



HAL
open science

Reaction-diffusion waves of blood coagulation

Tatiana Galochkina, Anass Bouchnita, Polina Kurbatova, Vitaly Volpert

► **To cite this version:**

Tatiana Galochkina, Anass Bouchnita, Polina Kurbatova, Vitaly Volpert. Reaction-diffusion waves of blood coagulation. *Mathematical Biosciences*, 2017, 288, pp.130 - 139. 10.1016/j.mbs.2017.03.008 . hal-01567320

HAL Id: hal-01567320

<https://hal.science/hal-01567320v1>

Submitted on 26 Jul 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Reaction-diffusion waves of blood coagulation[☆]

Tatiana Galochkina^{a,b,c,*}, Anass Bouchnita^{a,b,d,e}, Polina Kurbatova^d, Vitaly Volpert^{a,b,f}

^a*Camille Jordan Institute, University Lyon 1, Villeurbanne, 69622 France*

^b*INRIA Team Dracula, INRIA Antenne Lyon la Doua, Villeurbanne, 69603 France*

^c*Department of Biophysics, Faculty of Biology, M.V. Lomonosov Moscow State University, Leninskie gory 1, Moscow, 119992 Russia*

^d*Laboratoire de Biométrie et Biologie Evolutive, UMR 5558 CNRS, University Lyon 1, Lyon, 69376 France*

^e*Laboratory of Study and Research in Applied Mathematics, Mohammadia School of Engineers, Mohamed V university, Rabat, Morocco*

^f*Laboratoire Poncelet, UMI 2615 CNRS, Bolshoy Vlasievskiy Pereulok 11, Moscow, 119002 Russia*

Abstract

One of the main characteristics of blood coagulation is the speed of clot growth. This parameter strongly depends on the speed of propagation of the thrombin concentration in blood plasma. In the current work we consider a mathematical model of the coagulation cascade and study existence, stability and speed of propagation of the reaction-diffusion waves of blood coagulation. We also develop a simplified one-equation model that reflects the main features of the thrombin wave propagation. For this equation we estimate the wave speed analytically. The resulting formulas provide a good approximation for the speed of wave propagation in a more complex model as well as for the experimental data.

Keywords: blood coagulation, reaction-diffusion wave, speed of propagation

2000 MSC: 35C07, 92C45, 35K57

[☆]The last author was supported by the grant of Russian Science Foundation, project no.15-11-00029 and by the program PICS CNRS 6583 Matbio.

*tat.galochkina@gmail.com

1. Introduction

The main function of the coagulation system is terminating bleeding, caused by the vessel wall damage by covering the injury site with a fibrin clot. The reaction of fibrin polymerization appears at the final stage of the proteolytic enzymatic cascade where the activated clotting factors act as catalysts for activation of the others [1, 2]. Mature form of fibrin molecules can aggregate into long branching fibers and form a complex network which serves as a thrombus scaffold. The key enzyme of the coagulation cascade is thrombin as it catalyzes fibrinogen conversion to fibrin and distribution of the thrombin concentration has a crucial influence on the kinetics of the clot formation [3, 4, 1]. To prevent the spontaneous formation of thrombi the activation reactions are regulated by the action of plasma inhibitors [5, 6, 7, 8]. The balance between coagulation and anti-coagulation systems is important for the normal organism functioning and any alternations can lead to the severe pathological states: thrombosis or, on the contrary, disseminative bleeding [9, 10].

The key enzyme of the coagulation cascade is thrombin since it catalyzes fibrinogen cleavage to fibrin which in turn forms hemostatic clot. Formation of thrombin appears due to the prothrombin activation in the coagulation cascade. The process can be launched by the tissue factor expressed to the blood flow in case of the endothelium rupture (extrinsic pathway), or through the activation of factor XII which triggers activation of factor XI in case of the contact with the foreign surface (contact activation) [2, 11, 12]. Both pathways lead to the activation of factor X that contributes to the prothrombin conversion to thrombin [2]. Once the thrombin concentration reaches the threshold value, further prothrombin activation takes place due to the positive feedback loops of the coagulation cascade (intrinsic pathway) [11, 2, 13]. Thrombin controls activation of factor XI [12] and also of factors V [7] and VIII whose activated forms (Va, VIIIa) increase catalytic activity of factors Xa and IXa by formation of the prothrombinase and intrinsic kinase complexes respectively [14, 2, 15, 16] (Fig. 1).

Influence of different factors on the coagulation process was studied both experimentally and using theoretical approaches. As compared to the experiment, parameters in theoretical studies can be varied much easier allowing to detect not only experimentally observed regimes of blood coagulation [17, 18, 19, 20, 21] but also to suppose their possible variations for the conditions that are hard to reproduce in the experiment [22]. Model results

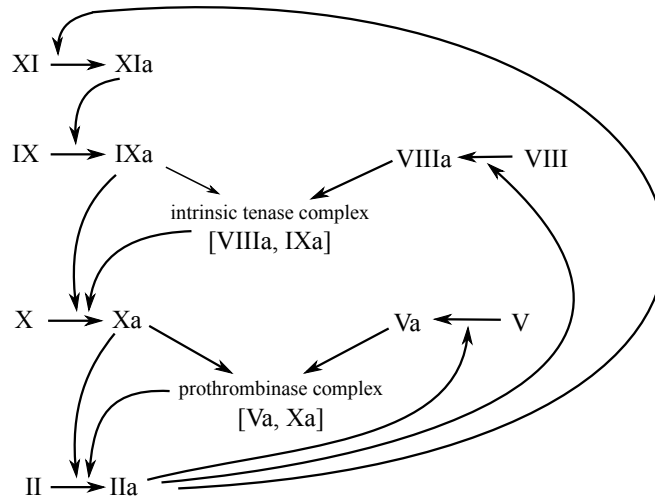


Figure 1: The main activation reactions of the intrinsic pathway of the coagulation cascade. Thrombin (IIa) catalyzes activation of factors V, VIII, XI; factors XIa and IXa catalyze activation of factors IX and X respectively; factors VIIIa and Va form active complexes with factors IXa and Xa respectively and further increase thrombin production.

38 also provide data about the possible spatiotemporal distribution of all the
 39 blood factors participating in the coagulation cascade, while the main pa-
 40 rameter used to measure the dynamics of the clot growth experimentally is
 41 fibrin clot density [20, 19, 23, 13, 24].

42 One of the main criteria used for the validation of the computational mod-
 43 els of coagulation system is the spatio-temporal distribution of the throm-
 44 bin concentration. During the amplification phase of the blood coagulation
 45 process, thrombin concentration propagates in the direction from the inju-
 46 ry site to the vascular lumen. According to the experimental data, after
 47 thrombin concentration exceeds some threshold value, the speed of the clot
 48 growth does not anymore depend on the way of the initial activation of
 49 the coagulation system [11, 24] and thrombin wave profile stays constant in
 50 time [14, 20, 25, 26]. In terms of mathematical models, such behavior cor-
 51 responds to the traveling wave solutions of the system of partial differential
 52 equations on the reactions of the coagulation cascade [19, 25, 26, 27, 22, 28].

53 Despite numerous evidence of the wave behavior of the thrombin con-
 54 centration profile, theoretical analysis of the observed phenomena is lacking
 55 in previous model studies of blood coagulation. That is why in our work
 56 we focus on the detailed theoretical investigation of the mathematical model

57 of the intrinsic pathway of the coagulation system (Section 2). We derive
 58 conditions on the existence and stability of the traveling wave solutions cor-
 59 responding to the amplification phase of coagulation cascade (Section 3) and
 60 demonstrate an important property of their speed of propagation (Section 4).

61 We also pay particular attention to the calculation of the speed of throm-
 62 bin propagation. Serving as an important indicator of blood coagulation
 63 disorders [9, 10], the speed of thrombin propagation in mathematical mod-
 64 els is usually measured according to the results of the computational sim-
 65 ulations [25, 28, 29] or using the combination of analytical and numerical
 66 approaches as it was done by [27]. In Section 5 of the current work we pro-
 67 pose an alternative approach and derive theoretical estimates for the speed
 68 of the thrombin wave propagation by the reduction of the initial system to
 69 one equation on thrombin concentration. We compare the estimates given
 70 by analytical formulas with computational values of the speed as well as with
 71 the experimental data.

