Pergamon

PII S0049-3848(96)00182-X

A MATHEMATICAL MODEL FOR THE SPATIO-TEMPORAL DYNAMICS OF INTRINSIC PATHWAY OF BLOOD COAGULATION. I. THE MODEL DESCRIPTION

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Abstract We developed and analyzed the mathematical model of the intrinsic pathway based on the current biochemical data on the kinetics of blood coagulation individual stages. The model includes eight differential equations describing the spatio-temporal dynamics of activation of factors XI, IX, X, II, I, VIII, V, and protein C. The assembly of tenase and prothrombinase complexes is considered as a function of calcium concentration. The spatial dynamics of coagulation was analyzed for the one-dimensional case. We examined the formation of active factors, their spreading, and growth of the clot from the site of injury in the direction perpendicular to the vessel wall, into the blood thickness. We assumed that the site of injury (in the model one boundary of the space segment under examination) becomes a source of the continuous influx of factor XIa. In the first part, we described the model, selected the parameters, etc. In the second part, we compared the model with experimental data obtained in the homogeneous system and analyzed the spatial dynamics of the clot growth.

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Molecular dynamics of blood coagulation is determined by the corresponding tasks of the organism: (i) to form rapidly the clot localized to the site of injury in response to the injury of the vessel wall, and (ii) to provide safe protection from the formation of spontaneous thrombi. Current biochemistry describes the coagulation system as a cascade of successively activated serine proteases interacting with a variety of inhibitors (1). The cascade includes a number of positive and negative feedbacks (1). Basic biochemical mechanisms that operate in blood coagulation to solve the temporal problem (which provides the necessary rate of clotting) and the spatial problem (which provides the localization of the clot to the site of injury) may be revealed by analyzing

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the contributions of individual reactions of the cascade to the entire coagulation process. Mathematical modeling is a useful tool to study this process.

Several mathematical models of blood coagulation were proposed earlier (2-5). One of the earliest models (2) contributed greatly to the understanding of how the kinetics of thrombin generation is affected by positive feedbacks of activation of cofactors V and VIII by thrombin. It was predicted that the existence of these feedbacks necessarily results in the threshold behavior of the coagulation process with respect to its activators. When stimulation is subthreshold, thrombi are not formed. The threshold response to damage is likely to be the best protection from spontaneous clot formation. The threshold properties of blood coagulation were experimentally demonstrated (6).
Mathematical models describing the coagulation kinetics of the extrinsic pathway (3-5) were proposed. These models include basic reactions of the extrinsic pathway with the reaction rates derived from the experiments in purified systems. Such detailed models enable more precise estimations of the kinetic rate constants for some reactions. They also allow the evaluation of those characteristics of the process that can not be measured directly in experiments: the threshold concentration of Factor Xa was calculated and appeared to be 10 pM (3). Such models are a valuable tool to predict the behavior of the system under different clinical or experimental conditions. For example, the kinetics of thrombin generation at different hirudin concentrations was correctly predicted (3). The complete mathematical model of the extrinsic pathway of blood coagulation constructed in (5) harmonized well with their coagulometric data.
All these models describe the homogeneous kinetics and do not examine a very important aspect of the problem - the dynamics of spreading of activated coagulation factors and the clot growth in space. Studying the spatio-temporal dynamics of the clot growth experimentally is a complicated problem. Theoretical examination of the spatial aspects of coagulation may help solve this problem. The model based on the kinetic description of individual stages of coagulation predicts how clots should grow.

