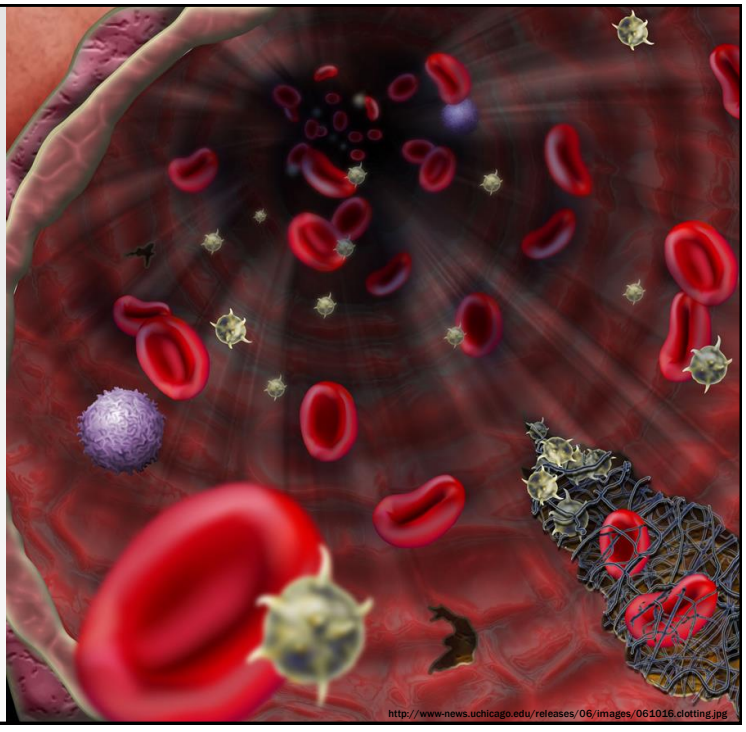
Blood Clotting

ANDREW WONG

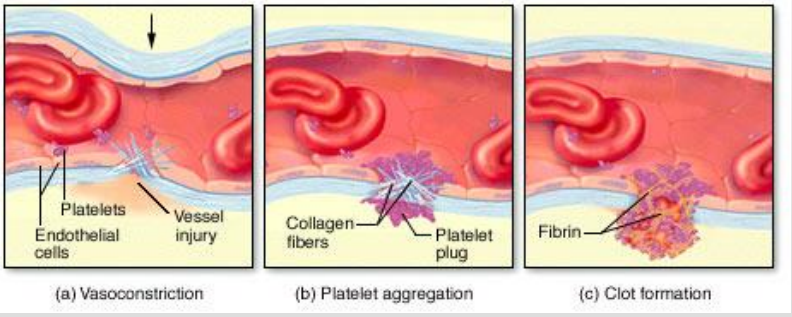
JOEL TAN



Background

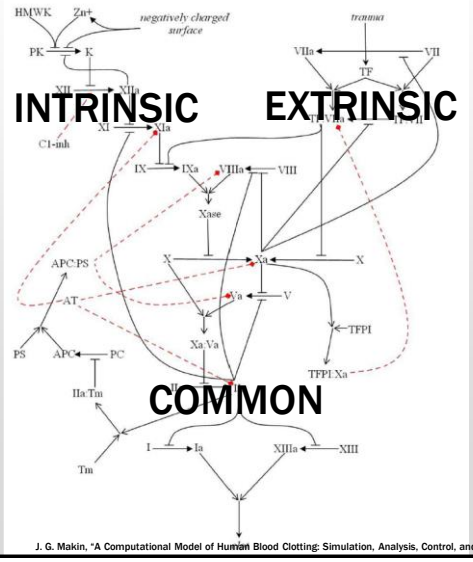
WHAT IS BLOOD CLOTTING?

