# Model Credibility Plan - Fall 2018 Update

U01HL143336: *Multiscale Modeling of Clotting Risk in Atrial Fibrillation*
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## Summary

This project aims to develop clinically validated multiscale models of cardiac dynamics that integrate fluid dynamics, electromechanical coupling, and fluid-structure interaction (FSI) to simulate intracardiac flows and blood coagulation in atrial fibrillation (AF). AF is the most common sustained arrhythmia in the U.S. and is associated with serious complications, including thromboembolism and stroke. Anticoagulation is commonly prescribed to patients who have an elevated stroke risk. However, current risk assessment indices, which lack individualization based upon atrial structure or function, classify most AF patients as being at *intermediate risk*. The overarching hypothesis motivating this research is that treatment guidelines using current risk assessment metrics result in many AF patients receiving unneeded anticoagulation and unnecessary monitoring for thrombosis. The long-term objective of this research program is to develop new, broad-spectrum approaches to clotting risk assessment in AF that provide personalized risk prediction. The premise of this specific project is that comprehensive models of atrial dysfunction will enable mechanistic studies of flow and clotting in AF that will ultimately facilitate individualized treatment.

The specific aims of this project involve developing dynamic computational models of blood flow and coagulation dynamics in the left atrium (LA) and left atrial appendage (LAA), and to use these models in the context of percutaneous LAA exclusion (e.g. via the *WATCHMAN* device), and LAA isolation in catheter ablation therapy. Clinical data will be obtained for both types of procedures within the project.

## Simulation methods

- Computational fluid dynamics (CFD): finite volume-type methods for the incompressible Navier-Stokes equations with block-structured adaptive mesh refinement (AMR)
- Computational solid dynamics (CSD): stabilized mixed nodal finite element methods for incompressible and nearly incompressible nonlinear elasticity
- Computational fluid-structure interaction (FSI): immersed boundary (IB) type methods
- Computational electrophysiology (EP): nodal finite element methods
- Computational thrombogenesis: finite volume-type methods for reaction-advection-diffusion equations with structured adaptive mesh refinement (SAMR)

### Software

The *IBAMR* software (ibamr.github.io) will serve as the primary software framework for CFD, FSI, and continuum thrombosis modeling, and for developing integrative models. IBAMR is a C++ infrastructure for

constructing FSI models using the immersed boundary (IB) method and related methods. The majority of its development occurs within the open IBAMR GitHub project pages (github.com/IBAMR).

The *BeatIt* software (github.com/rossisimone/beatit) will serve as the primary software framework for CSD and EP modeling. Although IBAMR provides a nonlinear solid mechanics module, we are currently developing FSI coupling algorithms that will allow us to use BeatIt to handle the solid mechanics, electrophysiology, and electro-mechanical coupling.

IBAMR and BeatIt both rely on the libMesh finite element library (libmesh.github.io) to treat complex geometries, and PETSc (www.mcs.anl.gov/petsc) for core computational infrastructure (distributed vectors and matrices, and linear and nonlinear solvers and preconditioners).

## Verification and validation

Software and method verification will primarily be carried out via benchmark problems with known analytic solutions (e.g. using the *method of manufactured solutions*), or via benchmark problems with consensus solution values. An automated verification test suite, based on the *Google Test* framework (github.com/google/googletest), already exists for the IBAMR software. Similar tests will also be developed for the BeatIt software. We shall improve the methods used for reporting the results from these tests (e.g. using a "dashboard" on GitHub).

Validation tests will include comparisons to data from in vitro models of the fluid dynamics of the heart and great vessels (e.g. obtained from a commercial pulse duplicator), including quantitative flow mappings obtained using particle image velocimetry, and by comparisons to in vivo data on flow patterns, local tissue stiffnesses, and electrical activation in the LA obtained intraoperatively during catheter ablation along with pre-/post-operative patient imaging data.

For CFD, we shall rely on benchmark datasets collected within the FDA's Critical Path program on validating cardiovascular fluid dynamics (pubmed/21428676, pubmed/25180887, pubmed/28114192), which include laboratory studies of flow-induced hemolysis. Additionally, we shall carry out qualitative comparisons to previous clinical measurements of LA blood flow (e.g., pubmed/11559688).

