



## Contact Activation of Blood Coagulation: Trigger Properties and Hysteresis

### Kinetic Recognition of Foreign Surfaces upon Contact Activation of Blood Coagulation: A Hypothesis

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A mathematical model of contact activation of blood coagulation was developed and analysed. The model variables are concentrations of factor XIIa, kallikrein and activated high-molecular-weight kininogen. Concentrations of active factors were shown to depend on the activating signal value in a hysteretic manner. Within a range of relatively small signals, two (activated and non-activated) stable states coexist (bistability). Signals of the natural environment (surfaces of endothelial and blood cells) seem to be in the range of bistability; therefore, contact activation that persists for a short time can induce a transition of the system to the activated state, and, correspondingly, the formation of a clot. The system cannot return to the initial state, which is characterized by low activation levels, until the activating signals decrease significantly below those present in the circulation.

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#### 1. Introduction

The intrinsic pathway of blood coagulation is activated in plasma contacting any foreign surface. Blood coagulation can also be activated through the extrinsic pathway, which is thought to be a major pathway by many researchers (Colman & Schmaier, 1986; Lawson *et al.*, 1994; Willems *et al.*, 1991). This pathway is extensively studied, both experimentally and by means of mathematical modelling (Beguin *et al.*, 1988; Lawson *et al.*, 1994; Willems *et al.*, 1991). The physiological function of the intrinsic pathway and even its involvement in the blood coagulation process *in vivo* are yet to be discussed. This pathway comprises more reactions than the extrinsic pathway. Both reaction cascades, which culminate in the activation of prothrombin and formation of a clot (Van Dam-Mieras & Muller, 1986), exhibit similar kinetics (Beguin *et al.*, 1988; Lawson *et al.*, 1994; Ataullakhanov *et al.*, 1994). The known models of the intrinsic pathway describe it beginning from the appearance of activated factor XI (Khanin & Semenov, 1989; Zarnitsina *et al.*, 1996). Factor XI is

activated in a complicated set of reactions, which is considered as a separate system, the so-called contact activation system. It remains unclear what are the kinetic tasks of this system.

The first enzyme, which triggers all other events, is factor XII (Colman & Schmaier, 1986). Upon contact with the activating surface, factor XII becomes activated and initiates the reactions that lead to the activation of factor XI. The coagulation process exhibits threshold properties (Khanin & Semenov, 1989; Ataullakhanov *et al.*, 1994). When the level of activation exceeds the threshold, an irreversible transition of blood from liquid to solid occurs at exponentially increasing rates. It is vitally important that the blood coagulation system remained unresponsive to all substances and surfaces that normally contact the blood. In other words, the system should recognise “self” and “foreign” elements in its environment. Note that artificial surfaces, as well as cell surfaces that normally do not contact the blood (e.g. those from connective tissue), are recognised as foreign. The recognition function is very important; however, the mechanisms involved have yet to be

clarified. No relevant data are available in the literature. A similar function is inherent to the immune system. A huge spectrum of immunoglobulins is involved in the immune recognition. Each immunoglobulin distinguishes only one antigenic determinant. Current data and concepts do not suggest that similar diversity exists in the blood coagulation system (Colman & Schmaier, 1986; Kaplan & Silverberg, 1987). We believe that the recognition function is implemented by the contact activation system, although only factor XII and several additional proteins are involved in the process.

From theoretical analysis of the kinetics of reactions of contact activation, we suggested that a kinetic mechanism operates to implement the recognition function. It is possible that the reactions of contact activation are organised as a biochemical trigger exhibiting strong hysteretic properties. Below, we show that such kinetics provide effective recognition.

## 2. Mathematical Model of the Blood Contact Activation System

Let us consider in detail the reactions of contact activation. Active enzymes (factors) are indicated by a subscript a. Factor XII is the first protease in this system. It is converted into the activated form by changing its conformation upon binding to a foreign surface. Factor XIIa cleaves a small peptide from factor XI giving factor XIa. Activation of factor XI is the first reaction of the proteolytic cascade leading to the appearance of fibrin and clot formation (Van Dam-Mieras & Muller, 1986).

Activation of factors XII and XI is greatly contributed to by two proteins, kallikrein and activated high-molecular-weight kininogen (HMWKa), which are generated from their precursors, prekallikrein (PK) and high-molecular-weight kininogen (HMWK). Kallikrein is a protease, and HMWK plays a cofactor role in the activation of kallikrein and factor XI. A large variety of reactions between these four proteins and activating surfaces are described in the literature (Colman & Schmaier, 1986; Kaplan & Silverberg, 1987).

