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Mathematical modelling of platelet rich plasma clotting. Pointwise unified model

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Abstract: The mechanistic modelling of blood clotting and fibrin-polymer mesh formation is of significant value for medical and biophysics applications. This paper presents a combination of two pointwise kinetic models represented by system of ODEs. One of them represents the reaction dynamics of clotting factors including the role of the platelet membranes. The second one describes the fibrin-polymer formation as a multistage polymerization process with a sol-gel transition at the final stage. Complex-value second order Rosenbrock method (CROS) is employed for the computational experiments. A sensitivity analysis method built into the computational scheme helps clarify non-evident dependencies in the exhaustive system of ODEs. The unified model was primarily verified using conditions of factor VII deficiency. The model, however requires a significant effort to be tested against experimental data available.

Keywords: Blood coagulation, differential equations, platelet membrane.

MSC 2010: 65L04, 65L12, 92C05, 92C40, 92C45, 92C50

Mathematical modelling of blood coagulation involves the attempts to describe ever expanding experimental data for coagulation in increasingly comprehensive theoretical frameworks. *In vivo*, injury to the blood vessel is followed by constriction of the vessel and the formation of a temporary platelet plug. The formation of a fibrin clot occurs through multistage plasmic coagulation process providing longevity to the temporary platelet seal.

Different mathematical models for post primary (plasmic) hemostasis have been described in reviews [4, 5]. The realistic mathematical models for the coagulation process, considering that one of its key active ingredients thrombin, can exist in two different forms, were proposed in [36]. More detailed mathematical models [3, 16, 19] to describe the hemostasis plasma component have been developed since then.

The distinction of blood coagulation into stages, albeit very convenient for many reasons, is still a scientific construct. Apparently, the entire interlocked set of processes of plasma hemostasis takes place as soon as the first thrombin molecules appear in the vicinity of the injury spot. Since the activated platelets play a significant role in thrombin production during coagulation [15], incorporation of platelet related reactions from the primary coagulation stage into the models of the plasmic stage was done [31]. This model demonstrates a clotting time lag in the order of magnitude similar to the lag shown by the whole blood clotting tests like Lee-White, Sukharev or Mas-Magro.

Until recently, most of the mathematical models for the blood coagulation system have described the fibrin polymerization in a simplistic manner [3, 31, 36]. As a rule, it was assumed that the fibrin-polymer network

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originates immediately in the volume where the concentration of fibrin monomers exceeds a certain threshold level. The threshold level was estimated from a variety of experimental data. At best, such estimations were taken from the experiments held under the conditions close to the regimes modelled. Thus, there is a need to develop a mathematical model for coagulation which vastly improves upon the description of the fibrin polymerization. We briefly survey the literature on such models (with particular attention to the aspect of fibrin polymerization) before proceeding to develop a new model.

One of the first pointwise mathematical models for fibrin polymerization is described in [34]. This simplified model had three stages: fibrinogen decomposition, protofibrils origin and growth, fibrils origin and growth. The model operated four velocity constants; however, two of them had no published values by the time this paper was written making investigation of the model difficult. The main limitation of the simplified model was that it did not simulate the polymerization lag period observed in experiments. In [13] fibrin polymerization is described as a process having two stages: first, linear polymerization of fibrin monomers into linear oligomers (protofibrils); second, the association of protofibrils, resulting in a three-dimensional network formation. It is rather difficult to predict the time taken for clot formation in the framework of this model. So that time was represented as a function of the initial concentration of fibrinogen. It has also been found that the clot formation period depends on the presence or absence of Ca^{2+} in the system. It was demonstrated that clot formation requires the initial concentration of fibrinogen not less than a certain threshold level. The mathematical model formulated in [20, 26, 27] describes in detail the clotting of blood plasma in case of damage to the vessel wall. It includes the formation of semi-activated and then activated fibrin from fibrinogen by thrombin, the composition of all possible oligomers to form oligomers of greater length or protofibrils, the fixation of protofibrils in fibrils and the fibril growth as well. The number of equations depends on the maximum order of oligomers under consideration. The formation of clot is tracked by the formation of fibrils. The model assumes a reversible formation of complexes by fibrinogen and a semi-activated fibrin with all oligomers. Some of the model constants are taken from the experiments while others are obtained by fitting. The results of the investigation revealed that the model points to the existence of a threshold in the formation of a clot. This effect occurs since at low fibrin concentrations there is no fibrin clot formation in the presence of fibrinogen, and the delay with clot formation is caused by the formation of complexes of fibrinogen with the fibrin oligomers.

In [23] authors emphasized the fact that the fibrin polymerization process is a nonlinear process and during polymerization in the fluid flow some additional nonlinear effects could take place. To describe the polymerization process, the method for calculation of the fibrin oligomer distribution moments was applied.

In [11] authors proposed a detailed model of the fibrin polymerization, based on the current knowledge of molecular mechanisms of this reaction. This model takes into account the growth of oligomers up to the threshold length: this process includes activation of fibrinogen to fibrin, the formation of small fibrin oligomers from monomers and their growth in length, the formation of fibrils by long oligomers, and their junction to fibrils. The model also features the transition from semi-diluted solution of fibrin oligomers to the fibrin mesh. A process of oligomers elongation is the main contributor to the clotting lag period in this model.

A comprehensive 'reaction-diffusion-convection' type of model is necessary for accurate description of the nonlinear process of the fibrin polymerization in the presence of platelets. Considering the role of the platelets and the reactions on their surface thrombin generation allows us to model the process of clotting in the whole blood, not only in plasma. The development of appropriate finite difference schemes to solve these equations is still an important problem. Since the problem contains a large number of parameters, to investigate the properties of the mathematical model in detail, it is important to execute preliminary study of the pointwise system that takes into account only the polymerization kinetics, but skirts the spatial aspects of the polymerization. The roles of platelet-related reactions and fibrin multistage polymerization in clotting lag should be estimated and compared as well.

