Boundary Element Method for the Cell-by-Cell Model in Cardiac Electrophysiology

Giacomo Rosilho de Souza, Simone Pezzuto, Rolf Krause

Università della Svizzera Italiana, Lugano, Switzerland

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Contents

- Microcard Project and Cell-by-Cell model,
- Crash course on Boundary Element Method,
- Reduction of Cell-by-Cell model to system of ODEs,
- Numerical experiment.

Bidomain and Cell-by-Cell Models

In the mono and bidomain models for cardiac electrophysiology, every mesh element contains hundreds of physical cells:

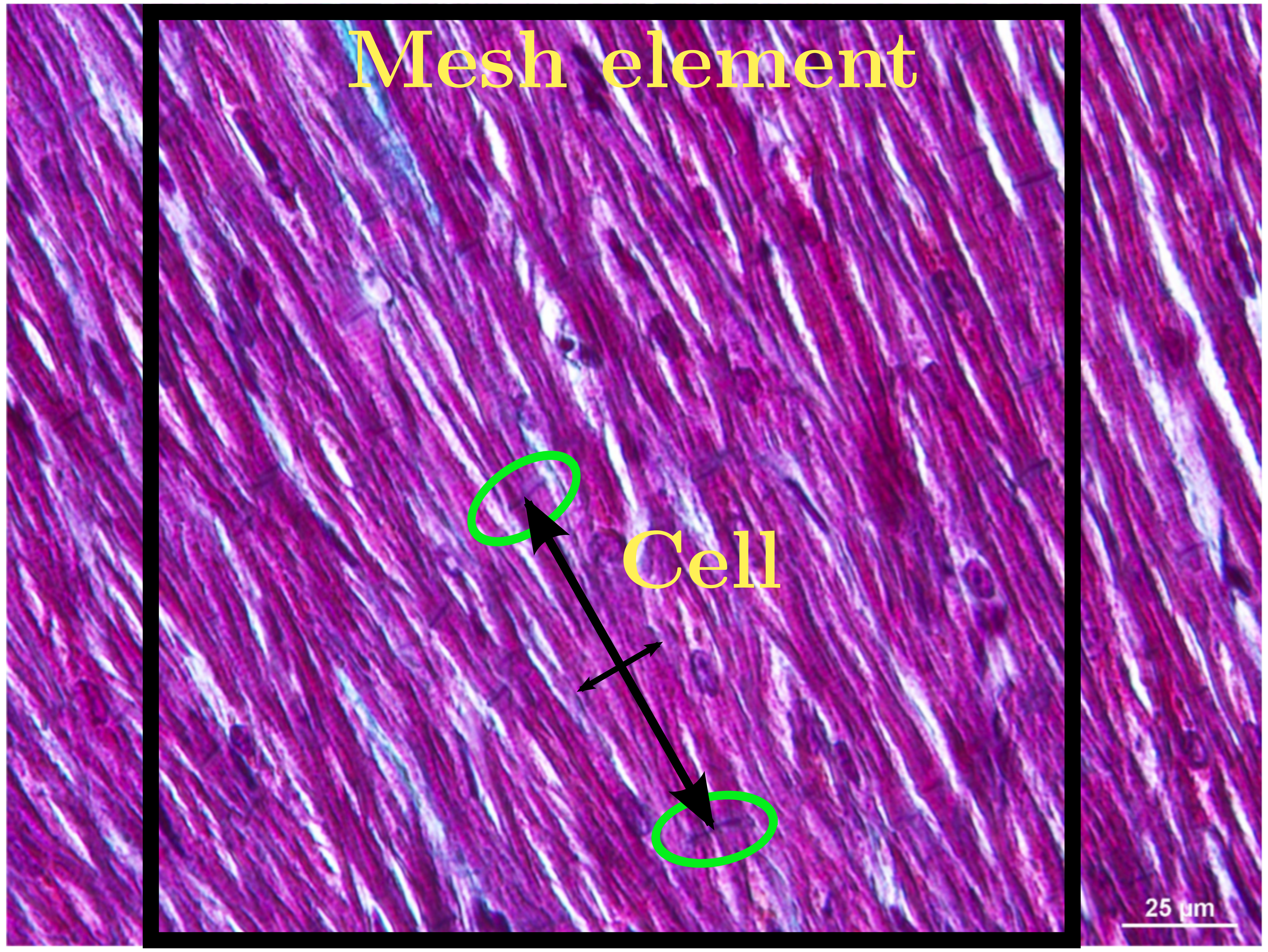


Image courtesy of Dr. D. Benoist, IHU Liryc.

This is insufficient to simulate abnormal tissues:

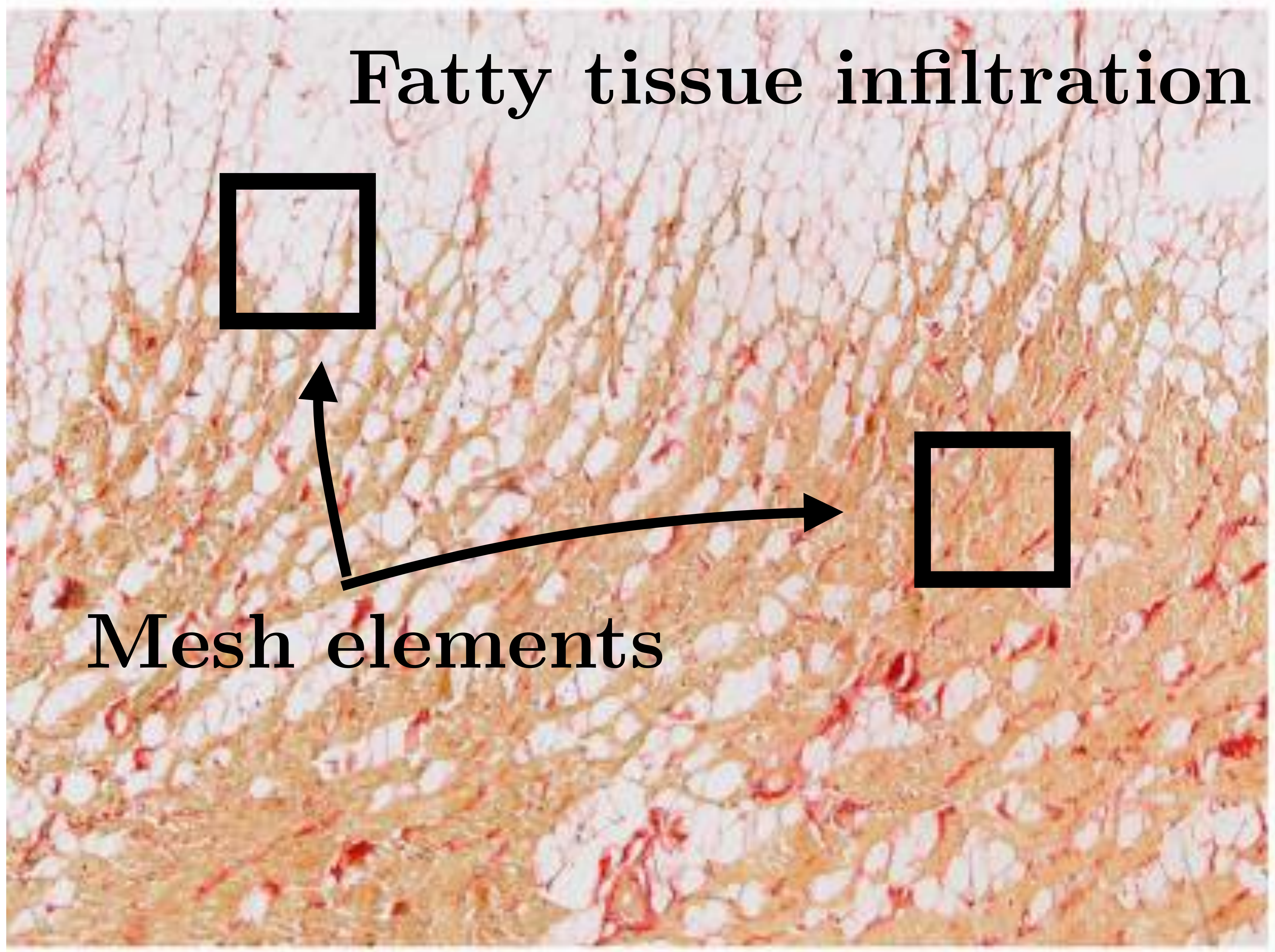


Image courtesy of Dr. M. Hoogendijk, AMC, Amsterdam.

