

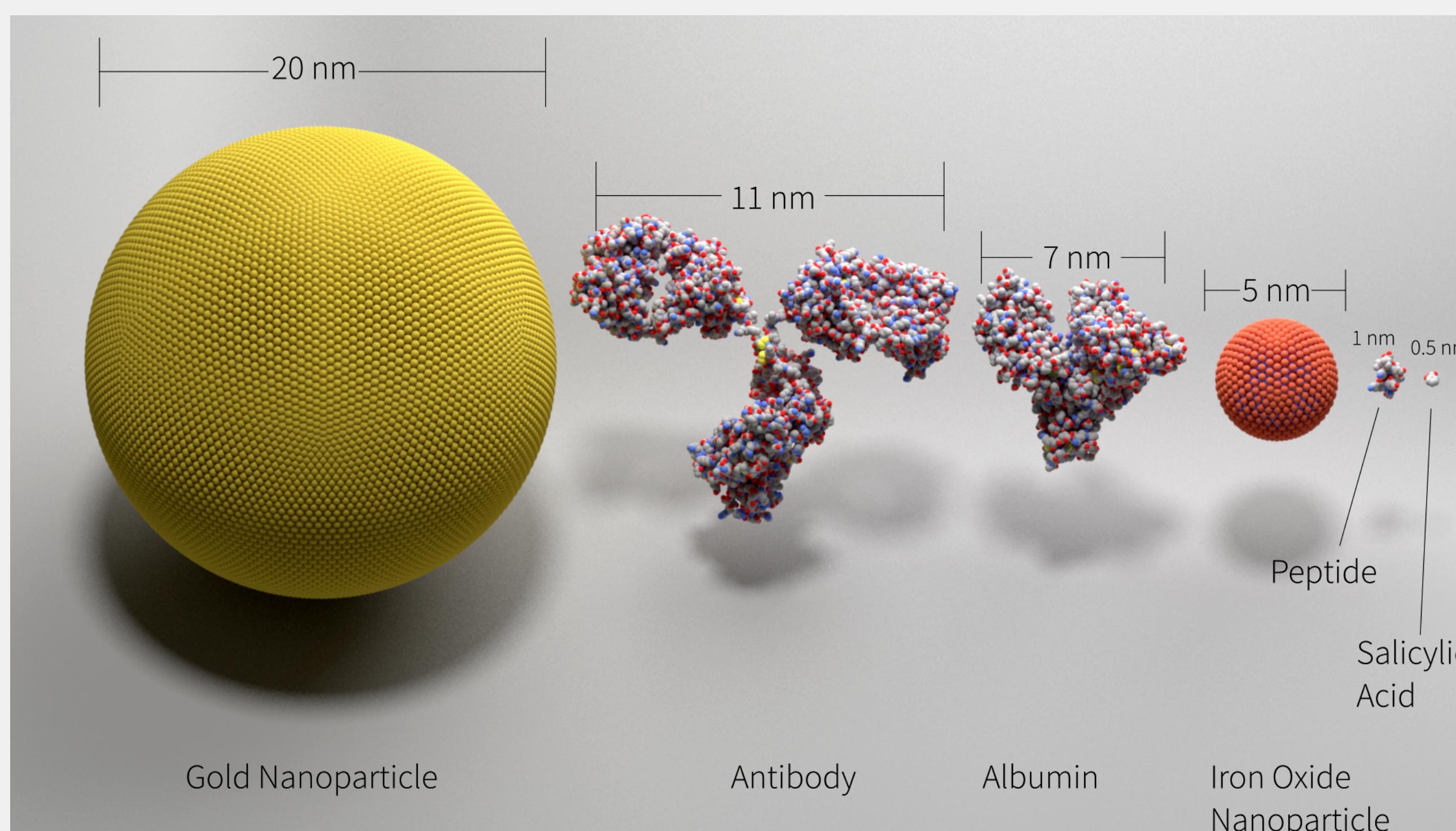
# A Multiscale Description of Biomolecular Active Matter: THE VOTH GROUP

## The Chemistry Underlying Many Life Processes

### Molecular simulation

Theoretical and computational chemistry can be used 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, molecular simulation has been used 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. This poster describes examples of biomolecular systems that have phenomena at time and length scales inaccessible to atomic-resolution molecular dynamics (MD) simulations, and hence require groundbreaking new coarse-graining methods in order to study them.

