



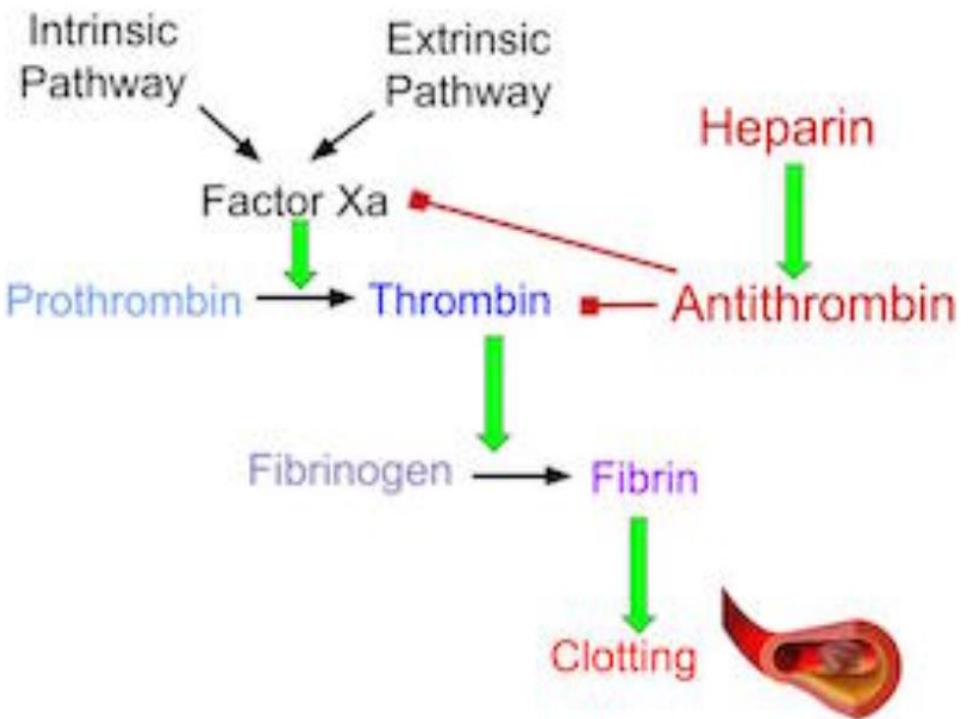
BLOOD COAGULATION REGULATION VIA INTRAVENOUSLY-ADMINISTERED ANTICOAGULANTS

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OVERVIEW

1. Basic background on the blood coagulation cascade
2. Aim of our model
3. Assumptions of our model
4. Defining relevant equations in the coagulation cascade
5. Building a transfer function
6. Building a block diagram
7. Assessing our open-loop bode diagram
8. Results: System response
9. Applications

