Numerical Simulation of Rheological, Chemical and Hydromechanical Processes of Thrombolysis

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Abstract. Mathematical model of clot lysis in blood vessels is developed on the basis of equations of convection-diffusion. Fibrin of the clot is considered stationary solid phase, and plasminogen, plasmin and plasminogen-activators - as dissolved fluid phases. As a result of numerical solution of the model predictions of lysis process are gained. Important influence of clot swelling on the process of lysis is revealed.

1. Introduction
Lysis of blood clots has been a subject of intensive investigation for a long time. Importance of such investigations is concluded in extreme significance of thrombosis and thrombolysis processes for human organism.

In critical situations caused by clot plugging of main blood vessels, necessity of clot lysis with special chemical agents arises. Such agents are tissue plasminogen-activator, urokinase plasminogen-activator and plasminogen. In mutual reaction plasminogen and activator produce plasmin that dissolves material of the clot (fibrin).

Rate of lysis process depends on several aspects: clot structure, clot disposition, volume of injected lytic agents. It is important to remark that the lysis strategy - volume and period of injection of lytic agents - are critical factors of thrombolysis process. In every case it is important to consider the necessity of fast clot lysis from one side, and the risk of system bleeding from another.

Structure of blood clot is very complicated and various. Mechanisms of clot formation are described in [1-3]. Physical and biochemical structures of a clot depends on such factors as: concentration of thrombin, concentration of fibrinogen, ionic forces in solution, hemodynamic force [2,4]. Platelets caught during the clot formation are able to compact fibrin down to the 0.1 of its initial volume, by pressing plasma from the clot. Compacted clots are especially resistant to lysis, perhaps because of minor fluid phase of plasminogen in clot. Clots in arteries are able to contain extremely dense fibrin net.

Clot consists of long dendrite fibrin fibers of approximately equal diameter [5]. It's possible to sort out fibrin structures, which were formed under low ionic strength (0.1 mM) and high ionic strength (0.3 mM).

First type are "coarse" structures - fibrin fibers have radius about 100-300 nm, permeability about 10-8 sm2, diameter of pores 3-10 um. Structures formed under high ionic strength are "fine" - fibrin fibers have radius about 8-100 nm, permeability about 10-10 cm2, diameter of pores 0.1-0.5 um [4-6]. The process of lysis is concluded in reaction between activator and plasminogen with production of active dissolving agent - plasmin. The latter reacts with fibrin fibers, destroying them gradually and
moving into the clot material under the convection and diffusion. Tissue plasminogen-activator reacts with plasminogen on the surface of fibrin, urokinase reacts with plasminogen in fluid phase.

The problem is that transport of lytic agents arises from convection and diffusion. Convection in clot is hampered and diffusion takes a lot of time. The process of plasminogen transmutation to plasmin takes only few seconds, but it takes about an hour to destroy even average clot. Taking into account limits of therapeutic window it is necessary to have as much information about lysis dynamics and agents transport as possible.

The aim of this work was to develop clot lysis model with respect to peculiarities of its structure and properties as a porous deformable body with elastic and viscous-elastic rheology. On the basis of the model numerical scheme was established and processes taking place during the clot lysis were examined. Also, the aim was to investigate dynamic of lysis, transport of agents in both fluid and solid phases. Influence of clot characteristics on the lysis was examined as well.

2. Mathematical model
To obtain mathematical model of the process we have to build a system of filtration equations in deformable porous space with porous skeleton with variable mass. From the definition of the coefficient of dilatation [7]

$$\theta = \frac{V - V_0}{V_0}, \quad (1)$$

where $V$ and $V_0$ – current and initial values of the volume of the deformable porous media. Supposing values of $\theta$ to be small, we obtain the following equation

$$V = V_0 \exp \theta. \quad (2)$$

Then for the mass of the porous skeleton we have

$$M_s = (1 - \varepsilon) \rho_s V_0 \exp \theta. \quad (3)$$

Consider $\rho_s$ constant and taking time derivative in the last equation, after some transformations, we receive:

$$\frac{\partial \varepsilon}{\partial t} = (1 - \varepsilon) \frac{\partial \theta}{\partial t} - \frac{(1 - \varepsilon) \partial M_s}{M_s}. \quad (4)$$

