Synapses in distress

Differential sensitivity to energy deprivation at the tripartite synapse

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Joint work with: Hil Meijer (UT), Stephan van Gils (UT), Michel van Putten (UT), Christine Rose (HHU Düsseldorf)

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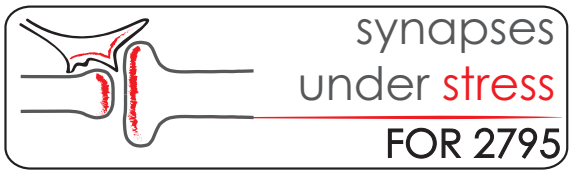
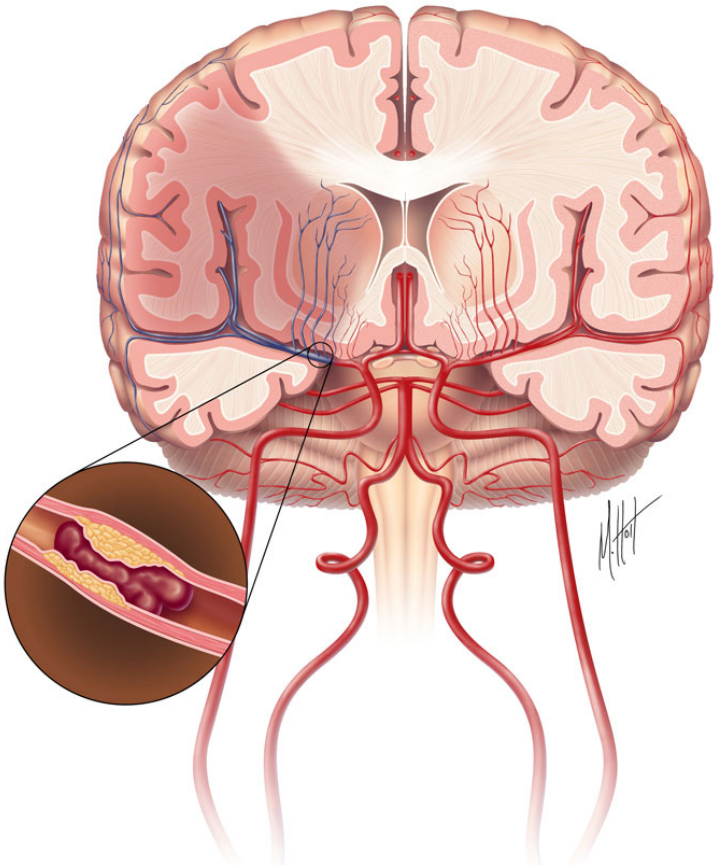
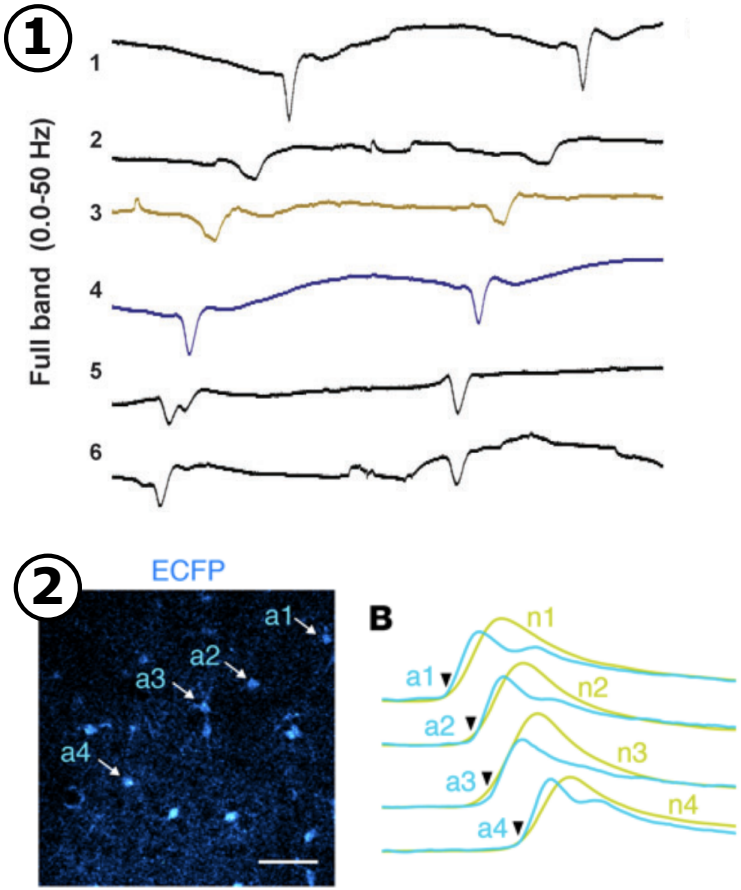


Ischemic stroke



Stroke: core vs penumbra

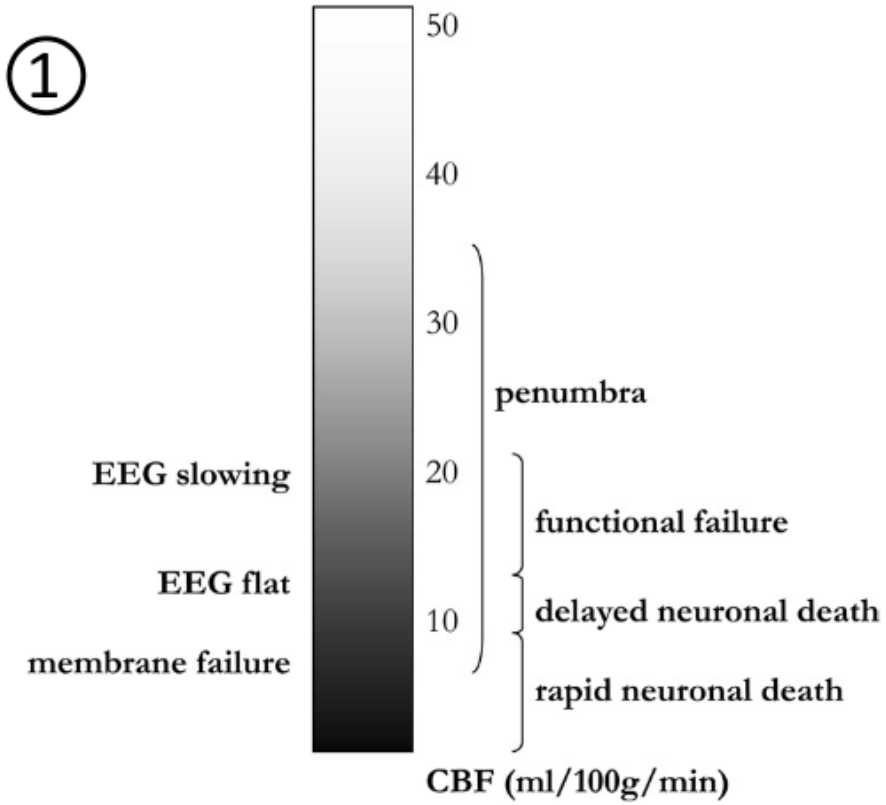


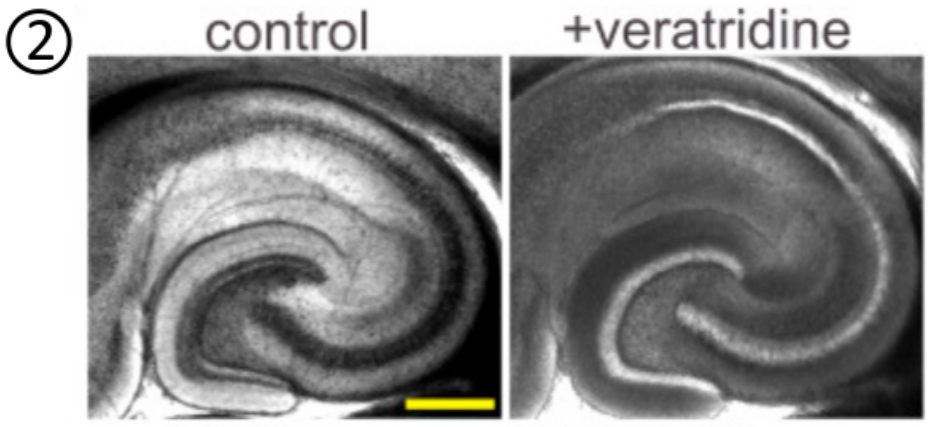
Clinical pathophysiology: SD/PID

[1] Hartings et al., *JCBFM* (2017)

[2] Rakers and Petzold, *J. Clin. Invest.* (2017)

Clinical outcome





Cell swelling accompanies damage

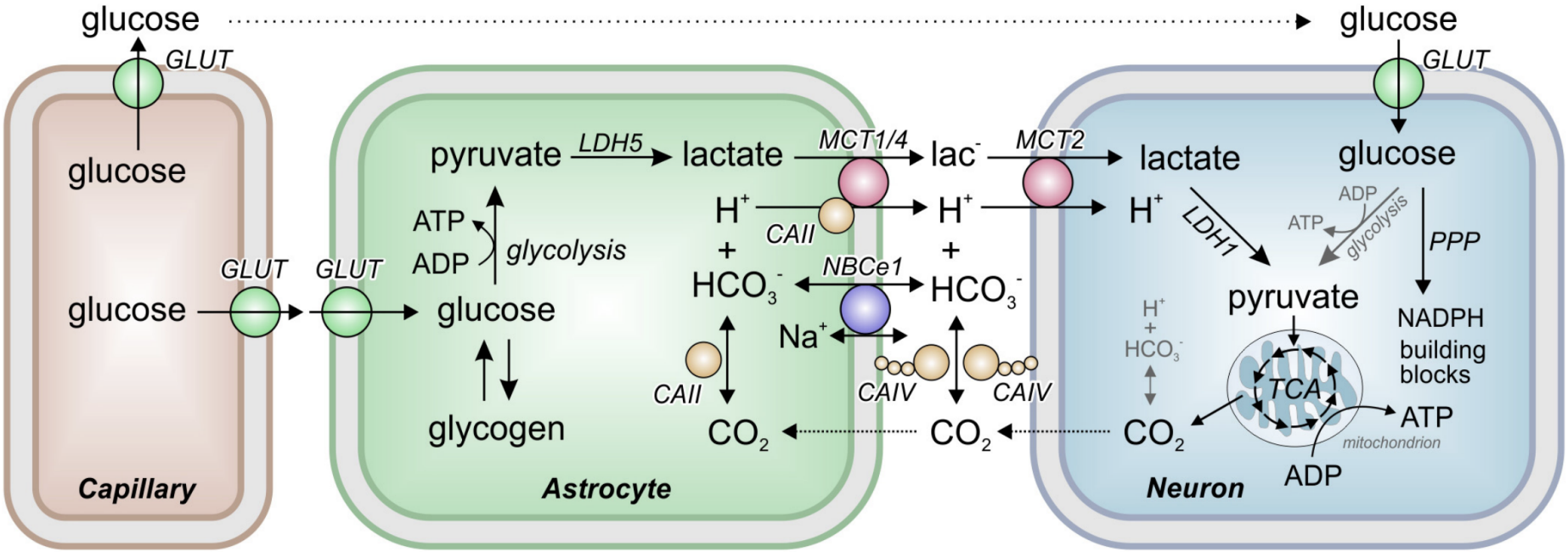
Functional failure precedes neuronal death

[1] Hofmeijer and van Putten, *Stroke 43* (2012)

[2] Rungta et al., *Cell 161* (2015)

Key question: Can we qualify/quantify the point-of-no-return?
Idea: Investigate at synaptic level!

