BLOOD PRESSURE REGULATION MODELING IN MATLAB

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Abstract

A bio-cybernetical model of blood pressure regulation in rats is presented. Time-responses of blood pressure after administration of selected drugs are identified and linear dynamic models of the cardiovascular system using genetic algorithms are calculated in the Matlab environment. The three major regulation systems – sympathetic nervous system, renin-angiotensin-aldosterone system and L-Arginine/nitric oxide system are considered.

1 Introduction

Blood pressure (BP), generally characterized as the pressure exerted by blood against the walls of the arteries and veins, is one of the principal vital signs. In general, level of BP is the result of cardiac output and total peripheral (systemic) vascular resistance [1]. Cardiac output, i.e. the volume of blood flow from the heart, is a function of heart rate and stroke volume (volume of blood ejected by the heart during contraction). Furthermore, stroke volume is affected by contractility of the heart and venous return, which is modulated by blood volume, venous tone, renal water and sodium retention and by thirst. Total peripheral vascular resistance is the sum of the resistance of the entire peripheral vasculature. Total peripheral vascular resistance is affected by the viscosity of blood, local and circulating substances as well as autonomic nervous systems – sympathetic and parasympathetic.

As the maintenance of normal BP is critical in order to keep normal oxygenation of tissues and organs and thus homeostasis of the all living organisms including humans, level of BP is controlled and regulated on several levels. Besides continual central regulation, the first and the fastest way of BP regulation is the immediate beat-to-beat regulation that includes Frank-Starling mechanism and myogenic regulation. Additional mechanisms, such as baroreflex and chemoreflex are involved in short-term regulation, several seconds after BP is altered from its normal level. The major regulatory systems involved in baroreflex mechanism are the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). When these mechanisms are not able to return BP back to its normal level, additional humoral factors and local autacoids start to affect BP. Furthermore, long-term mechanism such as natriuresis regulates BP for hours and days (Fig. 1). Finally, there are additional mechanisms that affect BP on long-term basis – circadian, seasonal and ontogenetic.

There are three major powerful regulatory systems – sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS) and L-Arginine/nitric oxide (L-Arg/NO) system, which affect BP via modulation of various pathways involved in this complex network. The enhancement of the SNS (via increased release of noradrenalin) and RAAS (via increased release of angiotensin II) result in the rising of BP, while increased release of NO leads to BP decrease. In fact, NO, well known neurotransmitter, neuromodulator and vasodilator, has to be released continually, to act against vasoconstriction produced by SNS and RAAS, and its inhibition results in hypertension in rats [2]. Additionally, all mediators noradrenaline, NO and Ang II, are produced and play a significant role in BP regulation at both central and peripheral level (for details see [3]). Thus, in order to maintain normal level of BP, there is significant cross-talk among these three systems (Fig 2).

