

Reversible Markov chain models for ion channels

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Abstract—Three reversible continuous time Markov chain models for ion channels based on the reversibility of these biological systems are presented. It is shown that the single ion *trans paths* from left to right and those from right to left are equivalent in distribution. This explains an interesting phenomenon observed by biophysicists, that the distribution of time needed for ions to transit an ion channel is the same in either direction, even if there is an electric potential difference across the channel. The distribution of transit time is important in determining the capacity of cell to cell signaling.

The first model assumes that there is no interaction between the ions in order to obtain a reversible open system model as the infinite ion limit of a reversible closed system. Then, interaction is brought into the model in two different ways to obtain the *doormat model* and the *floor mat model*. The entrance rates do not depend on the channel state in the *doormat model*, but do in the *floor mat model*. The effects of trans-membrane potentials, interaction strength and entrance rates are discussed.

I. INTRODUCTION

Biological cells interact with their surrounding medium through their membranes, which act as gate-keepers. The flow of particles between the interior and the exterior of the cell takes place through channels formed by proteins in the membrane. The transport of ions through these channels plays an important role in the functionality of the cells and hence in many processes of biological interest.

Ions diffuse and drift through an aqueous pore in a protein as they move from a bath of one concentration to a bath of another concentration. Ions diffuse from regions of high concentration to regions of low concentration, as described by Fick in the absence of electric fields [2], [3]. They drift due to electric fields caused by fixed charges in the channel walls, charges from the other ions in the channel, the dielectric properties of the channel and trans-membrane potential, according to Ohm's law [2], [3].

This behavior is described by the Nernst-Planck electro-diffusion equation [1], [6], [8], which can be obtained from the diffusion limit of some Markov chains. This paper presents three reversible Markov chain models whose diffusion limit correspond to the Nernst-Planck electro-diffusion equation, in order to facilitate simulation of this type of biological systems and of their understanding. The details concerning these limits are beyond the scope of this paper but can be found in the forthcoming thesis of the first author of this paper.

These three models are based on the reversibility of these biological systems, and this reversibility is helpful in analyzing these models for a better understanding of ion channels. For example, the distribution of transit time is important in determining the capacity of cell to cell signaling. Reversibility

shows that the distribution of time needed for ions to transit an ion channel is the same in either direction, even if there is an electric potential difference across the channel. This explains why the mean passage times obtained in [4] for channels with single ion occupancy are symmetrical around zero trans-membrane potential.

Section II presents the Markov chain model that describes the behavior of a single ion, as well as the equivalence of the its *trans path* distribution. Section III assumes that there is no interaction between the ions in order to obtain a reversible open system model as the infinite ion limit of a reversible closed system. It also discusses the equivalence in distribution of the *trans paths* in this model. Then, Section IV brings interaction into the model in two different ways to obtain the *doormat model* and the *floor mat model*. It also discusses conditions for the equivalence in distribution of the *trans paths* in both of these models. Finally, Section V discusses the effects of trans-membrane potentials, interaction strength and entrance rates.

II. SINGLE ION PROCESS

This section presents a reversible continuous time Markov chain model for the behavior of a single ion that diffuses across a channel between two baths. The channel is assumed to be narrow enough that the channel can be considered one-dimensional. The definition of a *trans path* is given and the equivalence in distribution of the *trans paths* from left to right and those from right to left is established.

A. Model

Let $N \in \mathbb{N}$ be fixed and divide the inside of the channel into N sites labeled $1, \dots, N$. There is a bath on each end of the channel where the ion can also be located. These baths are considered as sites 0 and $N+1$. Let ϕ_i be the energy of an ion at site $i \in \{0, \dots, N+1\}$, which can include the energy due to fixed electric potentials, image charges and Borne energy.

The ion follows a continuous time Markov chain on $0, \dots, N+1$ with equilibrium distribution $\pi \in \mathbb{R}^{N+2}$ given by

$$\pi = \frac{1}{c} \left(\frac{M}{\lambda} e^{-\phi_0}, e^{-\phi_1}, \dots, e^{-\phi_N}, \frac{M}{\lambda} e^{-\phi_{N+1}} \right) \quad (1)$$

where $M \in \mathbb{N}$, $\lambda \in \mathbb{R}$ and c is a normalizing constant given by

$$c = \frac{M}{\lambda} e^{-\phi_0} + e^{-\phi_1} + \dots + e^{-\phi_N} + \frac{M}{\lambda} e^{-\phi_{N+1}} \quad (2)$$

The significance of M, λ will be discussed later.

