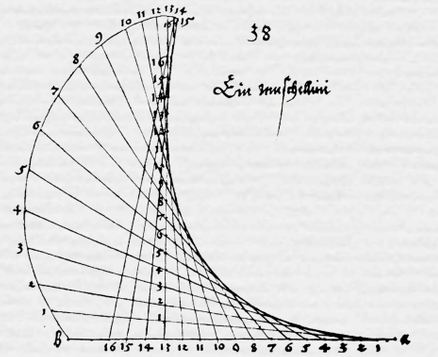
Detailed Three-Dimensional Modeling of Cellular Signaling

M. Wittmann, A. Eder, J.S. Wiegert, C.P. Bengtson, A. Hellwig, M. Knodel, R. Geiger, L.H. Ge, D. Bucher, C.M. Schuster, H. Bading, G. Wittum, G. Queisser

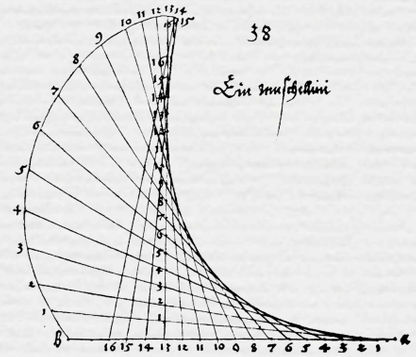
Gillian Queisser
G-CSC
University of Frankfurt



Detailed Modeling

- Describe biophysical processes in space and time => Set up systems of partial differential equations.
- Resolve morphology, ideally from microscopy image reconstruction => Discretization of computational domain.
- Simulate biophysical signal processing on detailed morphologies in space and time => Numerics: Discretization schemes, fast solvers.

Gillian Queisser
G-CSC
University of Frankfurt



1. Modeling Nuclear Calcium Dynamics

2. Modeling Synaptic Transmission at the Drosophila NMJ

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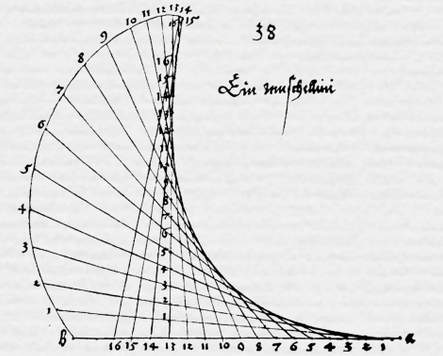
G-CSC
University of Frankfurt



1. Modeling Nuclear Calcium Dynamics

Wittmann et al. (2009) The Journal of Neuroscience 29(47):14687-14700

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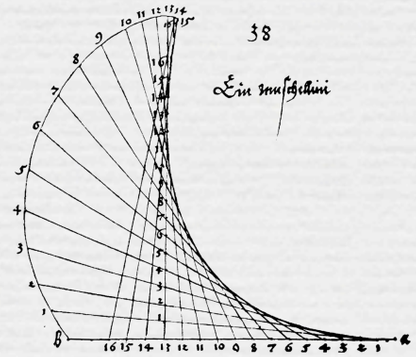
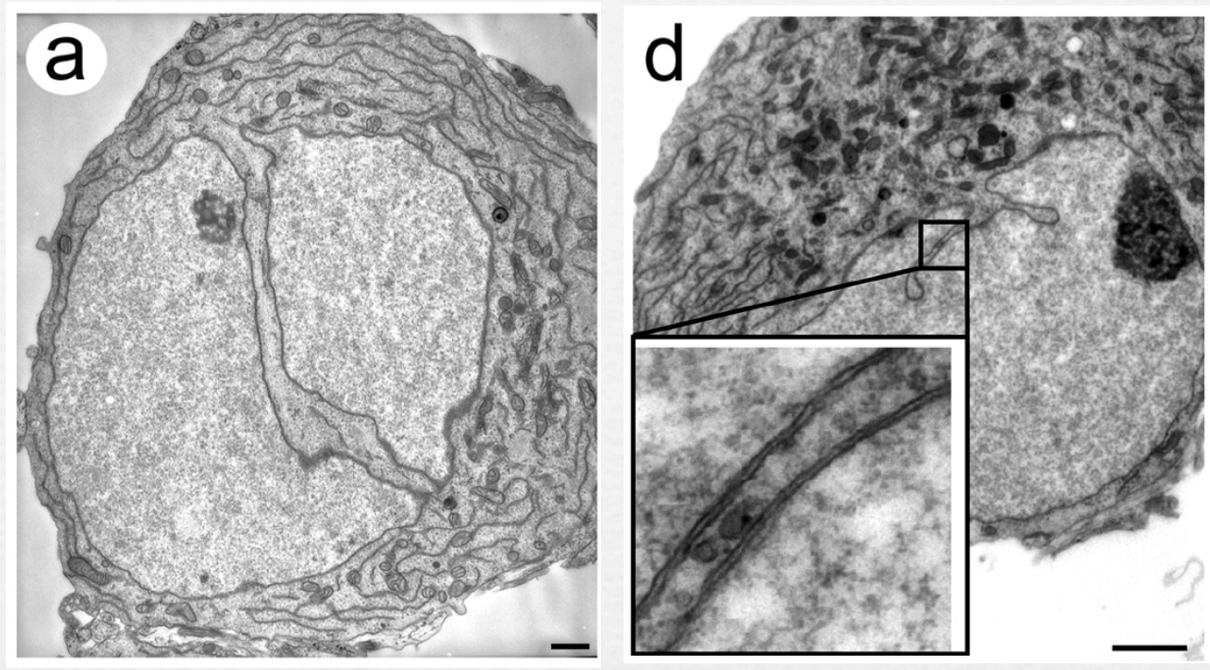
G-CSC
University of Frankfurt

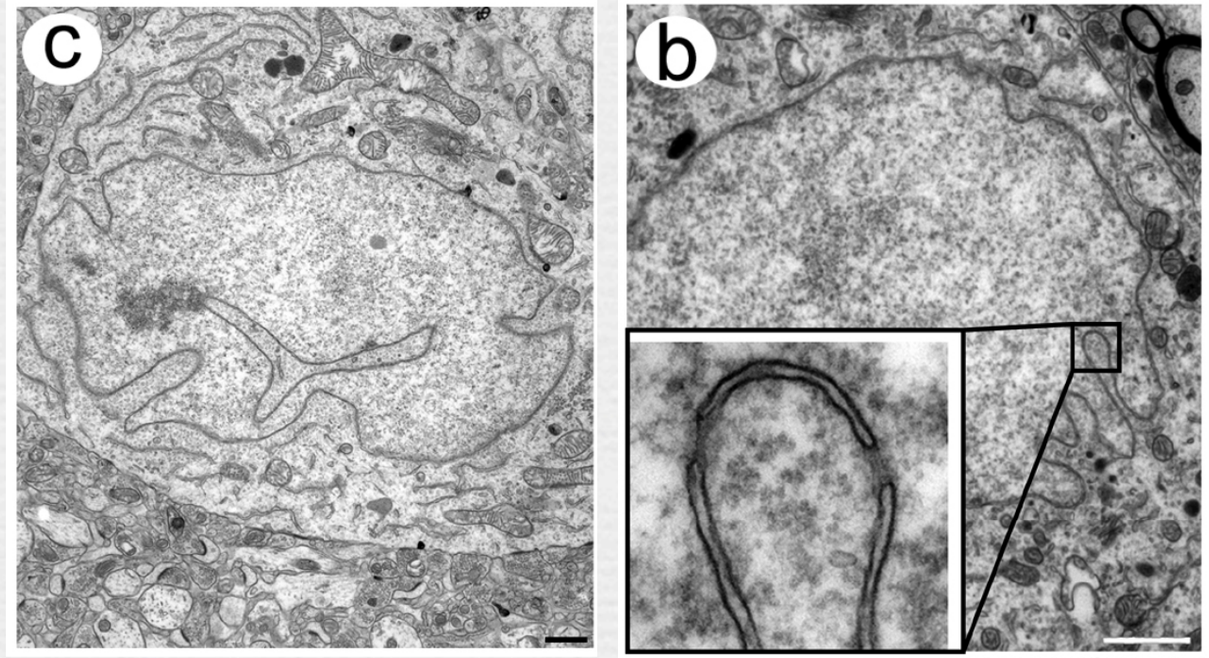


Infoldings are formed by a membrane bilayer

Dissociated hippocampal culture



Hippocampal brain slice



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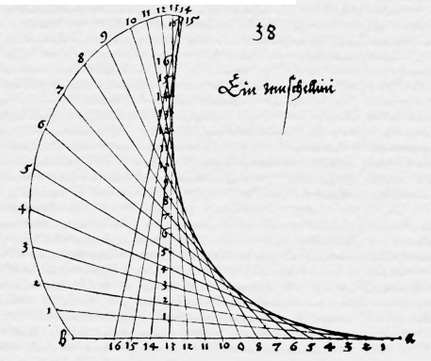
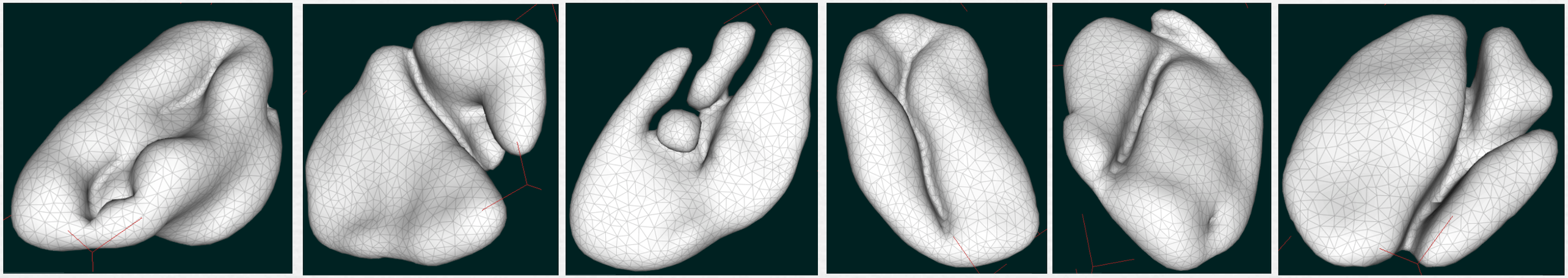
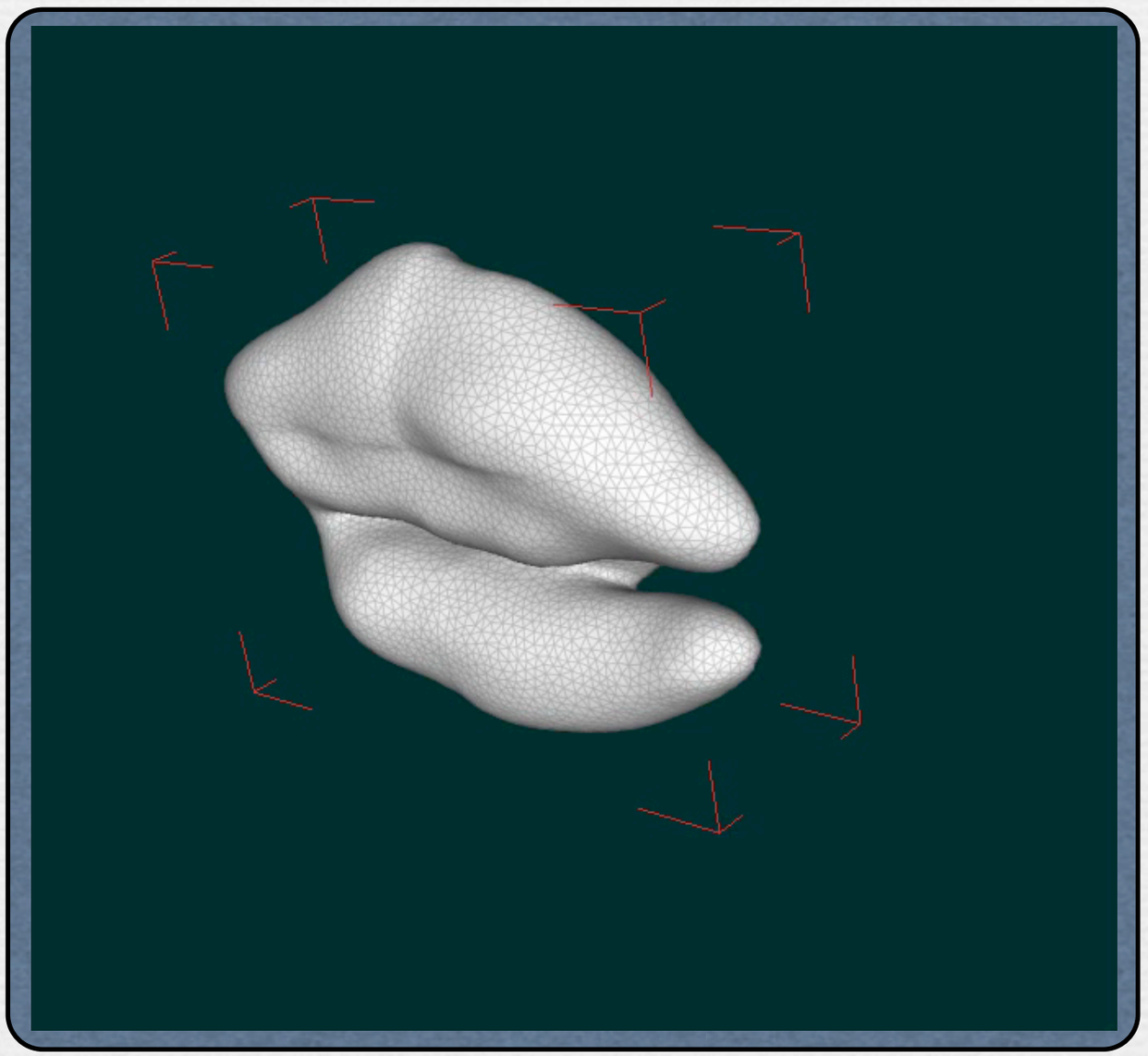
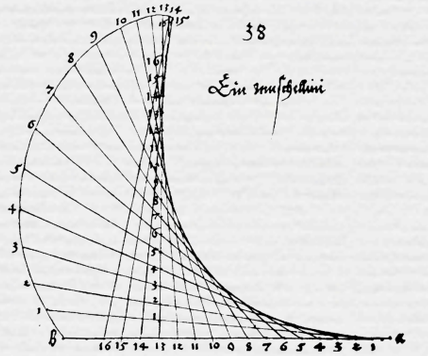


Surface Reconstructions

Cell nuclei from hippocampal neurons







Volume Reconstruction

- Create volume mesh by tetrahedra grid generation (TetGen, http://tetgen.berlios.de/).
- Integrate TetGen with Simulation Environment UG.

