Applications in Engineering Science 10 (2022) 100103

Contents lists available at ScienceDirect

Applications in Engineering Science

journal homepage: www.elsevier.com/locate/apples

Computational models of hemostasis: Degrees of complexity

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ARTICLE INFO

Keywords:
Coagulation
Hemostasis
Thrombosis
Computational models
Model design

ABSTRACT

The history of studies on blood clotting goes back to the emergence of civilized society itself. The foundations of the modern scientific study of hemostasis are based on the discovery of erythrocytes in blood in 1674 and, later, that of platelets in 1842. The causes of thrombosis are encapsulated in the Virchow Triad (dated to 1856), which refers, in modern terms, to hypercoagulability, alterations of hemodynamics (stasis), and endothelial injury. The understanding of coagulation, the network of reactions that underlies hemostasis and thrombosis, has evolved from a cascade (in 1964) into spatially distinct sets of reactions dependent on co-factors occurring on different cells in different tissues and linked together by diffusion and flow (as of 2015). Correspondingly, mathematical/computational models for hemostasis and thrombosis (which involve coagulation along with platelet aggregation in the presence of flow) have evolved in design complexity from Continuum temporal (or "homogeneous") models to Continuum spatio-temporal models (with or without the flow) and lately into Discrete-Continuum spatio-temporal models with the flow. After a brief listing of the discoveries and historical personae that contributed to the understanding of hemostasis up to the present, the development of mathematical/computational models is traced from the late 1980s when they started gaining importance. Influential models are then highlighted. The models are reviewed in increasing order of design complexity (one of four possible methods of classification). The physiological significance of each and the insights they offer into hemostasis regulation are explained.

1. Introduction

A significant challenge for modern medicine is to correct pathologies of the physiological process that stops bleeding on injury (hemostasis) without causing pathological vessel occlusion (thrombosis). Hemostasis consists of platelet aggregation accompanied by coagulation- a complex biochemical network that plays a critical role in this process. Mathematical modeling of hemostasis and thrombosis first emerged, beginning with the coagulation network alone, in the late 1980s (Khanin and Semenov, 1989). By the mid-2000s, it had included platelet aggregation and emerged as a valuable tool for the identification of novel reaction mechanisms which experimental methods could not distinguish. This trend continued, and mathematical modeling has expanded in applications like, for instance, suggesting the efficacy and plan of dosing of a novel drug in a patient. Further, mathematical modeling also finds use in investigating the effect of dysfunctions (in particular, deficiencies) on pathologies of the hemostatic system (particularly, bleeding disorders). The mathematical models referred to here are highly non-linear, coupled and consist, in some cases, of a large number of equations: they require increasing computational effort, depending on complexity, to obtain a solution, and we will refer to them interchangeably in this review as computational models.

Mathematical/Computational models of hemostasis and thrombosis save resources and provide an alternative when clinical studies are difficult or expensive to implement. For instance, their use in modeling of device thrombosis can inform the design, in the preclinical stage, of several medical devices (stents, heart valves, ventricular assist devices, etc.) used to treat cardiovascular diseases (Manning et al., 2021). They are of interest to a broad spectrum of researchers working on problems involving hemostasis or thrombosis, like biologists, biochemists, doctors, pharmacologists, biomedical engineers, theoretical biologists, and mathematicians. Each class of researchers is interested in a different aspect of these models. Based on the class(es) of researchers, the models may be categorized into different classifications which denote the aspect of interest of the researcher class(es). These classifications are not mutually exclusive groups of models, and within each classification (one of which we will explore), there is an organization/ordering of models. The classifications are as follows:

1. Degree of complexity,
2. Physiological properties,

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https://doi.org/10.1016/j.apples.2022.100103
Received 12 November 2021; Received in revised form 10 March 2022; Accepted 13 April 2022
Available online 29 April 2022

Table 1
Classifications, organizing principle, and target audience of models of hemostasis/thrombosis.

Number	Type of classification	Focus	Target audience
1	Degree of complexity	Model design	Theoretical Biologists, Mathematicians
2	Physiological properties	Type of phenomenon	Doctors, Biologists, Pharmacologists
3	Anatomical features	Scale of system	Doctors
4	Properties and stages	Insights into regulation	Physiologists, Systems biologists

3. Anatomical features, and
4. Stages and Properties of a growing thrombus (Insights into regulation).

Models classified according to the degree of complexity focus on model design. Models in this class are organized into those that model changes at continuum level alone and those that model changes using hybrid Discrete-Continuum methods. Continuum models are further organized into those which focus on temporal changes alone and those which capture spatio-temporal aspects. (Hybrid) Discrete-Continuum models are those that combine discrete methods to track the movement and interactions of cells (platelets and, if feasible, erythrocytes) with continuum models for the species involved in coagulation and for the flow of suspending medium (blood or plasma, as the case may be). A related terminology encountered in the literature is the "multiscale model". This simply refers to models (Continuum or Discrete-Continuum) that capture changes at the sub-cellular coagulation reactant level, cellular platelet/erythrocyte level, and vessel wall/flow level. These models are of great interest to theoretical biologists and mathematicians. Models classified according to the physiological properties focus on the type of the phenomenon to be described: coagulation in vitro, coagulation in arterial thrombosis, coagulation in venous thrombosis, coagulation in a hemostatic plug, etc. This organization is of interest to doctors, biologists, and pharmacologists. Models can also be classified according to the anatomical features they are appropriate for, i.e., whether they are arterial or venous models, are for large or small vessels, the size of the damage, and the shear rates where applicable. This organization is primarily of interest to doctors. On the other hand, models classified according to the stages and properties of a growing thrombus focus on the insights that they provide for the understanding of the regulation of hemostasis. This is of great interest to physiologists and systems biologists, but less for doctors. The classifications of models are displayed in Fig. 1, and their organizing principle and target audience are summarized in Table 1. Here, we provide a historical context to the study of hemostasis by briefly listing the discoveries and personae that contributed to the understanding of blood clotting from ancient times up to the present day. We then review the state of the art of models from the point of view of theoretical biologists/mathematicians (i.e., classified according to the degree of complexity, and ordered from simple to complex), and bring out the physiological significance of these models and the insights they offer into the regulation of hemostasis and thrombosis as we currently understand it.

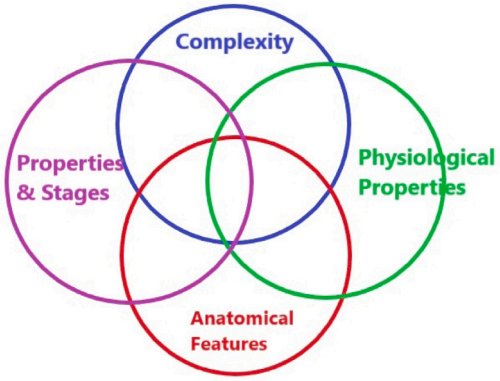

Fig. 1. Classifications of models of hemostasis/thrombosis based on target audience.

