Supplementary Information

Blood Clot Formation Under Flow: The Importance of Factor XI Depends Strongly on Platelet Count

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We present here the equations of the model used to generate the results of the paper as well as a listing of parameters and their values.

Notation and Example Terms:

The coagulation reactions we consider are listed in Tables 1-8. Z_i and E_i refer to zymogen i and enzyme i in solution. A superscript 'm' indicates a membrane-bound versions of these proteins (e.g., E_7^m refers to the TF:VIIa complex and E_5^m refers to Factor Va bound to the platelet surface). Concentrations are denoted in a similar way but with lower-case z and e. A complex of Z_i and E_j is denoted $Z_i : E_j$ and its concentration is denoted $[Z_i : E_j]$. Special symbols are used for the platelet-bound 'tenase' VIIIa:IXa and 'prothrombinase' Va:Xa complexes, $TEN =$ VIIIa:IXa and $PRO=$ Va:Xa, and $[TEN]$ and $[PRO]$ denote their respective concentrations. The special symbol $TFPIa$ is used for the fluid-phase complex TFPI:Xa, and $[TFPIa]$ denotes its concentration. The inhibitors are denoted APC and $TFPI$ and their concentrations are denoted $[APC]$ and $[TFPI]$.

The concentrations of unactivated, subendotelial bound, and activated but not subendothelial bound platelets are denoted PL, PL_s^a, and PL_a^v, respectively. Platelet binding sites for coagulation proteins are denoted P_i or P_i^*. The former refers to binding sites for the zymogen i or for zymogen and enzyme i. The latter refers to binding sites only for enzyme i. The number of P_i or P_i^* binding sites is denoted N_i or N_i^*. The concentration p_i or p_i^* of each of these binding sites is needed in the model equations. It is obtained by multiplying the corresponding N_i or N_i^*, respectively, by the concentration of activated platelets $PL_s^a + PL_v^a$.

Most of the terms in the equations which follow reflect straightforward mass-action kinetic descriptions of

i) binding and unbinding from surface binding sites, *e.g.*,

$$k_7^{\text{on}} e_7 [TF]^{\text{avail}} - k_7^{\text{off}} e_7^m;$$

ii) association and dissocation of chemical species in the fluid or on a surface, *e.g.*,

$$k^+_{e_5^m:e_{10}^m} e_5^m e_{10}^m - k^-_{e_5^m:e_{10}^m}[PRO];$$

iii) enzyme-substrate complex formation and dissociation and activation of the substrate, *e.g.*,

$$k^+_{z_{10}:e_7^m} z_{10} e_7^m - (k^{\text{cat}}_{z_{10}:e_7^m} + k^-_{z_{10}:e_7^m})[Z_{10} : E_7^m].$$

In the first of these, $[TF]^{\text{avail}}$ is the concentration of TF molecules that are not already bound to fVII or fVIIa and are therefore available for binding by these factors.

Other terms describe transport of chemicals or platelets into or out of the reaction zone, *e.g.*,

$$k_{\text{flow}}(z_7^{\text{up}} - z_7)$$

or between the reaction zone and the adjacent endothelial zone, *e.g.*,

$$k_{\text{diff}}(e_2 - e_2^{ec}).$$

The transport coefficients are given by the formulas

$$k_{\text{flow}} = 3/4 \left(\frac{\gamma^2 D}{4L^2}\right)^{1/3} \qquad \text{and} \qquad \mathrm{k_{diff}} = \frac{\mathrm{2D}}{\mathrm{W_{ec}}\left(\frac{\mathrm{W}}{2} + \mathrm{W_{ec}}\right)}, \qquad \text{where} \qquad \mathrm{W_{ec}} = \sqrt{4/3}\left(\frac{\mathrm{2LD}}{\gamma}\right)^{1/3},$$

is the effective width of the endothelial zone. In these formulas, γ is the shear rate of the flow, D is the diffusion coefficient, and L and W are the length and width of the injury, respectively. These expressions are derived in (Fogelson and Tania, 2005; Kuharsky and Fogelson, 2001). A number of equations include terms of the form

$$-e_7^m \frac{d}{dt}\left[PL_a^s\right] \frac{1}{p_{PLAS}^{\text{avail}}}$$

which describe the reduction in activity of a subendothelial species due to progressive coverage of the subendothelium by adherent platelets. Further discussion of these terms, model assumptions, and parameter estimation can be found in (Fogelson and Tania, 2005; Kuharsky and Fogelson, 2001).

Prothrombin and Thrombin Binding to Platelets:

In the earlier version of our model (Fogelson and Tania, 2005; Kuharsky and Fogelson, 2001), we assumed that prothrombin and thrombin competed for binding sites on an activated platelet. Since these papers were published, it has become increasingly clear that this is an inaccurate description of the biology (Kamath and Krishnaswamy, 200). In our new model, we assume that there are separate binding sites on the platelet for prothrombin and thrombin. Now, when a prothrombin molecule bound to a platelet is activated by prothrombinase, the resulting thrombin molecule immediately is released into the plasma, where it is subject to inhibition by ATIII and to being carried away by the flow. We assume it can also rebind to a thrombin-specific site on an activated platelet. It is well-documented that thrombin activates fV, fVIII, and fXI on the platelet surface, but the platelet site(s) at which thrombin is bound while doing so has not been identified (Lundblad and II, 2005) and so no kinetic data is available for these putative sites. (Thrombin is known to bind to GPIbα (Baglia et al., 2004; Celikel et al., 2003) and this might put it in a good position to activate fXI since fXI also binds to GPIbα (Emsley et al., 2010; White-Adams et al., 2009). Thrombin also binds to platelet PAR1 and PAR4 receptors Coughlin (2005)) The number of binding sites per platelet and the rates at which thrombin binds to and unbinds from these sites are parameters required by the model. In the face of these facts, we proceeded by adjusting the value of these parameters to achieve results which matched those of the earlier model over a range of levels of TF exposure and shear rates. Our rationale is that, since the earlier model made predictions that have been validated experimentally, that model is a reasonable standard against which to assess the quality of the new model with separate prothrombin and thrombin binding sites. In this way, we found that rather than using 2000 binding sites shared by prothrombin and thrombin as before, we should use 1000 binding sites specific to prothrombin, 1000 additional sites specific to thrombin, and a dissociation constant for thrombin of 20 nM. These are all physiologically plausible values.

We note that thrombin may be inhibited by other chemicals in addition to ATIII, including protese nexin I and heparin cofactor II Boulaftali et al. (2011); Rau et al. (2011). These are not included in the model. We emphasize that in model simulations at shear rates of $50s^{-1}$ or more, flow-mediated removal of thrombin is,far and away, the dominant inhibitor of thrombin activity in the reaction zone.

Equations of the Model:

Terms in blue are new terms added to the models in (Fogelson and Tania, 2005; Kuharsky and Fogelson, 2001) to incorporate the fXI reactions. Terms in red are changes to the earlier models to reflect our current assumption that prothrombin and thrombin have distinct binding sites on activated platelets.

$$
\begin{aligned}
[TF]^{\text{avail}} &= [TF] - z_7^m - e_7^m - [Z_7^m : E_{10}] - [Z_7^m : E_2] - [Z_{10} : E_7^m] \\
&\quad -[Z_9 : E_7^m] - [TPFI : E_{10} : E_7^m] - [Z_7^m : E_9] \\
p_{PLAS}^{\text{avail}} &= p_{PLAS} - [PL_a^s] \\
p_5^{\text{avail}} &= p_5 - z_5^m - e_5^m - [Z_5^m : E_{10}^m] - [Z_5^m : E_2^m] \\
&\quad -[APC : E_5^m] - [PRO] - [Z_2^m : PRO] \\
p_8^{\text{avail}} &= p_8 - z_8^m - e_8^m - [TEN] - [Z_8^m : E_{10}^m] - [Z_8^m : E_2^m] \\
&\quad -[Z_{10}^m : TEN] - [APC : E_8^m] - [TEN^*] - [Z_{10}^m : TEN^*] \\
p_9^{\text{avail}} &= p_9 - z_9^m - e_9^m - [TEN] - [Z_{10}^m : TEN] \\
&\quad -[Z_9^m : E_{11}^{h,m}] - [Z_9^m : E_{11}^{m*}] \\
p_9^{*,\text{avail}} &= p_9^* - e_9^{m*} - [TEN^*] - [Z_{10}^m : TEN^*] \\
p_{10}^{\text{avail}} &= p_{10} - z_{10}^m - e_{10}^m - [Z_5^m : E_{10}^m] - [Z_8^m : E_{10}^m] \\
&\quad -[PRO] - [Z_2^m : PRO] - [Z_{10}^m : TEN] - [Z_{10}^m : TEN^*] \\
p_2^{\text{avail}} &= p_2 - z_2^m - [Z_2^m : PRO] \\
p_2^{*,\text{avail}} &= p_2^* - e_2^m - [Z_5^m : E_2^m] - [Z_8^m : E_2^m] - [Z_{11}^m : E_2^m] - [E_{11}^{h,m*} : E_2^m] \\
p_{11}^{\text{avail}} &= p_{11} - z_{11}^m - e_{11}^{h,m} - [Z_9^m : E_{11}^{h,m}] - [Z_{11}^m : E_2^m] \\
p_{11}^{*,\text{avail}} &= p_{11}^* - e_{11}^{h,m*} - e_{11}^{m*} - [Z_9^m : E_{11}^{m*}] - [E_{11}^{h,m*} : E_2^m] \\
[TM]^{\text{avail}} &= ([TM] - [TM : E_2^{ec}] - [TM : E_2^{ec} : APC])
\end{aligned}
$$

