Baroreflex Modeling in the Genesis of Stress Reactivity Using Sigmoidal Characteristic

Pedram Ataee, Guy A. Dumont, and W. Thomas Boyce

Abstract—According to a physiological hypothesis, children are separated into the two groups, (1) non-reactive and (2) high-reactive based on their different autonomic reactivity characteristics. In the non-reactive group, blood pressure (BP) and heart rate (HR) are regulated in a timely manner following external disturbances such as a stressful condition. However, this regulation process does not operate properly, or may even behave in an opposite direction for at least a period of the process in the high-reactive group. The purpose of this research is to analyze and compare the behavioral differences of the autonomic reactivity characteristic, represented by the short-term blood pressure regulation system (STBPRS), between these two groups of individuals. Similar to any regulation system, each component of this system has a specific role. For example, the autonomic nervous system (ANS) can be considered a controller while the heart and vasculature can be considered a plant under control. The arterial baroreceptor nerves - fiber endings in the arterial walls - play the role of sensor and feedback path. The STBPRS is called as baroreflex or baroreceptor reflex including the ANS and baroreceptors. We applied the Windkessel model and sigmoidal function as the model structures of the vasculature and baroreflex, respectively. To obtain the most similar simulated HR in comparison with measured HR, an optimization problem was defined. Due to the non-convex nature of the optimization problem, a genetic algorithm (GA) was applied to identify all of the corresponding unknown parameters for each component of the system. The obtained results of the system identification problem, verify the mentioned physiological hypothesis. Moreover, these results lead to a better understanding of the deficient baroreflex in high-reactive children. Furthermore, necessities of invasive blood pressure measurement in baroreflex studies is eliminated by using our proposed method.

I. INTRODUCTION

Multiple cardiovascular regulatory mechanisms, short-term and long-term, have evolved in the human body [1]. These mechanisms guarantee that active organs always receive adequate amounts of blood, even in the presence of stressful situations. The circulatory adjustments are functioned by altering the output of the heart, changing the diameter of the resistance vessels (the arterioles), or altering the amount of blood pooled in the capacitance vessels (the veins) [2]. The autonomic reactivity characteristic - the ANS response to an external stimulus - is represented by the STBPRS. Therefore, the autonomic reactivity can be measured by cardiovascular indices such as heart rate, blood pressure, and cardiac output.

In the STBPRS, the baroreflex works as a body homeostatic mechanism [3]. The normal baroreflex provides a negative feedback loop in which an elevated blood pressure reflexively causes itself to decrease. Similarly, decreased blood pressure depresses the baroreflex and causes itself to increase. The system relies on specialized neurons (baroreceptors) at various places in the circulatory system (aortic arch, carotid sinuses, and etc.) to monitor the changes in blood pressure and relay them to the ANS.

The purpose of the proposed research is to analyze and compare the differences of the STBPRS, represent the autonomic reactivity characteristic, among two groups of children. According to a physiological hypothesis, individuals are separated into the two groups, (1) non-reactive and (2) high-reactive, based on their different stress reactivity behaviors. In the non-reactive group, blood pressure and heart rate are regulated in a timely manner following external disturbances such as a stressful condition. In the high-reactive group, this regulation process does not operate properly, or may even behave in an opposite direction for at least a period of the process. Observing these behaviors in the results of mathematical model extracted from clinical data confirms the physiological hypothesis. Moreover, the achieved model may also lead to achieve a better understanding of system functionality in future experiments. Besides, the early development of mental and physical health problems are associated with the child’s autonomic reactivity in stressful conditions [4]–[7] which cause many researchers study the autonomic reactivity characteristics.

