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Predicting Thrombin and Fibrin during Thrombosis under Flow

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Biological Background

MOTIVATION:

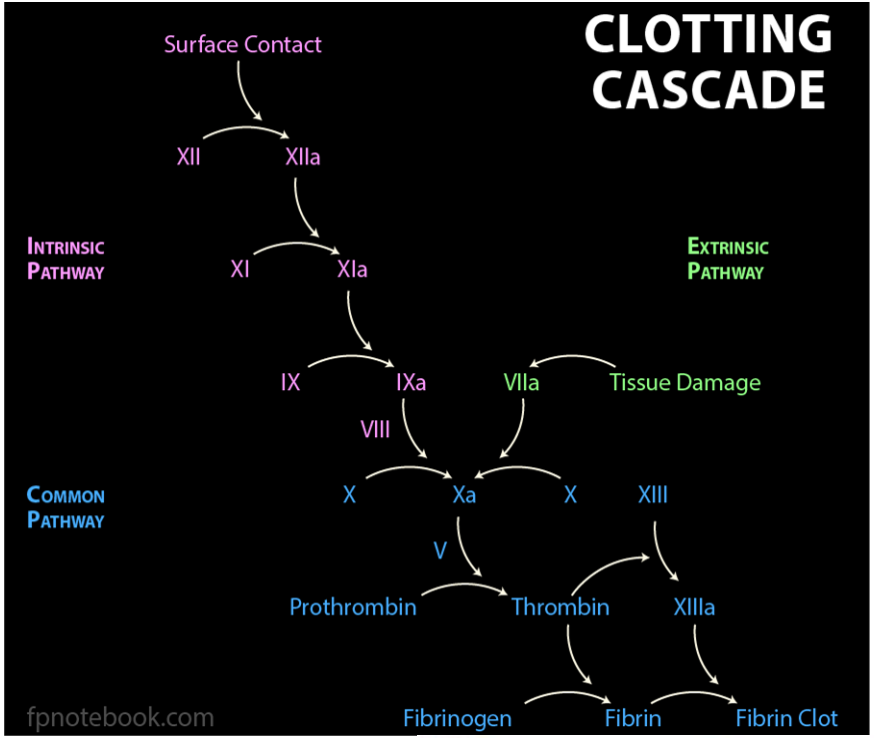
- Clotting mechanisms have many implications in human disease
- Coagulation cascade is difficult to model and study

AIM:

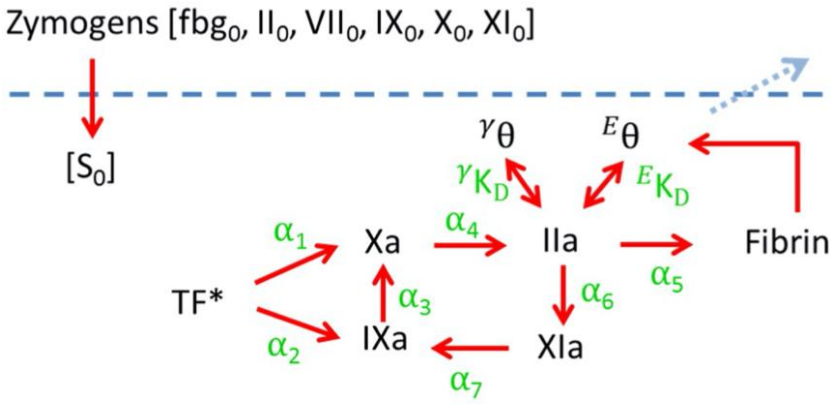
- Create a simplified computational model to determine coagulation factor concentrations during thrombosis under venous flow

SIGNIFICANCE:

- Multiscale simulation of thrombosis in venous vasculature
- Study and development of therapies that impact the coagulation cascade



Key Equations and Parameters



ODE 1. $\frac{d\,TF^*}{dt} = -k_{i,TF} \cdot TF^*$ for $k_{i,TF} = \ln(2)/180s$

ODE 2. $\frac{d\,Xa}{dt} = \alpha_1 \cdot TF^* + \alpha_3 \cdot IXa - k_i \cdot Xa$

ODE 3. $\frac{d\,IXa}{dt} = \alpha_2 \cdot TF^* + \alpha_7 \cdot XIa - k_i \cdot IXa$

ODE 4. $\frac{d\,XIa}{dt} = \eta_6 \cdot \alpha_6 \cdot IIa - k_{elute} \cdot XIa - k_i \cdot XIa$ for $\eta_6 = 0.36$

