Cell-based modelling of electrical and chemical interplay in excitable tissue

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simula waterscales EMIx erc Forskningsrådet
The Research Council of Norway

The emerging EMI framework use a geometrically explicit representation of the cellular domains

Find the intracellular and extracellular potentials $\phi_i = \phi_i(x,t)$ and $\phi_e = \phi_e(x,t)$, and the transmembrane current $I_M = I_M(x.t)$ s.t.:

$$-\nabla \cdot (\sigma_i \nabla \phi_i) = 0 \quad \text{in } \Omega_i, \tag{1}$$

$$-\nabla \cdot (\sigma_e \nabla \phi_e) = 0 \quad \text{in } \Omega_e, \tag{2}$$

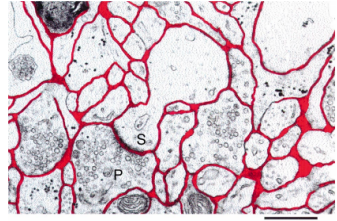
$$\phi_M = \phi_i - \phi_e \quad \text{at } \Gamma, \tag{3}$$

$$\sigma_e \nabla \phi_e \cdot n_e = -\sigma_i \nabla \phi_i \cdot n_i = I_M \quad \text{at } \Gamma, \tag{4}$$

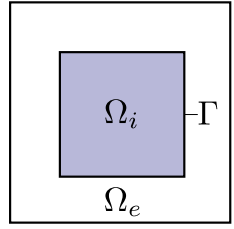
$$\frac{\partial \phi_M}{\partial t} = \frac{1}{C_M}(I_M - I_{\text{ion}}) \quad \text{at } \Gamma. \tag{5}$$

Ion concentrations are assumed to be constant in space and time – often an accurate approximation, but not always . . .

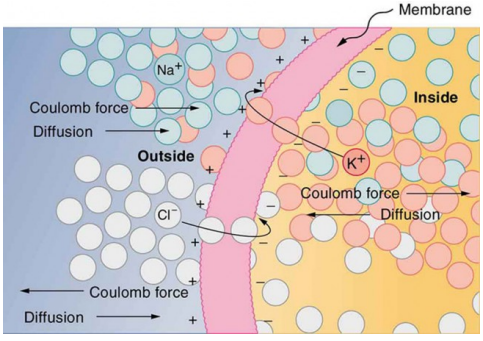
[Krassowska & Neu 1994],
[Ying & Henriquez 2007],
[Tveito et al. 2017]



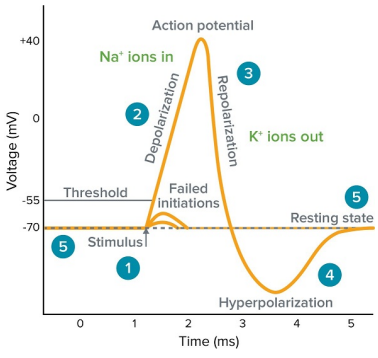
Rat cortex with ECS in red [Nicholson, 1998]



Movement of ions is fundamental in brain signalling and various mechanisms ensure ionic homeostasis



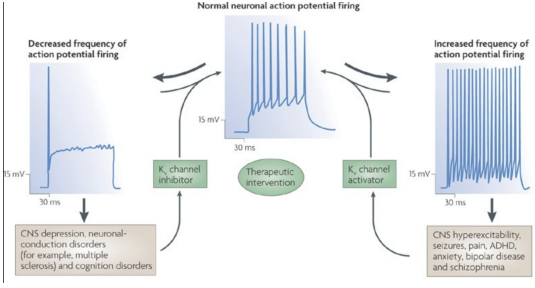
[courses.lumenlearning.com]

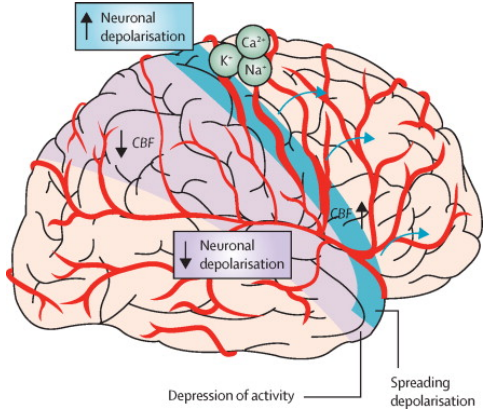


Homeostatic mechanisms will take the ionic concentrations back towards baseline levels, e.g.:

- Na^+/K^+/ATPase pumps (3 Na^+ out, 2 K^+ in),
- cotransporters (KCC2, NKCC1),
- glial K^+ buffering.

