Understanding Surgical and Traumatic Coagulopathy: Computation Meets Experiment

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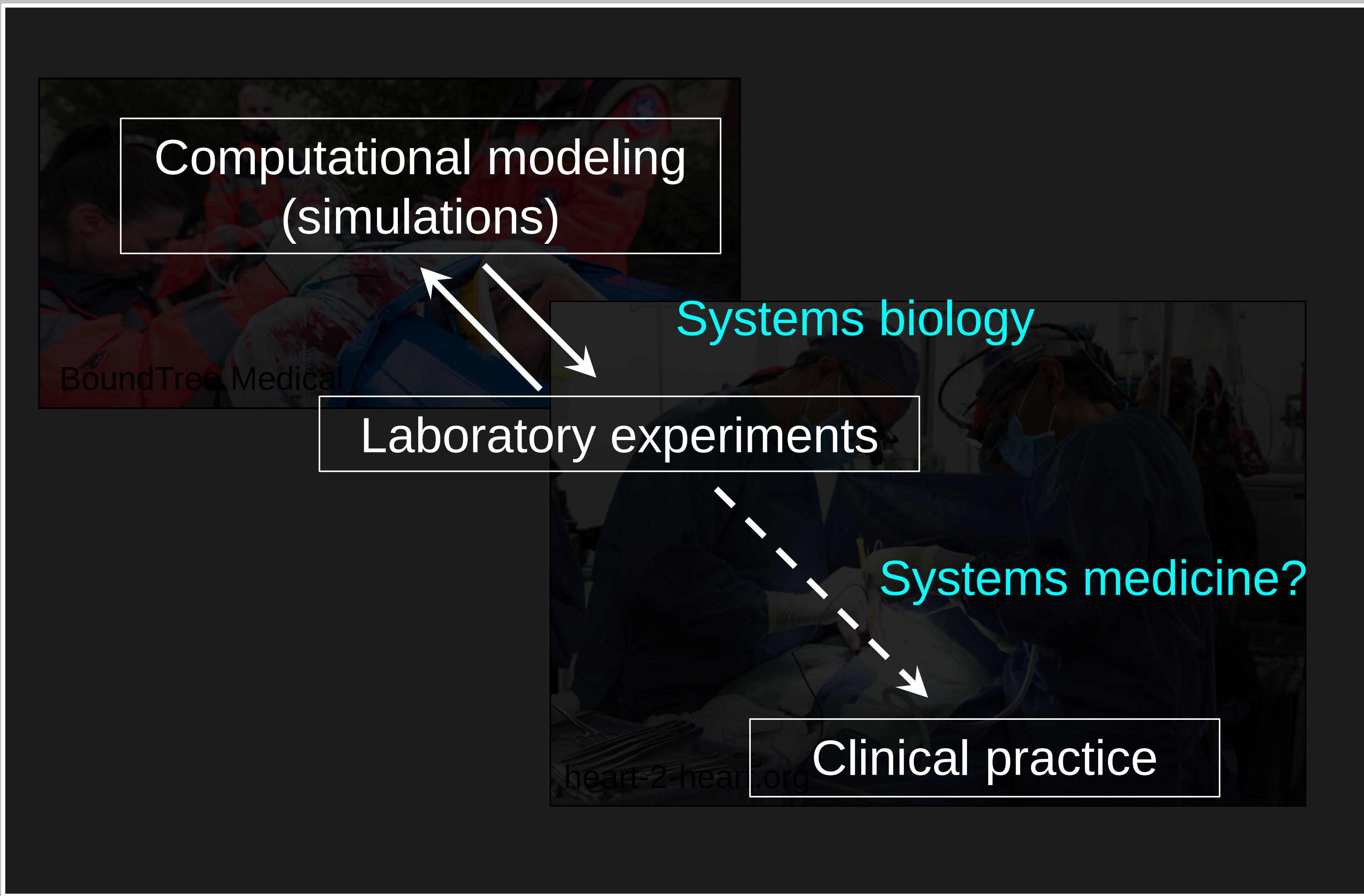
Grand Rounds
8 October 2020

Surgical and traumatic coagulopathy

BoundTree Medical

heart-2-heart.org

Surgical and traumatic coagulopathy



Coagulopathy is multifactorial

Dilution of coagulation factors

Hypothermia

Acidosis

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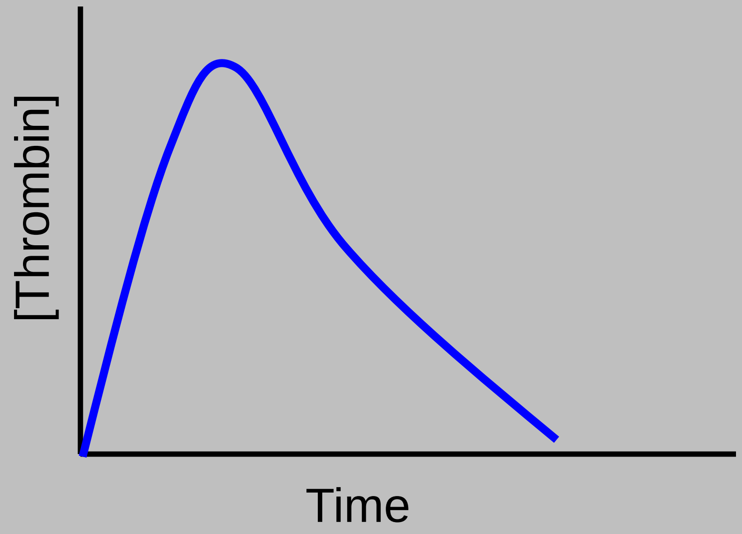
Coagulation impairment

Campbell et al., *J Trauma Acute Care Surg* (2015)

