# *System insights into hemostasis: open questions and the role of mathematical modelling: comment on "Modeling thrombosis in silico: Frontiers, challenges, unresolved problems and milestones" by A.V. Belyaev et al.*

# System insights into hemostasis: Open questions and the role of mathematical modelling

Commentary on "Modeling thrombosis in silico: Frontiers, challenges, unresolved problems and milestones"

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The emergence of system sciences such as Systems Biology, Systems Medicine and Systems Pharmacology [8,9] over the past two decades has seen a rapid growth in the application of mechanistic mathematical and computational models in the biological, biomedical and pharmacological sciences. Such models have been formulated to elucidate understanding and provide predictive simulations in areas as diverse as tumour growth [1], immunology [4], pharmacology [5], bacterial motility [10] and the physiology of the heart [6]. In seeking to provide insight, models have been formulated to tackle problems at the subcellular, tissue, organ and cohort scales. In doing so, a range of mathematical modelling approaches have been employed including differential equations and multiscale modelling [3], right through to more computationally based ones such as cellular automata and hybrid agent based modelling [7]. Each approach brings with it its own benefits and issues, but ultimately is focused on advancing knowledge of the underlying system to which it has been applied.

The review of Belyaev and colleagues [2] in this issue of Physics of Life Reviews highlights both modelling to date and the need for further modelling in the field of hemostasis and thrombosis formation. Whilst critically important for human health – the largest causes of death are a result of disorders in the area, the field has only recently begun to receive more focused attention from the mathematical and computational modelling communities. This is important because as a whole the hemostasis system is difficult, if not impossible to isolate via *in vitro* or *in vivo* studies. Whilst "pieces" of it can be isolated *in vitro*, for instance platelet aggregration at the cellular scale, an informed predictive framework is required which is able to combine individual aspects such as subcellular biochemistry, cell signalling, cell adhesion and fluid dynamics (in often complex geometries), to understand the regulation of *in vivo* regulated processes such as thrombosis formation. This is important for a number of reasons.

Firstly, such a framework will allow aspects of the system, either components of it or it as a whole, to be elucidated. Secondly, such a tool can be used to provide future clinical predictions of an individual's hemostasis wellbeing based on their current status. Indeed, we can envisage a world in which blood samples from patients allows their risk of hemostasis related diseases to be stratified, the effect of their therapeutic treatments to be regularly evaluated and the need for future interventions to be identified, all via patient sample informed predictive modelling. Finally, at the level of basic science and drug discovery, such a framework can also be used to test hypotheses regarding therapeutic strategies and identify which are the most fruitful routes for future investigation. Mechanistic mathematical modelling provides a plausible platform for undertaking this task

and as the authors point out, has already in a short period of time, been effective within the field.

This review makes clear the wide range of areas within the hemostatis system that have already been mathematically modelled and the modelling approaches which have been employed. These range from multiscale discrete models of platelet adhesion and aggregration through to full cell models of erythrocyte regulation along with continuum models describing coagulation under flow. As Belyaev et al. [2] rightly point out, each approach is able to provide different levels of insight to the system. Whilst a full multiscale model of homeostasis and thrombosis regulation (from the subcellular to whole individual scale) would be ideal, the size and computational cost of constructing such a model is currently prohibitive. Whilst the reviewers highlight the need for informed methods for parallelising such largescale models, as with many other System Science application areas, there remains an open requirement for mathematical models of hemostasis which are simultaneously able to capture the key features from the subcellular to whole individual scale, whilst providing useful clinical level detail in real time.

Within their work the authors provide a helpful list of key challenges, both biologically and modelling, within the field. These provide useful entry points to those new to the field from both backgrounds and make it clear that tackling such challenges will not only further our understanding of hemostasis systems, but greatly aid in ensuring the future goal of an integrated predictive model of hemostasis becomes a reality.

**References**


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