Silicon Heart: An Easy to Use Interactive Real-Time Baroreflex Simulator

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Abstract

A simulator of the baroreflex loop is implemented as a distributed system, including independent functional units with each of them running without synchronisation and in real-time. Individual components are build from extended equations of the well established Seidel-Herzel-model.

The system includes five small computers representing five independent sub-models. Each component has a computer mouse connected that allow for real-time manipulation of simulation parameters in the respective part of the model. This way, numerical values of variables, such as neurotransmitter concentrations or breathing frequency, can easily be altered by turning the associated adjusting wheel.

Virtual administration of drug substances and virtual disease simulations are performed and show that the asynchronous simulation is robust enough to be used as an intuitive model to study heart rate dynamics.

1. Introduction

The baroreflex loop is a well researched field of physiology, but reliable prognosis and finding truly objective diagnostic criteria for baroreflex-related heart diseases is still difficult.

The required level of objectivity can probably only be achieved with the help of mathematical models. There are already numerous examples of such models in literature; however, to use them for diagnosis we must enable physicians to understand and use these models. Most existing models only allow to set parameters before execution while not providing any live feedback of the stimulus responses. This is not sufficient in order to analyse the dynamic behaviour of a living system.

Therefore we use extended equations of the well established Seidel-Herzel model of the baroreflex loop to build a simulator that runs in real time, and allows live monitoring and manipulation of physiological parameters.

2. Seidel-Herzel Model

The model was first published by Seidel and Herzel in 1995 [1] with the main purpose of analyzing heart rate variability (HRV). It was later extended by Kotani et.al. including a noise model and an additional feedback loop that enables the model to display cardiorespiratory synchronization. We chose this model for our research because, although it is rather compact, it is in good agreement with measured data regarding heart rate characteristics including respiratory sinus arrhythmia (RSA), Mayer waves, bifurcations and the simulation of diseases such as baroreceptor hypersensitivity, congestive heart failure and primary autonomic failure [1–4].

In this paper we use an extended version of the model published in 2005 by Kotani et.al. It includes the function of baroreceptors, the lung, the autonomic nervous system, the sinus node, AV node, the heart itself and the Windkessel arteries. The baroreceptor model assumes that there is a constant minimal pressure at which the baroreceptors start firing. The firing rate increases both with the static blood pressure level as well as with the dynamic increase in blood pressure. The baroreceptor signal is then passed on to the autonomic nervous system (ANS) and to the lung. The lung model assumes a constant breathing rate that is only modulated by the baroreceptor signal during expiration, as experimental results have shown that high baroreceptor activity can lengthen the period of expiration. As an additional influence, we added a term for the mechanical respiratory influence on the contractility. The ANS is effectively modeled as a black box. Seidel and Herzel assume a linear connection between the baroreceptor signal and the ANS that decreases sympathetic (SNS) activity and increases parasympathetic (PNS) activity and a second linear connection to the respiratory neurons that modulates the SNS and PNS response with a simple sine wave. The ANS is the second part of the model where Kotani et.al. include a noise term that changes on a beat-to-beat interval. The transmitter kinetics for the SNS neurotransmitter Norepinephrine are modeled explicitly as two different concentrations at the sinus node (as neurotransmitter) and in the vascular system (as hormone) while the faster kinet-

ics of the PNS neurotransmitter Acetylcholine are modeled by a delay of the raw neural signal. Both the concentration of Norepinephrine and the delayed PNS signal are modulated with a saturation term before they reach the sinus node, which is described as a simple integrate-and-fire model. In addition to the sinus node, we also modeled the function of the AV node by simply issuing a heartbeat and resetting the sinus phase prematurely, when no sinus signal has been received for 1.7 seconds. The strength of the contraction depends both on the time that has passed since the last contraction (via the Frank-Starling mechanism) and on the Norepinephrine concentrations that increase both the contractility and the venous return to the heart. After a fixed time period of 0.125 seconds has passed, the heart model switches from the systole to the diastole, where the decrease of blood pressure is determined by the vascular concentration of Norepinephrine. For a more detailed discussion of the formulas involved, the reader is referred to Kotani 2005 [4].

3. Distributed simulation and analysis

In order to implement the extended model of the baroreflex a system with five separated computers is set up. Each computer solves the differential equations belonging to one component of the baroreflex model. The components are the heart (including sinus node and Windkessel arteries), sympathicus, parasympathicus, baroreceptors, and lung. The computers are five Raspberry Pis, which are fully functional small computers. For communication, the computers are attached to a local area network (LAN). Each computer runs multiple threads to both calculate new values and send and receive values from other computers.

Except of the explicit communication the computers are independent. This setup leads to an asynchronous behaviour: Components are not waiting for others to run in the same step. The distributed simulation is even able to run with one or more parts missing.