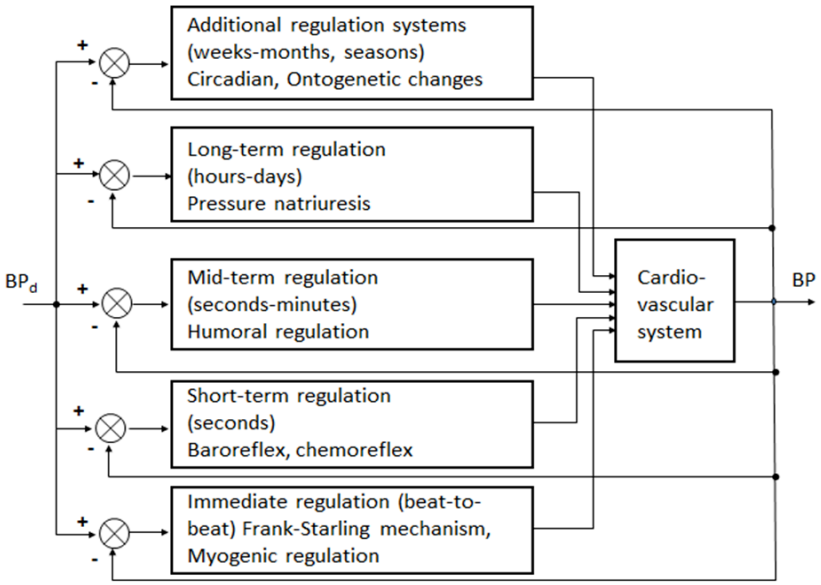

Figure 1: The main blood pressure regulation mechanisms
(BP- blood pressure, BP_d – desired value of BP)

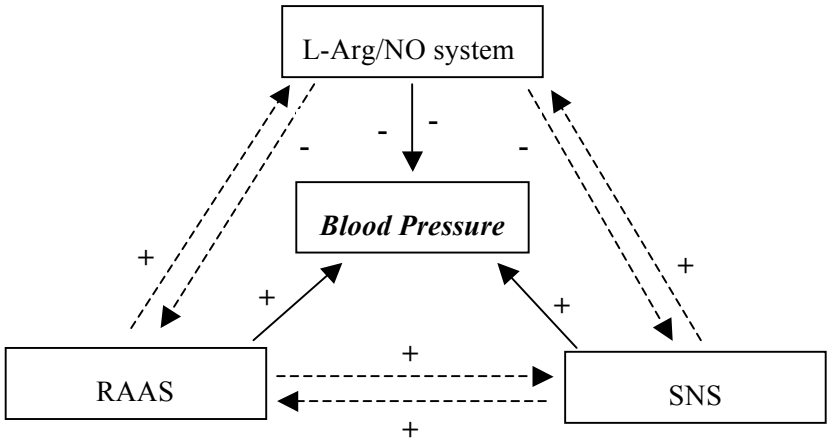

Figure 2: Interactions between BP regulation systems. SNS -sympathetic nervous system, RAAS - renin-angiotensin-aldosterone system, L-Arg/NO - L-Arginine/nitric oxide, BP – blood pressure; sign "plus" means activation, sign "minus" means inhibition.

However, despite concerted action of the all above mentioned mechanisms, there are many genetic and environmental factors that – alone or in combination – can increase the risk of BP dysregulation and developing primary hypertension. Arterial hypertension is one of the most significant risk factors for cardiovascular diseases. It is often called a "silent killer" because many people have hypertension for years without realizing it. Despite our current knowledge and extensive clinical and experimental research in the field of hypertension, the cause of hypertension remains unknown in about 95% of all cases in human population [4]. Thus, several animal experimental models of hypertension have been developed to study the mechanisms of blood pressure regulation in rats in order to better understand the cause of human arterial hypertension and to improve the treatment of this disease of civilization.

The aim of this project is to design mathematic models of the mid-term and long-term BP regulation in rats (Fig. 1, Fig. 2). The responses of three major regulatory systems – SNS, RAAS and L-Arg/NO are modeled. Such models can be used for simulation and better understanding of the BP regulation mechanisms in rats and supposedly later also for medicament dosing/timing optimization. The first step of this study, which is presented in this paper, was the modeling of BP response after administration of selected drugs, which inhibit the three major pressor regulatory systems.

