tilde{\boldsymbol{x}}_j^p)$, determined from

$$\nabla_{\boldsymbol{x}}\cdot\varepsilon(\boldsymbol{x})\nabla_{\boldsymbol{x}}\phi_j^p(\boldsymbol{x},\tilde{\boldsymbol{x}}_j^p)=-\frac{1}{\varepsilon_0}\left[e\rho_{perm}(\boldsymbol{x})+e\sum_{j'\neq j}\ \delta(\boldsymbol{x}-\boldsymbol{x}_{j'}^p)-e\sum_k\ \delta(\boldsymbol{x}-\boldsymbol{x}_k^n)\right], \quad (2.6)$$

with the same boundary and continuity conditions mentioned above, for the potential $\phi(\boldsymbol{x})$. Here $\nabla_{\boldsymbol{x}}$ denotes the gradient with respect to the variable $\boldsymbol{x}$,

$$\nabla_{\boldsymbol{x}}=\left(\frac{\partial}{\partial x},\frac{\partial}{\partial y},\frac{\partial}{\partial z}\right).$$

In terms of this potential, the first component of the force $\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}},P)$, is given by

$$\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}},P)=-e\nabla_{\boldsymbol{x}}\phi_j^p(\boldsymbol{x},\tilde{\boldsymbol{x}}_j^p)|_{\boldsymbol{x}=\boldsymbol{x}_j^p}. \quad (2.7)$$

The second component of the force $\boldsymbol{f}_D(\boldsymbol{x}_j^p)$, is given by

$$\boldsymbol{f}_D(\boldsymbol{x}_j^p)=-e\nabla_{\boldsymbol{x}}\left(\phi_D(\boldsymbol{x},\boldsymbol{x}_j^p)-\frac{1}{4\pi\varepsilon(\boldsymbol{x}_j^p)\varepsilon_0}\frac{e}{|\boldsymbol{x}-\boldsymbol{x}_j^p|}\right)\Bigg|_{\boldsymbol{x}=\boldsymbol{x}_j^p}, \quad (2.8)$$

where $\phi_D(\boldsymbol{x},\boldsymbol{y})$ satisfies Poisson's equation

$$\nabla_{\boldsymbol{x}}\cdot\varepsilon(\boldsymbol{x})\nabla_{\boldsymbol{x}}\phi_D(\boldsymbol{x},\boldsymbol{y})=-\frac{e}{\varepsilon_0}\delta(\boldsymbol{x}-\boldsymbol{y}), \quad (2.9)$$

with zero potential boundary conditions at the electrodes (see Appendix A for derivation).

III. DERIVATION OF THE PNP EQUATIONS

Equations (2.1)–(2.4) form a discrete high-dimensional system of coupled stochastic and partial differential equations that describe the time evolution of this many particle system. We derive a simplified, though approximate, description of this system in which ions are represented by *continuum* charge densities. In this approximation the description of the system is reduced to averaged charge densities and electric potentials governed by Nernst-Planck and Poisson equations.

The outline of the computation is as follows. First, the connection between the positive-ion concentration and the stationary probability density function (pdf) of a single ion, is derived in Sec. III A. In Sec. III B, the Fokker-Planck equation for the joint pdf of all ions in the system is formulated. The probability density of a single positive ion is obtained by integration of the joint pdf over the phase space of all ions, excluding a single positive ion. This procedure results in a Fokker-Planck type equation (FPE) for the pdf of the phase-space coordinates of a single ion. The resulting equation, however, is not a standard FPE because it contains an average force term that depends on the probability density of all other ions. Since this probability density depends on the unknown solution of the full FPE for all ions, the force term in the FPE equation is in general unknown. In Sec. III D

we consider the large friction limit of this FPE, resulting in a reduced Smoluchowski equation for only the pdf of the location of the ion, with a still unknown force function. According to the results of Sec. III A, this Smoluchowski equation turns into a Nernst-Planck equation for the averaged charge density.

The average force appearing in these equations, which depends on the probability density of all other ions, is evaluated in Sec. III E. We separate the average force into two components. One is the self-induced force that an ion exerts on itself arising from the charge induced by the ion at boundaries between regions of different dielectric coefficient. It might be called a dielectric boundary force. The other component is an average force due to the interaction of the ion with all other charges in the system, e.g., the permanent charge on the protein, the ions in the bath, and the charges on the electrodes that maintain the voltage clamp boundary condition. The second term can be written as the gradient of an averaged potential, described by an averaged Poisson equation. The averaged Poisson equation, however, contains *conditional* charge densities, rather than the unconditional charge densities present in the Nernst-Planck equation just described. This key result is a direct consequence of the averaging procedure, and is not an assumption. Thus, the resulting system, denoted CPNP, is not closed, i.e., it is incomplete. In Sec. III F, we examine one specific closure relation and its consequences. This closure relation replaces the conditional charge densities by the unconditional ones, neglecting the finite size of ions. This approximation leads to a (closed) PNP-type system of equations, but with an additional effective induced force term in the NP equations.

A. Charge density and probability density

We use $c_p(\boldsymbol{x})$ to describe the time-averaged steady-state charge density of the positive species at location $\boldsymbol{x}$, and $p_j^p(\boldsymbol{x})$, $j=1,\ldots,N$, to define the stationary probability density function (PDF) of the location of the jth positive ion.

These two quantities are related as follows. By definition, for a small volume $\Delta\boldsymbol{x}$ around the point $\boldsymbol{x}$, the product $c_p(\boldsymbol{x})\Delta\boldsymbol{x}$ denotes the time-averaged number of ions in this volume. We introduce $\chi(\boldsymbol{x},\Delta\boldsymbol{x})$ as the indicator function of the volume $\Delta\boldsymbol{x}$,

$$\chi(\boldsymbol{x},\Delta\boldsymbol{x})=\begin{cases}1 & \text{if} \quad \boldsymbol{x}\in\Delta\boldsymbol{x},\\ 0 & \text{otherwise.}\end{cases}$$

We abbreviate $\chi_j=\chi(\boldsymbol{x}_j^p(t),\Delta\boldsymbol{x})$. By definition,

$$c_p(\boldsymbol{x})\Delta\boldsymbol{x}=\sum_j E\{\chi_j\}=\sum_j \Pr\{\chi[\boldsymbol{x}_j^p(t),\Delta\boldsymbol{x}]=1\},$$

where $E\{\cdot\}$ denotes the expected value operator.

In the steady state, for small volumes $\Delta\boldsymbol{x}$

$$\Pr\{\chi[\boldsymbol{x}_j^p(t),\Delta\boldsymbol{x}]=1\}=p_j^p(\boldsymbol{x})\Delta\boldsymbol{x}+O[(\Delta\boldsymbol{x})^2].$$

Moreover, for a stationary system in steady state with a single species of positive ions, from symmetry considerations, the probability of finding the jth positive ion at location $\boldsymbol{x}$ is the same as that of finding any other positive ion there. Thus, the probability density $p_j^p(\boldsymbol{x})$ is independent of the index j, and we denote it simply by $p(\boldsymbol{x})$. Hence, in the limit $|\Delta\boldsymbol{x}|\to 0$,

$$c_p(\boldsymbol{x})=Np(\boldsymbol{x}). \tag{3.1}$$

Thus, the density $c_p(\boldsymbol{x})$ is N times the stationary pdf of the jth positive ion. Similarly, the charge density of negative ions $c_n(\boldsymbol{x})$ is N times the stationary marginal, i.e., integrated pdf of the kth negative ion. These densities are independent of the indices j and k, respectively. The density $c_p(\boldsymbol{x})$ is the physical density of positive ions and it integrates to the total number of positive ions in the solution.

In mixed solutions, for example, Na^+, Ca^{2+}, and Cl^-, the analog of Eq. (3.1) holds for each species separately. This will lead to different Nernst-Planck equations for each species and other complexities in the analysis, as discussed later on.

B. The multidimensional Fokker-Planck equation

Equation (3.1) shows the connection between the stationary PDF of a single positive ion $p(\boldsymbol{x})$ and the macroscopic charge density $c_p(\boldsymbol{x})$. Therefore, we can now derive an equation for $p(\boldsymbol{x})$, which by relation (3.1), readily turns into an equation for $c_p(\boldsymbol{x})$. We start from an equation for the stationary joint probability density of *all* ions, and integrate it over the phase-space coordinates of all ions, excluding a single positive ion, to obtain an equation for the marginal, i.e., integrated, density of this ion.

