ESTIMATION OF PERIPHERAL RESISTANCE IN THE CAPILLARY NETWORK USING MATLAB OPTIMIZATION TOOLBOX

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Abstract

Blood pressure (BP) is one of the basic vital signs in living organisms, and is the most widespread marker used for diagnostics of cardiovascular diseases. Understanding of BP behavior and its native regulation in human body is thus critical. Various medical descriptions exist, yet no quantitative model has been published so far. In our research we aim to create a model that would describe BP regulation in a living organism. Body controls BP in various ways, usually by manipulating one of following: heart activity, volume and viscosity of blood, and *peripheral resistance (PR) of capillary network*, eg. how much are the capillaries opened / closed. It is not possible to measure PR directly with known contemporary methods. However it is possible to estimate it if we feed measured heart activity and BP data to a relatively simple 'Windkessel model'. In this article we describe one such experiment which was carried out on a normotense WKY-type rat, and we monitor effect of various standard drugs for hypertension on PR.

1 Introduction

Hypertension is one of contemporary civilization diseases with significant contribution to human mortality. In 5% of cases it is caused either by unhealthy lifestyle or as a consequence of another disease - in this case we distinguish the 'secondary' hypertension. In remaining 95% of cases hypertension is assumed to be inborn, without any explicit cause - the 'primary' hypertension. This disease is rightfully called 'the silent killer', since although not dangerous on its own, it significantly heightens predisposition towards heart attack, stroke, aterosclerosis and other diseases. We have over 200 thousand patients suffering from this disease in Slovakia (2005), and this number is expected to double by 2030. This motivates significant research in the field of physiological as well as biochemical causes of hypertension and possibilities of treatment.

1.1 Blood pressure control

As we have mentioned in our preliminary works [1, 2, 3, 4], the goal of blood flow control is to guarantee sufficient perfusion of tissues with oxygen and nutrients. Every individual has its own BP operating range at which this condition is satisfied, while according to WHO [5] range of 120 / 80 [mmHg] is considered to be a standard for healthy individual and 165 / 95 [mmHg] is considered to be a disease. Maintaining this BP level in body is usually only a byproduct of other control mechanisms, however it s most commonly used in diagnostics of cardiovascular problems since it is easy to measure and heightened values reliably indicate a diseased state. On the other hand, since exact blood pressure values depend on a variety of factors, it is problematic to tell something more apart from that the diseased individual has cardiovascular problems.

According to our preliminary works, as well as standard physiology literature [6] we may distinguish 4 dominant control systems which affect BP, and therefore high BP indicates some-

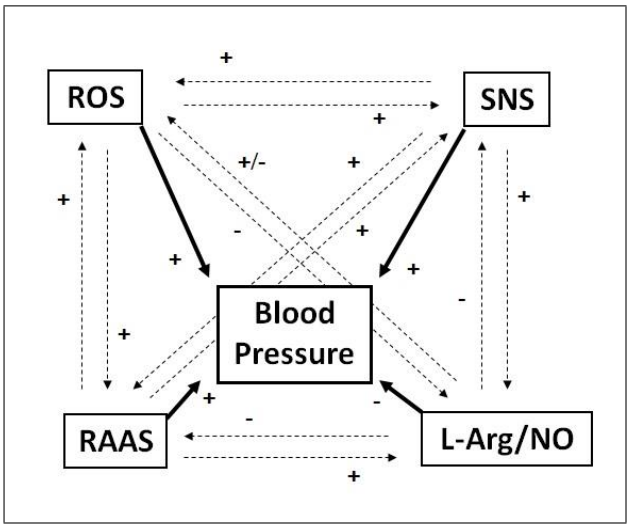


Figure 1: Assumed interactions between basic BP control systems [3]

thing may be wrong with some of them. We focus on fast (seconds - minutes) and mid-term (minutes - hours) control systems, namely: Radical Oxygen Species (ROS), Sympaticus Neural System (SNS), Renine Angiotensine-Aldosterone system (RAAS) and L-Arginine Nitric Oxide system (L-Arg/NO). Those systems either directly affect vasoconstriction / vasodilatation (and therefore PR), or water absorption into blood (RAAS), and therefore blood density. On the other hand those systems catalyze / inhibit each other. Assumed interactions between those systems are shown in the fig. 1.

