Closed loop baroreflex regulation of blood flow in the cardiovascular system

Andrew Armean Wright*, Adam Mahdi**, Mette S. Olufsen***
Dept of Mathematics, NC State University, Raleigh 26795
*armean.wright@gmail.com, **amahdi@ncsu.edu, ***msolufse@ncsu.edu

SUMMARY
This paper presents a lumped parameter model predicting baroreflex regulation during head-up tilt. Blood flow and pressure are predicted using an electrical circuit analogy. This model is coupled with a control model that regulates heart rate, cardiac contractility, and peripheral resistance in response to changes in blood pressure. The model was applied to predict patient specific measurements of blood pressure and heart rate obtained during head-up tilt. Submitted for MS 3, Inverse Problems in Cardiovascular Mathematics.

Key Words: 1D arterial blood flow modeling, elastic and viscoelastic wall models

1 INTRODUCTION
A simple change of the body from supine to sitting or standing position requires activation of a series of control mechanisms to maintain homeostasis. Upon postural change, the baroreceptors register a fall in arterial blood pressure and reduced filling of the heart. Activation of the autonomic nervous system then adjusts the heart and vessel properties to increase pressure and pump function of the heart back toward their reference level. This regulation can be disrupted in patients with peripheral and central nervous system diseases. Such patients usually experience dizziness and syncope due to altered function of the autonomic nervous system. These defects are often observed in patients with diabetes, hypertension, and other neurological diseases of which Parkinson’s disease is the most dominating.

The autonomic nervous system is complex with many interacting components. This is why analysis of separate elements does not give a satisfactory view of the state of the physiological system. In this study we aim to achieve a better understanding of the control mechanisms and their dynamics via patient specific mathematical modeling where knowledge of the individual elements and their dynamics is integrated. To this end, we are developing a closed loop cardiovascular system level model coupled with a control model that allows us to predict the autonomic nervous system’s ability to adjust the heart and vessel properties to maintain blood pressure and pumping function at reference levels. These models are composed of nonlinear differential equations whose solution poses considerable computational challenges. Their application to analysis of clinical data involves computational and conceptual complications due to the inherent noise in the model and data. To ensure high fidelity of our model, we employ methodologies allowing computation of parameter sensitivity, identifiability, and estimation.

2 METHODS
A drop in blood pressure, e.g. in response to head-up tilt, sensed by the arterial baroreceptors located in the aortic arch and carotid sinuses, inhibits firing of afferent baroreceptors. Sensory signals for these receptors are integrated in the nucleus solitary tract from where efferent signals are
transported via sympathetic and parasympathetic chain eventually impacting heart rate, cardiac contractility, and vascular tone. Fig. 1 shows a schematic of physiological pathways.

This system can be represented by a lumped parameter model illustrated in Fig. 2. This model includes the arteries and veins in the systemic circulation, as well as the left heart facilitating transport of blood. In addition we have included a neural control model predicting afferent and efferent baroreceptor firing, which modulate heart rate, peripheral resistance, and cardiac contractility. This coupled model was used to predict the response to head-up tilt induced by accounting for gravitational pooling of blood in the lower body.

Similar to previous studies [1], we use the electrical circuit analogy shown in Fig. 2 to predict blood flow and pressure in the systemic circulation. The model includes four compartments representing arteries and veins in the upper and lower body as well as a compartment representing the heart. For each compartment $i$, a pressure-volume relation can be defined as

$$V_i - V_{uni} = C_i(p_i - p_{ext}),$$  \hspace{1cm} (1.1)

where $V_i$ (ml) is the compartment volume, $V_{uni}$ (ml) is the unstressed volume, $C_i$ (ml/mmHg) is the compartment compliance, $p_i$ (mmHg) represents blood pressure, and $p_{ext}$ (mmHg) (assumed constant) is denotes the pressure of the surrounding tissue. Moreover, for each compartment, the change in volume is given by
where \( q \text{ (ml/s)} \) denotes the volumetric flow. Using a linear relationship analogous to Ohm's law, the volumetric flow \( q \text{ (ml/s)} \) between compartments can be computed as

\[
q = \frac{p_{in} - p_{out}}{R},
\]

where \( p_{in} \) and \( p_{out} \) denote the pressure on either side of the resistor \( R \text{ (mmHg s/ml)} \). A system of differential equations was obtained by differentiating equation (1.1), using (1.2) and (1.3), giving

\[
\frac{dp_i}{dt} = C p_i - \frac{1}{R_i} - p_i R_i - \frac{1}{R_i} \left( p_i - p_{out} \right).
\]