The joint *transition* probability density of all ions is defined as

$$p(\tilde{\boldsymbol{x}},\tilde{\boldsymbol{v}},t\mid\tilde{\boldsymbol{\xi}},\tilde{\boldsymbol{\eta}},s)=\Pr\{\tilde{\boldsymbol{x}}(t)=\tilde{\boldsymbol{x}},\tilde{\boldsymbol{v}}(t)=\tilde{\boldsymbol{v}}\mid\tilde{\boldsymbol{x}}(s)=\tilde{\boldsymbol{\xi}},\tilde{\boldsymbol{v}}(s)=\tilde{\boldsymbol{\eta}}\}, \tag{3.2}$$

where $\tilde{\boldsymbol{\xi}}$ and $\tilde{\boldsymbol{\eta}}$ are the phase-space coordinates of all ions at some initial time s. The stationary PDF of all ions is defined as the long-time limit of the transition PDF (3.2),

$$p(\tilde{\boldsymbol{x}},\tilde{\boldsymbol{v}})=\lim_{t\to\infty} p(\tilde{\boldsymbol{x}},\tilde{\boldsymbol{v}},t\mid\tilde{\boldsymbol{\xi}},\tilde{\boldsymbol{\eta}},s), \tag{3.3}$$

and is independent of the initial values $\tilde{\boldsymbol{\xi}}$, $\tilde{\boldsymbol{\eta}}$ at time s.

The motion of all ions is governed by the Langevin system (2.1), so the stationary PDF (3.3) satisfies the multidimensional stationary Fokker-Planck equation [20]

$$0=\sum_j \mathcal{L}_j^p\, p+\sum_k \mathcal{L}_k^n\, p, \tag{3.4}$$

where $\mathcal{L}_j^p$ and $\mathcal{L}_k^n$ are the Fokker-Planck operators acting on the phase-space coordinates of the jth positive and kth negative ion, respectively. They are given by

$$\mathcal{L}_j^c p = -\boldsymbol{v}_j^c \cdot \nabla_{\boldsymbol{x}_j^c} p + \nabla_{\boldsymbol{v}_j^c} \cdot \left(\gamma^c(\boldsymbol{x}_j^c)\boldsymbol{v}_j^c - \frac{\boldsymbol{f}_j^c}{m^c} \right) p$$

$$+ \Delta_{\boldsymbol{v}_j^c} \frac{\gamma^c(\boldsymbol{x}_j^c) k_B T}{m^c} p, \quad (c = p, n),$$

where the operators $\nabla_{\boldsymbol{x}}$ and $\Delta_{\boldsymbol{x}}$ denote the gradient and the Laplacian with respect to the variable $\boldsymbol{x}$, respectively. Equation (3.4) is defined in the $12N$ dimensional region $\tilde{\boldsymbol{x}} \in \tilde{\Omega}$ and $\tilde{\boldsymbol{v}} \in \boldsymbol{R}^{6N}$.

The FPE (3.4) can be written as a conservation law

$$0 = -(\nabla_{\tilde{\boldsymbol{v}}}, \nabla_{\tilde{\boldsymbol{x}}}) \cdot (\boldsymbol{J}_{\tilde{\boldsymbol{v}}}, \boldsymbol{J}_{\tilde{\boldsymbol{x}}}),$$

$$= -\sum_{\substack{j=1..N, \\ c=p,n}} (\nabla_{\boldsymbol{v}_j^c} \cdot \boldsymbol{J}_{\boldsymbol{v}_j^c} + \nabla_{\boldsymbol{x}_j^c} \cdot \boldsymbol{J}_{\boldsymbol{x}_j^c}), \tag{3.5}$$

where $\boldsymbol{J}_{\tilde{\boldsymbol{v}}} = (\boldsymbol{J}_{\boldsymbol{v}_j^p}, \boldsymbol{J}_{\boldsymbol{v}_k^n})$, and $\boldsymbol{J}_{\tilde{\boldsymbol{x}}} = (\boldsymbol{J}_{\boldsymbol{x}_j^p}, \boldsymbol{J}_{\boldsymbol{x}_k^n})$, $(j = 1, \ldots, N, k = 1, \ldots, N)$, are $2N$ -dimensional flux density vectors whose components are the three-dimensional flux densities

$$\boldsymbol{J}_{\boldsymbol{v}_j^c} = -\left(\gamma^c(\boldsymbol{x}_j^c)\boldsymbol{v}_j^c - \frac{\boldsymbol{f}_j^c(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}})}{m^c} \right) p(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}})$$

$$- \nabla_{\boldsymbol{v}_j^c} \frac{\gamma^c(\boldsymbol{x}_j^c) k_B T}{m^c} p(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}}), \tag{3.6}$$

$$\boldsymbol{J}_{\boldsymbol{x}_j^c} = \boldsymbol{v}_j^c \, p(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}}).$$

These three-dimensional components of the flux density vector represent the probability flux densities of the individual ions [21].

The boundary conditions for the FPE (3.4) are determined from the boundary behavior imposed on the trajectories of the Langevin equations (2.1) and can be expressed in terms of the three-dimensional components of the flux vector $\boldsymbol{J} = (\boldsymbol{J}_{\tilde{\boldsymbol{x}}}, \boldsymbol{J}_{\tilde{\boldsymbol{v}}})$. Specifically, on the insulating (reflecting) part of the boundary, where particle trajectories are reflected, the following condition holds:

$$\boldsymbol{J}_{\boldsymbol{x}_j^c}(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}}) \cdot \boldsymbol{n}|_{\boldsymbol{x}_j^c \in \partial\Omega, \boldsymbol{v}_j^c \cdot \boldsymbol{n} = v} = -\boldsymbol{J}_{\boldsymbol{x}_j^c}(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}}) \cdot \boldsymbol{n}|_{\boldsymbol{x}_j^c \in \partial\Omega, \boldsymbol{v}_j^c \cdot \boldsymbol{n} = -v}, \tag{3.7}$$

where $\boldsymbol{n}$ denotes the unit normal to the boundary.

On the electrode boundaries, where particles are recycled and the electric potential is controlled, the boundary condition specifies that the influx at one electrode equals the efflux on the other, for each component of the probability flux density. Therefore, the total flux on the boundary vanishes for each one of the $2N$ components of the flux vector $\boldsymbol{J}_{\tilde{\boldsymbol{x}}}$,

$$\int_{\partial\Omega} \boldsymbol{J}_{\boldsymbol{x}_j^c} \cdot \boldsymbol{n} \, dS = 0, \tag{3.8}$$

where dS is a surface element on the boundary.

Last, but not least, the hard wall potentials at a finite distance from the center of each ion also transform into reflecting boundary conditions for the fluxes of other ions, thus preventing the collapse of positive and negative ions onto each other.

C. The probability density of a single ion

We now consider the probability density of the jth positive ion. This is the *marginal* (integrated) density of the joint probability density of all ions,

$$p(\boldsymbol{x}_j^p, \boldsymbol{v}_j^p) = \int \int_{\tilde{\Omega}_j^p \times \boldsymbol{R}^{6N-3}} p(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}}) d\tilde{\boldsymbol{x}}_j^p \, d\tilde{\boldsymbol{v}}_j^p, \tag{3.9}$$

where $\tilde{\Omega}_j^p$ is the configuration space of all ions in Ω, except the jth positive ion and $\boldsymbol{R}^{6N-3}$ is the space of velocities of all ions except the jth positive ion. That is, the right-hand side contains an integration over the $12N-6$ positions and velocities of all particles, excluding the jth positive ion.

