Computational Biomechanical Modeling of Fibrin Networks and Platelet-Fiber Network Interactions

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Keywords: Computational model, fibrin mechanics, platelet, blood clot, thrombus, deformation, contraction, hemostasis, thrombosis.

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Highlights:

- Multiscale models are needed to describe fibrin mechanics, deformation and contraction.
- Role of biomechanical interactions between platelets and fiber networks in blood clot stretching and contraction models.
- Models predicted that local strain-stiffening of individual fibers and pairwise interactions between individual fibers contribute to mechanical responses of fibrin networks undergoing stretching or contraction.
- Open problems and challenges: study of microscale mechanisms of lateral aggregation of protofibrils and of the structure of fibrin fibers, detailed description of fibrin-fluid

interactions; coupling of submodels at different space and time scales into a multiscale model and its calibration; experimental verification of multiscale model predictions.

Abstract

Fibrin deformation and interaction of fibrin with other blood components play critical roles in hemostasis and thrombosis. In this review, computational and mathematical biomechanical models of fibrin network deformation and contraction at different spatio-temporal scales as well as challenges in developing and calibrating multiscale models are discussed. The long-standing challenges include careful evaluation of the applicability of models to identify and test potential mechanisms of the biomechanical processes mediating interactions between platelets and fiber networks in blood clot stretching and contraction. Also, there is a need to use modeling approaches to determine how exactly structural and mechanical properties of major blood clot components can influence biomechanical responses of the entire clot subjected to external forces, such as blood flow or vessel wall deformations.

1. Introduction

Through in vivo, *in vitro*, and *in silico* studies, significant progress have been made in developing a better understanding of the role of fibrin fiber networks in, among others, halting bleeding (hemostasis) and the development of obstructive pathological blood clots impairing blood flow (thrombosis)[1–3]. The latter can be associated with various disorders such as cardiovascular disease, cancer and viral diseases including COVID-19 [4–6].

The fibrin fiber network, an end product of the enzymatic cascade of blood clotting, is a proteinaceous polymer present in intra- and extravascular blood clots that forms at the sites of vascular injury and serves as scaffolding for blood clots [7] (see **Figure 1A-B**). Fibrin fibers and

fiber networks are the results of the conversion of fibrinogen into fibrin monomers and their consequent polymerization. Although this review does not focus on discussing modeling of polymerization of fibrin to form a network of fibrin fibers, this process has been extensively studied both experimentally [8–10] and through computational modeling [11–15].

