Mathematical Modeling of Human Blood Clotting Formation

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Abstract— **Over the last two decades, mathematical modeling has become a popular tool in study of blood coagulation. This paper describes the coagulation pathway and presents a mathematical model for the generation of blood clot in human vasculature. Parameters of interest in this study include procoagulants and anticoagulants whose activity may be enhanced by various activator enzymes. The process of human blood clotting involves a complex interaction between these parameters and continuous time and state processes. In this work, we propose to model these highly inter-relational processes by a set of nonlinear chemical rate equations. We have modeled this process as a dynamical system, as chemical reaction of blood clot is similar to the Michaelis-Menten kinetics. Simulation result reveals that for zero concentration of certain activators, blood clot can't embark and for positive concentration of those activators, the clot is formed. In our analytical model some particular anticoagulants are studied and their role in the clotting process is evaluated. Furthermore simulation results for low concentrations of APC, the active protein C, which acts as a anticoagulant, states formation of blood clot.**

Keywords—**Blood clot, Dynamic model, Thrombin, Fibrin**

I. INTRODUCTION

Cardiovascular disease is responsible for an estimated 17 million deaths per year worldwide [1]. Atherosclerosis is a disease leading to the formation of plaques, which may cause localized narrowing of the vessel, creating regions of stagnation and recirculation downstream of the obstruction, or even occlusion [2].

The process of blood coagulation in mammals is complicated, and involves the interaction of more than a dozen coagulation factors as well as a number of proteins from the kinin-kallikrein system and protein inhibitors([3], [4] and [5]).

In 1964, Davie and Ratnoff first brought forward the cascade theory of blood coagulation and divided the coagulation process into three phases of initiation, amplification and propagation [6]. Subsequently, blood coagulation process was studied as a comparatively independent biochemical system. But these studies were somewhat confined to assay and emphasis on single component through clinical test and did not describe the complete dynamical aspect of the biochemical reaction process. In order to facilitate the study of blood coagulation process, it is helpful to have available mathematical model of the system. Mathematical modeling method has been used in the field of blood coagulation and a series of conclusions which fit closely to experimental results have been presented ([7], [8] and [9]). But for a long time, only linear models were described, which only reflected a limited description of the complicated dynamic process of blood coagulation. In 1989, Khanin and Semenov put forward a non-linear model for external blood coagulation for the first time and made some profound analysis [10]. Later Stortelder studied intrinsic blood coagulation and suggested a parameter estimation method [11]. Recently, great progress has been made in blood coagulation studies through mathematical-modeling techniques. In 2002, Xu and co-workers constructed a mathematical model to simulate the dynamic role of platelets and found that if coagulation system was normal, there must be a proportion of activated platelets on which activated factors assembled into functional coagulation complexes. They explained the bleeding tendency in most of the clinically recognized deficiencies; however did not discuss the reason of thrombosis complications [12]. In this study, a non-linear model is proposed to explain the clotting obstruction and thrombosis complication in most of the clinically recognized deficiencies by introducing the function of an anticoagulant protein. This part of coagulation and inhibition is of great importance to homeostasis.

II. Blood Coagulation Process

Homeostasis is a fundamental defense mechanism of all vertebrates and involves two complementary processes: the formation of a blood clot, or thrombus, to stop blood loss from a damaged vessel, and the process of thrombus dissolution, or fibrinolysis which commences once endothelial repair has occurred. These are complex processes involving multiple interdependent interactions among platelets, endothelial cells, white cells and plasma proteins. By convention, some of the procoagulant plasma proteins are referred to as factors with assigned Roman numeral designations. The proteases involved in clot formation circulate in their inactive, or zymogen state in healthy animals, only becoming biologically active when the vasculature is perturbed ([13] and [14]).

Fig. (1) shows a coagulation cascade. The cascade is simultaneously initiated by two different mechanisms whose resulting "pathways" intersect when the activation of factor X is transformed into factor Xa (thrombokinase). The intrinsic pathway is triggered when vascular cell damage exposes blood plasma to a negatively charged surface (phospholipids)—hence the term "contact system." It is also believed that vascular injury precipitates a rise in plasma zinc concentration, which in turn enables certain initiating reactions of the intrinsic pathway ([15] and [16]).

