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The Influence of Hindered Transport on the Development of Platelet Thrombi Under Flow

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Abstract

Vascular injury triggers two intertwined processes, platelet deposition and coagulation, and can lead to the formation of an intravascular clot (thrombus) that may grow to occlude the vessel. Formation of the thrombus involves complex biochemical, biophysical, and biomechanical interactions that are also dynamic and spatially-distributed, and occur on multiple spatial and temporal scales. We previously developed a spatial-temporal mathematical model of these interactions and looked at the interplay between physical factors (flow, transport to the clot, platelet distribution within the blood) and biochemical ones in determining the growth of the clot. Here we extend this model to include reduction of the advection and diffusion of the coagulation proteins in regions of the clot with high platelet number density. The effect of this reduction, in conjunction with limitations on fluid and platelet transport through dense regions of the clot, can be profound. We found that hindered transport leads to the formation of smaller and denser clots compared to the case with no protein hindrance. The limitation on protein transport confines the important activating complexes to small regions in the interior of the thrombus and greatly reduces the supply of substrates to these complexes. Ultimately, this decreases the rate and amount of thrombin production and leads to greatly slowed growth and smaller thrombus size. Our results suggest a possible physical mechanism for limiting thrombus growth.

Keywords

multiscale model; hindered advection; hindered diffusion; coagulation; thrombus

1 Introduction

The formation of intravascular blood clots (thrombi) in vessels of the arterial tree is the proximal cause of most heart attacks and many strokes as well as other serious health problems. Extensive research has been and continues to be done to determine the processes by which these thrombi form and much progress has been made in identifying the players (proteins, cells, etc.) and many of the biochemical and cell-biological interactions in which they participate. Much less progress has been made in understanding how physical processes, including flow-mediated transport, might modify the picture of thrombus formation that has been developed from the biochemical studies. Experimental investigation

of the interplay between biochemical and physical processes in clot formation is extremely difficult and requires wide expertise from the experimenters. Only recently have a few groups begun carrying out such investigations using either in vitro flow chambers [8, 33, 35] or intravital microscopy in animal models [3, 18]. Some of the experimental work [20, 35] was motivated by predictions from our earlier modeling efforts, and the model extensions we explore in this paper are, in turn, motivated by preliminary observations from recent experiments [3] suggesting an important role for intracLOT transport.

In the remainder of this introduction we give a brief description of the salient biological facts for thrombus formation initiated by injury to an artery, we review our previous models, and we describe the motivation for and nature of the extensions to the most sophisticated of those models whose influence we explore in this paper.

Injury to the endothelial-cell lining of a blood vessel wall exposes the subendothelium and initiates the intertwined processes of platelet deposition and coagulation. Platelet deposition is predominantly a physical process and begins with platelet adhesion to the exposed subendothelium. Adhesion to molecules embedded in the subendothelium, such as collagen, causes these platelets to become activated and to secrete platelet-activating chemicals into the surrounding fluid. The secreted chemicals may activate platelets in the blood (without their contacting the subendothelium directly) making them able to cohere to one another and to the already subendothelium-adherent platelets. The platelet mass that results is called a platelet thrombus or platelet plug. Coagulation is a biochemical process initiated by either enzymatic reactions on the exposed subendothelium (tissue factor pathway, which is what we model in this study) or by contact with a negatively charged surface (contact pathway); it progresses by means of other enzymatic reactions on the surfaces of activated platelets. A major product of coagulation is the critical enzyme thrombin which i) affects earlier reaction steps to speed its own production, ii) activates platelets, and iii) acts on the soluble plasma protein fibrinogen to produce insoluble fibrin that spontaneously polymerizes to form a stabilizing protein gel (fibrous mesh) surrounding the platelet mass.

A schematic of these processes is given in Fig. 1, and a detailed discussion of the reactions and interactions can be found in [28]. Excellent reviews can be found in [21, 23, 32]. Here we briefly describe some of the important features of coagulation and platelet deposition. We use the following abbreviations: TF tissue factor, APC activated protein C, TFPI tissue factor pathway inhibitor, ADP adenosine diphosphate, AT antithrombin-III.

- The coagulation proteins, often called clotting factors, come in pairs, either inactive zymogen/active enzyme pairs, factors VII and VIIa, factors IX and IXa, factors X and Xa, and factors II and IIa (prothrombin and thrombin), or inactive/active cofactor pairs, factors V and Va and factors VIII and VIIIa.
- Three enzyme complexes play major roles in coagulation, the TF:VIIa complex on the subendothelium, and the ‘tenase’ (VIIIa:IXa) and ‘prothrombinase’ (Va:Xa) complexes on the surfaces of activated platelets. In these complexes, a cofactor TF, VIIIa, or Va helps increase the catalytic effectiveness of the corresponding enzyme (VIIa, IXa, and Xa, respectively) by 5 to 6 orders of magnitude compared to that of the same enzyme molecule without its cofactor.

- The reactions are initiated when VIIa binds to TF molecules exposed to the blood by the injury. The complex TF:VIIa activates zymogens IX and X to enzymes IXa and Xa, respectively. Each of these enzymes can become part of an enzyme complex on the surface of an activated platelet. For these complexes to form, there must be activated platelets nearby, the enzymes must make their way through the fluid from the subendothelial surface to the surface of one of the activated platelets, and the active cofactor molecules, VIIIa and Va, must be available and bound to that activated platelet's surface. Early in the process, platelet-bound Xa activates the cofactors VIIIa and Va on the platelet surface.
- When a tenase (VIIIa:IXa) complex is formed on the activated platelet surface, it can activate platelet-bound X to Xa (this is a second mechanism for Xa activation in addition to its activation by TF:VIIa on the subendothelium). A Xa molecule can bind with a platelet-bound Va molecule to form a prothrombinase (Va:Xa) complex on the platelet surface. Prothrombinase can activate platelet-bound prothrombin to the enzyme thrombin.
- Thrombin is released from the activated platelet's surface and may activate other platelets. It may activate cofactor molecules Va and VIIIa in the plasma or it may rebound to an activated platelet surface and activate these cofactor molecules on the platelet's surface. Furthermore, thrombin converts fibrinogen into fibrin monomers which then polymerize into a fibrin gel. (In this paper, we do not model the conversion of fibrinogen to fibrin monomer or fibrin polymerization.)
- Upon a platelet's activation, specific binding sites become expressed on its surface for each of the zymogen/enzyme pairs IX/IXa, X/Xa, prothrombin/thrombin, and for each of the inactive/active cofactor pairs V/Va and VIII/VIIIa. The quantity of these binding sites that are available controls the formation and/or activity of the platelet-bound enzyme complexes.
- Platelets can be activated by contact with the subendothelium (not shown), or by exposure to thrombin or ADP. A finite quantity of ADP is released by a platelet from internal stores during a time interval following the platelet's activation.
- Several chemical inhibitors (AT, TFPI, and APC) act on various species in the reaction network. A platelet adhering to the subendothelium physically inhibits the activity of the molecules on the portion of subendothelium it covers (not shown).

The current paper extends our earlier work which looked at the interplay among coagulation biochemistry, platelet deposition, and flow. In some of that work [17, 16, 28], flow was treated very simply as delivery and removal of materials from a reaction zone above a small vascular injury. Even in this limited role, flow had a profound effect on the dynamics: flow-mediated washout was the dominant inhibitor of fluid-phase enzymes while the chemical inhibitors TFPI and APC had insignificant effects. Because TFPI was ineffective in shutting down TF:VIIa activity, the factor VIII or factor IX deficiencies associated with hemophilia A or B, respectively, would have had little effect on thrombin production unless something else blocked TF:VIIa activity. This led us to postulate that as a platelet adheres to the

subendothelium, it covers a portion of the subendothelium and physically inhibits the TF:VIIa activity there. This idea was later confirmed experimentally [20], and gives platelets an *anti-coagulant* role in addition to their pro-coagulant roles described above. We showed that the tension between the platelets' dual pro- and anti-coagulant roles underlies the model's predictions of threshold behavior (subsequently confirmed experimentally [35]), its kinetic explanations of the effects of hemophilia (factor VIII or IX deficiency) and of moderately or severely reduced platelet count on thrombin production, and its possible explanation of the highly varying phenotypes seen in patients with factor XI deficiency [39] (Reactions involving factor XI are not included in Fig. 1, see [16] for further discussion.)