2. History of the study of blood clotting

The history of the study of blood clotting goes back, naturally, to the emergence of civilized societies in the corresponding part of the world. We will briefly touch upon some important theories and personae in this history. We refer the reader to the excellent historical account given by Fasano and Sequeira (2017) from which the information given below is extracted.

Egyptian physicians were well versed with the inside of the human body due to their practice of mummification (which was done intentionally from about 2600 BC). They knew that the main blood vessels (46 in number) reached every part of the body and that the heart had a central role in the human body. The primary reference texts of the Egyptian civilization available to us today are the Edwin Smith Papyrus (written circa 1700 BC), the Ebers Papyrus (existing in a sixteenth-century BC copy), and the Kahun Gynecological Papyrus (nineteenth-century BC). However, there is no mention of blood coagulation in the known medical papyri of the Egyptian civilization. The Greek civilization (1200BC to 323BC) which emerged next revered the Egyptians' expertise in medicine. The central figure in Greek and Western civilization was the physician Hippocrates (circa 460BC–370BC), who postulated that health depends on the equilibrium of four "humors" (blood, phlegm, black bile, and yellow bile). This notion of health due to an equilibrium of entities is also mentioned in the references surviving from this period of the traditional Indian and Chinese systems of medicine. The traditional Indian system of medicine is known as Ayurveda and is attributed by orthodox Hindus to being a little more than 5100 years old. The Charaka Samhita is one of the oldest surviving and widely referred texts of this system; it is dated between the fifth and the third century BC. Ayurveda states that an individual's health is determined by the equilibrium of three internal forces or doshas (Vata, Pitta, and Kapha). Traditional Chinese medicine is also as old and is based on the equilibrium of two "principles": Yin and yang. The reference text available now for this system is the *Inner Canon of Huangdi* which was probably written between the sixth and the third century BC. In both systems of medicine, bloodletting is emphasized as a treatment for diseases. Galen of Pergamon (131 CE–201 CE) was a Greek physician who acquired great fame in ancient Rome. He refined Hippocrates' theory of the four "humors" and raised bloodletting as a cure for diseases into an art. Galen's views dominated western medicine for the next at least 1400 years. In particular, the practice of bloodletting continued for several centuries afterward and peaked in the first half of the nineteenth century before being discarded as ordinarily useless. We will now look at the historical developments concerning blood clotting alone.

Anning (1957) in his review of the history of venous thrombosis (mainly that which occurred in the lower limb), states that "the painful swelling of the lower limb appearing suddenly during the first two or three weeks after delivery could scarcely escape the attention of the mother, her midwife, her physician or her relatives". However, despite this, he noted that there were few references to it before the eighteenth century. Hippocrates observed limb swelling during pregnancy and termed it "leucophlegmatia", though the term was used for a variety of other conditions (Anning, 1957). Galen was the first to use the word "thrombosis" (Greek for curdling) in connection

Fig. 2. Antonie van Leeuwenhoek.
Source: Obtained from Anon (1723).

Fig. 3. Rudolph Carl Virchow.
Source: Obtained from Anon (1902).

with limb swelling. The discoveries that laid the foundations for a modern scientific approach to blood clotting were those made starting in seventeenth-century Europe that we highlight next.

Antonie van Leeuwenhoek (1632–1723) (Fig. 2) described and measured erythrocytes in blood around 1674. In this study, he was assisted by the availability of microscopes built by Dutch inventors at the end of the sixteenth century and refined afterward. "The famous French surgeon Jean-Louis Petit (1674–1750) recognized that blood clotting was part of the process of hemostasis (Fasano and Sequeira, 2017)". The English surgeon Richard Wiseman (1601–1686) recognized two causes of thrombosis: stasis and hypercoagulability. The German pathologist Rudolph Carl Virchow (1821–1902) (Fig. 3) identified three factors as contributing to thrombosis (Virchow, 1856): this is the famous "Virchow Triad" which is still helpful to understand the causes of this disease. The Virchow Triad refers, in modern terminology, to hypercoagulability, alterations of hemodynamics (stasis), and endothelial injury. However, as an aside, recent articles have questioned the attribution of the triad to Virchow and state that there is evidence only that he proved that pulmonary thrombi originated in the legs and ruled out inflammation in the process (see Bagot and Arya (2008)). Modern investigations in blood coagulation are said to have started from the discovery of platelets in the blood (which was possible with the advent of more powerful microscopes) by Max Johann Sigismund Schultze in 1865. However, earlier observations of platelets were made by Alfred Donné (1801–1878), and he is credited with the discovery.

3. Current understanding of hemostasis

The traditional view of coagulation is the "cascade model" first proposed by Macfarlane (1964) in 1964, wherein clot formation is the result of a sequence of enzymatic reactions that are facilitated on the membrane surface of "activated platelets". The biochemical changes that occur in the cascade model of coagulation are detailed in Mann (2003). Physiological blood coagulation is initiated via the so-called extrinsic pathway, upon contact of blood-borne serine protease factor VIIa with extravascular transmembrane protein tissue factor (TF). The complex so-formed is a functional enzyme that initiates the cascade of proteolytic reactions ending with the formation of a fibrin network. In addition, there is an intrinsic factor XII-dependent pathway (also called contact pathway) initiated by contact with foreign material, as well as complement-dependent coagulation activation. Excellent reviews of the coagulation pathways in the cascade model, their feedback mechanisms, and the inhibitory reactions can be found in Bauer and Rosenberg (1995), Jesty and Nemerson (1995). The cascade model has a beautiful, logical design and is biochemically correct. However, it fails to explain the rich diversity in the composition of hemostatic clots and thrombi in the organism. Examination of thrombi led to the realization that there is no location in the vasculature where the sequential cascade reactions co-exist. This evidence, along with several other ideas, inspired groups of researchers to turn, in the 1990-s, from "homogeneous" biochemistry towards the study of spatial regulation, compartmentalization, diffusion, and flow on coagulation. The cascade model is now understood to be restricted in applicability to in vitro experiments. Such in vitro experiments for coagulation typically report thrombin concentration evolution in time (Thrombin generation assay—TGA) and are one of the most widely used global assays of hemostasis (Brummel-Ziedins and Wolberg, 2014).

An influential line of thought that proposed that the blood coagulation reactions were spread between different cell types, was the "cell-based model" of hemostasis detailed by Hoffman and Monroe in Hoffman and Monroe (2001), Hoffman (2003). A "reaction–diffusion experimental model" for hemostasis was detailed by Ataullakhanov et al. (1998) and Ovanesov et al. (2002), and a thrombodynamics assay for experimental data collection was proposed in Dashkevich et al.

