Biomechanical modeling of the heart:
From multi-scale multi-physics formulations to patient-specific simulations, with experimental validations and clinical applications

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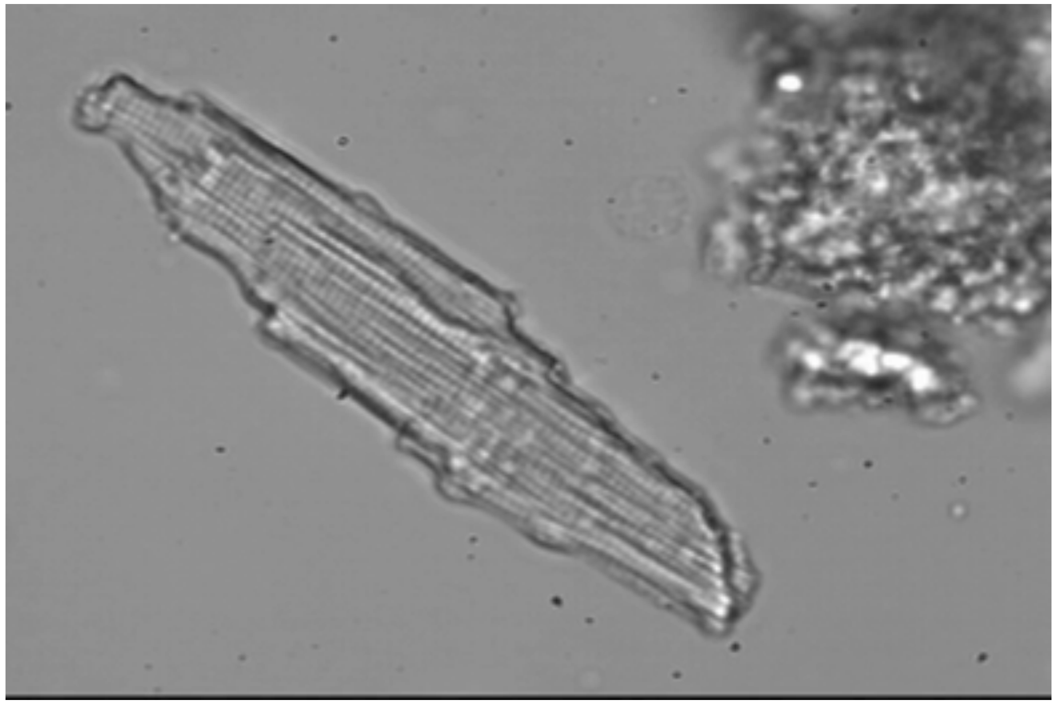
Inria Saclay-Ile-de-France, M∃DISIM *team*

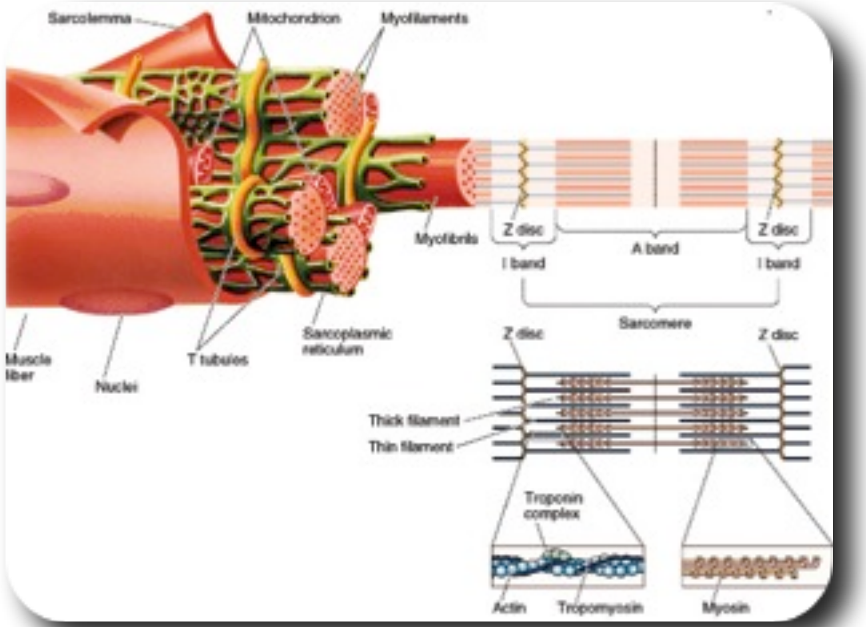
Outline

- Multiscale modeling of the myocardium
  Focus on *mechanical* behavior, with chemical / electrical input
- Validation against *experimental* data (papillary muscles)
- Modeling and validation at the organ scale:
  ➔ Illustration with CRT simulations
- Specific considerations on *estimation* for patient-specific modeling:
  ➔ Detailed validation with infarct characterization
- Conclusions

Multiscale heart modeling: (I) Micro



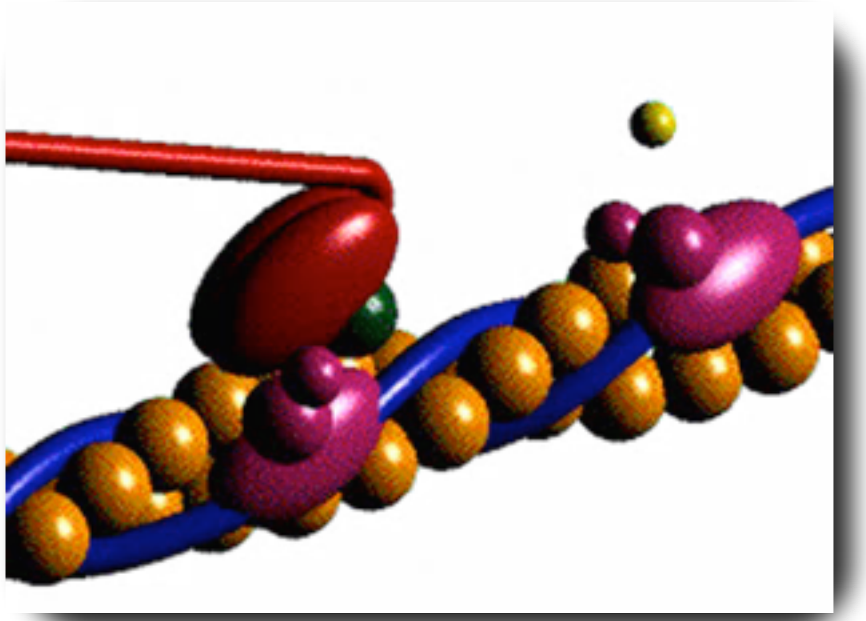
Courtesy: R. Peyronnet (Imperial)



Multiscale heart modeling: (I) Micro

- **Actin-Myosin bridges**: Huxley 57 revisited

$$\frac{\partial n}{\partial t} + \dot{e}_c \frac{\partial n}{\partial s} = (n_0 - n)f - ng$$



n(s,t) : ratio attached bridges for heads at distance *s* from actin site / time *t*

f / *g* : binding / unbinding rate

n_0 : ratio of actually available sites (Frank-Starling, perfusion, etc.)

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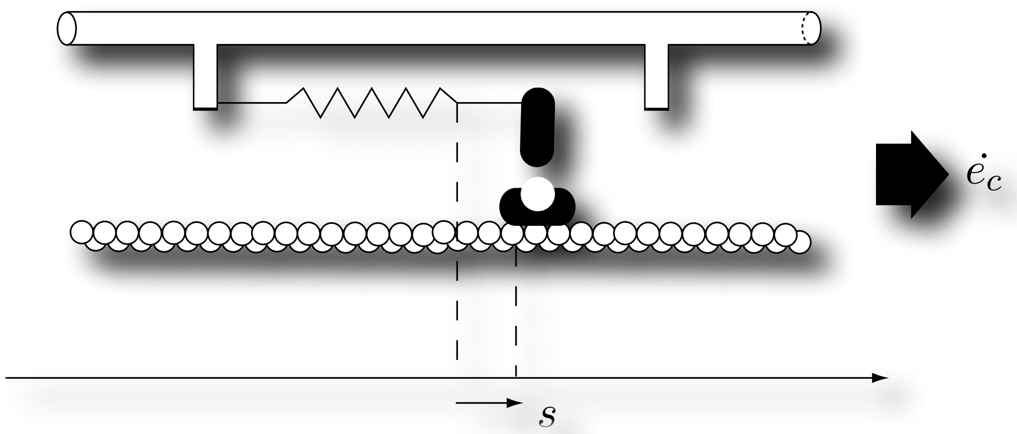


n(s,t) : ratio attached bridges for heads

at distance *s* from actin site / time *t*

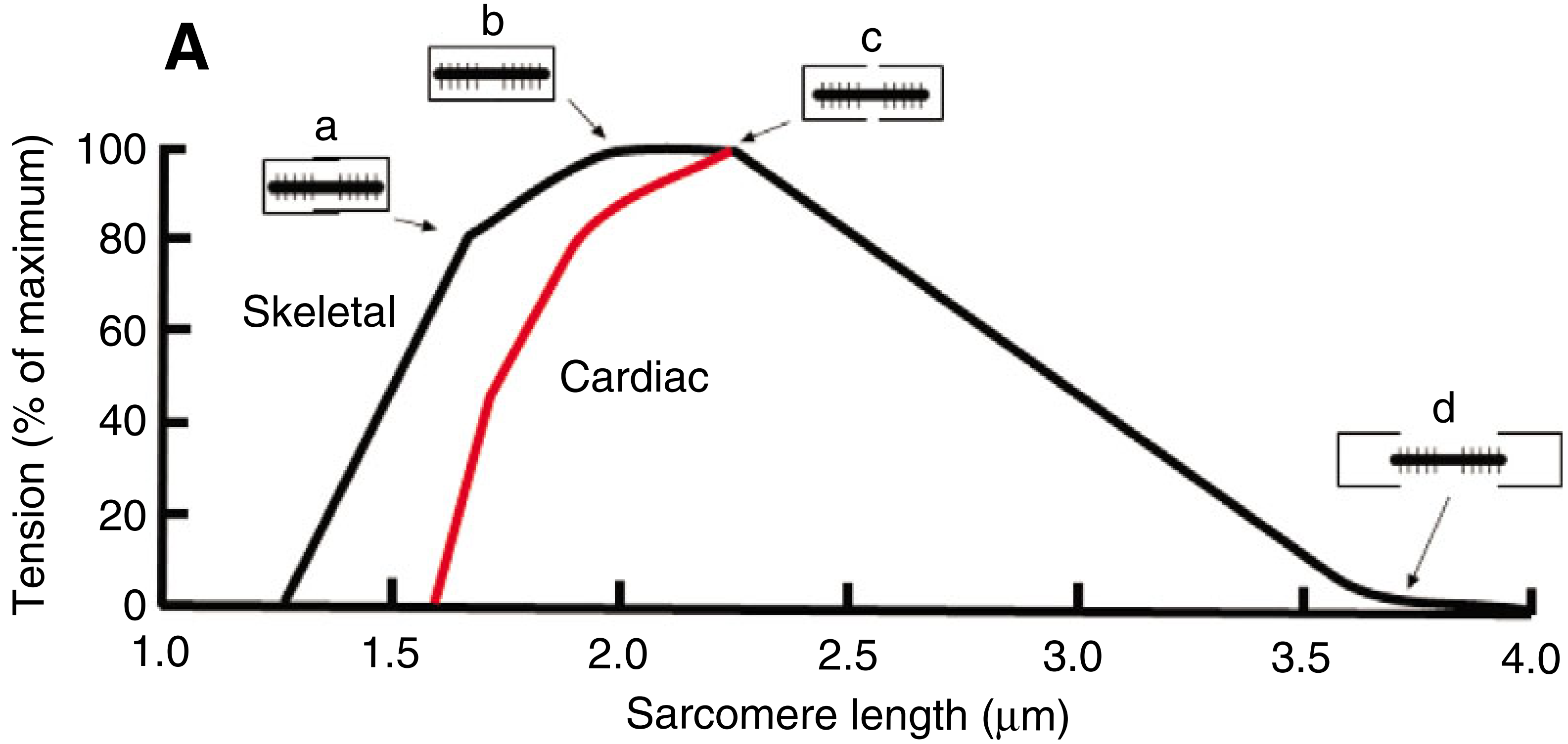
f / *g* : binding / unbinding rate

n_0 : ratio of actually available sites

(Frank-Starling, perfusion, etc.)

- To be modeled: *f(s,t)*, *g(s,t)*, $W_m(s,t)$ (elastic energy of bridge)
- Resulting sarcomere (active) stress: $\tau_c(t) = \int_s \frac{\partial W_m(t,s)}{\partial s} n(t,s)\, ds$

Active force vs. sarcomere length



H.A. Shiels and E. White, Journal of Experimental Biology 211, 2005 (2008).

→ $n_0(e_c)$

Multiscale heart modeling: (2) Meso

- **Moment equations**: $\mu_p = \int_s s^p n(s,t)\, ds$

  $\dot{\mu}_p = n_0 f_p - (f+g)\mu_p + p\dot{e}_c \mu_{p-1}$

  assuming $f+g$ independent of s (see also Guérin et al. 11)

- Modeling choices:

  $f(t,s) = k_{ATP} 1_{s\in[0,1]} 1_{[Ca^{2+}]>C}$

  $g(t,s) = \alpha\, |\dot{e}_c| + k_{ATP} 1_{s\notin[0,1]} 1_{[Ca^{2+}]>C} + k_{RS} 1_{[Ca^{2+}]<C}$

  $W_m(t,s) = \frac{k_0}{2}(s+s_0)^2$ (Symmetry breaking)

- Papers:
  - ✓ Bestel, Clément, Sorine - *LNCS*, vol. 2208, 2001
  - ✓ Chapelle, Le Tallec, Moireau, Sorine - *IJMCE*, 2012

Multiscale heart modeling: (3) Macro

- **Active constitutive relation for sarcomeres**

$$k_c = k_0 \int_{\mathbb{R}} n(s,t)\, ds, \qquad \tau_c = k_0 \int_{\mathbb{R}} (s+s_0) n(s,t)\, ds$$

(stiffness) (stress)

$$\begin{cases} \dot{k}_c = -(|u| + \alpha\, |\dot{e}_c|) k_c + n_0 k_0\, |u|_+ \\ \dot{\tau}_c = -(|u| + \alpha\, |\dot{e}_c|) \tau_c + \dot{e}_c k_c + n_0 \sigma_0\, |u|_+ \end{cases}$$

with $u = k_{ATP} \mathrm{I}_{[Ca^{2+}]>C} - k_{RS} \mathrm{I}_{[Ca^{2+}]<C}$

(action potential related input)

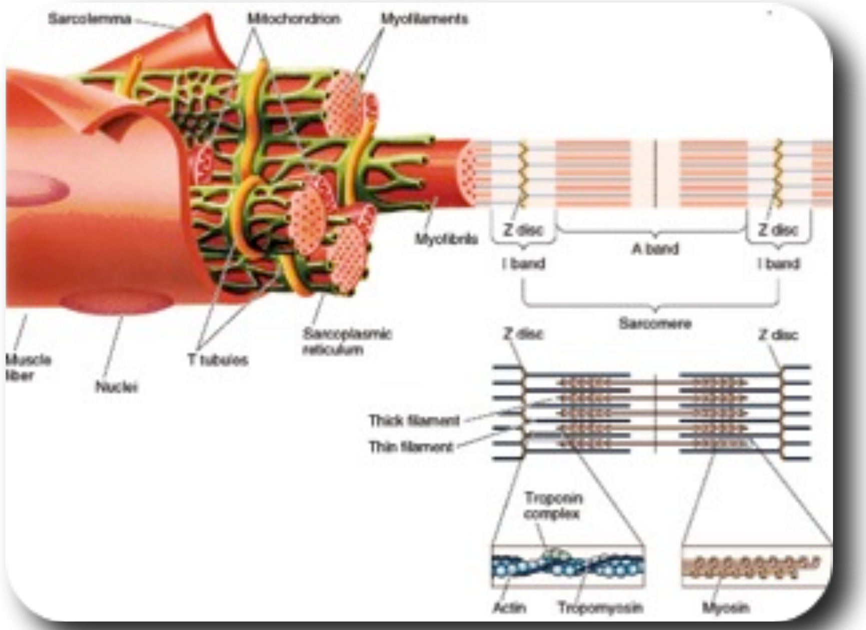
- Microscopic energy $U_c = \frac{k_0}{2} \int_s (s+s_0)^2 n(s,t)\, ds$

$$\dot{U}_c = -(|u| + \alpha\, |\dot{e}_c|) U_c + \dot{e}_c \tau_c + n_0 U_0\, |u|_+$$

Complete rheological modeling

- **Passive components:**

  Z-disks, intra- and extra-cellular media, collagen, etc.