II. METHODS

A. Data set

A 20-minute experiment eliciting the autonomic reactivity characteristics in different types of stressful conditions was performed by 4-6 year old children in separate, quiet rooms at their schools. Experimenters recorded several signals corresponding to the autonomic reactivity such as cardiac output, heart rate, and respiratory rate. Data were acquired using the Biopac MP150 (Biopac Systems, Santa Barbara, CA) interfaced to a PC-based computer. The details of the protocol were completely explained in [4], [8]. This data-set was acquired by a group of scientist conducted by W. Thomas Boyce at the University of California Berkeley. The experiment protocol was pre-approved by the Committee for the Protection of Human Subjects of the University of California, Berkeley as well as the Committee on Human Subjects of the University of California, San Francisco [4].
B. Circulation System Modeling

Many models describing the blood circulation system [3], [9]–[13] have been proposed in recent years. These models are described by a set of mathematical relations among some variables of the system, mainly blood pressure, heart rate, and cardiac output. These variables are interrelated by a set of parameters such as vessel dimensions, elasticity of the arterial wall, and blood viscosity, which are difficult or impossible to be directly measured [14]. One of the most well-known models in circulatory dynamics studies is Windkessel [11], [14].

In this study, the vasculature is simulated by 4-parameter Windkessel model (WM) [15]. WM represents circulatory system as a hydraulic/electrical circuit as shown in Fig. 1. In this model, elasticity of the whole arterial tree (from the major arteries, to minor arteries, to arterioles, and to capillaries) is modeled as an elastic chamber with a constant compliance called total arterial compliance or C [14]. In addition, the resistance of flowing blood due to the vessel diameter changes (Poiseuille theorem [16]) is usually referred to as total peripheral resistance or R. The third and fourth elements, r and L, represents aortic characteristic impedance which accounts for the pressure loss and local inertia of the very proximal ascending aorta [17]. The describing equations of a 4-parameter Windkessel model in the frequency domain are given in 1.

\[
P(s) = \frac{Q(s)}{s} \cdot \left( \frac{RL}{r + L} \cdot s + \frac{R}{RC \cdot s + 1} \right) \quad (1)
\]

\[
P(s) = \frac{Q(s)}{s} \cdot \left( rRCL \cdot s^2 + L(r + R) \cdot s + r + Rr \right) \quad (2)
\]

where P is the mean arterial pressure and Q is the mean aortic flow. The corresponding time-domain equation describing the WM is shown below.

\[
RCL \cdot \ddot{p}(t) + (L + RCr) \cdot \dot{p}(t) + r \cdot p(t) = rRCL \cdot \ddot{q}(t) + L(r + R) \cdot \dot{q}(t) + Rr \cdot q(t) \quad (3)
\]

In practice, due to computation difficulties and discrete data acquisition methods, instead of solving the differential equations the corresponding difference equations are solved. By applying Z-transform to discretized form of (3), the transfer function between blood pressure (P) and cardiac output (Q) is obtained. The relation between P and Q in Z-domain is shown in (4).

\[
P(z) = \frac{A_2 \cdot z^{-2} + A_1 \cdot z^{-1} + A_0}{B_2 \cdot z^{-2} + B_1 \cdot z^{-1} + B_0} \cdot Q(z) \quad (4)
\]

\[
A_2 = rRCL, \quad B_2 = RCL
\]

\[
A_1 = -2rRCL - Lr - LR, \quad B_1 = -2RCL - L - RCr
\]

\[
A_0 = Rr + Lr + LR + rRCL, \quad B_0 = r + L + RCr + RCL
\]

C. Baroreflex Modeling

The baroreceptors are stretch-sensitive mechanoreceptors. When blood pressure rises, baroreceptors stretch and activate. Active baroreceptors fire action potentials more frequently than inactive baroreceptors. The greater the stretch, the more rapidly baroreceptors fire action potentials. These action potentials are relayed to the ANS, which uses frequency as a measure of blood pressure [18]. As receptors sense both absolute stretch and the rate of stretch change, both mean arterial pressure and arterial pulsatile pressure affect baroreceptor firing rate [16] (Fig. 2). Baroreceptor activation finally leads to inhibition or activation of the ANS. The baroreceptor firing rate pattern is not fixed; its pattern may change with permanent changes in blood pressure or special physiological conditions. For example, in stressful conditions the characteristics will change to maintain blood pressure in an appropriate range for the current situation.