To obtain an equation for $p(\boldsymbol{x}_j^p, \boldsymbol{v}_j^p)$, we integrate equation (3.5) with respect to the phase-space coordinates of all ions except those of the jth positive ion

$$0 = -\int \int_{\tilde{\Omega}_j^p \times \boldsymbol{R}^{6N-3}} \nabla \cdot \boldsymbol{J}(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}}) d\tilde{\boldsymbol{x}}_j^p \, d\tilde{\boldsymbol{v}}_j^p. \tag{3.10}$$

We separate the integrand $\nabla \cdot \boldsymbol{J}(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}})$ into the component of the jth positive ion, and to the remaining $2N-1$ other components. For these $2N-1$ components, we apply the divergence theorem in the $12N-6$ dimensional phase space of the integration. First, we consider the velocity flux components $\boldsymbol{J}_{\boldsymbol{v}_j^c}$. For these components, the integration is over all possible velocities. These terms vanish after the application of the divergence theorem because the velocity flux decreases exponentially fast for large absolute velocities, simplifying Eq. (3.10) to

$$0 = -\int \int_{\tilde{\Omega}_j^p \times \boldsymbol{R}^{6N-3}} (\nabla_{\boldsymbol{v}_j^p} \cdot \boldsymbol{J}_{\boldsymbol{v}_j^p} + \nabla_{\boldsymbol{x}_j^p} \cdot \boldsymbol{J}_{\boldsymbol{x}_j^p}) d\tilde{\boldsymbol{x}}_j^p \, d\tilde{\boldsymbol{v}}_j^p$$

$$- \sum_{i \neq j} \int \int_{\partial\Omega_i^p \times \boldsymbol{R}^{6N-3}} \boldsymbol{J}_{\boldsymbol{x}_i^p}(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}}) \cdot \boldsymbol{n}(\boldsymbol{x}_i^p) dS_{\boldsymbol{x}_i^p} \, d\tilde{\boldsymbol{v}}_i^p$$

$$- \sum_k \int \int_{\partial\Omega_k^n \times \boldsymbol{R}^{6N-3}} \boldsymbol{J}_{\boldsymbol{x}_k^n}(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}}) \cdot \boldsymbol{n}(\boldsymbol{x}_k^n) dS_{\boldsymbol{x}_k^n} \, d\tilde{\boldsymbol{v}}_k^n, \tag{3.11}$$

where $\boldsymbol{J}_{\boldsymbol{v}_j^p}$ and $\boldsymbol{J}_{\boldsymbol{x}_j^p}$ are given by Eq. (3.6) and $dS_{\boldsymbol{x}_k^n}$ denotes integration over the surface of the boundary. By definition, the last two terms in Eq. (3.11) are the total probability flux on the boundary $\partial\Omega$ of all ions besides the jth positive ion. Due to the specified boundary conditions (3.7) for the Fokker-Planck equation, the total probability flux of each ion on the boundary is zero, Eq. (3.8), so the last two terms in Eq. (3.11) vanish.

Consider the remaining first term on the right-hand side of Eq. (3.11). Inserting Eq. (3.6) into Eq. (3.11) gives

$$0=\int\int_{\tilde{\Omega}_j^p\times\mathbf{R}^{6N-3}}\nabla_{\boldsymbol{v}_j^p}\cdot\left(\gamma^p(\boldsymbol{x}_j^p)\boldsymbol{v}_j^p-\frac{\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}})}{m^p}+\frac{\gamma^p(\boldsymbol{x}_j^p)k_BT}{m^p}\nabla_{\boldsymbol{v}_j^p}\right)p(\tilde{\boldsymbol{x}},\tilde{\boldsymbol{v}})\,d\tilde{\boldsymbol{x}}_j^p\,d\tilde{\boldsymbol{v}}_j^p+\int\int_{\tilde{\Omega}_j^p\times\mathbf{R}^{6N-3}}\nabla_{\boldsymbol{x}_j^p}\cdot\boldsymbol{v}_j^p\,p(\tilde{\boldsymbol{x}},\tilde{\boldsymbol{v}})\,d\tilde{\boldsymbol{x}}_j^p\,d\tilde{\boldsymbol{v}}_j^p.$$

Note that since integration is over the phase-space coordinates of all ions excluding the jth positive ion, the differentiation operators $\nabla_{\boldsymbol{x}_j^p}$ and $\nabla_{\boldsymbol{v}_j^p}$, as well as all other terms that depend only on $\boldsymbol{x}_j^p$ or $\boldsymbol{v}_j^p$, can be taken out of the integration. Using definition (3.9), we obtain

$$0=\nabla_{\boldsymbol{v}_j^p}\cdot\gamma^p(\boldsymbol{x}_j^p)\boldsymbol{v}_j^p p(\boldsymbol{x}_j^p,\boldsymbol{v}_j^p)-\nabla_{\boldsymbol{v}_j^p}\cdot\int\int_{\tilde{\Omega}_j^p\times\mathbf{R}^{6N-3}}\frac{\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}})}{m^p}p(\tilde{\boldsymbol{x}},\tilde{\boldsymbol{v}})\,d\tilde{\boldsymbol{x}}_j^p d\tilde{\boldsymbol{v}}_j^p+\frac{\gamma^p(\boldsymbol{x}_j^c)k_BT}{m^p}\Delta_{\boldsymbol{v}_j^p}p(\boldsymbol{x}_j^p,\boldsymbol{v}_j^p)-\boldsymbol{v}_j^p\cdot\nabla_{\boldsymbol{x}_j^p}p(\boldsymbol{x}_j^p,\boldsymbol{v}_j^p).\tag{3.12}$$

The only term for which the marginal PDF of the jth positive ion $p(\boldsymbol{x}_j^p,\boldsymbol{v}_j^p)$ could not be recovered from the integration, is the mixed term $\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}})p(\tilde{\boldsymbol{x}},\tilde{\boldsymbol{v}})$. To recover the PDF $p(\boldsymbol{x}_j^p,\boldsymbol{v}_j^p)$ from this term as well, we denote by $p(\tilde{\boldsymbol{x}}_j^p,\tilde{\boldsymbol{v}}_j^p\mid\boldsymbol{x}_j^p,\boldsymbol{v}_j^p)$ the conditional PDF of all ions excluding the jth positive ion, given the phase-space coordinates of the jth positive ion. We write

$$p(\tilde{\boldsymbol{x}},\tilde{\boldsymbol{v}})=p(\tilde{\boldsymbol{x}}_j^p,\tilde{\boldsymbol{v}}_j^p\mid\boldsymbol{x}_j^p,\boldsymbol{v}_j^p)\,p(\boldsymbol{x}_j^p,\boldsymbol{v}_j^p),$$

and set

$$\overline{\boldsymbol{f}}^p(\boldsymbol{x}_j^p,\boldsymbol{v}_j^p)=\int_{\tilde{\Omega}_j^p\times\mathbf{R}^{6N-3}}\int\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}})p(\tilde{\boldsymbol{x}}_j^p,\tilde{\boldsymbol{v}}_j^p\mid\boldsymbol{x}_j^p,\boldsymbol{v}_j^p)d\tilde{\boldsymbol{x}}_j^p\,d\tilde{\boldsymbol{v}}_j^p.\tag{3.13}$$

In Eq. (3.13), the integration over the velocity vector $\tilde{\boldsymbol{v}}_j^p$ can be carried out since the force $\boldsymbol{f}_j^p$ depends only on the locations of the ions, and not on their velocities. This simplifies the last equation to

$$\overline{\boldsymbol{f}}^p(\boldsymbol{x}_j^p,\boldsymbol{v}_j^p)=\int_{\tilde{\Omega}_j^p}\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}})p(\tilde{\boldsymbol{x}}_j^p\mid\boldsymbol{x}_j^p,\boldsymbol{v}_j^p)d\tilde{\boldsymbol{x}}_j^p,\tag{3.14}$$

where $p(\tilde{\boldsymbol{x}}_j^p\mid\boldsymbol{x}_j^p,\boldsymbol{v}_j^p)$ denotes the conditional density of the locations of all other ions, excluding the jth positive ion, given the location and velocity of the jth positive ion.

