Simulating cell signaling networks in realistic geometries, from dendritic spines to whole neurons

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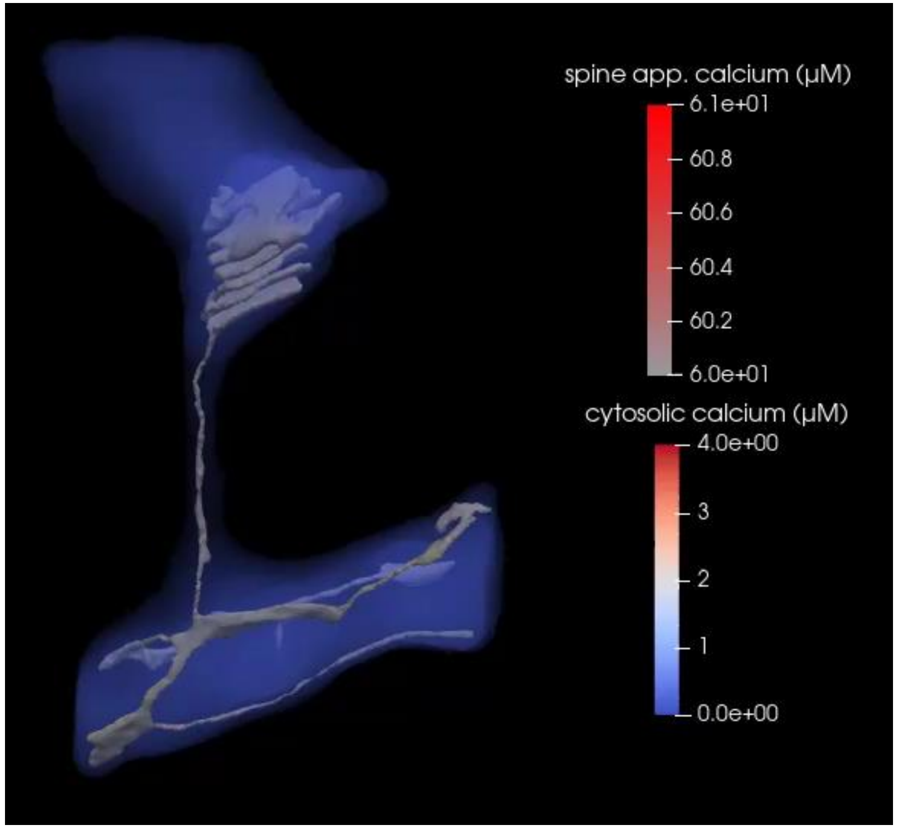
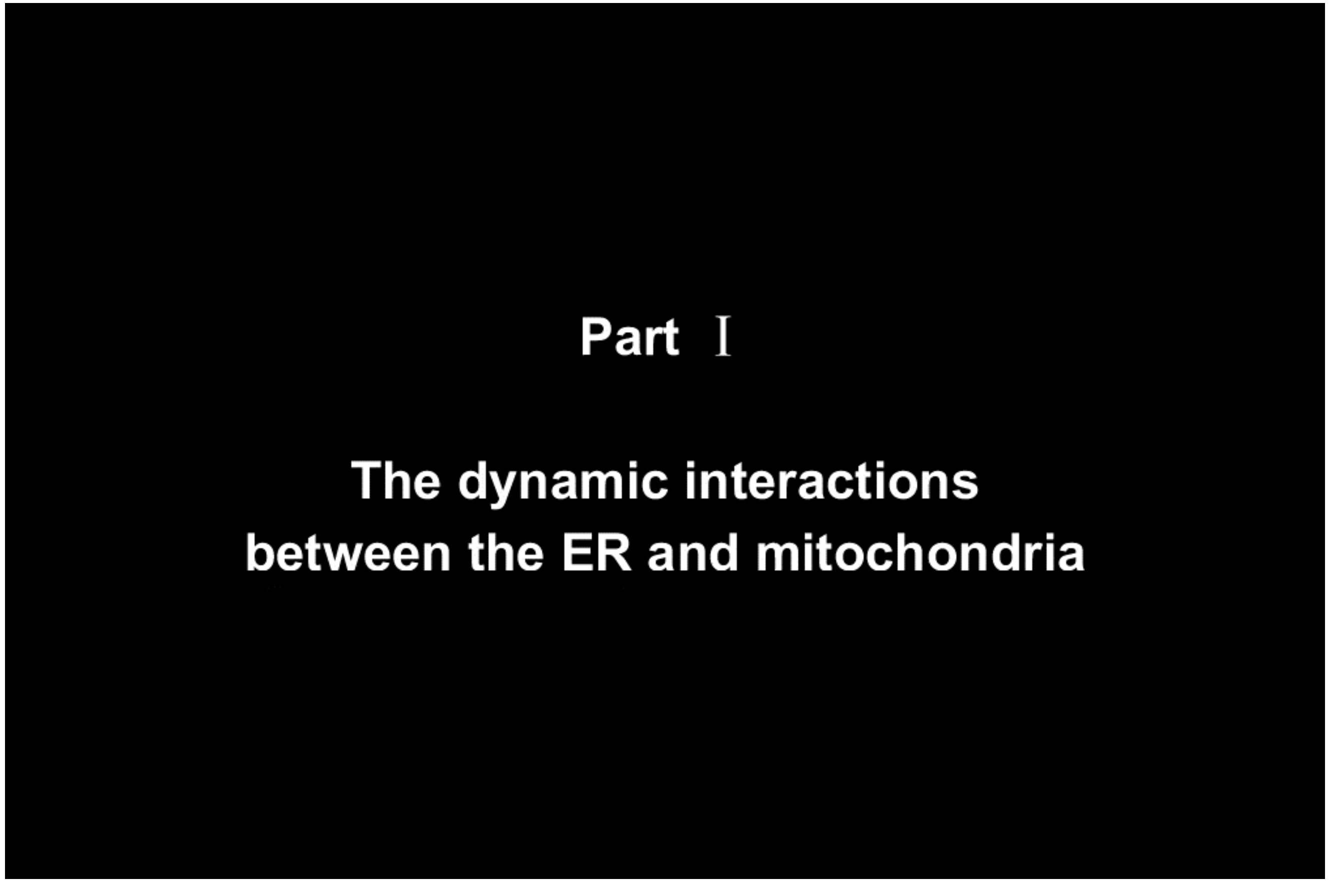


Difficulties of solving reaction-transport equations in cells

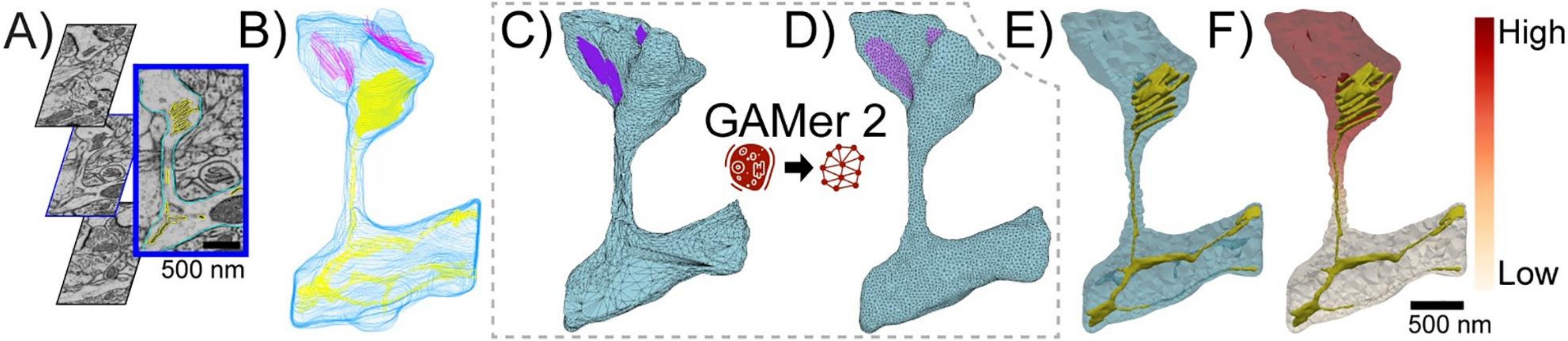
1. The equations are large, mixed dimensional systems of PDEs coupled across many cellular sub-compartments (plasma membrane, cytosol, organelle membranes, organelle interiors)
2. Many reactions depend nonlinearly on chemical constituents
3. Reaction and transport may involve many different physical mechanisms (diffusion, convection, electrodynamics, coupling to mechanics)
4. Cell geometries are complicated!

Example: ER-mitochondria geometry and dynamics (Guo et al 2018, *Cell*)



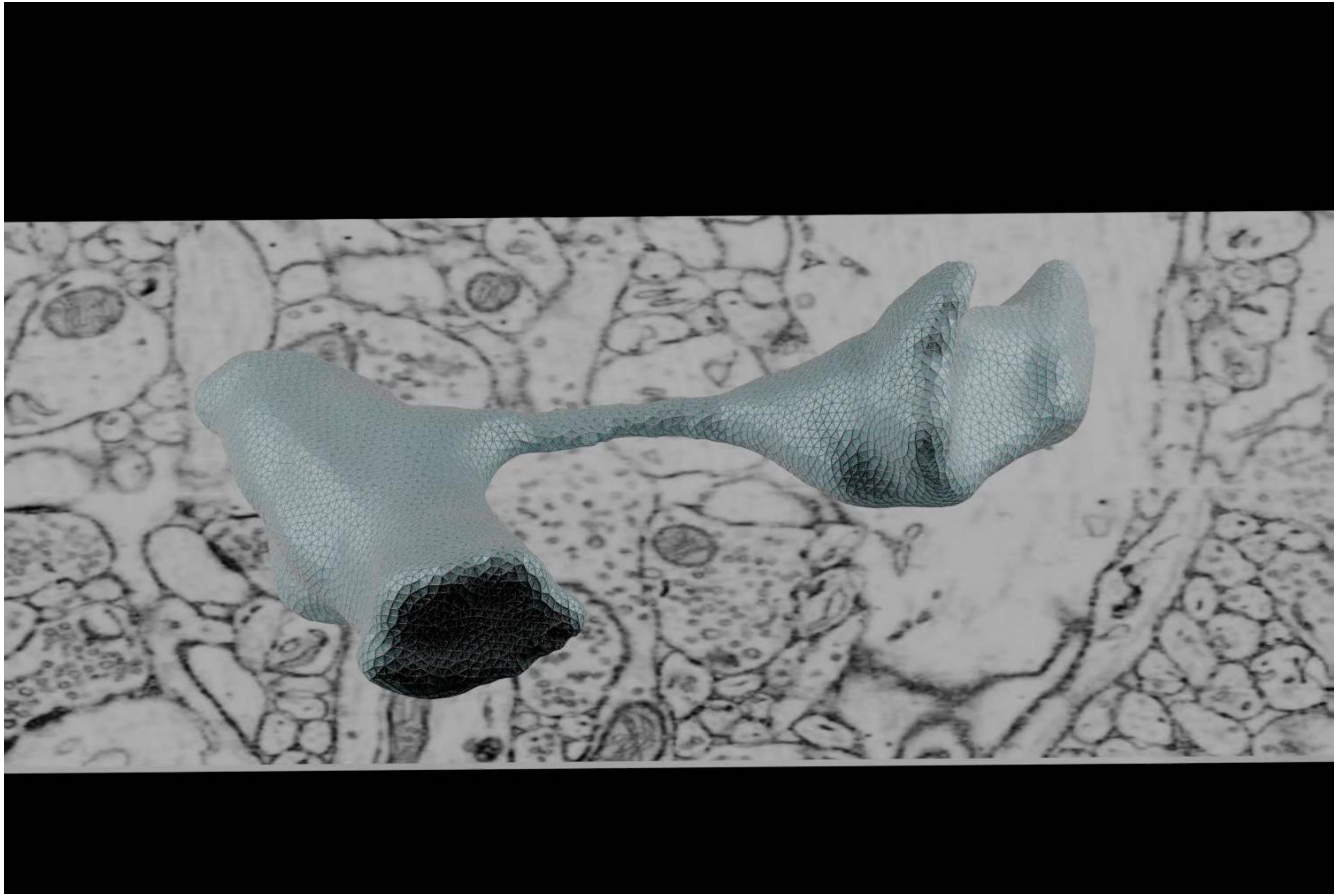
Creation of meshes for complicated cell geometries – GAMer2

- Example below: meshes for a dendritic spine (bulbous protrusion from the dendrite of a neuron)
- GAMer2 allows for preservation of geometrical features while providing a smoother, better conditioned mesh for FEA



