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Decoding thrombosis through code: a review of computational models

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Abstract

From the molecular level up to a blood vessel, thrombosis and hemostasis involves many interconnected biochemical and biophysical processes over a wide range of length and time scales. Computational modeling has gained eminence in offering insights into these processes beyond what can be obtained from *in vitro* or *in vivo* experiments, or clinical measurements. The multiscale and multiphysics nature of thrombosis has inspired a wide range of modeling approaches that aim to address how a thrombus forms and dismantles. Here, we review recent advances in computational modeling with a focus on platelet-based thrombosis. We attempt to summarize the diverse range of modeling efforts straddling the wide-spectrum of physical phenomena, length scales, and time scales; highlighting key advancements and insights from existing studies. Potential information gleaned from models is discussed, ranging from identification of thrombus-prone regions in patient-specific vasculature to modeling thrombus deformation and embolization in response to fluid forces. Furthermore, we highlight several limitations of current models, future directions in the field, and opportunities for clinical translation, to illustrate the state-of-the-art. There are a plethora of opportunity areas for which models can be expanded, ranging from topics of thromboinflammation to platelet production and clearance. Through successes demonstrated in existing studies described here, as well as continued advancements in computational methodologies and computer processing speeds and memory, *in silico* investigations in thrombosis are poised to bring about significant knowledge growth in the years to come.

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1 | INTRODUCTION

Computational modeling provides a major beneficial avenue for investigating mechanisms in thrombosis. Simulations (*in silico* experiments) can enable investigators to probe underlying phenomena that are otherwise challenging or intractable to investigate experimentally. Simulations can reduce the need to sacrifice animals for experimentation, and are typically less expensive than bench-top experiments. The ability to quickly generate large volumes of data, makes computational models useful for testing several "what-if" scenarios, an aspect that has been referred to as *data-driven discovery or computational discovery* [1]. Alternatively, combining simulations with non-invasive human clinical imaging can be beneficial for surgical planning based on predictions of potential sites of thrombosis [2]. Here, we explored current advancements in computational models of thrombosis, with a particular focus on multiscale platelet-dependent processes.

Thrombus initiation, growth, deformation, and dissolution, are inherently multiscale processes as illustrated in Figure 1. At the largest spatial scales (millimeters to centimeters), blood flow is redirected or fully obstructed. Within a thrombus, micron-sized platelets interact with proteins to form a heterogeneous aggregate, as fibrin forms a mesh-like network further stabilizing this aggregate that may be tens to hundreds of microns large. Microscale platelet aggregation and coagulation involves nanoscale molecular interactions between receptors and counter-receptors interplaying with biochemical reactions. Within individual platelets, molecular machinery drives shape change and cytoskeletal contraction. Moreover, there is a range of temporal scales underlying the dynamics of thrombus growth. While macroscopic thrombus grows over minutes to hours, platelet adhesion and aggregation occurs on the order of seconds to minutes, and molecular interactions can occur within microseconds to milliseconds. In addition, thrombus formation and growth are inherently multiphysics processes, comprising multiple interacting physical phenomena which in turn require multiple modeling approaches often coupled with each other (Figure 1). Biochemical reactions underlie coagulation processes and regulate cellular or platelet behavior. Fluid mechanics drives biochemical transport and defines the flow-induced stress environment. Structural mechanics determines the forces exerted on the thrombus and describes its deformation and structural stability. Encapsulating relevant space-time scales and physics motivates the evolution of a large and rich variety of modeling approaches, to be reviewed here.

"How to *effectively model the multiple underlying coupled phenomena in thrombosis across multiple spatial and temporal scales?"* This question remains central to modern advancements and renders key challenges in developing robust computational models of thrombosis. In this review, we aimed to outline general modeling methodology (section 2) and describe state-of-the-art examples of modeling specific processes involved in hemostasis and thrombosis, spanning multiple scales using multiphysics modeling (section 3), while

compiling insights from existing literature to identify challenges and opportunity areas in computational thrombus modeling (section 4). Although many stateof-the-art example models discussed in section 3 may focus on thrombosis, the underlying techniques are typically generalizable to modeling hemostasis. We note that the range of methodologies and applications is truly immense, and consequently the review of literature discussed here is not exhaustive.

2 | OVERVIEW ON MODELING TYPES

Computational thrombosis models involve numerical approximations of equations that govern the spatial and temporal distribution of cells and key biochemical species in blood flow. Techniques to obtain such numerical solutions can be commonly classified as (a) *continuum models* in which quantities such as velocity or concentration of blood constituents are spatially averaged and mapped onto finite regions in the domain of interest (referred to as a grid or a mesh); or (b) *particle models* in which flow and chemical quantities are, instead, represented as a collection of particles (Figure 1). Continuum models commonly model large-scale processes on the order of millimeters [3–5], for instance, arterial thrombus growth [6,7]. For the continuum example in Figure 1, aggregated platelets are treated as a homogeneous species (core), while adhering platelets are treated as a different species (shell) and where yet another species, blood, flows around these regions [6–9]. In these models, cells are much smaller than the modeling domain and are commonly treated as an averaged homogeneous species. Particle models, alternatively, can capture deformation and collision physics of platelets and erythrocytes in flow [10–14]. Particles can be combined to simulate the boundary or membrane of a platelet, while other particles can be assigned separate properties to simulate blood (Figure 1) [15–19]. At the cellular length scale (up to 10s of microns), particle-based models become more suitable compared with continuum models, because they can account for the stochastic or fluctuating nature of cellular interactions. Continuum models can also be coupled with particle-based models [20–22] to represent the interplay of particles with a background flow field (platelets treated as individual particles in Figure 1 example). Given the variety of existing approaches, an important question we highlight is: "*How is a modeling method chosen?*" Generally, the choice of method is based on the end-goal for the model (which underlying process is being studied and at what length/time scales)—described more in section 3, and is largely driven by the practical constraints of computational cost. Computational cost refers to the time and computational power (ie, number and speed of processors, and memory) required for a simulation. Current laptops (in 2023) can sufficiently characterize steady flow in a patient-specific vessel using continuum models within hours. However, transient flow in complex vasculature involving turbulence, or particle models of hundreds to thousands of cells can take weeks to months (sometimes more) on a supercomputing cluster and may not be feasible on a standard computer. Continued gains in processing speed, combined with the advancements in techniques discussed in section 3, will lead to a bright future in what we can discover from computational models in thrombosis.

