Modelling astrocyte functions with NEST

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What are glial cells?

Glial cells are **non-neuronal cells** in the central and peripheral nervous system that contribute to various functions in the developing and adult brain.

Types of glial cells:
Schwann cells – Axonal conduction
Oligodendrocytes – Axonal conduction
Astrocytes – Neuronal and vascular control
Microglia - Maintenance
Ependymal cells – Cerebrospinal fluid control
Radial glia – Guidance of neuronal development
NG2 glia – ”Multipotent” cells

Discovered by a pathologist Rudolf Virchow in 1856.

Glial complexity and number increases with the overall complexity of the nervous system.

Kettenmann & Ransom, 2013
Kettenmann & Verkhartsky, 2013

Astrocytes have important roles in many brain functions

Pre- and postnatal development

- Initiate neurogenesis
- Structure the brain
- Maturate and prune synapses

Energy metabolism

- Support blood-brain barrier functions
- Control glucose
- Provide nutrients

Homeostasis and survival

- Maintain extracellular ionic balance
- Take up neuro-transmitters

Neurology and neuropsychiatry diseases

- Epilepsy
- Schizophrenia
- Parkinson's disease
- Dementias, Alzheimer's

Plasticity learning memory cognition

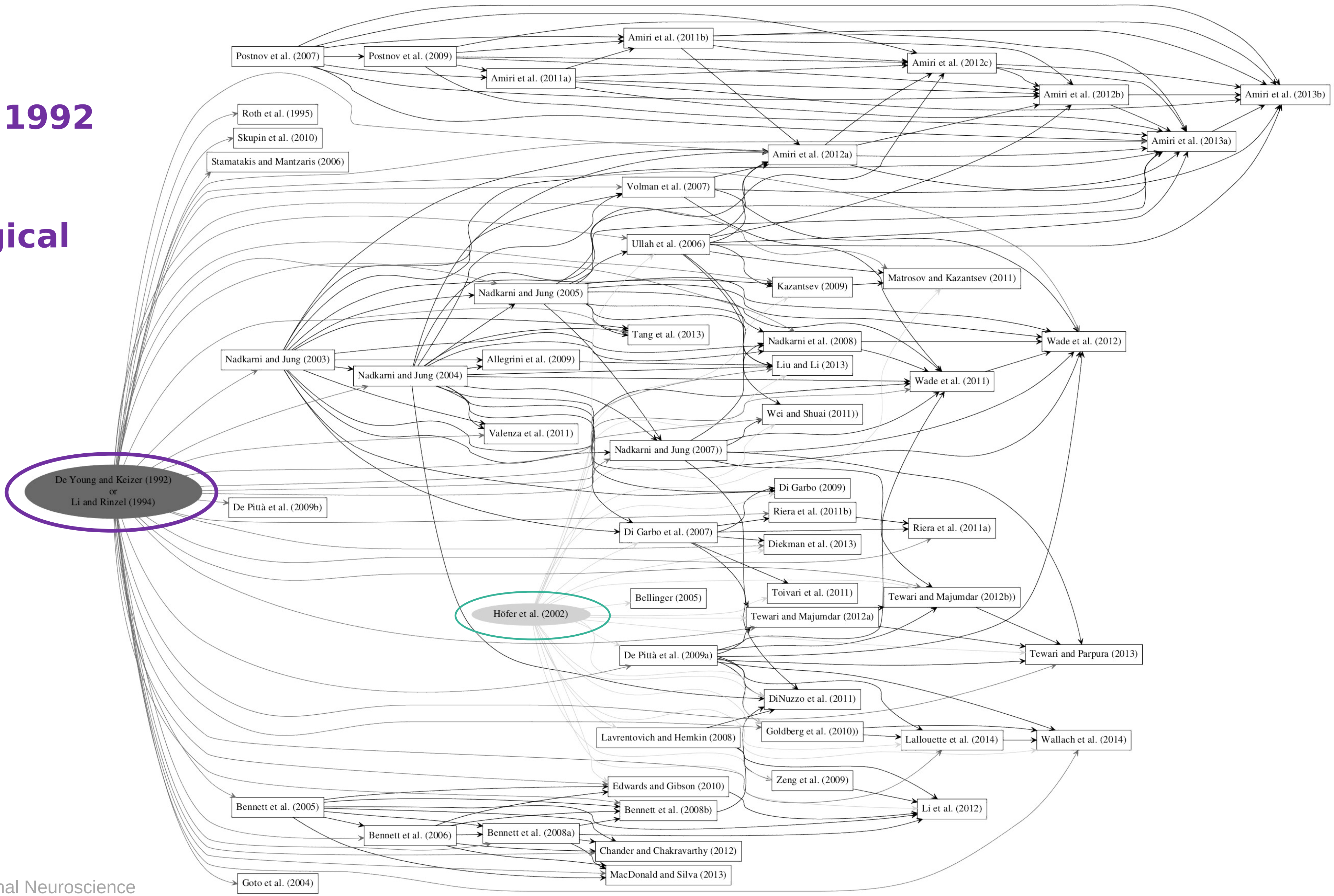
- Synaptic transmission ~~(controversy)~~
- Synaptic plasticity ~~(controversy)~~