72 2. Mathematical model

73 We consider the following model of the intrinsic pathway of blood coag-
 74 ulation:

$$\begin{aligned}
 \frac{\partial T}{\partial t} &= D\Delta T + \left(k_2 U_{10} + \overline{k_2} \frac{k_{510}}{h_{510}} U_{10} U_5 \right) \left(1 - \frac{T}{T_0} \right) - h_2 T, \\
 \frac{\partial U_5}{\partial t} &= D\Delta U_5 + k_5 T - h_5 U_5, \\
 \frac{\partial U_8}{\partial t} &= D\Delta U_8 + k_8 T - h_8 U_8, \\
 \frac{\partial U_9}{\partial t} &= D\Delta U_9 + k_9 U_{11} - h_9 U_9, \\
 \frac{\partial U_{10}}{\partial t} &= D\Delta U_{10} + k_{10} U_9 + \overline{k_{10}} \frac{k_{89}}{h_{89}} U_9 U_8 - h_{10} U_{10}, \\
 \frac{\partial U_{11}}{\partial t} &= D\Delta U_{11} + k_{11} T - h_{11} U_{11}.
 \end{aligned} \tag{1}$$

75 Here, T , U_i denote the concentrations of thrombin and activated forms of
 76 the i -th factor respectively, T_0 denotes the initial prothrombin concentra-
 77 tion. First term of each equation corresponds to the diffusion of the factors
 78 in blood plasma while other terms describe chemical reactions of the coagu-
 79 lation cascade. $k_i, \overline{k_i}$ denote the rates of activation reactions and h_i denote

80 inhibition of the activated factors. k_{ij} and h_{ij} denote the rates of forma-
 81 tion and inhibition respectively for the intrinsic kinase and prothrombinase
 82 complexes. Corresponding equation terms have the given form due to the
 83 assumption of the fast reactions of the complex formation.

84 In the current study we focus on the propagation stage of the coagula-
 85 tion cascade and thus suppose the initial amount of activated factors to be
 86 formed in the proximity of the vessel wall. Therefore we use step functions
 87 of thrombin and activated factor concentrations as initial conditions for the
 88 simulation. In order to take into account the activation of factor XI by fac-
 89 tor XIIa we take constant influx boundary condition on the left side of the
 90 domain and zero-flux boundary conditions on the right side.

91 The similar model has previously demonstrated a good agreement with
 92 experimental data [30, 28]. The main assumption of the model concerns
 93 taking inactivated factor concentrations to be constant. Numerical com-
 94 putations showed that concentrations of the precursors of active factors do
 95 not significantly change during the simulation [28]. Therefore, depletion of
 96 the precursors can be ignored. The only precursor whose concentration was
 97 considered as variable in the model of [30] is prothrombin. Thus, the first
 98 equation of our model replaces two following equations considered in [30, 28]:

$$\frac{\partial T}{\partial t} = D\Delta T + k_2 U_{10} \frac{\bar{T}}{\bar{T} + K_{2m}} + \frac{k_2 k_{510}}{h_{510}} U_{10} U_5 \frac{\bar{T}}{\bar{T} + K_{2m}} - h_2 T, \quad (2)$$

$$\frac{\partial \bar{T}}{\partial t} = D\Delta \bar{T} - k_2 U_{10} \frac{\bar{T}}{\bar{T} + K_{2m}} - \frac{k_2 k_{510}}{h_{510}} U_{10} U_5 \frac{\bar{T}}{\bar{T} + K_{2m}}, \quad (3)$$

99 with \bar{T} denoting prothrombin concentration. For $h_2 = 0$ both models coin-
 100 cide, and for low values of h_2 they would be very close. For the physiological
 101 values of thrombin inhibition, in the model of [28] we observe propagation
 102 of non-monotone thrombin wave while system (1) gives monotone traveling
 103 waves with higher value of maximal concentration (Fig. 2). Despite this dif-
 104 ference, the speed of thrombin wave propagation appears to be very close for
 105 both models (Fig. 2) and thus further we use system (1) as an approximation
 106 of the thrombin propagation process.

107 3. Existence and stability of the traveling wave solutions

108 Let us set $u = (T, U_5, U_8, U_9, U_{10}, U_{11})$. Then system (1) can be written
 109 in the vector form:

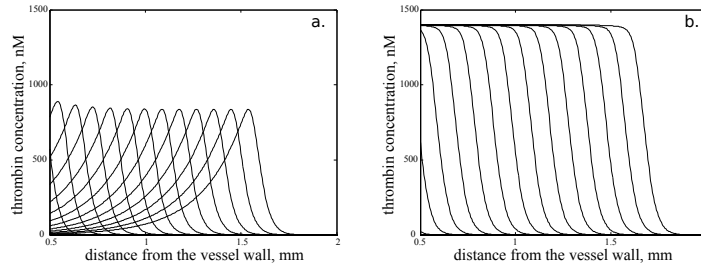


Figure 2: Propagation of thrombin wave for the model of [28] (a) and for the reduced model (1) (b). Concentration profiles are plotted every 2 min of physical time, the speed of the wave propagation is about 0.05 mm/min. Parameters of the simulations are provided in Tab. C.1.

$$\frac{\partial u}{\partial t} = D\Delta u + F(u), \quad (4)$$

110 where $F = (F_1, \dots, F_6)$ is the vector of reaction rates in equations (1). It
 111 satisfies the following property:

$$\frac{\partial F_i}{\partial u_j} \geq 0, \quad \forall i \neq j.$$

112 This class of systems is called monotone systems and has a number of proper-
 113 ties similar to those for one scalar equation including the maximum principle.
 114 It allows the proof of existence and stability of the wave solutions for mono-
 115 tone systems as well as the estimation of the wave propagation speed [31].
 116 In order to apply these results to the considered system describing intrinsic
 117 pathway functioning we start with the analysis of the existence and stability
 118 of the stationary points of system (1).

119 3.1. Stationary points of the kinetic system

120 Consider the system of ordinary differential equations:

$$\frac{du}{dt} = F(u). \quad (5)$$

121 Its equilibrium points satisfy the following relations:

$$U_5 = \frac{k_5}{h_5}T, U_8 = \frac{k_8}{h_8}T, U_{11} = \frac{k_{11}}{h_{11}}T, U_9 = \frac{k_9 k_{11}}{h_9 h_{11}}T, \quad (6)$$

$$U_{10} = \frac{k_9 k_{11}}{h_{10} h_9 h_{11}} \left(k_{10}T + \overline{k_{10}} \frac{k_{89}}{h_{89}} T^2 \right), \quad (7)$$

122 where T is a solution of the equation $P(T) = 0$. Here $P(T) = aT^4 + bT^3 +$
 123 $cT^2 + dT$,

$$\begin{aligned} a &= \frac{\overline{k_{10}} k_{89} k_8 \overline{k_2} k_5 k_{510} k_9 k_{11}}{h_{89} h_8 h_5 h_{10} h_{510} h_9 h_{11}}, & d &= -\frac{k_2 k_{10} k_9 k_{11}}{h_9 h_{11} h_{10}} + h_2 T_0, \\ b &= -\frac{\overline{k_{10}} k_{89} k_8 \overline{k_2} k_5 k_{510} k_9 k_{11}}{h_{89} h_8 h_5 h_{10} h_{510} h_9 h_{11}} T_0 + \frac{k_{10} \overline{k_2} k_5 k_{510} k_9 k_{11}}{h_5 h_{10} h_{510} h_9 h_{11}} + \frac{\overline{k_2} \overline{k_{10}} k_{89} k_8 k_9 k_{11}}{h_{89} h_8 h_9 h_{11}}, \\ c &= -\frac{k_{10} \overline{k_2} k_5 k_{510} k_9 k_{11}}{h_5 h_{10} h_{510} h_9 h_{11}} T_0 + \frac{k_2 k_{10} k_9 k_{11}}{h_9 h_{11}} - \frac{k_2 k_{89} k_8 k_9 k_{11}}{h_{89} h_8 h_9 h_{11} h_{10}} T_0. \end{aligned}$$

124 Hence, the stationary points of system (5) can be found through the station-
 125 ary points T^* of the equation

$$\frac{dT}{dt} = -P(T), \quad (8)$$

126 and equalities (6), (7).

127 Let us determine the number of positive roots of the polynomial $P(T)$.
 128 We set $P(T) = TQ(T)$, where $Q(T) = aT^3 + bT^2 + cT + d$. The number of
 129 positive roots of $Q(T)$ can be found as follows. First, we consider a function
 130 $Q'(T) = 3aT^2 + 2bT + c$. If it has no zeros, then $Q(T)$ is increasing and has
 131 one positive root if and only if $Q(0) < 0$. Otherwise, we denote by T_1, T_2 the
 132 nonzero solutions of the equation $Q'(T) = 0$: $T_{1,2} = (-b \pm \sqrt{b^2 - 3ac})/(3a)$.
 133 Then, the polynomial $Q(u)$ has one positive root in one of the cases:

- 134 • $T_1 \leq 0, Q(0) < 0$,
- 135 • $0 \leq T_1 < T_2, Q(0) < 0$ and $Q(T_1) > 0, Q(T_2) > 0$ or $Q(T_1) < 0$

136 and it has two positive roots if $0 < T_2, Q(0) > 0, Q(T_2) < 0$.

