Reaction-diffusion waves of blood coagulation

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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
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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

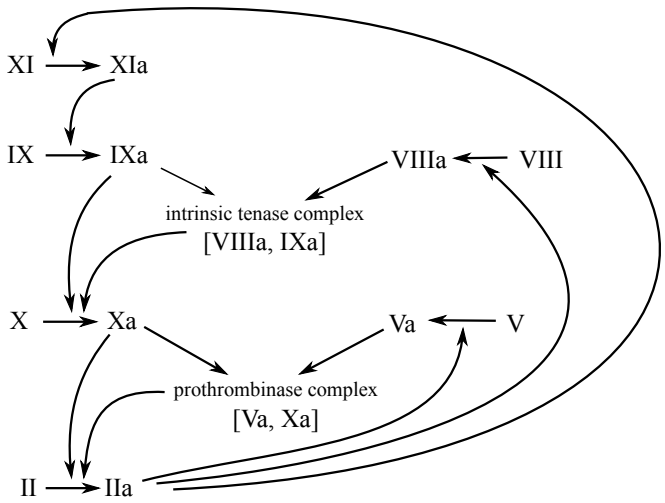

Figure 1: The main activation reactions of the intrinsic pathway of the coagulation cascade. Thrombin (IIa) catalyzes activation of factors V, VIII, XI; factors XIa and IXa catalyze activation of factors IX and X respectively; factors VIIIa and Va form active complexes with factors IXa and Xa respectively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

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

One of the main criteria used for the validation of the computational models of coagulation system is the spatio-temporal distribution of the thrombin concentration. During the amplification phase of the blood coagulation process, thrombin concentration propagates in the direction from the injury site to the vascular lumen. According to the experimental data, after thrombin concentration exceeds some threshold value, the speed of the clot growth does not anymore depend on the way of the initial activation of the coagulation system [11, 24] and thrombin wave profile stays constant in time [14, 20, 25, 26]. In terms of mathematical models, such behavior corresponds to the traveling wave solutions of the system of partial differential equations on the reactions of the coagulation cascade [19, 25, 26, 27, 22, 28].

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

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

We also pay particular attention to the calculation of the speed of thrombin propagation. Serving as an important indicator of blood coagulation disorders [9, 10], the speed of thrombin propagation in mathematical models is usually measured according to the results of the computational simulations [25, 28, 29] or using the combination of analytical and numerical approaches as it was done by [27]. In Section 5 of the current work we propose an alternative approach and derive theoretical estimates for the speed of the thrombin wave propagation by the reduction of the initial system to one equation on thrombin concentration. We compare the estimates given by analytical formulas with computational values of the speed as well as with the experimental data.

2. Mathematical model

We consider the following model of the intrinsic pathway of blood coagulation:

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

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

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

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

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

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

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

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

3. Existence and stability of the traveling wave solutions

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

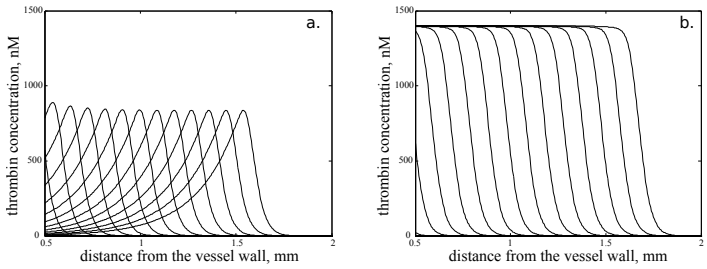

Figure 2: Propagation of thrombin wave for the model of [28] (a) and for the reduced model (1) (b). Concentration profiles are plotted every 2 min of physical time, the speed of the wave propagation is about 0.05 mm/min. Parameters of the simulations are provided in Tab. C.1.

