From Cell to Heart: A Multi-scale Lumped Parameter Model of the Cardiovascular System

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Introduction

In cardiovascular computational physiology the importance of understanding cardiac contraction as a multi-scale process is of paramount importance to understand causality across different scales. In this study, a multi-scale model of a left ventricle [1] which includes the cross-bridge sliding mechanism (at protein level), the action potential and the intracellular calcium concentration ($[Ca^{2+}]$) (at cellular level), was extended (at the organ level) to the whole CV system by incorporating heart chambers, heart valves and blood vessels including resistance, compliance and inertance effects [2].

Materials and Methods

A multi-scale model of the heart has been produced, with biological scales ranging from the protein to the organ level. At the protein level, the four state model represents the interactions between $[Ca^{2+}]$ and the cardiac myofilaments within a sarcomere. It describes the crossbridges kinetics based on the evaluation of data from isolated hearts in guinea pigs. The different states of the four state model are dependent on $[Ca^{2+}]$ and governed by ordinary differential equations based on [3]. In order to simulate the $[Ca^{2+}]$ and the action potential, the Livshitz-Rudy model has been used [4]. This model accounts for the dynamic changes in ionic concentrations, such as $[Ca^{2+}]$, and ionic fluxes during the action potential. The $[Ca^{2+}]$ is the key signaling ion that initiates the contraction of the heart within this model. To simulate the cardiac dynamic of the ventricles, a lumped parameter model described in [5] is used as a blueprint. This model encompasses different biological scales, from the mechanism of contraction to the hemodynamics of the ventricles, in a coherent, modular and unified

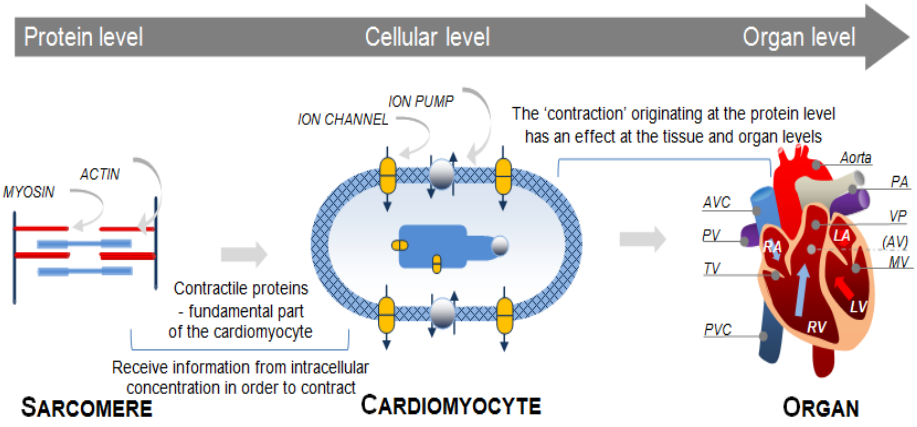

Figure 1. Multi-scale model from protein level to organ level, sarcomere unit at protein level, cardiomyocyte at cellular level, heart chambers and blood vessels at organ level (aortic valve (AV), anterior vena cava (AVC), mitral valve (MV), pulmonary arteries (PA), pulmonary valve (PV), pulmonary veins (VP), posterior vena cava) (PVC) and tricuspid valve (TV). The four heart chambers included in this model are the left atrium (LA), left ventricle (LV), right atrium (RA) and right ventricle (RV).

fashion. The models of the left and right ventricle are based on the same principle described in [5]. The hemodynamics of both ventricular models are highly dependent on according atrial filling pressures. A lower filling pressure in the right ventricle than in the left ventricle distinguishes its hemodynamical behaviour. A schematic diagram of the multiscale model from the protein (microscopic) level to the organ (macroscopic) level is shown in Figure 1.

The heart valves are modelled as ideal diodes which allow one-way direction of blood flow. The main blood vessels (systemic and pulmonary arteries and veins) are modelled using electrical analogs [2]. The heart and the electric-analogue of blood vessels are provided in Figure 2. C, R and L denote the compliances, resistances and inertances, while their index indicate the compartment of systemic arteries (va), systemic veins (vs), pulmonary arteries (ap) and pulmonary veins (vp).