In case of lysis, when clot consists of fibrin fibers of variable radius $R_s$, we can obtain the following equation:

$$\frac{1}{M_s} \frac{\partial M_s}{\partial t} = 2 \frac{\partial R_s}{R_s} \frac{\partial t}{\partial t}. \quad (5)$$

Here $M_s$ – mass of the clot’s solid phase. Equations of mass balance of the fluid phase, the dissolved fibrin and the fibrin of the porous skeleton:

$$\frac{\partial (\varepsilon \rho_f)}{\partial t} + \text{div}(\varepsilon \rho_f \vec{V}_f) = 0 \quad (6)$$

$$\frac{\partial (\varepsilon \rho_c)}{\partial t} + \text{div}(\varepsilon c \vec{V}_f) = j \quad (7)$$

$$\frac{\partial [(1 - \varepsilon) \rho_s]}{\partial t} + \text{div}[(1 - \varepsilon) \rho_s \vec{V}_s] = -j \quad (8)$$
Here $\varepsilon$ is porosity; $\rho_s$ and $\rho_f$ are densities of the solid and fluid phases correspondingly; $\bar{V}_f$ is the velocity of the fluid phase; $V_s$ is the velocity of the solid phase. Then we divide the equation (6) by $\rho_f$, equations (7) and (8) by $\rho_s$. Designating $c / \rho_s = C$, $\varepsilon(\bar{V}_f - \bar{V}_s) = \bar{v}$ and consider $\text{div} \bar{V}_s = \partial \theta / \partial t$, we calculate sum of equations (6)-(8). Ignoring second-order infinitesimals, we obtain

$$\frac{\partial \varepsilon C}{\partial t} + \text{div} \bar{v} + \text{div} c \bar{v} + \varepsilon \frac{\partial \theta}{\partial t} = 0 \ .$$  

(9)

Here $C$ is the dimensionless concentration of the dissolved fibrin; $c$ is the concentration of the dissolved fibrin. Adding (7) and (8), after dividing them by $\rho_s$, with respect to (4), one can obtain the following equation

$$\frac{\partial \varepsilon C}{\partial t} + \text{div} \bar{v} = -\frac{2(1-\varepsilon)}{R_s} \frac{\partial R_s}{\partial t} \ .$$  

(10)

Subtracting the last equation from (9)

$$\frac{\partial \theta}{\partial t} + \text{div} \bar{v} = \frac{2(1-\varepsilon)}{R_s} \frac{\partial R_s}{\partial t} \ .$$  

(11)

Equations (4), (10) and (11) and Darcy law describe filtration in deformable porous media with porous skeleton of variable mass. So we can now write obtained equations of general mathematical model. Equations of mass transport are:

$$\frac{\partial}{\partial t} \left( \varepsilon c^f + (1-\varepsilon) c^b \right) + \varepsilon \frac{\partial \theta}{\partial t} = \text{div} \left( \varepsilon D^{\text{PA}}_L \nabla c^f_{\text{PA}} - \bar{v} c^f_{\text{PA}} \right) \ ,$$  

(12)

$$\frac{\partial}{\partial t} \left( \varepsilon c^f + c^f_{\text{PA}} \right) + \varepsilon \frac{\partial \theta}{\partial t} = \text{div} \left( \varepsilon D^{\text{PA}}_L \nabla c^f_{\text{PA}} - \bar{v} c^f_{\text{PA}} \right) \ ,$$  

(13)

$$\frac{\partial}{\partial t} \left( \varepsilon c^f_{\text{plg}} + (1-\varepsilon) c^b_{\text{plg}} \right) + \varepsilon c^f_{\text{plg}} \frac{\partial \theta}{\partial t} = \text{div} \left( \varepsilon D^{\text{plg}}_L \nabla c^f_{\text{plg}} - \bar{v} c^f_{\text{plg}} \right) + \frac{k^{\text{PA}}_{\text{plg}} c^b_{\text{plg}}}{K^{\text{plg}}_{\text{m}}} \ ,$$  