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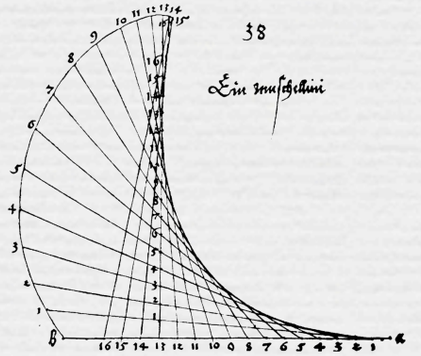
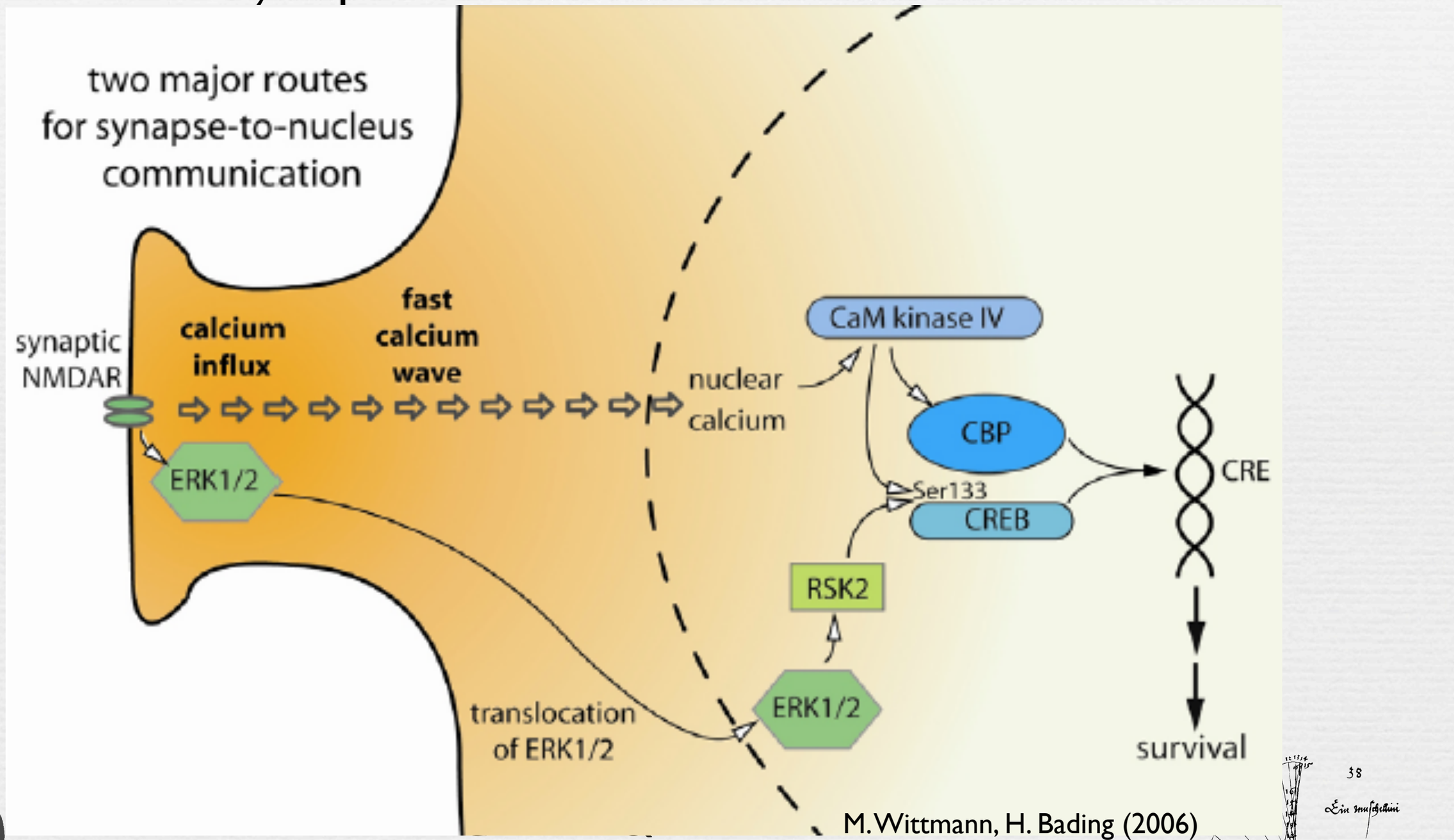
G-CSC
University of Frankfurt



Simulations on Reconstructed Morphologies – Cellular Calcium Signaling

Synapse to nucleus communication



M. Wittmann, H. Bading (2006)

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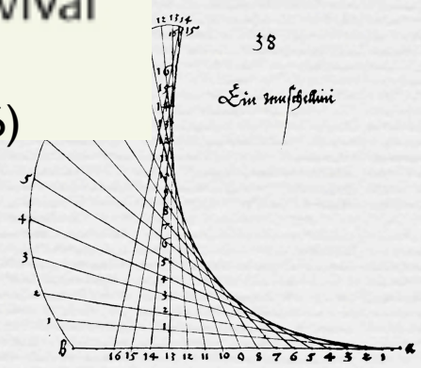
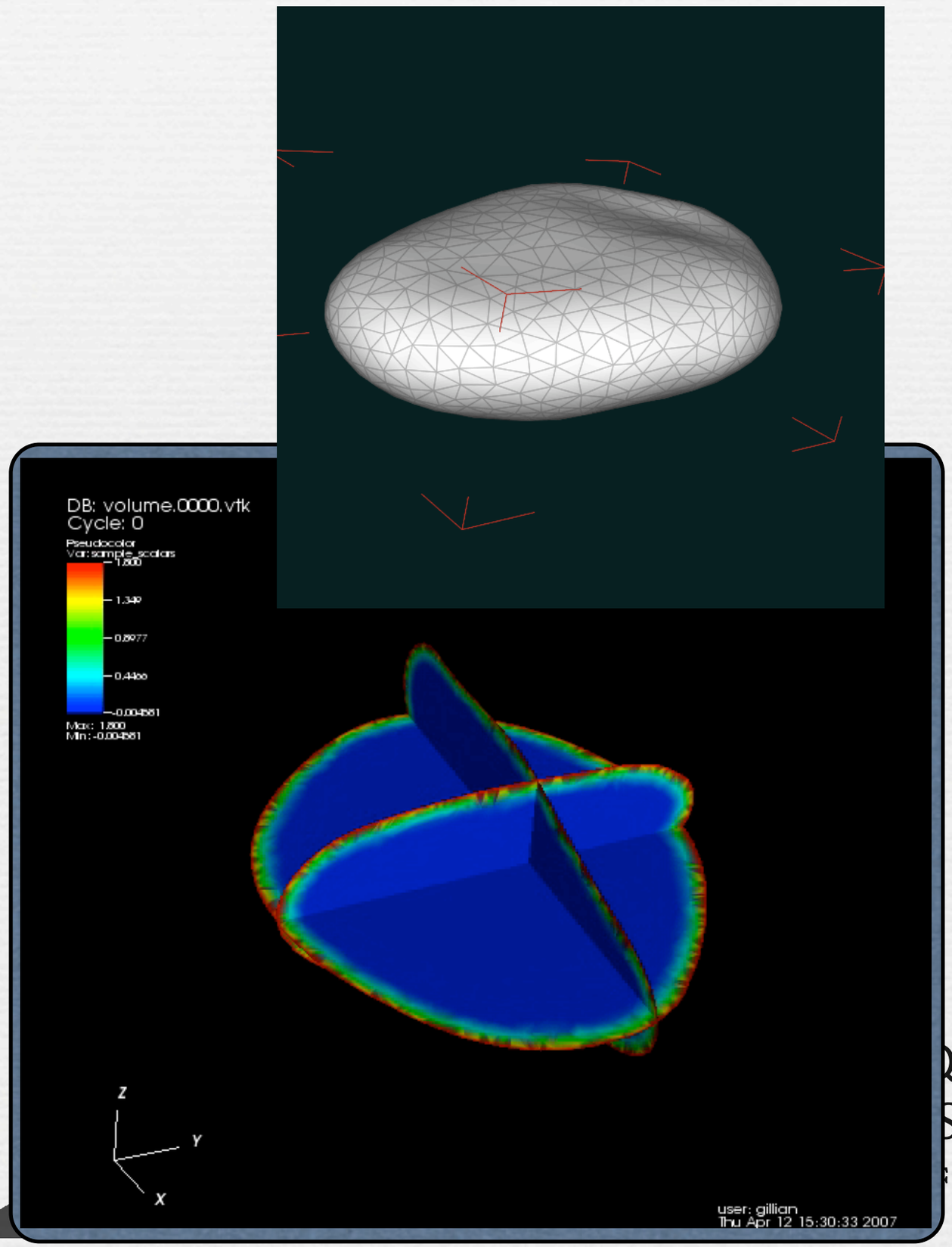
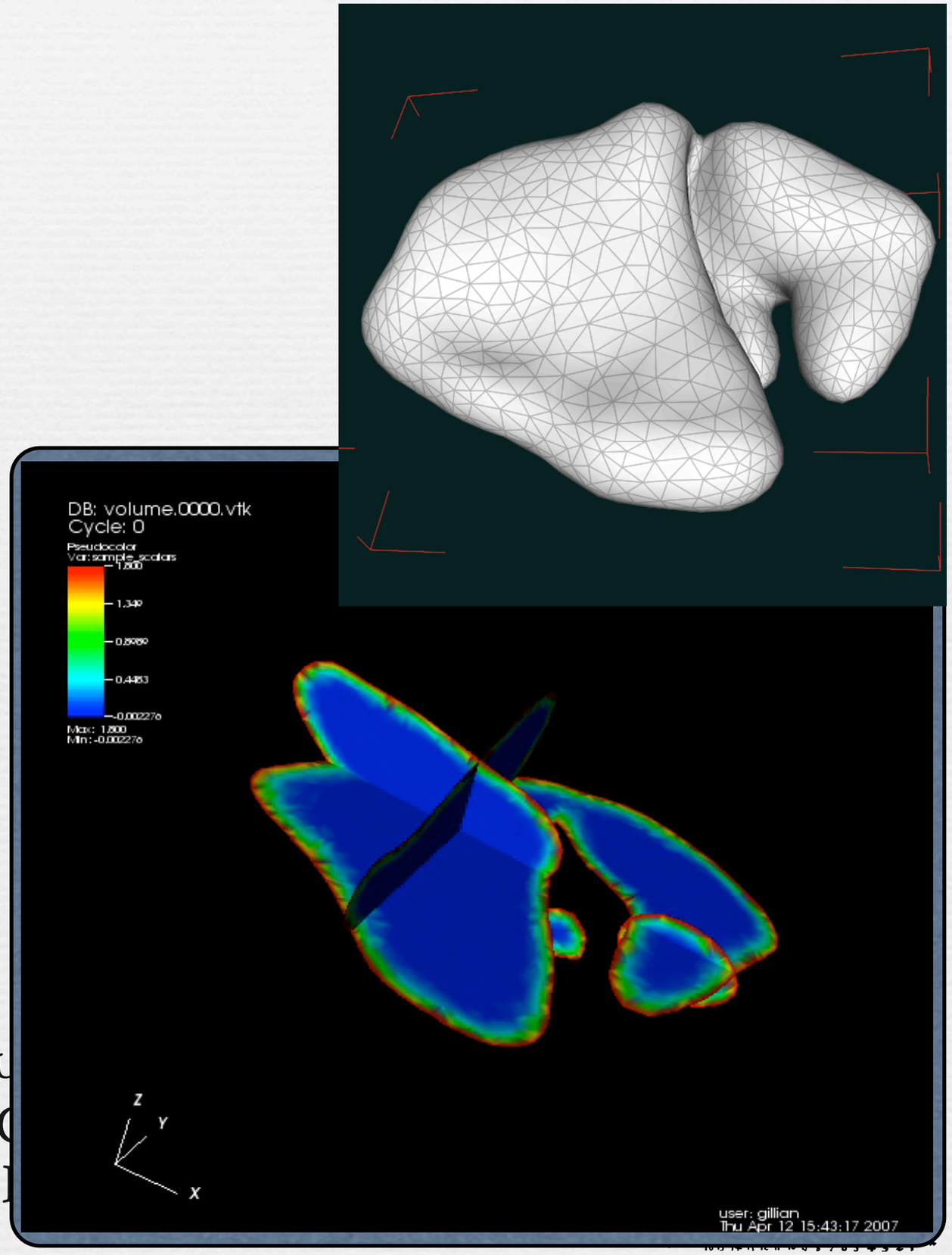