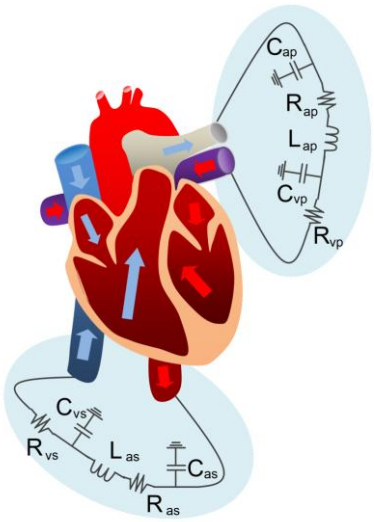

Figure 2. Electric-analogue of blood vessels and heart

The simulations were performed using the MATLAB Simulink solver ODE45 with a maximum step size of 0.25 ms. The heart rate was kept at 60 bpm while a body surface area of 1.9 m^2 was assumed to calculate the cardiac index.

Results and Discussion

Simulations were performed in order to obtain healthy (appropriate) hemo-dynamics (Figure 3e). Figures 3a and b show the AP and $[Ca^{2+}]$ as results from the cellular level leading to the hemodynamics shown in 3c and d. These graphs present ventricular and arterial pressures, as well as ventricular volumes (Figure 3e). The resulting pressure-volume relationships in the ventricles are presented in Figure 3f.

The Livshitz-Rudy model constitutes the base level of the mathematical model for the cardiomyocyte and provides the $[Ca^{2+}]$ and the resulting AP. It shows the characteristic phases starting from a negative resting potential at around -90 mV, reaching a peak of around +48 mV, while a transient increase in $[Ca^{2+}]$ accompanies the AP. The left ventricular pressure changes between 5 and 124 mmHg while the aortic pressure changes between 78 and 125 mmHg. The right ventricular pressure is changing between 1 and 28 mmHg with a pulmonary arterial pressure between 13 and 28 mmHg. The stroke volume is ~86 mL whilst the cardiac output for the defined heart rate is 5.16 L/min. A cardiac index of 2.72 L/min/m^2 and an ejection fraction of 60% are obtained in this simulation.

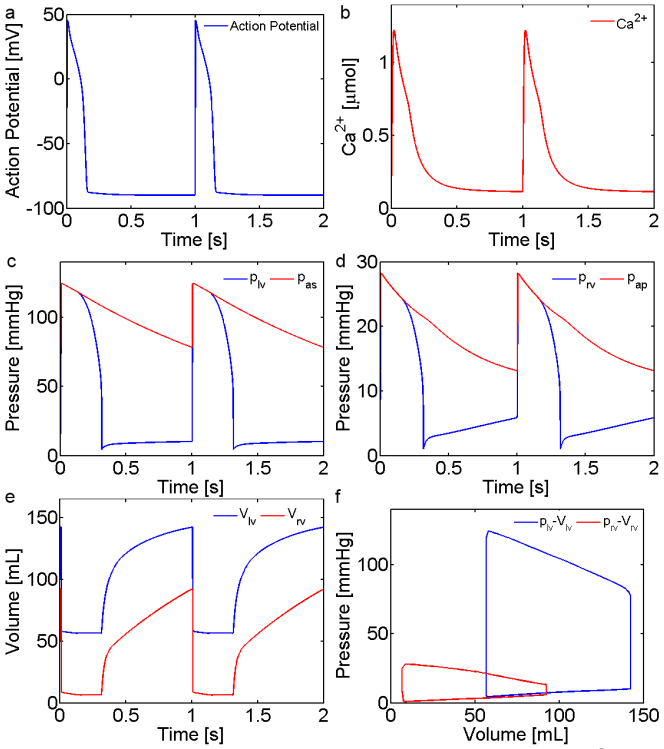

Figure 3. a) Action potential, b) intracellular $[Ca^{2+}]$, c) pressures in left ventricle (p_{lv}) and systemic arteries (p_{as}), d) pressures in right ventricle (p_{rv}) and pulmonary arteries (p_{ap}), d) volumes in left ventricle (V_{lv}) and right ventricle (V_{rv}), f) pressure-volume relationship in the ventricles.

There are limitations in this model due to the coupling of different scales described with different degrees of complexity. Hence, some harmonisation might be required to refine the steepness of the left ventricular pressure gradient, which will follow as an ongoing research.

Conclusion

The extended multiscale model is applied to obtain the cardiac hemodynamics within the chambers and blood vessels of a healthy heart. As an outlook the presented multiscale model can be applied to predict and simulate the effects of arrhythmias or pharmacological intervention studying cause-effect relationships from the microscopic to the macroscopic level.

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