Mathematical model for blood flow autoregulation by endothelium-derived relaxing factor

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Abstract

The fluid shear stress is an important regulator of the cardiovascular system via the endothelium-derived relaxing factor (EDRF) that is Nitric Oxide. This mechanism involves biochemical reactions in an arterial wall. The autoregulation process is managed by the vascular tonus and gives the negative feedback for the shear stress changing. A new mathematical model for the autoregulation of a blood flow through arteria under the constant transmural pressure is presented. Endothelium-derived relaxing factor Nitric Oxide, the multi-layer structure of an arterial wall, and kinetic-diffusion processes are taken into consideration. The limit case of the thin-wall artery is analytically studied. The stability condition for a stationary point of the linearized system is given. The exact stationary solutions of the origin system are found. The numerical simulation for the autoregulation system is presented. It is shown the arteria adaptation to an initial radial perturbation and the transition of the system to new equilibrium state in response on the blood flow changing.

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I. INTRODUCTION

The modeling of a cardiovascular system is the problem of great importance due to it should be aid for understanding and prediction of various diseases like atherosclerosis, arteriosclerosis, hypertension, etc. The most often approaches to the problem is a direct applying of classical hydrodynamics models of fluid flow through elastic shells or tubes. But in some cases, for example, for muscular resistance arteries, it is necessary to take into account the difference between an ordinary passive and a "biological" active tube.

The one way to reach the purpose is a wide discussed effect of the flow-induced vasodilation by Nitric Oxide (NO) radical. For a long time the endothelium cells, covering the arterial bed surface, was supposed to provide only the friction reduction for the blood flow through artery. But since the EDRF was discovered via the comparison of two arterial rings with and without endothelium by the ability to acetylcholine-dependent smooth muscle relaxation and due to later investigations it was shown the endothelium plays the main role for the local blood flow regulation. The so-called Endothelium Derived Relaxing Factor (EDRF) was discovered in 1980 by Robert F. Furchgott. Nitric oxide was proposed as a signal molecule to set a connection from endothelium to the smooth muscles. The EDRF-NO mechanism enabled to explain the principle of action for the first-aid medicine Nitroglycerine being used before without understanding.

The mechanical nature of an arterial wall tonus regulation is highlighted in the works. It is perceived that the increasing of a shear stress between the blood flow and inner arterial surface causes the relaxation in a smooth muscle layer of an arterial wall. This necessary induces the increasing of the arterial radius and the decreasing of the shear stress itself. Therefore the process in a whole gives the system with a negative feedback.

There are three main layers in an arterial wall. The first, internal layer is intima (i), the second layer is media (m) and the last one is adventitia (a). The inner boundary of the intima layer, i.e. the internal arterial surface, is covered with endothelium cells. The media layer is full of smooth muscle cells. The thicknesses of the layers depend on the type of artery or arteriole. We mainly consider the muscle resistance arteries which have well developed muscle layer (media) and non-vanishing intima layer. The typical ratio of intima thickness to the media one is about $10^{-1}$.

The scenario of the flow-induced relaxation is as follows. The increasing shear stress $\sigma_{\text{shear}}$...
on the surface of endothelium cells opens calcium channels which launch the production of NO from L-arginine with NO-synthase (NOS) catalysis and then NO diffuses with descending through the intima layer towards the smooth muscle cells in the media layer. As a lipophilic molecule NO easily penetrates through a cell membrane of a muscle cell and initiate synthesis of the cyclic guanosine monophosphate (cGMP). Ultimately, cGMP stimulates the outflow of intracellular $Ca^{2+}$ that leads to relaxation of the smooth muscle cell. The flow-induced contraction is realized vise versa.

The aim of this paper is to develop and to study the mathematical model for description of blood flow autoregulation that accumulates a viscoelastic nature of an arterial wall and the two-layer diffusion and kinetic processes for concentrations of the key agents: Nitric Oxide (NO) and Calcium ions ($Ca^{2+}$).

The outline of the article is as follows. In the section II we introduce the assumptions of the model. In the section III we derive the closed system for description of the autoregulation process. In the section IV the steady-state concentrations of NO and $Ca^{2+}$ are obtained. In the section V we study the limit case of a thin-wall artery. In this case the stability condition of an equilibrium state of the system is given. In the section VI we consider the case of passive dilation of an arteria with the fully relaxed muscles. The exact kink-shaped solution is found. In the section VII the numerical simulation of the autoregulation process near the stationary state is presented. In the section VIII we summarize and discuss the obtained results. The appendix A includes the essential notations. The appendix B gives the approach for finding exact solution of the passive vessel model.

II. MAIN ASSUMPTIONS OF THE MODEL

We consider the arteria to be axial-symmetric, viscoelastic and incompressible. The blood is also assumed to be incompressible and Newtonian. The flow is quasi-stationary, the transmural pressure is constant and the velocity profile is the power generalization of the Poiseuille’s law. We suppose the dependence of muscular force on calcium concentration to be linear and the dependence of $Ca^{2+}$ concentration decreasing ratio on Nitric Oxide concentration is also linear. The concentration of NO in the endothelium is assumed to be proportional to the shear stress on an arterial wall [6].
III. THE STATEMENT OF THE PROBLEM

Let us consider an arterial segment of length $l$ in the cylindrical coordinate system $(r, \theta, x \equiv z)$. The intima, media, and adventitia layers have coordinates $R_i, R_m, R_a$ respectively.