In this article we develop a unified pointwise mathematical model for plasma coagulation that includes the detailed progress of the fibrin polymer mesh formation. We analyze the effect of factor VII and VIIa deficiencies on the thrombin concentration, and describe the sensitivity of the fibrin oligomer concentration to the rate constant of factor VII activation by fIIa.

Tab. 1: Model parameters.

Name	Value	Units	References	Name	Value	Units	References
k_{pp}	0.012	$nM^{-1}s^{-1}$	[32] and [17] estimation	K_{10M}	63.0	nM	[12]
k_{p2}	0.017	s^{-1}	[32] and [17] estimation	k^{+}_{PRO}	0.4	$nM^{-1}s^{-1}$	[7]
k^{+}_{T7}	0.0032	$nM^{-1}s^{-1}$	[7]	k^{-}_{PRO}	0.2	s^{-1}	[7]
k^{-}_{T7}	0.0031	s^{-1}	[7]	k^{+}_{2}	0.01	$nM^{-1}s^{-1}$	[9]
k^{+}_{T7a}	0.023	$nM^{-1}s^{-1}$	[7]	k^{-}_{2}	5.9	s^{-1}	[9]
k^{-}_{T7a}	0.0031	s^{-1}	[7]	k_{2}	22.4	s^{-1}	[3]
k_{TF7}	0.00044	$nM^{-1}s^{-1}$	[7]	K_{2M}	1060.0	nM	[3]
$k_{10,7}$	0.013	$nM^{-1}s^{-1}$	[7]	k^{+}_{8}	0.0043	$nM^{-1}s^{-1}$	[3]
$k_{2,7}$	0.000023	$nM^{-1}s^{-1}$	[7]	k^{-}_{8}	0.00246	s^{-1}	[3]
h^{AT}_{7}	0.00000045	$nM^{-1}s^{-1}$	[10]	k^{m}_{8}	0.9	s^{-1}	[9]
h^{TP}_{7}	0.05	$nM^{-1}s^{-1}$	[7]	K^{m}_{8M}	200.0	nM	[9]
$k_{7,9}$	0.26	s^{-1}	[12]	k^{m}_{8t}	0.023	s^{-1}	[9]
$K_{7,9M}$	243.0	nM	[12]	K^{m}_{8tM}	20.0	nM	[9]
h_{9}	0.0002223	$nM^{-1}s^{-1}$	[35]	k^{+}_{5}	0.057	$nM^{-1}s^{-1}$	[9]
$k_{7,10}$	1.15	s^{-1}	[12]	k^{-}_{5}	0.17	s^{-1}	[9]
$K_{7,10M}$	450.0	nM	[12]	k^{m}_{5}	0.23	s^{-1}	[9]
h^{AT}_{10}	0.00000305	$nM^{-1}s^{-1}$	[35]	K^{m}_{5M}	71.7	nM	[9]
h^{TP+}_{10}	4.381	$nM^{-1}s^{-1}$	[31]	k^{m}_{5t}	0.046	s^{-1}	[9]
h^{TP-}_{10}	0.00000005293	$nM^{-1}s^{-1}$	[31]	K^{m}_{5tM}	10.4	nM	[9]
k_{2t}	0.0000075	$nM^{-1}s^{-1}$	[7]	k_{f}	59.0	s^{-1}	[3]
h_{2}	0.000179	$nM^{-1}s^{-1}$	[31]	K_{fM}	3160.0	nM	[3]
k_{8}	0.9	s^{-1}	[9]	K_{14}	1400.0	nM	[21] estimation
K_{8M}	147.0	nM	[9]	N_{x}	25000	—	[21]
h_{8}	0.0037	s^{-1}	[3]	N_{II}	30000	—	[24]
k_{5}	0.233	s^{-1}	[9]	N_{IIa}	1000	—	[33]
K_{5M}	71.7	nM	[9]	N_{IX}	250	—	[1]
h_{5}	0.0028	s^{-1}	[3]	N_{IXa}	550	—	[1]
k^{+}_{9}	0.01	$nM^{-1}s^{-1}$	[9]	N_{V}	2700	—	[9]
k^{-}_{9}	0.0257	s^{-1}	[9]	N_{VIII}	750	—	[1]
k^{+}_{TEN}	0.01	$nM^{-1}s^{-1}$	[7]	C^{*}_{10}	120	nM	[11]
k^{-}_{TEN}	0.005	s^{-1}	[7]	β	0.66	—	[11]
k^{+}_{10}	0.029	$nM^{-1}s^{-1}$	[8]	k_{p}	0.00066	$nM^{-1}s^{-1}$	[11]
k^{-}_{10}	3.3	s^{-1}	[8]	k_{lat}	0.0004	$nM^{-1}s^{-1}$	[11]
k_{10}	8.3	s^{-1}	[12]	k_{vol}	10000	s^{-1}	[11]

1 Mathematical model

As a starting point to model platelet rich plasma processes related to clotting we took the model published by Susree and Anand in [31]. We combined it with the previously described elaborate model of the fibrin polymerization [11] by using the thrombin (fIIa) concentration as a joint. Thus we developed a combined model describing cascades of clotting reactions and the detailed fibrin polymerization. In the model [31] we have made minor modifications related to the affinity of clotting factors to platelet lipid membranes. In [24, 33] it was shown that the activation of prothrombin leads to cutting off a lipophilic segment greatly diminishing capability of thrombin itself to attach lipid bilayer. So we have split the number of effective sites on platelets for fII and fIIa, and assigned them different values. Also we transferred the first term from equation (17) from [31] describing on-membrane activation of prothrombin to equation (15) from [31] as activated thrombin goes to solution immediately after reaction. These modifications are related to equations (14)–(17) from [31]:

$$\frac{\mathrm{d}\,[II]}{\mathrm{d}t} = -k_{2t}\,[X_a]\,[II] - k^{+}_{2}N_2\,[AP]\,[II] + k^{-}_{2}\,[II^m] \qquad ([31].14)$$

