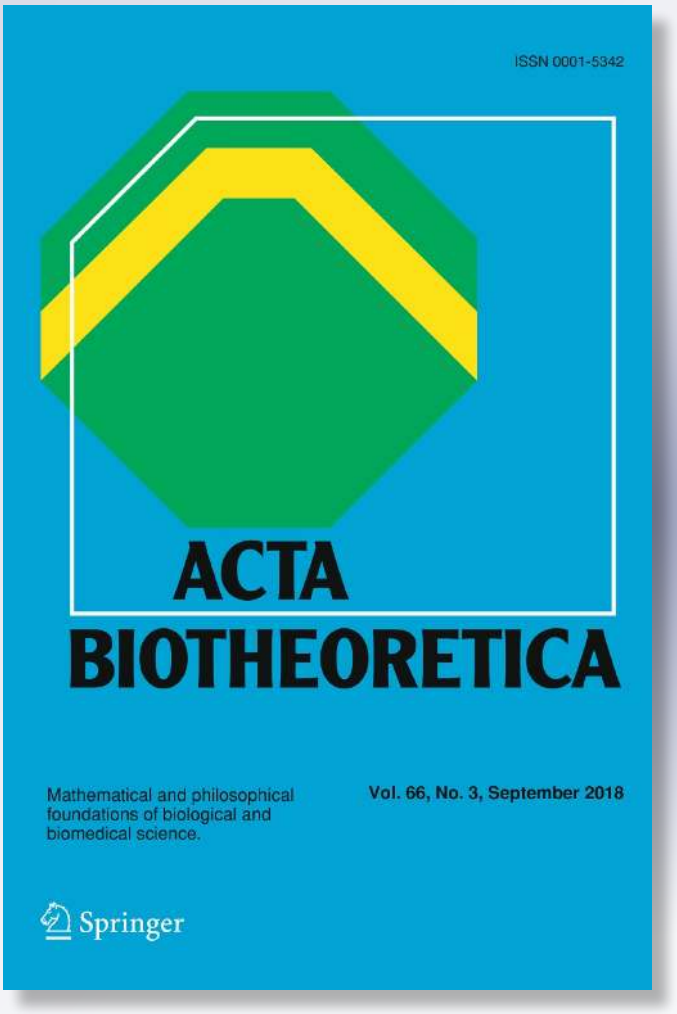
Importance of Initial Concentration of Factor VIII in a Mechanistic Model of In Vitro Coagulation

M. Susree & M. Anand

Acta Biotheoretica
Mathematical and philosophical foundations of biological and biomedical science

ISSN 0001-5342
Volume 66
Number 3

Acta Biotheor (2018) 66:201-212
DOI 10.1007/s10441-018-9329-8



Springer

Acta Biotheor (2018) 66:201–212
https://doi.org/10.1007/s10441-018-9329-8

REGULAR ARTICLE

Importance of Initial Concentration of Factor VIII in a Mechanistic Model of In Vitro Coagulation

M. Susree[1] · **M. Anand**[1]

Received: 30 September 2017 / Accepted: 2 May 2018 / Published online: 14 May 2018

Abstract This computational study generates a hypothesis for the coagulation protein whose initial concentration greatly influences the course of coagulation. Many clinical malignancies of blood coagulation arise due to abnormal initial concentrations of coagulation factors. Sensitivity analysis of mechanistic models of blood coagulation is a convenient method to assess the effect of such abnormalities. Accordingly, the study presents sensitivity analysis, with respect to initial concentrations, of a recently developed mechanistic model of blood coagulation. Both the model and parameters to which model sensitivity is being analyzed provide newer insights into blood coagulation: the model incorporates distinct equations for plasma-phase and platelet membrane-bound species, and sensitivity to initial concentrations is a new dimension in sensitivity analysis. The results show that model predictions are most uncertain with respect to changes in initial concentration of factor VIII, and this hypothesis is supported by results from other models developed independently.

