

Modelling ionic electrodiffusion in brain tissue - the KNP-EMI framework

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Slides courtesy of Ada Johanne Ellingsrud.

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simula

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.:

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

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

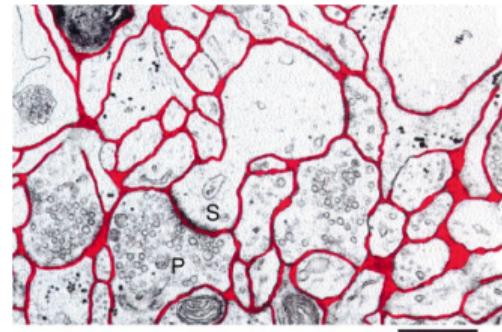
$$\phi_M = \phi_i - \phi_e \quad \text{at } \Gamma, \quad (3)$$

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

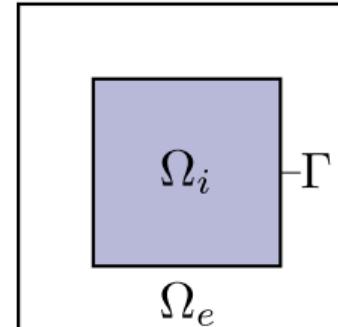
$$\frac{\partial \phi_M}{\partial t} = \frac{1}{C_M} (I_M - I_{\text{ion}}) \quad \text{at } \Gamma. \quad (5)$$

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

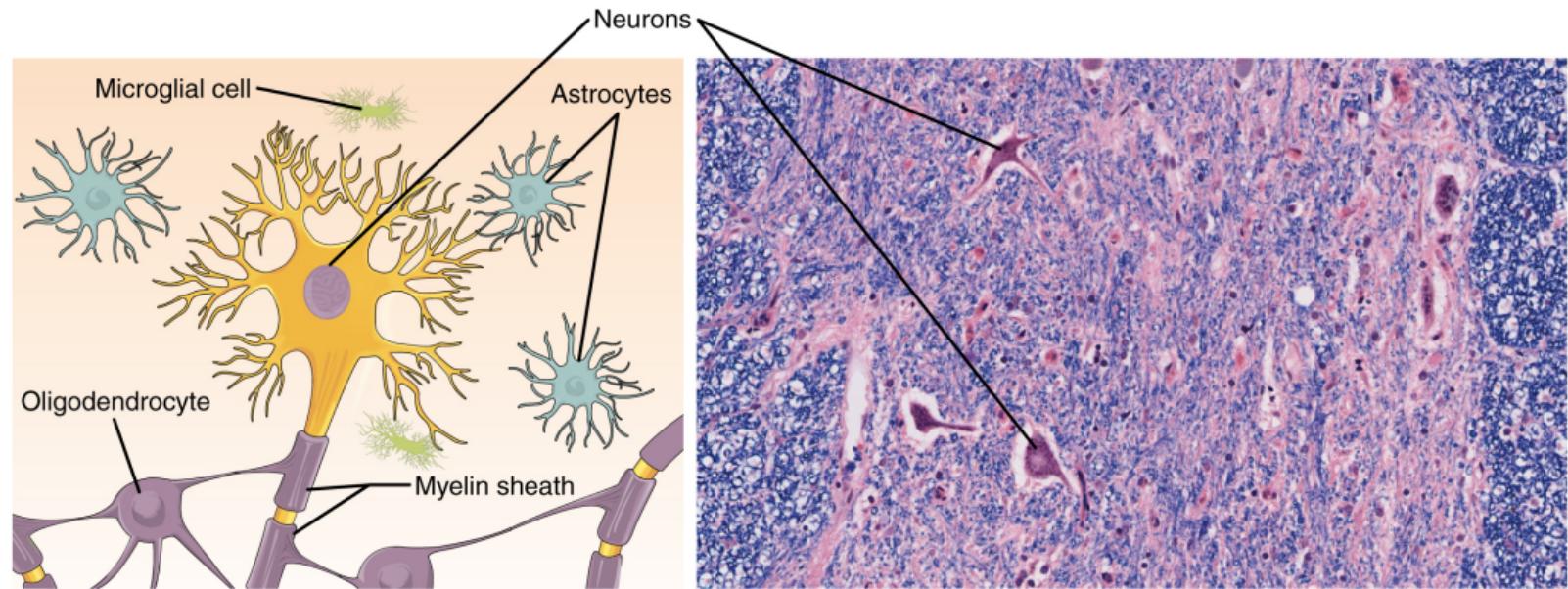
[Krassowska & Neu 1994],
[Ying & Henriquez 2007],
[Tveito et al. 2017]



Rat cortex with ECS in red [Nicholson, 1998]

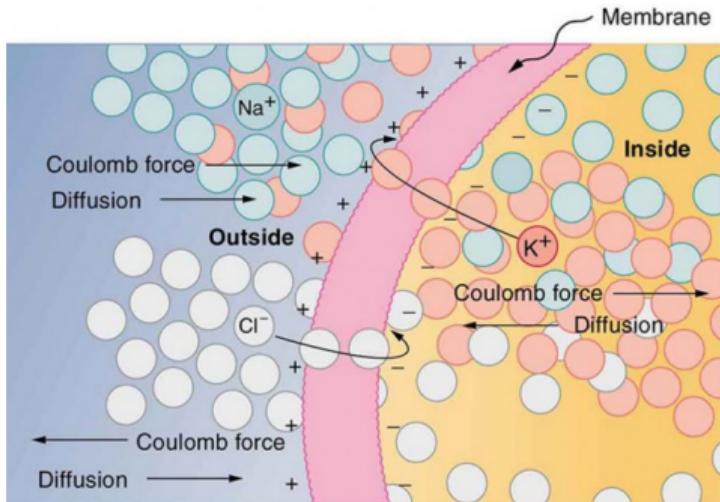


Brain tissue is composed of networks of extracellular spaces and primarily two classes of cells: neurons and glial cells