137 Stability of the stationary points of system (5) can be determined from
 138 the stability of stationary points of equation (8). The following theorem
 139 holds (see Appendix A for the proof).

140 **Theorem 1.** *There is one to one correspondence between stationary solutions*
 141 *$u^* = (T^*, U_5^*, U_8^*, U_9^*, U_{10}^*, U_{11}^*)$ of system (1) and the stationary points T^* of*
 142 *equation (8) given by (6), (7). The principal eigenvalue of the matrix $F'(u^*)$*
 143 *is positive (negative) if and only if $P'(T^*) < 0$ ($P'(T^*) > 0$).*

144 Thus, we can make the following conclusions about the existence and
 145 stability of stationary points of the kinetic system of equation (5). It always
 146 has a trivial solution $u^* = 0$. It has one (two) positive solution if and only if
 147 the polynomial $P(T)$ has one (two) positive root(s). A positive solution u^*
 148 is stable if and only if $P'(T^*) > 0$.

149 3.2. Wave existence and stability

150 We can now formulate a theorem on the existence of wave solutions in
 151 system (1).

152 **Theorem 2.** *Suppose that $P(T^*) = 0$ for some $T^* > 0$ and $P'(0) \neq$
 153 0 , $P'(T^*) \neq 0$. Let $u^* = (T^*, U_5^*, U_8^*, U_9^*, U_{10}^*, U_{11}^*)$ be the corresponding
 154 stationary solutions of system (5) determined by relations (6), (7).*

- 155 • *Monostable case. If there are no other positive roots of the polynomial*
 156 *$P(T)$, then system (1) has monotonically decreasing traveling wave so-*
 157 *lutions $u(x, t) = w(x - ct)$ with the limits $u(+\infty) = 0, u(-\infty) = u^*$ for*
 158 *all values of the speed c greater than or equal to the minimal speed c_0 ,*
- 159 • *Bistable case. If there is one more positive root of the polynomial $P(T)$*
 160 *in the interval $0 < T < T^*$, then system (1) has a monotonically*
 161 *decreasing traveling wave solutions $u(x, t) = w(x - ct)$ with the limits*
 162 *$u(+\infty) = 0, u(-\infty) = u^*$ for a unique value of c .*

163 The proof of Theorem 2 follows from the general results on the existence
 164 of waves for monotone systems of equation [31, 32]. Let us note that the
 165 conditions on the stability of stationary points follow from the assumption
 166 of Theorem 2 and Theorem 1. We have $P'(T^*) > 0$ in both cases since it is
 167 the largest root of the polynomial increasing at infinity. The sign of $P'(0)$
 168 is negative if there is no other root of $P(T)$ in between of 0 and T^* and the
 169 sign is positive if $P(T)$ has one more root.

170 Monotone traveling wave solutions of monotone systems are asymptoti-
 171 cally stable [31, 32] that gives global stability in the bistable case. In the
 172 monostable case the wave is globally stable for the minimal speed c_0 and
 173 stable with respect to small perturbations in a weighted norm for $c > c_0$ [32].

174 The unique wave speed in the bistable case and the minimal wave speed
175 in the monostable case admit minimax representations. Below we use such
176 representations for the bistable system since this case is more appropriate
177 for the applications considered in the current work. Indeed, traveling wave
178 solution of system (1) describes propagation of the thrombin concentration
179 in blood plasma due to the reactions of the coagulation cascade. In this
180 system the convergence to the traveling wave solution takes place only if the
181 initial concentrations of blood factors exceed some critical level, otherwise the
182 clot formation does not start because of the action of plasma inhibitors. This
183 dependency on the initial conditions and stability of zero solution correspond
184 to the bistable case. In the monostable case, on the contrary, any small
185 perturbation would result in the solution converging to the propagating wave.
186 In terms of the coagulation system functioning, monostable case corresponds
187 to the spontaneous disseminated coagulation blocking blood circulation.

188 Finally, let us note that in Theorem 2 we consider only the case of a
189 single positive root of the polynomial and the case of two positive roots. If
190 $P(T)$ has three positive roots the system would be monostable with a stable
191 intermediate stationary point. While this case is interesting from the point
192 of view of wave existence and stability, it is less relevant for the modeling of
193 blood coagulation, and we will not discuss it here.

194 4. Speed of wave propagation

195 One of the main objectives of this work is to obtain an analytical approx-
196 imation of the wave speed for the blood coagulation model (1). We proceed
197 in two steps. First, we reduce system (1) to a single equation and justify
198 this reduction. Then, we obtain some estimates of the wave speed for one
199 reaction-diffusion equation.

200 4.1. System reduction

201 In order to simplify the presentation, we describe the method of reduction
202 for the system of two equations:

$$u'' + cu' + f(u, v) = 0, \tag{9}$$

$$v'' + cv' + \frac{1}{\varepsilon}(au - bv) = 0, \tag{10}$$

203 where ε is a small parameter, $\frac{\partial f}{\partial v} > 0$ and system (9)–(10) is bistable. If we
 204 multiply the second equation by ε and take a formal limit as $\varepsilon \rightarrow 0$, then we
 205 have $v = \frac{a}{b}u$, and the first equation can be rewritten as follows:

$$u'' + cu' + f\left(u, \frac{a}{b}u\right) = 0. \quad (11)$$

206 Let us recall that the value of the speed $c = c_\varepsilon$ in system (9)–(10) and $c = c_0$
 207 for the scalar equation (11) are unknown, and in general they are different
 208 from each other. We will demonstrate that $c_\varepsilon \rightarrow c_0$ as $\varepsilon \rightarrow 0$:

209 **Theorem 3.** *The speed of wave propagation for system (9)–(10) converges*
 210 *to the speed of the wave propagation for equation (11) as $\varepsilon \rightarrow 0$.*

211 Singular perturbations of traveling waves are extensively studied by [31].
 212 Here we present another method of proof based on the estimates of the wave
 213 speed. This method is simpler and gives not only the limiting value of the
 214 speed for $\varepsilon = 0$ but also the estimates of the speed value for any positive ε .
 215 In the following sections we describe the approach in details and construct
 216 the wave speed estimates for system (9)–(10).

217 4.2. Wave speed estimate

218 We get the following estimates from the minimax representation of the
 219 wave speed in the bistable case [32] :

$$\min\left(\inf_x S_1(\rho), \inf_x S_2(\rho)\right) \leq c \leq \max\left(\sup_x S_1(\rho), \sup_x S_2(\rho)\right), \quad (12)$$

220 where

$$S_1(\rho) = \frac{\rho_1'' + f(\rho_1, \rho_2)}{-\rho_1'}, \quad S_2(\rho) = \frac{\rho_2'' + (a\rho_1 - b\rho_2)/\varepsilon}{-\rho_2'},$$

221 $\rho = (\rho_1, \rho_2)$ is an arbitrary test function continuous together with its second
 222 derivatives, monotonically decreasing (component-wise) and having the same
 223 limits at infinity as the wave solution, $\rho(+\infty) = 0$, $\rho(-\infty) = u^*$.

224 Let us choose the following test functions:

$$\rho_1 = u_0, \quad \rho_2 = \frac{a}{b}u_0 - \varepsilon f\left(u_0, \frac{a}{b}u_0\right) \frac{a}{b^2}, \quad (13)$$

225 where u_0 is the solution of (11). Neglecting the second-order terms with
 226 respect to ε , we get:

$$\begin{aligned} S_1(\rho) &= \left(u_0'' + f \left(u_0, \frac{a}{b} u_0 - \varepsilon \frac{a}{b^2} f \left(u_0, \frac{a}{b} u_0 \right) \right) \right) / (-u_0') = \\ & \left(u_0'' + f \left(u_0, \frac{a}{b} u_0 \right) - \varepsilon \frac{a}{b^2} f_v \left(u_0, \frac{a}{b} u_0 \right) f \left(u_0, \frac{a}{b} u_0 \right) \right) / (-u_0') = c_0 + \varepsilon \varphi(x), \end{aligned} \quad (14)$$

227 where

$$\varphi(x) = \frac{a}{b^2 u_0'} f_v \left(u_0, \frac{a}{b} u_0 \right) f \left(u_0, \frac{a}{b} u_0 \right),$$

228 and c_0 is the value of the speed in (11). Next,

$$S_2(\rho) = \frac{u_0'' + f \left(u_0, \frac{a}{b} u_0 \right) - \frac{\varepsilon}{b} \left(f \left(u_0, \frac{a}{b} u_0 \right) \right)''}{-u_0' + \frac{\varepsilon}{b} \left(f \left(u_0, \frac{a}{b} u_0 \right) \right)'} = c_0 + \varepsilon \psi(x), \quad (15)$$

229 where

$$\psi = \frac{c_0}{b u_0'} \left(f \left(u_0, \frac{a}{b} u_0 \right) \right)' + \frac{1}{b u_0'} \left(f \left(u_0, \frac{a}{b} u_0 \right) \right)''.$$

230 Hence, from (14), (15) we obtain the estimate

$$c_0 + \varepsilon \max \left\{ \min_x \varphi, \min_x \psi \right\} \leq c \leq c_0 + \varepsilon \min \left\{ \max_x \varphi, \max_x \psi \right\}, \quad (16)$$

231 where c_0 is the wave propagation speed for (11), the functions $\varphi(x)$, $\psi(x)$
 232 are bounded. The proof of Theorem 3 follows from this estimate.