2 Experiment setup

Adult male normotensive Wistar-Kyoto (WKY) rats and spontaneously hypertensive rat (SHR) were used in this study. All experiments were approved by the Ethical Committee of the Institute of Institute of Physiology AS CR, conform to European Convention on Animal Protection and Guidelines on Research Animal Use. In all rats RAAS was attenuated by inhibition of the angiotensin-converting enzyme, responsible for production of Ang II, by captopril at the dose of 10 mg/kg. Next two regulatory systems were depressed using inhibitors – pentolinium and N^G-nitro-L-arginine methyl ester (L-NAME), respectively. Ganglionic blocking agent, pentolinium, which inhibits the release of noradrenaline, was used at the dose of 5 mg/kg. Finally, L-Arg/NO system was attenuated by inhibition of nitric oxide synthase using L-NAME in the dose of 30 mg/kg. Moreover, reversibility of nitric oxide synthase inhibition was tested using direct exogenous NO donor sodium nitroprusside in the dose of 20 µg/kg. All substances were given to circulation via the catheter inserted into the jugular vein. BP was determined directly by the catheter inserted into the carotic artery (for details see [5]). Systolic BP (SBP) and diastolic BP (DBP) were recorded with sampling period 0.0025s. Mean arterial pressure (MAP) was calculated as *MAP = DBP + 1/3(SBP-DPB)*. Data were recorded and then transformed to Matlab [6] for further analyses and model identification. Data recorded in WKY rats are shown in the Fig.4 and Fig. 5 respectively. In this paper only the results of modeling of WKY rats are presented. The modeling procedure of SHR rats is analogical.

3 Dynamic model identification

In this paper for modeling of the BP dynamics linear models are considered in form of the n^{th} order differential equation

$$a_n \frac{dy^n}{dt} + a_{n-1} \frac{dy^{n-1}}{dt} + \ldots + a_1 \frac{dy}{dt} + a_0 = b_{n-1} \frac{du^{n-1}}{dt} + \ldots + b_1 \frac{du}{dt} + b_0$$

where *u(t)* is the system input signal (drug dosage, step function is considered), *y(t)* is the system output signal (BP time-response) b_i and a_i are coefficients of the linear differential equation. This form is equal to following transfer function representation

$$BP_1(s) = \frac{y(s)}{u(s)} = \frac{B(s)}{A(s)} = \frac{b_{n-1}s^{n-1} + \ldots + b_1 s + b_0}{a_n s^n + \ldots + a_1 s + a_0} \tag{1}$$

Alternatively also the following model has been used:

$$BP_2(s) = \frac{B_1(s)}{A_1(s)} + \frac{B_2(s)}{A_2(s)} e^{-Ds} = \frac{b_{1,n-1}s^{n-1} + \ldots + b_{1,1}s + b_{1,0}}{a_{1,n}s^n + \ldots + a_{1,1}s + a_{1,0}} + \frac{b_{2,n-1}s^{n-1} + \ldots + b_{2,1}s + b_{2,0}}{a_{2,n}s^n + \ldots + a_{2,1}s + a_{2,0}} e^{-Ds} \tag{2}$$

where *u(s)* is the Laplace transformation of the system input signal (drug), *y(s)* is the Laplace transformation of system output signal (BP), b_i and a_i are coefficients of the nominator or denominator of the linear model transfer function, *D* is transport delay and *s* is the Laplace operator.

For identification of coefficients a_i and b_i the genetic algorithm has been used. The genetic algorithm (GA) [7, 8, 9] is a powerful, stochastic based search/optimization method, which imitates the biological evolution. It is based on following steps:

1. initialization of population (set of individuals)
2. fitness function calculation of the population
3. if termination conditions are met then end, else continue in step 4
4. parent selection (more fit individuals have higher probability to be selected)
5. modification of parents by crossover and/or mutation - children
6. new population completion (children + selected unchanged individuals)
7. continue in step 2

An individual is a string containing parameters of the optimized object. In our case the individual is in the form:

$individual_i = \{a_n, a_{n-1}, \ldots, a_1, a_0, b_{n-1}, b_{n-2}, \ldots, b_1, b_0\}$.

Mutation is an operation, where a parent individual is randomly changed. Crossover is an operation, where properties of two parent individuals are randomly combined to produce a child.