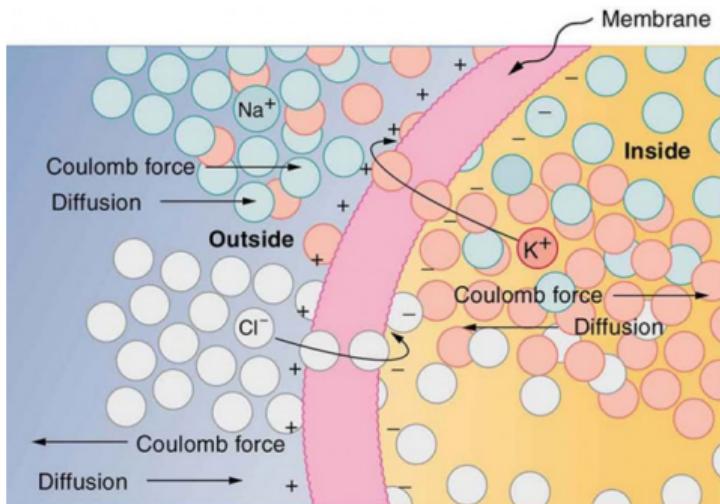
Left panel: Sketch of neurons and glial cells. Right panel: Micrograph of brain tissue. [OpenStax CNX, 2016]

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

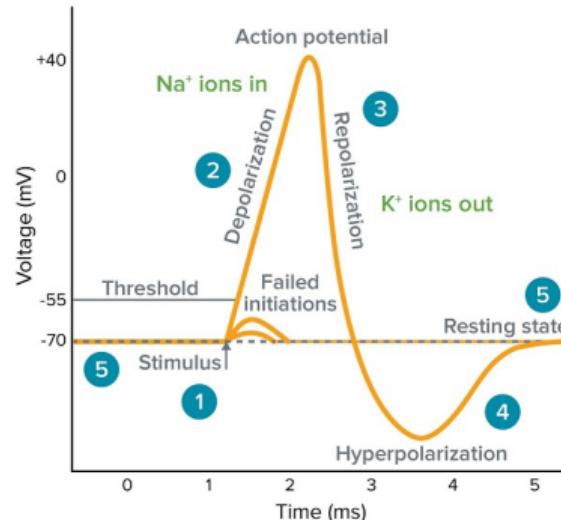


[courses.lumenlearning.com]

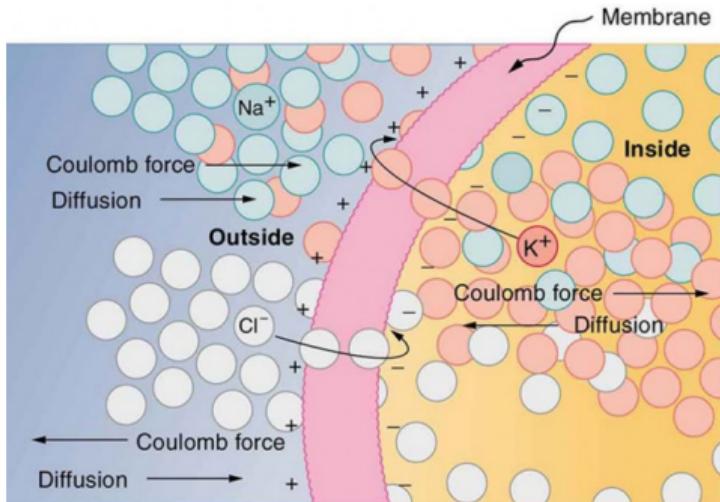
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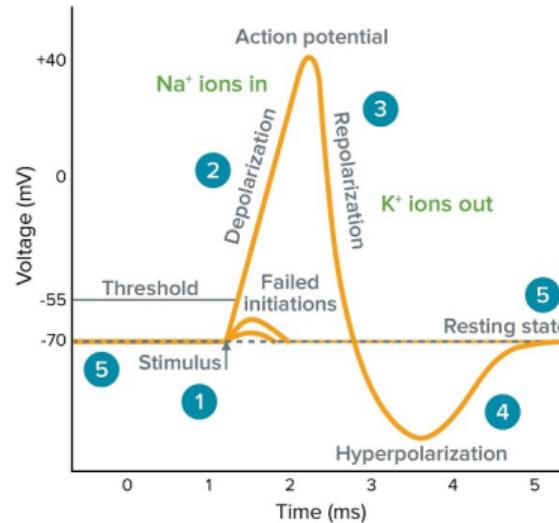
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Movement of ions is fundamental in brain signalling and various mechanisms ensure ionic homeostasis



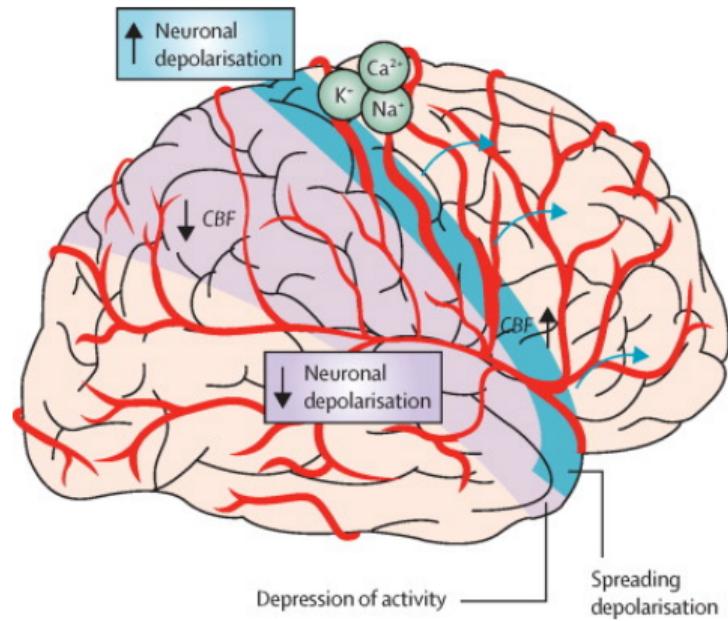
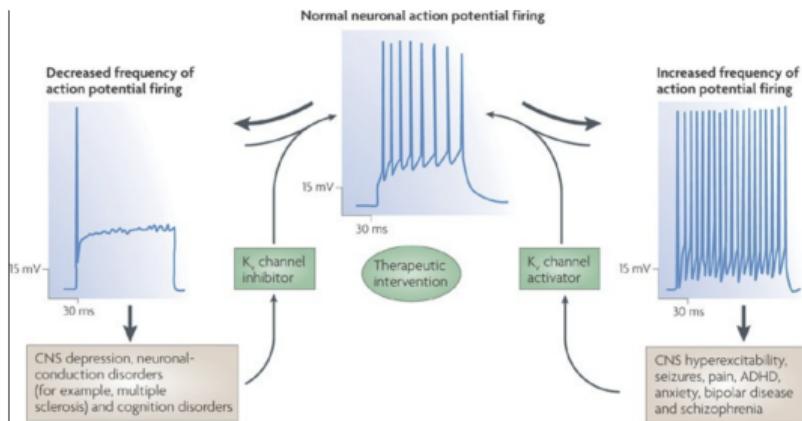
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Homeostatic mechanisms will take the ionic concentrations back towards baseline levels, e.g.:

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

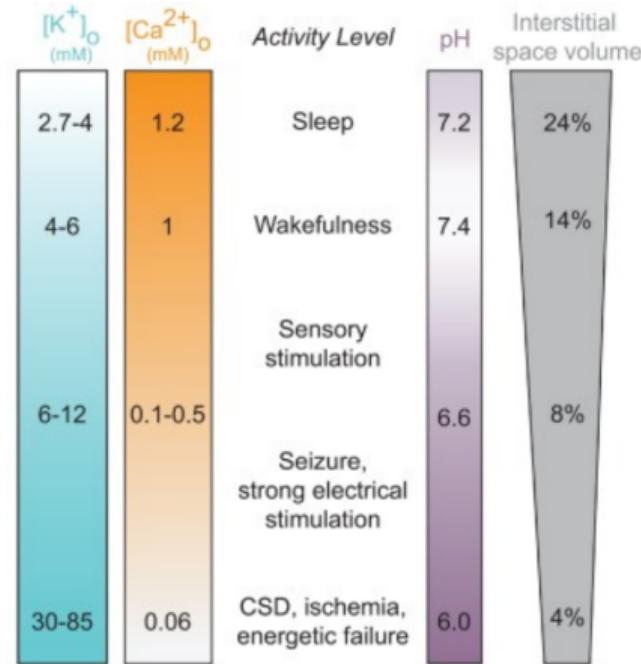
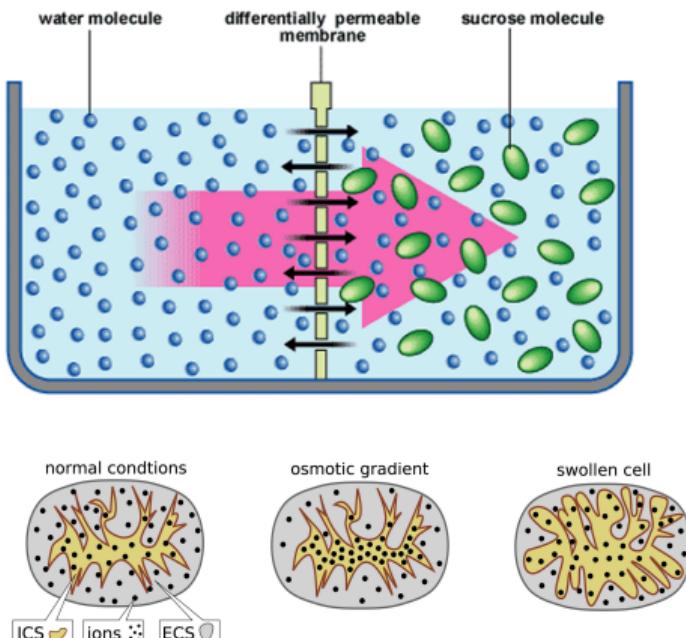
Ion concentration changes are a trademark of several pathological conditions, such as epilepsy or spreading depression



- Homeostatic mechanisms are not able to "keep up"
- Shifts in the ECS ion concentrations

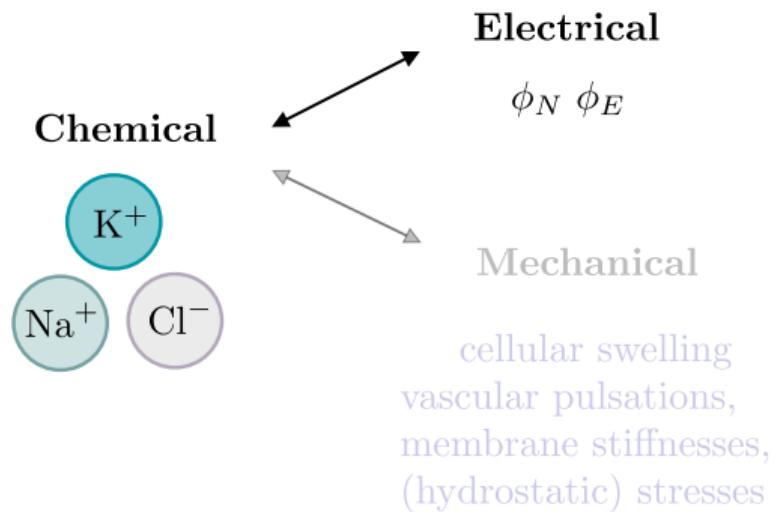
The extracellular ion composition changes with local neuronal activity and across brain states

Ionic shift may set up osmotic gradients causing cellular swelling.



[Rasmussen, 2021]

We need computational models describing electrical, chemical and mechanical interplay in brain tissue



Outline

Modelling electrodiffusion: main assumptions and core ideas

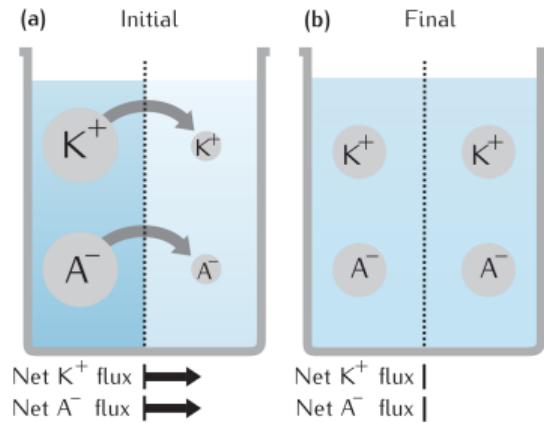
The KNP-EMI framework

A study of ephaptic coupling

Modelling electrodiffusion: main assumptions and core ideas

Electrodiffusion is governed by the Nernst–Planck equation, stating that ions move due to diffusion or drift in the electrical field