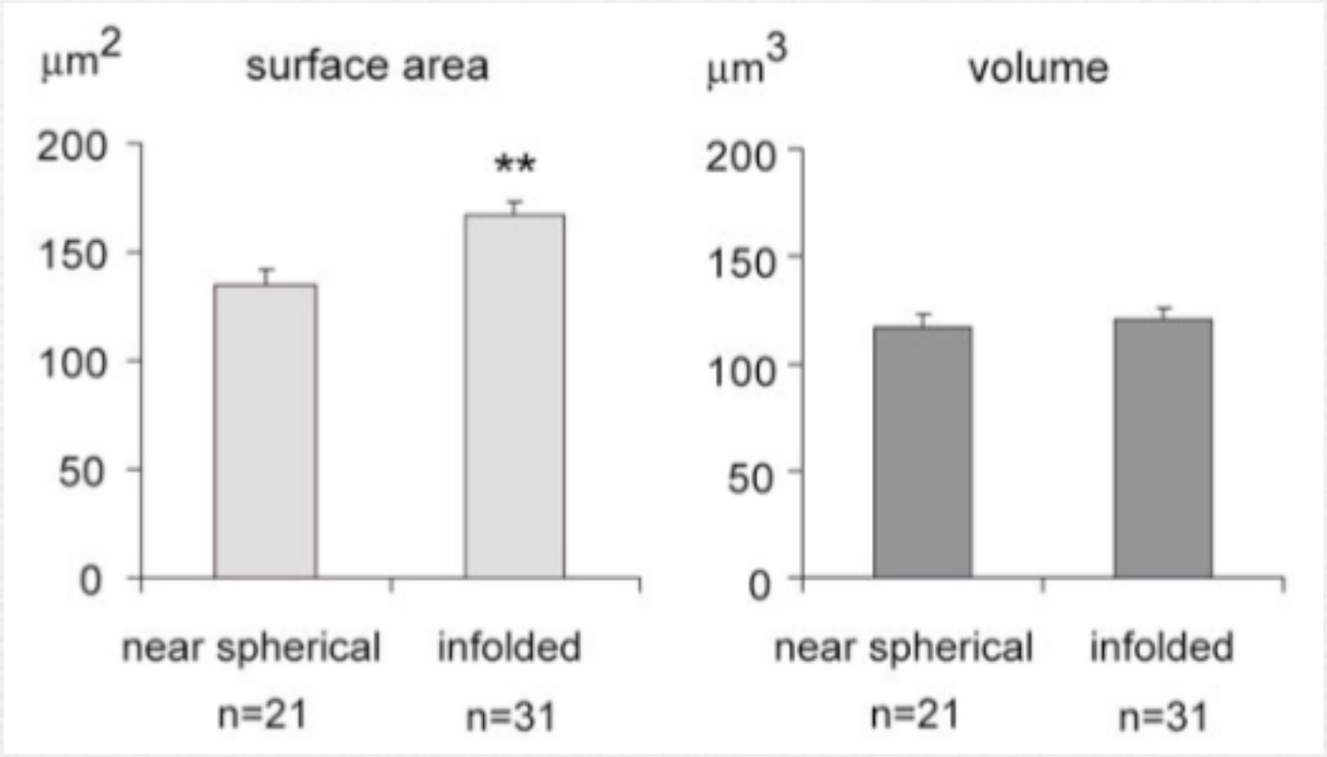
Single CCT Simulation





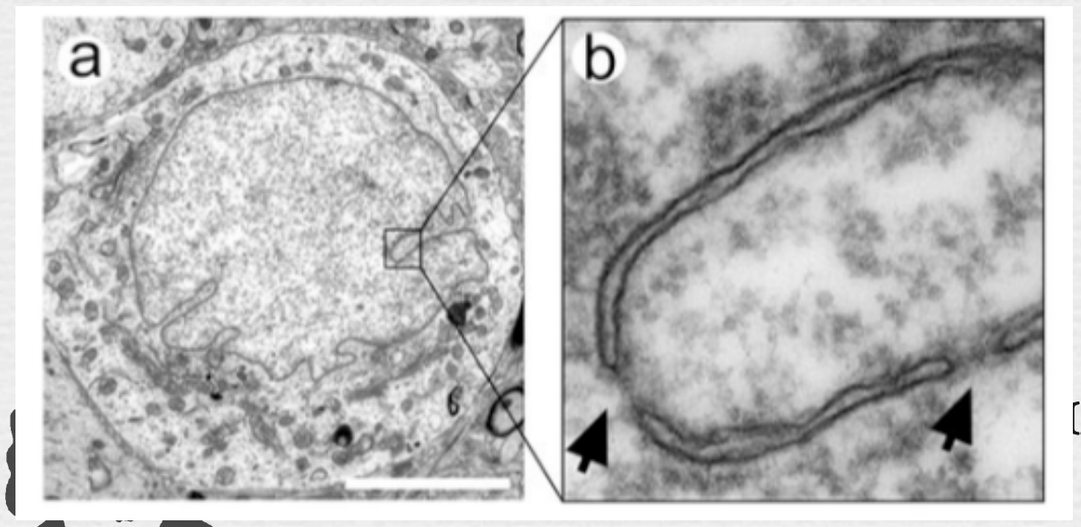
Reconstructed Nuclei – Measurements

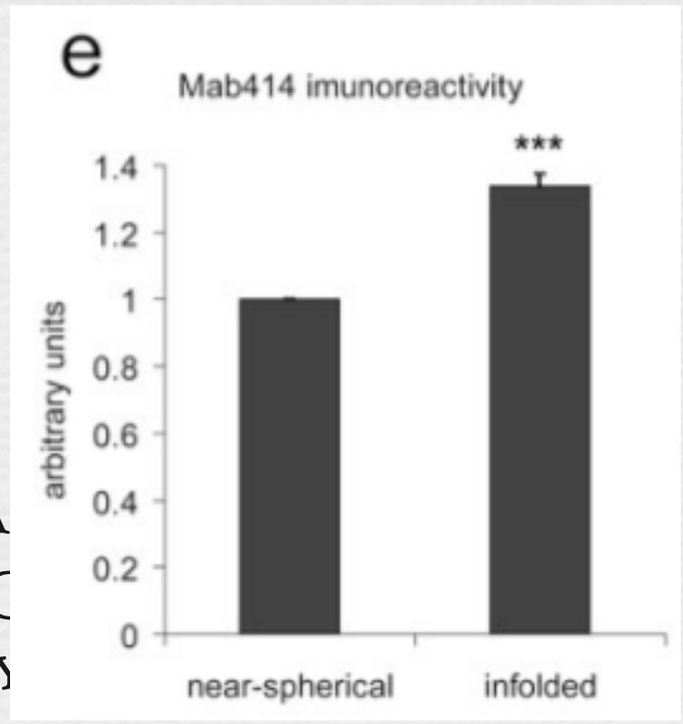
- Infolded nuclei have larger surface area compared to spherical nuclei.
- Volume of nuclei is nearly constant independent of morphology.

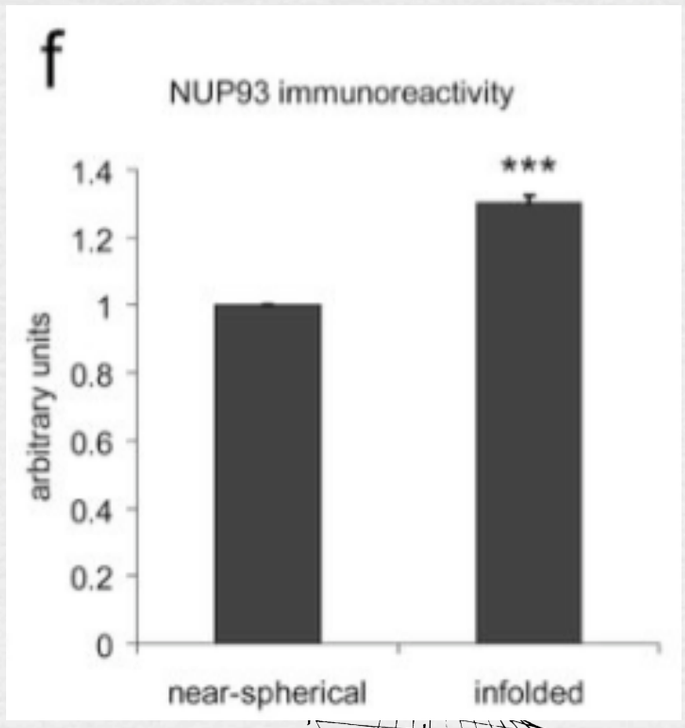


Nuclear pore counts by imunoreactivity

Increased membrane area leads to increase in nuclear pore complexes (NPCs)







