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A mathematical model to describe the change in the constitutive character of blood due to platelet activation

Mohan Anand, Kumbakonam R. Rajagopal

Department of Mechanical Engineering, Texas A&M University, College Station, TX 77843, USA

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Note presented by Évariste Sanchez-Palencia.

Abstract Though a minor component by volume, platelets can have a profound influence on the flow characteristics of blood and thereby have serious consequences with regard to cardiovascular functions. Platelets are extremely sensitive to chemical agents as well as mechanical inputs and platelet activation is a necessary precursor to many life threatening medical conditions such as acute myocardial infarction, most strokes, acute arterial occlusion, venous thrombosis and pulmonary embolism. In cardiovascular devices such as ventricular assist devices and prosthetic heart valves, high shear stresses can trigger platelet activation. Moreover, such devices have artificial surfaces that are thrombogenic, the thrombotic deposition contributing to the failure of the device. Thus, there is a need to develop a mathematical model for the flow of blood that takes into account platelet activation, no such model being available at the moment. While there has been considerable amount of work in blood rheology, the role of platelets in the flow characteristics of blood has been largely ignored. This study addresses this lacuna. ***To cite this article: M. Anand, K.R. Rajagopal, C. R. Mecanique 330 (2002) 557–562.*** © 2002 Académie des sciences/Éditions scientifiques et médicales Elsevier SAS

rheology / platelet activation / shear thinning / viscoelasticity

Un modèle mathématique décrivant le changement du caractère constitutif du sang dû à l'activation des plaquettes

Résumé Les plaquettes peuvent avoir une profonde influence sur les caractéristiques de l'écoulement sanguin, même si elles ne forment qu'une faible composante du volume du sang. De ce fait, elles peuvent avoir des conséquences graves sur le fonctionnement cardiovasculaire. Les plaquettes sont extrêmement sensibles aux agents chimiques et aux efforts physiques, et le phénomène appelé « activation des plaquettes » est toujours le précurseur de maladies graves telles que : l'infarctus aigü du myocarde, la plupart des attaques, l'embolie pulmonaire, la thrombose veineuse, et les occlusions artérielles aigües. Les appareils cardiovasculaires comme les appareils d'assistance ventriculaire et les valves cardiaques, peuvent produire des forts tenseurs de cisaillement qui causent l'activation de plaquettes. De plus, les surfaces artificielles de ces appareils sont thrombogènes et favorisent la formation de caillots, les dépots thrombotiques pouvant être la cause de pannes de ces appareils. Par conséquent, il y a un besoin criant de développer des modèles mathématiques de l'écoulement sanguin qui prennent en compte l'activation des plaquettes, car un tel modèle n'existait pas auparavant. Bien qu'un travail considérable ait été accompli en rhéologie

E-mail addresses: ananda@tamu.edu (M. Anand); KRajagopal@mengr.tamu.edu (K.R. Rajagopal).

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sanguine, le role des plaquettes dans les caractéristiques de l'écoulement sanguin avait toujours été largement ignoré. Le but de cette Note est de combler cette lacune. ***Pour citer cet article : M. Anand, K.R. Rajagopal, C. R. Mecanique 330 (2002) 557–562.*** © 2002 Académie des sciences/Éditions scientifiques et médicales Elsevier SAS

rhéologie / activation des plaquettes / amincissement par cisaillement / viscoélasticité

1. Introduction

Blood is a multicomponent mixture of plasma, red and white blood cells (RBCs and WBCs), platelets, and various other proteins. Platelets constitute only approximately three percent by volume of the particulate matter of human blood, but play a significant role in blood rheology. Platelets are cell fragments derived from precursor cells of bone marrow origin termed megakaryocytes, approximately 6 μm^3 in size, and within this cell are found a variety of chemicals, within three types of granules:

1. α granules that contain thrombospondin (which serves as a mediating factor between activated platelets and other platelets), fibrinogen and platelet-derived growth factors.
2. Dense granules that contain adenosine diphosphate (ADP), adenosine triphosphate (ATP), calcium ions and serotonin.
3. Lysosomal granules that contain acid hydrolases.

