Tampereen yliopisto
Tampere University

Part 2:
Computational Models of Single Cell Astrocytes and Neuron-Astrocyte Interactions

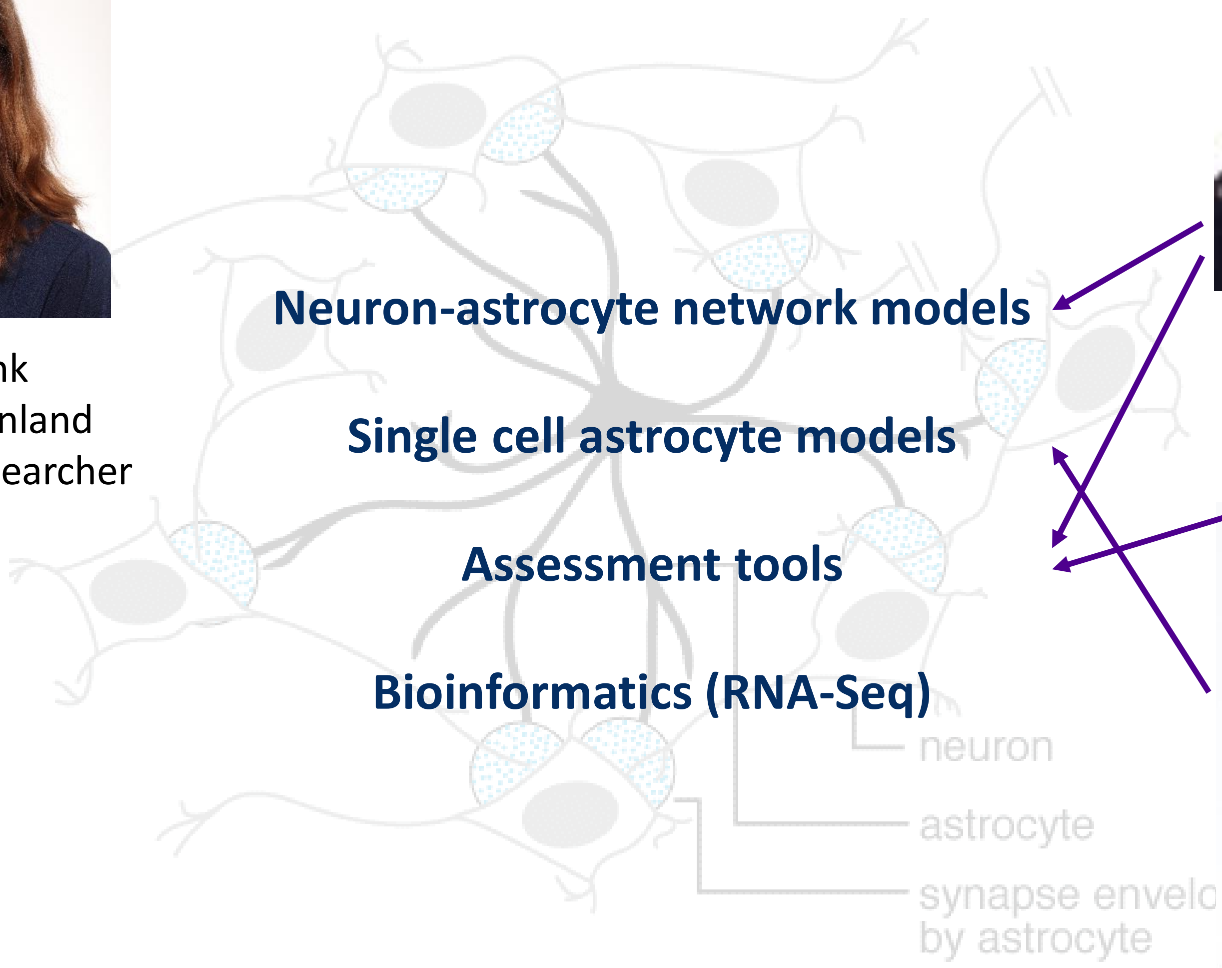
Dr. Kerstin Lenk

Tampere University, Finland

Faculty of Medicine and Health Technology

Astrocyte centered modeling (current members)

Kerstin Lenk
Academy of Finland
Postdoctoral Researcher



Neuron-astrocyte network models

Single cell astrocyte models

Assessment tools

Bioinformatics (RNA-Seq)

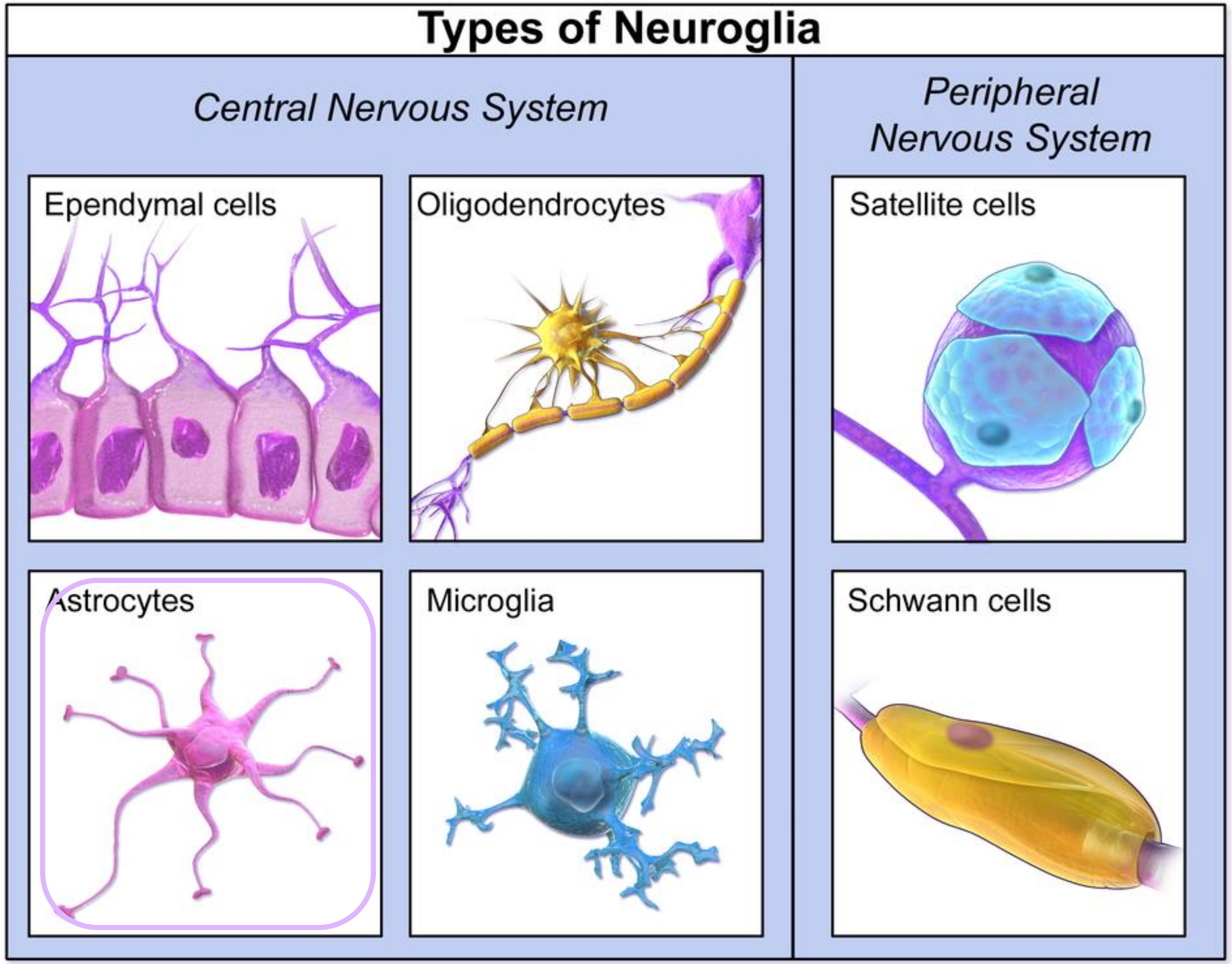
Barbara Genocchi
PhD student

Sama Saeid
Master's student

Aapo Tervonen
PhD student

Image: www.antanitus.com

Glia cell types



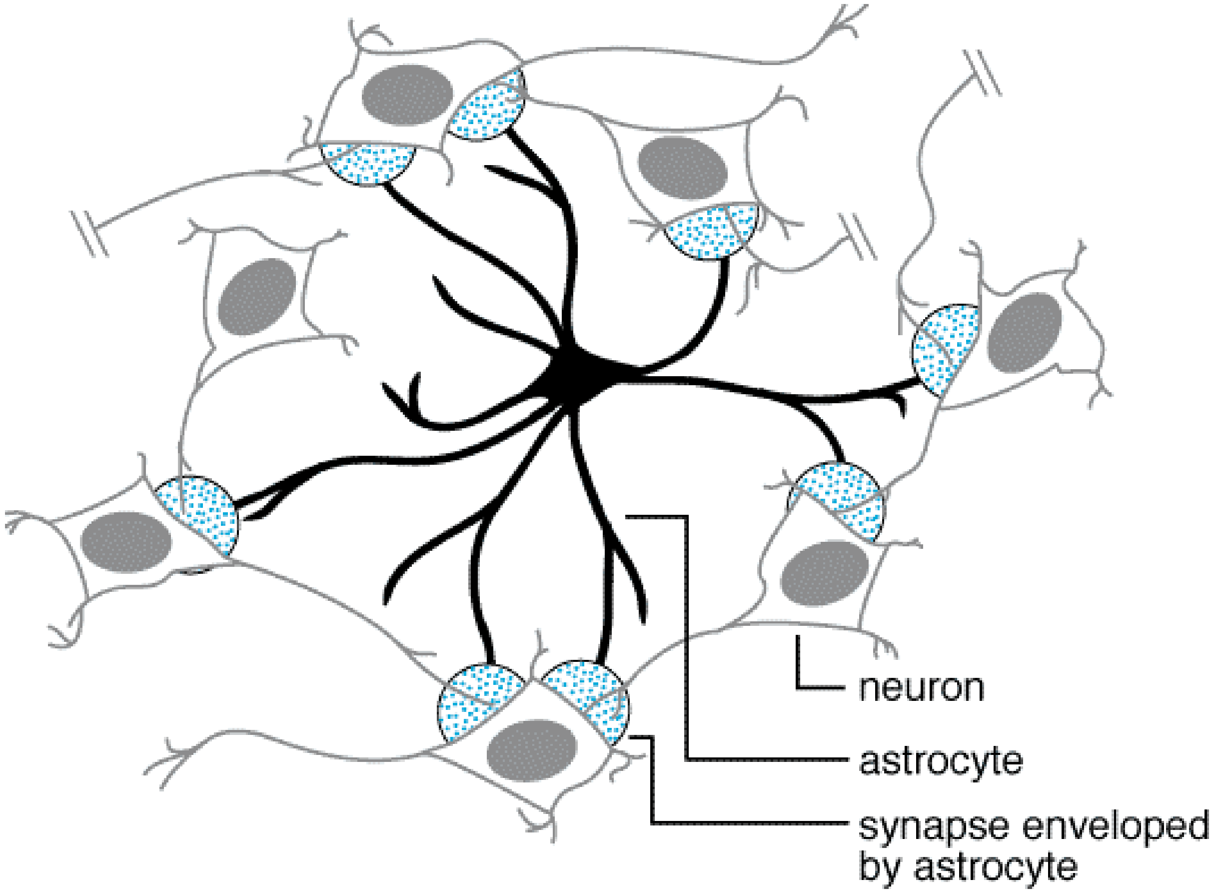
- Ependymal cells – spinal cord, blood-cerebrospinal fluid barrier
- Oligodendrocyte – insulation
- Microglia – immune response, synapse formation/pruning
- Astrocyte – tight junctions, nutrients, modulation of neuronal activity

- Satellite cells – regulate the external chemical environment
- Schwann cell – insulation of axons in peripheral nervous system

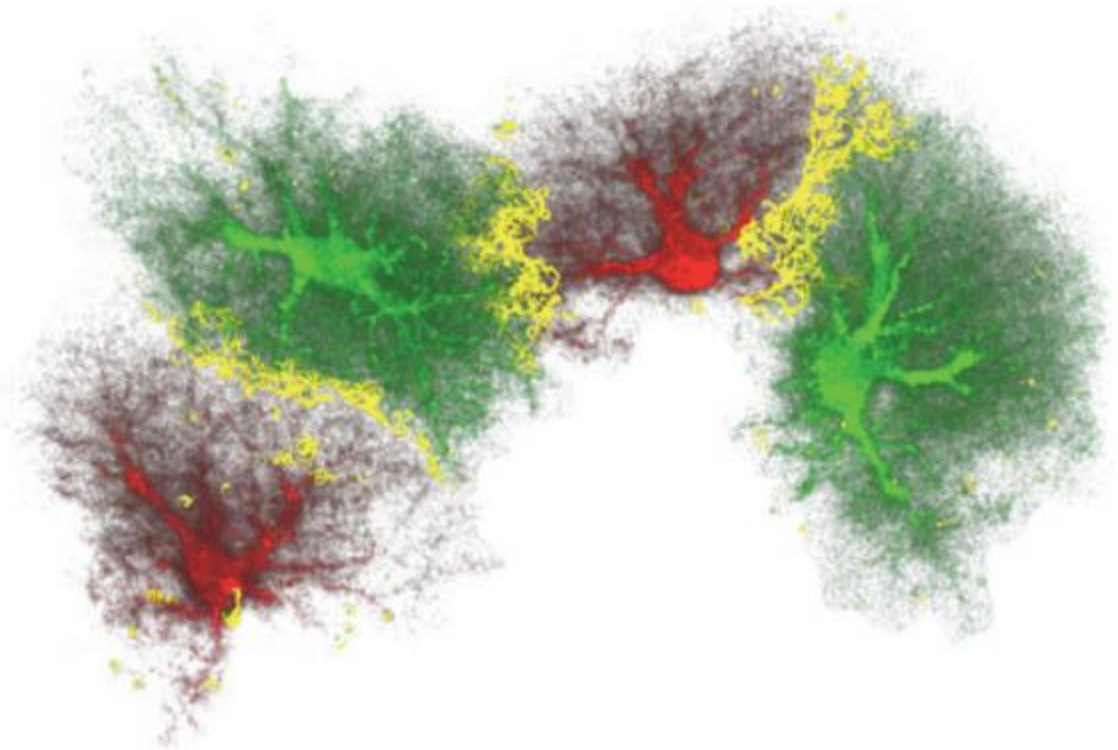
Image: https://en.wikipedia.org/wiki/Glia

Astrocytes are more than support cells

Neuron-astrocyte connections

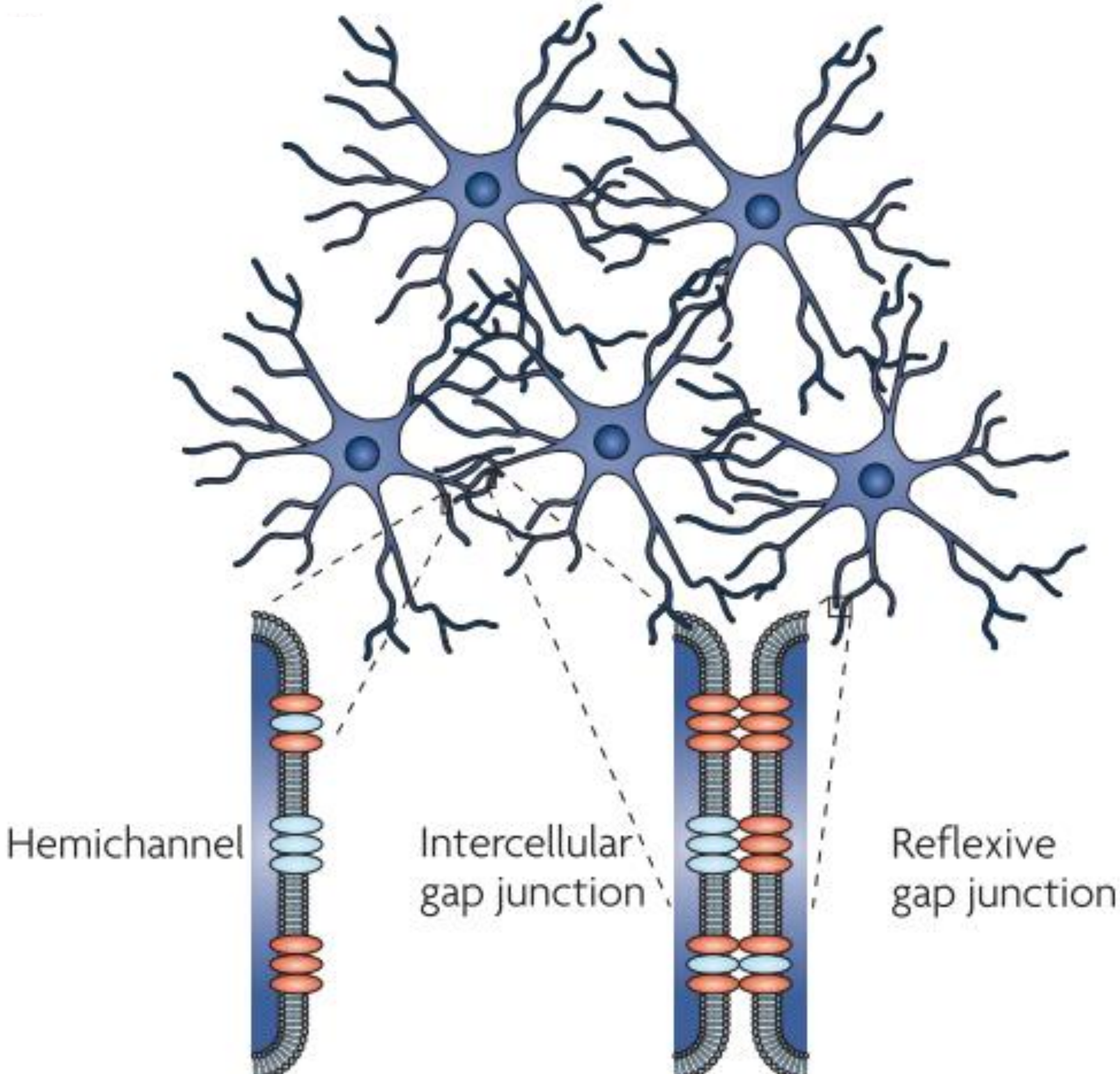


Astrocyte-astrocyte connections



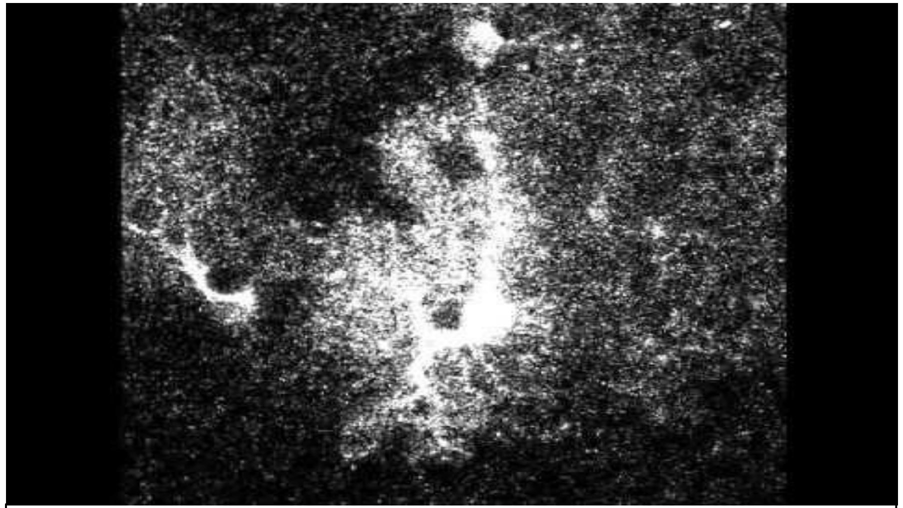
Images: www.antanitus.com, Wilhelmsson et al., PNAS 2006

Gap junction coupling between astrocytes



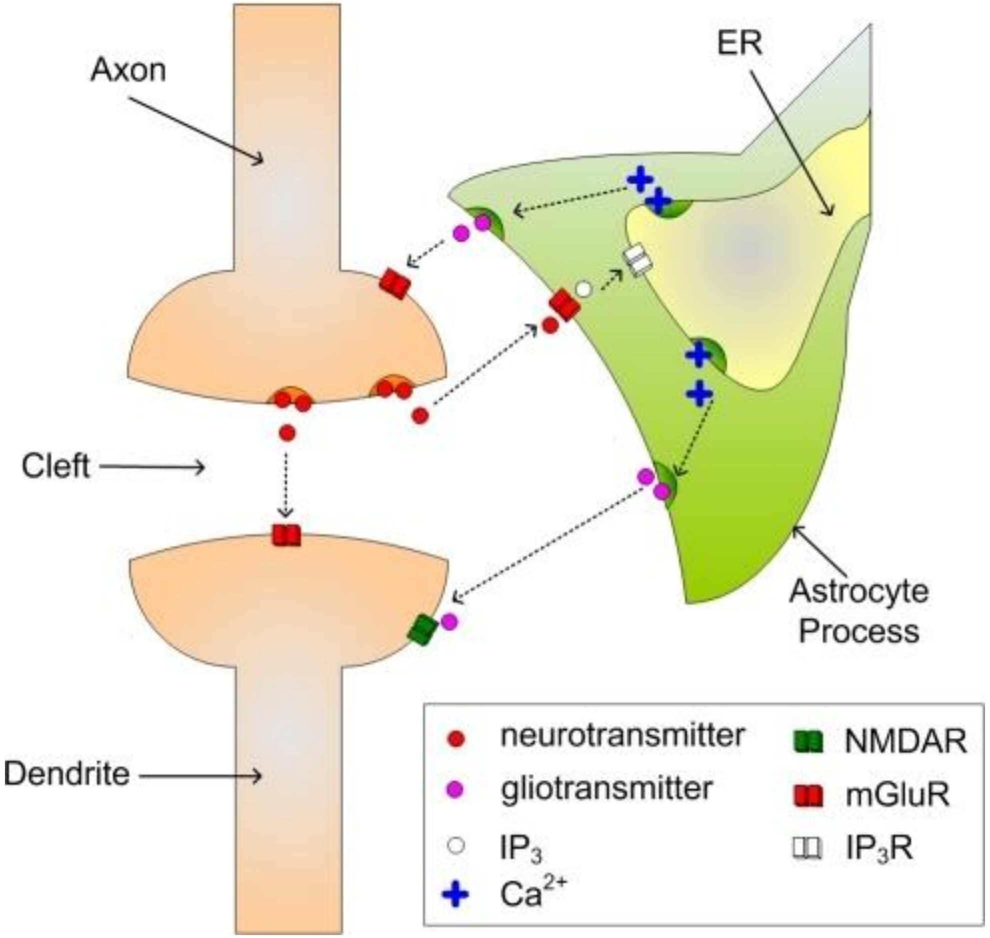
Giaume et al., Nat Rev Neurosci 2010

Calcium signalling in the tripartite synapse

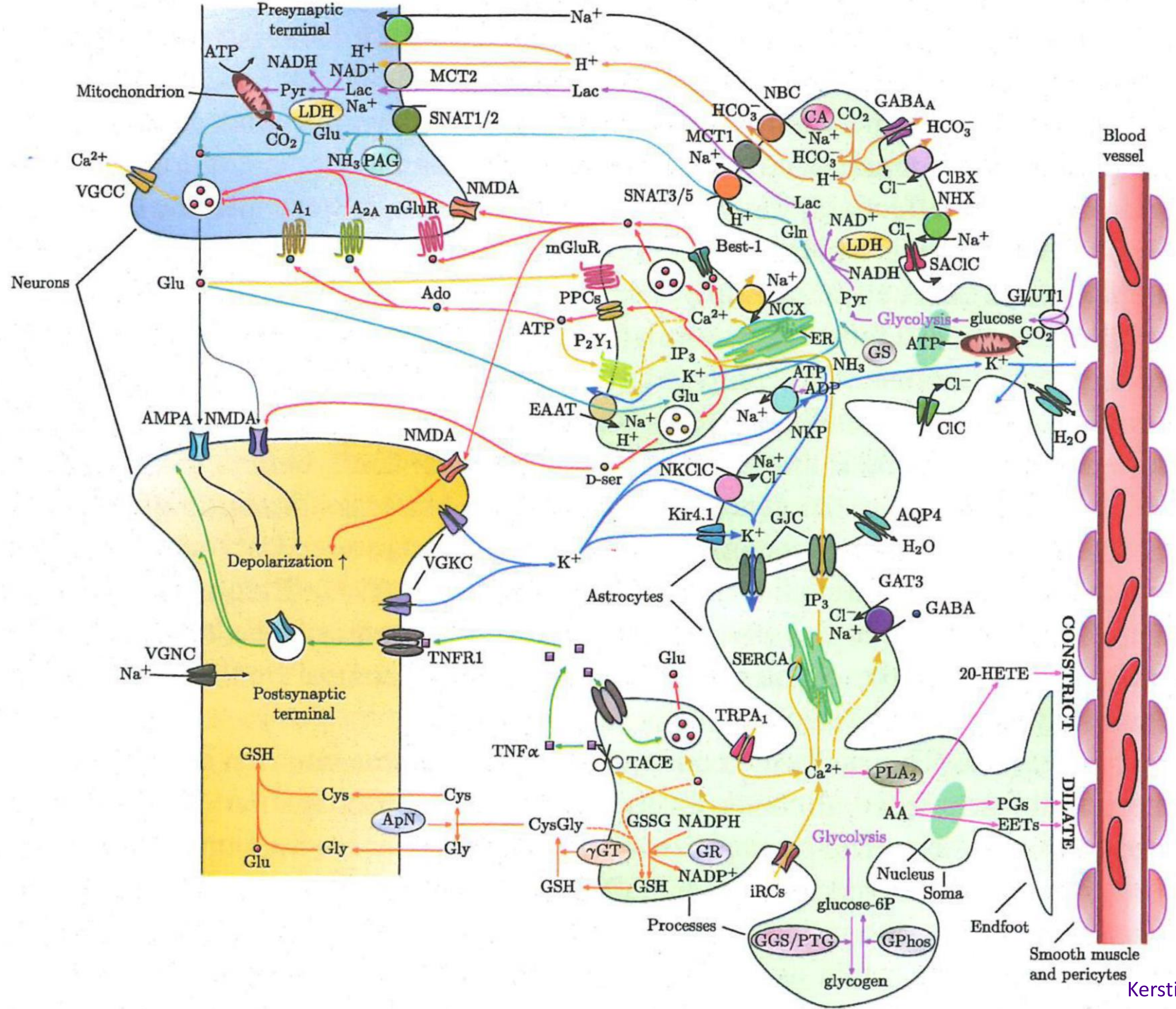


Video:
https://www.youtube.com/watch?v=y7Yg1mlvLlc

- Neurotransmitters trigger IP3 release in astrocytes
- IP3 triggers calcium release from the endoplasmic reticulum
- IP3 can diffuse through gap junctions; calcium only locally in the astrocytes