Thrombin generation *in vitro*

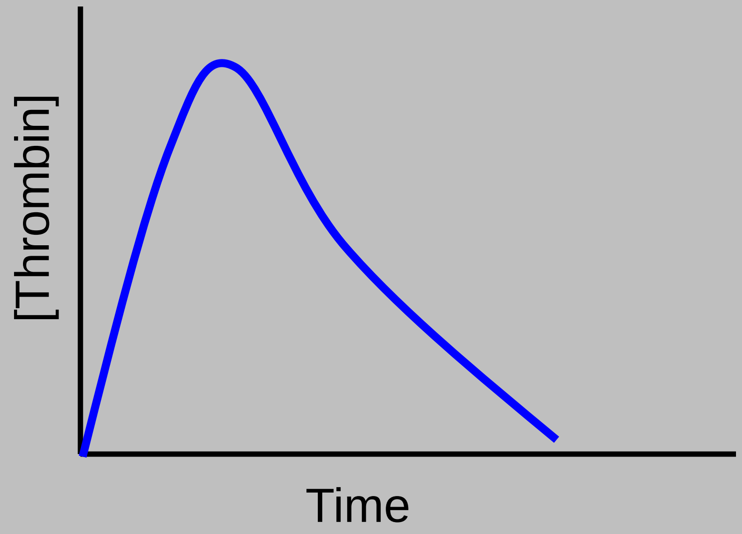
Normal thrombin generation



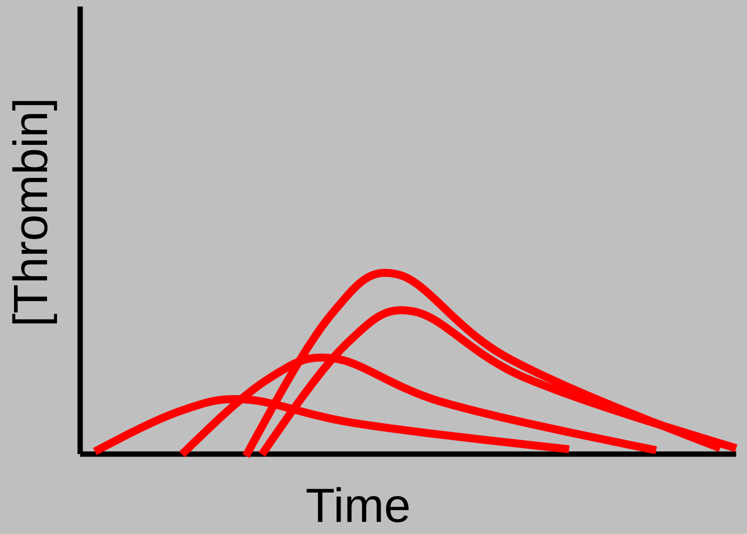
Thrombin → fibrin → blood clot

Thrombin generation *in vitro*

Normal thrombin generation



Coagulopathy

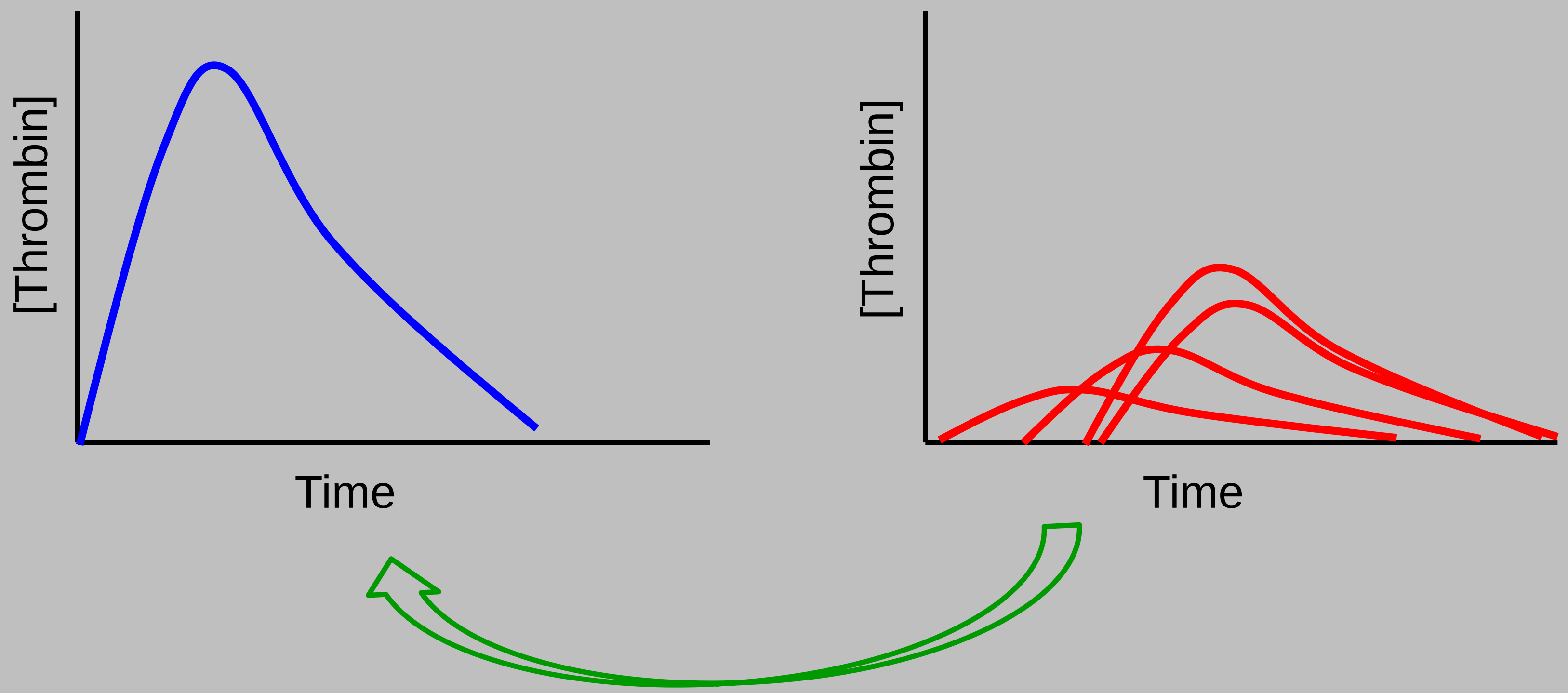


Thrombin → fibrin → blood clot

Therapeutic solutions for diverse scenarios

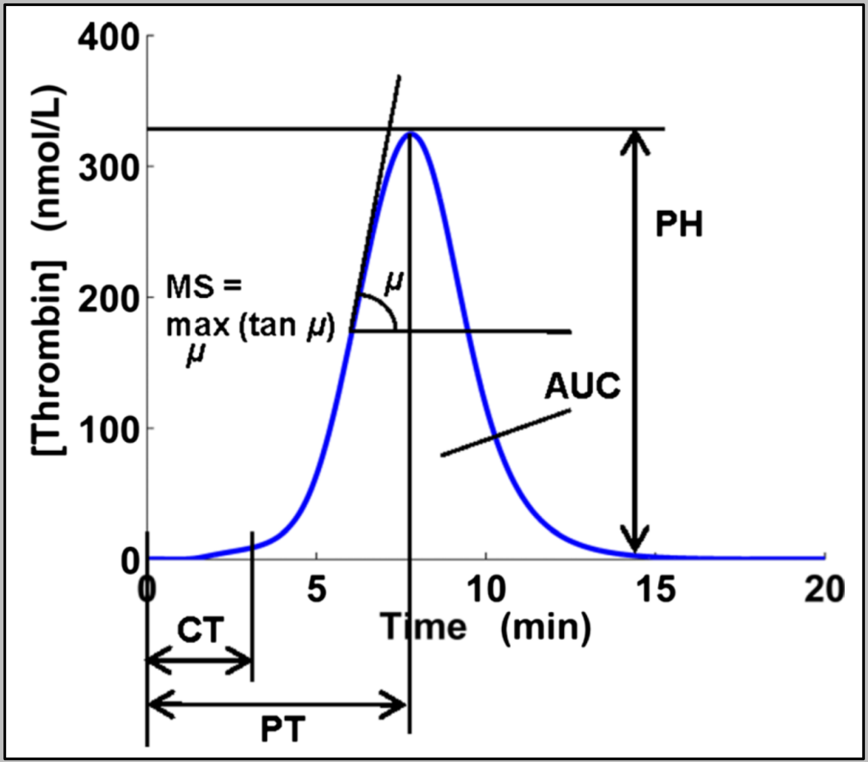
Normal thrombin generation

Coagulopathy



Thrombin → fibrin → blood clot

Thrombin-generation quantification

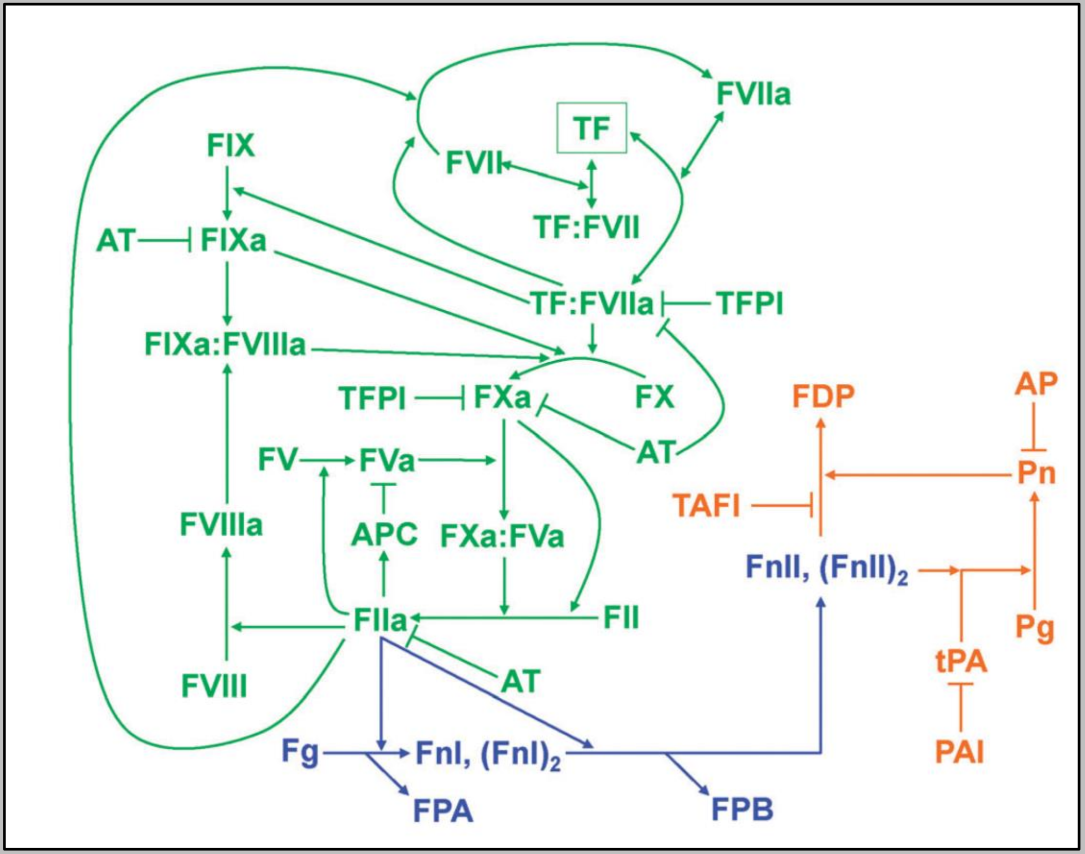


Mitrophanov et al., *J Trauma* (2012)

CT: clotting (lag) time
PH: thrombin peak height
AUC: area under the curve
MS: maximum slope
PH: peak height

Large system: intuition alone is not enough

Coagulation proteins (factors)