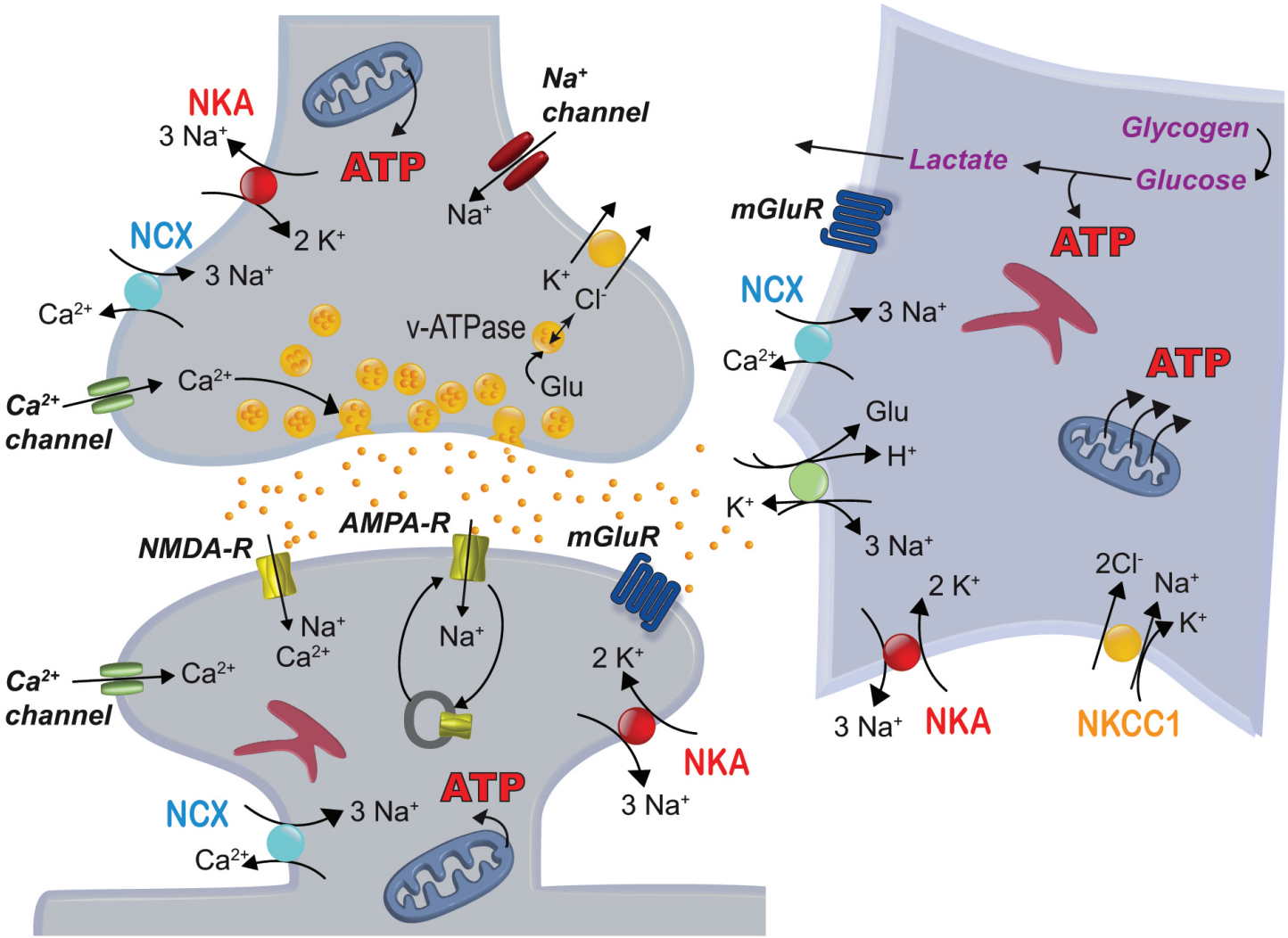
Energy dynamics at the synapse



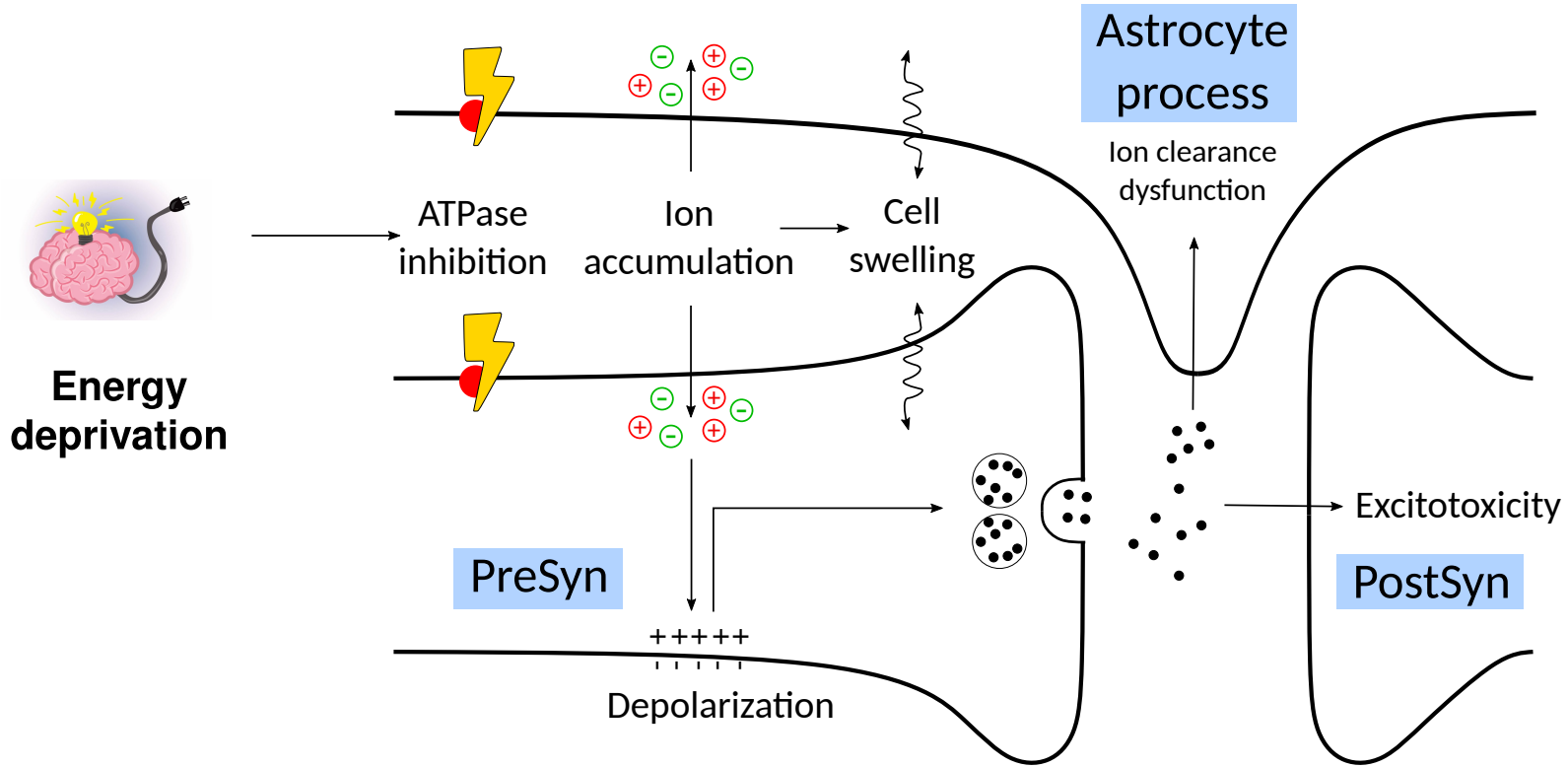
Takeaway: Investigate ion dynamics at the tripartite synapse.