Complete rheological modeling

- **Passive components:**

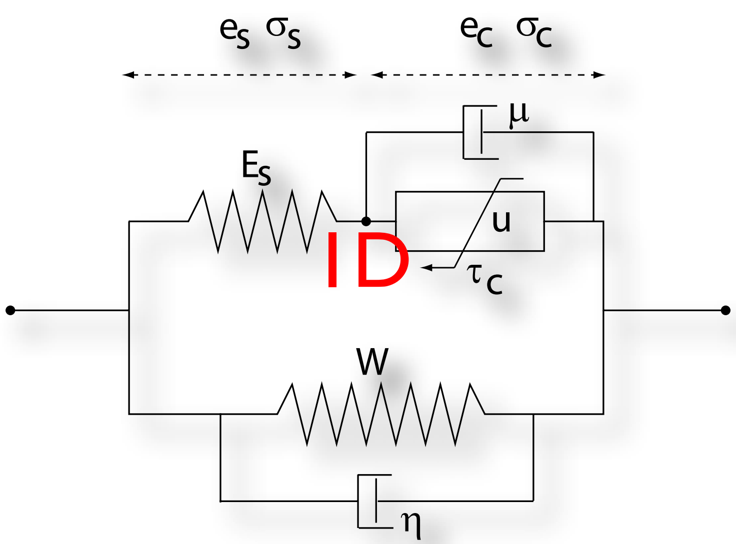
  Z-disks, intra- and extra-cellular media, collagen, etc.

- Hill-Maxwell rheological model

- Note: sarcomeres generate stresses in *fiber* direction (1D)

- More sophisticated modeling ingredients can be considered in micro-macro approach: addit. chemical states and internal variables...

- Complete energy balance here:



$$\frac{d}{dt}\left(\mathcal{K}+\mathcal{E}_e+\frac{1}{2}\int_{\Omega_0} E_s e_s^2\,d\Omega+\int_{\Omega_0} U_c\,d\Omega\right)=$$

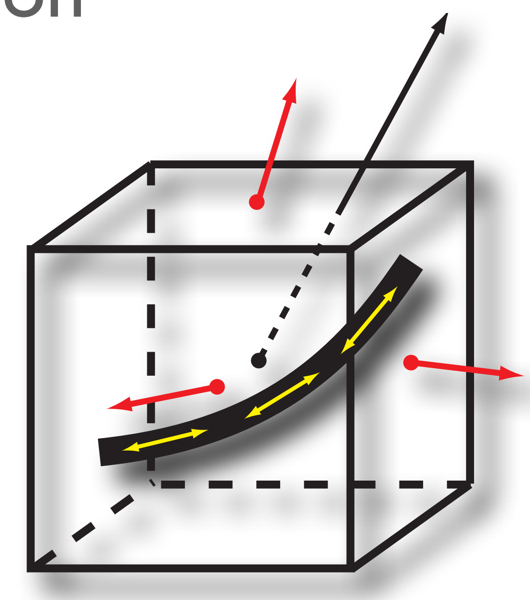
$$\mathcal{P}_{ext}(v)+\int_{\Omega_0} n_0 U_0\,|u|_+\,d\Omega-\int_{\Omega_0}(|u|+\alpha\,|\dot{e}_c|)U_c\,d\Omega-\int_{\Omega_0}\mu(\dot{e}_c)^2\,d\Omega-\int_{\Omega_0}\frac{\partial W_v}{\partial \underline{\underline{\dot{e}}}}:\underline{\underline{\dot{e}}}\,d\Omega$$

Myocardium modeling summary

Myocardium modeling summary

- Principle of dynamics in total Lagrangian formulation

$$\int_{\Omega_0} \rho \ddot{\underline{y}} \cdot \delta \underline{v} \, d\Omega_0 + \int_{\Omega_0} \underline{\underline{\Sigma}} : \delta \underline{\underline{e}} \, d\Omega_0 + \int_{\Gamma} P_V \, \underline{\nu} \cdot \underline{\underline{F}}^{-1} \cdot \delta \underline{v} \, J \, d\Gamma = 0, \quad \forall \delta \underline{v} \in V$$



- Constitutive law

$$\underline{\underline{\Sigma}} = \frac{\partial W^e}{\partial \underline{\underline{e}}} + \frac{\partial W^\eta}{\partial \dot{\underline{\underline{e}}}} + \sigma_{1D}(e_{1D}, e_c) \underline{n} \otimes \underline{n}$$

✓ Hyperelastic term $W^e = c_0 \, e^{c_1 (J_1 - 3)^2} + c_2 \, e^{c_3 (J_4 - 1)^2} + \kappa \left[(J - 1) - \ln J \right]$

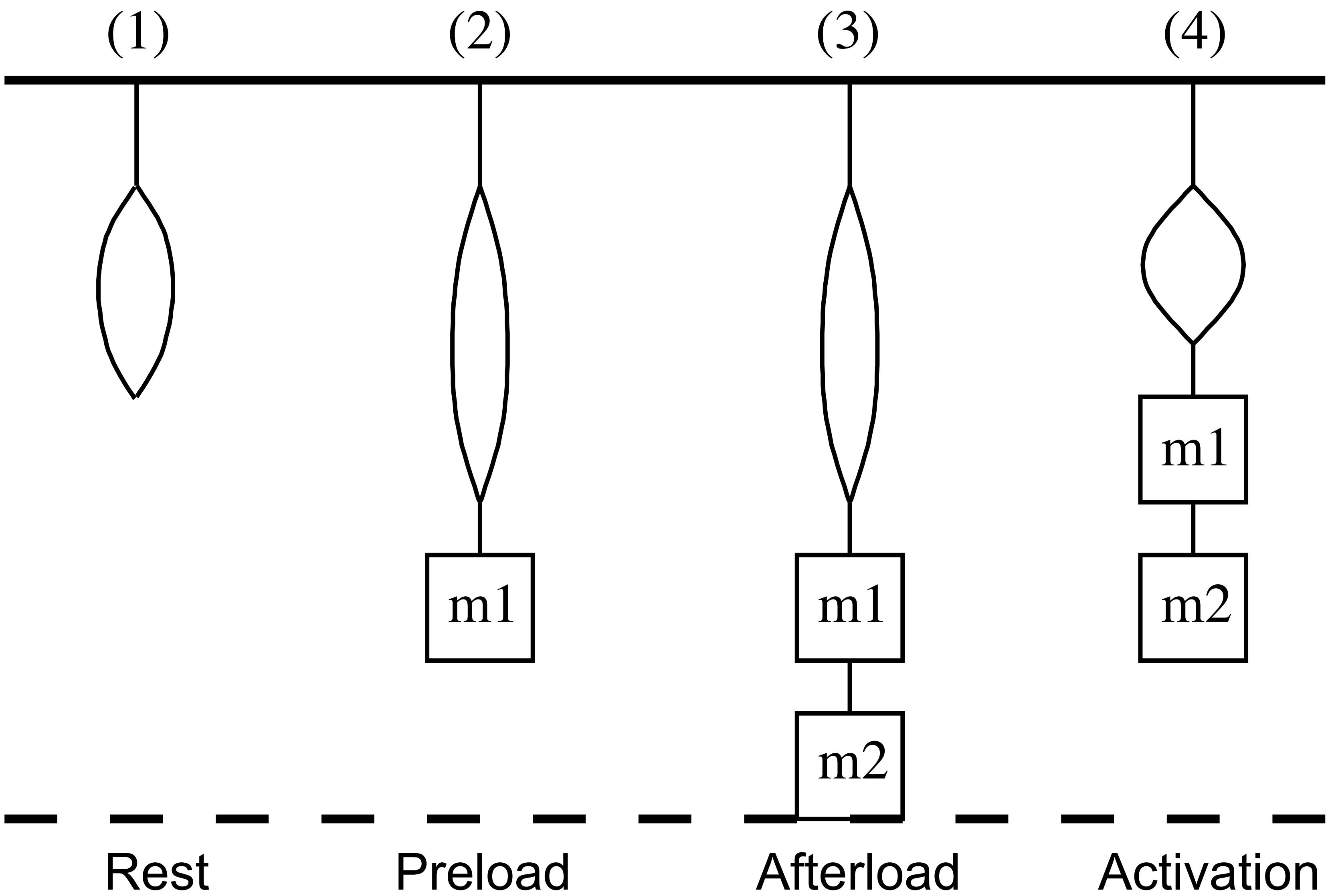
with reduced invariants $J_1 = \left(\mathrm{tr} \underline{\underline{C}}\right) J^{-\frac{2}{3}}, \quad J_4 = \left(\underline{n} \cdot \underline{\underline{C}} \cdot \underline{n}\right) J^{-\frac{2}{3}}$

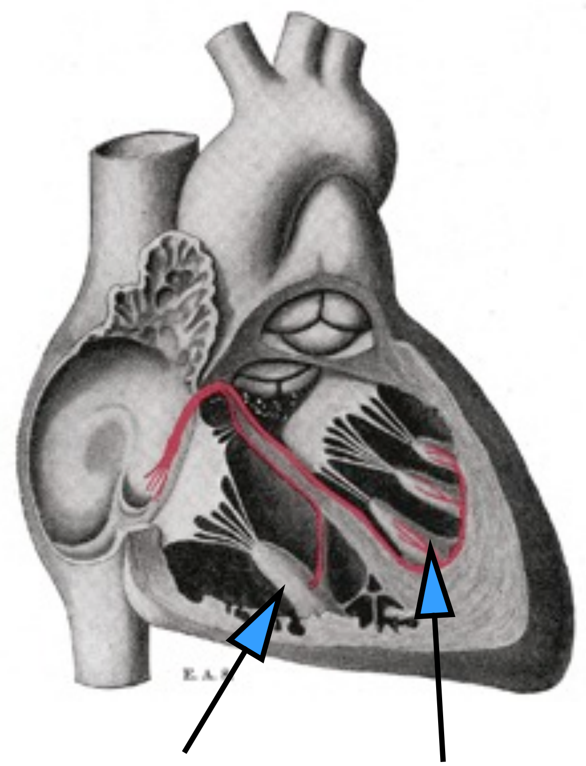
See Prot et al. 07, and also Humphrey&Yin 87, Guccione et al. 91, Fung 93, Costa et al. 96, Holzapfel&Ogden 09 (review/analysis)...

✓ Viscous term $W^\eta = \frac{\eta}{2} \mathrm{tr}(\dot{\underline{\underline{e}}}^2)$

✓ Active part (fiber directed)

Experimental validation

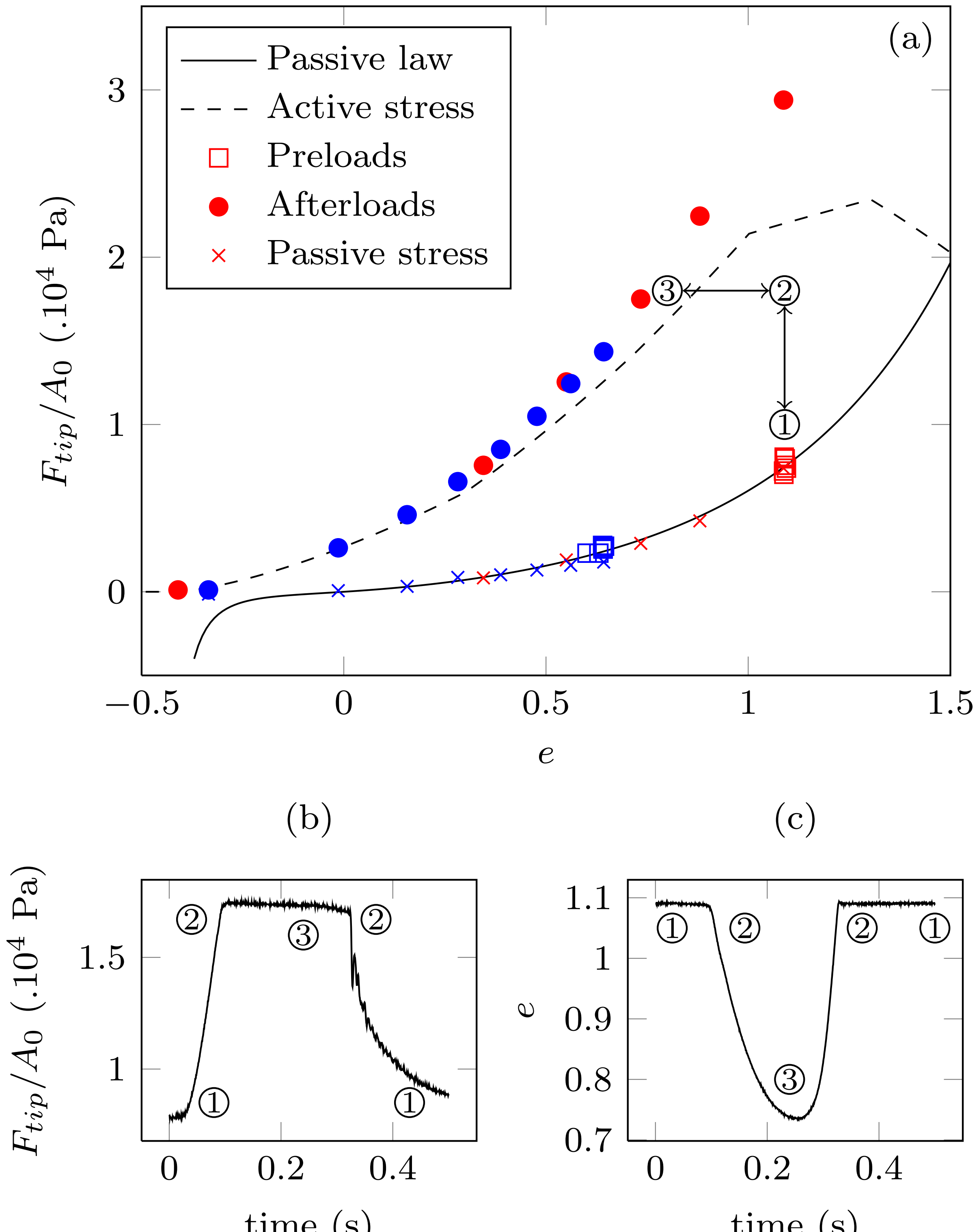




Experimental data : Y. Lecarpentier (Institut du Coeur & Meaux hosp.)

