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Intra- and inter-beat modeling of cardiovascular dynamics and control: assessing haemodynamic stability and responsiveness

Nicola Toschi, Andrea Duggento, Antonio Canichella, Filadelfo Coniglione, Mario Dauri, Alessandro F. Sabato and Maria Guerrisi

Abstract— **In critical care patient management, extensive and invasive patient monitoring is routinely performed in order to quantify patient status in view of therapeutic interventions. Little quantitative integration is performed when collecting information from multiple monitors, and processing algorithms are often based on little physiological understanding. Mechanistic modeling can offer insight into the mechanisms underlying patient stability and sensitivity to alterations in physiological variables. Starting from existing models, we construct an integrated model which combines detailed neural cardiovascular regulation with realistic circulation modeling, using Monte-Carlo techniques for reparameterisation when merging the two models. The combined model is analyzed in terms of its dynamical stability and sensitivity to parameter perturbations under simulated conditions of fluid deficit, anaesthesia, and dilatative cardiomyopathy. The results exemplify how a structural model can serve as a quantitative guide in assessing how different underlying patient states can alter the haemodynamics impact of external therapeutic intervention.**

I. Introduction

A. Management of high-risk surgery and ICU patients

In the care of critically ill patients requiring major, high-risk interventions such as organ transplant or cardiac surgery, sudden episodes of hemodynamic instability, hypotension and cardiac arrest can often result in severely insufficient perfusion of vital organs. Choosing the wrong intervention can result in a dramatic decrease in survival chances, as well as in an increase in the need for peri- and post-operative care and associated social and financial burden for patients, hospitals and governments. Since the outcome (or even the direction of the outcome [1]) of a particular intervention (such as inotrope administration or fluid resuscitation) is highly dependent on the underlying patient state (due to e.g. influence on anaesthesia on neural control of heart rate, current fluid balance, pathological subsystem alteration) it is imperative that acute risk-assessment and subsequent action be guided by informative, integrated intra- and peri-operative patient monitoring systems [1] that should ideally provide a comprehensive, real-time picture of organ function and interplay.

While in principle recent technological advances target the estimation of parameters that correlate well with patient physiopathology (fluid status, stroke volume, cardiac output, tissue oxygenation, pulmonary edema), such estimates are obtained through stand-alone devices implementing single-channel averaging/thresholding algorithms that do not operate in an integrated manner and are based on little physiological understanding. This subjects patients to cumbersome instrumentation, may produce conflicting estimates and generates a significant number of inaccurate/false alarms [2].

B. Clinically targeted modeling environment

The implementation of physical modeling tools in a patient-care setting can provide a major access pathway to information which may be readily re-cast into clinically useful form. In particular, if the physiological subsystem at hand is modeled from a mechanistic point of view [3,4] (i.e. injecting *a priori* knowledge about system dynamics), model output as well as parameter values can be readily related to their real-world physiological counterparts, which often cannot be directly measured (e.g. neural cardiovascular control gains, ventricular contractility, stroke volume, peripheral resistances), and translated into clinical intervention strategies. The aim of this study is to design a model which integrates:

a) detailed description of neural blood pressure control dynamics, allowing to separate afferent baroreceptor activity from efferent sympathetic/parasympathetic activity as well as describe intra-beat transmitter dynamics

b) a lumped-parameter representation of the whole circulatory system able to reproduce main features of arterial and venous pressure waveforms as well as to separate upper body, renal, splanchnic and lower body circulations.

The integrated model is analyzed in terms of its dynamical stability and parameter sensitivity of output variables which are representative of patient status (e.g. heart rate, cardiac output, arterial and venous pressures, pulse pressure) as well as their variability under the simulation of variety of circumstances (fluid deficit, anaesthesia, pathological subsystem alterations) which are relevant to the OR and ICU setting. The results of such simulation can serve as a guide in choosing the right patient-state dependent intervention based on the particular therapeutic goal at hand.

