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A PDE FORMULATION OF NON-EQUILIBRIUM STATISTICAL MECHANICS FOR IONIC PERMEATION

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Abstract. When there is a steady net flux in a system of interacting particles, the microscopic structure of the system can no longer be determined from the Boltzmann equilibrium distribution (partition function). Nonetheless, the pair correlation function can be calculated for a non-equilibrium system of diffusing particles with pair wise interactions by solving partial differential equations. These are Poisson-Nernst-Planck-type equations that involve the pair correlation function, as described below. Equilibrium results are recovered when no-flux boundary conditions are imposed on the solutions. When non-homogeneous boundary conditions are given for these equations, the solutions describe densities and electrostatic potentials of particle systems not in equilibrium. The construction of a pair function under these conditions will be a new result in statistical physics. A relation between a higher and a lower order correlation function has to be assumed, as in equilibrium statistical mechanics. In applications to channel permeation the iterative scheme used to construct the pair correlation function will lead to a prediction of current through an open channel, given the spatial structure and fixed charge distribution. The pair correlation function contains finite size effects that lead to blocking in a narrow channel and possibly to selectivity.

1 Definitions

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. Specifically, we consider a solution containing N_h ions of type h ($h = \mathrm{Na}^+, \mathrm{Cl}^-, \mathrm{Ca}^{++}, \ldots$), $\sum_h N_h = N$. 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 j-th positive ion at time t by $\boldsymbol{x}_j^h(t)$ and $\dot{\boldsymbol{x}}_j^h(t)$, respectively, the coordinate vector

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of all ions in configuration space is denoted $\tilde{\boldsymbol{x}} = \left(\boldsymbol{x}_1^{Na^+}, \dots, \boldsymbol{x}_{N_{\cdots}^{\cdots}}\right)$, 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 j-th ion of type h is denoted $\tilde{\boldsymbol{x}}_j^h$. Our point of departure is the following memoryless system of Langevin equations. For $h = \mathrm{Na}^+, \mathrm{Cl}^-, \mathrm{Ca}^{++}, \dots$

$$\ddot{\boldsymbol{x}}_j^h + \gamma^h\left(\boldsymbol{x}_j^h\right)\dot{\boldsymbol{x}}_j^h \;=\; \frac{\boldsymbol{f}_j^h(\tilde{\boldsymbol{x}})}{m^h} + \sqrt{\frac{2\gamma^h(\boldsymbol{x}_j^h)k_BT}{m^h}}\,\dot{\boldsymbol{w}}_j^h, \quad (j = 1, 2, \dots, N_h), \tag{1.1}$$

where a dot on a variable denotes differentiation with respect to time, $\boldsymbol{f}_j^h(\tilde{\boldsymbol{x}})$ denotes the electrostatic force acting on the j-th ion of type h, $\gamma^h(\boldsymbol{x})$ is the location dependent friction coefficient per unit mass of the ionic species of type h, and $\dot{\boldsymbol{w}}_j^h$ are, by assumption, independent standard Gaussian white noises. The parameter k_B is Boltzmann's constant, T is absolute temperature, and m^h is an effective mass of an ion of type h. The electrostatic forces consist of inter-ionic attractions and repulsions, the imposed external field, and a self force near dielectric interfaces. When Lennard-Jones repulsions are included and no flux boundary conditions are imposed, the equilibrium theory of [?]-[?] applies. It does not apply when a steady flux is flowing through the system.

2 Densities

We denote by $c^h(\boldsymbol{x})$ the time-averaged steady state concentration of ions of species h at location $\boldsymbol{x}$. In the scaling

$$c^h(\boldsymbol{x}) = \rho^h p^h(\boldsymbol{x}), \tag{2.1}$$

the factor ρ^h is the average density of ions of type h in the bath,

$$\rho^h = \frac{1}{|\Omega|}\int_\Omega c^h(\boldsymbol{x})\,d\boldsymbol{x}, \tag{2.2}$$

where $|\Omega|$ is the volume of Ω. Thus the function $p^h(\boldsymbol{x})$ is the probability density function of finding an ion of type h at the point $\boldsymbol{x}$ in the bath.