$$
\begin{aligned}
\frac{d}{dt}\, z_7 \;&=\; k_{\text{flow}}(z_7^{\text{up}} - z_7) - k_7^{\text{on}} z_7 [TF]^{\text{avail}} + k_7^{\text{off}} z_7^m - \; k^+_{z_7:e_2} z_7 e_2 \\
&\quad + k^-_{z_7:e_2}[Z_7 : E_2] - \; k^+_{z_7:e_{10}} z_7 e_{10} + k^-_{z_7:e_{10}}[Z_7 : E_{10}]
\end{aligned} \tag{1}
$$

$$
\frac{d}{dt}\, e_7 \;=\; k_{\text{flow}}(e_7^{\text{up}} - e_7) - k_7^{\text{on}} e_7 [TF]^{\text{avail}} + k_7^{\text{off}} e_7^m + k^{\text{cat}}_{z_7:e_2}[Z_7 : E_2] + k^{\text{cat}}_{z_7:e_{10}}[Z_7 : E_{10}] \tag{2}
$$

$$
\begin{aligned}
\frac{d}{dt}\, z_7^m \;&=\; k_7^{\text{on}} z_7 [TF]^{\text{avail}} - k_7^{\text{off}} z_7^m - k^+_{z_7^m:e_{10}} z_7^m e_{10} + k^-_{z_7^m:e_{10}}[Z_7^m : E_{10}] \\
&\quad - k^+_{z_7^m:e_2} z_7^m e_2 + k^-_{z_7^m:e_2}[Z_7^m : E_2] - z_7^m \frac{d}{dt}\,[PL_a^s]\frac{1}{p^{\text{avail}}_{PLAS}}
\end{aligned} \tag{3}
$$

$$
\begin{aligned}
\frac{d}{dt}\, e_7^m \;&=\; k_7^{\text{on}} e_7 [TF]^{\text{avail}} - k_7^{\text{off}} e_7^m \\
&\quad - k^+_{TPFI:e_{10}:E_7^m} e_7^m [TFPI : E_{10}] + k^-_{TPFI:e_{10}:E_7^m}[TPFI : E_{10} : E_7^m] \\
&\quad + k^{\text{cat}}_{z_7^m:e_{10}}[Z_7^m : E_{10}] + k^{\text{cat}}_{z_7^m:e_2}[Z_7^m : E_2] \\
&\quad + (k^{\text{cat}}_{z_{10}:e_7^m} + k^-_{z_{10}:e_7^m})[Z_{10} : E_7^m] - k^+_{z_{10}:e_7^m} z_{10} e_7^m \\
&\quad + (k^{\text{cat}}_{z_9:e_7^m} + k^-_{z_9:e_7^m})[Z_9 : E_7^m] - k^+_{z_9:e_7^m} z_9 e_7^m - e_7^m \frac{d}{dt}\,[PL_a^s]\frac{1}{p^{\text{avail}}_{PLAS}}
\end{aligned} \tag{4}
$$

$$
\frac{d}{dt}\, z_{10} \;=\; k_{\text{flow}}(z_{10}^{\text{up}} - z_{10}) - k_{10}^{\text{on}} z_{10}\; p_{10}^{\text{avail}} + k_{10}^{\text{off}} z_{10}^m - k^+_{z_{10}:e_7^m} z_{10} e_7^m + k^-_{z_{10}:e_7^m}[Z_{10} : E_7^m] \tag{5}
$$

$$
\begin{aligned}
\frac{d}{dt}\, e_{10} \;&=\; k_{\text{flow}}(e_{10}^{\text{up}} - e_{10}) - k_{\text{diff}}(e_{10} - e_{10}^{ec}) - k_{10}^{\text{on}} e_{10}\; p_{10}^{\text{avail}} + k_{10}^{\text{off}} e_{10}^m + k^{\text{cat}}_{z_{10}:e_7^m}[Z_{10} : E_7^m] \\
&\quad + (k^{\text{cat}}_{z_7:e_{10}} + k^-_{z_7:e_{10}})[Z_7 : E_{10}] - k^+_{z7:e10} z_7 e_{10} \\
&\quad + (k^{\text{cat}}_{z_7^m:e_{10}} + k^-_{z_7^m:e_{10}})[Z_7^m : E_{10}] - k^+_{z_m^7:e_{10}} z_7^m e_{10} \\
&\quad - k^+_{TFPI:e_{10}} e_{10}[TFPI] + k^-_{TFPI:e_{10}}[TFPI : E_{10}] - k^{\text{in}}_{AT:e_{10}} e_{10}
\end{aligned} \tag{6}
$$

$$
\begin{aligned}
\frac{d}{dt}\, z_{10}^m \;&=\; k_{10}^{\text{on}} z_{10}\; p_{10}^{\text{avail}} - k_{10}^{\text{off}} z_{10}^m - k^+_{z_{10}^m:ten} z_{10}^m [TEN] + k^-_{z_{10}:ten}[Z_{10}^m : TEN] \\
&\quad - k^+_{z_{10}^m:ten} z_{10}^m [TEN^*] + k^-_{z_{10}:ten}[Z_{10}^m : TEN^*]
\end{aligned} \tag{7}
$$

$$
\begin{aligned}
\frac{d}{dt}\, e_{10}^m \;&=\; k_{10}^{\text{on}} e_{10}\; p_{10}^{\text{avail}} - k_{10}^{\text{off}} e_{10}^m + k^{\text{cat}}_{z_{10}^m:ten}[Z_{10}^m : TEN] \\
&\quad + (k^{\text{cat}}_{z_5^m:e_{10}^m} + k^-_{z_5^m:e_{10}^m})[Z_5^m : E_{10}^m] - k^+_{z_5^m:e_{10}^m} z_5^m e_{10}^m \\
&\quad + (k^{\text{cat}}_{z_8^m:e_{10}^m} + k^-_{z_8^m:e_{10}^m})[Z_8^m : E_{10}^m] - k^+_{z_8^m:e_{10}^m} z_8^m e_{10}^m \\
&\quad + k^-_{e_5^m:e_{10}^m}[PRO] - k^+_{e_5^m:e_{10}^m} e_{10}^m e_5^m + k^{\text{cat}}_{z_{10}^m:ten}[Z_{10}^m : TEN^*]
\end{aligned} \tag{8}
$$

$$\frac{d}{dt}\ z_5 = k_{\text{flow}}(z_5^{\text{up}} - z_5) - k_5^{\text{on}} z_5\ p_5^{\text{avail}} + k_5^{\text{off}} z_5^m - k^+_{z_5:e_2} z_5 e_2 + k^-_{z_5:e_2}[Z_5 : E_2]$$
$$+ n_5\Big(k^+_{\text{adh}}\ p^{\text{avail}}_{PLAS} + k^{\text{act}}_{\text{plt}}\Big([PL^v_a] + [PL^s_a]\Big) + k^{\text{act}}_{\text{e2}}\frac{e_2}{(e_2 + 0.001)}\Big)[PL] \quad (9)$$

$$\frac{d}{dt}\ e_5 = k_{\text{flow}}(e_5^{\text{up}} - e_5) - k_5^{\text{on}} e_5\ p_5^{\text{avail}} + k_5^{\text{off}} e_5^m$$
$$+ k^{\text{cat}}_{z_5:e_2}[Z_5 : E_2] + k^-_{e5:APC}[APC : E_5] - k^+_{e5:APC}[APC]e_5 \quad (10)$$

$$\frac{d}{dt}\ z_5^m = k_5^{\text{on}} z_5\ p_5^{\text{avail}} - k_5^{\text{off}} z_5^m - k^+_{z_5^m:e_{10}^m} z_5^m e_{10}^m + k^-_{z_5^m:e_{10}^m}[Z_5^m : E_{10}^m]$$
$$- k^+_{z_5^m:e_2^m} z_5^m e_2^m + k^-_{z_5^m:e_2^m}[Z_5^m : E_2^m] \quad (11)$$

