Monte Carlo Probabilities for Unimolecular Transitions

\[
\frac{(S^0)_T}{(S^0)_o} = \exp\left[-\left(\sum_{i=1}^{n} k_i \right) t\right]
\]

From this, the lifetime of \( S^0 \) is exponentially distributed with a mean value given by \( \tau \):

\[
\tau = \frac{1}{\sum_{i=1}^{n} k_i}
\]

And finally:

\[
p_{\Delta t} = 1 - \exp\left[-\left(\sum_{i=1}^{n} k_i \right) \Delta t\right]
p_{k_i} = p_{\Delta t} \frac{k_i}{\sum_{i=1}^{n} k_i}, \ldots, p_{\Delta \omega} = p_{\Delta t} \frac{k_{\omega}}{\sum_{i=1}^{n} k_i}, \quad \sum_{i=1}^{n} p_{\Delta t} = p_{\Delta t}
\]

If this reaction proceeds for any time \( t \) from an initial concentration \( (S^0)_o \), the total probability \( (p_{\Delta t}) \) that a single molecule in the \( S^0 \) state undergoes a transition is given by the fraction of \( (S^0)_o \) that undergoes any transition during time \( t \):

\[
p_{\Delta t} = \frac{(S^1)_o + (S^2)_o + \ldots + (S^n)_o}{(S^0)_o} = 1 - \left(\frac{(S^0)_o}{(S^0)_o}\right)
\]

From:

\[
\frac{(S^0)_L}{(S^0)_o} = \exp\left[-\left(\sum_{i=1}^{n} k_i \right) t\right]
\]

and:

\[
p_{\Delta t} = \frac{(S^1)_o + (S^2)_o + \ldots + (S^n)_o}{(S^0)_o} = 1 - \left(\frac{(S^0)_o}{(S^0)_o}\right)
\]

we obtain:

\[
p_{\Delta t} = 1 - \exp\left[-\left(\sum_{i=1}^{n} k_i \right) t\right]
\]

Interactive MCcell Demos:
Monte Carlo Probabilities for Bimolecular Associations

\[
\begin{align*}
A + R & \xrightarrow{\kappa,} AR^1 \\
R + A & \xrightarrow{k_{o}} A + R
\end{align*}
\]

\[
p_o = 1 - (1 - p_i)^n \\
p_i = \zeta = \left(\sum k_n\right)A_i \Delta t \\
1 - (1 - p_i)^n = p_o = \zeta = \left(\sum k_n\right)A_i \Delta t
\]

Monte Carlo Probabilities for Bimolecular Associations

**Reality check:**

From these equations, the probability \( p_o \) that a single R molecule becomes bound during an arbitrarily long interval of time \( \Delta t \) depends on all the \( k_n \) values, \( A_i \) and \( (R)_o \). \( p_o = 0 \) for \( t = 0 \), and for \( t = \infty \), \( p_o = 1 \) if \( (A)_o \geq (R)_o \), or \( p_o = (A)_o/(R)_o \) if \( (A)_o < (R)_o \).

Monte Carlo Probabilities for Bimolecular Associations

After integration, final analytic expressions for \( p_o \) are:

\[
p_o = \sum \left(\frac{(A)}{(R)}\right) = \frac{1}{(R)} \left( \frac{\sum k_n}{(A)} \right) \Delta t
\]

if \( (A)_o \neq (R)_o \), where

\[
b = \Delta \gamma; (R)_o \text{ and } \gamma = 40 \Delta \gamma \text{ or } -1^t
\]

\[
p_o = \sum \left(\frac{(A)}{(R)}\right) = \frac{1}{(R)} \left( \sum k_n \right) (A)_o \Delta t
\]

if \( (A)_o = (R)_o \).

Monte Carlo Probabilities for Bimolecular Associations

\[
p_o = \sum \left(\frac{(A)}{(R)}\right) = \frac{1}{2N_c(A)} \frac{\pi \Delta t}{D}
\]

\[
p_o = \sum \left(\frac{(A)}{(R)}\right) = \frac{1}{2N_c(A)} \frac{\pi \Delta t}{D}
\]

Cells Are Complicated ...

“Results to date show a dizzying array of signaling systems acting within and between cells. … In such settings, intuition can be inadequate, often giving incomplete or incorrect predictions. … In the face of such complexity, computational tools must be employed as a tool for understanding.” Fraser & Harland, Cell 100:41 (2000).

