Multiscale Analysis of Trauma

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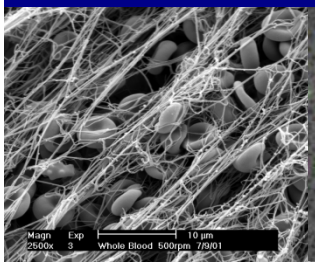

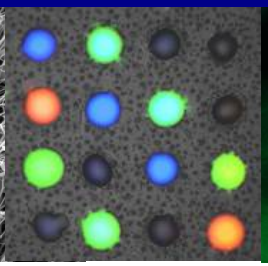

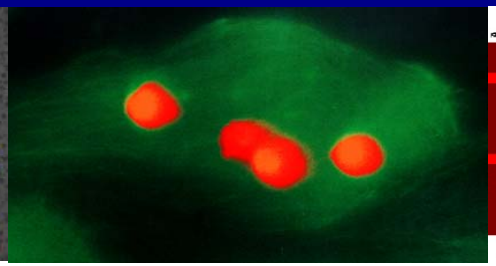

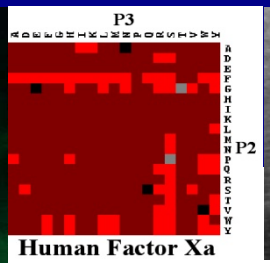

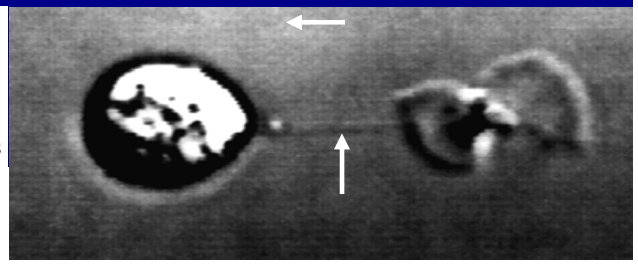

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PENN CENTER FOR MOLECULAR DISCOVERY

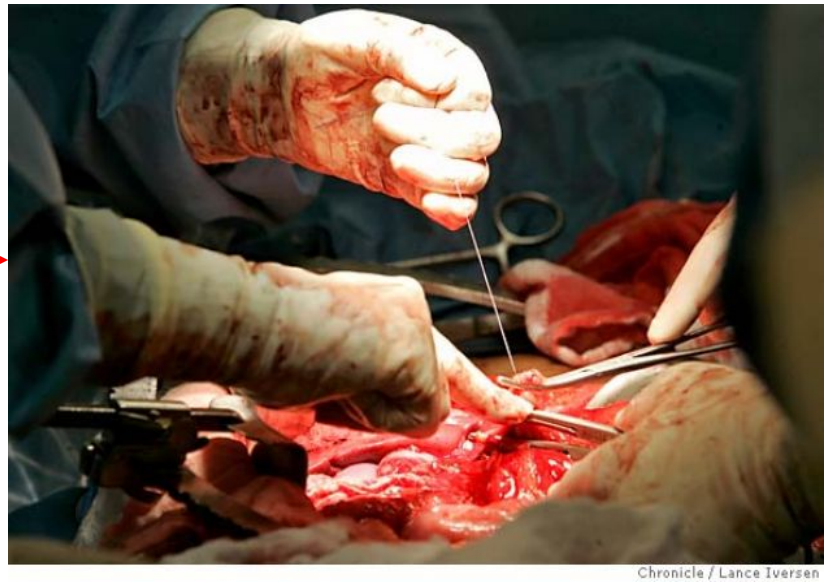
Penn Engineering

blood systems biology

Trauma Induced Coagulopathy (TIC)

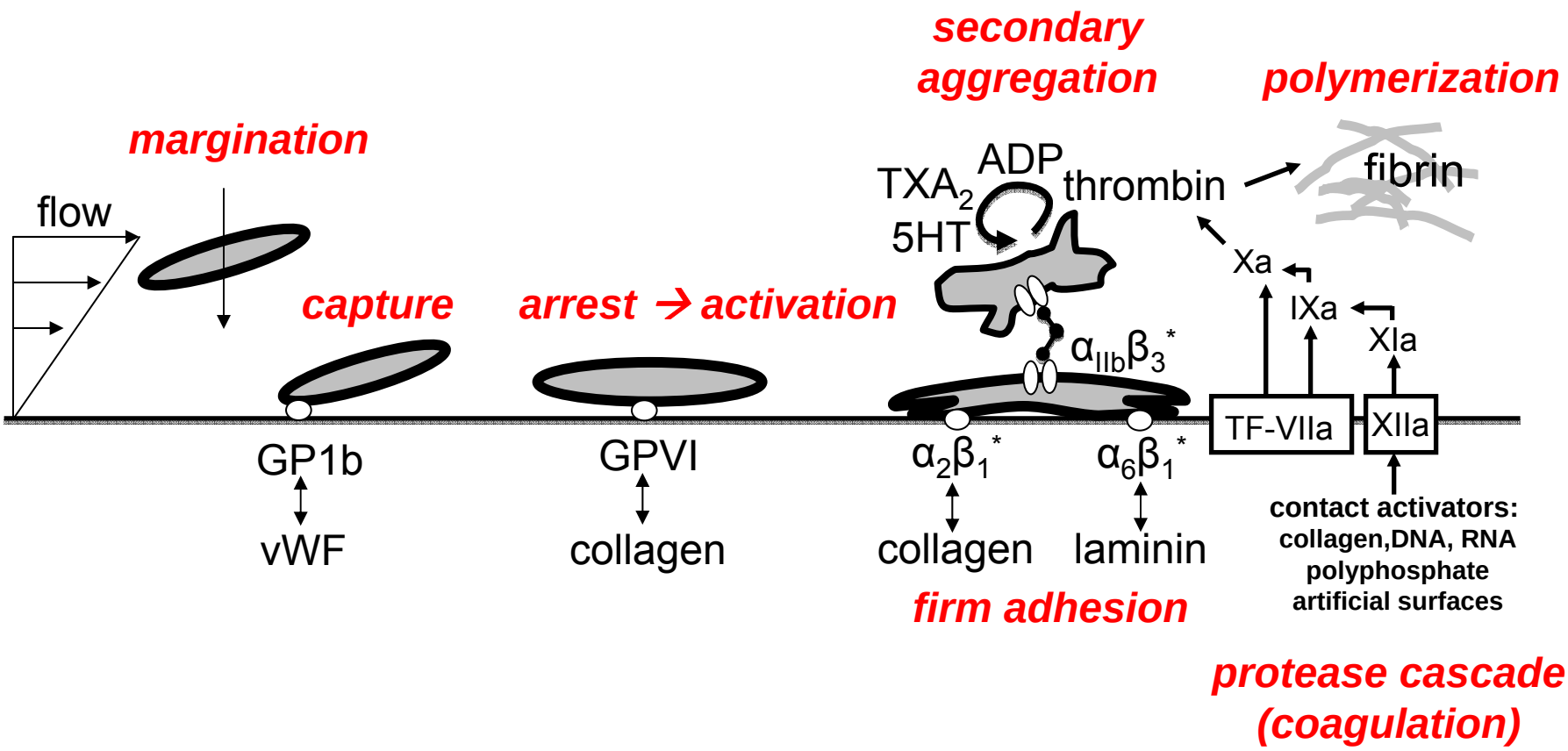
Predicting when and why certain patients bleed and what to do before its too late…

