Solved Problems

5A.Blood Coagulation. Many metabolic reactions involve a large number of sequential reactions, such as those that occur in the coagulation of blood.

$$\text{Cut} \rightarrow \text{Blood} \rightarrow \text{Clotting}$$

Cut
↓
A+B
↓
C
↓
D
↓
E
↓
F
↓
Clot

Blood coagulation is part of an important host defense mechanism called hemostasis which causes the cessation of blood loss from a damaged vessel. The clotting process is initiated when a non-enzymatic lipoprotein (called the tissue factor) contacts blood plasma because of cell damage. The tissue factor (TF) normally remains out of contact with the plasma (See Figure B) because of an intact endothelium. The rupture (e.g., cut) of the endothelium exposes the plasma to TF and a cascade of series reaction proceeds (Figure C). These series reactions ultimately result in the conversion of fibrinogen (soluble) to fibrin (insoluble) which produces the clot. Later, as wound healing occurs, mechanisms that restrict formation of fibrin clots, necessary to maintain the fluidity of the blood, start working.

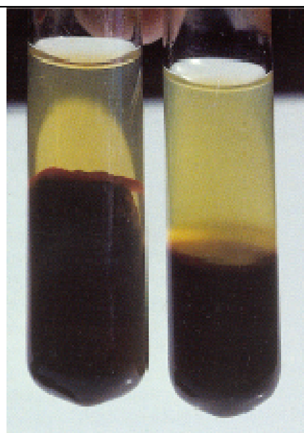

Figure A. Normal Clot Coagulation of blood. (picture courtesy of: Mebs, Venomous and Poisonous Animals, Medpharm, Stugart 2002, Page 305).

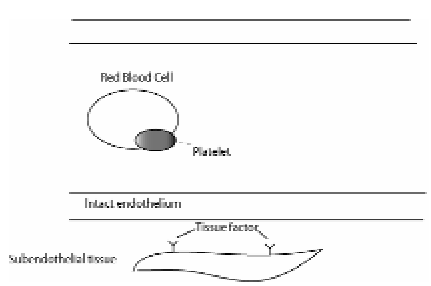

Figure B. Schematic of separation of TF and TF and plasma before cut occurs.

*Platelets provide procoagulant phospholipids-equivalent surfaces upon which the complex-dependent reactions of the blood coagulation cascade are localized.

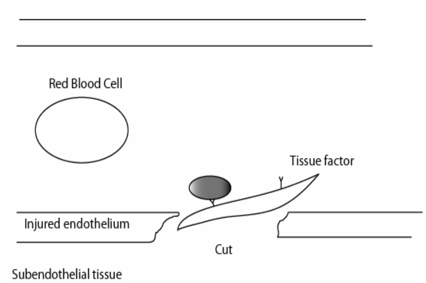

Figure C. Cut allows contact of plasma to initiate coagulation.

In the text we presented an abbreviated solution to blood coagulation kinetics. Here we present the full solution.

The blood coagulation can be modeled using the chemical expressions in Table I, where the notation $\xrightarrow{k5}$ signifies a forward reaction dictated by rate constant k_5.

The notation $\underset{k_2}{\overset{k_1}{\leftrightarrow}}$ indicates a reversible reaction with a forward rate constant of k_1 and a reverse constant of k_2. Binding between components is indicated by the notation =.

Table I.

$$TF + VII \overset{k_1}{\underset{k_2}{\longleftrightarrow}} TF = VII$$

$$TF + VIIa \overset{k_3}{\underset{k_4}{\longleftrightarrow}} TF = VIIa$$

$$TF = VIIa + VII \xrightarrow{k_5} TF = VIIa + VIIa$$

$$Xa + VII \xrightarrow{k_6} Xa + VIIa$$

$$IIa + VII \xrightarrow{k_7} IIa + VIIa$$

$$TF = VIIa + X \overset{k_8}{\underset{k_9}{\longleftrightarrow}} TF = VIIa = X \xrightarrow{k_{10}} TF = VIIa = Xa$$

$$TF = VIIa + Xa \overset{k_{11}}{\underset{k_{12}}{\longleftrightarrow}} TF = VIIa = Xa$$

$$TF = VIIa + IX \overset{k_{13}}{\underset{k_{14}}{\longleftrightarrow}} TF = VIIa = IX \xrightarrow{k_{15}} TF = VIIa + IXa$$

$$Xa + II \xrightarrow{k_{16}} Xa + IIa$$

$$IIa + VIII \xrightarrow{k_{17}} IIa + VIIIa$$

$$VIIIa + IXa \overset{k_{18}}{\underset{k_{19}}{\longleftrightarrow}} IXa = VIIIa$$

$$IXa = VIIIa + X \overset{k_{20}}{\underset{k_{21}}{\longleftrightarrow}} IXa = VIIIa = X \xrightarrow{k_{22}} IXa = VIIIa + Xa$$

$$VIIIa \overset{k_{23}}{\underset{k_{24}}{\longleftrightarrow}} VIIIa_1 \cdot L + VIIIa_2$$

$$IXa = VIIIa = X \xrightarrow{k_{25}} VIIIa_1 \cdot L + VIIIa_2 + IXa + X$$

$$IXa = VIIIa \xrightarrow{k_{25}} VIIIa_1 \cdot L + VIIIa_2 + IXa$$

$$IIa + V \xrightarrow{k_{26}} IIa + Va$$

$$Xa + Va \overset{k_{27}}{\underset{k_{28}}{\longleftrightarrow}} Xa = Va$$

$$Xa = Va + II \overset{k_{29}}{\underset{k_{30}}{\longleftrightarrow}} Xa = Va = II \xrightarrow{k_{31}} Xa = Va + mIIa$$

