An Agent-Based Simulation of Blood Coagulation Processes

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***Abstract*—This article describes the creation of an agent-based model of blood coagulation within the Lindsay Composer (LC) computational framework, which can be used to simulate and visualize physiological processes inside the human body. Swarm Graph Grammars (SGG), a generic modelling language, are used to design the interaction behaviours of the involved bio-agents which represent the cellular and chemical structures found in human blood. Physical interactions among the agents, such as collisions and binding, are computed by an embedded physics engine. In order to effectively retrace and to accurately model coagulation, comparisons with the results of established mathematical models are drawn. The blood coagulation simulation accounts for the formation, expression, and propagation of blood clots within the injured area of a blood vessel. We demonstrate how 3-dimensional, interactive agent-based models and programming frameworks provide complementary tools for research, for learning and for exploring the complicated nature of physiological processes.**

Keywords: Agent-based Simulation, Blood Coagulation, Swarm Graph Grammars, Lindsay Composer

I. Introduction

THE human circulatory system is responsible for transporting materials (such as nutrients, hormones, and immune cells) within the entire body [1]. One of the important aspects of this system is its coordination with the homeostatic system to limit the loss of blood after an injury. The natural process of stopping the flow and loss of blood, occurs in three stages: (a) vascular spasm, or intense contraction of blood vessels in the area of the injury, (b) formation of a platelet plug, and (c) blood clotting. Once blood loss has stopped, the tissue healing process begins [1]. Understanding the biological and physiological processes of blood coagulation is important for applications in the biomedical sciences. For instance, there are many disorders, which can be resolved given that the blood coagulation process is well understood, such as improper regulation of thrombus growth, thrombotic complication with cancer, or vessel blocking effects of clots [2].

Computational and mathematical models can be used as one of the available tools for grasping the complexities of biological processes. There have been numerous studies to simulate the blood coagulation process computationally. However, this process is an extremely complicated homeostatic mechanism, which involves various biochemical and mechanical factors. Therefore, most of these attempts are focused on specific aspects of the entire system. For instance, there are only a few models that couple the formation of the platelet plug with the formation of the clot. Almost all of these studies rely on ordinary differential equations (ODEs) or partial differential equations (PDEs) to model the process [2]. These studies generally lack stochasticity, which is greatly important for biological systems. Furthermore, these mathematical models are not able to propose an easy way to demonstrate accurate 3D visualizations and interactivity. Blood coagulation, as well as other biological processes can be computationally modelled using an agent-based modelling (ABM) paradigm. ABMs describe the interactions between autonomous, decision-making entities called agents [3]. As a whole, the local interactions between these agents may result in a system-wide change. In fact, systems that are modelled using this paradigm can be highly sensitive to small details, such as specific local agent interactions or the order of execution of the agents.

Swarm graph grammars (SGGs) provide a unified algorithmic language for developing such agent-based models. The SGG modelling language is able to address the complexity of biological systems across different scales [4]. A SGG describes agent behaviours by a set of rules. Each rule consists of a set of predicates and a set of actions. At each step in a simulation, the predicate set of a rule is tested, and if it is true, its action set is executed. Thus, a simulation is driven by the sequential executions of if-then rules.

The blood coagulation simulation is developed within a computational framework called the Lindsay Composer (LC) that contains various embedded computational engines such as the Swarm Graph Grammar Engine. This framework utilizes efficient embedded computational engines with visualization technologies and is considered an ideal simulation environment for developing visual and complex biological and physiological models. Based on the materials discussed above, the goals of this project are: (1) Developing an accurate computational simulation to study the blood coagulation process, and (2) providing a semi-realistic 3D visualization and an intuitive way for composing, computing and demonstrating different model scenarios.

The remainder of this article is organized as follows. In section 2, we review related work with respect to the blood coagulation process. Section 3 presents the biological details of blood coagulation as well as the bio-agents that can be identified. Section 4 describes our model and its methodology. Section 5 is dedicated to the computational framework used

in this study, and in Section 6 the results of the simulation are presented. Section 7 draws the conclusion for this study.