Keywords Coagulation · Factor VIII · Initial concentration · Mechanistic model · Sensitivity analysis

Mathematics Subject Classification 49Q12 · 92C40 · 93B35

✉ M. Anand
anandm@iith.ac.in

M. Susree
ch12p1003@iith.ac.in

[1] Department of Chemical Engineering, Indian Institute of Technology Hyderabad, Kandi, Sangareddy, Telangana 502285, India

1 Introduction

A key underpinning for the effective function of blood clotting (coagulation) is that zymogen and platelet concentrations are neither too deficient nor in large excess. Any departure from the normal course of functioning can lead to either hemorrhage (uncontrolled blood loss from blood vessels) or thrombosis (excessive clot formation within blood vessel). It therefore becomes important to understand the possibilities of both the occurrence and subsequent outcome of such abnormalities. Such an investigation can be done in a simple manner using a mathematical model of the blood coagulation process.

Various simple and complex clinical activities like drug target selection, drug design, patient-specific dosing, etc. are now assisted by the application of mathematical models of blood coagulation and their simulation (Panteleev et al. 2007). Mechanistic models of coagulation bring together a large amount of component biochemical data into a self-consistent and meaningful description that can be used to computationally test various hypotheses on coagulation and hence design experiments accordingly (Mann 2012). With computations, restrictions with respect to the number of samples that can be taken, or the type of input perturbations that can be applied, are mitigated. Sensitivity—defined as the extent and nature of change in a dependent variable due to perturbations of an input variable- can also be measured.

The mechanistic model for coagulation developed by Susree and Anand (2017) (hereafter, referred to as the Susree-Anand model) includes not only platelet activation but also a variable binding site density of clotting proteins on platelets. The model is one of the most inclusive pseudo-homogeneous models that distinguishes between reactions in plasma and on platelet surface. A sensitivity analysis of this model can therefore be expected to yield valuable insights. Sensitivity of this model with respect to change in reaction constants has already been performed in Susree and Anand (2017). In this article, we perform a sensitivity analysis of the Susree-Anand model using the procedure elucidated by Danforth et al. (2009) so as to find the initial concentrations to which the model is most/least sensitive. The results will provide insights for possible experimental studies.

This article includes a section on problem formulation (Sect. 2) which also outlines the solution procedure for the model equations. We then review the procedure for sensitivity analysis in Sect. 3. We present the results of the analysis in Sect. 4. A brief discussion of the results is finally given in Sect. 5 and conclusions are made about the role of uncertainty in initial concentrations of model species in affecting the model predictions.

2 Problem Formulation

Blood coagulation is the physiological phenomenon responsible for maintaining the integrity of the human vasculature. In vitro blood coagulation follows the cascade model of enzymatic reactions leading to thrombin formation (see Furie

and Furie 2008) whereas, in vivo, it follows the spatio-temporally distributed and compartmentalised model (see Panteleev et al. 2015). Based on the mechanism of initiation, blood coagulation follows two pathways : extrinsic and intrinsic. The extrinsic pathway of coagulation is the more significant initiation mechanism *in vivo* (see Furie and Furie 2008). A brief explanation of the extrinsic pathway of coagulation as it occurs in vitro, and as described in Furie and Furie (2008) is given below. We restrict our explanation to this phenomenon because the model we analyze, namely the model in Susree and Anand (2017), describes clotting in vitro via the extrinsic pathway.

In order to initiate clot formation in vitro via the extrinsic pathway, a known concentration of the activator, tissue factor (TF), is added to platelet-rich plasma collected in a test tube. The added TF subsequently forms a complex with active factor VII (fVIIa). Following this, a series of enzymatic reactions is set into action leading to thrombin generation and finally, clot formation. The TF:VIIa complex directly activates factor X. Activated factor X converts prothrombin to thrombin in the plasma at a much lower rate than that by the prothrombinase complex in the plasma (Xa:Va action is however localized at the platelets in plasma). The thrombin in plasma activates platelets which provide the necessary procoagulant surface for formation of intrinsic tenase (IXa:VIIIa) and prothrombinase complexes which activate factor X and prothrombin, respectively. While platelets localize clotting activity, inhibitors like antithrombin III (ATIII) and TFPI keep a check on unregulated clotting. Consequently, this implies an influential role for these inhibitors on the dynamics of clot formation. Figure 1 shows an overview of the coagulation cascade as it would occur in vitro.

Sensitivity to initial conditions is a characteristic of the complex process of blood clotting : this aspect can be conveniently investigated using a mechanistic model of coagulation. Considering how biochemical reactions are represented, that is, in terms of concentrations and kinetic rate constants, we can see that the result of simulating a biochemical network is critically dependent on these two factors. Mechanistic models for hemostasis are understood to comprise of four elements: reaction network, mechanism of reaction, kinetic parameters, and initial conditions (Diamond 2013). Sensitivity analysis with respect to each of these elements aids in understanding alterations in blood function in response to a pathogenic condition as well as to treatment.

