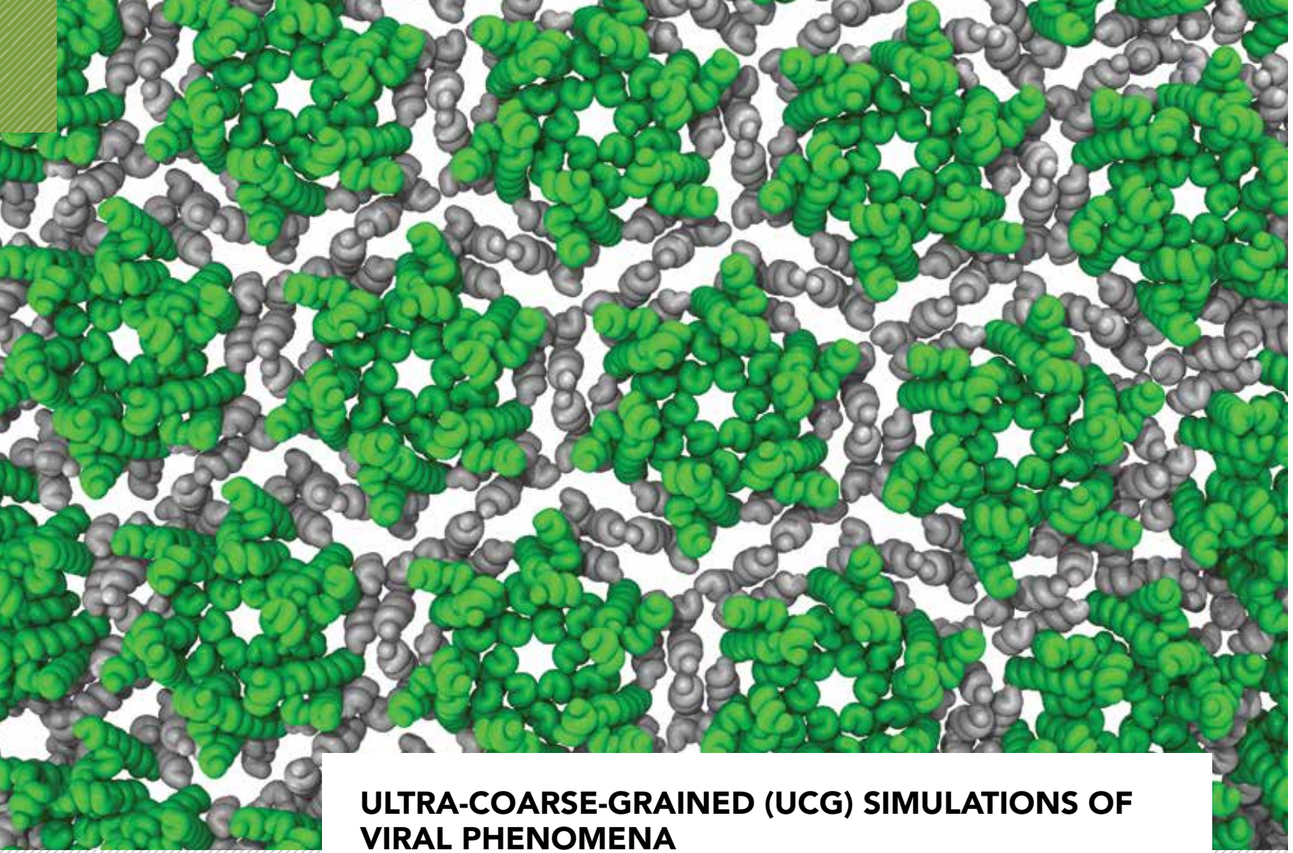

ULTRA-COARSE-GRAINED (UCG) SIMULATIONS OF VIRAL PHENOMENA

FIGURE 1: Detail of the mature capsid protein lattice of HIV-1. The N-terminal regions of each capsid protein molecule are shown in green to highlight the hexagonal lattice structure, with the C-terminal regions of each capsid protein in gray.

