Journal of
Computer Science & Systems Biology
ISSN: 0974-7230

Madrahimov and Lu, J Comput Sci Syst Biol 2016, 9:5
DOI: 10.4172/jcsb.1000e113

Editorial Open Access

Predicting Virus Evolution for Improved Influenza Vaccine Decision

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Influenza viruses are a persistent threat to public health causing annual epidemics and sporadic pandemics. Globally, influenza results in three to five million cases of severe illness and up to a half million deaths each year, with the number of human infections and fatalities much higher during pandemics [1]. Despite decades of research, only two classes of antiviral drugs (adamantanes and neuraminidase inhibitors) are FDA approved for the treatment of influenza infection. Increasing concern for drug resistance highlights the importance of vaccines in public health preparedness for the prevention and control of infection during seasonal epidemics as well as pandemic preparedness. The current vaccination strategy, however, has long-recognized challenges associated with the update and manufacture of vaccines [2].

The World Health Organization (WHO) Global Influenza Surveillance and Response System coordinates a worldwide effort to monitor the evolution and geographic distribution of various strains for recommendations on the composition of influenza virus vaccines. As part of the influenza surveillance, the hemagglutination inhibition (HI) assay is routinely used to identify antigenic variants. It detects the ability of reference antisera to prevent the attachment of influenza hemagglutinin to red blood cells that results in agglutination. Traditionally, the HI data were presented in a tabulated format with difficulty to identify trends of antigenic evolution. To address this issue, antigenic cartography was developed to assemble HI data and visualize antigenic distance of H3N2 viruses [3]. Large movements within the antigenic maps or formation of new clusters represent antigenically novel strains that are potential candidates for future vaccines. This cartography method has been extended with the incorporation of genetic data to investigate the dynamics of circulating influenza viruses including H1N1 and B viruses [4]. The study used a statistical approach to correlate antigenic drift with influenza incidence patterns, thereby demonstrating the possibility of predicting which lineage will predominate.

The development of computational tools to predict antigenicity based on sequences has the potential to rapidly identify antigenic variants for vaccine seed-strain selection. Immunological assays are labor-intensive and only few strains are antigenically characterized. A high-throughput sequencing method can be used to screen potential vaccine strains for further experimental validation by immunological assays. The addition of prediction tools will shorten vaccine development time, improve coverage, and be more cost-effective. In this effort, several methods have been developed to incorporate data from genomic sequences and antigenic assays.

A machine learning method trained with historic serologic and HA sequence data was developed to create a sequence-based antigenicity scoring function for H3N2 [5]. The method known as Antigen-Bridges allows the antigenic distance between a novel influenza virus and known virus to be quantified solely from its sequence. A web-based tool was developed for tracking changes of seasonal H3N2 influenza viruses through mapping antigenic changes to a phylogenetic tree constructed from HA sequences (nextflu.org) [6]. Another computational platform, PREDAC-H3, implements a feature-based model to predict antigenic variation of H3N2 viruses with HA sequences (http://biocloud.hnu.edu.cn/influ411/html/index.php) [7]. This bioinformatics tool has been proven to have improved vaccine strain recommendation for China. To predict the frequencies of influenza clades, a population-fitness model has been formulated to incorporate the adaptive epitope changes and deleterious mutations outside the epitopes [8]. The ability of this model to forecast which strains are likely to become dominant appears to be less informative for H1N1 than H3N2.

Although computational prediction of influenza virus evolution is challenging, recent progress has shown promise in identifying emerging strains for vaccines. An integration of different methods is needed to expand the prediction range of the focal viruses besides H3N2 and improve accuracy. Further improvements must have the ability to weigh specific antigenic mutations, as single amino acid changes have been shown to cause large differences in antigenicity. In addition, current prediction tools rely on training datasets from previously identified antigenic sites. Therefore, an accurate understanding of the molecular dynamics between the globular head domain of HA and antibody binding is needed to further characterize specific antigenic sites conferring antibody-escape. To address inherent variations in immune response and human antibody landscape, a systems biology approach may yield insight on improving vaccine efficacy in immunocompromised populations. Further research on molecular interaction between influenza virus and human and improvement of computational methods could eventually address the challenges of vaccine strain selection for enhanced influenza control and prevention.

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Received August 04, 2016; **Accepted** August 06, 2016; **Published** August 10, 2016

Citation: Madrahimov A, Lu G (2016) Predicting Virus Evolution for Improved Influenza Vaccine Decision. J Comput Sci Syst Biol 9: e113. doi:10.4172/jcsb.1000e113