$$\frac{\mathrm{d}\,[II_a]}{\mathrm{d}t} = k_{2t}\,[X_a]\,[II] - k^{+}_{2}N_2\,[AP]\,[II_a] + k^{-}_{2}\,[II^m_a] - h_2\,[ATIII]\,[II_a] \qquad ([31].15)$$

$$\frac{\mathrm{d}\left[II^m\right]}{\mathrm{d}t} = -\frac{k_2\left[X_a^m : V_a^m\right]\left[II^m\right]}{K_{2M} + \left[II^m\right]} + k_2^+ N_2\left[AP\right]\left[II\right] - k_2^-\left[II^m\right] \quad ([31].16)$$

$$\frac{\mathrm{d}\left[II_a^m\right]}{\mathrm{d}t} = \frac{k_2\left[X_a^m : V_a^m\right]\left[II^m\right]}{K_{2M} + \left[II^m\right]} + k_2^+ N_2\left[AP\right]\left[II_a\right] - k_2^-\left[II_a^m\right]. \quad ([31].17)$$

In equations (5.15) and (5.17) we have introduced a new constant N_{2a} instead of N_2 into term responsible for activated thrombin binding to the activated platelet membrane with different value (see Table 1). The same split of constants we made for (5.7) and (5.9) introducing N_{9a} instead of N_9 for fIX/fIXa, basing on [1].

Moreover, we changed the number of sites for fX/fXa [21]. We also modified equations (18) and (19) from [31] to get better fit for the platelet activation kinetics in accordance with experiments [32]. Accordingly, we decreased the activation constant values for platelets k_{pp} and k_{p2} and introduced constant K_{14} which effectively resulted in shifting the characteristic time for the platelet activation from a few seconds to approximately 1 minute. Mentioned equations (18) and (19) in [31] are taken from [9]. In the present paper these equations were introduced as an empirical function (see [9], Section 'Terms in the model equations', equation (49) description) for platelet activation kinetics. So we considered our modification of equations (18) and (19) from [31] justifiable. The new values for the constants are given in Table 1. The resulting model equations are presented in Appendix A.

2 Numerical scheme

The set of ODEs (5.1)–(5.45) is stiff. Despite the presence of a lag-period and the 'slow' reactions, in (5.43)–(5.44) a rapid polymerization is introduced when a C_{10} oligomer concentration achieves the threshold value of a half-diluted state [11]. This results in mutual binding of the protofibrils to a fibrin polymer network. Since the main hypothesis of a mathematical model is the presence of fast bulk aggregation reactions leading to the emergence of a new phase nucleus, the ODE set must be solved with a numerical method that is stable for stiff systems.

The essential requirements in solving the stiff problems are the monotonic method (no non-physical oscillations in the solution) and the asymptotic (L) stability. Furthermore, it is desirable to use the methods of an approximation order above the first. Therefore, to solve system (5.1)–(5.45) the integrated one-step complex-value Rosenbrock method (CROS), implemented in C programming language, is used. The method is monotonic and has a second-order approximation and a record L^2-stability. For more information about properties of the method see [28].

The system of about 50 equations has a large numbers of feedbacks, implicit dependencies and the reaction constants are measured with significant experimental errors. So we applied the standard methods for sensitivity analysis based on the numerical solution of the equations in response to variations. The main idea of the approach initially described in [18] is reproduced below.

Let us consider the non-linear ODEs dependent on parameter k:

$$\dot{\mathbf{u}} = \mathbf{f}(\mathbf{u},\ k)$$

$$\mathbf{u}(0) = \mathbf{u}_0.$$

The main part of the solution increment due to parameter change is the following:

$$\mathbf{u}(t,\ k) = \mathbf{u}(t,\ k_0) + (k - k_0)\frac{\partial \mathbf{u}(t,\ k_0)}{\partial k} + O(k - k_0)^2.$$

Thus, for each component of $\mathbf{u}$ one can obtain the linear extrapolation:

$$u_i(t,\ k) = u_i(t,\ k_0) + (k - k_0)\frac{\partial u_i(t,\ k_0)}{\partial k} + O(k - k_0)^2.$$

So the first-order estimation for ith component has the form:

$$\|u_i(t,\ k)\| \leqslant \|u_i(t,\ k_0)\| \cdot \left|1 + \frac{|k - k_0|}{\|u_i(t,\ k_0)\|} \cdot \left\|\frac{\partial u_i(t,\ k_0)}{\partial k}\right\|\right|.$$

Linear approximation gives an estimation for each component variation:

$$\frac{|k - k_0|}{\|u_i(t,\ k_0)\|} \cdot \left\| \frac{\partial u_i(t,\ k_0)}{\partial k} \right\|.$$

So the time-dependent functions:

$$\frac{1}{u_i(t,\ k_0)} \cdot \frac{\partial u_i(t,\ k_0)}{\partial k}$$

in our work will be named as 'sensitivity functions' for *i*th component depending on k.

Let us consider the linear ODEs simultaneously with the initial non-linear set:

$$\frac{\partial}{\partial k}\dot{\mathbf{u}} = \frac{\partial \mathbf{f}(\mathbf{u},\ k)}{\partial k} + \frac{\partial \mathbf{f}(\mathbf{u},\ k)}{\partial \mathbf{u}} \frac{\partial \mathbf{u}}{\partial k}$$

If the non-linear differential operator is differentiable by Frechet we have:

$$\mathbf{p} = \frac{\partial \mathbf{u}}{\partial k}, \qquad \mathbf{g} = \frac{\partial \mathbf{f}(\mathbf{u},\ k)}{\partial k}, \qquad \mathbf{J} = \frac{\partial \mathbf{f}(\mathbf{u},\ k)}{\partial \mathbf{u}}$$

$$\dot{\mathbf{p}} = \mathbf{J}\mathbf{p} + \mathbf{g}.$$

It should be noted that the existence of all partial derivatives on parameters means that we used only Gateaux derivatives. So for estimation of the sensitivity of the ODEs we calculate the partial derivatives on the parameter. The last set is the system in variations. It must be solved using the same method CROS. One has to note that obtaining of sensitivity functions of the numerical solution does not lead to the significant increase in computation complexity as the Jacobi matrix **J** has already been used to solve the non-linear ODEs.