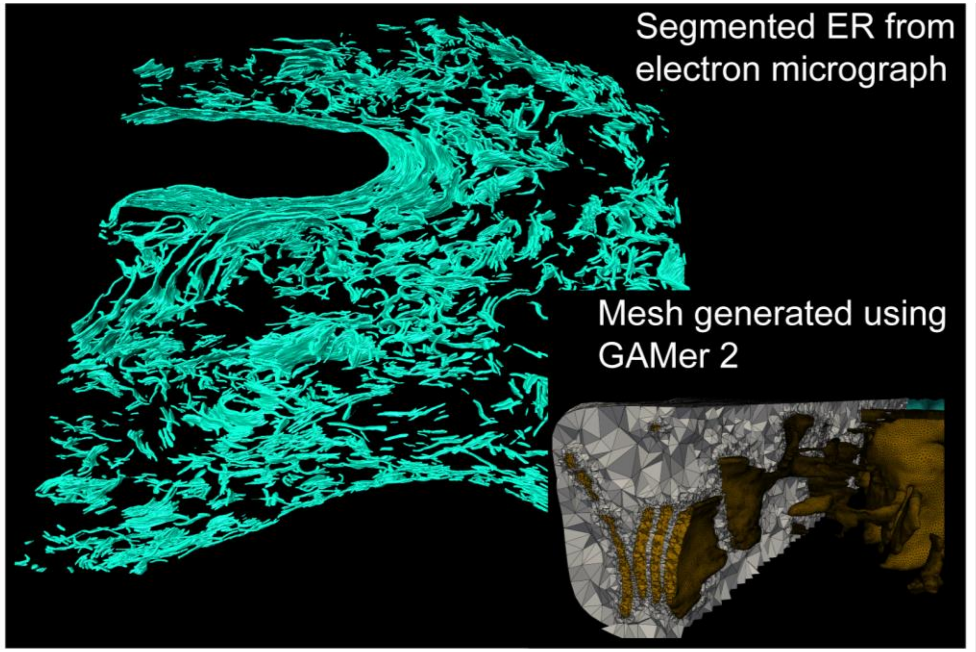
Lee et al 2020, *PLOS Comp Bio*

Creation of meshes for complicated cell geometries – GAMer2

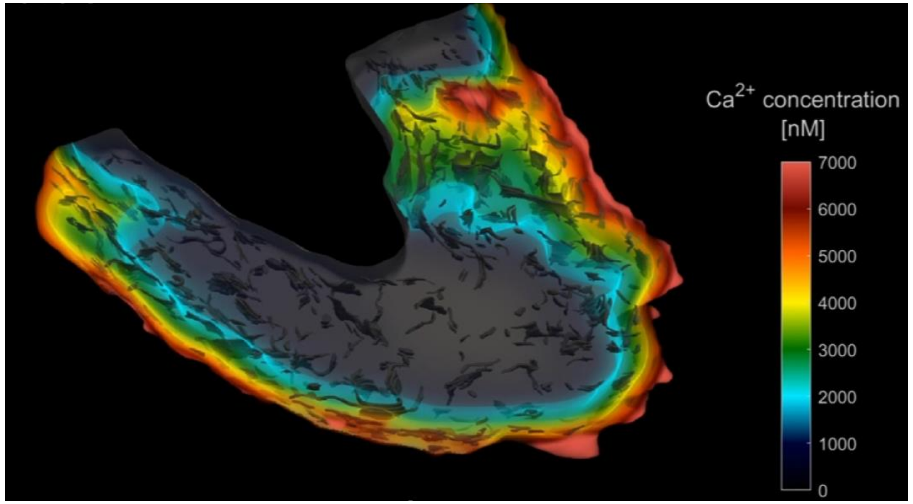


Lee et al 2020, *PLOS Comp Bio*

Spatial algorithms for reaction and transport (SMART) – modeling signaling networks in realistic cell geometries



SMART



Outline for today's talk:

1. Brief overview of formulation of equations and solution techniques in SMART.
2. Calcium dynamics in dendritic spines
3. Calcium dynamics in Purkinje neuron soma

Formulation of mixed dimensional reaction-transport systems

Consider a volumetric compartment, Ω^m, with boundary Γ^q and normal $\mathbf{n}^m$, and adjacent to other volumetric compartments Ω^n

For each species in this compartment, with concentration u_i^m,

Diffusion **Volume reactions**

$$\partial_t u_i^m - \nabla \cdot (D_i \nabla u_i^m) - f_i^m(u^m) = 0 \qquad \text{in } \Omega^m$$

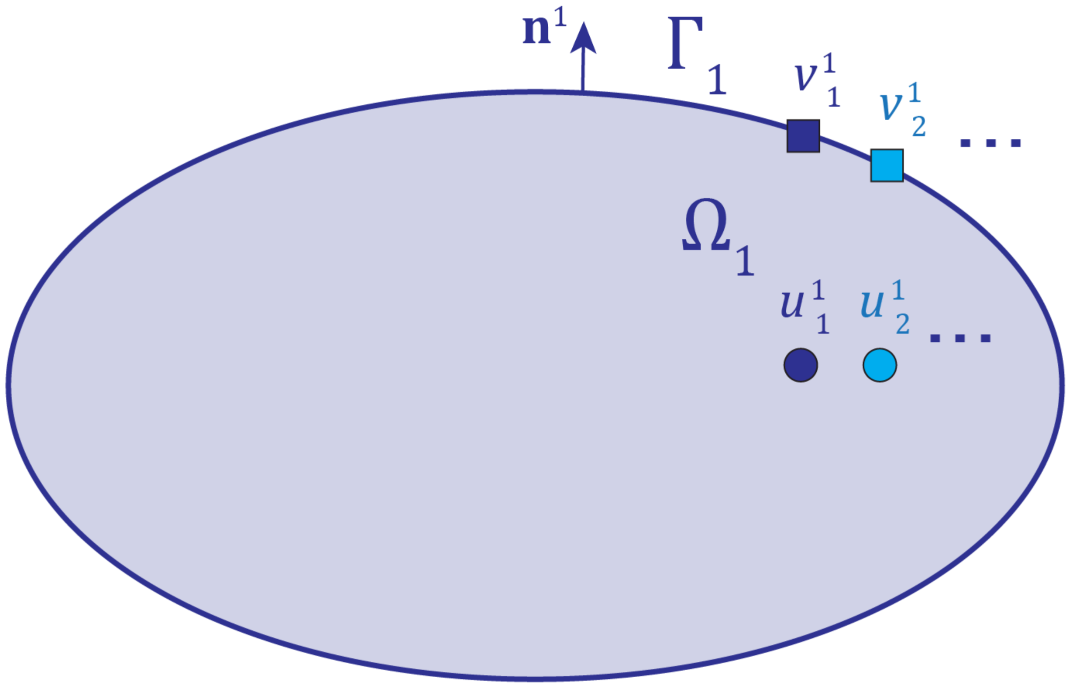
Diffusive flux **Surface reactions**

$$D_i \nabla u_i^m \cdot \mathbf{n}^m - R_i^q(u^m, u^n, v^q) = 0 \qquad \text{on } \Gamma^q$$

For each species on the boundary of this compartment, with concentration v_j^q,

Surface diffusion **Surface reactions**

$$\partial_t v_j^q - \nabla \cdot \left(D_j \nabla v_j^q\right) - g_j^q(u^m, u^n, v^q) = 0 \qquad \text{on } \Gamma^q$$



Francis and Laughlin, in preparation

Formulation of mixed dimensional reaction-transport systems

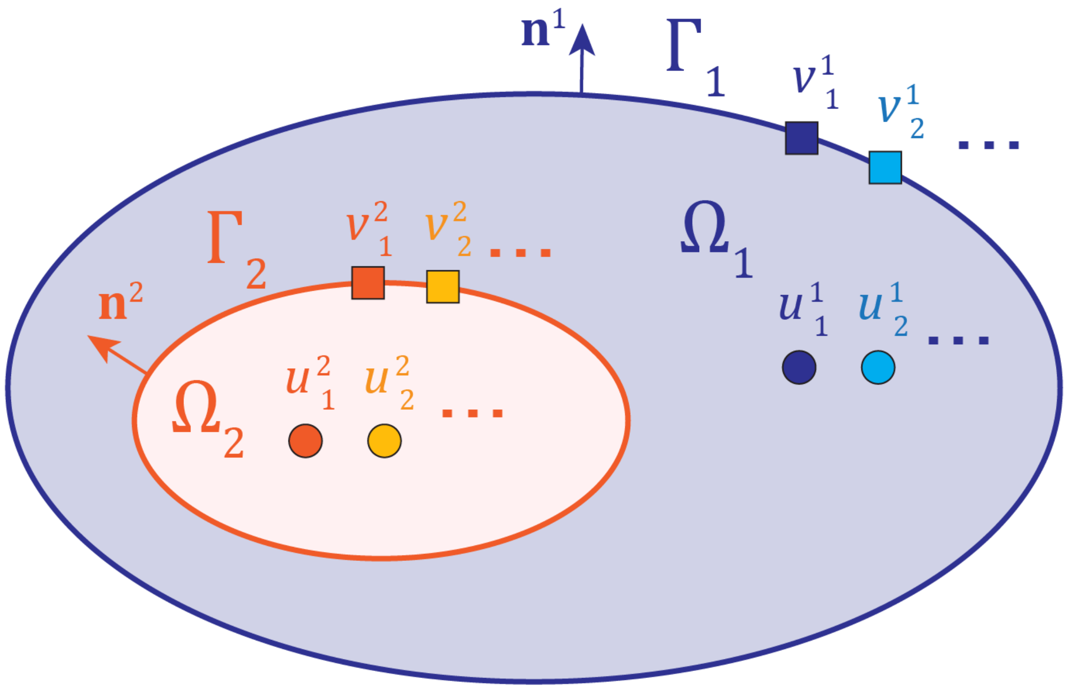
$$\partial_t u_i^m - \nabla \cdot (D_i \nabla u_i^m) - f_i^m(u^m) = 0 \qquad \text{in } \Omega^m$$

$$D_i \nabla u_i^m \cdot \mathbf{n}^m - R_i^q(u^m, u^n, v^q) = 0 \qquad \text{on } \Gamma^q$$

$\rightarrow$ Variational form F_i^m

$$\partial_t v_j^q - \nabla \cdot \left(D_j \nabla v_j^q\right) - g_j^q(u^m, u^n, v^q) = 0 \qquad \text{on } \Gamma^q$$

$\rightarrow$ Variational form G_j^q



Monolithic formulation – consider the sum of all variational forms for each subproblem:

$$F(u, v; \phi) + G(u, v; \psi) = 0,$$

where both forms F and G are composed of sums over domains or surfaces and species:

$$F(u, v; \phi) = \sum_{m \in \mathcal{M}} \sum_{i \in \mathcal{I}^m} F_i^m(u, v; \phi_i^m), \qquad G(u, v; \psi) = \sum_{q \in \mathcal{Q}} \sum_{i \in \mathcal{I}^q} G_i^q(u, v; \psi_i^q).$$

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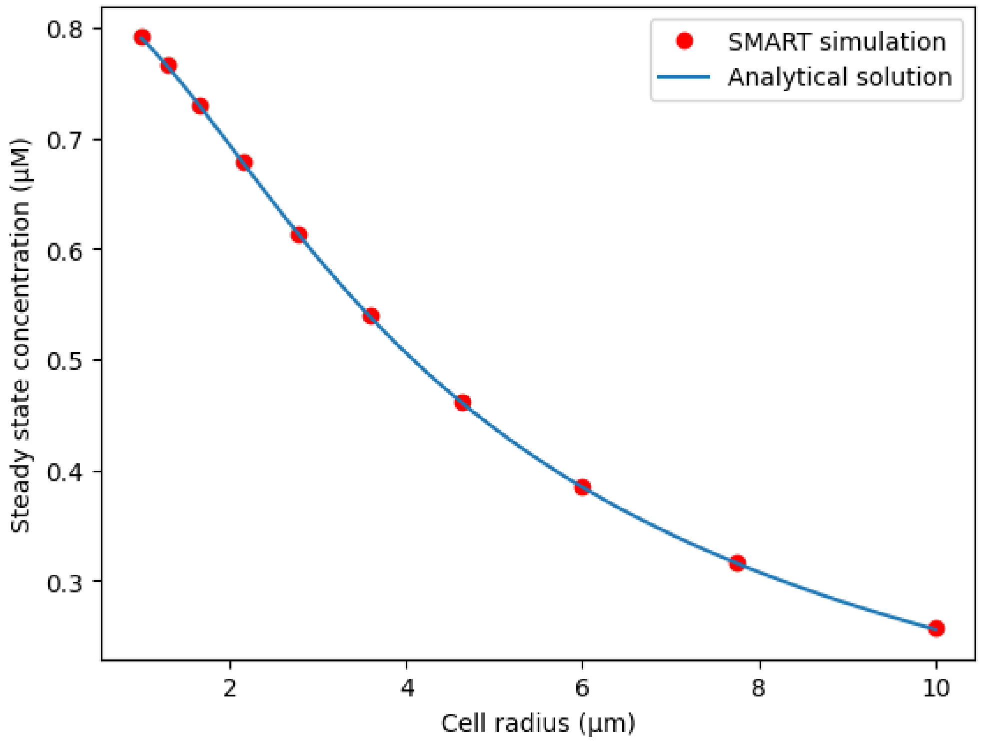
Numerical methods and validation in SMART

- Use backward Euler for time discretization
- Assemble nonlinear finite element system using FEniCS
- Solve this system using Newton-Raphson iteration in PETSc

