# A reduced equation mathematical model for blood coagulation and lysis in quiescent plasma

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#### Abstract

A mathematical model for blood coagulation is comprised of a complex set of interactions between clotting components found in whole blood. Previous mathematical models have simulated coagulation by incorporating an ever expanding list of components and reactions to try and encapsulate as much of the process as possible. The goal of the work presented herein was to minimize the complexity without sacrificing accuracy. The final model presented uses 15 factors interacting within 8 partial-differential equations to simulate the formation and subsequent fibrinolysis of a clot in quiescent plasma. By adjusting the initial concentration of anti-thrombin III, the model is able to replicate the size of the clot. Additionally, adjusting the degradation constant of fibrin due to plasmin in conjunction with the initial concentration of anti-thrombin III, the model is able to closely follow size and time of clot formation and degradation of a more complex coagulation model.

### 1. Introduction

Blood coagulation is the result of a complicated series of positive and negative feedback loops that results in the formation of a clot. Mathematical models have been developed in order to provide a theoretical underpinning for clinical tests as well as predict responses to the hemostatic system due to fluctuations in specific factors (Anand et al. 2003). The models have been able to capture the phenomena of clotting with varying degrees of complexity and accuracy. The aim of this work was to reduce complexity of a model without sacrificing accuracy. A reduced factor model could be used to decrease the computational time required for large calculations.

The clotting mechanism is discussed in the next section before a survey of models is conducted. The full model is then presented; the methods used to pare down the model are discussed;tfinally, the model predictions are shown in comparison to a previous, more complex simulation.

Blood is comprised of formed cellular elements and proteins suspended in an aqueous solution. The formed cellular elements include erythrocytes (or red blood cells), leukocytes (or white blood cells), and platelets. The aqueous solution is plasma and consists of mostly water as well as dissolved proteins (such as fibrinogen and prothrombin) and ions (such as Ca+, HCO3-, etc.). During times of vascular damage, a clot is formed in a process known as thrombosis to prevent blood loss. Blood coagulation is an involved combination of positive and negative feedback mechanisms. During normal flow, the negative feedback factors dominate to halt the unnecessary formation of blood clots. When the blood vessel wall (or endothelium) is ruptured, it triggers three pathways, often referred to as Virchow's Triad (Anand et al. 2003). The first, is initiated by the activation of platelets. The second, the extrinsic pathway, so called because it involves factors not found in whole blood, is initiated by the release of tissue factor (TF) by the subendothelium. The final pathway is the intrinsic pathway because it is triggered by factors found in whole blood. The final result of thrombosis is a fibrin net or mesh to which platelets adhere, thus forming a thrombotic plug. Figure 1 shows a graphical image of the coagulation cascade (adapted from Rajagopal and Lawson 2005).

The platelet pathway is characterized by the activation of blood platelets. When activated, a platelet changes from a smooth disc into a spindly orb. Platelets can be activated by high shear stress as well as by chemical agonists. After the vessel wall is damaged, platelets attach to von Willebrand factor, collagen, and fibronectin located in the sublayer of the endothelium. As the platelets bond with the von Willebrand factor, they begin to resist the shear stress imparted by the passing blood. Additionally, as the platelet bonds to the collagen of the wall, platelet receptors are activated that initiate thrombaxane A2 formation as well as the release of storage granules (including ADP). The thrombaxane A2 and ADP are recognized by receptor sites on passing platelets,

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Figure 1: Image of clotting cascade adapted from Rajagopal and Lawson (2007)

which are then activated and change shape to form an aggregate around the established platelets. The granules also cause the release of procoagulant phospholipids to the platelet surface which act to accelerate the thrombus formation by acting as catalysts and speeding up reactions (Rand et al. 2003).

The extrinsic pathway is triggered by the release of tissue-factor (TF) from the subendothelium following rupture of the endothelium. TF binds with factor VIIa to form the TF-VIIa complex, which in turn activates factors IX and X to IXa andXa, respectively (Anand et al. 2008). The extrinsic pathway is counteracted by tissue factor pathway inhibitor (TFPI) and antithrombin-III (ATIII).

The intrinsic pathway is activated by factor XII (or Hageman factor) coming into contact with a negatively charged surface, such as that found in the subendothelium. For this reaction, high molecular weight kininogen (HMWK) is present as a cofactor. When factor XII is activated, it splits into equal amounts of  $\alpha$ -XIIa and  $\beta$ -XIIa (Revak 1977). These two factors, with independent rate constants, convert pre-kallikrein (preK) to kallikrein (kalli), which serves to activate more factor XII. This positive feedback loop serves as the main form of factor XII activation and greatly increases the amount of factor XIIa being produced (Tankersley and Finlayson 1984). Factor XIIa activates XI to XIa, and XIa then activates IX to IXa. Protein C1-inhibitor (C1INH) serves to inhibit XIIa, kallikrein, and XIa.