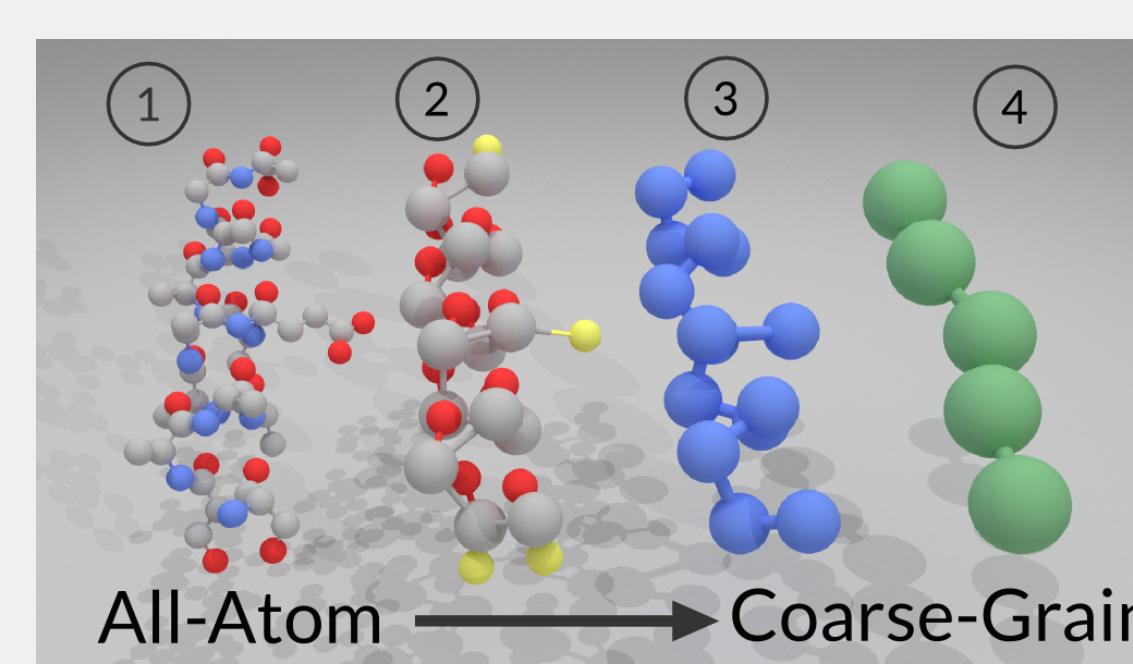
### Increasing system size and timescale



These challenging systems span a wide range of length-scales and time-scales, from a few atoms when studying a drug molecule to millions of atoms to understand how viruses assemble. The figure above depicts some of the length scales in biologically relevant molecular systems.

### Ultra-Coarse-Graining (UCG)

Although computational approaches are pushing the envelope of simulation size and speed, many important biological systems are still out of reach of traditional MD simulations. For example, a simulation of a cell ( $10^{14}$  atoms) for an hour will not be feasible until 2130 given the current rate of increase in computational power.



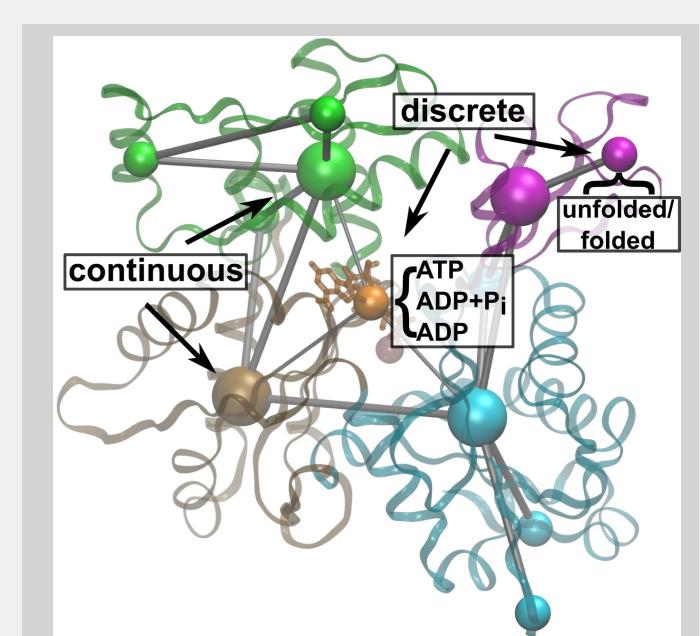
“Coarse-grained” (CG) models can remove rapidly changing degrees of freedom for significantly increased computational efficiency. While CG models can accurately represent a single molecular state, e.g., multiple molecular conformations or different bonding topologies cannot be captured by normal CG techniques. The new “ultra-coarse-grained” (UCG) **theoretical framework** has been developed to capture this kind of state-dependence (and many other kinds) in CG models.