A. The shear stress dependence on the blood flow

Consider the power generalization velocity profile of the Poiseuille’s flow \[3\]:

$$V_x(r, x, t) = \frac{\gamma + 2}{\gamma} \left[ 1 - \left( \frac{r}{R(t)} \right)^\gamma \right] \bar{u}(x, t) \tag{1}$$

Here $V_x$ is the axial velocity, $\bar{u}$ is the cross-sectional averaged axial velocity, $R$ is the arterial radius and $\gamma$ is the profile sharpness.

In case of Newtonian fluid with dynamical viscosity $\mu$ the shear stress on the wall of elastic tube is

$$\sigma_{\text{shear}} = -\mu \frac{\partial V_x}{\partial r} \bigg|_{r=R} = (\gamma + 2)\mu \frac{\bar{u}}{R} = (\gamma + 2)\mu \frac{Q}{\pi R^3} \tag{2}$$

where $Q = A\bar{u}$ is the blood discharge through the cross-section with the area $A$.

Summarize all the assumptions for the laminar stationary flow, the cross-section averaged Navier-Stokes equation takes the form of the generalized Hagen-Poiseuille equation:

$$\frac{\Delta P}{l} = 2(\gamma + 2)\mu \frac{Q}{\pi R^4} \tag{3}$$

where $\Delta P$ is the pressure difference on an arterial segment with the length $l$.

It shows the linear dependence of the pressure gradient from the discharge and inversely proportionality to the fourth power of the arterial radius.

In case of axial-symmetric radial perturbations $R(t) = R_0 + \eta(t)$ we have from \[2\]:

$$\sigma_{\text{shear}} = \frac{(\gamma + 2)\mu}{\pi R_0^3} \frac{Q}{\left(1 + \frac{\eta}{R_0}\right)^3} \tag{4}$$

There is a hypothesis of maintaining the shear stress principle $\sigma_{\text{shear}} = \text{const} \ [6, 13]$. One can conclude the increasing of the flow necessitate the increasing of the steady-state arterial radius to compensate the changing of the shear stress. The estimated relation between the new steady-state discharge and new stationary radius is as follows:

$$\eta = \left( \sqrt[\gamma]{\frac{Q}{Q_0}} - 1 \right) R_0 \tag{5}$$
It is remarkable the difference of reaction for increasing and decreasing the blood flow near the previous stationary value. The changing of the radius in response to higher flow is smaller than for the same lower flow. It is explained by the inversely cubic dependence of shear stress from the radius.

One can see there is the linear dependence between radial perturbation and mean blood flow in case of small radial perturbations ($|\eta| < < R_0$).

**B. The synthesis and diffusion of Nitric Oxide**

According to the EDRF-mechanism mediated by the fluid flow, the concentration of Nitric Oxide produced by an endothelium cell is managed by the shear stress value. We consider the NO transport to the smooth muscle tissue as a diffusion process (diffusion coefficient is $D_1$) with a descending (reaction coefficient is $\delta_1$). Then it continues to diffuse through the media layer but with another diffusion coefficient $D_2$ and reaction coefficient $\delta_2$.

The production of Nitric Oxide in an endothelium cell has the shear stress $\sigma_{\text{shear}}$ as one of essential regulators, therefore this process can be described with a kinetic equation:

$$\frac{d n_e}{d t} = -k_e n_e + \psi \sigma_{\text{shear}}(t)$$  \hspace{1cm} (6)

where $n_e$ is the NO concentration in an endothelium cell, $k_e$ is the rate of mass transfer of NO from the cell, and $\psi$ is the production rate constant.

Under the assumption of quasi-stationary NO production, i.e. that characteristic time of NO mass transfer from an endothelium cell towards intima layer ($\tau_{\text{NO-mass-transfer}} \sim \Delta r^2/D \simeq 1/528 \text{ sec}$, where $D = 3300 \mu m^2/\text{sec}$, $\Delta r \simeq 2.5 \mu m$) is smaller than the typical time of $\sigma_{\text{shear}}$ changing ($\tau_{\text{shear}} \sim \tau_{\text{radius-oscillations}} \sim 1/2 \text{ sec}$), from equation (6) we have the following relation between the $n_e$ and $\sigma_{\text{shear}}$:

$$n_e(t) = \frac{\psi}{k_e} \sigma_{\text{shear}}(t)$$  \hspace{1cm} (7)

The relation (7) is used as inner boundary condition for Nitric Oxide diffusion through an arterial wall ($n|_{r=R_{\text{intima}}} = n_e$). Ultimately, at the inner boundary of intima layer we assume the concentration of NO to be proportional to the shear stress (proportionality coefficient is $k_3$). Between the intima and media layers we use the continuity of concentrations and fluxes. On the external layer we take the impenetrability condition into account. Thus the
system of equations and the boundary conditions for the Nitric Oxide concentration are as follows:

\[
\frac{\partial n_j}{\partial t} = D_j \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial n_j}{\partial r} \right) - \delta_j n_j,
\]