The joint pdf of ions of types h, h' at points $\boldsymbol{x}, \boldsymbol{y}$ is denoted $p^{h,h'}(\boldsymbol{x}, \boldsymbol{y})$. The conditional pdf of ions of type h' at $\boldsymbol{y}$, given an ion of type h at $\boldsymbol{x}$ is denoted $p^{h'|h}(\boldsymbol{y}\,|\,x)$. It is related to the joint densities by

$$p^{h'|h}(\boldsymbol{y}\,|\,x) = \frac{p^{h,h'}(\boldsymbol{x}, \boldsymbol{y})}{p^h(\boldsymbol{x})}. \tag{2.3}$$

Similarly, $p^{h,h',h''}(\boldsymbol{x}, \boldsymbol{y}, \boldsymbol{z})$ denotes the joint density of ions of types h, h', h'' located at $\boldsymbol{x}, \boldsymbol{y}, \boldsymbol{z}$, respectively, $p^{h''|h',h}(\boldsymbol{z}\,|\,\boldsymbol{y}, \boldsymbol{x})$ denotes the conditional density of ions of type h'' at $\boldsymbol{z}$, given ions of types h' and h located at $\boldsymbol{y}$ and $\boldsymbol{x}$, respectively, and so on. We have

$$p^{h''|h',h}(\boldsymbol{z}\,|\,\boldsymbol{y}, \boldsymbol{x}) = \frac{p^{h,h',h''}(\boldsymbol{x}, \boldsymbol{y}, \boldsymbol{z})}{p^{h,h'}(\boldsymbol{x}, \boldsymbol{y})}. \tag{2.4}$$

3 Nernst-Planck equations for one and two ion densities

We denote by $p_j^h(\boldsymbol{x})$, $j = 1, \ldots, N^h$, the stationary probability density function (pdf) of the location of the j-th ion of species h. By definition, the pdf of a single particle is simply the marginal density of all particles integrated over all particle locations except the j-th ion of species h,

$$p_j^h(\boldsymbol{x}_j^h) = \int_{\tilde{\Omega}_j^h} p_N(\tilde{\boldsymbol{x}}) d\tilde{\boldsymbol{x}}_j^h. \tag{3.1}$$

Since all ions of a given species are indistinguishable, $p_j^h(\boldsymbol{x}) = p^h(\boldsymbol{x})$, for all j. The quantities $c^h(\boldsymbol{x})$ and $p^h(\boldsymbol{x})$ are related by

$$c^h(\boldsymbol{x}) = N^h p^h(\boldsymbol{x}). \tag{3.2}$$

The concentration $c^h(\boldsymbol{x})$ is the physical density of ions and it integrates to the total number of ions of species h in the solution. An equation for $p^h(\boldsymbol{x})$ readily turns into an equation for $c^h(\boldsymbol{x})$ by the relation (**??**).

Starting from the Langevin model (**??**), the following equation for the single particle probability density was derived in [**?**]-[**?**],

$$0 = \nabla_{\boldsymbol{x}} \cdot \boldsymbol{J}^h(\boldsymbol{x}) = -\nabla_{\boldsymbol{x}} \cdot \left(\frac{\bar{\boldsymbol{f}}^h(\boldsymbol{x})}{M^h \gamma^h(\boldsymbol{x})} p^h(\boldsymbol{x}) - \frac{k_B T}{M^h \gamma^h(\boldsymbol{x})} \nabla_{\boldsymbol{x}} p^h(\boldsymbol{x}) \right). \tag{3.3}$$

where $\boldsymbol{J}^h(\boldsymbol{x})$ is the probability flux density of a single ion of type h, given by

$$\boldsymbol{J}^h(\boldsymbol{x}_j^h) = \int_{\tilde{\Omega}_j^h} \boldsymbol{J}_{\boldsymbol{x}_j^h}(\tilde{\boldsymbol{x}}) d\tilde{\boldsymbol{x}}_j^h \tag{3.4}$$

and

$$\bar{\boldsymbol{f}}^h(\boldsymbol{x}) = \int_{\tilde{\Omega}_j^h} \boldsymbol{f}_j^h(\tilde{\boldsymbol{x}}) p_{N-1}(\tilde{\boldsymbol{x}}_j^h \,|\, \boldsymbol{x}_j^h = \boldsymbol{x}) \, d\tilde{\boldsymbol{x}}_j^h. \tag{3.5}$$

is the average force on an ion of type h.

Equation (**??**) is a Fokker-Planck type equation for the probability density of a single ion of species h. It is defined in the finite domain Ω, and contains an average force $\bar{\boldsymbol{f}}^h(\boldsymbol{x})$ whose calculation, according to eq.(**??**), depends on the conditional probability density of all ions, given the phase space coordinates of the j-th ion of species h. However, this conditional density depends on the solution of the full Fokker-Planck equation for all N particles. 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, equation (**??**) is not very useful as long as its force term is not known.