- Need to accurately assess the variability of biological systems, and their propensity to switch between different operating modes and/or to fail

Interactive MCell Demos:
Cells Are Complicated …

Requires: Stochastic methods applied to complex 3D reaction-diffusion and cells-as-machines problems - largely embryonic due to the scope of necessary software development.

Microphysiological (3-D Reaction/Diffusion) Simulations

Cellular Structures
Molecular Locations
Mass Action Rate Constants

MCell & DReAMM
Build models and use Monte Carlo SSL algorithms to couple Brownian dynamics diffusion with binding, unbinding, conformational changes…

Molecular Diffusion
Molecular Mechanisms
Molecular Structure-

10^7 µs

10^8 µs

10^5 µs

10^3 µs

10^-1 fs

5 - 15 fs

~ 10 s

~ 10 t

5 - 10 ps

Cells Are Complicated …

Microphysiological Modeling

Various Software Packages
e.g., FormZ, XVoxTrace, NWGrid, Mesquite, LaGrIt, PSC Volume Browser

DReAMM
Design, Render & Animate MCell Models

GenMer
General Monte Carlo Simulator of Microcellular Physiology

Microphysiological Modeling

Model Design

Material Design

Model Generation

Simulation

Analysis

MCell Simulations

Computer script files (e.g., control of multiple simulations)

Read MOL files and begin initialization

Steady state

Create simulation objects

Polymer mesh surfaces, attractor sites, and affecter sites

Molecules and molecule sources

Reaction mechanisms

Output visualization results as required

Output numerical results

Stopping criteria

"I think you should be more explicit here in step two."
Microphysiological Modeling

MCeII simulations of miniature endplate currents

PSC's Biomedical Supercomputing Initiative – An NIH Resource Center

**Insight #1: Junctional Folds Decrease mepc Amplitude**

<table>
<thead>
<tr>
<th>Planar NMJ Model</th>
<th>Fold spacing</th>
<th>Fold depth</th>
<th>Peak current</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACHE active</td>
<td>μm</td>
<td>μm</td>
<td>nA</td>
</tr>
<tr>
<td>No folds</td>
<td>0</td>
<td>0.5</td>
<td>7.36 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>0.5</td>
<td>6.29 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>0.29</td>
<td>0.8</td>
<td>5.48 ± 0.1</td>
</tr>
<tr>
<td>ACHE inactive</td>
<td>μm</td>
<td>μm</td>
<td>nA</td>
</tr>
<tr>
<td>No folds</td>
<td>0</td>
<td>0.5</td>
<td>9.06 ± 0.15</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>0.5</td>
<td>9.27 ± 0.17</td>
</tr>
<tr>
<td></td>
<td>0.29</td>
<td>0.8</td>
<td>7.38 ± 0.04</td>
</tr>
</tbody>
</table>

**Testing Prediction for Untreated mepc t; Simultaneous Broadband EC and VC Recordings**

Skipping over …
- Parameter Fitting for NMJs:
  - Untreated; ACHE inhibited; ACHE inhibited + AChR Blockade
  - Predicted Untreated mepc t

**Insight #2: mepc t, and ACh Exocytosis**

Averaged Experimental maps

Predicted Effects of Fusion pore Expansion Rate

**Insight #3a: Temperature Sensitivity of mepcs is Mostly Governed by Offset Effects on Channel Gating**

Experimental maps (Lizard, VC and EC)

