Quantitative Insights into the Closed Loop Cardiovascular System using an Electrical Lumped Element Physiological Model

Athanasios Tsanas[1], Gari D. Clifford[1,2], Vassiliki Vartela[3], Petros Sfirakis[3]

[1]University of Oxford, Oxford, UK
[2]Emory University, Atlanta, USA
[3]Onassis Cardiac Surgery Centre, Athens, Greece

Abstract

This study extends a comprehensive closed-loop physiological model of the circulatory system based on lumped electrical analogue components. The model associates subject specific factors such as age, gender, body surface area, fitness and smoking habits, with cardiovascular parameters including vascular blood pressures, blood volumes, and cardiac output, providing physiological insight via the interpretation of the model's parameters. The model parameters were determined using multi-objective constrained optimization in a typical inverse problem setup, and were subsequently associated with the subject specific factors using least squares polynomial relationships with ℓ_1–ℓ_2-norm regularization. We validated the performance of the model using data from 289 subjects, replicating arterial blood pressure accurately (about 4.8% relative deviation from the measured values), whilst also providing physiologically realistic estimates of vascular blood pressures, blood volumes, and cardiac output.

1. Introduction

The study of the circulatory system has attracted considerable attention because of its vital importance to sustain life and the large prevalence of cardiovascular disease (CVD). For example, the world health organization estimated that 17.3 million people died from CVD in 2008, and it is estimated that by 2030 more than 23 million people will die annually from CVD [1]. Therefore, accurate, frequent, and ideally inexpensive assessment of cardiovascular functionality has the potential to save lives. Cardiovascular functionality can be assessed reasonably accurately, relatively easily, and fairly inexpensively by experts using the electrocardiogram (ECG), heart rate (HR), and arterial blood pressure (ABP) [2]. More elaborate tests are possible to investigate potential cardiovascular system related malfunctions, if required [2]. One of the clinical protocols cardiologists often rely on to assess the state of the cardiovascular system is the exercise treadmill test (ETT). During an ETT a person is required to complete a test of progressive physical difficulty, which requires increasing their cardiac output (CO), i.e. the volume of blood pumped by the heart every minute. An experienced clinician may then diagnose CVD pathologies including ischemia and cardiac failure, or refer the subject for additional tests.

Mathematical models may provide valuable qualitative and quantitative insight into the understanding of physiological processes, complementing the information available to clinicians and offering sophisticated, robust decision support tools. The mathematical modeling of data can be broadly divided into two categories: *first-principles* and *data-driven* [3]. The first category employs physical principles which are believed to govern the modeled system, whereas the second category focuses on forming mathematical and statistical relationships whose only constraint is that they must approximate as well as possible the measured data. Both approaches have merits, but the results of first-principle models may also be interpreted and understood by specialists who are not necessarily mathematically oriented, facilitating the means for multi-disciplinary interaction.

Although it is widely accepted that the Navier-Stokes equations may provide the means to the most precise quantitative description of the circulatory system, the computational cost is prohibitive for anything but assessing restricted vascular regions [4]. The windkessel model (WM) [5] provides a simplified electrical lumped element analogue of vascular regions of the circulatory system on the basis of resistors and capacitors. Additional electrical components such as inductors could be introduced improving the properties of the model, at the cost of additional complexity [6]. Although WM-types have been widely adopted to study the circulatory system, their application has often been limited to vascular regions, e.g. [6,7]. Studying independently regions of the circulatory system obscures insight into vital physiological phenomena of substantial clinical

importance such as feedback, arterial-venus interactions, and systemic-pulmonary interactions. Alternatively, some researchers proposed sophisticated models of the *closed-loop* circulatory system, but these are tremendously complicated [4,8]: having a cardiovascular model with multiple free parameters complicates the task of parameter identification for subject-specific analysis [9], and hinders its adaptation by the medical community. Motivated by these considerations, a computationally simple and efficient closed-loop WM-type of the circulatory system was introduced and numerically solved by Tsanas et al. [10], accounting for changes in vascular regions of the circulation by expressing the regional WM parameters as linear functions of *subject specific factors* (age, gender, fitness, and smoking habits).