In this study, we perform the sensitivity analysis with respect to initial conditions on the coagulation model developed by Susree and Anand (2017). Being a model that is inclusive of platelet activation, and having a reaction network that clearly distinguishes reactions based on whether they occur in plasma or on the platelet membrane surface [the latter distinction is not made in an earlier model proposed in Anand et al. (2008)], it is a good choice for conducting sensitivity analysis.

2.1 Mechanistic Model and Simulation

The model is formulated using ODEs which represent the generation and depletion of various constituents of the extrinsic pathway of blood coagulation. These are :

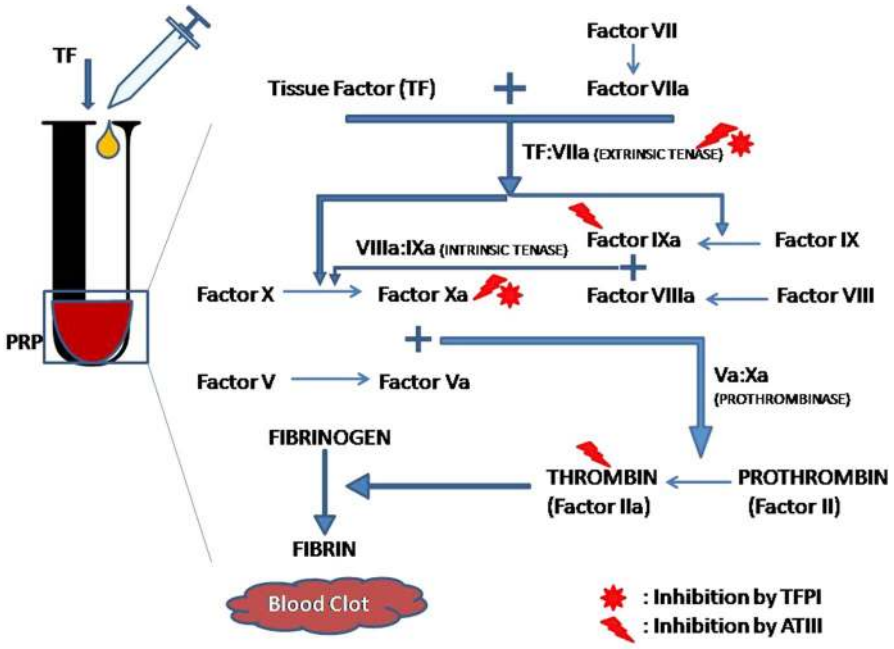


Fig. 1 Overview of the extrinsic-pathway reactions used to develop the model in Susree and Anand (2017). Reproduced with permission from the Indian Academy of Sciences, copyright 2017 Susree and Anand (2017)

tissue factor (*TF*), platelets (PL/AP), plasma-phase enzymes and zymogens (*IXa* / *IX*, *Xa* / *X*, *IIa* / *II*, *VIIIa* / *VIII*, *Va* / *V*, *VII* / *VIIa*), **membrane-bound** enzymes and zymogens ($IXa^m/IX^m, Xa^m/X^m, IIa^m/II^m$, $VIIIa^m/VIII^m, Va^m/V^m$), surface bound enzyme complexes ($VIIIa^m : IXa^m$, $Va^m : Xa^m$, $TF : VII$ and $TF : VIIa$), inhibitors (*ATIII*, *TFPI*, and $Xa : TFPI$), and fibrin & fibrinogen (*Ia* / *I*). The model incorporates platelets as a soluble phase (it is a pseudo-homogeneous model) with variable concentrations of binding sites for clotting factors. The schemes of the various reactions involved in the process of platelet and zymogen activation, inhibition and clot formation incorporated in the model have been outlined in Table 1a–c. The equations corresponding to each reaction can be found in Susree and Anand (2017). All the kinetic parameters and initial conditions used are those for human plasma at physiological conditions ($37\,^{\circ}C$, $pH = 7.2 - 7.4$, $[Ca^{2+}] = 2.1 - 2.8\,mM$). For more details on assumptions, reaction mechanisms, kinetic rate constants, and binding site densities used to develop the model, the reader is referred to Susree and Anand (2017).

