Electrodiffusion Simulations of Neurons and Extracellular Space

Models of the Axonal Membrane and Surrounding Fluids Based on the PNP Equations of Electrodiffusion

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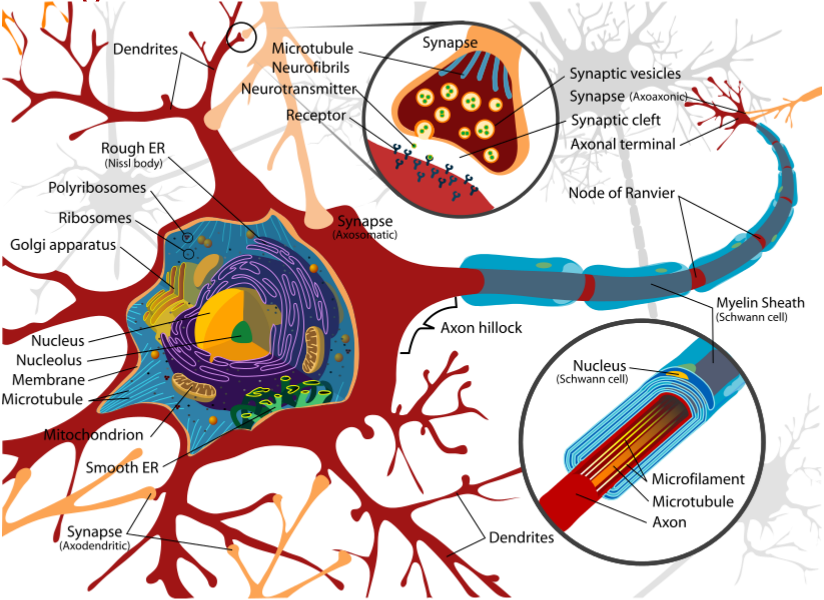
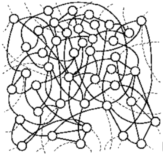
Biological Neuron Models: Levels of Abstraction



http://en.wikipedia.org/wiki/Myelin_sheath_gap

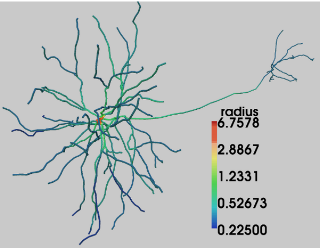
Biological Neuron Models: Levels of Abstraction

Point neurons (“0D”)



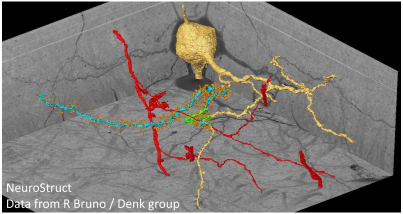
University of Minnesota, 2004

Compartment models (“1D”)



Dan Popovic, IWR

Panos Drouvelis, Stefan Lang, IWR



Detailed 2D and 3D electrodiffusion models

IWR

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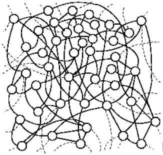

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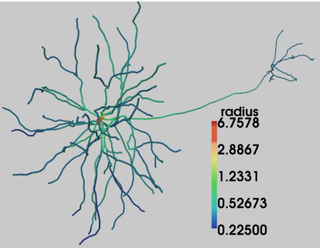

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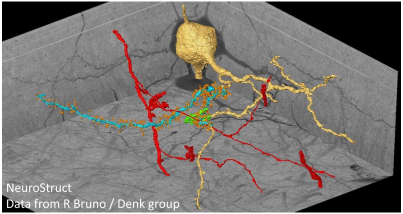

Detailed 2D and 3D electrodiffusion models

IWR

The Nernst-Planck-Poisson System

describes ion drift through a static solvent.