After the intrinsic and extrinsic pathways are initiated, they converge at the activation of factor X. Together, Xa and Va make up the complex prothrombin, which converts II to IIa. As thrombin production continues, it converts fibrinogen (I) to fibrin (Ia). The strands of fibrin bind with platelets as the clot begins to form. As thrombin (and fibrin) production continue, the extravascular space above the damaged endothelium becomes filled. Now fully developed, the clot covers the damaged area and prevents blood from making further contact as well as preventing more pro-coagulant zymogens from reaching the extra-vascular compartment. Within the intravascular compartment, two different mechanisms serve to inhibit enzymes from escaping the clot. The first is Antithrombin III-Heparin Sulfate complex (HS-ATIII), which serves to inactivate IIa, Xa, and IXa. The second is Activated Protein C (APC) which is formed when Protein C binds to thrombin bound to endothelial thrombomodulin. APC suppresses the formation of thrombin and fibrin by inactivating Va and VIIIa.

The breakdown of the clot, or fibrinolysis, is initiated by the same thrombin that promotes clot development. Thrombin (IIa) as well as fibrin (Ia) induce endothelial cells within the intravascular compartment to release tissue-plasminogen activator (tPA). Plasminogen (PLS) binds with tPA and Ia to form a complex that

converts plasminogen to plasmin (PLA), the main degradation agent of fibrin (Ia). As the fibrin mesh breaks down, more binding sites are revealed to convert more PLS to PLA, thus advancing the dissolution of the clot. A higher concentration of PLA will result in a faster rate of degradation. Fibrinolysis is complete when the clot is completely dissolved. Any remaining plasmin is deactivated by  $\alpha$ 2-antiplasmin ( $\alpha$ 2 AP).

At a similar time, papers authored by MacFarlane (1964) and Davie and Ratnoff (1964) showed the coagulation pathways as enzyme cascades. As a result, mathematical models have emerged to illustrate and predict coagulation processes. The first such model was by Levine (1966) who mathematically characterized general enzyme cascades using the work of MacFarlane and Wald (1965) as guides. In 1984, Nesheimet. al. designed a program to mathematically simulate the functional properties of prothrombin using experimentally determined kinetic parameters. Simulations were carried out for a given set of initial concentrations of reaction components. The distribution of enzymatic components and substrates were then calculated from the distribution, fractional binding, and local and bulk concentrations. In 1986, Nemerson and Gentry proposed a model showing that the activation of factors IX and X is predicated on their interaction with tissue factor and factor VIIa. Equations were derived to show that product formation is accompanied by the release of the enzyme activator complex. The model was verified by experiments using bovine tissue factor.

Khanin and Semenov (1989) proposed a non-linear model of the activation using factors VIII, X, V, II, I, and their activated forms. The model is notable because it shows the reciprocal activation of IIa and Va. Deactivations of the factors used were also taken into account. Jones and Mann (1994) proposed a more involved model showing the full extrinsic pathway to activation utilizing TF, VIIa, IX, IXa, X, Xa, V, Va, II, and IIa. The end result is 18 first order differential 16 equations. The thrombin, Xa, and IXa production levels were compared to experimental data. The model stops short of showing fibrin activation and thus clot development. It also neglects to include the inhibiting factors of the extrinsic pathway. In 1996, Zarnitsinaet. al. proposed a model that included the formation of fibrin and also incorporated the anticoagulation effects of Activated Protein C (APC). The end result is a spatial model of eight differential equations and one ordinary differential equation. Though the authors call it a model of the intrinsic pathway, the factors most associated with the intrinsic pathway (XII, XIIa, XI, XIa) were not included.

The extrinsic pathway was modeled in more detail by Kuharsky and Fogelson in 2001. Though fibrin is not included, the full extrinsic pathway along with the inhibitors TFPI, APC, and ATIII and platelet interactions are modeled. The final model is a system of 59 ordinary differential equations. Bungayet. al. 2003 modeled the extrinsic pathway and its inhibitors in a static fluid environment. The model is significantly different because it differentiates between fluid and lipid bound factors and complexes. Thus, reactions take place between factors and complexes both in the fluid and on the lipid membrane. The result is 73 ordinary differential equations using first and second order kinetics.