(14)

$$\frac{\partial}{\partial t} \left( \varepsilon c^f_{\text{plm}} + (1-\varepsilon) c^b_{\text{plm}} \right) + \varepsilon c^f_{\text{plm}} \frac{\partial \theta}{\partial t} = \text{div} \left( \varepsilon D^{\text{plm}}_L \nabla c^f_{\text{plm}} - \bar{v} c^f_{\text{plm}} \right) + \frac{k^{\text{PA}}_{\text{plm}} c^b_{\text{plm}}}{K^{\text{plm}}_{\text{m}}} \ .$$  

(15)

Here $c^j_i$ is the concentration of the $i$-th component in the $j$-th phase; $D^j_L$ – coefficient of dispersion of the $i$-th component; $k_2, k_b, k_s, K_m$ are dynamic constants of the process(values have been taken from [8]). For upper indexes we have: $b$ – concentrations which are bounded to the fibrin; $f$ – fluid; $L$ – value on the exit of the clot; plg – plasminogen; plm – plasmin; s – solid phase; tPA – tissue plasminogen-activator; uPA – urokinase plasminogen-activator; 0 – initial value. Equations (12)-(15) are gained in similar way as (10), with replacement of source in right part of (10) by corresponding source [8]. In one-dimensional case physical interpretation of coefficient of cubic widening $\theta$ (which can be both positive and negative, in latter case it is the measure of shrinkage) is concluded in accounting linear deformations of clot - part of clot is characterized by positive values of $\theta$, the other part - by negative values of $\theta$. The total length of the clot is considered to be constant.

Equations for components in solid phase are as follows [8]:

$$\frac{\partial c^b_{\text{PA}}}{\partial t} = k^{\text{PA}}_{\text{plg}} c^b_{\text{PA}} \left( \Psi_{\text{PA}} - c^b_{\text{plg}} \right) - c^b_{\text{plg}} \frac{\partial \theta}{\partial t} \ .$$  

(16)
\[
\frac{\partial c^b_{\text{plg}}}{\partial t} = k^b_{\text{plg}} f c^b_{\text{plg}} \left( \psi_{\text{plg/m}} - c^b_{\text{plg}} - c^b_{\text{plm}} \right) - k^b_{r} c^b_{\text{plg}} - \frac{k^b_{2pA} c^b_{\text{plg}} c^b_{pA}}{K_{m}^P} + c^b_{\text{plg}}, \quad (17)
\]
\[
\frac{\partial c^b_{\text{plm}}}{\partial t} = k^b_{f} f c^b_{\text{plm}} \left( \psi_{\text{plg/m}} - c^b_{\text{plg}} - c^b_{\text{plm}} \right) - k^b_{r} c^b_{\text{plm}} + \frac{k^b_{2pA} c^b_{pA} c^b_{\text{plm}}}{K_{m}^P} + c^b_{\text{plm}}. \quad (18)
\]

Rate of radius variation is described as [8]
\[
\bar{R}_i = \frac{k_x c^b_{\text{plm}} \psi_{\text{plm}}}{K_m + \psi_{\text{plm}}}, \quad \psi_{\text{plm}} = 4 \pi \rho_0 R_0 \left\{ \frac{L_T}{2} \frac{2 \text{ fibrin monomers}}{45 \text{ nm}} \frac{1}{N_{AV}} \left( 10^6 \text{ µmol} / \text{ mol} \right) \right\}. \quad (19)
\]
\[
\psi_{\text{plm}} \text{ is an auxiliary function; it helps to recalculate destroyed dimensional (45nm) fibrin monomers into the value with concentration dimension.}
\]
Degree of lysis is calculated from the following equation [8]
\[
L = C_1 \int_0^t \bar{R}_i \, dt, \quad C_1 = \text{const} \quad (20)
\]

Equation for the radius of fibrin fiber, \( L \) is the length [8]
\[
R_s = \sqrt{R_0^2 - \frac{1}{\pi \rho_0}} \left\{ \frac{L_T}{2} \frac{2 \text{ fibrin monomers}}{45 \text{ nm}} \frac{1}{N_{AV}} \left( 10^6 \text{ µmol} / \text{ mol} \right) \right\}. \quad (21)
\]

