Mathematical and Numerical Models for Anisotropic and Heterogeneous Ventricular Cardiac Tissue

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Outline

- Mathematical models of cardiac bioelectrical activity :
  - **Cellular model and membrane models**
  - **Homogenized model: Bidomain system** (in collaboration with M. Pennacchio and G. Savarè, Univ. of Pavia)
  - **Approximated models: Eikonal and Relaxed Monodomain**
- Numerical models :
  - **Parallel solver** on uniform meshes using PETSc library
  - **Adaptive solvers**: adaptivity in space and time with KARDOS library
- 3D Simulations of Excitation and Repolarization :
  - in rotational anisotropic ventricular wall blocks with homogeneous, transmural heteregeneous and ischemic cellular properties
  - reentry dynamics

MACROSCOPIC CARDIAC STRUCTURE

FIBER STRUCTURE WITH JUNCTIONS:
longitudinal and transversal

VENTRICULAR FIBER ARCHITECTURE

INTRAMURAL FIBERS ROTATION
on toroidal layers nested into the ventricular wall

— — — —

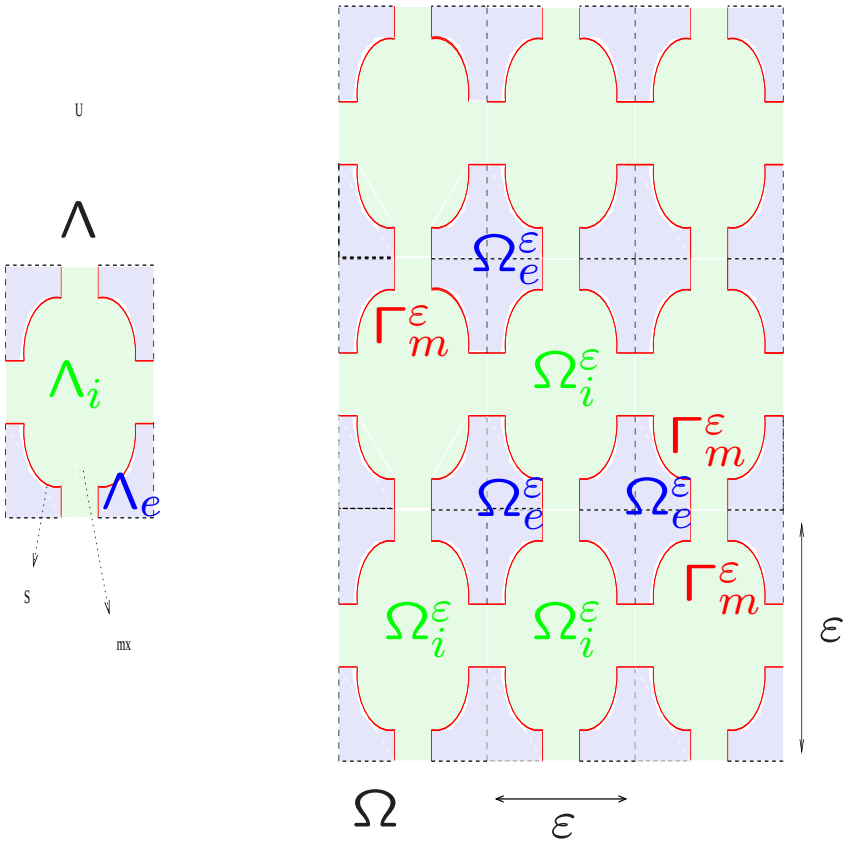
LAMINAR ORGANIZATION OF MYOCARDIUM
muscle sheets separated by clefts running into the wall radially from epi- to endo

Cardiac bisyncytium:

Homogenization ideal periodic geometry in a bidimensional section of the simplified 3–D periodic network of interconnected cells.

Collection of cells, connected end-to-end and side-to-side by junctions surrounded by the extracellular fluid Unit cell in the microscopic variable:

$$\xi = x/\varepsilon.$$



Dimensionless Model at a cellular level

microscopic space scale of the *cells* : $l = \begin{cases} \text{cell length} & \sim 100\mu m \\ \text{cell diameter} & \sim 20\mu \end{cases}$

macroscopic space scale of the *tissue* $L \approx 0.5 \dot{-} 1mm \quad \varepsilon \approx \dfrac{l}{L} \approx 10^{-2} \dot{-} 10^{-1}$

$$\begin{cases} -\operatorname{div} \sigma_i^\varepsilon(x) \nabla u_i{}^\varepsilon = 0 & \text{in } \Omega_i \\ -\operatorname{div} \sigma_e^\varepsilon(x) \nabla u_e{}^\varepsilon = 0 & \text{in } \Omega_e \end{cases}$$

$$J_m{}^\varepsilon = \begin{cases} -\sigma_i^\varepsilon(x), \boldsymbol{n}_m \cdot \nabla u_i{}^\varepsilon \\ -\sigma_e^\varepsilon(x), \boldsymbol{n}_m \cdot \nabla u_e{}^\varepsilon \end{cases}$$

$$\begin{aligned} \varepsilon \; [\, C_m \partial_t v^\varepsilon + I_{ion}(v^\varepsilon, w^\varepsilon, c^\varepsilon) \,] &= J_m{}^\varepsilon \\ \partial_t w^\varepsilon - R(v^\varepsilon, w^\varepsilon) &= 0 \quad \text{on } \Gamma_m^\varepsilon \\ \partial_t c^\varepsilon - S(v^\varepsilon, w^\varepsilon, c^\varepsilon) &= 0 \end{aligned}$$

where $\sigma_{i,e}^\varepsilon(x) = \sigma_{i,e}(x, \frac{x}{\varepsilon})$

+ Boundary conditions of Dirichlet or Neumann type on $\partial\Omega$
+ Initial Cauchy conditions on $(v^\varepsilon, w^\varepsilon, c^\varepsilon)$.

The Limit Problem on $\Omega := {\Omega_i}^{\varepsilon} \cup {\Omega_e}^{\varepsilon} \cup {\Gamma_m}^{\varepsilon}$: **Bidomain Model**

$$\operatorname{div} j_e = -\operatorname{div} j_i = J_m = c_m \partial_t v + j_{ion}(v,w,c) \begin{cases} j_i = -M_i \nabla u_i \\ j_e = -M_e \nabla u_e \end{cases} \quad \text{in } \Omega,$$

where $v := u_i - u_e, \quad c_m = \rho\, C_m, \quad j_{ion} = \rho\, I_{ion}$

$$\begin{aligned} c_m\,(\partial_t u_i - \partial_t u_e) - \operatorname{div}(M_i \nabla u_i) + j_{ion}(v,w,c) &= I^i_{app} && \text{in } \Omega \times (0,T) \\ -c_m\,(\partial_t u_i - \partial_t u_e) - \operatorname{div}(M_e \nabla u_e) - j_{ion}(v,w,c) &= I^e_{app} && \text{in } \Omega \times (0,T) \\ \partial_t w - R(v,w) = 0, \quad \partial_t c - S(v,w,c) &= 0 && \text{in } \Omega \times (0,T) \end{aligned}$$

+ Boundary conditions of Dirichlet or Neumann type on $\partial\Omega$ related to (u_i, u_e)
+ Initial Cauchy conditions on (v,w,c).

Here the nonlinear terms I_{ion} , R and S have the same form as before.

$\rho := S_m/\Lambda$ membrane surface area in the unit cell

$\rho_{i,e} := \Lambda_{i,e}/\Lambda$ intra or extracellular volume in the unit cell

$M_i, M_e :=$ homogenized conductivity tensors

$$-\operatorname{div}(M_i \nabla u_i) - \operatorname{div}(M_e \nabla u_e) = I^i_{app} + I^e_{app}$$

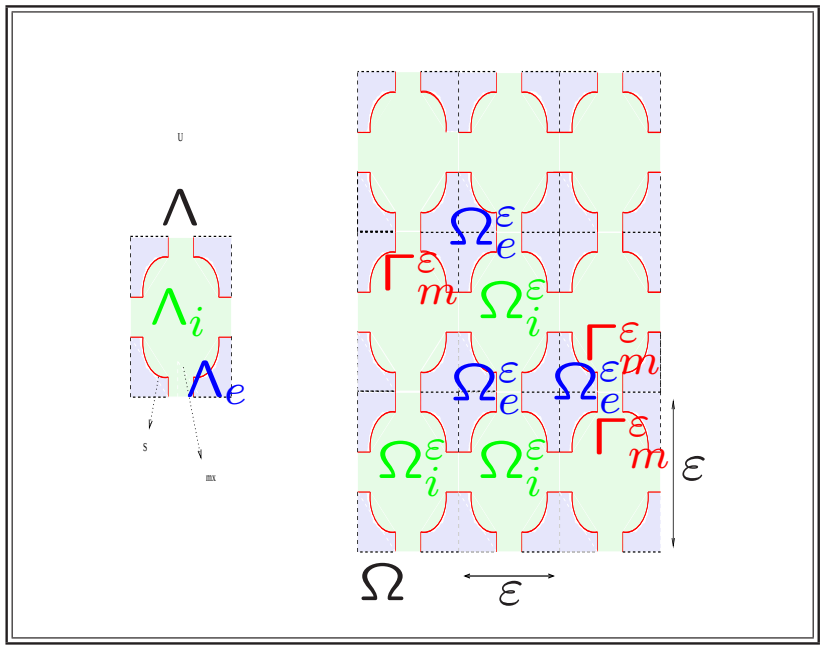
Homogenization formula for M_i, M_e

If Λ_i, Λ_e is the decomposition of the unit reference cell Λ into the intra- and extra- cellular region, then (the quadratic forms associated to) $M_i(x), M_e(x)$ can be calculated by solving the cellular problems for every $y \in \mathbb{R}^3$:

$$M_{i,e}(x)\, y \cdot y := $$

$$= \min \left\{ \frac{1}{|\Lambda|} \int_{\Lambda_{i,e}} \sigma_{i,e}(x,\xi)\Big(\nabla u(\xi) + y\Big) \cdot \Big(\nabla u(\xi) + y\Big)\, d\xi : \right.$$

$$\left. u \in H^1_{loc}(\mathbb{R}^d),\ u\ \Lambda\text{-periodic} \right\}$$



$M_i(x), M_e(x)$ are]
symmetric and positive definite matrices

Homogenization process : Pennacchio- Savaré - C. F Multiscale modeling for the electrical activity of the heart. SIAM J. Math. Anal. 2005.