\( R_i < r < R_m \) for \( j = 1 \) (intima)

\( R_m < r < R_a \) for \( j = 2 \) (media)

\( n_1|_{r=R_i} = k_3 \sigma_{\text{shear}} \)

\( n_1|_{r=R_m} = n_2|_{r=R_m}, \quad D_1 \frac{\partial n_1}{\partial r} \bigg|_{r=R_m} = D_2 \frac{\partial n_2}{\partial r} \bigg|_{r=R_m} \)

\( \frac{\partial n_2}{\partial r} \bigg|_{r=R_a} = 0 \)

The system of equations (8) together with initial conditions describes the two-layer diffusion-kinetic process for the Nitric Oxide in an arterial wall.

C. The equation for the kinetics of the Calcium ions in a smooth muscle cell

To derive the balance-equation for concentration of \( Ca^{2+} \) in a smooth muscle cell it is necessary to describe the ways of \( Ca^{2+} \) in- and out-fluxes. There are two source of the calcium ions: the extracellular space and the intracellular containers – sarcoplasmic reticulum. The concentration of \( Ca^{2+} \) in these sources is about \( 10^4 \) greater than in the intracellular space. The balance of calcium ions in the muscle cell at the point \( r \) may be described, similarly to [6], as

\[
\frac{\partial C(r,t)}{\partial t} = -\alpha(C - C_0) + \beta(C_{ext} - C) - k_1 n_2(r,t)
\]

where the first term is responsible for the natural active outflow transport of \( Ca^{2+} \) compared to the minimal observed concentration \( C_0 \), the second term is described a passive diffusion provided by the difference between the intracellular calcium concentration \( C \) and extracellular ones \( C_{ext} \), and the last term is presented the NO-mediated active outflow.

Taking into account the relation \( C_{ext} >> C \) we can treat it as a constant source: \( \varphi_0 = \alpha C_0 + \beta C_{ext} = const \). In this case the equation (9) can be transformed to the form:

\[
\frac{\partial C(r,t)}{\partial t} = -\alpha C - k_1 n_2(r,t) + \varphi_0
\]

The equation (10) is used to describe the Calcium-balance in the smooth muscle layer.
D. The equation for an arterial wall movement

In order to obtain the close system of a blood flow autoregulation we need to have a link between the radial perturbation and the external forces such as pressure and muscular force \[14\]. The constitutive equation \[15\] can be found from the movement equation for an arterial wall segment.

Let us consider the incompressible viscoelastic wall element with mass \(\Delta m\), density \(\rho_w\), width \(h\), radius \(R\), and length \(\Delta x\). According to the movement law

\[
\Delta m \frac{d^2 R}{dt^2} = f_{\text{radial}} + f_{\text{pressure}},
\]

\[
f_{\text{radial}} = -\sigma_{\theta\theta} 2\pi \Delta x h, \quad f_{\text{pressure}} = (\bar{P} - P_{\text{ext}}) 2\pi \Delta x h
\]

where \(\Delta m = \rho_w 2\pi R \Delta x h\), \(f_{\text{radial}}\) is proportional to the circumference component of a stress tensor \(\sigma_{\theta\theta}\) and \(f_{\text{pressure}}\) is the resulting transmural pressure (the difference between the internal and external pressure).

The stress tensor component \(\sigma_{\theta\theta}\) consists of three parts: a passive elastic force (weakly nonlinear with quadratic addition), a viscous force and an active force due to the muscle tonus

\[
\sigma_{\theta\theta} = \frac{E(<C>) R - R_0}{1 - \xi^2} + \frac{E_1 (R - R_0)}{R_0}^2 + \lambda \frac{d R}{d t} + k_2 F(C)
\]

here \(E(<C>)\) is the Young’s modulus dependent on averaged concentration of \(Ca^{2+}\) in a muscle cell layer, \(\xi\) is the Poisson’s ratio, \(E_1\) is the small nonlinear elastic coefficient for a square addition, \(\lambda\) is the viscous characteristic of the wall, \(F(C)\) is the active force component determined also by the integral calcium concentration level above the threshold one \(C_{th}\), \(k_2\) is the coefficient of proportionality for the muscular tonus response on the \(Ca^{2+}\) level.

Substitute \(12\) in \(11\) and take into consideration the linear dependence of muscle force on calcium and the incompressibility condition \(h_0 R_0 = h R\). Then the constitutive equation for the radial perturbations \((R = R_0 + \eta, \ |\eta| << R_0)\) has a form

\[
\rho_w \frac{d^2 \eta}{dt^2} + \frac{\lambda h_0}{R_0} \frac{d \eta}{dt} + \frac{\varepsilon(C) h_0}{R_0} \eta + \frac{E_1 h_0}{R_0^3} \eta^2 = \bar{P} - P_{\text{ext}} - \frac{h_0}{R_0} k_2 F(C)
\]
where
\[ \kappa(C) = \kappa_0(1 + \varepsilon F(C)), \quad \kappa_0 = \frac{E_0}{R_0(1 - \xi^2)}, \quad \varepsilon << 1 \]
\[ F(C) = \int_{R_m}^{R_a} [C - C_{th}] \theta(C - C_{th}) r \, dr, \] \hspace{1cm} (14)
\[ \theta \text{ – the Heaviside’s step function} \]

Renormalize the constants \( \lambda, \kappa, k_2 \) with the value \( \frac{h_0}{R_0} \) and denote the constant, under the assumptions, transmural pressure \( P_0 = \bar{P} - P_{ext} = \text{const} \) and \( \kappa_1 = \frac{E_1 h_0}{R_0} \).