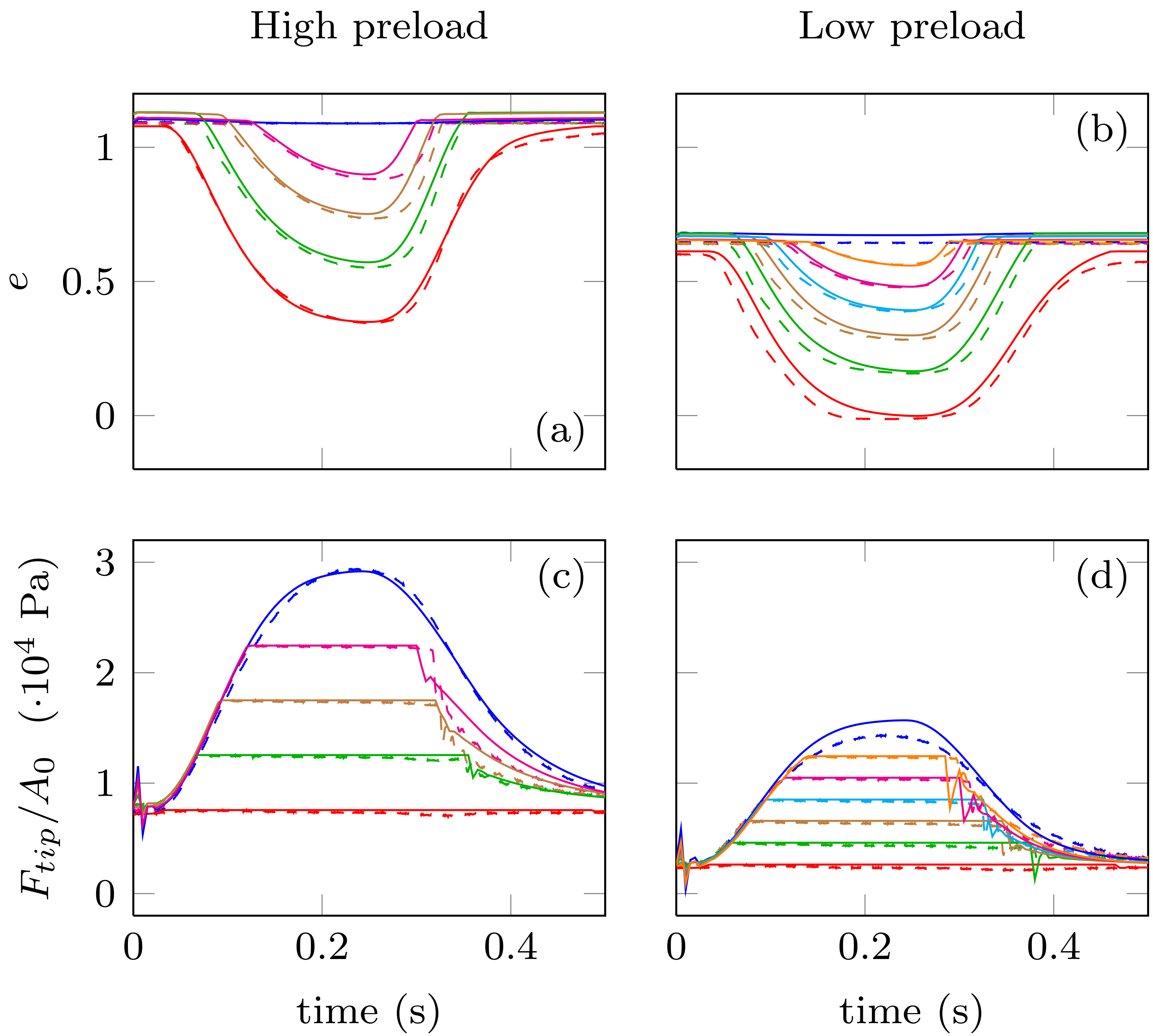
Paper: Caruel, Chabiniok, Moireau, Lecarpentier & Chapelle, *BMMB'13*

Model vs. experiment: (1) statics



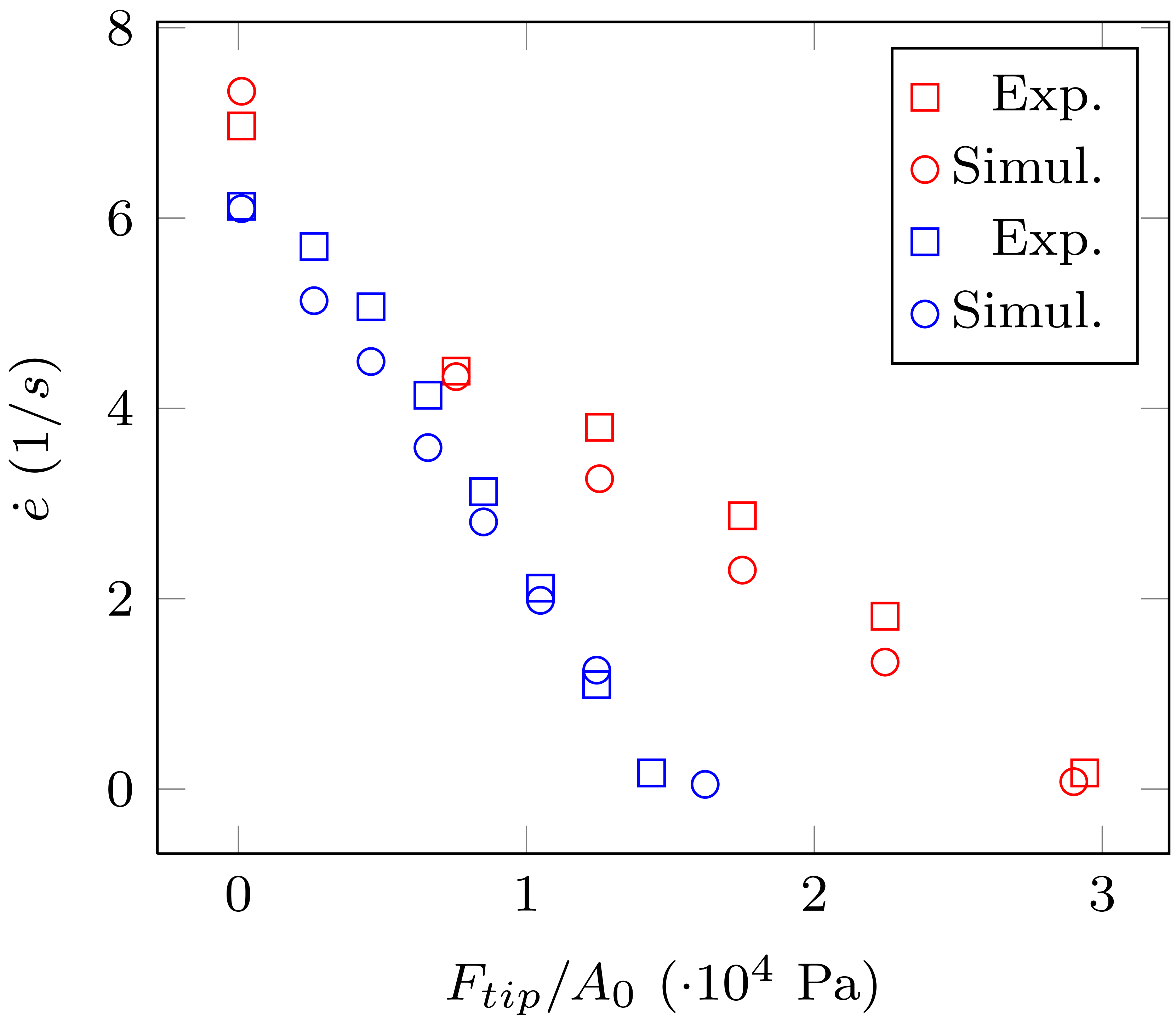
Stress/strain data for initial loading (1) and max. shortening (3)

Model vs. experiment: (2) dynamics

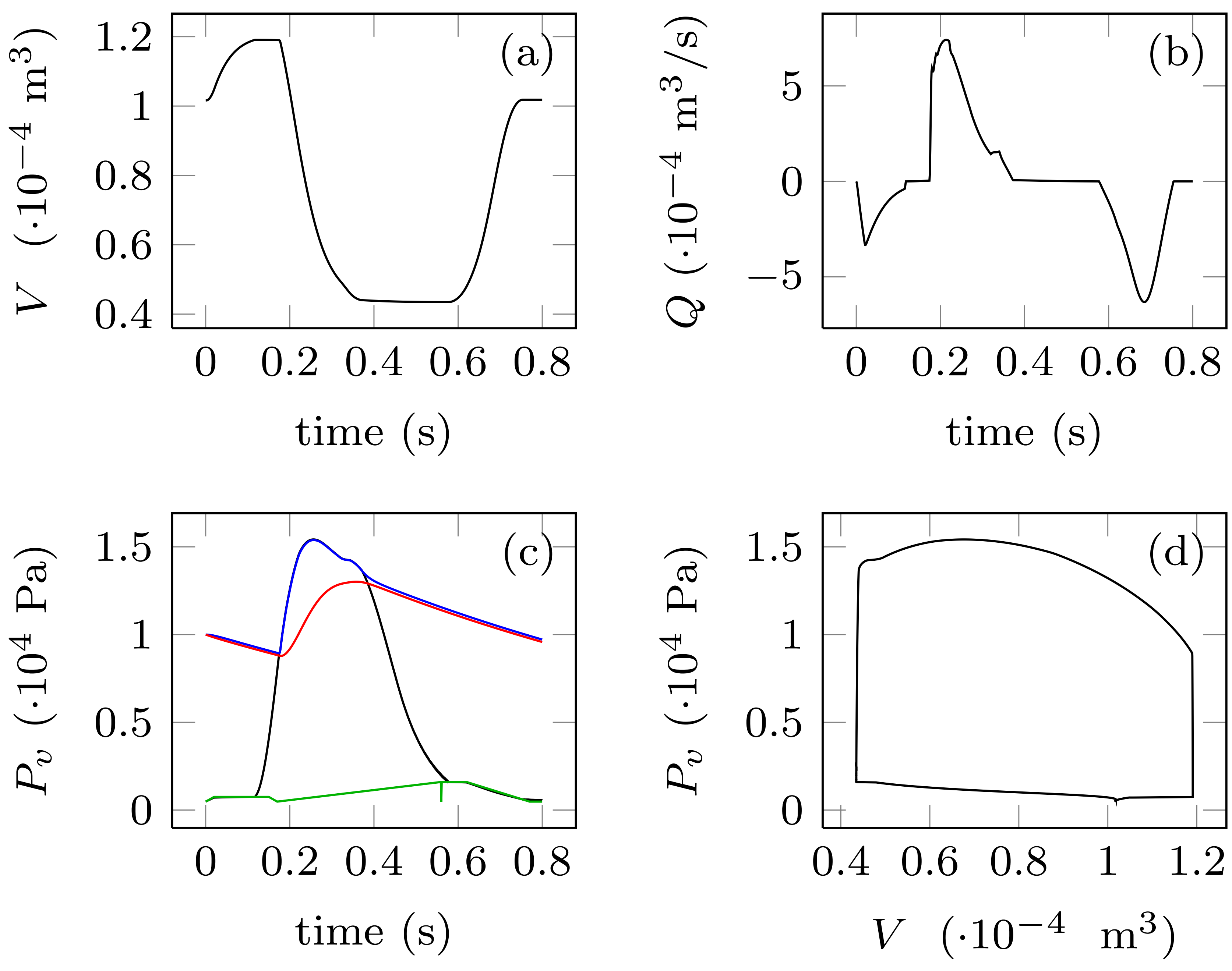


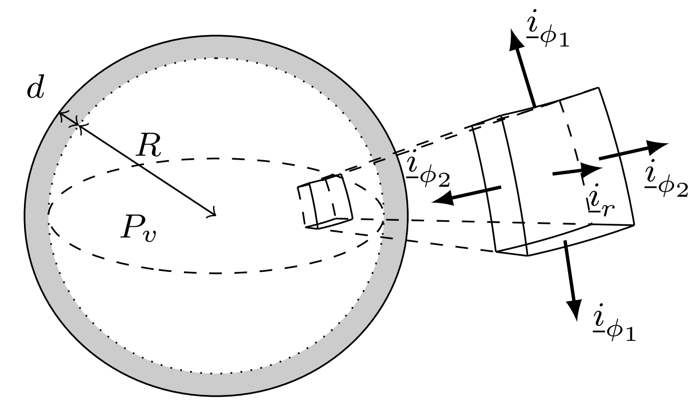
Dashed / solid lines for simul. / exp. results