The initial concentrations of the zymogens, inhibitors and platelets (Table 2) have been obtained from literature. They have been used previously in the models developed in Anand et al. (2008) and Hockin et al. (2002). The number in parentheses represents the species number in the model described in Susree and Anand (2017).

The system of stiff ODEs and initial conditions (which are the initial concentrations listed in Table 2) are non-dimensionalised according to the following

Table 1 Reactions and kinetic constants

Reaction	Description
(a) For reactions involving platelets	
$PL + AP \xrightarrow{kpp} 2AP$	platelet-activation of platelet
$PL + IIa \xrightarrow{kp2} AP$	platelet activation by IIa
(b) For enzymatic reactions in plasma	
$TF + VII \underset{k_{T7}^{-}}{\overset{k_{T7}^{+}}{\rightleftharpoons}} TF : VII$	binding of TF & VII
	dissociation of TF:VII
$TF + VIIa \underset{k_{T7a}^{-}}{\overset{k_{T7a}^{+}}{\rightleftharpoons}} TF : VIIa$	binding of TF & VIIa
	dissociation of TF : VIIa
$TF : VIIa + VII \xrightarrow{k_{TF7}} TF : VIIa + VIIa$	auto-activation of VII
$VII + Xa \xrightarrow{k_{10,7}} VIIa + Xa$	Xa-activation of VII
$VII + IIa \xrightarrow{k_{2,7}} VIIa + IIa$	IIa-activation of VII
$TF : VIIa + ATIII \xrightarrow{h_7^{AT}} TF : VIIa_i + ATIII$	ATIII inactivation of TF:VIIa
$TF : VIIa + Xa : TFPI \xrightarrow{h_7^{TP}} TF : VIIa_i + Xa : TFPI$	Xa:TFPI inactivation of TF:VIIa
$TF : VIIa + IX \xrightarrow{k_9, K_{9M}{}^2} TF : VIIa + IXa$	TF:VIIa activation of IX
$IXa + ATIII \xrightarrow{h_9} IXi + ATIII$	ATIII inactivation of IXa
$TF : VIIa + X \xrightarrow{k_{7,10}, K_{7,10M}} TF : VIIa + Xa$	TF:VIIa activation of X
$Xa + ATIII \xrightarrow{h_{10}} Xi + ATIII$	ATIII inactivation of Xa
$Xa + TFPI \underset{h_{10}^{TP-}}{\overset{h_{10}^{TP+}}{\rightleftharpoons}} Xi + TFPI$	binding of Xa with TFPI and dissociation of Xa:TFPI
$II + Xa \xrightarrow{k_{2i}} IIa + Xa$	Xa-activation of II
$IIa + ATIII \xrightarrow{h_2} IIi + ATIII$	ATIII inactivation of IIa
$VIII + IIa \xrightarrow{k_8, K_{8M}} VIIIa + IIa$	IIa-activation of VIII
$VIIIa \xrightarrow{h_8} VIIIi$	spontaneous decay of VIIIa
$V + IIa \xrightarrow{k_5, K_{5M}} Va + IIa$	IIa-activation of V
$Va \xrightarrow{h_5} Vi$	spontaneous decay of Va
$I + IIa \xrightarrow{k_f, K_{fM}} Ia$	IIa-activation of fibrinogen
(c) For enzymatic reactions on membrane surface	
$IX/IXa + AP_9 \underset{k_9^{-}}{\overset{k_9^{+}}{\rightleftharpoons}}$	platelet-binding of fIX/IXa, and
IX^m/IXa^m	dissociation of fIX/IXa from platelets

Table 1 (continued)