The definition of deformation tensor is:
\[
e_{ij} = (1/2)(u_{ij} + u_{ji}), \quad i, j = x, y, z; \quad (22)
\]
Conditions of mechanical equilibrium are as follows:
\[
\frac{\partial \sigma_{\alpha \alpha}}{\partial x} + \frac{\partial \sigma_{\alpha \alpha}}{\partial y} + \frac{\partial \sigma_{\alpha \alpha}}{\partial z} = 0,
\]
\[
\frac{\partial \sigma_{\alpha \alpha}}{\partial x} + \frac{\partial \sigma_{\alpha \alpha}}{\partial y} + \frac{\partial \sigma_{\alpha \alpha}}{\partial z} = 0
\]
\[
\frac{\partial \sigma_{\alpha \alpha}}{\partial x} + \frac{\partial \sigma_{\alpha \alpha}}{\partial y} + \frac{\partial \sigma_{\alpha \alpha}}{\partial z} + \frac{\partial p}{\partial z} = 0. \quad (23)
\]

Equations for elastic and visco-elastic rheology of skeleton correspondently, assuming that the load on clot material is equal to zero (effective tensions are equal to the pressure), are as follows:
\[
\sigma_{ij}^{(e)} = -(K - \frac{2}{3} G) \varepsilon_{ij} - 2G \varepsilon_{ij}, \quad \varepsilon = \sum_i \varepsilon_{ii} \quad (24)
\]
\[
\sigma_{ij} = 2G \varepsilon_{ij} + 2\eta \dot{\varepsilon}_{ij} \quad \text{; } i \neq j; \quad \sigma_{ii} = 3K \varepsilon_{ii} \quad \text{; } i = x, y, z; \quad (25)
\]

Here \( K, G \) are stress and shear elastic modules of the fibrin; \( \eta \) – effective viscosity of the fibrin in the Kelvin-Voigt model. Variation of porosity is described by the equation:
\[ \frac{\partial \varepsilon}{\partial t} = (1 - \varepsilon) \frac{\partial \theta}{\partial t} - \frac{2(1 - \varepsilon)R'_t}{R_t}, \quad R'_t = \frac{\partial R_t}{\partial t}, \]  
Equation for shrinkage takes a form  
\[ \frac{\partial \theta}{\partial t} + \text{div} \vec{v} = \frac{2(1 - \varepsilon)R'_t}{R_t} \]  
Darcy law (form of permeability coefficient is taken from [8])  
\[ \vec{v} = -\frac{k}{\mu} \nabla p, \quad k = \frac{4R_t^2}{70(1 - \varepsilon)^{3/2}\left[1 + 52(1 - \varepsilon)^{3/2}\right]} \]  
where \( k \) is the coefficient of the permeability of clot, \( p \) is the pressure in fluid; \( \mu \) is the viscosity of blood. Boundary conditions for concentration on the left border are as follows:  
\[ \vec{v} c_{\text{inlet}} = \left( \nabla c_i - D_L \nabla c_i \right) \big|_{x, y, z = 0}, \quad i = tPA, uPA, plg, plm. \]  
Condition (28) describes regime of medicament injection and dosage. In the specified period of time specified amount of lytic agents are injected (tPA, uPA, plasminogen).  
Boundary conditions on the right border:  
\[ \frac{\partial c_i}{\partial n} = 0 \big|_r. \]  
Boundary conditions for the pressure  
\[ p = p_0 \big|_{x=0}, \quad p = p_L \big|_{x=L}. \]  
Initial conditions are  
\[ c_i = c_{i,0} \big|_{t=0}. \]  
Rheological constants \( K \) and \( G \) in (24) are taken from [9]. So, according to [9] \( G = 0.8 \) [cmHg]. We did not succeed in defining the value of \( \eta \) from literature, so that is why we've taken the value \( \eta = 80 \) [cmHg][s], which corresponds to some superpolymers (natural caoutchous (raw rubbers, nitrocellulose [10]). It's supposed that values of \( G \) and \( \eta \) are constant during the lytic process. The initial value of porosity is \( \varepsilon_0 = 0.9 \). The length of the clot was set to 1 cm, the initial value of coefficient of cubic widening is zero. At first we run calculations of one-dimensional case with no account taken of rheological properties of the clot, fluid flow rate was considered constant (values were taken from [8]). Results of calculations were compared with results of [8]. Then calculations of the three-dimensional model with the elastic and viscous-elastic rheology were performed.