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In order for the process to be reversible, it must satisfy the detailed balance equations [7], i.e., its transition rates $q_{i,j}$ must be $\pi - symmetric$ [5] :

$$\pi_i q_{i,j} = \pi_j q_{j,i} \quad (3)$$

Since the equilibrium distribution π is given, (3) gives a condition on the ratio of the transition rates, so there are infinitely many that would make the process reversible. As mentioned in the introduction, ion transport through this type of channel is considered an electro-diffusion process, where the drift is proportional to the gradient of the electric potential. A choice of transition rates that is consistent with this theory is:

$$q_{0,1} = \frac{1}{2} \frac{\lambda}{M} \exp\left(-\frac{1}{2}(\phi_1 - \phi_0)\right) \quad (4)$$

$$q_{N+1,N} = \frac{1}{2} \frac{\lambda}{M} \exp\left(-\frac{1}{2}(\phi_N - \phi_{N+1})\right) \quad (5)$$

For $i \neq \{0, N+1\}$ and $|i-j|=1$

$$q_{i,j} = \frac{1}{2} \exp\left(-\frac{1}{2}(\phi_j - \phi_i)\right) \quad (6)$$

and $q_{i,j} = 0$ otherwise.

The model for the single ion process has been defined.

B. Trans path distribution

A trans path is one that starts at one bath and is truncated when it reaches the other bath without having reached the starting bath.

For the sake of simplicity and easy of notation, this section considers the discrete time version of the Markov chain from Section II-A, but the result can be extended to the original chain. The time discretization is done by setting the slot duration to be $1/\alpha$, where $\alpha = \max_{i \in \{0, \dots, N+1\}} \{q_{i,i-1} + q_{i,i+1}\}$. and by defining

$$p_{i,j} = \frac{q_{i,j}}{\alpha}$$

Let \mathcal{S}_{LR} be the set of trans paths from left to right inside the channel, i.e. $\gamma \in \mathcal{S}_{LR}$ is of the following form:

$$\gamma = (\gamma_0 = 1, \gamma_1, \dots, \gamma_{n-1}, \gamma_n = N)$$

where n is the length of the path inside the channel, $\gamma_i \in \{1, \dots, N\}$ and $|\gamma_i - \gamma_{i-1}| \leq 1$. It is implicit that the ion jumped from the left bath, site 0, into site 1 during slot -1 and that it jumped from site N to the right bath, site $N+1$, during slot $n+1$.

Similarly, let \mathcal{S}_{RL} be the set of trans paths from right to left inside the channel, i.e. $\gamma \in \mathcal{S}_{RL}$ is of the following form:

$$\gamma = (\gamma_0 = N, \gamma_1, \dots, \gamma_{n-1}, \gamma_n = 1)$$

where again n is the length of the path inside the channel, $\gamma_i \in \{1, \dots, N\}$ and $|\gamma_i - \gamma_{i-1}| \leq 1$. In this case, it is implicit that the ion jumped from the right bath, site $N+1$, into site N during slot -1 and that it jumped from site 1 to the left bath, site 0, during slot $n+1$.

For $\gamma \in \mathcal{S}_{LR}$ let $\tilde{\gamma}$ be the concatenation of γ and site $N+1$, i.e. $\tilde{\gamma} = (\gamma_0, \dots, \gamma_n, N+1)$ and let

$$\begin{aligned} P_{LR}[\gamma] &:= P^1[\tilde{\gamma} | T_{N+1} < T_0] = \frac{P^1[\tilde{\gamma}, T_{N+1} < T_0]}{P^1[T_{N+1} < T_0]} \quad (7) \\ &\stackrel{(a)}{=} \frac{P^1[\tilde{\gamma}]}{P^1[T_{N+1} < T_0]} \stackrel{(b)}{=} \frac{P^1[\tilde{\gamma}]}{\sum_{\gamma' \in \mathcal{S}_{LR}} P^1[\tilde{\gamma}']} \stackrel{(c)}{=} \frac{P^1[\gamma]}{\sum_{\gamma' \in \mathcal{S}_{LR}} P^1[\gamma']} \end{aligned}$$

where T_i is the time to hit site i , (a) follows because $\tilde{\gamma}$ implies $T_{N+1} < T_0$, (b) because all paths that start at site 1 and reach the right bath before the left bath belong to \mathcal{S}_{LR} , and (c) because $P^1[\tilde{\gamma}] = P^1[\gamma] p_{N,N+1}$ and $p_{N,N+1}$ in the numerator and denominator cancel each other out.

Similarly, for $\gamma \in \mathcal{S}_{RL}$ let

$$P_{RL}[\gamma] := P^N[\hat{\gamma} | T_0 < T_{N+1}] = \frac{P^N[\hat{\gamma}]}{\sum_{\gamma' \in \mathcal{S}_{RL}} P^N[\gamma']} \quad (8)$$

where $\hat{\gamma}$ is the concatenation of γ and site 0.

