A multiscale modeling of LV growth that incorporates myosin ATPase to drive concentric growth and intracellular sarcomeric passive stress to drive eccentric growth

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Keywords: Multiscale modeling, LV growth, ATPase, Sarcomeres, Baroreflex, Concentric growth, Eccentric growth (Min.5-Max. 8)

Abstract

The mechanism in which heart undergoes changes in its size and shape due to abnormal ventricular loading is known as cardiac growth. Mathematical models of the heart have been significantly used to study different mechanisms of cardiovascular function including cardiac/ left ventricle (LV) growth. From such models, multiscale models that allow to quantitatively investigate the effects of molecular-level mechanisms on organ level function of the heart can potentially improve the patients care. PyMyoVent is a multiscale computer model that simulates the left ventricular function within a systemic circulation model by bridging effects from molecular-level to organ level. In our previous work we showed how an implemented module of baroreflex feedback loop into PyMyoVent could maintain arterial pressure at setpoint level by regulating heart rate, intracellular Ca2+ dynamics, the molecular-level function of both the thick and the thin myofilaments, and vascular tone. In this manuscript, we extend that model further by adding a module of LV growth that simulates both concentric growth (wall thickening) and eccentric growth (chamber dilation). The new module essentially uses a molecular-level metabolic mechanism, myosin ATPase per volume of myofibrillar, as the driving signal for concentric growth. Whereas the eccentric growth was driven by intracellular passive stress in half-sarcomeres. The new framework’s predictions for LV growth in response to three types of valvular disease, namely aortic stenosis (AS), mitral regurgitation (MR), and aortic regurgitation (AR), were adequately in agreement with clinical patient data. Furthermore, the new framework could fully recover the LV size and function (reversal of growth) for all valvular disorders when the underlying overloading was removed. As a conclusion, results of this study suggest that myosin ATPase per volume of myofibrillar and intercellular passive stress in half-sarcomeres could be the potential driving signals for concentric and eccentric growth, respectively.

# Introduction

Heart can adapt and change its shape and size in response to altered ventricular loading or mutant sarcomeric proteins under a mechanism named cardiac growth. (Frey and Olson, 2003; Watkins et al., 2011; Pitoulis and Terracciano, 2020). Based on ventricular geometry, there are two conventional types of growth. 1) Concentric growth that is defined as thickening of wall and increase of ventricular mass with small or no change in the ventricular chamber size due deposition of sarcomeres in parallel (Hill and Olson, 2008). 2) Eccentric growth that is characterized by addition of sarcomeres in series which results into ventricular dilation, elevated ventricular mass with small or no change in the wall thickness (Hill and Olson, 2008). In general, cardiac growth initiates as an early adaptive response of the heart to the abnormal loading. However, if the underlying cause does not resolve it can lead to myocardial fibrosis, myocyte dysfunction, impaired cardiac function and ultimately heart failure (Hill and Olson, 2008; Shimizu and Minamino, 2016; Nakamura and Sadoshima, 2018).

Computer based models of cardiac growth have provided insightful understanding on the growth mechanisms specially when they are validated with experimental data. Concept of choosing best driving growth stimulus/ stimuli for computational models are still controversial. Conventionally, computational models of cardiac growth have utilized either myofiber stress (Rausch et al., 2011; Klepach et al., 2012), strain (Guterl et al., 2007; Kerckhoffs et al., 2012; Witzenburg and Holmes, 2018), or some combination of the two (Goktepe et al., 2010; Arts et al., 2012) as their driving signal. Rondnina and Bovendeerd (Rondanina and Bovendeerd, 2020a) tested four combinations of myofiber stress and strain for both types of growth and concluded that using at least one stress-driven growth law would predict more reliable growth. In another work, Mojumder et al. (Mojumder et al., 2021) showed concentric growth of LV due to pressure overloading has a better correlation with myofiber stress than stretch.

Though current models have shown promising results, the underlying mechanism is more complex and accompanied by perturbations in the molecular level (signaling pathway, hormones level, energy production, etc.) which have not been thoroughly investigated. Therefore, the focus of computational modeling in cardiac growth is shifting from phenomenological towards more realistic multi-scale mechanistic models to incorporate the effect of cellular events in driving the cardiac growth (Sharifi et al., 2021a). From which, Yoshida et al. (Yoshida et al., 2020b) incorporated a model of cell level signaling pathway network with a compartmental model of rat heart to investigate the cardiac growth in response to volume overloading and surge in hormones level during pregnancy. Their model showed that most of the growth, especially during the first half of pregnancy was due to rise in progesterone (i.e. hormonal signal) and not from the volume overloading (i.e. mechanical signal) of the heart. Estrada et al. (Estrada et al., 2021) incorporated the effect of hormonal signals with mechanical ones in a finite element model of LV to predict the cardiac hypertrophy in response to transverse aortic constriction (TAC). They essentially showed that the effect of hormonal inputs on the prediction of cardiac hypertrophy was larger than the mechanical stimulus.

Myosin ATP phosphohydrolase (ATPase) activity is another cell-level mechanism that has been reported to have a correlation with abnormal ventricular loading (Kozlovskis et al., 1987). Essentially, myosin ATPase hydrolyzes ATP to a complex of ADP and phosphate (Pi) molecules and a release of energy that is required for the contraction of myosin heads in the next cross-bridge cycle. It has been shown that abnormal LV loadings such as pressure overloading can perturb the myocardial metabolism and thus leading to a decrease in cardiac efficiency (Tuomainen and Tavi, 2017; Nakamura and Sadoshima, 2018). In a recent work, Lopez et al. (Lopez et al., 2020) studied the effects of energetic dysfunction in a failing heart on mechanical function of rat hearts using a multiscale model of cardiac mechanoenergetics. Their finding was that elevated levels of inorganic phosphate in a TAC model of rat kinetically impair the myosin ATPase cross bridge cycle in heart failure.