3 | STATE-OF-ART MODELING OF PLATELET-BASED THROMBOSIS

3.1 | Macroscale modeling of hemodynamic descriptors of thrombosis

Simulations of blood flow in patient-specific vascular geometries have evolved into a well-established technique [2,4,5]. These map how blood flow velocity and pressure vary in space and time over a vascular geometry, reconstructed from non-invasive imaging such as *computed tomography or magnetic resonance imaging*. Doppler ultrasound, among other methods, can inform the velocity inflow to the vascular geometry. From computed data, hemodynamic descriptors can be derived and correlated with thrombotic phenomena. One commonly used descriptor is shear stress, a surface force (per area) parallel to the flow, where low or high levels have been used to identify thrombus-prone regions. Another is *residence time*, which measures the time blood stays in a particular region (blood stasis).

High shear stress has been correlated to thrombus growth using simulation-based studies in stenotic geometries [23,24], and in prosthetic mechanical heart valve hinge regions [25,26]. This may relate to von Willebrand factor extension based on velocity gradients, as predicted through particle-based and continuum-based simulations [27,28]. These flow environments can act as a mechano-signal to platelets [29] and can induce *shear-induced platelet activation and aggregation*. Shear-induced platelet activation and aggregation is predicted to occur in simulations through a combination of shear stress magnitude and exposure time [30], as recently reviewed [31]. Although the interplay with high shear has most commonly been used to predict regions prone to thrombosis, a recent computational study of a puncture model [32] suggests that high shear and elongational flow may also be involved in hemostasis.

Alternatively, low shear stress and flow stasis can be used to predict locations prone to thrombosis based on propensity for coagulation and platelet aggregation. Computer simulations of coronary aneurysms in Kawasaki disease [33] demonstrate that low wall shear stress (WSS) correlates to locations of thrombus formation, helping to identify at-risk patients for thrombosis (Figure 2A). Flow and transport simulations have been shown to identify procoagulant environments in aneurysms that co-locate with regions of thrombus development [34,35]. Combined indices of WSS and residence time have been proposed to improve predictions of thrombus deposition in abdominal aortic aneurysms (Figure 2B) [35]. Low WSS has also been found to facilitate thrombus formation and growth in the false lumen [36] (Figure 2C), which may synergize with high residence time (Figure 2D) [37]. Similar methods have been extended to blood-contacting devices, eg, transcatheter valve-in-valve procedures [38]. These models are largely based on simplified hemodynamic descriptors of flow stasis where coagulation proteins are unlikely to wash away and reactions are expected to have ample time to proceed.

Although macroscale models using hemodynamics descriptors have not been broadly translated into clinical practice for identifying at-risk patients for thrombosis, similar approaches have shown utility and efficacy in preprocedural surgical planning. For instance, modeling is used as a non-invasive alternative to fractional flow reserve measurements to assess coronary artery disease severity [39]. Simulations have been helpful in sizing and positioning decisions for medical devices used in surgical interventions [40–44]. One major

barrier preventing similar clinical adoption for thrombosis models includes challenges in defining generalized relationships between thrombus risk and flow-based descriptors; it may be necessary to incorporate some reduced order patient-specific blood parameters or more detailed models described below. The successful precedents mentioned here and the increasing research in this field provide a promising outlook for computational models that can clinically predict the location of thrombus-prone regions and guide surgical practices to minimize hemodynamic features that may trigger a thrombotic response.

3.2 | Modeling of processes leading to thrombus growth

Models of thrombus growth typically require the coupling of flow with platelet phenomena including transport, adhesion, and aggregation. Further, models of coagulation biochemistry leading to predictions of thrombin generation can be further incorporated for a systems-level understanding of thrombus growth. Through careful coupling of these various models, multiple scales can be studied in the context of thrombus growth, with trade-offs between fidelity and computational cost.

3.2.1 | Platelet transport—It is critical to characterize platelet transport for modeling platelet interactions. Generally, cells and proteins move with fluid flow, known as advective transport. However, blood is a dense suspension of colliding, rotating, and deforming cells and proteins traveling within plasma. These interactions lead to an additional source of platelet transport perpendicular to flow. This lateral or transverse transport is defined using two interlinked terminologies: enhanced diffusivity and platelet margination. Briefly, enhanced diffusivity refers to an enhanced rate of platelet transport lateral to the flow direction as a function of hematocrit and shear rate [45]; this leads to faster lateral motion when compared with Brownian motion. Platelet margination, refers to the directed motion, where an enhanced concentration of platelets can be found directly adjacent to a vessel surface [46]. This region, devoid of erythrocytes, is also referred to as the “cell-free layer.” Continuum models can account for both modes of enhanced transport by augmenting transport equations [6,9] or by prescribing concentration profiles [47], enabling the platelet distribution to be predicted after a flow disturbance (Figure 3A), and can be used to predict rates of platelet interactions with a surface [6]. Erythrocytes also centralize after a stenosis (flow constriction depicting atherosclerotic plaque), while platelets are pushed into a flow recirculation region, based on the aforementioned model. Alternatively, some studies have modeled the physics of individual colliding cells in flow to demonstrate the centralization of erythrocytes based on shear-induced lift forces and collisions with other erythrocytes [10–14]. With the localization of platelets to the vessel walls and the constraints imposed by erythrocytes, simulations show that near-wall tumbling platelets get pushed to the wall, increasing the rate of surface collisions [11,13]. For a stenosis, there is further enhancement in platelet margination leading to increased tumbling and sliding of platelets along the wall of the stenosis (Figure 3B) [11,12], with increasing margination as a function of hematocrit and stenosis severity, and further enhancement if the stenosis is considered porous, typical of a growing thrombus [11]. Increased platelet collisions around a stenosis may provide some evidence for why thrombosis is experimentally found near a stenotic peak [23,24]. Overall, platelet transport is critical to many simulations of thrombosis and due to the ability

to drive rates of interactions, it should be carefully considered in most practical models of platelet-dependent thrombus growth.

