Reversible Markov Chain Models for Ion Channels and Equivalence of Trans Paths

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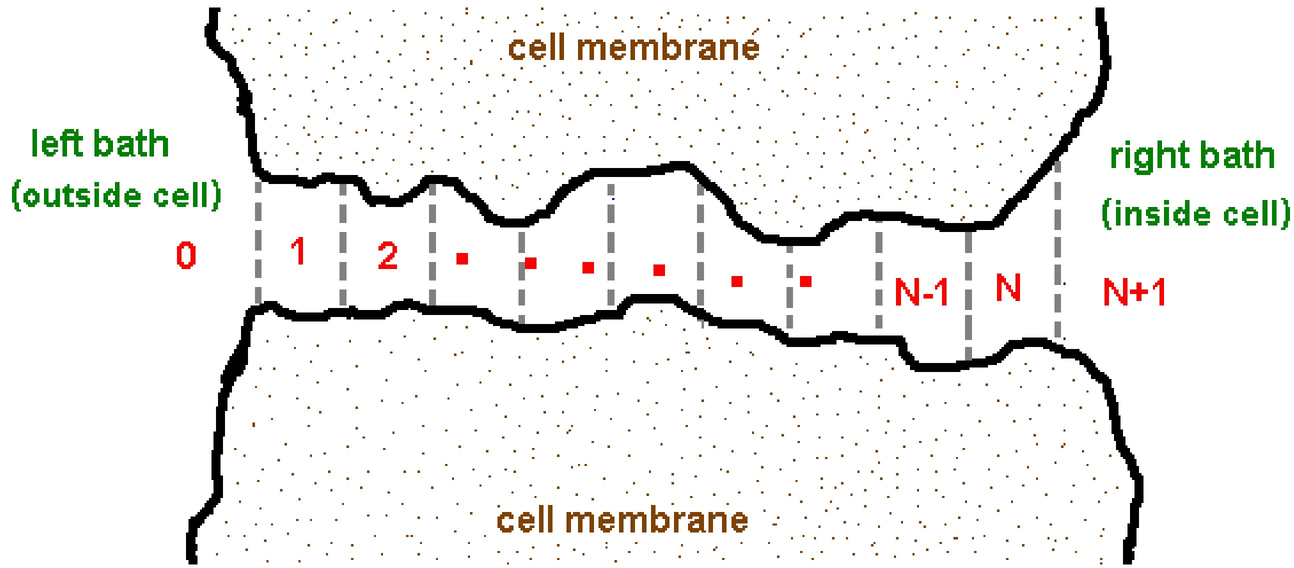
General description

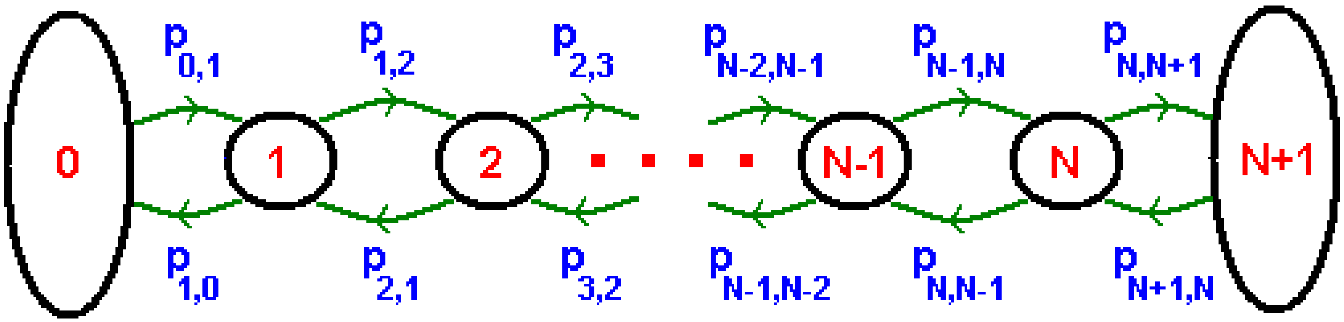
- Transport of ions between the interior and the exterior of the cell takes place through channels formed by proteins

- Divide the channel into N sites labeled $1, \ldots, N$ and consider the left and right baths as sites 0 and $N+1$, respectively.