$$mIIa + Xa = Va \xrightarrow{k_{32}} Xa = Va + IIa$$

$$Xa + TFPI \overset{k_{33}}{\underset{k_{34}}{\longleftrightarrow}} Xa = TFPI$$

$$TF = VIIa = Xa + TFPI \underset{k_{36}}{\overset{k_{35}}{\longleftrightarrow}} TF = VIIa = Xa = TFPI$$

$$TF = VIIa + Xa = TFPI \xrightarrow{k_{37}} TF = VIIa = Xa = TFPI$$

$$Xa + ATIII \xrightarrow{k_{38}} Xa = ATIII$$

$$mIIa + ATIII \xrightarrow{k_{39}} mIIa = ATIII$$

$$IXa + ATIII \xrightarrow{k_{40}} IXa = ATIII$$

$$IIa + ATIII \xrightarrow{k_{41}} IIa = ATIII$$

$$TF = VIIa + ATIII \xrightarrow{k_{42}} TF = VIIa = ATIII$$

Courtesy of Hockin, M.F., Jones, K.C., Everse, S.J. and Mann, K.G. (2002). A model for the stoichiometric regulation of blood coagulation. *The Journal of Biological Chemistry* **277** (21), 18322-18333.

All the species involved in these reactions are either proteins naturally present in blood or complexes formed from other protein reactions.

Notation

Species symbol	Nomenclature
TF	Tissue factor
VII	proconvertin
TF=VIIa	factor TF=VIIa
VIIa	factor novoseven
TF=VIIa	factor TF=VIIa complex
Xa	Stuart prower factor activated
IIa	thrombin
X	Stuart Prower factor
TF=VIIa=X	TF=VIIa=X complex
TF=VIIa=X	TF=VIIa=X complex
IX	Plasma Thromboplastin Component
TF=VIIa=IX	TF=VIIa=IX complex
IXa	factor IXa
II	prothrombin
VIII	antihemophilic factor
VIIIa	antihemophilic factor activated
IXa=VIIIa	IXa=VIIIa complex
IXa=VIIIa=X	IXa=VIIIa=X complex

$VIIIa_1L$	factor $VIIIa_1L$
$VIIIa_2$	factor $VIIIa_2$
V	proaccelerin
Va	factor Va
Xa=Va	Xa=Va complex
Xa=Va=II	Xa=Va=II complex
mIIa	meizothrombin
TFPI	tissue factor pathway inhibitor
Xa=TFPI	Xa=TFPI complex
TF=VIIa=Xa=TFPI	TF=VIIa=Xa=TFPI complex
ATIII	antithrombin
Xa=ATIII	Xa=ATIII complex
mIIa=ATIII	mIIa=ATIII complex
IXa=ATIII	IXa=ATIII complex
TF=VIIIa=ATIII	TF=VIIIa=ATIII complex
IIa=ATIII	IIa=ATIII complex

One can model the clotting process in a manner identical to the series reactions by writing a mole balance and a rate law for each species such as

$$\frac{dC_{TF}}{dT} = k_2 \cdot C_{TFVII} - k_1 \cdot C_{TF} \cdot C_{VII} - k_3 \cdot C_{TF} \cdot C_{VIIa} + k_4 \cdot C_{TFVIIa}$$

$$\frac{dC_{VII}}{dt} = k_2 \cdot C_{TFVII} - k_1 \cdot C_{TF} \cdot C_{VII} - k_6 \cdot C_{Xa} \cdot C_{VII} - k_7 \cdot C_{IIa} \cdot C_{VII} - k_5 \cdot C_{TFVIIa} \cdot C_{VII}$$

$$\frac{dC_{TFVII}}{dt} = -k_2 \cdot C_{TFVII} + k_1 \cdot C_{TF} \cdot C_{VII}$$

$$\frac{dC_{VIIa}}{dt} = k_4 \cdot C_{TFVIIa} - k_3 \cdot C_{TF} \cdot C_{VIIa} + k_5 \cdot C_{TFVIIa} \cdot C_{VII} + k_6 \cdot C_{Xa} \cdot C_{VII} + k_7 \cdot C_{IIa} \cdot C_{VII}$$

$$\frac{dC_{TFVIIa}}{dt} = -k_4 \cdot C_{TFVIIa} + k_3 \cdot C_{TF} \cdot C_{VIIa} + k_9 \cdot C_{TFVIIaX} - k_8 \cdot C_{TFVIIa} \cdot C_X - k_{11} \cdot C_{TFVIIa} \cdot C_{Xa} +$$
$$k_{12} \cdot C_{TFVIIaXa} - k_{13} \cdot C_{TFVIIa} \cdot C_{IX} + k_{14} \cdot C_{TFVIIaIX} + k_{15} \cdot C_{TFVIIaIX} - k_{37} \cdot C_{TFVIIa} \cdot C_{XaTFPI} -$$
$$k_{42} \cdot C_{TFVIIa} \cdot C_{ATIII}$$

$$\frac{dC_{Xa}}{dt} = -k_{11} \cdot C_{TFVIIa} \cdot C_{Xa} + k_{12} \cdot C_{TFVIIaXa} + k_{22} \cdot C_{IXaVIIIaX} + k_{28} \cdot C_{XaVa} - k_{27} \cdot C_{Xa} \cdot C_{Va} +$$
$$k_{34} \cdot C_{XaTFPI} - k_{33} \cdot C_{Xa} \cdot C_{TFPI} - k_{38} \cdot C_{Xa} \cdot C_{ATIII}$$

