Boundary integral formulation and numerical experiments on the Cell-by-Cell (EMI) model for electrophysiology

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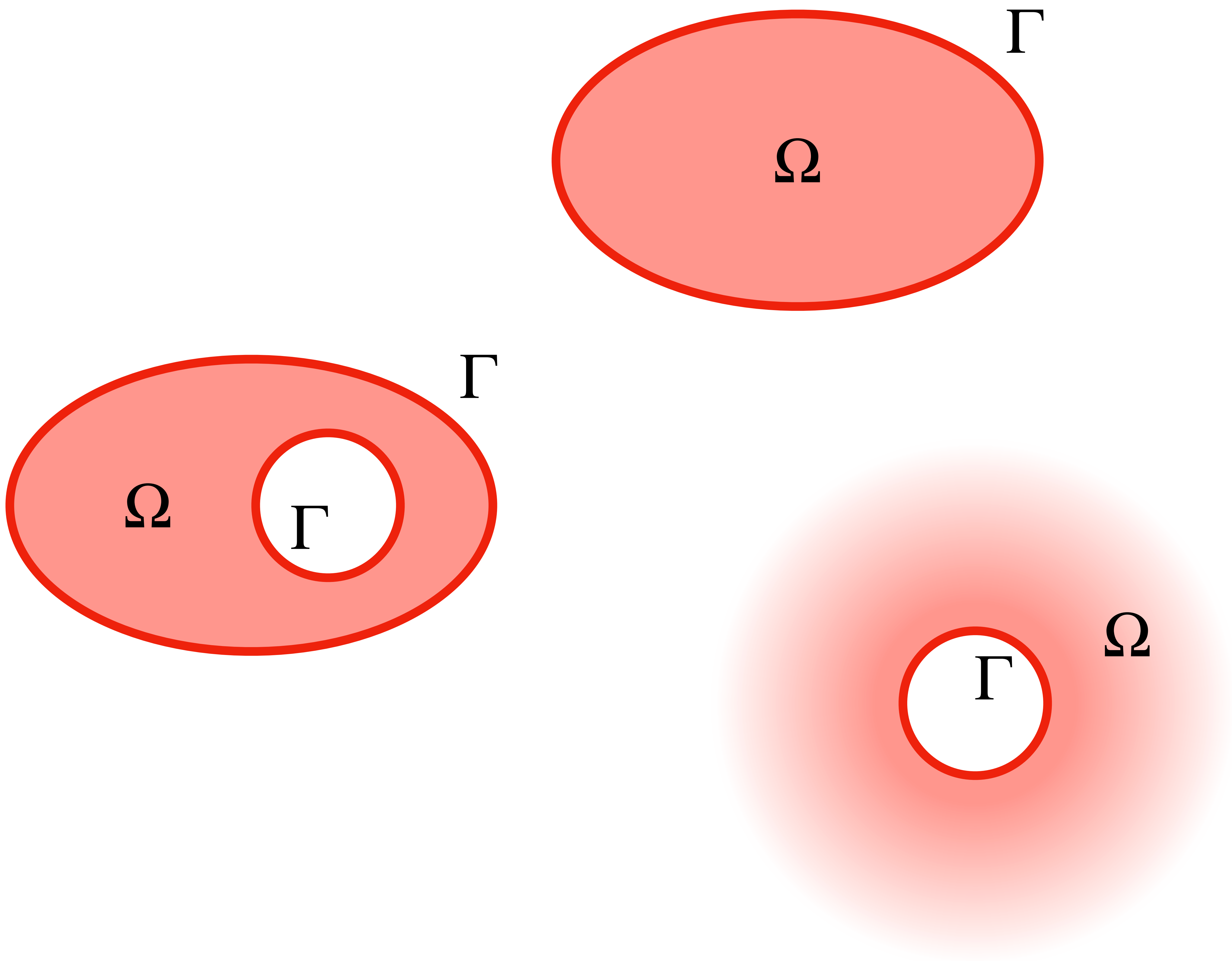
Boundary Integral Equations

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

Collocation Boundary Integral Method

Taking the trace yields

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

with

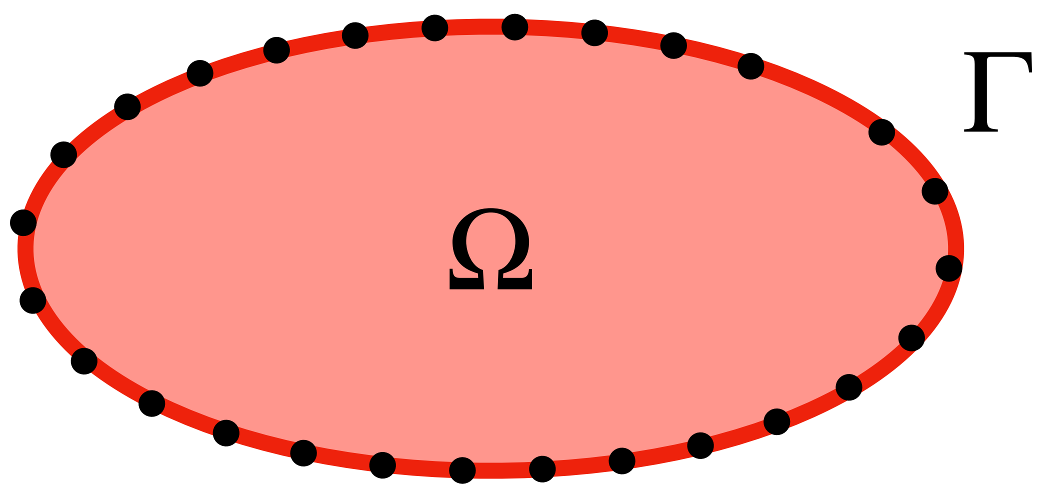
$$\mathscr{V}\rho(x) = \int_\Gamma G(x,y)\rho(y)\mathrm{d}s_y, \qquad x \in \Gamma,$$

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

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

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

Discretize Γ in M points x_j



and impose (2) on x_j only

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

With $\mathbf{u} \leftrightarrow u$, $\tilde{\mathbf{u}} \leftrightarrow \partial_n u$, $\mathbf{V} \leftrightarrow \mathscr{V}$, $\mathbf{K} \leftrightarrow \mathscr{K}$:

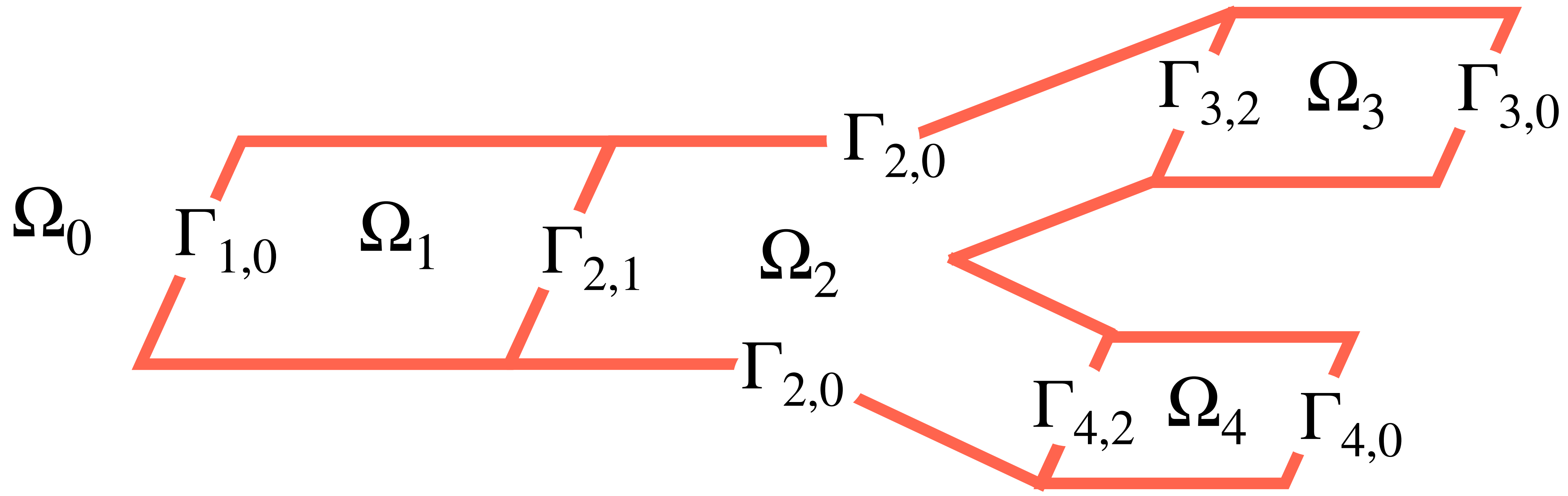
$$V\tilde{\mathbf{u}} = (K + \tfrac{1}{2})\mathbf{u}$$

$$\tilde{\mathbf{u}} = P_S\mathbf{u}, \quad P_S = V^{-1}(K + \tfrac{1}{2})$$

Discretization of the EMI model with BEM

We solve model

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



Discretization is done in three steps:

1. Space discretization via BEM:

   a. Requires single, double layer operators V, K in every subdomain and Dirichlet to Neumann map $P_S = V^{-1}(K + \frac{1}{2} I)$.

   b. Evaluation of projections to subdomains A_i, B_i.