With these definitions, and suppressing the index j, Eq. (3.12) becomes

$$0=-\boldsymbol{v}\cdot\nabla_{\boldsymbol{x}}p(\boldsymbol{x},\boldsymbol{v})+\nabla_{\boldsymbol{v}}\cdot\left(\gamma^p(\boldsymbol{x})\boldsymbol{v}-\frac{\overline{\boldsymbol{f}}^p(\boldsymbol{x},\boldsymbol{v})}{m^p}\right)p(\boldsymbol{x},\boldsymbol{v})+\Delta_{\boldsymbol{v}}\frac{\gamma^p(\boldsymbol{x})k_BT}{m^p}p(\boldsymbol{x},\boldsymbol{v}).\tag{3.15}$$

Equation (3.15) is a Fokker-Planck equation for the probability density of a single positive ion. It contains an average force $\overline{\boldsymbol{f}}^p(\boldsymbol{x},\boldsymbol{v})$ whose calculation, according to Eq. (3.14), depends on the conditional probability density of all ions, given the phase-space coordinates of the jth positive ion. However, this conditional density depends on the solution of the full Fokker-Planck equation (3.4). Therefore all of these quantities are coupled, and the Fokker-Planck equation for the stationary probability density of a single ion cannot be solved independently of the full Fokker-Planck equation of all other ions. Obviously, Eq. (3.15) is not very useful as long as its force term is not known. Note that although the forcing function $\overline{\boldsymbol{f}}^p(\boldsymbol{x},\boldsymbol{v})$ is not known, Eq. (3.15) is *exact*.

D. The overdamped limit

We consider the Smoluchowski limit of large friction, because the motion of a single ion is strongly overdamped. The first approximation assumes that (in this limit) the conditional probability density of the locations of all ions, excluding the jth positive ion, given its phase-space coordinates, depends only on the position of the ion and not on its velocity,

$$p(\tilde{\boldsymbol{x}}_j^p\mid\boldsymbol{x}_j^p,\boldsymbol{v}_j^p)=p(\tilde{\boldsymbol{x}}_j^p\mid\boldsymbol{x}_j^p).\tag{3.16}$$

This approximation makes the force $\overline{\boldsymbol{f}}^p$ in Eq. (3.14) dependent only on the location of the ion, and not on its velocity,

$$\overline{\boldsymbol{f}}^p(\boldsymbol{x})=\int\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}})p(\tilde{\boldsymbol{x}}_j^p\mid\boldsymbol{x}_j^p=\boldsymbol{x})d\tilde{\boldsymbol{x}}_j^p,\tag{3.17}$$

where $p(\tilde{\boldsymbol{x}}_j^p\mid\boldsymbol{x}_j^p=\boldsymbol{x})$ is the stationary marginal (integrated) conditional density of the locations of all ions, excluding the jth positive ion, given it is located at $\boldsymbol{x}$.

With this approximation, the stationary PDF of the phase-space coordinates of a single positive ion, $p(\boldsymbol{x},\boldsymbol{v})$, satisfies the FPE (3.15) with a forcing function that depends only on the location of the ion. In this case — in the limit of large friction — the marginal PDF of the ions's location $p(\boldsymbol{x})$ satisfies the Smoluchowski equation [18]

$$0=-\nabla\cdot\boldsymbol{J}(\boldsymbol{x})=-\nabla\cdot\left(\frac{\overline{\boldsymbol{f}}^p(\boldsymbol{x})}{m^p\gamma^p(\boldsymbol{x})}p(\boldsymbol{x})-\frac{k_BT}{m^p\gamma^p(\boldsymbol{x})}\nabla p(\boldsymbol{x})\right),\tag{3.18}$$

while the full PDF $p(\boldsymbol{x},\boldsymbol{v})$ has the form

$$p(\boldsymbol{x},\boldsymbol{v})=\left(\frac{2\pi k_BT}{m^p}\right)^{-3/2}\exp\left(-\frac{m^p\boldsymbol{v}^2}{2k_BT}\right)\left[p(\boldsymbol{x})+\frac{m^p}{k_BT}\boldsymbol{J}(\boldsymbol{x})\cdot\boldsymbol{v}+O\left(\frac{1}{\Gamma^2}\right)\right],$$

where $\boldsymbol{J}$ is the flux defined by the Smoluchowski equation (3.18) and Γ is a measure of the friction.

Relation (3.1) converts Eq. (3.18) for the PDF of a single particle into a Nernst-Planck equation for the macroscopic positive charge density $c_p(\boldsymbol{x})$, depending on the yet undetermined average force $\overline{\boldsymbol{f}}^p$,

$$0=-\boldsymbol{\nabla}\cdot\left(\frac{\overline{\boldsymbol{f}}^p(\boldsymbol{x})}{m^p\gamma^p(\boldsymbol{x})}c_p(\boldsymbol{x})-\frac{k_BT}{m^p\gamma^p(\boldsymbol{x})}\boldsymbol{\nabla}c_p(\boldsymbol{x})\right). \tag{3.19}$$

Equation (3.19) depends on the approximation (3.16)–(3.17) but is otherwise exact. Obviously, a similar equation holds for the negative charge density $c_n(\boldsymbol{x})$, albeit with a different force $\overline{\boldsymbol{f}}^n(\boldsymbol{x})$, and the respective friction and mass coefficients $\gamma^n(\boldsymbol{x})$ and m^n.

E. The averaged force

The Nernst-Planck equation (3.19) for the stationary charge density of the positive ions contains a yet undetermined average force $\overline{\boldsymbol{f}}^p(\boldsymbol{x})$, given by Eq. (3.17). This force can be simplified considerably by noting that the force term $\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}})$ can be represented as a sum of two terms $\boldsymbol{f}_D(\boldsymbol{x}_j^p)$ and $\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}},P)$, according to Eq. (2.5). The latter term can be decomposed, even further, as follows:

$$\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}})=\boldsymbol{f}_D(\boldsymbol{x}_j^p)+\boldsymbol{f}_j^p(\tilde{\boldsymbol{x}},P)=\boldsymbol{f}_D(\boldsymbol{x}_j^p)-e\boldsymbol{\nabla}_{\boldsymbol{x}}\left(\phi_{perm}(\boldsymbol{x})+\sum_{i\neq j}\phi_D(\boldsymbol{x},\boldsymbol{x}_i^p)-\sum_k\phi_D(\boldsymbol{x},\boldsymbol{x}_k^n)\right)\Bigg|_{\boldsymbol{x}=\boldsymbol{x}_j^p}, \tag{3.20}$$

where $\boldsymbol{f}_D(\boldsymbol{x}_j^p)$ is the self-induced force of the ion, given by Eq. (2.8), $\phi_{perm}(\boldsymbol{x})$ is the potential at $\boldsymbol{x}$ created by the permanent charge and the applied voltage, and $\phi_D(\boldsymbol{x},\boldsymbol{y})$ is the potential at $\boldsymbol{x}$ created by a positive ion located at $\boldsymbol{y}$, with no applied voltage. The potential $\phi_D(\boldsymbol{x},\boldsymbol{y})$ satisfies Poisson's equation (2.9).

We now insert decomposition (3.20) of $\boldsymbol{f}_j^p$, into Eq. (3.17). The first two terms in Eq. (3.20) depend only on the location of the jth positive ion and are thus constant with respect to the integration variables. Furthermore, each one of the remaining terms in the two sums is a function of only *one* of the integration variables. Thus, integration with respect to the other variables can be performed. This integration reduces the conditional PDF $p(\tilde{\boldsymbol{x}}_j^p\,|\,\boldsymbol{x}_j^p=\boldsymbol{x})$ to the *marginal* (integrated) conditional PDF $p(\boldsymbol{x}_i^c\,|\,\boldsymbol{x}_j^p=\boldsymbol{x})$ of the variable not integrated so far,

$$p(\boldsymbol{x}_i^c\,|\,\boldsymbol{x}_j^p=\boldsymbol{x})=\int p(\tilde{\boldsymbol{x}}_j^p\,|\,\boldsymbol{x}_j^p=\boldsymbol{x})\prod_{\boldsymbol{x}_k\neq\boldsymbol{x}_j^p,\,\boldsymbol{x}_i^c}d\boldsymbol{x}_k.$$

Performing these integrations in Eq. (3.17) yields

$$\begin{aligned}\overline{\boldsymbol{f}}^p(\boldsymbol{x})=&\boldsymbol{f}_D(\boldsymbol{x})-e\boldsymbol{\nabla}_{\boldsymbol{y}}\phi_{perm}(\boldsymbol{y})\big|_{\boldsymbol{y}=\boldsymbol{x}}\\&-e\boldsymbol{\nabla}_{\boldsymbol{y}}\left\{\sum_{i\neq j}\int_\Omega\phi_D(\boldsymbol{y},\boldsymbol{x}_i^p)p(\boldsymbol{x}_i^p\,|\,\boldsymbol{x}_j^p=\boldsymbol{x})d\boldsymbol{x}_i^p\right\}_{\boldsymbol{y}=\boldsymbol{x}}\\&+e\boldsymbol{\nabla}_{\boldsymbol{y}}\left\{\sum_k\int_\Omega\phi_D(\boldsymbol{y},\boldsymbol{x}_k^n)p(\boldsymbol{x}_k^n\,|\,\boldsymbol{x}_j^p=\boldsymbol{x})d\boldsymbol{x}_k^n\right\}\Bigg|_{\boldsymbol{y}=\boldsymbol{x}},\end{aligned} \tag{3.21}$$

where $\boldsymbol{\nabla}_{\boldsymbol{y}}$ denotes the gradient with respect to $\boldsymbol{y}$. In the steady state, all positive ions of the same species are indistinguishable and therefore *interchangeable*, so the conditional PDF's of the different positive ions, given the position of the jth positive ion, are all equal. The same property holds, of course, for the negative ions as well. Thus, we conclude that all terms in the first sum in Eq. (3.21) are equal to each other, and so are the terms in the second sum.