[1] Deitmer et al., *Front. Neurosci.* (2019)

Ion dynamics at the tripartite synapse



Ischemic pathophysiology

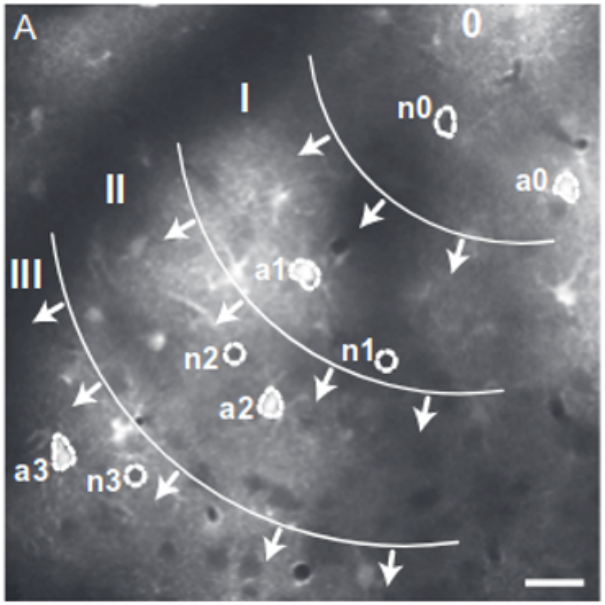


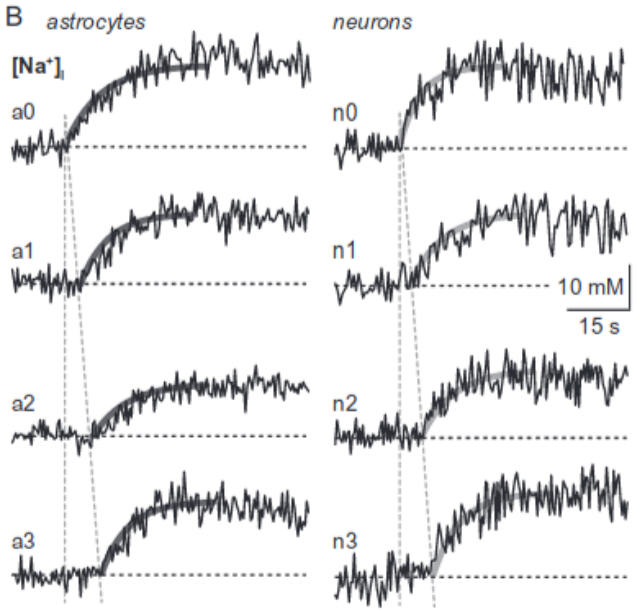
Previous work

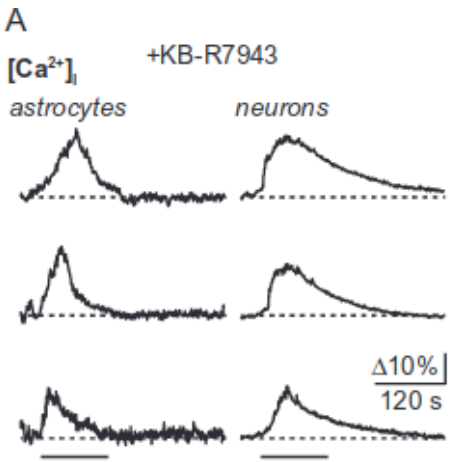
- Neuron-astrocyte interactions: Somjen et al. (2002); Kager et al. (2007); Østby et al. (2009); ;
- Ca^{2+}-induced-Ca^{2+}release + EPSP: Nadkarni and Jung (2007)
- Gliotransmission (feedback loop): De Pittà and Brunel (2016); Tewari and Majumdar (2012); Wade et al. (2011)

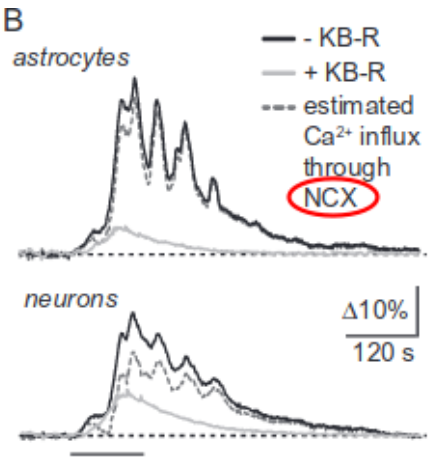
Our novelty: Couple 'bulk' ion concentrations with 'synaptic' ion concentrations and volume changes in a biophysical setting.

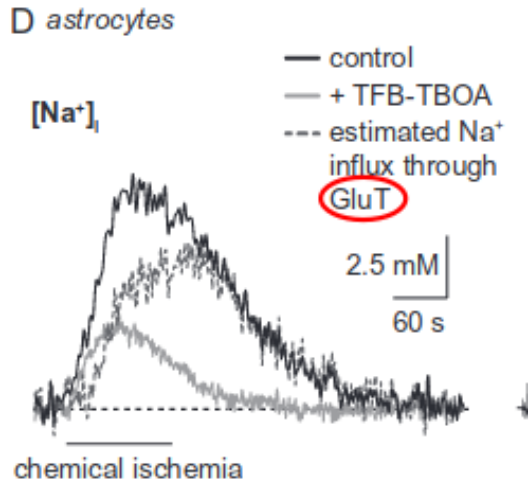
Chemical ischemia: a common protocol





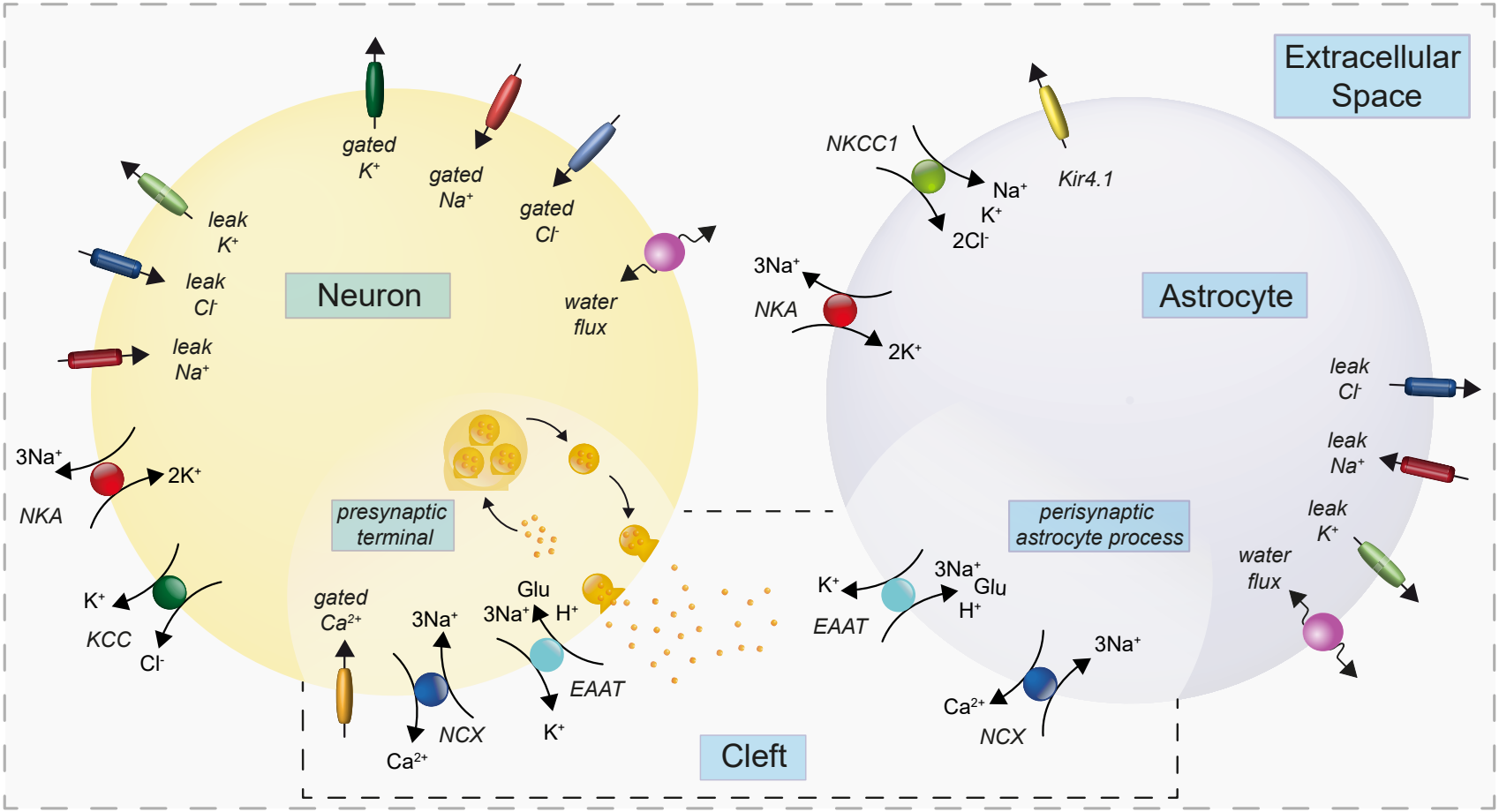






Gerkau et al., *Cerebral Cortex* (2018)

Novel model


Extracellular Space
Neuron
Astrocyte
presynaptic terminal
perisynaptic astrocyte process
Cleft
gated K+
gated Na+
gated Cl-
leak K+
leak Cl-
leak Na+
water flux
3Na+
2K+
NKA
K+
KCC
Cl-
gated Ca2+
3Na+
NCX
Ca2+
Glu
3Na+
H+
EAAT
K+
NKCC1
Na+
K+
2Cl-
Kir4.1
3Na+
NKA
2K+
K+
EAAT
3Na+
Glu
H+
Ca2+
NCX
3Na+
leak Cl-
leak Na+
leak K+
water flux

