

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

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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

Goals of this project

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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

- Programming-free

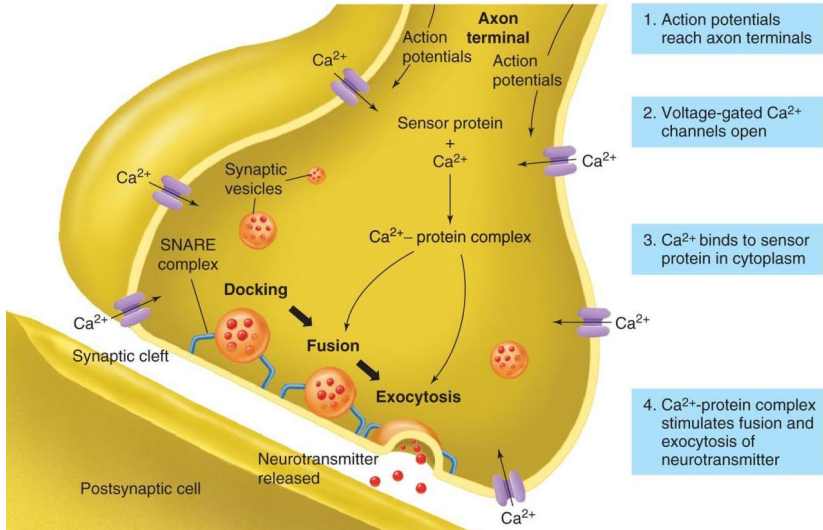
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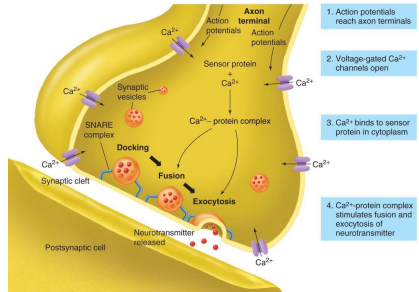
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- Simulation results are easy to interpret
- Easily adaptable model

An overview of synaptic transmission



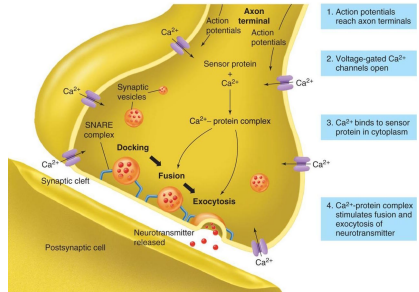
Synaptic Transmission

- 1 Action potential depolarises cell and opens VGCCs



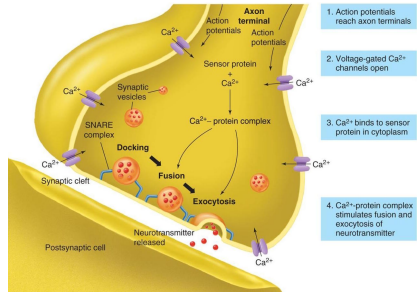
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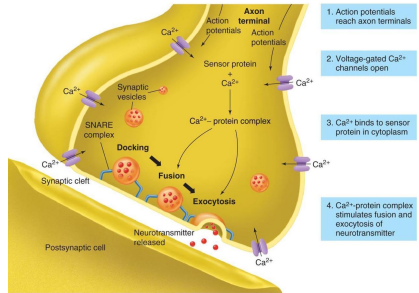
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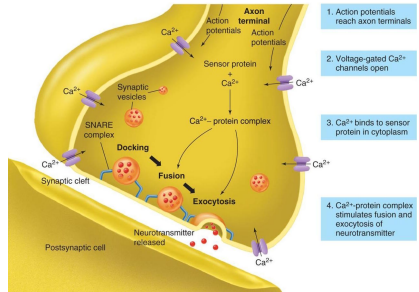
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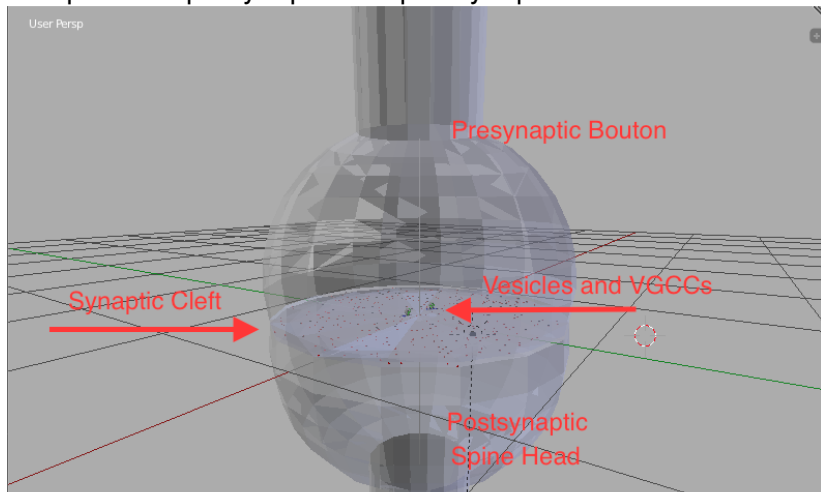
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- 5 Excess neurotransmitter are taken up by glial cells to be reused



