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

Pre-Meeting Abstract Submission Form

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Title of Grant: Modeling Brainstem Inflammation's Role in Systemic Dysfunction during Sepsis

Abstract

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

We identified numerous major challenges in the IMAG 2009 report and our work addresses:

1) II. Population Modeling, models need … to integrate diverse and disparate data.

2) IV. Cell-Tissue-Organ Modeling, extending multi-scale models in time to the time courses of … disease progression.

3) IX. Conclusions, #5: The wide range of biological timescales makes it difficult to integrate from atomic, molecular-cellular times and events to organ-body-population levels. Similarly, spatial organization enormously complicates cell systems biology.

We propose to investigate and model the dynamics of the ventilatory pattern variability and cardiorespiratory coupling during systemic infection, to the onset of sepsis and through the course of sepsis. We propose to integrate diverse and disparate data in two distinct modeling approaches. The experimental data we need to integrate will be obtained from male and female rats (Thomas E Dick, PI) and consists of: 1) biologic waveform data, which we quantify with linear and nonlinear measures, 2) cytokine expression in the peripheral and central tissues, focusing on brainstem nuclei which control homeostasis and 3) measures of severity of illness: temperature, leukocytes, C-reactive protein and lactate. The two model types are: agent-based models; Dynamic Network Analysis (DyNA) and Dynamic Bayesian Network (DyBN) models developed by Yoram Vodovotz (CoPI) to track the peripheral inflammatory response and computational models of brainstem circuitry of cardiorespiratory control developed by Yaroslav Molkov (CoPI). Our hypothesis is that integrating these models (joint effort Vodovotz, Molkov&Ken Loparo, CoPI) will provide cross-scale mechanistic explanations for the loss of cardiorespiratory coupling observed during sepsis, identify critical cytokines for therapeutic intervention, and establish a scientific rationale for using variability measures as complementary and sensitive biomarkers of predicting sepsis in severely patient in the medical ICU (Frank Jacono, CoPI). This project will continuously track ventilation and blood pressure, periodically measure cytokines and assess severity of illness over the time course of disease progression. The values of biologic variability, cytokines and severity scores will be incorporated in the DyNA and DyBN models to determine the relationships between peripheral and central inflammatory patterns and between changes in variability and cytokine expression in the spatially organized circuitry controlling homeostasis.

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

While we are not using machine learning, Professor Yoram Vodovotz and his group have utilized DyNA and DyBN models to elucidate networks of cytokine interactions in the periphery that develop during trauma, sepsis, endotoxemia, liver failure, and chronic venous insufficiency. The Vodovotz group

has also used Principal Component Analysis to define subsets of animals and patients undergoing trauma, sepsis, and endotoxemia, as well as defining the dynamic, spatiotemporal propagation of endotoxin-induced inflammation in mice. They have also used novel variants of hierarchical clustering (e.g. fuzzy C-means clustering) to define subsets of trauma patients. In a complementary fashion but applied to very different data, Dr Slava Molkov and his group have developed Bayesian inference methods to characterize synaptic interactions between brainstem neural groups involved in autonomic and respiratory control and afferents based on systems-level physiologic data (ventilation, heart rate, blood pressure). Ultimately, their approach will test hypotheses on the structure of the central control network, its sepsis-related alterations. Further, through iterative processing and accumulation of more data sets, Dr. Molkov will can perform model validation, verification and uncertainty quantification.

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

We just received our funding Oct 1, 2017, so we expect that modeling will provide the following insights: 1) plausible explanation of underlying environment conducive or permitting the observed dynamics in the biologic waveforms. 2) identification of nodal points in the cytokine network at which intervention would alter the projection to uncontrolled inflammation and 3) determination of whether or not ventilatory pattern variability and cardio-respiratory coupling are sensitive biomarkers indicating the magnitude of sickness and the transition from a control inflammatory response defending the body to an uncontrolled inflammation associated with sepsis and with multi-organ dysfunction

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

Granularity: Biologic waveforms can be assessed continually whereas brainstem cytokines are measured at designated time points from homogenized tissue, thus unique sets of animals are required for each time point. We proposed to align samples post hoc. However, our measurements ventilatory pattern variability over 5-min epochs are can vary in the transition period. Once our measures indicate low variability and high predictability stably, the animal may already be in sepsis

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

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