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Modeling of the Blood Pressure Regulation System in Rats Using Genetic Algorithms

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Abstract: Blood pressure (BP) is one of the principal vital signs. The regulation of normal BP is critical for maintaining the normal functioning of an organism. The structure of the BP regulation in vertebrates, including humans, is very complex and it is not yet fully understood. There are several BP regulation subsystems which interact together. In this study, we analysed and modelled the role of the most important BP regulation systems (sympathetic nervous system, renin-angiotensin-aldosterone system, L-Arginine/nitric oxide) as well as the role of reactive oxygen species, the imbalance of which is implied in the development of hypertension disease. Our aim is to design a dynamic model of the BP regulation in normotensive rats, which can help us better understand the complex process of BP regulation. The BP responses were measured in conscious rats after acute stress with or without the application of selected drugs, which can inhibit particular regulation subsystems. Linear dynamic models of particular regulation subsystems were identified using genetic algorithms. Each subsystem is a feedback loop, which contains both the system dynamics and the controller. We describe the simulation-based identification procedure of these particular models as well as of the entire BP regulation system.

Keywords: blood pressure regulation, rat, stress response, linear dynamic model, model identification, genetic algorithm

1. INTRODUCTION

Blood pressure (BP), which is generally characterised as the pressure exerted by blood against the walls of the blood vessels, is one of the principal vital signs. In general, the BP level is the result of cardiac output and total peripheral (systemic) vascular resistance e.g. Klabunde (2011). 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 for maintaining the normal oxygenation of tissues and organs and thus the homeostasis of all vertebrates, including humans, BP is regulated on several levels. The first and fastest way of BP regulation is the immediate beat-to-beat regulation. Additional mechanisms, such as baroreflex and chemoreflex, are involved in short-term regulation shortly after BP is altered from its normal level. The major regulatory systems involved in the 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 mechanisms, such as natriuresis, regulate BP for hours and days (Fig. 1). Finally, there are additional mechanisms that affect BP on a long-term basis – circadian, seasonal, and ontogenetic.

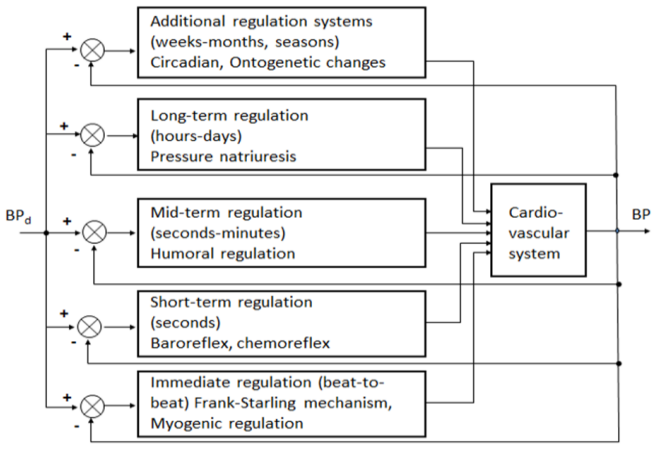

Fig. 1. Blood pressure regulation (BP- blood pressure, BP_d - desired value of BP)

There are three major powerful regulatory systems that modulate the final level of BP in mammals – the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), and L-Arginine/nitric oxide (L-Arg/NO) system. In

addition, reactive oxygen species (ROS) were shown to participate in BP regulation via interaction with all three above mentioned systems. These systems regulate the BP level via various metabolic pathways that are involved in a complex network (Fig. 2), and they cooperate and affect each other by the negative and positive interactions.

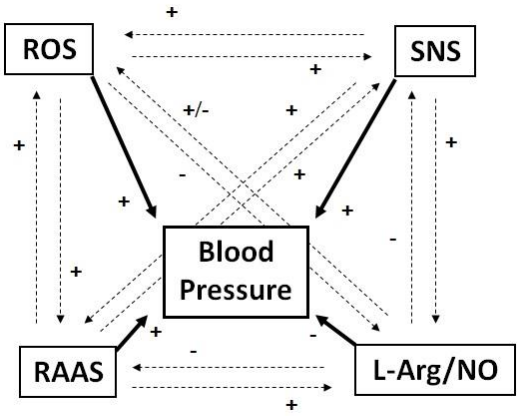

Fig. 2. Assumed interactions between BP regulation subsystems. (SNS – sympathetic nervous system, RAAS – renin-angiotensin-aldosterone system, L-Arg/NO – L-Arginine/nitric oxide, BP – blood pressure; the "+" sign means activation, and the "-" sign means inhibition.)

