Sensitivity Analysis of an Elastance-based Cardiovascular Model for CRT Optimization

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Abstract

Cardiac resynchronization therapy (CRT) is an implant-based treatment for patients suffering from heart failure with desynchronized ventricular contraction. A number of parameters have been proposed in the literature to characterize this cardiac desynchronization, in order to optimize CRT patient selection and delivery. One of such parameters is the left pre-ejection interval (LPEI). Cardiovascular lumped-parameters models have been previously used to analyze cardiac desynchronization. However, the choice of elastance driver functions, which generate the cardiac mechanical activity in these models, remains challenging. Most of the previously proposed models use symmetric functions, limiting the possibility to reproduce some physiopathological phenomena, especially in heart failure. In this work, we integrate an asymmetric double-Hill elastance driver function into a cardiovascular lumped-parameters model and perform global and local sensitivity analyses of this function's parameters on LPEI. Results highlight the major role of the parameters characterizing the upward (systolic) and downward (diastolic) slopes of the driving function, as well as the interactions between these parameters. These results provide meaningful insight for an improved physiological interpretation of the LPEI dynamics on CRT and for patient-specific parameter identification strategies.

1. Introduction

Cardiac resynchronization therapy (CRT) is an implant-based treatment for mechanically uncoordinated hearts for heart failure patients [1]. Positive response to CRT partially depends on the appropriate selection of the atrio- and inter-ventricular (AV and VV) delays, which are two sensitive configuration parameters of the CRT device [1]. In order to characterize resynchrony and determine whether the therapy is efficient or whether it can be optimized, the left pre-ejection interval (LPEI) has been proposed as a useful echocardiography marker [2]. LPEI represents the time interval between QRS onset and the beginning of aortic Doppler velocity curve. In a population of CRT candidates, the Prospect trial [2] has reported LPEI values comprised between 120 and 190 ms.

Pulsatile, lumped-parameters, cardiovascular computational models have already been applied to search for optimized AV and VV delays CRT settings [3, 4]. These models involve several intertwined state variables, particularly sensitive to certain model parameters, which can make it harder to understand the model and to correctly fit it to patient data. For instance, parameters associated with the elastance driver functions that control contraction and relaxation properties of each cardiac chamber have a significant impact on the simulated volumes, pressures and transvalvular flows. Therefore, a proper definition of these elastance driver functions and their parameters is essential to simulate properly the wide range of possible LPEIs. Symmetrical functions are generally chosen for these elastance drivers (i.e. sinusoidal form [5] or exponential form in [3] [4]). However, such symmetrical forms do not allow for a correct physiological representation of the systolic and diastolic dynamics.

To the best of our knowledge, no exhaustive sensitivity analyses have been performed to assess the impact of asymmetric elastance functions parameters on LPEI, nor any other biological marker of cardiac dyssynchrony. In this work, we propose to investigate the effect on LPEI of an asymmetric double-Hill elastance function, as introduced in [6], through a global statistical sensitivity analysis, completed by local sensitivity analyses.

2. Methods

The proposed model is based on previous works presented in [3] and [4]. It is a lumped-parameters model made of a set of ordinary differential equations, integrating a cellular automata-based conduction system, elastance-based atrial and ventricular chambers, and systemic and pulmonary circulations. Contrary to [3], interventricular

coupling is not represented and different elastance driver functions are used.

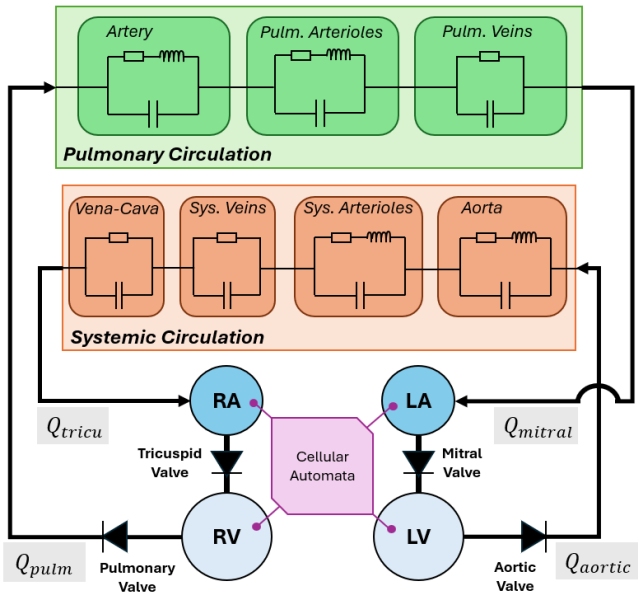

Figure 1. Cardiovascular model's equivalent electric circuit diagram

The model is summarized in Figure 1. Pressure and flow variables inside pulmonary and systemic blocks are described by two- and three-elements Windkessel models using equivalent inductive, capacitive and resisitive components, as shown in Figure 1. Blood flow going through these blocks is pulsed at the rate dictated by the electrical conduction system (ECS) submodel.