A much more sophisticated treatment of flow and platelet deposition was included in our spatial-temporal model [29] which we refer to as the LF model. In that model, we represented the platelet thrombus as a porous material. We showed how advective and diffusive transport of coagulation proteins and platelets to and within the porous clot influence its growth at different stages and different spatial locations. In particular these results showed that diffusive transport of coagulation proteins within the clot contributes to its upstream growth, and that transport also contributes to the structural heterogeneity of the clot, that is, to variations of bound platelet density.

In the LF model, we assumed that the permeability to flow of each portion of the thrombus decreased as the density of bound platelets in that portion grew. We also assumed that transport of platelets in the thrombus was restricted further because of their finite size. However, in that model we assumed that the movement of coagulation proteins through the thrombus was hindered no more than was that of the fluid in which they were suspended. This is reasonable if one regards the protein molecules as sufficiently small relative to the spaces between platelets in the thrombus. However, the coagulation proteins are macromolecules, and the spaces between platelets become progressively smaller as the density of platelets in the thrombus grows, which suggests that considering additional hindrance to the movement of the coagulation proteins may be warranted. Support for this idea comes from experiments by Hathcock and Nemerson [20]. They showed that even a few layers of activated platelets can drastically reduce the transport by diffusion of coagulation proteins between the bulk plasma and the reactive surface to which the platelets are attached. Further support comes from recent experiments by Brass *et al.* [3] in which fluorescent dextrans of various molecular weights were perfused past thrombi that had formed within the microvasculature of mice. The experiments showed a size-dependent penetration of the dextrans into different portions of the thrombi.

In this paper, we extend the LF model to include the hindered transport of coagulation proteins inside of a thrombus. To do this, we have to specify how the advection and diffusion of these proteins is reduced as the thrombus grows and becomes more dense. As in [29], we also have to specify how the permeability of the thrombus to flow decreases as the density of platelets within it increases. There is only scarce data on the permeability of a platelet thrombus to flow [1] or on the transport of proteins through it [20], and the data is far from sufficient to specify these dependencies.

There is a large literature describing experimental and theoretical explorations of the permeability and transport properties of porous materials, for example, see [6, 7, 11, 27, 34, 37, 43], but the relevance of these studies for the present work is far from clear. To understand why this is the case, consider what happens to a platelet that becomes part of a thrombus. Before doing so, the platelet circulates as a semi-rigid ellipsoid. Upon its activation, it begins to change shape, becoming more spherical and extending membrane protrusions known as pseudopodia and filopodia. It also becomes sufficiently flexible so that portions of its surface membrane can come into close apposition to those of other platelets to which it is bound. In fact, recent studies [44] show that aggregating platelet membranes become close enough to one another to allow gap junctions to form. Because of these changes, the packing of platelets within a thrombus, and therefore the shapes and sizes of the spaces between them, is complex and dynamic. Therefore the usefulness of theories based on simple geometries, such as packed beds of uniform spheres, is questionable. Further, as the thrombus develops the volume fraction of bound platelets within it changes greatly from a few percent to upwards of 75%, and the volume fraction may be significantly different in different regions of the thrombus. This is problematic since most existing studies of flow and transport in porous materials are concerned with situations in which the solid volume fraction is either very low, as in fibrous gels [27], or very high, as in porous rocks [38], while growing thrombi display a wide range of volume fractions.

Given the lack of knowledge about transport within a developing thrombus and of appropriate theories, modeling of intracLOT transport currently can only be qualitative. In this paper, we have made what we believe are reasonable assumptions about how rapidly the transport of fluid, platelets, and proteins is reduced by changes in the platelet density within the thrombus, and we explored the consequences of these assumptions on the model's dynamics as well as the sensitivity of model results to different choices of the reduced-transport functions. In particular, we look at two different permeability functions; the one we used in [29] and the Kozeny-Carman relation [19] used, for example, for predicting flow through soils [41]. The two permeability functions behave quite differently in terms of how quickly the permeability decreases as the solid (here bound platelet) volume fraction increases. For transport of the coagulation proteins, we use a mixture model approach [26] to derive hindered advection and diffusion functions. These functions depend only on the local fraction of the thrombus volume occupied by bound platelets and on a quantity r which is a measure of the drag a protein experiences moving through a group of platelets to that it experiences moving through plasma. It is reasonable that r is, itself, also a function of the bound platelet volume fraction. For a very low volume fraction of platelets, $r = 1$ and for high volume fraction, we use the data from [20] to estimate that $r \approx 1000$. We consider a family of r functions constrained by these values, which differ in how rapidly the function increases (leading to reductions in transport) as the bound platelet volume fraction increases from 0.

The major goal of this paper is to begin to look at how hindered protein transport could affect the dynamics and extent of thrombus growth and the structure of the thrombus that is formed. The main results of this paper are that there are two major differences between thrombus growth with and without hindered protein transport: (i) reduced transport of proteins through a growing thrombus can speed early development of the thrombus by

reducing the washout of critical enzymes, and (ii) reduced protein transport within the thrombus can slow or stop later thrombus development by limiting how far from the injury the platelet coagulation enzyme complexes are formed and how far into the thrombus the substrates for these enzymes penetrate. As the thrombus develops, the size of the regions where both an enzyme complex (tenase or prothrombinase) and its substrate (factor X or prothrombin) are found becomes progressively smaller and the concentrations of the enzymes and substrates in these regions becomes progressively lower. That we see these effects of hindered protein transport for two very different permeability functions and for a range of advection-diffusion hindrance functions suggests that this behavior is qualitatively robust and not sensitive to the particular permeability and hindrance functions considered.

2 Model

In this section we begin with a brief description of our previous spatial-temporal model (LF model) of the processes that occur when a blood clot forms inside of a blood vessel [29]. We then describe how we modify this model to account for hindered transport of macromolecules within the growing blood clot.

2.1 LF Model Review

In [29], we presented a model of coagulation and platelet deposition within a segment of blood vessel. Parts of the domain boundary represent the blood vessel walls which are either lined with endothelial cells or by exposed subendothelial material. Blood, which is taken to be a mixture of fluid (plasma), platelets and chemicals, enters the vessel through the upstream boundary with a fixed velocity profile and exits at the downstream boundary. Platelets and chemicals have prescribed concentrations at the upstream boundary and can reside at any location within the domain. Red blood cells are not explicitly considered here but their influence on the platelets is incorporated in two ways. First, the fact that at sufficiently high shear rates (our simulations are at 500/sec), red-blood-cells induce an enhancement of platelet concentration near the vessel wall [13, 42] is taken into account in specifying the concentration profile for platelets along the upstream boundary of the domain. Second, mobile platelets have a diffusion coefficient two orders of magnitude higher than that from Brownian motion to account for the erratic motions imparted to platelets by tumbling and colliding red blood cells. For theoretical investigations of these effects of red-blood-cell on platelet location and motion, see [9, 10, 45].

Platelets are tracked in four groups: mobile and unactivated (set to a physiological concentration at the upstream boundary), mobile and activated, bound and activated, and bound directly to exposed subendothelium and activated. Mobile platelets advect and ‘diffuse’ (to reflect red-blood-cell-induced motions) through the fluid. Mobile, unactivated platelets may bind directly to the subendothelium; if they do so, they become subendothelium-bound and are considered immobile. Mobile activated platelets may bind either to the subendothelium directly or to other bound platelets; if they do so, they become part of the appropriate platelet population and are considered immobile. Chemicals, primarily coagulation proteins, are tracked in three groups. Fluid-phase chemicals advect

and diffuse, unhindered, through the fluid and regions of bound platelets. Platelet-bound chemicals and subendothelium-bound chemicals are immobile unless they unbind.

Platelets are modeled as continua, that is, we track platelet densities (number/volume), not discrete objects, for the four populations of platelets just described. The total platelet number density at each spatial point cannot be larger than P_{max} whose value, 6.67×10^7 , is calculated under the assumption that twenty platelets fit tightly into $300 \mu m^3$. We denote by $\phi^B(\mathbf{x}, t)$ and $\phi^T(\mathbf{x}, t)$ the bound platelet fraction and total platelet fraction, respectively. The quantity ϕ^B is the ratio of the density of bound platelets (bound plus subendothelium-bound) to P_{max} and similarly, ϕ^T is the ratio of the density of all platelet species to P_{max} . That these ratios cannot be greater than one is one way that platelet size is incorporated into the model. The notion of platelet size enters the model in three additional ways. These are discussed in detail in [29] we give a brief overview here. First, we modify the advective and diffusive flux of mobile platelets so that platelet movement through a region of clot is restricted more so than is that of the fluid by a factor that increases with the total platelet fraction ϕ^T in that region. Second, the binding rate at which mobile platelets adhere to the subendothelium is defined to be a positive constant for spatial locations less than one platelet's diameter distance above the subendothelium. Finally, the cohesion rate at which mobile activated platelets bind to the already-formed clot is defined so that it is positive both within the clot and at distances from the clot that are less than a platelet's diameter. This rate increases with proximity to the clot and with the density of nearby bound platelets.