Key events in this complicated network begin from binding of factor XII to the surface. Bound factor XII can be either autoactivated or activated by kallikrein. Factor XIIa activates PK on the surface more effectively than in solution. HMWK and HMWKa play an important role in this process. They form complexes with PK and provide its target delivery to the surface. Compared with HMWK, HMWKa

exhibits a higher affinity to activating surfaces. Kallikrein cleaves HMWK giving HMWKa. Factor XIIa also activates HMWK, but does it less effectively. We did not consider in the model that Factor XIa inactivates HMWKa, because the rate of this reaction is lower than the rate of activation of HMWK (Scott *et al.*, 1985). Therefore, this simplification can have some effect on the behavior of the system only at large times, but leaves the qualitative characteristics of the system (in particular, the existence of hysteresis) unaffected. Also, we did not take into account activation of Factor XI and prekallikrein in solution, because the rate of these reactions are much lower than for those at the surface (Griffin & Cochrane, 1976; Akiyama *et al.*, 1986). All active forms are progressively inactivated by inhibitors.

The most important reactions that occur at the surface are shown in Fig. 1. We assume that (1) in reversible binding reactions, quasiequilibrium is rapidly achieved and (2) only surface-bound factor XII and PK can be activated. Therefore, the rates of their activation are determined by the concentration of free binding sites at the surface. The amount of these free binding sites depends on the concentrations of factor XIIa and HMWKa. Let us first consider the case where the consumption of the precursors can be neglected. The scheme in Fig. 1 is then described by the following equations:

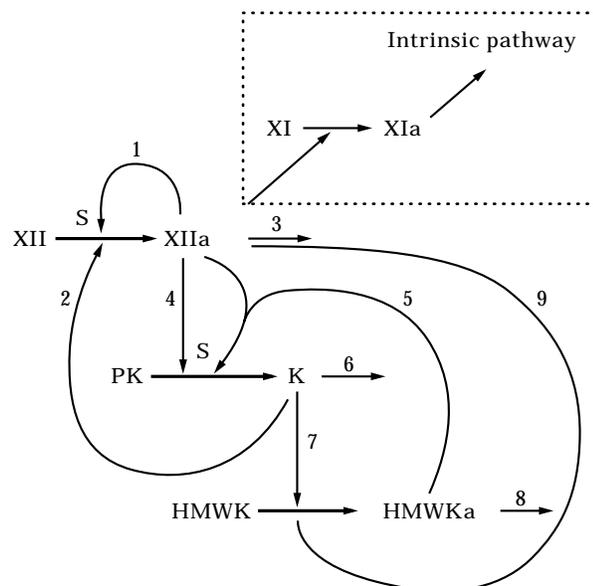


Fig. 1. Scheme of major reactions of the contact activation. See text for designations. "S" denotes the reactions that run at the surface. Box: Relationship of contact activation to the intrinsic pathway of blood coagulation. Figures marking arrows correspond to rate constant indexes [see set (1)].

TABLE 1  
Constant values to solve set (1)

Constant	Value	Units	References	Comments
$K_1$	$2 \cdot 10^{-6}$	$\text{nM}^{-1} \text{sec}^{-1}$	Tankersley & Finlayson, 1984	
$K_2$	$4 \cdot 10^{-4}$	$\text{nM}^{-1} \text{sec}^{-1}$	Tankersley & Finlayson, 1984	
$K_3$	0.007	$\text{sec}^{-1}$	Pixley <i>et al.</i> , 1985	
$K_4$	0.1	$\text{nM}^{-2} \text{sec}^{-1}$		Varied, see text
$K_5$	0.012	nM	Tankersley & Finlayson, 1984	$K_5 K_4 = 1.2 \text{sec}^{-1} \mu\text{M}^{-1}$
$K_6$	0.011	$\text{sec}^{-1}$	Graaf <i>et al.</i> , 1983	
$K_7$	0.2	$\text{sec}^{-1}$	Tayeh <i>et al.</i> , 1994	[HMWK] = 700 nM
$K_9$	0.01	$\text{sec}^{-1}$	Wiggins <i>et al.</i> , 1983	$K_7/K_9 = 20$
$K_8$	0.002	$\text{sec}^{-1}$		Assumption, see text