Reaction	Description
$IXa^m + VIIIa^m \underset{k^-_{TEN}}{\overset{k^+_{TEN}}{\rightleftharpoons}} VIIIa^m : IXa^m$	binding of IXa^m and $VIIIa^m$, and dissociation of IXa^m :$VIIIa^m$
$X/Xa + AP_{10} \underset{k^-_{10}}{\overset{k^+_{10}}{\rightleftharpoons}} X^m/Xa^m$	platelet-binding of fX/Xa, and dissociation of fX/Xa from platelets
$X^m + VIIIa^m : IXa^m \xrightarrow{k_{10},K_{10M}} Xa^m + VIIIa^m : IXa^m$	IXa^m :$VIIIa^m$ activation of X^m
$Xa^m + Va^m \underset{k^-_{PRO}}{\overset{k^+_{PRO}}{\rightleftharpoons}} Va^m : Xa^m$	binding of Xa^m and Va^m, and dissociation of Xa^m :Va^m
$II/IIa + AP_2 \underset{k^-_2}{\overset{k^+_2}{\rightleftharpoons}} II^m/IIa^m$	platelet-binding of fII/IIa, and dissociation of fII/IIa from platelets
$II^m + Xa^m : Va^m \xrightarrow{k_2,K_{2M}} IIa^m + Xa^m : Va^m$	Xa^m :Va^m activation of II^m
$VIII/VIIIa + AP_8 \underset{k^-_8}{\overset{k^+_8}{\rightleftharpoons}} VIII^m/VIIIa^m$	platelet-binding of fVIII/VIIIa, and dissociation of fVIII/VIIIa from platelets
$VIII^m + IIa^m \xrightarrow{k^m_8,K^m_{8M}} VIIIa^m + IIa^m$	IIa^m-activation of $VIII^m$
$VIII^m + Xa^m \xrightarrow{k^m_{8i},K^m_{8iM}} VIIIa^m + Xa^m$	Xa^m-activation of $VIII^m$
$V/Va + AP_5 \underset{k^-_5}{\overset{k^+_5}{\rightleftharpoons}} V^m/Va^m$	platelet-binding of fV/Va, and dissociation of fV/Va from platelets
$V^m + IIa^m \xrightarrow{k^m_5,K^m_{5M}} Va^m + IIa^m$	IIa^m-activation of V^m
$V^m + IIa^m \xrightarrow{k^m_{5i},K^m_{5iM}} Va^m + Xa^m$	Xa^m-activation of V^m

[2]M stands for Michaelis Menten; K9M stands for Michaelis Menten constant for TF:VIIa activation of IX

procedure: $t^* = t/T$, $Y^*_i = Y_i/Y_i(t = 0)$, $G^*_i = G_iT/Y_i(t = 0)$. They are then solved using the 'ode15s' algorithm in MATLAB (version R2012a), and simulations are performed for 1800s (i.e. 30 min).

3 Sensitivity Analysis Procedure

Sensitivity analysis calculates the effect of variations of input parameters (in this case, initial concentrations of model species) on the model predictions (species concentrations), and determines the input parameter to which the predictions are most/least sensitive. Variations in the initial concentration of each of the model species are predesignated, and the consequential differences arising in each species' concentration are analyzed. Two procedures of sensitivity analysis for coagulation models, one described by Danforth et al. (2009) and the other by Luan et al. (2007), are prominent in literature. Danforth et al. (2009) illustrate a sampling based method

Table 2 Initial concentrations of the proteins and platelets

Species (number)	Initial Conc. (nM)	References
TF (1)	Variable	
VII (2)	10.0	Hockin et al. (2002)
TF:VII (3)	0.0	
VIIa (4)	0.1	Hockin et al. (2002)
TF:VIIa (5)	0.0	
IX (6)	90.0	Anand et al. (2008)
IXa (7)	0.009	
IX^m (8)	0.0	
IXa^m (9)	0.0	
X (10)	170.0	Anand et al. (2008)
Xa (11)	0.017	
X^m (12)	0.0	
Xa^m (13)	0.0	
II (14)	1400.0	Anand et al. (2008)
IIa (15)	0.140	
II^m (16)	0.0	
IIa^m (17)	0.0	
PL (18)	10.0	Anand et al. (2003)
AP (19)	0.001	
VIII (20)	0.7	Anand et al. (2008)
VIIIa (21)	0.00007	
$VIII^m$ (22)	0.0	
$VIIIa^m$ (23)	0.0	
IXa^m:$VIIIa^m$ (24)	0.0	
V (25)	20.0	Anand et al. (2008)
Va (26)	0.002	
V^m (27)	0.0	
Va^m (28)	0.0	
Xa^m:Va^m (29)	0.0	
I (30)	7000.0	Anand et al. (2008)
Ia (31)	0.70	
TFPI (32)	2.5	Anand et al. (2008)
Xa:TFPI (33)	0.0	
ATIII (34)	3400.0	Anand et al. (2008)

