Modelling Ca^{2+}-dependent proteins in the spine - challenges and solutions

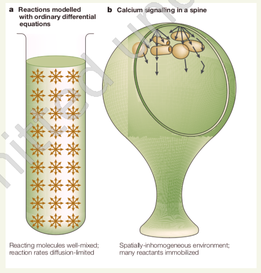
Melanie I. Stefan[1], Shirley Pepke[1], Stefan Mihalas[1], Thomas Bartol[2], Terrence Sejnowski[2] and Mary B. Kennedy[1]

1) Biology Division, California Institute of Technology, Pasadena, CA
2) Salk Institute, La Jolla, CA

Biology

- Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is important in LTP induction and memory formation.
- Ca^{2+} entering through NMDA receptors activates CaMKII through calmodulin.
- CaMKII is necessary for normal synaptic plasticity and activates many downstream pathways.
- CaMKII function is fine-tuned through interaction with other proteins, autophosphorylation, and inter-subunit regulation.
- We combine computational modelling and simulations with biochemical experiments in order to understand CaMKII regulation.
- Modelling synaptic proteins poses three kinds of problems: Small molecule numbers, large numbers of possible states, and complex geometries.

Small molecule numbers

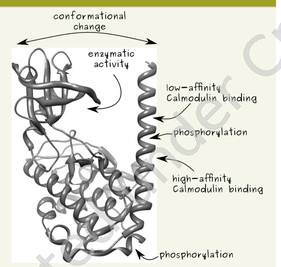


- In small biological compartments, absolute molecule numbers are low
- This makes reactions stochastic and changes discrete
- Biological reaction systems are spatially heterogeneous
- ODEs are designed for well-mixed, continuous, deterministic systems and are therefore not well suited to model such systems

Kennedy et al., *Nat Rev Neurosci*, 2005.

Large numbers of possible states

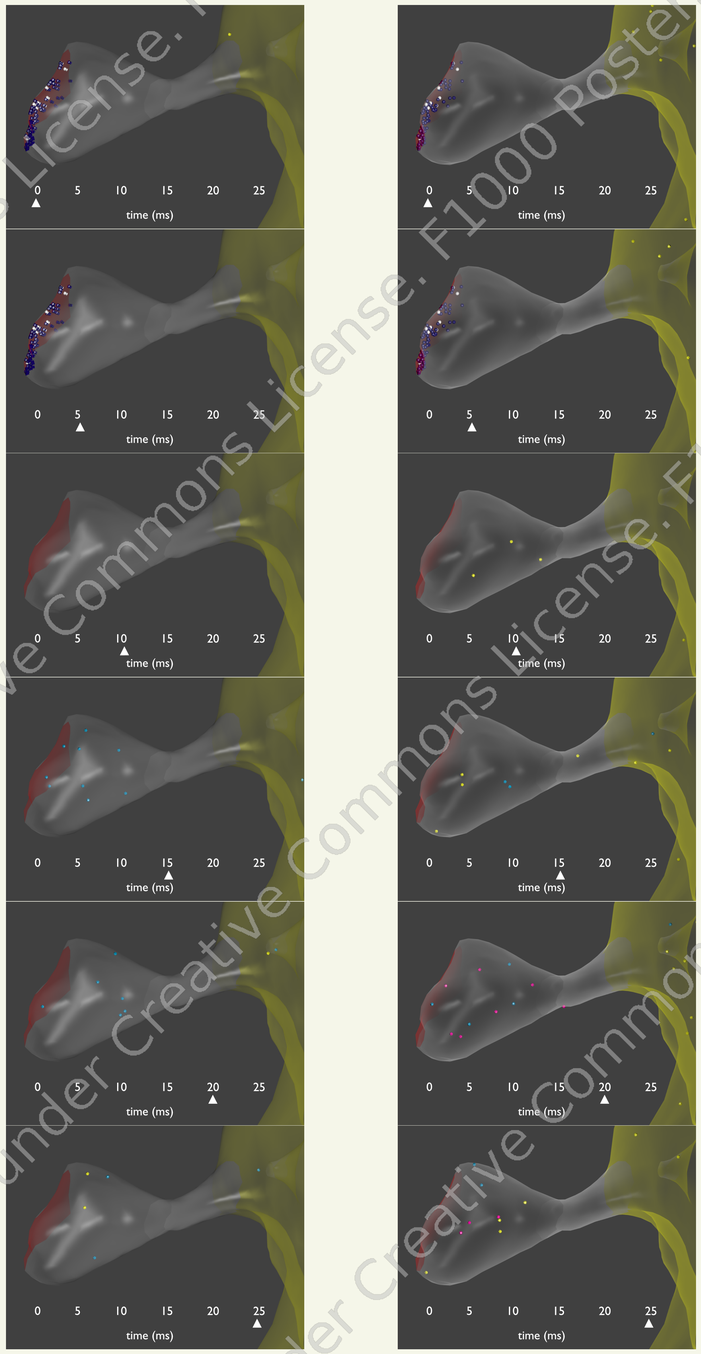
- Proteins like CaMKII can be modified by post-translational modifications, ligand binding, conformational change, complex formation, subcellular location etc.
- This results in a wide variety of possible functionally different states
- Enumerating all these states can be tedious or, for larger systems, impossible