2.1.1 Fluid—The motion of the fluid is governed by the modified Navier-Stokes equations for incompressible viscous flow

$$\rho(\mathbf{u}_t + \mathbf{u} \cdot \nabla \mathbf{u}) = -\nabla p + \mu \Delta \mathbf{u} - \mu \alpha(\phi^B) \mathbf{u}, \quad (1)$$

$$\nabla \cdot \mathbf{u} = 0, \quad (2)$$

where $\mathbf{u}(\mathbf{x}, t)$ and $p(\mathbf{x}, t)$ are the fluid velocity and pressure, respectively, at location $\mathbf{x}$ and time t ; ρ is the fluid's mass density and μ is the fluid's dynamic viscosity. The term $-\mu \alpha(\phi^B) \mathbf{u}(\mathbf{x}, t)$, which we call the Brinkman term, represents the frictional resistance applied to the fluid due to the presence of bound and stationary platelets at the location $\mathbf{x}$. The function $\alpha(\phi^B)$ is set to be a second-order Hill function of the bound platelet fraction:

$$\alpha(\phi^B) = \frac{\alpha_{max}(\phi^B)^2}{0.5^2 + (\phi^B)^2}. \quad (3)$$

We assume this form of the function so that as the platelet fraction reaches half of its maximum, the fluid resistance begins to increase sharply.

2.1.2 Platelets—We denote by $P^{m,u}$, $P^{m,a}$, $P^{b,a}$ and $P^{se,a}$ the number densities of the four groups of platelets, mobile unactivated, mobile activated, platelet-bound activated and subendothelium-bound activated, respectively. Each of these is a function of $\mathbf{x}$ and t . Here we describe the evolution equation for the mobile, activated platelets because it incorporates all of the types of terms found in the four platelet equations:

$$\begin{aligned} \frac{\partial P^{m,a}}{\partial t} = & - \nabla \cdot \underbrace{\{W(\phi^T)(\mathbf{u}P^{m,a} - D \nabla P^{m,a})\}}_A - \underbrace{K_{adh}(\mathbf{x}) \{P_{max} - P^{se,a}\} P^{m,a}}_B \quad (4) \\ & + \underbrace{\{A_1(e_2) + A_2([ADP])\} P^{m,u}}_C - \underbrace{k_{coh} g(\eta) P_{max} P^{m,a}}_D. \end{aligned}$$

Term A is the flux of platelets due to advection with the fluid and diffusion through the fluid. The function $W(\phi^T)$ ($0 \leq W(\phi^T) \leq 1$) is used to restrict the movement of platelets into regions already containing dense populations of platelets. Term B describes the rate of platelet adhesion to the exposed subendothelium as the product of a spatially-varying adhesion rate, the remaining subendothelial binding space and the platelet density itself. Term C represents the rate of chemical activation of platelets by the coagulation enzyme thrombin (whose concentration is e_2) or by the platelet-secreted chemical ADP. Finally, term D represents the rate of cohesion of mobile activated platelets to thrombus-bound platelets. The binding affinity function $g(\eta)$ is positive only in the region that contains the bound platelets and in a strip of approximately one platelet diameter surrounding this region. The activation rate functions $A_1(e_2)$ and $A_2([ADP])$ are Hill functions of their respective arguments. Details about the functions $W(\phi^T)$, $g(\eta)$, A_1 , and A_2 are in [29]. Equations for $P^{m,u}$, $P^{b,a}$ and $P^{se,a}$ have terms similar to those described here.

2.1.3 Chemicals—We describe the three groups of chemicals by $\mathbf{C}^{fp}$, $\mathbf{C}^{pb}$, and $\mathbf{C}^{se}$, which denote the vectors of concentrations of the set of fluid-phase, platelet-bound, and subendothelium-bound chemicals, respectively. The general form of the evolution equation for the concentration of the i th fluid-phase chemical is

$$\frac{\partial C_i^{fp}}{\partial t} = - \nabla \cdot (\mathbf{u} C_i^{fp} - D_i \nabla C_i^{fp}) + R^f(\mathbf{C}^{fp}) - B^p(C_i^{fp}, C_i^{pb}, P^{b,a}, P^{se}), \quad (5)$$

$$-D \frac{\partial C_i^{fp}}{\partial n} = B^s(C_i^{fp}, C_i^{se}), \quad (6)$$

where $\mathbf{u}$ is the fluid velocity, D_i is the free diffusion coefficient for the i th chemical species, R^f incorporates all reactions with other chemicals in the fluid, and B^p represents the net loss per unit time due to binding/unbinding to/from bound platelets. We note that D_i is set to the same value for all protein species ($5 \times 10^{-7} \text{ cm}^2/\text{s}$) and to $5 \times 10^{-6} \text{ cm}^2/\text{s}$ for the smaller

ADP molecules. Equation (6) describes a boundary condition in which the diffusive flux is equated to B^s , the net rate of production of the chemical on the boundary. The function B^s is nonzero only at points on the subendothelium. Equation (6) holds for all points of the boundary except those along the upstream inlet where the chemical concentration is prescribed.

The general form of the evolution equation for the concentration of the i th platelet-bound chemical is

$$\frac{\partial C_i^{pb}}{\partial t} = B^p(C_i^{fp}, C_i^{pb}, P^{b,a}, P^{se}) + R^p(C^{pb}). \quad (7)$$

The first term, B^p , describes the net gain per unit time due to binding/unbinding to/from bound platelets and R^p gives the rate of reactions that occur on bound-platelet surfaces. Similarly, the general form of the evolution equation for the concentration of the i th subendothelium-bound chemical is

$$\frac{\partial C_i^{se}}{\partial t} = B^s(C_i^{fp}, C_i^{se}) + R^s(C^{se}), \quad (8)$$

where B^s is the same as in Equation (6) and R^s describes the rate of reactions that occur on the exposed subendothelium. A complete description of the equations and parameters of the LF model is given in [29].

2.2 Hindrance of Macromolecular Transport

To derive the factors by which protein advection and diffusion within the blood clot are hindered, we (temporarily) consider a multiphase mixture model consisting of three phases, fluid, bound platelets, and protein, which can coexist at each point in space [26]. The fluid, platelet, and protein phases have volume fractions and velocities, $(\theta_f, \mathbf{u}_f)$, $(\theta_{pl}, \mathbf{u}_{pl})$, and $(\theta_{pr}, \mathbf{u}_{pr})$, respectively. At each spatial point the sum of the three volume fractions is 1 and we assume that the protein volume fraction is small, $\theta_{pr} \ll 1$. Each volume fraction evolves according to a continuity equation, and each phase has a corresponding momentum equation (aka force-balance equation). Because we are interested in the protein phase, we consider the momentum and continuity equations for that phase, which, because the protein concentration is dilute, are

$$0 = \xi_{pr,f} \theta_{pr} \theta_f (\mathbf{u}_f - \mathbf{u}_{pr}) + \xi_{pr,pl} \theta_{pr} \theta_{pl} (\mathbf{u}_{pl} - \mathbf{u}_{pr}) - \theta_{pr} \nabla \mu_{pr} \quad (9)$$

and

$$(\theta_{pr})_t + \nabla \cdot (\mathbf{u}_{pr} \theta_{pr}) = 0, \quad (10)$$

respectively. Here, $\xi_{pr,f}$ and $\xi_{pr,pl}$ are the drag coefficients between the protein and the fluid and the protein and the platelets, respectively, and μ_{pr} is the protein chemical potential. For a dilute species, such as a coagulation protein, $\mu_{pr} = k_B T \log c_{pr}$ where c_{pr} is the concentration of protein, k_B is Boltzmann's constant, and T is the absolute temperature [12].