For the heart compartment, a differential equation of the form (1.2) is used to describe the change in volume, which is related to pressure via equation (1.1), but described in terms of elastance \( E = \frac{1}{C} \text{ (mmHg/ml)} \) rather than compliance. Pumping is achieved by introducing a variable elastance function of the form

\[
E_{in}(\tilde{t}) = \begin{cases} 
(E_M - E_m)(1 - \cos(\pi \tilde{t} / T_M)) + E_m / 2, & \tilde{t} \leq T_M \\
(E_M - E_m)\left(\left(\cos\left(\pi \left(\tilde{t} - T_M\right) / T_R\right) + 1\right) + E_m\right) / 2, & \tilde{t} \leq T_M + T_R \\
E_m, & \tilde{t} > T
\end{cases}
\]

where \( \tilde{t} \) is the time within a cardiac cycle \( T = \frac{1}{H}; E_M \) and \( E_m \) denote the maximum and minimum elastance, respectively.

Head-up tilt, \( \theta = 0.60^\circ \) at speed \( v_t \) is achieved by accounting for pooling of blood in the lower extremities, by adding gravity \( \rho g h_{tilt} \) to equations predicting flow between the upper and lower body.

\[
q = \rho g h_{tilt} \sin(\theta(t)) + p_{in} - p_{out}, \quad \theta(t) = \frac{\pi}{180} \begin{cases} 0 & t < t_s \\
v_t (t - t_s) & t_s \leq t \leq t_s + t_{ad} \\
60 & t > t_s + t_{ad}
\end{cases}
\]

As suggested in [2, 3], the baroreflex model uses blood pressure \( p_{atu} \) as an input to predict baroreflex firing rate \( f \) proportional to the difference between the stretch of the arterial wall \( \varepsilon_w \) and the stretch of the baroreceptor cells \( \varepsilon \).

\[
f = \varepsilon_w - \varepsilon, \quad \frac{d\varepsilon}{dt} = - (\alpha + \beta) \varepsilon + \alpha \varepsilon_w, \quad \varepsilon_w = g(p),
\]

where \( \varepsilon_w \) is the wall stress, modelled as a nonlinear function of pressure, \( \varepsilon \) is the strain of the baroreceptor cells, and \( \alpha \) and \( \beta \) are parameters. A drop in afferent firing rate elicits inhibition of parasympathetic tone \( T_p \), decreasing the acetylcholine concentration \( C_A \), and stimulation of sympathetic tone \( T_s \) increasing the noradrenaline concentration \( C_N \). As suggested in [2], these can be modeled using first order kinetic equations of the form

\[
\frac{dC_N}{dt} = - \frac{C_N + T_s}{\tau_N}, \quad \frac{dC_A}{dt} = - \frac{C_A + T_p}{\tau_A},
\]

\[
T_s = T_{SM} - (T_{SM} - T_{Sm}) \frac{f^q}{(f^q + f_s^q)}, \quad T_p = T_{pm} - (T_{pm} - T_{pm}) \frac{f^p}{(f^p + f_s^p)}.
\]

Modulation of neurotransmitters increases heart rate, cardiac contractility, and peripheral vascular resistance. Similar to previous work [2] we suggest to compute heart rate \( h \) as
\[ h = h_0 + dh_{M0} C_N - dh_{m0} C_A - \frac{dh_{M0} dh_{m0} C_A}{h_0}, \quad dh_{M0} = h_M - h_0, \quad dh_{m0} = h_0 - h_m, \quad (1.4) \]

while we predict cardiac contractility \( E_m \) and peripheral vascular resistances \( R_{aup} \) and \( R_{alp} \) using
\[
\frac{d^2 X}{dt^2} + \delta \frac{dX}{dt} + \kappa X = \lambda C_i, \quad X = E_m, R_{aup}, R_{alp},
\]
where \( \delta, \kappa, \lambda \) are constants that vary depending on the neurotransmitter \( (C_i, i = N, A) \) in question.

This form of the equation was motivated by studying the Bowditch effect proposed by Klabunde [4] and Batzel et al. [5]. It should be noted, that parasympathetic withdrawal is significantly faster than sympathetic stimulation, i.e., timescales for the two responses differ significantly.

### 3 RESULTS AND CONCLUSIONS

Preliminary results shown in Fig. 3A and B include predictions of arterial blood pressure, using heart rate as an input, and predictions of heart rate using blood pressure as an input. These results were computed for humans (3A) and rats (3B). Future results will be used to discuss how the baroreflex model can be scaled to predict heart rates in humans, and how to incorporate the control model with the cardiovascular model to form a closed model. Preliminary results were obtained using sensitivity analysis and optimization to estimate model parameters that allows patient specific predictions. The advantage of the closed model is that it can easily be adapted to study impacts of disease, e.g., by incorporating disease in equations.

![Fig 3: Model predictions of arterial blood pressure using HR as an input (A) and heart rate, using blood pressure as an input (B)](image)

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### REFERENCES