$$\frac{dC_{IIa}}{dt} = k_{16} \cdot C_{Xa} \cdot C_{II} + k_{32} \cdot C_{mIIa} \cdot C_{XaVa} - k_{41} \cdot C_{IIa} \cdot C_{ATIII}$$

$$\frac{dC_X}{dt} = -k_8 \cdot C_{TFVIIa} \cdot C_X + k_9 \cdot C_{TFVIIaX} - k_{20} \cdot C_{IXaVIIIa} \cdot C_X + k_{21} \cdot C_{IXaVIIIaX} + k_{25} \cdot C_{IXaVIIIaX}$$

$$\frac{dC_{TFVIIaX}}{dt} = k_8 \cdot C_{TFVIIa} \cdot C_X - k_9 \cdot C_{TFVIIaX} - k_{10} \cdot C_{TFVIIaX}$$

$$\frac{dC_{TFVIIaXa}}{dt} = k_{10} \cdot C_{TFVIIaX} + k_{11} \cdot C_{TFVIIa} \cdot C_{Xa} - k_{12} \cdot C_{TFVIIaXa} + k_{36} \cdot C_{TFVIIaXaTFPI} - k_{35} \cdot C_{TFVIIaXa} C_{TFPI}$$

$$\frac{dC_{IX}}{dt} = k_{14} \cdot C_{TFVIIaIX} - k_{13} \cdot C_{TFVIIa} \cdot C_{IX}$$

$$\frac{dC_{TFVIIaIX}}{dt} = -k_{14} \cdot C_{TFVIIaIX} + k_{13} \cdot C_{TFVIIa} \cdot C_{IX} - k_{15} \cdot C_{TFVIIaIX}$$

$$\frac{dC_{IXa}}{dt} = k_{15} \cdot C_{TFVIIaIX} - k_{18} \cdot C_{VIIIa} \cdot C_{IXa} + k_{19} \cdot C_{IXaVIIIa} + k_{25} \cdot C_{IXaVIIIaX} + k_{25} \cdot C_{IXaVIIIa} - k_{40} \cdot C_{IXa} \cdot C_{ATIII}$$

$$\frac{dC_{II}}{dt} = -k_{16} \cdot C_{Xa} \cdot C_{II} + k_{30} \cdot C_{XaVaII} - k_{29} \cdot C_{XaVa} \cdot C_{II}$$

$$\frac{dC_{VIII}}{dt} = -k_{17} \cdot C_{IIa} \cdot C_{VIII}$$

$$\frac{dC_{VIIIa}}{dt} = k_{17} \cdot C_{IIa} \cdot C_{VIII} - k_{18} \cdot C_{VIIIa} \cdot C_{IXa} + k_{19} \cdot C_{IXaVIIIa} - k_{23} \cdot C_{VIIIa} + k_{24} \cdot C_{VIIIa_1 \cdot L}$$

$$\frac{dC_{IXaVIIIa}}{dt} = k_{18} \cdot C_{VIIIa} \cdot C_{IXa} - k_{19} \cdot C_{IXaVIIIa} + k_{21} \cdot C_{IXaVIIIaX} - k_{20} \cdot C_{IXaVIIIa} \cdot C_{X} - k_{25} \cdot C_{IXaVIIIa} + k_{22} \cdot C_{IXaVIIIaX}$$

$$\frac{dC_{IXaVIIIaX}}{dt} = -k_{21} \cdot C_{IXaVIIIaX} + k_{20} \cdot C_{IXaVIIIa} \cdot C_{X} - k_{22} \cdot C_{IXaVIIIaX} - k_{25} \cdot C_{IXaVIIIaX}$$

$$\frac{dC_{VIIIa_1 \cdot L}}{dt} = k_{23} \cdot C_{VIIIa} - k_{24} \cdot C_{VIIIa_1 \cdot L} \cdot C_{VIIIa_2} + k_{25} \cdot C_{IXaVIIIaX} + k_{25} \cdot C_{IXaVIIIa}$$

$$\frac{dC_{VIIIa_2}}{dt} = k_{23} \cdot C_{VIIIa} - k_{24} \cdot C_{VIIIa_1 \cdot L} \cdot C_{VIIIa_2} + k_{25} \cdot C_{IXaVIIIaX} + k_{25} \cdot C_{IXaVIIIa}$$

$$\frac{dC_{V}}{dt} = -k_{26} \cdot C_{IIa} \cdot C_{V}$$

$$\frac{dC_{Va}}{dt} = k_{26} \cdot C_{IIa} \cdot C_{V} + k_{28} \cdot C_{Xa} \cdot C_{Va} - k_{27} \cdot C_{Xa} \cdot C_{Va}$$

$$\frac{dC_{XaVa}}{dt} = -k_{28} \cdot C_{Xa} \cdot C_{Va} + k_{27} \cdot C_{Xa} \cdot C_{Va} - k_{29} \cdot C_{IIaVa} \cdot C_{II} + k_{30} \cdot C_{XaVaII} + k_{31} \cdot C_{XaVaII}$$

$$\frac{dC_{XaVaII}}{dt} = k_{29} \cdot C_{IIaVa} \cdot C_{II} - k_{30} \cdot C_{XaVaII} - k_{31} \cdot C_{XaVaII}$$

$$\frac{dC_{mIIa}}{dt} = k_{31} \cdot C_{XaVaII} - k_{32} \cdot C_{mIIa} \cdot C_{XaVa} - k_{39} \cdot C_{mIIa} \cdot C_{ATIII}$$