2 Windkessel model of blood pressure waveform

In the previous section we have discussed means of BP control native to the human body. It is evident that dominant mechanism which is used is tightening and loosening of the blood vessels (vasoconstriction / vasodilatation). If we imagine the circulatory system as an 'elastic' plumbing with certain basal volume (at zero pressure), certain elasticity, certain resistance at the end (PR) and some heart inflow model, we end up with a so called 'Windkessel' model, which is an electric RLC circuit analogy used for circulatory system modeling since 1970's. Standard forms of this model can be found for example in [7]. We have used a simple model from [8]. We hereby restate the most important equations:

$$Rq(t) = \frac{1}{\alpha}\frac{dp}{dt} + p(t) \tag{1a}$$

$$\alpha = \frac{E_r}{2V_a R} \tag{1b}$$

$$\text{If we name:} \qquad \frac{E_r}{2V_a} = k \tag{1c}$$

and apply Laplace transform, we will get simple transfer function:

$$\frac{P(s)}{Q(s)} = \frac{R^2}{ks + R} \tag{1d}$$

where $p(t)$ $[mmHg]$ is the blood pressure, $q(t)$ $[m^3/s]$ is the cardiac output, E_r $[GPa]$ is the radial Young's modulus of blood vessels, V_a $[m^3]$ is the basal volume of blood vessels, R $[GPa/m^3]$ is PR. Variables E_r, V_a, R and k cannot be directly measured. However, with continuous measurement of $p(t)$ and a reasonable estimation of $q(t)$ it is possible to estimate R and k while feeding input data to the equation (1d) in a nonlinear least squares manner.