We can solve Equation (9) for $\mathbf{u}_{pr}$ to obtain

$$\mathbf{u}_{pr} = \frac{1}{\xi_{pr,f} \theta_f + \xi_{pr,pl} \theta_{pl}} (\theta_f \xi_{pr,f} \mathbf{u}_f + \theta_{pl} \xi_{pr,pl} \mathbf{u}_{pl} - k_B T \nabla \log(c_{pr})). \quad (11)$$

Since we assume that bound platelets are stationary, $\mathbf{u}_{pl} = 0$, and the expression for $\mathbf{u}_{pr}$ reduces to

$$\mathbf{u}_{pr} = \frac{\xi_{pr,f}(1 - \theta_{pl})}{\xi_{pr,f} + (\xi_{pr,pl} - \xi_{pr,f})\theta_{pl}} \mathbf{u}_f - \frac{1}{\xi_{pr,f} + (\xi_{pr,pl} - \xi_{pr,f})\theta_{pl}} k_B T \nabla \log c_{pr}. \quad (12)$$

Let $r = \xi_{pr,pl}/\xi_{pr,f}$ be the ratio of the drag coefficients and note that $D_0 = k_B T/\xi_{pr,f}$ is the diffusion coefficient of protein in pure fluid. Then

$$\mathbf{u}_{pr} = \frac{(1 - \theta_{pl})}{1 + (r - 1)\theta_{pl}} \mathbf{u}_f - \frac{1}{1 + (r - 1)\theta_{pl}} D_0 \nabla \log c_{pr}. \quad (13)$$

We substitute this into Equation 10, and recall that c_{pr} is a constant multiple of θ_{pr} to find that

$$\frac{\partial c_{pr}}{\partial t} + \nabla \cdot \left(\frac{1 - \theta_{pl}}{1 + (r - 1)\theta_{pl}} \mathbf{u}_f c_{pr} - \frac{D_0}{1 + (r - 1)\theta_{pl}} \nabla c_{pr} \right) = 0. \quad (14)$$

Hence, the protein is advected in the thrombus with a velocity $\frac{1 - \theta_{pl}}{1 + (r - 1)\theta_{pl}} \mathbf{u}_f$ that is a fraction of the fluid velocity $\mathbf{u}_f$ and it has diffusion coefficient $\frac{D_0}{1 + (r - 1)\theta_{pl}}$. We refer to the expressions $H_a = \frac{1 - \theta_{pl}}{1 + (r - 1)\theta_{pl}}$ and $H_d = \frac{1}{1 + (r - 1)\theta_{pl}}$, respectively, as the advective and diffusive hindrance factors. Note that if $r = 1$ so it is as 'easy' for protein to diffuse in the

platelet phase as in the fluid phase, the diffusion coefficient is just that in a simple fluid, D_0 . In the coagulation model, we do not actually track three separate phases. In making use of Equation (14), we identify $\mathbf{u}$ from the coagulation model with $\mathbf{u}_f$, and we set the bound platelet volume fraction $\theta_{pl} = k\phi^B$, where ϕ^B is the bound platelet fraction (ratio of bound platelet density to maximum possible platelet density), and k is a constant factor no greater than 1. In Figure 2 we plot the advective and diffusive hindrance factors for several values of the ratio r .

To demonstrate the effect of the hindered advection and diffusion in a relatively simple setting, we consider a prescribed and fixed distribution ϕ^B of bound platelets, the modified Navier-Stokes equations used in the coagulation model, and transport of a single protein species with concentration c_{pr} . The relevant equations are then

$$\rho(\mathbf{u}_t + \mathbf{u} \cdot \nabla \mathbf{u}) = -\nabla p + \mu \Delta \mathbf{u} - \mu \alpha(\theta) \mathbf{u}, \quad (15)$$

$$\nabla \cdot \mathbf{u} = 0, \quad (16)$$

and

$$(c_{pr})_t + \nabla \cdot \left(\frac{1 - \theta}{1 + (r - 1)\theta} \mathbf{u} c_{pr} - \frac{D_0}{1 + (r - 1)\theta} \nabla c_{pr} \right) = 0. \quad (17)$$

We set $\phi^B = 0.5$ within a semicircular region along the bottom wall of a channel and zero elsewhere. We set $k = 1$, so that $\theta = \phi^B$. The velocity along the left-edge of the domain has vanishing vertical component and a horizontal component that is the parabolic function of y for channel flow used in the full model simulations described below (the wall shear rate is 500/sec). The chemical concentration c_{pr} is initially zero throughout the domain and c_{pr} is set to 1 along the upstream edge of the domain. The function α in Equation (15) is $\alpha(\phi^B) = \alpha_{\max}(\phi^B)^2 / (0.25 + (\phi^B)^2)$ with $\alpha_{\max} = 500$, and the free-space diffusion coefficient $D_0 = 5(10)^{-7}$ cm²/sec.

The right panel of Figure 2 shows the distribution of protein after 10 min of simulated time for the cases $r = 10$, $r = 100$, and $r = 1000$. We see that for $r = 10$, protein is distributed throughout the semicircle (though not homogeneously), for $r = 100$, protein has penetrated part way into the semicircle, and for $r = 1000$, there is little protein inside the semicircle except along its edges. We note that without the Brinkman term in the fluid-dynamics equations, the velocity 1 μm above the bottom wall would be 500 $\mu\text{m}/\text{sec}$ so chemical at this height would be advected across the entire length of the 240 μm long domain in about 0.5 sec. Also, with $D_0 = 5(10)^{-7}$ cm²/sec, the typical distance that a protein would diffuse in 10 minutes is about 173 μm , and so if diffusion were unhindered, protein would fill the semicircular region.

2.3 Estimation of the drag ratio, r

From the studies in the previous section we see that changing the drag ratio r by an order of magnitude significantly alters the amount of protein that can enter a region filled with porous material on timescales relevant to clot formation. To get a sense of what this parameter should be, we looked for experimental measurements of hindered transport within blood clots. In the study by Hathcock and Nemerson [20], the effect of platelet deposition on the transport of factor Xa was investigated. Preformed fibrin or platelet-fibrin clots were placed on TF-phospholipid-covered surfaces, and factor X was added to the mixture and allowed to sit until it had saturated the entire mixture, that is, it had made its way to the TF-coated surface below the clot where it could be activated to factor Xa. Finally, the surrounding factor-X-filled fluid was replaced with a fresh solution and the flux of factor Xa out of the clots was measured. Hathcock and Nemerson found an effective, or hindered, diffusion coefficient of $5.3(10)^{-10}\text{cm}^2/\text{sec}$, three orders of magnitude smaller than that of free diffusion of the macromolecules. The average platelet packing density in their preformed clots was $0.11\text{ platelets}/\mu\text{m}^3$ and exhibited clear gaps between platelets. The height of the platelet layers was estimated to be either $14\text{ }\mu\text{m}$ or $27\text{ }\mu\text{m}$. Equating the value $5.3(10)^{-10}\text{cm}^2/\text{sec}$ to the hindered diffusion coefficient derived in the previous section (the hindrance factor, H_d , times the free diffusion coefficient, D_0) and using their stated platelet packing density we estimate a reasonable value of r to be 1000. Hathcock and Nemerson performed similar studies but with the platelets replaced by spherical beads. For those studies, the flux of factor Xa was significantly less hindered than with platelets which indicated that much of the reduction in diffusion for the platelet case was attributable to their asymmetrical shape. This last result and the fact that the clots in their experiments were preformed suggests that the distribution and density of platelets in these experimental clots may in fact be very different than those that form in vivo within ten or twenty minutes. So 1000 should be viewed as an upper bound for the drag ratio, r .

While $r = 1000$ is used to match experimental data when the bound-platelet fraction is high, use of this value at low bound-platelet fraction would restrict protein transport more than is physically plausible. A natural value of r for low bound-platelet fractions is $r = 1$, because for this value the hindrance factors H_d and H_a have values very near one (no hindrance). It is clear then that r should vary as a function of the bound-platelet fraction ϕ^B but it is not clear how r should increase from its lower bound of 1 to its upper bound of 1000. We consider a family of piecewise linear functions $r(\phi^B)$ differing by the value of a transition parameter ϕ_{tr}^B . For each of these functions, $r(\phi^B) = 1$ for $\phi^B < \phi_{tr}^B$, and then increases linearly to 1000 as ϕ^B approaches 1

$$r(\phi^B) = \begin{cases} 1, & \text{if } 0 < \phi^B \leq \phi_{tr}^B \\ \frac{999}{1 - \phi_{tr}^B}(\phi^B - \phi_{tr}^B) + 1, & \text{if } \phi_{tr}^B < \phi^B \leq 1 \end{cases} \quad (18)$$

We systematically vary ϕ_{tr}^B through the values 0.1, 0.2, 0.3, 0.4, and 0.5, and investigate the model's sensitivity to the choice of ϕ_{tr}^B . We report on this sensitivity later in the results section. To give the reader a sense of how r affects H_d and H_p in Figure 3, we plot several of the r functions and the corresponding hindrance factors.

