Model-Based Parameter Estimation Using Cardiovascular Response to Orthostatic Stress

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Abstract

This paper presents a cardiovascular model capable of simulating the short-term ($\lesssim$ 3 min) transient hemodynamic response to gravitational stress and a gradient-based optimization method that allows for automated estimation of model parameters from simulated or experimental data. We perform a sensitivity analysis of the transient heart rate response to determine which parameters of the model impact the heart rate dynamics sigificantly. We subsequently include only those parameters in the estimation routine that impact the transient heart rate dynamics substantially. We apply the estimation algorithm to both simulated and real data and show that restriction to the 20 most important parameters does not impair our ability to match the data.

1. Introduction

Orthostatic intolerance (OI) is a debilitating and potentially serious syndrome that affects young women and virtually every astronaut returning from space. Affected individuals show a drop in arterial blood pressure and a marked increase ($\geq$ 30 beats/min) of heart rate upon assumption of the upright posture along with symptoms of dizziness, blurred vision, and lightheadedness [1]. While several mechanisms have been shown to contribute to the clinical presentation of OI, the number of hypotheses still under consideration and the lack of a unifying theory of the pathophysiology of orthostatic intolerance testify to the difficulty of the problem. To understand the effects of some of the proposed mechanisms on the transient, closed loop dynamics of the cardiovascular system we have developed a computational model that is capable of simulating the short-term response ($\lesssim$ 3 mins) to orthostatic stress such as head up tilt (HUT) and lower body negative pressure (LBNP). The model consists of a 14-compartment lumped parameter representation of the hemodynamic system coupled to set-point models of the two major neural reflex mechanisms: the arterial baroreflex and the cardiopulmonary reflex. Previous work in our laboratory has focused on matching the simulated heart rate response to HUT to individual astronaut data by changing some parameters in the model until a visual best fit was achieved [2]. The choice of which parameter to change was guided by a limited number of documented space-flight induced changes in the cardiovascular system and model exploration.

A more systematic way of matching our simulations to a given experimental data set is the focus of this paper. First we perform a sensitivity analysis to determine which parameters of the model impact the transient heart rate response to head-up tilt. We subsequently demonstrate that we can fit a simulated heart rate response by minimizing a cost function using only the parameters that contribute significantly to the transient heart rate response.

2. Hemodynamic model

We have modified a previously reported [3] closed loop lumped parameter representation of the cardiovascular system to allow for simulation of gravitational stress and regional blood pooling in the systemic circulation (see Fig. 1).

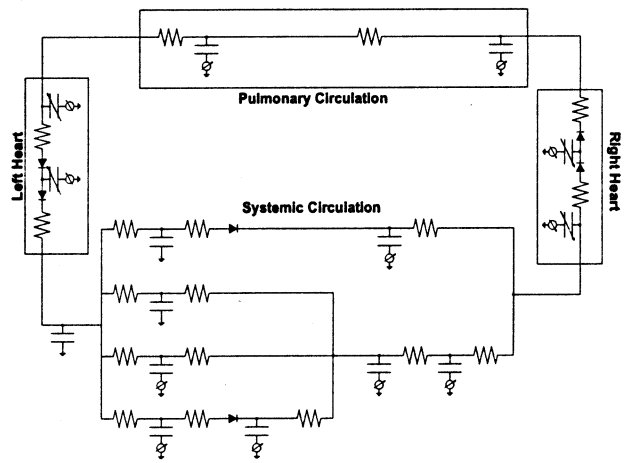

Figure 1. Hemodynamic model

Briefly, the hemodynamic system is represented by fourteen compartments each of which consists of an inflow