$$\frac{dC_{TFPI}}{dt} = k_{34} \cdot C_{XaTFPI} - k_{33} \cdot C_{Xa} \cdot C_{TFPI} + k_{36} \cdot C_{TFVIIaXaTFPI} - k_{35} \cdot C_{TFVIIaXa} \cdot C_{TFPI}$$

$$\frac{dC_{XaTFPI}}{dt} = -k_{34} \cdot C_{XaTFPI} + k_{37} \cdot C_{Xa} \cdot C_{TFPI} - k_{37} \cdot C_{TFVIIa} \cdot C_{XaTFPI}$$

$$\frac{dC_{TFVIIaXaTFPI}}{dt} = -k_{36} \cdot C_{TFVIIaXaTFPI} + k_{35} \cdot C_{TFVIIaXa} \cdot C_{TFPI} + k_{37} \cdot C_{TFVIIa} \cdot C_{XaTFPI}$$

$$\frac{dC_{ATIII}}{dt} = -k_{38} \cdot C_{Xa} \cdot C_{ATIII} - k_{39} \cdot C_{mIIa} \cdot C_{ATIII} - k_{40} \cdot C_{IXa} \cdot C_{ATIII} - k_{41} \cdot C_{IIa} \cdot C_{ATIII} - k_{42} \cdot C_{TFVIIa} \cdot C_{ATIII}$$

$$\frac{dC_{XaATIII}}{dt} = k_{38} \cdot C_{Xa} \cdot C_{ATIII}$$

$$\frac{dC_{mIIaATIII}}{dt} = k_{39} \cdot C_{mIIa} \cdot C_{ATIII}$$

$$\frac{dC_{IXaATIII}}{dt} = k_{40} \cdot C_{IXa} \cdot C_{ATIII}$$

$$\frac{dC_{TFVIIIaATIII}}{dt} = k_{42} \cdot C_{TFVIIa} \cdot C_{ATIII}$$

$$\frac{dC_{IIaATIII}}{dt} = k_{41} \cdot C_{IIa} \cdot C_{ATIII}$$

Initial concentrations of pro and anticoagulants proteins in blood:

TF= $25x10^{-12}$ (M)
VII=$1.0x10^{-8}$ (M)
VIIa=$1x10^{-10}$ (M)
X=$1.6x10^{-7}$ (M)
IX=$9x10^{-8}$ (M)
II=$1.4x10^{-6}$ (M)
VIII=$0.7x10^{-9}$ (M)
V=$2.0x10^{-8}$ (M)
TFPI=$2.5x10^{-9}$ (M)
ATIII=$3.4x10^{-6}$ (M)

The rest of the species initial concentrations are equal to 0.0 M.

List of rate constants in the model

k_1=$3.2x10^{6}$ ($M^{-1}s^{-1}$)
k_2=$3.1x10^{-3}$ (s^{-1})
k_3=$2.3x10^{7}$ ($M^{-1}s^{-1}$)
k_4=$3.1x10^{-3}$ (s^{-1})
k_5=$4.4x10^{5}$ (s^{-1})
k_6=$1.3x10^{7}$ ($M^{-1}s^{-1}$)
k_7= $2.3x10^{4}$ ($M^{-1}s^{-1}$)
k_8= $2.5x10^{7}$ ($M^{-1}s^{-1}$)
k_9= 1.05 (s^{-1})
k_{10}=6 (s^{-1})
k_{11}= $2.2x10^{7}$ ($M^{-1}s^{-1}$)
k_{12}= 19 (s^{-1})

k_{17}=$2.0x10^{7}$ ($M^{-1}s^{-1}$)
k_{18}=$1.0x10^{7}$ ($M^{-1}s^{-1}$)
k_{19}=$5.0x10^{-3}$ (s^{-1})
k_{20}=$1.0x10^{8}$ ($M^{-1}s^{-1}$)
k_{21}=$1.0x10^{-3}$ (s^{-1})
k_{22}=8.2 (s^{-1})
k_{23}=$6.0x10^{-3}$ (s^{-1})
k_{24}=$2.2x10^{4}$ ($M^{-1}s^{-1}$)
k_{25}=$1.0x10^{-3}$ (s^{-1})
k_{26}=$2.0x10^{7}$ ($M^{-1}s^{-1}$)
k_{27}=$4.0x10^{8}$ ($M^{-1}s^{-1}$)
k_{28}=0.2 (s^{-1})

k_{33}=$9.0x10^{5}$ ($M^{-1}s^{-1}$)
k_{34}=$3.6x10^{-4}$ (s^{-1})
k_{35}=$3.2x10^{8}$ ($M^{-1}s^{-1}$)
k_{36}=$1.1x10^{-4}$ (s^{-1})
k_{37}=$5.0x10^{7}$ ($M^{-1}s^{-1}$)
k_{38}=$1.5x10^{3}$ ($M^{-1}s^{-1}$)
k_{39}=$7.1x10^{3}$ ($M^{-1}s^{-1}$)
k_{40}=$4.9x10^{2}$ ($M^{-1}s^{-1}$)
k_{41}=$7.1x10^{3}$ ($M^{-1}s^{-1}$)
k_{42}=$2.3x10^{2}$ ($M^{-1}s^{-1}$)

$k_{13}=1x10^7$ ($M^{-1}s^{-1}$) $k_{29}=1.0x10^8$ ($M^{-1}s^{-1}$)
$k_{14}= 2.4$(s^{-1}) $k_{30}=103$ (s^{-1})
$k_{15}=1.8$ (s^{-1}) $k_{31}=63.5$ (s^{-1})
$k_{16}=7.5x10^3$ ($M^{-1}s^{-1}$) $k_{32}=1.5x10^7$ ($M^{-1}s^{-1}$)

Elena Mansilla Díaz (visiting scholar U of M 9/03-6/04) gathered the information and developed the Polymath code to solve the coupled ODE to predict the total thrombin (IIa+1.2mIIa), TFVIIa and other species concentration as a function of time as well as to determine the clotting time. Figure D mimics the clothing of the blood. You can load the *Polymath Living Example Problem* program directly and vary some of the parameters. Laboratory data are also shown below.