BACKGROUND: BLOOD COAGULATION CASCADE

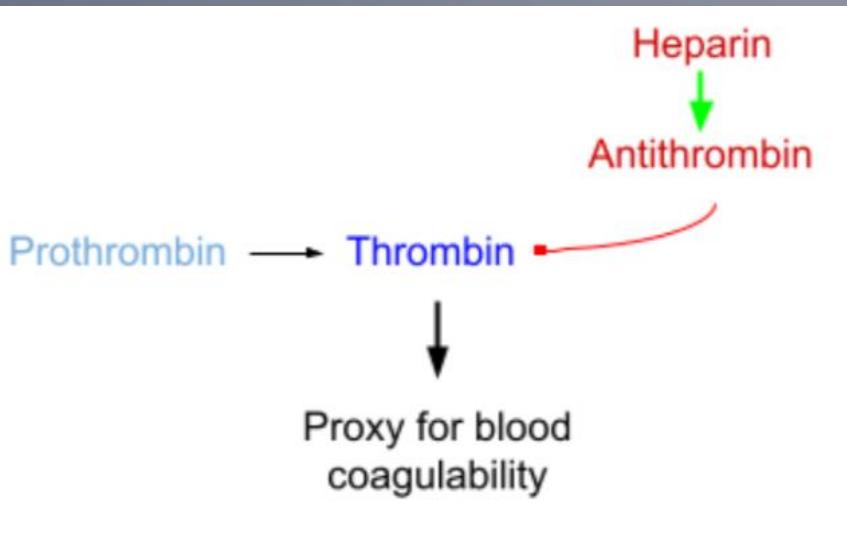


- The cascade can be simplified as two separate pathways, intrinsic and extrinsic, that work to activate clotting factor Xa.
- Factor Xa transforms prothrombin into thrombin and thrombin then turns fibrinogen into fibrin, formalizing a clot. This is the body's way of preventing excessive bleeding.
- Unfractionated Heparin is an anticoagulant (input) which already exists in our bodies but can also be injected intravenously.
- Heparin advances antithrombin's effect on various clotting factors specifically factor Xa and Thrombin (output) by inhibiting them from activating and therefore inhibiting the blood coagulation cascade.

AIM OF OUR STUDY: MODELING THROMBIN REGULATION

1. Create a simplified model of the coagulation cascade biosystem
2. Model the dynamics of thrombin concentration under steady doses of the anticoagulant heparin
3. Identify values of the PID controller that keep the system stable
4. Account for the measurement delay between input (insertion of blood sample into the device) and output (thrombin concentration)

ASSUMPTIONS



1. The scope of our biosystem is limited to the actions of Heparin and Antithrombin on Thrombin
2. The concentrations of Antithrombin and Thrombin are much greater than of Heparin
3. Heparin is dosed at a steady rate after $t=0$
4. The conversion of Prothrombin to Thrombin is negligible
5. The initial concentrations of Prothrombin and Thrombin are the same
6. There is a 5 min time delay in the measurement system

