

LECTURE 25:

Modeling Neuron-Glia Interactions 2

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<https://research.tuni.fi/computational-neuroscience/>

LASCON X: Three lectures and one tutorial

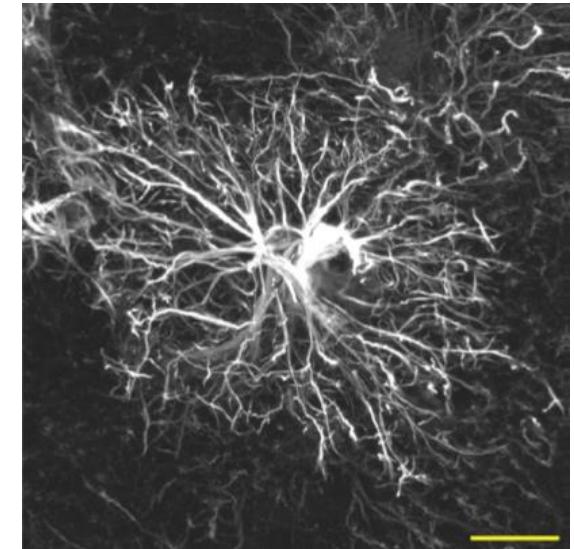
1. Modeling Neuron-Glia Interactions 1: Biology of the Glial Cells & Background to Modeling
- 2. Modeling Neuron-Glia Interactions 2: Modeling Single Cells**
3. Modeling Neuron-Glia Interactions 3: Modeling Networks with Neuron-Glia Interactions
4. Tutorial: NEST Astrocyte Modeling Tool

Contents

1. Computational modeling of astrocyte activity and morphology

2. Examples of published cellular level models

3. Reproducibility and replicability of models



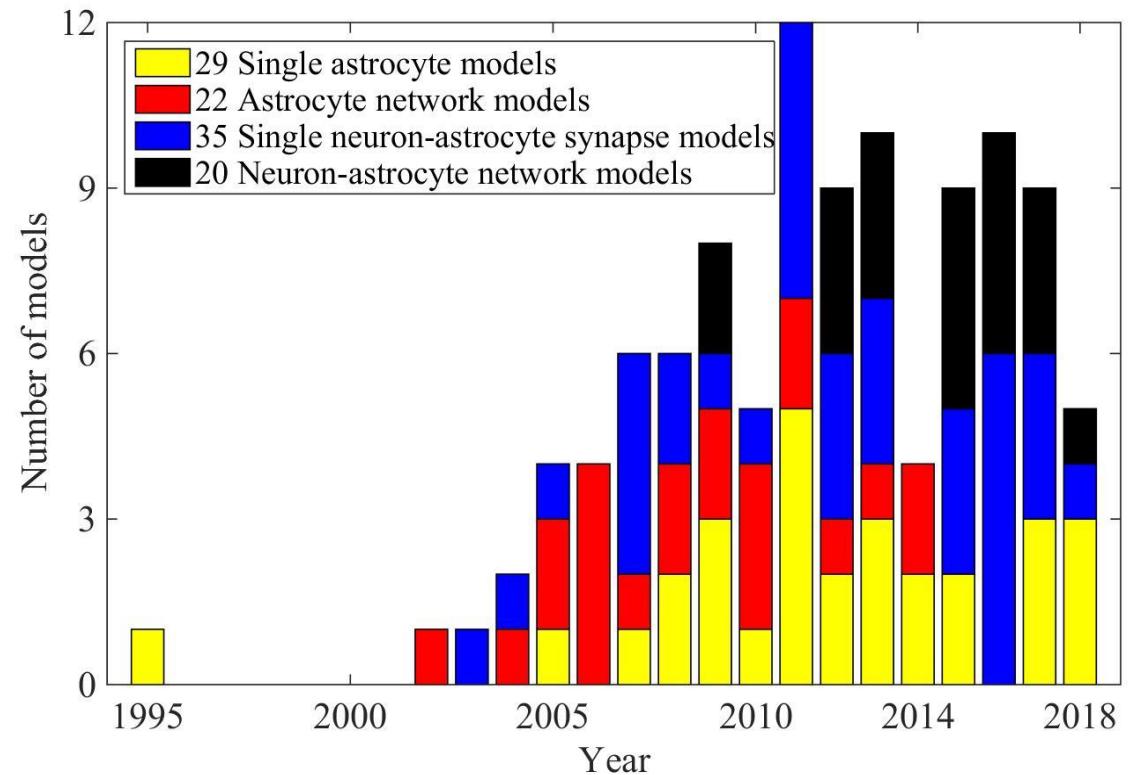
Cortical astrocyte *in vivo*

1.

Computational modeling of astrocyte activity and morphology

Neurons are modeled far more than astrocytes

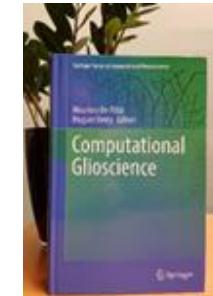
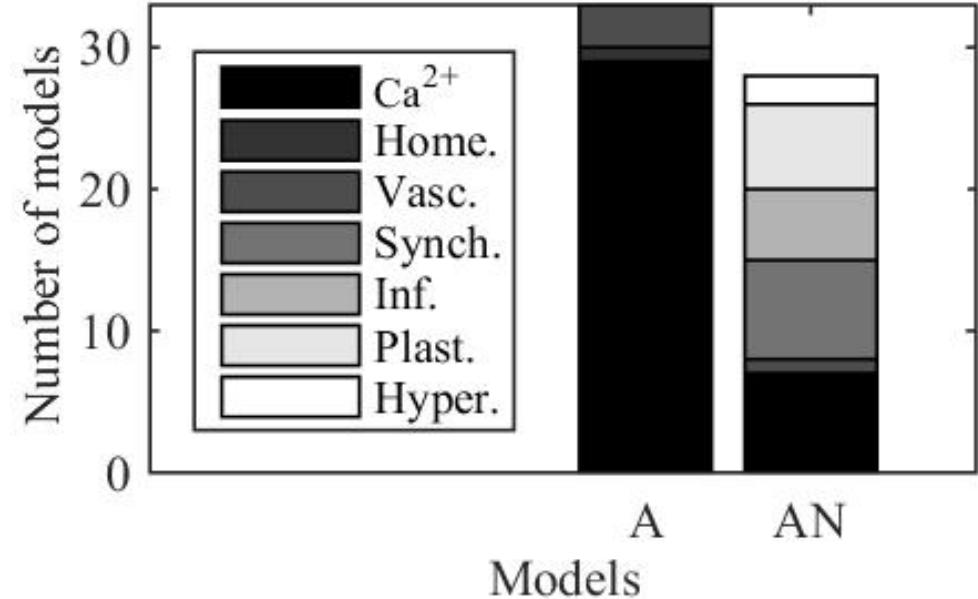
- Thousands of models for different kinds of neuronal cells (see e.g., ModelDB)
- Hundreds of models for astrocytes
- **106** biophysical models for astrocytic calcium dynamics (in 2018)



Manninen, Havela, Linne (2018). Computational Models for Calcium-Mediated Astrocyte Functions. *Frontiers in Computational Neuroscience*.

What do astrocyte models capture?

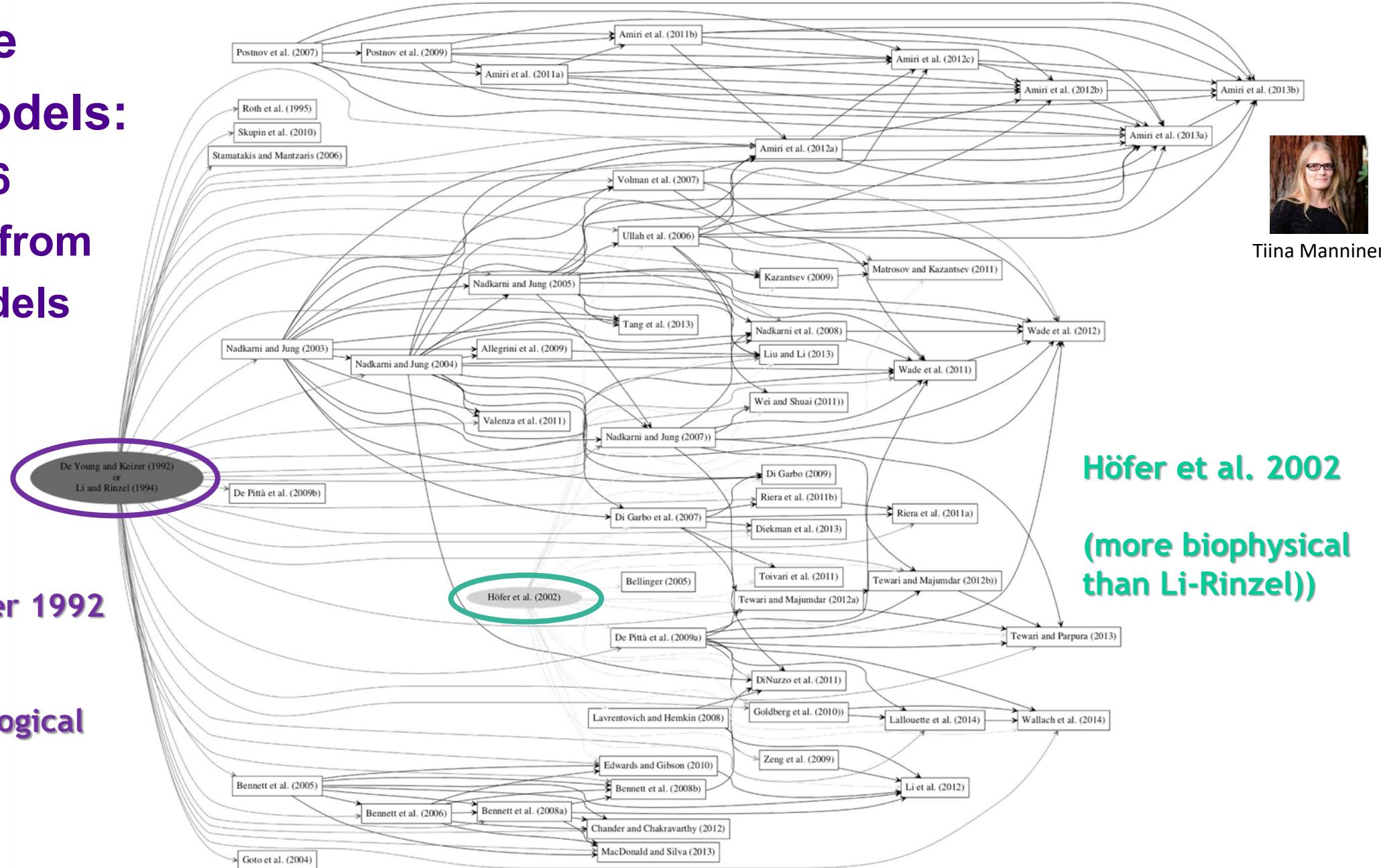
- About half of the models are generic, thus not built for any certain brain area.
- **Astrocyte models:**
 - Ca dynamics
 - Homeostasis
 - Vascular coupling
- **Neuron-astrocyte models:**
 - Ca dynamics
 - Vascular coupling
 - Network synchronization
 - Information transfer
 - Synaptic plasticity
 - Hyperexcitability
- Disease aspect: e.g., Alzheimer's, epilepsy, and stroke



Mapping the origin of models: Almost all 106 models stem from two early models

De Young and Keizer 1992
Li and Rinzel 1994

(more phenomenological
than Höfer et al.)



