Simplified Model of the Blood Coagulation Cascade

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***Abstract* — Blood coagulation is an essential body process that is used to combat inflammatory stimuli. It is a complex process that involves platelets, red blood cells, and dozens of coagulation factors. When a tissue injury is detected, platelets aggregate and release blood clotting agents. However, thrombosis is a serious condition where blood flow is impeded in a normal healthy vessel. This paper focuses on modeling a healthy blood clotting cascade, and comparing it to other scenarios that cause thrombosis. A mathematical model to describe the dynamics of blood clotting was created in Simulink, and further characterization was performed using the Laplace Transform.**

Keywords— Blood Coagulation, Blood clotting cascade, thrombosis, platelets

I. Introduction

Blood coagulation is a term that describes the ability for blood to form clots, responding to inflammatory stimuli and preventing excessive bleeding from an open wound [1]. While this process is an extremely important biological response, it can cause immense medical complications when blood coagulates in a vessel that does not have injuries, as they do not dissolve naturally [2]. Acute arterial thrombosis is the leading cause of myocardial infarctions, and a majority of strokes, making it the most common cause of death in the developed world.

The blood clotting cascade is a complicated process that involves platelets, red blood cells, along with dozens of blood clotting factors [3]. The cascade has two separate pathways that activate the clotting factors, the intrinsic and extrinsic pathways. In the intrinsic pathway, plasma comes into contact with certain artificial surfaces such as glass. In the extrinsic pathway, plasma comes into contact with a membrane protein called tissue factor (TF) that initiates the cascade. Regardless of the pathway, however, the end result is that an enzyme called fibrin is polymerized, and platelets are activated, which leads to a blood clot [4]. In this project, we attempt to create a basic mathematical model of the blood clotting cascade in Simulink.

II. Methods

In order to model this complex system, we needed to simplify and make assumptions when making the Simulink model. In particular, we used the ordinary differential equations (ODEs) [4]:

$$\frac{dP}{dt} = -(k_5 u + k_6 T + k_7 T^2 + k_8 T^3)P \quad (1)$$

$$\frac{dT}{dt} = (k_5 u + k_6 T + k_7 T^2 + k_8 T^3)P - k_9 T \quad (2)$$

$$\frac{du}{dt} = (k_1 + k_2 T + k_3 T^2)(u^0 - u) - k_4 u \quad (3)$$

in order to represent the concentration of prothrombin, thrombin and an activated tissue factor X that helps catalyze the blood coagulation reaction. These were made with the assumptions that the initial concentrations of prothrombin and thrombin are equal, the effect of spatial variation and diffusion were negligible, and that the blood clotting cascade upstream of activated tissue factor X were not as significant on thrombin concentrations, allowing us to simplify to nine kinetic constants (**Figure A**).

k_1	k_2	k_3	k_4	k_5	k_6	k_7	k_8	k_9	D
4.8e-5	1.1e-5	2.4e-7	4.8e–4	1.9e-5	3.8e-6	1.3e-10	4.1e-10	0.02	5e-5

Figure A: List of constants used for the Simulink gains [4].

The following equations are partial differential equations (PDEs) that can also be used to model the system [4]. This system of equations is more complex than the first, as it extends the framework to consider spatial variations in addition to temporal dynamics. In an effort to simplify our model, we choose to only model equations 1-3, but equations 4-6 are available for reference here:

$$\frac{\partial P}{\partial t} = D\frac{\partial^2 P}{\partial x^2} - (k_5 u + k_6 T + k_7 T^2 + k_8 T^3)P \quad (4)$$

$$\frac{\partial T}{\partial t} = D\frac{\partial^2 T}{\partial x^2} - (k_5 u + k_6 T + k_7 T^2 + k_8 T^3)P - k_9 T \quad (5)$$

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} - (k_2 T + k_3 T^2)(u^0 - u) - k_4 u \quad (6)$$

Normally, the blood clotting process is too complex to model simply due to the many variables present in the human

body. However, we can make reasonable assumptions to minimize the amount of things that need to be considered in our system. For example, we will be neglecting the spatial variation and diffusion processes which normally would take place to balance out the blood concentration spread throughout the body. We also will be considering the initial concentrations of prothrombin and thrombin are equivalent. This results in a block diagram outlined in **Figure B**.