General Mechanism



http://www.mhhe.com/biosci/esp/2001_saladin/folder_structure/tr/m1/s7/assets/images/trm1s7_1.jpg

Pathway



J. G. Makin, "A Computational Model of Human Blood Clotting: Simulation, Analysis, Control, and Validation," Ph.D. dissertation, Elec. Eng. Comp. Sci., Univ. California, Berkley, 2008

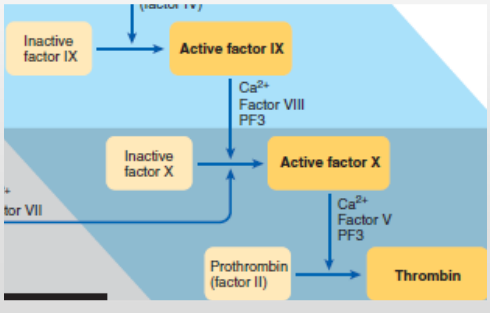
Thrombin (Factor IIa)

- Converts fibrinogen to fibrin, resulting in the fibrin mesh
- Normally in inactive form (Factor II), but production greatly enhanced due to cascade
- Acts in its own positive-feedback mechanism to facilitate the conversion from prothrombin to thrombin
- Thus, a good marker to measure how well the blood coagulates

Human Physiology: From Cells to Systems 7E, Sherwood.

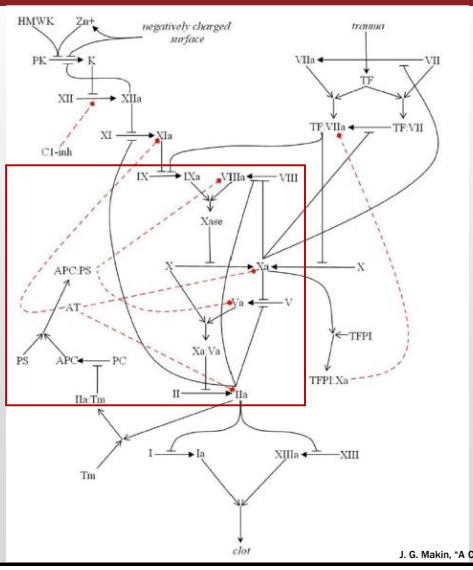
Disease – Haemophilia A

- Inability to control blood clotting or coagulation due to lack of fibrin formation
  - Caused by Factor VIII deficiency
- 1 in 5,000–10,000 male births
  - X-Linked recessive trait
- Causes increased bleeding
- Thrombin positive feedback mechanism cannot activate more Factor VIIIa to increase production of Factor Xa and thus Thrombin

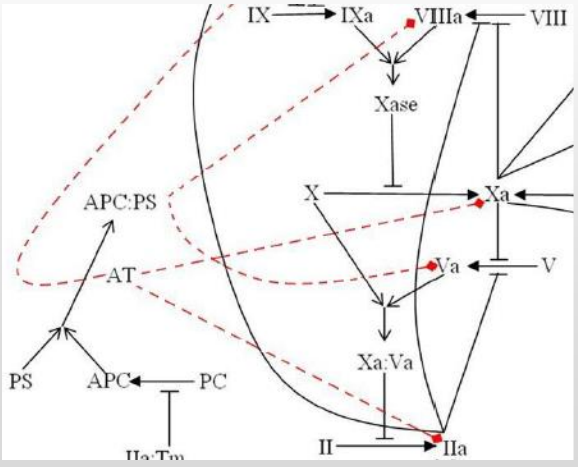


Human Physiology: From Cells to Systems 7E, Sherwood. Figure 11-14

Pathway



Factor VIII Mechanism



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Current Treatments

- Haemophilia treatment mainly depends on its severity.
- On demand
  - Giving treatment to stop prolonged bleeding when it occurs.
  - More commonly used for patients with mild haemophilia.

Source: Medical News Today, http://www.medicalnewstoday.com/info/hemophilia/treatment-for-hemophilia, accessed 29 Oct 2013

Current Treatments

- Haemophilia treatment mainly depends on its severity.
- Preventative treatment (prophylaxis)
  - Medication to prevent bleeding episodes, and subsequent complications, such as joint and/or muscle damage.
  - More commonly used for patients with moderate or severe haemophilia.
  - Clotting factor replacement therapy (Factor VIII infusion)
    - Inject the factors into the bloodstream through a vein.
    - However, some people develop antibodies against the transfused factor VIII
      - Approximately 30% of people with severe haemophilia A

Source: Medical News Today, http://www.medicalnewstoday.com/info/hemophilia/treatment-for-hemophilia, accessed 29 Oct 2013

Project Objectives

FOR MODEL VALIDATION

Objectives

- To critique or validate a current mathematical model for blood clotting
  - Created a mathematical model from existing literature
- Examine a disease mechanism from the model
  - Haemophilia A

