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waterscales



The Research Council
of Norway

Cell-based modelling and simulation of excitable tissue

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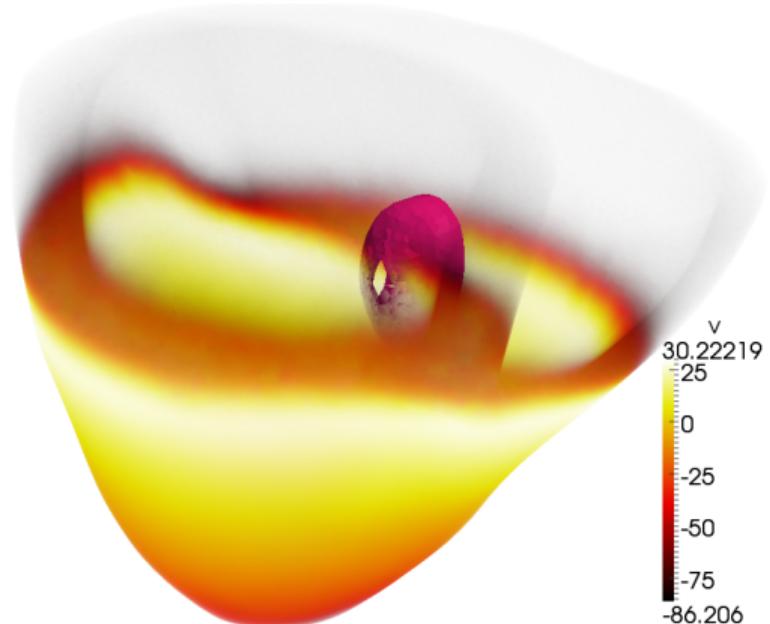
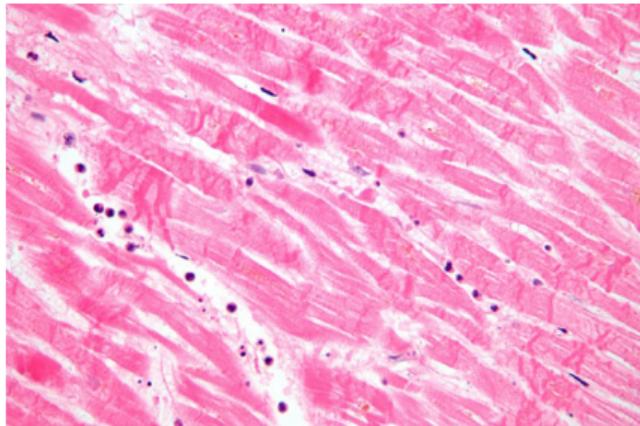
SUURPh Summer School in Computational Physiology
June 2022

Classical excitable tissue models require numerical resolutions below model resolution

$$v_t - \operatorname{div}(M_i \nabla v + M_i \nabla u_e) = -I_{\text{ion}}(v, s)$$

$$\operatorname{div}(M_i \nabla v + (M_i + M_e) \nabla u_e) = 0$$

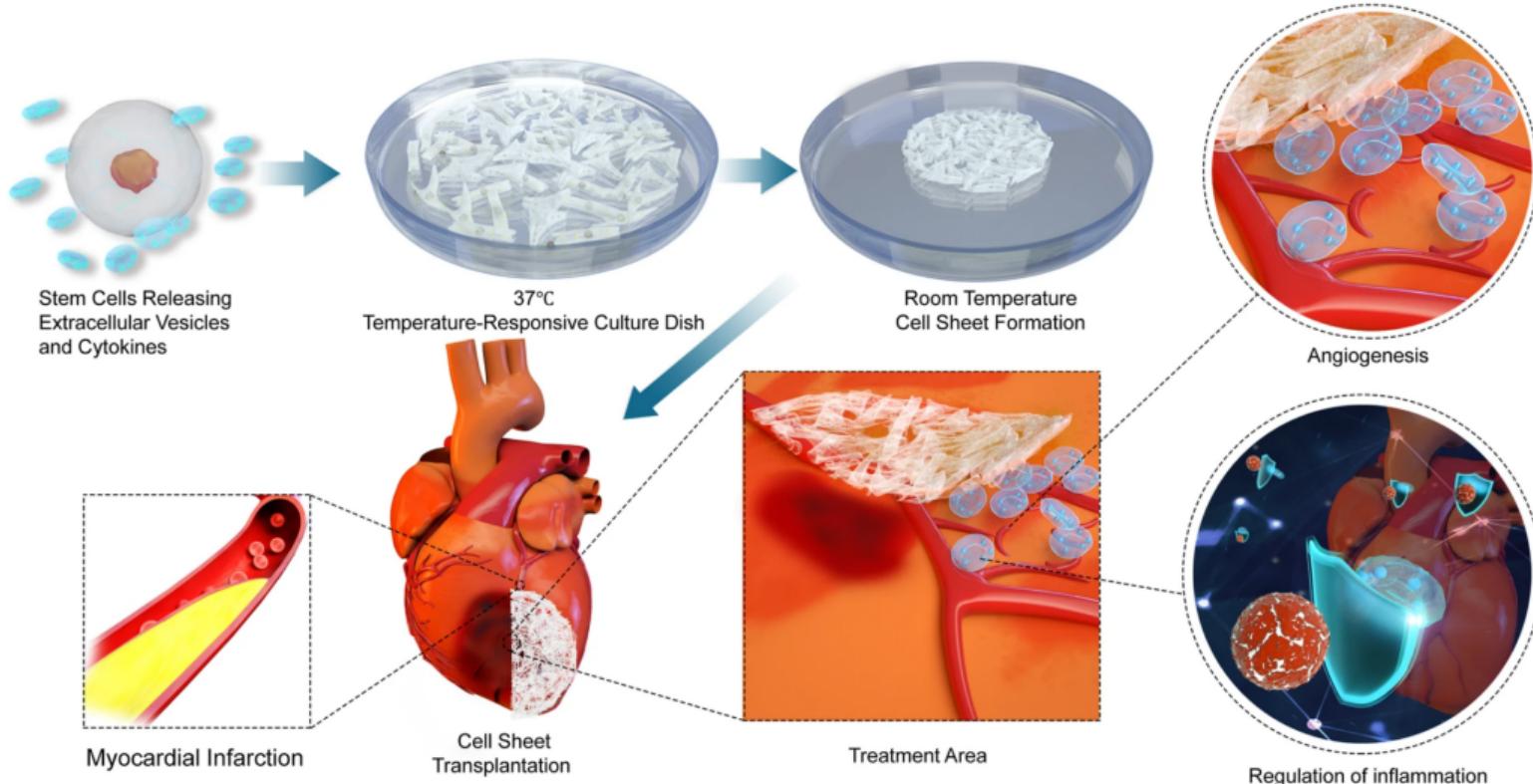
$$s_t = F(v, s)$$



Physiological heart cell: $h \approx 100\mu\text{m}$
Computational mesh cell: $h \leq 100\mu\text{m}$