Diffusion

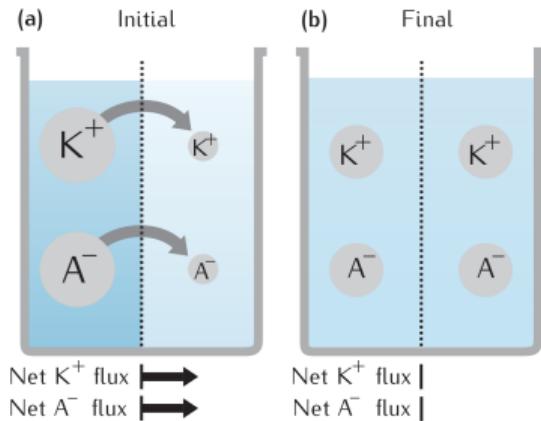


$$\mathbf{J}^k = -D^k \nabla [k]$$

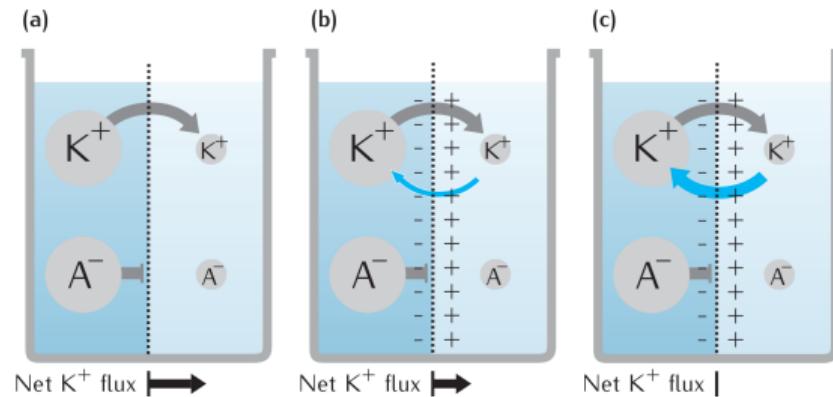
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Diffusion



Electrodiffusion



$$\mathbf{J}^k = -D^k \nabla [k]$$

diffusion

$$\mathbf{J}_r^k = -D^k \nabla [k] - \underbrace{D^k \frac{z_k F}{RT} [k] \nabla \phi_r}_{\text{electrical drift}}$$

Ions are conserved within each region and move due to diffusion or drift in the electrical field (Nernst–Planck)

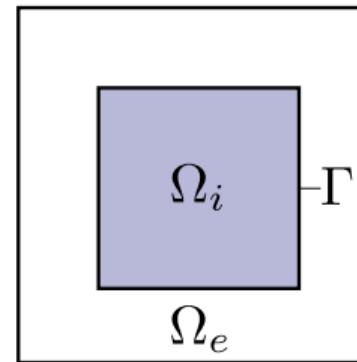
Let $[k]_r = [k]_r(x, t)$ denote the concentration of (ion) species k in compartment r . Conservation of ions in the bulk of each compartment yields:

$$\frac{\partial [k]_r}{\partial t} + \nabla \cdot \mathbf{J}_r^k = 0,$$

where the ion flux density is given by:

$$\mathbf{J}_r^k = -D_r^k \nabla [k]_r - D_r^k \underbrace{\frac{z_k F}{RT} [k]_r \nabla \phi_r}_{\text{electrical drift}}$$

diffusion electrical drift



Tissue domain $\Omega = \Omega_i \cup \Omega_e \subset \mathbb{R}^d$, with (ion) species $k \in K$ (e.g. Na^+ , K^+ , Cl^-).

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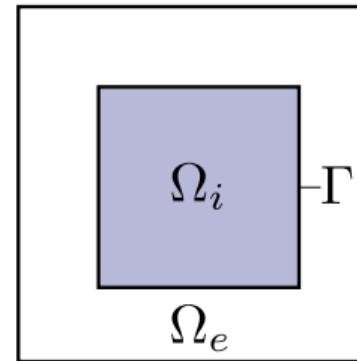
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diffusion electrical drift

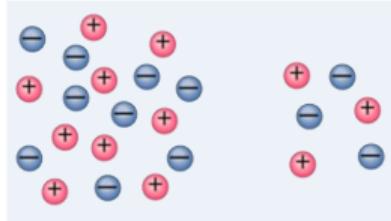
$2|K| + 2$ unknowns, but only $2|K|$ equations:

- Poisson–Nernst–Planck (PNP)
- Kirchhoff–Nernst–Planck (KNP)

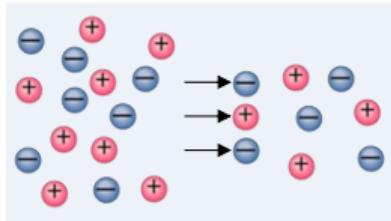


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A charge imbalance in the ECS will typically vanish within nanoseconds

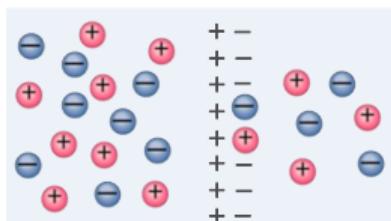


$t = 0$



$t < 10 \text{ ns}$

$D_{\text{Cl}^-} > D_{\text{Na}^+}$: Diffusion
give net (-) charge
transport from left to right.

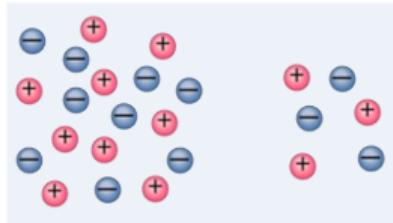


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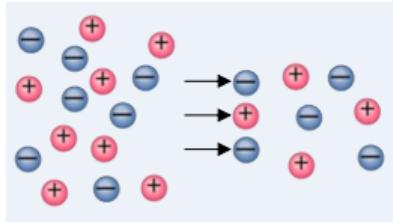
Quasi steady state: the potential ϕ_e prevents further charge separation.