2. Maps ψ_i that given V_m return the fluxes $-\sigma_i \partial_n u_i$

3. Transform the DAE into ODE.

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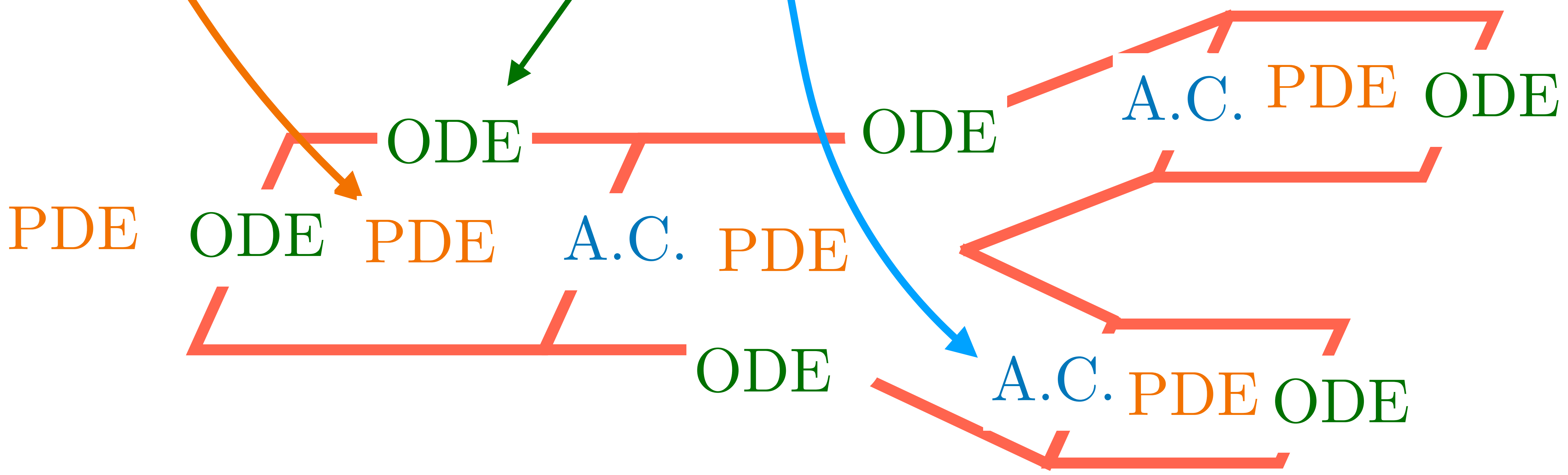

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Reduction to an ODE system

Employing P_S, A_i, B_i, ψ_i we obtain:

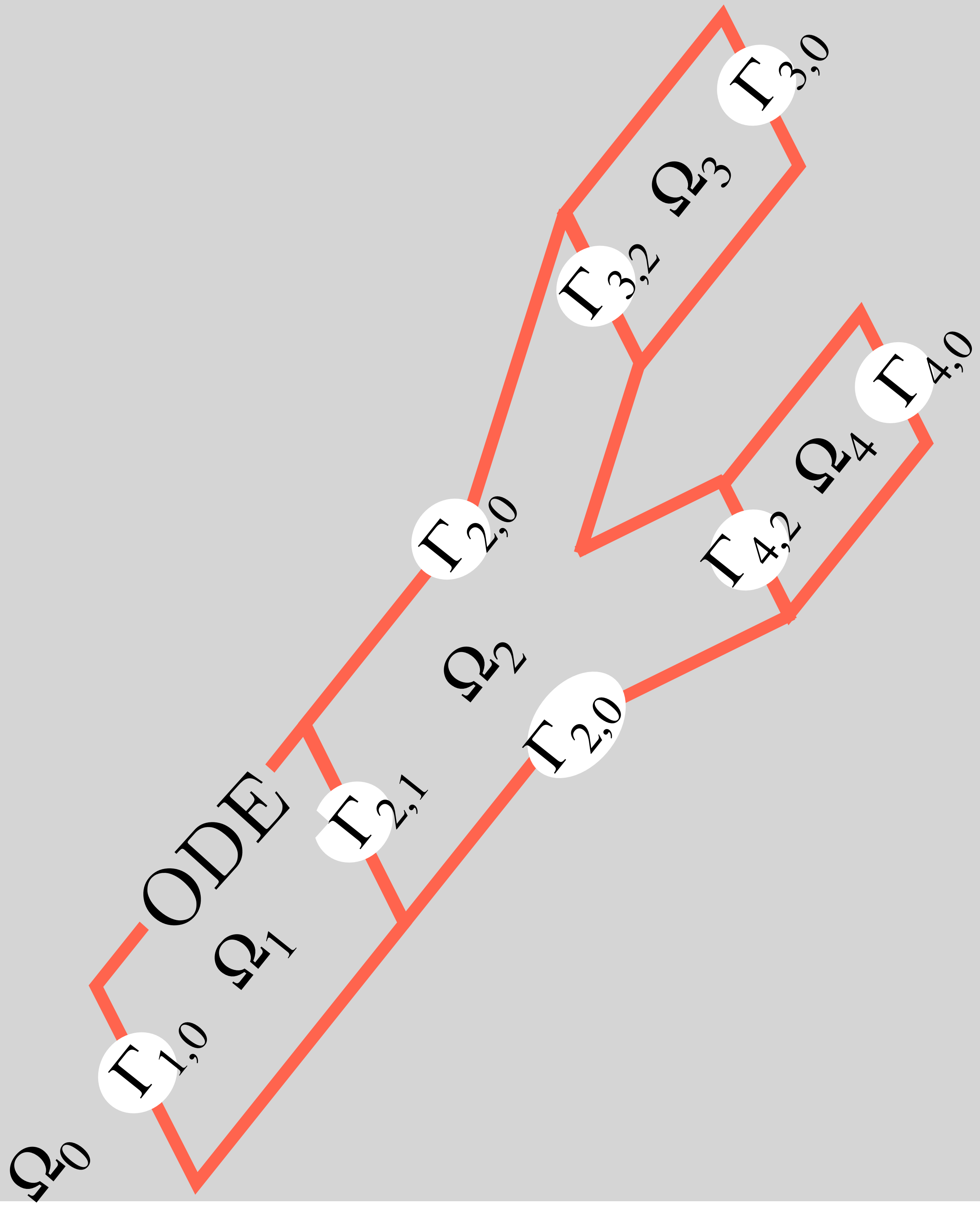
Theorem: the ODE system.

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

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



Reduction to an ODE system

Employing P_S, A_i, B_i, ψ_i we obtain:

$$
\begin{aligned}
-\sigma_i \Delta u_i &= 0, && \text{in } \Omega_i \quad i = 0,\dots,N,\\
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-\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}
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Theorem: the ODE system.

The spatially discretized Cell-by-Cell model is equivalen

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\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,\\
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$$