By the Markov property, the probability of a particular path γ of length n is given by

$$P^{\gamma_0}[\gamma] = p_{\gamma_0, \gamma_1} p_{\gamma_1, \gamma_2} \dots p_{\gamma_{n-2}, \gamma_{n-1}} p_{\gamma_{n-1}, \gamma_n} \quad (9)$$

For any finite path $\gamma = (\gamma_0, \gamma_1, \dots, \gamma_{n-1}, \gamma_n)$ define its reverse path $\gamma^r = (\gamma_n, \gamma_{n-1}, \dots, \gamma_1, \gamma_0)$. Then, $\gamma \in \mathcal{S}_{LR}$ implies that $\gamma^r \in \mathcal{S}_{RL}$ and vice-versa. The mapping of $\gamma \in \mathcal{S}_{LR}$ to γ^r is a one-to-one and onto mapping of \mathcal{S}_{LR} to \mathcal{S}_{RL} .

Now, the equivalence in distribution of the trans paths from left to right and the ones from right to left will be established.

Proposition 2.1: For $\gamma \in \mathcal{S}_{LR}$

$$P_{LR}[\gamma] = P_{RL}[\gamma^r]$$

Proof:

The detailed balance condition (3) and the equilibrium distribution (1) indicate that for $i, j \in \{1, \dots, N\}$

$$\exp(-\phi_i) p_{i,j} = \exp(-\phi_j) p_{j,i} \quad (10)$$

So that

$$\begin{aligned} \frac{P^1[\gamma]}{P^N[\gamma^r]} &\stackrel{(a)}{=} \frac{p_{1, \gamma_1} p_{\gamma_1, \gamma_2} \dots p_{\gamma_{n-2}, \gamma_{n-1}} p_{\gamma_{n-1}, N}}{p_{\gamma_1, 1} p_{\gamma_2, \gamma_1} \dots p_{\gamma_{n-1}, \gamma_{n-2}} p_{N, \gamma_{n-1}}} \\ &\stackrel{(b)}{=} \frac{\exp(-\phi_{\gamma_1})}{\exp(-\phi_1)} \dots \frac{\exp(-\phi_N)}{\exp(-\phi_{\gamma_{n-1}})} = \frac{\exp(-\phi_N)}{\exp(-\phi_1)} \quad (11) \end{aligned}$$

where (a) follows from (9) and reordering terms, and (b) follows from (10).

Let

$$c = \exp(-(\phi_N - \phi_1))$$

which is independent of the the path taken, it depends only on the beginning and ending sites. Then, (11) becomes

$$P^1[\gamma] = c P^N[\gamma^r] \quad (12)$$

Thus,

$$P_{LR}[\gamma] \stackrel{(a)}{=} \frac{P^1[\gamma]}{\sum_{\gamma' \in \mathcal{S}_{LR}} P^1[\gamma']} \stackrel{(b)}{=} \frac{cP^N[\gamma^r]}{\sum_{\gamma' \in \mathcal{S}_{LR}} cP^N[\gamma'^r]} \\ \stackrel{(c)}{=} \frac{P^N[\gamma^r]}{\sum_{\gamma' \in \mathcal{S}_{RL}} P^N[\gamma'^r]} \stackrel{(d)}{=} P_{RL}[\gamma^r]$$

where (a) follows from (7), (b) from (12), (c) because the mapping of $\gamma \in \mathcal{S}_{LR}$ to γ^r is a one-to-one and onto mapping of \mathcal{S}_{LR} to \mathcal{S}_{RL} , and (d) from (8). ■

Since γ in Proposition 2.1 was arbitrary and there is a one-to-one and onto mapping of \mathcal{S}_{LR} to \mathcal{S}_{RL} , the conditioned process from left to right is equal in distribution to the conditioned process from right to left. Therefore, the trans paths from left to right are equivalent in distribution to the trans paths from right to left.

This explains why the mean passage times obtained analytically in [4] for channels with single ion occupancy are symmetrical around zero trans-membrane potential. This means that it takes a crossing ion the same average amount of time to cross the channel when the drift due to trans-membrane potential is μ as when it is $-\mu$. This sounds counterintuitive at first, but it results from that fact that an ion that diffuses against a strong electric potential must do so quickly or else it will not be able to cross at all.

III. NO INTERACTION MODEL

This section presents a reversible open system model for ion channels as the infinite ion limit of a reversible closed system. It assumes that there is no interaction between the ions in order to simplify the calculation of the system's equilibrium distribution. It also discusses the equivalence in distribution of this model's trans paths.

Notice from (1), (4), (5) and (6) that as $M \rightarrow \infty$, the transition rates for the single ion process $q_{0,1}, q_{N+1,N} \rightarrow 0$, the other transition rates remain the same, and

$$\pi \rightarrow \left(\frac{e^{\phi_{N+1}}}{e^{\phi_0} + e^{\phi_{N+1}}}, 0, \dots, 0, \frac{e^{\phi_0}}{e^{\phi_0} + e^{\phi_{N+1}}} \right) \quad (13)$$

Therefore, for large M , an ion will tend to stay out of the channel. It is desired to obtain a model where the aggregation of a very large number of independent ions causes most of the ions to be located at the baths, sites 0 and $N+1$, and some ions inside the channel.

