Realistic modelling of transmitter release at neocortical nerve terminals using CellBlender and MCell

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June 3, 2015

Motivation of this project

- Modelling in biology is important - narrowing down the scientific questions, predicting experimental outcomes, providing hypotheses for results
- Modelling in biology is difficult - requires skills and knowledge which fall outside biology itself

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- Parameterise the model to mimic biological conditions where possible
- Document the process to allow for easy replication

Software

CellBlender - an addon written for Blender

Advantages of the approach

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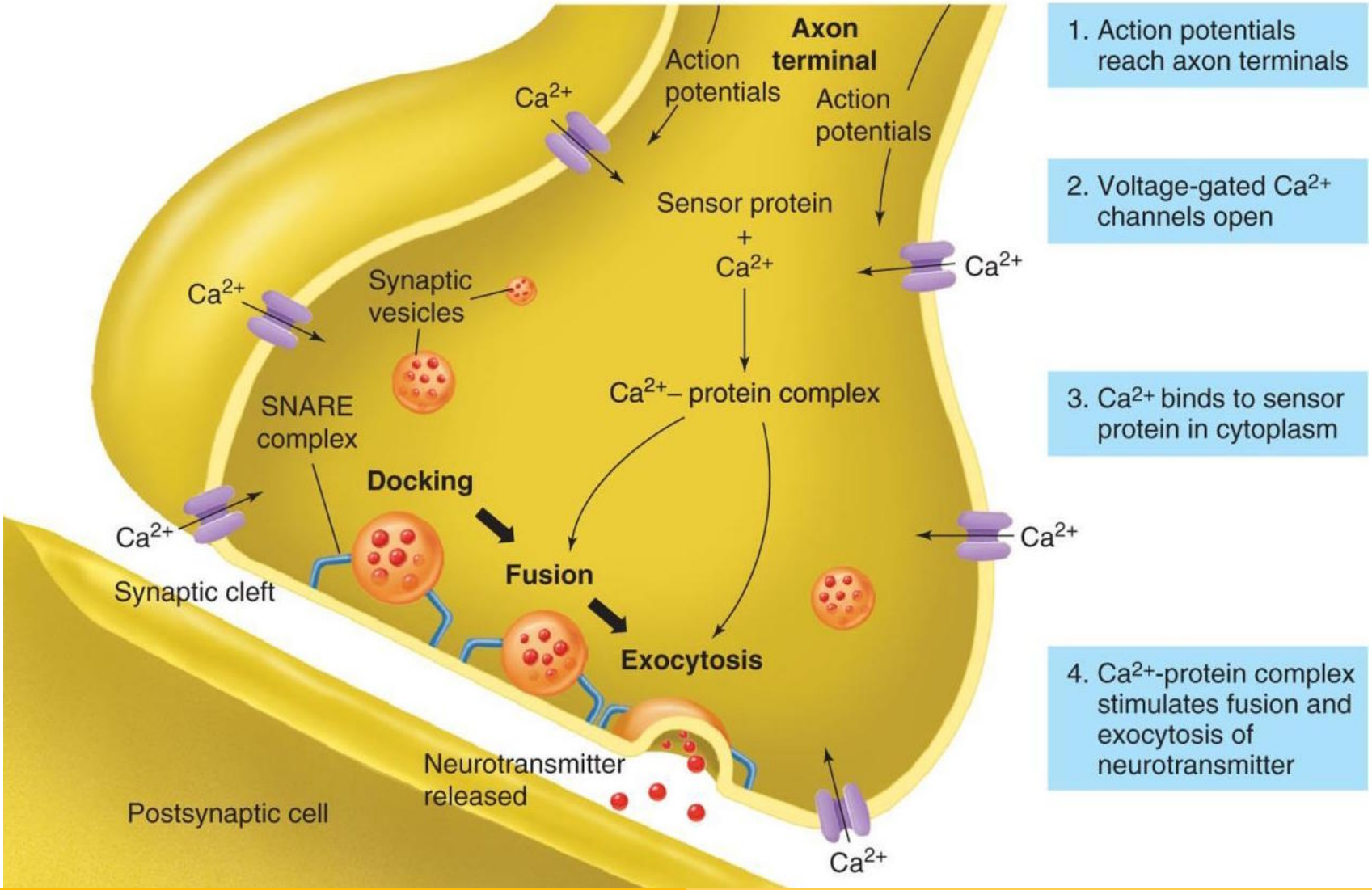
- Easily adaptable model

