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Review Article

A Model Incorporating some of the Mechanical and Biochemical Factors Underlying Clot Formation and Dissolution in Flowing Blood

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Multiple interacting mechanisms control the formation and dissolution of clots to maintain blood in a state of delicate balance. In addition to a myriad of biochemical reactions, rheological factors also play a crucial role in modulating the response of blood to external stimuli. To date, a comprehensive model for clot formation and dissolution, that takes into account the biochemical, medical and rheological factors, has not been put into place, the existing models emphasizing either one or the other of the factors. In this paper, after discussing the various biochemical, physiologic and rheological factors at some length, we develop a model for clot formation and dissolution that incorporates many of the relevant crucial factors that have a bearing on the problem. The model, though just a first step towards understanding a complex phenomenon, goes further than previous models in integrating the biochemical, physiologic and rheological factors that come into play.

Keywords: Clot; Hemostasis; Endothelium; Platelet; Thrombin; Fibrinolysis

INTRODUCTION

Numerous mechanisms have evolved to maintain blood in a state of delicate balance. Factors and processes exist both to promote and inhibit clot formation, as well as, clot maintenance. A fluid tissue under normal conditions, blood coagulates due to an imbalance in favor of prothrombotic factors. In turn, clot maintenance is determined by various stimuli, such as vessel wall injury, endothelial dysfunction, abnormally high shear stresses, flow recirculation and stasis. Under normal circumstances, the process of clot formation, or hemostasis, has evolved to seal defects in the cardiovascular system and stem hemorrhage as part of a physiological response that precedes healing. The eminent pathologist Rudolf Virchow (1856), well over a century ago, laid out the broad stimuli for thrombus formation: (1) local flow stasis/stagnation, (2) blood vessel injury/endothelial dysfunction, and (3) 'hypercoagulability', or an augmented native tendency for blood to clot. Typically, clot formation occurs only if the hemostatic stimulus reaches a certain threshold; this threshold is conditioned by both hemodynamic and biochemical factors including local flow conditions, availability of membrane binding sites for catalysis, concentration of di/multivalent ions like calcium (Ca^{2+}), and finally, concentrations of the reagents involved in clot formation: platelets and coagulation factors. It is apt to think of the hemostatic system as being in a state of 'system idling' due to subthreshold stimuli, which is primed to respond explosively once the threshold is crossed. During hemostasis, the system responds in a manner that eventually returns it to its idling state while at the same time redressing the initial stimulus. Pathological conditions may result as a consequence of either hypo or hyper function of any or all of the components of the hemostatic system. On the one hand, hypofunction of these components results in impairments in clot function or maintenance, i.e. bleeding disorders. On the other hand, hyperfunction of these functions results in inappropriate clot formation or maintenance, i.e. thrombotic or thromboembolic disorders. These conditions will be discussed in this article. An integrated model is yet to emerge that incorporates all of these factors in a physiologically accurate scheme.

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The endothelium plays a critical role in maintaining blood fluidity by balancing a natural tendency to clot in isolation with a set of counteracting mechanisms (e.g. secretion of thrombomodulin, release of nitric oxide and PGI_2 etc.). When the endothelium is disrupted, blood comes into contact with proteins in the sub-endothelial layers, and this initiates the formation of a clot. Platelet activation and subsequent adhesion to the sub-endothelial surface is accompanied by platelet aggregation. Simultaneously, the extrinsic pathway of coagulation, particularly active in the setting of tissue damage, leads to the formation of thrombin, and hence the cleavage of fibrinogen to form fibrin monomers that polymerize to form fibrin strands. Fibrinolysis, the process leading to the degradation of fibrin molecules is signalled almost simultaneously with clot formation, and leads to the dissolution of the clot. This broad picture is host to multiple interacting mechanisms that are integrated so as to heal vascular injury and stem blood loss, with only transient or no resultant tissue ischemia. In addition, rheological factors also play a crucial role (Goldsmith and Turitto, 1986; Turitto and Hall, 1998; Lowe, 1999) in modulating the response at each level. A systematic quantification of the various factors has proved elusive thus far.

Mathematical modeling has emerged as a useful tool in supplementing experimental data and hence forming a clearer picture of the hemostatic system. A model that could predict regions susceptible to clot formation and also track the extent of clotting, once initiated, would also be of immense value to engineers seeking to minimize such an occurrence within a cardiovascular device. There is a need to develop models that can help us understand the interplay of the rheological and biochemical factors under the diverse flow conditions found in the human vasculature. Such models are in their infancy at present, tending to focus on single aspects of this multifaceted problem. In this article, we present a model that accounts for the rheology of the blood and the clot while at the same time incorporating the basic reactions of platelet activation, the extrinsic coagulation pathway, and fibrinolysis, and allowing for surface modulation of these reactions. We view clot formation and dissolution in flowing blood as a moving boundary problem involving two viscoelastic liquids, the dynamics of the interface being governed by both mechanical and biochemical factors. This is but a first step in the direction of modeling and understanding the problem of clot formation and its dissolution in flowing blood.

As a proper mathematical model requires a proper understanding of the myriad of factors that play a role in the formation and dissociation of clots, we feel the need to discuss the biochemical, rheological and medical factors at some length, before starting to develop the model.

The rest of this article is divided into five sections. In the next section, the problem is outlined along with a brief survey of the various modeling approaches that have been employed so far. In the section 'Pathologies of Clot Formation', the clinical relevance of this study is brought out by documenting the disorders of the hemostatic system manifesting themselves in either pathologic clot formation and maintenance or impaired clot formation and maintenance. In the section 'Model Development', the features of the model used to simulate the flow of blood with clot formation and dissolution are explained in detail. In the section 'Application of Model System to Simple Flow Problems', the procedure to corroborate the model with experimental data is provided. To test the efficacy of the proposed model a simple problem is solved within the context of a simplified version of the model. The results predicted by the simpler model are in keeping qualitatively with physical expectation. The 'Discussion' is devoted to a summary of the model, its relevance and applicability, and some remarks concerning the limitations and possible extensions to the model.

PROBLEM FORMULATION AND LITERATURE SURVEY

Two important interacting processes, platelet activation followed by adhesion, aggregation and coagulation, are initiated when there is an imbalance in favor of prothrombotic factors in flowing blood. This occurs in response to a variety of stimuli; an injury in the vessel wall, for instance, or contact with an exogenous foreign surface like glass, or imbalances between pro- and anti-thrombotic factors in the intact endothelium itself ('Endothelial dysfunction' Gimbrone, 1999), or due to certain flow conditions like stagnation and recirculation zones. We focus on the extrinsic coagulation pathway stimulated in response to vessel injury. Platelets can adhere to collagen, and to various adhesive glycoproteins, found in the sub-endothelial layer and undergo morphological and chemical changes as part of a process of activation that occurs in conjuction with the coagulation reactions. Platelet activation can also occur due to prolonged exposure to high shear stresses. These activated platelets (AP) can then form aggregates by binding to each other and also to fibrin. The extrinsic coagulation pathway, initiated by the exposure of tissue factor (TF), a cell membrane protein, is thought to begin with the formation of the TF-VIIa molecular complex on the injured vessel surface. Coagulation involves a core cascade of enzymatic reactions (MacFarlane, 1964) involving plasma zymogens, anionic phoshpholipids on the membranes of AP, and calcium ions resulting, ultimately, in the formation of thrombin from prothrombin. Thrombin cleaves the peptide bonds in fibrinogen resulting in fibrin, a stringy polymeric molecule. The platelet aggregates along with the fibrin mesh constitute the blood clot, and their formation comprises hemostasis, the normal response to vessel injury. Fibrin, along with other intermediates of the coagulation pathway and enzymes produced by endothelial cells, catalyze and participate in a set of reactions (fibrinolysis) that lead to the conversion of plasminogen (PLS) to plasmin, thus initiating clot dissolution. Clot dissolution may also occur due to elevated shear stresses. This broad picture

(an excellent overview of the hemostatic system can be found in Colman *et al.* (2001)) includes multiple positive and negative feedback loops and regulatory processes that involve the molecules in blood, its flow and the surface of the vessel (Virchow's triad). It is crucial that these processes act in a controlled fashion for the maintenance of vascular integrity without significant impairment to the flow of blood. Thus, the formation and dissolution of clots is a highly complex process that at the moment cannot be modeled in its entirety. The biochemical reactions that come to bear upon the problem are too numerous to be captured fully and we are then left with the task of making a judicious choice of the quintessential biochemical reactions and mechanical inputs that need to be put into place to develop a mathematical model that is capable of describing the essential features of the problem. A brief review of the main components and processes that are involved in and lead to the formation, development and dissolution of clots that will be incorporated in the model is given in the following subsections.

Whole Blood: Components and Rheological Behavior

Whole blood consists of gel-like 'cell' matter in an aqueous plasma solution. The cell matter (which makes up around 46% of the volume in human blood) consists of formed elements: primarily (around 98%) red blood cells (RBCs) or erythrocytes, white blood cells (WBCs) or leukocytes, and platelets. The volume concentration of RBCs in whole blood is termed hematocrit. Plasma consists primarily in water (92–93%) in which various proteins (f-I or fibrinogen, f-II or prothrombin, f-V, f-VIII, f-IX, f-X, f-XI, f-XII, f-XIII, anti-thrombin III (ATIII), tissue-factor pathway inhibitor (TFPI) , protein C (PC), protein S, PLS, α_1-antitrypsin, α_2-anti-plasmin, etc.) are dissolved along with various ions (sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), chloride (Cl^-), bicarbonate (HCO_3^-), phosphate (PO_4^{3-}), etc.). Plasma is a Newtonian liquid with a viscosity of approximately 1.2 cP (Chien *et al.*, 1966). Erythrocytes are biconcave deformable discs that lack nuclei. The RBC membrane comprises 3% by weight of the entire RBC and consists of proteins (spectrin) and lipids. The RBC cytoplasm is a solution of hemoglobin in water (32 g/100 ml). Evans and Hochmuth (1976) performed micropipette aspiration experiments that showed that RBCs display viscoelastic behavior. They also claimed that the viscoelastic nature of the RBC is only due to the viscoelastic properties of the RBC membrane. Eukocytes are classified as granulocytes, monocytes and lymphocytes, and form less than 1% of the volume of blood. Their influence on the rheology of blood is not considered to be significant except in extremely small vessels like capillaries. Granulocytes exhibit viscoelastic properties (Schmidschonbein and Sung, 1981) in micropipette aspiration experiments. Thus, the various constituents of blood exhibit different rheological properties.

The shear-thinning properties (Charm and Kurland, 1965; Chien *et al.*, 1966) and stress-relaxation behavior (Thurston, 1972) of whole blood are well known. The shear-thinning nature of blood has been tied to the disaggregation of the RBC-rouleau aggregates that form at low shear and the deformability of the RBCs (Chien *et al.*, 1967a,b), while its stress-relaxation properties are tied to the viscoelastic nature of the RBC membrane (Evans and Hochmuth, 1976; Chien *et al.*, 1978). The viscoelastic behavior of blood is less prominent at higher shear rates (Thurston, 1973). We model whole blood as a shear-thinning viscoelastic fluid continuum with a deformation dependent relaxation time (Anand and Rajagopal, 2004a). The properties of this continuum are assumed to depend on, and regulated by the various biochemical processes that take place and this is reflected in the basic balance laws for the continuum being coupled to and augmented by a system of convection-reaction-diffusion equations.

Platelet Activation, Adhesion and Aggregation

Platelets form a small fraction (by volume) of the particulate matter in human blood (around 3%). They are among the most sensitive of all the components of blood to chemical and physical agents (Lasslo, 1984). Platelets are small discoid cell fragments, approximately 6 μm^3 in volume, derived from megakaryocytes. Platelet activation is the process by which the resting discoid platelet undergoes a series of chemical and morphological changes as a result of which the organelles within the platelet are centralized, glycoproteins on the platelet membrane undergo a change in conformation, and long pseudopods are extended so that the activated platelet is a sticky spiny sphere. Platelet activation occurs due to interaction with collagens and adhesive glycoproteins exposed by damage (endotheli, for instance, or due to interactional damage) with thrombin or adenosine diphosphate (ADP) that circulate in the blood. A transient rise in cytoplasmic levels of calcium ion (Ca^{2+}) resulting, ultimately, in the formation of an actino–myosin complex that facilitates contraction of the platelet is one of the key features of platelet activation. Various chemicals are contained in three organelles (α granules, dense bodies, lysosomal granules) within the platelet, and some of these, like ADP and thromboxane, are released during activation and facilitate the activation of other platelets. Platelet activation is followed by[¶] interaction with plasma proteins like Factor-IX (IX), Factor-V (V), and vWF, fibrinogen, and fibrin so as to adhere to sub-endothelial tissue, and

[¶]It is somewhat simplistic to envisage the formation of clot as the end product of a sequence of processes. Many of the processes, like platelet activation, aggregation, coagulation and fibrinolysis, are interlinked, and interact much earlier than was previously thought; for instance, Factor VIII (f-VIII) circulates in the plasma bound to von Willebrand Factor (vWF), and requires cleavage by thrombin to release f-VIII (required for thrombin production) and vWF (required for platelet aggregation).

the platelet form platelet aggregates and ultimately form a clot. The membrane-bound complexes GpIb and GpIIb-IIIa play an important role in this process (Frojmovic, 1998; Ruggeri *et al.*, 1999). The extension of long pseudopods, usually after a time lag (Frojmovic *et al.*, 1991; 1994), facilitates aggregation, by increasing the probability of collisions with other platelets and by increased membrane fluidity. The shape change, followed by binding of macromolecules, leads to enhanced 'stickiness' thus promoting clot formation. Activated platelets also serve as the assembly site for enzyme complexes that are essential for clot formation. The details surrounding the process of platelet activation, adhesion and aggregation can be found in Lasslo (1984), Yamazaki and Mustard (1987) and Anthony Ware and Coller (1995). Macroscopic studies of platelet adhesion, deposition and thrombus formation in annular flow chambers Baumgartner (1973) (or in the stagnation point flow chamber (Affeld *et al.* (1995)) have shown that the rate and extent of platelet adhesion, platelet deposition and platelet thrombus (or mural thrombus) formation are affected by the flow conditions (shear rates) (Weiss *et al.*, 1978; Tschopp *et al.*, 1979; Turitto and Baumgartner, 1979; Turitto *et al.*, 1980; see also Alevriadou *et al.* (1993) for the effect of flow conditions on vWF mediated platelet aggregation), the presence of citrate (Baumgartner *et al.*, 1980), and surface properties (Baumgartner *et al.*, 1976; Baumgartner, 1977; see also Hubbell and McIntire, 1986). Platelet activation itself (Kroll *et al.*, 1996; Christodoulides *et al.*, 1999), and sometimes lysis, is known to occur in response to prolonged exposure to high shear stresses (Wurzinger *et al.*, 1985). Platelet aggregates, by themselves, are susceptible to break-up by high shear stresses (Wurzinger, 1990). Shear stresses also, play an additional role in platelet activation by damaging erythrocytes to release hemoglobin. Hemoglobin is known to hinder the natural platelet (activation) inhibition mechanisms. The stresses required to damage erythrocytes are much higher than those required to damage platelets, and the role of hemoglobin in platelet activation is probably insignificant.

The Extrinsic Coagulation Pathway

The exposure of TF (a cell membrane bound protein) in the subendothelium to the mainstream blood flow results in a chain of coagulation reactions that lead to the formation of thrombin, an enzyme that catalyzes fibrin production and a very important enzyme for platelet activation. It is generally accepted that the formation of the TF-VIIa complex on the sub-endothelium leads to the formation of the enzymes, Factor-IXa (IXa) and Xa (Xa), both of which are serine proteases, from the respective plasma zymogens (enzyme antecedents), Factor-IX (IX) and X (X), after the cleavage of the prosequences. These enzymes, in turn, catalyze the formation of Factor-Va (Va) and VIIIa (VIIIa) from Factor-V (V) and VIII (VIII), respectively. The enzyme complex IXa-VIIIa bound to the membrane of the activated platelet (or negatively charged phospholipid, to be precise) catalyzes the formation of Xa from X. The membrane bound IXa-VIIIa complex is termed 'tenase'. The next important step in this chain is the formation of enzyme complex Xa-Va on the membrane of the activated platelet. The membrane-bound Xa-Va complex ("prothrombinase") catalyzes the production of thrombin from prothrombin. Thrombin acts on fibrinogen (a plasma protein) to convert it to yield fibrin monomers that later polymerize and are cross-linked to form a fibrin matrix. The role of fibrinogen and fibrin in the coagulation reactions has been highlighted in a recent review (Blömback, 1996).

Thrombin and Xa play a major role in the positive feedback mechanisms by catalyzing the production of almost all the intermediates required for their production. Thrombin activates platelets that then release ADP which lead in turn to the activation of other platelets. Thrombin activates Factor-XI (XI), a zymogen that is linked to the intrinsic coagulation pathway, which in turn activates IX. Thrombin also plays a role in the inhibition of coagulation by catalysing the formation of active protein C (APC) in plasma through the thrombin–thrombomodulin complex.

There are three major inhibitory mechanisms in blood that regulate the coagulation cascade: those that involve Antithrombin III (ATIII), TF pathway inhibitor (TFPI) or APC. ATIII inhibits thrombin, Xa and, to a lesser extent, IXa, and blocks the active sites of these enzymes. ATIII activity is increased manifold by the presence of heparin (which is produced in sulfated form by the endothelial cells). Plasma ATIII concentration is greater than that of all the coagulation zymogens put together; its concentration-dependent kinetics (second order) however seems to warrant such an excess as even at 50% of the normal concentration, a level at which there is still a significant excess of ATIII, the partial deficiency is linked with a high risk of thrombosis. TFPI binds with Xa to block the action of the TF-VIIa complex and also inhibits the Xa in the prothrombinase complex. APC is derived from protein C by the catalytic action of thrombin bound to thrombomodulin (secreted by endothelial cells). APC binds with Protein S in the presence of anionic phospholipid and deactivates Va and VIIIa. Normally prothrombinase is not affected by the action of APC, but APC bound Va binds to Xa and blocks the action of the Xa-Va complex.

An excellent review of the extrinsic and intrinsic coagulation pathways, the various positive and negative feedback mechanisms, and the inhibitory reactions that control coagulation may be found in Bauer and Rosenberg (1995) and Jesty and Nemerson (1995). The biochemistry of coagulation is quite complicated and involves various positive and negative feedback loops within the broad framework outlined above.

The coagulation reactions and clot formation are known to be affected by mechanical factors. We have already mentioned the role of shear stresses in platelet activation; this has ramifications for the availability of

phospholipid binding sites for the assembly of tenase and prothrombinase. Experimental evidence seems to suggest a shear-rate dependence for the kinetics of fibrin formation (Tippe and Müller, 1993), and fibrin coagulation seems to occur in disturbed flow, especially flow recirculation zones, even with intact endothelium (Reininger *et al.*, 1994). However, a perusal of (Blömback, 2000) seems to suggest that there is a subtle difference here in that a variant of fibrin (fibrin-I) is formed by activation with an intact endothelium, and that this variant will lead in turn to the formation of another variant (fibrin-II) at lesions, further downstream so that rapid clotting occurs only where needed. At recirculation zones, it seems possible that the fibrin-I itself will lead to the formation of a thrombotic plaque over an extended period of time.

Fibrinolysis and Clot Dissolution

The set of enzymatic reactions that constitute fibrinolysis is initiated when thrombin and fibrin, formed during coagulation, activate endothelial cells resulting in enhanced production of tissue PLS activator (tPA) and urokinase-like PLS activator (uPA). tPA and uPA catalyze the transformation of PLS into the active enzyme plasmin. tPA is the more active among these two; its activity increases manifold in association with fibrin. Plasmin degrades the fibrin polymer into smaller units leading to the dissolution of the clot. Like the extrinsic coagulation pathway that precedes it, fibrinolysis too has its share of regulatory mechanisms.

tPA, uPA and, to a lesser extent, the enzyme Factor-XIIa (XIIa) contribute to the formation of plasmin in the presence of fibrin. tPA is secreted by the endothelial cells in response to thrombin, and other factors like exercise and venous stasis. Thus, an intact endothelium plays a significant role in localizing the formation and dissolution of clots. APC, which is generated by the thrombin–thrombomodulin interaction with protein C, is an accelarator of fibrinolysis as it deactivates PLS activator inhibitor-1 (PAI-1). α_2-Anti-plasmin (L2AP), and PAI-1 are plasma-phase enzymes that inhibit fibrinolysis by binding to fibrin.α_2-Anti-plasmin deactivates free plasmin. The concentration of PAI-1 in plasma increases manifold in the initial stages of clotting, and this facilitates the formation of fibrin by preventing premature fibrinolysis. PAI-1 is released from AP, a process that is greatly amplified by the presence of thrombin. The presence of AP also results in the presence of Factor-XIIIa (XIIIa) in the clot (XIIIa is formed from Factor-XIII (XIII) through the action of thrombin). XIIIa binds to fibrin and anti-plasmin rendering fibrin less vulnerable to the action of plasmin. It also promotes cross linking between fibrin molecules, and stabilizes the clot. There is thus an inhibitory role on fibrinolysis by the same thrombin and fibrin which also initiate and accelerate fibrinolysis. An exhaustive review of the mechanisms of fibrinolysis is given in Francis and Marder (1995). Clot dissolution, or at least the changes in the fibrin network, as a result of fibrinolysis has been visualized in experiments. These indicate a gradual process and, after a certain period, a breaking away of larger portions of the network (Collet *et al.*, 2003).

Clot dissolution can also occur due to mechanical factors such as high shear stress. In Riha *et al.* (1999), clots are subject to increasing levels of stresses (in a cone-plate geometry) until the fibrin matrix ruptures. It is seen that different clots are disrupted at different shear stresses depending on their composition. If one assumes that the clot could be modeled as a linear viscoelastic fluid, then one can correlate the clot strength with the final value of G' in the experiments of Glover *et al.* (1975a,b). This final value, and also the value of the shear stress at which clots rupture depend on the concentration of platelets and fibrin within the clot.

