The energy deprived tripartite synapse: a biophysical model

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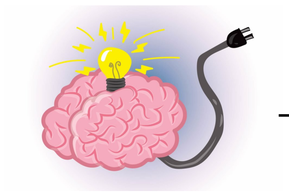
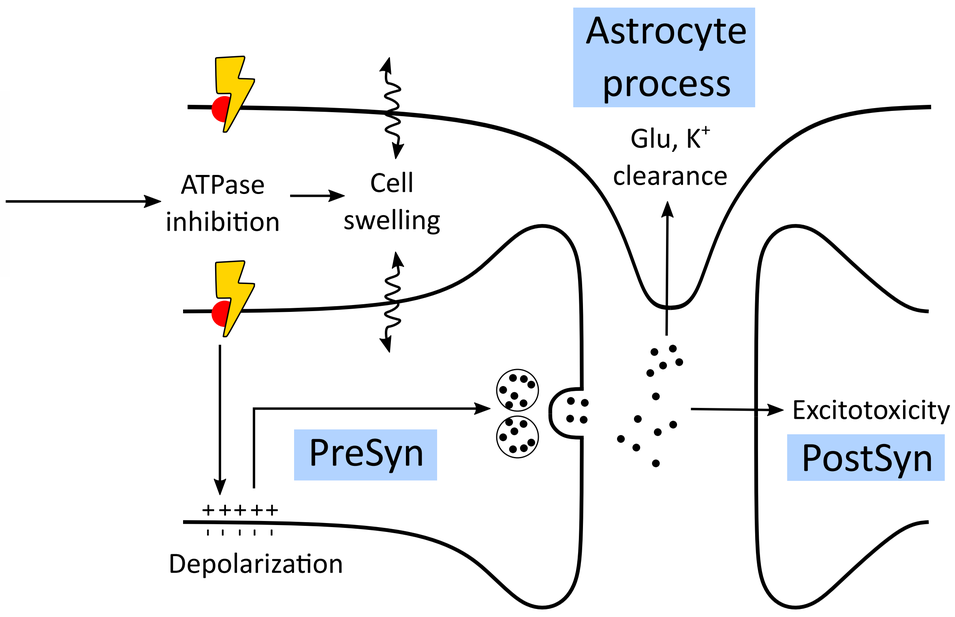
Pathways to pathology during energy deprivation

Energy deprivation to the nervous system occurs during **ischemic stroke**, which is one the leading causes of death. The epicenter of physiological breakdown is at the **tripartite synapse**.