In this study, a mathematical model of the intrinsic pathway of blood coagulation is proposed. No comprehensive dynamic model for this coagulation pathway is available in the literature. The aims of the modeling were: (i) to describe quantitatively the intrinsic pathway kinetics (6) and to analyze the threshold dependencies of thrombin generation kinetics on concentrations of Ca and the activator of coagulation; and (ii) to describe the spatial growth of fibrin clots.
The mathematical model is based on the well-known scheme of the reaction cascade with two positive feedbacks which are realized through the activation of cofactors V and VIII and the assembly of tenase and prothrombinase complexes. Negative feedbacks which are realized through the inactivation of factors Va and VIIIa by thrombin-activated protein C (APC) were also included into the model. The rate constants were estimated from the *in vitro* kinetics measured in purified systems of the isolated factors. The rates of the main reactions were written as functions of calcium. The model was verified by comparison with experimentally measured kinetics of thrombin generation at different concentrations of calcium (6).
This study comprises two parts. The first part describes the mathematical model of coagulation, its assumptions and limitations. We present the data for selecting the values of constants and fit them to the experimental kinetics of thrombin generation, measured for various concentrations of free calcium. The second part contains analysis

of the model. The model well describes experimental kinetics of the coagulation factors under assumption that a positive feedback involving factor V affects the kinetics of the whole system to a larger extent than that involving factor VIII. The model predicts several unexpected phenomena:

1. An increase in the effectiveness of protein C activation by thrombin (the effect equivalent to that of thrombomodulin) gives rise to several successive pulses of thrombin generation;

2. Analysis of spatial propagation of active factors shows that the successively arising thrombin pulses have the largest amplitude near the boundary of the clot; therefore, the edges of the clot should be denser than its core;

3. The pattern of thrombin propagation in the space dramatically depends on whether or not factor XI is activated by thrombin. The clot growth becomes unlimited at so small values of the rate constant for this reaction at which its contribution to the kinetics of the formation of active factors in a homogeneous system is negligible.

METHODS.

Numerical computations.
Numerical computations of the system of differential equations (appendix [1]-[8]) was performed by Merson's method (7). The spatial problem was numerically solved by the embedded Runge-Kutta-Fehlberg method (RKF2(3)) (7).

The model.
A set of differential equations (appendix [1]-[8]) corresponds to the scheme of biochemical reactions of the intrinsic pathway (TABLE I). Activation of the cascade leads to generation of thrombin which cleaves fibrinogen with formation of fibrin-monomers. Polymerization and clot formation were regarded as quick processes. 1a, 1b, 2a, 2b, 3a, 3b, 6a, 6b, 6c, 7c, 8a, 8b, 9, 10a and 10b (TABLE II) are the first-order reactions: $V = k \cdot E$. Reactions 7a, 7b obey to the Michaelis - Menten mechanism: $V = k_{cat} \cdot E \cdot S / (S + k_m)$. 2c, 3c, 4a, 4b, 5a and 5b are the second-order reactions: $V = k \cdot S1 \cdot S2$ (all necessary explanations are given below).

The kinetic constants for the reactions that form positive feedback loops differ only in the values of activation rates of cofactors V and VIII by thrombin (k_5 and k_8). Because of the lack of information in the literature, all the other constants (for degradation of the cofactors, association and dissociation of tenase and prothrombinase, and inactivation of the cofactors by APC) were assumed to be equal for both loops.

Fitting unknown rate constants.
The model was verified by comparison with experimental curves of thrombin generation recorded until first fibrin strands appeared (6). Numerical computations showed that concentrations of the precursors of active factors do not significantly change during this time interval. Therefore, depletion of the precursors was ignored, for the exception of that for thrombin. For reactions 6a, 6b, and 9, the Michaelis-Menten scheme was approximated by the first-order reaction scheme, and for reactions 2c, 3c, 4b, and 5b - by the second-order reaction scheme.

Initial concentrations of activated clotting factors (except for factor XIa concentration which is an indicator of the activation level) were set to zero. The initial concentration of prothrombin was 1000 nM.

TABLE I

Scheme of the cascade reactions.

