

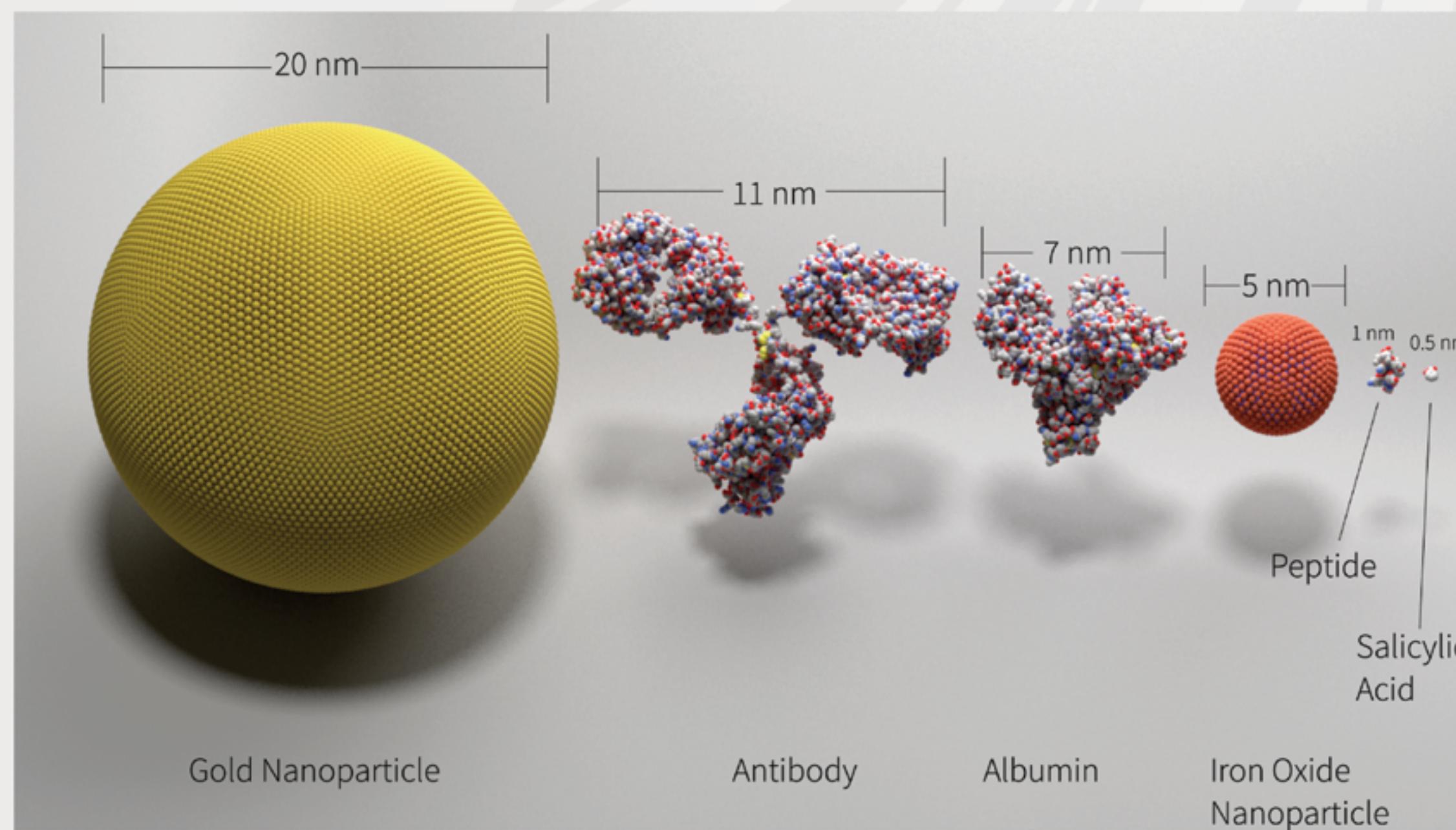
Coarse-grained (CG) Computer Simulations of Biomolecular Phenomena