Convergence result stated for Instantaneous Reaction without recovery

$\boxed{\langle \mathscr{F}^\varepsilon(U^\varepsilon), \hat{U}\rangle} := \int_{\Gamma_m^\varepsilon} \varepsilon\ I_{ion}(v^\varepsilon)\hat{v}d\gamma$, and G is a primitive of $I_{ion}(v)$.

Φ^ε , Φ : ***Lyapunov functionals*** for micro and macro evolution systems:

$$\Phi^\varepsilon(U) := \frac{1}{2}\int_{\Omega_i{}^\varepsilon} \sigma_i{}^\varepsilon |\nabla u_i|^2\,dx + \frac{1}{2}\int_{\Omega_e{}^\varepsilon} \sigma_e{}^\varepsilon |\nabla u_e|^2\,dx + \varepsilon\int_{\Gamma_m^\varepsilon} G(v)$$

$$\Phi(U) := \frac{1}{2}\int_\Omega M_i(x)|\nabla u_i|^2\,dx + \frac{1}{2}\int_\Omega M_e(x)|\nabla u_e|^2\,dx + \int_\Omega G(v)$$

If (suitable extensions of) $u_{i0}^\varepsilon, u_{e0}^\varepsilon$ converge to u_{i0}, u_{e0} in $L^2_{loc}(\Omega)$ and

$$\lim_{\varepsilon\downarrow 0} \Phi^\varepsilon(u_{i0}^\varepsilon, u_{e0}^\varepsilon) = \Phi(u_{i0}, u_{e0})$$

Cellular Model $\boldsymbol{u}^\varepsilon = (u_i^\varepsilon, u_e^\varepsilon)$: $\int_{\Omega_0\cap\Omega^\varepsilon} u_e^\varepsilon dx = 0$, with $\Omega_0 \subset\subset \Omega$

Averaged Model $\boldsymbol{u} = (u_i, u_e)$: $\int_{\Omega_0\cap\Omega} u_e dx = 0$

Then there exist extensions $(\mathscr{T}^\varepsilon{}_i u_i{}^\varepsilon, \mathscr{T}^\varepsilon{}_e u_e{}^\varepsilon)$ in Ω which converge in

$L^2(0,T; H^1_{loc}(\Omega))$ **to the unique solution** $(u_i, u_e) \in \mathbb{V}$

of the macroscopic averaged problem P**.**

Variational approach for the convergence of evolution problems

A general strategy to pass to the limit

Evolution Problem

$P^\varepsilon \quad : \quad U^\varepsilon$

$\longrightarrow$

Stationary problem

$U_\tau^{\varepsilon,n+1}$:

$\min_{\boldsymbol{W}} \frac{1}{2\tau} b^\varepsilon(\boldsymbol{W} - U_\tau^{\varepsilon,n}) + \Phi^\varepsilon(\boldsymbol{W})$

$\varepsilon \downarrow 0$

Limit of the Evolution Problem

$P \quad : \quad U$

$0 \leftarrow \tau$

Limit of the stationary problem

U_τ^{n+1} :

$\min_{\boldsymbol{W}} \frac{1}{2\tau} b(\boldsymbol{W} - U_\tau^{n}) + \Phi(\boldsymbol{W})$

APPROXIMATE MODELS

Eikonal approach: Travelling wave
Motion of the excitation front

$$\mathcal{B}\,\partial_t \begin{pmatrix} u_i \\ u_e \end{pmatrix} + \eta\mathcal{A}\begin{pmatrix} u_i \\ u_e \end{pmatrix} + \frac{1}{\eta}\mathcal{F} = 0$$

fast reaction and slow diffusion

$$\eta \approx 10^{-3} \div 10^{-2}$$

Normal wave front velocity

$$\theta_\eta(\boldsymbol{\nu}) = \Phi(\mathrm{x},\boldsymbol{\nu})(c - \eta\ \mathrm{div}\ \Phi_{\boldsymbol{\xi}}(\mathrm{x},\boldsymbol{\nu}))$$

$$\Phi(\mathrm{x},\boldsymbol{\xi}) = \sqrt{(q_i(\mathrm{x},\boldsymbol{\xi})^{-1} + q_e(\mathrm{x},\boldsymbol{\xi})^{-1})^{-1}}$$

$$q_{i,e}(\mathrm{x},\boldsymbol{\xi}) = \boldsymbol{\xi}^T M_{i,e}(\mathrm{x})\boldsymbol{\xi}$$

Monodomain Approach
Reaction-Diffusion in v

$$c_m\,\partial_t v + \mathcal{D}\,v + j_{ion} = \mathcal{S}_{tot}$$

$$(\mathcal{A}_i + \mathcal{A}_e)u_e = -\mathcal{A}_i v$$

$$\mathcal{D} = -\mathrm{div} M_i(M_i + M_e)^{-1}M_e\nabla$$

$$\mathcal{S}_{tot} = \mathrm{div}[M_i(M_i + M_e)^{-1}I_{tot}]$$

$$I_{tot} = -M_i\nabla u_i - M_e\nabla u_e$$

$$\mathrm{div}\, I_{tot} = 0$$

$$\mathcal{B} = c_m\begin{bmatrix} \mathrm{I} & -\mathrm{I} \\ -\mathrm{I} & \mathrm{I} \end{bmatrix} \quad \mathcal{A} = \begin{bmatrix} \mathrm{A}_i & 0 \\ 0 & \mathrm{A}_e \end{bmatrix} \quad \begin{matrix} \mathcal{A}_{i,e} = -\,\mathrm{div}\, M_{i,e}\nabla \\ j_{ion} = \rho I_{ion}(v.w, c) \end{matrix} \quad \mathcal{F} = \begin{bmatrix} j_{ion} \\ -j_{ion} \end{bmatrix}$$

Relaxed System

(v, u_e)

$$c_m \partial_t v + \text{div}\, \mathcal{T}(\mathbf{x}, \nabla v) + I_{ion}(v, ..) \approx 0$$

$$\mathcal{T}(\mathbf{x}, \boldsymbol{\xi}) = -\Phi(\mathbf{x}, \boldsymbol{\xi})\, \Phi_{\boldsymbol{\xi}}(\mathbf{x}, \boldsymbol{\xi}) = -Q(\mathbf{x}, \boldsymbol{\xi})\boldsymbol{\xi}$$

non linear diffusion

$$(\mathcal{A}_i + \mathcal{A}_e) u_e = -\mathcal{A}_i v$$

Monodomain System

(v, u_e)

$$c_m \partial_t v - \text{div}\, \mathcal{D}(\mathbf{x}) \nabla v + I_{ion}(v, ..) \approx 0$$

$$\mathcal{D}(\mathbf{x}) = M_i(\mathbf{x})\, (M_i(\mathbf{x}) + M_e(\mathbf{x}))^{-1} M_e(\mathbf{x})$$

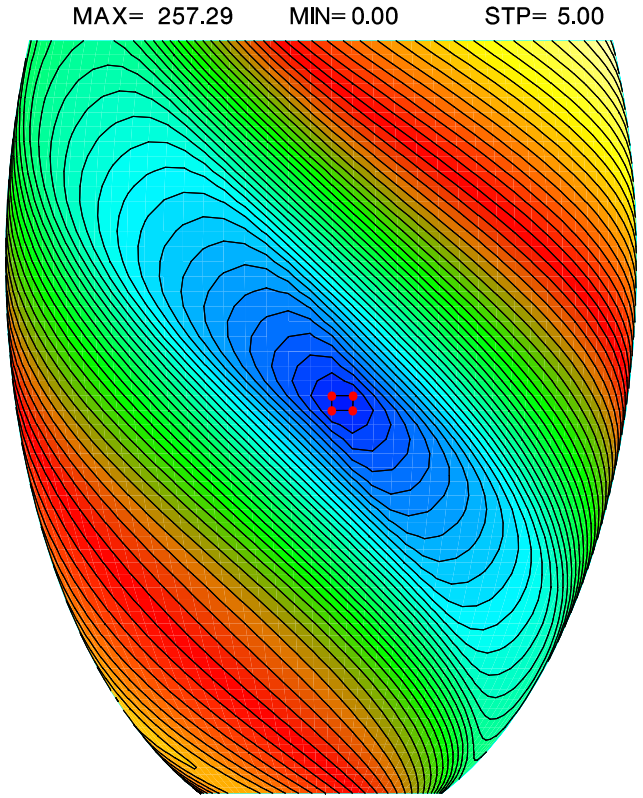
linear diffusion

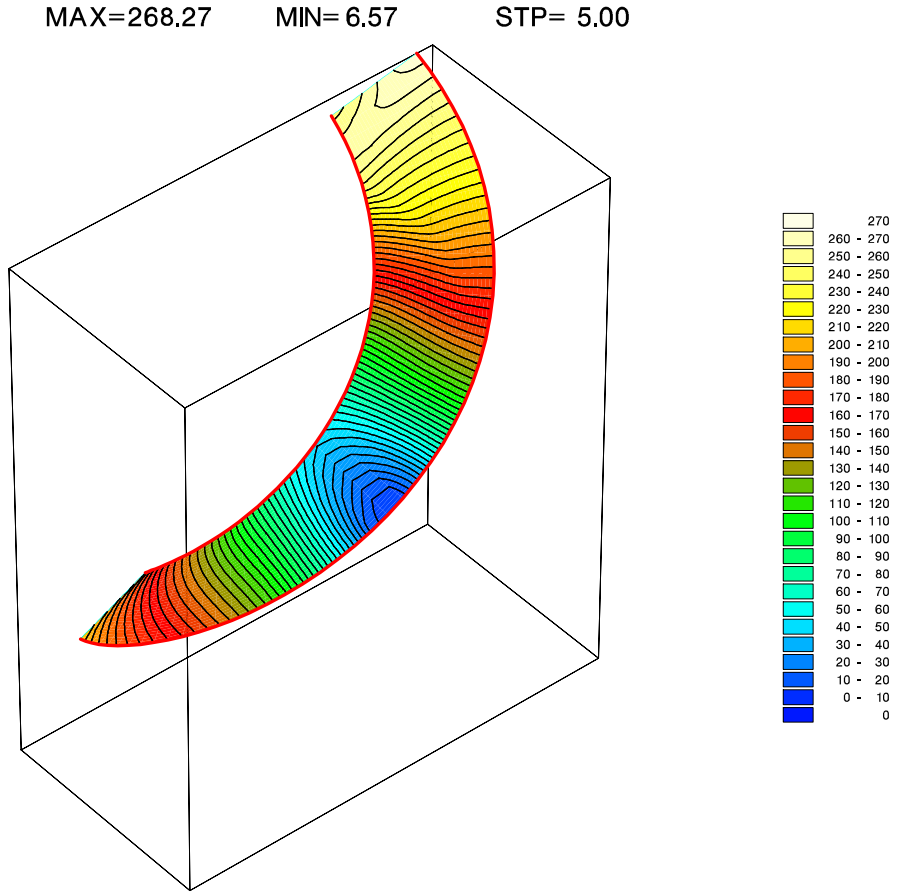
$$(\mathcal{A}_i + \mathcal{A}_e) u_e = -\mathcal{A}_i v$$

