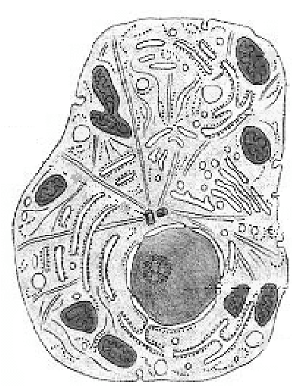
Ion channels, or stochastic networks with charged customers

Juan Alvarez and Bruce Hajek

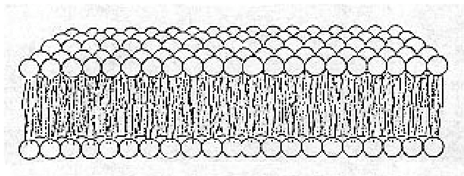
This work addresses the problem of modeling the flow of ions through channels formed by proteins embedded in cell membranes. Reversibility, diffusion limits, and excursions are useful tools in the analysis.

I. Overview of ion channels

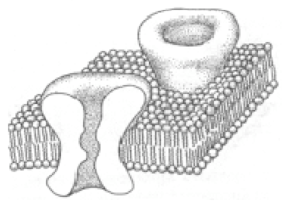
How does a cell communicate with its surroundings?



The cell membrane is impermeable . . .



except for channels (pores) formed by embedded proteins



Some basic questions about ion channels

(only a few addressed in rest of talk)

Concentration, flux, transit times vs. concentration outside channel, and applied external potentials. Both means and time variations are of interest.

Dependence of these quantities on interaction potentials, fixed charges in walls of channel, image charges caused by dielectric effects.

Explaining and modeling burst behavior.

Channel performance vs. protein structure.

Can the information transmission rate of ion channels be identifed?

Biologists can add dozens of additional questions.

Note: Engineers are fabricating ion channels
(so far, larger diameters: 10 nm for engineers vs. 1 nm for biology)

Approaches to study

Measurements/experiments (measure conductance, identify protein structure through crystallography and modeling)

Molecular dynamics simulation: Track position of all the water molecules in addition to the ions. (Typically there are at least 100 water molecules per ion)

Brownian dynamics simulation: Track positions (and possibly velocities) of ions only. Interaction with water is accounted through diffusion coefficient (related to viscosity) and electric permittivity constant.

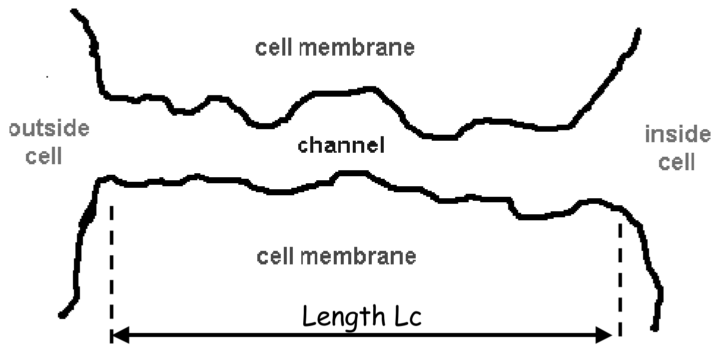
Partial differential equation approach: (Such as forward equations, but with incorporation of ion-ion interaction. Leads to Poisson-Nernst-Planck equations.)

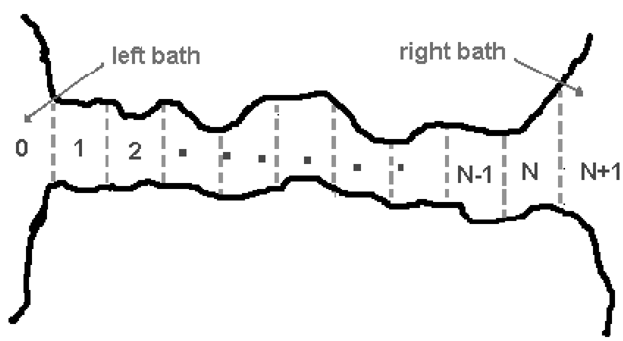
Reaction rate models (reduced complexity PDE approach)