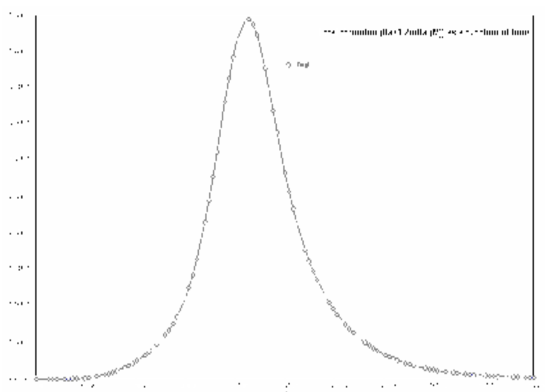

Figure D. Total thrombin (IIa+1.2mIIa) as a function of time with an initiating TF concentration of 25 pM.

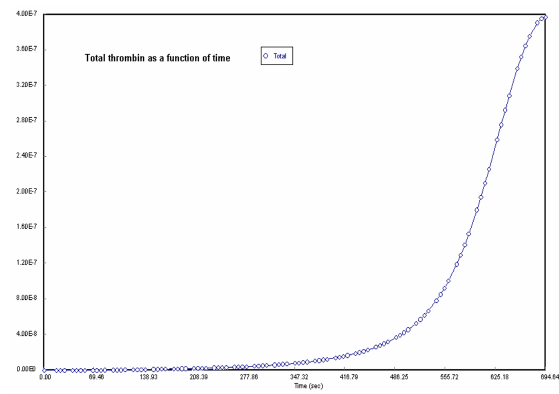

Figure E. Total thrombin (IIa+1.2mIIa) as a function of time with an initiating TF concentration of 5 pM.

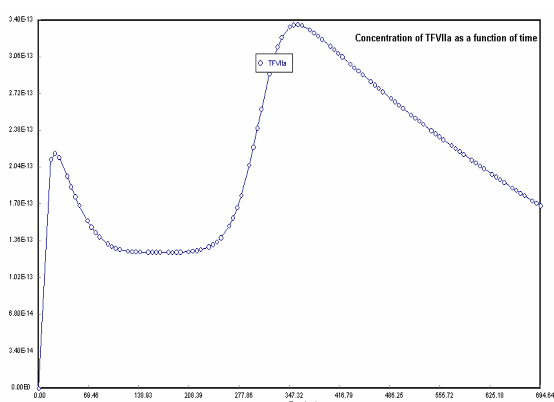

Figure F. TFVIIa as a function of time with an initiating TF concentration of 25 pM.

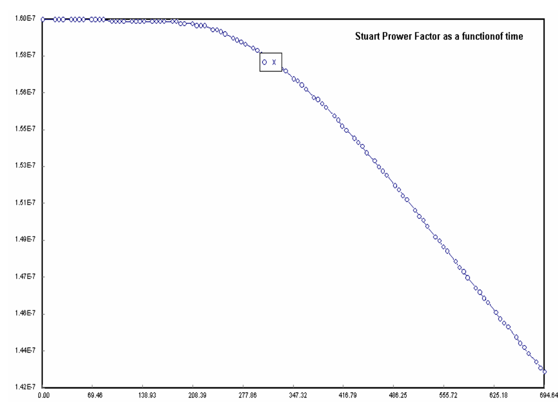

Figure G. Stuart Prower Factor (X) as a function of time with an initiating TF concentration of 25 pM.

Bleeding disorders

Bleeding disorders is a general term for a wide range of medical problems that lead to poor blood clotting and continuous bleeding. Deficiencies in any of the procoagulants can lead to a state where there is a propensity to bleed. Deficiencies in any of the anticoagulants can lead to a hypercoagulable state.

You can check any of the blood disorders by varying the initial concentrations and rate constants of some or all of the following proteins below.

Deficiency of procoagulant factors:
Factor VIII (hemophilia A)
Factor IX (hemophilia B)
Factor II
Factor V
Factor VII
Factor X
Factor XI (hemophilia C)
Factor XIII

Deficiency of anticoagulants:
Factor ATIII (thrombophilia)

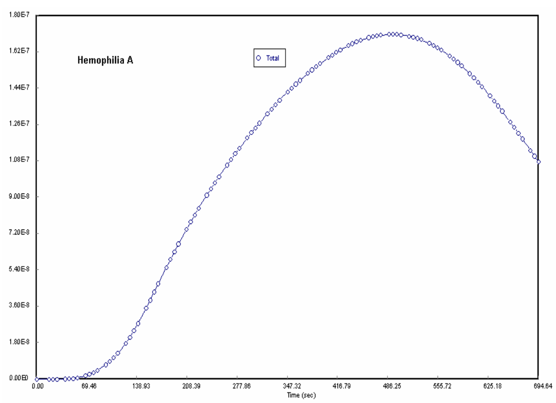

Figure H. Total thrombin (IIa+1.2mIIa) as a function of time with an initiating TF concentration of 25 pM with a factor VIII deficiency (hemophilia A).