Validated SMART by testing problems with known analytical solutions



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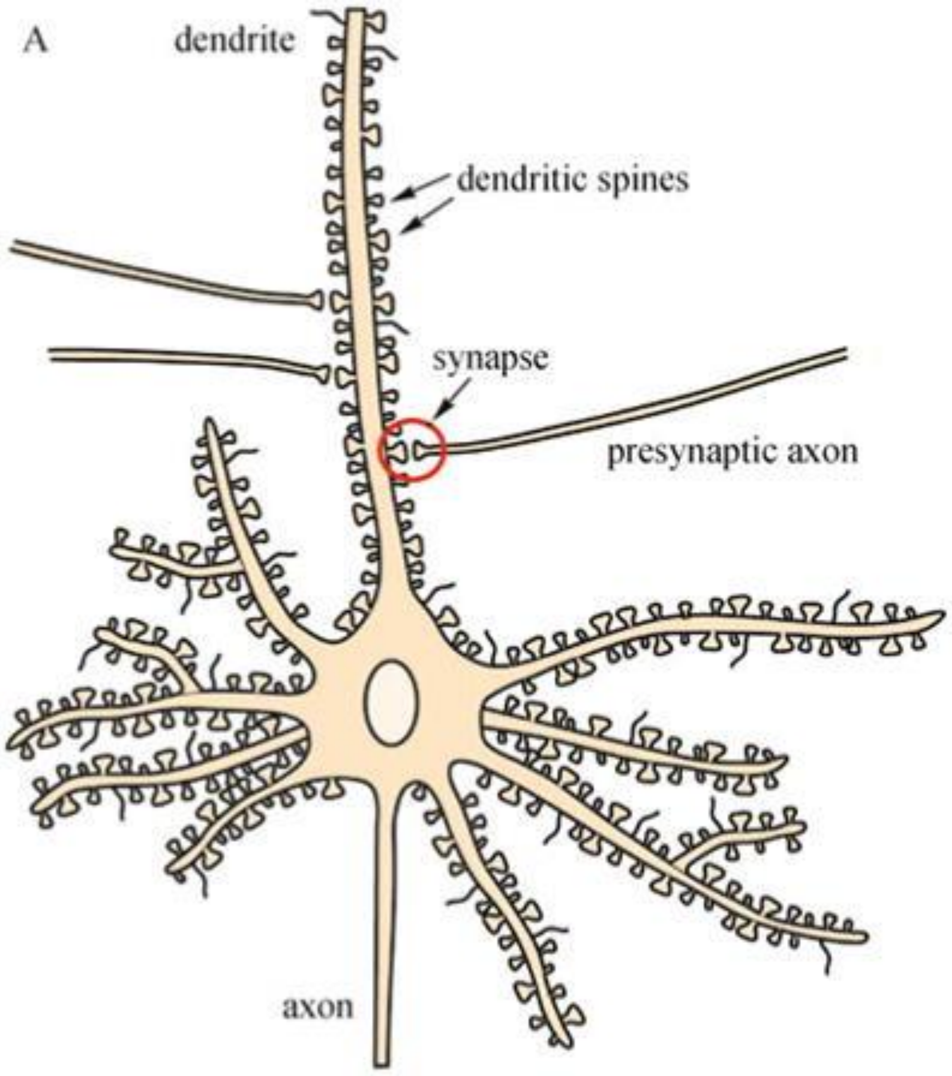
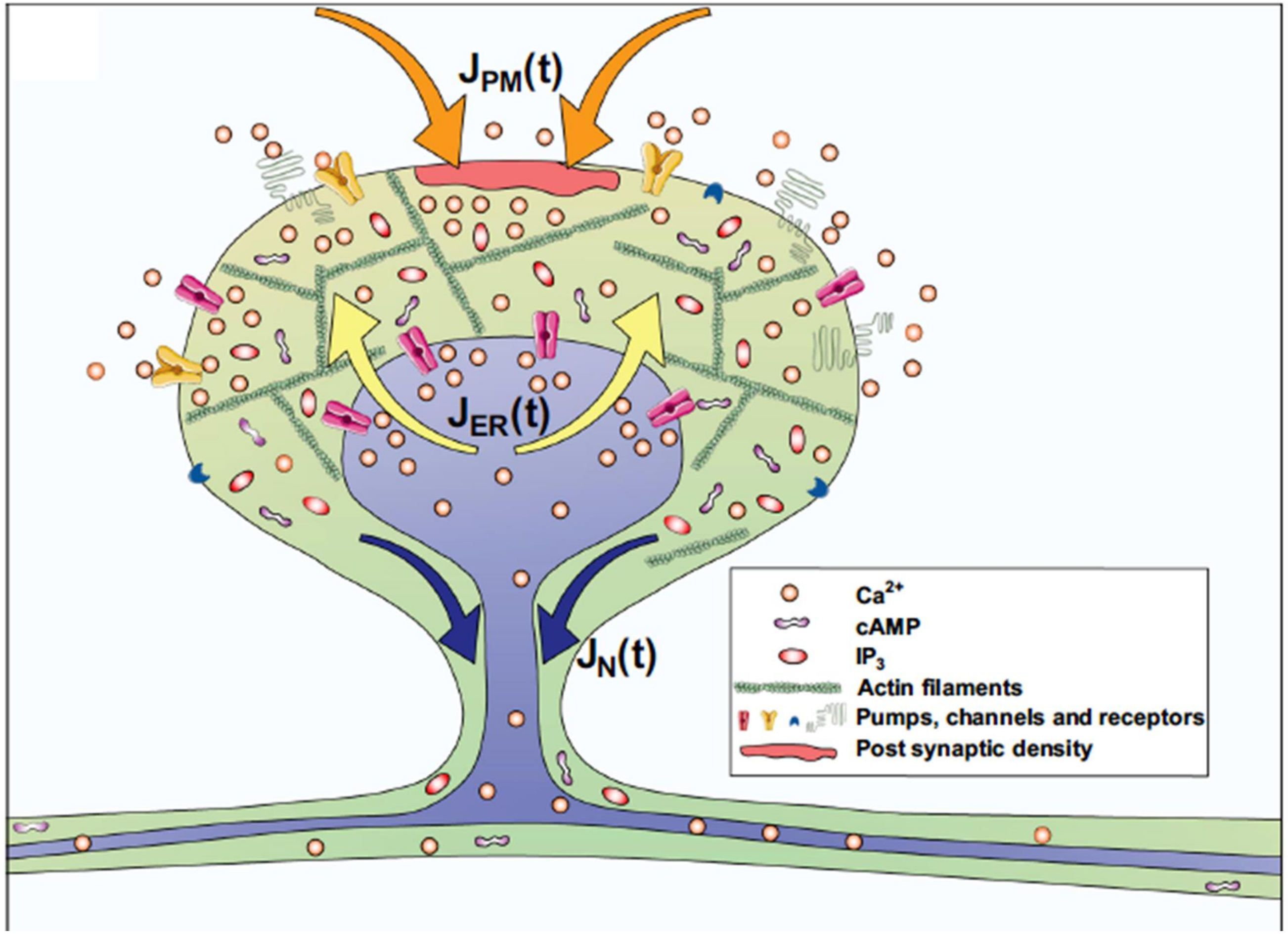
Overview of Ca^{2+} signaling networks in neurons

Neuron morphology - Smrt and Zhao, *Front Biol* 2015



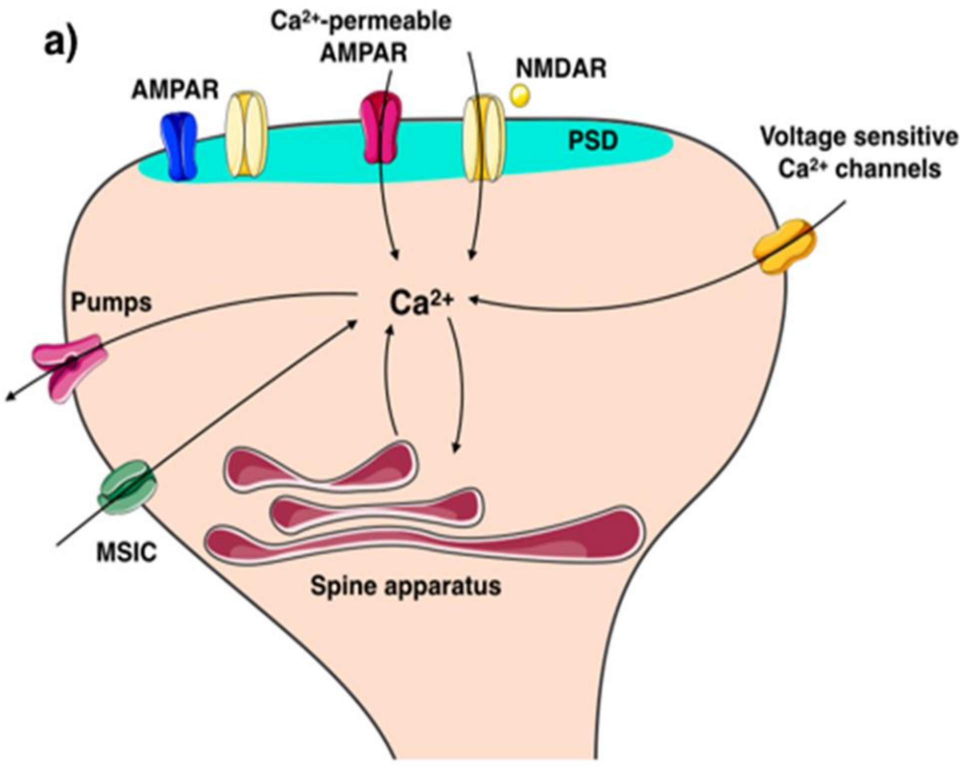
The complex signaling environment within a dendritic spine - Cugno et al. *Sci Rep* 2019



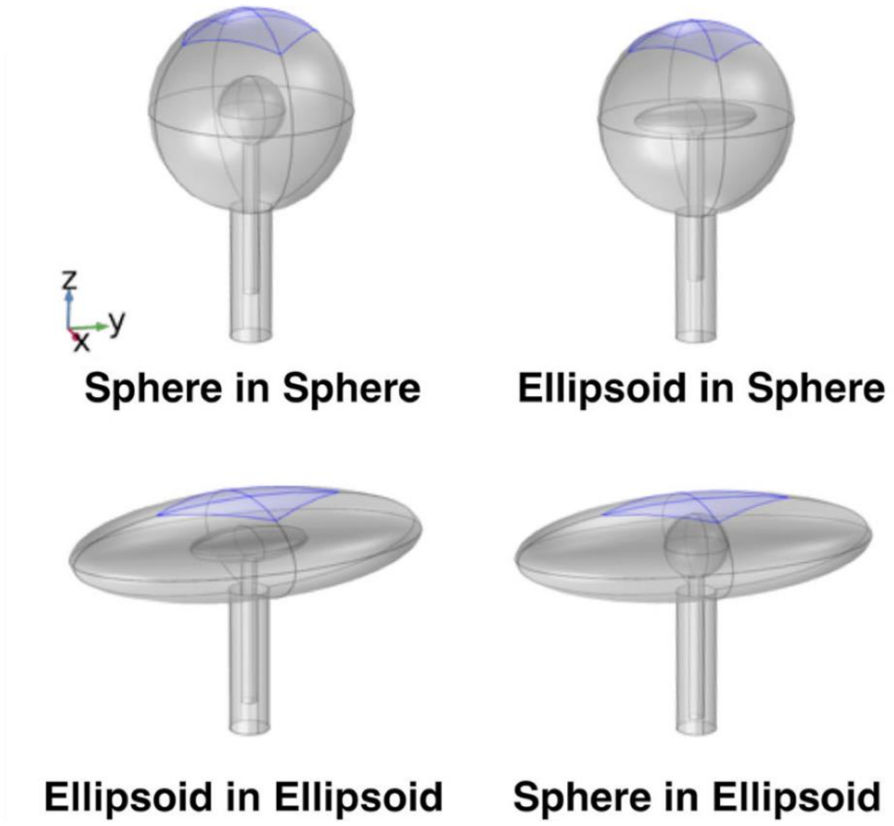
Testing Ca^{2+} dynamics in idealized geometries for dendritic spines

Model from Bell et al 2019:

- Ca^{2+} influx through VSCCs and NMDARs
- Ca^{2+} exits the cytosol through pumps into the spine apparatus (SA) or out of the PM

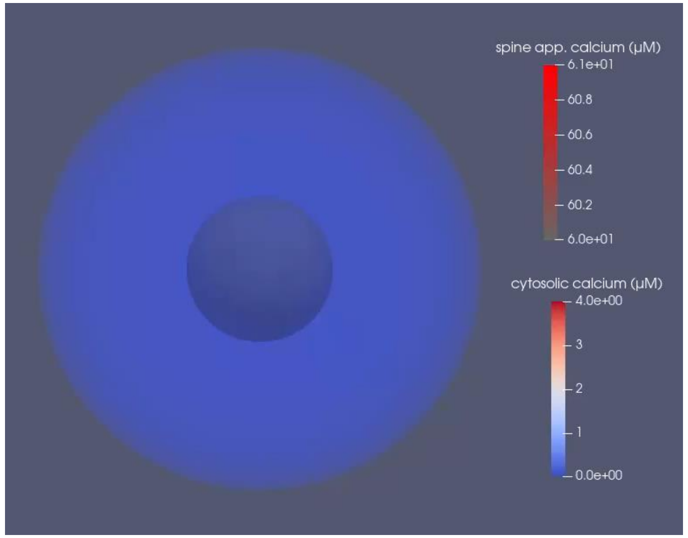


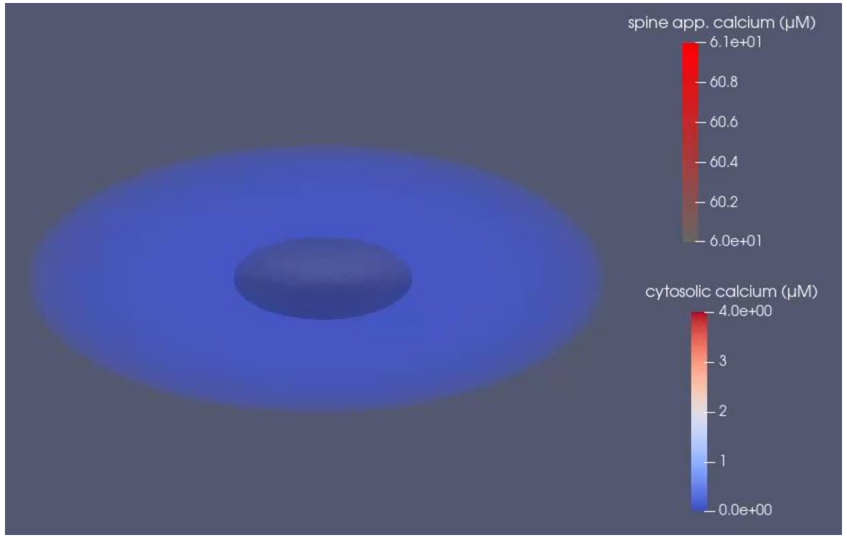
- 4 different geometries of spines with spine apparatus; volumes equal in all cases



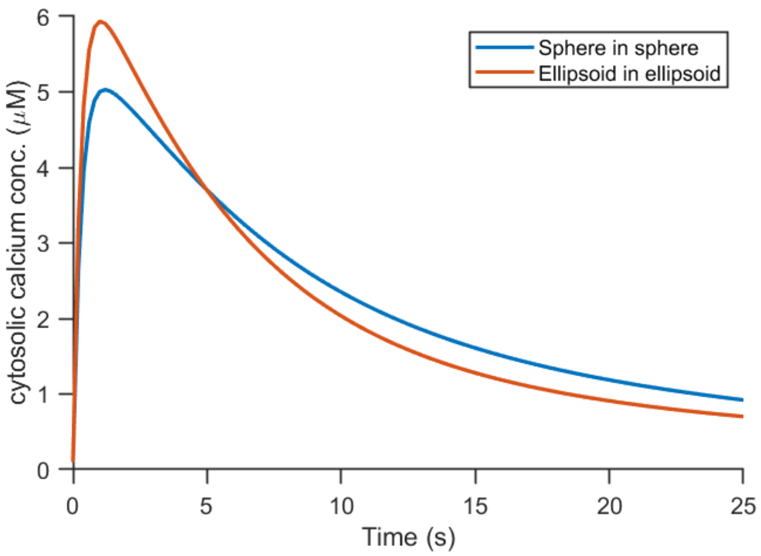
Bell et al 2019, *J Gen Physiology*

Increased spine apparatus surface area allows for faster pumping of Ca^{2+} out of the cytosol

