Cell-based description of ventricular contraction in a model of the human cardiovascular system

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Abstract: A multiscale model of the cardiovascular system (CVS) is presented. Hemodynamics is described by a lumped parameter model, while heart contraction is described at the cellular scale. An electrophysiological model and a mechanical model were coupled and adjusted so that the pressure and volume of both ventricles are linked to the force and length of a half-sarcomere. Particular attention was paid to the extremal values of the sarcomere length, which must keep physiological values. This model is able to reproduce healthy behavior, preload variations experiments, and ventricular failure.

Keywords: Mathematical models - Physiological models - Multiscale models - Cardiovascular system - Sarcomere contraction

1. INTRODUCTION

Mathematical models of biological systems have become a powerful tool for cardiovascular sciences. These models allow for a variety of studies that are generally difficult to implement experimentally. A model of the whole cardiovascular system (CVS) basically needs a mathematical description of the following two components:

- The hemodynamics of the systemic and pulmonary circulation
- The active contraction of the heart

The hemodynamics, **i.e.** the blood flow evolution inside the blood vessels, is described here with a lumped-parameter model. The heart contraction is often decribed with *ad hoc* models, like the varying elastance model. Such *macroscopic* models are not based on the cardiac tissue properties and can not reproduce behaviors that arise from the *microscopic* scale. In this work we use a cardiac cell contraction model that we connect to the organ scale in order to get a multiscale model of the human CVS. The purpose of this model is to link macroscopic properties to the microscopic behaviors they originate from, a correlation impossible to establish with phenomenological models.

2. METHODS

Our lumped-parameters model of the CVS consists of a 6-chamber model, two of which being able of active contraction (Burkhoff and Tyberg (1993)). A schematic representation of this model is depicted on Fig. 1.

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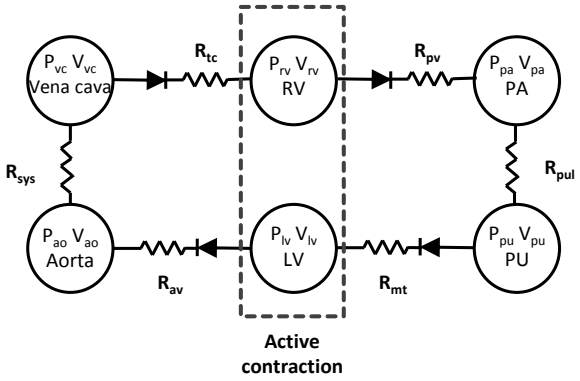

Fig. 1. Diagram of the 6-chamber hemodynamic model: left ventricle (LV), right ventricle (RV), pulmonary artery (PA), pulmonary vein (PU), aorta (AO), vena cava (VC).

2.1 Flow in the CVS

The flow inside the systemic and pulmonary circulation can be written as:

$$Q(t) = \frac{P_i(t) - Po(t)}{R} \tag{1}$$

where P_i is the pressure at the entrance of the chamber, Po the pressure at the exit, and R is the hydraulic resistance of the blood vessels.

The four cardiac valves (mitral, aortic, tricuspid, and pulmonary) act as diodes and allow for the unidirectionnality of the flow.

2.2 Passive chambers

The aorta (AO), vena cava (VC), pulmonary artery (PA), and pulmonary vein (PU) are considered as passive chamber (unable of active contraction). The pressure-volume relationship in these chambers is written as:

$$P(t) = E \cdot V(t) \tag{2}$$

where E is the elastance of the corresponding chamber. Finally, the chamber volume changes are described by the following differential equation:

$$\frac{\mathrm{d}V}{\mathrm{dt}} = Q_{in} - Q_{out} \tag{3}$$

where Q_{in} and Q_{out} are the flows that respectively enters and leaves the chamber.

2.3 Active chambers

Cell model The left and right ventricles are capable of active contractions, which are described at the cellular scale. Cardiac cells are excitable and contractile. We use the electrophysiological model of ten Tusscher and Panfilov (2006) to describe the ionic currents across the cell membrane and the mechanical model of Negroni and Lascano (2008) to describe the contraction. The cellular force is derived from the contraction of a half-sarcomere (basic unit of cell contraction), as shown on Fig. 2.