Dynamics: Hill's maximum velocity



Cross-validation with simplified single-cavity heart model



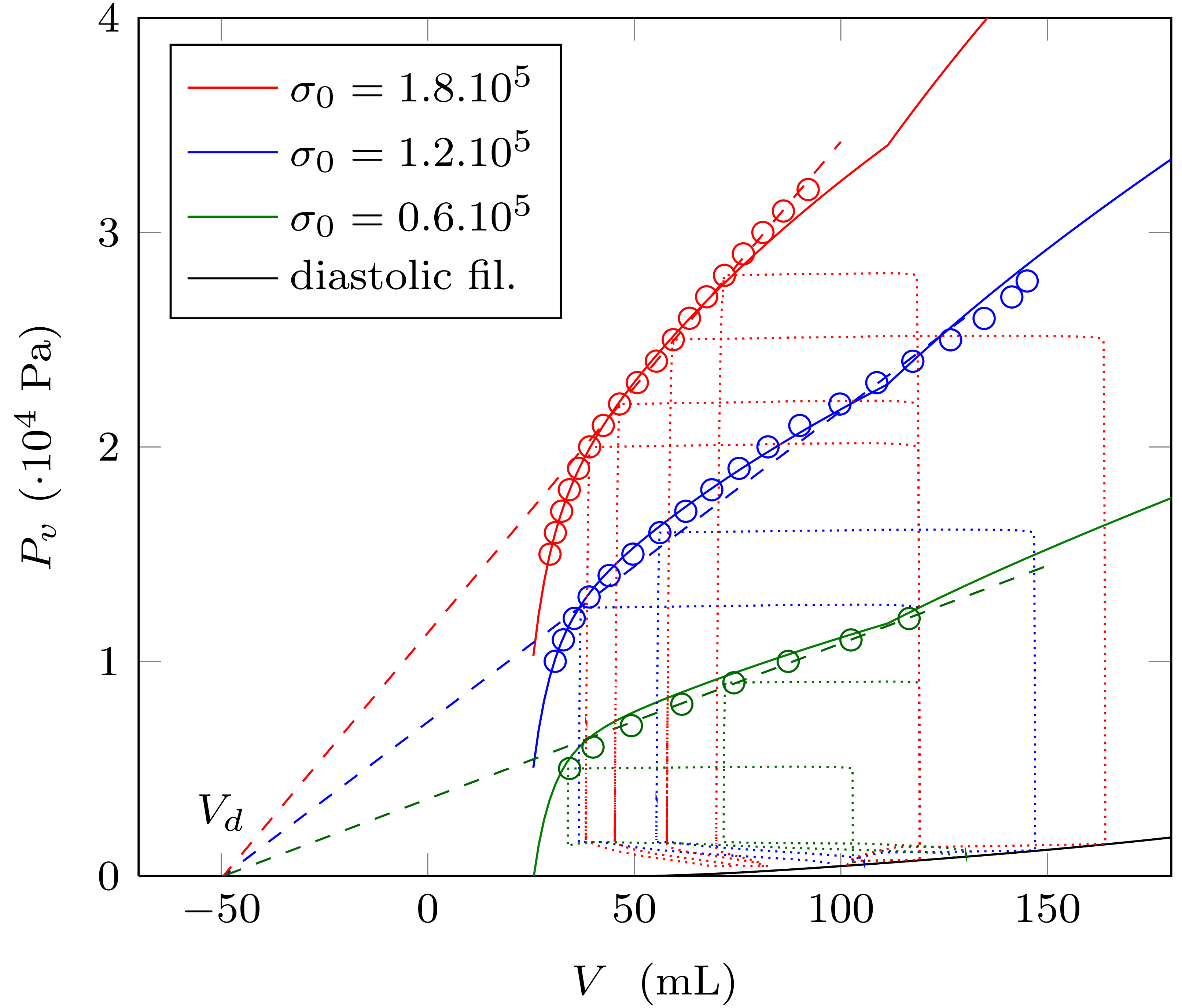


Simplified spherical symmetry assumption

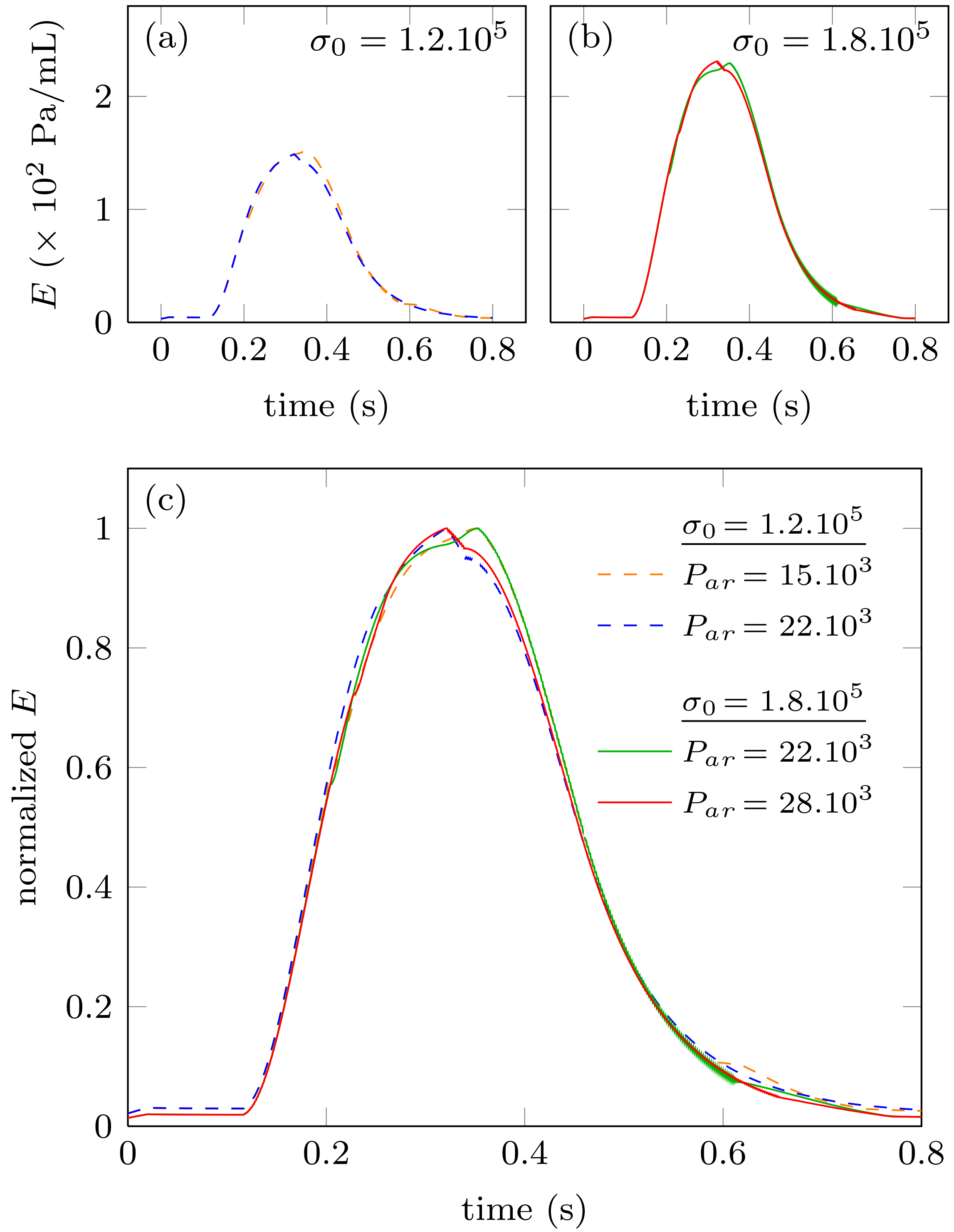
Geometric param. adj. for left ventricle

Physical param.unchanged except contractility x10

End-systolic pressure-volume relation (ESPVR) with simplified model



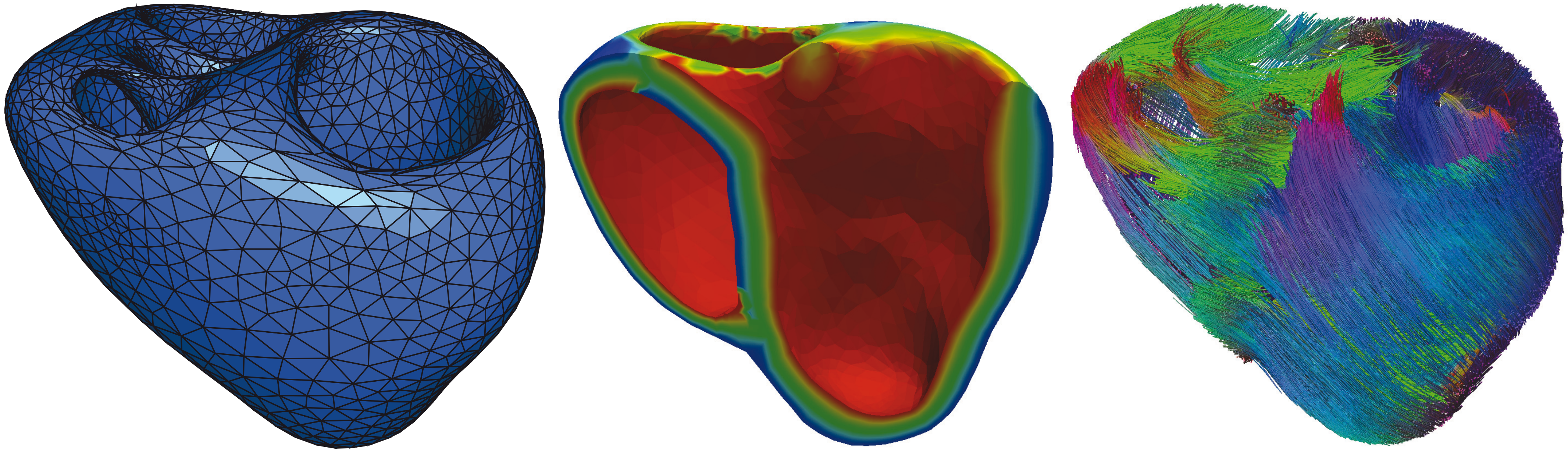
Suga-Sagawa elastance signature



$$E(t) = \frac{P_v(t)}{V(t) - V_d}$$

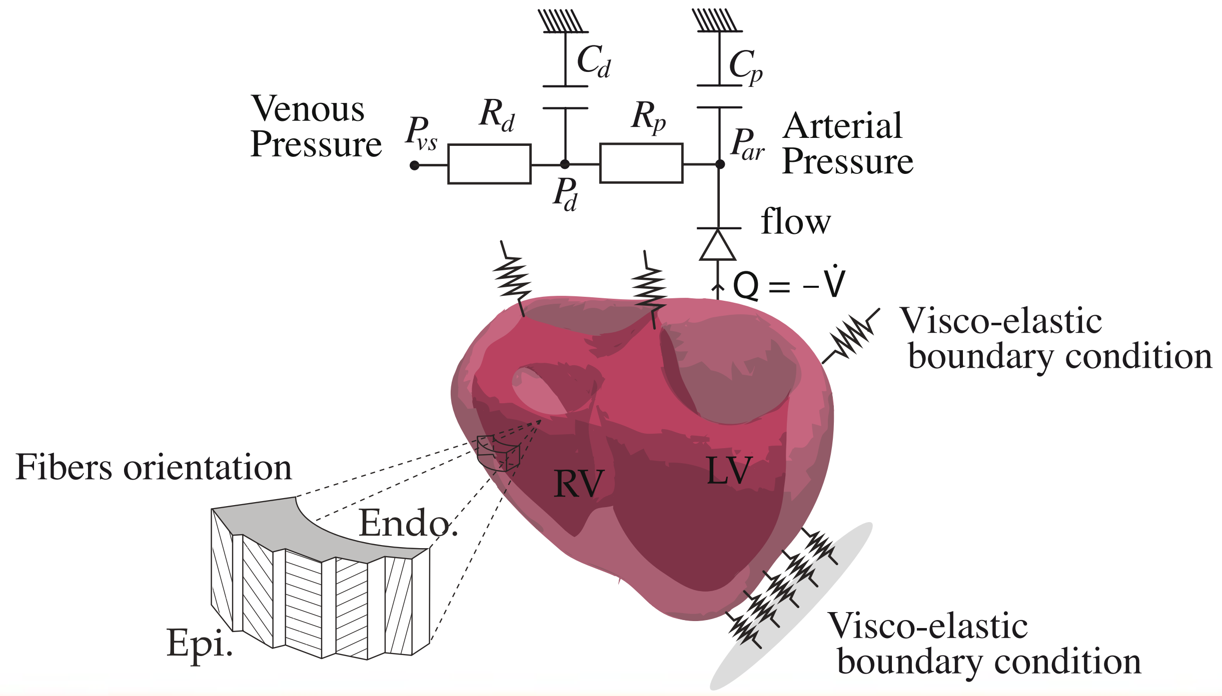
Modeling the organ heart

- Fiber directions: not quite at hand *in-vivo* yet, hence difficulty for *patient-specific* ➔ prescribed based on anatomical knowledge



Modeling the organ heart

- Fiber directions: not quite at hand *in-vivo* yet, hence difficulty for *patient-specific* ➔ prescribed based on anatomical knowledge
- Boundary conditions: complex interactions with surrounding structures and organs ➔ viscoelastic support and sliding contact
- Closure of the system to account for pressure variables: Windkessel model (0D) for artery flows



Modeling the organ heart

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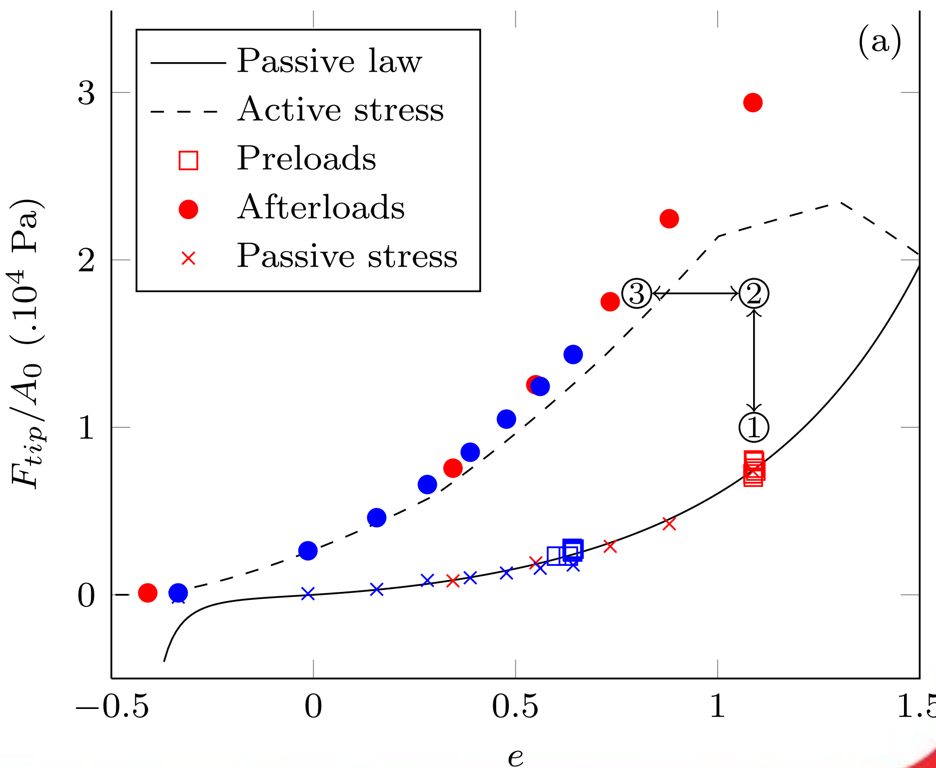
- Boundary conditions: complex interactions with surrounding structures and organs ➔ viscoelastic support and sliding contact
- Closure of the system to account for pressure variables: Windkessel model (0D) for artery flows
- Difficulty with reference configuration: end-diastole not stress-free
  ➔ *inverse problem* to be solved
  (Gee, Förster & Wall, IJNMBE, 2010)



Cardiac Resynchronization Therapy patient-specific modeling... and optimization

M. Sermesant, R. Chabiniok, P. Chinchapatnam, T. Mansi, F. Billet, P. Moireau, J.M. Peyrat, K. Wong, J. Relan, K. Rhode, M. Ginks, P. Lambiase, H. Delingette, M. Sorine, C.A. Rinaldi, D. Chapelle, R. Razavi and N. Ayache
Patient-Specific Electromechanical Models of the Heart for the Prediction of Pacing Acute Effects in CRT: a Preliminary Clinical Validation
Medical Image Analysis, 16(1):201-215, 2012

Protocol

Patient

60 years old woman with congested heart failure (NYHA III) and LBBB

Clinical intervention

Pacing using several resynchronization schemes (number and location of pacing leads, timing)

Data

Non-contact electrophysiological mapping of the LV endocardial potentials using Ensite 3000 multi-electrode array catheter system (St Jude, Sylmar, CA)