Let there be M ions in the system at all times, let $n_i \in \{0, \dots, M\}$ be the number of ions at site i and let $\vec{n} = (n_0, \dots, n_{N+1})$, where $n_0 + \dots + n_{N+1} = M$.

The ions are assumed to be independent so the joint equilibrium distribution of the ions, denoted by Π , can be obtained from (1) as

$$\Pi(\vec{n}) = \frac{\binom{M}{n_0, \dots, n_{N+1}}}{c^M} \cdot \frac{\left(\frac{M}{\lambda} e^{-\phi_0}\right)^{n_0} (e^{-\phi_1})^{n_1} \dots (e^{-\phi_N})^{n_N} \left(\frac{M}{\lambda} e^{-\phi_{N+1}}\right)^{n_{N+1}}}{c^M} \quad (14)$$

where $\binom{x}{y} = \frac{x!}{(x-y)! y!}$ and $x!$ denotes the factorial of x .

Since the total number of ions is fixed, the number of ions at $N+1$ of the $N+2$ sites is sufficient for a complete description. Let $m = n_1 + \dots + n_N = M - (n_0 + n_{N+1})$ and use this to remove n_0 from (14). Substituting (2) and removing n_0 from (14) along with some rearranging of terms yields

$$\Pi(\vec{n}) = \frac{M!}{(M-m)!} \frac{(e^{-\phi_1})^{n_1}}{n_1!} \dots \frac{(e^{-\phi_N})^{n_N}}{n_N!} \left(\frac{M}{\lambda} e^{-\phi_0}\right)^{M-m} \\ \cdot \left(\frac{M}{\lambda} e^{-\phi_0} + e^{-\phi_1} + \dots + e^{-\phi_N} + \frac{M}{\lambda} e^{-\phi_{N+1}}\right)^{-M} \\ \cdot \left(1 + \frac{\frac{M}{\lambda} e^{-\phi_{N+1}}}{\frac{M}{\lambda} e^{-\phi_0}}\right)^{M-m} \\ \cdot \frac{(M-m)!}{(M-m-n_{N+1})! n_{N+1}!} \frac{\left(\frac{\frac{M}{\lambda} e^{-\phi_{N+1}}}{\frac{M}{\lambda} e^{-\phi_0}}\right)^{n_{N+1}} (1)^{M-m-n_{N+1}}}{\left(1 + \frac{\frac{M}{\lambda} e^{-\phi_{N+1}}}{\frac{M}{\lambda} e^{-\phi_0}}\right)^{M-m}}$$

where the last line is the binomial distribution for $M-m$ trials and so its sum over n_{N+1} from 0 to $M-m$ equals 1.

Let \hat{n} be the vector of ions inside the channel, i.e. $\hat{n} = (n_1, \dots, n_N)$. The marginal density of the ions inside the channel, denoted by $\hat{\Pi}(\hat{n})$, can be obtained by summing over the number of ions at the baths:

$$\hat{\Pi}(\hat{n}) = \sum_{n_{N+1}=0}^{M-m} \Pi(\vec{n}) \quad (15) \\ = \frac{(M-m+1)(M-m+2) \dots (M-1)M}{M^m} \\ \cdot \frac{(e^{-\phi_1})^{n_1}}{n_1!} \dots \frac{(e^{-\phi_N})^{n_N}}{n_N!} \rho^m \\ \cdot \left(1 + \frac{1}{M} \rho (e^{-\phi_1} + \dots + e^{-\phi_N})\right)^{-M}$$

where

$$\rho = \lambda \left(\frac{1}{\exp(\phi_0)} + \frac{1}{\exp(\phi_{N+1})} \right)^{-1}$$

This equilibrium distribution of the ions inside the channel is restricted by the total number of ions since $0 \leq n_1 + \dots + n_N \leq M$. An open system, where an arbitrary number of ions can be inside the channel, can be obtained by letting the number of ions get very large. The equilibrium distribution of such a system, denoted by \mathcal{P} , can be obtained from (15) as

$$\mathcal{P}(\hat{n}) = \lim_{M \rightarrow \infty} \hat{\Pi}(\hat{n}) \quad (16) \\ = \left(\frac{(\rho e^{-\phi_1})^{n_1}}{n_1!} e^{-\rho e^{-\phi_1}} \right) \dots \left(\frac{(\rho e^{-\phi_N})^{n_N}}{n_N!} e^{-\rho e^{-\phi_N}} \right)$$

which is the distribution corresponding to N independent Poisson random variables with parameters $\rho \exp(-\phi_i)$. It also shows that the number of ions at site i can be considered to be the probabilistic thinning of a Poisson random variable with parameter ρ , where the thinning is due to the energy of each site.

