Discussion Document on the Future of the IMAG/MSM Working Group Multiscale Modeling and Viral Pandemics

1) **Role of the WG:**

Original statement from web site: The community of modelers developing epidemiological and population-scale models is already extensive and well-integrated, in part due to the NIGMS MIDAS program. Within-host modeling of viral pathogens is much more limited. Therefore, the working group will initially focus on within-host scales, in particular the complex interactions between viral infection, host physiology, and the immune system. A main long-term deliverable of the working group will be an overall strategy for a coordinated multi-scale modeling effort which becomes a customizable translational technological platform for rapidly creating improved personalized prognoses and therapies in response to emerging viral pandemics. It will also include a plan on how to mobilize and coordinate the modeling community to support this effort.

What is an appropriate role for the WG vis-a-vis the many other organizations related to either MSM or to infectious disease and immune response?

2) **Activities:**

The WG has organized seminars, connected people and advocated for the role of MSM in viral infection and immune response (*e.g.* outreach to the Bridge2AI program and assisting with the organization of the annual IMAG/MSM meeting). WG members have worked on several articles and white papers covering multiple areas covered by subgroups.

What are some appropriate activities for the coming year?

Are there specific activities that we could develop which would be valuable and increase impact/engagement?

Reed Shabman: Contribute to the IMAG meeting

Reed Shabman: Organize Short Workshops:

Suggestions for Workshop Topics?

Amanda Skarlupka: A grant opportunity/teaming workshop to develop collaborations focused on targeting specific RFAs

- **MJ Colebank:** In light of the annual IMAG/MSM meeting, **would it be possible to organize a MSM-VP meeting with potential funding from a R13/U13 NIH grant?**
- **J Rice & J Sluka: d**evelop a “co-op” or “collaboatium” that shares online data and models.

Are there activities we should deemphasize?

3) **Expertise and Community Building:**

We have assembled a substantial list of members covering a very broad range of skills and experience.

What projects would leverage this collection of expertise most effectively?

- **MJ Colebank:** If I recall, many members have expertise in one or two scales that contribute to the modeling of viral pandemics. **One solution may be to schedule brainstorming sessions between researchers/groups that work at the interface between model scales**. E.g.:
    - those working on models of inflammatory cascades at the cell level meet with individuals simulating whole body adaptation to increases in inflammatory agents;
    - Individuals with expertise in epidemiological spread at the county/state level work with those who model within host development of disease

What projects could we develop that would increase the intensity of community engagement?

What expertise is missing in our community that we should be seeking out?

- **MJ Colebank:** This falls in line with my comments on scientific aims, but if one of the short comings in our group is advertising the importance of modeling to experimentalists, we need an expert in experimental design to help guide us. If the model accurately describes the biological process (big "if" here), it can be used to test scientific hypotheses more rapidly and guide the design of future experiments.
    - As a reference, see the review by Herzg et al. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5735541/

4) **Scientific Aims:**

We have evolved our focus somewhat in the direction of immune digital twins.

Are there other scientific aims or foci that would match our community interests better, expand our community or make our activities more effective?

What other scientific aims should we focus on that would bring in more active members?

- **MJ Colebank**: Towards the end goal of digital twins, mechanistic and statistical models need to be tested against patient data. I believe one of the current areas of open research in physiological modeling is understanding parameter inference, parameter identifiability, and model uncertainty. These are dense scientific areas, but I believe there is less attention dedicated to these topics in mechanistic, physiological modeling.

- To recruit more active members **perhaps we should emphasize a subgroup dedicated to parameter inference and model uncertainty.**
- This would still focus on deriving mechanistic, multiscale models of viral pandemics, but with greater emphasis on parameter identifiability, which is necessary if one wants to consistently integrate serial data recordings in a digital twin.
- What kind of data need to be collected to permit the creation of effective models of infection and in host response?
- **MJ Colebank:** Apologies for missing the meeting yesterday. Following the last points on interacting with experimentalists, understanding **what parameters affect model forecasts** can be used to inform **experimental design**. If we know certain inputs reduce uncertainty or impact model simulation, we can tell experimentalists to measure the data/parameters that would reduce uncertainty in the outputs.

What is a digital twin?
Necessary

A near-real time data feed characterizing the state of an individual

- The data stream informs both the individual DT and is deposited into a population data repository.
- The DT for an individual uses both the individual's data as well as population data.

A model that predicts how that state of that individual will change over time (usually fairly short)
The time choice bifurcates into short-time prediction [on-line] and longer-time [off-line]
I'd like to distinguish model structure, model parameters and model state variables

A comparator that assesses divergence between measured and model states in that individual

A model updater that updates the system in response to divergence [this is controversial but could be as simple as--use the current measured state for the next prediction or it could be as sophisticated as complex learning and automated model structure updating]

An assertion on the range of uncertainty or validity context of the twin

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There are many additional things you **might** want in a digital twin:

A background (static or low frequency) characterization of the individual that provides static parameters which tune the model

A model of the environment that modifies the predicted evolution of the individual state which recognizes that the state evolution is not fully autonomous

A coupling to an ensemble of digital twins that allows model updating based on ensemble performance and therefore allows bootstrapping and model improvement

A system to use the digital twin off-line to evaluate control strategies

Identify control strategies to take individual states from current state to desired state using arbitrary control. [This is parallel to drug development]

Models of possible control interventions.

Inverse problem solvers to identify control strategies to take individual states from current state to desired state using available control.

These are purely generic statements

Now you can begin to ask what special issues come up when developing digital twins for humans and medical digital twins…

Issues with Medical Digital Twins

Specific Demonstration Problems

Specific Examples Related to the Immune System

Generic Representation of the Immune System [Virtual Tissue]--Open source immune system model as a component

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Why do we need mechanistic models to improve on current disease process and treatment process models?

Use of models in hypothesis testing

Because they will be more accurate at predicting time evolution. Because we can establish trustworthiness, because we can evaluate novel strategies which are not present in the training data.

We need examples where nearby initial conditions lead to wildly different outcomes.

Reinhard makes the case that current medical practice is “digital twin” in caricature.

What kinds of data are needed for specific analyses? Key is time series not snapshots.

I come back to the issue the difficulty of comparing actual and predicted observations in the case of medical stochasticity and the question of what we do with observed variance. How do we use these divergences to update our models of individuals (parameters) or our template models (model structure)