

Blood Coagulation Regulation Via Intravenously-Administered Anticoagulants

Vanessa Cini¹, Taryn Geivet², Anton Gerasimov³, Theresa Slaiwa⁴, Andrew Steward⁵

¹²³⁴⁵ *Department of Bioengineering, University of California San Diego*
(all authors contributed equally)

¹vcini@ucsd.edu

²tgeivet@ucsd.edu

³agerasimov@ucsd.edu

⁴tslaiwa@ucsd.edu

⁵asteward@ucsd.edu

Abstract - Blood coagulation can be regulated by intravenously administered anticoagulants such as heparin. A simplified model of the coagulation cascade biosystem is used to allow for correlations to be made such as changes in prothrombin and thrombin concentrations with respect to time and the rate of thrombin production to the rate of prothrombin consumption. These correlations are then used to solve and describe other relevant relationships between anticoagulants heparin and antithrombin. The equations are then used to model the dynamics of thrombin concentration under steady state doses of an anticoagulant such as heparin. The Laplace transform of these equations are used to form a transfer function that allows for the identification of values for a proportional-derivative (PD) controller that serves to relay the appropriate heparin dosage, keeping the system stable. A measurement delay is accounted for between the input, the blood sample, and the output, thrombin concentration.

Keywords - Blood coagulation, Thrombin, Heparin, PID Control.

I. INTRODUCTION

An important property of blood is its ability to coagulate in response to inflammatory stimuli. While this is a vital function in the case of wounding or soft tissue injuries, it is a response that must be dampened when undergoing invasive procedures such as heart bypass surgery, cardiac catheterization, or kidney dialysis.^{1,2} To prevent fatal blood clotting for such procedures, anticoagulant drugs such as heparin are administered intravenously. However, heparin dosage must be tightly controlled, as high concentrations of the drug can lead to excessive and fatal bleeding.¹ Thus, it is critical to develop a model of blood coagulation control that can be used alongside

point-of-care (POC) coagulation measurement devices to guide clinicians in administering proper doses of heparin. Our approach in this project is to formulate a transfer function describing ordinary blood coagulation in the human body. With this, we will be able to map out a control diagram of this system and define a controller that can keep blood coagulation at a desired level.

II. BACKGROUND

Although the blood coagulation cascade involves over 76 factors, it can be simplified into two pathways: the intrinsic and extrinsic pathways, which both work to activate the clotting factor Xa.¹ Essentially, Factor Xa aids in the conversion of prothrombin into thrombin which in-turn allows fibrinogen to be turned into fibrin, formalizing a clot. Unfractionated heparin, or heparin in its natural form, is an anticoagulant which already exists in our bodies but can also be injected intravenously. Unfractionated heparin advances antithrombin's effect on various clotting factors specifically factor Xa and prothrombin, inhibiting them from activating and therefore halting the cascade.¹

III. SPECIFIC AIMS

One of the aims of this study is to create a simplified model of the coagulation cascade biosystem by relying on assumptions made in other literature and within this paper. In doing so the dynamics of thrombin concentration can be observed under steady state doses of the anticoagulant heparin. When heparin is administered it is crucial to ensure proper dosage is given to the patient so the dosage will be regulated with the use of a PID controller. Using the transfer function derived from the simplified model we aim to find the values of

the PID controller that keeps the system stable when administering heparin to the blood. The last aim is to account for the measurement delay between the input and output of the system. In this model the input is the blood sample from the patient that is inserted into the device and the output is the thrombin concentration. The device used to analyze the blood takes time and cannot be assumed to be an instantaneous measurement so a time delay must be accounted for.

IV. ASSUMPTIONS & LIMITATIONS

The cascade being analyzed, while it can be simplified into two main pathways as seen in **Figure 1**, involves a larger network of pathways and to model it entirely will require the use of higher order systems. While it may be possible to model the entire system, there are simplifications that can be made based on some assumptions made from relevant literature in order to make this project possible given the amount of time allocated to it.