Outline of talk

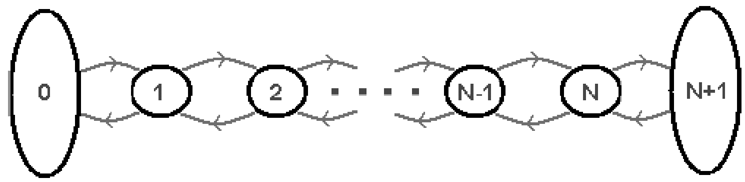
I. Overview of ion channels (just completed)
II. Diffusion limits, kernel representations
III. Equilibrium for a 3-dimensional channel model
IV. Equivalence of transit in either direction
V. A model for interacting ions

II. Diffusion limits, kernel representations





Closed channel model, with no interaction: Ions independently move as Markov process:



Open channel model:

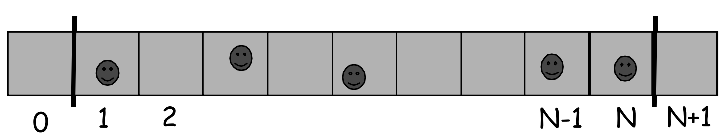
At beginning of each time slot, add a random number of new ions at sites 0 and N+1

Open channel model. For each time slot:

1. Lay new ions at sites 0 and N+1. The mean number of them is proportional to the concentration of external bath.

2. Ions have one chance to move into channel

3. Ions at sites 0 and N+1 at end of slot are cleared.



Relation between random walk and diffusion models for single ion (assuming no interaction among ions):

$\mu(x), D(x)$ are drift and diffusion functions on $[0, L_c]$
(Diffusion coefficient is often denoted $\sigma^2(x)$ by probabilists, and $D(x)$ by biologists, where $\sigma^2(x) = 2D(x)$.)

Random walk with jump probabilites:

$$\begin{aligned} r_i &= \frac{\triangle t}{2\triangle x}\mu(\frac{iL_c}{N}) + \frac{\triangle t}{(\triangle x)^2}D(\frac{iL_c}{N}) \\ l_i &= -\frac{\triangle t}{2\triangle x}\mu(\frac{iL_c}{N}) + \frac{\triangle t}{(\triangle x)^2}D(\frac{iL_c}{N}) \end{aligned}$$

Diffusion limit ($\triangle x, \triangle t \to 0$ with $\frac{(\triangle x)^2}{\triangle t}$ converging) Limit diffusion can be described by a stochastic differential equation:

$$\begin{aligned} dx_t &= \mu(x_t)dt + \sqrt{2D(x_t)}dw_t \qquad \text{(Itô form)} \\ dx_t &= \tilde{\mu}(x_t)dt + \sqrt{2D(x_t)} \circ dw_t \qquad \text{(Stratonovich form)} \end{aligned}$$

where $\tilde{\mu} = \mu - (\nabla \cdot D)^T$ (in scaler case: $\tilde{\mu} = \mu - \frac{\partial D}{\partial x}$)
Forward equation:

$$\frac{\partial p}{\partial t} = \mathcal{L}^* p$$

where

$$\begin{aligned} \mathcal{L}^* p(x) &= -\frac{\partial(\mu(x)p(x))}{\partial x} + \frac{\partial^2(D(x)p(x))}{\partial x^2} \qquad \text{(Itô form)} \\ &= \frac{\partial}{\partial x}\left\{-\tilde{\mu}(x)p(x) + D(x)\frac{\partial p}{\partial x}\right\} \qquad \text{(Stratonovich form)} \end{aligned}$$

Single Ion vs. System of Noninteracting Ions

The concentration at time t for a system of non-interacting ions is similar to the probability density at time t for a single ion.