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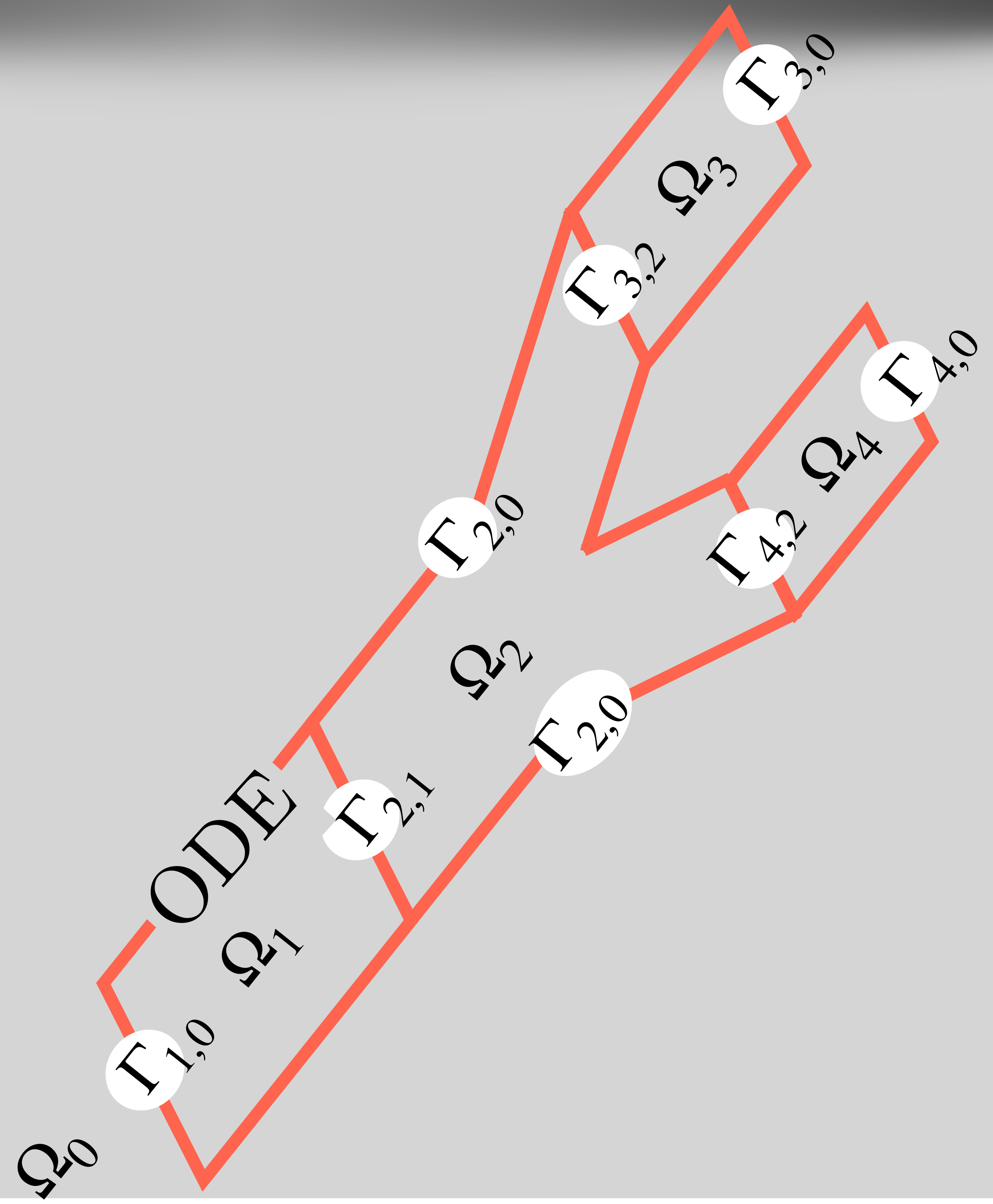
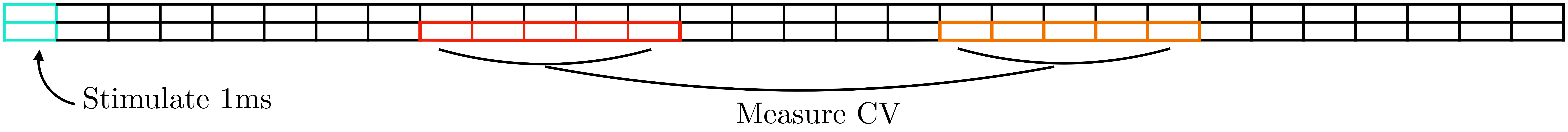
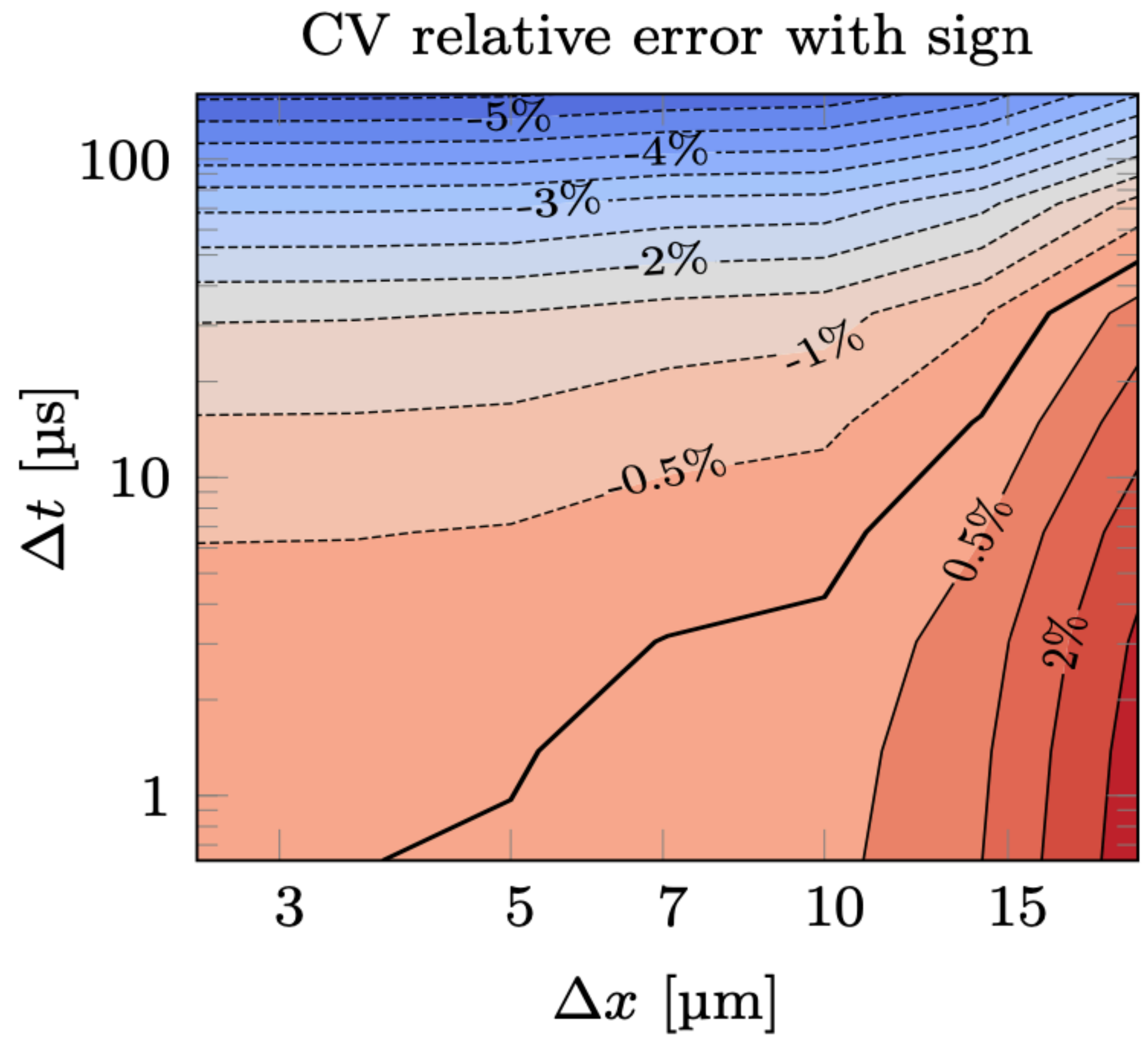
\begin{pmatrix} F_{00} & F_{0g} & A_0 G \\ F_{g0} & F_{gg} - \kappa^{-1} I & A_g G \\ G^\top A_0^\top & G^\top A_g^\top & 0 \end{pmatrix}
\begin{pmatrix} \lambda_m \\ \lambda_g \\ \beta \end{pmatrix}
=
\begin{pmatrix} \mathbf{V}_m \\ \mathbf{0} \\ \mathbf{0} \end{pmatrix}.
$$



CV vs Δx, Δt

Consider an array of 2×30 cells of length $c_l = 100\mu m$ and width $c_w = 20\mu m$