2.4 Modifications to the LF model

The main modification to the LF model is to incorporate the hindrance factors for advection and diffusion into the fluid-phase protein concentration equations of the model. Instead of these equations having the form Equation 5, they now have the form

$$\frac{\partial C_i^{fp}}{\partial t} = -\nabla \cdot (H_a \mathbf{u} C_i^{fp} - H_d D_i \nabla C_i^{fp}) + R^f(C^{fp}) - B^p(C_i^{fp}, C_i^{pb}, P^{b,a}, P^{se}). \quad (19)$$

Two other small modifications to the LF model are also made. In the earlier version of our model [29], we assumed that when platelet-bound prothrombin is activated to thrombin, it remained bound to the platelet surface. Recently, it has become increasingly clear that this is an inaccurate description of the biology [25]. In our new model, we assume that when platelet-bound prothrombin is activated to thrombin, it is immediately released from the platelet surface into the fluid. It may then rebind to the platelet if it is not first carried away by the flow or inhibited by reaction with antithrombin. Further discussion of this change can be found in [16]. The other change, again to reflect an improved understanding of the biological literature, is to use smaller values of the (pseudo-first-order) rates of inhibition of thrombin, factor Xa, and factor IXa by antithrombin [4, 24]. Use of the higher values in the earlier papers was of little consequence because of the rapid removal of these enzymes by flow and diffusion. In the new situation in which protein transport may be severely hindered, using the correct inhibition rates is important.

2.5 Numerical Methods

We solve the model equations in a rectangular spatial region $R = [0, x_{max}] \times [0, y_{max}]$. For all of the variables, including the fluid, we use a uniform mesh placed over R with equal mesh spacing in both the x and y directions. For each differential equation, we use a finite-difference approximation defined at points on this mesh. During each timestep of the computation, we perform the following series of updates for the unknowns:

1. The discretized Navier-Stokes equations with Brinkman term are solved using a second-order projection method, details of which can be found in [30], to give new fluid velocities u , v , and pressure, p .
2. Platelets activated within the previous timestep are counted and the ADP release function, $\sigma_{release}$ is updated (see [29] for details about this function).
3. Mobile platelets and fluid-phase chemical concentrations are updated to account for advection using LeVeque's high-resolution advection algorithm [31].

4. Mobile platelet and fluid-phase chemical concentrations are updated to account for diffusion using a Crank-Nicolson time discretization and a spatial-difference approximation to the spatially-varying diffusion operator.
5. All species are updated to account for reactions using a second-order Runge-Kutta solver.
6. The platelet fractions of bound platelets, ϕ^B and ϕ^T , are calculated and $\alpha(\phi^B)$, $W(\phi^T)$, and the protein transport hindrance factors H_a and H_d are updated.

These steps are repeated until the prescribed final time for the simulation.

3 Results

In all results described in this paper, we use the following simulation conditions: (i) blood flows from left to right with a prescribed parabolic inflow velocity profile, (ii) platelets and fluid-phase chemicals have prescribed concentrations at the inlet and move downstream with the flow, (iii) the channel has height $60\ \mu\text{m}$, and length $240\ \mu\text{m}$ and there is an injury of length $90\ \mu\text{m}$ centered at the midpoint of the bottom wall, (iv) the initial TF density in the injury is set to $15\ \text{fmol}/\text{cm}^2$, (v) the wall shear rate is $500\ \text{s}^{-1}$, and (vi) the nonuniform platelet profile is set to the one we called P_1 in [29]. With this profile, the platelet concentration near each wall is approximately 3 times its value at the channel midpoint. For use in the hindrance factors, we set $\theta_p = 0.75\phi^B$, and although we tested five different values of ϕ_{tr}^B , we show results only for the extreme cases when $\phi_{tr}^B = 0.5$ and 0.1 .

Figure 4 shows snapshots at 5, 10, and 15 minutes (top to bottom) of platelet deposition for three different scenarios: unhindered transport (left) and the use of two drag ratio parameter functions that vary from 1 to 1000 where $\phi_{tr}^B = 0.5$ (middle), and $\phi_{tr}^B = 0.1$ (right) as in Figure 3. After 5 minutes, in each of the three cases, bound platelets cover the injury site completely and have grown slightly beyond the initial subendothelium-bound platelets. The clots are similar and each clot has only a slight effect on the flow over it. By 10 minutes, the clot in the case of no hindrance has grown substantially, both upstream and into the lumen, and, as indicated by the uneven distribution of dark-red patches, the platelet distribution in the thrombus has significant spatial heterogeneity. When the transport is hindered in the other two cases, the clots are small and more dense throughout (except on their luminal edges) and do not grow upstream. There is some heterogeneity in the downstream portion of the clots in both variable r cases. After 15 minutes, in the no hindrance case a large heterogeneous clot has developed that significantly affects the flow, while in the hindered transport cases there are clots that are relatively uniform and dense throughout, and have notably slowed growth both upstream and into the lumen. To display this quantitatively, Figure 5A shows the relative total number of bound platelets in each of the three cases. With no hindered transport, there is a little more than twice as many bound platelets as in both of the cases with hindered transport. To better understand the reasons for the differences in clot size and heterogeneity in the three cases, we describe below the production, or lack thereof, of major players in the clotting system.

First, we compare the number of platelets that become activated by thrombin and ADP throughout each of the three simulations. Because only activated platelets can cohere with the already formed clot, these quantities essentially describe the potential for clot growth at each time. Mobile activated platelets which do not cohere with the growing clot are washed away after activation. Figure 5B shows that during the first 100 seconds of the simulation, there are more platelets activated per 10 second interval in the hindered cases than in the unhindered case. By 200 seconds the situation has reversed and there are about twice as many platelets activated per 10 second interval in the unhindered case as in the hindered cases. By 900 seconds this ratio increases to about 10. The larger number of activated platelets in the hindered cases early in the simulation results in an increase in the number of bound platelets during that same time (see Figure 5A). That this increase in bound platelets is small is due to the fact that many of the activated platelets do not cohere and are washed downstream (not shown). We note that ADP is the main activator of platelets for the first 50–60 seconds in the hindered cases and for the first 90–100 seconds in the unhindered case. After these times, thrombin becomes the main activator of platelets, and, overall, thrombin activates about 10 times as many platelets as ADP in all three simulations (not shown). Although the higher number of platelets activated early in the hindered-transport simulations does not lead to a proportionally larger clot, it is interesting to understand how and why more platelets are being activated. Because thrombin is the main platelet activator, we compare the thrombin production in the three cases.

Figure 5F shows the cumulative thrombin production over 15 minutes for the three simulations. To obtain these plots, we integrate the rate of thrombin production over space and in time since the start of the simulation. More thrombin is produced during the first few minutes in the hindered cases, which correlates to the larger number of activated platelets just described. This can be traced back to the fact that there is a higher concentration of the enzyme complex, prothrombinase, that is responsible for cleaving prothrombin into thrombin. In Figure 5D, we show the amount of the prothrombinase complex as a function of time in each simulation. We count both prothrombinase itself and prothrombinase (transiently) bound to its substrate platelet-bound prothrombin. The thrombin production shown in Figure 5F follows the behavior of the prothrombinase concentration shown in Figure 5D during the first few minutes of the simulation. After about 120 seconds, however, there is a large burst of thrombin production in the unhindered case which leads to total produced thrombin levels close to 100 times larger than the hindered cases over the next 600 seconds. In the unhindered case, cumulative thrombin production increases throughout the rest of the simulation. In contrast, the cumulative thrombin production graphs are relatively flat in both hindered cases after 300 seconds; this indicates that little or no thrombin is produced during these times. The continued rise in thrombin production in the unhindered case is consistent with the rise in the prothrombinase concentration in that case. But the fact that a low level thrombin production occurs in the hindered cases despite the continued presence of a substantial quantity of the prothrombinase complex is, initially, counterintuitive.