Nernst-Planck: $$\frac{\partial n_i}{\partial t} - \nabla \cdot \mathbf{F}_i = 0$$ (conservation of charge)

with the ion flux $$\mathbf{F}_i = D_i \left(\nabla n_i + z_i n_i \nabla \phi \right)$$

Poisson: $$\nabla \cdot (\epsilon \nabla \phi) = -\frac{e^2 n^*}{\epsilon_0 k T} \sum_i z_i n_i$$

- For ion species i:
  - n_i: relative concentration (with respect to scaling concentration n^*)
  - z_i: valence ($\pm$ 1)
  - D_i: (position-dependent) diffusion coefficient
- ϕ: relative electric potential energy with respect to the thermal energy ($\phi = \frac{e}{kT} U$ with U in Volts)
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- T: temperature of the solvent
- e, ϵ_0, k: natural constants

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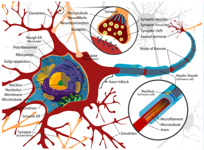
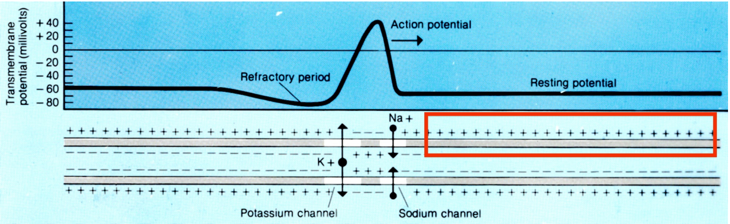
Assumptions of a reduced model: Single Axon

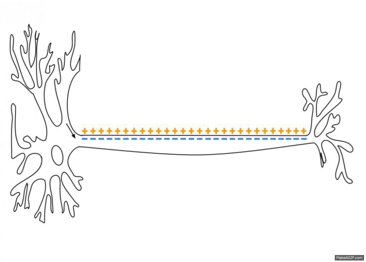


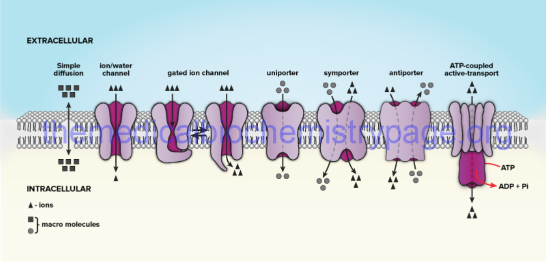


http://courses.washington.edu/psy222/psy222actionpotential.htm

- 3 ion species: Na^+, K^+, Cl^-
- homogeneous intra- and extracellular medium: water
- membrane thickness: 5 nm
- No ions inside the membrane $\Rightarrow$ Additional boundary conditions at membrane interfaces representing ion channels
- In a first approximation, an axon is a cylinder
  Assume rotational symmetry $\Rightarrow$ Reduction to 2D problem!

Special Part: Membrane





Membrane dynamics are taken from Hodgkin-Huxley model with a one voltage dependent one (voltage-independent) leak channel for each cation (Na^{+}, K^{+})

The Hodgkin-Huxley System

For each channel type C:

$I_C = g_C[\phi]$ $\qquad g_C$: conductance, $[\phi]$: membrane potential

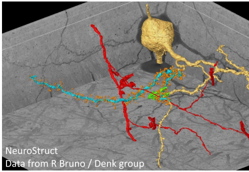
$$g_{\mathrm{K}_v} = \bar{g}_{\mathrm{K}_v} n^4$$
$$g_{\mathrm{Na}_v} = \bar{g}_{\mathrm{Na}_v} m^3 h$$

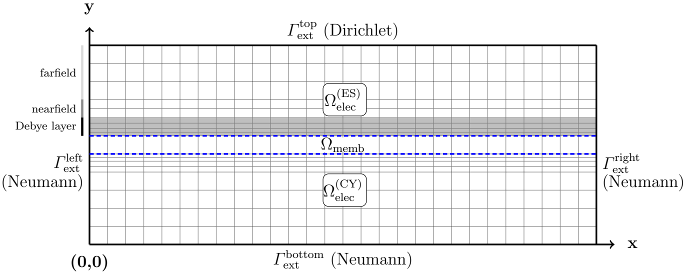
with maximum conductances $\bar{g}_{\mathrm{K}_v}, \bar{g}_{\mathrm{Na}_v}$ and gating particles $n, m, h \in [0\ 1]$, following time- and voltage-dependent kinetics