Tiina Manninen

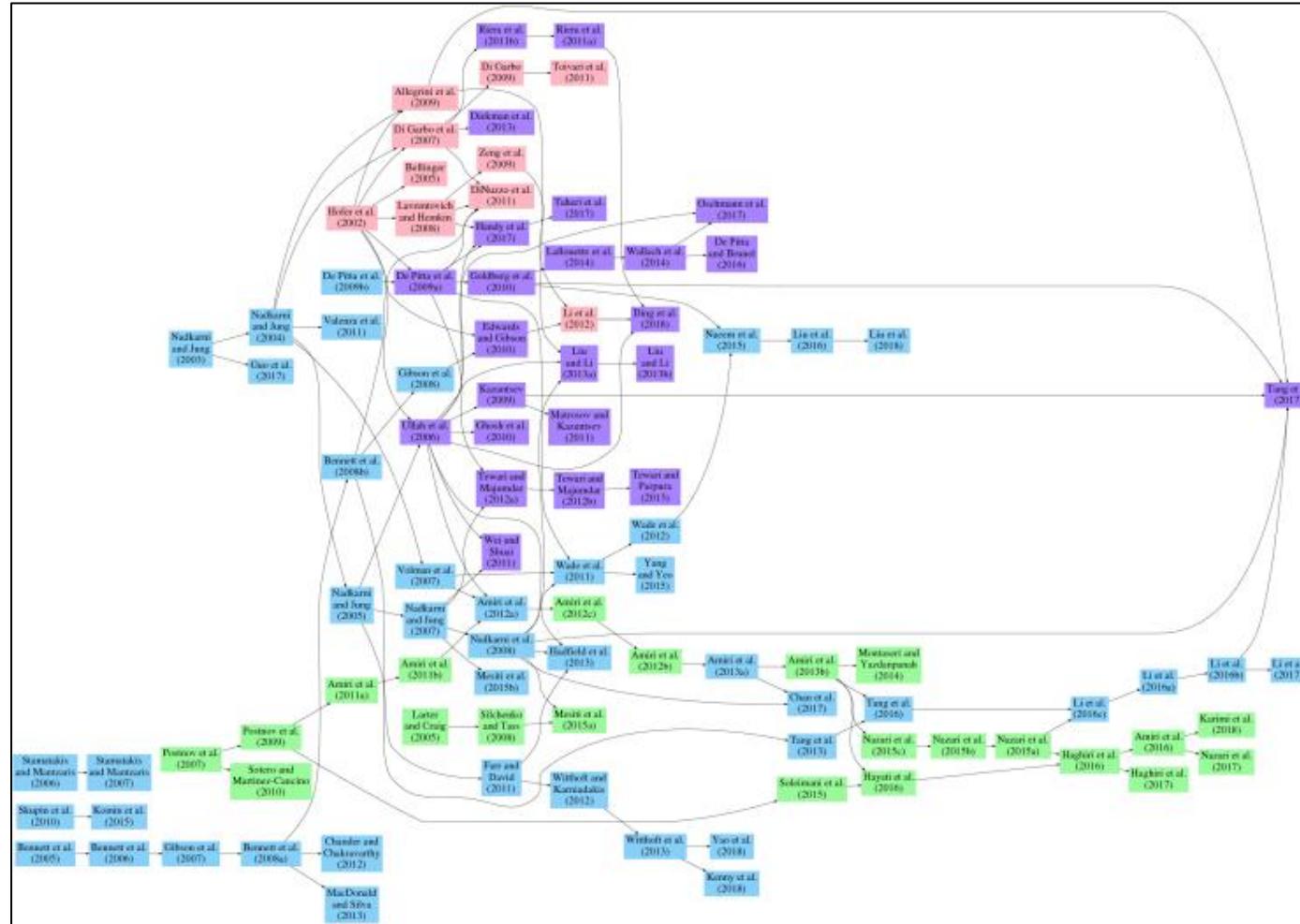
Höfer et al. 2002

(more biophysical
than Li-Rinzel))



Tiina Manninen

Mapping the origin of models: A more detailed view

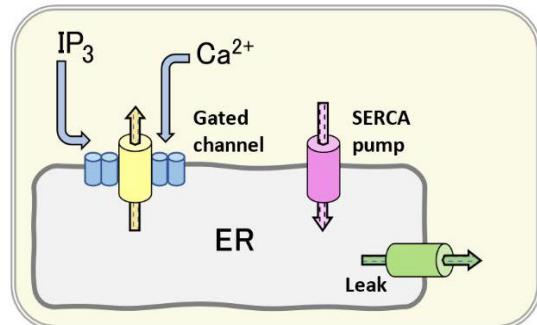


De Young-Keizer and Li-Rinzel -type models

Höfer-type models

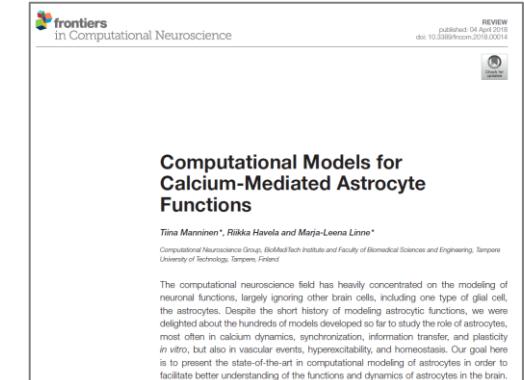
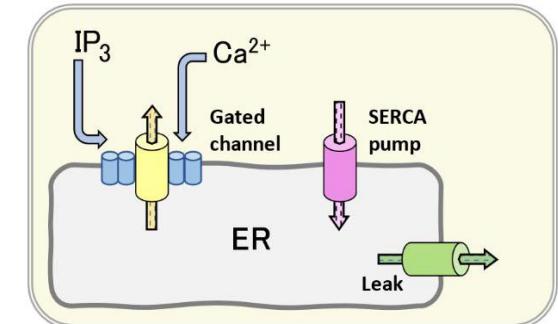
De Young-Keizer, Li-Rinzel, and Höfer -type models

All the other types of models

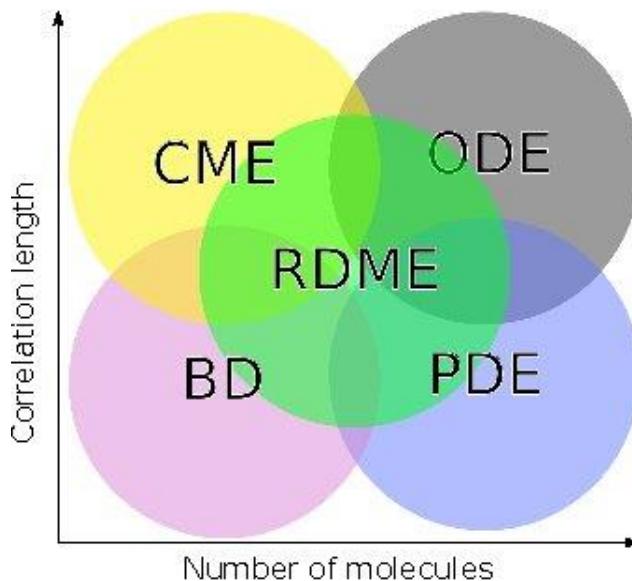


Computational models of astrocytes: Model components

Model	No.	Input	Variables	Ca ²⁺ fluxes	Diffusion	GJ	Output	Event	
De Young and Keizer (1992) and Li and Rinzel (1994) -TYPE MODELS									
Bennett et al., 2005	19-57	[ATP] _{ext}	x , [ATP] _{ext} , [Ca ²⁺] _{cyt} , h , [IP ₃]	CICR, endogenous buffer, leak from ER into cyt, SERCA	D _{cyt} : [IP ₃], D _{ext} : [ATP] _{ext}	No	[ATP] _{ext}	Ca ²⁺	
Bennett et al., 2006	19-95	[ATP] _{ext}	x , [ATP] _{ext} , [Ca ²⁺] _{cyt} , h , [IP ₃]	CICR, endogenous buffer, leak from ER into cyt, SERCA	D _{cyt} : [IP ₃], D _{ext} : [ATP] _{ext}	No	[ATP] _{ext}	Ca ²⁺	
Bennett et al., 2008a	1-7	[Glu] _{syn}	[Ca ²⁺] _{cyt} , [EET] _{ext} , h , [IP ₃]	CICR, endogenous buffer, leak from ER into cyt, SERCA	D _{cyt} : [IP ₃], D _{ext} : [EET] _{ext}	No	[EET] _{ext}	Vasc.	
Goto et al., 2004	200	[Glu] _{syn}	[Ca ²⁺] _{cyt} , [IP ₃], detailed IP ₃ R	CICR, leak from ER into cyt, SERCA	No		Ca ²⁺ , [Ca ²⁺] _{cyt}	Ca ²⁺	
MacDonald and Silva, 2013	1-200	[Glu] _{syn}	[ATP] _{ext} , [Ca ²⁺] _{cyt} , [Ca ²⁺] _{ER} , h , [IP ₃]	CICR, endogenous buffer, leak from ER into cyt, leak from ext into cyt, PMCA, SERCA	D _{ext} : [ATP] _{ext}	No	[ATP] _{ext}	Ca ²⁺	
Stamatakis and Mantzaris, 2006	1-n/a	[ATP] _{ext}	[ATP] _{ext} , [Ca ²⁺] _{cyt} , h , [IP ₃]	CICR, leak from ER into cyt, SERCA	D _{cyt} : [IP ₃], D _{ext} : [ATP] _{ext}	No	[ATP] _{ext}	Ca ²⁺	
Stamatakis and Mantzaris, 2007	1-n/a	[ATP] _{ext}	[ATP] _{ext} , [Ca ²⁺] _{cyt} , h , [IP ₃]	CICR, leak from ER into cyt, SERCA	D _{ext} : [ATP] _{ext}	No	[ATP] _{ext}	Ca ²⁺	
Höfer et al. (2002) -TYPE MODELS									
Bellinger, 2005	9	[IP ₃]	[ATP] _{ext} , [Ca ²⁺] _{cyt} , [Ca ²⁺] _{ER} , [Glu] _{ext} , [IP ₃], R	CCE, CICR, efflux via pump, Glu-dependent ER release, Glu-dependent influx, leak from ER into cyt, leak from ext into cyt, P2XR, SERCA	No		Ca ²⁺ , IP ₃ , [ATP] _{ext} , [Glu] _{ext}	Ca ²⁺	
Höfer et al., 2002	1-361	Rate of [PLC β]	[Ca ²⁺] _{cyt} , [Ca ²⁺] _{ER} , [IP ₃], R	CCE, CICR, efflux via pump, leak from ER into cyt, leak from ext into cyt, SERCA	D _{cyt} : [Ca ²⁺] _{cyt} , [IP ₃]		Ca ²⁺ , IP ₃ , [Ca ²⁺] _{cyt}	Ca ²⁺	
Li et al., 2012	3-300	Spon.	[Ca ²⁺] _{cyt} , [Ca ²⁺] _{ER} , [Ca ²⁺] _{ext} , H-H channel kinetics, [IP ₃], [K ⁺] _{cyt} , [K ⁺] _{ext} , P , R_k	CICR, efflux, efflux via pump, leak from ER into cyt, SERCA, VGCC	D _{cyt} : [Ca ²⁺] _{cyt} , [IP ₃], D _{ext} : [Ca ²⁺] _{ext} , [K ⁺] _{ext}	IP ₃	[Ca ²⁺] _{cyt}	Ca ²⁺	
De Young and Keizer (1992), Li and Rinzel (1994), and Höfer et al. (2002) -TYPE MODELS									
Edwards and Gibson, 2010	361	[ATP] _{ext}	x , [ATP] _{ext} , [Ca ²⁺] _{cyt} , h , [IP ₃]	CICR, endogenous and exogenous buffers, leak from ER into cyt, SERCA	D _{cyt} : [Ca ²⁺] _{cyt} , [IP ₃], D _{ext} : [ATP] _{ext}	IP ₃	[ATP] _{ext}	Ca ²⁺	
Ghosh et al., 2010	2	[GLC] _{ext} , [Gln] _{ext} , [Glu] _{ext}	[Ca ²⁺] _{cyt} , h , [IP ₃]	CCE, CICR, efflux, leak from ER into cyt, leak from ext into cyt, SERCA	No		IP ₃	[LAC]	Vasc.
Goldberg et al., 2010	1-100	[IP ₃]	[Ca ²⁺] _{cyt} , h , [IP ₃]	CICR, leak from ER into cyt, SERCA	No		IP ₃	[Ca ²⁺] _{cyt}	Ca ²⁺
Kazantsev, 2009	30	Spon.	[Ca ²⁺] _{cyt} , h , [IP ₃]	CCE, CICR, efflux, leak from ER into cyt, leak from ext into cyt, SERCA	No		IP ₃	[Ca ²⁺] _{cyt}	Ca ²⁺