233 5. One equation model

234 5.1. Reduction to the equation on thrombin concentration

235 If the reaction rate constants in the equations of system (1) for the vari-
 236 ables U_9 , U_{10} , U_5 and U_8 are sufficiently large, then we can replace these
 237 equations by the following algebraic relations (Section 4.1):

$$U_5 = \frac{k_5}{h_5}T, U_8 = \frac{k_8}{h_8}T, U_9 = \frac{k_9}{h_9}U_{11}, U_{10} = U_{11} \frac{k_9}{h_9 h_{10}} \left(k_{10} + \frac{\overline{k_{10} k_{89}}}{h_{89}} \frac{k_8}{h_8} T \right).$$

238 Then, instead of system (1) we obtain the following system of two equations:

$$\begin{aligned} \frac{\partial T}{\partial t} &= D\Delta T + U_{11} \frac{k_9}{h_9 h_{10}} \left(k_{10} + \frac{\overline{k_{10} k_{89}}}{h_{89}} \frac{k_8}{h_8} T \right) \left(k_2 + \frac{\overline{k_2 k_{510}}}{h_{510}} \frac{k_5}{h_5} T \right) \left(1 - \frac{T}{T_0} \right) - h_2 T, \\ \frac{\partial U_{11}}{\partial t} &= D\Delta U_{11} + k_{11} T - h_{11} U_{11}. \end{aligned} \tag{17}$$

239 Similarly, we can reduce this system to the single equation:

$$\frac{\partial T}{\partial t} = D\Delta T + \frac{k_9 k_{11}}{h_9 h_{10} h_{11}} T \left(k_{10} + \frac{\overline{k_{10} k_{89}}}{h_{89}} \frac{k_8}{h_8} T \right) \left(k_2 + \frac{\overline{k_2 k_{510}}}{h_{510}} \frac{k_5}{h_5} T \right) \left(1 - \frac{T}{T_0} \right) - h_2 T. \tag{18}$$

240 We realize this reduction in two steps in order to compare the one-equation
 241 model to system (1) as well as to the intermediate model of two equa-
 242 tions (17). Numerical simulations show that for the values of parameters
 243 in the physiological range [33, 25], all three models give the wave speed of
 244 the same order of magnitude (Fig. 3). The two equation model (17) gives a
 245 better approximation of model (1) than the single equation (18). However,
 246 the latter demonstrates the same parameter dependence of the wave speed
 247 as other models. Taking into account the complexity of the initial model (1),
 248 the approximation provided by one equation is acceptable. Below we obtain
 249 the analytical formulas for the wave speed for the one equation model.

250 5.2. Dimensionless model

251 In dimensionless variables

$$T = T_0 u, t = \frac{\tilde{t}}{h_2}, D = \tilde{D} h_2, \tag{19}$$

252 we rewrite equation (18) in the following form:

$$\frac{\partial u}{\partial \tilde{t}} = \tilde{D} \Delta u + M_1 u (1 + M_2 u) (1 + M_3 u) (1 - u) - u, \tag{20}$$

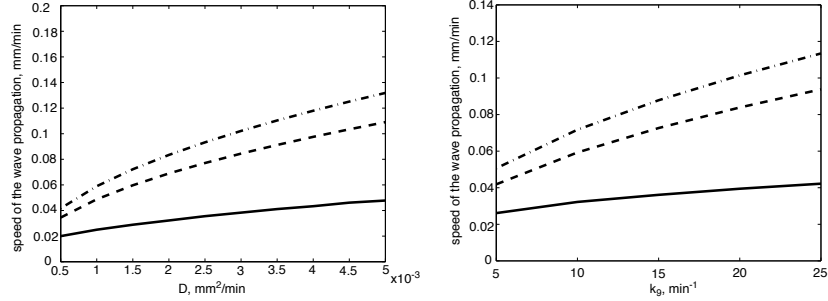


Figure 3: Speed of wave propagation (mm/min) as a function of D (left) and k_9 (right). Solid line: reduced model (1); dashed line: two-equation model (17); dash-dot line: one equation model (18). Parameters of the simulations are provided in Tab. C.1.

where:

$$M_1 = \frac{k_2 k_9 k_{10} k_{11}}{h_2 h_9 h_{10}}, \quad M_2 = \frac{k_8 k_{89} \overline{k_{10}}}{k_{10} h_8 h_{89}} T_0, \quad M_3 = \frac{\overline{k_2} k_5 k_{510}}{k_2 h_5 h_{510}} T_0.$$

253 Analysis of the rate constant values allows us to further simplify the equation.
 254 As $M_3 \gg 1$ we can approximate equation (20) by the following equation:

$$\frac{\partial u}{\partial \tilde{t}} = \tilde{D} \Delta u + M_1 M_3 u^2 (1 + M_2 u) (1 - u) - u. \quad (21)$$

255 Let us note that the first component of the term $u_1^2(1 + M_2 u_1)$ corresponds to
 256 the prothrombin activation by the factor Xa and the second one corresponds
 257 to the prothrombin activation by the [Va, Xa] complex. Since during the
 258 propagation phase the rate of activation by prothrombinase complex is several
 259 orders of magnitude higher than the activation by Xa itself [33], we can
 260 neglect the first component. Thus, applying the assumption of the detailed
 261 equilibrium for the second equation, we finally obtain the following equation
 262 for the thrombin concentration:

$$\frac{\partial u_1}{\partial \tilde{t}} = \tilde{D} \Delta u_1 + b u_1^3 (1 - u_1) - u_1, \quad (22)$$

263 where:

$$b = M_1 M_2 M_3. \quad (23)$$

264 *5.3. Wave speed estimate*

265 Equation (22) can be rewritten in the more general form:

$$\frac{\partial u}{\partial t} = D\Delta u + bu^n(1-u) - \sigma u. \quad (24)$$

266 Traveling wave solution of (24) satisfies the equation:

$$Dw'' + cw' + bw^n(1-w) - \sigma w = 0. \quad (25)$$

267 Here we will present two analytical methods to approximate the wave speed.

268 *5.3.1. Narrow reaction zone method*

269 One of the methods to estimate the wave speed for the reaction-diffusion
 270 equation is the narrow reaction zone method developed in combustion the-
 271 ory [34]. Let us rewrite equation (25) in the form:

$$Dw'' + cw' + F(w) - \sigma w = 0, \quad F(w) = w^n(1-w). \quad (26)$$

272 We assume that the reaction takes place at one point $x = 0$ in the coordinates
 273 of the moving front. Then, outside of the reaction zone we consider the linear
 274 equations:

$$\begin{cases} Dw'' + c_1w' - \sigma w = 0, & x > 0, \\ Dw'' + c_1w' = 0, & x < 0. \end{cases} \quad (27)$$

275 These equations should be completed with the jump conditions at the reac-
 276 tion zone. In order to derive them, we omit the first derivative w' at the
 277 reaction zone since it is small in comparison with two other terms:

$$Dw'' + F(w) = 0. \quad (28)$$

278 Multiplying (28) by w' and integrating through the reaction zone we obtain
 279 the following jump conditions:

$$(w'(+0))^2 - (w'(-0))^2 = \frac{2}{D} \int_0^{w^*} F(w)dw, \quad (29)$$

280 considered together with the condition of the continuity of solution $w(+0) =$
 281 $w(-0)$.

282 Solving (27) we have:

$$w = \begin{cases} w_*, & x < 0, \\ w_* \exp\left(\frac{-c - \sqrt{c^2 + 4D\sigma}}{2D}\right), & x > 0. \end{cases} \quad (30)$$

283 Then, from (29) and (30) we obtain the following equation for the wave speed:

$$c_1^2 + c_1 \sqrt{c_1^2 + 4D\sigma} + 2D\sigma = A, \quad A = \frac{4D}{w_*^2} \int_0^{w_*} F(w) dw. \quad (31)$$

284 Hence,

$$c_1 = \frac{A - 2D\sigma}{\sqrt{2A}}, \quad A = 4bD \left(\frac{w_*^{n-1}}{n+1} - \frac{w_*^n}{n+2} \right). \quad (32)$$

285 This formula gives a good approximation of the wave speed found numerically
 286 for $n \geq 3$ (Fig. 4). The approximation improves with increasing values of n .
 287 The obtained formula provides an estimation of the speed from below (see
 288 Appendix B for the justification of the method).

