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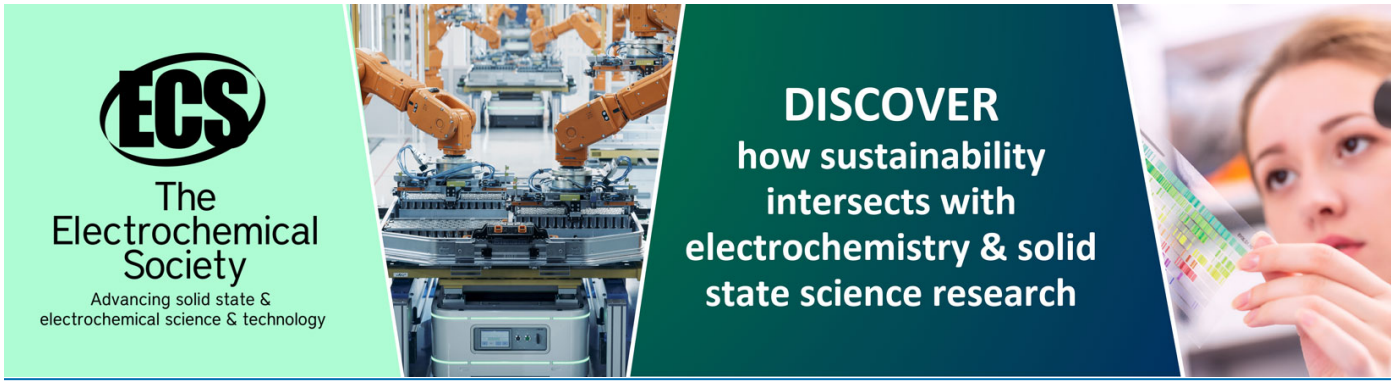

Relaxation oscillation model of hemodynamic parameters in the cerebral vessels

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Abstract. Simulation of a blood flow under normality as well as under pathology is extremely complex problem of great current interest both from the point of view of fundamental hydrodynamics, and for medical applications. This paper proposes a model of Van der Pol - Duffing nonlinear oscillator equation describing relaxation oscillations of a blood flow in the cerebral vessels. The model is based on the patient-specific clinical experimental data flow obtained during the neurosurgical operations in Meshalkin Novosibirsk Research Institute of Circulation Pathology. The stability of the model is demonstrated through the variations of initial data and coefficients. It is universal and describes pressure and velocity fluctuations in different cerebral vessels (arteries, veins, sinuses), as well as in a laboratory model of carotid bifurcation. Derived equation describes the rheology of the "blood stream – elastic vessel wall – gelatinous brain environment" composite system and represents the state equation of this complex environment.

1. Introduction

Modelling of a blood flow in a system such as cerebral vascular network is very complicated and can be realized in different ways. One of them involves building a model based on general equations of composite continuum describing fluid flow (possibly non - Newtonian), in an elastic tube of complex geometry, placed in the viscoelastic gel brain environment. Such models should consider physiology laws and use the parameters obtained during the experiments [1]. Obtaining information about the brain rheology is a complex problem.

Another way is to construct a relatively simple empirical model based on the values obtained directly during the clinical measurements and laboratory experiments. This is a classic approach for inverse incorrect problems of differential equations. It proved to be effective in different applications, and this approach is described and used in this paper [2].

The main preconditions, underlying the construction of relaxation oscillations model of hemodynamic in the cerebral vessels, are the following:

- Experimental clinical data due to measuring system Combo Map device specifics describes the blood rate and pressure connection, implemented in a multicomponent system "the blood stream – the elastic wall of the vessel – the brain surrounding environment". The model should bind experimentally measured values with the parameters (consumption, energy flow) calculated based on their basis [3].