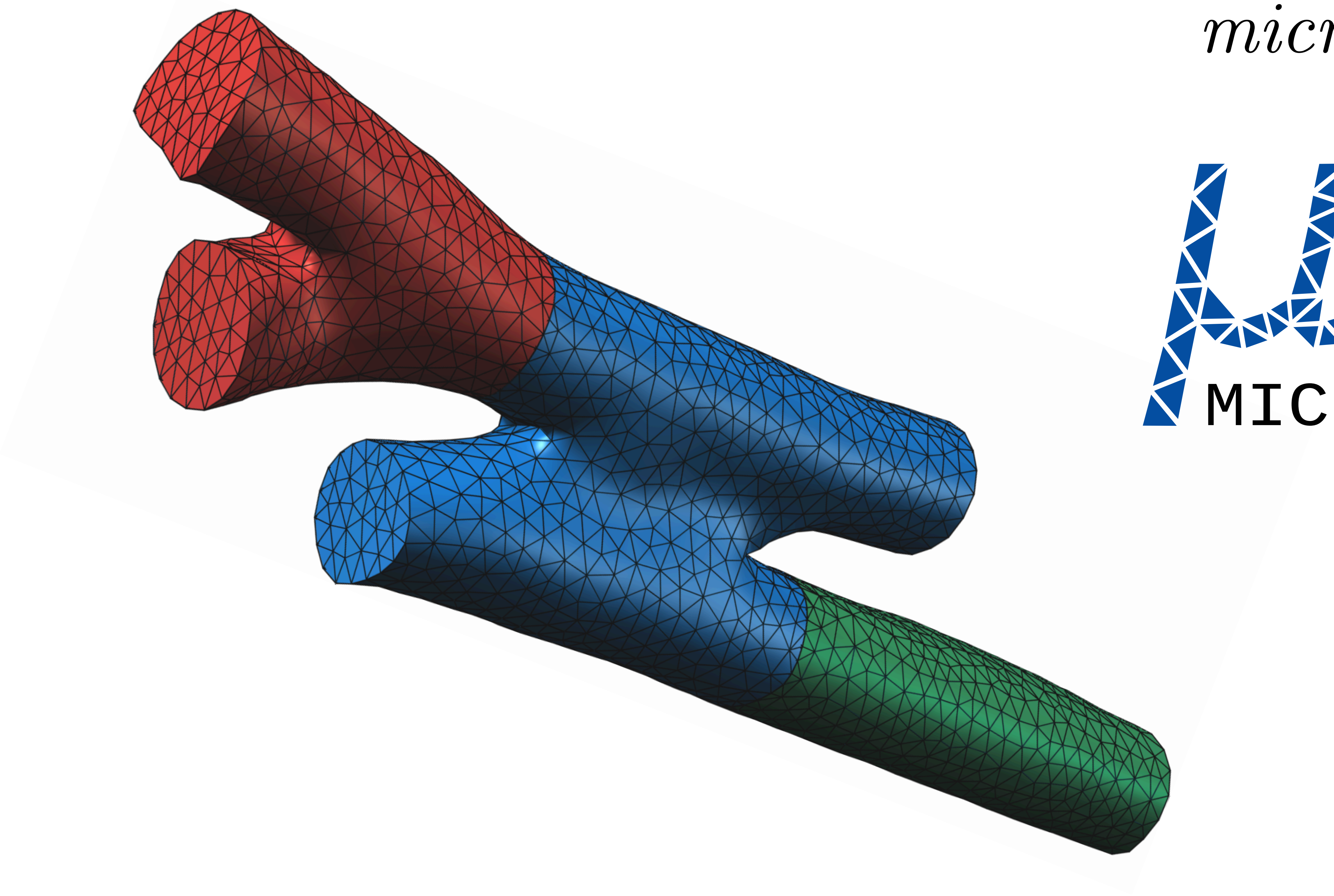
The MICROCARD Project

Università della Svizzera italiana

"MICROCARD is a European research project to build software that can simulate cardiac electrophysiology using whole-heart models with <u>*sub-cellular resolution*</u>*, on future exascale supercomputers."*

microcard.eu

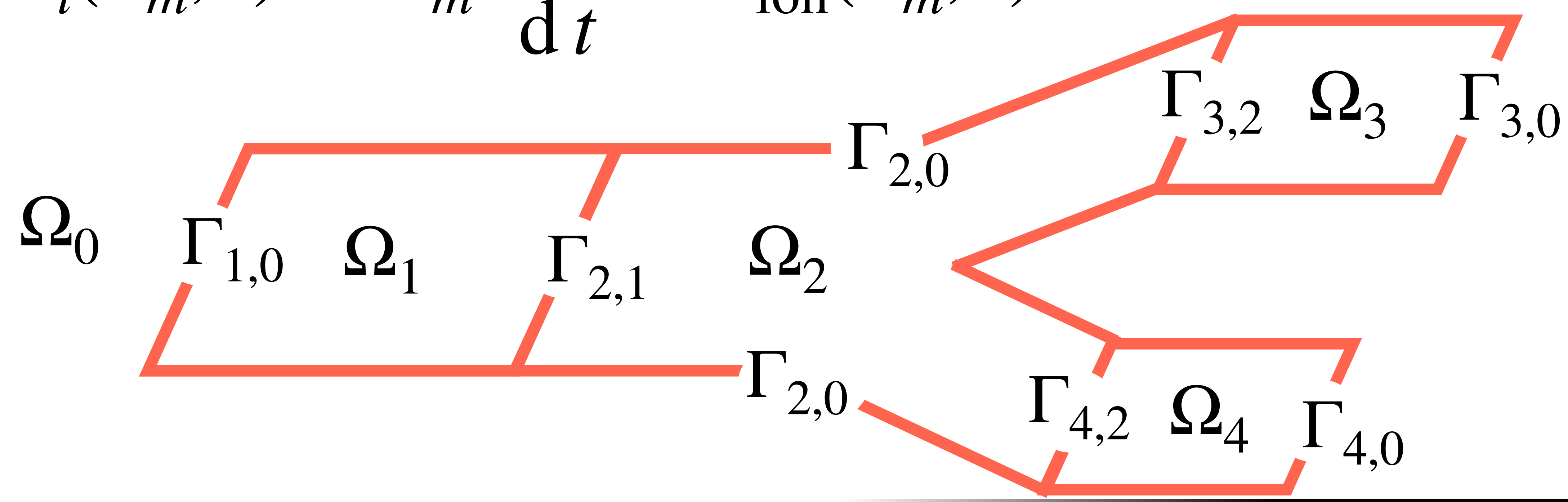
MICROCARD



To do so, we solve the cell-by-cell model

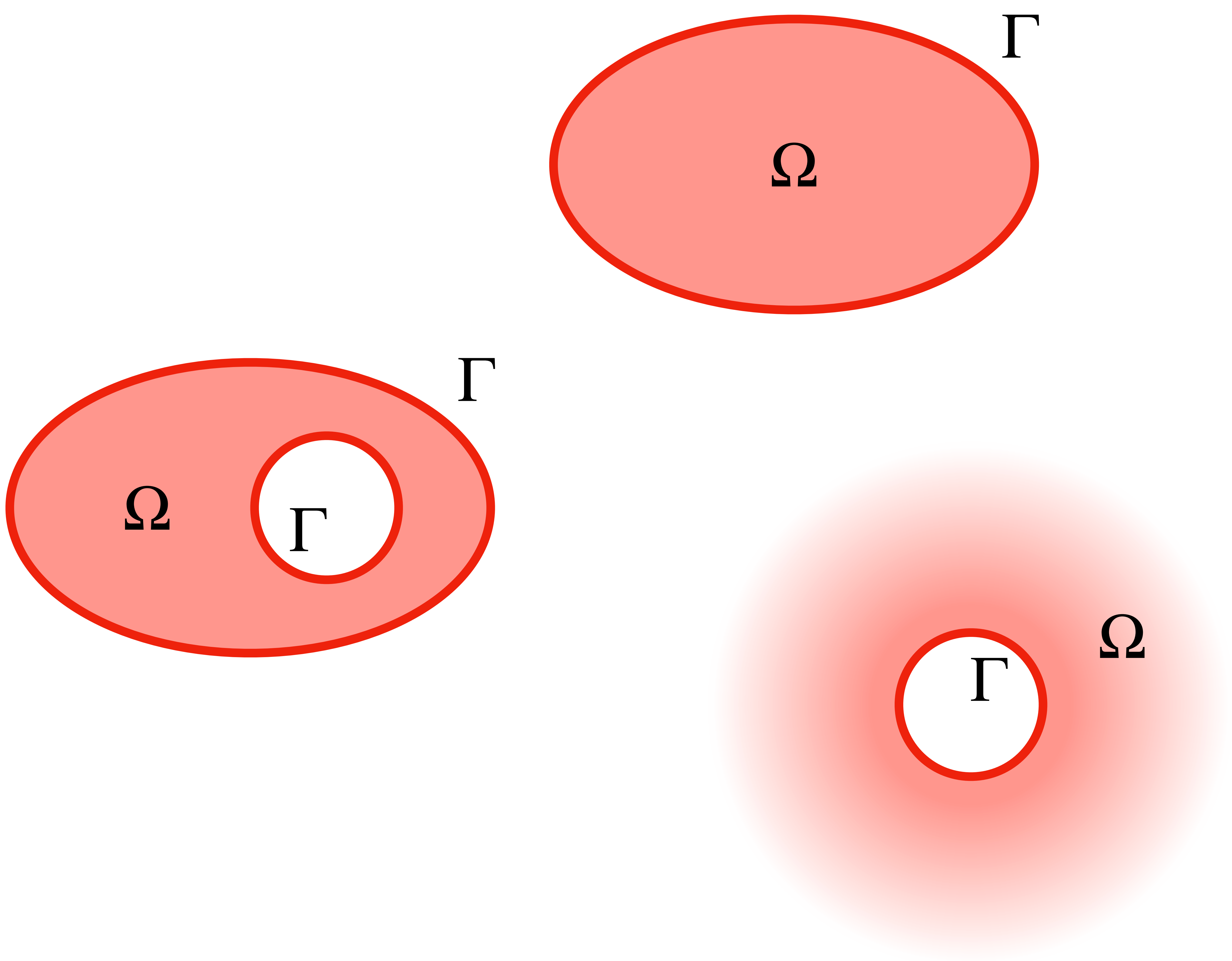
$$
\begin{aligned}
-\sigma_i \Delta u_i &= 0, && \text{in } \Omega_i \quad i = 0,\dots,N,\\
-\sigma_i \partial_n u_i &= I_t(V_m, z), && \text{on } \Gamma_{i,0} \quad i = 1,\dots,N,\\
-\sigma_0 \partial_n u_0 &= -\, I_t(V_m, z), && \text{on } \Gamma_0,\\
u_i - u_0 &= V_m, && \text{on } \Gamma_{i,0} \quad i = 1,\dots,N,\\
\frac{\mathrm{d}\, z}{\mathrm{d}\, t} &= g(V_m, z), && \text{on } \Gamma_0,\\
-\sigma_i \partial_n u_i &= \kappa(u_i - u_j), && \text{on } \Gamma_{i,j} \quad 1 \le j, i \le N,
\end{aligned}
$$

With $I_t(V_m, z) = C_m \frac{\mathrm{d}\, V_m}{\mathrm{d}\, t} + I_{\text{ion}}(V_m, z)$



Boundary Integral Equations

Let $\Omega \subset \mathbb{R}^d$ a domain and its boundary $\Gamma = \partial\Omega$ be as one of:



Let u be any solution to

$$-\Delta u = 0 \quad \text{in } \Omega.$$

The Green representation formula gives

$$u(x) = \int_\Gamma G(x,y)\partial_n u(y) \mathrm{d}s_y - \int_\Gamma \partial_n G(x,y) u(y) \mathrm{d}s_y \quad x \in \Omega,$$

with $u(y)$ the Dirichlet and $\partial_y u(y)$ the Neumann data, and $G(x,y)$ is the fundamental solution.

