Finite element simulation of ionic electrodiffusion in cellular geometries

Ada Johanne Ellingsrud

CAIMS/SCMAI 2022 Conference,
Kelowna, Canada,
June 2022

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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.:

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

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

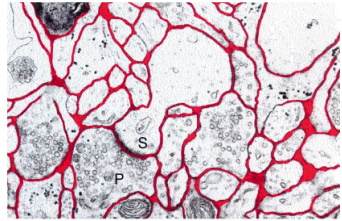
$$\phi_M = \phi_i - \phi_e \qquad \text{at } \Gamma, \quad (3)$$

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

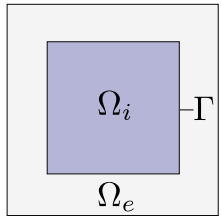
$$\frac{\partial \phi_M}{\partial t} = \frac{1}{C_M}(I_M - I_{\text{ion}}) \qquad \text{at } \Gamma. \quad (5)$$

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

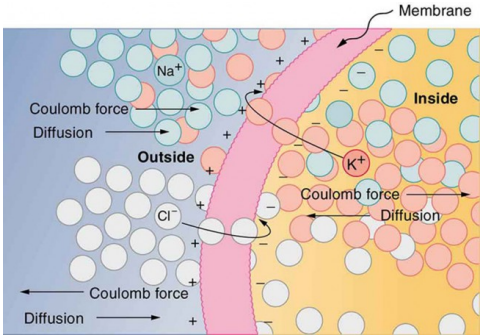
[Krassowska & Neu 1994], [Ying & Henriquez 2007], [Tveito et al. 2017]



Rat cortex with ECS in red [Nicholson, 1998]



Movement of ions is fundamental in brain signalling and cellular swelling



[courses.lumenlearning.com]

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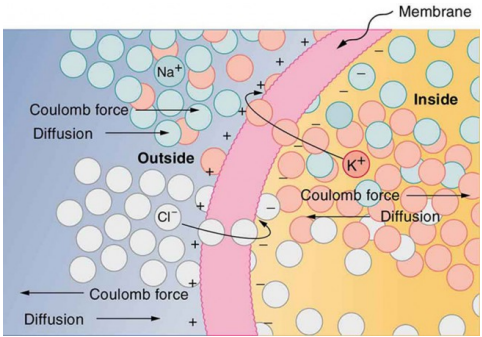

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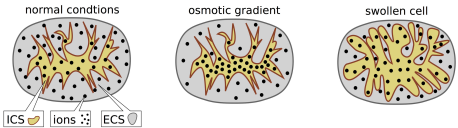

[Hubel, 2016]

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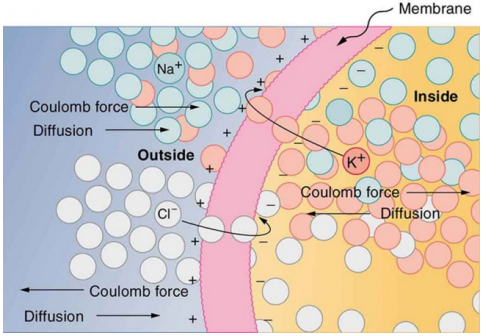

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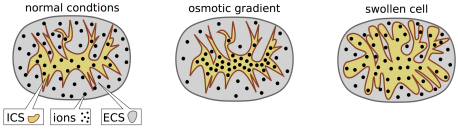
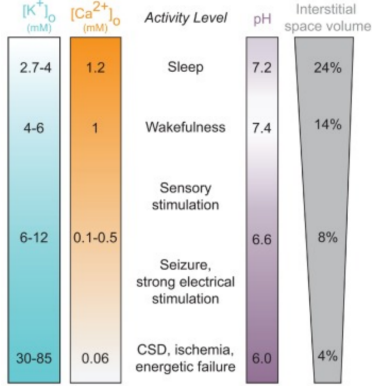


[Hubel, 2016]

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



[Rasmussen, 2021]

A computational framework for ionic electrodiffusion in brain tissue with geometrical explicit representation of the cells

KNP-EMI

In a (tissue) domain $\Omega = \Omega_i \cup \Omega_e \subset \mathbb{R}^d$, where Ω_i (with boundary Γ) and Ω_e represent respectively intracellular and extracellular regions, with (ion) species $k \in K$ (e.g. Na^+, K^+, Cl^-).