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(\phi)(1-n) - \beta_n(\phi)n$$
$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(\phi)(1-m) - \beta_m(\phi)m$$
$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_n(\phi)(1-h) - \beta_h(\phi)h$$

Computational Domain / Boundary Conditions

Multidomain setup / Dimension reduction

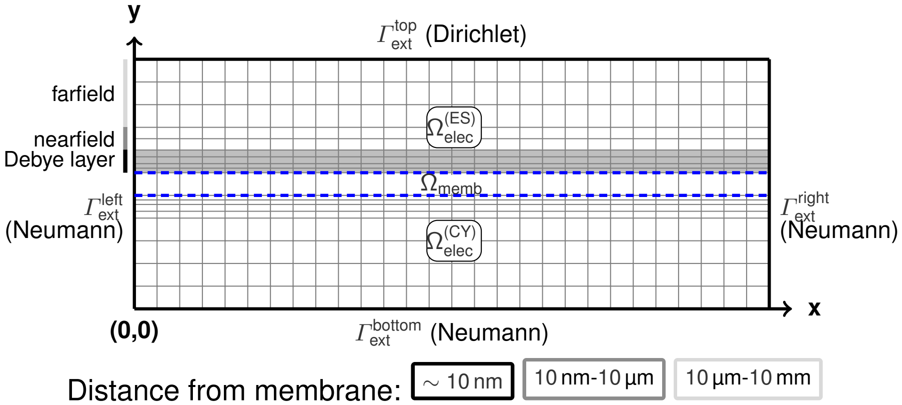




Internal Neumann boundary for concentrations:

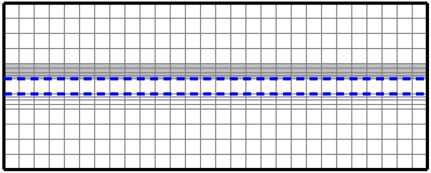
$$F_i(\mathbf{x}) = f_i^{memb}(\mathbf{x}) = g_i(\phi, t)\frac{kT}{e^2 z^2 n^*}\left(z[\phi] + \ln\frac{n_i^{ES}}{n_i^{CY}}\right)$$

Computational Domain



- Debye length needs to be resolved close to the membrane (Debye length $<<$ membrane thickness $\Rightarrow$ electrolytes are electrically decoupled)
- Grid is highly anisotropic ($dx = 100\,\mu m$, $dy_{min} = 0.5\,nm$, factor 200,000)

Implementation in DUNE



Grid:

- 2D Tensor grid
  - Sequential: `UGGrid`
  - Parallel: `YaspGrid` + `GeometryGrid`
  - Test stage: Tensor-`YaspGrid`
- Multiple domains: `MultidomainGrid`

Discretization:

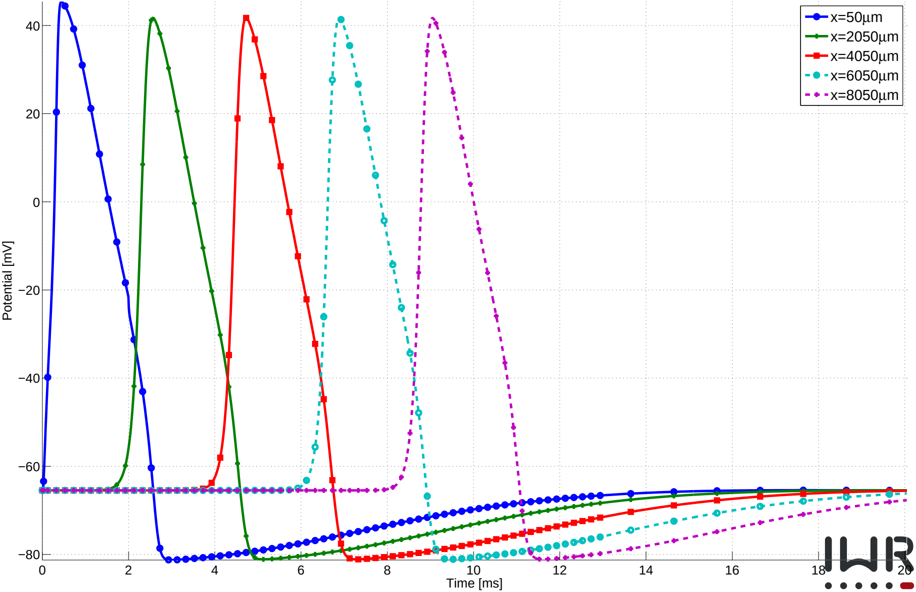
- Heidelberg ⇒ PDELab

Used modules: Core modules, `dune-multidomaingrid`, `dune-multidomain`, `dune-pdelab`