II. Related Work

Due to the complex nature of coagulation and its serious clinical consequences, there have been a number of studies focusing on different perspectives. Over the past 30 years, a reasonably comprehensive understanding of the processes involved in blood coagulation has been developed. The following is a brief overview of research conducted in this area over the last decade.

The kinetics of the extrinsic and intrinsic pathways and their feedback loops have been modeled using a PDE system in a study conducted in 1989 [5]. Later on in 1993 and 1994, this study has been enriched with more details with closer correlation to experimental results [6], [7]. In 2001, it was shown that the activation threshold for the coagulation chemical cascade is affected by the flow rate, size of the wound site, and the initial concentration of the chemicals [8]. In 2004, a PDE model was introduced to describe the interactions between platelets and sub-endothelial layers and cohesion of activated platelets [9]. A relatively comprehensive model of coagulation was proposed in 2005, in which rheological properties of the clot, Newtonian fluid models, biochemical interactions, and fibrogenesis were incorporated. This study employed convection-reaction-diffusion equations to model platelet activation, whereas the formation of the clot is modelled as a sheer thinning viscoelastic region, which first forms over time and then gradually dissolves [10].

We present two recent studies in some more detail, as they proved seminal in informing our own work. The first study is a PDE model of coagulation, which encompasses all the chemicals that are known to be involved in the process [11]. The second model is a hybrid of PDEs and a Cellular Potts Model (CPM); it is considered one of the most comprehensive models of coagulation today [2]. These two studies are not only used to compare the results obtained in our work, but they also show how an ABM approach like ours can be considered a complementary tool and method for the study of complex biological systems in general.

A. A Model for Stoichiometric Regulation of Blood Coagulation

A PDE system is used to describe the vitamin K-dependent coagulation process [11]. The coagulation kinetics in this model contains 27 equations, which describe the fate of 34 chemical species. The final result of this system describes how the concentration of thrombin at the injury site changes over the course of the simulation. The concentration of thrombin varies, based on the initial concentration of tissue factors released at the wound site. The initial concentration of tissue factors is a function of the size and characteristics of the wound site.

Even though there is a relatively close correlation between the results of this model and in vivo experiments, this model did not consider the role of platelets in the formation of the clot. Neither were the physical and hydrodynamical factors reflected in this study.

B. A Multiscale Model of Thrombus Development

Xu et al. present a two dimensional multi-scale model of the blood coagulation process [2]. The biochemical structures used in this model are blood cells, blood plasma, activated and inactivated platelets, fibrinogen, activating chemicals, and vessel walls. The multi-scale hierarchy of this model is divided into three levels: 100 micrometer, 1 micrometer for cellular structures, and 0.1 micrometer for sub cellular and chemical structures. The modelling approach used is a hybrid of three main sub-models: cell sub-model, biochemical reaction sub-model, and flow sub-model. The cell sub-model is a discrete stochastic Cellular Potts Model (CPM) that represents different types of cells such as platelets and blood cells [12]. CPM is a lattice based computational model, wherein the simulation environment is divided into many lattice sites represented as pixels. Each pixel is associated with an index and an energy state. Pixels that share the same index belong to the same cell. The behaviours of the cells and their interactions are defined in terms of effective energies. At each CPM time step, a pixel is randomly chosen and, based on its energy state, a change of its index is attempted. When a pixel changes its index, it means that the pixel is shifted from one type of cell to another. Over the course of the simulation, the CPM evolves to minimize the total energy of the simulation [12].

The biochemical reaction sub-model is basically a PDE system that is used to describe the biochemical nature of the system. Navier-Stokes equations are used to describe the hydrodynamics of blood flow. The intention for hybridizing these modelling paradigms is to capture the discrete aspects of the coagulation process at the micro-scale level, such as enzyme threshold effects in cells, as well as its continuous aspects at the macro-scale level, such as continuous extension of the clot at the wound site. At each iteration of this simulation, both equation systems are solved and used for updating the CPM.