$$\frac{d}{dt}\ e_5^m = k_5^{\text{on}} e_5\ p_5^{\text{avail}} - k_5^{\text{off}} e_5^m + k^{\text{cat}}_{z_5^m:e_{10}^m}[Z_5^m : E_{10}^m] + k^{\text{cat}}_{z_5^m:e_2^m}[Z_5^m : E_2^m]$$
$$+ k^-_{e_5^m:APC}[APC : E_5^m] - k^+_{e_5^m:APC}[APC]e_5^m$$
$$- k^+_{e_5^m:e_{10}^m} e_5^m e_{10}^m + k^-_{e_5^m:e_{10}^m}[PRO] \quad (12)$$

$$\frac{d}{dt}\ z_8 = k_{\text{flow}}(z_8^{\text{up}} - z_8) - k_8^{\text{on}} z_8\ p_8^{\text{avail}} + k_8^{\text{off}} z_8^m - k^+_{z_8:e_2} z_8 e_2 + k^-_{z_8:e_2}[Z_8 : E_2] \quad (13)$$

$$\frac{d}{dt}\ e_8 = k_{\text{flow}}(e_8^{\text{up}} - e_8) - k_8^{\text{on}} e_8\ p_8^{\text{avail}} + k_8^{\text{off}} e_8^m + k^{\text{cat}}_{z_8:e_2}[Z_8 : E_2] - 0.005 e_8$$
$$+ k^-_{e_8:APC}[APC : E_8] - k^+_{e_8:APC}[APC]e_8 \quad (14)$$

$$\frac{d}{dt}\ z_8^m = k_8^{\text{on}} z_8\ p_8^{\text{avail}} - k_8^{\text{off}} z_8^m - k^+_{z_8^m:e_{10}^m} z_8^m e_{10}^m + k^-_{z_8^m:e_{10}^m}[Z_8^m : E_{10}^m]$$
$$- k^+_{z_8^m:e_2^m} z_8^m e_2^m + k^-_{z_8^m:e_2^m}[Z_8^m : E_2^m] \quad (15)$$

$$\frac{d}{dt}\ e_8^m = k_8^{\text{on}} e_8\ p_8^{\text{avail}} - k_8^{\text{off}} e_8^m + k^{\text{cat}}_{z_8^m:e_{10}^m}[Z_8^m : E_{10}^m] + k^{\text{cat}}_{z_8^m:e_2^m}[Z_8^m : E_2^m]$$
$$- k^+_{e_8^m:APC}[APC]e_8^m + k^-_{e_8^m:APC}[APC : E_8^m] - 0.005 e_8^m$$
$$- k^+_{e_8^m:e_9^m} e_9^m e_8^m + k^-_{e_8^m:e_9^m}[TEN] - k^+_{e_8^m:e_9^m} e_8^m e_9^{m*} + k^-_{e_8^m:e_9^m}[TEN^*] \quad (16)$$

$$\frac{d}{dt}\, z_9 = k_{\text{flow}}(z_9^{\text{up}} - z_9) - k_9^{\text{on}}\; p_9^{\text{avail}} z_9 + k_9^{\text{off}} z_9^m - k^+_{z_9:e_7^m} z_9 e_7^m + k^-_{z_9:e_7^m}[Z_9 : E_7^m] \quad (17)$$
$$-k^+_{z_9:e_{11}^h} z_9 e_{11}^h + k^-_{z_9:e_{11}^h}[Z_9 : E_{11}^h] - k^+_{z_9:e_{11}} z_9 e_{11} + k^-_{z_9:e_{11}}[Z_9 : E_{11}]$$

$$\frac{d}{dt}\, e_9 = k_{\text{flow}}(e_9^{\text{up}} - e_9) - k_{\text{diff}}(e_9 - e_9^{ec}) - k_9^{\text{on}}\; p_9^{\text{avail}} e_9 + k_9^{\text{off}} e_9^m + k^{\text{cat}}_{z_9:e_7^m}[Z_9 : E_7^m] - k^{\text{in}}_{AT:e_9} e_9 \quad (18)$$
$$+(k^{\text{cat}}_{z7:e9} + k^-_{z_7:e_9})[Z_7 : E_9] - k^+_{z_7:e_9} z_7 e_9$$
$$+(k^{\text{cat}}_{z_7^m:e_9} + k^-_{z_7^m:e_9})[Z_7^m : E_9] - k^+_{z_7^m:e_9} z_7^m e_9$$
$$-k_9^{\text{on}}\; p_9^{*,\text{avail}} e_9 + k_9^{\text{off}} e_9^{m*} + k^{\text{cat}}_{z_9:e_{11}^h}[Z_9 : E_{11}^h] + k^{\text{cat}}_{z_9:e_{11}}[Z_9 : E_{11}]$$

$$\frac{d}{dt}\, z_9^m = k_9^{\text{on}}\; p_9^{\text{avail}} z_9 - k_9^{\text{off}} z_9^m - k^+_{z_9^m:e_{11}^{h,m}} z_9^m e_{11}^{h,m} + k^-_{z_9^m:e_{11}^{h,m}}[Z_9^m : E_{11}^{h,m}] \quad (19)$$
$$-k^+_{z_9^m:e_{11}^{m*}} z_9^m e_{11}^{m*} + k^-_{z_9^m:e_{11}^{m*}}[Z_9^m : E_{11}^{m*}]$$

$$\frac{d}{dt}\, e_9^m = k_9^{\text{on}}\; p_9^{\text{avail}} e_9 - k_9^{\text{off}} e_9^m + k^-_{e_8^m:e_9^m}[TEN] - k^+_{e_8^m:e_9^m} e_8^m e_9^m \quad (20)$$
$$+k^{\text{cat}}_{z_9^m:e_{11}^{h,m}}[Z_9^m : E_{11}^{h,m}] + k^{\text{cat}}_{z_9^m:e_{11}^{m*}}[Z_9^m : E_{11}^{m*}]$$

$$\frac{d}{dt}\, z_2 = k_{\text{flow}}(z_2^{\text{up}} - z_2) - k_2^{\text{on}}\; p_2^{\text{avail}} z_2 + k_2^{\text{off}} z_2^m \quad (21)$$

$$\frac{d}{dt}\, e_2 = k_{\text{flow}}(e_2^{\text{up}} - e_2) - k_{\text{diff}}(e_2 - e_2^{ec}) + k^{\text{cat}}_{z2m:PRO}[Z_2^m : PRO] \quad (22)$$
$$-k_{2*}^{\text{on}}\; p_2^{*,\text{avail}} e_2 + k_{2*}^{\text{off}} e_2^m - k^{\text{in}}_{AT:e_2} e_2$$
$$+(k^{\text{cat}}_{z_5:e_2} + k^-_{z_5:e_2})[Z_5 : E_2] - k^+_{z_5:e_2} z_5 e_2$$
$$+(k^{\text{cat}}_{z_8:e_2} + k^-_{z_8:e_2})[Z_8 : E_2] - k^+_{z_8:e_2} z_8 e_2$$
$$+(k^{\text{cat}}_{z_7:e_2} + k^-_{z_7:e_2})[Z_7 : E_2] - k^+_{z_7:e_2} z_7 e_2$$
$$+(k^{\text{cat}}_{z_7^m:e_2} + k^-_{z_7^m:e_2})[Z_7^m : E_2] - k^+_{z_7^m:e_2} z_7^m e_2$$
$$-k^+_{z_{11}:e_2} z_{11} e_2 + (k^-_{z_{11}:e_2} + k^{\text{cat}}_{z_{11}:e_2})[Z_{11} : E_2]$$
$$-k^+_{e_{11}^h:e_2} e_{11}^h e_2 + (k^-_{e_{11}^h:e_2} + k^{\text{cat}}_{e_{11}^h:e_2})[E_{11}^h : E_2]$$

$$\frac{d}{dt}\, z_2^m = k_2^{\text{on}}\; p_2^{\text{avail}} z_2 - k_2^{\text{off}} z_2^m - k^+_{z_2^m:PRO} z_2^m PRO + k^-_{z_2^m:PRO}[Z_z^m : PRO] \quad (23)$$

$$\frac{d}{dt}\, e_2^m = k_{2*}^{\text{on}}\; p_2^{\text{avail}} e_2 - k_{2*}^{\text{off}} e_2^m + (k^{\text{cat}}_{z_5^m:e_2^m} + k^-_{z_5^m:e_2^m})[Z_5^m : E_2^m] - k^+_{z_5^m:e_2^m} z_5^m e_2^m \quad (24)$$
$$+(k^{\text{cat}}_{z_8^m:e_2^m} + k^-_{z_8^m:e_2^m})[Z_8^m : E_2^m] - k^+_{z_8^m:e_2^m} z_8^m e_2^m$$
$$-k^+_{z_{11}^m:e_2^m} z_{11}^m e_2^m + (k^-_{z_{11}^m:e_2^m} + k^{\text{cat}}_{z_{11}^m:e_2^m})[Z_{11}^m : E_2^m]$$
$$-k^+_{e_{11}^{h,m*}:e_2^m} e_{11}^{h,m*} e_2^m + (k^-_{e_{11}^{h,m*}:e_2^m} + k^{\text{cat}}_{e_{11}^{h,m*}:e_2^m})[E_{11}^{h,m*} : E_2^m]$$