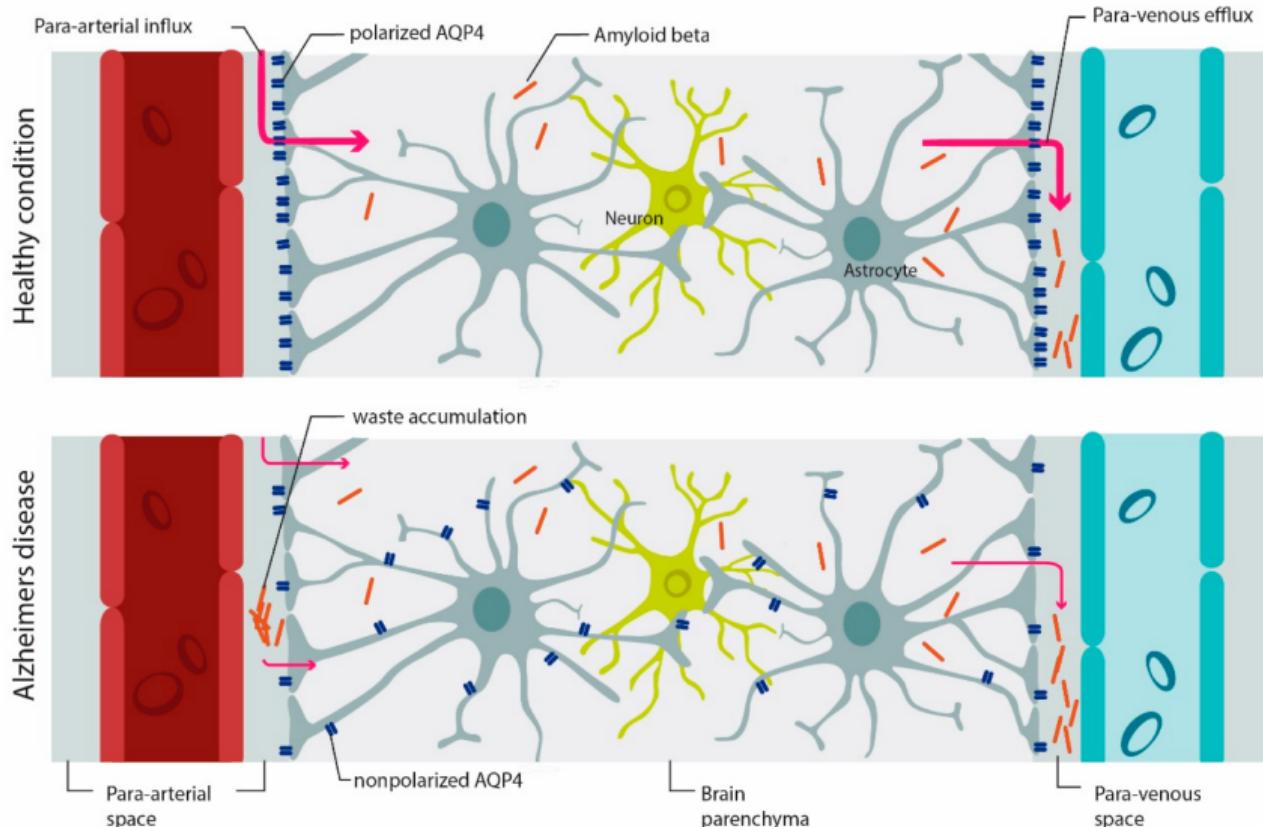
How to model and simulate a small collection of excitable cells?

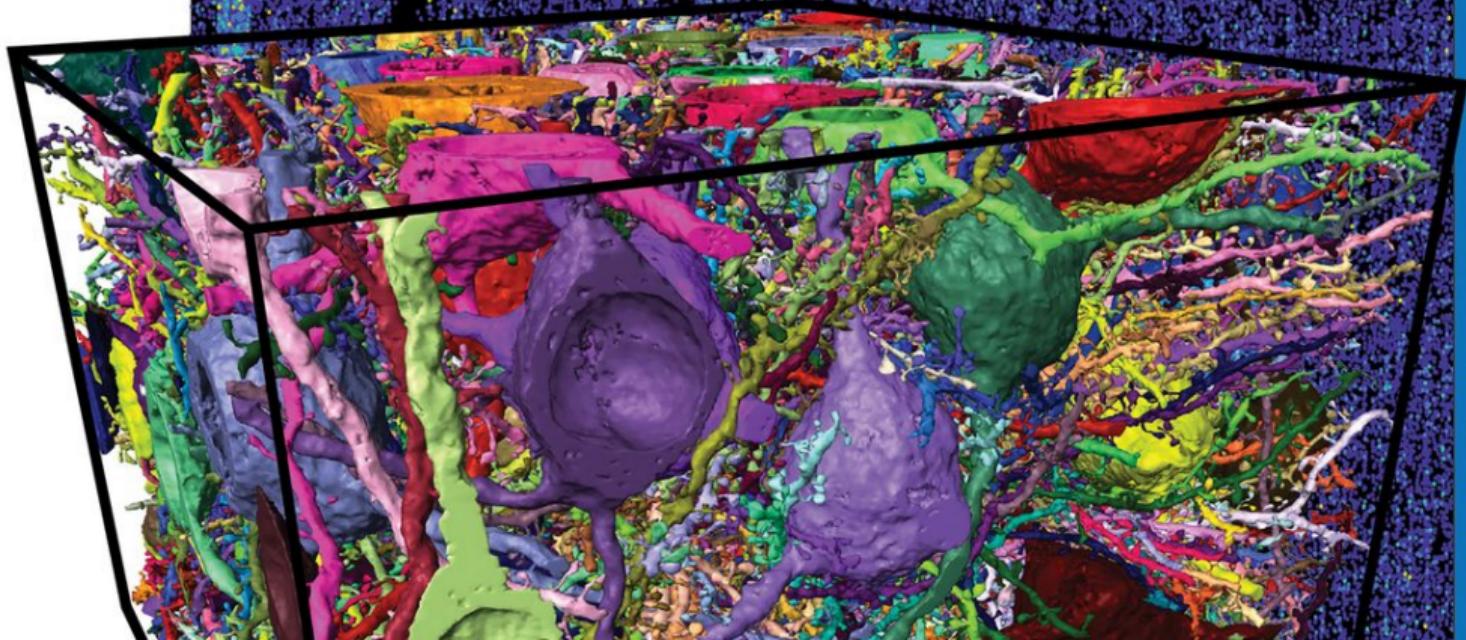
[Guo et al (2020)]



How to model spatial variations in astrocyte membrane properties?

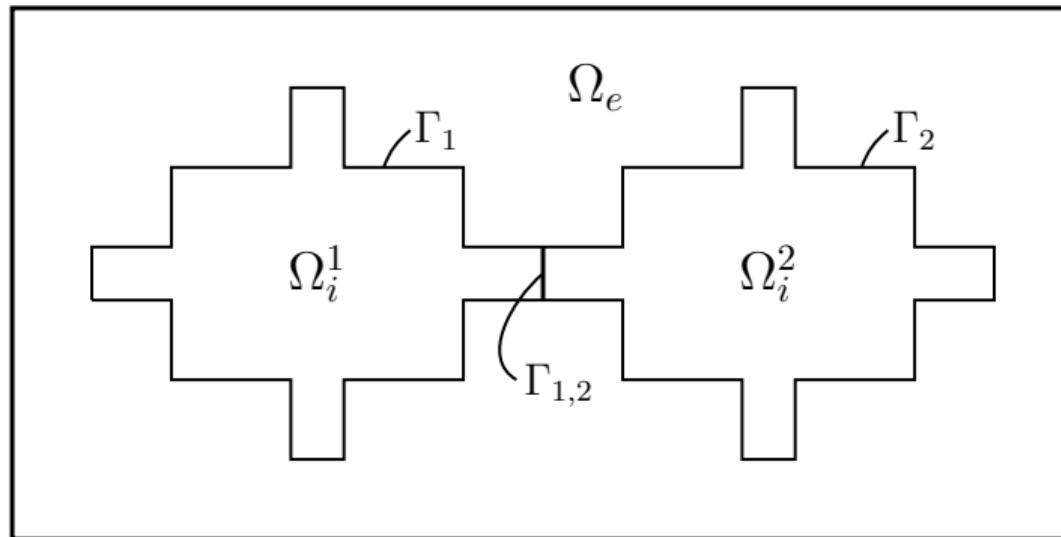
[Mader and Brimberg (Fig 2, 2019)]





The EMI framework uses an explicit geometry representation

Consider the **extracellular** domain $\Omega_e \subset \mathbb{R}^d$, the **intracellular** domain(s) $\Omega_i = \cup_k \Omega_i^k \subset \mathbb{R}^d$, and **membrane(s)** Γ .



