computational modeling of eccentric and concentric cardiac growth through sarcomerogenesis

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http://biomechanics.stanford.edu
heart disease

- primary cause of death in industrialized nations
- affects 80 mio americans
- damaged cardiac tissue does not self regenerate

forms of cardiac growth

- case I - cardiac dilation
  strain driven eccentric growth
- case II - cardiac wall thickening
  stress driven concentric growth
organ level - human heart and its characteristic microstructure

Figure 1. Normal healthy heart, courtesy of Chengpei Xu (left). Microstructural architecture of the heart (right). The orthogonal unit vectors $f_0$ and $s_0$ designate the muscle fiber direction and the sheet plane vector in the undeformed configuration. The orthogonal vector $n_0$ completes the local coordinate system, where the constitutive response of the heart is typically viewed as orthotropic.

goktepe, abilez, kuhl [2010]

motivation - cardiac growth
Figure 1. Adult ventricular cardiomyocyte. The sarcomeric actin is labeled in green and the periodically spaced t-tubule system is marked in red, giving the cell its characteristic striated appearance. Healthy cardiomyocytes have a cylindrical shape with a diameter of 10-25µm and a length of 100µm, consisting of approximately 50 sarcomere units in series making up a myofibril and 50-100 myofibrils in parallel. Cardiac disease can be attributed to structural changes in the cardiomyocyte, either through eccentric growth in dilated cardiomyopathy or through concentric growth in hypertrophic cardiomyopathy.
Figure 2. Sarcomere units of human embryonic stem cell-derived cardiomyocyte. Sarcomeres are defined as the segment between two neighboring Z-lines, shown in red, which appear as dark lines under the transmission electron microscope. Healthy sarcomeres are 1.9-2.1µm long characterized through a parallel arrangement of thick filaments of myosin, displayed in grey, sliding along thin filaments of actin, labeled in green. Although cardiac cells are known to change length and thickness in response to mechanical loading, the individual sarcomeres maintain an optimal resting length.
how do local changes in cellular morphology and cytoskeletal architecture translate into global alterations in cardiac form and function?

how are these changes regulated by mechanical factors?
organ level - pathophysiology of maladaptive growth

Figure 2. Pathophysiology of maladaptive growth of the heart viewed in transverse heart sections, reprinted with permission from Robbins & Cotran. Compared with the normal heart (left), eccentric hypertrophy is associated with ventricular dilation in response to volume overload (center). Concentric hypertrophy is associated with ventricular wall thickening in response to pressure overload (right).
cellular level - pathophysiology of maladaptive growth

<table>
<thead>
<tr>
<th>healthy cardiomyocyte</th>
<th>eccentric hypertrophy</th>
<th>concentric hypertrophy</th>
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</thead>
<tbody>
<tr>
<td><img src="image1" alt="Healthy cardiomyocyte" /></td>
<td><img src="image2" alt="Eccentric hypertrophy" /></td>
<td><img src="image3" alt="Concentric hypertrophy" /></td>
</tr>
<tr>
<td>physiological loading</td>
<td>volume overload</td>
<td>pressure overload</td>
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<tr>
<td>$p, \lambda$</td>
<td>$\varnothing^| (\lambda)$</td>
<td>$\varnothing^\perp (p)$</td>
</tr>
<tr>
<td>healthy heart</td>
<td>ventricular dilation</td>
<td>wall thickening</td>
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</table>

**Figure 3.** Eccentric and concentric growth on the cellular and organ levels. Compared with the normal heart (left), volume-overload induced eccentric hypertrophy is associated with cell lengthening through the serial deposition of sarcomere units and manifests itself in ventricular dilation in response to volume-overload (center). Pressure-overload induced concentric hypertrophy is associated with cell thickening through the parallel deposition of sarcomere units and manifests itself in ventricular wall thickening in response to pressure-overload (right).
**Figure 3.** Controlled cardiomyocyte remodeling in vitro. Cardiomyocytes adapt their size, shape, and intracellular architecture when spatially confined in vitro through patterning on fibronectin islands at different aspect ratios (2:1, 3:1, 5:1, and 7:1). Isolated confocal slices display 2D morphology of myofibrils with respect to actin (top) and alpha-actinin (bottom). Although overall cardiomyocyte size changes, the individual sarcomere units remain at constant length.