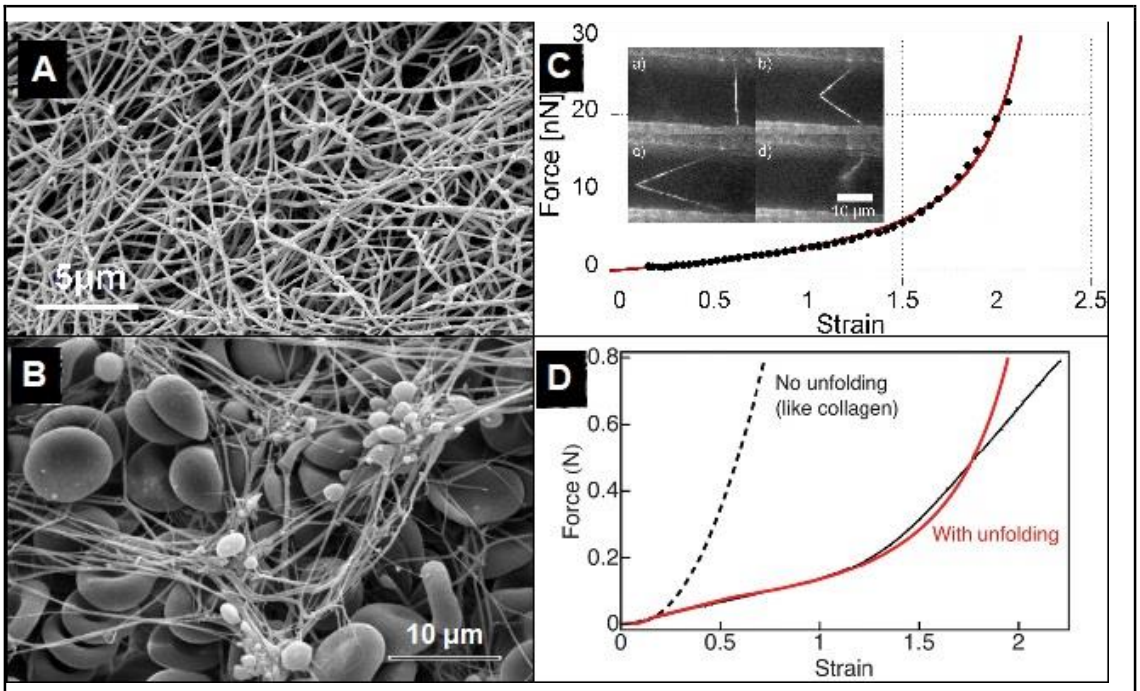

Figure 1. Electron microscopy images of (A) unperturbed fibrin clot (reproduced from [16], with permission) and (B) whole blood clot. (Reproduced from [7], with permission.). (C) Force-strain curve for single fibrin fiber: inset (a)–(d) single fibrin fiber at different levels of strain before breakage (d) stretched using an atomic force microscopy (AFM) tip. In the plot, single fibrin fiber force-strain data (black dots) were obtained via AFM measurements. The fitting (red curve) was done using the worm-like-chain (WLC) equation. (Reproduced from [17], with permission.) (D) Force-extension curve of a cylindrical fibrin clot. The force-extension curve (black solid line) was fitted using two versions of a constitutive model that considers clot microstructure. The best agreement is obtained when protein unfolding is included (red line), while without molecular unfolding (black dashed line) the fitting only reproduces the experimental results (black solid line) for low strains. (Reproduced from [18], with permission.)

(For a more detailed review on the structure and function of fibrin and fibrinogen see [19].) Individual fibrin fibers reveal extraordinary extensibility and viscoelasticity, referred to as strain-stiffening, which are important for fibrin biological functions [16] (see **Figure 1C-D**).

As a major component of the extracellular matrix, fibrin participates in various cellular processes, including adhesion, migration, proliferation, differentiation, wound healing, angiogenesis, inflammation, and others. The formation of fibrin networks in blood vessels is one of the key events contributing to hemostasis and thrombosis [8,20]. Fibrin networks of *in vivo* blood clots are subjected to various mechanical forces including external forces generated by blood flow and deformation of the vessel wall, as well as internal forces generated by platelets within a clot [9]. Activated platelets attach to fibrin via their αIIbβ3 integrin receptors and use filopodia to pull on fibrin fibers of a blood clot, causing compaction of the entire clot (clot contraction) [21].

The structure and mechanical responses of fibrin [22–24], exposed to various forces, determine changes in the stiffness and size of the clot, extent of clot deformation, and clot structural stability and embologenicity [25], therefore defining the course and outcomes of thrombotic and hemostatic disorders, such as heart attacks and ischemic strokes and bleeding. Despite the fact that hemostasis and thrombosis studies can take advantage of computational and mathematical modeling [26–30], biomechanical processes mediating these experimentally observed fibrin network responses are still ambiguous.

This article reviews models studying the mechanics of individual fibrin fibers and fiber networks, fiber-fiber and fiber-platelet interactions, as well as clot deformation and contraction.

Process and Scales	Models
Process: individual fibrin fiber mechanics Space scales: nanoscale and microscale Fibrin fiber diameter: 20 to 100 nm Fibrin fiber length: up to 10 μm Critical extension of α-helices (the equilibrium distance between the □-state and the transition state): 0.25 nm Three-stranded α-helical coiled-coils: 17 nm Folded fibrin molecule: 45 nm Molecular scale: ~10-100 nm Time scales: 2 μs to 0.1 – 0.4 s (Molecular dynamics)	Molecular Dynamics (α-to-β transition in α-helical) [14]; Self-organized Polymer Model and Molecular Dynamics (γ-nodules, α-helical) [33]; Monomer as Wormlike Chain (WLC) [38];
Process: Fibrin fiber-fiber interactions Space scale: microscale Fibrin fibers length: from < 1 μm to > 10 μm Time scales: N/A	2D Lattice Model for Fibrin Network Compression [44]; Cohesive Fibrin-Fibrin Crisscrossing Model [39];
Process: Mechanical properties of fibrin networks Space scales: microscale and mesoscale Fibrin network volume: 1 – 1000 μm^3 Time scales: N/A	Entropic Elastic Filament Networks Models [19, 34, 38, 53]; Enthalpic Elastic Filament Networks Models [54 – 57];
Process: Deformation and stretching of fibrin fibers Space scales: mesoscale to macroscale Fibrin network volume: > 1000 μm^3 fibrin network clots Fibrin network length: a few μm to around 1 cm Time scales: A few seconds to a few minutes	Three-chain Model [61]; Eight-chain Model [62]; Isotropic Network Model [34]; Phase Transition Method [51]; Continuous Models for 2D Layered Materials [64, 65]; Multiscale Model with Non-linear Elastic Cylinder, Anisotropic Biphasic Theory (ABT), and Structural Model of Tissue Mechanics [66 – 68]; Continuum Chemo-elastic Theories Model for Gels [69]; Liquid Crystal Models are for Biological Materials [70];
Process: Clot deformation Space scales: multiscale from microscale to macroscale Fibrin network volume: > 1000 μm^3 Fibrin network length: a few μm to around 1 cm Time scales: Contraction time: 20 – 90 minutes	Coarse-Grain Molecular Dynamics for Filopodia Formation [87]; Modification of Elastic Fibrin Network Models to Include Fibrin-Platelet interactions [88 – 90] and including red blood cells [91];
Process: Clot fluid interactions Space scales: multiscale from microscale to macroscale Fibrin network volume: > 1000 μm^3 Fibrin network length: a few μm to around 1 cm	Immersed Boundary Method [92 – 95]; Two-fluid model [96]; Continuous Visco-hyperelastic Model [97];