Activation			inactivation		
(1a)	k_9	IX $\xrightarrow{\text{XIa}}$ IXa	(1b)	h_9	IXa+AT $\longrightarrow$ IXa-AT
(2a)	k_8	VIII $\xrightarrow{\text{IIa}}$ VIIIa	(2b)	h_8	VIIIa $\longrightarrow$ VIIIi
			(2c)	k_a	VIIIa $\xrightarrow{\text{APC}}$ VIIIi
(3a)	k_5	V $\xrightarrow{\text{IIa}}$ Va	(3b)	h_5	Va $\longrightarrow$ Vi
			(3c)	k_a	Va $\xrightarrow{\text{APC}}$ Vi
(4a)	$k_{8,9}$ $h_{8,9}$	VIIIa+IXa $\leftarrow$ $\longrightarrow$ VIIIa-IXa	(4b)	k_a	VIIIa-IXa $\xrightarrow{\text{APC}}$ VIIIi+IXa
(5a)	$k_{5,10}$ $h_{5,10}$	Va+Xa $\leftarrow$ $\longrightarrow$ Va-Xa	(5b)	k_a	Va-Xa $\xrightarrow{\text{APC}}$ Vi+Xa
(6a)	k_{10}	X $\xrightarrow{\text{IXa}}$ Xa	(6c)	h_{10}	Xa+AT $\longrightarrow$ Xa-AT
(6b)	$\overline{k_{10}}$	X $\xrightarrow{\text{IXa-VIIIa}}$ Xa			
(7a)	k_2	II $\xrightarrow{\text{Xa}}$ IIa	(7c)	h_{10}	IIa+AT $\longrightarrow$ Xa-AT
(7b)	$\overline{k_2}$	II $\xrightarrow{\text{Xa-Va}}$ IIa			
(8a)	k_{apc}	PC $\xrightarrow{\text{IIa}}$ APC	(8b)	h_{apc}	APC+L1-AT $\longrightarrow$ APC-L1-AT
(9)	k_1	fibrinogen $\xrightarrow{\text{IIa}}$ fibrin			
(10a)	k_{11}	XI $\xrightarrow{\text{IIa}}$ XIa	(10b)	h_{11}	XIa $\longrightarrow$ XIi

AT - antithrombin III, L1-AT - α1-antitrypsin, PC - protein C, APC - activated protein C. VIIIi and Vi - inactivated factors VIIIa and Va correspondingly, VIIIa-IXa - tenase, Va-Xa - prothrombinase.

Although the existence of thrombin activation of factor XI in plasma is controversial (8-10), we studied the possible effect of this reaction on the blood coagulation kinetics in a separate part of this paper (see part II. Results).

Activation of the system.
Factor XI is rapidly activated in plasma by contact with foreign surfaces (e.g., walls of a

TABLE II

Reactions rates of the simulation model.

Reaction		Kinetic parameters	References
(1a)	F	$k_9 = 20$ min^{-1}, [XIa] = 0.3 nM	(11,6)
(1b)	F	$h_9 = 0.2$ min^{-1}	(12)
(2a)	F	$k_8 = 0.00001$ min^{-1}	was varied
(2b)	F	$h_8 = 0.31$ min^{-1}	(13)
(2c)	S	$k_a = 1.2$ nM^{-1} min^{-1}	see text
(3a)	F	$k_5 = 0.17$ min^{-1}	was varied
(3b)	F	$h_5 = 0.31$ min^{-1}	see text
(3c)	S	$k_a = 1.2$ nM^{-1} min^{-1}	(14)
		($k_{cat} = 24$ min^{-1}, $k_m = 20$ nM)	
(4a)	S	$k_d = 1$ nM	(15)
(4b)	S	$k_a = 1.2$ nM^{-1} min^{-1}	see text
(5a)	S	$k_d = 1$ nM, $k_{5,10} > 100$ nM^{-1} min^{-1}	(16)
(5b)	S	$k_a = 1.2$ nM^{-1} min^{-1}	see text
(6a)	F	$k_{10cat.max} = 0.003$ min^{-1} for saturating concentrations of Ca^{2+}	(17)
(6b)	F	$\overline{k_{10cat.max}} = 500$ min^{-1} for saturating concentrations of Ca^{2+}	(17)
(6c)	F	$h_{10} = 1$ min^{-1}	(18)
(7a)	M	$k_{2cat.max} = 2.3$ min^{-1}, $k_{2m} = 58$ nM for saturating concentrations of Ca^{2+}	(19)
(7b)	M	$\overline{k_{2cat.max}} = 2000$ min^{-1}, $\overline{k_{2m}} = 210$ nM for saturating concentrations of Ca^{2+}	(19)
(7c)	F	$h_2 = 1.3$ min^{-1}	(3)
(8a)	F	$k_{apc} = 0.0014$ min^{-1}	(3)
(8b)	F	$h_{apc} = 0.1$ min^{-1}	(20)
(9)	F	$k_1 = 2.82$ min^{-1} (0.047 s^{-1})	(5)
(10a)	F	$k_{11} = 0.0078$ min^{-1}	(8)
(10b)	F	$h_{11} = 0.2$ min^{-1}	(21)

