INFLUENCE VIRULENCE AND TRANSMISSIBILITY THROUGH THE COMPUTATIONAL MICROSCOPE

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EXECUTIVE SUMMARY

This work explores Influenza A Virus (IAV) biology using the "computational microscope": a powerful, continually improving tool capable of disclosing moving pictures of the unseen atomic world of biological systems, including viruses. The team has integrated experimental structural data to push the boundaries of computer simulations toward larger scales while increasing the complexity and realism of the modeled constructs. This allowed the team to build a mesoscale IAV model of the currently circulating A/Michigan/45/2015 (H1N1) strain, and to perform all-atom molecular dynamics (MD) simulations of the massive (161-million-atom) system. MD provided unique insights on virus dynamics and glycoprotein interplay that is otherwise not accessible through individual protein simulations, which will shed light on the role played by glycans in modulating IAV virulence and transmissibility.

RESEARCH CHALLENGE

IAV causes severe illness and thousands of deaths every year. The virus can undergo random resorting of its segmented genome that may result in devastating worldwide pandemics. In this concerning scenario, the most critical mutations are usually found in two membrane glycoproteins: hemagglutinin (HA) and neuraminidase (NA), characterized by a wide population of carbohydrates located on their surface. Glycans are implicated in numerous viral processes, such as infectivity, pathogenicity, transmissibility, protein cooperativity, and small-molecule binding, thus deeply affecting IAV biology [1]. The number of glycosites exposed by HA and NA changes at regular temporal intervals and alters IAV antigenic properties [2], providing one explanation for why IAV represents a relentless health threat requiring vaccines to be updated every few years.

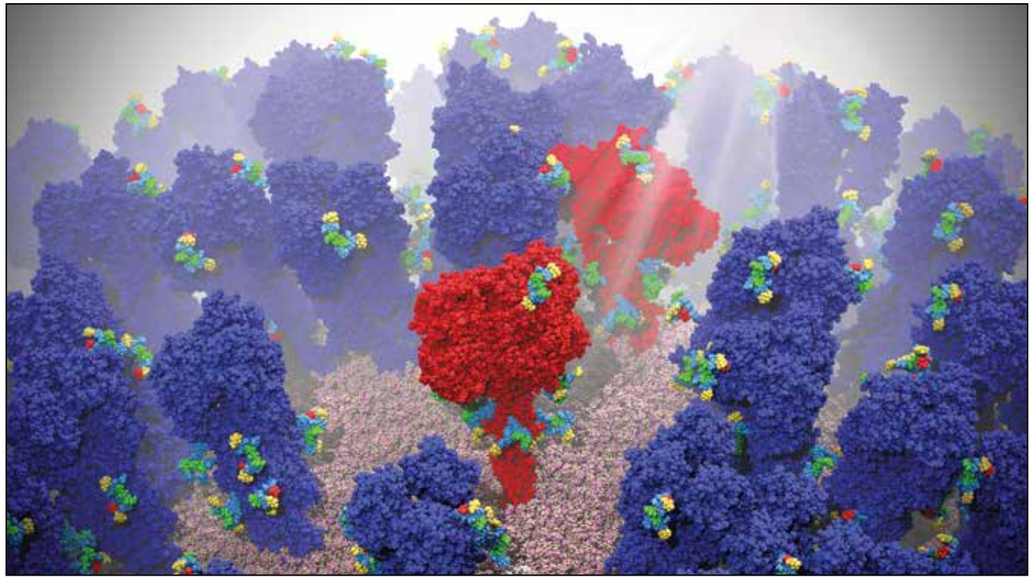

Figure 1: Snapshot after 420 nanoseconds of all-atom molecular dynamics simulation on the whole Influenza A/Michigan/45/2015 (H1N1) viral coat. Glycans (colored using the Symbol Nomenclature for Glycans standard) have been added on the two fundamental glycoproteins, neuraminidase and hemagglutinin (shown in red and blue, respectively), deeply affecting their dynamics and interplay. Credit: Dr. Lorenzo Casalino.

Experiments aimed at deciphering how minute modifications in glycoprofiles can impact IAV functions are strongly hampered by glycans' high variability, flexibility, and small size. Computer simulations and modeling techniques, assisted by a continual growth of hardware and software technologies, constitute a viable alternative approach [3,4].

With access to Blue Waters' high-performance resources, the research team was able to build and simulate a realistic all-atom viral coat model of the A/Michigan/45/2015 (H1N1) virus, crossing multiple spatial and temporal scales. Mutations that occurred within the antigenic site located on the HA head of this pathogen were so dramatic that in 2017 the World Health Organization decided to change the vaccine composition to target this specific strain. The research team seeks to elucidate the key roles of glycans in IAV biology and their impact on immune response escape.

METHODS & CODES

The preparation of the glycosylated A/Michigan/45/2015 (H1N1) system was based on the pandemic 2009 H1N1 viral coat built by Durrant *et al.* [4], which was in turn shaped upon cryoelectron tomography structural data [5]. This model, including NA, HA, and M2 proton channels embedded in a lipid bilayer, was overall ameliorated and upgraded with the addition of glycans on the glycoproteins' spikes, thus notably increasing its complexity. After setting the glycosylation profiles and detecting all the N–X–S/T sequons exhibited by HA and NA, specific oligo-mannose, hybrid, and complex glycans were iteratively added on all the 236 HA trimers and 30 NA tetramers using the doGlycans tool [6] integrated with in-house scripts. After the addition of glycans and model refinement, the resulting 161-million-atom virion was ready to undergo MD simulations in explicit water and isothermal–isobaric conditions (NPT), using the memory-optimized version of NAMD 2.13 [7] and the CHARMM36 all-additive force field [8].

RESULTS & IMPACT

In this work, the research team has dramatically increased the level of accuracy of its previous IAV construct [4] by adding a total of 1,791 glycans on the HA and NA spikes. The extreme variability of the glycoprofiles exhibited by NA and HA has often discouraged investigators from modeling the glycans in computer simulations, thus neglecting their critical functional and structural contributions. By incorporating information from collaborators, bioinformatics, and experimental data into this computational approach, the research team has given rise to an even more realistic system crossing different spatial scales, from the atomic/molecular level of single glycans and proteins to the subcellular scale of the viral coat as a whole. MD simulations were conducted on Blue Waters using 4,096 XK nodes, which allowed us to collect an average of 15 nanoseconds (ns)/day, for a total of 420 ns and 18 terabytes of generated data. Although this research is still in progress, preliminary inspection and analyses have revealed an exceptional interplay among the glycoproteins co-adjuvated by the attached glycans (Fig. 1). The observation of similar behavior with this level of accuracy and statistics, and the same biological significance, could have not been ascertained from single glycoprotein simulations. This work, embracing a multiscale computational protocol without losing the atomic detail, represents a cutting-edge attempt to bridge some gaps in the understanding of the IAV biology deriving from current experimental limitations.

WHY BLUE WATERS

Having access to a platform such as Blue Waters was absolutely crucial in order to perform MD simulations of such a massive system and to achieve a relevant amount of sampling. Carrying out the research on lesser supercomputers would have been beyond the bounds of possibility. Blue Waters' efficient parallelism and tremendous scale provided outstanding performance in a timely fashion, enabled by using a memory-optimized version of the NAMD code specifically tweaked for XK and XE nodes and suitable for running MD simulations of multimillion-atom systems.