$$\frac{dX}{dT} = K_1(S - X - Z)X + K_2(S - X - Z)Y - K_3X$$

$$\frac{dY}{dT} = K_4X(S - X - Z)(Z + K_5) - K_6Y$$

$$\frac{dZ}{dT} = K_7Y + K_9X - K_8Z \quad (1)$$

$$\frac{dx}{dt} = k_1x(s - x - z) + y(s - x - z) - k_3x$$

$$\epsilon_1 \frac{dy}{dt} = x(s - x - z)(z + k_5) - k_6y$$

$$\epsilon_2 \frac{dz}{dt} = y + k_9x - k_8z \quad (2)$$

where  $X$ ,  $Y$ , and  $Z$  denote the concentrations of factor XIIa, kallikrein, and HMWKa, respectively;  $K_i$  are constants for the reactions shown in Fig. 1.  $S$  and  $(S - X - Z)$  are the initial and current concentrations of the binding sites at the surface. For simplicity, we assume that factor XII and HMWKa compete for the same binding sites at the surface.

In the equation for  $X$ , the first term describes the autoactivation of factor XII upon binding with the activating surface. The second term describes the activation of factor XII by kallikrein. The last term describes the inactivation of factor XIIa.

In the equation for  $Y$ , we assume that activation of PK depends on multicomponent interaction between factor XIIa ( $X$ ), the surface ( $S - X - Z$ ), and HMWKa. Kallikrein can also be formed in the absence of HMWKa (in this case, a prekallikrein-non-activated HMWK complex enters the reaction). Therefore, we took a sum of HMWKa ( $Z$ ) and a certain constant  $K_5$  rather than only HMWKa as a multiplier in the product of concentrations. The second term in this equation describes the inactivation of kallikrein.

The equation for  $Z$  describes the activation of HMWK by kallikrein and factor XIIa (the first and second terms, respectively). As in the previous equations, the last term describes the inactivation of HMWKa.

Taking  $x = X/C_0$  ( $C_0 = 1 \text{ nM}$ ),  $y = Y/C_0$ ,  $z = Z/C_0$ ,  $t = K_2 C_0 T$ ,  $s = S/C_0$ ,  $k_1 = K_1/K_2$ ,  $k_3 = K_3/(K_2 C_0)$ ,  $k_5 = K_5/C_0$ ,  $k_6 = K_6/(K_4 C_0^2)$ ,  $k_9 = K_9/K_7$ ,  $k_8 = K_8/K_7$ ,  $\epsilon_1 = K_2/(K_4 C_0)$ , and  $\epsilon_2 = K_2 C_0/K_7$ , we can rewrite (1) in the dimensionless form:

Table 1 shows the rate constants for the reactions described by set (1), which were estimated from data available in the literature. We scaled the values of  $K_1$ ,  $K_2$ , and  $K_5$  (which were measured in Tankersley & Finlayson, 1984) to a unit concentration of surface binding sites, suggesting from the data in Tankersley & Finlayson (1984) that 1 nM dextran sulfate contains binding sites at a concentration of 0.6 nM.  $K_7$  was scaled to the concentration of HMWK in plasma (see Table 1). We are not aware of any data to estimate  $K_4$  and  $K_8$ . Therefore, we arbitrarily set  $K_8$  to  $0.002 \text{ sec}^{-1}$  and varied the value of  $K_4$  in a broad range. For  $K_4$  from  $0.01$  to  $100 \text{ nM}^{-2} \text{sec}^{-1}$ , the hysteresis (see below) was observed. Table 2 shows the dimensionless constants used in set (2).

Let us consider the dynamics of model (2) for various values of  $s$ . Activation of factor XII is the slowest stage. As seen from Table 1  $\epsilon_1$  and  $\epsilon_2 < 1$ . It should be noted that

$$\epsilon_1 > \epsilon_2 \quad (3)$$

Then, at long times, model (2) asymptotically approaches to:

$$\frac{dx}{dt} = k_1x(s - x - z) + y(s - x - z) - k_3x$$

$$\epsilon_1 \frac{dy}{dt} = x(s - x - z)(z + k_5) - k_6y \quad (4)$$

TABLE 2  
Constant values used to solve set (2)

Constant	$k_1$	$k_3$	$k_5$	$k_6$	$k_8$	$k_9$
Value	0.005	17.5	0.012	0.11	0.01	0.05

