Homeostasis and spreading depolarization in multiscale simulation of ischemic stroke.

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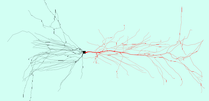
NEURON simulation platform

Reaction-diffusion (*rxd*)

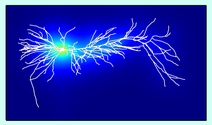
neuron.yale.edu

NEURON's reaction-diffusion module (*rxd*) expanded support for 1D and 3D intracellular and extracellular reaction-diffusion models.

Where?



r = rxd.Region(apicals, geometry=???)



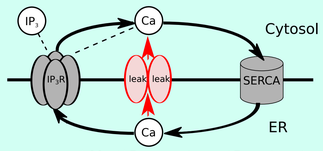
ecs = rxd.Extracellular(xlo=-30, ylo=-30, zlo=-30, xhi=30,yhi=30, zhi=30, dx=20, tortuosity=1.6, volume_fraction=0.2)

Who?

Ca

ca = rxd.Species([cyt, er], name='ca', charge=2)

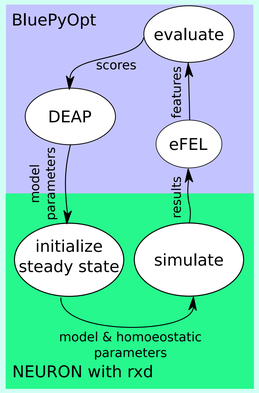
What?



leak = rxd.MultiCompartmentReaction(ca[er], ca[cyt], kf, kb, membrane=ermem)

(McDougal et. al. Frontiers in neuroinformatics 2013)
(Newton et. al. Frontiers in neuroinformatics 2018)

Homeostasis



Ionic homeostasis in neurons is essential for maintaining stable electrophysiological properties. Disruption of homeostasis is a characteristic of several pathologies.

We use **BluePyOpt**, which combines;
Distributed Evolutionary Algorithms in Python (DEAP) to explore the parameter space.
NEURON to run the simulation.
Electrophys Feature Extraction Library (eFEL) to help score the results.

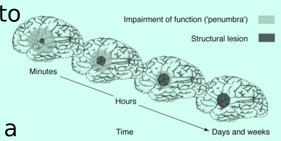
(Van Geit W., et al. Frontiers in neuroinformatics 2016)

We have add reaction-diffusion to the NEURON model and included **homoeostatic parameters** that are initialized to a steady-state.

Spreading depolarization and ischemic stroke

Ischemic stroke is a **multiscale phenomenon**.
We consider two models;

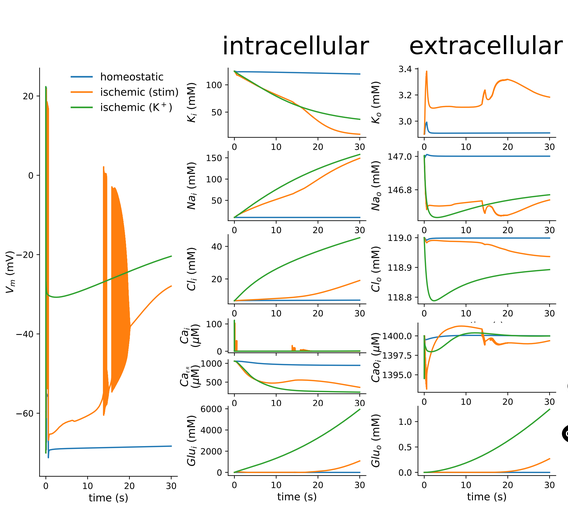
1) a **morphologically detailed** model to evaluate subcellular vulnerabilities of neurons in the penumbra.



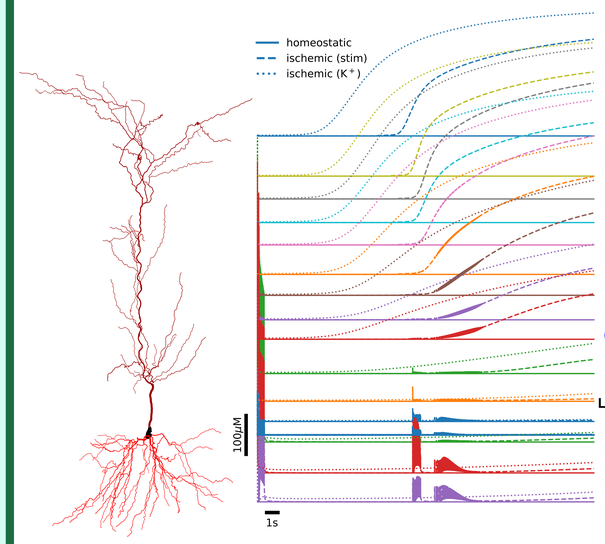
2) multiple **point models** embedded in a coarse grained approximation of extracellular space to simulate spreading depolarization.

