The effect of dendritic spine morphology on synaptic crosstalk

Literature review

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1 Modeling receptor trafficking at synapses

2 Research questions

3 Model and results so far

4 Future directions
Synapses in the central nervous system
Anatomy and function of synapses

When a signal arrives:

- Exocytosis of neurotransmitter;
- Activation of receptors;
- Initiation of action potential.

Image: Remy Kusters.
Factors influencing receptor trafficking:

- Endo- and exocytosis of receptors;
- Anchoring at the PSD;
- Surface diffusion.
Synaptic crosstalk

Crosstalk between synapses refers to instances in which components from one synapse influences the signal transmission in other synapses.

Synaptic crosstalk undermines the ability of the body to specifically control the strength of individual synapses.
### Number of synapses

<table>
<thead>
<tr>
<th>Considered domains</th>
</tr>
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<tr>
<td>Flat two-dimensional geometries;</td>
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<td>Curved surfaces in three dimensions.</td>
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Modeling synaptic receptor trafficking

Number of synapses

- Single synapse models;
- Multisynapse models.

Considered domains

- Flat two-dimensional geometries;
- Curved surfaces in three dimensions.
Modeling synaptic receptor trafficking

Number of synapses

- Single synapse models;
- Multisynapse models.

Considered domains

- Flat two-dimensional geometries;
- Curved surfaces in three dimensions.
How does the shape of the spines alter the escape dynamics of receptors?

Simulations:
Brownian motion on curved surface.
\[
\begin{align*}
    r(s + ds) &= r(s) + \frac{dr(s)}{ds} \, ds + \frac{1}{2} \frac{d^2r(s)}{ds^2} \, ds^2 + \mathcal{O}(ds^3). \\
    \frac{d^2r(s)}{ds^2} &= -\Gamma_{ik} \frac{dr^l}{ds} \frac{dr^k}{ds}.
\end{align*}
\]

Analytically:
Mean first passage time.
\[
\nabla^2 W = -\frac{1}{D},
\quad \nabla^2_g W = \frac{1}{\sqrt{|\det g|}} \sum_{i,j=1}^{2} \partial_i \left( \sqrt{|\det g|} g^{ij} \partial_j W \right)_{i,j = 1,2}.
\]

Multisynapse model: Czöndör et al., PNAS (2012)

- Random walk simulation on a flat surface;
- Includes endo/exocytosis, anchoring and surface diffusion;
- No integration of 3D morphologies.
Multisynapse model:

- Diffusion equation on a flat surface
  \[ \frac{\partial c}{\partial t} = D \Delta c; \]
- Constant flux of receptors from one side of the domain;
- Synapses modeled as partially absorbing holes,
  \[ \epsilon \partial_n c(r, t) = -\frac{\omega_j}{2\pi D} (c(r, t) - \tilde{c}_j); \]
- No integration of 3D morphologies.
Main research question:

*How does the morphology of dendritic spines influence the synaptic crosstalk?*
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*How does the morphology of dendritic spines influence the synaptic crosstalk?*

Subquestions:

*How should the morphology of dendritic spines be defined?*
*What constitutes a good comparison between shapes?*
*What is a measure for the amount of synaptic crosstalk?*
Multisynapse model integrating 3D morphologies

Domain of computation

\[ y = \pi \cdot R_d \]

\[ y = -\pi \cdot R_d \]

\[ x = 0 \quad \text{to} \quad x = l \]
Multisynapse model integrating 3D morphologies

Domain of computation


Canham-Helfrich model for bending energy, based on minimum energy principle.
Multisynapse model integrating 3D morphologies
Simulating a stochastic process on a curved surface

Application of the method described by Christensen, J. of Comp. Phys. (2004). Based on the insights:
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A Monte Carlo updating scheme moving a particle from $r_0$ to $r$ in $\Delta t$ dictates a transition rate $T(r|r_0)$. 
Multisynapse model integrating 3D morphologies
Simulating a stochastic process on a curved surface

Application of the method described by Christensen, J. of Comp. Phys. (2004). Based on the insights:

A Monte Carlo updating scheme moving a particle from $r_0$ to $r$ in $\Delta t$ dictates a transition rate $T(r|r_0)$.