Platelets are activated due to high shear stresses, and when activated the above constituents are released. In addition, there are various biochemical issues involved, namely, those due to the agonists released or already present in the flow field (like thrombin, ADP or prothrombin acting on platelet phospholipid membranes) and interaction with the sub-endothelial tissue etc (see Yamazaki and Mustard [1]). During the activation process, extra-cellular chemicals interact with intra-cellular constituents through the calcium ion (Ca^{2+}) pathway. The membrane proteins play a critical role in the interaction with plasma proteins and the injured endothelial wall. Glycoprotein Ib (GpIb) interacts with von Willebrand Factor (vWF: a plasma protein) to bind with the collagen of the sub-endothelium, and with the thrombin to attach with other platelets. Glycoprotein IIb-IIIa (GpIIb-IIIa) complex gets activated due to an increase in intra-cellular Ca^{2+} concentration during the activation process, and interacts with fibrinogen and vWF to bind with other platelets and the sub-endothelium respectively. Platelet aggregates that are formed by this process are susceptible to shear stresses; high shear stress zones in the flow, for instance, can break these up, apart from damaging platelets. However, once the activated platelets bind with the sub-endothelium, the aggregate interacts with fibrin to form a haemostatic plug that cannot normally be broken by mechanical stresses that arise due to the flow. Thus, despite the great strides made in blood biochemistry and blood rheology, the pathway to blood coagulation is not yet well understood as regards the flow of blood in blood vessels. Recently, Kuharsky and Fogelson [2] have developed a model to describe the role of binding site densities and platelet deposition that takes into account the role of the plasma-phase, surface bound enzymes and zymogens, coagulation inhibitors, and activated and unactivated platelets. This model consists in fifty nine (59) first order differential equations and a plethora of kinetic and other parameters to describe the problem and might capture many of the biochemical aspects related to the problem, however, the rheological considerations in our opinion are most rudimentary. In fairness to the authors, they recognize the criticism of a model that has a set of 59 equations and they state "all kinetic constants and concentrations used in this paper are based on the literature; no fitting was done". The work of Kuharsky and Fogelson [2] has been hailed as an important achievement (see Diamond [3]). However, one could question why the kinetics in the first place should only be first order kinetics and why they should be ordinary differential equations. It is possible that a totally different set of equations which are in fact coupled non-linear equations are necessary. Moreover, as mentioned earlier the hydrodynamical issues are given scant attention in [2]. We shall not discuss biochemical issues any further as our interest lies at the other end, the rheological issues, and thus

we develop a phenomenological model in which we incorporate variables that can take into consideration the biochemical reactions that take place in flowing blood. These parameters will be governed by reaction-diffusion equations which will then be coupled to the model we propose. We shall however completely ignore these reaction-diffusion equations and concentrate on the rheological aspects of the problem. This in itself leads to a most interesting and challenging problem in rheology. One hopes that at some future date, the various aspects to the modeling would all be put together to form a coherent model.

We start with the development of a stress dependent activation criterion in tune with the experimental observations of platelet activation, and subsequent aggregation, under prolonged shear. Our aim here is to merely develop a constitutive model for blood that is capable of incorporating platelet activation and that reflects distinctly different response characteristics before and after activation.

2. Constitutive modeling

Blood is a multicomponent mixture that exhibits complex response characteristics. Its rheological characteristics are markedly different in sufficiently large versus sufficiently small blood vessels, and this is to be expected as we could get to vessels whose diameters are merely a few diameters of the red blood cells. Flow of blood in large blood vessels is usually modeled as a Newtonian fluid. However, in smaller vessels it is usually modeled as a shear-thinning fluid. Neither of these homogenized models for the multicomponent mixture is capable of describing viscoelastic response. As blood is comprised of cells that are essentially elastic membranes filled with a fluid and platelets that are elastic solids, it seems reasonable to expect it to behave like a viscoelastic fluid. It is of course possible that the elastic response is insignificant under certain flow conditions. At low shear rates, blood seems to have a high apparent viscosity (due to RBC aggregation) while at high shear rates it seems to have a low viscosity (due to RBC disaggregation) (see [4–6]). There is some experimental data (see Thurston [7]) that indicates that blood behaves like a viscoelastic fluid.

Walburn and Schneck [8] used a shear-thinning fluid model, and Vlastos et al. [9] used a modified Carreau model to describe the flow of blood. Thurston [10] seems to have been the first to use a viscoelastic model for blood. Quemada [11] proposed a non-linear Maxwell model which included an internal variable (structural parameter) which could evolve and which allowed the viscosity to change with the internal variable. Sharp et al. [12] used a generalization of the Maxwell model, while Phillips and Deutsch [13] used a four constant Oldroyd-B type of model that seemed to capture the rheological characteristic reasonably well. More recently, Yeleswarapu [14] proposed a generalization of a three constant Oldroyd-B model that captures the shear-thinning behavior of blood over very large shear rates.