Linne (2024) Current Opinion in Neurobiology
De Ceglia et al. (2023) Nature
Bazargani & Attwell (2016) Nature Neuroscience

Tampere University

De Young and Keizer 1992
Li and Rinzel 1994

(more phenomenological than Höfer et al.)



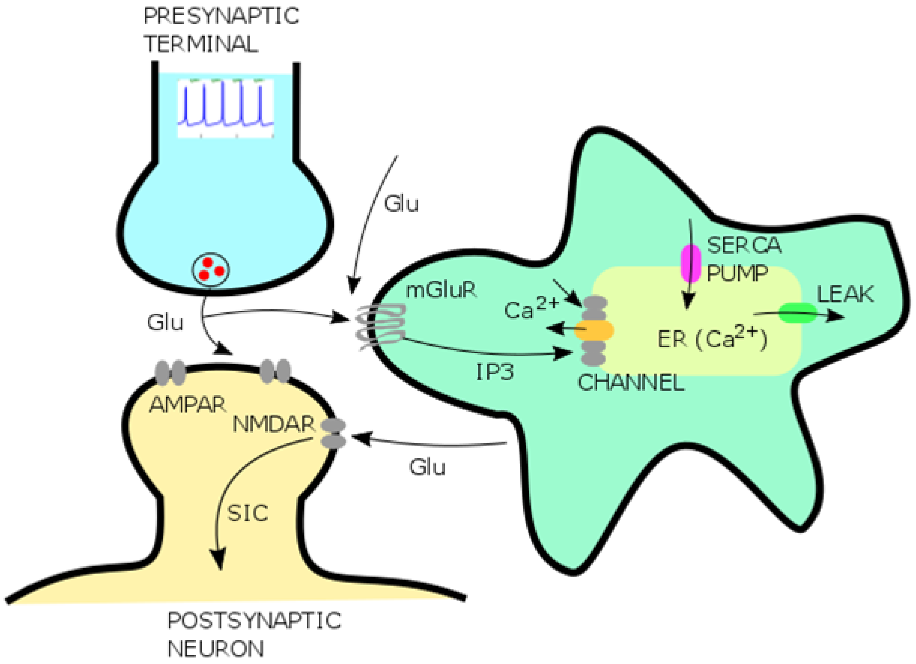
Höfer et al. 2002

(more biophysical)

Linne et al. (2018) Frontiers in Computational Neuroscience
Manninen et al. (2023) Neuroinformatics