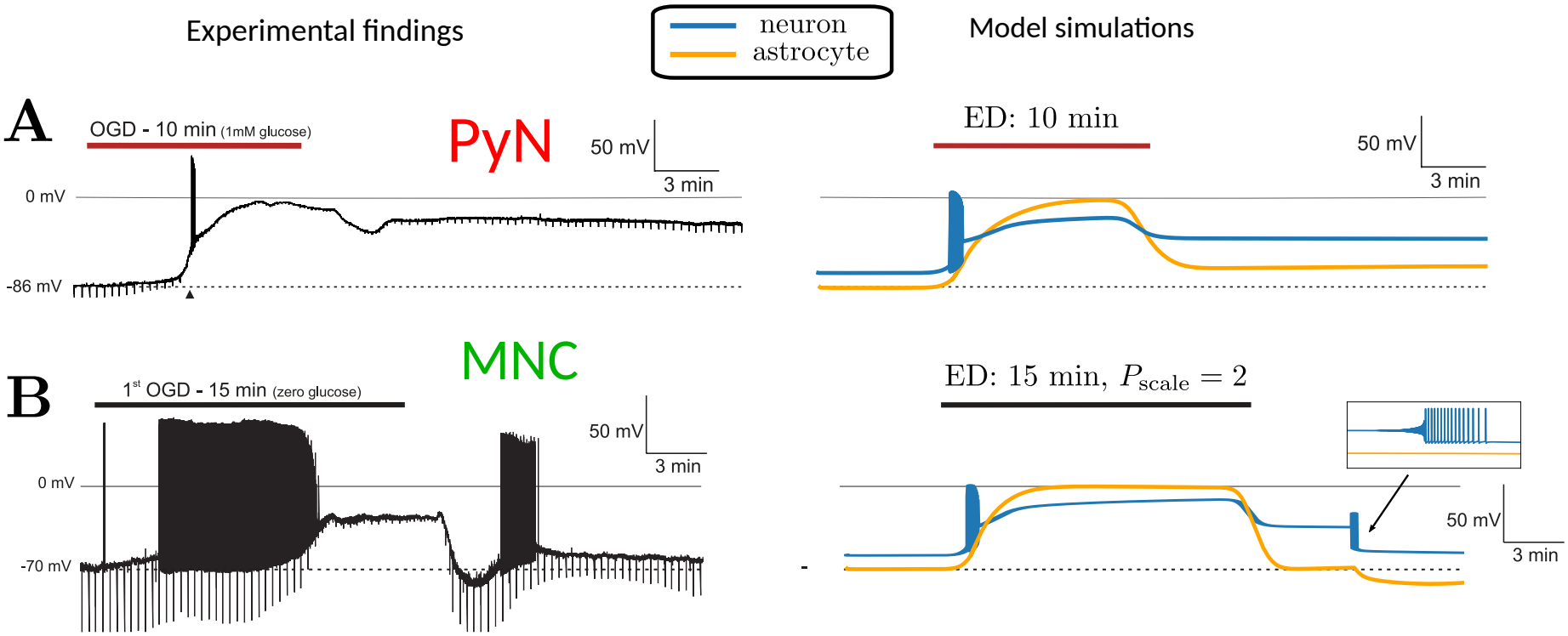
Key measurements

- Ion molar amounts and concentrations $\rightarrow \mathrm{Na}^{+}$,$\mathrm{K}^{+}\mathrm{Cl}^{-}$,$\mathrm{Ca}^{2+}$and Glu.
- Compartmental volumes
- Relative contribution of ion transporters to respective ion gradients.

Key ideas explored

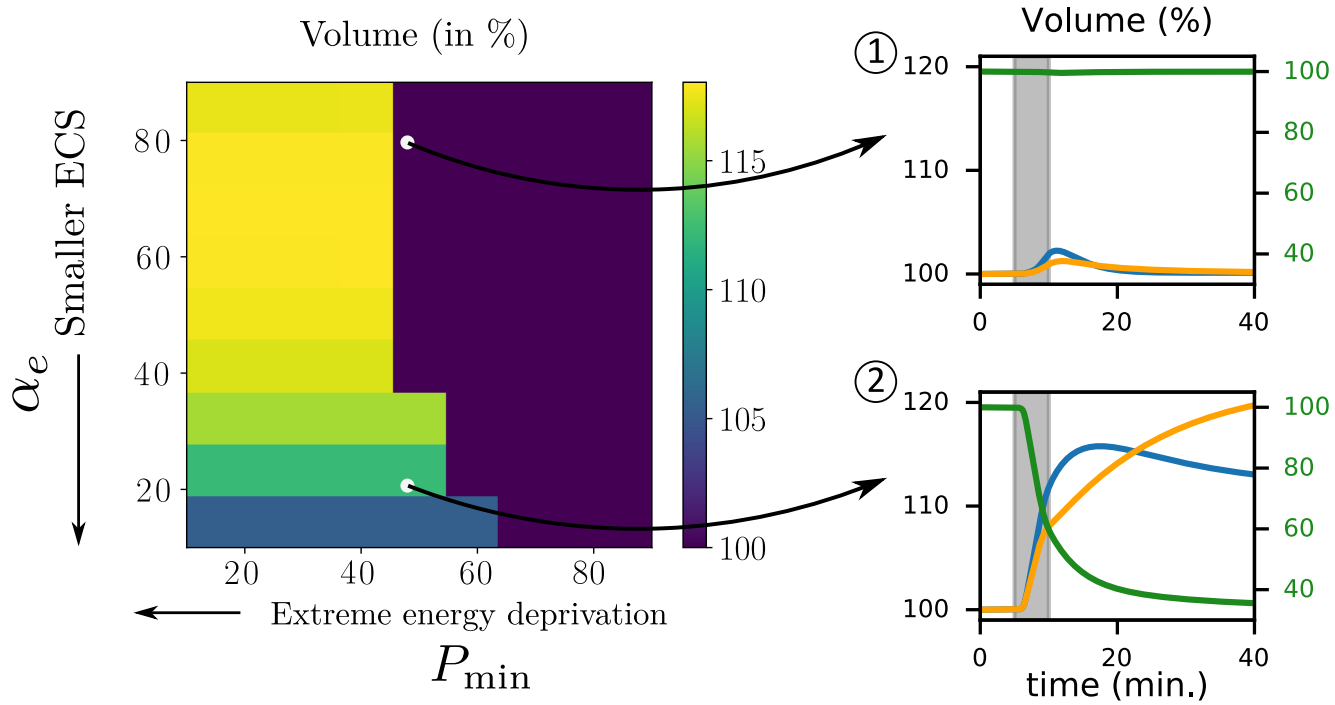
1. [**Validation**] Differential sensitivity to $\mathrm{Na}^+/\mathrm{K}^+$-ATPase strength
2. [**Analysis**] Vulnerability to varying ECS volume fraction
3. [**Prediction**] Predicting cleft Ca^{2+} and glutamate transients $\rightarrow$ synaptic failure
4. **Prediction**] Recovering from pathological state with additional blockers

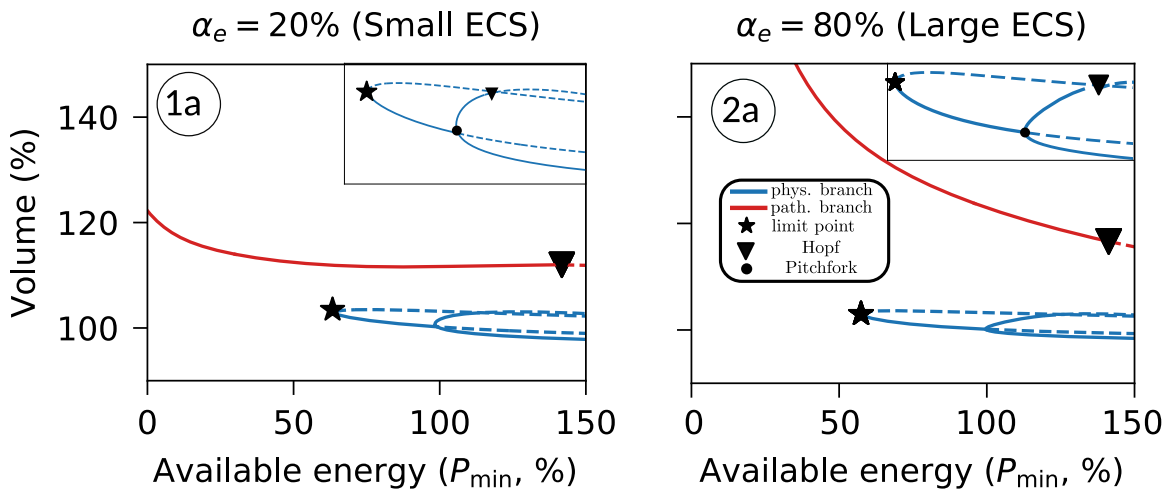
Validation: explaining isolated experiments



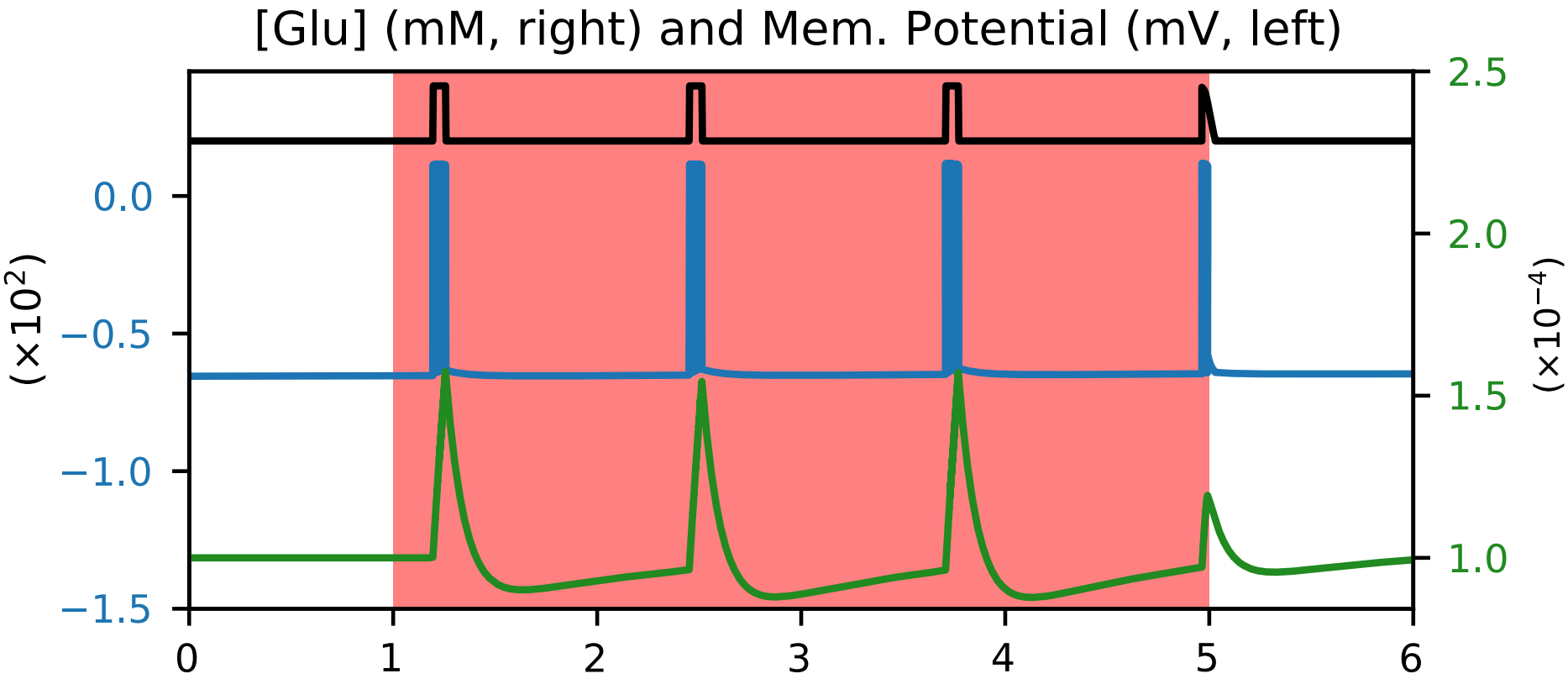
Experiments from Brisson and Andrew *J. Neurophysiol.* (2012)