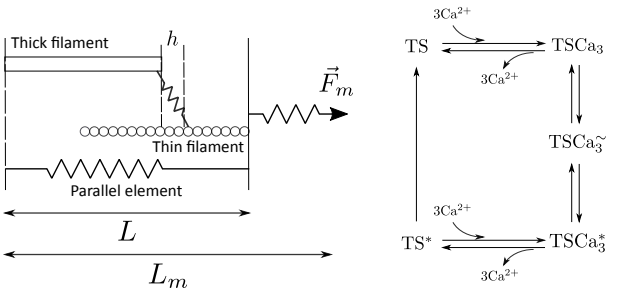

Fig. 2. Sarcomere contraction model (adapted from Negroni and Lascano (2008)). *Left*: Representation of a half-sarcomere of length L. L_m is the total length and allows to account for the compliant (elastic) ends of the muscle. *Right*: Calcium kinetics.

Myosin heads (also called crossbridges) of the thick filament attach to the thin filament and initiate the muscular contraction. This model describes the behavior of an equivalent crossbridge that represents all the crossbridges of the half-thick filament. It is assimilated to a linear spring of horizontal elongation h. The active force is proportionnal to this elongation. A parallel elastic element is added to account for the passive force of the muscle.

Calcium kinetics is described with a 5-state model represented on Fig. 2 (two states from the original paper were merged into one, see Negroni et al. (2015)) . A troponin system (TS) is composed of three adjacent troponin-tropomyosin units and can fix three calcium ions in one step ($\mathrm{TSCa_3}$). Then three crossbridges can attach to the actin molecules in a weak pre-power stroke state ($\mathrm{TSCa_3^{\sim}}$), then in a state where they are able to develop a power stroke ($\mathrm{TSCa_3^*}$). Finally the three calcium ions can detach ($\mathrm{TS^*}$) and the crossbridges eventually detach to end the cycle. The active force is also proportionnal to the concentrations of the three states with attached crossbridges ($\mathrm{TSCa_3^{\sim}}$, $\mathrm{TSCa_3^*}$, and $\mathrm{TS^*}$). Troponin currents were added in the equation governing calcium concentration from the Ten Tusscher and Panfilov model, thus linking the electrophysiology and the mechanical contraction of the cell. We then had to reduce the total cytosolic calcium buffer concentration to 100 μM provided that the buffering due to troponin was taken into account in the calcium kinetics described previously.

Ventricle model To connect the force F_m and total length L_m of the half-sarcomere to the pressure and volume of the active chamber, both ventricles are simply considered as spheres, as shown on Fig. 3.

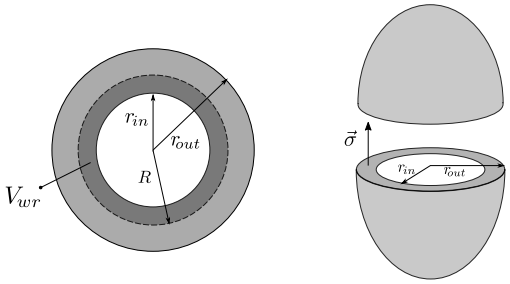

Fig. 3. Spherical ventricle model. *Left*: Top view of the ventricle. N sarcomeres are aligned along a circle of radius R (dotted black). *Right*: Both ventricles are assimilated to thin spheres. The wall stress σ is related to the force produced by the sarcomeres and allows for the calculus of the pressure inside the ventricle.

As already done by Shim et al. (2007), we assume that N half-sarcomeres of total rest length L_{m0} are aligned along a circle of radius R_0:

$$L_{m0} = \frac{2\pi R_0}{N}. \tag{4}$$

This radius was chosen so that the total half-sarcomere length L_m during a heartbeat varies between physiologically relevant extremes, **i.e.** between 0.98 and 1.115 μm (Rodriguez et al. (1992)). There is indeed an important (yet not fully elucidated) relationship between the force and the length of the cardiac muscle. This leads to important properties at the organ scale, especially the Franck-Starling mechanism. Thus it was essential to get the correct interval of variation for L_m in our multiscale model.