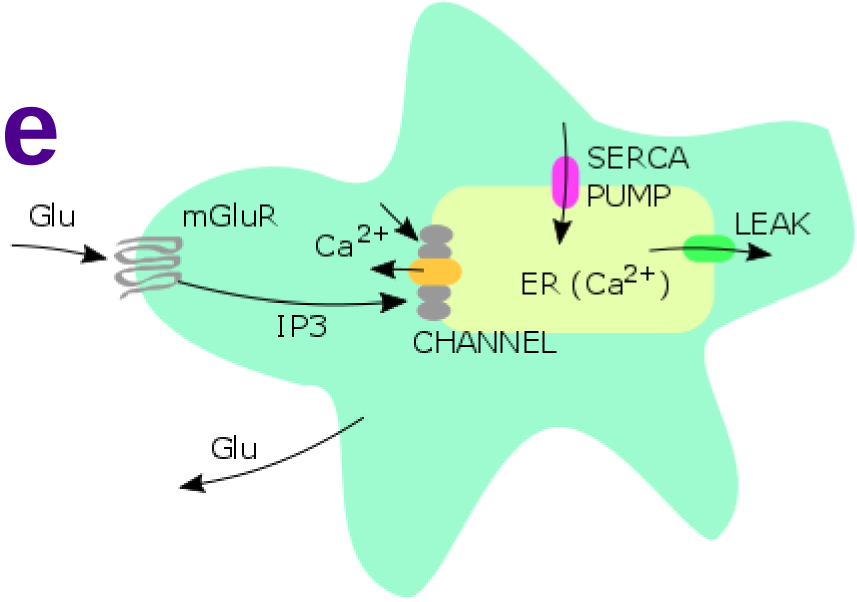
Modelling Slow Inward Current (SIC)

- Modelled astrocyte components (dynamic states):
  - Cytosolic calcium $[\mathrm{Ca}^{2+}]_{\mathrm{c}}(t)$
  - Free Inositol Trisphosphate (IP3) $[IP3](t)$
  - Fraction of open IP3 receptor channels h
- The total amount of calcium in astrocyte is fixed
- SIC is given as a logarithmic transformation from a scaled $[\mathrm{Ca}^{2+}]_{\mathrm{c}}(t)$



See Refs.
Young&Keizer (1992) Proceedings of National Academy of Sciences,
Li&Rinzel (1994) Journal of Theoretical Biology,
Nadkarni&Jung (2003) Physical Review Letters

Calcium dynamics in astrocyte



IP3 concentration: $$\frac{d[\mathrm{IP3}](t)}{dt} = \frac{[\mathrm{IP3}]_0 - [\mathrm{IP3}](t)}{\tau_{IP3}} + r_{IP3}\delta(t - t_{spike})$$

Cytosolic calcium: $$\frac{d[\mathrm{Ca}^{2+}]_\mathrm{c}(t)}{dt} = -J_\mathrm{SERCA} + J_\mathrm{LEAK} + J_\mathrm{CICR}$$

Calcium currents: $$J_\mathrm{SERCA} = v_{SERCA}^{max}\frac{[\mathrm{Ca}^{2+}]_\mathrm{c}^2(t)}{[\mathrm{Ca}^{2+}]_\mathrm{c}^2(t) + K_{SERCA}^2}$$

$$J_\mathrm{LEAK} = v_{LEAK}([\mathrm{Ca}^{2+}]_\mathrm{ER} - [\mathrm{Ca}^{2+}]_\mathrm{c}(t))$$

$$J_\mathrm{CICR} = v_{CICR}n_\infty^3 m_\infty^3 h^3(t)([\mathrm{Ca}^{2+}]_\mathrm{ER} - [\mathrm{Ca}^{2+}]_\mathrm{c}(t))$$

IP3R gating variable: $$\frac{dh}{dt} = \alpha(1-h) - \beta h$$

Intermediate variables: $$m_\infty = \frac{[\mathrm{IP3}](t)}{[\mathrm{IP3}](t) + K_{IP3,1}} \qquad n_\infty = \frac{[\mathrm{Ca}^{2+}]_\mathrm{c}(t)}{[\mathrm{Ca}^{2+}]_\mathrm{c}(t) + K_{act}}$$