3 Results

The validity of the new combined model and the associated sensitivity analysis method was verified using the factor VII/VIIa concentration variations commonly observed in medical practice. The factor VII deficiency studies have been carried out over the last years [25]. Lately, there have been plenty of reports on the contradictory results of therapeutic schemes using recombinant factor VII [6, 29, 30]. Congenital or acquired deficiency of factor VII combined with the deficiency of other factors (IX, X, XI) create complicated and ambiguous situations during the treatment or surgery when life-threatening hemorrhage develops. Still the deficiency does not prevent the occurrence of thromboembolism [22].

We have varied the initial factor VII concentrations from 10 nM (normal concentration) to 0.1 nM (deficiency) as well as the initial factor VIIa concentrations from 0.1 nM to 10pM. The corresponding dynamics for the factor IIa is presented in Fig. 1. A significant delay in, as well as a broadening of, the factor IIa peak is observed. Yet, we observe an insignificant decrease in the amplitude of the IIa peak relative to the changes in initial concentrations of the factor VII/VIIa. The factor VIIa dynamics is shown in Fig. 2 (logarithmic scale on concentration axis). Besides, the apparent proportional changes in amplitude of the peak, we observe a delay in peak closely similar to that of thrombin. The dynamics of the polymer is presented in Fig. 3. Delays in the fibrin polymer growth coincide with the delays in the thrombin peak, but surprisingly the fibrin polymer density increases significantly for the factor VIIa deficient clots.

The sensitivity analysis of fVIIa for the value of $k_{10,7}$ constant (activation of fVII by the fXa) is presented in Fig. 4. It shows that fVIIa significantly depends on $k_{10,7}$ from platelet activation moment up to beginning of the thrombin concentration growth. This time frame coincides with the polymerization lag as well.

4 Summary and discussion

The present paper proposes a unified point model for processes of the platelet rich plasma clotting including the blood plasma reaction, platelets and the detailed fibrin formation mechanism. The overall system consists

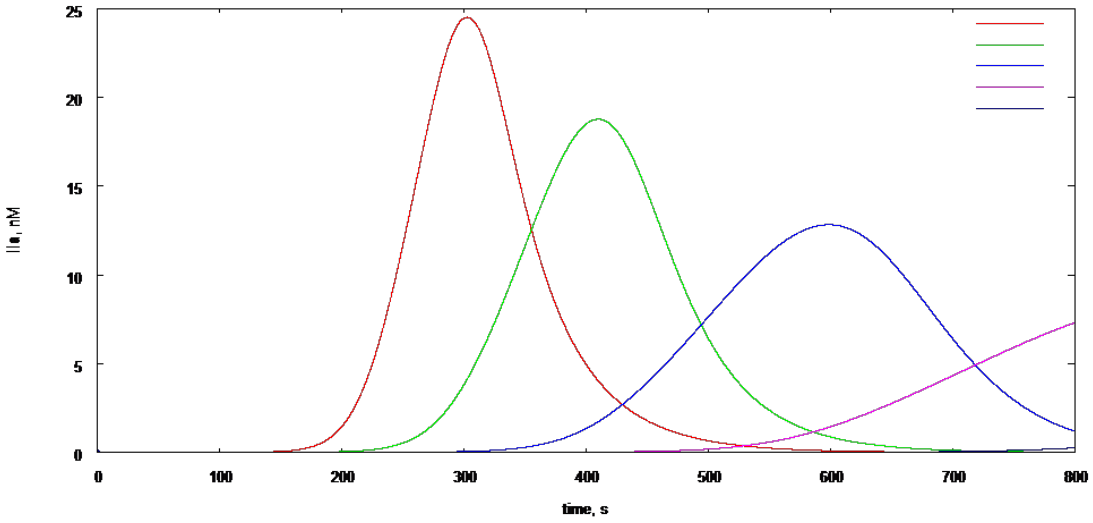

Fig. 1: Dynamics of thrombin ([fIIa]) depending on the initial concentration of fVII. Red graph corresponds to 10 nM (physiological norm), green 3.3 nM, blue 1 nM (mild deficiency), cyan 0.33 nM, black 0.1 nM (acute fVII deficiency). Notably the peak of thrombin delays considerably and drops with decreasing of total initial concentration of fVII, but the overall integral under thrombin concentration curve increases, which effectively means more fibrinogen is activated to fibrin.