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

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

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

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

3.1. Stationary points of the kinetic system

Consider the system of ordinary differential equations:

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

Its equilibrium points satisfy the following relations:

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

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

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

$$a = \frac{\overline{k_{10}}k_{89}k_8\overline{k_2}k_5k_{510}k_9k_{11}}{h_{89}h_8h_5h_{10}h_{510}h_9h_{11}}, \quad d = -\frac{k_2k_{10}k_9k_{11}}{h_9h_{11}h_{10}} + h_2T_0,$$

$$b = -\frac{\overline{k_{10}}k_{89}k_8\overline{k_2}k_5k_{510}k_9k_{11}}{h_{89}h_8h_5h_{10}h_{510}h_9h_{11}}T_0 + \frac{k_{10}\overline{k_2}k_5k_{510}k_9k_{11}}{h_5h_{10}h_{510}h_9h_{11}} + \frac{\overline{k_2k_{10}}k_{89}k_8k_9k_{11}}{h_{89}h_8h_9h_{11}},$$

$$c = -\frac{k_{10}\overline{k_2}k_5k_{510}k_9k_{11}}{h_5h_{10}h_{510}h_9h_{11}}T_0 + \frac{k_2k_{10}k_9k_{11}}{h_9h_{11}} - \frac{k_2k_{89}k_8k_9k_{11}}{h_{89}h_8h_9h_{11}h_{10}}T_0.$$

Hence, the stationary points of system (5) can be found through the stationary points T^* of the equation

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

and equalities (6), (7).

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

- $T_1 \le 0,\ Q(0) < 0,$
- $0 \le T_1 < T_2,\ Q(0) < 0$ and $Q(T_1) > 0,\ Q(T_2) > 0$ or $Q(T_1) < 0$

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

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

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

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

3.2. Wave existence and stability

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

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

- *Monostable case. If there are no other positive roots of the polynomial* $P(T)$*, then system* (1) *has monotonically decreasing traveling wave solutions* $u(x,t) = w(x - ct)$ *with the limits* $u(+\infty) = 0, u(-\infty) = u^*$ *for all values of the speed* c *greater than or equal to the minimal speed* c_0*,*

- *Bistable case. If there is one more positive root of the polynomial* $P(T)$ *in the interval* $0 < T < T^*$*, then system* (1) *has a monotonically decreasing traveling wave solutions* $u(x,t) = w(x - ct)$ *with the limits* $u(+\infty) = 0, u(-\infty) = u^*$ *for a unique value of* c*.*

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

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

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

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

4. Speed of wave propagation

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

4.1. System reduction

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

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

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

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

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

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

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

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

4.2. Wave speed estimate

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

$$\min\left(\inf_x S_1(\rho), \inf_x S_2(\rho)\right) \le c \le \max\left(\sup_x S_1(\rho), \sup_x S_2(\rho)\right), \tag{12}$$

where

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

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

Let us choose the following test functions:

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

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

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

where

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

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

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

where

$$\psi = \frac{c_0}{bu_0'}\left(f\left(u_0, \frac{a}{b}u_0\right)\right)' + \frac{1}{bu_0'}\left(f\left(u_0, \frac{a}{b}u_0\right)\right)''.$$

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

$$c_0 + \varepsilon\max\left\{\min_x\varphi, \min_x\psi\right\} \le c \le c_0 + \varepsilon\min\left\{\max_x\varphi, \max_x\psi\right\}, \tag{16}$$

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

5. One equation model

5.1. Reduction to the equation on thrombin concentration

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

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

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

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

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

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

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

5.2. Dimensionless model

In dimensionless variables

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

we rewrite equation (18) in the following form:

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

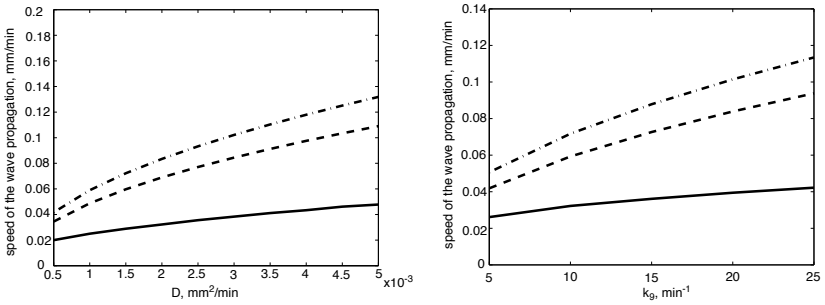

Figure 3: Speed of wave propagation (mm/min) as a function of D (left) and k_9 (right). Solid line: reduced model (1); dashed line: two-equation model (17); dash-dot line: one equation model (18). Parameters of the simulations are provided in Tab. C.1.