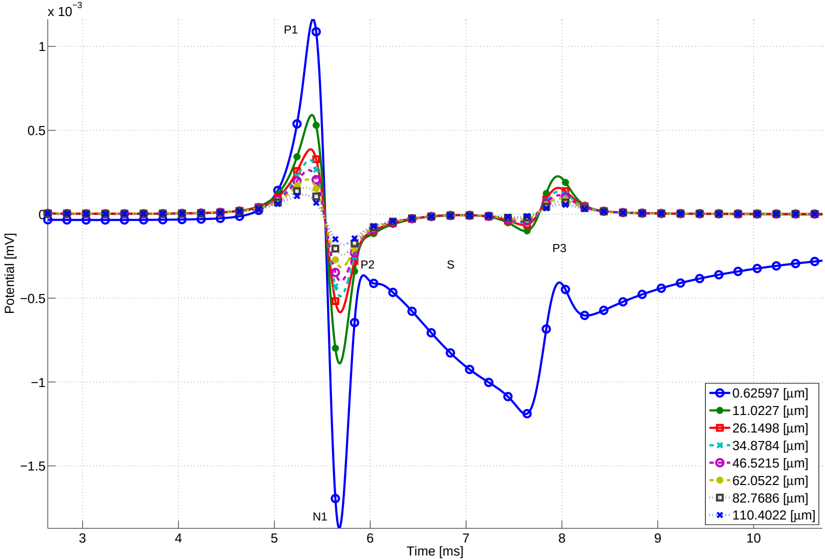
Numerical methods

- Linear Finite Elements (Continuous Galerkin)
- Time stepping: Implicit Euler
- PDE system is solved fully-coupled (Newton's method with line search) $\Rightarrow$ significantly higher time step!
- ODE system for HH kinetics (membrane flux) is solved separately (implicit Euler), once at the beginning of each time step
- linear solvers (ISTL):
  - direct solver (SuperLU)
  - BiCGStab + ILUn preconditioner
  - Restarted GMRes + AMG preconditioner (ILU smoother)
  - In parallel: Use overlapping versions of the above solvers

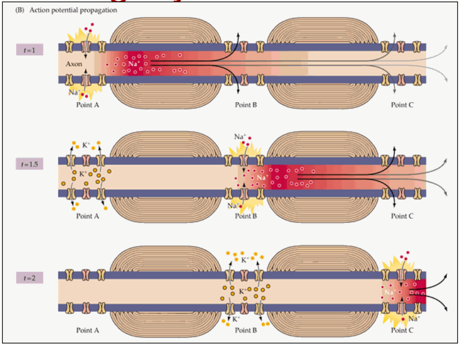
Intracellular potential



LFP signals for increasing distance from the membrane



Adding myelin to the axon



- Myelin serves as an insulating layer around the axon $\Rightarrow$ faster conduction
- Areas between myelin sheats are called nodes of Ranvier
- Action ptential is “refreshed” at nodes by membrane currents
- “Saltatory conduction” from node to node

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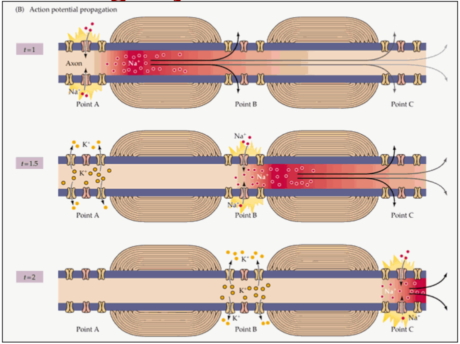

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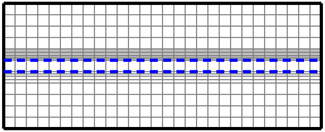

How to get the new geometry into the existing setup?

