

Provisional Patent Application: Hybrid System Modeling of Human Blood Clotting

Joseph Makin, Srini Narayanan, and Roopa Ramamoorthi
International Computer Science Institute

1947 Center Street
Berkeley, CA 94704

Email: makin@eecs.berkeley.edu, snarayan@icsi.berkeley.edu

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1 Written Description

The process of blood coagulation in mammals is complicated, and involves the interaction of more than a dozen coagulation factors as well as a number of proteins from the kinin-kallikrein system and protein inhibitors. Attempts to model coagulation mathematically have previously focused on a smaller subset of interactions, perhaps one of the pathways or just a portion of one of them (cf. [1],[2], [3],[4],[5], [6] and [7]) using continuous-time chemical rate differential equations. There are, however, at least two reasons why this methodology is inadequate for modeling the entire coagulation cascade. First, there is reason to believe [8] that certain events in the cascade are better modeled by punctuated phase changes, rather than as evolving continuously. For example, antithrombin III and α_2 -macroglobulin are only able to inhibit thrombin activation below a certain threshold of thrombin [9]. Similarly, concentrations of free zinc ions are thought to toggle the activation of several of the proteins of the contact activation portion of the clotting cascade [10],[11]. Second, the problem with modeling coagulation as a purely continuous-time phenomenon is that the process is too complicated (with thresholds and discontinuous phase changes) to permit a precise description of the various parameters and their interactions in terms of differential equations.

Our invention is a novel modeling framework and software program which constructs a robust, faithful, interactive, and graphical computer simulation of the entire coagulation process. The framework is faithful in that it accurately models mammalian blood clotting; robust in the sense of doing so over a wide range of parameter settings; interactive in that the system operation and parameter settings can be interactively changed while the software program is executing, and hypothetical “what-if” simulations performed; and graphical in that the model is a formal graphical structure that supports visualization of the clotting process as well as exact quantitative analysis. Technically, the invention uses an emerging alternative modeling paradigm in which the coagulation cascade is viewed as a “hybrid

system” (HS), i.e. one consisting of interacting continuous and discrete dynamics. Hybrid-system theory is a fairly new area of research at the intersection of control theory and computer science which has made considerable progress in the last decade along a number of different but related frontiers. Chief among these are analysis, in the form of verification and decidability; controller synthesis; and modeling and simulation.

Our hybrid system model of the blood clotting pathway is a novel computer program that is accurate enough to be able to simulate the quantitative impact of potential therapeutic interventions to patients with hyper- and hypocoagulatory diseases. Clinicians can decide on treatment choices, including dosage levels for specific diseases and for specific patients, through computer simulation and analysis, potentially lessening the need for expensive, time consuming human trials. The invention also provides an ideal tool for researchers in the field to refine their understanding of the complex blood-clotting process: parameters, equations, and model structure are easily modified, adding new reactions is straightforward, and simulations provide detailed information about (*inter alia*) the concentrations of clotting factors with time. The framework further supports research, exchange, and dissemination of information (with common data and model formats) on the impact of disease pathologies (including combinations of diseases) that are caused by a deficiency or surfeit of blood factors. Some of the conditions that can be readily studied include various manifestations of hæmophilia A, which results from deficiencies, moderate to severe, of factor VIII; hæmophilia B, which is a consequence of factor IX deficiency; the hypercoagulation disorder antithrombin deficiency, which affects about 0.02% of the population [12]; etc. Other blood-clotting diseases can be modeled as mutated forms of clotting factors; patients suffering from factor V Leiden, for example, are prone to thrombophilia (excessive coagulation) because their factor V proteins are resistant to inactivation by activated protein C. Our model can simulate this disorder at multiple levels of detail incorporating extant empirical studies and clinical data. Importantly, the model can be used predictively to better quantify the risk of Deep Vein Thrombosis (DVT) or Ischemic Stroke in patients with Factor V Leiden (heterozygote and homozygote) with other risk factors (age, smoking, usage of birth control methods). The framework is open and modifiable to incorporate new pathologies and study the impact on clotting processes.

From a technology perspective, this invention allows us to make use of all the available knowledge—both quantitative and qualitative—to construct an accurate, robust, and predictive model of the coagulation cascade. Unlike previous models, our invention is a graphical, hybrid model of the clotting process which supports visualization as well as exact quantitative analysis and simulation. We expect the software to benefit clinicians who will routinely compute dosage levels for specific INR ratios for patients on anti-coagulants (such as heparin or warfarin), including the impact of various dietary choices and vitamin-K levels. Drug manufacturers will use the software for evaluating the impact of new therapeutic interventions without the need for expensive clinical trials. Researchers will benefit by having an interactive and accurate model for studying clotting disorders, for refining their understanding of the clotting process, for identifying possible leads for new therapies based on analysis of the model, and for dissemination and instruction of quantitative information of the clotting process in classroom, laboratory, and clinical settings.

The hybrid system model of the blood clotting pathway will be released as a software

package with the options for simulating a variety of blood clotting disease pathologies and associated therapeutic interventions already installed. The software will thus be usable off-the-shelf to conduct evaluations of treatment choices and dosage levels for specific interventions on the clotting cascade. The software package will come with a graphical display of the coagulation cascade, allowing the user to monitor, display, and manipulate specific pathways or factors of interest (such as thrombin production). Researchers and power users would be able to add components to the model in an “object-oriented” manner, where the component is designed with maximum reuse of existing structure and functionality. Newly constructed components will be integrated into the graphical model using its visualization tools, where modules can be attached to and integrated into the appropriate points in the visual representation of the clotting pathway. The model modification process can be incremental, in that the model changes can be made interactively; or model editing can be a batch process, where changes are made, stored, and the entire model executed from start to finish. This way, the impact of selected component modifications and “what-if” propositions can be evaluated incrementally in an on-line fashion, or the entire clotting process can be simulated and analyzed for one or more parameter settings in a batch mode.

2 Reduction to Practice

We have achieved initial reduction to practice by building a model which incorporates all the essential functionality described in the written description of this provisional patent application.

The model was implemented using hybrid Petri nets (HPNs), a graphical modeling formalism for modeling hybrid systems. Classical Petri nets are a well known computational formalism for the modeling and simulation of discrete-event dynamical systems, with constructs for sequential and concurrent process execution, for resource consumption and production, and for inhibition. HPNs extend classical Petri nets from the domain of purely discrete phenomena to the domain of hybrid dynamics. HPNs are thus able to incorporate continuous-time and continuous-state phenomena by supplementing the traditional discrete event architecture with continuously varying events and states. Our current implementation is based on the *Visual Object Net++* platform, a dedicated HPN modeling and simulation environment [13], which includes a graphical language that offers a suite of object-oriented programming (OOP) features: hierarchical organization, inheritance and object reuse.

We built the HPN model of the complete clotting pathway and performed simulations of a) the normal clotting process, b) clotting processes for specific blood disorders, and c) effects of interventions on the clotting process. To date, ours is the most comprehensive model of the entire clotting pathway that we are aware of. Using published clinical data on the normal clotting pathway, we simulated the baseline clotting process for the normal case, including time to clot and thrombin production. We then simulated disorders and interventions to the normal process as model changes to either a) the relevant coagulation factors and associated protein complexes, or b) to the structure of the network. Our initial results are very encouraging. In all cases, the predictions on clotting time and thrombin

production were congruent with clinical observations.

We attach a more technical description of the hybrid system model implementation including pictures of the model and the results obtained thus far. The attachments show overall hierarchical structure of the graphical HPN framework and the detailed implementation with of the coagulation cascade. Also described are the initial results and predictions of the model on representative use cases for our invention.

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