A model for enhanced and selective transport through biological membranes with alternating pores

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Abstract
We investigate the outflux of ions through the channels in a cell membrane. The channels undergo an open/close cycle according to a periodic schedule. Our study is based both on theoretical considerations relying on homogenization theory, and on Monte Carlo numerical simulations. We examine the onset of a limiting boundary behavior characterized by a constant ratio between the outflux and the local density, in the thermodynamics limit. The focus here is on the issue of selectivity, that is on the different behavior of the ion currents through the channel in the cases of the selected and non-selected species.

Keywords: ionic currents, random walk, homogenization, Monte Carlo method, alternating pores, Fokker-Planck equation.

1. Introduction
1.1. The model
Potassium currents across cell membranes have been widely studied, since they play many important and different functional roles (see, e.g., the reviews [12, 15]). Indeed, ionic channels selecting the flux of Potassium ions are ubiquitous in all organisms.

We confine ourselves here to recall that ionic channels form selective pores in the cell membrane which open and close and, when in the open state, allow permeation of ions favoring selection of a species (Potassium in K\(^+\)-channels). The processes turning on and off ion conduction, i.e., gating, and the channel ability to allow the flux of a particular ionic species, i.e., selectivity, are not yet completely understood, but it has been known for some time in the literature the conjecture that they are functionally linked [18]. The idea is that the density of selected ions is higher in a region close to the pore where the affinity is higher; when the pore opens, passive diffusion together with such an unbalance in concentration is enough to cause a selective outflux.

We model this phenomenon as a diffusion problem in a domain with alternating pores on the boundary. The latter are holes periodically and simultaneously cycling through open and closed phases. We model the affinity to the selected species by setting the corresponding diffusivity smaller in a suitably chosen small region in the neighborhood of the pores. Assuming that the pores are many
and with small diameter with respect to the dimensions of the domain and also that the period of
the cycle is much smaller than the characteristic time of diffusion, it is possible to approximate the
problem with its homogenized version, where the number of pores and the number of cycles both
diverge to infinity and the diffusion in the affinity region goes to zero. In [3] we introduced four
parameters: the distance between neighboring pores ε, the diameter of each pore σ, the period of
the opening/closing cycle τ, and finally στ as the length of the time sub-interval of each cycle in
which the pores are open. If the parameters ε, σ, τ and στ are properly related, in the asymptotic
limit when they become vanishingly small we obtain a limiting boundary condition of the type
\[ D_0 \frac{\partial u}{\partial \nu}(x, t) = \varphi(x) D_0 u(x, t), \] (1)
where \( D_0 \) is the diffusivity of the ions in the cytosol, \( \varphi \) is a function connected to the distribution
and to the shape of pores and \( u \) denotes the concentration of ions. Notice that \( D_0 \) appears on both
sides of (1) so that the left hand side equals the flux at the boundary.

However in [3] we considered the case where no selection is present, and therefore diffusivity is
a constant; this is for example the case when looking at the flux of Sodium ions through Potassium
channels. When considering flux of \( K^+ \) ions through the same channels, a variable diffusivity is
to be taken into account. Thus we model the phenomenon by using the Fokker-Planck Equation
\[ u_t - \Delta(Du) = 0, \]
where we let \( D = D_1 \) in a suitably chosen neighborhood of the pores, and \( D_1 \) is a
vanishingly small value, in the asymptotic or homogenization limit described above. We obtain
in the limit an asymptotic boundary condition of the type (1), but in this case the function \( \varphi \)
also depends on the asymptotics of \( D_1 \). We will show that two different asymptotic standards are
admissible, in order to obtain the limiting interface condition (1). They are discriminated by the
limiting behavior of the ratio \( \frac{\sigma}{\sqrt{D_1}} \) according to the two cases

\[ \lim_{\varepsilon, \tau \to 0} \frac{\sigma}{\sqrt{D_1}} = +\infty, \quad \text{which we call the case of fast pores}, \] (2)

\[ \lim_{\varepsilon, \tau \to 0} \frac{\sigma}{\sqrt{D_1}} \leq A_0, \quad \text{which we call the case of small pores}; \] (3)

here \( A_0 \) is a positive constant. We will see that the introduction of selection, that is of the asymp-
totically vanishing diffusivity \( D_1 \), yields a flux enhancement only in the case of fast pores. The
latter case was introduced in [3] and tested numerically in [3], and is specific to evolutive problems,
while the small pores behavior is connected with the stationary case considered for example in [16, 13, 11, 8, 14, 6], but it does appear in evolutive problems as well. A relevant difference between
the two cases from the point of view of selectivity will be outlined in Subsection 2.4.2.

Section 2 is devoted to the theoretical analysis of the diffusion problem. Subsection 2.5 prepares
the way to Sections 3 and 4 where the problem will be attacked via a stochastic discrete space
model. This approach is strictly related to that adopted in [2, 4, 5], in connection with ion currents,
and in [3, 10], in connection with crowd dynamics. We note, however, that in the model proposed
and studied in [3, 5] the open/close cycles of the pore are not prescribed a priori on a deterministic
schedule. There gating is realized in a stochastic fashion as a result of a stochastic flipping of the
pore between a low and a high affinity state.
2. Statement of the problem and main results

2.1. Geometry and alternating pores

The quantities \( \varepsilon, \sigma_\varepsilon, \sigma_\tau D_1 \) are defined as functions of \( \tau \), vanishing as \( \tau \to 0 \)

\[
\varepsilon = \varepsilon(\tau) \to 0, \quad \sigma_\varepsilon = \sigma_\varepsilon(\tau) \to 0, \quad \sigma_\tau = \sigma_\tau(\tau) \to 0, \quad D_1 = D_1(\tau) \to 0.
\]