A correct numerical method method matches first and second moments of this transition rate to the ones of the original diffusion equation.
Multisynapse model integrating 3D morphologies

Design of test cases

Boundary conditions

\[
V(x, \pi R_d, t) = V(x, -\pi R_d, t),
\]

\[
\frac{\partial V}{\partial y}(x, \pi R_d, t) = \frac{\partial V}{\partial y}(x, -\pi R_d, t),
\]

\[
\frac{\partial V}{\partial x}(0, y, t) = \frac{\partial V}{\partial x}(l, y, t) = 0.
\]
Multisynapse model integrating 3D morphologies

Results

Exocytosis in the middle between the two spines.

<table>
<thead>
<tr>
<th>Shape parameter</th>
<th>$\hat{\mu}_{FPT}[s]$</th>
<th>$\hat{\sigma}_{FPT}[s]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A = 1.5$</td>
<td>75 ± 1.8</td>
<td>66.3 [65.0, 67.6]</td>
</tr>
<tr>
<td>$A = 3.5$</td>
<td>144 ± 3.6</td>
<td>128.6 [126.1, 131.2]</td>
</tr>
<tr>
<td>$A = 5.0$</td>
<td>199 ± 4.7</td>
<td>171.1 [167.8, 174.5]</td>
</tr>
</tbody>
</table>

Intervals are 95% confidence intervals.
Multisynapse model integrating 3D morphologies

Results

\begin{tabular}{l|ccc}
 & $\hat{\mu}_{FPT}$ [s] & $\hat{\sigma}_{FPT}$ [s] & Exit % \\
\hline
$A = 1.5$ & & & \\
Overall & 50.8 & 63.9 & 5000 (100\%) \\
Spine 1 & 39.6 & 57.9 & 4049 (81 \%) \\
Spine 1, direct & 2.7 & 2.0 & 1150 (23\%) \\
Spine 1, indirect & 54.3 & 62.6 & 2899 (58\%) \\
Spine 2 & 98.3 & 66.5 & 951 (19\%) \\
\hline
$A = 3.0$ & & & \\
Overall & 83.3 & 113.7 & 5000 (100\%) \\
Spine 1 & 61.9 & 100.3 & 4117 (82\%) \\
Spine 1, direct & 9.8 & 7.7 & 2130 (42\%) \\
Spine 1, indirect & 117.9 & 121.4 & 1987 (40\%) \\
Spine 2 & 182.9 & 119.7 & 883 (18\%) \\
\hline
$A = 5.0$ & & & \\
Overall & 108.1 & 148.9 & 5000 (100\%) \\
Spine 1 & 82.8 & 131.0 & 4260 (85\%) \\
Spine 1, direct & 22.5 & 19.9 & 2740 (55\%) \\
Spine 1, indirect & 191.5 & 170.3 & 1520 (30\%) \\
Spine 2 & 253.6 & 162.2 & 740 (15\%) \\
\end{tabular}

Intervals are 95\% confidence intervals.

Exocytosis in spine 1.

Result for $A = 5$. 

![Graph showing EPDF for different spine types and conditions](image)
Future directions

- Design test cases to answer the research question;
- Solve PDE-counterpart of stochastic process and compare (diffusion on curved surface);
- How can we model the PSD?
  - Now: absorbing boundary, but that does not reflect the high density of receptors at the PSD.
  - Idea: let the diffusion coefficient tend to zero.
Confirmation of results Kusters et al.

\[ d_2 = 0.05, A = 4.9917 \]

![Graphs showing concentration and equilibrium progress over time for domain 1 and domain 2.](image-url)