- The experimentally observed velocity and pressure oscillations have a relaxation character. The simplest model for the description of these processes is the equation of a nonlinear oscillator of Van der Pol - Duffing (VdPD), where one of the values – pressure $p = p(t)$ or velocity $v = v(t)$ – acts as the control function, i.e, a right-hand side of the equation. It is important that equation (VdPD) has a stable periodic solution. At the same time, the equation of this form has a large and complex set of solutions, the structure of which is determined by the values of its coefficients. Cartwright and Littlewood obtained a remarkable result on the exact structure of the set of solutions of the equation (VdPD) for a specific selection of the coefficients. If they are changed, the systems of sub-harmonics and solutions that are not periodic appear in the equation [4]. There are a number of works studying the solutions of type (VdPD) equations [5, 6].

2. Intraoperative endovascular monitoring of blood flow

The studies are carried out using ComboWire intravascular guidewire with the diameter of 0.34 mm. Intravascular Doppler sonography is performed by using Combo Map unit (frequency 12 MHz) during the operation. The velocity and pressure in vessels readings are recorded from the Combo Map unit via analog-digital converter at frequency 200 Hz and processed on the computer to produce hydrodynamic quantities. The procedures for monitoring, clinical data processing, data clearing from the noise, and presenting data in the form of "operation map" are developed [3].

Many of various physiological processes occurring in living organisms are periodic. Such living system can be simulated by a system of interconnected oscillators, which produce modeling of heartbeats, breathing cycle, Mayer waves, etc. [7]

These oscillatory processes are observed on the wavelet diagrams, created using Gabor wavelet of frequency 6, obtained from processed monitoring data. Since we are interested in relaxation oscillations associated with the blood pulsing, such wavelet decomposition of the entire spectrum of vibrations is used to filter out the high-frequency noise, the vibrations corresponding to the respiratory rhythm (0.2 Hz) and the low-frequency oscillations [8]. The comparison and analysis of obtained skeylogramms with the original ones show that relaxation oscillation information is completely preserved.

Currently, this procedure of intravascular blood flow monitoring was conducted for 50 neurosurgical operations to cure anomalies in the vascular system of the brain such as arteriovenous malformations and cerebral aneurysms. The operations were performed in the Lavrentyev Institute of Hydrodynamics, and data processing was conducted in the Meshalkin Novosibirsk Research Institute of Circulation Pathology. The measurements were performed in all areas of the vascular network of the brain: in the arteries, veins and sinuses. The monitoring of this type can be considered unique as it was performed for the first time in the world practice. It represents unique experimental data for construction of mathematical models of hemodynamics in brain vessels.

3. Construction of the oscillator model

Van der Pol - Duffing's equation of nonlinear oscillator

$$\varepsilon q'' + P_2(q)q' + Q_3(q) = ku(t), \tag{1}$$

where $q = q(t)$ and $u = u(t)$ - dimensionless normalized values of blood flow, $|q| \le 1$, $|u| \le 1$; polynomials $P_2(q) = a_0 + a_1 q + a_2 q^2$, $Q_3(q) = b_1 q + b_2 q^2 + b_3 q^3$ characterize friction and elasticity of the system, real coefficients $\{a_i, b_j, k\}$ $(i = 0, 1, 2; j = 1, 2, 3)$ correspond to the individual patients data, ε - a small relaxation parameter. Control function $u(t)$ is the speed of blood flow on the right hand side of the equation (1) for brain arteries, function $q(t)$ is the normalized

pressure. These roles are changing for veins and sinuses, which lie beyond the resistive zone created by capillaries: control function $u(t)$ is the pressure and function $q(t)$ is the normalized velocity. This can be explained by the fact, that the phase shift between pressure and speed in arteries as it was shown in the experiments [3] is positive and it is negative in veins and sinuses. In other words, the speed outpaces the pressure and controls it in arteries, and conversely in veins and sinuses. Accordingly, for the arteries the "pressure-velocity" diagrams traversed anticlockwise with increasing time, and vice versa for the veins and sinuses [3].