An overview of synaptic transmission



Synaptic Transmission

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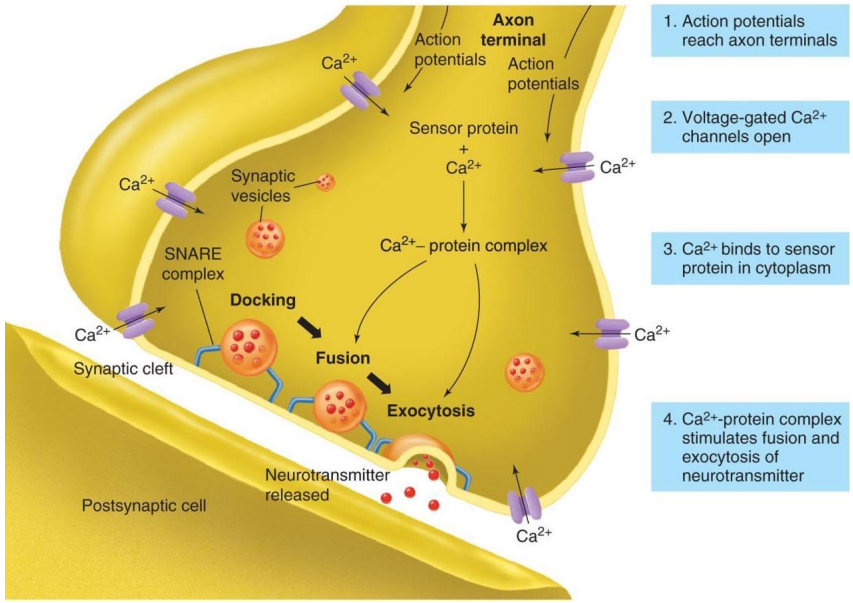

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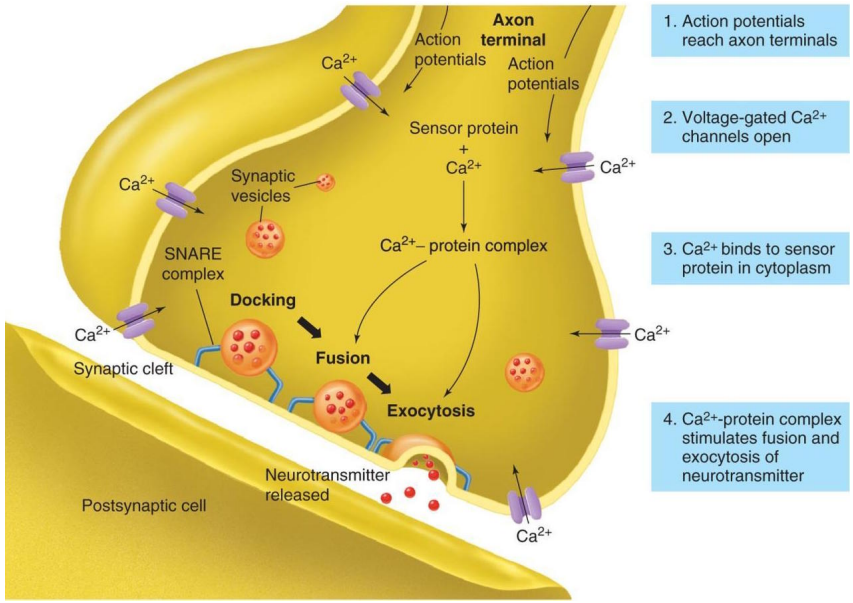

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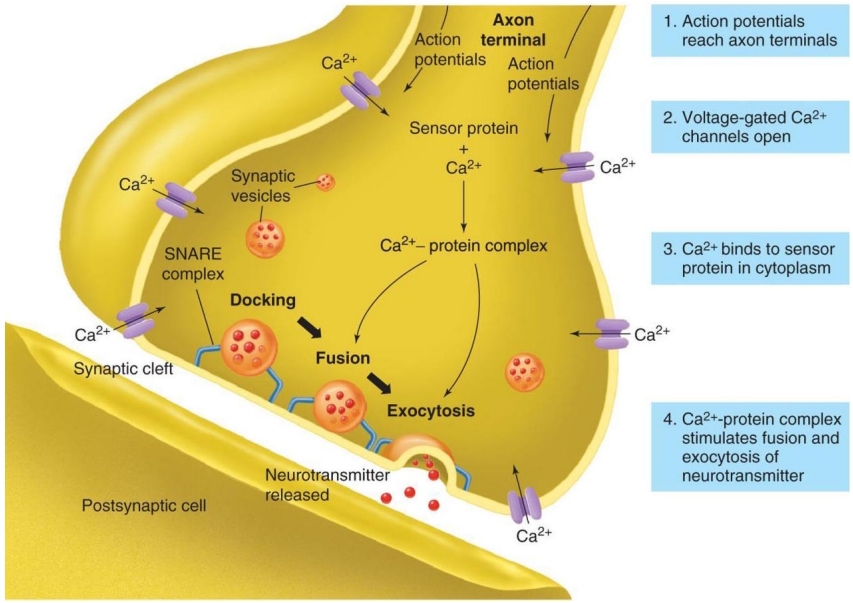