The resulting simulation successfully demonstrates the formation of the clot at the wound site. This model is fairly comprehensive. However, it does not fully describe some aspects of coagulation. For instance, the biophysical complexity of the system is not well captured, as the physical interactions are limited to the 2-dimensional environment of the CPM. Therefore, it is suggested that other modelling approaches are easier to employ and still more successful in simulating complex biological systems [13].

III. Biological Aspects and Agent-based Model

The coagulation process is initiated after any vascular damage is sustained, which results in the contact between blood cells, thrombogenic factors and sub-endothelial proteins such as collagen. According to the classic view, there are two ways to initiate the blood coagulation process: via the intrinsic and extrinsic pathways. The intrinsic pathway is initiated when blood cells touch the chemicals released from the damaged membranes of the endothelial and sub-endothelial cells at the injury site. These activating chemicals are able to activate the inactivated platelets within the blood flow. The extrinsic pathway takes place when the chemicals released

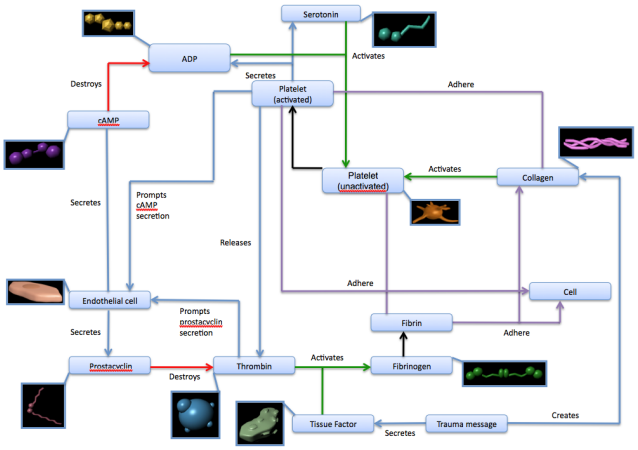

Fig. 1. The interactions between the agents involved in the blood coagulation process initiated by a trauma message.

from activated platelets meet those that have not been activated yet [14]. After these two pathways, the coagulation process enters the common pathway, where the complex structure of fibril networks is formed. These pathways are complex and involve many chemical activities. The outcome of this process is the formation of a clot, which is basically a multi-layer mesh of platelet plugs covered with fibril networks.

In order to model the blood coagulation process the body should be considered as a set of multiple swarms. In fact, the human body is essentially a swarm of swarms, in which multiple types of swarms interact with each other [3], [15]. In this study, it is assumed that all the agents involved essentially behave like swarms. For instance, platelets would be swarm agents that interact and aggregate together based on a set of interaction rules. By studying the process of blood coagulation from a swarm perspective, the interaction between the agents can be formulated as a set of rules. All the interactions are local and occur via collisions. There is no central control in the system directing the agents to form a clot, or even to direct them toward the wound site. This means that the formation of the clot is the result of the independent interactions of individual agents. The strength of this approach is that the agents interact based on simple rules, which eventually results in the complex structure of the clot.

Our simulation contains 12 types of agents (Fig. 1). The main interactions in the simulation are adhesion, activation, and secretion. For example, in a simple scenario, collagen proteins at the wound site activate inactivated platelets within the blood flow. Activated platelets then secrete thrombin, ADP, and serotonin. The activating chemicals activate other inactivated platelets in the blood flow. Activated platelets adhere to each other to form the platelet plug. Any fibrinogen that comes into contact with thrombin molecules becomes activated. Activated fibrinogens are called fibrins, which adhere to each other to form a fibril network. In combination, the platelet plug and fibril networks form the clot at the wound site. These interactions are specified in the form of simple rules, which we formulate as Swarm Graph Grammars as explained in the following section.

