LARGE-SCALE COARSE-GRAINED SIMULATIONS OF HIV-1: NEW THERAPEUTIC TARGETS

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EXECUTIVE SUMMARY

A key step in the proliferation of human immunodeficiency virus type-1 (HIV-1) is the so-called maturation of viral particles that have been released from infected cells. Proteins within these particles are "activated" through proteolytic cleavage and subsequently assemble into conical cores that house the viral genome. Hence, one viable therapeutic strategy is to develop drugs that prevent proteolytic activity; e.g., protease inhibitors or maturation inhibitors. Recently, a promising class of antiretroviral drugs (GS-CA1 from Gilead Sciences) has been proposed that targets the capsid protein directly. Enabled by Blue Waters, we performed large-scale coarse-grained (i.e., with reduced representation) molecular simulations of capsid proteins to elucidate the putative mechanism of these capsid inhibition drugs.

RESEARCH CHALLENGE

The infectious form of HIV-1 is prepared during a stage called "maturation," during which viral proteins are processed through proteolytic cleavage and freed capsids assemble into protein cores that host the viral genome. Understanding the molecular mechanisms of this process is important since disruption of capsid assembly may be a viable target for therapeutics. Drugs that specifically target capsid proteins (e.g., in comparison to other viral constituents, such as protease) are known as capsid inhibitors. One such drug—GS-CA1—has recently been reported as a potential long-acting, highly potent antiretroviral. However, the mechanisms of action of these drugs remain unclear. A fundamental understanding of these mechanisms will facilitate the future design of this relatively unexplored class of antiretroviral drugs.

METHODS & CODES

To investigate the self-assembly of the mature capsid core, we leveraged previously developed coarse-grained (CG) molecular models of the relevant viral components, which are based on experimental data [1]. These CG models are computationally efficient representations of molecules, thereby enabling computer simulations to be performed at time- and length-scales that are otherwise inaccessible. We performed molecular dynamics simulations using our CGMD software package that was developed during a previous PRAC proposal, which was designed to take full advantage of Blue Waters' hardware and network capabilities [2]. Our simulation results were used to understand potential mechanisms of capsid inhibition drugs during HIV-1 maturation, a key step in the viral lifecycle.

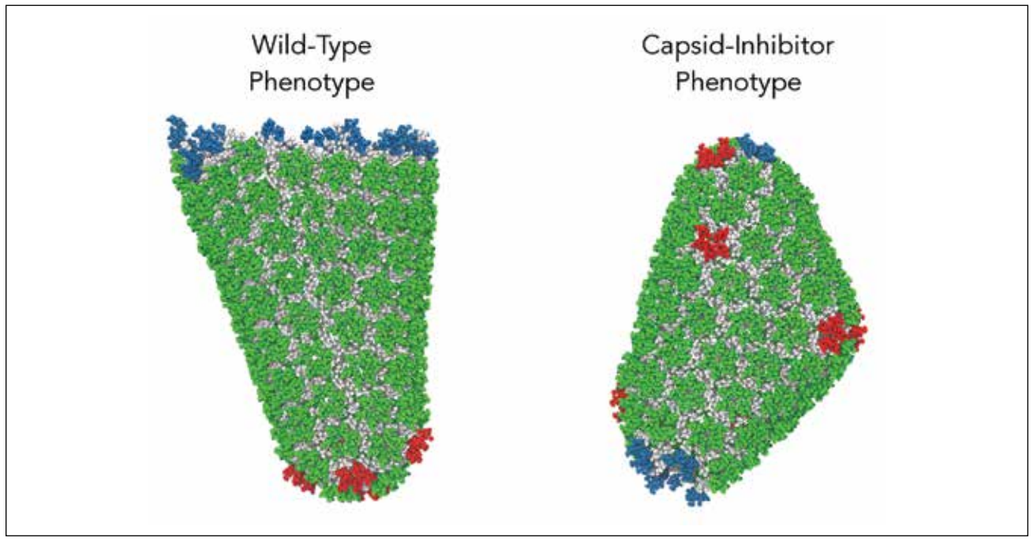

Figure 1: Comparison of example end-point structures from wild-type (left) and capsid-inhibited (right) assembly pathways; the N-terminal domains of edge-case dimers, hexamers, and pentamers are shown in blue, green, and red, respectively. In the latter case, accelerated pentameric assembly increases structural polymorphism with notable curvature variability and incomplete enclosures.

RESULTS & IMPACT

Building on the biophysical insights we have developed during our previous CG simulation studies [1,3], we investigated the putative mechanism of capsid inhibitors on mature capsid assembly. We found that even at small concentrations of drugs, which over-stabilize protein assembly intermediates, a plethora of nonideal capsid assembly pathways emerge (Fig. 1). As a result, the population of canonical and infectious capsid cores is dramatically reduced. Here, the mechanism of action is notably different from classic antiretrovirals; whereas most drugs aim to disrupt or weaken certain interactions, the current class of drugs aims to strengthen interactions. We anticipate that these insights can be easily extended to other viral systems and justify further research into capsid inhibition. Our simulation results are also exemplary of an emerging paradigm for biomedical research in which theory and experiment combine to accelerate drug design.

WHY BLUE WATERS

The primary benefit of CG models is that their reduced representations enable access to large numbers of molecules (e.g., proteins) that interact over long lengths of time. In biology, especially in the context of macromolecular complexes, these length- and time-scales are necessarily large and are otherwise inaccessible using conventional molecular simulations. However, communication bottlenecks during runtime prevent efficient use of standard high-performance computing resources. It was therefore crucial to have access to large amounts of computational power, especially combined with superior network performance. The Blue Waters compute platform thus presented a natural choice for our work; the combination of leadership-class compute capabilities with cutting-edge network hardware allowed us to successfully investigate a system of significant biomedical interest. Our large-scale CG simulations were performed using techniques developed for previous work on the Blue Waters platform [2], while existing relationships with Blue Waters technical project staff greatly assisted in their deployment.

PUBLICATIONS & DATA SETS

Pak, A., et al., Immature HIV-1 lattice assembly dynamics are regulated by scaffolding from nucleic acid and the plasma membrane. *Proc. Natl. Acad. Sci. U.S.A.*, 114:47 (2017), pp. E10056–E10065.

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