Collocation Boundary Integral Method

Taking the trace yields

$$u = \mathscr{V}\partial_n u - (\mathscr{K} - \frac{1}{2}I)u \quad \text{on} \quad \Gamma \quad (1)$$

with

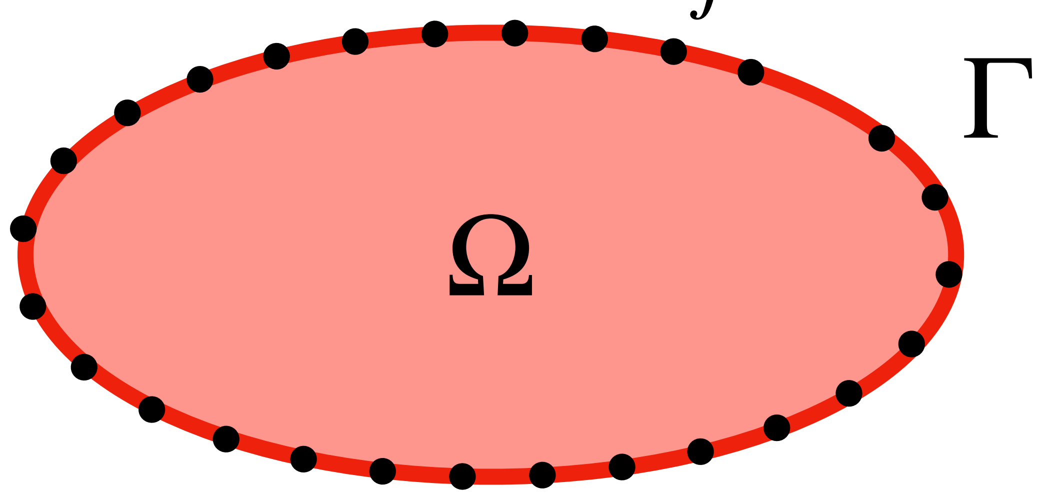
$$\mathscr{V}\rho(x) = \int_\Gamma G(x,y)\rho(y)\mathrm{d}s_y, \qquad x \in \Gamma,$$

$$\mathscr{K}\rho(x) = \int_\Gamma \partial_n G(x,y)\rho(y)\mathrm{d}s_y, \qquad x \in \Gamma$$

the single and double layer potentials.
Rearranging (1):

$$\mathscr{V}\partial_n u = (\mathscr{K} + \frac{1}{2}I)u, \quad \text{on} \quad \Gamma. \quad (2)$$

Discretize Γ in M points x_j



and impose (2) on x_j only

$$\mathscr{V}\partial_n u(x_j) = (\mathscr{K} + \frac{1}{2}I)u(x_j) \quad \forall j.$$

We represent $u, \partial_n u$ with trigonometric Lagrangian basis $L_j(x)$, with $L_j(x_k) = \delta_{jk}$:

$$\partial_n u = \sum_{j=1}^{M} \tilde{u}^j L_j, \quad u = \sum_{j=1}^{M} u^j L_j$$

Collocation Boundary Integral Method

$$\mathscr{V}\partial_n u(x_j) = (\mathscr{K}+\tfrac{1}{2}I)u(x_j) \quad \forall j$$

$$\partial_n u = \sum_{j=1}^{M} \tilde{u}^j L_j, \quad u = \sum_{j=1}^{M} u^j L_j$$

Matrix formulation

$$V\tilde{\mathbf{u}} = (K+\tfrac{1}{2}I)\mathbf{u}, \qquad \tilde{\mathbf{u}} = P_S\mathbf{u}$$

with

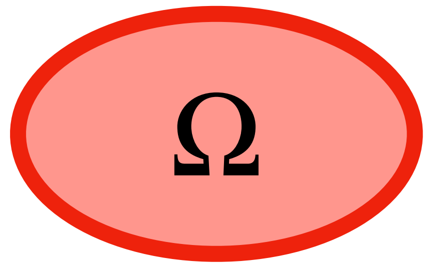
$$P_S = V^{-1}(K+\tfrac{1}{2}I)$$

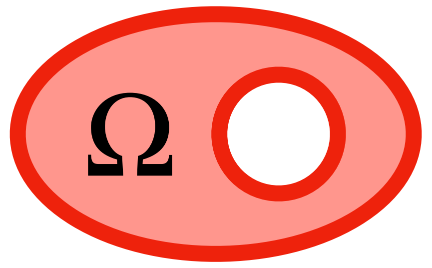
the Poincaré-Steklow operator (or Dirichlet-to-Neumann map).

Henceforth on the boundary Γ:

$$u \longrightarrow \mathbf{u} \qquad \partial_n u \longrightarrow P_S\mathbf{u}$$

Fun facts:

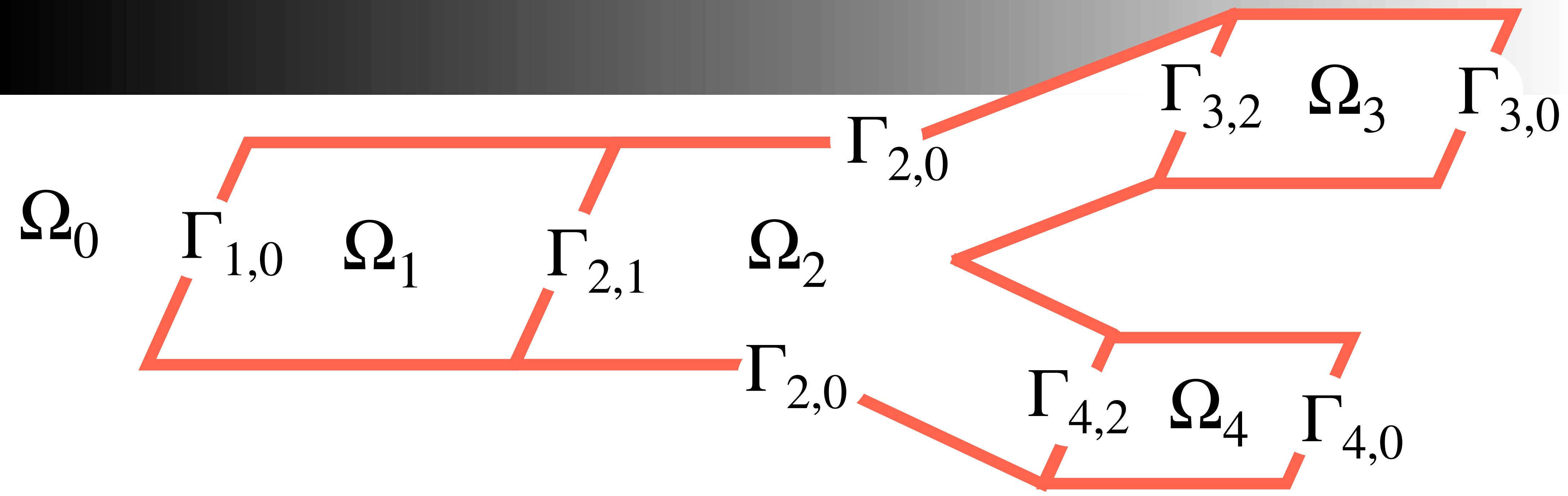
- P_S is symmetric,
- For 

and 

it is singular with
$$P_S\mathbf{e} = 0, \qquad \mathbf{e} = (1,\ldots,1)^\top.$$
- For 

it is invertible due to decaying conditions, which fix the constant.

Model reformulation



Consider a problem with N cells $\boldsymbol{\Omega}_i$, $i = 1, \dots, N$ and *unbounded* extracellular matrix Ω_0 with boundary Γ_0:

$$
\begin{aligned}
-\sigma_i \Delta u_i &= 0, && \text{in } \Omega_i \quad i = 0, \dots, N,\\
-\sigma_i \partial_n u_i &= I_t(V_m, z), && \text{on } \Gamma_{i,0} \quad i = 1, \dots, N,\\
-\sigma_0 \partial_n u_0 &= -I_t(V_m, z), && \text{on } \Gamma_0,\\
u_i - u_0 &= V_m, && \text{on } \Gamma_{i,0} \quad i = 1, \dots, N,\\
\frac{\mathrm{d}\,z}{\mathrm{d}\,t} &= g(V_m, z), && \text{on } \Gamma_0,\\
-\sigma_i \partial_n u_i &= \kappa(u_i - u_j), && \text{on } \Gamma_{i,j} \quad 1 \le j, i \le N,
\end{aligned}
$$

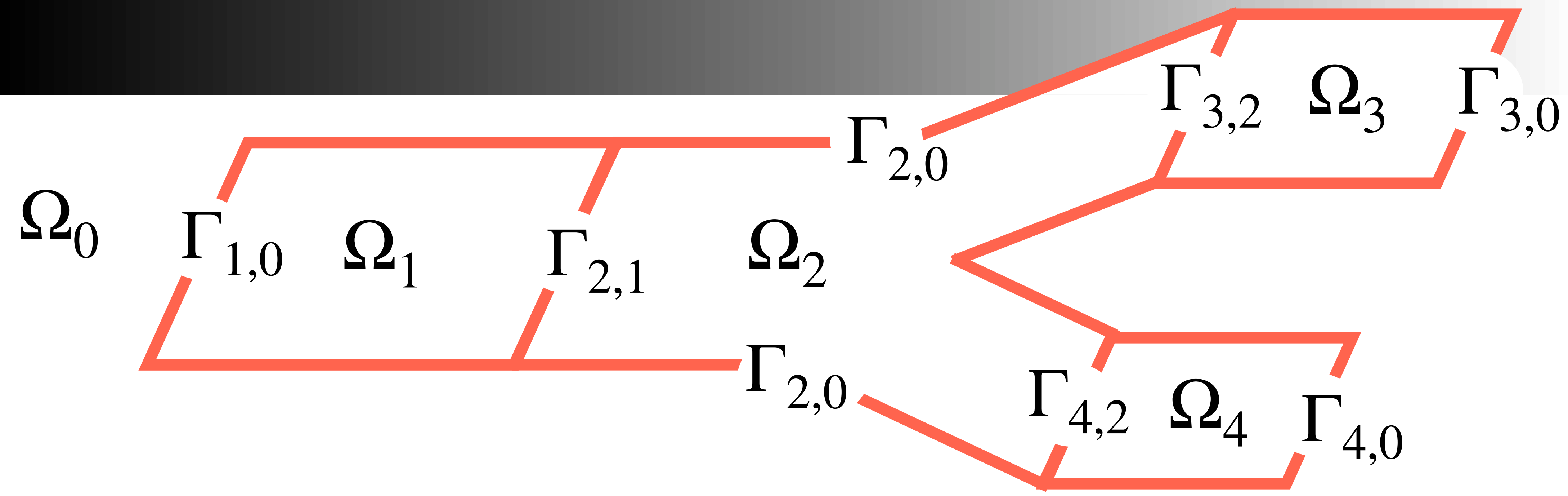
$\Rightarrow$

$$
\begin{aligned}
-\sigma_i \Delta u_i &= 0, && \text{in } \Omega_i \quad i = 0, \dots, N,\\
\sigma_0 \partial_n u_0 &= I_t(V, z), && \text{on } \Gamma_0,\\
\frac{\mathrm{d}\,z}{\mathrm{d}\,t} &= g(V, z), && \text{on } \Gamma_0,\\
\sigma_i \partial_n u_i + \sigma_j \partial_n u_j &= 0, && \text{on } \Gamma_{i,j} \quad 0 \le j < i \le N,\\
u_i - u_j &= V, && \text{on } \Gamma_{i,j} \quad 0 \le j < i \le N,\\
\sigma_j \partial_n u_j - \sigma_i \partial_n u_i &= 2\kappa V, && \text{on } \Gamma_{i,j} \quad 1 \le j < i \le N,
\end{aligned}
$$

with $\quad I_t(V_m, z) = C_m \dfrac{\mathrm{d}\,V_m}{\mathrm{d}\,t} + I_{\text{ion}}(V_m, z).$