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Molecular Simulation

The Voth group uses theoretical and computational chemistry to study biomolecular, condensed phase, and novel materials systems. The primary goal of this effort is to develop and apply new computational methods to explain and predict the behavior of these complex systems. For example, the Voth group uses molecular simulations to study protein-protein self-assembly, membrane-protein interactions, biomolecular and liquid state charge transport, complex fluids, nanoparticle self-assembly, and charge mediated energy storage. Visualizations of some systems studied in the Voth group are shown above.

Increasing system size and timescale

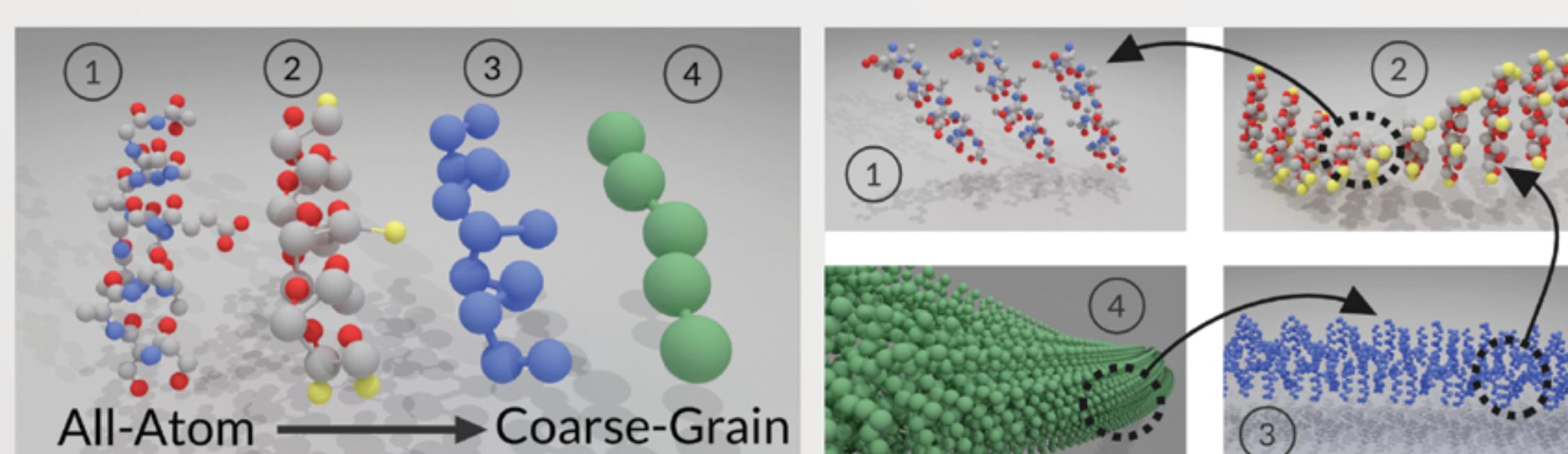


One of the biggest challenges in systems studied in the Voth group is the wide-range of length-scales and time-scales. Scales range from a few atoms for studying a drug molecule to millions of atoms when understanding how a virus is assembled in a cell. The figure above shows some of the relevant length scales in biological systems.

Coarse-graining (CG)

Although computational resources and algorithms are pushing the envelope of simulation size and speed, many important biological systems are still out of reach of traditional simulations. For example, simulating an entire ribosome for 10 milliseconds will not be possible until about 2025 at current simulation speed and size improvements. A simulation of a cell (10^{14} atoms) for an hour will not be feasible until 2130.