[Stinstra et al, 2010; Agudelo-Toro and Neef, 2013]

The EMI equations describe the dynamics of extracellular, membrane and intracellular electrical potentials

Find the **electrical potential** $u(t) : \Omega \rightarrow \mathbb{R}$ (mV), and the **transmembrane potential** $v(t) : \Gamma \rightarrow \mathbb{R}$ (mV) such that:

$$\operatorname{div} \sigma \nabla u = 0 \quad \text{in } \Omega_i, \Omega_e,$$

and the **interface conditions** on Γ :

$$\begin{aligned} u_i - u_e &= v, \\ -\sigma_i \nabla u_i \cdot n_i &= \sigma_e \nabla u_e \cdot n_e \equiv I_m \\ C_m \frac{\partial}{\partial t} v &= I_m - I_{\text{ion}}(v) \end{aligned}$$

with conductivity σ (mS/cm) and capacitance C_m ($\mu\text{F}/\text{cm}^2$).

In the simplest cases, $I_{\text{ion}}(v) = -gv$, $g > 0$. Generally $I_{\text{ion}} = I(v, s)$ highly non-linear.

Boundary condition (e.g. $u = 0$) on $\partial\Omega$ and initial conditions for v .

Derivation of the EMI framework

Geometrically representing extracellular and intracellular domains separated by a membrane

EMI modelling of the electrical potential in the intracellular and extracellular domains

Maxwell

EMI modelling of the electrical potential in the intracellular and extracellular domains

Maxwell

Find $u_i : \Omega_i \rightarrow \mathbb{R}$ and
 $u_e : \Omega_e \rightarrow \mathbb{R}$ such that

$$\begin{aligned} \operatorname{div} \sigma_i \nabla u_i &= 0 && \text{in } \Omega_i \\ \operatorname{div} \sigma_e \nabla u_e &= 0 && \text{in } \Omega_e \end{aligned}$$

Modelling of ionic currents across the cellular membrane I

Modelling of ionic currents across the cellular membrane II

The EMI equations describe the dynamics of extracellular, membrane and intracellular electrical potentials

Find the **electrical potential** $u(t) : \Omega \rightarrow \mathbb{R}$ (mV), and the **transmembrane potential** $v(t) : \Gamma \rightarrow \mathbb{R}$ (mV) such that:

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Boundary condition (e.g. $u = 0$) on $\partial\Omega$ and initial conditions for v .

Applications of EMI models

Simulating neuronal electrical activity and external field interplay

[Agudelo-Toro and Neef (2013)]

J. Neural Eng. **10** (2013) 026019

A Agudelo-Toro and A Neef

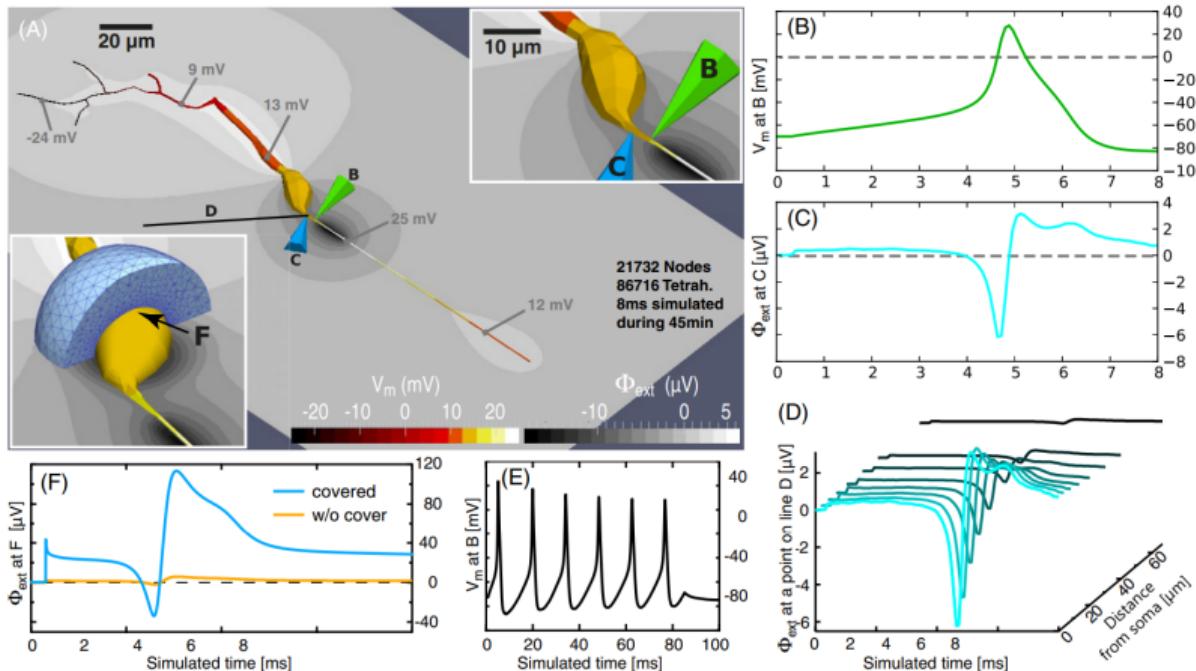
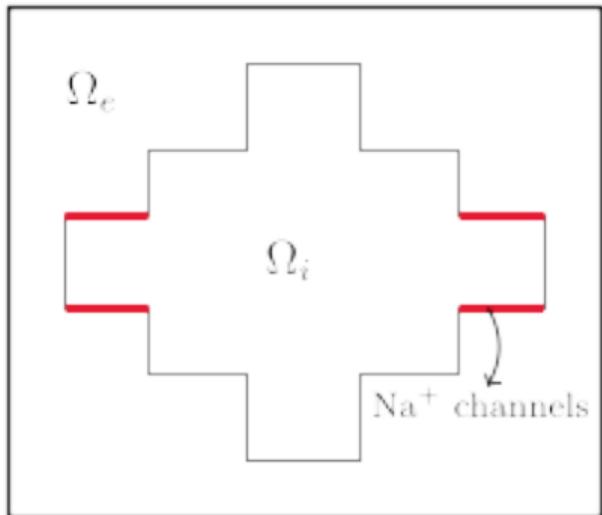


Figure 8. Potentials in and around a cultured neuron firing APs. (A) Color/grayscale indicate the membrane potential V_m and EP Φ_e at the bottom of the dish in a snapshot just after the initiation of the AP ($t = 4.72$ ms, $\Delta t = 40 \mu$ s). The cell was stimulated by the injection of 100 pA into the soma beginning at $t = 0.3$ ms. The AP started in the axon initial segment ($\sim 20 \mu$ m away from the soma) which has a higher

How do ion channel density affect conduction velocity?