ϕ_e

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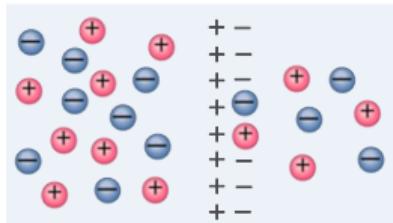


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Poisson–Nernst–Planck (PNP):

$$\nabla^2 \phi_r = -\frac{\rho_r}{\epsilon_r}, \quad \rho_r = F \sum_k z_k [k]_r.$$



$t > 10 \text{ ns}$

Quasi steady state: the
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Kirchhoff–Nernst–Planck (KNP):

$$\frac{\partial \rho_r}{\partial t} = 0, \quad \rho_r = F \sum_k z_k [k]_r.$$

The electroneutrality condition (KNP) is a good approximation on spatiotemporal scales larger than \sim nanoseconds / nanometers

Poisson–Nernst–Planck (PNP)

Explicit modelling of charge relaxation processes - requires fine resolution

[Lopreore et al., 2008]

[Pods et al., 2013]

[Holcman and Yuste, 2015]

[Cartailler et al., 2017, 2017]

[Sacco et al., 2017]

Kirchhoff–Nernst–Planck (KNP)

Electroneutrality assumption - good approximation on larger scales ($>$ nano)

[Mori, 2009]

[Ellingsrud et al., 2020]

The KNP-EMI model

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

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,

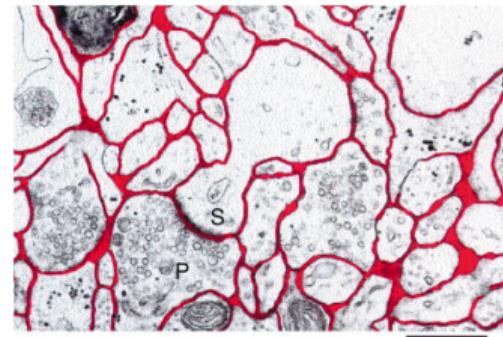
For each compartment $r \in \{i, e\}$,
 $x \in \Omega_r$, $t > 0$, find the:

- electrical potentials $\phi_r(x, t)$,

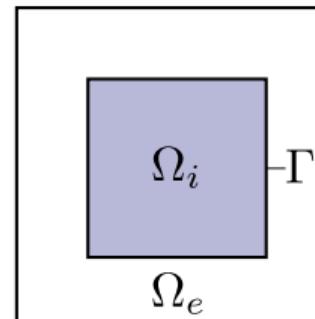
and at the interface, $x \in \Gamma$, $t > 0$, find the:

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

[Krassowska & Neu, 1994]
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Rat cortex with ECS in red [Nicholson, 1998]



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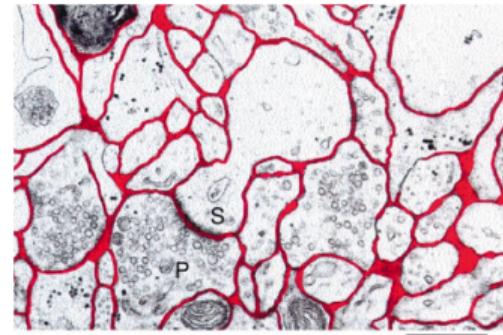
- concentrations $[k]_r(x, t)$,
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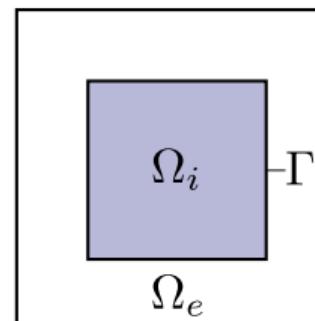
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A computational framework for ionic electrodiffusion in brain tissue with explicit representation of the cells (KNP-EMI)

Conservation of ions for the bulk of each region:

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

Ion flux densities are given by:

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

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"KNP assumption" of bulk electroneutrality:

$$-F \sum_k z^k \nabla \cdot J_r^k = 0, \quad \text{in } \Omega_r.$$

[Pods, 2017]

[Solbrå et al., 2018]

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Changes in the membrane potential are proportional to the transmembrane currents:

$$C_M \frac{\partial \phi_M}{\partial t} - F \sum_k z^k J_i^k \cdot n_i + I_{\text{ion}} = 0, \quad \text{on } \Gamma.$$

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Interface conditions:

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

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

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

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

[Pods, 2017]

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Channels and mechanisms for ion movement across membranes are subject to modelling

Transmembrane ion fluxes are subject to modelling:

$$I_{\text{ion}}^k = I_{\text{ion}}^k(\phi_M, [k], s)$$

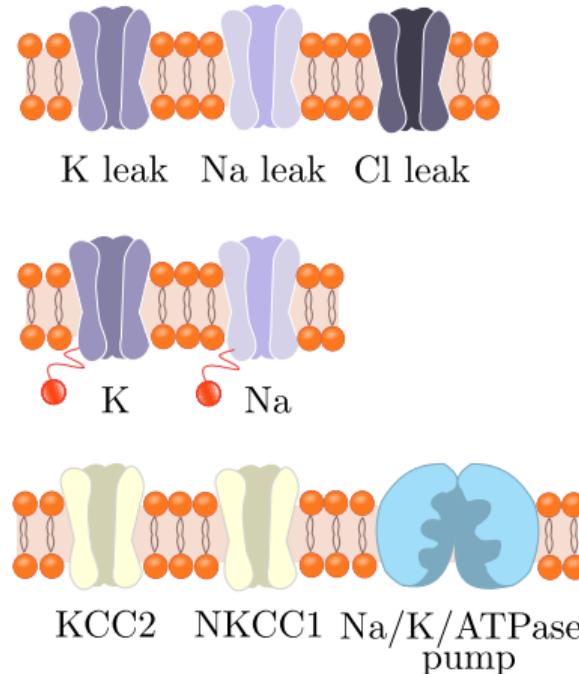
We apply the standard Hodgkin-Huxley model and homeostasis mechanisms ([cotransporters](#) and [Na/K/ATPase-pumps](#)):

$$I_{\text{ion}}^{\text{Na}} = I_{\text{leak}}^{\text{Na}} + I_{\text{Na}} + 3I_{\text{ATP}} + I_{\text{NKCC1}}$$

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

$$I_{\text{ion}}^{\text{Cl}} = I_{\text{leak}}^{\text{Cl}} - 2I_{\text{NKCC1}} - I_{\text{KCC2}},$$

including leak currents and voltage gated Na^+ and K^+ currents ([depending on gating variables governed by ODEs](#)).



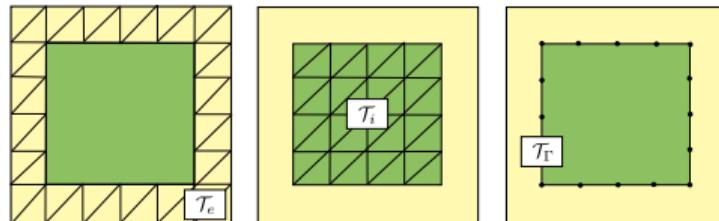
The strongly coupled and non-linear KNP-EMI equations are numerically and computationally challenging to solve

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.