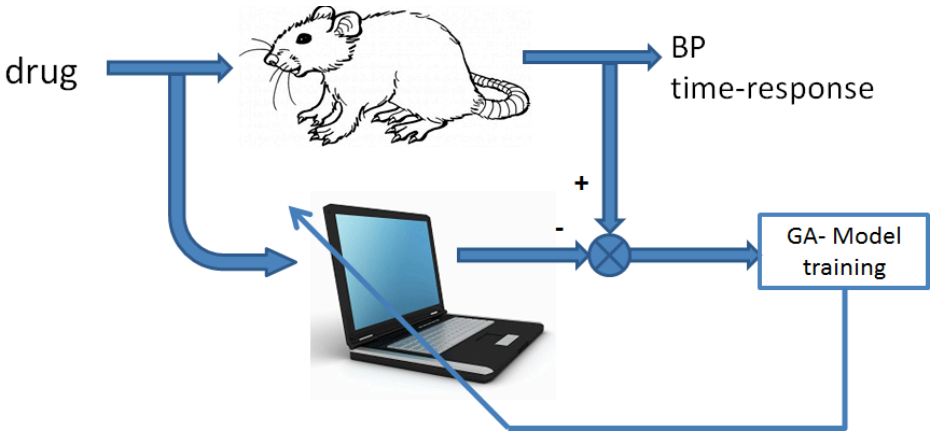

Figure 3: Dynamic model identification based on the genetic algorithms
(BP - blood pressure)

The fitness evaluation contains simulation of the dynamic system output (time-response to the input signal) and a performance measure evaluation, which is in form

$$J = \sum_{i=1}^{N} (y_i - y_{m,i})^2$$

where N is the number of simulation steps (number of measured samples), y is the measured time-response of BP, and y_m is model output. A block scheme of the identification procedure is depicted in Fig. 3. Using such identification procedure the linear models in form (1) for the BP response after pentolinium administration and after L-NAME administration has been obtained. The comparison of the measured data and the obtained models are in Figs. 6 and 7. The last case is the model of the reaction after administration of NO donor sodium nitroprusside. In this case the model in form (2) was considered. The time-response is depicted in Fig. 8.

4 Conclusion

In this paper identification of mathematical models of some particular reactions of the BP regulatory system after application of selected inhibitors is described. At this stage of our research linear dynamical model has been used, which was parameterized using genetic algorithms. The GA-based approach was used because it gives better results as compared to other conventional identification methods. Because behavior of BP gets non-linear, the linear models, which are described in this study, are not able to approximate exactly the dynamics of the cardiovascular system in all (other) working points (for example using different drug dosing). From this reason a non-linear model will be proposed in next steps. Our aim is to design a simulation model of the BP-regulation (at least of the three main regulation systems: SAS, RAAS, NO), which can help better understand the BP-regulation mechanisms in biological systems and supposedly later also for medicament dosing/timing optimization.

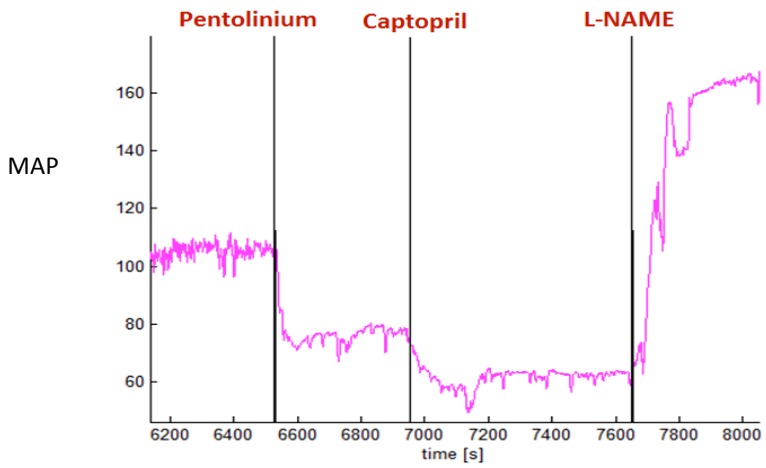

Figure 4: Blood pressure time-responses after administration of various drugs (example) in normotensive Wistar/Kyoto rat