Model discretisation

Discretize the skeleton Γ with M points. Every domain's boundary $\Gamma_i = \partial\Omega_i$ has M_i points.
Recall: $\partial_n u \longrightarrow P_S \mathbf{u}, \quad u \longrightarrow \mathbf{u}.$



$$\begin{aligned}
\varnothing & \quad \text{in } \Omega_i \quad i = 0,\dots,N,\\
\sigma_0 P_{S,0}\mathbf{u}_0 = I_t(\mathbf{V},\mathbf{z}), & \quad \text{on } \Gamma_0,\\
\frac{\mathrm{d}\,\mathbf{z}}{\mathrm{d}\,t} = g(\mathbf{V},\mathbf{z}), & \quad \text{on } \Gamma_0,\\
\sigma_i P_{S,i}\mathbf{u}_i + \sigma_j P_{S,j}\mathbf{u}_j = 0, & \quad \text{on } \Gamma_{i,j} \quad 0 \le j < i \le N,\\
\mathbf{u}_i - \mathbf{u}_j = \mathbf{V}, & \quad \text{on } \Gamma_{i,j} \quad 0 \le j < i \le N,\\
\sigma_j P_{S,j}\mathbf{u}_j - \sigma_i P_{S,i}\mathbf{u}_i = 2\kappa\mathbf{V}, & \quad \text{on } \Gamma_{i,j} \quad 1 \le j < i \le N,
\end{aligned}$$

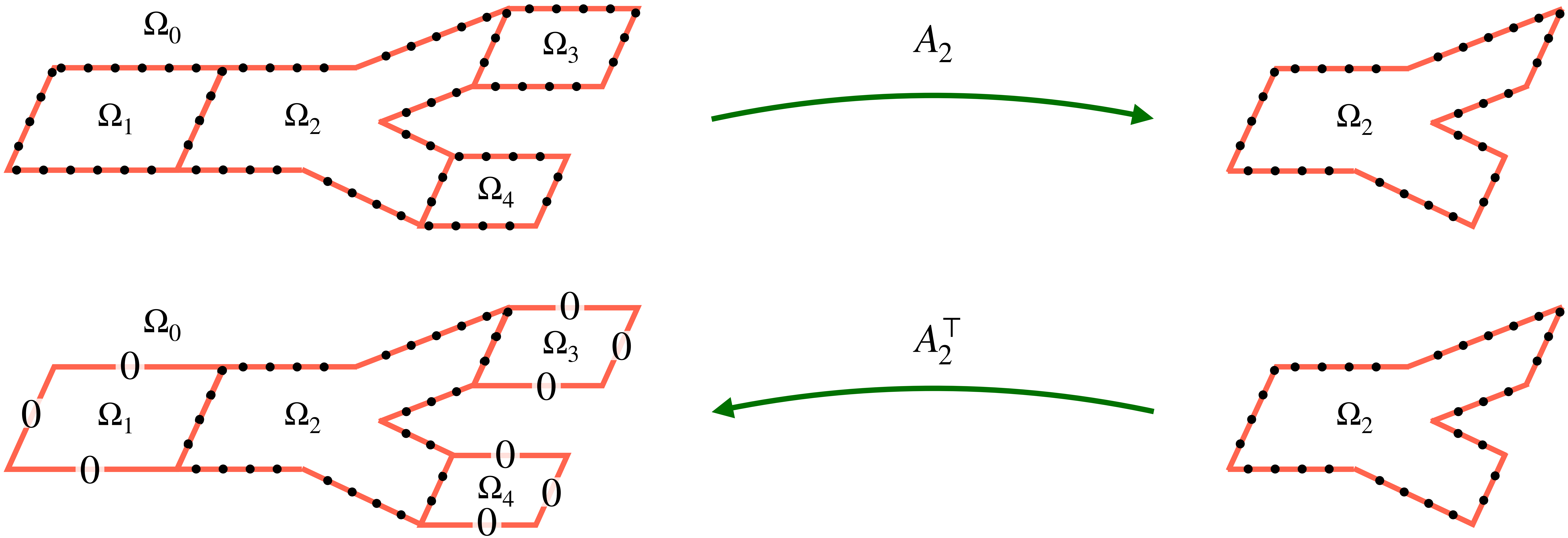
$\longleftarrow$

$$\begin{aligned}
-\sigma_i \Delta u_i = 0, & \quad \text{in } \Omega_i \quad i = 0,\dots,N,\\
\sigma_0 \partial_n u_0 = I_t(V,z), & \quad \text{on } \Gamma_0,\\
\frac{\mathrm{d}\,z}{\mathrm{d}\,t} = g(V,z), & \quad \text{on } \Gamma_0,\\
\sigma_i \partial_n u_i + \sigma_j \partial_n u_j = 0, & \quad \text{on } \Gamma_{i,j} \quad 0 \le j < i \le N,\\
u_i - u_j = V, & \quad \text{on } \Gamma_{i,j} \quad 0 \le j < i \le N,\\
\sigma_j \partial_n u_j - \sigma_i \partial_n u_i = 2\kappa V, & \quad \text{on } \Gamma_{i,j} \quad 1 \le j < i \le N,
\end{aligned}$$

Now, we need to define some restriction $\Gamma \to \Gamma_i$ and extension $\Gamma_i \to \Gamma$ operators.

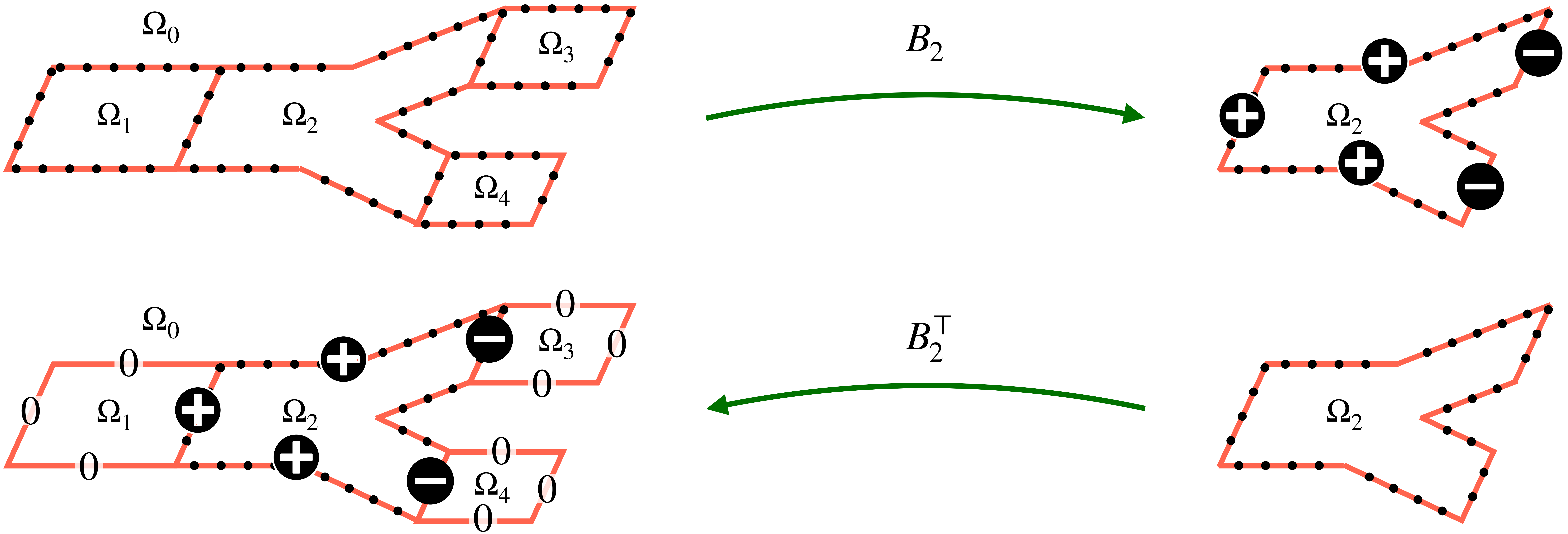
Global to local operators

The boolean connectivity matrix $A_i : \mathbb{R}^M \to \mathbb{R}^{M_i}$ maps a global vector on Γ to a local vector on Γ_i. The transpose $A_i^\top$ maps local to global.