$$\frac{d}{dt}[TEN] = -k^{-}_{e_8^m:e_9^m}[TEN] + k^{+}_{e_8^m:e_9^m} e_8^m e_9^m + (k^{\text{cat}}_{z_{10}^m:TEN} + k^{-}_{z_{10}:TEN})[Z_{10}^m : TEN] - k^{+}_{z_{10}^m:TEN} z_{10}^m [TEN] \quad (25)$$

$$\frac{d}{dt}[PRO] = -k^{-}_{e_5^m:e_{10}^m}[PRO] + k^{+}_{e_5^m:e_{10}^m} e_{10}^m e_5^m + (k^{\text{cat}}_{z_2^m:PRO} + k^{-}_{z_2^m:PRO})[Z_2^m : PRO] - k^{+}_{z_2^m:PRO} z_2^m [PRO] \quad (26)$$

$$\frac{d}{dt}[PL_a^s] = k^{+}_{\text{adh}}\, p^{\text{avail}}_{PLAS}[PL] - k^{-}_{\text{adh}}[PL_a^s] + k^{+}_{\text{adh}}[PL_a^v]\, p^{\text{avail}}_{PLAS} \quad (27)$$

$$\frac{d}{dt}[PL] = k^{p}_{\text{flow}}\Big([PL]^{\text{up}} - [PL]\Big) - \Big(k^{+}_{\text{adh}}\, p^{\text{avail}}_{PLAS} + k^{\text{act}}_{\text{plt}}\Big([PL_a^v] + [PL_a^s]\Big) + k^{\text{act}}_{\text{e2}} \frac{e_2}{e_2 + 0.001}\Big)[PL] \quad (28)$$

$$\frac{d}{dt}[PL_a^v] = k^{-}_{\text{adh}}[PL_a^s] - k^{+}_{\text{adh}}[PL_a^v]\, p^{\text{avail}}_{PLAS} + \Big(k^{\text{act}}_{\text{plt}}\Big([PL_a^v] + [PL_a^s]\Big) + k^{\text{act}}_{\text{e2}} \frac{e_2}{e_2 + 0.001}\Big)[PL] \quad (29)$$

$$\frac{d}{dt}[TFPI] = k_{\text{flow}}([TPFI]^{\text{up}} - [TFPI]) - k^{+}_{TFPI:e_{10}} e_{10}[TFPI] + k^{-}_{TFPI:e_{10}}[TFPI : Xa] \quad (30)$$

$$\frac{d}{dt}[TFPI : E_{10}] = -k_{\text{flow}}[TFPI : E_{10}] + k^{+}_{TFPI:e_{10}} e_{10}[TFPI] - k^{-}_{TFPI:e_{10}}[TFPI : E_{10}] + k^{-}_{TFPI:e_{10}:e_7^m}[TFPI : E_{10} : E_7^m] - k^{+}_{TFPI:e_{10}:e_7^m} e_7^m [TFPI : E_{10}] \quad (31)$$

$$\frac{d}{dt}[TFPI : E_{10} : E_7^m] = -k^{-}_{TFPI:e_{10}:e_7^m}[TFPI : E_{10} : E_7^m] + k^{+}_{TFPI:e_{10}:e_7^m} e_7^m [TFPI : E_{10}] - [TFPI : E_{10} : E_7^m] \frac{d}{dt}[PL_a^s] \frac{1}{p^{\text{avail}}_{PLAS}} \quad (32)$$

$$\frac{d}{dt}[APC] = k_{\text{flow}}\Big([APC]^{\text{up}} - [APC]\Big) - k_{\text{diff}}\Big([APC] - [APC^{ec}]\Big) + (k^{\text{cat}}_{e_5^m:APC} + k^{-}_{e_5^m:APC})[APC:E_5^m] - k^{+}_{e_5^m:APC}\ e_5^m[APC] + (k^{\text{cat}}_{e_8^m:APC} + k^{-}_{e_8^m:APC})[APC:E_8^m] - k^{+}_{e_8^m:APC}\ e_8^m[APC] + (k^{\text{cat}}_{e_5:APC} + k^{-}_{e_5:APC})[APC:E_5] - k^{+}_{e_5:APC}\ e_5[APC] + (k^{\text{cat}}_{e_8:APC} + k^{-}_{e_8:APC})[APC:E_8] - k^{+}_{e_8:APC}\ e_8[APC] \quad (33)$$

$$\frac{d}{dt}[APC:E_8^m] = k^{+}_{e_8^m:APC}\ e_8^m[APC] - (k^{\text{cat}}_{e_8^m:APC} + k^{-}_{e_8^m:APC})[APC:E_8^m] \quad (34)$$

$$\frac{d}{dt}[APC:E_5^m] = k^{+}_{e_5^m:APC}\ e_5^m[APC] - (k^{\text{cat}}_{e_5^m:APC} + k^{-}_{e_5^m:APC})[APC:E_5^m] \quad (35)$$

$$\frac{d}{dt}[APC:E_5] = k^{+}_{e_5:APC}\ e_5[APC] - (k^{\text{cat}}_{e_5:APC} + k^{-}_{e_5:APC})[APC:E_5] \quad (36)$$

$$\frac{d}{dt}[APC:E_8] = k^{+}_{e_8:APC}\ e_8[APC] - (k^{\text{cat}}_{e_8:APC} + k^{-}_{e_8:APC})[APC:E_8] \quad (37)$$

$$\frac{d}{dt}[Z_7:E_2] = k_{\text{flow}}\Big([Z_7:E_2]^{\text{up}} - [Z_7:E_2]\Big) + k^{+}_{z_7:e_2} z_7 e_2 - (k^{\text{cat}}_{z_7:e_2} + k^{-}_{z_7:e_2})[Z_7:E_2] \quad (38)$$

$$\frac{d}{dt}[Z_7:E_{10}] = k_{\text{flow}}\Big([Z_7:E_{10}]^{\text{up}} - [Z_7:E_{10}]\Big) + k^{+}_{z_7:e_{10}} z_7 e_{10} - (k^{\text{cat}}_{z_7:e_{10}} + k^{-}_{z_7:e_{10}})[Z_7:E_{10}] \quad (39)$$

$$\frac{d}{dt}[Z_7^m:E_{10}] = k^{+}_{z_7^m:e_{10}} z_7^m e_{10} - (k^{\text{cat}}_{z_7^m:e_{10}} + k^{-}_{z_7^m:e_{10}})[Z_7^m:E_{10}] - [Z_7^m:E_{10}]\frac{d}{dt}[PL_a^s]\frac{1}{p^{\text{avail}}_{PLAS}} \quad (40)$$

$$\frac{d}{dt}[Z_7^m:E_2] = k^{+}_{z_7^m:e_2} z_7^m e_2 - (k^{\text{cat}}_{z_7^m:e_2} + k^{-}_{z_7^m:e_2})[Z_7^m:E_2] - [Z_7^m:E_2]\frac{d}{dt}[PL_a^s]\frac{1}{p^{\text{avail}}_{PLAS}} \quad (41)$$

$$\frac{d}{dt}[Z_{10}:E_7^m] = k^{+}_{z_{10}:e_7^m} z_{10} e_7^m - (k^{\text{cat}}_{z_{10}:e_7^m} + k^{-}_{z_{10}:e_7^m})[Z_{10}:E_7^m] - [Z_{10}:E_7^m]\frac{d}{dt}[PL_a^s]\frac{1}{p^{\text{avail}}_{PLAS}} \quad (42)$$

$$\frac{d}{dt}\,[Z_{10}^m:TEN] = k^+_{z_{10}^m:TEN} z_{10}^m [TEN] - (k^{\text{cat}}_{z_{10}^m:TEN} + k^-_{z_{10}:TEN})[Z_{10}^m:TEN] \tag{43}$$

$$\frac{d}{dt}\,[Z_5:E_2] = k_{\text{flow}}\Big([Z_5:E_2]^{\text{up}} - [Z_5:E_2]\Big) + k^+_{z_5:e_2} z_5 e_2 - (k^{\text{cat}}_{z_5:e_2} + k^-_{z_5:e_2})[Z_5:E_2] \tag{44}$$

$$\frac{d}{dt}\,[Z_5^m:E_{10}^m] = k^+_{z_5^m:e_{10}^m} z_5^m e_{10}^m - (k^{\text{cat}}_{z_5^m:e_{10}^m} + k^-_{z_5^m:e_{10}^m})[Z_5^m:E_{10}^m] \tag{45}$$

$$\frac{d}{dt}\,[Z_5^m:E_2^m] = k^+_{z_5^m:e_2^m} z_5^m e_2^m - (k^{\text{cat}}_{z_5^m:e_2^m} + k^-_{z_5^m:e_2^m})[Z_5^m:E_2^m] \tag{46}$$