After exposure to stressors, the first pressor system that is activated is the SNS. The activation of SNS leads to an increased release of noradrenalin (NA) from the nerve endings which activate a further release of NA, together with adrenalin, from the adrenal glands. This causes a significant BP disturbance. The activation of SNS is followed by the activation of RAAS and the release of angiotensin II (Ang II), which participates in the maintenance of increased BP. Recently, the vascular L-Arg/NO system has been shown to act as an anti-stress system (Puzserova et al. 2013) in addition to its obvious functions in the cardiovascular regulation. NO has to be released continually in order to act against vasoconstriction which is produced by SNS and RAAS in the vasculature. All of the mediators NA, NO, and Ang II are produced and play a significant role in BP regulation at both the central and peripheral level. For details, see Pinterova et al. (2011). Thus, in order to maintain normal BP, there are significant interactions among these systems (Fig. 2). Disruption of any of them, due to stress, genetic disorders, or pharmacological interventions might results in an imbalance leading to pathological consequences.

The detailed function, internal structure, and interactions of all the BP regulation subsystems are still not exactly known as it is not possible to measure the function of individual subsystems continuously.

Thus, we established the experimental procedure of the BP regulation model identification in rats on the basis of acute stress-induced BP responses. The physiological function of the major regulatory systems – SNS, RAAS, and L-Arg/NO and also ROS were pharmacologically modified in order to isolate the responses of particular subsystems. BP time-responses achieved in vivo in rats were used for the identification of particular linear dynamic models and finally of the entire BP regulation system.

From a bio-cybernetic point of view, BP regulation is a complex closed-loop regulation structure consisting of several interconnected subsystems. As mentioned, we are not able to separate the particular regulation systems and to identify them as isolated subsystems. In such case, the "conventional" identification methods either cannot be used or they do not lead to satisfactory results. That is why a genetic algorithm-based procedure was proposed. The genetic algorithm (GA) is an efficient meta-heuristic search and optimisation approach, which is able to find solutions from various application domains, wherein the cost function can also contain model simulations with many optimised parameters e.g. Goldberg (1989), Eiben (2007), and others. The model design process proposed in this study is based on the set of steps where particular regulation subsystems are sequentially attenuated and the remaining currently active subsystem is identified as a closed-loop model.

The main goal of this model is to better understand the role and relative contribution of the above mentioned BP regulation subsystems, which cannot be analysed separately and also to better understand the entire system of short-term or mid-term BP regulation.

2. EXPERIMENTAL METHODS AND BP MEASUREMENT

Adult male normotensive Wistar rats were used in this study. In all rats, acute stress was induced by a 3 second pulse of air to the face of the rat. For the attenuation of particular regulation subsystems, the following drugs were used:

RAAS was attenuated by the inhibition of the angiotensin-converting enzyme (responsible for production of Ang II) by Captopril (C) at a dose of 10 mg/kg.

Ganglionic transmission blocking agent Pentolinium (P), which inhibits the release of noradrenaline in the SNS, was used at a dose of 5 mg/kg.

The L-Arg/NO system was attenuated by the inhibition of nitric oxide synthase using N^G-nitro-L-arginine methyl ester (L-NAME, L) in a dose of 30 mg/kg.

The effect of ROS was reduced by Tempol (T), which is a radical scavenger that mimics the activity of superoxide dismutase at a dose of 25 mg/kg.

All substances were administered to the circulation of conscious rats via a catheter inserted into the jugular vein. BP was continuously measured by the catheter inserted into the carotic artery, for details see Zicha et al. (2006). Systolic BP (SBP) and diastolic BP (DBP) were recorded from the animal with the sampling period T_s=0.0025s. An example of the BP measurement is depicted in Fig. 5. Mean arterial pressure (MAP) was calculated as

$$MAP = DBP + \frac{1}{3}(SBP - DBP) \cdot \quad (1)$$

Data were recorded and then transformed into Matlab, MathWorks (2008) for further analyses and model identification. Time-responses after stress of more (3-10) rats (for each combination of drugs) were collected and the mean values of MAP of all the animals were used for the identification procedure.