Other important quantities that we present in Figure 5 are the concentration of the platelet-bound tenase complex and the cumulative production of factor Xa. Tenase is the platelet-bound enzyme complex that activates platelet-bound factor X. Recall that factor Xa,

produced by tenase on platelets or by TF:VIIa on the subendothelium, is the enzyme part of the prothrombinase complex that produces thrombin. Figures 5C and 5E show that for tenase concentration and Xa production, there is a very rapid rise early in the hindered-transport simulations but little change after that. Later, there is a somewhat more gradual and persistent rise in these quantities in the unhindered-transport simulation. For tenase there is again a puzzle, similar to that with prothrombinase, for the hindered-transport simulations. With high levels of tenase remaining from time 200 seconds through the end of the simulation, why has production of Xa essentially ceased?

The initial observations we make are that: (i) during early stages of clotting activity, more platelets are activated in the hindered transport cases because of the higher thrombin concentration but a proportionally larger clot does not form because of wash-out of the activated platelets, and (ii) after about 120 seconds, there is more thrombin production in the unhindered case, which eventually leads to a substantially larger clot after 15 minutes of activity. Counterintuitively, during these later times, there are much higher concentrations of tenase in the hindered cases but they do not translate into larger concentrations of prothrombinase and thrombin production. The questions we explore below are: Why, in the hindered transport cases, is there more thrombin during the early stages of the simulation and why does thrombin production slow during the later stages even though there is an abundance of both prothrombinase and tenase?

3.1 Early events near the subendothelium

Figure 5 shows that the system's strong response to injury occurs earlier when protein transport is hindered than when it is not. The production of factor Xa, the rate of activation of platelets, the concentrations of the platelet-surface tenase and prothrombinase complexes, and the production of thrombin successively rise sharply beginning at about 30 sec in both hindered-transport simulations and only after closer to 100 sec in the unhindered case.

The origin of the faster response is the decreased washout of factors Xa and IXa produced by TF:VIIa on the subendothelium as a consequence of reduced transport of these fluid-phase species from the near-wall region over the injury. Interestingly, the effect is more than can be accounted for just by reduced transport. We can see from Figure 6C that early factor Xa *production* by TF:VIIa is also substantially greater in the hindered transport cases (note that Figure 6C shows only the production of Xa by TF:VIIa at the subendothelium whereas Figure 5E included both production by platelet-bound tenase and TF:VIIa). The explanation for this is the positive feedback that occurs because factor Xa can activate TF:VII to TF:VIIa. The higher near-injury factor Xa concentrations in the hindered-transport simulations lead to much greater activation of TF:VIIa by factor Xa (see Figure 6A) so that much more TF:VIIa becomes available (see Figure 6B); the peak amount of TF:VIIa in the hindered cases is approximately 20 times that in the unhindered case. As a consequence, much more factor Xa (see Figure 6C) and factor IXa (not shown) are produced on the subendothelium. These additional amounts of factors Xa and IXa are also relatively protected against washout, and so can strongly contribute to formation of the tenase (VIIIa:IXa) complex on the surfaces of activated platelets near the subendothelium. (Recall

that platelet-bound Xa is the primary activator of platelet-bound VIII early in the response to injury when little thrombin is present.)

3.2 Limitations on growth

To see why, in the hindered transport cases, thrombin production slows so profoundly, we first look at the concentration and spatial distribution of prothrombin, thrombin's precursor, and the enzyme complex prothrombinase, which is responsible for cleaving prothrombin into thrombin. Figure 7 shows the values and spatial distribution of 'total prothrombin' and 'total prothrombinase' after 15 minutes of clotting activity. By total prothrombin, we mean the sum of the concentrations of fluid-phase and platelet-bound prothrombin. Similarly, total prothrombinase is the sum of the concentrations of all of the platelet-bound prothrombinase species including that transiently in complex with prothrombin. From top to bottom are the unhindered transport case and the hindered-transport cases with $\phi_{tr}^B = 0.5$ and $\phi_{tr}^B = 0.1$. For prothrombin to be cleaved it must first bind to an available site on the surface of an activated platelet and then bind with prothrombinase. We see that with unhindered transport, there is a significant region of overlap where both the prothrombin and prothrombinase concentrations are high. It is in this region of overlap that most of the new thrombin is being produced. In contrast, when transport is hindered, prothrombin and prothrombinase have at most a small region of overlap. Even though there is an abundance of prothrombin available just outside of the growing clot, the clot itself imposes a severe limitation on prothrombin's access to the clot's interior, and consequently little prothrombin reaches the parts of the clot with high prothrombinase concentrations. This is shown clearly in Figure 8 in which we plot the concentration of the complex of prothrombin bound to prothrombinase. The rate of thrombin production at any spatial location is directly proportional to the value of this concentration at that location. While the complex is found throughout the clot in the unhindered transport case, it is limited to a thin layer along the edge of the growing clot in the hindered-transport cases (The $\phi_{tr}^B = 0.1$ case is shown, the $\phi_{tr}^B = 0.5$ case is qualitatively similar.) Furthermore, the amount of prothrombinase formed in the edge-layer of the clot decreases as the clot grows. This can be inferred from Figure 5D which shows that the total amount of prothrombinase grows much more slowly after about 120 seconds in the hindered-transport cases than in the unhindered case. It can also be inferred from the progressively lower concentrations of the prothrombin-prothrombinase complex shown in Figure 8 as time advances.

We just saw that hindered transport decreases thrombin production, in part, by limiting the propagation of prothrombinase formation to the edge of the clot. This prompts the question of why prothrombinase formation is limited in this way. Recall that prothrombinase is a complex of factors Xa and Va on the surface of an activated platelet. Hence, to form prothrombinase, factor Xa must be available. Hindered transport affects the production and distribution of factor Xa in a similar way to that with which it affects thrombin production. Figure 9 shows the concentrations of 'total factor X' and 'total platelet tenase' after 15 minutes of clotting activity. Total factor X is the sum of the concentrations of the fluid-phase and platelet-bound factor X, and total platelet tenase is the sum of the concentrations of platelet tenase and of the complex of factor X and platelet tenase. The plot shows that while

the maximum concentrations of tenase in the hindered-transport cases are ten times more than in the unhindered case, the spatial distribution is restricted to a region very near the subendothelium. The higher concentration of tenase in the hindered-transport cases is, in part, a consequence of the greater production of factors IXa and Xa by TF:VIIa in these cases, and this, in turn, is a consequence of the feedback activation of TF:VIIa by factor Xa discussed in Section 3.1. It is also a consequence of the reduced removal of the factors IXa and Xa made by TF:VIIa in the hindered-transport cases. As we can see in Figure 9, the regions in which significant concentrations of both factor X and tenase co-exist are small or nonexistent. Although the tenase concentration is high in the hindered-transport cases, even at late stages in the simulation, it is only high in spatial regions that are physically inaccessible to factor X. As with prothrombin and prothrombinase, not only does the hindrance to transport limit the access of factor X into the clot, it also limits the formation of tenase to the near-wall parts of the clot. Production of factor Xa by tenase is limited to this region (until factor X there is exhausted), and the factor Xa molecules that are produced by tenase are limited in their ability to move towards the clot edge to contribute to prothrombinase formation. So, the much-reduced thrombin formation in the transport-hindered cases is the end result of a series of transport-limitations in the reactions that lead up to prothrombinase formation, as well as, the limited ability of prothrombin to penetrate into the clot.

3.3 Other Model Choices

3.3.1 The parameter, ϕ_{tr}^B —We chose the form of the drag ratio parameter, r , to be a piecewise linear function that transitions at the point ϕ_{tr}^B . We carried out simulations with five different values (0.1, 0.2, 0.3, 0.4, 0.5) for ϕ_{tr}^B . Recall that the larger ϕ_{tr}^B , the less protein transport is hindered at each bound platelet fraction ϕ^B . To see how the value of ϕ_{tr}^B affected thrombus size after 15 minutes of clotting activity, we computed the area of thrombus in which the bound platelet concentration was more than 10% of the maximum allowed concentration P_{max} . The area was calculated by counting the number of computational grid cells in which the 10% platelet concentration level was exceeded. We found that as ϕ_{tr}^B increased, there were only small increases in the area of the clots that form. From $\phi_{tr}^B = 0.1$ to $\phi_{tr}^B = 0.2$ the change in area was 4.8%. As ϕ_{tr}^B increased, the percent-change in area decreased, and from $\phi_{tr}^B = 0.4$ to $\phi_{tr}^B = 0.5$ there was only a 2.5% change. Furthermore, the interiors of the thrombi became slightly more heterogeneous as ϕ_{tr}^B increased. This is because for large values of ϕ_{tr}^B , the model behaves more like the unhindered case, at least for low bound-platelet fractions.