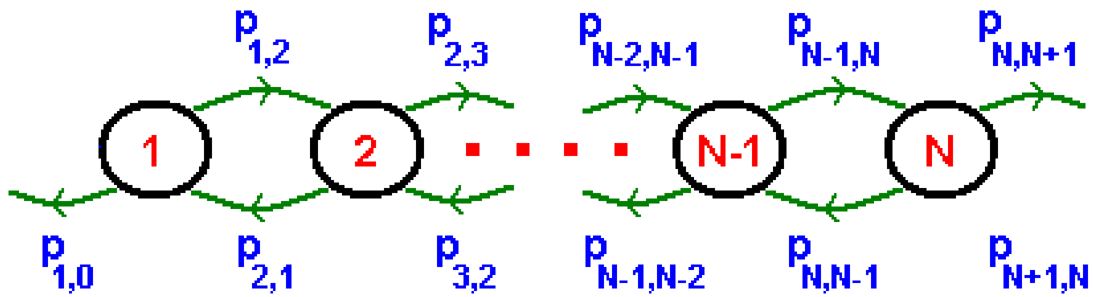


Single ion

- Closed model: conservative birth-death process

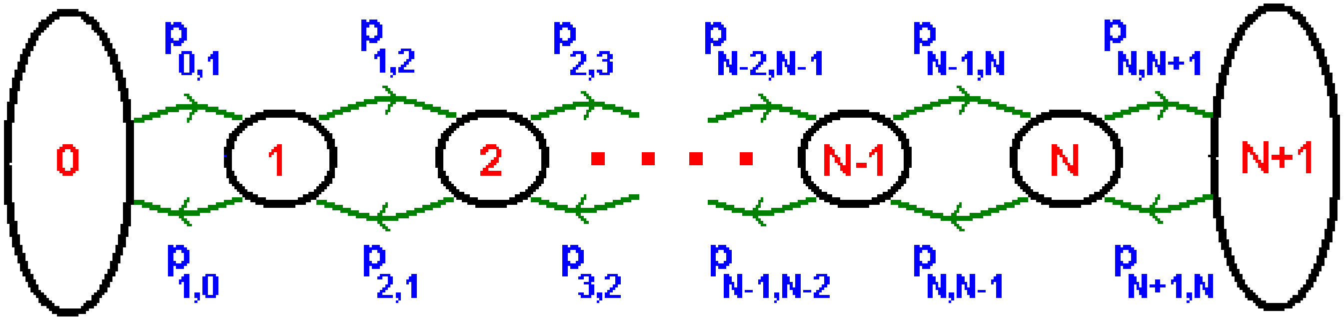


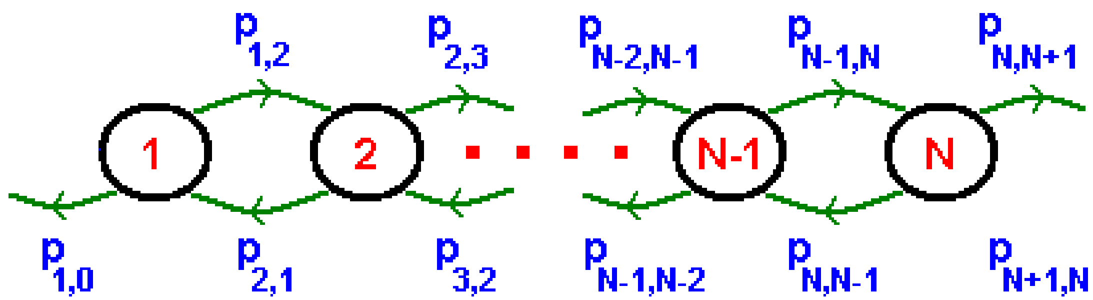
- Open model: birth-death process killed at the boundaries



Single ion - Equivalence of trans paths

- A *trans* path is a path that starts at a boundary and ends at the other boundary
- Reversibility





Single ion - Equivalence of trans paths

- $\mathcal{V} - symmetry$
  - $\mathcal{V}_i p_{i,j} = \mathcal{V}_j p_{j,i}$ for all $i, j \in \{1, \ldots, N\}$
- For birth-death process

$$\mathcal{V}_i \ := \begin{cases} 1 & i = 1 \\ \dfrac{p_{1,2} p_{2,3} \cdots p_{i-2,i-1} p_{i-1,i}}{p_{i,i-1} p_{i-1,i-2} \cdots p_{3,2} p_{2,1}} & i \in \{2, \ldots, N\} \end{cases}$$

Markov chains associated to reversible diffusion processes

- An m-dimensional diffusion with generator $\mathcal{L}$ is said to be $v - symmetric$ with respect to a strictly positive twice differentiable function v if for all twice differentiable functions p

$$v\mathcal{L}p \;=\; \mathcal{L}^*(vp)$$

- If the diffusion process is $v - symmetric$ with equilibrium distribution $v := \alpha \exp(-u)$ and with diffusion matrix field D, then its drift vector field is given by
  - $\mu \;=\; -\,D \cdot \nabla u \;+\; (\nabla \cdot D)^T$, when $\mathcal{L}$ is given in Itô form
  - $\mu \;=\; -\,D \cdot \nabla u$, when $\mathcal{L}$ is given in Stratonovich form