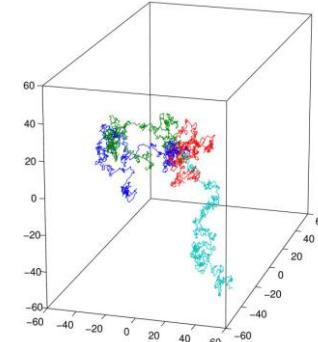


Computational methods for modeling biochemical systems



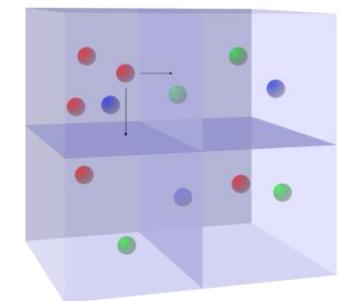
Well-mixed system

- ODE = ordinary differential equation
- SDE = stochastic differential equation
- **CME = chemical master equation**



Spatiotemporal system: reaction-diffusion

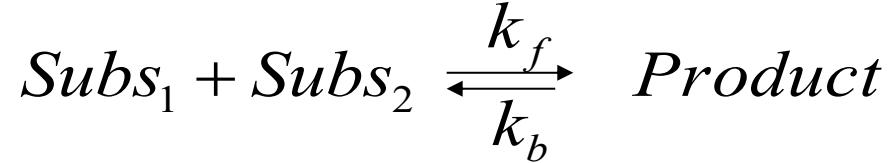
- PDE = partial differential equation
- BD = Brownian dynamics
- **RDME = reaction-diffusion master equation**



For SDE's, see: Linne et al. (2008) PLoS Comput Biol; Manninen, Linne et al. (2006) Comput., Biol. Chem.

Computational modeling of astrocyte activity: ER

Signaling pathways and interactions can be described by **mass action law**:

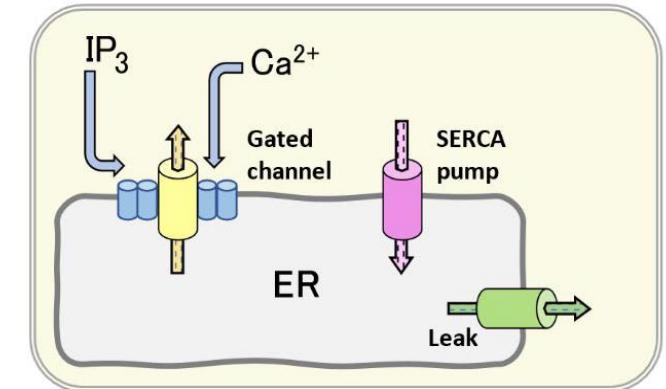


Ordinary differential equation to model concentration changes:

$$\frac{d[Product]}{dt} = k_f[Subs_1][Subs_2] - k_b[Product]$$

Ordinary differential equation (ODE) model of **endoplasmic reticulum (ER)** calcium dynamics in response to glutamate ([TUTORIAL](#)):

$$\begin{aligned}\frac{d[Ca^{2+}]_{cyt}}{dt} &= (r_{CICR} m_\infty^3 n_\infty^3 h^3 + r_{LEAK}) \\ &\times ([Ca^{2+}]_{free} - (1 + c_1)[Ca^{2+}]_{cyt}) \\ &- V_{SERCA} \frac{[Ca^{2+}]_{cyt}^2}{[Ca^{2+}]_{cyt}^2 + K_{SERCA}^2}\end{aligned}$$

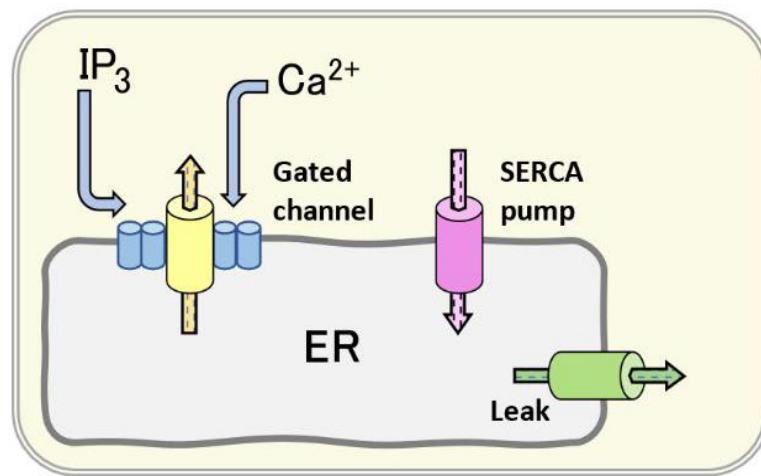


Li and Rinzel (1994) J. Theor. Biol.
Manninen, Havela, Linne (2017) Front. Neuroinf.

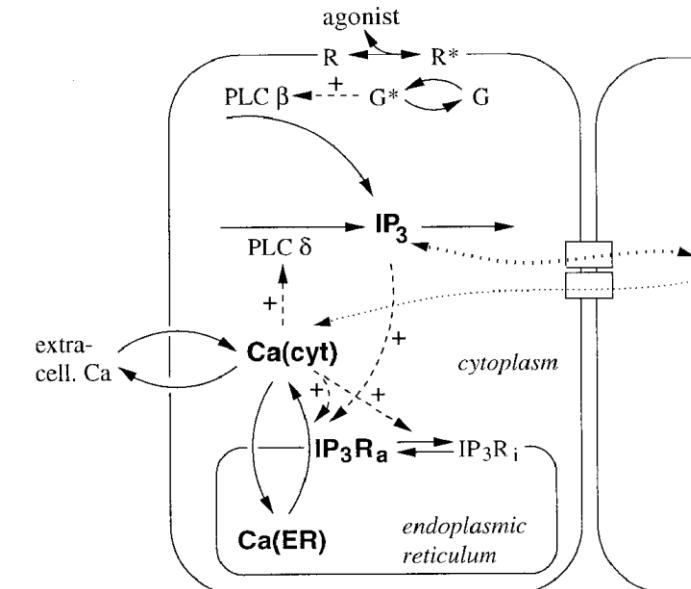
Two generic astroglial models widely used in the field

Two models are commonly used as basic building blocks of all published astrocyte models

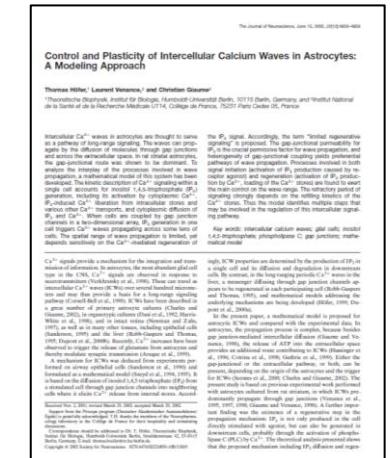
- **Li and Rinzel (1994):** Equations for IP₃-receptor mediated [Ca²⁺]_i oscillations derived from a detailed kinetic model: A Hodgkin-Huxley like formalism. *J. Theor. Biol.* (simplified from De Young and Keiser, 1992).
- **Höfer et al. (2002):** Control and plasticity of intercellular calcium waves in astrocytes: A modeling approach (*J. Neurosci.*).



Li and Rinzel (1994) *J. Theor. Biol.*



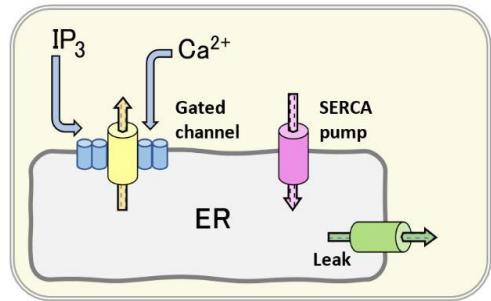
Höfer et al. (2002) *J. Neurosci.*



Two astrocyte models: Equations

Li and Rinzel (1994) type models for astrocytic Ca^{2+} :

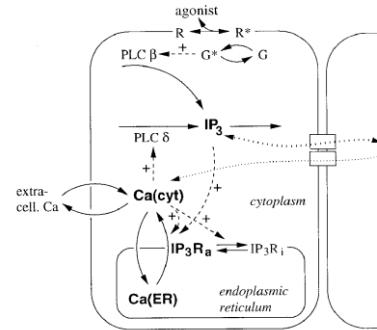
Differential equation for Ca^{2+} concentration



$$\frac{d[\text{Ca}^{2+}]_{\text{cyt}}}{dt} = (r_{\text{CICR}} m_\infty^3 n_\infty^3 h^3 + r_{\text{LEAK}}) \times ([\text{Ca}^{2+}]_{\text{free}} - (1 + c_1)[\text{Ca}^{2+}]_{\text{cyt}}) - V_{\text{SERCA}} \frac{[\text{Ca}^{2+}]_{\text{cyt}}^2}{[\text{Ca}^{2+}]_{\text{cyt}}^2 + K_{\text{SERCA}}^2}$$

Höfer et al. (2002):