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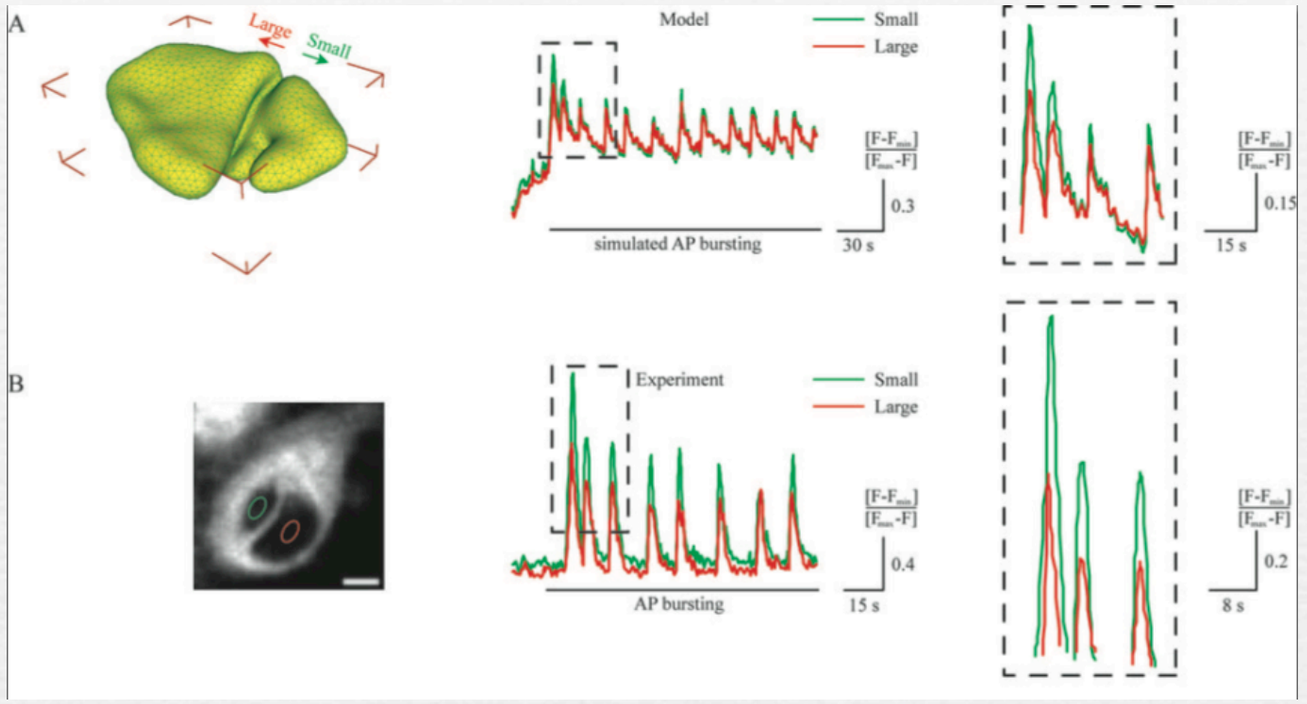
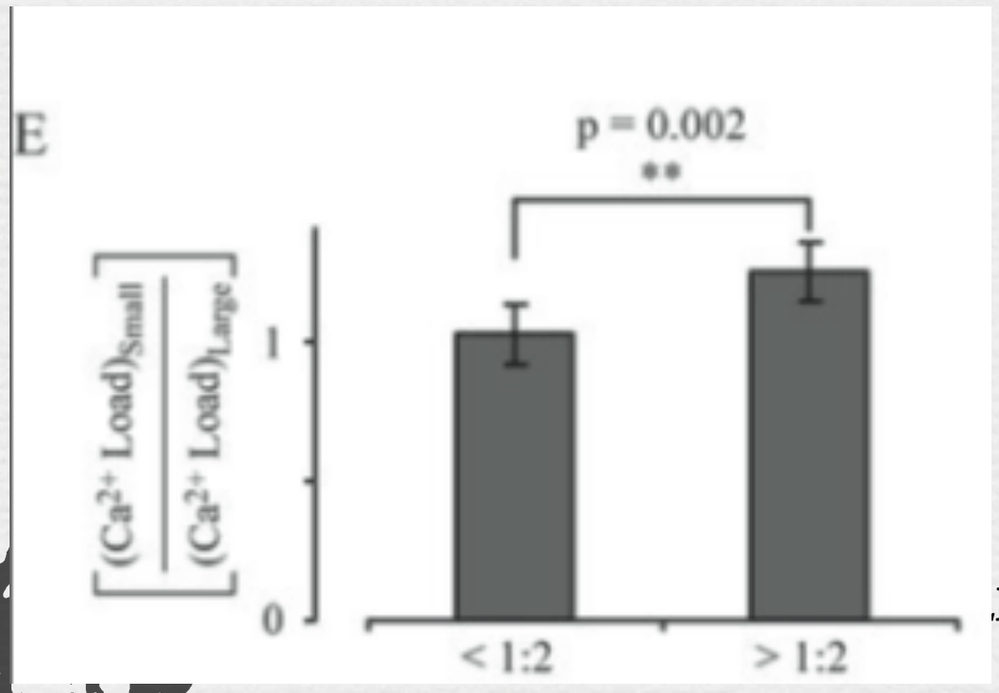
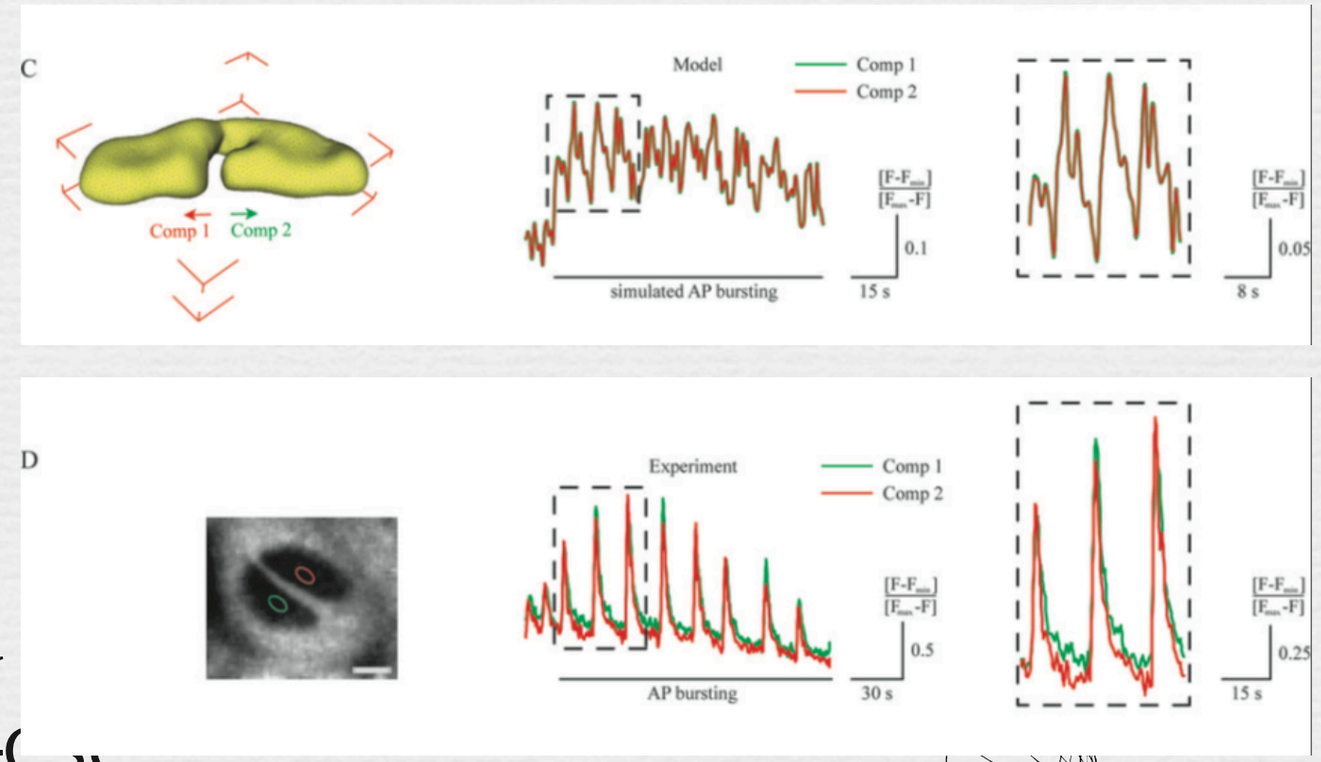
Nuclei form nuclear signaling microdomains

- Depending on the compartment size, nuclei show different calcium dynamics in their microdomains (A-D).
- With increased compartment ratio microdomain calcium levels become significantly higher (E).







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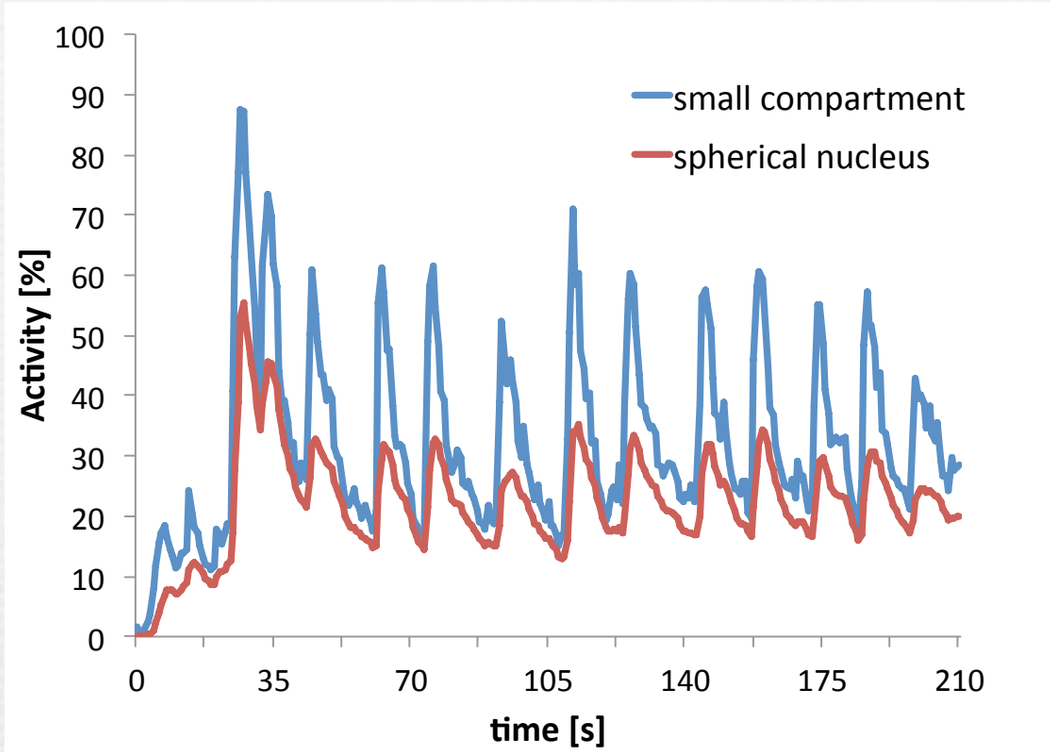
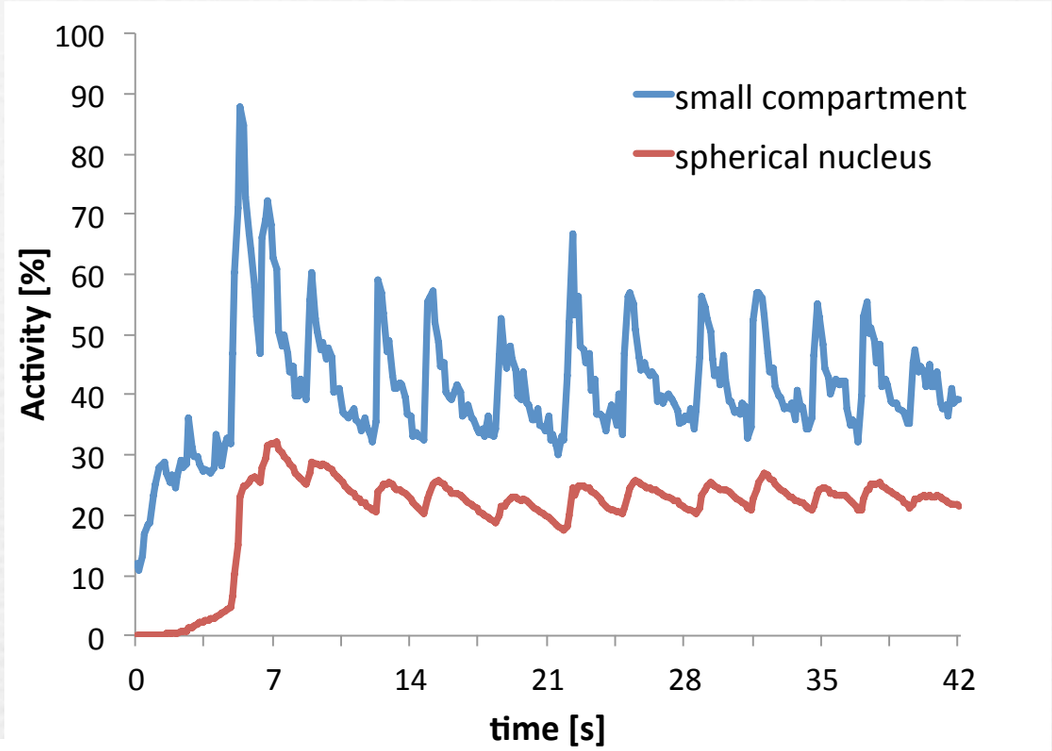
Frequency dependent dynamics

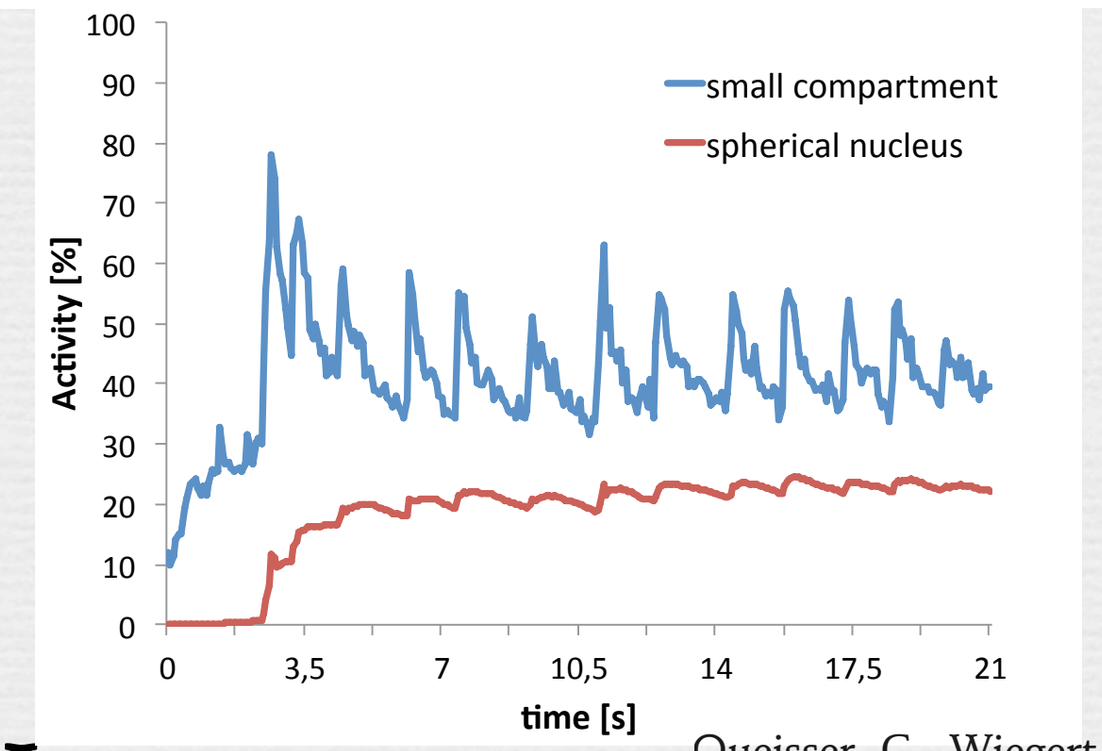
Changes of activity dynamics due to a change in frequency