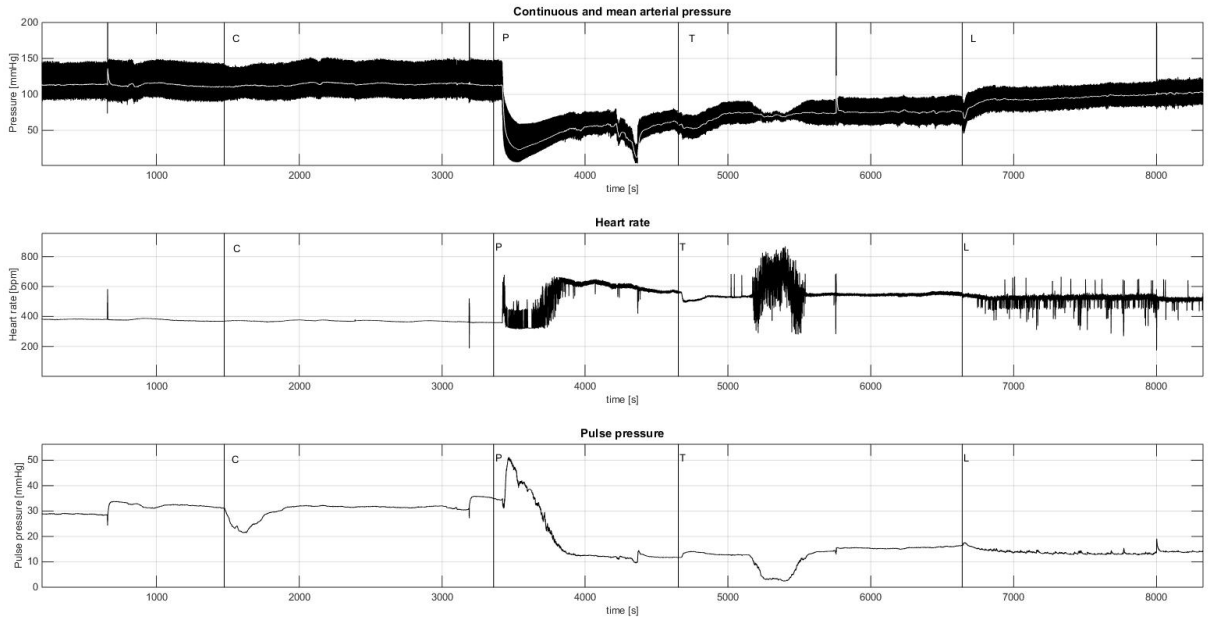


Figure 2: Measured input BP, HR and Pulse Pressure data

3 Experimental setting

In hypertension research it is considered a standard to experiment either on Wistar Kyoto (WKY) or spontaneously hypertensive (SHR) rats. In our experiment we have continuously measured blood pressure with invasive method. Catheter was operated into jugular vein and directly connected to a BP transducer. We have measured cardiac activity markers with Doppler sonography at discrete times. Experiment was executed on a sedated 15 weeks old SHR male being treated for hypertension. Four types of drugs were administered during the experiment - Captopril (dampens RAAS system), Pentolinium (dampens SNS and NO-SNS systems), Tempol (dampens ROS system) and L-Name (dampens L-arg/NO system).

BP was measured with equipment from AD Instruments: Reusable BP Transducer for bridge amplifiers, Quad Bridge Amplifier, PowerLab 4/26 Transducer, Labjack - U6 Transducer, recorded by LabChart v4.2 and consequently processed with Matlab R2014b. Sonography was measured with echosonocardiograph Vivid 7 dimension, linear matrix probe (max. 14 MHz) and since the cardiograph yielded only printed data, those had to be recorded by hand and consequently processed in Matlab R2014b. Data from echosonograph were recorded in multiple samples prior to, during and after every drug administration as well as during the initial stabilization period of 30 minutes. In other times those data were linearly interpolated. BP data can be seen in fig. 2 and data from echosonograph in fig. 3.

BP was measured directly, while heart rate (HR) and pulse pressure (PP - deviation between systolic and diastolic pressure) were computed for every blood pressure wave. Echosonograph recorded average stroke volume (SV - volume of blood pumped by one heartbeat), maximal heart outflux velocity (vMax), velocity time integral (VTI - integral of outflux speed during one heartbeat) and Aortic cross section.