Clots: Types and Rheological Behavior

A clot consists of a fibrin matrix bound to platelet aggregates, RBCs, and WBCs, within which plasma is entrapped. The fibrin fibers typically form less than 1% of the volume of the entire structure. There are three kinds of clots mentioned in the literature: fibrin-rich clots, plasma clots and whole blood clots. The reactions leading to their formation are the polymerisation of fibrinogen by thrombin, and the stabilization of the fibrin through XIIIa; Immobilization of other constituents proceeds alongside. Clots where the fibrin fibers are crosslinked (through addition of XIIIa) are referred to as ligated clots, whereas unligated clots are those where the fibrin structure does not have these crosslinks. Fine fibrin clots are formed at a relatively high pH (around 8.0 and above), while coarse fibrin clots are formed at lower pH (around 7.4–7.5, or near physiological conditions). Fibrin-rich clots are usually formed by treating fibrinogen solutions with thrombin. Plasma clots are formed by treating plasma with thrombin and calcium chloride (added to enhance platelet activation) while whole blood clots are formed from (usually citrated) blood upon addition of calcium chloride.

There is evidence to support the premise that the clot, or at least the fibrin matrix, exhibits viscoelastic behavior, and that this behavior varies dramatically based on the fibrin architecture (Ferry and Morrison, 1947). Clot properties vary in response to a multitude of other factors like the concentration of fibrinogen in the solution, the ionic strength (concentration of NaCl and phosphates) of the solution, and the levels of Calcium ion (Ca^{2+}) (Ferry and Morrison, 1947). In addition, the flow conditions (shear rate etc.) during clot formation (Riha *et al.*, 1997) and the age of the clot also affect the rheological behavior of the clot.

We model the coarse ligated clot formed from human plasma as a very viscous viscoelastic liquid.

Literature Survey of Models for Coagulation

There are various aspects to the complex problem of coagulation in flowing blood, and a plethora of approaches

that seek to understand them. We survey the literature for the various aspects of the problem as formulated above.

Blood has been modeled as a single continuum, as a mixture of interacting continua, or as a suspension of interacting drops in an all-enveloping fluid. A review of the various one-dimensional single continuum models for blood, and the myriad expressions for its apparent viscosity, can be found in Cho and Kensey (1991). A review of three-dimensional continuum models for blood flow can be found in Yeleswarapu (1996). Additional three-dimensional and one-dimensional models that have appeared since then are mentioned in Anand and Rajagopal (2002; 2004a). Mixture theory models for blood flow are quite sparse. A binary mixture theory model for blood has been proposed in Trowbridge (1984) but it predicts an overall Newtonian behavior for the mixture, and cannot be used to model blood flow. Blood has been modeled as a dilute suspension of Newtonian drops in a Newtonian liquid in Kline (1972). A two-fluid model for blood flow in small arteries has also been proposed (Chaturani and Upadhya, 1979).

The early work of MacFarlane (1964) and Davie and Ratnoff (1964) proposed that the extrinsic and intrinsic coagulation pathways as enzyme cascades. Mathematical models for the coagulation pathway have since then expanded upon this idea and investigated various aspects of the coagulation pathway by considering different sets of conditions and reaction schemes. Levine (1966) was the first to come up with a linear system of first order ODEs to describe this set of enzymatic reactions. Models later emerged for the individual reactions of the coagulation pathway (Nesheim *et al.*, 1984; 1992; Nemerson and Gentry, 1986; Gir *et al.*, 1996; Noe, 1996; Panteleev *et al.*, 2002), as the understanding of the coagulation mechanism grew. These models focussed on the factors affecting the kinetics of individual reactions. Models of greater complexity, which brought together the kinetics of various sets of reactions and included feed back loops and inhibitors under different reaction conditions (like flow, extent of stimulus, etc.), emerged towards the late 1980s (Khanin and Semenov, 1989; Willems *et al.*, 1991; Jesty *et al.*, 1993; Baldwin and Basmadjian, 1994; Jones and Mann, 1994; Pohl *et al.*, 1994). This trend has continued with the emergence of models characterized by extremely large systems of equations (ODEs or reaction-diffusion equations) with inclusion of a greater number of aspects (flow rates, membrane binding site densities, availability of phospholipid sites, concentration of calcium, extent of activating stimulus, etc.) like those in Liepold *et al.* (1995), Zarnitsina *et al.* (1996a,b), Kuharsky and Fogelson (2001), Ataullakhanov *et al.* (2002a,b), Hockin *et al.* (2002) and Bungay *et al.* (2003). At this stage, investigators are also beginning to consider whether these model systems can effectively capture the growth of clots or thrombi; our model is a step in this direction.

Within the context of this historical trend, individual research groups have focussed on certain important questions related to the coagulation response. Beltrami and Jesty (1995; 2001) and Jesty *et al.* (1993) focussed on the threshold response of simple representative systems of the enzyme cascade (two or four zymogen–enzyme pairs with positive feed back loops and inhibition), and found that the activation threshold of these systems was affected by flow rate, the size of the patch/injury (related to the availability of binding sites for surface bound enzyme complexes, observed earlier by Fogelson and Kuharsky (1998)), initial concentrations of active enzymes, etc. They also reported that the responses of their models are conditioned by the enzyme kinetics, the presence of feed back loops, and the extent of inhibition. Jones and Mann (1994) presented an early large scale model for thrombin generation via the extrinsic pathway, and extended it to include the role of inhibitors (Hockin *et al.*, 2002). Basmadjian and coworkers investigated the possible steady states of their models, and also studied the regulation of the activation threshold by flow rate, surface area (of injury, say) and the type of surface (Baldwin and Basmadjian, 1994; Gregory and Basmadjian, 1994; Basmadjian *et al.*, 1997). Khanin and coworkers presented one of the earliest models of thrombin generation in plasma (extrinsic pathway) that integrated five zymogen conversion reactions (Khanin and Semenov, 1989), and investigated the regulation of the activation threshold by levels of stimulation of Factor-VII (VII) and XII (Khanin and Semenov, 1989; Khanin *et al.*, 1991), and the sensitivity of clotting time to concentrations of zymogens (Khanin *et al.*, 1998). These models primarily described spatially homogenous systems, i.e. ODEs were used. They were later extended to include spatially inhomogenous systems (Obraztsov *et al.*, 1999) (involving reaction-diffusion equations), and also hypothesised that the flow rate plays a crucial role in the termination of clotting (Barynin *et al.*, 1999). The recent work of Kuharsky and Fogelson (2001), and Bungay *et al.* (2003) was concerned with spatially homogenous systems. While one included the role of bulk flow in controlling the mass transfer of reactants to and from a thin shell where they are well mixed and also different levels of binding site densities, the other documented the role of lipid concentration (or phospholipid availability) in a static well mixed case. Such studies eliminate the role that convection and diffusion may in all probability play in clot formation and, especially, clot dissolution (see Diamond, 1999) but remain significant in view of the insight into the coagulation pathway that they offer. Ataullakhanov and coworkers studied the growth and termination of clot formation in spatially inhomogenous unstirred systems primarily due to contact activation (intrinsic pathway) by means of a mathematical model (Zarnitsina *et al.*, 1996a,b), and recently presented a model that included the role of the extrinsic pathway (Ataullakhanov *et al.*, 2002a,b). The role of TFPI, although acknowledged by them to be important (Panteleev *et al.*, 2002), is not included in these models. Among the earliest to present a large scale model for the intrinsic pathway and investigate its threshold response to

levels of XIa, they noted the effect of calcium ion concentration [Ca^{2+}] on the threshold concentrations of XIa (Ataullakhanov *et al.*, 1995) and also observed that the system cannot return to its pre-activation state without a steep drop in levels of activating signals (in this case, XIa surface concentration) (Pokhilko and Ataullakhanov, 1998). Noting that the XIa threshold at physiological concentrations of [Ca^{2+}] was quite low (Pokhilko, 2000), they determined the actual threshold value by making careful measurements near the activating surface (Kondratovich *et al.*, 2002). Their experiments on clot growth around glass surfaces in unstirred human blood and plasma led them to two hypotheses. One was the presence of an as yet unidentified mechanism that was responsible for inhibition of clot growth (Ataullakhanov *et al.*, 1998). This hypothesis was built upon in their models in 2002 and they postulated the existence of an as-yet unidentified 'effector' that was critical to the termination of clot growth by helping thrombin switch between its role in the catalysis of fibrinogen and its role in PC activation. The appearance of an inhomogenous structure (solid clot alternating with liquid plasma) (Sinauridse *et al.*, 1998) led to the other hypothesis that the coagulation mechanism of blood was a 'bi-excitablemedium' that was best characterized by reaction-diffusion equations which can lead to stationary spatially non-uniform solutions as first described by Turing (1952). This idea was fleshed out by documenting the solutions for the concentrations of the coagulation enzymes (Zarnitsina *et al.*, 2001) and the behavior of the thrombin pulse (the unstable trigger wave) that triggered clot formation (Lobanova and Ataullakhanov, 2003).

There are few constitutive models for clots. Although there are many studies that characterize the viscoelastic behavior of clots there are few that posit constitutive models along these lines. The model proposed in (Thurston and Henderson, 1995) for the plasma clot is a linear viscoelastic model of the three parameter fluid type. It is restricted to application in one-dimensional situations. A three-dimensional Maxwell model for coagulating whole blood has also been proposed (Riha *et al.*, 1997). This model is used to correlate the apparent viscosity, as inferred from steady flow between coaxial cylinders, for a sample of whole blood that is allowed to coagulate.

In almost all the mathematical models that have been published thus far the rheological aspects have not been given the consideration that they deserve. Newtonian models have been used to simulate the flow of blood; an inaccurate assumption. In addition, the effect of the growing thrombus on the flow itself has been neglected. While, for large vessels with clots of minimal thickness, such an assumption may be acceptable, in pathological situations or in small vessels, it may prove unacceptable. In unstirred systems neither the effect of flow on diffusion nor the convection of the reactants themselves are issues that can be addressed; consequently these aspects have been neglected. In addition, scant attention has been paid to the role of the fibrinolytic mechanisms or shear stresses in clot dissolution. Studies on the growth of clots upon the activation of a series of enzymatic reactions, chosen to represent various features of the coagulation pathway, have emerged since 1990. Zarnitsina *et al.* (1996a,b), for instance, postulated a model consisting in eight differential equations representing the intrinsic coagulation pathway culminating in the formation of fibrin. Post-activation, the growth of the fibrin clot into the blood zone was studied in one spatial dimension. In a similar study, Ataullakhanov *et al.* (2002a,b) described and corroborated a slightly improved version of this model, and again investigated the spatial growth of a clot on a segment. In these studies, the influence of flow rate or the constitutive models for the blood and clot on the clot growth was neglected. Sorensen *et al.* (1999a,b) built upon some of the ideas of Fogelson (1992), and proposed a set of coupled convection-reaction-diffusion equations to govern six components that the authors believed were crucial to the processes governing platelet activation and deposition in flowing human blood. They, however, incorporated these reactions as taking place in a Newtonian (Navier-Stokes) fluid (which is not influenced by the presence of the platelet deposit), and solved the equations governing the platelets and platelet agonists while ignoring the effect of the growing thrombus on the flow field. Our approach is an attempt to bridge these gaps by coupling the rheology to the biochemistry (incorporated via convection-reaction-diffusion equations).

Our model focusses on the rheological aspects of the problem while allowing for the introduction of multiple biochemical indicators that are critical to the phenomena of platelet activation and aggregation, coagulation and fibrinolysis. We model clot formation and dissolution as the growth/diminishment of a singular (viscoelastic liquid clot) front in a (shear-thinning viscoelastic) whole blood region. We introduce convection-reaction-diffusion equations that account for platelet activation, the extrinsic coagulation pathway and fibrinolysis (a novelty given that fibrinolysis has been neglected in mathematical modeling[§]), a criterion for shear-stress induced platelet activation, different diffusion coefficients for proteins and a shear-rate enhanced diffusivity of platelets. The clot itself can undergo dissolution due to either fibrinolysis being well advanced or very high shear stresses.

PATHOLOGIES OF CLOT FORMATION

The morbidity and mortality of diseases that are either wholly or substantially governed by disorders in thrombus

[§]Although there is mention of a model in Nesheim and Fredenburgh (1988), the details are absent.

formation or destruction are of significant importance (Fuster, 1994; Epstein, 1996; Nabel, 2003). As discussed below, most of the common pathologies of the cardiovascular system result in deleterious consequences, in large part, due to abnormalities of coagulation. Collectively, these diseases are the leading cause of death in the developed world. This section is organized in two subsections, which discuss: (1) disorders of pathologic thrombus formation and maintenance and conversely, (2) disorders characterized by impaired thrombus formation/maintenance. In turn, the first subsection is organized anatomically based on the sites of pathologic thrombus or thrombo-embolus. This is done because the clinical manifestation of these diseases and often the requisite therapies are governed by the site of thrombus/thrombo-embolus. In contrast, the second section is organized based on the defective hemostatic system component(s). This is because these diseases, while differing with regards to etiology and pathogenesis, typically manifest as bleeding disorders. Furthermore, treatment generally involves simple replacement of deficient/defective components, or in some cases, pharmacologic enhancement of hemostatic system function.

Disorders of Pathologic Thrombus Formation and Maintenance

Atrial Thrombosis

Intra-atrial thrombus formation is most often a consequence of atrial dysrhythmias, namely, atrial fibrillation and atrial flutter. These dysrhythmias are characterized by ineffective or absent atrial contraction. At baseline, diastolic flow of blood into the ventricles is both lower ($t_{\text{diastolic filling}} > t_{\text{systolic ejection}}$) (here, t denotes time) and slower (atrioventricular valve cross-sectional area $>$ semi-lunar valve cross-sectional area) than systolic ejection flow of blood out of the ventricles into the great arteries. Impaired atrial contraction exacerbates this, and thus satisfies the condition of local flow stagnation for thrombus formation. Intra-atrial thrombi generally cause pathologic results due to downstream embolization, rather than from *in situ* effects. These are discussed in the 'Arterial Thrombosis' section.

Treatment of these conditions (dysrhythmias) centers, in the acute setting, on rate control, and when possible, rhythm conversion (cardioversion) which may be pharmacologic or electrical. In the chronic setting, although pharmacologic or surgical treatment (Gillinov and McCarthy, 2003) such as the Maze procedure developed by Cox (1991a,b) may treat the dysrhythmia, atrial thrombus formation and embolization is often a greater concern (Shively *et al.*, 1996; Hart *et al.*, 2003). This is treated via anti-coagulants (inhibitors of coagulation system proteins), typically either an intravenous heparin infusion, low molecular weight heparin (LMWH) subcutaneous injections, or the oral vitamin K competitive antagonist, warfarin. In some situations, unconventional modalities of anti-coagulation such as direct thrombin antagonist infusions (e.g. argatroban, lepirudin, bivalirudin) may be used (Hirsh, 2003). Of note, while anti-platelet therapy does have some benefits in outcomes of patients with atrial fibrillation (Hohnloser and Connolly, 2003), it is substantially and significantly inferior to anti-coagulation (Ezekowitz and Netrebko, 2003). The reasons for these findings are unclear.

Ventricular Thrombosis

As stated, intraventricular cavitary thrombus should be much less likely to form than intra-atrial thrombus, for simple hemodynamic reasons. The existent data support this hypothesis (Ozdemir *et al.*, 2002). However, there are two circumstances in which the native ventricles (typically, the left) may form intracavitary thrombus. First, severe systolic ventricular dysfunction (either primary or secondary to 'afterload mismatch') may result in cavitary thrombus although the incidence is rare (4–15% Sharma *et al.*, 2000). This is thought to be due to low and slow systolic ventricular ejection outflow in the setting of adequate to high ventricular preload, i.e. low and slow flow with global or regional ventricular hypokinesis. Supporting this hypothesis, interestingly, it is that, in patients with mitral regurgitation in which the left ventricle is "auto" afterload-reduced by a parallel low afterload ejection pathway, the incidence of cavitary thrombus is decreased (Ozdemir *et al.*, 2002). Second, and more importantly as an extreme case of regional ventricular dysfunction, ventricular aneurysm (most commonly in the left, and a result of prior myocardial infarction) characterized by regional ventricular wall dilatation and thinning with paradoxical expansion during ventricular systole (dyskinesis) is associated with a high rate of intracavitary thrombus formation (Natterson *et al.*, 1995). As is the case with atrial thrombi, many of the adverse effects of ventricular thrombi also directly impair ventricular systolic (and diastolic) function (Sharma *et al.*, 2000).

Unlike chronic atrial fibrillation, where anti-coagulation is perhaps as or more important than treatment of the underlying dysrhythmia, treatment of the conditions leading to ventricular thrombus centers on treatment of the underlying pathology.

This is for two reasons: (1) the underlying condition is more responsive to treatment than is AF, and (2) there is little evidence, and no prospective randomized data to suggest a benefit to anti-platelet therapy or anti-coagulation. Pharmacologic (inotropic support and afterload reduction; diuretic agents) treatment of severe systolic dysfunction/heart failure reduces the risk of thrombus formation by augmenting cardiac output, although anti-coagulation is often yet utilized despite poor data to support its use. Additionally, surgical 'reverse ventricular

remodeling' procedures particularly in patients with left ventricular aneurysm/severe regional dysfunction generally ischemic/infarctional in origin are increasingly utilized as heart failure treatments. The mechanics underlying the beneficial effects of these procedures are thought to center on the reduction of ventricular size and restoration of normal ventricular geometry resulting in enhanced pump function (increased pressure head/decreased wall stress) (Buckberg, 2001).

Artificial device technology in the form of ventricular assist devices (VADs) represents another modality in the treatment of heart failure. However, the principal limitations of VADs as long-term treatment approaches for heart failure are those affecting any non-endothelialized foreign body: (1) infection, and (2) thrombo-embolic and bleeding complications (Oz *et al.*, 2003). These data are well documented in a prospective, randomized clinical trial (REMATCH Rose *et al.*, 2001). All of the current commercially available VADs require either anti-platelet (Heartmate) or anti-coagulant (Abiomed; Thoratec) therapy to prevent thrombus formation within the device components. Despite this, the incidence of thrombo-embolic events is approximately 6% in a series of 100 LVAD recipients at Columbia Presbyterian Medical Center (Sun *et al.*, 1999), the single institution with the largest VAD experience. Furthermore, as a consequence of both iatrogenic over-anti-coagulation/anti-platelet therapy and the implantation operation itself, there is a substantial early and late risk of bleeding complications (Graham, 2001).

Valvular Thrombosis

Thrombus formation on cardiac valves most frequently occurs in the setting of artificial mechanical valves but may rarely occur on native valves. Mechanical valve prostheses (Akins, 1996; Copeland, 1996), as they possess a thrombogenic non endothelialized surface, require anti-coagulation with either heparin or warfarin; long-term LMWH as opposed to heparin or warfarin therapy has not yet been shown to be a viable alternative anti-coagulant. Anti-platelet therapy alone is not efficacious, although it confers a benefit of decreased thrombus formation/thrombo-embolism in comparison to anti-coagulation alone. Additionally, due to the lower and slower flows across the atrioventricular valves, it is established practice to anti-coagulate mechanical mitral and tricuspid valves to a greater degree than aortic and pulmonic valves. Data support this practice (Butchart *et al.*, 2002; Ezekowitz, 2002). This requirement of anti-coagulation is the primary disadvantage of mechanical valve prostheses, as they are more durable than allograft or xenograft prostheses. The consequences of thrombus formation are more commonly embolic (see Adams *et al.*, 1986; Cannegieter *et al.*, 1994). *In situ*, thrombus formation can result in stenosis/occlusion of the valve and resultant cardiac failure (Katircioglu *et al.*, 1999; Massetti *et al.*, 1999).

Arterial Thrombosis

The disorders discussed in this section are all characterized by arterial insufficiency, or impaired local arterial blood flow (ischemia) and oxygen delivery. In general, arterial insufficiency is either acute or chronic. Acute insufficiency is either *in situ* or embolic in etiology. *In situ* insufficiency is the acute setting which is due to acute thrombus formation on the surface of an atherosclerotic plaque; it is important to note that the pre-existent plaque is often not substantially stenotic in nature, but may be. Under much less common circumstances, a large stable plaque causing arterial stenosis may manifest in the acute setting; usually, however, these lesions manifest episodically (periodically) over an extended period of time, rarely causing severe or irreversible ischemia/infarction (i.e. the manifestations of stable plaques tend to be chronic).

As stated, different arterial plaques may manifest with acute or chronic *in situ* arterial insufficiency based on plaque instability or stability, respectively. Acute insufficiency, however, is also caused by embolic processes. These embolic processes are generally either athero-embolic or thrombo-embolic in origin (Laperche *et al.*, 1997; Rossi *et al.*, 2002). Accordingly, based on differing pathophysiologic mechanisms, treatment strategies for these various types of arterial insufficiency differ. Two common and important examples of pathologic thrombosis/thrombo-embolism will be discussed: (1) acute coronary syndromes, and (2) extremity arterial insufficiency.

Acute Coronary Syndromes

Perhaps the most prevalent, most important, and best understood disorder of pathologic thrombus formation is in the setting of acute coronary syndrome (ACS). While the majority of ACS are due to thrombus formation over unstable plaque, other etiologies exist: (1) critical stenosis finally reached by a stable plaque, (2) coronary vasospasm or, (3) acute increase in myocardial oxygen consumption demand not met by a needed increase in oxygen delivery. Unstable atherosclerotic lesions in the coronary arteries are inherently thrombogenic ("endothelial dysfunction"), and regions of stenosis are characterized by zones of blood flow instability and stagnation. Platelet recruitment and activation over the unstable plaque ensues, and local coagulation is initiated via these AP and exposure of blood to the components (sub-endothelial) of the unstable plaque (Ross, 1999). Once thrombus propagation occurs to enough of an extent to reduce downstream arterial blood flow to levels inadequate for myocardial oxygen demands, i.e. ischemia, deleterious consequences result. Manifestations are variable and include: (1) malignant arrhythmias and sudden death; (2) ischemia with or without acute chest pain (unstable angina and silent ischemia, respectively); (3) acute myocardial infarction, with or without symptoms. Again, it should be emphasised that non-thrombotic mechanisms can result in any one of these ACS manifestations.