II. Methods

A. Integrated Model Structure

We base our analysis on a hybrid model [5] where

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variables are a continuous function of time, and a continuous sinus node phase is introduced whose velocity is influenced by neural firing rates thorough autonomic neurotransmitter kinetics. When the sinus node phase crosses a certain threshold, a new heart beat is generated (integrate and fire model) and discrete beat-to-beat valued are realized (sample and hold mechanism). The pacemaker model includes characteristic baroreceptor sigmoid responses, the dependency of the sinus node response to neurotransmitter stimulation (modeled through a phase effectiveness curve, see below) and separate time delays for sympathetic and parasympathetic nervous system dynamics, and is described as follows (the dot denotes a time derivative):

- Baroreceptor activity ν_b as a function of pressure p:

$$\nu_b = k_1(p - p_0) + k_2\dot{p} \quad (1)$$

- Sympathetic firing rate ν_s:

$$\nu_s = \max[0, \nu_s^0 - k_s^b \nu_b] \quad (2)$$

- Parasympathetic firing rate ν_p:

$$\nu_p = \max[0, \nu_p^0 + k_p^b \nu_b] \quad (3)$$

- Cardiac concentration of sympathetic transmitter (accounting for delays in sympathetic action) c_{cNa}:

$$\dot{c}_{cNa} = -\frac{c_{cNa}}{\tau_{cNa}} + k_{CcNa}^s \nu_s(t - \theta_{cNa}) \quad (4)$$

- Phase of the sinus node φ:

$$\dot{\varphi} = \frac{f_s f_p}{T_0} \quad (5)$$

- Sympathetic influence on the phase velocity of the sinus node f_s:

$$f_s = 1 + k_\varphi^{cNa}\left[c_{cNa} + (\hat{c}_{cNa} - c_{cNa})\frac{c_{cNa}^2}{\hat{c}_{cNa}^2 - c_{cNa}^2}\right] \quad (6)$$

- Parasympathetic influence on the phase velocity of the sinus node, assuming rapid transmitter kinetics and including the phase effectiveness function $F(\varphi)$ [6] f_p:

$$f_p = 1 - k_\varphi^p\left[\nu_p(t - \theta_p) + (\hat{\nu}_p - \nu_p(t - \theta_p))\frac{\nu_{p,\theta_p}^2}{\hat{\nu}^2 - \nu_{p,\theta_p}^2}\right]F(\varphi), \quad (7)$$

$$F(\varphi) = \varphi^{1.3}(\varphi - 0.45)\frac{(1-\varphi)^3}{(1-0.8)^3 + (1-\varphi)^3}$$

The neural control model is parameterised by the vector $\mathbf{T} = [p_0, k_1, k_2, \ldots]^T$ (see [5] for values). Further, the circulatory system is described by adapting a 21-compartment model [7] based largely on the circuit analog representation of a vascular segment, comprising of seventeen vascular and four cardiac compartments as well as a neural control model of peripheral resistances whose 153 parameter values have been carefully adjusted to reproduce human physiology and pathology in a variety of circumstances, both steady-state and transient (see [8] for values). The resulting full system is parameterized by a 182-element vector $\mathbf{\Psi}$. A fourth order Runge-Kutta scheme with 10^{-3} s fixed step size [5] was used in all simulations.

B. Monte-Carlo based reparameterisation of neural control model

In adapting the neural control model [5] for integration with the circulation model, it is crucial to carefully tune parameter values in order for the combined model to faithfully reproduce physiological behaviour. The default parameter values in [5] result in model output which is not representative of a healthy population average (e.g. mean arterial pressure at approximately 110 mmHg with a mean heart rate of approximately 50 bpm). We therefore chose to partially reparameterize the model through a Metropolis-Hastings based Monte-Carlo algorithm, adopting the output of the original circulation model as a "gold standard". Specifically, we chose to re-estimate values for the parameters which are most likely to reflect patient-specific physiology (arterial pressure set point, gains which enter the dynamics in a non-mutually multiplicative way and phase velocity time constant), i.e. the vector $\mathbf{\Theta} \subset \mathbf{T}$, where $\mathbf{\Theta} = [p_0, k_1, k_2, k_{CcNa}^s, k_\varphi^p, T_0]^T$. We generated a 1000 second long arterial pressure (ABP) and RR interval time series ($\mathbf{p}$ and $\mathbf{r}^{\text{target}}$, respectively) from the circulation model. In order for this data to contain as rich as sample of model dynamics as possible, we included several physiological and pathological maneuvers in the simulation (Fig. 1).