$$Q(\mathbf{x}, \boldsymbol{\xi}) = \left(\frac{\boldsymbol{\xi}^T M_i \boldsymbol{\xi})}{\boldsymbol{\xi}^T M \boldsymbol{\xi})}\right)^2 M_e(\mathbf{x}) + \left(\frac{\boldsymbol{\xi}^T M_e \boldsymbol{\xi})}{(\boldsymbol{\xi}^T M \boldsymbol{\xi})}\right)^2 M_i(\mathbf{x})$$

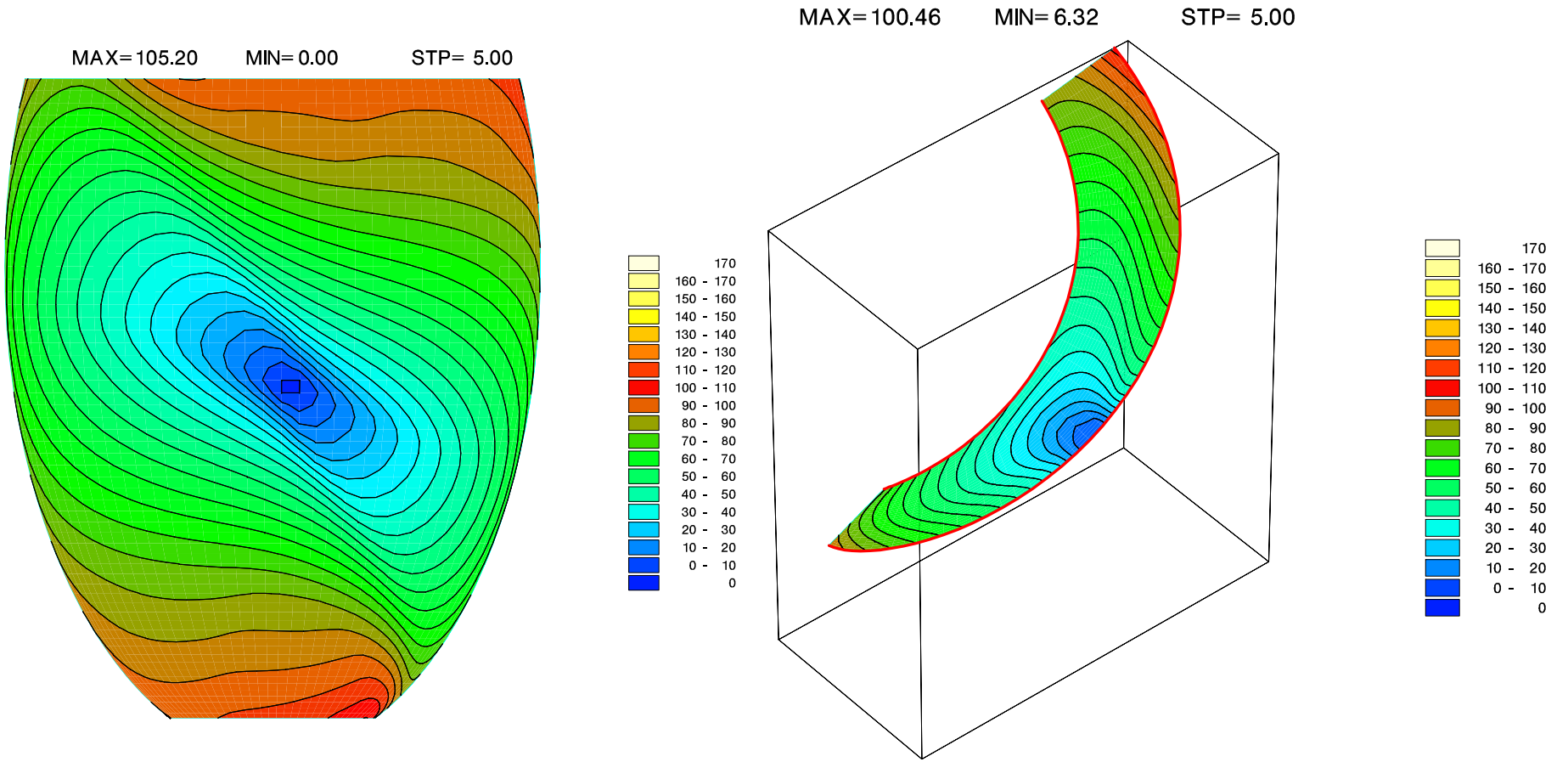
$$M(\mathbf{x}) = M_i(\mathbf{x}) + M_e(\mathbf{x})$$