Differential equation for Ca^{2+} concentration



$$\frac{\partial [\text{Ca}^{2+}]_{\text{cyt}}}{\partial t} = v_{\text{Rel}} - v_{\text{SERCA}} + v_{\text{in}} - v_{\text{out}} + D_{\text{Ca}} \left(\frac{\partial^2 [\text{Ca}^{2+}]_{\text{cyt}}}{\partial x^2} + \frac{\partial^2 [\text{Ca}^{2+}]_{\text{cyt}}}{\partial y^2} \right)$$

$$\frac{\partial [\text{Ca}^{2+}]_{\text{ER}}}{\partial t} = \beta (v_{\text{SERCA}} - v_{\text{Rel}})$$

$$\frac{\partial [\text{IP}_3]_{\text{cyt}}}{\partial t} = v_{\text{PLC}\beta} + v_{\text{PLC}\delta} - v_{\text{deg}} + D_{\text{IP}_3} \left(\frac{\partial^2 [\text{IP}_3]_{\text{cyt}}}{\partial x^2} + \frac{\partial^2 [\text{IP}_3]_{\text{cyt}}}{\partial y^2} \right)$$

$$\frac{\partial R}{\partial t} = v_{\text{rec}} - v_{\text{inact}}$$

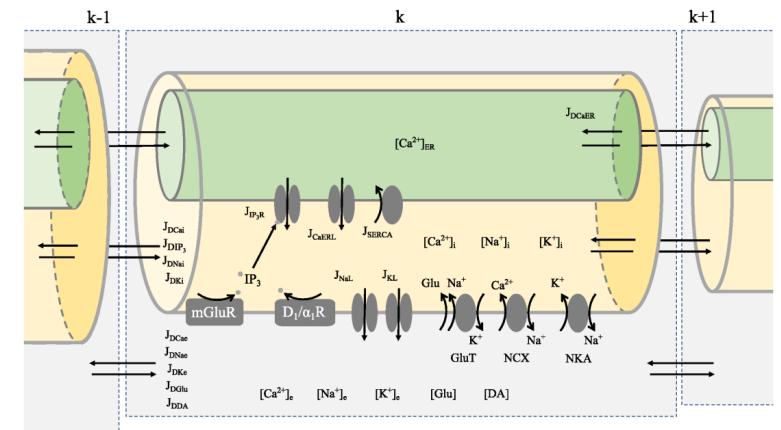
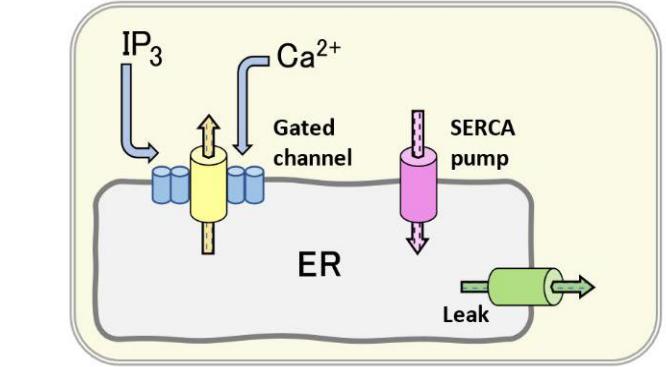
Li and Rinzel (1994) J. Theor. Biol.

Höfer et al. (2002) J. Neurosci.

Manninen, Havela, Linne (2018) Front. Comput. Neurosci.

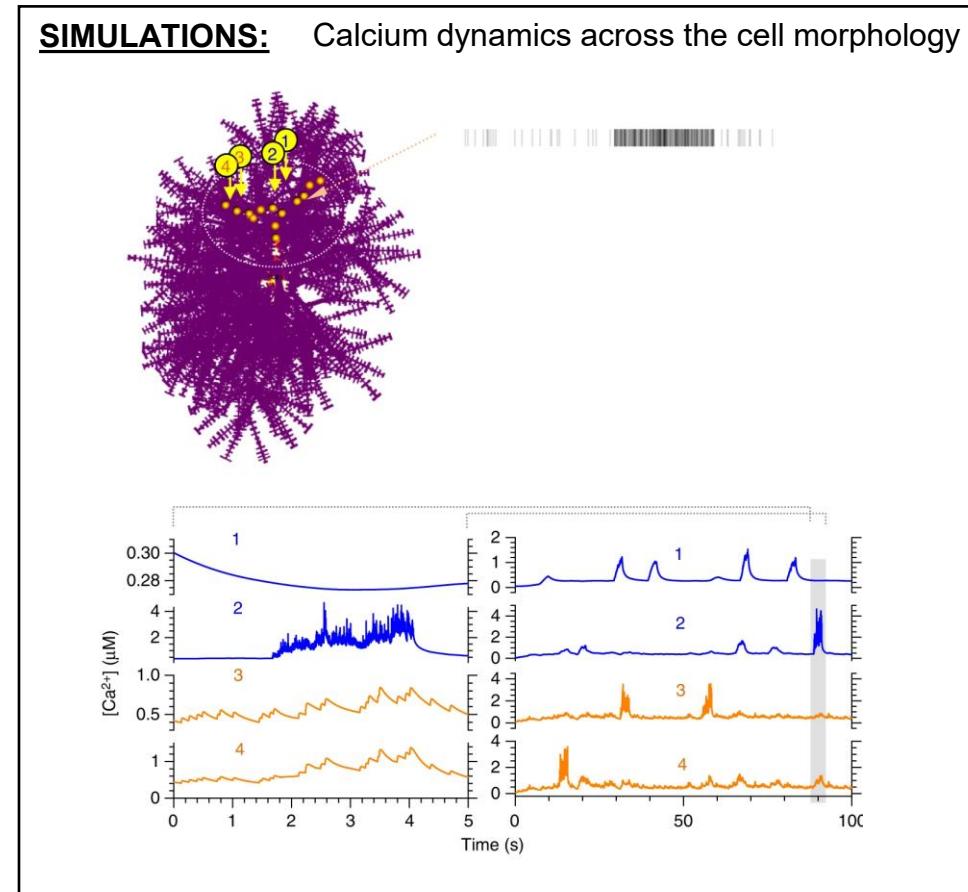
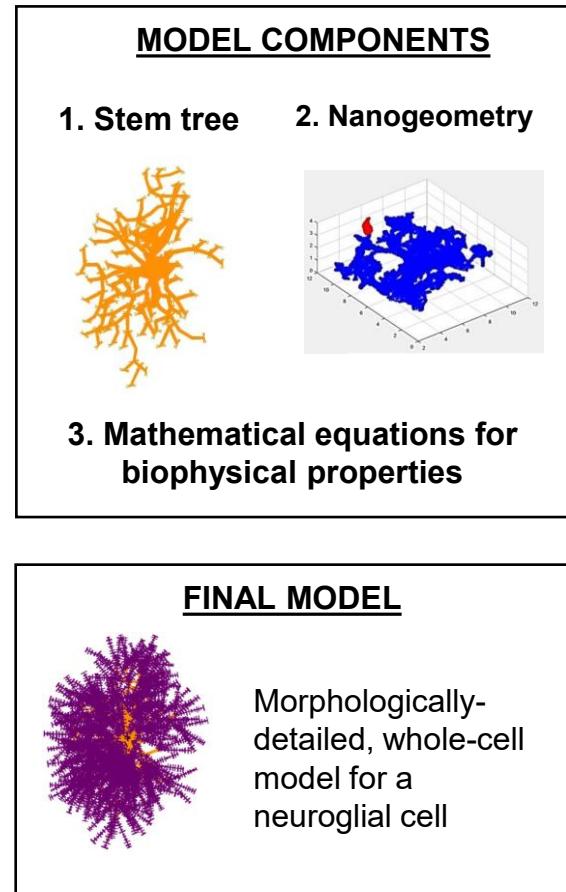
Most astrocyte models exclude cell membrane components

- Only a few models describe the **cell membrane** and its role in somatic calcium signaling.
- An **underdeveloped research area** due to:
 - Lack of experimental data from slice preparations and *in vivo* studies (most ion channel data is from cell cultures)
- Lack of suitable theoretical frameworks for modeling astrocytic ion channels
 - The Hodgkin–Huxley formalism does not apply to most astroglial ion channels, which are instead treated as **fluxes**.
 - This remains an open problem in glioscience modeling.



Bezerra, T. O., & Roque, A. C. (2024). Dopamine facilitates the response to glutamatergic inputs in astrocyte cell models. *PLoS Computational Biology*.

Reconstruction of astrocyte morphology



ASTRO + NEURON

(Morphology data from:
Neuromorpho.org)

ASTRO tool:
Savchenko et al. (2018) Nat. Commun.

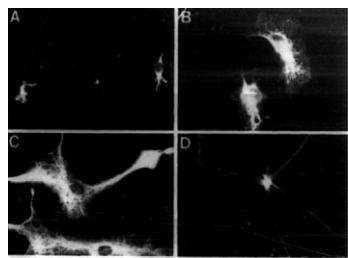
2.

Examples of published cellular level models

(by year)

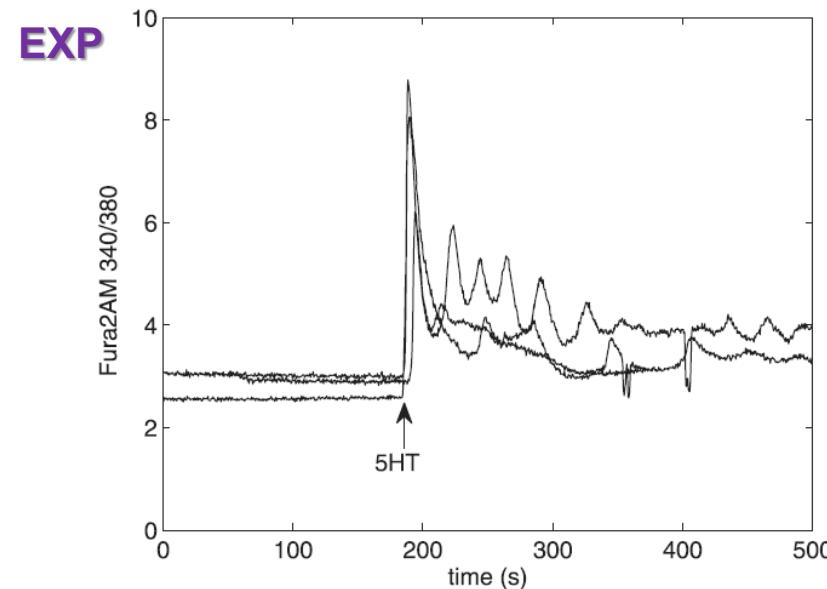
Example: Modeling astrocytic Ca^{2+} activity (both ER and cell membrane)

Acutely isolated cortical astrocytes



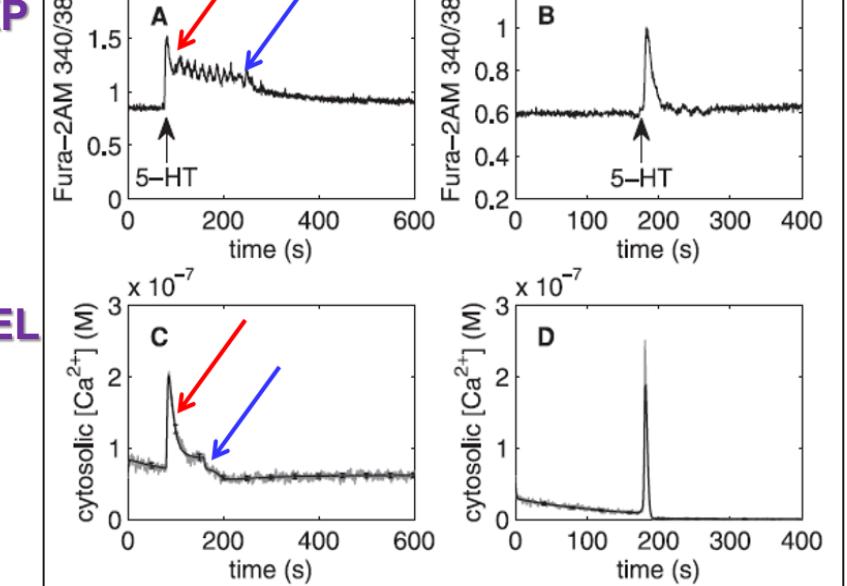
Tool:
Matlab

Model:
1-compartment
astrocyte model



Jalonens, Linne, Kimelberg et al. (1997)