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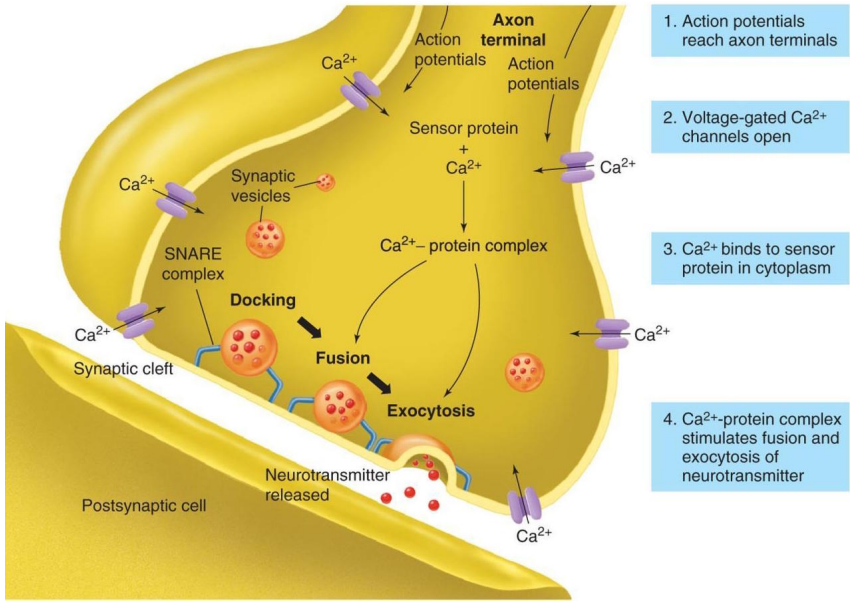