This study extends our closed-loop model [10] in three main aspects, specifically: (a) we included the additional subject specific factor *body surface area* (BSA, a function of height and weight) which is known to affect both ABP and CO [2], (b) the determination of the model parameters was achieved via robust multi-objective constrained optimization instead of the trial and error method employed previously, and (c) first and second order terms were used to associate the subject specific factors with the regional WM parameters. This was achieved using a regularized framework promoting sparsity and shrinkage of the coefficients (instead of the standard least squares approach used previously). Ultimately, this study extends the WM framework and proposes novel quantitative relationships of subject specific factors evaluating ABP, CO, and blood volumes for all major vascular regions of the circulatory system.

2. Data

We used data from 289 participants (18-80 years old, mean±standard deviation: 48±13 years) who were referred to Onassis Cardiac Surgery Centre (Athens, Greece) for an ETT. Detailed demographics and medical records (e.g. prior ultrasound scans) were available for most of the participants. Approximately 20% of the participants were without any known cardiovascular-related disease (control group). Subjects younger than 18 years old and subjects with implanted devices were excluded from the study. Systemic ABP and HR were measured at rest, and approximately every 3 minutes during the ETT by the same cardiologist and nursing staff using arm-manometer. The study protocol was reviewed and approved by the local ethics committee.

3. Methods

This section summarizes the original lumped element electrical model [10], and elaborates on the association between subject specific factors and the WM elements.

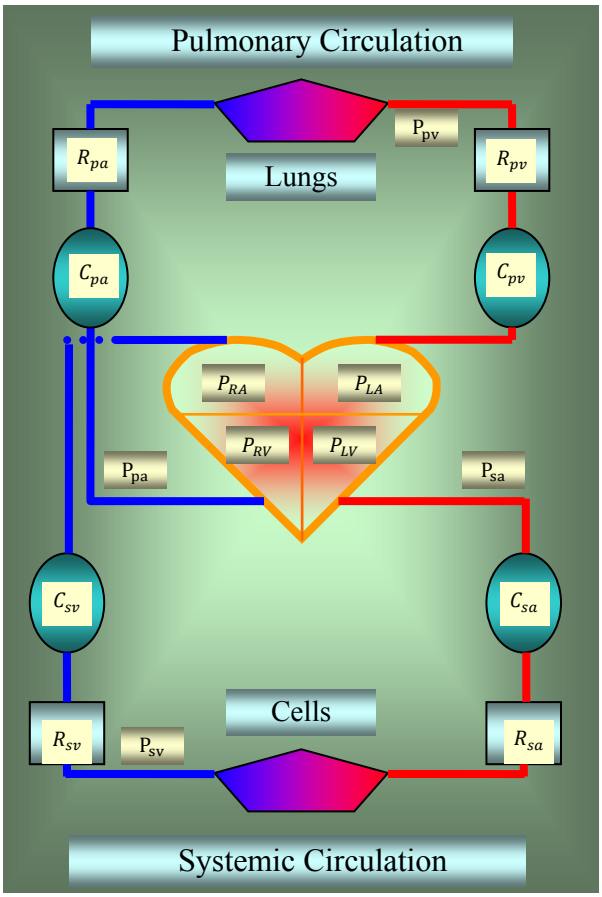

Fig.1. Schematic diagram of the proposed model. The ovals represent the large vessels (compliance vessels). The rectangles represent the smaller vessels (resistance vessels). We used intuitive subscripts: s – systemic, p – pulmonary, a – arterial, and v – venous. By convention, capital subscripts refer to the heart: R – right, L – left, A – atrium, V – ventricle.