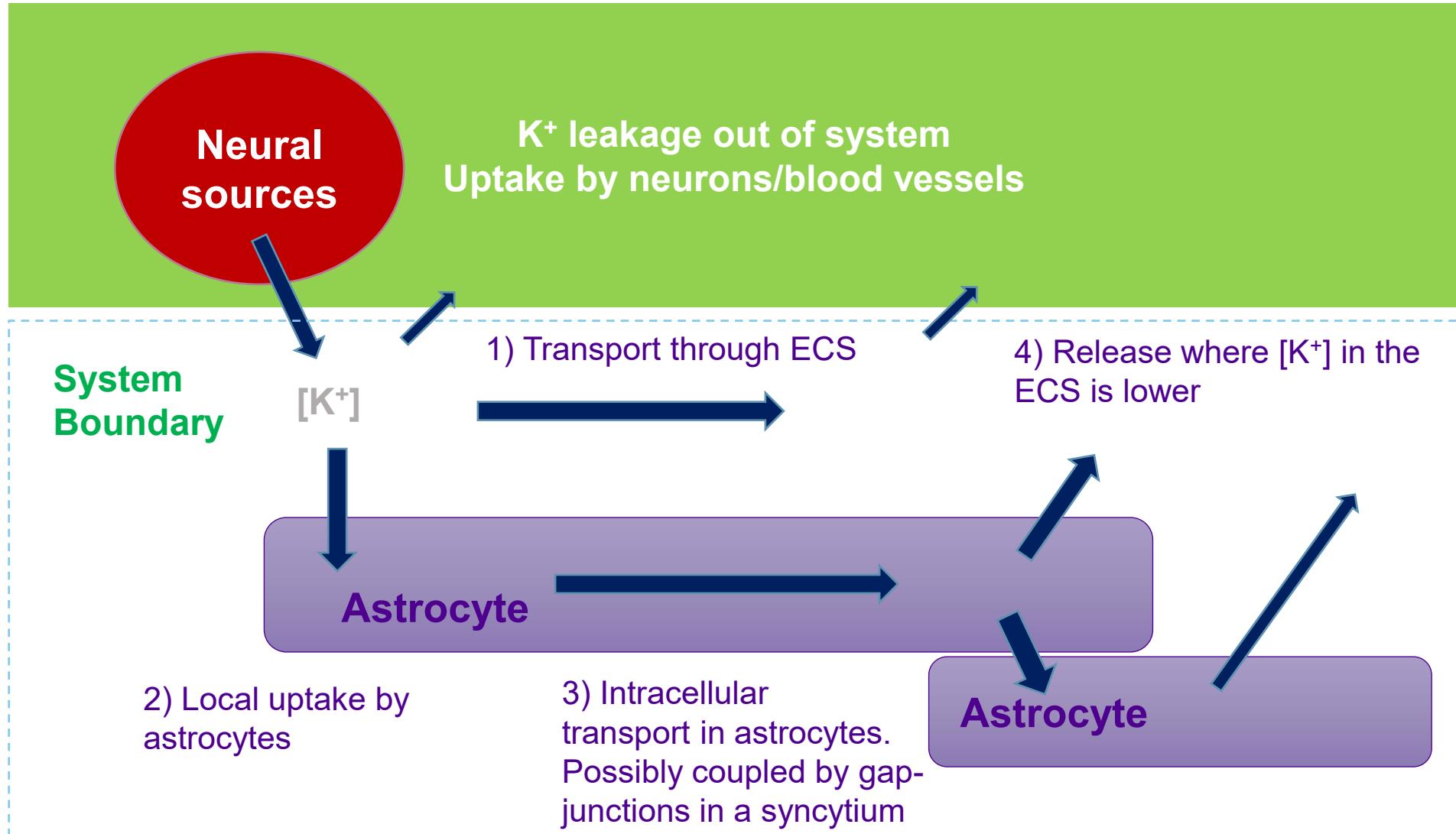
First peak due to
ER IP₃ receptor



Toivari, Linne et al. (2011)

Oscillation due to
cell membrane
 Ca^{2+} channel

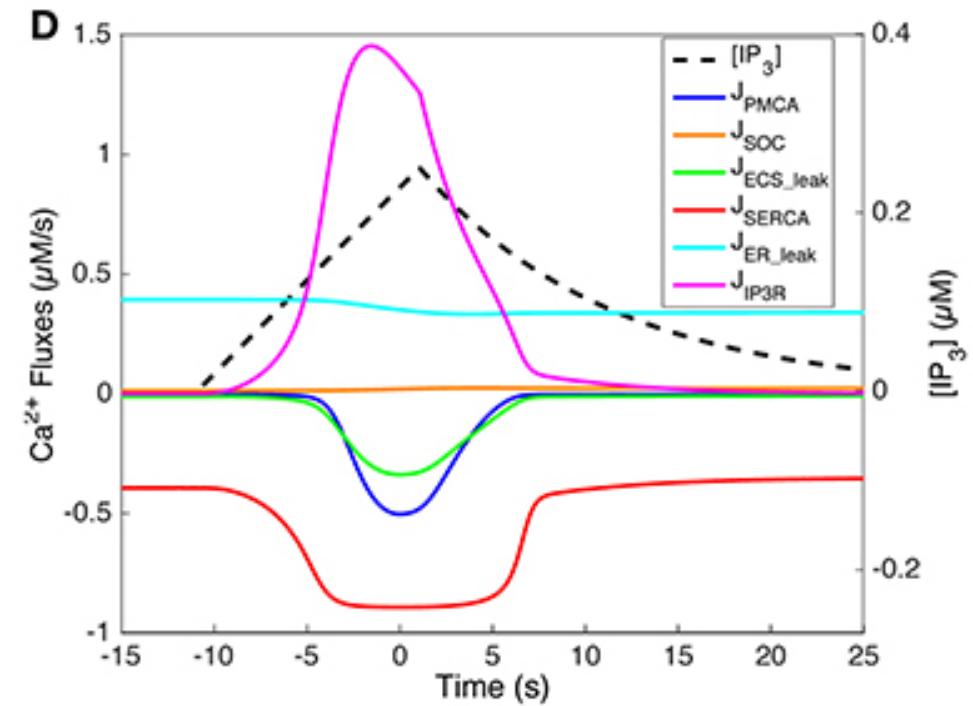
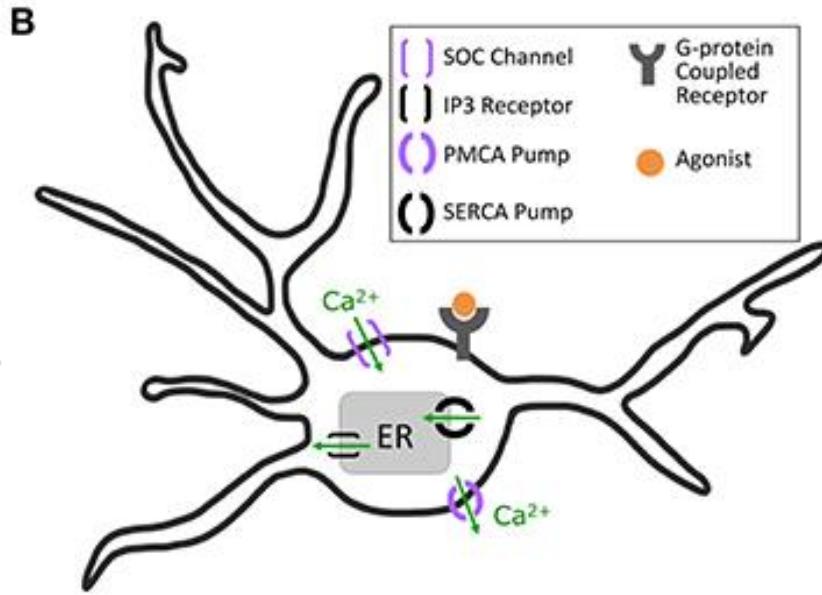
Example: Modeling spatial potassium buffering by astrocytes



Example: Modeling astrocyte activity (both ER and cell membrane)

Tool:
Matlab

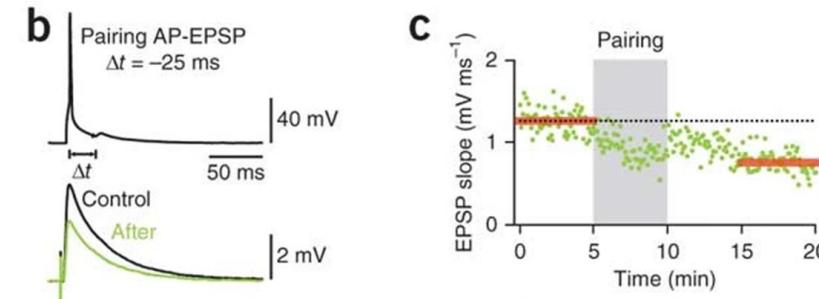
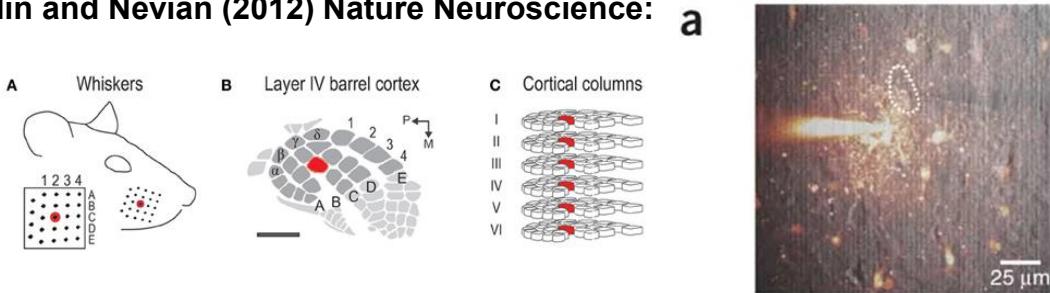
Model:
1-compartment for soma and process
(not a continuous multi-compartment spatial model)



Results: The distribution of experimentally-recorded response types depends on the **location** within an astrocyte, with **somatic** responses dominated by **Single-Peak (SP) responses** and **large and small processes** generating more **Multi-Peak responses**.

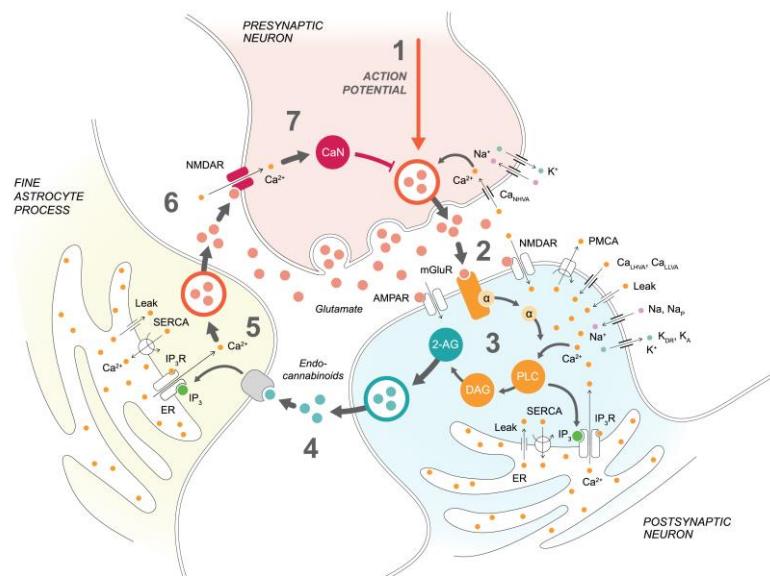
Example: Modeling neuron-astrocyte interactions in developing synapse

Min and Nevian (2012) Nature Neuroscience:



We predict the complex molecular machinery in t-LTD induction.