tanks, pipes, pumps, reactions, leaks

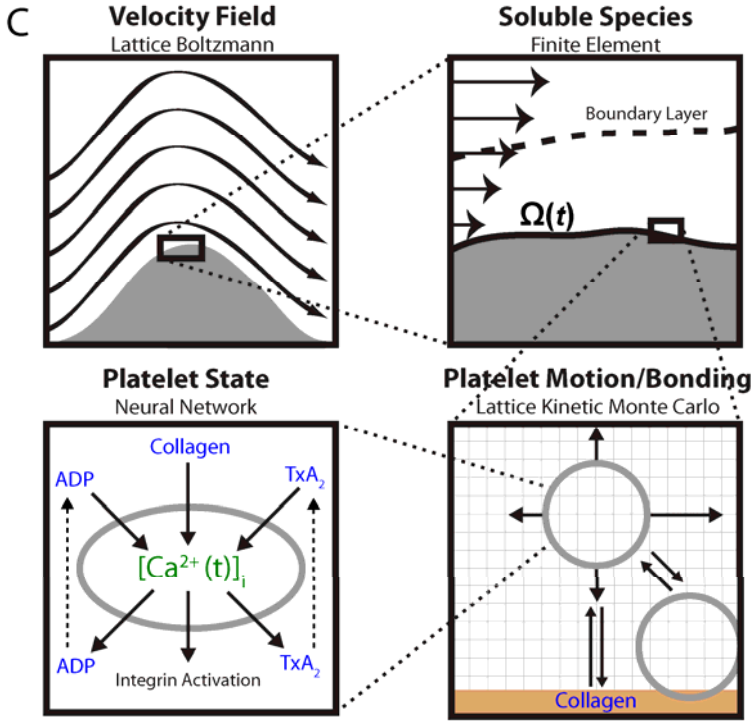


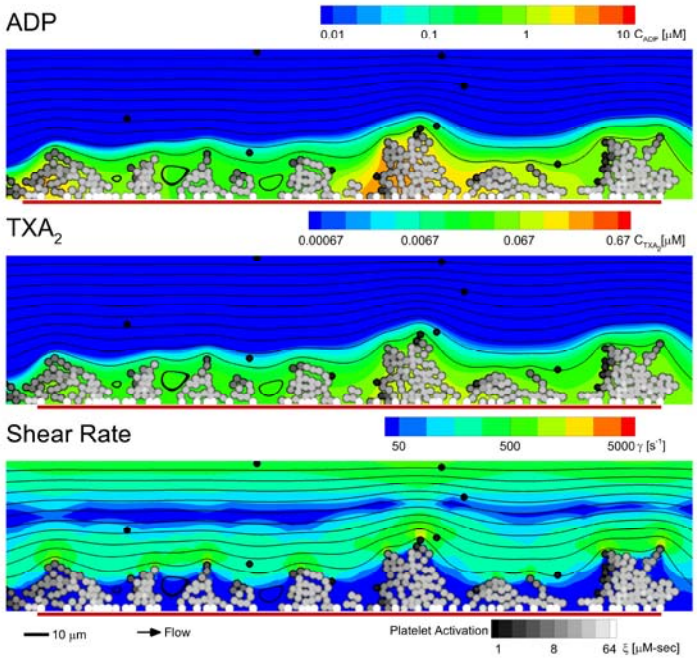
trauma patient

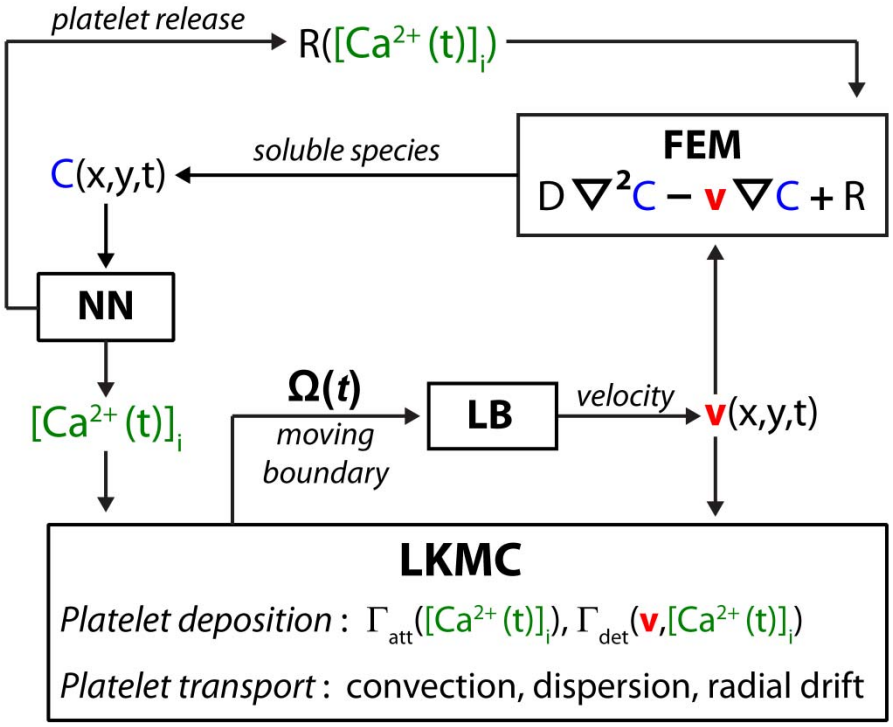
Platelet function during thrombosis and hemostasis



Colace et al. *Annual Reviews* 2013
Diamond SL. *Circ. Res*. 2016
Brass & Diamond. *JTH* 2016







Flamm et al. *J. Chem. Phys.* (2009)