However, even if the force term is known, boundary conditions on $\partial\Omega$ must be specified in order to determine the unique solution for $p^h(\boldsymbol{x})$. Obviously, on $\partial\Omega_R$, $p^h(\boldsymbol{x})$ satisfies no flux boundary conditions,

$$\boldsymbol{J}^h(\boldsymbol{x}) \cdot \boldsymbol{\nu}\Big|_{\boldsymbol{x}\,\in\,\partial\Omega_R} = 0. \tag{3.6}$$

In addition, on $\partial\Omega_F$, according to our assumptions, the concentrations $c^h(\boldsymbol{x})$ are maintained at fixed known values by the feedback mechanism. Therefore, regardless of the exact method by which the feedback mechanism maintains these concentrations,

$$p^h(\boldsymbol{x})\Big|_{\boldsymbol{x}\,\in\,\partial\Omega_F} = \frac{c^h(\boldsymbol{x})}{N^h}. \tag{3.7}$$

3.1 The average force

In the case of charged ions in solution, the ion-ion interaction forces are pair-wise additive, and thus the force on the j-th ion of species h can be written as

$$\boldsymbol{f}_j^h(\tilde{\boldsymbol{x}}) = \boldsymbol{f}_{ed}^h(\boldsymbol{x}_j^h) + \sum_{(i,h')\neq(j,h)} \boldsymbol{f}^{h,h'}(\boldsymbol{x}_i^{h'}, \boldsymbol{x}_j^h), \tag{3.8}$$

where $\boldsymbol{f}^{h,h'}$ is the ion-ion interaction force that an ion of type h' acts on an ion of type h. It includes both Coulombic interactions as well as short range interactions, such as excluded volume or Lennard-Jones potentials. Note that this force is not necessarily radial, due to boundary conditions on $\partial\Omega$ for the corresponding Poisson equation. The force $\boldsymbol{f}_{ed}^h$ contains both the effects of an applied external field as well as the dielectric self-force near dielectric boundaries [?], [?].

As shown in [?], with the specific form (??) for the force on a single ion, equation (??) for the average force $\bar{\boldsymbol{f}}^h$ simplifies to

$$\begin{aligned}\bar{\boldsymbol{f}}^h(\boldsymbol{x}) \;=\;& \boldsymbol{f}_{ed}^h(\boldsymbol{x}) + \\ & (N^h-1)\int_\Omega \boldsymbol{f}^{h,h}(\boldsymbol{y},\boldsymbol{x})p^{h|h}(\boldsymbol{y}|\boldsymbol{x})d\boldsymbol{y} + \sum_{h'} N^{h'}\int_\Omega \boldsymbol{f}^{h,h'}(\boldsymbol{y},\boldsymbol{x})p^{h'|h}(\boldsymbol{y}|\boldsymbol{x})d\boldsymbol{y},\end{aligned} \tag{3.9}$$

where $p^{h'|h}(\boldsymbol{y}|\boldsymbol{x})$ is the conditional probability density of a type h' ion at location $\boldsymbol{y}$, given that an ion of species h is located at $\boldsymbol{x}$,

$$p^{h'|h}(\boldsymbol{y}|\boldsymbol{x}) = \frac{p^{h,h'}(\boldsymbol{x},\boldsymbol{y})}{p^h(\boldsymbol{x})}. \tag{3.10}$$

According to equations (??),(??) and (??), the solution for the single particle density $p^h(\boldsymbol{x})$ depends on the pair probability density functions $p^{h,h'}(\boldsymbol{x},\boldsymbol{y})$.

Thus, we now write an equation for the pair densities. Employing similar methods to those of [?], we obtain that $p^{h,h'}(\boldsymbol{x},\boldsymbol{y})$ satisfies the following equation

$$\nabla_{\boldsymbol{x}^h} \boldsymbol{J}^{h,h'}_{\boldsymbol{x}^h}\Big(\boldsymbol{x},\boldsymbol{y}\Big) + \nabla_{\boldsymbol{y}^{h'}} \boldsymbol{J}^{h,h'}_{\boldsymbol{y}^{h'}}\Big(\boldsymbol{x},\boldsymbol{y}\Big) = 0 \tag{3.11}$$

where $\boldsymbol{J}^{h,h'}_{\boldsymbol{x}^h}(\boldsymbol{x},\boldsymbol{y})$ is given by

$$\boldsymbol{J}^{h,h'}_{\boldsymbol{x}^h}(\boldsymbol{x},\boldsymbol{y}) = -\nabla_{\boldsymbol{x}} \cdot \left(\frac{\bar{\boldsymbol{f}}^{h,h'}(\boldsymbol{x},\boldsymbol{y})}{M^h\gamma^h(\boldsymbol{x})} p^{h,h'}(\boldsymbol{x},\boldsymbol{y}) - \frac{k_B T}{M^h\gamma^h(\boldsymbol{x})} \nabla_{\boldsymbol{x}} p^{h,h'}(\boldsymbol{x},\boldsymbol{y}) \right), \tag{3.12}$$

and $\boldsymbol{J}^{h,h'}_{\boldsymbol{y}^{h'}}$ is given by a similar expression.