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resistance, a capacitance, and an outflow resistance. The systemic portion of the model consists of four parallel circulatory branches (representing the upper body, kidneys, splanchnic, and leg circulation) feeding into central venous compartments representing the abdominal, inferior, and superior venae cavae. The pumping action of the heart is modeled by time-varying atrial and ventricular compliances. Centrally, diodes mimic cardiac valves and ensure unidirectional blood flow through the heart whereas distally, they represent venous valves in the lower extremities. Bias pressures across the dependent compartments are used to simulate changes in posture by changing regional transmural pressures (see below). The compliances of the legs, splanchnic, and abdominal venous compartments are non-linear to account for the non-linearity of the veous pressure-volume relations at high levels of transmural pressure. Sequestration of blood plasma into the interstitial fluid compartment is modeled by reducing overall blood volume as a function of orthostatic stress and time. The resultant model is described by fourteen coupled linear first order differential equations which are integrated using an adaptive step-size 4th order Runge-Kutta integration routine. Parameter values for the hemodynamic parameters are largely based on literature values.

3. Reflex model

The reflex model consists of set-point representations of the arterial baroreflex and cardiopulmonary reflex. Five effector mechanisms (heart rate, venous tone, peripheral arteriolar resistance, and left and right ventricular contractility) respond to perturbations in blood pressure (see Fig. 2).

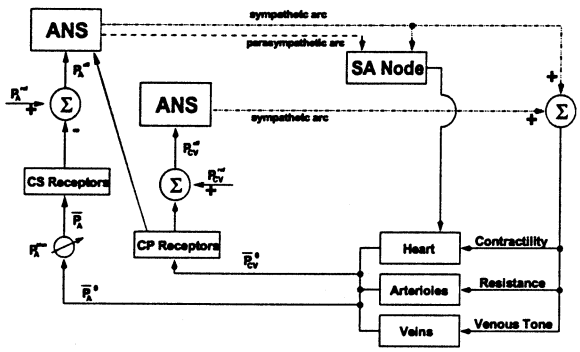

Figure 2. Reflex model

Briefly, pre-defined set-point pressures are subtracted from locally sensed time averaged pressures to yield an error signal. To mimic the effect of receptor saturation at large deviations from the set-points, the error signal is mapped onto an inverse tangent. This signal is then convolved with effector-specific impulse response functions to yield the effector variable for the next time step. Two impulse response functions are implemented to allow for differentiation of the fast acting parasympathetic arc from the slower acting sympathetic arc (see Figure 3). To account for a reduced hydrostatic pressure component at the carotid sinus, a bias pressure modifies the sensed arterial pressure during tilt.

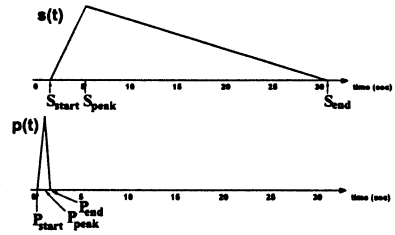

Figure 3. Sympathestic (top) and parasympathetic (bottom) impulse response functions

4. Tilt/stand simulation

To simulate the rapid redistribution of blood volume during the initial phase of a change in posture, we change the bias pressures at the dependent venous compartments according to:

$$P_{bias-i} = P_{max-i} \cdot \sin(\alpha(t))$$

where $\alpha(t)$ is a linear ramp function from zero to the maximal tilt angle and P_{max-i} is the maximal bias pressure across the respective compartment. We simulate the slower acting reduction of blood volume due to sequestration of plasma into the interstitium by reducing overall blood volume as a function of time, t, after the onset of tilt [4]:

$$V_{total} = 4800ml + 500ml \cdot 0.9^{t/60s}$$

5. Least squares estimation and Gauss-Newton method

Modeling efforts frequently aim at matching model output to experimental data by adjusting the parameter vector, θ, of the model until a best-fit criterion is met. The parameters of the model are frequently determined by minimizing a suitably chosen cost function between simulation output, $\hat{\mathbf{y}}(\theta)$, and experimental data, $\mathbf{y}$ (see, e.g. [5]). The most commonly used cost function is the sum of the squared elements of the residual vector $\mathbf{r}(\theta) = \hat{\mathbf{y}}(\theta) - \mathbf{y}$. An acceptable change in parameters from the initial guess θ_0 to an updated parameter vector θ_1 has to decrease the value of the cost function, i.e.:

$$\|\mathbf{r}(\theta_1)\|^2 = \|\hat{\mathbf{y}}(\theta_1) - \mathbf{y}\|^2 < \|\mathbf{r}(\theta_0)\|^2$$

Once a suitable vector θ_1 has been found, it assumes the role of θ_0 in the next iteration. This process will be repeated until a termination criterion has been met.