3.3.2 The function, $\alpha(\phi^B)$ —The function $\alpha(\phi^B)$ in Equation (3) is the one that we used previously in the LF model [29], and, in order to be able to compare with the results from that paper, we have also used this function for the simulations we have discussed so far. The rationale for the functional form of $\alpha(\phi^B)$ is not strong, but, in fact, it is not clear how to choose an appropriate function to reflect the (inverse-)permeability of an actual growing

thrombus. To investigate how sensitive the results we have presented are to the choice of this function, we also carried out simulations with another function α whose dependence on ϕ^B is very different. The form of this new function was motivated by that of a well-known permeability-porosity model known as the Kozeny-Carman relation [19]. According to this relation, the dependence of the permeability K of a porous material on that material's void fraction or porosity ε has the form $K = C \frac{\varepsilon^3}{(1 - \varepsilon)^2}$ where C is a constant whose value depends on the characteristics of the porous material in a poorly defined way. Recalling that $\alpha = 1/K$ and that $\varepsilon = 1 - \theta_p$ in our context, we defined $\alpha_{kc} = C' \frac{\theta_p^2}{(1 - \theta_p)^3}$ and we chose the constant $C' = 11.11$ so that the maximum of α_{kc} is the same as that of the function α we have used thus far. In making use of this function, we also set $\theta_p = 0.75\phi^B$ as before. See Figure 10 for a comparison of the two functions.

Figure 11 shows snapshots at 5, 10, and 15 minutes (top to bottom) of platelet deposition in simulations using α_{kc} with unhindered transport (left) and with hindered transport and the transition value $\phi_{tr}^B = 0.1$ (right). Compared to the clots shown in Figure 4, these clots are slightly smaller in size and the platelet density is more homogenous in the interior. This is true for both the hindered and unhindered cases. More importantly though, there are striking qualitative similarities with the results in Figure 4: the growth of the clot in the hindered case stopped and the clot in the unhindered case did not. The spatial distribution of the activating complexes tenase and prothrombinase (not shown) was again confined to relatively small areas within the core of the thrombus and the flux to the complexes of the substrates was greatly reduced compared to the unhindered case. Although the permeability of the clot is modeled differently here, the limitation on protein transport again provides the mechanism that stops thrombus growth.

4 Discussion

The issue of how the small-scale internal structure of a growing blood clot influences transport of plasma, platelets, and coagulation proteins within the clot has received increased attention recently [3, 20]. Hathcock and Nemerson [20] reported greatly reduced diffusion of coagulation proteins (by a factor of about 1000) through preformed platelet-fibrin clots of only 14–27 μm height. Intuitively, it seems reasonable to expect that if transport of the players involved in clot formation is hindered during the clot's development, the ultimate structure of the clot will be affected.

In our earlier paper [29], we presented a spatial-temporal model of clot formation under flow in which some aspects of hindered transport were accounted for. In that model, the growing clot was modeled as a porous medium whose local resistance to flow was a function of the local density of bound platelets. In addition, even if there was flow of plasma into a particular region of the clot, if the density of platelets in that region was near the maximum allowed platelet density, then transport of additional platelets into that region was limited. In that model, however, we did not account for reduction in the transport of the coagulation factors within the clot beyond that due to reduced fluid flow. But the coagulation proteins

are not small molecules, and so it is reasonable to expect that their finite size might lead to additional hindrance to their advective and diffusive transport within the clot, and this expectation is supported by the experimental data in [3, 20].

In this paper, we modified our spatial-temporal model of clot formation to account for hindrance of protein transport within the clot. To do so, we derived hindrance factors for advective and diffusive transport that multiply the advective flux and diffusive flux terms, respectively, in the transport equations for the proteins. Our derivation of these factors used ideas from multiphase mixture models. The hindrance factors that we derived are decreasing functions of the local density of bound platelets and we examined a number of hindrance factors differing in how quickly this decrease occurred. We compared the results of simulations with the new model to those from the earlier model in which protein transport was not explicitly hindered (beyond the reduction due to reduced plasma flow). We found that the additional hindrance of protein transport can have a profound effect on the size and internal structure of the clot.

Clots formed in the simulations without hindered protein transport grew well into the vessel lumen and upstream of the injury site. The presence of the clot reduced the fluid motion that advected proteins inside the clot and it was this reduction that allowed transport of proteins by diffusion throughout the clot's interior and in the upstream direction. Even after 15 minutes of clot growth, there was still substantial enzymatic activity throughout the clot, leading to continued platelet activation and clot growth. At 15 minutes, the clot was large and the density of bound platelets within the clot was heterogeneous with denser regions at the upstream and downstream ends of the clot.

In simulations with hindered protein transport, the growth of the clot essentially stopped by 15 minutes (it was very slow between 10 and 15 minutes) and the clot was much more compact and uniformly dense except in a thin layer along its edge. There was little clot growth in the upstream direction and growth into the lumen was much less than in the unhindered transport case. Thus limitations on protein transport within the clot provide one mechanism by which clot size might be limited.

Of particular importance in limiting the late growth of the clot in the hindered-transport cases was the spatial distribution of the platelet-bound tenase and prothrombinase enzyme complexes relative to the edge of the clot, and to the spatial distribution of their substrates, factor X and prothrombin. Compared to the unhindered-transport case, tenase was restricted to a smaller region over the injury. This was because the deposition of platelets limited transport of factor IXa, used to form tenase, from where it was produced on the subendothelium. The concentration of tenase in this region was 10-fold higher than in the unhindered-transport case, and early on this led to rapid production of factor Xa. But, as platelets continued to deposit on the clot, and transport of plasma factor X into the clot was substantially reduced, tenase had little opportunity to continue to produce factor Xa. Similarly, prothrombinase was restricted to a smaller region in the hindered-transport cases than in the unhindered case. This region extended somewhat further from the injured wall than the region in which tenase was found. The reason is that factor Xa activated by tenase was produced at locations already some distance from the wall and so its transport to the

edges of the clot was strongly limited only when the clot was larger than the size that limited factor IXa transport from the subendothelium. Prothrombinase activity decreased with clot growth because it became more and more difficult for its substrate to get from the bulk flow to the prothrombinase. For much of the development of the clots in the hindered-transport cases, the production of thrombin by prothrombinase occurred mainly in a thin strip along the edge of the clot and the rate of thrombin production in this strip decreased as the clot grew.

While hindered transport of proteins limited late growth of the clot, it actually promoted early clotting activity. Because factor Xa produced by TF:VIIa on the subendothelium was less able to be carried away by flow than in the unhindered transport case, its concentration near the injury was higher. This had a positive feedback effect because the factor Xa activated additional TF:VII to TF:VIIa. This led to greater production of factor IXa on the subendothelium and to much higher near-injury concentrations of tenase. In the unhindered transport case, there was little of this feedback activity.

The different thrombus growth behaviors we observed for unhindered and hindered protein transport were qualitatively very similar for two substantially different thrombus permeability-porosity relations $\alpha(\phi^B)$. The effect of hindered protein transport was also quite similar for simulations that differed substantially in the value of the bound platelet density (ϕ_{tr}^B) above which strong transport hindrance occurred. The basic story that hindered protein transport within the growing clot leads to formation of a dense thrombus of limited size is thus robust for a range of assumptions about how the thrombus changes fluid and protein transport within it.