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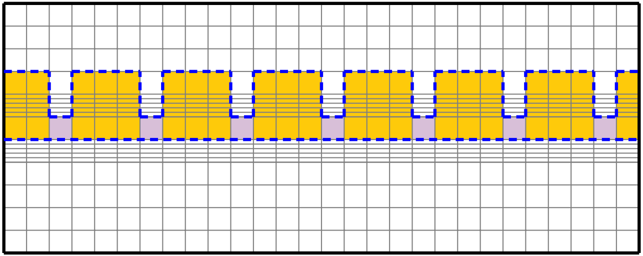
Precondition: I want to keep my beloved tensor grid!

- One could explicitly include the myelin sheath



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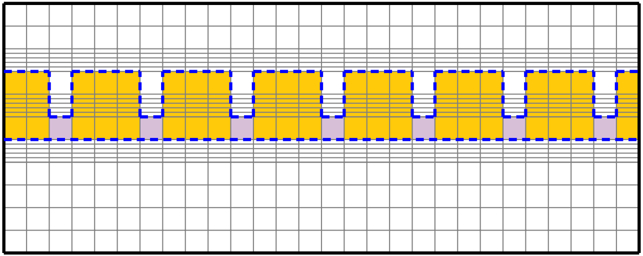

How to get the new geometry into the existing setup?

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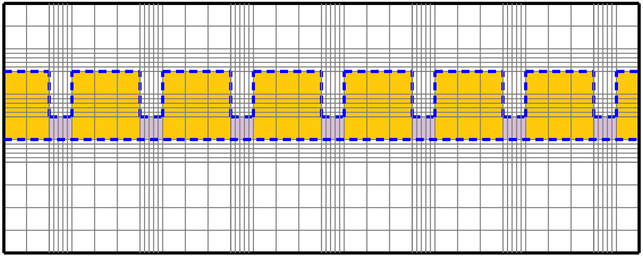
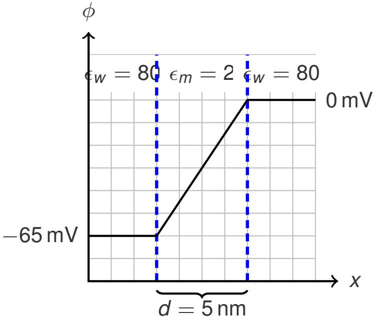
- One could explicitly include the myelin sheath
- ... but we would have to resolve the Debye layer twice!
- A vertical part of the membrane appears, how to handle that?



How to get the new geometry into the existing setup?

Observation: Potential is approximately a linear function over the membrane

$\Rightarrow$ A membrane with permittivity $\epsilon = 2$ and thickness $d = 5\,\text{nm}$ will cause the same potential decay than one with $\epsilon = 4$ and $d = 10\,\text{nm}$



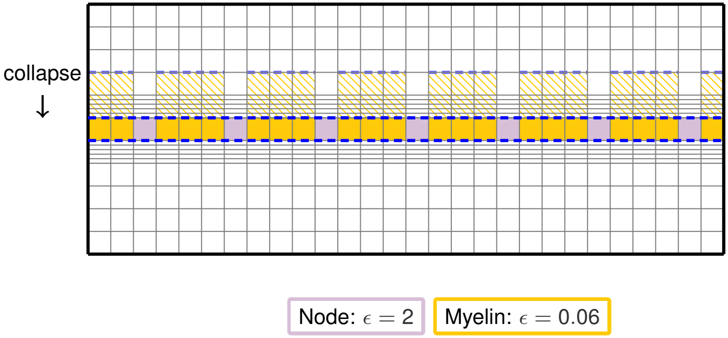
$C = \frac{\epsilon_w}{\epsilon_m}$ is the factor by which the potential gradient changes

How to get the new geometry into the existing setup?

