VIRTUAL FLU, A DIFFERENT KIND OF COMPUTER VIRUS

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EXECUTIVE SUMMARY:

Influenza infection is routinely responsible for hundreds of thousands of deaths annually, punctuated by catastrophic pandemics roughly every 25 years. Some experimental techniques used to study the virus suffer from serious drawbacks. For example, structural biology methods like electron microscopy and X-ray crystallography typically lack either the atomic resolution or size scaling required to answer a number of pharmacologically important questions. Additionally, "gain-of-function experiments," aimed at anticipating the genetic changes that might produce the next pandemic, could prove disastrous were artificially enhanced viral strains to escape the lab [1].

To address these concerns, we have constructed an atomic-resolution model of the entire influenza viral coat, containing 210 million atoms. We are presently performing simulations of this large-scale system in order to gain a more complete understanding of the influenza infection process. This research will allow us to explore novel opportunities for drug and vaccine development *in silico* and test how structural changes impact virulence without having to create novel strains with pandemic potential.

INTRODUCTION

We have focused our research on the viral surface coat because of the important role it plays in both the initial and final stages of the influenza infection process. The viral coat is comprised of a lipid bilayer from which two spike-like glycoproteins, neuraminidase and hemagglutinin, protrude (fig. 1). When a viral particle first approaches a host cell, the hemagglutinin proteins latch onto sialic-acid molecules attached to the cell surface. Once bound to the human cell through these molecular linkers, the virus enters the cell and reproduces. Following replication, the viral progeny bud out from the cell but remain attached to its external surface by the same sialic-acid connections. Influenza's second glycoprotein, neuraminidase, is responsible for severing those tethers, allowing the newly formed viruses to depart and infect the next cell [2].

The viral coat has been extensively studied precisely because it is so critical for infection. By analyzing the molecular structures of the various components of the surface coat in isolation, researchers have produced a number of anti-flu drugs currently used clinically (e.g., Tamiflu). Unfortunately, flu is highly adaptable and resistance to these medicines has already been documented [3–14]. There is an urgent need for novel therapeutics. Studying the structures and motions of the various surface-coat components when assembled into their natural multi-component environment, rather than in isolation, will provide pharmacologically relevant insights that will help us combat future pandemics. No current experimental technique is capable of providing an accurate model of the entire surface coat at the resolution needed for drug discovery; fortunately, modeling and simulation can serve as a "computational microscope" that provides the needed information.

Additional influenza studies have shown how changes in the components of the influenza surface coat affect virulence. By evolving viruses in the lab that are more infectious than the corresponding natural strains, researchers seek to anticipate future virus mutations that might lead to the next pandemic [15–25]. But the possibility that an artificially enhanced virus might escape the lab concerns some people [1]. Indeed, accidents have happened in the past. The 1977 flu pandemic may have come from a lab-preserved strain [26–28], and in 2014 the CDC accidentally contaminated a biological sample sent to external collaborators with a highly pathogenic influenza virus [29]. The latter accident was only discovered during an investigation into a similar anthrax contamination. By providing a reliable computational model of the viral surface, we hope to reduce the need for these kinds of risky experiments.

METHODS & RESULTS

Guided by experimental data, we have successfully constructed several surface-coat models. When immersed in a bath of virtual water with the appropriate electrolytes, each system contains over 200 million atoms (fig. 2). Our collaborator (Steven) used electron microscopy to identify the general shape of the influenza virus and the approximate locations of the glycoprotein spikes [30]. We then used computational methods developed in our lab to wrap this virus volume in a virtual lipid bilayer [31] and position atomic-resolution models of the glycoproteins at the appropriate locations. We were thus able to transform the low-resolution microscopic data into a high-resolution, atomistic model suitable for molecular dynamics simulations and, ultimately, drug discovery. We are currently running a simulation of one of these virtual viruses on the Blue Waters supercomputer.

WHY BLUE WATERS?

Blue Waters has been critical for this project. To our knowledge, a molecular dynamics simulation on so grand a scale has never before been attempted. Very few supercomputers are capable of the petascale performance required. Without the Blue Waters NSF PRAC allocation, the current work would be impossible.

In the coming year we anticipate completing the first simulation of this large-scale system. This simulation will provide important information about the surface motions and electric fields that surround the viral particle. These "dynamics" and "electrostatics" govern not only the infection process, but also drug and vaccine binding. They will allow us to study important characteristics of the virus without having to actually create new, potentially lethal flu strains in the lab.

FIGURE 1 (BACKGROUND): The influenza surface coat. The hemagglutinin & neuraminidase glycoproteins of our model are represented in lavender and magenta, respectively. The enveloping lipid bilayer is represented in glossy pink. Credit: Jacob D. Durrant.

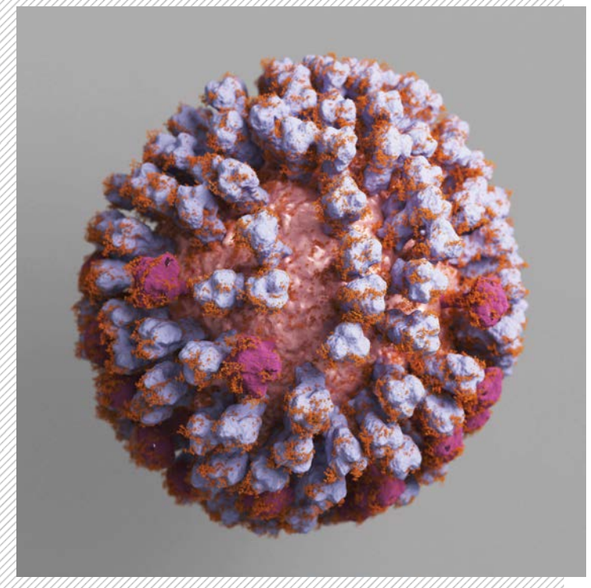

FIGURE 2: The viral surface coat, with selected neuraminidase and hemagglutinin glycoproteins rendered transparent, revealing the underlying protein backbone. This image highlights the fact that these renderings were generated from high-resolution (ultimately atomic-resolution) data. Credit: Jacob D. Durrant.