For reasons of technical simplicity we choose

\[
\Omega = (-a, a)^{N-1} \times (0, a), \quad \Gamma = [-a, a]^{N-1} \times \{a\},
\]

for a given \( a > 0 \). We model the pores as a subset \( \mathcal{P} \) of \( \Gamma \), i.e.,

\[
\mathcal{P} = \bigcup_{i=1}^{m_\varepsilon} P_i^\varepsilon, \quad P_i^\varepsilon := \sigma_\varepsilon P_0 + z_i^\varepsilon,
\]

where \( m_\varepsilon \) is the number of pores, \( \sigma_\varepsilon > 0 \), the \( z_i^\varepsilon \) are points of \( \Gamma \), \( P_0 \) is an open set in \( \mathbb{R}^{N-1} \) such that \( \partial P_0 \in C^3 \) and, for a given \( \delta_0 \in (0, 1) \)

\[
(-\delta_0, \delta_0)^{N-1} \subset P_0 \subset (-1, 1)^{N-1}.
\]

We define the total open phase and the union of the open pores as

\[
A_\tau = \bigcup_{j=0}^{m_\tau-1} [j\tau, j\tau + \sigma_\tau), \quad \mathcal{P}_{A_\tau} = \bigcup_{i=1}^{m_\varepsilon} P_i^\varepsilon \times A_\tau.
\]

Here \( \sigma_\tau > 0 \) is the opening interval in each cycle, \( \tau > 0 \) is the period of the cycle and \( m_\tau \) is the total number of the cycles, related by

\[
\tau = \frac{T}{m_\tau}, \quad m_\tau \in \mathbb{N},
\]

so that \( m_\tau \to \infty \) as \( \tau \to 0 \). The length \( \varepsilon \) satisfies the following requirements. Define the domains \( B_\varepsilon(z_i^\varepsilon) := B_\varepsilon(0) + z_i^\varepsilon \), where

\[
B_\varepsilon(0) = (-\varepsilon, \varepsilon)^{N-1} \times (-\varepsilon, 0).
\]

Then we assume that

\[
B_\varepsilon(z_i^\varepsilon) \subset \Omega; \quad B_{2\varepsilon}(z_i^\varepsilon) \cap B_{2\varepsilon}(z_m^\varepsilon) = \emptyset, \quad \text{for any } i \neq m.
\]

In addition, we stipulate the existence of a function \( M(x) \in L^\infty(\Gamma) \) such that \( M(x) \geq 0, M(x) \neq 0 \) and

\[
\lim_{\tau \to 0} \sum_{i=1}^{m_\varepsilon} \sum_{j=0}^{m_\tau-1} \tau \varepsilon^{N-1} \varphi(z_i^\varepsilon, j\tau) = \int_0^T \int_\Gamma M(x) \varphi(x, t) \, ds \, dt,
\]

for any \( \varphi \in C(\Gamma \times [0, T]) \). Then taking \( \varphi \equiv 1 \) in (10) we get

\[
m_\varepsilon \sim \frac{M_0}{\varepsilon^{N-1}}, \quad \text{as } \varepsilon \to 0, \quad \text{where } M_0 = \int_\Gamma M(x) \, ds > 0.
\]
The function $M$ measures the density of pores on $\Gamma$.

Then the diffusivity for Potassium ions is given by

$$D_K(x) = \begin{cases} D_1, & x \in \Omega^r \\ D_0, & x \in \Omega \setminus \Omega^r \end{cases}, \quad \text{where} \quad \Omega^r = \bigcup_{i=1}^{m_s} B_{\varepsilon}(z_i^r), \quad (12)$$

$0 < D_1(\tau) < D_0$ and $D_0$ is a constant. We understand that $D_1(\tau) \to 0$ as $\tau \to 0$ unless otherwise noted (as in Subsection 2.3). In turn the diffusivity for Sodium is constant and, given the theoretical character of our analysis, denoted for simplicity of comparison with the same symbol $D_0$:

$$D_{Na}(x) = D_0, \quad x \in \Omega. \quad (13)$$

2.2. Formulation of the approximating problem

For any set $A \subset \mathbb{R}^N$ we use below the notation $\partial_+ A = \partial A \cap \{x_N < a\}$. For any function $F(x,t)$, with $x \in \Omega$, we will denote with $[F]$ the jump across $\partial_+ \Omega^r$

$$[F] := F_{\text{ext}} - F_{\text{int}}, \quad F_{\text{int}} := \text{trace of } F|_{\Omega^r} \text{ on } \partial_+ \Omega^r, \quad F_{\text{ext}} := \text{trace of } F|_{\Omega \setminus \Omega^r} \text{ on } \partial_+ \Omega^r.$$

We consider the problem for the concentration $u^r \geq 0$

$$u^r_0 - \Delta(D u^r) = 0, \quad (x,t) \in \Omega \times [0,T], \quad (14)$$

$$u^r = 0, \quad (x,t) \in \mathbb{P}_{A_r}, \quad (15)$$

$$\nabla(D u^r) \cdot \hat{\nu} = 0, \quad (x,t) \in \{\Gamma \times [0,T]\} \setminus \mathbb{P}_{A_r}, \quad (16)$$

$$\nabla(D u^r) \cdot \hat{\nu} = 0, \quad (x,t) \in \partial_+ \Omega \times [0,T], \quad (17)$$

$$[D u^r] = [\nabla(D u^r) \cdot \nu] = 0, \quad (x,t) \in \partial_+ \Omega^r \times [0,T], \quad (18)$$

$$u^r(x,0) = u_0(x), \quad x \in \Omega. \quad (19)$$

Here $\hat{\nu}$ is the outer normal to $\Omega$, $\nu$ is the outer normal to $\Omega^r$ and we suppose that $u_0 \in L^\infty(\Omega)$.