Ultimately, we obtain a new integro-differential equation describing the wall movement in the presence of smooth muscle tonus
\[ \rho_w h_0 \frac{d^2 \eta}{dt^2} + \lambda \frac{d \eta}{dt} + \kappa(C) \eta + \kappa_1 \eta^2 = P_0 - k_2 \int_{R_m}^{R_a} [C - C_{th}] \theta(C - C_{th}) r \, dr \] \hspace{1cm} (15)

One can see in the case of absence of muscle force (full relaxation) it is the equation of a nonlinear damping oscillator with an external force. The presence of calcium-dependent force term is provided the feedback and makes the arteria different from a passive viscoelastic tube.

E. The problem statement for the blood flow autoregulation in dimensionless variables

Summarize the equations obtained above we have the complete system to describe the process of blood flow autoregulation due to EDRF-NO mechanism:
\[ \frac{\partial C(r,t)}{\partial t} = -\alpha C - k_1 n_2(r,t) + \varphi_0, \quad R_m < r < R_a \] \hspace{1cm} (16)
\[ \frac{\partial n_1}{\partial t} = D_1 \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial n_1}{\partial r} \right) - \delta_1 n_1, \quad R_i < r < R_m \] \hspace{1cm} (17)
\[ \frac{\partial n_2}{\partial t} = D_2 \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial n_2}{\partial r} \right) - \delta_2 n_2, \quad R_m < r < R_a \] \hspace{1cm} (18)
\[ \rho_w h_0 \frac{d^2 \eta}{dt^2} + \lambda \frac{d \eta}{dt} + \kappa(C) \eta + \kappa_1 \eta^2 = P_0 - k_2 \int_{R_m}^{R_a} [C - C_{th}] \theta(C - C_{th}) r \, dr \] \hspace{1cm} (19)
with the boundary conditions:

\[ n_1|_{r=R_i} = k_3 \sigma_{\text{shear}} = \frac{k_3(\gamma + 2)\mu Q}{\pi R_0^3 \left( 1 + \frac{\eta}{R_0} \right)^3} \]

\[ n_1|_{r=R_m} = n_2|_{r=R_m}, \quad D_1 \frac{\partial n_1}{\partial r}|_{r=R_m} = D_2 \frac{\partial n_2}{\partial r}|_{r=R_m} \]

\[ \frac{\partial n_2}{\partial r}|_{r=R_a} = 0 \]  \hspace{1cm} (20)

As the initial values it is taken the perturbed steady-state solutions.

Here equation (16) describes the Ca\(^{2+}\)-balance in a smooth-muscle cell, equations (17), (18) characterize the diffusion of Nitric Oxide in intima and media respectively, and the equation (19) gives the relation establishing the arterial wall movement under the influence of the average calcium ions concentration.

In order to pass on to the non-dimensional system of equation setting up the new dimensionless variables:

\[ C = C_{th} C', \quad n_1 = n_1^0 n_1', \quad n_2 = n_2^0 n_2', \]

\[ \eta = \eta_0 \eta', \quad t = t_0 t', \quad r = r_0 r' \]  \hspace{1cm} (21)

were for convenience choosing

\[ n_0^0 \equiv n_0^0 = \frac{D_2}{D_1} n_2^0 = k_3 \sigma_{\text{shear}} = \frac{k_3(\gamma + 2)\mu Q}{\pi R_0^3} \]

\[ r_0 = \eta_0 = R_0, \quad t_0 = \frac{1}{\alpha}, \quad R_0 = R_i \]  \hspace{1cm} (22)

After substitution (21) the system (16) – (19) turns into a dimensionless form (primes over the variables are omitted):

\[ \frac{\partial C}{\partial t} = -C - k_1' n_2 + \varphi_0', \quad R_m' < r < R_a' \]  \hspace{1cm} (23)

\[ \frac{\partial n_1}{\partial t} = D_1' \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial n_1}{\partial r} \right) - \delta_1' n_1, \quad 1 < r < R_m' \]  \hspace{1cm} (24)

\[ \frac{\partial n_2}{\partial t} = D_2' \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial n_2}{\partial r} \right) - \delta_2' n_2, \quad R_m' < r < R_a' \]  \hspace{1cm} (25)