which uses an ensemble standard deviation to characterize the extent of variation resulting from perturbing one parameter at a time. On the other hand, Luan et al. (2007) provide a local variance decomposition method which uses the derivative of the output concentration with respect to the input parameters. We choose the sampling based method described in Danforth et al. (2009) for the model in question not only since it has greater accuracy (see appendix in Naidu and Anand 2014) but also since the range of perturbation (utilized previously by Allen et al. 2004) being

used—10 to 200%—is in the expected range of variability of experimentally measured concentrations. We list the model species' initial concentrations to which the model prediction of all species' concentrations is most/least sensitive in decreasing order of a parameter denoted as explained variance, E^m_{var}. The mathematical procedure involved in the sensitivity analysis is described below [this is largely derived from the description given in Danforth et al. (2009)].

3.1 Ensemble Standard Deviation

An ensemble standard deviation ($\sigma^f_{IC_i}(t)$) is first calculated for each model species (f)

at any selected time (t) from the set of predicted time courses for that species generated by varying a given initial concentration (IC_i) across a linearly spaced range (denoted by $n : 11$) of values. This characterizes the variation due to that particular species concentration.

$$\sigma^f_{IC_i}(t) = \left(\frac{\sum_{i=1}^{n} (C^f_i(t) - \bar{C}^f(t))^2}{n-1} \right)^{\frac{1}{2}} \tag{1}$$

In Equation (1), $C^f_i(t)$, $\bar{C}^f(t)$ represent the instantaneous & average instantaneous concentration, respectively, of species f.

3.2 Coefficient of Variation

The coefficient of variation ($W^f_{ICi}(t)$) is calculated by dividing the ensemble standard deviation of each species f by the respective peak value ($\hat{C}^f(t)$) of the species' concentration obtained using the standard model (100% initial condition values).

$$W^f_{ICi}(t) = \frac{\sigma^f_{IC_i}(t)}{max(\hat{C}^f(t))} \tag{2}$$

3.3 Mean Coefficient of Variation

The coefficient of variation obtained in the previous step is averaged for all species (n_f), which is equal to 34 in case of the model being investigated, and the mean coefficient of variation ($\gamma_{IC_j}(t)$) is thereby obtained.

$$\gamma_{IC_i}(t) = \frac{\sum_f W^f_{ICi}(t)}{n_f} \tag{3}$$

3.4 Time-Averaged Coefficient of Variation

From the mean coefficient of variation, the time-averaged coefficient of variation (Γ_{IC_i}) for each initial concentration (IC) is evaluated. The mean coefficient of variation is averaged over the entire time of the simulation (that is, 30 minutes in this case). The overall sensitivity of all factors to variation in a single initial concentration is represented by this statistical measure. A comparative assessment of these values gives a simple measure of the response of each species to perturbations in the initial concentrations.

$$\Gamma_{IC_i} = \frac{\sum_t \gamma_{IC_i}(t)}{n_t} \tag{4}$$

3.5 Explained Variance

The comparative assessment mentioned above is performed by computing the *explained variance* (E^m_{var}) which provides the relative importance of the m^{th} initial concentration. The time-averaged coefficient of variation (Γ_{IC_i}) for each initial concentration is arranged in decreasing order of magnitude and the explained variance is thus calculated as shown in Equation (5). It is therefore a means of weighting the respective initial concentrations, uncertainties in which render the model most/least sensitive to that species' (i.e., protein's) initial concentration.

$$E^m_{var} = \frac{\sum_{i=1}^{m} \Gamma_{IC_i}}{\sum_{i=1}^{34} \Gamma_{IC_i}} \tag{5}$$

4 Results

The model equations are solved as per the procedure in Sect. 2.1. Sensitivity analysis is performed for perturbations (10–200%) in initial concentrations of model species, and this gives the time-averaged coefficient of variation (see Table 3). Figure 2 displays the ranks (in decreasing order) of each model protein (referred by species number given in Table 2) with respect to the variation they cause in model predictions. We observe that the model predictions are most sensitive to perturbations in initial concentration of factor VIII, activated form of which is the cofactor and crucial for formation of the intrinsic tenase complex.

Figure 3 shows the effect of perturbing factor VIII concentration on resultant thrombin concentration. Thrombin is the choice analyte for analyzing model sensitivity because it is responsible for the various feedback processes in blood coagulation in addition to concluding it by fibrinogen conversion.