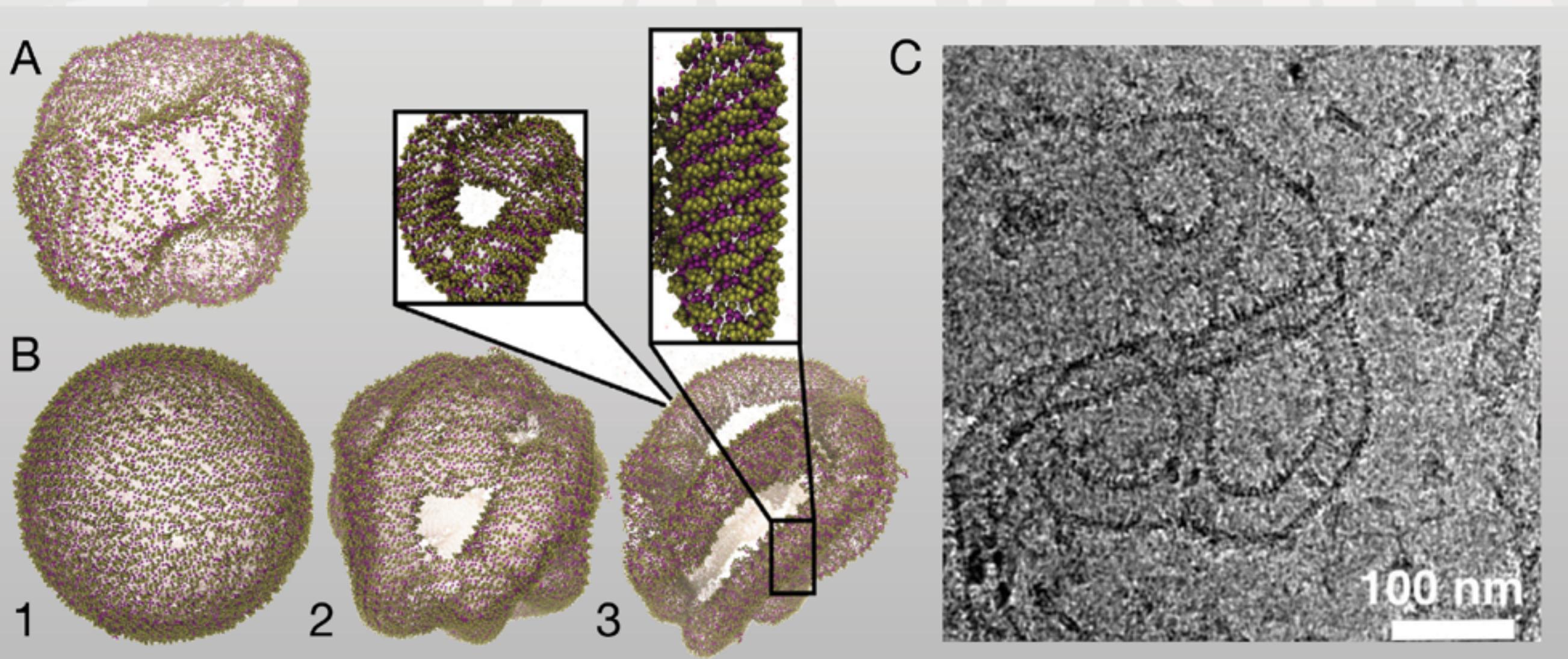
One method of simulating such systems today is to remove rapidly changing degrees of freedom through coarse-graining. An example of coarse-graining to reach increasing length-scales of the self-assembly of a peptide molecule is shown below. Studying the increasingly larger length-scale features of the self-assembled fiber requires more coarse models of the component peptide molecules.