The force $\bar{\boldsymbol{f}}^{h,h'}(\boldsymbol{x},\boldsymbol{y})$ appearing in (??) is the average force on an ion of species h, given an ion of species h' located at $\boldsymbol{y}$. In general it is given by

$$\bar{\boldsymbol{f}}^{h,h'}(\boldsymbol{x},\boldsymbol{y}) = \int_{\tilde{\Omega}^{h,h'}_{i,j}} \boldsymbol{f}_{\boldsymbol{x}^h_i}(\tilde{\boldsymbol{x}}) p_{N-2}\left(\boldsymbol{x}^{h,h'}_{i,j} | \boldsymbol{x}^h_i = \boldsymbol{x},\, \boldsymbol{x}^{h'}_j = \boldsymbol{y}\right) d\tilde{\boldsymbol{x}}^{h,h'}_{i,j} \tag{3.13}$$

while for the case of pair-wise additive forces, it can be simplified to

$$\begin{aligned} \bar{\boldsymbol{f}}^{h,h'}(\boldsymbol{x},\boldsymbol{y}) \;\; = \;\; & \boldsymbol{f}^h_{ed}(\boldsymbol{x}) + \boldsymbol{f}^{h,h'}(\boldsymbol{x},\boldsymbol{y}) + (N^h - 1)\int_\Omega \boldsymbol{f}^{h,h}(\boldsymbol{x},\boldsymbol{z}) p^{h|h,h'}(\boldsymbol{z}|\boldsymbol{x},\boldsymbol{y})\, d\boldsymbol{z} \\ & + (N^{h'} - 1)\int_\Omega \boldsymbol{f}^{h,h'}(\boldsymbol{x},\boldsymbol{z}) p^{h'|h,h'}(\boldsymbol{z}|\boldsymbol{x},\boldsymbol{y}) d\boldsymbol{z} \\ & + \sum_{h''\neq h,h'} N^{h''} \int_\Omega \boldsymbol{f}^{h,h'}(\boldsymbol{x},\boldsymbol{z}) p^{h''|h,h'}(\boldsymbol{z}|\boldsymbol{x},\boldsymbol{y}) d\boldsymbol{z} \end{aligned} \tag{3.14}$$

for $h \neq h'$ and a similar expression for $h = h'$. In these equations $p^{h''|h,h'}(\boldsymbol{z}|\boldsymbol{x},\boldsymbol{y})$ is the conditional density of a type h'' ion located at $\boldsymbol{z}$, given the presence of a type h ion at $\boldsymbol{x}$ and a type h' ion at $\boldsymbol{y}$,

$$p^{h''|h,h'}(\boldsymbol{z}|\boldsymbol{x},\boldsymbol{y}) = \frac{p^{h,h',h''}(\boldsymbol{x},\boldsymbol{y},\boldsymbol{z})}{p^{h,h'}(\boldsymbol{x},\boldsymbol{y})} \tag{3.15}$$

As seen from (??), the determination of the forces $\bar{\boldsymbol{f}}^{h,h'}(\boldsymbol{x},\boldsymbol{y})$ appearing in eq. (??), requires the determination of the triplet densities $p^{h,h',h''}(\boldsymbol{x},\boldsymbol{y},\boldsymbol{z})$. In the case of either equilibrium or non-equilibrium infinite systems, closure relations relating the triplet densities to the pair densities are employed in order to close the system [?], [?].

However, since in our case we are concerned with a finite system, a closure relation between the triplet and the pair densities is not enough to close the system. Specifically, the Smoluchowski type equation (??) is defined in the finite domain $(\boldsymbol{x},\boldsymbol{y}) \in \Omega \times \Omega$. Therefore, to uniquely determine its solution, boundary conditions have to be prescribed on the domain boundaries, e.g. for $(\boldsymbol{x},\boldsymbol{y}) \in \partial\Omega \times \Omega$ and

$(\boldsymbol{x},\boldsymbol{y}) \in \Omega \times \partial\Omega$. Only after these boundary conditions are specified, the pair correlation function $p^{h,h'}(\boldsymbol{x},\boldsymbol{y})$ is completely determined, provided the forces $\bar{\boldsymbol{f}}^{h,h'}(\boldsymbol{x},\boldsymbol{y})$ are known.