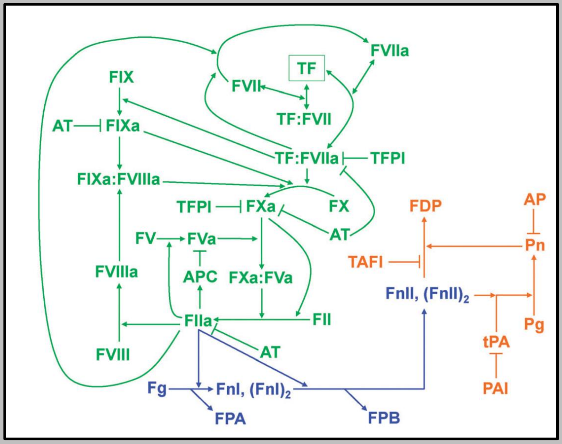
(gross oversimplification)

Mitrophanov et al., *Mol BioSyst* (2014)

- **How can we anticipate the effects of coagulopathy on thrombin generation?**
- **How do we know what coagulation factors are key?**

Approach: model computationally and then test

Blood coagulation system



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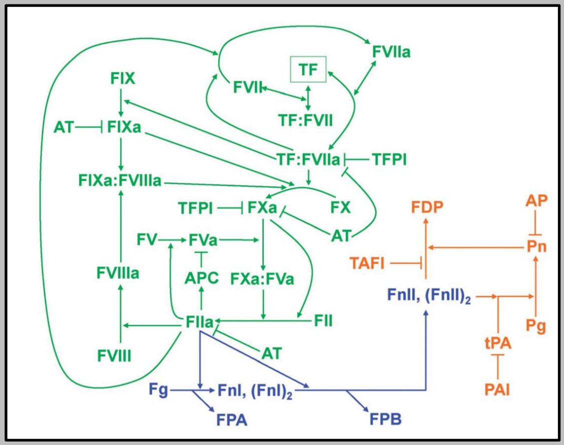
Blood coagulation system



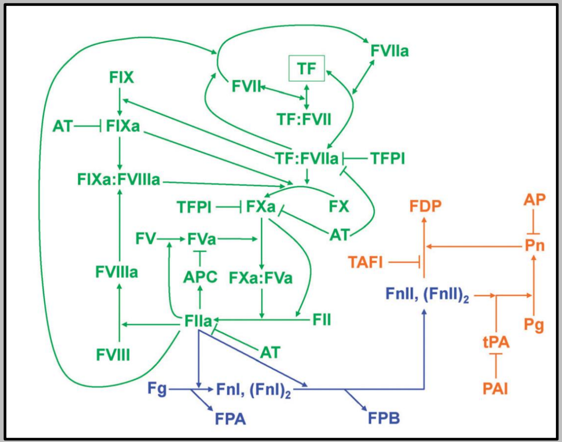
Computational kinetic modeling

C(t) = species concentration;

dC(t)/dt = (production rate) − (depletion rate)

Approach: model computationally and then test

Blood coagulation system



In vitro experiments
(plasma or whole blood)


coronapathology.org

Computational kinetic modeling

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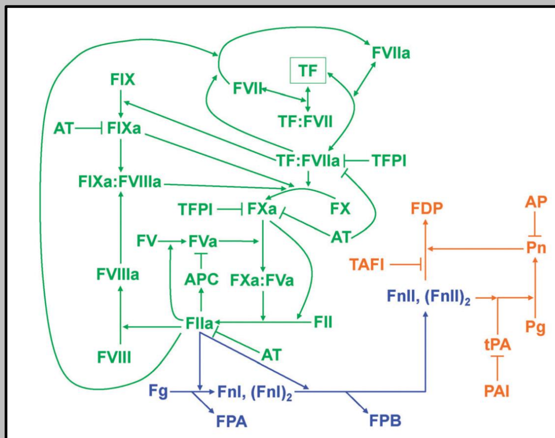


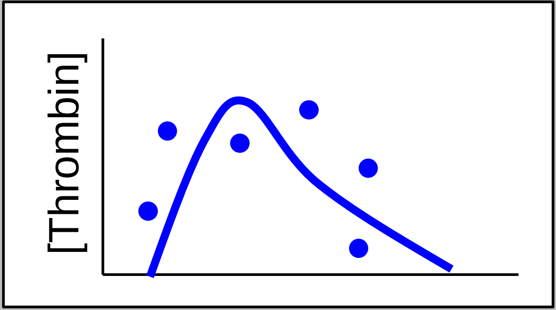
In vitro experiments
(plasma or whole blood)

Computational kinetic modeling

C(t) = species concentration;

***d*C(t)/*d*t = (production rate)**
− (depletion rate)

Comparison: validation



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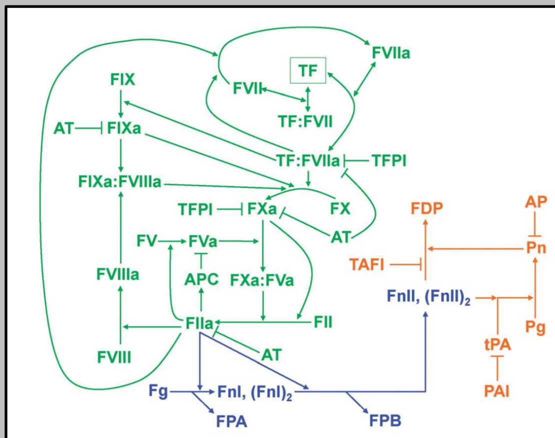

In vitro experiments
(plasma or whole blood)

Computational kinetic modeling

C(t) = species concentration;

***d*C(t)/*d*t = (production rate)**
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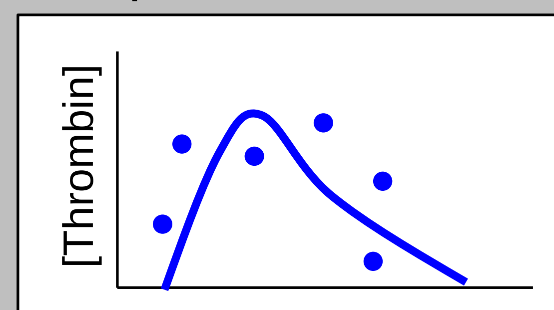
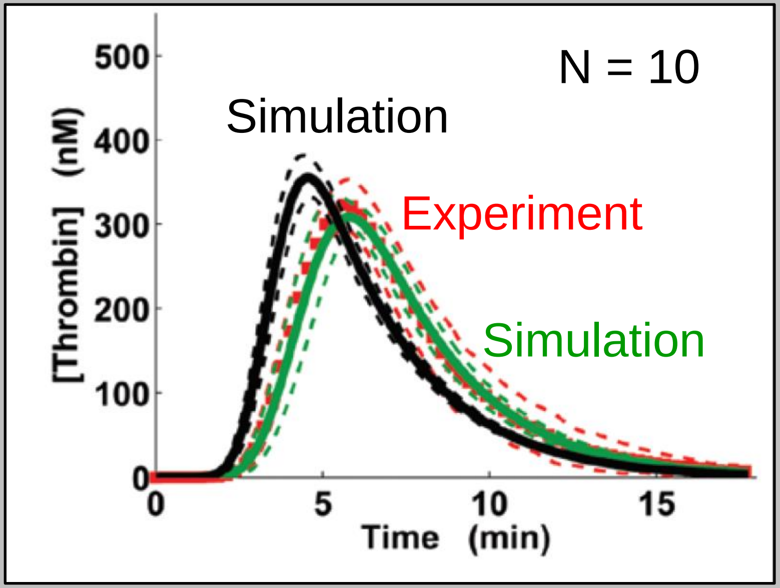
Learning

Comparison: validation



Simulations can reproduce experimental results

Undiluted plasma



Mitrophanov et al., *Anesth Analg* (2016)