The blood volume inside the ventricle is given by:

$$V_{int} = \frac{4}{3}\pi {r_{in}}^3. \tag{5}$$

During a heartbeat, this volume varies according equation (3). Thus L_m is given by:

$$L_m = \frac{2\pi R}{N} \tag{6}$$

where R is calculated using:

$$V_{int} + V_{wr} = \frac{4}{3}\pi R^3. \quad (7)$$

In this relation, V_{wr} is the constant volume of the incompressible wall included between r_{int} (at the beginning of diastole) and R.

Now we have to connect the pressure P inside the ventricular cavity to the force F produced by the half-sarcomeres. We assume that many contractile units are distributed homogeneously in all directions on the ventricular wall (Shim et al. (2007)), so that the wall stress σ can be considered uniform. With a constant wall stress σ, the equilibrium of the two hemispheres of the ventricles gives the following expression of the pressure inside the active chambers:

$$P = \sigma(\frac{{r_{out}}^2}{{r_{in}}^2} - 1) \quad (8)$$

where σ is given by:

$$\sigma = \frac{F}{A} \quad (9)$$

with F the force and A the cross-sectional area.

The mechanical contraction model actually provides F_m, the force normalized with respect to the muscle cross-sectional area measured at a defined reference state, A_r:

$$F_m = \frac{F}{A_r}. \quad (10)$$

Assuming that muscle units have constant volume, we also have:

$$L_r \cdot A_r = L_m \cdot A \quad (11)$$

where L_r is the total sarcomere length at the reference aera A_r.

From (9) - (11) , we can obtain the pressure-force relation of our multiscale model :

$$P = 7.5\, F_m\, \frac{L_m}{L_r}(\frac{{r_{out}}^2}{{r_{in}}^2} - 1) + \gamma(V_{in} - V_0)^3. \quad (12)$$

The 7.5 factor stands for the units change (pressure is expressed in mmHg) and the last term is a passive pressure that accounts globally for the elastic properties of the tissue surrounding the ventricle (γ is the stiffness and V_0 is the unstressed volume).

The multiscale model presented above depends on many parameters, which can be split into microscopic (or cellular) parameters and macroscopic (or hemodynamic) parameters. The hemodynamic parameters (resistances and elastances of passive chambers, wall thickness of the ventricles) were optimized so that the following quantities range around human physiological values: systolic pressure (for both ventricles), amplitude of the aortic pressure, amplitude of the pulmonary artery pressure, systolic volume (for both ventricles), and stroke volume. The values of the cellular parameters can be obtained in the original papers in which the electrophysiological model and the contractile model were developed (ten Tusscher and Panfilov (2006); Negroni and Lascano (2008)). However, when these values of the cellular parameters are used in the complete multiscale model of the CVS, the ventricular pressure calculated at the end of diastole (filling phase of the ventricle) was found too high, while the systolic pressure (ejecting phase of the ventricle) was too low compared to physiological values. This difficulty originates from the too simple geometrical description of the ventricles, which are here considered as spheres. In a real heart, bundles of cardiac fibers are actually wrapped around the ventricular cavity so that the ventricle is also twisted in a very complex way during contraction. Of course the spherical model of ventricles presented above cannot take into account this aspect of contraction and an adaptation of the values of some parameters was necessary to compensate for the simplicity of the model. From (8), it is easy to understand that the systolic pressure, which is related to the maximum active force generated in the sarcomeres, can be increased by increasing the ventricle wall thickness. However, since the diastolic pressure, which is related to the passive force in the myocytes, also increases with the wall thickness, we had to drastically reduce the intensity of the sarcomere passive force in order to recover physiological diastolic pressures. In summary, the price to pay for the spherical model of the ventricles is a value of the wall thickness which is higher than standard physiological values and an important reduction factor to apply to the cellular parameter measuring the passive force of the sarcomere. All other cellular parameters keep however their original values, except for the total cytosolic calcium buffer concentration, as explained previously. The adjusted parameters are summarized in Table 1.

