Towards finite volume methods for the cardiac micromodel

Z. Chehade Y. Coudière

IMB – UMR 5251, Liryc, Inria Carmen – Université de Bordeaux – CNRS – Bordeaux-INP,
yves.coudiere@u-bordeaux.fr

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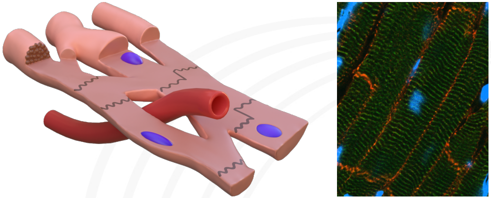
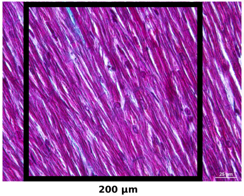
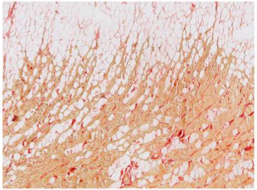
Why are we interested in the micromodel



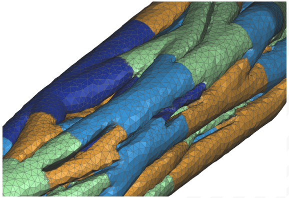
(a) Cardiomyocytes are specific



(b) Current models have 200 myocytes / mesh element

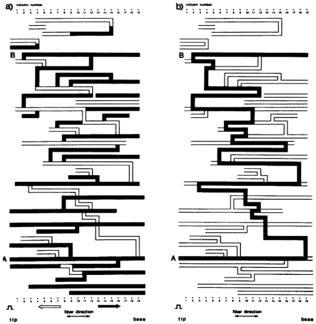


(c) What we want to describe [Hoo+11]

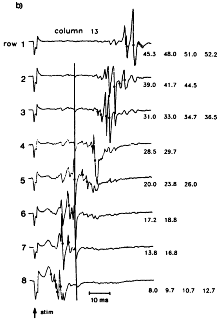


(d) We may need 100 – 1000 elements / myocyte

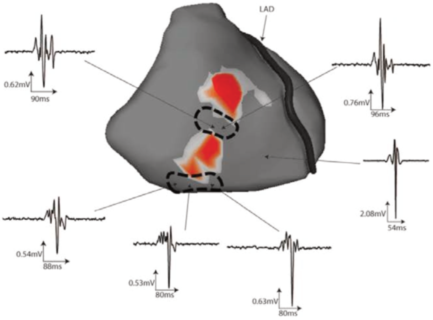
The medical reasons



(a) Zigzag propagation



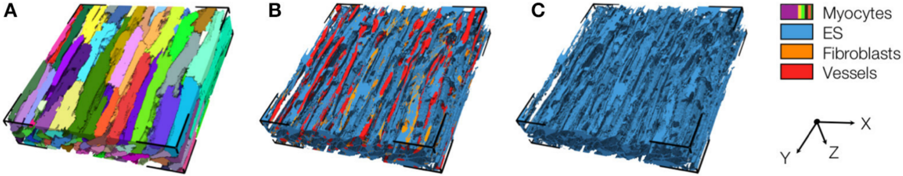
(b) Fractioned signals are a signature for it ?



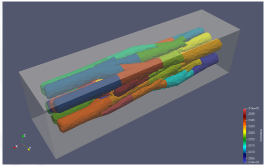
(c) And a signature of VF in human ?

See [Bak+93] (left 2 images) and [Hai+18] (right image)

The cardiac micromodel: histological meshes



(a) Confocal microscopy gives details, but it is yet too limited [Gre+18]

