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Comput. Methods Appl. Mech. Engrg. 197 (2008) 2087–2104
Computer methods in applied mechanics and engineering
www.elsevier.com/locate/cma

Immersed-boundary-type models of intravascular platelet aggregation ☆

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Received 28 February 2007; received in revised form 20 June 2007; accepted 21 June 2007
Available online 11 August 2007

Abstract

The formation of platelet aggregates during blood clotting is modeled on two scales using ideas motivated by Peskin's immersed boundary method. The microscopic scale models track individual platelets, their mechanical interactions with one another and the surrounding fluid, their detection of and response to chemical activators, and the formation of cohesive and adhesive 'links' between platelets and between platelets and the vascular wall. These models allow inclusion of detailed mechanisms of binding–unbinding, platelet stimulus-response, and chemistry on the platelets' surfaces. The macroscopic scale models treat the same interactions in terms of concentrations of platelets and distributions of cohesive and adhesive links, and can be used to study platelet aggregation in vessels of clinical interest including the coronary and cerebral arteries. In both types of model, the development of platelet aggregates affects the fluid motion only through an evolving fluid force density, and consequently, Cartesian grid methods are effective in solving the model equations.

MSC: 65M06; 76Z05; 92C10; 92C45

Keywords: Thrombosis; Multiscale modeling; Biofluid dynamics; Blood clotting; Cartesian grid

1. Introduction

Intravascular blood clots (thrombi) are initiated by damage to the endothelial cell lining of a blood vessel and involve the formation on the damaged surface of clumps of cells intermixed with a fibrous protein gel. This happens in the face of continued blood flow past the injury, and the interplay between the development of the clot and the local fluid dynamics is one of our principal concerns. Under some conditions, the clot grows to completely occlude the vessel. In other situations, it grows to a maximum size and then portions of it break away and the clot's size may settle into a rough steady state. One of our major goals is to be able to capture both kinds of behavior in our models, and to understand why they occur.

Clot formation involves two intertwined processes both of which are initiated by damage to the vessel lining. One process is platelet aggregation and begins when circulating blood platelets adhere to the damaged wall. Other platelets can be activated by chemicals released by these first platelets and then bind to the already wall-adherent platelets; this results in the buildup of a platelet aggregate or thrombus. The other process is coagulation which we view as itself comprised of two distinct subprocesses. The first of these involves a network of tightly regulated enzymatic reactions that begins with reactions on the damaged vessel wall and continues with important reactions on the surfaces of activated platelets. The end product of this reaction network

☆ Supported, in part, by grants from the National Science Foundation: DMS-9805518, DMS-0139926, and DMS-0540779.
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doi:10.1016/j.cma.2007.06.030

is the enzyme thrombin which (i) activates additional platelets and (ii) creates monomeric fibrin which polymerizes into the fibrous protein gel component of the clot. This polymerization process is the second subprocess of coagulation. Both platelet aggregation and the two parts of coagulation occur in the presence of moving blood, and are strongly affected by the fluid dynamics in ways that are as yet poorly understood. One indication of the effect of different flow regimes is that clots that form in the veins, where blood flow is relatively slow, are comprised mainly of fibrin gel (and trapped red blood cells), while clots that form under the rapid flow conditions in arteries are made up largely of platelets. Understanding why there is this fundamental difference between venous and arterial clotting should give important insights into the dynamics of the clotting process.

In this paper, we review our development of models of platelet aggregation and we point how these models are designed with the future inclusion of coagulation in mind. Thus, for example, we make provision for the later inclusion of coagulation chemistry on surfaces of model activated platelets. We describe two classes of platelet aggregation model. One involves the behavior of a collection of individual platelets interacting with the suspending fluid, the vessel wall, and platelet activating chemicals. We refer to these as our *microscale platelet models*, and note that they are appropriate for small diameter arterioles and venules (approximately 50 μm in diameter), as well as, perhaps, for detailed studies of the aggregation process in small portions of a larger clot. The other, our *macroscale platelet models*, tracks the dynamics of the same sorts of interactions but on a larger scale appropriate for larger vessels. These continuum models involve the spatial–temporal evolution of a platelet thrombus using density functions to describe the distribution of the relevant platelets and other species. For the microscale modeling a major tool is the immersed boundary (IB) method. For the macroscale models, the classical immersed boundary method motivates our modeling approach.