We denote by $c_p(\boldsymbol{y}\,|\,\boldsymbol{x})$ and $c_n(\boldsymbol{y}\,|\,\boldsymbol{x})$ the positive and negative conditional charge densities at $\boldsymbol{y}$, given that a positive ion is located at $\boldsymbol{x}$. Arguments similar to those in Sec. III A show that

$$\begin{aligned}c_p(\boldsymbol{y}\,|\,\boldsymbol{x})&=(N-1)p(\boldsymbol{x}_i^p=\boldsymbol{y}\,|\,\boldsymbol{x}_j^p=\boldsymbol{x}),\\c_n(\boldsymbol{y}\,|\,\boldsymbol{x})&=Np(\boldsymbol{x}_k^n=\boldsymbol{y}\,|\,\boldsymbol{x}_j^p=\boldsymbol{x}).\end{aligned} \tag{3.22}$$

In terms of these quantities, the total force can be written as

$$\overline{\boldsymbol{f}}^p(\boldsymbol{x})=\boldsymbol{f}_D(\boldsymbol{x})-e\boldsymbol{\nabla}_{\boldsymbol{x}}\phi_{perm}(\boldsymbol{x})-e\boldsymbol{\nabla}_{\boldsymbol{z}}\left\{\int_\Omega\phi_D(\boldsymbol{z},\boldsymbol{y})[c_p(\boldsymbol{y}\,|\,\boldsymbol{x})-c_n(\boldsymbol{y}\,|\,\boldsymbol{x})]d\boldsymbol{y}\right\}\Bigg|_{\boldsymbol{z}=\boldsymbol{x}}. \tag{3.23}$$

We define a potential $\overline{\phi}^p(\boldsymbol{z}\,|\,\boldsymbol{x})$ by

$$\overline{\phi}^p(\boldsymbol{z}\,|\,\boldsymbol{x})=\phi_{perm}(\boldsymbol{z})+\int_\Omega\phi_D(\boldsymbol{z},\boldsymbol{y})[c_p(\boldsymbol{y}\,|\,\boldsymbol{x})-c_n(\boldsymbol{y}\,|\,\boldsymbol{x})]d\boldsymbol{y}.$$

Since $\phi_D(\boldsymbol{y},\boldsymbol{x})$ satisfies Eq. (2.9), it follows that $\overline{\phi}^p(\boldsymbol{z}\,|\,\boldsymbol{x})$ satisfies the Poisson equation

$$\boldsymbol{\nabla}_{\boldsymbol{y}}\cdot[\varepsilon(\boldsymbol{y})\boldsymbol{\nabla}_{\boldsymbol{y}}\overline{\phi}^p(\boldsymbol{y}\,|\,\boldsymbol{x})]=-\frac{e}{\varepsilon_0}[\rho_{perm}(\boldsymbol{y})+c_p(\boldsymbol{y}\,|\,\boldsymbol{x})-c_n(\boldsymbol{y}\,|\,\boldsymbol{x})], \tag{3.24}$$

with the applied voltage conditions on the electrodes. Obviously, the average force $\overline{\boldsymbol{f}}^n(\boldsymbol{x})$ appearing in the NP equation for the negative charge densities can be written as the sum of the self-force and the gradient of an analogous electric potential $\overline{\phi}^n(\boldsymbol{y}\,|\,\boldsymbol{x})$.

To conclude, the averaging procedure described in Secs. III A–III D shows that the macroscopic charge densities $c_p(\boldsymbol{x})$ and $c_n(\boldsymbol{x})$ satisfy the following Nernst-Planck equations

$$0=\boldsymbol{\nabla}_x\cdot\left[\frac{1}{m^p\gamma^p(\boldsymbol{x})}c_p(\boldsymbol{x})[e\boldsymbol{\nabla}_y\overline{\phi}^p(\boldsymbol{y}\,|\,\boldsymbol{x})|_{y=x}-\boldsymbol{f}_D(\boldsymbol{x})]+\frac{k_BT}{m^p\gamma^p(\boldsymbol{x})}\boldsymbol{\nabla}_x c_p(\boldsymbol{x})\right],$$

$$0=\boldsymbol{\nabla}_x\cdot\left[\frac{1}{m^n\gamma^n(\boldsymbol{x})}c_n(\boldsymbol{x})[-e\boldsymbol{\nabla}_y\overline{\phi}^n(\boldsymbol{y}\,|\,\boldsymbol{x})|_{y=x}-\boldsymbol{f}_D(\boldsymbol{x})]+\frac{k_BT}{m^n\gamma^n(\boldsymbol{x})}\boldsymbol{\nabla}_x c_n(\boldsymbol{x})\right], \tag{3.25}$$

with averaged mean-field potentials that satisfy Poisson equations with *conditional* charge densities, and with the additional self-force term $\boldsymbol{f}_D(\boldsymbol{x})$. The charge densities in the Poisson equation are different from the unconditional charge densities in the NP equations. We denote the resulting system (3.24)–(3.25) as the CPNP system. This system differs from the standard PNP system, because (i) it contains *conditional* potentials satisfying Poisson equations with conditional charge densities, and (ii) it contains the self-induced force.

Note that there are different conditional Poisson equations for the positive and negative species. For a mixed solution, we would have a separate NP equation and a separate conditional Poisson equation for each ionic species.

Finally, we note that calculations with conditional charge densities play a central role in statistical mechanics of liquids [14,8]. Our paper shows that conditional densities arise inevitably in a stochastic analysis of averaged macroscopic charge densities.

F. Conditional and unconditional charge densities

To solve Eqs. (3.25) for the unconditional densities $c_p(\boldsymbol{x})$ and $c_n(\boldsymbol{x})$ it is necessary to solve Poisson's equation (3.24) for $\overline{\phi}^p$ and a similar equation for $\overline{\phi}^n$. However, these equations contain the conditional charge densities $c_p(\boldsymbol{y}\,|\,\boldsymbol{x})$ and $c_n(\boldsymbol{y}\,|\,\boldsymbol{x})$ so that the CPNP system (3.24)–(3.25) is not closed. These conditional charge densities at location $\boldsymbol{y}$, given a positive (or negative) ion at location $\boldsymbol{x}$, are in general *different* from the unconditional charge densities at the same location $c_p(\boldsymbol{y})$ and $c_n(\boldsymbol{y})$. Therefore, to close the CPNP system, it is necessary to either derive an additional set of equations for the conditional charge densities, or to determine *closure relations* between the conditional and unconditional charge densities.

At this point, we note that according to Eq. (3.22), the conditional charge densities are related to the well-studied pair-correlation functions [8], which are the conditional pdf, $p(\boldsymbol{y}\,|\,\boldsymbol{x})$, of a positive or negative ion at $\boldsymbol{y}$, given a positive or negative ion at $\boldsymbol{x}$. There are several theories for computing the pair-correlation functions under various assumptions [8]. The outcome of each of these theories is a different, and often rather complicated, *closure relation* between the conditional and the unconditional charge densities. Applying either one of these existing theories to the CPNP system yields a closed system of Poisson and Nernst-Planck equations that can be solved simultaneously, at least in principle. In this way, our paper can relate to the substantial literature of statistical mechanics of ionic solutions and to their recent applications to channels [22,23].