To further investigate this hypothesis, we first incorporate a growth module to a multiscale model of cardiovascular function named PyMyoVent published in our previous works (Campbell et al., 2020; Sharifi et al., 2021b). Implemented growth module uses myosin ATPase per myofibrillar volume and intracellular passive as the driving signals for concentric and eccentric growth laws, respectively. Secondly, we will test our model’s ability in capturing different types of cardiac growth in response to three types of valvular disorders namely 1) aortic stenosis (AS), 2) mitral regurgitation (MR), and 3) aortic regurgitation (AR). Thirdly, we will investigate how the new framework can recover the LV size and function when the underlying overload is removed. Finally, we will validate the model’s predictions for valvular disorders against the collected clinical data from the literature.

# Materials and Methods

## Overview

The current study study extends our previous work (Sharifi et al., 2021b) by adding a module of LV growth to a multiscale model of cardiovascular function named PyMyoVent. Figure 1 shows the overview of PyMyoVent framework and illustrates how different modules communicate with each other. The original framework was initially published by Campbell et al. (Campbell et al., 2020) where they showed how a variation in model parameters (e.g. myosin rate constants) would change the system level parameters (e.g. end-systolic pressure-volume relationship). The original framework is essentially built on four main modules where it uses a pacing stimulus to drive the Ca2+ handling in the electrophysiology module. The contraction model called MyoSim (Campbell, 2014; Campbell et al., 2018) then uses calculated Ca2+ transient to predict the ventricular wall stress which is then transformed into ventricular pressure via *Laplace’s Law*. Finally, the single hemispherical model of LV pumps blood into a lumped parameter model of systemic circulation based on *Ohm’s law*. More details on these modules are already described (Campbell et al., 2020).

Diagram

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**Figure** **1.** **Overview of PyMyoVent’s framework.** Baroreflex feedback loop regulates the arterial pressure towards a setpoint by modulating heart rate, intracellular Ca2+ transients, myofilament contractility, and vascular tone. Growth algorithm uses myosin ATPase per myofibrillar volume and intracellular passive stress in half-sarcomeres to control the concentric growth (wall thickening) and eccentric growth (ventricular dilation), respectively. Figure need to be updated!

## Baroreflex feedback loop module

In our previous work (Sharifi et al., 2021b) we extended the original framework of PyMyoVent (Campbell et al., 2020) by incorporating a module of baroreflex feedback loop (Fig 1) to drive the arterial pressure towards the setpoint level. The feedback model was inspired by the underlying biology where an afferent signal was driven from a sigmoidal relationship with arterial pressure to drive the net results of neural processing in medulla. The efferent pathway signal was constrained between the maximum sympathetic and maximum parasympathetic drive and could regulate the heart rate, intracellular Ca2+ transient, contractility of both the thick and the thin filaments, and vascular tone. It was shown that the baroreflex feedback loop was able to regulate the system towards a user-defined level of setpoint for the arterial pressure between ~30 mm Hg to 150 mm Hg, as well as maintaining the arterial pressure at the setpoint level under perturbed ventricular loading, such as acute blood loss or aortic stenosis. More details on the baroreflex feedback loop module can be found in the main work (Sharifi et al., 2021b).

## Growth module

Growth module was consisted of two growth laws for concentric (wall thickening) and eccentric (ventricular dilation) growth. Each growth law is driven via a normalized growth signal Ga,i that can vary between 0 and 1 due to a deviation in the corresponding stimulus signal Si. The rate of change in Ga,i is defined as



where i represents the growth type (i.e. concentric or eccentric), kdrive is a constant rate factor and sets the speed at which Ga,i responds to a change in Si. Si,set is the homeostatic level (setpoint) for stimulus signal Si. For a positive feedback, Ga,i tend towards one when Si is higher than Si,set and towards zero when Si is less than Si,set.

The normalized growth signal then transduces into a controller signals Gc,i that control how wall volume or number of half-sarcomeres respond to a change in the corresponding normalized growth signal Ga,i. The rate of change in Gc,i is defined as



where γgrowth and γanti growth are gain factors for increasing and decreasing reflex-sensitive parameters in the cardiovascular model. For the purpose of simplicity, both factors are chosen to have similar magnitudes but in the opposite directions. Calculated controller signals then drive the change in the controlled parameter as described in the following sections.

### Eccentric growth

Eccentric growth is controlled by the serial number of half-sarcomeres (nhs) around the circumference of LV in the cardiovascular model. The driving signal for eccentric growth (Secc) was assumed to be the intracellular passive stress in half-sarcomeres τpassive, in which has a nonlinear relationship with the half-sarcomere length (equation ).



where xhs is the length of half-sarcomere, Lslack is the half-sarcomere length at which the passive stress is zero, L sets the curvature of the relationship, and is the scaling factor. The rate of change in the serial number of half-sarcomeres is controlled via equation , where Gc,ecc is the controller growth signal for eccentric growth law. According to equation , an increase in the driving signal (i.e. passive stress in half-sarcomeres) would increase the serial number of half-sarcomeres (equation ) to reduce the passive stress back to its homeostatic level (setpoint). A reduction in passive stress, on the other hand, reduces the serial number of half-sarcomeres to stretch more half-sarcomeres for a given LV circumference and thus elevate the passive stress towards the setpoint.