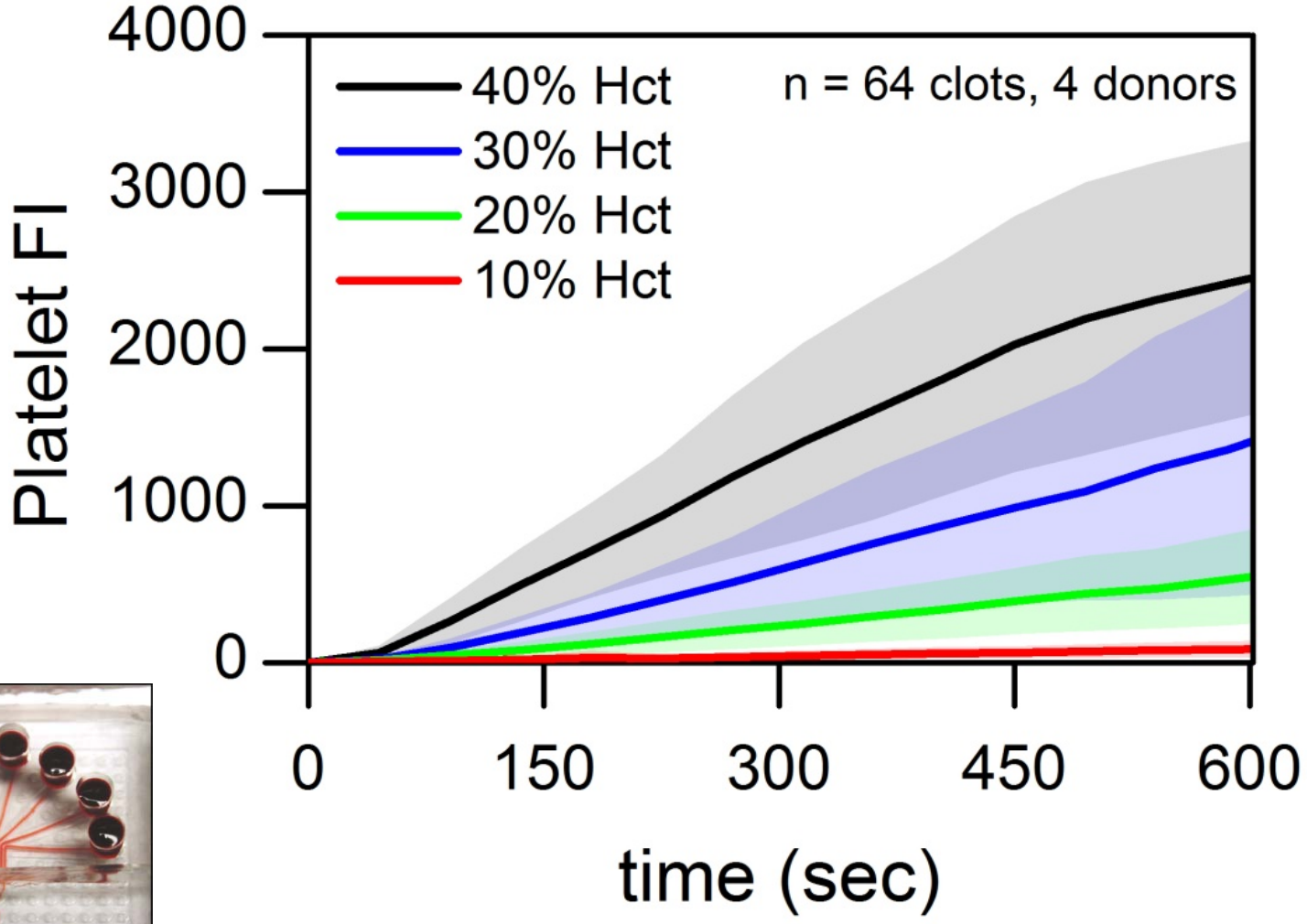
Flamm et al. *J. Chem. Phys.* (2011)

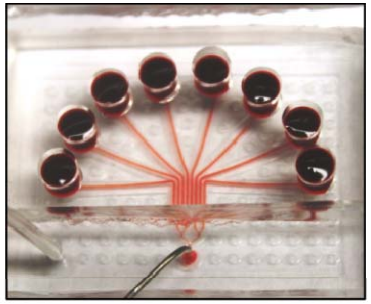
Flamm et al. *Blood* (2012)

Lee et al. *PLoS Comp. Biol* (2014).

Lu et al. *Math Med Biol.* (2016)

Dilution of whole blood with PRP decreases platelet deposition on collagen





100 µM PPACK, 200 s^{-1}

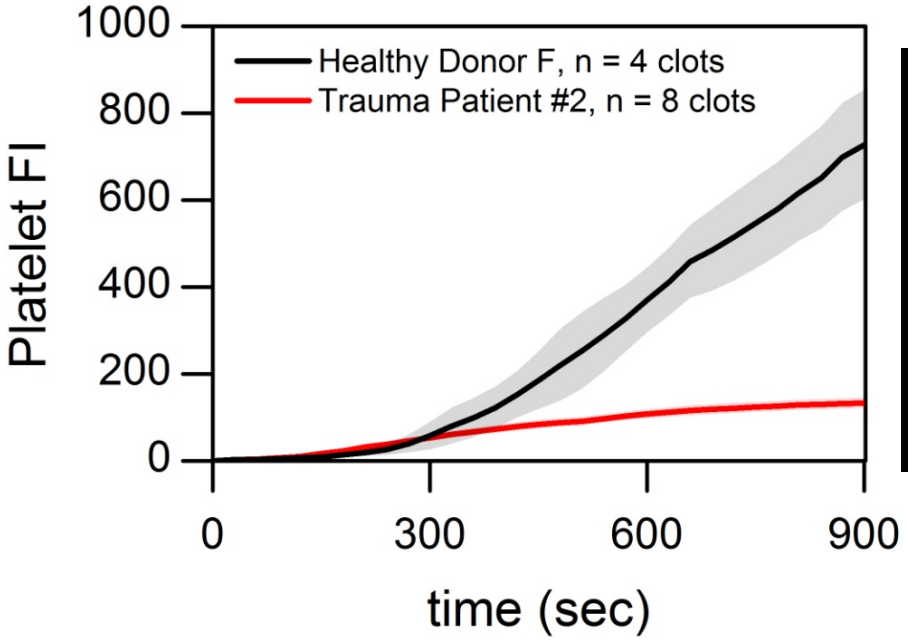
collagen (no thrombin/fibrin)

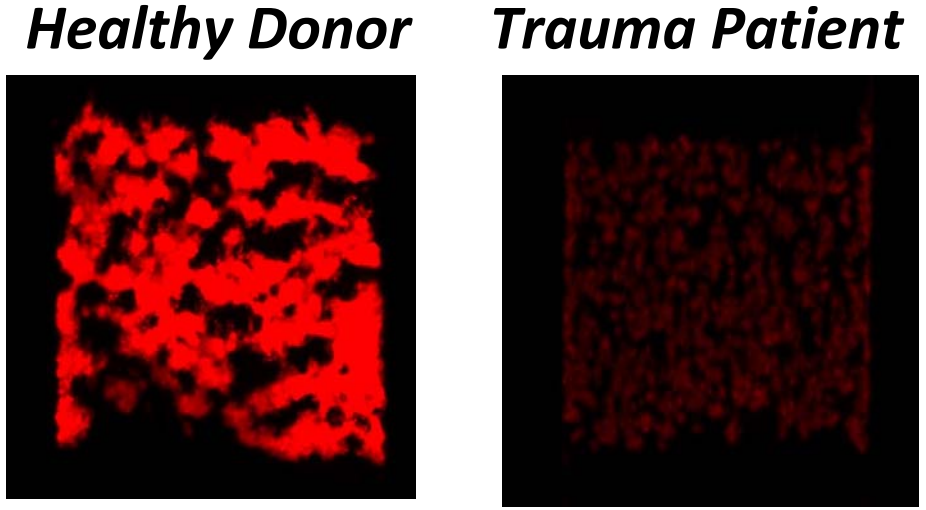
Li et al. J. Trauma (2016)