The ECS submodel is constituted of eight interconnected cellular automata, representing the SA node, the AV node, the atria, the His bundle, the left and right bundle branches and the ventricles. Each cellular automaton (CA) can be in four different states; successively, "idle" state or "systolic depolarization period" (SDD), "upstroke depolarization period" (UDP), "absolute refractory period" (ARP) and "relative refractory period" (RRP). Each state is characterized by a given duration. Transition to the next state occurs automatically when a CA reaches the end of its current state phase. Furthermore, when a CA reaches the end of UDP, it directly causes all CAs in its neighborhood that are not in ARP or RRP to switch to UDP.

The mechanical activity of each chamber is characterized by relationships between chambers volumes, pressures and elastances, as shown in the following equations:

$$\begin{aligned} P_a(t) &= E_a(t)(V_a(t) - V_{a,0}) \\ E_a(t) &= E_{a,min} + E_{a,max} e_a(t) \end{aligned} \tag{1}$$

$$\begin{aligned} P_v(t) &= e_v(t)P_{v,es}(t) + (1 - e_v(t))P_{v,ed}(t) \\ P_{v,es}(t) &:= E_{v,es}(V_v(t) - V_{v,0}) \\ P_{v,ed}(t) &:= P_{v,0}(\mathrm{e}^{\lambda_v(V_v(t) - V_{v,0})} - 1) \end{aligned} \tag{2}$$

Where P_c, V_c and e_c represent the atrial ($c = a$) or ventricular ($c = v$) pressures, volumes and elastance driver functions, respectively. Each cardiac chamber is represented explicitly, with $a \in \{RA, LA\}$ and $v \in \{RV, LV\}$. Notations ed and es represent "end-diastolic" and "end-systolic" contributions to ventricular pressures. The link between electrical and mechanical parts of the model lies in e_a and e_v. In fact, each time a chamber's CA reaches the end of UDP, its elastance driver function switches from zero to a double-Hill function f_{DH} defined as:

$$f_{DH}(t) := k \frac{(\frac{t-\tau}{\alpha_1 T})^{n_1}}{(1 + (\frac{t-\tau}{\alpha_1 T})^{n_1})(1 + (\frac{t-\tau}{\alpha_2 T})^{n_2})} \mathbb{1}_{t>\tau} \tag{3}$$

Where T is the cardiac period. As suggested by the form of Equation 3, different sets of parameters $(k, \tau, \alpha_1, \alpha_2, n_1, n_2)$ can lead to a great diversity of profiles, including assymetric ones, suggesting a high sensitivity of the model to these parameters.

Numerical resolution is achieved using a classical 4th order Runge-Kutta method with a time step of 0.1 milliseconds. To make sure that the system is in its stationary state when studied, an 8 seconds evolution is simulated and only the last cycle is taken for analyses.

After implementation of the model, sensitivity analyses have been performed. The global sensitivity analysis of the double-Hill function parameters on LPEI requires the definition of ranges for each parameter. In this work, we applied a two-step parameter configuration method: 1) identifying through iterative semi-automatic adjustments an initial set of parameters leading to plausible values, in particular for mitral and aortic trans-valvular flows as well as LV pressure; 2) defining each parameter ranges bounds as $\pm 20\%$ of the initial parameters values.