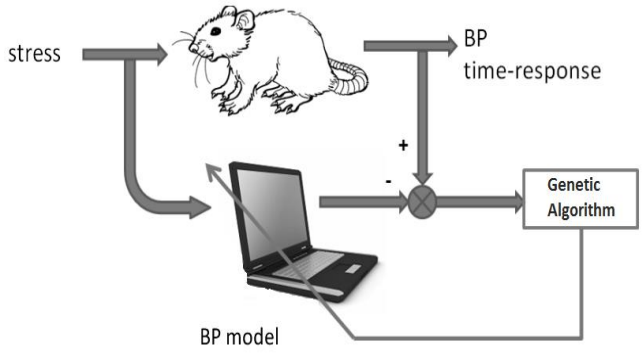

Fig. 3. Principal scheme of model identification

3. MATHEMATICAL MODEL OF BP REGULATION

3.1 Linear model of BP regulation

Let us consider the model structure of the BP regulation system as shown in Fig. 4. Each of the five subsystems consists of the controller part (Regulator) and the part representing the subsystem dynamics. For the second part, a linear model was considered in the form of the third order linear dynamic system

$$S_x(s) = \frac{y(s)}{u(s)} = \frac{B(s)}{A(s)} = \frac{b_1 s + b_0}{a_3 s^3 + a_2 s^2 + a_1 s + a_0} \quad (2)$$

where *u(s)* is the Laplace transformation of the system input signal, *y(s)* is the Laplace transformation of system output signal, a_i and b_i are the coefficients of the nominator and denominator, respectively. We consider that the thirh order dynamics can approximate the system wih sufficient accuracy. The controller part of the model of each subsystem is represented as a PID controller in the form

$$C_x(s) = P_x + I_x / s + D_x s \quad (3)$$

where *x* denotes each regulation subsystem. As described above, the BP regulation investigated in this study (Fig. 2.) comprises the three main subsystems (SNS, RAAS, L-Arg/NO) and the ROS, but there are other factors that affect BP. Thus, a subsystem called "Remaining" was considered which represents additional regulation mechanisms such as the mechanical properties of the cardiovascular system (self-regulation), remaining parts of the four above mentioned regulation systems which might not be completely depressed using C, L, P, T, as well as other systems and autacoids that may regulate BP in stress. BP_d is the reference value of the BP which represents the lowest BP needed for the optimal perfusion of all organs and tissues. The stress input (stressor) acts as a disturbance affecting the neuronal NO production by nNOS (nNO in Fig. 4) which is acting in both the SNS and Remaining subsystems and it is eliminated by the actions of all the controllers. Each control loop (subsystem) can be attenuated (switched off) using an appropriated drug as shown in the right part of Fig. 4.

3.2 Genetic algorithm – based model computation

For the identification of the dynamic model the genetic algorithm has been used as described in Sekaj (1999, 2011). Each individual of the GA population is a string containing the parameters of the optimised object. In our case, each individual is in the form:

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

The algorithm consists of the following steps:

Initialisation of the population (set of 450 random generated individuals).

Genotype to phenotype transformation (the items of each string are copied into the simulation model in Matlab/Simulink environment) and the cost function of each individual of the population according to (4) is calculated.

If the termination condition is met (in our case - predefined number of calculated generations) then end, else continue in step 4.

Parent selection using tournament selection (70% of all the individuals of the population).

Selection of 30% unchanged individuals using tournament selection (including the best individual of the population).

Modification of parents by crossover and mutation = children. A single point crossover was performed. Up to 10% of all genes of the population were mutated using global or local mutation. Global mutation means a random change of randomly selected genes (parameters), the maximal mutation step is equal to the entire search space, local mutation means a small random change of randomly selected genes, and the maximal mutation step has the size of 1% of the search space range.

New population completion (children + selected unchanged individuals).

Continue in step 2.

The cost function J evaluation contains the simulation of the BP model output (time-response after stress) and a performance measure evaluation, which is in the form

$$J = \sum_{i=1}^{N} (y_i - y_{m,i})^2 \rightarrow \min \quad (4)$$

where *N* is the number of simulation steps (which is equal to the number of samples measured), *y* is the measured time-response of BP after stress, and y_m is BP model output. The stress input in the model is represented as a 3-second pulse

with the amplitude equal 1. A block scheme of the identification procedure is depicted in Fig. 3.