Treatment strategies generally focus on immediate revascularization (increasing coronary arterial oxygen delivery, or $\dot{D}_{O_2}$), and in the interim, reduction of myocardial oxygen consumption ($\dot{V}_{O_2}$) requirements. The determinants of myocardial oxygen consumption are: (1) the 'pressure–volume area' (PVA) (Suga *et al.*, 1981; Silvestry *et al.*, 1997); (2) heart rate; (3) the efficiency of extraction of delivered oxygen; (4) and the mechanical efficiency of the myocardium (conversion of chemical energy to work). Strategies utilized to reduce myocardial oxygen consumption ($\dot{V}_{O_2}$) include: (1) negative chronotropes (reduce heart rate); (2) negative inotropes and afterload-reducing agents as hemodynamics tolerate (reduce myocardial contractility and after load to decrease PVA); (3) mechanical assistance (typically, intra-aortic balloon counter-pulsation) to effect after load reduction and reduce PVA, which also augments coronary $\dot{D}_{O_2}$). Various other therapies can be utilized to decrease myocardial oxygen consumption, which are well described, but these are beyond the scope of this discussion (Fuster *et al.*, 1992). Revascularization may be pharmacologic, interventional, or surgical. Patients with acute coronary syndromes are initially given aspirin as anti-platelet therapy; this clearly demonstrates survival benefits. Further anti-platelet therapy in the form of intravenous GpIIb/IIIa antagonists is also initiated, and anti-coagulation with either unfractionated or LMWH is also utilized. All of these strategies are targeted at decreasing clot formation and propagation. As an established thrombus is responsible for ischemia/infarction, thrombolytic therapy (tPA, urokinase/streptokinase) is often implemented, although urgent coronary arteriography with percutaneous coronary intervention (PCI), balloon arterioplasty +/− stent placement with or without local thrombolytic infusion has demonstrably superior results (Zijlstra *et al.*, 1993; Grines *et al.*, 1999; Dalby *et al.*, 2003; Keeley *et al.*, 2003). A substantial subset, typically those with multi-artery disease or anatomic disease not amenable to PCI (left main artery disease, complex disease), meet criteria for requiring surgical revascularization in the form of coronary artery bypass grafting (CABG) after coronary arteriography. The choice of revascularization procedure, i.e. PCI or CABG, is unclear in many cases and is the subject of many clinical trials. Regardless of the mode of revascularization, PCI or CABG, maintenance post-revascularization anti-platelet therapy (typically ASA) is ultimately routine. Additionally, agents with plaque stabilizing properties (e.g. statins) are used.

Extremity Arterial Insufficiency

Lower extremity ischemia in the acute setting may be either due to: (1) thrombus formation over unstable plaque, which by definition occurs when patients have pre-existent atherosclerotic disease; and (2) thrombo- or athero-embolism. Unlike acute myocardial ischemia, which when due to coronary arterial insufficiency is most often due to *in situ* thrombosis over unstable plaque, acute lower extremity ischemia may be caused by either one of the afore-mentioned mechanisms (Eliason *et al.*, 2003).

As in the case with acute coronary syndromes, acute extremity arterial insufficiency treatment centers on urgent revascularization (Yeager *et al.*, 1992; Ouriel *et al.*, 1994). Anti-coagulation, typically heparin, is instituted. Anti-platelet therapy (ASA or other agents) is often also utilized. Percutaneous catheter-based approaches are increasingly common as initial management, with local thrombolytic administration (Ouriel, 2002). However, some studies suggest that percutaneous interventions (arterioplasty with or without stenting) may be inferior to surgical revascularization (Messina *et al.*, 1991). Thus, patients with known underlying atherosclerotic disease of the lower extremity, or those who fail percutaneous catheter-based thrombolysis, undergo operative management. This consists of operative thrombectomy/thrombo-embolectomy with or without bypass grafting. Post-operative anti-platelet therapy and, in those with atherosclerotic disease, statins are routinely utilized.

Capillary Thrombosis

Microvascular thrombosis is an incompletely understood process with unclear clinical impact. The most clinically relevant example is that of sepsis +/− associated disseminated intravascular coagulation. Other examples include many vasculitides. Endothelial damage in the setting of inflammation, as well as bacterial surface moieties, result in thrombus formation. This may result in focal (small vessel) ischemia and infarction. Studies (the PROWESS trial and follow-up studies) suggest that activated protein C, an anticoagulant, improves outcomes in sepsis (Bernard *et al.*, 2001; Vincent *et al.*, 2003). The mechanisms underlying these improved outcomes are unclear, but may be due to a reduction in microvascular thrombosis and improved tissue perfusion, or due to anti-inflammatory or other effects of activated protein C.

Venous Thrombosis and Pulmonary Thrombo-embolism

Formation of deep venous thrombi (DVT), with or without resultant pulmonary thrombo-embolism (PE), is a major cause of morbidity and mortality, and, in particular, is one of the leading causes of death in hospitalized patients (Fedullo and Tapson, 2003). Virchow's classic triad provides a framework for understanding the pathogenesis of DVT/PE (Dahl, 1999).

A myriad of hypercoagulable states increase the risk of DVT formation (Barger and Hurley, 2000). These are typically genetic disorders in which coagulation factors are synthesized in excessive amounts or in mutant hyperfunctional forms, or in which anti-coagulant or fibrinolytic factors are synthesized in inadequate amounts or in mutant dysfunctional forms (Franco and Reitsma, 2001). Common disorders include: (1) Factor V Leiden (the most common genetic hypercoagulable state Alhenc-Gelos *et al.*, 1994; Tans *et al.*, 1997); (2) mutant

prothrombin; (3) protein C deficiency (Tollefson *et al.*, 1988); (4) protein S deficiency (Berruyer *et al.*, 1994); and (5) ATIII deficiency (Thaler and Lechner, 1981).

Hemodynamics also govern DVT formation (Morris and Woodcock, 2004). The afore-mentioned hypercoagulable states are generally more likely to result in venous, rather than arterial thrombi. This is thought to be because flow in the venous system is low-pressure and in many cases is slower, additionally, venous valves are sites of flow separation prone to thrombus formation. Factors that exacerbate venous stasis, such as venous valvular insufficiency, extremity immobility, and extremity positioning below the level of the right atrium, also augment the risk of DVT formation. This is most relevant in post-surgical patients, who are in a transiently hypercoagulable and often minimally ambulatory state.

Finally, endothelial dysfunction or injury is a risk factor for DVT formation. Damage to venous endothelium, from indwelling venous devices or secondary to instrumentation, is known to augment the risk of DVT.

The pathologic results of DVT, as with arterial thrombi, are either local or distal (as a result of embolization) (Line, 2001). Impairment of extremity venous drainage may cause extremity edema. In severe cases, with deep venous occlusion and inadequate superficial venous system collateral venous return, this results in diminished trans-extremity blood flow (i.e. deep venous occlusion reduces extremity arterial blood flow, Eklof *et al.*, 2000). This is exacerbated by interstitial edema in the afflicted limb and ensuing capillary collapse.

In spite of these local effects, however, it is pulmonary embolism from DVT that causes the majority of morbidity and mortality (Goldhaber, 1998). DVT with pulmonary arterial embolization has significant cardiac and pulmonary effects. From a cardiac standpoint, PE increases RV afterload, both directly and via reactive pulmonary arteriolar constriction. From a pulmonary standpoint, PE results in ventilation–perfusion mismatching. In the majority of cases, PE can be treated via anti-coagulation alone, which prevents thrombo-embolus propagation and allows for endogenous fibrinolytic pathways to lyse the thrombo-embolus (Kakkar, 1990). Patients who fail anti-coagulation, or cannot be anticoagulated successfully, as well as those for whom anticoagulation is contraindicated, undergo placement of a vena caval filter. This prevents DVT embolization. Indications for putting in a vena caval filter are as follows: (1) DVT in a patient who should not be anticoagulated, (2) DVT in a patient who cannot be anticoagulated successfully, or (3) recurrent PE in a patient who is therapeutically anticoagulated with DVT. In rare cases, predominantly those in which RV failure occurs, or in some with severe refractory respiratory failure, thrombolytics are administered to rapidly treat PE (Goldhaber, 2000). In patients with PE causing RV failure/shock or severe respiratory failure who either fail lytic therapy or for whom thrombolytics are contraindicated, surgical thrombo-embolectomy may be performed. This procedure was first performed by the famed surgeon Friedrich Trendelenburg, and is of historical interest in that the motivation of a safe surgical treatment of PE led to Gibbon's development of the cardio-pulmonary bypass. A subset of patients have chronic PE; for these patients, thrombendarterectomy is often a necessary treatment measure (Jamieson *et al.*, 2003). This operation, first performed by Sabiston (Sabiston *et al.* (1977), Sabiston (1979)), carries with it a high mortality.

Bleeding Disorders

These disorders all have in common either inadequate levels of components in the hemostatic system or dysfunction of these components. Broadly, treatment approaches involve: (1) blood product administration and, (2) pharmacologic agents that augment platelet function, coagulation factor function, or inhibit fibrinolysis.

Platelet Disorders

Thrombocytopenia (decreased blood platelet concentration) due to either impaired platelet synthesis or enhanced platelet sequestration or destruction results in an impairment in hemostasis (Editorial, 1991; Provan and Newland, 2003; Drachman, 2004). Above platelet counts of 80,000–1,00,000, platelet-related bleeding is uncommon. Below counts of 20,000 spontaneous bleeding may occur. Platelet transfusion is generally indicated either with platelet counts $<$ 20,000 regardless of bleeding or when bleeding is present with a subnormal platelet count.

Multiple processes result in platelet dysfunction, that may promote bleeding in the setting of a normal platelet count. Many of these are iatrogenic, since as discussed, anti-platelet pharmacotherapy is common (Tinmouth and Freedman, 2003). ASA acetylates and irreversibly inactivates cyclooxygenase and thromboxane A2, which impairs platelet adhesion, recruitment and thus hemostasis. Clopidogrel interferes with platelet ADP release, and thus diminishes platelet adhesion. Finally, antibody (abcixi-mab) and non-antibody (integrin, tirofiban) agents that antagonise the GpIIb/IIIa receptor/ligand pair, as discussed earlier, antagonise platelet adhesion (Cines *et al.*, 2003).

Endogenous disease states may result in platelet dysfunction. An important example of this occurs in the setting of uremia. Uremia results in impaired platelet function and hemostasis via mechanisms that are unclear. This may result in physiologically significant bleeding. In this subset of patients, DDAVP, a peptide that stimulates release of vWF (and other compounds) from the Weibel-Palade bodies of endothelial cells, has been shown to have a significant beneficial effect on bleeding (Kaufmann and Vischer, 2003).

Disorders of Coagulation Factors and Fibrinolysis

The majority of bleeding disorders are characterized predominantly by reduced levels and activity of

coagulation factors (Kane and Davie, 1988; Nichols *et al.*, 1998). Many also involve pathologically accelerated fibrinolysis. Clinical relevant examples include specific factor deficiencies: for example, (1) hemophilia A, (2) hemophilia B; and disease states with global depression of coagulation factor levels, such as: (1) liver failure, and (2) disseminated intravascular coagulation (DIC). These examples are discussed below.

Hemophilia A and hemophilia B (christmas disease) are X (chromosome)-linked recessively inherited deficiencies in Factor VIII and IX, respectively (Lawn, 1985; Rees *et al.*, 1985). This results in defective intrinsic pathway-mediated coagulation. Patients with these disorders present with a history of easy bruising and late bleeding (early hemostasis with subsequent bleeding). Frequently, bleeding into joints (hemarthroses) occurs. Laboratory testing demonstrates an elevated PTT, but normal PT/INR. Treatment of hemophilia involves administration of cryoprecipitate (plasma product which is enriched in Factor VIII and vWF) or plasma in the acute setting (Contreras *et al.*, 1992; Hellstern *et al.*, 2002), or DDAVP as maintenance therapy. In contrast, hemophilia B is generally treated via plasma administration alone. Liver failure results in impaired synthesis of Factors II, VII, IX and X, as well as the inhibitory factors protein C and protein S (Amitrano *et al.*, 2002). This results in impaired coagulation via both the extrinsic and intrinsic pathway. Patients present with easy bruising and delayed bleeding. Unlike hemophilias A and B, both the PT/INR and PTT are often elevated. Bleeding in end-stage liver disease results in considerable morbidity and mortality. In fact, one of the components assessing the severity of liver disease as it pertains to need for liver transplantation (the MELD score) is the PT/INR. Treatment in the acute setting involves transfusion of platelets (in patients with thrombocytopenia secondary to splenic sequestration), plasma, and cryoprecipitate (Pereira *et al.*, 1996). Additionally, treatment of the etiology of the underlying liver disease, as well as liver transplantation (when indicated) are important elements in the treatment of bleeding complications.

Disseminated intravascular coagulation (DIC) is a complex entity that has numerous potential stimuli (Toh and Dennis, 2003). DIC usually presents with early formation of intravascular thrombi, and subsequent coagulation factor depletion and augmented fibrinolysis, with resultant bleeding. Inflammatory responses including sepsis and trauma, as well as those that occur in response to extracorporeal circulation, may result in DIC. The clinical picture of DIC depends on the stage in which it is first noted. Initially, microvascular thromboses may be appreciated, whereas late, bleeding complications (for example, at venipuncture sites) are found. Laboratory testing is noteworthy for elevated levels of fibrin degradation products (FDPs) such as the D-dimer. Therapy generally focuses on the treatment of the underlying causes (Levi, 2001). However, adjunctive measures are also important and are targeted to the stage of DIC. Early/thrombotic DIC is treated via anti-coagulation, which not only prevents thrombus formation but also prevents coagulation factor depletion. In contrast, bleeding complications of DIC are treated with agents to augment native coagulation system function or inhibit fibrinolysis, as well as blood products (Nishiyama *et al.*, 2000; Esmon, 2001).

Finally, it is important to note that there are multiple non-blood product measures that are used to prevent bleeding. These include: Ca^{2+} (a requisite cofactor for many coagulation reactions), bicarbonate (as coagulation cascade reactions are impaired by acidosis), warming (since these reactions are also impaired by hypothermia), and anti-fibrinolytic agents (aprotinin Molenaar *et al.*, 2001; Mossinger *et al.*, 2003, aminocaproic acid Kang *et al.*, 1987; Porte *et al.*, 1989; Greilich *et al.*, 2003).

MODEL DEVELOPMENT

The salient features of our modeling approach are:

- A model for whole blood as a shear-thinning viscoelastic fluid within which the reactants involved in clot formation and dissolution are uniformly present.
- Development of coupled convection-reaction-diffusion equations that govern the flow, generation/depletion of plasma zymogens/enzymes (II/IIa, V/Va, VIII/VIIIa, IX/IXa, X/Xa, XI/XIa, PLS/PLA), regulatory proteins (PC/APC), inhibitors (ATIII, TFPI, L1AT, L2AP), platelets (activated/resting; AP/RP), tPA and fibrinogen/fibrin. The role of membrane bound enzyme complexes (IXa-VIIIa and Xa-Va) is embedded in these reactions.
- Platelet activation occurs either due to action by thrombin and agonists like ADP, or due to prolonged exposure to shear stresses. A supplementary criterion is introduced for the latter.
- Flux boundary conditions that represent the level of stimulation at the surface, namely: the extent of injury (as reflected in the concentration of surface bound TF-VIIa complex), the level of endothelial cell activity (constitutive, or induced by the action of thrombin and fibrin), and the extent of sub-endothelium-platelet interaction (related to the presence of surface binding sites and the extent of injury). The flux boundary conditions govern the concentration of the various reactants in the flow domain and regulate the threshold response of the system.
- Clot formation is initiated upon the attainment of a threshold concentration of surface-bound TF-VIIa complex. This represents a threshold response to vessel wall injury. The clot is the region where fibrin concentration equals or exceeds a specific critical concentration $[FIB]_{cr}$ (600 nM in our case).
- A model for the clot as a (highly viscous) viscoelastic fluid within which the reactants involved in clot formation and dissolution are uniformly present.

- Clot growth is determined by tracking, in time, the extent of the region, within the flow domain, where concentration of fibrin equals or exceeds a specific critical concentration $[\mathrm{FIB}]_{\mathrm{cr}}$.
- Clot dissolution occurs due to either a decrease in fibrin concentration below 600 nM (which may be due to fibrinolysis being well advanced) or due to attainment of a critical shear stress, the value of this shear stress depending on the concentration of platelets and fibrin at every point in the clot.

We model whole blood and the clot within a framework that recognises that viscoelastic fluids possess multiple natural (stress-free) configurations. More importantly, our models arise in a thermodynamic setting that involves specifying the manner of the rate of dissipation and the manner in which energy is stored by the material in question. The procedure also guarantees constitutive relations that automatically meet the second law of thermodynamics and in order to ensure this we do not appeal to a procedure that is often used to place restrictions on allowable constitutive relations that presumes that the body can be subjected to arbitrary processes (see Rajagopal and Tao, 2002 for a detailed discussion of these issues). We ensure that the rate of dissipation is non-negative and we maximize the rate of dissipation to select the final constitutive equation (see Rajagopal and Srinivasa, 2000).

Preliminaries

The framework for the development of the constitutive theory for viscoelastic fluids (possessing multiple natural configurations) has been outlined in Rajagopal and Srinivasa (2000), and the notation introduced in that article is adhered to here. Let $\kappa_{\mathrm{R}}(\mathrm{B})$ and $\kappa_t(\mathrm{B})$ denote the reference and the current configuration of the body B at time t, respectively. Let $\kappa_{p(t)}(\mathrm{B})$ denote the stress-free configuration that is reached by instantaneously unloading the body which is at the configuration $\kappa_t(\mathrm{B})$ (Fig. 1). As the body continues to deform these natural configurations $\kappa_{p(t)}(\mathrm{B})$ can change (the suffix $p(t)$ is used in order to highlight that it is the preferred stress free state corresponding to the deformed configuration at time t. See, Rajagopal (1995) for a detailed discussion of the notion of natural configurations).

By the motion of a body we mean a one to one mapping that assigns to each point $\mathbf{X} \in \kappa_{\mathrm{R}}(\mathrm{B})$, a point $\mathbf{x} \in \kappa_t(\mathrm{B})$, for each t, i.e.

$$\mathbf{x} = \chi_{\kappa_{\mathrm{R}}}(\mathbf{X}_{\kappa_{\mathrm{R}}}, t). \tag{1}$$

We assume that the motion is sufficiently smooth and invertible. We suppress B in the notation κ_{R} (B), etc., for the sake of convenience.

The deformation gradients, $\mathbf{F}_{\kappa_{\mathrm{R}}}$, and the left and right Cauchy-Green stretch tensors, $\mathbf{B}_{\kappa_{\mathrm{R}}}$ and $\mathbf{C}_{\kappa_{\mathrm{R}}}$, are defined through:

$$\mathbf{F}_{\kappa_{\mathrm{R}}} = \frac{\partial \chi_{\kappa_{\mathrm{R}}}}{\partial \mathbf{X}_{\kappa_{\mathrm{R}}}},\ \mathbf{B}_{\kappa_{\mathrm{R}}} = \mathbf{F}_{\kappa_{\mathrm{R}}}\mathbf{F}^{T}_{\kappa_{\mathrm{R}}},\ \text{and}\ \mathbf{C}_{\kappa_{\mathrm{R}}} = \mathbf{F}^{T}_{\kappa_{\mathrm{R}}}\mathbf{F}_{\kappa_{\mathrm{R}}}. \tag{2}$$

The left Cauchy-Green stretch tensor associated with the instantaneous elastic response from the natural configuration $\kappa_{p(t)}$ is defined as:

$$\mathbf{B}_{\kappa_{p(t)}} = \mathbf{F}_{\kappa_{p(t)}}\mathbf{F}^{T}_{\kappa_{p(t)}}. \tag{3}$$

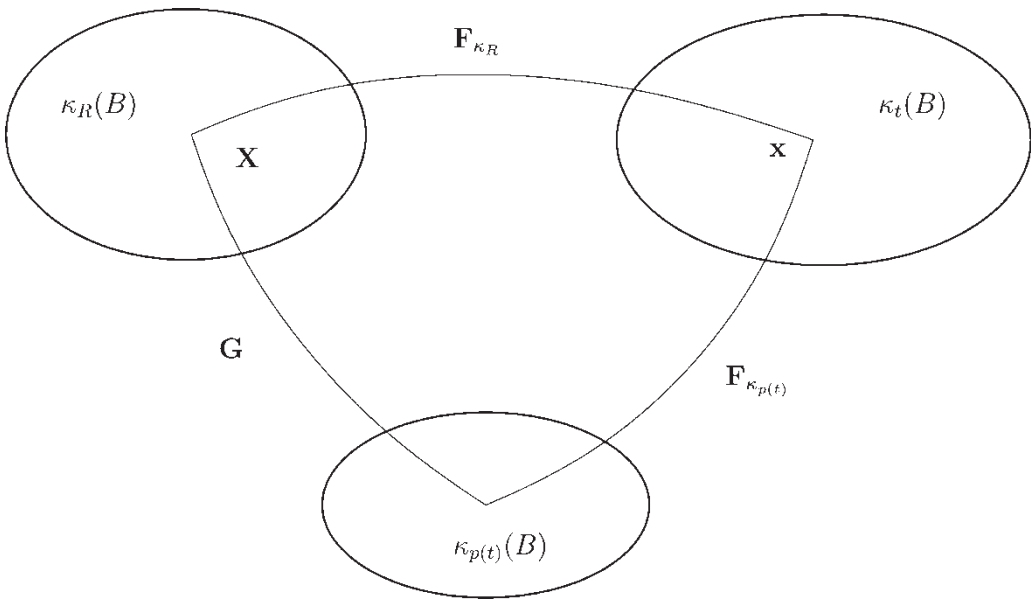

FIGURE 1 Schematic of the natural configurations associated with a viscoelastic fluid having a single relaxation mechanism, and capable of instantaneous elastic response.

