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Multiscale-in-time modeling of myocardial growth & disease progression

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A multiscale-in-time framework for simulation of maladaptive growth and remodeling (G&R) in the heart is presented. G&R is assumed to be driven by a deviation of mechanical stress or strain with respect to a homeostatic baseline state. Since ventricular loads vary on a much shorter time scale than processes of G&R occur, a staggered solution scheme discriminating between "small scale" heart beat dynamics and "large scale" G&R is chosen.

On the small scale, a coupled monolithic problem of 3D finite strain elasticity for the heart and 0D lumped-parameter flow is solved, using a closed-loop systemic and pulmonary circulation model to account for physiologic loading conditions on the myocardium. After computing a homeostatic reference state, the system is perturbed by introducing a cardiovascular disease (ie regurgitation of the mitral valve or aortic stenosis), eventually leading to a state of chronic volume or pressure overload for the ventricle.

On the large scale, the spatial field of fiber overstretch or tissue overstress is then imposed, and a pure solid mechanics problem of strain- or stress-mediated volumetric growth is solved together with a remodeling law that allows for change in elastic material parameters depending on the amount of growth.

Small and large time scales are mutually revisited until no further volume change occurs. Physiologically meaningful changes in ventricular pressure-volume relationship are obtained for ventricular volume and pressure overload and comply with general observations.

Nonlinear deformation-dependent growth requires local Newton updates at integration point level and is implemented in FEniCS by expressing growth residual and increments as forms at quadrature points. Inner virtual work is expressed explicitly with help of the fourth-order material tangent operator to account for all tangent contributions arising from the nonlinear G&R model.

This talk was awarded a prize: Best talk by a postdoc (runner up).

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Multiscale-in-Time Modeling of Myocardial Growth & Disease Progression

FEniCS conference

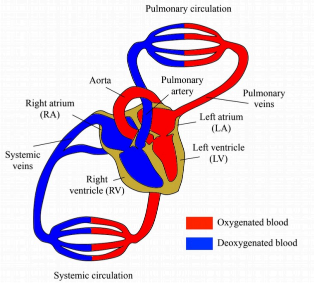
Marc Hirschvogel
King's College London

22 Mar 2021

Outline

1.1 Heart Models and the Cardiac Cycle

- **Cardiovascular disease entities** most prevalent in industrialized world [Dimmeler 2011, Luepker 2011]

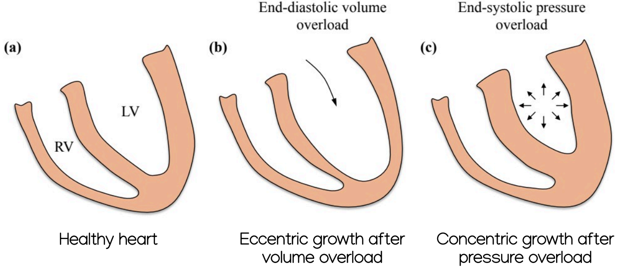


- Diseases of the myocardium (heart muscle) are multifactorial and yet to be fully understood
  - ➢ Altered **mechanical loads**
  - ➢ **Neurohormonal changes**

- Heart may undergo **adaptations in structure and shape** if loading conditions are chronically above a certain physiological level, referred to as **Growth and Remodeling** (G & R) [Rossi et al. 1991]

- **Volume overload** (Fig. (b)):
  - ➢ Heart adapts by **eccentric growth** (systolic heart failure)

- **Pressure overload** (Fig. (c)):
  - ➢ Heart adapts by **concentric growth** (diastolic heart failure)



Outline

2.1 Patient-specific Geometric 3D-0D Heart Model

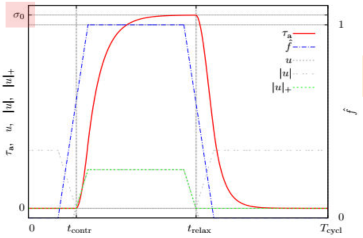
- **Heart muscle:** Nonlinear nearly-incompressible hyperelastic, anisotropic solid [Guccione et al. 1991]

$$\boldsymbol{S} = 2\frac{\partial \Psi}{\partial \boldsymbol{C}} + \tau_{\mathrm{a}}(t)\boldsymbol{f}_0 \otimes \boldsymbol{f}_0 \qquad \Psi = \frac{C_0}{2}e^{Q} + \frac{\kappa}{2}(J-1)^2 \qquad Q = b_f E_{ff}^2 + b_t\left(E_{ss}^2 + E_{nn}^2 + 2E_{sn}^2\right) + b_{fs}\left(2E_{fs}^2 + 2E_{fn}^2\right)$$