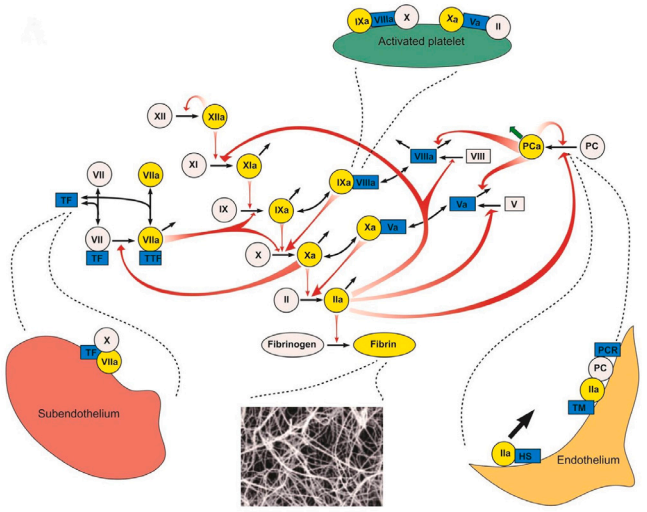

Fig. 4. Hemostasis occurring on different tissue and cell surfaces (Reproduced from Panteleev et al. (2020)). Red arrows denote catalytic activation. Black arrows denote conversion of zymogen to enzyme. Black arrows from enzyme to empty space denote deactivation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(2014). Reviews of the "cell-based model" of hemostasis can be found in Roberts et al. (2006), Hoffman and Monroe (2005). Based on these and other developments in the decade that followed, the description of hemostasis was reviewed by Panteleev et al. (2015) and said to occur in three stages – initiation, spatial propagation, and termination – which occur on different tissue and cell surfaces, which may overlap, and with the flow, transport, and diffusion playing a critical role in linking the distinct stages into a single functional system. The reader is referred to Panteleev et al. (2015) for the details of the description of hemostasis as we refer to here, and the "spatial" terminology used for the stages. A schematic of this description is given in Fig. 4.

The new understanding of hemostasis, in brief, necessitates models that capture spatio-temporal changes influenced by flow, as opposed to temporal changes alone in a well-mixed solution. Accordingly, mathematical and computational models developed alongside may be classified based on the design principles we have noted earlier. We will review these models in the following sections, highlight the more recent ones in greater detail, and explain their physiological significance and insights on hemostasis regulation.

4. Continuum description of blood and constituents

The continuum description of a fluid of interest – whether whole human blood or plasma – is a mathematical construct that assumes that the properties of the fluid (like density or viscosity) can be defined pointwise, and the velocity and stress in the fluid can be defined as field variables in the entire domain occupied by the fluid. This construct is assumed to be a valid description if the Knudsen number, the dimensionless ratio of the molecular/particle mean free path to the representative length of the domain is much less than 1 (of the order of 0.01 or less). The continuum description for plasma gives satisfactory results for flow characterization in blood vessels of diameter/domains of characteristic length > 0.1 mm since plasma consists primarily (92% to 93%) of water, and the size of a water molecule is only about 0.27 nm. However, the continuum description for whole human blood in blood vessels of diameter $\leq$ 0.1 mm is a crude approximation. Satisfactory results can be obtained only in larger diameter blood vessels (say, > 1.0 mm). This is because blood typically consists of $\approx 45\%$ v/v of erythrocytes (which are disc-shaped cells with diameters of 6–8 μm). The continuum description of whole human blood, though widely used, is thus only a first step before its treatment as a medium where erythrocytes are transported in plasma. Fibrinogen and other coagulation factors are considered to be suspended in this continuum. Fibrinogen and coagulation factors consist only around 0.3% by volume of whole human blood. Further, fibrinogen, the largest coagulation protein, has a size of 475 Angstrom. Hence, in blood vessels of diameter > 0.1 mm, the Knudsen number for fibrinogen is exceedingly small, and the continuum assumption for fibrinogen is valid. Thus, blood is assumed to consist of several interacting continua (the coagulation factors) whose volume fractions (and, equivalently, concentrations) are defined pointwise. When modeling platelets as a separate species, it should be noted that platelets are nuclear blood cells that constitute only around 3% of whole human blood. The typical diameter of platelets is 2–3 μm: hence, the Knudsen number for platelets in blood vessels of diameter > 0.1 mm is of the order of 0.01 or less, and the continuum description can approximate platelet transport. However, there are limitations to the continuum description of platelet transport since platelet collision interactions with erythrocytes and their sliding/rolling during adhesion generates complex forces that cannot be captured adequately by just an extra body force term. This has led to the development of models that explicitly account for the particle-nature of platelets (and later, erythrocytes), as we shall describe later in this review.

5. Continuum temporal models

Continuum temporal models are those continuum models which assume that only time changes in concentrations are important. They are suited to describe "homogeneous" biochemical changes involved in hemostasis in a well-mixed system. The earliest mathematical models for hemostasis were continuum temporal models for coagulation alone. These models emerged in the late 1980s and included those of Khanin and Semenov (1989) and Willems et al. (1991). They were sets of Ordinary Differential Equations (ODEs) written in the form:

$$\frac{d[Y_i]}{dt} = G_i \ , \tag{1}$$

where $[Y_i]$ is the concentration of reactant Y_i, G_i represents the net rate of production (by generation and depletion reactions) of Y_i, and t is time.

The most influential of these models was the one proposed by Hockin et al. (2002) (referred to from here on as the Hockin–Mann model), which was an extension of the model of Jones and Mann (1994) to include inhibitors that were integral to coagulation. This model was applied to coagulation in the presence of phospholipid vesicles. A different model consisting of 59 ODEs was proposed by Kuharsky and Fogelson (2001) which described the progress of coagulation reactions in the presence of platelets (not vesicles) in a thin layer and accounted for the effect of flow in a simplified manner by assuming the layer thickness was determined by the flow. They explored the role of binding site densities of TF and various enzymes on platelets and found a threshold response to changes in particular site densities. Bungay et al. (2003) proposed a model consisting of 73 ODEs for coagulation in the presence of lipid surfaces, which incorporated several of the reactions mentioned in the Hockin–Mann model. They aimed to discuss the role of phospholipid availability on coagulation progress, and they predicted that lipid concentration affected how inhibitors modulate thrombin production. Luan et al. (2007) used a model consisting of 92 ODEs to model 92 proteins and 148 protein-protein interactions to show that mathematically-determined points of fragility coincided with clinical data and thus advocated the use of such models for determining therapeutic targets. This kind of approach, called "sensitivity analysis", is a fundamental method of analyzing complex models, particularly models of biological networks. However, the sensitivity analysis methodology is still poorly developed for time-dependent systems. Several other papers carry out sensitivity analyses of blood coagulation, but we shall not discuss them here. Chatterjee et al. (2010a) extended the Hockin–Mann model and developed a model consisting of 76 ODEs to capture

the clot initiation that occurred even in blood treated with a corn-trypsin inhibitor to block the contact pathway. The model of Chatterjee et al. includes a coarse-grained description of platelet activation using a single variable. Integrating platelet signaling reactions is essential to obtain a representative model for in vitro hemostasis, but this can be unwieldy if one uses ODEs due to the large number of equations involved.[1] A convenient method to incorporate platelet signaling is to use data-driven neural networks. Anand et al. (2018) implemented such a method and combined the data-driven platelet calcium calculator of Lee and Diamond (2015) with the large-scale ODE model of Chatterjee et al. (2010a). The combined model was used to predict the relative importance of platelet modulators on thrombin production in blood clotting in vitro. Susree and Anand (2017) developed a purely temporal model for coagulation in the presence of platelets which combined the strengths of the models in Hockin et al. (2002), Kuharsky and Fogelson (2001), Anand et al. (2008): they used the "cascade model". After validation with data from reconstituted (synthetic) plasma, model predictions showed that inhibition of platelet activation by other platelets had a much more significant effect on thrombin production than inhibition of platelet activation by thrombin. Susree et al. (2018) moved away from the "cascade model" to incorporate the localization due to, and the central role of, platelet membrane on thrombin generation described in Monroe et al. (2002), Walsh (2004) as well as the latest hypotheses of "coated" platelets (London et al., 2004), thrombin dose-dependence for coated platelets (Kotova et al., 2008), and competitive binding of coagulation factors on platelet membrane (Podoplelova et al., 2016). Their model predicted a significant delay in the onset of peak Va production and thrombin production when dose dependence is incorporated instead of a fixed theoretical maximum percentage of coated platelets.