The principal invariants of $\mathbf{B}_{\kappa_{p(t)}}$ are

$$\mathrm{I}_{\mathbf{B}} = \mathrm{tr}(\mathbf{B}_{\kappa_{p(t)}}),$$
$$\mathrm{II}_{\mathbf{B}} = \frac{1}{2}\left\{[\mathrm{tr}(\mathbf{B}_{\kappa_{p(t)}})]^2 - \mathrm{tr}(\mathbf{B}^2_{\kappa_{p(t)}})\right\}, \tag{4}$$

and

$$\mathrm{III}_{\mathbf{B}} = \det(\mathbf{B}_{\kappa_{p(t)}}).$$

For homogeneous deformations, $\mathbf{F}_{\kappa_{p(t)}}$ denotes the deformation gradient between the natural configuration and the current configuration. The mapping $\mathbf{G}$ is defined through:

$$\mathbf{G} = \mathbf{F}_{\kappa_{\mathrm{R}} \to \kappa_{p(t)}} = \mathbf{F}^{-1}_{\kappa_{p(t)}} \mathbf{F}_{\kappa_{\mathrm{R}}}. \tag{5}$$

The velocity gradients, $\mathbf{L}$ and $\mathbf{L}_{\kappa_{p(t)}}$, are defined through

$$\mathbf{L} := \dot{\mathbf{F}}_{\kappa_{\mathrm{R}}} \mathbf{F}^{-1}_{\kappa_{\mathrm{R}}} \text{ and } \mathbf{L}_{\kappa_{p(t)}} = \dot{\mathrm{G}}\mathrm{G}^{-1}, \tag{6}$$

where the dot signifies the material time derivative.

The symmetric parts of $\mathbf{L}$ and $\mathbf{L}_{\kappa_{p(t)}}$, are defined through

$$\mathbf{D} = \frac{1}{2}(\mathbf{L} + \mathbf{L}^T) \text{ and } \mathbf{D}_{\kappa_{p(t)}} = \frac{1}{2}(\mathbf{L}_{\kappa_{p(t)}} + \mathbf{L}^T_{\kappa_{p(t)}}). \tag{7}$$

The upper convected Oldroyd derivative of $\mathbf{B}_{\kappa_{p(t)}}$, $\overset{\nabla}{\mathbf{B}}_{\kappa_{p(t)}}$, is given through

$$\begin{aligned}\overset{\nabla}{\mathbf{B}}_{\kappa_{p(t)}} &= \dot{\mathbf{B}}_{\kappa_{p(t)}} - \mathbf{L}\mathbf{B}_{\kappa_{p(t)}} - \mathbf{B}_{\kappa_{p(t)}}\mathbf{L}^T \\ &= -2\mathbf{F}_{\kappa_{p(t)}}\mathbf{D}_{\kappa_{p(t)}}\mathbf{F}^T_{\kappa_{p(t)}}.\end{aligned} \tag{8}$$

As we shall assume that blood and the clot are incompressible, we shall require that

$$\mathrm{tr}(\mathbf{D}) = 0, \tag{9}$$

and

$$\mathrm{tr}(\mathbf{D}_{\kappa_{p(t)}}) = 0. \tag{10}$$

A Shear-thinning Viscoelastic Model for Describing the Flow of Blood

A shear-thinning viscoelastic model with a deformation dependent relaxation time has been developed for describing the flow of blood (Anand and Rajagopal, 2004a). This model has been corroborated over the range of flow conditions expected in the human vasculature, and is an improvement over many of the models mentioned in the surveyed literature including the one in Yeleswarapu (1996). The model is defined through the following set of equations:

$$\mathbf{T} = -p\mathbf{1} + \mathbf{S}, \tag{11}$$

$$\mathbf{S} = \mu^b \mathbf{B}_{\kappa_{\mathbf{p}(\mathbf{t})}} + \eta^b_1 \mathbf{D}, \tag{12}$$

$$\overset{\nabla}{\mathbf{B}}_{\kappa_{p(t)}} = -2\left(\frac{\mu^b}{\alpha^b}\right)^{1+2n^b} (\mathrm{tr}(\mathbf{B}_{\kappa_{\mathbf{p}(\mathbf{t})}}) - 3\lambda)^{n^b} [\mathbf{B}_{\kappa_{p(t)}} - \lambda\mathbf{1}], \tag{13}$$

$$\lambda = \frac{3}{\mathrm{tr}(\mathbf{B}^{-1}_{\kappa_{\mathbf{p}(\mathbf{t})}})}, \tag{14}$$

$$n^b = \frac{\gamma^b - 1}{1 - 2\gamma^b}; n^b > 0. \tag{15}$$

This model is a generalization of the classical Oldroyd-B model, and we can rewrite the model equations in a manner that makes this clear (see Rajagopal and Srinivasa, 2000 for details). Upon rearranging the terms in the above expressions, the model can be expressed through:

$$\mathbf{T} = -p\mathbf{1} + \mathbf{S}, \tag{16}$$

$$\mathbf{S} + \frac{1}{\chi(\mathbf{S},\mathbf{D})}\overset{\nabla}{\mathbf{S}} = \eta_1 \left[\mathbf{D} + \frac{1}{\chi(\mathbf{S},\mathbf{D})}\overset{\nabla}{\mathbf{D}}\right] + \frac{3}{\mathrm{tr}\,(\mathbf{S} - \eta_1\mathbf{D})^{-1}}\mathbf{1}. \tag{17}$$

Here

$$\mathbf{S} = \mu^b \mathbf{B}_{\kappa_{\mathbf{p}(\mathbf{t})}} + \eta^b_1 \mathbf{D}, \tag{18}$$

$$\Rightarrow \mathbf{B}_{\kappa_{\mathbf{p}(\mathbf{t})}} = \frac{1}{\mu^b}\left(\mathbf{S} - \eta^b_1 \mathbf{D}\right), \tag{19}$$

$$\begin{aligned}\chi(\mathbf{S},\mathbf{D}) &= \chi^*(\mathbf{B}_{\kappa_{\mathbf{p}(\mathbf{t})}}) \\ &= 2\left(\frac{\mu^b}{\alpha^b}\right)^{1+2n^b} \left(\mathrm{tr}(\mathbf{B}_{\kappa_{\mathbf{p}(\mathbf{t})}}) - 3\lambda\right)^{n^b}\end{aligned} \tag{20}$$

$$\lambda = \frac{3}{\mathrm{tr}\left(\mathbf{B}^{-1}_{\kappa_{\mathbf{p}(\mathbf{t})}}\right)}. \tag{21}$$

We see that the model as given through Eqs. (16) and (17) is very similar, in form, to the classical Oldroyd-B model as written in Eqs. (22) and (23) except for the extra term associated with the identity tensor, and the absence of a separate retardation time:

$$\mathbf{T} = -p\mathbf{1} + \mathbf{S}, \tag{22}$$

$$\mathbf{S} + \Lambda_1 \overset{\nabla}{\mathbf{S}} = \nu[\mathbf{D} + \Lambda_2 \overset{\nabla}{\mathbf{D}}]. \tag{23}$$

This is easily addressed by taking advantage of the indeterminacy of the Lagrange multiplier "p". If we set $\hat{p} = p + \delta$, and $\hat{\mathbf{S}} = \mathbf{S} + \delta\mathbf{1}$, and define

$$\delta = \frac{\nu}{2\Lambda_1}\left(1 - \frac{\Lambda_2}{\Lambda_1}\right), \tag{24}$$

then Eqs. (22) and (23) for the Oldroyd-B fluid can be rewritten as

$$\mathbf{T} = -\hat{p}\mathbf{1} + \hat{\mathbf{S}}, \tag{25}$$

$$\hat{\mathbf{S}} + \Lambda_1 \overset{\nabla}{\hat{\mathbf{S}}} = \nu' \left[\mathbf{D} + \Lambda_1 \overset{\nabla}{\mathbf{D}}\right] + \delta\mathbf{1}, \tag{26}$$

where $\nu' = \nu\Lambda_2/\Lambda_1$. If ν, Λ_1 and Λ_2 are functions of $\mathbf{S}$ and $\mathbf{D}$, the form of the resulting model is the same. The resulting model is given by Eqs. (27) and (28):

$$\mathbf{T} = -\hat{p}\mathbf{1} + \hat{\mathbf{S}}, \tag{27}$$

$$\begin{aligned}\hat{\mathbf{S}} + \Lambda_1(\mathbf{S},\mathbf{D})\overset{\nabla}{\hat{\mathbf{S}}} = {} & \nu'(\mathbf{S},\mathbf{D})\left[\mathbf{D} + \Lambda_1(\mathbf{S},\mathbf{D})\overset{\nabla}{\mathbf{D}}\right] \\ & + (\delta(\mathbf{S},\mathbf{D}) + \dot{\delta}(\mathbf{S},\mathbf{D}))\mathbf{1}.\end{aligned} \tag{28}$$

Here $\dot{\delta}$ is the material time derivative of δ. Equations (27) and (28) match the modified version of the proposed model for blood (Eqs. (16) and (17)) much more closely than Eqs. (22) and (23).

The zero-shear viscosity inferred from the proposed model tends to ∞, and in order to ensure that the zero-shear viscosity is finite, we introduce a Heaviside function into the expressions for the viscosity and shear thinning index,

$$\alpha^b = \alpha_f^b H(\mathrm{I}_{\mathbf{B}} - \mathrm{I}_0^b) + \alpha_0^b(1 - H(\mathrm{I}_{\mathbf{B}} - \mathrm{I}_0^b)), \tag{29}$$

$$\gamma^b = \gamma^b H(\mathrm{I}_{\mathbf{B}} - \mathrm{I}_0^b) + (1 - H(\mathrm{I}_{\mathbf{B}} - \mathrm{I}_0^b)), \tag{30}$$

$$\alpha_0^b = 2(\eta_0^b - \eta_\infty^b), \tag{31}$$

where η_0^b, η_∞^b are the asymptotic viscosities of blood at low and high shear rates, and I_0^b is a suitably chosen constant. The introduction of I_0^b does not imply an additional parameter; it is only introduced to investigate the numerical problems that may arise due to the shear rate reaching zero in the computational domain.

We introduce the notation

$$K^b = \left(\frac{\mu^b}{\alpha^b}\right)^{1+2n^b}. \tag{32}$$

The following constants pertain to human blood with a zero shear viscosity of 73.6 cP and infinite shear viscosity of 5.0 cP: $K^b = 1.2056\,\mathrm{s}^{-1}$, $\mu^b = 0.0227\,\mathrm{Pa}$, $n^b = 0.7525$ and $\eta_1^b = 0.01\,\mathrm{Pa\,s}$.

A Mathematical Model for the Initiation and Progress of Platelet Activation, the Extrinsic Pathway of Coagulation, and Fibrinolysis Resulting in Clot Formation and Dissolution

We model the initiation and progress of clot formation, and clot dissolution in the following manner. A set of convection-reaction-diffusion equations governs the flow, generation and depletion of various enzymes, proteins and platelets in the entire domain. Clot formation is initiated when an activation threshold in the flux boundary conditions is exceeded (this is related to the appearance of TF-VIIa complex on the injured surface, the concentration of TF-VIIa depending on the extent of injury). Platelet activation, and the appearance of phospholipid binding sites for the assembly of enzyme complexes, occurs either due to biochemical factors, namely the action of thrombin or platelet generated agonists like ADP, or due to mechanical factors, namely the prolonged exposure to supra-critical shear stress (this mimics stress-dependent platelet activation). The clot is said to have formed in regions where the concentration of fibrin equals or exceeds 600 nM, and clot growth is determined by tracking, in time, the extent of these regions. Fibrinolysis starts as soon as thrombin appears at the surface and induces a rapid endothelial cell response. Clot dissolution is said to have occured in those regions where fibrin concentration drops below 600 nM or when the shear stress exceeds a certain critical value causing the clot to rupture. The enzyme cascade of the extrinsic pathway of coagulation upto the formation of thrombin is modeled by means of a system of reactions that captures the most important part of the biochemistry.

Convection-diffusion-reaction Equations for the Various Constituents

The equations governing the flow and generation/depletion of the various constituents are all of the following form:

$$\begin{gathered}\frac{\partial[Y_i]}{\partial t} + \mathrm{div}([Y_i]\mathbf{v}) = \mathrm{div}(D_{Y_i}(\mathbf{D})\nabla[Y_i]) + G_{Y_i}; \\ i = 1, \ldots, 25.\end{gathered} \tag{33}$$

Here, and elsewhere below, $[Y_i]$ represents the concentration of the reactant Y_i, G_{Y_i} represents the production or depletion of Y_i due to the enzymatic reactions, $\mathbf{v}$ is the velocity, and D_{Y_i} represents the diffusion coefficient of Y_i which could be a function of the shear rate (captured by means of the stretching tensor $\mathbf{D}$).

We assume that these constituents exist at every point in the domain, and that, being of extremely small composition, they do not affect the velocity of the bulk flow. Our framework for studying the reaction-diffusion equations coupled with the flow equations is such that it allows a natural extension into a mixture theory model should the need arise.

Equations Governing the Generation and Depletion (Reactions) of the Various Enzymes, Enzyme Complexes, and Phospholipid Binding Sites, and Platelet Activation due to Thrombin or Platelet Derived Agonists

The reactions chosen to represent the extrinsic coagulation pathway, the generation of phospholipid binding sites due to platelet activation, the influence of thrombin on Factor XIa generation, the formation of fibrin, and the generation of plasmin are listed in Table I, and a schematic representation of these reactions is given in Fig. 2. The corresponding kinetic constants are summarized in Table II along with the relevant sources. Some of the reactions are assumed to follow Michaelis-Menten kinetics, others first order kinetics, and yet others second order kinetics.

TABLE I Scheme of enzymatic reactions $Z = \text{IXa–VIIIa–AP}$, $W = \text{Xa–Va–AP}$

		Activation			Inactivation
(1a)	k_9	$\text{IX} \xrightarrow{\text{XIa}} \text{IXa}$	(1b)	h_9	$\text{IXa} + \text{ATIII} \rightarrow \text{IXa–ATIII}$
(2a)	k_8	$\text{VIII} \xrightarrow{\text{IIa}} \text{VIIIa}$	(2b)	h_8	$\text{VIIIa} \rightarrow \text{VIIIa}_i$
			(2c)	k_a	$\text{VIII} \xrightarrow{\text{APC}} \text{VIIIa}_i$
(3a)	k_5	$\text{V} \xrightarrow{\text{IIa}} \text{Va}$	(3b)	h_5	$\text{V} \rightarrow \text{Va}_i$
			(3c)	k_a	$\text{Va} \xrightarrow{\text{APC}} \text{Va}_i$
(4a)	$k_{8,9}$	$\text{VIIIa} + \text{IXa} + \text{AP} \rightarrow Z$	(4b)	k_a	$\text{VIIIa–IXa} \xrightarrow{\text{APC}} \text{VIII}_i + \text{IXa}$
	$h_{8,9}$	$Z \rightarrow \text{VIIIa} + \text{IXa} + \text{AP}$			
(5a)	$k_{5,10}$	$\text{Va} + \text{Xa} + \text{AP} \rightarrow \text{W}$	(5b)	k_a	$\text{Va–Xa} \xrightarrow{\text{APC}} \text{V}_i + \text{Xa}$
	$h_{5,10}$	$W \rightarrow \text{Va} + \text{Xa} + \text{AP}$			
(6a)	k_{10}	$\text{X} \xrightarrow{\text{IX–VIIIa–AP}} \text{Xa}$	(6b)	h_{10}	$\text{Xa} + \text{ATIII} \rightarrow \text{Xa–ATIII}$
			(6c)	k_{TFPI}	$\text{Xa} + \text{TFPI} \rightarrow \text{Xa–TFPI}$
(7a)	k_2, K_{2m}	$\text{II} \xrightarrow{\text{Xa–Va–AP}} \text{IIa}$	(7b)	h_2	$\text{IIa} + \text{ATIII} \rightarrow \text{IIa–ATIII}$
(8a)	k_{APC}	$\text{PC} \xrightarrow{\text{IIa}} \text{APC}$	(8b)	h_{APC}	$\text{APC} + \text{L1AT} \rightarrow \text{APC–L1AT}$
(9a)	k_1, K_{1m}	$\text{I} \xrightarrow{\text{IIa}} \text{Ia}$	(9b)	h_1, H_{1m}	$\text{Ia} + \text{PLA} \rightarrow \text{I}_i$
(10a)	k_{11}	$\text{XI} \xrightarrow{\text{IIa}} \text{XIa}$	(10b)	h_{11}	$\text{XIa} \rightarrow \text{XI}_i$
(11a)	$k_{\text{AP}}^{\text{IIa}}$	$\text{RP} \xrightarrow{\text{IIa}} \text{AP}$			
(11b)	$k_{\text{AP}}^{\text{AP}}$	$\text{RP} \xrightarrow{\text{AP}} \text{AP}$			
(12a)	$k_{\text{PLA}}^{\text{tPA–Ia}}$	$\text{PLS} \xrightarrow{\text{tPA–Ia}} \text{PLA}$	(12b)	h_{PLA}	$\text{PLA} + \text{L2AP} \rightarrow \text{PLA-L2AP}$

The assumptions regarding the reaction kinetics are similar, for some reactions, to those of the models in Zarnitsina *et al.* (1996a); Ataullakhanov *et al.* (2002). Additional reactions have been introduced for platelet activation, the role of TFPI, and fibrinolysis ('Assumptions for Reactions 6c, 7a, 9a, 9b, 11a, 11b, 12a, 12b' section). The role of phospholipid binding sites has also been included in the reaction kinetics ('Assumptions Governing Inclusion of Phospholipid Binding Site Density in Reactions 4a, 5a' section). The role of the surface bound TF-VIIa enzyme complex is incorporated in the boundary conditions.

Among the many constituents involved in the extrinsic coagulation pathway, we assume the following to be of primary importance: resting platelets (RP), AP, fibrinogen

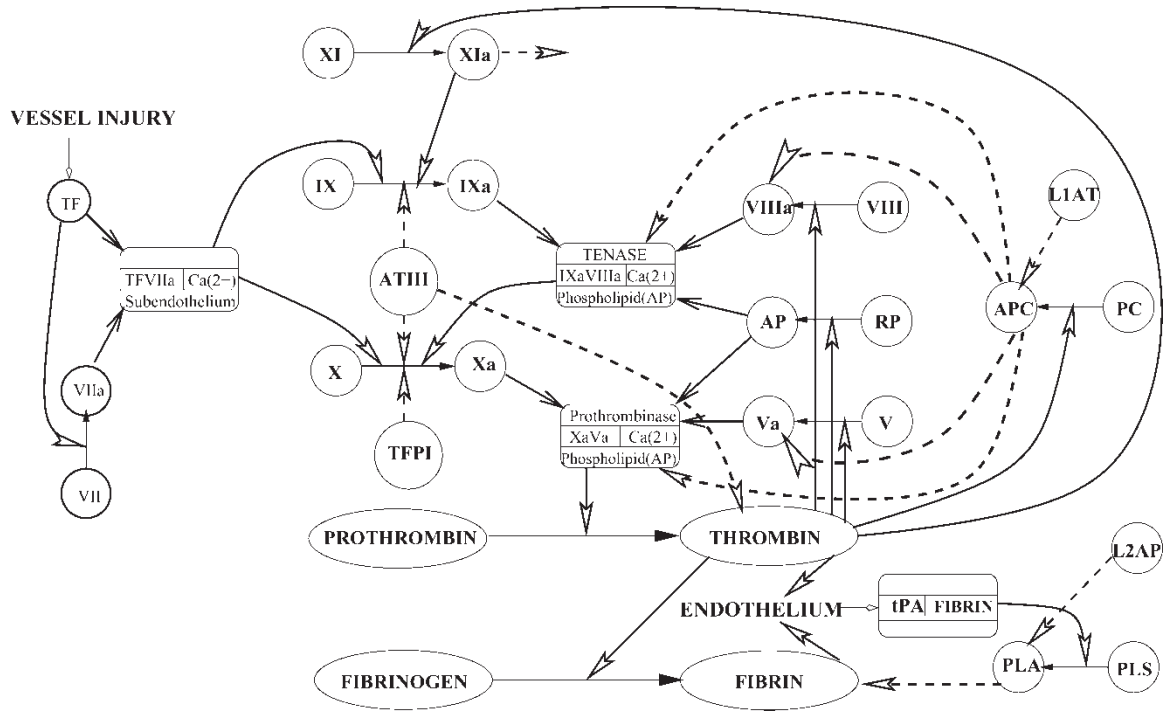

FIGURE 2 Schematic of selected reactions involved in platelet activation, the extrinsic coagulation pathway and fibrinolysis. Solid lines denote zymogen activation or enzymatic catalysis. Broken lines denote enzymatic deactivation. Filled in arrow heads denote zymogen activation. Arrow heads that are not filled in denote enzymatic catalysis. Open arrow heads with solid lines denote participation in complex formation. (See also Kuharsky and Fogelson, 2001; Ataullakhanov *et al.*, 2002 for similarly drawn schematics).