Time scales: Simulations from a few seconds to a few minutes	

Table 1. List of models of processes determining blood clot mechanics at different space and time scales

(See **Table 1**.) It concludes with a description of several formidable challenges that remain, as well as the potential for successful development of a systems approach to understanding fibrin mechanics in hemostasis/thrombosis.

2. Modeling Studies of Fibrin Mechanics and Platelet-Fiber Network Interactions

In this section, we present an overview of the main processes related to fibrin mechanics and the main models used to simulate them (see also **Table 1**).

Modeling individual fibrin fiber mechanics. At the molecular scale, fibrin fiber mechanics is defined by the properties of monomeric fibrin, an elementary structural unit that shares structural and mechanical similarity with fibrinogen, a blood plasma protein, converted enzymatically to monomeric fibrin [9,31]. While this review does not mainly focus on single fiber mechanics, we are providing a short overview of some of the most important models. For a detailed review on individual fibrin fiber mechanics, see [20,32,107]. To model the dynamics of human fibrin(ogen) undergoing forced elongation, which is considered to be an important mechanism to accommodate strain, Zhmurov *et al.* [33] focused on describing the microscale/nanoscale level and used molecular dynamics (MD) simulations to characterize the α-to-β transition in α-helical

coiled-coil connectors of the fibrin(ogen) molecule, revealing the molecular origin of distinct elastic, plastic, and non-linear regimes in force-extension profiles. Zhmurov *et al.* then further improved their model [34] and used a self-organized polymer model and MD simulations to elucidate structural mechanisms of forced elongation of fibrin(ogen) based on the stepwise unfolding of γ-nodules concomitant with partial stretching and contraction of α-helical connectors. Similar results from this and other groups [9], that used MD simulations, suggest that extensibility of fibrin(ogen) may be due, on the microscale level, to the following molecular processes: (1) unfolding of coiled-coil connectors; (2) unfolding of the globular γ-nodule; (3) straightening and unfolding of αC region; and (4) combinations of them.

Other approaches, that focused on the microscale level but with reduced computational cost, utilized a coarse-grained approach to represent the response of a single elastic filament to an applied force [35–38]. For example, Houser *et al.* [39] modeled each fiber monomer as a unit consisting of a wormlike chain (WLC) nonlinear spring. They report that the success of WLC in replicating the behavior of a single fibrin fiber under tension, suggests that the straightening of otherwise unstructured polypeptides might be responsible for the mechanical properties of fibrin observed during stretching and that the elasticity of fibrin is entropic in nature. (See also [9,35] for a comprehensive review of relevant models.)

Neither molecular dynamics (MD) nor coarse-grained modeling approaches alone can accurately describe fibrin mechanics across different spatio-temporal scales. Nevertheless, because MD simulations are computationally expensive and limited to microseconds or at most milliseconds, the WLC approach (see, among others, [39]) has been largely used as a foundation

for models for studying mesoscale and macroscale deformation of a single fiber or fibrin fiber networks due to its demonstrated relevance when the molecular origin of fibrin(ogen) elasticity is not the main focus of the research.

