LARGE-SCALE COARSE-GRAINED MOLECULAR SIMULATIONS OF THE VIRAL LIFECYCLE OF HIV-1

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EXECUTIVE SUMMARY

A key step in the lifecycle of human immunodeficiency virus type-1 (HIV-1) is the production of enveloped particles containing viral proteins and genomes from infected cells. Experimental data suggest that the HIV-1 Gag polyprotein orchestrates this process through subdomains that specifically interact with the cell membrane, viral nucleic acid, or other Gag polyproteins. Nonetheless, the molecular details of this process have remained elusive. Using large-scale coarse-grained molecular simulations, enabled by the use of Blue Waters, we investigate a network of critical interactions that regulate the early stages of HIV-1 assembly, packaging, and budding (Fig. 1).

RESEARCH CHALLENGE

The proliferation of HIV-1 requires the aggregation of viral proteins and genetic material at the membrane of an infected cell, leading to the release of viral particles that spread the infection. Specifically, thousands of copies of the HIV-1 Gag polyprotein self-assemble into the so-called immature lattice at the cell membrane in the presence of viral RNA [1]. Disruption of this highly dynamical process is therefore a potential therapeutic target, and offers a blueprint for treating a range of viral infections. However, we lack a detailed molecular understanding of the factors that regulate this process due to limitations in conventional experimental techniques. Controlled study of the aggregation and interactions of large numbers of biomolecules at cell membranes is a challenging problem but can provide significant benefits for biomedical research and advance fundamental biophysical knowledge.

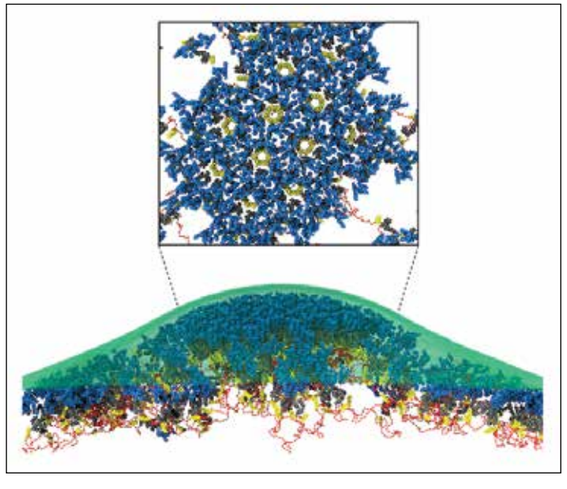

Figure 1: Molecular snapshot depicting early assembly of Gag polyprotein (blue, yellow, and grey tubes) as catalyzed by RNA (red chain) at the site of a deforming membrane puncta (translucent green sheet).

METHODS & CODES

To investigate the self-assembly of the immature protein lattice of HIV-1, we created large-scale coarse-grained (CG) molecular models of the relevant viral components and the cell membrane based on experimental data from collaborators [2,3]. CG models are computationally efficient representations, enabling computer simulations to be performed at time- and length-scales that are otherwise impossible. We performed molecular dynamics simulations using the LAMMPS software package (Sandia National Laboratories, USA) to examine the self-assembly of viral proteins, and the influence of the cell membrane and viral genome on the "budding" of viral particles. In collaboration with experimental colleagues from around the globe, we combined our simulation results with experimental data to better understand key aspects of the early stages of the HIV-1 viral lifecycle.

RESULTS & IMPACT

By combining computer simulations with fluorescence localization experiments [4], we elucidate the interactions that regulate HIV-1 viral assembly dynamics. Specifically, analysis of our results reveals the influence of nucleic acids and the cell membrane in promoting the aggregation of HIV-1 Gag polyprotein via a multi-step, self-correcting nucleation process. We also illustrate the functional importance of the N-terminal, C-terminal, and spacer peptide 1 (SP1) protein domains, which are each responsible for regulating different lattice qualities. These aspects are difficult or impossible to control precisely in conventional experimental approaches but are tractable in the context of our large-scale CG models. The success of our simulations, and the methodology we use to generate CG models of complicated biomolecules, suggest a simple and robust approach to the direct incorporation of experimental data into CG model generation. We envisage that our general methodology will be transferable to the study of other biomolecular processes and open up new avenues of research into phenomena that occur at physiologically relevant time and length scales. The insight gained by large-scale CG analysis can then be used to assist in the design of new therapeutic approaches to viral infection.

WHY BLUE WATERS

Despite the relative efficiency of CG models, our simulations require large numbers of individual molecules interacting over relatively long molecular time scales. Furthermore, in order to study the influence of viral RNA and the cell membrane on protein self-assembly, we must probe the behaviors of this system under a wide range of biologically relevant conditions. It was therefore crucial to the success of our project that we had access to very large amounts of computational power, and that power needed to be combined with superior network performance: the tightly coupled parallel nature of our simulations require latency and bandwidth characteristics that are simply not available in cloud computing. The Blue Waters computing platform thus presented a natural choice for our work; the combination of leadership-class computing capabilities with cutting-edge network hardware allowed us to successfully investigate a system of significant biomedical interest. Our large-scale CG models are generated using techniques developed for previous work on the Blue Waters platform [5], and existing relationships with Blue Waters technical project staff greatly assisted in the deployment of novel simulations on Blue Waters.

PUBLICATIONS AND DATA SETS

Grime, J., et al., Coarse-grained simulation reveals key features of HIV-1 capsid self-assembly. *Nat. Commun.*, 7 (2016), p. 11568.