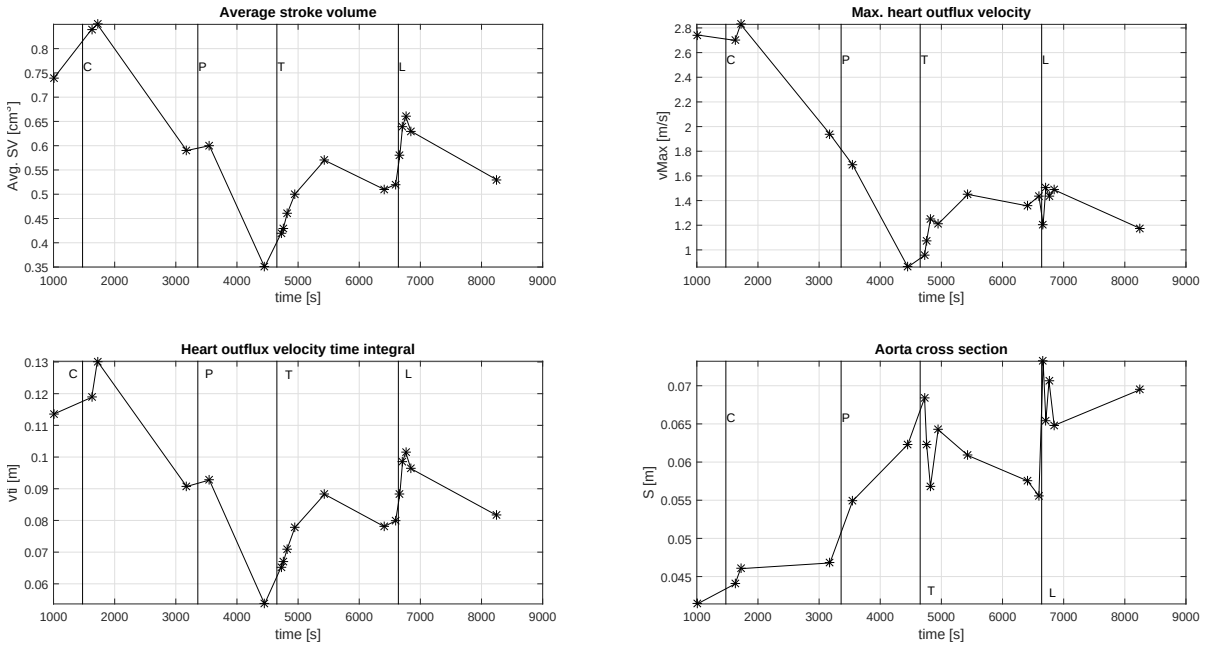
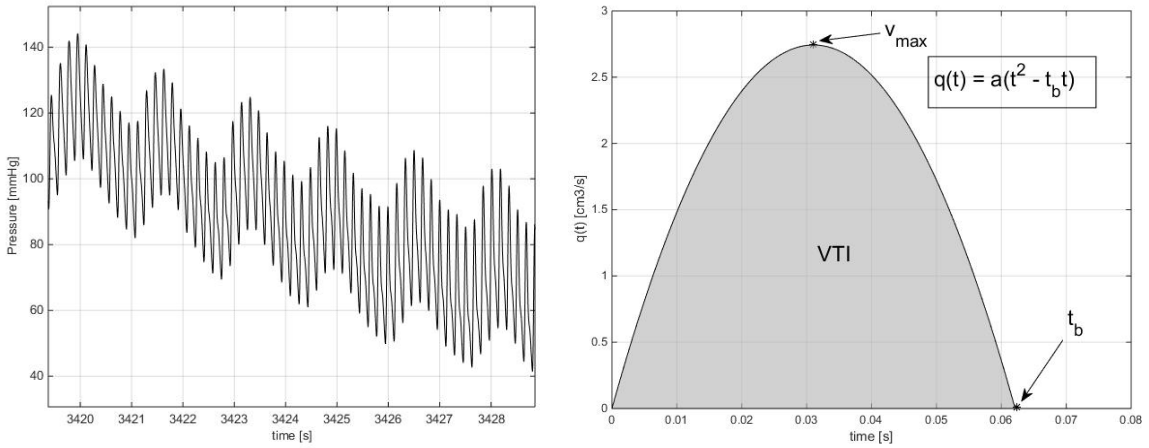


Figure 3: Measured input data from echosonograph



(a) Example zoom of fig. 2 - setup of Pentolinium and its effect on BP waweform shape

(b) Estimation of continuous heart outflux velocity during one heartbeat

Figure 4

4 Estimation of immeasurable parameters

After introduction into available I/O data we may now approach the core problem. For every heartbeat (one BP wave) we want to estimate coefficients R and k of eq. (1d). Format and shape of output data (BP) can be seen in fig. 2 and 4a. Regarding the heart outflux $q(t)$ situation is more complex - we have to estimate it. Parabolic curve of continuous outflux can be analytically computed with knowledge of $vMax$, VTI, t_b (duration of the heartbeat) and aortic cross section for every given BP wave, as is on fig. 4b. Exact method can be found in [9].

Therefore we want to 'slice' measured BP signal into specific waves (systole - systole), and wave - by - wave compute according $q(t)$ and perform a nonlinear fitting task which would yield coefficients R and k for the given wave. This is a standard ODE least squares fitting task which can be solved by any nonlinear optimization solver. In our case we have chosen to use Matlab solver *lsqnonlin* which deploys trust-region-reflective algorithm with the use of Jacobian matrix. Detailed reference for the algorithm and its properties can be found in [10]. Reference on formulating an ODE-fitting task with creation of the Jacobian matrix can be found in [11].