Once the support of the parameter space ($\mathcal{E}$) has been defined, the Morris' screening method is applied to rank parameters depending on their influence on a given output [7]. Briefly, this method consists in sampling N vectors $\mathbf{P}_j$ in $\mathcal{E}$, making them evolve by m consecutive increments with a step size of $\delta \in]0, 1[$ in randomly chosen directions $\mathbf{u}_p$, and computing the so-called "elementary effects" EE_j^p of each parameter p as:

$$EE_j^p := \frac{\mathcal{M}(\mathbf{P}_j + \delta |I_p| \, \mathbf{u}_p) - \mathcal{M}(\mathbf{P}_j)}{\delta} \tag{4}$$

Where $\mathcal{M}(\mathbf{X}) \in \mathbb{R}$ is the result of a model evaluation at point $\mathbf{X} \in \mathcal{E}$ and $|I_p|$ is the length of parameter p's interval. The mean of absolute elementary effects μ^* and their standard deviation σ are then computed for each parameter. They are classically represented in a (μ^*, σ) graph.

Finally, we performed local sensitivity analyses on aortic trans-valvular flow. The latter has been plotted together with left ventricle's elastance driver function while varying each of the most influential parameters that were identified with Morris' screening. Non-varying parameters were chosen equal to medians of corresponding parameters' space intervals, while the varying parameter was moved from -50% to $+50\%$ around this median.

3. Results and discussion

A simulation of the main cardiovascular variables to be studied, using the initial set of parameters obtained during the calibration phase, is shown in Figure 2, for an imposed heart rate of 80 bpm. The ranges for the model parameters to be analyzed are presented in Table 1.

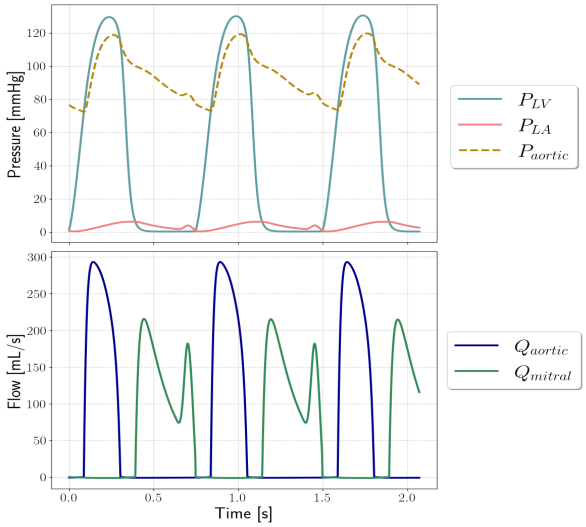

Figure 2. Simulation results for the initial set of model parameters. P_{LV}= Left ventricular pressure; P_{LA}= Left atrial pressure; P_{aortic}= Aortic pressure; Q_{aortic}= Aortic trans-valvular blood flow ; Q_{mitral}= Mitral trans-valvular blood flow

The following hyper-parameters for the Morris' analysis method were chosen: $N = 500$, $m = 40$ and $\delta = 0.01$. The (μ^*, σ) parameter sensitivity graph is shown in Figure 3 and the (μ^*, σ) values for each parameter are listed in Table 2. Local sensitivity analyses are consolidated in Figure 4.

Table 1. Parameters' ranges for global sensitivity analysis. All parameters are dimensionless, but τ, in seconds.

Parameter	Atria	Ventricles
k	$[0.2, 0.3]$	$[1.2, 1.8]$
τ	$[0.04, 0.06]$	–
α_1	$[0.08, 0.12]$	$[0.28, 0.42]$
α_2	$[0.12, 0.18]$	$[0.36, 0.54]$
n_1	$[3.2, 4.8]$	$[1.2, 1.8]$
n_2	$[14.4, 21.6]$	$[16.0, 24.0]$

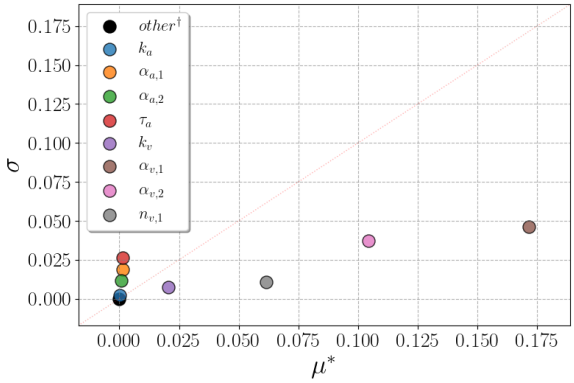

Figure 3. Morris screening elementary effects on LPEI of double-Hill parameters. $^\dagger other$: parameters such that μ^* and σ are lower than 10^{-3}.