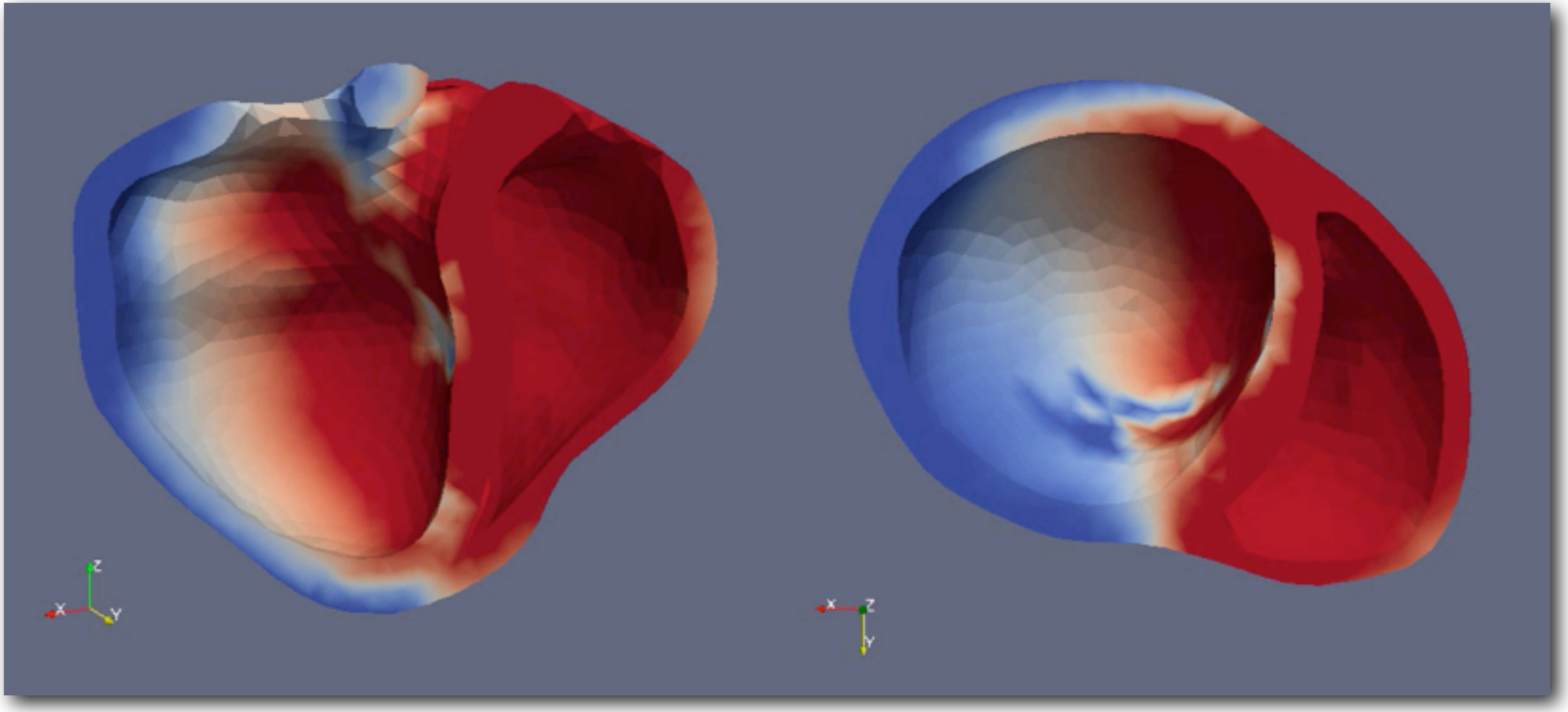
LV pressure measurements

Objective

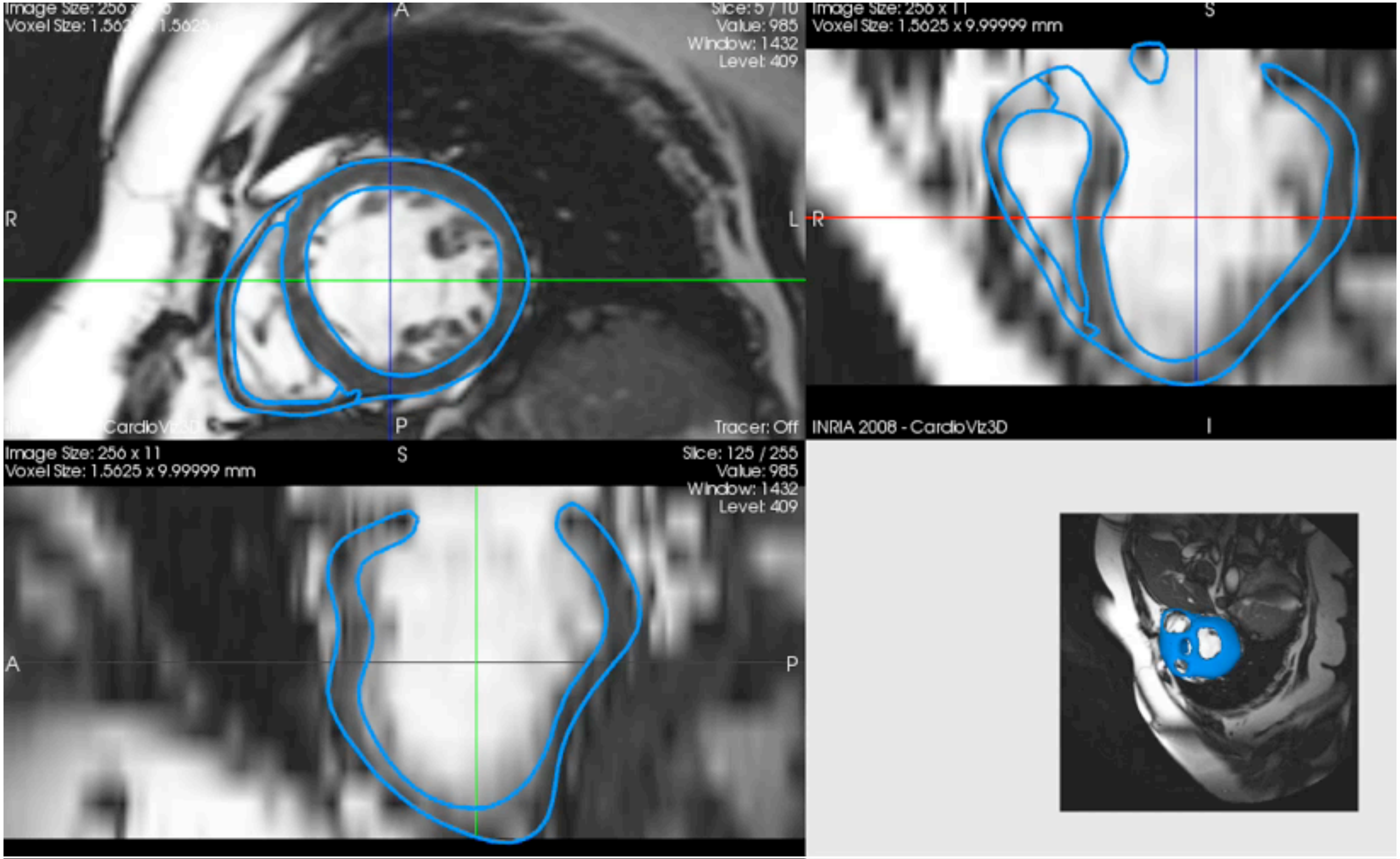
Short term effect of CRT can be assessed by measuring left ventricular pressure and its time derivative:

$$\max\left(\frac{dp}{dt}\right)$$

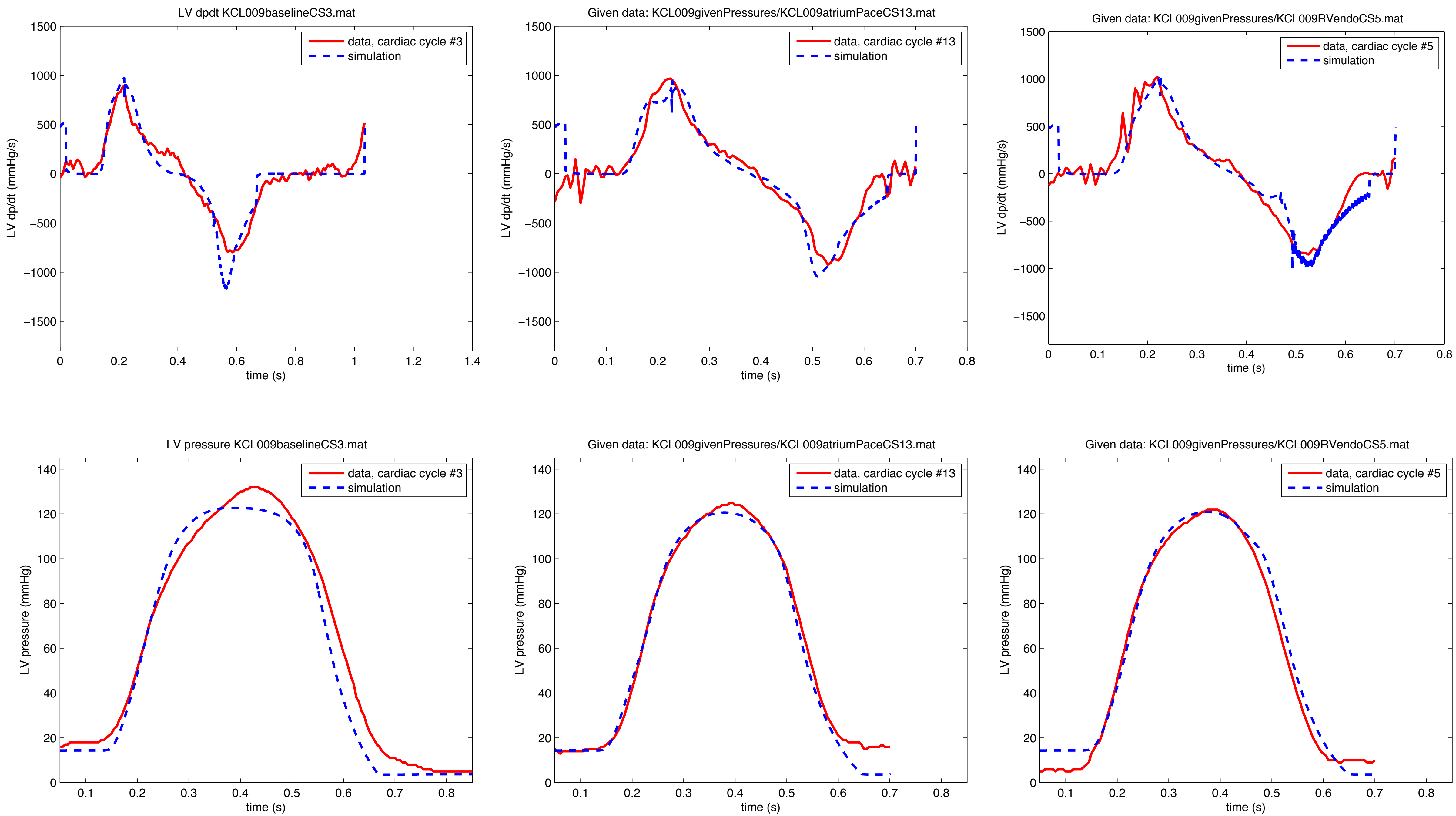
Model Calibration - Baseline simulation



Baseline simulation immersed in MRI



Optimization of CRT procedure [1]



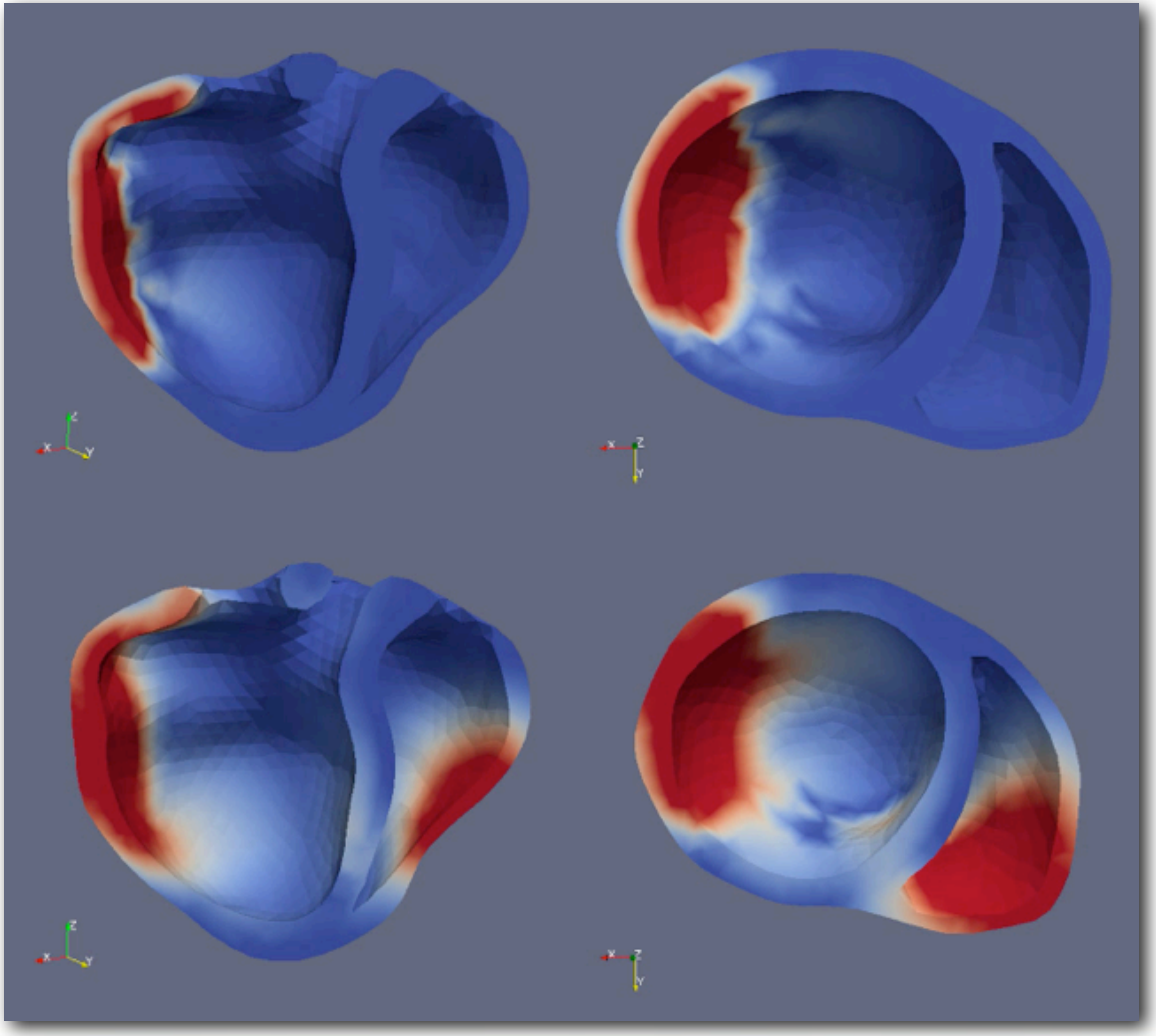
baseline (LBBB)

right atrial pacing

RV endo pacing

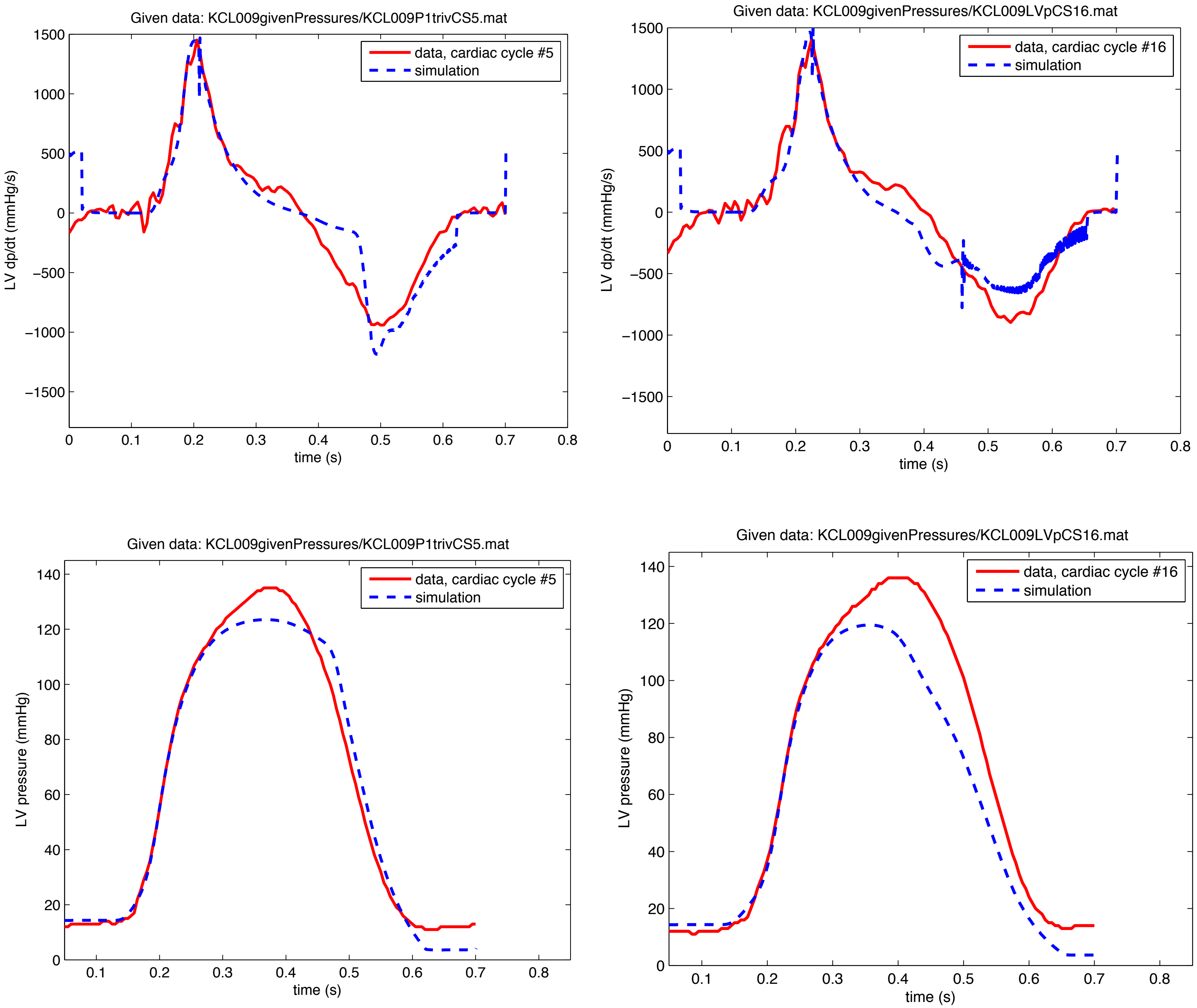
Optimization of CRT: effective strategies

p1triv
(LV endo, coronary sinus, RV endo)



LVp
(LV endo)

