

# The effect of dendritic spine morphology on synaptic crosstalk

Literature review

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# Synapses in the central nervous system

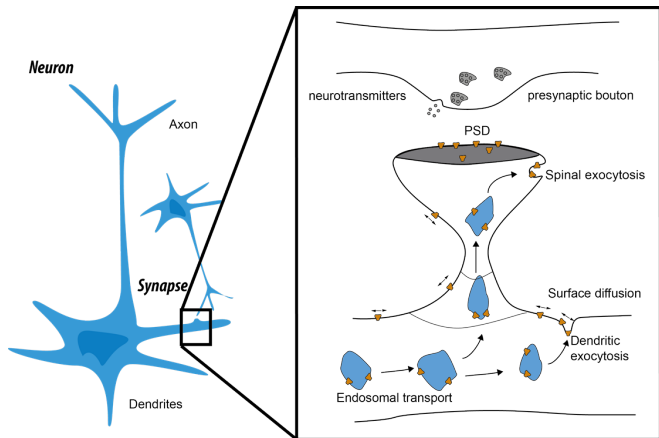


Image: Remy Kusters.

# Anatomy and function of synapses

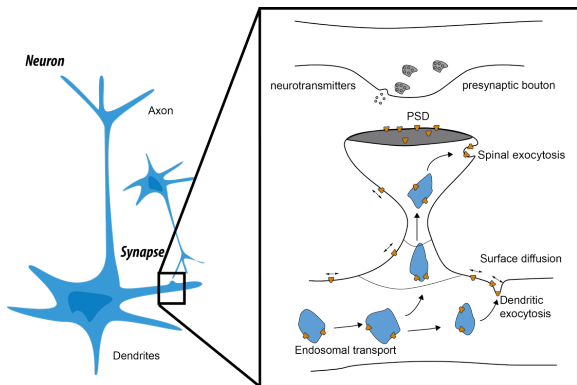


Image: Remy Kusters.

When a signal arrives:

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

# Receptor trafficking

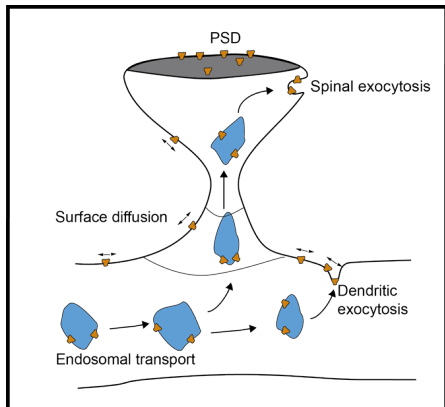


Image: Remy Kusters.

Factors influencing receptor trafficking:

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

# Synaptic crosstalk

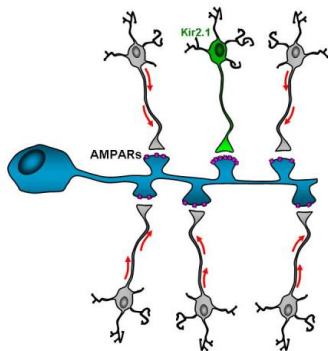


Image: Dr. Heng-Ye Man.

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.

# Modeling synaptic receptor trafficking

**Number of synapses**

**Considered domains**

# Modeling synaptic receptor trafficking

## Number of synapses

- Single synapse models;
- Multisynapse models.

## Considered domains



# Modeling synaptic receptor trafficking

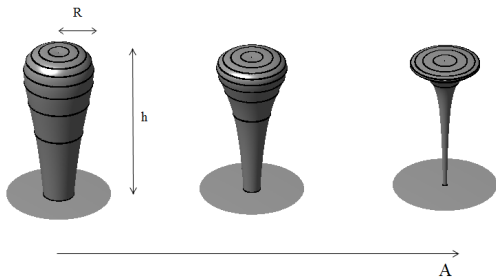
## Number of synapses

- Single synapse models;
- Multisynapse models.

## Considered domains

- Flat two-dimensional geometries;
- Curved surfaces in three dimensions.