### Concentric growth

Concentric growth law handles LV wall volume (Vwall) to mimic the parallel deposition of sarcomeres. The ratio of myosin ATPase per wall volume (equation ) was assumed to be the stimulus signal for concentric growth (Scon). Where N0 is the density of myosin heads over a cross section of 1 m2, ∆G is the free energy produced by ATP hydrolysis (70 kJ mol-1), L0 is the reference length of half-sarcomere (1.1 μm), NA is Avogardo’s number (6.02 × 1023 mol-1), and J4 is the detachment flux of myosin heads from force generating state (MFG) to disordered relaxed state (MDRX).



The rate of change in Vwall is defined via equation in which is consisted of two components. The first components Gc,con responds to a change in the stimulus signal for concentric growth (Scon). Whereas the second component Gc,ecc incorporates the proportional change due to the eccentric growth (Pitoulis and Terracciano, 2020).



## Simulations

### Implementation and computer code

The code was written in python language using Numpy (S. et al., 2011), Scipy (Virtanen et al., 2020), and pandas (al., 2021) libraries. The source code and the instruction on how to reproduce all figures shown in this manuscript are available at <https://campbell-muscle-lab.github.io/PyMyoVent/>.

### Baseline

As described in previous works with PyMyoVent (Campbell et al., 2020; Sharifi et al., 2021b) no data fitting was obtained to optimize the model parameters. Instead, parameters were tuned in a way to mimic cardiovascular function of a healthy adult according to reported normal range of characteristics (Maceira et al., 2006; Petersen et al., 2017). Total blood volume for the systemic circulation system was set to 4.5 liters. All simulations in this manuscript started by using default values for model parameters and assigning all stressed volume into the veins. At 20 s when all compartmental blood volume and pressure in the circulation system were at steady state, the baroreflex feedback module was activated to move the arterial pressure towards the setpoint of 90 mm Hg. The characteristics of baseline simulation are shown in Table 1.

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| --- | --- |
| **Table** **1** Baseline simulated cardiovascular function of a healthy adult. | |
| Heart rate (BPM) | ~63 |
| End-diastolic LV volume (ml) | ~146 |
| Pulse pressure (mm Hg) | ~117 / 61 |
| Stroke volume (ml) | ~94 |
| Ejection fraction (%) | ~64 |

### Valvular disorders

Three types of valvular disorders namely aortic stenosis (AS), mitral regurgitation (MR), and aortic regurgitation (AR) were simulated by applying the relevant perturbations to the baseline simulation. Aortic stenosis (AS) is a valvular disease that aortic valve becomes narrowed, poorly opens during systole and induces pressure overloading of left ventricle (LV). To form the aortic stenosis condition, aortic resistance in the systemic circulatory module was increased to pressure overload LV. According to Poiseuille equation, resistance of a vessel has an inverted relation with squared of the cross-sectional area. For instance, a 500 percent increase in the aortic resistance is equivalent with a ~60 percent reduction in the aortic valve area, from a mean value of 2.5 cm2 for healthy adults (Luszczak et al., 2012; Chin et al., 2014; Chin et al., 2017) to a mean value of 1 cm2 for patients with aortic stenosis (Spath et al., 2019; Everett et al., 2020). In accordance with American Heart Association guideline (Otto et al., 2021), the aortic valve area of 1 cm2 is one of the key thresholds for categorizing the severity of the disease. Therefore, three levels of AS mimicking different levels of severity were simulated as shown in Table 2.

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| --- | --- | --- |
| **Table** **2.** Simulated different levels of AS severity | | |
| % Increase in the aortic resistance | Equivalent % reduction in aortic valve area | Represented level of severity according to AHA guideline (Otto et al., 2021) |
| 250 % | 46.55  (From 2.50 cm2 to 1.33 cm2) | At risk of AS / Progressive AS |
| 500 % | 60  (From 2.50 cm2 to 1.00 cm2) | Asymptomatic severe AS |
| 750 % | 65  (From 2.50 cm2 to 0.86 cm2) | Symptomatic severe AS |

Mitral regurgitation (MR) is another type of valvular disorder in which the mitral valve does not close properly during systole and allows a retrograde blood flow to occur. Regurgitant blood volume yields to volume overloading of LV and thus excessive diastolic filling of LV (Carabello et al., 1992). In the current framework, The retrograde blood flow through the mitral valve was controlled via a model parameter named “leaking factor” (Gleak,mitral in equation ) that is zero for a proper valve (i.e. “baseline simulation”) and is nonzero for an insufficient valve.



The following values for “leaking factor” (Table 3) were used to simulate three levels of severity for patients with MR with respect to the thresholds of 60 (ml beat-1) for regurgitant volume based on AHA guideline (Otto et al., 2021).

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| **Table** **3.** Simulated different levels of MR severity | | |
| Gleak,mitral | Equivalent regurgitant volume (ml beat-1) | Represented level of severity according to AHA guideline (Otto et al., 2021) |
| 1e-3 | 30 | At risk of MR / Progressive MR |
| 2e-3 | 60 | Asymptomatic severe  MR |
| 3e-3 | 80 | Symptomatic severe MR |

Aortic regurgitation (AR) is another prevalent valvular disease which is characterized with backward diastolic flux of blood from the aorta into LV. The regurgitant blood volume generates excess diastolic filling of LV, but the initial ejection of the forward stroke volume alongside the regurgitant volume surge the systolic pressure and hence lead to a wide pulse pressure and systolic hypertension (Bekeredjian and Grayburn, 2005). Therefore, AR imposes a combination of volume and pressure overloads on LV which undergoes a combination of both types of eccentric and concentric growth (Carabello, 2002; Bekeredjian and Grayburn, 2005; Akinseye et al., 2018). The backward diastolic flux through the aortic valve was handled via a model parameters named Gleak,aorta (equation ) which is zero for a healthy valve (i.e. “baseline simulation”) and nonzero for a leaking aortic valve.



