Multiscale modeling of cardiac valve disease using cell-level signals to regulate concentric and eccentric myocardial growth

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Abstract

Multiscale models of the cardiovascular system are becoming effective tools for investigating the mechanisms that drive ventricular growth and biological remodeling. Some of these models can also predict how perturbations to molecular-level mechanisms impact organ-level function. This type of research might yield insights that lead to improved patient care. PyMyoVent is a multiscale computer model that bridges from molecular to organ-level function and simulates a left ventricle pumping blood around a systemic circulation. In previous work, we implemented baroreflex control of arterial pressure by using feedback to regulate heart rate, intracellular Ca2+ dynamics, the molecular-level function of both the thick and the thin myofilaments, and vascular tone. In this paper, we extend PyMyoVent with concentric growth (wall thickening / thinning) and eccentric growth (chamber dilation / constriction) driven by cell-level signals. Specifically, concentric growth is controlled by the energy used by the myocytes for contraction (expressed as myosin ATPase normalized to myofibrillar volume) while eccentric growth responds to intracellular passive stress. The new framework reproduced clinical measures of left ventricular growth in three types of valvular disease, namely aortic stenosis, aortic insufficiency, and mitral insufficiency. Furthermore, simulations of each valvular disorder reversed growth, returning the ventricle to its default size, when the disease-mimicking perturbation was removed. In conclusion, these simulations suggest that myosin ATPase normalized to myofibrillar volume and intracellular passive stress can be used to drive concentric and eccentric growth in simulations of valve disease.

Introduction

The heart adapts to its environment and changes its shape in response to hemodynamic loads, including pathological conditions associated with valvular disease. Throughout this work, the changes in shape will be referred to as cardiac growth. The inherent structure of the myocardium can also change, a process that is described as remodeling [1, 2].

The heart can grow in two modes. Concentric growth is defined by wall thickening and an increase in ventricular mass, due to the deposition of sarcomeres in parallel, with little or no change in the internal size of the ventricular chambers [3]. Eccentric growth reflects the addition of sarcomeres in series, which dilates the chamber and increases wall mass with minimal change in wall thickness [3]. In valvular disease, cardiac growth initiates as an early adaptive response that can progress to remodeling and subsequent heart failure if the valvular dysfunction persists [3-5].

Computer models are providing new insights into cardiac growth. Most of the simulations performed to date have used myocardial stress [6, 7], myocardial strain [8-10], or some combination of stress and strain [11, 12] to drive growth. Building on these ideas, Rondanina and Bovendeerd [13] compared simulations driven by different combinations of stress and strain. They concluded that growth responses simulated using stress-based laws were more realistic than growth patterns driven by strain. Mojumder et al. [14] reached similar conclusions after simulating LV growth following pressure overload.

Mechanical loads are clearly important for growth but models driven solely by these signals cannot reproduce the cardiac growth that follows changes to hormone levels, metabolic function, and/or the status of biochemical signaling pathways. Accordingly, researchers have also begun to develop models that are sensitive to molecular and cellular-level events [15]. Yoshida et al. [16] used one of these systems to compare how volume overload and hormone surges affected cardiac growth during pregnancy. They concluded that the rise in progesterone (a biological signal) was more important for cardiac growth than volume overload (a mechanical signal). In related work, Estrada et al. [17] demonstrated that hormonal changes were also the dominant driving signal for cardiac growth in pressure overload.

Although it is possible to separate mechanical and biochemical signals in a computer model, doing so in vivo is much more difficult. This is because changes to the intracellular environment will alter the way that the heart contracts and thus the mechanical signals that it experiences. Mechanics and biochemistry are inter-twined. In pioneering work, Davis et al. [18] incorporated this behavior in an innovative model that integrated mechanics and molecular signaling. They postulated that the aspect ratio of myocytes responded to MEK1-ERK signaling with myocytes becoming wider with increasing values of the contractile force-time integral. They also suggested that ventricular mass was regulated by calcineurin signaling, and increased if the force-time integral deviated (in either direction) from a homeostatic setpoint. These elegant assumptions allowed Davis et al.’s model to reproduce the different magnitudes of concentric and eccentric growth measured in several strains of genetically-modified mice.

Very recently, Bischof et al. [19] inactivated a subunit of ATP synthase in mice and demonstrated that this reduced cell-level concentrations of ATP. Intriguingly, the intervention also induced cardiomyocyte hypertrophy. One interpretation of this result is that it reflects a completely new pathway for cardiac growth. Alternatively, it could be related to the same mechanisms that Davis et al. described.

Specifically, Bischof et al. demonstrated that hearts undergo concentric hypertrophy when the supply of ATP is restricted. Davis et al., on the other hand, showed that concentric hypertrophy is associated with an increased force-time integral. As the latter authors pointed out, the integral reflects the mechanical work performed by the heart, and thus its demand for ATP. It may therefore be possible to explain the observations of both Davis et al. and Bischof et al. using a single mechanism in which concentric hypertrophy responds to changes in the availability of ATP. Put simply, the heart hypertrophies when the supply of ATP is compromised (as investigated by Bischof et al.) and also if the demand for ATP increases (as shown by Davis et al.).