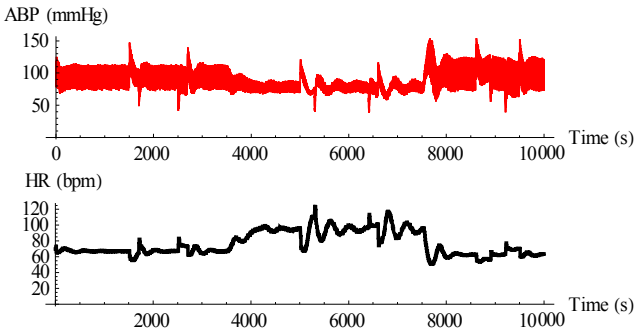

Fig. 1. Target time series of ABP (red, top) and RR interval (black, bottom) used for Monte-Carlo simulations generated with the circulation model. Simulations include various breath-hold maneuvers, hemorrhage and fluid administration (increase in blood volume after hemorrhage).

After an initial random guess $\mathbf{\Theta}_0$ for the parameter vector $\mathbf{\Theta}$ (compatible with theoretical parameter bounds and contained within a 1%-1000% range of the default parameter values in [5]) the neural control model was evolved iteratively with $\mathbf{p}$ as input while cyclically varying the elements of $\mathbf{\Theta}$ by a random amount sampled from a triangular distribution between ±30% of the current value and employing the resulting jth RR interval time series $\mathbf{r}^j$ in the calculation of the log-likelihood $ll^j = -\sum_i (r_i^j - \mathrm{r}_i^{\text{target}})^2$. A parameter variation at the

$(j+1)$th step was accepted and the Monte-Carlo chain was stepped forward if $\exp[ll^{j+1} - ll^{j}] > 1$. Upon failure in satisfying this condition, the chain was stepped forward if $\exp[ll^{j+1} - ll^{j}] > \alpha$, where α was sampled from a constant distribution with bounds [0,1]. Whenever the acceptance rate reached a bottom threshold, the width of the distribution from which parameter variations were sampled was restricted to ±10%. 10^4 Chains of 2×10^4 iterations each were computed (approximately 2×10^4 hours of CPU time) and the chain which ended in the point in parameter space yielding the highest log-likelihood was chosen as the new parameter vector for the neural control part of the integrated model.

C. *Parameter sensitivity of full model*

The combined model provides values for a number of variables such as compartmental blood pressures, vascular volumes, flows, cardiac capacitances, peripheral capacitances and resistances. In order to be able to employ the model as an interventional guide for clinical settings, we investigated the local sensitivity of model output to variations in parameter values. Specifically, we computed the sensitivity of mean values (computed over 100 s of simulation after discarding the first 70 s in order to allow the system to reach equilibrium) of 11 output variables (heart rate, mean arterial pressure, mean venous pressure, cardiac output, systolic arterial pressure, diastolic arterial pressure, pulse pressure, systolic pressure slope, systolic time, diastolic time) and of the variability (standard deviation) of the last 7 variables in this list to local perturbations between -8% and +8% in all 181 parameter values. Denoting the parameter set-point around which we operate as $\mathbf{\Psi}^0$ (see above) which produces a local equilibrium output vector $\mathbf{H}^0$ containing averaged variables and standard deviations, we compute the (approximate) "normalized" Jacobian $\mathbf{J}$, where $J_{ij} = \frac{\Psi_j^0}{H_i^0}\frac{\partial H_i}{\partial \Psi_j}$ using a five-point, fourth-order accuracy difference scheme. We also compute "pure" second order sensitivities as $JJ_{ij} = \frac{\left(\Psi_j^0\right)^2}{H_j^0}\frac{\partial^2 H_i}{\partial \Psi_j^2}$, as a measure of the reliability of the first order sensitivity.

