**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: William R. Cannon and Jay C. Dunlap**

**Institution(s): Pacific Northwest National Laboratory, Dartmouth, and Rennsselaer Polytechnic Institute**

**MSM U01 Grant Number: U01EB022546**

**Title of Grant:** **Multiscale Modeling of Circadian Rhythms**

**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*

**3)** Novel methods to fuse data-rich and data-poor scales to enable predictive modeling.

**5)** Reproducible/reusable multiscale models that will be integrated and adopted into model-poor fields.

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

**9)** Model predictions that drive experimentalists towards systematic testing and validation.

**10)** Predictive multiscale models that strongly incorporate uncertainty quantification.

**16)** Novel computational modeling approaches for big data that account for simultaneous sources of data on multiple scales; from biological and physiological measures.

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

*You may insert images by copying and pasting below*

Yes. Most likely we will be using regression methods to learn regulation points.

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

*You may insert images by copying and pasting below*

Prediction of metabolite concentrations in the cell, both those free in solution and bound to enzymes. Prediction of reaction rate constants. Prediction of reaction thermodynamics. Prediction of enzyme and pathway regulation. Integration of stochastic and deterministic formalisms for representing reaction networks. Ability to simulate non-steady state dynamics.

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*

* Modeling complexity – that is, going beyond single steady state situations to model how cells adapt to changing internal and external conditions. Internal conditions may be due to inherent cycles or oscillations within metabolism or the cell cycle, for instance. Non-equilibrium, non-steady state dynamics.
* Technology that allows us to identify putative drug targets or interventions that take into account that the system is complex and adaptive. Technology that allows us to also predict unintended cellular consequences that are manifest as side-effects of interventions –and how to mitigate these.
  + Metabolism is modeled using constraint-based approaches that only model steady states. Even so-called dynamic constraint-based approaches are simply a series of steady states strung together. There is no adaptivity in these approaches.
  + What happens when one perturbs a metabolic community?
* Machine learning that takes into account physical principles. More often than not, the data is not only noisy with higher uncertainty than precision but it also does not represent a measurement of the underlying processes. The use of physical principles will enable inferences in spite of noisy data.
* Methods to predict regulation from principles (could be combined with inference from data). That heterotrophic central metabolism is generally conserved across metazoans implies that there are common principles for regulation of metabolism. Understanding why cells are regulated – from an operational or dynamic perspective, will lead to predicting how cells are regulated.
* Physical understanding of natural selection. How much physical work/energy is required to replicate different cell types? The work/energy required to replicate is the physical quantity that determines the outcome of natural selection, and hence long-term adaptivity. This is especially important for understanding, predicting and controlling human microbiomes and cancers. But it is also important for brain and tissue repair, as well.
* Models of inter-cellular interactions, from microbiomes to the brain. How do cells turn material and energy gradients into information and knowledge? How do the principles of thermodynamics, control theory and dynamical systems lead to abstractions that become encoded as knowledge? How does perception lead to specific molecular interactions between specific cells/neurons and how do these specific interactions lead to self-awareness?

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

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

* *Statistical thermodynamics (physics and math applied to biological systems) – Bill Cannon (*[*William.cannon@pnnl.gov*](mailto:William.cannon@pnnl.gov)*)*
* *Circadian biology and Genetic Engineering – Jay Dunlap (Jay.C.Dunlap@dartmouth.edu), Jennifer Hurley (hurlej2@rpi.edu);*
* *Math, Knowledgebases – Jeremy Zucker (Jeremy.Zucker@pnnl.gov).*

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