The present study was developed based on this general hypothesis. An additional research goal was to investigate pathophysiological conditions that are directly relevant to clinical care. Accordingly, the first step was to extend an multiscale model of the systemic circulation named PyMyoVent [20, 21] so that it grew in response to both biochemical and mechanical signals. Concentric growth responded to the myosin ATPase associated with contraction while eccentric growth was driven by passive intracellular stress. Multiple simulations were then performed to investigate how the ventricle responded to changes in hemodynamic load associated with different types of valvular disease.

These tests showed that the new framework reproduced clinical changes in left ventricular size measured during aortic stenosis, aortic insufficiency, and mitral insufficiency. The results reinforce the potential importance of cellular ATP concentrations as a driving signal for concentric hypertrophy and lay a foundation for future studies integrating cell-level signaling, hemodynamic loads, and cardiac growth.

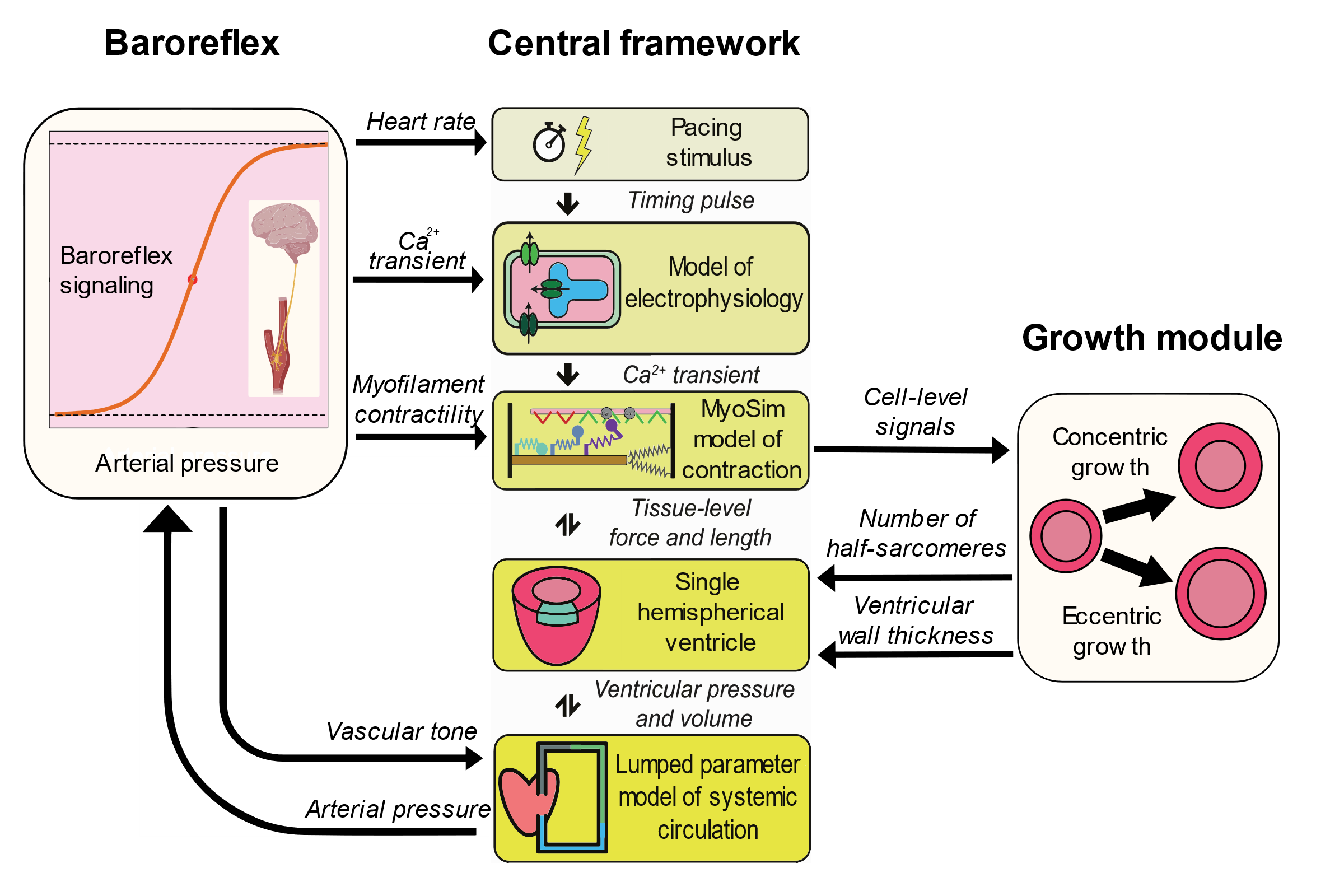
Methods

Overview

Fig 1 illustrates the PyMyoVent model that was used in this work. As originally described by Campbell et al. [22], the central framework consists of a pacing stimulus that drives an electrophysiological model which predicts a Ca2+ transient. A contraction model called MyoSim [23, 24] then uses the calculated Ca2+ transient to predict ventricular wall stress, which is then transformed into ventricular pressure via *Laplace’s Law*. Finally, a simple hemispherical model of the LV pumps blood through a lumped parameter representation of the systemic circulation.