In addition, an open system has ions entering from the boundaries. Leads, for example, to the following "kernel representation" of concentration at time t for the open channel model:

$$c(y,t) = \int_0^{L_c} c_0(x)p(t,x,y)dx + D(0)\int_0^t c_L(t-s)g(s,0,y)ds - D(L_c)\int_0^t c_R(t-s)g(s,L_c,y)ds$$

where

- $p(t,x,y)$ is the transition density of a single ion, killed at endpoints
- $g(t,x,y) = \frac{\partial p(t,x,y)}{\partial x}$

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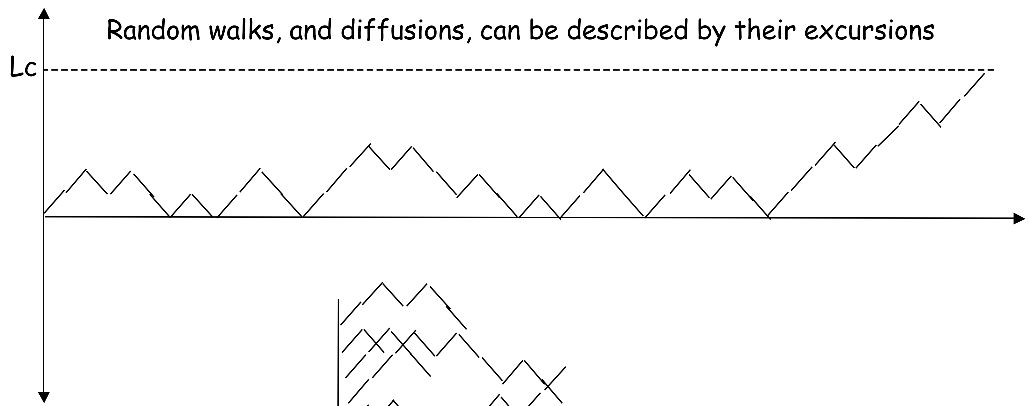
Above describes the concentration for an open channel with noninteracting ions, operating in continuous time.

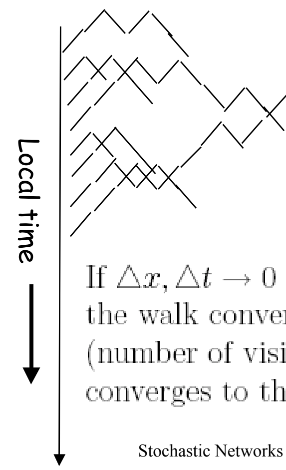
So certainly the concentration functions exist.

But does the channel model itself exist mathematically?

Yes -- see construction on next slide.

Random walks, and diffusions, can be described by their excursions



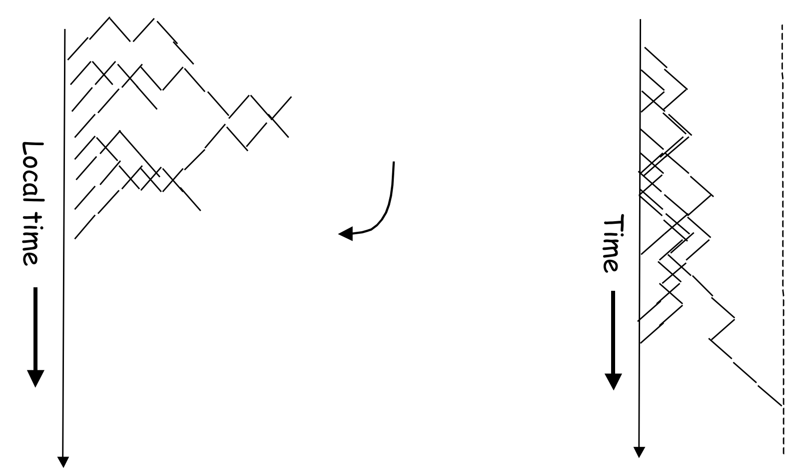


If $\triangle x, \triangle t \to 0$ with $\frac{(\triangle x)^2}{\triangle t}$ converging,
the walk converges to a diffusion, and
(number of visits to zero up to time t) $\times \frac{\triangle t}{\triangle x}$
converges to the local time at state x=0 at time t.

