MODEL CREDIBILITY PLAN

Title: **Multiscale Analysis of Trauma (NIH U01-HL131053)**

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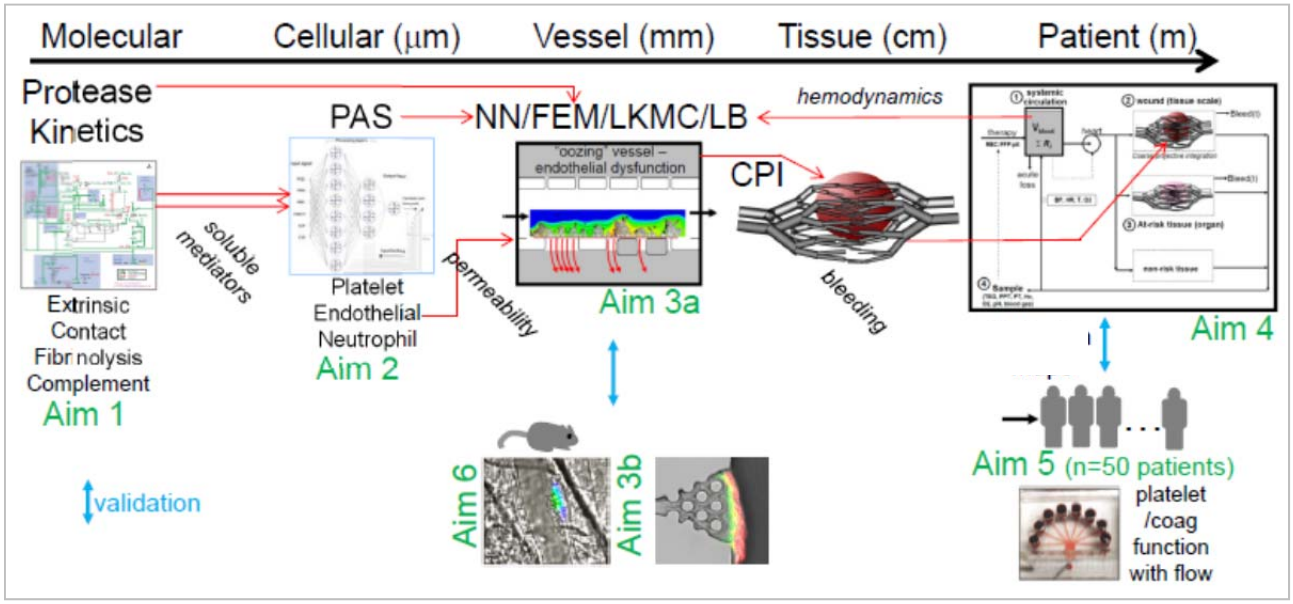
MODEL INTRODUCTION

Trauma presents complex and rapidly evolving scenarios for clinical decision making. As a patient bleeds, the individual's life may be at extreme risk if their systemic blood function changes in a manner that is unable to stop further bleeding. The overall research goal is to achieve multiscale simulation of the trauma patient by accounting for changes in the systemic circulation and the traumatized blood and tissue so as to better stratify patient bleeding (or clotting) risks, prioritize improved biomarkers of risk, and potentially identify new opportunities for safer treatments.

The multiscale model integrates:

(1) **Global hemodynamics**
(2) **Local tissue trauma**
(3) **Single vessel bleeding**



CREDIBILITY PLAN

1) Appropriateness of model selection at each length scale

The Global Hemodynamics Scale is modeled using a **hydraulic circuit model** represented by a system of **ODEs** and governing controller equations to simulate the time dynamics of heart rate, blood pressure, blood oxygen as a patient bleeds, receives pressor agents, and receives blood resuscitation/transfusion products. This is a multi-compartment model that defines compartment states (e.g. BP, HR, O2) without spatially resolving each compartment. The blood at the global scale is considered well mixed with respect to species component concentrations (proteins, plasma, cells).

The Local Tissue Trauma is modeled with a **vascular network resistance model** in which each vessel is characterized by length and radius. The overall vascular network structure is described by mathematical models consistent with measured branching. Flow through the network is based on Poiseuille's law to give pressures and flowrate distributions. Tissue bleeding rates will be calculated as a function of the extent and spatial distribution of vascular damage. Several vascular network topologies will be tested to understand geometry sensitivity.

The Single Vessel Bleeding Model, explicit at the single cell scale, builds upon an existing neural network/finite element method/Lattice Boltzmann/lattice kinetic Monte Carlo **(NN/FEM/LB/LKMC) simulator**, previously validated for blood reactions under flow and operative at the single cell to whole vessel scale. This model has **2D resolution** of soluble species, flow, and single platelet locations. This model is extensible to 3D as required. Model inputs are prevailing flow, cellular concentration, and blood biochemistry/pharmacology. Model outputs are rate of clot growth and bleeding rate dynamics.

These frameworks are well established at each length scale, with respect to credibility.

2) Validation of each length scale model with scale appropriate data

The Global Hemodynamics Scale model will predict variables that can be measured (HR, BP, O2, pH, Hc, Na) and variables that are unmeasurable ($H20_{interstitial}$, total blood volume, cardiac output). Model credibility will be assessed by direct comparison of simulation with individual trauma patient trajectories (HR, BP, O2) for 50 well annotated cases obtained at the Hospital of the University of Pennsylvania (HUP). Since blood pressure is a central attribute of the global scale, off-line research data relevant to pressure control (plasma biomarkers such as vasopressin, aldosterone, angiotensin II, etc.) will be merged with *EPIC*-extracted data and stored in firewalled *RedCa*p repository for analysis of Global Hemodynamics credibility.

The Local Tissue Trauma model will predict bleeding rate of a traumatized tissue. This is the most difficult length scale to establish credibility in the human patient. To validate this scale of the model, mouse studies will be conducted that include both shock (controlled blood loss) and trauma (calibrated injury) prior to assessment of hemostatic function. The volume of blood products for each patient will be used as a metric of blood loss and injury severity at the tissue scale for each trauma patient for establishment of credibility at the tissue trauma scale.

The Single Vessel Bleeding model will be data-driven with real time measurement of patient blood function: platelet calcium signaling, clotting dynamics and mechanics (thromboelastography data), and clotting rates under flow using microfluidic tests. Tests of the model include prediction of blood function at both venous and arterial flow conditions and comparison to microfluidic tests at these two flow extremes. Microfluidics allows large replicates for testing of stochastic model components, often 4 to 8 individual tests under the same conditions for each patient at various times, which provides a standard deviation for statistical comparison of stochastic processes. There are numerous patient-specific measured dynamic metrics (platelet growth rate, fibrin formation rate, thrombin production rate, clot strength) to establish credibility at the single vessel scale. Conservation of species mass and interplay with the global scale are relevant credibility checks at the vessel scale.

3) Credibility of interfacing varying scales

The Global Hemodynamic model 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, the single vessel model can only be solved over a mm-scale domain for a time interval of 20 min. By contrast the patient trajectory could last over 24 hr. Methods to bridge scales include, for example, coarse projective integrative (CPI). Validation of bridging will be performed through parameter variation, analogous to mesh refinement.

4) Criteria of end-user acceptance

In the context of trauma induced coagulopathy (TIC), the purpose of the model is to help identify: (1) patients at risk, (2) new mechanisms of risk, (3) biomarkers of risk. Users of the model may include trauma surgeons, blood biochemists, diagnostics designers, and bioengineers. Ultimately, the multiscale simulator could serve as a virtual trauma patient for training of anesthesiologists or surgeons, however such an application is well beyond the scope of the present project period.

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.

5) Operability of model 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.