Platelet defect in trauma

Trauma patient platelet and coag function:

Dr. Carrie A. Sims, Emergency Medicine (HUP)



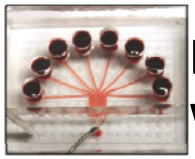


clot @ t = 15 min

Recalcified citrated whole blood, 100 s^{-1} , collagen type I

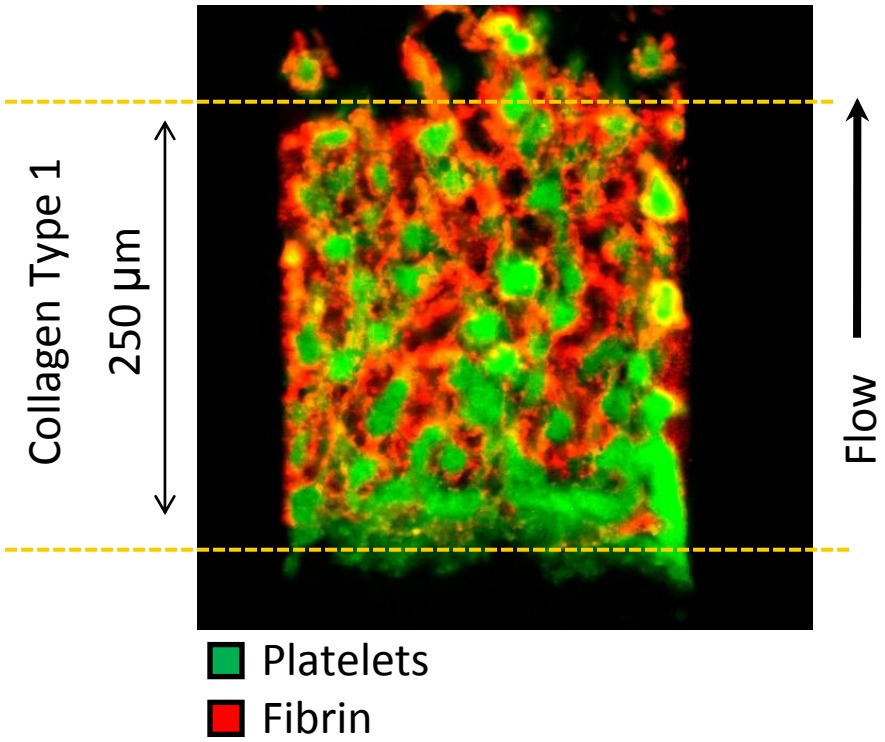
7.5 mM Ca^{2+}, 100 µM PPACK

Hemophilic Bleeding



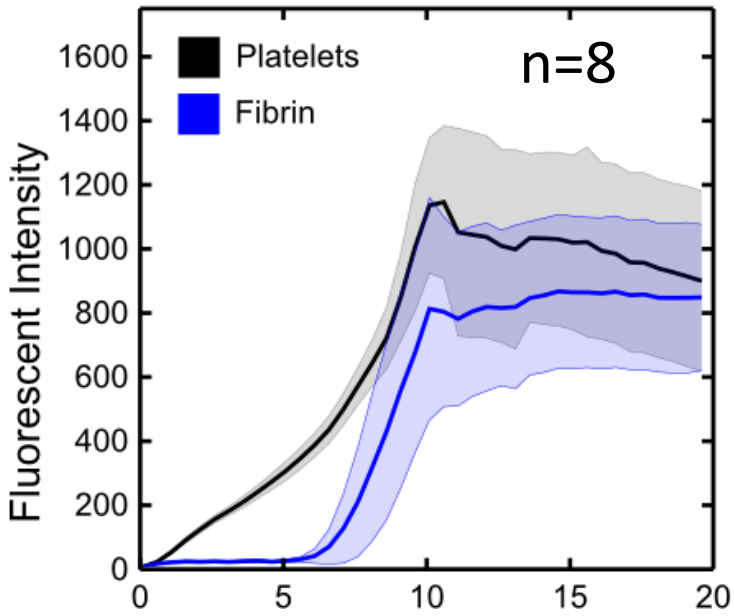
Healthy/Patient Donor (4 µg/mL CTI)
Wall shear rate (100 s^{-1})