Various models for baroreflex have been introduced in the literature [13], [15], [16], [18]. A sigmoidal characteristic is an example of these models which represents the relationship between baroreceptor activity and blood pressure [15], [19]–[21]. This sigmoidal function represents baroreceptor activity or the equivalent interbeat interval (IBI or T) , versus both mean arterial pressure and arterial pulsatile pressure (Fig. 2). IBI is a measure of the actual time interval between heart beats and it is usually measured in milliseconds. The sigmoidal characteristic of baroreflex is more well-known in baroreceptor feedback studies. This method has been studied and approved by a large number of physiologists [15], [19], [21]. In the current work, we chose the sigmoidal characteristic for the baroreflex. The sigmoidal function showing the relation between P and T is presented as follows.

\[
T(P) = T_s + \frac{T_m - T_s}{1 + e^{-\alpha (P - P_0)}} \quad (5)
\]
Fig. 3. The utilized chromosome including 6 genes

$T_s$ and $T_m$ represent the shortest and longest IBI. $\alpha$ and $P_0$ determine range and slope of the linear region of the corresponding sigmoidal function.

**D. Optimization Problem**

In the previous sections, the applied circulation model and baroreflex characteristic were precisely described. By combining (4) and (5), the relation between $T$ and $Q$ is determined as shown below.

$$IBI(Q) = T(Q) = T_s + \frac{T_m - T_s}{1 + e^{-\alpha(2^x(P(z))-P_0)}} \tag{6}$$

Now, we need to define an optimization problem to estimate unknown parameters of each part. In (6), six unknown parameters named $L, R, r, C, \alpha,$ and $P_0$ exist which must be estimated through a system identification method using two measured signals $Q$ and $T$. In other words, all parameters of the model, both Windkessel model and baroreflex characteristic, are obtained by minimizing the error between the measured and simulated IBI. Therefore, the simulated IBI becomes maximally similar to the measured IBI.

$$\arg\min_{L,R,r,C,\alpha,P_0} \|IBI_{Simulated} - IBI_{Measurement}\| \tag{7}$$

In this case, we conclude that these extracted parameters can represent the ANS characteristics and cardiovascular system of each individual.

**E. Parameter Estimation**

As explained in the previous section, an optimization problem was defined to find unknown parameters. In fact, estimating unknown parameters is identical to finding the optimum point of fitness landscape in the 6-dimensional space of parameters which is precisely explained in II-E.1. Therefore, potentially any searching method can be used to find the proper result. However, due to the non-convex nature of the desired optimization problem, the classic methods such as gradient based methods are not applicable. Genetic Algorithm (GA) is not guaranteed to extract out the global optimum, but it is less likely to get locked into a local optimum compared to traditional optimization techniques. Therefore, all the parameters are simultaneously estimated in this research work by an approach based on the genetic algorithm.

1) Genetic Algorithm: GA is a stochastic search method that operates based on the principle of natural selection and evolution using mutation and crossover operators. It operates through maximizing a fitness function value assigned to each solution among a population of trial solutions. In the applied GA, each solution is abstractly represented by a chromosome containing 6 genes corresponding to 6 desired parameters (Fig. 3). Each gene is a real number representing the value of the corresponding parameter. The desired ranges of these parameters are shown in (8).

$$\begin{cases} L,R,r,C \sim \text{Exp}(\lambda = 0.25) \\ 0.03 < \alpha < 0.5 \\ 80 < P_0 < 160 \end{cases} \tag{8}$$

In this research, the fitness function was defined as a similarity function between the measured and simulated IBI. Indeed, we investigate a fitness function capable of representing similarity between behavior of simulated and measured signals showing the quality of the solution. Our empirical result showed that $L_{inf}$, (9), makes the most appropriate fitness landscape to achieve the best result.

$$SI(X,Y) = L_{inf} = \max |X_i - Y_i| \tag{9}$$

Obviously, if all the data points in the simulated signal are equal to the corresponding points in the measurement data, these two discrete signals are identical. However, GA is not able to ensure achieving the equity of all the data points in simulation and measurement, representing the global optimum solution. Therefore, we defined a fitness function to obtain the most well-behaved or similar simulated signal as possible. Our experiments showed that we have to consider the amplitude of the signal as well as the first derivative of the signal in the implementation of the fitness function, (10), to achieve a proper result.

$$FF(T_M, T_S) = f \left( SI(T_M, T_S), SI \left( \frac{dT_M}{dt}, \frac{dT_S}{dt} \right) \right) \tag{10}$$

In (10), $T_M$ and $T_S$ stand for the measured and simulated IBI signal, respectively.