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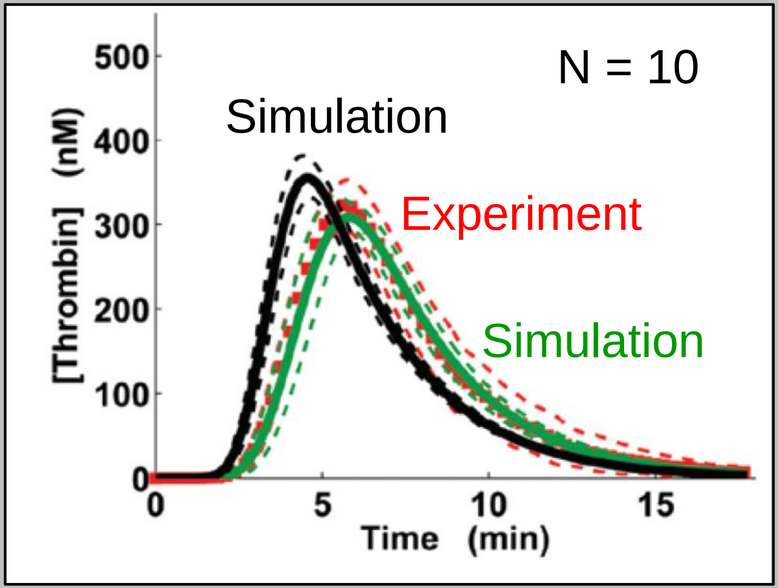
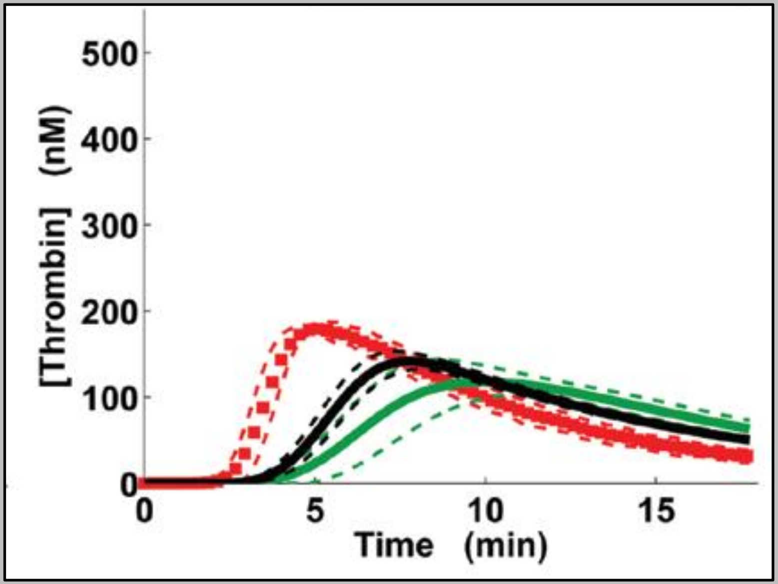
Undiluted plasma



3-fold dilution

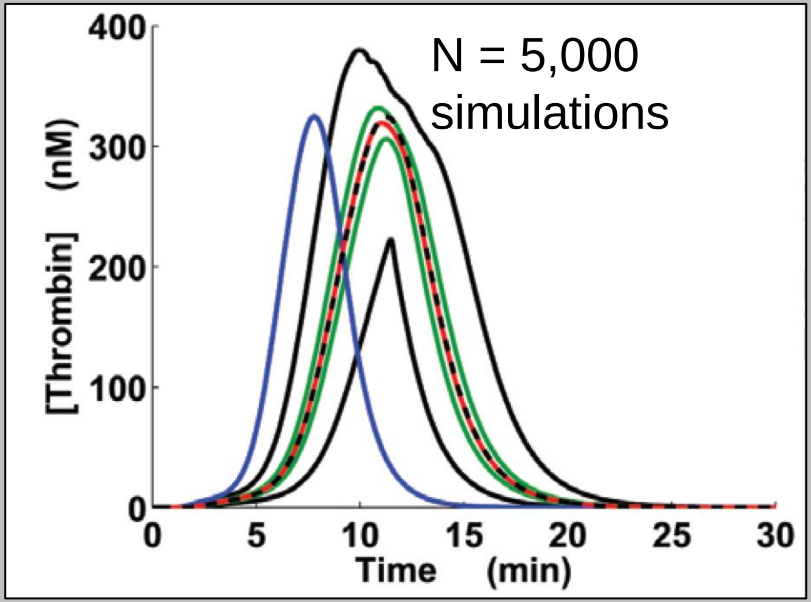


Dilution reduces peak height

Mitrophanov et al., *Anesth Analg* (2016)

Hypothermia: simulated effects for the "average" subject

Hypothermia at 33 ºC

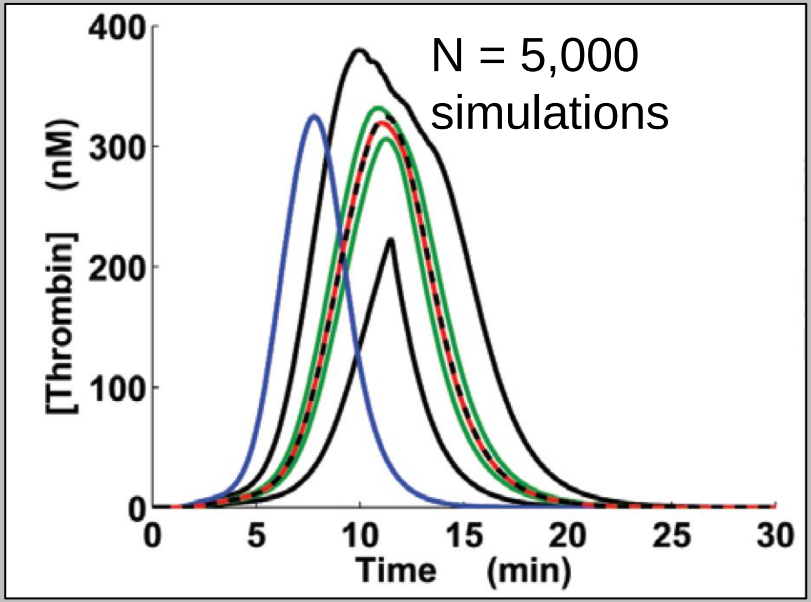


37 ºC (normal) prediction
33 ºC prediction range
33 ºC prediction quartiles
33 ºC prediction median

Mitrophanov et al., *Anesth Analg* (2013)

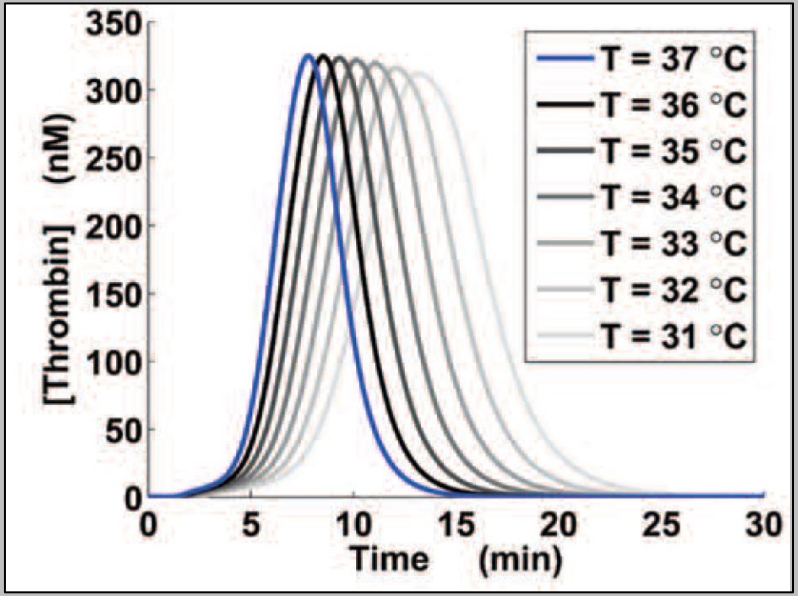
Hypothermia: simulated effects for the "average" subject

Hypothermia at 33 ºC



37 ºC (normal) prediction
33 ºC prediction range
33 ºC prediction quartiles
33 ºC prediction median

Varied temperature

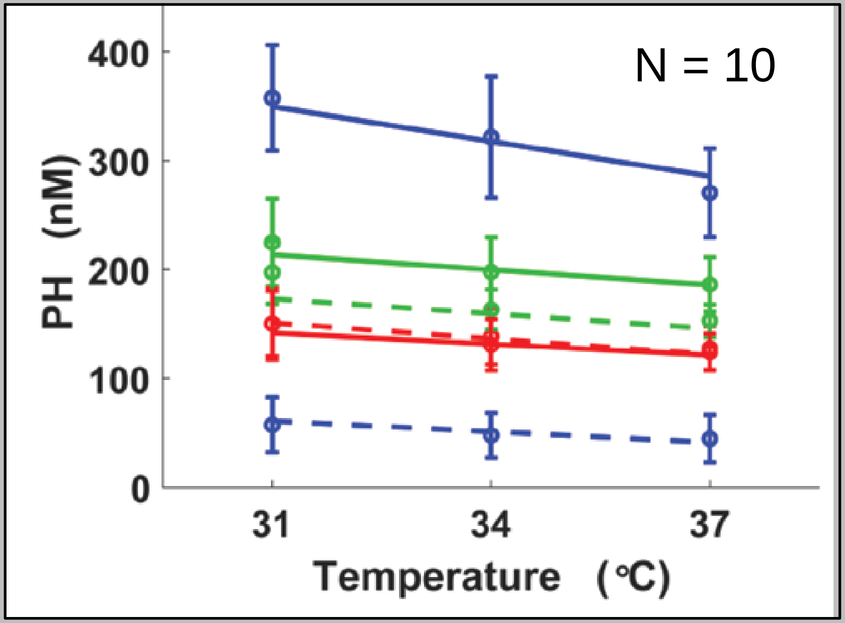


Peak height practically unchanged

Mitrophanov et al., *Anesth Analg* (2013)