0.1 Hz



0.5 Hz



1 Hz

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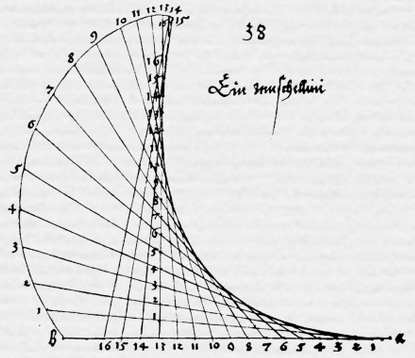
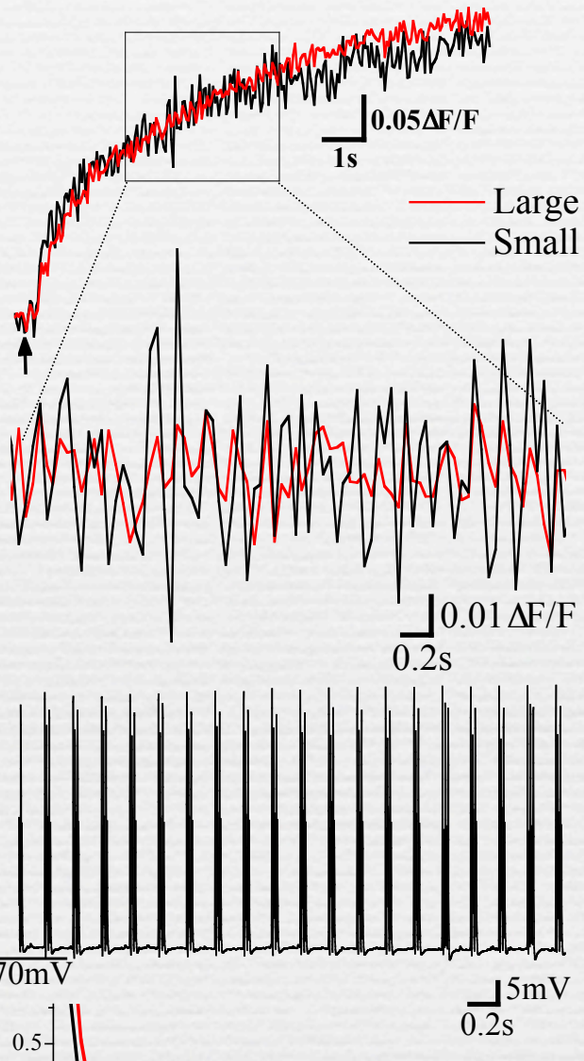
Queisser, G., Wiegert, S., Bading, H. (in press) Nucleus

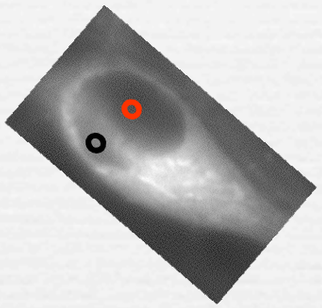


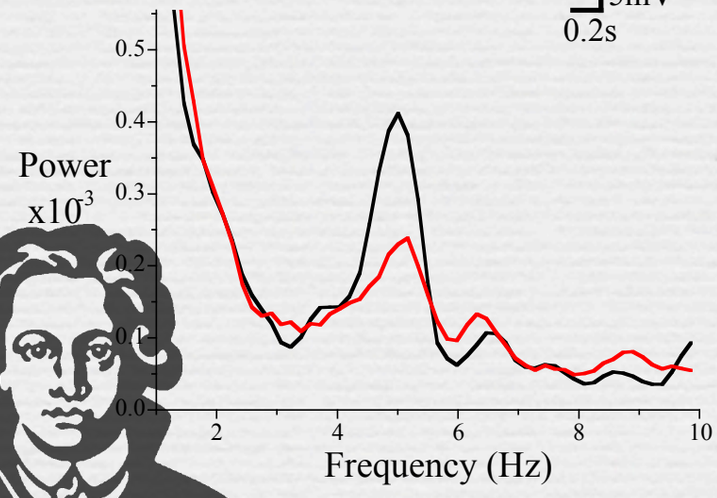
Small Compartments Better Resolve Oscillating Ca^{2+} Signals

Experiment

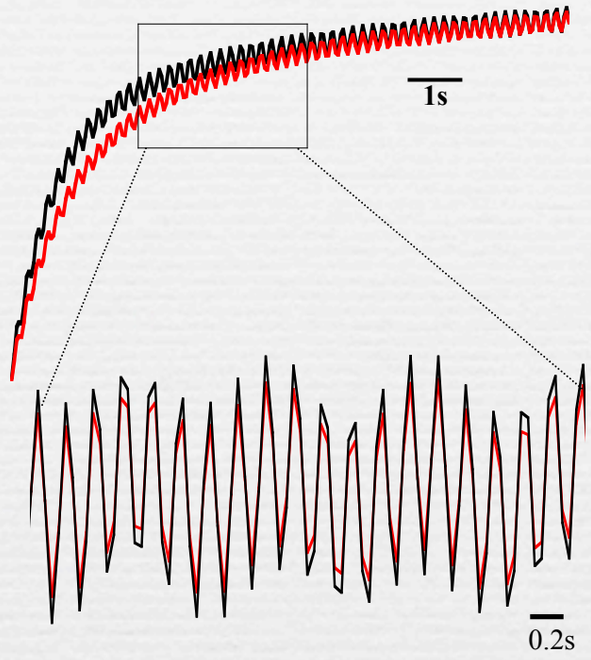


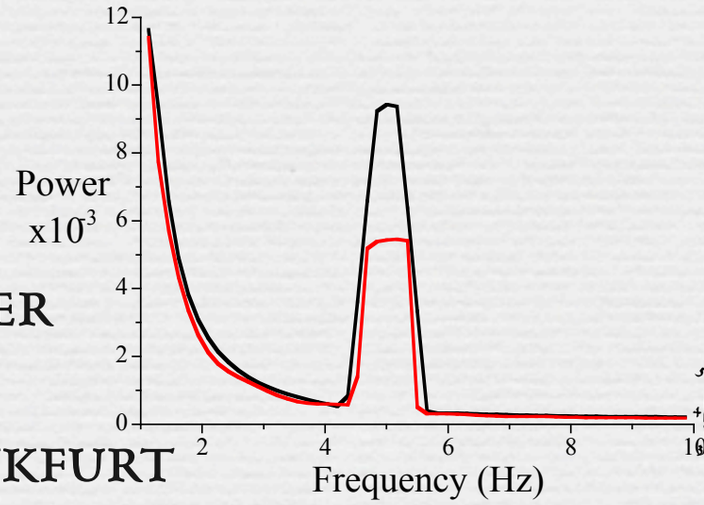
ER Tracker
Blue White DPX AM





Model





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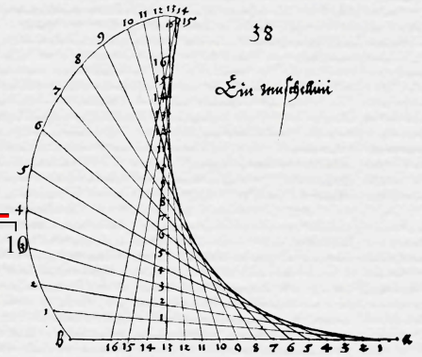
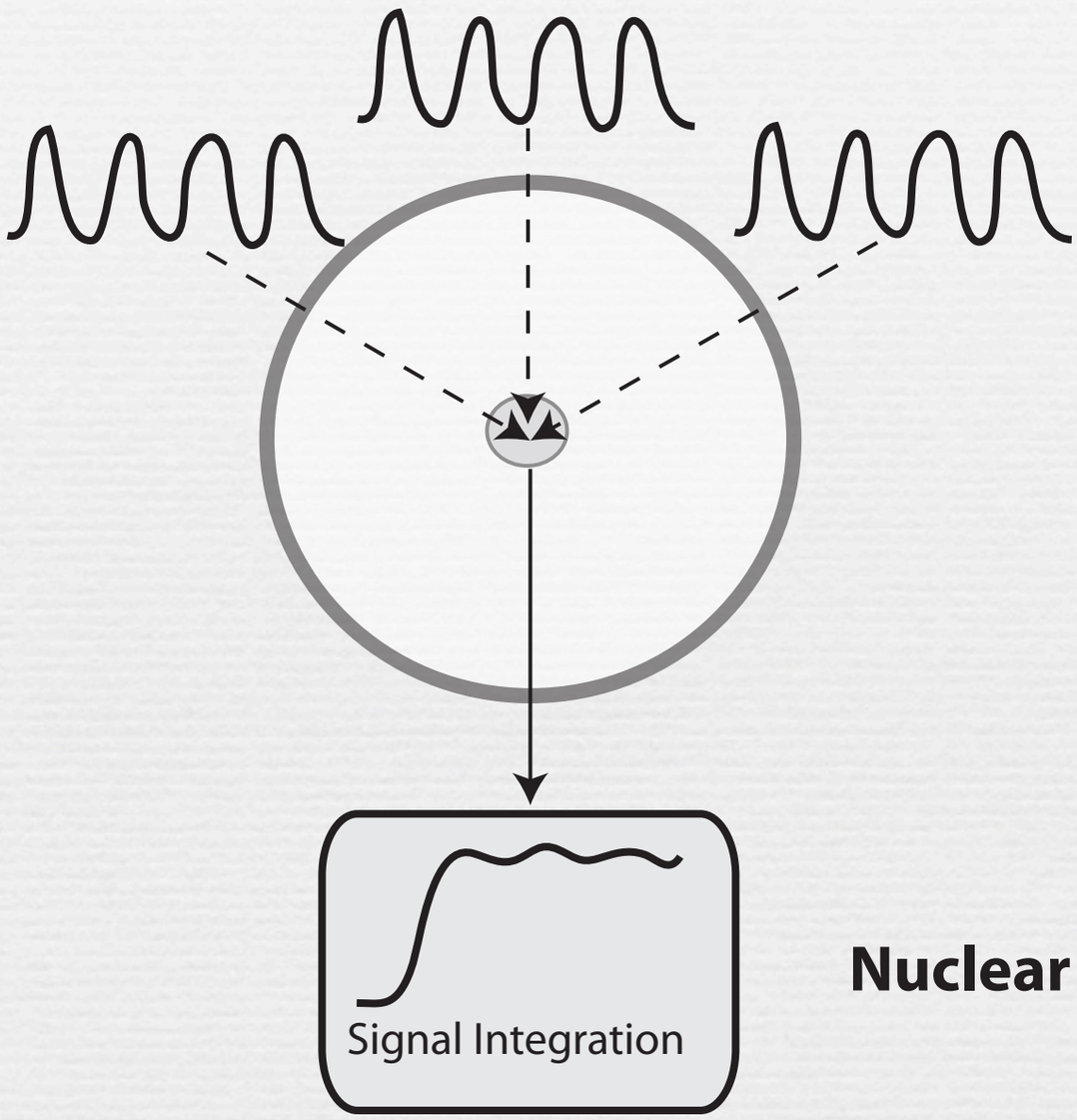
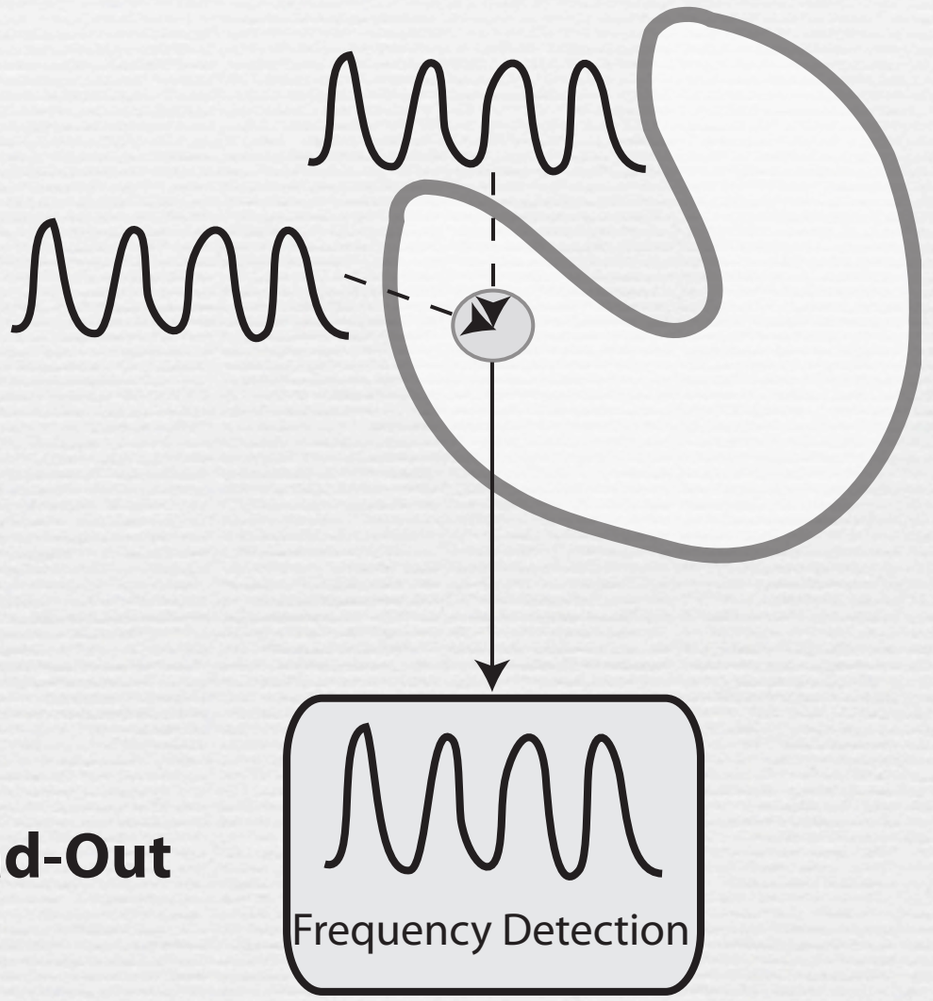


Integration vs. Detection

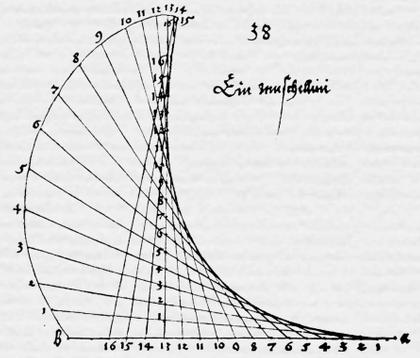


Nuclear Read-Out



Queisser, G., Wiegert, S., Bading, H. (in press) Nucleus

Gillian Queisser
G-CSC
University of Frankfurt



Some Results

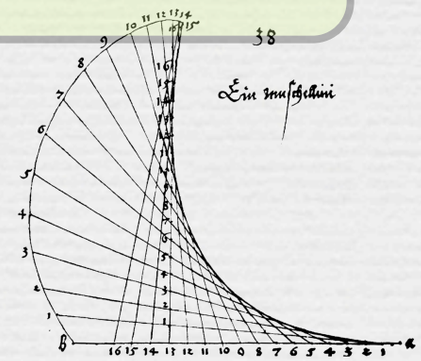
Signal-regulation of Nuclear Geometry

- Neuronal nuclei are extremely plastic and their geometry is controlled by NMDA receptor activation.
- Synaptic NMDA receptors promote the formation of infoldings.
- Extrasynaptic NDMA receptors – they direct neurons towards degeneration and cell death – lead to loss of nuclear infoldings.
- How calcium signals are translated into structural alterations is still unknown.
- ERK-MAP kinase pathway is required for the formation of infoldings (not presented).