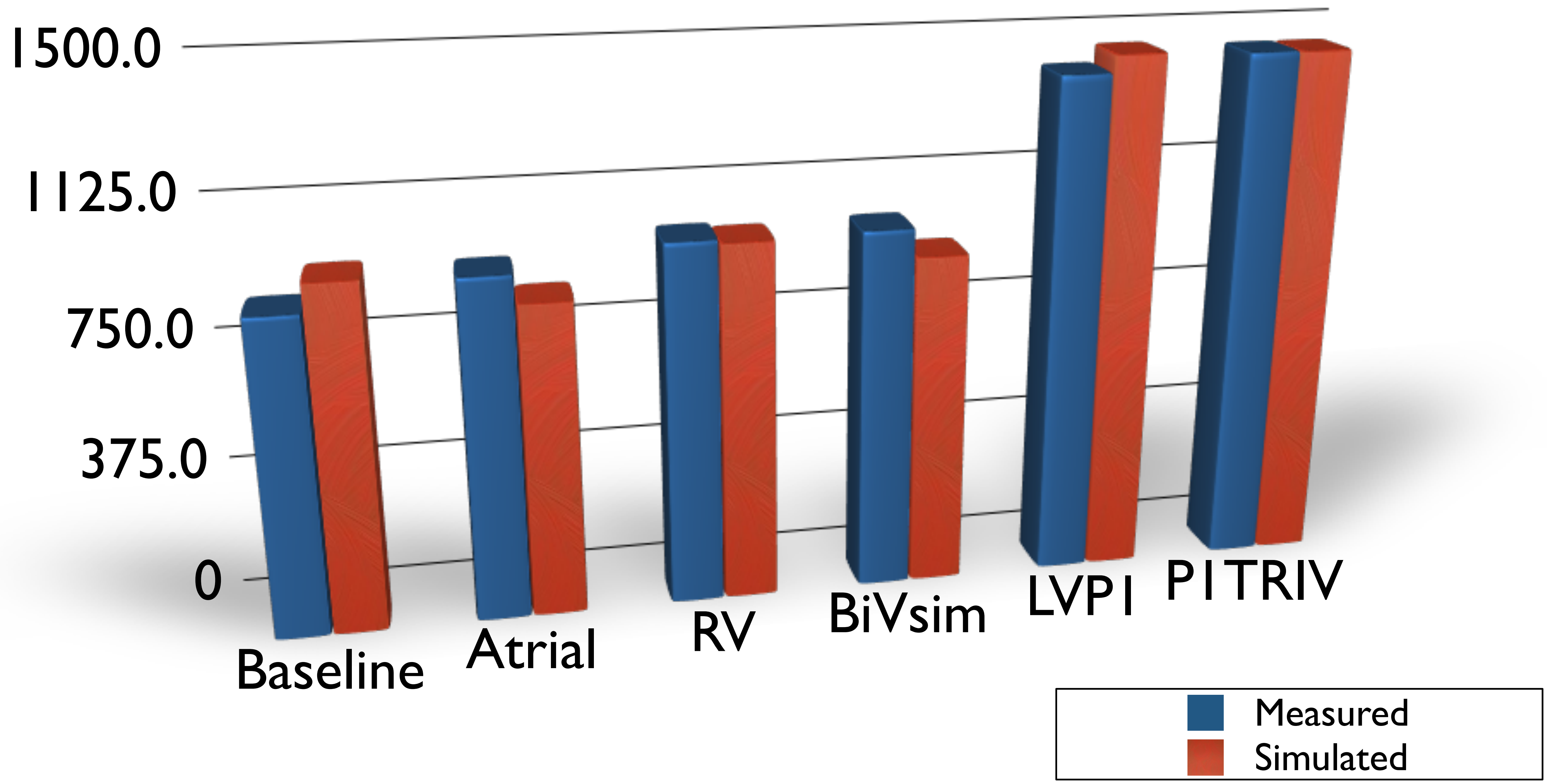
Optimization of CRT procedure [2]



P1triv

LV endo pacing

$$\max\left(\frac{dp}{dt}\right)\ (mmHg/s)$$



Estimation problem setup

Models (dynamical system)

$$\dot{X} = A(X, \theta, t)$$

Arising from:
solid / fluid mechanics, etc.

Equation types: PDEs, variational formulations (FEs), ODEs...

To be estimated:
$X(0)$ and $\theta \rightarrow X$

Typical sizes:
$X(0)$: 10^3 to 10^6 dofs
θ : 10 to 100 parameters

Measurements (images & signals)

$$Z = H(X) + \chi$$

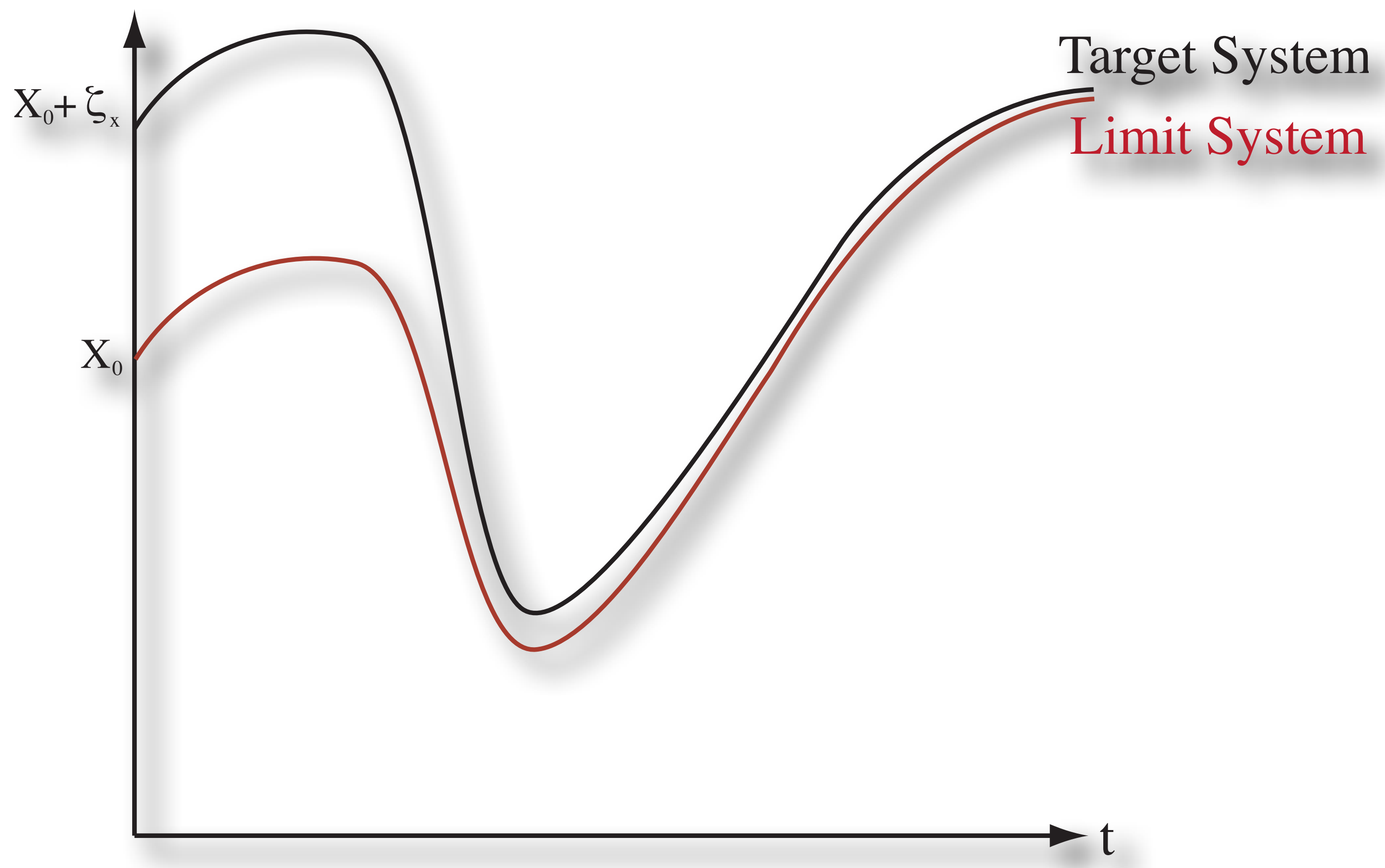
in raw (?) or processed form, e.g.:
✓ MRI or US with segmentation and/or optical flow
✓ Tagged MRI with extracted displacements and/or velocity...

Note:
some modeling may be involved in pre-processing, statistical modeling in noise.

Sequential data assimilation (filtering)

Basic principle:

$$\dot{X} = A(X), \quad \text{with } X(0) = X_0 + ?, \quad \text{but } Z = H(X) + \chi,$$
$$\dot{\hat{X}} = A(\hat{X}) + K(Z - H(\hat{X})), \quad \text{with } \hat{X}(0) = X_0,$$



Sequential data assimilation (filtering)

Basic principle:

$$\dot{X} = A(X), \quad \text{with } X(0) = X_0 + ?, \quad \text{but } Z = H(X) + \chi,$$
$$\dot{\hat{X}} = A(\hat{X}) + K(Z - H(\hat{X})), \quad \text{with } \hat{X}(0) = X_0,$$

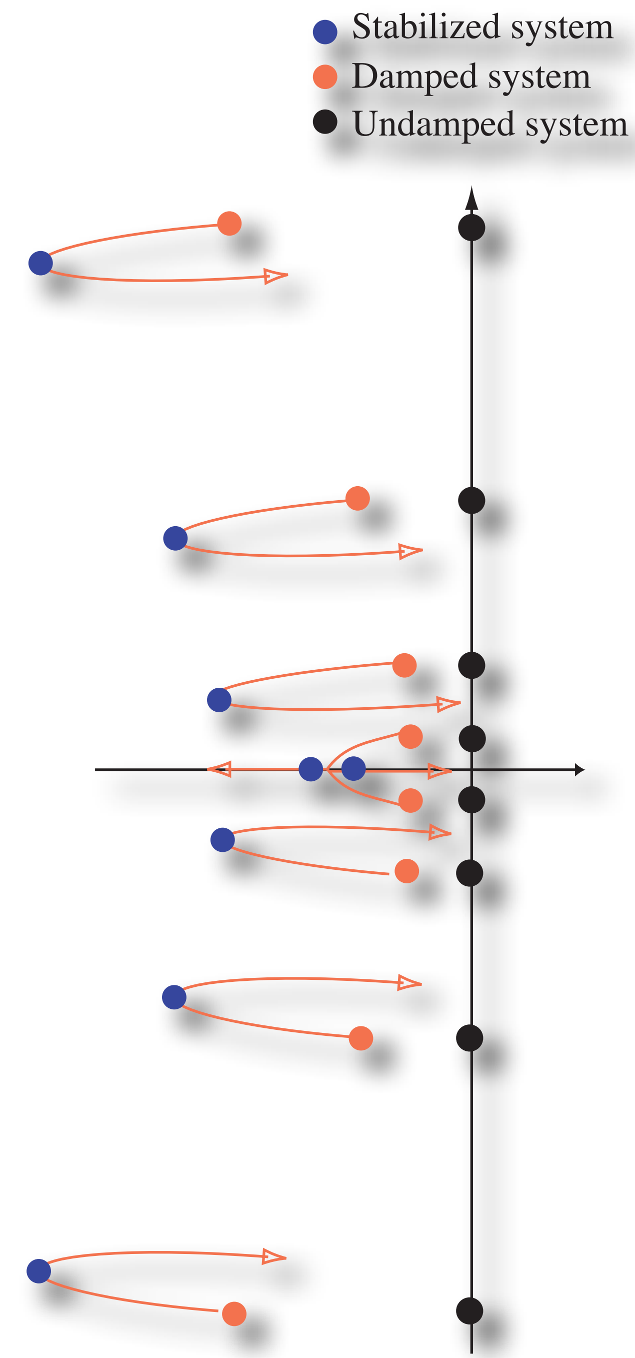
✓ **Kalman** equations for **optimal** filter (in linear case)

$$\begin{cases} \dot{\hat{X}}(t) = A\hat{X} + PH^T W^{-1}(Z - H\hat{X}) \\ \dot{P} - PA^T - AP + PH^T W^{-1} HP = 0 \\ P(0) = P_0 \\ \hat{X}(0) = X_0 \end{cases}$$

✓ In non linear case, you must solve a HJB equation, or an approximate "Extended Kalman Filter"

✓ **Major drawback:** computation of Kalman filter is untractable in practice (full covariance)

Effective state estimators



<u>Luenberger observers:</u>

Design K filter "easy to compute" and effective, i.e. fast $\hat{X} \to X$ convergence
When A and H *linear*, error $\tilde{X} = X - \hat{X}$ gives

$$\dot{\tilde{X}} = (A - KH)\tilde{X} - K\chi,$$

hence effective *feedback stabilization* provides adequate filter

Advantages:

✓ Many dissipative feedbacks known for energy-preserving systems (or other invariants)
✓ *Physics-based* operators easy to implement in simulation software
✓ Reasonable cost (sparse operators)
✓ *Robustness* much preferable to "optimality"
✓ Here, the control is applied on a *virtual system*: more possibilities!

Joint state-parameter estimation

<u>Aim:</u> estimate (ζ_X, θ) in $\dot{X} = AX + B\theta + R$, with $X(0) = X_0 + \zeta_X$

Classical path: introduce *augmented* dynamical system

$$\begin{cases} \dot{X} = AX + B\theta + R, & \text{with } X(0) = X_0 + \zeta_X \\ \dot{\theta} = 0, & \text{with } \theta(0) = \theta_0 + \zeta_\theta \end{cases}$$

✓ Kalman filter applied to augmented system

$$\begin{cases} \dot{\hat{X}} = A\hat{X} + B\theta + R + K^X_{Kal}(Z - H\hat{X}), & \text{with } \hat{X}(0) = X_0 \\ \dot{\hat{\theta}} = K^\theta_{Kal}(Z - H\hat{X}), & \text{with } \hat{\theta}(0) = \theta_0 \end{cases}$$

✓ Kalman untractable, so here we wish to substitute K_{stab} for K^X_{Kal}

✓ No physics-based filter available for *virtual* parameter dynamics

<u>Key idea:</u> *two-stage estimation* (optimal *reduced-order* for param.)

$$\begin{cases} \dot{\hat{X}} = A\hat{X} + B\theta + R + K_{stab}(Z - H\hat{X}) + \text{``}\frac{\partial \bar{X}}{\partial \theta}\text{''}\dot{\hat{\theta}}, & \text{with } \hat{X}(0) = X_0 \\ \dot{\hat{\theta}} = K^{\theta\flat}_{Kal}(Z - H\hat{X}), & \text{with } \hat{\theta}(0) = \theta_0 \end{cases}$$

Joint estimation bibliography

✓ Moireau, Chapelle & Le Tallec: Joint state and parameter estimation for distributed mechanical systems. *CMAME*, 2008

✓ Chapelle, Moireau & Le Tallec: Robust filtering for joint state parameter estimation for distributed mechanical systems. *DCDS/A*, 2009

✓ Moireau & Chapelle: Reduced-order Unscented Kalman Filtering with application to parameter identification in large-dimensional systems. *ESAIM: COCV*, 2010

✓ Moireau, Chapelle & Le Tallec: Filtering for distributed mechanical systems using position measurements: perspectives in medical imaging. *Inverse Problems*, 2009

Infarct characterization (by estimation)

R. Chabiniok, P. Moireau, P.-F. Lesault, A. Rahmouni, J.-F. Deux and D. Chapelle

Estimation of tissue contractility from cardiac cine-MRI using a biomechanical heart model

Biomechanics and Modeling in Mechanobiology, 11(5):609-630, 2012

Protocol

Subject

Animal data obtained with a farm pig of 25kg (the study was approved by Institutional Animal Care and Use Committee of “Faculté de Créteil”)

Infarction protocol

Healthy heart at T0: Baseline

Infarct creation by a 2-hour occlusion of the LAD coronary artery by a balloon catheter

Follow-up of the animal 10 days (T0+10) and 38 days (T0+38) after the infarct creation

Data

Cine MRI, Late Enhancement (ground truth), Tagged MRI (optional), ECG

Objective of patient-specific modeling

Locate (compare with LE) and characterize the infarct tissue (contractility)

