MODELING HOST-PATHOGEN INTERACTIONS: COMPUTATIONAL BIOLOGY AND BIOINFORMATICS FOR INFECTIOUS DISEASE RESEARCH

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Introduction

Infections are a major cause of both human disease and loss of crop yields and animal stocks and thus cause immense damage to the worldwide economy. The significance of infectious diseases is expected to increase in an ever more connected warming world, in which new viral, bacterial and fungal pathogens can find novel hosts and ecologic niches. At the same time, the complex and sophisticated mechanisms by which diverse pathogenic agents evade defense mechanisms and subvert their hosts networks to suit their lifestyle needs is still very incompletely understood especially from a systems perspective [1]. Thus, understanding host-pathogen interactions is an important and timely topic.

Recently technological advances have afforded the opportunity to investigate host-pathogen interactions on a level of detail and scope that offers immense computational and analytical possibilities. Genome sequencing was pioneered, in part, with pathogens; and, the number of strains and variants of pathogens sequenced to date vastly outnumbers the number of host genomes available. At the same time, for both plant and human hosts more and more data on population level genomic variation becomes available and offers a rich field for analysis into the genetic interactions between host and pathogen.

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On a molecular level deep-sequencing [2], increasingly sophisticated proteomic tools [3] and recently interactome analysis [4-7] have emerged as powerful tools to dissect pathogen virulence programs and to investigate how pathogens rewire cellular transcriptional and protein networks [8]. However, very difficult problems are posed by these interactions in terms of data analysis, making useful predictions, and modeling. The rapid evolution of pathogens, coupled with the strong selection exerted by the host defense system means that pathogens can be exquisitely adapted to their environments. The exploitation of the host by the pathogen can prove difficult to extract from experimental observation of these interactions [9, 10]. Knowledge of these interactions has direct applications in terms of improved therapeutic strategies. Historically, the molecular and structural differences pathogens and their hosts have been exploited as targets and led to some of the most successful treatments of disease ever developed, for example vaccines, antibiotics and antivirals. However, a major problem confronting the medical and research communities currently is that of the development and rapid growth of antibiotic resistance in a large number of important pathogens for a range of traditional antibiotics. Accordingly, developing methods to study these pathogens with the eventual goal of developing novel therapies is of utmost importance.

This session is focused on discussing computational approaches to studying the interactions between pathogens and their hosts. The session is composed of an invited talk, three selected papers, and a discussion panel.

The invited speaker, Dr. Ram Samudrala Department of Microbiology University of Washington, is a pioneer in the area of structural prediction. His recent work employs modeling approaches to aid in drug discovery, and he is a recipient of a prestigious NIH Pioneer award to identify novel drugs that target various pathogens using computational approaches.

Interactions between a pathogen and its host are dynamic with the pathogen executing a complicated virulence program during infection and the host activating a number of orchestrated defense responses to counter the pathogen. Gordan, et al. employ comparative genomics, promoter analysis and transcriptional data from the fungal pathogen Candida albicans to identify a set of genes that may have a role in the activating or maintaining the virulent hyphal state.

Franzosa, et al. and Nouretdinov, et al. describe methods for predicting protein-protein interactions (PPIs) between pathogen effector proteins and their host targets. These interactions

form the interface between host and pathogen and are targets for further experimental investigation and potentially therapeutic drug development. Franzosa, et al. describe a careful evaluation of their method for predicting PPIs based on homology modeling of protein structures and corresponding interactions. Nouretdinov, et al. use a novel statistical approach, the conformal method, to predict PPIs between HIV proteins and the human host and provide a corresponding confidence measure.

In the discussion panel we will discuss issues related to the computational analysis and modeling of host-pathogen interactions, outline major barriers to current work, and identify upcoming challenges given the state of the field today. We believe this session will provide a solid basis for further discussion in this important area.

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