1. Project title:

Multiscale Modeling for Treatment Discovery in Duchenne Muscular Dystrophy

1. A one/two sentence summary of the project topic with a hyperlink to more detailed information via the [IMAG wiki](https://www.imagwiki.nibib.nih.gov/content/msm-participants).

The goal of this project is to create multi-scale models that recapitulate disease progression in Duchenne muscular dystrophy and then to use those models to as a platform for treatment discovery.

**Detailed information (Summary from our submitted grant):**

Duchene muscular dystrophy (DMD) is an inherited, severe muscle degenerative disease that affects 1 in every 3,500 boys. Pervasive and progressive skeletal muscle atrophy and weakness is generally first observed in patients at 3-5 years of age, leaves patients wheelchair bound by age 12 years, and ultimately leads to death due to respiratory or cardiac failure by the mid 20s. There is no cure for DMD, and currently, the only FDA approved treatment is corticosteroids, which targets inflammation in muscle degeneration. However, corticosteroids are merely palliative: they extend the time of mobility and life by only a few years. Furthermore, corticosteroids have major troublesome side effects, causing boys to gain weight, have early-onset cataracts, and potentially develop significant behavioral issues, all of which make lives of boys and families extremely difficult. The initiating cause of DMD is due to a mutation in the dystrophin gene, which renders muscle fibers prone to membrane tearing during everyday movements and initiating a cascade of muscle fiber necrosis, chronic inflammation, and ultimately muscle degeneration. This cascade of pathological remodeling events involves multiple different mechanisms that span spatial and temporal scales and pertain to biomechanical signals and inflammation in the muscle tissue. **We hypothesize that it is the feedback between biomechanical signals and inflammatory signals that ultimately leads to muscle degeneration.** We posit that testing this hypothesis requires a multiscale computational model. We propose to couple biomechanical modeling with agent-based modeling to develop and then experimentally validate a unified multiscale computational model (Aim 1). We then propose to use our multiscale model of muscle remodeling to test our hypothesis by challenging the model to predict the response to different treatment interventions and to explore why the most widely used murine model of DMD, the *mdx* mouse, poorly recapitulates human disease (Aim 2). Finally, we propose to make a human version of the multiscale model and use it to simulate different DMD patients in order to test different front-running treatments that have had variable degrees of efficacy and to identify new treatments that are informed by understanding how biomechanics and inflammation feedback on one another to cause this terrible disease (Aim 3).

1. Details regarding Model Credibility plan following the [CPMS Ten Simple Rules (TSR)](https://simtk.org/plugins/moinmoin/cpms/Ten%20Simple%20Rules%20of%20Credible%20Practice) format.  It is requested that these details be presented as deemed appropriate for each modeling approach.  This will be used to help define best practices for future reporting activities. These details should include:
   1. List of planned actions outlined in Model Credibility plan

§Part 1. Download and run each other’s models [Rule 1 (define context), Rule 6 (document)]

§Part 2. Cross-evaluate model design and implementation with a focus on the use of experimental data in model specification and validation [Rule 1 (define context), Rule 2 (use of data), Rule 3 (evaluate within context), Rule 4 (limitations)]

§Part 3. Version control best practices sharing [Rule 5 (version control), Rule 6 (document), Rule 9 (competing implementations)]

§Part 4. Publication strategy [Rule 7 (disseminate broadly), Rule 8 (independent reviews), Rule 10 (conform to standards)]

§Part 5. Journal the experience!

* 1. Brief description of information gained by each credibility action

§Part 1. By running each other’s models and providing feedback about this experience, we are helping each other improve how we are documenting and sharing our models. Specifically, we are focusing on the user experience and identifying bottlenecks or points of possible confusion and making recommendations for how these issues can be enhanced or resolved.

§Part 2. By discussing how experimental data is used for model specification and validation by each of our groups, we are enabling ourselves to re-consider fundamental assumptions of our own models. For example, our conversations are calling into question how we develop and compare 2D and 3D model simulations given the available 2D vs. 3D experimental data. An interesting aspect of this conversation is the recognition that the Kirschner/Linderman lab deals with primarily spheroidal shapes (granulomas), while the Blemker/Peirce-Cottler lab deals primarily with cylindrical shapes (muscle fibers). Two-dimensional approximations of these tissues both take the form of circles, whereas the 3D representations are quite different.

§Part 3. By sharing our best practices for version control with one another, we have validated our own approaches and reinforced the adherence to these strategies with the modelers and trainees in our own laboratories. We also hope to gain input from other modelers in the MSM community by posting this document on the IMAG Wiki.

§Part 4. By sharing near final versions of manuscripts that we are within range of submitting to peer reviewed journals, we are enabling the other group to provide input on how well the models are described and to ensure that the models conform to standards, even before the paper is submitted for peer review.

§Part 5. By journaling the experience of serving as co-reviewers on one another’s projects, we are showcasing the evolution of our ideas about model credibility, as we check and their implementation in our workflow. We hope to contribute a template of activities that could be encouraged or required by other modelers in the MSM community.

* 1. Actions and activities classified within the CPMS TSR framework (item-by-item summary table). If any of the TSR items are not being implemented/considered or additional items are being implemented, this information should also be explicitly stated

§***Part 1 Action items:* [Rule 1 (define context), Rule 6 (document)]**

Peirce-Cottler/Blemker held a joint lab meeting on 9.27.18 for UVA students to download models on <http://malthus.micro.med.umich.edu/GranSim/>

and provide feedback to Kirschner and Linderman. In the future, Kirsher and Linderman will have their lab groups do the same thing with the multiscale models that Blemker and Peirce-Cottler have already posted on FEBio.