Protein-mediated membrane remodeling

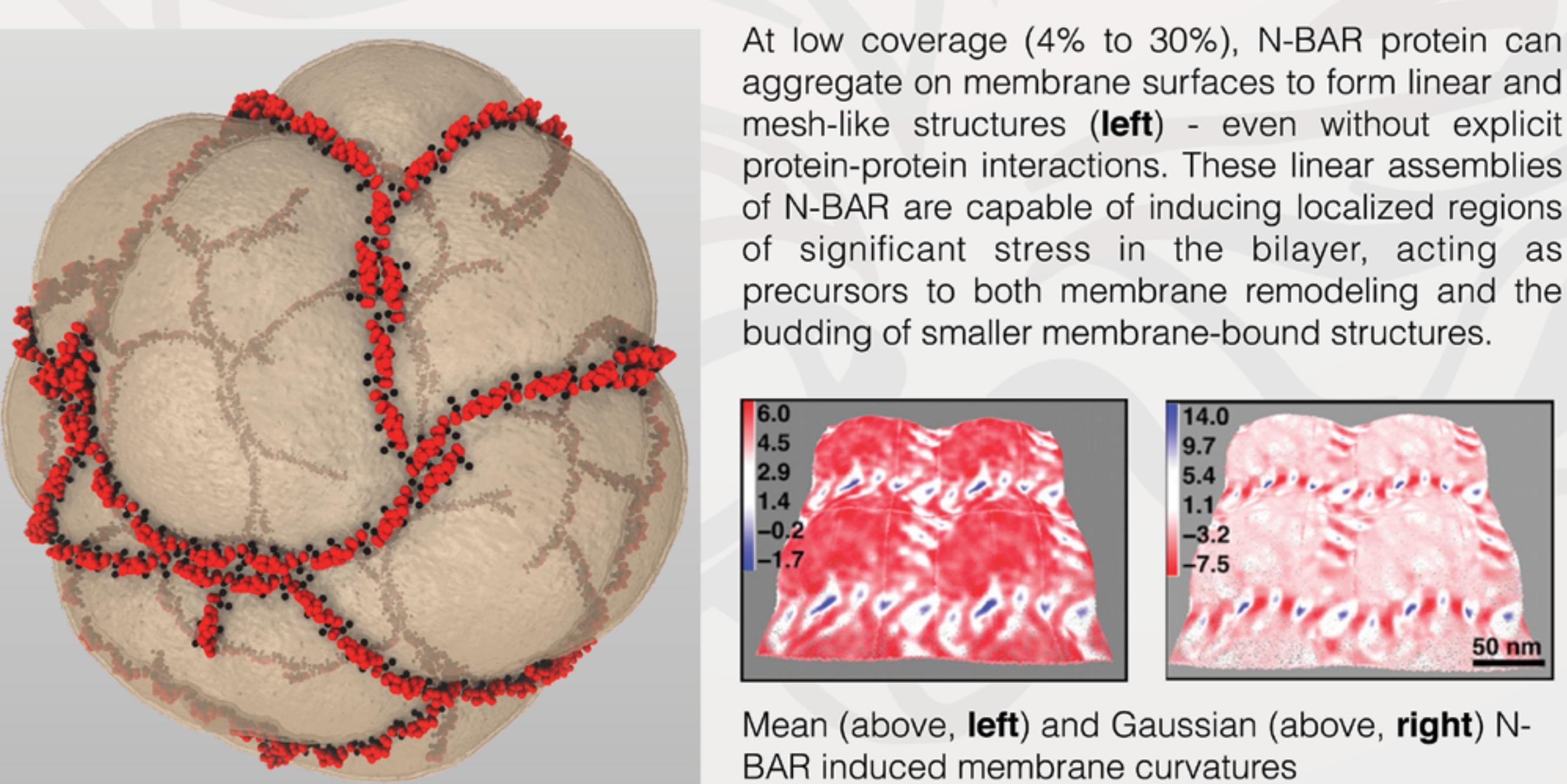
Remodeling of cellular membranes is intimately associated with many biological phenomena. This process is possible due to a highly dynamic relationship between proteins and lipids, which allows membranes to form an impressive variety of shapes to divide, migrate, communicate with other cells, initiate organelle biogenesis, and enable trafficking. BAR-domain proteins have been implicated in the generation and stabilization of local curvature in biological membranes, with low protein concentrations sensing existing membrane curvature and high concentrations of protein interacting to induce the formation of characteristic "tubulated" membrane structures.