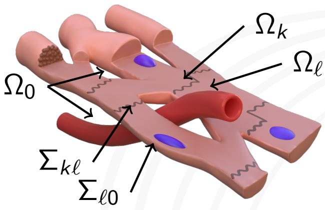


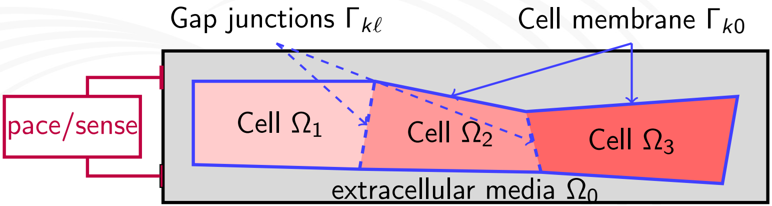
(b) We invent our own tissue

(c) A larger sample, video

Geometries / meshes are necessarily complex, and may be huge

The cardiac micromodel: equations

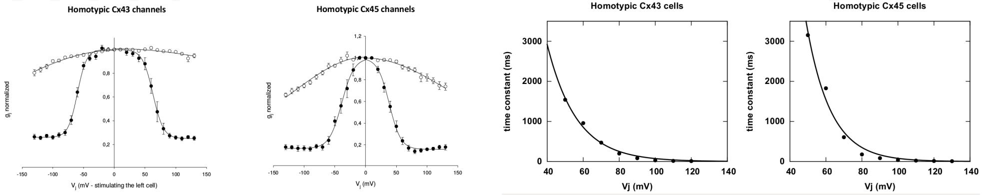




$-\operatorname{div}(G_k \nabla u_k) = 0$	Ω_k	electrostatic balance
$v^k = u_k - u_0$	Σ_{k0}	transmembrane voltage
$-G_k \nabla u_k \cdot n_k = G_0 \nabla u_0 \cdot n_0 = C_m \partial_t v^k + I_{\text{ion}}(v^k, y^k)$	Σ_{k0}	transmembrane currents
$v^{k\ell} = u_\ell - u_k$	$\Sigma_{k\ell}$	gap junction (GJ) voltage
$-G_k \nabla u_k \cdot n_k = G_\ell \nabla u_\ell \cdot n_\ell = \kappa v^{\ell k}$	$\Sigma_{k\ell}$	gap junctions current

Coupled to non linear ODES

- Membrane electrophysiology : ionic models, same as for the previous talk
- Gap junctions electrophysiology may be linear (previous slide) :
  $-G_k \nabla u_k \cdot n_k = G_\ell \nabla u_\ell \cdot n_\ell = \kappa\,(u_k - u_\ell)$
- or we have nonlinear gap junctions [Dav+15]



  - the conductance $\kappa = \kappa(u_k - u_\ell, \ldots)$ is non linear
  - with time-dependant state variables
  - and may also have a capacitive component

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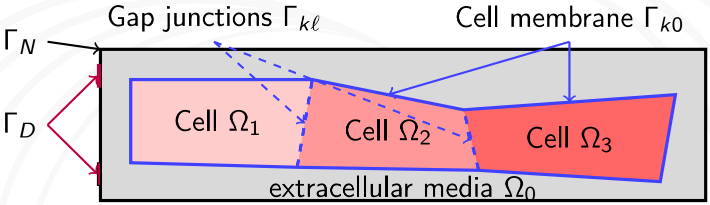
Boundary condition on the extracellular external boundary



- May be complex, e.g. for modeling a pacing or sensing device, using EIT techniques
- We assume mixed Dirichlet / Neumann conditions

$$-G_0 \nabla u_0 \cdot n_0 = g_N \quad \text{on } \Gamma_N$$
$$u_0 = g_D \quad \text{on } \Gamma_D$$

Weak solution – initial data

- We worked first on the case of 1 cell (no gap junctions), and assuming $I_{\text{ion}} = I_{\text{ion}}(v)$
- A weak solution on the time interval $[0, T]$ is defined by

$$\int_0^T \int_{\Omega_0} G_0 \nabla u_0 \cdot \phi_0 + \int_0^T \int_{\Omega_1} G_1 \nabla u_1 \cdot \phi_1$$
$$- \int_0^T \int_\Sigma \left(C_{\text{m}} (u_1 - u_0) \partial_t (\phi_1 - \phi_0) - I_{\text{ion}}(u_1 - u_0) \right) (\phi_1 - \phi_0)$$
$$= \int_\Sigma C_{\text{m}} v^0 (\phi_1 - \phi_0)_{t=0} - \int_0^T \langle g_N, \phi_0 \rangle_{\Gamma_N}$$

for all test functions ϕ_0 in $C_c^\infty([0, T[\times \overline{\Omega_0})$ and ϕ_1 in $C_c^\infty([0, T[\times \overline{\Omega_1})$, with $\phi_0 = 0$ on Γ_D.