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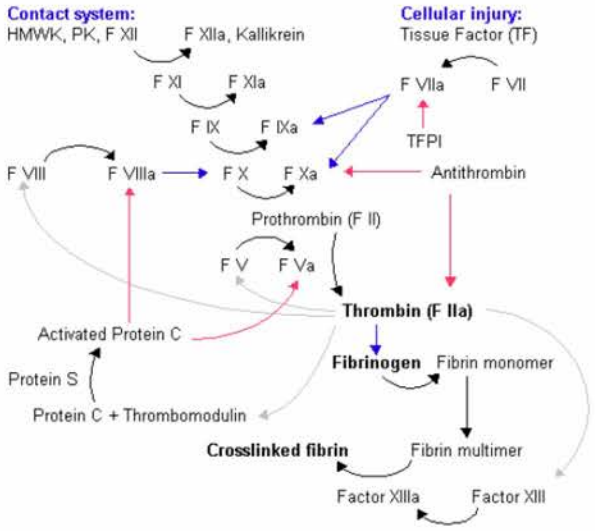

Fig.1 The coagulation cascade comprises of multiple interacting pathways. This figure is taken from http://en.wikipedia.org/wiki/Coagulation. Legend: HWMK = High molecular weight kininogen, PK = Prekallikrein, TFPI =Tissue factor pathway inhibitor. Black arrow = conversion/activation of factor. Red arrows = action of inhibitors. Blue arrows = reactions catalyzed by activated factor. Gray arrow = various functions of thrombin

The extrinsic pathway is initiated when the ruptured blood vessel releases tissue factor (sometimes called factor III or tissue thromboplastin) into the plasma, which subsequently binds with unactivated factor VII (proconvertin). The details of this pathway are discussed below along with a description of the model. The common pathway begins at the activation of factor X and terminates ultimately in the production of a fibrin clot. The most important product of this pathway is thrombin (activated factor II), which is directly involved in the formation of a blood clot but also participates in feedback reactions in both the intrinsic and common pathways. To speed up, both the intrinsic and extrinsic pathways feed the common pathway, but in fact it is now widely believed that the extrinsic pathway serves to "kick-start" the intrinsic pathway into action via feedback from thrombin (IIa) and thrombokinase (Xa) activating factors VIII and XI . Thus the extrinsic pathway directly achieves minimal thrombin production but does so on the order of seconds, whereas the intrinsic pathway generates large quantities of thrombin in minutes [16].

During the amplification phase, factor X activation is only catalyzed by the complex of activated factors IX (IXa) and VIII (VIIIa). Factor VIIIa functions as a cofactor to IXa. Factor X activating complex also comprises of negatively charged phospholipids and Ca2+, and is usually referred to as tenase complex. The role of tenase complex is similar to prothrombinase, which is composed of factor Xa, Va, negatively charged phospholipids and Ca2+. Factor Va functions as a cofactor of factor Xa which activates prothrombin (factor II) transformation to thrombin (IIa). In this stage, thrombin acts as feedback coagulant. It not only activates factor V transformation to Va and VIII to VIIIa, but also activates platelet. The surface of activated platelet provides the membrane (full of negatively charged phospholipids) which is essential to the formation and expression of tenase complex and prothrombinase complex. Once sufficient numbers of tenase and prothrombinase complexes are assembled on the platelet surface, a large amount of thrombin is produced by tenase complex activating X transformation to Xa. Subsequently, prothrombinase complex activates prothrombin transformation to thrombin which in turn provides sufficient fibrinogen to fibrin, resulting in fibrin clot formation.

APC is an anticoagulant serine protease take from the two chains, namely vitamin K-dependent zymogen and protein C. Protein C is transformed to APC with an effect of TM (Thrombomodulin). APC functions as an anticoagulant to inactivate cofactors VIIIa and Va and follows to inhibit the active prothrombinase and factor tenase complex. The inactivation of factor VIIIa and Va by APC is strengthened by protein S, and both are Ca2+ and phospholipids dependent. The physiological importance of the anticoagulant pathway is most clearly demonstrated by the increased risk for venous TM associated with both protein C deficiency and massive thrombosis complications occurring in infants [18].

Most recently, it has become evident that all dual pathways interact drastically during the clotting process. In fact, the pathway appellations are in some respects merely holdovers from early, more limited models of blood clotting; they are presently retained primarily to indicate initiation mechanism [17].

III. METHODOLOGY

It is interesting to examine the model of single enzyme system following what is referred to as the Michaelis-Menten kinetics. The concentration relationships in such a system may be expressed by:

$$E + S \underset{k_2}{\overset{k_1}{\leftrightarrow}} X \xrightarrow{k_3} E + P \qquad (1)$$

where E is the enzyme, S the substrate, X the enzyme-substrate complex (often called ES), P the product or metabolite, and k_1,k_2 and k_3 are rate constants [19].

Physiological analysis of blood clotting, and Michaelis-Menten kinetics, give rise to a reaction cascade for fibrin generation depicted in Fig.1. Here β is the concentration of a coagulant which can activate factor IX transformation to IXa. Based on this scheme, a mathematical model is proposed to describe the reaction. We considered the activation and inhibition of factors Xa and VIIIa where factor VIII is mainly activated by thrombin and factor Xa may also contribute to activation of VIII while VIIIa is inactivated by APC due to its inherent instability.