\[ \frac{d^2\eta}{dt^2} + \lambda' \frac{d\eta}{dt} + \chi' \eta + \chi_1' \eta^2 = P_0' - k_2' \int_{R_m'}^{R_a'} [C - 1] \theta(C - 1) r dr \]  \hspace{1cm} (26)
where dimensionless constants are
\[ k'_1 = \frac{k_1 n^0}{\alpha C_{th}}, \quad \varphi'_0 = \frac{\varphi_0}{\alpha C_{th}} = \frac{\beta C_{ext}}{\alpha C_{th}}, \]
\[ D'_{1,2} = \frac{D_{1,2}}{\alpha R_0^2}, \quad \delta'_{1,2} = \frac{\delta_{1,2}}{\alpha}, \quad \lambda' = \frac{\lambda}{\alpha \rho_w h_0}, \]
\[ \kappa' = \frac{\kappa}{\alpha^2 \rho_w h_0}, \quad \kappa'_1 = \frac{\kappa_1 R_0}{\alpha^2 \rho_w h_0}, \]
\[ P'_0 = \frac{P_0}{\alpha^2 \rho_w h_0 R_0}, \quad k'_2 = \frac{k_2 C_{th} R_0}{\alpha^2 \rho_w h_0} \]

(27)

Then the boundary conditions take the form:
\[ n_1|_{r=1} = \frac{1}{(1 + \eta)^3} \]
\[ n_1|_{r=R'_m} = n_2|_{r=R'_m}, \quad \frac{\partial n_1}{\partial r}|_{r=R'_m} = \frac{\partial n_2}{\partial r}|_{r=R'_m} \]
\[ \frac{\partial n_2}{\partial r}|_{r=R'_a} = 0 \]

(28)

where \( R_0 = R_i, \quad R'_m = R_m/R_0, \quad R'_a = R_a/R_0 \) and initial values are the perturbed solutions of the steady-state system.

From the non-dimensional system of equations one can make a remark that the stationary blood flow discharge through the vessel’s cross-section \( Q \) has implicit influence on the \( Ca^{2+} \) concentration in the smooth muscle cell via term \( k'_1 n_2 \) in the equation (23) due to the coefficient \( k'_1 \sim n^0 \sim Q \).

IV. THE SOLUTION OF THE PROBLEM IN A STEADY STATE

To consider the stationary case letting the following:
\[ C = \tilde{C}(r), \quad n_1 = \tilde{n}_1(r), \quad n_2 = \tilde{n}_2(r), \quad R = R_0 = \text{const} \]

(29)

Under the assumptions the system of equations (23) – (26) takes the form:
\[ \tilde{C}(r) = -k'_1 \tilde{n}_2(r) + \varphi'_0, \quad R'_m \leq r \leq R'_a \]
\[ \frac{d^2 \tilde{n}_1}{dr^2} + \frac{1}{r} \frac{d \tilde{n}_1}{dr} - \frac{\delta'_1}{D'_1} \tilde{n}_1 = 0, \quad 1 \leq r \leq R'_m \]
\[ \frac{d^2 \tilde{n}_2}{dr^2} + \frac{1}{r} \frac{d \tilde{n}_2}{dr} - \frac{\delta'_2}{D'_2} \tilde{n}_2 = 0, \quad R'_m \leq r \leq R'_a \]

(30)(31)(32)
\[ P'_0 = k' \int_{R'_m}^{R'_i} [\tilde{C}(r) - 1] \theta(\tilde{C} - 1) r \, dr \]  

(33)

with the boundary conditions:

\[
\tilde{n}_1|_{r=R'_i} = 1 \\
\tilde{n}_1|_{r=R'_m} = \tilde{n}_1|_{r=R'_a}, \quad \frac{d \tilde{n}_1}{dr}|_{r=R'_m} = \frac{d \tilde{n}_2}{dr}|_{r=R'_m} \\
\frac{d \tilde{n}_2}{dr}|_{r=R'_a} = 0
\]  

(34)

The ODEs (31), (32) for NO concentration have general solution via modified Bessel functions \( I_0(z) \), \( K_0(z) \):

\[
\tilde{n}_1(r) = A_1 I_0 \left( \sqrt{\frac{\delta'_1}{D'_1}} r \right) + A_2 K_0 \left( \sqrt{\frac{\delta'_1}{D'_1}} r \right) \\
\tilde{n}_2(r) = B_1 I_0 \left( \sqrt{\frac{\delta'_2}{D'_2}} r \right) + B_2 K_0 \left( \sqrt{\frac{\delta'_2}{D'_2}} r \right)
\]  

(35)

where \( A_1, A_2, B_1, B_2 \) are the arbitrary constants defining by the boundary conditions (34):

\[
A_1 I_0(\xi_1) + A_2 K_0(\xi_1) = 1 \\
B_1 I_1(\xi_2 R'_a) - B_2 K_1(\xi_2 R'_a) = 0 \\
A_1 I_0(\xi_1 R'_m) + A_2 K_0(\xi_1 R'_m) = \\
= B_1 I_0(\xi_2 R'_m) + B_2 K_0(\xi_2 R'_m) \\
\xi_1 (A_1 I_1(\xi_1 R'_m) - A_2 K_1(\xi_1 R'_m)) = \\
= \xi_2 (B_1 I_1(\xi_2 R'_m) - B_2 K_1(\xi_2 R'_m))
\]  

(36)

where \( \xi_1 \equiv \sqrt{\frac{\delta'_1}{D'_1}}, \quad \xi_2 \equiv \sqrt{\frac{\delta'_2}{D'_2}} \)

Using the typical experimental data for the muscular resistance artery [16, 17, 18]: \( R_i = 1.0 \text{ mm}, \quad h = 0.5 \text{ mm}; \quad R'_m = 1.05, \quad R'_a = 1.3 \) and assuming \( \xi_1 = 6, \ \xi_2 = 2 \) we can find the constants \( A_1, A_2, B_1, B_2 \) from the boundary conditions (36).