Methodology

- Model Validation
  - Looked at thrombin concentration
  - Activated different pathways
    - Intrinsic Pathway
    - Extrinsic Pathway
  - Changed the intensity of each pathway
- Examine a disease mechanism from the model
  - Added a “haemophilia constant” factor
  - Looked at how that constant changed the thrombin concentration as the different pathways are activated

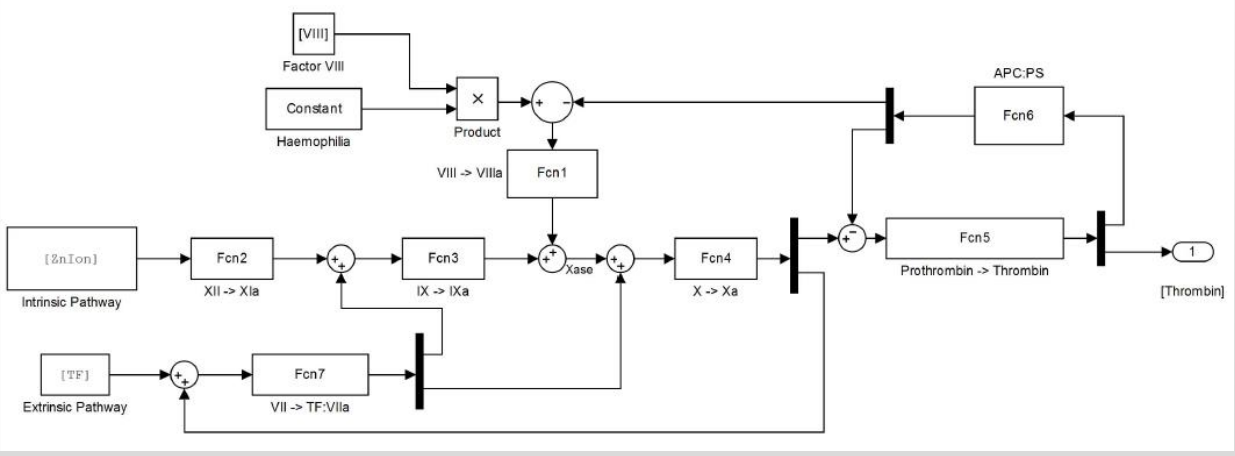
Rationale

- While we understand how the pathway works, there is currently no model for this
- Will help understand the different factors involved in the cascade
- Will help us find a way to target haemophilia A and hopefully find more effective methods to cure it

MODEL

WHAT WE BUILT

Simplification and Specific Modification



J. G. Makin, "A Computational Model of Human Blood Clotting: Simulation, Analysis, Control, and Validation," Ph.D. dissertation, Elec. Eng. Comp. Sci., Univ. California, Berkley, 2008

Modelling Equations

- IN1 - - - - - - - > OUT (catalyzed by IN2)

$$\frac{d[IN_1]}{dt} = k_{off}[IN_1{:}IN_2] - k_{on}[IN_1][IN_2]$$

$$\frac{d[IN_2]}{dt} = k_{off}[IN_1{:}IN_2] - k_{on}[IN_1][IN_2] + k_{cat}[IN_1{:}IN_2]$$

$$\frac{d[IN_1{:}IN_2]}{dt} = k_{on}[IN_1][IN_2] - k_{off}[IN_1{:}IN_2] - k_{cat}[IN_1{:}IN_2]$$