$$\frac{d}{dt}\,[Z_8^m:E_{10}^m] = k^+_{z_8^m:e_{10}^m} z_8^m e_{10}^m - (k^{\text{cat}}_{z_8^m:e_{10}^m} + k^-_{z_8^m:e_{10}^m})[Z_8^m:E_{10}^m] \tag{47}$$

$$\frac{d}{dt}\,[Z_8^m:E_2^m] = k^+_{z_8^m:e_2^m} z_8^m e_2^m - (k^{\text{cat}}_{z_8^m:e_2^m} + k^-_{z_8^m:e_2^m})[Z_8^m:E_2^m] \tag{48}$$

$$\frac{d}{dt}\,[Z_8:E_2] = k_{\text{flow}}\Big([Z_8:E_2]^{\text{up}} - [Z_8:E_2]\Big) + k^+_{z_8:e_2} z_8 e_2 - (k^{\text{cat}}_{z_8:e_2} + k^-_{z_8:e_2})[Z_8:E_2] \tag{49}$$

$$\begin{aligned}\frac{d}{dt}\,[Z_9:E_7^m] &= k^+_{z_9:e_7^m} z_9 e_7^m - (k^{\text{cat}}_{z_9:e_7^m} + k^-_{z_9:e_7^m})[Z_9:E_7^m] \\ &\quad -[Z_9:E_7^m]\frac{d}{dt}\,[PL_a^s]\frac{1}{p^{\text{avail}}_{PLAS}}\end{aligned} \tag{50}$$

$$\frac{d}{dt}\,[Z_2^m:PRO] = k^+_{z_2^m:PRO} z_2^m [PRO] - (k^{\text{cat}}_{z_2^m:PRO} + k^-_{z_2^m:PRO})[Z_2^m:PRO] \tag{51}$$

$$\frac{d}{dt}\,[TF] = -[TF]\frac{d}{dt}\,[PL_a^s]\frac{1}{p^{\text{avail}}_{PLAS}} \tag{52}$$

$$\frac{d}{dt}\,e_9^{m*} = k_9^{\text{on}}\,p_9^{*,\text{avail}} e_9 - k_9^{\text{off}} e_9^{m*} + k^-_{e_8^m:e_9^m}[TEN^*] - k^+_{e_8^m:e_9^m} e_8^m e_9^{m*} \tag{53}$$

$$\begin{aligned}\frac{d}{dt}\,[TEN^*] &= -k^-_{e_8^m:e_9^m}[TEN^*] + k^+_{e_8^m:e_9^m} e_8^m e_9^{m*} \\ &\quad +(k^{\text{cat}}_{z_{10}^m:TEN} + k^-_{z_{10}:TEN})[Z_{10}^m:TEN^*] - k^+_{z_{10}^m:TEN} z_{10}^m [TEN^*]\end{aligned} \tag{54}$$

$$\frac{d}{dt}\,[Z_{10}^m:TEN^*] = k^+_{z_{10}^m:TEN} z_{10}^m [TEN^*] - (k^{\text{cat}}_{z_{10}^m:TEN} + k^-_{z_{10}:TEN})[Z_{10}^m:TEN^*] \tag{55}$$

$$\frac{d}{dt}\, e_2^{ec} = k_{\text{flow}}(e_2^{\text{up}} - e_2^{ec}) + k_{\text{diff}}(e_2 - e_2^{ec}) - -k_{AT:e_2}^{\text{in}} e_2^{ec} - k_{TM}^{\text{on}} e_2^{ec} [TM]^{\text{avail}} + k_{TM}^{\text{off}} [TM : E_2^{ec}] \tag{56}$$

$$\frac{d}{dt}\, [APC^{ec}] = k_{\text{flow}}\Big([APC]^{\text{up}} - [APC^{ec}]\Big) + k_{\text{diff}}([APC] - [APC^{ec}]) + k_{PC:TM:e_2^{ec}}^{\text{cat}} [TM : E_2^{ec} : APC] \tag{57}$$

$$\frac{d}{dt}\, [TM : E_2^{ec}] = k_{TM}^{\text{on}} e_2^{ec} [TM]^{\text{avail}} - k_{TM}^{\text{off}} [TM : E_2^{ec}] - k_{PC:TM:e_2^{ec}}^{+} [TM : E_2^{ec}] + (k_{PC:TM:e_2^{ec}}^{-} + k_{PC:TM:e_2^{ec}}^{\text{cat}})[TM : E_2^{ec} : APC] \tag{58}$$

$$\frac{d}{dt}\, [TM : E_2^{ec} : APC] = k_{PC:TM:e_2^{ec}}^{+} [TM : E_2^{ec}] - (k_{PC:TM:e_2^{ec}}^{-} + k_{PC:TM:e_2^{ec}}^{\text{cat}})[TM : E_2^{ec} : APC] \tag{59}$$

$$\frac{d}{dt}\, e_9^{ec} = k_{\text{flow}}(e_9^{\text{up}} - e_9^{ec}) + k_{\text{diff}}(e_9 - e_9^{ec}) - k_{AT:e_9}^{\text{in}} e_9^{ec} \tag{60}$$

$$\frac{d}{dt}\, e_{10}^{ec} = k_{\text{flow}}(e_{10}^{\text{up}} - e_{10}^{ec}) + k_{\text{diff}}(e_{10} - e_{10}^{ec}) - k_{AT:e_{10}}^{\text{in}} e_{10}^{ec} \tag{61}$$

$$\frac{d}{dt}\, z_{11} = k_{\text{flow}}(z_{11}^{\text{up}} - z_{11}) - k_{z_{11}}^{\text{on}} z_{11}\, p_{11}^{\text{avail}} + k_{z_{11}}^{\text{off}} z_{11}^{m} - k_{z_{11}:e_2}^{+} z_{11} e_2 + k_{z_{11}:e_2}^{-} [Z_{11} : E_2] \tag{62}$$

$$\frac{d}{dt}\, e_{11}^{h} = k_{\text{flow}}(e_{11}^{h,\text{up}} - e_{11}^{h}) - k_{e_{11}^{h}}^{\text{on}*} e_{11}^{h}\, p_{11}^{*,\text{avail}} + k_{e_{11}^{h}}^{\text{off}*} e_{11}^{h,m*} - k_{e_{11}^{h}}^{\text{on}} e_{11}^{h}\, p_{11}^{\text{avail}} + k_{e_{11}^{h}}^{\text{off}} e_{11}^{h,m} - k_{z_9:e_{11}^{h}}^{+} z_9 e_{11}^{h} + (k_{z_9:e_{11}^{h}}^{-} + k_{z_9:e_{11}^{h}}^{\text{cat}})[Z_9 : E_{11}^{h}] + k_{z_{11}:e_2}^{\text{cat}} [Z_{11} : E_2] - k_{e_{11}^{h}:e_2}^{+} e_{11}^{h} e_2 + k_{e_{11}^{h}:e_2}^{-} [E_{11}^{h} : E_2] - k_{AT:e_{11}}^{\text{in}} e_{11}^{h} \tag{63}$$

$$\frac{d}{dt}\, e_{11} = k_{\text{flow}}(e_{11}^{\text{up}} - e_{11}) - k_{e_{11}}^{\text{on}*} e_{11}\, p_{11}^{*,\text{avail}} + k_{e_{11}}^{\text{off}*} e_{11}^{m*} - k_{z_9:e_{11}}^{+} z_9 e_{11} + (k_{z_9:e_{11}}^{-} + k_{z_9:e_{11}}^{\text{cat}})[Z_9 : E_{11}] + k_{e_{11}^{h}:e_2}^{\text{cat}} [E_{11}^{h} : E_2] - k_{AT:e_{11}}^{\text{in}} e_{11} \tag{64}$$

$$\frac{d}{dt}\; z_{11}^m = k_{z_{11}}^{\text{on}} z_{11}\; p_{11}^{\text{avail}} - k_{z_{11}}^{\text{off}} z_{11}^m - k_{z_{11}^m:e_2^m}^{+} z_{11}^m e_2^m + k_{z_{11}^m:e_2^m}^{-} [Z_{11}^m : E_2^m] \tag{65}$$

$$\begin{aligned}\frac{d}{dt}\; e_{11}^{h,m} &= k_{e_{11}^h}^{\text{on}} e_{11}^h\; p_{11}^{\text{avail}} - k_{e_{11}^h}^{\text{off}} e_{11}^{h,m} + k_{z_{11}^m:e_2^m}^{\text{cat}} [Z_{11}^m : E_2^m] \\ &\quad - k_{z_9^m:e_{11}^{h,m}}^{+} z_9^m e_{11}^{h,m} + (k_{z_9^m:e_{11}^{h,m}}^{-} + k_{z_9^m:e_{11}^{h,m}}^{\text{cat}})[Z_9^m : E_{11}^{h,m}]\end{aligned} \tag{66}$$