Input: $[A_1, A_2, \ldots, A_n]_{agents}$
Output: Executions of Possible Rules

foreach *Agent* $\in \{A_1, A_2, ..., A_j\}$ **do**
  /* R *is the set of rules of each agent.* */
  /* p *is the probability of each* $rule$ */
  /* P_R *is the set of possible rules at each iteration* */
  R = rules defined at each iteration
  foreach $rule \in R$ **do**
    if p != 0
      if ($rule$'s predicate == True)
        Append $rule$ to P_R
  end
end
Sort rules in P_R based on their p
foreach *rule* $\in P_R$ **do**
  retrieve the action
  Perform the action's execution
end

Fig. 2. Algorithm for the SGG engine in Lindsay Composer, which takes care of the ordered execution of the rules.

IV. Methodology

Swarm graph grammars (SGGs) are a unified modelling language for developing complex agent-based systems [4]. The behaviour of an SGG's agent is described by a set of rules. Each rule is composed of a set of if-conditions known as predicates and a set of associated actions. The actions are executed if and only if the set of all predicates is true. The application of each rule is associated with a probability. For instance, if the probability associated with a SGG rule is 0.4, it means that if the set of predicates of this rule is true, the probability of execution of the rule's actions is 0.4 per given evaluation of that set of rules. The algorithm, which takes care of the ordered execution of actions in each simulation step, works through the Lindsay Composer SGG engine as outlined in Figure 2 [4].

Agents are aware of their neighbors within a specified distance and can interact with them. As a result of these interactions, agents may change their directions, velocities, and states [4]. The state of an agent is associated with its energy level. Its state may be changed due to a specific rule. The agent's characteristics and graphical representation are also influenced by its state. For instance, platelets can have three different states: inactivated, activated, and deactivated. The color and rate of activation of a platelet are determined by its state.

V. The Computational Framework

Lindsay Composer (LC) is a 3-dimensional, component-based modelling framework, which utilizes various computational engines and visualization technologies. The objective of the LC framework is to integrate the computational models of physiological functions across the human body. Each object in Lindsay Composer is represented as a hierarchy of components. Each of these components are handled by one

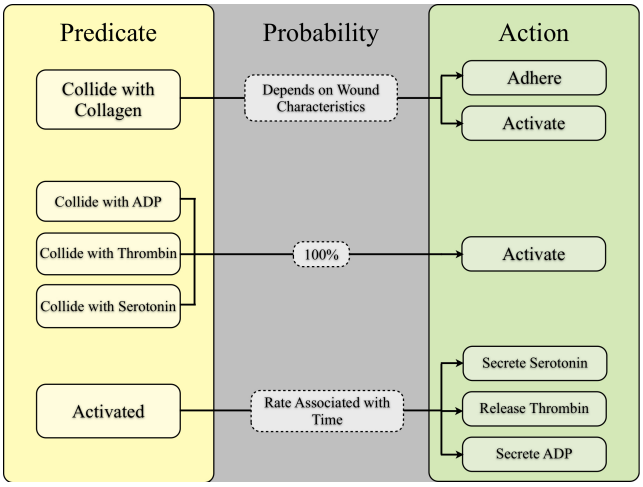

Fig. 3. SGG rules of a platelet. Each component is defined by the aggregation of its child components. For instance, a platelet has a physics, behaviour, transform, and graphics component. The behaviour component contains the SGG rules of the agent.