Eikonal model: orthotropic anisotropy with parallel fiber

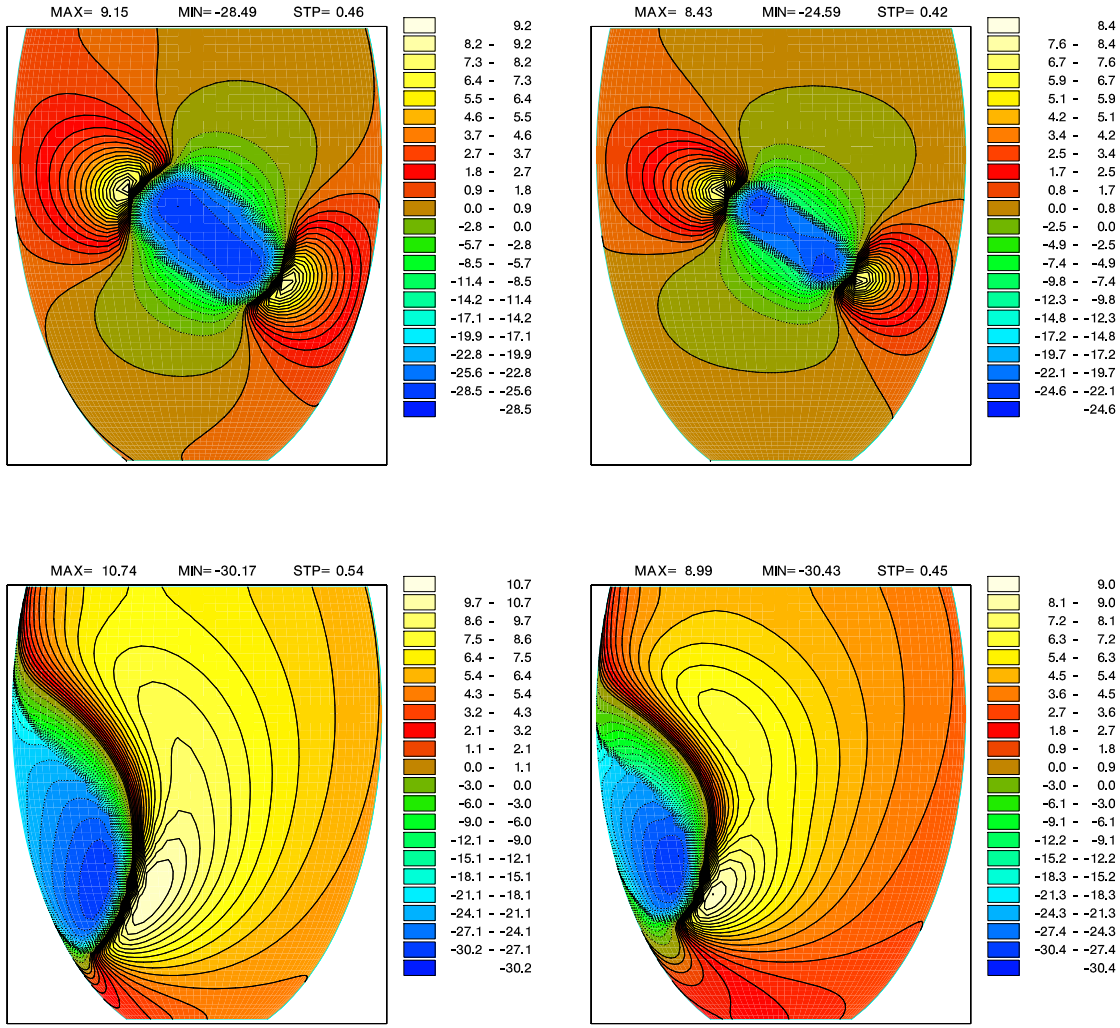




Eikonal model: orth. anisotropy with intramural fiber rotation

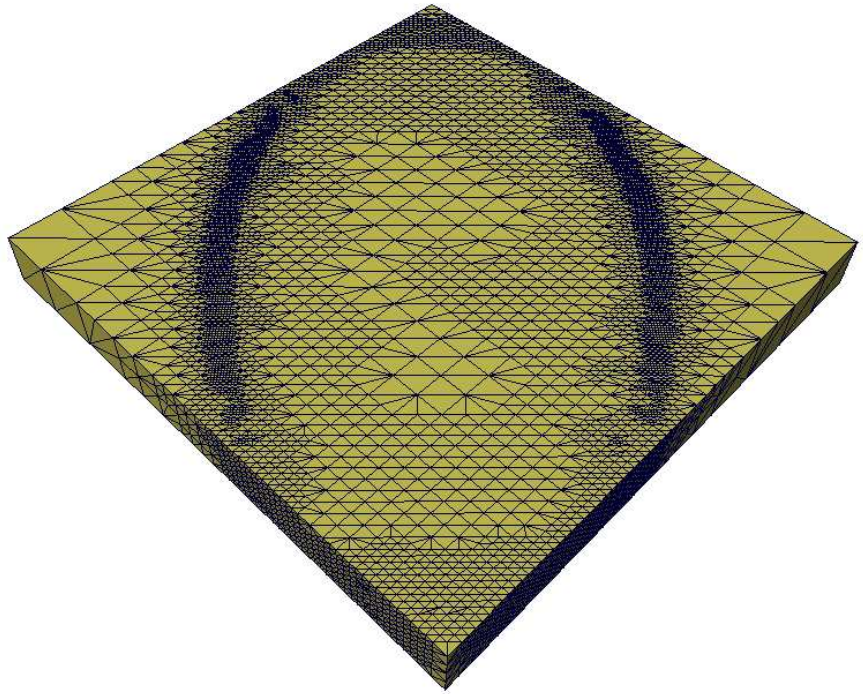


extra-cellular potential



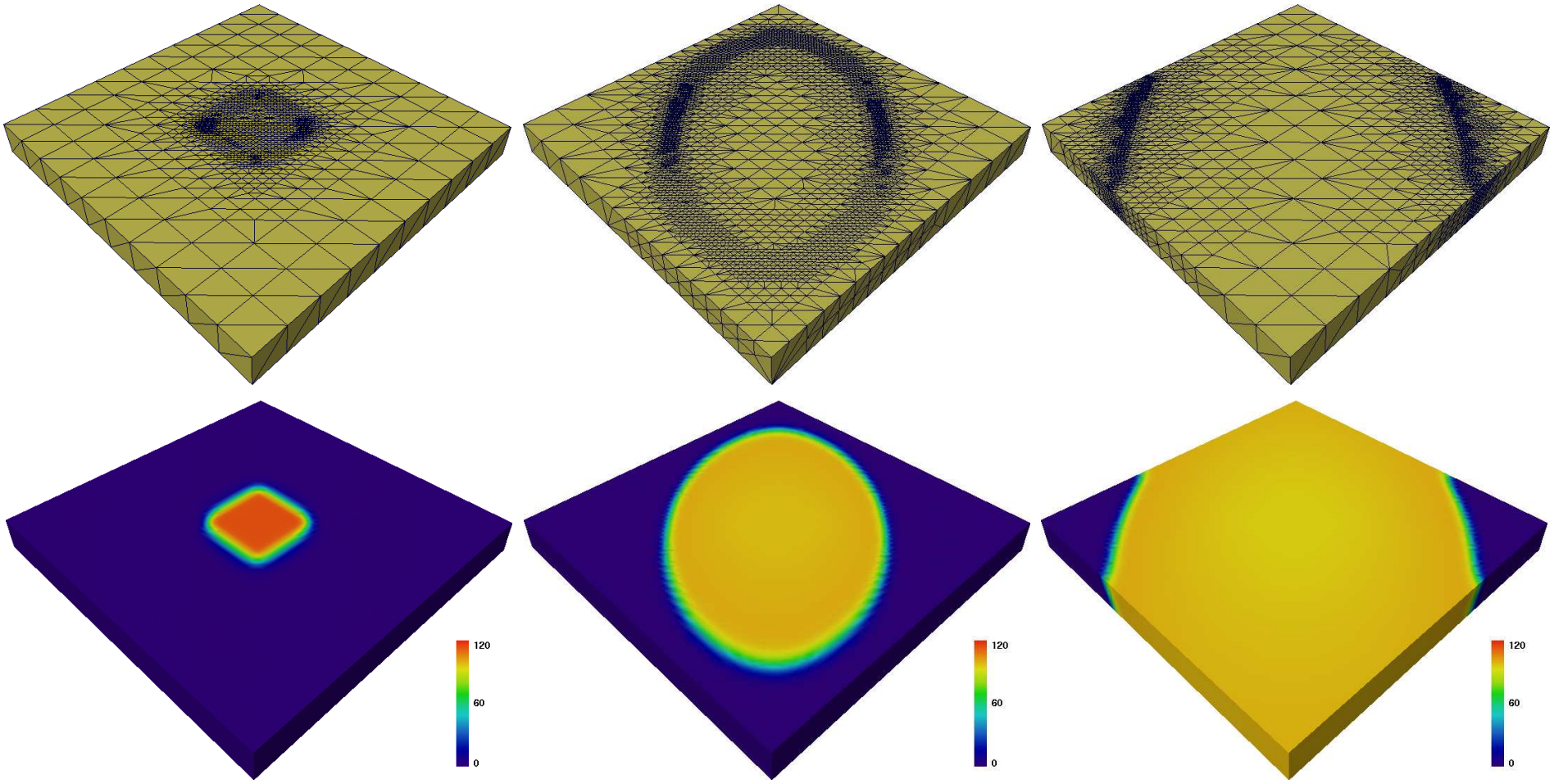
A) Adaptive solver in space and time with KARDOS library

- Idea: refine mesh only near propagating fronts (excitation and repolarization) and refine time step size only during excitation and repo phases
- KARDOS code from ZIB
  start with simplest case:
  - on a small cartesian slab
  - with constant fiber direction
  Monodomain - FHN or LR1
  Bidomain - FHN or LR1



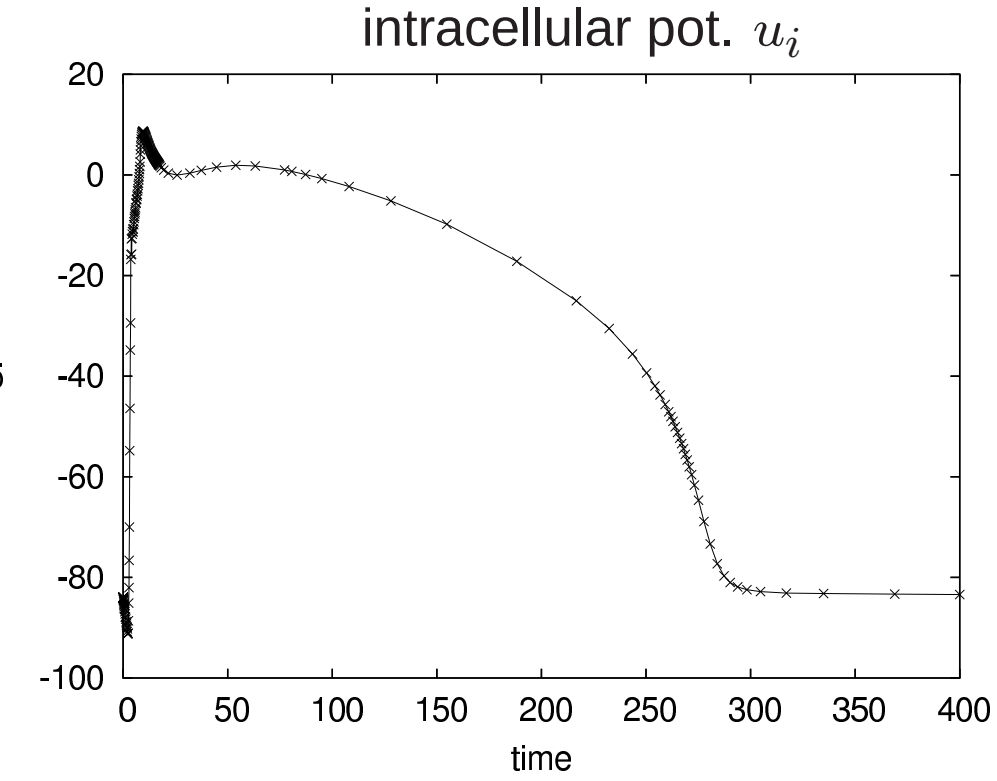
Tech rep.: P. Colli Franzone, P. Deuflhard, B. Erdmann, J. Lang, L.F. Pavarino, *Adaptivity in Space and Time for reaction-Diffusion Systems in Electrocardiology*, ZR-05-30, Konrad-Zuse-Zentrum Berlin, 2005.

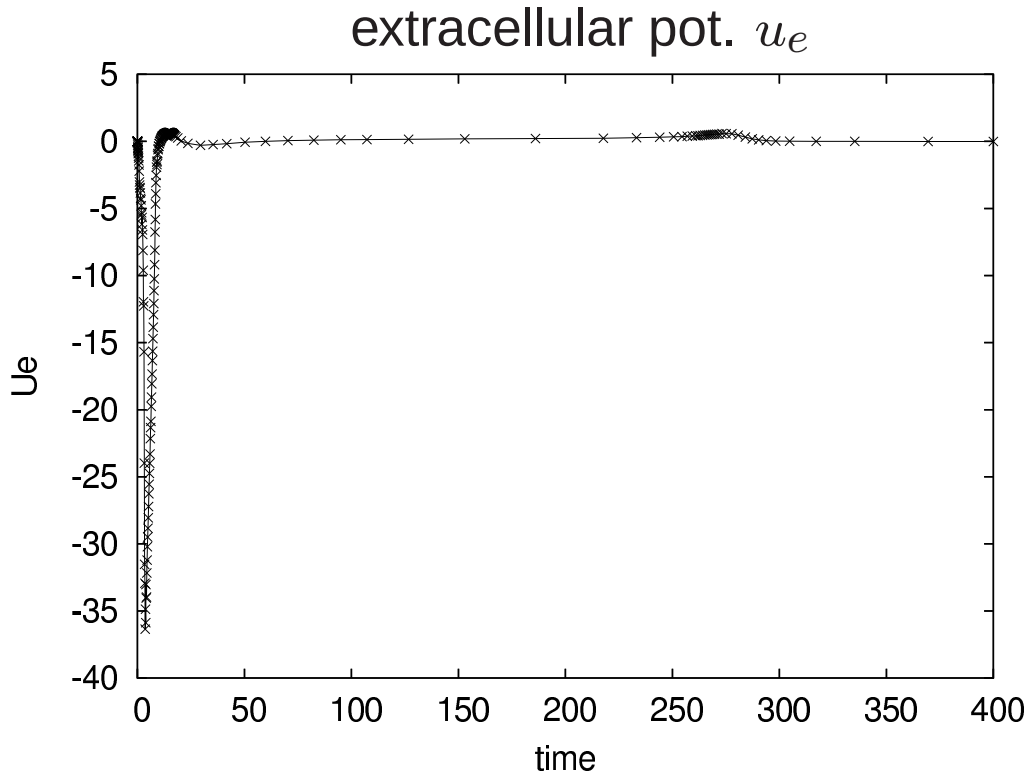
Central stimulus, excitation-recovery



- mesh (top) and potential v (bottom) at times 1, 7, 13 msec.
- mesh size: $242 \longleftrightarrow \sim 10^5$ nodes
- time step size: $10^{-4} \longleftrightarrow 25$ msec

