MULTISCALE MULTIPHYSICS MODEL OF THROMBUS BIOMECHANICS IN AORTIC DISSECTION

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Summary

This project seeks to build experimentally driven multiscale models to predict the development, growth, or arrest of an intramural thrombus within the dissected aortic wall. Whereas medical imaging now enables one to quantify the patient-specific geometry of a false lumen and to construct associated computational fluid dynamics models, no existing model can predict the development, growth, or arrest of an intramural thrombus. To address this gap, we developed the first data-driven, multiscale, multiphysics model of the biomechanics of intramural thrombus in aortic dissection.

Model Credibility Plan

A. List of Planned Actions

During the first and second years of this study, we focused on initial model development and data collection. Specifically, we extended two complementary multiscale models (i.e., flow thrombus model of Karniadakis and thrombus-wall remodeling model of Humphrey). A novel multiscale coupling framework was developed as a plug-in library in the second year to couple any heterogenous solvers. These multiscale/multiphysics models span scales from platelet dynamics to continuum flows and from fibrin/collagen fiber remodeling to whole wall stress analysis. More specifically, the following actions have been taken during the course of this project:

Year 1: Mesoscale models of vascular and blood flow processes essential to thrombus biomechanics:

- Platelet and red blood cell whole cell models were developed using a coarse-grained molecular dynamics method called Dissipative Particle Dynamics (DPD)
- A discrete particle-based DPD model of fiber-reinforced anisotropic arterial wall was developed

Year 2: Macroscale models of coagulation dynamics and thrombus formation processes:

- Spectral element fluid solver (Nektar) with the advection-diffusion-reaction (ADR) to solve the coagulation cascade
- Particle/continuum model based on Force Coupling Method to model the initial aggregation and growth of thrombus in a dissecting artery
- Multiscale universal interface (MUI) for efficient numerical coupling

Year 3: Further development of macro- and mesoscale models:

- Elastodyanmics modeling using spectral element method and Nektar solver along with the fluid-structure interaction
- Transport DPD to address the ADR of chemical components at the mesoscale
- Extended smoothed particle hydrodynamics model (SPH) developed for the aortic wall, to capture both elastic and damage processes

Year 4-5: Development of multiphasic continuum model and adhesive dynamics:

- Considering that thrombus that is formed in blood as another phase, their interactions can be addressed by a phase field
- Sub-cellular level platelet adhesion depends strongly on receptor-ligand interactions. Coarse-grained atomistic models of adhesive dynamics are under development.

We are now in a NCE extension to finalize our Aims. Some of these solvers are thus still under production and hence not finalized for dissemination. A few others are already published online and available to the public (please see below). Data collected during the course of this study have been presented in large part in archival journals, wherein we further clarified that complete data sets can be made available in electronic form upon request. These data include in vivo micro-CT, ultrasound, and blood pressure data from the mice; histological and immuno-histological images (TIFF format); and associated spreadsheets that summarize quantitative findings.

B. Information Gained by Each Credibility Action

Model validation: Our models (Brown and Yale) are data-driven and validated by the experimental data collected at Yale.

Reproducibility: We have made or will make all the data along with the solvers available in the repositories for independent use.

C. Actions and Activities Classified within the CPMS TSR Framework

Item	Description	Actions/Activities
1	Define context clearly	The context of the proposed project was to study thrombus bio-chemo-mechanics in aoritc dissections at different scales i.e., from sub-cellular adhesive dynamics and coagulation kinetics to cellular interactions in blood flow and macroscopic blood hemodynamics and arterial wall deformations.
2	Use appropriate data	Most of the data used for model development and validation in murine dissection was generated at Yale, though some by other collaborators. Generic data such as coagulation kinetic rates were taken from the literature.
3	Evaluate within context	We have shown that our data, which drives the modeling, are reproducible across mouse models, across users, and across the years because of standardized protocols and validated software for data collection and analysis.
4	List limitations explicitly	Simplifying assumptions and limitations of our methods are explicitly described in publications describing our models. Some limitations include the disparate time scales involved in the whole process from microseconds to hours and days. This requires a multiscale framework that bridges time scales in addition to spatial scales.
5	User version control	Currently the following software and libraries have been published and maintained regularly:

		• MUI for efficient and parallel coupling of different solvers. • UserMeso which is a GPU-accelerated package for DPD and its extensions such as transport DPD and is released in (refer to LAMMPS-Documentation)
6	Document adequately	Most of the published solvers and libraries are documented properly either through LAMMPS documentation or separately.
7	Disseminate broadly	We regularly present our results in the conferences and seminars nationally and abroad. Most solvers are open-source and more will be available soon with examples and tutorials. LAMMPS has a new set of DPD libraries that the Karniadakis group developed – the DPD alphabet for transport problems at the mesoscale.
8	Get independent reviews	Extensive assessments of our work have been made through peer review of the resulting manuscripts. In addition, our models and solvers are used by independent researchers, and are under constant evaluations. We will also look for experts on DPD and on Spectral elements to evaluate our codes at various stages of development.
9	Test competing implementations	Finite element solvers for fluid and solid mechanics are established and validated for decades and regardless of the programming language (e.g. Fortran vs. C++) are totally reproducible. Similarly, most atomistic models implemented in different platforms (e.g. LAMMPS vs. Gromacs) are the same and produce similar results.
10	Conform to standards	We have adopted accepted standards for the programming of computational schemes using standard libraries in C++ in addition to highly optimized math and linear algebra libraries such as BLAS and ScaLapack. Data types and formats are all binary and can be used by popular visualization software such as ParaView and Tecplot for postprocessing.

D. How Planned Activities Will Lead to a Credible Model

The final constitutive equations and associated ranges of all material parameters will be deposited on-line at the same sites used for software sharing. A user guide will provide complete derivations of all basic equations and constitutive relations with illustrative fits to data that will be supplied in tabular form.

E. Progress To-Date and Plans for Next Reporting Cycle

We will take the following actions for the next cycle (NCE):

- Create a common repository for the raw and processed data generated for the project.

- Continue publishing tools, tutorials, trainings and software through GitHub repositories
- Posting new information about the project on IMAG Wiki to introduce the software and create an open forum for discussion and review and bug reports.

4. Issues/Concerns Identified

A light-weight version of Nektar solver is published on GitHub by one of the contributors in this project: https://github.com/alirezayazdani1/NEKTAR-3D

However, unlike ODE solvers, the Nektar solver, like other parallel finite-element solvers, consists of many routines and depends heavily on other libraries, and requires more time and effort before it can be published with proper documentation.

5. Other Factors

None

DATA MANAGEMENT

Data are acquired as images (DICOM) or digital information (loads, geometries, displacements) and are achieved on a lab server and backed-up. The raw data are converted into physical units and stored within excel worksheets in most cases.