2016

Mathematical Modeling of Blood Coagulation

Joana L. Perdomo
Harvey Mudd College

Mathematical Modeling of Blood Coagulation

Joana L. Perdomo

Lisette G. de Pillis, Advisor

Darryl H. Yong, Reader

Department of Mathematics

May, 2016

Abstract

Blood coagulation is a series of biochemical reactions that take place to form a blood clot. Abnormalities in coagulation, such as under-clotting or over-clotting, can lead to significant blood loss, cardiac arrest, damage to vital organs, or even death. Thus, understanding quantitatively how blood coagulation works is important in informing clinical decisions about treating deficiencies and disorders. Quantifying blood coagulation is possible through mathematical modeling. This review presents different mathematical models that have been developed in the past 30 years to describe the biochemistry, biophysics, and clinical applications of blood coagulation research. This review includes the strengths and limitations of models, as well as suggestions for future work.

Contents

List of Figures

Acknowledgments

I would like to express my gratitude to several people who have made the completion of my Senior Thesis all the more enjoyable. First and foremost, I would like to thank my thesis advisor, Prof. Lisette de Pillis, for her continued guidance and support over the past year. Her technical expertise, advice, and words of encouragement helped me learn and push myself. I would also like to thank my second reader, Prof. Darryl Yong, for his helpful suggestions.

In addition, I would like to thank UC Merced Profs. Karin Leiderman and Suzanne Sindi. Working under their supervision for a year to perform a global sensitivity analysis of a mathematical model of blood coagulation inspired me to pursue this Senior Thesis topic.

Lastly, I would like to thank Harvey Mudd College and the Mathematics Department for its support over the past four years.

Chapter 1

Introduction

A person's survival is dependent on various physiological systems functioning properly, including the cardiovascular system. One of the subsystems of the cardiovascular system is known as hemostasis, or the process by which clots are formed when blood vessels are damaged. Hemostasis prevents blood loss while maintaining blood in a fluid state within the vascular system (Barrett et al., 2010). Using complex, interrelated mechanisms in the bloodstream, our bodies keep a balance between coagulation and anticoagulation. If an imbalance occurs within this system, such as a deficiency of certain proteins, our blood may not clot enough, resulting in severe bleeding episodes. Conversely, our blood may clot too much, resulting in severe thrombotic (clotting) events. Some of the problems that may arise from abnormal clotting include significant blood loss, pulmonary embolism, deep vein thrombosis, stroke, cardiac arrest, or even death (Cattaneo et al., 1998; Tanaka et al., 2009). Therefore, blood coagulation research is important because it helps find and test treatments for many clotting abnormalities (Tanaka et al., 2009).

Blood coagulation is a complex process. Some areas of interest include coagulation kinetics, the spatial organization of blood coagulation, the effects of blood flow on clotting, and the effects of drugs on the coagulation system. However, studying these aspects of coagulation using only experiments can be difficult because many of the nuances of blood coagulation are difficult to recreate, observe and measure. Outside of research labs, it is difficult to predict thrombotic events (like deep vein thrombosis or pulmonary embolism) and it is challenging to determine how to treat these disorders with current medications, particularly because so many genetic, environmental, and dietary factors come into play (Oakley and Larjava,

2012). As a result, various mathematical and computational models have been developed in the past couple of decades to address some of these areas. Mathematical models can provide details about blood coagulation that may otherwise be unfeasible to attain with experiments. Despite the insight these models can provide, there are also many simplifying assumptions that limit the models. In this chapter, we present a brief summary of the biology and chemistry of blood coagulation, some of the complications that arise in current clinical practices and therapies, and the uses of current mathematical models.

In Chapter 2, we discuss mathematical models of the chemical kinetics of coagulation. In particular, we will explore cascade-based and cell-based models of coagulation, and the different mathematical approaches taken in these models. Chapter 3 presents models of clot formation that incorporate the physiological, biochemical, and physical dynamics of blood flow. In Chapter 4, we describe the clinical and pharmaceutical applications of blood coagulation models including the complexity of modeling pharmacokinetic-pharmacodynamic (PK-PD) data and clotting abnormalities, the role of models in drug development, and the potential use of mathematical models for individualistic medicine (i.e., developing individual profiles of disease risk). We present some concluding remarks in Chapter 5.

1.1 What is blood coagulation?

Blood is a vital part of the human body that functions to transport nutrients and oxygen throughout our system and eliminate waste via blood vessels. Blood has two main components: cells and plasma. Blood cells include red blood cells, whites blood cells, and cell fragments known as platelets (Barrett et al., 2010). Platelets are important in coagulation because they aggregate at the site of injury of the blood vessel (Barrett et al., 2010; Furie and Furie, 2008). Plasma is the liquid part of blood. It is composed of proteins, clotting factors, gases, and other small particles (Figure 1.1).

However, damage to blood vessels occurs frequently. When this happens, the body has a system in place, known as hemostasis, to stop bleeding. The first part of hemostasis involves vascoconstriction, or the constriction of the vessel wall, to reduce the blood flow to the injury site and decrease blood loss (Barrett et al., 2010). Platelets then start to stick to the injured blood vessel to form a soft plug. Platelets also activate the last step of hemostasis, blood coagulation, which changes blood from a liquid to a gel and ultimately forms a blood clot.

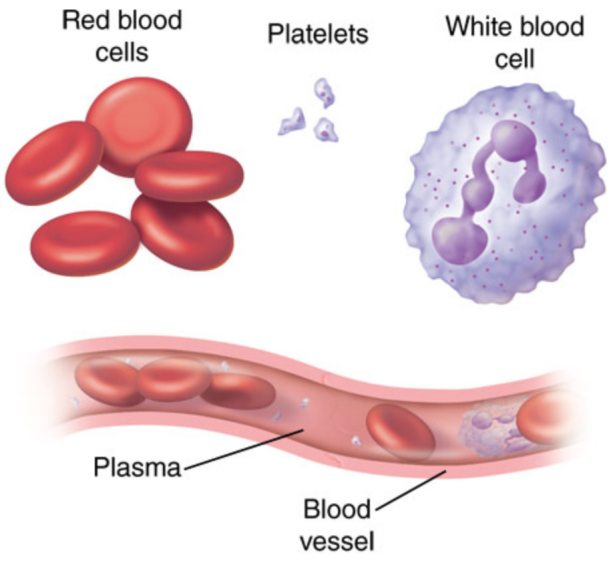

Figure 1.1 Blood is composed of various substances including red blood cells, white blood cells, platelets, and plasma. *Image taken from Understanding Blood and Blood Components. Fairview Health Services, n.d. Web. <https://www.fairview.org/HealthLibrary/Article/40309>.*

1.1.1 Biological Models of Coagulation

In order to solidify the initial clot that is formed in the first part of hemostasis, there are substances known as clotting factors that biochemically interact with one another. These interactions result in the formation of fibrin, which is initially a loose mesh of strands that interlace with platelets to form a clot, as seen in Figure 1.2 (Barrett et al., 2010).

One important thing to note is that there are two different biological models that are used to describe hemostasis: the coagulation cascade and a cell-centric model. Developed in the mid-1960s, the coagulation cascade model was the first widely accepted model of coagulation (Oakley and Larjava, 2012). The cell-centric model was developed in the early 2000s (Oakley and Larjava, 2012). Today, it is important to understand these biological models because they are both being used to develop mathematical models, diagnostics and therapies. In particular, several of the diagnostic tests used to evaluate an individual's ability to clot are based on the coagulation cascade (Oakley and Larjava, 2012). The cell-centric model of hemostasis is important because researchers are starting to incorporate the cellular constraints from the model into their work (Butenas et al., 2009; Riddel et al., 2007). We will discuss what the differences between these two models are and what their roles are in this area of study.

Notation

The notation used to name clotting factors are Roman numerals, with an "a" following the Roman numeral if the clotting factor is activated (Barrett et al., 2010). They can abbreviated by placing an "f" before the Roman numeral (e.g., factor IIa $\rightarrow$ fIIa, factor V $\rightarrow$ fV).

Extrinsic and Intrinsic Pathways

Most of the reactions that take place during coagulation occur via two different pathways: the extrinsic pathway and the intrinsic pathway. The extrinsic pathway is the faster of the two pathways and is initiated by a protein known as tissue factor (TF). TF is one of the proteins that is released by damaged blood vessels to initiate coagulation (Butenas and Mann, 2002; Jesty and Beltrami, 2005; Jones and Mann, 1994; Mann et al., 2003; Tanaka et al., 2009). Note that TF is also found on the surfaces of other blood cells, which can also initiate blood coagulation *in vivo*. In the extrinsic pathway, thrombin is generated by the interactions of fVII (See Figure 1.2). In con-

trast, the intrinsic pathway is much slower than the extrinsic pathway and is activated by a number of factors including: platelets, the small amount of thrombin produced by the extrinsic pathway, exposed subendothelium, or damage to the inside of the vascular system. In particular, the intrinsic pathway reactions involve fVIII, fIX, and fXI. These clotting factors and their associated biochemical reactions are responsible for sustaining coagulation once the cascade has started to generate thrombin (Butenas and Mann, 2002; Jesty and Beltrami, 2005; Jones and Mann, 1994; Tanaka et al., 2009).

Blood Coagulation Cascade

The coagulation cascade is governed by the concentration and reactions of the clotting factors and proteins. This model of coagulation has three principal components (See Figure 1.2).

1. **Extrinsic Pathway.** Coagulation can be initiated by the extrinsic pathway, meaning the subendothelium is damaged and TF is released. Eventually this results in the formation of fXa (Jesty and Beltrami, 2005; Jones and Mann, 1994; Mackman et al., 2007; Riddel et al., 2007).

2. **Intrinsic Pathway.** Coagulation can also be initiated through this pathway, meaning that all the necessary components needed to clot are found in the blood, without the need to expose other cells. This pathway also results in the activation of fX to fXa (Jesty and Beltrami, 2005; Jones and Mann, 1994; Riddel et al., 2007).

3. **Common Pathway.** Regardless of how the cascade is initiated, the complex known as prothrombinase (fXa:fVa) is formed. Both pathways eventually meet in the common pathway, where they finish forming a clot. The common pathway involves fI, fII, fV, and fX. In this pathway, the end result is the activation of fibrinogen (fI) to fibrin (fIa), and the fibrin forms a polymer that helps stabilize the location of the soft plug originally made in the first steps of hemostasis (Butenas et al., 1997; Jesty and Beltrami, 2005; Jones and Mann, 1994; Tanaka et al., 2009).

Even though coagulation can be initiated by either the intrinsic or extrinsic pathway, in general, it is thought that the extrinsic pathway initiates coagulation in tissue factor (TF) induced-coagulation. It is faster and forms a temporary plug that is stabilized by the longer intrinsic pathway and the

common pathway (Jesty and Beltrami, 2005; Jones and Mann, 1994; Oakley and Larjava, 2012).

This model of coagulation is adequate enough to explain plasma-based *in vitro* coagulation. As a result, many of the diagnostic tests that are used to detect clotting abnormalities in patients are based on this model. Note that in many of the models, the results are often presented by the amount of thrombin produced over time. This is because the formation of thrombin (fIIa) is the penultimate step in clotting and necessary for the activation of fibrinogen to fibrin, which is catalyzed by thrombin (See Figure 1.2). This makes thrombin an important species in the reaction, and thus an appropriate concentration to keep track of when evaluating coagulation.

Cell-Centric Model of Hemostasis

In contrast, the cell-centric model of hemostasis has four different phases, listed below (Hoffman and Monroe-III, 2001; Oakley and Larjava, 2012).

1. **Initiation Phase.** Just as in the coagulation cascade, the clotting process is initiated by TF from the subendothelial cells, and ultimately results in the production of small concentrations of the following clotting factors: fXa, fIXa, and thrombin.

2. **Amplification Phase.** If there are enough procoagulant substances generated, then the amplification phase is activated (Oakley and Larjava, 2012). In the amplification phase, the coagulation moves from the tissue factor (TF) bearing cells to platelets. The thrombin that is generated in the initiation phase activates the platelets and the platelets begin to stick together and form a clot (Oakley and Larjava, 2012).

3. **Propagation Phase.** Once the platelets are activated, the other clotting factors necessary to form fibrin bind to the platelet and react, resulting in even more thrombin production (Oakley and Larjava, 2012).

4. **Termination Phase.** Lastly, the termination phase ends with the formation of the stable clot (Oakley and Larjava, 2012).

An overview of this model can be seen in Figure 1.3.

Unlike in the coagulation cascade, in the cell-centric model the extrinsic and intrinsic pathways do not operate separately to initiate coagulation.

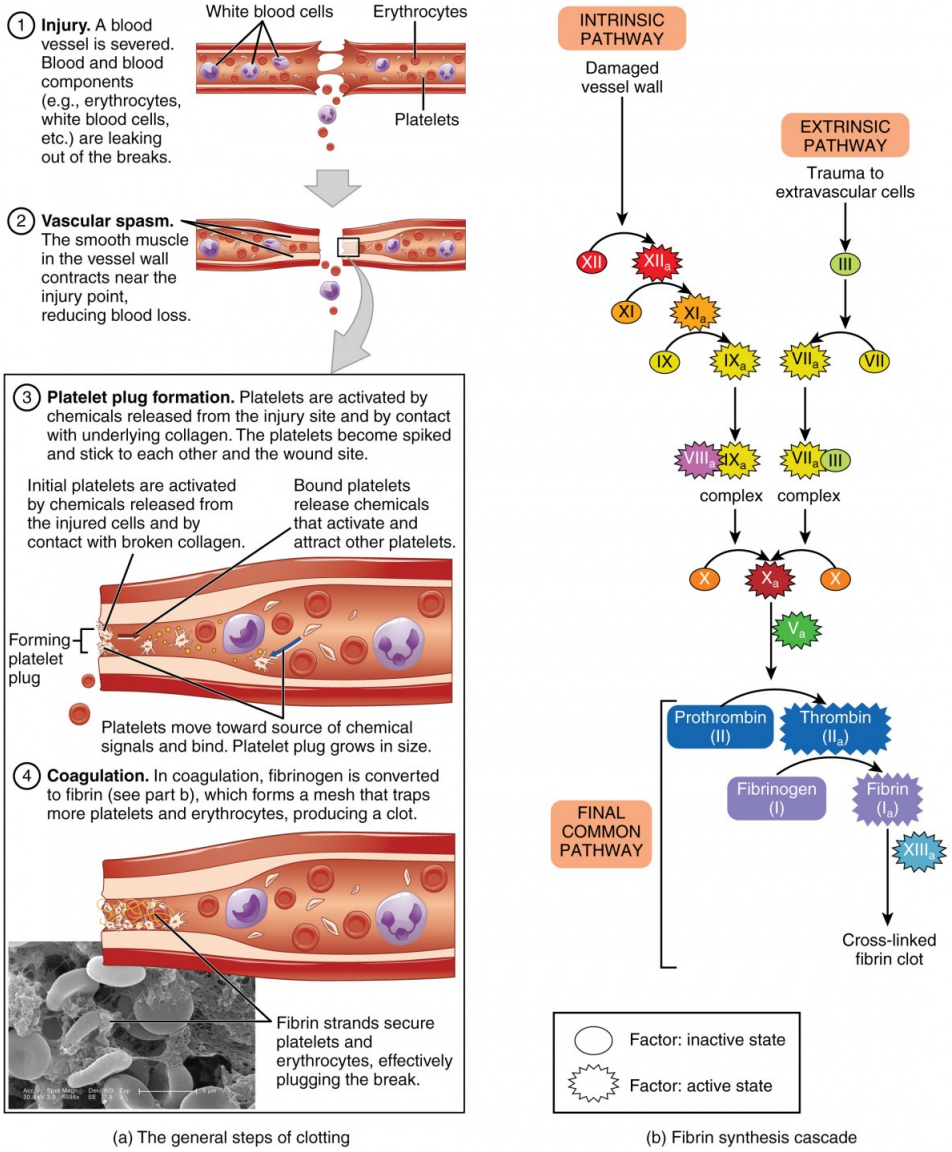

Figure 1.2 (a) An overview of hemostasis. (b) The coagulation cascade model. The extrinsic and intrinsic pathways work separately and eventually meet in the final common pathway. In the common pathway, thrombin and fibrin are generated, leading to the formation of a fibrin clot. *Image taken from Hemostasis. Candela Open Courses: Anatomy and Physiology II, n.d. Web. <https://courses.candelalearning.com/ap2x2master/chapter/hemostasis/>.*

Rather, both pathways work together to form a clot but the pathways function on different blood vessel surfaces (Oakley and Larjava, 2012). The extrinsic pathway operates on the TF-bearing cell that initiates and amplifies coagulation (Oakley and Larjava, 2012). The intrinsic pathway works on platelet surfaces to generate the large concentrations of thrombin and other substances needed to form a fibrin clot (Oakley and Larjava, 2012).

Spatial Organization of Blood Coagulation

Platelets play an important role in blood coagulation because they stick together at the site of injury on a blood vessel (Barrett et al., 2010). Also, several of the reactions that take place in blood coagulation are only possible in the presence of platelets. This is because many of the proteins in blood need to be bound to platelets on binding sites for reactions with other proteins to take place (See Figure 1.4).

Because of the finite number of binding sites available on platelets, platelets also regulate blood coagulation. In addition, platelet binding sites come in two states: an activated and inactivated state. When platelets are activated, they begin to bind to the subendothelium at the injury site and to each other (Oakley and Larjava, 2012).

Another component of blood clotting that contributes to the spatial organization of coagulation is blood flow. Blood flow not only transports different clotting factors throughout the blood vessel, but also affects the rate at which a clot is formed (Figure 1.5) (Tanaka et al., 2009). Because blood flow diffuses clotting factors throughout the body, blood flow adds more complexity to the understanding of blood coagulation. Blood flow creates a spatial heterogeneity in clotting, meaning that where reactions take place matters (Oakley and Larjava, 2012). For instance, different types of blood vessels (i.e., arteries and veins) have different physiological characteristics that affect how a clot is formed (see Chapter 3).