As in the case of the single ion densities, the boundary conditions for the pair densities should also be determined by the action of the feedback mechanism. For the case of the single ion densities we assumed that the action of the feedback mechanism is to keep an average fixed concentration on the domain boundaries. This leads to the natural concentration boundary conditions (**??**).

4 Boundary Conditions and the feedback mechanism

To understand the need for boundary conditions, we consider the full Fokker-Planck equation for the joint pdf of all particles, p_N. Since all trajectories are confined to the finite domain Ω, this equation is defined in $\tilde{\Omega}$. By definition, a complete physical description of the system is one that yields a unique solution for p_N. However, in defining the problem the exact injection method of new particle trajectories by the feedback mechanism is not specified in detail. Rather, it is only stated that the action of the feedback mechanism is instantaneous, leading to conservation of the number of particles, and that the feedback mechanism keeps fixed average concentrations at the boundaries. This is obviously not a complete physical description as it does not describe the exact method employed by the feedback mechanism in injecting new particle trajectories (for example, their location, etc.).

For the derivation of boundary conditions for the joint pair density function, we first consider two exactly solvable cases. The first one is that of equilibrium, which is characterized by vanishing flux. The other is that of a system of independent (non-interacting) ions diffusing in an external potential $V(\boldsymbol{x})$ between two fixed concentrations. The equilibrium case, as far as boundary conditions are concerned, is trivial and un-instructive. However, it can be used as a benchmark, because non-equilibrium results have to reduce to equilibrium results in the limit of vanishing flux. Specifically, we assume now that the interaction forces are pairwise additive, so that the total potential of the system, denoted U_N, is given by

$$U_N(\tilde{\boldsymbol{x}}) = \sum_{1\leq i<j\leq N} U(|\boldsymbol{x}_i - \boldsymbol{x}_j|). \tag{4.16}$$

We also assume, for the sake of simplicity, that the friction is state-independent. Thus the Langevin equations (**??**) take the form

$$\ddot{\boldsymbol{x}}_i + \gamma\dot{\boldsymbol{x}}_i + \frac{1}{M^h}\nabla_{\boldsymbol{x}_i^h} U_N(\tilde{\boldsymbol{x}}) = \sqrt{2\varepsilon}\,\dot{\boldsymbol{w}}_i^h, \qquad i = 1,2,\ldots,N, \tag{4.17}$$

where

$$\varepsilon^h = \frac{\gamma k_B T}{M^h}.$$

In an overdamped system the stationary Smoluchowski equation for the joint pdf of all ions takes the form

$$0=\sum_i \nabla_i\cdot\left[\frac{1}{M\gamma}\nabla_i U_N(\tilde{\boldsymbol{x}})p_N(\tilde{\boldsymbol{x}})+\frac{k_BT}{M\gamma}\nabla_i p_N(\tilde{\boldsymbol{x}})\right]=-\sum_{j=1}^N\nabla_{\boldsymbol{x}_j}\cdot\boldsymbol{J}_j(\tilde{\boldsymbol{x}}). \tag{4.18}$$

The equilibrium condition of vanishing flux is

$$\boldsymbol{J}_j(\tilde{\boldsymbol{x}})=0,\quad \text{for all } j,$$

and the solution of the Smoluchowski equation (**??**) in this case is

$$p_N(\tilde{\boldsymbol{x}})=\frac{e^{-U_N(\tilde{\boldsymbol{x}})/k_BT}}{Z_N},$$

where Z_N is the configurational partition function of equilibrium statistical mechanics [**?**], [**?**]. An insight into non-equilibrium problems can be gleaned from the second case, that is, from a system of independent (non-interacting, i.e., uncharged) particles diffusing in an external potential $V(\boldsymbol{x})$ between two fixed concentrations. In this case,

$$U_N(\tilde{\boldsymbol{x}})=\sum_{j=1}^N V(\boldsymbol{x}_j). \tag{4.19}$$

Since the ions are independent, the solution of the Nernst-Planck equation for the joint probability density in configuration space is given by

$$p_N(\tilde{\boldsymbol{x}})=\prod_{j=1}^N p(\boldsymbol{x}_j), \tag{4.20}$$

where $p(\boldsymbol{x}_j)$, the probability density of the j-th ion, is the solution of the three-dimensional Smoluchowski equation

$$0=\nabla_{\boldsymbol{x}_j}\cdot\frac{1}{M\gamma}\left[\nabla_{\boldsymbol{x}_j}V(\boldsymbol{x}_j)p(\boldsymbol{x}_j)+k_BT\nabla_{\boldsymbol{x}_j}p(\boldsymbol{x}_j)\right]=-\nabla_{\boldsymbol{x}_j}\cdot\mathcal{J}_j(\boldsymbol{x}_j) \tag{4.21}$$