III. RESULTS

The Monte-Carlo reparameterisation yielded the vector $\mathbf{\Theta}^{new} = \begin{bmatrix} p_0 = 57.3, k_1 = 0.016, k_2 = 0.004, \\ k_{CcNa}^s = 1.6, k_\varphi^p = 13.06, T_0 = 1.13 \end{bmatrix}^T$. These parameter values were adopted in the stability and sensitivity analyses.

A. *Bifurcations in the full model*

Bifurcations can occur as a function of the coupling between the two oscillators (cardiac pacemaker and baroreflex control loop). Following our reparameterisation, we carry out a bifurcation analysis in the full model in order to check which regime we are operating our model in. Varying the gain k_p^b (default value 0.3) in steps of 0.005 results in a period-tripling bifurcation at approximately $k_p^b = 0.5$, which could be interpreted as a form of *alternans*, followed by Hopf bifurcations at approximately $k_p^b = 1.26$ (Fig. 2). No other bifurcations were found when investigating variations in gains [5].

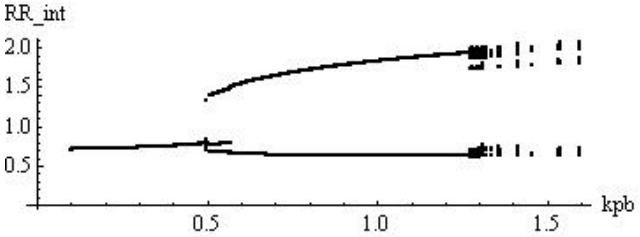

Fig 2. Bifurcations in RR interval generated by full model response when varying k_p^b.

B. *Sensitivity analysis*

We performed a local sensitivity analysis as described above a) in our baseline model, b) subtracting 1 liter of blood (fluid deprivation before and during surgery) c) reducing all central nervous system gains to half their original value (simulation of sedation/anaesthesia) and d) doubling left ventricular compliance (simulation of left dilatative cardiomiopathy).

We present a subset of the results of analyzing the first (selected data shown) and second order (data not shown) sensitivities of 20 output variables to 182 parameters. All figures show the top-10 parameters (those to which the output variable was found to be most sensitive) in situation a), and the corresponding sensitivities in b)-d) (see [8] for details on the insets).

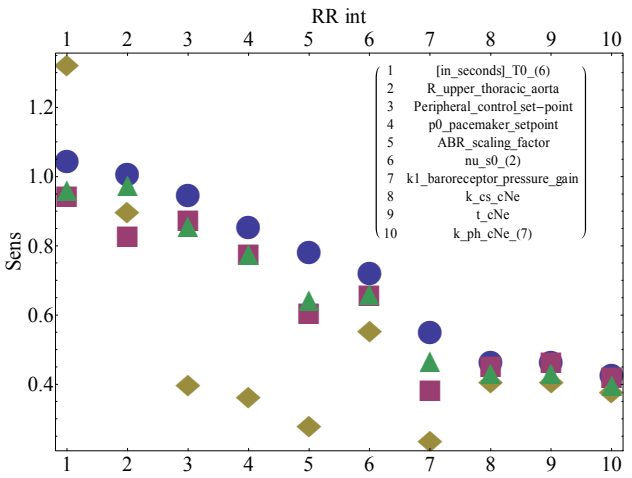

Fig. 3a. Sensitivity of RR interval to parameter variations. Inset shows parameter ranking. Blue circles: healthy. Red Squares: Fluid deprived. Yellow Diamonds: Anaesthesia. Green Triangles: Left dilatative cardiomyopathy.

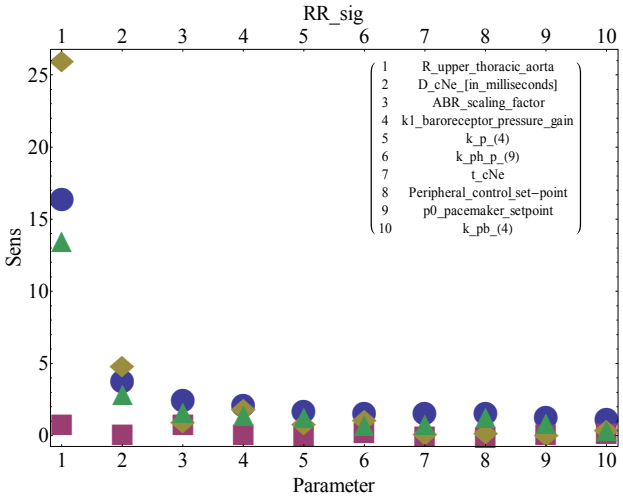

Fig. 3b. Sensitivity of RR interval to parameter variations. Inset shows parameter ranking. See Fig. 3a for symbols.

