## Objective

In this project, **you will reproduce the six figures *of “A Model for the Tissue Factor Pathway to Thrombin II.: A mathematical simulation,”*** using MATLAB.

## Contents

Please see the following project files:

|  |  |
| --- | --- |
| **File** | **Description** |
| Jones1994.pdf | Paper describing mathematical model of the clotting cascade. **You will reproduce all six of the figures.** |
| Lawson1994.pdf | Paper describing experimental determination of key model parameters. You will obtain starting concentrations here. |
| tutorialfunction.m | A MATLAB function demonstrating how to encode a system of equations for numerical integration. |
| tutorialscript.m | A MATLAB script that uses example.m in simulations and plots figures of the output. |
| **coagulation.m** | **A template for your coagulation function, with the first equation encoded.** |
| **figure2.m** | **A starting point for running the simulation and generating figures. Once coagulation.m is completed, this script will generate figures 2** |
| figure2a-correct.png | Output of Figure2.m. This is what a correct coagulation.m produces. |
| figure2b-correct.png | Output of Figure2.m. This is what a correct coagulation.m produces. |
| figure2c-correct.png | Output of Figure2.m. This is what a correct coagulation.m produces. |
| figure3-correct.png | What your figure 3 should look like. |
| **template.docx** | **Writing prompt** |

## Instructions

Read the introduction to Lawson1994.pdf (the text up until the section entitled “Experimental Procedures”).This section introduces the coagulation cascade which you will model in the project. Then read Jones1994.pdf.

Two MATLAB files, tutorialfunction.m and tutorialscript.m, are provided to demonstrate how to encode systems of ordinary differential equations, how to solve them, and how to create several types of plots. **Read through these files and make sure you understand how they work.**

Two other MATLAB files, coagulation.m and figure2.m, are provided as starting points.

1. Fill in the missing governing equations in coagulation.m
2. Fill in the rate constants and initial values in figure2.m
3. When you run figure2.m, you should get three figures that match figure2a\_correct.png, figure2b\_correct.png, figure2c\_correct.png.
4. At this point, you are on your own. Expand figure2.m so that it generates all of the other figures in Jones1994.pdf

Submit the following components to iLEARN (**100 pts** possible):

1. **One matlab script** (.m file) that:
   1. Calls the differential equation script to reproduce each figure, complete with axes labels, titles, and legends **(6 × 10pts)**
   2. Contains a function encoding the differential equations that describe the coagulation cascade **(10 pts).** This must be at the end of the script.
2. **A 1 page write up (see template) that:**
   1. Summarizes the main goal and results of the paper **(20 pts)**
   2. Discusses the implications of the model/results (i.e. “So what?”) **(10 pts)**

**VERY IMPORTANT NOTES:**

* While Jones1994 is a fantastic paper, the published version has many typos. The PDF distributed here has been corrected. Review the Additions and Corrections (last page of PDF) for more details.
* You do not have to plot the squares in Figure 1A.
* Prothrombin is Factor II; Thrombin is IIa; meizothrombin is mIIa
* In the model, d[VIIIa•IXa]/dt (Eq. 8) has a final component based on I: “ – (fabs(I-[VIIIa•IXa])) + (I – [VIIIa•IXa])” where I is the maximal concentration of enzyme. This component describes the decay of [VIIIa•IXa].
  + **This component is replaced with “ –k20 [VIIIa•IXa]” and has been provided for you in coagulation.m**
  + **Do NOT use Eq. 20 in your simulation.**
  + **Your results will appear a little different from the paper. The most significant changes are in Figure 2 & 3 (hence I am providing Fig. 2 as the example). Figure 3 also changes, and so we include a picture of what Figure 3 should look like.**
* Initial conditions are provided in Table I of Lawson et al., unless altered as described in figure legends. Not everything listed in Table I will be used in the simulations, and **factors not explicitly listed have initial values of 0.**
* **Make sure your units are appropriately matched. MATLAB will not know the difference between mM and μM, so convert everything to M. See Lecture 2 Slide 17 for help.**
* Note that to remove an enzyme’s contribution to the cascade, we don’t just set the enzyme concentration to zero, **we set its rate constant equal to zero.**
* Most figures plot Thrombin Formation as the dependent variable (y-axis), however, if you read the figure captions and the methods section closely, you’ll see this is a combination of Thrombin and Meizothrombin where the relative contributions of each enzyme is given by its specific activity and normalized **by the expected concentration of “complete” formation as expected from starting concentrations.**

Figure 1A, for example, the y-axis can be calculated as:

% Thrombin Formation = (1.2 \* [mIIa] + 1.0 \* [IIa]) / (1.4 × 10-6 M) \* 100