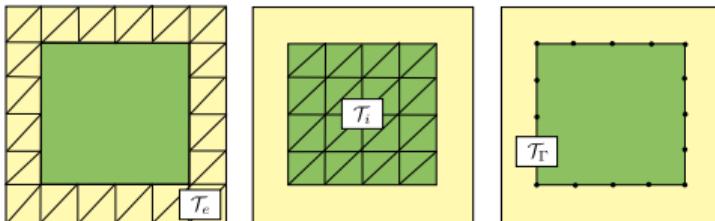
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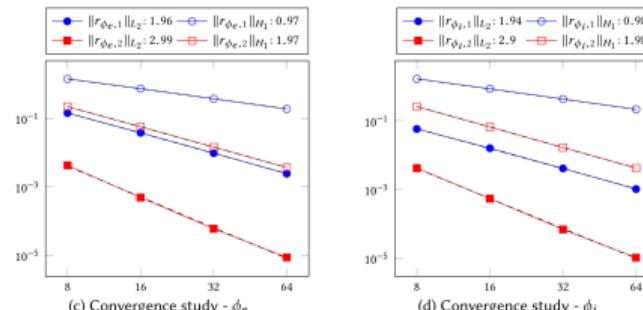
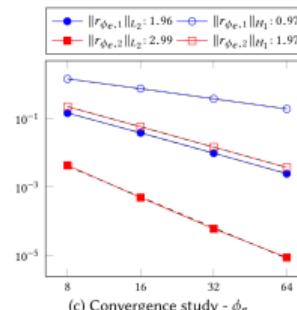
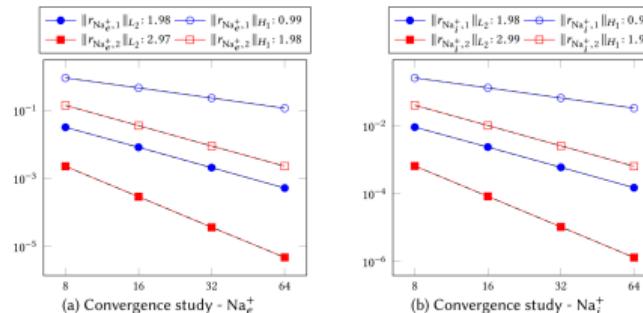
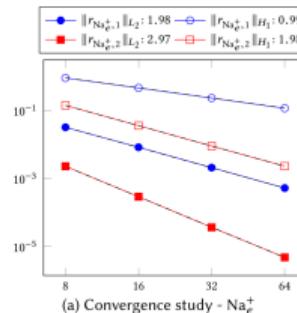
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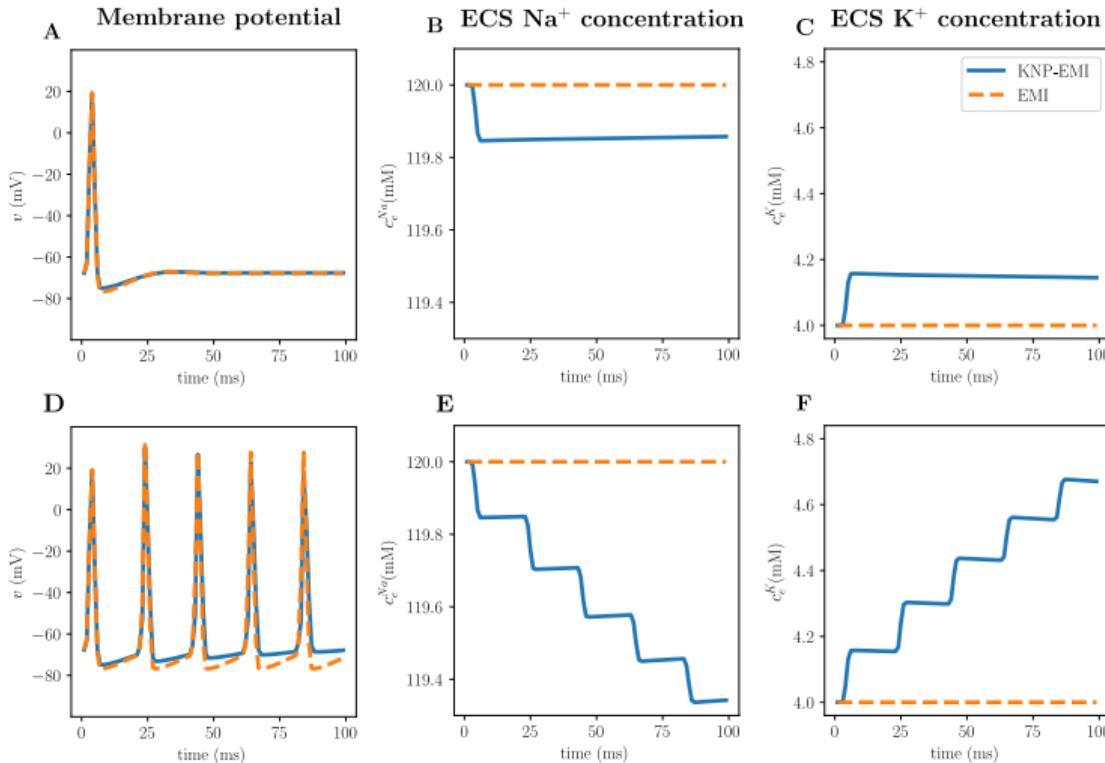
where $V_{r,h}$, $T_{r,h}$, S_h are constructed using continuous piecewise linear polynomials.