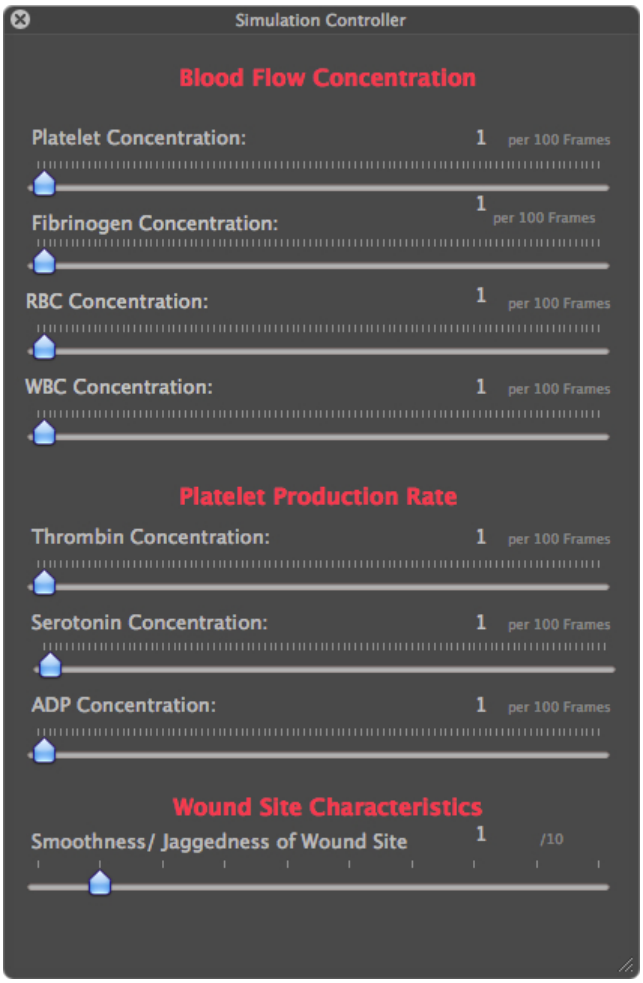

Fig. 4. The graphical user interface to adjust parameters during a simulation.

of the engines of the LC [16]. For instance, if an object has a rigid body component, its physical interactions with other physical objects in the simulation context are handled by the LC physics engine. Dependencies among components, such as binding the 3D representation of an object to its physical state, are described through hierarchal relationships between components. In addition, there is a LC Swarm Graph Grammar Engine to simulate agent interactions. For instance, when two or more agents collide, a message is sent to this engine, which then executes any possible if-then rules between those agents. Figure 3 demonstrates the hierarchal structure of a platelet in the Lindsay Composer. Each platelet has a physics, behaviour, transform, and graphics component. The behaviour component encompasses the SGG rules of the agent. In the case of blood clotting, these rules are activation, adhesion, and secretion. One of the benefits of the framework is that it provides a number of graphical user interfaces (GUI) that are used to adjust simulation parameters dynamically. Figure 4 is the GUI for coagulation simulation. Other GUIs enable users of the system to add or remove agents, or apply new behaviours to agents within the simulation. These features make the Lindsay Composer a good framework for developing an interactive, 3-dimensional blood coagulation simulation with illustrative visuals that help in the understanding of the underlying processes.

VI. Results

We used previous experimental and modelling studies to calibrate our own model, with parameters adopted from [2]. Figure 5 shows different steps of a typical run of our simulation. At the beginning of the simulation, red blood cells and other blood components are flowing out of the ruptured vessel (t1). Some platelets are activated and adhere to the wound site as a result of their interactions with collagen proteins. These activated platelets secrete activating chemicals such as thrombins (shown as blue spheres), which in turn activate fibrinogen molecules and other inactivated platelets (t2). The simulation proceeds with the formation of the platelet plug as well as some fibril networks (shown in white, t3). Finally, the clot is completely formed and prevents the blood components to drip out of the vessel (t4). Activated platelets also reached their deactivated state, with no further thrombogenesis. Continued generation of thrombin could lead to the condition known as stasis, where the normal flow of blood stops within the vessel as the clot blocks its way, which we discuss in more detail in subsection 6.2.

A. Normal Blood Coagulation

Figure 6 shows the graphs plotted for a typical blood coagulation experiment. Graph 1 compares the number of activated (cyan) and inactivated (green) platelets. At the beginning of the simulation, the number of activated platelets increases rapidly. Over time, the rate of platelet activation decreases until there is no more platelet activation by the end of the simulation. This activation trend closely correlates with the results presented in [17]. Graph 2 shows the number of fibrins (dark blue) and number of fibrinogens (purple). Graph 3 plots