Nucleoplasmic Reticulum - Yes or No?

- 3D reconstructions and EM results show that the invaginations are lined by both the inner and outer nuclear envelope, therefore the invaginated space is filled with cytosol, NOT ER lumen.
- Nucleoplasmic reticulum does not exist in hippocampal neurons.
- Infoldings enhance nuclear calcium signaling:
  1. larger nuclear surface and increased number of NPCs
  2. diffusion distances from cytosolic to nuclear locations are smaller.
  3. Compartmentalization occurs allowing microdomains to regulate calcium dynamics differently from one another.

Gillian Queisser
G-CSC
University of Frankfurt



Some Results

Nuclear Geometry and Calcium Signaling

- Compartments are often unequal in size, smaller ones better resolve high frequency calcium signals.
- May be relevant for activation of calmodulin, the principal calcium sensor.
- Calcium oscillations may be important to activate CREB-dependent transcription during LTP and memory formation.
- This information relay may be optimized in small microdomains.
- Spatial re-organization of chromosome territories may be caused due to changes in nuclear architecture and therefore affect gene transcription.

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G-CSC
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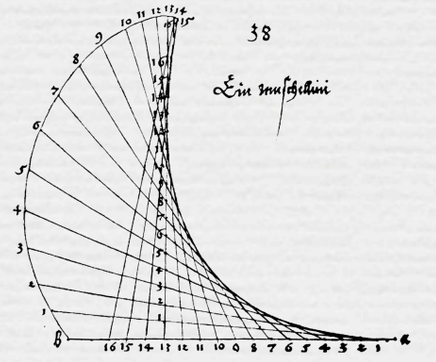

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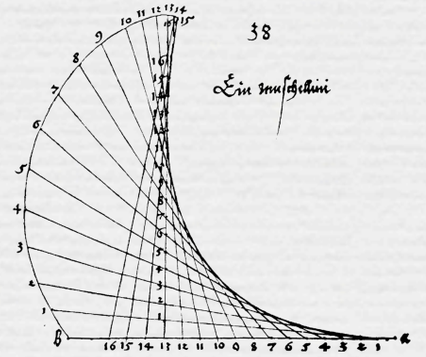
G-CSC
University of Frankfurt



Biological Framework

- The morphology of presynaptic specializations can vary greatly ranging from classical single-release-site boutons in the central nervous system to boutons of various sizes harboring multiple vesicle release sites.
- Basis of this analysis were the well-characterized glutamatergic synapses of larval neuromuscular junctions (NMJs) of Drosophila.

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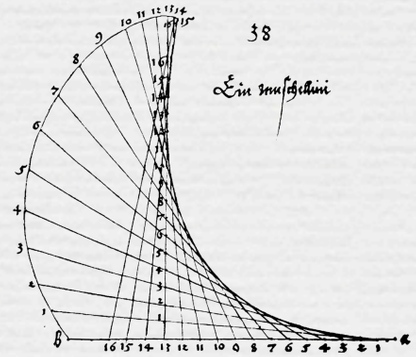
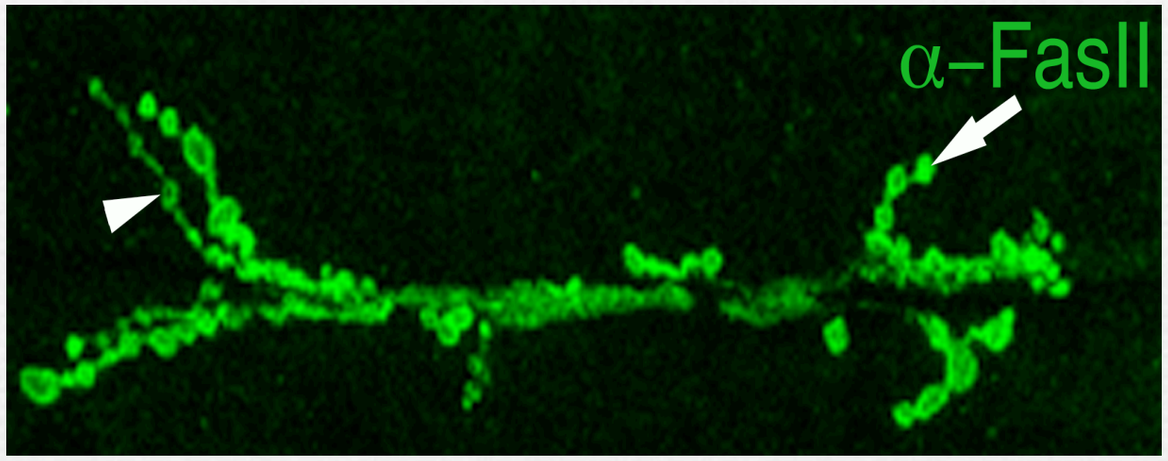
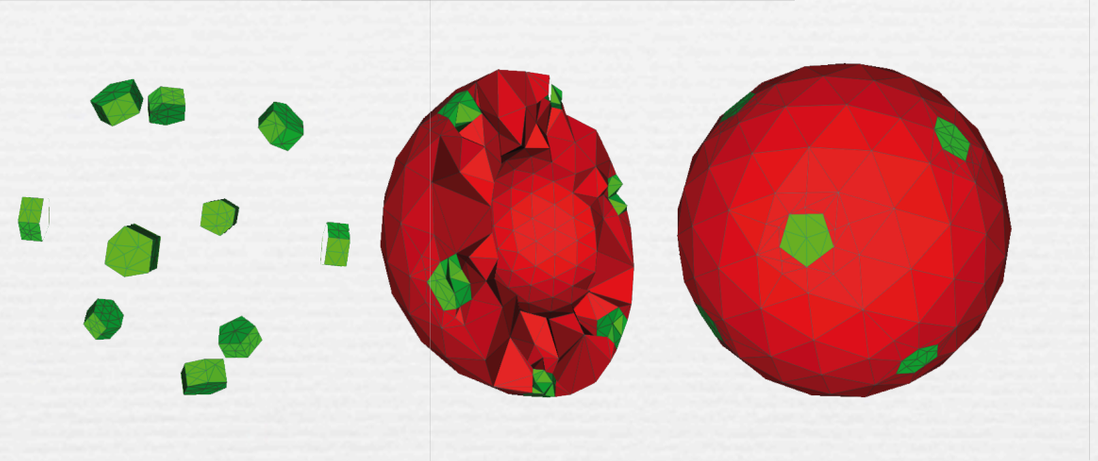


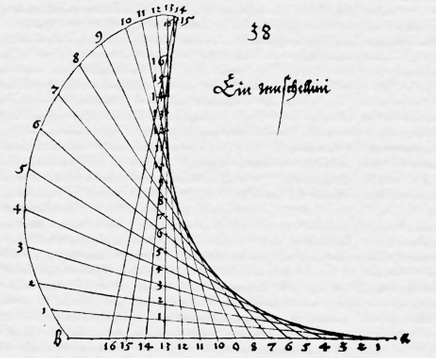
Two types of Boutons





- Larval bodywall muscles of Drosophila are typically innervated by two motor neurons of which one forms large ball-like Ib boutons and a second motor neuron forms smaller type Is boutons.
- Generate three-dimensional density profiles of presynaptic vesicles to monitor the local distribution and dynamics of vesicles as **a function of bouton morphology**.

Gillian Queisser
G-CSC
University of Frankfurt



Important Parameters

- Frequency
- Vesicle output probability P_0
- Bouton size

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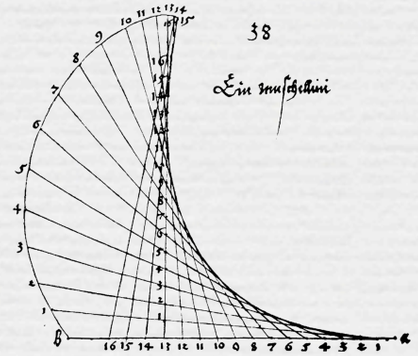
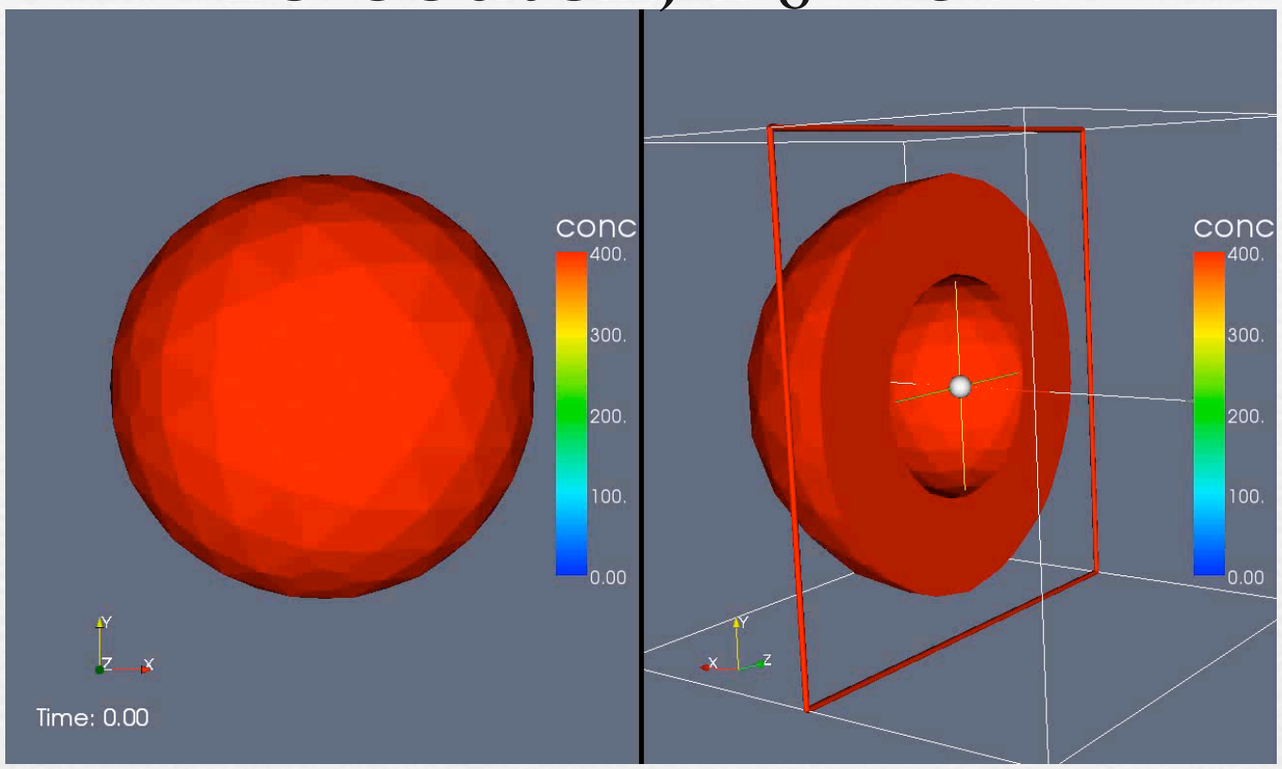
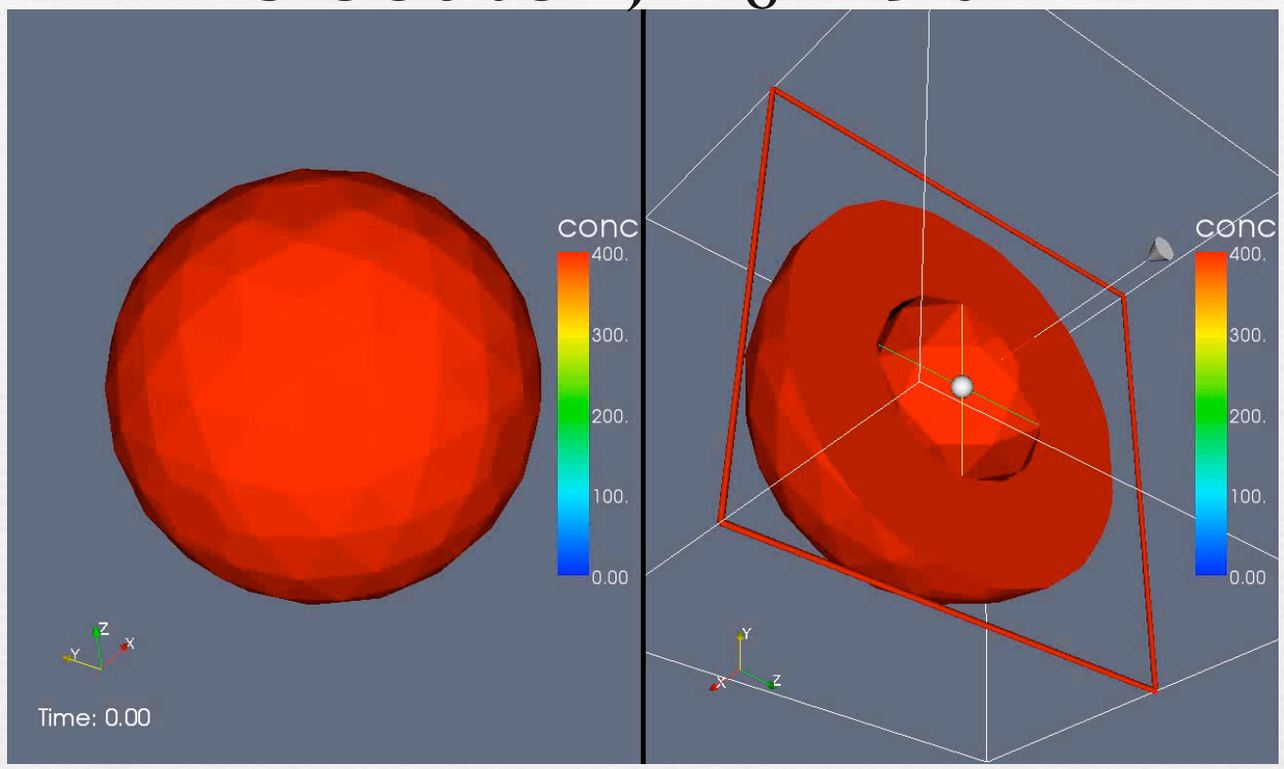