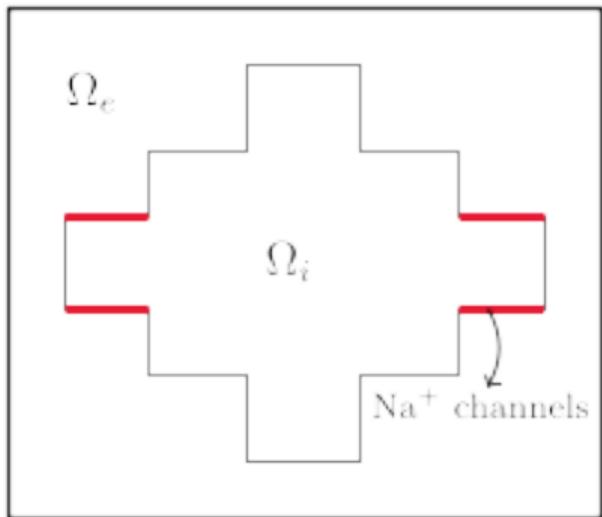
[Tveito, Jæger et al (2017)]



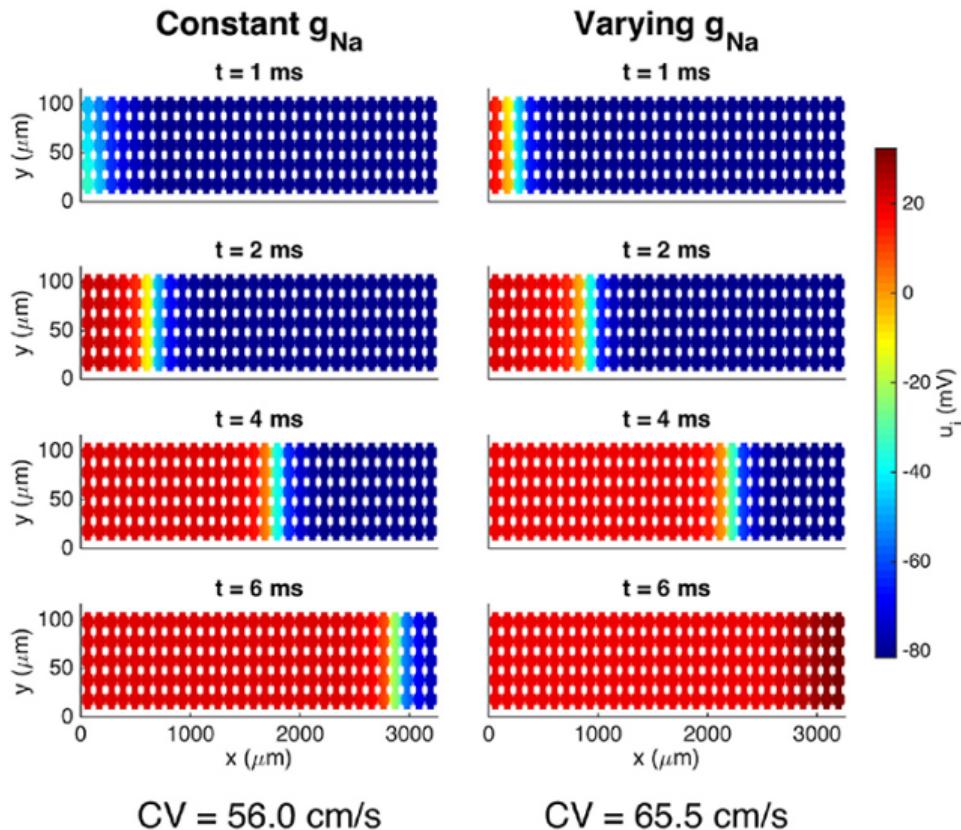
Sodium channel conductance g_{Na}
uniform at Γ or only non-zero at Γ
near Ω_w, Ω_E .

How do ion channel density affect conduction velocity?

[Tveito, Jæger et al (2017)]

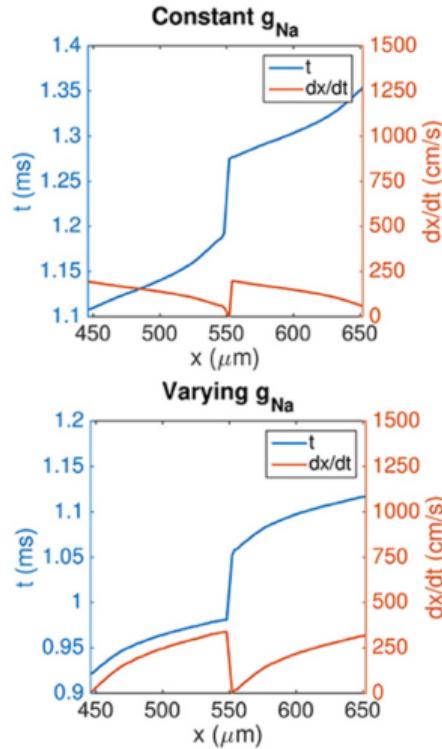
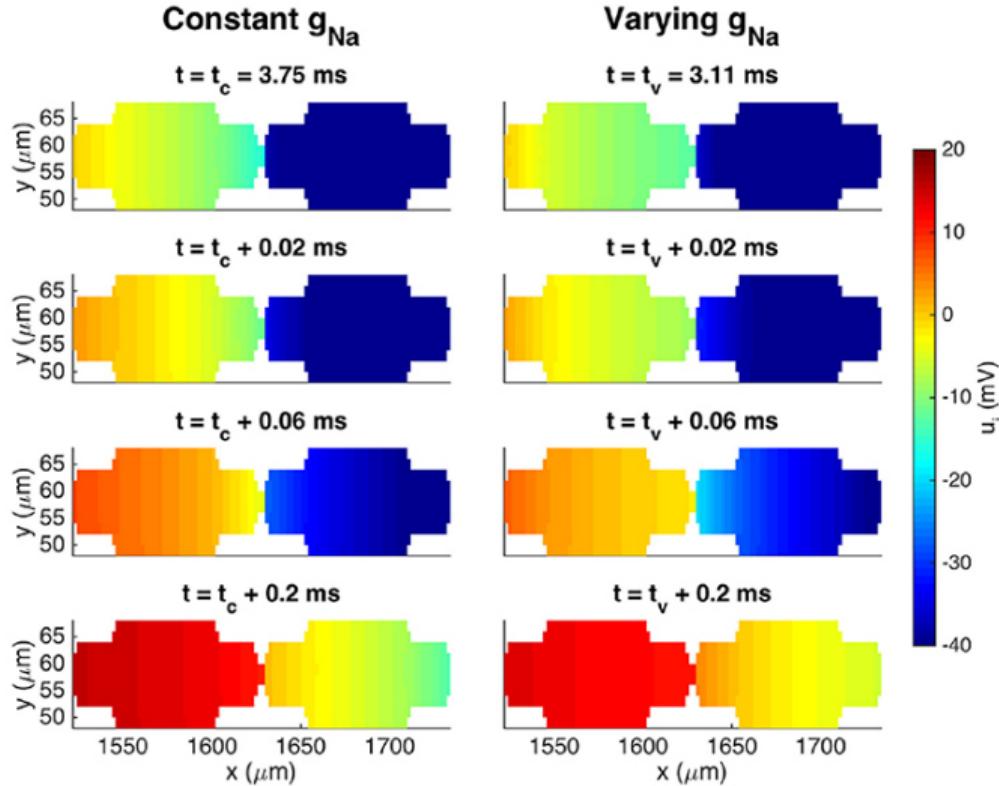


Sodium channel conductance g_{Na} uniform at Γ or only non-zero at Γ near Ω_w, Ω_E .