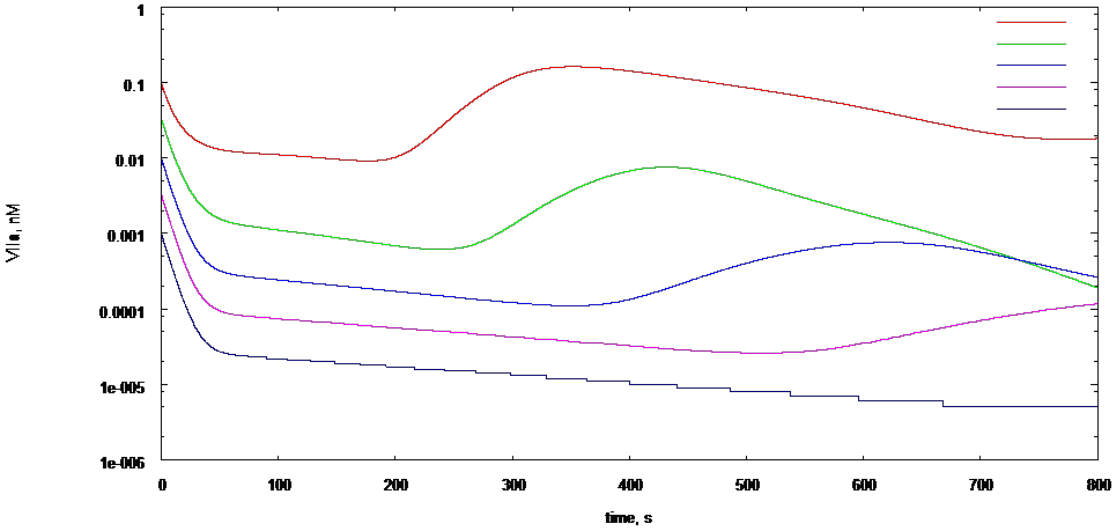

Fig. 2: Dynamics of Factor VIIa (log-scale on ordinate axis) on initial concentration of fVII. Curve color legend is the same as in Fig. 1. Total initial concentration of fVII varies from 10 nM (red) to 0.1 nM (black). Apparently, the peak of fVIIa shifts nearly synchronously with peak of fIIa.

of 44 equations. The sensitivity analysis method was incorporated in the computational scheme with minimal overhead. Application of this method allows to check for non-evident dependencies in large ODE sets such as the one in hand. The mathematical model has been preliminary tested against factor VII deficiency conditions and it gives good qualitative agreement with clinical observations. Albeit being comprehensive the unified model still requires significant research regarding clarification of some values of reaction constants, and verification of some equations against experimental data.

The current model demonstrates that the clot formation process is relatively insensitive to the initial concentration of fVII/fVIIa: a hypothesis supported sufficiently by medical observations [14]. The increase in the density of the fibrin polymer can be explained by the significant fIIa peak broadening.

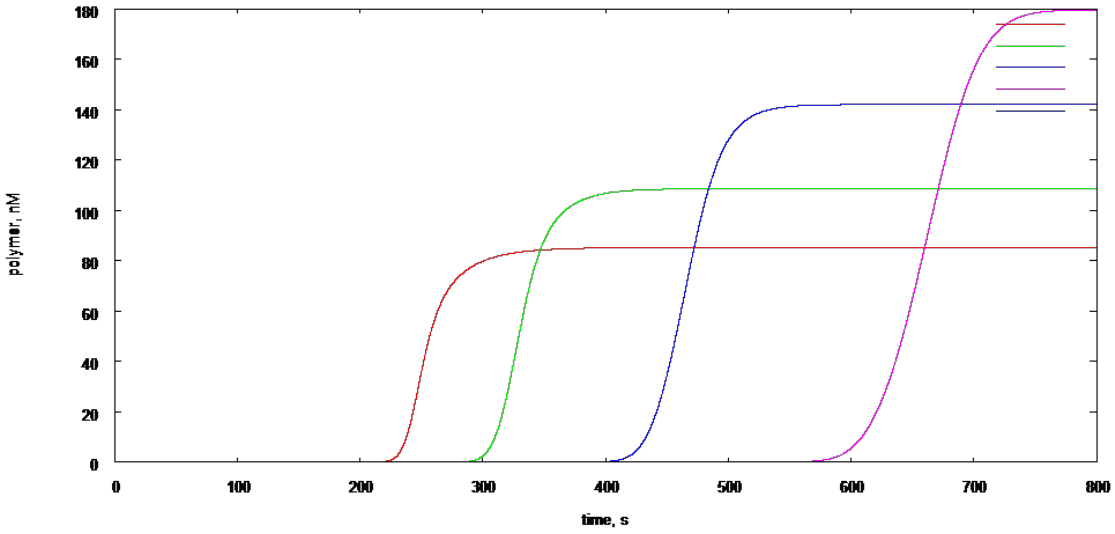

Fig. 3: Dynamics of total fibrin depending on initial concentration of fVII. Curve color legend is the same as in Fig. 1. Total initial concentration of fVII varies from 10 nM (red) to 0.1 nM (black). The maximum speed of fibrin formation corresponds to peak of thrombin concentration. Also the amount of fibrin formed increased considerably for factor VII deficient cases.

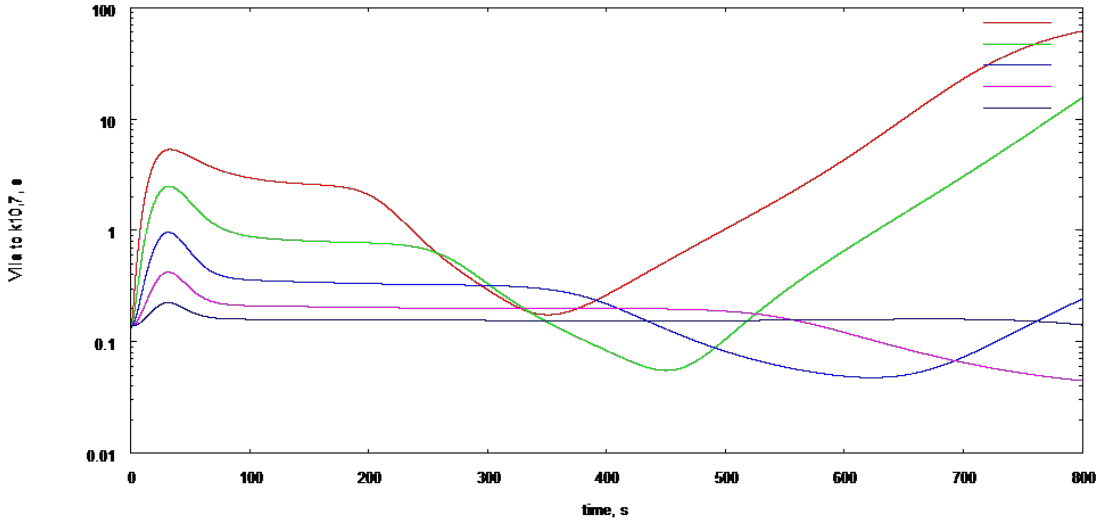

Fig. 4: Sensitivity function component represents sensitivity of fVIIa on $k_{10,7}$ from equations (5.2), (5.4) (log-scale on ordinate axis). Curve color legend is the same as in Fig. 1. Total initial concentration of fVII varies from 10 nM (red) to 0.1 nM (black). Notably the peak of IIa precedes the groove on sensitivity curve approximately 20 seconds. The logical interpretation of such groove is that while thrombin peak and shortly afterwards the term $+/- k_{10,7}[Xa][VII]$ in equations (5.2), (5.4) has virtually no significant influence on fVIIa concentration, so the activation of fVII by fXa plays no significant role while thrombin peak.