3.3 Model identification procedure and results

The only measured output of the cardiovascular system, which has been considered in this study, is MAP. The example of an experiment with the following events: stress, administration of Captopril, L-NAME, Tempol, Pentolinium and finally stress is given in Fig. 5.

The following sequence of steps has been performed in order to obtain all the particular regulation models:

1. Administration of C, P, L, and T. All main regulation subsystems were attenuated (see Fig. 4), except for the Remaining system and the nNO-Rem.

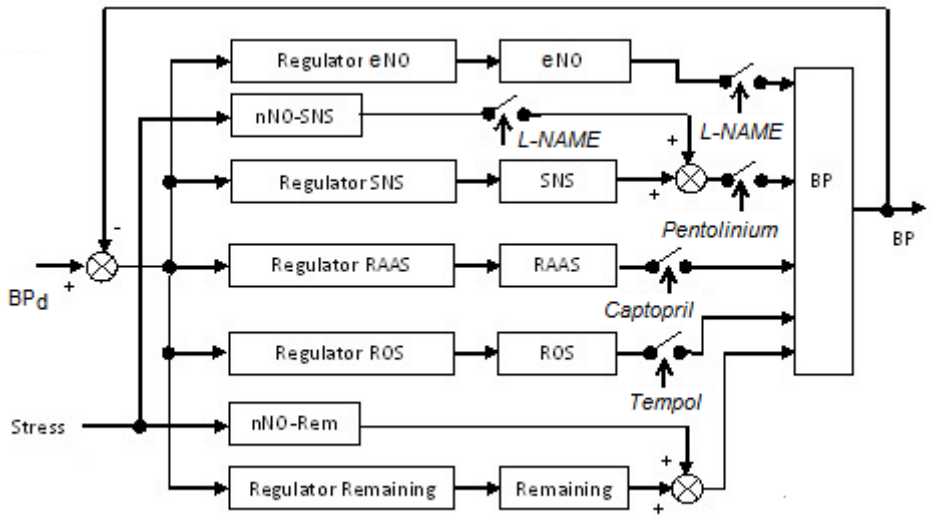

Fig. 4. Block scheme of the model of the BP regulation system, particular regulation subsystems SNS, RAAS, L-Arg/NO, nNO (i.e. NO produced by neuronal NOS), eNO (i.e. NO produced by endothelial NOS), the ROS, and the Remaining subsystem.

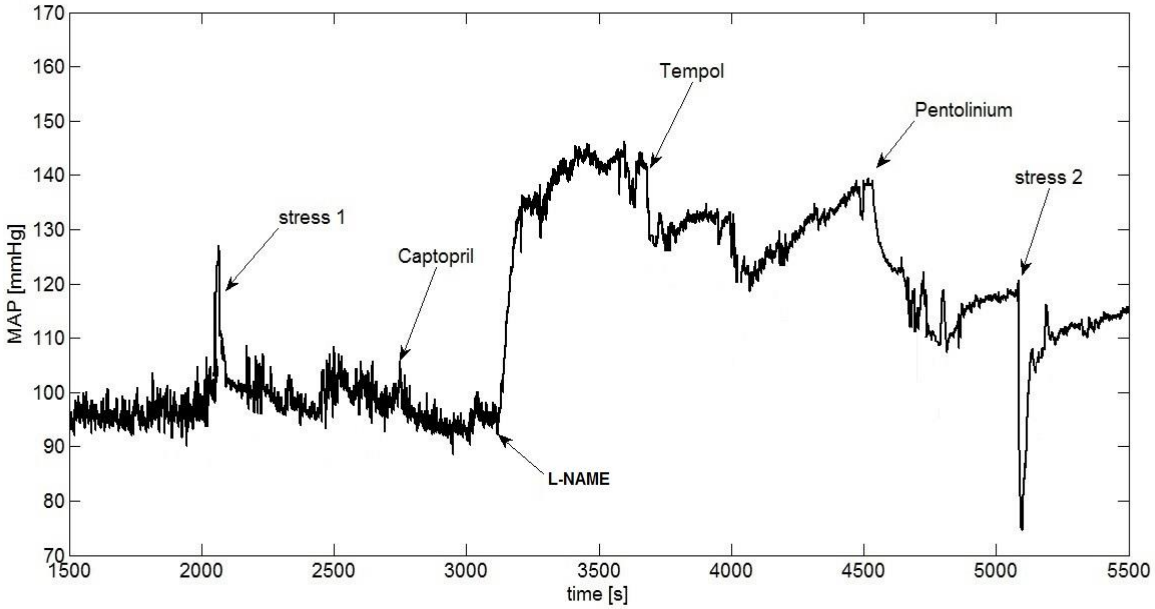

Fig. 5. Example of the BP measurement during an experiment: stress disturbances and drug (C,L,T,P) administration.