Healthy donor

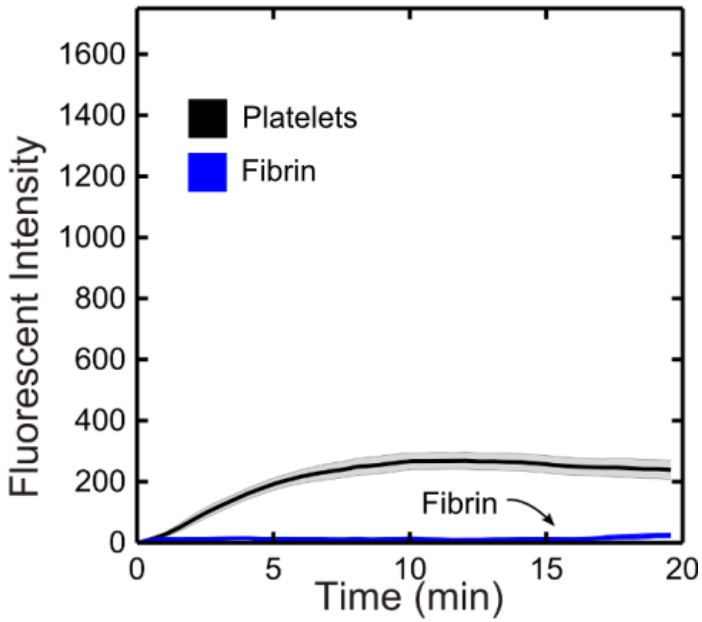


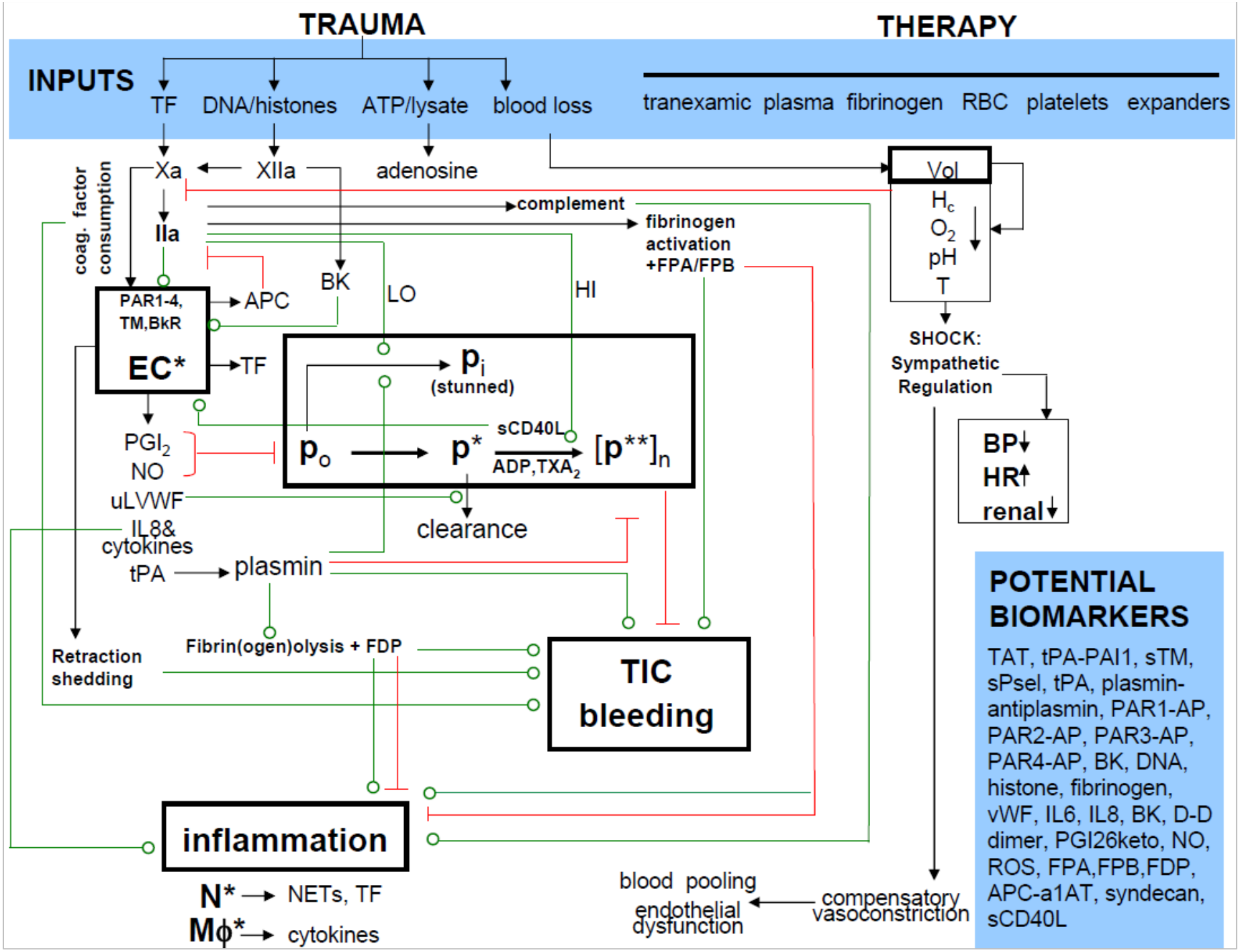
Colace et al. J. Thromb. Haem. (2013)