TABLE II Reaction rates and kinetic constants

Reaction	Type	Kinetic parameters	Sources
(1a)	F	$k_9 = 20\,\mathrm{min}^{-1}$	Zarnitsina *et al.* (1996a)
(1b)	F	$h_9 = 0.2\,\mathrm{min}^{-1}$	Zarnitsina *et al.* (1996a)
(2a)	F	$k_8 = 10^{-5}\,\mathrm{min}^{-1}$	Zarnitsina *et al.* (1996a)
(2b)	F	$h_8 = 0.31\,\mathrm{min}^{-1}$	Zarnitsina *et al.* (1996a)
(2c)	S	$k_a = 1.2\,\mathrm{nM}^{-1}\,\mathrm{min}^{-1}$	Zarnitsina *et al.* (1996a)
(3a)	F	$k_5 = 0.17\,\mathrm{min}^{-1}$	Zarnitsina *et al.* (1996a)
(3b)	F	$h_5 = 0.31\,\mathrm{min}^{-1}$	Zarnitsina *et al.* (1996a)
(3c)	S	$k_a = 1.2\,\mathrm{nM}^{-1}\,\mathrm{min}^{-1}$	Zarnitsina *et al.* (1996a)
(4a)	S	$k_{8,9} = 100[\mathrm{AP}]/[\mathrm{RP}]\|_{t=0}\,\mathrm{nM}^{-1}\,\mathrm{min}^{-1}$, $h_{8,9} = 100[\mathrm{AP}]/[\mathrm{RP}]\|_{t=0}\,\mathrm{min}^{-1}$	(Sec.4.3.3)
(4b)	S	$k_a = 1.2\,\mathrm{nM}^{-1}\,\mathrm{min}^{-1}$	Zarnitsina *et al.* (1996a)
(5a)	S	$k_{5,10} = 100[\mathrm{AP}]/[\mathrm{RP}]\|_{t=0}\,\mathrm{nM}^{-1}\,\mathrm{min}^{-1}$, $h_{5,10} = 100[\mathrm{AP}]/[\mathrm{RP}]\|_{t=0}\,\mathrm{min}^{-1}$	(Sec.4.3.3)
(5b)	S	$k_a = 1.2\,\mathrm{nM}^{-1}\,\mathrm{min}^{-1}$	Zarnitsina *et al.* (1996a)
(6a)	F	$k_{10} = 1200\,\mathrm{min}^{-1}(20\,\mathrm{s}^{-1})$	Kuharsky and Fogelson (2001)
(6b)	F	$h_{10} = 1\,\mathrm{min}^{-1}$	Zarnitsina *et al.* (1996a)
(6c)	S	$k_{\mathrm{TFPI}} = 0.96\,\mathrm{nM}^{-1}\,\mathrm{min}^{-1}(1.6 \times 10^7\,\mathrm{M}^{-1}\,\mathrm{s}^{-1})$	Kuharsky and Fogelson (2001)
(7a)	M	$k_2 = 1344\,\mathrm{min}^{-1}$, $K_{2m} = 1060\,\mathrm{nM}$	Krishnaswamy *et al.* (1987)
(7b)	F	$h_2 = 1.3\,\mathrm{min}^{-1}$	Zarnitsina *et al.* (1996a)
(8a)	F	$k_{\mathrm{APC}} = 0.0014\,\mathrm{min}^{-1}$	Zarnitsina *et al.* (1996a)
(8b)	F	$h_{\mathrm{APC}} = 0.1\,\mathrm{min}^{-1}$	Zarnitsina *et al.* (1996a)
(9a)	M	$k_1 = 3540\,\mathrm{min}^{-1}(59\,\mathrm{s}^{-1})$, $K_{1m} = 3160\,\mathrm{nM}$	Tsiang *et al.* (1996)
(9b)	M	$h_1 = 6.97\,\mathrm{min}^{-1}(0.1161\,\mathrm{s}^{-1})$, $H_{1m} = 2900\,\mathrm{nM}$	Bickford *et al.* (1964)
(10a)	F	$k_{11} = 0.0078\,\mathrm{min}^{-1}$	Zarnitsina *et al.* (1996a)
(10b)	F	$h_{11} = 0.2\,\mathrm{min}^{-1}$	Zarnitsina *et al.* (1996a)
(11a)	F	$k_{\mathrm{AP}}^{\mathrm{IIa}} = 30\,\mathrm{min}^{-1}(0.5\,\mathrm{s}^{-1})$	Kuharsky and Fogelson (2001)
(11b)	S	$k_{\mathrm{AP}}^{\mathrm{AP}} = 18\,\mathrm{nM}^{-1}\,\mathrm{min}^{-1}(3 \times 10^8\,\mathrm{M}^{-1}\,\mathrm{s}^{-1})$	Kuharsky and Fogelson (2001)
(12a)	F	$k_{\mathrm{PLA}}^{\mathrm{tPA-Ia}} = 12\,\mathrm{min}^{-1}(0.2\,\mathrm{s}^{-1})$	Madison *et al.* (1995)
(12b)	S	$h_{\mathrm{PLA}} = 0.096\,\mathrm{nM}^{-1}\,\mathrm{min}^{-1}(160 \times 10^4\,\mathrm{M}^{-1}\,\mathrm{s}^{-1})$	Kolev *et al.* (1994)

The following notation is used: M = Michaelis-Menten kinetics, F = First order kinetics, S = Second order kinetics. The enzyme kinetic data for all the reactions is for zymogens, enzymes and platelets derived from human plasma and blood.

and fibrin (I and Ia), prothrombin and thrombin (II and IIa), V and Va, VIII and VIIIa, IX and IXa, X and Xa, tenase (IXa-VIIIa-AP or 'Z'), prothrombinase (Xa-Va-AP or 'W'), XI and XIa, ATIII, PC and APC, TFPI, α1-Antitrypsin (L1AT), tPA, PLS and Plasmin (PLA), and α2-Antiplasmin (L2AP). The role of the TF-VIIa complex, sub-endothelium-platelet interaction (the role of collagen and reactive proteins like vitronection, vWF, etc., in platelet activation, and the density of platelet binding sites), and Endothelial cell tPA generation are included by means of flux boundary conditions. This list captures the broad aspects of clot formation but it is by no means comprehensive.

The generation of 'W' (prothrombinase) and 'Z' (tenase) is so fast that their concentration is determined solely by the concentrations of their contributing reactants. Separate convection-diffusion reactions are not written for 'W' and 'Z', as they are embedded in the equations for Va, VIIIa, IXa, Xa and APC. The relations between the concentrations of 'W' and 'Z' and the concentrations of Va, VIIIa, IXa, Xa and APC are given in Eqs. (40) and (41). Some interactions have not been included because of their relative insignificance like, for instance, the effect of Xa on V and VIII (Eaton *et al.*, 1986; Monkovic and Tracy, 1990), the effect of Xa on prothrombin (insignificant compared to the much faster reaction catalyzed by prothrombinase; see Krishnaswamy *et al.* (1987), the effect of IXa on X (Rosing *et al.*, 1980), or the role of circulating TF (Balasubramanian *et al.*, 2002).

The rate of depletion of a zymogen is equal to the rate of its activation into the corresponding enzyme. The corresponding enzyme is generated from the zymogen and is depleted by inactivation due to inhibitors. Based on their reaction kinetics, ordinary differential equations to describe the generation and depletion of the species are formulated. These equations are given below:

$$\frac{\mathrm{d}[\mathrm{IXa}]}{\mathrm{d}t} = k_9[\mathrm{XIa}] - h_9[\mathrm{IXa}] = G_{\mathrm{IXa}}, \tag{34}$$

$$\frac{\mathrm{d}[\mathrm{IX}]}{\mathrm{d}t} = -k_9[\mathrm{XIa}] = G_{\mathrm{IX}}, \tag{35}$$

$$\frac{\mathrm{d}[\mathrm{VIIIa}]}{\mathrm{d}t} = k_8[\mathrm{IIa}] - h_8[\mathrm{VIIIa}] - k_a[\mathrm{APC}]\cdot([\mathrm{VIIIa}] + [Z]) = G_{\mathrm{VIIIa}}, \tag{36}$$

$$\frac{\mathrm{d}[\mathrm{VIII}]}{\mathrm{d}t} = -k_8[\mathrm{IIa}] = G_{\mathrm{VIII}}, \tag{37}$$

$$\frac{\mathrm{d}[\mathrm{Va}]}{\mathrm{d}t} = k_5[\mathrm{IIa}] - h_5[\mathrm{Va}] - k_a[\mathrm{APC}]\cdot([\mathrm{Va}] + [W]) = G_{\mathrm{Va}}, \tag{38}$$

$$\frac{\mathrm{d}[\mathrm{V}]}{\mathrm{d}t} = -k_5[\mathrm{IIa}] = G_{\mathrm{V}}, \tag{39}$$

$$[Z] = \frac{k_{8,9}[\mathrm{VIIIa}][\mathrm{IXa}]}{h_{8,9} + k_a[\mathrm{APC}]}, \tag{40}$$

$$[W] = \frac{k_{5,10}[\mathrm{Va}][\mathrm{Xa}]}{h_{5,10} + k_a[APC]}, \tag{41}$$

$$\frac{\mathrm{d[Xa]}}{\mathrm{d}t} = k_{10}[Z] - h_{10}[\mathrm{Xa}] - k_{\mathrm{TFPI}}[\mathrm{TFPI}][\mathrm{Xa}] = G_{\mathrm{Xa}}, \quad (42)$$

$$\frac{\mathrm{d[X]}}{\mathrm{d}t} = -k_{10}[Z] = G_{\mathrm{X}}, \quad (43)$$

$$\frac{\mathrm{d[IIa]}}{\mathrm{d}t} = \frac{k_2[W][\mathrm{II}]}{K_{2m} + [\mathrm{II}]} - h_2[\mathrm{IIa}] = G_{\mathrm{IIa}}, \quad (44)$$

$$\frac{\mathrm{d[II]}}{\mathrm{d}t} = \frac{-k_2[W][\mathrm{II}]}{K_{2m} + [\mathrm{II}]} = G_{\mathrm{II}}, \quad (45)$$

$$\frac{\mathrm{d[Ia]}}{\mathrm{d}t} = \frac{k_1[\mathrm{IIa}][\mathrm{I}]}{K_{1m} + [\mathrm{I}]} - \frac{h_1[\mathrm{PLA}][\mathrm{Ia}]}{H_{1m} + [\mathrm{Ia}]} = G_{\mathrm{Ia}}, \quad (46)$$

$$\frac{\mathrm{d[I]}}{\mathrm{d}t} = \frac{-k_1[\mathrm{IIa}][\mathrm{I}]}{K_{1m} + [\mathrm{I}]} = G_{\mathrm{I}}, \quad (47)$$

$$\frac{\mathrm{d[XIa]}}{\mathrm{d}t} = k_{11}[\mathrm{IIa}] - h_{11}[\mathrm{XIa}] = G_{\mathrm{XIa}}, \quad (48)$$

$$\frac{\mathrm{d[XI]}}{\mathrm{d}t} = -k_{11}[\mathrm{IIa}] = G_{\mathrm{XI}}, \quad (49)$$

$$\frac{\mathrm{d[ATIII]}}{\mathrm{d}t} = -h_9[\mathrm{IXa}] - h_{10}[\mathrm{Xa}] - h_2[\mathrm{IIa}] = G_{\mathrm{ATIII}}, \quad (50)$$

$$\frac{\mathrm{d[TFPI]}}{\mathrm{d}t} = -k_{\mathrm{TFPI}}[\mathrm{TFPI}][\mathrm{Xa}] = G_{\mathrm{TFPI}}, \quad (51)$$

$$\frac{\mathrm{d[APC]}}{\mathrm{d}t} = k_{\mathrm{APC}}[\mathrm{IIa}] - h_{\mathrm{APC}}[\mathrm{APC}] = G_{\mathrm{APC}}, \quad (52)$$

$$\frac{\mathrm{d[PC]}}{\mathrm{d}t} = -k_{\mathrm{APC}}[\mathrm{IIa}] = G_{\mathrm{PC}}, \quad (53)$$

$$\frac{\mathrm{d[L1AT]}}{\mathrm{d}t} = -h_{\mathrm{APC}}[\mathrm{APC}] = G_{\mathrm{L1AT}}, \quad (54)$$

$$\frac{\mathrm{d[tPA]}}{\mathrm{d}t} = 0 = G_{\mathrm{tPA}}, \quad (55)$$

$$\frac{\mathrm{d[PLA]}}{\mathrm{d}t} = k_{\mathrm{PLA}}^{\mathrm{tPA-Ia}}[\mathrm{tPA}] - h_{\mathrm{PLA}}[\mathrm{PLA}][\mathrm{L2AP}] = G_{\mathrm{PLA}}, \quad (56)$$

$$\frac{\mathrm{d[PLS]}}{\mathrm{d}t} = -k_{\mathrm{PLA}}^{\mathrm{tPA-Ia}}[\mathrm{tPA}] = G_{\mathrm{PLS}}, \quad (57)$$

$$\frac{\mathrm{d[L2AP]}}{\mathrm{d}t} = -h_{\mathrm{PLA}}[\mathrm{PLA}][\mathrm{L2AP}] = G_{\mathrm{L2AP}}. \quad (58)$$

The equation governing platelet activation (tied to generation of phospholipid sites) is as follows:

$$\frac{\mathrm{d[AP]}}{\mathrm{d}t} = +k_{\mathrm{AP}}^{\mathrm{AP}}[\mathrm{AP}][\mathrm{RP}] + k_{\mathrm{AP}}^{\mathrm{IIa}}[\mathrm{RP}] = G_{\mathrm{AP}} \quad (59)$$

$$\frac{\mathrm{d[RP]}}{\mathrm{d}t} = -G_{\mathrm{AP}} = G_{\mathrm{RP}}. \quad (60)$$

In addition, [AP] also changes upon prolonged exposure to supra-critical shear stresses (see the 'Platelet Activation due to Prolonged Exposure to Shear Stresses' section).

Assumptions Governing Inclusion of Phospholipid Binding Site Density in Reactions 4a, 5a

The role of phoshpholipid binding site density is included in the following manner: The values for $k_{8,9}$ and $k_{5,10}$ reported in Ataullakhanov *et al.* (2002) are measured with saturating concentrations of phospholipids. This saturating concentration is assumed to be tied to the total concentration of RP at time $t = 0$, i.e. phospholipid sites are found only on the surface of AP, and their total number is linearly related to the maximum concentration of AP which is also the initial concentration of RP. During the course of the reactions, the availability of these binding sites is governed by the concentration of AP at any particular instant; this yields the expression for $k_{8,9}$ and $k_{5,10}$ mentioned in Table II. We neither make a distinction between the number and type of phospholipid binding sites associated with each enzyme complex, nor allow for any competition between the enzyme complexes in binding to these sites.

Assumptions for Reactions 6c, 7a, 9a, 9b, 11a, 11b, 12a, 12b

The inhibition of Xa by TFPI (Reaction 6c) is assumed to be a second order irreversible reaction with the kinetics governed by the association constant given in Kuharsky and Fogelson (2001). The dissociation of the TFPI-Xa complex is neglected given that the controlling factor is TFPI, and the association parameter $k_{\mathrm{TFPI}}[\mathrm{TFPI}]|_{t=0} = 4.0 \times 10^{-2}\,\mathrm{s}^{-1}$ is two orders of magnitude greater than the dissociation constant of $3.0 \times 10^{-4}\,\mathrm{s}^{-1}$ (Kuharsky and Fogelson, 2001). The activation of prothrombin by prothrombinase (Reaction 7a) follows Michaelis-Menten kinetics with $K_m = 1.06\,\mu\mathrm{M}$. Given that normal physiological concentration of prothrombin is $1.4\,\mu\mathrm{M}$, we retain the Michaelis-Menten kinetics in describing this reaction.

The cleavage of fibrinogen by thrombin resulting in fibrin (Reaction 9a) is a reaction of the Michaelis-Menten

type as reported in Tsiang *et al.* (1996). Data for the degradation of fibrin by plasmin (Reaction 9b) was not found; hence we approximate it with the data for plasmin deactivation of fibrinogen (Bickford *et al.*, 1964). This reaction has $K_m = 2.9\,\mu$M, and, given that the initial concentration of fibrinogen is $7\,\mu$M, fibrin will probably be produced in concentrations of similar magnitude, hence we prefer a Michaelis-Menten description for the kinetics of this reaction.

The reactions governing the activation of RP by thrombin and by other AP (Reactions 11a and 11b, respectively) follow the kinetics outlined in Kuharsky and Fogelson (2001) (in turn estimated from the data in Gear (1994)).

The concentration of tPA is controlled entirely by its flux boundary condition that represents its production by intact endothelial cells, either by a constitutive process or/and due to activation by thrombin and fibrin (see subsection "Assumptions Involved in the Derivation of Parameters Governing the Flux Boundary Conditions"). tPA is always assumed to be bound to fibrin. The action of tPA (bound to fibrin) on (Lys) PLS (Reaction 12a) is approximated by a first order reaction given that $K_m =$ 18 nM (Madison *et al.*, 1995), and that PLS is present in a large excess in the plasma (2180 nM). The action of tPA (bound to fibrin) on Glu-PLS is a reaction of Michaelis-Menten kinetics with $K_m = 160$ nM and $k_{\text{cat}} = 0.1\,\text{s}^{-1}$ (Hoylaerts *et al.*, 1982). We will not concern ourselves with this distinction between the two forms of PLS, and will use the data for Lys-PLS. Plasmin deactivation by α2-Antiplasmin (Reaction 12b) is a second order reaction as reported in (Kolev *et al.*, 1994). We use the enzyme kinetic data obtained for the action of α2-Antiplasmin in the presence of a physiologically relevant amount of fibrinogen.

Treatment of Diffusion Coefficients

The diffusion coefficients, and their dependence on the shear rate, are tabulated in Table III. Our treatment of the diffusion coefficients is more detailed than those in previous studies.

The phenomenon of diffusion, of a solute in a solvent, can be tied to the independent Brownian motion of the solute molecules as they undergo random collisions with the solvent molecules. The diffusion coefficient is related to the parameter characterizing the Brownian displacement of such solute molecules and the drag that these molecules experience as they move within the solvent. The Stokes-Einstein equation quantifies this idea for spherical solute molecules at infinite dilution in a solvent, and is a useful tool to estimate diffusion coefficients.

On the other hand, diffusion coefficients can also be measured directly by experiments or inferred from experiments that report sedimentation coefficients (see Freifelder (1982) for a detailed account of such measurement techniques). Ultracentrifugation techniques typically measure the sedimentation velocity of solutes in a variety of solvents, extrapolate the measured values to infinite dilution in water at 20°C and report this value. This sedimentation coefficient can then be used to obtain the diffusion coefficient given the relation between the two expressed in Svedberg's formula (this relation can also be obtained by means of arguments in linear non-equilibrium thermodynamics Haase, 1963).

Experimental data on diffusion coefficients for the coagulation factors and proteins in human plasma (Fasman, 1975; Lentner, 1984) is reported in water at 20°C. These values cannot be used to characterize diffusion in blood at 37°C; the molecules collide with each other with greater probability and experience frictional forces that are different, possibly higher. It is well documented that platelet diffusivity is enhanced by orders of magnitude due to collisions with RBCs during blood flow (Antonini *et al.*, 1978). Goldsmith and Turitto (1986) state that measured diffusivity values are enhanced, over that inferred from just Brownian motion, for platelets and also for proteins, like fibrinogen and vWF, which have high molecular weights. They state that proteins of molecular weight $< 10^5$ Daltons are not much influenced by RBC motion.

Keeping these observations in mind, we will obtain diffusion coefficients for low molecular weight proteins in plasma (1.2 cP) at 37°C using a generalized form of the Stokes-Einstein equation, namely the correlation in Young *et al.* (1980). This requires knowledge of the molecular weights and specific partial volumes for each protein. Complete data was not found for the specific partial volumes, and hence a value of 0.73 cc/g was chosen where this data was unavailable (see Young *et al.* (1980) for a rationale for this assumption). We will use the correlation in Young *et al.* (1980) for high molecular weight proteins ($> 10^5$ Daltons) also. As evidence that such an assumption will not yield diffusion coefficients that are much different from the actual value, we point to the data in Le and Dejardin (1998) (data for diffusion coefficient on kininogen in a kininogen-fibrinogen solution in a Tris buffer) and (Nagamatsu *et al.*, 1992, data for diffusion coefficient of fibrinogen–fibronectin complex at dissociation at 37°C in a Tris buffer). The diffusion coefficients reported in these studies are of the same order of magnitude as that predicted by the correlation in the appropriate solvents.

For platelets, we estimate the Brownian diffusion coefficient in plasma (using the Stokes-Einstein formula), and enhance it with a shear rate and RBC diameter-dependent factor: $D_{\dot{\gamma}}$. There are many models that estimate the enhanced diffusivity of platelets due to RBC motion (Keller, 1971; Antonini *et al.*, 1978; Zydney and Colton, 1982). We use the formula suggested by Keller (1971), generalizing it so as to apply in a three-dimensional frame invariant setting. The enhancement of platelet (resting and activated) diffusivity is given by

TABLE III Diffusion coefficients

Species	Molecular weight (g/mol)	$\overline{\nu}$ (cc/g)	Diffusion coefficients (cm^2/s)	References
RP	–	–	$D_{RP} = 1.58 \times 10^{-9} + D_{\dot{\gamma}}$	–
AP	–	–	$D_{AP} = 1.58 \times 10^{-9} + D_{\dot{\gamma}}$	–
I	3,40,000	0.723	$D_{I} = 3.1 \times 10^{-7}$	Fasman (1975), Young *et al.* (1980) and Furie and Furie (2000)
Ia	≈6,60,000	0.730	$D_{Ia} = 2.47 \times 10^{-7}$	Young *et al.* (1980) and Furie and Furie (2000)
II	72,000	0.719	$D_{II} = 5.21 \times 10^{-7}$	Fasman (1975), Young *et al.* (1980) and Furie and Furie (2000)
IIa	37,000	0.730	$D_{IIa} = 6.47 \times 10^{-7}$	Young *et al.* (1980) and Furie and Furie (2000)
V	3,30,000	0.730	$D_{V} = 3.12 \times 10^{-7}$	Furie and Furie (2000) and Young *et al.* (1980)
Va	1,79,000	0.730	$D_{Va} = 3.82 \times 10^{-7}$	Furie and Furie (2000) and Young *et al.* (1980)
VIII	3,30,000	0.730	$D_{VIII} = 3.12 \times 10^{-7}$	Furie and Furie (2000) and Young *et al.* (1980)
VIIIa	1,66,000	0.730	$D_{VIIIa} = 3.92 \times 10^{-7}$	Furie and Furie (2000) and Young *et al.* (1980)
IX	56,000	0.730	$D_{IX} = 5.63 \times 10^{-7}$	Fasman (1975), Young *et al.* (1980) and Furie and Furie (2000)
IXa	41,000	0.730	$D_{IXa} = 6.25 \times 10^{-7}$	Furie and Furie (2000) and Young *et al.* (1980)
X	56,000	0.730	$D_{X} = 5.63 \times 10^{-7}$	Fasman (1975), Young *et al.* (1980) and Furie and Furie (2000)
Xa	25,000	0.730	$D_{Xa} = 7.37 \times 10^{-7}$	Fasman (1975), Young *et al.* (1980) and Furie and Furie (2000)
XI	1,60,000	0.730	$D_{XI} = 3.97 \times 10^{-7}$	Fasman (1975), Young *et al.* (1980) and Furie and Furie (2000)
XIa	80,000	0.730	$D_{XIa} = 5.0 \times 10^{-7}$	Furie and Furie (2000) and Young *et al.* (1980)
PC	62,000	0.730	$D_{PC} = 5.44 \times 10^{-7}$	Fasman (1975), Young *et al.* (1980) and Furie and Furie (2000)
APC	60,000	0.730	$D_{APC} = 5.50 \times 10^{-7}$	Bauer and Rosenberg (1995) and Young *et al.* (1980)
ATIII	58,000	0.730	$D_{ATIII} = 5.57 \times 10^{-7}$	Lentner (1984) and Young *et al.* (1980)
TFPI	40,000	0.730	$D_{TFPI} = 6.30 \times 10^{-7}$	Colman *et al.* (2001) and Young *et al.* (1980)
L1AT	51,000	0.728	$D_{L1AT} = 5.82 \times 10^{-7}$	Young *et al.* (1980) and Lentner (1984)
tPA	68,000	0.730	$D_{tPA} = 5.28 \times 10^{-7}$	Lijnen and Collen (2000) and Young *et al.* (1980)
PLS	92,000	0.715	$D_{PLS} = 4.81 \times 10^{-7}$	Fasman (1975), Young *et al.* (1980) and Lijnen and Collen (2000)
PLA	85,000	0.715	$D_{PLA} = 4.93 \times 10^{-7}$	Fasman (1975), Young *et al.* (1980) and Lijnen and Collen (2000)
L2AP	70,000	0.720	$D_{L2AP} = 5.25 \times 10^{-7}$	Young *et al.* (1980) and Lentner (1984) and Lijnen and Collen (2000)

(assuming RBC diameter of 8 μm)

$$D_{\dot{\gamma}} = 2.88 \times 10^{-8} \sqrt{2\mathrm{tr}(\mathbf{D}^2)}\,\mathrm{cm}^2/\mathrm{s}. \tag{61}$$

A slightly more sophisticated equation than the one in Young *et al.* (1980) is proposed in Tyn and Gusek (1990) which includes the role of protein shape and sizes by means of the radius of gyration (R_{gyr}). Measurements of R_{gyr} are not available for all the coagulation factors, and hence we have not used this correlation. An accurate treatment of diffusion coefficients should consider this aspect of protein molecules as well.