Table 1. Adjusted parameters

Parameter	Value
K_e (In passive force)	31500 $\mathrm{mNmm^{-2}\mu m^{-5}}$
L_e (In passive force)	3 $\mathrm{mNmm^{-2}\mu m^{-1}}$
SBV (Stressed Blood Volume)	$1.085\,10^3$ ml
R_{sys} (Systemic resistance)	$1.35\,10^3$ $\mathrm{mmHg\,ms\,ml^{-1}}$
R_{pul} (Pulmonary resistance)	73.20 $\mathrm{mmHg\,ms\,ml^{-1}}$
R_{mt} (Mitral valve resistance)	22.09 $\mathrm{mmHg\,ms\,ml^{-1}}$
R_{tc} (Tricuspid valve resistance)	11.56 $\mathrm{mmHg\,ms\,ml^{-1}}$
R_{vaor} (Aortic valve resistance)	48.0 $\mathrm{mmHg\,ms\,ml^{-1}}$
R_{pv} (Pulmonary valve resistance)	3.51 $\mathrm{mmHg\,ms\,ml^{-1}}$
E_{ao} (Aorta elastance)	0.85 $\mathrm{mmHg\,ml^{-1}}$
E_{vc} (Vena cava elastance)	0.01 $\mathrm{mmHg\,ml^{-1}}$
E_{pa} (Pulmonary artery elastance)	0.34 $\mathrm{mmHg\,ml^{-1}}$
E_{pv} (Pulmonary vein elastance)	0.04 $\mathrm{mmHg\,ml^{-1}}$
V_{lvw} (Left ventricular wall volume)	201.24 ml
V_{rvw} (Right ventricular wall volume)	30.34 ml

3. RESULTS

We first simulated a baseline situation corresponding to a healthy individual. Some important microscopic variables are presented on Fig. 4 with their corresponding macroscopic variables. The action potential, the intracellular calcium, and the force time evolutions are correctly reproduced. It is important to stress that the sarcomere length lies between physiological values (Rodriguez et al. (1992)).

The pressure-volume loops are also correctly reproduced. Some hemodynamic variables are also shown on Fig. 5.