It can be observed in (16) that there is a positive probability of $n_i > 0$ for at least some site $i \in \{1, \dots, N\}$. Therefore, the aggregation of a very large number of independent ions will contribute to having some ions inside the channel.

A choice of reversible transition rates for this process that are consistent with electro-diffusion theory is given by

$$q_{(n_1, \dots, n_N), (n_1-1, \dots, n_N)} = n_1 \frac{1}{2} e^{-\frac{1}{2}(\phi_0 - \phi_1)} \quad (17)$$

$$q_{(n_1, \dots, n_N), (n_1, \dots, n_N-1)} = n_N \frac{1}{2} e^{-\frac{1}{2}(\phi_{N+1} - \phi_N)} \quad (18)$$

$$q_{(n_1, \dots, n_N), (n_1+1, \dots, n_N)} = \frac{\rho e^{-\phi_0}}{\lambda} \frac{1}{2} \lambda e^{-\frac{1}{2}(\phi_1 - \phi_0)} \quad (19)$$

$$q_{(n_1, \dots, n_N), (n_1, \dots, n_N+1)} = \frac{\rho e^{-\phi_{N+1}}}{\lambda} \frac{1}{2} \lambda e^{-\frac{1}{2}(\phi_N - \phi_{N+1})} \quad (20)$$

and for $j \in \{i-1, i+1\}$

$$q_{(n_1, \dots, n_i, n_j, \dots, n_N), (n_1, \dots, n_i-1, n_j+1, \dots, n_N)} = n_i \frac{1}{2} e^{-\frac{1}{2}(\phi_j - \phi_i)} \quad (21)$$

All these transition rates are proportional to the corresponding transition rates between sites in the individual ion processes. This is not surprising since this process is simply the aggregation of independent ions.

Notice that the proportionality constants for the exit rates, (17) and (18), and the rates of ion movement between sites inside the channel, (21), is the number of ions at the corresponding site. However, the proportionality constants for the entrance rates of ions into the channel, (19) and (20), are given by $\rho e^{-\phi_i}$ and are independent of the channel state \hat{n} . This can be interpreted as having constant concentrations $\rho e^{-\phi_i}$ at the baths.

It can also be noticed by rearranging (19) and (20) that the entrance rates at both ends are affected by changes in the transmembrane energy $\phi_{N+1} - \phi_0$. This is very reasonable in order to preserve reversibility under changes in the driving force.

The equilibrium distribution of this infinite ion system can be expressed in terms of an energy function V as

$$\mathcal{P}(\hat{n}) = \hat{c} \exp(-V(\hat{n}))$$

where the energy function is given by

$$V(\hat{n}) = \sum_{i=1}^N n_i \phi_i - (\ln \rho) \sum_{i=1}^N n_i + \sum_{i=1}^N \ln n_i! \quad (22)$$

and \hat{c} is the normalizing constant

$$\hat{c} = \exp(-\rho(\exp(-\phi_1) + \dots + \exp(-\phi_N)))$$

The first summation in (22) comes from the energy at each site for individual ion processes. The second summation's effect is to discourage channel occupancy. The third summation comes from the indistinguishability of the ions, and perhaps should not be considered part of the energy function, but rather as a normalizing factor as is done in the grand canonical ensembles of statistical mechanics.

It is established in Section II-B that the single ion trans paths from left to right are equivalent in distribution to those from right to left. Since there is no interaction between ions in the model of this section, the trans path equivalence still holds. This is true independently of the concentrations on either side of the channel. Furthermore, it is not necessary for the system to be in equilibrium for the equivalence to be present.

The equilibrium distribution of an infinite ion system has been presented in the case where there is no interaction between ions. This distribution has also been expressed in terms of an energy function, which will be modified in the next section to account for interaction between ions.

IV. INTERACTION MODELS

Section III presents a model that arises from the infinite ion limit of a closed system, and it also presents its equilibrium distribution in terms of an energy function V . The assumption of no interaction between ions made it possible to easily obtain the joint distribution of a finite number of ions.

It is assumed in this section that there is interaction between ions but that it occurs only inside the channel, not in the baths. This is reasonable since the baths are assumed to be large and rapidly mixing. Let $\psi_{i,j}$ denote the interaction energy between an ion at site i and an ion at site j , which can be of due to Coulomb or Lennard-Jones potentials, for example. It is assumed that this energy function is symmetric, i.e. $\psi_{i,j} = \psi_{j,i}$.

This section incorporates the interaction directly into the energy function of the infinite ion model in two different ways. First, Section IV-A presents the *doormat* model, which assumes the existence of an interaction-free entrance site between the baths and the channel. Then, Section IV-B presents the *floor*mat model, which assumes that ions jump directly from the baths into the channel. The nomenclature for this interaction models tries to make an analogy to the difference between a doormat, which is placed right before a door, and the floormat, which is placed right after a door. In the models presented in this section, the mat is the site where ions enter the channel and the door is the imaginary line between sites with and without interaction.