Various algorithms exist for determining the updated parameter vector θ_1 from the initial guess θ_0 [5]. The Gauss-Newton algorithm linearizes the optimization problem around the current parameter vector θ_0. It determines the parameter update according to

$$\theta_1 = \theta_0 + \alpha \cdot \mathbf{q}$$

where α is a scalar stepsize and the direction of the parameter update $\mathbf{q}$ is determined by solving the normal equation

$$\mathbf{J}^\top \mathbf{J} \cdot \mathbf{q} = \mathbf{J}^\top \cdot \mathbf{r}(\theta)\big|_{\theta=\theta_0}$$

where

$$\mathbf{J}(\theta) = \frac{\partial \mathbf{r}(\theta)}{\partial \theta}\bigg|_{\theta=\theta_0} = \begin{pmatrix} \frac{\partial \hat{y}_1}{\partial \theta_1} & \cdots & \frac{\partial \hat{y}_1}{\partial \theta_m} \\ \vdots & \ddots & \vdots \\ \frac{\partial \hat{y}_n}{\partial \theta_1} & \cdots & \frac{\partial \hat{y}_n}{\partial \theta_m} \end{pmatrix}$$

is the Jacobian matrix. For notational convenience we assume that the model has m parameters and we are interested in n samples of the output. Standard numerical methods exist to solve the normal equation numerically [6].

6. Sensitivity analysis

While the Gauss-Newton method can be implemented to fit simulations to a given data set, in our case an insufficient amount of data are available to determine all parameters of the model. The following sensitivity analysis helps us decide which parameters to use in the optimization process.

We take the elements of the output vector $\hat{\mathbf{y}}$ to be the heart rate response to tilt as a function of time sampled at a fixed frequency. To study the sensitivity of $\hat{\mathbf{y}}$ to perturbations of the parameter vector, we compute a normalized Jacobian matrix, $\tilde{\mathbf{J}}$. We determined the entries of J by a numerical approximation in which we computed a normalized finite difference quotient of the model output for different settings of the same parameter:

$$\tilde{J}_{ij} = \frac{\partial \hat{y}_j}{\partial \theta_i} \approx \theta_i^0 \cdot \frac{\hat{y}_j(\theta_i + \Delta\theta_i) - \hat{y}_j(\theta_i - \Delta\theta_i)}{2\Delta\theta_i}$$

Here θ_i^0 is the nominal value of the parameter under consideration and $\Delta\theta$ is a 5% change in the nominal value.

To rank-order the cummulative impact a particular parameter has on the entire output vector, we compute the diagonal entries of the matrix $\tilde{\mathbf{J}}^\top\tilde{\mathbf{J}}$ where $\tilde{\mathbf{J}}^\top$ is the transposed of the matrix J:

$$(\tilde{\mathbf{J}}^\top\tilde{\mathbf{J}})_{ii} = \sum_{j=0}^{n} \left(\theta_i^0 \cdot \frac{\partial \hat{y}_j}{\partial \theta_i}\right)^2$$

Table 1. Rank-order of model parameters

Category	Order of Magnitude	Number of Parameters
1	$O(10^6)$	1
2	$O(10^5)$	0
3	$O(10^4)$	4
4	$O(10^3)$	24
5	$O(10^2)$	37
6	$O(10^1)$	4

A comparatively large numeric value of $(\tilde{\mathbf{J}}^\top\tilde{\mathbf{J}})_{ii}$ indicates that the parameter θ_i contributes significantly to the transient heart rate response. Table 1 shows the rank-order of the parameters by the order of magnitude of their diagonal elements in $\tilde{\mathbf{J}}^\top\tilde{\mathbf{J}}$ along with the number of parameters belonging to each category. The top four parameters are total blood volume, the sympathetic heart rate gain, the compliance of the venous circulatory bed, and the end points of the sympathetic and parasympathetic impulse response functions. While no clear break-point in this hierarchy is discernable that would allow us to partition the parameter vector naturally into two groups, it seems reasonable to investigate a break-point somewhere in categories 4 or 5.