Healthy Donor

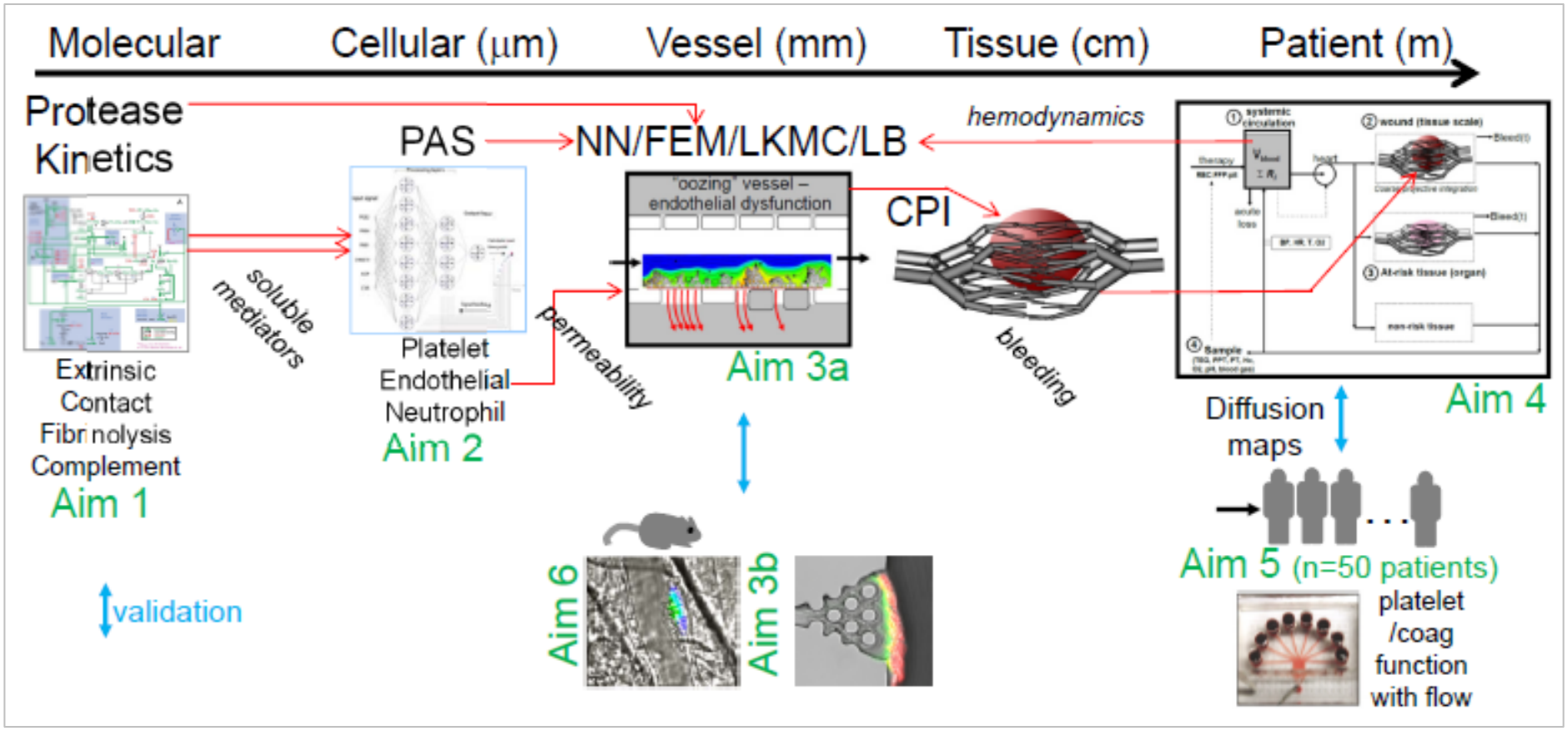


Severe Hemophilia A

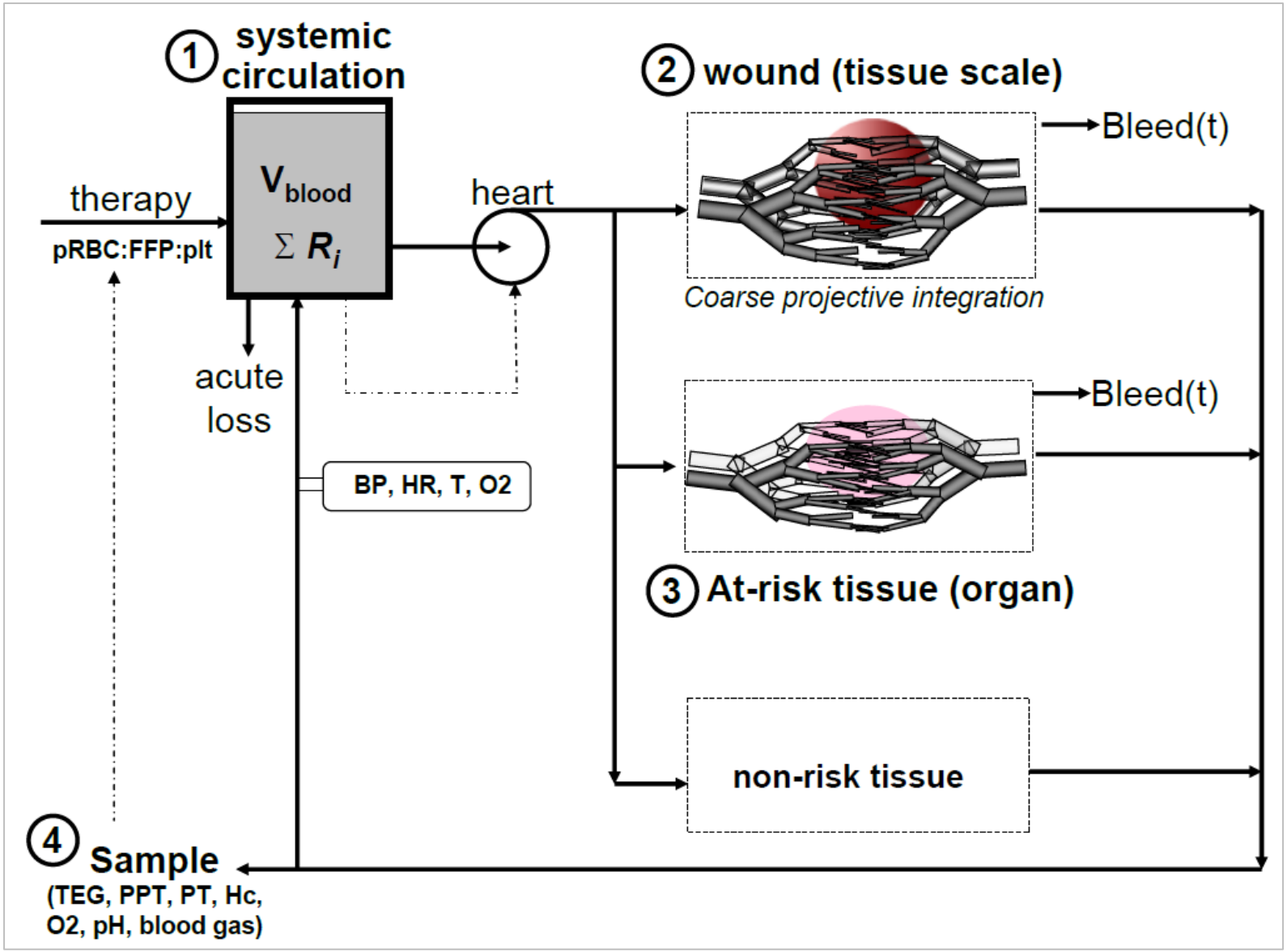



TRAUMA
THERAPY
INPUTS
TF
DNA/histones
ATP/lysate
blood loss
tranexamic
plasma
fibrinogen
RBC
platelets
expanders
Xa
XIIa
adenosine
Vol
Hc
O2
pH
T
coag. factor consumption
complement
fibrinogen activation +FPA/FPB
IIa
BK
LO
HI
PAR1-4, TM,BkR
APC
EC*
TF
pi
(stunned)
po
p*
sCD40L
ADP,TXA2
[p**]n
PGI2
NO
uLVWF
IL8& cytokines
tPA
plasmin
clearance
SHOCK:
Sympathetic Regulation
BP↓
HR↑
renal↓
Retraction shedding
Fibrin(ogen)olysis + FDP
TIC
bleeding
inflammation
N* → NETs, TF
Mϕ* → cytokines
blood pooling
endothelial dysfunction
compensatory vasoconstriction
POTENTIAL BIOMARKERS
TAT, tPA-PAI1, sTM, sPsel, tPA, plasmin-antiplasmin, PAR1-AP, PAR2-AP, PAR3-AP, PAR4-AP, BK, DNA, histone, fibrinogen, vWF, IL6, IL8, BK, D-D dimer, PGI26keto, NO, ROS, FPA,FPB,FDP, APC-a1AT, syndecan, sCD40L