In limit, excursions of a given type (such as those transiting to Lc) appear according to a Poisson process (Ito)
The Poisson process of excursions can also be used to construct an open ion channel model:

Poisson process of excursions

Open channel model



Details of construction of open channel model (Notation of Ikeda and Watanabe, *Stochastic Differential Equations and Diffusion Processes*, 1981)

- $\mathcal{U}$ denotes the set of continuous functions from R_+ to $[0, L_c]$ with initial value 0, endowed with the topology of uniform convergence on compact intervals.
- $\sigma(w) = \inf\{t : w(t) = 0 \text{ or } w(t) = L_c\}$ for $w \in \mathcal{U}$.
- $\mathcal{B}(\mathcal{U})$ is the Borel σ-algebra on $\mathcal{U}$
- ν is the σ-finite measure on $(\mathcal{U}, \mathcal{B}(\mathcal{U}))$ such that

  $$\nu(\{w : w(t_1) \in A_1, \ldots, w(t_k) \in A_k\}) = \int_{A_1} g(t_1, 0, x_1)dx_1 \int_{A_2} p(t_2 - t_1, x_1, x_2)dx_2 \cdots \int_{A_k} p(t_k - t_{k-1}, x_{k-1}, x_k)dx_k$$

  The definition of ν is the same as the definition of n^+ in Ikeda and Watanabe, except the function p is different.
- N_p is a Poisson point process with time varying characteristic measure $D(0)c_L(t)\nu$. For example, for a time interval $[a, b]$ and set $U \in \mathcal{B}(\mathcal{U})$ with $\nu(U) < \infty$, $N_p([a, b] \times U)$ is a Poisson random variable with mean $\int_a^b D(0)c_L(t)dt\nu(U)$.
- $\beta_t = \int_0^t \int_{\mathcal{U}} I_{\{s \le t \le s+\sigma(w)\}} \delta_{w(t-s)} N_p(ds\ dw)$. In words, the location of an ion arriving at time s with excursion w which is still in the channel at time t contributes a unit mass at location $w(t-s)$.

For such channel, the concentration is given by the expectation of the Poisson process. Thus,

$$\begin{aligned} c(y,t)dy &= E[\beta_t(dy)] = E[N_p(\{(s,w) : s \le t \le s + \sigma(w),\ w(t-s) \in dy\})] \\ &= D(0) \int_0^t c_L(t) g(t-s, 0, y) ds dy \end{aligned}$$

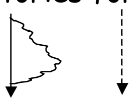
This explains in a direct way the terms arising from the boundaries in the kernel representation of the concentration density.

Example: Standard Open Channel

Ions in channel undergo Brownian motion (no drift, $\square=0,\square^2=1$)
Channel length $L_c=1$
Concentration two in left bath, zero in right bath
Type 0 trajectories are the trans paths:

Type k trajectories for k>0: Make it to 1/(k+1), but not 1/k.

Type 2:



Arrival rate of each type is one.
Total arrival rate is infinite.
Number of type k in system is number in an M/M/

Example: Standard Open Channel (continued)

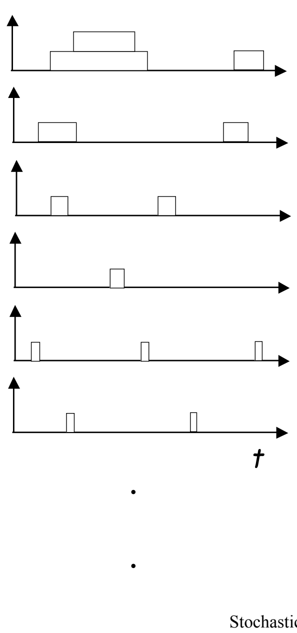
number in channel

Type 0

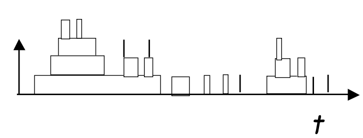
Type 1

Type 2

.
.
.