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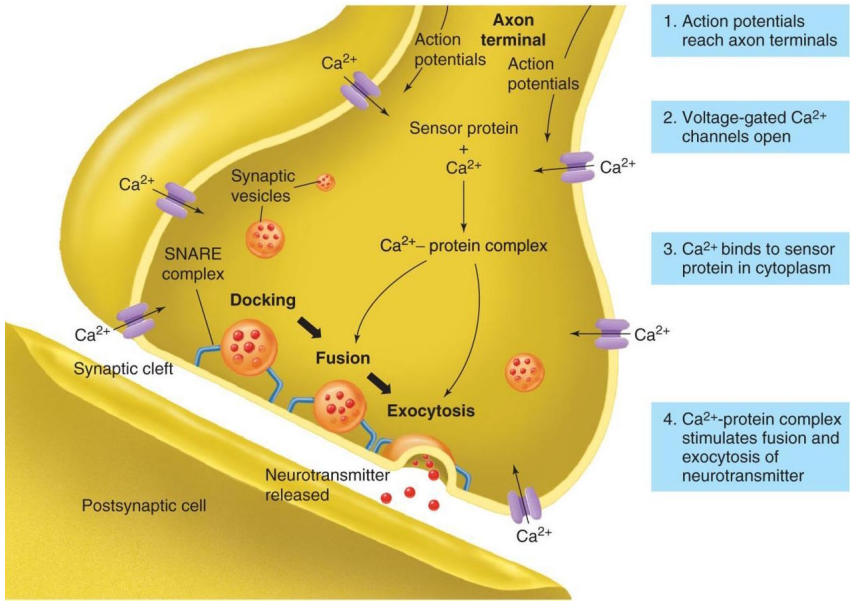
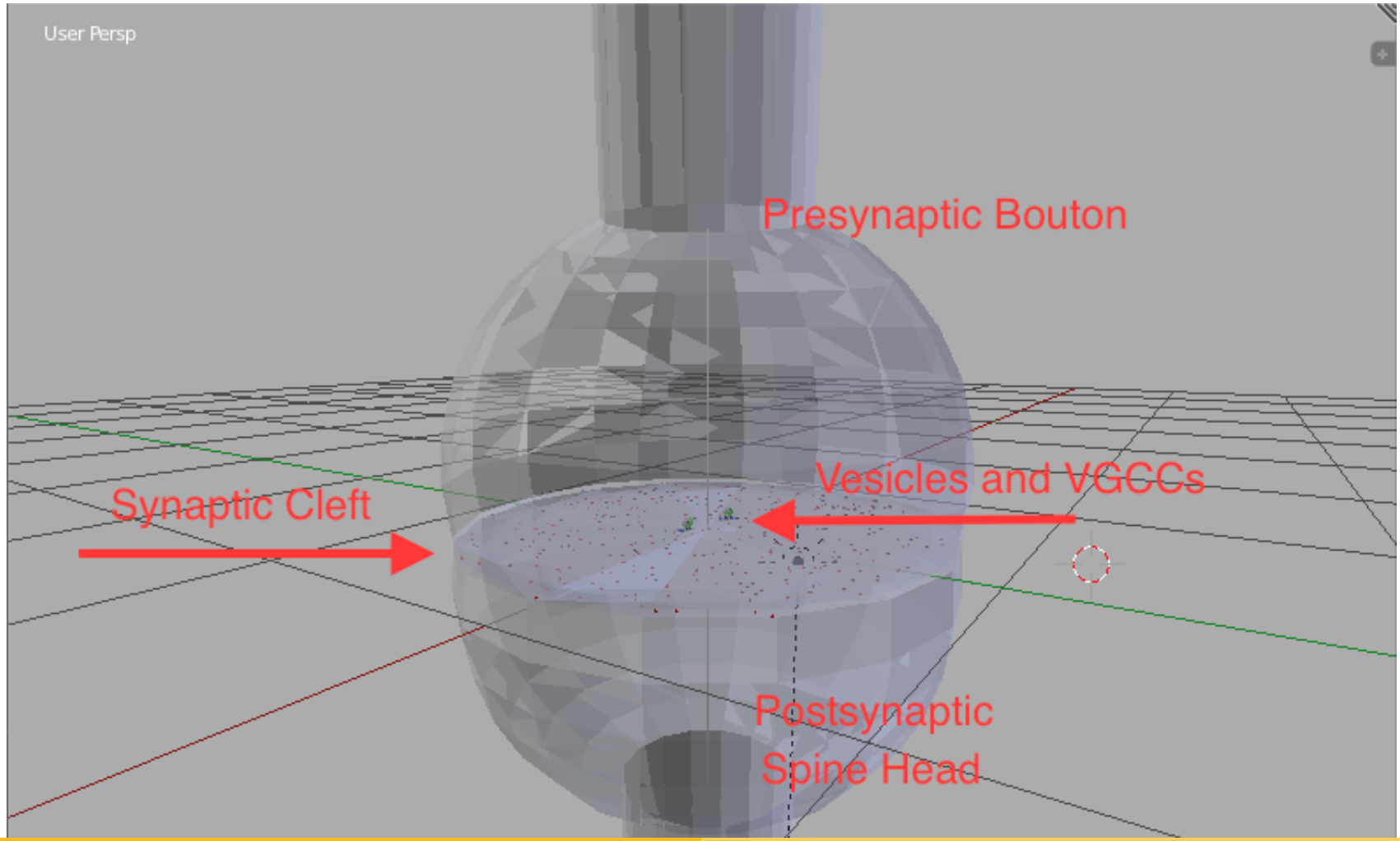
5. Excess neurotransmitter are taken up by glial cells to be reused