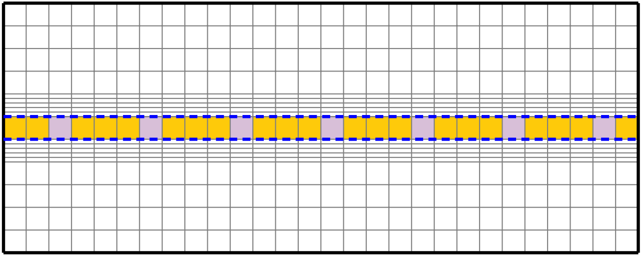
Idea: Do not include node geometry explicitly, but calculate effective permittivities for a “collapsed” myelin sheath!

- Membrane: Thickness $d_{\text{node}} = 5\,\text{nm}$, permittivity $\epsilon_{\text{node}} = 2$
- Myelin: Thickness $d_{\text{myelin}} = 500\,\text{nm}$, permittivity $\epsilon_{\text{myelin}} = 6$

$\Rightarrow$ Effective permittivity $\epsilon^{\text{eff}}_{\text{myelin}} = \epsilon_{\text{myelin}} \frac{d_{\text{node}}}{d_{\text{myelin}}} = 0.06$



Grid for the myelinated axon

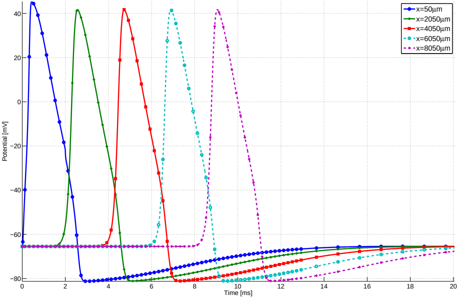


- Length of a node of Ranvier: 1 µm
- Length of the axon: 10 mm
- Equidistant spacing in x-direction not possible anymore
- Finer resolution at nodes of Ranvier and transitions to myelin, coarser spacing at myelin sheath

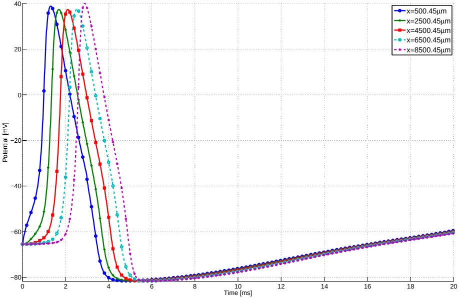
⇒ Strongly varying grid sizes in both x- and y-direction

Intracellular potential

Propagation is faster!