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deisse, sheehy, parker [2009]
Figure 6. Generic biventricular heart model generated from two truncated ellipsoids, with heights of 70mm and 60mm, radii of 30mm and 51mm, and wall thicknesses of 12mm and 6mm, respectively. In the healthy heart, cardiomyocytes are assumed to be cylindrical, 100µm long with a diameter of 16.7µm. They consist of 50 serial sarcomere units in length and 91 parallel units per cross section, each of them 2µm long and 2µm in diameter. They are arranged helically around the long axis of the heart with a transmurally varying inclination of -55° in the epicardium, the outer wall, to +55° in the endocardium, the inner wall, measured with respect to the basal plane.

goktepe, abilez, parker, kuhl [2010], collaboration with dan ennis, dept radiology, UCLA
kinematics of finite growth

\[ F = F^e \cdot F^g \]

\[ B_0 \quad \Phi \quad B_t \]

concept of incompatible growth configuration


motivation - cardiac growth
case I - cardiac dilation

- chronic **enlargement** at constant wall thickness
- cardiac **mass increases 3x** to 1000 g
- cardiomyocyte number remains constant ~6 billion
- cardiomyocytes **lengthen 40%** at constant cell diameter
- sarcomere number increases **from ~50 to ~70** in series
- sarcomere length remains constant at 1.9-2.1μm

References: Eckblom, Hermansen [1968], Gerdes et al. [1992], Hunter, Chien [1999], Plum et al. [2000], Yoshida et al. [2010]
governing equations

- multiplicative decomposition
  \[ F = F^e \cdot F^g \quad \text{with} \quad F = \nabla x \varphi \]
- growth tensor
  \[ F^g = I + [\lambda^g - 1] \ f_0 \otimes f_0 \]
- evolution of eccentric growth multiplier
  serial sarcomere deposition rate
  \[ \dot{\lambda}^g = k^g(\lambda^g) \phi^g(\lambda^e) \quad \text{with} \quad k^g = \frac{1}{\tau} \left[ \frac{\lambda_{\text{max}} - \lambda^g}{\lambda_{\text{max}} - 1} \right]^\gamma \]
- growth criterion
  \[ \phi^g = \lambda^e - \lambda_{\text{crit}} = \frac{\lambda}{\lambda^g} - \lambda_{\text{crit}} \]

maximum serial sarcomere deposition \( \lambda_{\text{max}} \), sarcomere deposition time \( \tau \), deposition nonlinearity \( \gamma \), critical sarcomere stretch \( \lambda_{\text{crit}} \)

cardiac dilation - eccentric growth
algorithmic treatment

given $F$ and $\lambda_n^g$
initialize $\lambda^g \leftarrow \lambda_n^g$

local Newton iteration

check growth criterion $\phi^g = \lambda^e - \lambda^e_{\text{crit}} \geq 0$ ?

- calculate growth function $k^g = \frac{[(\lambda_{\text{max}}^g - \lambda^g)/(\lambda_{\text{max}}^g - 1)]^{su}}{\tau}$
- calculate residual $R = \lambda^g - \lambda_n^g - k^g \phi^g \Delta t$
- calculate tangent $K = \partial R / \partial \phi^g$

update growth stretch $\lambda^g \leftarrow \lambda^g - R / K$

check convergence $R \leq \text{tol}$ ?

- calculate growth tensor $F^{\text{eg}} = I + [\lambda^g - 1] f_0 \otimes f_0$
- calculate elastic tensor $F^{e} = F \cdot F^{\text{eg}}^{-1}$
- calculate elastic right Cauchy Green tensor $C^e = F^{et} \cdot F^e$
- calculate elastic second Piola Kirchhoff stress $S^e = 2 \partial \psi / \partial C^e$

- calculate second Piola Kirchhoff stress $S = F^{\text{eg}}^{-1} \cdot S^e \cdot F^{\text{eg}}$
- calculate Lagrangian moduli $L$

- push forward to Kirchhoff stress $\tau = F \cdot S \cdot F^t$
- push forward to Eulerian moduli $e = [F \otimes F] : L : [F^t \otimes F^t]$

Table 2. Algorithmic treatment of strain-driven transversely isotropic growth.
pathophysiology of cardiac dilation

Figure 8. Strain-driven eccentric growth, cardiac dilation, and increase in cavity size at constant wall thickness. The heart is usually enlarged, rounded, flabby, and heavy with a weight of up to three times its normal weight (left), reprinted with permission from Robbins and Cotran. Heart specimen from a patient with cardiac dilation who died in end-stage heart failure. The ventricles are significantly dilated while the wall thickness has remained unaltered, courtesy of Allen P. Burke.
Figure 10. Strain-driven eccentric growth. The eccentric growth multiplier gradually increases from 1.00 to 1.50 as the individual cardiomyocytes grow eccentrically. On the structural level, eccentric growth manifests itself in a progressive dilation of the left ventricle accompanied by a significant increase in cardiac mass, while the thickness of the ventricular wall remains virtually unchanged.
**in vivo model of sarcomerogenesis**