where:

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

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

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

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

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

where:

$$b = M_1 M_2 M_3. \tag{23}$$

5.3. Wave speed estimate

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

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

Traveling wave solution of (24) satisfies the equation:

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

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

5.3.1. Narrow reaction zone method

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

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

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

$$\begin{cases} Dw'' + c_1 w' - \sigma w = 0, & x > 0, \\ Dw'' + c_1 w' = 0, & x < 0. \end{cases} \tag{27}$$

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

$$Dw'' + F(w) = 0. \tag{28}$$

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

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

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

Solving (27) we have:

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

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

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

Hence,

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

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

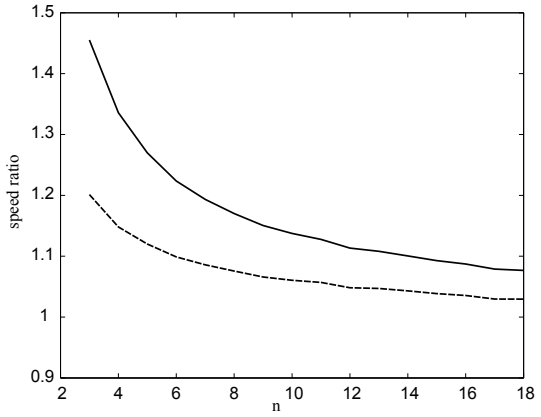

Figure 4: Ratio of wave speeds found numerically and analytically for different values of n; $\sigma = 0.01,\ D = 2,\ b = 10$. Solid line: $\dfrac{c}{c_1}$, dashed line $\dfrac{c}{c_2}$. Parameters of the simulations are provided in Tab. C.1.

5.3.2. Piecewise linear approximation

Consider equation (26) written in the form

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

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

$$Dw'' + c_2 w' + f_0(w) = 0, \tag{33}$$

with

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

where

$$\alpha = f'(0),\ \beta = f'(w_*). \tag{35}$$

In case of equation (24) we have:

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

We find the value of w_0 from the additional condition:

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

Hence we obtain the following equation with respect to w_0:

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

where

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

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

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

From (38) we get:

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

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

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

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

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

We find the explicit solution:

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

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

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

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

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

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

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

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

where

$$b = \frac{k_9 k_{11} \overline{k_{10}} k_8 k_{89} \overline{k_2} k_5 k_{510} T_0^2}{h_9 h_{10} h_{11} h_8 h_{89} h_5 h_{510}}, \tag{46}$$

and by the piecewise linear approximation:

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

where:

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

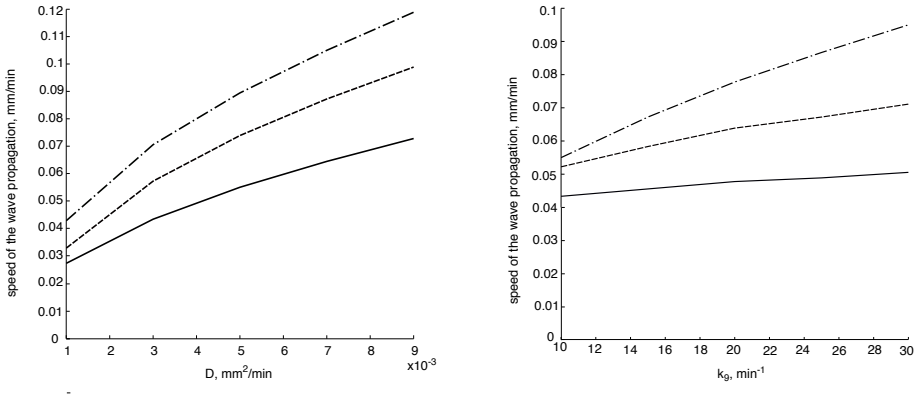

Figure 5: Speeds of wave propagation (mm/min) as function of D (left) and k_9 (right). Solid line: model (1); dashed line: narrow reaction zone approximation; dash-dot line: piecewise linear approximation. Parameters of the simulations are provided in Tab. C.1.