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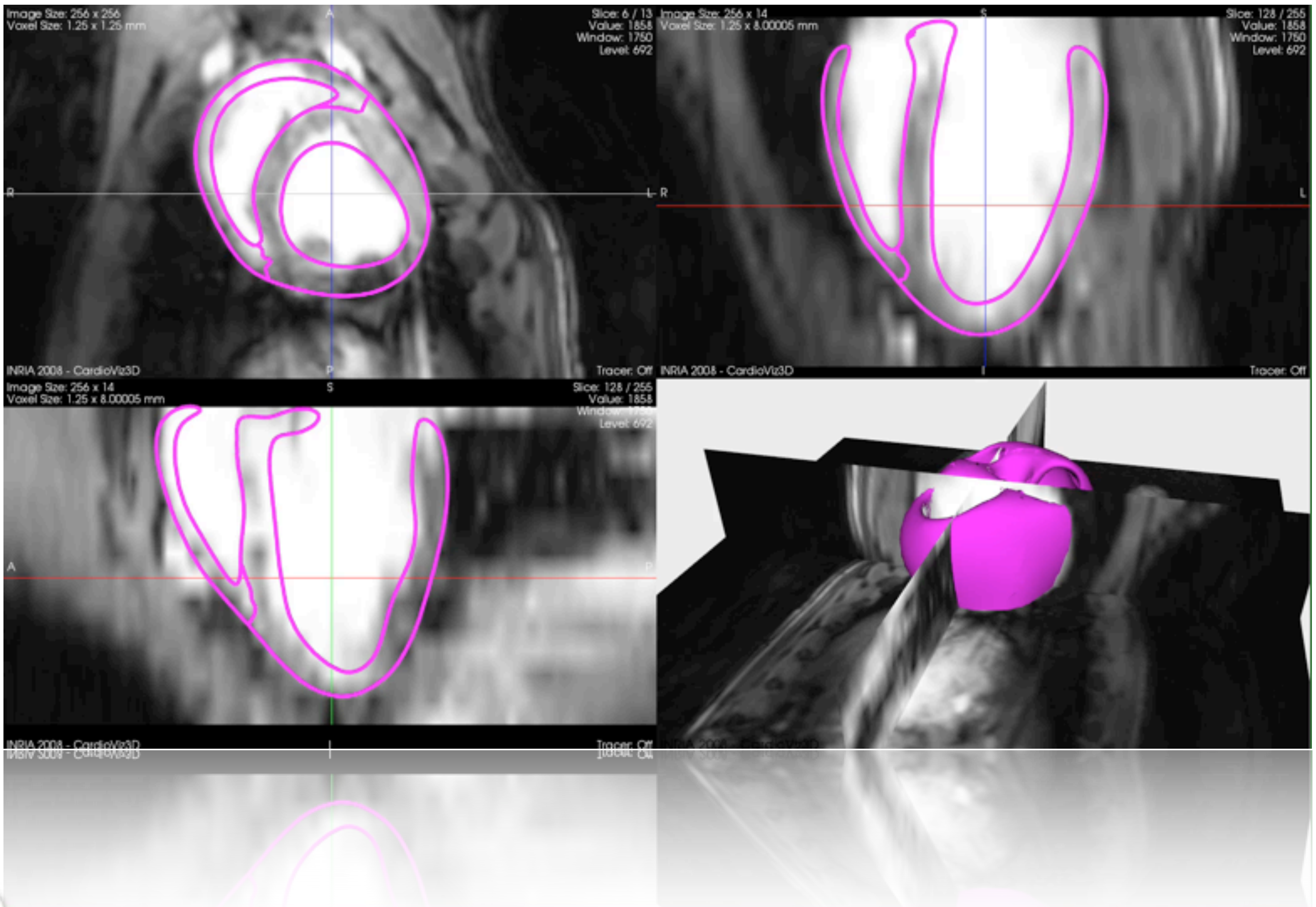
$$\begin{cases} \dot{k}_c = -(|u| + \alpha\,|\dot{e}_c|)k_c + n_0 k_0\,|u|_+ \\ \dot{\tau}_c = -(|u| + \alpha\,|\dot{e}_c|)\tau_c + \dot{e}_c k_c + n_0 \sigma_0\,|u|_+ \end{cases}$$

Model calibration for baseline (T0)



Baseline (T0) compared to T38

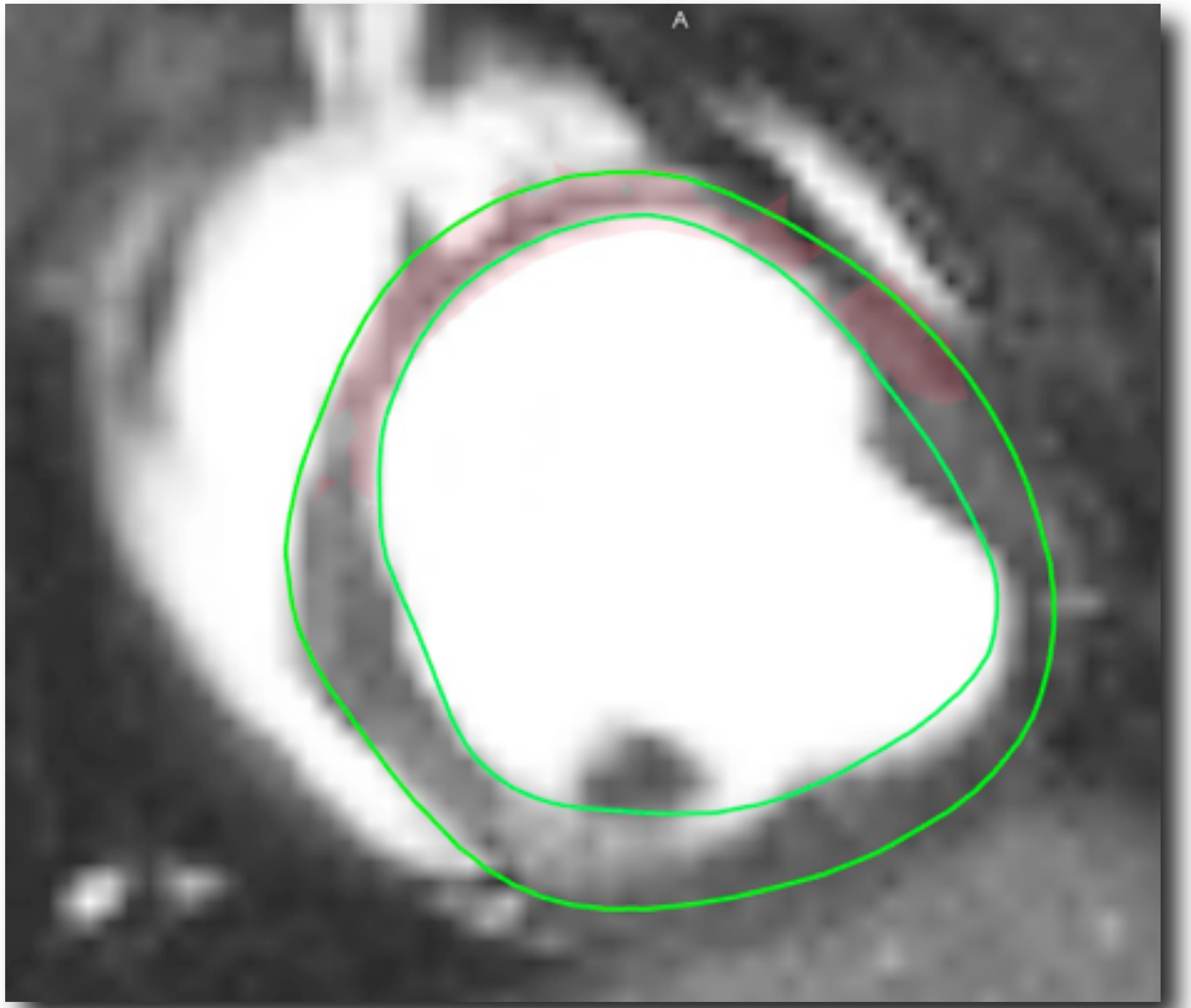


Image contours extraction

Model without infarct modeling

Baseline (T0) compared to T38

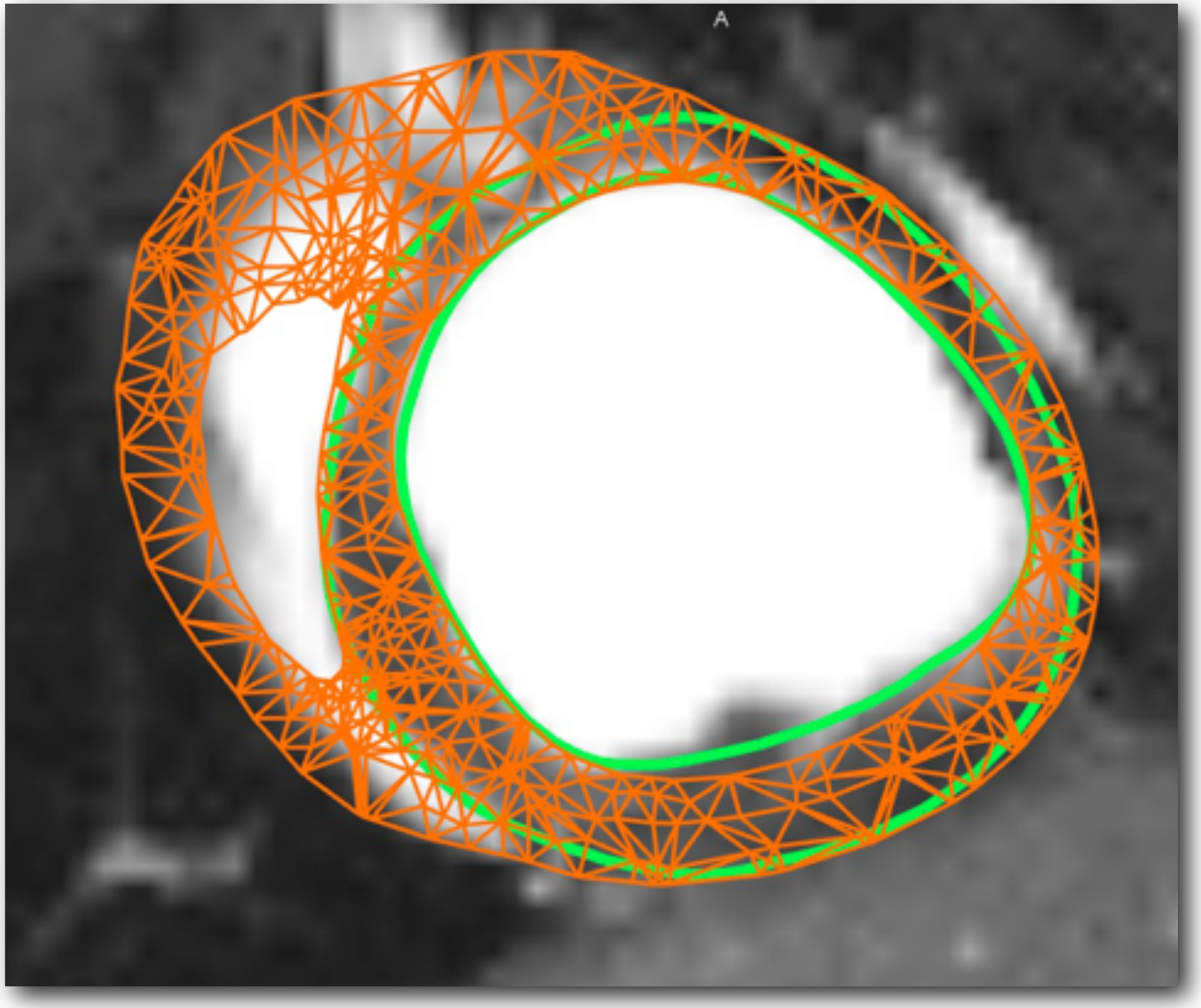
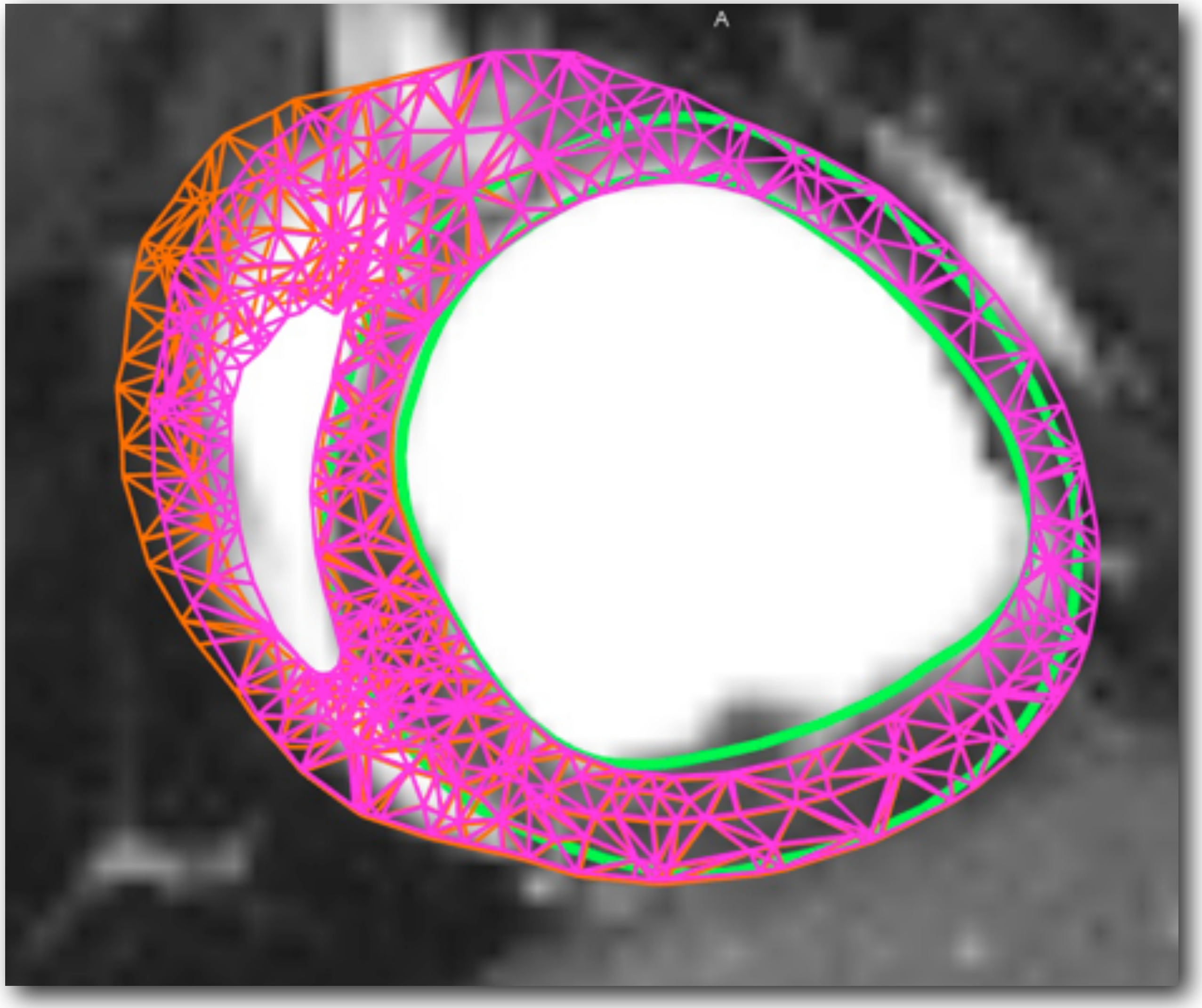


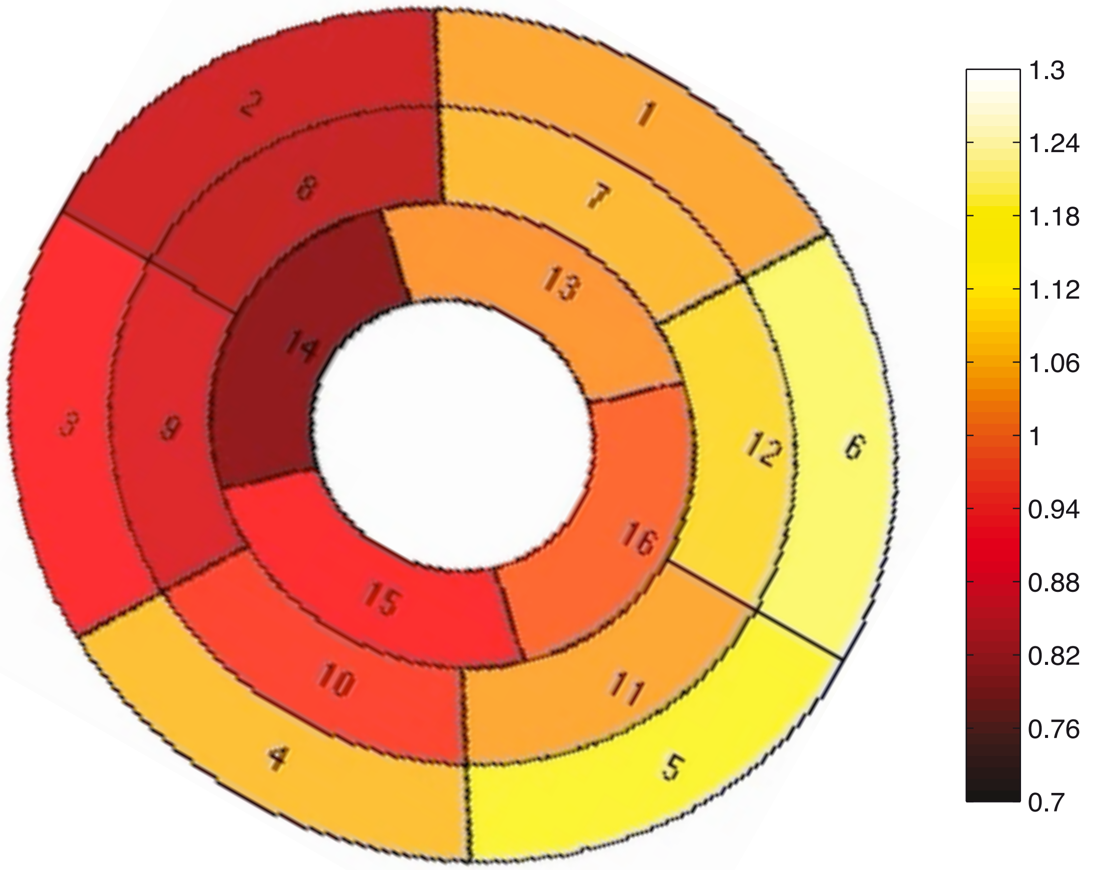
Image contours extraction

Model without infarct modeling

Estimation at work (actual cine-MR data)