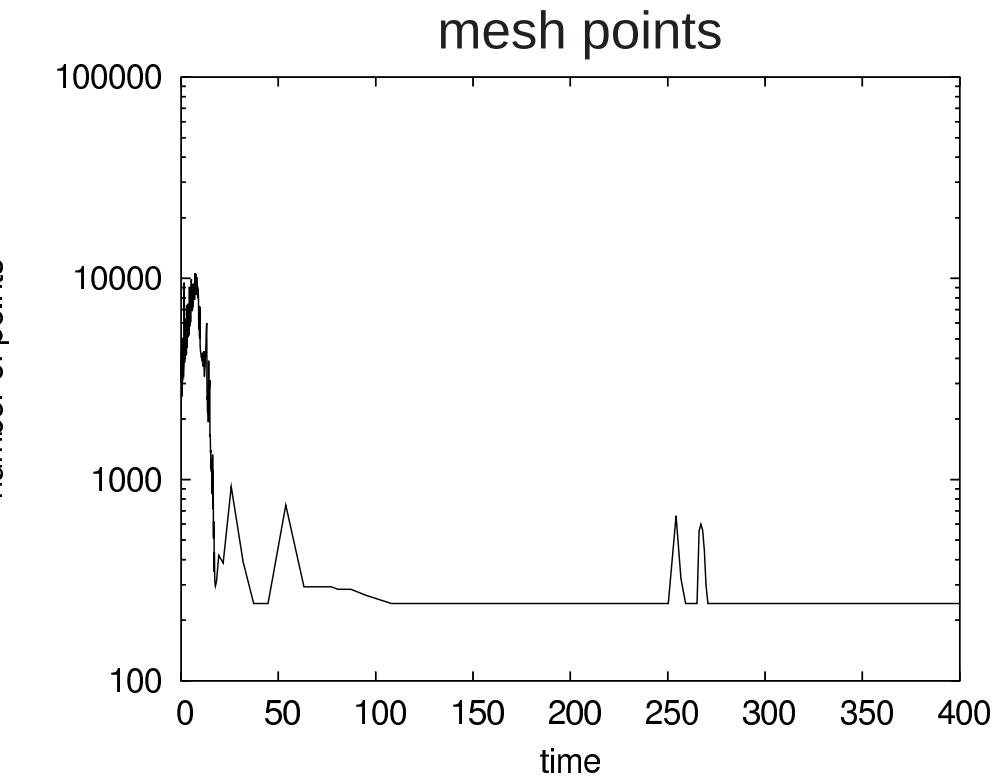
Bidomain - LR1: time course of u_i, u_e

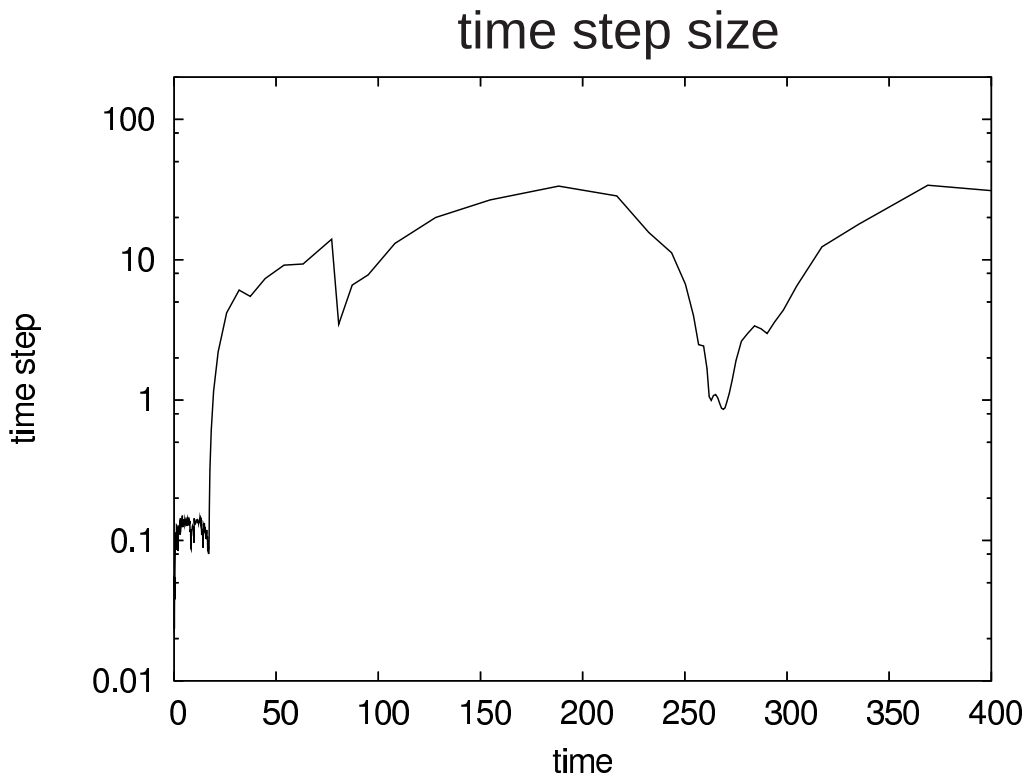




- Time course of intra- and extra-cellular electric potentials u_i, u_e at point $x = (1.65, 1.65, 1.1)$
- Time integrator: ROS3P

Bidomain - LR1: number of vertices and time step size as functions of time





Time integrator: ROS3P

B) Parallel solver on uniform grids with PETSc library

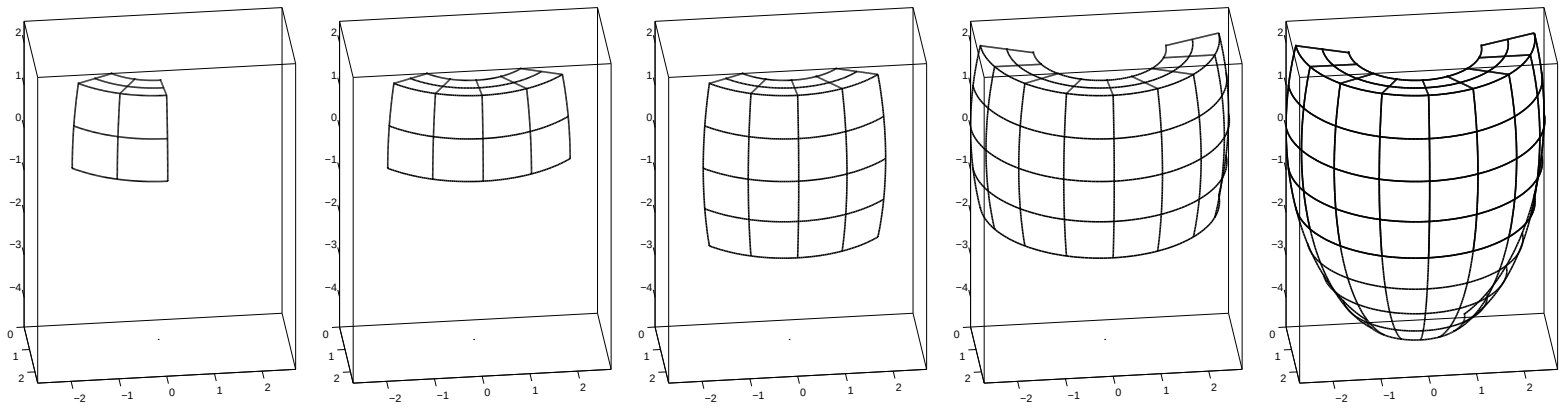
- Structured grid, Q_1 isoparametric finite elements in space
- Left ventricle is modeled with a family of truncated ellipsoids or slabs
- Semi-implicit method (IMEX) in time:
  - implicit Euler for diffusion term + explicit for nonlinear reaction term I_{ion}^{h}
  - implicit Euler for membrane ODEs model (LR1 or LRd)
- Adaptive time-stepping strategy based only on $dv = max(\mathbf{v}^{n+1} - \mathbf{v}^{n})$
- parallel library PETSc from Argonne National Laboratory (www.mcs.anl.gov/petsc)
  - preconditioned Krylov space methods (KSP PETSc object)
  - PCG with ILU(0) block Jacobi preconditioner (not scalable from DD theory, but cheap; work in progress on two level solver)

- *Colli Franzone, Pavarino, Taccardi*, Math. Biosci. 197, 2005
- " " " FIMH05, Springer LNCS, 2005
- *Colli Franzone, Pavarino*, Math. Mod. Meth. Appl. Sci., 14 (6), 2004
- " " Computers in Cardiology 30, IEEE Proc., 2003

B1) Scalability

Monodomain and Bidomain with LR1 on ellipsoidal block

Platform: IBM SP4 of Cineca (512 cpu, 1.3 GHz, 64 Gb every 32-node)
Initial depolarization of ellipsoidal block: 1 stimulus on epicardium, 30 time steps of 0.05 msec, computation of $v, u_i, u_e, w_1, \cdots, w_7$ and activation time at each point