3.2.2 | Platelet adhesion and aggregation under flow—Simulations of platelet adhesion and aggregation at the vessel (large) scale often employ continuum models for the spatio-temporal distribution of an averaged concentration of platelets in distinct states (eg, resting, activated, and adhered) [7,9,48,49]. These models can be simulated using one-way coupling with the flow (thrombus diverts flow, but flow does not deform the thrombus) by modeling depositing platelets as porous media [6,7] or as artificially increased viscosity regions [9] (Figure 4A, B). Through these approaches, flow is slowed where the platelet aggregate is forming. Using this method, patterns of platelet deposition can be verified relative to clinical [7] or *ex vivo* experiments [6], enabling results to be extrapolated to additional conditions, eg, changing flow in a continuous flow ventricular assist device (Figure 4A) [7]. In this latter axial ventricular assist device simulation, an increase in flow leads to less simulated in-device platelet aggregation, whereas a decrease leads to increased simulated in-device aggregation especially at leading and trailing edges of the stator. Additionally, this modeling method has been used as a way to quantify the role of platelet transport in driving platelet aggregation (Figure 4B). As an outcome, it was shown that platelet aggregation rates are limited by platelet arrival rates to a stenotic vessel. Continuum methods are particularly suited to model large regions and typically aim to predict where platelet aggregation is prominent and how rapidly it can block blood flow.

At the mesoscale, individual platelets are modeled via continuum-particle coupled, or particle-based models [48,50–52]. These models include individual platelet responses to the mechanical (shear rates) and biochemical environment (agonist concentration). These models capture platelet interactions in more detail by combining receptorligand binding with hemodynamic calculations to predict individual platelet motion and adhesion, eg, tumbling and sliding along a substrate [18,53,54]. Simulations using this approach demonstrate that platelet shape leads to fundamentally different collision behavior with a surface compared with a sphere [53,54]. Platelet rigidity also affects aggregation, as illustrated in a simulation of diabetic blood (Figure 4C) [52]. As demonstrated, biomechanical characteristics of platelets are best studied with these mesoscale models. Platelet aggregation models can also test how plasma proteins interact with individual platelets, eg, potentiating platelet aggregation through von Willebrand factor extension and entanglement in high shear flow [55] (Figure 4D), or testing fibrinogen-based binding at low shear based on interplatelet contact area and platelet deformability [17,18]. These models also have the potential to predict patient-specific bleeding and platelet aggregation [56]. Employing a systems biology approach, these models can use patient-specific platelet calcium mobilization in response to combinations of agonists to predict platelet aggregation and the spatial distribution of platelet activation within an aggregate [48,51,56]. These mesoscale models are generally calibrated using experimental ex vivo data, providing credence to findings. Overall, mesoscale models are most useful for investigating single cell biomechanical behavior and interactions, but are not practical to implement at large scales (millimeters).

At the subcellular scale, platelet deformation models [15–18] offer an opportunity to capture microstructural changes (eg, actin polymerization) as platelets undergo shape change during

activation. The membrane, cytoskeleton, and cytoplasm can be included in these models to simulate general platelet structure to quantify the stress distribution along a platelet membrane during collisions and while transporting in shear flow [19]. These models make it possible to quantify stress distributions on a platelet surface, which otherwise cannot be determined with experimental techniques, and could be useful for predicting stimulation of stretch-sensitive ion channels. However, these models are challenging to validate and few subcellular models have been developed to-date. These models afford greater detail while modeling platelet adhesion and aggregation, but the extent of the simulations are highly constrained in time and space.

3.2.3 | Thrombin generation—Secondary hemostasis or coagulation involves a series of biochemical reactions comprising the coagulation cascade. Models of coagulation can be broadly categorized into models of biochemistry; models incorporating flow; and models integrating coagulation into a spatiotemporal simulation of clot formation and growth. Instead of attempting an exhaustive review on the large topic of coagulation within the limited scope of our discussion, we refered to several existing comprehensive modeling reviews [57–60]. A central theme across many coagulation modeling studies is to numerically describe the time evolution of key biochemical species involved in the coagulation cascade [61,62], by accounting for the role of platelet surface receptors, and for flow bringing chemicals to or from reaction sites [63–65]. In addition to modeling thrombin generation, subsequent fibrin polymerization has been investigated using similar approaches. Studies include rate kinetics-based models of the polymerization process [66]; interplay of fibrin gel formation with coagulation and flow [67]; and models of fibrin-thrombin interaction in polymerized gels [68]. A detailed review on state-of-the-art fibrin polymerization models has been presented previously [69].

Flow and flow-mediated transport are key features throughout many of these modeling efforts [70]. Several models have incorporated effects of flow using reduced order (simplified) compartmental models of species concentration changes due to flow [63,64]. This approach leverages an assumption that most concentration changes occur within a thin layer near the wall for specific vessels. More recent efforts have combined coagulation biochemical reaction models with spatiotemporally varying flow models, and a growing clot that subsequently diverts the flow [47,71,72]. One model [71] integrates coagulation in solution phase with flow and stochastic microscale models of cellular interactions. In another coagulation model [47], surface-reactions are integrated with flow and a porous media model of a platelet clot, an approach that is further extended [72] to study venous thrombus formation. Such coupled models enable studying the role of proteins like tissue factor in thrombus growth [48], where greater thrombus growth is shown in the presence of tissue factor for both experiments and simulations (Figure 5A, B). Flow-mediated transport of coagulation agonists has been further characterized in presence of a clot, through computational models of hindered transport in the clot interstices as a function of microstructural features [8,73,74], and more recent modeling of species transport from the clot to luminal flow [21]. In addition to quantitatively describing the fate of various biochemical species in relation to thrombus growth, coagulation models have found several additional utilities. For example, in computer simulations [1] of a large number of what-if

scenarios led to the identification of factor V as a key modifier of thrombin generation in mild or moderate hemophilia A. In another example [75], coagulation reaction models were used to study the effects of dosing for two anticoagulant drugs, warfarin and rivaroxaban. Future opportunities through computational advancements may enable coupling such biochemical intervention investigations with multiscale vessel thrombosis simulations, for specific disease applications.

3.3 | Modeling of processes leading to thrombus breakdown

In addition to thrombus growth, thrombus size is also driven by dismantling processes like embolization or dissolution via biochemical reactions. Modeling of such processes must deal with the challenges of heterogeneity underlying thrombus composition and structure, and thrombus-hemodynamic interactions.

3.3.1 | Thrombus mechanics, deformation, and embolization—Models of thrombus mechanical behavior and deformation in response to applied forces from fluid flow are useful for predicting thrombus structure, flow interactions, and embolization. Mechanical responses depend not only on the force magnitude but also how rapidly or slowly the force is applied (loading rate), referred to as viscoelasticity. Realistic thrombus deformation behavior also depends on heterogeneous thrombus composition, involving multiple-phases, eg. fibrin, platelets, and erythrocytes. This again poses a multiscale problem: resolving interactions of each individual constituent, although accurate, is computationally expensive, requiring a need for continuum models that describe averaged aggregate mechanical properties that account for behavior of each component phase within the mixture that forms the thrombus structure. Additional challenges are encountered in modeling the interplay of the deformation and flow around the clot.