<table>
<thead>
<tr>
<th>Individual Experimental (Lizard) maps</th>
<th>W</th>
<th>Aβ</th>
<th>Aβ</th>
<th>Aβ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change for 1°C increase (°C, °C)</td>
<td>(Δ)</td>
<td>(Δ)</td>
<td>(Δ)</td>
<td>(Δ)</td>
</tr>
<tr>
<td>Constant:</td>
<td></td>
<td>ΔAβ</td>
<td>ΔAβ</td>
<td>ΔAβ</td>
</tr>
<tr>
<td>lA</td>
<td></td>
<td>10036 eV</td>
<td>10036 eV</td>
<td>10036 eV</td>
</tr>
<tr>
<td>dp</td>
<td></td>
<td>4050 eV</td>
<td>4050 eV</td>
<td>4050 eV</td>
</tr>
<tr>
<td>CP</td>
<td></td>
<td>1.50 x 10^4 M^-1</td>
<td>1.50 x 10^4 M^-1</td>
<td>1.50 x 10^4 M^-1</td>
</tr>
<tr>
<td>fusion per expansion rate</td>
<td></td>
<td>50 ms^-1</td>
<td>50 ms^-1</td>
<td>50 ms^-1</td>
</tr>
<tr>
<td>ΔlA</td>
<td></td>
<td>3.39 x 10^16 eV</td>
<td>3.39 x 10^16 eV</td>
<td>3.39 x 10^16 eV</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td>5043 molecules</td>
<td>5043 molecules</td>
<td>5043 molecules</td>
</tr>
<tr>
<td>Δγ</td>
<td></td>
<td>2061 µM</td>
<td>2061 µM</td>
<td>2061 µM</td>
</tr>
<tr>
<td>ΔAβ</td>
<td></td>
<td>58 µM</td>
<td>58 µM</td>
<td>58 µM</td>
</tr>
</tbody>
</table>
Insight #3a: Temperature Sensitivity of mepc is Mostly Governed by Offsetting Effects on Channel Gating

Insight #3b: Highly Nonlinear Sensitivity of mepc t to AChE Parameters

Insight #4: Synaptic Pathophysiology in a Novel Form of Slow Channel Congenital Myasthenic Syndrome (SCCMS)

Patient followed from birth:
- Progressive weakness and impaired neuromuscular transmission without early degenerative endplate changes typically associated with SCCMS
- Prolonged, low amplitude synaptic currents at early and late stages
- Atypical, initially mild (focal) ultrastructural changes progressed over time
- Novel C-to-T substitution in exon 8 of the δ subunit of AChR: serine to phenylalanine mutation in the second transmembrane domain (M2) that lines the ion channel
- AChR numbers not significantly reduced
Insight #4: Synaptic Pathophysiology in a Novel Form of Slow Channel Congenital Myasthenic Syndrome (SCCMS)

- Typical of SCCMS, mutant neurotransmitter receptors showed dramatically slowed deactivation (ion channel closing rate)
- However, simulations of synaptic signals predicted an additional novel slowing of receptor activation (ion channel opening rate)
- Based on model predictions, opening rate was measured and found to be decreased - likely explains unique early course of disease in this patient

Insight #5: Spatio-Temporal Correlations and Synaptic Noise
Insight #5: Spatio-Temporal Correlations and Synaptic Noise

Presynaptic calcium dynamics & neurotransmitter release

Normal

Developing/Regenerating

Presynaptic calcium dynamics & neurotransmitter release

Normal

CRR = 3.91
Presynaptic calcium dynamics & neurotransmitter release

Synaptic topology & current variability

3-D reconstruction of verterate neuromuscular junction

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Synaptic topology & current variability

Synaptic topology & current variability – synaptic AChE distribution

Developing/Regenerating

Synaptic topology & current variability
"Computational biology today is in a state analogous to weather prediction 25 years ago, when it was not very reliable or highly respected. ... Now we routinely rely on accurate global weather forecasting. Similarly, we foresee a new age of cell biology, when computational modeling plays an integral role in our understanding of the molecular basis of cell physiology and human disease. The impact of computational cell biology on biomedicine will be just as great as the impact of modern weather prediction on the transportation industry, the military, and civil defense."

Developers & Collaborators

MCell and DReAMM:
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Edwin E. Salpeter (Physics and Astronomy, Cornell)

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Casamayor, R. (UCSD)
Dongarra, J. (U. Tennesse)
Ellman, M. (UCSD)
Wolski, R. (UCSD)

MCell Developers &

Salse J., Martin, S. (U. Pittsburgh)
Belzer, G. (U. Pittsburgh)
Van Orden, D. (U. Newcastle)

Expanding User Group & Range of Applications

Usage Scenarios:
- Maintenance
- Workstation
- Parallel
- Grid
- Serial or Parallel - Look & See, Parameter Fitting, Parameter Sweep

Outside Users:
- Registration & Download Website Maintained at PSC – UNIX, PC, Mac, >200 Registered

Web-based Instruction
www.mcell.psc.edu
www.mcell.psc.edu/DReAMM

Workshops
1997 – Cornell Theory Center, NSF support (MCell test group)
1999 – SOSC, NSF support (MCell last group)
2001 – PSC, NCBR support (open, MCell & DReAMM)
2003 – PSC, Pittsburgh Informatics research, MCell & DReAMM

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