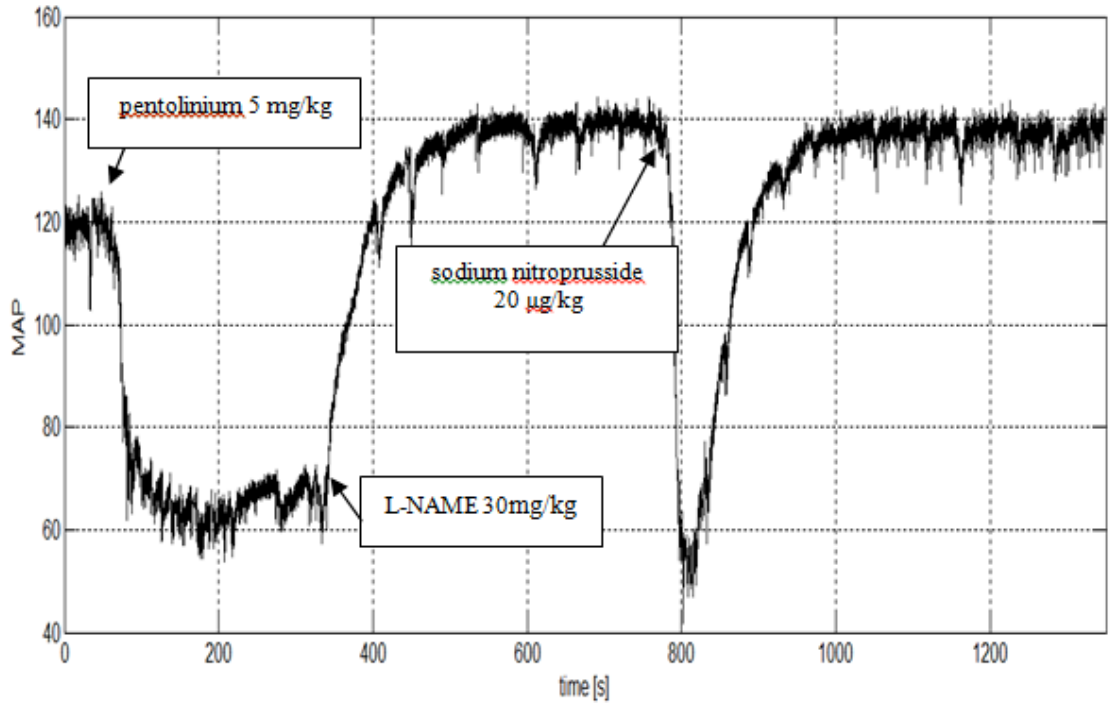

Figure 5: Blood pressure time-responses after administration of 3 drugs in normotensive Wistar/Kyoto rat (MAP – Mean arterial pressure [mmHg])

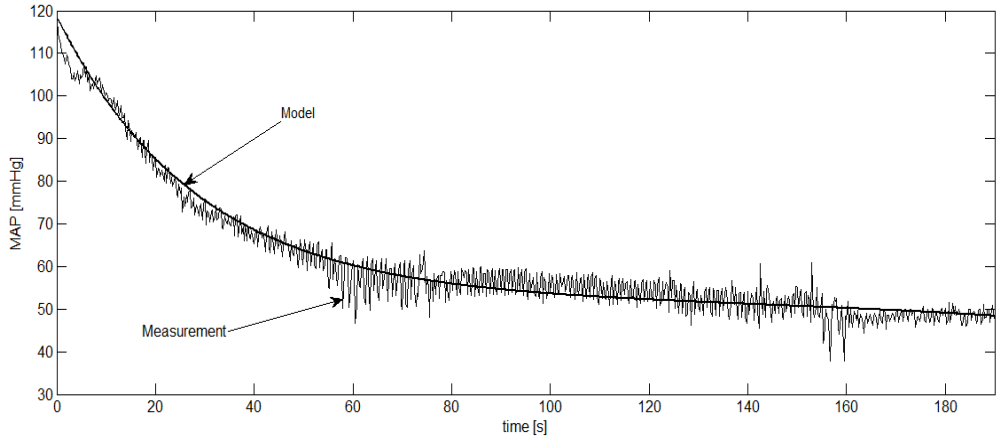

Figure 6: Comparison of measured time-responses of mean arterial pressure (MAP [mmHg]) and the linear model after pentolinium in normotensive Wistar/Kyoto rat

