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Multiscale model of the human cardiovascular system: Description of heart failure and comparison of contractility indices

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ABSTRACT

A multiscale model of the cardiovascular system 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 extreme values of the sarcomere length, which must keep physiological values. This model is able to reproduce healthy behavior, preload variations experiments, and ventricular failure. It also allows to compare the relevance of standard cardiac contractility indices. This study shows that the theoretical gold standard for assessing cardiac contractility, namely the end-systolic elastance, is actually load-dependent and therefore not a reliable index of cardiac contractility.

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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 complete model of the whole human cardiovascular system (CVS) requires a mathematical description of two components:

- The cardiac pump, composed of two atria and two ventricles;
- The vascular network (veins, arteries, capillaries, ...).

The heart contraction is often described with *ad hoc* models, like the time-varying elastance model [1–3]. Such *macroscopic* models are not based on the cardiac tissue properties and cannot reproduce behaviors that arise from the *microscopic* scale. In this work, a cardiac cell contraction model is used and integrated at the organ level in order to get a multiscale model of the human CVS [4,5]. 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

There is always a balance to be found between a sophisticated model and computational efficiency. When modeling complex biological systems like the CVS, assumptions and simplifications have to be made in order to get a reasonable computational time. As far as our CVS model is concerned, we wanted a short computational time in order to study physiological behaviors at the whole CVS scale. In this section we describe our CVS model and the assumptions we had to make in order to get a computationally efficient model.

2.1. The vascular network

Blood travels unidirectionally across the body through blood vessels. Leaving the left atrium and ventricle, it flows successively through systemic arteries, capillaries, veins and goes back to the right atrium and ventricle. It is then sent through pulmonary arteries, capillaries and veins. It eventually goes back to the left atrium and ventricle and the cycle starts all over again, as depicted in Fig. 1. In this work, we assimilate this complex system composed of many different vessels to a 6-chamber model. Four chambers are assimilated to elastic “balloons” that can be filled with blood and the other two represent the cardiac pump. The fluid mechanics equations that govern such a system are described elsewhere [2,5,6] and only the cardiac pump model will be described in detail in the next section.

Abbreviations: CVS, cardiovascular system; ESPVR, end-systolic pressure-volume relationship; AP, action potential; E_{es}, end-systolic elastance.

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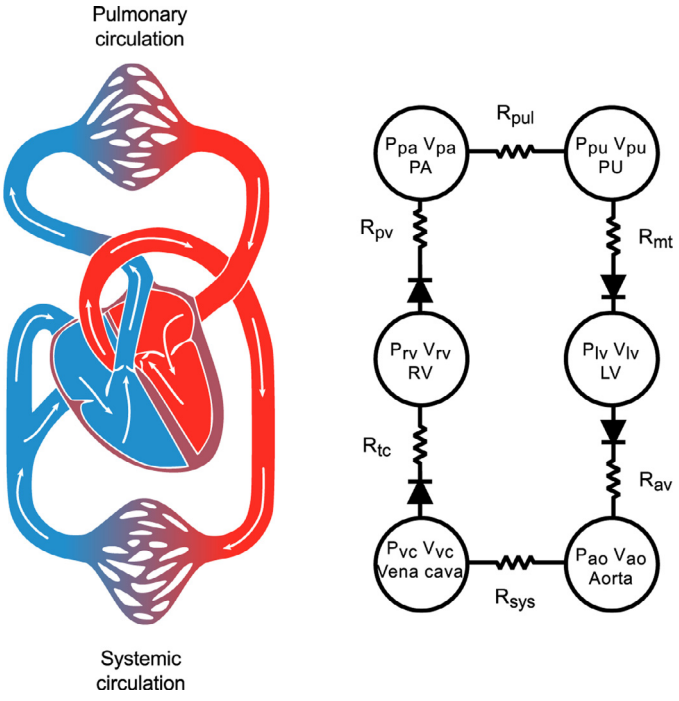

Fig. 1. Left: representation of the cardiovascular system. Right: diagram of the 6-chamber hemodynamic model. Left ventricle (LV), right ventricle (RV), pulmonary artery (PA), pulmonary vein (PU), aorta (AO), vena cava (VC).

2.2. The cardiac pump

The cardiac pump is composed of two atria and two ventricles. Here we only model the ventricles, as they hold the major role in ejecting the blood through the systemic and pulmonary circulations. Thus we described the cardiac pump with only two chambers, the left and right ventricles.