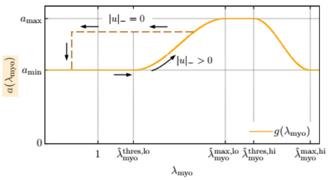
- **Contraction:** Time- and fiber stretch-dependent active stress law [Bestel et al. 2001]

$$\dot{\tau}_{\mathrm{a}} = -|u|\tau_{\mathrm{a}} + a\,\sigma_0|u|_+ \qquad \dot{a}(\lambda_{\mathrm{myo}}) = \dot{g}(\lambda_{\mathrm{myo}})\,\mathbb{I}_{|u|_->0}$$

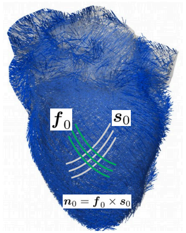
$$u = \hat{f}(t)\cdot\alpha_{\max} + (1-\hat{f}(t))\cdot\alpha_{\min}$$



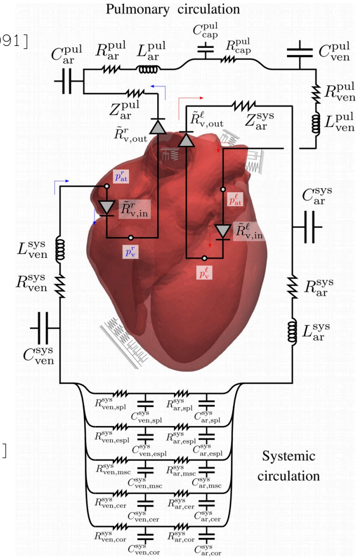
Frank-Starling mechanism [Solaro 2007]



$$\lambda_{\mathrm{myo}} = \sqrt{\boldsymbol{f}_0 \cdot \boldsymbol{C}\boldsymbol{f}_0}$$



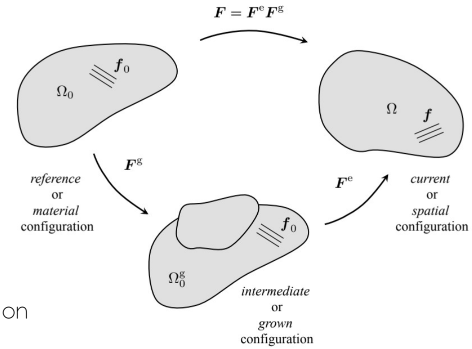
Rule-based fiber directions
Transmural variation (-60°, 60°)
[Doste et al. 2019, Bayer et al. 2012]



- **Circulatory system** is modeled with a lumped-parameter 0D flow model (compliances, resistances inertances) [Hirschvogel et al. 2017, Trenhago et al. 2016, Ursino and Magosso 2000a,b]

Free heart STL geometry from https://www.icmm.ru/tomogram-to-fem

2.2 Continuum Mechanical Modeling of G&R



- G&R computed in a **kinematic growth framework** with multiplicative split of deformation gradient into elastic and inelastic (growth) part
  [Lee et al. 1969, Rodriguez et al. 1994]

$$\boldsymbol{F} = \boldsymbol{F}^{\mathrm{e}}\boldsymbol{F}^{\mathrm{g}}$$

- Growth deformation gradient is function of growth stretch ϑ and possibly of preferred directions $\boldsymbol{f}_0$:

$$\boldsymbol{F}^{\mathrm{g}} = f(\vartheta, \boldsymbol{f}_0, ...)$$

- Growth stretch usually is governed by an evolution equation and can depend on mechanical or other stimuli:

$$\dot{\vartheta} = f(\vartheta, \boldsymbol{C}, \boldsymbol{S}, \boldsymbol{f}_0, ...)$$