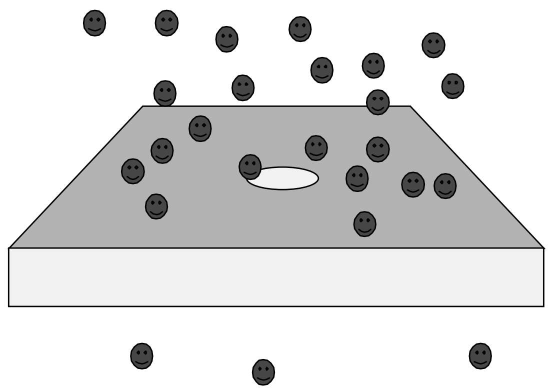


Total number in channel



The total number of ions in the channel at a fixed time t has the Poisson distribution with mean one.

III. Equilibrium for a 3-dimensional channel model



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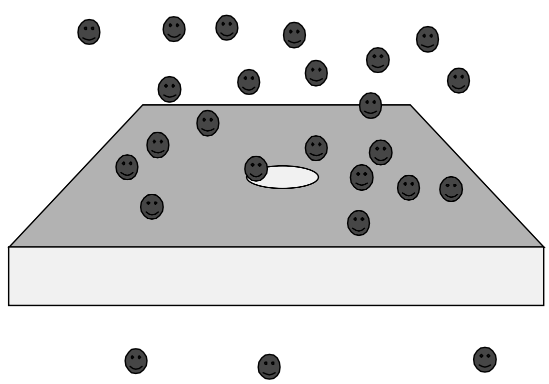

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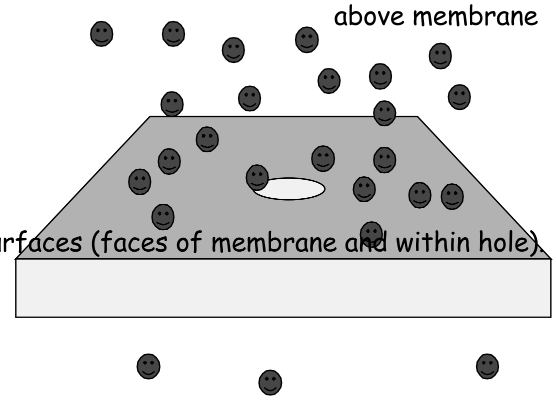
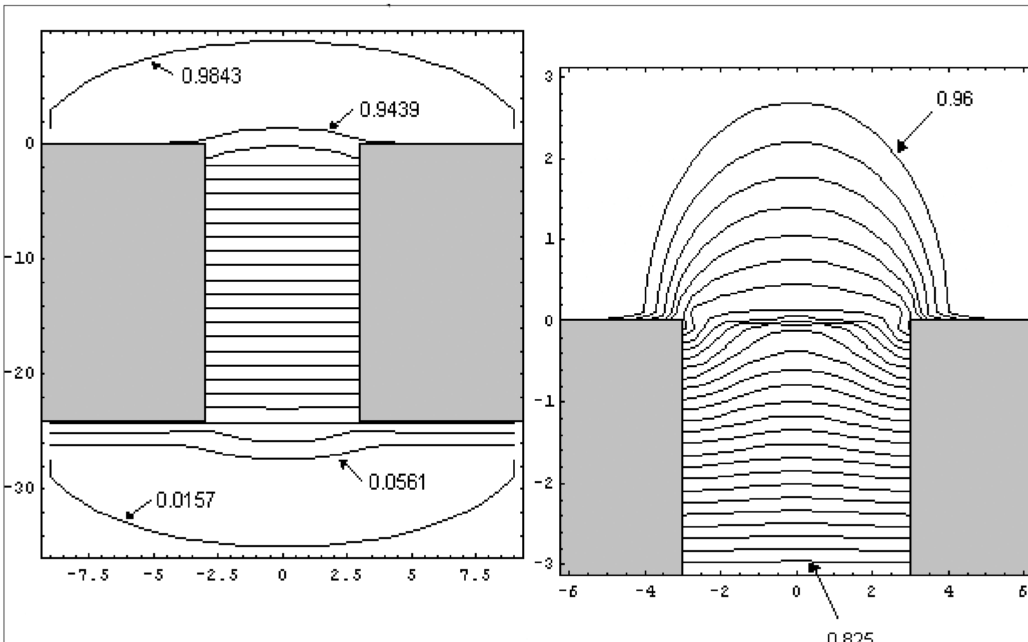
Concentration is the harmonic function with specified boundary conditions