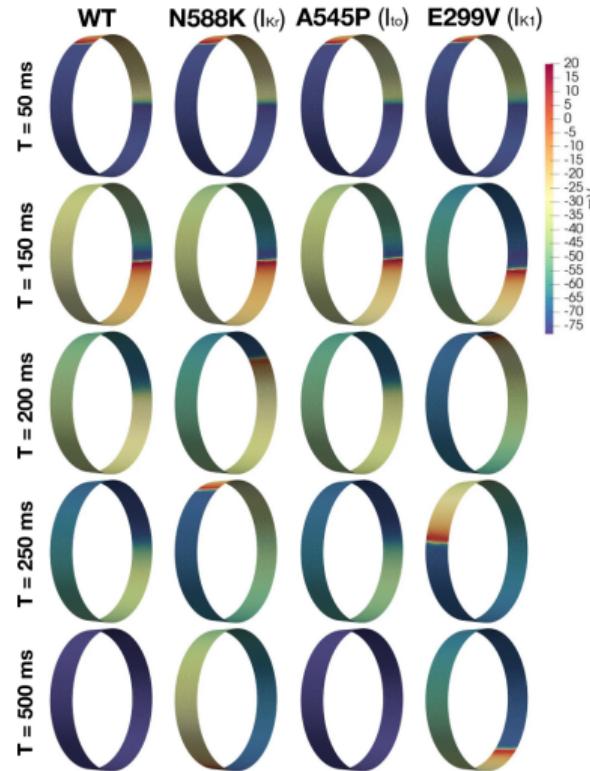
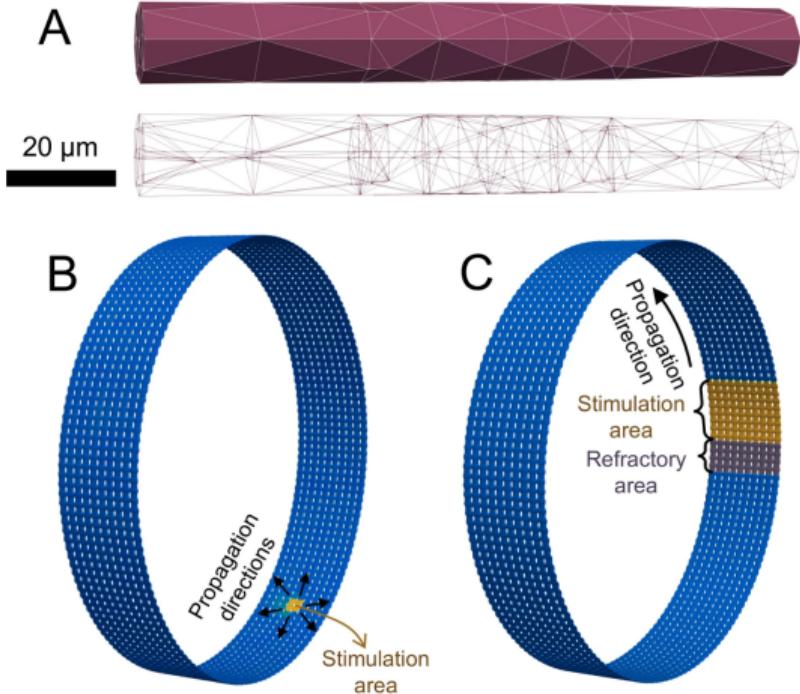
Higher conductances across gap junctions compensate for lower interior conductances and accelerate signalling

[Tveito, Jæger et al (2017)]



Computationally investigating how genetic ion channel mutations alter excitability in the myocardial sleeve of the pulmonary vein

[Jæger et al (2022)]



Numerical methods for EMI models

**GLOBAL EXISTENCE AND UNIQUENESS OF A
THREE-DIMENSIONAL MODEL OF CELLULAR
ELECTROPHYSIOLOGY**

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An implicit-explicit time discretization decouples the EMI equations

Recall:

$$\operatorname{div} \sigma \nabla u = 0 \quad \text{in } \Omega_i, \Omega_e,$$

$$u_i - u_e = v \quad \text{on } \Gamma,$$

$$-\sigma_i \nabla u_i \cdot n_i = \sigma_e \nabla u_e \cdot n_e \equiv I_m \quad \text{on } \Gamma,$$

$$C_m \frac{\partial}{\partial t} v = I_m - I_{\text{ion}}(v) \quad \text{on } \Gamma,$$

The EMI PDEs define a coupled, mixed-dimensional, linear system of equations to be solved at each time step

[Tveito et al (2017), Kuchta et al (2021)]

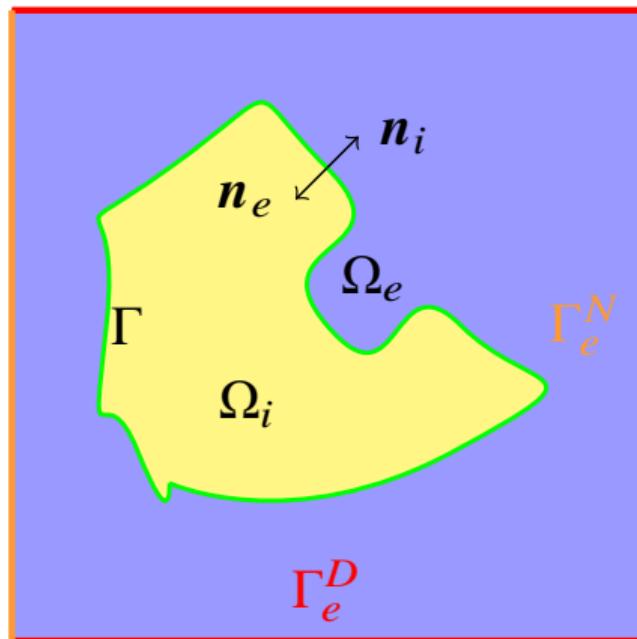
$$\operatorname{div} \boldsymbol{\sigma} \nabla u = 0 \quad \text{in } \Omega_i, \Omega_e,$$

$$u_i - u_e = v \quad \text{on } \Gamma,$$

$$-\boldsymbol{\sigma}_i \nabla u_i \cdot \mathbf{n}_i = \boldsymbol{\sigma}_e \nabla u_e \cdot \mathbf{n}_e \equiv I_m \quad \text{on } \Gamma,$$

$$v = \mathbf{C}_m^{-1}(\Delta t) I_m - f \quad \text{on } \Gamma,$$

Open research question: How to design numerical methods that solve these equations flexibly, accurately, robustly and efficiently?



Single-dimensional primal approach: eliminate I_m , solve for u_i and u_e

[Kuchta et al (2021)]

Single-dimensional primal approach: eliminate I_m , solve for u_i and u_e

[Kuchta et al (2021)]

Multiply by any ϕ_i, ϕ_e , integrate (by parts), and eliminate $I_m = -\sigma_i \nabla u_i \cdot n_i$ via:

$$I_m = C_m(\Delta t)^{-1}(u_i - u_e + f).$$

Write $\alpha = C_m(\Delta t)^{-1}$.