Ellipsoidal blocks of increasing sizes decomposed into 8, 16, 32, 64 and 128 subdomains of fixed size (scaled speedup)

Monodomain - LR1 well-conditioned, good performance

# proc.	mesh	unknowns (nodes)	assem. time	∼PCG/time step it.	∼PCG/time step time	∼LR1/ time step
8 = 2·2·2	150·150·100	2.250.000	7.7 s	4	2.7 s	1.4 s
16 = 4·2·2	300·150·100	4.500.000	8.5 s	4	3 s	1.4 s
32 = 4·4·2	300·300·100	9.000.000	9.1 s	5	3.6 s	1.4 s
64 = 8·4·2	600·300·100	18.000.000	9.2 s	5	3.6 s	1.4 s
128 = 8·8·2	600·600·100	36.000.000	10.6 s	8	5.1 s	1.4 s

Bidomain - LR1 very ill-conditioned, DD work in progress

# proc.	mesh	unknowns (2× nodes)	assem. time	∼PCG/time step it.	∼PCG/time step time	∼LR1/ time step
8 = 2·2·2	100·100·70	1.400.000	12.9 s	98	40.2 s	0.45 s
16 = 4·2·2	200·100·70	2.800.000	13.3 s	127	55.5 s	0.45 s
32 = 4·4·2	200·200·70	5.600.600	15.7 s	148	72 s	0.45 s
64 = 8·4·2	400·200·70	11.200.000	16.2 s	176	91.9 s	0.45 s
128 = 8·8·2	400·400·70	22.400.000	18.4 s	244	129.7 s	0.45 s

B2) Simulation of full cardiac cycle (excitation - repolarization)

- activation (ACTI) time: when $v > -60\ mV$ upward
- repolarization (REPO) time: when $v < 90\%\ v_r\ mV$ downward
- action potential duration (APD = REPO - ACTI)

Effects of anisotropy and fiber rotation are still a research topic, e.g.:

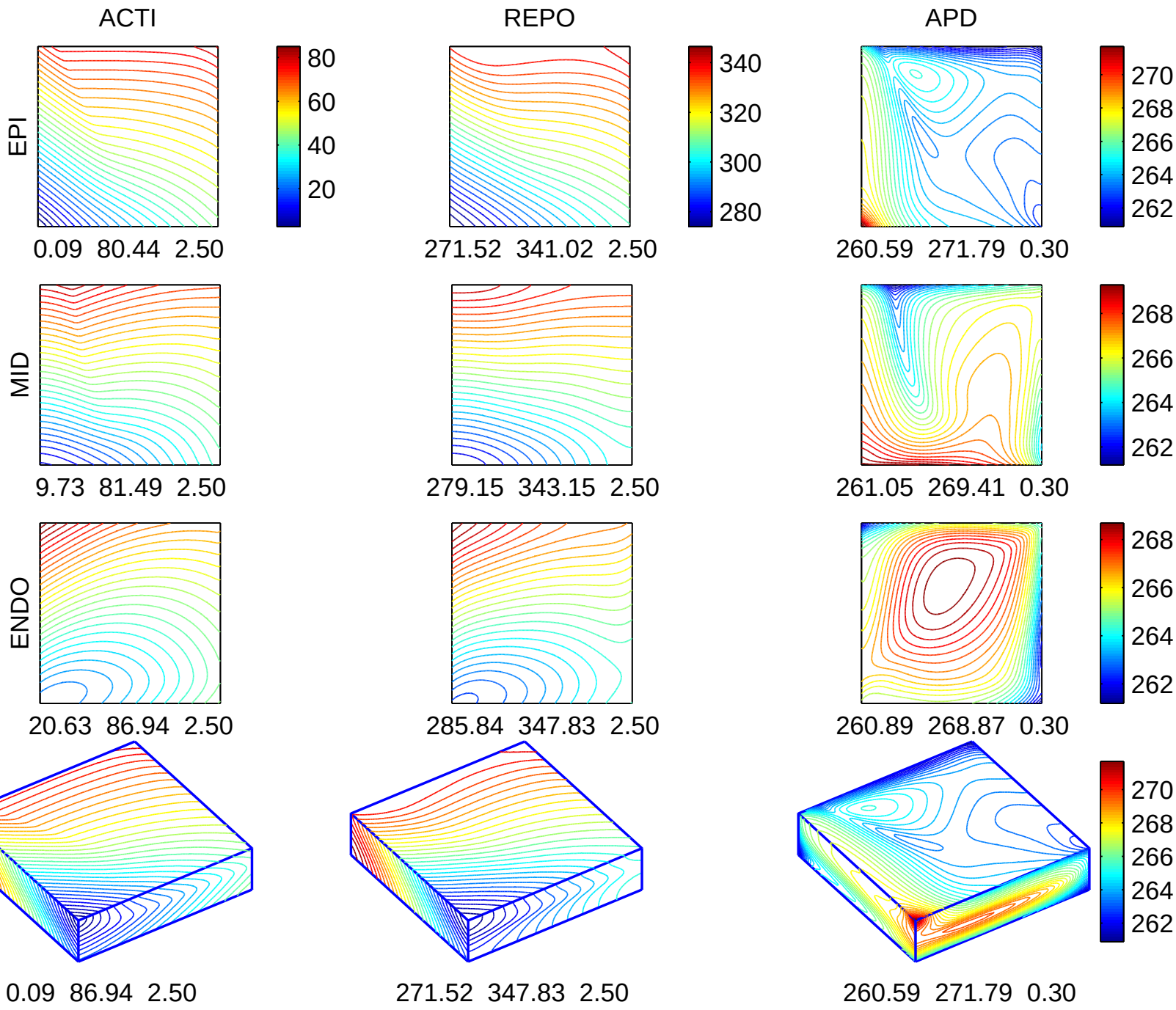
- repolarization as a wavefront or a phase wave
- all cells have same intrinsic APD, but the tissue shows APD modulation

Platforms: IBP SP4, HP SuperDome (64 procs), Cluster Linux (72 procs.)

Runs: Stimulus: 200 $\mu A/cm^3$ at corner or center of epicardium

Computation of $v, u_i, u_e, w_i, i = 1, \cdots, 7$ and isochrones of ACTI, REPO

Full heartbeat, Bidomain - LR1 , block 2·2·0.5 cm^3



ORTHOTROPIC BIDOMAIN − LR1. SIZE = 2*2*0.5 CM^3. ROTATION = 90^o

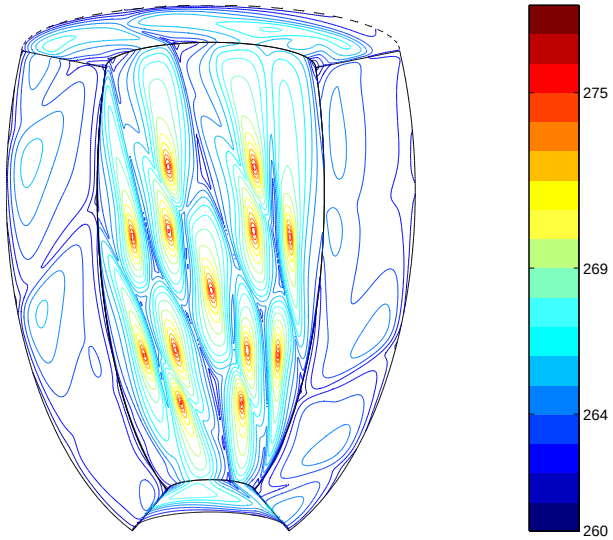
Stimulus with idealized Purkinje network