To take on this task, the first step was to choose a segment of this biosystem to focus on, and in this case it is limited to the actions of heparin and antithrombin on thrombin. Making this our focus assumes that the blood coagulation factors upstream of thrombin do not have a significant effect on thrombin concentration. We also assume when heparin is administered into the bloodstream the concentrations of heparin are much smaller than the concentrations of antithrombin and thrombin. Next, the dosing of heparin is done so at a steady rate after time equals zero. In clinical practice this steady rate dosage is important as the drug concentrations will consistently stay within the therapeutic limits for long periods of time determining the way the body absorbs, distributes, metabolises and eliminates the substance.³ The next three assumptions are made within this paper to further simplify the blood coagulation model. One assumption is that the conversion of prothrombin to thrombin is negligible to focus on the effects of just antithrombin and thrombin from heparin. The other assumption is the initial concentrations of prothrombin and thrombin are the same to establish a first order system. Lastly, we assume there is a 5 minute time delay in the measurement system from the time the system receives the blood sample to when it outputs the thrombin concentration.

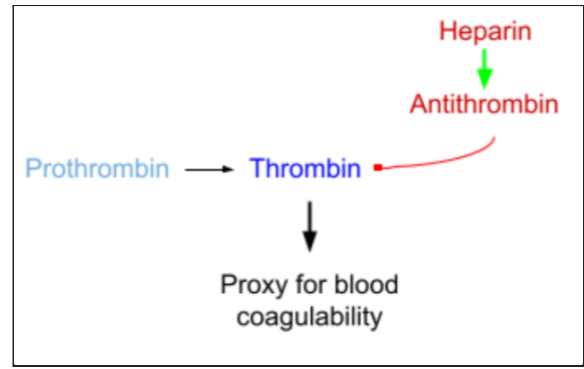


Figure 1: A simplified model of the final interactions in the blood coagulation cascade. This model defines the scope of the biosystem analyzed in this project.

V. METHODS & EQUATIONS

In order to mathematically describe our simplified model, we start with the equations describing the change in prothrombin concentration with time, and the change in thrombin concentration with time, which correspond to equations (1) and (2), respectively:

$$\frac{d[Prothrombin]}{dt} = \frac{d[II]}{dt} = - (b_1[Xa] + k_3[IIa] + k_4[IIa]^2 + k_5[IIa]^3)[II] \quad (1)$$

$$\frac{d[Thrombin]}{dt} = \frac{d[IIa]}{dt} = (b_1[Xa] + k_3[IIa] + k_4[IIa]^2 + k_5[IIa]^3)[II] - b_2[ATIII][IIa] \quad (2)$$

The right-hand side of (1) describes the consumption of prothrombin as it is converted to thrombin, which is why the entire equation tends to a negative value. Each individual term in (1) accounts for the activation of prothrombin by blood factors in the initiation and propagation phases of coagulation, namely factors FXa, FV, FVIII, and FXI. These factors are activated by thrombin [II]. Thus, their concentration values are mediated by thrombin concentration. Equation (2) consists of two terms on the right-hand side, the first describing the production of prothrombin as thrombin is consumed, and the other the direct downregulation of thrombin by antithrombin.⁴ Because the first term in (1) is equal to the rate of prothrombin consumption, we can substitute (1) into (2) to yield (3):

$$\frac{d[IIa]}{dt} = -\frac{d[II]}{dt} - b_2[ATIII][IIa] \quad (3)$$

Next, we can describe the concentration of the endogenous anticoagulant antithrombin as time varies with (4). The equation was empirically derived by observing the reaction kinetics of the heparin-enhanced inhibitory action of antithrombin on thrombin.⁵ Thus, (4) yields a relationship between the anticoagulants heparin and antithrombin, meaning we can substitute (4) into the last term of (3). Finally, using the assumption that the conversion of prothrombin to thrombin is negligible, we can simply substitute the change in prothrombin term in (3) for thrombin concentration over time. These assumptions and substitutions allow us to come to (5), which describes all interactions of the biosystem within the scope of this project.

$$[Anti-Thrombin] = [ATIII] = \frac{v}{k} \frac{[H]}{[IIa]} \quad (4)$$

$$\frac{d[IIa]}{dt} = k_3[IIa] - b_2 \frac{v}{k} [H] \quad (5)$$

With the self-contained equation for our biosystem, we can then take its Laplace transform to yield:

$$s \cdot IIa(s) + IIa(0) = k_3 IIa(s) - b_2 \frac{v}{k} H(s) \quad (6)$$

From (6), we can reorder the terms to find the transfer function of our biosystem, as described in (7) with the Laplace transform of the output thrombin over the input heparin. Finally, we can use the biosystem transfer function to formulate the closed-loop transfer function of our system in (8). All the simulation variables involved in the aforementioned equations are listed in **Table 1**.