Normalized average values (q, u) of blood flow can be expressed through physical ones (p, v), measured during observed time operation in interval I by the formulae

$$q = \alpha_0 + \alpha_1 p, \quad u = \beta_0 + \beta_1 v, \tag{2}$$

where

$$\alpha_0 = -\xi M_p^{-1}, \quad \alpha_1 = M_p^{-1}, \quad \beta_0 = -\eta M_v^{-1}, \quad \beta_1 = M_v^{-1}, \tag{3}$$

$$M_p = \max_{i\in I}|p_I - \xi|, \quad M_v = \max_{i\in I}|v_I - \eta|. \tag{4}$$

The values of ξ and η in (4) are the average values of p and v on the time interval I. During data processing, either integral averages or arithmetic mean values for v and p on I are used, whatever produces the best result. Formulae (2) - (4) are written to normalize the data in the arteries, and they change for veins and sinuses as described above.

The linear replacing (2) transforms (1) into the equation of the same type

$$\varepsilon q'' + \hat{P}_2(p)p' + \hat{Q}_3(p) = \lambda v(t) + \mu, \tag{5}$$

describing the relationship between the physical flow values (p, v). The transformed coefficients $\{\hat{a}_i, \hat{b}_i\}$ in $\hat{P}_2$ and $\hat{P}_3$ polynomials, λ and μ are calculated according to the formulae, the specific form of which we do not present here.

Discretization of equation (1) is performed by transition to normalized clinical data at the time of measurements:

$$q_i = q(t_i), \quad u_i = u(t_i), \quad t_i = t_0 + (i-1)\Delta t \tag{6}$$

$$q' = (\Delta t)^{-1}(q_i - q_{i-1}), \quad q'' = (\Delta t)^{-2}(q_{i+1} - 2q_i + q_{i-1}), \tag{7}$$

where $i = \overline{1, N}$, the N number determines the measurement gap I_N, Δt is the time measuring step.

After substituting (6), (7) in (1), we get the nonlinear ARX model [9] – a system of linear algebraic equations

$$q_i = Ax, \quad (i = \overline{3, N}). \tag{8}$$

Matrix A in (8) has 7 columns and $N-2$ lines:

$$A = (q_{i-1},\ q_{i-2},\ (q_{i-1} - q_{i-2})q_{i-1},\ q_{i-1}^2,\ (q_{i-1} - q_{i-2})q_{i-1}^2,\ q_{i-1}^3,\ u_{i-1}), \tag{9}$$

with seven-dimensional unknown vector $x = (c_1, \ldots, c_7)^T$, the sign T means transposition, so that x is a column vector. And values c_i have relations with unknown $\{a_i, b_j, k\}$, $(i = 0, 1, 2;\ j = 1, 2, 3)$, by the next formulae:

$$\begin{aligned} a_0 &= \varepsilon(1 + c_2)/\Delta t \\ a_1 &= -\varepsilon c_3/\Delta t \\ a_2 &= -\varepsilon c_5/\Delta t \\ b_1 &= \varepsilon(1 - c_1 - c_2)/\Delta t^2 \\ b_2 &= -\varepsilon c_4/\Delta t^2 \\ b_3 &= -\varepsilon c_6/\Delta t^2 \\ k &= \varepsilon c_7/\Delta t^2. \end{aligned} \tag{10}$$

In our case the value of ε is equal to 10^{-3}. So many of unknowns have values of order 1.

The system (8) is strongly overdetermined in the experimental data processing, as rule, $N \gg 7$. Such system has not exact solution. Instead of exact solution, with respect to inverse problems theory [2, 10], we give pseudo-solutions, which minimize the residual norm for system (8). For minimization of residual uses the combination of Gauss-Newton and Levenburg-Marquardt line search, and Trust-region reflective Newton approach.

Applying the algorithm described to (8) - (10) gives the solution as a vector of the coefficients x. The equation (1) is constructed on the basis of this vector. The calculation is made in the Matlab program using the System Identification Toolbox Package.