$$\begin{aligned}\frac{d}{dt}\; e_{11}^{h,m*} &= k_{e_{11}^h}^{\text{on}*} e_{11}^h\; p_{11}^{*,\text{avail}} - k_{e_{11}^h}^{\text{off}*} e_{11}^{h,m*} \\ &\quad - k_{e_{11}^{h,m*}:e_2^m}^{+} e_{11}^{h,m*} e_2^m + k_{e_{11}^{h,m*}:e_2^m}^{-} [E_{11}^{h,m*} : E_2^m]\end{aligned} \tag{67}$$

$$\begin{aligned}\frac{d}{dt}\; e_{11}^{m*} &= k_{e_{11}}^{\text{on}*} e_{11}\; p_{11}^{*,\text{avail}} - k_{e_{11}}^{\text{off}*} e_{11}^{m*} + k_{e_{11}^{h,m*}:e_2^m}^{\text{cat}} [E_{11}^{h,m*} : E_2^m] \\ &\quad - k_{z_9^m:e_{11}^{m*}}^{+} z_9^m e_{11}^{m*} + (k_{z_9^m:e_{11}^{m*}}^{-} + k_{z_9^m:e_{11}^{m*}}^{\text{cat}})[Z_9^m : E_{11}^{m*}]\end{aligned} \tag{68}$$

$$\frac{d}{dt}\; [Z_9 : E_{11}^h] = k_{\text{flow}}\Big([Z_9 : E_{11}^h]^{\text{up}} - [Z_9 : E_{11}^h]\Big) + k_{z_9:e_{11}^h}^{+} z_9 e_{11}^h - (k_{z_9:e_{11}^h}^{-} + k_{z_9:e_{11}^h}^{\text{cat}})[Z_9 : E_{11}^h] \tag{69}$$

$$\frac{d}{dt}\; [Z_9 : E_{11}] = k_{\text{flow}}\Big([Z_9 : E_{11}]^{\text{up}} - [Z_9 : E_{11}]\Big) + k_{z_9:e_{11}}^{+} z_9 e_{11} - (k_{z_9:e_{11}}^{-} + k_{z_9:e_{11}}^{\text{cat}})[Z_9 : E_{11}] \tag{70}$$

$$\frac{d}{dt}\; [Z_9^m : E_{11}^{h,m}] = k_{z_9^m:e_{11}^{h,m}}^{+} z_9^m e_{11}^{h,m} - (k_{z_9^m:e_{11}^{h,m}}^{-} + k_{z_9^m:e_{11}^{h,m}}^{\text{cat}})[Z_9^m : E_{11}^{h,m}] \tag{71}$$

$$\frac{d}{dt}\; [Z_9^m : E_{11}^{m*}] = k_{z_9^m:e_{11}^{m*}}^{+} z_9^m e_{11}^{m*} - (k_{z_9^m:e_{11}^{m*}}^{-} + k_{z_9^m:e_{11}^{m*}}^{\text{cat}})[Z_9^m : E_{11}^{m*}] \tag{72}$$

$$\begin{aligned}\frac{d}{dt}\; [Z_{11} : E_2] &= k_{\text{flow}}\Big([Z_{11} : E_2]^{\text{up}} - [Z_{11} : E_2]\Big) \\ &\quad + k_{z_{11}:e_2}^{+} z_{11} e_2 - (k_{z_{11}:e_2}^{-} + k_{z_{11}:e_2}^{\text{cat}})[Z_{11} : E_2]\end{aligned} \tag{73}$$

$$\begin{aligned}\frac{d}{dt}\; [E_{11}^h : E_2] &= k_{\text{flow}}\Big([E_{11}^h : E_2]^{\text{up}} - [E_{11}^h : E_2]\Big) \\ &\quad + k_{e_{11}^h:e_2}^{+} e_{11}^h e_2 - (k_{e_{11}^h:e_2}^{-} + k_{e_{11}^h:e_2}^{\text{cat}})[E_{11}^h : E_2]\end{aligned} \tag{74}$$

$$\frac{d}{dt}\; [Z_{11}^m : E_2^m] = k_{z_{11}^m:e_2^m}^{+} z_{11}^m e_2^m - (k_{z_{11}^m:e_2^m}^{-} + k_{z_{11}^m:e_2^m}^{\text{cat}})[Z_{11}^m : E_2^m] \tag{75}$$

$$\frac{d}{dt}\; [E_{11}^{h,m*} : E_2^m] = k_{e_{11}^{h,m*}:e_2^m}^{+} e_{11}^{h,m*} e_2^m - (k_{e_{11}^{h,m*}:e_2^m}^{-} + k_{e_{11}^{h,m*}:e_2^m}^{\text{cat}})[E_{11}^{h,m*} : E_2^m] \tag{76}$$

Kinetic and Physical Parameters:

Platelets	$2.5{\times}10^{-7}$ cm^2/s	a
Proteins	$5{\times}10^{-7}$ cm^2/s	b

Table 1: DIFFUSION COEFFICIENTS FOR PLATELETS AND FLUID-PHASE CHEMICAL SPECIES (a) From (Turitto and Leonard, 1972). (b) From (Young et al., 1980).

Prothrombin	1.4 μM	a
Factor V	0.01 μM	b
Factor VII	0.01 μM	a
Factor VIIa	0.1 nM	c
Factor VIII	1.0 nM	a
Factor IX	0.09 μM	a
Factor X	0.17 μM	a
Factor XI	30.0 nM	a
TFPI	2.5 nM	d
Protein C	65 nM	e
Platelet count	$2.5(10)^5/\mu$l	f
N_2	1000/plt	g
N_2^*	1000/plt	g
N_5	3000/plt	h
N_8	450/plt	i
N_9	250/plt	j
N_9^*	250/plt	j
N_{10}	2700/plt	k
N_{11}	1500/plt	l
N_{11}^*	250/plt	l
n_5	3000/plt	m
p_{PLAS}	0.167 nM	n

Table 2: NORMAL CONCENTRATIONS AND SURFACE BINDING SITE NUMBERS (a) From (Mann et al., 1990). (b) From (Mann et al., 1991). (c) (Morrissey, 1995) suggests that normal plasma concentration of fVIIa is about 1% of the normal fVII concentration. (d) From (Novotny et al., 1991). (e) (f) From (Weiss, 1975). (g) Estimated as described in the text of the Supplementary Information. (h) From (Walsh, 1994). (i) From (Nesheim et al., 1988). (j) From (Ahmad et al., 1989). (k) From (Mann et al., 1992). (l) From (Baglia et al., 1995; Miller et al., 2007). (m) Number of fV molecules released per activated platelet (Tracy et al., 1982). (n) Maximum concentration of platelets in a 2 μm high reaction zone assuming that 20 platelets can cover a 10μm-by-10μm injured surface (Hubbell and McIntire, 1986).

Reaction	Reactants	Complex	Product	$M^{-1}sec^{-1}$	sec^{-1}	sec^{-1}	Note
Activation (of -, by -)							
(TF:VII,fXa)	E_{10}, Z_7^m	$Z_7^m : E_{10}$	E_7^m	$k^{+}_{z_7^m:e_{10}}$=$5.0 \cdot 10^6$	$k^{-}_{z_7^m:e_{10}}$=1.0	$k^{cat}_{z_7^m:e_{10}}$=5.0	a
(TF:VII, fIIa)	E_2, Z_7^m	$Z_7^m : E_2$	E_7^m	$k^{+}_{z_7^m:e_2}$=$3.92 \cdot 10^5$	$k^{-}_{z_7^m:e_2}$=1.0	$k^{cat}_{z_7^m:e_2}$=$6.1 \cdot 10^{-2}$	b
(fX, TF:VIIa)	E_7^m, Z_{10}	$Z_{10} : E_7^m$	E_{10}	$k^{+}_{z_{10}:e_7^m}$=$5.0 \cdot 10^6$	$k^{-}_{z_{10}:e_7^m}$=1.0	$k^{cat}_{z_{10}:e_7^m}$=1.15	c
(fIX, TF:VIIa)	E_7^m, Z_9	$Z_9 : E_7^m$	E_9	$k^{+}_{z_9:e_7^m}$=$9.4 \cdot 10^6$	$k^{-}_{z_9:e_7^m}$=1.0	$k^{cat}_{z_9:e_7^m}$=1.15	d
Binding (of -, with -)							
(fVII, TF)	Z_7, TF		Z_7^m	k_7^{on}=$5.0 \cdot 10^7$	k_7^{off}=$5.0 \cdot 10^{-3}$		e
(fVIIa, TF)	E_7, TF		E_7^m	k_7^{on}=$5.0 \cdot 10^7$	k_7^{off}=$5.0 \cdot 10^{-3}$		e

Table 3: REACTIONS ON SUBENDOTHELIUM (a) $k^{cat}_{z_7^m:e_{10}} = 5.0\ sec^{-1}$ and $K_M = 1.2 \cdot 10^{-6}$ M (Butenas and Mann, 1996). (b) $k^{cat}_{z_7^m:e_2} = 6.1 \cdot 10^{-2}\ sec^{-1}$ and $K_M = 2.7 \cdot 10^{-6}$ M (Butenas and Mann, 1996). (d) $k^{cat}_{z_{10}:e_7^m} = 1.15\ sec^{-1}$ and $K_M = 4.5 \cdot 10^{-7}$ M (Mann et al., 1990). (d) $k^{cat}_{z_9:e_7^m} = 1.15\ sec^{-1}$ and $K_M = 2.4 \cdot 10^{-7}$ M (Limentani et al., 1994). (e) $K_d = 1.0 \cdot 10^{-10}$ M (Nemerson, 1992).