3. Results and Discussion

At the beginning of each time step we calculated values of concentrations in solid phase, and then with these new values we solved equations for concentrations in fluid phase. From obtained concentrations we calculated radius of fibrin. After that, on the basis of received data, we determined distribution of pressure and shrinkage. Then the program went on the new time iteration.
For calculation of lytic agents in fluid phase the explicit scheme was used because of complicated structure of correspondent equations (12)-(15). Space and time steps were determined according to the stability condition of the explicit scheme. This scheme has been found to be rather stable for variations of parameters of the model.

Stability of the scheme was increased, after usage of the common fourth-order Runge-Kutta method for calculation of concentrations in the solid phase.

Model was calculated in two variants. In first case parameters of the model were set in compliance with parameters from [8] and 1-dimensional case was investigated. The aim was to compare results with predecessors. Obtained coincidence is good enough; more detailed information can be found in [11].

In second case model was calculated for three-dimensional case with elastic and viscous-elastic rheology. PETSc solvers were used for calculations. Visualization of obtained results was performed in ParaView open-source software. (Contributors: National Center for Supercomputing Applications (NCSA) at the University of Illinois at Urbana-Champaign (UIUC), Lawrence Livermore National Laboratory (LLNL), Sandia National Laboratories (SNL), Los Alamos National Laboratory (LANL), Jean-Loup Gailly and Mark Adler (gzip library)).

Some of the results are provided below.

We performed three-dimensional numerical simulation of an injection of dissolving agent into homogeneous porous layer with vertical borehole as an example of the real physical problem. The carbonate rock was considered as the layer, water was considered as the dissolving agent. Data for speed of dissolution, solubility and other parameters were taken from [8].

![Figure 1. Distribution of tPA agent. Middle of the process.](image-url)
Figure 2. Plasmin wave through the clot. Middle of the process.

Figure 3. Pressure distribution. Middle of the process. Red color shows zone where pressure is equal to the blood pressure.
4. Conclusion

The main result of this work in our opinion is the clot lysis model. Clot is considered as porous body with skeleton which is dissolving in chemical reactions during the filtration. At first we developed general formulation of the problem, which describes the variation of the skeleton and porosity caused by the filtration of chemical active fluid. This formulation also takes in the account deformations of the skeleton under a load (in our case it happens because of pressure drop in the clot, with zero total load). Then the obtained model was specified for the case of reaction of fibrin with active agents of blood, which cause lysis of the clot. This model corresponds to the case of blood vessel plugging by the clot with the risk of thromboembolism propagation. The purpose was to investigate the influence of rheological properties and deformations of the clot on the process of lysis, and on the volumes and periods of injection of lytic agents. This interest was caused by anticipation of nonuniform deformation (and of variable porosity) zones appearance, in which lysis goes different from the case investigated in [8]. Computations for the 3-dimension model of flow and deformations show that zones of entrance and exit of the fluid in the clot also suffer significant deformations, which depend on rheological properties of the clot. In this article the simplest 1-dimension problem is investigated. The computations fully affirmed our predictions.

Obtained results show the significant influence of rheological properties of the porous matrix of the clot on the process of lysis. As it follows from computations the higher the clot material elasticity is, the faster lysis goes. The rate of lysis is even faster in case of elastic-viscous rheology of the fibrin. In the latter case lesser values of $\eta$ lead to higher rate of the lysis. The rate of clot destruction was non-constant, and the process was going faster in the ending phase. Model also has opportunities for future enhancements (complex form of the clot, non-linear properties of the material, anisotropic binding sites concentration).

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