The major difference with the other four chambers of the CVS model is that ventricles are able to actively contract and generate pressure. Therefore a passive pressure-volume relationship of the form $P(t) = E \cdot V(t)$ (where E is the constant elastance of the chamber) is not suitable in this case. A convenient solution would be to use a similar equation, but with a time-dependent elastance. The time dependence would then be fitted to experimental data in order to get physiological results. This *ad hoc* approach (called the time-varying elastance model) has been extensively used to model cardiac contraction [1–3]. It has the advantage of providing a very simple mathematical description of active contraction and can lead to consistent results. However this model has some limitations. It is based on the assumptions that the end-systolic pressure-volume relationship (ESPVR) is linear and unique, even though experiments have shown this curve to be more parabolic than linear [7,8] and load-dependent [9]. Furthermore, the ventricular pressure has been shown to be dependent on the flow out of the ventricle [10,11]. Subsequent modifications to this model have been proposed to account for the non linear ESPVR and the flow-dependent pressure [10–12]. However, these *ad hoc* modifications can not overcome the main drawback of this model, namely the absence of connection with the physiology of cardiac contraction.

We chose a more physiological approach and described cardiac contraction at the cellular scale instead [4,5,13]. This heart model is portrayed in the following sections.

2.2.1. Cell model

Cardiac cells are excitable and contractile. When an action potential (AP) arises, the cell is able to contract through the excitation-contraction process. We followed the approach of Puglisi et al. [14] to build a human cardiac cell model: we connected an electrophysiological model of a human ventricular cell [15] to a mechanical contraction model of a half-sarcomere [16–18]. Those two models are described below.

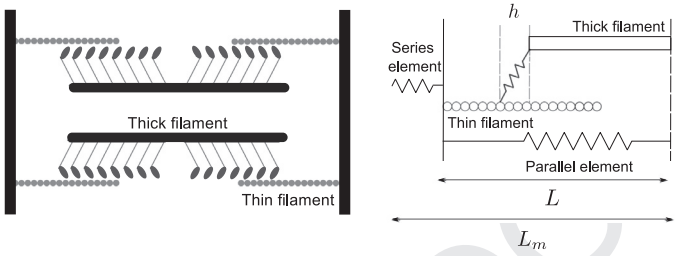

Fig. 2. Left: representation of the thin and thick filaments of a sarcomere. Right: mechanical model of a half-sarcomere (adapted from [16]).

Electrophysiology

An electrophysiological model of an excitable cell is able to reproduce the AP across the cell membrane, *i.e.* the time evolution of the membrane electric potential V. This potential varies because massive quantities of ions cross the membrane (leading to ionic currents) during an AP. The equation governing the time evolution of V is given by:

$$C_m \frac{dV}{dt} + \sum_j I_j + I_{stim} = 0$$

where C_m is the membrane capacitance, I_j is the electrical current carrying ion j and I_{stim} is a stimulation current that triggers the AP.

From the ionic currents we can also obtain the time evolution of the intracellular concentrations for each type of ions:

$$\frac{d[\text{Ion}]_i}{dt} = \frac{I_{in} - I_{out}}{z_{ion} V_c F} \quad (1)$$

where I_{in} (resp I_{out}) is the global electrical current carrying the ions inside (resp. outside) the intracellular compartment of volume V_c, z_{ion} is the valence of the ion, and F is the Faraday constant.

An appropriate description of the ionic currents is required to obtain physiological results. More information can be found in the original paper [15] regarding the mathematical expressions of all the ionic currents.

Mechanical contraction

Cardiac cells contain basic contractile units called sarcomeres, schematized in Fig. 2. A sarcomere is mainly composed of actin (thin) and myosin (thick) filaments. In presence of calcium and ATP, a myosin head (also called a crossbridge) is able to attach to an actin molecule and rotate its head, thus pulling the actin filament. The active force produced by a sarcomere is related to the force produced by the pulling (also called the power stroke) of the myosin head. There is also a passive contribution to the total produced force because of the sarcomere elastic properties.

We use the model of Negroni and Lascano [16–18] to describe the contraction of a half-sarcomere, composed of a half-thick and a half-thin filaments (see Fig. 2). Only a brief summary of the model is given below, but a more detailed explanation can be found in the original papers. This model focuses on 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 that is always attached to the half-thin filament (otherwise the force would suddenly go to zero, which is not physiological).

The active force is proportional to the spring elongation h but also to the concentrations of attached myosin heads. These concentrations can be determined from the intracellular calcium kinetics depicted in Fig. 3. Calcium kinetics is described with a

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