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



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



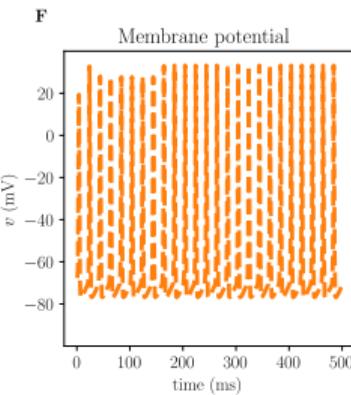
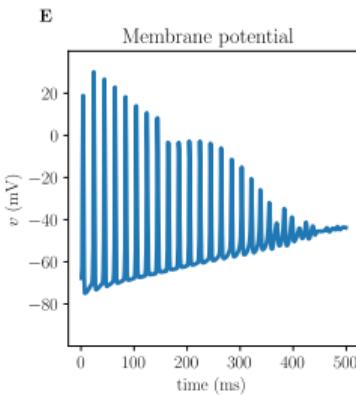
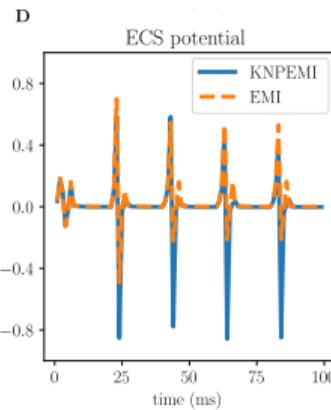
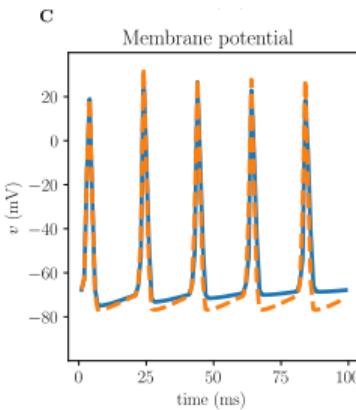
Normal activity (A, B, C):

- 1 Hz
- KNP-EMI and EMI give comparable results

Hyperactivity (D, E, F):

- 50 Hz
- Membrane potential predicted by KNP-EMI slightly (and persistently) depolarizes for each AP

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Normal activity (not shown):

- 1 Hz
- KNP-EMI and EMI give comparable results

Hyperactivity (C, D, E, F):

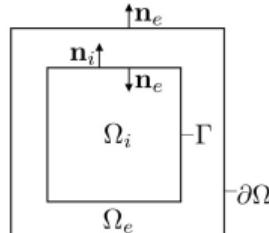
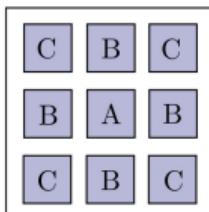
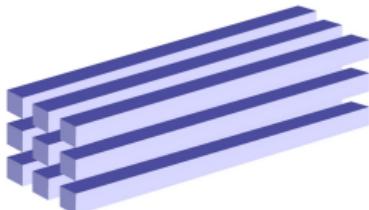
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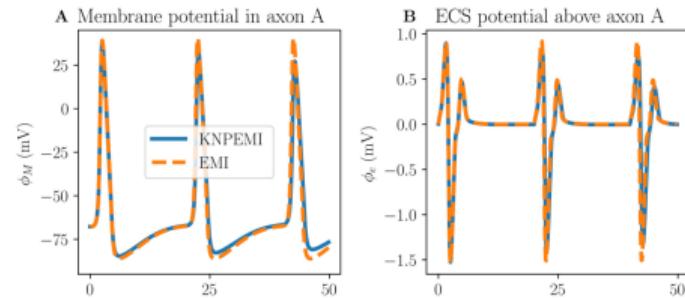
Comparing KNP-EMI and EMI: Do diffusive currents affect ephaptic coupling through the ECS in unmyelinated axon bundles?

In an **idealized axon bundle** with cell gaps of $0.1\mu\text{m}$, 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]

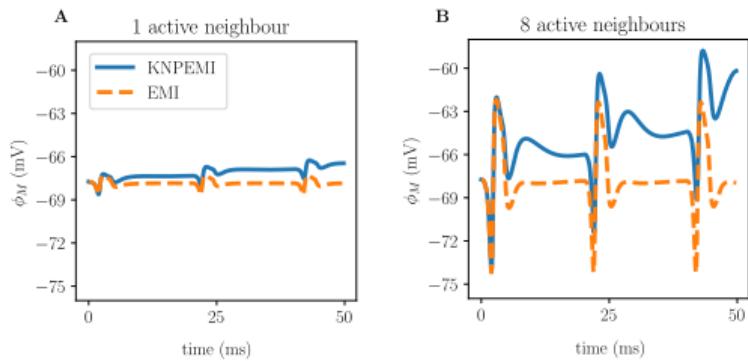


Diffusive currents contribute to ECS potential shifts in the KNP-EMI framework:

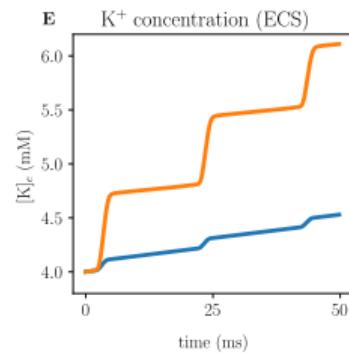
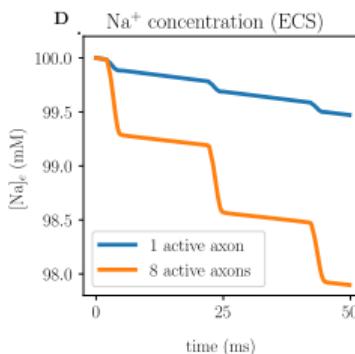
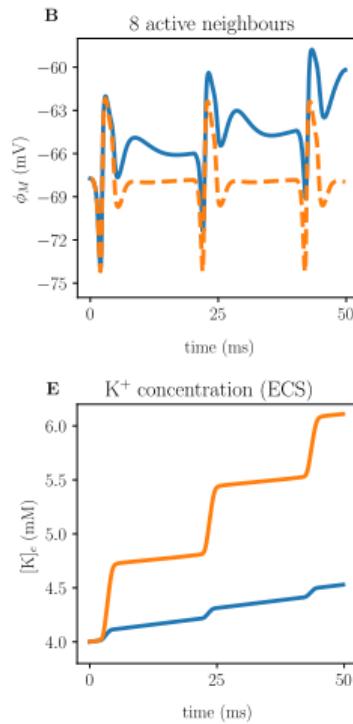
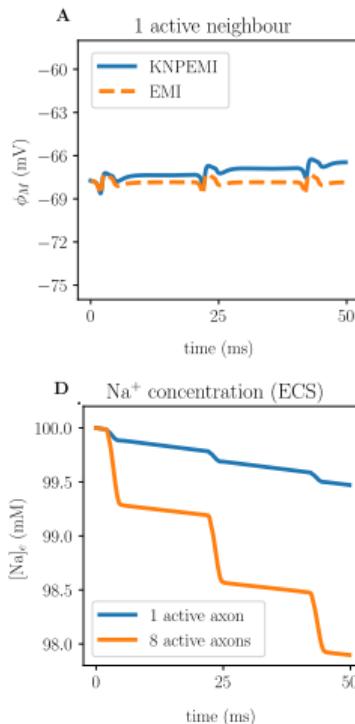
$$\begin{array}{ll} \text{EMI} & \nabla \cdot (\sigma_e \nabla \phi_e) = 0, \text{ in } \Omega_e, \\ \text{KNP-EMI} & \nabla \cdot (\sigma_e \nabla \phi_e + \nabla b_e) = 0, \text{ in } \Omega_e, \end{array}$$