The sensitivity curves give clues not only on the relative significance of parameters for the analyzed variable value, but also provide a zero level estimation for the possible additional process delay dictated by the parameter variations.

Still the overall combined model needs to be reconciled with the modern experimental data. For example, now the model lacks the reactions for factor XI and for the activation of fVII complexed with TF. Both these groups form positive feedback for fIIa formation and can significantly change the kinetics of model. Current model also lacks another important feature completely: the protein C which provides a negative feedback loop in the process of thrombin formation. Currently, ATIII is the inhibitor which deactivates thrombin and

thereby halts the reaction. And thus, the ATIII reaction constants play an important role in the whole system and should be carefully checked and estimated.

5 Appendix A

The model equations are the following:

$$\frac{\mathrm{d}\,[TF]}{\mathrm{d}t} = -k_{T7}^{+}\,[TF]\,[VII] + k_{T7}^{-}\,[TF:VII] - k_{T7a}^{+}\,[TF]\,[VII_a] + k_{T7a}^{-}\,[TF:VII_a] \tag{5.1}$$

$$\frac{\mathrm{d}\,[VII]}{\mathrm{d}t} = -k_{T7}^{+}\,[TF]\,[VII] + k_{T7}^{-}\,[TF:VII] - k_{TF7}\,[TF:VII_a]\,[VII] - k_{10,7}\,[X_a]\,[VII] - k_{2,7}\,[II_a]\,[VII] \tag{5.2}$$

$$\frac{\mathrm{d}\,[TF:VII]}{\mathrm{d}t} = k_{T7}^{+}\,[TF]\,[VII] - k_{T7}^{-}\,[TF:VII] \tag{5.3}$$

$$\begin{aligned}\frac{\mathrm{d}\,[VII_a]}{\mathrm{d}t} = {} & -k_{T7a}^{+}\,[TF]\,[VII_a] + k_{T7a}^{-}\,[TF:VII_a] + k_{TF7}\,[TF:VII_a]\,[VII] \\ & + k_{10,7}\,[X_a]\,[VII] + k_{2,7}\,[II_a]\,[VII]\end{aligned} \tag{5.4}$$

$$\begin{aligned}\frac{\mathrm{d}\,[TF:VII_a]}{\mathrm{d}t} = {} & k_{T7a}^{+}\,[TF]\,[VII_a] - k_{T7a}^{-}\,[TF:VII_a] \\ & - h_7^{TP}\,[X_a:TFPI]\,[TF:VII_a] - h_7^{AT}\,[ATIII]\,[TF:VII_a]\end{aligned} \tag{5.5}$$

$$\frac{\mathrm{d}\,[IX]}{\mathrm{d}t} = -\frac{k_9\,[TF:VII_a]\,[IX]}{K_{9M} + [IX]} - k_9^{+}N_9\,[AP]\,[IX] + k_9^{-}\,[IX^m] \tag{5.6}$$

$$\frac{\mathrm{d}\,[IX_a]}{\mathrm{d}t} = \frac{k_9\,[TF:VII_a]\,[IX]}{K_{9M} + [IX]} - k_9^{+}N_{9a}\,[AP]\,[IX_a] + k_9^{-}\,[IX_a^m] - h_9\,[IX_a]\,[ATIII] \tag{5.7}$$

$$\frac{\mathrm{d}\,[IX^m]}{\mathrm{d}t} = k_9^{+}N_9\,[AP]\,[IX] - k_9^{-}\,[IX^m] \tag{5.8}$$

$$\frac{\mathrm{d}\,[IX_a^m]}{\mathrm{d}t} = -k_{TEN}^{+}\,[VIII_a^m]\,[IX_a^m] + k_{TEN}^{-}\,[VIII_a^m:IX_a^m] + k_9^{+}N_{9a}\,[AP]\,[IX_a] - k_9^{-}\,[IX_a^m] \tag{5.9}$$

$$\frac{\mathrm{d}\,[X]}{\mathrm{d}t} = -\frac{k_{7,10}\,[TF:VII_a]\,[X]}{K_{7,10M} + [X]} - k_{10}^{+}N_{10}\,[AP]\,[X] + k_{10}^{-}\,[X^m] \tag{5.10}$$

$$\begin{aligned}\frac{\mathrm{d}\,[X_a]}{\mathrm{d}t} = {} & \frac{k_{7,10}\,[TF:VII_a]\,[X]}{K_{7,10M} + [X]} - h_{10}^{TP+}\,[TFPI]\,[X_a] + h_{10}^{TP-}\,[X_a:TFPI] \\ & - h_{10}^{AT}\,[ATIII]\,[X_a] - k_{10}^{+}N_{10}\,[AP]\,[X_a] + k_{10}^{-}\,[X_a^m]\end{aligned} \tag{5.11}$$

$$\frac{\mathrm{d}\,[X^m]}{\mathrm{d}t} = -\frac{k_{10}\,[VIII_a^m:IX_a^m]\,[X^m]}{K_{10M} + [X^m]} + k_{10}^{+}N_{10}\,[AP]\,[X] - k_{10}^{-}\,[X^m] \tag{5.12}$$

$$\begin{aligned}\frac{\mathrm{d}\,[X_a^m]}{\mathrm{d}t} = {} & \frac{k_{10}\,[VIII_a^m:IX_a^m]\,[X^m]}{K_{10M} + [X^m]} - k_{PRO}^{+}\,[V_a^m]\,[X_a^m] + k_{PRO}^{-}\,[X_a^m:V_a^m] \\ & + k_{10}^{+}N_{10}\,[AP]\,[X_a] - k_{10}^{-}\,[X_a^m]\end{aligned} \tag{5.13}$$