# Single synapse model: Kusters et al., Physical Review E (2014)



$$\begin{aligned}x(u, \theta) &= R \sin(u) \cos(\theta), \\y(u, \theta) &= R \sin(u) \sin(\theta), \\z(u, \theta) &= h - \frac{R \cos(u)}{Au}.\end{aligned}$$

*How does the shape of the spines alter the escape dynamics of receptors?*

# Single synapse model:

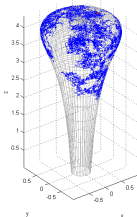
## Kusters et al., Physical Review E (2014)

### Simulations:

Brownian motion on curved surface.

$$\mathbf{r}(s+ds) = \mathbf{r}(s) + \frac{d\mathbf{r}(s)}{ds} ds + \frac{1}{2} \frac{d^2\mathbf{r}(s)}{ds^2} ds^2 + \mathcal{O}(ds^3).$$

$$\frac{d^2\mathbf{r}(s)}{ds^2} = -\Gamma_{kl}^i \frac{dr^l}{ds} \frac{dr^k}{ds}.$$



### Analytically:

Mean first passage time.

$$\nabla^2 W = -\frac{1}{D},$$

$$\nabla_g^2 W = \frac{1}{\sqrt{|\det g|}} \sum_{i,j=1}^2 \partial_i \left( \sqrt{|\det g|} g^{ij} \partial_j W \right)$$

$i, j = 1, 2.$



Method for simulations constructed by Christensen, 2004.

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

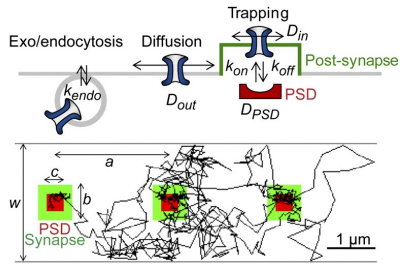


Image: Czöndör et al., PNAS (2012)

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

# Multisynapse model: Bressloff et al., SIAM J. Appl. Math.(2008)

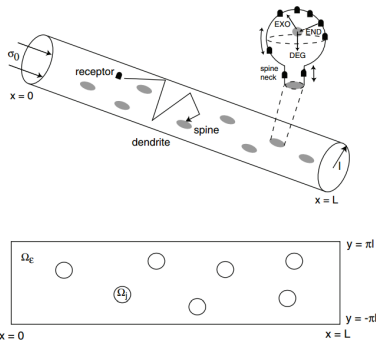


Image: Bressloff et al., SIAM J. Appl. Math.(2008)

- 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,

$$c \partial_n c(\mathbf{r}, t) = -\frac{\omega_j}{2\pi D} (c(\mathbf{r}, t) - \tilde{c}_j);$$

- No integration of 3D morphologies.

# Research questions

Main research question:

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

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Subquestions:

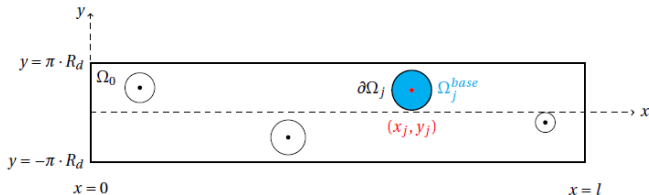
*How should the morphology of dendritic spines be defined?*

*What constitutes a good comparison between shapes?*

*What is a measure for the amount of synaptic crosstalk?*

# Multisynapse model integrating 3D morphologies

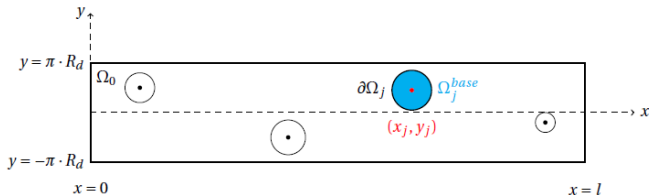
## Domain of computation



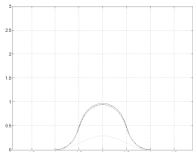


# Multisynapse model integrating 3D morphologies

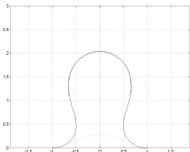
## Domain of computation



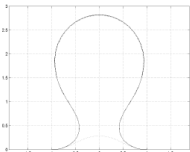
(a)  $\mathcal{A} = 1.500 \cdot \mathcal{A}_0$ .