Markov chains associated to reversible diffusion processes

- Given a reversible diffusion process $\widehat{W}$, a sequence of Markov chains $\left\{\widehat{X}^N\right\}_{N\in\mathbb{N}}$ is said to be associated to $\widehat{W}$ if:
  - $\widehat{X}^N \Rightarrow \widehat{W}$ where "$\Rightarrow$" denotes convergence in distribution as $N \to \infty$.
  - $\widehat{X}^N$ is reversible and has the same equilibrium distribution (within discretization constraints) as $\widehat{W}$ for each N.

Markov chains associated to reversible diffusion processes

- Consider a one-dimensional reversible diffusion $\widehat{W}$ on $[0, L_c]$ with equilibrium distribution $v(x) = \alpha \exp(-u(x))$ and diffusion coefficient $D(x) > 0$

- For $i, j \in \{1, \ldots, N\}$, let
  - $\Delta x = \frac{L_c}{N}$
  - $U_i = u(i\Delta x)$
  - $D_i = D(i\Delta x)$
  - Δt be such that $\frac{(\Delta x)^2}{\Delta t} \quad \rightarrow \quad G \geq \max_{x \in [0, L_c]} 2D(x)$, as $\Delta x, \Delta t \rightarrow 0$
  - for $j \in \{i-1, i+1\}$

$$p_{i,j} \;=\; \frac{\Delta t}{(\Delta x)^2} \, \frac{D_i + D_j}{2} \exp\left(-\frac{1}{2}(U_j - U_i)\right)$$

- We get a sequence (in N) of Markov chains associated to $\widehat{W}$

Multiple non-interacting ions

- Consider a closed continuous time birth-death process on $i \in \{0, \ldots, N+1\}$
- For $i, j \in \{0, \ldots, N+1\}$, let $\Delta x = \frac{L_c}{N}$, $U_i = u(i\Delta x)$, and $D_i = D(i\Delta x)$
- Let

$$\begin{aligned}
q_{i,j} &= \frac{D_i + D_j}{2} e^{-\frac{1}{2}(U_j - U_i)}, \qquad for|i-j| = 1,\ i \neq \{0, N+1\} \\
q_{0,1} &= \frac{1}{M} \frac{D_0 + D_1}{2} e^{-\frac{1}{2}(U_1 - U_0)} \\
q_{N+1,N} &= \frac{1}{M} \frac{D_{N+1} + D_N}{2} e^{-\frac{1}{2}(U_N - U_{N+1})}
\end{aligned}$$

- $q_{i,j} = 0$ for all other $i \neq j$.
- $q_{i,i} \;=\; -(q_{i,i-1} + q_{i,i+1})$

Multiple non-interacting ions

- The equilibrium distribution is

$$\pi \; = \; \frac{1}{\alpha}\left(Me^{-U_0}\;,\; e^{-U_1}\;,\;\ldots\;,\; e^{-U_N}\;,\; Me^{-U_{N+1}}\right)$$

- Process is $\pi - symmetric$
  - Distribution of trans paths from left to right is equal to that of the time-reversed trans paths from right to left

- Diffusion limit corresponds to an electrodiffusion process with diffusion coefficient $D(x)$ and drift $\tilde{\mu}(x) = -\, D(x)\frac{du(x)}{dx}$

Multiple non-interacting ions - Closed model

- Let there be M independent ions in the system
- Let $n_i \in \{0, \ldots, M\}$ be the number of ions at site i
- Let $\vec{n} = (n_0 \ , \ \ldots \ , \ n_{N+1})$
- The rates at which ions jump from one site to the other are

$$q_{(n_1,\ldots,n_i,n_j,\ldots,n_N),(n_1,\ldots,n_i-1,n_j+1,\ldots,n_N)} \ = \ n_i \ q_{i,j}$$

- The joint equilibrium distribution of the ions is

$$\Pi(\vec{n}) \ = \ \binom{M}{n_0 \cdots n_{N+1}} (\pi_0)^{n_0} \ldots (\pi_{N+1})^{n_{N+1}}$$

Multiple non-interacting ions - Open model

- Denote the total number of ions inside the channel, not at the baths, by $a = n_1 + \ldots + n_N$

- Let $\widehat{n} = (n_1\ ,\ \ldots\ ,\ n_N)$

- The marginal distribution of the ions inside the channel, denoted by $\widehat{\Pi}$, is given by

$$\widehat{\Pi}(\widehat{n}) \;=\; \binom{M}{n_1 \cdots n_N \;\; M-a} (\pi_1)^{n_1} \ldots (\pi_N)^{n_N} \, (\pi_0 + \pi_{N+1})^{M-a}$$