we need only an initial data on the jump (voltage) $(u_1 - u_0)_{t=0} = v^0$ on Σ

Existence of a solution

For any $T > 0$, there exists a weak solution $u := (u_0, u_1)$ such that

$$u_0 \in L^2\left(0, T; H^1(\Omega_0)\right), \quad u_1 \in L^2\left(0, T; H^1(\Omega_0)\right)$$

such that $u_0 = g_D$ in $L^2(0, T; H^{1/2}(\Gamma_D)$.
In addition, the jump function (transmembrane voltage) is such that

$$v = u_1 - u_0 \in L^2\left(0, T; L^2(\Sigma)\right), \quad \partial_t v \in L^2\left(0, T; L^2(\Sigma)\right)$$

Sketch of the proof I

- Work after lifting the solution to homogeneous Dirichlet BC
- Semi-implicit Euler *in time* → sequence of functions $\left(u_0^k, u_1^k\right)_{k=1\dots N}$ and $(v^k)_{k=0\dots N}$
- A priori, energy estimate:

$$\max_{k=0\dots N} \|v^k\|_{L^2(\Sigma)} \leq C_T, \qquad \sum_{k=1}^{N} \Delta t \sum_{j=0,1} \|\nabla u_j\|^2_{L^2(\Omega_j)} \leq C_T^2.$$

- Work a little more to obtain estimates on time translation, on v only

$$\sum_{k=1}^{N} \Delta t \left\| \frac{v^k - v^{k-1}}{\Delta t} \right\|^2_{L^2(\Sigma)} \leq C_T$$

under additional time regularity of the boundary data g_D and g_N.

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Sketch of the proof II

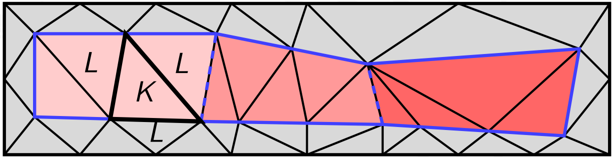
- Use a discrete Aubin-Simon thm [GL12], so that $(v^k)_{k=0\dots N}$ defines a sequence of functions compact in $L^2\left(0, T; L^2(\Sigma)\right)$
- Pass to the limit, use the strong convergence for the nonlinear reaction term $I_{\text{ion}}(v)$: weak convergence of (u_0^k, u_1^k) and strong convergence of the jump $v^k = u_1^k - u_0^k$ towards a weak solution.

Uniqueness is not proved, in general

The proof generalizes to the case of $N > 1$ cells with nonlinear gap junctions [Bec18]

The TPFA adapted to the micromodel

- $\mathcal{T} = \{K\}$, split in $\mathcal{T}_0$, $\mathcal{T}_1$
- $\mathcal{E} = \{e := K|L \text{ or } K|\cdot\}$ the itfs
- $\mathcal{E}^{\Sigma}$ the itfs on the membrane
- $\mathcal{E}_0^D$, $\mathcal{E}_0^N$, $\mathcal{E}_0^\star$, $\mathcal{E}_1^\star$



1. *Assume that we have an FV-admissible mesh*
2. Electrical field $\rightarrow$ 3D unknowns $(u_K)_{K\in\mathcal{T}}$ everywhere, solving the usual FV eqs $-\sum_{e=K|L\in\mathcal{E}_K} F_{KL} = 0$
3. Several formulation of the flux $F_{KL} \simeq \int_e \{G\nabla u \cdot n\}_e$
   - internal interfaces, external boundary ones: usual TPFA
   - membrane Γ_{k0} or GJ $\Gamma_{k\ell}$: TPFA with *an additional unknown, the jump on the interface*

Voltages $\rightarrow$ 2D interface unknowns $(v_e)_{e\in\Gamma_{k\ell}}$

for $k > 0$, $\ell > 0$ for GJ, and $k > 0$, $\ell = 0$ for membrane

Dicrete flux on the interfaces in $\Sigma_{k\ell}$ or Σ_{k0}

Introduce auxiliary unknowns $u_{K,e}$ and $u_{L,e}$, and the flux are now

$$F_{Ke} = \tau_{Ke}(u_{K,e} - u_K), \quad F_{Le} = \tau_{Le}(u_{L,e} - u_L), \qquad \text{with } \tau_{Ke} = G_K \frac{|e|}{d_{K,e}}$$