We have also deployed Matlab parallel computing toolbox, so that coefficients for multiple waves were computed simultaneously. Computation ran on Mathworks Heavy Horse computer which is specifically designed for scientific computations, and the estimation took around 52 hours for one rat (plotting and backing up excluded), on 8 CPU cores and with 16 GB of RAM memory.

5 Experimental results

In this section we present fig. 5 which shows estimated coefficients of (1d) which are normalized to their basal values so we can see percentual changes after drug administrations. Since those data were obtained by fitting task, in order to get some measure of fit quality, we have used standard root mean square error (RMSE) which is computed for every wave separately and is depicted in fig 7a. RMSE holds dominantly around 4 [mmHg] and rarely exceeds 6 [mmHg], which is an acceptable error if we take into consideration that we use a very simple model (1'st order transfer function with parabolic input), we have only inaccurate data to estimate input signal $q(t)$, and we are moving in range 90 - 150 [mmHg] which results in error approx. 2.5 - 5 %. Fig. 7b depicts histogram of function evaluations needed in order to solve given fitting task for specific wave. Maximum number of iterations was set to 50. As the figure suggest, this number was rarely exceeded which means that the convergence was usually stable, rarely stopped prematurely and found reasonable solution in most of the cases. To sum it up we may say that fit quality is sufficient in order to proceed towards estimated data analysis.

In fig. 6 we depict fit quality. BP waves were sliced according to found minimizers in the signal (systole - next systole). Figure also depicts an erratic case when one of the minimizers is omitted and fitting task cannot consequently find reasonable solution. This has happened in around 5% of cases, and those cases were omitted from fig. 5. In general we may say that excluding those cases, fitted waveform matches reference data well enough.

In order to evaluate obtained data, we have to evaluate figures (2), (3) and (5) simultaneously. We must take into consideration that the test subject was sedated, and therefore SNS system was dampened from the very beginning of the experiment. Let's assume that E_r from (1d) is a material constant and therefore k is only a weighted invariant of V_a.

Administration of Captopril didn't affect level of mean arterial pressure, but caused a drop in pulse pressure (fig. 2). On the other hand it caused almost immediate vasodilatation of large arteries (fig. 3 - Aorta cross section) which held it's level afterwards and slow continuous drop in cardiac output markers. It caused significant (approx. 50%) temporary increase in k (and therefore drop in V_a - which is in contrary to vasodilatation and should be investigated further) and smaller (20%) temporary drop in R (which also suggests drop in BP). We can consequently see small but steady growth in both R and k and drop in cardiac output markers which suggests body adaptation (assumed action of other yet undampened control systems) to permanently dilatated large arteries in order to maintain same operating level of BP.

Administration of Pentolinium has shown further significant growth of aortal cross-section (suggests vasodilatation of big arteries and drop in V_a). It also caused further drop in cardiac output (suggests drop in pressure level). It has caused significant drop in k (growth in V_a) (almost 100%) as well as drop in R. When compared to fig. 2 the results are as were expected - significant drops in both mean arterial pressure as well as pulse pressure. This suggests that SNS ans NO-SNS systems are responsible for keeping some basal level of constriction for both large arteries and capillary network.