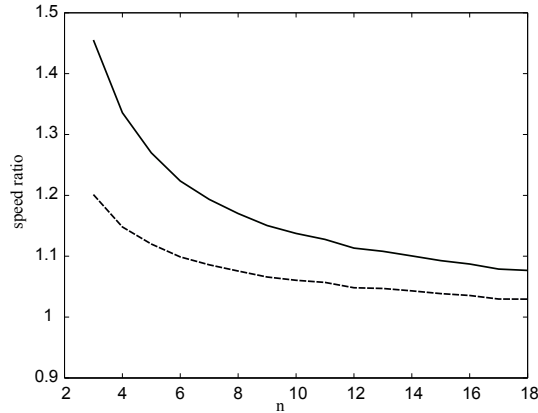


Figure 4: Ratio of wave speeds found numerically and analytically for different values of n ; $\sigma = 0.01$, $D = 2$, $b = 10$. Solid line: $\frac{c}{c_1}$, dashed line $\frac{c}{c_2}$. Parameters of the simulations are provided in Tab. C.1.

289 5.3.2. Piecewise linear approximation

290 Consider equation (26) written in the form

$$Dw'' + cw' + f(w) = 0,$$

291 where $f(w) = w^n(1 - w) - \sigma w$ and $f(0) = f(w_*) = 0$. Let us introduce the
292 following approximation of this equation:

$$Dw'' + c_2w' + f_0(w) = 0, \quad (33)$$

293 with

$$f_0(w) = \begin{cases} \alpha w, & 0 < w < w_0, \\ \beta(w - w_*), & w_0 < w < w_*, \end{cases} \quad (34)$$

294 where

$$\alpha = f'(0), \quad \beta = f'(w_*). \quad (35)$$

295 In case of equation (24) we have:

$$\alpha = -\sigma, \quad \beta = bnw_*^{n-1} - b(n+1)w_*^n - \sigma. \quad (36)$$

296 We find the value of w_0 from the additional condition:

$$\int_0^{w_*} f(w)dw = \int_0^{w_*} f_0(w)dw. \quad (37)$$

297 Hence we obtain the following equation with respect to w_0 :

$$\frac{\alpha - \beta}{2}w_0^2 + \beta w_* w_0 + r = 0, \quad (38)$$

298 where

$$r = -\beta w_*^2 - \int_0^{w_*} f(w)dw. \quad (39)$$

299 Taking into account the explicit form of function $f(w)$, we obtain:

$$r = bw_*^{n+1} \left(-\frac{n}{2} - \frac{b}{n+1} \right) + bw_*^{n+2} \left(\frac{n+1}{2} + \frac{1}{n+2} \right) + \sigma w_*^2. \quad (40)$$

300 From (38) we get:

$$w_0 = \frac{-\beta w_* + \sqrt{\beta^2 w_*^2 - 2(\alpha - \beta)r}}{\alpha - \beta}. \quad (41)$$

301 Thus, instead of (33) we consider the following equations:

$$\begin{cases} Dw'' + cw' + \beta(w - w_*) = 0, & x < 0, \\ Dw'' + cw' + \alpha w = 0, & x > 0, \end{cases} \quad (42)$$

302 with the additional conditions on the continuity of solution and its first
303 derivative:

$$w(0) = w_0, \quad w'(-0) = w'(+0).$$

304 We find the explicit solution:

$$\begin{cases} w = (w_0 - w_*) \exp\left(x \frac{\sqrt{c_2^2 - 4\beta D} - c_2}{2D}\right) + w_*, & x < 0, \\ w = w_0 \exp\left(x \frac{-\sqrt{c_2^2 - 4\alpha D} - c_2}{2D}\right), & x > 0. \end{cases} \quad (43)$$

305 From the condition of continuity of the derivative we obtain the following
306 formula:

$$c_2 = \frac{\sqrt{D}(\alpha\bar{w}^2 - \beta)}{\sqrt{(\bar{w} - 1)(\alpha\bar{w}^2 - \beta\bar{w})}}, \quad \bar{w} = \frac{w_0}{w_0 - w_*}. \quad (44)$$

307 It gives a good approximation of the wave speed for equation (26) (Fig. 4).

308 *5.4. Comparison of the estimated speed of the wave propagation with the*
309 *complete model and experimental data*

310 *5.4.1. Comparison of the estimated speed with the computational speed in*
311 *system (1)*

312 Considering system (1) and taking the parameter values for (32), (44)
313 according to (23), we approximate the speed of wave propagation by the
314 following formula obtained by the narrow reaction zone method:

$$c_1 = \sqrt{D} \frac{bT_0^2 - \frac{4}{5}bT_0^3 - 2h_2}{\sqrt{2\left(bT_0^2 - \frac{4}{5}bT_0^3\right)}}, \quad (45)$$

315 where

$$b = \frac{k_9 k_{11} \bar{k}_{10} k_8 k_{89} \bar{k}_2 k_5 k_{510} T_0^2}{h_9 h_{10} h_{11} h_8 h_{89} h_5 h_{510}}, \quad (46)$$

316 and by the piecewise linear approximation:

$$c_2 = \frac{\sqrt{D} (-3bT_0^2 - h_2\bar{T} + 4bT_0^3 - h_2)}{\sqrt{(T_0 - 1)\bar{T} (-h_2\bar{T} - 3bT_0^2 + 4bT_0^3 + h_2)}}, \quad (47)$$

317 where:

$$\bar{T} = \frac{T_*}{T_* - T_0}, \quad T_* = \frac{-3bT_0^2 + 4bT_0^4 + h_2}{4bT_0^2 - 3bT_0} + \frac{\sqrt{(3bT_0^2 - 4bT_0^3 - h_2)^2 - 2b(4T_0 - 3)T_0^2 (-\frac{3}{2}bT_0^2 - \frac{b^2}{4}T_0^2 + \frac{11}{5}bT_0^3 + h_2)}}{4bT_0^2 - 3bT_0}. \quad (48)$$

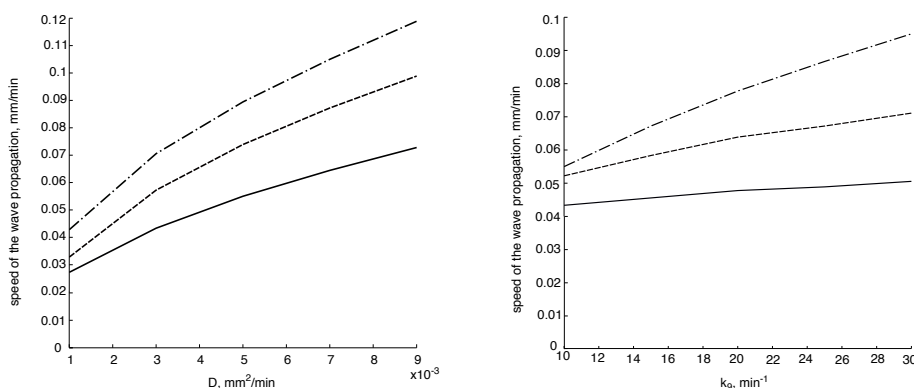


Figure 5: Speeds of wave propagation (mm/min) as function of D (left) and k_9 (right). Solid line: model (1); dashed line: narrow reaction zone approximation; dash-dot line: piecewise linear approximation. Parameters of the simulations are provided in Tab. C.1.

318 We compare the speed of wave propagation for model (1) found numer-
 319 ically with the analytical formulas (Fig. 5). As it was demonstrated above,
 320 the computational speed for the one-equation model is higher than for the
 321 complete model (Fig. 3). The analytical formulas for the speed of the wave
 322 propagation for one-equation model in turn provide the estimates from be-
 323 low (Fig. 4). As the result, the analytical estimates for one equation give
 324 better approximations of the speed in the complete model than the numerical

325 speed for one equation (Fig. 5). If we then compare two different analytical
326 estimates for the wave speed in one-equation model, we can conclude that
327 narrow reaction zone method gives the speed further from the one-equation
328 computational speed than piecewise linear approximation (Fig. 4) but at the
329 same time it better approximates the wave speed in the complete model (the
330 narrow reaction zone speed is 1.5 times higher than the computational one).

