Title: A Multi-Scale Systems Pharmacology Approach to TB Treatment (Dartois, Flynn, Kirschner, Linderman)

Summary: TB causes ~8 millions deaths per year. The project aims to integrate state-of-the-art computational modeling and experimental data from humans, primates and rabbits to identify optimal antibiotics, and antibiotic regimens, to improve TB treatment. More details information can be found at http://malthus.micro.med.umich.edu/MSM/

Model credibility plan updates:

Overall plan. In our original proposal's model credibility plan, we described plans to (i) verify the computational codes, (ii) validate and calibrate models, and (iii) work with MSM member(s) to independently evaluate the models. Here we describe primarily our work on a 5-part plan that we are pursuing with a partner group, Blemker and Peirce-Cottler at the University of Virginia (Multi-scale modeling for treatment discovery in Duchenne muscular dystrophy). Our team of four presented a detailed outline of our plans of what we had done and future plans in a talk given at the MSM annual meeting in March 2018. This report outlines progress since that report. Our 5-Part plan incorporates all 10 of the CPMS Ten Simple Rules (indicated at each Part below).

Part 1. Download and run each other's models [**Rule 1 (define context), Rule 6 (document)**]. We are working with our students and postdocs to run each other's models as they are developed, prior to publication. This provides an opportunity to question key assumptions and trouble-shoot at multiple levels of implementation. It also provides a learning opportunity for the students and postdocs. Most recently the Peirce-Cottler lab used a September 2018 joint group meeting to run our TB models and provided extensive feedback for our interactive websites that provide executable versions of our codes. This required support from our technical staff to make sure that models could run as planned. We expect to do the same for their newest model this fall. Note that we post our compiled code for published work on our website.

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)]. This provides an opportunity to discuss critical issues around using data to inform model design, parameterize models, validate models, and test models. We meet using the "bluejeans" video conferencing system or in person (before/after the MSM meeting), often including our students and postdocs. At our most recent meeting (September 2018), we identified issues regarding 2D models for systems that are in reality 3D, and discussed ways to compare our approaches. Two prior meetings this year have included presentations given by a student from each group.

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

different practices here, so it is useful to discuss. We created a shared document on this that may ultimately be helpful to the community.

Part 4. Publication strategy [Rule 7 (disseminate broadly), Rule 8 (independent reviews), Rule 10 (conform to standards)]. Prior to publication, we plan to share manuscripts and provide feedback on how the model is described (reproducibility), technical aspects, and possible routes to publication. Papers are in early stages of preparation now, so this will be a focus in the next few months.

Part 5. Journal the experience. Our community's efforts around model credibility are relatively new and evolving. We have been documenting our work together in a google document that is accessible to all 4 PIs with the goal of producing a "reflection" paper or similar to summarize our experiences.

Concerns: None identified.