3.1. Model formulation

The founding blocks of the WM are the electrical equivalents *resistance R* and *capacitance C* (which is most frequently referred to as *compliance* in physiology). Both lumped elements directly relate to physiologically interpretable properties: the resistance corresponds to the difficulty in blood flow through a vessel and is a function of its radius, whereas the compliance corresponds to the elasticity of the vessel. Large vessels are modeled as compliances, and smaller vessels are modeled as resistances; this simplifying assumption often works well in practice. Following Ohm's law for electrical circuits, a resistive vessel is characterized by Eq. (1):

$$Q = \left(P_{\text{input}} - P_{\text{output}}\right)/R \quad (1)$$

where Q represents the flow (electrical equivalent of current), and P represents the pressure (electrical equivalent of voltage). Similarly, applying the standard electrical equations for capacitors, the compliant vessel is characterized by Eqs. (2) and (3):

$$V = V_0 + C \cdot P \quad (2)$$

$$dV/dt = Q_{\text{inflow}} - Q_{\text{outflow}} \quad (3)$$

where V represents the blood volume, and V_0 the residual blood volume. Combining Eq. (2) and (3) we derive:

$$C \cdot dP/dt = Q_{\text{inflow}} - Q_{\text{outflow}} \quad (4)$$

We modeled each of four major parts of the circulatory system (systemic arteries, systemic veins, pulmonary arteries, pulmonary veins) as combinations of a single resistance and a single compliance (see Fig. 1). The compartment to which each of the lumped elements corresponds to appears as a subscript, for example the resistance in the systemic arteries is represented by R_{sa}. Multiple distributed lumped elements could in principle be used to refine specific vascular regions of interest. The derivation of the closed loop model uses Eqs. (1)-(4), solving the differential equations via backward Euler approximations (for details about the resulting systems of equations see [10]). The heart was modeled using the double sigmoid function to model the two ventricles as time-varying elastic components [10].

3.2. Determining the model parameters for each participant and their relationship with subject specific factors

In our previous study, the determination of the six model parameters which were subject to optimization (R_{sa}, R_{pa}, C_{sa}, C_{pa}, $C_{LV,\text{diastolic}}$, $C_{RV,\text{diastolic}}$) was achieved manually by trial and error. In this study, we applied multi-objective nonlinear constrained optimization using the interior point approach [11]. The bound constraints for each of the six model parameters were set to reasonable values following manual experimentation. The goal of the optimization in all cases was set as follows: determine the six WM parameters so that (a) the measured ABP is replicated, (b) the SV for the left ventricle (LV) and the right ventricle (RV) is practically equal, (c) the pulmonary pressures have physiologically reasonable values (in the region 25/9 mmHg), and (d) the CO has physiologically reasonable values (4-6 L/min). Since pulmonary pressures and CO data were not available, the weight for determining model parameters to match the systemic ABP in the multi-objective optimization goal was set to be larger.

The model developed so far associated the electrical lumped elements with CO, pressures and volumes in the associated vascular regions of the circulatory system. Next, we expressed each of these model parameters as functions of five subject specific factors: age, gender (0 denoting males and 1 females), smoking, fitness (quantified by the participant's performance during the ETT protocol). Specifically, each of the six model parameters was expressed as a linear function (in terms of the coefficients) of the subject specific factors: $(R_{\text{xx}}\ or\ C_{\text{xx}}) = a_0 + a_1 \cdot age + a_2 \cdot gender + a_3 \cdot smoking + a_4 \cdot fitness + a_5 \cdot BSA + a_6 \cdot (age \cdot BSA) + a_7 \cdot (gender \cdot BSA) + a_8 \cdot (fitness \cdot BSA) + a_9 \cdot (age \cdot smoking) + a_{10} \cdot (gender \cdot fitness)$. (5)

The polynomial coefficients were computed using penalized least squares with ℓ_1–ℓ_2 regularization to promote sparsity and shrinkage [12].