Steady-state \( Ca^{2+} \)- concentration \( \tilde{C}(r) \) is given by (30).

The equilibrium distribution of concentrations is depicted on the figure.
V. THE CASE OF A THIN-WALL ARTERY

To understand the qualitative behavior of the system consider the limit case of a thin wall artery. The similar model was studied by A. Rachev, S.A. Regirer et al. in [6, 19]. There are estimations to come to the limit case. The first relation is \( h_i / h_m << 1 \) that enables to come to a one-layer wall model. The second one is \( \tau_{\text{diffusion}} << \tau_{\text{kinetic}} \), were the typical time of the diffusion process is \( \tau_{\text{diffusion}} = \frac{h^2}{D} \) and the typical time of the kinetic process is \( \tau_{\text{kinetic}} = \min\{ \frac{1}{\delta}, \frac{1}{\alpha} \} \). Here \( h_i, h_m \) are the wall thickness of intima and media layers, \( h \) is the spatial scale of the wall thickness. Considering that the kinetic processes for Nitric Oxide are faster than for Calcium ions we have as follows:

\[
h << \sqrt{\frac{D}{\delta}} \equiv h_0 \tag{37}
\]

where \( h_0 \) is the characteristic wall thickness to compare with. Taking into account the typical values of the parameters as \( D = 3300 \, \mu m^2/sec \) and \( \delta = 1 \, sec^{-1} \), we obtain \( h_0 = 57 \, \mu m \).

It is also should be note the default condition of quasi-stationary diffusion: \( \tau_{\text{diffusion}} << T_{\text{osc}} \), where \( T_{\text{osc}} \) is the typical period of radial oscillations. The typical value of \( T_{\text{osc}}^{-1} \) is about \( 1 \div 2 \, sec^{-1} \) then the \( h_0 \) value is close to \( 57 \, \mu m \) or a bit less.

The large and medium resistance muscle arteries have the specific wall thickness \( h \approx 100 \div 1000 \, \mu m \) whereas the small arteries and arterioles have the much smaller thickness \( h \approx 10 \, \mu m \). Therefore the limit case covers the case of flow in a small artery with \( h << 50 \, \mu m \).
Thus the intima and media layers are so thin to neglect the multi-layer nature of the wall and eliminate the diffusion processes.

After the averaging of the calcium feedback $F(C)$ over the wall thickness the system (16) – (19) takes a simplified form:

$$\frac{dx}{dt} = -\alpha x - \frac{a}{(1 + \frac{y}{c})^3} + b$$
$$\frac{dy}{dt} = z$$
$$\frac{dz}{dt} = -Ax - \kappa y - \beta z - \kappa_1 y^2 - \kappa_2 xy + B$$

where $x = x(t) \equiv C(x,t) - C_{th}$ is the average concentration of $Ca^{2+}$ in the arterial smooth muscle layer, $y = y(t) \equiv \eta(t)$ is the deviation of the radius of the vessel ($y > -c$), $z = z(t)$ is the velocity of radius oscillation; $\alpha$ is the rate of a natural ”pumping” of the free calcium ions from the intracellular space, $a$ is represents the blood flow level ($a \sim Q$), $c$ is the non-perturbed arterial radius, $b$ is the rate of the calcium inflow in a smooth muscle cell, $A$ is the coefficient of proportionality for the calcium-feedback force, $\kappa$ is the linear elasticity coefficient, $\kappa_1$ is the nonlinear elasticity coefficient, $\kappa_2$ is the small calcium-induced elasticity coefficient, $\beta$ is the viscous (resistance) coefficient of an arterial wall, $B$ represents the mean constant transmural pressure.

Look for the stationary points of the system (38). One can obtain under the condition $b - a = \alpha \frac{B}{A}$

there is a stationary point $\{x = B/A, y = 0, z = 0\}$. It corresponds to the non-perturbed state of an artery. All the rest real stationary points of the system have $y < -c$ and hence they are out of physical sense. The relation (39) reflects the balance between the muscle forces mediated by calcium concentration and the pressure forces in the blood. The steady-state $Ca^{2+}$ concentration is equal to $x = B/A \sim P_0/(h_0R_0)$.