The above models contain a large number of kinetic reaction constants which varies based on the number of reactions and the corresponding reaction mechanisms. Since these models are deterministic, this raises the question of how accurate their results are if there is measurement uncertainty in the parameters. Some parameters of blood coagulation are known pretty well, while others have a wide range of uncertainty. The latter is particularly true for membrane-dependent reactions of blood coagulation which are known to depend on the phospholipid concentration and composition (Panteleev et al., 2006a). However, thorough validation at different levels (Shibeko and Panteleev, 2016) and robustness of the blood coagulation network (Kuprash et al., 2018) allows the use of these models for reliable predictions.

The coagulation network produces the enzyme thrombin in its penultimate stage: thrombin activates platelets and finally produces fibrin monomers that polymerize into a fibrous gel that stabilizes the clot. This last step of coagulation is quite complex, and the vast majority of the models mentioned above did not include it or included it in a simplified form. The earliest models for fibrin polymerization include those developed by Naski et al. (1991) and Weisel and Nagaswami (1992). The Naski-Shafer model was a kinetic model for α-thrombin catalyzed conversion of fibrinogen to fibrin in the presence of antithrombin III at pH 7.4 and 37 °C. It consisted of 8 ODEs with kinetic parameters obtained from the literature for the individual reactions in the model. The model provided a method to estimate the concentration of α-thrombin required to produce a clot of known composition. Weisel and Nagaswami considered fibrin polymerization to consist of three steps: "(a) the cleavage of the A fibrinopeptides by the enzyme thrombin; (b) association of fibrin monomers to form two-stranded protofibrils; and (c) aggregation of protofibrils to produce fibers which cross-link to yield a gel". These changes were reflected in the development of clot turbidity and were effectively captured by a kinetic model consisting of 4 ODEs. Lobanov et al. (2011) proposed a more detailed model consisting of 12 ODEs for fibrin formation, polymerization, and aggregation by including additional stages involving the formation of complex aggregates, polymer scaffold formation and gelation, and scaffold thickening. The model was able to predict the total length of fibrin polymer fibers per unit volume, and it can be used to determine the position of the border between the gel and the liquid region. Andreeva et al. (2018) combined the models in Susree and Anand (2017), Lobanov et al. (2011) to come up with a comprehensive model for coagulation followed by fibrin polymerization and gelation. This model predicted that clot formation is insensitive to initial concentrations of f-VII/f-VIIa: a hypothesis supported by medical observations (de Moerloose et al., 2016).

6. Continuum spatio-temporal models

Continuum spatio-temporal models for hemostasis were first proposed in the mid-1990s when research focus shifted from the biochemistry of coagulation to its regulation in space and time (Panteleev et al., 2015). The initial models in this category neglected the role of flow. They consisted of reaction–diffusion equations described by partial differential equations (PDEs) (In contrast to continuum temporal models characterized by ODEs). These PDEs were written in the form:

$$\frac{\partial [Y_i]}{\partial t} = D_i \frac{\partial^2 [Y_i]}{\partial x^2} + G_i \ , \tag{2}$$

where $[Y_i]$ is the concentration of reactant Y_i, D_i is the diffusion coefficient governing its motion in the absence of flow, G_i represents the net rate of production (by generation and depletion reactions) of Y_i, and t, x are time and space (1-dimension) variables, respectively.

The earliest spatio-temporal model was that of the Ataullakhanov group (Zarnitsina et al., 1996a,b). This model was for coagulation due to the contact pathway alone in unstirred systems and consisted of 8 PDEs. Panteleev et al. (2006b) developed a spatio-temporal model for hemostasis consisting of 27 PDEs: the model incorporated the extrinsic pathway, the understanding of coagulation at that time (the "cell-based model" described in Hoffman and Monroe (2001)) as well as competitive binding of fXa and fIIa on activated platelets. The model predicted that the intrinsic pathway regulated spatial propagation of coagulation while the Protein C pathway facilitated the localization of coagulation. Anand et al. (2008) developed a spatio-temporal model for hemostasis consisting of 23 PDEs which, while based on the "cascade model", was the first to include equations for fibrinolysis and was able to quantitatively predict the effects of antithrombin III (ATIII) deficiency and Protein C (PC) deficiency. Zhalyalov et al. (2017) later developed a spatio-temporal model for hemostasis by combining the model for coagulation in Ovanesov et al. (2002) with equations for fibrinolysis that were of greater detail than those in Anand et al. (2008). Their model includes plasminogen in Glu- and Lys- forms, and plasmin—all three in fibrin-bound form, α2-macroglobulin and plasminogen activator inhibitor-1 (PAI-1). Simulations revealed that fibrin formation was the rate-limiting step in the fibrinolysis front. Additionally, tissue plasminogen activator (tPA) at high concentrations increased lysis onset time and decreased lysis propagation velocity. Kuprash et al. (2018) compared spatio-temporal clot formation in a 1D region over a TF-coated surface and a control sample of "homogeneous" clot formation both experimentally and computationally using a model derived from the one in Zhalyalov et al. (2017). They thus investigated the sensitivity of hemostasis to coagulation factor deficiencies. They found that the velocity of spatial clot propagation correlated linearly with the concentration of thrombin at the clot wavefront but not with overall thrombin wave amplitude. Further, spatial clot growth in normal plasma was neither reaction nor diffusion limited in the early stages but became diffusion-limited later.

None of the above models account for the effects of flow; we now list some important continuum spatio-temporal models which include flow.

[1] The model of Purvis et al. (2008) for adenosine diphosphate (ADP)-mediated signaling of platelets has 77 reactions.

Integrating flow with the reaction–diffusion equations proposed for hemostasis is done in a continuum framework by writing convection–diffusion–reaction equations to govern the flow and transport of the species involved in coagulation and solving them along with the equations for mass and momentum balance of the suspending medium (blood or plasma). The suspending medium is described by a suitably chosen constitutive model that specifies its Cauchy stress tensor. This is implemented as given below.