RR interval is seen to be most sensitive to resting heart period, aortic resistance, peripheral and cardiac control set points and all gains of the neural control model, but this sensitivity is somewhat reduced under fluid deprivation and strongly reduced when under (simulated) anesthesia – i.e. lowering gains also lowers the sensitivity to them.

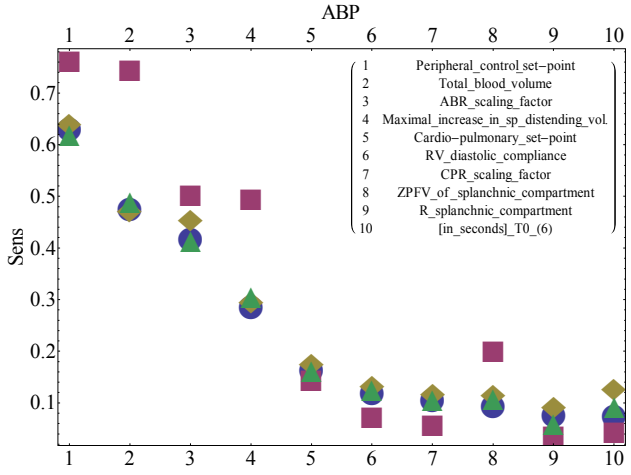

Fig. 4. Sensitivity of mean ABP to parameter variations. Inset shows parameter ranking. See Fig. 3a for symbols.

Fluid deprivation strongly reduces the sensitivity of RR interval variability to all parameters, while under depressed control mechanisms the aortic resistance becomes dominant in determining RR variability (data not shown). Control set points (and obviously total blood volume) are most efficient in altering mean ABP, and this sensitivity is strongly increased under fluid deprivation. A similar pattern is observed for CVP, however the latter seems to be much more sensitive to zero-pressure filling volumes.

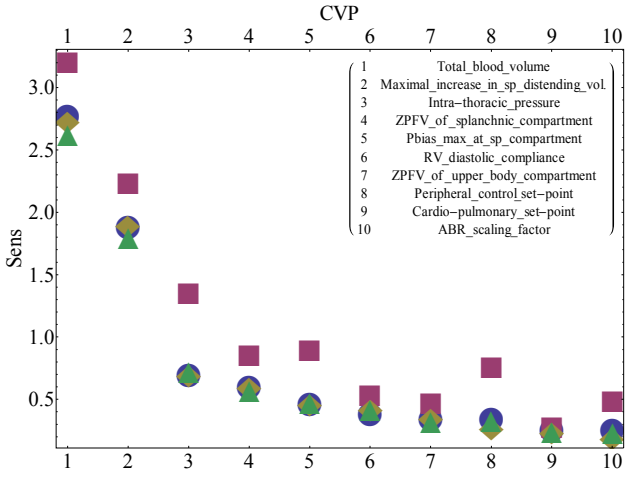

Fig. 5. Sensitivity of CVP to parameter variations. Inset shows parameter ranking. See Fig. 3 for symbols.

IV. Discussion and Conclusion

The combined model is able to reproduce original circulation model dynamics while providing more detailed information and control about the neural part of heart rate dynamics, and exhibits complex nonlinear behaviour in parameter regions which are beyond physiological range, but could possibly become relevant in pathological situations. Monte-Carlo based reparameterisation allows sensible integration of models and possibly patient specific model titration, which will be the object of future work. Subsequent Sensitivity analysis reveals a wealth of subtle interconnected and operating point-dependent regulatory mechanisms, which we plan to explore as a potential quantitative guideline for model-guided patient management algorithms.

Acknowledgment

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