Ion concentration changes are a trademark of several pathological conditions, such as epilepsy or spreading depression

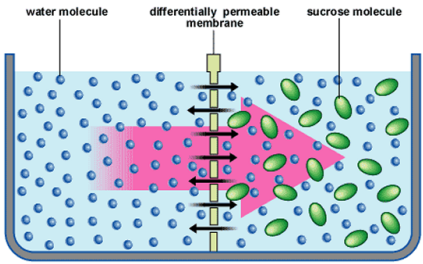


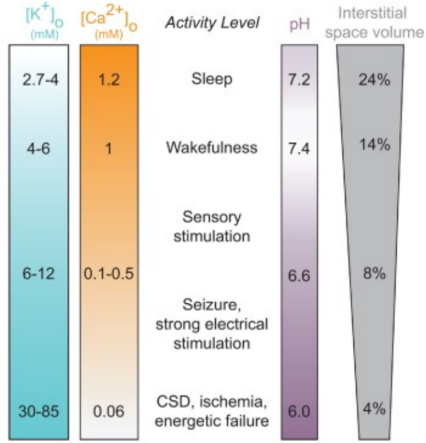


- Failure in homeostatic mechanisms
- High frequent firing - homeostatic mechanisms are not able to ”keep up”

The extracellular ion composition changes with local neuronal activity and across brain states

Ionic shift may set up osmotic gradients causing cellular swelling.





[Rasmussen, 2021]

A computational framework for ionic electrodiffusion in brain tissue with explicit representation of the cells (KNP-EMI)

For each ion species $k \in K$, find the *ion concentrations* $c_r^k : \Omega_r \times (0, T] \to \mathbb{R}$ and the *electrical potentials* $\phi_r : \Omega_r \times (0, T] \to \mathbb{R}$ such that:

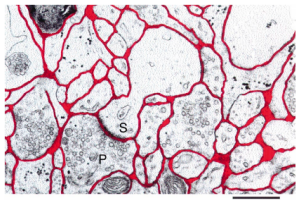
$$\frac{\partial c_r^k}{\partial t} + \nabla \cdot \mathrm{J}_r^k = 0 \qquad \text{in } \Omega_r, \tag{6}$$

$$F \sum_k z^k \nabla \cdot \mathrm{J}_r^k = 0 \qquad \text{in } \Omega_r, \tag{7}$$

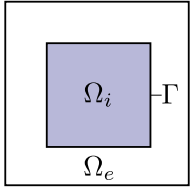
for $r = \{i, e\}$, where the ion flux densities are given by:

$$\mathrm{J}_r^k = -D_r^k \nabla c_r^k - z^k D_r^k \psi^{-1} c_r^k \nabla \phi_r, \qquad \text{in } \Omega_r. \tag{8}$$

The system remains to be closed by appropriate initial conditions, boundary conditions, and importantly interface conditions.



Rat cortex with ECS in red [Nicholson, 1998]



A computational framework for ionic electrodiffusion in brain tissue with explicit representation of the cells (KNP-EMI)

At the interface Γ, apply the following coupling conditions, and find the *total ionic current density* $I_M : \Gamma \times (0, T] \to \mathbb{R}$ such that:

$$\phi_i - \phi_e = \phi_M, \qquad \text{on } \Gamma, \quad (9)$$

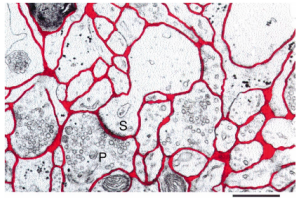
$$\frac{\partial \phi_M}{\partial t} = \frac{1}{C_M}(I_M - \sum_{k \in K} I^k_{\text{ion}}), \qquad \text{on } \Gamma, \quad (10)$$