$v \approx 1 \, \frac{\text{m}}{\text{s}}$

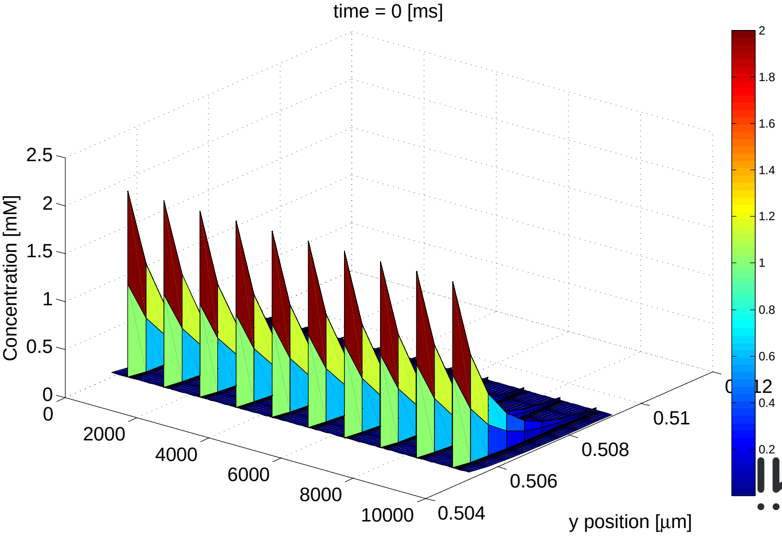


$v \approx 5 \, \frac{\text{m}}{\text{s}}$

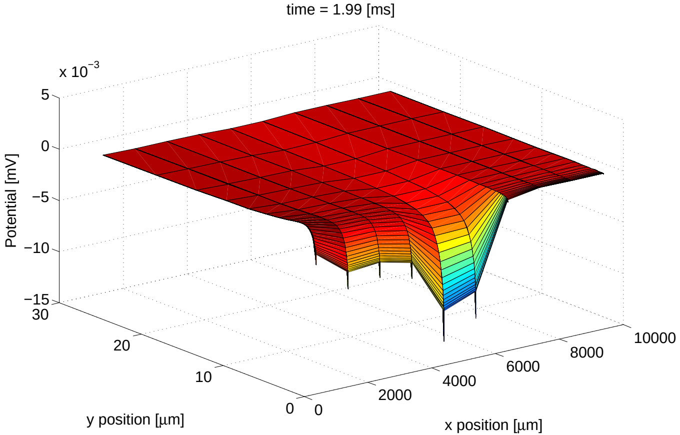
Equilibrium State

Varying permittivities ⇒ different membrane potentials

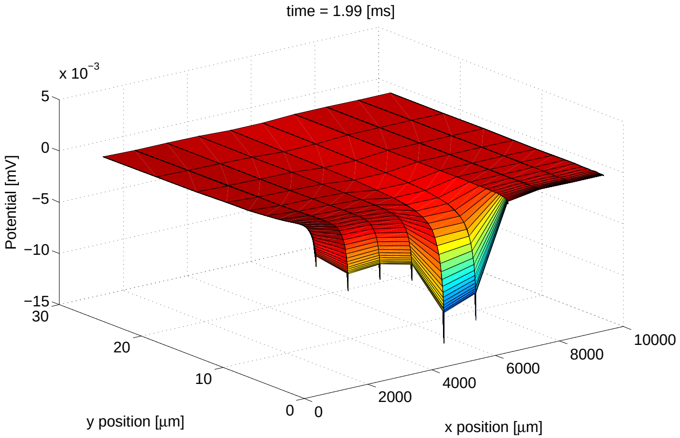
⇒ “comb-shaped” equilibrium concentration profile



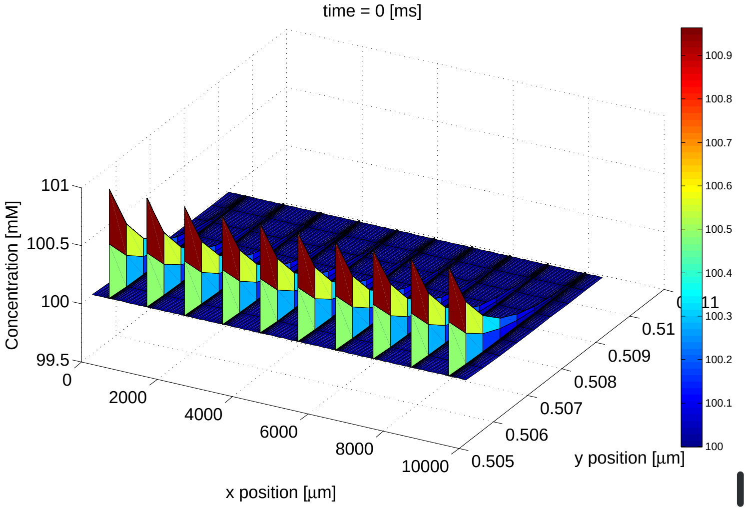
Extracellular potential near membrane (nodes of Ranvier)



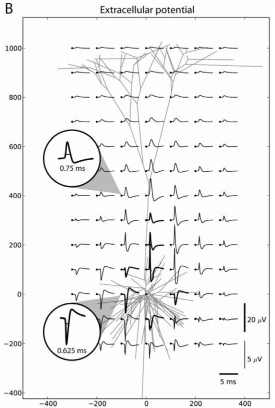
Extracellular potential near membrane (myelin)



Extracellular concentrations near membrane (myelin + nodes)



Comparison with an effective model: Line Source Approximation (LSA)



