

HOW MEMBRANE ORGANIZATION CONTROLS INFLUENZA INFECTION

Allocation: GLCPC/640 Kwh

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EXECUTIVE SUMMARY

Viruses such as influenza infect cells via a process of membrane fusion between the viral envelope and cellular membranes. We have shown experimentally that changing the membrane composition of either the influenza virus or its target cellular membranes can affect the rate and efficiency of infection, but a detailed molecular

explanation for these effects is not experimentally accessible. We are, therefore, using molecular dynamics simulations to study how both the viral and target membranes reorganize in response to changing composition. We analyze these via machine-learning approaches and compare to experimental data that our collaborators and we measure.

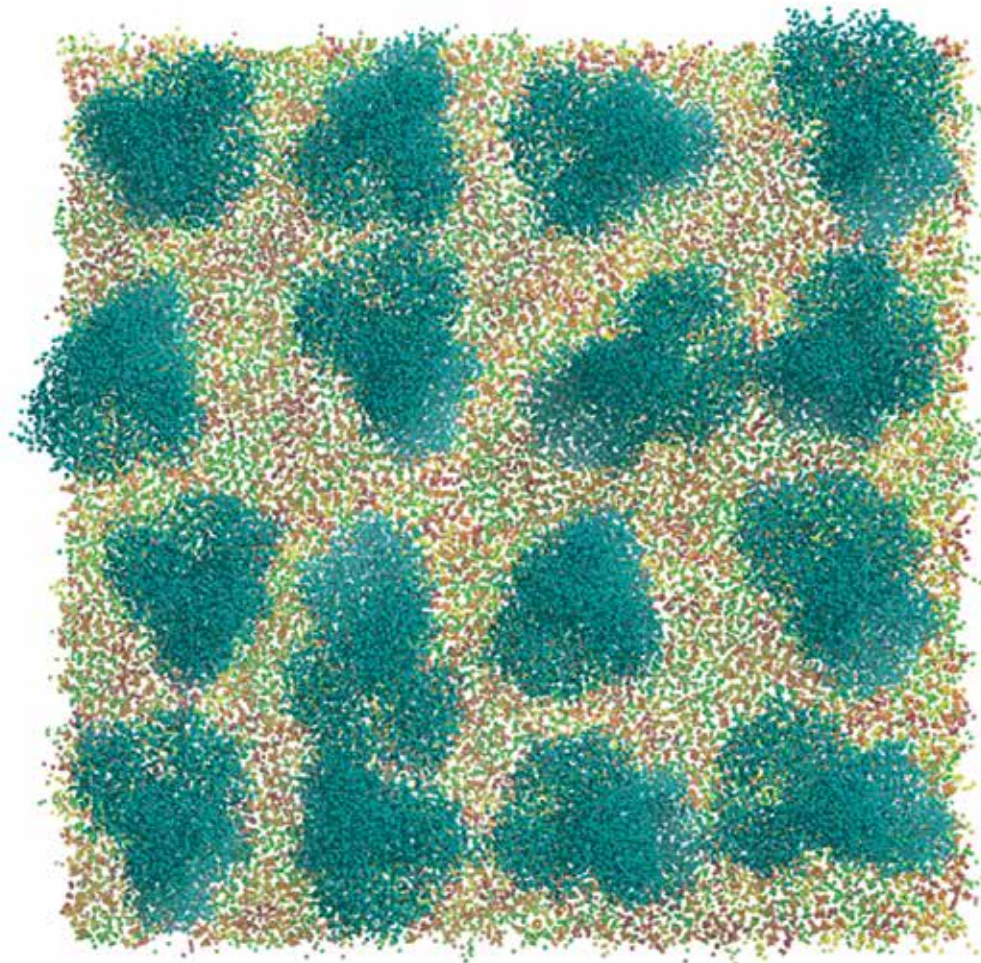


Figure 1: This image shows a model of an influenza membrane patch. Components of the membrane are varied to match experimental perturbations and compared to experimental measurements.

RESEARCH CHALLENGE

We seek to understand how influenza viral infection responds to membrane perturbation. Initial data suggest that lipid-modifying drugs may have potential as antivirals, but we do not understand their mechanism. Even the fundamental lipid biophysics of viral membrane organization is unknown, and the link from atoms to patients is a grand challenge in understanding and treating viral infection.

METHODS & CODES

We incorporate structural data from X-ray crystallography and cryo-electron microscopy along with mass spectrometry to construct initial models of influenza viral and target membranes. These membrane patches are then simulated using the molecular simulation software that we helped develop, Gromacs, and are measured under perturbations that match what we do experimentally. We use in-house machine-learning methods to analyze the simulations and connect them back to experiments. This then yields a model of the membrane response and its infectious consequences at a high level of molecular detail yet also with experimental validation.

RESULTS & IMPACT

Our results thus far have yielded a new membrane-organizing principle that explains our experimental data on influenza virus binding and cell entry. This molecular explanation helps us understand how the influenza virus responds to membrane changes and is likely applicable to cellular signaling as well. Such detailed molecular models of mesoscale phenomena would not be possible without this combination of precise biophysical experiments and large-scale computing.

WHY BLUE WATERS

Blue Waters offers a large number of GPUs that are tightly coupled by a fast Cray interconnect, permitting us to run many simultaneous simulations that each use a number of GPUs to accelerate the calculation.