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MODELING OF A ZIKA VIRUS ENVELOPE AT ATOMIC RESOLUTION

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EXECUTIVE SUMMARY

In 2015, a rampant epidemic of Zika virus infection spread from Brazil to the rest of the Americas. The responsible pathogen, the Zika virus, continues to pose a major health concern. Infections have been linked to the development of Guillain–Barré syndrome in adults and microencephaly in infants. The dangers posed by the Zika virus and other flaviviruses such as the West Nile and Dengue viruses call for a better understanding of their structures and infection mechanisms.

Enhanced knowledge about such viruses can allow scientists to design effective drugs and vaccines to combat future outbreaks. The goal of this project is to provide an atomic-level description of the structure and dynamics of the Zika virus envelope—the outer shell of the virus particle made of protein and lipid—via modeling and molecular dynamics simulations. The team also explored how the stability of the viral envelope depends on the presence of a lipid bilayer and its composition.

RESEARCH CHALLENGE

Zika virus, a flavivirus, is a 40-nm-diameter particle consisting of an envelope and a nucleocapsid. The viral envelope of a mature Zika virus has three components: E proteins, M proteins, and a lipid bilayer (Fig. 1). Recent cryo-electron microscopy [1,2] studies have shown that 180 copies of each E and M protein are icosahedrally arranged in the viral envelope. Both E and M proteins are embedded (either fully or peripherally) into a lipid bilayer lining the inner shell of the Zika virus envelope.

The modeling of E and M proteins anchored into the lipid vesicle with proper lipid packing density is the most challenging part of this project. The number of lipid molecules needs to be as accurate as possible to assemble a reliable and structurally stable viral envelope with correct "breathing" dynamics. The goal is to develop a model for the Zika virus envelope with full atomistic detail in explicit aqueous medium (20 million atoms) and to thereby gain dynamic information on the particle.

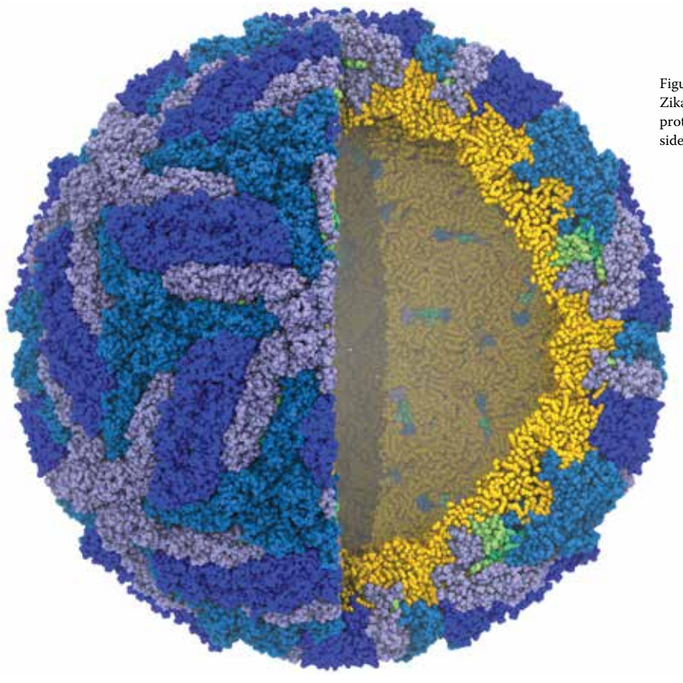

Figure 1: Cross-section of an atomistic model of a complete Zika virus envelope consisting of a protein shell (E and M proteins shown in blue and green, respectively) on the outer side and a lipid bilayer (yellow) forming the inner part.