- **14% dilation** due to volume overload
- dilation by **cardiomyocyte elongation**
- elongation by **serial sarcomere deposition**
- sarcomere number increases **linearly** from 62 to 85
- sarcomere deposition **rate is linear** in weeks 1 to 4 decays smoothly to **saturation** at week 26

Figure 7. Strain-driven eccentric growth. Overall, eccentric growth is clearly heterogeneous with a transmural variation in serial sarcomere deposition. Cardiomyocytes in the endocardium, the inner wall, reach their maximum length of 150µm through the serial deposition of 25 additional sarcomere units of 2µm each. Cardiomyocytes in the epicardium, the outer wall, reach a stable state at a length of 130µm through the serial deposition of 15 additional sarcomere units. Eccentric growth along the septum is almost identical to eccentric growth along the free wall initiating an overall shape change from elliptical to spherical.
case II - cardiac wall thickening

- chronic **wall thickening** at constant cardiac size
- wall thickness **increases from 1cm to 3cm**
- cardiomyocyte number remains constant ~6 billion
- cardiomyocyte diameter **increases from 15um to 40um**
- sarcomere number **increases in parallel**
- sarcomere length remains constant at 1.9-2.1um

opie [2003], maron, mc kenna [2003], kumar, abbas, fausto [2005]
governing equations

- multiplicative decomposition
  \[ F = F^e \cdot F^g \] with \( F = \nabla x \varphi \)

- growth tensor
  \[ F^g = \mathbf{I} + [\dot{\vartheta}^g - 1] \mathbf{s}_0 \otimes \mathbf{s}_0 \]

- evolution of concentric growth multiplier
  parallel sarcomere deposition rate
  \[ \dot{\vartheta}^g = k^g(\vartheta^g) \phi^g(M^e) \quad \text{with} \quad k^g(\vartheta^g) = \frac{1}{\tau} \left[ \frac{\vartheta_{\max} - \vartheta^g}{\vartheta_{\max} - 1} \right]^{\gamma} \]

- growth criterion
  \[ \phi^g = \text{tr}(M^e) - M^{e\text{crit}} \]

maximum parallel sarcomere deposition \( \vartheta_{\max} \), sarcomere deposition time \( \tau \), deposition nonlinearity \( \gamma \), critical pressure level \( M^{e\text{crit}} \)
given $F$ and $\vartheta^g_n$
initialize $\vartheta^g \leftarrow \vartheta^g_n$

<table>
<thead>
<tr>
<th>local Newton iteration</th>
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<tbody>
<tr>
<td>calculate growth tensor $F^g = I + [\vartheta^g - 1] s_0 \otimes s_0$</td>
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<td>calculate elastic tensor $F^e = F \cdot F^g^{-1}$</td>
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<tr>
<td>calculate second Piola Kirchhoff stress $S^e = 2 \partial \psi / \partial C^e$</td>
</tr>
</tbody>
</table>

| check growth criterion $\phi^g = \text{tr}(C^e \cdot S^e) - M^{e, \text{crit}} \geq 0$ |
| calculate growth function $k^g = [[\vartheta^{\text{max}} - \vartheta^g]/[\vartheta^{\text{max}} - 1]]^{\gamma} / \tau$ |
| calculate residual $R = \vartheta^g - \vartheta^g_n - k^g \phi^g \Delta t$ |
| calculate tangent $K = \partial R / \partial \vartheta^g$ |
| update growth multiplier $\vartheta^g \leftarrow \vartheta^g - R / K$ |

check convergence $R \leq \text{tol}$?

calculate second Piola Kirchhoff stress $S = F^g^{-1} \cdot S^e \cdot F^g$ |
| calculate Lagrangian moduli $L$ with (19), (20), (53), (60) |

push forward to Kirchhoff stress $\tau = F \cdot S \cdot F^t$ |
| push forward to Eulerian moduli $e = [F \otimes F] : L : [F^t \otimes F^t]$ |

**Table 3.** Algorithmic treatment of stress-driven transversely isotropic growth.
pathophysiology of cardiac wall thickening

Figure 10. Stress-driven concentric growth, cardiac wall thickening, and transmural muscle thickening at constant cardiac size, reprinted with permission from Robbins & Cotran. Left ventricular outflow obstruction has caused pressure-overload hypertrophy associated with a significant wall thickening (left). A pronounced septal hypertrophy has caused the significantly thickened septal muscle to bulge into the left ventricular outflow tract (right).
cardiac wall thickening through stress-driven concentric growth