M = Michaelis-Menten mechanism: $V = k_{cat} \cdot E \cdot S / (S + k_m)$

F = First-order reaction: $V = k \cdot E$

S = Second-order reaction: $V = k \cdot S1 \cdot S2$

quartz cuvette). The quasi-stationary concentration of factor XIa was established in less than 0.2 min and then did not change during an hour (6). We interested in the coagulation kinetics from 0 to 1 - 100 minutes. Therefore, the concentration of factor XIa was treated as constant. To describe experimental results (6), factor XIa was

assumed to be 0.3 nM, according to our estimates derived from the values of amidolytic activity of plasma towards a synthetic substrate S2366 (6).

Formation and inactivation of factor IXa.
Kinetic constants for the activation of factor IX by factor XIa and inactivation of factor IXa by ATIII were estimated from the experiments described in (11,12).

Formation and inactivation of tenase and prothrombinase.
According to (16), the assembly of prothrombinase can be considered as a reaction of binding of factors Va and Xa to phospholipid membrane followed by the association of phospholipid-bound factors Va and Xa.
The rate of prothrombinase assembly increases with increasing concentration of phospholipids (PL) and reaches maximum at 10 uM (22). The experiments to verify the model were performed at saturating concentrations of PL (6). Therefore, we considered the binding of active factors to PL to be fast and the assembly of prothrombinase complex to be a second-order reaction between factors Va and Xa, already bound to PL.
Information on tenase assembly is scarce (17,23). We assumed that the binding of factors VIIIa and IXa to PL when PL present in excess (10 uM (17,23)) occurs quickly and that the rate constants for the association of the PL-bound factors VIIIa and IXa are equal to the corresponding constants for factors Va and Xa (15). Thus, the two positive feedbacks differed only in constants for the activation of factors V and VIII by thrombin (k_5 and k_8). These constants were varied to find the best fit to the experimental data (6). Large rate constants for the prothrombinase and tenase reactions justify a suggestion that concentrations of the complexes are quasi-stationary (see appendix).
The rate constants for inactivation by APC of cofactors bound to the corresponding complex were assumed to be equal to those of free (uncomplexed) cofactors.