AHA guideline (Otto et al., 2021) categorizes three levels of severity for AR based on the regurgitant volume namely: mild AR (regurgitant volume < 30 ml beat-1), moderate AR (30 ml beat-1 < regurgitant volume < 59 ml beat-1), and severe AR (regurgitant volume > 60 ml beat-1). These levels of AR were simulated by using values for Gleak,aorta shown in Table 4.

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| **Table** **4.** Simulated different levels of AR severity | | |
| Gleak,aorta | Equivalent regurgitant volume (ml beat-1) | Represented level of severity according to AHA guideline (Otto et al., 2021) |
| 5e-4 | 20 | Mild AR |
| 1e-3 | 40 | Moderate AR |
| 2e-3 | 70 | Severe AR |

## Model’s validation

To validate our model, the simulated results were compared with clinical data acquired by cardiac magnetic resonance from the literature (Table 5). Clinical data were categorized into four cases named “control volunteers”, “patients with AS”, “patients with MR”, and “patients with AR”. For each category, measured data were collected from eight different studies. Ventricular dimensions were quantified with LV end-diastolic volume index (LVEDVi), LV end-systolic volume index (LVESVi), and LV mass index (LVMi). Systolic function was assessed with LV stroke volume index (LVSVi) and ejection fraction (EF). An averaged body surface area of 1.9 m2 (Verbraecken et al., 2006; Lang et al., 2015) was used to normalize the simulated results. Some studies in Table 5 did not report the measured LVSVi, so the absolute difference of reported LVEDVi and LVEDSi was used as LVSVi.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table** **1.** List of studies with quantified clinical data for LV dimensions and systolic function acquired by cardiac magnetic resonance. | | | | | | | | | | | |
| **Control volunteers** | | | **Patients with AS** | | | **Patients with MR** | | | **Patients with AR** | | |
| Study | Year | n | Study | Year | n | Study | Year | n | Study | Year | n |
| Lee et al. (Lee et al., 2020) | 2020 | 30 | Lee et al. (Lee et al., 2020) | 2020 | 191 | Liu et al. (Liu et al., 2020) | 2020 | 104 | Malahfji et al. (Malahfji et al., 2020) | 2021 | 392 |
| Spath et al. (Spath et al., 2019) | 2019 | 41 | Everett et al. (Everett et al., 2020) | 2020 | 440 | Seldrum et al. (Seldrum et al., 2019) | 2019 | 59 | Seldrum et al. (Seldrum et al., 2019) | 2019 | 29 |
| Seldrum et al. (Seldrum et al., 2019) | 2019 | 30 | Spath et al. (Spath et al., 2019) | 2019 | 159 | Bakkesstrom et al. (Bakkestrom et al., 2018) | 2018 | 46 | Geiger et al. (Geiger et al., 2018) | 2017 | 16 |
| Lee et al. (Lee et al., 2015b) | 2015 | 15 | Singh et al. (Singh et al., 2019) | 2019 | 174 | Polte et al. (Polte et al., 2017) | 2017 | 40 | Polte et al. (Polte et al., 2017) | 2017 | 38 |
| Edwards et al. (Edwards et al., 2014) | 2014 | 35 | Everett et al. (Everett et al., 2018b) | 2018 | 61 | Myerson et al. (Myerson et al., 2016) | 2016 | 152 | Fairbairn et al. (Fairbairn et al., 2013) | 2013 | 50 |
| Chin et al. (Chin et al., 2014) | 2014 | 33 | Chin et al. (Chin et al., 2014) | 2014 | 133 | Edwards et al. (Edwards et al., 2014) | 2014 | 35 | Myerson et al. (Myerson et al., 2012) | 2012 | 158 |
| Barone-Rochette et al. (Barone-Rochette et al., 2013) | 2013 | 20 | Barone-Rochette et al. (Barone-Rochette et al., 2013) | 2013 | 128 | Schiros et al. (Schiros et al., 2012) | 2012 | 94 | Uretsky et al. (Uretsky et al., 2010) | 2010 | 34 |
| Schiros et al. (Schiros et al., 2012) | 2012 | 51 | Steadman et al. (Steadman et al., 2012) | 2012 | 41 | Uretsky et al. (Uretsky et al., 2010) | 2010 | 23 | Grotenhuis et al.(Grotenhuis et al., 2007) | 2007 | 20 |
| Data were reported as mean ± standard deviation (SD) or median (interquartile range). | | | | | | | | | | | |

# Results

## Concentric growth occurred in response to induced aortic stenosis (pressure overloading)

Figure 2 depicts the response of PyMyoVent framework to an example of induced pressure overloading, mimicking aortic stenosis. Once the simulation was at initial steady state representing “baseline” simulation, the growth module activated (first vertical dashed line in all panels from the left). The setpoints for both concentric and eccentric growth laws were chosen to be close to the average of driving signals at the initial steady state. At 300 s (second vertical dashed lines) when the simulation was at steady state while the growth module was activated, the aortic resistance gradually (in 100 s between the second and third vertical lines) increased by 500% from 20 to 120 (mm Hg L-1 s) to mimic 60% reduction in aortic valve area according to Table 2. In response to induced pressure overloading, growth module increased LV wall volume (Vwall) by ~30% whereas the serial number of half-sarcomeres around the circumference of LV almost remained unchanged. Due to these changes, LV wall thickness increased by ~21% and ~29% at end-systole and end-diastole, respectively, while the LV cavity (chamber) volume shrunk by ~8% at end-diastole but remined unchanged at end-systole. These are the characteristic features of concentric growth. Baroreflex feedback loop maintained arterial pressure at setpoint of 90 mm Hg (middle column in Fig 2) via increasing heart rate, contractility of both thick and thin myofilaments, and vascular tone.