1.2 Clinical Importance of Blood Coagulation

Research in blood coagulation is motivated by the clinical importance of understanding abnormalities in clotting. Two ways that research in blood coagulation is applied to medicine includes diagnostics and pharmacology. Current understanding of blood coagulation directly influences the types of screening tests that are used to detect and diagnose clotting abnormalities in individuals. Similarly, this knowledge is applied to the development

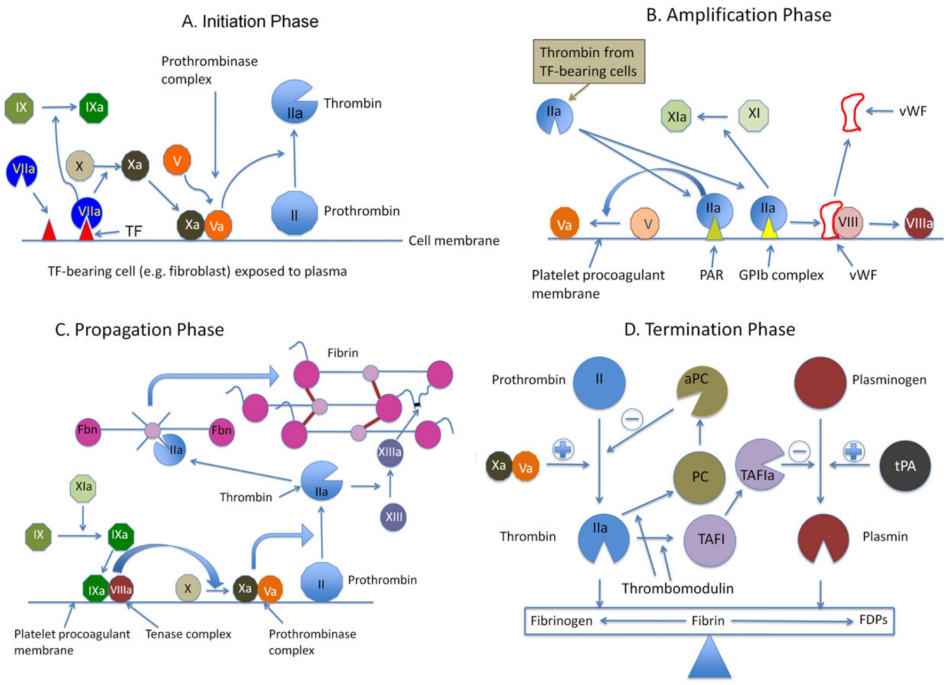

Figure 1.3 The cell-centric model of hemostasis has four principle phases: (A) the initiation phase, (B) the amplification phase, (C) the propagation phase, and (D) the termination phase. In this model, the extrinsic and intrinsic pathways work in parallel but on different surfaces. The extrinsic pathway operates on the initiation and amplification phases on the TF-bearing cells that initiate coagulation. The intrinsic pathway works in the propagation and termination phase on platelet surfaces to generate the thrombin burst needed to form a clot. *Image taken from Oakley and Larjava (2012).*

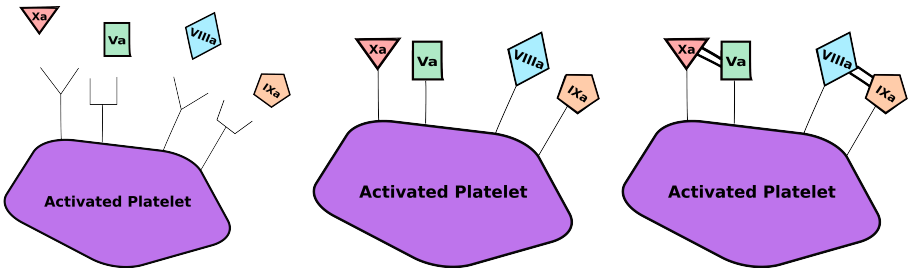

Figure 1.4 Platelets have a finite number of binding sites on their surface that are available for proteins and clotting factors to adhere to. These binding sites are designed so that only specific clotting factors can bind to these sites, making platelets another mechanism of regulation in coagulation. Many of the reactions that take place in blood coagulation can only take place if they are bound to the surface of activated platelets.

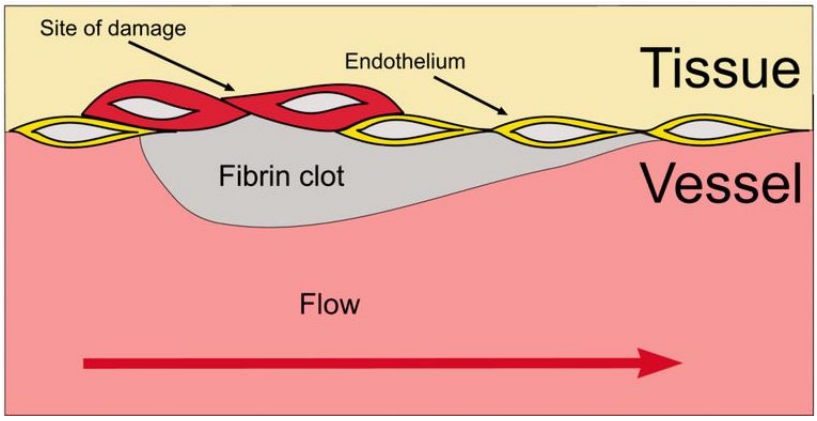

Figure 1.5 Blood coagulation takes place in spatially heterogeneous environment, meaning that different reactions occur at different locations. Blood flow is essential in regulating blood coagulation because it diffuses active factors throughout the system. *Image taken from Shibeko and Panteleev (2015).*

of drug treatments for individuals with clotting abnormalities. Ultimately, researchers would like to develop individual profiles of disease risk, but there are several external factors (i.e., preexisting health conditions, environmental factors) that complicate this endeavor (Brummel-Ziedins et al., 2014).

1.2.1 Clotting Abnormalities

When an individual has clotting abnormalities, it can result in over-clotting or under-clotting. An example of a hereditary clotting disorder is hemophilia. There are two types of hemophilia: hemophilia A (fVIII deficiency) and hemophilia B (fIX deficiency) (Bjorkman and Berntorp, 2001; Tanaka et al., 2009). Both of these deficiencies slow down clotting times, which leads to under-clotting. The severity of the under-clotting can vary greatly such that injuries to some individuals may not pose a great risk but for those with more extreme deficiencies, a small injury could lead to over-bleeding, or even death (Tanaka et al., 2009). Similarly, over-clotting can lead to dangerous conditions like coronary thrombosis or deep vein thrombosis. These can lead to strokes, cardiac arrest, or death (Oakley and Larjava, 2012). As in hemophilia, the symptoms and severity of thrombosis can vary from individual to individual.

However, other diseases and health conditions can also lead to acquired bleeding disorders. For instance, liver diseases affect the production of clotting factors (Oakley and Larjava, 2012). Regular use of medications taken to manage chronic pain or heart conditions also affects platelet functions or clotting factor expression (Oakley and Larjava, 2012).

Because of the great risk that clotting abnormalities pose for individuals, several prophylactic and therapeutic treatments have been developed. One of the major goals of anticoagulant treatments is to reduce the risk of over-bleeding without increasing the risk of other thrombotic events (Bjorkman and Berntorp, 2001; Tanaka et al., 2009). As a result, it is increasingly important to understand the pharmacokinetic-pharmacodynamic profiles of the new drugs and the residual effects of other treatments on blood coagulation. Some of the more common medications prescribed for thrombosis include heparin, warfarin, coumadin and rivaroxaban (Bjorkman and Berntorp, 2001; Oakley and Larjava, 2012). These anticoagulants each target different parts of the coagulation system. While understanding these drugs is challenging because coagulation is a complex system, external factors can further complicate studying drug therapies. For example, many foods, medications, medicinal herbs, supplements and drugs can interact to

affect the pharmaceutical effects of prescribed therapies (Brummel-Ziedins et al., 2014; Oakley and Larjava, 2012).

1.2.2 Diagnostic Tests

Currently, two of the most common screening tests for coagulation abnormalities are the prothrombin time test (PT) and the activated partial thromboplastin time test (aPTT) (Dudek et al., 2011a; Lancé, 2015; Tanaka et al., 2009). The PT test evaluates the extrinsic pathway of the coagulation cascade. In this test, a large amount of TF is added to a blood plasma sample. This test uses significantly more TF than would be found *in vivo*, or in the body. This leads to faster thrombin generation than is observed in the body (Dudek et al., 2011a; Tanaka et al., 2009). In addition, these tests do not accurately measure clotting abnormalities in patients because normal PT levels are seen in patients with hemophilia (Tanaka et al., 2009). Thus, a PT test alone is not enough to determine what type of deficiency a patient has (Butenas and Mann, 2007).

To account for the inaccuracies presented in the PT test, the aPTT test was developed. In this test, there are lower concentrations of TF which limits the production of thrombin. As a result, more realistic thrombin levels are observed in these tests. Hence, aPTT is used to evaluate the effects of anticoagulants like heparin (Lancé, 2015; Tanaka et al., 2009). Just as the PT test, this test evaluates clotting assuming that the coagulation cascade is the correct biological model. The difference is that the aPTT looks at both the intrinsic and extrinsic pathways, whereas the PT test only looks at the extrinsic pathway (Lancé, 2015; Tanaka et al., 2009).

While these clot time tests provide useful insights into the blood coagulation of an individual, they fail to account for other aspects of blood coagulation. For example, both the PT and aPTT tests are stopped when fibrin is first formed (Lancé, 2015; Oakley and Larjava, 2012). This means the tests are not able to accurately determine the quality of the clot that is formed because they do not allow enough time for the clot to stabilize. They also do not describe the *in vivo* interaction of coagulation factors with platelets. Additionally, the results of these tests under prolonged conditions is highly dependent on the platelet count (Oakley and Larjava, 2012). The tests are also based on the coagulation cascade model. This assumes that the extrinsic and intrinsic pathways work separately, as opposed to them working in parallel and dependent on specific cellular surfaces, like in the cell-centric model (Oakley and Larjava, 2012).

1.3 Mathematical Modeling

Blood coagulation is a complex system. There exist different biological models to describe the system. There are several clotting abnormalities that can result in under-clotting and over-clotting. These abnormalities can lead to severe health complications in individuals. The interactions between different therapies that treat these abnormalities, along with other medications, food, supplements, drugs can complicate the investigations of these therapies. Even detecting the abnormalities in the first place can prove to be difficult. With such complexity involved in all aspects of blood coagulation, mathematical models become useful.

Mathematical modeling allows researchers to explore and quantitatively describe some of the nuances in blood coagulation that may not be obvious from experiments alone. They can provide a safe way to explore different treatments before testing and administering them to patients (Mann et al., 2006; Mann, 2012). Mathematical models can also provide a way to explore different screening tests. But, in order to investigate different areas and answer different questions, a variety of mathematical modeling approaches have been taken. In the following chapters, these different modeling approaches are discussed. They are put into context by identifying the motivations and significant results of key models.

Chapter 2

Modeling the Chemical Kinetics of Coagulation

Researchers are interested in understanding the theoretical underpinnings of blood coagulation but because coagulation is so complex modelers have tended to focus on specific parts of the process. One of the major areas of interest is the biochemistry of clotting. Many of these models only describe the coagulation cascade and ignore the spatial and flow components of coagulation (e.g. Bungay et al., 2003; Brummel-Ziedins et al., 2012a, b; Guo et al., 2006; Higgins et al., 1983; Hockin et al., 2002; Jones and Mann, 1994; Khanin et al., 1998; Kogan et al., 2001; Luan et al., 2007; Xu et al., 2002, 2005). These type of models primarily focus on describing the protein concentrations over time by using a series of nonlinear, ordinary differential equations (ODEs). While these types of deterministic models are common, in an effort to create more physiologically relevant models, there has been some work done to implement a stochastic model of the coagulation cascade (Lo et al., 2005). In this chapter, we will provide an overview of mathematical models that have been developed to describe the coagulation cascade.

Mathematical models that are concerned with describing the biochemical reactions of coagulation usually derive a system of ODEs or partial differential equations (PDEs) based on the reactions. To derive these equations, they use the law mass action, Michaelis-Menton equations, or other chemical considerations. The law of mass action and the Michaelis-Menten equations allow for a system of equations to be directly derived from a chemical reaction. This approach takes into account the different concentrations of proteins and the reaction rate constants of each reaction involved in coagulation. The concentrations and rate constants used in these models

are derived empirically and taken from literature.

2.1 Models of the Coagulation Cascade

Many of the mathematical models of the coagulation cascade have taken a deterministic approach (e.g. Brummel-Ziedins et al., 2012a, b; Bungay et al., 2003; da Cunha Orfao, 2007; Guo et al., 2006; Hockin et al., 2002; Jones and Mann, 1994; Khanin et al., 1998; Kogan et al., 2001; Lee et al., 2010; Luan et al., 2007, 2010; Makin, 2008; Mitrophanov and Reifman, 2011; Mitrophanov et al., 2012, 2014; Sagar and Varner, 2015; Xu et al., 2002, 2005). They use a system of equations that are solved numerically to track the concentration of proteins over time.

One of the most widely used models is presented by Hockin et al. (2002). This model uses a system of 34 nonlinear ODEs with 42 rate constants to describe the extrinsic blood coagulation system. It includes anticoagulants tissue factor pathway inhibitor (TFPI) and antithrombin-III (TFPI and AT-III), the vitamin K-dependent procoagulant complexes, and binding competition between TF and factors fVII and fVIIa, which are critical components of coagulation biochemistry (Butenas and Mann, 2002). This model is of particular importance because it was validated by comparing numerical simulations to empirical *in vitro* data (Figure 2.1). The model's ability to capture most experimentally observed parameters and behavior for both normal, enhanced, and deficient *in vitro* thrombin generation made it widely accepted. Many more complex models are based on this relatively simple model. However, this model fails to include the intrinsic pathway and platelet dynamics. Inclusion of the intrinsic pathway is important because the intrinsic pathway ensures the blood clot is stabilized and will remain in place to help the damaged vessel heal (Barrett et al., 2010). Without the intrinsic pathway, the temporary clot formed quickly in the extrinsic pathway could be dislodged. Platelets are also important to include in the model because the finite number of binding sites available on platelets is an added constraint on the amount of thrombin that can be produced (Oakley and Larjava, 2012). In reality, the number of platelets that are activated changes as coagulation takes place. However, Hockin et al. (2002) assumes a maximally activated platelet at $t = 0$. Another pitfall of this model is that it is able to accurately predict the initiation times of coagulation at picomolar levels of TF, but it fails to do so at sub-picomolar levels.

There exist more complete models of the coagulation cascade. For example, Bungay et al. (2003) includes a system of 73, nonlinear ODEs that

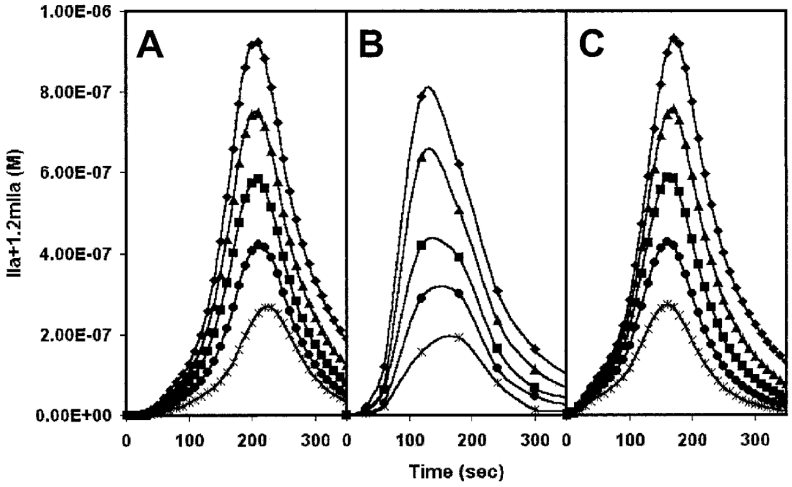

Figure 2.1 These figures are the results from numerical and experimental work that shows the active thrombin concentration as a function of time with varying concentrations of prothrombin. The experimental conditions include 150% (filled diamonds), 125% (filled triangles), 100% (filled squares), 75% (filled circles), and 50% (asterisk) of normal prothrombin concentrations. A: The numerical results of Hockin et al. (2002) with the aforementioned conditions. B: Empirical data. C: Numerical results of thrombin produced under the experimental conditions of A and B with the presence of 1% fVa contamination in fV. Note that this contamination was part of the experimental results. *Image taken from Hockin et al. (2002).*

describes all of the extrinsic pathway, a significant portion of the intrinsic pathway, and the presence of lipids, up to the formation of thrombin. A slightly more complete model is presented by Luan et al. (2007). This model includes 92 nonlinear ODEs and is similar to the Bungay et al. (2003) model, but includes the effects of platelets on overall thrombin production. Including these aspects of blood coagulation can better help detect and determine coagulation abnormalities.

2.1.1 Applications: Studying Coagulation Abnormalities

These simple models form the basis of other models that help researchers find potential ways to improve the diagnosis of abnormal clotting. To demonstrate, Brummel-Ziedins et al. (2012b) uses the Hockin et al. (2002) model with some modifications to compare fXa formation with thrombin

formation. Including this comparison is useful in modeling because the biology of coagulation shows that when fXa activates prothrombin, thrombin is formed (See Chapter 1). Making sure that this behavior is captured is essential in creating more accurate models. In the Brummel-Ziedins et al. (2012b) study, numerical simulations are run by using a mathematical model along with empirical data collected from patients with normal coagulation and deep vein thrombosis (DVT).

Understanding fXa generation has become increasingly important to the development of anticoagulants. By targeting fXa, which is needed for thrombin formation, clotting can be decreased (Brummel-Ziedins et al., 2012b). Thus, a more accurate way of monitoring and evaluating the effectiveness of these treatments is needed. While Brummel-Ziedins et al. (2012b) contributed to the current understanding of fXa and thrombin generations, the model did not include the protein C pathway, the effects of platelets, or the intrinsic pathway.

In addition, a similar type of model was developed by the same group, Brummel-Ziedins et al. (2012a). In this model, they add the protein C pathway to the extrinsic pathway model. The protein C pathway is a pathway that helps regulate anticoagulation in the system (Tanaka et al., 2009). Using this slightly different approach, the group is able to show that a large protein C (PC) deficient family is not prone to thrombosis simply because of this deficiency. In fact, regardless of an individual's PC status there appeared to be procoagulant tendency among family members. These procoagulant tendencies were multicausal, and were further explained by individual plasma composition (Brummel-Ziedins et al., 2012a). Hence, this model suggests that plasma-based composition models are useful in understanding coagulation tendencies in individuals, and may even provide insight into other parts of the coagulation cascade that may be leading to thrombotic events.

These models are also used to study the dynamics of the clotting abnormalities. For instance, (Shavlyugin et al., 2014) uses a modified version of the *in vitro* intrinsic pathway model presented by Khanin et al. (1998) to study pathologic clot formation (clots that cause, or are formed by, disease). Their work modeled the intrinsic pathway system, including platelets and their activation. In Shavlyugin et al. (2014), the authors made the assumption that rate of pathologic clot formation is much lower than the rate of formation of a normal clot. This allowed them to simplify their model and ultimately estimate the kinetic rate constants that initiate pathologic clot formation. Based off of their model, the authors were able to determine which factors may inhibit pathologic clot formation, which could ul-

timately inform the decisions of researchers and physicians.

Note that these models can also be used to study the effectiveness of treatments of clotting abnormalities. This is further discussed in Chapter 4.

2.1.2 Sensitivity Analysis

The deterministic models of blood coagulation are solved as if the empirically derived parameters, such as rate constants, are known with certainty. However, there is a certain amount of uncertainty associated with each of the parameters in these models. As such, sensitivity analysis has been performed on some of these models. This allows researchers to know where measurement accuracy should be improved and where a model's ability to predict coagulation behavior fails. Despite this being an area that should be studied, as of writing, there are only very few papers that perform a sensitivity analysis of mechanistic models (Danforth et al., 2009, 2012; Luan et al., 2007).

