**2018 IMAG Futures Meeting – Moving Forward with the MSM Consortium (March 21-22, 2018)**

*Pre-Meeting Abstract Submission Form*

*\*Please submit to the NIBIB IMAG mailbox (*[NIBIBimag@mail.nih.gov](mailto:NIBIBimag@mail.nih.gov)*) by* ***January 8th, 2018***

*\*Save your abstract as “MSM PI Last Name \_ 2018 IMAG Futures Pre-Meeting Abstract”*

**PI(s) of MSM U01: Eric Sobie and David Christini**

**Institution(s): Icahn School of Medicine at Mount Sinai and Weill Cornell Medical College**

**MSM U01 Grant Number: HL 136297**

**Title of Grant:** Multiscale modeling to map cardiac electrophysiology between species

**Abstract**

Which MSM challenges are you addressing from the IMAG 2009 Report and how?

<https://www.imagwiki.nibib.nih.gov/content/2009-imag-futures-report-challenges>

(indicate which challenge (#) you’re addressing)

*You may insert images by copying and pasting below*

6)    Multiscale models strongly coupled with standardized protocols for model-driven data collection

Our combined experimental and computational approach is identifying which experimental protocols are most useful for inferring model parameters

9)    Model predictions that drive a community of experimentalists towards systematic testing and validation

We are demonstrating the power of validating models through the use of systematic protocols and showing how un-validated models can fail

11)  Mechanistic multiscale models that bridge to the population level to capture more clinical and biological realism for the population

Simulations are performed in heterogeneous populations, and the experimental protocols are helping us to quantify the links between molecular-level heterogeneity and functional or phenotypic heterogeneity

Are you using machine learning and or causal inference methodsand how?

*You may insert images by copying and pasting below*

Yes, we have used machine learning algorithms for classifying drugs into dangerous and safe classes based on simulation results and for automatically constraining parameters in models.

Please briefly describe significant MSM achievements made (or expected).

*You may insert images by copying and pasting below*

We have published or submitted for publication several manuscripts. One of these, currently under review, describes a methodology to translate drug responses across cell types. This work will be presented at the meeting, and can be summarized as follows: Quantitative mismatches between human physiology and experimental models can be problematic for the development of effective therapeutics. When the effects of drugs on human adult cardiac electrophysiology are of interest, phenotypic differences with animal cells, and more recently stem cell-derived models, can present serious limitations. We addressed this issue through a combination of mechanistic mathematical modeling and statistical analyses. Physiological metrics were simulated in heterogeneous populations of models describing cardiac myocytes from adult ventricles and those derived from induced pluripotent stem cells (iPSC-CMs). These simulated measures were used to construct a cross-cell type regression model that predicts adult myocyte drug responses from iPSC-CM behaviors. We found that: (1) quantitatively accurate predictions of responses to selective or non-selective ion channel blocking drugs could be generated based on iPSC-CM responses under multiple experimental conditions; (2) altering extracellular ion concentrations is an effective experimental perturbation for improving the model’s predictive strength; (3) the method can be extended to predict and contrast drug responses in diseased as well as healthy cells, indicating a broader application of the concept. This cross-cell type model can be of great value in drug development, and the approach, which can be applied to other fields, represents an important strategy for overcoming experimental model limitations.

Please suggest any new MSM challenges that should be addressed by the MSM Consortium moving forward.

*You may insert images by copying and pasting below*

None to suggest at present.

What expertise are on your team (e.g. engineering, math, statistics, computer science, clinical, industry) and who?

*Please list as “Expertise – Name, email”*

*Biomedical Engineering -- Eric Sobie, eric.sobie@mssm.edu, Biomedical Engineering -- David Christini, dchristi@med.cornell.edu, Applied Physics, Trine Krogh-Madsen,trk2002@med.cornell.edu; Physiology -- Francis Ortega, Biomedical Sciences -- Jingqi Gong*

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