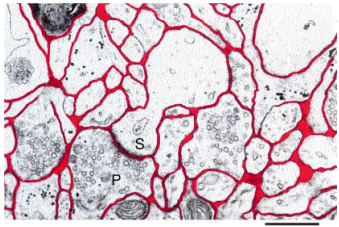
For each compartment $r \in \{i, e\}$ and species k, $x \in \Omega_r$, $t > 0$, find the:

- concentrations $[k]_r(x, t)$,
- electrical potentials $\phi_r(x, t)$,

and at the interface, $x \in \Gamma$, $t > 0$, find the:

- transmembrane current $I_M(x, t)$.

[Mori & Peskin, 2009]
[Ellingsrud et al., 2020]



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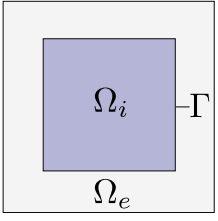

A computational framework for ionic electrodiffusion in brain tissue with explicit representation of the cells (KNP-EMI)

Conservation of ions for the bulk of each region:

$$\frac{\partial [k]_r}{\partial t} + \nabla \cdot J_r^k = 0, \qquad \text{in } \Omega_r.$$

Ion flux densities are given by:

$$J_r^k = -D^k \nabla [k]_r - \frac{D^k z^k}{\psi} [k] \nabla \phi_r. \qquad \text{in } \Omega_r,$$

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[Pods, 2017]
[Solbrå et al., 2018]

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Interface conditions:

$$\phi_i - \phi_e = \phi_M, \qquad \text{on } \Gamma,$$

$$I_M \equiv F \sum_k z^k J_i^k \cdot n_i = -F \sum_k z^k J_e^k \cdot n_e, \qquad \text{on } \Gamma,$$

$$J_i^k \cdot n_i = \frac{I_{\text{ion}}^k + \alpha_i^k I_{\text{cap}}}{F z^k}, \qquad \text{on } \Gamma,$$

$$-J_e^k \cdot n_e = \frac{I_{\text{ion}}^k + \alpha_e^k I_{\text{cap}}}{F z^k}, \qquad \text{on } \Gamma.$$

[Pods, 2017]
[Solbrå et al., 2018]

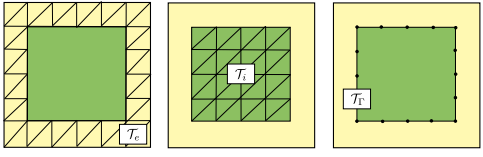
The strongly coupled and non-linear KNP-EMI equations are numerically and computationally challenging to solve

Numerical strategy:

- Split PDEs from ODEs (two-step first order)
- Finite difference ODE and PDE time discretizations (explicit handling of non-linear terms)
- Mortar finite element scheme for PDEs

$$[k]_{r,h}(t) \in V_{r,h}, \quad \phi_{r,h}(t) \in T_{r,h}, \quad I_{M,h}(t) \in S_h,$$

where $V_{r,h}$, $T_{r,h}$, S_h are constructed using continuous piecewise linear polynomials.