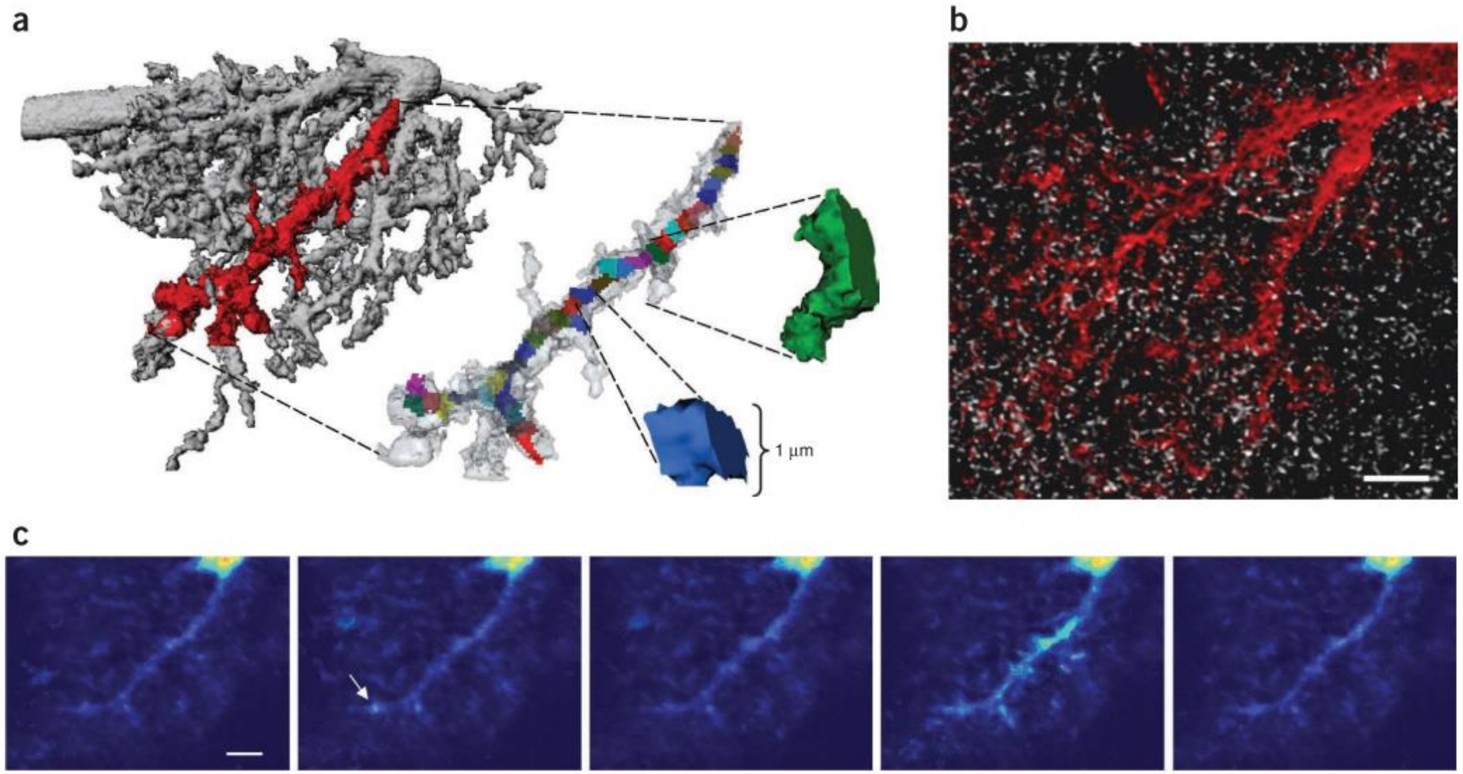
Astrocyte communication with neurons and vasculature

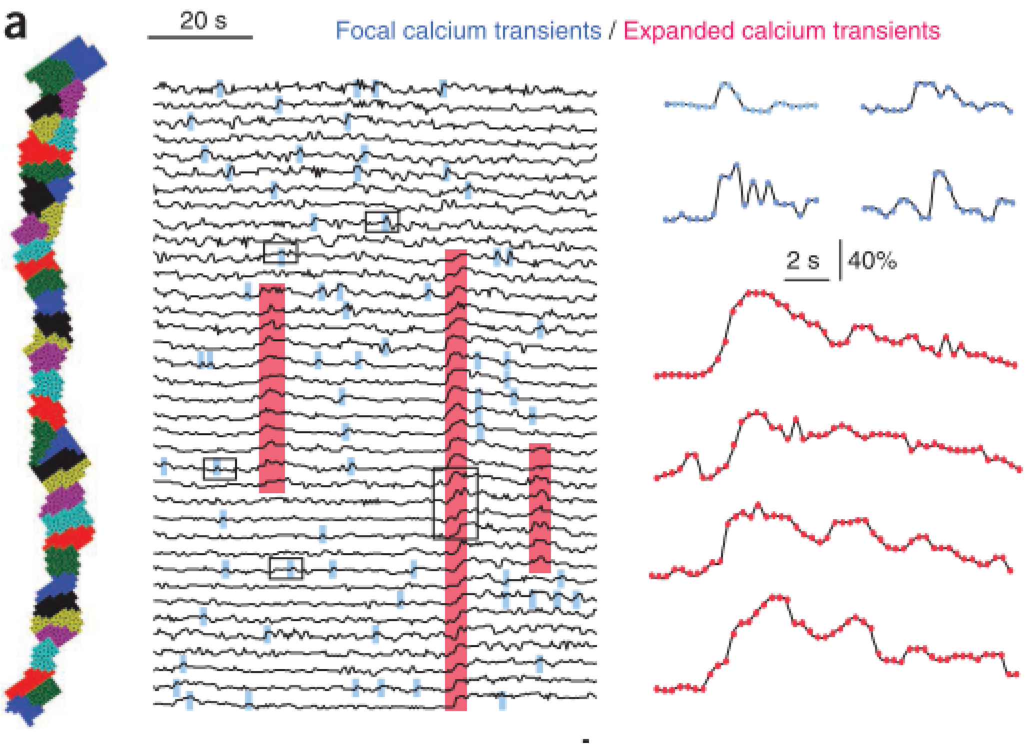


De Pitta and Hugues (eds): Computational Glioscience 2019

Kerstin Lenk

Different calcium signals within one astrocyte?





- ✓ Focal Ca^{2+} events depend on spontaneous synaptic release
- ✓ Expanded Ca^{2+} events are mostly the result of an individual action potential fired by an axon

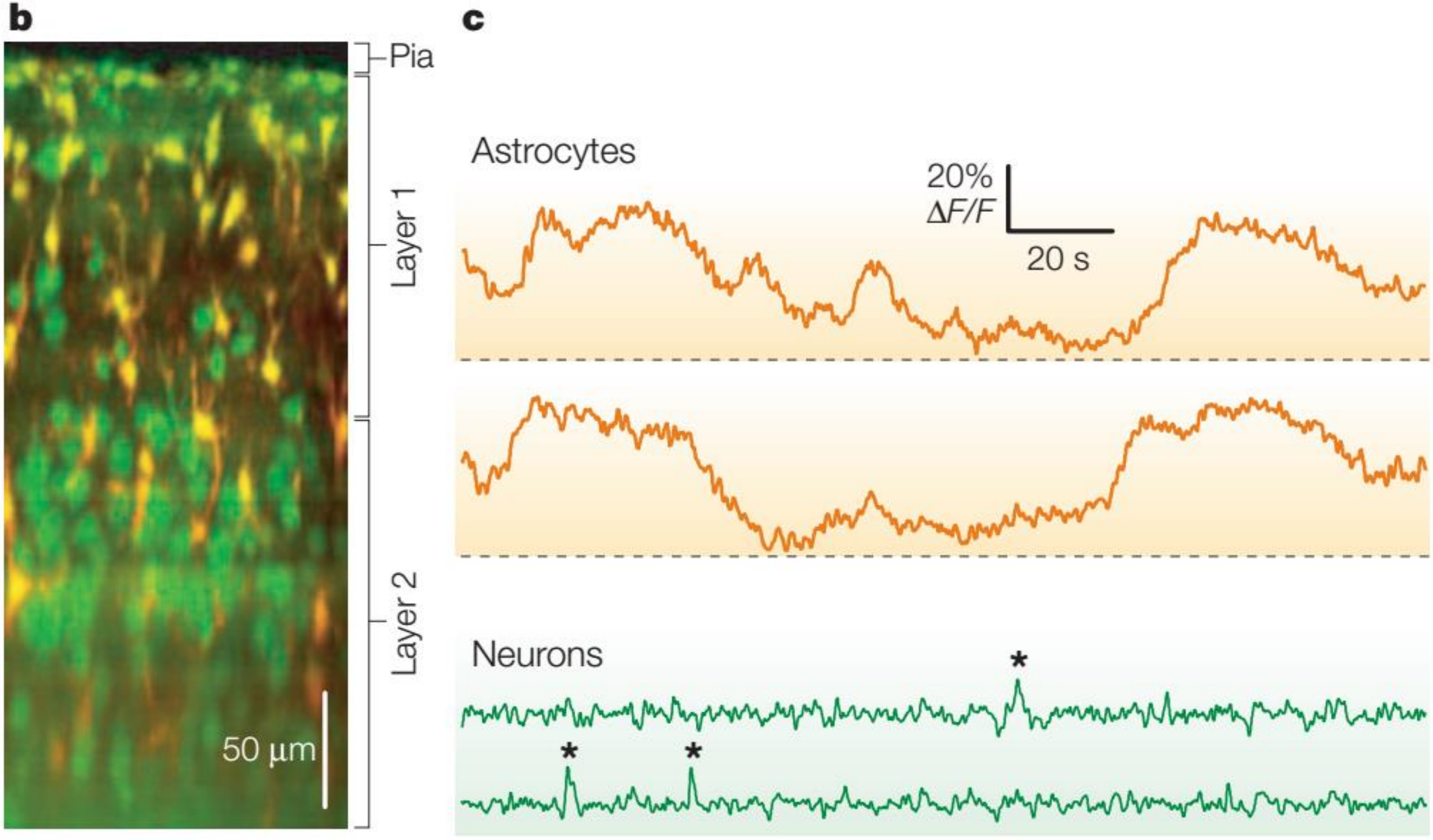
Di Castro et al., Nature Neurosci 2011

Potentially four levels of calcium dynamics

1) the **thinnest processes/branchlets** form an almost nano-scale dense sponge-like network that can be imaged only with electron microscopy or specific Ca^{2+} indicators *in situ*,
2) the **main largest (10-20) processes** that are seen in classical microscopy with dyes or immunostaining,
3) the **cell body/ soma**, and
4) in **cellular networks**

Shigetomi et al., 2013

Different time course of astrocytic Ca^{2+} and neuronal potentials



Pasti et al., J Neurosci 1997

Gliotransmission?

The Journal of Neuroscience, January 3, 2018 • 38(1):3–13 • 3

Dual Perspectives

Dual Perspectives Companion Paper: Gliotransmission: Beyond Black-and-White, by Iaroslav Savtchouk and Andrea Volterra

Multiple Lines of Evidence Indicate That Gliotransmission Does Not Occur under Physiological Conditions

Todd A. Fiacco[1] and Ken D. McCarthy[2]

14 • The Journal of Neuroscience, January 3, 2018 • 38(1):14–25

Dual Perspectives

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Gliotransmission: Beyond Black-and-White

Iaroslav Savtchouk and Andrea Volterra

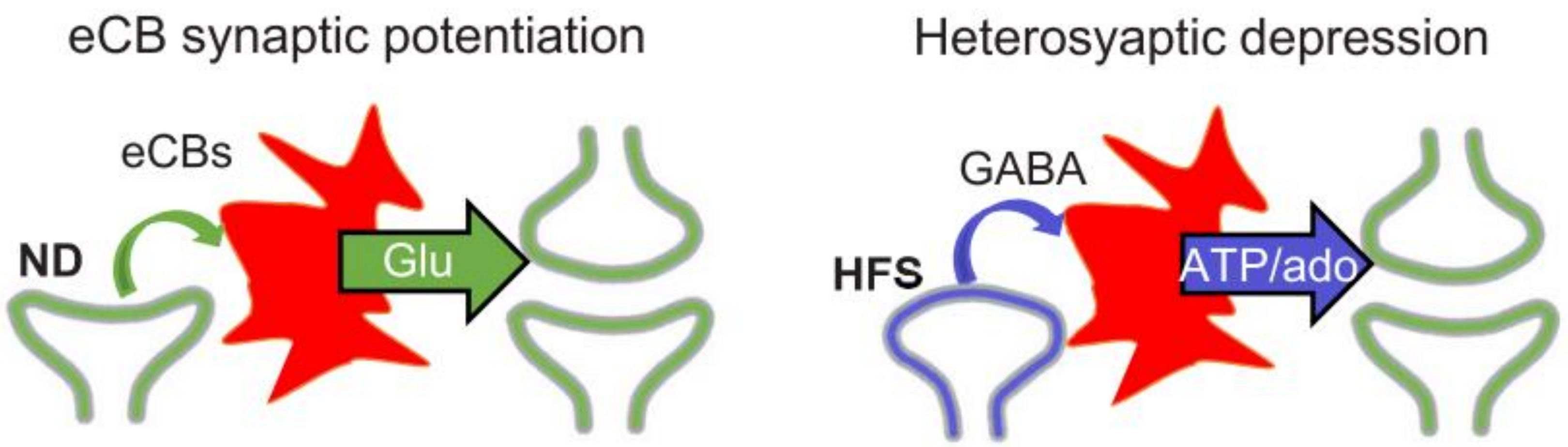
Co-release of gliotransmitters?

eLIFE
elifesciences.org

RESEARCH ARTICLE

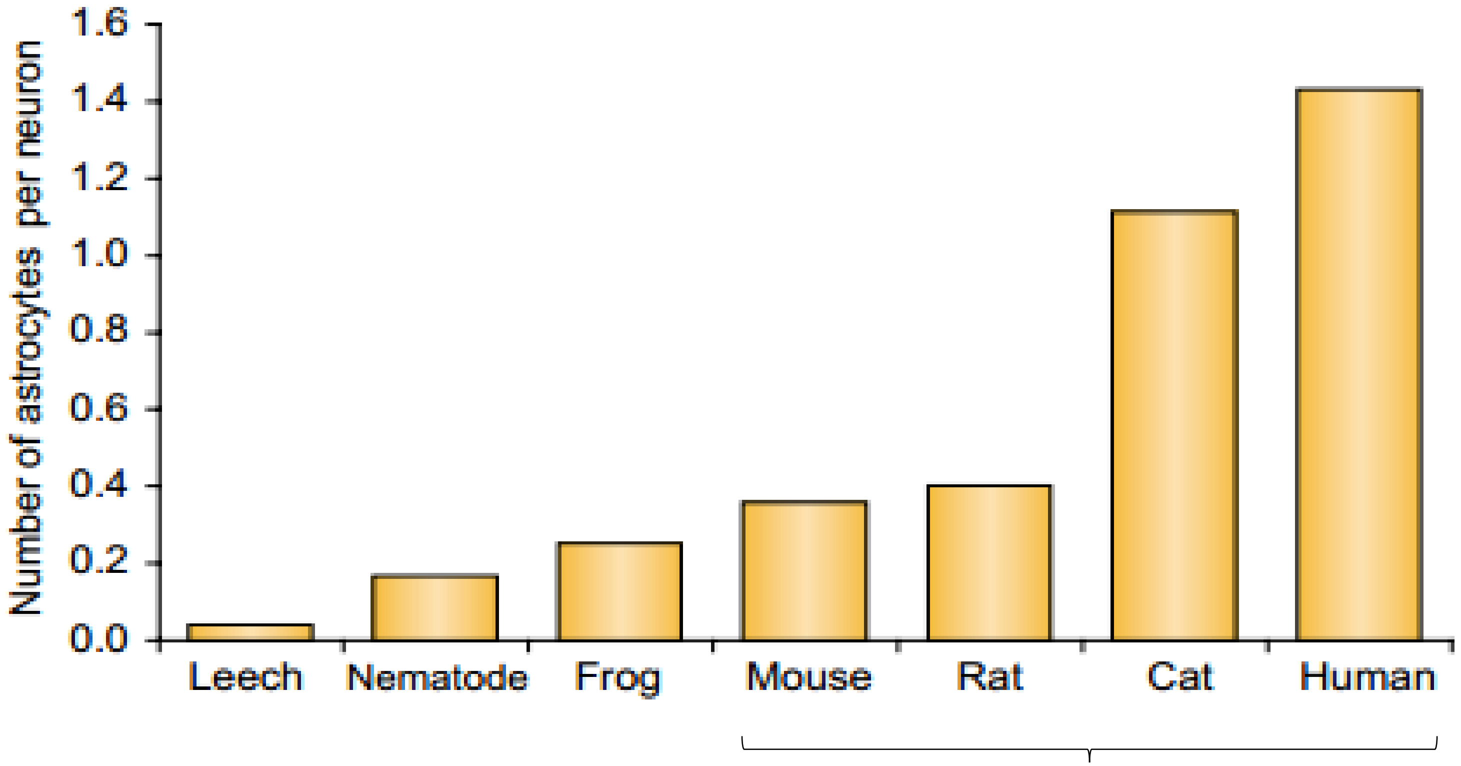
Neuronal activity determines distinct gliotransmitter release from a single astrocyte

Ana Covelo, Alfonso Araque*

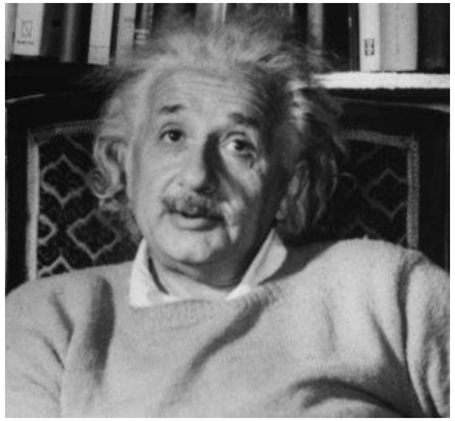


Astrocyte numbers across species

- ***C. elegans*** possesses 302 neurons, but only 56 glial cells (Oikonomou and Shaham 2011), astrocyte/neuron ratio is ~**0.2.**
- **Rat cerebral cortex** contains a mean astrocyte/neuron ratio of **0.4** (Bass et al. 1971).
- The **whole human adult brain** has a **one-to-one ratio** (Azevedo et al. 2009).
- **Human cerebral cortex** has a **ratio of 1.4** (Friede 1954; Pelvig et al. 2008).



Cortex only



EXPERIMENTAL NEUROLOGY **88**, 198–204 (1985)

On the Brain of a Scientist: Albert Einstein

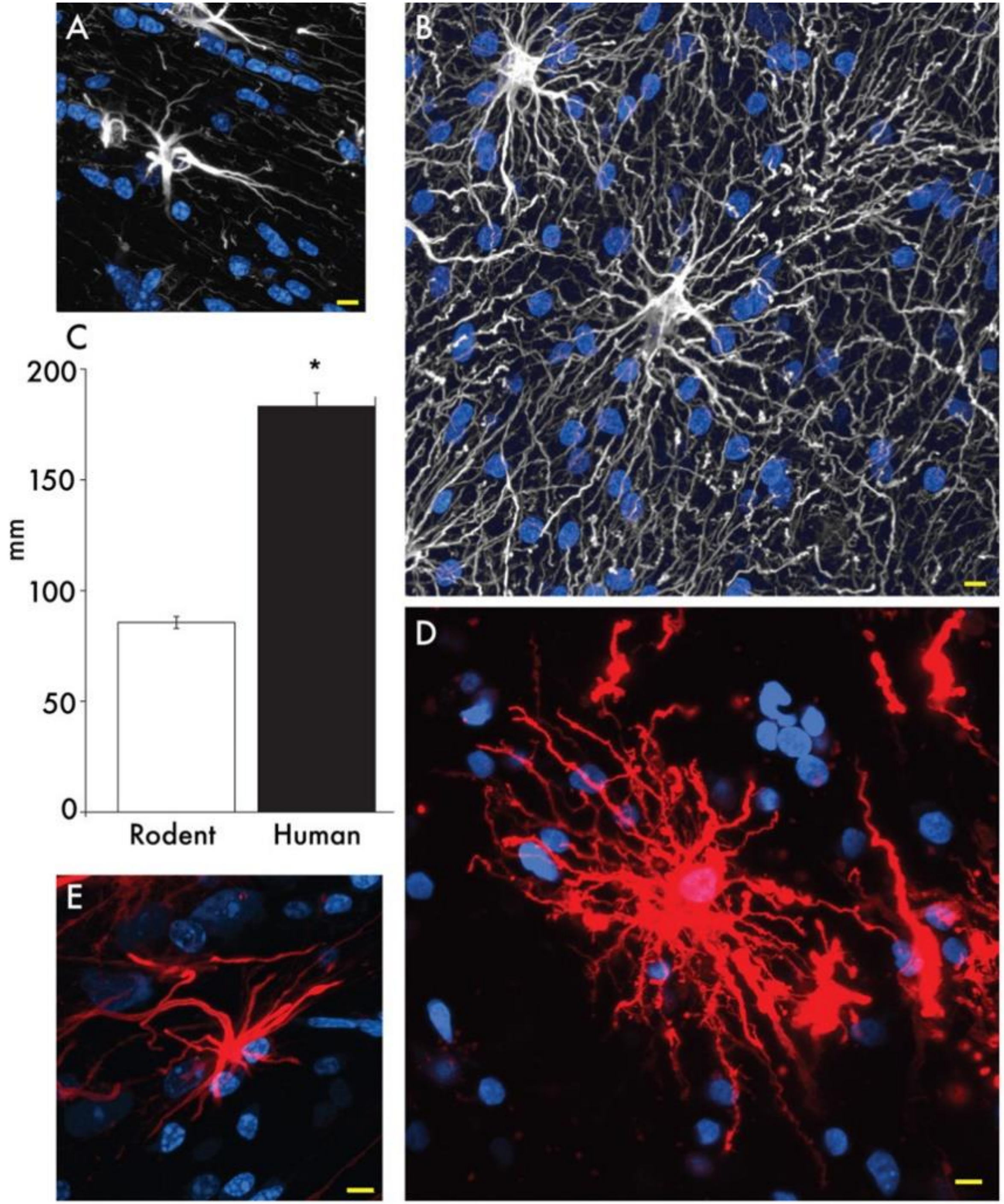
MARIAN C. DIAMOND,* ARNOLD B. SCHEIBEL,† GREER M. MURPHY, JR.,‡ AND THOMAS HARVEY[1]

Nedergaard et al., Trends in Neuroscience 2003

Kerstin Lenk

Human vs. mouse astrocytes

A) Mouse fibrous astrocyte in white matter. GFAP; white, sytox; blue. SB=10µm.
B) Human fibrous astrocytes in white matter. SB=10µm.
C) Human fibrous astrocytes are approximately 2.14 fold larger in diameter than the rodent counterpart. *p<0.0001; t-test.
D) Human fibrous astrocyte labeled with DiI revealing the full structure of the cell. DiI; red, Sytox; blue. SB=10µm.
E) Mouse fibrous astrocyte labeled with DiI. SB=10µm.