Analysis: Vulnerability w.r.t. ECS size



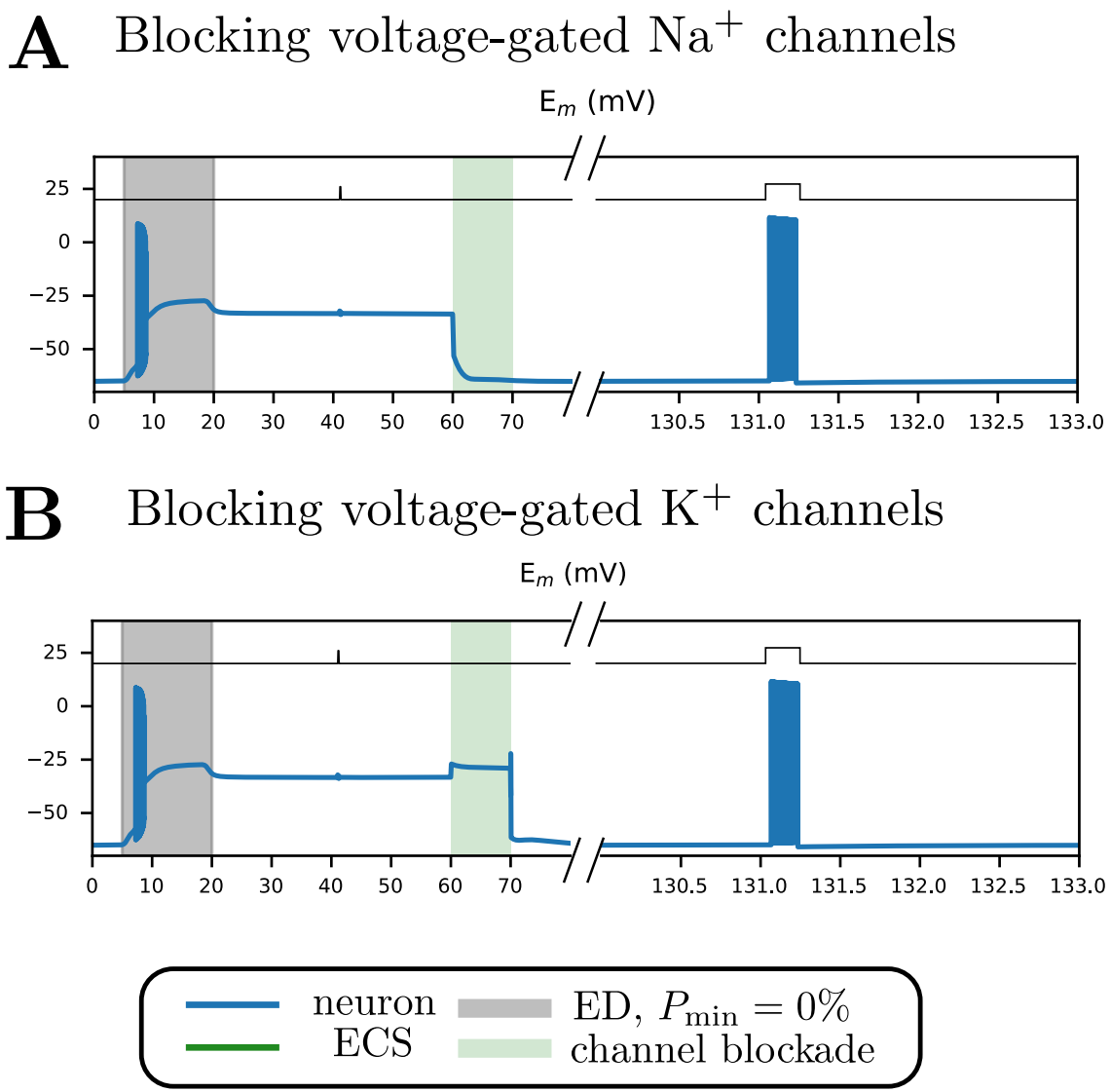


Prediction: Glutamate response in the cleft to bursts



Glutamate builds up after a few consistent spikes, followed by transient dip back to baseline.

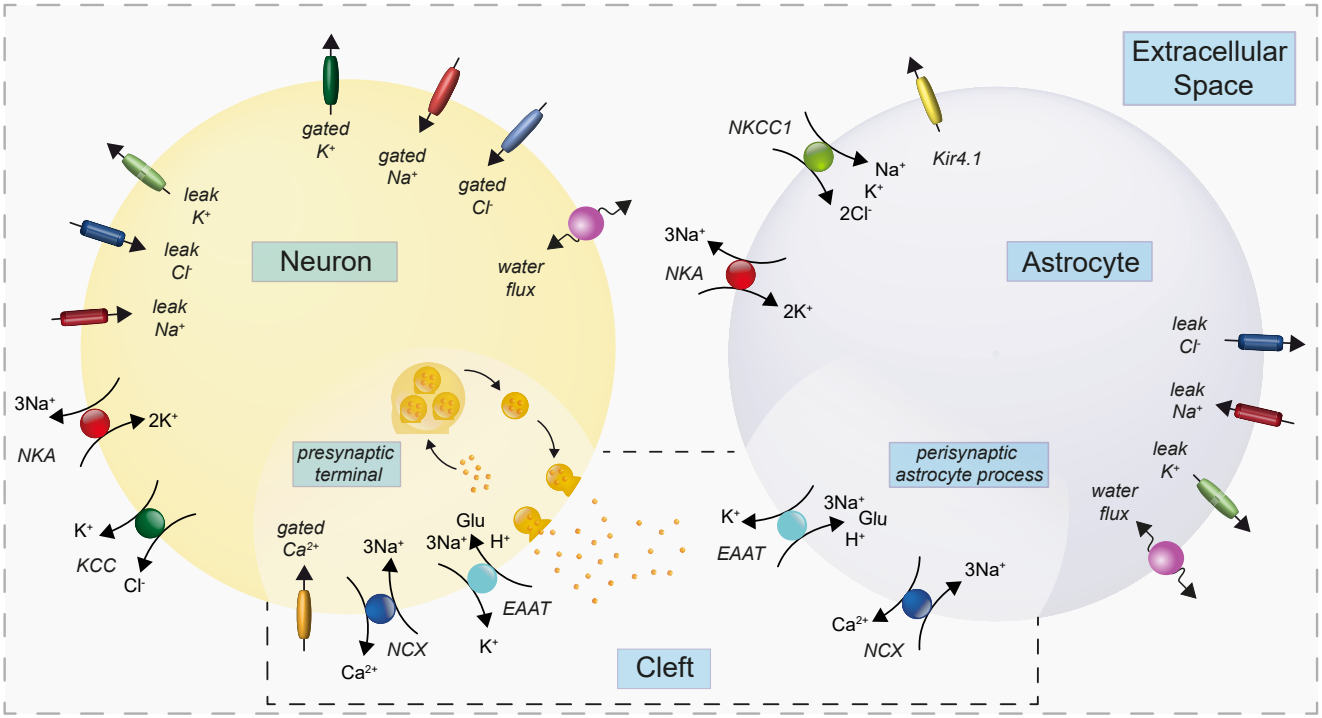
Prediction: Therapeutic measures help synapses recover



Takeaway

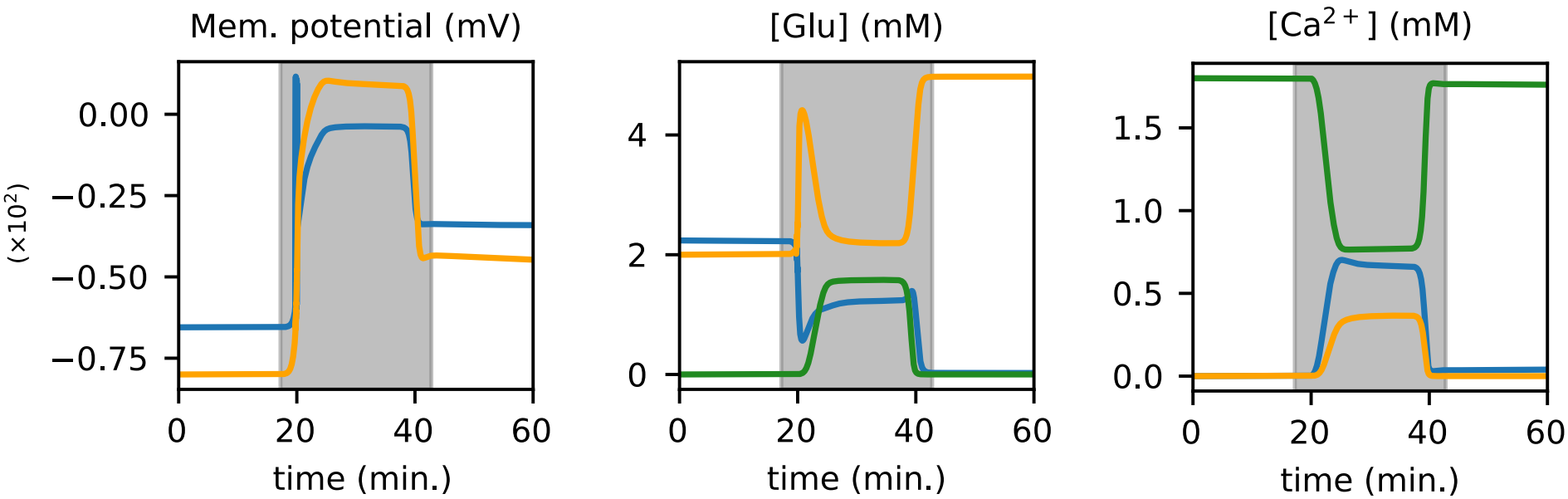
- Model that simulates Na^+, K^+, Cl^-, Ca^{2+} and glutamate dynamics during **low energy conditions** in:
  - soma: neuron, astrocyte
  - *synaptic processes*: presynaptic terminal, perisynaptic astrocyte process
  - extracellular space
- ECS size and pump strength are crucial in recovery from ischemic damage.
- Further, blocking voltage-gated Na^+ and K^+ channels assist in recovery from pathological state.
- Model can be further used to explain differential behaviour in different brain regions, aging etc.