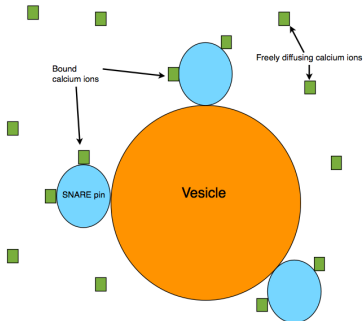
Summary

Two phases - presynaptic and postsynaptic



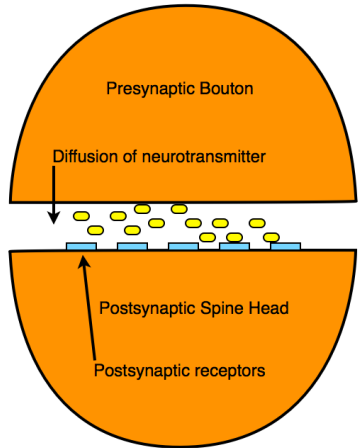
Presynaptic Simulation

- 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)



Postsynaptic

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

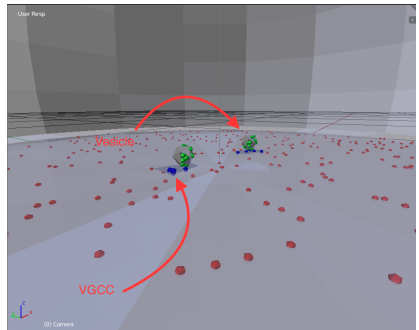


A question

- 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)

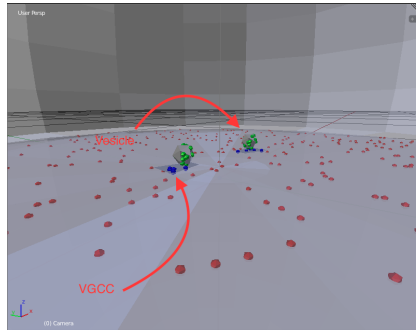
Model Components

1 Presynaptic bouton



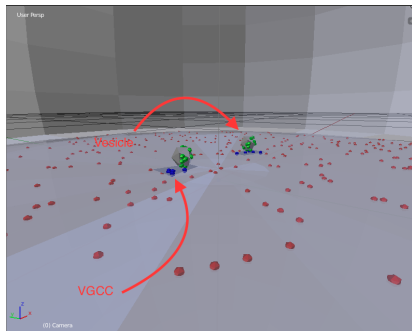
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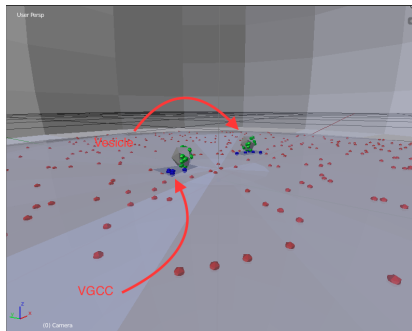
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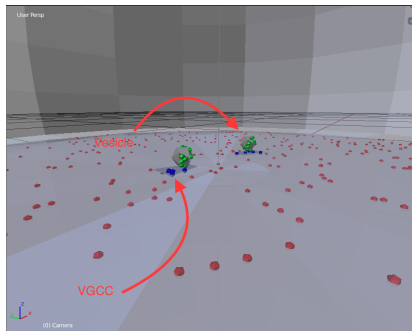
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- 2 Spine head
- 3 Voltage-gated calcium channels (2)
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- 5 Glial cells



Model Molecules

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- 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
$\text{VGCC_C} \rightarrow \text{VGCC_O}$	Calcium channel opening
$\text{VGCC_O} \rightarrow \text{VGCC_C}$	Calcium channel closing
$\text{VGCC_O} \rightarrow \text{VGCC_O} + \text{Ca}$	Calcium influx into bouton
$\text{Ca} + \text{CaBS} \rightarrow \text{CaBS_Ca}$	First calcium binding
$\text{CaBS_Ca} + \text{Ca} \rightarrow \text{TAG}$	Second calcium binding
$\text{NT} + \text{LGIC_C} \rightarrow \text{LGIC_O}$	Neurotransmitter binding

Model Parameters

Need to calibrate:

- Rates
- Dimensions
- Quantities

to get a realistic model.

Model Rates

Parameter	Value
Rate of calcium influx	$1 \times 10^3 \text{ mol}^{-1} \text{ l s}^{-1}$
SNARE complex binding rate	$1 \times 10^8 \text{ mol}^{-1} \text{ l s}^{-1}$
Glutamate binding rate	$4.6 \times 10^6 \text{ mol}^{-1} \text{ l s}^{-1}$
Rate of glutamate diffusion	$4 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$
Rate of calcium diffusion	$5.3 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$
Vesicle unzip time	200 μs
Estimate for bouton volume	0.36 μm^3
Derived estimate for bouton radius	0.7 μm
Estimate for synaptic vesicle radius	0.017 μm
Synaptic cleft width	0.023 μm
Number of Neurotransmitter molecules per vesicle	4700
Number of Neurotransmitter 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

See video...

Future Outlook

- Improve model details - postsynaptic receptor, VGCCs
- Increase the scale of the model - more vesicles
- Adapt model to different scenarios

References

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