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Reply to comment

Advancing research on blood coagulation and thrombosis

Reply to the comments on “Modeling thrombosis in silico: Frontiers, challenges, unresolved problems and milestones”

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First of all, we would like to thank the editorial board of the journal “Physics of Life Reviews” for the organization of this fruitful and interesting discussion, and also, of course, the commentators who shared their ideas about thrombosis and hemostasis raising most important questions in this field. We intend here to give some responses to the valuable and inspiring comments by Andrews and Gardiner [1], Yazdani and Karniadakis [2], Fedosov [3], Tomaiuolo and Brass [4], Hemker, Bloemen, and Hemker [5], and Tindall [6].

Andrews and Gardiner raise the importance of vascular shear and biorheological parameters in the control of platelet function within flowing blood [1]. It is now well recognised that platelets are sensitive to shear stresses to which they are exposed within the circulation, although the complex and adaptive nature of the vasculature renders this hard to model experimentally within the laboratory. In vitro analysis of thrombus formation in flow chambers or capillaries has provided extensive insight into the process of thrombus formation and the cell signalling mechanisms that regulate this [7], although we should remain cautious in our interpretation of data from such models since these largely have involved steady flow. Within the circulation arterial blood flow is pulsatile and the implications of this, and local changes in blood pressure, geometry, bifurcations, shear gradients and resultant complex flow pattern are largely uncharacterised. We agree that exploration of these phenomena represent an experimental priority and propose

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that modelling approaches may provide the means explore behaviour that is currently hard to visualise within the laboratory.

A second important aspect raised in this insightful response was the nature of the receptor biochemistry that controls platelet capture and the formation of a thrombus. The response to increased shearing stress is not purely passive (as the interaction between VWF and GPIb may be considered), and additional reactive shear sensitive mechanisms also contribute. Of note is the ability of high shear to regulate proteases that lead to irreversible receptor cleavage which may provide a means to limit or terminate responses (although inhibitory adhesion receptors may also be cleaved) [8]. Little is presently known of the mechanosensing mechanisms that control this process.

We agree with Drs Andrews and Gardiner that understanding of the real conditions in which platelets function *in vivo* represents an important area for further development before it will be possible to implement computational models that effectively model platelet behaviour. The potential to model platelet function in patient-specific flow represents an exciting future ambition.

Yazdani and Karniadakis raised a number of important questions about the physics and biology of thrombosis modelling [2]. One of them is the importance of mechano-transduction and mechano-biology involved in thrombus formation. We agree with this assessment. These terms in general may be addressed to a number of complex processes that take place at different levels of spatial organization and on different time-scales, e.g. platelet activation from its deformation due to the flow, or flow-induced von Willebrand factor extension that influences the additivity of platelets. Another intriguing question is how the porosity of fibrin mesh is influenced by fluid flows. It is a novel area of study in a field thrombosis and hemostasis, and only a limited number of experimental and theoretical models are available at the moment. These mechano-biological problems are also multiscale themselves – as correctly noticed by Yazdani and Karniadakis, there is a need of molecular-level characterization of mechano-transduction processes in activating platelets. The same applies to the modelling of ligand-receptor binding and unbinding and understanding the role of catch-slip dynamics, to the deformation and degradation of platelet cytoskeleton during the activation, and even to the affinity of coagulation factors to each other during enzymatic reactions in presence of flow. Another issue is an adequate integration of mechano-biological sub-models into a general framework. All these problems form a new fruitful field of interdisciplinary research. We agree that exploration of molecular mechanisms involved into thrombosis and hemostasis would lead to a new insight into the rheology of platelet aggregates, thus making possible a predictive patient-specific modelling of thrombotic occlusion and estimation of embolization risks, etc.