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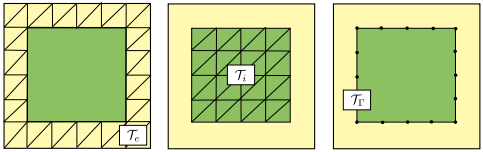
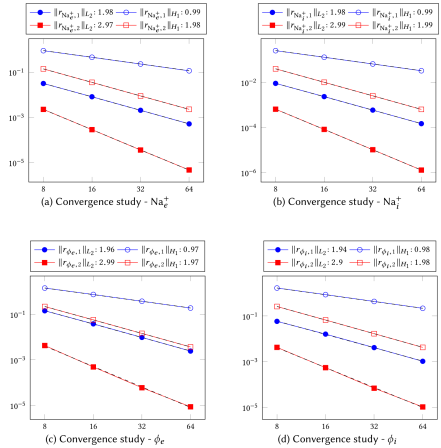


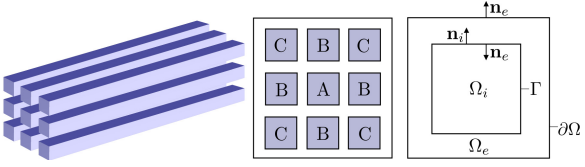
For a problem with a smooth manufactured solution we observe expected convergence rates:



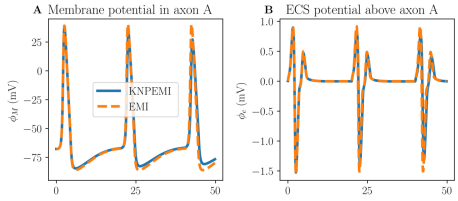
Comparing KNP-EMI and EMI: Do diffusive currents affect ephaptic coupling through the ECS in unmyelinated axon bundles?

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]



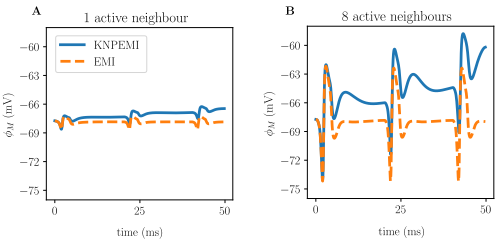
Diffusive currents contribute to ECS potential shifts in the KNP-EMI framework:

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

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

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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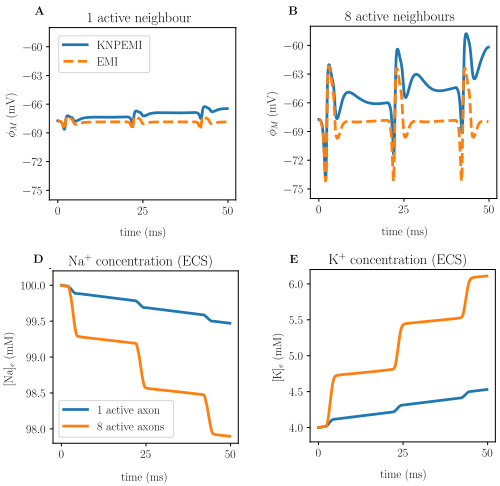

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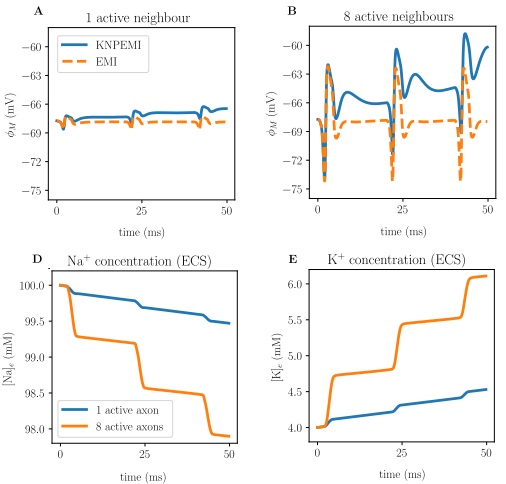
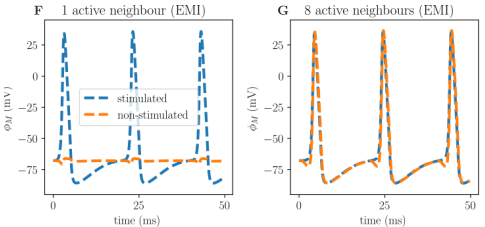