$$\frac{d[OUT]}{dt} = k_{cat}[IN_1{:}IN_2]$$

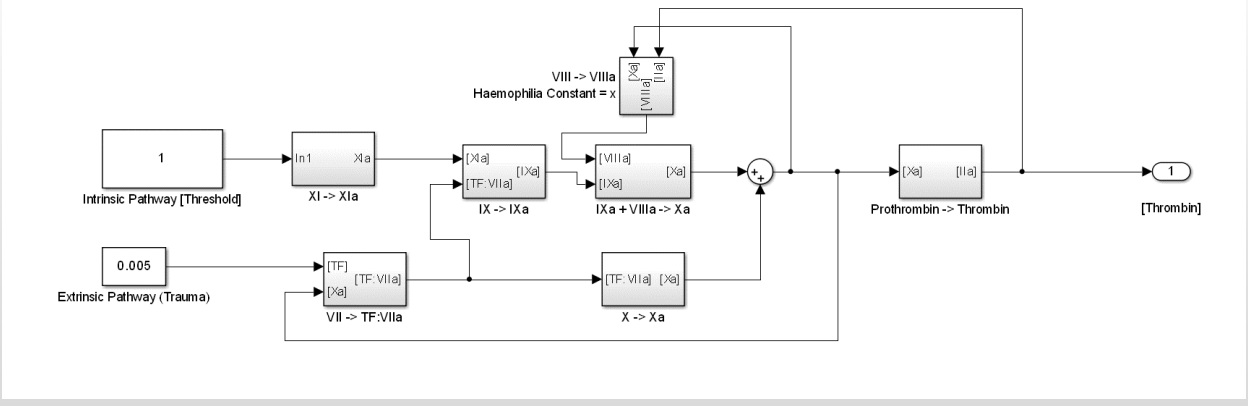
- IN1 + IN2 - - - - - - - > OUT (no catalyst)

$$\frac{d[IN_1]}{dt} = k_{off}[OUT] - k_{on}[IN_1][IN_2]$$

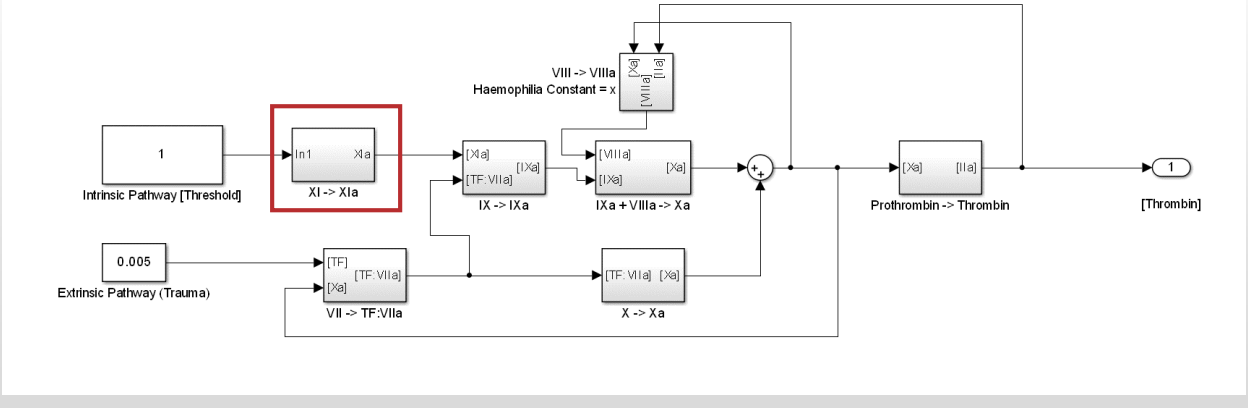
$$\frac{d[IN_2]}{dt} = k_{off}[OUT] - k_{on}[IN_1][IN_2]$$

$$\frac{d[OUT]}{dt} = k_{on}[IN1][IN2] - k_{off}[OUT]$$

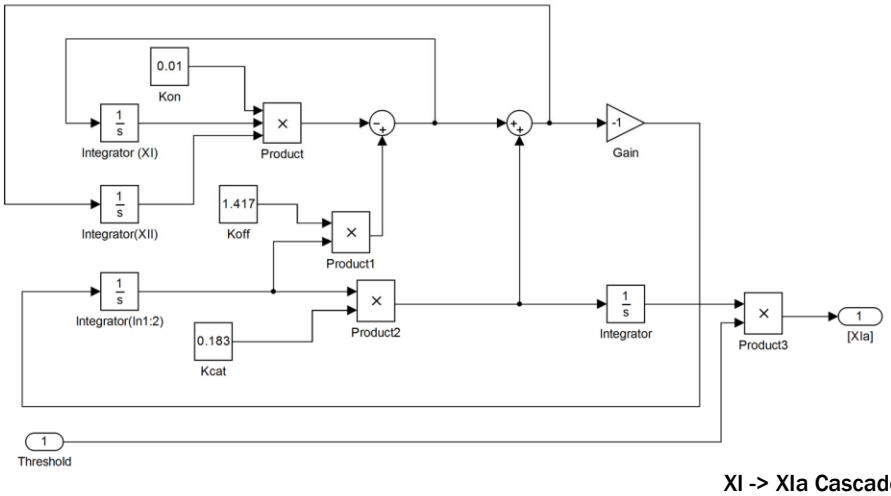
Model



Model (Intrinsic Pathway)