Diagram, schematic

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**Figure** **2.** **Predicted concentric growth due to pressure overloading (aortic stenosis**). Left hand column shows the response of central framework of PyMyoVent (Campbell et al., 2020) in multi-scale levels. Thin filament panel shows the fraction of actin binding sites in Noff and Non states. Thick filament panel shows the normalized population of myosin heads in super-relaxed (MSRX), disordered relaxed (MDRX), and force-generating (MFG) states. Middle column demonstrates the continues modulation of baroreflex module over reflex-sensitive parameters of model to maintain the arterial pressure at setpoint level of 90 mm Hg. Right hand column shows the properties relevant to growth module and metrics relevant to LV systolic function. The growth module was activated at 50 s (first dashed vertical line from left on all panels) when the system was at initial steady state. When the growth module was activated and the simulation was at steady state, the aortic resistance gradually increased by 500% between the second and third vertical lines from left on all panels (from time point of 300 s to 400 s). For pulsatile parameters (for example, ventricular pressure), envelope of extreme values are shown.

## Eccentric growth occurred in response to induced mitral regurgitation (volume overloading)

Fig 3 shows model response to an example of volume overloading condition through simulating an insufficient mitral valve. The simulation started with default model parameters representing “baseline” simulation. From time-points of 300 s to 400 s, Gleak, mitral factor (equation ) was gradually increased from 0 to 2e-3 to induce a mitral regurgitant volume of ~60 ml (Table 2). In response to volume overloaded LV, growth module increased serial number of half-sarcomeres by ~17% and resulted into LV cavity dilation of ~57% and ~68% at end-diastole and end-systole, respectively. LV wall volume (Vwall) was also increased by ~50% and thus slightly increased LV wall thickness by ~10% and ~12% at end-systole and end-diastole, respectively. Due to the excessive increase in LV cavity volume compared to wall thickness, model could correctly capture the eccentric growth in response to LV volume overloading. Again, baroreflex module maintained the arterial pressure setpoint level at 90 mm Hg via up-regulation of heart rate, myofilaments contractility, and vascular tone.

Diagram, schematic

Description automatically generated

**Figure** **3**. **Predicted eccentric growth for LV in response to volume overloading (mitral regurgitation).** Similar arrangement for panels as in Fig 2 except that mitral regurgitant volume is shown in place of aortic resistance in right hand column. Growth module activated at 50 s when the simulation was at initial steady state. The volume overloading condition was gradually (between the second and third vertical lines on all panels) simulated by increasing Gleak,mitral in equation from 0 to 2e-3 to induce a mitral regurgitant volume of ~60 ml (Table 2). For pulsatile parameters (for example, ventricular pressure), envelope of extreme values are shown.

## Growth module predicted LV dilation and LV wall hypertrophy due to aortic regurgitation (combination of pressure and volume overloading)

In another attempt, Fig 4 shows PyMyoVent’s response to a combination of both pressure and volume overloading by mimicking aortic regurgitation condition. Simulation started with similar configuration as in Figs 2 and 3 except LV overloaded with backward blood flow from aorta to LV during diastole. At 300 s (second vertical line on all panels) Gleak, aorta in equation was gradually increased from 0 to 1e-3 to make a regurgitant volume of ~40 ml. Serial number of half-sarcomeres grown by ~12% and thus increased LV cavity volume by ~37% and ~38% at end-systole and end-diastole, respectively. Furthermore, due to pressure overloading, LV wall volume (Vwall) increased by ~45% and developed hypertrophied wall via increasing LV wall thickness by ~16 at both end-diastole and systole. Although baroreflex module remained arterial pressure setpoint at 90 mm Hg, arterial pressure became more pulsatile and changed from ~116/61 mm Hg to ~128/46 mm Hg.

Diagram, schematic

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**Figure** **4. Predicted LV cavity dilation along LV wall hypertrophy in response to a combination of both pressure and volume overloading (aortic regurgitation).** Similar arrangement for panels as in Fig 2 except that aortic regurgitant volume is shown in place of aortic resistance in right hand column. Growth module activated at 50 s when the simulation was at initial steady state. The insufficiency in aortic valve induced by gradually (during 100 s between the second and third vertical lines on all panels) increasing Gleak, aorta in equation from 0 to 1e-3 to make a regurgitant volume of ~40 ml (Table 3). For pulsatile parameters (for example, ventricular pressure), envelope of extreme values are shown.

## Left ventricular Pressure-volume loop relationship

Pressure-volume (PV) loop is a metric for systolic function of LV. Fig 5 shows PV loops for simulated baseline (healthy) and three types of valvular dysfunction (overloaded LV) shown in Figs 2-4. For aortic stenosis condition, end-systolic LV pressure rose noticeably by ~40%, end-diastolic LV volume reduced by ~8%, but end-systolic LV volume remained unchanged, and thus, the stroke volume reduced by ~12%. The area enclosed by PV loop and hence the stroke work done by LV increased by ~17%.

For mitral regurgitation case, end-systolic LV pressure almost remained unchanged, however, LV volume increased significantly and shifted the whole loop to the right side of the diagram. Stroke volume increased by ~51% and consequently increased the enclosed area and LV stroke work by ~50%. Due to insufficient mitral valve, the relaxation phase was no longer isovolumic and LV volume kept shrinking.