(b)  $\mathcal{A} = 3.000 \cdot \mathcal{A}_0$ .



(c)  $\mathcal{A} = 5.000 \cdot \mathcal{A}_0$ .



Work of Miermans et al.,  
unpublished (2005).

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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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  $\mathbf{r}_0$  to  $\mathbf{r}$  in  $\Delta t$  dictates a transition rate  $T(\mathbf{r}|\mathbf{r}_0)$ .

# Multisynapse model integrating 3D morphologies

Simulating a stochastic process on a curved surface

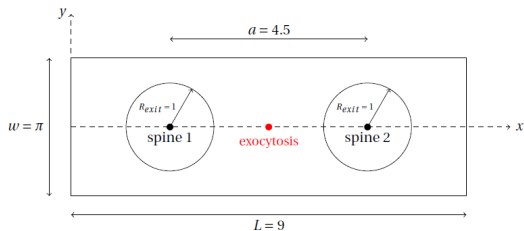
Application of the method described by Christensen, J. of Comp. Phys. (2004). Based on the insights:

A Monte Carlo updating scheme moving a particle from  $\mathbf{r}_0$  to  $\mathbf{r}$  in  $\Delta t$  dictates a transition rate  $T(\mathbf{r}|\mathbf{r}_0)$ .

A correct numerical method matches first and second moments of this transition rate to the ones of the original diffusion equation.

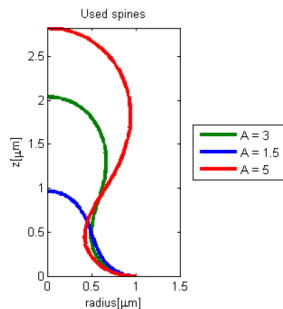
# Multisynapse model integrating 3D morphologies

## Design of test cases



## Boundary conditions

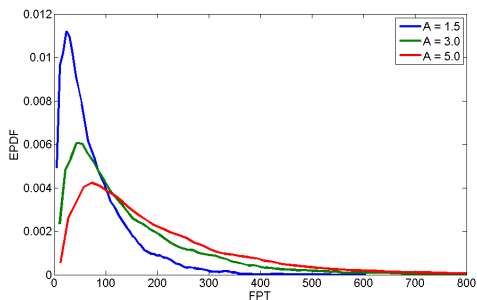
$$\begin{aligned}V(x, \pi R_d, t) &= V(x, -\pi R_d, t), \\ \frac{\partial V}{\partial y}(x, \pi R_d, t) &= \frac{\partial V}{\partial y}(x, -\pi R_d, t), \\ \frac{\partial V}{\partial x}(0, y, t) &= \frac{\partial V}{\partial x}(l, y, t) = 0.\end{aligned}$$



# Multisynapse model integrating 3D morphologies

## Results

Exocytosis in the middle between the two spines.



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

Intervals are 95% confidence intervals.

# Multisynapse model integrating 3D morphologies

## Results

$A = 1.5$	$\hat{\mu}_{FPT}[s]$	$\hat{\sigma}_{FPT}[s]$	Exit %
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%)

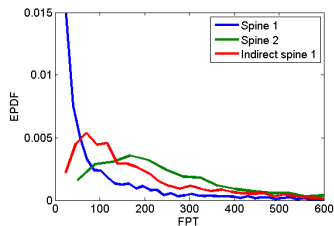
$A = 3.0$			
Overall	83.3	113.7	5000 (100%)
Spine 1	61.9	100.3	4117 (82 %)
Spine 1, direct	9.8	7.7	2130 (42%)
Spine 1, indirect	117.9	121.4	1987 (40%)
Spine 2	182.9	119.7	883 (18%)

$A = 5.0$			
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%)

Intervals are 95% confidence intervals.

## Exocytosis in spine 1.



Result for  $A = 5$ .

# 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.