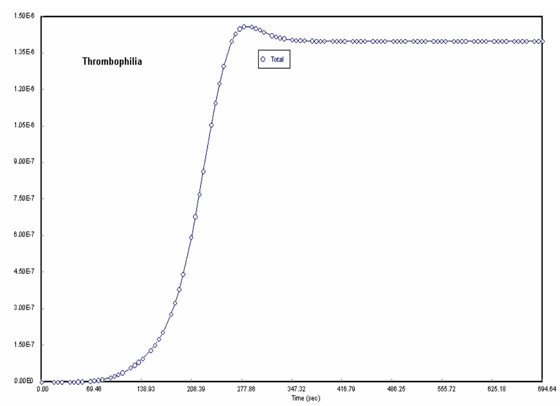

Figure I. Total thrombin (IIa+1.2mIIa) as a function of time with an initiating TF concentration of 25 pM when no inhibitors (ATIII) is present (thrombophilia).

POLYMATH Results [Code by Elena Mansilla Díaz]

No Title 06-05-2004, Rev5.1.230

Calculated values of the DEQ variables

Variable	initial value	minimal value	maximal value	final value
t	0	0	700	700
TF	2.5E-11	8.24E-14	2.5E-11	8.24E-14
VII	1.0E-08	3.513E-10	1.0E-08	3.513E-10
TFVII	0	0	2.027E-11	5.71E-12
VIIa	1.0E-10	1.0E-10	9.724E-09	9.724E-09
TFVIIa	0	0	3.361E-13	1.665E-13
Xa	0	0	1.481E-09	1.481E-09
IIa	0	0	2.487E-07	1.846E-09

X	1.6E-07	1.426E-07	1.6E-07	1.426E-07
TFVIIaX	0	0	1.869E-13	8.423E-14
TFVIIaXa	0	0	5.673E-14	2.608E-14
IX	9.0E-08	8.994E-08	9.0E-08	8.994E-08
TFVIIaIX	0	0	7.2E-14	3.568E-14
IXa	0	0	3.579E-11	3.579E-11
II	1.4E-06	-3.41E-24	1.4E-06	-1.05E-25
VIII	7.0E-10	-2.024E-28	7.0E-10	-1.026E-38
VIIIa	0	0	5.352E-10	3.366E-11
IXaVIIIa	0	0	2.988E-12	2.873E-12
IXaVIIIaX	0	0	5.372E-12	4.995E-12
VIIIa1L	0	0	6.585E-10	6.585E-10
VIIIa2	0	0	6.585E-10	6.585E-10
V	2.0E-08	-1.55E-52	2.0E-08	2.793E-90
Va	0	0	1.943E-08	5.077E-09
XaVa	0	0	1.492E-08	1.492E-08
XaVaII	0	-3.938E-26	2.281E-10	-6.977E-27
mIIa	0	-8.77E-25	3.788E-07	1.663E-25
TFPI	2.5E-09	2.094E-09	2.5E-09	2.094E-09
XaTFPI	0	0	3.867E-10	3.867E-10
TFVIIaXaT	0	0	1.881E-11	1.881E-11
ATIII	3.4E-06	2.001E-06	3.4E-06	2.001E-06
XaATIII	0	0	6.073E-10	6.073E-10
mIIaATIII	0	0	8.247E-07	8.247E-07
IXaATIII	0	0	1.301E-11	1.301E-11
TFVIIIaAT	0	0	8.354E-14	8.354E-14
IIaATIII	0	0	5.734E-07	5.734E-07
k1	3.2E+06	3.2E+06	3.2E+06	3.2E+06
k2	0.0031	0.0031	0.0031	0.0031
k3	2.3E+07	2.3E+07	2.3E+07	2.3E+07
k4	0.0031	0.0031	0.0031	0.0031
k5	4.4E+05	4.4E+05	4.4E+05	4.4E+05
k6	1.3E+07	1.3E+07	1.3E+07	1.3E+07
k7	2.3E+04	2.3E+04	2.3E+04	2.3E+04
k8	2.5E+07	2.5E+07	2.5E+07	2.5E+07
k9	1.05	1.05	1.05	1.05
k10	6	6	6	6
k11	2.2E+07	2.2E+07	2.2E+07	2.2E+07
k12	19	19	19	19
k13	1.0E+07	1.0E+07	1.0E+07	1.0E+07
k14	2.4	2.4	2.4	2.4
k15	1.8	1.8	1.8	1.8
k16	7500	7500	7500	7500
k17	2.0E+07	2.0E+07	2.0E+07	2.0E+07
k18	1.0E+07	1.0E+07	1.0E+07	1.0E+07
k19	0.005	0.005	0.005	0.005
k20	1.0E+08	1.0E+08	1.0E+08	1.0E+08
k21	0.001	0.001	0.001	0.001
k22	8.2	8.2	8.2	8.2
k23	0.006	0.006	0.006	0.006
k24	2.2E+04	2.2E+04	2.2E+04	2.2E+04
k25	0.001	0.001	0.001	0.001
k26	2.0E+07	2.0E+07	2.0E+07	2.0E+07
k27	4.0E+08	4.0E+08	4.0E+08	4.0E+08
k28	0.2	0.2	0.2	0.2
k29	1.0E+08	1.0E+08	1.0E+08	1.0E+08
k30	103	103	103	103
k31	63.5	63.5	63.5	63.5
k32	1.5E+07	1.5E+07	1.5E+07	1.5E+07
k33	9.0E+05	9.0E+05	9.0E+05	9.0E+05
k34	3.6E-04	3.6E-04	3.6E-04	3.6E-04
k35	3.2E+08	3.2E+08	3.2E+08	3.2E+08
k36	1.1E-04	1.1E-04	1.1E-04	1.1E-04
k37	5.0E+07	5.0E+07	5.0E+07	5.0E+07
k38	1500	1500	1500	1500