The Danforth et al. (2009) paper directly addresses the uncertainty in parameters. This is important because many of the rate constants are measured from experiments, and others are derived indirectly from other measured quantities (Danforth et al., 2009). This means that there is uncertainty associated with the parameters used in the model. In this work, the authors perform a sensitivity analysis of the widely used Hockin et al. (2002) model and the values used for the rate constants. The values of 44 rate constants are varied an order of magnitude above and below the used values. The variation of the concentrations are quantified using a normalized standard deviation. This study concludes that the model is most sensitive to uncertainty in five rate constants that are involved in regulation of fVII-TF complex, accounting for 50% of the aggregate variation. This suggests that the regulation of fVII-TF complex is a mechanism where more care should be taken when measuring the rate constants of the reactions.

Another paper by Luan et al. (2007) used sensitivity analysis of the coagulation cascade to determine the fragility of specific sites in the cascade. They developed a deterministic model that included all of the extrinsic pathway, most of the intrinsic pathway, and the effects of platelets on thrombin generation. The authors used a Monte Carlo strategy in which the best-guess parameter values were used to generate a random parameter set. Ultimately, they found that fX/fXa and prothrombin/thrombin (fII/fIIa) were the most sensitive parameters, which is consistent with thrombosis therapies that target fX and thrombin. This suggests that sensitivity analysis can be used to determine potential targets in coagulation therapies,

despite the uncertainties in the model parameters.

However, the uncertainties in the parameters still pose problems. In such cases, sensitivity analysis can help reveal problems with a model. For instance, a more recent study performed by Danforth et al. (2012) used a model similar to that used in the work of Luan et al. (2007) (based on Hockin et al. (2002)) to investigate how normal range variation of different initial concentrations of clotting factors normally found in plasma of *in vitro* experiments affects total thrombin output. Numerical simulations were run to create thrombin profiles of both healthy individuals and those with deficiencies. These results were compared to empirical data taken directly from patients. The results of this study found that the normal range of variation for healthy individuals was not significantly different from the profiles of individuals with clotting abnormalities, suggesting that more work should be done to address the uncertainty that exists in these models. While more extreme cases were distinguishable from normal variation, less extreme cases of clotting abnormalities were not distinguishable. In particular, this work is interesting because it seems to be in opposition to the work done by Luan et al. (2007), which states that despite the model's uncertainty it accurately describes what is seen in therapies. The work done by Danforth et al. (2012) shows that the normal variations observed in plasma content is not accurately described by the models. Thus, it seems that more work is necessary to confirm whether the uncertainties seen in the deterministic models are negligible because just looking at one part of the uncertainty yields different results. One possible study that could be done would be to do a sensitivity analysis that takes into account the rate constants (Danforth et al., 2009), the interactions of the different clotting factors (Luan et al., 2007) and the initial concentrations of clotting factors in plasma (Danforth et al., 2012).

2.2 Cell Based Models of Coagulation

One of the major milestones in blood coagulation modeling is the development of cell based models (Brummel-Ziedins, 2014; Chatterjee, 2011; Chatterjee et al., 2010; Diamond, 2013; Makin, 2008; Nielsen, 2008; Nielsen et al., 2009). Cell based models are important because they allow for more specific modeling of the chemical kinetics of coagulation. For instance, they more accurately capture the platelet dynamics by describing the activation process of platelets and the finite number of binding sites on a platelet (Hemker et al., 2012; Smith, 2009). Ultimately, these models allow for more

individualistic plasma profiles to be represented, leading to better diagnostics and research results (Brummel-Ziedins, 2014).

All of the models that have been discussed make the assumption that coagulation is TF-initiated. However, there exist other proteins that can trigger clot formation. For instance, Chatterjee et al. (2010) uses experiments to show that even when inhibitors, like corn trypsin inhibitor (CTI), are used to block specific factors (CTI blocks FXIIa), CTI can build up enough to initiate coagulation without TF being added to a blood sample. Using their experimental results, Chatterjee et al. (2010) developed an ODE-based platelet plasma model based on the work of Hockin et al. (2002). This model is important because it was the first model with the ability to predict the observed behavior of CTI treatments in blood that contains activated and inactivated platelets. This model takes a systems biology approach that focuses on accounting for the autocatalytic feedback loops, and the nonlinearity of reaction rates (Diamond, 2009; Shahzad and Loor, 2012), and the sensitivity of the model to initial conditions. Note that autocatalytic feedback loops occur when the product of a reaction is itself the catalyst for that same reaction. Overall, the Chatterjee et al. (2010) platelet plasma model agreed more with experimental data (taken from literature) than the Hockin et al. (2002) model (Figure 2.2).

The Chatterjee et al. (2010) model is well-suited for modeling *in vitro* blood coagulation. The main assumption made in the model is that the system is a well-mixed static system. While it does account for some of the platelet dynamics of coagulation, it does not take flow and spatiotemporal dynamics present in *in vivo* systems into consideration. Despite its inability to model *in vivo* coagulation, the platelet plasma model is a significant contribution to the field because it suggests that individual blood profiles can be taken into account in *in vitro* tests currently used in diagnostics and treatments (Flamm et al., 2012; Nielsen et al., 2009; Wang and King, 2012). This insight also helped inform other types of models that take into account flow dynamics (Bellini et al., 2014; Brummel-Ziedins, 2014; Brummel-Ziedins et al., 2012b; Colace et al., 2012; Diamond, 2013; Fogelson et al., 2012; Lee et al., 2012; Leiderman and Fogelson, 2014). The use of cell based models in more complex models, like those describing flow, spatiotemporal phenomena, or treatments, will be discussed in detail in Chapter 3.

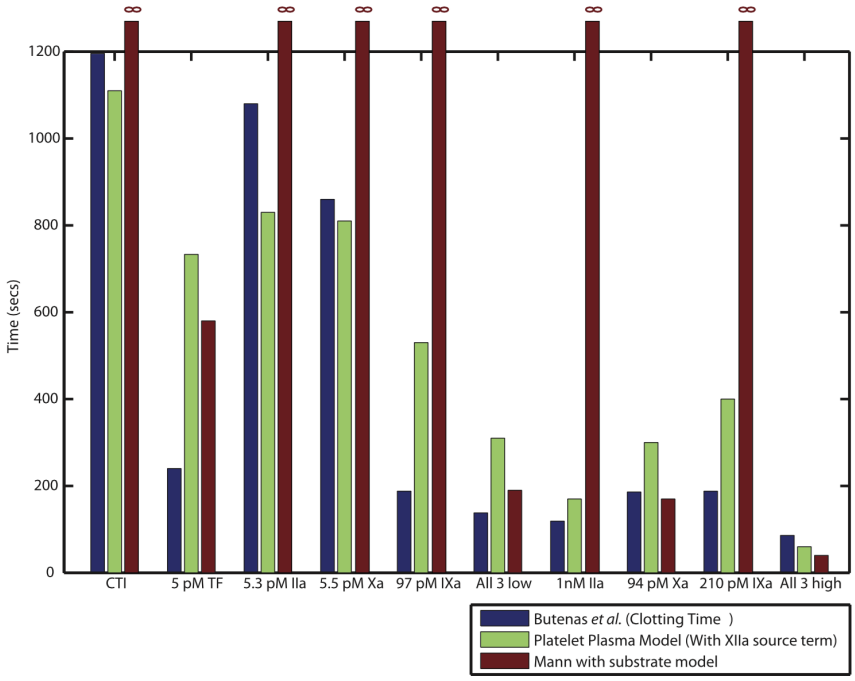

Figure 2.2 Simulations using the Chatterjee et al. (2010) (platelet plasma model) and Hockin et al. (2002) models computed clotting times with additions of TF, thrombin, fIXa, fXa, or combinations of the three clotting factors at low and high doses. Results were compared to experimental data (labeled as *Butenas et al.* in the figure). Note: the platelet plasma model more closely matched experimental results than the Hockin et al. (2002) model, which only predicted finite clotting times under high doses of TF or fXa. *Image taken from Chatterjee et al. (2010).*

2.3 Stochastic Model

A different approach that has been taken to these deterministic models is the development of stochastic models (Castaldi et al., 2013; Lo et al., 2005; Makin and Narayanan, 2008). This is important because a stochastic model can capture more of the variation associated with blood coagulation. One such stochastic model of the coagulation network is presented by Lo et al. (2005). Here, the authors aim to understand the dynamics of a system with small numbers of TF molecules in a small local volume of blood. In this model, Monte Carlo simulations are used along with the deterministic model from Hockin et al. (2002) to capture the variability seen in low con-

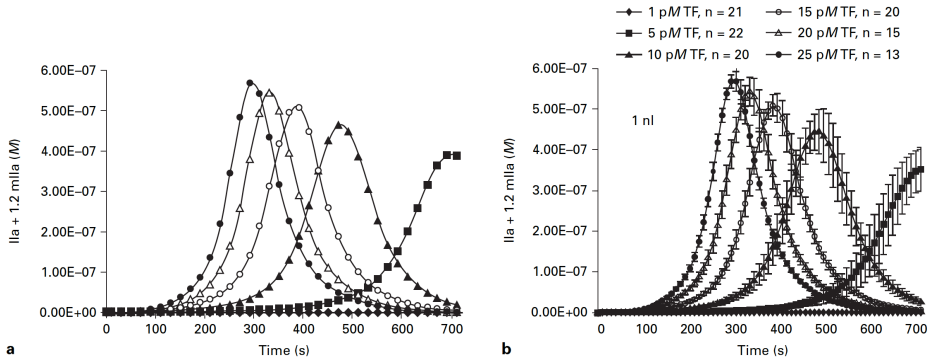

Figure 2.3 The total thrombin concentration for varying TF concentrations for two different models is presented here. a: Hockin et al. (2002), a deterministic model, results in the following numerical solutions of thrombin production over time. b: Lo et al. (2005), a stochastic Monte Carlo model, yields the following numerical solutions of thrombin production over time. *Image taken from Lo et al. (2005).*

centration experiments. These simulations are governed by two questions: (1) What time does the next reaction occur? (2) What kind of reaction will it be? Each species involved in the reactions has a specific probability of reacting with other species. The results from this model are comparable with the results from Hockin et al. (2002) (Figure 2.3). However, while this is a stochastic model that attempts to creates a more realistic description of when reactions occur, it was unable to model clotting times in low concentrations of TF, and still ignores the uncertainty that exists in the parameters that are used in the model.

In contrast, Castaldi et al. (2013) uses Petri nets to model the biochemical pathways of coagulation. A Petri net is defined as a weighted, directed bipartite graph that can be used to study complex models (Castaldi et al., 2013). This study is governed by the same questions as the work of Lo et al. (2005), but Castaldi et al. (2013) uses a tau-leaping method to determine when a reaction occurs. In this method, a small value τ is chosen such that in the simulation there is a leap along the time axis in steps of length τ. At each of these events, many single reactions can take place. Unlike Lo et al. (2005), this model is able to work accurately under low concentrations of TF.

2.4 Conclusions

Modeling the biochemistry of blood coagulation is complex, and one must choose the appropriate approach to answer the question at hand. Thus, several mathematical approaches have been taken, including ODE-based models, Monte Carlo simulations, and Petri net models. Modelers have come from several disciplines, such as mathematics, systems biology, and engineering. This suggests that modeling the chemical kinetics of coagulation is of great interest.

The current models that describe *in vitro* blood coagulation are useful in predicting coagulation behavior in experimental and non-vascular environments. Because of this assumption, they are unable to accurately represent the coagulation that characterizes *in vivo* environments, given that these models fail to account for flow and the spatial heterogeneity that exists in *in vivo* coagulation (Mann et al., 2009). Despite this, these models are able to provide valuable insight into the biochemistry of clotting and some of the diagnostic tests that are employed to evaluate an individual's ability to form a clot.

It seems that one of the major steps needed is to perform more analysis on the uncertainty of parameters in current models (Hopkins and Leipold, 1996; Tyurin and Khanin, 2005). There are some studies that have performed a sensitivity analysis and statistical analysis on these types of deterministic models. However, there has not been much work done to address the uncertainty in parameters in stochastic models. The stochastic models are more accurate because they account for the variation that takes place when reactions occur but they assume that the governing parameters of their model are known. More should be done to explore the uncertainty in parameters of these models, especially if these models are to be used to help make predictions for diagnostic and therapeutic procedures. Similarly, more work should be done to evaluate how the uncertainties from various sources (rate constants, individual plasma-content variation, and variation in clotting factor interactions) affects the overall thrombin production represented by a model.

Chapter 3

Mathematical Models of Clot Formation Under Flow

Physiologically, blood coagulation takes place in a dynamic fluid environment. Theoretical and experimental efforts have been made to understand the physical processes that specifically affect clot formation. Among these physical processes are flow-mediated transport and platelet deposition (Shibeko et al., 2009). However, one of the challenges facing modelers in this area is the lack of understanding of how the dynamics of blood flow affects clot formation (Leiderman and Fogelson, 2014; Shibeko et al., 2009). It is also still unclear how new insights into the effects of physical processes in coagulation may alter the current view of clot formation, which has been solely based on biochemical research (see Chapter 1). Because of the complexity and lack of thorough understanding of flow and thrombus formation, pharmaceutical companies and physicians do not use flow-based models to make diagnostic predictions or test drugs on patients (Shibeko and Panteleev, 2015).

In this chapter we will explore the different mathematical and computational models that have been developed to describe thrombus formation under flow. Some of the models have taken a biophysical-approach, focusing on how shear-thinning fluids, the rheology of blood and different types of flow (e.g., laminar, convective) affect thrombus growth (e.g. Appiah, 2013; Ataullakhanov and Panteleev, 2005b; Basmadjian et al., 1997; Beltrami and Jesty, 2001; Bodnár and Sequeira, 2008; Buravtsev et al., 2010; Capek, 2011; Jarm et al., 2007; Jordan, 2010; LaCroix, 2012; Lobanov and Starozhilova, 2005; Luan, 2009; Makin and Narayanan, 2008; Pavlova et al., 2015; Quarteroni, 2006; Robertson et al., 2008; Runyon et al., 2008; Sequeira

and Bodnar, 2014; Sequeira and Janela, 2007; Sequeira et al., 2011; Storti et al., 2014; van de Vosse, 2003; Weller, 2010; Xu et al., 2008, 2009, 2012). We will also discuss models that address both the dynamics of flow and the spatial organization of blood in blood vessels, including both the veins and arteries (Alenitsyn et al., 2010; Anor et al., 2010; Appiah et al., 2011; Fasano et al., 2013; Fragomeni et al., 2008; Xu et al., 2010). Noting the difference of whether veins or arteries are being modeled and simulated is important because of the differences in blood pressure associated with each. Arteries are high-pressure vessels, meaning that flow is generally faster in these vessels (Ku, 1997). In contrast, veins are low-pressure vessels and have slower blood flow (Ku, 1997). We will also focus on models that study platelet-mediated thrombosis and the spatial constraints associated with this (Alenitsyn et al., 2010; Anand et al., 2003, 2005; Buravtsev et al., 2010; Filipovic et al., 2008; Flamm et al., 2012; Fogelson et al., 2012; Fogelson and Tania, 2005; Jarm et al., 2007; Jordan, 2010; Kuharsky and Fogelson, 2001; Leiderman and Fogelson, 2011; Lobanov and Starozhilova, 2005; Luan, 2009; Panteleev et al., 2006; Pavlova et al., 2015; Robertson et al., 2008; Sequeira et al., 2011; Storti et al., 2014; van de Vosse, 2003; Weller, 2010; Xu et al., 2008, 2009, 2012; Zarnitsina et al., 1996).

3.1 Dynamics of Blood Flow

Many groups have focused on developing mathematical models of the effects of flow on clot formation. Taking into account the biophysical implications of physiological blood flow is a complicated endeavor, particularly because of the dynamic environment in which blood coagulation takes place. Physiological blood coagulation takes place under blood flow and is spatially nonuniform (Ataullakhanov and Panteleev, 2005a; Formaggia et al., 2009). Much of the emphasis of the models has been placed on shear-thinning fluid models, the rheology of blood, and how different types of flow (e.g., laminar or convective) affect thrombus growth (Pompano et al., 2008). Many of these models are concerned with modeling the heterogeneity observed in blood flow. As a result, most of the models use sophisticated multiscale PDE approaches to integrate coagulation kinetics, platelet deposition, and flow (Flamm, 2011; Flamm et al., 2012; Fogelson and Guy, 2008; Fogelson and Tania, 2005; Formaggia et al., 2009; Jarm et al., 2007; Jordan, 2010; Kim, 2002; Kim et al., 2013; Leiderman and Fogelson, 2011; Luan, 2009; Makin and Narayanan, 2008; Papadopoulos et al., 2014; Pavlova et al., 2015; Quarteroni, 2006; Robertson et al., 2008; Sequeira et al., 2011; Sequeira

and Janela, 2007; Sorensen et al., 1999; Storti et al., 2014; van de Vosse, 2003; Weller, 2010; Xu et al., 2009, 2010, 2012; Zarnitsina et al., 1996). However, Flamm (2011) uses lattice kinetic Monte Carlo simulations of platelet aggregation and deposition to account for the stochastic tendencies of the flow-driven particle motions of blood flow, and Mounts and Liebman (1997) uses stochastic activity networks (SANs). There are also models that focus on primarily on the blood flow effects (Appiah, 2013; Basmadjian et al., 1997; Beltrami and Jesty, 2001; Bessonov et al., 2016; Bodnár and Sequeira, 2008; Buravtsev et al., 2010; Capek, 2011; Formaggia et al., 2009; Jarm et al., 2007; Jordan, 2010; Kim, 2002; Kim et al., 2013; Lobanov and Starozhilova, 2005; Luan, 2009; Makin and Narayanan, 2008; Panteleev et al., 2006; Papadopoulos et al., 2014; Pavlova et al., 2015; Robertson et al., 2008; Sequeira and Bodnar, 2014; Sequeira and Janela, 2007; Sequeira et al., 2011; Weller, 2010; Xu et al., 2009, 2012). There are also models that include coagulation kinetics with simplified treatment of flow (de Pillis et al., 2015; Fogelson and Guy, 2008; Fogelson et al., 2012; Fogelson and Tania, 2005; Kuharsky and Fogelson, 2001; Wajima et al., 2009).

One of the aspects of blood flow that has been studied is blood rheology (Sequeira and Janela, 2007; Sequeira et al., 2011; Storti et al., 2014; van de Vosse, 2003). For example, Bodnár and Sequeira (2008) uses a generalized Newtonian model with shear-thinning viscosity to describe blood flow. In this particular model, a blood clot was treated as an area with 100 times higher viscosity than that of regular blood. The area was determined by tracking fibrin concentration values over the entire area of interest. This way of modeling blood flow is practical because it uses simplified rheological conditions to model thrombus formation at injured blood vessels.