We compare the speed of wave propagation for model (1) found numerically with the analytical formulas (Fig. 5). As it was demonstrated above, the computational speed for the one-equation model is higher than for the complete model (Fig. 3). The analytical formulas for the speed of the wave propagation for one-equation model in turn provide the estimates from below (Fig. 4). As the result, the analytical estimates for one equation give better approximations of the speed in the complete model than the numerical

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

5.4.2. Comparison with experimental data

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

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

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

6. Discussion and conclusions

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

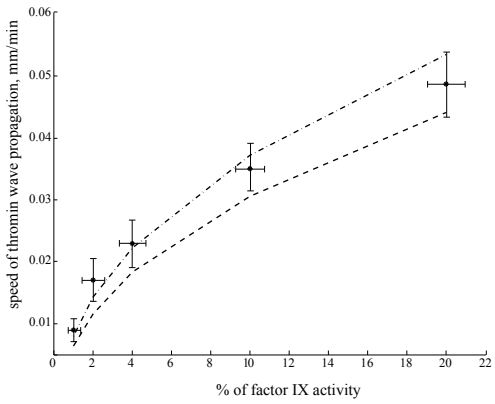

Figure 6: Speeds of the thrombin wave propagation (mm/min) as function of percentage of factor IX activity. Dots: experimental data [25]; dashed line: narrow reaction zone approximation; dash-dot line: piecewise linear approximation (Tab. 1)

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

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

wave solutions.

The most important parameter determining the dynamics of clot growth is the speed of the thrombin wave propagation or, in terms of the mathematical model, the speed of propagation of the reaction-diffusion wave. In the current work we obtain analytical formula for the speed of wave propagation in the model of blood coagulation. We reduce the system of equations to one equation on the thrombin concentration and then determine the wave speed for this equation. The method of reduction is based on the minimax representation of the wave speed applicable for monotone reaction-diffusion systems. One-equation model gives the speed of the wave propagation above the wave speed obtained in the initial system. The difference dues to the assumption on the fast reactions applied for the derivation of the one-equation model. Analytical estimates obtained for the wave speed in one-equation model in turn provide its approximation from below. Since narrow reaction zone method was originally developed for the description of the flame front propagation in the combustion theory with the exponential function in reaction term. In our work thrombin activation is described with the polynomial of the third degree that makes the obtained estimate less precise. Nevertheless, the obtained analytical estimates give good approximation of both computational and experimental speed of the thrombin propagation.

The described approach for system analysis and estimation of the wave propagation speed can be further expanded on other cascade models. Analytical formulas for the reaction front propagation can provide important information on the system response on different factors and is of big importance for the model validation.

Appendix A. Proof of the Theorem 1

Proof. Along with the system system

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

consider the system

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

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

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

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

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

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

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

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

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

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

□

Appendix B. Justification of the narrow reaction zone method

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

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

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

$$c = \frac{\int\limits_0^{u^*} F(u)du - \frac{1}{2}\sigma(u^*)^2}{\int\limits_{-\infty}^{\infty} (u'(x))^2 dx}\ . \tag{B.1}$$

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

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

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

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

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

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

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

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

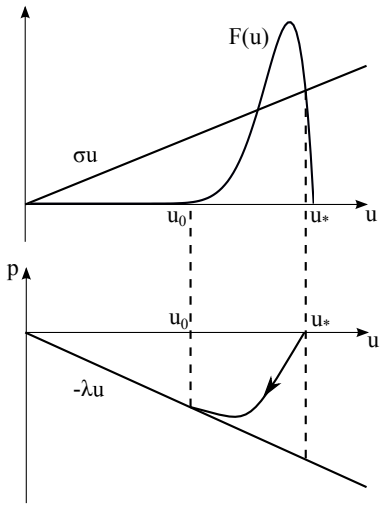

Figure B.7: Illustration of the narrow reaction zone method approximation.

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]

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