The most pertinent work to this study was done by Anandet. al. (2008) and LaCroix and Anand (2011). In 2008, Anand et al. showed the formation and lysis of a clot using 23 partial differential equations to mimic the full extrinsic pathway. The clot was modeled in one dimensional direction in quiescent plasma over a thrombogenic pane. Thrombin production results compared favorably with experimental data from Butenaset. al. 1999. The model failed to include the intrinsic pathway, an issue that was rectified by LaCroix and Anand (2011). Using the same methodology, inclusion of the intrinsic pathway showed a larger clot being formed more quickly.

The model to be reduced includes the intrinsic and extrinsic pathways and excludes the platelet pathway. With respect to modeling, the platelet pathway involves many different elements interacting in various ways. Among these are: the activation of platelets by shear stress, activation of platelets by chemical agents, platelet diffusion, platelet-platelet and platelet-surface interaction mechanics and kinetics, and the interplay between the platelet pathway and the other pathways of coagulation. For these reasons, the platelet pathway was neglected in this work. Further, the model is executed in quiescent plasma and thus would not be able to capture the shear stress activation of platelets.

## 2. Methodology

The model to be reduced was taken from LaCroix and Anand (2011) and uses 28 partial-differential equations of the form:

$$\frac{\partial [C_i]}{\partial t} = \operatorname{div}(D_i \frac{\partial [C_i]}{\partial X}) + G_i \qquad i = 1...28$$
(1)

The original 28 equations are featured in Appendix A. The original list of factors includes: The 28 constituents chosen for this model are: fibrinogen (I) and fibrin (Ia), prothrombin (II) and thrombin (IIa), V and Va, VIII and VIIa, IX and IXa, X and Xa, tenase (IXa-VIIIa-PL- written as Z), prothrombinase (Xa-Va-PL- written as W), XI and XIa, XII and XIIa (also known as Hageman factor), prekallikrein and kallikrein (preK and Kalli), Antithrombin-III (ATIII), Protein C (PC) and Activated Protein C (APC), Tissue Factor Pathway Inhibitor (TFPI), C1-Inhibitor (C1INH), [alpha1]-Antitrypsin ( $\alpha$ IAT ), Tissue Plasminogen Activator (tPA), Plasminogen

(PLS) and Plasmin (PLA) and  $\alpha$ 2-Antiplasmin ( $\alpha$ 2AP). Additionally, the TF-VIIa complex and endothelial cell tPA generation are taken into account in the boundary conditions. While not complete, the factors were able to capture the salient features of formation, depletion and dissolution of a blood clot according to biochemical and clinical studies. The values for all kinetic constants are listed in table 1. The values for initial concentrations and the diffusion coefficients are listed in tables 2 and 3, respectively.