$$U(s) = \frac{IIa(s)}{H(s)} = \frac{b_2 v}{k(s-k_3)} \quad (7)$$

$$CL(s) = \frac{-bv(k_p + k_d s)(s+1/5)}{ks^2 - (k\frac{4}{5} + \frac{1}{5}bv k_d)s - (\frac{k}{5} + \frac{bv k_p}{5})} \quad (8)$$

A block model was then generated using Simulink, shown in **Figure 2**. A steady dose of heparin is injected into the system, which then gets the concentration of heparin multiplied by constants v , k , and b_2 (Found in **Table 1**). To get the concentration of thrombin, an integral block is added. Based off equation (5) the amount of heparin down regulates the generation of thrombin. The concentration of thrombin then has a positive feedback loop on itself when it is multiplied by a constant k_3 (Found in **Table 1**). At the bottom of the simulink model there is a measurement system that measures the concentration of thrombin. This is meant to simulate the amount of time it takes to draw blood from a patient, place into a machine, and the time it takes the blood to coagulate. The estimated time delay was 5 minutes. The measured concentration then is compared to the target concentration of 1 nM, which is fed into the PD controller. Constants k_p and k_d are determined from equation (8) and are imputed into the simulink model (k_p and k_d can be found in **Table 1**). Finally, the PD controller inputs the necessary heparin dosage to reach the desired concentration, which closes the loop.

Lastly, our open-loop system can be described by (9)-(11) in order to generate an open-loop bode diagram.

$$OL(s) = F(s) \times U(s) \quad (9)$$

$$OL(s) = (K_d s + K_p) \times \frac{-bV}{k(s-k_3)} \quad (10)$$

$$OL(s) = \frac{39,837.07 + 18,731.83}{813s - 0.0122} \quad (11)$$

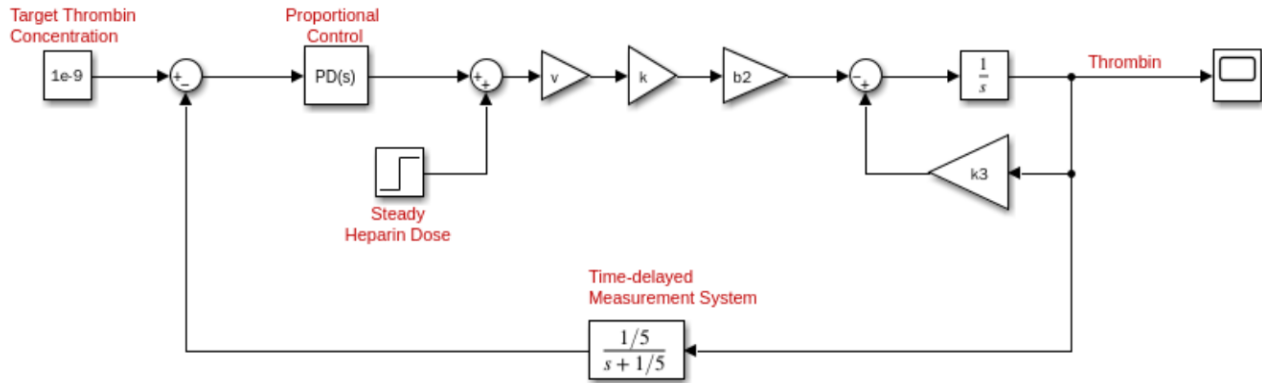


Figure 2: Simulink block model of the simplified blood coagulation cascade with closed loop feedback and PD controller

VI. RESULTS

To study the stability of the system a bode plot was generated from (11), which used the same k_p and k_d constants derived for the PD controller. Looking at **Figure 3** there are two plots generated: Magnitude Vs. Frequency and Phase Vs. Frequency.