The inactivation rate is proportional to substrate concentration and the production of VIIIa can be described by the following equation:

$$\frac{d[VIIIa]}{dt} = k_2[IIa] + k_3[Xa] - k_4[APC]\frac{[VIIIa]}{b_1 + [VIIIa]} - h_2[VIIIa] \qquad (2)$$

Here the concentrations of the reactants, $[VIIIa]$ in nM and the kinetic constants (k), determine the rate of each reaction and h is the dissipating or disassociating coefficient. According to Fay's plasma experiment, the relationship between the activated rate of factor Xa and the

concentration of factor VIIIa is an S curve[20]. Here Xa is dissipated in plasmin and its dissipating rate is proportional to the concentration of factor Xa. Therefore, the concentration variation of factor X with time can be given as:

$$\frac{d[Xa]}{dt} = \frac{k_5[IXa][VIIIa]}{b_2 + [VIIIa]} - h_3[Xa] \tag{3}$$

In order to discuss the effect of the APC on the whole reaction, we assume that the amount of coagulant of factor IX is limited, and it is only assumed to vary with time. Therefore, the activation model from Fig. 1 can be described by the following differential equations:

$$\begin{aligned}
&\frac{d[IXa]}{dt} = k_1\beta - h_1[IXa] \\
&\frac{d[VIIIa]}{dt} = k_2[IIa] + k_3[Xa] - k_4[APC]\frac{[VIIIa]}{b_1 + [VIIIa]} - h_2[VIIIa] \\
&\frac{d[Xa]}{dt} = k_5[IXa]\frac{[VIIIa]}{b_2 + [VIIIa]} - h_3[Xa] \\
&\frac{d[Va]}{dt} = k_6[IIa] - k_7[APC]\frac{[Va]}{b_3 + [Va]} - h_4[Va] \\
&\frac{d[APC]}{dt} = k_8[IIa] - h_5[APC] \\
&\frac{d[IIa]}{dt} = k_9[Xa]\frac{[Va]}{b_4 + [Va]} - h_6[IIa]
\end{aligned} \tag{4}$$

where k_i is the activation rate parameter for i=1, 2, 3, 5, 6, 7, 8, $k_9=k_{cat}[II]$, and h_i is the inactivation or dissipating coefficient.

Consider,

$$\begin{aligned}
&x1 = [IXa], x2 = [VIIIa], x3 = [Xa], x4 = [Va], \\
&x5 = [APC] and x6 = [IIa]
\end{aligned} \tag{5}$$

We substitute eq(5) in the dynamic model of eq(4).

It is easy to verify that for β=0, system (5) has a zero equilibrium point $(x1, x2, x3, x4, x5, x6) = (0,0,0,0,0,0)$. For β> 0, system (5) has a non-zero positive equilibrium point $(x1, x2, x3, x4, x5, x6) = (k_1\beta / h_1, 0,0,0,0,0)$. For the described non-linear system, it is difficult to provide other positive equilibrium points or to discuss their bifurcation [21].

IV. Results

The concentrations of proenzyme in plasma is given by [22]:

$$[IX] = 90nM, [VIII] = 0.7nM, [X] = 170nM,$$

$$[V] = 20nM, [PC] = 60nM, [II] = 1400nM$$

Here initial concentrations of each activated factor is *0.01 nM*. This model was simulated with MATLAB software. As noted earlier due to the important role that β, the concentration of coagulant, plays in the mathematical modeling of blood clotting its influence on the generation of factors Xa and IIa was investigated. Hence by Changing the value of β and fixing other parameters, noted in Table 1, its influence on the solution of the system was evaluated. Figures 2 through 4 depict the dynamic solution for the proposed model. The results show that as β is increased, the equilibrium point changes from zero to a positive equilibrium point and further to a positive amplifying equilibrium point. Note that equilibrium points are asymptotically stable.

To investigate the contribution of APC to blood coagulation, the contribution of k_8 parameter is considered. Hence by fixing all parameters in normal levels and changing k_8, we may utilize it to control the effect of APC generation. From a physiological point of view, when k_8 is less than its normal level (*0.87/min*), APC will be deficient. Also when k_8 is beyond its normal level, APC will be excessive, which means that VIIIa or Va cannot exert their cofactor role completely. Henceby observing the influence of APC to the positive solution of the system, valuable information about the role of VIIIa and Va is obtained. The results show that when the value of k_8 increases, the concentration of factors Xa and IIa begin to decrease and blood clot doesn't form. Figures 5 and 6 present the results for k_8 variation as noted above.