Generation and inactivation of factors VIIIa and Va.
We suggested that factors V and VIII are activated only by thrombin. In addition, thrombin cleaves several other substrates (fibrinogen, protein C, and a synthetic peptide which is used to determine the thrombin activity). The competition between many substrates for thrombin decreases the effective rate constants for cleavage of cofactors. Therefore, it is difficult to find out the correct values of effective constants k_5 and k_8 under real conditions. We estimated these constants from numerical experiments varying their values until the best agreement with experimental data was achieved (6).
Analysis of the model showed that passive inactivation of all active factors in plasma is a prerequisite for the experimentally demonstrated threshold behavior of the system with respect to calcium. Inactivation of factors Va and VIIIa is poorly studied. We suggested that these factors decay in plasma at equal rates. The rate constant for inactivation of factor VIIIa (h_8) in the purified system was 0.31 min^{-1} (13). We assumed that h_5 is also 0.31 min^{-1}.
In addition to passive degradation, factors Va and VIIIa in plasma are cleaved by APC (1,14). The kinetic constants for proteolysis of factor VIIIa by APC are unknown; therefore, we admitted that APC is equally effective with respect to catalytic inactivation of factors VIIIa and Va.
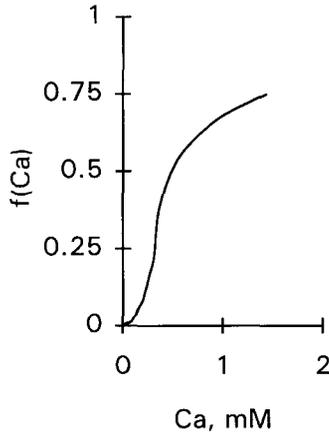
FIG. 1.

The function f(Ca) approximating the experimental data
(17,19,23,24) that was used in our numerical calculations.

Generation and inactivation of factor Xa and thrombin. Effect of calcium.
There are two ways of activation of factor X. It can be cleaved at a small rate by factor
IXa or at a significantly greater rate by tenase (17). Similarly, prothrombin is converted
to thrombin both by factor Xa and prothrombinase (19,24). The curve of changes in the
rate of each of these four reactions with increasing calcium concentration is S-shaped
(17, 19, 23, 24). The kinetic rate constants for them were written as
$k_{cat} = k_{cat.max} \cdot f(Ca) + k_{cat0}$, where $k_{cat.max}$ and k_{cat0} are the rate constants at
saturating and zero Ca^{2+} concentrations, respectively; f(Ca) is an S-shaped function,
which approximates the experimental data (17,19,23,24) $(0 \leq f(Ca) \leq 1)$. F(Ca) was
assumed to be the same for all four constants (Fig.1). In the absence of Ca^{2+} the
assembly of tenase or prothrombinase does not occur, i.e., k_{cat} is zero for these two
reactions. The rate constants for activation of factor X by factor IXa and factor II by
factor Xa in the absence of Ca^{2+}, are 0.0003 min^{-1} and 0.15 min^{-1}, respectively
(17,19). The kcatmax values for all four reactions are presented in Table II.
The inactivation of factors Xa and IIa in plasma with participation AT is a pseudofirst
order reaction (3,18).

Generation and inactivation of protein C.
Thrombin is activator of protein C in plasma (16,25,26). The rate constant for this
reaction (k_{apc}) is 0.0014 min^{-1} in the absence of thrombomodulin (3). Thrombomodulin
is a cofactor of this reaction and accelerates it significantly (16). There are other factors
that also can accelerate this reaction (26). Therefore, we analyzed the coagulation
kinetics varying kapc from 0.0014 to 0.1 min^{-1}.
APC is inactivated by inhibitors that are always present in plasma. Alpha-1-antitrypsin
is believed to be the main APC inhibitor (20). The rate constant for this pseudofirst-
order reaction was estimated from (20) to be 0.1 min^{-1}.

Spatial dynamics of the clot growth.
Using the model developed (see appendix), we examined how the concentrations of

active factors change in time and space for the simplest one-dimensional case corresponding to the activation by an infinite plane. The mathematical model of the spatial growth of the clot differs from the homogeneous model of thrombin generation by the diffusion terms. This leads to the set of differential equations in partial derivatives.

We considered the behavior of the system at a 1.5-mm segment of the straight line under assumption of equal diffusion coefficients D for all factors ($D = 6 \cdot 10^{-4} mm^2 min^{-1}$ (27)). The initial concentrations of all active factors were set to zero. Activation of the system was caused by a constant influx of factor XIa from the left boundary of the segment. The value of the influx from the boundary was estimated from observations on contact activation of coagulation by glass reported in (6). Zero fluxes were taken as the boundary conditions for factor XIa at the right end of the segment and for all other factors at both its ends.