One notes in Figure 3.1 that the concentration of fibrin on the blood vessel wall after 60 s of clotting activity is increased primarily in the clotting area. However, the blood flow advection causes some of the fibrin to be spread downstream from the injured vessel site (Furie and Furie, 2008). This ultimately changes the clot's shape. While this is a reasonable result, because of its simplicity in modeling blood coagulation as a single continuum model, Bodnár and Sequeira (2008) neglects the different types of flow that physiologically take place (Capek, 2011). Capek (2011) presents an argument against single continuum models. The author claims that single continuum models do not capture the stacking, or adhesion, of red blood cells (RBCs) on the inside of curved arteries. This is due to the lower values of wall shear rate that are present along these curves (Ku, 1997). Capek (2011) proposes using mixture theory, which involves modeling different aspects of whole blood using different fluid types. While other models have

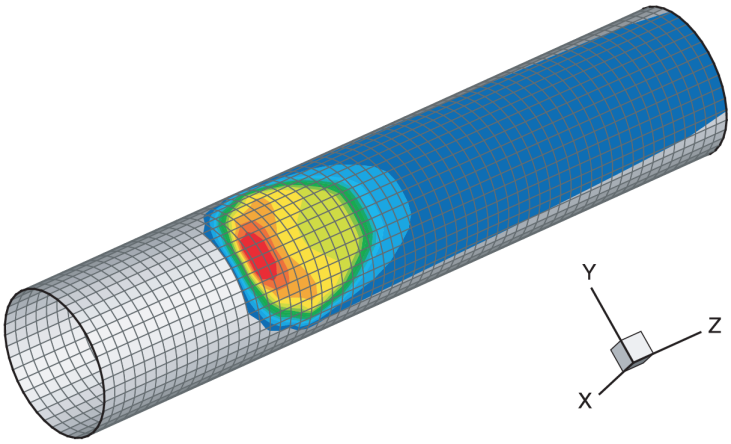

Figure 3.1 Fibrin concentration on a blood vessel surface is affected by blood flow after 60 s of clotting activity. *Image taken from Bodnár and Sequeira (2008)*

taken to using mixture theory, many continue to use the single continuum model. These models focus on small, specific regions of the circulatory system. More holistic models of both the arterial and venous system were not developed until very recently. One of the main reasons is because mixture theory presents challenges when trying to define boundary conditions (Capek, 2011).

3.2 Formation of Clots

The formation of clots (or thrombi) is an exciting topic to study because recently there has been more experimental work done toward understanding the interaction between the biophysical and biochemical processes involved in clot formation. In particular, experimental investigators have been researching thrombus permeability and the structural heterogeneity during clot formation under flow (Furie and Furie, 2008; Leiderman and Fogelson, 2014). Some of the methods used in this kind of experimental research include intravital microscopy, other experiments on animals and *in vitro* flow chambers (Cazzaniga et al., 2014; Colace et al., 2012; Dahlback, 2000; Jarm et al., 2007; Leiderman and Fogelson, 2014; Torres et al., 2009). These types of experiments have been critical in advancing the understanding of clot formation because they allow the measurement and visualiza-

tion of thrombin concentrations *in vitro*.

Based on the physical research done to date, mathematicians have been able to develop more accurate models of thrombus formation. Some of the models developed capture part or the full "lifespan" of a clot, which can be described in three stages: initiation, formation, and dissolution (or lysis) (Anand et al., 2003, 2005; Cito et al., 2013; Diamond, 1999; Flamm, 2011; Fogelson and Guy, 2008; Fogelson et al., 2012; Fogelson and Tania, 2005; Furie and Furie, 2008; Kim, 2002; Kim et al., 2013; Kuharsky and Fogelson, 2001; LaCroix, 2012; Leiderman and Fogelson, 2011; Luan, 2009; Jarm et al., 2007; Wang and King, 2012; Weller, 2010; Xu et al., 2008, 2009, 2011, 2012). One of the key characteristics of these types of models is that they are multiscale models. This means that they incorporate submodels of different aspects of clot formation (e.g., biochemistry, flow dynamics, or platelet dynamics, to name a few). In particular, they model the effects of flow, spatial heterogeneity of blood, platelet deposition, and coagulation kinetics. Some models take a broader approach and model dermal wound repair, as opposed to focusing on the small-scale healing in blood vessels (Dallon et al., 2000; Jorgensen and Sanders, 2015).

Models of Thrombus Formation and Lysis

One of the models of that captured the formation of clots is found in Anand et al. (2005). In this model, blood is modeled as a shear-thinning viscoelastic fluid that contains coagulation factors, however, the authors assume that these coagulation factors do not affect the velocity of the blood flow. The blood clot is modeled as a highly viscoelastic fluid where coagulation factors are also present. The flow dynamics are modeled as a single continuum fluid with simplified treatment of the coagulation kinetics that uses only 25 reactants (Capek, 2011).

The results of the Anand et al. (2005) model are presented in Figure 3.2. These results agree with physical intuition. One of the main findings of this study is that the model predicts that shear stresses are significantly higher in regions where there is a clot as opposed to regions with only whole blood. However, some of the drawbacks are that it is based on the coagulation cascade, and that it does not take account for the entire cascade. Specifically, it does not include the intrinsic pathway; it only includes the extrinsic pathway. The problem with using such a model today is that it is generally accepted that cell-based models of coagulation are correct (Fasano et al., 2013). It also oversimplifies the rheology of whole blood.

Since the work of Anand et al. (2005), more sophisticated models have

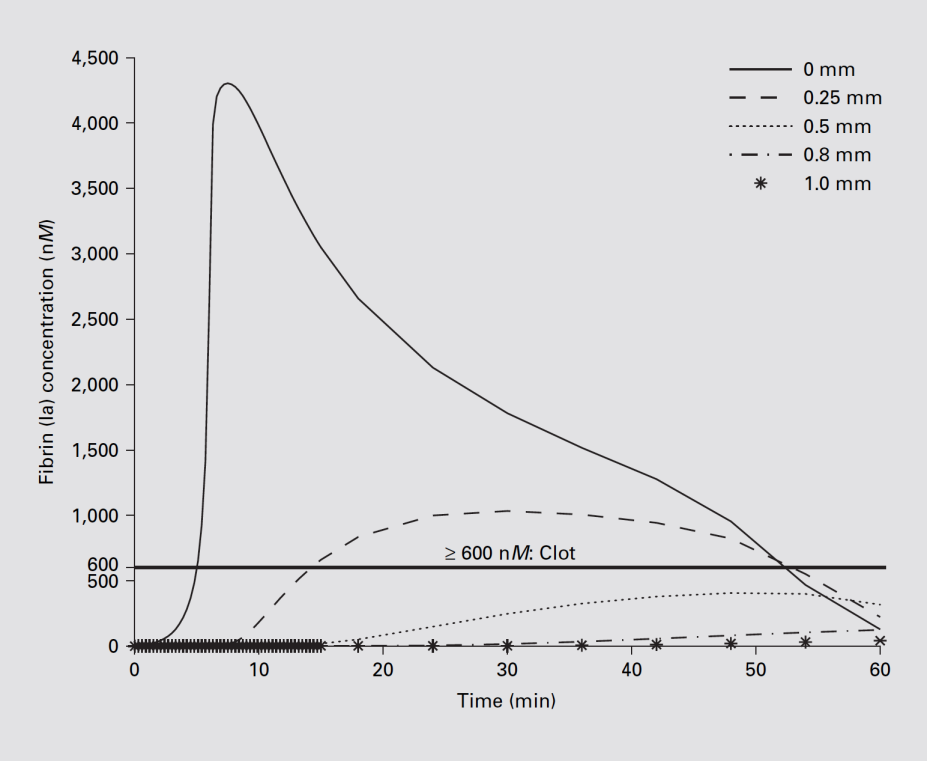

Figure 3.2 The spatial evolution of fibrin concentration during the lifespan of clot including the formation, growth and lysis in whole blood. *Image taken from Anand et al. (2005)*

been developed. For example, the first spatial-temporal model of platelet deposition and blood coagulation under flow was presented in Leiderman and Fogelson (2011). In this model, Leiderman and Fogelson (2011) successfully model platelet aggregation and blood coagulation under flow. They include coagulation kinetics, platelet deposition, and the interactions between blood flow and the growing mass.

One of the significant things about this work is that it models the thrombus as a porous substance, allowing for specific information to be drawn out about how advective and diffusive transport affects the growth of the clot at different stages and locations (Leiderman and Fogelson, 2011). For instance, one of the results presented in the paper is of a time sequence from 10 minutes of clotting activity (Figure 3.3). Note that platelets and fluid-phase clotting chemicals are flowing downstream. All of the results

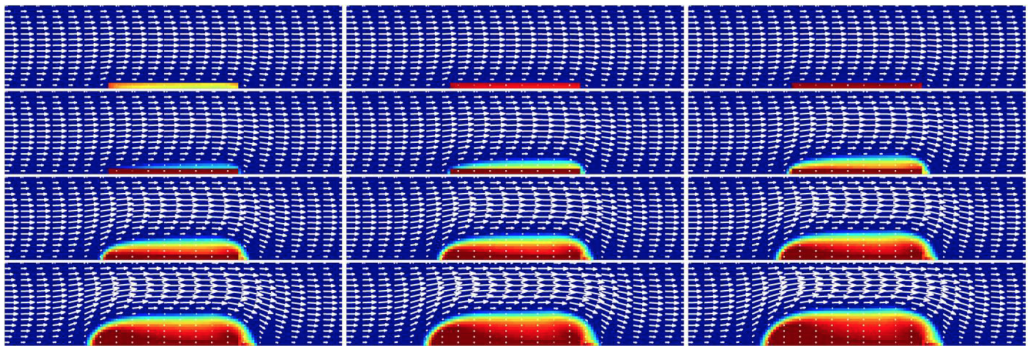

Figure 3.3 Using a novel spatial-temporal model of thrombus formation under flow, Leiderman and Fogelson (2011) generated a time sequence of thrombus growth at $50, 100, 150, \ldots, 600$ s (from left to right, top to bottom). The initial tissue factor (TF) density was 15 fmol cm^{-1}, with a shear rate of 1500 s^{-1}. The arrows represent the fluid velocity, which have uniform scaling. The bound platelet concentrations range from 0 (dark blue) to $P_{\max}$ (dark red). *Image taken from Leiderman and Fogelson (2011)*

used in this paper are modeled assuming that the channel height is 60μm and length 240μm. The injury that initiates the clotting is located at the midpoint of the bottom wall, with a length of 90μm. Leiderman and Fogelson (2011) found that after 50 s there is little effect to the flow despite the platelets partially covering the injury. As the thrombus grows, however, the flow is perturbed. In particular, we note in Figure 3.3 that there is spatial heterogeneity in the thrombus (indicated by the colors) and that the flow is increased where the vessel width decreases and the flow decreases when the vessel widens again.

The Leiderman and Fogelson (2011) model was the first comprehensive continuum blood clotting model that incorporated multiple aspects of blood coagulation. The model takes into account the porosity of the thrombus. The thrombus's resistance to flow is incorporated by adding a bound activated-platelet-dependent term to the Naiver-Stokes momentum equation. However, one of the caveats is that two of the biochemical parameters used in the model were not taken from experimental literature. Despite the uncertainty associated with these types of parameters, the study confirmed the model's results were consistent with experimental observations (Cito et al., 2013).

3.3 Arterial and Venous Thrombi Formation

Blood flow in arteries and veins is a complex system that involves flow loops with multiple branches where blood circulates (Ku, 1997). In arteries, the type of flow observed is unsteady, with normal arterial flow being laminar and secondary flows seen in curves and branches (Ku, 1997). One of the challenges for modelers is that arteries and veins are living organs that adapt and change to the various hemodynamic conditions to which they are subjected. Sometimes the changes that arteries and veins make can cause problems in clot formation. For instance, if velocity profiles are skewed it can create areas in which wall shear stress oscillates (Ku, 1997; Lowe, 2003/2004). It is in these regions that atherosclerotic disease is found. This disease causes the artery to become more narrow, creating a stenosis, which can ultimately induce thrombosis and block blood flow to the heart and brain (Ku, 1997). The reason this occurs is because the stenosis causes turbulence and reduces flow through an artery, inducing high shear stresses that can activate platelets and initiate clot formation (Ku, 1997). In addition, these types of pathologies can also change the viscoelastic properties and viscosity of an individual's blood (Fasano et al., 2012). Thus, it is important to understand the consequences of different types of flow in arteries and veins, and how different flow types can affect physiological systems connected to the arteries and veins.

Some researchers have focused on the rheology of the vessels in the arteries and veins. For example, Fasano et al. (2013) presents a model whose aim is to capture the effect of blood slip at vessel walls. The authors claim that the blood slip at vessel walls causes an increase in activated platelets to the clotting site, which in some cases can even dominate the clotting behavior of the system. Note that this model is based off of the cell-based biological model of blood coagulation. Fasano et al. (2013) models the propagation phase of the cell-based model of coagulation because this is when the largest quantity of fibrin is produced, thus making it an easy species to track. Because of the limited scope that was considered when modeling the coagulation process, the results of this paper are themselves limited. However, the authors recognize this and suggest that this model is a start toward integrating blood slip phenomena into other coagulation models. This model is significant because of its ability to predict blood slip consequences, which are normally found around the bends and curves of the venous and arterial systems (Fasano et al., 2013). These effects can be further augmented depending on the blood vessel system: the arteries have higher platelet counts than veins (Campbell et al., 2010; Fasano et al., 2013).

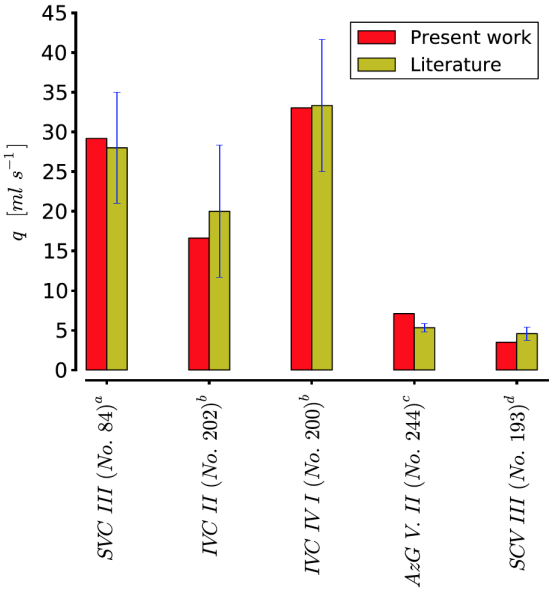

Figure 3.4 Blood flow in selected systemic veins of the model. The computational results from the model are compared to the accepted literature results. *Image taken from Muller and Toro (2014)*

On the other hand, other modelers have taken to directly modeling the circulatory system. To demonstrate, Muller and Toro (2014) developed a global multiscale mathematical model of the circulatory system, placing an emphasis on the venous system. This work is novel because it includes a majority of the circulatory system: arteries, veins, the heart, pulmonary circulation, and microcirculation. The detailed venous system is what makes Muller and Toro (2014) unique. In particular, the authors are interested in understanding how neck and head venous hemodynamic conditions are related to neurodegenerative diseases (Muller and Toro, 2014). In order to develop a more accurate model, the authors use MRI data from individual patients. Muller and Toro (2014) use a closed-loop, multiscale approach to develop their model.

Figures 3.4 and 3.5 both show how well the experimental and accepted literature values agree with the results of the model. To create these models, a 1D flow model was used in elastic vessels. Specifically, a first-order, nonlinear hyperbolic system was used. Ultimately, these results provided valuable insights and a holistic view of blood coagulation. However, one

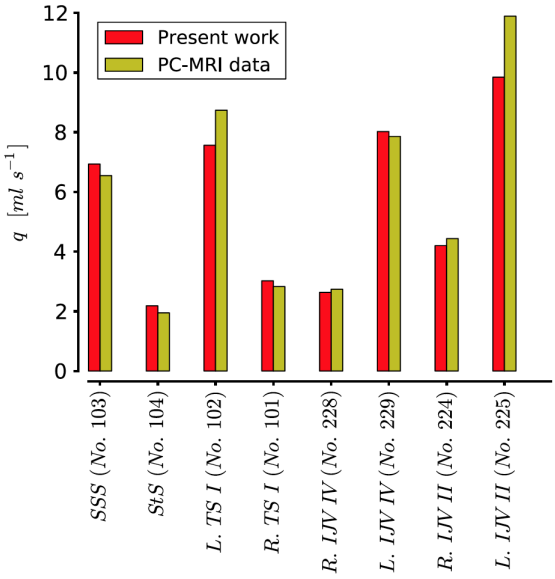

Figure 3.5 This figure shows the blood flow in the head and neck veins of an individual. The results from the model are directly compared to the results collected from the MRI flow quantification images. *Image taken from Muller and Toro (2014)*

of the disadvantages of such a model is that there is significantly more research on arterial systems and not venous systems. Thus, more experimental research needs to be done to validate the results of the venous system.

3.4 Conclusions

To make models of blood coagulation more accurate, researchers have incorporated the blood flow dynamics observed *in vivo*. One of the difficulties tog this type of modeling is that until the past decade, there were very limited ways of quantifying and visualizing what physiological blood coagulation was like. As a result, there is more uncertainty in flow-based models than in *in vitro* coagulation models.

Some of the fluid dynamics that have been successfully modeled include the rheology of blood, platelet deposition, flow-mediated transport, and the overall growth and dissolution of clots. While these models make several simplifications, they have helped move this field forward. How-

ever, one of the challenges faced by modelers is in capturing the behavior of whole blood as multiple types of fluids. Some of the earliest efforts include single continuum models. More recent work has used mixture theory to model the different fluid types observed in the different components of whole blood.

Future work may include more model validation. As limited experimental data was available before the past few years, access to more data will both help inspire different mathematical approaches and model validation techniques. It seems that it will become increasingly more important to understand how venous and arterial systems differ from one another and interact together in the coagulation system.

Chapter 4

Clinical and Pharmaceutical Applications of Blood Coagulation Models

Due to the critical role that blood coagulation plays in human physiology, it is necessary to understand how we can diagnose and treat coagulation abnormalities. It is also important to understand how other diseases affect the coagulation process. As a result, several mathematical models have been used to directly study the pharmacology and diagnostics of coagulation disorders and other diseases (Mann, 2012).

There are several challenges that researchers face in developing mathematical models of blood coagulation as they relate to pharmacology and diagnostics. For instance, although the overall network of blood coagulation is well-established, there is still not much understanding as to how it works *in vivo* (Shibeko and Panteleev, 2015).

In this chapter, we will focus on the applications of mathematical modeling directly to pharmacology and diagnostics. In particular, we will look at models for pharmacokinetic-pharmacodynamic data, which seeks to understand drug-drug interactions and has seen an increasing use of systems pharmacology models (e.g. Burghaus et al., 2011, 2014; Clegg and Gabhann, 2015; Cromme et al., 2010; de Pillis et al., 2015; Dydek and Chaikof, 2015; Gulati et al., 2014; Leipold et al., 1995; Luan et al., 2010; Lynd and O'Brien, 2004; Mueck et al., 2011; Nagashima, 2002; Nayak et al., 2015; Nielsen et al., 2009; Parunov et al., 2011, 2014; Vink et al., 2003; Wajima et al., 2009). Pharmacology models are models that use ideas from systems biology to simplify lumped parameter models (mostly multiscale models)

to develop more mechanistic-based approaches (Gulati et al., 2014). Additionally, models that focus on providing individual profiles of disease risk will be highlighted (e.g. Brummel-Ziedins, 2014; Brummel-Ziedins et al., 2005; Lynd and O'Brien, 2004; Undas et al., 2010, 2011). Other models address how preexisting conditions can affect coagulation (Clegg and Gabhann, 2015; Egger et al., 2013; Foley and Mackey, 2009; Lee et al., 2012; Lynd and O'Brien, 2004; Singh et al., 2015; Undas et al., 2010, 2011) and other possible areas of research such as using models to explore how biomedical devices and therapies, such as hemodialysis, affect coagulation (Barak et al., 2008; Boccaccio and Medico, 2006; Cohen, 2012; Ghosh and Shetty, 2008; Moiseyev and Bar-Yoseph, 2013).