Moreover, due to the complexity of the search space, which emerges by choosing a higher order of derivatives, we just considered the two most important terms.

Simultaneously optimizing the similarity criteria among several functions - signals and their derivatives - is a relatively broad field of research called Multi-Objective Optimization (MOO) [22]. In this work, we just selected a straightforward method for implementing the fitness function, a weighted linear combination of our objective functions (11).

$$FF(T_M, T_S) = 3 \times SI(T_M, T_S) + SI \left( \frac{dT_M}{dt}, \frac{dT_S}{dt} \right) \tag{11}$$

The evolution process started from a population of 100 randomly generated chromosomes and took place in transition from one generation to the other. During each successive generation, a group of the current population was selected to develop the next generation. This group is selected through a ranking process, where the solutions with more proper fitness function are more likely to be selected. Then, a new population was formed by applying crossover and mutation operators on the recent selection. In a mutation operator, only one gene of chromosome is changed, while the crossover operator builds a new chromosome (child) by two components taken from two different chromosomes (parents) in
the previous generation. The process continues until a new population of solutions with appropriate size is generated. We applied an exponential and uniform random generator to define these operators. The new population was utilized in the next iteration of the algorithm. The algorithm terminated when a maximum number of generations, 2000, had been produced.

III. RESULTS

The desired unknown parameters were estimated by using the genetic algorithm. These parameters represent the functionality of the circulatory system (4 parameters related to the Windkessel model) and baroreflex (2 parameters related to the sigmoidal function). After finding the parameters for 14 subjects given in Table (I) (7 high- and 7 non-reactive), their sigmoidal baroreflex characteristics were plotted in Fig.4. This figure shows the normalized amount of interbeat interval for the next heart period (derived by the ANS) as a function of the blood pressure. Indeed, Y-axis was normalized to the interval $[0 - 1]$ for all the case studies in order to compare these individuals to each other.

In comparing the two groups, separately considering each individual is not always necessary. Therefore, by averaging all characteristics within each group the characteristics representative of these two groups were obtained. Each of these curves, shown in Fig.5, represents the whole group instead of a specific subject. As previously expected, the explained differences in the shape of sigmoidal functions are also observed in the Fig. 5.

The shape of the sigmoidal characteristic is determined by the 4th and 5th parameters. Mathematically, if the 5th parameter or $P_0$ increases (by maintaining the other parameters constant) the sigmoidal function will be saturated in the higher amount of pressure. This statement is also observed in Fig. 6, the Boxplot demonstration, showing the distribution of $P_0$ in the last generation of the GA method. This different distribution of population in the last generation of simulation also supports the results depicted in Fig. 5.

In order to validate the result of each subject, estimated parameters were applied to generate a simulated heart rate signal. The results of several subjects were neglected because their simulated and measured HR signal did not have similar behavior. In other words, the applied methods were not able to estimate proper amounts for their unknown parameters. However, the results of the shown 14 subjects were satisfying in terms of similarity between measured and simulated HR signal. Figs. 7 and 8 show two subjects, a satisfying and an unsatisfying case.

IV. DISCUSSION

The under-reviewed physiological hypothesis stated that

"Not only the BP regulation system in high-reactive children, unlike non-reactive children, does not work effectively, but also some positive feedback effects were observed in their regulation process."