4. Experimental validation of the model

The algorithm for constructing the equation VdPD (1) described in section 3 has been applied to a variety of experimental data. First of all, it is flow data measured in arteries as well as veins and sinuses of the cerebral vessels during neurosurgery in Meshalkin Novosibirsk Research Institute of Circulation Pathology [3]. Secondly, it is experimental data of pressure and velocity obtained during laboratory experiments on elastic model of carotid artery bifurcation using the Combo Flow pump and Combo Wire sensor with Combo Map apparatus [11]. The adequacy of the model (1) describing the relaxation oscillations in a composite system "blood stream – elastic vessel wall – gelatinous brain environment" is justified by the following factors.

4.1. Approximation of clinical data

After finding the $\{a_i, b_j, k\}(i = 0, 1, 2; j = 1, 2, 3)$ coefficients on I_N interval we write down the equation of relaxation oscillations (1) for a particular patient in a specific location of the vessel. Adequacy check for the solution of this equation to the experimental data is carried out as follows: we solve the equation (1) with the well-known right-hand side $ku(t)$ and obtained coefficients $\{a_i, b_j, k\}$. The obtained data shows a very good quality of approximation. Typical clinical plots (black) and calculated (red) ones for the pressure are shown in Figure 1. It is

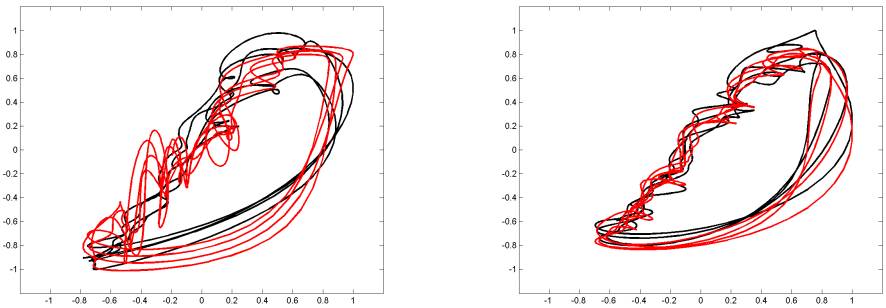


Figure 1. Typical plots of blood pressure in the cerebral artery: the clinical data (black), the calculated data (red).

shown that even the greater approximation property is satisfied, namely the restoration of the coefficients of equation (1) in the long period of time I_{N_1} from the coefficients obtained in the measurement on a smaller interval of I_{N_0}, where $N_1 > N_0$. It is also shown that it is possible to construct the equation (5), which describes the process of embolization. Parameters of blood flow are changing during embolization and, accordingly, the coefficients of equation (5), which describe the physical values of the blood flow, are changing. The equation (1) represents an invariant as the normalized blood flow values do not change. Figure 2 shows the sequence of

"pressure – velocity" (p, v) diagrams during the operation of AVM embolization: the clinical data (black), the calculated data (red) [12]. Figure 2 illustrates the success of the operation: diagram drift occurs in the direction of the speed decrease and the pressure increase, and there is a good conformity of clinical and calculated data.

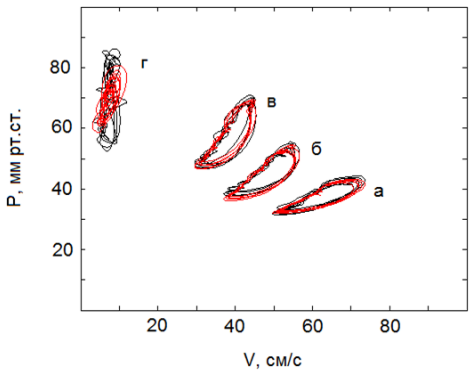


Figure 2. Diagram (p, v) drift during the AVM embolization.

In this case, the coefficients of (5) have been restored to the fifteen minute interval I_{900} according to the five-second interval I_5.

Figure 3 shows plots of velocity and pressure and their average values at 15-minute interval.