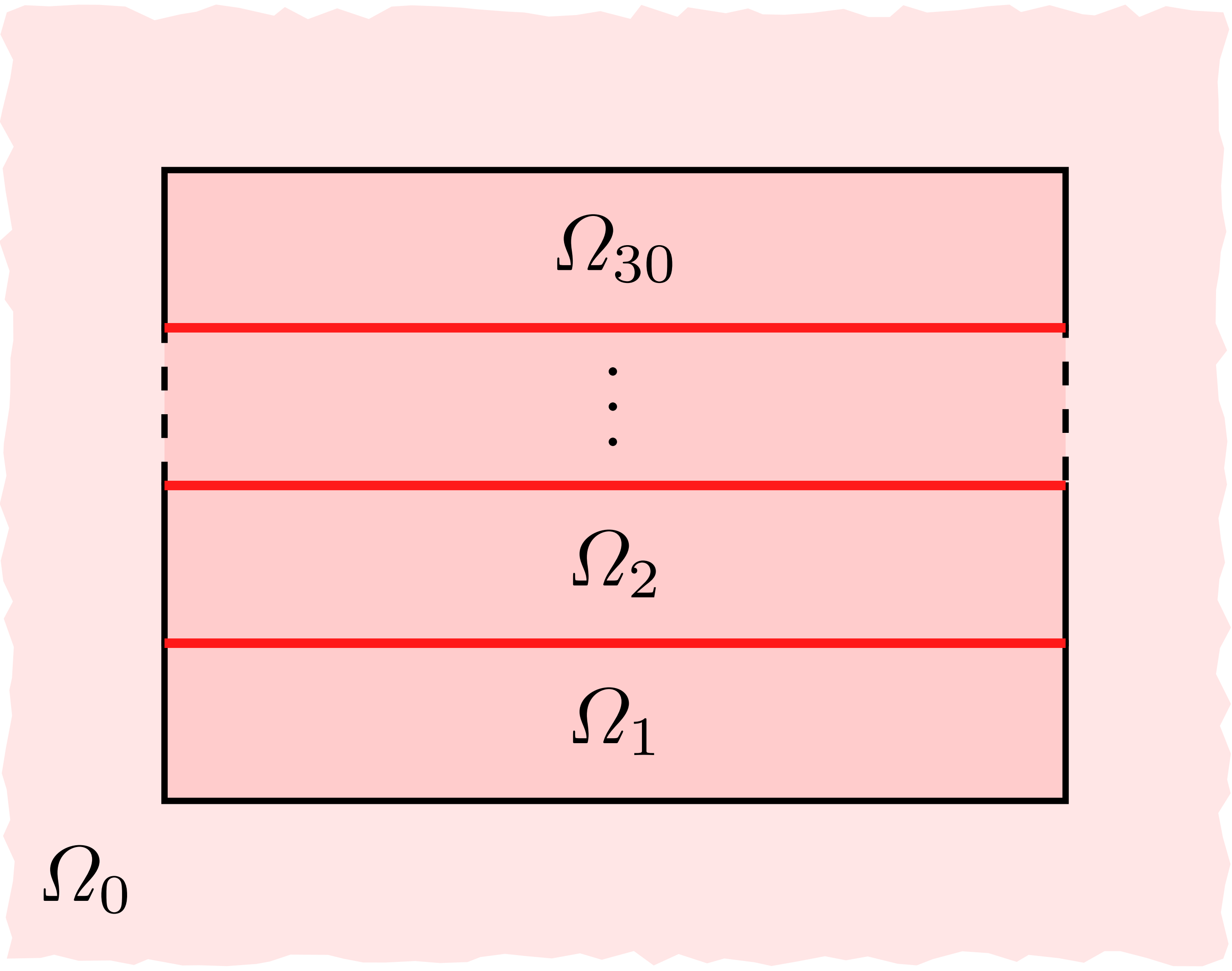


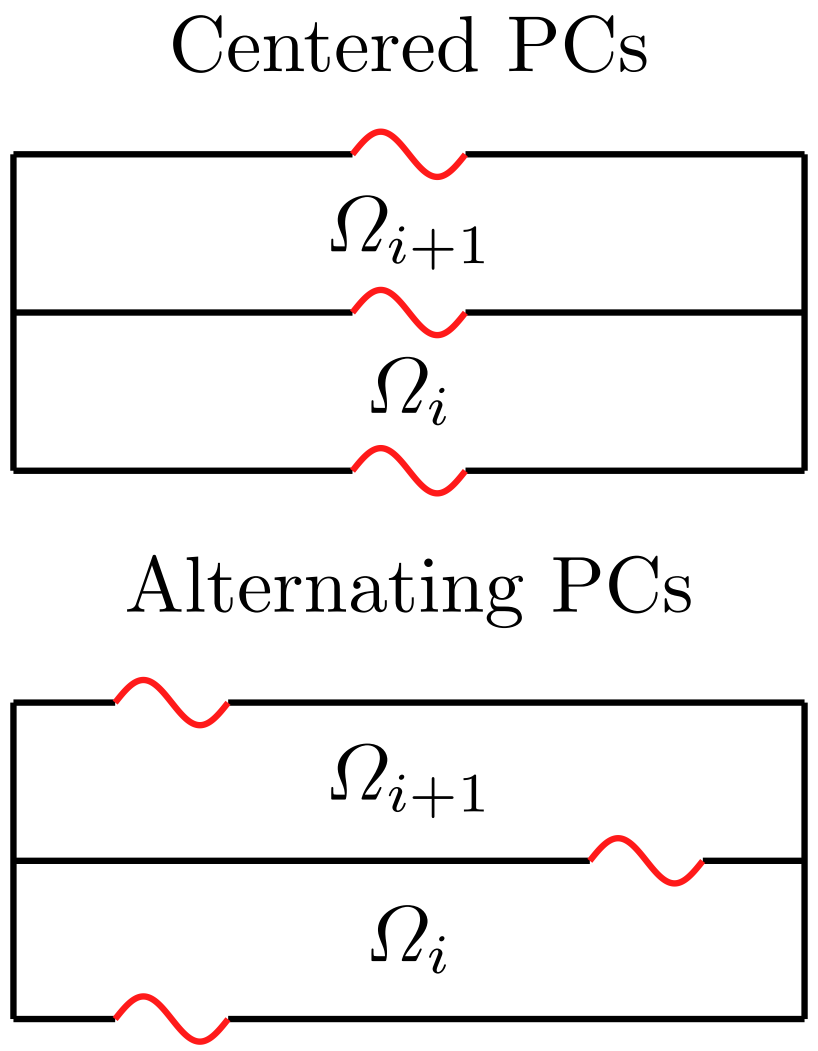
- Large $\Delta x = 15\mu m$ yield small errors 2 % ,
- Large $\Delta t = 100\mu s = 0.1ms$ yield errors 4 % .

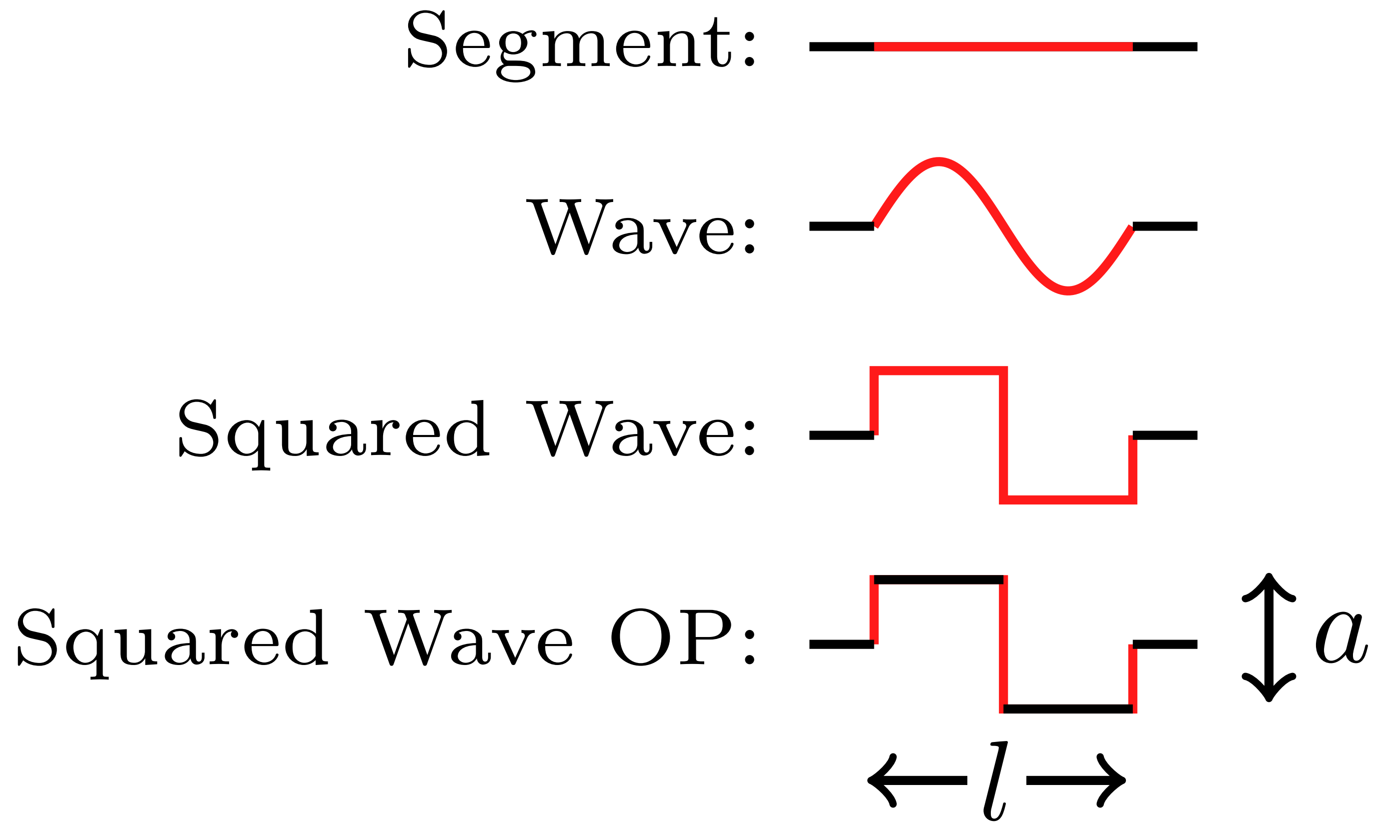
Transversal Conduction Velocity study

Here simulate block of 30x1 cells and study transversal CV dependence on gap junctions:

- shape,
- size,
- position.







Transversal CV dependence on gap junction properties

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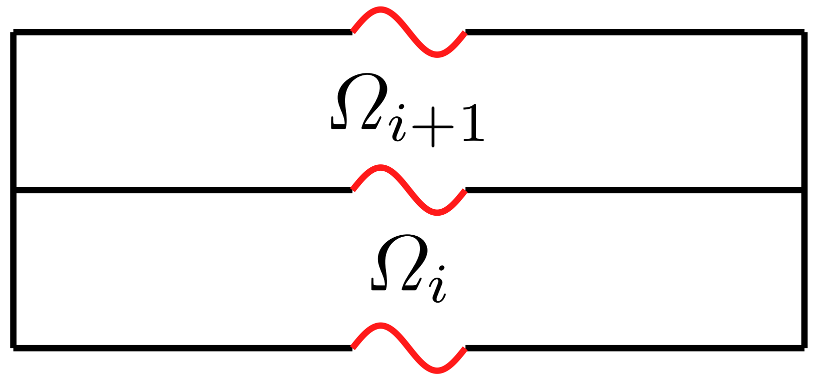
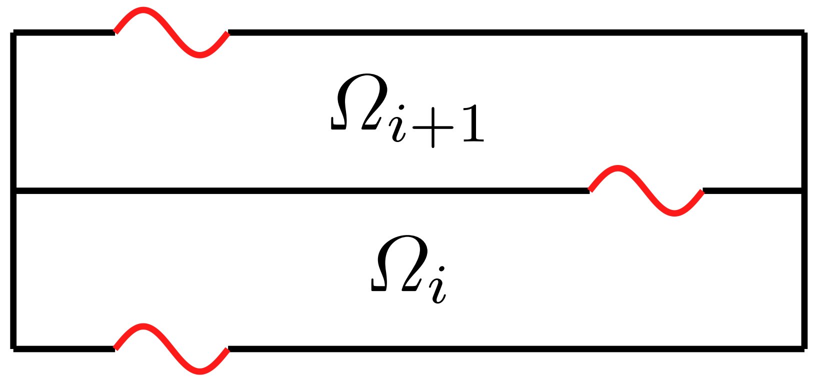
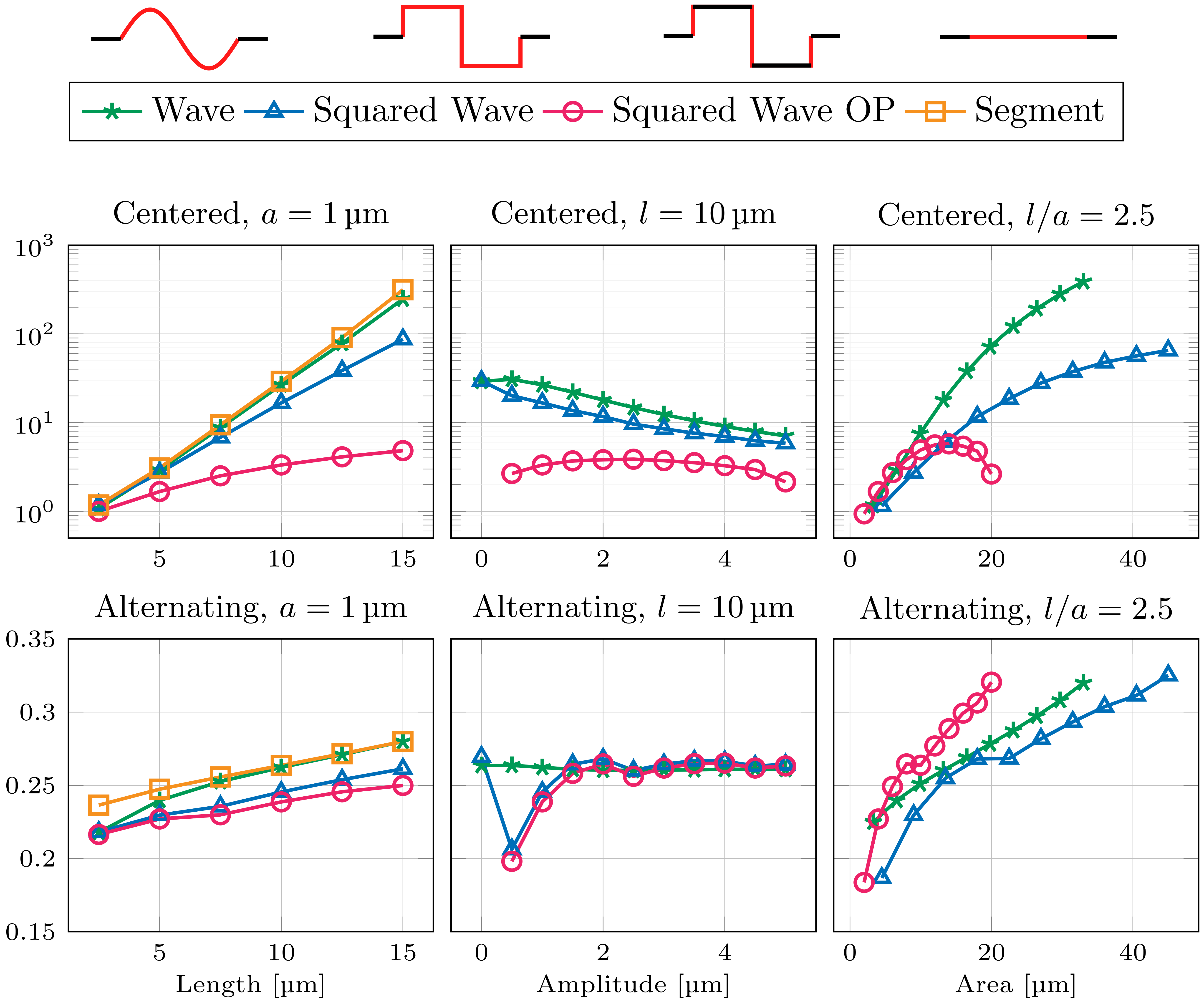
Centered PCs