Simulations

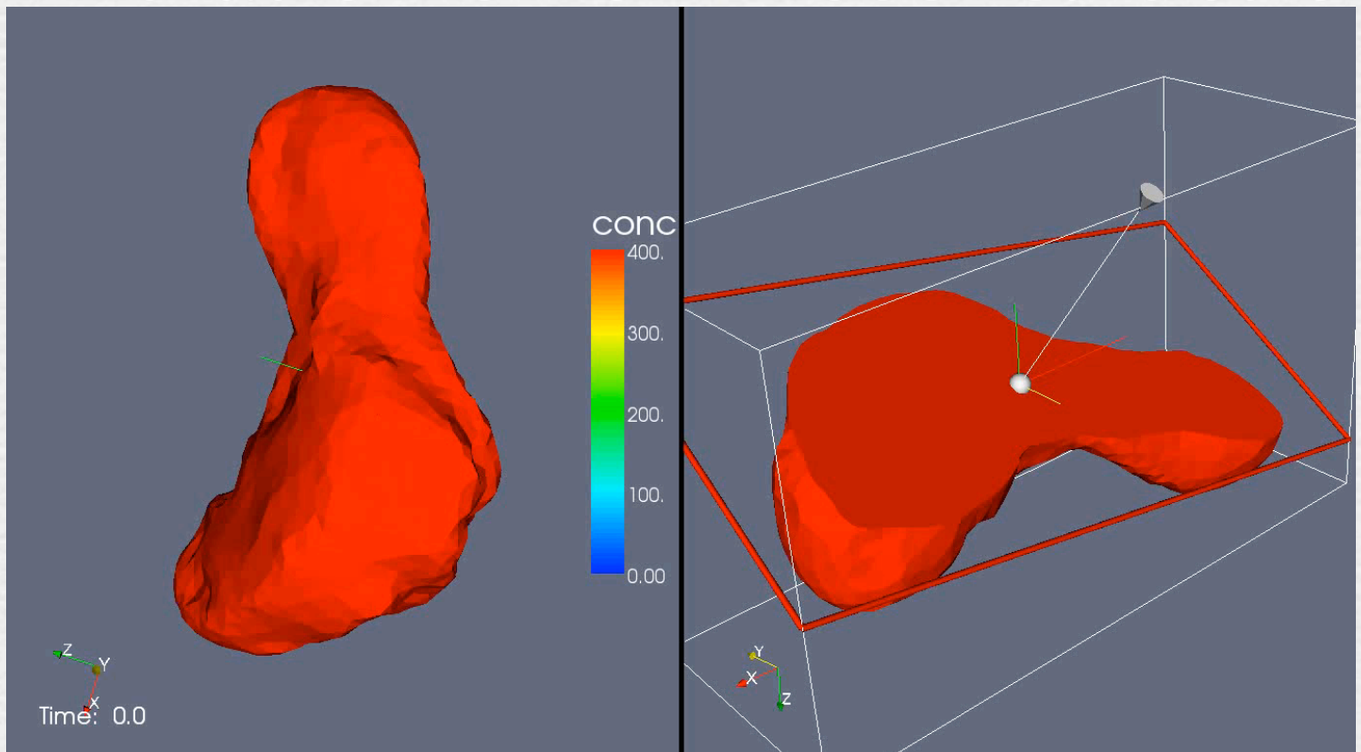
Ib bouton, P_o = 5%

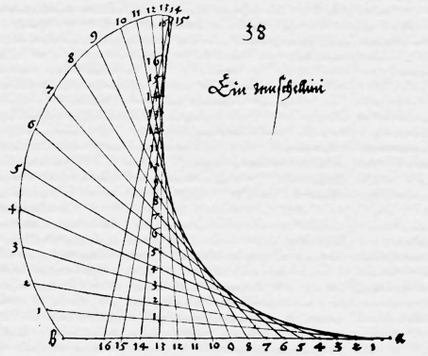


Is bouton, P_o = 90%



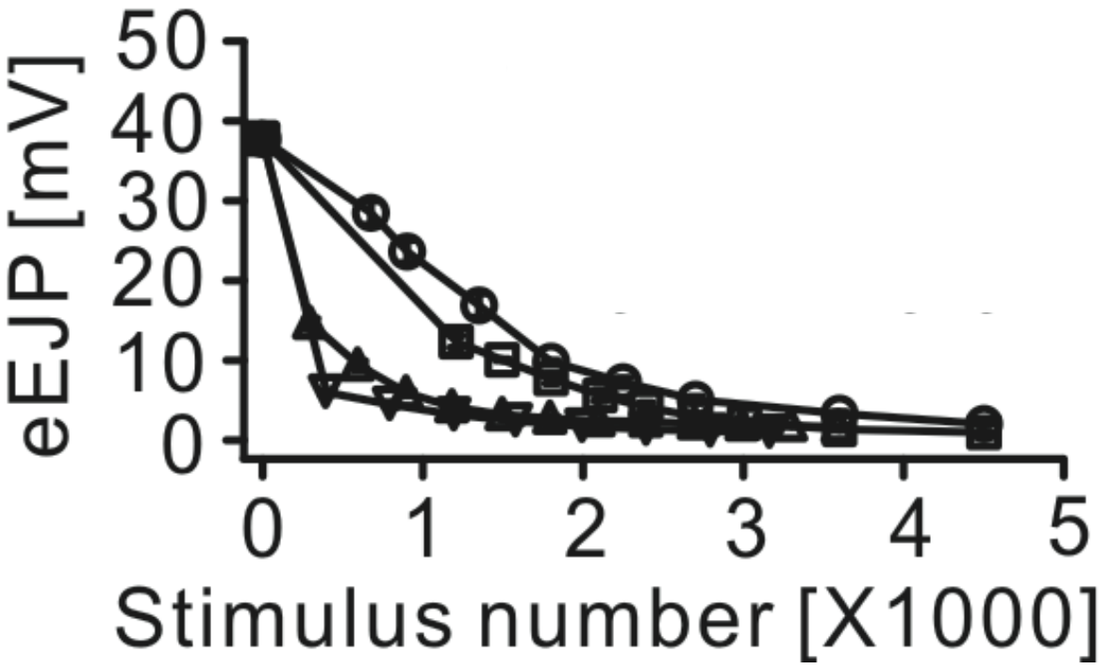
Simulation on 3D-reconstruction



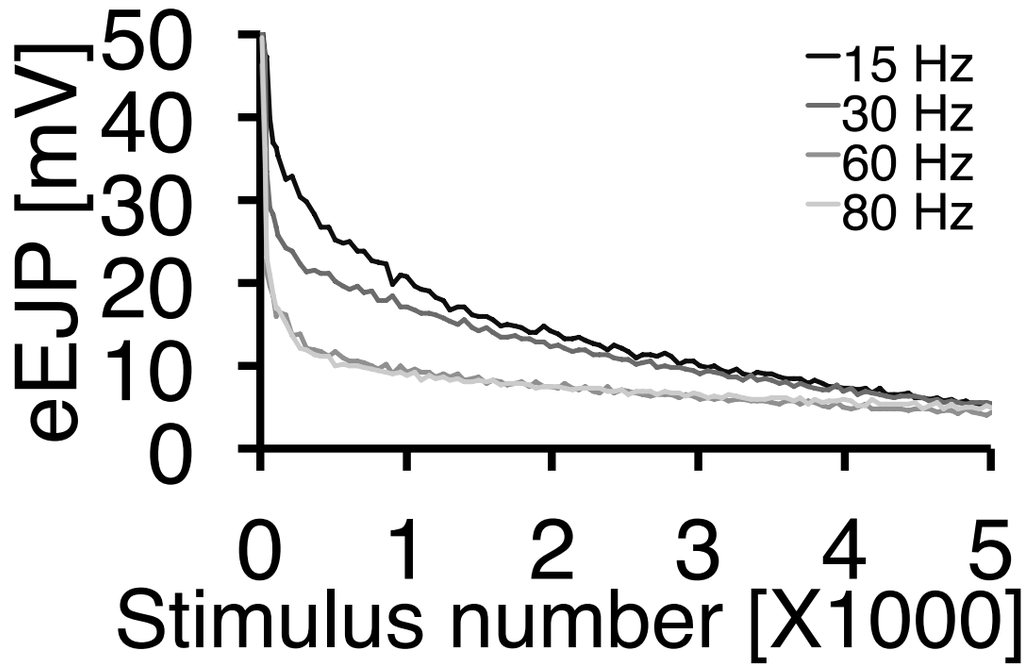


Synaptic Transmission at different input Frequencies

In vivo



In silico



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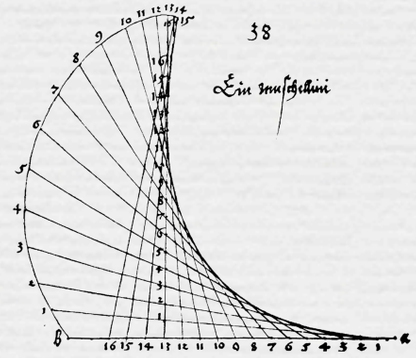
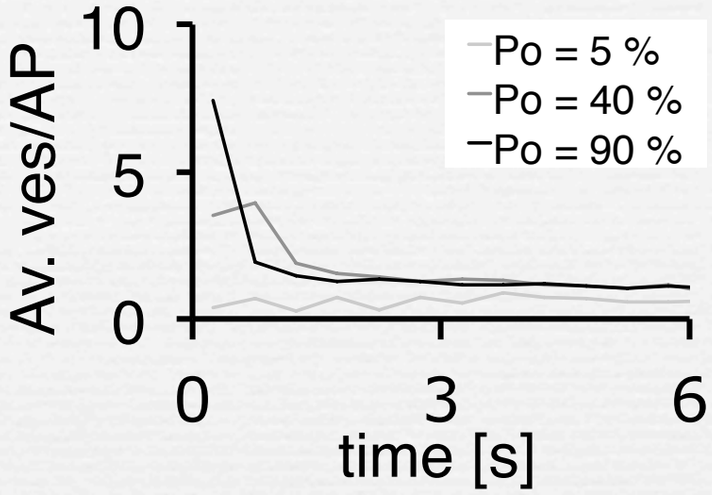
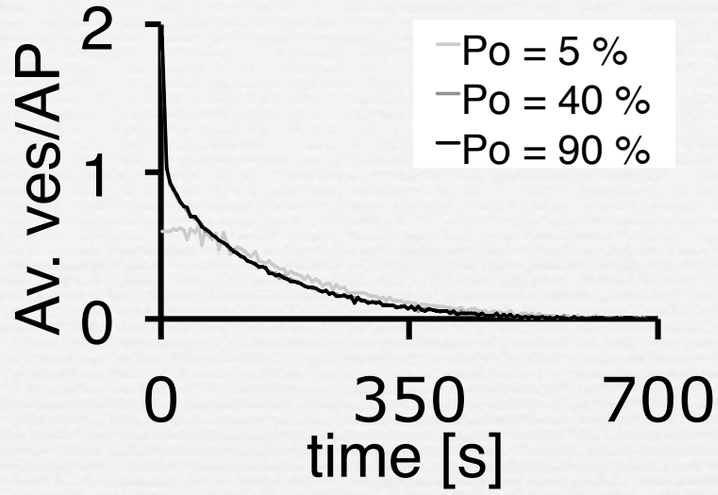
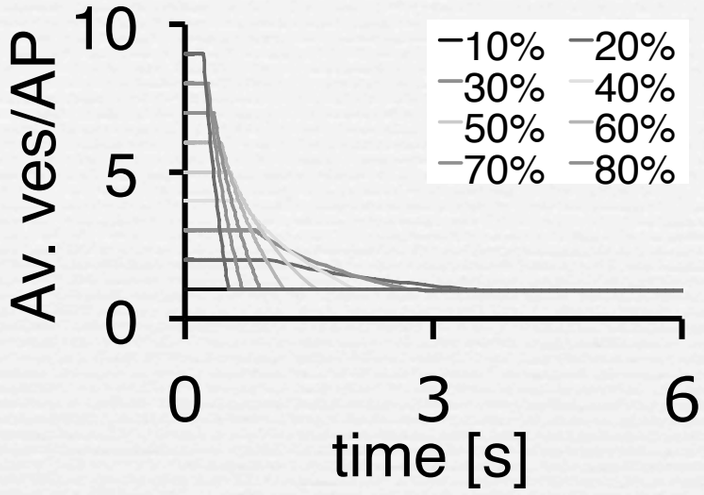
G-CSC
University of Frankfurt