In aortic regurgitation case, end-systolic LV pressure slightly elevated by ~9% and LV cavity volume dilated at both end-systole and diastole. Stroke volume and stroke work were increased by ~38% and ~41%, respectively. Similar to MR case, the relaxation phase was no longer isovolumic and LV volume was increasing because of the retrograde flow from aorta.

Diagram

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**Figure** **5**. **Left ventricular pressure-volume (PV) loop relationship for baseline (control) and three types of valvular dysfunction (overloaded LV).** Baseline loop belongs to time range of (298 s – 299 s) in Figs 2-4 before applying any overloads. All other three loops belong to time range of (780 s – 781 s) from the relevant simulation shown in Figs 2-4.

## LV growth was recovered when overloading was removed

Fig 6 depicts an attempt in capturing the reversal of LV growth when the abnormal loadings were removed. Each column represents a simulated valvular dysfunction shown in Figs 2-4. All three cases started and overloaded exactly as are shown in Figs 2-4. At 900 s (forth vertical line on all panels) the overloading were gradually removed, for instance, aortic resistance was reduced from 120 to 20 (mm Hg L-1 s) for AS case. In all cases, LV dimensions (Fig 6) and cardiovascular functions (Figs S1-3) were fully recovered to their homeostatic range once the overloading was lifted

Diagram

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**Fig** **6. Reversal of LV growth in response to removal of overloading.** Left hand column shows reversal of concentric growth due to removal of aortic stenosis condition. Middle column shows reversal of eccentric growth in response to removal of insufficient mitral valve. Right hand column shows reversal of LV growth due to removal of an insufficient aortic valve. On all panels, first vertical line shows when the growth module is activated. Second and third vertical line demonstrate the onset and ending of the applied relevant overloading. Fourth and fifth vertical lines shows the onset and ending of the relevant removed overloading.

## Predicted LV size agreed with collected clinical data

Fig 7 shows model validation in predicting LV size with respect to the collected clinical data (Table 5). For aortic stenosis, model perditions were in line with clinical data such that as the level of narrowness increased, end-diastolic LV volume indexed (EDLVi) slightly reduced, end-systolic LV volume indexed (ESLVi) almost remained unchanged, but LV mass indexed (LVMi) increased notably. For mitral regurgitation case, model predictions were in the range of clinical data in a way that as the mitral regurgitant volume increased, LV volume indexed at end-diastole and systole and LV mass indexed increased as well. Ultimately, predicted LV size parameters for aortic regurgitation were adequately in the range of clinical data and demonstrated that an increase in the severity of insufficient aortic valve would increase LV volume indexed and LV mass indexed.

## Diagram, schematic Description automatically generated

**Fig** **7. Model validation for LV size in comparison to collected clinical data from the literature (Table 5).** Left hand column shows model validation for aortic stenosis. Middle column shows model validation for mitral regurgitation. Right hand column shows model validation for aortic regurgitation. In all panels, clinical data are shown with circle markers in two groups of “control” and “patients”. Model predictions are shown with star markers. For each valvular disease case, three levels of severity for model simulations are shown in accordance with Tables 2-4. Model results are indexed by an average body surface area of 1.9 m2 (Verbraecken et al., 2006; Lang et al., 2015).

## Predicted LV systolic function versus clinical data

Fig 8 depicts model validation in predicting systolic function in comparison to collected clinical data (Table 5). For aortic stenosis, increasing the level of stenotic valve decreased the systolic function of LV as both stroke volume indexed (SVi) and ejection fraction reduced. Similarly, the LV systolic function (ejection fraction) decreased as the severity of mitral regurgitation elevated, although SVi increased. For aortic regurgitation, intensified insufficient valve did not change the ejection fraction, however, increased the stroke volume indexed. In all cases, model predictions were in the range of clinical data, except for the ejection fraction of mitral regurgitation.

Diagram, schematic

Description automatically generated

**Fig** **8. Model validation for LV systolic function in comparison to collected clinical data from the literature (Table 5.)** Figure panels are arranged as in Fig 7. In all panels, clinical data are shown with circle markers in two groups of “control” and “patients”. Model predictions are shown with star markers. For each valvular disease case, three levels of severity for model simulations are shown in accordance with Tables 2-4. Model predictions for stroke volume are indexed by an average body surface area of 1.9 m2 (Verbraecken et al., 2006; Lang et al., 2015).

# Discussion

This study extends a multiscale model of cardiovascular function by incorporating a growth module that simulates both concentric growth (wall thickening) and eccentric growth (chamber dilation). Calculated results in this manuscript showed that the new framework could predict the correct form of LV growth in response to three forms of valvular diseases namely aortic stenosis, mitral regurgitation, and aortic regurgitation which were validated with clinical data from the literature. Furthermore, the presented framework could also capture the reversal of growth when the overloading was removed.

## Role of myosin ATPase in driving concentric growth

Adenosine triphosphate (ATP) molecule provides required energy for many energy-demanding mechanisms in cardiomyocytes. Cross-bridge cycling of myosin accounts for ~70% of ATP consumption (Watkins et al., 2011) under a mechanism named myosin ATPase. Myosin ATPase is a molecular-level mechanism that hydrolyzes ATP to form a complex of adenosine diphosphate (ADP) and phosphate (Pi) molecules to detach the myosin heads from actin binding sites. The underlying reaction includes a release of energy that is essential for contraction of myosin heads in the next cross-bridge cycle. ATP stock in heart is limited and only is enough for few beats (Ingwall, 2009). Therefore, cardiomyocytes need to continuously re-synthesize ATP to hold the balance between the ATP demand and consumption.