The asynchronous setup and network communication has side effects on the behaviour. Calculated values can be omitted while calculating new values, or the new values can be calculated before the previous are sent. This introduces an additional noise into the system, also present in real living organisms.

A standard computer mouse is attached to each computer. The scroll wheel allows to manipulate parameters of the components simulated on the respective computer while the model is running. Modifiable parameters include concentrations of neurotransmitters, PNS or SNS influence breathing frequency as well as the hypertension factor.

With help of these manipulators different conditions, such as diseases or influence of medication, can be simulated easily. The behaviour under altered conditions can immediately be observed in the plots.

Multiple lights are connected to the sinus node computer to display each beat. All components of the model are attached to a board for display. Figure 1 shows the board from the front view.

For logging purpose an additional part of the system is set up on a laptop. This optional passive unit only receives values.

Figure 1. The board on which the model is set up.

Our analysis includes long-range correlations in the time series of the heart beat intervals. They are calculated by estimating local Hurst exponents by means of a sliding window algorithm. The size of the window is set to 101 heart beats. For each window R/S analysis is performed and the resulting Hurst exponent is assigned to the 3 heart beats in the centre of each window [5, 6].

The multifractal properties of the series of heart beat intervals are evaluated by calculating the scaling exponents $\tau(q)$ from the partition function $Z_q(a) \sim a^{\tau(q)}$ [7, 8]. The partition function is derived as the sum of the qth power of the maxima of the modulus of the wavelet decomposition at scale a. The third derivative of the Gaussian is used as analysing wavelet. A range of $-3 < q < 3$ is used for the multifractal order. Multifractal spectra are obtained with a scaling $0.5 < \log_{10} a < 2.5$. Fractal dimensions $D(h)$ and singularity spectra, displaying the fractal dimensions of parts of the dataset with a local Hurst exponent of h, are obtained by Legendre transform $D(h) = qh - \tau(q)$ [9].

4. Results

Baseline: Figure 2 displays the baseline behaviour of the model. Beats per minute (BPM) are shown in the upper right. The blood pressure follows the BPM. The influence of SNS and PNS are shown in the lower plots.

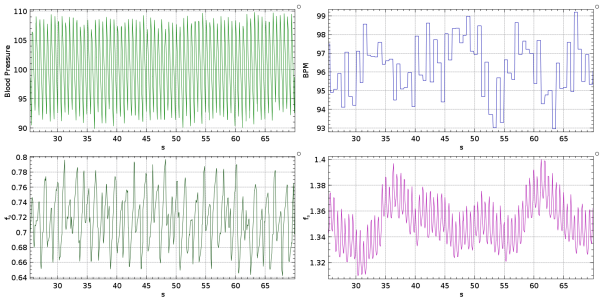


Figure 2. Baseline plots for blood pressure, beats per minute and influence of parasympathicus and sympathicus.

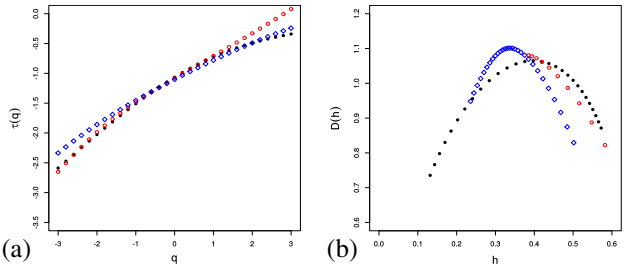
In order to evaluate the characteristics of the distributed simulation, we performed multifractional analysis of the baseline heart rate as well as conditions that simulate medication.

Multifractal spectrum and singularity spectrum of the baseline simulation are displayed in figure 3 (a) and (b) respectively as black solid circles. The multifractal spectrum shows a change of slope of $\tau(q)$ and the singularity spectrum shows a dependency of the fractal dimension $D(h)$ from the local Hurst exponent h, similar to experimental data from healthy subjects [10, 11].

Virtual medication: Administration of a betablocker, such as metoprolol, that suppresses SNS signals leads to a weak decrease in multifractal complexity of heart rate dynamics [10]. In order to simulate administration of a betablocker we turned the mouse-wheel of the sympathicus computer until the SNS gain has decreased to 80% of the baseline value. After a waiting time of 100 s we recorded heart beat intervals and analysed multifractal properties. The results are displayed as blue diamonds in figure 3 (a) and (b). The model shows a slight decrease in the curvature of the $\tau(q)$-spectrum and a narrowing of the $D(h)$-spectrum.

In a similar way virtual administration of atropine, as an example for a PNS blocking substance, is simulated by decreasing the gain of the parasympathicus to 80%. The results are displayed as red empty circles in figure 3. The almost linear curve of $\tau(q)$ and the reduced singularity spectrum $D(h)$ suggest almost monofractal signals. Both, the responses to blockade of SNS and to PNS activity are consistent with experimental data and indicate a realistic behaviour of the distributed simulation [10].