Table 3 Variables documenting model sensitivity to perturbations in initial concentrations

Γ_{IC_i}	Protein (IC number)	E_{var}
Most sensitive		
0.0804	VIII (20)	0.0415
0.0785	VIIIa (21)	0.0821
0.0773	PL (18)	0.1220
0.0772	ATIII (34)	0.1619
Least sensitive		
0.0197	TF:VII (3)	0.9770
0.0173	VIIa (4)	0.9859
0.0156	TF:VIIa (5)	0.9940
0.0117	TF (1)	1.0000

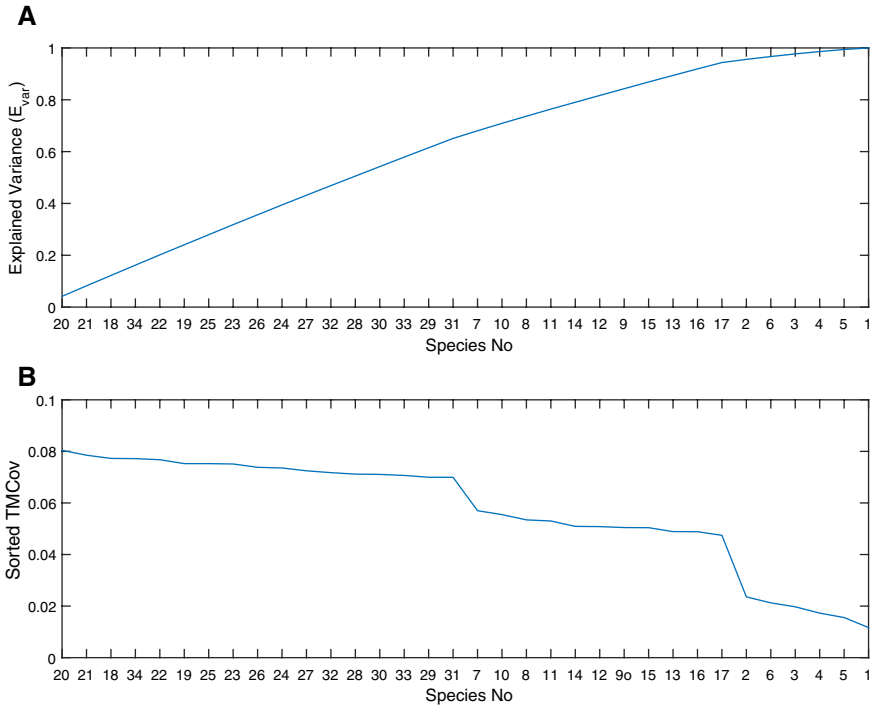


Fig. 2 Sensitivity of the model in Susree and Anand (2017) to initial concentrations of species

5 Discussion

The current study adds a different perspective to the sensitivity analysis given in Susree and Anand (2017) of the Susree-Anand model: in this article the focus is on sensitivity to changes in initial concentrations of clotting proteins/ inhibitors/ platelets. Perturbations in rate constants as well as in initial conditions influence not only

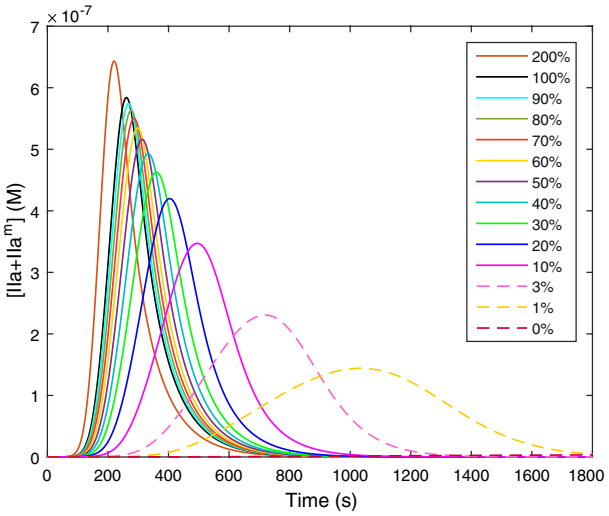


Fig. 3 Effect of varying initial concentration of VIII (10–200%) on thrombin concentration

the initiation of clotting but also the progress of clot formation and lysis. And this can, in turn, affect the course of blood clotting as a whole. This study shows that the model in Susree and Anand (2017) is most sensitive to perturbations in the initial concentration of factor VIII.