Hypothermia: experimental validation

Thrombin peak height

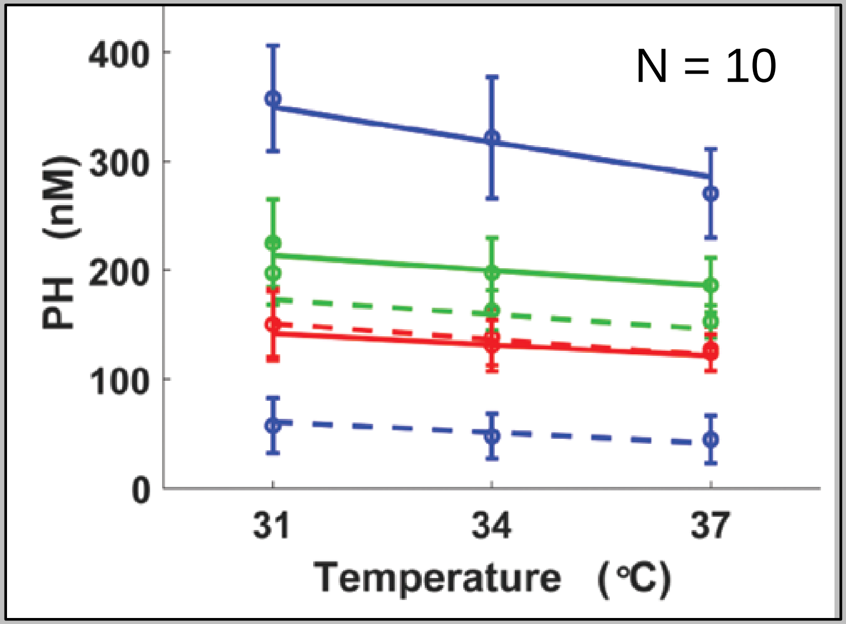


Undiluted 3-fold dilution 5-fold dilution
Dashed: 15 nM thrombomodulin

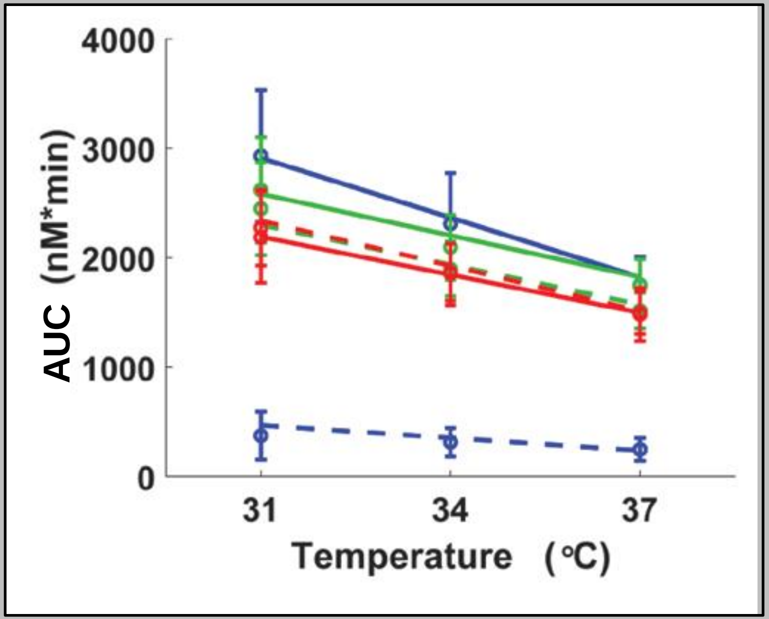
Mitrophanov et al., *Anesth Analg* (2020)

Hypothermia: experimental validation

Thrombin peak height



Area under the curve



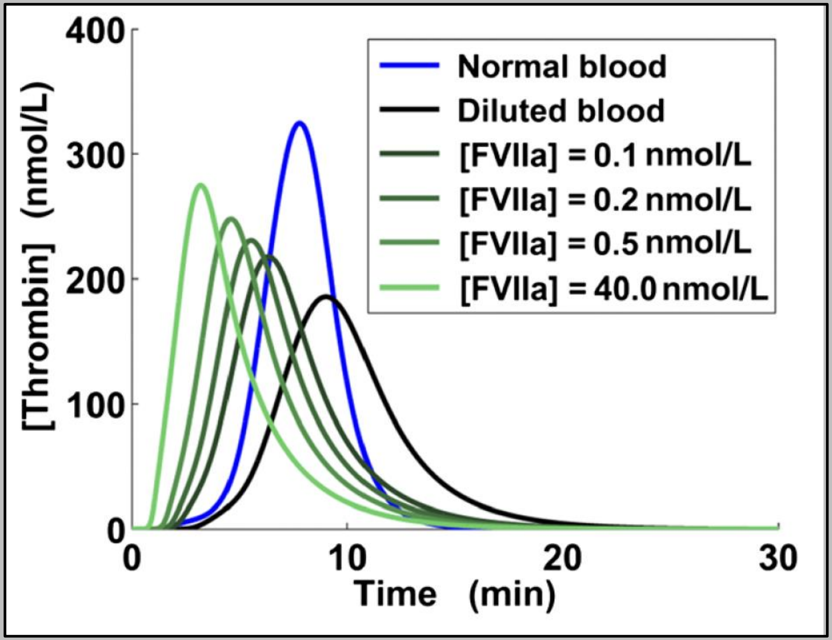
Undiluted 3-fold dilution 5-fold dilution
Dashed: 15 nM thrombomodulin

Hypothermia inhibits anticoagulant mechanisms

Mitrophanov et al., *Anesth Analg* (2020)

FVIIa supplementation skews thrombin generation

Simulations for the "average" subject*



(r)FVIIa = (recombinant) activated Factor VII

*Mitrophanov et al., *J Trauma* (2012)

FVIIa supplementation skews thrombin generation

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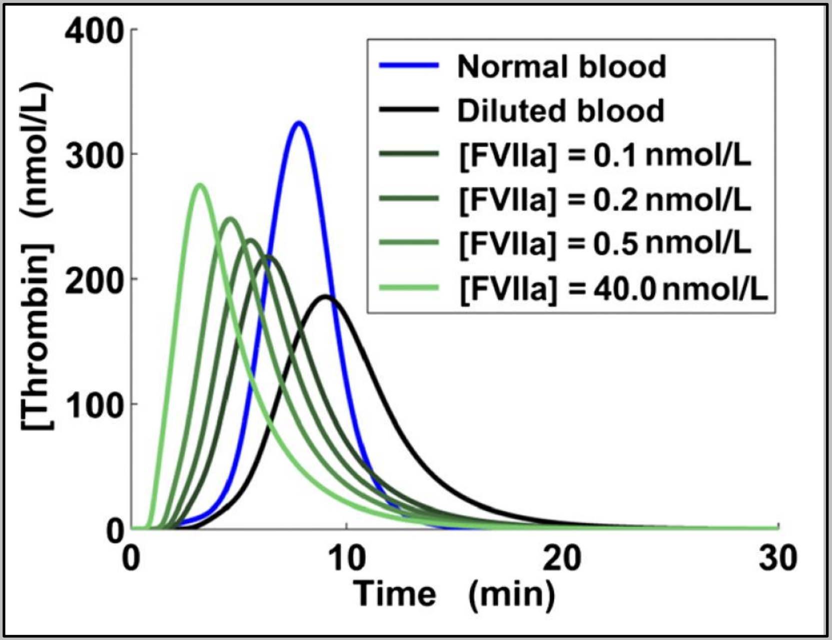
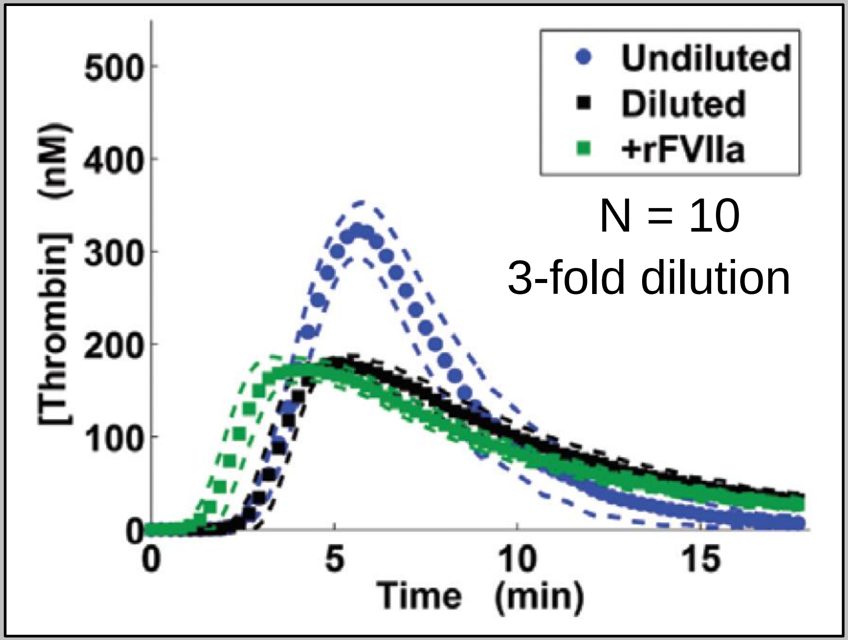