Virtual disease: Congestive heart failure (CHF) and primary autonomic failure (PAF) involve changes in long-



(a) (b)

Figure 3. Response of the model to SNS and PNS blockade. (a) Multifractal spectra $[\tau(q)]$ and (b) singularity spectra $[D(h)]$ that display the fractal dimension of patterns of heartbeat interval time series with the respective local Hurst exponents h. Black solid circles denote the baseline experiment simulated with default parameters. Red empty circles show the results for a 20% blocking of the PNS influence by virtual administration of atropine. Blue diamonds show the results for a 20% blocking of the SNS influence by virtual administration of metoprolol

range scaling properties of heart rate [12].

In CHF PNS activity is decreased and SNS activity is increased. According to Kotani et al. CHF can be simulated by decreasing the gain parameters for PNS influence and increasing the gain for cardiac and vascular branches of the SNS activity [4]. For disease simulation with the distributed simulator, we ran the model in baseline condition for some minutes before PNS gain is decreased to 60% and SNS gain is increased to 120% by turning the respective mouse wheels. The resulting heart rate is shown in figure 4 (b). Both the decrease of average heart beat interval and the decrease of multifractality are consistent with Konati's results and with experimental data from CHF patients.

In PAF both, PNS activity and SNS activity are decreased due to neuronal degeneration. We performed the simulation in a similar way as for CHF by reducing PNS influence to 80% and SNS influence to 50%. Results are displayed in figure 4 (c). As reported by Kotani for his model [4], the multifractality is only slightly reduced while heart beat intervals and variability of heart beat intervals are significantly reduced.

5. Discussion

The distributed simulation seems to be robust and displays similar properties as conventional implementations. In contrast to these, our model features asynchronous communication between organs leading to a more realistic model. Additionally the different organs become exchangeable modules. Although we currently use only one implementation for each organ, the setup allows to switch between different versions, which include or exclude certain physiological effects. This is possible during run-time.

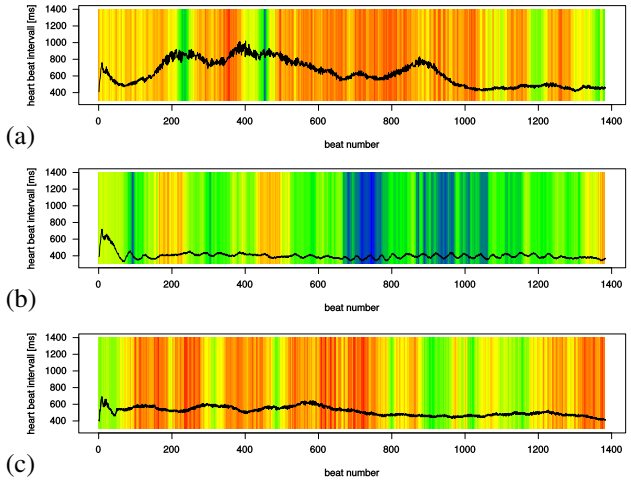


Figure 4. Heartbeat intervals of simulated diseases with the local Hurst exponent as background colour. The local Hurst exponent is coded as colour ramp from blue (minimum h=0.6) to green to yellow to red (maximum h=1.2). (a) Baseline simulation of a healthy subject. (b) Simulation imitating subjects suffering from CHF by blocking PNS influence by 40% and increasing SNS influence by 20%. (c) Simulation imitating subjects suffering from PAF by blocking PNS influence by 20% and SNS influence by 50%.

The real-time simulation also allows to manipulate single values by turning the respective adjusting wheel. This is much more flexible than conventional method of changing a certain value for a fixed amount and time period before simulation.

Live updating curves and flashing light provide direct feedback of consequences. This makes the simulation of diseases or medications intuitively explorable for users. Domain experts can evaluate the plausibility of the model behaviour without knowledge of the implementation and suggest further extensions. Students can learn about physiological modelling or about the baroreflex by experimenting with the model. This allows a playful and practical introduction to the topic with a gamification approach.

6. Conclusion

We have presented a new type of baroreflex simulator, that utilises distributed virtual functional units (i.e. *organs*) sinus node, windkessel arteries, lung, parasympathicus, sympathicus and baroreceptors. Simulations run in an asynchronous manner in real-time and aim to be notably realistic, because components only share information that is also shared between organs in a living organism.

The distributed simulator shows realistic responses to virtual medication and virtual diseases. The influence of these virtual experiments can be monitored as change of heart rate dynamics. Furthermore, the model can be intuitively operated without knowledge of the implementation. This can make the model a valuable tool to familiarise students and domain experts with the concepts of mathematical modelling.

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