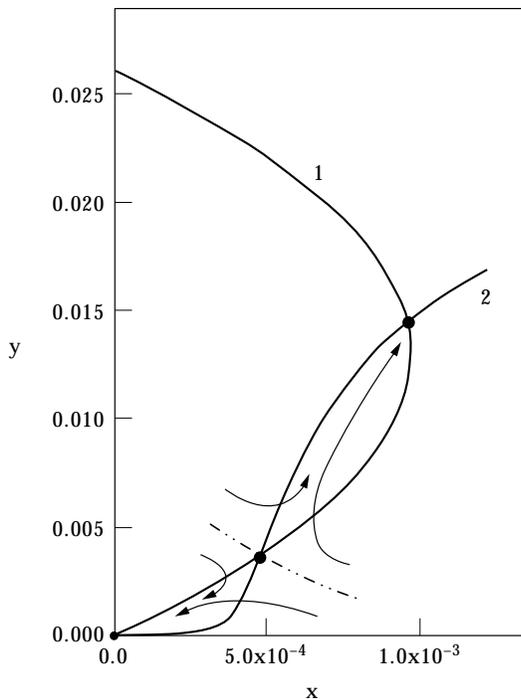


FIG. 2. Phase portrait of set (4) for  $s = 2.6$ . Null-clines  $dx/dt = 0$  and  $dy/dt = 0$  are marked by figures 1 and 2, respectively. (---) is a separatrix of the saddle point.

where  $z = (y + k_9x)/k_8$ . Numerical computation of the systems of differential equations was performed by the embedded Runge–Kutta–Fehlberg method (Hairer *et al.*, 1987).

### 3. Results

Figure 2 shows the phase portrait of model (4) for  $s = 2.6$ . Within a certain range of parameters, as many as three steady states are possible in this system. Let us consider the bifurcations occurring with increasing  $s$ . For small  $s < s_1^*$ ,  $s_1^* = 2.35$ , a single zero steady state of the stable node type exists. In the range  $s_1^* < s < s_2^*$ ,  $s_2^* = 12.64$ , two new singular points are born (Fig. 2). The zero steady state remains to be a stable node, and the second stable node appears. The third singular point, a saddle, is located between these two. At  $s > s_2^*$ , the saddle coalesces with the zero singular point. Upon this bifurcation, the zero singular point is retained, but its stability changes. This point converts to an unstable node.

Figure 3 shows the steady-state concentration of  $y$  as a function of  $s$ . As can be seen, in the range  $s_1^* < s < s_2^*$ , the system is bistable and exhibits a strong hysteresis. In other words, the system, which is initially in the zero singular point, does not become activated when  $s$  increases to  $s_2^*$ .

The value of  $s_2^*$  can be easily determined from the condition of tangency of the null-clines at the point  $(0, 0)$ . Linearization of set (4) in the vicinity of the zero singular point leads to the following equations:

$$\begin{aligned} \frac{dx}{dt} &= x(k_1s - k_3) + ys \\ e_1 \frac{dy}{dt} &= xs k_5 - y k_6 \end{aligned} \quad (5)$$

Using this set, we obtain

$$s_2^* = \frac{\sqrt{(k_1k_6)^2 + 4k_5k_3k_6} - k_1k_6}{2k_5}.$$

At  $s$  exceeding  $s_2^*$ , a jump into the activated state (the upper branch of the hysteresis, see Fig. 3) is observed. After the jump, the system remains in the activated state until  $s > s_1^*$ . The hysteretic behavior is observed over the range of fivefold changes in  $s$ . If  $s > s_2^*$ , an increase in  $s$  causes a proportional increase in the concentration of activated factors. Qualitative behavior of the system does not change upon varying other parameters of the model in a broad range: a region in the parameter space could be always identified where hysteresis exists. Small variations in the parameters caused the proportional changes in the phase portrait and the kinetics of the system.

In model (1), we neglected that the precursors of active factors can be depleted. Using the values of constants shown in Table 2, we obtained under this assumption that kallikrein can reach a maximum of 0.15 nM (Fig. 3). This value is lower than the concentration of prekallikrein (600 nM) by three orders of magnitude (Bouma & Griffin, 1986). The concentrations of activated factors do not increase unlimitedly, because binding sites at the surface are