Experimental data**



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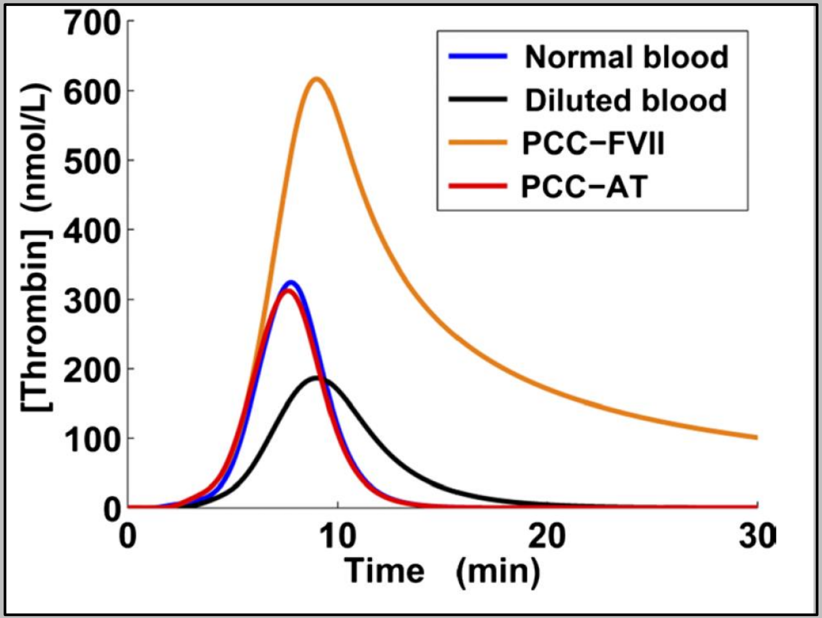
*Mitrophanov et al., *J Trauma* (2012)

**Mitrophanov et al., *Anesth Analg* (2016)

PCC-AT: thrombin-generation normalization

Simulations for the “average” subject*



(r)FVIIa	= (recombinant) activated Factor VII
PCC-FVII	= FII + FIX + FX + FVII
PCC-AT	= FII + FIX + FX + antithrombin (AT)

*Mitrophanov et al., *J Trauma* (2012)

PCC-AT: thrombin-generation normalization

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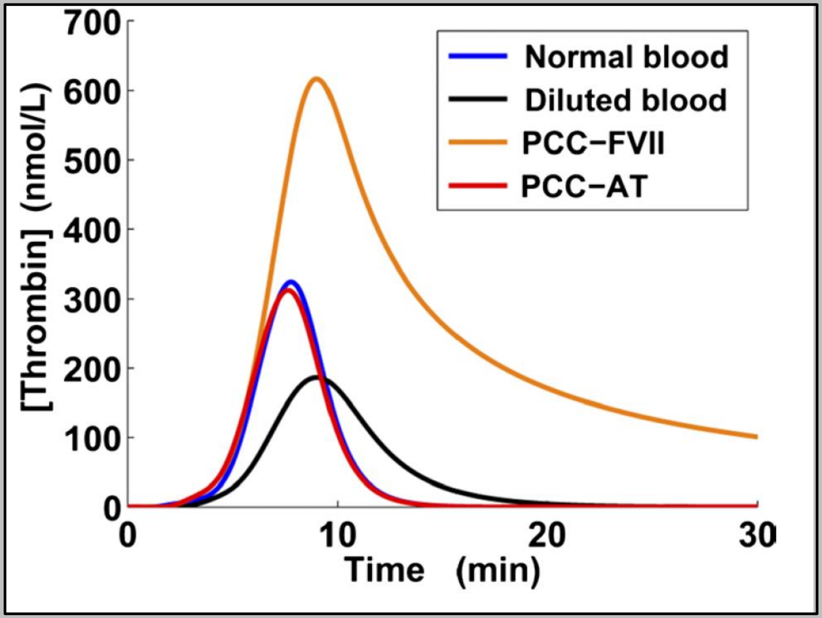

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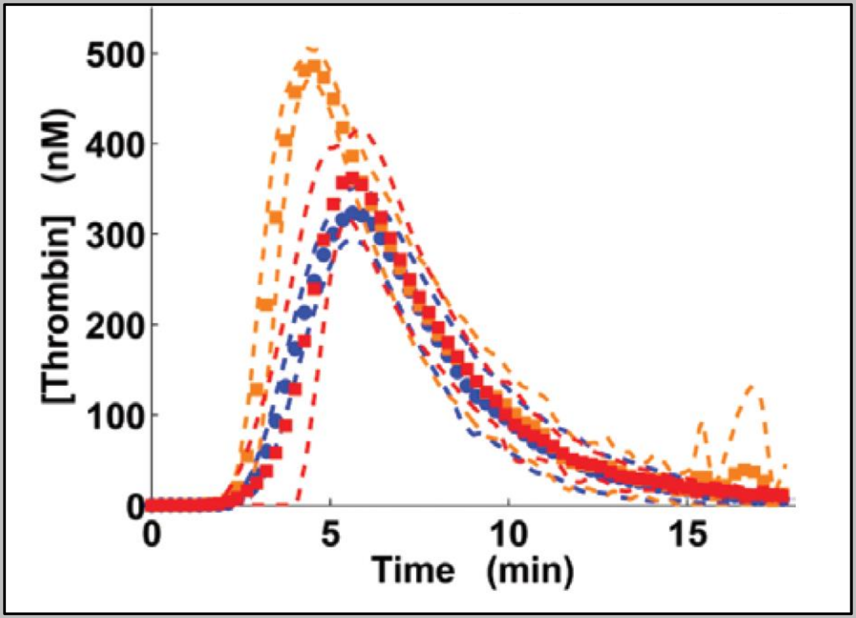

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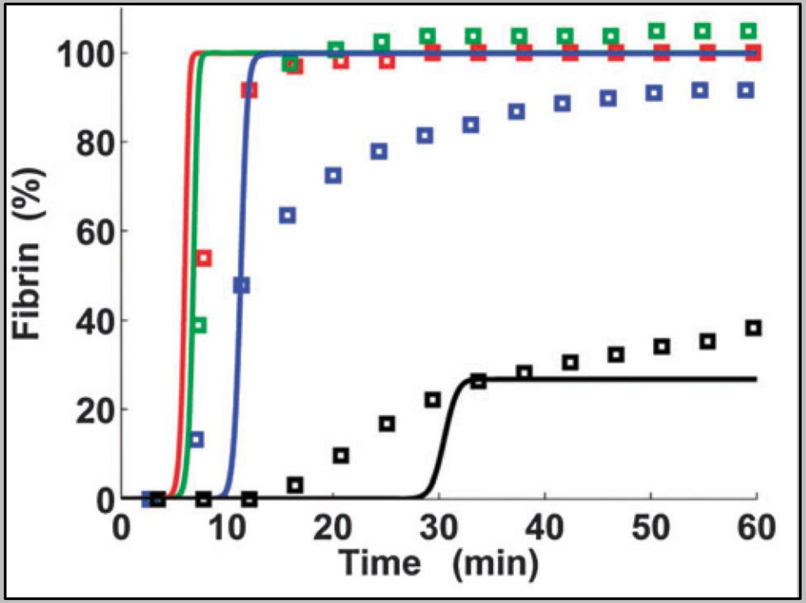
*Mitrophanov et al., *J Trauma* (2012) **Mitrophanov et al., *Anesth Analg* (2016)

Fibrin generation: simulations and validation

Prothrombin titration



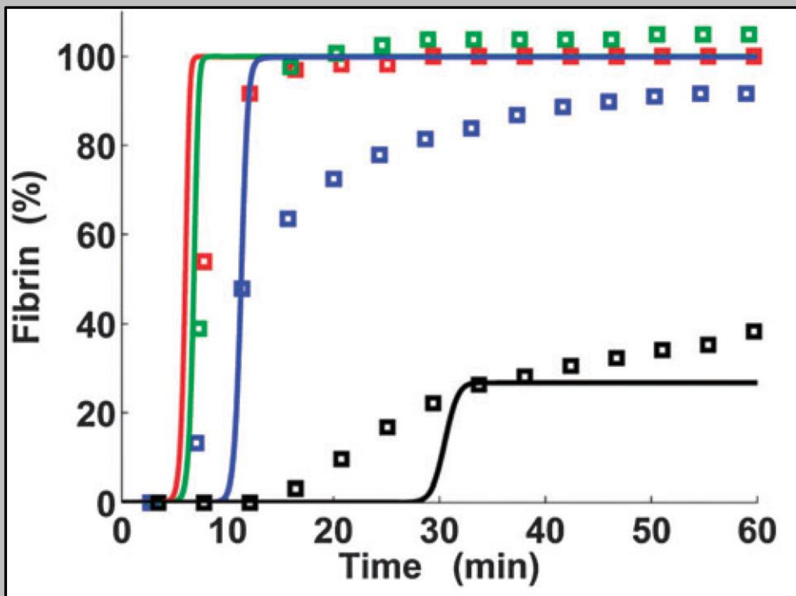
Lines: model simulations **Squares:** experimental data