The influence of N-BAR protein concentration on membrane remodeling¹



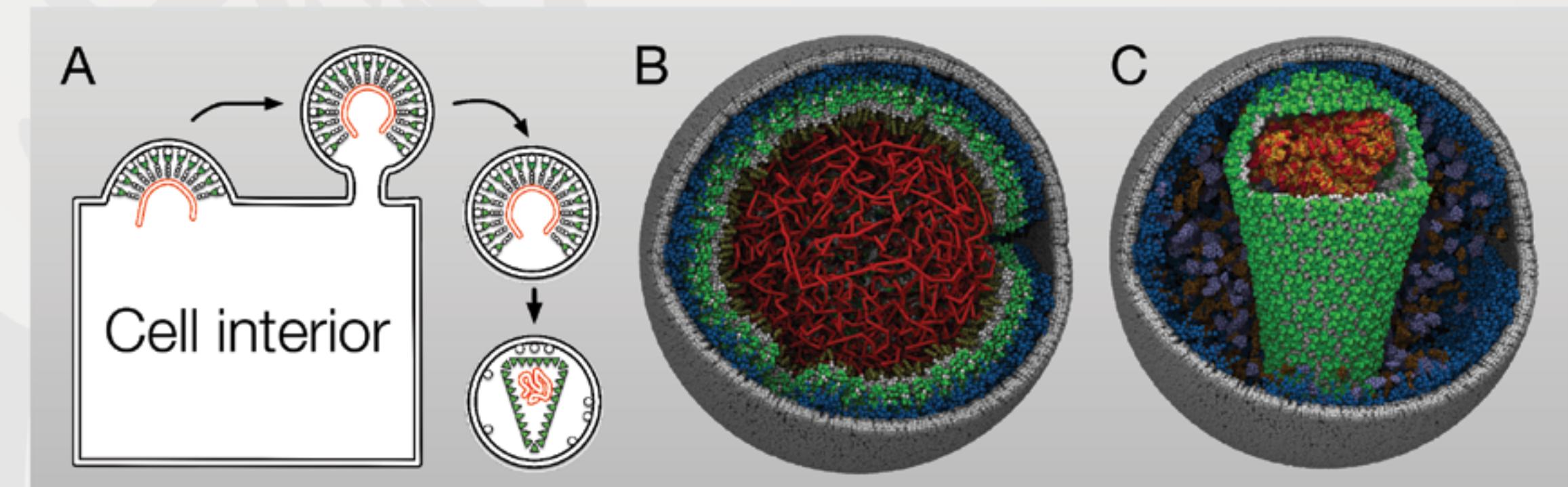
Members of the N-BAR protein family contain two or more amphipathic helix structures at their N-termini. The insertion of these helices into a membrane is thought to be a key mechanism in generating membrane curvature, and CG molecular dynamics simulations were used to examine the effects of varying the concentration of N-BAR proteins on a cell membrane with no explicit protein-protein interactions. At 50% protein coverage (A, above) instabilities and lateral tabulations emerged in the membrane, with a protein coverage of 90% inducing reticulation in the membrane (B1-3, membrane remodeling shown as the simulation progressed). The CG simulation results are very similar to experimental images of N-BAR membrane remodeling (C, above), and imply that the rapid binding and aggregation of N-BAR proteins can overwhelm the ability of the membrane to relax - leading to reticulation of the membrane surface.