The governing equation(s) for the species involved in coagulation are:

$$\frac{\partial [Y_i]}{\partial t} + div([Y_i]\mathbf{v}) = D_i \Delta [Y_i] + G_i \ ; i = 1 \cdots n \ . \tag{3}$$

Here, the symbols Y_i, D_i, G_i have the same meaning as that in Eq. (2), $div()$ is the (Eulerian) divergence operator, $\mathbf{v}$ is the velocity of the suspending medium, and Δ denotes the Laplacian operator.

The equations for balance of mass, linear momentum, and angular momentum that need to be solved alongside to obtain $\mathbf{v}$ are, respectively,

$$\frac{\partial \rho}{\partial t} + div(\boldsymbol{\rho}\mathbf{v}) = 0 \ , \tag{4}$$

$$\rho \frac{D\mathbf{v}}{Dt} = div\mathbf{T} + \rho\mathbf{b} \ , \tag{5}$$

$$\mathbf{T} = \mathbf{T}^T \ . \tag{6}$$

Here ρ is the density of the suspending medium, $\mathbf{T}$ is the Cauchy stress tensor of the suspending (fluid) medium and $\mathbf{b}$ denotes the body force field. Further, $\frac{D}{Dt}$ is the Lagrangian time derivative expanded as $\frac{\partial}{\partial t} + grad(.)\mathbf{v}$ where $grad$ is the (Eulerian) gradient operator.

The Cauchy stress tensor for the fluid is given by:

$$\mathbf{T} = -p\mathbf{1} + \mathbf{S}, \tag{7}$$

where p is the Lagrange multiplier introduced to enforce the constraint of incompressibility, and $\mathbf{S}$ is the extra stress tensor. Different representations for $\mathbf{S}$ allow one to select an appropriate constitutive model for the fluid. The generalized Newtonian fluid is one where

$$\mathbf{S} = 2\mu(\mathbf{D})\mathbf{D}. \tag{8}$$

Here $\mathbf{D}$ denotes the symmetric part of the velocity gradient as in

$$\mathbf{D} = \left(\frac{\mathbf{L} + \mathbf{L}^T}{2} \right) ; \tag{9}$$

$$\mathbf{L} = grad(\mathbf{v}). \tag{10}$$

If μ is not a function of $\mathbf{D}$, i.e., it is a constant, then the constitutive model is that of the classical Navier–Stokes fluid. In the generalized case $\mu(\mathbf{D})$ is given by a function which captures the shear-thinning viscosity of blood in terms of $\dot{\gamma} = \sqrt{2tr(\mathbf{D}^2)}$. The viscoelastic nature of blood is incorporated, usually by a Maxwell model or by an Oldroyd-B model, by representing the extra stress tensor in the following ways, respectively:

$$\mathbf{S} + \lambda_1 \overset{\nabla}{\mathbf{S}} = 2\mu\mathbf{D} \ , \text{or} \tag{11}$$

$$\mathbf{S} + \lambda_1 \overset{\nabla}{\mathbf{S}} = 2\mu\left[\mathbf{D} + \lambda_2 \overset{\nabla}{\mathbf{D}}\right] \ . \tag{12}$$

Here λ_1 represents the relaxation time, $\overset{\nabla}{\mathbf{S}}$ is the upper-convected Oldroyd derivative given by

$$\overset{\nabla}{\mathbf{S}} = \frac{D\mathbf{S}}{Dt} - \mathbf{L}\mathbf{S} - \mathbf{S}\mathbf{L}^T \ , \tag{13}$$

and λ_2 is the retardation time ($<\lambda_1$). The above equations assume that μ is a constant; incorporating variable viscosity is simply a matter of selecting $\mu(\mathbf{D})$ as we did in the generalized Newtonian case. Reviews of various constitutive models for blood can be found in Fasano and Sequeira (2017), Anand and Rajagopal (2017).

We first list the models that deal with only platelet deposition and aggregation in flow, and then proceed to models that also include coagulation reactions; in each class, we first list those models that approximate blood as a Navier–Stokes fluid (of constant viscosity) before listing those that model blood as a non-Newtonian fluid. This arrangement is based on the aspects of hemostasis we consider as determining the complexity of models in this class.

The first model consisting of convection–diffusion–reaction equations for hemostasis in the presence of flow was that of Basmadjian (1990) who presented closed-form solutions under various simplifying assumptions (where the equations reduce to convection–diffusion equations). Sorensen et al. (1999a,b) proposed a set of coupled convection–diffusion–reaction equations involving the transport and reactions of 7 components (that they believed were crucial to platelet activation and deposition) in flowing human blood modeled as a Navier–Stokes fluid. Their model was able to predict the deposition of platelets for parallel-plate Poiseuille flow of blood over collagen at high and low shear rates. Storti and van de Vosse (2014) used the equations of Sorensen et al. (1999a) to track the growth of the platelet plug in the flow of a Navier–Stokes fluid. They modeled the platelet aggregate (clot) as an elastic neo-Hookean solid and incorporated fluid–structure interaction. In this, the stress within the fluid is transmitted to the platelet plug and produces a displacement, and the final deformed plug is used to determine the extent of the fluid domain at the next time step. They then used a finite element method to determine the solution for both low and high shear rates and varying shear moduli of the plug. Wu et al. (2017) extended the model in Sorensen et al. (1999a) to include three more categories of platelets and simulated growth of a thrombus in the flow of a Navier–Stokes fluid using a set of 10 convection–diffusion–reaction equations allowing for irregular thrombus shape, alteration of flow field due to the growth of the thrombus, and thrombus embolization due to shear. These extensions are important when simulating blood flow over blood-wetted devices. The authors presented illuminating results for thrombus growth on an injured blood vessel in vivo and in a micro-crevice in vitro. Taylor et al. (2016) assessed that increasing number of species/complexity would increase computational costs, especially in complex geometries. They developed a reduced model for device thrombosis consisting of 3 convection–diffusion–reaction equations for transport of activated/non-activated platelets and ADP in a Navier–Stokes fluid. This was done by making major modifications – inclusion of mechanical platelet activation, and a Brinkman term (like that in Leiderman and Fogelson (2011), see below) which included the effect of local platelet aggregation – to the model originally proposed by Fogelson (1992). After validation, predictions from the model correctly identified the locations of thrombus deposition during the flow of human blood in an in vitro flow cell of expansions and contractions; this makes the model a promising tool for device-induced thrombosis. Du et al. (2020) developed a two-phase continuum model for platelet aggregation in flowing blood (modeled as a Navier–Stokes fluid) which included five convection–diffusion–reaction equations to track the progress of platelet aggregate formation. The uniqueness of their work lies in the modeling of the platelet aggregate (thrombus) as a porous viscoelastic fluid; relative motion between thrombus and blood produces a drag force that they exert on one another. Further, and more importantly, the growth of the aggregate is affected by the rate at which the bonds between platelets form or break, with the latter being determined by a strain-sensitive bond-breaking rate function. The model was used to simulate the growth of a thrombus in a straight tube of the size of a coronary artery under corresponding flow conditions, and various hypotheses were explored; for instance, a high shear rate was found to limit the thrombus growth into the vessel lumen.