3.3. Model generalization

To objectively evaluate the generalization performance of the proposed model in estimating systemic ABP, we used the standard 10-fold cross-validation with 100 iterations for statistical confidence [12]. Specifically, the model parameters were obtained using 90% of the data, and its performance was tested using the model inputs on the remaining 10% of the data (*out of sample* data); errors over the 100 iterations were averaged and are presented in the form mean ± standard deviation. Similarly to our previous study [10], we used the mean relative error (MRE): $\text{MRE} = 100 \cdot \frac{1}{N} \sum_{i \in \Omega} |y_i - \hat{y}_i| / y_i$, where $\hat{y}$ is the estimated value, y is the measured value, i is the sample index, Ω contains the indices in the out of sample subset, and N is the cardinality of the out of sample subset.

4. Results

Table 1. Polynomial coefficients associating the subject specific factors with the model parameters.

	R_{sa}	R_{pa}	C_{sa}	C_{pa}	$C_{LV,d}$	$C_{RV,d}$
$\mathbf{a_0}$	5.821	1.932	0.006	0.008	0.007	0.018
$\mathbf{a_1}$	0.022	0.001	-2.1e-5	-3.9e-6	4.3e-5	9.4e-5
$\mathbf{a_2}$	-1.062	0.201	0.001	-0.0006	-0.001	-0.005
$\mathbf{a_3}$	-0.0008	0.003	2.3e-5	-1.9e-5	-1.5e-5	-5.1e-5
$\mathbf{a_4}$	-0.451	-0.844	-0.002	-0.002	0.006	0.017
$\mathbf{a_5}$	1.590	-0.325	-0.0007	-0.001	0.002	0.006
$\mathbf{a_6}$	-0.002	0.001	6.1e-6	4.7e-6	-1.4e-5	-3.1e-5
$\mathbf{a_7}$	0.323	-0.237	-0.0004	-0.0002	0.0008	0.002
$\mathbf{a_8}$	-0.547	0.383	0.0006	0.001	-0.002	-0.006
$\mathbf{a_9}$	0.0001	-4.5e-5	-6.9e-7	5.5e-7	7.0e-7	1.8e-6
$\mathbf{a_{10}}$	-0.391	0.094	-6.1e-5	0.001	-0.001	-0.0006

See Eq. (5) for the association of model parameters with the polynomial coefficients and the corresponding model inputs.

The application of the nonlinear constrained optimization algorithm led to WM parameters which satisfied the constraints in all cases, and matched the measured systemic ABP very accurately. Subsequently, we applied the ℓ_1–ℓ_2 regularized least squares method to determine the polynomial coefficients. Table 1 summarizes the relationships between the subject specific factors and the WM parameters. The interpretation of the polynomial coefficients depends on the magnitude and the sign of the coefficient. For example, the systemic arterial resistance increases with age and BSA, whilst it is lower in females (higher resistance corresponds to higher

blood pressure). The errors in replicating ABP were: $P_{sa,systolic} = 4.9 \pm 0.05$ and $P_{sa,diastolic} = 4.7 \pm 0.04$. Several simulations revealed physiologically reasonable values for volumes and CO, although these values cannot be quantitatively verified with the available data.

5. Discussion

This study extended a previously proposed *closed loop* model of the circulatory system [10], and set to determine functional relationships between the subject specific factors with each of the associated causative WM parameters. The results in Table 1 can be intuitively understood qualitatively, and it is reassuring that the signs of the associated polynomial coefficients with the subject specific factors are in agreement with physiological understanding. The model was validated by replicating accurately the measured ABP, and providing realistic estimates of blood volumes, pulmonary pressures, venous pressures, SV, and CO. We demonstrated that the estimated ABP was more accurate compared to our previous model [10], which is attributed to three factors: (a) automatic determination of the model parameters avoids the bias of manual trial and error, (b) the introduction of BSA as a critical factor, (c) introduction of a more detailed polynomial form associating the subject specific factors with the outputs of the model. To the best of our knowledge, there are no other closed-loop subject-specific models of the circulatory system which are validated against actual data in terms of replicating ABP, blood volumes, and CO in the research literature.