In the case of Sodium the diffusivity is constant in the whole domain so that (14) is essentially the heat equation, and (15) implies continuity of $u^r$ and of the flux through $\partial_+ \Omega^r$. This problem has been already studied in detail in [3]; actually the boundary condition (17) is replaced there with vanishing Dirichlet data, but this doesn’t affect the well posedness of the model and its asymptotics. Instead, in the case of Potassium, condition (18) implies the discontinuity of the unknown $u^r$ across $\partial_+ \Omega^r$, namely

$$u^r_{\text{int}} = \frac{D_0}{D_1} u^r_{\text{ext}}. \quad (20)$$

Thus $u^r|_{\Omega^r}$ can not be bounded as $\tau \to 0$. But even in the case of Potassium we can prove the existence of a unique weak solution $u^r$ for problem (14)-(19) in the space $V_K$ defined by

$$\sqrt{D} u^r \in C \left(0,T,L^2(\Omega)\right), \quad D u^r \in L^2 \left(0,T,H^1(\Omega)\right), \quad u^r|_{\mathbb{P}_{A_r}} = 0. \quad (21)$$

The proof is standard, see however [3, 5]. For this solution we prove the following, less standard, maximum principle.

**Proposition 1.** The solution $u^r$ to (14)-(19) in the case of Potassium satisfies

$$0 \leq D(x) u^r(x,t) \leq D_0 \|u_0\|_\infty, \quad (x,t) \in \Omega \times [0,T], \quad (22)$$

$$0 \leq u^r(x,t) \leq \|u_0\|_\infty, \quad (x,t) \in (\Omega \setminus \Omega^r) \times [0,T]. \quad (23)$$
Proof. Let us consider the function \( v(x,t) = D(x)u^\tau(x,t) \). Let \( \Lambda > 0 \) be a constant to be chosen. Using \( (v - \Lambda)_+ \) as a test function in the weak formulation of the problem solved by \( v \) we get

\[
0 = \frac{1}{D_1} \int_0^\tau \int_\Omega v_t(v - \Lambda)_+ \, dx \, dt + \frac{1}{D_0} \int_0^\tau \int_{\Omega \setminus \Omega^*} v_t(v - \Lambda)_+ \, dx \, dt - \int_0^\tau \Delta v(v - \Lambda)_+ \, dx \, dt , \tag{24}
\]

and then, setting \( \Lambda = D_0 \| u_0 \|_\infty \sup_{0 < t < T} \frac{1}{D_1} \int_\Omega (v - \Lambda)_+^2 \, dx + \frac{1}{D_0} \int_{\Omega \setminus \Omega^*} (v - \Lambda)_+^2 \, dx \leq \frac{1}{D_1} \int_\Omega (v - \Lambda)_+^2(x,0) \, dx + \frac{1}{D_0} \int_{\Omega \setminus \Omega^*} (v - \Lambda)_+^2(x,0) \, dx = 0 . \tag{25}
\]

Hence (22) follows, and (23) is an immediate consequence of (22).

2.3. Fast and small pores

The limiting behaviour of the problem (14)–(19) as \( \tau \to 0 \) depends sharply on the relative sizes of the quantities introduced above. Specifically we need define two possible cases.

Considering the model for Potassium, the cases of fast pores and small pores are defined respectively by the assumptions (2) and (3). We also need assume that as \( \tau \to 0 \)

\[
l_{fK}^\tau := \frac{\sqrt{\sigma_\tau}}{\sigma_\tau \varepsilon^{N-1}} \to l_{fK} \, , \quad \text{in the case of fast pores,} \tag{26}
\]

\[
l_{sK}^\tau := \frac{\sigma_\tau}{\varepsilon^{N-1}} \to l_{sK} \, , \quad \text{in the case of small pores,} \tag{27}
\]

where \( l_{fK}, l_{sK} \in (0, +\infty) \) unless otherwise noted.

Considering Sodium, the cases of fast pores and small pores are defined again by (2) and (3) where we formally let \( D_1 = 1 \). In each case, we need assume that as \( \tau \to 0 \)

\[
l_{fNa}^\tau := \frac{\sqrt{\sigma_\tau \varepsilon^{N-1}}}{\tau \varepsilon^{N-1}} \to l_{fNa} \, , \quad \text{in the case of fast pores,} \tag{28}
\]

\[
l_{sNa}^\tau := \frac{\sigma_\tau}{\tau \varepsilon^{N-1}} \to l_{sNa} \, , \quad \text{in the case of small pores,} \tag{29}
\]

where \( l_{fNa}, l_{sNa} \in (0, +\infty) \) unless otherwise noted.

2.4. Formulation of the limiting problem

In this Subsection, we always assume that for a constant \( \gamma_0 > 0 \),

\[
\varepsilon = \gamma_0 \sqrt{D_1 \tau} \, , \quad \tau > 0 ; \quad D_1(\tau)^{-1} \to +\infty \, , \quad \tau \to 0 . \tag{30}
\]
Under the stipulations above, the solution to (14)–(19) is proven to approximate as \( \tau \to 0 \) the solution to

\[
\begin{align*}
&u_t - \Delta(D_0 u) = 0, & &\text{in } \Omega \times (0, T), \\
&\nabla(D_0 u) \cdot \mathbf{\bar{v}} = 0, & &\text{on } \partial_+ \Omega \times (0, T), \\
&\nabla(D_0 u) \cdot \mathbf{\bar{v}} = -\varrho M(x) D_0 u, & &\text{on } \Gamma \times (0, T), \\
&u(x, 0) = u_0(x), & &\text{in } \Omega,
\end{align*}
\]

where the constant \( \varrho \) is defined in Theorem 2 below.

**Theorem 2.** As \( \tau \to 0 \) the solution to (14)–(19) converges to the solution of (31)–(34), in the sense of \( L^2(\Omega \times (0, T)) \), provided one among (2)–(3) is in force, and the corresponding assumption (26) or (27) also holds true.