Leiderman and Fogelson (2011) proposed a detailed set of convection–diffusion–reactions to model hemostasis (coagulation with platelet aggregation) in flowing blood modeled as a Navier–Stokes fluid. This model carefully extended the model of Kuharsky and Fogelson (2001) to incorporate spatial variations: four classes of platelets

were tracked, and chemical species were classified into those that diffused and were advected with the flow and those that were immobile by being bound to the subendothelium or platelets. Simulations for thrombus growth in a two-dimensional (2D) domain showed that increasing shear rate led to increased platelet deposition (and thrombus growth) only if inlet platelet distribution was non-uniform (with pronounced near-wall excess of platelets). Results also showed that the density of bound platelets within the thrombus was highest when near-wall platelet concentration increased (whether due to shear rate or not). This work was extended by Leiderman and Fogelson (2013) to study the effect of hindered transport of proteins within the thrombus, and results showed that hindrance led to a smaller thrombus with a less dense outer shell as one would expect. Rojano et al. (2018) developed a model which included the reactions of the contact pathway and critical coagulation reactions (a total of 26) from the model in Chatterjee et al. (2010a). This model consisted of convection–diffusion–reaction equations for coagulation during the flow of a Navier–Stokes fluid. Unlike the model in Leiderman and Fogelson (2011), this model did not prescribe a finite injury zone but instead developed a boundary condition suitable for use in devices where the entire surface can trigger the contact pathway. Simulations for the flow of bovine blood over a backward-facing step configuration (encountered in many medical devices) showed that the region with higher concentrations of total thrombin aligned well with the experimental data.

Anand et al. (2003) built on the framework of Sorensen et al. (1999a) and posited an integrated framework for the study of hemostasis accompanied by clot lysis in flowing blood. The framework included thermodynamically robust shear-thinning viscoelastic fluid continuum models for blood (Anand and Rajagopal, 2004), for the clot (Anand et al., 2006), along with a set of reactions for 27 species involved in coagulation, platelet activation and aggregation, and fibrinolysis. As a preliminary study, the shear-thinning viscoelastic fluid models were used along with an activation criterion (based on prolonged exposure to shear stress) to obtain results for the moving boundary problem of radial (1D) clot growth from the wall of a cylindrical pipe into flowing blood. These showed a decrease in amplitude of average velocity as the clot grew and the presence of high shear stress in the clot region. The numerical simulation of this framework of models was attempted by Sequeira and co-workers: first in a simplified manner by Bodnar and Sequeira (2008), and later with the complete framework (but neglecting platelets) by Sequeira and Bodnar (2014). The results for flowing human blood over a region of injury in a straight cylindrical tube showed fibrin concentration growing on top of the injury and decreasing away from the injury. Correspondingly, velocity magnitude decreased and later recovered. Fasano et al. (2013) reduced the model in Anand et al. (2008) to capture only the changes in the "propagation phase" of the "cell-based model" of hemostasis and included platelets and the effect of blood slip at the vessel wall. Pavlova et al. (2015) determined the coefficients required in this reduced model by validating it with the results in Anand et al. (2008), and performed preliminary simulations for hemostasis and clot lysis in flowing blood (modeled using the shear-thinning Cross model) in a 2D domain: these showed that slip enhances the amount of fibrin produced and the thrombin burst occurs sooner when slipping is included. These results were reiterated in the three-dimensional (3D) simulations reported by Pavlova et al. (2016). A review of these articles was given by Anand and Rajagopal (2017).

It was recognized that solving a large set of PDEs was expensive and non-trivial. To simplify the equations and yet capture the spatio-temporal variations during hemostasis, Chen and Diamond (2019) assumed, in like manner to Kuharsky and Fogelson (2001), that coagulation reactions are restricted to a well-mixed thin film (15 μm-thick) above collagen- or tissue factor-bearing surface. They reduced the number of equations for coagulation to 8 ODEs but also excluded platelet aggregation. The zymogen concentrations in the thin film core are identical to those in the plasma flow. They then assumed that the transport of these zymogens and thrombin (generated in the clot core) in the outer plasma is modeled by convection–diffusion equations (presumably in a constant viscosity Navier–Stokes fluid, since this is not mentioned). The model simulations over 800 s showed "cascade amplification" from 30 pM levels of intrinsic tenase to 15 nM prothrombinase to 15 μM thrombin to 90 μM fibrin; factor XIa pathways contributed significantly after 500 s. This reduced model was proposed for use as a supplement to more complex models which incorporated platelet aggregation like those that are discussed in the next section.

In summary, continuum spatio-temporal models are classified into those that describe hemostasis in unstirred systems and those that describe hemostasis in the presence of flow. The former is very useful to examine the regulatory mechanisms of hemostasis in suitably designed experimental set-ups, and models in this class continue to be proposed. The latter is used to predict thrombus size, morphology, and embolization in flowing blood, usually in idealized geometries of arteries and veins (diameter >1 mm). This is especially useful in designing blood-wetted devices like stents, ventricular assist devices, and total artificial hearts. While many models in this class assume blood to be a constant viscosity Navier–Stokes fluid, models that accurately capture the biochemistry *and* the mechanics of hemostasis are tools of much greater value. Admittedly, advanced mechanics necessitate additional investment in advanced numerical techniques and computing power. It is envisaged that the future will see more simulations of hemostasis in the presence of flow.

7. Discrete-continuum spatio-temporal models

Discrete-Continuum models for hemostasis in the presence of flow emerged in the mid-2000s. These models use diverse particle tracking methods to track the cellular-level interactions and movement of platelets (and, if feasible, erythrocytes) in combination with models for the coagulation network (which capture changes at the continuum level) in flowing blood (or plasma, as per the case) modeled as a continuum. Initially, such models were developed for platelet adhesion and aggregation alone with continuum models for platelet activators (but not the coagulation network) in flowing blood. We will mention some of these models for the sake of completeness, but our focus will be on models for hemostasis and thrombosis, i.e., those that include coagulation. When these models were formulated, it was recognized that the effect of the growing thrombus on the flow and the flow on the thrombus needed to be coupled; further, the structures of the thrombi required to be captured accurately. These models offer significant advantages over continuum models in this aspect as they capture inter-cell interactions and thrombus rupture, which the continuum models can only do simplistically.

The early Discrete-Continuum models were proposed for platelet adhesion and aggregation with platelet activators alone in flowing blood and were those of Pivkin et al. (2006) and Fogelson and Guy (2007). The former modeled blood as a Navier–Stokes fluid and included a body force term in the momentum balance equations that captured all platelets' interactions. Platelet motion and aggregate formation were tracked by updating the position of all platelets at each time step. The latter used an Immersed Boundary (IB) method in which platelet interactions with blood and the vessel wall were tracked in a Lagrangian framework, while the Navier–Stokes equations were solved for blood flow in an Eulerian grid. They also explained how to include convection–diffusion–reaction equations for platelet activators in their method. Preliminary results were presented for the growth of small platelet aggregates in 2D and 3D flow and were consistent with intuition. The IB method described in Fogelson and Guy (2007) is briefly reproduced here for the sake of clarity.