The determination of the values of the WM parameters for each participant is a classical optimization problem: a number of parameters within certain bound constraints need to be identified, so that a goal is attained. This was achieved using multi-objective nonlinear constrained optimization with the interior point approach [11]. We also experimented with the frequently used Nelder-Mead algorithm [13]: the bound constraints were introduced by sinusoidal transformation of the variables (variable transformation is a standard approach to include bound constraints with non-constrained optimization solvers). We found that the interior point approach provided faster and better solutions.

The current study presented a general framework for the association of subject specific factors with cardiovascular parameters *at rest*. In practice, CVD characteristics may be revealed during the ETT: we are currently working on integrating additional aspects such as baroreceptor control as part of the model to study these effects. The methodology described to estimate the values of the WM parameters can be applied during exercise in the ETT protocol: changes in the values of the model parameters for each participant can then be quantitatively expressed as functions of sympathovagal innervation.

Acknowledgements

A. Tsanas is supported by the Wellcome Trust through a Centre Grant No. 098461/Z/12/Z, "The University of Oxford Sleep and Circadian Neuroscience Institute (SCNi)".

References

[1] World Health Organisation. A global brief on hypertension Silent killer, global public health crisis 2013, Ref. number: WHO/DCO/WHD/2013.2, Available at: www.who.int/cardiovascular_diseases/publications/global_brief_hypertension/en/ (last accessed 22 August 2014)

[2] Guyton AC, Hall JE. Textbook of Medical Physiology, 12th ed., USA, Saunders Elsevier, 2010.

[3] Tsanas A. Accurate telemonitoring of Parkinson's disease symptom severity using nonlinear speech signal processing and statistical machine learning, PhD thesis, University of Oxford, UK, 2012

[4] Formaggia L, Quarteroni A, Veneziani A. Cardiovascular Mathematics: Modeling and simulation of the circulatory system, Milano, Springer, 2009.

[5] Sagawa K, Lie RK, Schaefer J. Translation of Otto Frank's paper "Die Grund- form des Arteriellen Pulses". Zeitschrift für Biologie 1990;37:483–526 [J Mol Cell Cardiol 1899:22;253–77].

[6] Stergiopulos N, Westerhof BE, Westerhof N. Total arterial inertance as the fourth element of the Windkessel model. Am J Physiol 1999;276:H81–8.

[7] Fogliardi R, Di Donfrancesco M, Burattini R. Comparison of linear and nonlinear formulations of the three-element windkessel model. Am J Physiol Heart Circ Physiol 1996;271:H2661–8.

[8] Heldt T, Shim EB, Kamm RD, Mark RG. Computational modeling of cardiovascular response to orthostatic stress, J Appl Physiol 2002; 92:1239-1254.

[9] Olufsen MS, Ottesen JT. A practical approach to parameter estimation applied to model predicting heart rate regulation, Journal of Mathematical Biology 2013; 67:39-68.

[10] Tsanas A, Goulermas JY, Vartela V, Tsiapras D, Theodorakis G, Fisher AC, Sfirakis P. The Windkessel model revisited: a qualitative analysis of the circulatory system, Med Engineering and Physics 2009, 31: 581-588.

[11] Waltz RA, Morales JL, Nocedal J, Orban D. An interior algorithm for nonlinear optimization that combines line search and trust region steps. Mathematical Programming 2006; 107:391–408

[12] Hastie T, Tibshirani T, Friedman J. Elements of statistical learning, New York, Springer, 2009

[13] Lagarias JC, Reeds JA, Wright MH, Wright PE. Convergence properties of the Nelder-Mead simplex method in low dimensions. SIAM Journal of Optimization 1998; 9:112-147

Address for correspondence:
Athanasios Tsanas
Institute of Biomedical Engineering, Old Road Campus Research Building, University of Oxford, Headington, Oxford, UK, OX3 7DQ
tsanas@maths.ox.ac.uk, tsanasthanasis@gmail.com