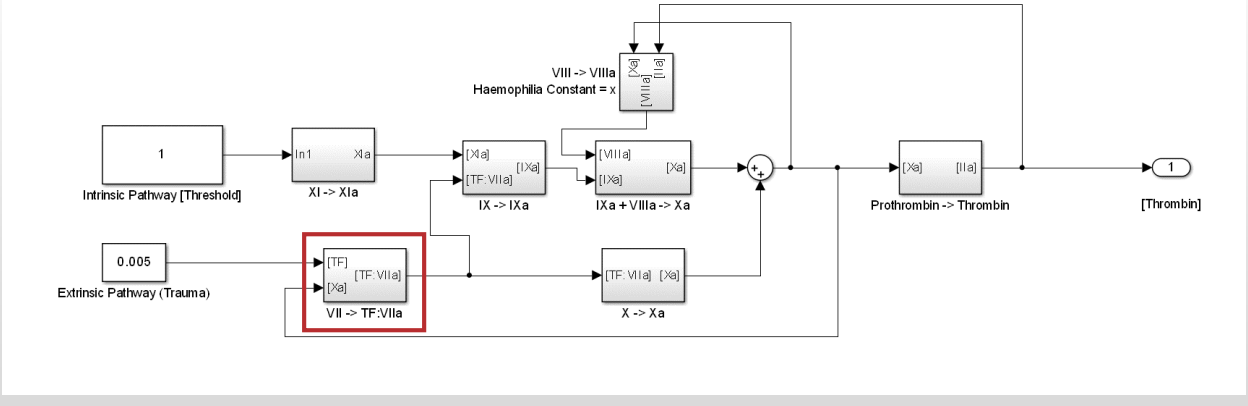


Model (Intrinsic Pathway)

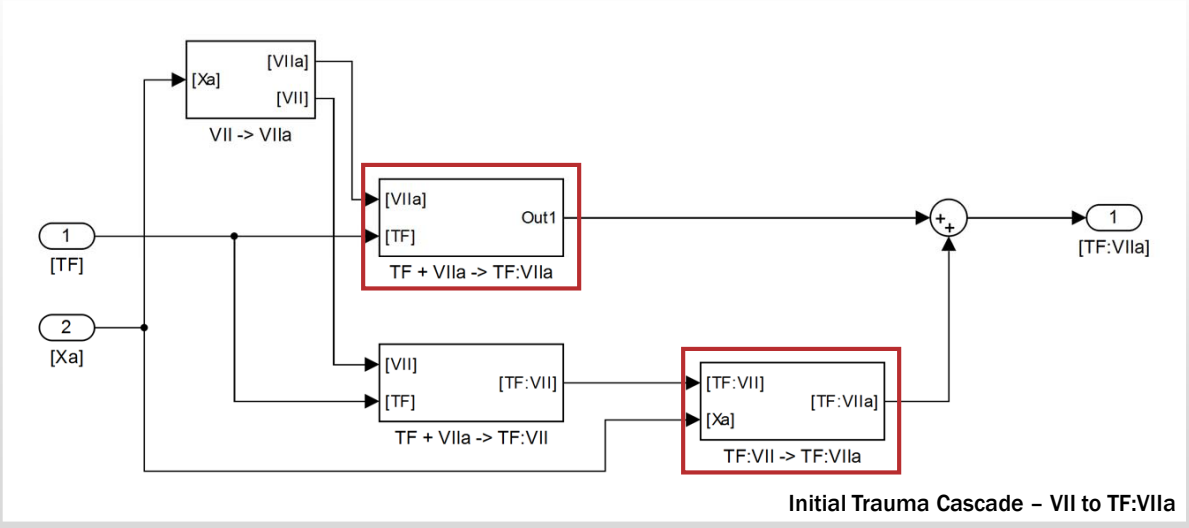


XI -> XIa Cascade

Model (Extrinsic Pathway)