Slide courtesy to Jari Hyttinen

Oberheim et al. J Neuroscience 2009

Homeostatic functions of astrocytes

Molecular homeostasis

- Ion homeostasis (K^+, Cl^-, Ca^{2+})
- Regulation of pH
- Water transport and homeostasis
- Neurotransmitter homeostasis (glutamate, GABA, adenosine, monoamines)

Systemic homeostasis

- Chemosensing (O_2, CO_2, pH, Na^+, glucose)
- Regulation of energy balance and food intake
- Sleep homeostat

Cellular & network homeostasis

- Neurogenesis
- Neuronal development and neuronal guidance
- Defining cyto-architecture of the CNS
- Synaptogenesis, synaptic maintenance and synaptic elimination
- Synaptic plasticity

Organ homeostasis

- Control over blood-brain barrier
- Operation of the lymphatic system

Metabolic homeostasis

- Formation of neuro-glio-vascular unit and glial-vascular interface
- Regulation of local blood flow
- Metabolic support
- Glycogen synthesis and storage

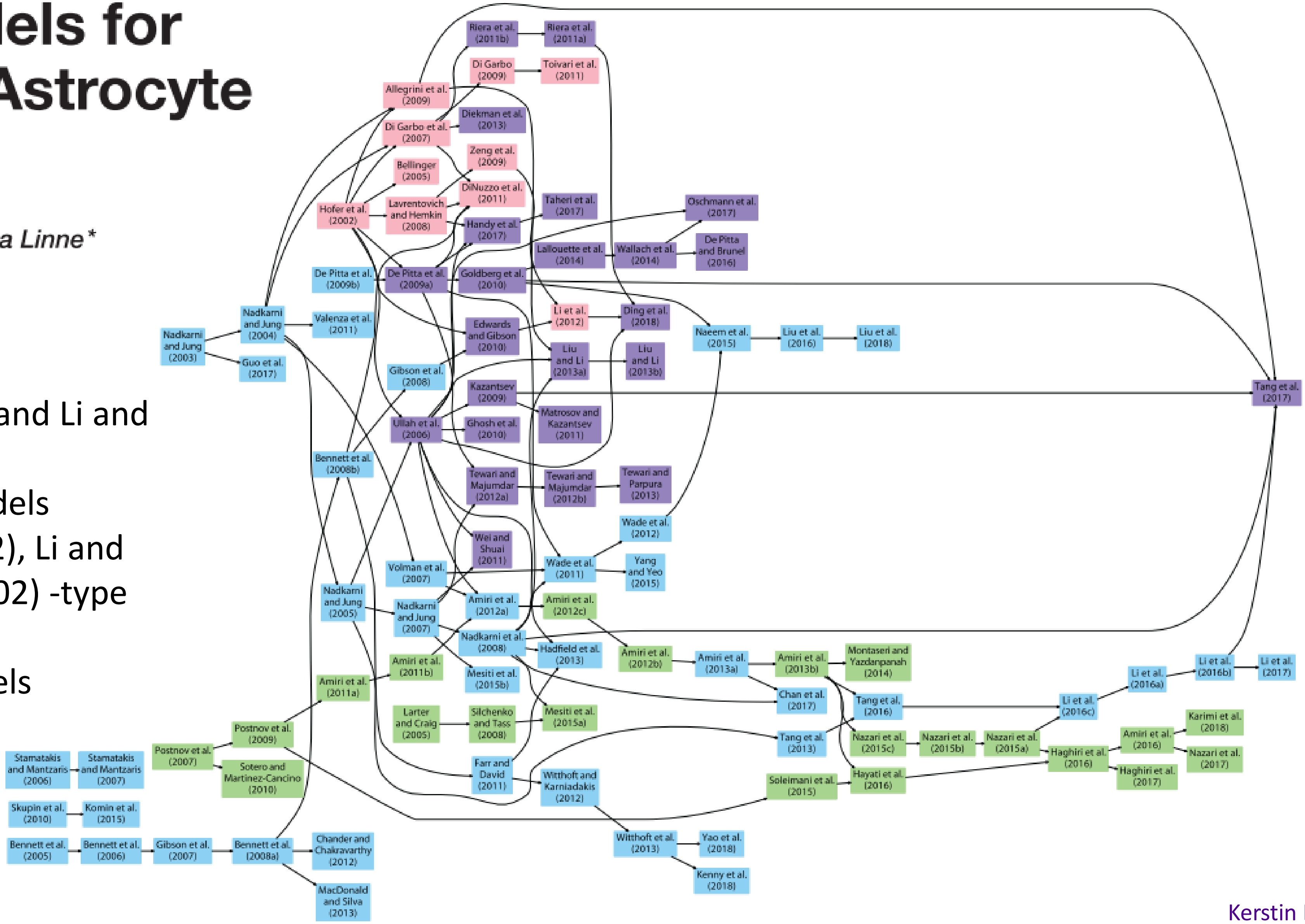
Modified from Verkhratsky & Nedergaard, Physiol Rev. 2018

frontiers in Computational Neuroscience

REVIEW
published: 04 April 2018
doi: 10.3389/fncom.2018.00014

Computational Models for Calcium-Mediated Astrocyte Functions

Tiina Manninen, Riikka Havela and Marja-Leena Linne**



- Blue: De Young and Keizer (1992) and Li and Rinzel (1994) -type models
- Pink: Höfer et al. (2002) -type models
- Purple: De Young and Keizer (1992), Li and Rinzel (1994), and Höfer et al. (2002) -type models
- Green: all the other types of models

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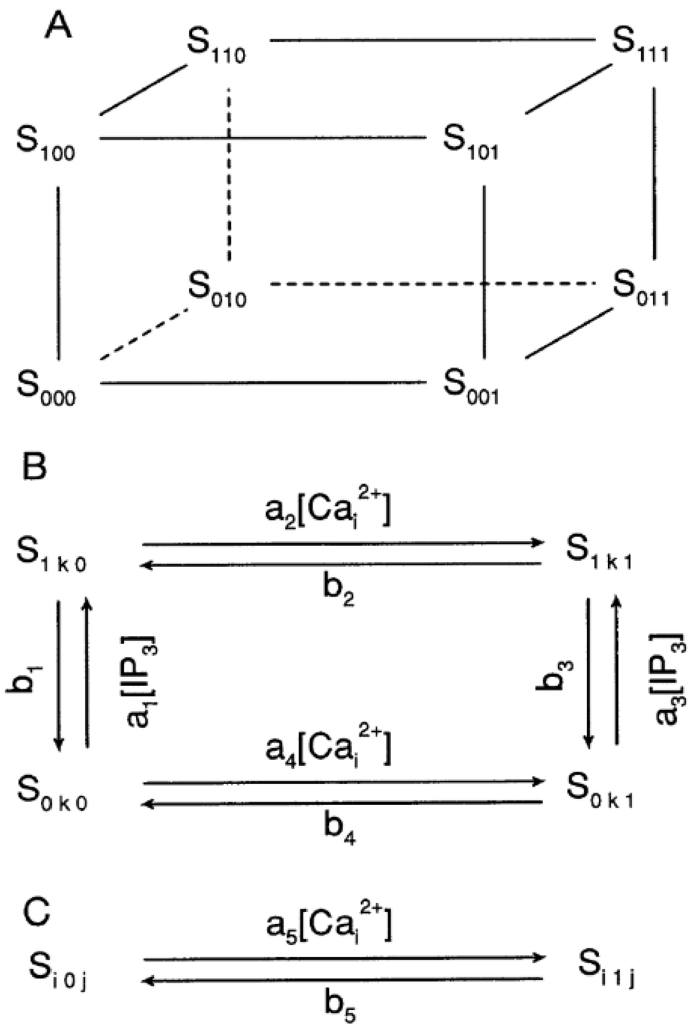
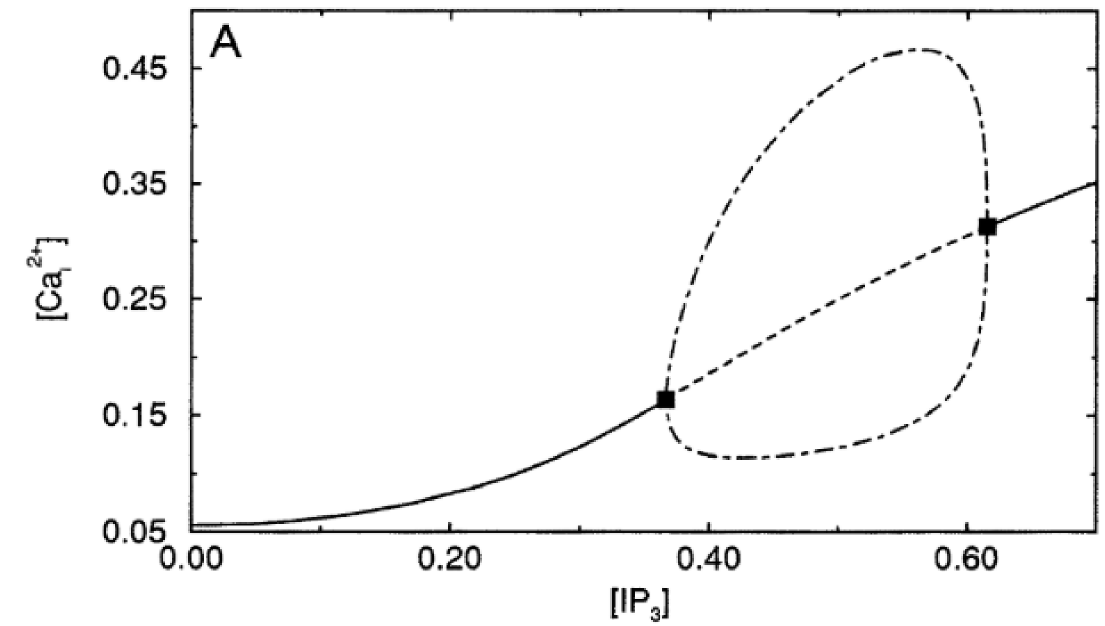
De Young and Keizer model (1992)



$State_{xyz}=S_{xyz}$
x = activating IP_3 binding site
y = activating Ca^{2+} binding site
z = inactivating Ca^{2+} binding site
0 = unoccupied binding site
1 = occupied binding site

Channel is open
when 3 subunits are open:

$$\rho = \frac{N_{\text{Open}}}{N_{\text{Total}}} = (x_{110})^3$$



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Li and Rinzel model (1994)

$$\frac{dC}{dT} = -V_1 m_\infty^3 h^3 (C - C_0) - V_2(C - C_0) - \frac{V_3 C^2}{1 + C^2}$$

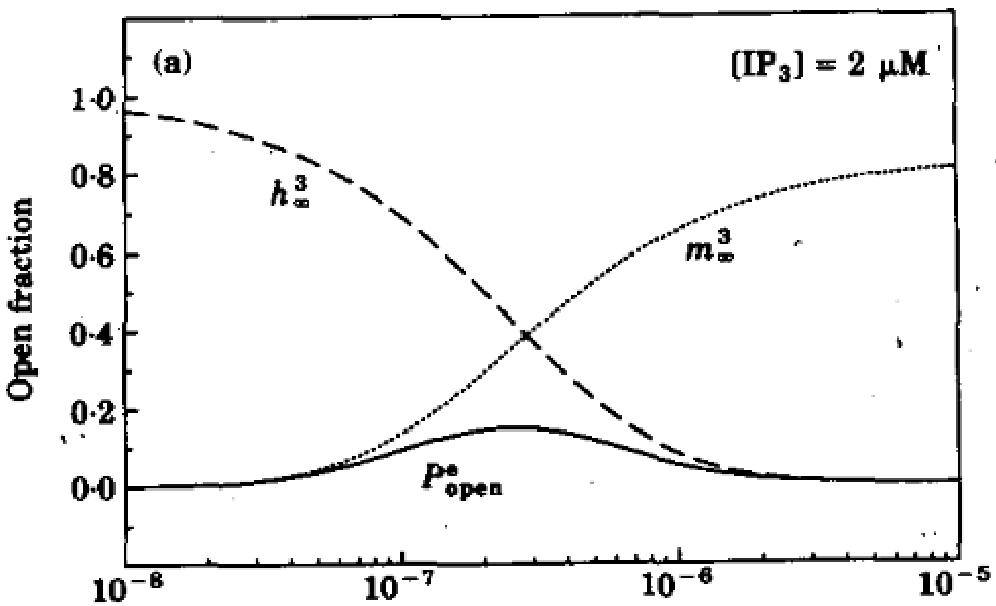
Hodkin-Huxley like equations to describe IP_3 induced Ca^{2+} release

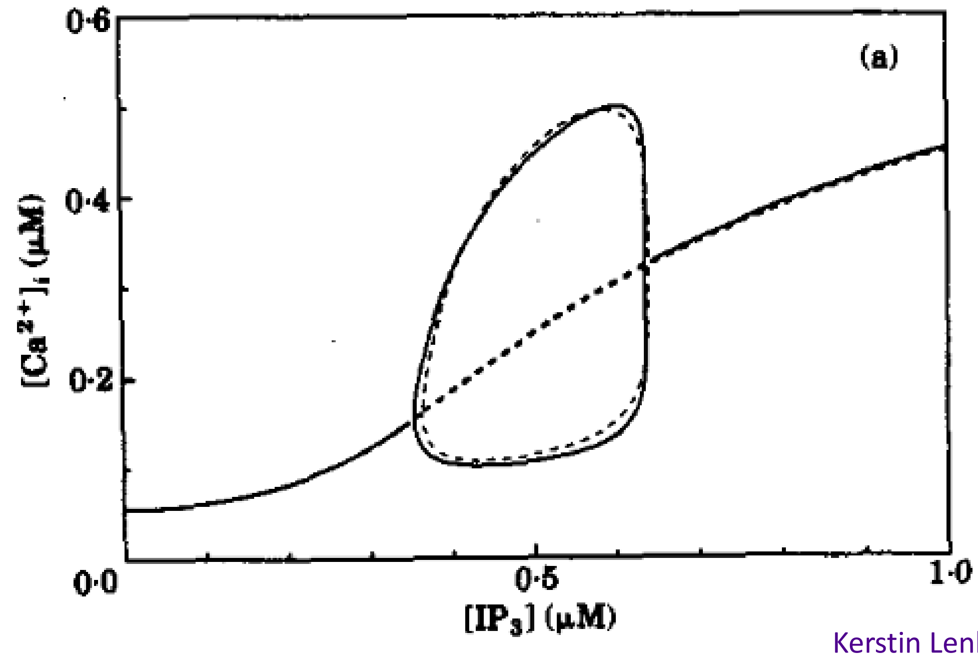
$$\frac{dh}{dT} = \frac{h_\infty - h}{\tau_h}.$$

Slow, time dependent inactivation

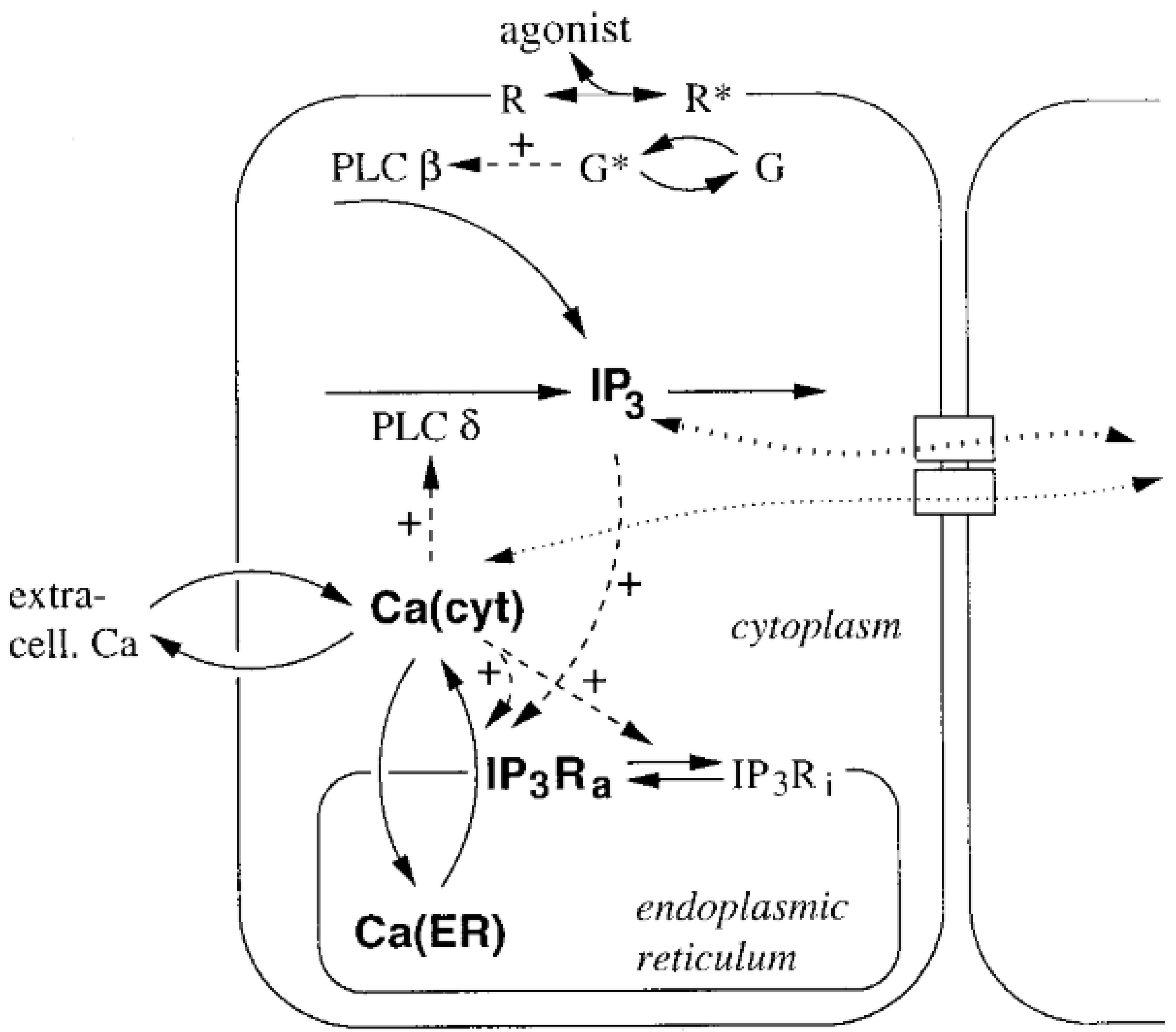
$$m_\infty = \left(\frac{[IP_3]}{[IP_3] + d_1}\right)\left(\frac{[Ca]}{[Ca] + d_5}\right)$$

Fast, time independent activation by Ca^{2+} and IP_3

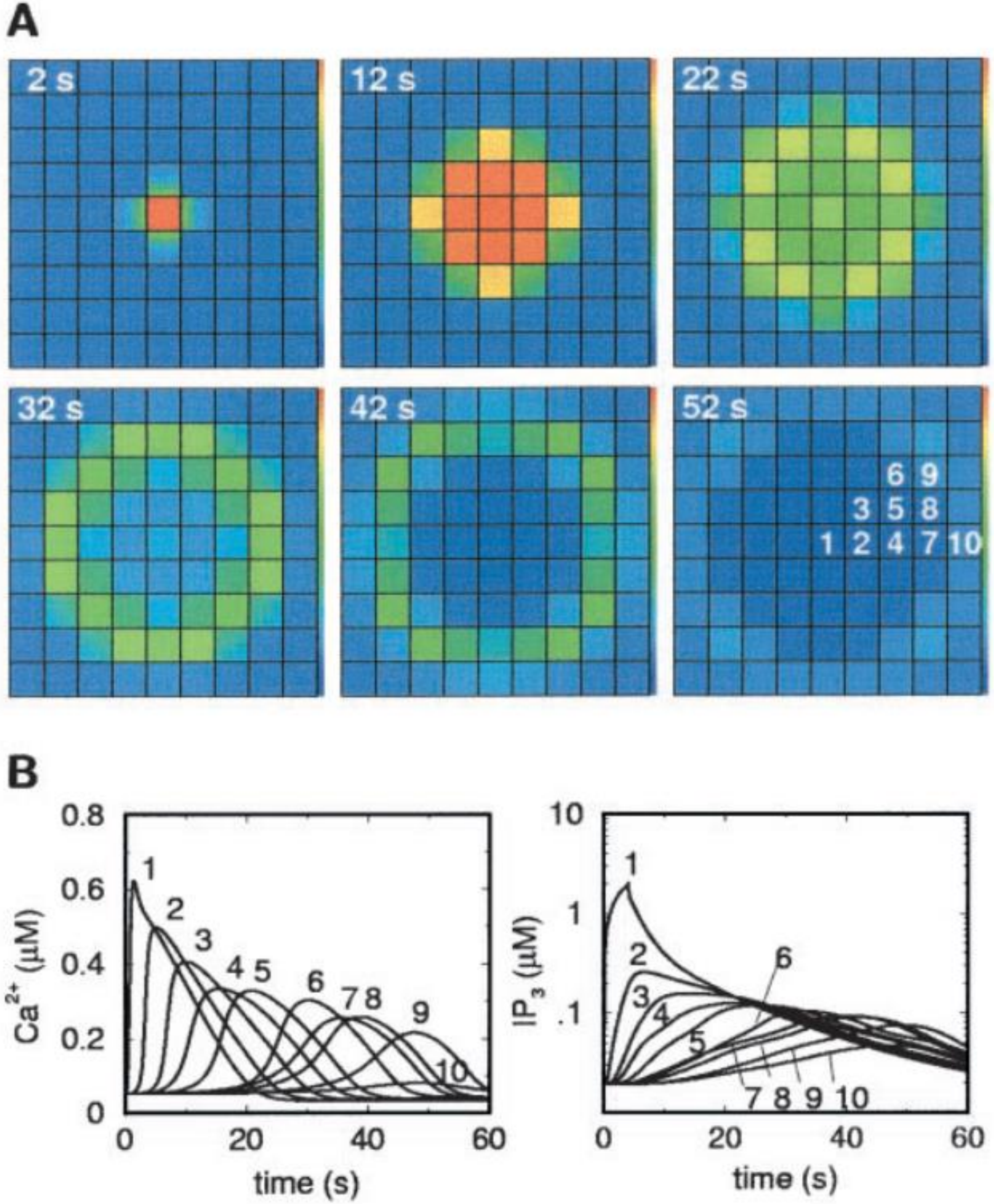




Höfer et al. model (2002)



System of balance equations for the four variables: cytoplasmic Ca^{2+} concentration (C), ER store Ca^{2+} concentration (S), IP_3 concentration (I), and active fraction of IP_3R(R).



Brain Research Bulletin 136 (2018) 76–84

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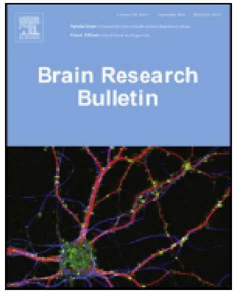


Review

From in silico astrocyte cell models to neuron-astrocyte network models: A review

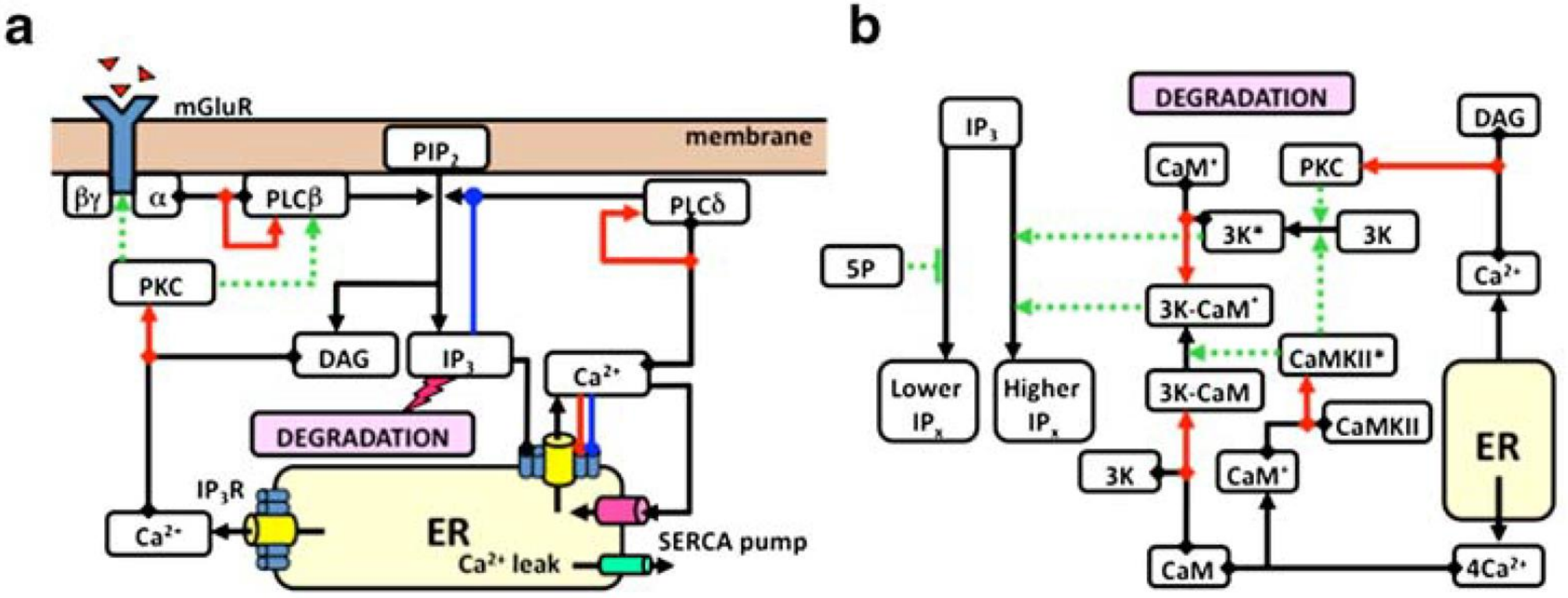
CrossMark

Franziska Oschmann[a,b], Hugues Berry[c,d], Klaus Obermayer[a,b], Kerstin Lenk[e,*]

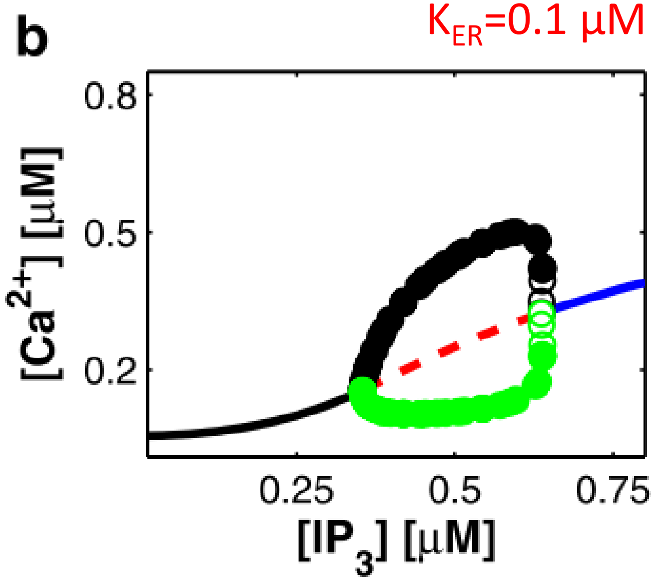
35 models investigated:

1. Single astrocytic cell models
2. Tripartite synapse models
3. Astrocyte network models
4. Neuron-astrocyte network models

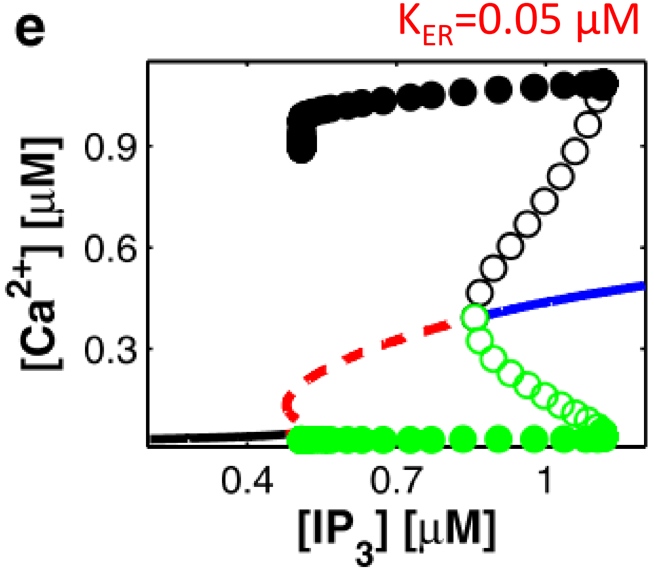
Single astrocytic cell model by De Pittà et al., 2009



