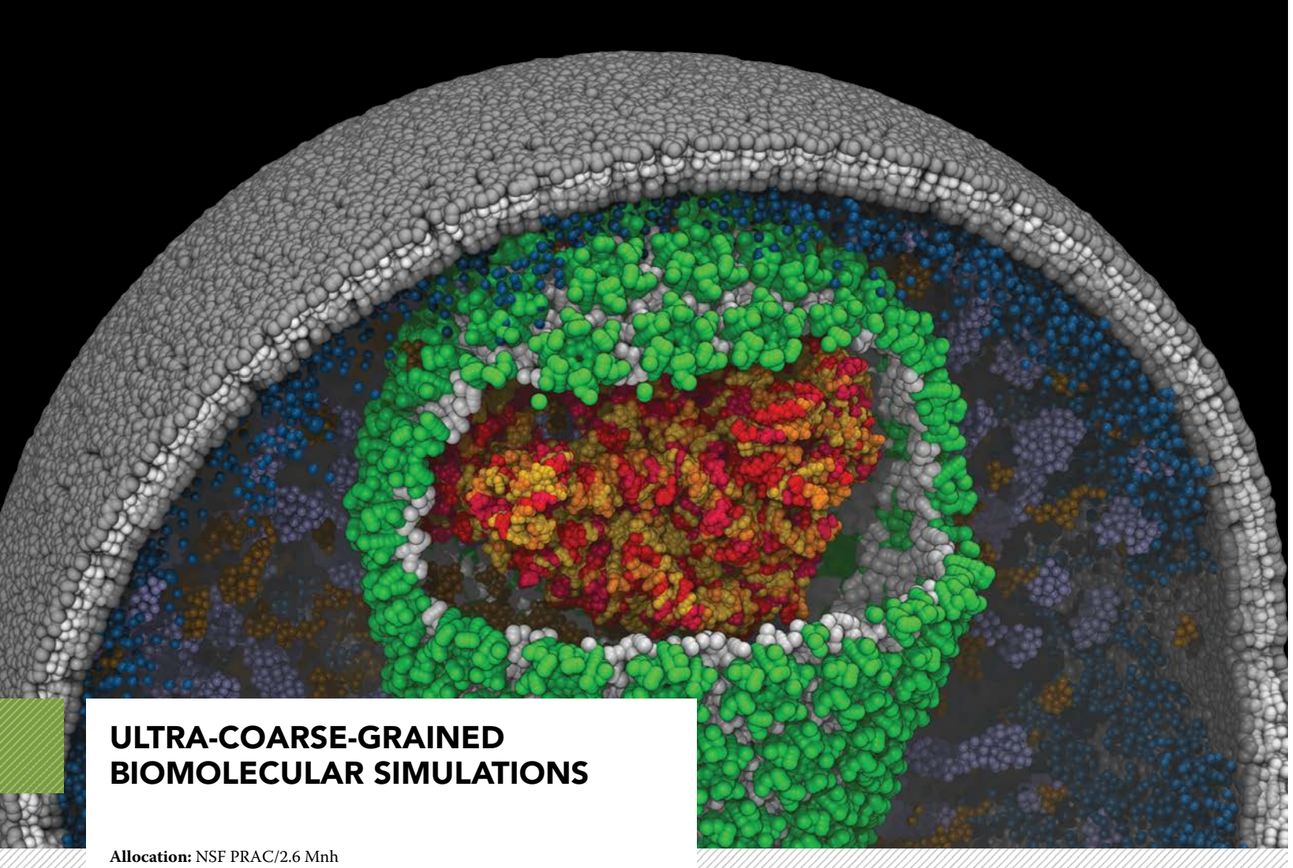

ULTRA-COARSE-GRAINED BIOMOLECULAR SIMULATIONS

Allocation: NSF PRAC/2.6 Mnh
PI: Gregory A. Voth[1]
Collaborator: John Grime[1]

[1]The University of Chicago

EXECUTIVE SUMMARY:

The spread of HIV-1 infection requires the release of a viral particle, or virion, from an infected cell. A newly released virion is non-infectious, and so a sophisticated process of "maturation" occurs in order to produce a mature and infectious virion. One critical aspect of maturation is the self-assembly of many copies of the viral capsid protein to generate a cone-shaped capsid structure that surrounds the viral RNA; where a suitable capsid is not formed, the virion remains non-infectious. In order to study the critical early stages of capsid formation, we use a simplified model of the capsid protein and examined the capsid self-assembly behaviors in a range of environments relevant to the maturing HIV-1 virion. The results of these computer simulations revealed the critical importance of protein concentration, molecular crowding, and dynamic changes in capsid protein structure in the nucleation and growth of the mature viral capsid.

INTRODUCTION

The lifecycle of human immunodeficiency virus type 1 (HIV-1) involves a complicated series of processes to successfully spread the viral infection. After the initial aggregation of many copies of the Gag polypeptide at the interior membrane of an infected cell, a viral particle (or virion) is released from the cell to potentially infect additional cells. However, the initial virion is non-infectious and must undergo a process of "maturation" before an infectious form is produced. One key process in virion maturation is the self-assembly of many copies of a single-capsid protein molecule to generate a cone-shaped viral capsid to enclose the viral RNA. The molecular nature of capsid nucleation and growth phenomena renders the experimental study of the critical early stages of capsid assembly extremely difficult with conventional experimental techniques.

Given the known natural variability across virions, it is important to consider how the spontaneous nucleation and growth of capsid protein structures is controlled in order to generate the single cone-shaped capsid expected in a prototypical mature virion. We therefore used simplified computational models of the capsid protein to examine the effects of protein concentration, molecular crowding, and protein flexibility on the spontaneous nucleation and growth of capsid structures in a variety of virion-relevant conditions. These simulations elucidated important natural contributions to both on- and off-pathway capsid assembly processes, providing insights into aspects of virion maturation that are otherwise inaccessible and furthering our understanding of the critical maturation phenomena for the HIV-1 viral lifecycle.

FIGURE 1 (BACKGROUND): Coarse-grained representation of a "mature" HIV-1 viral particle, or virion. The virion membrane *(gray)* encloses a wide variety of molecules, and the spontaneous self-assembly of a cone-shaped "capsid" structure *(green)* is necessary for the virion to infect cells. The capsid is formed by many identical copies of a specific protein molecule, and acts as a container for the viral genome *(red/orange, local capsid surface removed for clarity)*.

METHODS & RESULTS

Simplified "ultra-coarse-grained" (UCG) models [1,2] of the HIV-1 capsid protein were used in combination with specialized, highly scalable molecular dynamics software [3] to examine the self-assembly of viral capsid structures. The simulations illustrated the pronounced sensitivity of capsid protein concentration on the nucleation and growth of capsid structures, with the concentration known to vary significantly across natural HIV-1 virions. Furthermore, the effects of capsid protein structural flexibility were shown to be critical for the controlled growth of capsid structures under the highly crowded molecular conditions expected in virions. The simulations therefore elucidated the critical early stages of capsid self-assembly, providing valuable insight into a process of critical importance to HIV-1 infectivity.

WHY BLUE WATERS?

The Blue Waters HPC resource was critical for both the development of cutting-edge software and the application of this software to perform large-scale biomolecular simulations. Of particular importance was the Blue Waters project staff, providing in-depth technical information and timely advice with respect to the optimal deployment and performance tuning of our software. The next generation Track-1 supercomputing platforms will enable the application of our cutting-edge simulation techniques to still larger systems, enabling the computational study of cell-scale phenomena while retaining microscopic levels of detail.