- Continuity of the flux of current: $F_{Ke} + F_{Le} = 0$
- The jump is an unknown of the equations: $u_{L,e} - u_{K,e} = v_e$
- Eliminate the auxiliary unknowns $u_{K,e}$ and $u_{L,e}$ to obtain the flux

$$F_{Ke} = \tau_e(u_L - u_K) - \tau_e v_e, \quad \text{if } v_e = u_{L,e} - u_{K_e}$$

with $\tau_e = \frac{\tau_{K,e}\tau_{L,e}}{\tau_{K,e}+\tau_{L,e}}$

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Overall numerical scheme I

- We cannot use an explicit scheme because u_0, u_1 may not be continuous in time $\rightarrow$ *semi-implicit Euler scheme*

$$- \sum_{e=K|L \in \mathcal{E}_K} F_{KL}^n = 0 \qquad \forall K \in \mathcal{T}_0 \cup \mathcal{T}_1$$

$$- F_{KL}^n = -|e| \left(C_\mathrm{m} \frac{v_e^n - v_e^{n-1}}{\Delta t} + I_\mathrm{ion}(v_e^{n-1}) \right) \qquad \forall e = K|L \in \mathcal{E}^\Sigma,\ K \in \mathcal{T}_0,\ L \in \mathcal{T}_1$$

- Where the flux are

$$F_{KL}^n = \begin{cases} \tau_e(u_L^n - u_K^n) & \text{internal itfs } e \in \mathcal{E}^\star \\ \tau_e(u_L^n - u_K^n) - \tau_e v_e^n & \text{membrane itfs } e \in \mathcal{E}^\Sigma \text{ s.t. } K \in \mathcal{T}_0,\ L \in \mathcal{T}_1 \\ \tau_e(g_{D,e}^n - u_K^n) & \text{Dirichlet boundary } e \in \mathcal{E}^D \\ g_{N,e}^n & \text{Dirichlet boundary } e \in \mathcal{E}^N \end{cases}$$

Overall numerical scheme II

- In matrix form with $\mathrm{U}^n = (u_K^n)_{K\in\mathcal{T}_0\cup\mathcal{T}_1}$ and $\mathrm{V}^n = (v_e^n)_{e\in\Sigma}$

$$\begin{pmatrix} A & B \\ B^T & C \end{pmatrix} \begin{pmatrix} \mathrm{U}^n \\ \mathrm{V}^n \end{pmatrix} = \begin{pmatrix} G^n \\ -|e| \left(C_\mathrm{m} \frac{\mathrm{V}^n - \mathrm{V}^{n-1}}{\Delta t} + I_\mathrm{ion}(\mathrm{V}^{n-1}) \right) \end{pmatrix}$$

- A: square matrix $\#\mathcal{T} \times \#\mathcal{T}$, usual TPFA matrix, NNZ $= \#\mathcal{E} + \#\mathcal{T}$
- B: matrix $\#\mathcal{T} \times \#\mathcal{E}^\Sigma$, with non zeros only for K and e such that $e \in \mathcal{E}_K$, NNZ $= 2\#\mathcal{E}^\Sigma$
- C: diagonal matrix $\#\mathcal{E}^\Sigma \times \#\mathcal{E}^\Sigma$, with entries τ_e
- Alternative Stecklov-Poincaré / Schur complement formulation

$$\left(C - B^T A^{-1} B \right) \mathrm{V}^n = -|e| \left(C_\mathrm{m} \frac{\mathrm{V}^n - \mathrm{V}^{n-1}}{\Delta t} + I_\mathrm{ion}(\mathrm{V}^{n-1}) \right) - B^T A^{-1} G^n$$