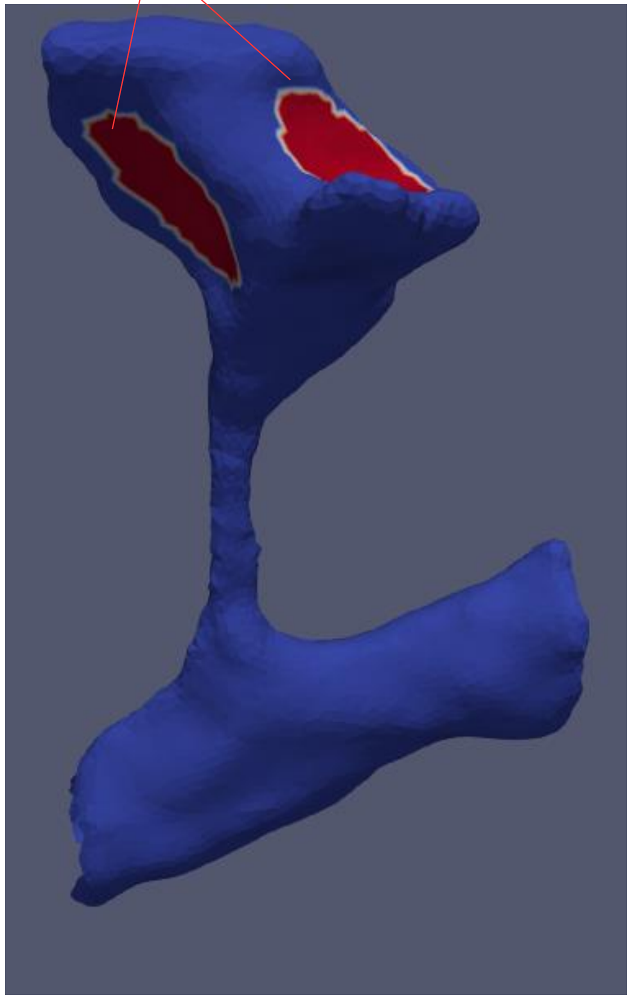


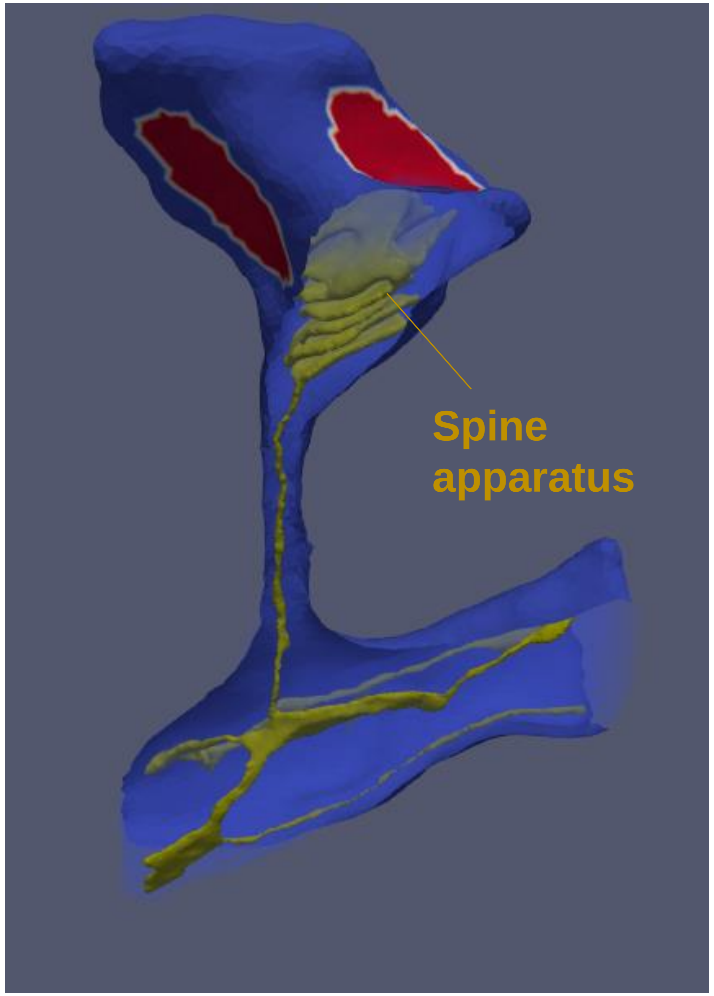


Ca^{2+} decreases fastest when surface area to volume ratios are maximized



Ca^{2+} dynamics in a realistic spine geometry





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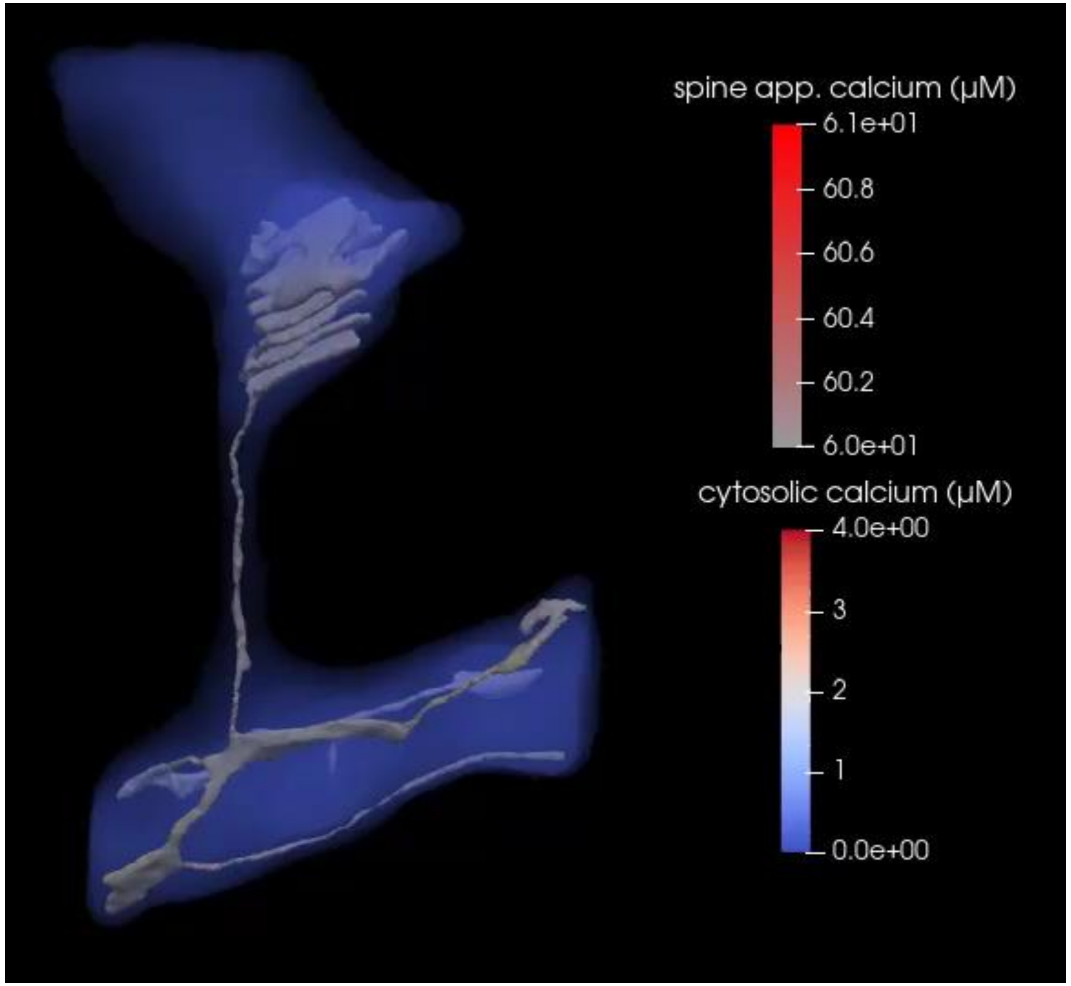
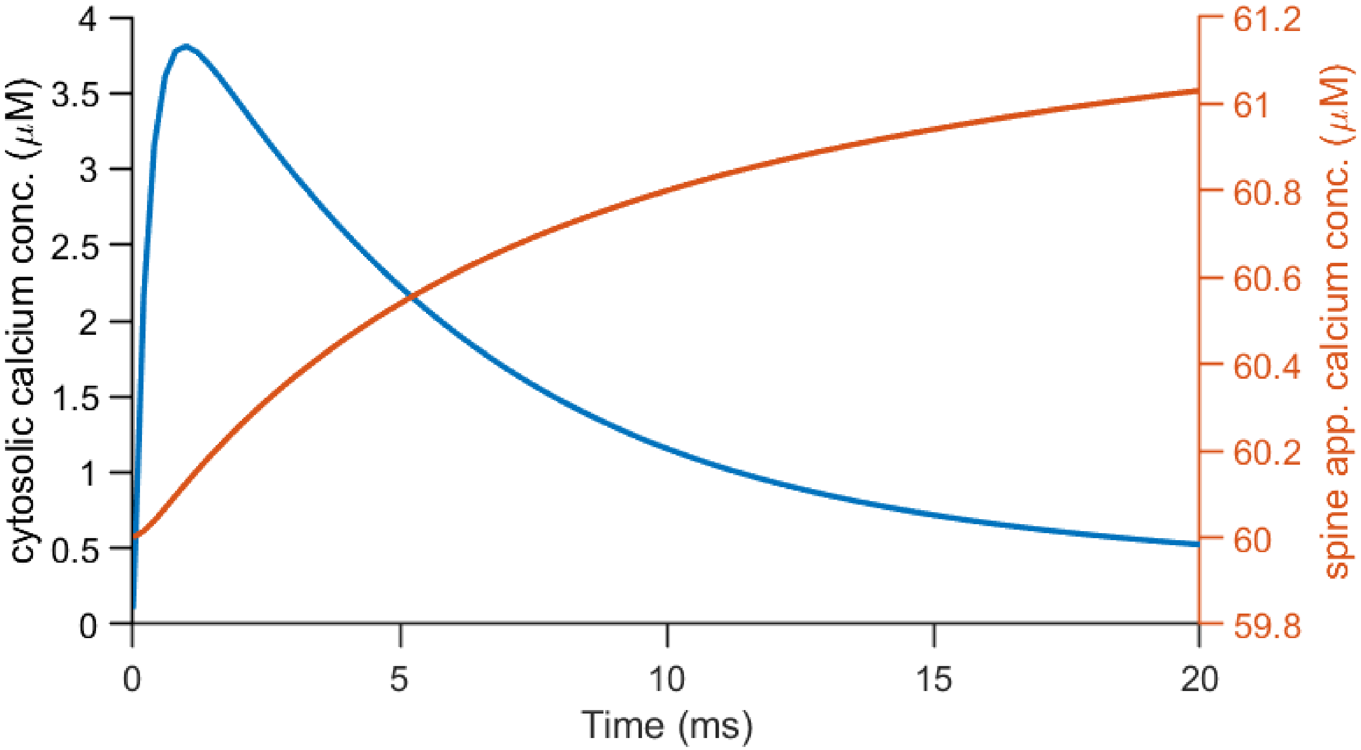
Calcium dynamics in a realistic spine geometry