§***Part 2 Action items:* [Rule 1 (define context), Rule 2 (use of data), Rule 3 (evaluate within context), Rule 4 (limitations)]**

Kirschner and Linderman are working on a short manuscript for the Bulletin of Mathematical Biology on the topic of a method for converting 2D to 3D model representations given data is 2D and 3D. Blemker and Peirce-Cottler will read and determine if they can make a contribution by providing an example that pertains to multi-cylindrical geometry (i.e. skeletal muscle).

§***Part 3 Action items:* [Rule 5 (version control), Rule 6 (document), Rule 9 (competing implementations)]**

Blemker/Peirce-Cottler and Linderman/Kirschner have worked together to implement the best practices document for version control and model documentation (attached) that their respective lab groups have crafted and swapped and we have posted this to the IMAG Wiki so that feedback can be solicited from the broader MSM community.

§***Part 4 Action items:* [Rule 7 (disseminate broadly), Rule 8 (independent reviews), Rule 10 (conform to standards)]**

Blemker/Peirce-Cottler and Linderman/Kirschner will share “near-final” drafts of papers for feedback from each other’s lab groups, and the feedback provided will focus on how well the model is described (reproducibility) and conforms to standards. In the near term (within the next two months), Blemker and Peirce-Cottler will send Kelley Virgilio’s paper and Michaela Rikard’s paper to Linderman and Kirschner for feedback.

§***Part 5 Action items:***

Ongoing on a shared Google Doc!

* 1. Description of how the planned activities will lead to a credible model

These activities will lead to the generation and more effective dissemination of more credible models because of the following reasons:

* Key decisions underpinning the model design, including the use of data and the representation of the biological system (ie. 2D vs. 3D) will have been more deeply questioned and vetted by getting feedback during the model building process from modeling experts outside the field of skeletal muscle disease who have a different perspective due to their biological focus on tuberculosis.
* The models we develop will be more usable by a broader audience because users who are not familiar with our model software will have a chance to test-drive our models and provide their suggestions for enhancing usability.
* The models we produce will conform more closely to standards in the field because by reviewing the models by the Kirschner/Linderman group, we will learn from their approaches in this regard and be emboldened to emulate and together converge to best practices.
  1. Progress to-date and plans for the next reporting cycle (6 months). What has been achieved since last reporting?

Our progress to date is summarized as follows:

* In April, a graduate student from the Linderman/Kirschner lab groups presented his model to the Peirce-Cottler/Blemker lab groups in a lab meeting-style teleconference, which familiarized the Peirce-Cottler/Blemker lab groups with both the biology and the model.
* Peirce-Cottler/Blemker labs downloaded and ran Linderman/Kirschner models and provided feedback via shared Google doc.
* Kirschner and Linderman drafted a paper for the Bulletin of Mathematical Biology on the topic of a method for converting 2D to 3D model representations, which will be shared with Blemker and Peirce-Cottler for their input
* Blemker/Peirce-Cottler and Linderman/Kirschner labs collaborated to implement and post a best practices document for version control and model documentation on the IMAG Wiki
* All meetings and interactions were journaled on the Google doc

Our plans for the next reporting cycle include:

* Linderman/Kirschner labs will downloaded and run the Blemker/Peirce-Cottler models which are posted on SimTK, and Linderman/Kirschner labs will provide feedback to the Blemker/Peirce-Cottler labs via our shared Google doc.
* Blemker and Peirce-Cottler will read, edit, and contribute to the paper drafted by Kirschner and Linderman for the Bulletin of Mathematical Biology, and this manuscript will be submitted
* Blemker/Peirce-Cottler and Linderman/Kirschner will share “near-final” drafts of their papers for feedback from each other’s lab groups, and the feedback provided will focus on how well the model is described (reproducibility) and conforms to standards. In the near term (within the next two months), Blemker and Peirce-Cottler will send two papers to Linderman and Kirschner for feedback (including papers by first author Kelley Virgilio’s and by first-author Michaela Rikard).
* All meetings and interactions will continue to be journaled on the Google doc

1. Issues/concerns identified as critical or problematic to achieve the standard of credibility set by MSM Consortium.

We have not experienced any problems carrying out our proposed model credibility plan, however, we would appreciate the opportunity to get feedback on it from the CPMS. We have carried out all of our discussions using Bluejeans video conferencing software, and that seems to be working well, and we have relied heavily on Google docs and email for written communication and discussion archiving. It would be beneficial to organize a once per year face-to-face visit (beyond meeting at the annual IMAG Meeting).

1. What other factors, if any, contribute to credibility but cannot be reported within the TSR structure? In requesting this information, we seek to identify credibility activities/issues and appropriate ways to report them at upcoming IMAG/MSM meetings.

Model credibility is best evaluated by the unbiased user who needs the information coming out of the model the most. If there is a way to identify these people during the model building process and solicit their feedback more regularly, that would be very beneficial to ensuring model credibility. Is it possible to engage non-modelers in the community early on in the model development process so that there is a “pull” in addition to a “push” when it comes to modeling complex biological & biomedical systems?