331 5.4.2. Comparison with experimental data

332 The speed of clot formation has crucial influence on the organism physi-
333 ology. Coagulation disorders such as hemophilia A, B or C are the result of
334 severe deficiency of the clotting factors. The effect of this deficiency on the
335 propagation phase is the most critical for situation *in vivo* [25, 35, 36]. Speed
336 of the thrombin propagation in mathematical model of the intrinsic pathway
337 functioning can provide estimation of the clot growth rate dependence on
338 different factors.

339 As an example, here we consider the experimental results obtained by [25]
340 on the patients with hemophilia B. Authors examined the effect of factor IX
341 deficiency on the spatial clotting dynamics. Plasma used was obtained from
342 hemophiliacs with different extent of the disease and from severe hemophil-
343 iacs treated with factor IX concentrate (Ahemphil B). Clotting process was
344 launched through the intrinsic pathway by small artificial contact activation
345 by plastic material. The obtained results show that the most pronounced
346 changes in clotting kinetics occurred at factor IX activity less than 20% [25].

347 Experimental data correlate well with the results given by the analytical
348 estimate of the thrombin propagation speed (Fig. 6). In the lack of precise
349 kinetic constants we had to fit the approximated speed value at the first point
350 of the plot corresponding to 1% of factor IX activity. While fitting, we varied
351 only the value of the parameter b . In terms of our model, factor IX activity is
352 reflected by the value of the parameter k_9 . Thus, analytical estimate provided
353 by (45) and (47) are plotted as functions of k_9 and give the values close to
354 the experimental ones for all the considered range.

355 6. Discussion and conclusions

356 Spatio-temporal dynamics of clot growth is of crucial importance for the
357 normal organism functioning. The key stage of the blood coagulation pro-
358 cess determining the dynamics of the clot formation is cumulative thrombin
359 production due to the intrinsic pathway functioning. Propagating from the

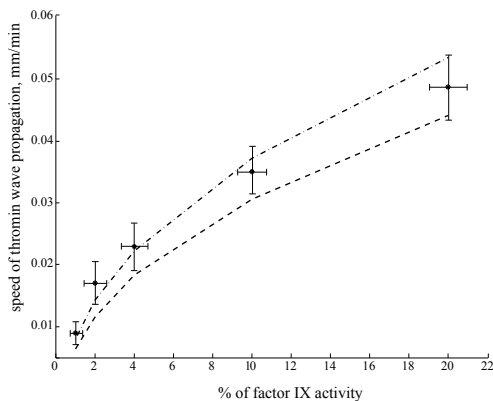


Figure 6: Speeds of the thrombin wave propagation (mm/min) as function of percentage of factor IX activity. Dots: experimental data [25]; dashed line: narrow reaction zone approximation; dash-dot line: piecewise linear approximation (Tab. 1)

360 injury site with constant velocity during the amplification phase, thrombin
 361 concentration can be modeled as traveling wave solutions in the PDE system
 362 on plasma factor concentrations [26]. In the current work we derive condi-
 363 tions on the existence and stability of the traveling wave solutions for the
 364 system describing intrinsic pathway of blood coagulation cascade.

365 Despite the general character of the methods used in this work, the de-
 366 veloped approaches imply some limitations. In our model we considered only
 367 a part of the coagulation cascade (intrinsic pathway) without taking into ac-
 368 count neither the initial activation, nor the role of the activated protein C
 369 pathway. In terms of our model, initial thrombin formation appears on the
 370 left boundary of the domain. However, since the problem of the existence of
 371 the traveling wave solutions is considered on the whole axis, the solutions do
 372 not depend on the boundary conditions. The independence of the speed of
 373 the thrombin wave propagation during the amplification phase on the nature
 374 of the stimuli that launched the clotting process was also demonstrated in
 375 multiple experimental studies [2, 11, 25]. Then, inhibition role of the acti-
 376 vated protein C appears only in the proximity of the vessel wall due to its
 377 activation by thrombomodulin and thus does not directly impact thrombin
 378 propagation on the distance from the vessel wall [37] and we do not incor-
 379 porate it in our model. As the result, considered model is monotone, that is
 380 equivalent to positive contribution of all factors to the activation reactions
 381 in terms of the chemical reaction network. This important feature of the
 382 coagulation cascade model allows us to study existence and properties of its

383 wave solutions.

384 The most important parameter determining the dynamics of clot growth
385 is the speed of the thrombin wave propagation or, in terms of the mathemat-
386 ical model, the speed of propagation of the reaction-diffusion wave. In the
387 current work we obtain analytical formula for the speed of wave propagation
388 in the model of blood coagulation. We reduce the system of equations to
389 one equation on the thrombin concentration and then determine the wave
390 speed for this equation. The method of reduction is based on the minimax
391 representation of the wave speed applicable for monotone reaction-diffusion
392 systems. One-equation model gives the speed of the wave propagation above
393 the wave speed obtained in the initial system. The difference dues to the as-
394 sumption on the fast reactions applied for the derivation of the one-equation
395 model. Analytical estimates obtained for the wave speed in one-equation
396 model in turn provide its approximation from below. Since narrow reaction
397 zone method was originally developed for the description of the flame front
398 propagation in the combustion theory with the exponential function in reac-
399 tion term. In our work thrombin activation is described with the polynomial
400 of the third degree that makes the obtained estimate less precise. Never-
401 theless, the obtained analytical estimates give good approximation of both
402 computational and experimental speed of the thrombin propagation.

403 The described approach for system analysis and estimation of the wave
404 propagation speed can be further expanded on other cascade models. An-
405 alytical formulas for the reaction front propagation can provide important
406 information on the system response on different factors and is of big impor-
407 tance for the model validation.

408 **Appendix A. Proof of the Theorem 1**

409 *Proof.* Along with the system system

$$\frac{du}{dt} = F(u), \tag{A.1}$$

410 consider the system

$$\frac{du}{dt} = F_\tau(u), \tag{A.2}$$

411 which depends on the parameter $\tau \in [0, 1]$. They differ only by the equation
412 for T which is considered now in the following form:

$$\frac{dT}{dt} = (\tau U_{10} + (1 - \tau)\varphi_{10}(T)) \left(k_2 + \overline{k_2} \frac{k_{510}}{h_{510}} (\tau U_5 + (1 - \tau)\varphi_5(T)) \right) \left(1 - \frac{T}{T_0} \right) - h_2 T.$$

413 Here the functions $\varphi_i(T)$ are determined by the equalities:

$$\begin{aligned} \varphi_{11}(T) &= \frac{k_{11}}{h_{11}} T, \quad \varphi_9(T) = \frac{k_9 k_{11}}{h_9 h_{11}} T, \quad \varphi_5(T) = \frac{k_5}{h_5} T, \quad \varphi_8(T) = \frac{k_8}{h_8} T, \\ \varphi_{10}(T) &= \frac{k_9 k_{11}}{h_{10} h_9 h_{11}} \left(k_{10} T + \overline{k_{10}} \frac{k_{89}}{h_{89}} T^2 \right). \end{aligned}$$

414 We can express U_i , $i = 5, 8, 9, 10, 11$ as functions of T from the corresponding
415 equations in (A.1) or, the same, from (A.2): $U_i = \varphi_i(T)$. Therefore the
416 solutions of the system of equations $F_\tau(T) = 0$ coincide with the solutions of
417 the system $F(T) = 0$.

418 Thus, systems (A.1) and (A.2) have the same stationary solutions for all
419 $\tau \in [0, 1]$. For $\tau = 1$ these two systems coincide. For $\tau = 0$ the equation
420 for T in (A.2) does not depend on other variables. This will allow us to
421 determined the eigenvalues of the corresponding linearized matrix.

422 It can be verified by the direct calculations that $\det F'_\tau(u^*) = 0$ if and
423 only if $\det F'(u^*) = 0$ for all $\tau \in [0, 1]$. Suppose that the latter is different
424 from zero. Then the principal eigenvalue of the matrix F'_τ , which is real and
425 simple, cannot change sign when τ changes from 0 to 1. Hence the sign of
426 the principal eigenvalue of the matrix $F'(u^*)$ is the same as for the matrix
427 $F'_0(u^*)$. This matrix has the form:

$$F'_0(u^*) = \begin{matrix} & T & U_5 & U_8 & U_{11} & U_9 & U_{10} \\ \begin{matrix} T \\ U_5 \\ U_8 \\ U_{11} \\ U_9 \\ U_{10} \end{matrix} & \left(\begin{array}{cccccc} -P'(T^*) & 0 & 0 & 0 & 0 & 0 \\ k_5 & -h_5 & 0 & 0 & 0 & 0 \\ k_8 & 0 & -h_8 & 0 & 0 & 0 \\ k_{11} & 0 & 0 & -h_{11} & 0 & 0 \\ 0 & 0 & 0 & k_9 & -h_9 & 0 \\ 0 & 0 & \overline{k_{10}} \frac{k_{89}}{h_{89}} U_9^* & 0 & k_{10} + \overline{k_{10}} \frac{k_{89}}{h_{89}} U_8^* & -h_{10} \end{array} \right) \end{matrix}$$

428 The principal eigenvalue of this matrix is positive if $P'(T^*) < 0$ and negative
429 if this inequality is opposite.