Another idea underlined by Yazdani and Karniadakis is the importance of the membrane-bounded biochemical reactions involved in coagulation of plasma, as the reduced dimensionality of the problem drastically alters the kinetics of signalling and coagulation processes. This also should be taken into account while extracting the unknown parameters from the experiments that have been carried using platelet-free plasma. This reduced dimensionality would also influence the computational performance. Stochastic modelling may be a better option over the continuum-based models in some cases when a low number of reacting molecules is inconsistent with the definition of the continuum. Yazdani and Karniadakis also presented a way to overcome the difficulties by using a DPD-based approach to reaction-diffusion problems in flow.

In addition, when discussing the technical point of multiscale modelling, Yazdani and Karniadakis have proposed a novel machine learning “hidden physics” approach to overcome the difficulties with parameter inference and uncertainty. We are grateful for this comment and share the optimism that the involvement of modern computational techniques would boost the modelling in thrombosis and hemostasis in a not-very-distant future.

Fedosov, is among others who, emphasises the importance in hemostasis of components that occur over many time and space scales [3]. As rightly highlighted in his response the complexity of the reactions involved in thrombus formation occur over multiple scales makes constructing reliable and indeed predictive models of hemostasis particularly challenging. This is an active area of research by the mathematical community but significant challenges still need to be overcome. The hybrid methods mentioned in this response are certainly promising and are being utilised to model many biological systems that bridge scales [9–11]. But, there is much work to be done on reducing the computational cost of such approaches as well as developing ways to reliably parameterise hybrid models from experimental data. The use of these approaches to model a growing thrombus is particularly challenging. Not only does the thrombus contain elements that interact over multiple scales (in time and space) but a thrombus grows in an environment of flowing blood that permeates and moulds the growing clot. These interactions greatly increases the theoretical challenge.

Comments by M. Tomaiuolo and L.F. Brass raise important questions about the role of mathematical modelling in the attempts to understand hemostasis and thrombosis [4]. The main thesis that modelling and simulations should be predictive is illustrated with several examples related to thrombin generation assays, extrinsic and intrinsic coagulation pathways, platelet aggregation. We share this view on the problem together with the expressed concerns about the limitations of current understanding of these questions. From a more general perspective, this comment brings our attention yet again to the multiscale and multicomponent aspects of blood coagulation with its various pathological manifestations. Indeed, multiscale modelling in biomedical applications is an important trend in modern science. In spite of visible progress achieved during the last decade, we are clearly at the very beginning of this adventure. This is particularly true in the area of hemostasis and thrombosis where multiscale and multicomponent approaches should still be developed. As we mentioned earlier the interaction of different space and time scales locally at the injury site or at the systemic level is particularly challenging and indeed remains out of the reach of current modelling approaches. The difficulties to develop such approaches are multiple: not only to identify appropriate questions and to elaborate the modelling tools, but also to bring together the specialists from different disciplines in order to provide a fruitful interdisciplinary environment. As it is indicated in the comments, the multidisciplinary approach remains rather an exception in the field of thrombosis and hemostasis.

The comment by Hemker, Bloemen and Hemker [5] brings our attention to the important set of interlinked problems that are persistent in the complex systems modelling, and, in particular, in the models of thrombin generation: reliability of model assumptions based on the limits of our knowledge, choice of the level of detail, and of the model validation. They show that a small model based of a simplified clotting scheme is perfectly capable of describing experimentally observed thrombin generation patterns. We whole-heartedly agree that optimal choice of the model size and content, as well as clear evaluation of the model relevance, are critical in order for the model to be efficient and reliable. Too many researchers, unfortunately, still think of the computational models of biological reaction networks in terms “the bigger, the better”. This, in turn, raises a new question: is it possible to develop a set of rules, or laws, aimed at the identification of the minimal model required to describe a biological system? One interesting possibility could be use of the reduction approaches that allow mathematically precise simplification of a large set of ordinary differential equations, as was shown for thrombin generation [12].

Comments by M Tindall again emphasise the importance of the multiscale approach alongside the difficulties of its implementation, this is clearly an area of concern. But in his comments he points to the importance of overcoming these issues, and that the interdisciplinary approach holds out great promise and could greatly aid in ensuring the future goal of predictive models could become a reality.

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