K_{ER}=0.1 μM



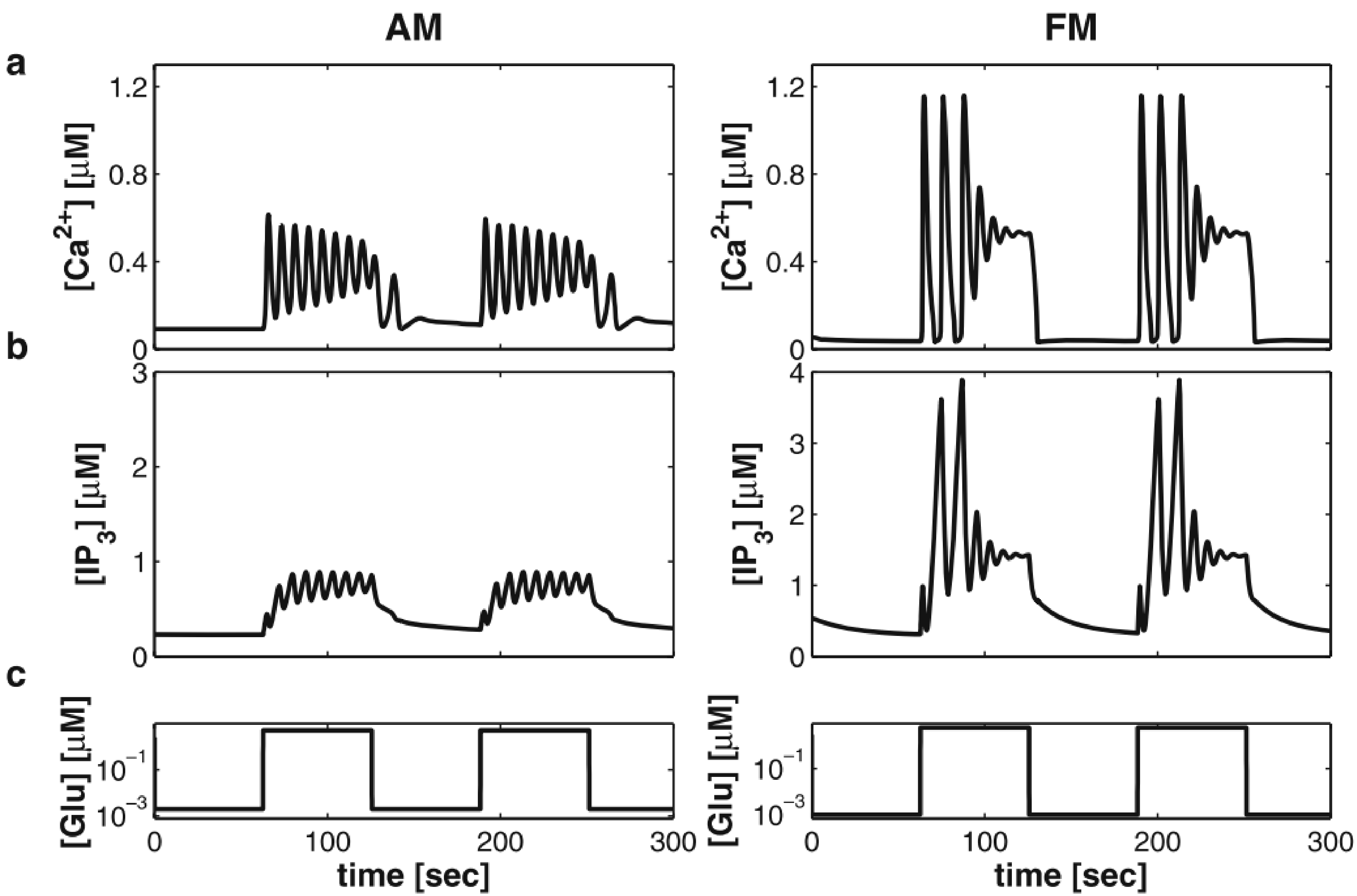
K_{ER}=0.05 μM



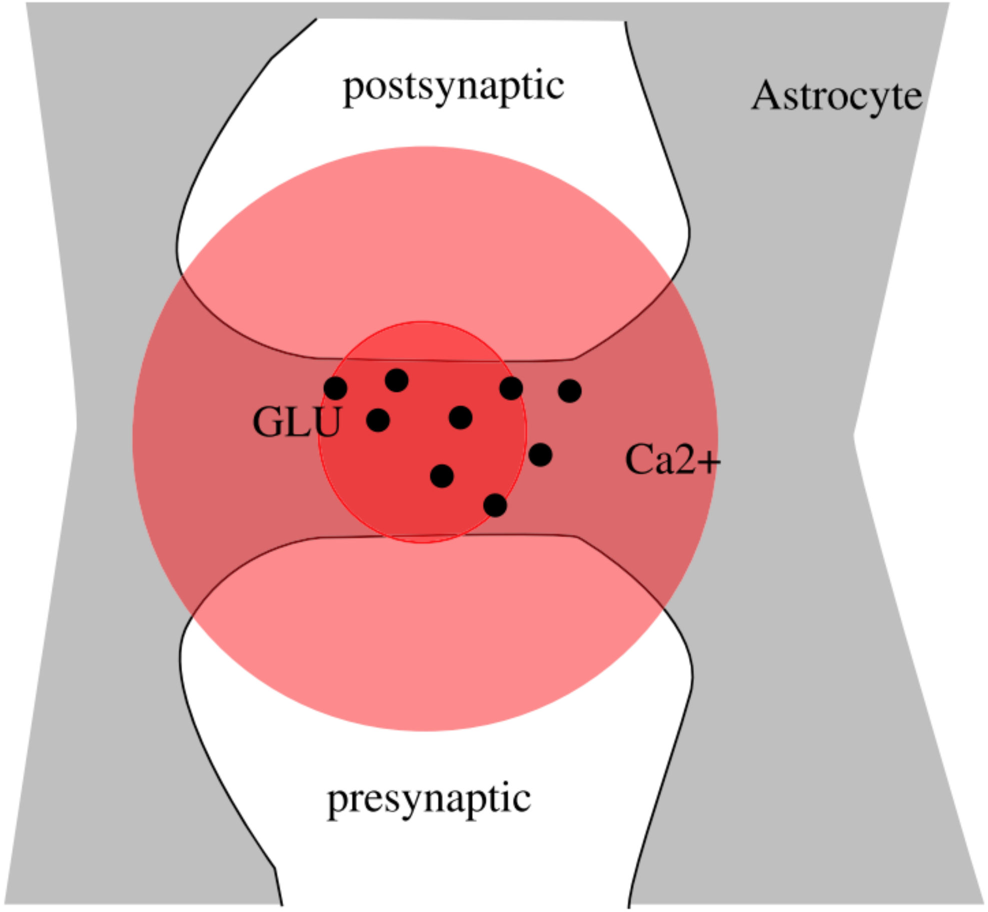
K_{ER} is the SERCA Ca^{2+} affinity

- Based on De Young & Keizer, Li-Rinzel and Höfer et al. models
- Three pathways: glutamate induced IP_3, Ca^{2+} induced Ca^{2+} activation, and reduction through IP_3 degradation

Single astrocytic cell model by De Pittà et al., 2009

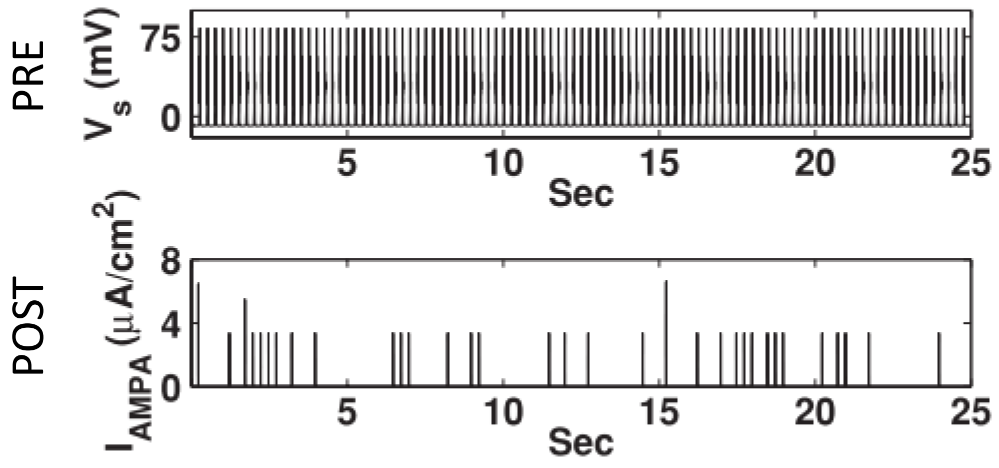


Tripartite synapse model by Nadkarni and Jung, 2007



De Young & Keizer and Li and Rinzel -type model
Neuron-astrocyte interaction

Without astrocyte:



With astrocyte:

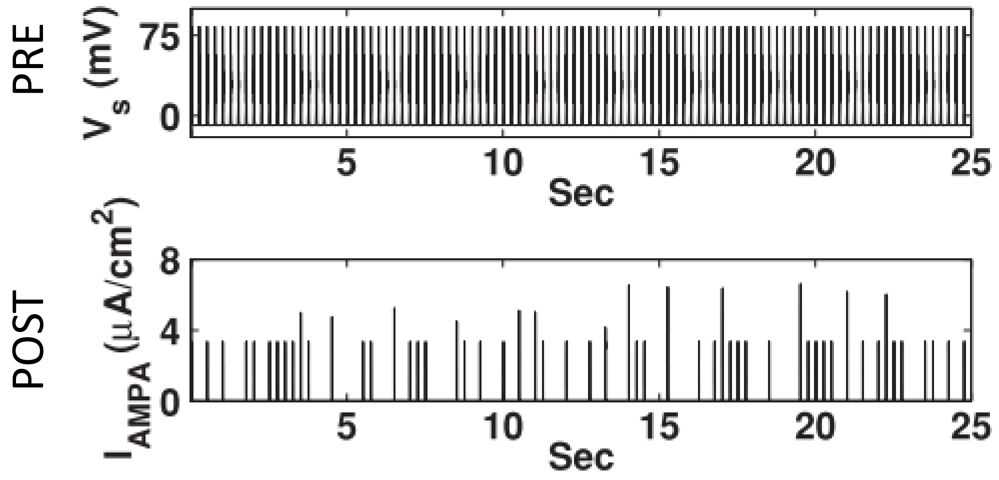
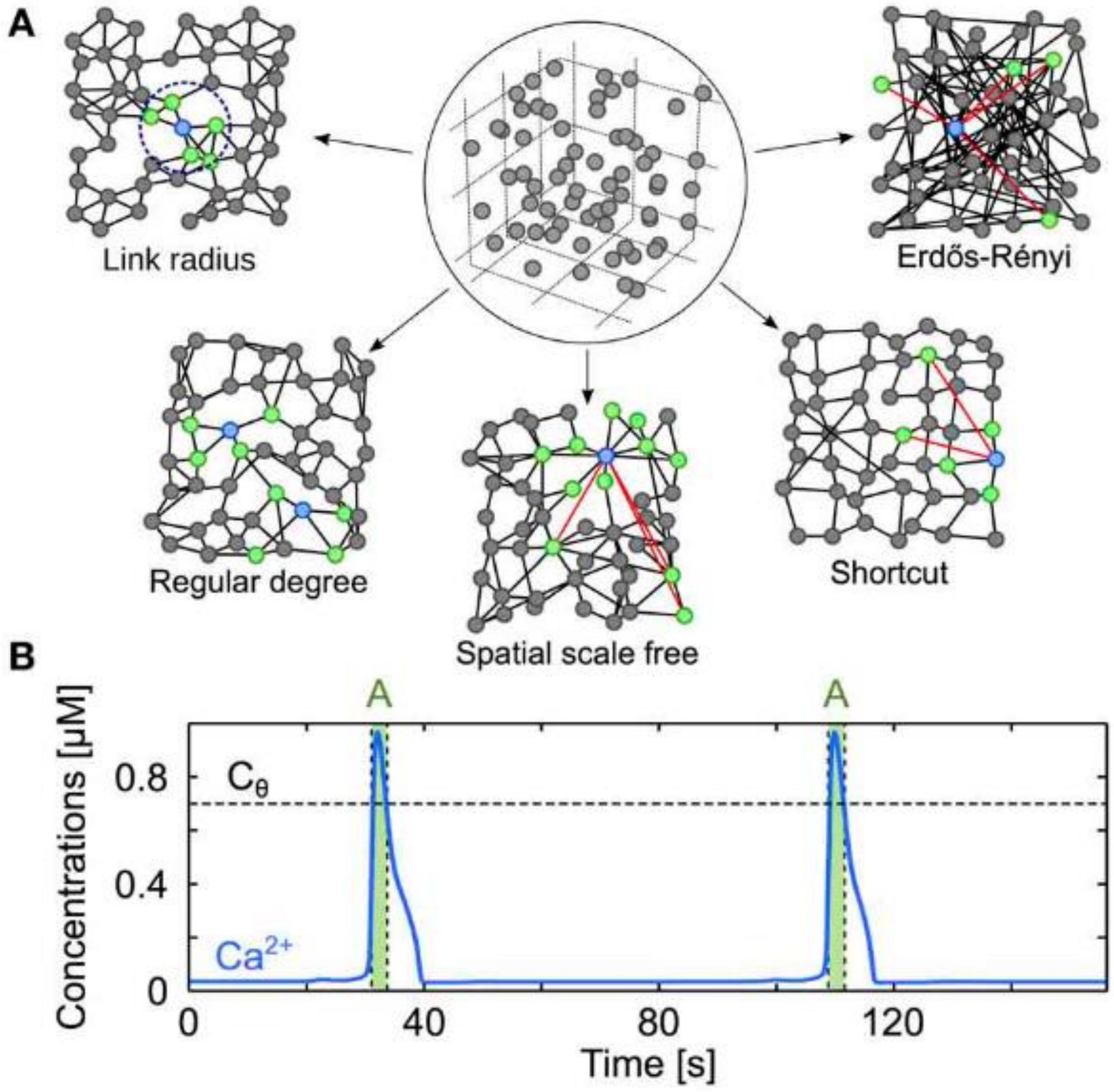


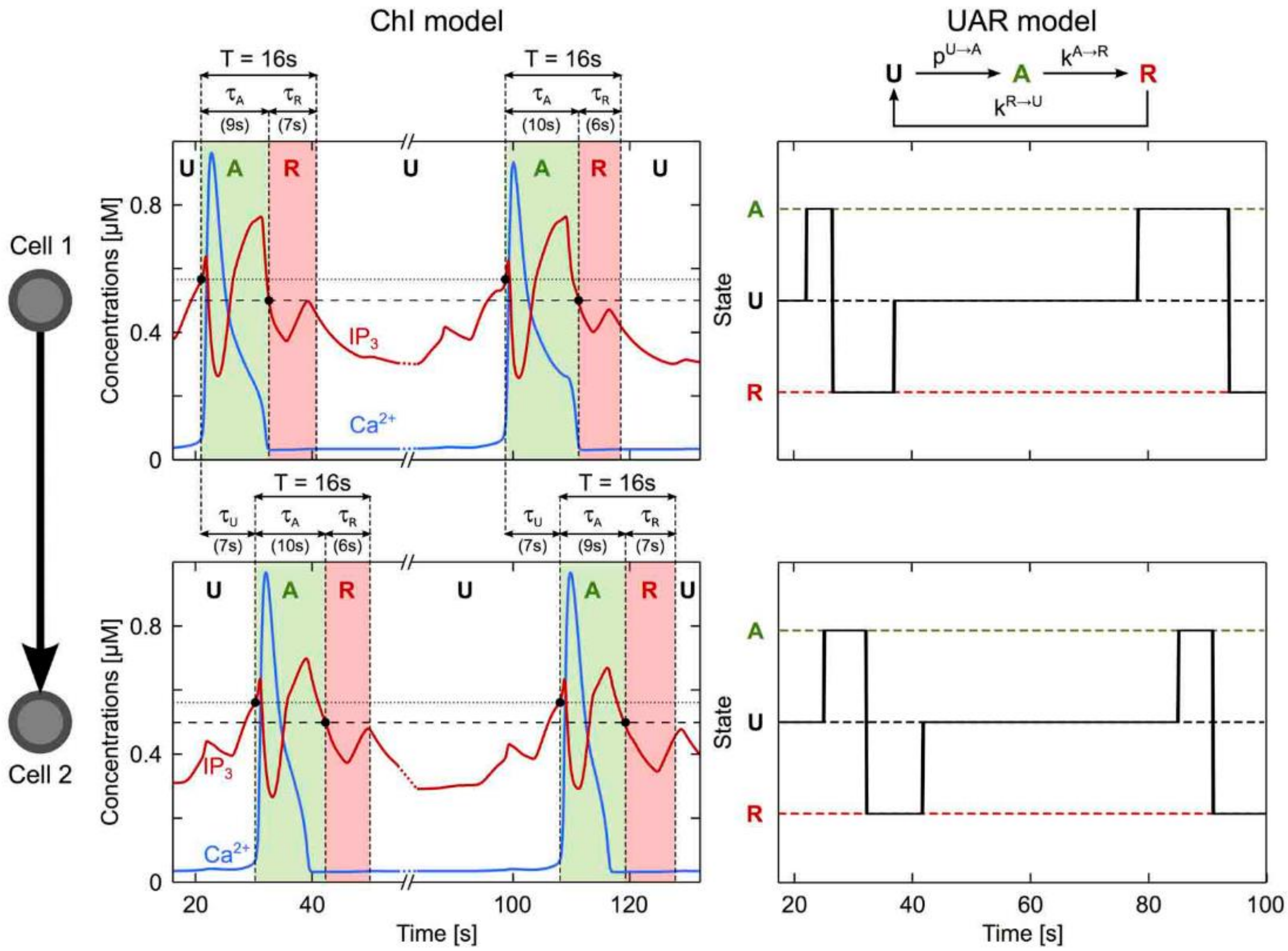
Image: Nadkarni & Jung, Physical Biology 2004

Astrocyte network model by Lallouette et al., 2014

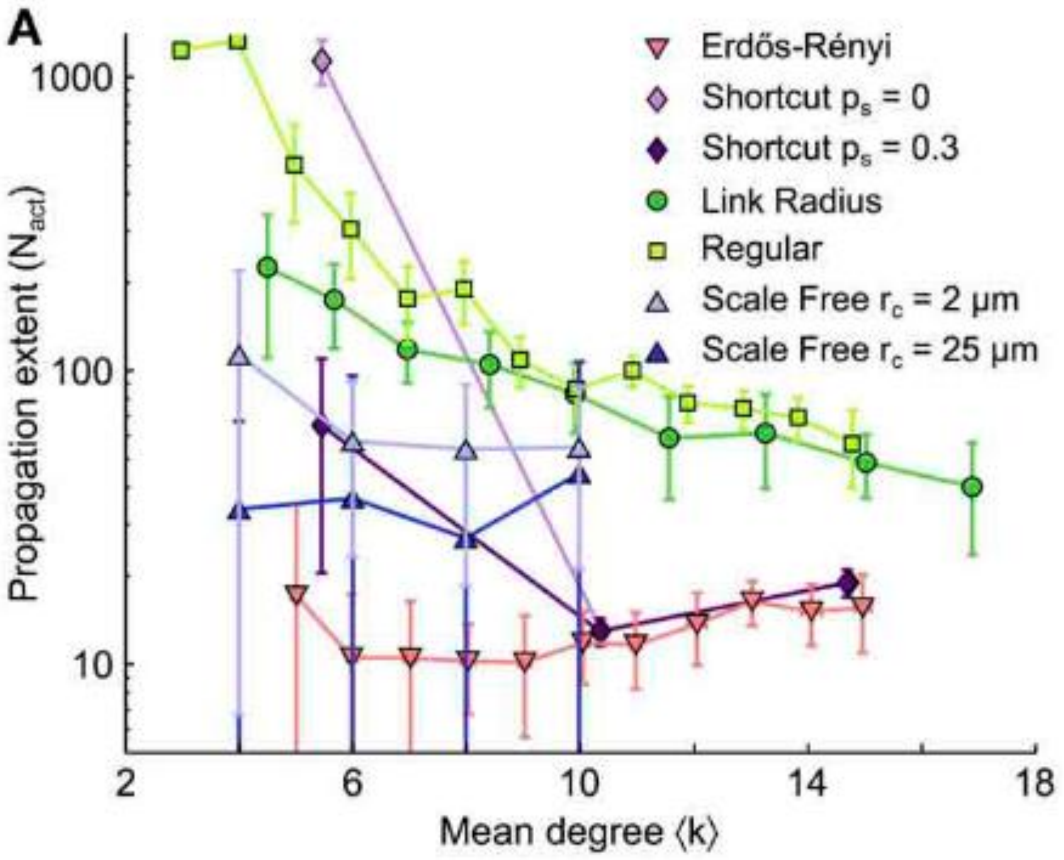


Based on De Pittà et al., 2009 and 2012

Astrocyte network model by Lallouette et al., 2014



Astrocyte network model by Lallouette et al., 2014



Neuron-astrocyte network model

frontiers

A computational model of interactions between neuron and astrocyte networks: role of astrocytes on stability of the neuronal firing rate

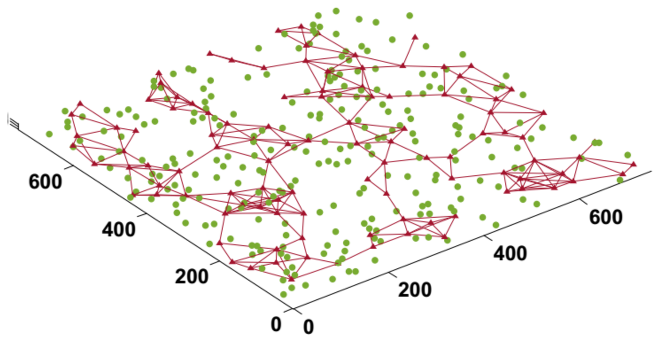
Kerstin Lenk[1,†,*], Eero Satuvuori[1,2,3,4,†], Jules Lallouette[5,6], Antonio Ladrón-de-Guevara[1], Hugues Berry[5,6], Jari AK Hyttinen[1]

(submitted)

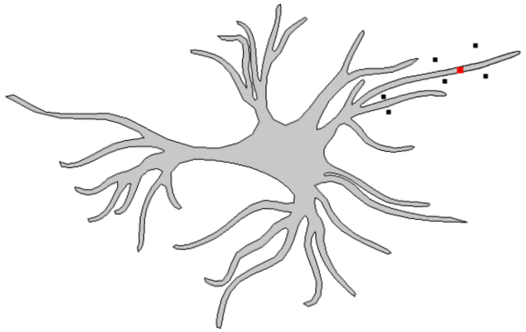
Motivation

- Astrocytes may influence neuronal network function → What are the mechanism/ pathways? How do astrocytes change the neuronal activity and vice versa?
- How are the astrocytic calcium dynamics influenced by morphology and topology?
- Role and functions of astrocytes in epilepsy and Alzheimer's?

Neuron-astrocyte network model

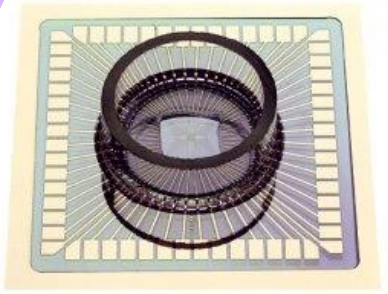


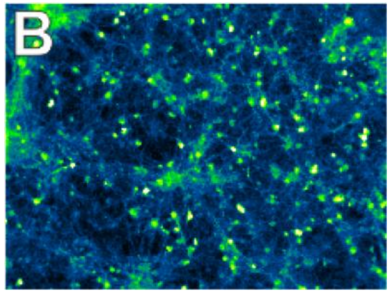
Single cell astrocyte model

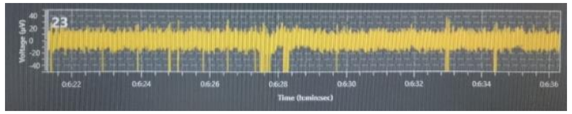


Our modeling approach

Experiments







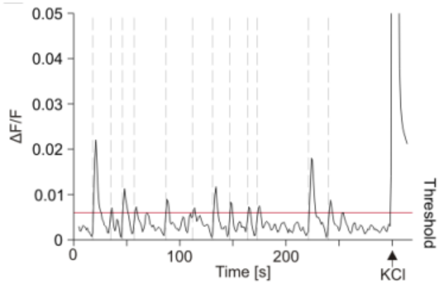
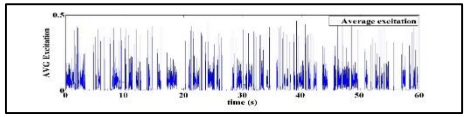


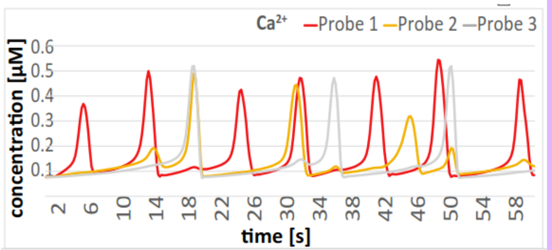
Table 1. Initial values of the ion concentrations, the membrane voltage, IP_3 and the fraction of the activated IP_3 receptor channels. For the calculation of $[Ca^{2+}]_{ER}$, $[IP_3]_i$ and h see Model section **Model parameter values.**

Parameter	Value	Source
$[Ca^{2+}]_i$	0.073 μM	[23]
$[Ca^{2+}]_{ER}$	25 μM	see text
$[Ca^{2+}]_o$	1800 μM	[18]
$[Na^+]_i$	15 mM	[19]
$[Na^+]_o$	145 mM	[19]
$[K^+]_i$	100 mM	[19]
$[K^+]_o$	3 mM	[19]
V	-85 mV	[24]
$[IP_3]_i$	0.15659 μM	see text
h	0.7892	see text

Computational models

$$\frac{d[Ca^{2+}]_i}{dt} = \frac{A}{F \cdot Vol} \cdot I_{NCX} + \frac{A \cdot \sqrt{ratio_{ER}}}{F \cdot Vol} \cdot (I_{IP_3R} - I_{Serca} + I_{CERleak}),$$





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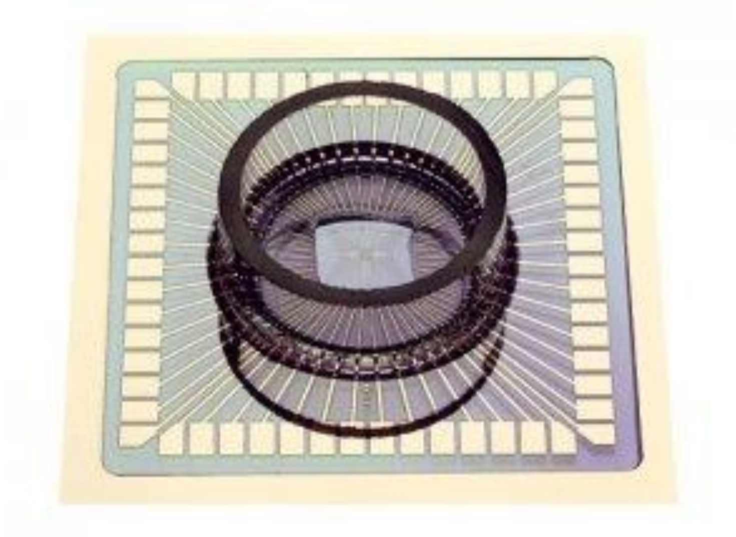
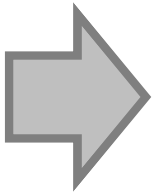
V	-85 mV	[24]
$[IP_3]_i$	0.15659 μM	see text
h	0.7892	see text

Images: www.multichannelsystems.com; Simon Klapper; Oschmann et al., PLOS Comp Biol 2017