The discrete system is SDP

Scalar product of the equations with a discrete test function $(\phi_K)_{K\in\mathcal{T}_0\cup\mathcal{T}_1}$ and $(\psi_e)_{e\in\mathcal{E}^\Sigma}$

$$\sum_{k=0,1}\sum_{e\in\mathcal{E}_k^\star}\tau_e(u_L^n-u_K^n)(\phi_L-\phi_K)+\sum_{e\in\mathcal{E}_0^D}\tau_e u_K^n\phi_K$$

$$+\sum_{e\in\mathcal{E}^\Sigma}\tau_e\left((u_L^n-u_K^n)-v_e^n\right)(\phi_L-\phi_K)-\sum_{e\in\mathcal{E}^\Sigma}\tau_e\left((u_L^n-u_K^n)-v_e^n\right)\psi_e$$

$$+\frac{C_\mathrm{m}}{\Delta t}\sum_{e\in\mathcal{E}^\Sigma}v_e^n\psi_e|e|=\frac{C_\mathrm{m}}{\Delta t}\sum_{e\in\mathcal{E}^\Sigma}v_e^{n-1}\psi_e|e|-\sum_{e\in\mathcal{E}^\Sigma}I_\mathrm{ion}(v_e^{n-1})\psi_e|e|+\sum_{e\in\mathcal{E}_0^D}\tau_e g_{D,e}^n\phi_K+\sum_{e\in\mathcal{E}_0^N}g_{N,e}^n\phi_K$$

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$$\sum_{k=0,1}\sum_{e\in\mathcal{E}_k^\star}\tau_e(u_L^n-u_K^n)(\phi_L-\phi_K)+\sum_{e\in\mathcal{E}_0^D}\tau_e u_K^n\phi_K$$

$$+\sum_{e\in\mathcal{E}^\Sigma}\tau_e\left((u_L^n-u_K^n)-v_e^n\right)\left((\phi_L-\phi_K)-\psi_e\right)$$

$$+\frac{C_\mathrm{m}}{\Delta t}\sum_{e\in\mathcal{E}^\Sigma}v_e^n\psi_e|e|=\frac{C_\mathrm{m}}{\Delta t}\sum_{e\in\mathcal{E}^\Sigma}v_e^{n-1}\psi_e|e|-\sum_{e\in\mathcal{E}^\Sigma}I_\mathrm{ion}(v_e^{n-1})\psi_e|e|+\sum_{e\in\mathcal{E}_0^D}\tau_e g_{D,e}^n\phi_K+\sum_{e\in\mathcal{E}_0^N}g_{N,e}^n\phi_K$$

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Scalar product of the equations with a discrete test function $(\phi_K)_{K\in\mathcal{T}_0\cup\mathcal{T}_1}$ and $(\psi_e)_{e\in\mathcal{E}^\Sigma}$

$$\sum_{k=0,1}\sum_{e\in\mathcal{E}_k^\star}\tau_e(u_L^n-u_K^n)(\phi_L-\phi_K)+\sum_{e\in\mathcal{E}_0^D}\tau_e u_K^n\phi_K$$

$$+\sum_{e\in\mathcal{E}^\Sigma}\tau_e\left((u_L^n-u_K^n)-v_e^n\right)\left((\phi_L-\phi_K)-\psi_e\right)$$

$$+\frac{C_m}{\Delta t}\sum_{e\in\mathcal{E}^\Sigma}v_e^n\psi_e|e|=\frac{C_m}{\Delta t}\sum_{e\in\mathcal{E}^\Sigma}v_e^{n-1}\psi_e|e|-\sum_{e\in\mathcal{E}^\Sigma}I_{\text{ion}}(v_e^{n-1})\psi_e|e|+\sum_{e\in\mathcal{E}_0^D}\tau_e g_{D,e}^n\phi_K+\sum_{e\in\mathcal{E}_0^N}g_{N,e}^n\phi_K$$

The linear system is symetric and positive definite,

and we define $((u,v),(\phi,\psi))_{1,\mathcal{T}}$ and $|(u,v)|_{1,\mathcal{T}}$
the discrete semi norm and inner product with the terms in red

Discrete equation of the error

- Integrate the exact solution on (t^{n-1}, t^n), and over K, and e:

$$-\sum_{e=K|L\in\mathcal{E}_K} \overline{F}_{KL}^n = 0$$

$$-\overline{F}_{KL}^n = -|e|\left(C_\mathrm{m}\frac{\overline{v}_e^n - \overline{v}_e^{n-1}}{\Delta t} + \overline{I_{\mathrm{ion}}}_e^n\right)$$

where $\overline{F}_{KL}^n$ are the exact flux, $\overline{v}_e^n = \frac{1}{|e|}\int_e v(t^n, x)dx$, and $\overline{I_{\mathrm{ion}}}_e^n = \frac{1}{\Delta t}\frac{1}{|e|}\int_{t^{n-1}}^{t^n} I_{\mathrm{ion}}(v)$.