$$I_M \equiv F \sum_k z^k \mathbf{J}^k_i \cdot n_i = -F \sum_k z^k \mathbf{J}^k_e \cdot n_e, \qquad \text{on } \Gamma, \quad (11)$$

$$\mathbf{J}^k_i \cdot n_i = \frac{I^k_{\text{ion}} + \alpha^k_i I_{\text{cap}}}{F z^k}, \qquad \text{on } \Gamma, \quad (12)$$

$$-\mathbf{J}^k_e \cdot n_e = \frac{I^k_{\text{ion}} + \alpha^k_e I_{\text{cap}}}{F z^k}, \qquad \text{on } \Gamma. \quad (13)$$

The transmembrane ion fluxes $I^k_{\text{ion}} = I^k_{\text{ion}}(\phi_M, [k], s)$ are subject to modelling, and typically depend on gating variables governed by ODEs.



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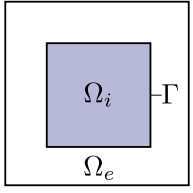
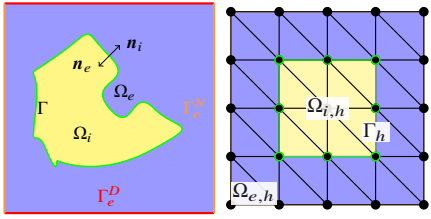


The KNP-EMI system (strongly coupled, non-linear, mixed dimensional) is numerically and computationally challenging to solve

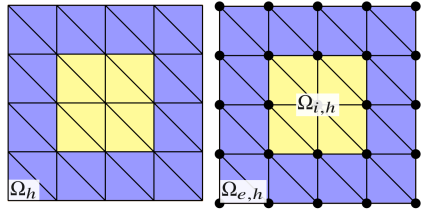
Numerical strategy:

- Split PDEs from ODEs (two-step first order)
- Finite difference PDE and ODE time discretizations (explicit handling of non-linear terms)
- Three different finite element based spatial discretization schemes:

Multi-dimensional form with mortar method



Single-dimensional form with (i) DG elements and (ii) broken CG elements



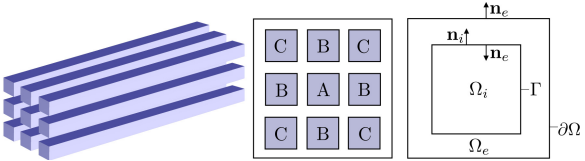
[Illustrations taken from Tveito et al. 2021. Modeling Excitable Tissue: The EMI Framework, chapter 5, Springer Nature]

A computational study of ephaptic coupling

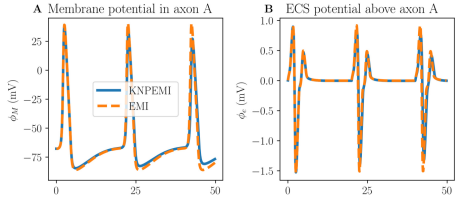
Do diffusive currents affect ephaptic coupling through the ECS in unmyelinated axon bundles?

In an idealized axon bundle with cell gaps of 0.1μm, action potentials are induced (via a synaptic current) every 20 seconds in either:

- Axon A (1 active neighbour), or
- Axons B and C (8 active neighbour).



[Ellingsrud et al., 2020]



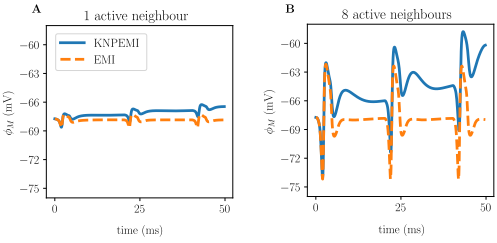
Diffusive currents contribute to ECS potential shifts in the KNP-EMI framework:

EMI $$\nabla \cdot (\sigma_e \nabla \phi_e) = 0, \text{ in } \Omega_e,$$

KNP-EMI $$\nabla \cdot (\sigma_e \nabla \phi_e + \nabla b_e) = 0, \text{ in } \Omega_e,$$

where $b_e = F \sum_k z^k D_e^k [k]_e$.