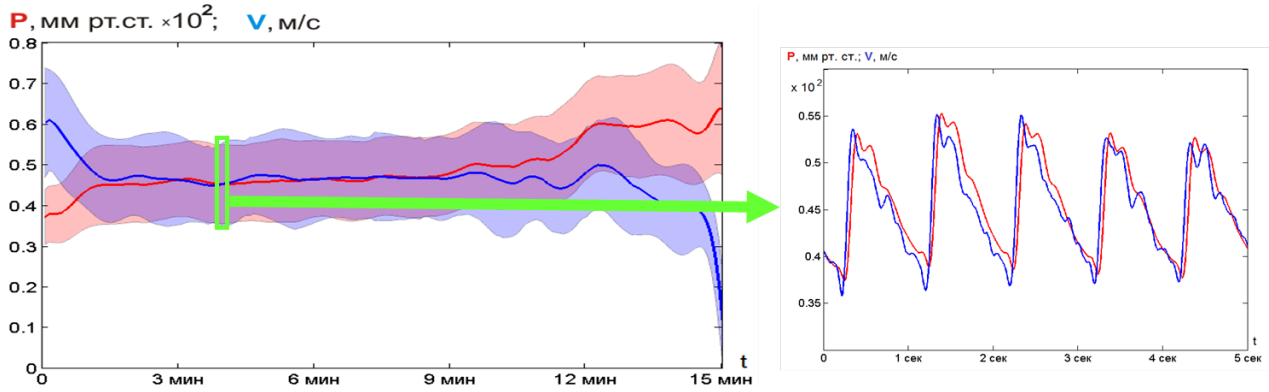


Figure 3. Graphs of velocity and pressure recovered on a large period of time including embolization of AVM.

4.2. The stability of the model relative to the initial data variations

A series of calculations were performed, where the initial data changed for the equation (1): large deviations from the clinical data were set. Calculations have shown that there is a vast area of limit cycle attraction – (q, u) - diagram – corresponding to the diagram (q, q') on the phase plane. This result allows claiming that there is an experimental proof of the asymptotic stability of the solution. A typical calculation of decisions output on the limit attracting cycle with a large deviation from the clinical data is illustrated on Figure 4. Even small perturbations of the initial data are "forgotten" for the time close to the time of the cardiac cycle. A characteristic feature of living systems is the presence of periodic modes of changes in physiological variables,

such as rate and blood pressure. This corresponds to the attracting limit cycle presence in the plane (p, v).

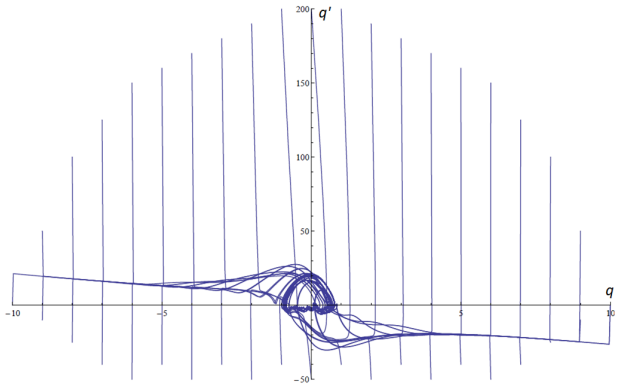


Figure 4. The (q, q') diagram is attractor.

We can assume that a treatable anomaly (such ones recorded during all operations with measurements) is characterized by the presence of attractive cycle and variation of parameters that do not come out of the domain of attraction of the attractor. It appears plausible that the incurable pathology, leading to the disruption of the living system functioning, is responsible for the destruction of periodic solutions.

4.3. The stability of the model relative to the variation of coefficients
Series of calculations was performed for the equation (1), where the deviation of coefficients ai, bj was defined by up to 2% of their values. Calculations showed stability of the solution of equation (1) with respect to such perturbations (Figure 5).