Neuron-astrocyte network model





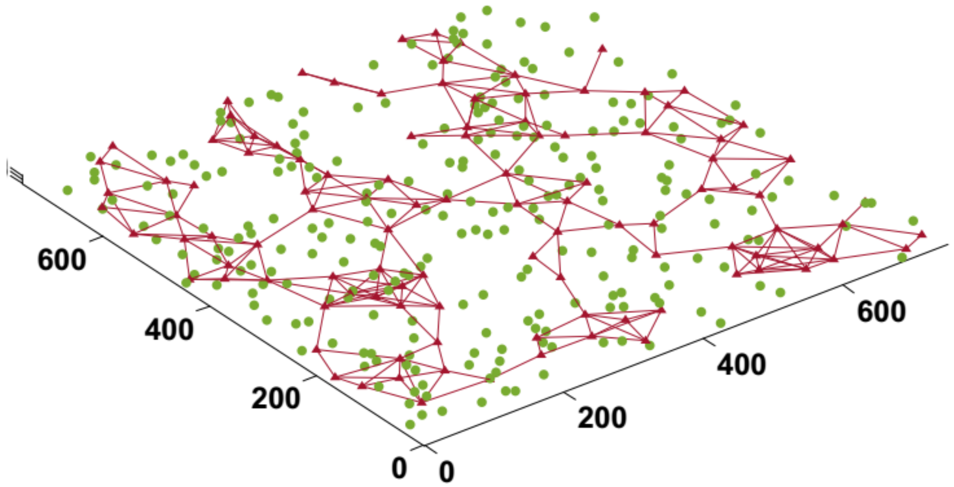
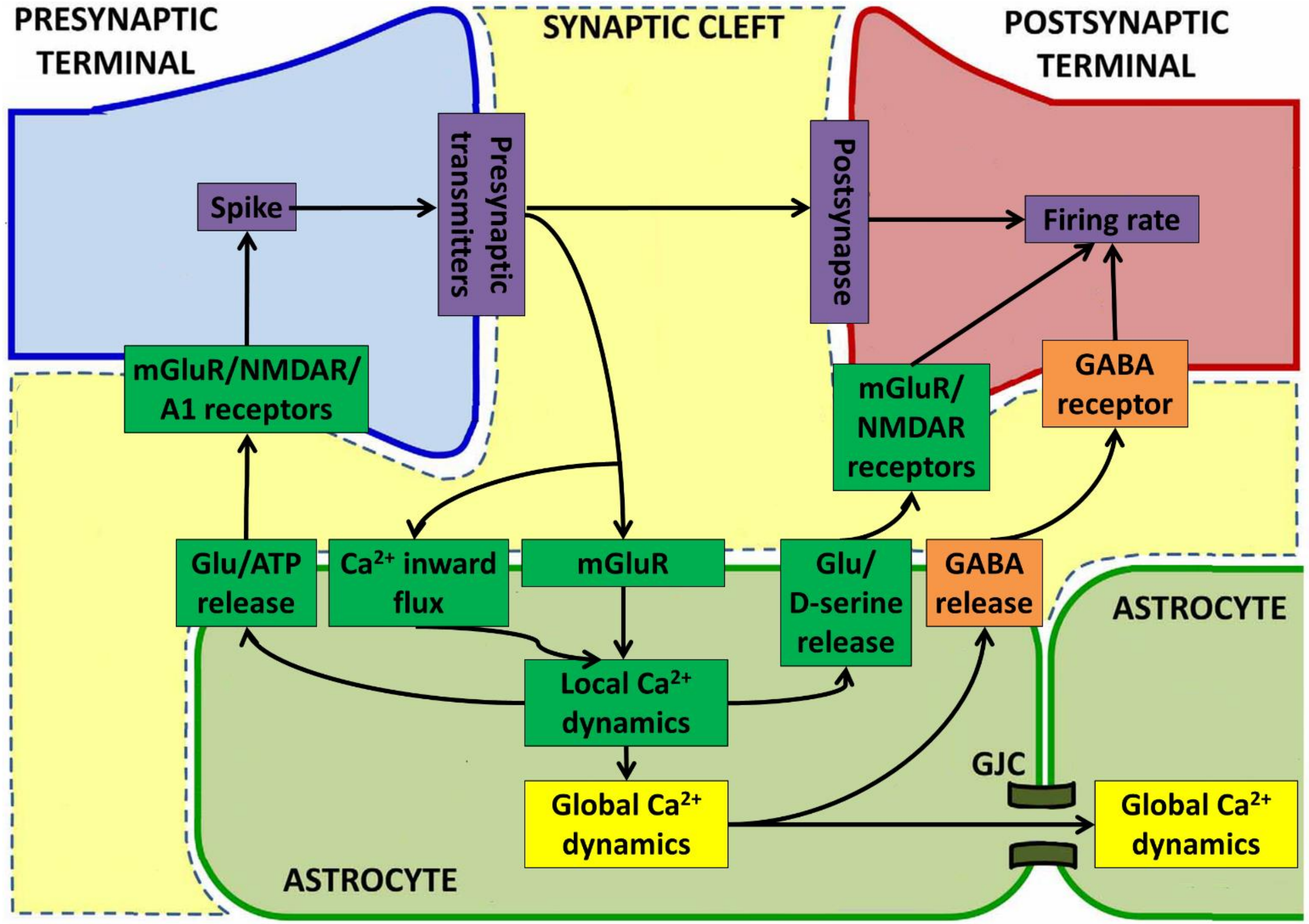
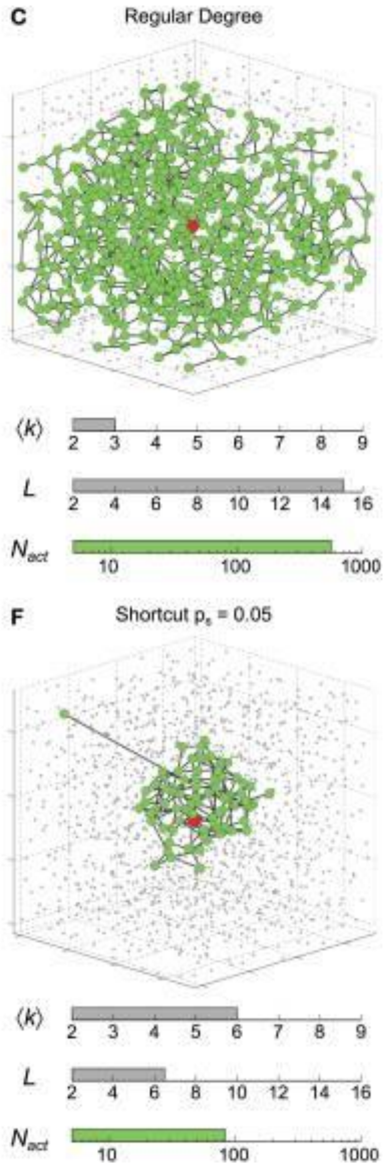


Image: www.multichannelsystems.com

Kerstin Lenk

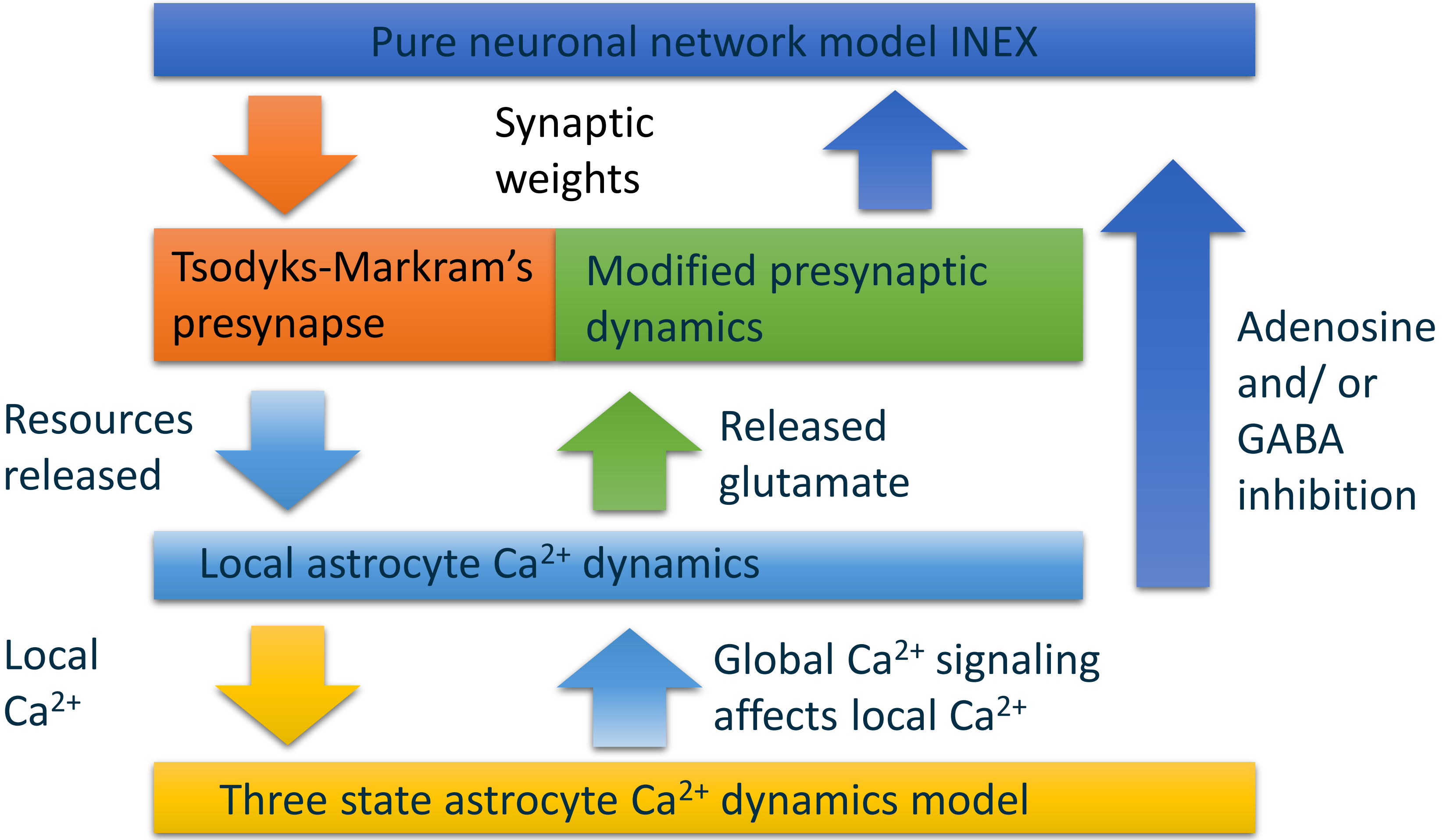
Model with presynaptic and astrocytic calcium dynamics





Oschmann et al., Brain Res Bull. 2017
De Pittà et al., PLoS Comput Biol 2011
De Pittà et al., Frontiers in Comput Neurosci 2012
Lallouette et al., Front. Comput Neurosci 2014

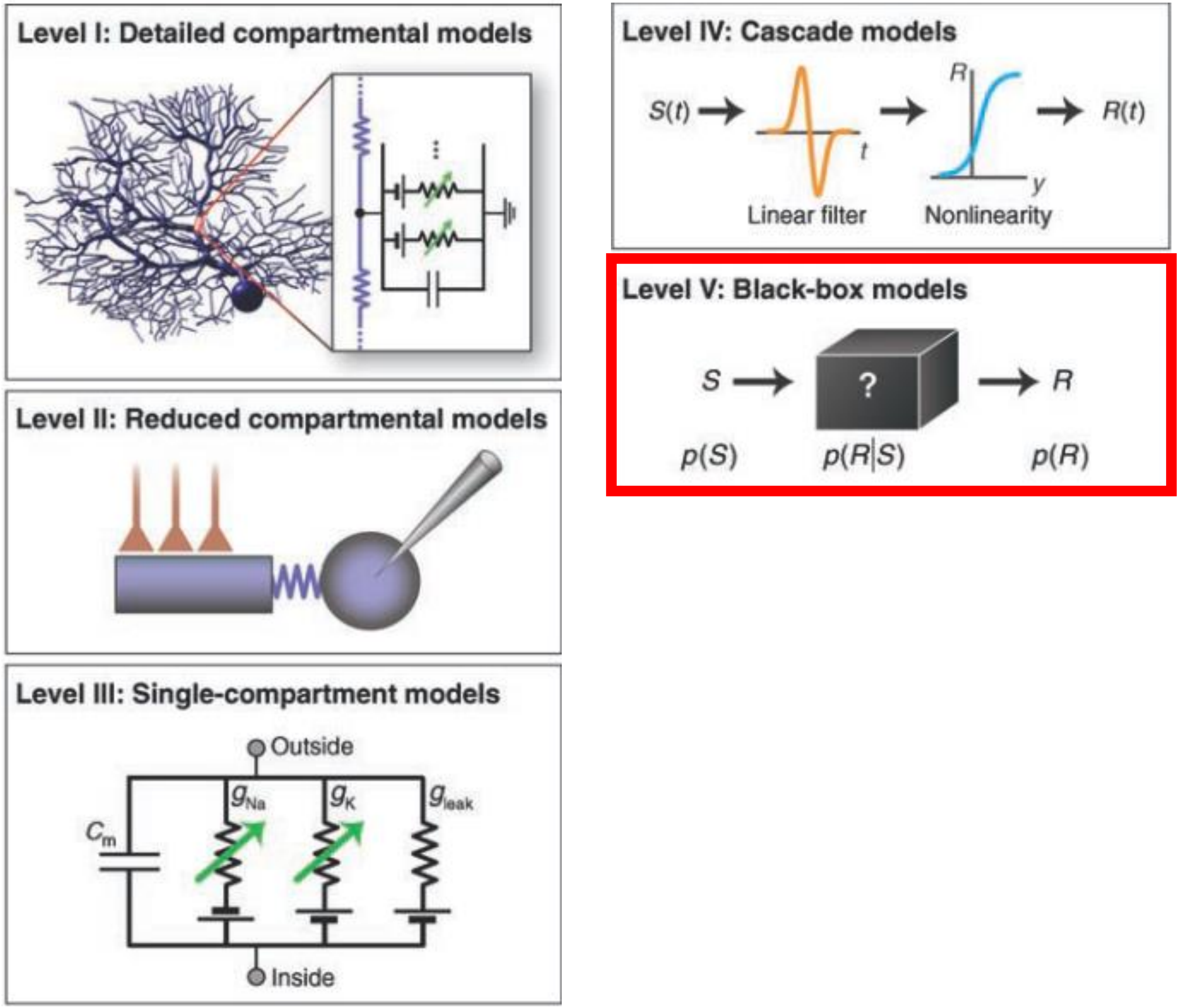
Neuron-astrocyte network model INEXA

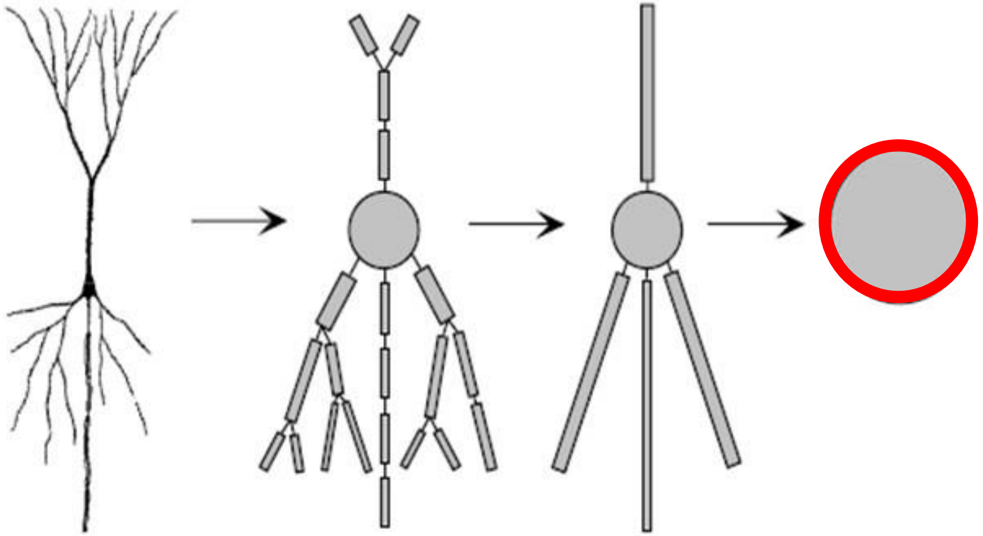


Lenk, 2011
De Pittà et al., PLoS Comput. Biol. 2011
De Pittà et al., Frontiers in Comput. Neurosci. 2012
Lallouette et al., Front. Comput. Neurosci. 2014

Work together with Eero Satuvuori, Antonio Ladrón-de-Guevara, Barbara Genocchi

We start from the neuronal network





Images: Herz et al., Science 2006; https://slideplayer.com/slide/6975345/

Relevant model characteristics

Target: Neuronal model for simulating neuronal activity as observed in *in vitro* experiments with MEAs

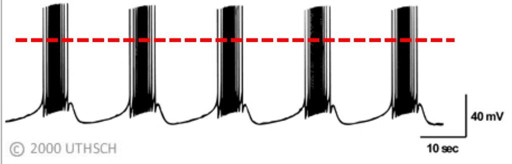
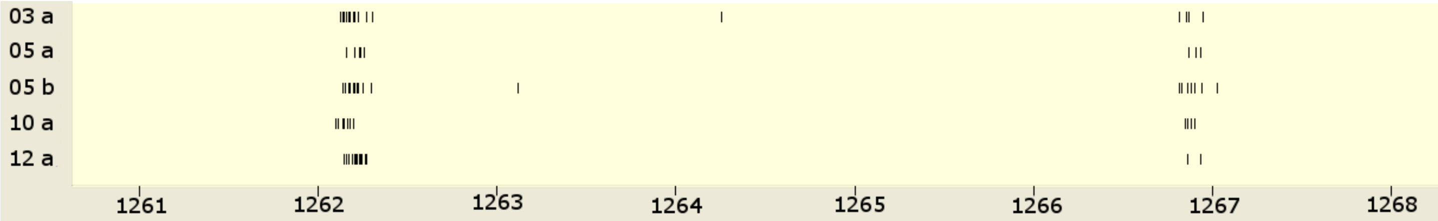


Figure 12. From Byrne, Canavier, Lechner, Clark and Baxter, 1996.



Following characteristics:

- Simulation of a whole neuronal network
- Bursts
- Spontaneous activity
- Noise
- Simple model with a few parameters

Kerstin Lenk

INEX model consists of Poisson neurons

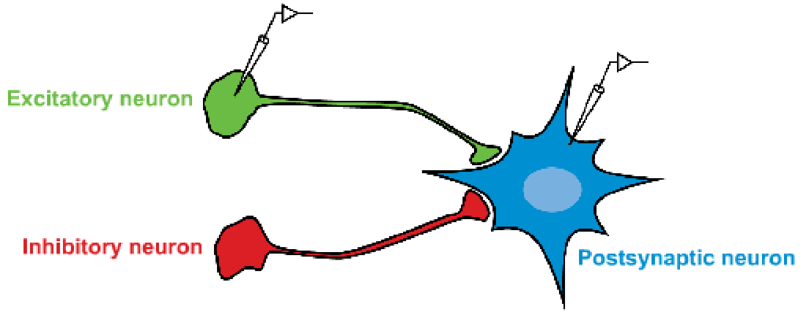
- Phenomenological model
- Cellular automaton
- Firing rate:

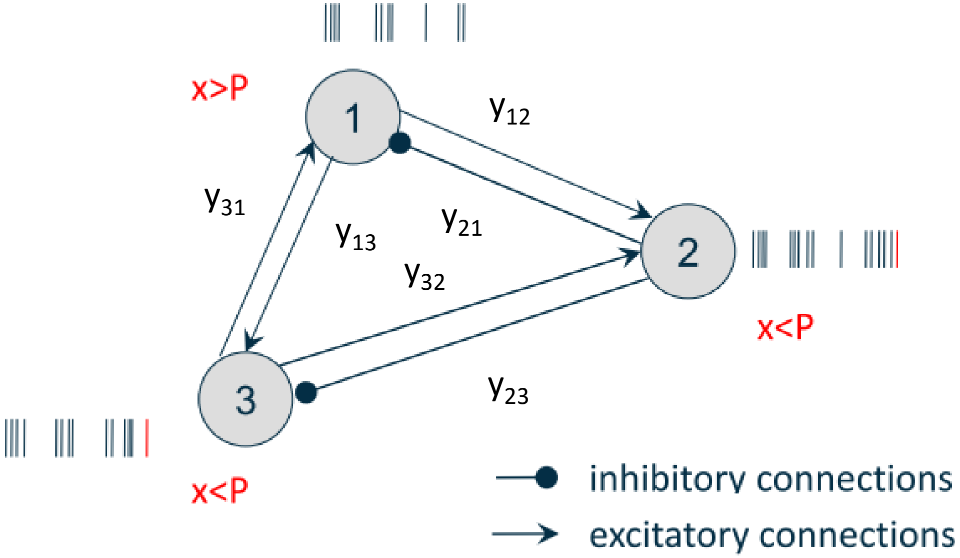
$$\lambda_i(t_k) = c_i + \sum_j y_{ji} s_j(t_{k-1})$$

- Inhomogeneous Poisson processes:

$$P_i\{1\,\text{spike within } \Delta t\} = e^{-\lambda_i \Delta t} \cdot \lambda_i \Delta t$$

- Spike Time History
- Parameters obtained by brute force approach with the goal functions spike and burst rate
- Each neuron makes connection to e.g. 10-30% of the population

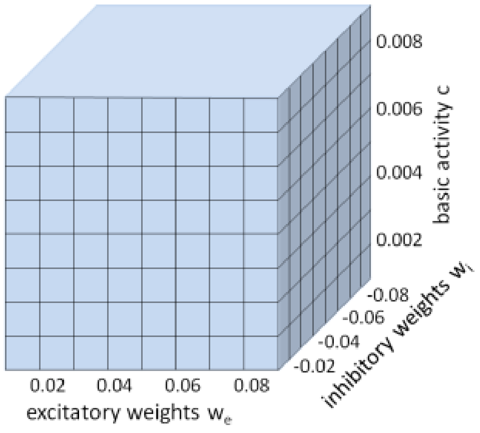




Lenk, NoLISP 2011
Lenk et al., Biomed Eng *Online* 2016

INEX model consists of Poisson neurons

Brute Force Approach for Parameter Search:

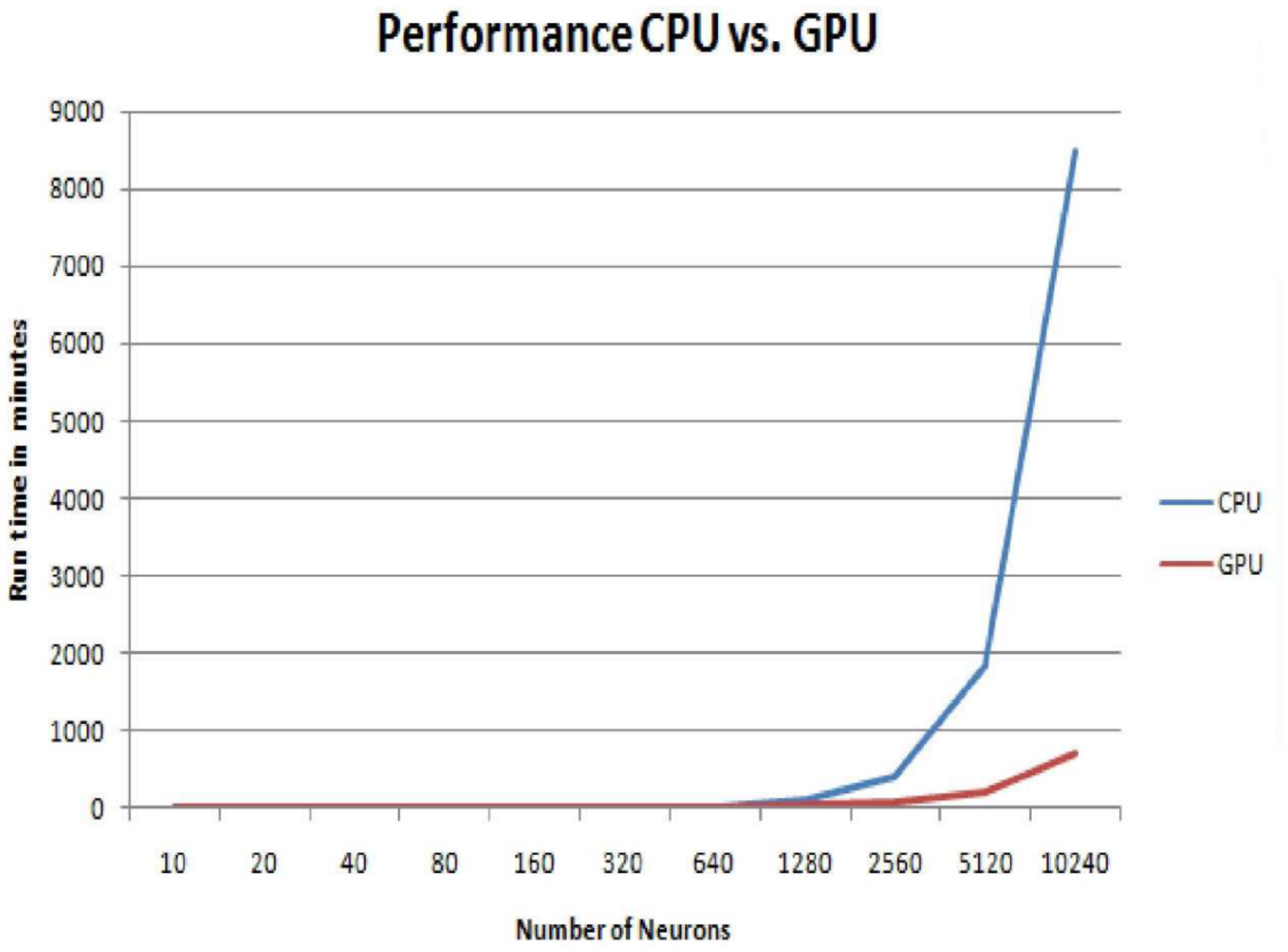


Goal functions:

spike rate + burst rate

Validation:

4-12 calculated features from experimental data



Lenk *et al. BioMed Eng OnLine (2016) 15:105*
DOI 10.1186/s12938-016-0226-6

BioMedical Engineering OnLine

RESEARCH **Open Access**

Simulation of developing human neuronal cell networks

Kerstin Lenk[1*], Barbara Priwitzer[2], Laura Ylä-Outinen[3], Lukas H. B. Tietz[1], Susanna Narkilahti[3] and Jari A. K. Hyttinen[1]