Modeling fibrin fiber-fiber interactions. Fibrin networks are three-dimensional, consisting of branched fibrin fibers resulting from self-assembly of fibrin monomers and oligomers further stabilized via intermolecular covalent isopeptide bonds (fibrin cross linking) introduced by Factor XIIIa [23,40]. The mechanical responses of fibrin networks to shear, tensile, and compressive loads are highly nonlinear and referred to as strain-stiffening [24,41–43]. These types of responses are mediated by molecular unfolding, interactions within and between individual fibers, spatial rearrangement of filamentous networks, and other mechanisms that are not fully understood [16,40]. Several discrete models have been developed to simulate the formation of connections between individual fibers. One of such models, based on a bead and spring representation of individual fibers, was used by Kim *et al.* [23] to determine fibrin network elastic modulus for networks with different structures. A similar model was later developed by Sharma et al. [44] to study how network connectivity affects the mechanical properties and structural integrity of the tissue. This modeling approach was also later simplified and used [45] to provide a minimal 2D lattice model that was used to show that fiber-fiber interactions could influence clot stiffness in compressed fibrin networks. However, the extent to which such interactions contribute to overall clot stiffness could not be quantified.

Most existing models do not consider bending of individual fibers or physical contacts between them, which can significantly alter the mechanical response of the entire fibrin network.

The recently developed Cohesive Fibrin-Fibrin Crisscrossing Model (CFFCM) introduced by Britton *et al.* [40] includes these components. The CFFCM uses a general bead and spring modeling approach to simulate single fibrin fibers. Each fiber in a network is represented as a segment between two nodes (branch points) containing a series of sub-nodes connected by nonlinear worm-like-chain springs. The sub-nodes along a single fiber are placed equidistant to each other to represent a uniform distribution of mass and physical properties within one fiber. Moreover, a fixed spacing of sub-nodes serves to equally distribute possible fiber-fiber cohesion sites and points of fiber bending. Model simulation results showed that the nascent cohesive crisscrossing of fibers in stretched fibrin networks increased the strain of individual fibers in the network, revealing an underappreciated important structural mechanism of fibrin network stiffening under external mechanical stresses.

While all previous models used MD or coarse-grained representations of fibrin fibers, a multiscale model, which would include all structural mechanisms of fibrin crosslink formation and account for fiber bending, stretching, buckling, and fiber-fiber interactions is yet to be developed. Given the fact that the mechanisms span from (sub)molecular to individual fiber and multiple fibers scales, such development is extremely challenging and new mathematical and computational methodologies to rigorously bridge these scale gaps are needed.

Mechanical properties of fibrin networks. Several modeling frameworks have been introduced for simulating fibrin structural mechanics at different spatial scales [26,32,46–51]. Storm *et al.* [35] developed a molecular theoretical model that accounts for strain-stiffening in a range of molecularly distinct gels. Subsequently, to explain the strain-stiffening behavior of stretched

fibrin networks, two conceptually different types of models of cross-linked filamentous networks were developed and applied in Kang *et al.* [52]. The first type of models, referred to as entropic models, assumed the existence of semi-flexible filaments that undergo thermal fluctuations [35,53]. On the other hand, the second type, referred to as enthalpic models, represented filaments as elastic rods that can bend and stretch but do not exhibit thermal fluctuations [54–56]. One entropic approach used by Hudson and Houser *et al.* [17,39], implemented the WLC model to simulate the force-strain profile of single fibrin fibers under stretching, with fitting parameters obtained using data from atomic force microscopy experiments, suggesting that the natively unfolded area of the αC region mediates the mechanical response of fibrin fibers. Moreover, their simulations show that the strain-stiffening behavior of individual fibers helps to redistribute the strain within the fibrin network effectively strengthening it. On the other hand, Vahabi *et al.* [57] used an enthalpic extensible WLC model to represent bending and stretching contributions of the filaments and a 3D face-centered cubic lattice to generate the network structure showing that the onset of fibrous network stiffening depended strongly on the imposed uniaxial strain.

Both types of models were capable of capturing the strain stiffening behavior of fibrin networks, but gave different predictions for the degree and onset of stiffening, suggesting that further studies are required to calibrate these entropic and enthalpic models to quantifiably reproduce mechanical properties of fibrin networks [52]. (See Janmey *et al.* [20] for a more extensive review of other mechanical models of fibrin networks.) Similar to fiber-fiber

interaction models, none of these models have yet incorporated many of the multiscale structural mechanisms accounting for the highly nonlinear responses of fibrin networks.