In this state, the model of the Remaining subsystem and the nNO-Rem are the only active and they can be calculated according to part 3.2. In Fig. 6, the MAP time-responses of the rat after stress (delivered in the 20th second) and the time-response obtained from the particular model are compared.

2. Administration of C, P, and L. Three regulation subsystems are attenuated except for the Remaining system and ROS. As the model of the Remaining system and nNO-Rem were already determined in the previous step, the model of ROS is calculated (Fig. 7).

3. Administration of P, L, and T. Three regulation subsystems are attenuated except for the Remaining subsystem and RAAS. The model of RAAS is calculated (Fig. 8).

4. Administration of C, L, and T. The model of SNS is calculated (Fig. 9).

5. Administration of C, P, and T. The model of NO (eNO in Fig.4) is calculated (Fig. 10).

6. No drugs are administrated. The last unknown nNO-SNS interaction is calculated. The time response of BP determined in the rats is compared to the model response in Fig. 11.

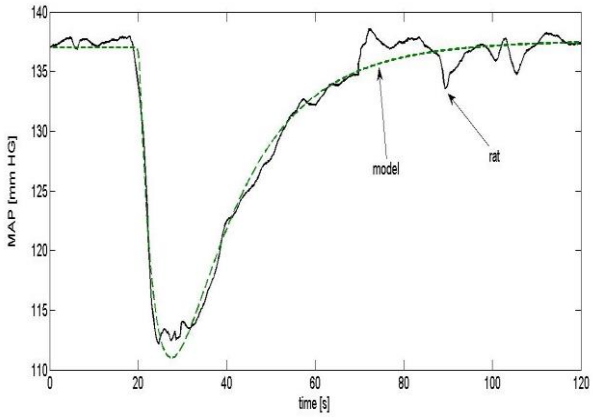

Fig. 6. Comparison of the measured MAP response to stress (delivered in the 20th second) and the model response after the inhibition of all regulation subsystems by administration of C, P, L, and T.

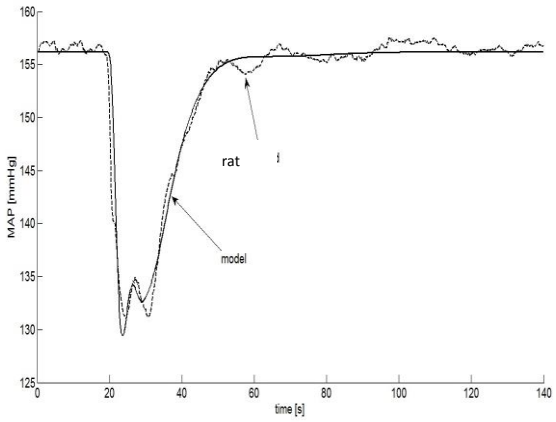

Fig. 7. Comparison of rat and model responses after the administration of C, P, L. ROS and Remaining are active.

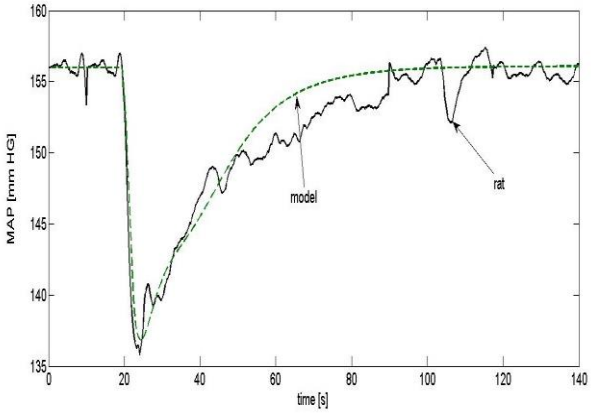

Fig. 8. Comparison of rat and model responses after the administration of P, L, T. RAAS and Rem are active.