Because the approach of the IB method underlies our modeling of platelet aggregation in both scales of models, we briefly review the fundamentals of the IB method. Then we describe aspects of platelet biology important in our modeling efforts. After that we describe the microscale aggregation models based on the immersed boundary method. Finally, we discuss how these ideas are extended to much larger spatial scales in our macroscale models.

2. Immersed boundary method

The fundamental problem for which the IB method has been developed concerns the interactions of a viscous incompressible fluid with one or more moving and/or deformable elastic objects in contact with that fluid. The motion of the fluid influences the motion of the elastic objects and *vice versa*, and so the IB method involves coupled equations of motion for both types of material (fluid and elastic) and solves for both motions simultaneously. To introduce the IB method we focus on a simple model problem in which a single fluid-filled closed elastic membrane is immersed in a viscous fluid (see Fig. 1). For simplicity we describe a two-dimensional model problem, but emphasize that the IB method has been used extensively for three-dimensional studies in a number of application areas. We also assume that the fluid inside and outside the membrane has the same density and viscosity (although this is not essential). The physics of the model problem is that the elastic membrane is under tension and exerts force on the adjacent fluid. These forces may cause the fluid to move and, in that case, points on the membrane move along with the fluid. In the IB method, the fluid is described in Eulerian terms through a velocity field $\mathbf{u}(\mathbf{x},t)$ and pressure field $p(\mathbf{x},t)$ defined at every point $\mathbf{x}$ in the physical domain Ω. The elastic membrane is described in Lagrangian terms. Let the elastic membrane be parameterized by q, and denote by $\mathbf{X}(q,t)$ the spatial coordinates at time t of the membrane point labeled by q. The IB equations are coupled equations of motion for the fluid variables $\mathbf{u}(\mathbf{x},t)$ and $p(\mathbf{x},t)$ and the membrane configuration $\mathbf{X}(q,t)$. The basic IB equations are:

$$\rho(\mathbf{u}_t + \mathbf{u}\cdot\nabla\mathbf{u}) = -\nabla p + \mu\Delta\mathbf{u} + \mathbf{f}, \quad \nabla\cdot\mathbf{u} = 0, \tag{1}$$

$$\mathbf{F}(q,t) = \mathbf{F}(\mathbf{X}(q,t), \mathbf{X}_q(q,t)), \tag{2}$$

$$\mathbf{f}(\mathbf{x},t) = \int \mathbf{F}(q,t)\delta(\mathbf{x} - \mathbf{X}(q,t))\mathrm{d}q, \tag{3}$$

$$\frac{\partial \mathbf{X}}{\partial t}(q,t) = \int_\Omega \mathbf{u}(\mathbf{x},t)\delta(\mathbf{x} - \mathbf{X}(q,t))\mathrm{d}\mathbf{x}. \tag{4}$$

Eqs. (1) are the Navier Stokes equations which describe the dynamics of a viscous incompressible fluid, of constant density ρ and constant viscosity μ, driven by a force density $\mathbf{f}$ which here arises because of the elastic deformation of the immersed membrane. Eq. (2) specifies the elastic force (per unit q) at each point of the immersed boundary object. The functional dependence of this force on the state of the boundary is specified appropriately to the material being modeled. An example is given below. Eq. (3) defines the fluid force density $\mathbf{f}(\mathbf{x},t)$ in terms of the immersed boundary elas-

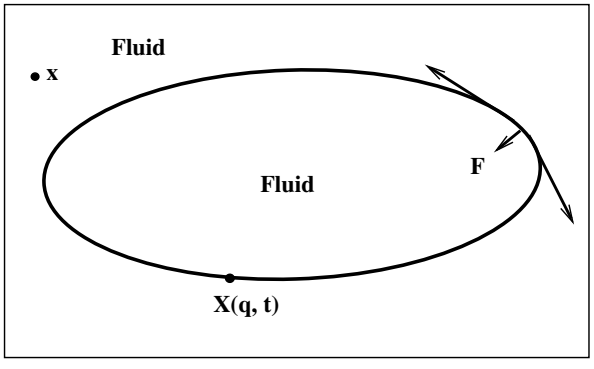

Fig. 1. Model Problem: Massless elastic membrane immersed in fluid. Here, $\mathbf{x}$ is a point in the fluid, $\mathbf{X}(q,t)$ is the location of a material point on the immersed elastic membrane, and $\mathbf{F}$ is the force generated at a point in the membrane because the membrane is stretched.