- **Remodeling** is taken into account by additively decomposing the stress response into a part governing the reference and one describing the remodeled material (similar to [Thon et al. 2018]):

$$\boldsymbol{S} = \phi(\vartheta)\boldsymbol{S}_{(\mathrm{remod})} + (1-\phi(\vartheta))\boldsymbol{S}_{(\mathrm{base})}$$

$\phi(\vartheta)$: Fraction of grown material

Outline

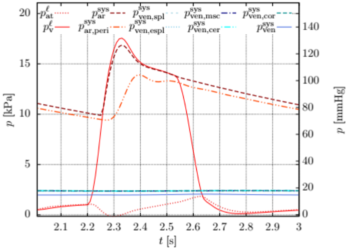
3.1 3D-0D Coupled Elastodynamics

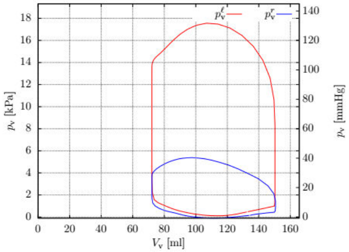
- **Nonlinear elastodynamics** using Generalized-alpha time integration [Chung and Hulbert 1993]
- Strongly coupled 3D-0D monolithic solution of **solid mechanics** and **lumped flow models** [Hirschvogel et al. 2017]
- Use of direct solver (SuperLU) or block-pre-conditioned GMRES [Elman et al. 2008]

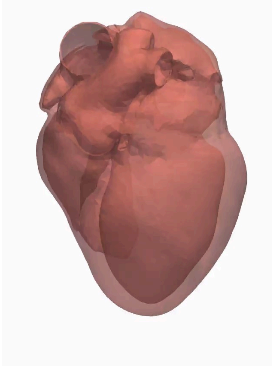
$$\begin{bmatrix} \mathbf{K}^{uu} & \mathbf{K}^{us} \\ \mathbf{K}^{su} & \mathbf{K}^{ss} \end{bmatrix}_{n+1}^{i} \begin{bmatrix} \Delta\mathbf{d} \\ \Delta\mathbf{s} \end{bmatrix}_{n+1}^{i+1} = - \begin{bmatrix} \mathbf{r}^{u} \\ \mathbf{r}^{s} \end{bmatrix}_{n+1}^{i}$$

- ~90'000 linear displacement-based tetrahedral elements, ~60'000 unknowns

➢ Example healthy heart cycle simulation:







Open-source Python FEniCS-based solver for cardiac mechanics
https://github.com/marchirschvogel/ambit

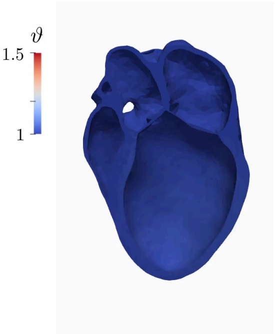
3.2 Inelastic Deformation-Dependent Growth & Remodeling

- Fiber stretch-driven **anisotropic growth** in fiber direction

$$\boldsymbol{F}^{\mathrm{g}} = \mathbf{1} + (\vartheta - 1)\boldsymbol{f}_0 \otimes \boldsymbol{f}_0 \qquad \dot{\vartheta} = k(\vartheta)\left(\lambda_{\mathrm{myo}}^{\mathrm{e}} - \hat{\lambda}_{\mathrm{myo}}^{\mathrm{crit}}\right)$$

$$k(\vartheta) = \begin{cases} \frac{1}{\tau}\left(\frac{\vartheta_{\max}-\vartheta}{\vartheta_{\max}-\vartheta_{\min}}\right)^{\gamma}, & \lambda_{\mathrm{myo}}^{\mathrm{e}} \geq \hat{\lambda}_{\mathrm{myo}}^{\mathrm{crit}}, \\ \frac{1}{\tau_{\mathrm{rev}}}\left(\frac{\vartheta-\vartheta_{\min}}{\vartheta_{\max}-\vartheta_{\min}}\right)^{\gamma_{\mathrm{rev}}}, & \lambda_{\mathrm{myo}}^{\mathrm{e}} < \hat{\lambda}_{\mathrm{myo}}^{\mathrm{crit}}, \end{cases}$$

$$\lambda_{\mathrm{myo}}^{\mathrm{e}} = \frac{1}{\vartheta}\lambda_{\mathrm{myo}} = \frac{1}{\vartheta}\sqrt{\boldsymbol{f}_0 \cdot \boldsymbol{C}\boldsymbol{f}_0}$$