Kinetics	Parameters	Sources
М	$k_{12} = 19.8 \text{ min}^{-1}, K_{12M} = 7500 \text{ nM}$	Tankersley and Finlayson (1984)
М	$k_{kalli} = 435 \text{ min}^{-1}, K_{kalliM} = 780 \text{ nM}$	Tankersley and Finlayson (1984)
F	$h_{12} = 0.85 \text{ min}^{-1}$	Silverberg and Kaplan (1982)
S	$h_{PCI-12a} = 2.2 \text{ x } 10^{-4} \text{ nM}^{-1} \text{ min}^{-1}$	Pixley et al. (1985)
S	$h_{ATIII} = 1.3 \text{ x } 10^{-9} \text{ nM}^{-1} \text{ min}^{-1}$	Pixley et al. (1985)
S	$h_{\alpha AP} = 1.1 \text{ x } 10^{-5} \text{ nM}^{-1} \text{ min}^{-1}$	Pixley et al. (1985)
М	$k_{PreKA} = 216 \text{ min}^{-1}, K_{PreKAM} = 91 \text{ nM}$	Tankersley and Finlayson (1984)
М	$k_{PreKB} = 2400 \text{ min}^{-1}, K_{PreKBM} = 36000 \text{ nM}$	Tankersley and Finlayson (1984)
F	$h_{kalli} = 0.68 \text{ min}^{-1}$	Van der Graaf et al. (1983)
М	$k_{11} = 0.0078 \text{ min}^{-1}, K_{11M} = 50 \text{ nM}$	Gailani and Boze (1987)
М	$k_{12a} = 0.034 \text{ min}^{-1}, K_{12aM} = 2000 \text{ nM}$	Gailani and Boze (1987)
S	$h_{11A3} = 1.6 \text{ x } 10^{-3} \text{ mM}^{-1} \text{ min}^{-1}$	Soons et al. (1987)
S	$h_{11L1} = 1.3 \times 10^{-5} \text{ nM}^{-1} \text{ min}^{-1}$	Scott et al. (1982)
М	$k_9 = 11 \text{ min}^{-1}, K_{9M} = 160 \text{ nM}$	Sun and Gailani (1996)
S	$h_9 = 0.0162 \text{ nM}^{-1} \text{ min}^{-1}$	Wiebe et al. (2003)
М	$k_8 = 194.4 \text{ min}^{-1}, K_{8M} = 112000 \text{ nM}$	Cristofaro and Filipis (2003)
F	$h_8 = 0.222 \text{ min}^{-1}$	Neuenschwander and Jesty (1992)
М	$h_{C8} = 10.2 \text{ min}^{-1}, H_{C8M} = 14.6 \text{ nM}$	Anand et al. (2008)
S	$K_{\rm DZ} = 0.56 \text{ nM}$	Ahmad et al. (1989)
М	$k_5 = 27 \text{ min}^{-1}, K_{5M} = 140.5 \text{ nM}$	Monkovic and Tracy (1990)
F	$h_5 = 0.17 \text{ min}^{-1}$	Freyssinet et al. (1991)
М	$h_{C5} = 10.2 \text{ min}^{-1}, H_{C5M} = 14.6 \text{ nM}$	Solymoss et al. (1988)
М	$k_{10} = 2391 \text{ min}^{-1}, K_{10M} = 160 \text{ nM}$	Rawalasheikh et al. (1990)
S	$h_{10} = 0.347 \text{ nM}^{-1} \text{ min}^{-1}$	Wiebe et al. (2003)
S	$h_{\rm TFPI} = 0.48 \ \rm nM^{-1} \ \rm min^{-1}$	Anand et al. (2008)
S	$K_{\rm DW} = 0.1 \text{ nM}$	Mann (1987)
М	$k_2 = 1344 \text{ min}^{-1}, K_{2M} = 1060 \text{ nM}$	Krishnaswamy et al. (1987)
S	$h_2 = 0.714 \text{ nM}^{-1} \text{ min}^{-1}$	Wiebe et al. (2003)
М	$k_{PC} = 39 \text{ min}^{-1}, K_{PCM} = 3190 \text{ nM}$	Tsiang et al. (1996)
S	$h_{PC} = 6.6 \text{ x } 10^{-7} \text{ nM}^{-1} \text{ min}^{-1}$	Diamond and Anand (1993)
М	$k_1 = 3540 \text{ min}^{-1}, K_{1M} = 3160 \text{ nM}$	Tsiang et al. (1996)
М	$h_1 = 1500 \text{ min}^{-1}, H_{1M} = 250000 \text{ nM}$	Diamond and Anand (1993)
М	$k_{PLA} = 12 \text{ min}^{-1}, K_{PLAM} = 18 \text{ nM}$	Madison et al. (1995)
S	$h_{PLA} = 0.096 \text{ nM}^{-1} \text{ min}^{-1}$	Kolev et al. (2005)

Table 1. Kinetic constants for reaction equations. (M is for Michaelis-Mentenkinetics,S is for second order activation, F is for first order activation.)

Species	Initial Concentration (nM)	Source
Ι	7000	Mann et al. (1995)
Ia	7.0	
II	1400	Mann et al. (1995)
IIa	1.4	
V	20	Mann et al. (1995)
Va	0.02	
VIII	0.7	Mann et al. (1995)
VIIIa	0.0007	
IX	90	Mann et al. (1995)
IXa	0.09	
Х	170	Mann et al. (1995)
Xa	0.17	
XI	30	Bungay et al. (2003)
XIa	0.03	
XII	500	Brummel-Ziedens et al. (2004)
XIIa	5	
preK	485	Brummel-Ziedens et al. (2004)
Kalli	4.85	
C1INH	1625	Brummel-Ziedens et al. (2004)
PC	60	Mann et al. (1995)
APC	.06	
ATIII	3400	Kalafatis et al. (1997)
TFPI	2.5	Mann et al. (1995)
$\alpha_1 AT$	45000	Colman et al. (2001)
tPA	0.08	Booth (1995)
PLS	2180	Lijnen and Collen (2000)
PLA	2.18	
$\alpha_2 AP$	105	Colman et al. (2001)