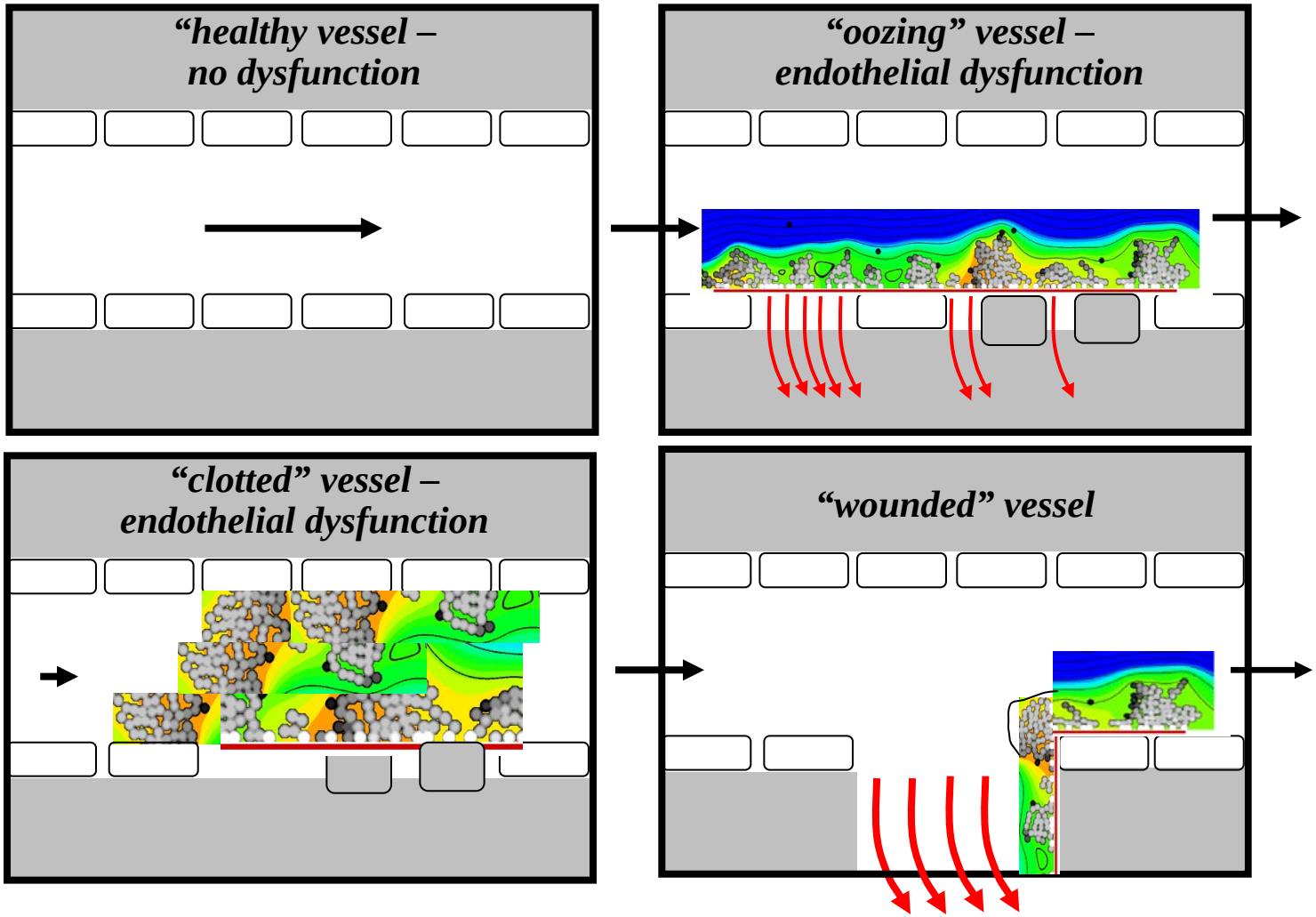
Multiscale Analysis of Trauma



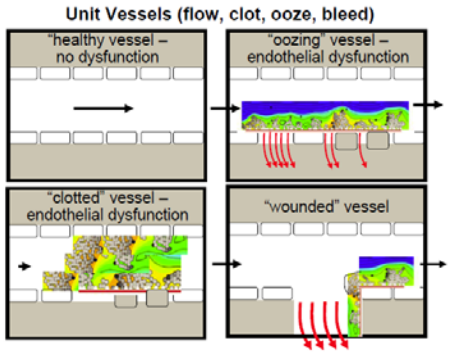
Multiscale Analysis of Trauma

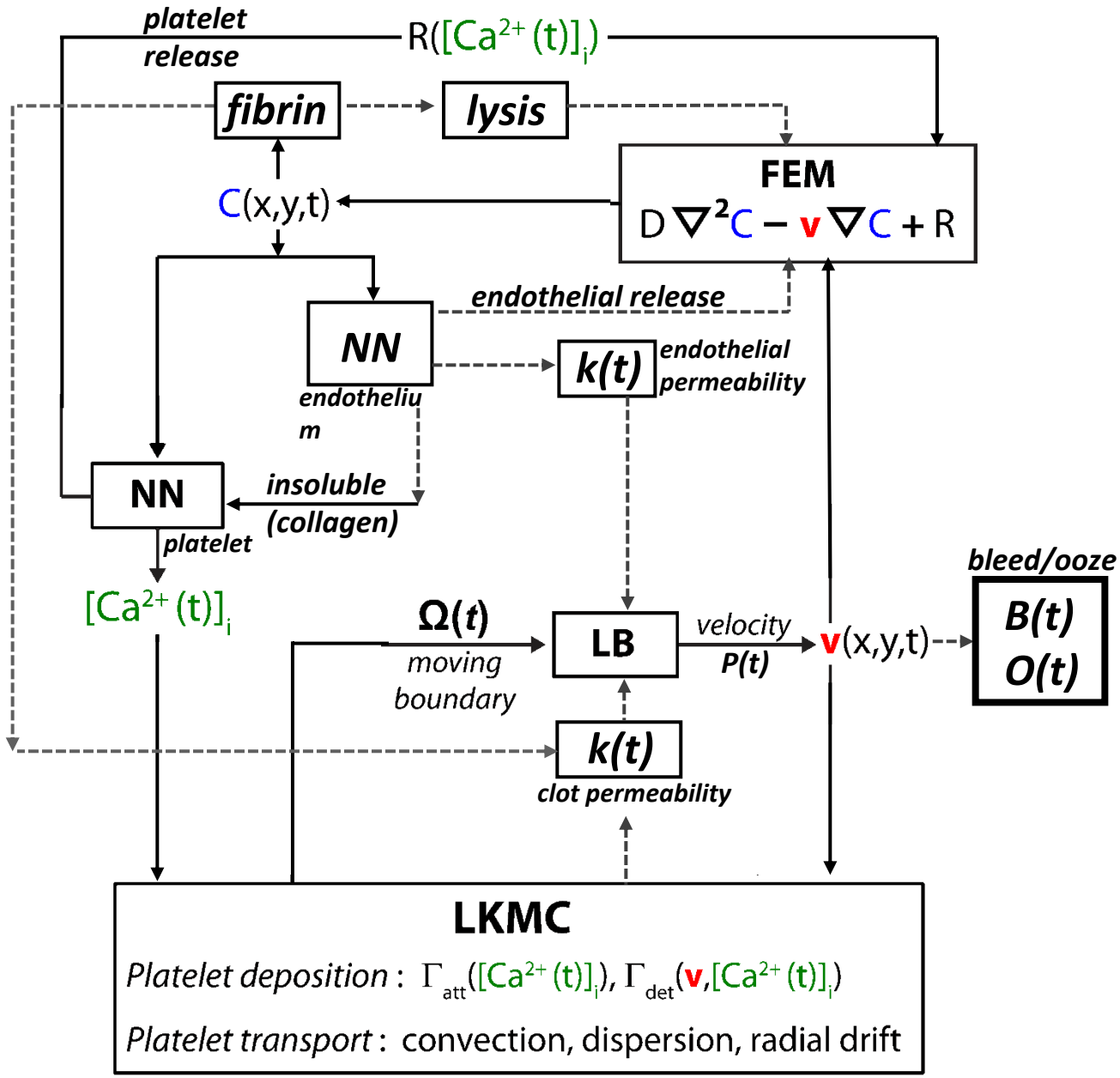


Unit Vessels (flow, clot, ooze, bleed)



Bleeding: Vessel-Cellular Scale



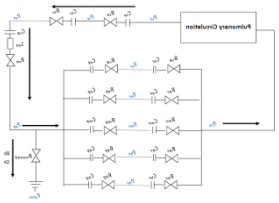


Multiscale Analysis of Trauma: CREDIBILITY PLAN

Appropriateness of MODEL SELECTION at each length scale

Global Hemodynamics:

Hydraulic Circuit Model (ODE)

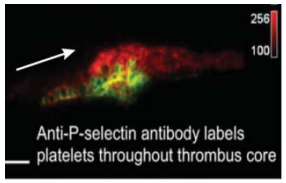


Well-mixed compartments (no spatial resolution)

Predict: BP, HR, O2, blood factor concentrations

Local Tissue Trauma:

Vascular Network Resistance Model



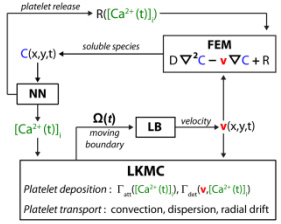
Mouse Cremaster Injury

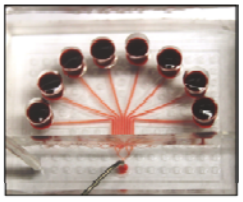
Branching network model with 1D resistances

Predict: Pressure and flow in tissue vasculature

Single Vessel Bleeding:

Single platelet resolution (NN/FEM/LB/LKMC) simulator





2D resolution (3D possible as required)

Predict: local bleeding rate, clotting rate, hemostasis

Multiscale Analysis of Trauma: CREDIBILITY PLAN

VALIDATION of each length scale with scale appropriate data

Global Hemodynamics:

Predict: BP, HR, O2, blood factor concentrations

Patient data: HR, BP, O2, pH, Hc, Na for n = 50 patients.