DISCUSSION

Intrinsic and extrinsic pathways of coagulation share several common stages. Therefore, it was reasonable to compare our estimates of the rate constants for these stages with those obtained in studies modeling the extrinsic pathway (3,4). Mathematical models of the extrinsic pathway describe well the activation kinetics of various coagulation factors (including thrombin generation). Under conditions of those experiments, an explosive rise in the thrombin concentration is observed at times of the order of 1 min; therefore, in the corresponding models, the contribution of activation processes significantly exceeded that of the processes of inactivation of activated factors. In contrast, we were interested in the behavior of the system in response to small activations when the accelerated thrombin generation begins tens min after triggering. Numerical computations showed that both activation and inactivation characteristics determine the kinetics of the coagulation process. Particularly important characteristics are the rate constants for inactivation of factors Va and VIIIa in plasma. However, at present, there is little relevant information (only the proteolysis by activated PC is studied).

The model shows that passive inactivation of active factors in plasma is a prerequisite for the existence of the threshold dependence of coagulation on free calcium concentration. There is little information on inactivation of factors Va and VIIIa in plasma. We assumed that the constants of inactivation of these factors coincide and are equal to the value determined for factor VIIIa decay in the purified system (13). Their values affect the values of generalized parameters k_5 and k_8 which characterize the intensity of the positive feedbacks in the model. When new information on the inactivation kinetics of factors Va and VIIIa in plasma becomes available, new values will be easily calculated for these parameters.

We also assumed that only thrombin activates cofactors V and VIII. Analysis of the model showed that, at any moment of time, thrombin concentration far exceeds the factor Xa concentration; therefore, the relative contribution of factor Xa to the activation of factors V and VIII is very small in the intrinsic pathway. This is in contrast to the extrinsic pathway where, at initial stages after its triggering, factor Xa is essential for activation of the cofactors (4).

To describe the experimental results reported in (6), we varied k_5 and k_8 which characterize the strength of the feedbacks. The best coincidence of the theoretical and

experimental curves was achieved when k_5 was assumed to exceed k_8 significantly (Table II). This implies that the feedback through factor Va is much stronger than that through factor VIIIa. Note that k_5 and k_8 are not equal to the rate constants for activation of the cofactors by thrombin determined in the purified systems because they are the generalized model parameters constructed with regard for the competition of several substrates for thrombin and the uncertainties in the rates of degradation of factors Va and VIIIa in plasma and rates of the assembly and dissociation of tenase and prothrombinase complexes.

The lack of information on the kinetic constants characterizing the feedback through factor VIIIa (including those characterizing the assembly of tenase) leads to some uncertainty in their values. For example, in the mathematical model of the extrinsic pathway of coagulation (4), it was suggested that tenase assembly is slow $(k_{8,9} = 0.6 \text{ nM}^{-1}\text{min}^{-1})$ and is accompanied by passive degradation of the complex. The rate constants for activation of factors V and VIII were assumed to be equal. With regard for the concentrations of both factors in plasma, this implies that the rate for factor V activation is 30 times greater than that for factor VIII. K.C. Jones and K.G. Mann (4) also indicated that, because of insufficient information, other values of the kinetic constants characterizing the strength of the feedbacks are also possible.

The model described in (4) is based on the experimental data which show the stronger effect of factor V (vs. factor VIII) on the coagulation kinetics. There was no thrombin formation in the absence of factor V, whereas the absence of factor VIII only somewhat decreased the rate of thrombin production. Moreover, a tenfold decrease in the rate of tenase assembly significantly decreased the rate of thrombin production. This effect was equivalent to the switch of the feedback through factor VIII off (i.e., to the absence of factor VIII in the system). Our results that the feedback through factor VIII only slightly affects the coagulation kinetics are consistent with the observations described in (4).