4.1 Modeling Pharmacokinetic-Pharmacodynamic Data

Understanding how therapeutic drugs affect the coagulation network is important because it can help researchers quantify the effectiveness of each drug. Mathematical models of coagulation can help researchers do this. For example, a model of the biochemical network of coagulation can be analyzed for points of fragility. These points could help indicate possible pathways or clotting factors that can be furthered explored for therapeutic intervention (Csajka and Verotta, 2006; Luan et al., 2010). Thus, the uncertainties in mechanistic models can help focus the intervention of researchers in clotting abnormalities.

4.1.1 Drug-Drug Interactions

Some of the questions that researchers are interested in exploring, among many others, include:

1. How do different drug treatments affect the various coagulation pathways and thrombus formation?
2. How do different drugs interact with one another in the context of coagulation?
3. How safe and effective are certain drugs when compared to others?
4. When do *in vitro* tests inaccurately portray *in vivo* conditions?

Similar types of questions have guided several of the models that have been developed to date.

An important note is that many of the models that specifically look at the effectiveness of therapies use the international normalized ratio (INR) measurements to quantify the effectiveness of anticoagulant treatments that target vitamin-K antagonists (VKAs), such as warfarin (Christensen and Larsen, 2012; Lazzaro and Zaidat, 2012). These values are based on PT and aPTT tests (see Chapter 1). Note that higher INR values mean that it takes longer for blood to clot. A safe target range for patients on anticoagulants is an INR between 2.0 and 4.0 (Lazzaro and Zaidat, 2012). The INR of a healthy individual is approximately 1.0 (Lazzaro and Zaidat, 2012).

Understanding Treatments of Clotting Abnormalities

Several models have been developed to understand clotting abnormalities such as hemophilia or thrombosis. However, most of these models are not developed with the purpose of modeling the disease itself. Instead, the strategy employed is modeling healthy blood coagulation, modifying parameters associated with the clotting disorders, and ultimately modeling how treatments of the clotting abnormalities affect the coagulation process. In this section, we will focus on models that look at how drugs can help patients with hemophilia or thrombosis (Cromme et al., 2010; de Pillis et al., 2015; Leipold et al., 1995; Nagashima, 2002; Nayak et al., 2015; Nielsen et al., 2009; Parunov et al., 2011, 2014; Wajima et al., 2009). Some models focus on thrombus formation and how it is affected by anticoagulants like warfarin (Nielsen et al., 2009; Parunov et al., 2011), while other models incorporate spatial and flow dynamics, along with drug interactions and their effect on thrombus growth (de Pillis et al., 2015; Parunov et al., 2014).

One recent model that describes how the anticoagulant, warfarin, affects thrombus growth was developed by de Pillis et al. (2015). In this model, the authors extend past models of *in vitro* clot time tests and *in vivo* thrombus formation that include warfarin treatments. de Pillis et al. (2015) was particularly interested in describing possible conditions in which injury-induced thrombi may form *in vivo* even when clot time tests (which are used to diagnose and determine a patient's ability to clot well) suggest that warfarin treatments are performing at acceptable levels of anticoagulation. In this study, the authors used a system of ODEs to model biochemical reactions and 1D laminar flow. Numerical simulations are used to compare situations when warfarin dosages and flow conditions are varied under normal physiological ranges. Ultimately, de Pillis et al. (2015) found that one of the conventionally used clot time tests, INR measurements, do not accurately describe *in vivo* clotting times. This model suggests that because

the INR measurement does not account for the flow dynamics of blood, it cannot describe *in vivo* clotting. Despite this meaningful claim, this model makes several simplifications in its treatment of flow, warfarin interactions, and coagulation biochemistry that limit the scope of its use. More details and complexity can be added to this model to capture the effects of blood flow, the pharmacokinetic-pharmacodynamic data, and even extend its use to other treatments and applications (e.g., understanding biomedical implants and their effects on coagulation and treatments).

Another comprehensive model that looks at *in vitro* tests, treatments, and other applications is presented in Wajima et al. (2009). In this model, the authors look at different *in vitro* tests and drug therapies using a simplified treatment of flow and the coagulation network. This model is extended for applications to snake bites, hemophilia A and B, warfarin treatments, and heparin treatments.

In Figure 4.1, the authors present the application of their model to aPTT tests for hemophilia. Note that the x-axis shows % factor concentrations of the normal plasma and the dotted lines show the 1%, 5%, and 25% of physiological level for the respective factor concentrations. These concentrations correspond to severe, moderate and mild disease, respectively. Ultimately, Wajima et al. (2009) found that the standard aPTT results were consistent with accepted literature values. The simulation showed that clotting time ranges were 73-98 s and 79-123 s for patients with severe hemophilia A and B, respectively (literature values are > 60 and > 80 s, respectively); 56-73 s and 59-79 s for patients with moderate hemophilia A and B, respectively (literature values are 40-80s and 40-80 s, respectively); 43-56 s and 44-59 s for patients with severe hemophilia A and B, respectively (literature values are 40-60 s and 40-60 s for hemophilia A and B, respectively). Thus, the Wajima et al. (2009) model accurately captures *in vitro* aPTT results for patients with hemophilia A and B.

Similarly, in Figure 4.2 the authors show the results of simulations for other clot time tests, namely the PT and aPTT results for literature data. In general, the simulated tests agreed well with the measured values of the tests, with the exception of the measurement of aPTT at 95 s. In this case, the value was higher in the simulation than what was measured. Because this model consistently reflects the measured values in its simulations, it suggests the Wajima et al. (2009) model accurately captures the important aspects of *in vitro* tests. While this model is able to successfully do this, it simplifies the treatment of *in vivo* coagulation by using ODEs. However, this model can be used in drug development and in predicting coagulation kinetics.

Rivaroxaban

Traditionally, warfarin and heparin are commonly used as anticoagulants (Dahlback, 2000). However, a more recent oral anticoagulant known as rivaroxaban has been receiving more attention because it is a direct fXa inhibitor. Rivaroxaban is principally used to prevent venous thromboembolism in adult patients.

When new drugs are developed, some of the many questions that arise are: How safe and effective is the drug? How does the drug compare to other therapies? What are the residual effects when a patient is switched from one drug therapy to another? With regards to rivaroxaban, there are two interesting models that have recently been developed (Burghaus et al., 2011, 2014).

In Burghaus et al. (2011), the authors use a model to evaluate the efficacy and safety of various rivaroxaban dosages. This model was based on several published models (Bungay et al., 2003; Hockin et al., 2002; Kogan et al., 2001; Kuharsky and Fogelson, 2001). The Burghaus et al. (2011) model takes into account both the intrinsic and extrinsic pathways, blood flow dynamics and pharmacological mechanisms for certain drugs of interest. This model was also applied to clinical studies.

Figure 4.3 shows the efficacy of rivaroxaban when compared with warfarin. In the image, we note that at low TF concentrations, there is a large overlap between warfarin and rivaroxaban. In contrast, at higher TF concentrations warfarin has a larger effect on clotting times. In particular, this means that rivaroxaban has a higher dependency on TF concentrations than warfarin when determining its anticoagulant effect. Thus, the model suggests that at the particular dosage being looked at, rivaroxaban has higher efficacy at low TF concentrations, where efficacy/potency are defined as the ability to keep a patient's clotting time at a safe level. At higher concentrations, rivaroxaban is less effective than warfarin because the higher TF concentrations induce stronger anticoagulant effects. This is particularly important for patients with thrombosis since low potency at high TF concentrations could lead to bleeding from the strong anticoagulant effects of rivaroxaban. This is problematic because the drug therapies should prevent over-clotting, but not at the risk of under-clotting.

Figure 4.4 shows the safety and efficacy of different doses of rivaroxaban by comparing it with the following anticoagulants: ximelagatran, enoxaparin, DX-9065a, and warfarin (Burghaus et al., 2011). Typical doses for each of these drugs were compared with rivaroxaban doses ranging from 5 mg to 40 mg. Based on the measure presented in Burghaus et al.

(2011), all rivaroxaban doses were deemed safe up to 20 mg once daily (OD) and doses were effective above 5 mg. It appears, from Figure 4.4, that the optimal dose is at 20 mg OD. In this paper, a safe treatment was defined as a treatment that had a safe INR level between 1.0 and 3.0. This is because a safe INR for patients on anticoagulants is between 2.0 and 4.0 (Lazzaro and Zaidat, 2012). Thus, this model captures the observed behavior of the drugs and can be used to predict safe and effective rivaroxaban dosages for treatment.

Later on Burghaus et al. (2014) used a similar model to investigate potential dosing schedules for patients switching from warfarin to rivaroxaban therapies. This is an important question because patients can have severe drug reactions when they are switched to another anticoagulant therapy, especially since residual effects of old treatments can remain present for some time (Burghaus et al., 2014). This study used data from atrial fibrillation patients in Caucasian and Japanese populations. Ultimately, Burghaus et al. (2014) found that there was a synergetic reaction during the first 2-3 days from warfarin discontinuation but the effect of warfarin was additive after these first few days. Therefore, this model could be used to determine dosage schedules for patients switching from one drug therapy to another.

4.1.2 Systems Pharmacology Models

Many blood coagulation models are sophisticated multiscale models. However, the problem with using such models in clinical settings is that they are so complex and detailed. One question of interest in modeling coagulation is how might multiscale models be simplified so they can be used as a mechanistic basis to estimate parameters that describe the relationship of interest (Diamond, 2009). In Gulati et al. (2014), the authors present scale reduction techniques to encourage the use of mechanistic models in clinical pharmacology. Specifically, Gulati et al. (2014) uses a pharmacokinetic-pharmacodynamic (PK-PD) model to describe the time course of recovery after a brown snake bite. The authors use a lumping technique to simplify a 62-state model to a 5-state model. The model describes the brown snake venom-fibrinogen interaction and maintains an accurate mechanistic relationship of coagulation that agrees with experimental data.

4.2 Developing Individual Profiles of Disease Risk

One of the goals of physicians is to be able to provide individualized care for patients. Thus, it is of interest to understand an individual's disease risk. With regards to clotting disorders, one way that this may be done is by using plasma-composition based models. These models are based on earlier models of aPTT and PT diagnostics (Nayak et al., 2015). As more experimental and clinical data is accessible for evaluation, new computational and mathematical models are developed (Brummel-Ziedins, 2013, 2014).

One part of the coagulation network that is generally studied in individual patients with possible prothrombotic phenotypes (or other types of disease risk) is fXa generation (Brummel-Ziedins et al., 2012a, b, 2009). In these types of models, factor levels of specific species were computed and then used in the thrombin generation model to evaluate and determine possible causes of prothrombotic risk (Panteleev et al., 2014).

Thrombus formation in individuals can also be studied by looking at platelet responses of patients. One such model is Flamm et al. (2012). Here, a multiscale model of platelet deposition was used to compare simulated thrombus formation with microfluidic experiments of thrombus growth (Panteleev et al., 2014). This type of model can be used to assess thrombotic phenotypes, diagnose new clotting abnormalities, and even evaluate drug responses.

Other models look at individual thrombotic phenotypes based on preexisting health conditions associated with coagulation abnormalities. Among the many health conditions explored are chronic obstructive pulmonary disease (Undas et al., 2011), rheumatoid arthritis (Undas et al., 2010), cancer (Clegg and Gabhann, 2015; Lee et al., 2012), and deep vein thrombosis (Brummel-Ziedins et al., 2005).

4.2.1 Areas of Further Research

Models of blood coagulation can provide great insight into various clinical and pharmacological settings, as well as enhance the theoretical understanding of the coagulation phenomenon. Some possible extensions of such models include further investigations of other diseases and disorders linked with coagulation abnormalities, such as atrial fibrillation, malaria, or cancer Boccaccio and Medico (2006); Clegg and Gabhann (2015); Foley and Mackey (2009); Ghosh and Shetty (2008); Kulo et al. (2011); Vogler and Siedlecki (2009).

Other applications may include analysis of blood coagulation of patients undergoing surgery or the consequences of long-term use of biomedical implants or therapies (Barak et al., 2008; Cohen, 2012; Diamond, 1999; Dudek et al., 2011b, a; Moiseyev and Bar-Yoseph, 2013; Spahn and Casutt, 2000; van de Vosse, 2003). For instance, patients with end-stage renal failure that are under hemodialysis (HD) can take in microbubbles created in the HD machine (Barak et al., 2008). This is problematic because microbubbles can obstruct blood flow, initiate coagulation, and even cause platelets to adhere to the bubble itself, further triggering coagulation (Barak et al., 2008). Thus, coagulation models can serve to develop engineering systems that are less harmful for patients. In fact, some of these same principles can be extended to develop models for bone regeneration and tissue engineering (Geris et al., 2010).

4.3 Conclusions

The clinical and pharmaceutical applications of blood coagulation models are numerous. They can be used to understand the drug pathways involved in treatments and the effect of those pathways on the overall coagulation network. Additionally, models can be used to determine the safety and efficacy of drug therapies and diagnostic tests. Recently, more work has been done in understanding how the plasma composition of an individual can be used to determine the individual's risk of disease. These types of models take into account thrombus formation under flow, possible treatments the individual may be taking, and even preexisting health conditions that have been linked with coagulation abnormalities. Ultimately, these types of models are useful in quantifying the effectiveness of certain drug developments and the health risks of an individual.

Despite the wealth of insight these models can provide, they are not yet commonly used in developing drugs (Shibeko and Panteleev, 2015). These models continue to be used as theoretical models for understanding coagulation biochemical mechanisms. Some of the disadvantage of using these models is that many of them continue to rely on the coagulation cascade biological model. The problem with basing work off of these biological coagulation models is that the general consensus is that a cell-based model is more accurate (Bodnár et al., 2014; Fasano et al., 2013). It is not yet clear how using the cell-based model of blood coagulation would alter some of these findings, particularly since it seems that these coagulation cascade-based models reflect the observed results of clinical and PK-PD data.

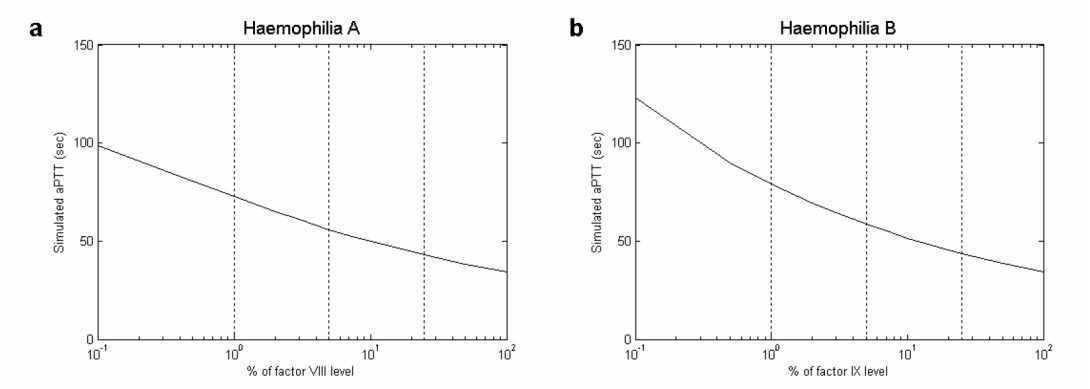

Figure 4.1 This figure shows simulation results of the influence of (a) deficiency of fVIII (for hemophilia A) and (b) deficiency of fIX (for hemophilia B), as seen in aPTT tests. The x-axis is shows % factor concentrations of the normal plasma and the dotted lines show the $1\%, 5\%$, and 25% of physiological level for the respective factor concentrations. The aPTT simulations had initial concentrations of 14.8% of fXI and fXIa. *Image taken from Wajima et al. (2009)*

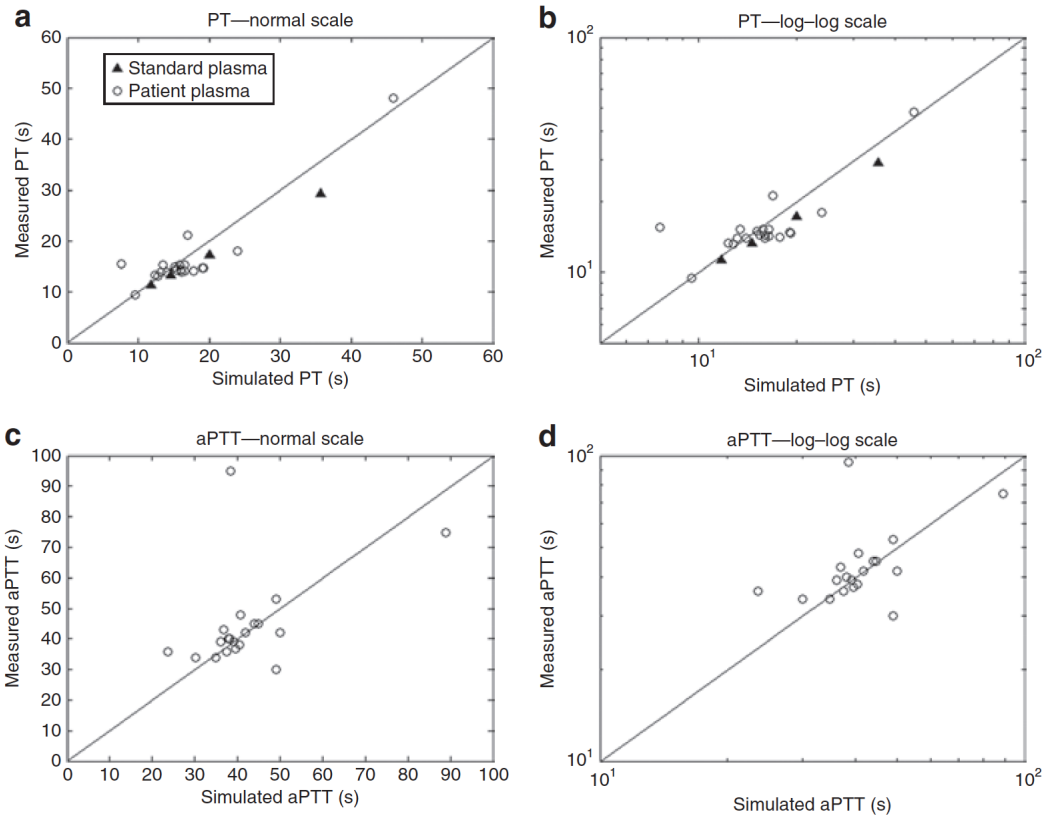

Figure 4.2 The simulated PT and aPTT compared withe measured literature values. (a) PT on a normal scale graph, (b) PT on a log-log scale, (c) aPTT on a normal scale graph, and (d) aPTT on a log-log scale graph. The aPTT and PT were simulated using factor concentrations from literature. The PT simulations assumed an initial TF concentration of 300 nmol/l, meaning there was an excess of fVII concentration. The aPTT simulations assumed and initial concentration of 14.8% and 33.9% for fXI and fXIa in plasma samples, respectively. *Image taken from Wajima et al. (2009)*