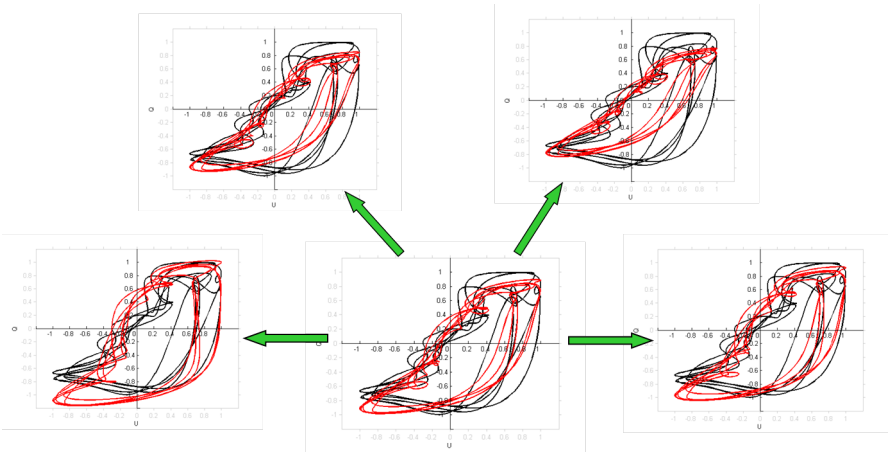
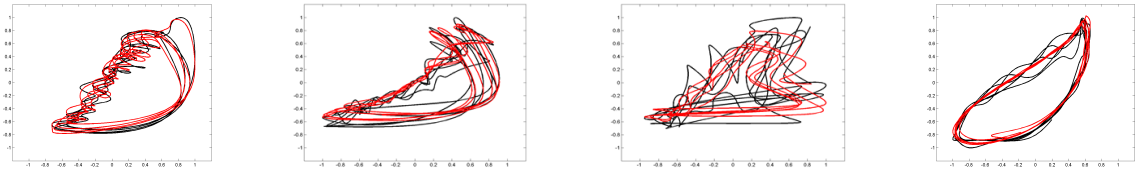


Figure 5. Stability (q, u) of diagrams obtained under the coefficients variation of 2% in the equation (1).

4.4. Model universality for different vessels
Model of relaxation oscillations (1) was tested on the arrays of 137 measurements in the arteries, 9 – in the sinuses, 17 – in the cerebral veins. It accurately describes the relaxation oscillations

in the elastic model of the tee with different unsteady flow conditions (40 measurements) [3, 11].

Figure 6 shows (q, u) - diagrams constructed from the experimental (black) and calculated (red) data for various types of composite systems.



a b c d

Figure 6. (q, u)- diagrams, constructed for arteries (**a**), venous (**b**), sinuses (**c**) of the brain and for the carotid bifurcation elastic model (**d**).

It should be noted that the coincidence of the experimental and calculated data has the highest quality for the arteries and lower quality for the veins and sinuses.

5. Conclusion

In this paper, the mathematical model, which describes the relaxation oscillations of pressure and velocity in the healthy vessels of the brain as well as in the vessels in the presence of abnormalities such as arteriovenous malformations and cerebral aneurysms, was constructed. The model is described by Van der Pol - Duffing type nonlinear oscillator equation (1). It is built implementing the theory of inverse problems for differential equations on the basis of experimental clinical data on pressure and velocity obtained during the endovascular intraoperative monitoring in the Meshalkin clinic. A set of coefficients of the equation (1) describes the individual patient. It is shown that the model is stable with respect to perturbations of the initial data and the coefficients of the equation. The equation for the normalized dimensionless quantities represents the flow invariant. It characterizes the rheology of the composite system "the blood stream – the elastic wall of the vessel – the brain surrounding environment ". The model was tested on data sets of 50 neurosurgical operations and laboratory experiments with elastic tee. Her unconditional advantages are simplicity and versatility. This model allows to describe the characteristics of blood flow in the presence of anomalies.

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