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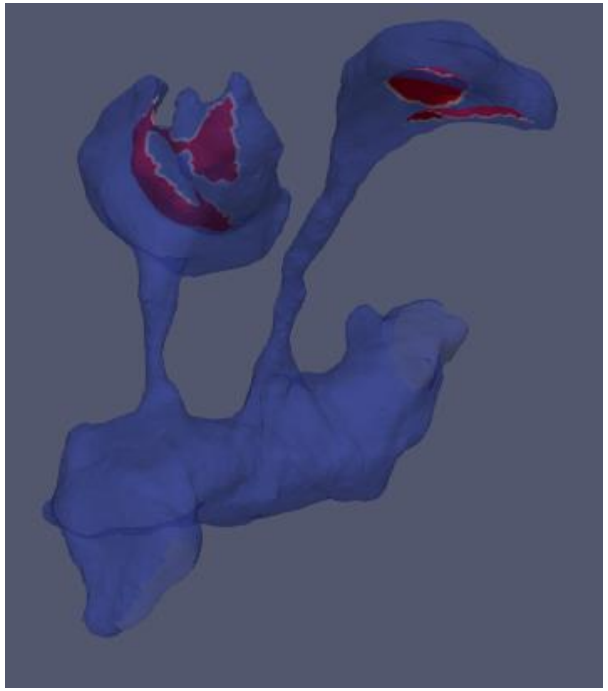
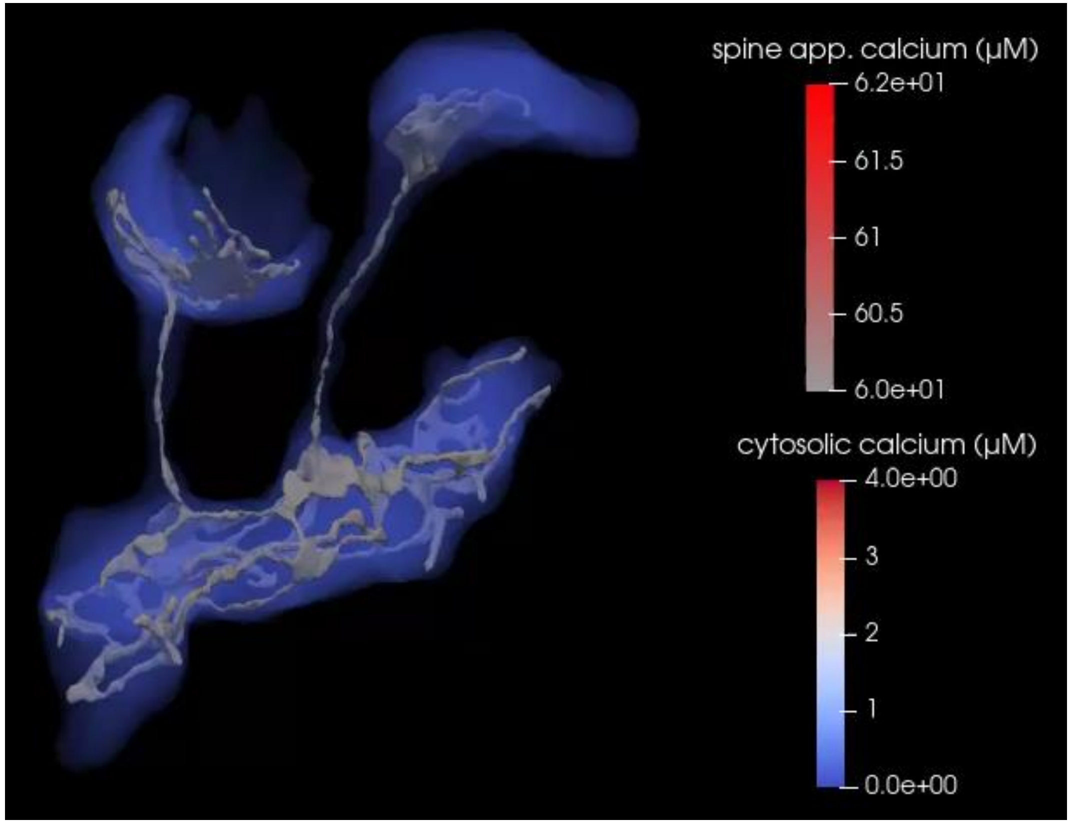
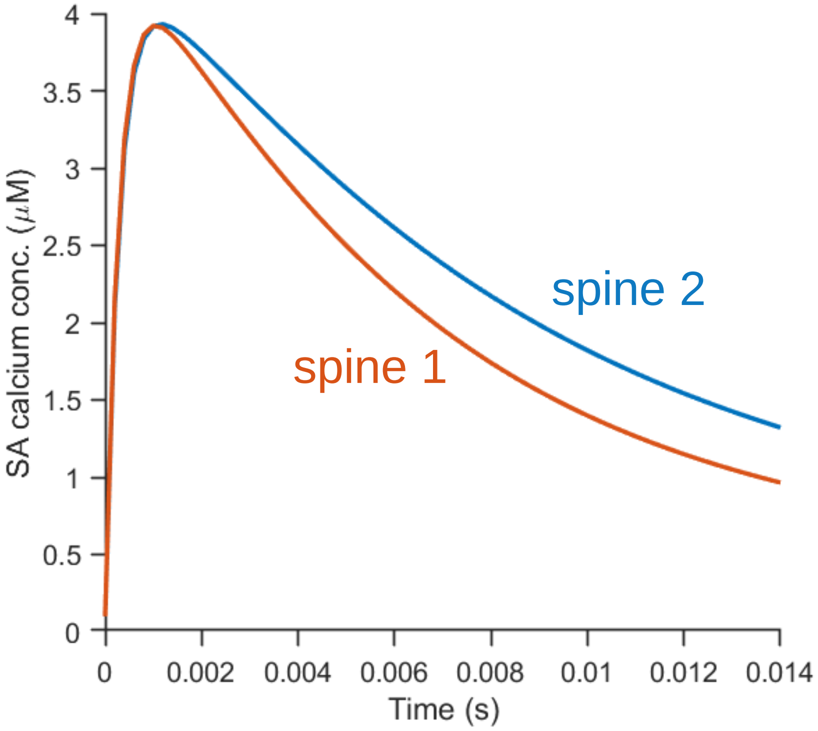
Calcium dynamics in two realistic dendritic spines

spine 1 spine 2





Ca^{2+} decreases faster in spine 1, where the spine apparatus surface area to cytosolic volume ratio is highest



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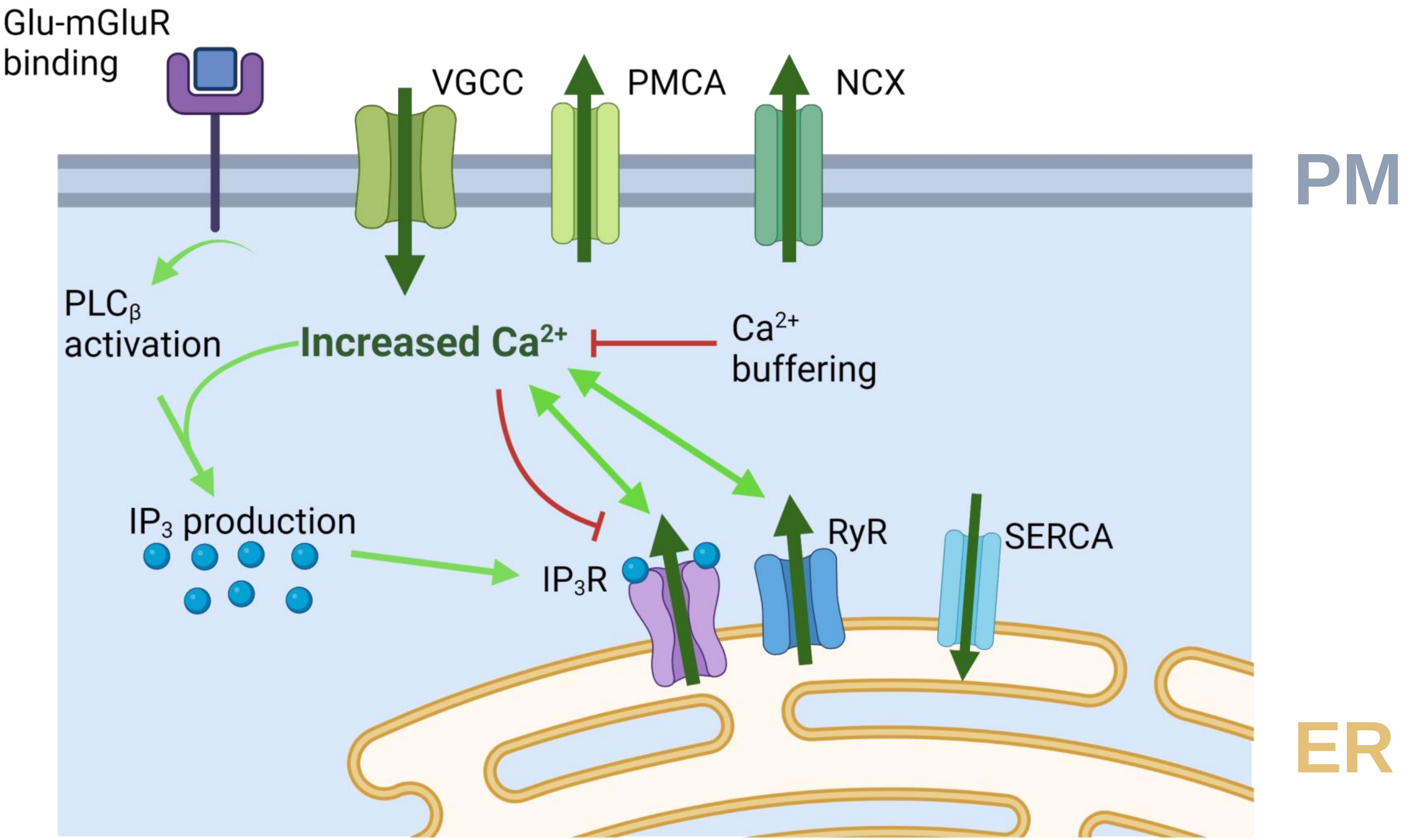
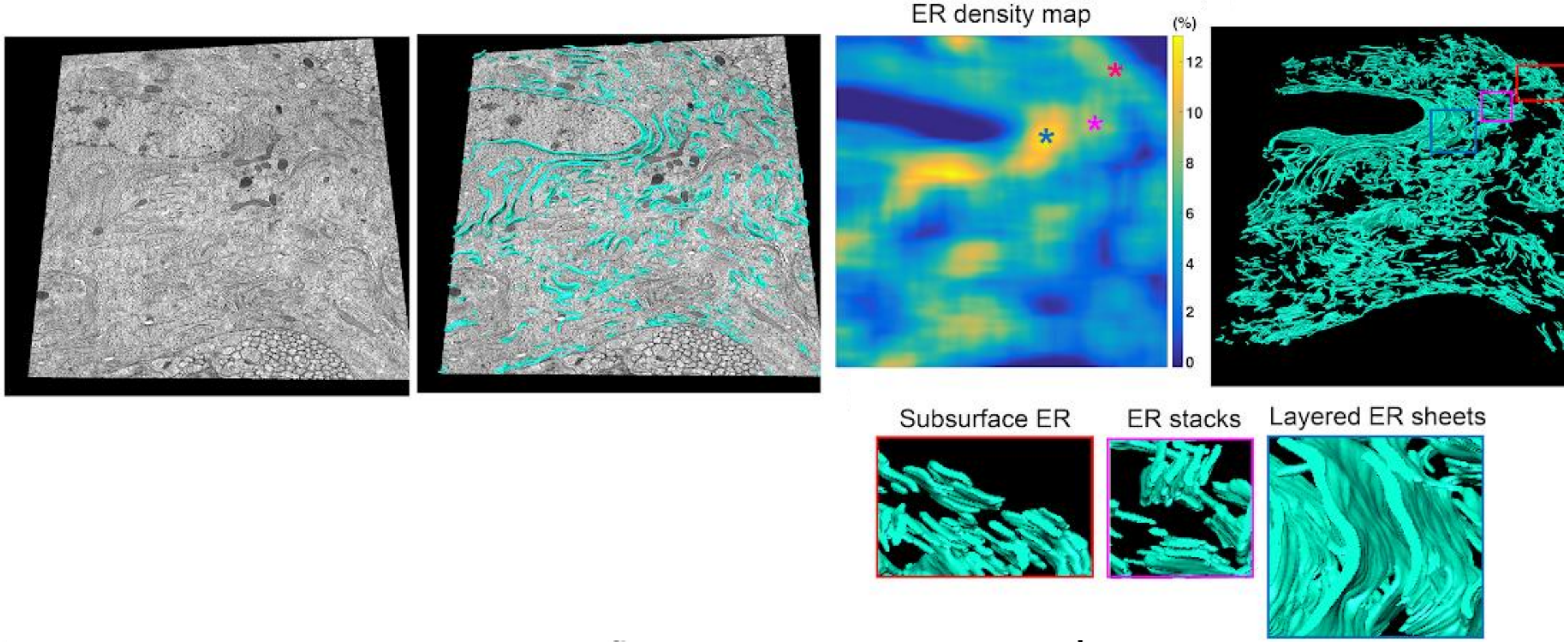
Including Ca^{2+} release through IP_3Rs and RyRs



Electron microscopy provides detailed characterization of the ER in the soma of Purkinje neurons

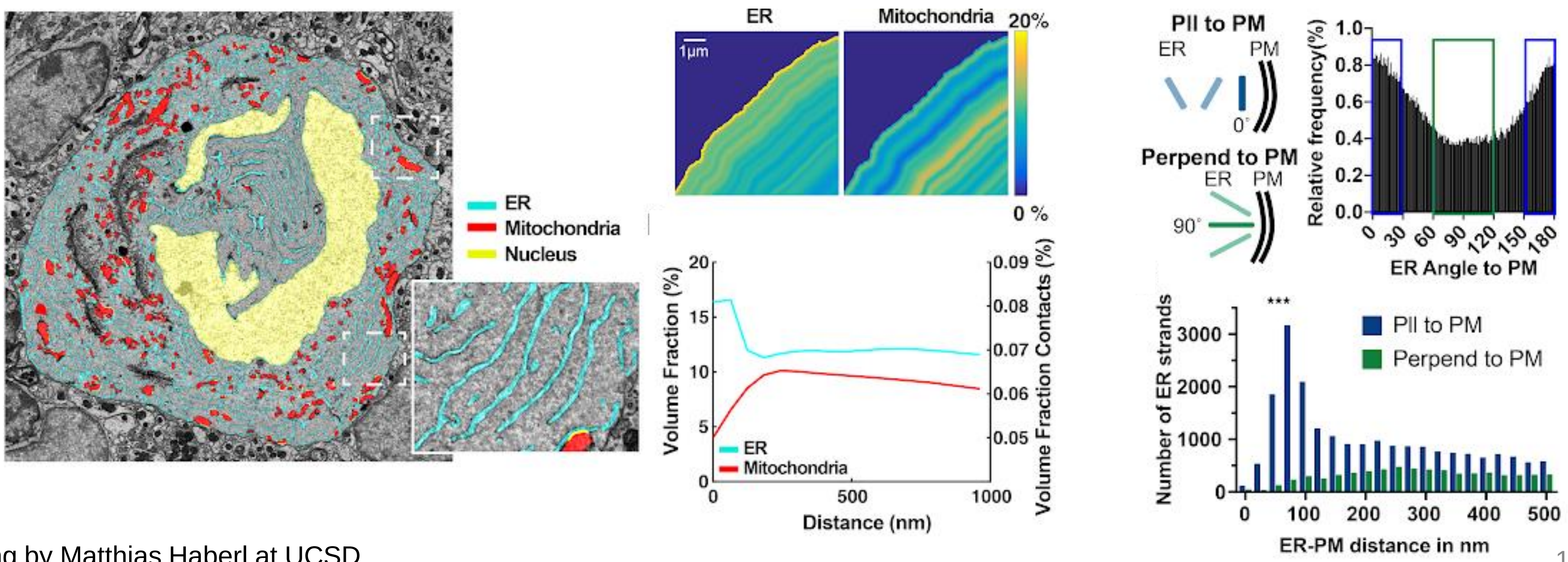
- Segmentation of electron micrographs identifies the ER within the main body (soma) of Purkinje neurons (collaboration with the Ellisman Lab)



Imaging by Matthias Haberl at UCSD

Electron microscopy provides detailed characterization of the ER in the soma of Purkinje neurons

- ER is localized close to the PM (within 100nm)
- Membrane-adjacent ER is preferentially oriented parallel to the PM