$$\alpha = \sum_{n=0}^{\infty} A_n J_0(k_n r) + \sum_{n=0}^{\infty} \hat{A}_n a J_0(k_n a) \int_0^{\infty} \frac{J_1(\zeta a)}{\zeta^2 - k_n^2} J_0(\zeta r) \zeta d\zeta$$

IV. Equivalence of transit in opposite directions

No interaction model - Trans path equivalence

"An interesting feature of the analytical mean passage times is that they are precisely symmetrical about zero voltage"

* Jakobsson, E. and Chiu, S. (1987) Stochastic theory of ion movement in channels with single-ion occupancy: Application to sodium permeation of gramicidin channels. *Biophys. J.* **52**, 33-45.

Explanation: For model with no interaction between ions:
Time reversal maps the left-right trans-path distribution into the right-left trans path distribution.

Claim 1. *For* $\gamma \in \mathcal{S}_{LR}$

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

Reversibility, or v symmetry ($v_i q_{ij} = v_j q_{ji}$) is key.

Implications?

Is same true for models with ion-ion interaction?

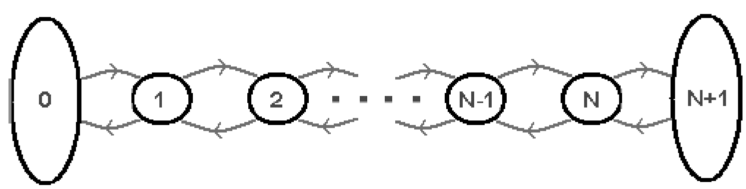
V. A model for interacting ions

Idea: Motion of interacting ions subject to electrical interaction and viscosity is reversible.

Therefore, expect symmetry of LR and RL trans path distribution to persist even when ions interact.

Need model of motion.

Idea: discretize closed physical system with interaction (which is reversible) to obtain a reversible discrete state model.



Obtain open channel model as bath size converges to infinity.

State of open system: $(n_1, \ldots, n_N)$, where n_i is the number of ions at site i.

The energy of a sta te of the open system is:

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

- Specification of transition rates that
  - preserve reversibility
  - are consistent with Nernst-Planck electro-diffusion theory

$$q_{(n_1,\ldots,n_N),(n_1+1,\ldots,n_N)} = \rho\exp(-\phi_0)\ \frac{1}{2}\exp\left(-\frac{1}{2}(\phi_1-\phi_0)\right)$$

$$q_{(n_1,\ldots,n_N),(n_1-1,\ldots,n_N)} = n_1\frac{1}{2}\exp\left(-\frac{1}{2}(\phi_0-\phi_1)\right)$$

$$q_{(n_1,\ldots,n_i,n_j,\ldots,n_N),(n_1,\ldots,n_i-1,n_j+1,\ldots,n_N)} = n_i\frac{1}{2}\exp\left(-\frac{1}{2}(\phi_j-\phi_i)\right)\cdot$$

$$\exp\left(-\frac{1}{2}\left((n_i-1-n_j)\psi_{i,j}+n_j\psi_{j,j}-(n_i-1)\psi_{i,i}+\sum_{\substack{k=1 \\ k\neq i,j}}^{N} n_k(\psi_{k,j}-\psi_{k,i})\right)\right)$$

Basic observation:

Open system is reversible if *ion entry rates on left and right sides balance* (corresponds to limit of closed systems in equilibrium).