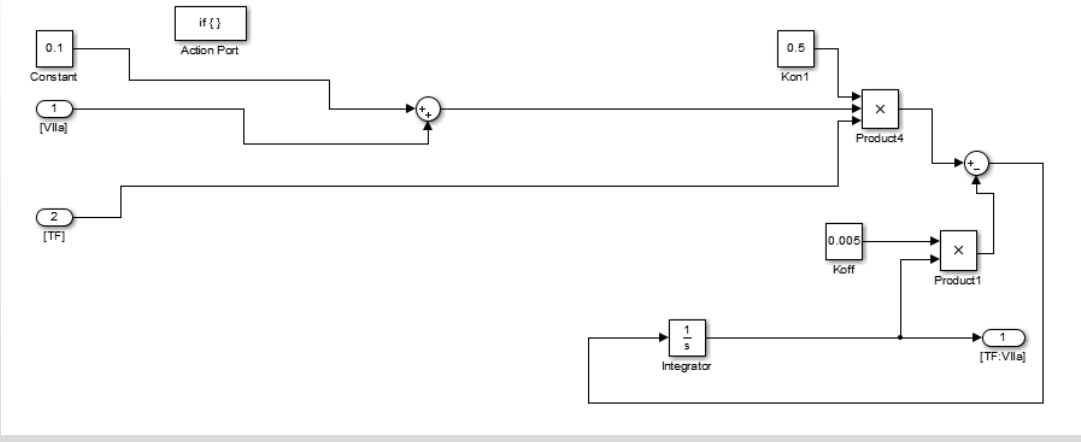


Model (Extrinsic Pathway)



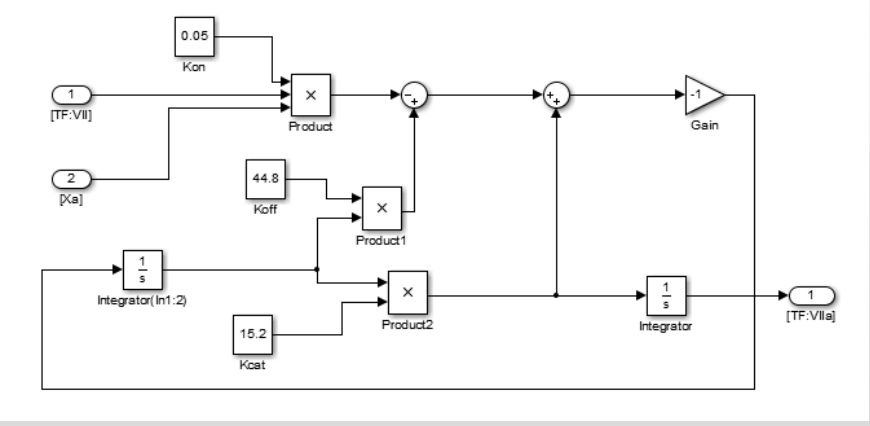
Initial Trauma Cascade – VII to TF:VIIa

Model (Extrinsic Pathway)



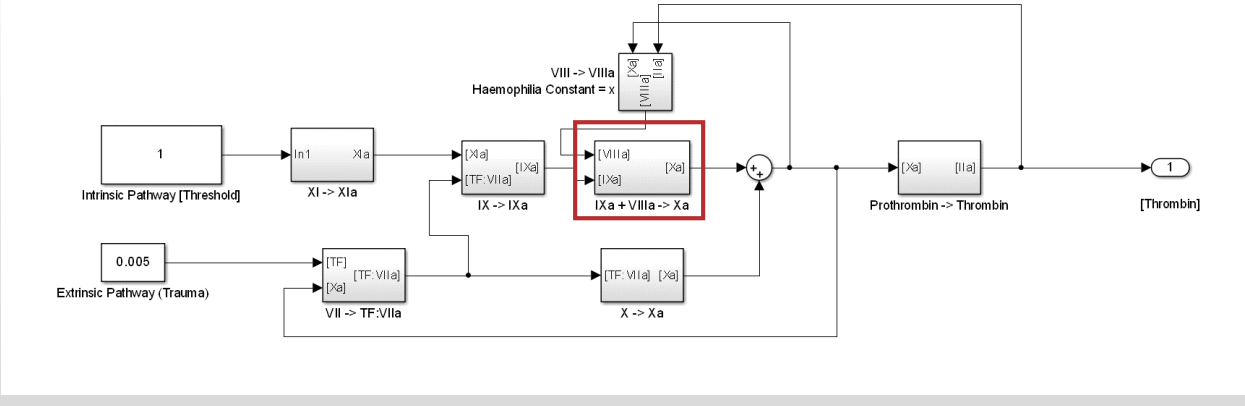
Initial Trauma Cascade – TF + VIIa to TF:VIIa