k39	7100	7100	7100	7100
k40	490	490	490	490
k41	7100	7100	7100	7100
k42	230	230	230	230
r1	8.0E-13	9.728E-17	8.0E-13	9.728E-17
r2	0	0	6.283E-14	1.782E-14
r3	5.75E-14	1.735E-14	5.75E-14	1.855E-14
r4	0	0	1.042E-15	5.189E-16
r5	0	0	9.923E-16	2.696E-17
r6	0	0	1.444E-11	6.953E-12
r7	0	0	4.073E-11	1.602E-14
r8	0	0	1.318E-12	5.971E-13
r9	0	0	1.962E-13	8.896E-14
r10	0	0	1.121E-12	5.083E-13
r11	0	0	5.381E-15	5.381E-15
r12	0	0	1.078E-12	4.982E-13
r13	0	0	3.024E-13	1.506E-13
r14	0	0	1.728E-13	8.609E-14
r15	0	0	1.296E-13	6.456E-14
r16	0	-1.6E-29	2.883E-13	4.511E-30
r17	0	-9.831E-28	1.159E-11	-4.231E-40
r18	0	0	4.674E-14	1.217E-14
r19	0	0	1.494E-14	1.439E-14
r20	0	0	4.406E-11	4.106E-11
r21	0	0	5.372E-15	5.006E-15
r22	0	0	4.405E-11	4.105E-11
r23	0	0	3.211E-12	2.044E-13
r24	0	0	9.527E-15	9.527E-15
r25	0	0	5.372E-15	5.006E-15
r26	0	-2.108E-52	3.312E-10	1.152E-91
r27	0	0	2.999E-09	2.999E-09
r28	0	0	2.974E-09	2.974E-09
r29	0	-3.763E-24	3.764E-08	6.12E-25
r30	0	-4.056E-24	2.35E-08	1.105E-24
r31	0	-2.5E-24	1.449E-08	6.81E-25
r32	0	-1.733E-25	7.132E-09	7.062E-26
r33	0	0	2.762E-12	2.762E-12
r34	0	0	1.372E-13	1.372E-13
r35	0	0	4.492E-14	1.762E-14
r36	0	0	2.065E-15	2.065E-15
r37	0	0	3.19E-15	3.19E-15
r38	0	0	4.387E-12	4.387E-12
r39	0	-1.248E-26	7.708E-09	4.499E-27
r40	0	0	3.502E-14	3.502E-14
r41	0	0	4.224E-09	2.704E-11
r42	0	0	1.78E-16	7.705E-17
Total	0	0	5.749E-07	1.903E-09

ODE Report (STIFF)

Differential equations as entered by the user

[1] d(TF)/d(t) = r2-r1-r3+r4
[2] d(VII)/d(t) = r2-r1-r6-r7-r5
[3] d(TFVII)/d(t) = r1-r2
[4] d(VIIa)/d(t) = -r3+r4+r5+r6+r7
[5] d(TFVIIa)/d(t) = r3-r4+r9-r8-r11+r12-r13+r14-r42-r37+r15
[6] d(Xa)/d(t) = r11+r12+r22-r27+r28-r33+r34-r38
[7] d(IIa)/d(t) = r16+r32-r41
[8] d(X)/d(t) = -r8+r9-r20+r21+r25
[9] d(TFVIIaX)/d(t) = r8-r9-r10
[10] d(TFVIIaXa)/d(t) = r10+r11-r12-r35+r36
[11] d(IX)/d(t) = r14-r13
[12] d(TFVIIaIX)/d(t) = r13-r14-r15
[13] d(IXa)/d(t) = r15-r18+r19+r25-r40

[14] d(II)/d(t) = r30-r29-r16
[15] d(VIII)/d(t) = -r17
[16] d(VIIIa)/d(t) = r17-r18+r19-r23+r24
[17] d(IXaVIIIa)/d(t) = -r20+r21+r22+r18-r19
[18] d(IXaVIIIaX)/d(t) = r20-r21-r22-r25
[19] d(VIIIa1L)/d(t) = r23-r24+r25
[20] d(VIIIa2)/d(t) = r23+r25-r24
[21] d(V)/d(t) = -r26
[22] d(Va)/d(t) = r26-r27+r28
[23] d(XaVa)/d(t) = r27-r28-r29+r30+r31
[24] d(XaVaII)/d(t) = r29-r30-r31
[25] d(mIIa)/d(t) = r31-r32-r39
[26] d(TFPI)/d(t) = r34-r33-r35+r36
[27] d(XaTFPI)/d(t) = r33-r34-r37
[28] d(TFVIIaXaTFPI)/d(t) = r35-r36+r37
[29] d(ATIII)/d(t) = -r38-r39-r40-r41-r42
[30] d(XaATIII)/d(t) = r38
[31] d(mIIaATIII)/d(t) = r39
[32] d(IXaATIII)/d(t) = r40
[33] d(TFVIIIaATIII)/d(t) = r42
[34] d(IIaATIII)/d(t) = r41