7. Parameter estimation from simulated data

To evaluate the performance of the estimation routine, we simulated a heart rate response by randomly perturbing five parameters of the model. We subsequently reset these parameters to their original values and started the optimization algorithm. We restricted the number of parameters to be included in the optimization to the top 20 according to our sensitivity analysis. Figure 4 shows the target response (solid line), the baseline response from which the optimization algorithm was started (dashed line), and the best-fit response (dash-dotted line) after the optimization met the termination criterion.

Table 2. Parameter estimation results

Parameter:	TBV	C_{ab}	R_k	V_{ll0}	S_{end}
True	0.90	0.75	1.10	0.90	1.20
Estimation	0.93	0.77	1.25	1.00	1.18

We perturbed total blood volume (TBV), the abdominal venous compliance (C_{ab}), arterio-venous resistance of the kidney (R_k), cardiopulmonary venous tone gain of the leg compartment (V_{ll0}), and the end point of the sympathetic impulse response function (S_{end}). Table 2 shows the true fraction of the baseline values we used to simulate the solid

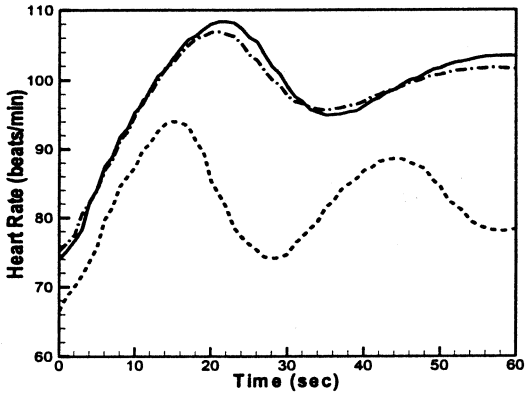

Figure 4. Simulated heart rate responses to tilt (see text for details)

line in Figure 3 and the estimated fractions according to the estimation process. During the estimation process, V_{110} did not change from baseline as it was not among the top 20 parameters inlcuded in the optimization process.

8. Simulation of real data

Finally, we applied the above algorithm to experimental data taken from the medical literature. Figure 5 shows the heart rate response (solid line) of a subject to a rapid head-up tilt (< 2 sec to 75° HUT) taken from Rossberg et al. [7]. After fitting the experimental recording, all parameters of

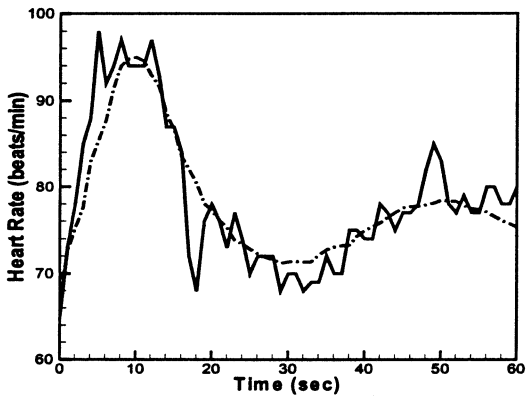

Figure 5. Actual and simulated heart rate responses to tilt

the model still fall within the range of what is considered physiologically reasonable.

9. Conclusions

We presented a computational model of the cardiovascular system, a sensitivity analysis of the transient heart rate response, and an estimation routine that allow us to match simulated and experimental data using only a subset of the entire parameter vector. The results presented indicate that we do not impair our ability to match simulated or experimental data by confining our analysis to a reduced set of parameters of the model.

While the results of this paper are encouraging, it is our belief that much work remains to be done in order to fully understand which parameters of the cardiovascular system can be estimated reliably from a single heart rate and possibly a blood pressure recording.

Acknowledgements

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