Table 2. Initial concentrations for all species

The boundary conditions are taken from Anand et al. (2003):

$$\frac{\partial [IXa]}{\partial x} = \frac{k_{7,9}[IX][TF - VIIa]}{K_{7,9M} + [IX]} \frac{L}{D_{IXa}}$$
(2)

$$\frac{\partial [IX]}{\partial x} = \frac{-k_{7,9}[IX][TF - VIIa]}{K_{7,9M} + [IX]} \frac{L}{D_{IX}}$$
(3)

$$\frac{\partial [Xa]}{\partial x} = \frac{-k_{7,10} [IX] [TF - VIIa]}{K_{7,10M} + [X]} \frac{L}{D_{Xa}}$$

$$\tag{4}$$

$$\frac{\partial [X]}{\partial x} = \frac{-k_{7,10} [IX] [TF - VIIa]}{K_{7,10M} + [X]} \frac{L}{D_X}$$
(5)

$$\frac{\partial [tPA]}{\partial x} = -(k_{C-tPA} + k_{IIa-tPA} [IIa] + K_{Ia-tPa} [Ia]) [ENDO] \frac{L}{D_{tPA}}$$
(6)

where the level of *TF-VIIa* is approximated using the work of Orfeo et al. (2005). The levels for *TF-VIIa* can be seen in fig 2. The values for boundary value kinetic coefficients can be seen in table 4.

The goal of the model is to mimic the fibrin production as it occurs in-vivo. Here, it is presented alongside the full coagulation model as presented in LaCroix and Anand (2011). All factors are considered with their respective impact to fibrin production for coagulation and subsequent destruction for fibrinolysis. The equation and factor reduction was done by examining the effects of the deactivation of pro-coagulation, the pro-coagulation mechanism, principal components in fibrinolysis, and finally, the necessary boundary conditions.

Species	Mol. Mass (Da)	(cc/g)	Diffusion Coefficient (cm <sup>2</sup> /sec)
I	340000	0.723	3.10 x 10 <sup>-7</sup>
Ia	~660000	0.730	2.47 x 10 <sup>-7</sup>
II	72000	0.719	5.21 x 10 <sup>-7</sup>
IIa	37000	0.730	6.47 x 10 <sup>-7</sup>
V	330000	0.730	3.12 x 10 <sup>-7</sup>
Va	179000	0.730	3.82 x 10 <sup>-7</sup>
VIII	330000	0.730	3.12 x 10 <sup>-7</sup>
VIIIa	166000	0.730	3.92 x 10 <sup>-7</sup>
IX	56000	0.730	5.63 x 10 <sup>-7</sup>
IXa	41000	0.730	6.25 x 10 <sup>-7</sup>
Х	56000	0.730	5.63 x 10 <sup>-7</sup>
Xa	25000	0.730	7.37 x 10 <sup>-7</sup>
XI	16000	0.730	3.97 x 10 <sup>-7</sup>
XIa	80000	0.730	5.0 x 10 <sup>-7</sup>
XII	80000	0.730	5.0 x 10 <sup>-7</sup>
XIIa	108000	0.730	2.93 x 10 <sup>-7</sup>
preK	84000	0.730	4.92 x 10 <sup>-7</sup>
Kalli	84000	0.730	4.92 x 10 <sup>-7</sup>
C1INH	105000	0.730	4.61 x 10 <sup>-7</sup>
PC	62000	0.730	5.44 x 10 <sup>-7</sup>
APC	60000	0.730	5.50 x 10 <sup>-7</sup>
ATIII	58000	0.730	5.57 x 10 <sup>-7</sup>
TFPI	40000	0.730	6.30 x 10 <sup>-7</sup>
$\alpha_1 AT$	51000	0.728	5.82 x 10 <sup>-7</sup>
tPA	68000	0.730	5.28 x 10 <sup>-7</sup>
PLS	92000	0.715	4.81 x 10 <sup>-7</sup>
PLA	85000	0.715	4.93 x 10 <sup>-7</sup>
$\overline{\alpha_2 AP}$	70000	0.720	5.25 x 10 <sup>-7</sup>

Table 3. Diffusion coefficients for all species calculated using Young (1980)

Following examination and brief modeling tests, it became clear that anti-thrombin III and APC are the principal deactivators of the pro-coagulant mechanism. This is due to ATIII's deactivation of the pro-coagulants thrombin and Xa. Similarly, APC works to deactivate Va and *VIIIa*. Thus,  $\alpha$ -1AT, C1INH,  $\alpha$ -2AP, and TFPI were eliminated from the model. Though these factors are involved in the deactivation of various factors involved in coagulation, either the kinetic constants or the concentration by which they produce results incites a smaller cumulative effect than those caused by ATIII and APC. Additionally, the inclusion of the activation/deactivation of ATIII and APC did not alter the production of fibrin in a significant manner. This discovery means that ATIII and APC are necessary in computations that affect other factors, but that their respective equations increase computational effort without significantly affecting fibrin production. That is, setting the concentration of ATIII and APC to constants is sufficient for their inclusion. Thus, by adjusting the concentration of ATIII, the size of the clot can be altered. A higher concentration of ATIII will yield a smaller clot and a lower concentration will cause a larger clot.