Macroscale viscoelastic thrombus deformation and predictions of thrombus rupture in the absence of flow has been studied under cyclic aspiration loads [76] to simulate thrombectomy processes for acute ischemic stroke. In these models coupled with individual fibrin [77] fiber mechanics, it is demonstrated that fiber mechanics and viscoelastic behavior originating from the fibrin phase determines the overall thrombus mechanical behavior. The state-of-the-art in simulations of fibrin networks and their interplay with platelets has been reviewed previously [78]. In another study, it is shown that microstructural features like permeability are not only relevant for transport phenomena but also influence thrombus deformation (Figure 6A) [79]. In a series of investigations on coupling fluid flow with clot shape and microstructure, a hybrid particle-continuum approach was used to investigate how thrombus microstructure heterogeneity influences thrombus-flow interactions and biochemical transport at the arterial scale (Figure 6B) [20,22]. Other studies [80,81] further illustrate that computational models of thrombus-flow interactions can reveal the interplay of factors like porosity, platelet packing, and bonding parameters, which can ultimately determine how thrombus deforms due to flow. One major take-away from these works is that computational models can be used to investigate how heterogeneous thrombus composition and microstructure inform thrombus deformation behavior—an aspect that remains challenging through conventional experiments or imaging alone.

Additionally, the ability to model embolization remains an emerging goal of computational models. In many studies [79,80], clot fragmentation and embolization potential were computationally demonstrated via macroscale continuum models with varying shear stress caused by blood flow. Alternatively, microscale bond rupture processes ultimately leading to embolization were studied using a model [82] that digitally reconstructed a thrombus using particles and fibers. Particles have also been used to represent thromboemboli that completely dislodge, causing subsequent occlusive disorders. Simulations have been used to predict movement of dislodged thromboemboli from the heart to the brain under hemodynamic forces [83], and to model distal embolization risks due to dislodged emboli during thrombectomy procedures in acute ischemic stroke [84]. In summary, these studies indicate that the discontinuous nature of fragmentation processes combined with microstructural heterogeneity preclude a clear understanding of thrombus stability, and how embolization progresses. As modeling advancements progress, expanding existing models to study thrombus structure, deformation, and embolization under realistic arterial or venous hemodynamic environments will be a key opportunity area.

3.3.2 | Thrombolysis—Thrombus breakdown can also occur through thrombolysis. Modeling efforts in thrombolysis are based on coupling reaction kinetics-based models for the fibrinolytic reaction system with fluid flow, mass transport, and thrombus properties. Reaction kinetic simulations refer to modeling the temporal rate of concentration changes for various species involved in a reaction. Unless combined with a mass transport model, they cannot define how the concentrations of these species change spatially within simulation domains of interest. In early work, one model [85] couples the fibrinolysis reaction cascade with a 1D transport model considering the thrombus as a porous material. This approach was able to resolve the propagation speed of the lysis front in fibrin clots. In another [86], the above approach was extended to include a 2D spatial model of porous fibrin clot lysis, demonstrating finger-like protruded shapes of the lysing patterns. Together, these identify the rate and spatial pattern of lysis as key targets for computational modeling, an aspect that further motivates the latest thrombolysis modeling efforts. Various mathematical approaches for compartmental reaction kinetics model underlying drug pharmacokinetics have been compared [87]. The coupling of reaction models for the fibrinolytic system with continuum porous media models of blood clots, was used to investigate lysis patterns along a vessel axis [88] and address how lysis drug dose affects recanalization efficacy. Recent models have increasingly focused on multiphysics spatiotemporally varying lysis of thrombi under flow. A multiscale model [89] is devised by combining thrombolysis reaction models with a macroscale fibrin clot model that encompasses a microscale model of fibrin fibers. In another study [90], a fully 3D multiscale model of lysis in presence of flow in a bifurcating cerebral vessel was described. Both studies illustrate how modeling can provide estimates of lysis rate and lysed volume, and demonstrate how overall lysis rate is determined by a combination of tissue plasminogen activator concentration and clot structure. Thrombolysis is a primary treatment choice for acute ischemic stroke and computational modeling that can be a viable method to investigate treatment efficacy and outcomes which otherwise remain poorly understood. While existing approaches have enabled quantitative understanding of lysis, precise patient-specific assessment of therapy requires modeling drug transport and

reactions in conjunction with vascular flow, clot structure, and composition, which remains a state-of-the-art challenge. Hence, with continued modeling advancements, patient-specific predictions on lysis, and efficacy of various thrombolytic drugs remain a key opportunity area for *in silico* applications.

4 | OUTLOOK AND FUTURE CONSIDERATIONS

4.1 | Insights on current state-of-art modeling approaches

Here, we discuss a few key insights on modeling in thrombosis research. First, our review of existing literature points to a wide range of modeling approaches applied to various phenomena spanning from microscale to macroscale. The question of *which modeling approach is suitable for a given phenomenon?* naturally emerges as we try synthesizing this information. Existing studies indicate that the choice of model is best informed by: (a) what spatial and temporal scales and (b) what underlying coupled phenomena (or physics) are being investigated. We also note that, although different modeling approaches can be coupled as informed by the scale and physics, the development of an all-encompassing computational model of thrombosis, combining all relevant underlying phenomena for patient-specific applications remains impractical for this field, and, instead, it is necessary to simplify models and to focus on specific questions.

Second, a model is only as good as the data used to inform the model. Therefore, model parameters must be identified robustly from reliable sources. It is necessary to know which parameters indicate a physiological or biological quantity, and which are mathematical model parameters with no direct biological meaning. Understanding how these parameters vary, and how these variations can influence the model is broadly referred to as sensitivity analysis. Sensitivity analysis can be used to: (a) make the model more computationally efficient by reducing parameters and/or equations and (b) identify key parameters to drive future experiments or hypotheses. If there is an error in the experiments used to quantify these parameters, then this error propagates into the model, which subsequently impacts the accuracy of model predictions. This aspect motivates *uncertainty quantification*, which refers to the quantitative characterization of uncertainties in model parameters, how these uncertainties propagate to model outputs, and how they compare to real-world measurements of the same outputs. Examples of such analysis have been reported in several recent studies [1,91].