- Stress in inner virtual work depending on deformation and internal variable ϑ, which is deformation-dependent itself in a nonlinear way (needs local Newton to solve)

$$\delta\mathcal{W}_{\mathrm{int}} = \int\limits_{\Omega_0} \boldsymbol{S}(\boldsymbol{C}(\boldsymbol{u}), \vartheta(\boldsymbol{C}(\boldsymbol{u}))) : \frac{1}{2}\delta\boldsymbol{C}\,\mathrm{d}V$$

- Full material tangent operator reads: $\mathbb{C} = 2\frac{\partial \boldsymbol{S}}{\partial \boldsymbol{C}} + 2\left(\frac{\partial \boldsymbol{S}}{\partial \boldsymbol{F}^{\mathrm{g}}} : \frac{\partial \boldsymbol{F}^{\mathrm{g}}}{\partial \vartheta}\right) \otimes \frac{\partial \vartheta}{\partial \boldsymbol{C}}$

  - ➢ FEniCS UFL can only take care of first term, since no analytic expression $\vartheta(\boldsymbol{C}) = \ldots$ possible

  - ➢ Express virtual work linearization directly as form without using “derivative” and add second term manually to $\mathbb{C}$

$$D_{\Delta\boldsymbol{u}}\delta\mathcal{W}_{\mathrm{int}} = \int\limits_{\Omega_0} \left(\mathrm{Grad}\delta\boldsymbol{u} : \mathrm{Grad}\Delta\boldsymbol{u}\,\boldsymbol{S} + \boldsymbol{F}^{\mathrm{T}}\mathrm{Grad}\delta\boldsymbol{u} : \mathbb{C} : \boldsymbol{F}^{\mathrm{T}}\mathrm{Grad}\Delta\boldsymbol{u}\right)\mathrm{d}V$$

$$\frac{\partial \boldsymbol{S}}{\partial \boldsymbol{F}^{\mathrm{g}}} = -\left(\boldsymbol{F}^{\mathrm{g}^{-1}} \overline{\otimes} \boldsymbol{S} + \boldsymbol{S} \underline{\otimes} \boldsymbol{F}^{\mathrm{g}^{-1}}\right) - \left(\boldsymbol{F}^{\mathrm{g}^{-1}} \overline{\otimes} \boldsymbol{F}^{\mathrm{g}^{-1}}\right) : \frac{1}{2}\check{\mathbb{C}}^{\mathrm{e}} : \left(\boldsymbol{F}^{\mathrm{g}^{-\mathrm{T}}} \overline{\otimes} \boldsymbol{C}^{\mathrm{e}} + \boldsymbol{C}^{\mathrm{e}} \underline{\otimes} \boldsymbol{F}^{\mathrm{g}^{-\mathrm{T}}}\right)$$

Elastic part of $2\frac{\partial \boldsymbol{S}}{\partial \boldsymbol{C}}$

  - ➢ Depending on growth law, can render excessive FFC-X compilation times! (between 5 and 30 minutes!)

3.3 Multiscale-in-Time Analysis: Volume Overload and Eccentric Growth in the Heart

- Homeostatic healthy heart beat computation
- Acute disease state (e.g. mitral valve regurgitation) computation, evaluation of **end-diastolic volume overload**
- **Set state "large time scale":**

$$\boldsymbol{u}^{(\mathcal{L})} \leftarrow \boldsymbol{u}(t_{\mathrm{ed}})^{(\mathcal{S})} \qquad \hat{p}_c^{i,(\mathcal{L})} \leftarrow p_c^{i,(\mathcal{S})}(t_{\mathrm{ed}}) \qquad \hat{\tau}_{\mathrm{a}}^{(\mathcal{L})} \leftarrow \tau_{\mathrm{a}}(t_{\mathrm{ed}})^{(\mathcal{S})}$$