ODE 5. $\frac{d\,Fibrin}{dt} = \eta_5 \cdot \alpha_5 \cdot IIa$ for $\eta_5 = 0.05$

where: $^{E}\theta_{total} = (1.6) \cdot fibrin$ and $^{\gamma}\theta_{total} = (0.3) \cdot fibrin$

ODE 6. $\frac{d\,IIa}{dt} = \eta_4 \cdot \alpha_4 \cdot Xa - \left(\frac{d^E S}{dt} + \frac{d^{\gamma} S}{dt}\right) - k_{elute} \cdot IIa - k_i \cdot IIa$ for $\eta_4 = 0.18$

ODE 7. $\frac{d^E S}{dt} = {}^{E}k_f \cdot IIa \cdot ({}^{E}\theta_{total} - {}^{E}S) - {}^{E}k_r \cdot {}^{E}S$

ODE 8. $\frac{d^{\gamma} S}{dt} = {}^{\gamma}k_f \cdot IIa \cdot ({}^{\gamma}\theta_{total} - {}^{\gamma}S) - {}^{\gamma}k_r \cdot {}^{\gamma}S$

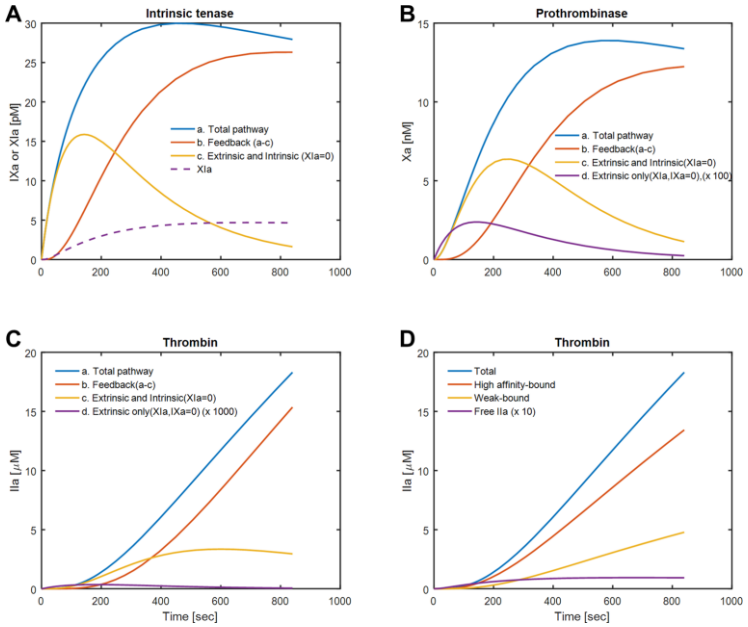
k_i, $k_{i,TF}$	Half-life constants
k_{elute}	Elution constant
$\boldsymbol{\alpha}$	Kinetic coefficients
$\boldsymbol{\eta}$	Effectiveness factors

Assumptions

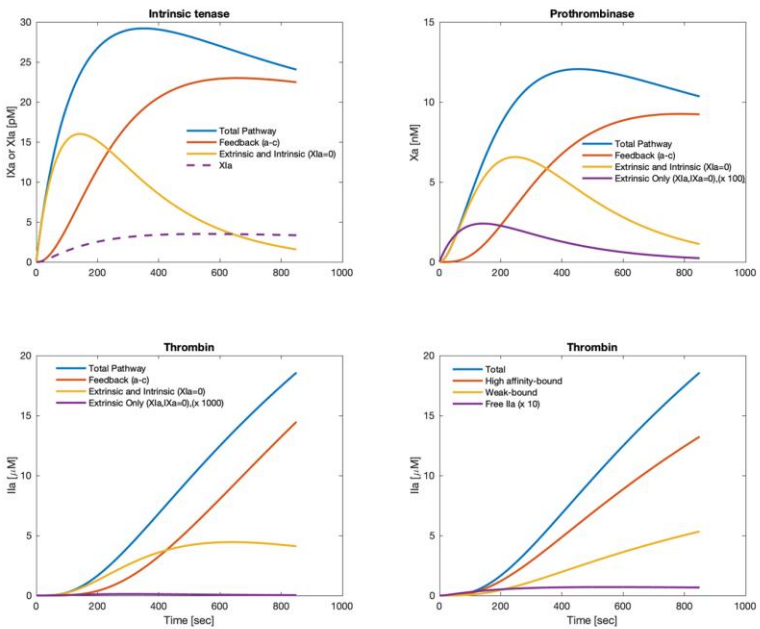
Assumptions and Limitations

- Thin film
  - Equal zymogen concentrations in clot and plasma
- Closed System
  - Ignores platelet metabolism
  - Anionic phospholipids
- Fibrinogen is strongly diffusion limited
- All enzymes had a half-life of 1 min other than TF which had a half-life of 3 mins

