Simulating calcium handling and buffering at nerve terminals with CellBlender/MCell

Jaron Lee

May 30, 2015

Motivation of this project

- Modelling in biology is important - widespread applications
- Modelling in biology is difficult - requires skills and knowledge which fall outside biology itself

Goals of this project

- Develop a thorough understanding of the software, biology
- Implement a working visualisation of calcium action at nerve terminals
- Parameterise the model to mimic biological conditions where possible
- Document the process to allow for easy replication

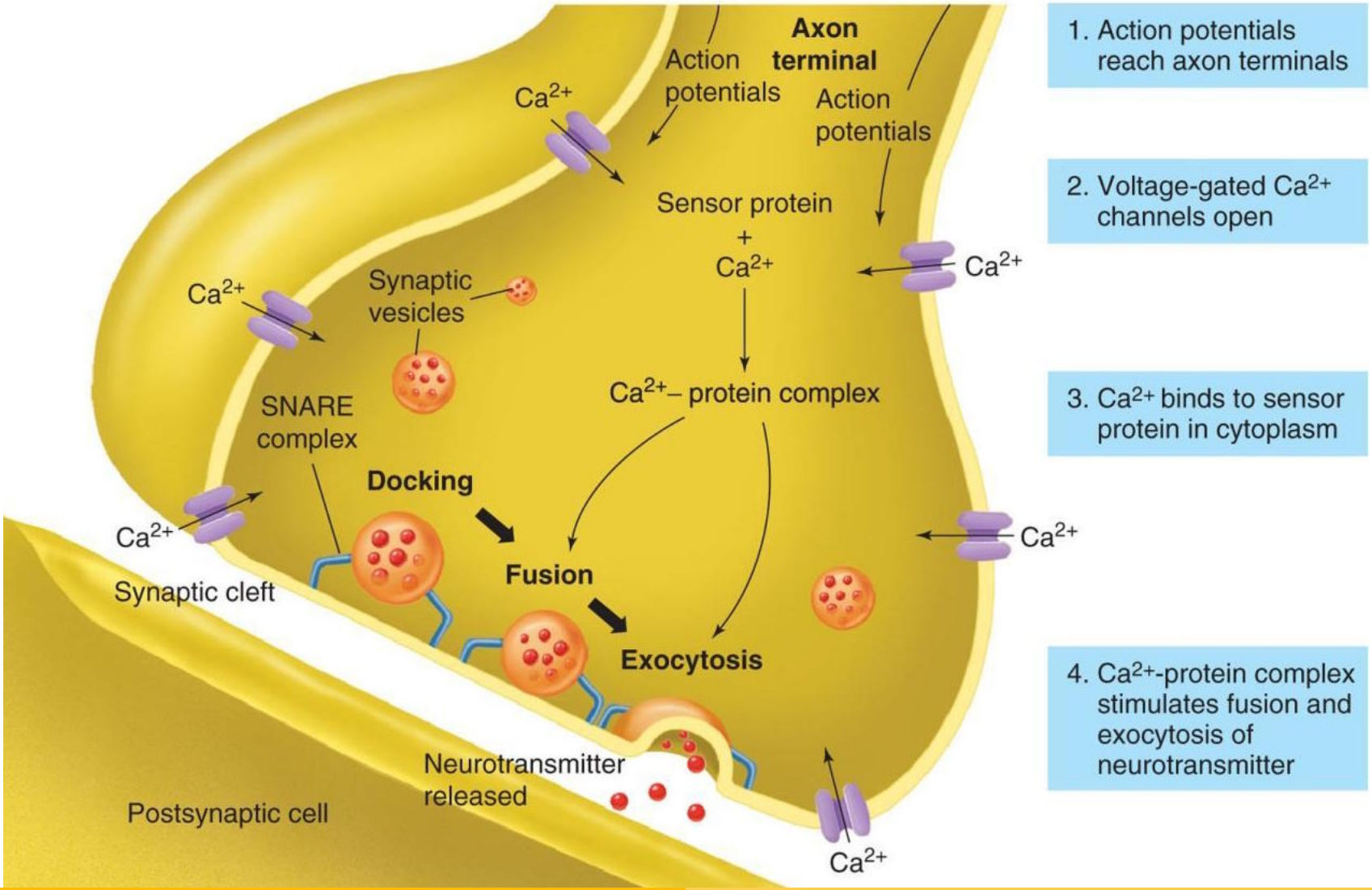
Software

- MCell - background Monte-Carlo simulation command-line tool
- Blender - 3D animation and design software
- CellBlender - interface between Blender and MCell
- Python - general-purpose programming language