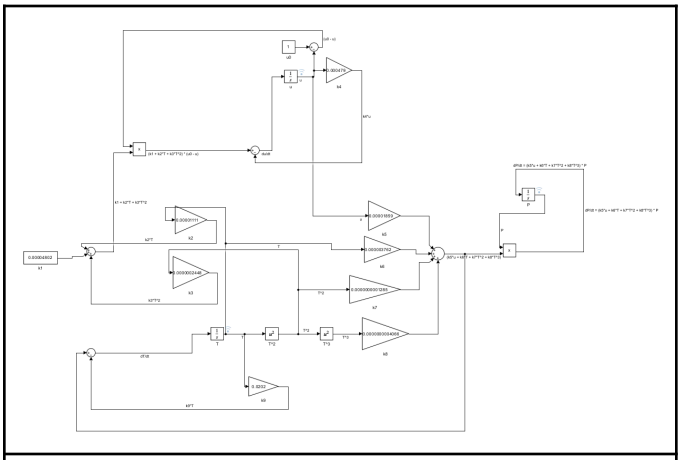

Figure B: Block Diagram of the blood clotting system.

III. Results

Using Simulink we modeled the blood clotting cascade to demonstrate the initial conditions that occur in the body. This gives us **Figure C** which displays the concentration of Thrombin vs Time at the site of the injury. It is clear that Figure C does not display the full behavior of the thrombin curve, so we decided to expand our model by recording the output over a longer time period.

We then set the initial conditions of T, u, and P to zero and produced **Figure D**. In **Figure D**, the concentration of Thrombin (T) at the site of injury rapidly increases from zero and then plateaus after approximately 900 seconds (15 minutes) with small oscillations between relative concentrations of 8.36e-5 to 8.50e-5. These oscillations signify an equilibrium achieved after the rapid surge, shedding light on the intricate balance achieved within this biochemical cascade.

Thrombin concentrations at the site of injury can plateau at approximately 20 minutes after the initial injury, which is reasonably close to our model, which plateau after approximately 15 minutes [5].

Unfortunately, our model's scope cannot currently encapsulate the behavior of T, u, and P beyond this initial plateau. However, within a more comprehensive system governed by a set of differential equations that account for the return to baseline levels of T, u, and P, we anticipate observing the trajectory of Thrombin levels as they gradually regress towards normalcy. This regression might unveil a gradual decline, possibly oscillating around a baseline concentration.

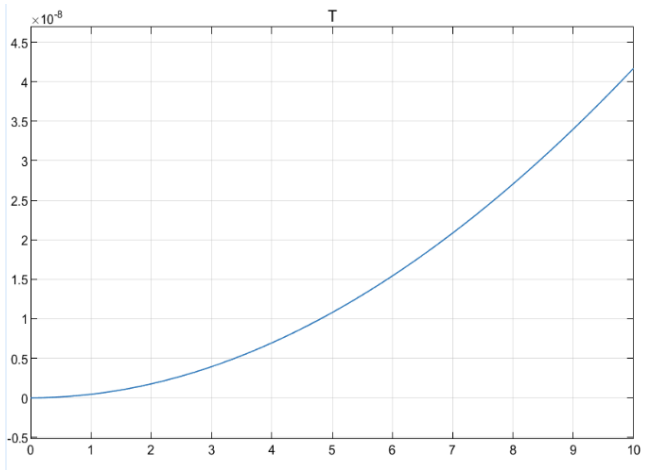

Figure C. Thrombin Concentration when initial conditions are applied.

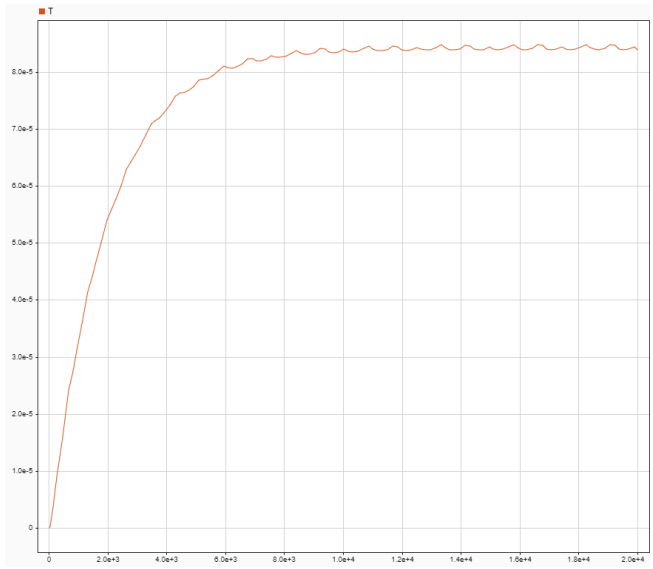

Figure D. Thrombin Concentration when initial conditions are set to zero.