Figure Reproduction



Original



Reproduction

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Novel Analysis:

Effect of factor deficiency on clotting cascade under flow

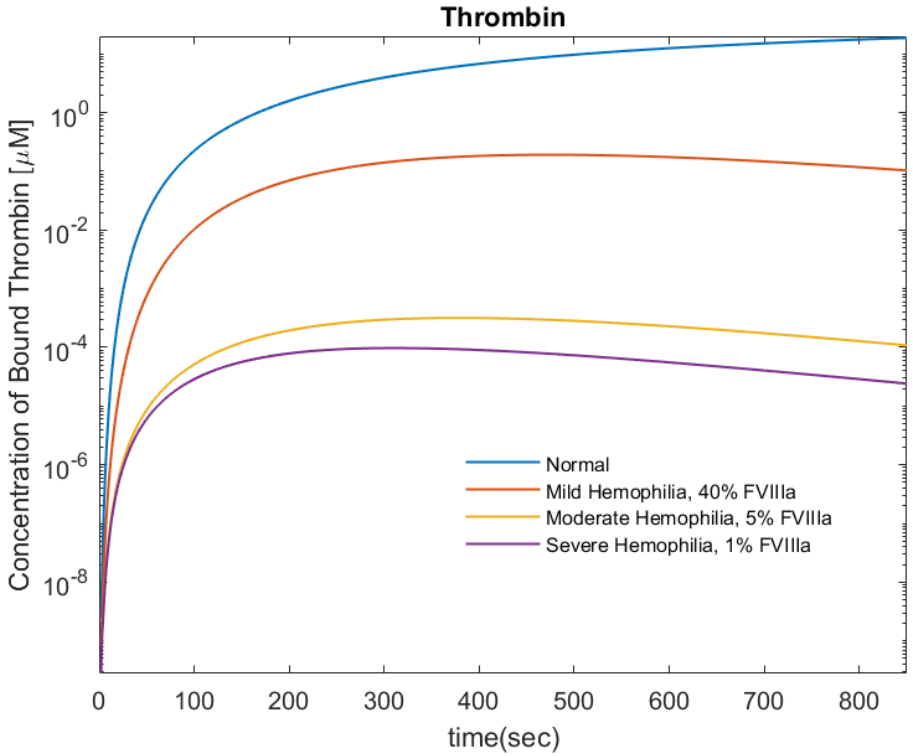
- Hemophilia A is characterized by FVIIIa deficiency
  - Clotting disorder
  - Frequency and severity of bleeds dependent on plasma concentration of FVIIIa

Severity	FVIIIa (compared to normal)	FVIIIa concentration
Mild	5-40%	0.05-0.4 IU/mL
Moderate	1-5 %	0.01-0.05 IU/mL
Severe	<1 %	< 0.01 IU/mL

Novel Analysis Methods

- Paper assumes cofactor activation is not rate limiting
- Alter parameters to represent plasma levels of FVIIIa associated with mild, moderate, and severe hemophilia
    - Effects ODEs 2 and 3 in the intrinsic pathway
- Model thrombin concentration over time in FVIIIa deficient systems

Results



- Model thrombin concentration over time in FVIIIa deficient systems
  - FVIIIa is not explicitly modeled but rather grouped into the effectiveness parameters
  - Despite model's simplicity, complexities of the wound healing cascade can still be factored into the model
- Clinical implication
  - Model can guide therapy

Questions?