Thanks! Any questions?



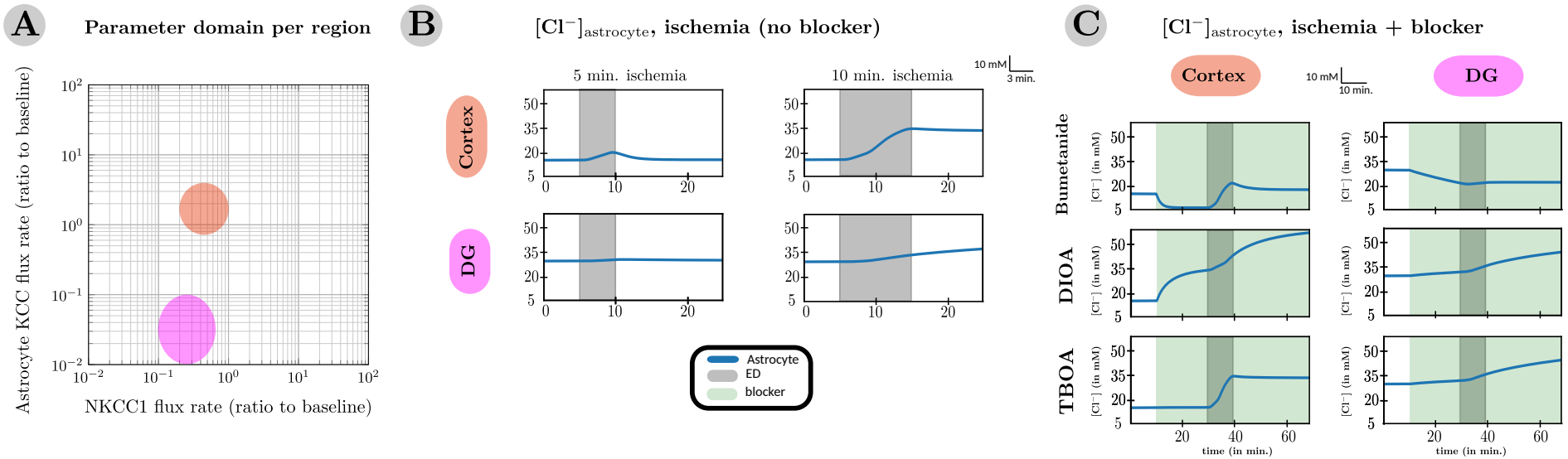
- **Peer-reviewed code:** `github.com/mkalia94/TripartiteSynapse`
- **Paper (accepted at PLOS Comp. Bio.):** `https://www.biorxiv.org/content/10.1101/2021.03.19.436129v1`

Ca^{2+} and Glu during energy deprivation



Energy deprivation sustains ≈ 1mM buildup of Glu in the cleft.
Demonstrates synaptic failure

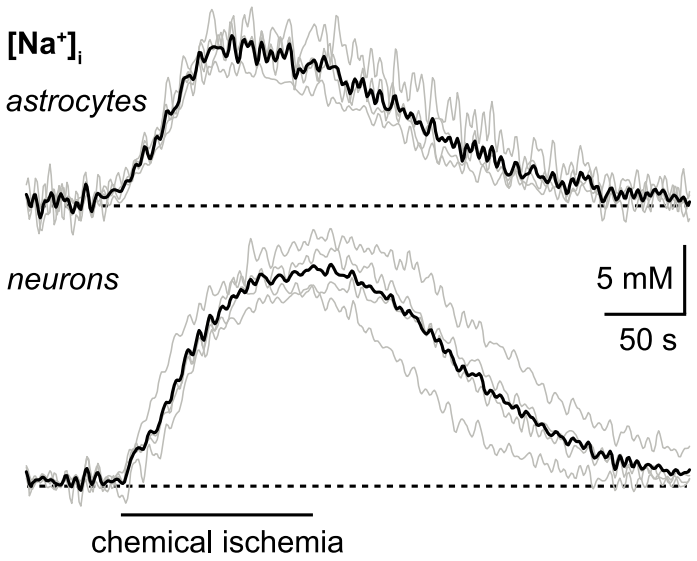
Explaining differing Cl^- transients in the brain

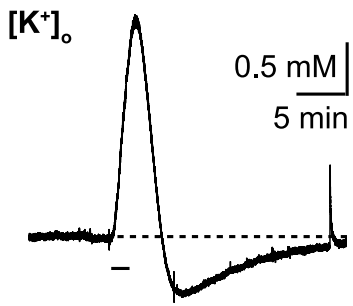


Engels et al. *J. Neurosci.* (submitted)

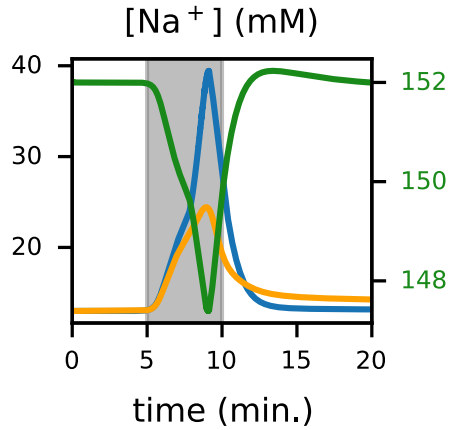
Calibration

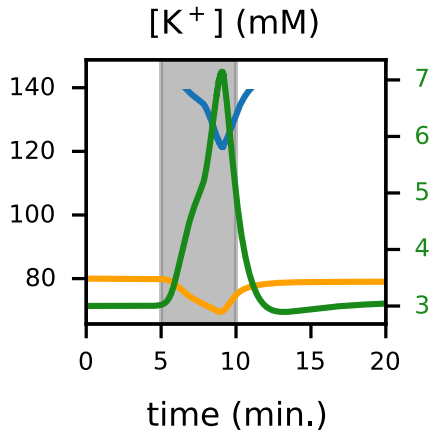
Experiments



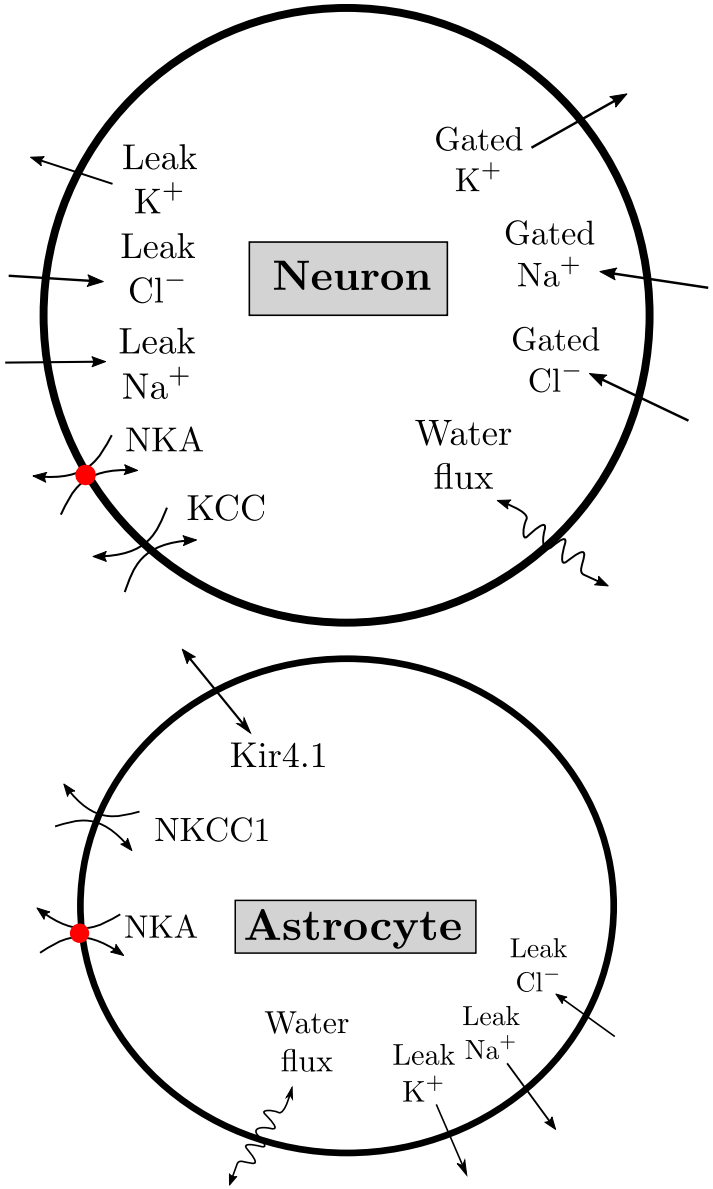


Model simulation





Model details: Soma



- Neuronal soma follows Dijkstra et al.
- Kir4.1 mediates nonlinear rates of K^+uptake after a certain threshold.
- NKCC1 mediates primary influx of Na^+, $K^+$and Cl^-
- Leaks maintain rest conditions

Currents/Fluxes should be consistent with Gibbs-Donnan equilibrium!