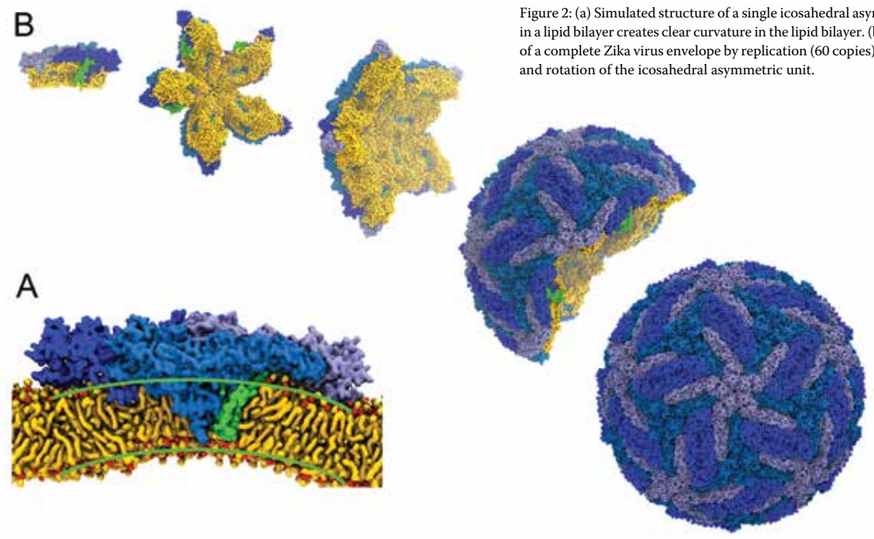

Figure 2: (a) Simulated structure of a single icosahedral asymmetric unit in a lipid bilayer creates clear curvature in the lipid bilayer. (b) Formation of a complete Zika virus envelope by replication (60 copies), translation, and rotation of the icosahedral asymmetric unit.

METHODS & CODES

The research team developed and simulated three different systems: (1) a viral protein envelope in the absence of llipids, to serve as a control; (2) a viral protein envelope enclosing a lipid membrane composed of only neutral lipids, to study how lipids contribute to the stability of the shell; and (3) a viral protein envelope enclosing a lipid membrane with a native composition, to examine the effect of specific lipids.

The molecular dynamics (MD) simulations were performed with NAMD [3], a highly parallelized, GPU-accelerated, publicly available MD program with demonstrated scalability to hundreds of thousands of processors for both single- and multiple-replica MD simulations. All-atom MD simulations rely on the accurate integration of the equations of motion for all atoms of the system. The total potential energy of the system was described by the CHARMM36m force field [4,5]. Periodic boundary conditions were used to avoid surface effects at the simulated system's boundary, allowing the efficient computation of nontruncated electrostatic interactions by the fast Fourier transform-based particle-mesh Ewald method [6].

RESULTS & IMPACT

To develop a structural model for the whole Zika virus envelope, the researchers first placed a single icosahedral asymmetric unit [2] containing three E and M proteins in a lipid bilayer with a native composition. They relied on lipidomic analysis of other flaviviruses [7,8] for the composition of the lipid bilayer. A short, 50-nanosecond simulation (Fig. 2a) showed some clear curvature generated in the lipid bilayer by the envelope proteins, which might be indicative of specific lipid–protein interactions leading to the budding process. The next step was to create a boundary defining the maximum spread of the single icosahedral asymmetric unit using a convex hull algorithm and to select a lipid patch that is covered by the proteins. This single protein–lipid patch is replicated 60 times to form the entire Zika virus envelope (Fig. 2b). Since the team's current model is still imperfect in terms of lipid packing density, they focused on estimating the number of lipid molecules as correctly as possible by measuring the volume in the lipid layer excluded by the stem and transmembrane helices of the proteins. To overcome the lipid–protein overlaps, the team is now designing a grid-force-based simulation protocol.

This project will have a great impact in the modeling of complete virus systems, which can then be used to study the viral infection mechanism.

WHY BLUE WATERS

The research team plans to simulate three 400-nanosecond simulations of approximately 20 million (M) atoms each by NAMD, which can only be achieved on a petascale computing platform such as Blue Waters. GPU acceleration on Blue Waters allows meaningful simulation timescales. NAMD has been extensively tested and optimized for Blue Waters and shows sustained petascale performance. The team's benchmarks on 20M atoms show efficient performance (> 82.6%) while using up to 362 Blue Waters GPU (XK7) nodes.