Platelet Activation due to Prolonged Exposure to Shear Stresses

The platelet activation criterion is similar to that outlined in Anand and Rajagopal (2002), and is a supplemental criterion to the activation due to biochemical reactions.

In order to quantify the idea of activation due to prolonged exposure to supra-threshold shear stresses, a phenomenological activation number, $A(t)$, is introduced. This number is associated with each platelet. The platelets are initially undamaged (i.e. $A(0) = 0$). The activation number can either increase or stay constant reflecting exposure to time varying shear stresses that are or are not above the threshold value (τ_{thr}). Platelet activation occurs when a threshold activation number (A_{cr}) is reached. Activated platelets are lysed if the activation number exceeds a critical value, A_{damage}, in the time period t_{act} that it takes for the RP to transform into the activated form. For the special flow fields that we consider, the activation of the platelets can be tracked quite easily by verifying the activation number at each point in the flow domain. We will still have to assume that the time scales over which diffusion occurs is much more than the time scale over which the shear stresses act. For a more general flow field, a different approach may have to be used to track the activation due to shear-stress exposure.

The activation criterion is as follows:

$$A(t) = A(0) + \frac{1}{A_0}\int_0^t \mathrm{e}^{k\left(\frac{|\tau_{rz}|}{\tau_{thr}} - 1\right)} H(|\tau_{rz}| - \tau_{thr})\mathrm{d}t \tag{62}$$

$$H(|\tau_{rz}| - \tau_{thr}) = \begin{cases} 1 & |\tau_{rz}| \geq \tau_{thr} \\ 0 & |\tau_{rz}| < \tau_{thr} \end{cases} \tag{63}$$

The criterion for activation of RP is as follows:

$$\text{If } A(t - t_{act}) > A_{thr} \text{ and } A(t) < A_{damage} \tag{64}$$

or

$$A(t - t_{act}) = A_{thr}, \dot{A}(t - t_{act}) > 0 \text{ and } A(t) < A_{damage}, \tag{65}$$

then

$$[\mathrm{AP}](t) = [\mathrm{AP}](t - t_{act}) + [\mathrm{RP}](t - t_{act}). \tag{66}$$

The criterion for lysis of platelets during activation is as follows: If

$$A(t - t_{act}) > A_{thr} \text{ and } A(t) > A_{damage}, \tag{67}$$

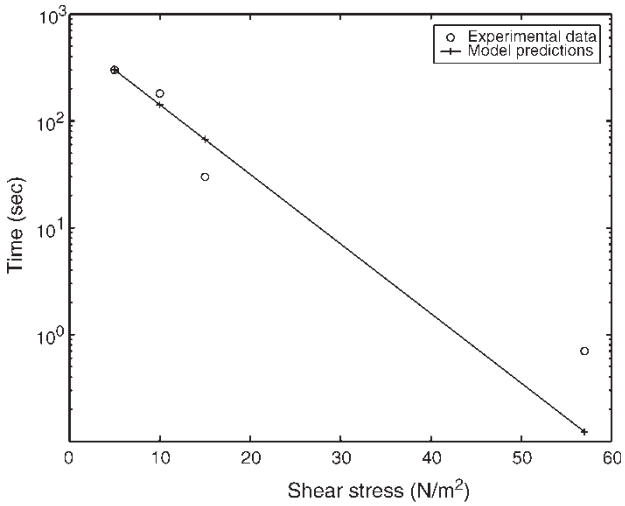

FIGURE 3 Comparison of stress-induced-activation criterion predictions of time for platelet activation with experimental data.

then

$$[\mathrm{AP}](t) = [\mathrm{RP}](t - t_{\mathrm{act}}). \tag{68}$$

The values of $A_0 = 300\,\mathrm{s}$, $t_{\mathrm{act}} = 1\,\mathrm{s}$, $k = 0.75$, $\tau_{\mathrm{thr}} = 5\,\mathrm{Nm}^{-2}$, $A_{\mathrm{thr}} = 1$, $A_{\mathrm{damage}} = 3$, fit the data from Brown *et al.* (1975a,b); Wurzinger *et al.* (1985). The curve fit for the data is shown in Figure 3. The data relates to low values of shear stress, while sometimes high stress can act for extremely short instants (in VADs for instance). Data that covers the region of very high shear stresses (1000–10,000 N/m^2) is not readily available. The data of Colantuoni *et al.* (1977) is not complete for purposes of checking the constants A_{thr}, A_{damage}. The estimate for the time lag between activation, and the onset of coagulation is obtained from Sorensen *et al.* (1999a). The initiation criterion brings out the idea that platelet activation is initiated by exposure to shear stresses, and that coagulation will begin if the platelets are not lysed between the instant of activation and coagulation. The possibility of lysis precluding coagulation is incorporated via Eqs. (67) and (68).

Criteria for the Initiation of Clot Formation, Clot Growth and Clot Dissolution

Initially, no clot exists; the entire flow domain has only blood. A clot is said to be formed when the concentration of fibrin [Ia] is $\geq 600\,\mathrm{nM}$, at any point in the flow domain. Initiation of clot formation is tied to a certain level of vessel wall injury reflected in a threshold concentration of the TF-VIIa complex.

Clot growth is determined by tracking, in time, the extent of the region, within the flow domain, where [Ia] $\geq$ 600 nM.

Clot dissolution occurs if [Ia] $< 600\,\mathrm{nM}$ at any location in the clot zone. This may happen, for instance, due to fibrinolysis becoming well advanced. Clot dissolution can also occur if shear stress exceeds a certain critical value at any location in the clot. The value of this shear stress depends on the concentration of platelets and fibrin at each location in the clot. The role of shear stress in clot dissolution is based on the data reported in Glover *et al.* (1975a,b) and Riha *et al.* (1999). Therefore, clot dissolution occurs if:

$$[\mathrm{Ia}] < 600\,\mathrm{nM} \ \text{ or if } \ |T_{rz}| \geq T_{\mathrm{crit}}([\mathrm{AP}], [\mathrm{Ia}]). \tag{69}$$

The critical stress values are quite high in comparison to the stresses required to activate platelets. For instance, compare the T_{crit} of 211 Pa for clots formed from 40% hematocrit human blood with τ_{thr} of 5 Pa for platelets derived from human plasma.

A Viscoelastic Fluid Model for a Coarse Ligated Plasma Clot

A viscoelastic fluid model has been developed to describe the flow of a coarse ligated human plasma clot (Anand and Rajagopal, 2004b). The model equations have been corroborated with data for oscillatory flow in a circular pipe (Thurston and Henderson, 1993), and as required the model predicts an apparent viscosity for the clot that is much greater than that of blood (Experimental constraints preclude actual measurements of this parameter for the plasma clot). The constitutive model for the viscoelastic response of the clot is similar in form to that for blood, but the material modulus has different values. For instance, the viscosity of the clot is more than 16 times the viscosity of blood.

$$\mathbf{T} = -p\mathbf{1} + \mathbf{S}, \tag{70}$$

$$\mathbf{S} = \mu^c \mathbf{B}_{\kappa_{\mathbf{p}(\mathbf{t})}} + \eta_1^c \mathbf{D}, \tag{71}$$

$$\overset{\nabla}{\mathbf{B}}_{\kappa_{p(t)}} = -2\left(\frac{\mu^c}{\alpha^c}\right)^{1+2n^c} \left(\mathrm{tr}(\mathbf{B}_{\kappa_{\mathbf{p}(\mathbf{t})}}) - 3\lambda\right)^{n^c} \left[\mathbf{B}_{\kappa_{p(t)}} - \lambda\mathbf{1}\right], \tag{72}$$

$$\lambda = \frac{3}{\mathrm{tr}\left(\mathbf{B}^{-\mathbf{1}}_{\kappa_{\mathbf{p}(\mathbf{t})}}\right)}, \tag{73}$$

$$n^c = \frac{\gamma^c - 1}{1 - 2\gamma^c}; \ \ n^c > 0. \tag{74}$$

We introduce the notation

$$K^c = \left(\frac{\mu^c}{\alpha^c}\right)^{1+2n^c}. \tag{75}$$

The zero-shear viscosity inferred from the proposed model tends to ∞, and in order to ensure that the zero-shear viscosity is finite and prevent computational problems that may arise as a result, we modify the form for the viscosity and the shear-thinning index by introducing a Heaviside function into the expressions for

the viscosity and shear thinning index,

$$\alpha^c = \alpha_f^c H(\mathrm{I}_{\mathbf{B}} - \mathrm{I}_0^c) + \alpha_0^c(1 - H(\mathrm{I}_{\mathbf{B}} - \mathrm{I}_0^c)), \tag{76}$$

$$\gamma^c = \gamma^c H\big(\mathrm{I}_{\mathbf{B}} - \mathrm{I}_0^c\big) + (1 - H(\mathrm{I}_{\mathbf{B}} - \mathrm{I}_0^c)), \tag{77}$$

$$\alpha_0^c = 2\big(\eta_0^c - \eta_\infty^c\big), \tag{78}$$

where η_0^c, η_∞^c are the asymptotic viscosities of the clot at low and high shear rates, and I_0^c is a suitably chosen constant.

The following constants pertain to the model for the human plasma clot: $K^c = 2.2\,\mathrm{s}^{-1}$, $\mu^c = 4.9\,\mathrm{Pa}$, $n^c = 0.10$ and $\eta_1^c = 0.1\,\mathrm{Pa\,s}$. Note that these constants are quite different from those obtained for human blood. The model predicts a viscosity of 2200 cP at a shear rate of $0.06\,\mathrm{s}^{-1}$ and a viscosity of 84 cP at a shear rate of $650\,\mathrm{s}^{-1}$ for the clot. The corresponding values for the viscosity of human blood are 73.6 cP and 5 cP.

APPLICATION OF MODEL SYSTEM TO SIMPLE FLOW PROBLEMS

Balance Equations

The equations for the balance of mass, linear momentum and internal energy are:

$$\frac{D\rho}{Dt} + \rho\,\mathrm{div}\mathbf{v} = 0, \tag{79}$$

$$\mathrm{div}\mathbf{T} + \rho\mathbf{b} = \rho\frac{D\mathbf{v}}{Dt}, \tag{80}$$

$$\mathbf{T} = \mathbf{T}^T, \tag{81}$$

$$\rho\dot{\epsilon} = \mathbf{T}\cdot\mathbf{D} + \rho\Gamma - \mathrm{div}\mathbf{q}. \tag{82}$$

Equation (81) is a statement of the balance of angular momentum in the absence of internal body forces. Here ρ is the density, $\mathbf{v}$ is the velocity field, $\mathbf{T}$ is the stress tensor, ϵ is the specific internal energy of the material, $\mathbf{D}$ is the stretching tensor, $\mathbf{q}$ is the heat flux, and Γ is the energy influx due to radiation. We use the second law of thermodynamics in the following form

$$\mathbf{T}\cdot\mathbf{D} - \rho\dot{\psi} - \rho\eta\dot{\theta} - \frac{\mathbf{q}\cdot\mathrm{grad}\,\theta}{\theta} = \rho\theta\xi = \zeta, \tag{83}$$

and enforce $\xi \geq 0$ or equivalently $\zeta \geq 0$. Here ψ is the specific Helmholtz potential, η is the entropy, θ is the temperature, ξ is the rate of entropy production, and ζ is the rate of dissipation.

The balance equation for the various coagulation constituents has already been written as the set of coupled advection-reaction-diffusion equations. This is just an approximation of the mass and linear momentum balance equations for a multicomponent mixture.

Initial and Boundary Conditions

The initial conditions are picked appropriately for each flow problem. No clot exists at time $t = 0$; therefore initial conditions specified are for the flow of blood. For the case of time varying poiseuille-type flow in a cylindrical annulus of inner radius R_i and outer radius R_o, where the velocity is assumed to be of the following form:

$$\mathbf{v} = u(r,t)\hat{\mathbf{e}}_z. \tag{84}$$

Initially, we assume that we have an unsteady flow that is fully developed. No other initial conditions are required, and the no slip condition is enforced at both the boundaries, i.e.

$$u(R_\mathrm{i}, t) = 0, \tag{85}$$

$$u(R_\mathrm{o}, t) = 0. \tag{86}$$

For oscillatory flow in a rigid circular pipe, the initial velocity profile is set to be the exact solution for a Newtonian fluid at small Womersley numbers (a parabolic profile), and $\mathbf{B}_{\kappa_{p(t)}}(t=0) = \mathbf{1}$ is the initial condition for the components of $\mathbf{B}_{\kappa_{p(t)}}$. The flow boundary conditions are picked appropriately depending on the geometry under consideration. For the case of oscillatory flow in a rigid cylindrical pipe of radius R, where the velocity is assumed to be of the form:

$$\mathbf{v} = u(r,t)\,\hat{\mathrm{e}}_z, \tag{87}$$

the boundary conditions for the velocity are:

$$u(R,t) = 0, \tag{88}$$

$$\frac{\partial u(0,t)}{\partial r} = 0. \tag{89}$$

The initial conditions for the concentrations of prothrombin (II), zymogens (II, V, VIII, IX, X, XI, PLS), inhibitors (ATIII, TFPI, L1AT, L2AP), regulatory protein (protein C), and tPA are their normal values in human blood. The initial concentrations for thrombin (IIa) and the enzymes (Va, VIIIa, IXa, Xa, XIa, PLA) and the active form of the regulatory protein (APC) are set to zero. The initial concentration of fibrinogen (I) is assumed to have an average value of 7 μM; typically this concentration varies between 4 and 10 μM in human blood (Mann *et al.*, 1995). The initial concentration of fibrin (Ia) is set to be zero. The initial concentration of RPs ($[\mathrm{RP}]|_{t=0}$) is set to be 10 nM based on the estimates in Kuharsky and Fogelson (2001) for human blood. The initial concentration of 10 nM of RP is set to correspond to the normal human platelet count of $2.5 \times 10^5/\mathrm{mm}^3$. We assume a linear relationship between the concentration of RPs and the platelet count at any given time. A 5% level of activation is assumed for the platelets initially

TABLE IV Initial conditions

Species	Initial concentrations (nM)	Sources
RP	10	Kuharsky and Fogelson (2001)
AP	0.5	Sorensen *et al.* (1999a)
I	7000	Mann *et al.* (1995)
Ia	0	
II	1400	Mann *et al.* (1995)
IIa	0	
V	20	Mann *et al.* (1995)
Va	0	
VIII	0.7	Mann *et al.* (1995)
VIIIa	0	
IX	90	Mann *et al.* (1995)
IXa	0	
X	170	Mann *et al.* (1995)
Xa	0	
XI	30	Bungay *et al.* (2003)
XIa	0	
ATIII	2410	Bauer and Rosenberg (1995)
TFPI	2.5	Mann *et al.* (1995)
PC	60	Mann *et al.* (1995)
APC	0	
L1AT	45000	Colman *et al.* (2001)
tPA	0.08	Booth (1999)
PLS	2180	Lijnen and Collen (2000)
PLA	0	
L2AP	105	Colman *et al.* (2001)

(see Sorensen *et al.*, 1999a), i.e. $[\mathrm{AP}]_{(t=0)} = 0.5\,\mathrm{nM}$. The initial concentrations are listed in Table IV.

The boundary conditions governing the concentration of the various species at the inner wall (consisting of injured human blood vessel segments), in the case of Poiseuille flow in an annular perfusion chamber (see subsection 'Procedure for Corroboration of Model with Experimental Data') are:

$$\left.\frac{\partial[Y_i]}{\partial r}\right|_{r=R_\mathrm{i}} = 0, \tag{90}$$

for all species Y_i except IXa and Xa (as also IX and X) which are influenced by the concentration of surface-bound [TF-VIIa] complex, AP (as also RP) which is influenced by the extent of subendothelium–platelet interaction, and tPA which is influenced by the extent of endothelial cell activity (constitutive or induced by thrombin and fibrin). For these seven species, the boundary conditions are (constants listed in Table V):

$$\left.\frac{\partial[\mathrm{IXa}]}{\partial r}\right|_{r=R_\mathrm{i}} = -\phi_{\mathrm{IXa}}[\mathrm{TF{-}VIIa}] = -\frac{D_{\mathrm{IX}}}{D_{\mathrm{IXa}}}\left.\frac{\partial[\mathrm{IX}]}{\partial r}\right|_{r=R_\mathrm{i}}, \tag{91}$$

$$\left.\frac{\partial[\mathrm{Xa}]}{\partial r}\right|_{r=R_\mathrm{i}} = -\phi_{\mathrm{Xa}}[\mathrm{TF{-}VIIa}] = -\frac{D_X}{D_{Xa}}\left.\frac{\partial[\mathrm{X}]}{\partial r}\right|_{r=R_\mathrm{i}}, \tag{92}$$

$$\left.\frac{\partial[\mathrm{AP}]}{\partial r}\right|_{r=R_\mathrm{i}} = -\phi_{\mathrm{AP}}[\mathrm{SUBENDO}][\mathrm{RP}]|_{r=R_\mathrm{i}} = -\frac{D_{\mathrm{RP}}}{D_{\mathrm{AP}}}\left.\frac{\partial[\mathrm{RP}]}{\partial r}\right|_{r=R_\mathrm{i}}, \tag{93}$$

$$\left.\frac{\partial[\mathrm{tPA}]}{\partial r}\right|_{r=R_\mathrm{i}} = -\left(\phi^{C}_{\mathrm{tPA}} + \phi^{\mathrm{IIa}}_{\mathrm{tPA}}[\mathrm{IIa}]|_{r=R_\mathrm{i}} + \phi^{\mathrm{Ia}}_{\mathrm{tPA}}[\mathrm{Ia}]|_{r=R_\mathrm{i}}\right)[\mathrm{ENDO}]. \tag{94}$$

Here [SUBENDO] refers to the concentration of subendothelial binding sites expressed in 'nM', [ENDO] refers to the number of intact endothelial cells per unit area expressed in cells/m^2. The negative sign is introduced to preserve physical meaning.

The outer (glass) wall is impermeable, and the boundary condition for all species (Y_i) is:

$$\left.\frac{\partial[Y_i]}{\partial r}\right|_{r=R_\mathrm{o}} = 0,\ i = 1, \ldots, 25. \tag{95}$$

The concentration boundary conditions appropriate for the case of oscillatory flow in a rigid cylindrical pipe of radius R are:

$$\left.\frac{\partial[Y_i]}{\partial r}\right|_{r=0} = 0,\ i = 1, \ldots, 25, \tag{96}$$

at the centerline for all species Y_i, and

$$\left.\frac{\partial[Y_i]}{\partial r}\right|_{r=R} = 0, \tag{97}$$

at the outer wall for all species Y_i except IXa, IX, Xa, X, AP, RP, and tPA. The boundary conditions at the wall for these seven species are:

$$\left.\frac{\partial[\mathrm{IXa}]}{\partial r}\right|_{r=R} = \phi_{\mathrm{IXa}}[\mathrm{TF{-}VIIa}] = -\frac{D_{\mathrm{IX}}}{D_{\mathrm{IXa}}}\left.\frac{\partial[\mathrm{IX}]}{\partial r}\right|_{r=R}, \tag{98}$$

$$\left.\frac{\partial[Xa\,]}{\partial r}\right|_{r=R} = \phi_{\mathrm{Xa}}[\mathrm{TF{-}VIIa}] = -\frac{D_{\mathrm{X}}}{D_{\mathrm{Xa}}}\left.\frac{\partial[X\,]}{\partial r}\right|_{r=R}, \tag{99}$$

$$\left.\frac{\partial[\mathrm{AP}]}{\partial r}\right|_{r=R} = \phi_{\mathrm{AP}}[\mathrm{SUBENDO}][\mathrm{RP}]|_{r=R} = -\frac{D_{\mathrm{RP}}}{D_{\mathrm{AP}}}\left.\frac{\partial[\mathrm{RP}]}{\partial r}\right|_{r=R}, \tag{100}$$

TABLE V Parameters for boundary conditions (see section "Assumptions involved in the derivation of parameters governing the flux boundary conditions")

Species	Boundary condition parameters
IXa	$\phi_{\mathrm{IXa}} = 9.6 \times 10^6\,\mathrm{m}^{-1}$
Xa	$\phi_{\mathrm{Xa}} = 3.12 \times 10^7\,\mathrm{m}^{-1}$
AP	$\phi_{\mathrm{AP}} = 2.53 \times 10^8\,\mathrm{nM}^{-1}\,\mathrm{m}^{-1}$
tPA	(Constitutive) $\phi^{C}_{\mathrm{tPA}} = 2.17 \times 10^{-7}\,\mathrm{nMm}$
tPA	(IIa-induced) $\phi^{\mathrm{IIa}}_{\mathrm{tPA}} = 4.61 \times 10^{-6}\mathrm{e}^{-134.8(t\,-\,T0)}\,\mathrm{m}$
tPA	(Ia-induced) $\phi^{\mathrm{Ia}}_{\mathrm{tPA}} = 1.68 \times 10^{-12}\,\mathrm{m}$

Note: $T0$ refers to the instant when thrombin concentration on the boundary becomes non-zero. t, $T0$ are in "seconds".

$$\left.\frac{\partial[\mathrm{tPA}]}{\partial r}\right|_{r=R} = \left(\phi^{C}_{\mathrm{tPA}} + \phi^{\mathrm{IIa}}_{\mathrm{tPA}}[\mathrm{IIa}]|_{r=R} + \phi^{\mathrm{Ia}}_{\mathrm{tPA}}[\mathrm{Ia}]|_{r=R}\right) \times [\mathrm{ENDO}]. \quad (101)$$

Assumptions Involved in the Derivation of Parameters Governing the Flux Boundary Conditions (see Table V)

The general principle used in deriving the parameters governing the boundary conditions is to reduce the net change in concentration of the activated species, usually reported within a sample volume, as if it were occuring due to diffusion of a concentration gradient at the surface. All data and estimates used are for platelets and enzymes derived from human plasma, and for human endothelial cell (HUVEC) cultures.