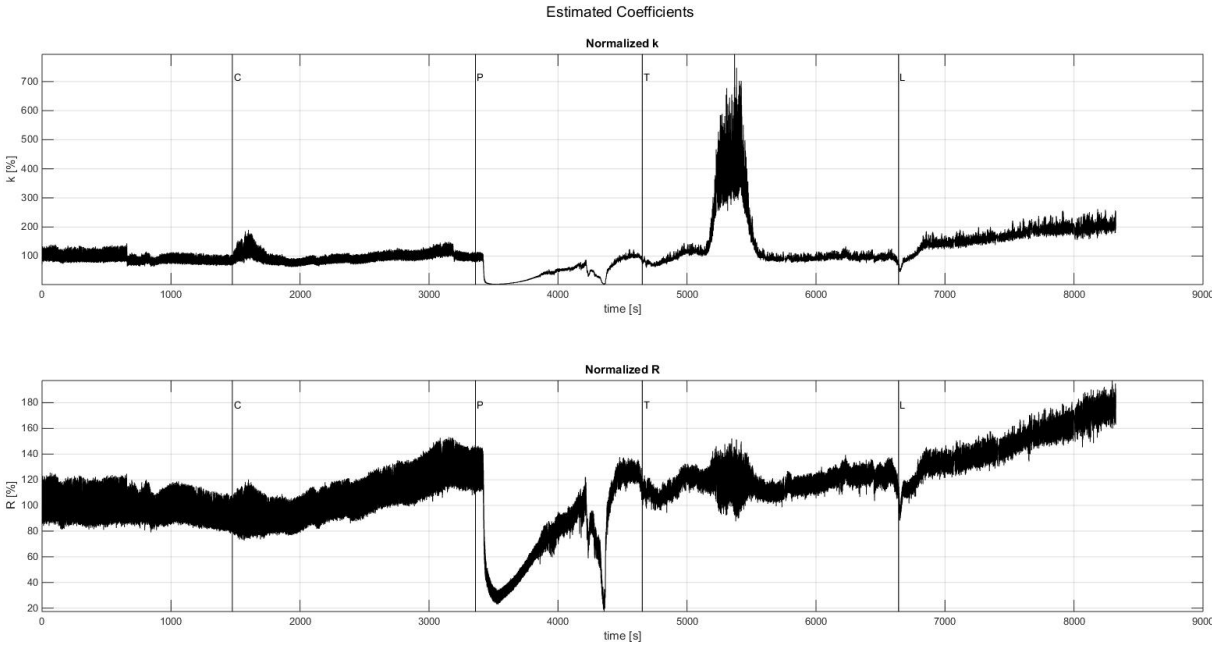


Figure 5: Estimated peripheral resistance and time constant of (1d). Both parameters were normalized to their basal values. Charts display percentual changes after drug administration.

Response of Tempol administration has to be split into two parts. Short term: has caused rapid increase in cardiac output, rapid drop in aortal cross - section, small drop in HR and small drops in both R and k. This suggests vasodilatation in both large arteries and the capillary network,but on the other hand increased influx from the heart. The resulting effect on the blood pressure is rather unpredictable since vasodilatation suggests drop while increased cardiac output increase in the BP. As figure 2 suggests, since increase in BP has occurred - the increase in cardiac output obviously played the dominant role. The long term effest is rather questionable since it occurred several minutes after administration of the initial dose. We can observe severe destabilization of HR and drop in PP, drastic increase in k while keeping mean level of R. However we consider this rather a disturbance caused by some unknown effect, probably a tachycardia but not the intended (and usually experienced) effect of Tempol.

Administration of L-Name is mentioned mainly for completeness sake, as it was found out that given dose of L-Name had significantly lesser effect than was expected (as is usually experienced in other experiments) which leads us to conclusion that given dosage was expired.