Monodomain -LR1

mesh $500 \times 500 \times 100$

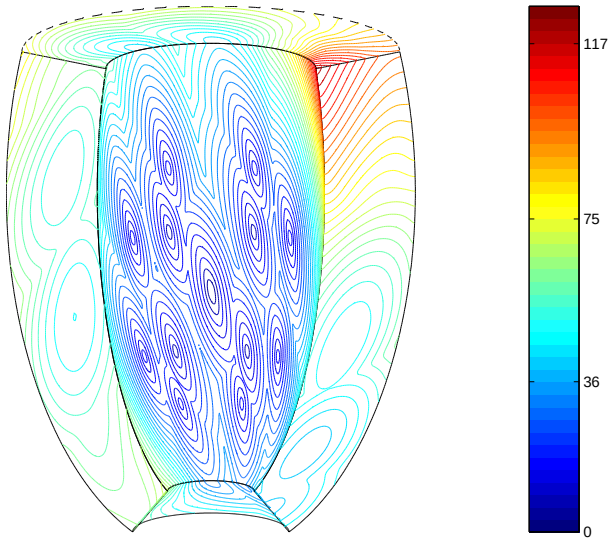
52 procs

APD



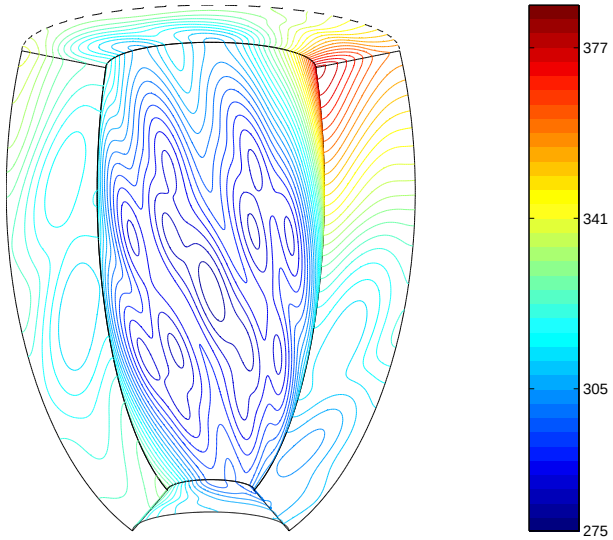
259.57 275.42 1.00

ACTI



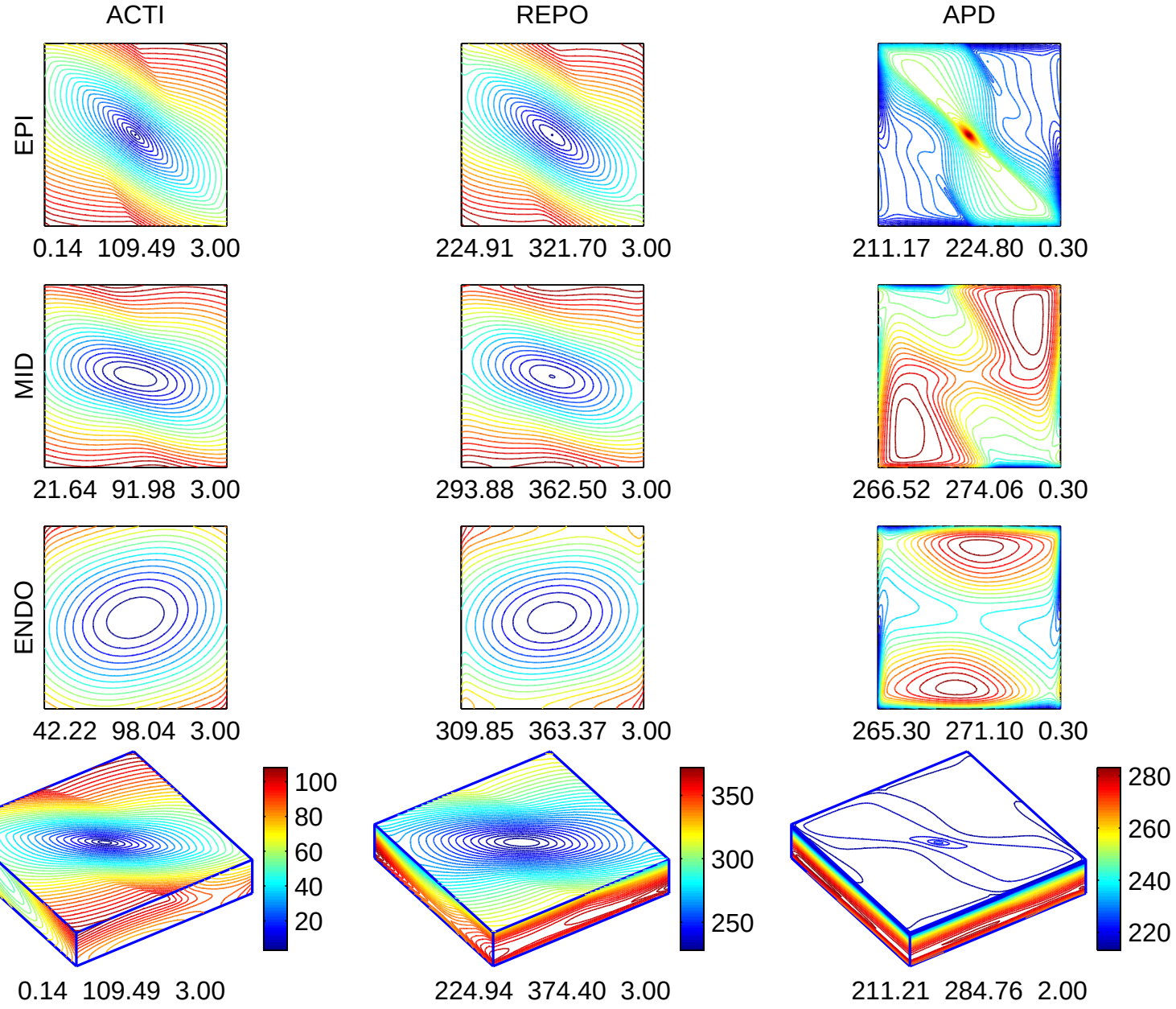
0.13 118.28 3.00

REPO



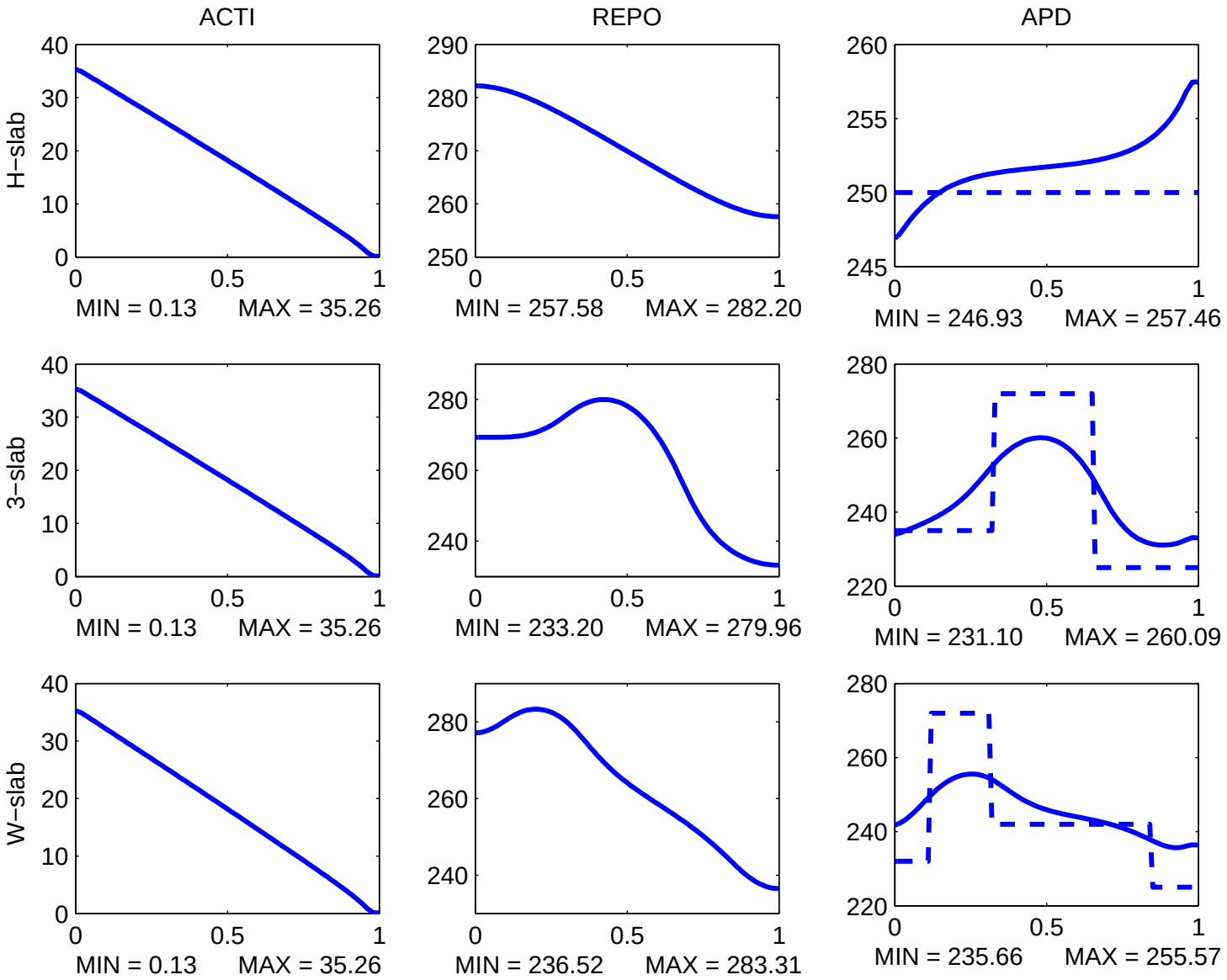
275.47 377.85 3.00

B3) Heterogeneous (M-cells) Monodomain - LR1, block 5·5·1 cm^3

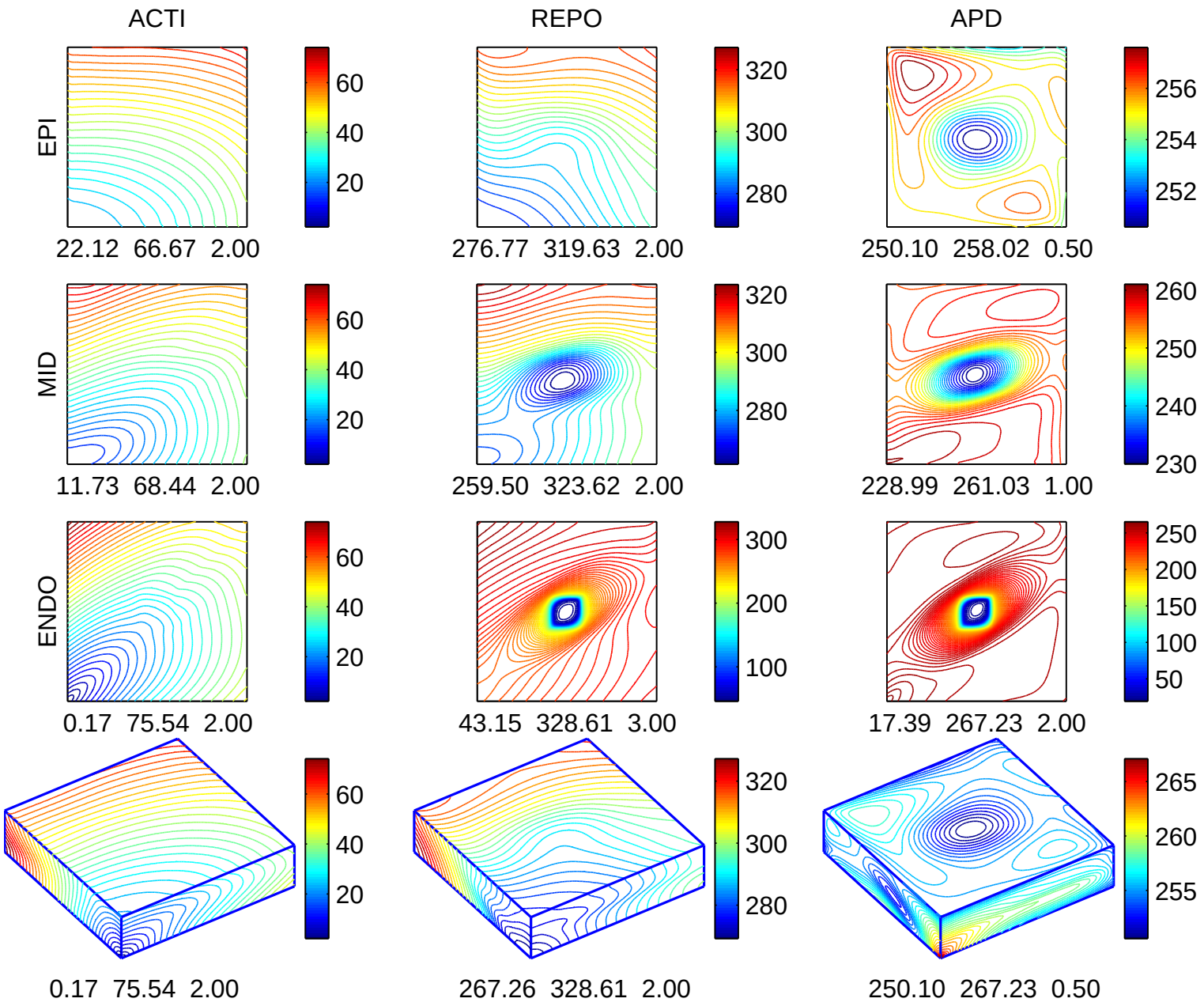


monoLR1 ortho Antze 500*500*100 fibers (−pi/4,5pi/12)

