Credibility Plan: Multiscale Analysis of Trauma



Evan Tsiklidis¹, Christopher Verni¹, Jason Chen¹, Jifu Tan², Yannis Kevrekidis³, Carrie Sims⁴, Talid Sinno¹, Scott L. Diamond¹

¹Chemical and Biomolecular Engineering (Penn), ³Northern Illinois University, ³Chemical Engineering (Princeton), ⁴Dept. of Trauma Surgery (Penn)

University of Pennsylvania, Philadelphia, PA 19104, USA. NIH U01-HL-131053

Componer	nt and Scale	Credibility	Reusability
Platelet	Signaling		
NN (Machine Learning)		Neural Network Available online	Matlab code available (www.seas.upenn.edu/~diamond/software.html)
A convulxin U46619 thrombin ADP iloprost GSNO $GPVI TP PAR1 PAR4 P2Y_1 P2Y_2 IP$ $Syk G_{G} RGS G_{i} G_{s} NO$ $PLC_{i} PLC_{i} AC GC$	Input Signal ADP CVX Thrombin CVX	Distribution with N-patients	In Progress
$\begin{array}{c} \hline P_{3} \\ \hline Ca^{2+} \\ \hline SERCA \\ \hline Stim1 \\ \hline Ca^{2+} \\ \hline Ca^$	U46619 Iloprost GSNO GSNO Time Signal feedback	U46619 INDIFICATION Signal feedback Network for Healthy Control Population Matlab Code / Lee et.al.	Matlab Code / Lee et.al, PLOS Computational Biology, 2015
Clotting in Flow			

Microfluidic Tests	Data Posted Online	Excel file
	Distribution with N-patients	Li et.al, J. Trauma, 2016
Clot-Flow Simulation		
Hypothesis Generation	Soluble Fibrin inhibits GPVI	Verni et,al. J. Thombosis. Haemostasis, 2017
$fbg \xrightarrow{ }{ }} fbg \xrightarrow{ }{ }} (Collagen \\ CVX, CRP \\ (VX, CRP \\$	New Hypothesis (DD blocks GPVI)	
Full Simulation	New Hypothesis (TF/tPA blocks GPVI)	
	Test against n-patients -> distribution	Lu et.al, Math.Med.Bio, 2016
	LB/NN/FEM/LKMC	Code available (www.seas.upenn.edu/~diamond/software.html

In vivo hemodynamics

Patient scale (m) \longrightarrow tissue (mm to cm) \longrightarrow single vessel (sub-mm) \longrightarrow cellular (μ M) Transfusion Products, vasopressors, clotting modulators Pulmonary "Damaged Vessel" "Healthy Vessel" —–II-w~ Peripheral Circulation Right Atrium Right Ventricle $P_{sys}(t)$ Left Atrium Left Ventric Systemic Circulation Splanchnic venous Splanchnic arteri Extra splanchnic Extra splanchnic P_{ATM} venous arterial Muscle venous Muscle arteria

T=300 T=400 T=0 T=200 T=100

Clot Mechanics

Project: Multiscale Analysis of Trauma U01-HL-131053, Start date: 5/01/2016, PI: Diamond SL (Univ. Penn.) **Context:** Help predict (a) risk, (b) optimized therapeutic choices, and (c) outcomes for traumatic bleeding by use of: blood biology diagnostics, hemodynamic readouts, and clinical/research data. Intended audience: Trauma Surgeons, Anesthesiologists, Medical Informaticists, Transfusion Units. Credibility Plan: Calibration with 50 well annotated trauma patients (Penn). Prediction of trauma trajectories for other trauma patient trials (eg. TACTIC consortium). Timeline and Milestones (*Code/data publically released):

Model selection across scales	Tsiklidis et,al. Wires System Bio, 2018 In Progress	
Define Unregulated Bleeding Space		
Epic Data Sets	In Progress	
Validate for 2-phase blood viscosity	Code Posted (Palabos/LAMMPS)	
Mechanism of shear induced NETosis	Tan et,al. J. Comp. Sci, 2018	
Hypothesis generation : shear induced NETs	Yu et,al. J. Thrombosis. Haemostasis, 2018	

Platelet NN model* (calibrated to 10 heathy donors) - PLoS Comp Biol.

- Clotting simulations* (calibrated against 3 drugs) Math. Med. Biol.
- Trauma blood testing and Hypothesis Generation J. Trauma, J. Thromb. Haem. Cell/Clot deformation model (Palabos/LAMMPS)* - J. Comp. Sci.
- Model selection WIRES Sys. Biol.
- NETosis model* J. Thromb. Haem
- Mouse penetrating injury data for model testing-J. Thromb. Haem. TF->thromb->Fibrin microfluidic data for model testing-J. Biol. Chem.
- Challenges: Annotating extracted EPIC data and anesthesiology record

Validate core-shell structure under flow



Validate clot deformation under flow