with vanishing flux conditions on reflecting boundaries and given concentrations on the other boundaries. Note that the concentrations have to be normalized so that the condition

$$\int_\Omega p(\boldsymbol{x})\,d\boldsymbol{x}=1$$

is satisfied. We denote the reflecting boundaries by $\partial\Omega_r$, and the part of the boundary, where the feedback mechanism maintains fixed concentrations, by $\partial\Omega_F$. The boundary conditions determine the boundary fluxes, $\mathcal{J}_j(\boldsymbol{x}_j)\cdot\boldsymbol{\nu}(\boldsymbol{x}_j)=0$ for $\boldsymbol{x}_j\in\partial\Omega_r$ and $\mathcal{J}_j(\boldsymbol{x}_j)\cdot\boldsymbol{\nu}(\boldsymbol{x}_j)\neq 0$ for $\boldsymbol{x}_j\in\partial\Omega_F$, which are the same for all j. We denote the single ion probability flux density on the boundary $\partial\Omega$ by $\mathcal{J}^1(\boldsymbol{x})$ and assume henceforward that it is known. The Smoluchowski equation for $p_N(\tilde{\boldsymbol{x}})$ in eq.(**??**) is eq.(**??**) with $U_N(\tilde{\boldsymbol{x}})$ given in eq.(**??**). This means that

$$\boldsymbol{J}_j(\tilde{\boldsymbol{x}}) = \mathcal{J}^1(\boldsymbol{x}_j)\prod_{i\neq j} p(\boldsymbol{x}_i) = \mathcal{J}^1(\boldsymbol{x}_j)p_{N-1}(\tilde{\boldsymbol{x}}_j) = \mathcal{J}^1(\boldsymbol{x}_j)p_{N-1}(\tilde{\boldsymbol{x}}_j\,|\,\boldsymbol{x}_j). \tag{4.22}$$

The last equality in eq.(**??**) expresses the independence of $\boldsymbol{x}_j$ of the remaining $\tilde{\boldsymbol{x}}_j$. This conditioning anticipates the case of dependent ions. This means that the boundary condition for the joint pdf $p_N(\tilde{\boldsymbol{x}})$, when $\boldsymbol{x}_j \in \partial\Omega$ and $\tilde{\boldsymbol{x}}_j \in \tilde{\Omega}_j$ is eq.(**??**). Equation (**??**) with the known $\mathcal{J}^1(\boldsymbol{x})$ means that the feedback mechanism removes and inserts ions into the system at the boundary, depending on the configuration of ions inside the domain, with a flux that maintains the boundary concentrations. With this interpretation in mind, we adopt the relation (**??**) as the connection between the j-th component of the $3N$-dimensional flux and the the 3-dimensional singlet flux of the j-th ion on the boundary. Thus the boundary condition for the joint pdf $p_N(\tilde{\boldsymbol{x}})$ is

$$\boldsymbol{J}_j(\tilde{\boldsymbol{x}})\cdot\boldsymbol{\nu}(\boldsymbol{x}_j) = \mathcal{J}^1(\boldsymbol{x}_j)\cdot\boldsymbol{\nu}(\boldsymbol{x}_j)p_{N-1}(\tilde{\boldsymbol{x}}_j\,|\,\boldsymbol{x}_j) \quad \text{for } \boldsymbol{x}_j\in\partial\Omega,\ \tilde{\boldsymbol{x}}_j\in\tilde{\Omega}_j, \tag{4.23}$$

where $\boldsymbol{\nu}(\boldsymbol{x}_j)$ is the unit normal to the boundary at the point $\boldsymbol{x}_j \in \partial\Omega$, and $\mathcal{J}^1(\boldsymbol{x})$ is the single ion boundary flux density, determined by the single ion density in eq.(**??**). The boundary condition (**??**) can be written as

$$\begin{aligned}
-k_BT\frac{\partial \log p_N(\tilde{\boldsymbol{x}})}{\partial\boldsymbol{\nu}(\boldsymbol{x}_i)} - \frac{\partial U(\tilde{\boldsymbol{x}})}{\partial\nu(\boldsymbol{x}_i)} &= M\gamma\mathcal{J}^1(\boldsymbol{x}_i)\cdot\boldsymbol{\nu}(\boldsymbol{x}_i)\frac{p_{N-1}(\tilde{\boldsymbol{x}}_i\,|\,\boldsymbol{x}_i)}{p_N(\tilde{\boldsymbol{x}})} &\quad (4.24)\\
&= M\gamma\frac{\mathcal{J}^1(\boldsymbol{x}_i)\cdot\boldsymbol{\nu}(\boldsymbol{x}_i)}{p(\boldsymbol{x}_i)} \quad \text{for } \boldsymbol{x}_i\in\partial\Omega,\ \tilde{\boldsymbol{x}}_i\in\tilde{\Omega}_i.
\end{aligned}$$