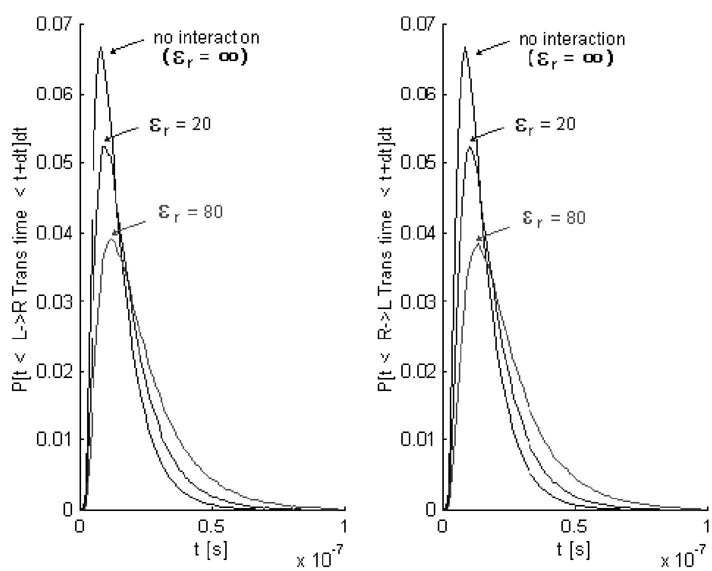
Yields symmetry of trans paths.

Q. If open system with interacting ions is in equilibrium but is not reversible, does symmetry of trans paths still hold?

A. No.

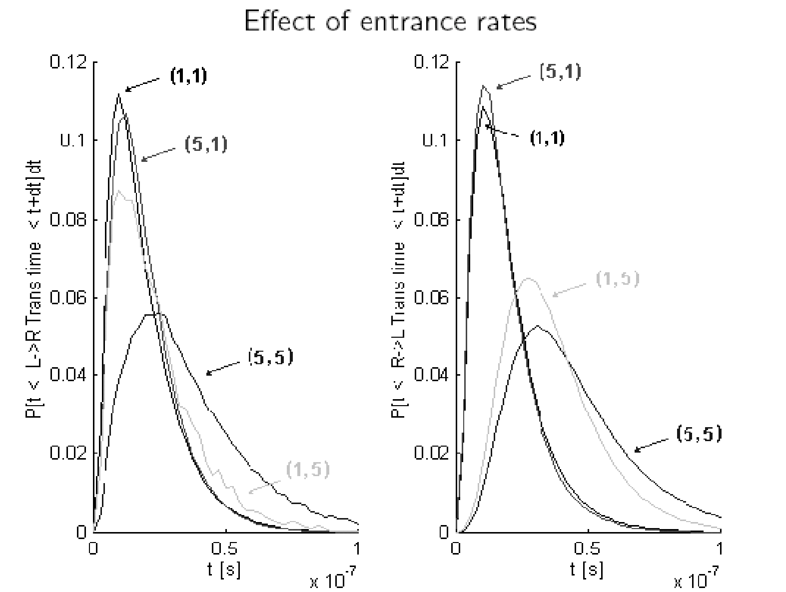
Interaction model - Observations (continued)

Effect of interaction strength



$D = 1\times10^{-9}\ m^2/s$ $L_c = 1\times10^{-8}\ m$ $V_m = -70\times10^{-3}\ V$ $dt = 1\times10^{-9}\ s$

Interaction model - Observations (continued)



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

See Ph.D. thesis (coming soon) of Juan Alvarez for details.

But much remains to be done in this area.

Thanks!