The parameters governing the boundary conditions for IXa and Xa are derived by assuming that rate of generation of IXa and Xa due to TF-VIIa mentioned in Ataullakhanov *et al.* (2002) ($k_{7,9}$[TF-VIIa] and $k_{7,10}$[TF-VIIa], respectively) occur as a result of diffusion from the surface. That is, given that

$$G^{\mathrm{TF-VIIa}}_{\mathrm{IXa}} = k_{7,9}[\mathrm{TF-VIIa}], \quad (102)$$

$$G^{\mathrm{TF-VIIa}}_{\mathrm{Xa}} = k_{7,10}[\mathrm{TF-VIIa}], \quad (103)$$

and that

$$G^{\mathrm{TF-VIIa}}_{\mathrm{IXa}} V_{\mathrm{clot}} = D_{\mathrm{IXa}} \left.\frac{\partial[\mathrm{IXa}]}{\partial r}\right|_{\mathrm{surface}} A_{\mathrm{clot}}, \quad (104)$$

$$G^{\mathrm{TF-VIIa}}_{\mathrm{Xa}} V_{\mathrm{clot}} = D_{\mathrm{Xa}} \left.\frac{\partial[\mathrm{IXa}]}{\partial r}\right|_{\mathrm{surface}} A_{\mathrm{clot}}, \quad (105)$$

we have

$$\phi_{\mathrm{IXa}} = \frac{k_{7,9} V_{\mathrm{clot}}}{D_{\mathrm{IXa}} A_{\mathrm{clot}}}, \quad (106)$$

$$\phi_{\mathrm{Xa}} = \frac{k_{7,10} V_{\mathrm{clot}}}{D_{\mathrm{Xa}} A_{\mathrm{clot}}}. \quad (107)$$

Using the values for $k_{7,9}$, $k_{7,10}$ mentioned in Ataullakhanov *et al.* (2002), the values for D_{IXa}, D_{Xa} as calculated in Table III, and setting the ratio $V_{\mathrm{clot}}/A_{\mathrm{clot}}$ to be 2 mm (given that the typical height of the clot formed in Ataullakhanov *et al.* (2002) is around 2 mm), we obtain the relevant values for ϕ_{IXa} and ϕ_{Xa}.

A similar procedure is adopted to find ϕ_{AP}. We use the volume generation of activated platelets due to interaction with subendothelial binding sites in Kuharsky and Fogelson (2001) (k^{+}_{pla}[PL]($p_{\mathrm{sub}} - [\mathrm{PL}^{s}_{a}]$)) to estimate

$$G^{\mathrm{SUBENDO}}_{\mathrm{AP}} = k^{+}_{\mathrm{pla}}[\mathrm{RP}][\mathrm{SUBENDO}]. \quad (108)$$

Using

$$G^{\mathrm{SUBENDO}}_{\mathrm{AP}} V_{\mathrm{clot}} = D_{\mathrm{AP}} \left.\frac{\partial[\mathrm{AP}]}{\partial r}\right|_{\mathrm{surface}} A_{\mathrm{clot}}, \quad (109)$$

we have

$$\phi_{\mathrm{AP}} = \frac{k^{+}_{\mathrm{pla}} V_{\mathrm{clot}}}{D_{\mathrm{AP}} A_{\mathrm{clot}}}. \quad (110)$$

Using the value for k^{+}_{pla} mentioned in Kuharsky and Fogelson (2001), D_{AP} in quiescent plasma, and setting the ratio $V_{\mathrm{clot}}/A_{\mathrm{clot}}$ to be 2 μm (given that the typical height of the platelet layer in Kuharsky and Fogelson (2001) is between 2–3 μm), we obtain the relevant value for ϕ_{AP}.

We repeat this procedure for tPA generation by endothelial cells, be it constitutive (see control cells in Schrauwen *et al.* (1994a,b), Schrauwen *et al.* (1995), and data for first 6 h in Levin *et al.* (1984)), or (rapid) induced by thrombin (Schrauwen *et al.*, 1995; data in Booyse *et al.* (1986) is the earliest record of this rapid release, but it is qualitative and cannot be reduced to a form that is usable), or induced by fibrin (Kaplan *et al.*, 1989). We neglect the delayed activation of endothelial cells by thrombin which occurs after 6 h (Levin *et al.*, 1984), since we will perform numerical simulations for less than 1 h (see section 'Procedure for Corroboration of Model with Experimental Data'). Again,

$$\phi^{C}_{\mathrm{tPA}} = \frac{G^{C}_{\mathrm{tPA}} V_{\mathrm{clot}}}{D_{\mathrm{tPA}} A_{\mathrm{clot}}[\mathrm{ENDO}]}, \quad (111)$$

$$\phi^{\mathrm{IIa}}_{\mathrm{tPA}} = \frac{G^{\mathrm{IIa}}_{\mathrm{tPA}} V_{\mathrm{clot}}}{D_{\mathrm{tPA}} A_{\mathrm{clot}}[\mathrm{ENDO}][\mathrm{IIa}]}, \quad (112)$$

$$\phi^{\mathrm{Ia}}_{\mathrm{tPA}} = \frac{G^{\mathrm{Ia}}_{\mathrm{tPA}} V_{\mathrm{clot}}}{D_{\mathrm{tPA}} A_{\mathrm{clot}}[\mathrm{ENDO}][\mathrm{Ia}]}. \quad (113)$$

Constitutive tPA generation refers to the constant turnover of tPA by intact endothelial cells; tPA is synthesised within the living cells, which absorb nutrients from the surrounding media, and released slowly. G^{C}_{tPA} is obtained from the data in Levin *et al.* (1984). Fibrin-induced tPA generation rate is dose dependent. $G^{\mathrm{Ia}}_{\mathrm{tPA}}$ is obtained from the data in Kaplan *et al.* (1989), and a linear dependence on [Ia] can be gleaned from the data. Thrombin-induced rapid tPA generation is dose dependent, and a linear dependence on [IIa] is assumed for the sake of simplicity (Up to thrombin concentration of 8 nM, the rate of tPA release increases dramatically (power law type) with [IIa]; above thrombin concentration of 8 nM, the rate of release increases in a weak manner (Schrauwen *et al.*, 1995). We assume linear dependence to cover both these regimes.). Thrombin-induced rapid tPA generation declines steeply within 1 min of thrombin administration. $G^{\mathrm{IIa}}_{\mathrm{tPA}}$ and its functional dependence on time are obtained from the data in Schrauwen *et al.* (1995). The value for D_{tPA} is that reported in Table III. For constitutive tPA generation and for fibrin induced tPA generation by endothelial cells, the ratio $V_{\mathrm{clot}}/A_{\mathrm{clot}}$ is equal to 1/9.5 cm and $[\mathrm{ENDO}] = 5 \times 10^{8}\,\mathrm{cells/m^2}$. For thrombin induced rapid tPA generation, the ratio $V_{\mathrm{clot}}/A_{\mathrm{clot}}$ is equal to

$0.315/2.0\,\text{cm}$, and $[\text{ENDO}] = 10^9\,\text{cells}/\text{m}^2$. Using these values, we obtain the relevant values for ϕ^C_{tPA}, $\phi^{\text{IIa}}_{\text{tPA}}$ and $\phi^{\text{Ia}}_{\text{tPA}}$.

Procedure for Corroboration of Model with Experimental Data

The (set of) model(s) is corroborated by comparing predictions with the experimental data in Tschopp *et al.* (1979) for thrombus formation and dissolution on the subendothelium of a human artery/vein exposed to citrated whole human blood in an annular perfusion chamber (see Baumgartner, 1973) over a time period of upto 40 min. Tschopp *et al.* (1979) have reported data for thrombus formation and dissolution on everted arterial/venous segments obtained from human subjects exposed to citrated human blood; the flow rate is held at a constant value. In their study, the endothelium is stripped off the vessel segment, and the segment is mounted onto a central rod. Citrated human blood is then perfused over these segments in a chamber (see Baumgartner, 1973). Although the data pertains to thrombi that are formed non-uniformly on parts of a surface, we will reduce it as if the thrombi were formed all over the surface; i.e. with the data for the percent coverage of the surface and the average height of the thrombi, a uniform layer of thrombi with a proportional height is assumed to have been formed. Data for maximum thrombus heights formed by perfusion of native human blood on segments of rabbit aorta has been reported in Baumgartner *et al.* (1980). The platelet rich deposits interspersed with fibrin fibers formed in these experiments is well approximated by a plasma clot. Additionally, we will model these thrombi as coarse ligated plasma clots assuming that physiologyical concentrations of XIIIa are present and that the pH is also near physiological levels (the original paper Tschopp *et al.* (1979) does not have the details of the XIIIa concentrations and the pH during the experiments; however nothing is said concerning the treatment of the samples of blood other than the addition of sodium citrate). We will use a viscoelastic liquid model since we are interested in the rheological behavior over a time period of around 40 min (2400 s) and the creep data for coarse ligated clots suggests liquid-like behavior over a time scale of around 3500 s (see Gerth *et al.*, 1974).

There are other sets of experimental data that can also be simulated using the (set of) model(s). For instance, the experimental results of Sorensen *et al.* (1999b) for Poiseuille flow of human blood over collagen can also be captured using this model by suitably modifying the parameters governing the platelet-surface reactivity (the corresponding flux boundary condition). Experimental data is also available that reports the distribution of thrombi along the length of collagen coated surfaces (Hubbell and McIntire, 1986; Wagner and Hubbell, 1990), and these too can be simulated by the model when the boundary conditions are specified appropriately, and a suitable numerical scheme is adopted for simulations involving two spatial dimensions. We will outline the approach, and the equations to be solved.

Time Varying, Fully Developed, Poiseuille-type Flow of Blood With An Evolving Clot in a Cylindrical Annular Region

The variation in time is due to the fact that although initially only blood flows, the extent of the flow domain, for both blood flow and clot flow, changes as the clot grows and evolves. The equations prior to the formation of the clot, when only blood flows, are derived first.

We will assume a flow field of the following form at each instant of time t:

$$\mathbf{v}|_t = u(r)\,\hat{\boldsymbol{e}}_z, \quad p|_t = p\,(r, z). \tag{114}$$

We also assume that the displacement field is such that the components of $\mathbf{B}_{\kappa_p(t)}|_t$ are functions of the radial coordinate r alone.

At each instant of time a steady pressure gradient of the form

$$\left.\frac{\partial p}{\partial z}\right|_t = -C|_t; \quad C|_t > 0, \tag{115}$$

is applied.

Henceforth, we drop the suffix t for the sake of convenience.

Initially, only blood flows in the annular region. The equations governing the flow, obtained after substituting the model equations for blood (Eqs. (11)–(15)) into the equation for the balance of linear momentum (Eq. (80)), are given below:

$$\frac{\mathrm{d}u}{\mathrm{d}r} = \left(\frac{\partial p}{\partial z}r + \frac{2k_1}{r}\right)\frac{1}{\left(\frac{\mu^b\lambda}{\chi} + \eta_1^b\right)}, \tag{116}$$

where

$$\lambda = \frac{1}{\left[1 + \frac{1}{4\chi^2}\left(\frac{\mathrm{d}u}{\mathrm{d}r}\right)^2\right]^{\frac{1}{3}}}, \tag{117}$$

$$\chi = K^b\left[\frac{\lambda}{2\chi^2}\left(\frac{\mathrm{d}u}{\mathrm{d}r}\right)^2\right]^{n^b}, \tag{118}$$

and k_1 is an integration constant that has to be evaluated.

The above equations are to be solved subject to the boundary conditions

$$u(R_{\text{i}}) = 0, \tag{119}$$

$$u(R_{\text{o}}) = 0, \tag{120}$$

where R_{i} and R_{o} are the inner and outer radii of the annular region between the surface of the mounted vessel segment and the wall of the perfusion chamber. The average thickness of the human arterial segment that is mounted is

291 μm, and the dimensions of the perfusion chamber ('Original' configuration, see Turitto and Baumgartner, 1979), are $R_{\rm i} = 0.2036\,{\rm cm}$, $R_{\rm o} = 0.305\,{\rm cm}$.

The solution has to satisfy the condition:

$$Q = \int_{R_{\rm i}}^{R_{\rm o}} 2\pi r u {\rm d}r = 160\,{\rm ml/min}. \tag{121}$$

This requires an iterative procedure which has been implemented.

Equations (116)–(120) hold as long as whole blood flows through the perfusion chamber, and clot formation has not been initiated. Clot formation occurs once the threshold boundary condition has been applied and the reactions are sufficiently advanced in time (see section 'Criteria for the Initiation of Clot Formation, Clot Growth and Clot Dissolution'). Clot formation occurs on the inner wall, and the clot grows into the annular gap, reducing the domain where blood flows. The location of the blood–clot interface at a given instant of time($s|_t$) is between, or at, the boundaries of the annulus, i.e. $R_{\rm i} \leq s|_t \leq R_{\rm o}$.

Assuming a flow field of the following form to exist at each instant of time t for blood:

$$\mathbf{v}^b|_t = u^b(r)\,\hat{\boldsymbol{e}}_z, \;\; p^b|_t = p^b(r,z). \tag{122}$$

We also assume that the displacement field is such that the components of $\mathbf{B}_{\kappa_p(t)}|_t$, for blood, are functions of the radial coordinate r alone.

A steady pressure gradient of the form

$$\left.\frac{\partial p^b}{\partial z}\right|_t = -C|_t; \;\; C|_t > 0, \tag{123}$$

is applied in the blood zone, and the same pressure gradient is applied in the clot zone as well.

The following equations pertain to the flow of blood:

$$\frac{{\rm d}u^b}{{\rm d}r} = \left(-C|_t r + \frac{2k_1^b}{r}\right) \frac{1}{\left(\frac{\mu^b \lambda^b}{\chi^b} + \eta_1^b\right)} \tag{124}$$

where

$$\lambda^b = \frac{1}{\left[1 + \frac{1}{4(\chi^b)^2}\left(\frac{{\rm d}u^b}{{\rm d}r}\right)^2\right]^{\frac{1}{3}}}, \tag{125}$$

$$\chi^b = K^b \left[\frac{\lambda^b}{2(\chi^b)^2}\left(\frac{{\rm d}u^b}{{\rm d}r}\right)^2\right]^{n^b}, \tag{126}$$

and k_1^b is an integration constant that has to be evaluated. These equations are solved subject to the boundary conditions

$$u^b(s|_t) = U_{\rm INT}, \tag{127}$$

$$u^b(R_{\rm o}) = 0. \tag{128}$$

Assuming a flow field of the following form to exist at each instant of time t for the clot:

$$\mathbf{v}^c|_t = u^c(r)\,\hat{\boldsymbol{e}}_z, \;\; p^c|_t = p^c(r,z). \tag{129}$$

We also assume that the displacement field is such that the components of $\mathbf{B}_{\kappa_p(t)}|_t$, for the clot, are functions of the radial coordinate r alone.

A steady pressure gradient of the form

$$\left.\frac{\partial p^c}{\partial z}\right|_t = -C|_t; \;\; C|_t > 0, \tag{130}$$

is applied in the clot zone; this pressure gradient is the same as that applied for blood flow.

The equations pertaining to the flow of the clot (obtained after substituting the model Eqs. (70)–(74) in Eq. (80) for the balance of linear momentum) are:

$$\frac{{\rm d}u^c}{{\rm d}r} = \left(-C|_t r + \frac{2k_1^c}{r}\right) \frac{1}{\left(\frac{\mu^c \lambda^c}{\chi^c} + \eta_1^c\right)}, \tag{131}$$

where

$$\lambda^c = \frac{1}{\left[1 + \frac{1}{4(\chi^c)^2}\left(\frac{{\rm d}u^c}{{\rm d}r}\right)^2\right]^{\frac{1}{3}}}, \tag{132}$$

$$\chi^c = K^c \left[\frac{\lambda^c}{2(\chi^c)^2}\left(\frac{{\rm d}u^c}{{\rm d}r}\right)^2\right]^{n^c}, \tag{133}$$

and k_1^c is an integration constant that has to be evaluated. These equations are solved subject to the boundary conditions

$$u^c(R_{\rm i}) = 0, \tag{134}$$

$$u^c(s|_t) = U_{\rm INT}. \tag{135}$$

In addition to solving the two sets of equations for the flow of blood and the flow of clot, for a given pressure gradient $-C|_t$, the following conditions are to be satisfied for the balance of mass and linear momentum across the interface:

$$u^b(s|_t) = u^c(s|_t) = U_{\rm INT}, \tag{136}$$

$$T^b_{rz}(s|_t) = T^c_{rz}(s|_t), \tag{137}$$

$$T^b_{rr}(s|_t) = T^c_{rr}(s|_t). \tag{138}$$

The density change between blood and clot is neglected in formulating these conditions. This seems reasonable

given that the density of human blood (ρ^b) is 1.05 g/cc, and the density of a human plasma clot (ρ^c) is 1.03 g/cc.

In addition, the solution has to satisfy the condition:

$$Q = \int_{R_i}^{s|_t} 2\pi r u^c \mathrm{d}r + \int_{s|_t}^{R_o} 2\pi r u^b \mathrm{d}r = 160\,\mathrm{ml/min}. \quad (139)$$

The solution of the blood-clot problem at each instant of time t, requires two levels of iteration: One untill the conditions in Eqs. (136)–(138) are met, and the other until the condition in Eq. (139) is met. This procedure is implemented.

Preliminary Results: Oscillatory Flow of a Shear-thinning Viscoelastic Liquid in a Rigid-walled Cylindrical Pipe with an Activation Criterion

In this section, we present preliminary results for the moving boundary problem involving two shear-thinning viscoelastic liquids with a simple activation criterion that denotes the switch between the model for the liquid prior to activation (referred to hereafter as Model1), and that for the liquid post activation (referred to hereafter as Model 2). We study this problem within the context of oscillatory flow in an infinitely long rigid-walled cylindrical pipe of radius R. This is done in order to yield a qualitative insight into the results that we might obtain when working with the more detailed model given in the section 'Model Development'.

Model

The model equations for the shear-thinning viscoelastic liquid prior to activation (Model1) are as follows:

$$\mathbf{T} = -p\mathbf{1} + \mathbf{S}, \quad (140)$$

$$\mathbf{S} = \mu^1 \mathbf{B}_{\kappa_{\mathbf{p}(\mathbf{t})}} + \eta_1^1 \mathbf{D}, \quad (141)$$

$$\overset{\nabla}{\mathbf{B}}_{\kappa_{p(t)}} = -2\left(\frac{\mu^1}{\alpha^1}\right)^{1+2n^1} (\mathrm{tr}(\mathbf{B}_{\kappa_{\mathbf{p}(\mathbf{t})}}) - 3\lambda)^{n^1} [\mathbf{B}_{\kappa_{p(t)}} - \lambda\mathbf{1}], \quad (142)$$

$$\lambda = \frac{3}{\mathrm{tr}\left(\mathbf{B}^{-1}_{\kappa_{\mathbf{p}(\mathbf{t})}}\right)}, \quad (143)$$

$$n^1 = \frac{\gamma^1 - 1}{1 - 2\gamma^1};\ n^1 > 0. \quad (144)$$

Let us introduce the notation

$$K^1 = \left(\frac{\mu^1}{\alpha^1}\right)^{1+2n^1}. \quad (145)$$

The parameters for Model1 are: $K^1 = 1.2056\,\mathrm{s}^{-1}$, $\mu^1 = 0.0227$ Pa, $n^1 = 0.7525$ and $\eta_1^1 = 0.01$ Pa s. The density of this liquid is $\rho^1 = 1050\,\mathrm{kg/m^3}$. Note that Model1 is the same as that used for modeling the flow of blood (see section 'A Shear-thinning Viscoelastic Model for Describing the Flow of Blood').

Activation is said to take place upon prolonged exposure to shear stresses above a threshold value. This is incorporated by means of an activation number $B(t)$ defined through:

$$B(t) = B(0) + \frac{1}{B_0}\int_0^t e^{k\left(\frac{|\tau_{rz}|}{T_{cr}} - 1\right)} H(|\tau_{rz}| - T_{cr})\mathrm{d}t \quad (146)$$

$$H(|\tau_{rz}| - T_{cr}) = \begin{cases} 1 & |\tau_{rz}| \geq T_{cr} \\ 0 & |\tau_{rz}| < T_{cr} \end{cases} \quad (147)$$

The criterion for activation and the subsequent use of Model2 for the clot in regions where we initially employed Model1 for blood is:

$$\text{If } B(t - t_{act}) > B_{thr} \text{ and } B(t) < B_{damage}, \quad (148)$$

$$\text{Or } B(t - t_{act}) = B_{thr}, \dot{B}(t - t_{act}) > 0 \text{ and } B(t) < B_{damage}, \quad (149)$$

$$\text{Then Model} = \text{Model2}. \quad (150)$$

The criterion for deactivation and the subsequent use of Model1 where the clot has dissociated is:

$$\text{If } B(t - t_{act}) > B_{thr} \text{ and } B(t) > B_{damage}, \quad (151)$$

$$\text{Then Model} = \text{Model1}. \quad (152)$$

The parameters for the activation criterion are $B_0 = 300\,\mathrm{s}$, $t_{act} = 0.02\,\mathrm{s}$, $k = 0.75$, $T_{cr} = 1\,\mathrm{Nm^{-2}}$, $B_{thr} = 0.0004$, $B_{damage} = 1$.