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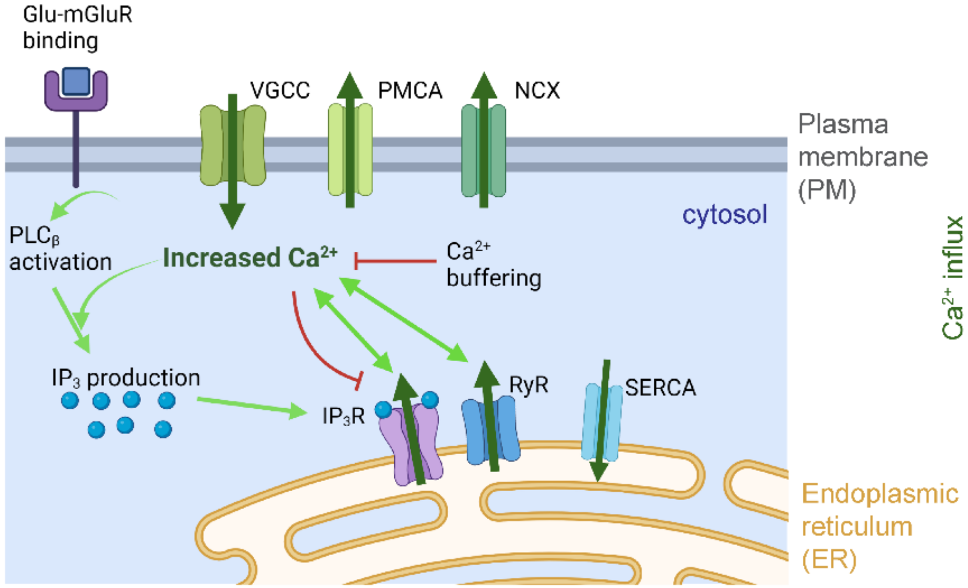
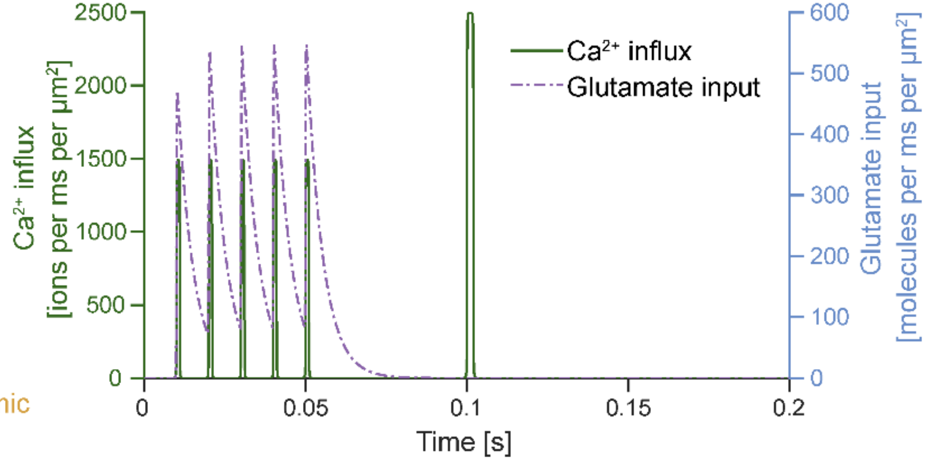
Model of calcium dynamics in the Purkinje neuron

- Detailed signaling model adapted from previous well-mixed model (Doi et al 2005, *J Neurosci*), converted to a spatial model – 26 species overall (21 surface, 5 volume)
- Inputs chosen to match physiological stimulus used in Doi et al





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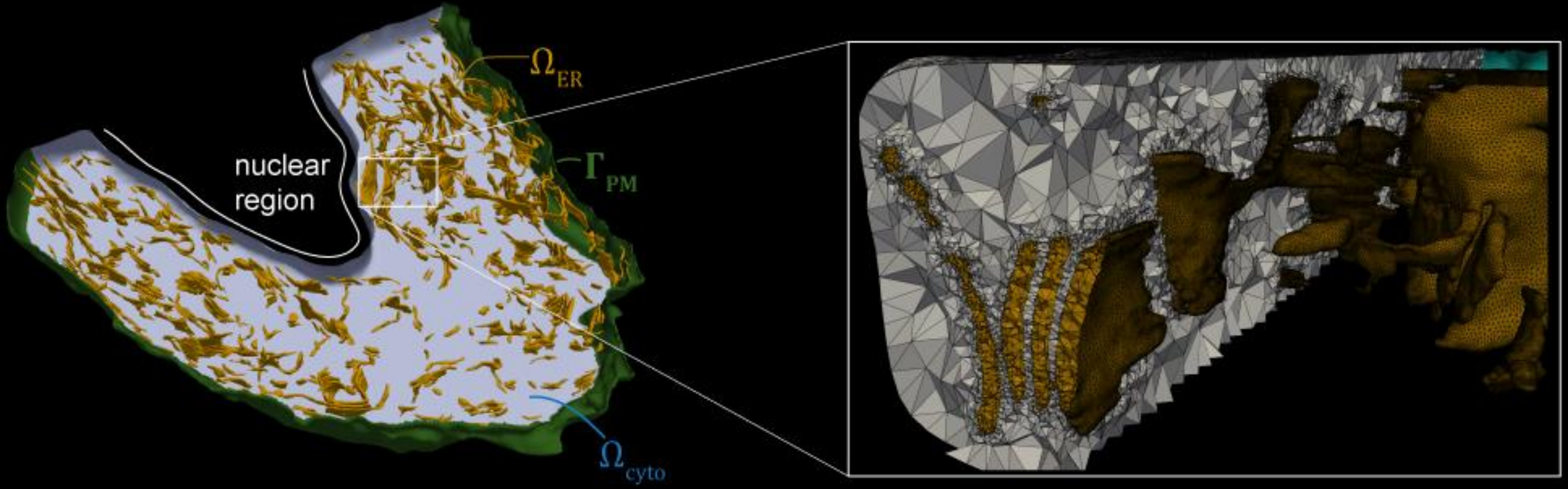
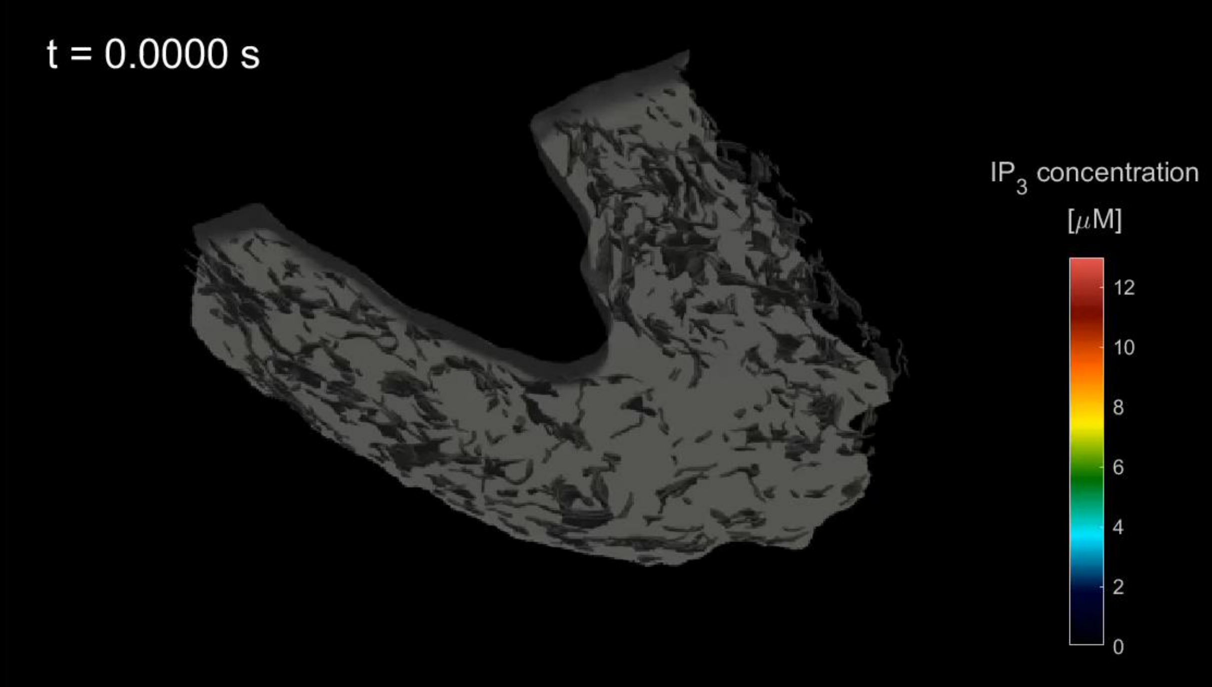
Examining Ca^{2+} dynamics in realistic soma geometries

- Region of Purkinje soma from electron microscopy was segmented into ER and cytosol
- Resulting mesh was conditioned using GAMer2
- Mesh statistics:
  - ~62 million tetrahedra total (25m in the cytosol, 37m in the ER)
  - ~11.6 million surface triangles (11.5m in ER membrane, .1m in the PM)
  - ~10 million points total in the whole geometry