Schematic illustration of the synapse model:
4 compartments, Matlab, Python



Computational modeling:
(80 ODEs, 170 params, 70 refs)

The presynaptic NMDA-mediated Ca^{2+} influx measured in Eq. (3) sensors presynaptic CaN [20], and the differential equation for the presynaptic CaN concentration can be given as [6]:

$$\frac{d\text{CaN}_{\text{pres}}}{dt} = k_{\text{act}} \mu_{\text{pres}} (\text{CaN}_{\text{pres},\text{act}} - \text{CaN}_{\text{pres}}) + k_{\text{inact}} \text{CaN}_{\text{pres},\text{inact}} - k_{\text{rec}} \mu_{\text{pres}} \text{CaN}_{\text{pres}}, \quad (6)$$

where k_{act} , μ_{pres} , and k_{inact} are the rate constants for the activation and inactivation of CaN , CaN represents the presynaptic CaN concentration, and $\text{CaN}_{\text{pres},\text{act}}$ is the fraction of presynaptic CaN that is active. We now turn to the specific phase of synaptic transmission cycling, influencing the vesicle release [28–31]. We model the effect of GABA on the release probability of presynaptic vesicles by the time constant of the release and recycling, by the presynaptic terminal with the following differential equation:

$$\frac{d\text{CaN}_{\text{pres}}}{dt} = -k_{\text{rec}} \mu_{\text{pres}} \text{CaN}_{\text{pres}} + k_{\text{act}} \mu_{\text{pres}} (\text{CaN}_{\text{pres},\text{act}} - \text{CaN}_{\text{pres}}), \quad (7)$$

where CaN_{pres} is the active concentration and $\text{CaN}_{\text{pres},\text{act}}$ is the total concentration of the unspecified proteins that affect the vesicle release. μ_{pres} is the rate constant for the time constant of the presynaptic CaN . Calculations were done to model the specific phase of synaptic transmission cycling, influencing the vesicle release [28–31]. We model the effect of GABA on the release probability of presynaptic vesicles by the time constant of the release and recycling, by the presynaptic terminal with the following differential equation:

$$\frac{d\text{CaN}_{\text{pres}}}{dt} = -k_{\text{rec}} \mu_{\text{pres}} \text{CaN}_{\text{pres}} + k_{\text{act}} \mu_{\text{pres}} (\text{CaN}_{\text{pres},\text{act}} - \sum_{i=1}^n \text{CaN}_{\text{pres},i} R_{\text{pres},i}(t)), \quad (8)$$

and the diffusion equation for the fraction of released presynaptic vesicles is [27–30]:

$$\frac{\partial f_{\text{pres}}}{\partial t} = -k_{\text{rec}} \mu_{\text{pres}} f_{\text{pres}} + k_{\text{act}} \mu_{\text{pres}} (\text{CaN}_{\text{pres},\text{act}} - \sum_{i=1}^n \text{CaN}_{\text{pres},i} R_{\text{pres},i}(t)), \quad (9)$$

where the fraction (f_{pres}) which is the active concentration ($\text{CaN}_{\text{pres},\text{act}}$) divided by the total concentration ($\text{CaN}_{\text{pres},\text{act}} + \sum_{i=1}^n \text{CaN}_{\text{pres},i}$) of the protein, affects the probability of presynaptic Glu vesicle release. Note that the time constant of the presynaptic CaN is $\tau_{\text{CaN}} = 1/k_{\text{act}} \mu_{\text{pres}}$. Parameters μ_{pres} , k_{act} , and k_{inact} describe the presynaptic memory rate constant from entry to active state, the rate constant for inactivation of presynaptic CaN , and the rate constant for the recycling used in calculation of Glu release, and HIE coefficient, respectively. The time constant of the presynaptic CaN is $\tau_{\text{CaN}} = 1/k_{\text{act}} \mu_{\text{pres}}$. The time constant of the presynaptic CaN was modified from previously published Glu equation [8–10] and Glu-induced postsynaptic equation related to model [17] and is given as:

$$\frac{d\text{CaN}_{\text{pres}}}{dt} = -\mu_{\text{pres}} (\text{CaN}_{\text{pres}} - \text{CaN}_{\text{pres},\text{act}}) + \sum_{i=1}^n \text{CaN}_{\text{pres},i} P_{\text{pres},i} R_{\text{pres},i}(t) + k_{\text{act}} \mu_{\text{pres}} \text{CaN}_{\text{pres}}, \quad (10)$$

$$2A + B \xrightleftharpoons[k_{-1}]{k_1} C$$

$$\frac{d[A]}{dt} = -2v_1 + 2v_{-1}$$

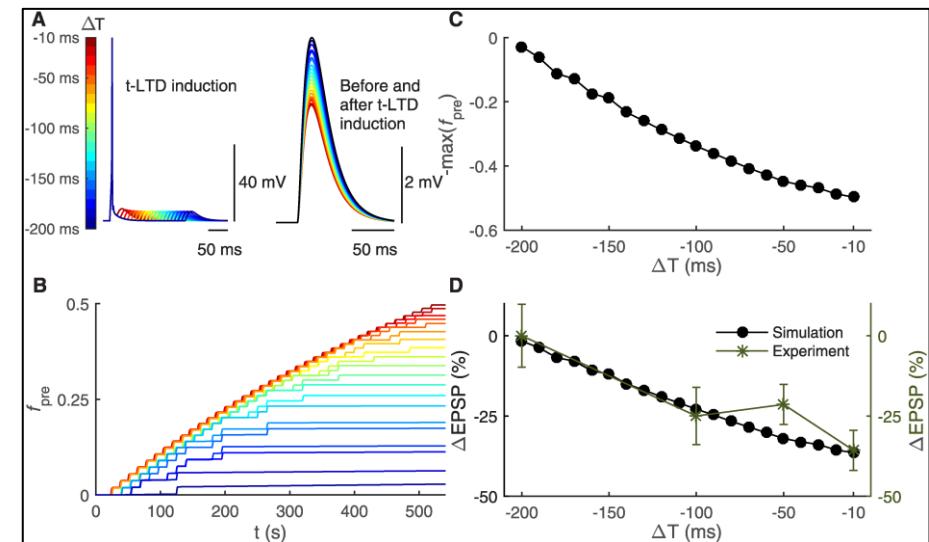
$$\frac{d[B]}{dt} = -v_1 + v_{-1}$$

$$\frac{d[C]}{dt} = v_1 - v_{-1}$$

$$v_1 = k_1[A]^2[B]$$

$$v_{-1} = k_{-1}[C]$$

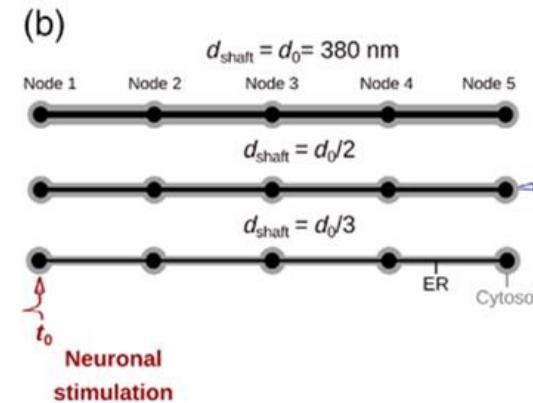
Simulations: confirming wet-lab results and predictions



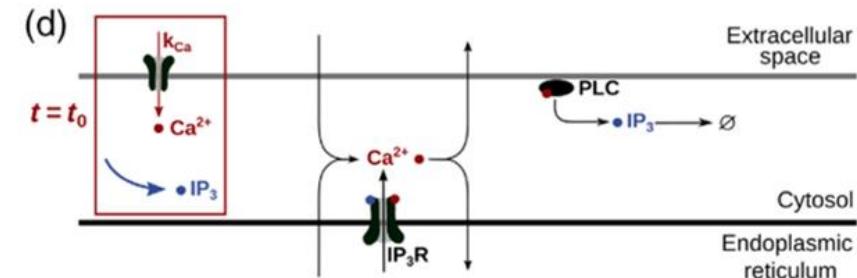
Manninen, Saudargiene, Linne (2020) Astrocyte-mediated spike-timing-dependent long-term depression modulates synaptic properties in the developing cortex. *PLoS Comput. Biol.*

Example: Control of calcium signals by astrocyte nanoscale morphology (both ER and cell membrane)

- **Study question:** The role of the nanomorphology of astrocytic processes on the spatio-temporal properties of Ca^{2+} in microdomains.
- **Simulator:** The STochastic Engine for Pathway Simulation (**STEPS**).
 - Spatial stochastic solver, based on Gillespie's Stochastic Simulation Algorithm (SSA) (Gillespie, 1977).
- **Experimental data:** Astrocyte branchlet geometries were designed with Trellis software from experimental characterization in live tissue at high spatial resolution (Arizono et al. 2020)
- **Model geometry:** Spherical structures (nodes) connected to each other via cylindrical structures (shafts). Hypo-osmotic cell swelling was modeled as increased shaft width.
- **Model components:** Both ER and cell membrane
- **Model prediction:** Swelling hinders astrocytic signal propagation.



Node/shaft geometries

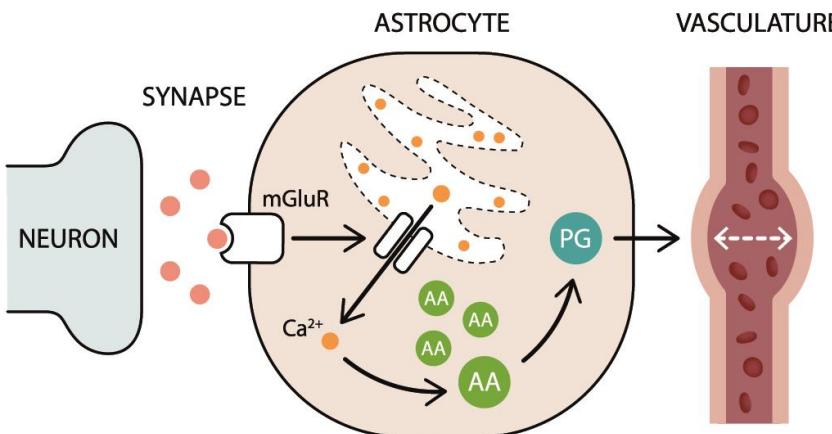


Kinetic scheme

Denizot et al. (2022) Control of Ca^{2+} signals by astrocyte nanoscale morphology at tripartite synapses. *Glia*.