However, none of these models are capable of describing the rheology of blood which suffers platelet action whereby its response characteristics are markedly different prior to and post platelet activation and aggregation. This study is devoted to the development of a model that is capable of describing the rheological characteristics of blood through its transition due to platelet activation.

2.1. Model prior to activation

A general thermodynamic framework has been put into place by Rajagopal and his coworkers to model the response of bodies with multiple natural configurations (e.g., stress free states). Such a framework can be used to develop models for complex viscoelastic fluids, and the models due to Maxwell, Oldroyd, Burgers and others can be shown to be special choices within the framework (see Rajagopal and Srinivasa [15], Murali Krishnan and Rajagopal [16]). More importantly, the framework is particularly well suited for describing bodies whose response functions change as it undergoes deformation. Thus, we can use this framework to develop models for blood as the framework allows for changes in the response of materials due to activation. For example, the crystallization of polymer melts has been studied using such a framework (see Rao and Rajagopal [17,18]). In the case of purely isothermal problems, the framework involves a choice for the Helmholtz potential and the rate of dissipation. The constitutive relation that is picked maximizes the rate of dissipation amongst the class of models that are possible candidates to describe the behavior of

the material in question. When applied to the problem on hand, such a procedure leads to models that are generalizations of the model developed by Yeleswarapu et al. [19]. Prior to activation, we shall consider models of the form (see Rajagopal and Srinivasa [15], Murali Krishnan and Rajagopal [16]):

$$\mathbf{T} = -p\mathbf{1} + \mu_1 \mathbf{B}_{\kappa_{p_1(t)}} + \mu_2 \mathbf{B}_{\kappa_{p_2(t)}} + \eta \mathbf{D} \tag{1}$$

with

$$\overset{\triangledown}{\mathbf{B}}_{\kappa_{p_i(t)}} = \mathbf{f}(\mathbf{B}_{\kappa_{p_i(t)}}) \tag{2}$$

where the triangle denotes the frame invariant Oldroyd time derivative, μ_1, μ_2 and η are in general functions of $\mathbf{B}_{\kappa_{p_i(t)}}$. It can be shown that this model (Eqs. (1), (2)) is a generalization of the Oldroyd-B model when $\mu_2 = 0$ and μ_1 is a constant. It is possible to express the above models in a different form. A special choice for the Helmholtz potential and the rate of dissipation would lead to a generalization of the model used by Yeleswarapu et al. [19], namely:

$$\mathbf{T} = -p\mathbf{1} + \mathbf{S} \tag{3}$$

$$\mathbf{S} + \lambda_1(\mathbf{A}_1)\big(\dot{\mathbf{S}} - \mathbf{L}\mathbf{S} - \mathbf{S}\mathbf{L}^{\mathrm{T}}\big) = \mu(\mathbf{A}_1)\mathbf{A}_1 + \lambda_2(\mathbf{A}_1)\big(\dot{\mathbf{A}}_1 - \mathbf{L}\mathbf{A}_1 - \mathbf{A}_1\mathbf{L}^{\mathrm{T}}\big) \tag{4}$$

where

$$\mathbf{L} = \operatorname{grad}\mathbf{v}, \quad \mathbf{A}_1 = \mathbf{L} + \mathbf{L}^{\mathrm{T}} \tag{5}$$

with

$$\mu(\mathbf{A}_1) > 0, \quad \lambda_1(\mathbf{A}_1) > 0 \quad \text{and} \quad \lambda_2(\mathbf{A}_1) > 0 \tag{6}$$

The model developed by Yeleswarapu et al. [19] corresponds to one in which λ_1 and λ_2 are constants and μ is given by:

$$\mu(\mathbf{A_1}) = \eta_\infty + (\eta_0 - \eta_\infty)\left[\frac{1 + \ln(1 + \Lambda\dot{\gamma})}{1 + \Lambda\dot{\gamma}}\right] \tag{7}$$

$$\dot{\gamma} = \left[\frac{1}{2}\operatorname{tr}\big(\mathbf{A_1^2}\big)\right]^{1/2} \tag{8}$$

and η_0 and η_∞ are the asymptotic values at very low and very high shear rates.