The reversibility of both of these models imply that the trans paths from left to right are equivalent in distribution to those from right to left, but only under the assumption that the entire system is in equilibrium. This assumption is not necessary for the model of Section III, which did not account for interaction between ions. However, this does not imply that rates that do not satisfy the reversibility conditions prevent the system from reaching an equilibrium. Equilibrium could be reached with rates that do not satisfy the reversibility conditions, but it will not be the equilibrium corresponding to the specified energy function and there will be no equivalence in distribution between the left to right trans paths and those from right to left. This is discussed in Section V.

A. Doormat model

The doormat model assumes that ions do not enter the channel directly from the baths. They go from the baths into entrance sites where there is no interaction between ions, and then from there they can enter the channel, where there is interaction.

Let sites 1 and N be the left and right interaction-free entrance sites, respectively. Then, the interaction is incorporated into the energy function (22) at sites $2, \dots, N-1$ to obtain

$$\begin{aligned} V(\hat{n}) = & \sum_{i=1}^N n_i \phi_i - (\ln \rho) \sum_{i=1}^N n_i + \sum_{i=1}^N \ln n_i! \\ & + \frac{1}{2} \sum_{\substack{i,j=2 \\ i \neq j}}^{N-1} n_i n_j \psi_{i,j} + \frac{1}{2} \sum_{i=2}^{N-1} n_i (n_i - 1) \psi_{i,i} \end{aligned}$$

The detailed balance condition for reversibility with this energy function again allows for infinite choices of transition rates. However, it is desired to preserve consistency with the Nernst-Planck electro-diffusion model and with the individual

ion processes. A choice of rates with this characteristics is given by

$$q_{(n_1, \dots, n_i, n_j, \dots, n_N), (n_1, \dots, n_{i-1}, n_{j+1}, \dots, n_N)} = n_i \frac{1}{2} \cdot \exp \left(-\frac{1}{2} (\phi_j - \phi_i + (n_i - 1 - n_j) \psi_{i,j} + n_j \psi_{j,j} - (n_i - 1) \psi_{i,i} + \sum_{\substack{k=2 \\ k \neq i,j}}^{N-1} n_k (\psi_{k,j} - \psi_{k,i})) \right) \quad (23)$$

for $j \in \{i-1, i+1\}$.

The transition rates for ions moving inside the channel, (23), depend on the channel state. This is because there is interaction between the moving ion and the rest of ions inside the channel. The interaction-free characteristic of site 0 and N indicate that $\psi_{1,j} = \psi_{N,j} = 0$.

However, the rates in and out of the baths are the same as the entrance and exit rates for the no interaction model (17), (18), (19) and (20). These rates do not depend on the channel state because there is no interaction between the incoming, or departing, ion and the ions that are already inside the channel.

The interaction-free characteristic of the entrance sites is also responsible for the distribution of the number of ions at those sites being independent of the interaction between the ions inside the channel.

B. Floormat model

The floormat model assumes that ions enter the channel, where there is interaction between ions, directly from the baths.

The interaction between ions is incorporated into the energy function (22) at all sites to obtain

$$V(\hat{n}) = \sum_{i=1}^N n_i \phi_i - (\ln \rho) \sum_{i=1}^N n_i + \sum_{i=1}^N \ln n_i! + \frac{1}{2} \sum_{\substack{i,j=1 \\ i \neq j}}^N n_i n_j \psi_{i,j} + \frac{1}{2} \sum_{i=1}^N n_i (n_i - 1) \psi_{i,i}$$

The detailed balance condition for reversibility with this energy function again allows for infinite choices of transition rates. A choice of reversible transition rates that are consistent with electro-diffusion theory and with the individual ion processes are given by

$$q_{(n_1, \dots, n_N), (n_1+1, \dots, n_N)} = \frac{\rho e^{-\phi_0}}{\lambda} \frac{1}{2} \lambda \exp \left(-\frac{1}{2} \left(\phi_1 - \phi_0 + \sum_{i=2}^N n_i \psi_{1,i} \right) \right) \quad (24)$$

$$q_{(n_1, \dots, n_N), (n_1, \dots, n_{N+1})} = \frac{\rho e^{-\phi_{N+1}}}{\lambda} \frac{1}{2} \lambda \exp \left(-\frac{1}{2} \left(\phi_N - \phi_{N+1} + \sum_{i=1}^{N-1} n_i \psi_{N,i} \right) \right) \quad (25)$$

$$q_{(n_1, \dots, n_N), (n_1-1, \dots, n_N)} = n_1 \frac{1}{2} \exp \left(-\frac{1}{2} \left(\phi_0 - \phi_1 - \sum_{i=2}^N n_i \psi_{1,i} \right) \right) \quad (26)$$

$$q_{(n_1, \dots, n_N), (n_1, \dots, n_{N-1})} = n_N \frac{1}{2} \exp \left(-\frac{1}{2} \left(\phi_{N+1} - \phi_N - \sum_{i=1}^{N-1} n_i \psi_{N,i} \right) \right) \quad (27)$$

The entrance rates into the channel, (24) and (25), depend on the channel state because of the interaction of the incoming ion and the ions that are already inside the channel. The exit rates, (26) and (27), also depend on the channel state because of the interaction between the departing ion and the rest of the ions inside the channel.