Alternating PCs





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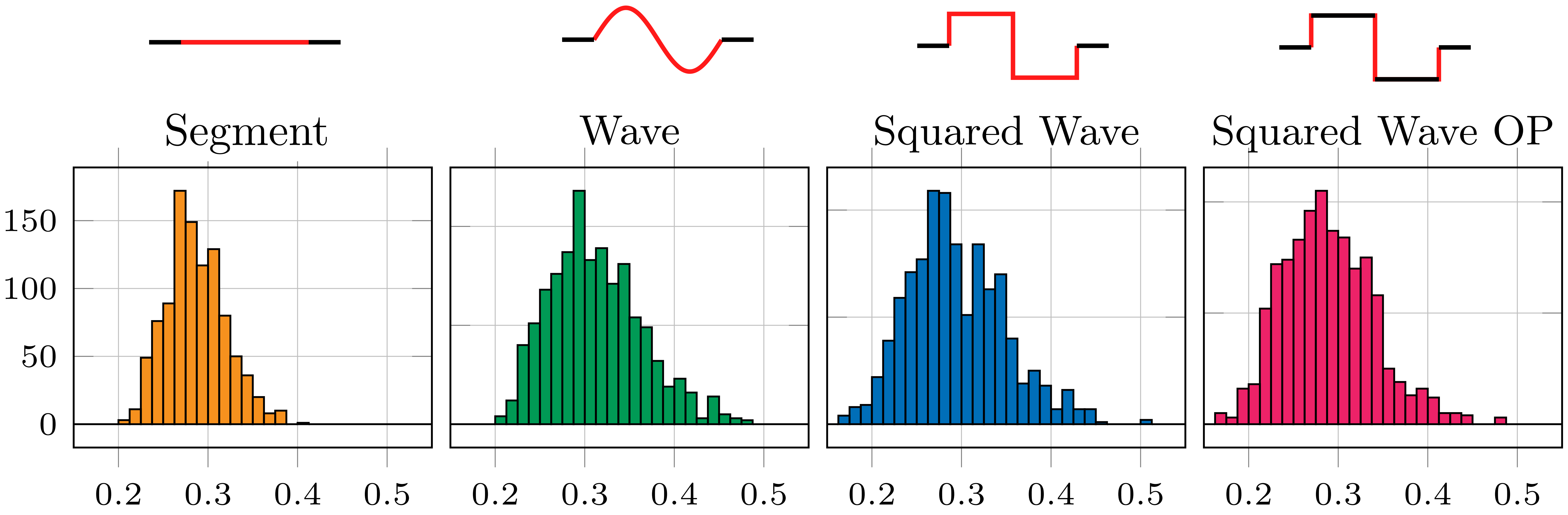
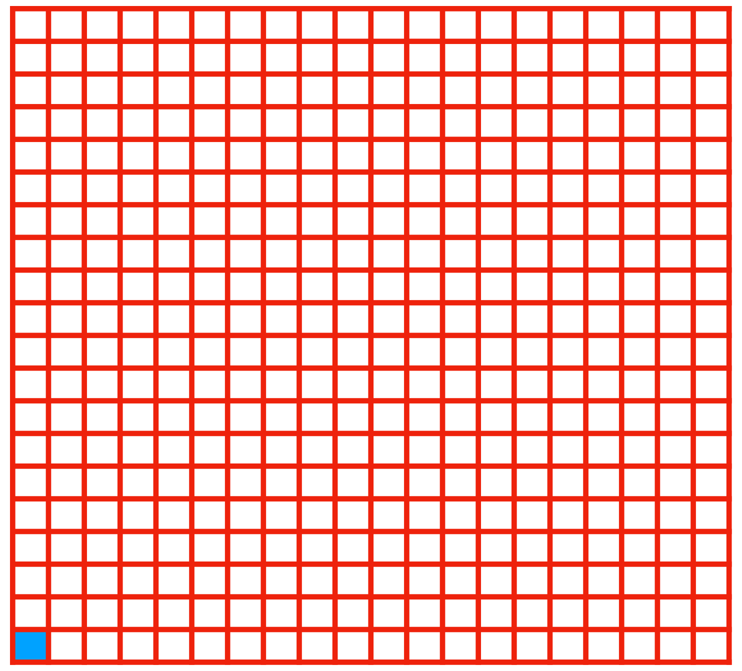
Randomly positioned gap junctions



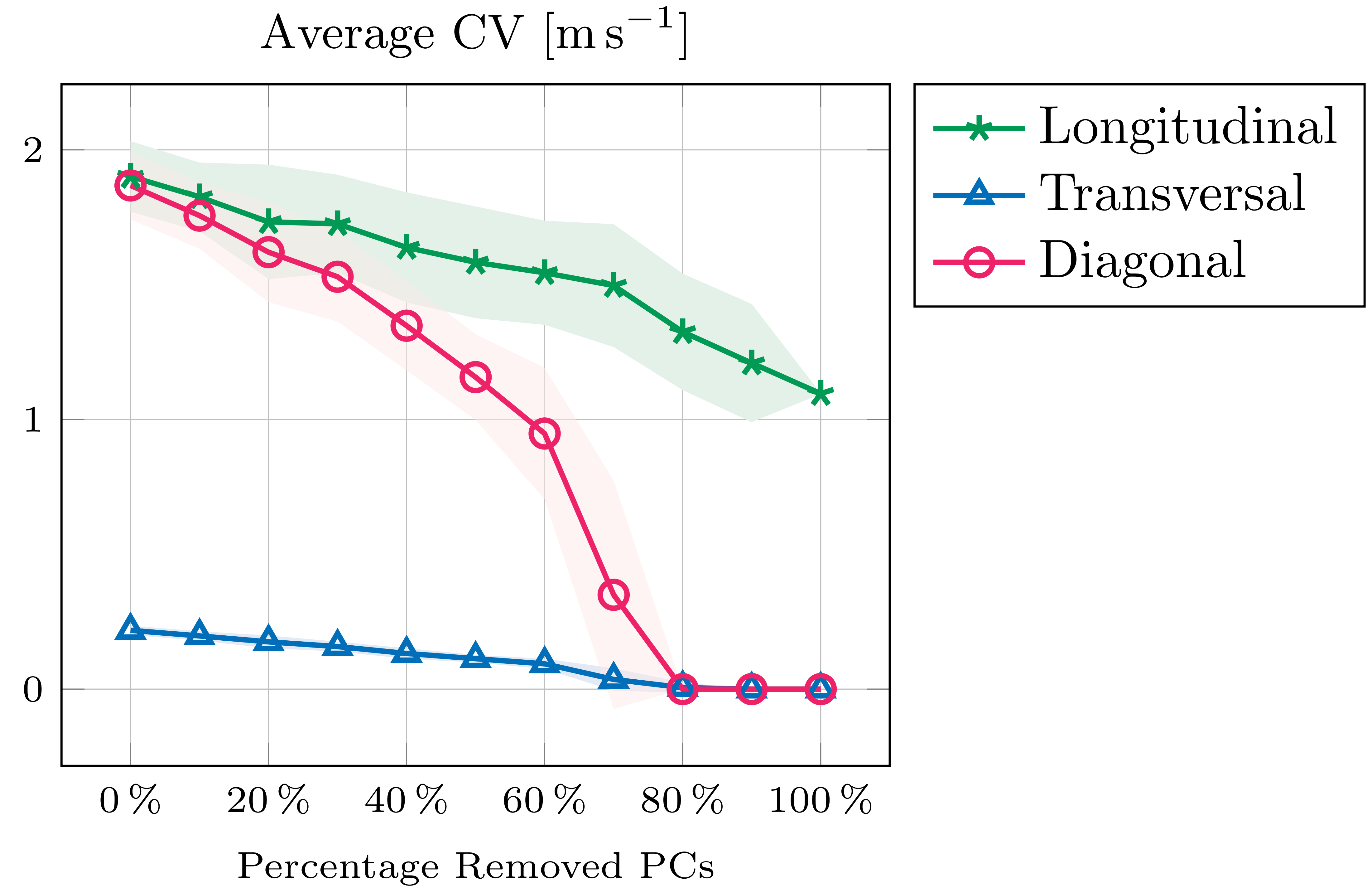
Distribution of transversal CV for randomly positioned gap junctions.

CV for randomly deactivated gap junctions

We consider here:



- Array of 20x20 cells,
- Stimulus at lower left corner,
- Transversal gap junctions are "segment" and randomly placed,
- Randomly deactivate transversal gap junctions (mimic fibrosis) with probability P.
- Study how P affects CV.