- Let the number of ions get very large, i.e., let $M \to \infty$

Multiple non-interacting ions - Open model

- The rates at which ions jump from one site to the other inside the channel are

$$q_{(n_1,\ldots,n_i,n_j,\ldots,n_N),(n_1,\ldots,n_i-1,n_j+1,\ldots,n_N)} = n_i \; q_{i,j}$$

- The exit rates from the channel into the baths are given by

$$\begin{aligned} q_{(n_1,\ldots,n_N),(n_1-1,\ldots,n_N)} &= n_1 \; q_{1,0} \\ q_{(n_1,\ldots,n_N),(n_1,\ldots,n_N-1)} &= n_N \; q_{N,N+1} \end{aligned}$$

- The entrance rates from the baths into the channel are given by

$$q_{(n_1,\ldots,n_N),(n_1+1,\ldots,n_N)} = \lim_{M\to\infty} M\pi_0 q_{0,1}$$

$$q_{(n_1,\ldots,n_N),(n_1,\ldots,n_N+1)} = \lim_{M\to\infty} M\pi_{N+1} q_{N+1,N}$$

Multiple non-interacting ions - Open model

- The equilibrium distribution of this open model, denoted by $\mathcal{P}$, is

$$\mathcal{P}(\widehat{n}) \;=\; \frac{1}{Z}\,\frac{\rho^{n_1+\cdots+n_N}}{n_1!\cdots n_N!}\,e^{-V(\widehat{n})}$$

- where

$$\rho \;:=\; \left(e^{-U_0}+e^{-U_{N+1}}\right)^{-1}$$

$$V(\widehat{n}) \;:=\; \sum_{i=1}^{N} n_i U_i$$

$$Z \;:=\; \sum_{\substack{j,n_1,\ldots,n_N=0:\\ n_1+\cdots+n_N=j}}^{\infty} \frac{1}{n_1!\cdots n_N!}e^{-V(\widehat{n})}\rho^j \;=\; \exp\left(\rho\left(e^{-U_1}+\ldots+e^{-U_N}\right)\right)$$

Multiple non-interacting ions - Open model

- The transition rates can be rewritten as

$$q_{\widehat{n}_i,\widehat{n}_j} \;=\; n_i \, \frac{D_i + D_j}{2} \, e^{-\frac{1}{2}\left(V(\widehat{n}_j) - V(\widehat{n}_i)\right)}$$

$$q_{(n_1,\ldots,n_N),(n_1-1,\ldots,n_N)} \;=\; n_1 \, e^{-\frac{1}{2}U_0} \, \frac{D_1 + D_0}{2} \, e^{-\frac{1}{2}(V((n_1-1,\ldots,n_N)) - V((n_1,\ldots,n_N)))}$$

$$q_{(n_1,\ldots,n_N),(n_1+1,\ldots,n_N)} \;=\; \rho \, e^{-\frac{1}{2}U_0} \, \frac{D_0 + D_1}{2} \, e^{-\frac{1}{2}(V((n_1+1,\ldots,n_N)) - V((n_1,\ldots,n_N)))}$$

- The transition rates are $\mathcal{P} - symmetric$

- Distribution of trans paths from left to right is equal to that of the time-reversed trans paths from right to left

Multiple interacting ions

- The ion-to-ion interaction is incorporated into the energy function

$$V(\widehat{n}) \; = \; \sum_{i=1}^{N} n_i U_i + \; \frac{1}{2} \sum_{\substack{i,j=1 \\ i \neq j}}^{N} n_i n_j \psi_{i,j} \; + \; \frac{1}{2} \sum_{i=1}^{N} n_i (n_i - 1) \psi_{i,i}$$

- Remember the transition rates for a single ion:

$$q_{i,j} \; = \; \frac{D_i + D_j}{2} e^{-\frac{1}{2}(U_j - U_i)}$$

  - Diffusion limit has drift function $\tilde{\mu}(x) = -D(x) \frac{du(x)}{dx}$

- Identify V, as a function of the position of one ion with all the other ions fixed, with U

Multiple interacting ions

- Then, when the system state in this interacting model is $\widehat{n}_i = (n_1, \ldots, n_{i-1}, n_i, n_{+1}, \ldots, n_N)$, the jump of a single ion from site i to site $j \in \{i \pm 1\}$ causes an energy difference $V(\widehat{n}_j) - V(\widehat{n}_i)$

