Computational Modeling to Guide Drug Target Discover and Treatment Design in Flu and COVID-19

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ABSTRACT
Computational modeling and controls engineering-based analytics offer the opportunity to drive drug development and treatment optimization for severe respiratory infection. Respiratory infection is a top 10 cause of death in the US in a “normal” year, and COVID-19 has propelled respiratory infection to the 3rd leading cause of death in the US. In the past decade, mounting evidence has suggested that deadly respiratory virus infections, such infections with H5N1 virus, the 1918 Spanish Flu, the 2009 pandemic H1N1 virus and SARS-Cov-2, are associated with distinct immune system dynamics. Complementing this, immunomodulation studies have demonstrated that interfering with our immune system can improve tissue pathology and disease outcome. Since June of 2020, immunomodulatory treatment via select corticosteroids have become the primary approach to treating severe COVID-19 infection.

However, the immune response is a highly complicated, self-regulating system. Systems engineering approaches are well suited to modeling immune complexity and can provide in silico tools for drug target candidate prioritization and immunomodulatory treatment optimization. Here, I will discuss our work on computational modeling of immunodynamics during influenza infection, in which we show evidence that, despite strong differences in the infection outcome, the mechanisms regulating the immune response between animals infected with mild H1N1 viruses or deadly H5N1 viruses are conserved. Moreover, we find that robust dynamic operation of the overall immune response is highly dependent on macrophage activity. Then, we will discuss network-based modeling approaches, including using global network controllability, for predicting host proteins (i.e. factors) that are essential for influenza virus replication. Using an siRNA screen to validate network predictions, we demonstrate that data-driven subnetwork construction is a successful approach for predicting novel drug target candidates. This approach has recently been applied to COVID-19 data, suggesting new possible molecules for therapeutic consideration.

BIO
Dr. Jason Shoemaker is an assistant professor in the Dept of Chemical and Petroleum Engineering with secondary appointments in the School of Medicine’s Dept of Computational and Systems Biology and the McGowan Institute for Regenerative Medicine at the University of Pittsburgh. He received his BS of chemical engineering at the University of Florida and his PhD of Chemical Engineering with emphasis on computer science from the University of California, Santa Barbara. After graduation, Dr. Shoemaker spent 6 years as a member and eventually the leader of the Japan Science and Technology Agency’s ERATO Infection-Induced Host Responses project’s Systems Biology Core. In 2015, he joined the University of Pittsburgh, where he is the program director (PD) and principal investigator (PI) of the ImmunoSystems Lab, where we develop and use cutting-edge computational tools to address questions on the mechanisms of disease and perform model-based treatment design. Our lab toolset includes model-based analysis, bioinformatics, machine learning and systems theory. Our recent research efforts have focused on modeling and improving immune responses during severe respiratory infection, with major emphasis on influenza virus infection and COVID-19. He was awarded the NSF CAREER Award in 2020 and Dr. Shoemaker is also the proud mentor of a Howard Hughes Gilliam Award winner, Emily Ackerman. Together, they work to promote more accessible and supportive research environments in academia.