The rates inside the channel are the same as those in the doormat model, (23), except that the summation goes from 1 to N instead of from 2 to $N-1$ since in this case there is interaction with ions at sites 1 and N .

V. EFFECTS OF SYSTEM PARAMETERS

This section discusses the effects of some of the system parameters of the doormat model on the trans path distribution. A channel of length $L_c = 1 \times 10^{-8} m$ is considered with a space scaling $\Delta x = L_c/(N+1)$ and time scaling $\Delta t = (\Delta x)^2/(2D)$, where D is the diffusion coefficient which is assumed to be $1 \times 10^{-9} m^2/s$.

It is assumed that the interaction energy is due to Coulomb potentials, i.e.

$$\psi(x, y) = \frac{(Ze)^2}{4\pi\epsilon_r\epsilon KT} \frac{1}{|x-y|}$$

where Z is the ion valence assumed to be $+1$ for Na^+ in this case, e is the proton charge number $\approx 1.602 \times 10^{-19} C$, ϵ_r is the relative permittivity of the medium, K is Boltzmann's constant $\approx 1.381 \times 10^{-23} \frac{J}{\circ K}$, T is the absolute temperature which is assumed to be $298 \text{ }^\circ K$ and x, y are the distances of the two ions from the left bath.

Let the energy be due to a linear electric potential given by

$$\phi(x) = \frac{Ze V_m}{KT L_c} x$$

where V_m is the trans-membrane potential, i.e. $V_m = V_{inside\ cell} - V_{outside\ cell}$, in units of *Volts*.

Throughout this section, the transition rates are as indicated in Section IV-A, the relative permittivity is assumed to be that of water (≈ 80) and the trans-membrane potential is assumed to be $-70 \times 10^{-3} V$, unless indicated otherwise.

It was observed in our simulations that larger trans-membrane potentials reduce the time it takes an ion to cross the channel. This is not surprising since larger trans-membrane potentials generate larger driving forces on the ions. It was also observed that the distribution of both types of trans paths are equivalent. This was expected since the entrance rates corresponding to reversibility were used.

Consider the effect of interaction strength. Figure 1 presents the distribution of the trans paths under three different interaction strengths. The interaction strength can be increased by reducing the relative permittivity, and it can be decreased by increasing the relative permittivity. The limit $\epsilon_r \rightarrow \infty$ would correspond to the case without interaction. Relative permittivities below that of water would correspond to channels that are so narrow that there are gaps between water molecules. It can be observed that the interaction strength does not have a monotonic effect on the time for ion crossing. At first glance it seems surprising that higher interaction strength

would yield faster transit times, but this is due to the fact that as the interaction strength increases, ions are discouraged from entering the channel and the system looks more like a single ion channel. The left plot corresponds to the distribution of the left to right trans paths and the right plot corresponds to the distribution of the right to left trans paths. Notice that the distribution of both types of trans paths are equivalent.

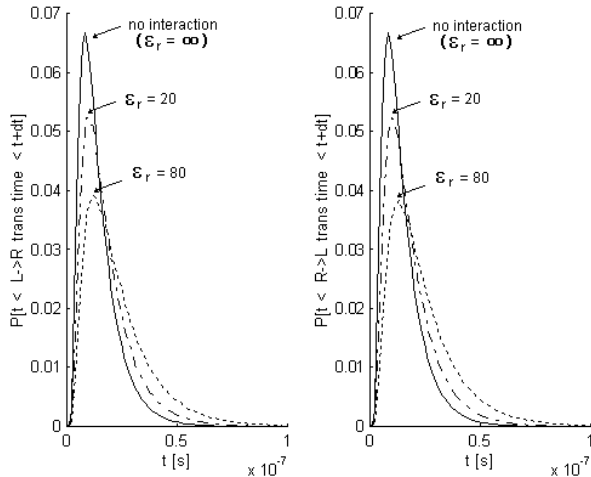


Fig. 1. Effect of interaction strength on trans path distribution, $dt = 1 \times 10^{-9}$ s.