Integration of eq.(**??**) over the domain with respect to any number of coordinates gives the boundary conditions

$$\boldsymbol{J}_i(\boldsymbol{x}_1,\boldsymbol{x}_2,\dots,\boldsymbol{x}_k)\cdot\boldsymbol{\nu}_i(\boldsymbol{x}_1,\boldsymbol{x}_2,\dots,\boldsymbol{x}_k) = \mathcal{J}^1(\boldsymbol{x}_i)\cdot\boldsymbol{\nu}(\boldsymbol{x}_i)p(\boldsymbol{x}_1,\boldsymbol{x}_2,\dots,\boldsymbol{x}_k\,|\,\boldsymbol{x}_i) \tag{4.25}$$

for $\boldsymbol{x}_i \in \partial\Omega,\ \boldsymbol{x}_1,\boldsymbol{x}_2,\dots,\boldsymbol{x}_k \in \Omega,\ (i > k)$. The boundary condition (**??**) holds for the flux of each species h, where the one-dimensional flux $\mathcal{J}^1(\boldsymbol{x}_i)$ is that of species h. This condition is equivalent to the boundary conditions

$$\begin{aligned}
-k_BT\frac{\partial \log p_k(\boldsymbol{x}_1,\boldsymbol{x}_2,\dots,\boldsymbol{x}_k)}{\partial\boldsymbol{\nu}_i(\boldsymbol{x}_1,\boldsymbol{x}_2,\dots,\boldsymbol{x}_k)} &+ \bar{\boldsymbol{f}}_i(\boldsymbol{x}_1,\boldsymbol{x}_2,\dots,\boldsymbol{x}_k)\cdot\boldsymbol{\nu}_i(\boldsymbol{x}_1,\boldsymbol{x}_2,\dots,\boldsymbol{x}_k)\\
&= M\gamma\frac{\mathcal{J}^1(\boldsymbol{x}_i)\cdot\boldsymbol{\nu}(\boldsymbol{x}_i)}{p(\boldsymbol{x}_i)}, \qquad (4.26)
\end{aligned}$$

for $\boldsymbol{x}_i \in \partial\Omega,\ \boldsymbol{x}_1,\boldsymbol{x}_2,\dots,\boldsymbol{x}_k \in \Omega,\ (i > k)$. The force $\bar{\boldsymbol{f}}_i(\boldsymbol{x}_1,\boldsymbol{x}_2,\dots,\boldsymbol{x}_k)$ is the force acting on ion i at the boundary point $\boldsymbol{x}_i$, given the coordinates of the first k ions, $(\boldsymbol{x}_1,\boldsymbol{x}_2,\dots,\boldsymbol{x}_k)$. In particular, the boundary conditions for the pair density are

$$\boldsymbol{J}_i^{h|h'}(\boldsymbol{x}_i,\boldsymbol{x}_j)\cdot\boldsymbol{\nu}(\boldsymbol{x}_i) = \mathcal{J}^h(\boldsymbol{x}_i)\cdot\boldsymbol{\nu}(\boldsymbol{x}_i)p^{h'|h}(\boldsymbol{x}_j\,|\,\boldsymbol{x}_i) \quad \text{for } \boldsymbol{x}_i\in\partial\Omega,\ \boldsymbol{x}_j\in\Omega \tag{4.27}$$

or equivalently,

$$-k_BT\frac{\partial}{\partial\boldsymbol{\nu}(\boldsymbol{x}_i)}\log p^{h,h'}(\boldsymbol{x}_i,\boldsymbol{x}_j)+\bar{\boldsymbol{f}}_i^{h|h'}(\boldsymbol{x}_i,\boldsymbol{x}_j)\cdot\boldsymbol{\nu}(\boldsymbol{x}_i)=M^h\gamma^h\mathcal{J}^h(\boldsymbol{x}_i)\cdot\boldsymbol{\nu}(\boldsymbol{x}_i)\frac{p^{h'|h}(\boldsymbol{x}_j\,|\,\boldsymbol{x}_i)}{p^{h,h'}(\boldsymbol{x}_i,\boldsymbol{x}_j)} \tag{4.28}$$

$$=M^h\gamma^h\frac{\mathcal{J}^h(\boldsymbol{x}_i)\cdot\boldsymbol{\nu}(\boldsymbol{x}_i)}{p^h(\boldsymbol{x}_i)}\quad\text{for } \boldsymbol{x}_i\in\partial\Omega,\ \boldsymbol{x}_j\in\Omega.$$