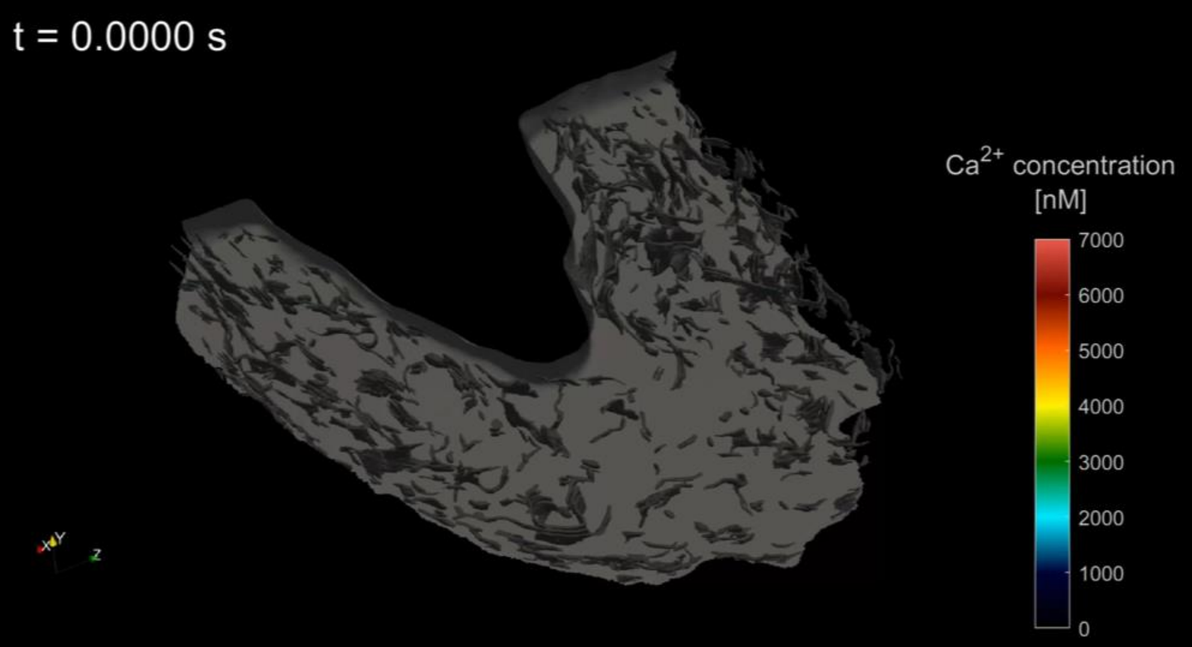


IP_3 and Ca^{2+} dynamics in a realistic Purkinje soma

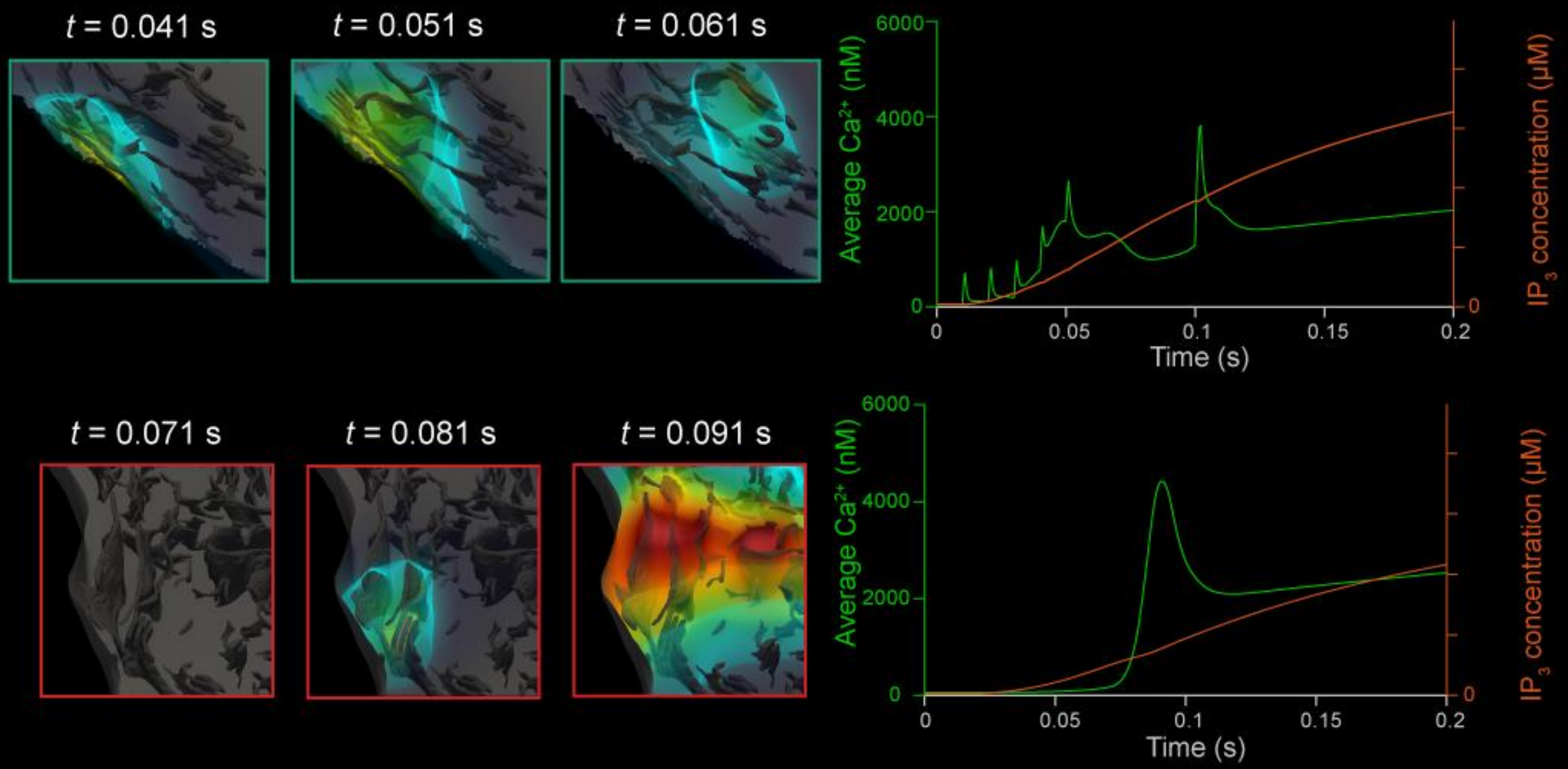
IP_3 dynamics



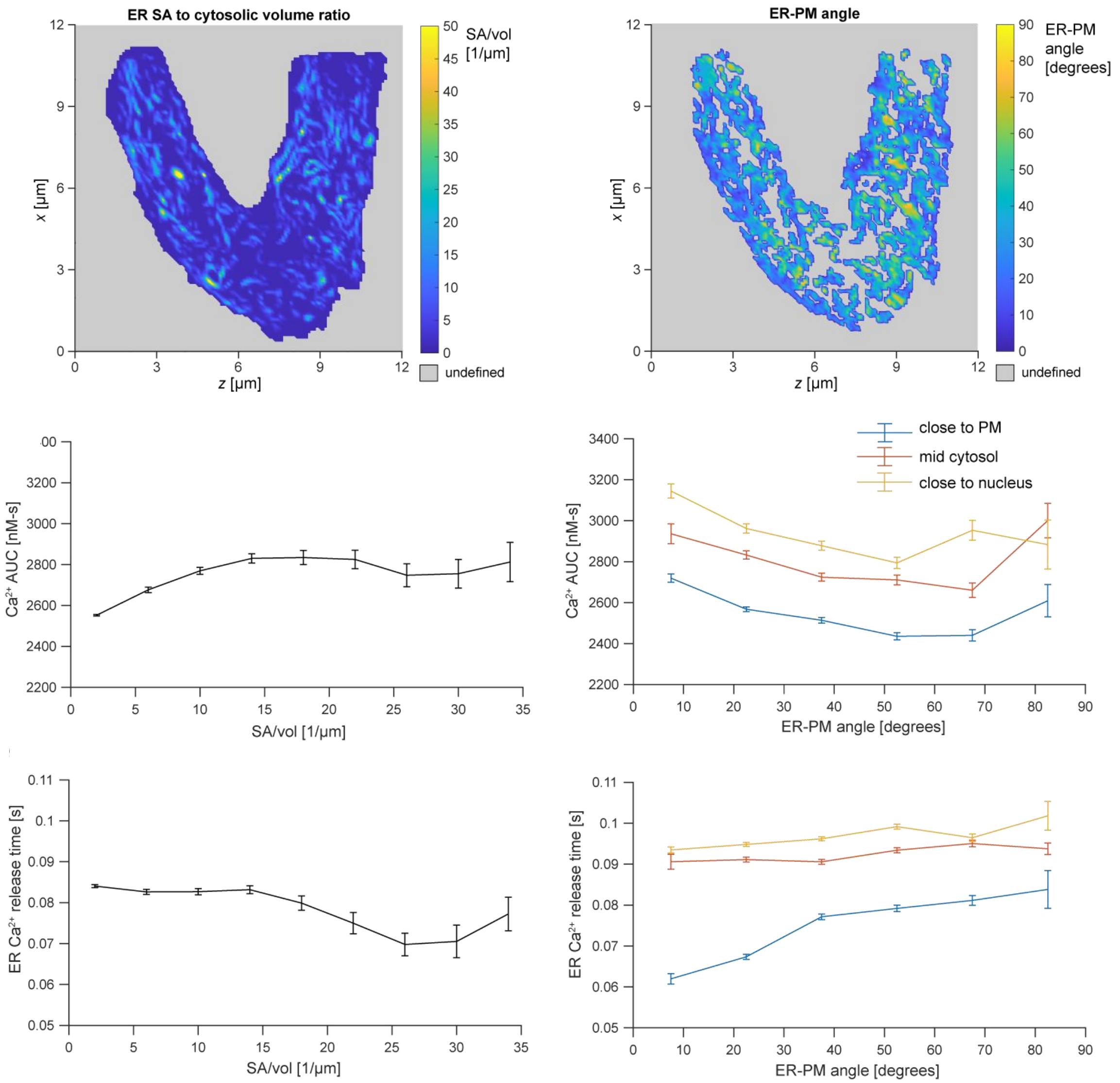
Ca^{2+} dynamics



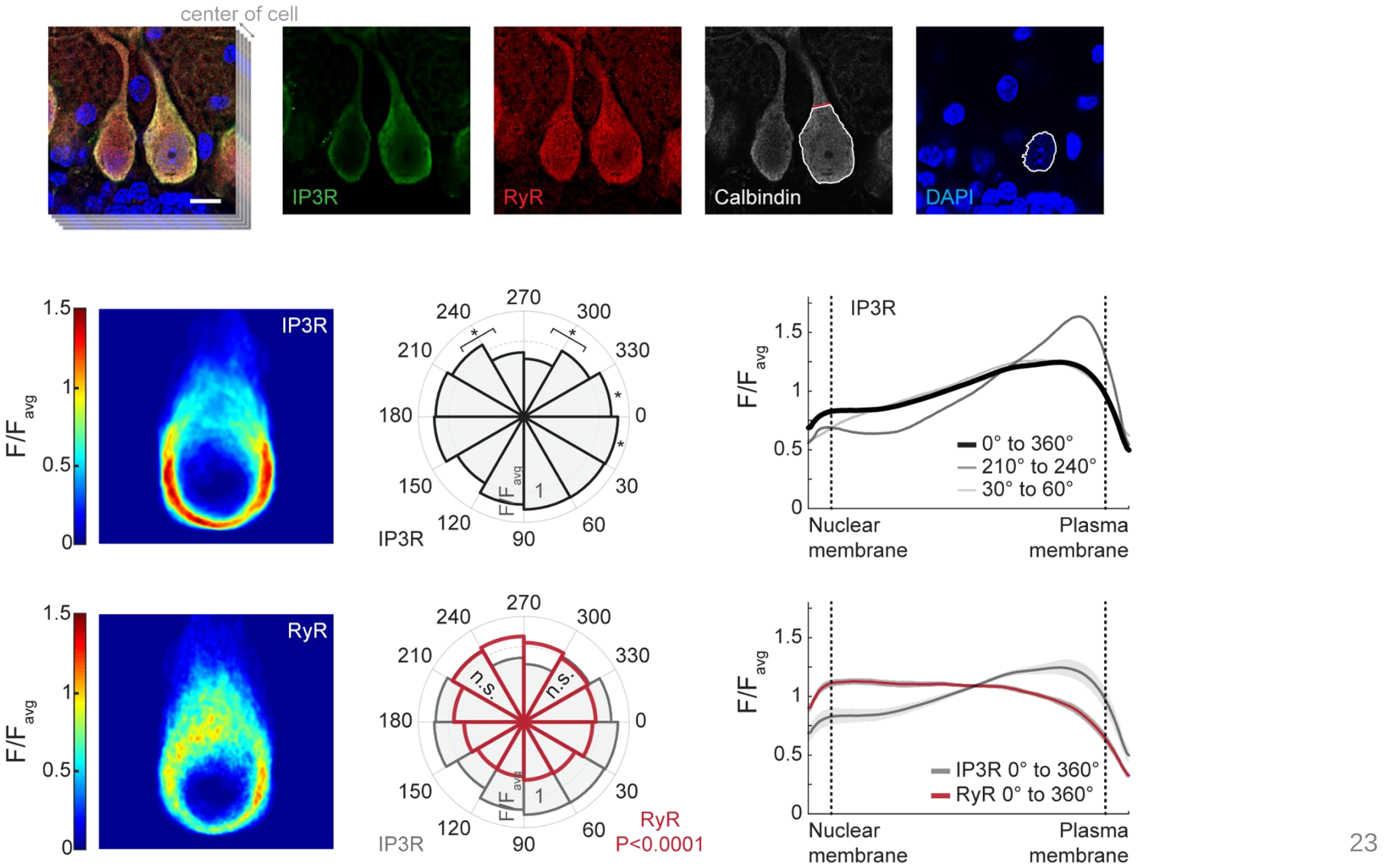
IP_3 and Ca^{2+} dynamics in a realistic Purkinje soma



ER spacing and orientation controls the timing and magnitude of calcium release



Experimental measurements of receptor distributions



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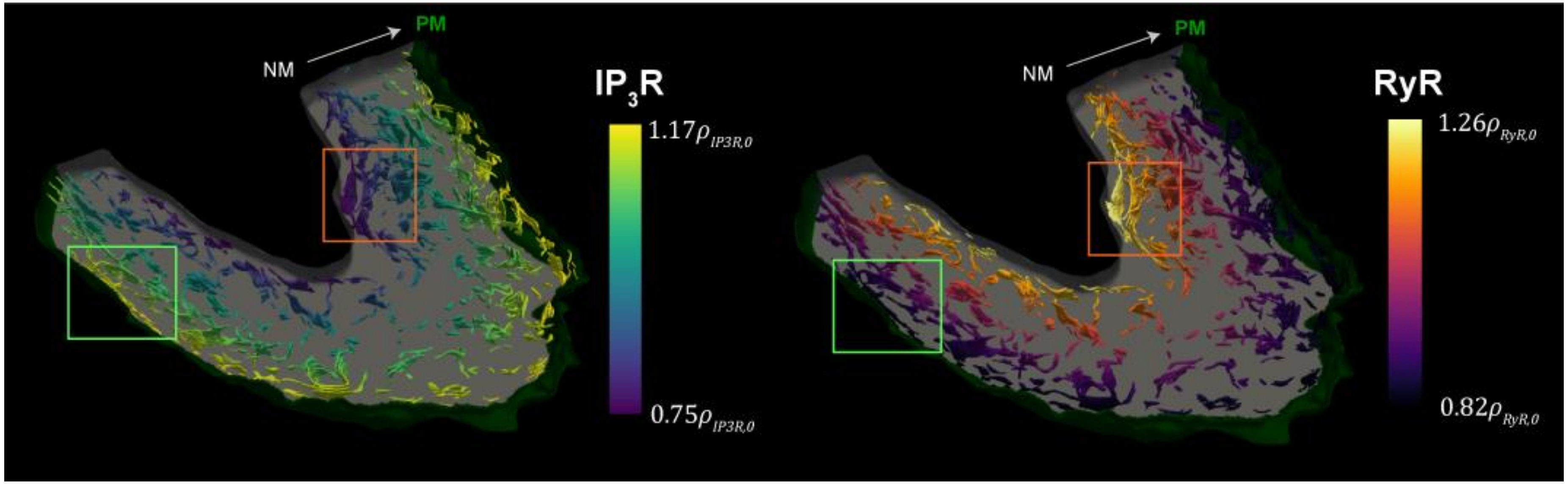
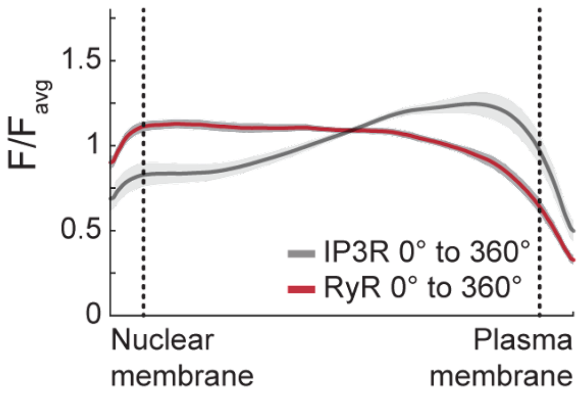
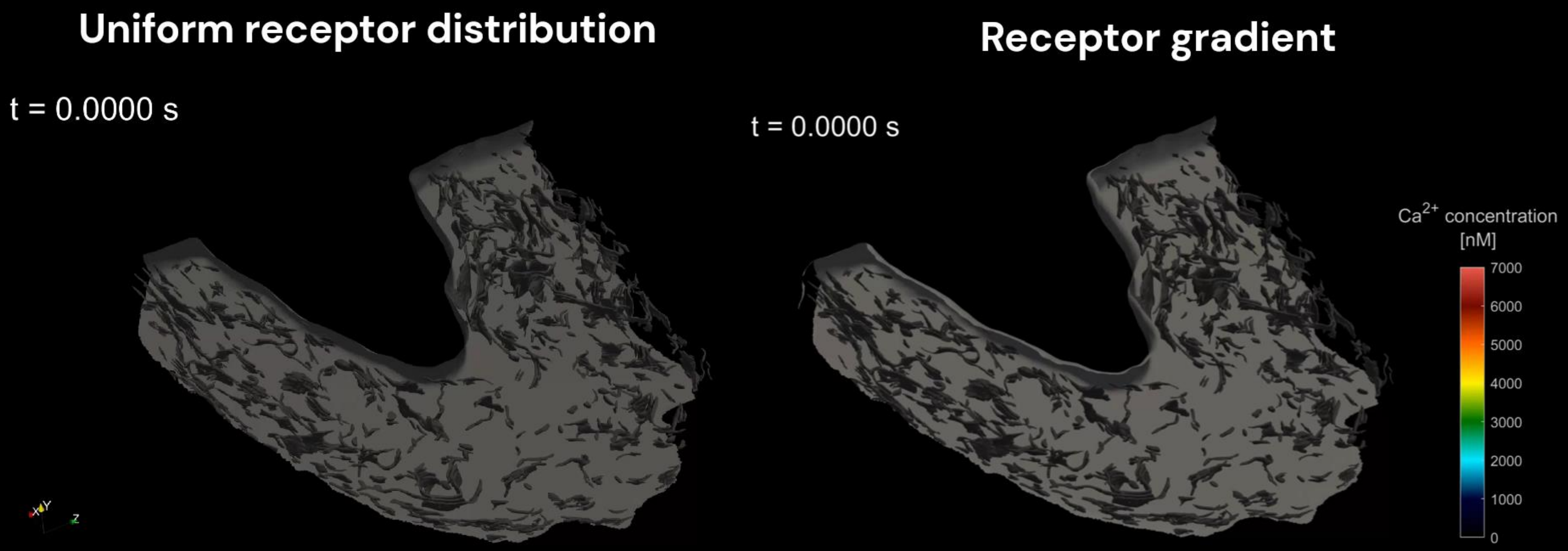
Whole-cell geometry with receptor gradients