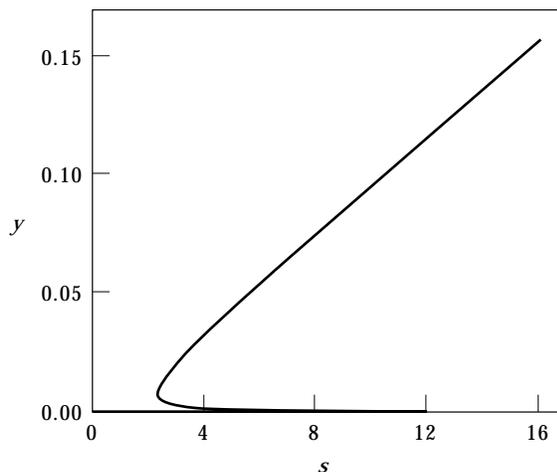


FIG. 3. Steady-state concentration of kallikrein ( $y$ ) as a function of the value of  $s$  calculated from set (4).

depleted. Let us consider the situation when depletion of the precursors can stop the process. To this end, we rewrite set (2) in the following form:

$$\begin{aligned}\frac{dx}{dt} &= k_1xs(1 - x/x_0) + ys(1 - x/x_0) - k_3x \\ \epsilon_1 \frac{dy}{dt} &= xs(1 - y/y_0)(z + k_5) - k_6y \\ \epsilon_2 \frac{dz}{dt} &= (y + k_9x)(1 - z/z_0) - k_8z\end{aligned}\quad (6)$$

where  $C_0 = 1$  nM;  $x = X/C_0$ ,  $y = Y/C_0$ , and  $z = Z/C_0$  are the dimensionless concentrations of factor XIIa, kallikrein, and HMWka, respectively; dimensionless  $x_0 = 400$ ,  $y_0 = 600$ , and  $z_0 = 700$  are the total concentrations of the precursors of factor XII, PK, and HMWK, respectively; (Bouma & Griffin, 1986) and  $s = S/C_0$ . The values of the constants are shown in Table 2. If conditions (3) are satisfied, set (6) is equivalent at long times to:

$$\begin{aligned}\frac{dx}{dt} &= k_1xs(1 - x/x_0) + ys(1 - x/x_0) - k_3x \\ \epsilon_1 \frac{dy}{dt} &= xs(1 - y/y_0)(z + k_5) - k_6y\end{aligned}$$

where  $z = z_0(y + k_9x)/(k_8z_0 + y + k_9x)$ . (7)

Figure 4 shows the steady-state concentration  $y$  as a function of  $s$ . As can be seen, effects of limitations upon the concentrations of precursors on the model kinetics are qualitatively similar to those produced by limitations upon the concentration of binding sites. However, compared with the previous model, the hysteresis exists in a significantly broader range of  $s$  values ( $5.8 \cdot 10^{-5} < s < 1.2 \cdot 10^{-2}$ ). At  $s > 1.2 \cdot 10^{-2}$ , the upper branch of stable states of the system reaches the plateau. Model (7) is also remarkable in that the branch corresponding to the unstable steady-state solution (saddle) is running in close proximity to the  $x$ -axis (Fig. 4, see the inset made on an enlarged scale).

#### 4. Discussion

Analysis of the mathematical model of the simplest reaction scheme of contact activation shows that it possesses bistable behavior, which is characterized by a strong hysteresis. In our opinion, such a kinetic of contact activation has many advantages: (1) coagulation should proceed rapidly and irreversibly. Within

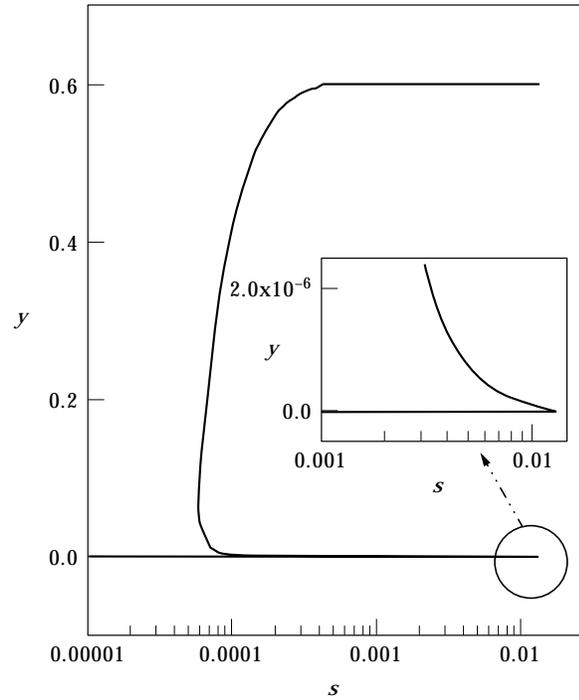


FIG. 4. Steady-state concentration of kallikrein ( $y$ ) as a function of the value of  $s$  calculated from set (7). The inset shows the encircled region on an enlarged scale.