Complex geometries

- Biological compartments have complex geometries
- This affects diffusion and protein access to small molecules, to targets and to modulators
- In the spine, CaMKII competes with other proteins for access to calcium and regulation by calmodulin
- Spatial models are necessary in order to understand events in signalling micro-domains

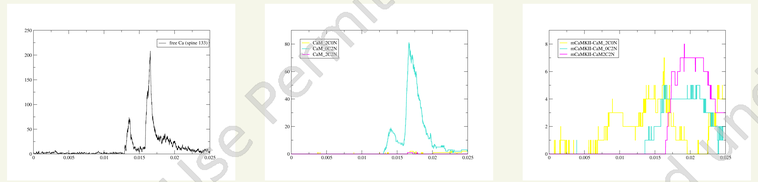
Target effects on Calcium binding to Calmodulin



yellow . . . CaM_2C0N, cyan . . . CaM_0C2N, magenta . . . CaM_4

Target effects on Calcium binding to Calmodulin

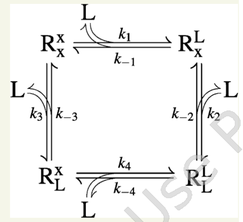
Free Calcium: free Calmodulin: CaMKII-bound Calmodulin:



- In the absence of CaMKII binding, CaM_0C2N is the dominant species, and there is hardly any fully saturated calmodulin
- Binding to CaMKII increases the probability of Calcium binding to the C-terminus and of calmodulin becoming fully saturated
- This has been shown before (Stefan et al, *PNAS*, 2008), but our present study adds dynamic effects and spatial resolution

Methods

- MCell (Kerr et al, *SIAM J Sci Comput*, 2008) is an agent-based, spatial Monte-Carlo simulator
- It allows for stochastic modelling of multi-state proteins in arbitrarily complex geometries
- MCell integrates with the animation software blender to visualise simulation results
- MCell files can be converted to SBML to allow for model sharing and integration with other modelling platforms (Tolnay et al., *submitted*)



Endler et al, in: Computational Systems Neurobiology (N. Le Novère, ed), Springer, 2012.

- Parameter determination involves performing experimental assays, mining the literature and applying biophysical considerations (e.g. microscopic reversibility)

Conclusions

- Modelling signal transduction in the dendritic spine can help us uncover the molecular basis of learning and memory
- The spine signalling machinery presents three problems often encountered in biochemical modelling: small total molecule numbers, large numbers of possible states, and complex geometrical arrangements
- MCell is a stochastic, agent-based, spatial simulator that solves all three of these problems and allows results to be animated using blender
- We can look at dynamic phenomena such as target effects on calmodulin during a Calcium signal, and track single molecules in time and space.

Funding

This work was supported by the United States NIH/NSF Collaborative Research in Neurosciences (CRCNS) program, grant DA030749 (to MBK) and by a postdoctoral fellowship from the European Molecular Biology Organisation (to MIS).

mstefan@caltech.edu