The model proposed describes how the kinetics of the intrinsic pathway of coagulation depends on calcium and activator concentrations, parameters of all individual stages of the process. The model also describes spreading of the activated factors in space without hydrodynamic fluxes in terms of their concentrations expressed as functions of the distance from the activating surface. The second part of this report contains the results obtained.

Appendix.
The mathematical model for the homogeneous case is presented by the following set of differential equations [1]-[8]:

[1] $$\frac{dIXa}{dt} = k_9 \cdot XIa - h_9 \cdot IXa = f_{IXa}$$

[2] $$\frac{dXa}{dt} = k_{10} \cdot IXa + \overline{k_{10}} \cdot Z - h_{10} \cdot Xa = f_{Xa}$$

[3] $\dfrac{dIIa}{dt} = k_2 \cdot Xa \cdot \dfrac{II}{(II + k_{2m})} + \overline{k_2} \cdot W \cdot \dfrac{II}{(II + \overline{k_{2m}})} - h_2 \cdot IIa = f_{IIa}$

[4] $\dfrac{dII}{dt} = -k_2 \cdot Xa \cdot \dfrac{II}{(II + k_{2m})} - \overline{k_2} \cdot W \cdot \dfrac{II}{(II + \overline{k_{2m}})} = f_{II}$

[5] $\dfrac{dVIIIa}{dt} = k_8 \cdot IIa - h_8 \cdot VIIIa - k_a \cdot APC \cdot (VIIIa + Z) = f_{VIIIa}$

[6] $\dfrac{dVa}{dt} = k_5 \cdot IIa - h_5 \cdot Va - k_a \cdot APC \cdot (Va + W) = f_{Va}$

[7] $\dfrac{dAPC}{dt} = k_{apc} \cdot IIa - h_{apc} \cdot APC = f_{APC}$

[8] $\dfrac{dIa}{dt} = k_1 \cdot IIa = f_{Ia}$

The model variables are concentrations of factors IXa, Xa, IIa (thrombin), II (prothrombin), VIIIa, Va, APC (activated protein C), and Ia (fibrin). The coagulation factors are designated by roman numerals according to the standard system of designations. Activated factors are supplemented with a subscript "a". K_i is the rate constant for activation of the i-th factor; h_i is the rate constant for inactivation of the i-th factor by plasma inhibitors.

Z (tenase) and W (prothrombinase) are assumed to be quick variables. Their quasistationary concentrations were calculated by setting the right-hand sides of the corresponding equations to zero:

$$Z = \dfrac{k_{8,9} \cdot VIIIa \cdot IXa}{(h_{8,9} + k_a \cdot APC)} \; ; \; W = \dfrac{k_{5,10} \cdot Va \cdot Xa}{(h_{5,10} + k_a \cdot APC)}$$

The initial concentration of prothrombin was taken equal to its concentration in normal plasma (1000 nM).

The spatial model was written as a set of eight differential equations in partial derivatives and one ordinary differential equation for fibrin production:

$$\dfrac{\partial F}{\partial t} = f_F + D \cdot \dfrac{\partial^2 F}{\partial x^2}$$

where F denotes IXa, Xa, IIa, II, VIIIa, Va, and APC; f_F are the right-hand side of the corresponding equations of the homogeneous model,

$$\frac{\partial XIa}{\partial t} = -h_{11} + D \cdot \frac{\partial^2 XIa}{\partial x^2} \; ;$$

$$\frac{dIa}{dt} = k_1 \cdot IIa$$

Boundary conditions used were as follows:

$$\left.\frac{\partial XIa}{\partial x}\right|_{x=0} = A \; , \; \left.\frac{\partial XIa}{\partial x}\right|_{x=L} = 0 \; , \; \left.\frac{\partial F}{\partial x}\right|_{x=0;L} = 0$$

where A is the activation level at the point $x = 0$; F = IXa, Xa, IIa, VIIIa, Va, and APC. XIa = IXa = Xa = IIa = Va = VIIIa = Ia = APC = 0 and II(t = 0)=1000 nM were chosen as initial conditions.

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