The IB method adapted for platelet deposition and aggregation in Fogelson and Guy (2007) "represented each platelet and vessel wall as an IB object (i.e., as a collection of elastically linked Lagrangian points that each move at the local fluid velocity)". Elastic links are created as and when platelets adhere to the wall or to one another.

This structure of links exerts forces on the surrounding fluid to resist breakage. The novel features of the paper are the incorporation of mechanical interaction of platelets with fluid and vessel wall, and the platelet's detection of, and response to, activating stimuli. In the implementation, the mass balance equation for an incompressible fluid given by

$$div(\mathbf{v}) = 0 \ , \tag{14}$$

and the Navier–Stokes equations given by

$$\frac{\partial \mathbf{v}}{\partial t} + grad(\mathbf{v})\mathbf{v} = \frac{1}{\rho}\left[-grad(p) + \mu\Delta\mathbf{v} + \mathbf{f}\right] \ , \tag{15}$$

are solved on a Cartesian grid placed over the flow domain Ω. Here, $\mathbf{v}(\mathbf{x},t)$ is the velocity field, $p(\mathbf{x},t)$ is the pressure field, μ is the (constant) viscosity, and Δ is the Laplacian operator (as mentioned previously). The term $\mathbf{f}(\mathbf{x},t)$ represents the force density arising due to the elastic deformation of the immersed membrane/boundary. A second (Lagrangian) grid of points is used to discretize the platelets. The elastic force on the membrane point q which occupies the location $\mathbf{X}(q,t)$ at time t is given (per unit q) by

$$\mathbf{F}(q,t) = \mathbf{F}\big(\mathbf{X}(q,t), \mathbf{X}_q(q,t)\big) \ . \tag{16}$$

The force density on the fluid $\mathbf{f}$ is obtained from the IB force density $\mathbf{F}$ as follows:

$$\mathbf{f}(\mathbf{x},t) = \int \mathbf{F}(q,t)\delta\big(\mathbf{x} - \mathbf{X}(q,t)\big)dq \ . \tag{17}$$

The δ function given above is approximated by smooth, localized functions to ensure that $\mathbf{f}$ is non-zero only for points close to the immersed boundary. The movement of the IB (and thus the Lagrangian grid) is calculated by assuming that the velocity of the IB point is the same as that of the fluid at the same location. This is expressed as

$$\frac{\partial \mathbf{X}(q,t)}{\partial t} = \int_{\Omega} \mathbf{v}(\mathbf{x},t)\delta\big(\mathbf{x} - \mathbf{X}(q,t)\big)d\mathbf{x} \ . \tag{18}$$

In this equation, the δ function ensures that the velocity of each IB point is a weighted average of the fluid velocity at grid points near that IB point. In addition to the above equations, platelet activation can be tracked with an 'activation flag' which reflects the platelet's exposure to supra-critical concentration of activator chemical (ADP or Thrombin or both). The transport of the activator chemical(s) is modeled by convection–diffusion–reactions of the form in Eq. (3) which can be solved on the Cartesian grid along with the mass balance and Navier–Stokes equations.

Xu et al. (2008) were the earliest to propose a Discrete-Continuum model that included coagulation reactions. They described the transport and aggregation of platelets and erythrocytes using a discrete stochastic Cellular Potts Method (CPM) in the 2D flow of plasma (modeled correctly as a constant viscosity Navier–Stokes fluid); a point-level description of coagulation reactions, taken from the homogeneous model of Jones and Mann (1994), was used. The methodology is briefly explained below, and is derived from the description given in Xu et al. (2008); the reader can get additional details therein.

The plasma flow is modeled using the balance of mass equation for an incompressible fluid, (Eq. (14)) and the Navier–Stokes equations (Eq. (15)) where the term $\mathbf{f}$, in this case, is the force density field due to cohesion of activated platelets (which is exerted on the plasma). The equations are solved using a finite-difference method on a fixed grid. Platelets and erythrocytes are transported as discrete particles in the plasma flow using CPM. CPM is "a cell-level, energy minimization lattice model which uses an effective energy 'E' coupled to external fields to describe the dynamics of formation of the inhomogeneous internal structure of the thrombus" (Xu et al., 2008). In this case, the external field is the concentration of diffusing thrombin produced due to the coagulation reactions. The CPM in their paper consists of seven types of cells, namely three types of platelets, erythrocytes, plasma, vessel wall, and injury surface. The CPM is implemented on a spatially superimposed lattice on top of the finite-difference grid used for the plasma flow.

Since solving the equations for all coagulation species using convection–diffusion–reaction equations would be computationally expensive, the authors solve the ODEs for coagulation (in the form of Eq. (1)) listed in Jones and Mann (1994) only on the surface of the platelets. The thrombin produced, however, is convected within the domain with the plasma. Thrombin transport is given by

$$\frac{\partial \theta}{\partial t} + grad(\theta)\cdot\mathbf{v} = D_\theta \Delta\theta + \sum_{i=1}^{N} Y\theta_i \ , \tag{19}$$

where θ is the concentration of thrombin, D_θ is the diffusion coefficient of thrombin, N is the number of cells, and $Y\theta_i$ is the thrombin generated by the ith activated platelet.

The solution procedure is as follows. The thrombus-plasma interface is first retrieved from the CPM lattice at a given time step. The balance of mass ((Eq. (14)), the Navier–Stokes equations (Eq. (15)), the equation for thrombus transport (Eq. (19)) and coagulation reactions are then solved to obtain the flow and species distributions. This is used to update the CPM lattice of cell positions, types, shapes, and cell production of species. The updated CPM data of interface geometry and species concentrations yield new boundary and initial conditions for the continuum model. The simulations predicted that erythrocytes are trapped in thrombi during formation (as suggested by experimental data); dependence of thrombus growth rate on blood flow rate was also close to that observed experimentally. Xu et al. (2009) used a simpler model for the biochemical reactions, namely the one in Sorensen et al. (1999a), with the same CPM method for seven cell types and found that increase in flow rates leads to greater structural heterogeneity of the clot. Xu et al. (2010b,a) extended the model in Xu et al. (2008) by considering the blood clot as a porous material, and used the more comprehensive Hockin–Mann coagulation model (Hockin et al., 2002) along with platelet-binding reactions from Kuharsky and Fogelson (2001) for the biochemical reactions. They showed that low levels of factor VII result in a significant delay in thrombin production consistent with experimental data. Sweet et al. (2011) used the method of Subcellular Elements (SCE) instead of the CPM to model the blood cell particle(s) and the interaction of the fluid atoms with the particle structures. These and other Discrete-Continuum models were reviewed in Xu et al. (2012).