2.2. Activation

If the shear stress in the flow domain attains a critical value, the platelets are activated. We introduce a function $A(t)$ that is a measure of the extent of activation. Platelet activation and the dynamics of the subsequent aggregation are quite complex. The activation function $A(t)$ is defined through:

$$A(t) = A(0) + \frac{1}{A_0}\int_0^t \exp\left(k\left(\frac{\theta(\tau)}{\theta_{\mathrm{cr}}} - 1\right)\right) H\big(\theta(\tau) - \theta_{\mathrm{cr}}\big)\,\mathrm{d}\tau \tag{9}$$

where

$$\theta = \theta(T_{ij}, C_{(\mathrm{act})k}), \quad i \neq j,\ k = 1, \ldots, n \tag{10}$$

H is the Heaviside function, $C_{(\mathrm{act})k}$ represents the concentration of a species affecting platelet activation, and θ_{cr} is some specific value. Thus θ depends on the shear stresses in the fluid, and the advection of various biochemical stimuli for platelet activation. Sorensen et al. [20] have simulated platelet-surface and platelet-platelet adhesion by a coupled set of convection-diffusion-reaction equations corresponding to the

various agonists for platelet activation. We shall restrict ourselves, initially, to looking at the effects of shear stresses. Thus, it is possible that

$$\theta = \max |T_{ij}|, \quad i \neq j \tag{11}$$

In a simple flow, such as a uniaxial flow in a pipe, θ could just be the shear stress $|T_{rz}|$.

Let t_{act} denote the time when the platelets get activated and let t_{ag} denote the time when the aggregation starts. In general, there is a time lag between aggregation and activation, i.e., $t_{\text{ag}} > t_{\text{act}}$. Let $T = t_{\text{ag}} - t_{\text{act}}$. We suppose that there is a threshold value for the activation function A_{cr} above which the platelets get activated. However, there is another threshold A_{dam} ($> A_{\text{cr}}$) which corresponds to the platelets getting damaged (lysed). When this occurs, the characteristic of blood undergoes a further change and it usually reverts to a structure that is similar to its structure before the platelet activation. Thus, we shall suppose that if:

$$A(t-T) > A_{\text{cr}} \quad \text{and} \quad A(t) < A_{\text{dam}} \tag{12}$$

or if:

$$A(t-T) = A_{\text{cr}}, \quad \dot{A}(t-T) > 0 \quad \text{and} \quad A(t) < A_{\text{dam}} \tag{13}$$

then:

$$\mathbf{T} = -p\mathbf{1} + \mathbf{S} \tag{14}$$

$$\mathbf{S} + \lambda_1(\mathbf{A_1})\big(\dot{\mathbf{S}} - \mathbf{LS} - \mathbf{SL}^{\mathrm{T}}\big) = \widehat{\mu}(\mathbf{A_1})\mathbf{A_1} + \lambda_2(\mathbf{A_1})(\dot{\mathbf{A}}_1 - \mathbf{LA_1} - \mathbf{A_1L}) \tag{15}$$

with $\widehat{\mu}(\mathbf{A_1})$ being significantly larger than $\mu(\mathbf{A_1})$, that is the viscosity is much greater while the relaxation and retardation times are not significantly different.

If the second threshold A_{dam} is attained, then the model reverts to the original model (Eqs. (3), (4)). Depending on the flow, it is possible that different locations in the flow domain exceed A_{cr}. In fact, what we have is a free boundary problem in which the domains in which Eqs. (3), (4) and Eqs. (14), (15) hold are determined by the evolution of the free boundary.

Preliminary calculations of unidirectional flows occurring in a pipe have been carried out. In this case Eq. (9) reduces to:

$$A(t) = A(0) + \frac{1}{A_0}\int_0^t \exp\left(k\left(\frac{|T_{rz}|}{T_{\text{cr}}} - 1\right)\right) H(T_{rz} - T_{\text{cr}})\,\mathrm{d}\tau \tag{16}$$

and the above expression agrees well with the experimental results of Brown et al. [21,22] and Wurzinger et al. [23].

The results show that activation of platelets can significantly change the structure of the flow. A detailed study of oscillatory flows has been carried out within the context of the above model and will be the subject matter of a forthcoming paper.

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