The constant appearing in (33) is defined by

\[
\varrho = \begin{cases} 
\frac{2}{\sqrt{\pi}} |P_0|_{N-1} l_{f_K}, & \text{in the case of fast pores}, \\
\Phi l_{s_K}, & \text{in the case of small pores},
\end{cases}
\]  

where \( \Phi \) is a positive constant related to the geometry of the pore \( P_0 \).

The value of \( \Phi \) can be found in [11, 3]. When the limits in (26), (27) are either zero or infinite, the limiting boundary condition corresponds to the case of minimal (null) or maximal flux respectively:

**Theorem 3.** Assume that (2), respectively (3) is in force. Then as \( \tau \to 0 \) the solution to (14)–(19) converges in the sense of \( L^2(\Omega \times (0, T)) \) to a function \( u \) satisfying (31), (32), (34) and

\[
\nabla(D_0 u) \cdot \mathbf{\bar{v}} = 0, \quad \text{on } \Gamma \times (0, T), \\
M(x) u = 0, \quad \text{on } \Gamma \times (0, T),
\]

provided \( l_{f_K} = 0, \text{ resp. } l_{s_K} = 0 \); \( l_{f_K} = +\infty, \text{ resp. } l_{s_K} = +\infty \).

2.4.1. Sketch of the proof of Theorems 2, 3

Assuming essentially the same hypotheses of Theorems 2 and 3, in [3] it has been proven that in the case of Sodium problem (14)–(19) has a unique solution converging in the sense of \( L^2 \) to the solution of (31)–(34), with

\[
\varrho = \begin{cases} 
\frac{2}{\sqrt{\pi}} |P_0|_{N-1} l_{f_{Na}}, & \text{in the case of fast pores}, \\
\Phi l_{s_{Na}}, & \text{in the case of small pores},
\end{cases}
\]  

where \( \Phi \) is the same constant as in (35).

Since the solution \( u^\tau \) of problem (14)–(19) satisfies energy estimates which are uniform with respect to \( \tau \), by extracting a subsequence if needed, and also using the bounds of Proposition 1, we have

\[
\begin{align*}
&u^\tau|_{x \in \Omega \setminus \Omega^\tau} \to u, \quad \text{strongly in } L^2(\Omega \times (0, T)) \text{ as } \tau \to 0; \\
&\nabla(D_0 u^\tau)|_{x \in \Omega \setminus \Omega^\tau} \to \nabla(D_0 u), \quad \text{weakly in } L^2(\Omega \times (0, T)) \text{ as } \tau \to 0.
\end{align*}
\]

Then it is easy to see that \( u \) satisfies (31), (32), (34) in a standard weak sense. This simple compactness argument leaves completely unsolved the problem of determining the limiting boundary
condition satisfied for \( x \in \Gamma \). The latter condition may be identified as in [3], relying on a careful analysis of the behaviour of a suitable oscillating test function defined in \( \Omega^\tau \). Actually, since in \( \Omega^\tau \) the diffusivity \( D_1 \) is constant, the analysis of [3] carries through essentially without technical changes.

However the introduction of a vanishing diffusivity \( D_1 \) in our problem is important in the function \( l^\tau_{f_K} \) approximating \( l_{f_K} \), and in the assumptions on \( \varepsilon \) stipulated in Theorems [2] and [3] the consequences of this are in our opinion interesting and will be discussed below.

2.4.2. Discussion: Potassium flux enhancement using Fokker-Planck equation

In this subsection we give an interpretation of the results stated above and show that using as a starting point the model in [3] modified as above by introducing a vanishingly small diffusivity in a neighborhood of the pores, we can mimic the selectivity mechanism present in many biological membranes. This effect also relies on the use of the Fokker-Planck equation, which implies the interface condition (18) and therefore the jump relation (20), which is instrumental in the enhancement of the local concentration, and therefore of the outflux; see also [17].

The Propositions below, together with Theorems [2] and [3] show that, if Sodium and Potassium share a common set of parameters \( \varepsilon, \sigma_\varepsilon, \sigma_\tau \), in the case of fast pores for Potassium (that could correspond either to fast or small pores for Sodium), if the limiting boundary condition on \( \Gamma \) for Potassium [Sodium] is (33), then for Sodium [Potassium] it is of Neumann [Dirichlet] type. Therefore, in this case we proved an enhanced asymptotic flux for Potassium with respect to Sodium.

On the other hand in the case of small pores for both Potassium and Sodium, if the species share the same set of parameters, they also share the limiting behaviour of the boundary condition on \( \Gamma \). The case of small pores is therefore not sensitive to the mechanism of selection we introduced for Potassium.

**Proposition 4.** Assume (2) and (26) with \( 0 < l_{f_K} < +\infty \). If either case of fast or small pores holds true for Sodium, then the corresponding limit relation in (28) or in (29) is satisfied with \( l_{f_Na} = 0 \) or \( l_{s_Na} = 0 \).

Conversely, assume (2) but not (26). If either case of fast or small pores holds true for Sodium, and if the corresponding limit relation in (28) or in (29) is satisfied with \( 0 < l_{f_Na} < +\infty \) or \( 0 < l_{s_Na} < +\infty \), then then the limit relation (26) is satisfied with \( l_{f_K} = +\infty \).

**Proposition 5.** Assume (3) and (27) with \( 0 < l_{s_K} < +\infty \). Then the case of small pores for Sodium holds true, and the limit relation (29) is satisfied with \( l_{s_Na} = l_{s_K} \).

Conversely, assume (3), but not (27). If the case of small pores for Sodium holds true, as well as (27) with \( 0 \leq l_{s_Na} < +\infty \), then the limit relation (27) is satisfied with \( l_{s_K} = l_{s_Na} \).