Diffusive currents do not strengthen the *electrical* ephaptic coupling (via the extracellular potential), however we see *diffusive* ephaptic coupling



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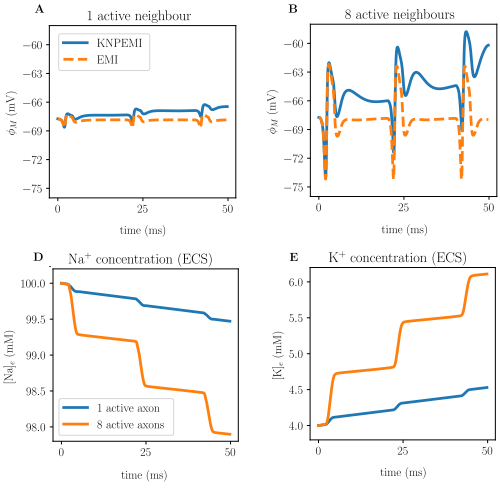

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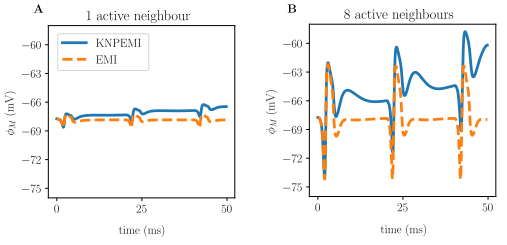
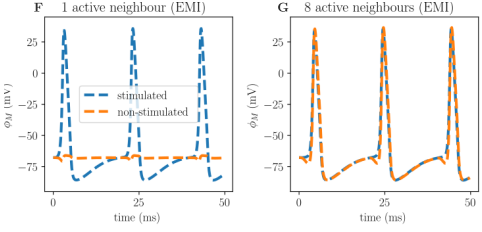


Ephaptic coupling is inversely proportional to the extracellular conductivity:

$$\sigma_i = \frac{F}{\psi}\sum_k D_i^k [k]_i (z^k)^2 = 2.01 \qquad \sigma_i = 1.0, \ \text{(S/m)}$$

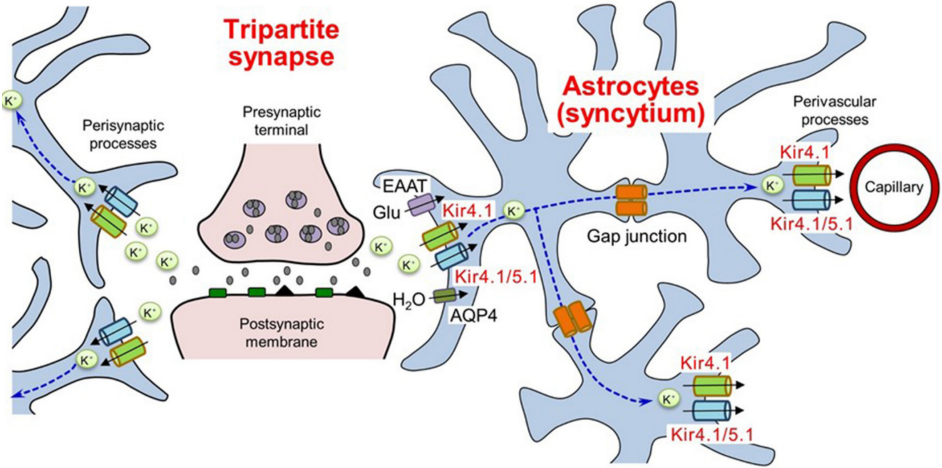
$$\sigma_e = \frac{F}{\psi}\sum_k D_e^k [k]_e (z^k)^2 = 1.31 \qquad \sigma_e = 0.1, \ \text{(S/m)}$$

[Bokil et al., 2001]