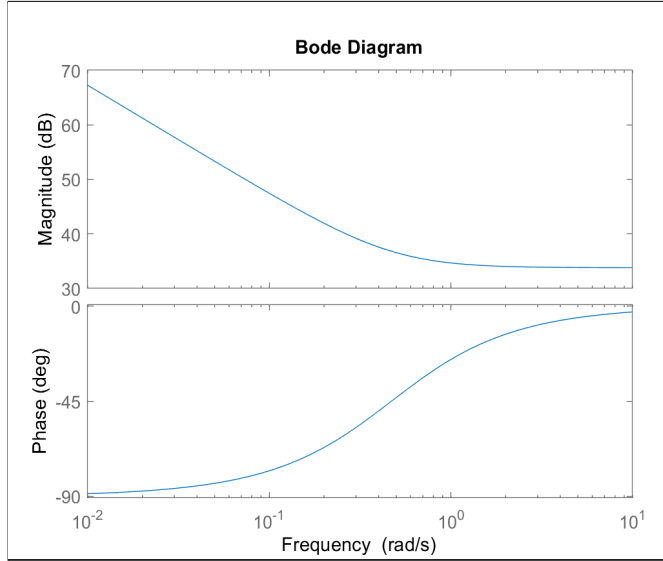


Figure 3: Bode plot response of the system with PD control

A block diagram was created in simulink without a PD controller and measurement delay to represent the natural response of the system. A graph of the Concentration of thrombin Vs. Time was plotted using that model and is shown in **Figure 4**. Using the block diagram from **Figure 2** another graph was generated of the Concentration of thrombin Vs. Time, shown in **Figure 5**.

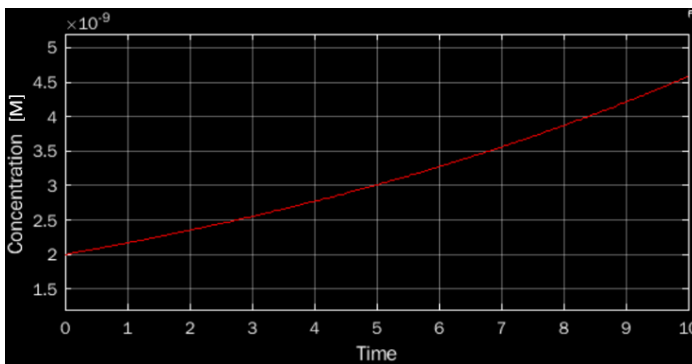


Figure 4: System response without PD control and measurement delay where time is represented in minutes

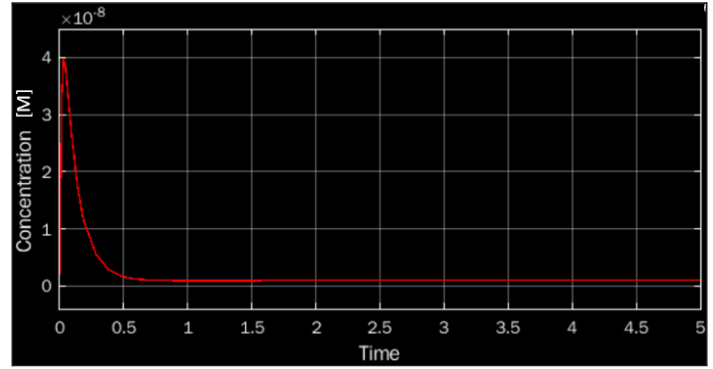


Figure 5: System response with PD control and 5 minute measurement delay.

VII. INTERPRETATIONS & CONCLUSIONS

Studying how the open loop system will respond gives insight into how the closed loop will behave. So a bode plot was created in **Figure 3**. A phase margin and gain margin can not be determined, because the phase never reaches -180 or 180 and the gain never reaches 0dB. Though phase margin and gain margin can not be determined, it still says a lot about the system. Systems go unstable when both values approach 0, the larger the margins the more room for error there is. In the case in **Figure 3**, the system will be stable no matter what, because neither gain goes to zero and the phase to -180. Looking at the magnitude plot it can be seen at low frequencies the magnitude goes to infinity, resulting in a DC error of 0.

From the graphs in **Figure 4** and **Figure 5**, we can see how the PD controller stabilizes our system's response. **Figure 4** illustrates how thrombin concentration varies throughout time without any modifications to our system (no PD control and no measurement delay). Because thrombin concentration continues to increase throughout the observation period, it does not reach a steady state value and thus, the system can be classified as unstable. In **Figure 5**, we can see the effect that a PD controller and 5 second measurement delay have on the system's stability. In the presence of PD control and a measurement delay, thrombin concentration reaches a steady state value of approximately 1 nM. Since thrombin concentration reaches a steady state value, the system can be classified as stable.