RELEVANT EQUATIONS IN COAGULATION CASCADE

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

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

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

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

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

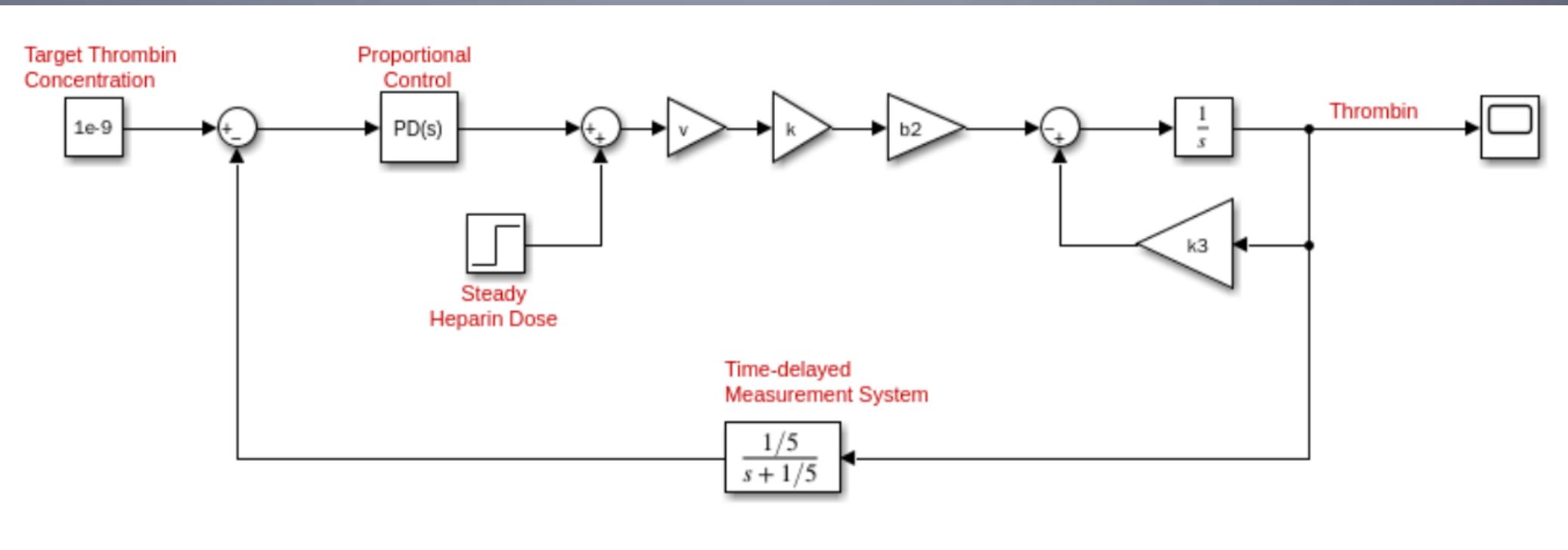
BIOSYSTEM TRANSFER FUNCTION

$$\frac{d[\text{IIa}]}{dt} = k_3[\text{IIa}] - b_2 \frac{v}{k} [H]$$

$$\Rightarrow S \cdot \text{IIa}(s) + \text{IIa}(0) = k_3 \text{IIa}(s) - b_2 \frac{v}{k} H(s)$$