Deformation and stretching of fibrin clots. At the macroscale level, discrete and continuous modeling approaches have been used to account for elastic responses of fibrin networks to external tensile and shear deformations inducing stiffening [40,52,58] as well as to suggest mechanisms of softening-stiffening behavior of compressed fibrin networks [51,57,59,60]. From a computational cost perspective, it is advantageous to adopt continuum approaches to model a meso- or macro-scale network (consisting of thousands or more nodes) and its interaction with the (fluid) environment. Several continuous models of fibrin networks, including a three-chain model [61], an eight-chain model [62], and one isotropic network model [35], were used to predict the force-strain response of stretched fibrin clots [18]. All these models were shown to correctly reproduce fibrin network behavior under tension in the linear regime. However, at large strains, the results significantly deviated from experimental data. This significant deviation can be attributed to the fact that all three models simulated isotropic networks and assumed affine network deformations. Meanwhile, biological networks such as those formed by fibrin *in vivo* are frequently anisotropic and their deformation is non-affine [63]. Additionally, these models neglect molecular level mechanisms accounting for fibrin nonlinearity such as the unfolding of coiled-coil connectors that are instead captured by discrete models using non-linear springs. However, continuous models have been successfully used to make predictions on the mesoscale and macroscale behavior of fibrin networks under specific conditions. Recently a phase transition method was used to predict the shear viscoelastic response of compressed networks,

which revealed a remarkable softening-stiffening behavior due to bent fibers and network densification [51]. Additionally, continuous models have also been developed to efficiently simulate the deformation of 2D layered materials at a mesoscale level [64,65]. Also, modeling approaches for fibrin networks can benefit from earlier introduced models of collagen and mixed collagen-fibrin gels. Barocas *et al.* [66–68] developed a multiscale model using non-linear elastic cylinder representations of fibers, the anisotropic biphasic theory (ABT) of tissue equivalent mechanics [67], and a structural model of tissue mechanics [68], in which the tissue is represented as a sum or integral of fiber contributions for a distribution of fiber orientations. Moreover, Sun *et al.* [69] utilized continuum chemo-elastic theories to also model the mechanical behavior of gels. Finally, liquid crystal models were widely developed to model biological materials, especially bio-gels [70]. Ideas introduced in these works can also be used in fiber network studies.

It remains a challenging task to develop discrete or continuous models for meso- or macro-scale networks to include subscale mechanisms. For instance, although continuous models [51,64,65] are important for studying layered materials, they are not designed to capture the impact of fiber cohesion on the dynamical changes of the 3D structure of fibrin networks under stretching [23,51].

Modeling clot contraction. Blood clot contraction, mediated by activated platelets [1], is essential for hemostasis, and proper wound healing and restoration of blood flow past an otherwise obstructive thrombus in prothrombotic patients [2,20]. Defective clot contraction can lead to more obstructive thrombi, which may exacerbate thrombotic conditions such as heart

attacks, strokes, and deep vein thrombosis. Biophysical regulation of blood clot contraction [71] is poorly understood. Mechanistic impacts of platelets, nonmuscle myosin IIa, red blood cells (RBCs), fibrin(ogen), factor XIIIa (FXIIIa), and thrombin all affect the kinetics and mechanics of the contraction process [71]. Studies of individual platelet dynamics and their interaction with the fibrin network substrate [72] are fundamental to get a better understanding of clot contraction as well as of a multitude of other biological processes, including tissue healing and development [73–75], phagocytosis [76], and cancer development [77]. While many experiments on platelet adhesion and aggregation have been carried out [78,79] and models have been developed [80–85], quantitative experimental and modeling studies of the emergent properties of contracting clots have yet to be extensively explored. Experimentally, measuring filopodial forces [86] is extremely difficult, and for modeling, platelet function during clot contraction encompasses multiple interdependent factors, including cell shape, number of filopodia, filopodia length, filopodia strength, and mechanical and adhesive properties of platelets. Notably, Pothapragada *et al.* [87] employed a coarse-grained molecular dynamics particle-based model to simulate filopodia formation during early activation of platelets but did not attempt to model clot contraction.

Similarly, some of the coarse grained models used to simulate the elastic fibrin network have recently been modified to include interactions between fibrin fibers and platelets and some even added interactions with red blood cells [88–91]. In particular, Tutwiler et. al [91] used their model to study how red blood cells influence the dynamics of clot contraction. These coarse-grained approaches allow us to simulate some details of the platelet/fibrin interactions driving

clot contraction. However, depending on the level of detail and number of coarse-grained elements used, they can be computationally expensive and are often limited in the size of the clots that they can simulate. Therefore, simulating contraction for clots that are more than a few tens of micrometers in diameter in a reasonable amount of time remains an open problem. Nevertheless the current availability of high performance computing facilities and in particular of high performance GPU computing is allowing for much faster computations than with single or even multiple CPUs, extending the size of the clots that can be simulated.