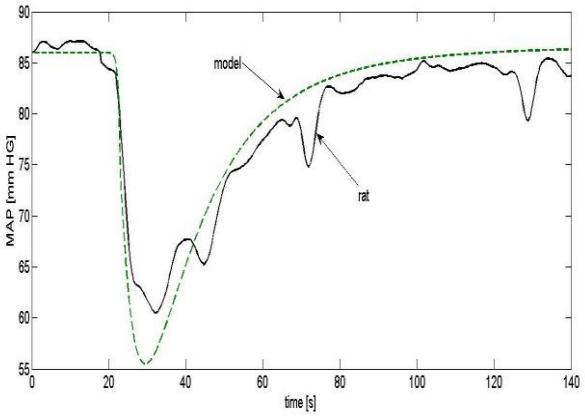

Fig. 9. Comparison of rat and model responses after the administration of C, L, T. SNS and Rem are active.

Remark: In the presented study we consider, that the changing order of drug administration has no impact on the change of the PB behaviour.

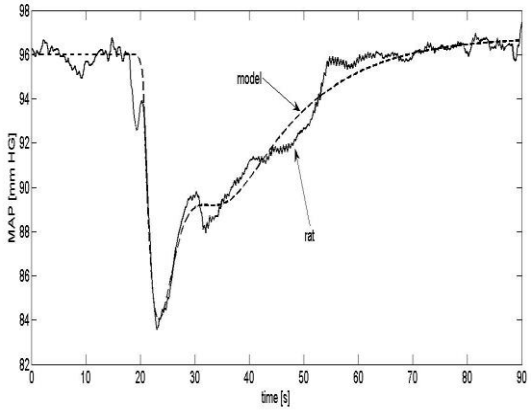

Fig. 10. Comparison of rat and model responses after the administration of C, P, T. NO and Rem are active.

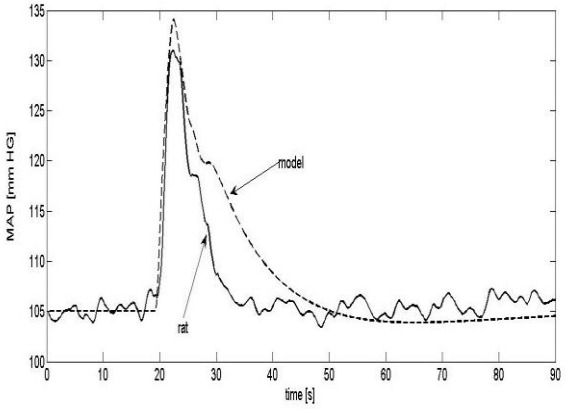

Fig. 11. Comparison of rat and model reactions when no drugs were administrated. All regulation subsystems are active. The stress response in cases when both SNS and NO subsystems are active has increasing direction, opposite to all other previous cases.

4. CONCLUSION

The identification procedure described in this study ensures that the obtained model is able to react similarly to the BP regulation system of the living rat, which is exposed to stress. Stress produced by an air jet stream was used in our experiments. We suppose that stress disturbances that are induced by other factors (such as noise, mechanical vibrations, etc.) will also be covered by our model with acceptable accuracy.

Another issue that has to be taken into account is that the dynamic behaviour of BP regulation is non-linear. Linear models, which were obtained in this study, can lose their accuracy in case of varying working points as a changing initial level of BP or if more powerful stressors are used, etc. Non-linear models will be used in the future in order to eliminate this drawback.

The presented GA-based approach of model identification is efficient and able to lead to good results. By such a procedure, we are able to identify the regulation subsystem including the controller and the controlled system in the closed-loop. A significant characteristic of this approach is the relatively high computation time needed to obtain each of the particular models. The number of generations (computation cycles) used for obtaining each particular model was between 1,000 and 10,000, which takes (with the population size of 450 individuals) between 450,000 and 4,500,000 cost function evaluations, each including model simulation. The average computation time for each particular model (in Fig. 6-11) takes on a single PC (4-core Intel processor, 3.4 GHz, 4 GB RAM) between 2-6 hours.

The appropriate model of the BP regulation process can be an important means for analysing and a better understanding of particular BP regulation subsystems and their interactions in the entire BP regulation system in rats and supposedly later also in humans. The model of BP regulation obtained in this study can help explain physiological and bio-cybernetic mechanisms of BP regulation, the interactions between particular regulation subsystems, as well as to identify the mechanisms which might be used for the prevention or treatment of high blood pressure.

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