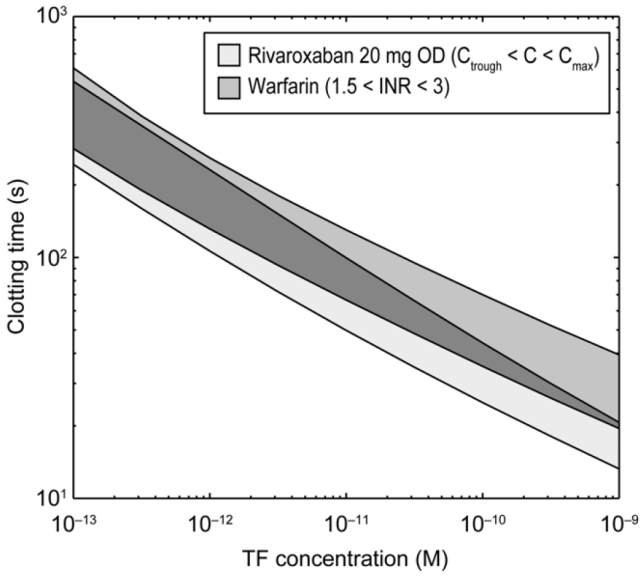

Figure 4.3 Efficacy of warfarin and rivaroxaban treatments are compared. A dose of 20 mg once daily (OD) of rivaroxaban was compared to warfarin with $1.5 < \mathrm{INR} < 3$. The clotting times are measured as functions of TF concentrations. The dark region represents the overlap of rivaroxaban and warfarin. *Image taken from Burghaus et al. (2011)*

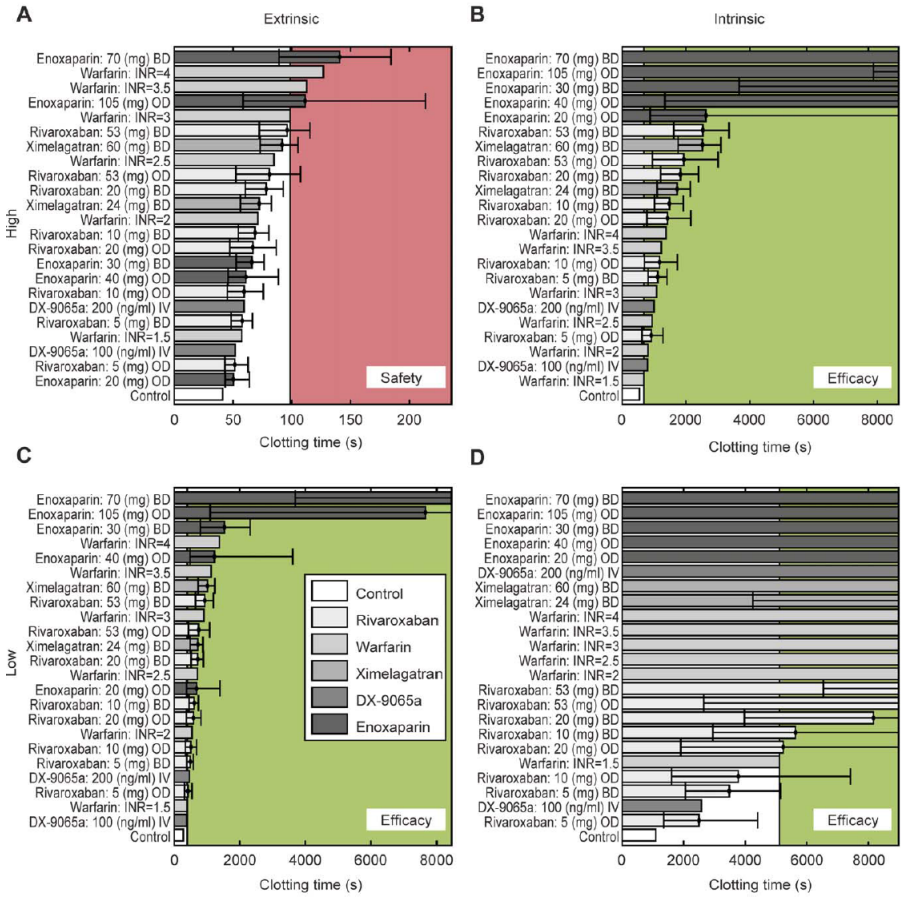

Figure 4.4 Safety and effectiveness of different anticoagulant treatments at varying dosages. The error bars show the spread of clotting times. (A) The red shaded area illustrates safe clotting times above the effect of warfarin titrated to an INR of 3. All therapies below the red area are considered safe. Here the trigger for coagulation is TF 10^{-11} mol/l. (B) The trigger is fXIIa 10^{-11} mol/l. (C) The trigger is TF 10^{-14} mol/l. (D) The trigger is TF 10^{-11} mol/l. The green area represents the effect of warfarin to an INR of 1.5. All values above the green shaded region are considered effective. *Image taken from Burghaus et al. (2011)*

Chapter 5

Conclusions

Blood coagulation is a complex physiological process that is critical to an individual's health. It involves a balance of various factors including biochemical reactions, clotting factors, platelets, binding sites, geometrical and spatial constraints from the blood vessels, and flow dynamics. When an imbalance exists, an individuals life can be at risk. Some of the dangers of abnormally clotting are significant blood loss, pulmonary embolism, thrombosis, stroke, cardiac arrest, or even death (Tanaka et al., 2009). As a result, blood coagulation research is an important topic in medical research. However, there are many disagreements as to the validity of the models because of the uncertainty in parameters and the disagreement between experimental and simulated data (Hemker and Ataullakhanov, 2005; Hemker et al., 2012). This is, in part, due to the lack of understanding of the physical effects of physiological coagulation (Hemker et al., 2012; Leiderman and Fogelson, 2014).

Given the complexity of coagulation, mathematicians can use mathematical models to quantify the coagulation process. Mathematical models allow researchers to gain insight into the nuances of clotting, as well as provide an avenue for testing potential treatments and drug therapies when a physical experiment may be too dangerous (Mann, 2012). In this review, we have grouped mathematical models based on what they attempt to describe: *in vitro* coagulation, *in vivo* coagulation, and clinical applications.

5.1 *In Vitro* Coagulation

In vitro models focus on understanding the basic biochemistry of coagulation. These models assume that there is no flow in the coagulation pro-

cess, making them ideal for predicting coagulation behavior in experimental and non-vascular environments. As a result, these models form the basis of mathematical models of diagnostic tests, such as the activated partial thromboplastin time test or prothrombin time test.

Mathematicians have primarily used ODE-based models to simulate clotting, honing in on specific biochemical mechanisms of the coagulation process. Given the deterministic nature of the models, the uncertainty in parameters plays a great role in the results of the models. There have, however, been several efforts to perform a sensitivity analysis of the *in vitro* models developed to date. Additionally, to account for the uncertainty in parameters and in the stochastic behavior observed, mathematicians have also used Monte Carlo simulations and Petri net models.

While these types of models have provided a greater understanding of the biochemical processes involved in coagulation, they do not accurately characterize physiological coagulation. There are several sources of uncertainty in coagulation models, including rate constant measurement, individual plasma-content variation, or clotting factor variations, that have yet to be thoroughly explored.

5.2 *In Vivo* Coagulation

Other models have incorporated the blood flow dynamics of *in vivo* coagulation. However, because of the greater uncertainty in how the physical parameters of coagulation affect clot formation, these models are difficult to construct. Despite the uncertainty, some of the aspects of coagulation that have been successfully modeled include the rheology of blood, platelet deposition, flow-mediated transport, and the dissolution of clots.

Most of these models use a PDE-based multiscale modeling approach. This work has even allowed for the modeling of different types of blood vessels (i.e., arteries and veins). With more experimental data becoming available, *in vivo* coagulation models promise to become more important in clinical research and drug development.

5.3 Clinical Applications

With more reliable models of *in vitro* and *in vivo* coagulation, clinical researchers and scientists are using mathematical models more and more in their work. Some of the topics that mathematical models have allowed researchers to explore include drug-drug interactions, the safety and efficacy

of drug therapies, dosing schedules, individual disease risk, and the design of biomedical technologies.

Models used in clinical and pharmaceutical applications are based on the simple mathematical models of *in vitro* coagulation. In spite of the inaccuracy of *in vitro* mathematical models, the use of these models has suggested the inadequacy of current diagnostic tests used by physicians. As such, more recent work has begun to include flow dynamics.

5.4 The Future of Mathematical Modeling of Coagulation

Over the past few years, there has been a growing interest in modeling clotting abnormalities and pharmacokinetic-pharmacodynamic data. In particular, emphasis has been placed in modeling the effects of different drug therapies on the coagulation system. This type of work has resulted in more sophisticated, computationally intensive multiscale models (Panteleev et al., 2007). Many of these models rely heavily on mathematical models of *in vitro* coagulation. However, doing so means that critical physiological factors (e.g., blood flow dynamics) are ignored, resulting in less accurate results. More recent models are starting to incorporate flow, spatial-temporal constraints, and even the individual plasma composition of patients.

Mathematical modeling of blood coagulation will continue to be relevant in years to come. As more accurate models continue to be developed, new uses for these models will emerge. Currently, these models are used to quantify *in vitro* diagnostics and understand the biochemical underpinnings of normal coagulation. They have also shown great potential in helping to develop drugs, understand how preexisting conditions in a patient affect drug therapies and coagulation, and design biomedical engineering systems that are beneficial for patients. However, until the mathematical models used in clinical settings better capture physiological coagulation behavior, clinicians will continue to use the less than perfect *in vitro* models. This could be improved by the development of a new diagnostic assay that better describes the current hemostatic state of a patient (Foley et al., 2013; Gulati et al., 2012; Shibeko and Panteleev, 2015), or by incorporating the physical constraints of coagulation in models. Ultimately, further investigations of the blood coagulation system and its physical parameters are needed to improve mathematical models.

Bibliography

Alenitsyn, A., A. Kondratyev, I. Mikhailova, and I. Siddique. 2010. Mathematical modeling of thrombus growth in mesenteric vessels. *Mathematical Biosciences* 224:29–34. doi:10.1016/j.mbs.2009.12.005.

Anand, M., K. Rajagopal, and K.R. Rajagopal. 2003. A model incorporating some of the mechanical and biochemical factors underlying clot formation and dissolution in flowing blood. *Journal of Theoretical Medicine* 5(3-4):183–218.

———. 2005. A model for the formation and lysis of blood clots. *Pathophysiology of Haemostasis and Thrombosis* 34:109–120. doi:10.1159/000089931.

Anor, T., L. Grinberg, H. Baek, J.R. Madsen, M.V. Jayaraman, and G.E. Karniadakis. 2010. Modeling of blood flow in arterial trees. *WIREs Systems Biology and Medicine* 2:612–623. doi:10.1002/wsbm.90.

Appiah, S.T. 2013. Using mathematical relations to deduce the rate of clot dissolution in the human circulatory system. *Internation Journal of Mathematical Archive* 4(7):221–233.

Appiah, S.T., I.A. Adetunde, and I.K. Dontwi. 2011. Mathematical model of blood clot in the human cardiovascular system. *Internation Journal of Research in Biochemistry and Biophysics* 1(2):9–16.

Ataullakhanov, F.I., and M.A. Panteleev. 2005a. Mathematical modeling and computer simulation in blood coagulation. *Pathophysiology of Haemostasis and Thrombosis* 34(2-3):60–70. doi:10.1159/000089927. URL http://dx.doi.org/10.1159/000089927.

———. 2005b. Towards virtual coagulation. *Pathophysiology of Haemostasis and Thrombosis* 34:58–59.

Barak, M., F. Nakhoul, and Y. Katz. 2008. Pathophysiology and clinical implications of microbubbles during hemodialysis. *Seminars in Dialysis* 21(3):232–238. doi:10.1111/j.1525-139X.2008.00424.x.

Barrett, K.E., S.M. Barman, S. Boitano, and H.L. Brooks. 2010. *Ganong's Review of Medical Physiology*. The McGraw-Hill Companies, Inc., 23rd ed.

Basmadjian, D., M.V. Sefton, and S.A. Baldwin. 1997. Coagulation on biomaterials in flowing blood: some theoretical considerations. *Biomaterials* 18(23):1511–1522.

Bellini, M., D. Besozzi, P. Cazzaniga, G. Mauri, and M.S. Nobile. 2014. Simulation and analysis of the blood coagulation cascade accelerated on gpu. In *22nd Euromicro International Conference on Parallel, Distributed, and Network-Based Processing*, 590–593. IEEE, IEEE. doi:10.1109/PDP.2014.52.

Beltrami, E., and J. Jesty. 2001. The role of membrane patch size and flow in regulating a proteolytic feedback threshold on a membrane: possible application in blood coagulation. *Mathematical Biosciences* 172:1–13.

Bessonov, N., A. Sequeira, S. Simakov, Yu. Vassilevskii, and V. Volpert. 2016. Methods of blood flow modelling. *Mathematical Modeling of Natural Phenomena* 11(1):1–25. doi:10.1051/mmnp/201611101.

Bjorkman, S., and E. Berntorp. 2001. Pharmacokinetics of coagulation factors: Clinical relevance for patients with haemophilia. *Clinical Pharmacokinetics* 40(11):815–832.

Boccaccio, C., and E. Medico. 2006. Visions and reflections: Cancer and blood coagulation. *Cellular and Molecular Life Sciences* 63:1024–1027. doi:10.1007/s00018-005-5570-9.

Bodnár, T., A. Fasano, and A. Sequeira. 2014. *Fluid-Structure Interaction and Biomedical Applications*, chap. 7: Mathematical Models for Blood Coagulation, 483–569. Advances in Mathematical Fluid Mechanics, Springer Basel. doi:10.1007/978-3-0348-0822-4__7.

Bodnár, T., and A. Sequeira. 2008. Numerical simulation of the coagulation dynamics of blood. *Computational and Mathematical Methods in Medicine* 9(2):83–104. doi:10.1080/17486700701852784.

Brummel-Ziedins, K.E. 2013. Models for thrombin generation and risk of disease. *Journal of Thrombosis and Haemostasis* 11(1):212–223. doi:10.1111/jth.12256.

———. 2014. Developing individualized coagulation profiling of disease risk: Thrombin generation dynamic models of the pro and anticoagulant balance. *Thrombosis Research* 133:S9–S11. URL http://dx.doi.org/10.1016/j.thromres.2014.03.004.

Brummel-Ziedins, K.E., S.J. Everse, K.G. Mann, and T. Orfeo. 2014. Modeling thrombin generation: plasma composition based approach. *Journal of Thrombosis and Haemostasis* 37:32–44. doi:10.1007/s11239-013-1006-9.

Brummel-Ziedins, K.E., T. Orfeo, P.W. Callas, M. Gissel, K.G. Mann, and E.G. Bovill. 2012a. The prothrombotic phenotypes in familial protein c deficiency are differentiated by computational modeling of thrombin generation. *PLoS ONE* 7(9):1–10.

Brummel-Ziedins, K.E., T. Orfeo, M. Gissel, K.G. Mann, and F.R. Rosendaal. 2012b. Factor xa generation by computational modeling: An additional discriminator to thrombin generation evaluation. *PLoS ONE* 7(1):1–11.

Brummel-Ziedins, K.E., T. Orfeo, F.R. Rosendaal, A. Undas, G.E. Rivard, S. Butenas, and K.G. Mann. 2009. Empirical and theoretical phenotypic discrimination. *Journal of Thrombosis and Haemostasis* 7(Suppl. 1):181–186. doi:10.1111/j.1538-7836.2009.03426.x.

Brummel-Ziedins, K.E., C.Y. Vossen, S. Butenas, K.G. Mann, and F.R. Rosendaal. 2005. Thrombin generation profiles in deep venous thrombosis. *Journal of Thrombosis and Haemostasis* 3(11):2497–2505.

Bungay, S.D., P.A. Gentry, and R.D. Gentry. 2003. A mathematical model of lipid-mediated thrombin generation. *Mathematical Medicine and Biology* 20:105–129.

Buravtsev, V.N., A.I. Lobanovb, and A.V. Ukrainets. 2010. Mathematical model of platelet thrombus growth. *Mathematical Models and Computer Simulations* 2(1):55–62. doi:10.1134/S2070048210010060.

Burghaus, R., K. Coboeken, T. Gaub, L. Kuepfer, A. Sensse, H.U. Siegmund, W. Weiss, W. Mueck, and J. Lippert. 2011. Evaluation of the efficacy and safety of rivaroxaban using a computer model for blood coagulation. *PLoS ONE* 6(4).

Burghaus, R., K. Coboeken, T. Gaub, C. Niederalt, A. Sensse, H.U. Siegmund, W. Weiss, W. Mueck, T. Tanigawa, and J. Lippert. 2014. Compu-

tational investigation of potential dosing schedules for a switch of medication from warfarin to rivaroxaban - an oral, direct factor xa inhibitor. *Frontiers in Physiology* 5(417):1–13. doi:10.3389/fphys.2014.00417.

Butenas, S., and K.G. Mann. 2002. Blood coagulation. *Biochemistry* 67(1):3–12.

———. 2007. Caution in the interpretation of continuous thrombin generation assays. *Journal of Thrombosis and Haemostasis* 5:1084–1085.

Butenas, S., T. Orfeo, and K.G. Mann. 2009. Tissue factor in coagulation: Which? where? when? *Arteriosclerosis, Thrombosis, and Vascular Biology* 29:1989–1996. doi:10.1161/ATVBAHA.108.177402.

Butenas, S., C. van't Veer, and K.G. Mann. 1997. Evaluation of the initiation phase of blood coagulation using ultrasensitive assays for serine proteases. *Journal of Biological Chemistry* 272(34):21,527–21,533.

Campbell, J.E., K.E. Brummel-Ziedins, S. Butenas, and K.G. Mann. 2010. Cellular regulation of blood coagulation: a model for venous stasis. *Blood* 116(26):6082–6091. doi:10.1182/blood- 2010-01-266395.

Capek, M. 2011. Overview of mathematical models for blood flow and coagulation process. *WDS'11 Proceedings of Contributed Papers* Part III:187–192.

Castaldi, D., D. Maccagnola, D. Mari, and F. Archetti. 2013. Stochastic simulation of the coagulation cascade: A petri net based approach. In *Euro-Par 2012 Workshops*, ed. Caragiannis et al., vol. LNCS 7640, 248–262. Springer-Verlag Berlin Heidelberg.

Cattaneo, M., F. Franchi, M.L. Zighetti, I. Martinelli, D. Asti, and P.M. Mannucci. 1998. Plasma levels of activated protein c in healthy subjects and patients with previous venous thromboembolism: Relationships with plasma homocysteine levels. *Arteriosclerosis, Thrombosis, and Vascular Biology* 18:1371–1375. doi:10.1161/01.ATV.18.9.1371.

Cazzaniga, P., M.S. Nobile, D. Besozzi, M. Bellini, and G. Mauri. 2014. Massive exploration of perturbed conditions of the blood coagulation cascade through gpu parallelization. *BioMed Research International* 2014(863298):1–20. URL http://dx.doi.org/10.1155/2014/863298.

Chatterjee, M.S. 2011. *Systems Biology of Blood Coagulation and Platelet Activation*. Dissertation, University of Pennsylvania.