It is well known that factor VIII is indispensable in the progress of clot formation by acting as a cofactor in the activation of factor X; congenital deficiency of factor VIII is also characterized by the more predominant form of hemophilia (Hemophilia A). Allen et al. (2004) have shown in their experimental investigation that the average rate of thrombin generation is reduced to one tenth when no factor VIII is added. In our analysis, we observe that the increase in peak thrombin concentration is nearly six-fold when factor VIII concentration is increased from 1 to 200%, which is in consensus with the thrombin generation assay reported in Allen et al. (2004). This indicates not only the robustness of this method but also presents sensitivity analysis as a non-invasive alternative to understand the effect of varying initial concentrations on the course of clot formation. Results of the sensitivity analysis of the Susree-Anand model lead us to identify the significance of initial factor VIII concentration in the activation of factor X which occurs during the initial stages of clotting. The hypothesis generated from this analysis is in concurrence with the results of the sensitivity analysis presented in Naidu and Anand (2014) in signifying the role of factor VIII in the progress of clot formation. The analysis also verifies the hypothesis presented by Ovanesov et al. (2002) that a deficiency in either factor VIII or IX can disrupt normal self-sustained thrombin production. It can, therefore, be proposed based on this study that uncertainty in the initial concentration of factor VIII has a critical impact on the rate of thrombin production, and hence clot formation, in general and not in hemophilic patients alone.

Acknowledgements We thank the Department of Science and Technology (DST) for financial support through Grant Number INT/RUS/RFBR/P-180.

References

Allen GA, Wolberg AS, Oliver JA, Hoffman M, Roberts HR, Monroe DM (2004) Impact of procoagulant concentration on rate, peak and total thrombin generation in a model system. J Thromb Haemost 2(3):402–413

Anand M, Rajagopal K, Rajagopal KR (2003) A model incorporating some of the mechanical and biochemical factors underlying clot formation and dissolution in flowing blood. J Theor Med 5(3–4):183–218

Anand M, Rajagopal K, Rajagopal KR (2008) A model for the formation, growth, and lysis of clots in quiescent plasma. a comparison between the effects of antithrombin III deficiency and protein c deficiency. J Theor Biol 253(4):725–738

Danforth CM, Orfeo T, Mann KG, Brummel-Ziedins KE, Everse SJ (2009) The impact of uncertainty in a blood coagulation model. Math Med Biol 26(4):323–336

Diamond SL (2013) Systems biology of coagulation. J Thromb Haemost 11(s1):224–232

Furie B, Furie BC (2008) Mechanisms of thrombus formation. N Engl J Med 359(9):938–949

Hockin MF, Jones KC, Everse SJ, Mann KG (2002) A model for the stoichiometric regulation of blood coagulation. J Biol Chem 277(21):18,322–18,333

Luan D, Zai M, Varner JD (2007) Computationally derived points of fragility of a human cascade are consistent with current therapeutic strategies. PLoS Comput Biol 3(7):e142

Mann KG (2012) Is there value in kinetic modeling of thrombin generation? yes. J Thromb Haemost 10(8):1463–1469

Naidu PP, Anand M (2014) Importance of VIIIa inactivation in a mathematical model for the formation, growth, and lysis of clots. Math Model Nat Phenom 9(06):17–33

Ovanesov MV, Krasotkina JV, Ul'yanova LI, Abushinova KV, Plyushch OP, Domogatskii SP, Vorob'ev AI, Ataullakhanov FI (2002) Hemophilia a and b are associated with abnormal spatial dynamics of clot growth. Biochimica et Biophysica Acta (BBA)-General Subjects 1572(1):45–57

Panteleev MA, Ananyeva NM, Ataullakhanov FI, Saenko EL (2007) Mathematical models of blood coagulation and platelet adhesion: clinical applications. Curr Pharm Des 13(14):1457–1467

Panteleev MA, Dashkevich NM, Ataullakhanov FI (2015) Hemostasis and thrombosis beyond biochemistry: roles of geometry, flow and diffusion. Thromb Res 136(4):699–711

Susree M, Anand M (2017) A mathematical model for in vitro coagulation of blood: role of platelet count and inhibition. Sādhanā 42(3):291–305