- The transition rates are

$$q_{\widehat{n}_i,\widehat{n}_j} \;=\; n_i \, \frac{D_i + D_j}{2} \, e^{-\frac{1}{2}\left(V(\widehat{n}_j) - V(\widehat{n}_i)\right)}$$

$$q_{(n_1,\ldots,n_N),(n_1-1,\ldots,n_N)} \;=\; n_1 \, e^{-\frac{1}{2}U_0} \, \frac{D_1 + D_0}{2} \, e^{-\frac{1}{2}(V((n_1-1,\ldots,n_N)) - V((n_1,\ldots,n_N)))}$$

$$q_{(n_1,\ldots,n_N),(n_1+1,\ldots,n_N)} \;=\; \rho \, e^{-\frac{1}{2}U_0} \, \frac{D_0 + D_1}{2} \, e^{-\frac{1}{2}(V((n_1+1,\ldots,n_N)) - V((n_1,\ldots,n_N)))}$$

Multiple interacting ions

- The transition rates are $\mathcal{P} - symmetric$

$$\mathcal{P}(\widehat{n}) \;=\; \frac{1}{Z}\,\frac{\rho^{n_1+\cdots+n_N}}{n_1!\cdots n_N!}\;e^{-V(\widehat{n})}$$

- Distribution of trans paths from left to right is equal to that of the time-reversed trans paths from right to left

- One can infer that the local drift experienced by an individual ion in the diffusion limit of this open interacting model is proportional to the gradient of the energy, with the other ions considered to be fixed, times the diffusion coefficient

- This interpretation relies on the fact that in these continuous time models only one ion jumps at a time.

Multiple interacting ions - Numerical results

- Channel length $L_c = 1 \times 10^{-8}$ m
- Space homogeneous diffusion coefficient $D = 1 \times 10^{-9}\ \mathrm{m}^2/\mathrm{s}$
- Space scaling $\Delta x = \frac{L_c}{N}$
- Time scaling $\Delta t = \frac{(\Delta x)^2}{2D}$
- Interaction energy is due to Coulomb potentials

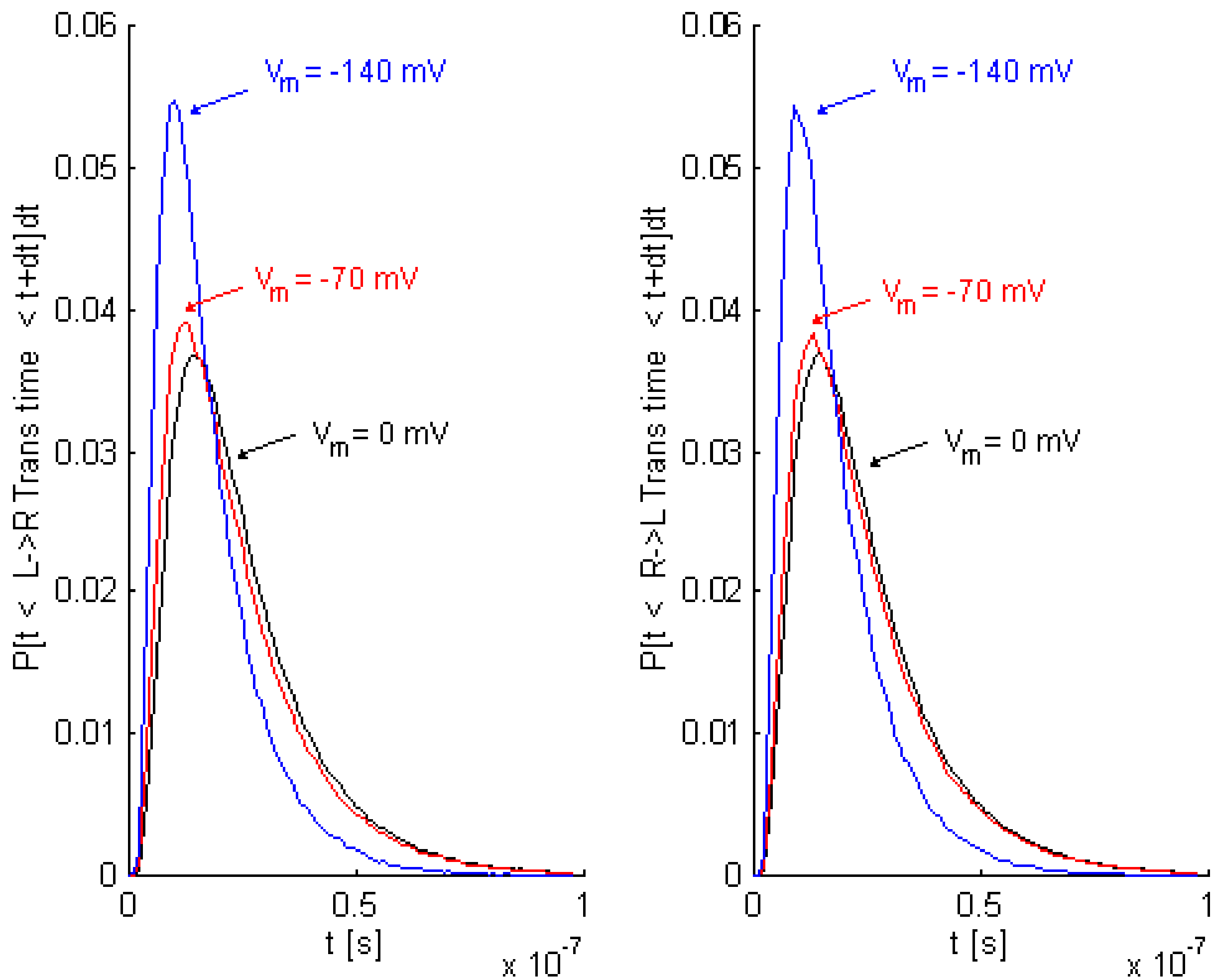
$$\psi(x, y) = \frac{(Ze)^2}{4\pi\epsilon_r\epsilon k_B T} \frac{1}{|x - y|}$$