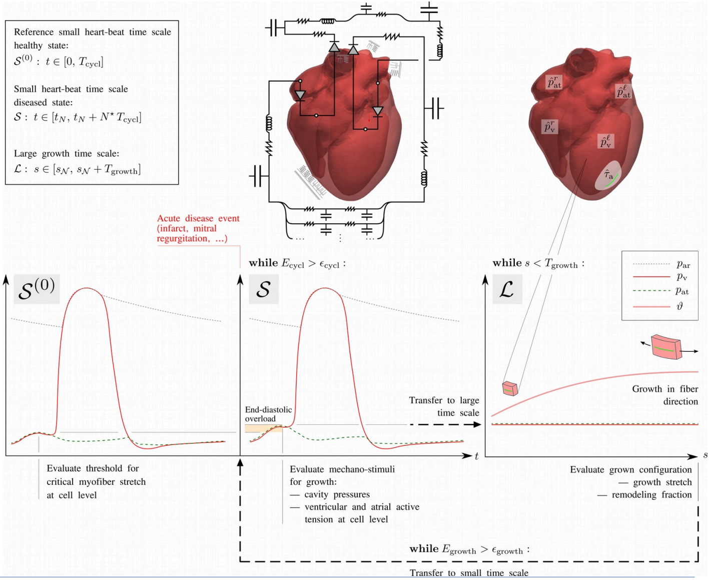
  ➢ Quasi-static growth computation

- **Set state "small time scale":**

$$\hat{\vartheta}^{(\mathcal{S})} \leftarrow \vartheta^{(\mathcal{L})} \qquad \boldsymbol{u}^{(\mathcal{S})} \leftarrow \boldsymbol{u}^{(\mathcal{L})} - \boldsymbol{u}(t_{\mathrm{ed}})^{(\mathcal{S})}$$

  ➢ Compute new homeostatic heat beat state

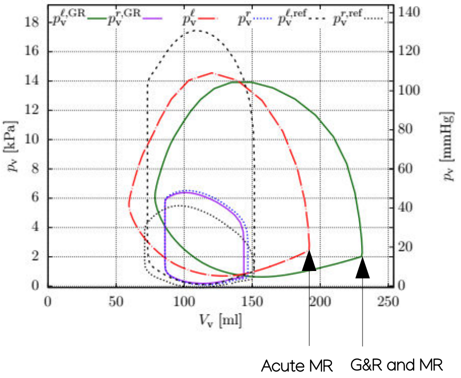
- Mutually revisit small and large scale until growth falls below a certain tolerance

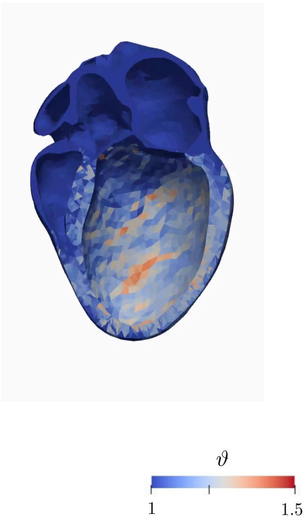


Outline

4.1 Eccentric Growth in the Heart: Results for Mitral Regurgitation (MR)

- G&R after mitral valve regurgitation
  - ➢ Loss of isovolumetric contraction phases
  - ➢ **Right-shift** of pressure-volume relationship
  - ➢ LV wall thinning
  - **"Heart failure with reduced ejection fraction"**





- **Remodeling:** Assumption that only active material is reduced with growth (cardio-myocytes are elongated, degradation and disruption of fibrillar collagen, impaired contractility [Aurigemma et al. 2006]):

$$\boldsymbol{S}_{(\mathrm{remod})} = 2\frac{\partial \Psi}{\partial \boldsymbol{C}}$$

Outline

5 Summary & Outlook

- Multiphysics and multiscale approach to cardiac growth and remodeling using FeniCS-X
  - ➢ 3D-0D coupled nonlinear **elastodynamics** and **reduced-dimensional flow**
  - ➢ **Inelastic deformation-dependent growth** solved at integration point level
- Physiological results and growth patterns, but ...
  - **Need of fine-tuning to match experimental data**
- Need for **higher-order spatial approximation** to avoid spurious effects of low-order finite elements, but ...
  - ➢ Missing Quadrature function spaces in FEniCS-X! For linear elements with one integration point (CG1), growth material is specified as discontinuous DG0 function pace
  - ➢ **No quadratic convergence for growth material living on DG1 space for higher-order mesh (CG2)**
- Need for strategies of reducing FFC-X compiler times for complex constitutive UFL expressions

Thank you for your attention!

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