One aspect requiring attention is the robust integration of computational models with experimental data. Experimental data can include flow-based *in vitro* or *ex vivo* assays, animal models, or patient records/outcomes. This can be used to establish the predictive power (ability to match experimental or clinical results) of the computational models; and for Verification and Validation of the model. Verification is used to determine if the model functions as intended, without underlying mathematical or programming errors. Verification is reported in several studies cited in section 3 through comparisons either ex vivo or clinical observations [6–8,48,72]. Validation refers to systematic quantitative confirmation that the model predictions are accurate within a bounded range of conditions, by statistically testing model predictions relative to a well-established benchmark system. Much of the foundational physics-based models have been validated over many decades against multiple

experiments. However, it is rare for whole thrombosis models to be validated against benchmarks. No well-established benchmarks exist for thrombus models since models are typically developed to encapsulate specific phenomena and separate benchmarks may be needed for each phenomenon. Verification and validation remains an essential requirement for clinical translation of thrombosis models, as they ensure credibility. Furthermore, models are limited in scope, and real conditions experienced clinically or *in vivo* can involve complex integrated physiological responses. It can be exceptionally challenging to include all potential responses within a single model. Therefore, validated models can provide excellent guidance, like clinical lab tests and *in vitro* experiments, but their limitations must always be considered.

Lastly, the identified need for data integration with mathematical models is significant and noteworthy when juxtaposed with the rapid advances in data-driven modeling, machine learning (ML), and artificial intelligence (AI). Thrombosis modeling can benefit from synergy with AI or ML approaches, which can further enable new methodologies and areas of investigation in the next decade. These methods are well-suited to identify complex patterns in thrombosis that are not currently captured by traditional physics-based models or where parameters are unknown or hard to define, like complex interdependent signaling pathways in platelet activation [92]. In addition, trained AI or ML models can also be used to build surrogate models from existing computational data, which are computationally less expensive to evaluate compared with physics-based models. However, presently, these methods require substantial volumes of data for model development and training. As informed by the existing literature, applications may also include rapid integration of imaging data from *in vivo* or *in vitro* models and more broadly to provide potential new avenues to transfer information across the multiple spatial and temporal scales involved.

4.2 | Challenges and opportunities in modeling

Here, we summarized some current challenges in thrombosis modeling and discussed future opportunity areas or applications for the field. Although computational algorithms must be limited in scope, simplified meso-scale or microscale models can still provide evidence that can help guide clinical decisions. One application with near-term feasibility is to guide decision-making in blood-contacting device design, operating conditions, and/or placement in patient-specific vasculature, with one example illustrated in Figure 4A. Another, is to guide patient-specific antithrombotic therapy based on patient-specific protein levels. There are several opportunity areas that can aid these goals including: (a) developing modeling approaches that can circumvent high-computational costs associated with multiscale phenomena by leveraging advancements in reduced order (0D and 1D) models; (b) minimizing the number of patient-specific parameters and variables that are incorporated into the models through techniques like AI or ML; and (c) developing fast computational algorithms and software implementations that can run the underlying calculations efficiently with less compute-resources. Integration of computational model development efforts with open-source software development practices, and infrastructure can be identified as a key area of opportunity. Collaborative efforts toward developing open-source tools and databases will not only accelerate the engineering of computational thrombosis models but also facilitate broader testing and validation of such models.

There are many opportunity areas for state-of-art thrombosis models. Few models consider the role and mechanisms of procoagulant platelets, clot contraction, new therapeutic targets for thrombolytics and bleeding disorders, and development of novel drug-eluting devices. Platelet production from megakaryocytes has received little attention from the modeling community, despite its importance in many diseases. Similarly, there has been little focus on platelet clearance and how an imbalance of production and clearance may lead to thrombocytopenia. Stroke is an important domain where increased prevalence of in silico models hold substantial promise in improving patient-care. Opportunities lie in understanding clot stability under flow for distal embolisms from thrombectomy therapy [93]; as well as regulation of transport as function of clot structure for thrombus growth and lysis [21,22]. In addition, models can be used as a method to identify mechanisms contributing to rare bleeding disorders [1]. As another example, trauma remains a major cause of death, and extending current thrombosis models could provide new insight into improving outcomes, especially when considering the variety of products used to restore blood volume and hemostatic function. Few models have investigated how platelet function may change in cold vs warm storage, and across healthy donors and trauma patients [94]. These are just some out of many emerging frontiers where computational modeling may enable key innovations.

Additional opportunities may also be driven by several emerging and promising interdisciplinary areas of thrombosis research. Platelet function and fibrin formation outside of thrombosis has received recent attention, providing potential directions for computational scientists. It has become clear that thrombosis is tightly integrated with inflammation (thromboinflammation). Neutrophil extracellular trap formation [95] and anucleate platelet migration [96] may aid in bacterial clearance. Fibrin, itself forms a biofilm that may defend against microbial invasions and may provide insight into wound healing [97]. Furthermore, platelets may form heterotypic interactions, eg, with neutrophils, after potent stimulation [98]; which is a proposed mechanism of microvascular obstruction in ischemiareperfusion injury of high significance in stroke and myocardial infarction. Also, platelets appear to play a role in tumor metastasis [99], which may provide a future direction for computational studies at the interface of thrombosis and cancer.

4.3 | Concluding remarks

In summary, we have synthesized information from different modeling approaches in thrombosis and discussed how computational models can be applied to simulate various thrombosis processes. Modeling advancements are motivated by the intrinsic multiscale, multiphysics nature of thrombosis, and its trajectory leads toward integrating techniques at various length or time scales into a single system. Such integration can enable simulations to bridge mouse models, bench-top assays, and patient-specific thrombosis. However, computational simulations are only as good as the current knowledge of the thrombosis field and the data used to build the underlying model(s). Therefore, simulations require reliable *in vitro*, *ex vivo*, or *in vivo* data. Also, current thrombosis models are tailored to the specific phenomenon being represented, and a compromise must be made when choosing an approach based on the scale of interest. There is currently no one size that fits all

models. However, with continued advancements, computational modeling shows promise in becoming a robust, accessible, and generalizable tool for thrombosis research.