Pressure-overload induced LV growth is accompanied by numerous changes in molecular-level events, including cardiac energy metabolism (Sankaralingam and Lopaschuk, 2015). The underlying perturbations in cardiomyocytes can increase the ATP (energy) demand for myosin ATPase which leads to deficient consumption of ATP within the cell. This, in particular, can compromise other ATP consuming mechanisms such as sarcoendoplasmic reticulum Ca2+ ATPase (SERCA) uptake. Eventually, the metabolic dysfunction can result into ATP depletion and heart failure (Ashrafian et al., 2007; Lopez et al., 2020; Pitoulis and Terracciano, 2020).

PyMyoVent uses myosin ATPase per myofibrillar volume to drive the concentric growth by modulating the LV myocardial volume. Increased afterload due to aortic stenosis causes myocardium to shorten more slowly since it needs to pump blood against an elevated resistance. Due to less shortening of half-sarcomeres during systole (Fig 9), the fraction of actin binding sites available for myosin heads (Noverlap), and hence, fraction of bound binding sites (Nbound) increases. This obviously, rises the number of myosin heads in MFG and consequently the detachment rate of myosin heads (J4). Based on equation , elevated detachment flux (J4) surges the demand for ATP consumption (myosin ATPase). Increased myosin ATPase per volume of myofibril drives the concentric growth law to grow the ventricle wall volume and thus thicken the wall thickness. According to *Laplace’s law*, hypertrophied LV wall, on the other hand, normalizes stress in wall and half-sarcomeres by reducing myosin heads in MFG, which in turn re-normalizes the detachment flux (J4) and myosin ATPase (Fig 9).

Similar pattern has been seen to occur in familial hypertrophic cardiomyopathy (HCM) due to mutant sarcomeric proteins. From numerous mutations leading to HCM, genetic mutations associated with myosin heavy chain (*MYH7*) and myosin binding protein C (*MYBPC3*) are among the prevalent ones (Maron and Maron, 2013; Toepfer et al., 2019). Such mutations essentially increase the magnitude of myofilaments tension developed over time (Davis et al., 2016) and result into hypercontractile sarcomeres. A review work by Spudich (Spudich, 2019) elegantly showed that hypercontractility could be induced by increased number of accessible myosin heads for binding and myosin ATPase activity. While not modeled/ tested in this study, we believe our ATPase driven concentric growth law could simulate hypertrophic cardiomyopathy (HCM) due to mutant myosin heads which is beyond the scope of this manuscript.

Chart, bar chart

Description automatically generated

**Fig** **9. Effects of pressure overloading on myosin ATPase and development of concentric growth**. Simulated results belong to Fig 2. Onset of growth module and timing of pressure overloading is as in Fig 2. Pulsatile parameters such as half-sarcomere length, are shown with envelope of responses. Nbound is fraction of bound actin binding sites. Noverlap is fraction of accessible binding sites for myosin heads. Scon is driving/stimulus signal for concentric growth. Sset is setpoint level for concentric growth law. Rest of panels are as in Fig 2.

## Role of intracellular sarcomeric passive stress in driving eccentric growth

Eccentric growth is the characteristic outcome of volume overloading. Excessive diastolic filling of LV due to insufficient aortic or mitral valves would overstretch the sarcomeres, and thus increase the end-diastolic wall stress or preload. Preload is associated with passive phase of myocardial twitch. Overstretched sarcomeres (elevated passive stress) trigger mechanotransduction pathways that initiate the serial addition of sarcomeres (Grossman, 1980). Sahli Costabal et al. (Sahli Costabal et al., 2019) has quantitatively showed that serial number of sarcomeres is correlated with myocyte length and ventricular dilation. Peirlinck et al. (Peirlinck et al., 2019) completed Sahli Costabal et al.’s work (Sahli Costabal et al., 2019) by using machine learning techniques and showed that their stretch driven growth model had 52.7% agreement with observed morphology.

In our model, intracellular passive stress has a nonlinear relationship with change in half-sarcomere length (equation ). Fig 10 summarizes how a volume overloading condition changes the serial number of half-sarcomeres. Essentially, increased diastolic filling of LV resulted into overstretching of half-sarcomeres and this increase in passive stress or preload. Deviation in intracellular passive stress from its homeostatic level (setpoint) drove the eccentric growth law to increase the serial number of half-sarcomeres (Fig 10). Increased number of half-sarcomeres then re-normalized the half-sarcomere length and associated passive stress back to the normal range.

Chart, box and whisker chart

Description automatically generated

**Fig** **10. Effects of volume overloading on intracellular passive stress and development of eccentric growth.** Results belong to the simulation shown Fig 3.Onset of growth module and timing of volume overloading is as in Fig 3. Envelope of response are shown for pulsatile variables. Secc is driving/stimulus signal for eccentric growth. Sset is setpoint level for eccentric growth law.

## Comparison with existing models of LV growth

In recent decades, many other computational models of LV growth have been developed. Although these models have shed lights on the underlying mechanics of LV growth, they still have some limitations (Sharifi et al., 2021a). One big limitation of existing models is that they generally do not operate under realistic cardiac cycle. For instance, some models (Goktepe et al., 2010; Klepach et al., 2012; Lee et al., 2015a) have only simulated LV growth during diastolic loading of LV and neglected systolic behavior of myocardium during ejection. Some others (Arts et al., 2005; Kerckhoffs et al., 2012; Lee et al., 2016) investigated the mechanics of LV growth performing under full cardiac cycle in which the contractile myocardium was simulated using phenomenological Hill-type models. Another group of works (Witzenburg and Holmes, 2018; Estrada et al., 2021) have used a time-varying elastance model of the ventricle to simulate full cardiac cycles. Rondanina and Bovendeerd (Rondanina and Bovendeerd, 2020a; b) recently investigated different combinations of mechanical growth stimuli where they used a one-fiber model of cardiac function to relate the mechanics of LV in organ-level to the mechanics at tissue level.