430

□

431 **Appendix B. Justification of the narrow reaction zone method**

432 Consider equation (26) and suppose for simplicity that $F(u) = 0$ for
 433 $u \leq u_0$ and $F(u) > 0$ for $u_0 < u < 1$. Let u^* be the maximal solution of the
 434 equation $F(u) = \sigma u$ (Figure B.7). We will look for a decreasing solution of
 435 equation (26) with the limits:

$$u(-\infty) = u^*, \quad u(+\infty) = 0.$$

436 Multiplying the equation (26) by u' and integrate through the hole axis we
 437 obtain:

$$c = \frac{\int_0^{u^*} F(u) du - \frac{1}{2}\sigma(u^*)^2}{\int_{-\infty}^{\infty} (u'(x))^2 dx}. \quad (\text{B.1})$$

438 Along with equation (26) we consider the system of two first-order equations:

$$\begin{cases} u' = p, \\ p' = -cp - F(u) + \sigma u. \end{cases} \quad (\text{B.2})$$

439 The wave solution of (26) corresponds to the trajectory connecting the sta-
 440 tionary points $(u^*, 0)$ and $(0, 0)$ (Figure B.7). This trajectory coincides with
 441 the line $p = \lambda u$ for $0 < u \leq u_0$, where λ is a negative solution of the equation

$$\lambda^2 + c\lambda - \sigma = 0.$$

442 The integral in the denominator of (B.1) can be approximated by replacing
 443 the trajectory function by the straight line $p = -\lambda u$:

$$\int_{-\infty}^{\infty} (u'(x))^2 dx = \int_0^{u^*} p(u) du \approx \frac{1}{2}\lambda(u^*)^2.$$

444 Substituting this expression into (B.1) we obtain the same formula for the
 445 speed as by the narrow reaction zone method (32).

446 Thus, narrow reaction zone method is equivalent to replacing the equa-
 447 tion trajectory by the straight line. Hence we can conclude that this method
 448 provides the estimate of the speed from below, and it also gives asymptoti-
 449 cally correct result in the limiting case as the support of the function $F(u)$
 450 converges to a point.

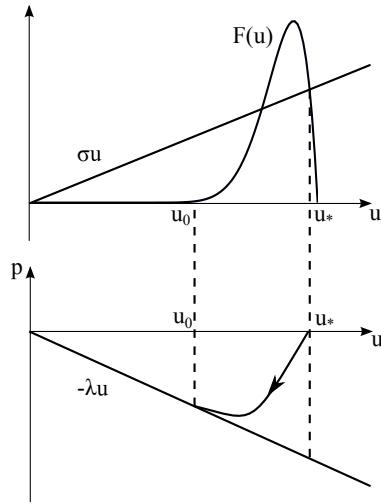


Figure B.7: Illustration of the narrow reaction zone method approximation.

451 **Appendix C. Parameter values used for the simulations**

Table C.1: Parameter rates used for the modeling of the coagulation cascade.

parameter	value	units	reference
k_{11}	0.000011	min^{-1}	[12]
h_{11}	0.5	min^{-1}	[38]
k_{10}	0.00033	min^{-1}	[39]
\overline{k}_{10}	500	min^{-1}	[39]
h_{10}	1	min^{-1}	[40]
k_9	20	min^{-1}	[41]
h_9	0.2	min^{-1}	[42]
k_{89}	100	$\text{nM}^{-1}\text{min}^{-1}$	[30]
h_{89}	100	min^{-1}	[30]
k_8	0.00001	min^{-1}	[30]
h_8	0.31	min^{-1}	[43]
k_5	0.17	min^{-1}	[30]
h_5	0.31	min^{-1}	[30]
k_{510}	100	$\text{nM}^{-1}\text{min}^{-1}$	[30]
h_{510}	100	min^{-1}	[30]
k_2	2.45	min^{-1}	[44]
\overline{k}_2	2000	min^{-1}	[44]
h_2	1.45	min^{-1}	[33]
K_{2m}	58	nM	[44]
\overline{K}_{2m}	210	nM	[44]
D	0.0037	$\text{mm}^2\text{min}^{-1}$	[30]
T_0	1400	nM	[1]

- 452 [1] S. Butenas, K. G. Mann, Blood coagulation., Biochemistry (Moscow)
453 61 (3) (2001) 3–12.
- 454 [2] T. Orfeo, S. Butenas, K. E. Brummel-Ziedins, K. G. Mann, The tissue
455 factor requirement in blood coagulation, Journal of Biological Chemistry
456 280 (52) (2005) 42887–42896. doi:10.1074/jbc.M505506200.
- 457 [3] H. C. Hemker, Thrombin generation, an essential step in haemostasis
458 and thrombosis, Haemostasis and thrombosis 3 (1993) 477–491.
- 459 [4] H. C. Hemker, S. Béguin, Thrombin generation in plasma: its assessment
460 via the endogenous thrombin potential., Thrombosis and haemostasis
461 74 (1) (1995) 134–8.

- 462 [5] J. Pieters, G. Willems, H. C. Hemker, T. Lindhout, Inhibition of Factor
463 Xa and Factor X , by Antithrombin III / Heparin during Factor X
464 Activation, *The Journal of biological chemistry* 263 (30) (1988) 15313–
465 15318.
- 466 [6] S. J. Koppelman, T. M. Hackeng, J. J. Sixma, B. N. Bouma, Inhibition
467 of the Intrinsic Factor X Activating Complex by Protein S: Evidence
468 for a Specific Binding of Protein S to Factor VIII, *Blood* 86 (3) (1995)
469 1062–1071.
- 470 [7] D. D. Monkovic, P. B. Tracy, Functional characterization of human
471 platelet-released factor V and its activation by factor Xa and thrombin,
472 *J Biol Chem* 265 (18) (1990) 17132–17141.
- 473 [8] M. A. Panteleev, V. I. Zarnitsina, F. I. Ataulakhanov, Tissue factor
474 pathway inhibitor: a possible mechanism of action, *Eur. J. Biochem.*
475 269 (2002) 118–122. doi:10.1046/j.1432-1033.2002.02818.x.
- 476 [9] R. W. Colman, *Hemostasis and thrombosis: basic principles and clinical
477 practice*, lippincott Edition, 2006.
- 478 [10] A. T. Askari, A. M. Lincoff, *Antithrombotic Drug Therapy in Cardio-
479 vascular Disease*, no. 1, 2010. doi:10.1007/978-1-60327-235-3.
- 480 [11] T. Orfeo, K. E. Brummel-Ziedins, M. Gissel, S. Butenas, K. G.
481 Mann, The nature of the stable blood clot procoagulant activities,
482 *Journal of Biological Chemistry* 283 (15) (2008) 9776–9786.
483 doi:10.1074/jbc.M707435200.
- 484 [12] D. Gailani, G. J. Broze, Factor XI Activation in a Revised Model of
485 Blood Coagulation, *Science* 253 (5022) (1991) 909–912.
- 486 [13] M. A. Panteleev, M. V. Ovanesov, D. A. Kireev, A. M. Shibeko,
487 E. I. Sinauridze, N. M. Ananyeva, A. A. Butylin, E. L. Saenko,
488 F. I. Ataulakhanov, Spatial Propagation and Localization of Blood
489 Coagulation Are Regulated by Intrinsic and Protein C Pathways,
490 *Respectively, Biophysical Journal* 90 (5) (2006) 1489–1500.
491 doi:10.1529/biophysj.105.069062.
- 492 [14] S. Butenas, T. Orfeo, M. T. Gissel, K. E. Brummel, K. G. Mann, The
493 significance of circulating factor IXa in blood, *Biochemistry* (2004) 1–41.