One complication of this system is that the concentration of thrombin with PD control moves far further past the set point of 10uM than desired. In other words, our PD controller was not able to minimize the overshoot of the system. This is an understandable outcome, as our system did not include an integral controller. Generally speaking, when the

measured value of the target variable in a system is approaching the set point as described in a feedback loop, proportional and integral controllers work in opposition to force the measured value to reach the set point quickly without extreme overshooting. As the measured value approaches the set point, the actions of the integral controller decreases, which allows the measured value to smoothly settle to the set point.⁶ Thus, it is expected that we have such a large overshoot directly after $t=0$. Nonetheless, it should be noted that this is not a physiologically accurate representation of the magnitude of thrombin overshoot possible in a human body. The production of thrombin would be mediated by the consumption of prothrombin, which we were unable to represent due to the complexity of the system, and the lack of literature prescribing mathematical models and values for the coagulation cascade. Thus, the initial overshoot of thrombin is likely not to be a substantial issue in clinical practice, although it does point out a substantial limitation of this project, given its scope and the amount of time given to create it.

VIII. CLINICAL APPLICATIONS

Our model for blood coagulation regulation has wide clinical applications. For example, clinicians can use our model to diagnose patients with clotting disorders. Since the output of our model is thrombin concentration, we can use this to find thrombin time, which is a measure of how long it takes for a blood clot to form in the presence of excess thrombin. A standard thrombin time will be between 15-19 seconds, and if one's thrombin time falls outside this range, it is often indicative of a clotting disorder.^{1,2} In addition to aiding in diagnostic processes, our model can also be used during surgery. This is because when patients are under operation, they are at risk of excess bleeding from low thrombin concentration. Thus, our system can be integrated into a device to be used during surgery to determine when thrombin concentration is too low, and remedy this by intravenously injecting more thrombin or lowering heparin dosages. In a similar vein, our system can be used for preventative care when a patient's thrombin concentration is too high. When there is too much thrombin in the body, a patient is at risk of excess clotting which can result

in venous or arterial thrombosis. Therefore, our system will be able to sense when a patient's thrombin concentration is abnormally high and correct this through the intravenous injection of an anticoagulant, such as heparin. Lastly, our blood coagulation regulation system can be used as a point of care device for patients with bleeding disorders. For example, patients with hemophilia are often at risk of excess bleeding from nose bleeds and minor injuries. Therefore, it is important that these patients can obtain medical assistance outside of the clinic when non-predictable instances of severe bleeding occur. Our blood coagulation regulation system will be able to sense when hemophilia patients are experiencing heavy bleeding and provide clinical care through the intravenous injection of a coagulant, such as thrombin.

IX. ACKNOWLEDGEMENTS

We thank Professor Gert Cauwenberghs and teaching assistants Siwen Wang and Ishan Gupta for their instruction and support throughout the quarter.

IX. REFERENCES

- [1] "Activated Coagulation Time." *Activated Coagulation Time - Health Encyclopedia - University of Rochester Medical Center*, <https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=act>.
- [2] "Activated Clotting Time (ACT)." *Testing.com*, 3 Sept. 2020, <https://labtestsonline.org/tests/activated-clotting-time-act>.
- [3] Wadhwa RR, Cascella M. "Steady State Concentration". Updated 2021 Mar 2. Treasure Island, FL: StatPearls Publishing; 2021 <https://www.ncbi.nlm.nih.gov/books/NBK553132/>
- [4] Xu, Xiangqun, et al. "Dynamic and Quantitative Assessment of Blood Coagulation Using Optical Coherence Elastography." *Nature News*, Nature Publishing Group, 19 Apr. 2016, <https://www.nature.com/articles/srep24294>.
- [5] Bouchnita, Anass et al. "A mathematical model to quantify the effects of platelet count, shear rate, and injury size on the initiation of blood coagulation under venous flow conditions." *PloS one* vol. 15,7 e0235392. 29 Jul. 2020, doi:10.1371/journal.pone.0235392
- [6] Griffith, M J. "The heparin-enhanced antithrombin III/thrombin reaction is saturable with respect to both thrombin and antithrombin III." *The Journal of biological chemistry* vol. 257,23 (1982): 13899-302.
- [7] "How to Tune a PID Loop." *CrossCo.com*, <https://www.crossco.com/resources/technical/how-to-tune-pid-loops/>

APPENDIX

TABLE 1: Simulation Variables and Values

Simulation Variable	Value	Unit	Description
k_3	1.5×10^{-5}	$1/nM \cdot s$	Rate of prothrombin production by thrombin consumption
b_2	10.05	$1/nM \cdot s$	Rate of thrombin inactivation by antithrombin
k	7.2	M/min	Rate of antithrombin activation by heparin
v	813	1/min	Reaction velocity constant of heparin-enhanced antithrombin
k_p	-258.87	n/a	Proportional control value
k_d	-550.54	n/a	Derivative control value