The proofs of Propositions 4 and 5 follow from some simple algebra and the definitions (2)–(3), (26)–(29).

2.5. The problem for \( N = 1 \) and \( D_1 \) not depending on \( \tau \)

Having in mind the application of next Sections, we look here at the approximating problem for Potassium given by the 1-dimensional version of (14)–(19), where however \( 0 < D_1 < D_0 \) are given constants and we set for \( 0 < \delta < a \)

\[
D(x) = \begin{cases} 
D_0, & x \in [0, a - \delta] \\
D_1, & x \in (a - \delta, a] 
\end{cases}
\]
Indeed in the numerical simulations it would be technically very difficult to mimic the limit $D_1 \to 0$. We remark that the boundary $x = a$ still is a pore alternating with period $\tau$ and open phase $\sigma_x$. By methods similar to those outlined in Subsection 2.4.1 we can prove that the solution $u^\tau$ to this problem approximates as $\tau \to 0$ the solution to

$$
\begin{align*}
\frac{\partial u}{\partial t} - (D_0 u)_{xx} &= 0, & \text{in } \Omega \times (0, T), \\
(D_0 u)_x &= 0, & \text{for } x = 0 \text{ and } t \in (0, T), \\
(D_0 u)_x &= -\varrho_1 \sqrt{D_1} u, & \text{for } x = a \text{ and } t \in (0, T), \\
u(x, 0) &= u_0(x), & \text{in } \Omega,
\end{align*}
$$

where the constant $\varrho_1$ is defined in Theorem 6 below.

**Theorem 6.** Let $\delta = \sqrt{D_1 \tau}$ and assume that

$$
\lim_{\tau \to 0} \sqrt{\frac{\sigma_x}{\tau}} = l_{1K},
$$

where $l_{1K}$ is a positive constant. As $\tau \to 0$ the solution $u^\tau$ converges to the solution of (40)–(43), in the sense of $L^2(\Omega \times (0, T))$. The constant $\varrho_1$ in (42) is defined by

$$
\varrho_1 = \frac{2}{\sqrt{\pi}} l_{1K}.
$$

When the limit in (44) is either zero or infinite, the limiting boundary condition is different.

**Theorem 7.** Assume $\delta = \sqrt{D_1 \tau}$ and (44). Then as $\tau \to 0$ the solution $u^\tau$ converges in the sense of $L^2(\Omega \times (0, T))$ to a function $u$ satisfying (40), (41), (43) and

$$
\begin{align*}
(D_0 u)_x &= 0, & \text{for } x = a \text{ and } t \in (0, T), & \text{provided } l_{1K} = 0; \\
u &= 0, & \text{for } x = a \text{ and } t \in (0, T), & \text{provided } l_{1K} = +\infty.
\end{align*}
$$

In the case of Sodium the same results hold, replacing $D_1$ with $D_0$ everywhere above in this Subsection.

If Theorem 6 holds, from (42) we have the following effect of enhanced flux by selection: The asymptotic ratio between outgoing flux and concentration $-(D_0 u)_x/u$ at $x = a$ in the case of Potassium is bigger with respect to the case of Sodium by a factor $\sqrt{D_0/D_1}$.

### 3. A discrete space model

Next we approach the problem via a discrete space model. In this section we first define the model and then discuss heuristically the relation between the outgoing flux and the ion density close to the pore. In next section this model will be studied via Monte Carlo simulations.

We consider $M$ one-dimensional independent random walkers on $H = H_0 \cup H_1$ with $H_0 = \{\ell, 2\ell, \ldots, n_0\ell\} \subset \ell \mathbb{Z}$ and $H_1 = \{(n_0 + 1)\ell, (n_0 + 2)\ell, \ldots, (n_0 + n_1)\ell\} \subset \ell \mathbb{Z}$, where $n_0$ and $n_1$ are non-negative integers. We denote by $t \in s\mathbb{Z}_+$ the time variable. We assume the following: (i) each random walk is symmetric, (ii) only jumps between neighboring sites are allowed, (iii) in the region
$H_1$ particles have the probability $r \in [0, 1]$ not to move, (iv) 0 is a reflecting boundary point, and (v) picked the two integers $1 \leq \sigma \leq \bar{\tau}$, we partition the time space $s \mathbb{Z}_+$ in

$$A = \bigcup_{i=1}^{\infty} \{s(i-1)\tau, \ldots, s[(i-1)\tau + \sigma - 1]\}$$

and

$$C = \bigcup_{i=1}^{\infty} \{s[(i-1)\tau + \sigma], \ldots, s[i\tau - 1]\}$$

and assume that the boundary point $(n_0 + n_1 + 1)\ell$ is absorbing at times in $A$ (open phase) and reflecting at times in $C$ (closed phase).

To be more precise, we write explicitly the probability $p(x, y)$ that the walker at site $x$ jumps to site $y$. We first set $r(x) = 0$ if $x \in H_0$ and $r(x) = r$ if $x \in H_1$, then we have

$$p(\ell, \ell) = \frac{1}{2}, \quad p(x, x + \ell) = \frac{1 - r(x)}{2} \quad \text{for} \quad x = \ell, \ldots, (n_0 + n_1 - 1)\ell,$$

and

$$p(x, x - \ell) = \frac{1 - r(x)}{2} \quad \text{for} \quad x = 2\ell, \ldots, (n_0 + n_1)\ell.$$ 

Moreover

$$p((n_0 + n_1)\ell, (n_0 + n_1)\ell) = \begin{cases} r(x) & \text{at times in } A \\ (1 + r(x))/2 & \text{at times in } C \end{cases}$$

and

$$p((n_0 + n_1)\ell, (n_0 + n_1 + 1)\ell) = \begin{cases} (1 - r(x))/2 & \text{at times in } A \\ 0 & \text{at times in } C \end{cases}.$$

Notice that when the walker reaches the site $(n_0 + n_1 + 1)\ell$ it is frozen there, so that this system is a model for the proposed problem in the following sense: each walker is an ion, the cell is the set $H_0 \cup H_1$, the low diffusivity region close to the pore is the set $H_1$ (indeed, there the particles move less frequently and, hence, diffuse at a slower rate), at the initial time there are $M$ ions in the cell, each ion absorbed at the site $(n_0 + n_1 + 1)\ell$ is counted as an ion which exited the cell. It is also important to note that the case $n_1 \geq 1$ models the Potassium problem, whereas the case $n_1 = 0$ models the Sodium problem. The Sodium–like case has been dealt upon in [5], hence from now on we assume $n_1 \geq 1$.