The pair-correlation functions, or equivalently, the conditional charge densities present in the Poisson equations, contain within them *excluded volume* effects. The simplest and most crude approximation, however, is to neglect these effects and replace the conditional charge densities in Eq. (3.24) by the unconditional charge densities. This approximation leads to the standard Poisson equation

$$\boldsymbol{\nabla}_x\cdot\varepsilon(\boldsymbol{x})\boldsymbol{\nabla}_x\overline{\phi}(\boldsymbol{x})=-\frac{e}{\varepsilon_0}[\rho_{perm}(\boldsymbol{x})+c_p(\boldsymbol{x})-c_n(\boldsymbol{x})]. \tag{3.26}$$

Equations (3.25)–(3.26), with $\overline{\phi}^c(\boldsymbol{y}\,|\,\boldsymbol{x})$ replaced by $\overline{\phi}(\boldsymbol{y})$, are the standard Poisson-Nernst-Planck model [3], but with an *additional* self-induced force term $\boldsymbol{f}_D(\boldsymbol{x})$.

More refined theories attempt to compensate for the error in the evaluation of the net force introduced in the above approximation. We consider this compensation in a typical bath-channel-membrane setup. First, we consider the net force on an ion located at $\boldsymbol{x}$ in the bulk solution far away (many Debye lengths [8]) from the membrane and channel. We assume that this region of the solution is approximately in equilibrium, and thus approximate the conditional charge densities $c(\boldsymbol{y}\,|\,\boldsymbol{x})$ by the simple Debye-Hückel theory [8].

This leads to an isotropic displacement of the ionic atmosphere, i.e., the charge cloud around the ion. According to the well-known sum rule, the total charge of the cloud equals the opposite charge of the fixed ion at $\boldsymbol{x}$ [14]. Since this displacement of the charge of the ionic atmosphere is isotropic, the direct Coulomb force on the ion, due to this cloud, is zero. The charge displacement of the ionic atmosphere, however, acts on the ion not only through the direct Coulomb force, but also through the surface charges induced at dielectric interfaces by the charge displacement. Since the spherically symmetric cloud centered at the ion has an equal but opposite charge as that of the ion, the spherically symmetric cloud induces equal and opposite surface charges at the far away dielectric interfaces. Therefore, the effect of the displacement cloud, or equivalently, of the *reaction field* computed from the conditional charge densities, is a *cancellation* of the self-induced force on the ion, due to the charge induced by the ion at dielectric boundaries. That is, the displacement cloud *screens* the self-induced force of the ion [see Fig. 2(a)].

The replacement of the conditional charge densities with unconditional densities in Poisson's equation (3.24) changes the distribution of positive and negative charges around the ion located at $\boldsymbol{x}$. While the conditional densities form a cloud around the ion, as described above, the unconditional densities do not. Thus, in a bath with an ion at $\boldsymbol{x}$ and unconditional densities around it, the surface charge induced by the ion at

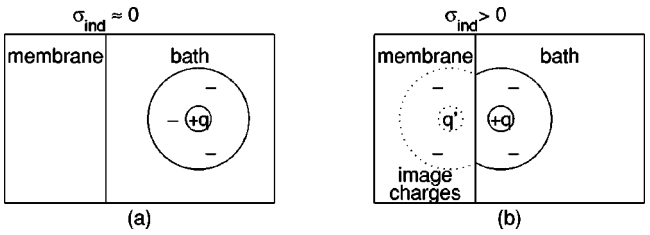

FIG. 2. (a) The displacement cloud around an ion located many Debye lengths from a membrane, and (b) around an ion located near a membrane.

dielectric boundaries is not compensated by a surface charge induced by a displacement cloud. This means that there is a *difference* in the net force acting on the ion between a bath with conditional densities, and a bath with unconditional densities. Specifically, in a bath with conditional densities, the self-induced force due to the induced surface charges is screened and decays exponentially fast with distance from dielectric boundaries. In contrast, in a bath with an ion at $\boldsymbol{x}$ and unconditional densities, the induced force is not screened and is therefore long range, decaying as the inverse square of the distance to the dielectric boundary.

Thus, for ions located far away from dielectric interfaces, the (long-range) self-induced force $\boldsymbol{f}_D(\boldsymbol{x})$ in Eq. (3.25) has to be *eliminated* to compensate for the replacement of the conditional charge densities with the unconditional ones. Related phenomena involving screening in ionic solutions, is seen in both modified Poisson Boltzmann theories and simulations [24,25].

As the ion approaches the dielectric interface, the isotropy of the displacement cloud is broken, so that the direct Coulombic force of the cloud on the ion no longer vanishes, and the induced surface charges of the screening cloud do not cancel the induced surface charges of the ion [see Fig. 2(b)]. These complexities also affect ions approaching the mouth of the pore, where the flux may not be considered negligible, so the ionic cloud may not be considered spherically symmetric [26].

The situation inside the channel is opposite to the situation in a bulk solution. Inside the channel there is usually only one mobile ion. Therefore, we expect that there will be almost no screening of the self-induced force on this ion by the conditional charge densities in the bath [27]. In replacing conditional charge densities by the unconditional ones, the self-force must be retained inside the channel.

To conclude, the replacement of conditional charge densities by unconditional ones has an effect on the net force acting on the ion. This effect can be compensated by replacing the self-induced force $\boldsymbol{f}_D(\boldsymbol{x})$ by an effective induced force $\boldsymbol{f}_D^{eff}(\boldsymbol{x})$, so that the net force in the NP equations for the positive and negative ions (of valence one) is given by

$$\overline{\boldsymbol{f}}^p(\boldsymbol{x}) = -e\nabla\overline{\phi}(\boldsymbol{x}) + \boldsymbol{f}_D^{eff,p}(\boldsymbol{x}),$$

$$\overline{\boldsymbol{f}}^n(\boldsymbol{x}) = +e\nabla\overline{\phi}(\boldsymbol{x}) + \boldsymbol{f}_D^{eff,n}(\boldsymbol{x}).$$

Note that if the positive and negative ions have the same diameter and valence, then the effective forces are equal.

Outside the channel, there is perfect screening of the self-induced force by the conditional densities, so their replacement with unconditional ones makes the effective induced force zero. Inside the channel there is almost no screening so the effective induced force approximately equals the self-induced force. In the intermediate region, between the membrane and the bulk solution (several Debye lengths away from the membrane), the situation is more complicated and has to be calculated from a more detailed theory.

IV. QUASI-IONS AND SIMULATION OF PERMEATION

A different approach to the study of the permeation process through the channel uses Langevin simulations instead of closure relations. In Sec. III C we have shown that the stationary probability density function $p(\boldsymbol{x},\boldsymbol{v})$, for the phase-space coordinates of a single positive ion is governed by an FPE type equation (3.15). This FPE corresponds to the Langevin equation

$$\ddot{\boldsymbol{x}} + \gamma^p(\boldsymbol{x})\dot{\boldsymbol{x}} = \frac{\overline{\boldsymbol{f}}^p(\boldsymbol{x})}{m^p} + \sqrt{\frac{2\gamma^p(\boldsymbol{x})k_BT}{m^p}}\dot{\boldsymbol{w}}, \qquad (4.1)$$

with the additional approximation (3.16)–(3.17) so that the force $\overline{\boldsymbol{f}}^p(\boldsymbol{x})$ depends only on $\boldsymbol{x}$. Note that this Langevin equation does not define the trajectories of a real positive ion, but rather defines trajectories of a *quasi-ion*, that is driven by the averaged force $\overline{\boldsymbol{f}}^p(\boldsymbol{x})$, and not by the real fluctuating force that drives a real ion. Yet, according to our analysis, the average flux computed from the trajectories of this quasiparticle, equals the averaged flux of real ions. Note also that the boundary behavior of the trajectories of this quasi-ion is the same as those of the real ions — reflection at hard walls and immediate recycling at the opposite electrode of ions reaching a given electrode. The idea of a quasi-ion (called a permion) has been mentioned before in the permeation literature [28].