$$\frac{\mathrm{d}\,[II]}{\mathrm{d}t} = -k_{2t}\,[X_a]\,[II] - k_2^{+}N_2\,[AP]\,[II] + k_2^{-}\,[II^m] \tag{5.14}$$

$$\frac{\mathrm{d}\,[II_a]}{\mathrm{d}t} = \frac{k_2\,[X_a^m:V_a^m]\,[II^m]}{K_{2M} + [II^m]} + k_{2t}\,[X_a]\,[II] - k_2^{+}N_{2a}\,[AP]\,[II_a] + k_2^{-}\,[II_a^m] - h_2\,[ATIII]\,[II_a] \tag{5.15}$$

$$\frac{\mathrm{d}\,[II^m]}{\mathrm{d}t} = -\frac{k_2\,[X_a^m : V_a^m]\,[II^m]}{K_{2M} + [II^m]} + k_2^+ N_2\,[AP]\,[II] - k_2^-\,[II^m] \tag{5.16}$$

$$\frac{\mathrm{d}\,[II_a^m]}{\mathrm{d}t} = k_2^+ N_{2a}\,[AP]\,[II_a] - k_2^-\,[II_a^m] \tag{5.17}$$

$$\frac{\mathrm{d}\,[PL]}{\mathrm{d}t} = -k_{pp}\,[PL]\,[AP] - \frac{k_{p2}\,[PL]\,[II_a]}{K_{14} + [II_a]} \tag{5.18}$$

$$\frac{\mathrm{d}\,[AP]}{\mathrm{d}t} = k_{pp}\,[PL]\,[AP] + \frac{k_{p2}\,[PL]\,[II_a]}{K_{14} + [II_a]} \tag{5.19}$$

$$\frac{\mathrm{d}\,[VIII]}{\mathrm{d}t} = -\frac{k_8\,[II_a]\,[VIII]}{K_{8M} + [VIII]} - k_8^+ N_8\,[AP]\,[VIII] + k_8^-\,[VIII^m] \tag{5.20}$$

$$\frac{\mathrm{d}\,[VIII_a]}{\mathrm{d}t} = \frac{k_8\,[II_a]\,[VIII]}{K_{8M} + [VIII]} - k_8^+ N_8\,[AP]\,[VIII_a] + k_8^-\,[VIII_a^m] - h_8\,[VIII_a] \tag{5.21}$$

$$\frac{\mathrm{d}\,[VIII^m]}{\mathrm{d}t} = -\frac{k_8^m\,[II_a^m]\,[VIII^m]}{K_{8M}^m + [VIII^m]} - \frac{k_{8t}^m\,[X_a^m]\,[VIII^m]}{K_{8tM}^m + [VIII^m]} + k_8^+ N_8\,[AP]\,[VIII] - k_8^-\,[VIII^m] \tag{5.22}$$

$$\begin{aligned}\frac{\mathrm{d}\,[VIII_a^m]}{\mathrm{d}t} = {} & \frac{k_8^m\,[II_a^m]\,[VIII^m]}{K_{8M}^m + [VIII^m]} + \frac{k_{8t}^m\,[X_a^m]\,[VIII^m]}{K_{8tM}^m + [VIII^m]} + k_8^+ N_8\,[AP]\,[VIII_a] \\ & - k_8^-\,[VIII_a^m] - k_{TEN}^+\,[VIII_a^m]\,[IX_a^m] + k_{TEN}^-\,[VIII_a^m : IX_a^m]\end{aligned} \tag{5.23}$$

$$\frac{\mathrm{d}\,[VIII_a^m : IX_a^m]}{\mathrm{d}t} = k_{TEN}^+\,[VIII_a^m]\,[IX_a^m] - k_{TEN}^-\,[VIII_a^m : IX_a^m] \tag{5.24}$$

$$\frac{\mathrm{d}\,[V]}{\mathrm{d}t} = -\frac{k_5\,[II_a]\,[V]}{K_{5M} + [V]} - k_5^+ N_5\,[AP]\,[V] + k_5^-\,[V^m] \tag{5.25}$$

$$\frac{\mathrm{d}\,[V_a]}{\mathrm{d}t} = \frac{k_5\,[II_a]\,[V]}{K_{5M} + [V]} - k_5^+ N_5\,[AP]\,[V_a] + k_5^-\,[V_a^m] - h_5\,[V_a] \tag{5.26}$$

$$\frac{\mathrm{d}\,[V^m]}{\mathrm{d}t} = -\frac{k_5^m\,[II_a^m]\,[V^m]}{K_{5M}^m + [V^m]} - \frac{k_{5t}^m\,[X_a^m]\,[V^m]}{K_{5tM}^m + [V^m]} + k_5^+ N_5\,[AP]\,[V] - k_5^-\,[V^m] \tag{5.27}$$

$$\begin{aligned}\frac{\mathrm{d}\,[V_a^m]}{\mathrm{d}t} = {} & \frac{k_5^m\,[II_a^m]\,[V^m]}{K_{5M}^m + [V^m]} + \frac{k_{5t}^m\,[X_a^m]\,[V^m]}{K_{5tM}^m + [V^m]} - k_{PRO}^+\,[X_a^m]\,[V_a^m] \\ & + k_{PRO}^-\,[X_a^m : V_a^m] + k_5^+ N_5\,[AP]\,[V_a] - k_5^-\,[V_a^m]\end{aligned} \tag{5.28}$$

$$\frac{\mathrm{d}\,[X_a^m : V_a^m]}{\mathrm{d}t} = k_{PRO}^+\,[X_a^m]\,[V_a^m] - k_{PRO}^-\,[X_a^m : V_a^m] \tag{5.29}$$