Model (Extrinsic Pathway)

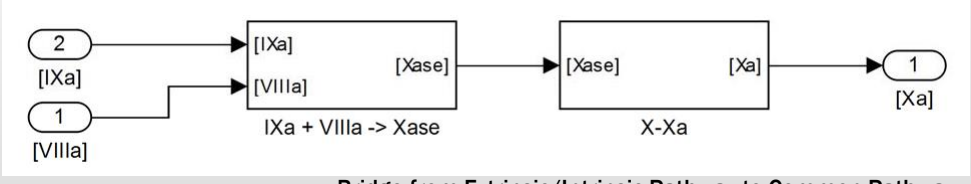


Initial Trauma Cascade – TF:VII to TF:VIIa

Model (Common Pathway)



Model (Common Pathway)

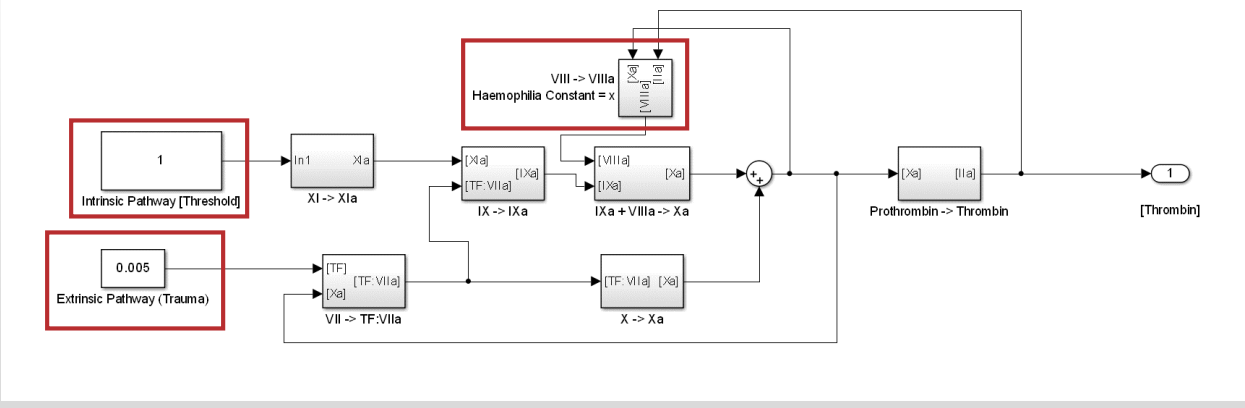


Bridge from Extrinsic/Intrinsic Pathway to Common Pathway

Variables Analyzed

- Intrinsic Pathway Threshold
  - From 0x to 1x factor XIa
- Extrinsic Pathway [TF] in nM
  - Ranged from 0.005 (“off”) to 15nM
- Haemophilia Constant
  - 0x to 1x factor VIII
- Looked at how long it took Prothrombin to convert to Thrombin
  - Hence why we see a plateau at 1400nM (initial concentration of prothrombin)