IV. Interpretations & Conclusion

Based on the frequency response in **Figure C**, thrombin concentration rapidly increases before plateauing at a value of 5.00e-5. The initial exponential growth observed for the thrombin concentration corresponds to the opening of wounds where such an increase in the concentration for this clotting factor is essential to expedite the clotting process to heal the wound. The exponential growth that thrombin experiences is also characteristic of biosystems in general. The plateau behavior exhibited by the frequency response of thrombin is reasonable given the set target value for thrombin values in the proposed block model for the blood coagulation cascade. In a physiological context, the thrombin concentration plateau makes sense for superficial tissue wounds. Blood clotting is a positive feedback process where the closing and healing of

wounds as a result of an increased amount of clots results in a decreased need and rate of coagulation. Furthermore, there is dilution as blood continues to flow throughout the body.

It should be noted that on the thrombin concentration frequency response, the values plateau but do not in fact reach a steady state value. The waveforms representative of thrombin concentration over time oscillate slightly and indicate that the blood coagulation biosystem model is unstable. However, this result is expected and is one potential limitation of our simplified model of the blood clotting cascade. The clotting factor is activated through two pathways, the extrinsic and intrinsic pathway. Regardless of the coagulation activation the thrombin concentration level increases very rapidly which leads to conversion of fibrinogen to fibrin as seen in **Figure B**. The proposed, simplified block diagram to view thrombin concentrations and gain a better understanding of the blood coagulation does not account for the output of prothrombin which directly corresponds to the initial amount of thrombin already present in the system. Although the objective of this project was to simplify blood clotting mechanisms to be more intuitive, adding complexity to the block diagram in the sense of more interactions between biosignals could produce more accurate results for clotting factors in coagulation.

V. Future Directions

As mentioned prior blood coagulation is an essential physiological process meant to prevent excessive blood loss in the case of superficial wounds on the body. In a healthy individual, the blood coagulation cascade is key in responding to inflammatory stimuli and mitigating any potential health complications [6]. With this in mind, there are numerous disorders relating to missteps in the blood clotting process that can be accounted for and treated with help from the generated, simplified model. As with most physiological processes, there are individual instances where the biosystem does not proceed as it is expected to, leading to blood clotting disorders. Furthermore, it is subject to extrinsic factors within and external from the body that has the potential to complicate the overall process and its applicable differential equations [1]. Regardless, the overall purpose of this simplified model is to provide an intuitive and accessible means to regulate clotting mechanisms as an indicator method for the overall health of an individual in regards to monitoring the proteins of interest in the blood clotting process.

In this project, we attempt to create a basic mathematical model of the blood clotting cascade in Simulink. The scope of this model will be focused on the role that platelets play in the blood clotting cascade.

In terms of future directions, as referenced prior, more clotting factors that contribute to the blood coagulation cascade could be added to provide a more accurate response of the biosystem. Regarding clinical applications, the proposed simplified model is more accessible and can be utilized by healthcare professionals to diagnose individuals who have clotting disorders. The primary scope and regulatory response for this biosystem is thrombin concentration, and generated values can be used to find thrombin time. Specifically, thrombin time is a point of reference for the duration of a blood clot formation in the presence of excess thrombin. Typically, thrombin time falls within a range of 12-19 seconds [7]. In addition to potentially being an accessible and intuitive diagnostic tool, the simplified model can have surgical applications. In medical devices, specifically in bioinstrumentation, the model can be used to help alert a surgeon when thrombin concentrations are too low during a procedure. This can help prevent excess bleeding and the negative repercussions associated with a high volume of blood loss [8]. Similarly, such a function in a surgical device can help alert a surgeon if a patient has a thrombin concentration that is unnaturally high. This would be associated with excess clotting that leads to complications such as venous or arterial thrombosis [8]. With this information, the surgeon could administer an anticoagulant such as heparin to mitigate the health complications associated with excess clotting.

Using a more complex version of this model can assist physicians and surgeons in incorporating patient-specific parameters. However, the utilization of more complex equations introduces the challenge of dealing with numerous unknown constants and equations, which is a limitation. Therefore, simplifying the ordinary differential equations becomes a manageable approach for analysis. Factors to be considered may include underlying medical conditions and inflammation. Enhancing this model to account for patient-specific parameters would support surgeons in comprehending thrombin concentration levels across diverse patients. This improvement could contribute to ensuring that patients are appropriately treated during surgery. To conclude, while our simplified model offers valuable insight into thrombin concentration dynamics and has practical applications in diagnosing clotting disorders and aiding surgical procedures, the consideration of patient-specific parameters remains crucial for a more comprehensive understanding. By introducing complexity and simplicity in modeling the blood cascade, future research can aim to refine our approach and enhance clinical relevance.

VI. Acknowledgement

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VII. References

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