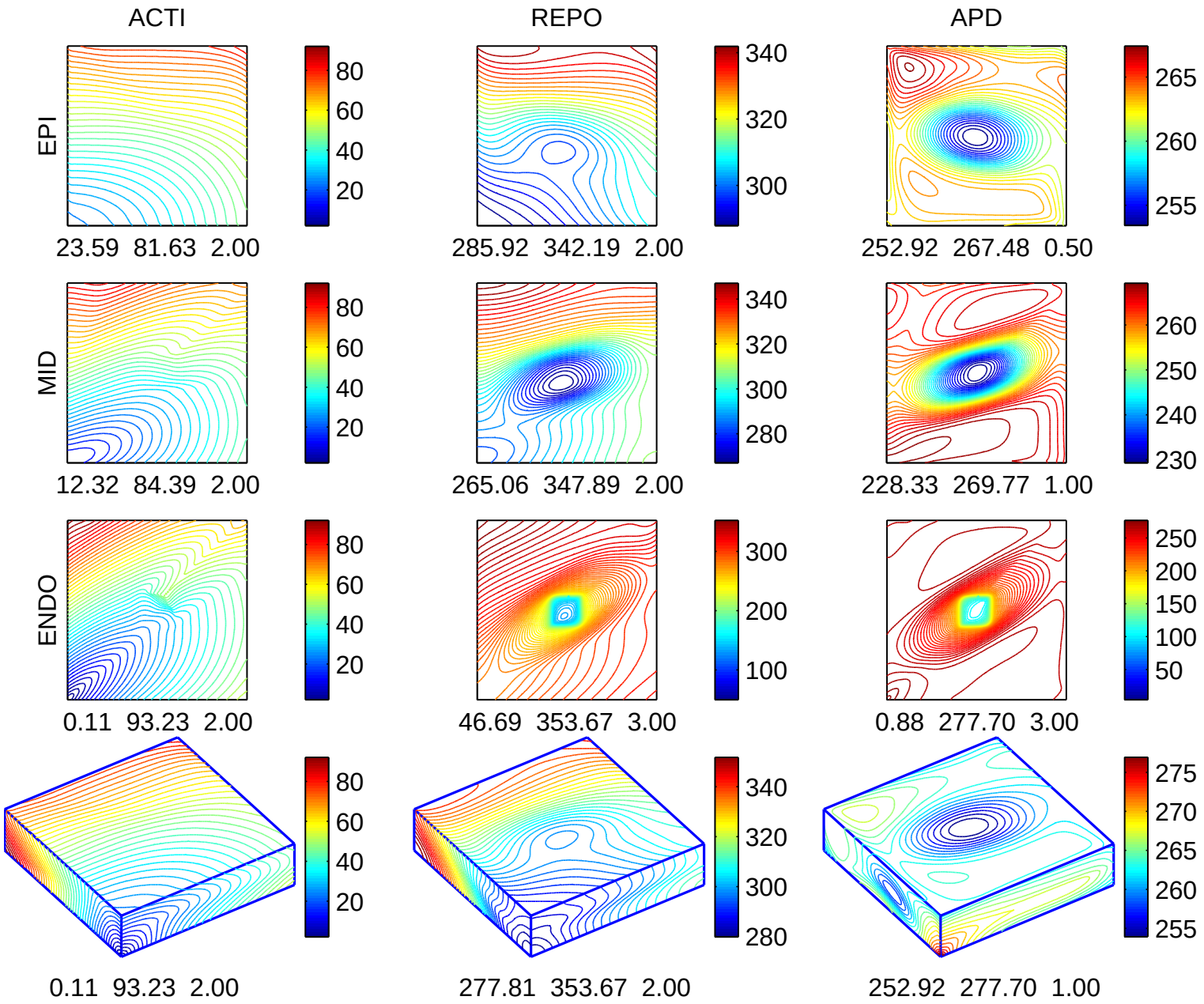
Transmural profiles along 1D line through the slab center



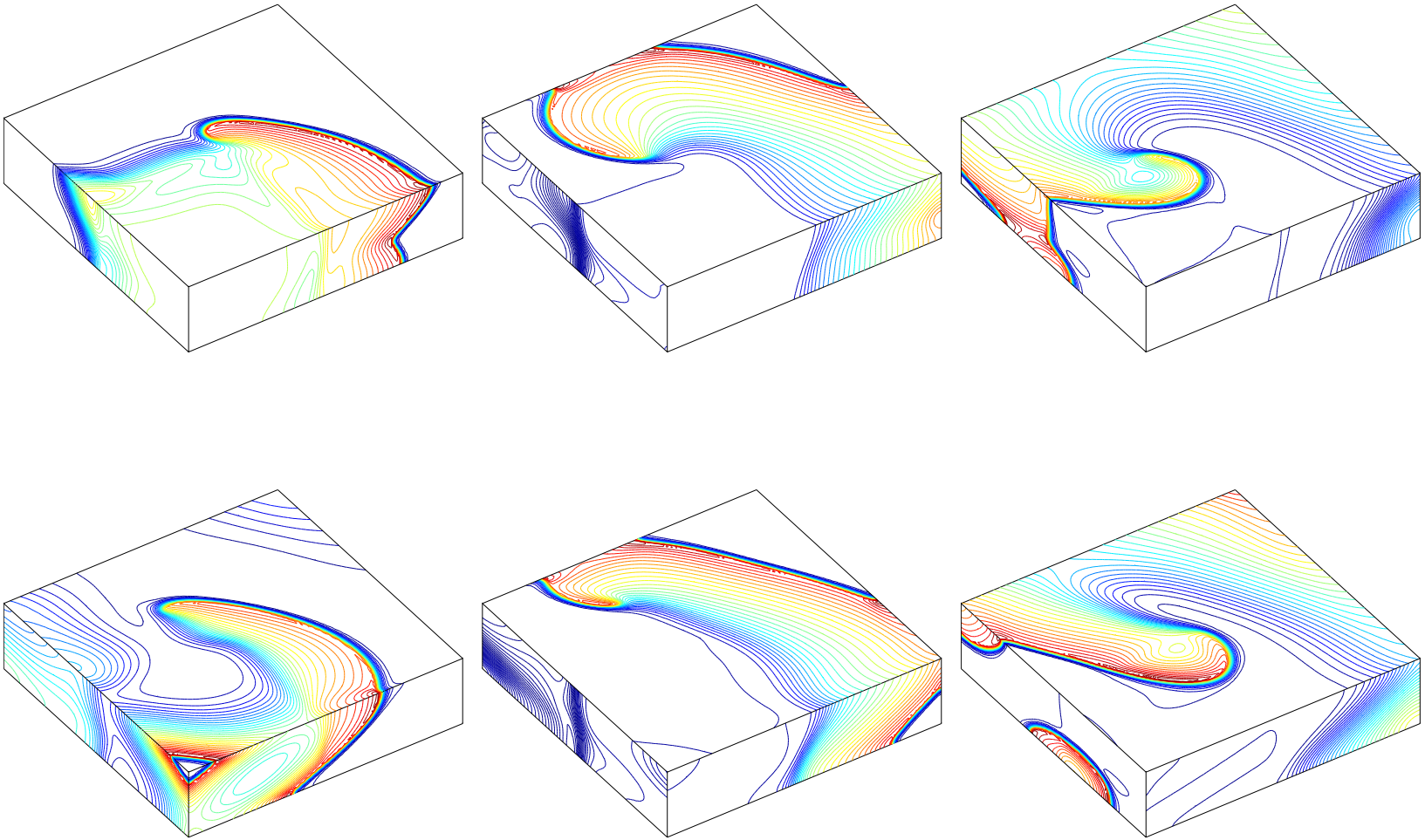
B4) Severe ischemia with Bidomain - LR1, block 2·2·0.5 cm^3



Severe ischemia, with Monomain - LRd00, block 2·2·0.5 cm^3



B5) Reentry with Bidomain - LR1, stable spiral



Block 2·2·0.5 cm, mesh 201·201·51, v at times 90 - 190 msec (step 20)

Conclusions

- 3D Adaptive solver in space and time developed using KARDOS library
  - efficiency requires careful tuning of KARDOS tolerances, small domains so far
- 3D Parallel solver adaptive only in time developed using PETSc library
  - lack of space adaptivity forces large-scale meshes
- Tissue model: Bidomain/Mono/Eikonal, 3D orthotropic rotational anisotropy,
- Membrane model: LR1/LRd

Work in progress and future work

- Nonlinear parallel solvers: NKS, nonlinear Schwarz, ...
- More general geometry: realistic geometries from public data,
  two ventricles, atria, ...
- Reentry phenomena: adaptivity $\Longrightarrow$ uniform grids?
- Tissue modelling: gap-junction, fibrous tissue (collagene, fibroblast),
  capillary ... $\Longrightarrow$ new reaction-diffusion PDEs?
- Coupled models: mechanical contraction, haemodynamics, cardiovascular, ...