Linear aggregation of N-BAR proteins can induce membrane budding²



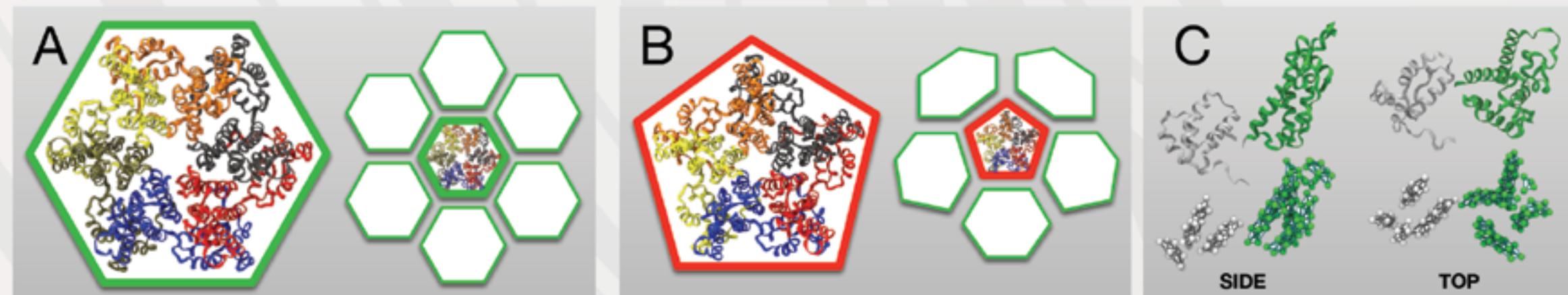
At low coverage (4% to 30%), N-BAR protein can aggregate on membrane surfaces to form linear and mesh-like structures (left) - even without explicit protein-protein interactions. These linear assemblies of N-BAR are capable of inducing localized regions of significant stress in the bilayer, acting as precursors to both membrane remodeling and the budding of smaller membrane-bound structures.

HIV-1 viral particle maturation



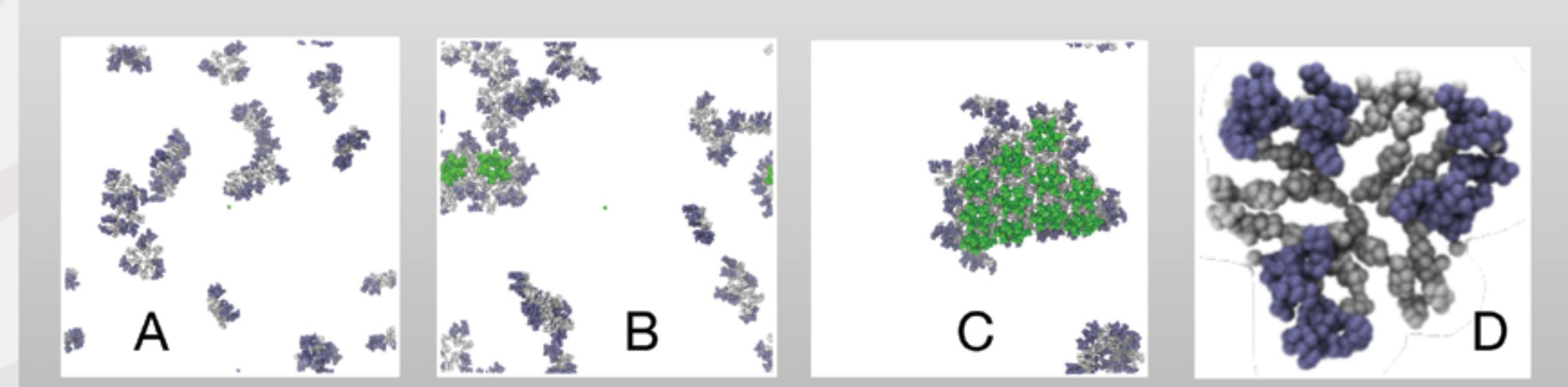
The viral lifecycle of HIV-1 requires the release and subsequent "maturation" of a membrane-bound virion from an infected cell (A). Significant internal changes must occur inside the initially non-infectious virion (B) to produce a mature and infectious form (C). A crucial aspect of viral maturation is the self-assembly of many copies of the HIV-1 capsid protein (CA), to form a conical capsid structure enclosing the viral RNA.