Chatterjee, M.S., W.S. Denney, H. Jing, and S.L. Diamond. 2010. Systems biology of coagulation initiation: Kinetics of thrombin generation in resting and activated human blood. *PLoS Computational Biology* 6(9):1–24. doi:10.1371/journal.pcbi.1000950.

Christensen, T.D., and T.B. Larsen. 2012. Precision and accuracy of point-of-care testing coagulometers used for self-testing and self-management of oral anticoagulation therapy. *Journal of Thrombosis and Haemostasis* 10:251–260. doi:10.1111/j.1538-7836.2011.04568.x.

Cito, S., M.D. Mazzeo, and L. Badimon. 2013. A review of macroscopic thrombus modeling methods. *Thrombosis Research* 131:116–124. URL http://dx.doi.org/10.1016/j.thromres.2012.11.020.

Clegg, L.E., and F.M. Gabhann. 2015. Systems biology of the microvasculature. *The Royal Society of Chemistry Integrative Biology* 7:498–512. doi:10.1039/c4ib00296b.

Cohen, M.J. 2012. Use of models in identification and prediction of physiology in critically ill surgical patients. *British Journal of Surgery Society Ltd* 99:487–493. doi:10.1002/bjs.7798.

Colace, T.V., R.W. Muthard, and S.L. Diamond. 2012. Thrombus growth and embolism on tissue factor-bearing collagen surfaces under flow: Role of thrombin with and without fibrin. *Arteriosclerosis, Thrombosis, and Vascular Biology* 32:1466–1476. doi:10.1161/ATVBAHA.112.249789.

Cromme, L., H. Voller, F. Gabler, A. Salzwedel, and U. Taborski. 2010. Computer-aided dosage in oral anticoaulation therapy using phenprocoumon: Problems and approaches. *Hamostaseologie* 30(4):183–189.

Csajka, C., and D. Verotta. 2006. Pharmacokinetic-pharmacodynamic modelling: History and perspectives. *Journal of Pharmokinetics and Pharmacodynamics* 33(3):227–279. doi:10.1007/s10928-005-9002-0.

da Cunha Orfao, S.M. 2007. *Mathematical Approaches to Modelling and Controlling Blood Thrombin Formation*. Dissertation, Rheinisch-Westfalischen Technischen Aachen University.

Dahlback, B. 2000. Haematology: Blood coagulation. *The Lancet* 355:1627–1632.

Dallon, J., J. Sherratt, P. Maini, and M. Ferguson. 2000. Biological implications of a discrete mathematical model for collagen deposition and alignment in dermal wound repair. *IMA Journal of Mathematics Applied in Medicine and Biology* 17:379–393.

Danforth, C.M., T. Orfeo, S.J. Everse, K.G. Mann, and K.E. Brummel-Ziedins. 2012. Defining the boundaries of normal thrombin generation: Investigations into hemostasis. *PLoS ONE* 7(2):1–12. doi:10.1371/journal.pone.0030385.

Danforth, C.M., T. Orfeo, K.G. Mann, K.E. Brummel-Ziedins, and S.J. Everase. 2009. The impact of uncertainty in a blood coagulation model. *Mathematical Medicine and Biology* 26:323–336.

de Pillis, L., E.J. Graham, K. Hood, Y. Ma, A. Radunskaya, and J. Simons. 2015. *Applications of Dynamical Systems in Biology and Medicine*, *The IMA Volumes in Mathematics and its Applications*, vol. 158, chap. Injury-Initiated Clot Formation Under Flow: A Mathematical Model with Warfarin Treatment, 75–98. doi:10.1007/978-1-4939-2782-1_4.

Diamond, S.L. 1999. Engineering design of optimal strategies for blood clot dissolution. *Annual Reviews of Biomedical Engineering* 1:427–461.

———. 2009. Systems biology to predict blood function. *Journal of Thrombosis and Haemostasis* 7:177–180. doi:10.1111/j.1538-7836.2009.03463.x.

———. 2013. Systems biology of coagulation. *Journal of Thrombosis and Haemostasis* 11(Suppl. 1):224–232. doi:10.1111/jth.12220.

Dudek, M.M., L.F. Harris, and A.J. Killard. 2011a. Evaluation of activated partial thromboplastin time (aptt) reagents for application in biomedical diagnostic device development. *International Journal of Laboratory Hematology* 33:272–280. doi:10.1111/j.1751-553X.2010.01283.x.

Dudek, M.M., N.J. Kent, P. Gu, Z.H. Fan, and A.J. Killard. 2011b. Development of a fluorescent method for detecting the onset of coagulation in human plasma on microstructured lateral flow platforms. *Analyst* 136(9):1769–1996. doi:10.1039/c0an00907e.

Dydek, E.V., and E.L. Chaikof. 2015. Simulated thrombin generation in the presence of surface-bound heparin and circulating tissue factor. *Annals of Biomedical Engineering* 1–13. doi:10.1007/s10439-015-1377-5.

Egger, J., A.S. Mallik, D. Szczerba, D.A. Ruefenacht, G. Szekely, and S. Hirsch. 2013. Spatial stabilization strategies applied to multiphysics modeling of blood clotting using a modified ptt model. *Procedia Computer Science* 18:996–1005. doi:10.1016/j.procs.2013.05.265.

Fasano, A., J. Pavlova, and A. Sequeira. 2013. A synthetic model for blood coagulation including blood slip at the vessel wall. *Clinical Hemorheology and Microcirculation* 54:1–14. doi:DOI:10.3233/CH-2012-1558.

Fasano, A., R.F. Santos, and A. Sequeira. 2012. *Modeling of Physiological Flows*, *Modeling, Simulation and Applications*, vol. 5, chap. 3: Blood Coagulation: a puzzle for biologists, a maze for mathematicians, 41–75. Springer-Verlag Italia. doi:10.1007/978-88-470-1935-5 3.

Filipovic, N., M. Kojic, and A. Tsuda. 2008. Modelling thrombosis using dissipative particle dynamics method. *Philosophical Transactions of the Royal Society of London* 366:3265–3279. doi:10.1098/rsta.2008.0097.

Flamm, M.H. 2011. *Lattice Kinetic Monte Carlo Simulations of Platelet Aggregation and Deposition*. Chemical and biomolecular engineering, University of Pennsylvania.

Flamm, M.H., T.V. Colace, M.S. Chatterjee, H. Jing, S. Zhou, D. Jaeger, L.F. Brass, T. Sinno, and S.L. Diamond. 2012. Multiscale prediction of patient-specific platelet function under flow. *Blood* 120(1):190–198. doi:10.1182/blood-2011-10-388140.

Fogelson, A.L., and R.D. Guy. 2008. Immersed-boundary-type models of intravascular platelet aggregation. *Computer Methods in Applied Mechanics and Engineering* 197:2087–2104. doi:10.1016/j.cma.2007.06.030.

Fogelson, A.L., Y.H. Hussain, and K. Leiderman. 2012. Blood clot formation under flow: The importance of factor xi depends strongly on platelet count. *Biophysical Journal* 102:10–18.

Fogelson, A.L., and N. Tania. 2005. Coagulation under flow: The influence of flow-mediated transport on the initiation and inhibition of coagulation. *Pathophysiology of Haemostasis and Thrombosis* 34(2-3):91–108. doi:10.1159/000089930. URL http://dx.doi.org/10.1159/000089930.

Foley, C., and M.C. Mackey. 2009. Dynamic hematological disease: a review. *Journal of Mathematical Biology* 58:285–322. doi:10.1007/s00285-008-0165-3.

Foley, J.H., T. Orfeo, A. Undas, K.C. McLean, I.M. Bernstein, G.E. Rivard, K.G. Mann, S.J. Everse, and K.E. Brummel-Ziedins. 2013. From principle to practice: Bridging the gap in patient profiling. *PLoS ONE* 8(1):1–9. doi: 10.1371/journal.pone.0054728.

Formaggia, L., A. Quarteroni, and A. Veneziani, eds. 2009. *Cardiovascular Mathematics: Modeling and simulation of the circulatory system*, *Modeling, Simulation and Applications*, vol. 1. Springer-Verlag.

Fragomeni, G., A. Merola, R. Serra, S. de Franciscis, and F. Amato. 2008. A nonlinear lumped parameters model to analyze the dynamics of venous reflux. *30th Annual International IEEE EMBS Conference* 30:1407–1410.

Furie, B., and B.C. Furie. 2008. Mechanisms of thrombus formation. *The New England Journal of Medicine* 359(9):938–949.

Geris, L., A. Gerisch, and R.C. Schugart. 2010. Mathematical modeling in wound healing, bone regeneration and tissue engineering. *Acta Biotheoretica* 58:355–367. doi:10.1007/s10441-010-9112-y.

Ghosh, K., and S. Shetty. 2008. Blood coagulation in falciparum malaria-a review. *Parasitology Research* 102:571–576. doi:10.1007/s00436-007-0832-0.

Gulati, A., J.M. Faed, G.K. Isbister, and S.B. Duffull. 2012. Development and evaluation of a prototype of a novel clotting time test to monitor enoxaparin. *Pharmaceutical Research* 29:225–235. doi:10.1007/s11095-011-0537-z.

Gulati, A., G.K. Isbister, and S.B. Duffull. 2014. Scale reduction of a systems coagulation model with an application to modeling pharmokinetic-pharmodynamic data. *CPT: Pharmacometrics Systems Pharmacology* 3(1):1–8. doi:10.1038/psp.2013.67.

Guo, Z., K.M. Bussard, K. Chatterjee, R. Miller, E.A. Vogler, and C.A. Siedlecki. 2006. Mathematical modeling of material-induced blood plasma coagulation. *Biomaterials* 27:796–806. doi:10.1016/j.biomaterials.2005.06.021.

Hemker, H.C., and F.I. Ataullakhanov. 2005. Good mathematical practice: Simulation of the hemostatic-thrombotic mechanism, a powerful tool but one that must be used with circumspection. *Pathophysiology of Haemostasis and Thrombosis* 34:55–57. doi:10.1159/000089925.

Hemker, H.C., S. Kerdelo, and R.M.W. Kremers. 2012. Is there value in kinetic modeling of thrombin generation? no (unless...). *Journal of Thrombosis and Haemostasis* 10:1470–1477. doi:10.1111/j.1538-7836.2012.04802.x.

Higgins, D.L., S.D. Lewis, and J.A. Shafer. 1983. Steady state kinetic parameters for the thrombin-catalyzed conversion of human fibrinogen to fibrin. *Journal of Biological Chemistry* 258(15):9276–9282.

Hockin, M.F., K.C. Jones, S.J. Everase, and K.G. Mann. 2002. A model for the stoichiometric regulation of blood coagulation. *The Journal of Biological Chemistry* 277(21):18,322–18,333. doi:10.1074/jbc.M201173200.

Hoffman, M., and D.M. Monroe-III. 2001. A cell-based model of hemostasis. *Thrombosis and Haemostasis* 85:958–965.

Hopkins, J.C., and R.J. Leipold. 1996. On the dangers of adjusting the parameter values of mechanism-based mathematical models. *Journal of Theoretical Biology* 183:417–427.

Jarm, T., P. Kramar, and A. Zupanic, eds. 2007. *Laminar Axially Directed Blood Flow Promotes Blood Clot Dissolution: Mathematical Modeling Verified by MR Microscopy*, *Medicon*, vol. 16. IFMBE, Springer-Verlag Berlin Heidelberg.

Jesty, J., and E. Beltrami. 2005. Positive feedbacks of coagulation: Their role in threshold regulation. *Arteriosclerosis, Thrombosis, and Vascular Biology* 25:2463–2469. doi:10.1161/01.ATV.0000187463.91403.b2.

Jones, K.C., and K.G. Mann. 1994. A model for the tissue factor pathway to thrombin. *Journal of Biological Chemistry* 269(37):23,367–23,373.

Jordan, S.W. 2010. *A Mathematical Model of Tissue Factor-Induced Blood Coagulation: Discrete Sites of Initiation and Regulation Under Conditions of Flow*. Biomedical engineering, Emory University and Georgia Institute of Technology.

Jorgensen, S.N., and J.R. Sanders. 2015. Mathematical models of wound healing and closure: a comprehensive review. *Medical and Biological Engineering and Computing* 1–20. doi:10.1007/s11517-015-1435-z.

Khanin, M.A., D.V. Rakov, and A.E. Kogan. 1998. Mathematical model for the blood coagulation prothrombin time test. *Thrombosis Research* 89:227–232.

Kim, O.V., Z. Xu, E.D. Rosen, and M.S. Alber. 2013. Fibrin network regulate protein transport during thrombus development. *PLoS Computational Biology* 9(6):e1003,095. doi:10.1371/journal.pcbi.1003095.

Kim, S. 2002. *A Study of Non-Newtonian Viscosity and Yield Stress of Blood in a Scanning Capillary-Tube Rheometer*. Ph.D. thesis, Drexel University.

Kogan, A.E., D.V. Kardakov, and M.A. Khanin. 2001. Analysis of the activated partial thromboplastin time test using mathematical modeling. *Thrombosis Research* 101:299–310.

Ku, D.N. 1997. Blood flow in arteries. *Annual Reviews of Fluid Mechanics* 29:399–434.

Kuharsky, A.L., and A.L. Fogelson. 2001. Surface-mediated control of blood coagulation: The role of binding site densities and platelet deposition. *Biophysical Journal* 80:1050–1074.

Kulo, A., J. Kusturica, E. Kapic, F. Becic, M. Rakanovic-Todic, L. Burnazovic-Ristic, A. Mehmedovic, O. Lepara, and N. Mulabegovic. 2011. Better stability of acenocoumarol compared to warfarin treatment in one-year observational, clinical study in patients with nonvalvular atrial fibrillation. *Medicinski Glasnik: Ljek Komore Zenicko-Doboj Kantona* 8(1):9–14.

LaCroix, D.E. 2012. A reduced equation mathematical model for blood coagulation and lysis in quiescent plasma. *International Journal of Structural Changes in Solids* 4:23–35.

Lancé, M.D. 2015. A general review of major global coagulation assays: thrombelastography, thrombin generation test and clot waveform analysis. *Thrombosis Journal* 13(1):1–6. URL http://www.thrombosisjournal.com/content/13/1/1.

Lazzaro, M.A., and O.O. Zaidat. 2012. Multimodal endovascular reperfusion therapies:adjunctive antithrombotic agents in acute stroke. *Neurology* 78:501–506.

Lee, A.M., G.W. Tormoen, E. Kanso, O.J.T. McCarty, and P.K. Newton. 2012. Modeling and simulation of procoagulant circulating tumor cells in flow. *Frontiers in Oncology* 2(108):1–9. doi:10.3389/fonc.2012.00108.

Lee, C.J., S. Wu, C. Eun, and L.G. Pedersen. 2010. A revisit to the one form kinetic model of prothrombinase. *Biophysical Chemistry* 149:28–33. doi:10.1016/j.bpc.2010.03.011.

Leiderman, K., and A. Fogelson. 2014. An overview of mathematical modeling of thrombus formation under flow. *Thrombosis Research* 133:S12–S14. doi:http://dx.doi.org/10.1016/j.thromres.2014.03.005.

Leiderman, K., and A.L. Fogelson. 2011. Grow with the flow: a spatial-temporal model of platelet deposition and blood coagulation under flow. *Mathematical Medcine and Biology* 28:47–84.

Leipold, R.J., T.A. Bozarth, A.L. Racanelli, and I.B. Dicker. 1995. Mathematical model of serine protease inhibition in the tissue factor pathway to thrombin. *Journal of Biological Chemistry* 270(43):25,383–25,387.

Lo, K., W.S. Denney, and S.L. Diamond. 2005. Stochastic modeling of blood coagulation initiation. *Pathophysiology of Haemostasis and Thrombosis* 34:80–90. doi:10.1159/000089929.

Lobanov, A.I., and T.K. Starozhilova. 2005. The effect of convective flows on blood coagulation processes. *Pathophysiology of Haemostasis and Thrombosis* 34:121–134. doi:10.1159/000089932.

Lowe, G.D.O. 2003/2004. Virchow's triad revisited: Abnormal flow. *Pathophysiology of Haemostasis and Thrombosis* 33:455–457.

Luan, D. 2009. *Computational Modeling and Simulation of Thrombus Formation*. Dissertation, Cornell University.

Luan, D., F. Szlam, K.A. Tanaka, P.S. Barie, and J.D. Varner. 2010. Ensembles of uncertain mathematical models can identify network response to therapeutic interventions. *Molecular BioSystems* 6:2272–2286. doi:10.1039/b920693k.

Luan, D., M. Zai, and J.D. Varner. 2007. Computationally derived points of fragility of a human cascade are consistent with current therapeutic strategies. *PLoS Computational Biology* 3(7):1347–1359. doi:10.1371/journal.pcbi.0030142.

Lynd, L.D., and B.J. O'Brien. 2004. Advances in risk-benefit evaluation using probabilistic simulation methods: an application to the prophylaxis of deep vein thrombosis. *Journal of Clinical Epidemiology* 57:794–803. doi:10.1016/j.jclinepi.2003.12.012.

Mackman, N., R.E. Tilley, and N.S. Key. 2007. Role of the extrinsic pathway of blood coagulation in hemostasis and thrombosis. *Arteriosclerosis, Thrombosis, and Vascular Biology* 27:1687–1693. doi:10.1161/ATVBAHA.107.141911.

Makin, J., and S. Narayanan. 2008. Hybrid-system modeling of human blood clotting. International Computer Science Institute.

Makin, J.G. 2008. *A Computational Model of Human Blood Clotting: Simulation, Analysis, Control, and Validation*. Engineering - electrical engineering and computer sciences, University of California at Berkeley.

Mann, K.G. 2012. Is there value in kinetic modeling of thrombin generation? yes. *Journal of Thrombosis and Haemostasis* 10:1463–1469. doi:10.1111/j.1538-7836.2012.04799.x.

Mann, K.G., K. Brummel, and S. Butenas. 2003. What is all that thrombin for? *Journal of Thrombosis and Haemostasis* 1:1504–1514.

Mann, K.G., K.E. Brummel-Ziedins, T. Orfeo, and S. Butenas. 2006. Models of blood coagulation. *Blood, Cells, Molecules, and Diseases* 26:108–117. doi:10.1016/j.bcmd.2005.12.034.

Mann, K.G., T. Orfeo, S. Butenas, A. Undas, , and K.E. Brummel-Ziedins. 2009. Blood coagulation dynamics in hemostasis. *Hamostaseologie* 29(1):7–16.

Mitrophanov, A.Y., and J. Reifman. 2011. Kinetic modeling sheds light on the mode of action of recombinant factor viia on thrombin generation. *Thrombosis Research* 128:381–390. doi:10.1016/j.thromres.2011.05.013.

Mitrophanov, A.Y., F.R. Rosendaal, and J. Reifman. 2012. Computational analysis of intersubject variability and thrombin generation in dilutional coagulopathy. *Transfusion* 52:2475–2486.

Mitrophanov, A.Y., A.S. Wolberg, and J. Reifman. 2014. Kinetic model facilitates analysis of fibrin generation and its modulation by clotting factors: implications for hemostasis-enhancing therapies. *Molecular BioSystems* 10:2347–2357. doi:10.1039/c4mb00263f.