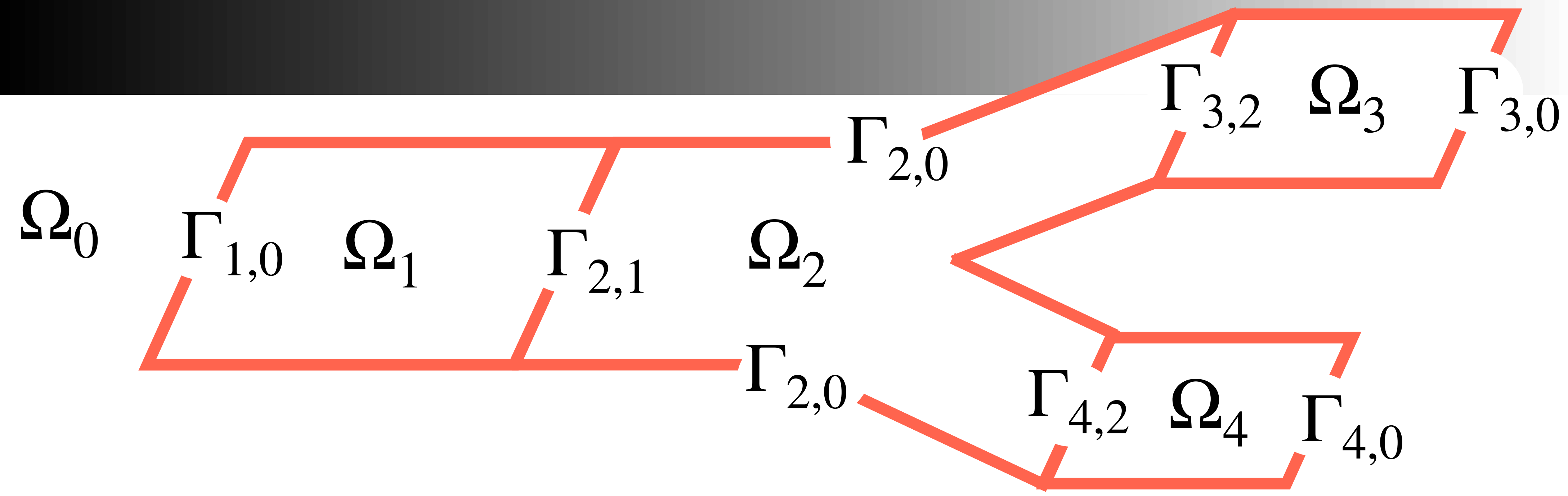
Global to local operators with sign change

The signed boolean connectivity matrix $B_i : \mathbb{R}^M \to \mathbb{R}^{M_i}$ maps a global vector on Γ to a local vector on Γ_i. A sign change occurs if the neighbouring domain has higher index.



Model discretisation

We transpose the equations below, living on $\Gamma_{i,j}$ and Γ_0, to the global domain Γ.



$$\begin{aligned}
\varnothing \qquad & \text{in } \Omega_i \quad i = 0,\dots,N,\\
\sigma_0 P_{S,0}\mathbf{u}_0 = I_t(\mathbf{V},\mathbf{z}), \qquad & \text{on } \Gamma_0,\\
\frac{\mathrm{d}\,\mathbf{z}}{\mathrm{d}\,t} = g(\mathbf{V},\mathbf{z}), \qquad & \text{on } \Gamma_0,\\
\sigma_i P_{S,i}\mathbf{u}_i + \sigma_j P_{S,j}\mathbf{u}_j = 0, \qquad & \text{on } \Gamma_{i,j} \quad 0 \le j < i \le N,\\
\mathbf{u}_i - \mathbf{u}_j = \mathbf{V}, \qquad & \text{on } \Gamma_{i,j} \quad 0 \le j < i \le N,\\
\sigma_j P_{S,j}\mathbf{u}_j - \sigma_i P_{S,i}\mathbf{u}_i = 2\kappa\mathbf{V}, \qquad & \text{on } \Gamma_{i,j} \quad 1 \le j < i \le N,
\end{aligned}$$

$$\begin{aligned}
\sigma_0 P_{S,0}\mathbf{u}_0 &= I_t(A_0\mathbf{V},\mathbf{z}) && \in \mathbb{R}^{M_0} = \Gamma_0\\
\frac{\mathrm{d}\,\mathbf{z}}{\mathrm{d}\,t} &= g(A_0\mathbf{V},\mathbf{z}) && \in \mathbb{R}^{M_0} = \Gamma_0\\
\sum_{i=0}^{N} \sigma_i A_i^\top P_{S,i}\mathbf{u}_i &= 0 && \in \mathbb{R}^{M} = \Gamma\\
\sum_{i=0}^{N} B_i^T \mathbf{u}_i &= \mathbf{V} && \in \mathbb{R}^{M} = \Gamma\\
\sum_{i=0}^{N} \sigma_i A_g B_i^\top P_{S,i}\mathbf{u}_i &= -2\kappa A_g\mathbf{V} && \in \mathbb{R}^{M_g} = \Gamma_g
\end{aligned}$$

With A_g the operator from Γ to the gap junctions.

Reduction to a DAE system

$$\begin{aligned}
\sigma_0 P_{S,0}\mathbf{u}_0 &= I_t(A_0\mathbf{V}, \mathbf{z}) && \in \mathbb{R}^{M_0} = \Gamma_0 \\
\frac{\mathrm{d}\,\mathbf{z}}{\mathrm{d}\,t} &= g(A_0\mathbf{V}, \mathbf{z}) && \in \mathbb{R}^{M_0} = \Gamma_0 \\
\sum_{i=0}^{N} \sigma_i A_i^\top P_{S,i}\mathbf{u}_i &= 0 && \in \mathbb{R}^{M} = \Gamma \\
\sum_{i=0}^{N} B_i^T \mathbf{u}_i &= \mathbf{V} && \in \mathbb{R}^{M} = \Gamma \\
\sum_{i=0}^{N} \sigma_i A_g B_i^\top P_{S,i}\mathbf{u}_i &= -2\kappa A_g \mathbf{V} && \in \mathbb{R}^{M_g} = \Gamma_g
\end{aligned}$$

Goal: Find maps

$$\psi_i : \Gamma \to \Gamma_i : V \mapsto \sigma_i P_{S,i}\mathbf{u}_i,$$

where $\mathbf{u}_i$ satisfies

$$\sum_{i=0}^{N} \sigma_i A_i^\top P_{S,i}\mathbf{u}_i = 0, \qquad \sum_{i=0}^{N} B_i^T \mathbf{u}_i = \mathbf{V}\,.$$

We obtain the DAE:

$$\begin{aligned}
\psi_0(\mathbf{V}) &= I_t(A_0\mathbf{V}, \mathbf{z}) && \text{on } \Gamma_0, \\
\frac{\mathrm{d}\,\mathbf{z}}{\mathrm{d}\,t} &= g(A_0\mathbf{V}, \mathbf{z}) && \text{on } \Gamma_0, \\
\sum_{i=0}^{N} A_g B_i^\top \psi_i(\mathbf{V}) &= -2\kappa A_g \mathbf{V} && \text{on } \Gamma_g\,.
\end{aligned}$$

Reduction to a DAE system

Theorem: computing ψ_i

The linear maps $\psi_i(\mathbf{V}) = \sigma_i P_{S,i} \mathbf{u}_i$ satisfy

$$\psi_i(\mathbf{V}) = -B_i \lambda$$

with $\lambda \in \mathbb{R}^M$ and $\beta \in \mathbb{R}^N$ solutions to

$$\begin{pmatrix} F & G \\ G^\top & 0 \end{pmatrix} \begin{pmatrix} \lambda \\ \beta \end{pmatrix} = \begin{pmatrix} \mathbf{V} \\ \mathbf{0} \end{pmatrix}.$$

Where

$$F = -\sum_{i=0}^{N} \sigma_i^{-1} B_i^\top (P_{S,i}^+)^{-1} B_i, \quad G = (B_1^\top \mathbf{e}_1, \ldots, B_N^\top \mathbf{e}_N),$$

$$P_{S,i}^+ = P_{S,i} + \alpha_i \, \mathbf{e}_i \mathbf{e}_i^\top, \quad \mathbf{e}_i = (1,\ldots,1)^\top \in \mathbb{R}^{M_i}, \quad \alpha_i > 0.$$

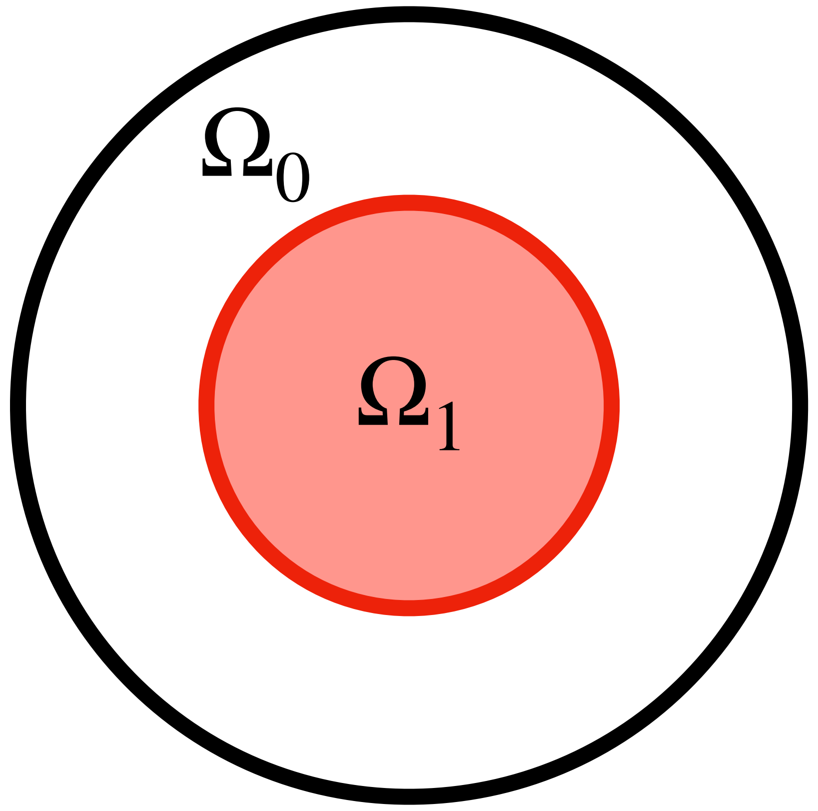
The boundary data $\mathbf{u}_i$ can be computed with

$$\mathbf{u}_i = -\sigma_i^{-1} (P_{S,i}^+)^{-1} B_i \lambda + \beta_i \mathbf{e}_i,$$

where β_0 is free.

Checking correctness of $\psi_i(\mathbf{V}) = \sigma_i P_{S,i}\mathbf{u}_i \approx \sigma_i \partial_{\mathbf{n}} u$

Consider two harmonic functions u_0, u_1 satisfying flux continuity.