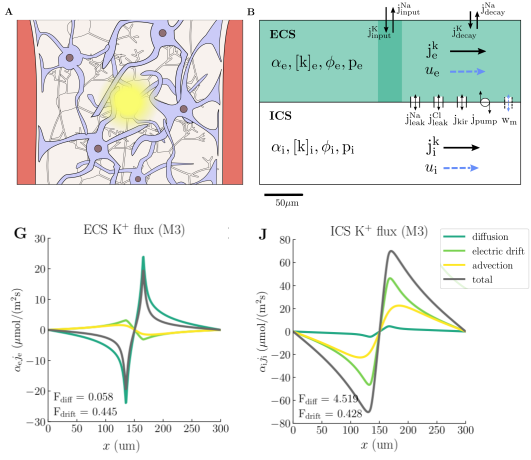


A computational study of potassium buffering

Connected glial cells transfer potassium ions from regions of elevated potassium concentration to regions of lower potassium concentration



We observe that K^+ is mainly transported through the ICS, and that electrical drift dominates both diffusive and advective transport



[Sætra et al. in prep 2023]

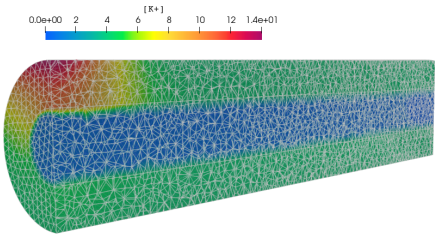
Key observations from modelling potassium buffering using the (1D) homogenized model:

- Potassium removal from high-concentration regions is driven by a local astrocytic membrane depolarization.
- ICS K^+ transport is dominated by drift, and ICS tranport dominates ECS tranport.
- Uptake in astrocytes mediated by $\mathrm{K}^+/\mathrm{Na}^+$ pumps, while release into ECS mediated by Kir4.1.

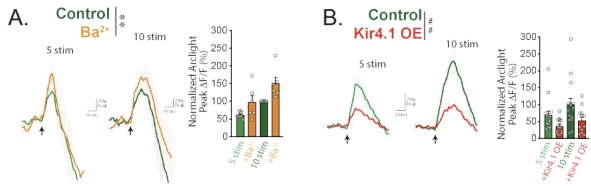
Ongoing work: what mechanisms drive astrocytic depolarization and potassium transport along astrocytic processes?

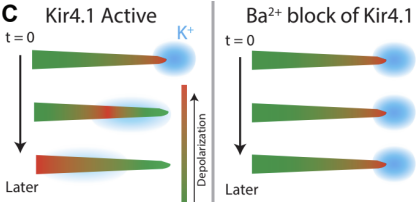
A more detailed model of K^+ transport using KNP-EMI:

- We induce potassium buffering by increasing ECS K^+ concentrations locally



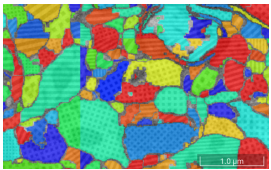
What drives propogation of depolarization along astrocytic processes? Kir4.1? Other K^+ channels?

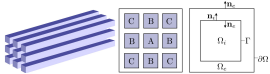




[Armbruster et al. Nat Neurosci 2022]

Exciting times: Extreme modelling of excitable tissue





EMIx

The Research Council of Norway

Ambition

To establish mathematical and technological foundations for modelling and simulation of electrical, chemical and mechanical interplay between brain cells at unprecedented detail, allowing for pioneering in-silico studies of brain signalling, volume balance and clearance.

Topics and expected outcomes

- Well-posed general mathematical and numerical framework allowing for geometrically-explicit representations of moving excitable cells;
- New computational geometries and models, highly scalable algorithms, and solution software for high-resolution high-realism simulations of excitable cell ensembles – all distributed as open source;
- New physiological insight into inter-neuronal and astrocyte membrane mechanisms and their role in brain homeostasis and learning.

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Collaborators: Pietro Benedusi, Gaute Einevoll, Geir Halnes, Halvor Herlyng, Miroslav Kuchta, Rami Masri, Marie Rognes, Marte Julie Sætra

KNP-EMI derivation and mortar formulation:
https://doi.org/10.3389/fninf.2020.00011

Abstractions and automated algorithms for mixed domain finite element methods: https://doi.org/10.1145/3471138

Modeling Excitable Tissue - The EMI Framework:
https://doi.org/10.1007/978-3-030-61157-6

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