- Z is the ion valence, assumed to be $+1$
- T is the absolute temperature, assumed to be $298\ \mathrm{K}$
- ϵ_r is the relative permittivity of the medium, assumed to be 80
- Energy U be due to a linear electric potential

$$U(x) \ = \ \frac{Ze}{k_B T}\frac{V_m}{L_c}\, x$$

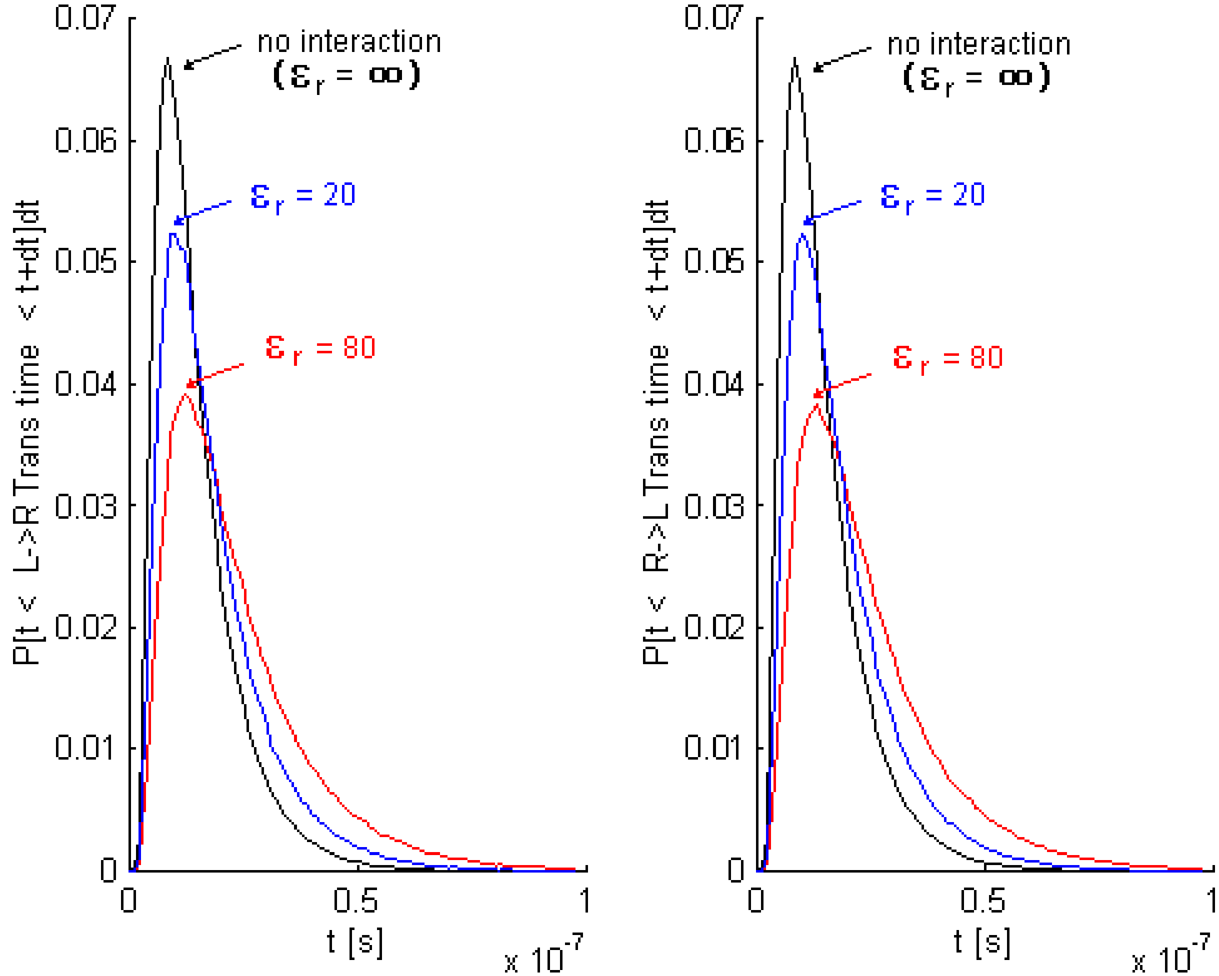
- V_m is the transmembrane electric potential, i.e., $V_m = V_{\{inside\ cell\}} - V_{\{outside\ cell\}}$, in units of volts, assumed to be $-70 \times 10^{-3}\ \mathrm{V}$