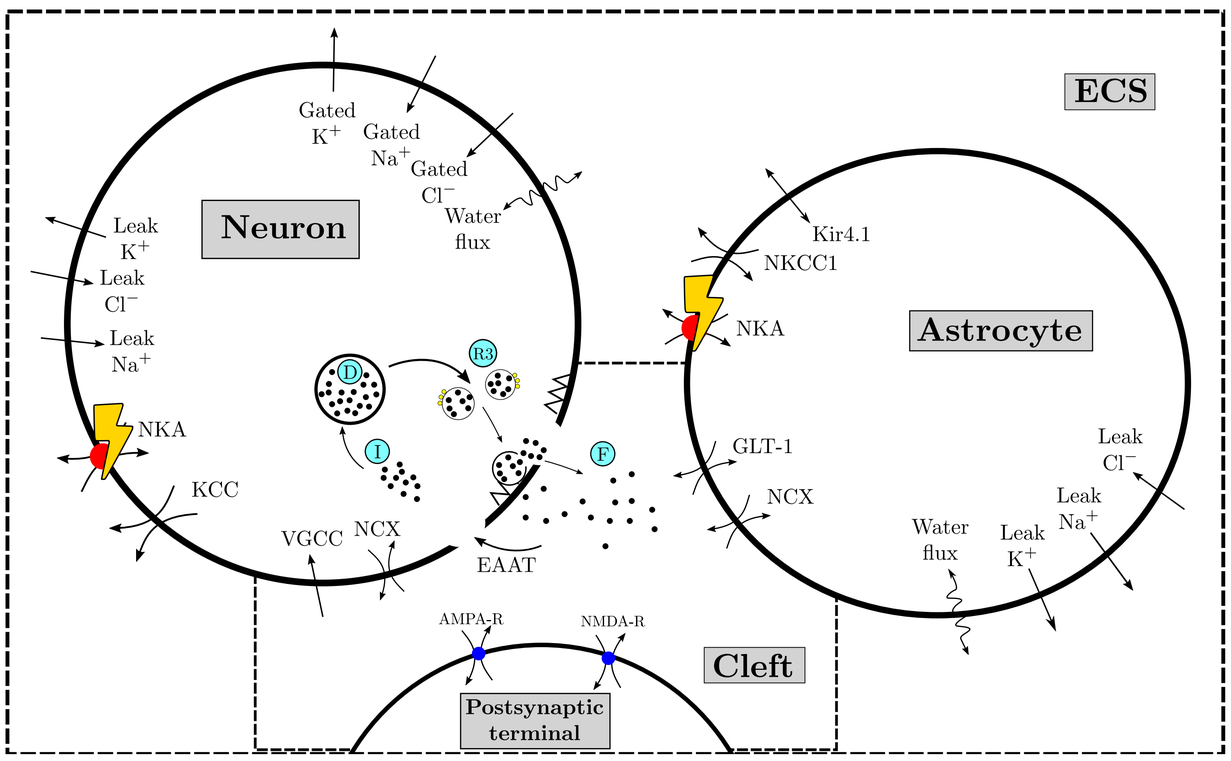
Energy deprivation



Goal

Describe **transitions** between normal and pathological states at energy deprived tripartite synapses by formulating a **biophysical model**.

Biophysical model of ion and volume dynamics

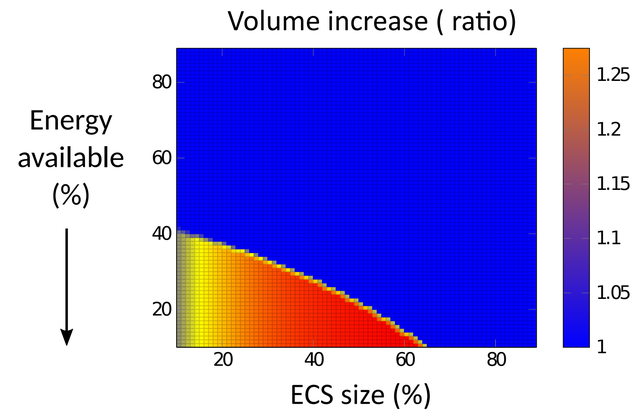


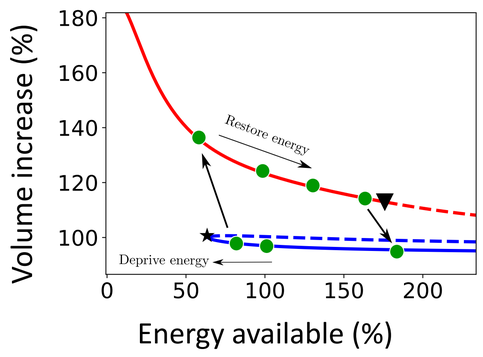
- Dynamics of **five ions: Na^+, K^+, Cl^-, Glu and Ca^{2+}**.
- Synaptic terminal + soma → one compartment
- Mass conservation, electroneutrality
- Calibrated to in-vitro ischemia experiments [1].

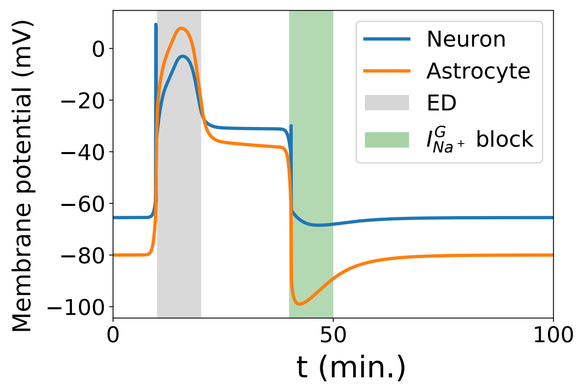
$$
\begin{cases}
\dfrac{d}{dt}N_X^i = -z_X \dfrac{1}{F}\left(\sum_j I_{X,i}^j + \sum_X I_{X,i}^{\mathrm{ATPase}}\right), \\
\dfrac{d}{dt}\mathrm{Vol}_i = \lambda_i \sum_{X,Y}\left([X]_i - [Y]_e\right), \\
\dfrac{d}{dt}q = \alpha_q(1-q) - \beta_q q, \\
\sum_{X,i} z_X N_X^i = 0, \\
\sum_i N_X^i = C_X = \text{constant}.
\end{cases}
$$