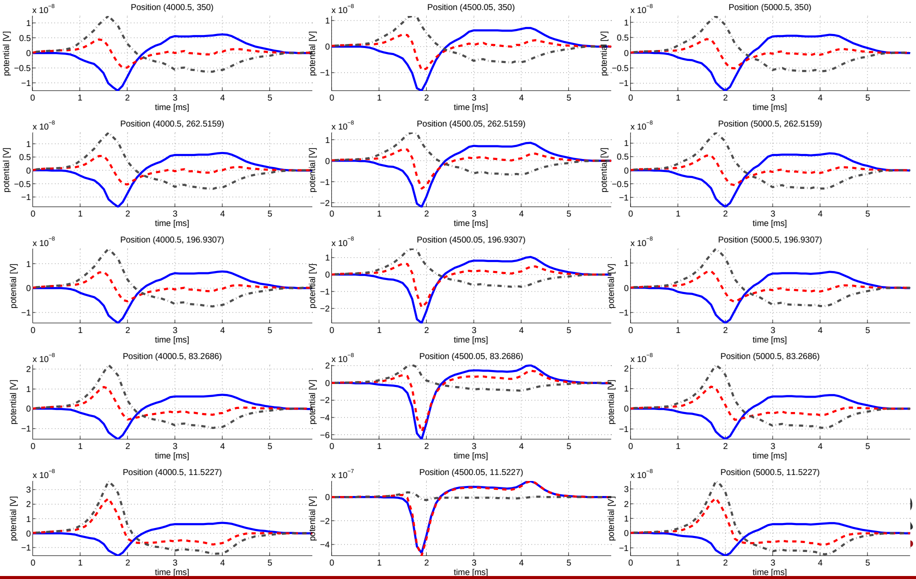
Pettersen & Einevoll 2009

Potential of one line segment:

$$\Phi(r,h) = \frac{\rho I}{4\pi \Delta s} \log \left| \frac{\sqrt{h^2 + r^2} - h}{\sqrt{l^2 + r^2} - l} \right|$$

- ρ: resistivity of the extracellular medium
- I: Total membrane current of line segment
- Δs: length of line segment
- r: radial distance from the line
- h: longitudinal distance from the end of the line
- $l = \Delta s + h$: distance from the start of the line

LFP signals for increasing distance from the membrane



Summary

- Electrodiffusion simulations of the brain using Poisson-Nernst-Planck equations
- Usage of a stacked meta grid hierarchy (`YaspGrid` in a `GeometryGrid` in a `MultidomainGrid`)
- Parallelization with custom overlapping partitioning (`YLoadBalance`) on a low number of processors $p \leq 10$
- 3D results, but only 2D cost by exploiting cylinder symmetry
- Results generally show deviations from effective LSA model for both unmyelinated and myelinated axon, good agreement at nodes of Ranvier

Outlook

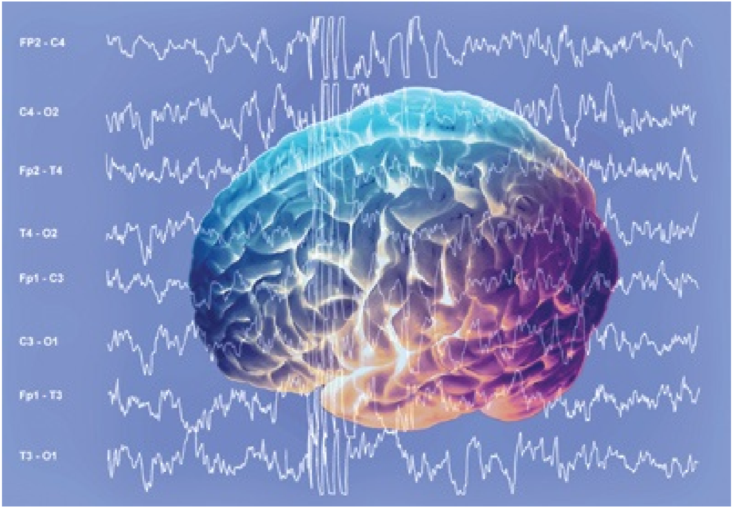
Next steps:

- Improve the modeling of the intra- and extracellular medium, i.e. effective diffusion coefficients and permittivities

- Run larger simulations of myelinated axon
  - larger domain
  - finer resolution (remove spurious oscillations, check grid convergence)

- Improve effective LSA model: Include AP echo as an additional term into the equation

Thank you for your attention!



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