- Gradients in realistic geometry chosen to match those observed experimentally (linear gradient as a function of distance from the PM)



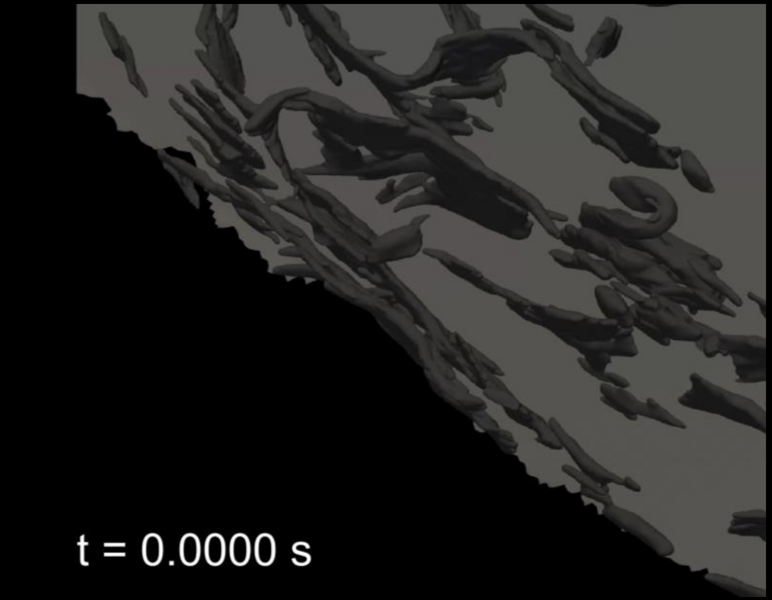


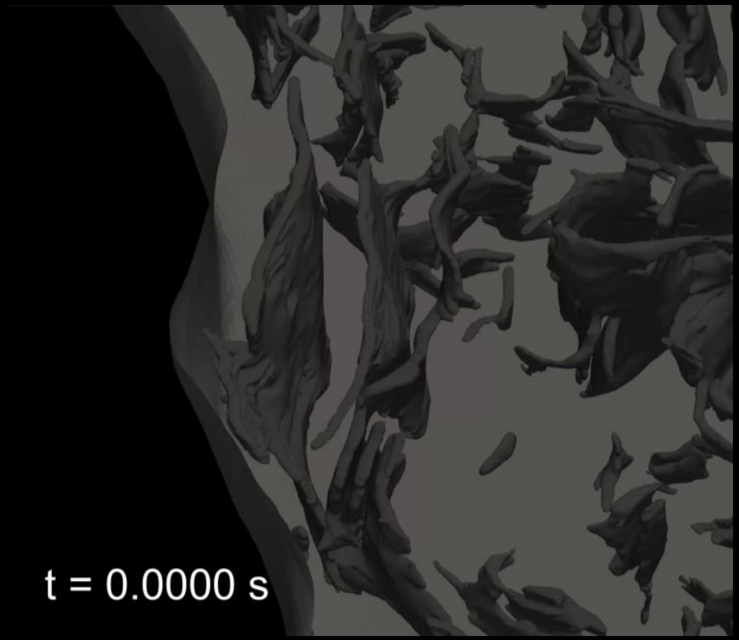
Ca^{2+} dynamics for uniform receptors vs. realistic receptor gradient



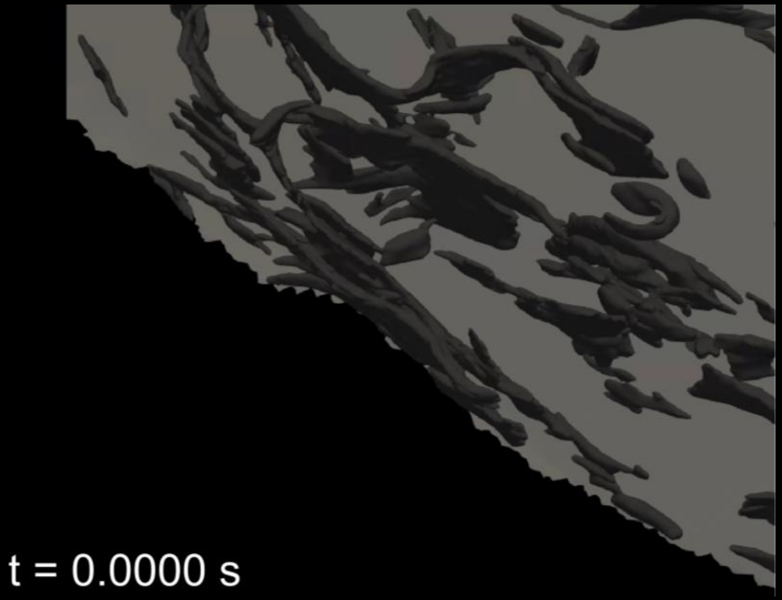
Ca^{2+} dynamics for uniform receptors vs. realistic receptor gradient

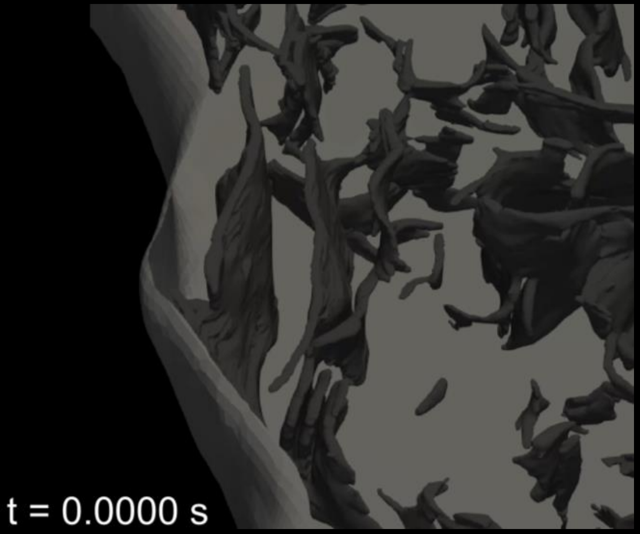
Control



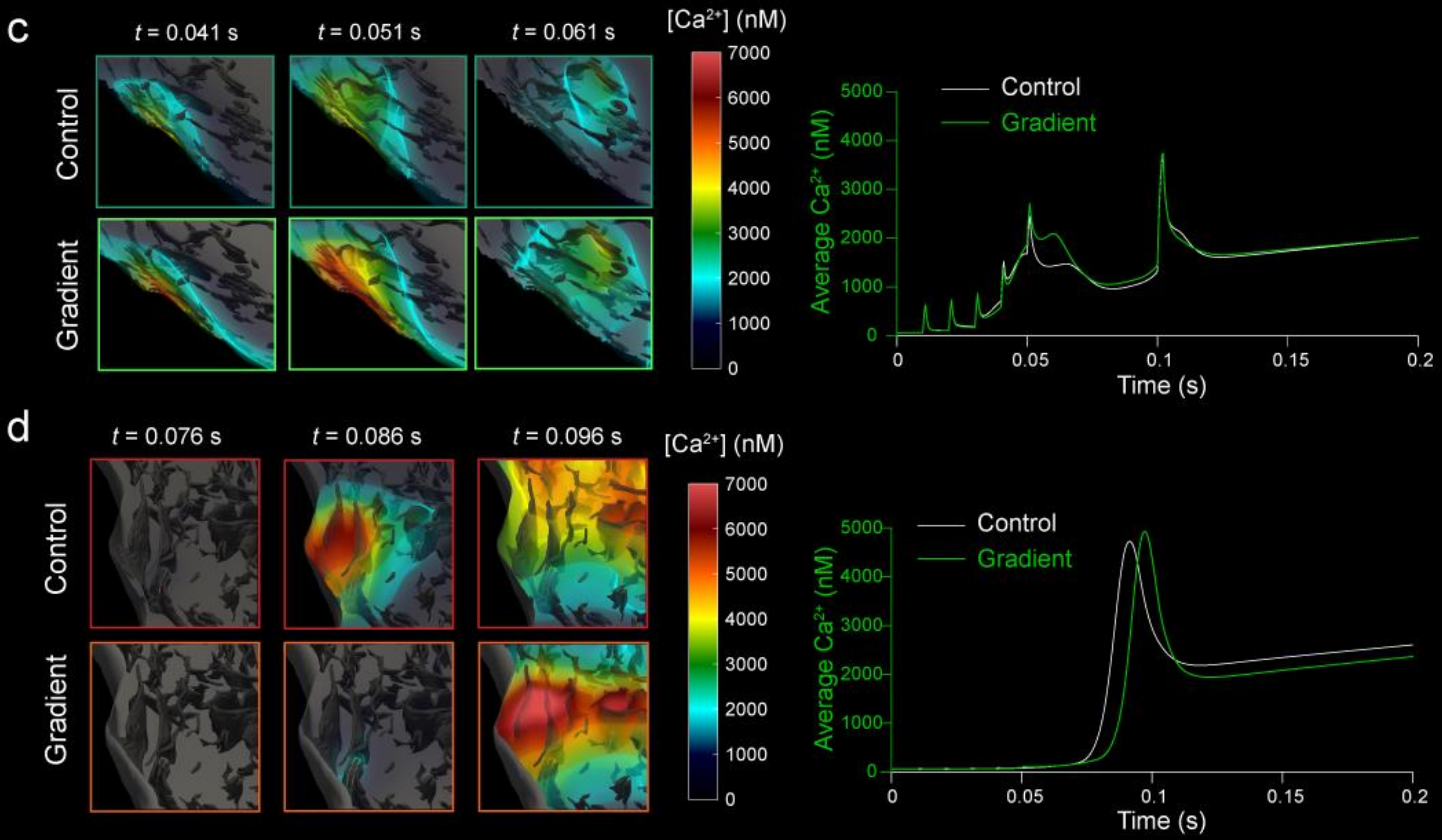


Receptor gradient





Ca^{2+} dynamics for uniform receptors vs. realistic receptor gradient

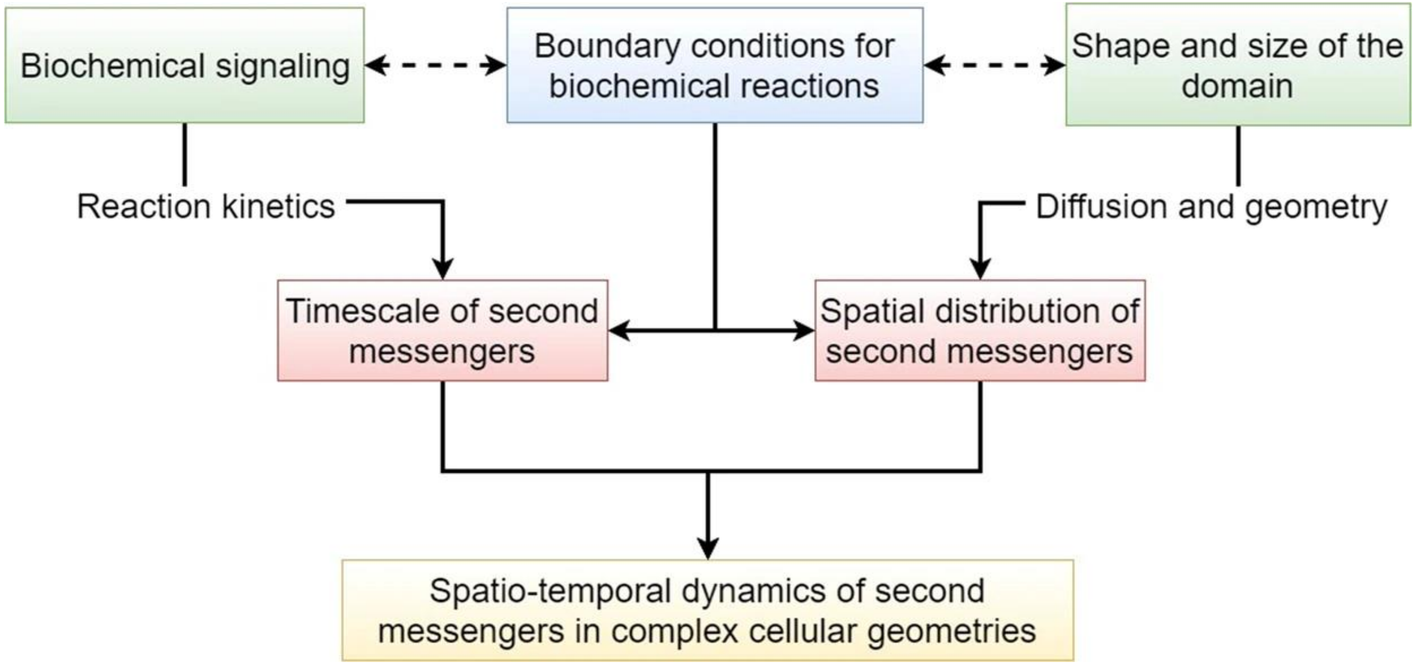


Conclusions / Summary

- Together with GAMer2, SMART offers a platform to specify biological signaling networks in realistic cell geometries
- Realistic representation of cell signaling requires consideration of nonlinear reaction kinetics, surface-volume coupling, and detailed cell geometries

Lessons from spine and Purkinje simulations:

1. Surface to volume ratios are important determinants of calcium influx, calcium release, and repackaging of calcium into the ER.
2. The orientation and spacing of ER with respect to the PM modulates the rate of calcium release.
3. Changes in receptor distribution influence calcium release dynamics.



Cugno et al 2019, *Sci Reports*

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