- Hence the equation on the error $\epsilon_K^n = \overline{u}_K^n - u_K^n$, $\eta_K^n = \overline{v}_e^n - v_e^n$ is

$$-\sum_{e=K|L\in\mathcal{E}_K} F_{KL}(\epsilon_K^n, \eta_e^n) = -\sum_{e=K|L\in\mathcal{E}_K} \delta F_{KL}^n$$

$$-F_{KL}(\epsilon_K^n, \eta_e^n) = -|e|\left(C_\mathrm{m}\frac{\eta_e^n - \eta_e^{n-1}}{\Delta t} + \delta {I_{\mathrm{ion}}}_e^n + I_{\mathrm{ion}}(\overline{v}_e^{n-1}) - I_{\mathrm{ion}}(v_e^{n-1})\right) - \delta F_{KL}^n$$

Energy estimate on the error

$$|(\epsilon^n, \eta^n)|^2_{1,\mathcal{T}} + \frac{C_\mathrm{m}}{\Delta t}\|\eta^n\|^2_{0,\Sigma} = \frac{C_\mathrm{m}}{\Delta t}(\eta^{n-1}, \eta^n)_{0,\Sigma} - (I_\mathrm{ion}(\overline{v}^n) - I_\mathrm{ion}(v^n), \eta^n)_{0,\Sigma}$$
$$- (\delta I_\mathrm{ion}{}^n, \eta^n)_{0,\Sigma} + \left(\left(\frac{\delta F^n}{\tau}\right), (\epsilon^n, \eta^n)\right)_{1,T}$$

- equation of the error – consistency errors on the flux and reaction term
- After a series of Young inequalities, *assuming that I_{ion} is Lipschitz*

$$\Delta t\,|(\epsilon^n, \eta^n)|^2_{1,\mathcal{T}} + C_\mathrm{m}\|\eta^n\|^2_{0,\Sigma} \le C_\mathrm{m}\left(1 + \frac{C_\mathrm{f}}{C_\mathrm{m}}\Delta t\right)^2 \|\eta^{n-1}\|^2_{0,\Sigma}$$
$$+ 2\frac{\Delta t}{C_\mathrm{m}}\|\delta I_\mathrm{ion}{}^n\|_{0,\Sigma}\|\eta^n\|_{0,\Sigma} + \Delta t\left|\frac{\delta F^n}{\tau}\right|^2_{1,T}$$

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Error estimate

- at last (1 more Young inequality with a well choosen coefficient)

$$\left(1+\frac{C_\mathrm{f}}{C_\mathrm{m}}\Delta t\right)\frac{\Delta t}{C_\mathrm{m}}\left|(\epsilon^n,\eta^n)\right|^2_{1,\mathcal{T}}+\|\eta^n\|^2_{0,\Sigma}\leq\left(1+\frac{C_\mathrm{f}}{C_\mathrm{m}}\Delta t\right)^3\|\eta^{n-1}\|^2_{0,\Sigma}$$
$$+\frac{\Delta t}{C_\mathrm{f}C_\mathrm{m}^2}\left(1+\frac{C_\mathrm{f}}{C_\mathrm{m}}\Delta t\right)^2\|\delta {I_\mathrm{ion}}^n\|^2_{0,\Sigma}+\Delta t\left(1+\frac{C_\mathrm{f}}{C_\mathrm{m}}\Delta t\right)\left|\frac{\delta F^n}{\tau}\right|^2_{1,T}$$