Study the stability of the dynamical system (38) near the stationary point $\{B/A, 0, 0\}$ taking into account relation (39). Consider the linearized system

$$\frac{d\vec{X}}{dt} = A\vec{X} + \vec{F},$$

$$\begin{align*}
\text{(38)}
\end{align*}$$

$$\begin{align*}
\text{(39)}
\end{align*}$$

$$\begin{align*}
\text{(40)}
\end{align*}$$
were

\[
\mathbf{A} = \begin{pmatrix}
-\alpha & \frac{3a}{c} & 0 \\
0 & 0 & 1 \\
-A - (\kappa + \kappa_2 \frac{B}{A}) & -\beta
\end{pmatrix}
\]

\[
\vec{X} = (x, y, z)^T, \quad \vec{F} = (b - a, 0, B)^T
\]

The Routh-Hurwitz criterion provides the condition then all eigenvalues of \(\mathbf{A}\) have negative real parts. Here the stability condition is as follows:

\[
\beta \left( \alpha^2 + \alpha \beta + \kappa + \kappa_2 \frac{B}{A} \right) > \frac{3aA}{c} \quad (41)
\]

Taking into consideration the strictly positiveness of the \(A, a, c, \alpha\) and non-negative values of the rest parameters one can conclude from (41) the condition for the wall viscosity \(\beta > 0\). It shows the importance of the viscoelastic nature of an arterial wall to maintain the stability of the stationary state. In general case, there is the critical wall viscosity \(\beta_{\text{critical}}\) below that oscillations demonstrate the lack of stability.

The qualitative analysis on the phase plane confirms the preliminary estimates (figure 2).

![Phase Plane Diagram](image)

**FIG. 2:** The two-dimensional projection of the phase trajectory of the system. For \(\beta = \beta_{\text{critical}}\) it is the periodic oscillations (left) and for \(\beta > \beta_{\text{critical}}\) it is the damping oscillations (right).

**VI. THE CASE OF A PASSIVE VESSEL**

One can see from the thin-wall approximation the more the discharge the less the equilibrium calcium level. In the general model we have a non-constant distribution of \(Ca^{2+}\)
concentration. If the stationary \( Ca^{2+} \) concentration for the whole arterial wall is below the threshold level \( C_{th} \) it becomes a fully relaxed. In this case the ‘active’ viscoelastic tube is reduced to the ‘passive’ one. The law of the arterial wall motion (26) in the dimensionless form (primes are omitted) is as follows:

\[
\frac{d^2 \eta}{dt^2} + \lambda \frac{d \eta}{dt} + \kappa_0 \eta + \kappa_1 \eta^2 = P_0
\]

(42)

The nonlinear differential equation (42) can be solved exactly via the simplest equation method [20, 21]. One can obtain

\[
\eta(t) = \eta_\infty \tanh \left( \frac{\lambda t}{10} \right) \left( 2 - \tanh \left( \frac{\lambda t}{10} \right) \right)
\]

(43)

\[
\eta_\infty = \sqrt{P_0 \frac{3}{\kappa_1}}, \quad \kappa = \sqrt{4 \kappa_1 P_0 \frac{3}{\lambda}}, \quad \lambda = \sqrt{\frac{2500 \kappa_1 P_0}{27}}
\]

The kink-shaped solution demonstrates the switch from one steady state to another under a constant force field.

Here the solution (43) satisfies a non-perturbed state of artery with \( \eta(0) = 0 \). The pressure and smooth-muscle force compensate each other. After a vanishing of the muscle force (due to the sharp decreasing of the calcium level) artery expands to a new equilibrium state.

The new arterial radius depends on the transmural pressure and the elastic properties of an arterial wall. It can be estimated by \( \eta_\infty \).

VII. THE NUMERICAL SIMULATION FOR THE PROBLEM OF BLOOD FLOW AUTOREGULATION

Consider the general case of the two-layer kinetic-diffusion system in the dimensionless form (23) – (28) for description of the blood flow regulation. In order to study the dynamics of the solutions of the system near the steady state the numerical simulation is performed. An implicit iterative finite-difference scheme is implemented. As the initial values the perturbed exact stationary solutions (30), (35) are taken.

The behavior of the solution for the initial stretching of the radius confirms the asymptotic stability of the stationary state (figure 3).

As a test solution in case of passive dilation the exact solution (43) is taken.
FIG. 3: The dynamics of the system relaxation to the previous steady state after an initial stretching of the artery $\eta(t = 0) = 0.1$.

The comparison gives a good agreement between the numerical solution and the exact one (figure 4).

FIG. 4: The passive expanding of the artery due to a constant transmural pressure. The exact solution (dotted line) and the numerical one (solid line).

In response on the changing of the blood flow, that is managed by the coefficient $k_1 \sim Q$, the system comes after the damping oscillations to a new steady state (figure 5). It is remarkable the different reaction of the system to the increasing and decreasing of the discharge. The relaxation time in case of flow decreasing is smaller than in case of flow increasing. It may be explained by the drop of the critical viscosity level in response on
the decreasing flow according to (41). Also the arterial radius deviation is bigger in case of decreasing of blood flow accordingly to the inverse cubic dependence of the shear stress on the radius. In case of increasing flow it is vice versa.

One can see the growth of the blood flow can potentially be a source of instability especially for small arterial wall viscosity near the critical one.

![Graph](image)

**FIG. 5**: The transition of the system to the new equilibrium state after the decreasing for 25% (left) and increasing for 25% (right) of the mean blood flow.