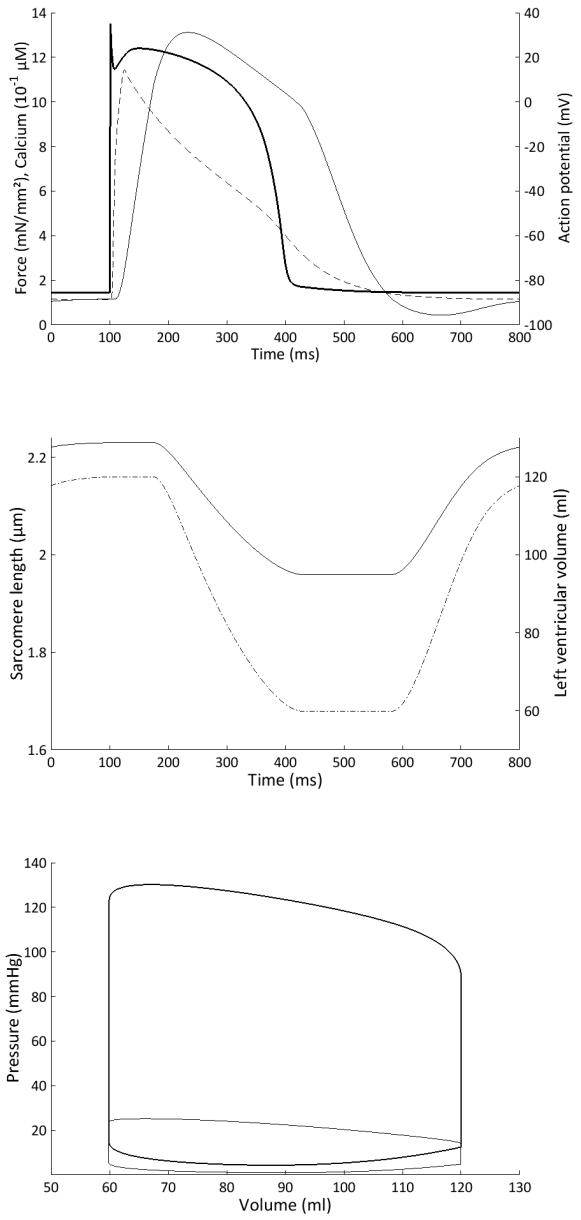

Fig. 4. Top panel: Action potential (bold), normalized force (normal), and intracellular calcium (dashed) time evolution during one heartbeat in the left ventricle. Middle panel: Sarcomere length (normal) and left ventricular volume (dash-dotted) time evolution during the same heartbeat. Bottom panel: Pressure-volume loop in the left (bold) and right (normal) ventricle during the same heartbeat.

We also simulated a preload variation experiment. To mimic the inflation of a Fogarty balloon, which is a current way of reducing preload, we have increased tricuspid valve resistance, thus allowing less blood to enter the right ventricle. The consequences on the pressure-volume loops on both ventricles are presented on Fig. 6. It is worth emphasizing that the upper left corners of the PV-loops are not exactly located on a straight line, as often postulated when varying elastance models of contraction are used.

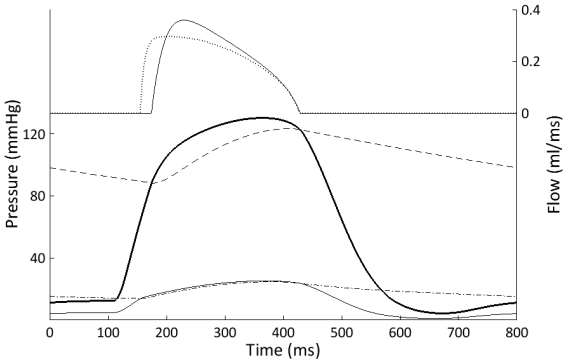

Fig. 5. Hemodynamic variables. The top two curves represent the flow through the aortic valve (normal) and through the pulmonary valve (dotted) during one heartbeat. Left ventricular pressure (bold), aortic pressure (dashed), right ventricular pressure (normal) and pulmonary pressure (dash-dotted) are also represented.

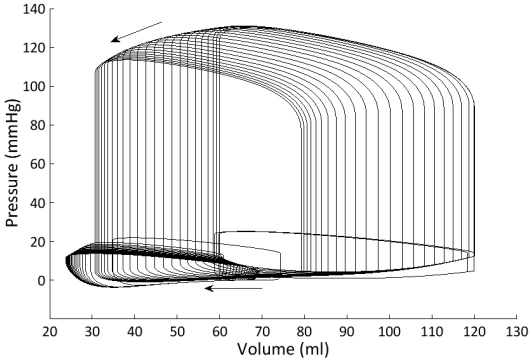

Fig. 6. Pressure-volume loops in the left and right ventricle during a decrease in preload in the right ventricle.

Eventually, we simulated a case of ventricular failure. It has been shown that heart failure symptoms originate at the cellular scale (Beuckelmann et al. (1992, 1993); Wang and Hill (2010)). Alterations in ionic currents and calcium handling lead to a prolonged action potential, a lower peak of intracellular calcium, and a lower force. Reduction in current densities of the inward rectifier K^+ current and the transient outward K^+ current, increased activity of the Na^+/Ca^{2+} exchanger and a reduced Ca^{2+} sequestration by the sarcoplasmic reticulum were implemented in our model. Our multiscale model is then able to connect these cellular altered properties to the hemodynamics variables, as shown on Fig. 7.

4. DISCUSSION

We have developed a multiscale model of the human CVS based on the ten Tusscher and Panfilov model of electrophysiology, the Negroni and Lascano model of sarcomere contraction, and a lumped parameter model of hemodynamics.