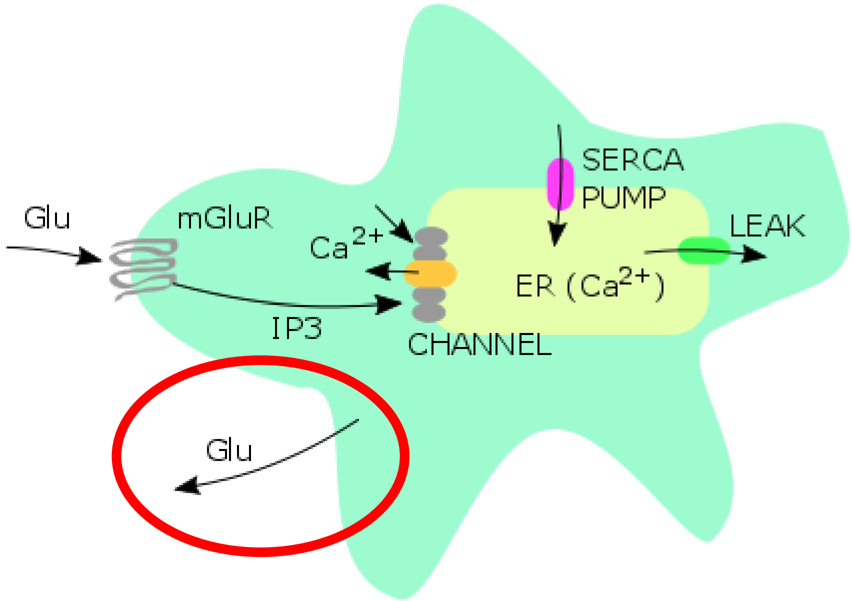
$$\beta = v_{IP3R}[\mathrm{Ca}^{2+}]_\mathrm{c}(t) \qquad \alpha = v_{IP3R}K_{inh}\frac{[\mathrm{IP3}](t) + K_{IP3,1}}{[\mathrm{IP3}](t) + K_{IP3,2}}$$

SIC to postsynaptic neuron

SIC from astrocyte to postsynaptic neuron is modelled as a logarithm of a scaled calcium (Nadkarni&Jung, 2003):

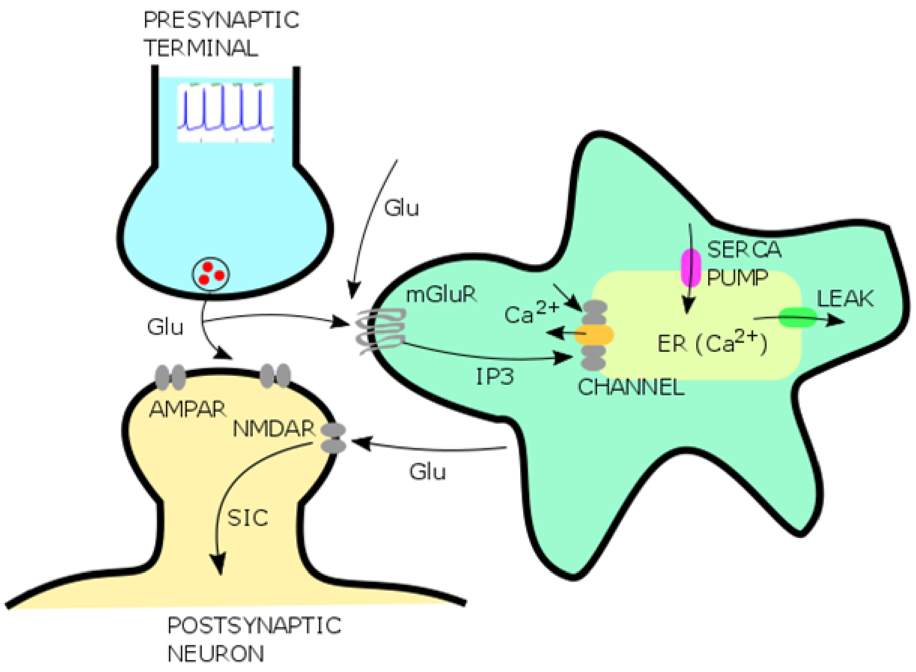
$$I^{\mathrm{SIC}} = a\Theta(\ln(y))\ln(y)$$

$$y = \frac{[\mathrm{Ca}^{2+}]_{\mathrm{c}}(t) - b}{1\ \mathrm{nM}}$$



Model in brief

1)Presynaptic excitatory spike releases glutamate which activates free IP3 production in astrocyte.
2)IP3 opens SERCA channel which releases calcium from ER to cytosol
3)Cytosolic calcium induces glutamate release to perisynaptic areas of the postsynpatic neuron.
4)Perisynaptic NMDA receptors are activated and SIC is generated.



Notebooks outlook

1) astrocyte_single.ipynb - calcium dynamics in astrocyte
2) astrocyte_interaction.ipynb - single astrocyte interacting with pre- and postsynaptic neurons
3) astrocyte_small_network.ipynb - exploring different coupling rules
4) astrocyte_brunel.ipynb - balanced network simulation with astrocytes