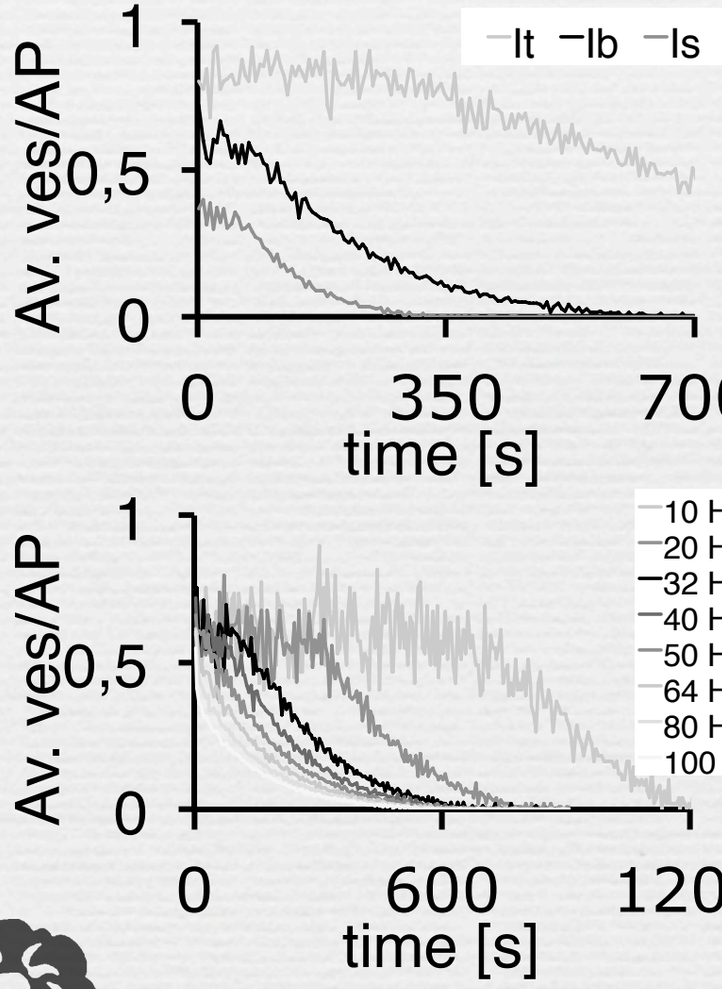


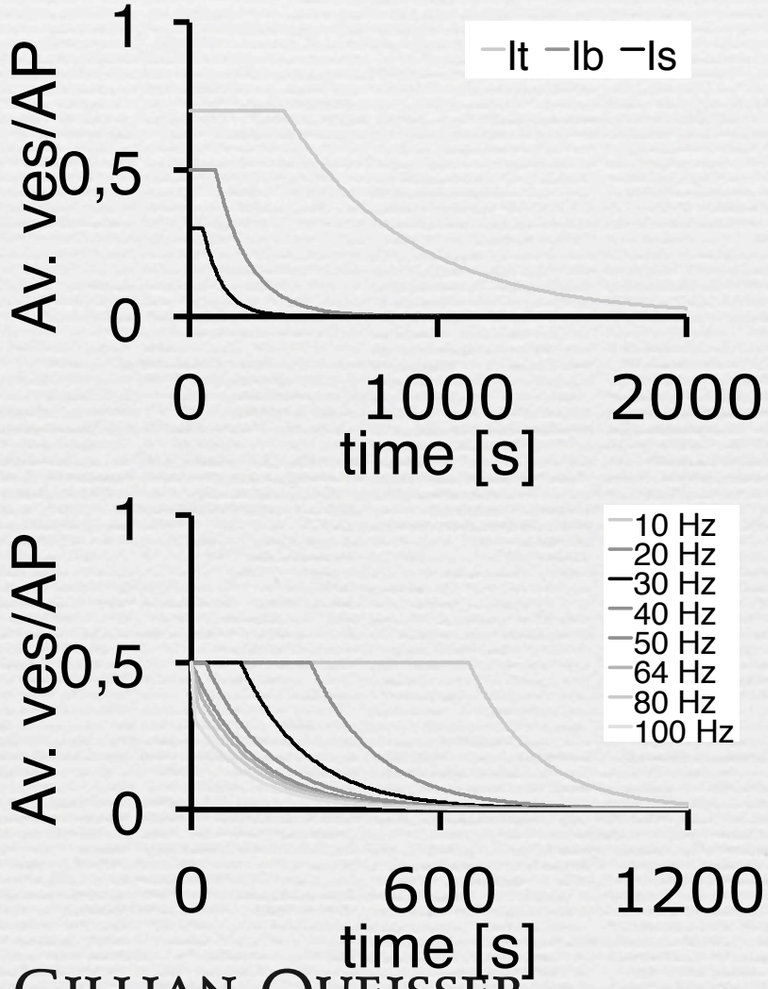
Output Probability, Size and Frequency







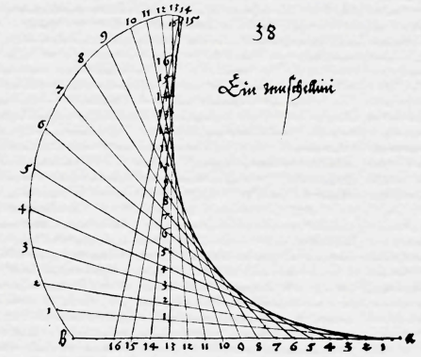




Gillian Queisser

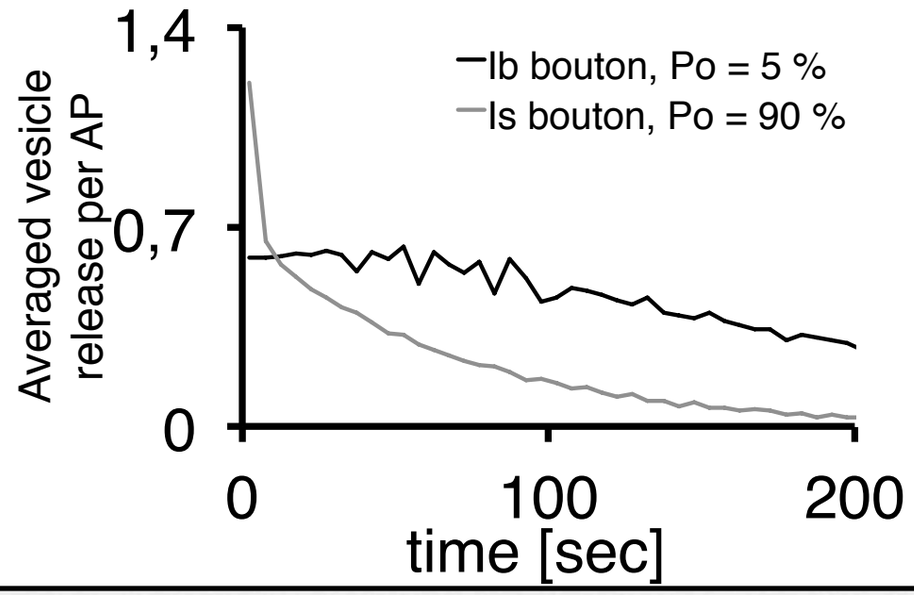
G-CSC

University of Frankfurt

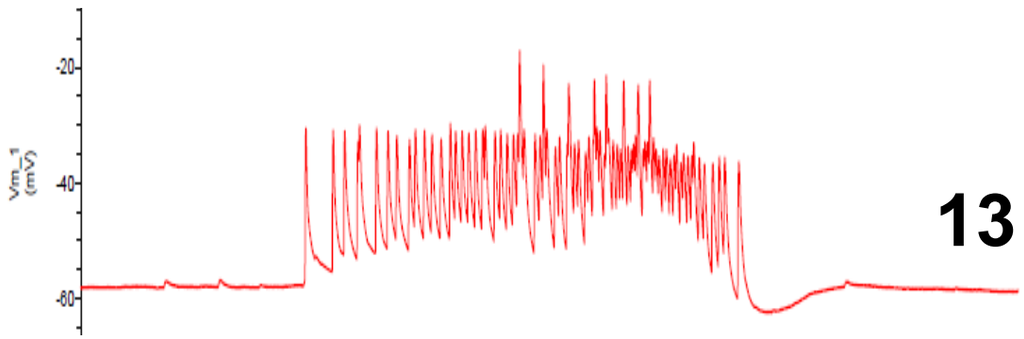


Bouton Configurations

Optimal bouton configurations predicted by model



Native pattern – in vivo vs. in silico



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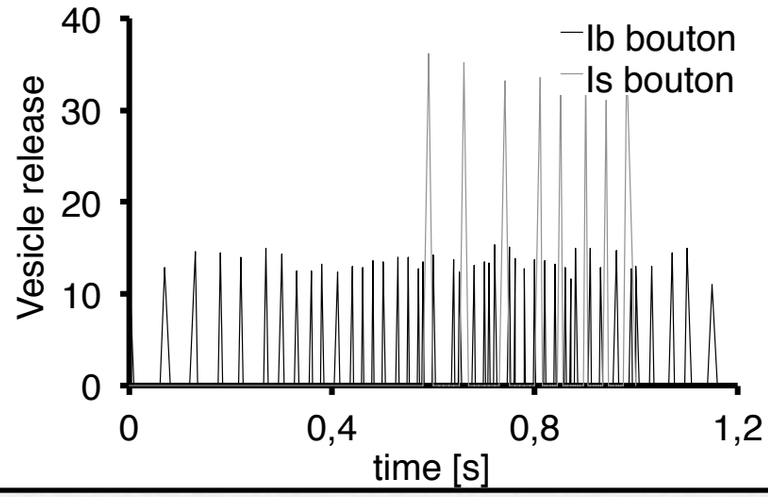
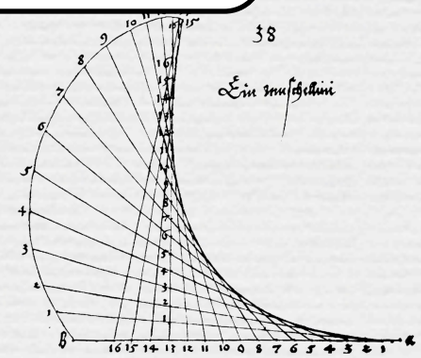


Gillian Queisser
G-CSC
University of Frankfurt



Conclusions

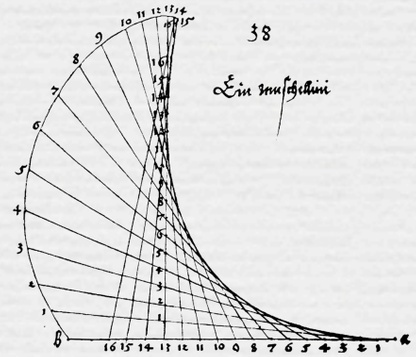
- P_o strongly affects the magnitude of total vesicle release at the beginning of stimulation

- Bouton size primarily affects the endurance of active vesicle release suggesting that larger boutons are better suited for long bouts of synaptic activity whereas smaller boutons are only reliable with short trains of stimulation.

- The model predicts that Ib boutons are utilized to transmit longer-lasting high-frequency stimuli whereas Is boutons are better suited for few low-frequency events at high amplitudes.

- Taken together Is and Ib boutons complement each others functionality, forming an efficient system across different time scales.

Gillian Queisser
G-CSC
University of Frankfurt



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Gillian Queisser
G-CSC
University of Frankfurt