## Title

THE HIV-1 CAPSID MECHANOELASTIC PROPERTIES REGULATE NUCLEAR IMPORT AND UNCOATING.


## Authors

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## Abstract

To support successful infection, the mature HIV-1 capsid must remain stable to facilitate nuclear trafficking and engender the chemistry of reverse transcription, while allowing the capsid to uncoat in a timely manner within the nuclei of infected cells. The fine balance of stability and propensity for timely uncoating is now recognized as a hallmark of HIV-1 infection, with capsid-stabilizing HIV-1 therapeutics recently emerging on the market. Despite this medical breakthrough, the molecular determinants of capsid stability and a causal understanding of uncoating remain unrealized. Full-scale molecular dynamics simulations of viral capsids provide a well-established platform for high spatial and temporal resolution analysis of capsid mechano-elastic properties. These simulations provide accurate molecular views – and movies – that are successfully validated against structural and mechanical virological assays, aiding in the burgeoning investigation of how capsid material properties enable successful proliferation. Here, we present a series of in silico AFM simulations that probe different regions of full-scale conical HIV-1 capsids. Our simulations provide molecular details of the structural deformations experienced by the capsid under varying loading forces. Analyses from our simulations reveal that the HIV-1 capsid strongly resists the introduction of force along its positive curvature while allowing equivalent negative-curvature deformations with a nearly fivefold reduction in loading force. We identify regions of the capsid that are more susceptible to external forces and characterize the out of equilibrium strength of different CA-CA interfaces. We extend our in silico AFM approach to probe and characterize the mechano-elastic properties of two HIV-1 capsid mutants: one that is hyper stable and noninfectious, and a compensatory mutant which has been shown experimentally to rescue infectivity. The latter two systems offer a valuable opportunity to elucidate the role, and determinants of, capsid stiffness

relevant to successful nuclear import and viral infection. We additionally subjected full-scale HIV-1 capsids to isotropic growth simulations, mimicking an expansive uncoating model where disassembly is driven by the build-up of reverse transcription products, where we observe failure of the capsid lattice consistent with what has been observed empirically using electron microscopy. Altogether, our results show that the HIV-1 capsid is a robust container with finely tuned viscoelastic properties that allow it to adapt to a range of constrained geometries during cytoplasmic trafficking and nuclear entry.