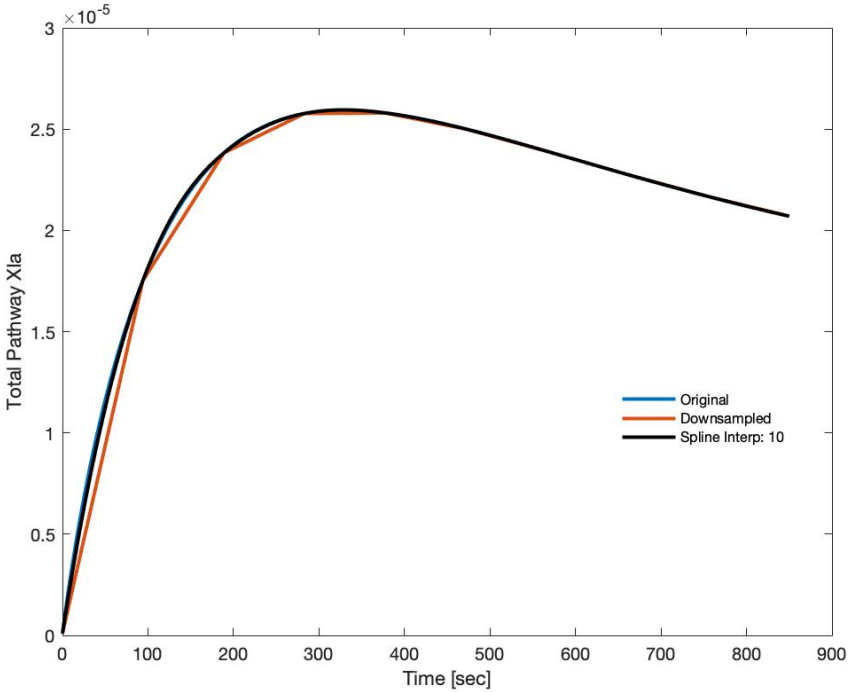
Citations

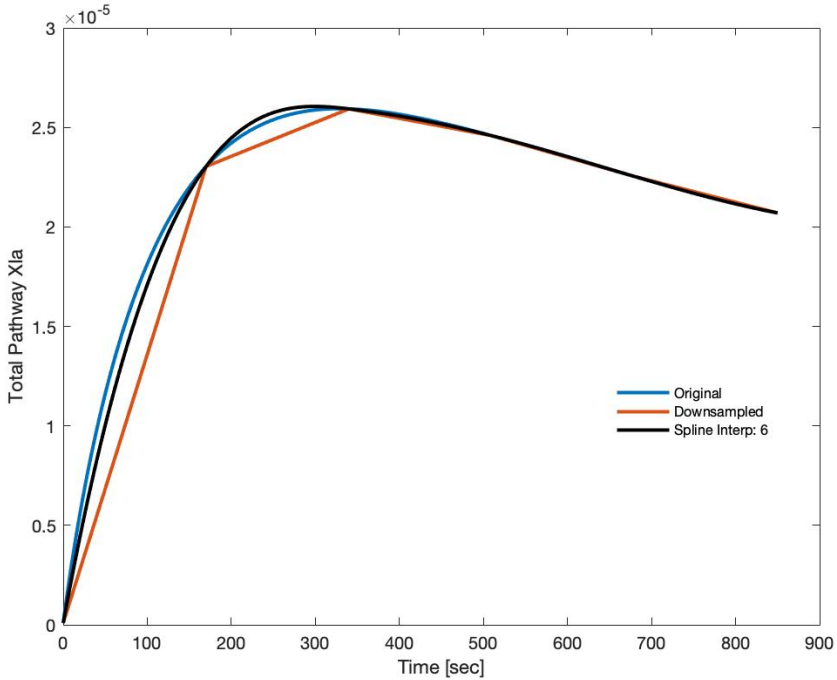
Chen, Jason, and Scott L. Diamond. “Reduced Model to Predict Thrombin and Fibrin during Thrombosis on Collagen/Tissue Factor under Venous Flow: Roles of γ’-Fibrin and Factor XIa.” Edited by Jeffrey J. Saucerman. *PLOS Computational Biology* 15, no. 8 (August 5, 2019): e1007266. https://doi.org/10.1371/journal.pcbi.1007266.

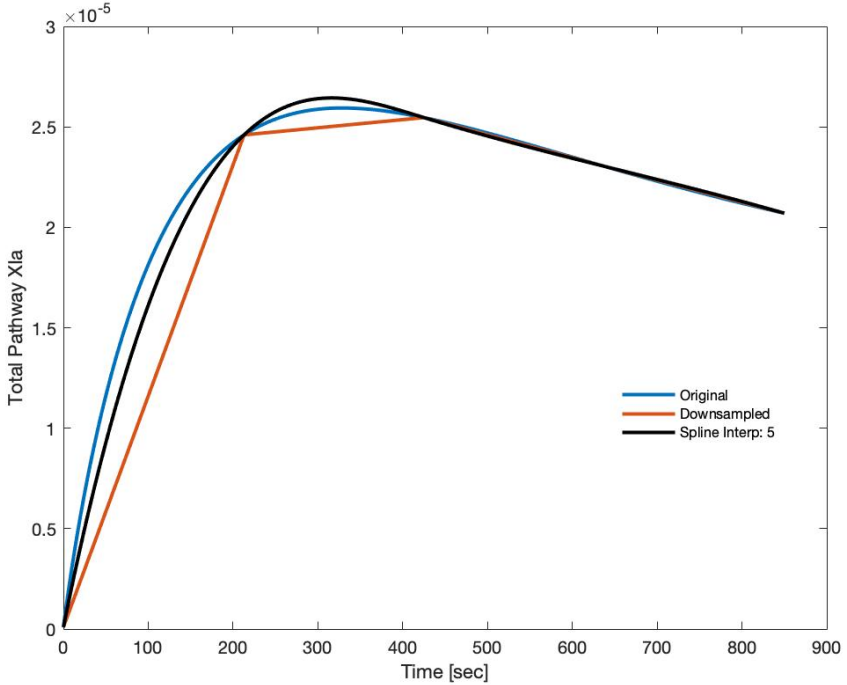
Preston, F. E., S. Kitchen, I. Jennings, T. a. L. Woods, and M. Makris. “SSC/ISTH Classification of Hemophilia A: Can Hemophilia Center Laboratories Achieve the New Criteria?” *Journal of Thrombosis and Haemostasis* 2, no. 2 (2004): 271–74. https://doi.org/10.1046/j.1538-7836.2003.00447.x.