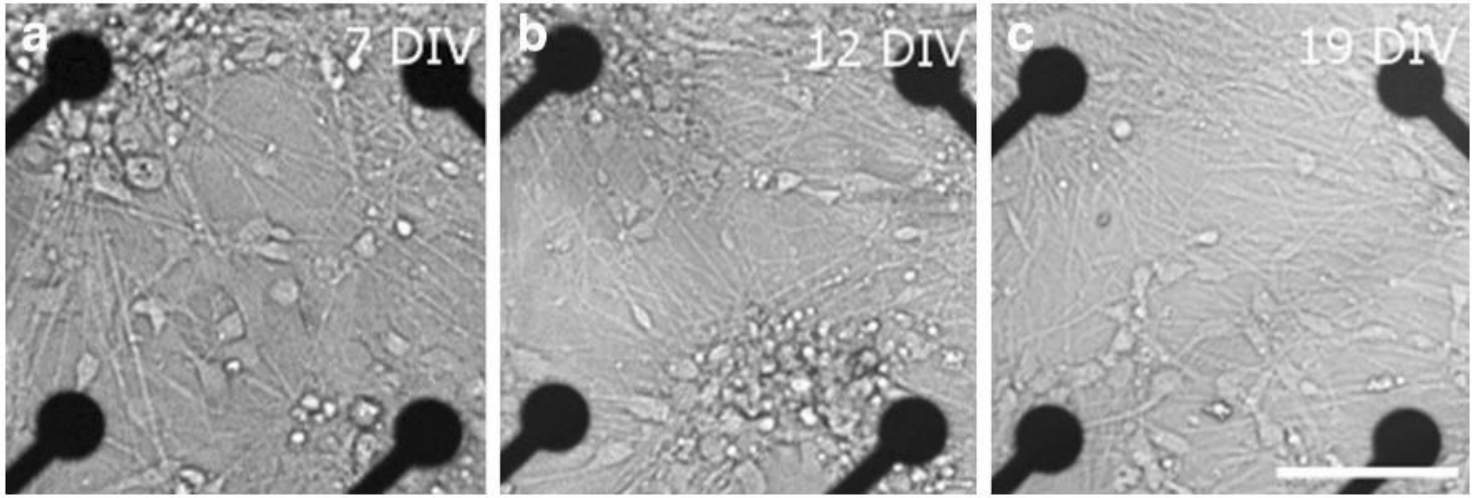
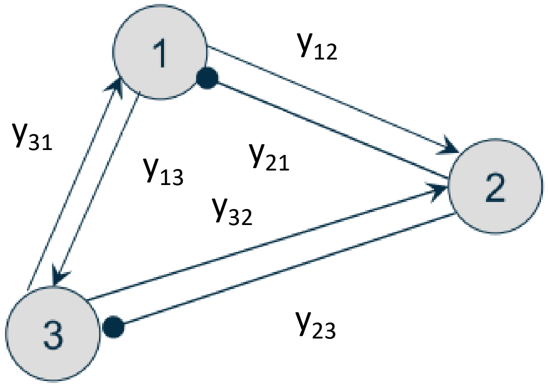


Fig. 1 Neuron distribution of dataset #3 (see Table 1) on the MEA for three points in time (**a** 7 days in vitro (DIV), **b** 12 DIV, and **c** 19 DIV). It is clearly visible that the number of neuronal connections increases and the neurons move over time. The *black dots* indicate the MEA electrodes. The *scale* is 100 µm

Simulation parameters

- 1000 neurons (80% excitatory/ 20% inhibitory)
- Connectivity is increased linearly between measurement time points (1, 2, 4, 6, 8 and 10 %)
- Brute force approach for synaptic strength and noise term



Maturation process reflected by connectivity and synaptic strength

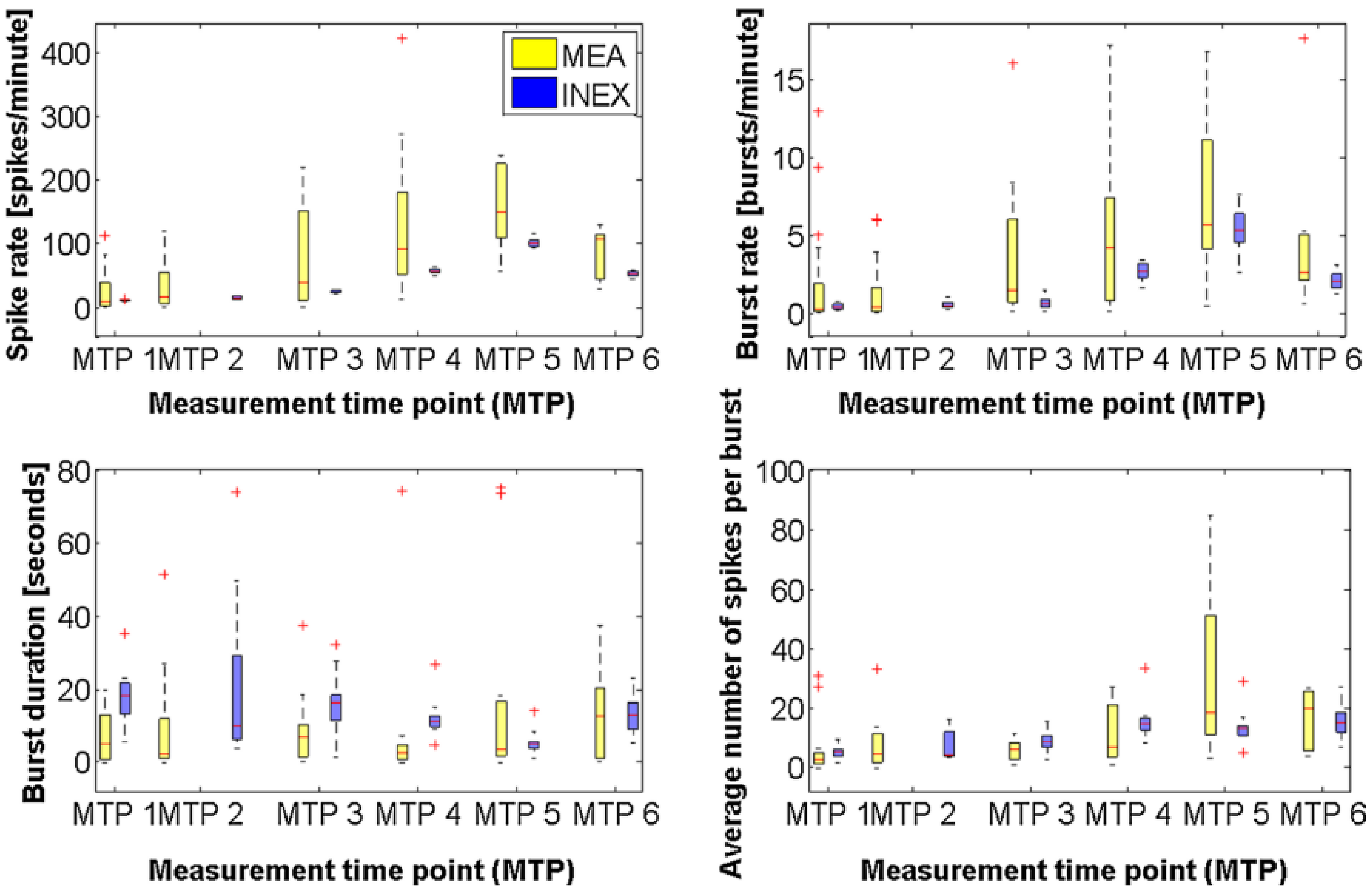
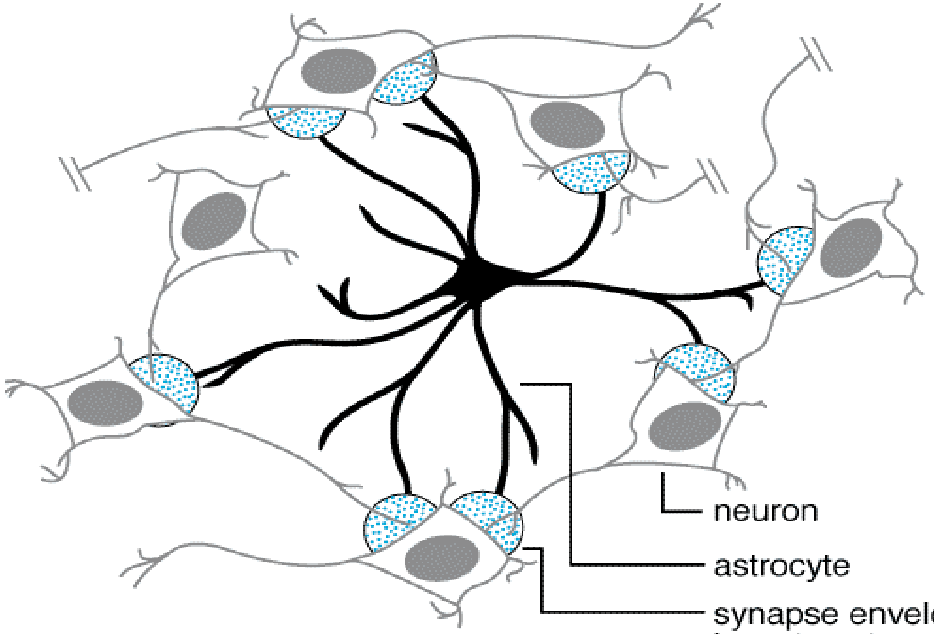


Fig. 3 Development of the neuronal activity over time (measurement time point 1–6). Clockwise: medians and quartiles of the spike rate, the burst rate, the average number of spikes per burst and the burst duration of all wells in the medium activity class, respectively. Note that some outliers are not shown in the last two graphs for visibility reasons. The values of each box plot are represented in Table 3

Lenk et al., Biomed Eng *Online* 2016

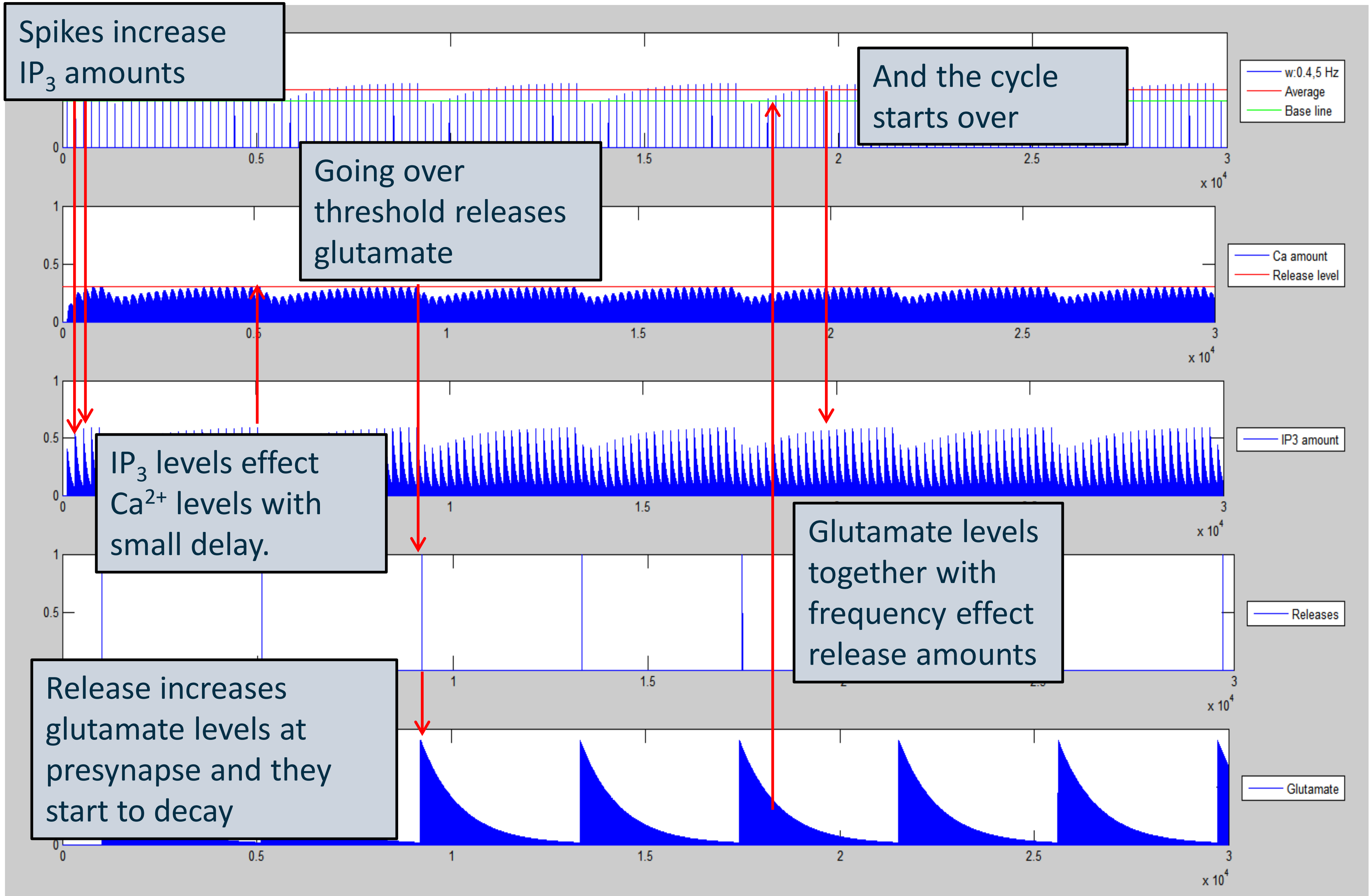
INEXA model: Astrocytes contribution to the neuronal signaling

$$\lambda_i(t_k) = \max\left(c_i + \sum_j y_{ij} \cdot s_j(t_{k-1}) - \sum_j y_{Astro} \cdot A_{ija}(t_{k-1}), 0\right),$$



Lenk*, Satuvuori* et al.
Image: www.antanitus.com

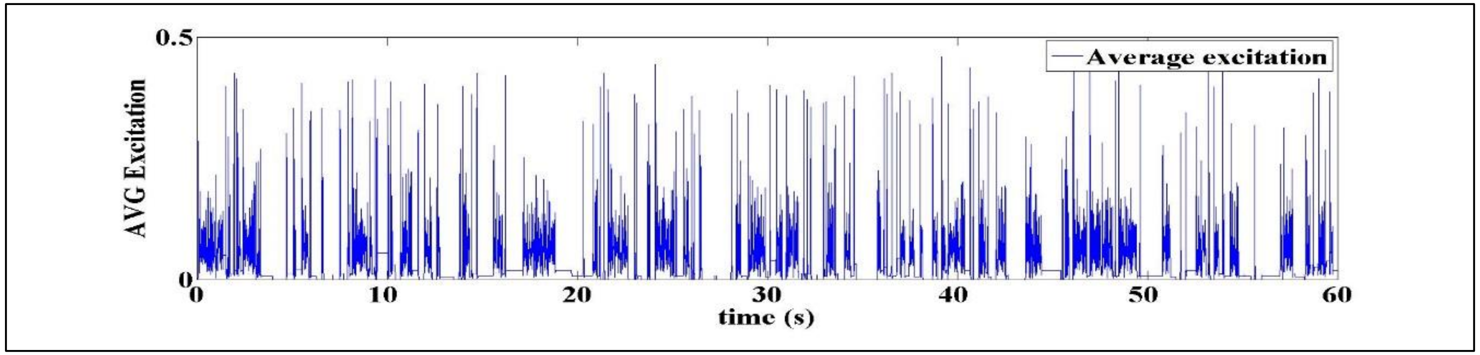
Spike-triggered calcium release



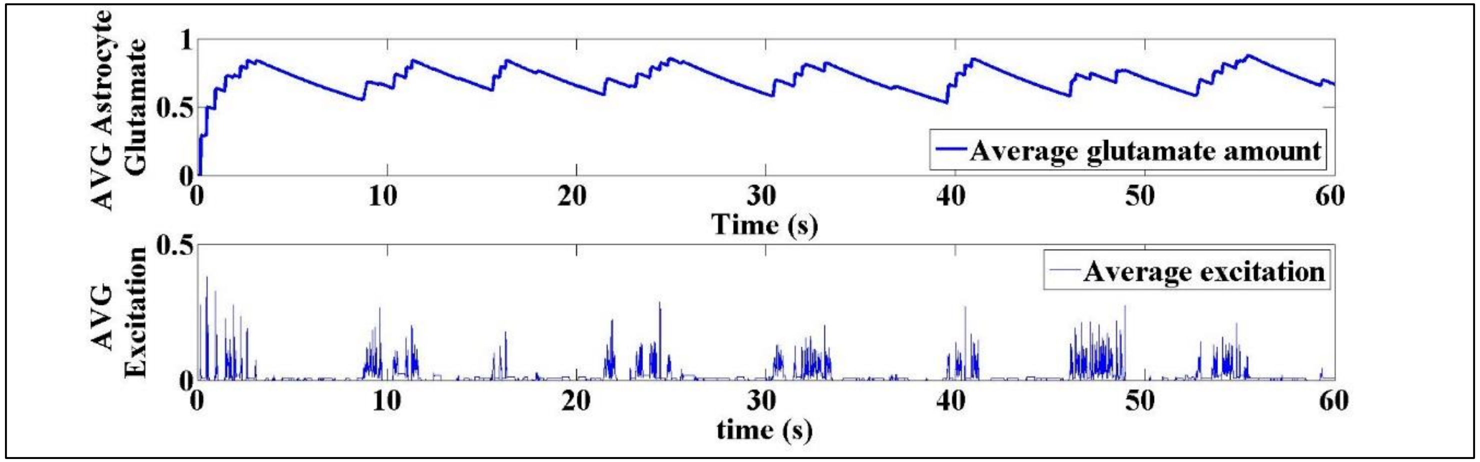
Kerstin Lenk

Activity of a single synapse alters from non-bursting behavior to bursting when astrocytes are present

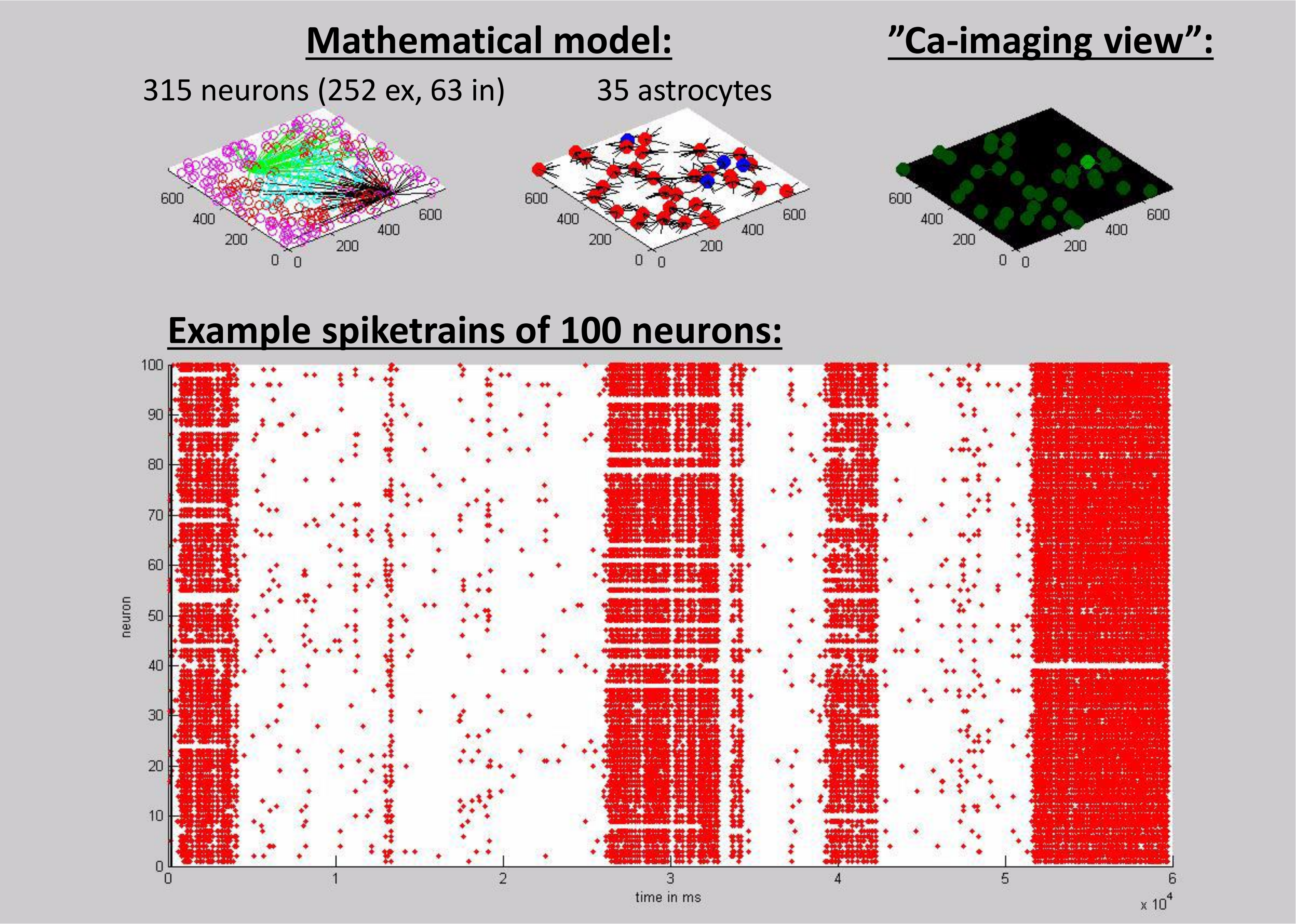
Without astrocyte control (100 neurons)



With astrocyte control (100 neurons, 80 astrocytes)



Neuronal firing follows astrocytic calcium dynamics



Kerstin Lenk

Number of astrocytes influences the neuronal network activity

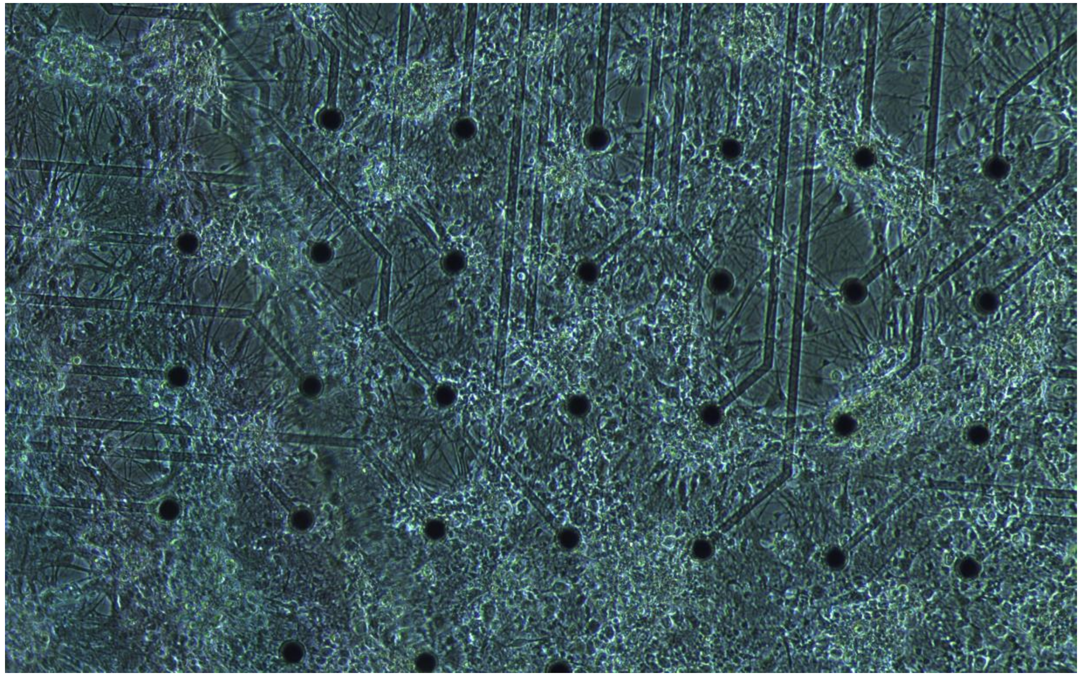
Connectivity

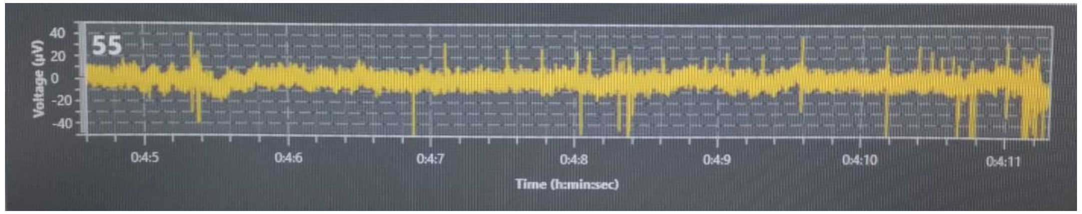
Signaling at the tripartite synapse

Astrocytes reduce the spike and burst rate but increase the burst duration

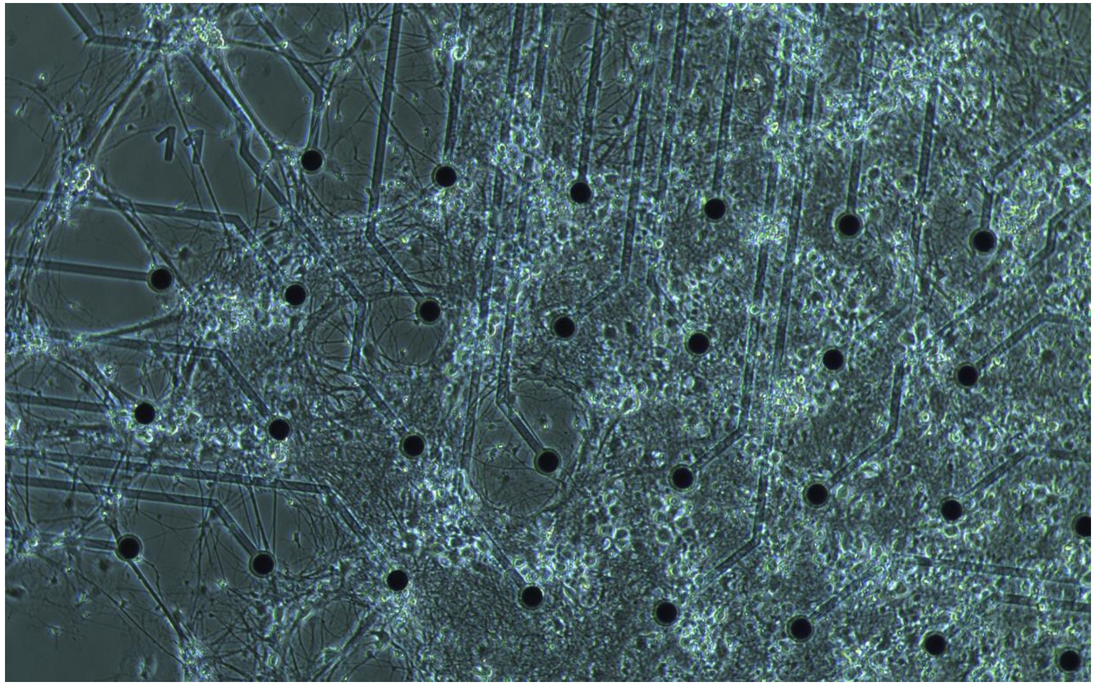
Experimental (rat) data on the way

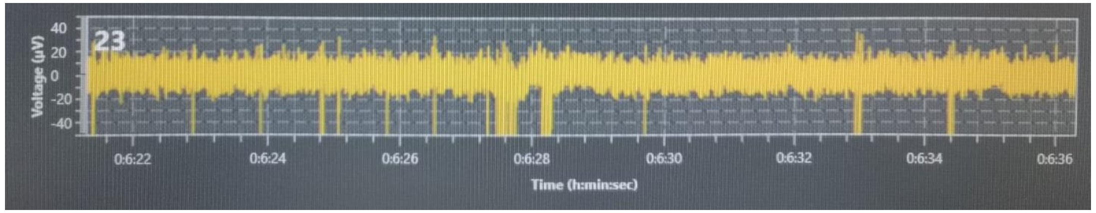
90% neurons, 10% astrocytes





70% neurons, 30% astrocytes



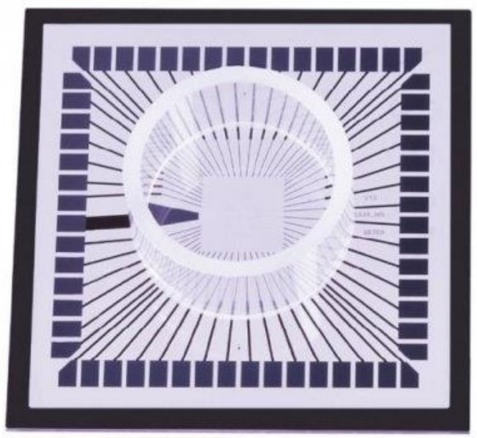


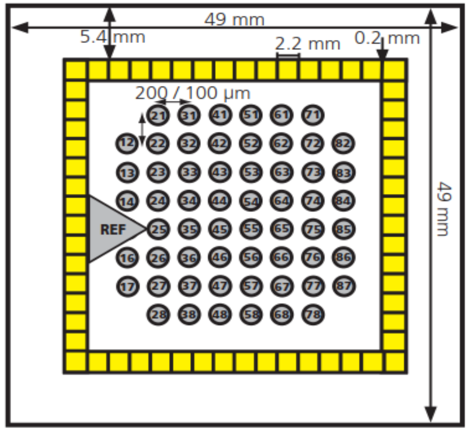
Work together with Barbara Genocchi and Annika Ahtiainen