It is important to note that for $\sigma = 0$, namely, when the pore is always closed, each walker admits the following unique stationary measure: the probability that a site in the region $H_0$ is occupied by the walker is equal to $(1 - r)/[(1 - r)n_0 + n_1]$, the probability that a site in the region $H_1$ is occupied by the walker is equal to $1/[(1 - r)n_0 + n_1]$. This state will be called in the sequel the closed pore stationary state. In this state, the typical number of particle on a site in $H_0$ (resp. in $H_1$) is given by $M(1 - r)/[(1 - r)n_0 + n_1]$ (resp. $M/[(1 - r)n_0 + n_1]$). We denote by $\mathbb{P}[]$ and $\mathbb{E}[]$ the probability and the average along the trajectories of the process started at the closed pore stationary state.

When the pore is opened for the first time, the initial state is perturbed as an effect of the outgoing flux of particles; at the end of the first opening cycle the total number of particles in the system will be smaller than $M$. When the pore is closed, the system tends to restore the closed pore stationary state with the new value of the total particle number. We will always assume that

$$\bar{\tau} \gg \sigma \quad \text{and} \quad \bar{\tau} > n_1^2$$

so that we can reasonably think that at the beginning of each opening cycle the distribution of particles throughout the region $H_1$ is approximatively constant. Indeed, under this hypothesis the
time interval in which the right hand boundary point is absorbing is much smaller than that in which it is reflecting; in other words in each cycle the pore is open in a very short time subinterval.

In the framework of this model an estimator for the ratio between the outgoing ion flux and the typical number of particles in the high diffusivity region but close to the low diffusivity one is given by

\[ K_i = \frac{\mathbb{E}[F_i]/(s\bar{\tau})}{(\mathbb{E}[U_i]/\bar{\tau})/\ell} \quad \text{for all } i \in \mathbb{Z}_+ \]  

where \( F_i \) is the number of walkers that reach the boundary point \((n_0 + n_1 + 1)\ell\) during the \( i \)-th cycle, \( U_i \) is the sum over the time steps in the \( i \)-th cycle of the number of walkers at the site \( n_0 \ell \).

We are interested in two main problems. The first question that we address is the dependence on time of the above ratio, in other words we wonder if this quantity does depend on \( i \). The second problem that we investigate is the connection between the predictions of this discrete time model and those provided by the continuous space one introduced in Subsection 2.5.

3.1. The estimator \( K_i \) is a constant

As remarked above, under the assumption (48), it is reasonable to guess that during any cycle the walkers in the region \( H_1 \) are distributed uniformly with a very good approximation. Hence, at each time and at each site of \( H_1 \) the number of walkers on that site is approximatively given a constant denoted by \( v_i \). Since \( \bar{\sigma} \) is much smaller than \( \bar{\tau} \), the mean number of walkers \( \mathbb{E}[F_i] \) that reach the boundary point \((n_0 + n_1 + 1)\ell\) during the cycle \( i \) is proportional to \( v_{i-1} \) and the constant depends on \( \bar{\sigma} \), so that we have

\[ \mathbb{E}[F_i] = \alpha(\bar{\sigma})v_{i-1}. \]  

We also note that, since \( \bar{\tau} \gg \bar{\sigma} \), we have that

\[ n_1 v_i = n_1 v_{i-1} - \mathbb{E}[F_i] + \Delta_i \]

where \( \Delta_i \) is the expected difference between the number of particles that during the cycle \( i \) moved from the region \( H_0 \) to the region \( H_1 \) and that of the particle that moved in the opposite direction; note that \( \Delta_i \) admits the obvious bound \( \Delta_i \leq M \). At the end of each cycle we can assume that a sort of stationarity is achieved on the boundary between \( H_0 \) and \( H_1 \); so that we can assume \( \mathbb{E}[U_i]/(2\bar{\tau}) = v_i(1 - r)/2 \). By using this remark, the two equations above, and the fact that \( \Delta_i \leq M \), we get that

\[ K_i \xrightarrow{n_1 \to \infty} K \equiv \alpha(\bar{\sigma}) \frac{1}{\bar{\tau}} \frac{\ell}{s} \frac{1}{1 - r} \]  

showing that, provided \( n_1 \) is large enough, the estimator (49) does not depend on time, namely, it is approximatively equal to \( K \) for each \( i \).

3.2. Behavior of the constant \( \alpha \) for large \( \bar{\sigma} \)

We are, now, interested in finding an estimate for \( \alpha(\bar{\sigma}) \) in the limit when \( \bar{\sigma} \) is large. The reason why we need this kind of result will be discussed in the following section.

If \( \bar{\sigma} \) is large, at time \( \bar{\sigma} \) each walker space distribution probability can be approximated by a Gaussian function with variance \( \sqrt{2\bar{\sigma}(1 - r)} \) (Central Limit Theorem). Hence, the number of particles that reach in \( \bar{\sigma} \) steps the boundary \((n_0 + n_1 + 1)\ell\) is approximatively given by the number
of walkers at the $\sqrt{2\sigma(1-r)}$ sites counted starting from the absorbing boundary point divided by 2. Hence, we find the rough estimate

$$\alpha(\sigma) \approx \frac{1}{2} \sqrt{2\sigma(1-r)} = \sqrt{\frac{\sigma(1-r)}{2}}$$

suggesting that, for large $\sigma$, the quantity $\alpha(\sigma)$ depends on $\sigma$ as $\sqrt{\sigma}$.