The pro-coagulant mechanism was reduced by first eliminating the intrinsic pathway reactions because they happen earlier in the coagulation assay and only serve to augment the effects caused by the extrinsic pathway. The model was further reduced by analyzing major changes in prothrombotic factors. Adjusting factors Va, Xa, and IIa have adverse effects on fibrin production. For this reason, these factors and their activation equations are left in the model. Factor *VIIIa* is retained and set as constant. However, only the activation equations for factors Va and Xa are used; the depletion of factors V and X is ignored. The activation and depletion of prothrombin to thrombin must be retained: thrombin plays an important role in fibrin production because it is the principal activator of fibrinogen while removing the deactivation of prothrombin creates an excess of thrombin resulting in a much larger clot.



Figure 2: Level of TF-VIIa fitted to match the data of Orfeo et al. (2005). For simulations the curve was scaled by a factor of 2000.

Table 4. Kine	etic coefficients	for boundary	conditions

Species	Kinetic Parameters
IXa	$k_{7,9} = 34.0 \text{ min}^{-1}, K_{7,9M} = 24 \text{ nM}$
Xa	$k_{7,10} = 103 \text{ min}^{-1}, K_{7,10} = 240 \text{ nM}$
tPA (Constitutive)	$k_{C-tPA} = 6.52 \text{ x } 10^{-13} \text{ nM m}^2 \text{ min}^{-1}$
tPA (IIa induced)	$k_{\text{IIa-tPA}} = 9.27 \text{ x } 10^{-12} \text{ e}^{-134.8(t-T0)} \text{ m}^2 \text{ min}^{-1}$
tPA (Ia induced)	$k_{\text{Ia-tPA}} = 5.059 \text{ x } 10^{-18} \text{ m}^2 \text{ min}^{-1}$

The main degradation agent of the fibrin mesh created is activated plasminogen, or plasmin (PLA). For this reason, it must be retained as the principal driver of fibrinolysis. If only clot formation were to be examined, these equations could also be disregarded. Plasminogen is activated by tissue plasminogen activator (tPA), which is included in the boundary conditions.

The boundary conditions can be reduced without significant repercussions. Factor IXa coupled with *VIIIa* incites production of Xa. However, the effect of keeping *VIIIa* in the pro-coagulant assay renders the retention of IXa to be largely unnecessary. The inclusion of Xa is vital as it is one of the components of prothrombinase, which converts prothrombin to thrombin. tPA is set as a constant because it does not change significantly and its value is only used in the production of PLA.

Uniform clot formation, growth, and dissolution are considered in one spatial dimension in 2 mm deep quiescent plasma exposed to a negatively charged surface and a thrombogenic pane. Thus, both the intrinsic and extrinsic pathways of coagulation are activated. A clot is considered to be formed when fibrin concentration meets or exceeds 350 nM (adapted from Ovanesonov et al. 2002). The size of the clot is determined by tracking, in time, the regions within the domain that meet or exceed this level. The simulation is carried out over a period of 3000 seconds.

To model the information, the equations, initial conditions, and boundary conditions are nondimensionalized according to:

$$t^* = \frac{t}{T} \tag{7}$$

$$x^* = \frac{x}{L} \tag{8}$$

$$C_i^* = \frac{C_i}{C_i(t=0)}$$
 (9)

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$$D_i *= \frac{D_i T}{L^2}$$
(10)

$$G_i *= \frac{G_i T}{C_i (t=0)}$$
(11)

The non-dimensionalized equations are then solved using the 'pdepe' routine in MATLAB with a mesh of  $\delta x^* = 0.005$ ,  $\delta t^* = 0.001$ , T = 3000, and L = 0.002.

## 3. Results and Discussion

The final form of the model involves fifteen factors (*VIIIa*, IXa, X, Xa, II, IIa, V, Va, I, Ia, ATIII, PLA, PLS, tPA, and APC) interacting:

$$G_X = 0$$
 (12)

$$[Z] = \frac{[VIIa][IXa]}{K_{dZ}}$$
(13)

$$[G_{Xa}] = \frac{k_{10}[VIIIa][Z]}{K_{10M} + [X]} - h_{10}[Xa][ATIII]$$
(14)

$$[W] = \frac{[Va][Xa]}{K_{dW}}$$
(15)

$$G_{IIa} = \frac{k_2[W][II]}{K_{2M} + [II]} - h_2[IIa][ATIII]$$
(16)

$$G_{II} = \frac{-k_2[W][II]}{K_{2M} + [II]}$$
(17)

$$G_{Va} = 0 \tag{18}$$

$$G_{Va} = \frac{k_5[IIa][V]}{K_{5M} + [V]} - h_5[Va] - \frac{h_{C5}[APC][Va]}{H_{C5M} + [Va]}$$
(19)