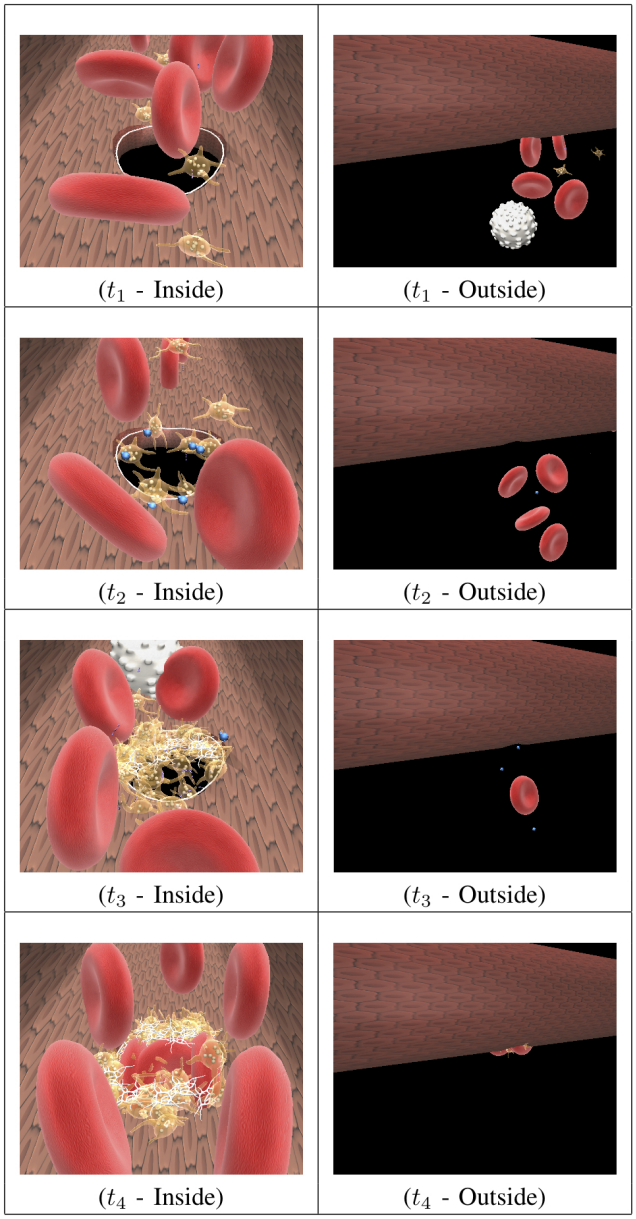

Fig. 5. The blood coagulation simulation at different time steps (t1 ¡ t2 ¡ t3 ¡ t4). The process is observed from two different perspectives: inside and outside of the vessel.

changes in the number of thrombin molecules (green) and the number of all the activating chemicals together (blue). As greater numbers of platelets get activated, the number of activating chemicals also increases. However, as the simulation proceeds more activated platelets reach their deactivated state. Consequently, the number of activating chemicals drops to zero. The trend observed for changes in the concentrations of activating chemicals is similar to the trends presented in [11]. Graph 4 compares the number of platelets that are activated by collagen proteins at the wound site (red) with the number of platelets that are activated by activating chemicals (blue). At the beginning of the simulation, clot formation is initiated by collagen proteins that are exposed to the bloodstream after the injury. However, as the wound is filled by platelet plugs

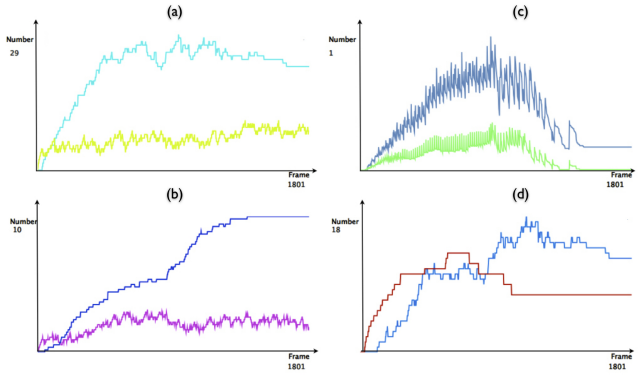

Fig. 6. Agent counts in the case of normal coagulation. (a) activated platelets (cyan) and inactivated platelets (lime green), (b) fibrinogens (purple) and fibrins (dark blue), (c) all the activating chemicals (azure blue) and changes in the number of thrombins (green), (d) collagen proteins in activation of platelets (red) and activating chemicals in activating platelets (blue).