Conclusion

- Relatively accurate even for large mesh sizes $\Delta x = 15\mu m$ and step sizes $\Delta t = 0.1ms$, with $<5\%$ error.
- The gap junction's position strongly affects transversal velocity, more than shape.

Thank you!

- Rosilho de Souza, G., Pezzuto, S., & Krause, R. (2023). Boundary Integral Formulation of the Cell-by-Cell Model of Cardiac Electrophysiology. Submitted to *Engineering Analysis with Boundary Elements*.
- Rosilho de Souza, G., Pezzuto, S., & Krause, R. (2023, June). Effect of Gap Junction Distribution, Size, and Shape on the Conduction Velocity in a Cell-by-Cell Model for Electrophysiology. To appear in *International Conference on Functional Imaging and Modeling of the Heart*.

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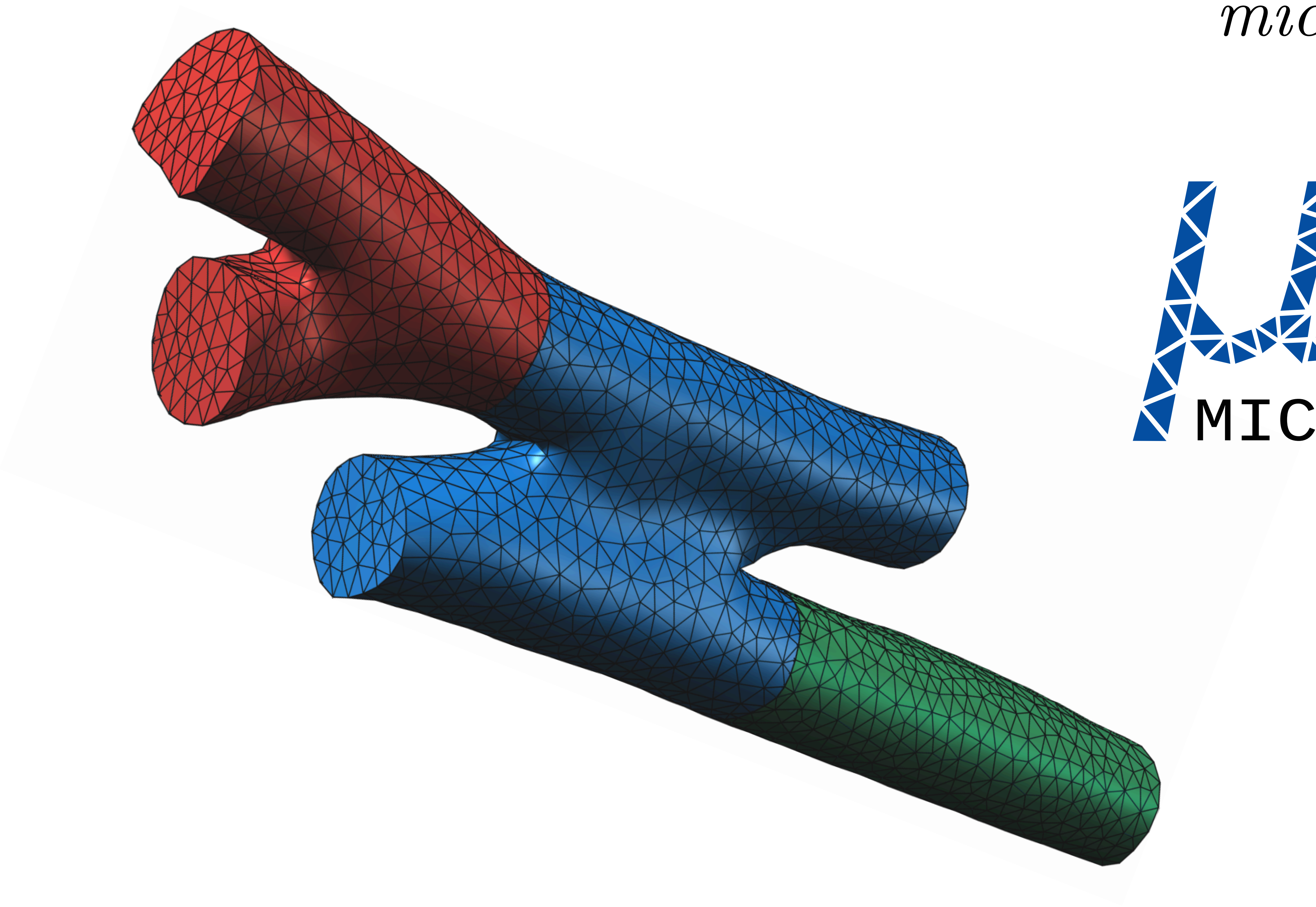
MICROCARD

Back up slides

The MICROCARD Project

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

microcard.eu



MICROCARD

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

$$
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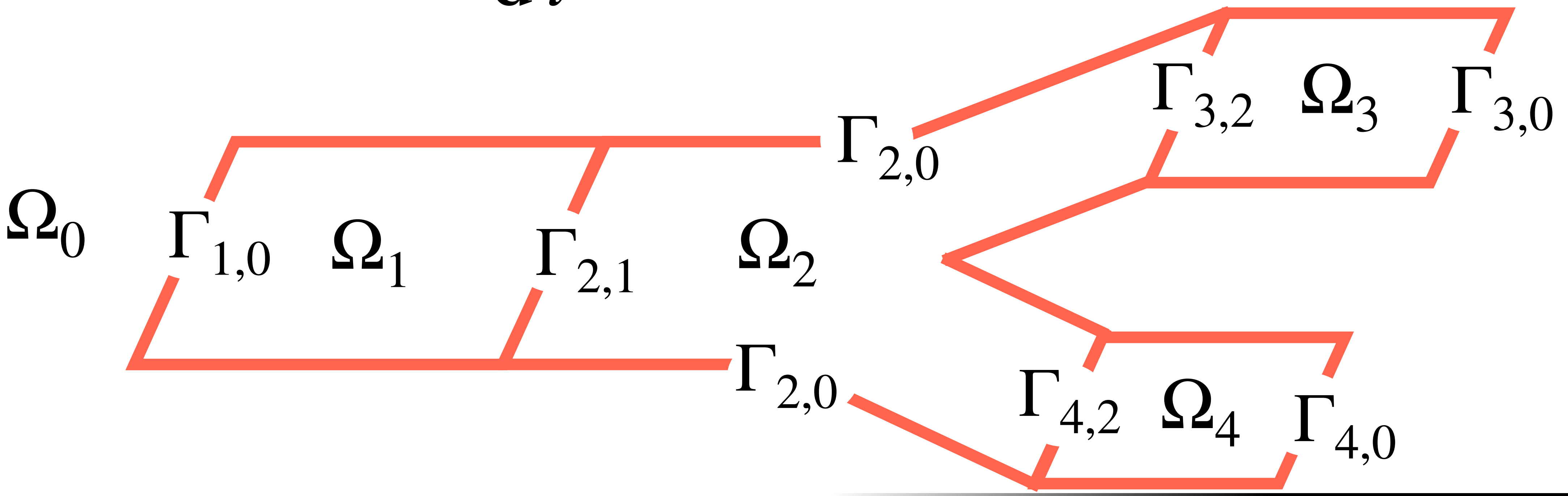
$$

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



Boundary Integral Equations

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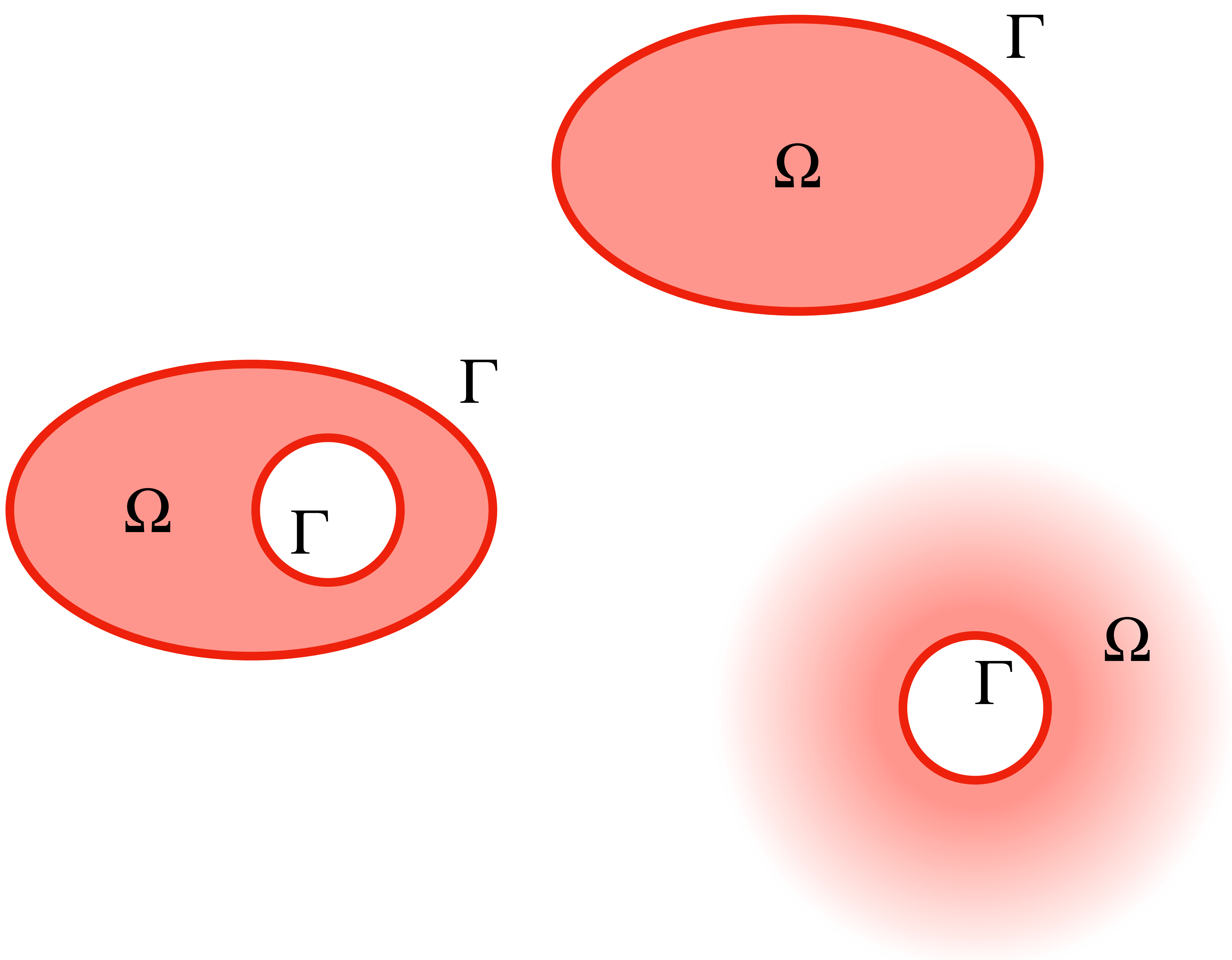