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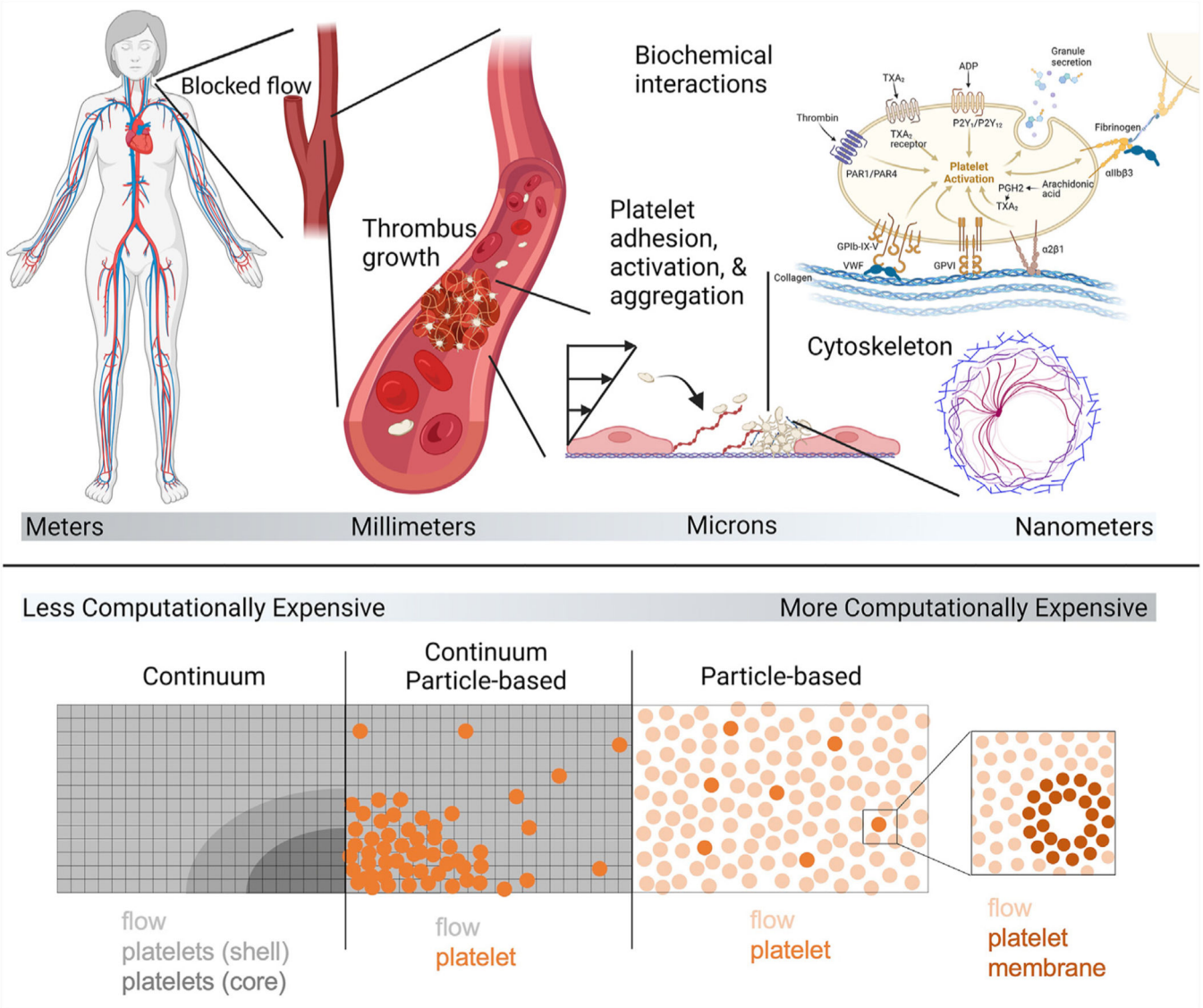

FIGURE 1.

Multiple scales involved in thrombus growth. At the largest scale, blocked flow can change flow and pressure waveforms in the circulation, while potentially preventing blood flow to vital organs. On the scale of a blood vessel, blood is often considered a continuum (fluid). On the scale of a thrombus, platelet aggregation and fibrin formation are sometimes modeled as a continuum for large-scale models or as particle-based models when the length scale of the simulation and thrombus approaches the size of platelets. Within the thrombus are platelets bind to plasma proteins and the sub-endothelium. On the platelet membrane, there are individual receptors, and a sufficient number of receptors require ligation in order to slow a platelet after transient interactions with a surface. Furthermore, granule secretion leads to release of proteins and platelet activation agonists. With outside-in and inside-out signaling, platelet activation can proceed with cytoskeletal rearrangement causing platelet shape change and contraction. Models of thrombus formation usually involve a continuum and/or a particle-based modeling method. In the bottom panel, a continuum method is used

to discretize a blood domain in order to solve algebraic equations that represent differential equations. Average values for parameters like blood velocity are assigned to this mesh (grid). Particle-based methods use particles, instead of a mesh, and can be used to represent flow, platelets, and/or subcellular features like a platelet membrane. Due to the nature of each of these types of models, continuum methods are most commonly used at macroscales, while particle-based methods are very advantageous at the microscale, noting that these methods can require more computational power and time.