Effect of transmembrane potential



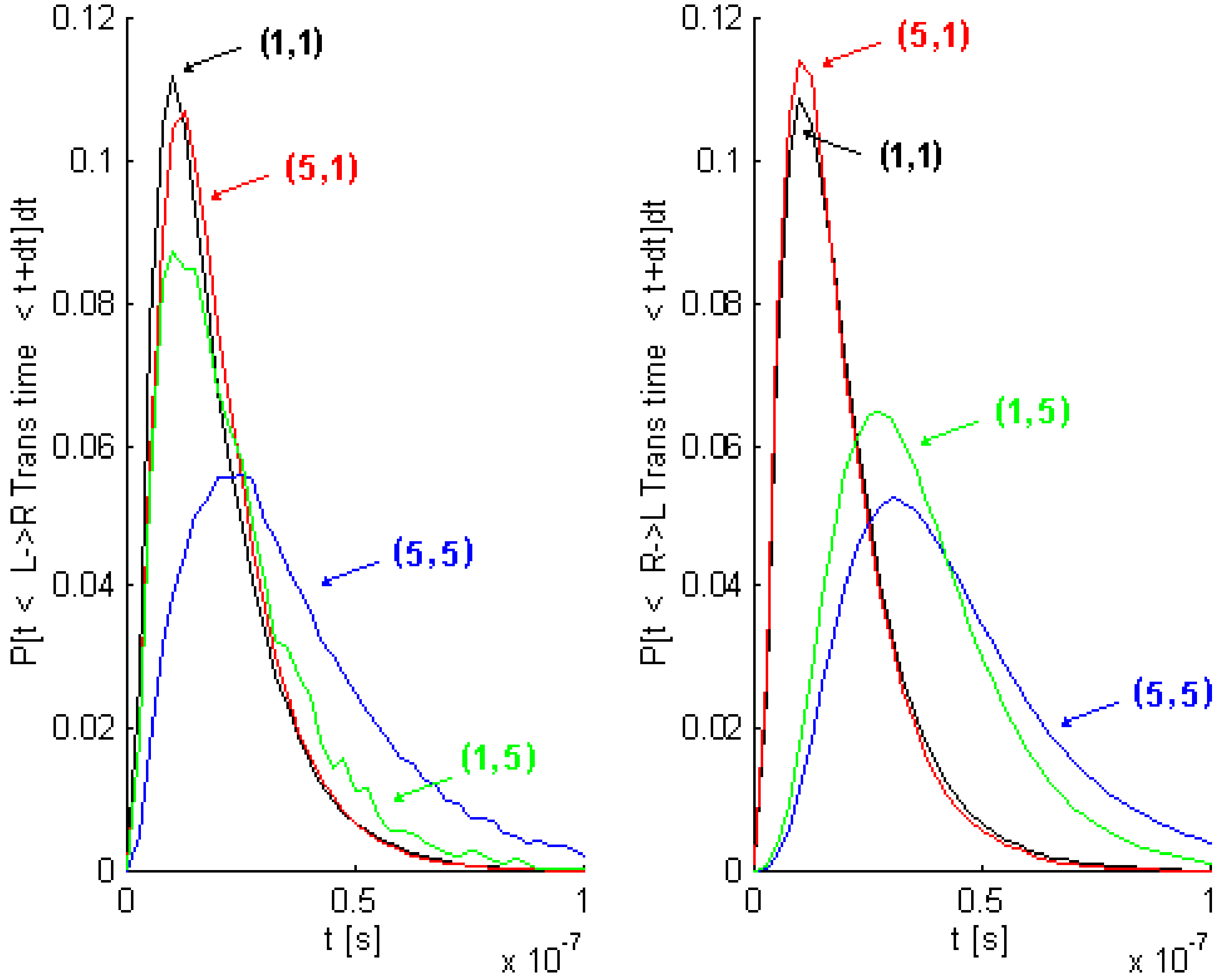
$D = 1 \times 10^{-9}\ m^2/s$ **$L_c = 1 \times 10^{-8}\ m$** **$dt = 1 \times 10^{-9}\ s$** **$\varepsilon_r = 80$**