Cellular and sub-cellular scales

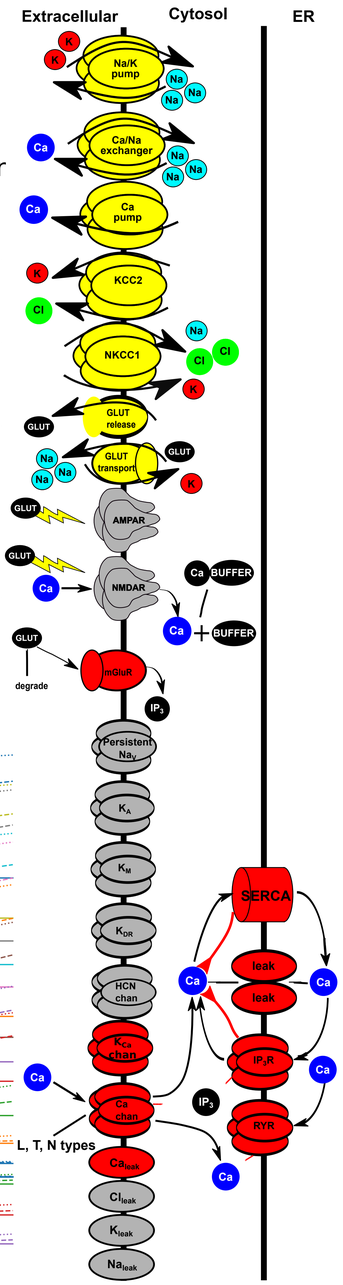
Simulation of a biophysically detailed neuron and astrocyte in extracellular space. The system maintains **homoeostasis** of K^+, Na^+, Ca^{2+}, Cl^- and glutamate.



Disruption of the ATP dependent pumps leads to a **breakdown in ion homoeostasis**.



Calcium increase is greatest in the **distal apical dendrites**, suggesting they may be more susceptible to damage.

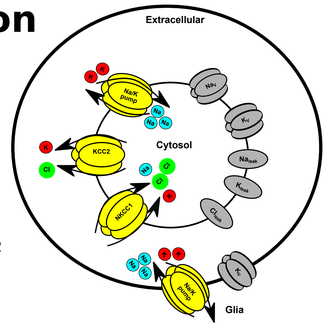


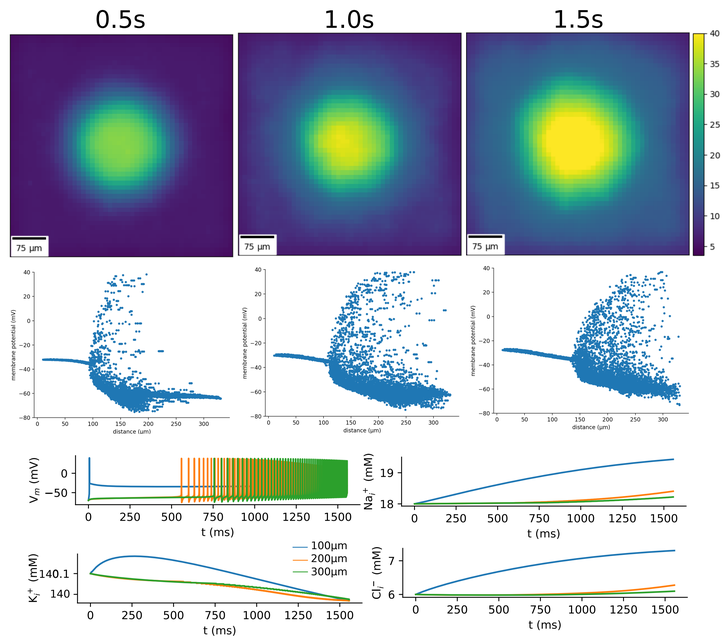
(Adapted from Frontiers in Pharmacology 2016).

Spreading depolarization

We simulate thousands of point neurons embedded in the **extracellular space**, each capable of producing a range of physiological and pathological behaviour. All mechanisms are defined by rxd.

Elevating extracellular K^+ with reduced O_2 gives rise to a wave of **ischemic spreading depolarization**.





Summary and future work

We used **NEURON rxd** to model spreading depolarization at the subcellular and tissue scales.

Our model suggests the **distal apical dendrites** are most susceptible to damage during ischemia.

Next we will **refine and validate** our model against experiments.

References

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