Current framework in this manuscript, however, simulates LV growth under full cardiac cycle in which the contractile behavior of LV is driven by a mechanistic model of half-sarcomere that simulates the sliding of myofilaments based on the Huxley crossbridge formation (Huxley, 1974) in the myosin level. Being able to model the mechanics of half-sarcomeres in myosin levels has provided the opportunity to study the effects of pathological processes in molecular level on development of disease in organ level. The application of this framework can go further and study the effects of pharmaceutical interventions on treatment of diseased states.

Absence of baroreflex feedback loop is another limitation of existing models (Sharifi et al., 2021a). Although valvular diseases impose abnormal loading on the heart, the arterial pressure remains unchanged (Everett et al., 2018a; Gotzmann et al., 2019). In general, existing models of LV growth are performed under constant heart rate with no mechanism to maintain the arterial pressure via modulating the contractility of myocardium and vascular tone. Kerckhoffs et al. (Kerckhoffs et al., 2012) has seen the absence of a hemodynamic feedback as the potential cause of mismatch between calculated peak LV pressure and the measured one in their model. Rondanina and Bovendeerd (Rondanina and Bovendeerd, 2020b) showed implementing a model of hemodynamic feedback loop into their growth model could address the observed reduction in mean arterial pressure and cardiac output in their initial work (Rondanina and Bovendeerd, 2020a) due to valvular disorders.

Reversal of cardiac growth is a favorable outcome of clinical interventions to dysfunctional valves. In computational models, as the overloading of LV is seemed to grow LV, it is assumed trivial to observe the reversal of growth when the overloading is lifted. Existing models, however, have seemed to be challenged when tried to predict the reversal of growth (Sharifi et al., 2021a; Yoshida and Holmes, 2021). From a few works that have studied the reversal of growth, Lee et al. (Lee et al., 2015a) modified an strain-driven eccentric growth law (Goktepe et al., 2010) and could capture the reversal of growth for a realistic LV geometry under certain types of loading. Yoshida et al. (Yoshida et al., 2020a) investigated the regression of growth due to removal of pressure overloading using Kerckhoffs et al.’s (Kerckhoffs et al., 2012) growth law. Although this growth law was performed the best in capturing LV growth in comparison to seven other growth laws (Witzenburg and Holmes, 2017), it could not predict the reversal of growth.

## Limitations

This manuscript still includes the limitations discussed in previous works with PyMyoVent (Campbell et al., 2020; Sharifi et al., 2021b). Following limitations are particularly related to the growth module added in this work. Firstly, current model can only capture uniform changes in the ventricular size and dimensions. This mainly is due to the simplified 1-D hemispherical geometry of LV assumed in this framework, and ignorance of the complex torsional motion of the heart (Russel et al., 2009), longitudinal and transmural variation of contractile properties (Sharma et al., 2003), and variational in myofibers orientations (Rodriguez-Cantano et al., 2019).

Secondly, the presented framework can only quantify the cardiac growth (i.e. change in the ventricular size and dimension), but not the myofiber remodeling. Alteration in mechanical loading (Pitoulis and Terracciano, 2020; Washio et al., 2020), or mutant sarcomere in familial cardiomyopathy (Watkins et al., 2011) can be accompanied by myofiber disarray and remodeling. However, PyMyoVent framework assumes half-sarcomeres and thus myofibers are uniformly placed around the circumference of LV at base and their orientation remain unchanged during LV growth.

# Conclusions

# This manuscript extends a multiscale model of cardiovascular function by incorporating a growth module that simulates both wall thickening (concentric growth) and LV dilation (eccentric growth). As a conclusion, results of this study suggest that myosin ATPase per volume of myofibrillar and intercellular passive stress in half-sarcomeres could be the potential driving signals for concentric and eccentric growth, respectively. Ultimately, the new framework could fully recover the LV size and function (reversal of growth) when the abnormal loading was removed.

**Acknowledgements**

# This study was supported by National Institutes of Health grant U01HL133359.

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# Supplementary material

Diagram, engineering drawing

Description automatically generated

**Fig S****1. Predicted recovery of LV size and function in response to removed pressure overloading.** Similar arrangement for panels as in Fig 2. Growth module activated at 50 s when the simulation was at initial steady state. On all panels, first vertical line shows when the growth module is activated. Second and third vertical line demonstrate the onset and ending of the applied pressure overloading. Fourth and fifth vertical lines shows the onset and ending of the removed pressure overloading.

Diagram, schematic

Description automatically generated

**Fig S****2. Predicted recovery of LV size and function in response to removed volume overloading.** Similar arrangement for panels as in Fig 3. Growth module activated at 50 s when the simulation was at initial steady state. On all panels, first vertical line shows when the growth module is activated. Second and third vertical line demonstrate the onset and ending of the applied volume overloading. Fourth and fifth vertical lines shows the onset and ending of the removed volume overloading.

Diagram, engineering drawing, schematic

Description automatically generated

**Figure S****3. Fig S1. Predicted recovery of LV size and function in response to removed aortic regurgitation.** Similar arrangement for panels as in Fig 3. Growth module activated at 50 s when the simulation was at initial steady state. On all panels, first vertical line shows when the growth module is activated. Second and third vertical line demonstrate the onset and ending of the applied aortic regurgitation. Fourth and fifth vertical lines shows the onset and ending of the removed aortic regurgitation.