prothrombin → thrombin fibrinogen
fibrin → blood clot

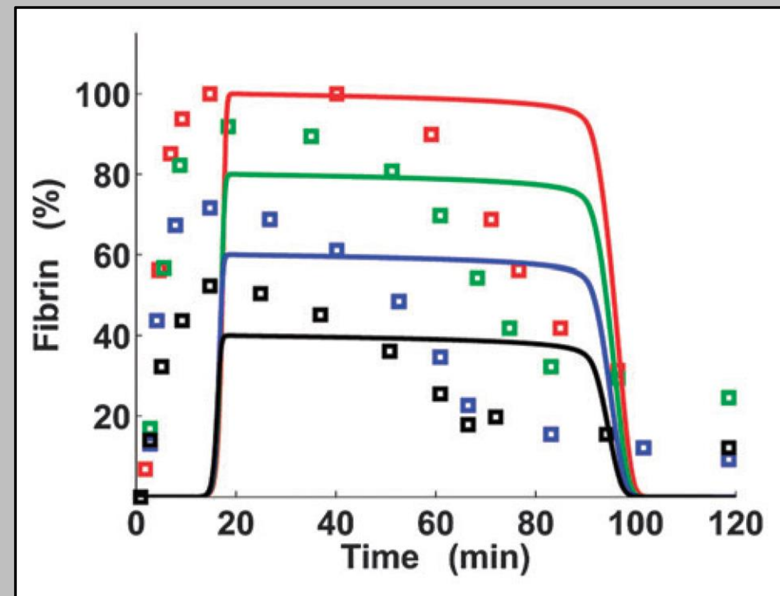
Mitrophanov et al., *Mol BioSyst* (2014)

Fibrin generation: simulations and validation

Prothrombin titration



Fibrinogen titration



Lines: model simulations **Squares:** experimental data

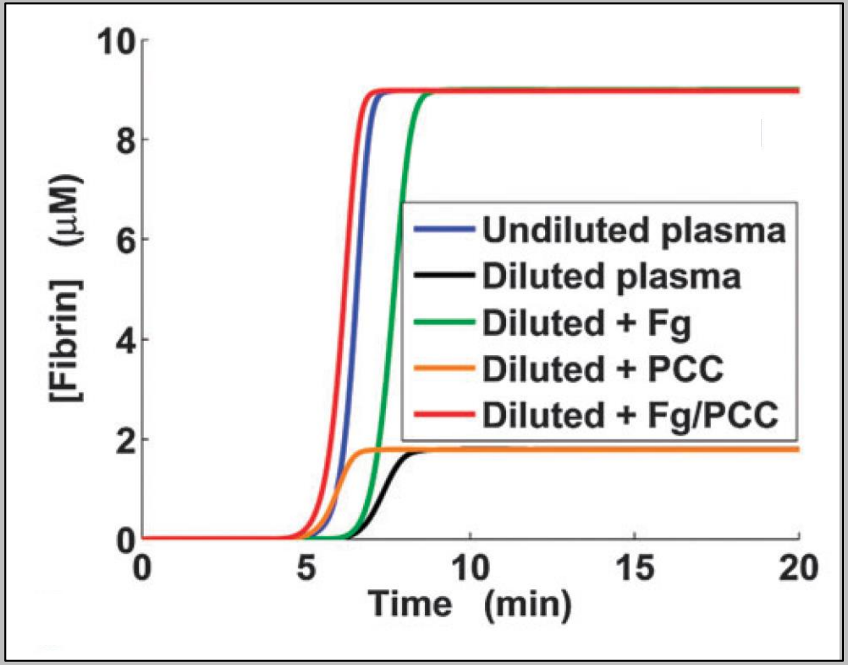
prothrombin → thrombin (fibrinogen
fibrin → blood clot

Mitrophanov et al., *Mol BioSyst* (2014)

Fibrinogen (Fg) + PCC-AT restore normal thrombin and fibrin generation in diluted plasma

Model simulations for the "average" subject

Fibrin



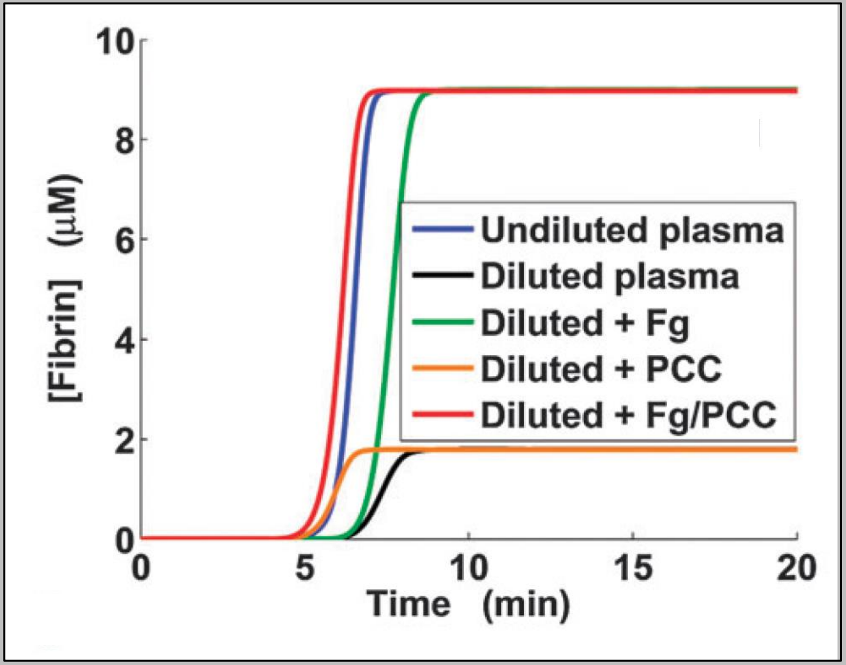
Dilution: 3-fold

Mitrophanov et al., *Mol BioSyst* (2014)

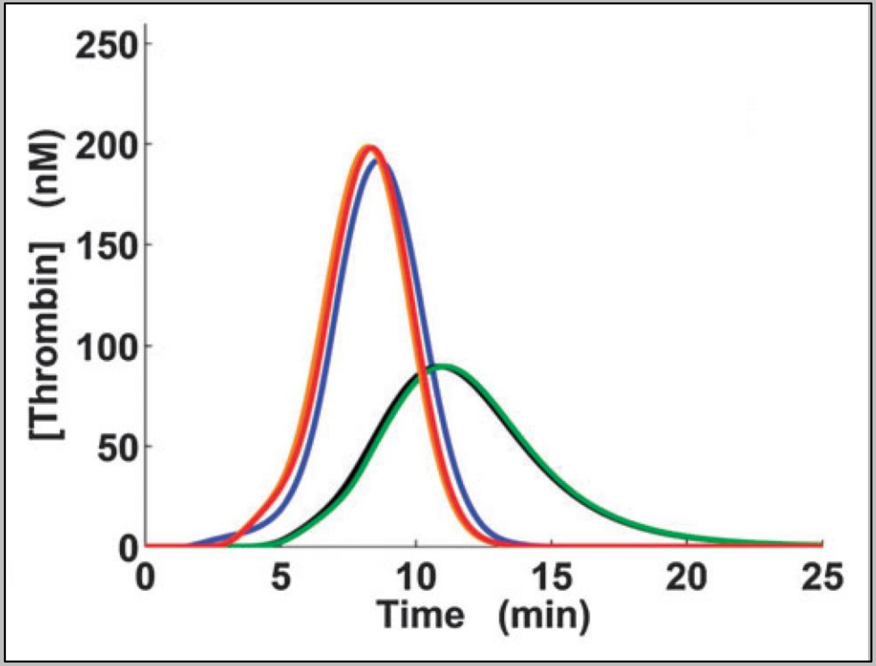
Fibrinogen (Fg) + PCC-AT restore normal thrombin and fibrin generation in diluted plasma

Model simulations for the “average” subject

Fibrin



Thrombin

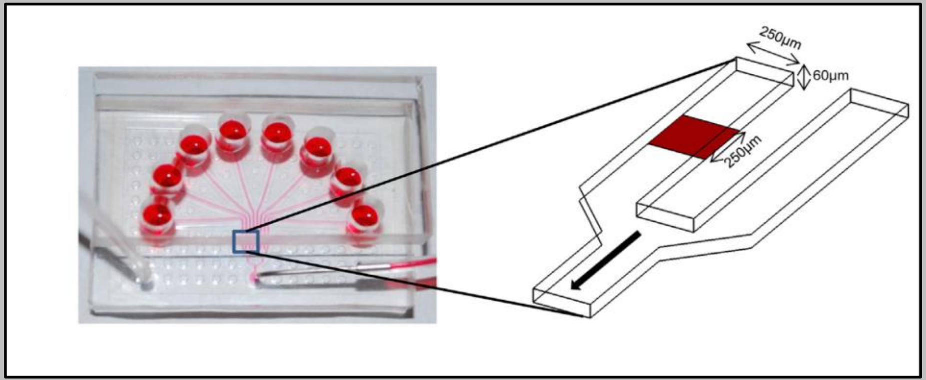


Dilution: 3-fold

Mitrophanov et al., *Mol BioSyst* (2014)