Reaction	Reactants	Complex	Product	$M^{-1}sec^{-1}$	sec^{-1}	sec^{-1}	Note
Activation (of -, by -)							
(fVII, fXa)	Z_7, E_{10}	$Z_7 : E_{10}$	E_7	$k^{+}_{z_7:e_{10}}$=5 $\cdot 10^6$	$k^{-}_{z_7:e_{10}}$=1.0	$k^{cat}_{z_7:e_{10}}$=5.0	a
(fVII, fIIa)	Z_7, E_2	$Z_7 : E_2$	E_7	$k^{+}_{z_7:e_2}$=3.92 $\cdot 10^5$	$k^{-}_{z_7:e_2}$=1.0	$k^{cat}_{z_7:e_2}$=6.1 $\cdot 10^{-2}$	b
(fV, fIIa)	Z_5, E_2	$Z_5 : E_2$	E_5	$k^{+}_{z_5:e_2}= 1.73 \cdot 10^7$	$k^{-}_{z_5:e_2}$=1.0	$k^{cat}_{z_5:e_2}$=0.23	c
(fVIII, fIIa)	Z_8, E_2	$Z_8 : E_2$	E_8	$k^{+}_{z_8:e_2}$=2.64 $\cdot 10^7$	$k^{-}_{z_8:e_2}$=1.0	$k^{cat}_{z_8:e_2}$=0.9	d
(fXI-fXI, fIIa)	Z_{11}, E_2	$Z_{11} : E_2$	E^h_{11}	$k^{+}_{z_{11}:e_2} = 2.0 \cdot 10^7$	$k^{-}_{z_{11}:e_2} = 1.0$	$k^{cat}_{z_{11}:e_2} = 1.3 \cdot 10^{-4}$	e
(fIX, fXIa)	Z_9, E^h_{11}	$Z_9 : E^h_{11}$	E_9	$k^{+}_{z_9:e^h_{11}} = 0.6 \cdot (10)^7$	$k^{-}_{z_9:e^h_{11}} = 1.0$	$k^{cat}_{z_9:e^h_{11}} = 0.21$	f

Table 4: REACTIONS IN THE PLASMA (a) $k^{cat}_{z_7:e_{10}} = 5.0$ sec^{-1} and $K_M = 1.2 \cdot 10^{-6}$ M (Butenas and Mann, 1996). (b) $k^{cat}_{z_7:e_2} = 6.1 \cdot 10^{-2}$ sec^{-1} and $K_M = 2.7 \cdot 10^{-6}$ M (Butenas and Mann, 1996) (c) $k^{cat}_{z_5:e_2} = 0.23$ sec^{-1} and $K_M = 7.17 \cdot 10^{-8}$ M (Monkovic and Tracy, 1990a). (d) $k^{cat}_{z_8:e_2} = 0.9$ sec^{-1} (Hill-Eubanks and Lollar, 1990) and $K_M = 2 \cdot 10^{-7}$ M (Lollar et al., 1985). (e) $k^{cat}_{z_{11}:e_2} = 1.3 \cdot 10^{-4}$, $K_M = 50$nM (Gailani and Broze Jr., 1991). Rate constants apply also for thrombin-activation of XIa-XI. (f) $k^{cat}_{z_9:e^h_{11}} = 0.21$, $K_M = 0.2\mu$M (Gailani et al., 2001; Sinha et al., 2007). Rate constants apply also for activation of IX by XIa-XIa.

Reaction	Reactants	Products	$M^{-1}sec^{-1}$	sec^{-1}	Note
Factor IX	Z_9, P_9	Z_9^m	k_9^{on}=$1.0 \cdot 10^7$	k_9^{off}=$2.5 \cdot 10^{-2}$	a
Factor IXa	E_9, P_9	E_9^m	k_9^{on}=$1.0 \cdot 10^7$	k_9^{off}=$2.5 \cdot 10^{-2}$	a
Factor IXa	E_9, P_9^*	$E_9^{m,*}$	k_9^{on}=$1.0 \cdot 10^7$	k_9^{off}=$2.5 \cdot 10^{-2}$	b
Factor X	Z_{10}, P_{10}	Z_{10}^m	k_{10}^{on}=$1.0 \cdot 10^7$	k_{10}^{off}=$2.5 \cdot 10^{-2}$	a
Factor Xa	E_{10}, P_{10}	E_{10}^m	k_{10}^{on}=$1.0 \cdot 10^7$	k_{10}^{off}=$2.5 \cdot 10^{-2}$	a
Factor V	Z_5, P_5	Z_5^m	k_5^{on}=$5.7 \cdot 10^7$	k_5^{off}=0.17	c
Factor Va	E_5, P_5	E_5^m	$k_5^{on} = 5.7 \cdot 10^7$	k_5^{off}=0.17	c
Factor VIII	Z_8, P_8	Z_8^m	$k_8^{on} = 5.0 \cdot 10^7$	k_8^{off}=0.17	d
Factor VIIIa	E_8, P_8	E_8^m	$k_8^{on} = 5.0 \cdot 10^7$	k_8^{off}=0.17	d
Factor II	Z_2, P_2	Z_2^m	$k_2^{on} = 1.0 \cdot 10^7$	k_2^{off}=5.9	e
Factor IIa	E_2, P_2	E_2^m	$k_2^{*,on} = 1.0 \cdot 10^7$	$k_2^{*,off} = 0.2$	f
Factor XI	Z_{11}, P_{11}	Z_{11}^m	$k_{z_{11}}^{on} = 1.0 \cdot 10^7$	$k_{z_{11}}^{off}$=0.1	g
Factor XIa	E_{11}, P_{11}^*	E_{11}^m	$k_{e_{11}}^{on} = 1.0 \cdot 10^7$	$k_{e_{11}}^{off}$=0.017	h

Table 5: BINDING TO PLATELET SURFACES (a) For fIX binding to platelets, $K_d = 2.5 \cdot 10^{-9}$ M (Ahmad et al., 1989), and for fX binding to platelets, K_d has approximately the same value (Walsh, 1994). For fX binding to PCPS vesicles, the on-rate is about 10^7 $M^{-1}sec^{-1}$ and the off-rate is about 1.0 sec^{-1} (Krishnaswamy et al., 1988) giving a dissociation constant of about 10^{-7} M. To estimate on- and off-rates for the higher-affinity binding of fX to platelets, we keep the on-rate the same as for vesicles and adjust the off-rate to give the correct dissociation constant. The rates for fIX binding with platelets are taken to be the same as for fX binding. (b) We assume binding constants for fIXa binding to the specific fIXa binding sites are the same as for shared sites. (c) fV binds with high-affinity to phospholipids (PCPS) (Krishnaswamy et al., 1988) and we use the same rate constants reported there to describe fV binding to platelets. (d) The K_d for fVIII binding with platelets is taken from (Nesheim et al., 1988). We set the off-rate k_8^{off} for fVIII binding to platelets equal to that for fV binding to platelets, and calculate the on-rate k_8^{on}. (e) For prothrombin interactions with platelets, K_d is reported to be $5.9 \cdot 10^{-7}$ M (Mann, 1994). We choose k_2^{off} and set $k_2^{on} = k_2^{off}/K_d$. (f) Estimated as described in the text of the Supplementary Information. (g) $K_d = 10$ nM (Greengard et al., 1986). (h) $K_d = 1.7$ nM (Miller et al., 2007).