While similar size and composition thrombi develop in our simulations for different transition values ϕ_{tr}^B for the onset of strong transport hinderance, there are small differences in the results that are worth noting, because they provide additional insight. Looking at Figures 6A, 6C, and 5C, respectively, we see a somewhat earlier rise in the density of TF:VIIa on the subendothelium, in the production of factor Xa by TF:VIIa, and in the concentration of platelet-bound tenase for the $\phi_{tr}^B = 0.1$ case than for the $\phi_{tr}^B = 0.5$ case. This is attributable to an early higher factor Xa concentration near the subendothelium because of the greater hindrance to its removal in the $\phi_{tr}^B = 0.1$ case, which leads to more feedback activation of TF:VIIa by factor Xa. The earlier rise in platelet-bound tenase in the $\phi_{tr}^B = 0.1$ case is because factor Xa and factor IXa (not shown) 'trapped' near the subendothelium have more opportunity to carry out the reactions necessary for tenase formation. Figure 9 shows that the eventual spatial distribution of tenase in the two simulations is very similar. There is a reduction in the extent of the spatial distribution of prothrombinase in the $\phi_{tr}^B = 0.1$ case (see Figure 7), presumably because less factor X is available where tenase is located and consequently less factor Xa is produced on the platelets, and even less of this factor Xa moves out toward the edge of the clot. The net result is that a somewhat smaller clot forms in the $\phi_{tr}^B = 0.1$ case.

The nature of the small dense thrombus that develops in the hindered-transport simulations seems to match reports from Brass *et al.* [40] of the ‘dense core’ they see form in response to injury to mouse arterioles. They describe the core as allowing little penetration by proteins and as consisting of platelets that are strongly activated. This is a good description of the thrombi that develop in our simulations, and so we think our results provide a possible explanation for formation of the dense core. They also report that this core is surrounded by a much looser ‘shell’ that consists of platelets that are only partially activated and in which the turnover of platelets is high. Groups of platelets in the shell are seen to break-away and are replaced, transiently, by new ones. Similar observations of thrombi with a stable core and transient outer part were made earlier by other groups [2, 5, 36].

Simulations with our model in its current form cannot capture the formation of a transient shell of platelets, because, in the model, once a platelet becomes bound it remains bound and does not move. That is, this model does not allow for transient binding of individual platelets to the thrombus nor does it allow internal stresses within the clot to cause remodeling of the clot’s structure or its release of clot fragments (emboli). Two reasons for using this simplified treatment of clot mechanics are (i) that it allowed us to simulate tens of minutes of physiological time, and (ii) that it allowed us to use differential equations for the concentrations of platelet-bound coagulation proteins that are much simpler than are the equations for such concentrations on moving platelets. (See [15, 14] for models that treat stress-induced changes in clot structure but which are limited to simulating much shorter periods of physiological time.) As it is, our model does not distinguish degrees of platelet activation nor does it permit unactivated platelets to bind to the thrombus. There is evidence that, under some conditions, even unactivated platelets can bind, albeit weakly and transiently, to a thrombus [22]. We plan to extend our current model to include a population of unactivated platelets (transiently) bound to the thrombus as well as a population of partially-activated platelets which also can attach and detach from the thrombus, but are not procoagulant. We can do this without voiding the advantages (i) and (ii) described above. We are confident that with these changes we will be able to capture the formation and dynamics of the ‘shell’, but this remains to be explored.

Our current model does not explicitly include fibrin formation and the possible feedback effects of fibrin on thrombus growth dynamics. One potentially important effect of fibrin is in further hindering protein transport through the spaces between platelets within a growing thrombus. Fibrin is also known to bind thrombin and so the fibrin gel that forms may serve as a ‘sink’ for thrombin which could affect the concentrations of thrombin available to activate platelets and coagulation proteins. Further examination of these issues is warranted.

In our simulations, hindering protein transport within the growing clot influenced the structure of the clot and limited its final size. It had the additional effect (not shown, but suggested by Figures 5B and 5F) of reducing the total amount of thrombin produced and the total number of platelets activated and, importantly, of reducing the amount of thrombin and number of activated platelets that were carried downstream away from the injury. Thus, the process of clot formation in the hindered-transport cases was more efficient in its use of materials, and less dangerous in terms of contributing to thrombotic events elsewhere in the circulation.

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Figure 1.

Schematic of coagulation reactions. Dashed magenta arrows show cellular or chemical activation processes. Blue arrows indicate chemical transport in the fluid or on a surface. Green segments with two arrowheads depict binding and unbinding from a surface. Rectangular boxes indicate surface-bound species. Solid black lines with open arrows show enzyme action in a forward direction, while dashed black lines with open arrows show feedback action of enzymes. Red disks indicate chemical inhibitors.

Figure 2. The left panel shows hindrance factors H_d and H_a for $r = 10$, $r = 100$, and $r = 1000$. Solid curves show H_d and dashed curves show H_a . The right panel shows chemical concentration after 10 minutes for (top) $r = 10$, (middle) $r = 100$, (bottom) $r = 1000$.

Figure 3.

Left: drag ratio parameter r as a function of bound-platelet fraction, ϕ^B . For each piecewise linear function, $r = 1$ up to the transition $\phi_{tr}^B = 0.1$ (solid), 0.3 (dashed), and 0.5 (dash-dot) and then increases linearly to 1000. Right: hindrance factors corresponding to the drag ratio parameters in the left plot. Solid curves show H_d and dashed curves show H_a for $\phi_{tr}^B = 0.1$ (black), 0.3 (dark grey), and 0.5 (light grey).

Figure 4.

Time sequence of growing clots at times 5, 10, and 15 minutes (top to bottom). From left to right is the case of no hindrance, $\phi_{tr}^B = 0.5, 0.1$. The arrows show the fluid velocity and have a uniform scaling through the sequence. Bound platelet concentrations vary from 0 (dark blue) to P_{max} (dark red).

Figure 5.

Simulations with unhindered transport (solid), $\phi_{tr}^B = 0.1$ (dashed), and $\phi_{tr}^B = 0.5$ (dash-dot).

A) Relative total number of bound platelets. B) Relative number of platelets activated by ADP and thrombin in ten second intervals. Each data point represents the number of platelets activated in the previous 10 seconds. C) Relative instantaneous concentration of tenase and tenase bound to factor X. D) Relative instantaneous concentration of prothrombinase and prothrombinase bound to prothrombin. E) Relative cumulative factor Xa production by tenase on platelet surfaces and by TF:VIIa at the subendothelium. F) Relative cumulative thrombin (factor IIa) production. Graphs in A, B, D, E, and F are scaled by the maximum in the unhindered case. Graphs in C are scaled by the maximum in the $\phi_{tr}^B = 0.1$ case.

Figure 6.

Simulations with unhindered transport (solid), $\phi_{tr}^B = 0.1$ (dashed), and $\phi_{tr}^B = 0.5$ (dash-dot).

A) Relative instantaneous concentration of TF:VIIa plus TF:VIIa bound to factor IX or factor X. B) Relative cumulative production of TF:VIIa by factor Xa at the subendothelium. C) Relative cumulative production of Xa by TF:VIIa at the subendothelium. All graphs are scaled by the maximum in the $\phi_{tr}^B = 0.1$ case.

Figure 7. Simulations with unhindered transport (top), $\phi_{tr}^B = 0.5$ (middle), and $\phi_{tr}^B = 0.1$ (bottom). Left: Spatial plot of the sum of the concentrations (nM) of fluid-phase prothrombin and platelet-bound prothrombin after 15 minutes of clotting activity. Right: Spatial plot of the sum of the concentrations (nM) of prothrombinase and prothrombin bound to prothrombinase after 15 minutes of clotting activity. Panels on the left are scaled uniformly by $1.8 \mu M$. Panels on the right have different scales.

Figure 8.

Simulations with unhindered transport (left) and hindered transport with $\phi_{tr}^B = 0.1$ (right).

Spatial plot of the concentration (nM) of the complex of prothrombin and prothrombinase after 5, 10, and 15 minutes of clotting activity (top to bottom). The panels have different scales.

Figure 9.

Simulations with unhindered transport (top), $\phi_{tr}^B = 0.5$ (middle), and $\phi_{tr}^B = 0.1$ (bottom). Left: Spatial plot of the sum of the concentrations (nM) of fluid-phase factor X and platelet-bound factor X after 15 minutes of clotting activity. Right: Spatial plot of the sum of the concentrations (nM) of platelet tenase and factor X bound to platelet tenase after 15 minutes of clotting activity. Panels have different scales.

Figure 10.
Plots of α (solid) and α_{kc} (dashed) as functions of the volume fraction θ_p .

Figure 11.

Time sequence of growing clots at times 5, 10, and 15 minutes (top to bottom) using α_{kc} . Left and right are the cases of no hindrance, and $\phi_{tr}^B = 0.1$, respectively. The arrows show the fluid velocity and have a uniform scaling through the sequence. Bound platelet concentrations vary from 0 (dark blue) to P_{max} (dark red).