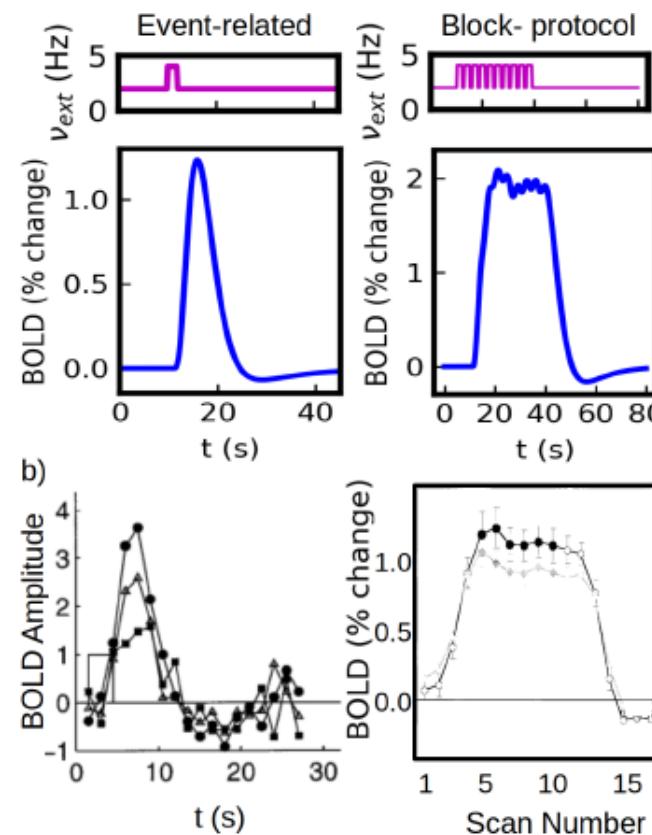
Example: Neuron-astrocyte-vasculature interactions to explain BOLD fMRI signal

A: Modified Li-Rinzel



N: Mean-field model,
10 000 neurons

V: Balloon model



THE VIRTUAL BRAIN.



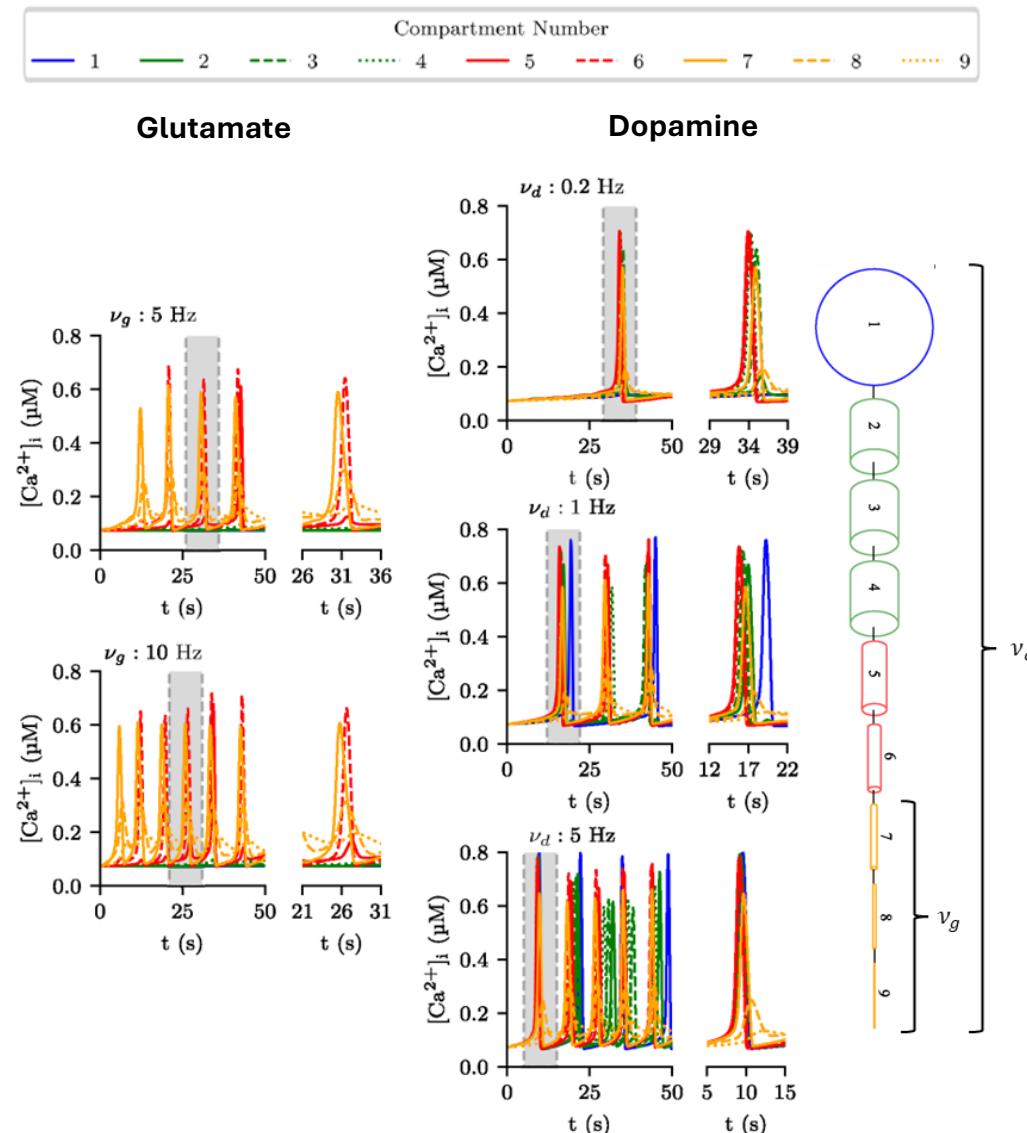
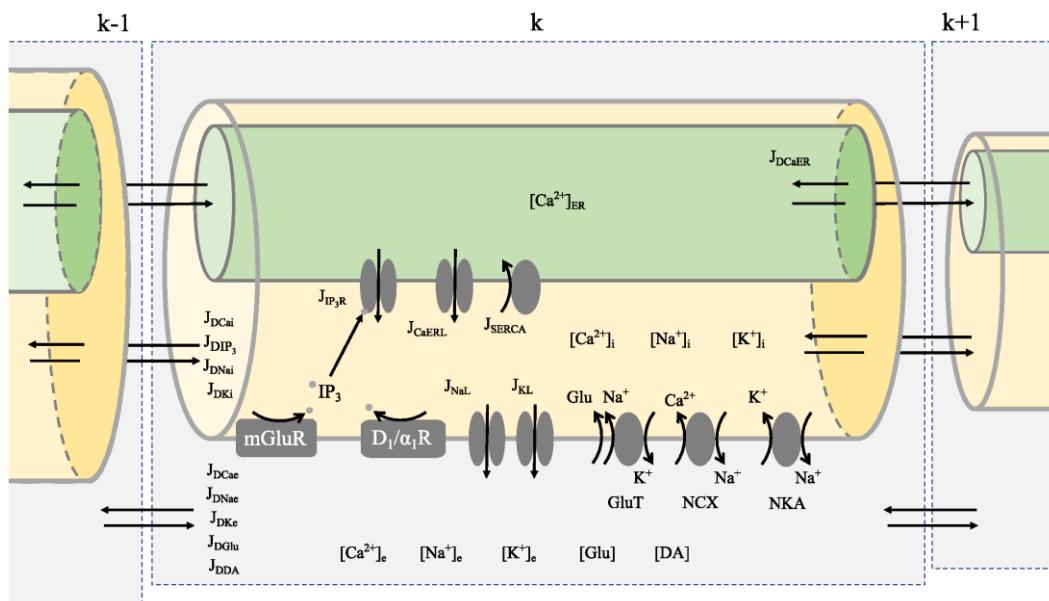
EBRAINS

We predict that
frequency modulation
of astrocytic calcium
dynamics plays a key
role in BOLD fMRI.

Example: Multi-compartmental astrocyte model (ER and cell membrane)

Compartmental modelling of astrocytes (C++):

- Interaction between local inputs (synaptic inputs, glutamate) and global stimulation (neuromodulators such as dopamine)
- Result: Global inputs enhance responses to local stimulation.



Bezerra, T. O., & Roque, A. C. (2024). Dopamine facilitates the response to glutamatergic inputs in astrocyte cell models. *PLoS Computational Biology*.

3.

Reproducibility and replicability of models

Reproducibility of neuron-astrocyte interaction models

Reproducibility means obtaining the same results using the same data and code, whereas replicability means obtaining consistent results using new data or an independent implementation.

Review, reproducibility and replicability study of existing models (up to 2018/2022)

- Astrocyte models
- Astrocyte network models (gap junction connected)
- Neuron-astrocyte interaction models
- Neuron-astrocyte network models

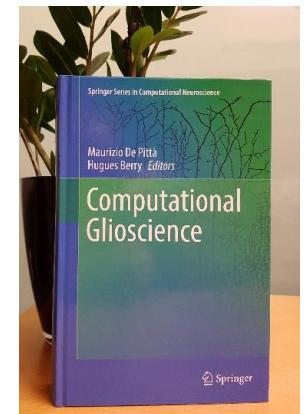
Manninen, Havela, Linne (2018) *Front. Comput. Neurosci.*

Manninen, Linne et al. (2018) *Front. Neuroinf.*

Manninen, Havela, Linne (2019) *Computational Glioscience Book (book chapter)*

Linne et al. (2022) *Computational Neuroscience Book (book chapter)*

Manninen, Acimovic, Linne (2023) (*Neuroinformatics*)



Model reproducibility

- Of the single cell models we have studied, only a few models can be easily reproduced.
- Several publications lack crucial details in how the model is presented.
- Only a few models are available in model databases.
- **Models describing the same physiological phenomena are not comparable to each other.**

Model	Reproducibility
Lavrentovich and Hemkin, 2008	+++
Di Garbo et al., 2007	+++
Riera et al., 2011a,b	-/+/+++
Nadkarni and Jung, 2003	-/++
De Pitta et al., 2009	++
Dupont et al., 2011	-/++
Silchenko and Tass, 2008	-
Wade et al., 2012	-
Wade et al., 2011	-

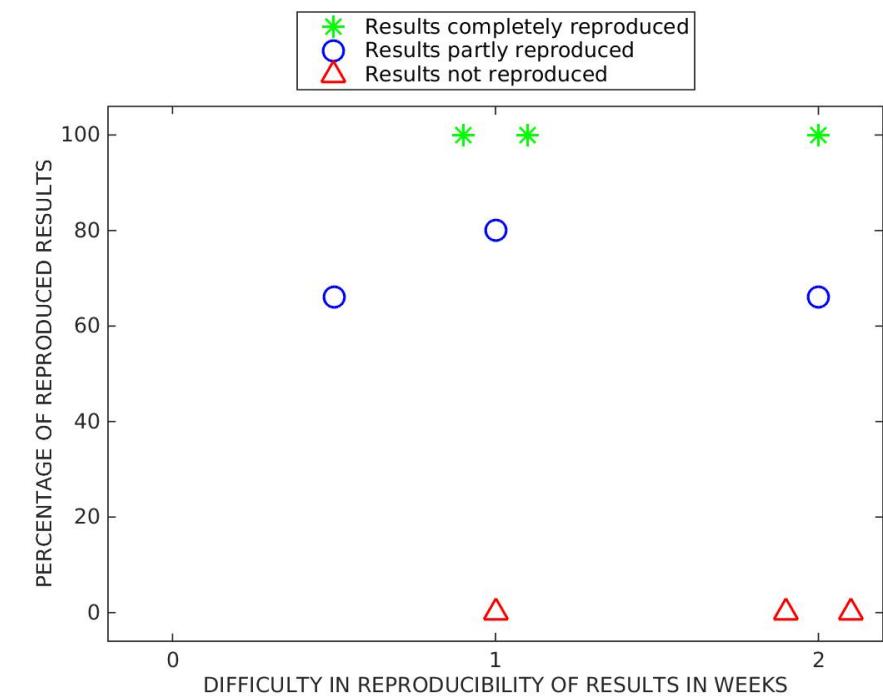
Manninen, Havela, Linne (2017) Reproducibility and Comparability of Computational Models for Astrocyte Calcium Excitability. *Frontiers in Neuroinformatics*.