Adding flow: whole blood *in vitro*

Microfluidic device



Govindarajan et al., *Biophys J* (2016)

Adding flow: whole blood *in vitro*

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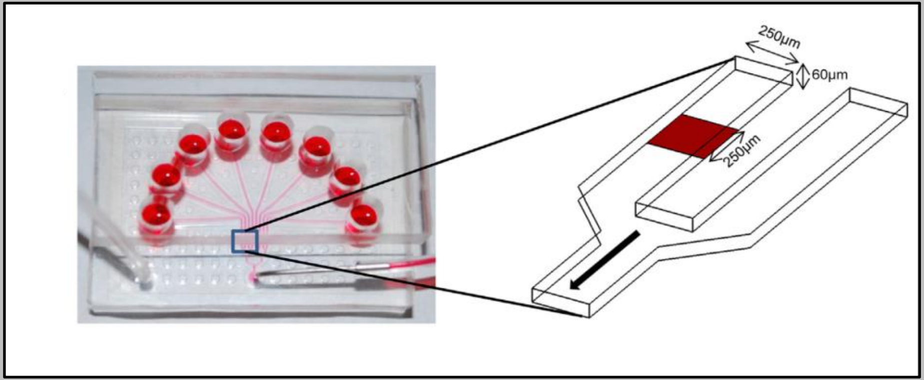
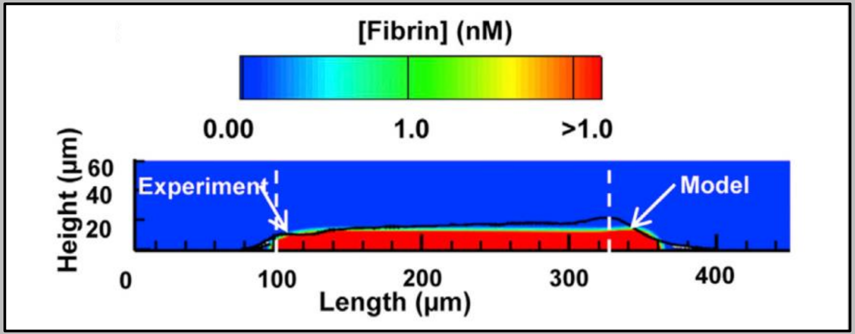


Fibrin generation: simulation and experiment

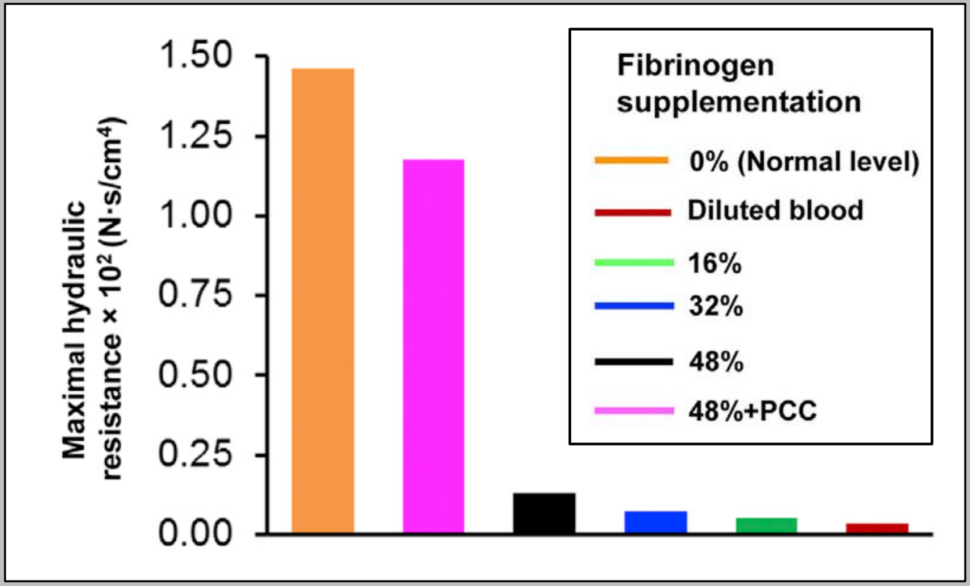


Platelet deposition: similar

Govindarajan et al., *Biophys J* (2016)

Coagulation factors + fibrinogen enhance coagulation in diluted blood

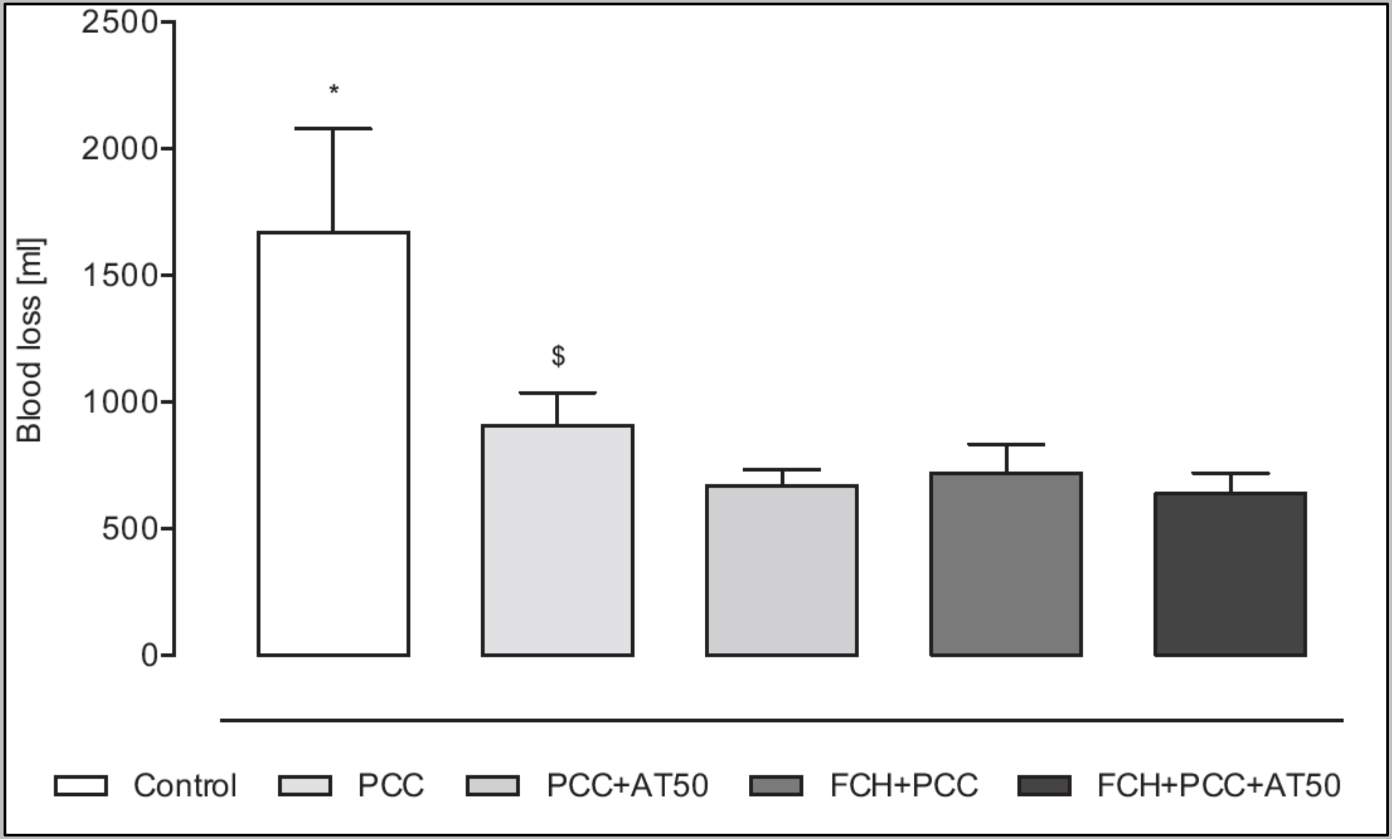
Clot resistance to flow
(the flow slows down accordingly)



PCC = FII + FIX + FX

Govindarajan et al., *Biophys J* (2016)

Antithrombin improves PCC effects in a porcine model of traumatic coagulopathy



Grottke et al., *Anesthesiology* (2019)

CONCLUSIONS

- Computational modeling can effectively guide experimentation in blood-coagulation research

- Thrombin generation may be normalized by a few pro/anti-coagulant factors (**balanced intervention**)

- Additional supplementation of fibrinogen may be useful

ACKNOWLEDGEMENTS

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