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

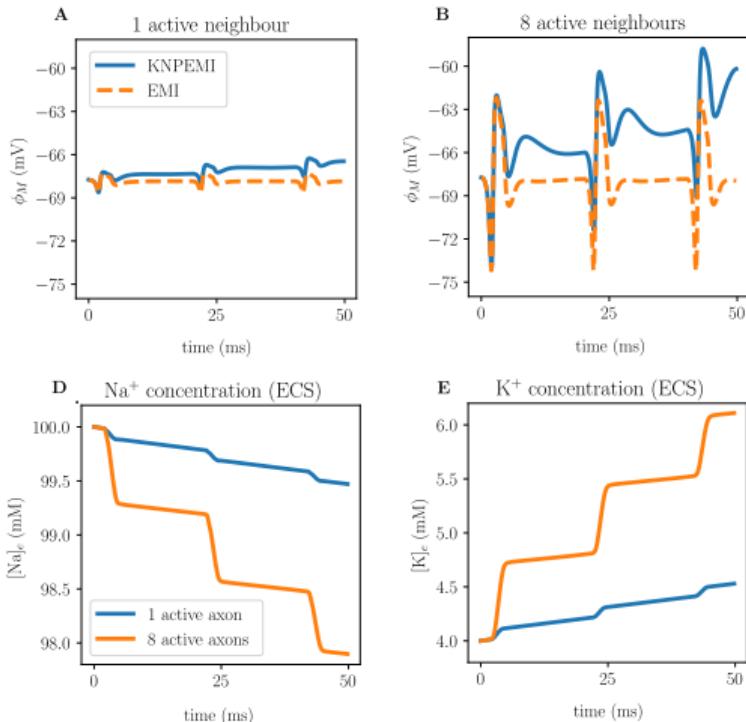
Diffusive currents do not strengthen the *electrical* ephaptic coupling (via the extracellular potential), however we see *diffusive* ephaptic coupling



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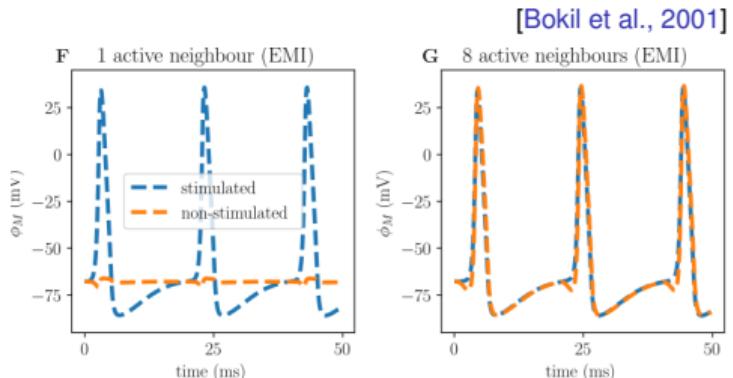
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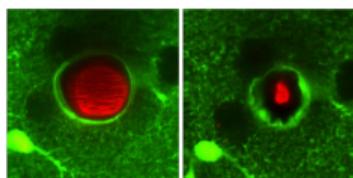
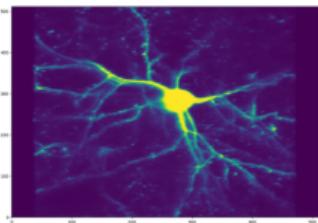
Ephaptic coupling is inversely proportional to the **extracellular conductivity**:

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

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

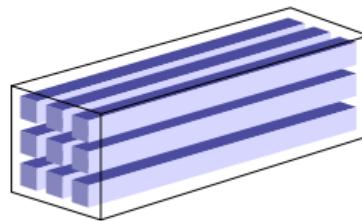


The KNP-EMI framework allows for detailed computational studies of the interplay between ion movement and electrical potentials.

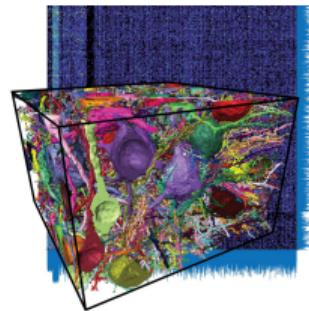


- Study **neuronal** group dynamics, synchronization and interplay
- The role of **astrocytes** in signalling, clearance, and buffering

KNP-EMI simulations call for further research into efficient and scalable solution methods



[Ellingsrud et al., 2020]



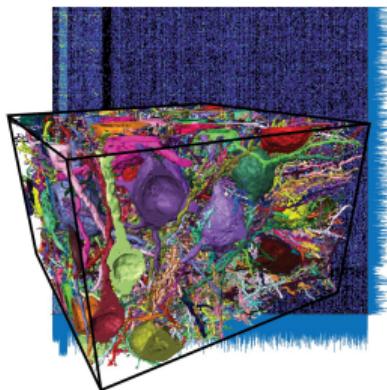
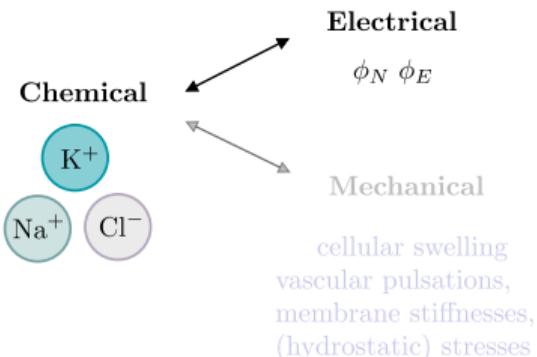
[Motta et al., 2019]

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European Research Council
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In the KNP framework, the only allowed non-zero charge density is that building up the membrane potential

Assume that the rate of change of the charge density ρ_r in each compartment r is zero (electroneutrality):

$$\frac{\partial \rho_r}{\partial t} = 0, \quad \rho_r = F \sum_k z_k [k]_r.$$

The only allowed nonzero charge density in the KNP-system is that building up the membrane potential across a capacitive membrane:

$$\frac{\partial \rho_M}{\partial t} = -I_{\text{cap}}.$$