First example of our current work: epilepsy model

Work mainly carried out by Barbara Genocchi (slide courtesy)

Second example of our current work: responses to stimuli





Work mainly carried out by Barbara Genocchi (slide courtesy)

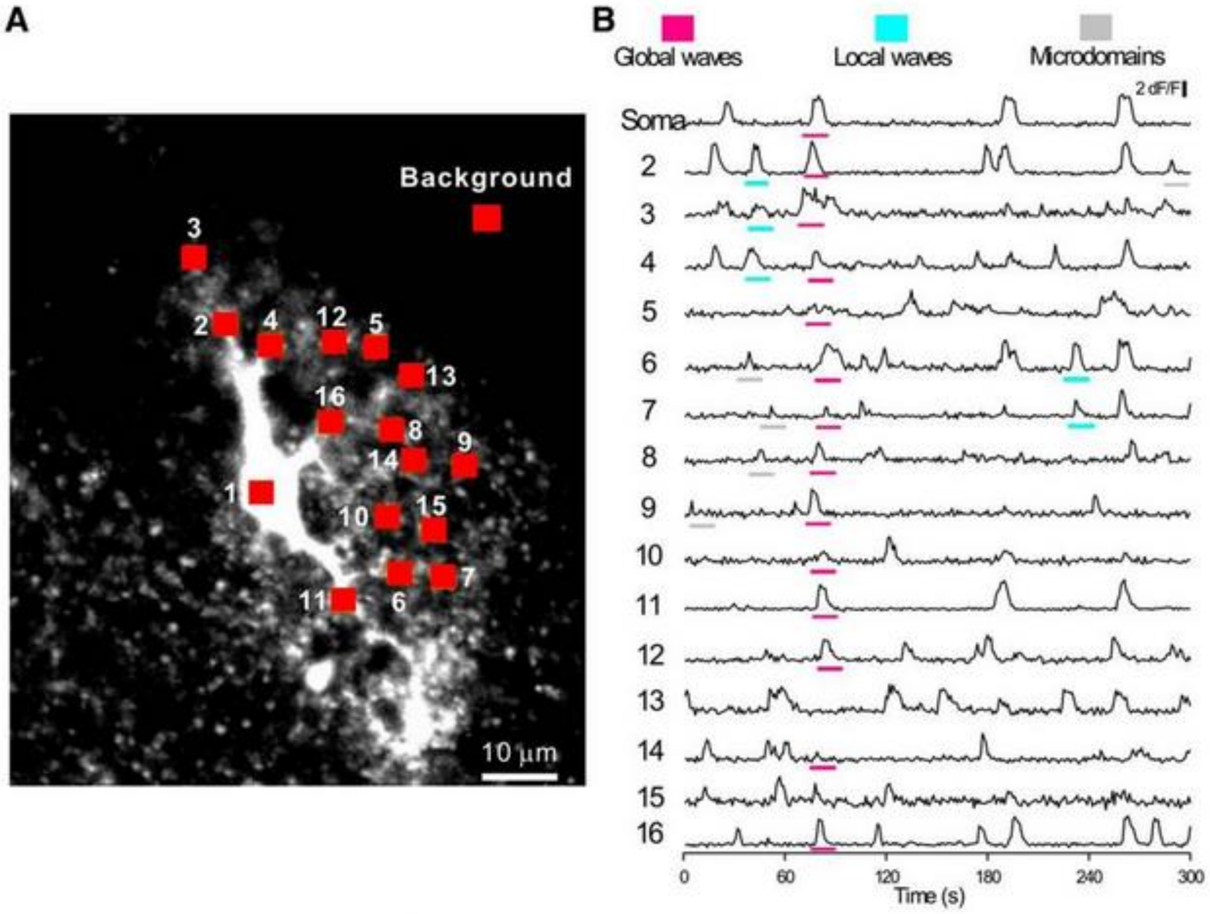
Astrocyte Ca activation; neuronal system driven by noise vs. stimulus

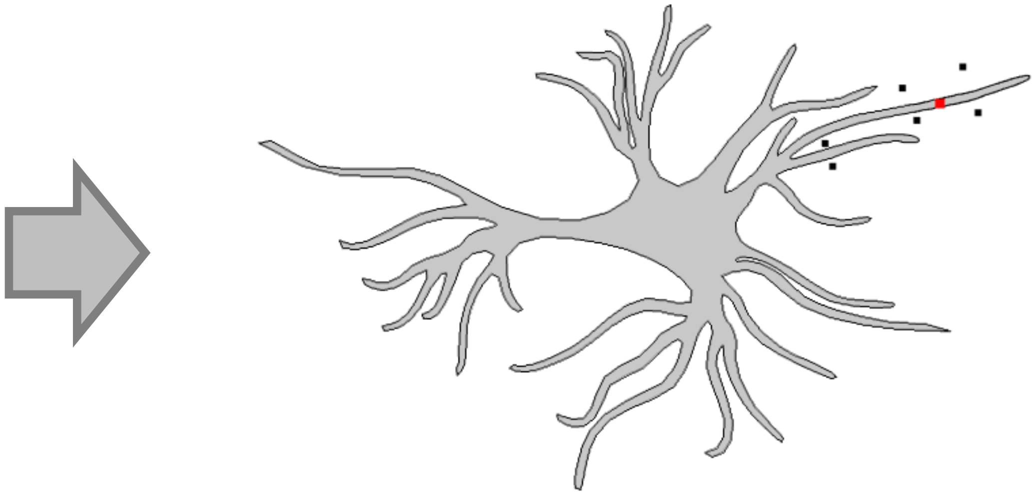
Work mainly carried out by Barbara Genocchi (slide courtesy)

Astrocyte Ca^{2+} activation in ”epileptic” neuronal activity

Work mainly carried out by Barbara Genocchi (slide courtesy)

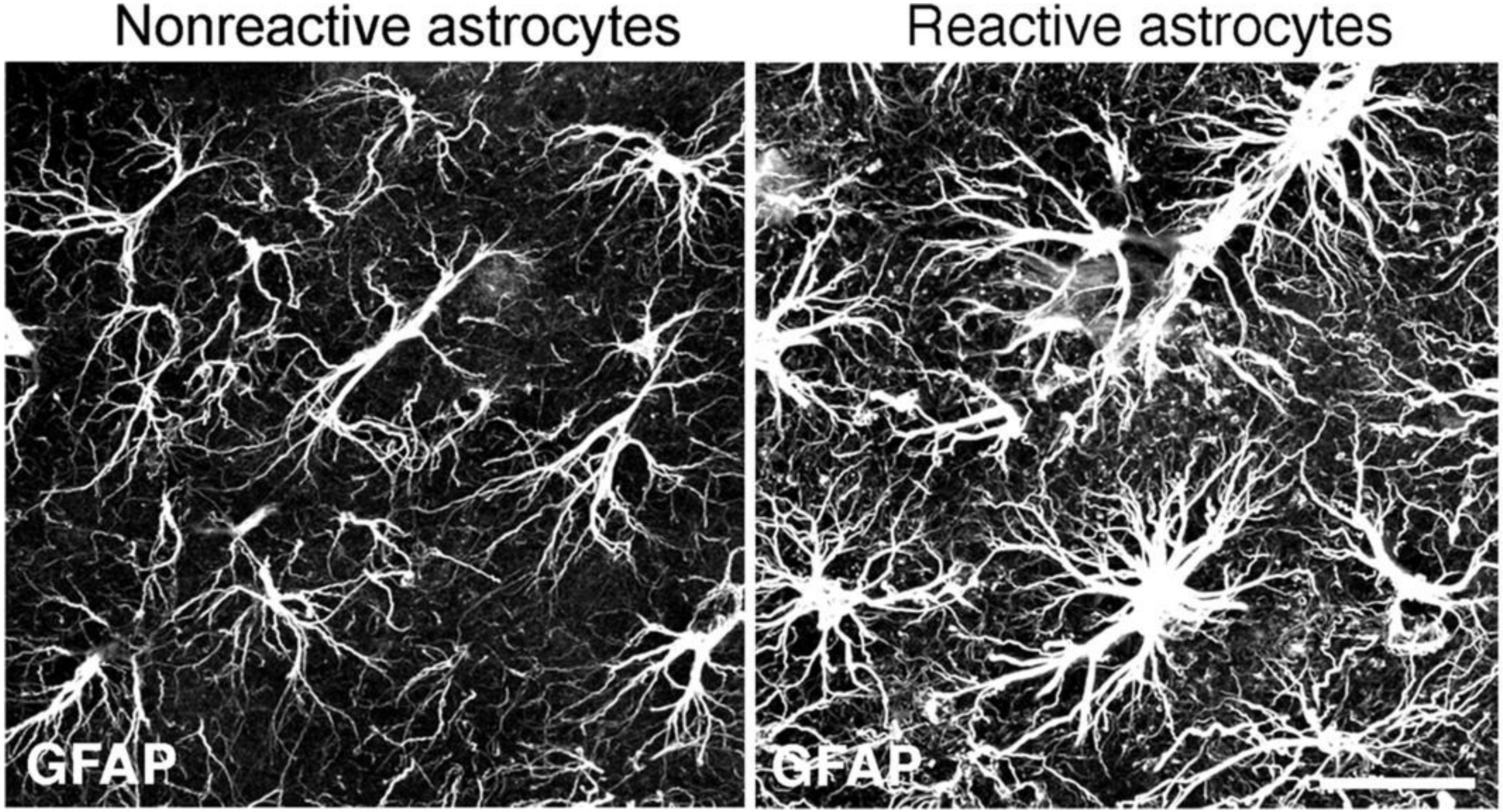
Single cell astrocyte model





Jiang et al., J Neurosci 2016

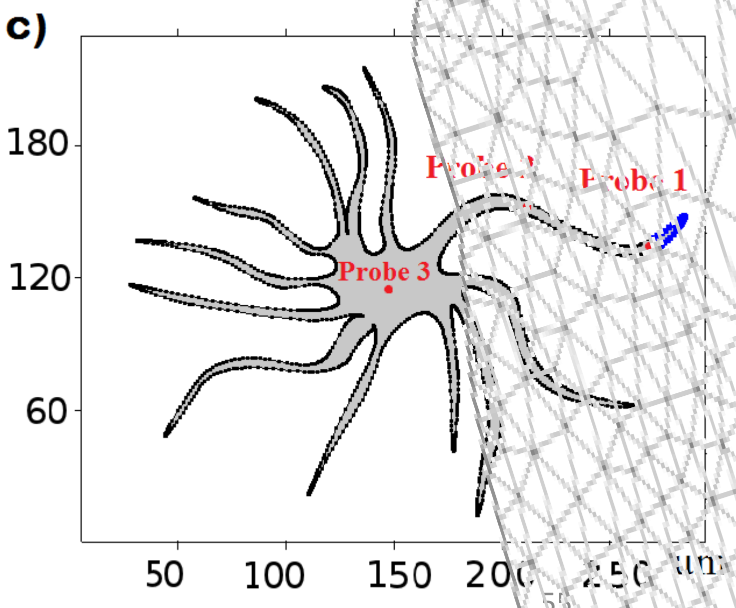
In Alzheimer’s disease, astrocytes undergo morphological and functional changes



Wilhelmsson et al., PNAS 2006

Model implementation as 2D FEM

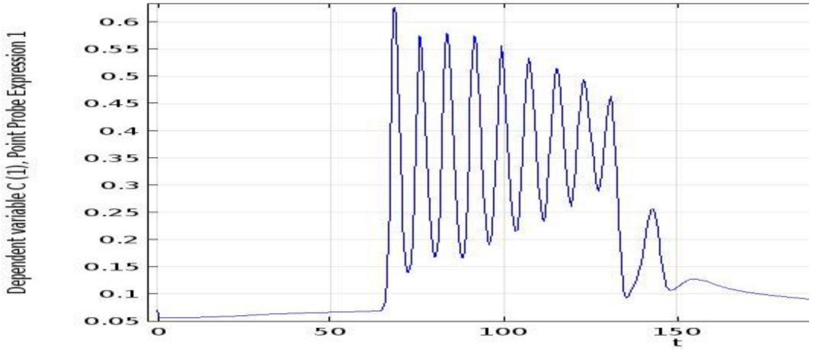
- Model Based on G-ChI model of De Pitta et al., 2009
- Implementation into COMSOL Multiphysics
- Addition: Diffusion of the IP_3 and calcium in cell
- Boundary condition: input of glutamate e.g. from synapses



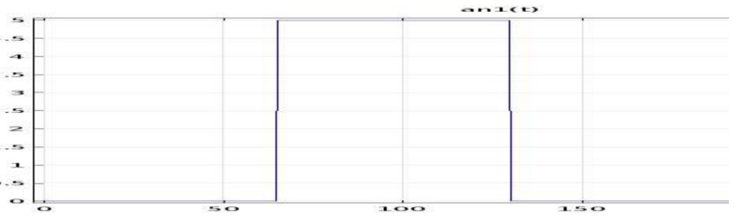
Kerstin Lenk

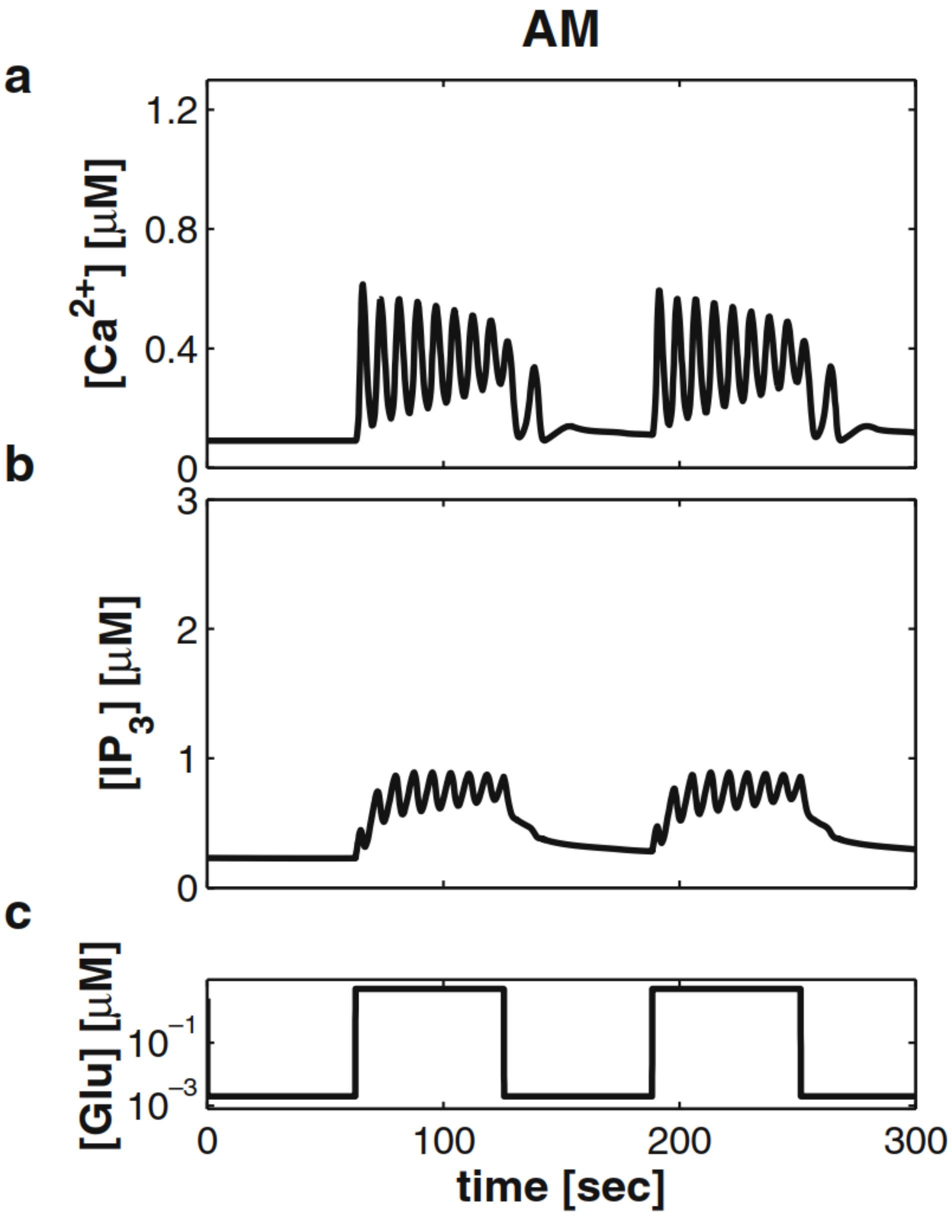
Replication of De Pitta – FEM simulation without spatial dimensions (”0D”)

Resulting Calcium in astrocyte



Glutamate stimulus

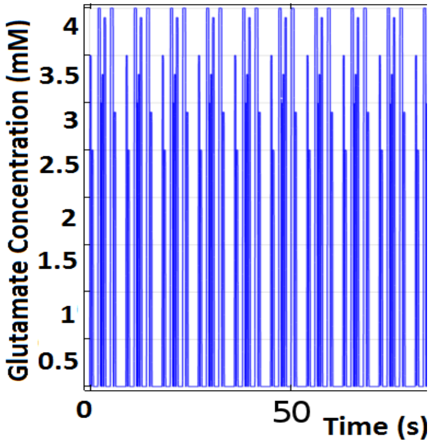


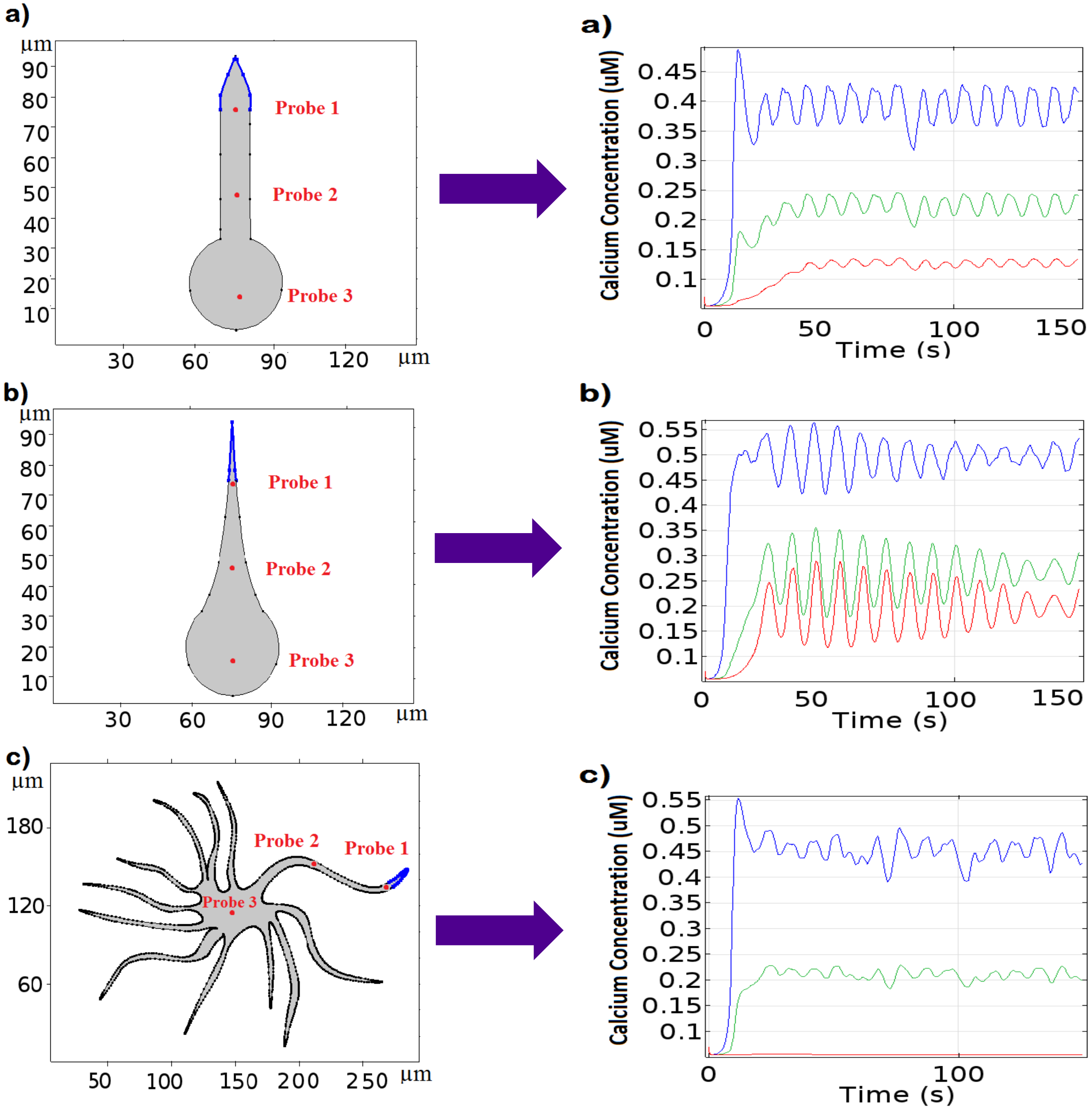


De Pitta et al., J Biolog Physics 2009

Different geometries

Input

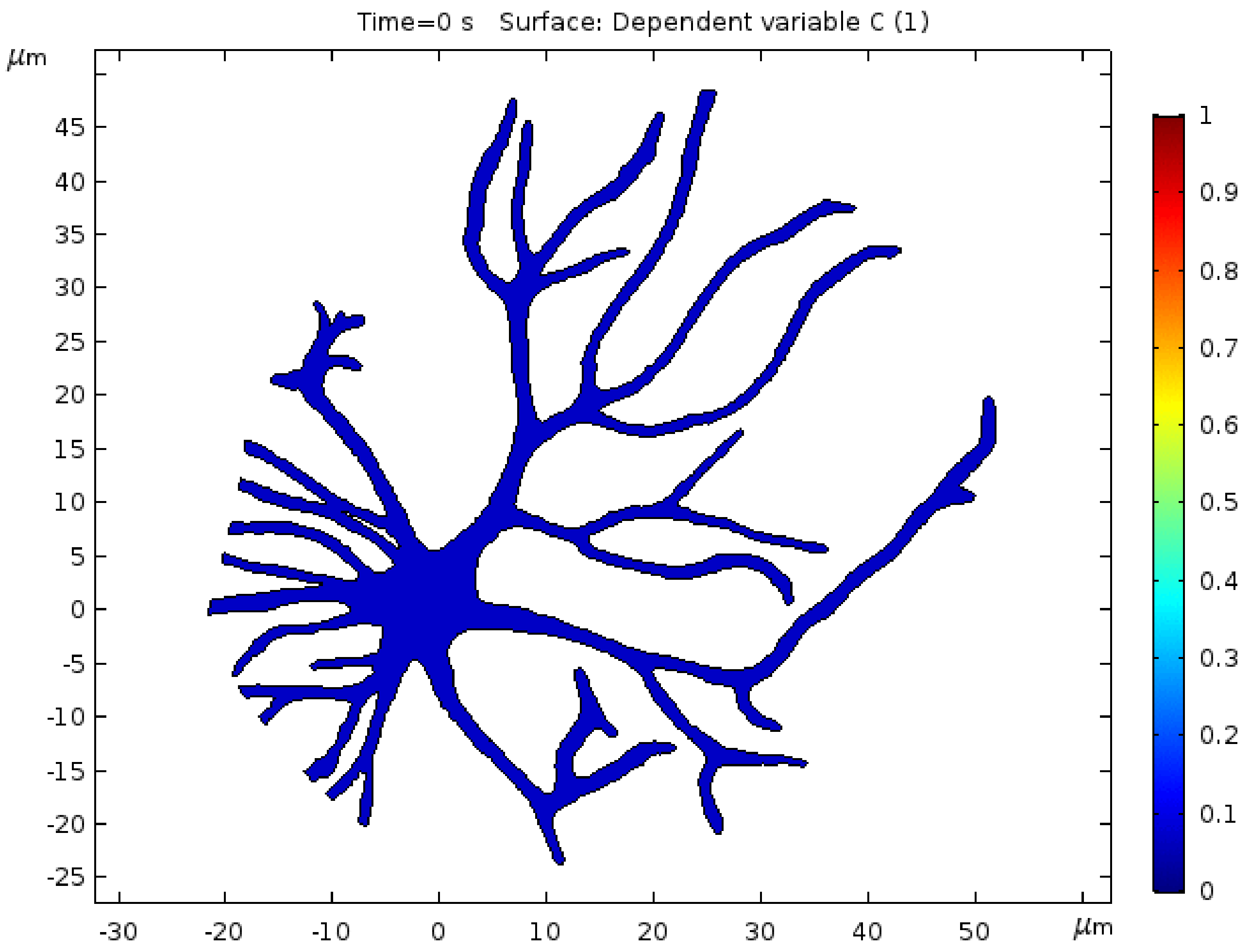




Khalid et al., Proc EMBEC 2017

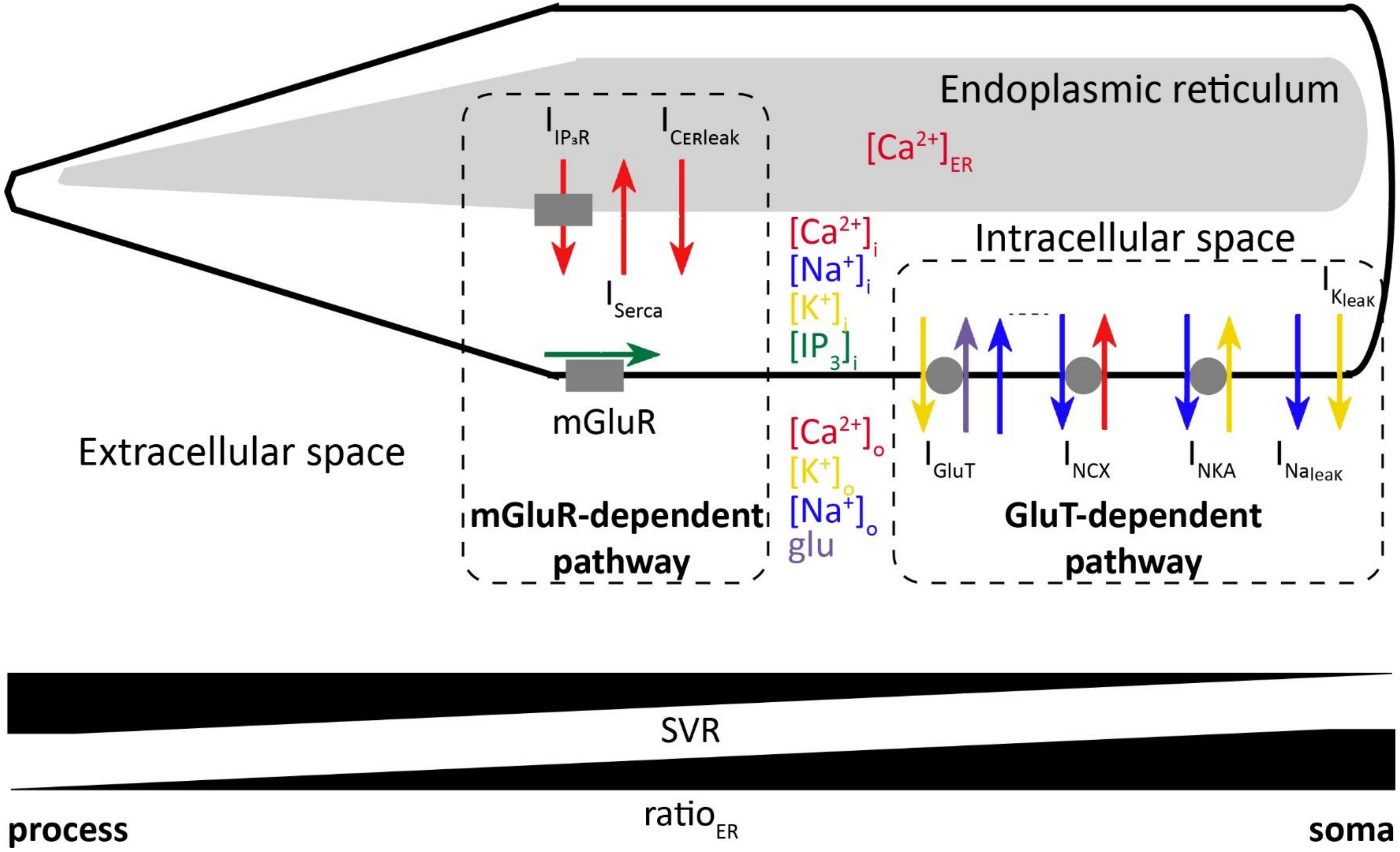
Kerstin Lenk

Astrocyte calcium after ”synaptic” local release of glutamate



Work together with Aapo Tervonen

Implementation of glutamate pathways and ER distribution



Modified from Oschmann et al., PLOS Comp Biol 2017

Governing equation

PLOS COMPUTATIONAL BIOLOGY

$$\frac{d[Ca^{2+}]_i}{dt} = \frac{A}{F \cdot Vol} \cdot I_{NCX} + \frac{A \cdot \sqrt{ratio_{ER}}}{F \cdot Vol} \cdot (I_{IP_3R} - I_{Serca} + I_{C_{ER}leak})$$