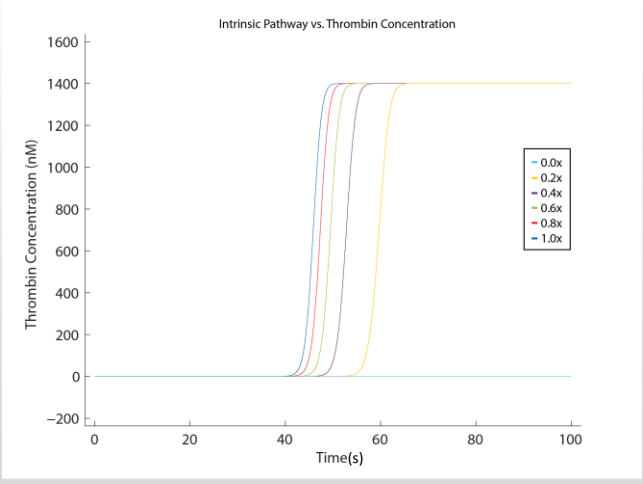
Model



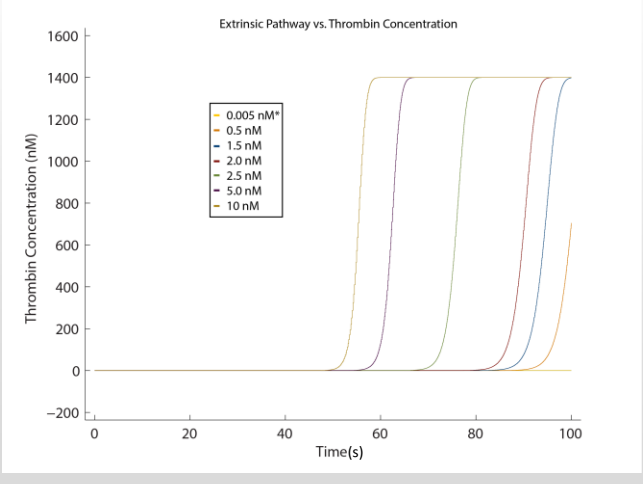
Discussion

HOW WELL DID OUR MODEL PERFORM

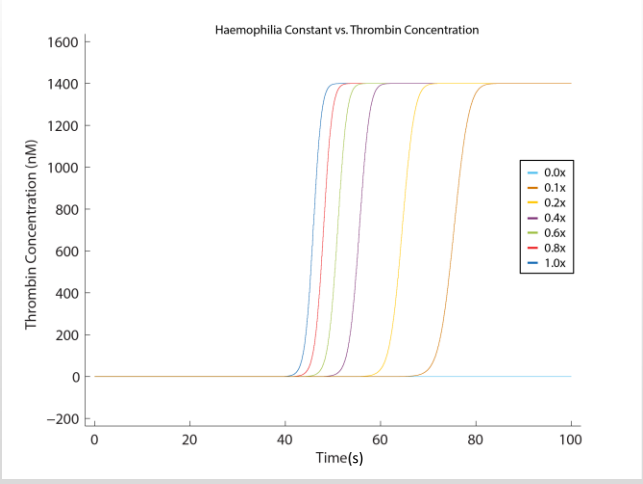
Summary of Results (Intrinsic Pathway)



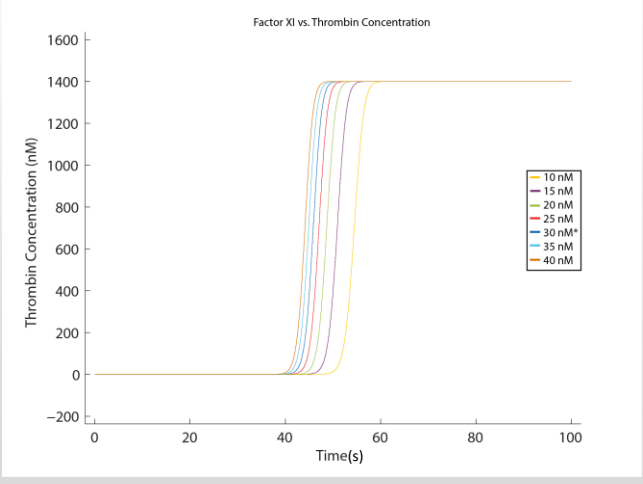
Summary of Results (Extrinsic Pathway)



Summary of Results (Haemophilia Constant)



Summary of Results (Factor XI)



Model Approximation

- The differential equations used assume that all the cascade pathways are similar and can be modelled using the same series of equations.
- Not all the cascade pathways were modelled.
- The constants used are assumed to correctly model that in the human body.

Model Limitations

- Very simplified – skips a lot of the more intricate mechanisms
- The model assumes all the cascade reactions follow the same set of equations.
- The model was simplified to not include lipid binding sites (LBS) which have different affinities for different factors which may affect the cascade reaction.

Possible Improvements

- Modelling the intrinsic pathway completely.
- Add the final stages of coagulation
  - Fibrinogen -> Fibrin
  - APC feedback mechanism
- Modelling the cascade using the LBS intermediates.

QUESTIONS?