The permeation properties of a channel can thus be studied by simulating trajectories of quasi-ions, according to Eq. (4.1), once the force $\overline{\boldsymbol{f}}^p(\boldsymbol{x})$ has been evaluated. One possible procedure for approximating the force $\overline{\boldsymbol{f}}^p$ is to *fix* the quasi-ion at various locations $\boldsymbol{x}$, and for every such location, compute the average force exerted on it, either by some theory or by a simulation in which the force is approximated by an ensemble average. In the latter method, for every system within the ensemble, the quasi-ion is kept fixed at its location, and the other ions are allowed to relax to a random realization of their stationary distribution. This procedure is only an approximation of the force, because keeping the quasi-ion fixed is not strictly consistent with the flux of the quasi-ion. However, the mean velocity of the quasi-ion associated with this flux is small compared to its thermal velocity, so this procedure is a reasonable first step [18]. Once the force is known, a simulation of Eq. (4.1) can be carried out.

Now consider the case of a channel that can contain more than one ion at a time. In this case, it might be necessary to simultaneously simulate two or more ionic trajectories at a time. In analogy to the case of a single simulated quasi-ion,

a simulation of the motion of two ions leads to forces of the form $\overline{\boldsymbol{f}}(\boldsymbol{x}_1,\boldsymbol{x}_2)$ which depend on the locations of the two simulated quasi-ions, and on the conditional charge densities, but conditioned now on the locations of *both* ions. In order to proceed in this direction, a theory must be derived or a simulation carried out to compute these forces.

There are, however, quite a few issues to be resolved before a practical simulation of a quasi-ion can be carried out. The first issue involves approximating the full phase-space coordinates $(\boldsymbol{x},\boldsymbol{v})$ with only the spatial coordinate $\boldsymbol{x}$. This approximation enables a simpler and faster simulation of the quasi-ion but is problematic because in simulating only the location of the ion and not its velocity, there is no way to distinguish between incoming and outgoing trajectories at the electrodes [18]. Thus, the recycling mechanism of ions at the electrodes has to be revised in this limit. Another issue is the size of the domain. In our formalism, the domain Ω in which the solution was confined is assumed large enough so that density fluctuations are neglected and the instantaneous recycling mechanism at the electrodes is assumed. However, running a simulation in such a large domain may prove to be too slow. Thus, ideally one would like to simulate a quasi-ion in a much smaller domain surrounding the protein channel. However, in this domain, the density fluctuations in the original formulation of the problem may not necessarily be negligible, and thus automatic reinjection of quasi-ions at the electrodes needs to be reconsidered. These issues require further investigation not covered in this paper.

V. DISCUSSION

In this paper, an averaging procedure of a Langevin model for the coupled motion of many interacting ions in an electrolyte solution is described, that results in an approximate description of the solution with averaged charge densities and mean electric fields. The result of the averaging procedure is a CPNP system (3.24)–(3.25) containing a set of conditional Nernst-Planck and conditional Poisson equations. The average charge density of each ionic species in the solution is described by a separate Nernst-Planck equation coupled to a separate Poisson equation for its conditional electrostatic potential. The force in each NP equation is the sum of two terms; one is the self-induced force on an ion of that species, and the other is the gradient of the corresponding conditional electrostatic potential. This potential is described by a Poisson equation that (1) depends on the *conditional* charge densities of all the ionic species, conditioned on the location of an ion of that species, (2) depends on the permanent charge, and (3) depends on the applied voltage boundary conditions. In a bi-ionic solution, the CPNP system consists of a total of four equations: two NP equations for the charge densities of the positive and negative ions, and two Poisson equations for the conditional potentials, each corresponding to one of the NP equations.

In equilibrium, the conditional charge densities appearing in the Poisson equations are closely related to the pair-correlation functions in the theory of fluids [8]. The conditional densities are *different* from the (unconditional) densities in the NP equations, and their difference is a measure of interionic repulsion and attraction forces, and in particular excluded volume effects. This difference renders the resulting CPNP system incomplete. As in the theory of fluids, a *closure relation* between the conditional and unconditional charge densities and between the conditional and unconditional potentials is needed to complete the system. With a closure relation, all the equations in the CPNP system are coupled to each other. One of the simplest closure relations is the mean spherical approximation (MSA) closure which expresses the excluded volume of ions of finite size. MSA-type closure relations are quite successful in describing properties of free solutions (with no dielectric interfaces and no narrow channels) [8]. These closure relations have recently been applied to ionic permeation in protein channels [22,23,29].

In this paper, we examine a specific closure relation, that replaces the conditional charge densities in the Poisson equations by the unconditional ones, and also replaces the self-induced force in the NP equations by an effective induced force $\boldsymbol{f}_D^{eff}$. The exact form of the effective induced force in the access region needs to be resolved by a higher resolution theory; but far away from channel and membrane, the effective induced force is approximately zero, as we have discussed, and near dielectric interfaces—in particular inside the channel—there is hardly any screening so the effective induced force approximately equals the self-induced force. We note that the proposed closure relation is not based on the Boltzmann distribution, and therefore may be also applied in nonequilibrium systems.

The replacement of conditional densities by unconditional ones leads to the PNP system, with the additional effective induced force term $\boldsymbol{f}_D^{eff}$. This replacement represents the finite-sized ions as point charges. Thus, excluded volume effects are *lost* in this description, and all the related phenomena of channels, such as single filing and flux saturation, cannot be recovered by the PNP system.

A different approach to include the finite sizes of the ions into an averaged PNP description introduces Lennard-Jones force terms between the individual ions in the Langevin system (2.1). Then, in the averaging procedure, an additional averaged conditional Lennard-Jones force term appears in the resulting Nernst-Planck equations of the CPNP system. The specific closure relation that replaces conditional densities by unconditional ones, must also evaluate this averaged Lennard-Jones force, thus leading to a PNP description with excluded volume effects. Note, however, that when short-range Lennard-Jones forces are present, in particular inside a multiply occupied channel, the assumption of independent noise terms in the Langevin equations of different ions should be re-examined. Last but not least, other closure relations, not necessarily leading to a PNP description of the system, are also possible, and should be examined.

In the derivation presented in this paper, the CPNP system (3.24)–(3.25) can be considered as the result of ensemble averaging over many independent realizations of the stochastic system (2.1)–(2.2). Obviously, for a rigid channel, in which the permanent charge does not move at all, the permanent charge density $\rho_{perm}(\boldsymbol{x})$, the dielectric constant $\varepsilon(\boldsymbol{x})$, and the boundary conditions remain unchanged in the averaging process. If, however, the permanent charge fluctuates

around a fixed position, then the dynamics of the permanent charge need to be described and coupled to the full Langevin system (2.1). The averaging procedure will result in a *conditional* permanent charge distribution appearing in the conditional Poisson equations.

In this way, the geometric and electrostatic properties of a channel carry over to the averaged system. However, the fluctuating state of the system with the (random) locations and velocities $\tilde{\boldsymbol{x}}(t)$ and $\tilde{\boldsymbol{v}}(t)$ of all the ions is replaced in the averaged system by the nonfluctuating averaged charge densities $c_p(\boldsymbol{x})$ and $c_n(\boldsymbol{x})$. Thus, potential fluctuations are lost in the PNP system. In steady state, these charge densities can be viewed as averages over many snapshots (samples) of a single system, taken at different times, sufficiently far apart for all correlations to vanish. In this view, the charge densities appearing in the NP equations are time averages of discrete ionic concentrations, over times much larger than the relaxation time of the system. This view defines a continuum description of the discrete contents of an ionic channel. This continuum description results from averaging over times much longer than the passage time of a single ion through a channel, so that all unidirectional fluxes meld into a single averaged net flux and lose their individual identity.

Finally, note that ion specific excess chemical potentials included in the Langevin model are *preserved* by the averaging process, and appear in the effective NP equations. Such excess chemical potentials might arise from a more detailed atomic model, describing ''chemical'' interactions of an ion (in the bulk phase) with its hydration shell, and of an ion (in the channel) with its solvation shell (of atoms of the protein as well as channel water).

Note added in proof. Rosalind Allen, Jean-Pierre Hansen, and Simone Melchionna have recently treated a similar problem by variational methods in a paper submitted to Physical Chemistry Chemical Physics.