Models used in reproducibility studies

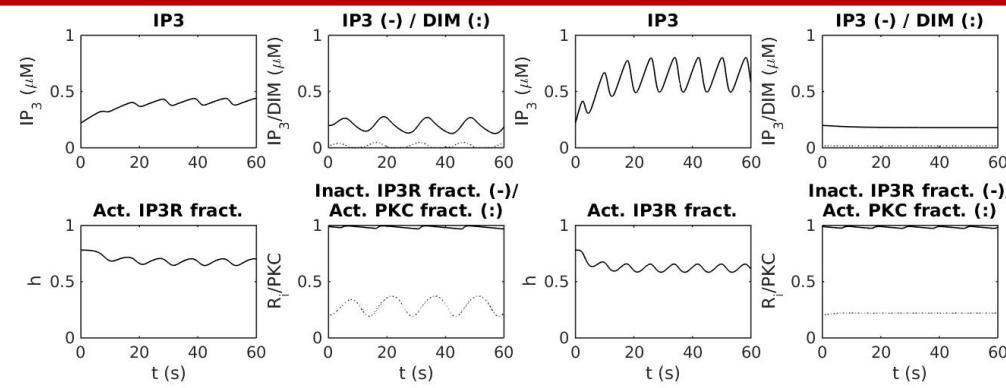
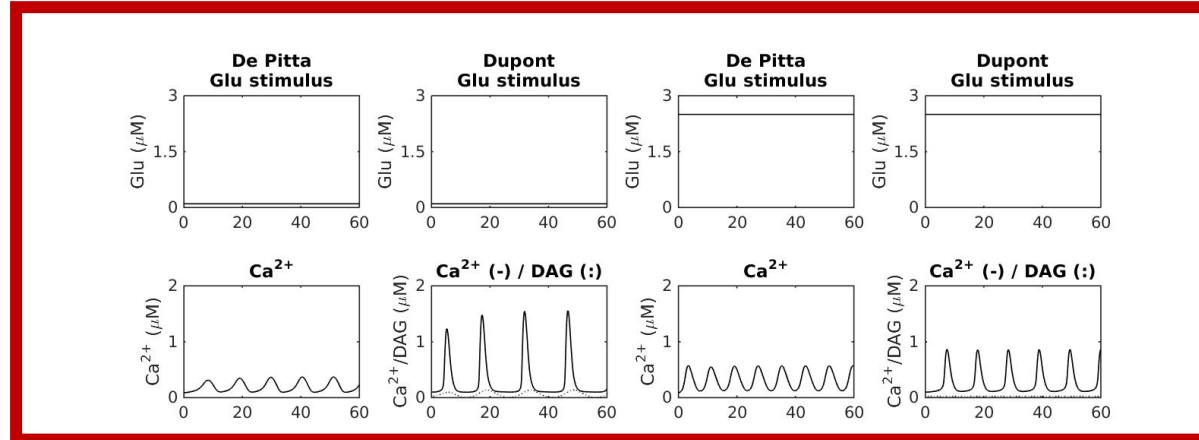
Model	Online Orig/us	Language Orig/Oth/us	Errors in equations/parameters
Lavrentovich and Hemkin, 2008	No/ModelDB	Fortran/XPP/Python	Authors fixed all errors in corrigendum
Di Garbo et al., 2007	No	Not given	We did not find any errors
Riera et al., 2011a,b	No/ModelDB	MATLAB/Python	We fixed errors we found
Nadkarni and Jung, 2003	No	Not given	We were not able to fix all errors
De Pitta et al., 2009	No/ModelDB	Not given/Python	We were not able to fix errors
Dupont et al., 2011	No/ModelDB	MATLAB/Python	We were not able to fix errors
Silchenko and Tass, 2008	No	Not given	Not all information given
Wade et al., 2012	No	MATLAB	We were not able to fix errors
Wade et al., 2011	No	MATLAB	Not all information given

Reproducibility of model behavior

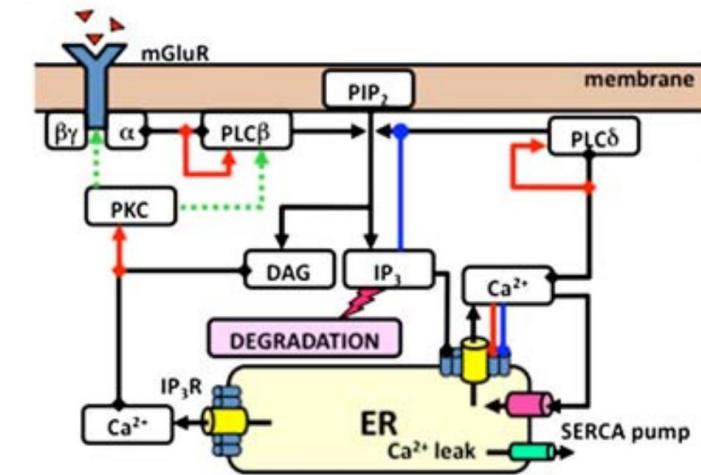
Model	Reproducibility
Lavrentovich and Hemkin, 2008	+++
Di Garbo et al., 2007	+++
Riera et al., 2011a,b	-/+/+++
Nadkarni and Jung, 2003	-/++
De Pitta et al., 2009	++
Dupont et al., 2011	-/++
Silchenko and Tass, 2008	-
Wade et al., 2012	-
Wade et al., 2011	-



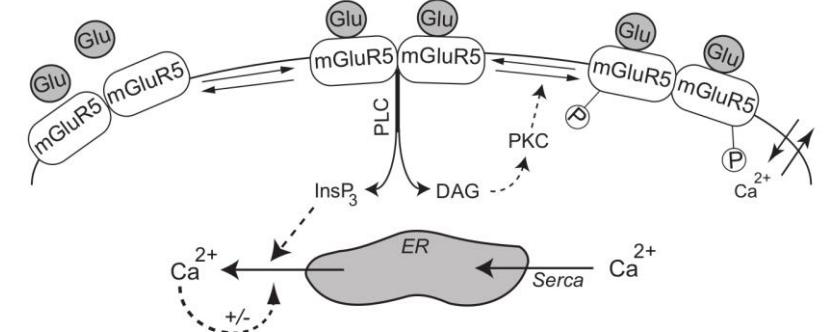
Comparability of neuron-astrocyte interaction models



Manninen, Havela, Linne (2017) *Front. Neuroinform.*



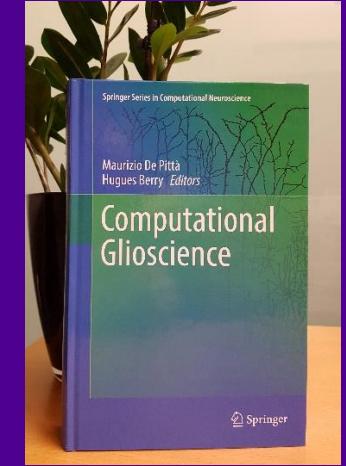
De Pitta et al. (2009) *J. Biol. Phys.*



Dupont et al. (2011) *Biochimie*

Conclusions from our reproducibility studies

- Astrocyte models are
 - less developed than neuronal models.
 - developed from a small set of previously published models.
 - developed based on data measured from cells other than astrocytes.
 - developed for one certain case and not always applicable to other cases.
 - often not available in model databases.
 - rarely reproducible.



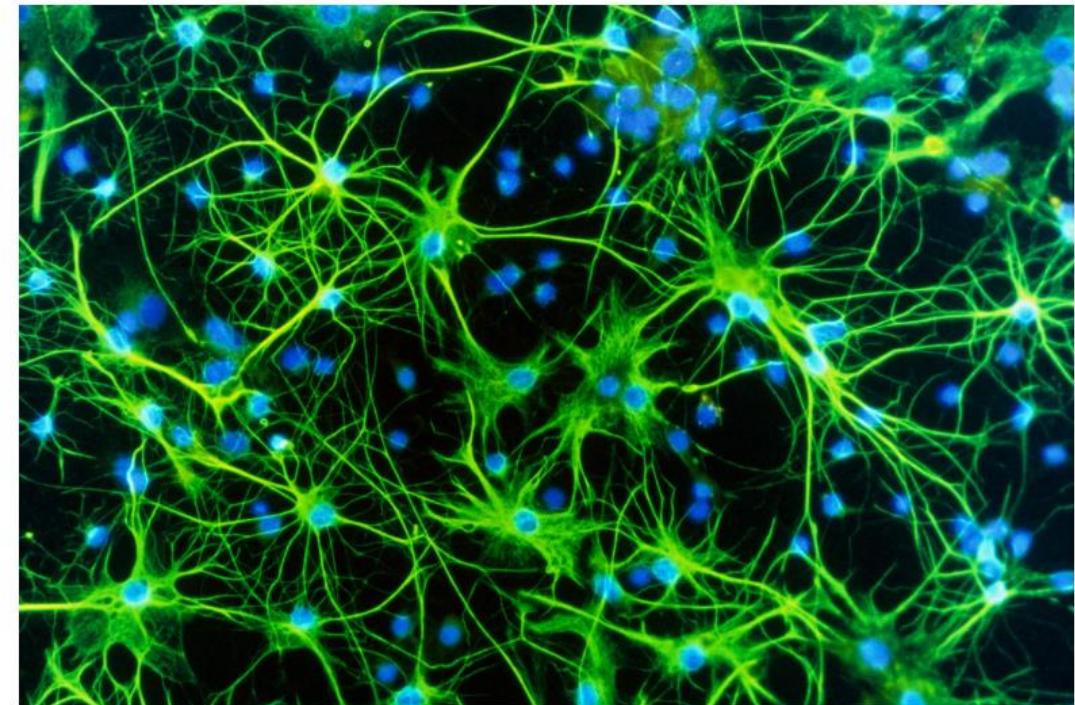
Feature article by science writer Allison Abbott (Nature, December 1, 2025)

NEWS FEATURE | 03 December 2025

The ‘silent’ brain cells that shape our behaviour, memory and health

Astrocytes make up one-quarter of the brain, but researchers are only now realizing their true value.

By Alison Abbott



Under a light microscope, brain cells called astrocytes look star-shaped. Credit: Nancy Kedersha/Science Photo Library

For decades, neuroscientists focused almost exclusively on only half of the cells in the brain. [Neurons](#) were the main players, they thought, and everything else was made up of uninteresting [support systems](#).

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Take-home message

Astrocyte modeling is still in early stages compared to neurons.

- Most models rely on limited early models and non-astrocyte data.
- Capturing Ca^{2+} dynamics requires detailed knowledge of complex intracellular mechanisms, but astrocyte-specific data are scarce.
- **Challenge 1:** How can highly complex astrocyte morphology be handled in single-cell modeling tools?
- **Challenge 2:** What can serve as a “ground truth” benchmark for astrocytes, analogous to the neuronal action potential? Calcium?
- **Challenge 3:** Which computational strategies can effectively simplify astrocyte modeling?

Advancing computational tools is key to understanding astrocytes' roles in neural processes.