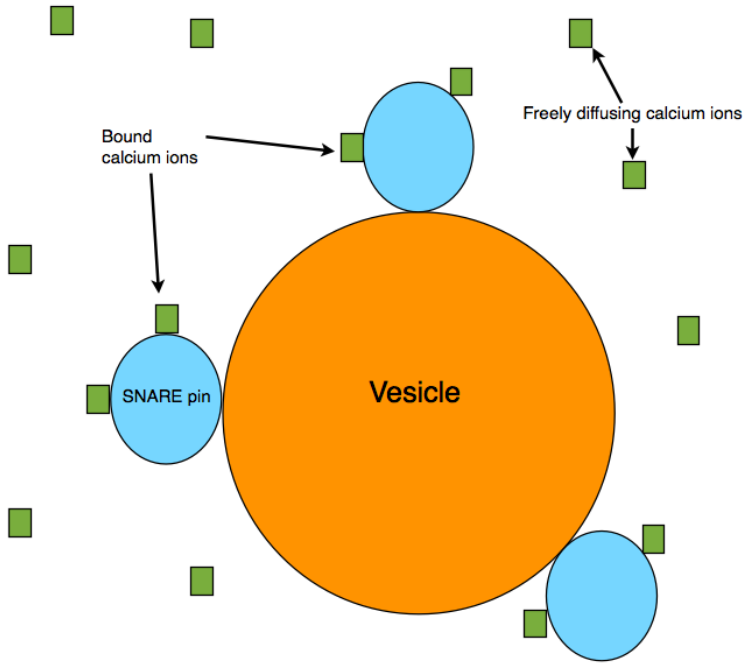
Summary

Two phases - Phase I and Phase II



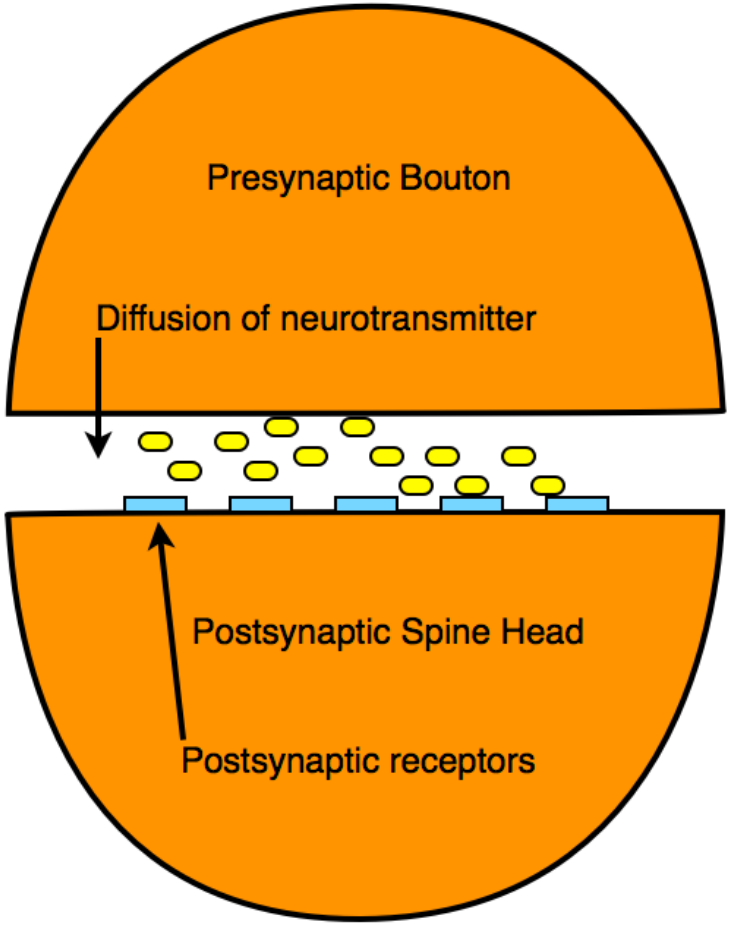
Phase I

- Simulate calcium ion diffusion - but not the electrophysiology
- Simulate calcium binding to SNAREpins (Need two calcium to activate)
- Record time of vesicle fusion (require three activated SNAREpins on a vesicle)



Phase II

- Simulate diffusion of neurotransmitter across synaptic cleft
- Simulate activation of neurotransmitter receptors