So far, the entrance rates, $q_{(n_1, \dots, n_N), (n_1+1, \dots, n_N)}$ and $q_{(n_1, \dots, n_N), (n_1, \dots, n_N+1)}$, have been assumed to be those that preserve the reversibility of the system. Consider now the effect of entrance rates away from reversibility conditions. Figure 2 presents the distribution of the trans paths under four different entrance rate pairs. The notation (a, b) indicates that the entrance rate from the left bath is scaled by a factor a and the entrance rate from the right bath is scaled by a factor b . The left plot corresponds to the distribution of the left to right trans paths and the right plot corresponds to the distribution of the right to left trans paths. It can be observed that if the ratio of both entrance rates is equal to that of the reversible entrance rates, e.g. case $(5, 5)$, then the distribution of both types of trans paths are equivalent. However, as the rates increase, the transit times slow down. Notice also that an imbalance in the ratios of the entrance rates, e.g. $(1, 5)$, causes the inequality of the trans path distribution. This is not surprising since this imbalance will be bias the system.

VI. CONCLUSION

Three different models for ion channels have been presented. The model with no interaction between ions is very unrealistic but can still provide some insight into the behavior of this type of biological system. It also serves as a starting point for more realistic models, which do include interaction between ions like the ones presented in Sections IV-B and IV-A. Each of the two models with interaction has its advantages and disadvantages, and they should be investigated further to realize their applicability for analysis of properties of this type of biological systems.

The reversibility of these three models is helpful in their analysis and contributes to a better understanding of ion channels. For example, it explains an interesting phenomenon observed by biophysicists, that the distribution of transit time

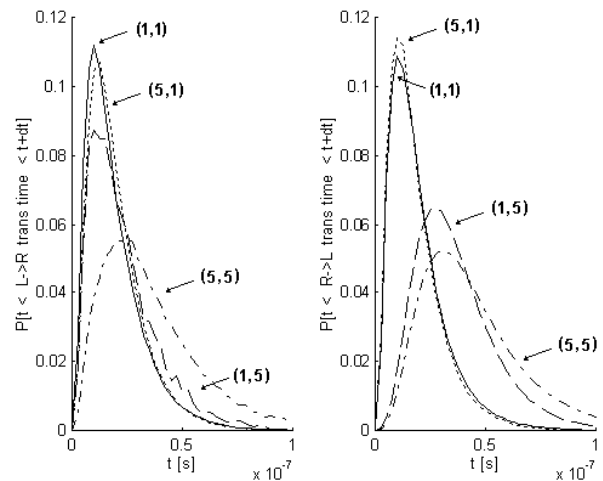


Fig. 2. Effect of entrance rates on trans path distribution, $dt = 2.5 \times 10^{-9}$ s.

needed for ions to transit an ion channel is the same in either direction, even if there is an electric potential difference across the channel.

It is shown that the reversibility of the single ion process implies that its trans paths from left to right and those from right to left are equivalent in distribution. It is also discussed that this equivalence holds in the model with no interaction and that it holds for the reversible models with interaction, but only under the assumption that the entire system is in equilibrium. If rates that do not satisfy the reversibility conditions are used in the interaction models, equilibrium could be reached, but it will not be the equilibrium corresponding to the specified energy function and there will be no equivalence in distribution between the left to right trans paths and those from right to left. Future work is aimed at investigating how the implications of reversibility of paths for a system in equilibrium can be extended to a system without such equilibrium.

A discretized procedure that preserves the reversibility of these processes is presented for a constant diffusion coefficient. A similar procedure can be used when the diffusion coefficient is spatially varying. This can be found in the forthcoming thesis of the first author of this paper.

REFERENCES

- [1] R.S. Eisenberg, M.M. Klosek and Z. Schuss, "Diffusion as a chemical reaction: Stochastic trajectories between fixed concentrations," *J. Chem. Phys.*, vol. 102 (4), pp. 1767-1780, 1995.
- [2] Bob Eisenberg, "Ionic channels in biological membranes-electrostatic analysis of a natural nanotube," *Contemporary Physics*, vol. 39 (6), pp. 447-466, 1998.
- [3] B. Hille, *Ionic Channels of Excitable Membranes*, 2nd edn. Sinauer Associates Inc., 1992.
- [4] Eric Jakobsson and See-Wing Chiu, "Stochastic theory of ion movement in channels with single-ion occupancy: Application to sodium permeation of gramicidin channels," *Biophys. J.*, vol. 52, pp. 33-45, 1987.
- [5] John Kent, "Time-reversible diffusions," *Adv. Appl. Prob.*, vol. 10, pp. 819-835, 1978.
- [6] David G. Levitt, "General continuum theory for multiion channel. I. Theory" *Biophys. J.*, vol. 59, pp. 271-277, 1991.
- [7] J.R. Norris, *Markov Chains*, Cambridge University Press, 1999.
- [8] Z. Schuss, B. Nadler and R.S. Eisenberg, "Derivation of Poisson and Nernst-Planck equations in a bath and channel from a molecular model," *Physical Review E*, vol. 64, pp. 036116-1 - 036116-14, 2001.