a body, it occurs under blood flow conditions. Therefore, slow transition of blood to the solid state or incomplete coagulation are extremely dangerous. Semisolid portions of the blood, which are saturated with activated coagulation factors, can be borne by circulation and induce multiple thrombi. The kinetics providing the formation of a solid well-developed thrombus, which is lysed when it is needed no longer, is superior over the slow kinetics leading to the appearance of semicoagulated blood. As seen from Fig. 4, the trigger pattern of concentration dependence of active factors (e.g. kallikrein) on the value of activating signals is best suited to this task. Actually, an entire range of transient low concentrations of kallikrein are unobservable at any activating signals. Once the activation threshold  $s_2^*$  is overcome, kallikrein rapidly increases, reaching high levels. Even if the source of activation is then eliminated, the kallikrein concentration remains at this high level. The thrombus will form rapidly and until completion; (2) there is no need for a special activation protein sensitive to physicochemical properties of activating surfaces. It will suffice that an entire diversity of self cells normally contacting the blood create activation signals, which do not exceed the threshold. The signal for activation can be dynamic. This is consistent with the induction of coagulation by severe shear stresses, which are experienced by circulating blood cells in the

site of vascular injury (O'Brien, 1990). After activation like this, even surfaces with activating properties comparable with those of the surface of blood cells will not prevent the coagulation.

Most inexplicable coagulation phenomena can be accounted for by the "hysteresis" hypothesis of activation of blood coagulation. For example, many materials with weak activating properties are known. Nevertheless, in blood containers made of any of them, blood coagulates (Merrill, 1987). *In vitro*, blood coagulates even upon contact with surfaces chemically modified with natural components of plasma, e.g. albumin (Eberhart *et al.*, 1987). It seems plausible that, at the moment of withdrawal, the blood is strongly activated (in model terms, the system appears on the branch corresponding to the activated state). If  $s$  then returns to the initial values, which correspond to the non-activated state of the blood, the activated state is retained due to hysteresis. As a result, we observe that blood coagulates *in vitro* under any conditions. Hysteresis in contact activation of blood coagulation displays one interesting feature. Usually, in systems with hysteresis, only two (high and low) levels of the output signal are possible. In contact activation, high input signals (outside the hysteretic loop) lead to proportional outputs (see Fig. 3), suggesting that the presence of hysteresis is unlikely. In experiments, activation signals are usually high. The proportionality between the input and output signals observed in these experiments is commonly suggested to extend to low levels of activation signals. For this reason, possibly, there exists no direct evidence for either the proportionality or hysteresis in contact activation under conditions of low-level activating signals.

Figure 3 shows the steady-state kallikrein concentration vs.  $s$ , calculated from model (2). Non-reduced set (1) has a qualitatively similar dependence, including hysteresis. The trigger behavior of model (1) is determined by two properties of its phase space topology: (1) the square law of the time dependence of the rate of production of  $x$  in the vicinity of zero, which makes it possible that three steady-state points appear in the system; (2) the existence of the positive feedback from kallikrein to factor XII, which is described by the second term of eqn (1). The presence of this feedback causes the slope of the null-cline  $dx/dt = 0$  to vary from a certain maximum to negative values with increasing  $s$ . Thus, the entire positive quadrant is scanned, including those ranges of  $s$  where the system behaves as a trigger with strong hysteresis. The appearance of hysteresis can also be provided by the autocatalysis in the production of  $x$ , which is described by the first term in eqn (1). Such

a behavior is general for all models displaying the same features as those described for model (1).

At the molecular level, the trigger properties of the contact activation reaction network are largely determined by the two long-known things: (1) factor XIIa can activate PK within its complex with already activated HMWK; (2) Factor XII can be activated by kallikrein.

In general, contact activation depends not only on these two reactions. Other processes, including complex formation between HMWK, HMWKA and kallikrein, PK, factors XI, XIa, binding of these complexes to the surface, reactions of free and surface-bound complexes with factor XII and XIIa (including  $\beta$ -XIIa), and cleavage of HMWK by factor XIa, are also very important for the overall result. However, our analysis showed that the two reactions mentioned above suffice to provide the hysteretic properties of the entire system. We believe that the contribution of other processes can modify, but does not cancel the hysteretic properties of contact activation of blood coagulation.

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