CG HIV-1 capsid protein models

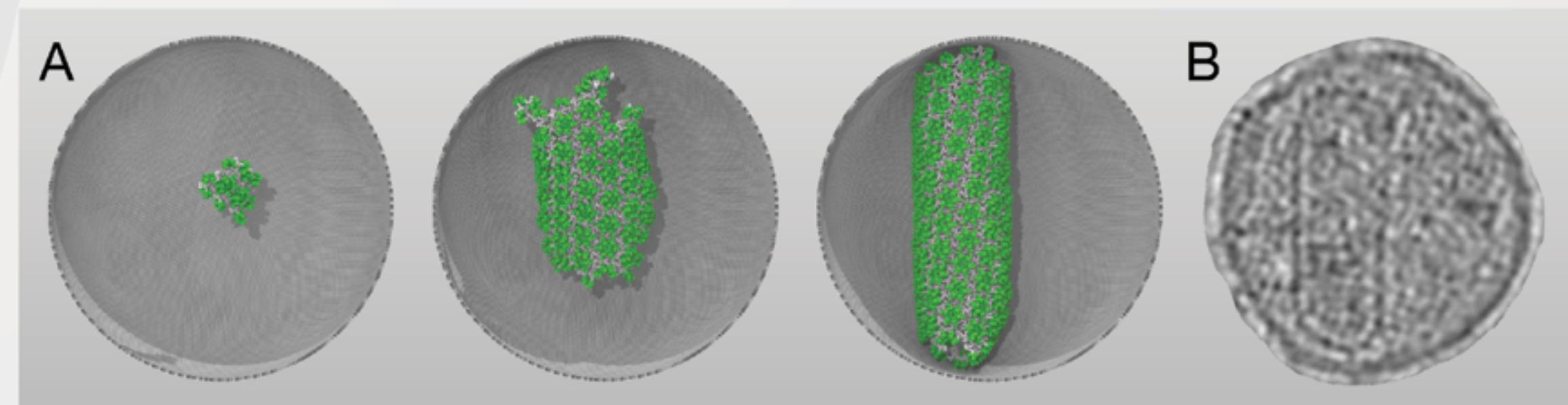


HIV-1 capsid protein can self-assemble into flexible sheets composed of quasi-equivalent hexagonal (A) and pentagonal (B) rings (monomers shown with separate colors, alongside schematics of adjacent ring packing). The ring structures are stabilized by interactions between the N-terminal domains of the CA monomers, with adjacent NTD rings connected by CA monomers forming dimer interfaces across their CTDs. Using experimental X-ray crystallographic and NMR structural data, a CG model of the capsid protein was generated (C: Top row: all-atom CA as ribbon plots. Bottom row: CG model as beads-and-springs representation. NTDs in green, CTDs in gray).

Capsid protein self-assembly



The CG model assembled rapidly in the presence of a simple, inert molecular crowding agent, in agreement with experimental results. The simulations indicate a two-stage process for capsid lattice formation: first, numerous triangular CA protein structures are rapidly assembled from the CG protein dimers in solution (A). Next, the triangular structures aggregate into the characteristic hexagonal lattice of the viral capsid (B,C). Detail of a triangular structure shown in D (NTDs blue, CTDs gray).



When placed into a model spherical virion with inert crowding agent but no viral RNA present, the CG capsid protein model spontaneously self-assembles into cylindrical capsid structures (A) in agreement with experimental observations (B).

¹ Mijo Simunovic, Carsten Mim, Thomas C. Marlovits, Guenter Resch, Virzenz M. Unger, and Gregory A. Voth. *Biophysical Journal* 105:711-719 (2013)

² Mijo Simunovic, Anand Srivastava, and Gregory A. Voth. *Proceedings of the National Academy of Sciences of the United States of America* 110:20396-20401 (2013)