Advantages of the approach

- The method developed essentially eliminates the need for the user to be proficient in programming
- Simulation results are presented in animation form - easy to interpret
- Easy to adapt the model to answer different scientific questions

An overview of synaptic transmission



Summary

Two phases - presynaptic and postsynaptic PICTURE

Presynaptic

- Simulate calcium ion movement
- Simulate calcium binding to SNARE complex (Need two calcium to activate)
- Record time of vesicle fusion (require three activated SNARE complexes on a vesicle)

A question

- Why not do everything in one step?
- The activation of SNARE complexes is randomly determined during the simulation (depends on the movement of calcium ions)
- The release of neurotransmitter must be specified before the simulation is run (due to the way CellBlender defines molecule placement and release)

Model Components

1. Presynaptic bouton
2. Spine head
3. Voltage-gated calcium channels (2)
4. Vesicles (2)
5. Glial cells

Picture

Model Molecules

1. VGCC - the calcium channels responsible for permitting flow of calcium into bouton. Has open and closed states.
2. Ca - calcium ion
3. CaBS - a SNARE complex which has a single calcium ion bound
4. TAG - a SNARE complex which has two calcium ions bound
5. NT - a neurotransmitter molecule (represents glutamate)
6. LGIC - a neurotransmitter receptor residing on spine head (receptive to NT). Has open and closed states.

Model Equations

Equation	Description
$VGCC\_C \rightarrow VGCC\_O$	Calcium channel opening
$VGCC\_O \rightarrow VGCC\_C$	Calcium channel closing
$VGCC\_O \rightarrow VGCC\_O + Ca$	Calcium influx into bouton
$Ca + CaBS \rightarrow CaBS\_Ca$	First calcium binding
$CaBS\_Ca + Ca \rightarrow TAG$	Second calcium binding
$NT + LGIC\_C \rightarrow LGIC\_O$	Neurotransmitter binding

Model Parameters

- Dimensions
- Quantities
- Rates

Model Rates

Parameter	Value
Rate of calcium influx	$1 \times 10^3\,\mathrm{mol}^{-1}\,\mathrm{l}\,\mathrm{s}^{-1}$
SNARE complex binding rate	$1 \times 10^8\,\mathrm{mol}^{-1}\,\mathrm{l}\,\mathrm{s}^{-1}$
Glutamate binding rate	$4.6 \times 10^6\,\mathrm{mol}^{-1}\,\mathrm{l}\,\mathrm{s}^{-1}$
Rate of glutamate diffusion	$4 \times 10^{-6}\,\mathrm{cm}^2\,\mathrm{s}^{-1}$
Rate of calcium diffusion	$5.3 \times 10^{-6}\,\mathrm{cm}^2\,\mathrm{s}^{-1}$
Vesicle unzip time	$200\,\mu\mathrm{s}$
Estimate for bouton volume	$0.36\,\mu\mathrm{m}^3$
Derived estimate for bouton radius	$0.7\,\mu\mathrm{m}$
Estimate for synaptic vesicle radius	$0.017\,\mu\mathrm{m}$
Synaptic cleft width	$0.023\,\mu\mathrm{m}$
Number of Neurotransmitter molecules per vesicle	4700
Number of Neurotransimtter receptors per spine head	100
Number of SNARE complexes per vesicle	15
Number of calcium ions to activate synaptotagmin/SNARE	2
Number of SNAREs to induce vesicle fusion	3
Number of vesicles	750

Final Result

References

- Synaptic terminal, obtained from https://classconnection.s3.amazonaws.com/811/flashcards/1418