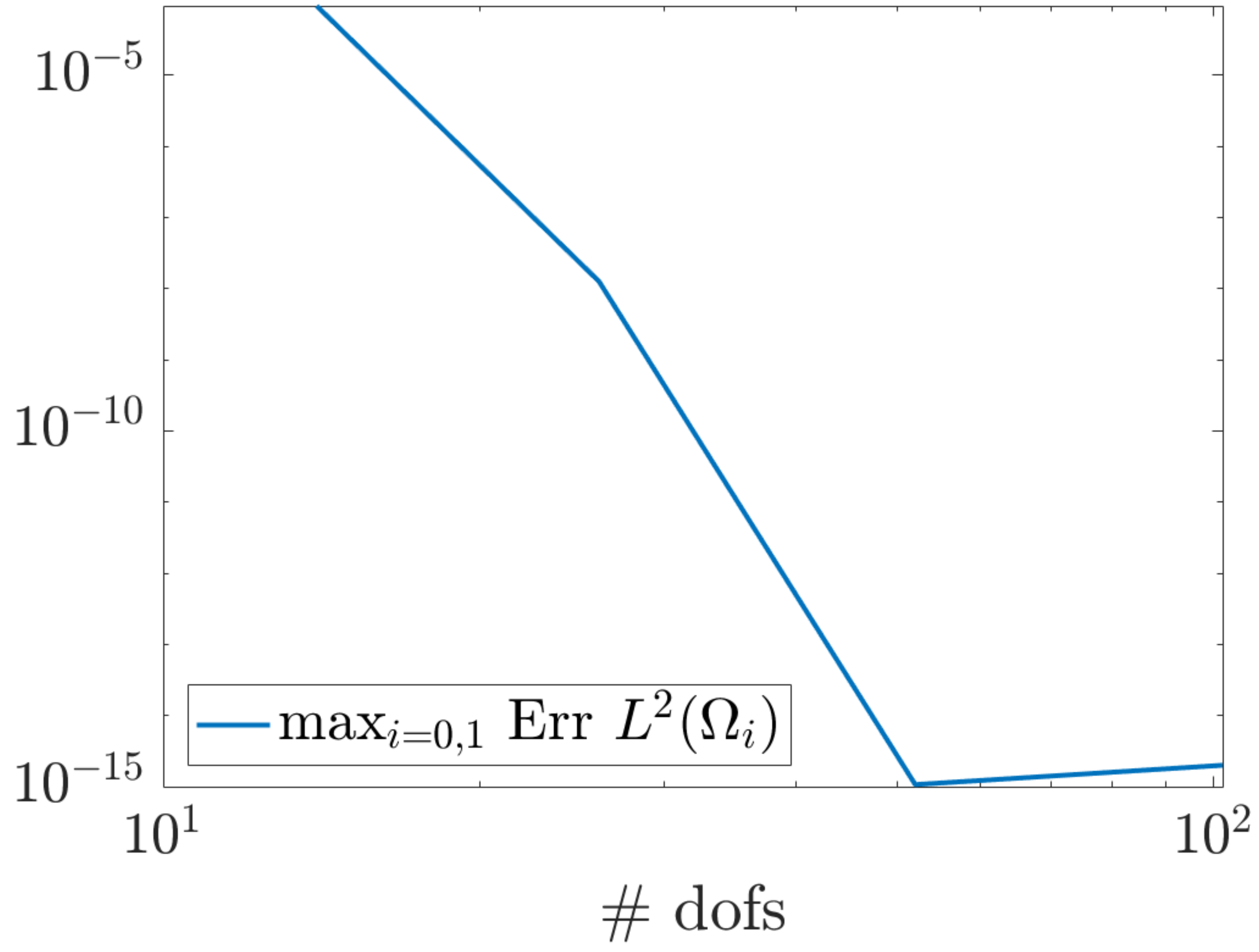


Define $V = u_i - u_j$, we recover the fluxes and traces as:

- $\sigma_i P_{S,i}\mathbf{u}_i = \psi_i(\mathbf{V})$,
- $\mathbf{u}_i = -\sigma_i^{-1}(P_{S,i}^{+})^{-1}B_i\lambda + \beta_i\mathbf{e}_i$.

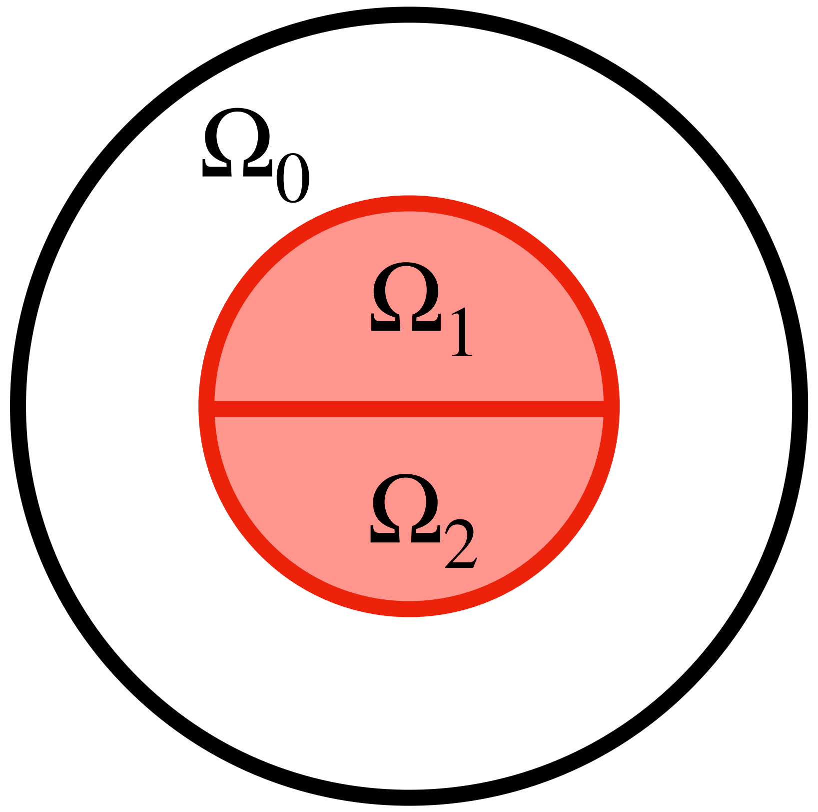
Given flux and trace, we compute u_0, u_1, u_2 inside Ω_i using the Green representation formula.

$$u(x) = \int_\Gamma G(x,y)\partial_n u(y)\mathrm{d}s_y - \int_\Gamma \partial_n G(x,y)u(y)\mathrm{d}s_y$$



Checking correctness of $\psi_i(\mathbf{V}) = \sigma_i P_{S,i}\mathbf{u}_i \approx \sigma_i \partial_{\mathbf{n}} u$

Consider three harmonic functions u_0, u_1, u_2 satisfying flux continuity $(u_1 = u_2)$

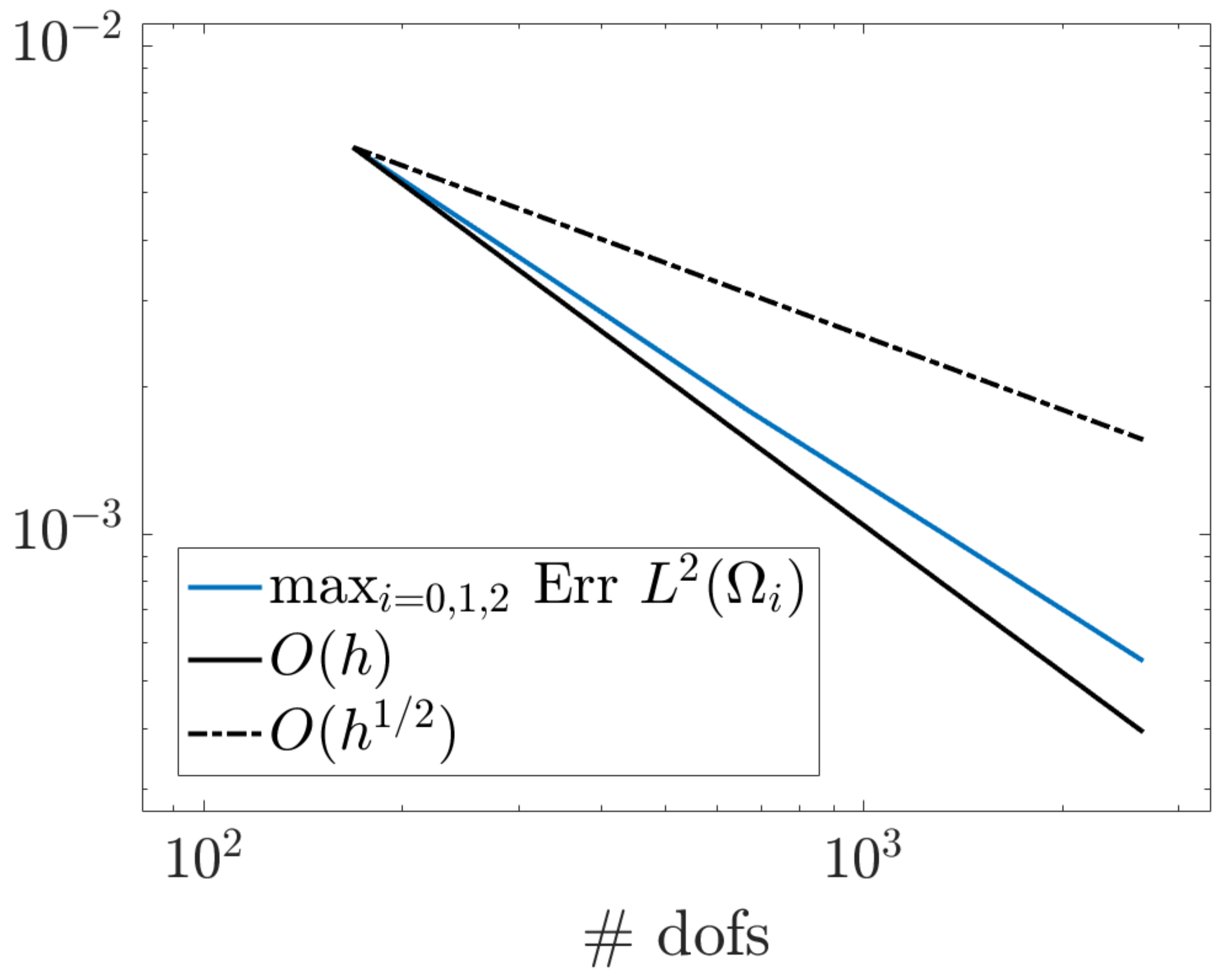


Define $V = u_i - u_j$, we recover the fluxes and traces as:

- $\sigma_i P_{S,i}\mathbf{u}_i = \psi_i(\mathbf{V})$,
- $\mathbf{u}_i = -\sigma_i^{-1}(P_{S,i}^{+})^{-1}B_i\lambda + \beta_i \mathbf{e}_i$.