$$G_{Ia} = \frac{k_{1}[IIa][I]}{K_{1M} + [I]} - \frac{h_{1}[PLA][Ia]}{H_{1M} + [Ia]}$$
(20)

$$G_{I} = \frac{-k_{1}[IIa][I]}{K_{1M} + [I]}$$
(21)

$$G_{PLA} = \frac{k_{PLA}[tPA][PLS]}{K_{PLAM} + [PLS]}$$
(22)

$$G_{PLS} = -\frac{k_{PLA}[tPA][PLS]}{K_{PLAM} + [PLS]}$$
(23)

$$G_{VIIIa} = 0$$
 (24)

$$G_{\text{ATIII}} = 0$$
 (25)

$$G_{tPA} = 0 \tag{26}$$

$$G_{APC} = 0 \tag{27}$$

And the boundary conditions are reduced to only the two equations:

$$\frac{\partial [Xa]}{\partial x} = \frac{-^{k}7,10^{[1X][1F-VIIa]}}{^{K}7,10M} \frac{L}{^{+}[X]} \frac{D}{^{Xa}}$$
(4)

$$\frac{\partial [X]}{\partial x} = \frac{-k_{7,10} [IX] [TF - VIIa]}{K_{7,10M} + [X]} \frac{L}{D_X}$$
(5)

Retaining all kinetic constants at their previously stated level in table 1, and all factors in their initial concentrations yields a smaller clot that lyses much quicker than the full model (not pictured). This is understandable given the simplifications that have been made; if a similar sized clot were formed from fewer constituents, it would render a more involved and complicated model to be trivial. Because the goal is to generate similar fibrin levels throughout the domain, the simplified model can be calibrated to a more complicated simulation by adjusting the initial level of ATIII, the prominent anti-coagulant. By adjusting its initial value to 1400nM, 100% of the size of the full model can be realized as seen in Fig 3.

In order attain a better match to size and time, the deactivation constant of fibrin is reduced from 1500 min-1 to 250 min-1 and the initial concentration of ATIII is changed to 2500nM. This extends the time necessary to accrue substantial amounts of plasmin to incite fibrinolysis. However, doing so has drawbacks. While the size is matched and the clot is lysed at a similar time, the time to clot creation is increased as can be seen in Fig. 4.



work of LaCroix and Anand (2011)

Figure 4: Clot size matched in time compared to LaCroix and Anand (2011). Here, the red line is the reduced model

The model is hindered by its inherent simplicity. As previously stated, the goal of the project was not to match fibrin production, but rather fibrin levels that rise above 350 nM. As such, actual fibrin production may be higher. Additionally, tracking the production and depletion of any single factor at a specific location will not match the results of a more involved model. The levels of individual factors were secondary concerns to the propagation of fibrin concentrations above the critical level into the considered domain. It is also crucial to note that the simplified model assumes a much lower initial concentration of ATIII than that found in-vivo. Thus, in order to calibrate the simplified model presented here, it is necessary to have relevant results from the full model.

In conclusion, the model is able to retain the critical effects caused by the clotting cascade while significantly reducing the complexity. As such, it serves as a serviceable substitute for the entire cascade reducing the computing power necessary to simulate coagulation.

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#### Appendix A

The equations for the full clotting model as originally presented in LaCroix and Anand (2011).

$$G_{XIa} = \frac{k_{11}[IIa][XI]}{K_{11M} + [XI]} + \frac{k_{12a}[XIIa][XI]}{K_{12aM} + [XI]} - [XIa](h_{11A3}[ATIII] + h_{11L1}[\alpha_1AT] + h_{CInh-11a}[C1INH])$$
(30)

$$G_{XI} = \frac{-k_{11} \left[ IIa \right] \left[ XI \right]}{K_{11M} + \left[ XI \right]} + \frac{-k_{12a} \left[ XIIa \right] \left[ XI \right]}{K_{12aM} + \left[ XI \right]}$$
(31)

$$G_{XII} = \frac{-k_{12}[XII]}{K_{12M} + [XII]} + \frac{-k_{kalli}[kalli][XII]}{K_{kalliM} + [XII]}$$
(32)

$$G_{XIIa} = \frac{k_{12} \left[ XII \right]}{K_{12} + \left[ XII \right]} + \frac{k_{kalli} \left[ Kalli \right] \left[ XII \right]}{K_{kalli} + \left[ XII \right]} - \left[ XIIa \right] \left[ h_{12} - h_{PCI-12a} \left[ C1INH \right] - h_{ATIII} \left[ ATIII \right] - h_{\alpha AP} \left[ \alpha_2 AP \right] \right]$$
(33)