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EXECUTIVE SUMMARY

The maturation of HIV-1 viral particles is crucial for viral infectivity, and one important aspect of maturation is the generation of a viral capsid. The viral capsid is formed by the self-assembly of many copies of a specific capsid protein, generating a complicated lattice structure (Fig. 1) that encloses the genetic material of the virus inside the viral particle. While experimental data exists to illustrate the characteristic features of mature capsid lattice, specific details regarding the early-stage mechanisms of capsid nucleation and growth remain elusive. Using the Blue Waters, we employed "coarse-grained" (CG) models of the capsid protein to investigate the self-assembly of capsid lattice under various conditions, and also the disassembly of capsid lattice structures when a viral capsid is transferred into an uninfected cell - a process crucial for viral infectivity.

INTRODUCTION

The lifecycle of human immunodeficiency virus (HIV) requires a complicated series of morphological changes to convert the initially non-infectious "immature" viral particle into a mature and infectious form, a process referred to as maturation. During the maturation process, many large Gag protein molecules are cut apart to release smaller proteins with important contributions for viral infectivity. One such protein is the viral capsid protein (CA).

Many copies of the CA self-assemble into a cone-shaped "capsid" structure that encloses the viral RNA in a mature and infectious viral particle. Viral particles which fail to generate suitable capsid structures are non-infectious, and so the specific details of capsid formation are of interest for the design of therapeutic treatments. The inherent variability of HIV-1 viral particles makes controlled studies with conventional experiments difficult, and the extremely small length scales over which capsid assembly occurs likewise present barriers to the study of capsid self-assembly using current experimental techniques.

Computational simulations of the CA self-assembly process can, therefore, play an important role in elucidating the details of capsid self-assembly. The use of CG molecular models, where full atomic detail is replaced with simplified and efficient molecular representations, is of particular interest for relatively large-scale molecular processes such as viral capsid self-assembly.

METHODS & RESULTS

We deployed **novel** ultra-CG models [1] of the capsid protein, based directly on experimental data, to study the early stages of viral capsid nucleation and growth. The simulations were performed on a custom, highly-parallel molecular dynamics package developed specifically for this type of system using the Blue Waters platform [2]. The model indicates the importance of metastable triangular structures, formed from several capsid protein molecules, in the initial nucleation of the viral capsid: progressive addition of capsid proteins to an existing (but unstable) triangle can eventually produce a stable nucleating structure from which mature lattice growth proceeds. Our simulations suggest that this nucleating structure contains a central hexagon, surrounded by a ring of supporting triangles. Simulations were performed under various conditions to examine the influence on self-assembly of capsid protein concentration and molecular crowding.

Importantly, a protocol was also devised to examine the influence of structural flexibility in the capsid protein, with the innate flexibility of the molecule found to be critically important in controlling the self-assembly process. Previously self-assembled capsid protein structures were exposed to a process of rapid dilution under fixed molecular crowding, to model the viral capsid entry into an uninfected cell. The results of the rapid dilution studies indicate the instability of viral capsids which contain seams or holes in their surfaces, adding further data to our understanding of cellular defense mechanisms (such as tripartite motif (TRIM) protein restriction) which are involved in fighting viral infection. The data produced by our computer simulations using Blue Waters thus elucidate the critical early stages of viral capsid self-assembly, while also providing insight into the eventual fate of viral capsids as they break down at a key stage in the viral lifecycle.

WHY BLUE WATERS

The Blue Waters platform was a crucial element for the development of **cutting-edge** software algorithms and the application of these technologies to enable large-scale and dynamic biomolecular simulations. One key aspect of Blue Waters was the availability of the project staff, who provided invaluable technical insight and frequent advice to tune the performance of our software.

NEXT GENERATION WORK

For the next-generation Track-1 system, we hope to significantly extend the scope of our biomolecular simulations. Rather than performing molecular simulations of isolated aspects of the viral lifecycle, we intend to design and implement CG models capable of encompassing both the early and late stages of viral infection using essentially the same model. These models will involve an ultra-CG [1] representation of the Gag molecule which is capable of representing the aggregation of immature Gag lattice at cell membranes (and subsequent budding events) and the specific enzymatic cleavage of the Gag model during viral maturation. By applying the techniques pioneered by the UCG theoretical framework [1] and closely-related software tools [2], we thus hope to generate models of viral infection capable of rich analysis of medically relevant aspects of the viral lifecycle.

PUBLICATIONS AND DATA SETS

Grime, J., et al, Coarse-grained simulations reveals key features of HIV-1 capsid self-assembly. *z* 7 (2016) 11568. doi:10.1038/ncomms11568