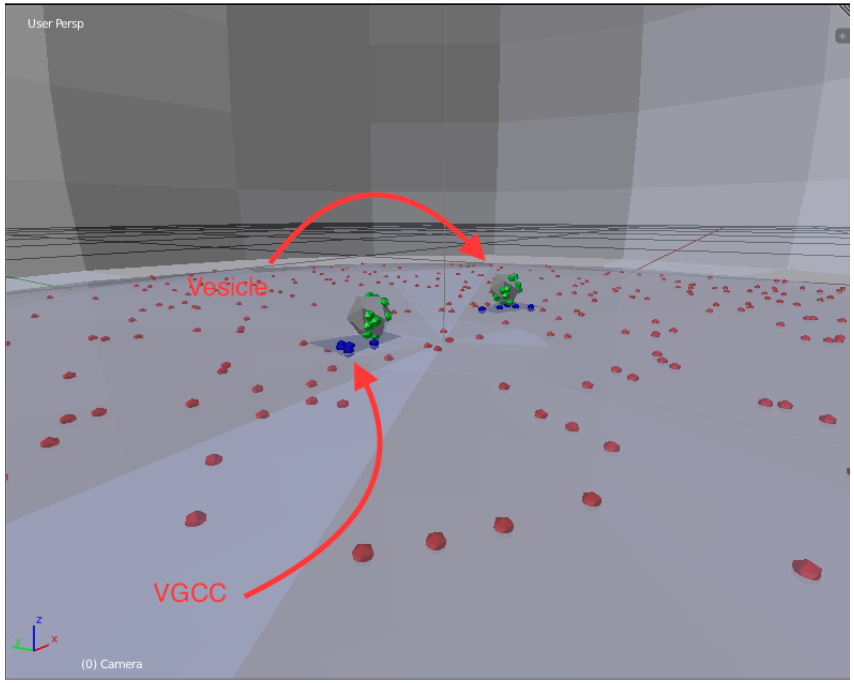


A question

- Why not do everything in one step?
- The activation of SNAREpins 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



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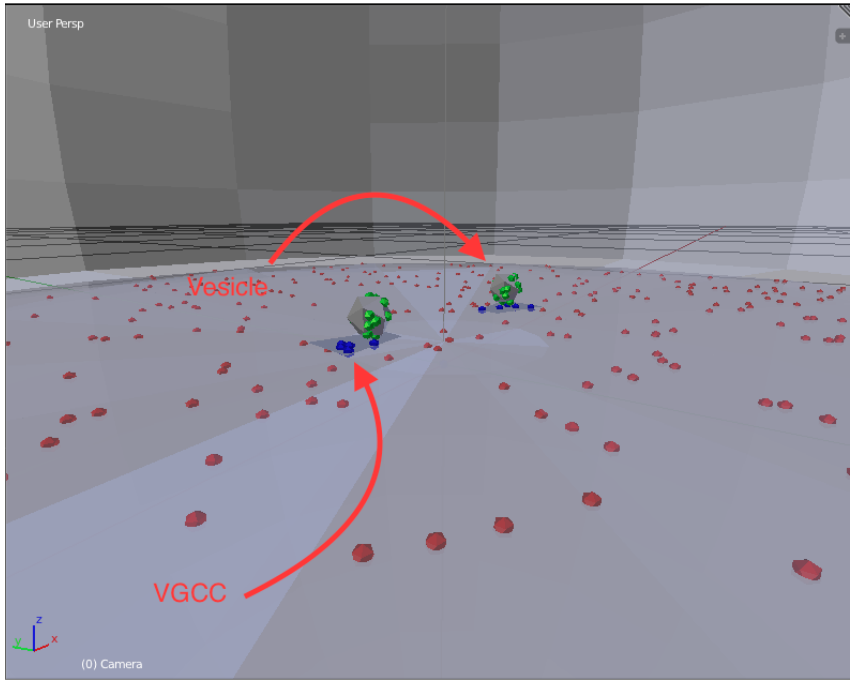

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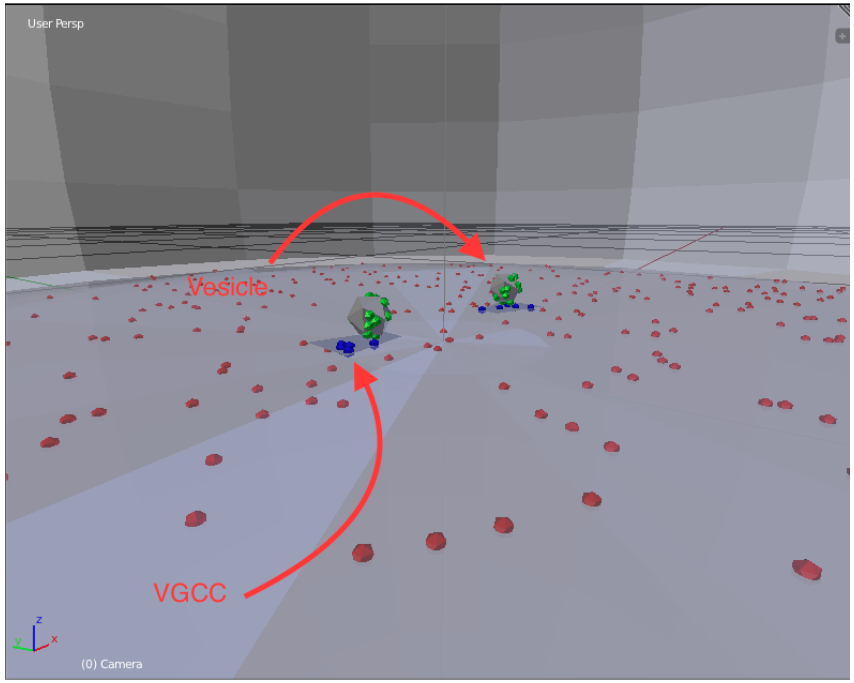
3. Voltage-gated calcium channel regions (2)