Convergence rate

$$\forall n=0\dots N,\quad \|\eta^n\|_{0,\Sigma}:=\left(\sum_{e\in\mathcal{E}^\Sigma}|\overline{v}^n_e-v^n_e|^2|e|\right)^{1/2}\leq C_1\exp(C_2T)\,(h+\Delta t)$$

$$\left(\sum_{k=1}^{n}\Delta t\left|(\epsilon^n,\eta^n)\right|^2_{1,\mathcal{T}}\right)^{1/2}\leq C_1\exp(C_2T)\,(h+\Delta t)$$

Expected Consistency properties

- For the diffusion terms

$$\left| \frac{1}{|e|} \frac{1}{\Delta t} \int_{n-1}^{n} \int_{e} \{G \nabla u \cdot n\}_{K,e} \; - \frac{1}{|e|} F_{KL}(\overline{u}^n, \overline{v}^n) \right| \leq Ch \quad \text{on all } e \in \mathcal{E}$$

We can choose the projection $\overline{u}_K^n$ to adapt to the regularity of u ($H^1(\Omega_0)$ and $H^1(\Omega_1)$ in the existence thm).

- For the reaction terms, we have that

$$\sum_{k=1}^{n} \Delta t \sum_{e \in \mathcal{E}^\Sigma} \left| \overline{I_{\text{ion}}}_e^n - I_{\text{ion}}(\overline{v}_e^{n-1}) \right|^2 |e| \leq C(h + \Delta t)^2$$

needs L^2 regularity on $\partial_t v$ (OK), and on $\partial_x v$ (?)

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Numerical analysis TPFA

- Complete the consistency analysis
- Convergence can be proved w/o error estimate under the minimal conditions of the existence thm.
- Error estimate needs more regularity than we actually obtained on v and (u_j)
- Error estimate on the error on $\partial_t v$?
- Extend the Poincaré inequality ?
- Order of convergence for v in practice ?
- Generalize to
  - complete ionic models (i.e. with ODEs)
  - $N > 1$ cells with nonlinear gap junctions
  - ionic models with polynomial growth instead of Lipschitz

Implementations

- Necessarily implicit because u_0 and u_1 solve Laplace equations

$$\begin{pmatrix} A & B \\ B^T & C \end{pmatrix} \begin{pmatrix} \mathrm{U}^n \\ \mathrm{V}^n \end{pmatrix} = \begin{pmatrix} G^n \\ -|e| \left(C_\mathrm{m} \frac{\mathrm{V}^n - \mathrm{V}^{n-1}}{\Delta t} + I_\mathrm{ion}(\mathrm{V}^{n-1}) \right) \end{pmatrix}$$

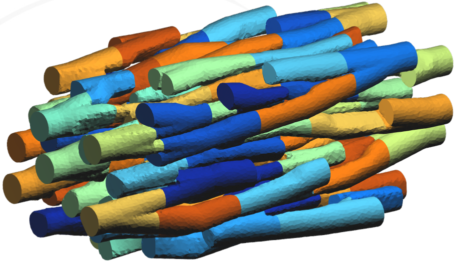
  Very large, sparse linear system, size $\#\mathcal{T} + \#\mathcal{E}^\Sigma$, at each time-step
- Or use the Stecklov-Poincaré / Schur complement formulation $\rightarrow$ parabolic PDE on the membranes

$$\left(C - B^T A^{-1} B \right) \mathrm{V}^n = -|e| \left(C_\mathrm{m} \frac{\mathrm{V}^n - \mathrm{V}^{n-1}}{\Delta t} + I_\mathrm{ion}(\mathrm{V}^{n-1}) \right) - B^T A^{-1} G^n$$

  - Compute $M := C - B^T A^{-1} B$ (offline) $\rightarrow \#\mathcal{E}^\Sigma$ sparse linear systems of size $\#\mathcal{T}$
  - depends only on the mesh and conductivity coefficients
  - use explicit time-stepping: matrix-product vector, with a full matrix of size $\#\mathcal{E}^\Sigma$
- How to parallelize ?

More flexible FV schemes

- The mesh will never be FV-admissible, because of the complexity of the geometry



- DDFV: 2 unknowns on the interface Σ, interested ?
- HOFV: can be generalized to discontinuous coefficient $\rightarrow$ handle the jump
- Other FV method ?

Thanks for your attention!

Other references I

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