Note that in the general case the single ion flux $\mathcal{J}^h(\boldsymbol{x})$ is not known on the boundary, due to the unknown forces $\bar{\boldsymbol{f}}_i(\boldsymbol{x}_1,\boldsymbol{x}_2,\ldots,\boldsymbol{x}_k)$ for all combinations of species. Thus the boundary conditions eq.(**??**) couple the equation and boundary conditions for $p^{h,h'}(\boldsymbol{x}_i,\boldsymbol{x}_j)$ to those of $p^h(\boldsymbol{x})$, and the same is true for all $p^{h_1,\ldots,h_k}(\boldsymbol{x}_1,\boldsymbol{x}_2,\ldots,\boldsymbol{x}_k)$ of all combinations of species. The probability flux density components $\boldsymbol{J}^{h,h'}_{\boldsymbol{x}_i}(\boldsymbol{x}_i,\boldsymbol{x}_j)\cdot\boldsymbol{\nu}(\boldsymbol{x}_i)$ for $\boldsymbol{x}_i\in\partial\Omega,\ \boldsymbol{x}_j\in\Omega$, of the six-dimensional flux of $p^{h,h'}(\boldsymbol{x}_i,\boldsymbol{x}_j)$ are the three-dimensional "normal components" of the boundary flux. The boundary condition (**??**) requires some clarification when $p^h(\boldsymbol{x})=0$ for $\boldsymbol{x}\in\partial\Omega,\ \boldsymbol{y}\in\Omega$. In this case the boundary condition for $p^{h,h'}(\boldsymbol{x},\boldsymbol{y})$ is

$$p^{h,h'}(\boldsymbol{x},\boldsymbol{y})=0\quad\text{for } \boldsymbol{x}\in\partial\Omega,\ \boldsymbol{y}\in\Omega. \tag{4.29}$$

because

$$p^{h,h'}(\boldsymbol{x},\boldsymbol{y})\le p^h(\boldsymbol{x})\quad\text{for all } \boldsymbol{x},\boldsymbol{y}\in\Omega.$$

With these boundary conditions, the Smoluchowski equations for all $p^h(\boldsymbol{x})$ and $p^{h,h'}(\boldsymbol{x},\boldsymbol{y})$ are coupled through the single ion fluxes $\mathcal{J}^h(\boldsymbol{x})$ and the forces. The the concentration and flux boundary conditions determine the single ion density and the joint pdfs, provided the forces are known. However, the forces are unknown and require further analysis.

5 Summary and Discussion

The feedback mechanism may be an actual device, as in a chemical reactor. Alternatively, one may think of a smaller macroscopic subsystem, containing a macroscopic or microscopic channel, that connects two effectively infinite reservoirs with fixed concentrations at infinity. In this case, the boundaries of the subsystem can be chosen anywhere in the reservoirs, far enough from the connecting channel, at a location where the concentrations can be assumed known. This is the case, for example, in the description of ionic permeation through a single protein channel: the diffusion current through the channel is so small and the two baths are so large that the concentrations of the two baths, sufficiently far from the channel, are effectively uniform and equal the bulk concentrations [**?**]. In this case the number of ions diffusing in the subsystem undergoes fluctuations in time. Neglecting these fluctuations is equivalent to assuming that there is an external feedback mechanism on the boundaries of the subsystem that maintains both fixed averaged concentrations at the boundaries and a fixed number of ions in the system. We have found the boundary conditions that the pair correlation function in a non-equilibrium system of uncharged diffusing ions satisfies on the boundary of a finite domain. The equations and boundary conditions are derived from a system of Langevin equations for all diffusing ions, coupled by the pairwise interaction forces. These forces may be Lennard-Jones interactions, excluded volume, or any other type of interactions. If a closure relation is assumed, the boundary conditions for the Nernst-Planck equations determine the singlet and pair correlation functions uniquely. The boundary conditions drive the system out of equilibrium, due to the net flux they create. In the absence of net flux the results of equilibrium theory are recovered. This seems to be a new result in non-equilibrium statistical mechanics.

The generalization of the present results to the diffusion of ions in solution is relevant to biological applications in the theory of protein channels of biological membranes. In this application the diffusion of ions through a protein channel embedded in an impermeable membrane can be described in terms of a system of simple partial differential equations and boundary conditions, thus reducing the enormous computations involved in MD or Langevin simulations. The interaction forces become significant within the confined volume of the protein, where ions block each other. This case will be discussed in a separate paper.

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