Given flux and trace, we compute u_0, u_1, u_2 inside $\mathbf{\Omega}_i$ using the Green representation formula.

$$u(x) = \int_\Gamma G(x,y)\partial_n u(y)\mathrm{d}s_y - \int_\Gamma \partial_n G(x,y)u(y)\mathrm{d}s_y$$



Reduction to an ODE system

Recall that we want to solve

$$\psi_0(\mathbf{V}) = I_t(A_0\mathbf{V}, \mathbf{z}) \qquad \text{on } \Gamma_0,$$
$$\frac{\mathrm{d}\,\mathbf{z}}{\mathrm{d}\,t} = g(A_0\mathbf{V}, \mathbf{z}) \qquad \text{on } \Gamma_0,$$
$$\sum_{i=0}^{N} A_g B_i^\top \psi_i(\mathbf{V}) = -2\kappa A_g \mathbf{V} \qquad \text{on } \Gamma_g\,.$$

Using $\psi_i(\mathbf{V}) = -B_i\lambda$ yields

$$\sum_{i=0}^{N} A_g B_i^\top B_i \lambda = 2\kappa A_g \mathbf{V},$$
$$A_g\lambda = \kappa A_g \mathbf{V}\,.$$

With this information we can dispose of the equations on Γ_g.

Multiply first line of

$$\begin{pmatrix} F & G \\ G^\top & 0 \end{pmatrix} \begin{pmatrix} \lambda \\ \beta \end{pmatrix} = \begin{pmatrix} \mathbf{V} \\ \mathbf{0} \end{pmatrix}.$$

with A_0 or A_g, use $A_g\lambda = \kappa A_g\mathbf{V}$ and get

$$\begin{pmatrix} F_{00} & F_{0g} & A_0G \\ F_{g0} & F_{gg} - \kappa^{-1}I & A_gG \\ G^\top A_0^\top & G^\top A_g^\top & 0 \end{pmatrix} \begin{pmatrix} \lambda_m \\ \lambda_g \\ \beta \end{pmatrix} = \begin{pmatrix} \mathbf{V}_m \\ \mathbf{0} \\ \mathbf{0} \end{pmatrix}.$$

With $\lambda_m = A_0\lambda, \lambda_g = A_g\lambda, \mathbf{V}_m = A_0\mathbf{V}$. Thus

$$\psi_0(\mathbf{V}) = -B_0\lambda = A_0\lambda = \lambda_m$$

and $\psi_0(\mathbf{V})$ is replaced with $\psi(\mathbf{V}_m) = \lambda_m$.

Reduction to an ODE system

Recall that: $I_t(\mathbf{V}_m, \mathbf{z}) = C_m \frac{\mathrm{d}\,\mathbf{V}_m}{\mathrm{d}\,t} + I_{\text{ion}}(\mathbf{V}_m, \mathbf{z})$.

$$
\begin{aligned}
-\sigma_i \Delta u_i &= 0, && \text{in } \Omega_i \quad i = 0,\dots,N,\\
-\sigma_i \partial_n u_i &= I_t(V_m, z), && \text{on } \Gamma_{i,0} \quad i = 1,\dots,N,\\
-\sigma_0 \partial_n u_0 &= -\, I_t(V_m, z), && \text{on } \Gamma_0,\\
u_i - u_0 &= V_m, && \text{on } \Gamma_{i,0} \quad i = 1,\dots,N,\\
\frac{\mathrm{d}\,z}{\mathrm{d}\,t} &= g(V_m, z), && \text{on } \Gamma_0,\\
-\sigma_i \partial_n u_i &= \kappa(u_i - u_j), && \text{on } \Gamma_{i,j} \quad 1 \le j, i \le N,
\end{aligned}
$$

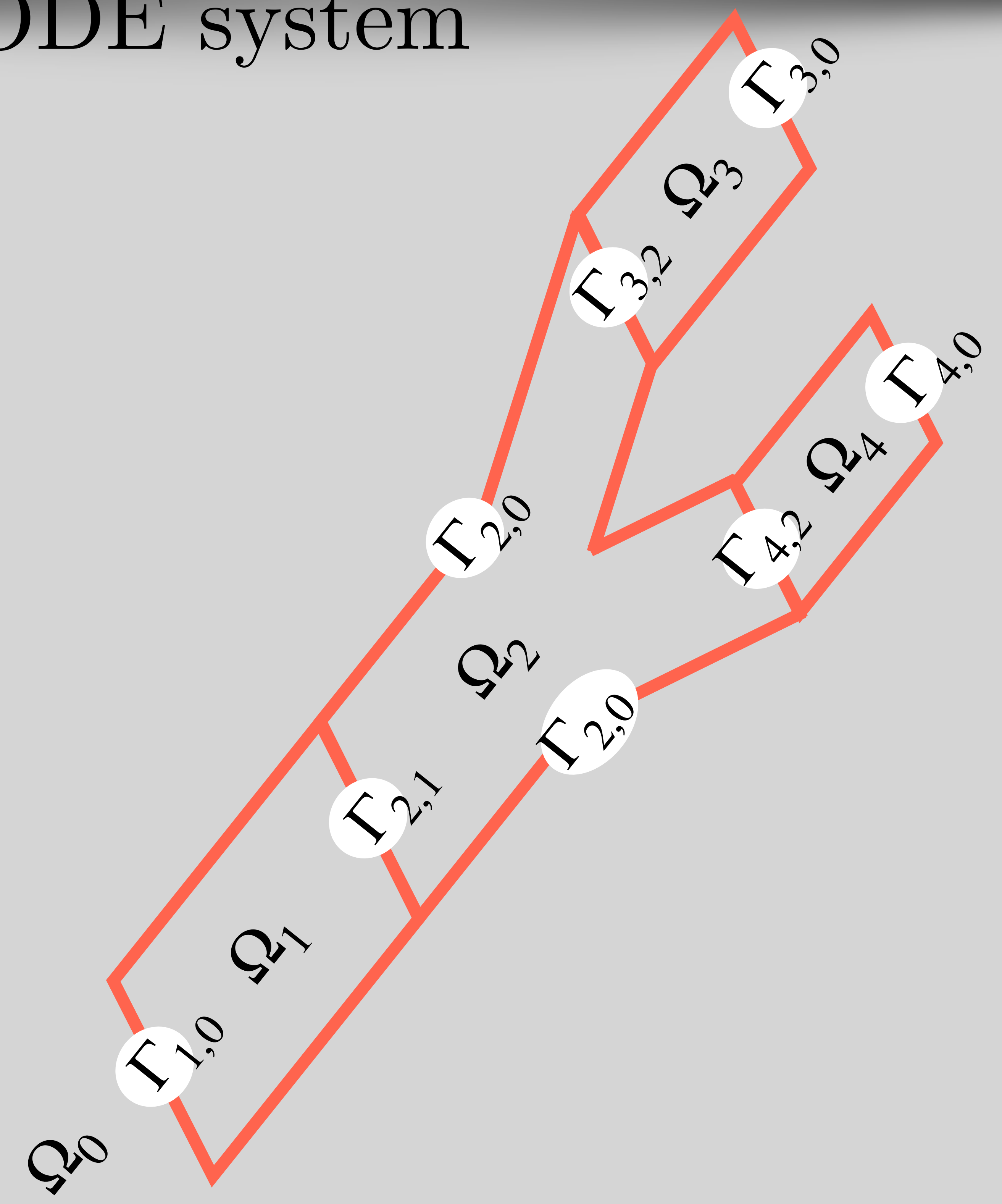
Theorem: the ODE system.

The spatially discretized Cell-by-Cell model is equivalent to the ODE system

$$
\begin{aligned}
\psi(\mathbf{V}_m) &= C_m \frac{\mathrm{d}\,\mathbf{V}_m}{\mathrm{d}\,t} + I_{\text{ion}}(\mathbf{V}_m, \mathbf{z}) && \text{on } \Gamma_0,\\
\frac{\mathrm{d}\,\mathbf{z}}{\mathrm{d}\,t} &= g(\mathbf{V}_m, \mathbf{z}) && \text{on } \Gamma_0,
\end{aligned}
$$

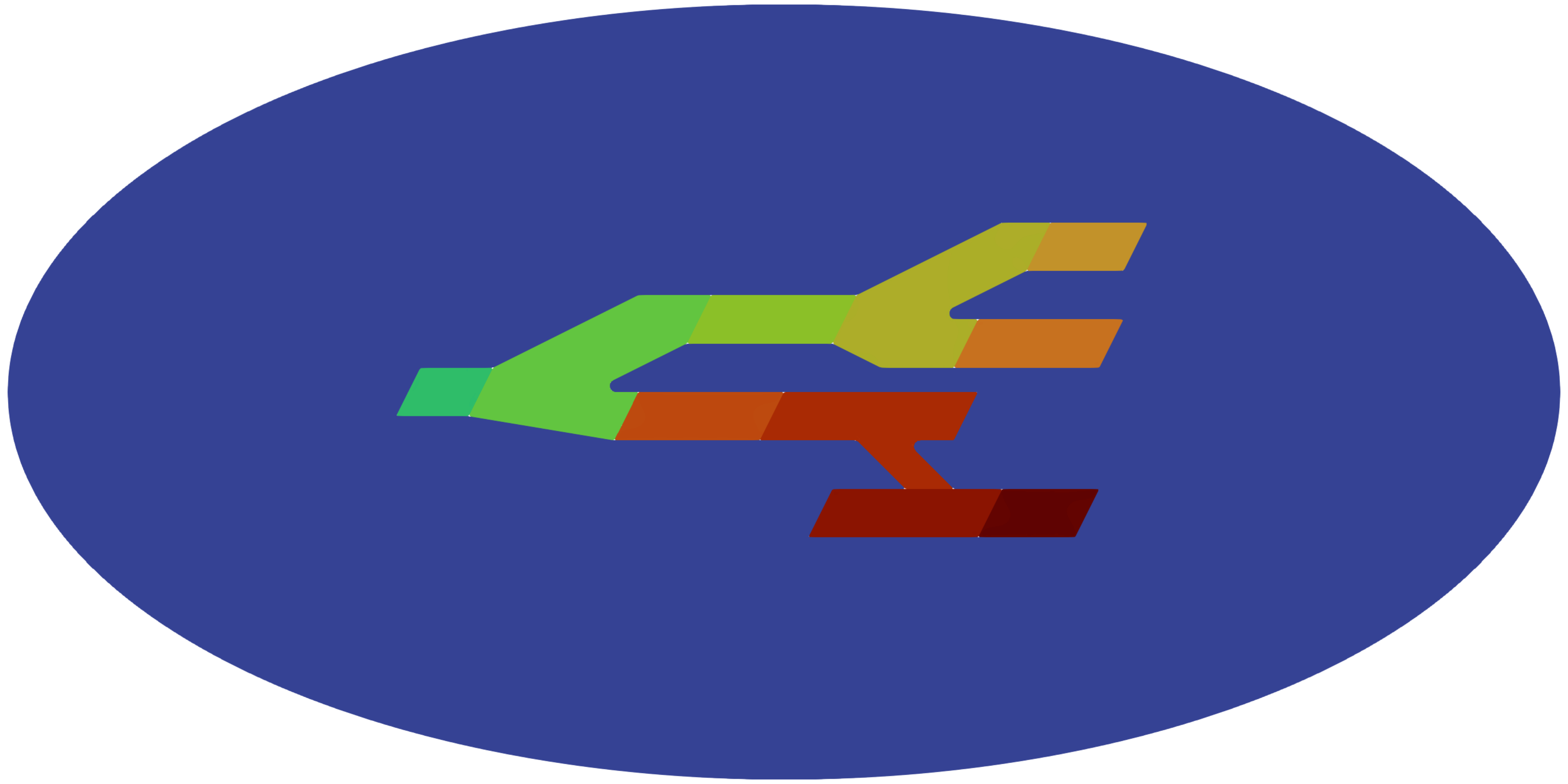
with $\psi(\mathbf{V}_m) = \lambda_m$ solution to