The model equations for the shear-thinning viscoelastic liquid post-activation (Model2) are as follows:

$$\mathbf{T} = -p\mathbf{1} + \mathbf{S}, \quad (153)$$

$$\mathbf{S} = \mu^2 \mathbf{B}_{\kappa_{\mathbf{p}(\mathbf{t})}} + \eta_1^2 \mathbf{D}, \quad (154)$$

$$\overset{\nabla}{\mathbf{B}}_{\kappa_{p(t)}} = -2\left(\frac{\mu^2}{\alpha^2}\right)^{1+2n^2} (\mathrm{tr}(\mathbf{B}_{\kappa_{\mathbf{p}(\mathbf{t})}}) - 3\lambda)^{n^2} \times [\mathbf{B}_{\kappa_{p(t)}} - \lambda\mathbf{1}], \quad (155)$$

$$\lambda = \frac{3}{\mathrm{tr}\left(\mathbf{B}^{-1}_{\kappa_{\mathbf{p}(\mathbf{t})}}\right)}, \quad (156)$$

$$n^2 = \frac{\gamma^2 - 1}{1 - 2\gamma^2}; \quad n^2 > 0. \quad (157)$$

Let us introduce the notation

$$K^2 = \left(\frac{\mu^2}{\alpha^2}\right)^{1+2n^2}. \tag{158}$$

The parameters for Model2 are: $K^2 = 1.2056\,\mathrm{s}^{-1}$, $\mu^2 = 0.0227\,\mathrm{Pa}$, $n^2 = 0.7525$ and $\eta_1^2 = 0.04\,\mathrm{Pa\,s}$; Note that the viscosity term η_1^2 for Model2 is four times the viscosity term η_1^1 for Model1, i.e. the clot while also a viscoelastic liquid is four times more viscous than blood. The density of this liquid is $\rho^2 = 1050\,\mathrm{kg/m^3}$.

Equations

A semi-inverse approach is adopted to obtain solutions for the model equations applied to a certain flow problem. Prior to activation, only Model1 for the blood is to be used in the entire domain.

We seek a solution for oscillatory flow in a pipe of the following form:

$$\mathbf{v}^1 = u^1(r,t)\hat{\mathbf{e}}_z, \;\; p^1 = p^1(r,z,t). \tag{159}$$

We will require that the components of $\mathbf{B}_{\kappa_{p(t)}}$ depend only on the radial coordinate, thus specifying the form for the deformation from the natural to the current configuration.

The pressure gradient imposed is:

$$-\frac{1}{\rho^1}\frac{\partial p^1}{\partial z} = A\cos(wt), \tag{160}$$

and a corresponding time periodic solution is sought for $\mathbf{v}^1$.

Upon substituting Eqs. (159) and (160) into the balance of linear momentum, and non-dimensionalising, we obtain that:

$$\frac{\partial (u^1)^*}{\partial t^*} = -\frac{\partial (p^1)^*}{\partial z^*} + \frac{(S^1_{rz})^*}{r^*} + \frac{\partial (S^1_{rz})^*}{\partial r^*}, \tag{161}$$

$$\frac{\partial B_{rz}}{\partial t^*} = \frac{\partial (u^1)^*}{\partial r^*} B_{rr} - 2\chi^1(\mathbf{B}_{\kappa_{p(t)}})\frac{R}{\mathbf{Ve}} B_{rz}, \tag{162}$$

$$\frac{\partial B_{rr}}{\partial t^*} = 2\chi^1(\mathbf{B}_{\kappa_{p(t)}})\frac{R}{\mathbf{Ve}}(\lambda - B_{rr}), \tag{163}$$

$$\frac{\partial B_{zz}}{\partial t^*} = 2\frac{\partial (u^1)^*}{\partial r^*} B_{rz} + 2\chi^1(\mathbf{B}_{\kappa_{p(t)}})\frac{R}{\mathbf{Ve}}(\lambda - B_{zz}), \tag{164}$$

where

$$(S^1_{rz})^* = \frac{\mu^1}{\rho^1 \mathbf{Ve}^2} B_{rz} + \frac{\eta_1}{2\rho R \mathbf{Ve}}\frac{\partial u^*}{\partial r^*}, \tag{165}$$

$$\lambda = \frac{3B_{rr}(B_{rr}B_{zz} - B_{rz}^2)}{B_{rr}^2 + 2B_{rr}B_{zz} - B_{rz}^2}, \tag{166}$$

$$\chi^1(\mathbf{B}_{\kappa_{p(t)}}) = K^1(2B_{rr} + B_{zz} - 3\lambda)^{n^1}, \tag{167}$$

and R, $\mathbf{Ve}$ are the pipe radius and characteristic velocity respectively. (Note: $B_{\theta\theta} = B_{rr}, B_{r\theta} = B_{\theta z} = 0$).

We use the following non-dimensionalisation: $t^* = t\mathbf{Ve}/R$, $w^* = wR/\mathbf{Ve}$, $(u^1)^* = u^1/\mathbf{Ve}$, $r^* = r/R$, $z^* = z/R$, $(S^1_{rz})^* = S^1_{rz}/\rho^1(\mathbf{Ve})^2$, $(p^1)^* = p^1/\rho^1(\mathbf{Ve})^2$, and $A^* = \mathrm{AR}/(\mathbf{Ve})^2$.

The above PDEs are solved over the domain $0 < r < 1$, for $t \geq 0$, subject to the following boundary condition:

$$(u^1)^*(1,t) = 0, \tag{168}$$

and the center-line condition:

$$\frac{\partial (u^1)^*(0,t)}{\partial r^*} = 0. \tag{169}$$

We use the exact solution for the velocity profile for pulsatile flow of a Newtonian fluid for small Womersley numbers (Womersley, 1955) as the initial guess for the velocity, and obtain the initial condition for the components of $\mathbf{B}_{\kappa_{p(t)}}$ by using $\mathbf{B}_{\kappa_{p(t)}}|_{t=0} = \mathbf{1}$.

Equations (161)–(167) hold as long as Model1 for the blood applies in the entire flow domain, and activation has not occurred. Upon activation, which will occur at the pipe wall given that the shear stresses are higher, Model2 for the clot is to be used, and the zone occupied by the clot grows larger as time progresses. The location of the interface between the blood and the clot at a given instant of time ($s|_t$) is between, or at, the boundaries of the flow domain, i.e. $0 \leq s|_t \leq R$. We define the non-dimensional interface location $s^*|_t = s|_t/R$.

We seek a solution of the following form in the domain occupied by blood ($0 \leq r \leq s^*|_t$) :

$$\mathbf{v}^1 = u^1(r,t)\,\hat{\mathbf{e}}_z, \;\; p^1 = p^1(r,z,t). \tag{170}$$

We will require that the components of $\mathbf{B}_{\kappa_{p(t)}}$ depend only on the radial coordinate, thus specifying the form for the deformation from the natural to the current configuration.

The pressure gradient imposed is:

$$-\frac{1}{\rho^1}\frac{\partial p^1}{\partial z} = A\cos(wt), \tag{171}$$

and a corresponding time periodic solution is sought for $\mathbf{v}^1$.

The equations to be solved are the same as that developed earlier for blood (Eqs. (161)–(167)), though the boundary conditions are different:

$$\frac{\partial (u^1)^*(0,t)}{\partial r^*} = 0, \tag{172}$$

$$(u^1)^*(s^*|_t, t) = U^*_{\text{INT}}. \tag{173}$$

We seek a solution of the following form in the domain occupied by the clot ($s^*|_t \le r \le 1$) :

$$\mathbf{v}^2 = u^2(r,t)\hat{\mathbf{e}}_z, \;\; p^2 = p^2(r,z,t). \tag{174}$$

We will require that the components of $\mathbf{B}_{\kappa_{p(t)}}$ depend only on the radial coordinate, thus specifying the form for the deformation from the natural to the current configuration.

The pressure gradient imposed is the same as that for blood:

$$-\frac{1}{\rho^2}\frac{\partial p^2}{\partial z} = A\cos(wt), \tag{175}$$

and a corresponding time periodic solution is sought for $\mathbf{v}^2$.

The equations to be solved are the same as that developed previously (Eqs. (161)–(167)) with superscripts changed accordingly. The non-dimensionalisation is also as outlined previously with superscripts changed. The boundary conditions are:

$$(u^2)^*(s^*|_t, t) = U^*_{\text{INT}}, \tag{176}$$

$$(u^2)^*(R, t) = 0. \tag{177}$$

In addition to solving the equations for the flow of blood and clot, for a given pressure gradient $-A$, the following conditions are to be satisfied for the balance of mass and linear momentum across the interface:

$$(u^1)^*(s^*|_t) = (u^2)^*(s^*|_t) = U^*_{\text{INT}}, \tag{178}$$

$$((T_{rz})^1)^*(s^*|_t) = ((T_{rz})^2)^*(s^*|_t), \tag{179}$$

$$((T_{rr})^1)^*(s^*|_t) = ((T_{rr})^2)^*(s^*|_t). \tag{180}$$

Numerical Scheme

The parameters used in the numerical simulations are as follows: Radius of the pipe; $R = 0.005$ m, $\mathbf{Ve} = 0.01$ m/s, and $f = 2$ Hz. In order to solve the equations, we decouple the equation for velocity from the equations for the components of $\mathbf{B}_{\kappa_{p(t)}}$ (B_{rr}, B_{rz}, B_{zz}). We then treat the equation for velocity as an IBVP, while the others are treated as IVPs. The coupling is brought about by means of an iterative process at each time step. We use a BTCS method with $\Delta t = 0.001$ and $\Delta r = 0.0005$ to discretize the equations. The resulting algebraic equations for velocity are solved by means of a Thomas algorithm, while the coupled nonlinear algebraic equations for the components of $\mathbf{B}_{\kappa_{p(t)}}$ are solved by means of the "fsolve" routine available in MATLAB.

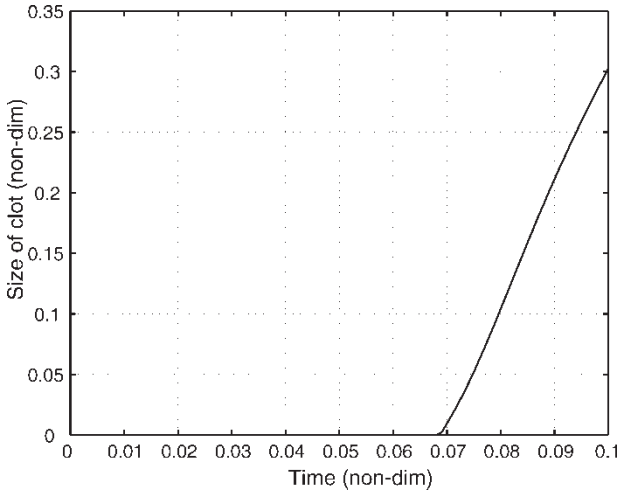

FIGURE 4 Increase of size of domain of the clot (described by Model2) $(1 - s^*|_t)$ with time ($R = 0.005$ m).

Results

The following results are obtained for the moving boundary problem outlined previously. Figure 4 tracks the location of $s^*|_t$ in time. Figures 5–8 document the velocity, shear stress, and normal stresses (B_{rr} and B_{zz}) at $t = 0.05$ s after the onset of oscillatory flow. Figure 9 documents the variation of centerline velocity in the course of the 0.05 s after the onset of oscillatory flow.

DISCUSSION

The model for the growth and dissolution of a clot in flowing blood has been detailed. All model parameters (rheological and biochemical) are obtained for human blood, for enzymatic reactions involving platelets and zymogens from human blood and plasma, and for human plasma clots. The procedure for the model corroboration has also been detailed. Preliminary results for the moving

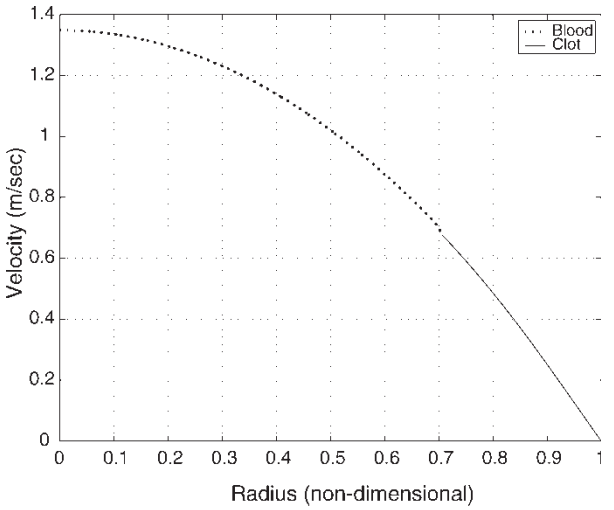

FIGURE 5 Predictions of blood-clot velocity profile (moving boundary, oscillatory flow) at $t = 0.05$ s ($t^* = 0.1$).

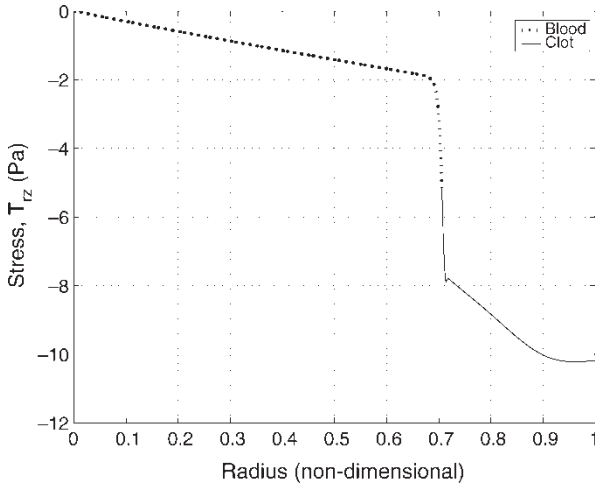

FIGURE 6 Predictions of blood-clot shear stress profile (moving boundary, oscillatory flow) at $t = 0.05$ s ($t^* = 0.1$).

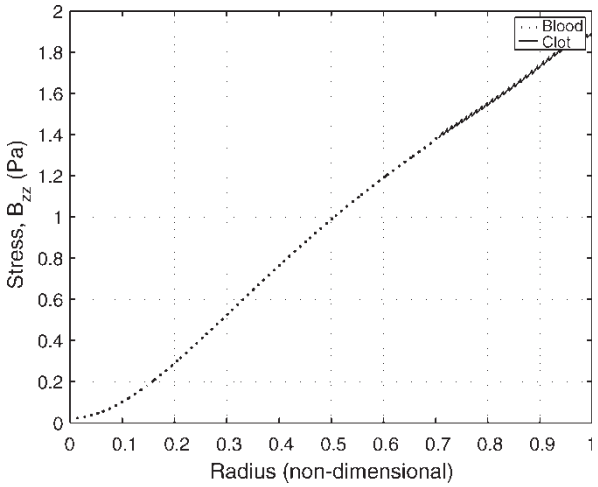

FIGURE 8 Predictions of blood-clot axial normal stress (B_{zz}) profile (moving boundary, oscillatory flow) at $t = 0.05$ s ($t^* = 0.1$).

boundary problem for a simplified model have also been presented.

Our model includes the key elements behind clot formation and dissolution in flowing blood. This model can be used to glean information concerning various questions that are of relevance to clinical practice and engineering strategy.

Some unresolved issues are, for instance, the factors responsible for the cessation of clot growth, and the process of clot dissolution (whether gradual or abrupt, and its impact on the probability of thrombo-embolism). This model is being studied under various flow conditions (pulsatile, steady) in a simple geometry (rigid-walled cylindrical pipe) with pressure gradients and flow rates that are close to normal physiological conditions so as to observe the manner of clot growth and dissolution. This model can be used to document the influence of clot growth and dissolution on blood flow and the role of blood flow on clot growth and dissolution. In addition, the model can be used to study the sensitivity of this process to the concentration of platelets and coagulation factors in blood, as also the influence of boundary conditions on this process.

There are many possible applications for this model. In quiescent plasma, the convection-reaction-diffusion equations for clot growth and dissolution can be studied within the context of standard laboratory coagulation tests such as the prothrombin time and partial thromboplastin time (PT and PTT, respectively), to assess the fidelity of these tests in assaying coagulation system function. These equations, along with the flow equations, can also be used to study the variables analysed in thromboelastography. This is a relatively rapid *in vitro* test of mechanical clot formation that allows for integrated assessment of the various components of the hemostatic system, i.e. platelets, coagulation system factors, and fibrinolytic factors (see Salooja and Perry, 2001; Whitten and Greilich, 1991). This model can also be used to predict regions susceptible to clot formation and track the extent of clot formation; it promises to be of value to engineers

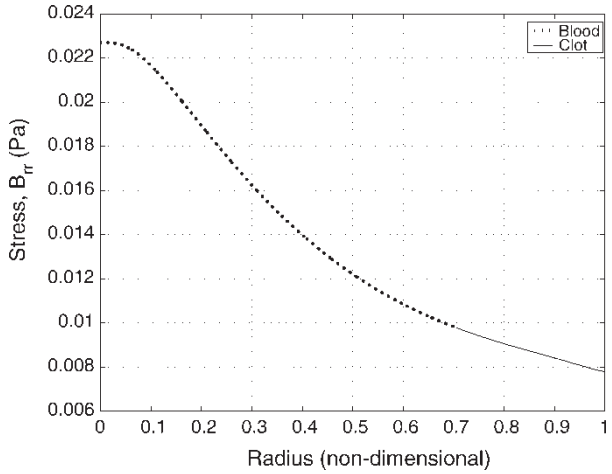

FIGURE 7 Predictions of blood-clot radial normal stress (B_{rr}) profile (moving boundary, oscillatory flow) at $t = 0.05$ s ($t^* = 0.1$).

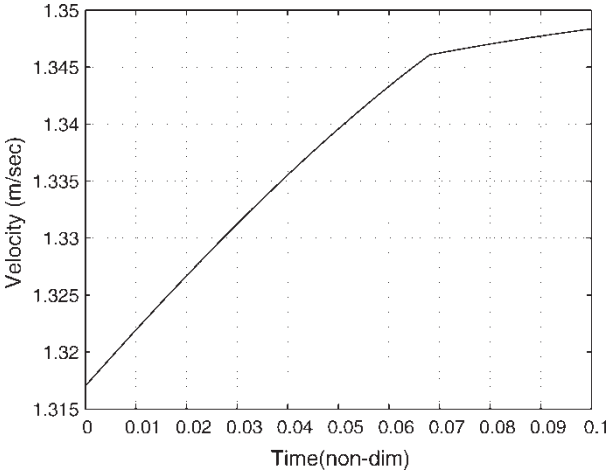

FIGURE 9 Variation of centerline velocity with time; oscillatory flow, Blood-clot moving boundary problem.

seeking to predict and minimize such occurrences within cardiovascular devices. Such applications require an understanding of the limitations of the proposed model and possible extensions that can redress these limitations. These are discussed next.

Limitations and Extensions

A model that treats blood as a single homogenized continuum has the inherent limitation that one cannot infer the distribution of the individual components during flow, nor their velocity and stress profiles. In addition, the interactions between the cellular components of blood and plasma that affect the flow of both of these components add a further level of complexity. A first extension in this direction would be a mixture theory model that has separate constitutive equations for RBCs, and plasma, and constitutive specifications for the interaction between the two. Such an extension adds the challenge of specifying boundary conditions for the partial stress of each component.

The reactions to model platelet activation, the extrinsic coagulation pathway and fibrinolysis, and the criteria governing initiation, growth and dissolution of clots are quite general, at this scale of modeling, and represent an initial attempt of developing a model that incorporates the relevant biochemical and mechanical features of hemostatis. However, additional details need to be introduced with a view towards developing a much more comprehensive picture. In this regard, the addition of the reactions of the intrinsic pathway is important to the development of a comprehensive model of hemostatis. Currently, the only means at hand to include these aspects of hemostatis is to modify the boundary conditions for Factor XIa (Zarnitsina *et al.*, 1996a). Other possible extensions are the inclusion of additional separate reactions for species and ions (like VII, XIII, vWF, PAI-1, Protein S, Ca^{2+}, etc.), the generation and depletion of the species, additional interactions between the species involved in clot formation, separate binding sites for enzyme complexes on phospholipid surfaces or on the subendothelium, allowing for dissociation of enzyme complexes (like tenase, prothrombinase) and enzyme-inhibitor complexes (like TFPI-Xa), additional interactions with intact endothelial cells (like the formation of thrombin–thrombomodulin complex that eventually activates Protein C, the section of urokinase plasminogen activator (uPA) or the secretion of PgI_2 that inhibits platelet aggregation, delayed thrombin-induced tPA generation), etc. In acknowledging these limitations we point to studies that have reported that even slight variations, as occurring in lumped parameter systems, in the parameters of such large scale models can cause significant differences in model predictions (Hopkins and Liepold, 1996).

There are additional simplifications in the model, which need to be altered to render a more physiologically accurate picture of thrombus formation and dissolution. First, the clot is modeled as a homogenized continuum, whereas it is a plasma-filled composite of fibrin matrix and cellular components. An extension for the rheologic model could be a two-component mixture theory that develops separate equations for the fibrin matrix and the blood cell-plasma aggregate. Second, this study is limited to flows in one spatial dimension; a study incorporating three-dimensional flow regimes is a next step in the development of a more complete model. Third and finally, although the blood/clot interface is modeled by a fixed sharp transition, the local environment of the thrombus and the interface with flowing blood changes as a function of clot growth and subsequent dissolution. The model can be altered by making the rheologic properties of the clot dependent upon the local concentrations of fibrin monomer, polymer, and cross-linked polymer. The modifications will help to create a model for thrombus formation and dissolution that is physiologically accurate, that may be of value in biomedical device development and in the clinical setting.

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