$$\frac{\mathrm{d}\,[I]}{\mathrm{d}t} = -\frac{k_f\,[II_a]\,[I]}{K_{fM} + [I]} \tag{5.30}$$

$$\frac{\mathrm{d}\,[I_a]}{\mathrm{d}t} = \frac{k_f\,[II_a]\,[I]}{K_{fM} + [I]} - 2k_p\,[I_a]^2 - k_p\,[I_a]\sum_{i=2}^{9}[c_i] \tag{5.31}$$

$$\frac{\mathrm{d}\,[TFPI]}{\mathrm{d}t} = -h_{10}^{TP+}\,[TFPI]\,[X_a] + h_{10}^{TP-}\,[X_a : TFPI] \tag{5.32}$$

$$\frac{\mathrm{d}\,[I_a : TFPI]}{\mathrm{d}t} = h_{10}^{TP+}\,[TFPI]\,[X_a] - h_{10}^{TP-}\,[X_a : TFPI] - h_7^{TP}\,[TF : VII_a]\,[X_a : TFPI] \tag{5.33}$$

$$\frac{\mathrm{d}\,[ATIII]}{\mathrm{d}t} = -\,[ATIII]\left(h_{10}^{AT}\,[X_a] + h_9\,[IX_a] + h_2\,[II_a] + h_7^{TP}\,[TF : VII_a]\right) \tag{5.34}$$

Component	Value (nM)	Component	Value (nM)
TF	5.0	$VIII$	0.7
VII	10.0	$IX_a^m : VIII_a^m$	0.0
$TF : VII$	0.0	V_a^m	0.0
VII_a	0.1	V^m	0.0
$TF : VII_a$	0.0	V_a	0.0002
IX_a^m	0.0	V	20.0
IX^m	0.0	$X_a^m : V_a^m$	0.0
IX_a	0.009	I	7000.0
IX	90.0	I_a	0.7
X_a^m	0.0	$TFPI$	2.5
X^m	0.0	$X_a : TFPI$	0.0
X_a	0.017	$ATIII$	3400.0
X	170.0	c_2	0.0
II_a^m	0.0	c_3	0.0
II^m	0.0	c_4	0.0
II_a	0.0	c_5	0.0
II	1400.0	c_6	0.0
PL	10.0	c_7	0.0
AP	0.001	c_8	0.0
$VIII_a^m$	0.0	c_9	0.0
$VIII^m$	0.0	c_{10}	0.0
$VIII_a$	0.00007	l	0.0

Tab. 2: Initial conditions.

$$\frac{\mathrm{d}\,[c_2]}{\mathrm{d}t} = k_p\,[I_a]^2 - k_p\,[c_2]\,[I_a] - 2k_p\,[c_2]^2 \tag{5.35}$$

$$\frac{\mathrm{d}\,[c_3]}{\mathrm{d}t} = k_p\,[c_2]\,[I_a] - k_p\,[c_3]\,[I_a] \tag{5.36}$$

$$\frac{\mathrm{d}\,[c_4]}{\mathrm{d}t} = k_p\,[c_3]\,[I_a] + k_p\,[c_2]^2 - k_p\,[c_4]\,[I_a] \tag{5.37}$$

$$\frac{\mathrm{d}\,[c_5]}{\mathrm{d}t} = k_p\,[c_4]\,[I_a] - k_p\,[c_5]\,[I_a] \tag{5.38}$$

$$\frac{\mathrm{d}\,[c_6]}{\mathrm{d}t} = k_p\,[c_5]\,[I_a] - k_p\,[c_6]\,[I_a] \tag{5.39}$$

$$\frac{\mathrm{d}\,[c_7]}{\mathrm{d}t} = k_p\,[c_6]\,[I_a] - k_p\,[c_7]\,[I_a] \tag{5.40}$$

$$\frac{\mathrm{d}\,[c_8]}{\mathrm{d}t} = k_p\,[c_7]\,[I_a] - k_p\,[c_8]\,[I_a] \tag{5.41}$$

$$\frac{\mathrm{d}\,[c_9]}{\mathrm{d}t} = k_p\,[c_8]\,[I_a] - k_p\,[c_9]\,[I_a] \tag{5.42}$$

$$\frac{\mathrm{d}\,[c_{10}]}{\mathrm{d}t} = k_p\,[c_9]\,[I_a] - k_{\mathrm{vol}}\,[c_{10}]\,f\,([c_{10}]) - 2k_{\mathrm{lat}}\,[c_{10}]^2 - k_{\mathrm{lat}}\,[l]\,[c_{10}] \tag{5.43}$$

$$\frac{\mathrm{d}\,[l]}{\mathrm{d}t} = \beta\left(k_{\mathrm{lat}}\,[c_{10}]^2 + k_{\mathrm{lat}}\,[l]\,[c_{10}] + k_{\mathrm{vol}}\,[c_10]\,f\,([c_{10}])\right) \tag{5.44}$$

where

$$f([c_{10}]) = \frac{\left(\frac{[c_{10}]}{c_{10}^*} - 1\right) + \left|\frac{[c_{10}]}{c_{10}^*} - 1\right|}{\left(\frac{[c_{10}]}{c_{10}^*} - 1\right) + \left|\frac{[c_{10}]}{c_{10}^*} - 1\right| + \varepsilon}. \tag{5.45}$$

Here f_g is the concentration of fibrinogen, c_i, $i = 2, \ldots, 10$, is the concentration of the oligomer of length i, l is the concentration of the fibrin polymer network, calculated as the concentration of oligomers of length 10, sequentially connected to fibrils. Function (5.45) describes the formation of a new phase nucleus at a concentration of oligomer of the maximum length above the threshold value, that is, at concentration of a semidilute solution. The constant ε in the denominator of equation (5.45) ensures the continuity of the switch function and is larger than machine ε_m but less than approximation errors ($\varepsilon \approx 2 \cdot 10^{-16}$ for this model).

The kinetic constants in the system are given in Table 1, while the initial conditions are presented in Table 2.

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