Table 1

Parameters that use in model ([22], [23], [24], [25] and [26]).

$$\begin{aligned}
&k1 = 15\min^{-1}, k2 = 1.4\min^{-1}, k3 = 2.3\min^{-1}, k4 = 4\min^{-1}, \\
&k5 = 221\min^{-1}, k6 = 2.6\min^{-1}, k7 = 05\min^{-1}, k8 = 0.87\min^{-1}, \\
&k9 = 1900\min^{-1}, h1 = 6.12\min^{-1}, h2 = 0.35\min^{-1}, h3 = 0.33\min^{-1}, \\
&h4 = 0.4\min^{-1}, h5 = 0.34\min^{-1}, h6 = 0.35\min^{-1}, b1 = 11nM, \\
&b2 = 23nM, b3 = 6.1nM, b4 = 250nM,
\end{aligned}$$

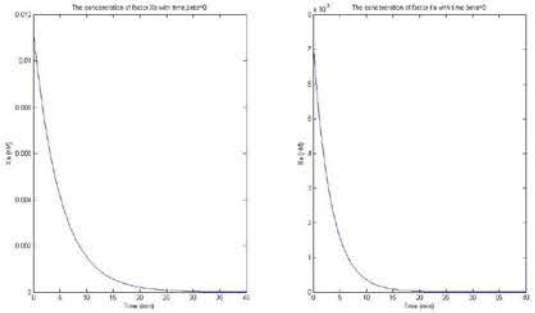

Fig.2 The concentration of factor Xa and IIa versus time for β = 0.

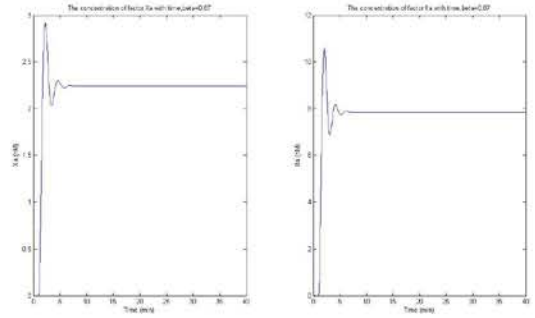

Fig.3 The concentration of factor Xa and IIa versus time for β = 0.87 .

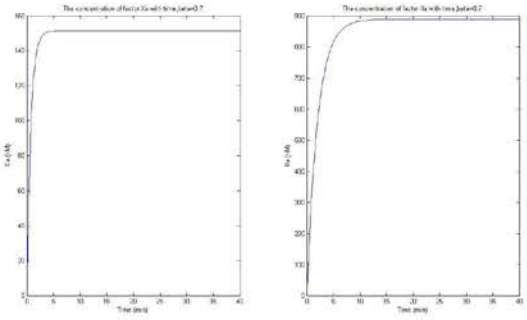

Fig.4 The concentration of factor Xa and IIa versus time for $\beta = 8.7$.

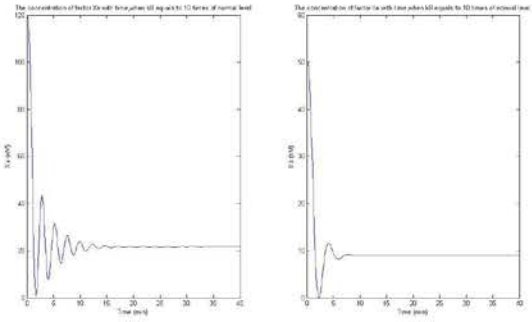

Fig.5 The concentration of factor Xa and IIa versus time for k8=10* normal value.

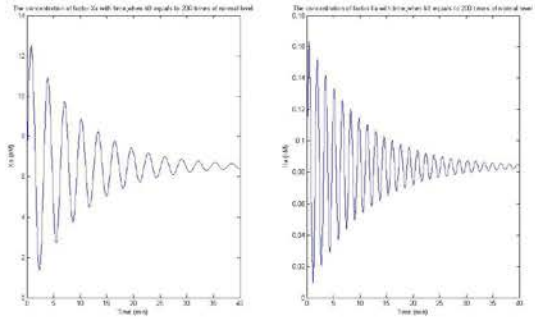

Fig.6 The concentration of factor Xa and IIa versus time for k8=200* normal value.

V. Conclusion

In this paper a mathematical model is proposed to describe the blood coagulation mechanism. We discussed the role of positive and negative feedback reactions in blood coagulation and the role of anticoagulant parameter through the proposed dynamic model. Our study demonstrated that anticoagulant parameters affect blood clotting similar to VIIIa and Va factors.

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