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

SIMULINK BLOCK MODEL



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

OPEN LOOP BODE PLOT

$K_d = -550.54$

$K_p = -258.87$

$V = 7.2$

$b = 10.05$

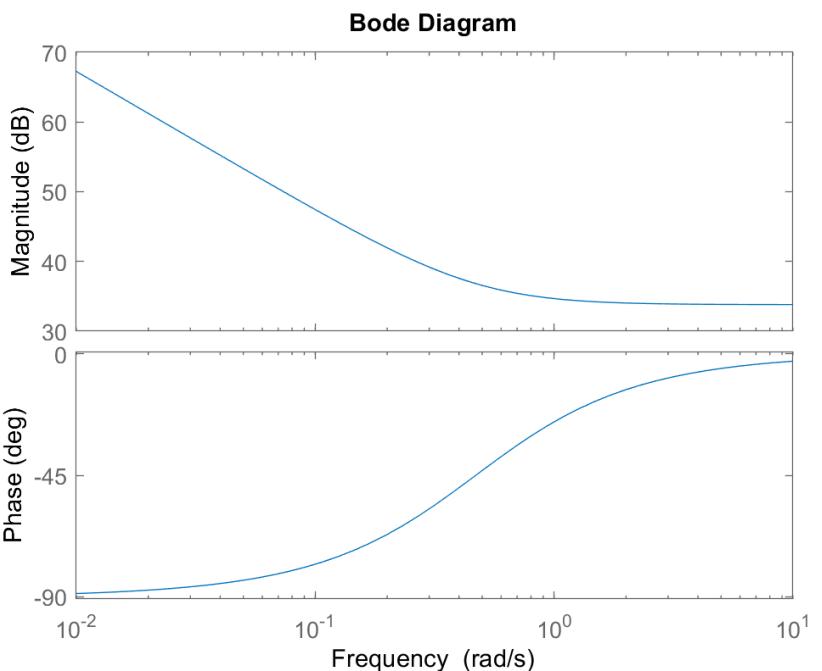
$k = 813$

$k_3 = 1.5E-5$

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

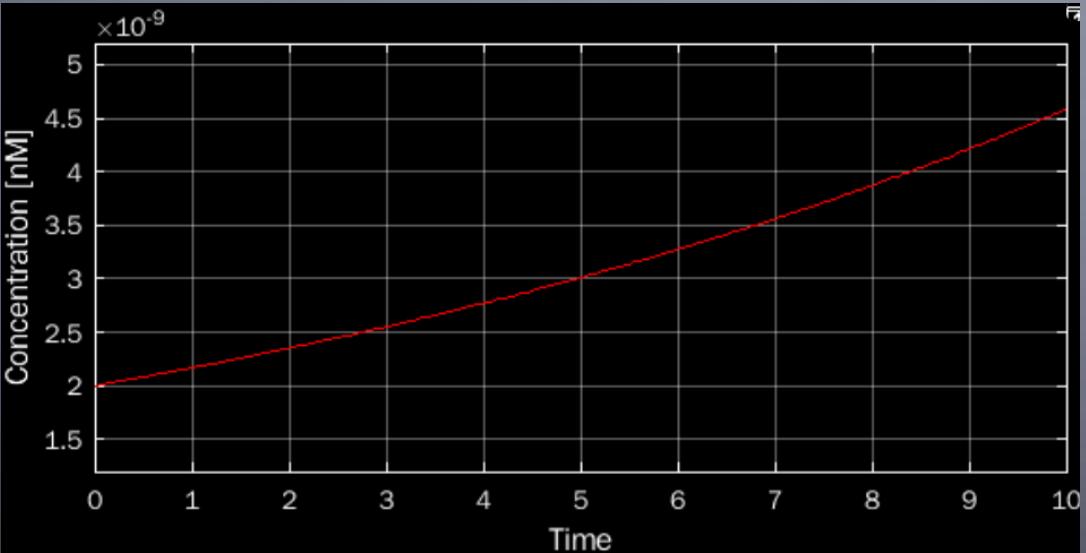
$$OL(s) = (K_d s + K_p) \times \frac{-bV}{k(s - k_3)}$$

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

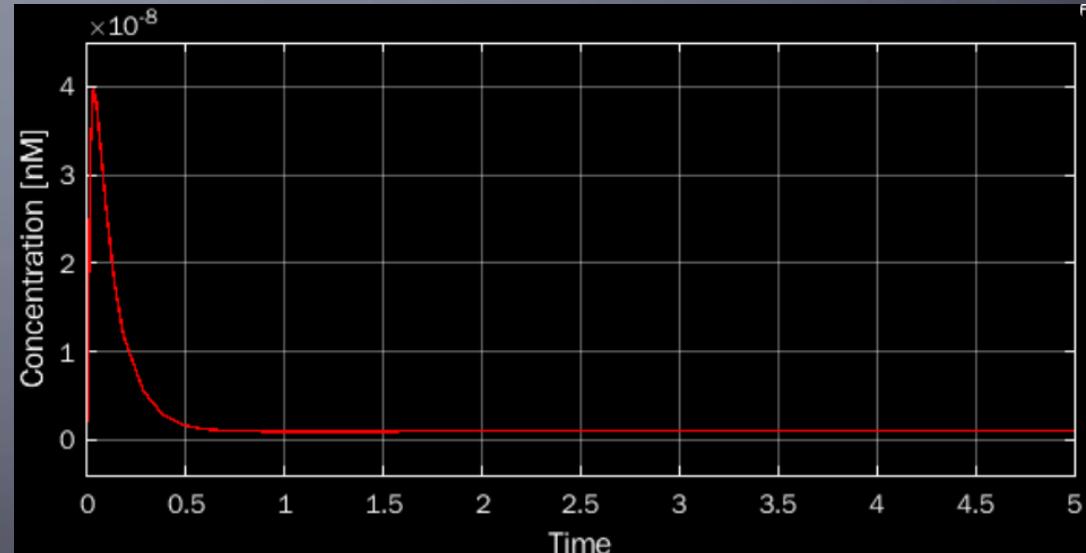


RESULTS: PD FEEDBACK STABILIZES SYSTEM RESPONSE

Without any PD Control & No Measurement Delay



With PD Control & 5 min Measurement Delay



CLINICAL APPLICATIONS

- Diagnosis – diagnose clotting disorders from thrombin time
- Surgery - prevent excessive bleeding from low [thrombin]
- Preventative care – prevent excessive clotting from high [thrombin]
- POC device - monitor patients with bleeding disorders
 - Hemophilia
 - Etc.

SOURCES

- [1] <https://www.ahajournals.org/doi/full/10.1161/jaha.116.003553>
- [2] https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=thrombin_time
- [3] <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7390270/>
- [4] <https://hal.archives-ouvertes.fr/tel-01672317v2/document>
- [5] <https://pubmed.ncbi.nlm.nih.gov/7164033/>