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the single and double layer potentials.
Rearranging (1):

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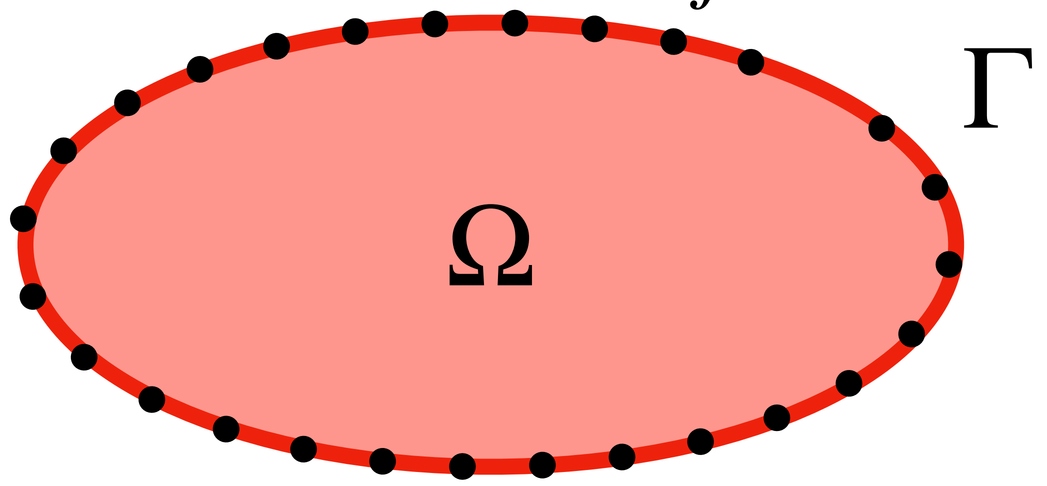
Discretize Γ in M points x_j



and impose (2) on x_j only

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

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

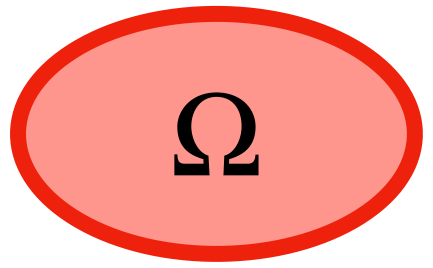
$$P_S = V^{-1}(K+\tfrac{1}{2}I)$$

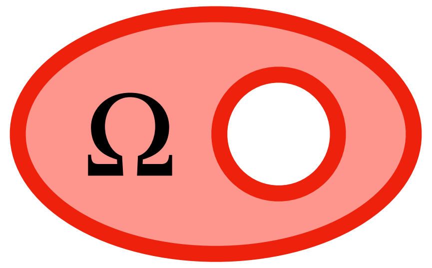
the Poincaré-Steklow operator (or Dirichlet-to-Neumann map).

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

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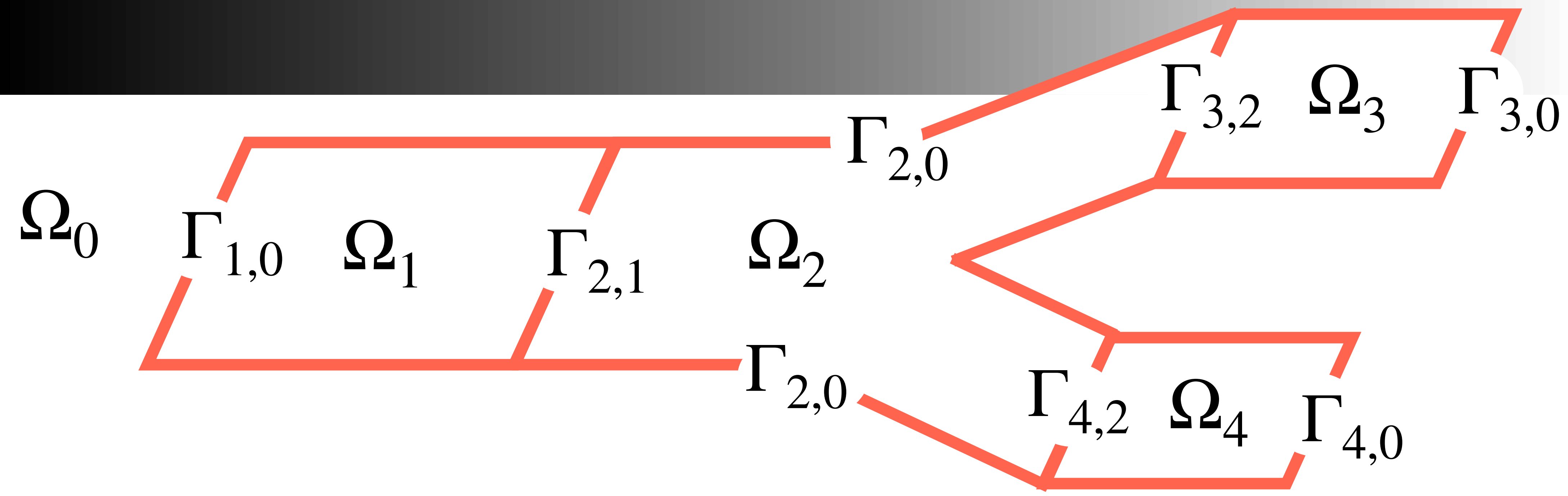
Consider a problem with N cells Ω_i, $i = 1, \ldots, N$ and *unbounded* extracellular matrix Ω_0 with boundary Γ_0:



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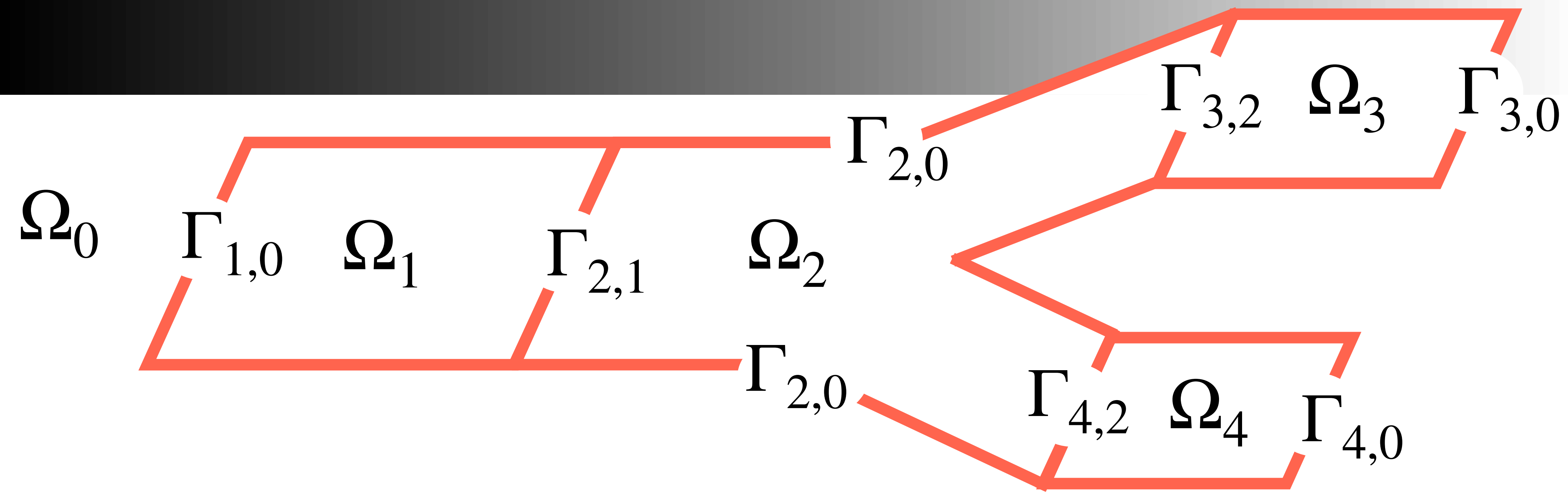
-\sigma_0 \partial_n u_0 &= -\, I_t(V_m, z), && \text{on } \Gamma_0,\\
u_i - u_0 &= V_m, && \text{on } \Gamma_{i,0} \quad i = 1, \ldots, N,\\
\frac{\mathrm{d}\, z}{\mathrm{d}\, t} &= g(V_m, z), && \text{on } \Gamma_0,\\
-\sigma_i \partial_n u_i &= \kappa(u_i - u_j), && \text{on } \Gamma_{i,j} \quad 1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