Moiseyev, G., and P.Z. Bar-Yoseph. 2013. Computational modeling of thrombosis as a tool in the design and optimization of vascular implants. *Journal of Biomechanics* 46:248–252. URL http://dx.doi.org/10.1016/j.jbiomech.2012.11.002.

Mounts, W.M., and M.N. Liebman. 1997. Qualitative modeling of normal blood coagulation and its pathological states using stochastic activity networks. *International Journal of Biological Macromolecules* 20:265–281.

Mueck, W., A.W.A. Lensing, G. Agnelli, H. Decousus, P. Prandoni, and F. Misselwitz. 2011. Rivaroxaban: Population pharmacokinetic analyses in patients treated for acute deep-vein thrombosis and exposure simulations in patients with atrial fibrillation treated for stroke prevention. *Clinical Pharmacokinetics* 50(10):675–686.

Muller, L.O., and E.F. Toro. 2014. A global multiscale mathematical model for the human circulation with emphasis on the venous system. *International Journal for Numerical Methods in Biomedical Engineering* 30(7):681–725. doi:10.1002/cnm.2622. URL http://dx.doi.org/10.1002/cnm.2622.

Nagashima, H. 2002. Studies on the different modes of action of the anticoagulant protease inhibitors dx-9065a and argatroban. *Journal of Biological Chemistry* 277(52):50,439–50,444. doi:10.1074/jbc.M208222200.

Nayak, S., D. Lee, S. Patel-Hett, D.D. Pittman, S.W. Martin, A.C. Heatherington, P. Vicini, and F. Hua. 2015. Using a systems pharmacology model of the blood coagulation network to predict the effects of various therapies on biomarkers. *CPT: Pharmacometrics Systems Pharmacology* 4:396–405. doi:10.1002/psp4.50.

Nielsen, V.G. 2008. Beyond cell based models of coagulation: Analyses of coagulation with clot "lifespan" resistance-time relationships. *Thrombosis Research* 122:145–152.

Nielsen, V.G., J.K. Kirklin, W.L. Holman, and B.L. Steenwyk. 2009. Clot lifespan model analysis of the effects of warfarin on thrombus growth and fibrinolysis: Role of contact protein and tissue factor initiation. *ASAIO Journal* 55(1):33–40.

Oakley, C., and H. Larjava. 2012. Hemostasis, coagulation, and complications. *Endodontic Topics* 24:4–25.

Panteleev, M.A., N.M. Ananyeva, F.I. Ataullakhanov, and E.L. Saenko. 2007. Mathematical models of blood coagulation and platelet adhesion: Clinical applications. *Current Pharmaceutical Design* 13(14):1457–1467.

Panteleev, M.A., M.V. Ovanesov, D.A. Kireev, A.M. Shibeko, E.I. Sinauridze, N.M. Ananyeva, A.A. Butylin, E.L. Saenko, , and F.I. Ataullakhanov.

2006. Spatial propagation and localization of blood coagulation are regulated by intrinsic and protein c pathways, respectively. *Biophysical Journal* 90:1489–1500. doi:10.1529/biophysj.105.069062.

Panteleev, M.A., A.N. Sveshnikova, A.V. Belyaev, D.Y. Nechipurenko, I. Gudich, S.I. Obydenny, N. Dovlatova, S.C. Fox, and E.L. Holmuhamedov. 2014. Systems biology and systems pharmacology of thrombosis. *Mathematical Modeling of Natural Phenomena* 9(6):4–16. doi:10.1051/mmnp/20149602.

Papadopoulos, K.P., M. Gavaises, and C. Atkin. 2014. A simplified mathematical model for thrombin generation. *Medical Engineering and Physics* 36:196–294. URL http://dx.doi.org/10.1016/j.medengphy.2013.10.012.

Parunov, L.A., O.A. Fadeeva, A.N. Balandina, N.P. Soshitova, K.G. Kopylov, M.A. Kumskova, J.C. Gilbert, R.G. Schaub, K.E. McGinness, F.I. Ataullakhanov, and M.A. Panteleev. 2011. Improvement of spatial fibrin formation by the anti-tfpi aptamer bax499: changing clot size by targeting extrinsic pathway initiation. *Journal of Thrombosis and Haemostasis* 9:1825–1834. doi:10.1111/j.1538-7836.2011.04412.x.

Parunov, L.A., N.P. Soshitova, O.A. Fadeeva, A.N. Balandina, K.G. Kopylov, M.A. Kumskova, J.C. Gilbert, R.G. Schaub, K.E. McGinness, F.I. Ataullakhanov, and M.A. Panteleev. 2014. Drug-drug interaction of the anti-tfpi aptamer bax499 and factor viii: Studies of spatial dynamics of fibrin clot formation in hemophilia a. *Thrombosis Research* 133:112–119. URL http://dx.doi.org/10.1016/j.thromres.2013.10.036.

Pavlova, J., A. Fasano, J. Janela, and A. Sequeira. 2015. Numerical validation of a synthetic cell-based model of blood coagulation. *Journal of Theoretical Biology* 380:367–379. URL http://dx.doi.org/10.1016/j.jtbi.2015.06.004.

Pompano, R.R., H.W. Li, and R.F. Ismagilov. 2008. Rate of mixing controls rate and outcome of autocatalytic processes: Theory and microfluidic experiments with chemical reactions and blood coagulation. *Biophysical Journal* 95:1531–1543. doi:10.1529/biophysj.108.129486.

Quarteroni, A. 2006. What mathematics can do for the simulation of blood circulation.

Riddel, J.P., B.E. Aouizerat, C. Miaskowski, and D.P. Lillicrap. 2007. Theories of blood coagulation. *Journal of Pediatric Oncology Nursing* 24(3):123–131.

Robertson, A.M., A. Sequeira, and M.V. Kameneva. 2008. *Hemodynamical Flows: Modeling, Analysis and Simulation*, *Oberwolfach Seminars*, vol. 37, chap. Hemorheology, 63–120. Verlag Basel/Switzerland: Birkhauser.

Runyon, M.K., C.J. Kastrup, B.L. Johnson-Kerner, T.G. Van Ha, and R.F. Ismagilov. 2008. Effects of shear rate on propagation of blood clotting determined using microfluidics and numerical simulations. *Journal of the American Chemical Society* 130(11):3458–3464. doi:10.1021/ja076301r.

Sagar, A., and J.D. Varner. 2015. Dynamic modeling of the human coagulation cascade using reduced order effective kinetic models. *Processes* 3:178–203. doi:10.3390/pr3010178.

Sequeira, A., and T. Bodnar. 2014. Blood coagulation simulations using a viscoelastic model. *Mathematical Modeling of Natural Phenomena* 9(6):34–45. doi:10.1051/mmnp/20149604.

Sequeira, A., and J. Janela. 2007. *A Portrait of State-of-the-Art Research at the Technical University of Lisbon*, chap. An Overview of Some Mathematical Models of Blood Rheology, 65–87. Springer.

Sequeira, A., R.F. Santos, and T. Bodnár. 2011. Blood coagulation dynamics: Mathematical modeling and stability results. *Mathematical Biosciences and Engineering* 8(2):425–443. doi:10.3934/mbe.2011.8.425.

Shahzad, K., and J.J. Loor. 2012. Application of top-down and bottom-up systems approaches in ruminant physiology and metabolism. *Current Genomics* 13(5):379–394.

Shavlyugin, E.A., L.G. Hanin, and M.A. Khanin. 2014. Dynamics of pathologic clot formation: A mathematical model. *Journal of Theoretical Biology* 340:96–104.

Shibeko, A.M., S.S. Karamzin, A.A. Butylin, M.A. Panteleev, and F.I. Ataullakhanov. 2009. The review of contemporary ideas about the influence of flow rate on blood clotting. *Biochemistry (Moscow) Supplement Series A: Membrane and Cell Biology* 3(4):388–394. doi:10.1134/S1990747809040047.

Shibeko, A.M., and M.A. Panteleev. 2015. Untangling the complexity of blood coagulation network: use of computational modelling in pharmacology and diagnostics. *Briefings in Bioinformatics* 1–11. doi:10.1093/bib/bbv040.

Singh, J.P., A. Agrawal, V. Upadhayay, and A. Kumar. 2015. Mathematical model and analysis of two phase hepatic blood flow through arterioles with the special reference of hepatitis a. *American Journal of Modeling and Optimization* 3(1):22–25. doi:10.12691/ajmo-3-1-3.

Smith, S.A. 2009. The cell-based model of coagulation. *Journal of Veterinary Emergency and Critical Care* 29(1):3–10. doi:10.1111/j.1476 - 4431.2009.00389.x.

Sorensen, E.N., G.W. Burgreen, W.R. Wagner, and J.F. Antaki. 1999. Computational simulation of platelet deposition and activation: I. model development and properties. *Annals of Biomedical Engineering* 27:436–448.

Spahn, D.R., and M. Casutt. 2000. Eliminating blood transfusions. *Anesthesiology* 93(1):242–255.

Storti, F., T.H.S. van Kempen, and F.N. van de Vosse. 2014. A continuum model for platelet plug formation and growth. *International Journal for Numerical Methods in Biomedical Engineering* 30:634–658. doi:10.1002/cnm.2623.

Tanaka, K.A., N.S. Key, and J.H. Levy. 2009. Blood coagulation: Hemostasis and thrombin regulation. *Anesthesia and Analgesia* 108(5):1433–1446.

Torres, A., T. Bentley, J. Bartels, J. Sarkar, D. Barclay, R. Namas, G. Constantine, R. Zamora, J.C. Puyana, and Y. Vodovotz. 2009. Mathematical modeling of posthemorrage inflammation in mice: Studies using a novel, computer-controlled, closed-loop hemorrhage apparatus. *Shock* 32(2):172–178. doi:10.1097/SHK.0b013e318193cc2b.

Tyurin, K.V., and M.A. Khanin. 2005. Optimality principle and determination of kinetic constants for biochemical reactions. *Mathematical Medcine and Biology* 22:1–14. doi:10.1093/imammb/dqh018.

Undas, A., M. Gissel, B. Kwasny-Krochin, P. Gluszko, K.G. Mann, , and K.E. Brummel-Ziedins. 2010. Thrombin generation in rheumatoid arthritis: dependence on plasma factor composition. *Thrombosis and Haemostasis* 104(2):224–230. doi:10.1160/TH10-02-0091.

Undas, A., M. Jankowski, P. Kaczmarek, K. Sladek, and K.E. Brummel-Ziedins. 2011. Thrombin generation in chronic obstructive pulmonary disease: dependence on plasma factor composition. *Thrombosis Research* 128(4):e24–e28. doi:10.1016/j.thromres.2011.05.004.

van de Vosse, F.N. 2003. Mathematical modelling of the cardiovascular system. *Journal of Engineering Mathematics* 47:175–183.

Vink, R., R.A. Kraaijenhagen, M. Levi, and H.R. Buller. 2003. Individualized duration of oral anticoagulant therapy for deep vein thrombosis based on a decision model. *Journal of Thrombosis and Haemostasis* 1:2523–2530.

Vogler, E.A., and C.A. Siedlecki. 2009. Contact activation of blood-plasma coagulation. *Biomaterials* 30:1857–1869. doi:10.1016/j.biomaterials.2008.12.041.

Wajima, T., G.K. Isbister, and S.B. Duffull. 2009. A comprehensive model for the humoral coagulation network in humans. *Clinical Pharmacology and Therapeutics* 86(3):290–298.

Wang, W., and M.R. King. 2012. Multiscale modeling of platelet adhesion and thrombus growth. *Annals of Biomedical Engineering* 40(11):2345–2354. doi:10.1007/s10439-012-0558-8.

Weller, F.F. 2010. A free boundary problem modeling thrombus growth: Model development and numerical simulation using the level set method. *Journal of Mathematical Biology* 61:805–818. doi:10.1007/s00285-009-0324-1.

Xu, C., X.H. Xu, Y. Zeng, and Y.W. Chen. 2005. Simulation of a mathematical model of the role of the tfpi in the extrinsic pathway of coagulation. *Computers in Biology and Medicine* 35:435–445. doi:10.1016/j.compbiomed.2004.02.007.

Xu, C., Y. Zeng, and H. Gregersen. 2002. Dynamic model and simulation of the platelets' role in blood coagulation. *Acta Mechanica Sinica* 18(4):420–428.

Xu, Z., N. Chen, M.M. Kamocka, E.D. Rosen, and M. Alber. 2008. A multiscale model of thrombus development. *Journal of the Royal Society Interface* 5:705–722. doi:10.1098/rsif.2007.1202.

Xu, Z., N. Chen, S.C. Shadden, J.E. Marsden, M.M. Kamocka, E.D. Rosend, and M. Alber. 2009. Study of blood flow impact on growth of thrombi using a multiscale model. *The Royal Society of Chemistry Soft Matter* 5:769–779. doi:10.1039/b812429a.

Xu, Z., M. Kamocka, M. Alber, and E.D. Rosen. 2011. Computational approaches to studying thrombus development. *Arteriosclerosis, Thrombosis, and Vascular Biology* 31:500–505. doi:10.1161/ATVBAHA.110.213397.

Xu, Z., O. Kim, M. Kamocka, E.D. Rosen, and M. Alber. 2012. Multiscale models of thrombogenesis. *WIREs Systems Biology and Medicine* 4:237–246. doi:10.1002/wsbm.1160.

Xu, Z., J. Lioi, J. Mu, M.M. Kamocka, X. Liu, D.Z. Chen, E.D. Rosen, and M. Alber. 2010. A multiscale model of venous thrombus formation with surface-mediated control of blood coagulation cascade. *Biophysical Journal* 98:1723–1732. doi:10.1016/j.bpj.2009.12.4331.

Zarnitsina, V.I., A.V. Pokhilko, and F.I. Ataullakhanov. 1996. A mathematical model for the spatio-temporal dynamics of intrinsic pathway of blood coagulation: I. the model description. *Thrombosis Research* 84(4):225–236.

Glossary

A

activated partial thromboplastin time test

A diagnostic test done to evaluate your blood's ability to clot. It measures the time needed for a plasma sample to clot. This test uses less TF to initiate clotting than the PT test, but still only evaluates the extrinsic pathway. 12, 49

B

binding sites

Regions on a surface (in this case, platelets), where specific proteins and clotting factors can bind to and form a chemical bond. Binding sites play a key role in coagulation because many of the reactions can only take place if the clotting factors and proteins are bound to an activated platelet. 8, 16, 20, 49

blood

Transports nutrients and oxygen throughout the body, and eliminates wastes via blood vessels. It contains plasma, red blood cells, white blood cells, platelets, and other proteins. 2

blood coagulation

A series of biochemical reactions that take place in order for a blood clot to form. This is the last step in hemostasis and is what stabilizes initial clots formed in hemostasis. 2

C

cell-centric model of hemostasis

A biological model of how blood coagulation works. This model is characterized by its treatment of the intrinsic and extrinsic pathway. It states that they work in parallel during coagulation but on different surfaces: the intrinsic pathway works on platelets and the extrinsic pathway works on TF-bearing cells. 4, 6

clotting factor

A protein in the blood that helps control blood coagulation and bleeding. 2, 4, 11, 49

coagulation cascade

A biological model of how blood coagulation works. The distinguishing feature of this model is that the intrinsic and extrinsic pathway work separately to address different steps in blood coagulation. Eventually, the two pathways meet up in a common pathway and form a stabilized clot. 4, 5, 12, 29

complex

A substance formed when one or more clotting factors or proteins are chemically bounded. 5

E

extrinsic pathway

An important pathway that forms part of blood coagulation. This pathway is faster than the intrinsic pathway and is initiated by tissue factor (TF). The extrinsic pathway generates small amounts of thrombin (fIIa) via interactions of fVII. 4, 12, 16, 29

F

fibrin

A fibrous mesh of polymer protein strands that form during coagulation. Fibrin and platelets stick and interlace to form a stabilized clot, which is the ultimate end goal of coagulation. 2, 5

H

hemophilia

A hereditary bleeding disorder that is characterized by under-clotting. There are two types of hemophilia: hemophilia A (corresponding to fVIII deficiency) and hemophilia B (corresponding to fIX deficiency). Hemophilia varies in the severity of its symptoms between individuals, but can be dangerous because of the potential for significant blood loss. 11, 12, 39, 40

hemostasis

A subsystem of the cardiovascular system whose purpose is to prevent blood loss while maintaining blood in a fluid state within the vascular system. In this process, clots are formed when blood vessels are damaged and anticoagulants, along with other processes, are used to regulate clot formation. 1, 2

I

international normalized ratio

A measurement of an individual's ability to clot. It is based on the PT and aPTT tests. When looking at international normalized ratio (INR) values, higher INR values mean it takes longer for blood clot to form. This suggests a risk of bleeding. Lower INR values indicate faster clot times, suggesting a risk of thrombosis. Note that a healthy individual with no coagulation abnormalities has an INR of approximately 1.0. INR values are usually used to measure the effectiveness of anticoagulant treatments that target vitamin-K antagonists (VKAs). 38

intrinsic pathway

An important pathway that forms part of blood coagulation. This pathway is slower than the extrinsic pathway and is initiated by internal trauma to the blood vessels. The intrinsic pathway is responsible for sustaining coagulation, produce a boost in thrombin concentration, and stabilize the soft plug formed in the early stages of hemostasis. 4, 16, 29

M

multiscale model

A sophisticated type of mathematical model that incorporates various submodels of different parts of a much larger system. By compartmentalizing different facets of a process, these models are able to

include more detail about the phenomena they seek to describe. 29, 37, 42, 43

P

plasma

The fluid part of blood. It contains all of the proteins, enzymes and clotting factors needed to form a blood clot. Note that plasma inside the body must be flowing and contain anticoagulants for it to remain a fluid. For experiments where plasma is left standing, a large concentration of anticoagulants are added to keep it from clotting completely. 2

platelet

Cell fragments that are found in blood. Platelets come in two states: activated and inactivated. When a platelet is activated, clotting factors can bind to corresponding binding sites on platelet surfaces to allow the necessary biochemical reactions to take place and form a clot. Platelets also adhere to the site of injury to form a plug. 2, 4, 8, 11, 16, 20, 49

prothrombin time test

A screening laboratory test, or diagnostic test, done to determine how long it takes for your blood to clot. It works by adding significant amounts of TF to a blood plasma sample. This particular test is only able to evaluate the extrinsic pathway, ignoring other major parts of the coagulation system. 12, 49

S

stenosis

The abnormal narrowing of a blood vessel. Note that this is different from vascoconstriction because vascoconstriction is part of hemostasis, whereas stenosis is a result of other health complications. 31

T

thrombin

Also known as factor IIa (fIIa). This is an enzyme that converts fibrinogen to fibrin. Its generation is the penultimate step before a clot can be stabilized. 6, 16

thrombosis

A bleeding disorder characterized by over-clotting. The symptoms and severity of thrombosis can vary greatly between individuals. Thrombosis poses a large risk because it can lead to strokes, cardiac arrest, damage to vital organs, or even death. 19, 31, 39

tissue factor

A protein that acts as the key initiator to blood coagulation. It is also known as thromboplastin, or factor II (fII). 4

V

vascoconstriction

The narrowing of blood vessels from the contraction of blood vessel tissues. This is the first, immediate step in hemostasis. It helps reduce blood loss when there is damage to the blood vessel. 2