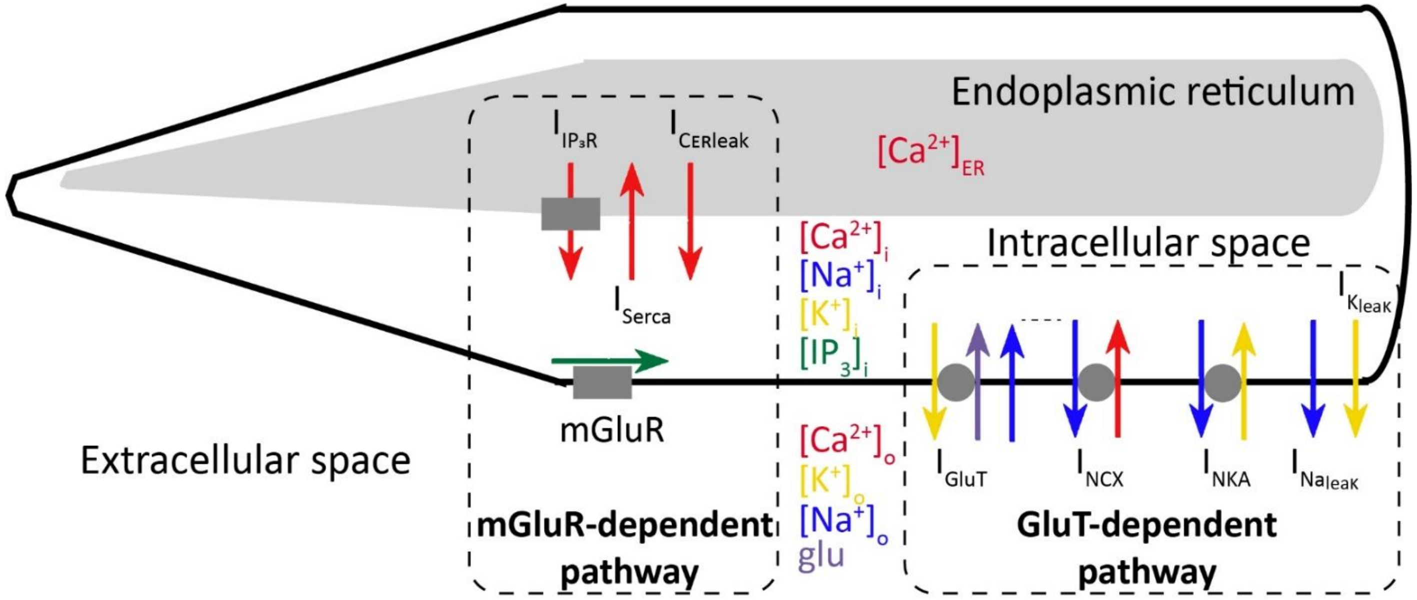
I_{NCX} = Na^+/Ca^{2+} exchanger
I_{IP_3R} = Ca^{2+} current through the IP3 receptor channel
I_{SERCA} = SERCA pump
$I_{C_{ER}leak}$ = Ca^{2+} leak from the ER

A = area of the outer cell membrane
F = Faraday constant
Vol = volume of the intracellular space
$A \cdot \sqrt{ratio_{ER}}$ = area of the internal Ca^{2+} store

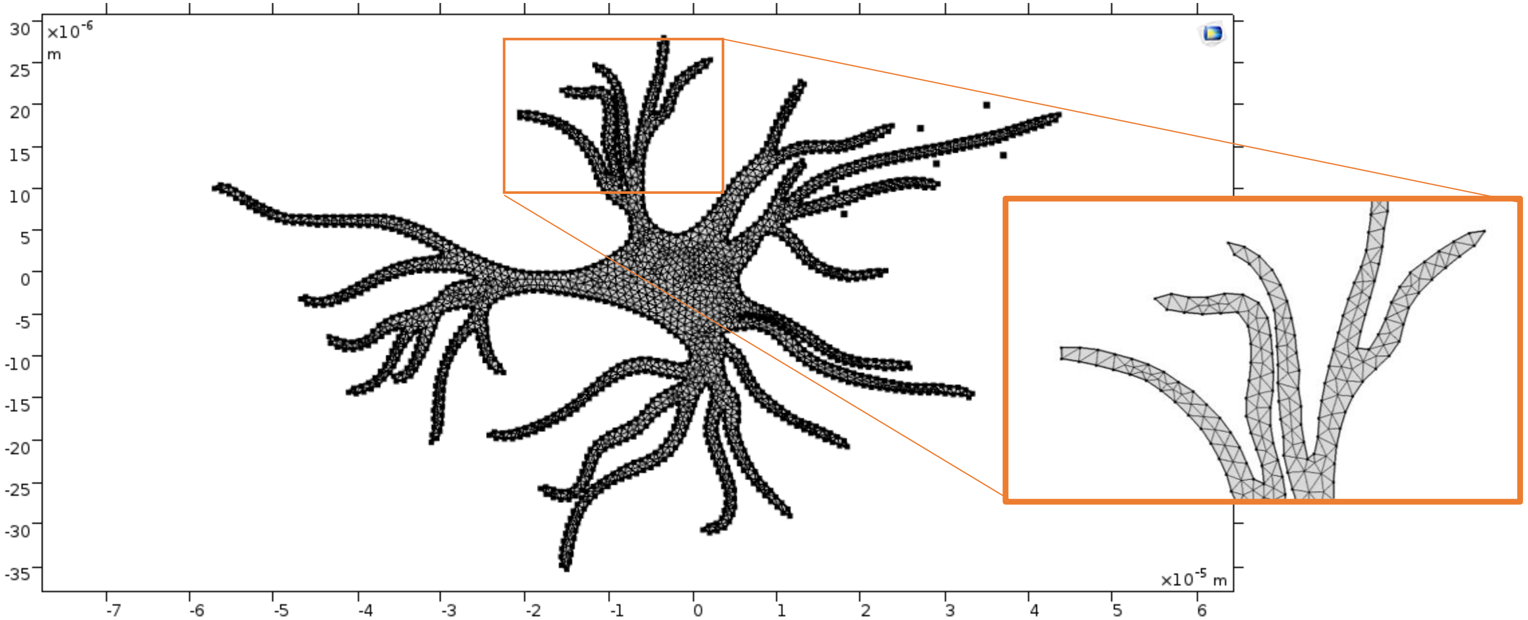
RESEARCH ARTICLE

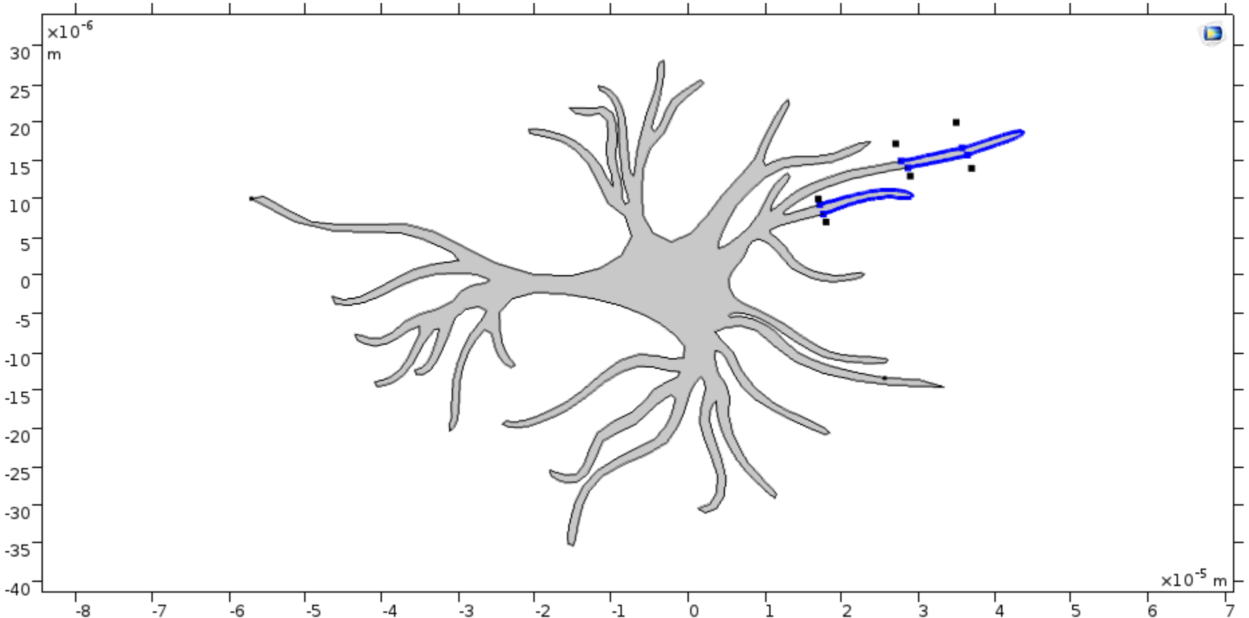
Spatial separation of two different pathways accounting for the generation of calcium signals in astrocytes

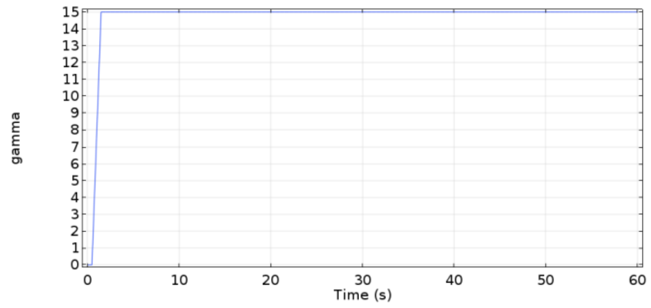
Franziska Oschmann[1,2¤]*, Konstantin Mergenthaler[1], Evelyn Jungnickel[1], Klaus Obermayer[1,2¤]



Constant glutamate stimulus at process(es)







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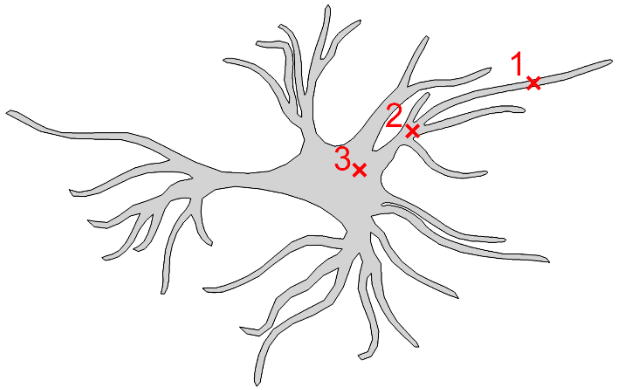
One stimulation site



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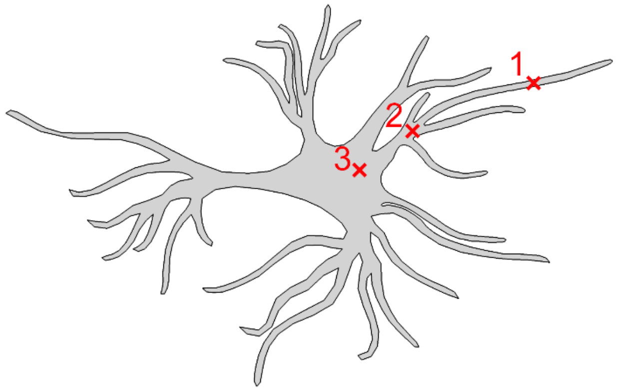
Three stimulation sites



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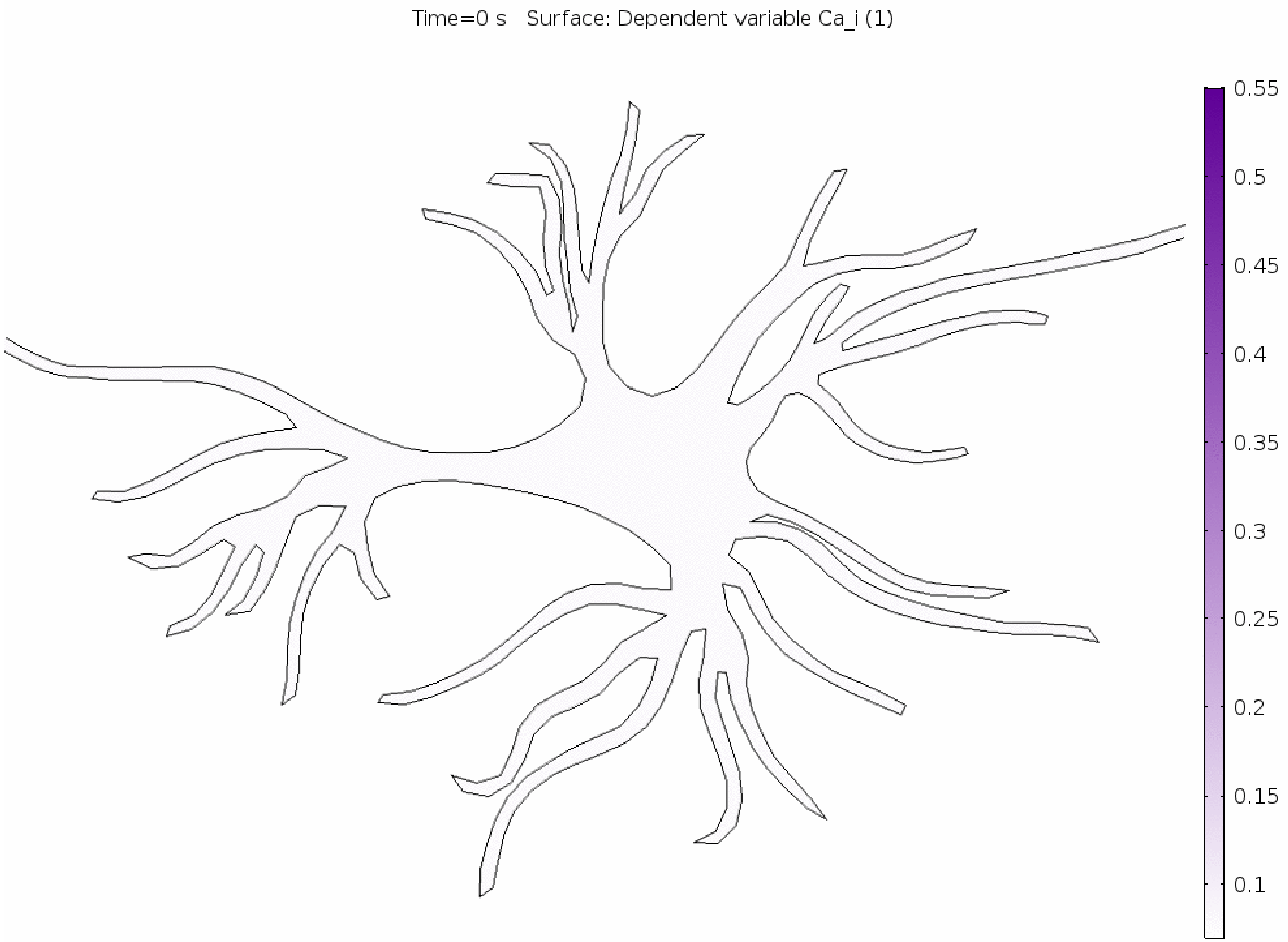
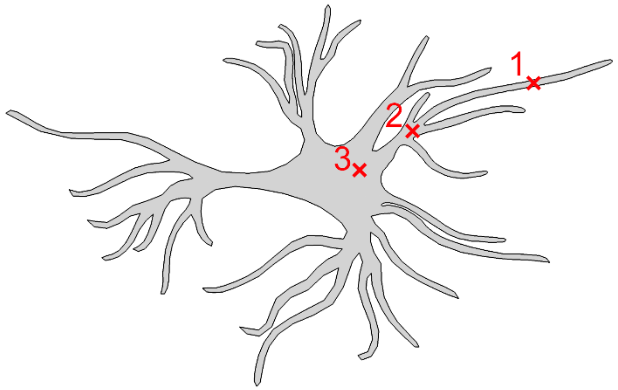
Three stimulation sites





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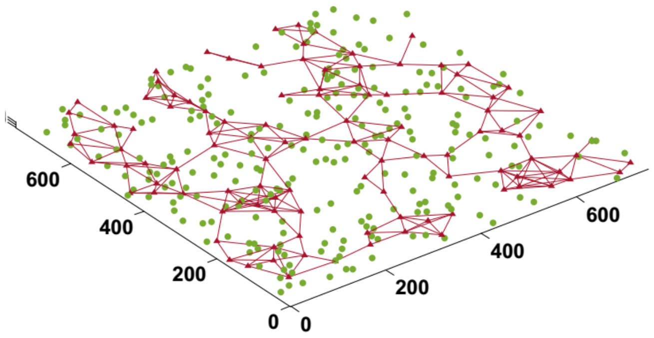
Conclusions

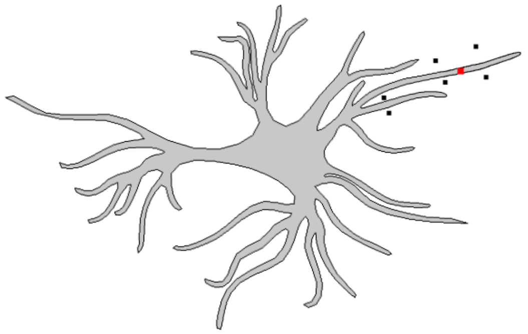
(1) INEXA model:

- One of the first neuron-astrocyte network models where one astrocyte is connected to several hundreds of excitatory synapses
- Astrocyte control over neurons can have profound effects to network behavior → astrocytes prolong the burst duration of neurons, while restricting hyperactivity
- The model is only using part of the pathways astrocytes are known to have



(2) Single cell astrocyte model:

- Calcium spread based on number of input sides
- Next steps: different morphologies, gap junction coupling with adjacent astrocyte, 2D vs 3D



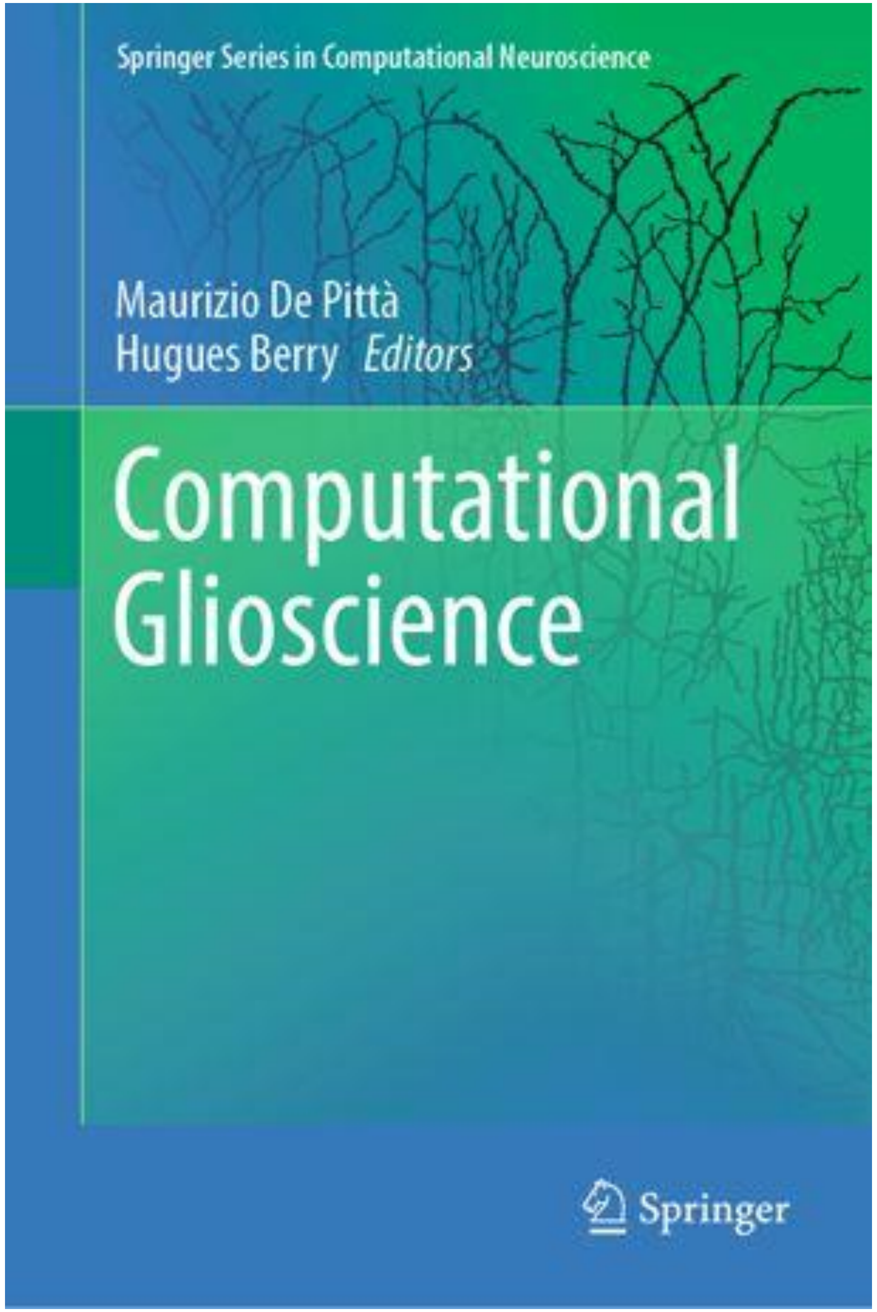
ModelDB - https://senselab.med.yale.edu/modeldb/

SenseLab ModelDB SimToolDB

Submit Model

ModelDB provides an accessible location for storing and efficiently retrieving computational neuroscience models. ModelDB is tightly coupled with NeuronDB . Models can be coded in any language for any environment. Model code can be viewed before downloading and browsers can be set to auto-launch the models. For further information, see model sharing in general and ModelDB in particular.

Browse or search through over 1000 models using the navigation on the left bar or in the menu button on a mobile device. To search papers instead of models, go here; this may be used to identify models whose paper cites or is cited by a given paper.



Main parts:

- Introduction
- Calcium Dynamics
- Tripartite Synapse and Regulation of Network Activity
- Homeostasis and Metabolic Coupling
- Computational Tools to Analyze and Model Astrocyte Experiments

Tampere University

CoEBoC

Centre of Excellence in Body-on-Chip Research

Save the date:

Nordic Organ on Chip Workshop

”3rd” NOoC Workshop

22-23 August 2019

Tampere, Finland

Workshop is for PIs and researchers. During the meeting we will arrange two workshop sessions with oral presentations and a poster session/ hands-on training. On Thursday evening we are planning to have a get-together with outdoor activities and dinner.

For more information, contact

mari.pekkanen-mattila@tuni.fi


49th Computing in Cardiology CinC2022
September 2022
Tampere, Finland

Many thanks to …

Funding

SUOMEN AKATEMIA
FINLANDS AKADEMI
ACADEMY OF FINLAND

3DNeuroN

SEVENTH FRAMEWORK PROGRAMME

Tekes
Human Spare Part 2

Tampere University, Finland
Jari Hyttinen
Eero Satuvuori (Räisänen; now lost to industry)
Antonio Ladron De Guevara (now in Madrid, Spain)
Barbara Genocchi
Aapo Tervonen
Annika Ahtiainen
Sama Saeid

Collaborations
Hugues Berry, INRIA, France
Jules Lallouette, INRIA, France
Katja Nieweg, Philipps-University Marburg, Germany

AND YOU!

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