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

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

Model discretisation

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



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

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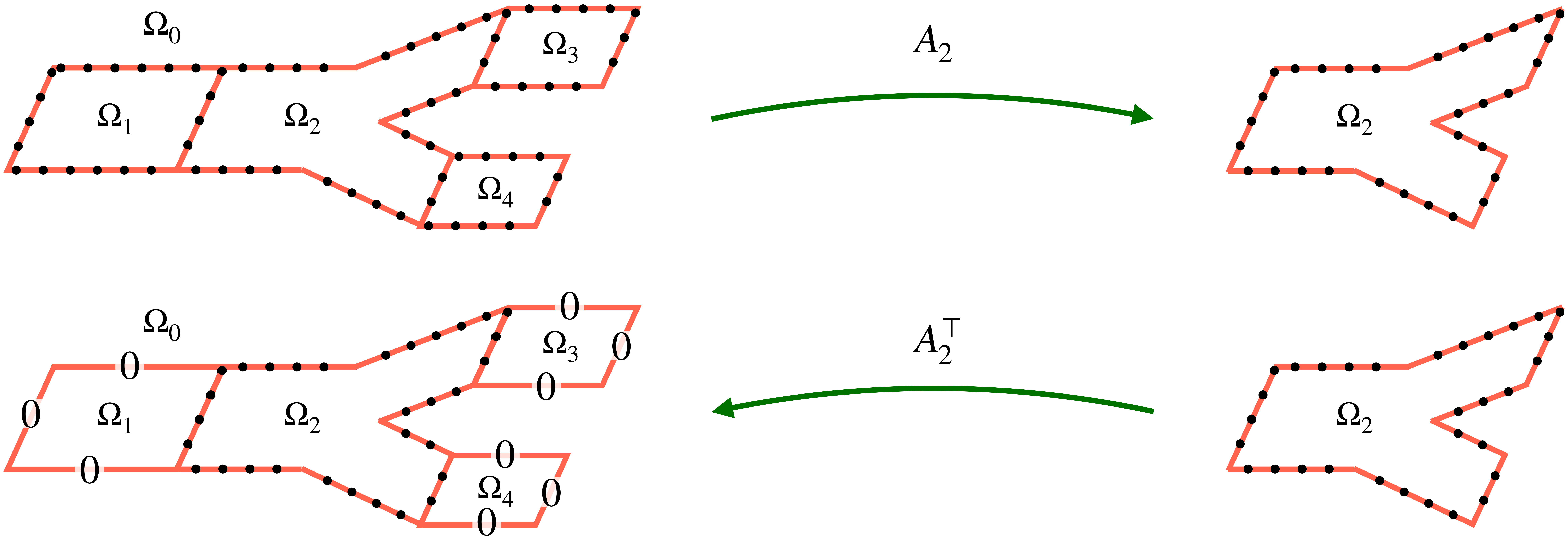
-\sigma_i \Delta u_i = 0, \qquad & \text{in } \Omega_i \quad i = 0,\dots,N,\\
\sigma_0 \partial_n u_0 = I_t(V,z), \qquad & \text{on } \Gamma_0,\\
\frac{\mathrm{d}\,z}{\mathrm{d}\,t} = g(V,z), \qquad & \text{on } \Gamma_0,\\
\sigma_i \partial_n u_i + \sigma_j \partial_n u_j = 0, \qquad & \text{on } \Gamma_{i,j}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

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

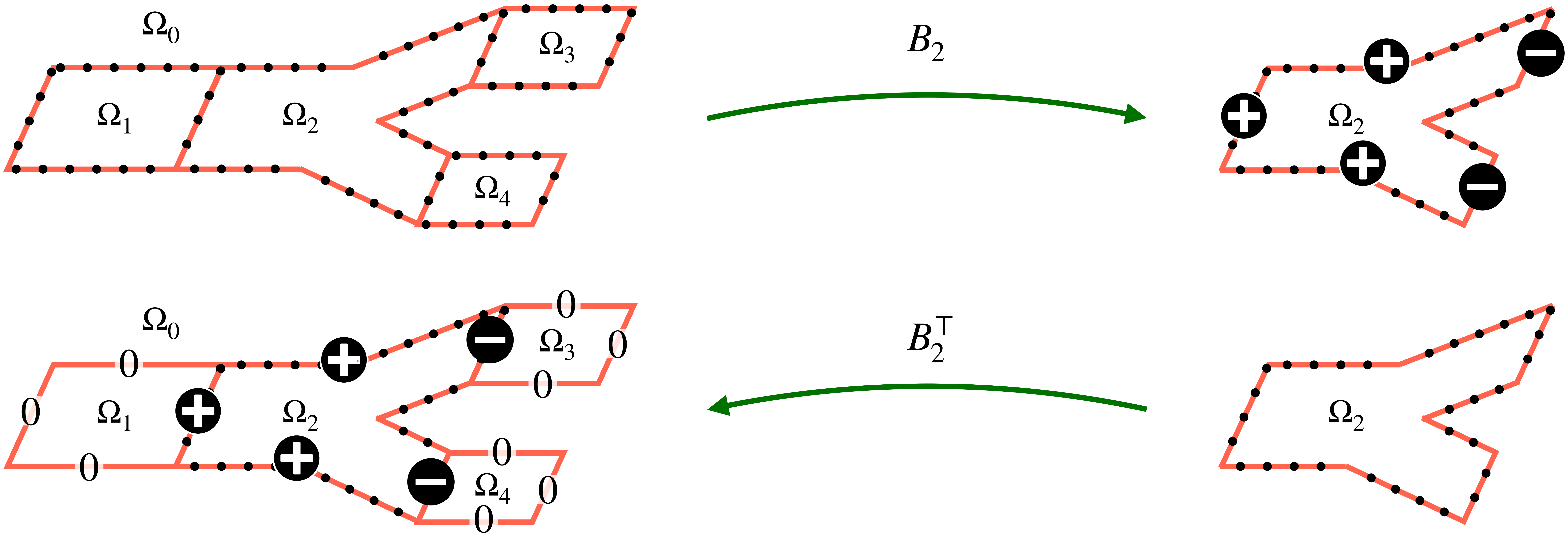
Global to local operators

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.



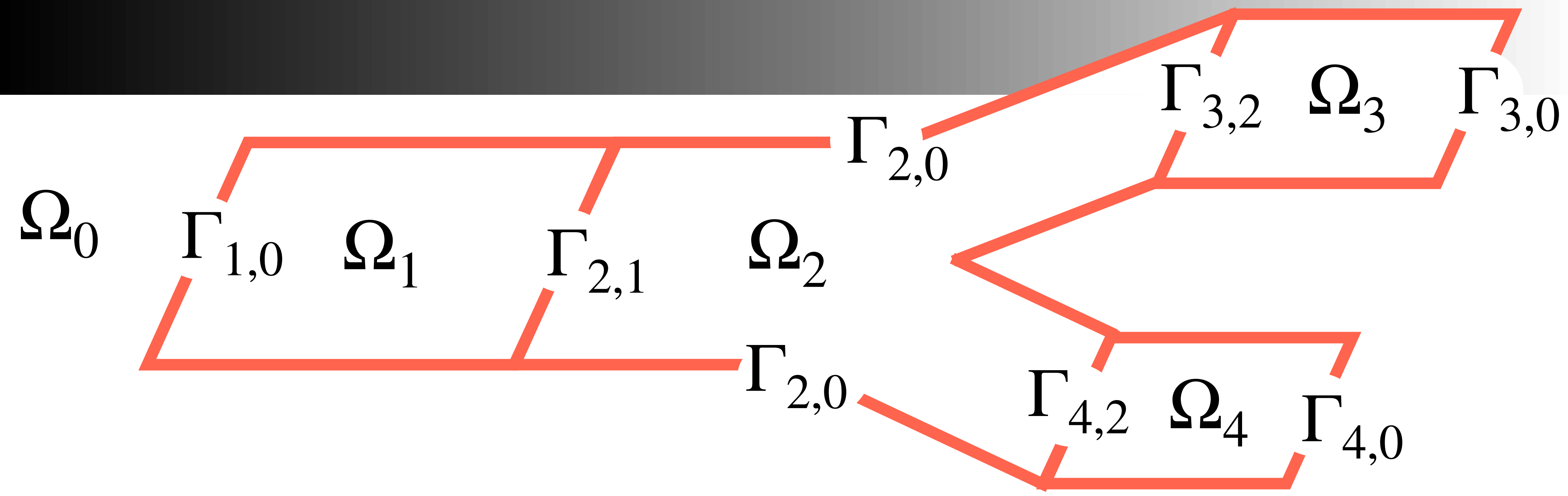
Global to local operators with sign change

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.



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

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

With A_g the operator from Γ to the gap junctions.

Reduction to a DAE system

$$\sigma_0 P_{S,0}\mathbf{u}_0 = I_t(A_0\mathbf{V},\mathbf{z}) \qquad \in \mathbb{R}^{M_0} = \Gamma_0$$

$$\frac{\mathrm{d}\,\mathbf{z}}{\mathrm{d}\,t} = g(A_0\mathbf{V},\mathbf{z}) \qquad \in \mathbb{R}^{M_0} = \Gamma_0$$

$$\sum_{i=0}^{N} \sigma_i A_i^\top P_{S,i}\mathbf{u}_i = 0 \qquad \in \mathbb{R}^{M} = \Gamma$$

$$\sum_{i=0}^{N} B_i^T \mathbf{u}_i = \mathbf{V} \qquad \in \mathbb{R}^{M} = \Gamma$$

$$\sum_{i=0}^{N} \sigma_i A_g B_i^\top P_{S,i}\mathbf{u}_i = -2\kappa A_g \mathbf{V} \qquad \in \mathbb{R}^{M_g} = \Gamma_g$$

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:

$$\psi_0(\mathbf{V}) = I_t(A_0\mathbf{V},\mathbf{z}) \qquad \text{on } \Gamma_0,$$

$$\frac{\mathrm{d}\,\mathbf{z}}{\mathrm{d}\,t} = g(A_0\mathbf{V},\mathbf{z}) \qquad \text{on } \Gamma_0,$$

$$\sum_{i=0}^{N} A_g B_i^\top \psi_i(\mathbf{V}) = -2\kappa A_g \mathbf{V} \qquad \text{on } \Gamma_g\,.$$

Reduction to a DAE system

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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.

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

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

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

Reduction to an ODE system

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

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

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

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