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APPENDIX A: THE SELF-INDUCED FORCE FROM DIELECTRIC BOUNDARIES

Consider the three-dimensional space $\boldsymbol{R}^3$ decomposed into an arbitrary number of dielectric regions of arbitrary shapes Ω_i. We assume that in each region Ω_i, the dielectric coefficient is constant, with respective value ε_i, and jumps abruptly only at the boundaries $\partial\Omega_i$ separating regions of different dielectric coefficients. Consider a point charge of strength q located at $\boldsymbol{r}_0 \in \Omega_1$, a region with dielectric coefficient ε_1. In this section we consider only the self-induced force on this point charge, due to the presence of dielectric boundaries, so we assume no other fixed or mobile charges are present in the system. As explained in the text, the interaction forces of this point charge with the other charges (and their induced surface charges) is treated separately [see Eq. (2.5)]. The presence of the charge at $\boldsymbol{r}_0$ induces surface charges at all the boundaries $\partial\Omega_i$, separating regions of different dielectric media. These surface charges, in turn, exert a force on this charge, which we denote by $\boldsymbol{F}_{ind}(\boldsymbol{r}_0)$. The following lemma states the connection between this force and the electric potential, $\Phi(\boldsymbol{r})$, in the entire space.

Lemma. Let $\Phi(\boldsymbol{r})$ denote the electric potential at $\boldsymbol{r}$, created by a point charge at $\boldsymbol{r}_0$, and let $\boldsymbol{F}_{ind}(\boldsymbol{r}_0)$ denote the resulting net force on that point charge, the dielectric boundary force. Then

$$\boldsymbol{F}_{ind}(\boldsymbol{r}_0) = -q\,\nabla_{\boldsymbol{r}}\left(\Phi(\boldsymbol{r}) - \frac{q}{4\pi\varepsilon_0\varepsilon_1|\boldsymbol{r}-\boldsymbol{r}_0|}\right)\Bigg|_{\boldsymbol{r}=\boldsymbol{r}_0}.$$

In other words, the dielectric boundary force acting on the charge can be computed by subtracting from the total electric potential the singular Coulombic term produced by the charge, and then computing the gradient at the charge's location.

Proof. The potential $\Phi(\boldsymbol{r})$ satisfies Poisson's equation

$$\nabla\cdot\varepsilon(\boldsymbol{r})\nabla\Phi(\boldsymbol{r}) = -\frac{q}{\varepsilon_0}\delta(\boldsymbol{r}-\boldsymbol{r}_0), \tag{A1}$$

with the standard jump conditions of the normal field at dielectric interfaces

$$[\varepsilon(\boldsymbol{r})\nabla\Phi(\boldsymbol{r})\cdot\boldsymbol{n}]|_{\partial\Omega_i} = 0, \tag{A2}$$

where $\boldsymbol{n}$ is a unit vector in the outer normal direction to a surface element on $\partial\Omega_i$, and the square brackets denote the difference in the variable enclosed within them, between the value outside the region Ω_i and inside it. Note that $\Phi(\boldsymbol{r})$ also vanishes as $|\boldsymbol{r}|\to\infty$.

The presence of the point charge at $\boldsymbol{r}_0$ induces surface charges, σ_{ind}, at the dielectric boundaries $\partial\Omega_i$, given by

$$\sigma_{ind}|_{\partial\Omega_i} = [\nabla\Phi\cdot\boldsymbol{n}]|_{\partial\Omega_i}. \tag{A3}$$

These induced surface charges create a force on the point charge. To compute this dielectric boundary force, it is necessary to compute the electric potential formed by the surface charges, denoted by $\Phi_{ind}(\boldsymbol{r})$. Then, the force on the ion is simply the gradient of this potential, computed at the ion's location,

$$\boldsymbol{F}_{ind}(\boldsymbol{r}_0) = -q\nabla\Phi_{ind}(\boldsymbol{r})|_{\boldsymbol{r}=\boldsymbol{r}_0}. \tag{A4}$$

We now consider the equation that the potential $\Phi_{ind}(\boldsymbol{r})$ satisfies. Since the polarization of the different regions Ω_i has already been taken into account in the computation of the induced surface charges via Eqs. (A1)–(A3), the potential $\Phi_{ind}(\boldsymbol{r})$ satisfies Laplace's equation *without* a dielectric coefficient, i.e., with $\varepsilon(\boldsymbol{r})=1$ throughout whole space

$$\Delta\Phi_{ind}(\boldsymbol{r}) = 0. \tag{A5}$$

In addition, as with $\Phi(\boldsymbol{r})$, the potential $\Phi_{ind}(\boldsymbol{r})$ also vanishes as $|\boldsymbol{r}|\to\infty$. No point charge is present at $\boldsymbol{r}_0$ in Eq. (A5), since

the potential Φ_{ind} is produced only by the surface charges induced on the dielectric interfaces.

While there are no dielectric boundaries for the potential $\Phi_{ind}(\boldsymbol{r})$ [$\varepsilon(\boldsymbol{r})=1$ everywhere], there are surface charges, given by (A3), located at these boundaries. This amounts to the following jump conditions,

$$[\nabla\Phi_{ind}\cdot\boldsymbol{n}]|_{\partial\Omega_i}=\sigma_{ind}|_{\partial\Omega_i}. \tag{A6}$$

The key point in the proof of the lemma is the observation that the potential $\Phi(\boldsymbol{r})$ created by the point charge at $\boldsymbol{r}_0$, that satisfies Eqs. (A1)–(A2), *equivalently* satisfies Poisson's equation with a constant dielectric coefficient, $\varepsilon(\boldsymbol{r})=\varepsilon_1$, throughout space,

$$\Delta\Phi(\boldsymbol{r})=-\frac{q}{\varepsilon_1\varepsilon_0}\delta(\boldsymbol{r}-\boldsymbol{r}_0), \tag{A7}$$

but with jump conditions across (now nonexistent) dielectric boundaries that depend on the induced surface charges found there,

$$[\nabla\Phi\cdot\boldsymbol{n}]|_{\partial\Omega_i}=\sigma_{ind}|_{\partial\Omega_i}. \tag{A8}$$

This equivalent representation of $\Phi(\boldsymbol{r})$ follows from the textbook pillbox treatment of Gauss' law at dielectric boundaries [19]. Note also that these jump conditions are exactly the same as those that Φ_{ind} satisfies.

To prove the lemma, we subtract the two potentials Φ_{ind} and Φ. Both potentials satisfy the same jump conditions, Eqs. (A6) and (A8). Then, according to Eqs. (A5) and (A7), their difference satisfies the following Poisson equation throughout space

$$\Delta[\Phi_{ind}(\boldsymbol{r})-\Phi(\boldsymbol{r})]=+\frac{q}{\varepsilon_0\varepsilon_1}\delta(\boldsymbol{r}-\boldsymbol{r}_0)$$

without any jump conditions at the boundaries $\partial\Omega_i$. The solution to this equation, with a plus sign in the right-hand side, is of course the free space potential created by a point charge of strength $-q/\varepsilon_1$ at $\boldsymbol{r}_0$,

$$\Phi_{ind}(\boldsymbol{r})-\Phi(\boldsymbol{r})=-\frac{1}{4\pi\varepsilon_0\varepsilon_1}\frac{q}{|\boldsymbol{r}-\boldsymbol{r}_0|}. \tag{A9}$$

Combining Eq. (A9) with Eq. (A4) concludes the proof of the lemma.

Note that the potential $\Phi(\boldsymbol{r})$ is proportional to the charge q at $\boldsymbol{r}_0$. Thus according to Eq. (A3) and Eqs. (A5)–(A6) both the induced surface charges and the potential Φ_{ind} are also proportional to q. This renders the self-induced dielectric boundary force, given by Eq. (A4), proportional to q^2. Thus, the force vector has the *same* direction and magnitude regardless of the sign of the charge at $\boldsymbol{r}_0$.

Note also that for the same problem in a finite domain Ω, with homogeneous boundary conditions on $\partial\Omega$ (grounded metal electrodes at the boundary), the lemma does not hold. This is because the solution of Eq. (A9) in a finite domain with zero boundary conditions, is not exactly the Coulomb term, but rather contains boundary effects as well. However, in terms of the force on the ion, these effects decay as the square distance from the outer boundary [30], so for many practical purposes, for an ion located far away from the outer boundaries of the domain, the lemma is still valid.

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