- 494 [15] R. J. Baugh, S. Krishnaswamy, Role of the Activation Peptide Domain
495 in Human Factor X Activation by the Extrinsic Xase Complex, *J Biol*
496 *Chem* 271 (27) (1996) 16126–16134.
- 497 [16] J. M. Scandura, P. N. Walsh, Factor X bound to the surface of activated
498 human platelets is preferentially activated by platelet-bound factor IXa,
499 *Biochemistry* 35 (27) (1996) 8903–13. doi:10.1021/bi9525031.
- 500 [17] W. Stortelder, P. W. Hemker, Mathematical modelling in blood co-
501 agulation ; Simulation and parameter estimation, Report - Modelling,
502 analysis and simulation 20 (1997) 1–11.
- 503 [18] K. Leiderman, A. L. Fogelson, Grow with the flow: A spatial-
504 temporal model of platelet deposition and blood coagulation un-
505 der flow, *Mathematical Medicine and Biology* 28 (1) (2011) 47–84.
506 doi:10.1093/imammb/dqq005.
- 507 [19] Y. V. Krasotkina, E. I. Sinauridze, F. I. Ataulakhanov, Spatiotem-
508 poral dynamics of fibrin formation and spreading of active thrombin
509 entering non-recalcified plasma by diffusion, *Biochimica et Biophysica*
510 *Acta - General Subjects* 1474 (3) (2000) 337–345. doi:10.1016/S0304-
511 4165(00)00019-2.
- 512 [20] F. I. Ataulakhanov, G. T. Guria, V. I. Sarbash, R. I. Volkova,
513 Spatiotemporal dynamics of clotting and pattern formation in hu-
514 man blood., *Biochimica et biophysica acta* 1425 (3) (1998) 453–468.
515 doi:10.1016/S0304-4165(98)00102-0.
- 516 [21] A. Bouchnita, A. Tosenberger, V. Volpert, On the regimes of
517 blood coagulation, *Applied Mathematics Letters* 51 (2016) 74–79.
518 doi:10.1016/j.aml.2015.07.010.
- 519 [22] V. I. Zarnitsina, F. I. Ataulakhanov, A. I. Lobanov, O. L. Morozova,
520 Dynamics of spatially nonuniform patterning in the model of blood co-
521 agulation, *Chaos* 11 (1) (2001) 57–70. doi:10.1063/1.1345728.
- 522 [23] F. I. Ataulakhanov, Y. V. Krasotkina, V. I. Sarbash, R. I. Volkova, E. I.
523 Sinauridse, A. Y. Kondratovich, Spatio-Temporal Dynamics of Blood
524 Coagulation and Pattern Formation: a Theoretical Approach, *Internation-*
525 *Journal of Bifurcation and Chaos* 12 (9) (2002) 1969–1983.

- 526 [24] M. V. Ovasenov, N. M. Ananyeva, M. A. Pantelev, F. I. Ataullakhanov,
527 E. L. Saenko, Initiation and propagation of coagulation from tis-
528 sue factor-benfin cell monolayers to plasma: initiator cells do not
529 regulate spatial growth rate, *J Thromb Haemost* 3 (2005) 321–31.
530 arXiv:arXiv:1011.1669v3, doi:10.1017/CBO9781107415324.004.
- 531 [25] A. Tokarev, Y. Krasotkina, M. Ovanesov, M. Pantelev, M. Azhi-
532 girova, Spatial Dynamics of Contact-Activated Fibrin Clot Forma-
533 tion in vitro and in silico in Haemophilia B : Effects of Severity and
534 Ahemphil B Treatment, *Math. Model. Nat. Phenom.* 1 (2) (2006) 124–
535 137. doi:10.1051/mmnp:2008007.
- 536 [26] N. M. Dashkevich, M. V. Ovanesov, . N. Balandina, S. S. Karamzin,
537 P. I. Shestakov, N. P. Soshitova, A. A. Tokarev, M. A. Pantelev, F. I.
538 Ataullakhanov, Thrombin activity propagates in space during blood co-
539 agulation as an excitation wave, *Biophysical Journal* 103 (10) (2012)
540 2233–2240. doi:10.1016/j.bpj.2012.10.011.
- 541 [27] E. A. Pogorelova, A. I. Lobanov, Influence of enzymatic reactions
542 on blood coagulation autowave, *Biophysics* 59 (1) (2014) 110–118.
543 doi:10.1134/S0006350914010151.
- 544 [28] V. I. Zarnitsina, A. V. Pokhilko, F. I. Ataullakhanov, A mathematical
545 model for the spatio-temporal dynamics of intrinsic pathway of blood
546 coagulation. II. Results, *Thrombosis Research* 84 (5) (1996) 333–344.
547 doi:10.1016/S0049-3848(96)00197-1.
- 548 [29] A. I. Lobanov, T. K. Starozhilova, The effect of convective flows on blood
549 coagulation processes., *Pathophysiology of haemostasis and thrombosis*
550 34 (2-3) (2005) 121–34. doi:10.1159/000089932.
- 551 [30] V. I. Zarnitsina, A. V. Pokhilko, F. I. Ataullakhanov, A mathematical
552 model for the spatio-temporal dynamics of intrinsic pathway of blood co-
553 agulation. I. The model description, *Thrombosis Research* 84 (4) (1996)
554 225–236. doi:10.1016/S0049-3848(96)00182-X.
- 555 [31] V. Volpert, *Elliptic Partial Differential Equations*, Vol. 104, 2014.
- 556 [32] A. I. Volpert, V. A. Volpert, V. A. Volpert, *Traveling Wave Solutions of*
557 *Parabolic Systems*, Vol. 140, 1994.

- 558 [33] M. F. Hockin, K. C. Jones, S. J. Everse, K. G. Mann, A model for
559 the stoichiometric regulation of blood coagulation, *Journal of Biological*
560 *Chemistry* 277 (21) (2002) 18322–18333. doi:10.1074/jbc.M201173200.
- 561 [34] Y. B. Zeldovich, D. A. Frank-Kamenetskii, A theory of thermal propa-
562 gation of flame, *Acta Physicochim. USSR* 9.
- 563 [35] M. V. Ovanesov, E. G. Lopatina, E. L. Saenko, N. M. Ananyeva, L. I.
564 Ul'yanova, O. P. Plyushch, A. A. Butilin, F. I. Ataullakhanov, Effect
565 of factor VIII on tissue factor-initiated spatial clot growth, *Thromb.*
566 *Haemost.* 2 (2003) 235–242.
- 567 [36] M. V. Ovanesov, J. V. Krasotkina, L. I. Ul'yanova, K. V. Abushinova,
568 O. P. Plyushch, S. P. Domogatskii, A. I. Vorob'ev, F. I. Ataullakhanov,
569 Hemophilia A and B are associated with abnormal spatial dynamics of
570 clot growth, *Biochimica et Biophysica Acta - General Subjects* 1572 (1)
571 (2002) 45–57. doi:10.1016/S0304-4165(02)00278-7.
- 572 [37] M. Anand, K. Rajagopal, K. R. Rajagopal, A model for the for-
573 mation, growth, and lysis of clots in quiescent plasma. A compar-
574 ison between the effects of antithrombin III deficiency and protein
575 C deficiency, *Journal of Theoretical Biology* 253 (4) (2008) 725–738.
576 doi:10.1016/j.jtbi.2008.04.015.
- 577 [38] C. F. Scott, M. Schapira, H. L. James, A. B. Cohen, R. W. Colman,
578 Inactivation of factor XIa by plasma protease inhibitors: predominant
579 role of alpha 1-protease inhibitor and protective effect of high molecular
580 weight kininogen., *The Journal of clinical investigation* 69 (4) (1982)
581 844–52.
582 URL <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=370139&tool=pmc>
- 583 [39] G. Van Dieijen, G. Tans, J. Rosing, H. C. Hemker, The role of phospho-
584 lipid and factor VIII(a) in the activation of bovine factor X, *Journal of*
585 *Biological Chemistry* 256 (7) (1981) 3433–3442.
- 586 [40] J. Jesty, Analysis of the generation and inhibition of activated coagula-
587 tion factor X in pure systems and in human plasma, *Journal of Biological*
588 *Chemistry* 261 (19) (1986) 8695–8702.

- 589 [41] F. I. Ataulakhanov, A. V. Pohilko, E. I. Sinauridze, R. I. Volkova, Cal-
590 cium threshold in human plasma clotting kinetics, *Thrombosis Research*
591 75 (4) (1994) 383–394. doi:10.1016/0049-3848(94)90253-4.
- 592 [42] J. S. Rosenberg, P. W. Mckenna, Inhibition of Human Factor IX , by
593 Human Antithrombin, *Journal of Biological Chemistry* 250 (23) (1975)
594 8883–8889.
- 595 [43] P. F. Neuenschwander, J. Jesty, Thrombin-activated and factor Xa-
596 activated human factor VIII: Differences in cofactor activity and decay
597 rate, *Archives of Biochemistry and Biophysics* 296 (2) (1992) 426–434.
598 doi:10.1016/0003-9861(92)90593-L.
- 599 [44] J. Rosing, G. Tans, J. W. P. Goversriemslag, R. F. A. Zwaal, H. C.
600 Hemker, Role of Phospholipids and Factor-Va in the Prothrombinase
601 Complex, *Journal of Biological Chemistry* 255 (1) (1980) 274–283.
602 URL <Go to ISI>://A1980JB74900042