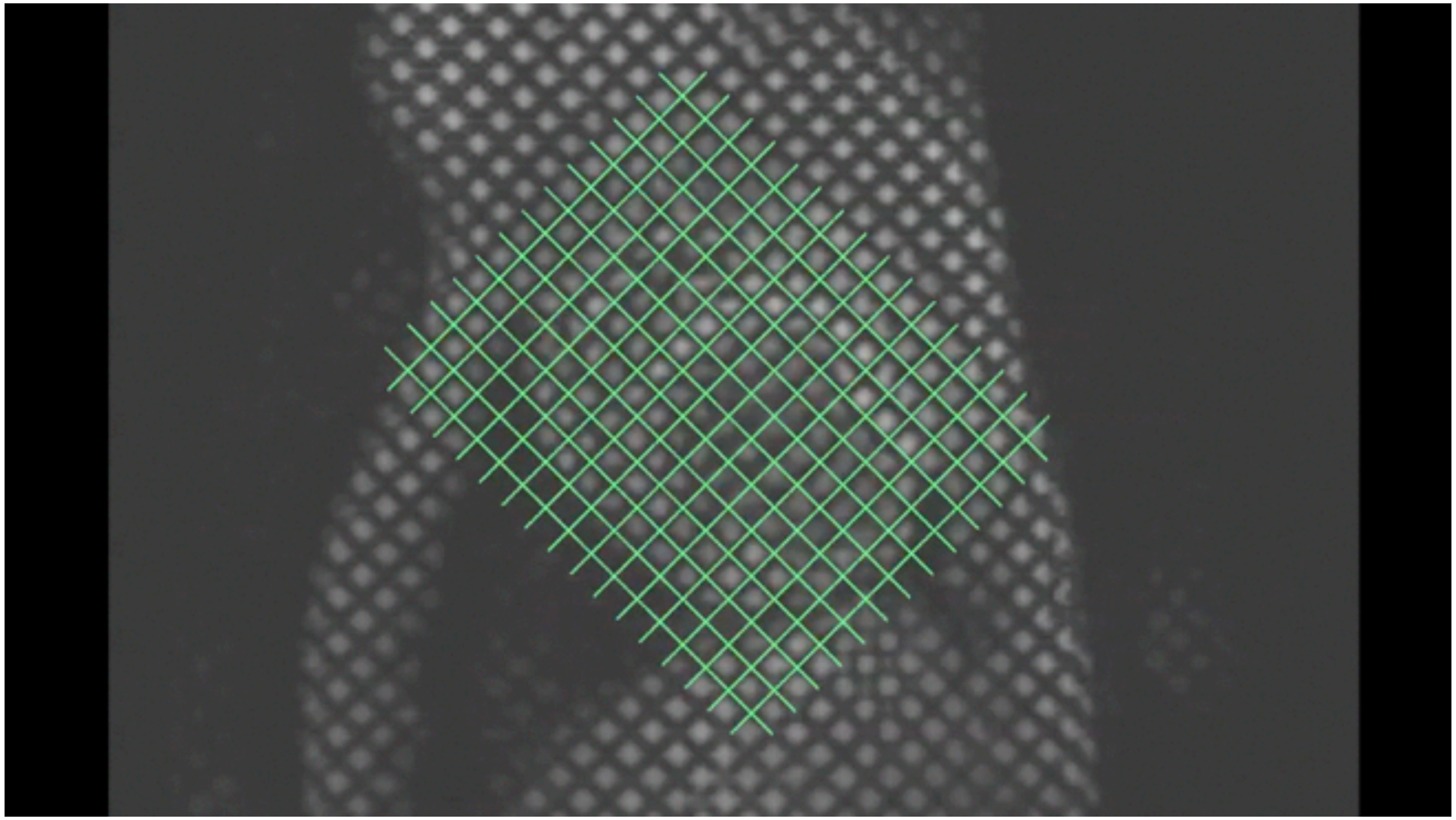


Estimator



Estimated contractility in AHA regions

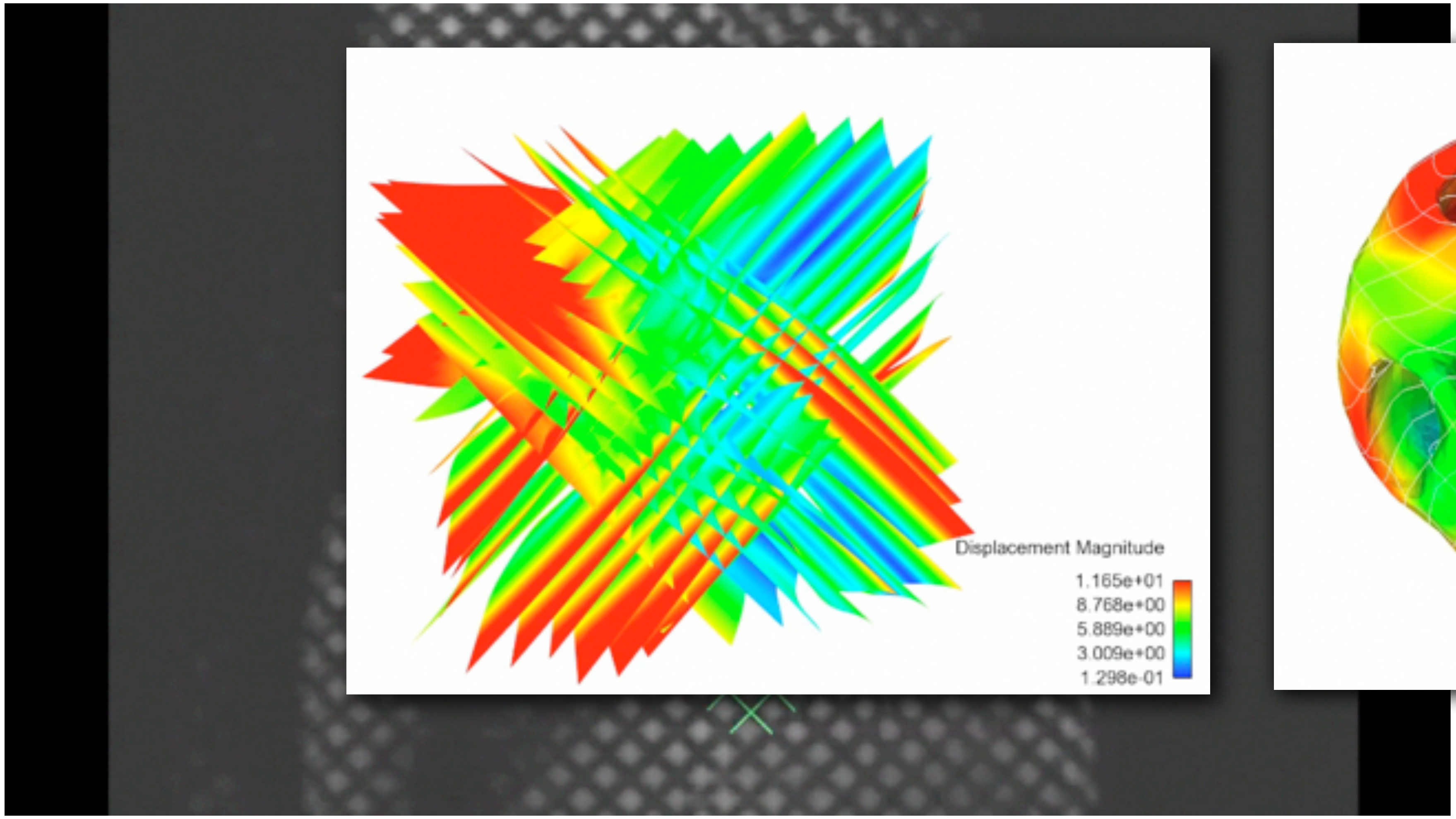
Enhanced estimation based on tagged-MR

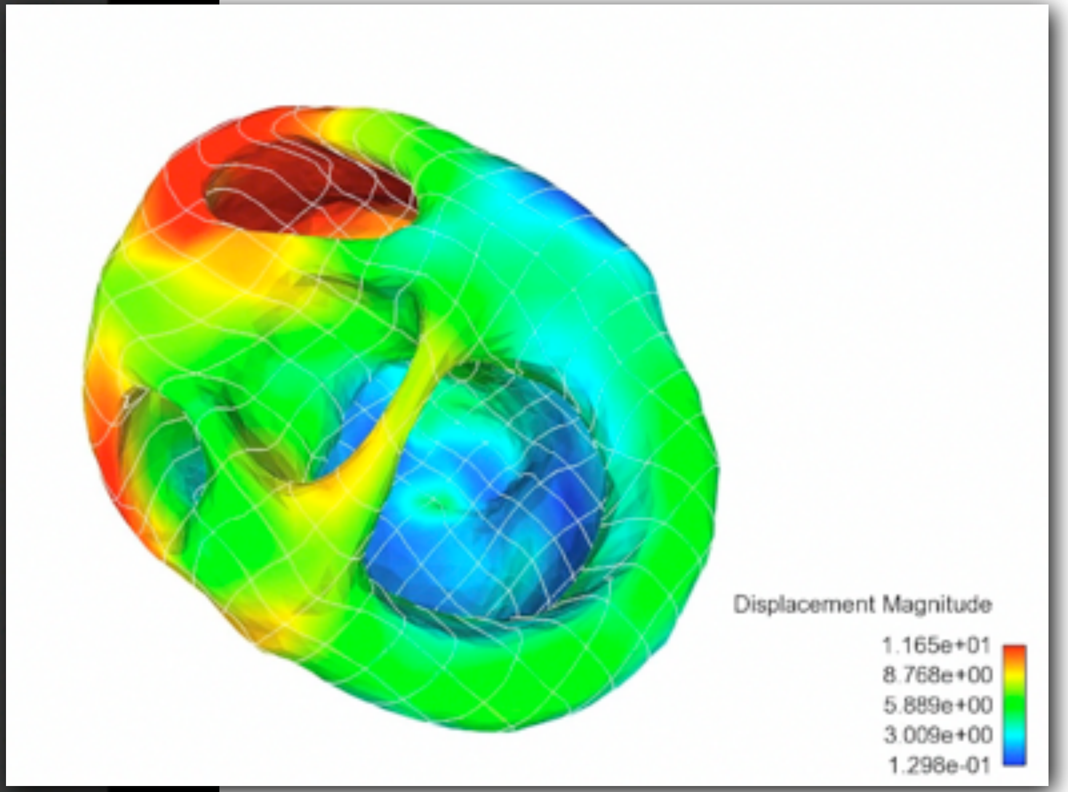


PhD A. Imperiale

Collaboration Creatis (INSA-Lyon)

Enhanced estimation based on tagged-MR

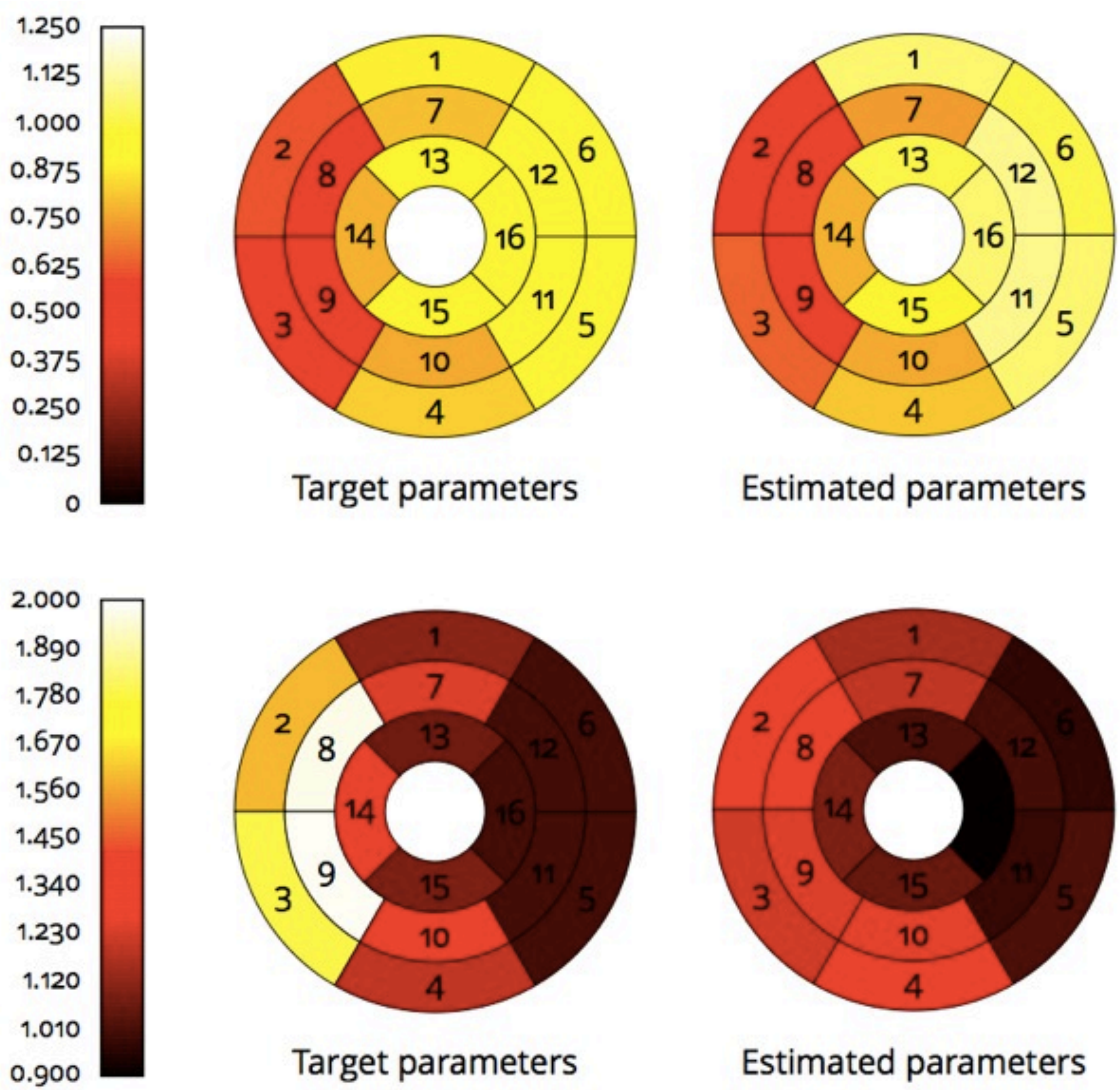




PhD A. Imperiale

Collaboration Creatis (INSA-Lyon)

Tagged-MR estimation results (synthetic)



Contractility

Stiffness

Concluding remarks

- Multiscale modeling of the myocardium based on physiological considerations at all scales (starting with nano-scale)
- Fundamental physical requirements (energy) satisfied throughout the scales, and associated consistent numerical procedures
  ➔ well-adapted to multi-physics coupling (e.g. perfusion and chemistry)
- Substantial experimental and clinical validation achieved
- *Inverse problems* handled via novel effective data assimilation methods
  ➔ provide key information for *diagnosis* and allow *patient-specific modeling*

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