It appears from Figure 3 and Table 2 that the most sensitive parameter on LPEI is $\alpha_{v,1}$. This parameter mainly impacts the slope of the ascending part of ventricular elastances (see Figure 4): a low value of $\alpha_{v,1}$ will produce a steeper slope, representing an increased inotropic effect, leading to an earlier start of ejection, which translates into a reduction of LPEI. This parameter has also a strong influence on the shape of the aortic flow.

The second most influential parameter is $\alpha_{v,2}$, which mainly affects the diastolic elastance profile and the time at which ventricular maximal elastance is reached (see Figure

Table 2. Elementary effects mean of absolute values μ^* and standard deviation σ

Parameter	μ^*	σ
$\alpha_{v,1}$	0.17	0.05
$\alpha_{v,2}$	0.10	0.04
$n_{v,1}$	0.06	0.01
τ_a	$< 10^{-2}$	0.03
k_v	0.02	$< 10^{-2}$
$\alpha_{a,1}$	$< 10^{-2}$	0.02
$\alpha_{a,2}$	$< 10^{-3}$	0.01
k_a	$< 10^{-3}$	$< 10^{-2}$

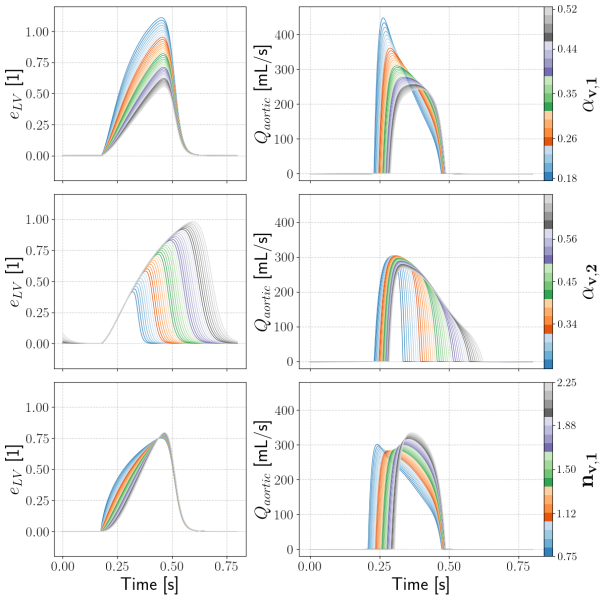

Figure 4. e_{LV} (left) and Q_{aortic} (right) evolution with most influential Morris screening parameters

4). High values of $\alpha_{v,2}$ lead to wider elastances and delayed diastole. Since the AV interval is constant in these simulations, a high $\alpha_{v,2}$ leads to a delayed mitral flow, a reduced early diastolic ventricular filling, lessening the Frank-Starling effect and delaying aortic flow ejection.

The third most sensitive parameter on LPEI is $n_{v,1}$. Its main effect is on the form (concave or convex) of the systolic part of the profile, with a very low effect on their maximum values. The resulting impact on the aortic ejection start time is hence similar to that of $\alpha_{v,1}$.

As expected, most influential parameters are from e_v, since they directly modify ventricular contraction properties, which feed through to ventricular ejection timing. We note a $\sigma > 0.025$ for parameters $\alpha_{v,1}$ and $\alpha_{v,2}$. This reflects the non-linear effect that these parameters have on LPEI, explained by the form of f_{DH}, but also their mutual influence. Furthermore, we observe that e_a's parameters have primarily a non-linear effect on LPEI (which remains small compared to e_v's) that arises from an influence on LV filling before ejection, by modifying either atrial contraction time or strength.

4. Conclusion

We proposed a lumped-parameters cardiovascular model integrating double-Hill elastance driver functions and applied a Morris screening method to rank the influence of atrial and ventricular elastance parameters on LPEI. Results showed the prominent role played by $\alpha_{v,1}$, $n_{v,1}$ and $\alpha_{v,2}$, for which a physical interpretation was given. These results are valuable for the calibration of this model in a patient-specific manner. This work also shows the interest of using asymmetric elastance functions in these models, that allow for finer representations of the hemodynamic profiles, resulting on a given LPEI. Nevertheless, the added degrees of freedom of the double-Hill function lead to a reduced identifiability. Significant non-linear and intertwined effects exist between its parameters. Future works are directed to the investigation of other, more identifiable, asymmetric elastances, such as for instance piecewise cumulative Kumuraswamy distribution functions, and the adaptation of our parameter identification methods to these functions.

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