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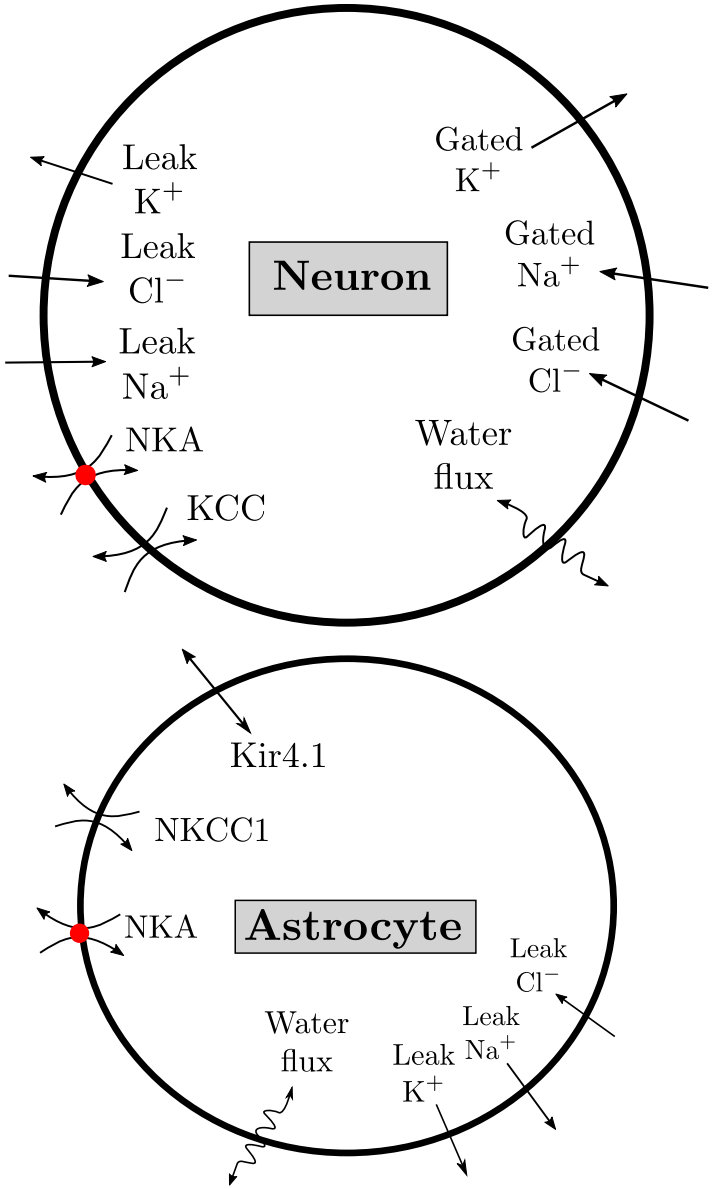

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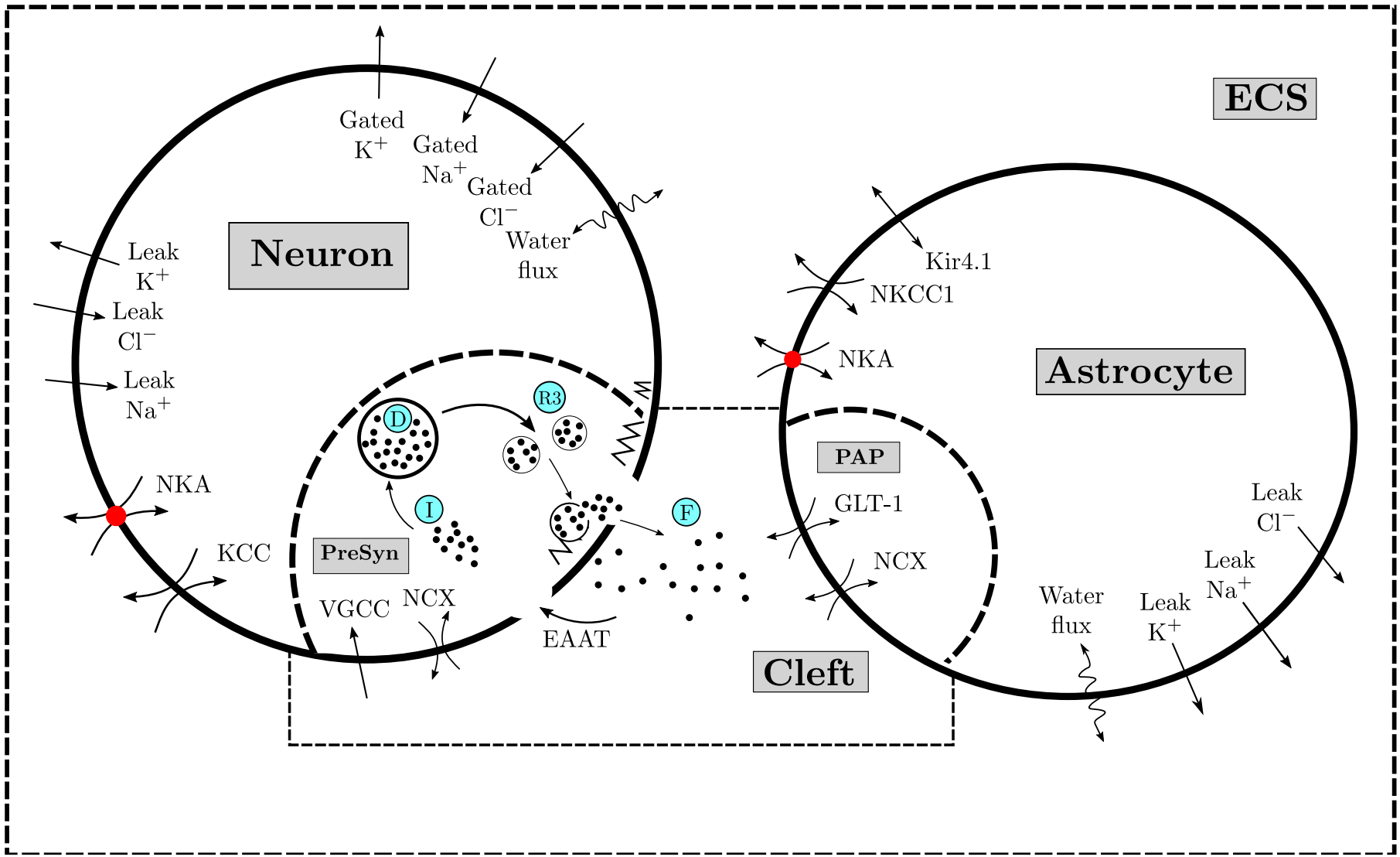

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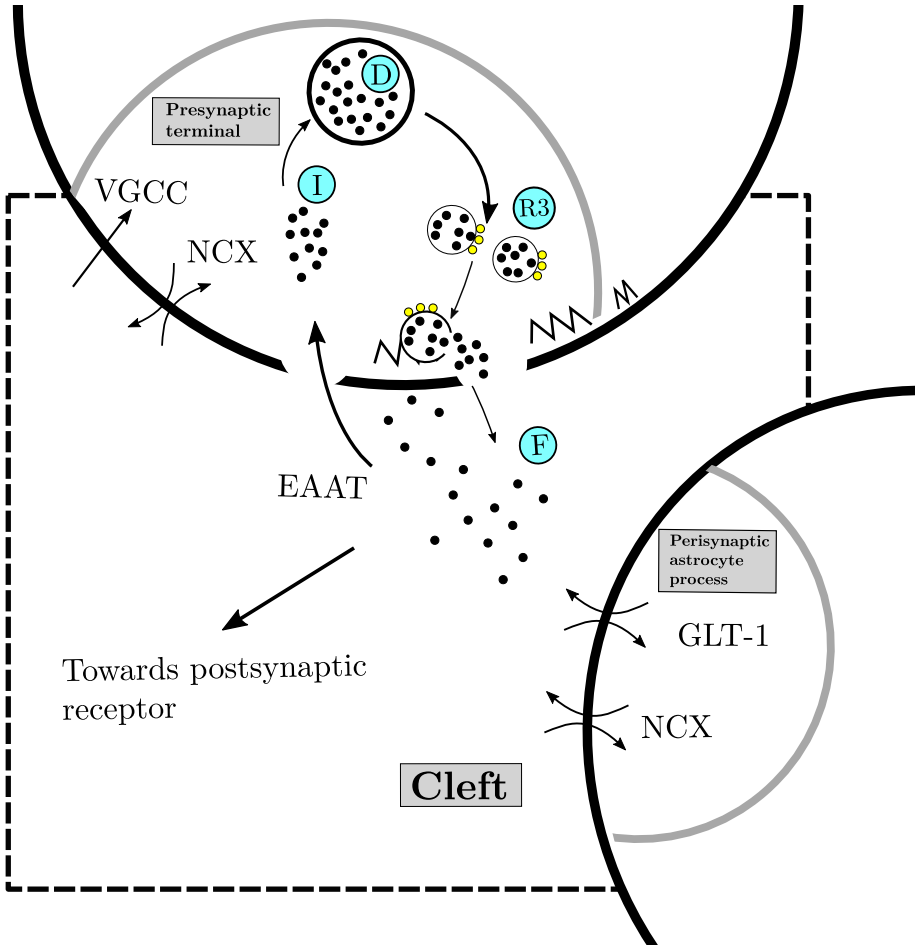

- Ca^{2+}-dependent sequential vesicle pool model [1] + neurotransmitter recycling [2].
- Fractional availability of neurotransmitter $\rightarrow$ Gluconcentrations.
- Cleft and synaptic volumes stay constant.

[1] Walter et al. *PLOS Comp. Bio.* (2013)

[2] Tsodyks and Markram, *PNAS 94(2)* (1997)

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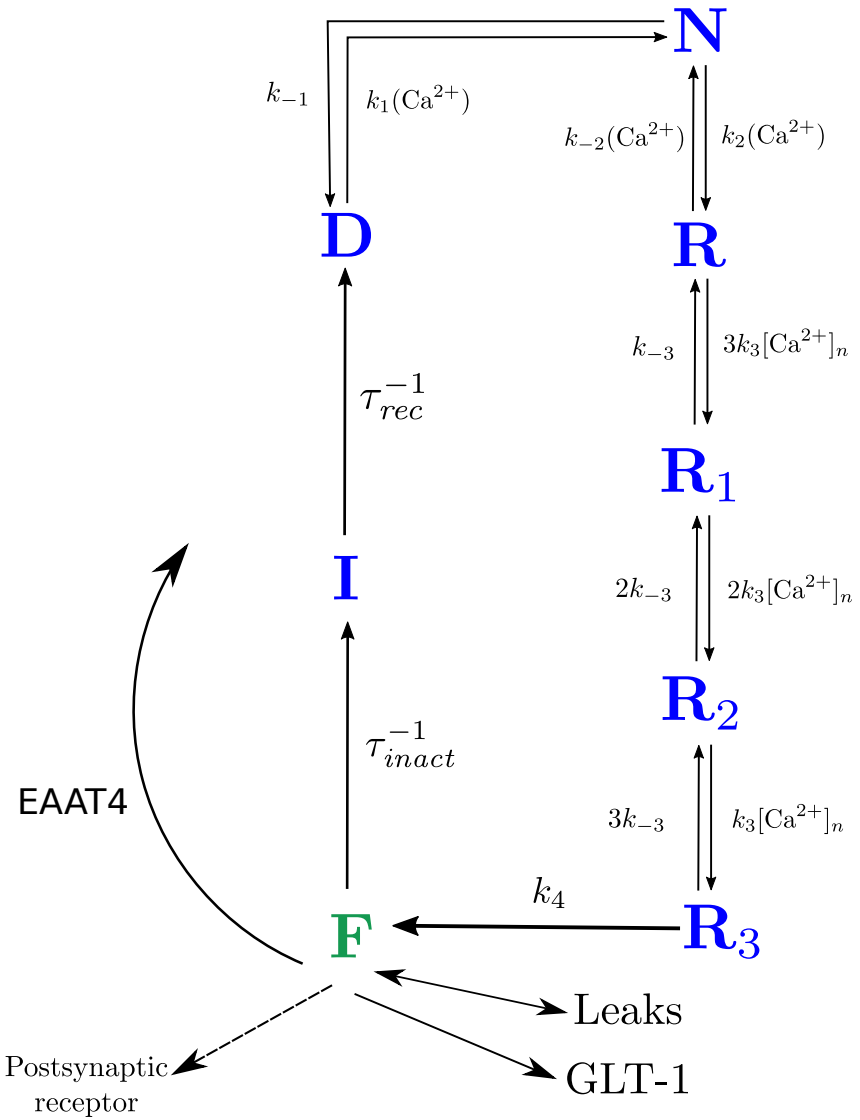