Flamm et al. (2009) extended a stochastic method for particle dynamics known as the kinetic Monte Carlo method to study problems involving both convection and diffusion: this method is termed the lattice kinetic Monte Carlo method (LKMC) by the authors. The LKMC method resolves particles (in this case, platelets) on a lattice just like the CPM. It can be used to simulate platelet transport in the fluid (human blood modeled as a Navier–Stokes fluid of viscosity 3cP) and aggregation to surface collagen or deposited platelets. The authors combined this method with the finite element method to predict concentration boundary layers of ADP and thromboxane (TXA_2) released from activated platelets (agonist transport was modeled by convection–diffusion–reaction equations); platelet activation kinetics was obtained from the neural network model of Chatterjee et al. (2010b) trained for platelets stimulated in dilute platelet-rich plasma. Finally, the velocity field of blood with the growing thrombus included was determined using the lattice Boltzmann method. Preliminary results were reported by Flamm and Diamond (2012), and more detailed results were reported in Flamm et al. (2012).

Filipovic et al. (2008) pioneered the use of the stochastic Dissipative Particle Dynamics (DPD) method to model the transport of plasma and platelets and used the continuum convection–diffusion–reactions *for the platelet activators alone* listed in Sorensen et al. (1999a) (velocity field obtained using a constant viscosity Navier–Stokes fluid). The method implemented in Filipovic et al. (2008) is briefly explained here and is largely derived from the description therein. The reader is encouraged to refer to their article for additional details.

In DPD, "the colloidal fluid components (plasma and platelets) are discretized by mesoscopic (micrometer-size) particles that move according to Newton's second law". These discrete 'soft' fluid particles replace the continuum description. Unlike the molecular dynamics approach where atomic-level analysis is required, such analysis is not needed here since the particles are much larger than atoms and can be tracked. The motion of the DPD particle is described by

$$m_i \dot{\mathbf{v}}_i = \sum_j (\mathbf{F}_{ij}^C + \mathbf{F}_{ij}^D + \mathbf{F}_{ij}^R) + \mathbf{F}_i^{ext} \ . \tag{20}$$

In the above equation, m_i is the mass of the particle i and $\dot{\mathbf{v}}_i$ is the acceleration of the particle. Additionally, $\mathbf{F}_{ij}^C$, $\mathbf{F}_{ij}^D$, and $\mathbf{F}_{ij}^R$ are the conservative (repulsive), dissipative and random (Brownian) interaction forces that particle j exerts on particle i, and $\mathbf{F}_i^{ext}$ is the external force on particle i (either due to the pressure gradient or gravity). The key addition in the DPD method in Filipovic et al. (2008) is the attractive force, $\mathbf{F}_{ij}^a$, used to incorporate platelet adhesion to the vessel walls; this force is parametrized by an "effective bond stiffness" k_{bw}.

The implementation involves first solving the convection–diffusion–reaction equations (of the type in Eq. (3)) for platelet activators . This is then used to scale $\mathbf{F}_{ij}^a$ by a factor between 0 and 1 depending on the concentration; the factor of one is for the maximum activator concentration. The DPD simulation is then performed for plasma flow (without platelets). Once a steady flow is achieved, DPD platelet particles are introduced, their displacements calculated, and the platelets that adhere to the wall are identified. The value of k_{bw} is adjusted until the results of simulations fit the data for in vitro platelet deposition on a collagen surface in a tubular chamber. Tosenberger et al. (2013) combined the DPD method for plasma and platelets with a single convection–diffusion–reaction equation for fibrin concentration to study thrombus growth during 2D flow in a channel. The model accounted for clot growth by initial weak attachment of platelets to the clot and later strengthening due to platelet adhesion. Fibrin mesh is formed inside the clot, which the flow does not penetrate. The model simulations predicted that the growth of a hemostatic plug could stop due to its exterior part being removed by the flow, thus exposing its non-adhesive core to the flow. Bouchnita and Volpert (2019) used an immersed boundary method to track the movement and aggregation of platelets along with eight convection–diffusion–reaction equations for coagulation, and a Navier–Stokes fluid model for blood and applied the framework to simulate thrombus formation in both arterial and venous flow conditions.

Yazdani et al. (2017) tracked the motion of platelets (modeled as rigid spherical particles) using a Lagrangian framework in the flow of blood (modeled as a constant viscosity Navier–Stokes fluid) which was solved on a fixed Eulerian grid along with the convection–diffusion–reactions for coagulation from Anand et al. (2008). They calibrated their model (without the coagulation reactions) with relevant experimental data for platelet aggregation over a wide range of shear rates. They then included the coagulation reactions and simulated thrombus formation in arteriole-sized vessels: they found a good match with experimental data, thus demonstrating the method's promise. In a recent article, an extended group of researchers comprising Yazdani et al. (2021) proposed and validated a comprehensive Discrete-Continuum model integrating blood cell mechanics in addition to platelet adhesive dynamics and the coagulation cascade for thrombus formation in the plasma flow. Their model comprised of the DPD method for plasma, the transport DPD method for the convection–diffusion–reactions for coagulation proteins taken from Anand et al. (2008),[2] the DPD method for erythrocytes including mechanical properties obtained from experiments, and the same DPD method for platelets as rigid cells by taking sufficiently large mechanical properties. This model was used to simulate platelet adhesion in normal and diabetic blood. Results showed that the altered mechanical properties of erythrocytes and platelets in diabetic blood lead to enhanced margination of platelets promoting enhanced platelet adhesion to the vessel wall. In contrast, modified coagulation protein concentrations lead to enhanced fibrin: these suggest a basis to interpret the enhanced prothrombotic status of Type 2 diabetes mellitus patients.

In summary, Discrete-Continuum spatio-temporal models (also known as hybrid models) are a more recent class of models developed to provide further insight into thrombus structure, their interaction with the flow field, and the manner of embolization. Point-wise detail of the fluid flow and the structures formed cannot be obtained. The computational cost of the DPD method is much higher owing to the large number of particles that need to be incorporated, and the CPM method is more efficient than the DPD method in this aspect. However, it is limited in describing cell properties (elasticity and shape) (Sweet et al., 2011). While initially restricted to platelet adhesion and aggregation with platelet activators in plasma, these models have been expanded to include erythrocytes and the coagulation network with varying levels of complexity, as we have detailed above. These methods show promise in testing or verifying experimental data using microfluidic systems where the continuum description has limited applicability.

8. Discussion

We have briefly listed the scientists and discoveries that contributed to the understanding of blood clotting from ancient times up to the present day. We then reviewed some essential mathematical/computational models for hemostasis and thrombosis, based on the complexity of design, developed since the late 1980s. The models are organized into those that are Continuum temporal, Continuum spatio-temporal without flow, Continuum spatio-temporal with the flow, and Discrete-Continuum spatio-temporal with the flow. We have also explained their physiological significance and their insights into the regulation of hemostasis. While by no means exhaustive or comprehensive, we have covered many influential models used to propose hypotheses, which integrate more aspects of this complex phenomenon or give greater insight into the cell-level detail of thrombi and the manner of their rupture. These models enable the generation of increasingly accurate in-silico predictions that can guide the planning of experiments, identify novel reaction mechanisms, help select targets for drugs, predict the effect of coagulation anomalies, and aid the design of diagnostic assays as well as of biomedical devices.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank the anonymous referees for their comments which significantly enhanced the detail and visual appeal of the manuscript. MAP was supported by grant 20-45-01014 of the Russian Science Foundation.

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