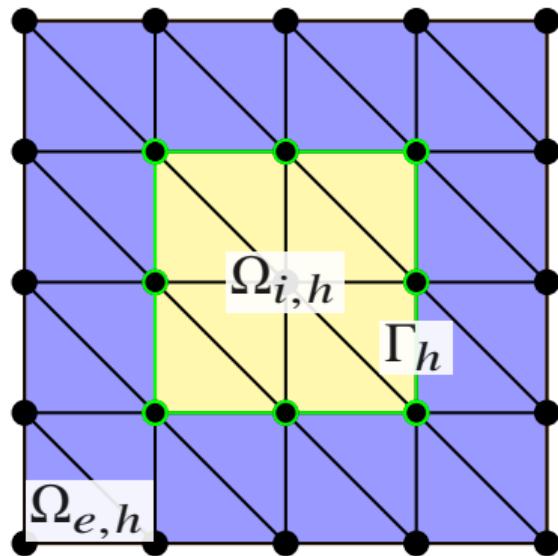
Find u_i and u_e such that

$$\int_{\Omega_i} \sigma_i \nabla u_i \cdot \nabla \phi_i \, dx + \int_{\Gamma} \alpha(u_i - u_e)\phi_i \, ds = \int_{\Gamma} \alpha f \phi_i \, ds,$$

$$\int_{\Omega_e} \sigma_e \nabla u_e \cdot \nabla \phi_e \, dx - \int_{\Gamma} \alpha(u_i - u_e)\phi_e \, ds = - \int_{\Gamma} \alpha f \phi_e \, ds.$$

Interpretation: Two Poisson problems with a Robin boundary condition

$\Delta t \rightarrow 0?$



Multi-dimensional primal approach: solve for I_m , u_i and u_e

[Kuchta et al (2021)]

Find $u_i : \Omega_i \rightarrow \mathbb{R}$, $u_e : \Omega_e \rightarrow \mathbb{R}$, and $I_m : \Gamma \rightarrow \mathbb{R}$ such that

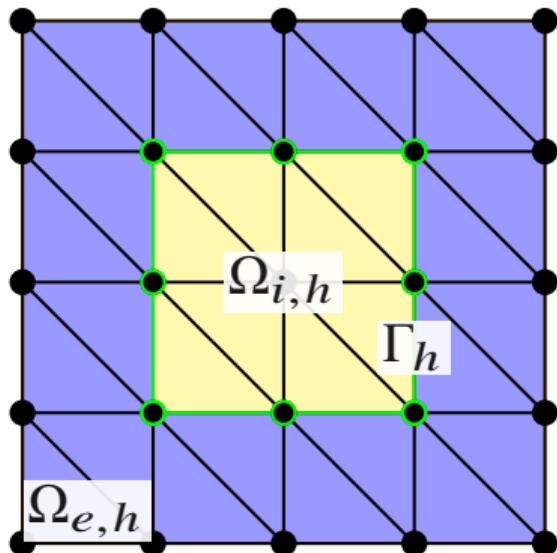
$$\int_{\Omega_i} \sigma_i \nabla u_i \cdot \nabla \phi_i \, dx + \int_{\Gamma} I_m \phi_i \, ds = 0,$$

$$\int_{\Omega_e} \sigma_e \nabla u_e \cdot \nabla \phi_e \, dx - \int_{\Gamma} I_m \phi_e \, ds = 0,$$

$$\int_{\Gamma} (u_i - u_e) \psi - \alpha^{-1} I_m \psi \, ds = - \int_{\Gamma} f \psi \, ds$$

Interpretation: Babuška problem for enforcing boundary/interface conditions via Lagrange multipliers, mortar finite element methods.

$\Delta t \rightarrow 0?$



Finite element formulations yield high quality EMI approximations

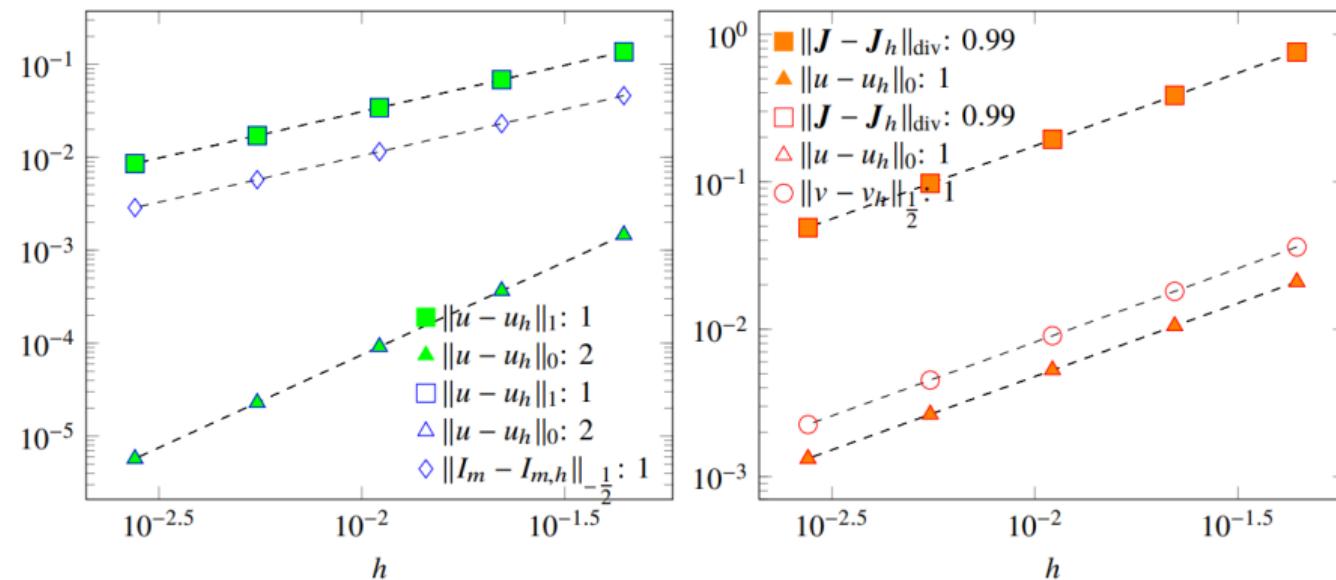
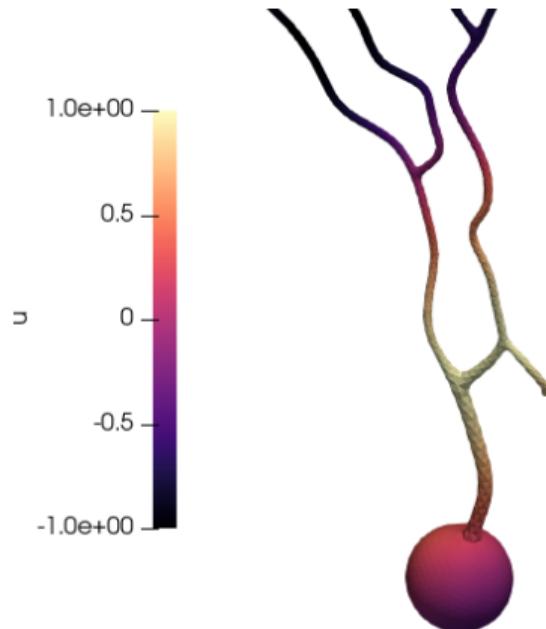
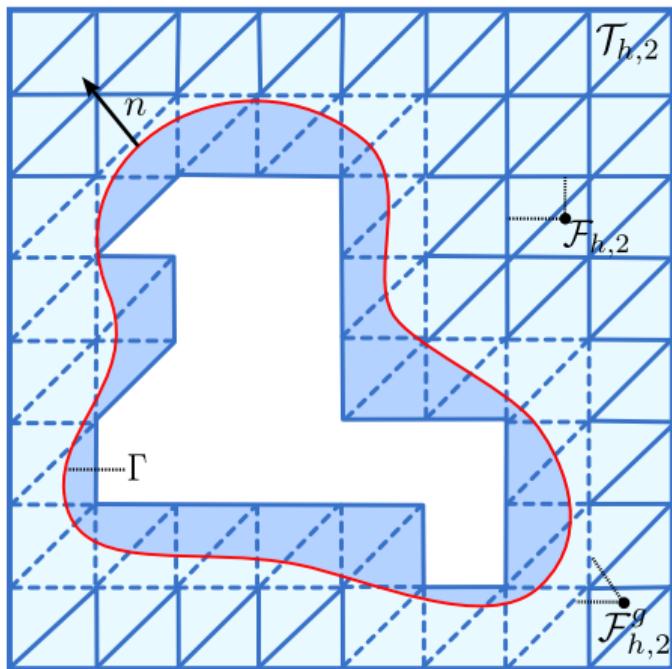