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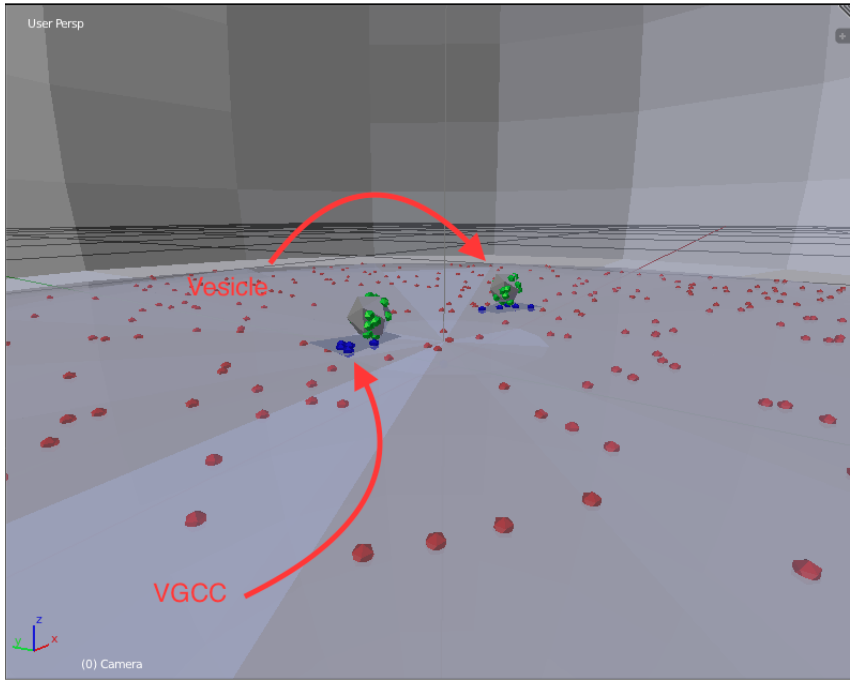
4. Vesicles (2)



Model Components

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2. Spine head
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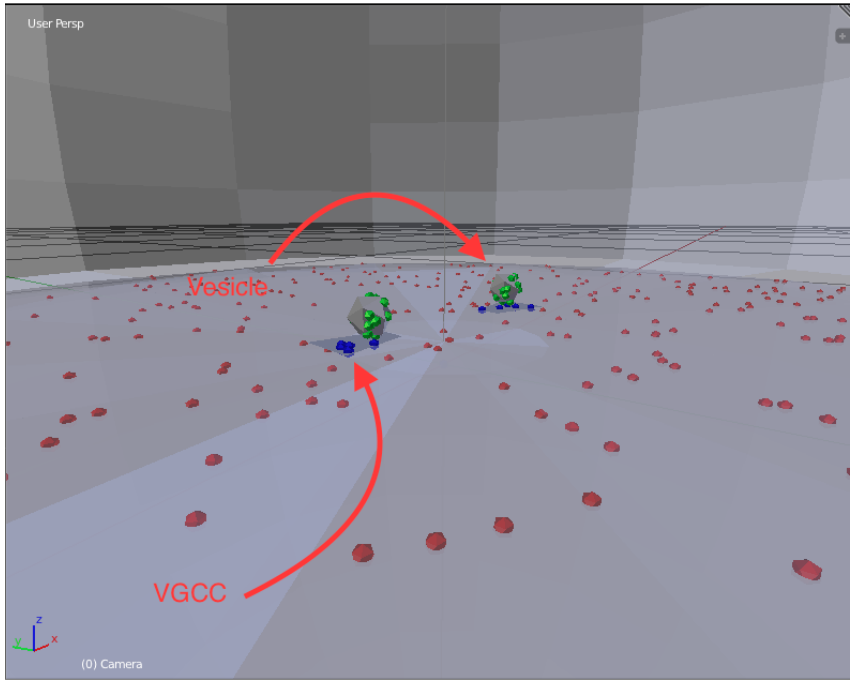
5. Glial cells