Explicit equations as entered by the user
[1] k1 = 3.2e6
[2] k2 = 3.1e-3
[3] k3 = 2.3e7
[4] k4 = 3.1e-3
[5] k5 = 4.4e5
[6] k6 = 1.3e7
[7] k7 = 2.3e4
[8] k8 = 2.5e7
[9] k9 = 1.05
[10] k10 = 6
[11] k11 = 2.2e7
[12] k12 = 19
[13] k13 = 1.0e7
[14] k14 = 2.4
[15] k15 = 1.8
[16] k16 = 7.5e3
[17] k17 = 2e7
[18] k18 = 1.0e7
[19] k19 = 5e-3
[20] k20 = 1e8
[21] k21 = 1e-3
[22] k22 = 8.2
[23] k23 = 6e-3
[24] k24 = 2.2e4
[25] k25 = 1e-3
[26] k26 = 2e7
[27] k27 = 4e8
[28] k28 = 0.2
[29] k29 = 1e8
[30] k30 = 103
[31] k31 = 63.5
[32] k32 = 1.5e7
[33] k33 = 9e5
[34] k34 = 3.6e-4
[35] k35 = 3.2e8
[36] k36 = 1.1e-4
[37] k37 = 5e7

```
[38] k38 = 1.5e3
[39] k39 = 7.1e3
[40] k40 = 4.9e2
[41] k41 = 7.1e3
[42] k42 = 2.3e2
[43] r1 = k1*TF*VII
[44] r2 = k2*TFVII
[45] r3 = k3*TF*VIIa
[46] r4 = k4*TFVIIa
[47] r5 = k5*TFVIIa*VII
[48] r6 = k6*Xa*VII
[49] r7 = k7*IIa*VII
[50] r8 = k8*TFVIIa*X
[51] r9 = k9*TFVIIaX
[52] r10 = k10*TFVIIaX
[53] r11 = k11*TFVIIa*Xa
[54] r12 = k12*TFVIIaXa
[55] r13 = k13*TFVIIa*IX
[56] r14 = k14*TFVIIaIX
[57] r15 = k15*TFVIIaIX
[58] r16 = k16*Xa*II
[59] r17 = k17*IIa*VIII
[60] r18 = k18*IXa*VIIIa
[61] r19 = k19*IXaVIIIa
[62] r20 = k20*IXaVIIIa*X
[63] r21 = k21*IXaVIIIaX
[64] r22 = k22*IXaVIIIaX
[65] r23 = k23*VIIIa
[66] r24 = k24*VIIIa1L*VIIIa2
[67] r25 = k25*IXaVIIIaX
[68] r26 = k26*IIa*V
[69] r27 = k27*Xa*Va
[70] r28 = k28*XaVa
[71] r29 = k29*XaVa*II
[72] r30 = k30*XaVaII
[73] r31 = k31*XaVaII
[74] r32 = k32*mIIa*XaVa
[75] r33 = k33*Xa*TFPI
[76] r34 = k34*XaTFPI
[77] r35 = k35*TFVIIaXa*TFPI
[78] r36 = k36*TFVIIaXaTFPI
[79] r37 = k37*TFVIIa*XaTFPI
[80] r38 = k38*Xa*ATIII
[81] r39 = k39*mIIa*ATIII
[82] r40 = k40*IXa*ATIII
[83] r41 = k41*IIa*ATIII
[84] r42 = k42*TFVIIa*ATIII
[85] Total = IIa+1.2*mIIa
```

Comments

```
[77] k1 =  3.2e6
     (s-1)
[78] k2 =  3.1e-3
     (M-1  s-1)
[79] k3 =  2.3e7
     ( s-1)
[80] k4 =  3.1e-3
     (M-1  s-1)
[81] k5 =     4.4e5
     (s-1)
```

[82] k6 = 1.3e7
(M-1 s-1)
[83] k7 = 2.3e4
(M-1 s-1)
[84] k8 = 2.5e7
(s-1)
[85] k9 = 1.05
(M-1 s-1)
[86] k10 = 6
(s-1)
[87] k11 = 2.2e7
(s-1)
[88] k12 = 19
(M-1 s-1)
[89] k13 = 1.0e7
(s-1)
[90] k14 = 2.4
(M-1 s-1)
[91] k15 = 1.8
(s-1)
[92] k16 = 7.5e3
(M-1 s-1)
[93] k17 = 2e7
(M-1 s-1)
[94] k18 = 1.0e7
(s-1)
[95] k19 = 5e-3
(M-1 s-1)
[96] k20 = 1e8
(s-1)
[97] k21 = 1e-3
(M-1 s-1)
[98] k22 = 8.2
(s-1)
[99] k23 = 6e-3
(M-1 s-1)
[100] k24 = 2.2e4
(s-1)
[101] k25 = 1e-3
(s-1)
[102] k26 = 2e7
(M-1 s-1)
[103] k27 = 4e8
(s-1)
[104] k28 = 0.2
(M-1 s-1)
[105] k29 = 1e8
(s-1)
[106] k30 = 103
(M-1 s-1)
[107] k31 = 63.5
(s-1)
[108] k32 = 1.5e7
(M-1 s-1)
[109] k33 = 9e5
(s-1)
[110] k34 = 3.6e-4
(M-1 s-1)
[111] k35 = 3.2e8
(s-1)
[112] k36 = 1.1e-4
(M-1 s-1)

[113] k37 = 5e7
(M-1 s-1)
[114] k38 = 1.5e3
(M-1 s-1)
[115] k39 = 7.1e3
(M-1 s-1)
[116] k40 = 4.9e2
(M-1 s-1)
[117] k41 = 7.1e3
(M-1 s-1)
[118] k42 = 2.3e2
(M-1 s-1)

Independent variable

variable name : t
initial value : 0
final value : 700

Precision

Independent variable accuracy. eps = 0.00001
First stepsize guess. h1 = 0.0001
Minimum allowed stepsize. hmin = 0.00000001
Good steps = 150
Bad steps = 0

General

number of differential equations: 34
number of explicit equations: 85
Elapsed time: 5.7870 sec
Data file: C:\Documents and Settings\foglelab\My Documents\Nuevo\Blood coagulation\Full solution.pol