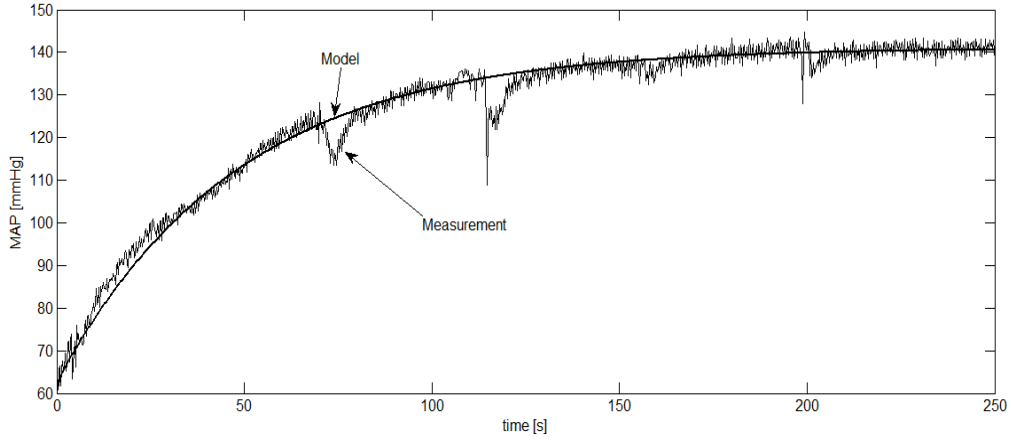

Figure 7: Comparison of measured time-responses of mean arterial pressure (MAP [mmHg]) and the linear model after L-NAME in normotensive Wistar/Kyoto rat

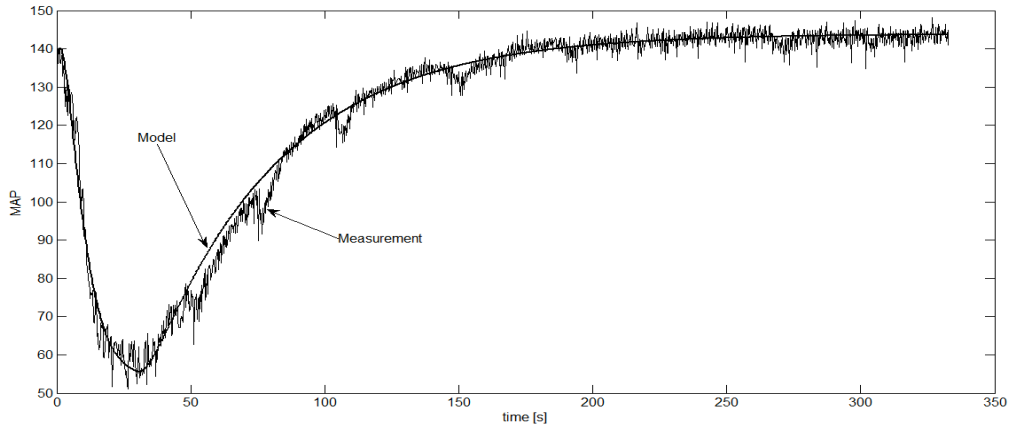

Figure 8. Comparison of measured time-responses of mean arterial pressure (MAP [mmHg]) and the linear model after sodium nitroprusside in normotensive Wistar/Kyoto rat

Acknowledgement

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