Fig. 5.2: Convergence properties of (left) primal formulations (5.6)–(5.8) and (right) mixed formulations (5.12)–(5.14). The EMI system (5.1) is solved with the exact solution given by (5.17) and $\Delta t = 1$. Filled symbols correspond to single-dimensional formulations. The number associated with each line indicates the convergence rate obtained from a least squares fit of the corresponding data.

Cut finite element methods can utilize non-conforming meshes and membrane representations

[Gurkan et al (2019), Nanna Berre (2022)]

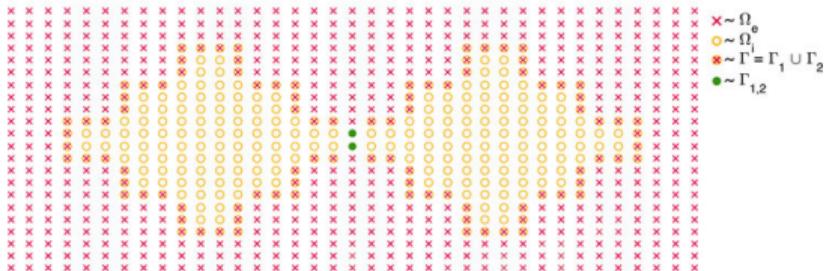


Aggressive splitting algorithms effectively reduce computational cost

[Jæger, Hustad et al (2021)]

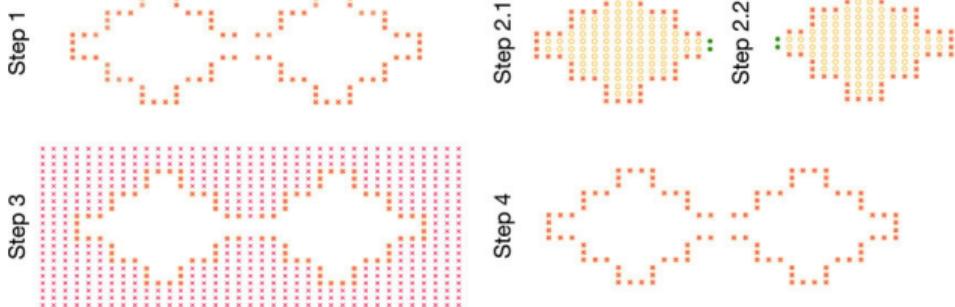
A

Coupled system



B

Splitting



Initial conditions: v^0, s^0, u_e^0 .

for $n = 1, \dots, N_t$:

Step 1: Find s^n and \bar{v} by solving a time step Δt from (s^{n-1}, v^{n-1}) of
 $v_t = -\frac{1}{C_m} I_{\text{ion}}(v, s)$,
 $s_t = F(v, s)$.

Define $\bar{u}_e = u_e^{n-1}$.

for $j = 1, \dots, N_l$:

Step 2: Find \bar{u}_i by solving

$$\begin{aligned} \nabla \cdot \sigma_i \nabla \bar{u}_i &= 0 && \text{in } \Omega_i, \\ \bar{u}_i + \frac{\Delta t}{C_m} \eta_i \cdot \sigma_i \nabla \bar{u}_i &= \bar{v} + \bar{u}_e && \text{at } \Gamma. \end{aligned}$$

Step 3: Find \bar{u}_e by solving

$$\begin{aligned} \nabla \cdot \sigma_e \nabla \bar{u}_e &= 0 && \text{in } \Omega_e, \\ \bar{u}_e &= 0 && \text{at } \partial \Omega_e^D, \\ \eta_e \cdot \sigma_e \nabla \bar{u}_e &= 0 && \text{at } \partial \Omega_e^N, \\ \eta_e \cdot \sigma_e \nabla \bar{u}_e &= -\eta_i \cdot \sigma_i \nabla \bar{u}_i && \text{at } \Gamma. \end{aligned}$$

end

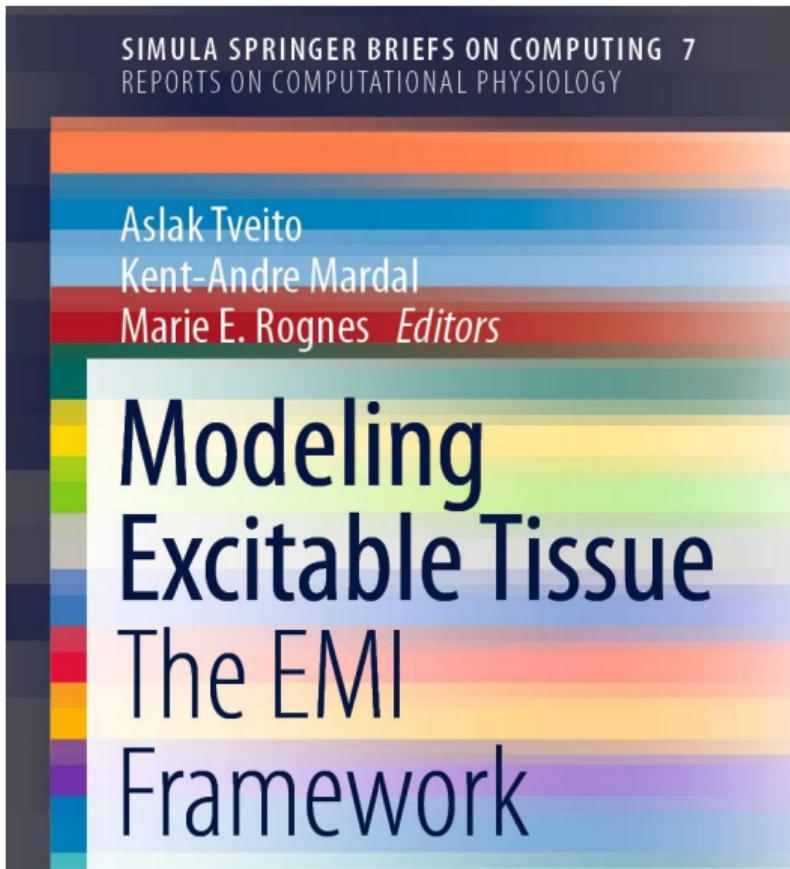
Define $u_e^n = \bar{u}_e$, $u_i^n = \bar{u}_i$.