N_X^i = Moles of ion X in compartment i
i = {Neuron, Astrocyte, PreSyn}
q = Gating variables
X = {Na^+, K^+, Cl^-, Ca^{2+},Glu}
$I_{X,i}^j$ = Current/Flux of type j w.r.t. ion X in

Key results







Cell swelling

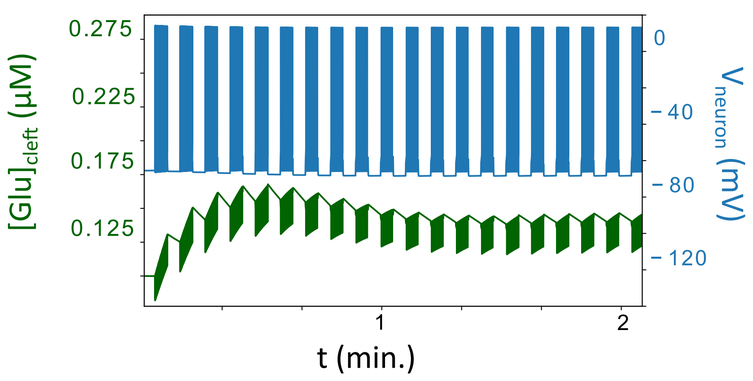
Smaller extracellular spaces are more vulnerable to ischemic injury. This may explain experiments in [2].

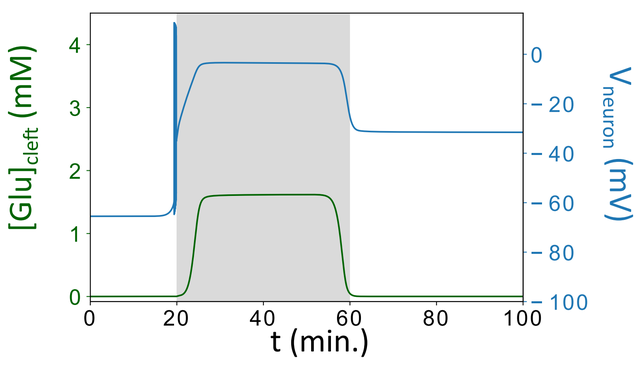
Bistability

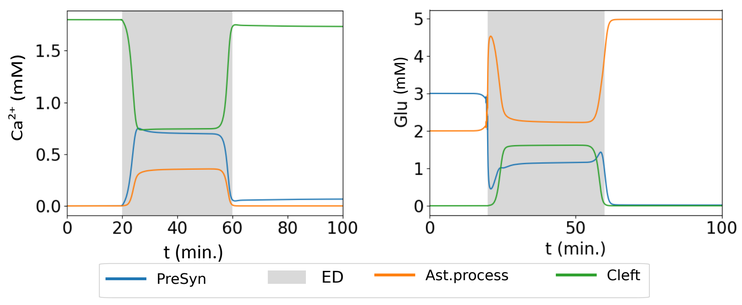
The synapse sustains ischemic injury upto an extent, but needs overpowered pumps to recover.

Depolarization

Blocking transient Na^+ current allows the system to recover back to a normal state, as first suggested in [3].







Healthy synapse

Healthy synaptic transmission is modeled by steady buildup of Glu in the cleft driven by square wave input.

Excitotoxicity

Toxic buildup of cleft Glu (1mM) occurs in energy deprived synapses which show anoxic oscillations before depolarization block.

PreSyn failure

Post energy deprivation, presynaptic Glu is depleted, leaving the synapses damaged. Ca^{2+} recovers.

References

[1] Gerkau, N.J. et al. "Reverse NCX attenuates cellular sodium loading in metabolically compromised cortex." Cerebral Cortex (2018) 28(12): 4264-4280.
[2] Brisson, C. D. and Andrew, R. D. "A neuronal population in hypothalamus that dramatically resists acute ischemic injury compared to neocortex." Journal of Neurophysiology (2002) 108(2): 419-303
[3] Dijkstra, K. et al. "A biophysical model for cytotoxic cell swelling." Journal of Neuroscience (2016) 36(47): 11881-11890

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