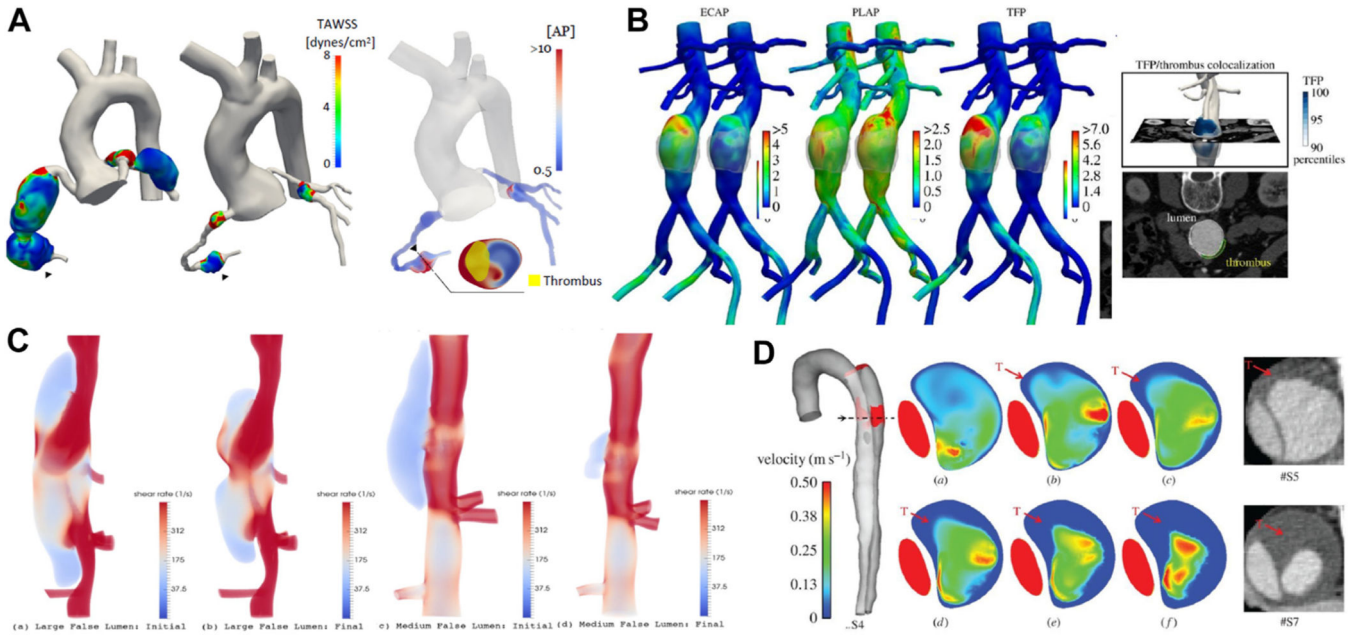

FIGURE 2.

Macroscale modeling of hemodynamic descriptors of thrombosis. (A) Spatial distribution of time averaged wall shear stress and activated platelet concentration in Kawasaki disease aneurysms [33,34]. (B) Spatial distributions of endothelial cell activation potential, platelet activation potential and thrombus formation potential in an abdominal aortic aneurysm having a thin thrombus on the central anterior surface [35]. (C) Aortic dissection volume rendering of scalar shear rate at peak systole for two lesions at the initial (left) and final (right) stages of thrombus formation upon dissection (blood flow direction is from top to bottom in all cases) [36]. (D) Type B aortic dissection velocity magnitude contours at peak systole just above second tear showing the effects of thrombus growth on the flow field at different time points, compared with follow-up CT scans. The velocity in the thrombosed region is gradually reduced as thrombus is formed. In the model S4 (left), in red, thrombus [37].

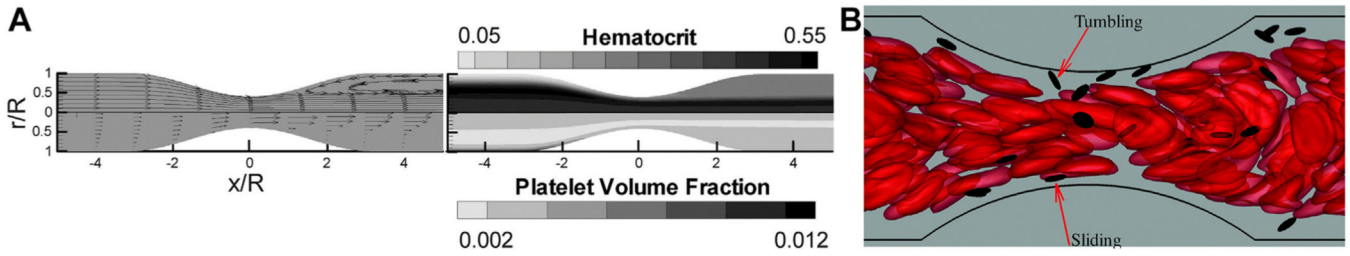

FIGURE 3.

Examples of transport modeling. (A) Continuum model to predict transport of erythrocytes and platelets [6]. (B) Modeling and simulation of platelet transport in a blood suspension with flow through a constriction using particle based methods [12].