$$G_{\text{preK}} = \frac{-k_{\text{PreKA}} [\text{XIIa}] [\text{PreK}]}{K_{\text{PreKAM}} + [\text{PreK}]} + \frac{-k_{\text{PreKB}} [\text{XIIa}] [\text{PreK}]}{K_{\text{PreKBM}} + [\text{PreK}]}$$
(34)

$$G_{kalli} = \frac{k_{PreKA}[XIIa][PreK]}{K_{PreKAM}+[PreK]} + \frac{k_{PreKB}[XIIa][PreK]}{K_{PreKBM}+[PreK]} - h_{kalli}[Kalli]$$
(35)

$$G_{C1INH} = -[C1INH](h_{CInh-12a}[XIIa]+h_{CInh-11a}[XIa])$$
(36)

$$G_{IXa} = \frac{k_9 [XIa][IX]}{K_{9M} + [IX]} - h_9 [IXa][ATIII]$$
(37)

$$G_{IX} = \frac{-k_9 [XIa][IX]}{K_{9M} + [IX]}$$
(38)

$$[Z] = \frac{[VIIa][IXa]}{K_{dZ}}$$
(39)

$$G_{Xa} = \frac{k_{10} [VIIIa][Z]}{K_{10M} + [X]} - h_{10} [Xa] [ATIII] - h_{TFPI} [TFPI] [Xa]$$
(40)

$$G_{X} = \frac{-k_{10} [VIIIa][Z]}{K_{10M} + [X]}$$
(41)

$$[W] = \frac{[Va][Xa]}{K_{dW}}$$
(42)

$$G_{IIa} = \frac{k_2[W][II]}{K_{2M} + [II]} - h_2[IIa][ATIII]$$
(43)

$$G_{II} = \frac{-k_2 [W][II]}{K_{2M} + [II]}$$
(44)

$$G_{\text{VIIIa}} = \frac{k_8 [\text{IIa}][\text{VIII}]}{K_{8M} + [\text{VIII}]} - h_8 [\text{VIIIa}] - \frac{h_{C8} [\text{APC}][\text{VIIIa}]}{H_{C8M} + [\text{VIIIa}]}$$
(45)

$$G_{\text{VIII}} = \frac{-k_8 [\text{IIa}][\text{VIII}]}{K_{8\text{M}} + [\text{VIII}]}$$
(46)

$$G_{Va} = \frac{k_{5} [IIa][V]}{K_{5M} + [V]} - h_{5} [Va] - \frac{h_{C5} [APC][Va]}{H_{C5M} + [Va]}$$
(47)

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$$G_{V} = \frac{-k_{5}[IIa][V]}{K_{5M} + [V]}$$
(48)

$$G_{APC} = \frac{k_{PC} [IIa] [PC]}{K_{PCM} + [PC]} - h_{PC} [APC] [\alpha_1 AT]$$
(49)

$$G_{PC} = \frac{-k_{PC} [IIa] [PC]}{K_{PCM} + [PC]}$$
(50)

$$G_{\text{ATIII}} = -[\text{ATIII}](h_9[\text{IXa}] + h_{10}[\text{Xa}] + h_2[\text{IIa}] + h_{11A3}[\text{XIa}] + h_{\text{ATIII}}[\text{XIIa}])$$
(51)

$$G_{TFPI} = -h_{TFPI} [TFPI] [Xa]$$
(52)

$$G_{\alpha_{1}AT} = -h_{PC} [APC] [\alpha_{1}AT] - h_{11L1} [XIa] [\alpha_{1}AT]$$
(53)

$$G_{Ia} = \frac{k_1 [IIa][I]}{K_{1M} + [I]} - \frac{h_1 [PLA][Ia]}{H_{1M} + [Ia]}$$
(54)

$$G_{I} = \frac{-k_{1} [IIa][I]}{K_{1M} + [I]}$$
(55)

$$G_{tPA} = 0 \tag{56}$$

$$G_{PLA} = \frac{k_{PLA} [tPA] [PLS]}{K_{PLAM} + [PLS]} + \frac{k_{PLA-12a} [XIIa] [PLS]}{K_{PLA-12aM} + [PLS]} - h_{PLA} [PLA] [\alpha_2 AP]$$
(57)

$$G_{PLS} = \frac{-k_{PLA} [tPA] [PLS]}{K_{PLAM} + [PLS]} - \frac{k_{PLA-12a} [XIIa] [PLS]}{K_{PLA-12aM} + [PLS]}$$
(58)

$$G_{\alpha_2 AP} = -\left[\alpha_2 AP\right] \left(h_{PLA} \left[PLA\right] + h_{\alpha AP} \left[XIIa\right]\right)$$
(59)