Effect of Coulomb interaction strength



$D = 1 \times 10^{-9}\ m^2/s$ $L_c = 1 \times 10^{-8}\ m$ $V_m = -70 \times 10^{-3}\ V$ $dt = 1 \times 10^{-9}\ s$

Effect of entrance rates



$D = 1 \times 10^{-9}\ m^2/s$ $L_c = 1 \times 10^{-8}\ m$ $V_m = -70 \times 10^{-3}\ V$ $dt = 2.5 \times 10^{-9}\ s$ $\varepsilon_r = 80$

Thanks.

Single ion - Equivalence of trans paths

- Let $\mathcal{S}_{LR}$ be the set of trans paths from left to right
- Let $\mathcal{S}_{RL}$ be the set of trans paths from right to left
- If γ in $\mathcal{S}_{LR}$ then $\gamma \;=\; (\gamma_0 = 1, \gamma_1, \ldots, \gamma_{m-1}, \gamma_m = N)$
- If γ in $\mathcal{S}_{RL}$ then $\gamma \;=\; (\gamma_0 = N, \gamma_1, \ldots, \gamma_{m-1}, \gamma_m = 1)$
- Define

$$P_{LR}[\gamma] \;:=\; P^1[(\gamma, N+1)|T_{N+1} < T_0] \;=\; \frac{P^1[\gamma]}{\sum_{\gamma\prime \in \mathcal{S}_{LR}} P^1[\gamma\prime]}$$

$$P_{LR}[\gamma] \;:=\; P^N[(\gamma, 0)|T_0 < T_{N+1}] \;=\; \frac{P^N[\gamma]}{\sum_{\gamma\prime \in \mathcal{S}_{RL}} P^N[\gamma\prime]}$$

Single ion - Equivalence of trans paths

- For any finite path $\gamma = (\gamma_0, \gamma_1, \ldots, \gamma_{m-1}, \gamma_m)$, define its time-reversed path $\gamma_{rev} = (\gamma_m, \gamma_{m-1}, \ldots, \gamma_1, \gamma_0)$

- $\gamma \in \mathcal{S}_{LR}$ implies that $\gamma_{rev} \in \mathcal{S}_{RL}$ and vice-versa

- The mapping of $\gamma \in \mathcal{S}_{LR}$ to γ_{rev} is a one-to-one and onto mapping of $\mathcal{S}_{LR}$ to $\mathcal{S}_{RL}$

- **Proposition :** For any $\gamma \in \mathcal{S}_{LR}$,

$$P_{LR}[\gamma] \;=\; P_{RL}[\gamma_{rev}]$$

Single ion - Equivalence of trans paths

- **Proposition :** For any $\gamma \in \mathcal{S}_{LR}$,

$$P_{LR}[\gamma] \;=\; P_{RL}[\gamma_{rev}]$$

  – *Sketch of proof:*

$$\frac{P^1[\gamma]}{P^N[\gamma_{rev}]} = \frac{p_{1,\gamma_1} p_{\gamma_1,\gamma_2} \cdots p_{\gamma_{m-2},\gamma_{m-1}} p_{\gamma_{m-1},N}}{p_{N,\gamma_{m-1}} p_{\gamma_{m-1},\gamma_{m-2}} \cdots p_{\gamma_2,\gamma_1} p_{\gamma_1,1}} = \frac{\mathcal{V}_N}{\mathcal{V}_1}$$

$$\begin{aligned} P_{LR}[\gamma] &= \frac{P^1[\gamma]}{\sum_{\gamma\prime \in \mathcal{S}_{LR}} P^1[\gamma\prime]} = \frac{\frac{\mathcal{V}_N}{\mathcal{V}_1} P^N[\gamma_{rev}]}{\sum_{\gamma\prime \in \mathcal{S}_{LR}} \frac{\mathcal{V}_N}{\mathcal{V}_1} P^N[\gamma\prime_{rev}]} = \frac{P^N[\gamma_{rev}]}{\sum_{\gamma\prime \in \mathcal{S}_{RL}} P^N[\gamma\prime_{rev}]} \\ &= P_{RL}[\gamma_{rev}] \end{aligned}$$