Models describing clot fluid interactions. Since fluid comprises a major part of clots, it is important to consider the fluid impact on fibers, platelets, and other blood cells (see **Figure 1B**). Models that include fluid are of particular interest in predicting the formation and impact of occlusion on blood circulation (e.g. deep vein thrombosis, strokes, and pulmonary embolisms). In the past decades, the powerful immersed boundary method [92] has been widely used to simulate single fiber and fiber networks, single to multiple platelets [93], and fluid interactions [94,95]. At the same time, the immersed boundary method simulations sometimes are very time consuming, because of the stiffness of the fibers and the small mesh size needed to resolve the interactions. In this regard, the two-fluid model of de Cagny *et. al* [96], which describes a polymer gel as a biphasic system composed of a linear elastic network immersed in a viscous and incompressible liquid, might provide a good alternative for simulating biopolymer gels. (For more details see [93,96] and references therein.) However, in this model, network structure is not directly resolved, and phenomenological parameters are used for coupling the network and the fluid. More recently, *Tashiro et. al* [97] used a continuous visco-hyperelastic model for blood

clots and finite element simulation to study stress transmission from a thrombectomy device to the blood clot. This model successfully reproduced the hyperelastic characteristics of clots under tensile load. However, since this model is continuous, it does not reveal how each major component of the blood clot responds to the tensile load.

3. Open Problems

Development and calibration of multiscale models coupling submodels, of different blood clot components and processes for studying hemostasis and thrombosis, remains the main challenge. In particular, combined experimental and computational studies of microscale mechanisms of lateral aggregation of protofibrils and of the structure of fibrin fibers [8,98–102] remains very challenging. Designing new models, simulation schemes, and efficient parallel algorithms is critical in any modeling study of the mechanical response of fiber networks of a considerable size under fluid flow. Some attempts [26–30,103,104] have been made to couple some aspects of fluid interactions and mechanical properties of blood clots. These efforts either use a continuum description for all components, which can miss important microscale or mesoscale phenomena, or apply a hybrid strategy in which cells are described by discrete submodels such as clusters of smooth particles, subcellular elements, or cellular Potts representations. For these hybrid models, spatio-temporal coupling of discrete models with continuum models with proven consistency, stability, and convergence present a significant mathematical challenge and more work needs to be done. (For a more detailed review, see [11,105,106].)

The study of clot contraction provides specific challenges for multiscale modeling. As previously mentioned, the clot contraction dynamics originate from platelets that act at a microscale or even nanoscale. This includes filopodia extension dynamics through deformation of the cell-membrane via actomyosin, filopodia adhesion to fibrin fibers, and filopodia retraction. All of these properties are difficult to measure experimentally. At the same time, some limited experimental data is already available. For example, measurements of forces exerted by platelets on substrates with different stiffness levels have shown that platelets exert higher pulling forces on stiffer substrates [72]. This is an important property to include in clot contraction models since fibrin fibers have strain-stiffening properties, and therefore are supposed to pull harder on more strained fibers as the clot contracts.

4. Conclusions

Hemostasis and thrombosis involve complex mechanical and biochemical interplays involving blood flow, millions of platelets, and the fibrin network. Despite many modeling and computational challenges, the potential to simulate a quantitative response of the fibrin fiber network and platelets to simultaneous variations in different hemostatic or thrombotic processes has major potential for medical and scientific applications. Existing detailed models need to be further extended and calibrated using experimental data for studying different types of network and clot deformations including compression. Then, with additional clot fracture data, they can be also applied for studying clot breakage and formation of thrombotic emboli under different

blood flow conditions as well as for studying other hydrogels including collagen, actin, and fibronectin, and for designing new biomaterials.

Conflict of interest statement

The authors declare no conflict of interest.

Acknowledgments This work was partially supported by NIH grant UO1 HL116330 (M.A.., J.W.W., O.V.K., Z.X. and F.P.). O.V.K. was partially supported by AHA 17SDG33680177 and NIH grant R21DE030294, Z.X. also was partially supported by NSF CDS&E-MSS 1854779, MA was partially supported by DMS-1762063, Joint NSF DMS/NIH NIGMS Initiative to Support Research at the Interface of the Biological and Mathematical Sciences, and DMS 2029814.

Competing Interests: The authors have declared that no competing interests exist.

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