Figure 10. Stress-driven concentric growth. The concentric growth multiplier gradually increases from 1.00 to 3.00 as the individual cardiomyocytes grow concentrically. On the structural level, concentric growth manifests itself in a progressive transmural wall thickening to withstand higher blood pressure levels while the overall size of the heart remains virtually unaffected. Since the septal wall receives structural support through the pressure in the right ventricle, wall thickening is slightly more pronounced in the free wall where the wall stresses are higher.
stress-driven concentric growth through sarcomerogenesis

**Figure 9.** Stress-driven concentric growth. Concentric growth is clearly heterogeneous with a transmural variation in parallel sarcomere deposition. Cardiomyocytes in the endocardium, the inner wall, reach a stable state at a thickness of 31.4 µm through the parallel deposition of 84 additional sarcomere units. Cardiomyocytes in the epicardium, the outer wall, reach their maximum thickness of 50 µm through the parallel deposition of 182 sarcomere units. Concentric growth at the free wall is slightly more pronounced than at the septum.
Figure. Stress-driven concentric growth, cardiac wall thickening, and transmural muscle thickening at constant cardiac size. Left ventricular wall thickening in response to systemic hypertension (left) from Kumar, Abbas, Fausto [2005]. Right ventricular wall thickening in response to pulmonary hypertension (right), from Padera.
cardiac mass increases more in systemic (+60%) than in pulmonary (+15%) hypertension

rausch, dam, goktepe, abilez, kuhl [2010]

cardiac wall thickening - concentric growth
systemic vs pulmonary hypertension

cavity volumes decrease significantly in both systemic and pulmonary hypertension

rausch, dam, goktepe, abilez, kuhl [2010]

cardiac wall thickening - concentric growth
systemic hypertension - LV wall thickening

cardiac wall thickening - concentric growth

rausch, dam, goktepe, abilez, kuhl [2010]
pulmonary hypertension - RV wall thickening

cardiac wall thickening - concentric growth
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nih simbios simgrowth, nsf efri engineering of cardiovascular cellular interfaces and tissue constructs, bio-x seed grant an integrated approach for cardiac repair, nsf career the virtual heart, hellman faculty scholarship


Figure 10. Ultrastructural changes of the intercalated disk after volume overload. A Control. After 6 hours of volume overload, the ICD becomes thick with one-sarcomere-long interdigitations. B After 12 hours, the ICD is folded to form one-sarcomere-deep grooves and contra-grooves with short interdigitations. C At 1 day, interdigitations elongate up to one-sarcomere long in the folded ICD, D, so that the ICD broadens to ~two sarcomere wide. Grooves and contra-grooves appear in this mode. At 1.5 days, the ICD is thin with mostly short interdigitations, but one-sarcomere-long interdigitations sporadically appear as spikes. E There appear spaces surrounded by several spikes. At 2 days, the ICD is thin and flat with short interdigitations similar to those of controls, finishing one cycle of serial sarcomere addition.

anisotropic baseline elasticity

\[ \psi = \kappa \left[ J^e - \ln(J^e) - 1 \right] + \frac{a}{2b} \exp(b[I_1^e - 3]) + \frac{a_s}{2b_s} \left[ \exp(b_s[I_s^e - 1]^2) - 1 \right] + \frac{a_f}{2b_f} \left[ \exp(b_f[I_f^e - 1]^2) - 1 \right] + \frac{a_{fs}}{2b_{fs}} \left[ \exp(b_{fs}I_{fs}^e - 2) - 1 \right] \]

\[ \tau = 2 \frac{\partial \psi}{\partial g} = J^e p g^{-1} + 2 \psi'_1 b^e + 2 \psi'_{fs} [f^e \otimes s^e]_{\text{sym}} + 2 \psi'_s s^e \otimes s^e \]

dokos, smaill, young, le grieece [2002], schmid, nash, young, hunter [2006].
holzapfel, ogden [2009], göktepe, acharya, wong, kuhl [2010]

cardiac wall thickening - concentric growth
strain-driven eccentric growth through sarcomerogenesis

**Figure 6.** Generic biventricular heart model generated from two truncated ellipsoids, with heights of 70mm and 60mm, radii of 30mm and 51mm, and wall thicknesses of 12mm and 6mm, respectively. In the healthy heart, cardiomyocytes are assumed to be cylindrical, 100µm long with a diameter of 16.7µm. They consist of 50 serial sarcomere units in length and 91 parallel units per cross section, each of them 2µm long and 2µm in diameter. They are arranged helically around the long axis of the heart with a transmurally varying inclination of -55° in the epicardium, the outer wall, to +55° in the endocardium, the inner wall, measured with respect to the basal plane.