The ventricle model is quite simple compared to other works (Arts et al. (1991), Bovendeerd et al. (1992)), but this approach was chosen for its low computational cost. The aim of our work is to connect two scales of cardiac

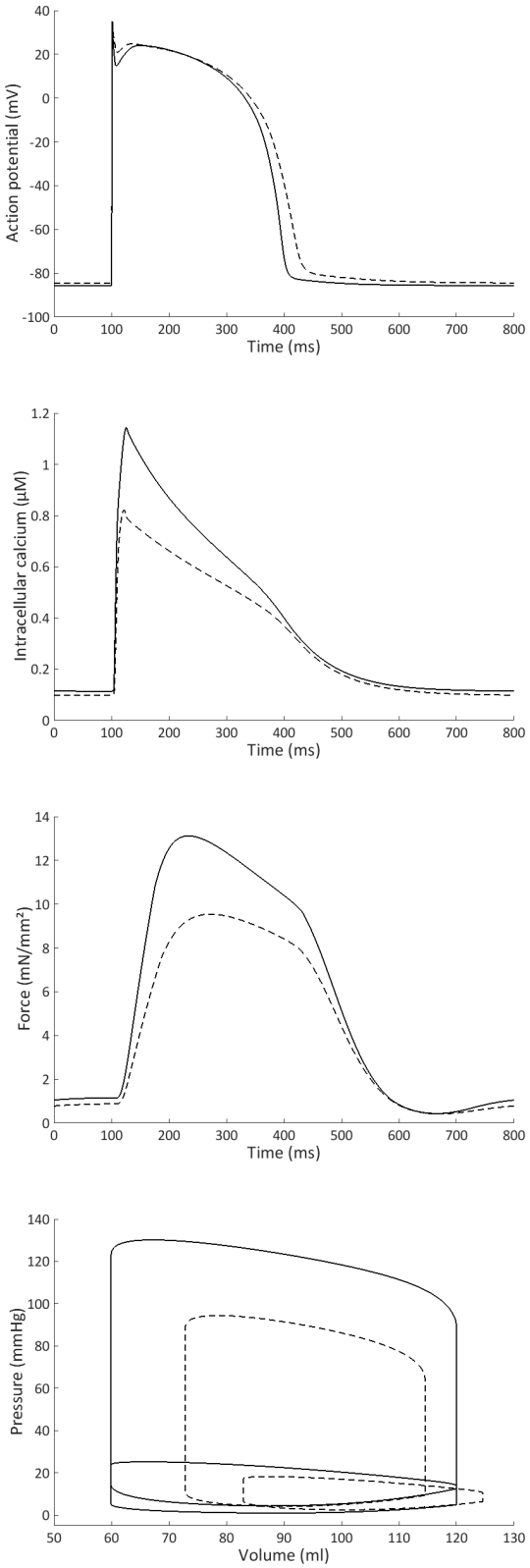

Fig. 7. Ventricular failure (dashed) versus normal ventricle. From top to bottom: action potential, intracellular calcium, normalized force, pressure-volume loops.

contraction and study the correlation of microscopic and macroscopic variables inside a complete CVS model. This implies the computation of many heart beats in a row, which is the reason we choose a simple spherical ventricle model. Our results, on the other hand, correlate well with experimental data. Our multiscale model can account for a healthy behavior as shown in Fig. 4 and 5. More importantly, it is also able to reproduce pathological behaviors that originate at the cellular scale, like heart failure, and the consequences on the whole CVS. It is also able to reproduce basic hemodynamic experiments like preload variations.

Our approach in building this multiscale model was similar to Shim et al. (2007) but with four major differences: we carefully choose the volume V_{wr} from Fig. 3 so that the sarcomere length ranges between extremal physiological values. The pressure-force relationship derived in (8) was also different from the one used by Shim et al. (2007). We also used the last version from the mechanical model of Negroni and Lascano (2008). Eventually, we used our model to reproduce heart failure symptoms.

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