Ephaptic coupling is inversely proportional to the extracellular conductivity:

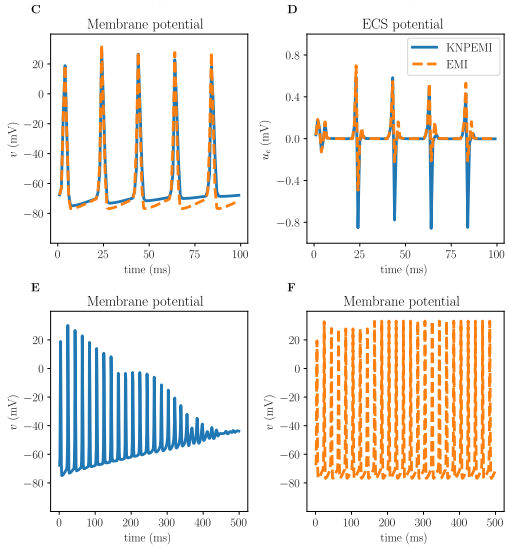
$$\sigma_i = \frac{F}{\psi}\sum_k D_i^k [k]_i (z^k)^2 = 2.01 \qquad \sigma_i = 1.0, \ \text{(S/m)}$$

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

[Bokil et al., 2001]

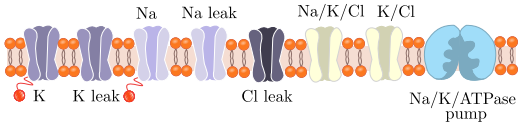


During hyperactivity, the KNP-EMI and EMI models differ due to shifts in the ion concentration gradients



Standard Hodgin-Huxley model and homeostasis mechanisms:

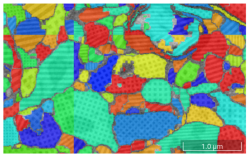
$$I_{\text{ion}}^{\text{Na}} = I_{\text{leak}}^{\text{Na}} + I^{\text{Na}} + 3I_{\text{ATP}} + I_{\text{NKCC1}}$$
$$I_{\text{ion}}^{\text{K}} = I_{\text{leak}}^{\text{K}} + I^{\text{K}} - 2I_{\text{ATP}} + I_{\text{NKCC1}} + I_{\text{KCC2}}$$
$$I_{\text{ion}}^{\text{Cl}} = I_{\text{leak}}^{\text{Cl}} - 2I_{\text{NKCC1}} - I_{\text{KCC2}},$$

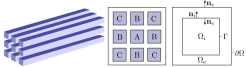


We consider two firing regimes:

- Normal activity (1 Hz, not shown)
- Hyperactivity (50 Hz)

Exciting time: Extreme modelling of excitable tissue





EMIx

The Research Council of Norway

Ambition

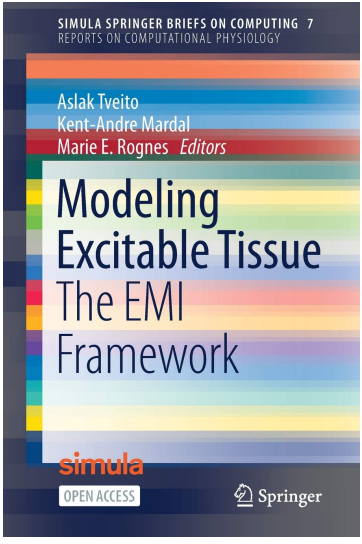
To establish mathematical and technological foundations for modelling and simulation of electrical, chemical and mechanical interplay between brain cells at unprecedented detail, allowing for pioneering in-silico studies of brain signalling, volume balance and clearance.

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.

Funding

Research Council of Norway, FRIPRO (12 MNOK, 2021–2025)



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ORIGINAL RESEARCH
published: 25 March 2020
doi: 10.3389/fninf.2020.00011

Finite Element Simulation of Ionic Electrodiffusion in Cellular Geometries

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This research is supported by the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme under grant agreement 714892 (Waterscales).