Local Tissue Trauma:

Predict: Pressure and flow in tissue vasculature

Mouse injury data: bleeding rates (shock + trauma)

Patient data: blood loss estimates, blood product usage

Single vessel Bleeding:

Predict: local bleeding rate, hemostasis

Patient ex vivo blood data:

TEG, platelet signaling, microfludic tests

platelet growth rate, thrombin/fibrin rates

Multiscale Analysis of Trauma: CREDIBILITY PLAN

Credibility of interfacing varying length scales:

The Global Hemodynamic scale depends on…

the tissue scale which depends on…

the single vessel scale.

A CENTRAL CHALLENGE involves the different computational costs of each scale since the models operate at different resolutions in time and space. For example:

Single vessel model for mm-scale and 20 min.

Patient trajectory could last over 24 hr.

Methods to bridge scales include: coarse projective integrative (CPI). Validation of bridging will be performed through parameter variation, analogous to mesh refinement.

Multiscale Analysis of Trauma

Criteria of end-user acceptance

The **purpose** of the model is to help identify:

(1) patients at risk
(2) new mechanisms of risk
(3) biomarkers of risk
(4) optimal strategies for treatment

Users of the model may include trauma surgeons, blood biochemists, diagnostics designers, and bioengineers. Could serve as a virtual trauma patient for training for anesthesiologists or surgeons, however, beyond scope of current project.

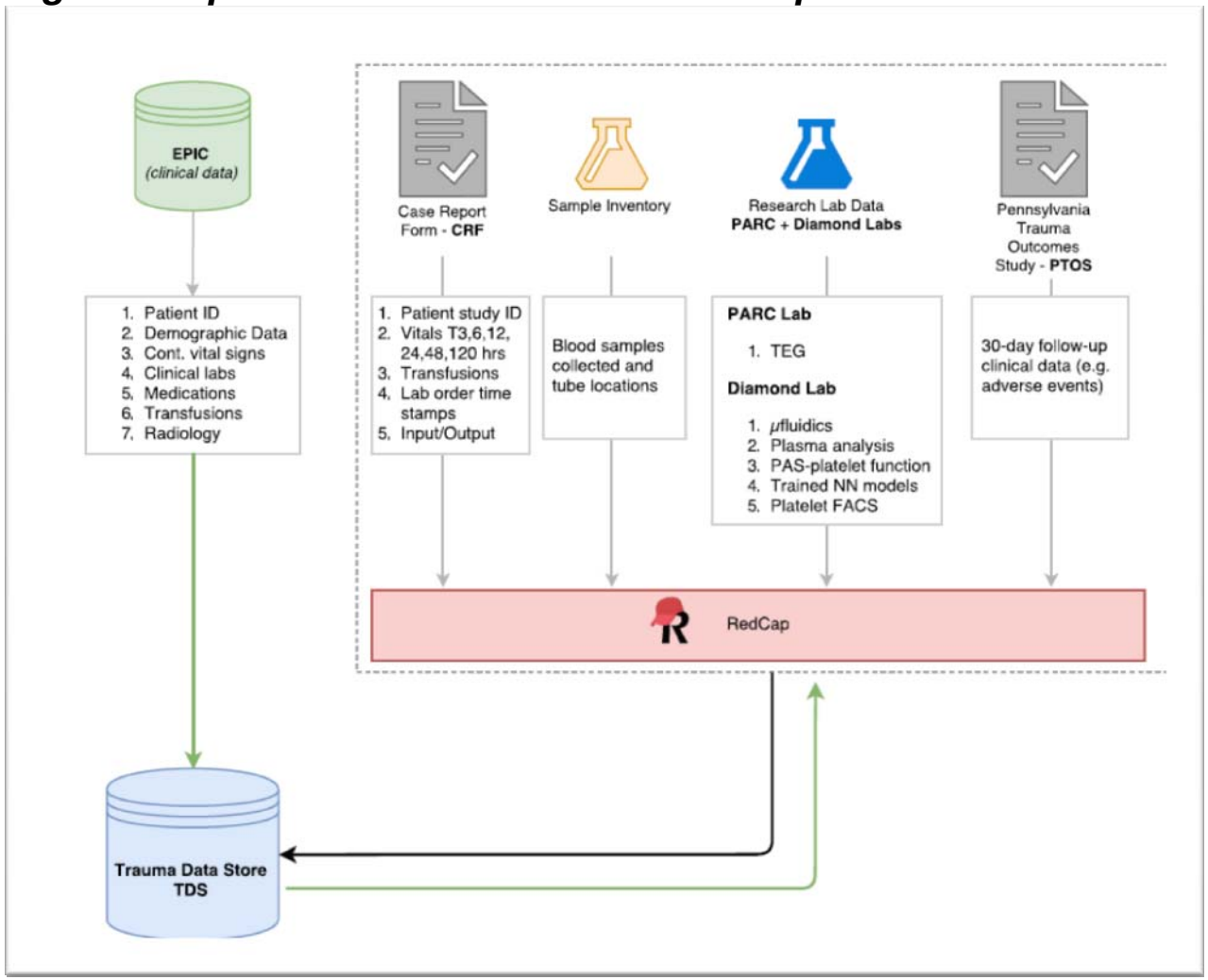
The project team meets weekly with co-Investigator Dr. Carrie Sims (Director, Penn Acute Research Collaboration, PARC) and Research Coordinator, Dr. Antonio Davila (Research Collaboration, PARC) to assess data capture, data extraction, data management, and modeling efforts.

→ Inclusion of the end-user in the model development at the start of the project period is an essential component of the credibility plan for end-user acceptance.

Multiscale Analysis of Trauma

Operability by developer-modeler community

One challenge with respect to patient data sharing involves issues of HIPAA that will likely preclude release of EPIC-extracted data and combined research data for individual patients. We will seek to develop smaller cohort data that averages metrics for several patients. Averaged composite data will be suitable for public domain release.



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Matt Flamm (LKMC)
Tom Colace (microfluidics)
Ryan Muthard (microfluidics)
Richard Li (ASA studies)
Evan Tsiklidis (trauma modeling)
Jason Chen (trauma blood stuidies)
Shu Zhu (PolyP, TAT, Patch Threshold)
Mei Yan Lee (PAS: thrombin, NO)
Yichen Lu (LKMC, LB, FEM)

Collaborators: Skip Brass,
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Yannis Kevrekidis
Carrie Sims