### VIII. CONCLUSION

The two-layer diffusion-kinetic model is proposed to describe the process of a local blood flow regulation in an artery. The exact stationary distributions of the key agents – Nitric Oxide and Calcium ions are obtained.

The limit case of a thin wall artery under the estimation of the wall thickness (37) is analytically studied. The stability condition for the equilibrium state is given by the formula (41). It is shown the necessity of the viscoelastic nature (non-zero viscosity) of the arterial wall to provide the stability of the system. The minimal critical viscosity value of a wall is obtained in the linearized case.

In case of full relaxation of the smooth muscles the exact solution in the kink form is found to describe the passive dilation of the artery.

The numerical simulation demonstrates the transition of the system to the new steady state with the new radius value in response of changing of the mean blood discharge. This
result is in agreement with the experimental observation [4]. It is confirmed the importance of the endothelium derived relaxing factor – Nitric Oxide for arterial haemodynamics.

The model can be applied to the study of the local autoregulation of the coronary, cerebral and kidney blood flow.

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APPENDIX A: THE SUMMARY OF NOTATION

Assuming the cylindrical coordinate system \((r, \theta, x \equiv z)\).
- \(R_i\) is the coordinate of intima layer boundary (equal to inner vessel radius);
- \(R_m\) is the coordinate of media layer boundary;
- \(R_a\) is the coordinate of adventitia layer boundary;
- \(R = R(t)\) is the radius of the arterial wall \((R = R_i\) is the inner radius); 
- \(\eta = \eta(t) = R(t) - R_0\) is the perturbation of the steady-state arterial radius \(R_0\);
- \(C = C(r, t)\) is the concentration of \(Ca^{2+}\)-ions in the smooth muscle cell;
- \(C_{th}\) is threshold concentration of \(Ca^{2+}\) to start the contraction in the smooth muscle cell;
- \(n_1 = n_1(r, t)\) is the concentration of \(NO\)-radical in the first (intima) layer;
- \(n_2 = n_2(r, t)\) is the concentration of \(NO\) in the second (media) layer;
- \(P_0 = \bar{P} - P_{ext} = const\) is the cross-section averaged stationary transmural pressure;
- \(\bar{u}\) is the cross-sectional averaged axial fluid velocity of a steady-state flow;
- \(Q = A \bar{u} = const\) is the fluid discharge through a cross-section of artery.

APPENDIX B: FINDING EXACT SOLUTION OF THE NONLINEAR ODE (B1)

To obtain an exact solution of the equation:

\[
\frac{d^2y}{dz^2} + \lambda \frac{dy}{dz} + \kappa_0 y + \kappa_1 y^2 = P_0
\]  
(B1)

we use the simplest equation method [20] that generalizes the existing approaches like the tanh-method, the method of trial elliptic functions [21], etc.
Taking into account the second order pole of the general solution of (B1) look for solution in the form of the following expansion:

$$y(z) = A_0 + A_1 G(z) + A_2 G(z)^2$$  \hspace{1cm} (B2)

where $G(z)$ is the solution with the first order pole of the equation

$$\frac{dG(z)}{dt} = k G(z) - k G(z)^2$$  \hspace{1cm} (B3)

and $A_0, A_1, A_2, k$ are the arbitrary constants to be determined.

Substituting the expansion (B2) into equation (B1) we find

$$A_0 = -\frac{30\lambda k + 25\kappa - \lambda^2 + 25k^2}{50\kappa_1}, \quad A_1 = \frac{6k(\lambda + 5k)}{5\kappa_1}, \quad A_2 = \frac{-6k^2}{\kappa_1}, \quad P_0 = -\frac{-36\lambda^4 + 625\kappa^2}{2500\kappa_1}, \quad k = \pm \frac{\lambda}{5}$$ \hspace{1cm} (B4)

Taking the solution $G(z) = \frac{1}{2} + \frac{1}{2} \tanh(\frac{1}{10}k(z - z_0))$ of the auxiliary equation (B3) and choosing $k = \frac{\lambda}{5}$ we have the exact solution of the ODE (B1) in the form:

$$y(z) = \frac{1}{50\kappa_1}\left(3\lambda^2 - 25\kappa + 6\lambda^2 \tanh[\frac{1}{10}\lambda(z - z_0)] - 3\lambda^2 \tanh^2[\frac{1}{10}\lambda(z - z_0)]\right)$$ \hspace{1cm} (B5)

where $z_0$ is an arbitrary constant.

Under the additional condition $y(0) = 0, z_0 = 0$ there are the following relations between the parameters:

$$\kappa = \sqrt{\frac{4\kappa_1 P_0}{3}}, \quad \lambda = \frac{\sqrt{2500\kappa_1 P_0}}{27}$$ \hspace{1cm} (B6)

After the simplification of (B5) taking into account (B6) we obtain finally the kink-shape solution of the equation (B1):

$$y(z) = y_\infty \tanh\left(\frac{\lambda z}{10}\right)\left(2 - \tanh\left(\frac{\lambda z}{10}\right)\right)$$ \hspace{1cm} (B7)

where $y_\infty = \sqrt{\frac{P_0}{3\kappa_1}}$.

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