“Bleeding Disorders | National Heart, Lung, and Blood Institute (NHLBI).” Accessed December 1, 2019. https://www.nhlbi.nih.gov/health-topics/bleeding-disorders.

Spline Interpolation



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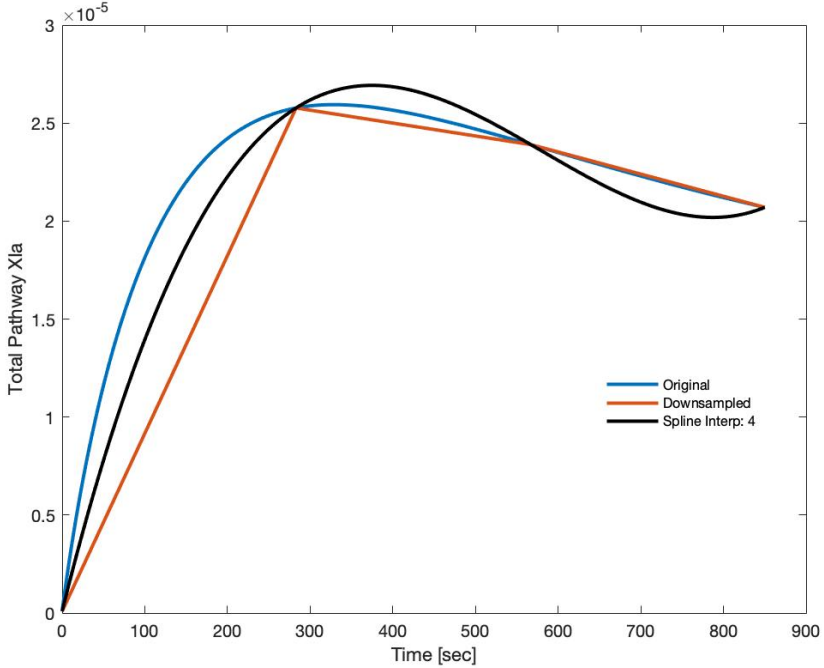
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Resources

Our Previous Presentation:

https://docs.google.com/presentation/d/1fura69Lllvz_mkbHlCeZBSAx9Tm_pFQY4ch9zQ2Vc-M/edit?usp=sharing

Item	Sub Item	Explaination	Points
Model Explaination			25
	Biological Background	Summarizes the paper selected, explains the biological mechanisms being modeled, and states significance of the model in research/clinical translation.	10
	Assumptions	States assumptions and characterizes the limitations of the model resulting from those assumptions.	10
	Key Parameters/Equations	Lists and broadly explains key parameters and equations in the model.	5
Figure Reproduction			30
	Figure	Acurately reproduces figure, including axis labels, units, legends, and labels. Compares figures side by side.	12
	Methods Used	Describes all numerical methods used in reproducing the figure.	10
	Difficulties Encountered	Provides discussion on any difficulties encountered in implementing the model.	8
Novel Analysis			30
	Purpose	States the goals and significance of the novel analysis being proposed.	12
	Methods Used	Outlines the numerical methods used to achieve the novel analysis. Should also offer discusion on alternative methods (if any) and why they were not selected.	8
	Results/Discussion	Offers discussion on the results of the analysis and any significant findings.	10
Overall Presentation			15
	Slide Organization	Consistent formatting and logical organization of slides.	5
	Clarity	Clearly and consisely verbalizes the contents of the presentation.	3
	Questions	Adresses questions appropriately.	5
	Timing		2
		Total	100