Reaction	Reactants	Complex	Product	$M^{-1}sec^{-1}$	sec^{-1}	sec^{-1}	Note
Activation (of -, by -)							
(V, Xa)	Z_5^m, E_{10}^m	$Z_5^m : E_{10}^m$	E_5^m	$k^+_{z_5^m:e_{10}^m}=1.0\cdot 10^8$	$k^-_{z_5^m:e_{10}^m}=1.0$	$k^{\text{cat}}_{z_5^m:e_{10}^m}=4.6\cdot 10^{-2}$	a
(V, IIa)	Z_5^m, E_2^m	$Z_5^m : E_2^m$	E_5^m	$k^+_{z_5^m:e_2^m}=1.73\cdot 10^7$	$k^-_{z_5^m:e_2^m}=1.0$	$k^{\text{cat}}_{z_5^m:e_2^m}=0.23$	b
(VIII, Xa)	Z_8^m, E_{10}^m	$Z_8^m : E_{10}^m$	E_8^m	$k^+_{z_8^m:e_{10}^m}=5.1\cdot 10^7$	$k^-_{z_8^m:e_{10}^m}=1.0$	$k^{\text{cat}}_{z_8^m:e_{10}^m}=2.3\cdot 10^{-2}$	c
(VIII, IIa)	Z_8^m, E_2^m	$Z_8^m : E_2^m$	E_8^m	$k^+_{z_8^m:e_2^m}=2.64\cdot 10^7$	$k^-_{z_8^m:e_2^m}=1.0$	$k^{\text{cat}}_{z_8^m:e_2^m}=0.9$	d
(X, VIIIa:IXa)	Z_{10}^m, TEN	$Z_{10}^m : TEN$	E_{10}^m	$k^+_{z_{10}^m:ten}=1.31\cdot 10^8$	$k^-_{z_{10}^m:ten}=1.0$	$k^{\text{cat}}_{z_{10}^m:ten}=20.0$	f
(X, VIIIa:IXa*)	Z_{10}^m, TEN^*	$Z_{10}^m : TEN^*$	E_{10}^m	$k^+_{z_{10}^m:ten}=1.31\cdot 10^8$	$k^-_{z_{10}^m:ten}=1.0$	$k^{\text{cat}}_{z_{10}^m:ten}=20.0$	f
(II, Va:Xa)	Z_2^m, PRO	$Z_2^m : PRO$	E_2^m	$k^+_{z_2^m:pro}=1.03\cdot 10^8$	$k^-_{z_2^m:pro}=1.0$	$k^{\text{cat}}_{z_2^m:pro}=30.0$	g
(XI-XI, IIa)	Z_{11}^m, E_2^m	$Z_{11}^m : E_2^m$	E_{11}^{hm}	$k^+_{z_{11}^m:e_2^m}=2.0\cdot 10^7$	$k^-_{z_{11}^m:e_2^m}=1.0$	$k^{\text{cat}}_{z_{11}^m:e_2^m}=1.3\cdot 10^{-4}$	h
(IX, XIa)	Z_9^m, E_{11}^{hm}	$Z_9^m : E_{11}^{hm}$	E_9	$k^+_{z_9^m:e_{11}^m}=0.6\cdot 10^7$	$k^-_{z_9^m:e_{11}^m}=1.0$	$k^{\text{cat}}_{z_9^m:e_{11}^m}=0.21$	i
Binding (of -, with -)							
(VIIIa, IXa)	E_8^m, E_9^m		TEN	$k^+_{\text{ten}}=1.0\cdot 10^8$	$k^-_{\text{ten}}=0.01$		e
(VIIIa, IXa*)	E_8^m, $E_9^{m,*}$		TEN^*	$k^+_{\text{ten}}=1.0\cdot 10^8$	$k^-_{\text{ten}}=0.01$		e
(Va, Xa)	E_5^m, E_{10}^m		PRO	$k^+_{\text{pro}}=1.0\cdot 10^8$	$k^-_{\text{pro}}=0.01$		e

Table 6: REACTIONS ON PLATELET SURFACES (a) $k^{\text{cat}}_{z_5^m:e_{10}^m}=0.046$ sec^{-1} and $K_M=10.4\cdot 10^{-9}$ M (Monkovic and Tracy, 1990b). (b) The rate constants for thrombin activation of fV on platelets are assumed to be the same as in plasma. (c) $k^{\text{cat}}_{z_8^m:e_{10}^m}=0.023$ sec^{-1} and $K_M=2.0\cdot 10^{-8}$ M (Lollar et al., 1985). (d) The rate constants for thrombin activation of fVIII on platelets are assumed to be the same as in plasma. (e) The formation of the tenase and prothrombinase complexes is assumed to be very fast with $K_d=1.0\cdot 10^{-10}$ M (Mann, 1987). (f) $k^{\text{cat}}_{z_{10}^m:ten}=20$ sec^{-1} and $K_M=1.6\cdot 10^{-7}$ M (Rawala-Sheikh et al., 1990). (g) $k^{\text{cat}}_{z_2^m:pro}=30$ sec^{-1} and $K_M=3.0\cdot 10^{-7}$ M (Nesheim et al., 1992). (h) $k^{\text{cat}}_{z_{11}^m:e_2^m}=1.3\cdot 10^{-4}$, $K_M=50$ nM (Gailani and Broze Jr., 1991). Rate constants apply also for thrombin-activation of Plt-XIa-XI. (i) $k^{\text{cat}}_{z_9^m:e_{11}^{h,m}}=0.21$, $K_M=0.2\mu$M (Gailani et al., 2001; Sinha et al., 2007). Rate constants apply also for activation of platelet-bound IX by Plt-XIa-XIa.

Reaction	Reactants	Product	$M^{-1}sec^{-1}$	sec^{-1}	sec^{-1}	Note
Inactivation (of -, by -)						
(IXa, AT-III)	E_9	none		$k^{in}_{AT:e_9}$=0.1		a
(Xa, AT-III)	E_{10}	none		$k^{in}_{AT:e_{10}}$=0.1		a
(IIa, AT-III)	E_2	none		$k^{in}_{AT:e_2}$=0.2		a
(XIa, AT-III)	E_{11}	none		$k^{in}_{AT:e_{11}}$=0.2		a
(APC, Va)	$APC,\ E_5^m$	none	$k^+_{e_5^m:APC} = 1.2 \cdot 10^8$	$k^-_{e_5^m:APC} = 1.0$	$k^{\text{cat}}_{e_5^m:APC} = 0.5$	b
(APC, VIIIa)	$APC,\ E_8^m$	none	$k^+_{e_8^m:APC} = 1.2 \cdot 10^8$	$k^-_{e_8^m:APC} = 1.0$	$k^{\text{cat}}_{e_8^m:APC} = 0.5$	b
Binding (of -, with -)						
(TFPI, Xa)	$TFPI$,E_{10}	$TFPIa$	$k^+_{tfpia:e_{10}}$=$1.6 \cdot 10^7$	$k^-_{tfpia:e_{10}}$=$3.3 \cdot 10^{-4}$		c
(TFPIa, TF:VIIa)	$TFPIa$,E_7^m	$TFPIa : E_7^m$	$k^+_{tfpia:e_7^m}$=$1.0 \cdot 10^7$	$k^-_{tfpia:e_7^m}$=$1.1 \cdot 10^{-3}$		c
(TM, Thrombin)	$TM,\ E_2^{ec}$	$TM : E_2^{ec}$	$k^{\text{on}}_{TM} = 1.0 \cdot 10^8$	$k^{\text{off}}_{TM} = 5.0 \cdot 10^{-2}$		d
Activation (of -, by -)						
(PC, TM:E_2^{ec})	$TM : E_2^{ec}$	APC	$k^+_{PC:TM:e_2^{ec}} = 1.7 \cdot 10^6$	$k^-_{PC:TM:e_2^{ec}} = 1.0$	$k^{\text{cat}}_{PC:TM:e_2^{ec}} = 0.16$	e

Table 7: INHIBITION REACTIONS (a) We estimate these parameters based on the half-lives of Factors IXa, Xa, IIa in plasma (Rosenberg and Bauer, 1994) and assume that the rate of fXIa inactivation is the same as that of fXa and thrombin. (b) For inhibition of fVa by APC, $k^{\text{cat}}_{e_5^m:APC} = 0.5$ sec^{-1} and $K_M = 12.5 \cdot 10^{-9}$ (Solymoss et al., 1988). We assume the same reaction rates for the inhibition of fVIIIa by APC. (c) From (Jesty et al., 1994). (d) $K_d = 0.5$ nM and $[PC] = 65$ nM (Griffin, 2001). (e) $k_{PC:TM:e_2^{ec}} = 0.167$ sec^{-1} , $K_M = 0.7 \cdot 10^{-6}$ M (Broze and Miletich, 1994).

Reactants	Reactants	Products	$M^{-1}sec^{-1}$	sec^{-1}	Note
Unactivated platelet adhering to SE	PL, SE	PL_a^s	k_{adh}^{+}=2 $\cdot 10^{10}$	k_{adh}^{-}=0	a
Activated platelet adhering to SE	PL_a^v, SE	PL_a^v	k_{adh}^{+}=2 $\cdot 10^{10}$	k_{adh}^{-}=0	a
Platelet activation by platelet in solution	PL, PL_a^v	$2PL_a^v$	$k_{plt}^{\text{act}} = 3 \cdot 10^8$		b
Platelet activation on SE	PL, PL_a^s	PL_a^v, PL_a^s	$k_{plt}^{\text{act}} = 3 \cdot 10^8$		b
Platelet activation by thrombin	PL, E_2	PL_a^v		$k_{e_2}^{\text{act}}$=0.50	b

Table 8: PLATELET TRANSITIONS (a) Estimated from data in (Turitto and Baumgartner, 1979; Turitto et al., 1980) as described in (Kuharsky and Fogelson, 2001). (b) Estimated from data in (Gear, 1994) as described in (Kuharsky and Fogelson, 2001). SE=subendothelium.

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