3.3. Comparison with the continuum space model

In order to compare the results discussed above in this section with those in Subsection 2.5 referring to the continuous space model defined therein, we have to consider two limits. The parameter $\sigma$ has to be taken large (recall, also, that we always assume $\tau \gg \sigma$, see (48)) so that, due to the Central Limit Theorem, the discrete and the continuous space model have similar behaviors provided the other parameters are related properly. With a correct choice of the parameters, then, we expect that the discrete space model will give results similar to those predicted by the continuous space one. In Subsection 2.5, see Theorem 6, the relation between the outgoing flux and the density close to the pore is worked out only in the limit $\tau \to 0$. We then have to understand how to implement such a limit in our discrete time model.

We perform this analysis in the critical case $\sigma = \mu^2 \tau^2$; note the hypothesis in Theorem 6 is weaker, indeed, there $\ell_{1K}$ is the limit for $\tau \to 0$ of the ratio $\sqrt{\sigma/\tau}$, see equation (44). From now on we let $L_0 = a - \delta$ and $L_1 = \delta$, see Subsection 2.5. We imagine to fix the continuous model parameters and then choose properly the discrete space model ones. More precisely we assume given $L_0$, $D_0$, $D_1$, and $\mu$, and recall that $L_1$ is related to the other parameters by the equation

$$L_1 = \sqrt{D_1 \tau}.$$  (53)

However, notice that, as an immaterial technical change, here $L_0$ is fixed rather than $L_0 + L_1$ as in Subsection 2.5.

We now describe our procedure in detail: in order to compare the discrete and the continuum space models we first let

$$L_0 = \ell n_0 \quad \text{and} \quad L_1 = \ell n_1.$$  (54)

These two equations yield an expression for $\ell$ and the relation that must be verified by $n_0$ and $n_1$, more precisely we get

$$\ell = \frac{L_0}{n_0} \quad \text{and} \quad n_1 = n_0 \frac{L_1}{L_0}.$$  (55)

As already remarked, from the Central Limit Theorem, it follows that the two models give the same long time predictions if $2D_0 s = \ell^2$ and $2D_1 s = \ell^2 (1-r)$. We then get an expression for the unit time and a relation between $D_1$ and $r$, namely,

$$s = \frac{\ell^2}{2D_0} = \frac{L_0^2}{2D_0 n_0^2} \quad \text{and} \quad D_1 = D_0 (1-r).$$  (56)

We then consider the random walk model introduced above by choosing $\sigma$ and $\tau$ such that the equality $\sigma s = (\mu \tau s)^2$ is satisfied as closely as possible (note that $\tau$ and $\sigma$ are integers). This can be done as follows: recall that $L_0$, and $\mu$ are fixed; we choose also $n_0$ and $\sigma$, and set

$$\bar{\tau} = \left\lfloor \frac{1}{\mu} \sqrt{\frac{\sigma}{s}} \right\rfloor = \frac{1}{\mu} n_0 \sqrt{2D_0 \sigma} - b$$  (57)
where \(\cdot\) denotes the integer part of a real number and \(b \in [0, 1)\). With the above choice of the parameters, the behavior of the random walk model has to be compared with that of the continuum space model in Subsection 2.5 with period

\[
\tau = s \bar{\tau} = \frac{1}{\mu} \frac{L_0 \sqrt{\bar{\sigma}}}{n_0 \sqrt{2D_0}} - \frac{L_0^2}{2D_0 n_0^2} b.
\]  

(58)

The equation (58) is very important in our computation, since it suggests that the homogenization limit \(\tau \to 0\) studied in the continuum model should be captured by the discrete space model via the thermodynamics limit \(n_0 \to \infty\). We also note that, from the equations above, one gets

\[
n_1 = n_0 \frac{L_1}{L_0} = \frac{n_0}{L_0} \sqrt{D_1 \tau} = \frac{n_0}{L_0} \sqrt{D_0 (1 - r) s \bar{\tau}} = \frac{n_0}{L_0} \sqrt{D_0 (1 - r)} \frac{L_0}{n_0} \frac{1}{\sqrt{2D_0}} \sqrt{\bar{\tau}} = \sqrt{\frac{1 - r}{2}} \sqrt{\bar{\tau}}
\]

showing that in the thermodynamics limit \(n_0 \to \infty\) also the parameter \(n_1\) tends to infinity. In conclusion, from the continuous space model, we expect that the estimator \(K\) converges to the constant \(2 \mu D_0 / \sqrt{\pi D_1}\) in this limit. In the next section we shall check this result via a Monte Carlo computation, but here we argue this guess has a chance to be correct on the basis of the rough estimate (52).

Indeed, we first note that by (51), (57), the first of equations (55), and the first of equations (56), we have that

\[
K = \alpha(\bar{\sigma}) \frac{1}{\sqrt{\bar{\sigma}}} \frac{1}{1 - r} \mu \sqrt{2D_0}.
\]  

(59)

Then, by (52), we get that

\[
K \xrightarrow{\bar{\sigma} \to \infty} \frac{1}{2} \sqrt{2(1 - r)} \frac{1}{1 - r} \mu \sqrt{2D_0} = \frac{\mu}{\sqrt{1 - r}} \sqrt{D_0} = \frac{\mu D_0}{\sqrt{D_1}}
\]

where in the last step we have used the second among the equations (56). Note that this heuristic result is very close to the desired limit, at least the dependence on the diffusion coefficient is correct. The prefactor is wrong due to the poor estimate (52) that we have for the constant \(\alpha(\bar{\sigma})\).