For cardiac mechanics, we shall use the cardiac mechanics benchmark (pubmed/26807042) developed by Land et al. as an initial test of the mechanics solvers, although these tests focus on the response of the left ventricle. Because strain imaging is used for the direct evaluation of LA function, validation tests on the LA mechanics will compare strains and strain rates during sinus rhythm (pubmed/22909795). Validation of the electromechanical model will compare the evolution of strain and strain rates data during AF, as reported previously (pubmed/20133512, pubmed/22265458). Within the project, we also shall collect acoustic radiation force impulse (ARFI) data that will characterize in vivo tissue mechanics, and these data will be used in the project for additional validation studies.

For FSI, we aim to follow a previously described cardiac FSI benchmark (pubmed/27813272) developed by Nordsletten and co-workers. We also shall collect data during the duration of the project within ongoing projects that will provide additional validation datasets.

For cardiac electrophysiology, we shall apply the N-version benchmark (pubmed/21969679) described by Niederer et al. This involves using the converged consensus result from multiple simulation codes as a gold

standard. An online database is available to facilitate the verification of cardiac tissue electrophysiology simulation codes such as the one we are developing. In addition, we shall collect multisite recordings on the posterior wall of the LA from multiple patents during clinical procedures, which will provide additional validation data sets with regard to conduction velocities and electrogram amplitudes and morphologies in diseased tissue.

For thrombosis, we shall compare simulation model outputs to in vitro microfluidic platelet deposition and fibrin formation assays (pubmed/18983510, pubmed/18203955, pubmed/23001359, pubmed/24236042, pubmed/28529666, pubmed/29472230), and to in vitro platelet deposition in stenotic arteries measurements (doi/10.1007/s13239-014-0180-z, doi/10.1007/s13239-012-0086-6).

## Distributing verification and validation model software

Dedicated web pages will be developed to document key verification and validation tests and to summarize results from those tests along with the software implementation of these tests. Where feasible, model geometries will be provided for validation models. Although we shall endeavor to use in vitro test geometries that can be readily distributed, redistribution of validation model geometries may be restricted if required by the intellectual property or human subjects research offices of the participating institutions. To improve reproducibility, we shall document specific software versions used to generate the model results.

# Model Credibility Plan Timeline and Milestones

Year 1: Core method implementation; verification and initial validation benchmarking; automated testing, archiving, and reporting framework. Research focus: electrophysiology models and comparisons to clinical data; LA and LAA tissue mechanics and fiber architecture; CFD-based flow models.

Year 2: Expand coverage of verification and validation tests to include method variants (e.g. differences in approximation methods) to map out failure modes; external evaluation. Research focus: electromechanics; FSI-based flow models; comparisons of modeling approaches to LAA trabeculation.

Years 3-5: Documentation of core tests; software and model distribution; external evaluation. Research focus: percutaneous LAA and catheter ablation models.

# Credible Practice Guidelines

**1. Define context clearly.**
The context of use is atrial dynamics in normal sinus rhythm and with arrhythmic activation in atrial fibrillation.

**2. Use appropriate data.**
Data sets will include in vivo and in vitro data relevant to cardiac fluid dynamics, muscle mechanics, electrophysiology, and thrombosis at the organ scale.

**3. Evaluate within context.**
Model results will be evaluated against benchmark data. We shall compare velocities (of the flow, muscle, and electrical activation) as well as quantities such as stress distributions. We aim for < 1% errors for verification tests and < 10% errors in validation tests.

**4. List limitations explicitly.**
We shall explore method and model limitations within the existing software (e.g. by comparing results obtained by different discretization methods), by comparison to benchmark simulation results (where available), and by comparison to benchmark experimental or clinical data (where available).

We plan to provide tests to analyze the effect of key model parameters on simulation outputs, including the parameters of the rule-based fiber structure models as well as tissue conductivities and anisotropy ratios, stiffnesses, and contractility. Because of the expected scale of the proposed simulations, it may not be feasible to analyze all plausible parameter variations. However, we shall aim to provide infrastructure for performing such tests.