$$
\begin{pmatrix} F_{00} & F_{0g} & A_0 G \\ F_{g0} & F_{gg} - \kappa^{-1} I & A_g G \\ G^\top A_0^\top & G^\top A_g^\top & 0 \end{pmatrix}
\begin{pmatrix} \lambda_m \\ \lambda_g \\ \beta \end{pmatrix}
=
\begin{pmatrix} \mathbf{V}_m \\ \mathbf{0} \\ \mathbf{0} \end{pmatrix}.
$$



Numerical experiment

We consider the extracellular matrix and 10 cells:



And solve

$$\psi(\mathbf{V}_m) = C_m \frac{\mathrm{d}\,\mathbf{V}_m}{\mathrm{d}\,t} + I_{\text{ion}}(\mathbf{V}_m, \mathbf{z}) \qquad \text{on } \Gamma_0,$$

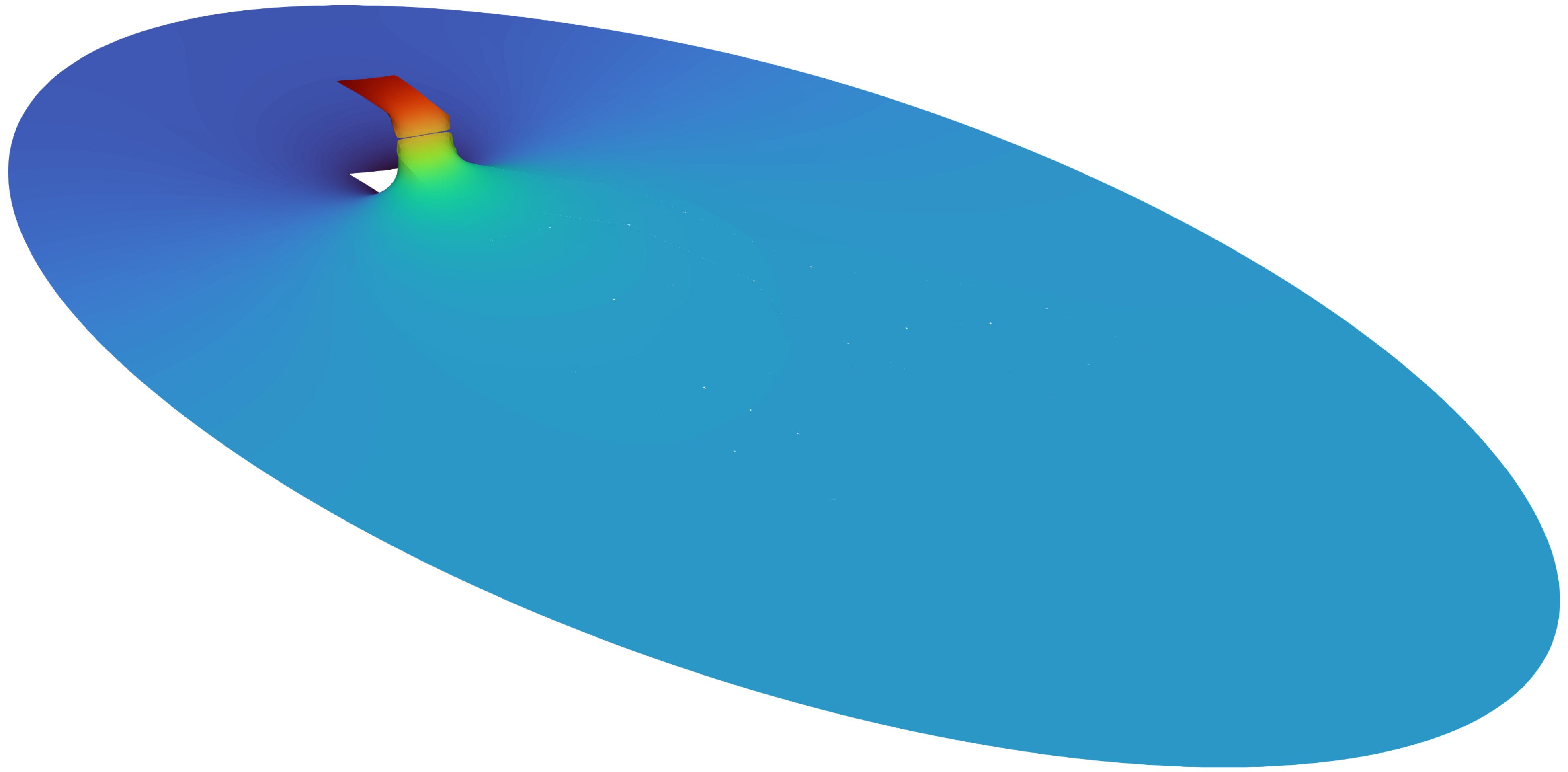
$$\frac{\mathrm{d}\,\mathbf{z}}{\mathrm{d}\,t} = g(\mathbf{V}_m, \mathbf{z}) \qquad \text{on } \Gamma_0\,.$$

With ionic model

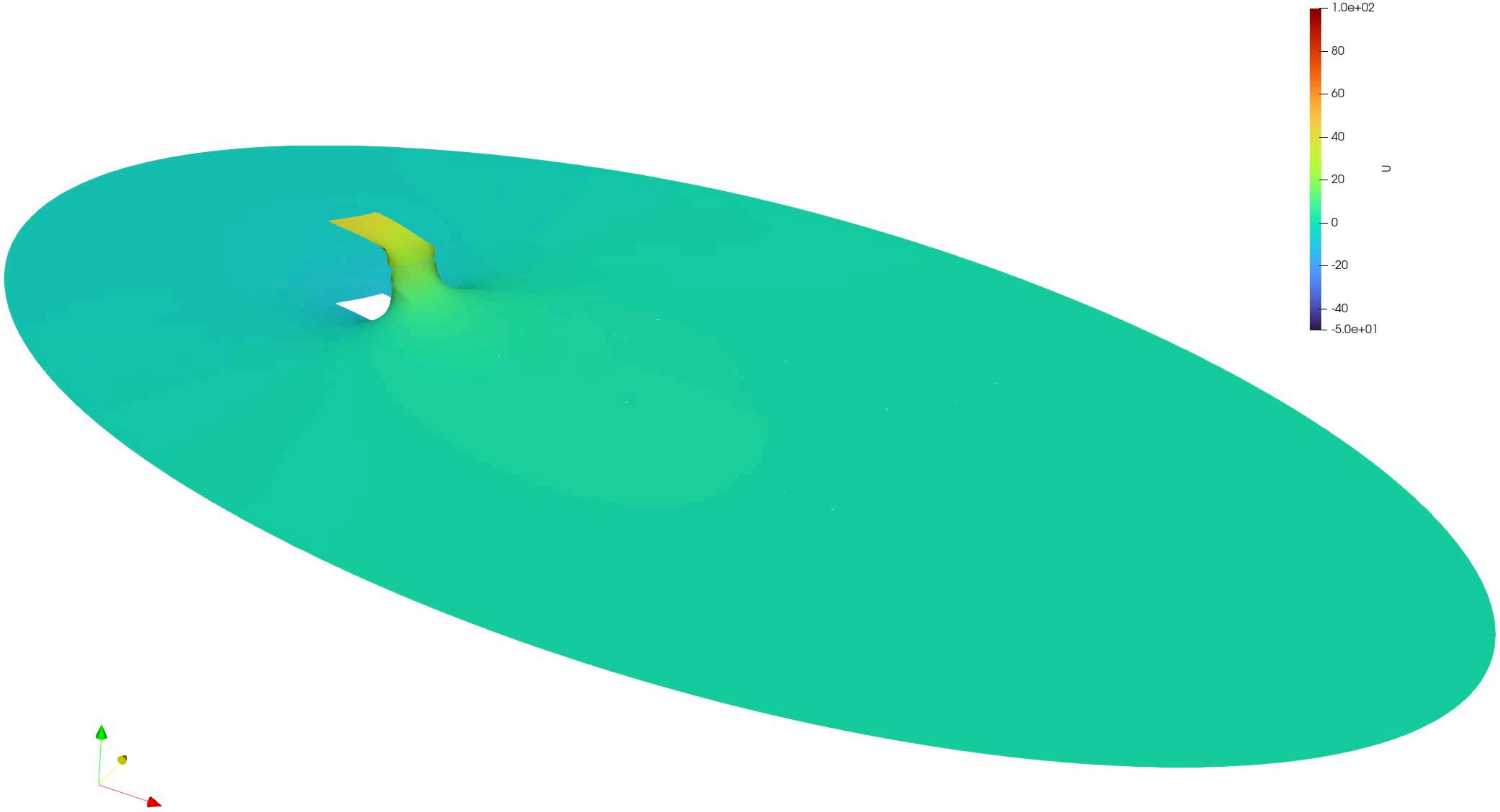
$$I_{\text{ion}}(V) = \eta_0 V(1 - V/V_{th})(1 - V/V_p),$$

without gating variables.

We stimulate the first cell:



Numerical experiment



The End

Thank you!

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