Step 4: Define $v^n = u_i^n - u_e^n$ at Γ .

end

Simulation software is openly available for many EMI applications

[Tveito et al (2021)]



A screenshot of the Zenodo website interface. The header includes a search bar, an upload button, and a communities section. The main content area displays the title 'Modeling excitable tissue - the EMI framework'.

Modeling excitable tissue - the EMI framework

Recent uploads

Search Modeling excitable tissue - the EMI framework

May 5, 2020 (0.1.0) Software Open Access

Supplementary material (code) for Chapter 7 in 'Modeling excitable tissue - the EMI framework'

by Alessio Paolo Buccino; Miroslav Kuchta; Jakob Schreiner; Kent-Andre Mardal;

This file or directory contains supplementary material (code) for Chapter 7 in 'Modeling excitable tissue - the EMI framework' by A. P. Buccino, M. Kuchta, J. Schreiner, and K. A. Mardal. The zip file is an archived zip of the neuronml Python package (<https://github.com/Miro/Neu>)

Uploaded on May 7, 2020

April 27, 2020 (v1) Software Open Access

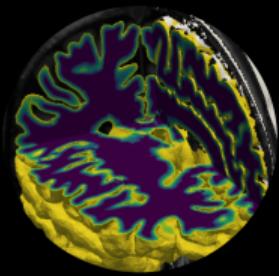
Software for EMI - Iterative solvers for EMI models

by Kuchta, Miroslav; Mardal, Kent-Andre;

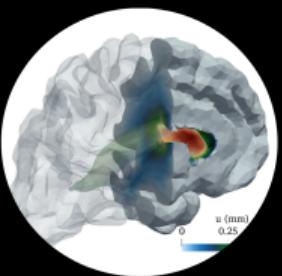
Source code used in producing the results of Chapter 6, Iterative solvers for EMI models, in the EMI book: Modeling excitable tissue - the EMI framework

Uploaded on April 27, 2020

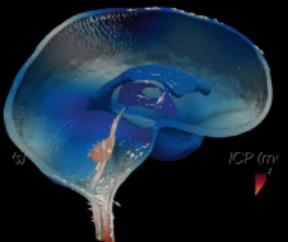
Outlook



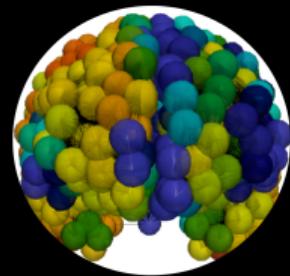
Solute transport



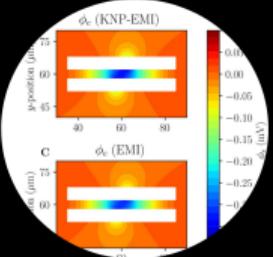
Brain mechanics



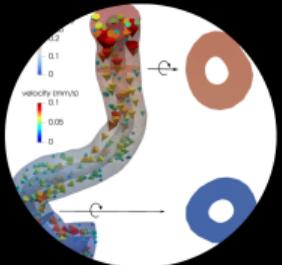
CSF flow



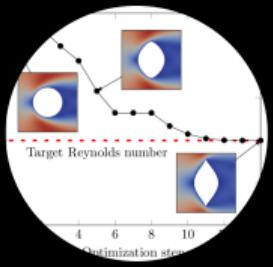
Neurodegeneration



Ions and osmosis



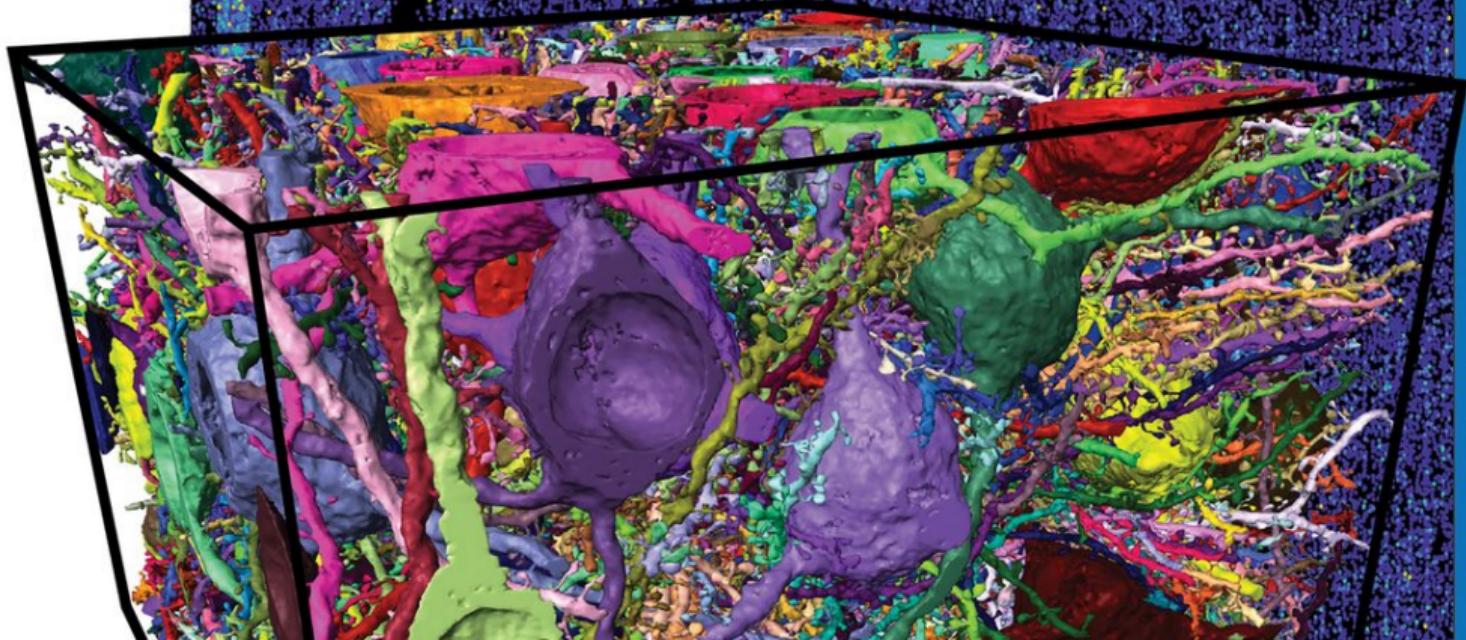
Model reduction



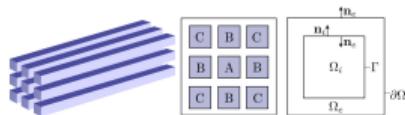
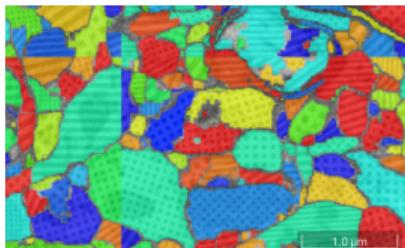
Optimal control



Software



Exciting times: Extreme modelling of excitable tissue



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

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Andreas Solbrå (Oslo)

Aslak Tveito (Simula)

... and many others

Core message

Mathematical models can give new insight into medicine, – and the human brain gives an extraordinary rich setting for mathematics and numerics!

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