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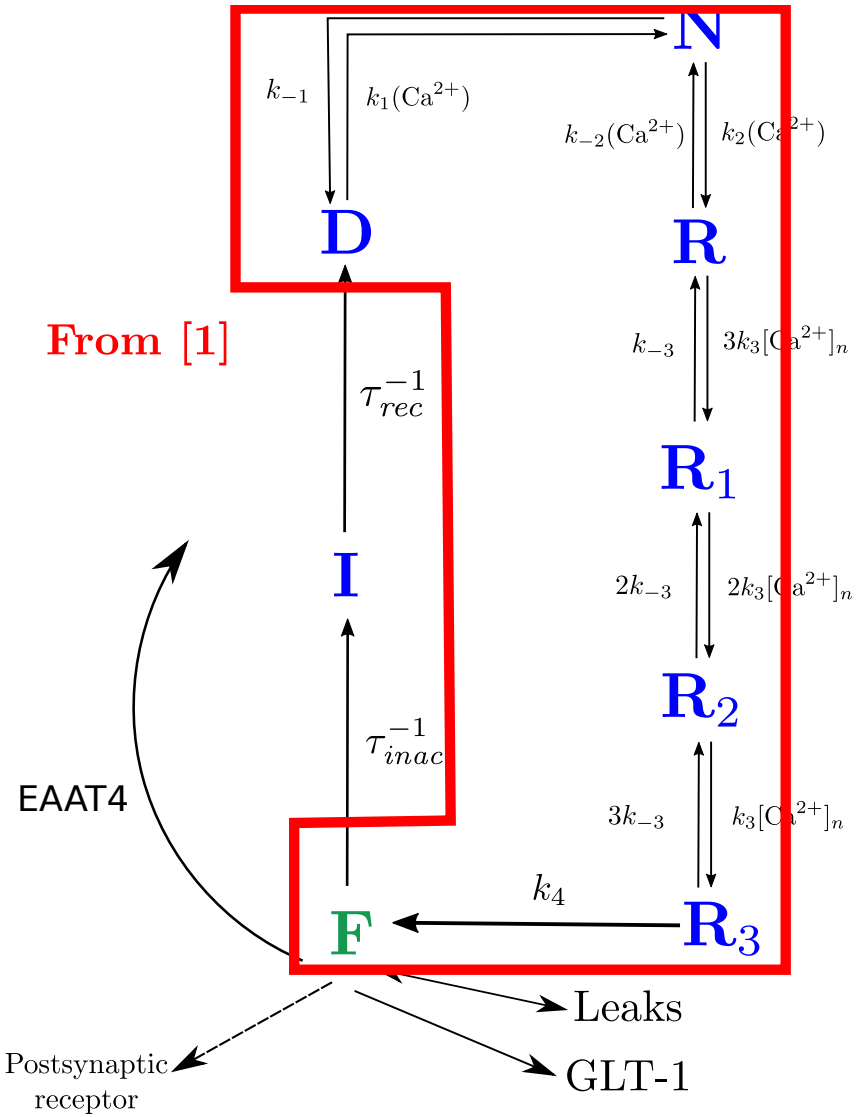

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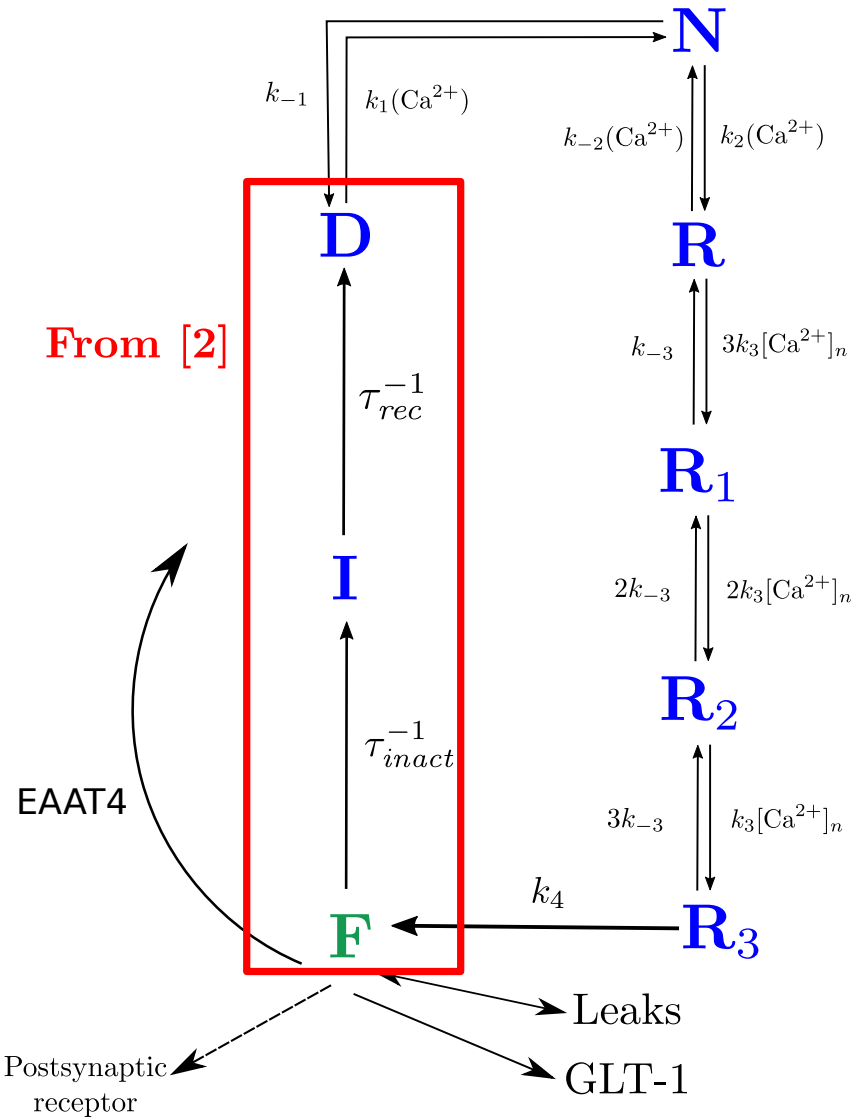

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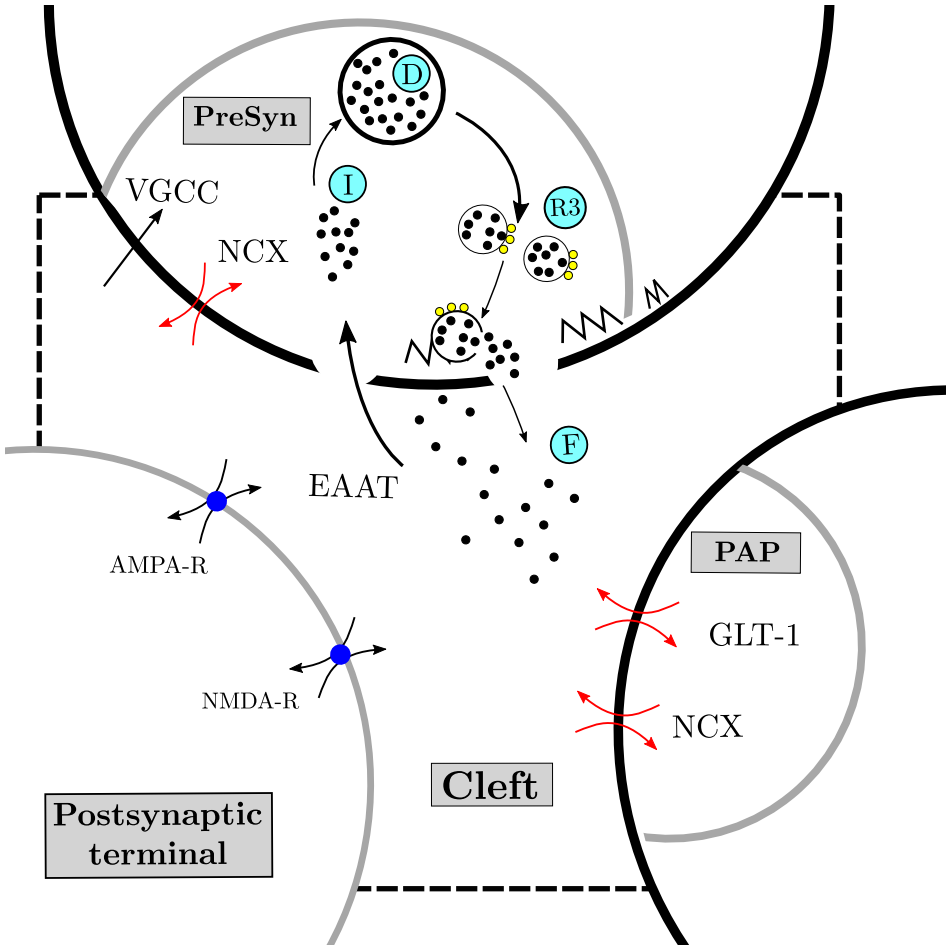

- Fused Gluin the cleft is taken up by neuronal and astrocyte EAATs.
- NCX and voltage gated-Ca^{2+}channels affect Ca^{2+}-dependent Glurecycling.
- NCX current follows [1].

[1] Luo and Rudy, *Circ Res. 74* (1994)