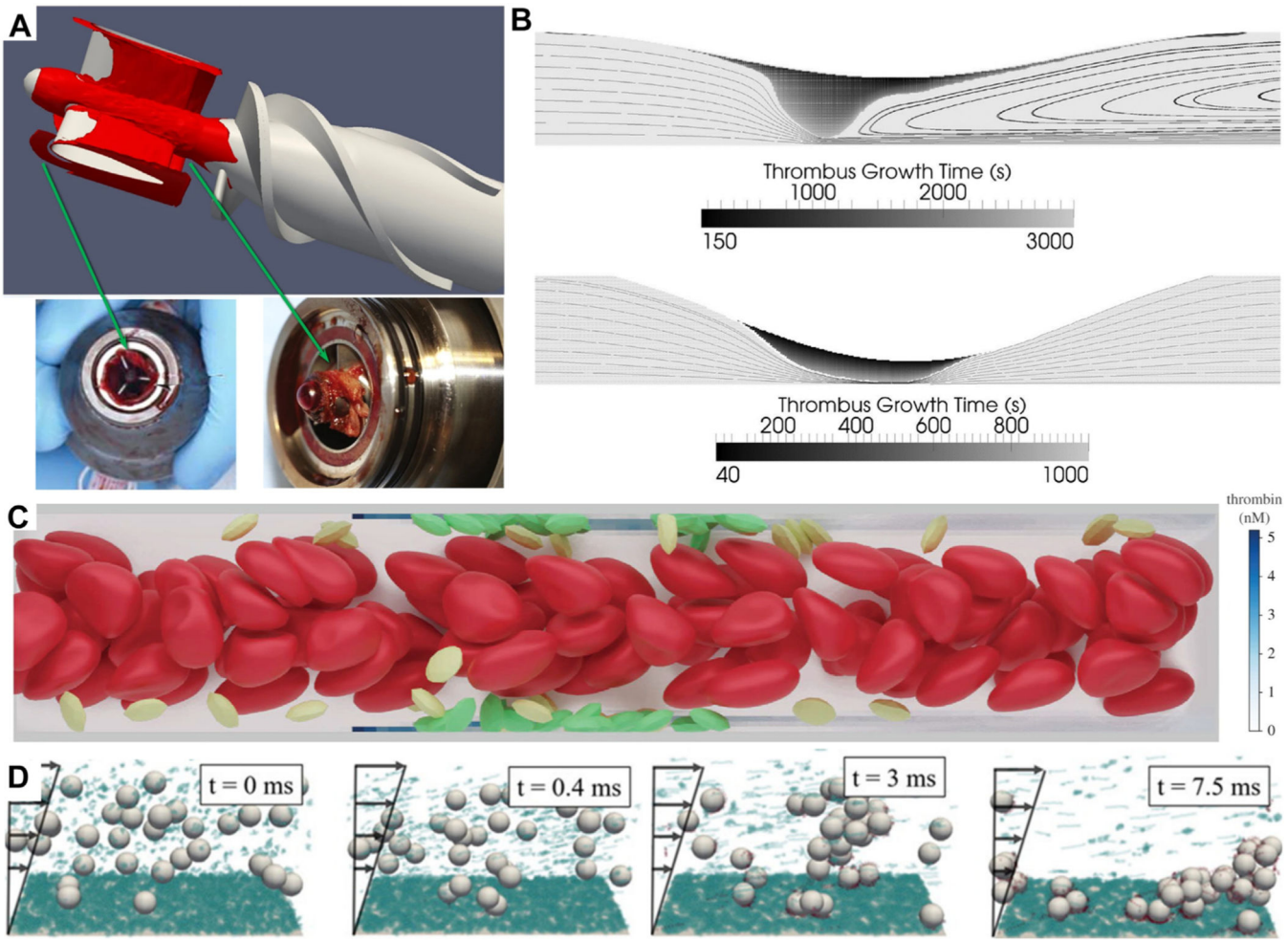

FIGURE 4.

Examples of platelet aggregation simulations using continuum models. (A) Depicts thrombus growth in an axial flow ventricular assist device relative to clinical observations [7]; and (B) shows thrombus growth modeling over a stenosis to investigate growth on an *ex vivo* stenosis [6]. Mesoscale models of individual cells can be used to (C) quantitate platelet aggregation behavior when individual cellular biomechanics are altered [52]. (D) Model of von Willebrand factor extension and interaction with platelet transport near a reactive surface using glycoprotein Ibα-von Willebrand factor A1 kinetics using particle based methods for a shear rate of 10,000 s^{-1} [55].

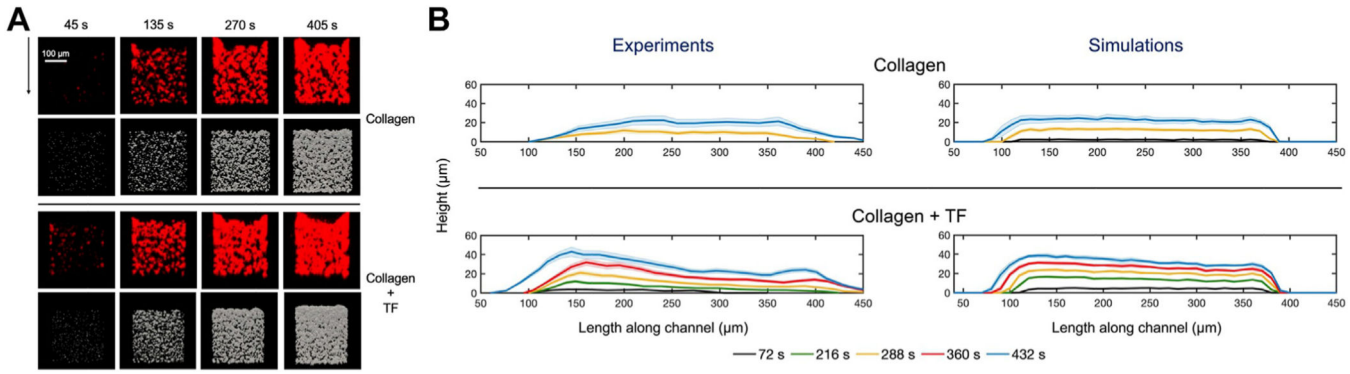

FIGURE 5.

A coupled model of thrombin production with platelet aggregation compared with *in vitro* microfluidic results [48]. (A) Images of the experimental platelet aggregation (red) relative to simulated platelet aggregation (gray) with (B) corresponding thrombus height measurements from experiments compared with predicted heights from simulations.

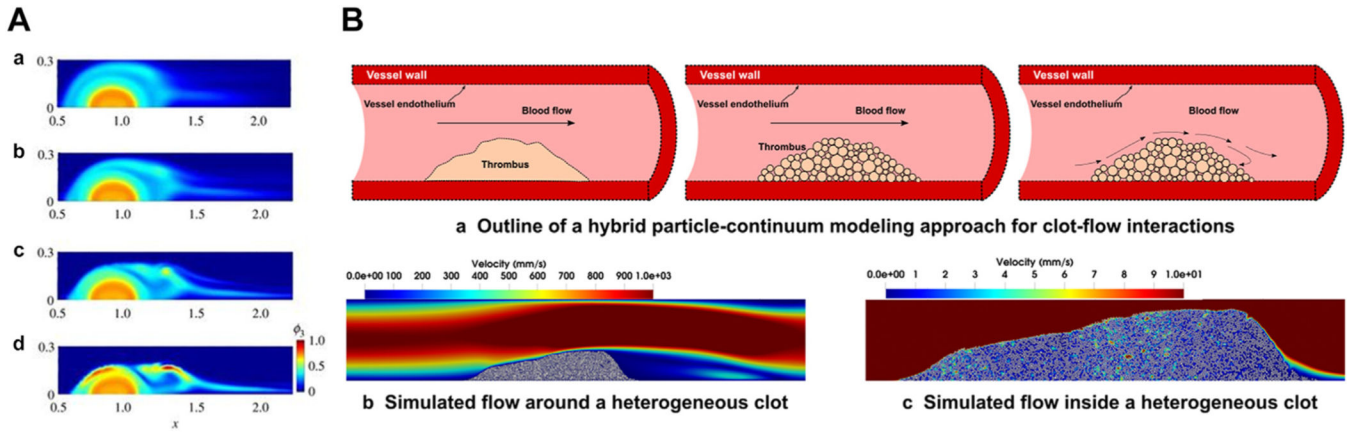

FIGURE 6.

Computational modeling of thrombus mechanics. (A) Impact of the flow shear rate on blood clot stability. (A–D) Spatial distributions of clot volume fraction at different shear rates: (a) 250 s^{-1}, (b) 500 s^{-1}, (c) 1000 s^{-1}, and (d) 2000 s^{-1} [79]. (B) Illustration of a hybrid particle–continuum fictitious domain modeling framework to incorporate clot shape and morphological heterogeneities in computational models [22].