The baroreflex algorithm was described by Sharifi et al. [20] and drives arterial pressure towards a user-defined setpoint by by modulating the heart rate, intracellular Ca2+ transient, molecular-level function of both the thick and the thin myofilaments, and vascular tone.

The growth algorithm was developed for this manuscript and is described below.



**Figure** **1.** **Overview of the PyMyoVent framework.** The baroreflex drives arterial pressure towards a user-defined setpoint by modulating heart rate, intracellular Ca2+ transients, myofilament contractility, and vascular tone and has been described in detail [20]. The growth algorithm was developed for this work and uses a biochemical signal (myosin ATPase) to drive concentric growth, and a mechanical signal (intracellular passive stress) to drive eccentric growth. Figure adapted from prior publications [20, 22].

Growth Module

The growth algorithm was designed to mimic the simpler aspects of the underlying biology. Specifically, a stimulus signal Si (where i represents concentric or eccentric growth) was transduced into a growth signal Gi that in turn drove changes in the architecture factor Ai. This approach is flexible and can be adapted tor many situations. As an example, Davis et al. [18] postulated that changes in the force-time integral modulated myocyte aspect ratio via calcineurin signaling. This could be implemented in the current framework by mapping Scon to the force-time integral, Gcon to the concentration of activated calcineurin, and Acon to the myocyte aspect ratio.

As explained in the Introduction, this work used a biochemical signal to drive concentric growth and a mechanical signal to drive eccentric growth. Accordingly, Scon was set to the myosin ATPase normalized to the myofibrillar volume, Acon was set to ventricular wall thickness, Secc was set to passive intracellular stress, and Aecc was set to the number of half-sarcomeres around the circumference of the ventricle. The Gcon and Gecc signals were not defined in molecular detail and were represented in the simulations by normalized variables. Some of the molecular mechanisms that may contribute to the Gi signals are described in the Discussion.

The rates of change of the Gi and Ai signals were defined as:

(1)

and

(2)

where kg,i is a rate constant that sets the speed at which Gi responds to a change in Si, Si, set is a homeostatic setpoint, and γi is a rate constant that sets the speed at which the architectural signal responds to changes in Gi. Equation 1 bounds the Gi signal between 0 and 1. These limits represent the minimum and maximum activities of the growth driving pathways.

The myosin ATPase and passive intracellular stress signals that stimulated concentric and eccentric growth were calculated as shown in equations 3 and 4 and as previously described [22] such that

(3)

where N0 is the number of myosin heads in a hypothetical half-sarcomere with a cross-sectional area of 1 m2, ΔG’ is the free energy produced by ATP hydrolysis (70 kJ mol-1), L0 is the reference length of the half-sarcomere (2.1 µm), and N0 is Avogadro’s number (6.02 x 1023 mol-1), and

(4)

where σ is a scaling factor, xhs is the length of the half-sarcomere, xslack is the half-sarcomere length when passive force is zero, and L sets the curvature of the passive force length relationship.

Simulation of valve disorders

Three types of valve disorders, aortic stenosis, aortic insufficiency, and mitral insufficiency were simulated in this work. (A fourth disorder, mitral stenosis, typically induces atrial rather than ventricular growth and cannot be simulated appropriately with the current framework.) Valvular dysfunction was initiated by adjusting the values of the resistance R and conductance G parameters in equations and which controlled the blood flows Q into and out of the ventricle.

(5)

and

(6)

Thus, aortic stenosis was simulated by increasing the value of Raorta above its default value, while valve insufficiencies were mimicked by increasing the Gaorta and Gmitral values from their default (non-leaking) values of zero.

Implementation and computer code

The code was written in Python using Numpy [25], Scipy [26], and pandas [27] libraries. The source code and instructions on how to reproduce all figures shown in this manuscript are available at <https://campbell-muscle-lab.github.io/PyMyoVent/>.

Equations to were discretized and added to the system of ordinary differential equations that underlie PyMyoVent calculations. Preliminary tests (Fig S in Supplementary Material showed that the values chosen for γi changed how long the ventricle took to grow to its steady-state size for a given condition but not the size of the chamber itself. Accordingly, myocardial growth was accelerated in the simulations by setting γi so that the ventricle reached its steady-state size in less than 1000 heart beats when a loading condition was changed. Since myocardial growth typically takes weeks to months in vivo, this simplification drastically reduced the time required to run the simulations.

The Si,set  values that define the homeostatic set-points for concentric and eccentric growth were fixed at the time-averaged values calculated during initial simulations performed without active growth.