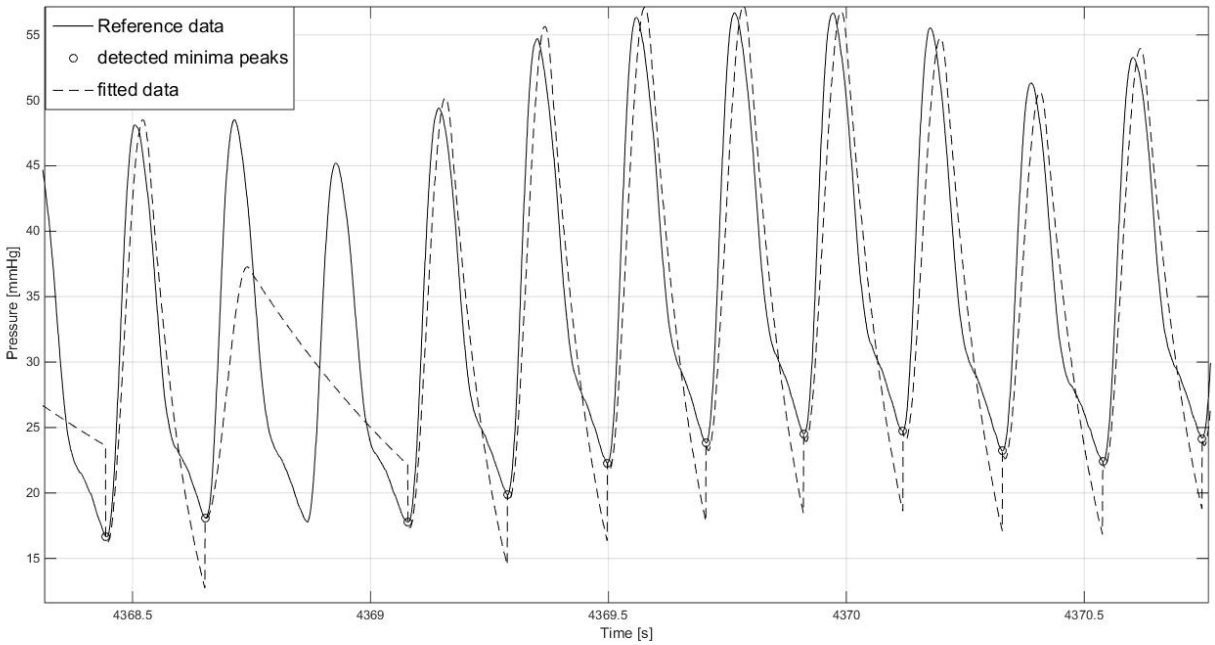
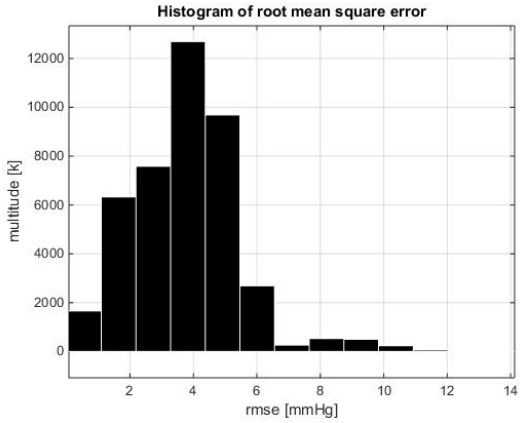
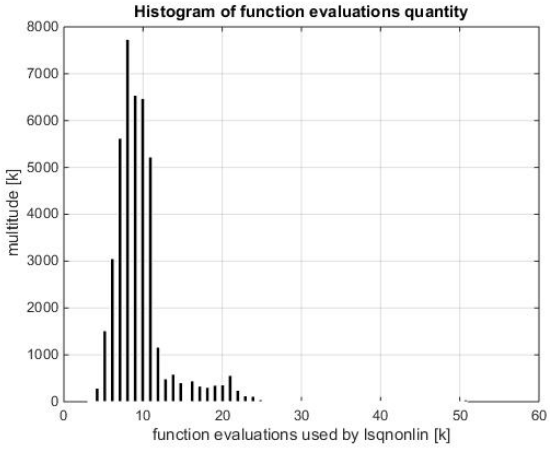


Figure 6: Example of fit quality for several consequent waves, including an erratic case



(a) Root mean square error of fits per wave



(b) Number of function evaluations (e.g. simulations) performed by the lsqnonlin solver in order to estimate R and k for given wave

6 Conclusion

We have carried out a prototype experimental measurement where we joined invasive continuous blood pressure measurement with Doppler sonography. Based on measured data we tried to estimate two critical variables which describe vasodilatation and vasoconstriction of both large arteries and capillary network. We have shown that such approach is viable and yields reasonable resulting values. This approach has broadened our understanding of how vasoconstriction and dilatation work in body and has given us suggestions about which blood pressure control mechanism in the body affects large arteries and which the capillary network. The results are rather puzzling and not completely explainable. This calls for carrying out other experiments of this kind since experiment on one specimen is definitely not enough. It also calls for improvement in methodics of sonography measurement - especially increase in measurement density.

References

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