4. Monte Carlo results

In this section we describe the Monte Carlo computation of the constant (59). This measure is quite difficult since in this problem the stationary state is trivial, in the sense that, since there is an outgoing flux through the boundary point \((n_0 + n_1 + 1) \ell\) and no ingoing flux is present, all the particles will eventually exit the system itself. On the other hand, the measure that we have to perform is intrinsically non–stationary. Indeed, our problem can be stated as follows: both the outgoing flux and the local density at the boundary between the low and the high diffusivity regions are two in average decreasing random variables, but their mutual ratio is constant in average. We then have to set up a procedure to capture this constant ratio.

We fix the parameters \(L_0 = 1, D_0 = 1, \) and \(\mu = 1\). For the diffusion close to the pore we shall consider two cases, \(D_1 = 0.1\) and \(D_1 = 0.25\); the corresponding values for the parameter \(r\), see the second of equations (56), are 0.9 and 0.75. We note that in these two cases the continuous space model limit for the constant \(K\) is respectively given by \(2 \mu D_0 / \sqrt{\pi D_1} = 3.568\) and \(2 \mu D_0 / \sqrt{\pi D_1} = 2.257\). For the time length of the open state, we shall consider the following values

\[
\bar{\sigma} = 500, 1000, 2000, 5000.
\]
For each of them, in order to perform the limit $\tau \to 0$, we shall consider different values of $n_0$, ranging from about 1000 to 20000, for the number of sites of the lattice $H_0$. All the other parameters will be computed via the equations discussed in Subsection 3.3. As initial number of particles we used $M = 10^5$.

For each choice of the two parameters $\bar{\sigma}$ and $n_0$ we shall run the process and compute at each cycle $i$ the quantity

$$k_i = \frac{F_i/\bar{\bar{\tau}}}{U_i/\bar{\bar{\tau}}}$$

where, we recall, $\bar{\bar{\tau}}$ is defined in (57) and $F_i$ and $U_i$ have been defined below (49).

The quantity $k_i$ is a random variable fluctuating with $i$, but, as it is illustrated in Figure 1, it performs random oscillations around a constant reference value. We shall measure this reference value by computing the time average of the quantity $k_i$. We shall average $k_i$ by neglecting the initial cycles and the very last one which are characterized by large oscillations due to the smallness of the number of residual particles in the system.

The product of the reference value for the random variable $k_i$ and the quantity $\ell/s$, see the equations (49), (55) and (56), will be taken as an estimate for $K$. In other words the output of our computation will be the quantity

$$K = \frac{\ell}{s} \times (k_i \text{ time average}) . \quad (60)$$

Our numerical results are illustrated in Figure 2. In [5], for the Sodium case, we noted that by increasing $\bar{\sigma}$ the numerical series tended to collapse to one limiting behavior. In that paper we discussed Monte Carlo results in the cases $\bar{\sigma} = 30, 50, 70, 100, 120, 150, 200$. In this paper we consider larger values of $\bar{\sigma}$ and, as we expected, the numerical series for the Sodium case collapse to one single curve whose $\tau \to 0$ limit is very close to the theoretical value $2\mu \sqrt{D_0}/\sqrt{\pi} = 1.1284$, see [5, Section 3.3].

Figure 1: The quantity $k_i$ is plotted vs. the cycle number $i$ in the case $D_1 = 0.1$, $\bar{\sigma} = 1000$, and $n_0 = 5023$. The top curve refers to the Potassium case, while the bottom one refers to the Sodium one ($n_1 = 0$).
Figure 2: Monte Carlo estimate of the constant $K$ measured as in (60) vs. the periodic time schedule $\tau$ for the Potassium model with $D_1 = 0.1$ at the top and $D_1 = 0.25$ in the middle, and for the Sodium case at the bottom. The symbols $\times$, $\ast$, and $\oslash$ refer, respectively, to the cases $\bar{\sigma} = 5000, 2000, 1000, 500$. The three arrows, from the top to the bottom, indicate the three theoretical limits $3.568$, $2.257$, and $1.1284$ corresponding respectively to the three cases Potassium $D_1 = 0.1$, Potassium $D_1 = 0.25$, and Sodium. Notice that the Monte Carlo $\tau \to 0$ limit approximate the theoretical one better and better when $\bar{\sigma}$ is increased.

The numerical study is more complicated in the Potassium case, since after each opening cycle the system tends to restore a new closed pore stationary state with two different typical densities in the regions $H_0$ and $H_1$. It is not really possible to estimate how efficient is this restoring process. However, our numerical estimates are perfectly in agreement with the theoretical prediction.

Again, we note that when $\bar{\sigma}$ is increased the numerical series tend to be mutually closer and closer, even if we cannot observe a precise collapse. But it looks reasonable to suppose that, if larger values of $\bar{\sigma}$ were considered, a complete collapse could be obtained. Considering larger value of $\bar{\sigma}$ would be extremely time consuming from the point of view of numerical simulations, indeed larger and larger values of the lattice size $n_0$ would have to be used.

The limiting behavior for $\tau \to 0$, that in this numerical scheme is achieved via a thermodynamics limit $n_0 \to \infty$, reproduces quite well the theoretical prediction based on the homogenization computation discussed in Subsection 2.5. Indeed, the data in Figure 2 show neatly that the series with the largest $\bar{\sigma}$ approach, for $\tau \to 0$, a value quite close to the theoretical predictions $3.568$ (case $D_1 = 0.1$) and $2.257$ (case $D_1 = 0.25$).

We can finally state that the Monte Carlo measure of the constant $K$ is in very good agreement with the theoretical predictions discussed above which, we recall, are based on a homogenization computation in presence of a spatial discontinuity of the diffusion coefficient.

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