**5. Use version control.**
The project will use git to manage software version control. Extensions to git for managing non-text files will be used to archive selected model specification data (e.g. computational meshes) and results. Ultimately, we plan to be able to link specific verification or validation result reports to specific software versions.

**6. Document adequately.**
The IBAMR project has already begun providing documentation for the core IBAMR software (through ibamr.github.io and github.com/IBAMR/IBAMR). Software documentation is generated through in line comments processed by Doxygen (www.doxygen.nl), and in IBAMR, this documentation is generated automatically (i.e. using *continuous deployment*) via Travis CI (travis-ci.org).

**7. Disseminate broadly.**
All core simulation software and verification/validation test software and data will be distributed via GitHub and GitHub Pages, except in cases in which it is not feasible or permissible to distribute the data sets, as described above. The core simulation software is already available as open-source software via GitHub.

**8. Get independent reviews.**
Models using the simulation platform are expected to be submitted to the FDA *Medical Device Development Tools* program as non-clinical assessment models to validate their ability to predict pre-clinical device performance in regulatory submissions.

**9. Test competing implementations.**
Where possible, we shall use community tests, as in the cardiac mechanics benchmark study of Land et al., to compare against alternative methods and implementations. As described above, our current simulation infrastructure also includes alternative methods, and we shall perform internal comparisons between various approaches provided by our framework.

**10. Conform to standards.**
All software to be developed in the project will be tested using a variety of compilers, as already done for the IBAMR software project using a dedicated Jenkins CI server (jenkins.io). Models will be specified in a combination of human-readable text files and geometry files that use accepted file standards (e.g. *ExodusII*). We also commit to using community standard formats for organ-scale model specification as such formats emerge.

# Data Management

Version control for the project will primarily use git and extensions of git suitable for archiving non-text files. Substantial infrastructure to facilitate data management is available at UNC-Chapel Hill through the Research Computing division of UNC Information Technology Services, including:

RC-Isilon: For comparatively large capacity permanent storage, Research Computing presents a 4 PB high-performance scale-out Dell EMC Isilon X-series storage cluster. Research groups may receive a 5 TB institutional allocation upon request. On a project-by-project basis, research groups may request additional storage space (usually not to exceed 25 TB of added space) for the duration of a time-delimited project, pending available capacity. For space in excess of 100 TB, Research Computing passes on the cost of the incremental infrastructure required for a term of 4 years.

Network Attached Storage (NAS): Research groups have access to NetApp file storage. High-performance storage to is delivered via SATA disks, and extreme-performance storage is delivered via SAS disks. All storage is configured with large controller caches and redundant hardware components to protect against single points of failure. This storage space is “snapshotted” to support file recovery in the event of accidental deletions. Research groups receive a 10 GB institutional allocation. Additional storage is available at incremental cost.

Active archive: Research Computing offers Quantum StorNext active archive with in excess of 4 PB tape storage and a 600 TB disk cache. Data are stored encrypted on tape and are protected against media failure by storing redundant copies. Individual researchers receive a 2 TB institutional allocation, and laboratories and project teams receive a 10 TB institutional allocation. Additional capacity is available at incremental cost.

Secure FTP: To facilitate the deposition of files/data from external organizations into UNC-Chapel Hill, Research Computing offers a secure file-transfer-protocol service that allows files/data to be uploaded but prohibits downloading. This file transfer service meets additional security requirements for sensitive data.

Globus: Research Computing supports Globus (www.globus.org) for secure data/file transfer between participating institutions.

Database services: Research Computing offers schemas on managed Oracle databases sufficient for many small to medium sized research projects. These included patching, general database administration, and transparent database/datafile encryption. MySQL and PostgreSQL are available within contexts where there is an ongoing engagement project, and it fits within available resources and projects. These are on a case-by-case basis. MySQL and PostgreSQL are also available via cloud self-services at cloudapps.unc.edu. The services at cloudapps.unc.edu are approved for sensitive data.

In addition, PI Griffith’s research group has a dedicated 12 TB file server with redundant off-site backup.