To discuss this statement, Figs. 4 and 5 must be considered. In these figures, the Y-axis shows the amount of interbeat interval at a certain blood pressure, derived by the ANS to regulate blood pressure in the next cardiac cycle. In other words, the Y-axis represents the strength of the ANS reaction in regulating process at each BP level. Figure 5
shows that the ability in the high-reactive children is clearly lower than that for the non-reactive children. Moreover, the curves corresponding to the high-reactive children are nearly saturated at the high blood pressure, while the other curves related to the non-reactive children are saturated in the lower blood pressure (Fig.4). That is, the BP regulation system in a high-reactive individual is not able to properly adjust the blood pressure comparing to a non-reactive individual. These differences support and validate the mentioned physiological hypothesis to some extent.

Many methods were introduced in the literature to find the unknown parameters of each sub-system, $L$, $R$, $r$ and $C$ for Windkessel model and $\alpha$ and $P_0$ for the sigmoidal characteristic. In some previous studies, the parameters were chosen from a so-called standard look-up table [15] or were calculated by some methods using the amount of blood pressure [23]. In our work, none of these approaches can be applied.

First, individuals have different cardiovascular systems and ANS reactivity characteristics. In other words, the parameters must be different in each individual. Our results shown in table (I) verify this opinion. It is concluded that look-up table is not suitable way to choose the parameters. In this work, in contrast to previous literature [10], [15], all parameters were independently estimated for each individual. This subject-specific approach enables more accurate analysis of the individual’s cardiovascular system.

Second, blood pressure measurement is not available in our data set due to the invasive issues of the measuring process. In [24], the blood pressure measurement is available while it is measured by inserting an intra-arterial catheter into the radial artery. Measuring accurate blood pressure in the aorta is an invasive process, so many clinicians prefer to not apply it on humans. Our proposed parameter estimation method is able to facilitate the ANS reactivity studies while the invasion issues are reduced [25]. Indeed, necessities of invasive aortic blood pressure measurement in baroreflex studies is eliminated by using this method in identifying system parameters. However, unavailability of the measured blood pressure resulted in having a more complicated estimation process. On the other hand, some concerns exist on the cardiac output measurement, but many relatively accurate non-invasive methods for cardiac output have been suggested in recent years [26]. In our data set, cardiac output was measured by the bio-impedance measuring tool produced by BIOPAC Systems Inc.

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The genetic algorithm, the applied searching technique in the proposed parameter estimation method, may converge to a local optimum or even an arbitrary point rather than the global optimum of the problem. The likelihood of this occurring depends on the shape of the fitness function landscape. The selected similarity index and applied method of multi-objective optimization for fitness function definition, have a significant effect on the shape of the fitness landscape. Therefore, choosing a proper fitness function and well-tuning the GA technique are important factors to have a rapid and efficient algorithm.

V. CONCLUSION AND FUTURE WORK

In this research, the sigmoidal characteristic of baroreflex, interbeat interval versus blood pressure, is successfully applied in studying of the ANS reactivity. It was shown that the sigmoidal baroreflex characteristics for high-reactive and non-reactive individuals, as expected, were noticeably different. It was also observed that the ANS in high-reactive individuals is not able to regulate blood pressure as well as the ANS in non-reactive individuals. These results support and validate the introduced physiological hypothesis to some extent. However, a possible positive feedback mechanism in the short-term blood pressure regulation system, as stated in the hypothesis, has not been studied yet.

In this work, a novel method in identifying the ANS reactivity characteristic is proposed by eliminating the necessities of BP measurement. Indeed, non-invasive cardiac output measurement is more accurate than non-invasive blood pressure measurement in the aorta. Therefore, it is valuable to find a mathematical method to be utilized in the ANS reactivity studies which takes advantages of cardiac output and heart rate but blood pressure. However, this achievement, the reduction of invasive issues, increases some complexities in the mathematical aspect of the method.

The proposed results are acquired from the data corresponding to the 14 individuals. We will study more cases in the future to increase the accuracy of the results. Besides, the parameter identification method can be improved by more precise tuning especially in terms of the fitness function. Moreover, several degrees of freedom will be added to the baroreflex and circulation model in the future to explore and obtain more concrete results in hidden behavioral aspects of cardiovascular system.

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