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6. NT - a neurotransmitter molecule (represents glutamate)
7. 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

Need to calibrate:

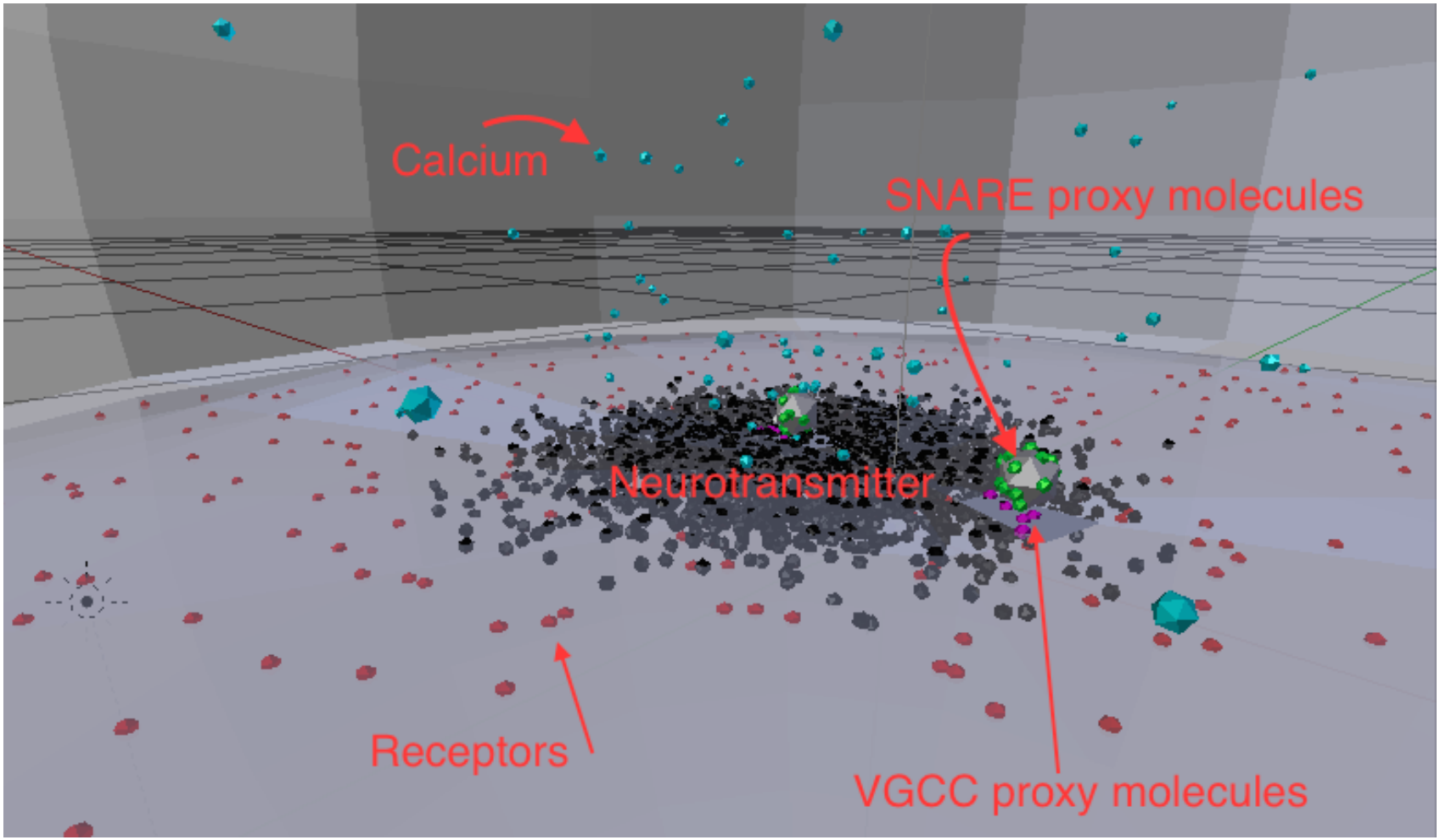
- Rates
- Dimensions
- Quantities

to get a realistic model.

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



Future Outlook

- Improve model details - postsynaptic receptor, VGCCs
- Simulate the electrophysiology of the synapse
- Adapt model to different scenarios

References

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