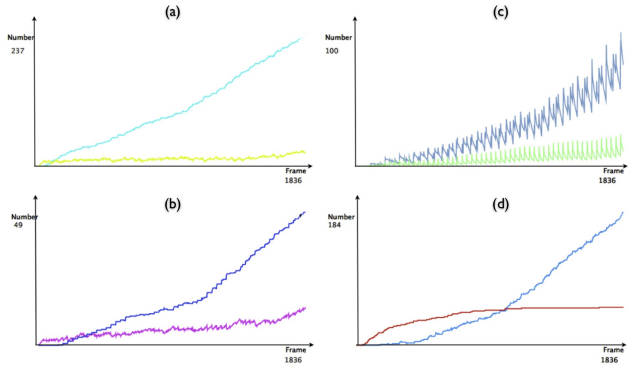

Fig. 7. Agent counts in the case of abnormal coagulation (thrombosis). (a) activated platelets (cyan) and inactivated platelets (lime green), (b) fibrinogens (purple) and fibrins (dark blue), (c) all the activating chemicals (azure blue) and changes in the number of thrombins (green), (d) collagen proteins in activation of platelets (red) and activating chemicals in activating platelets (blue).

and as there is no more room left for further interactions between flowing platelets and collagen proteins, the activating chemicals play a major role for the activation of other platelets.

B. Thrombosis

The presented model can also be used to study pathologic cases such as thrombosis, which results in the pathological development of a clot. There are many causes for this disorder, with one being overreaction of coagulation response. The response may be observed as an increase in the number of platelets in the bloodstream. Figure 7 shows a simulation in which the number of platelets in the bloodstream is 1.5 times more than normal, with their secretion rate increased by 25 percent. The simulation time is exactly the same as in the normal case.

The expansion of the clot (thrombogenesis) is not regulated properly and the clot occupies the cross section of the vessel and blocks the blood flow. Figure 7 shows the graphs plotted for this experiment. The number of activated platelets constantly increases (Graph 1, cyan line), which leads to

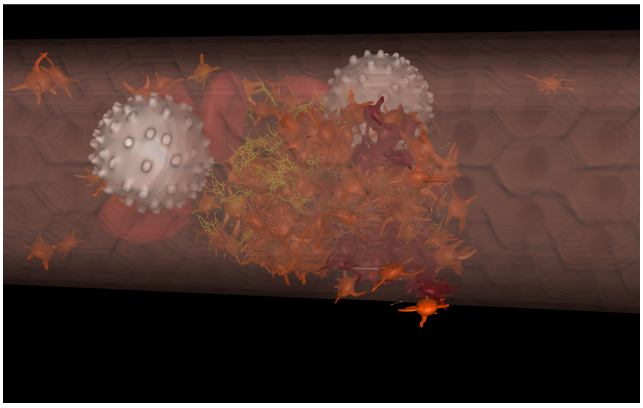

Fig. 8. Clot structure in an abnormal case (thrombosis). The clot blocks the blood flow, which means the vessel is no longer functional for the transportation of blood.

the oversecretion of activating chemicals (Graph 4, blue line and both lines in Graph 3). The oversecretion of activating chemicals leads to the formation of increased number of fibrin molecules as well (Graph 2, blue line). As a result, thrombogenesis is not stopped appropriately and blocks the blood components (such as red and white blood cells) to flow through the vessel (Fig. 8).

VII. Conclusion

We have presented a 3-dimensional, interactive, agent-based model of the blood coagulation process. Simulation accounts for biologically validated agent-based interactions, as well as a semi-realistic visualization of the process. Users are able to manipulate the parameters and observe their effects on the simulation in real time. This simulation is rendered in an interactive 3D environment and can be observed from different camera perspectives. The result of this study has the potential to be used as a tool for both educational exploration and research.

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