Ultra-coarse-graining allows one to construct CG models at much lower resolution (and hence much higher computational efficiency) while still capturing discrete conformational or chemical changes within CG sites. These discrete states are described using different interactions.

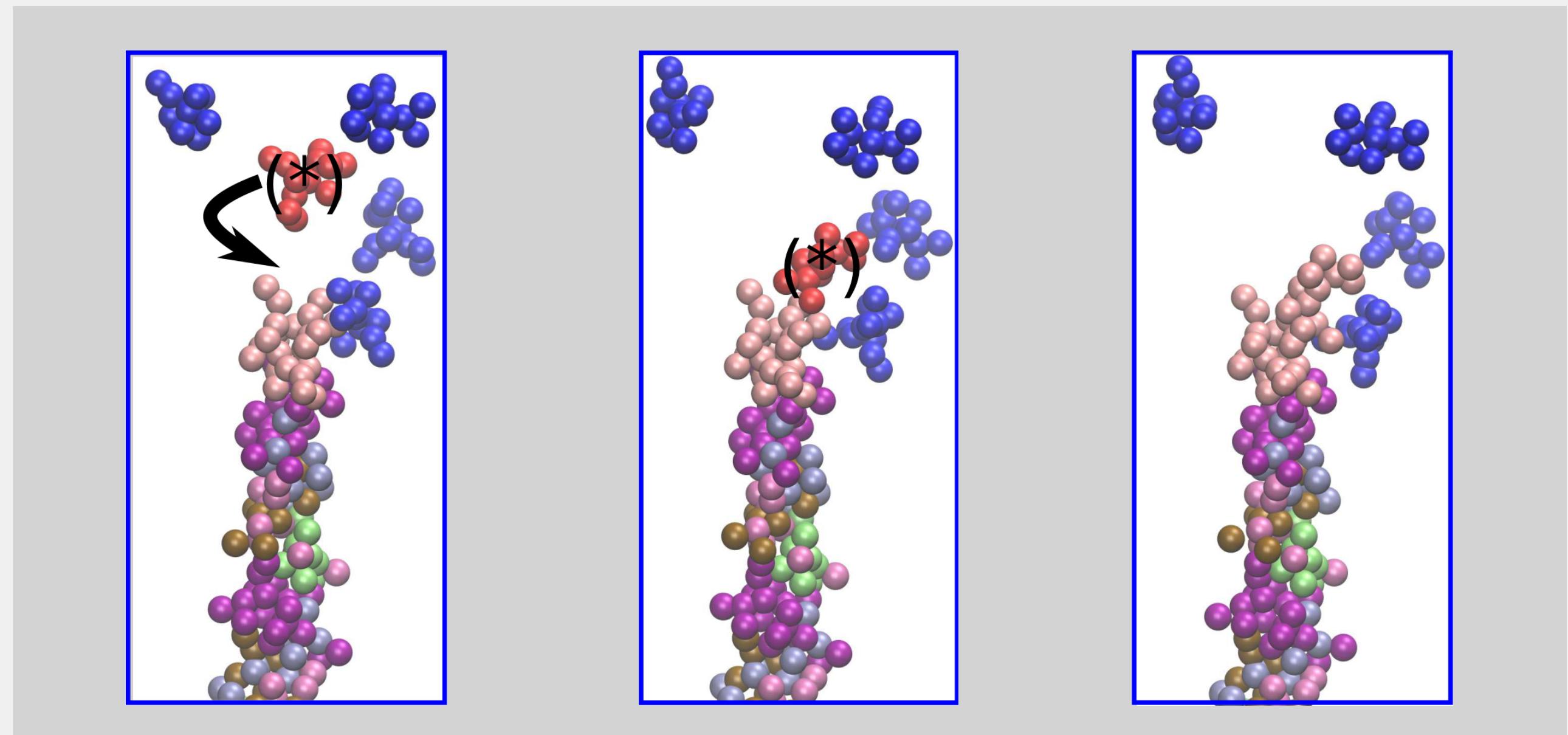
$$\frac{\partial U(v, \mathbf{R}^N v)}{\partial \mathbf{R}^N} = \left\langle M_{R,v}^N \left( \frac{\partial}{\partial \mathbf{r}^n} \left( u(\mathbf{r}^n) - \frac{1}{\beta} \ln p_\Sigma(v; \mathbf{r}^n) \right) \right) \right\rangle_{\mathbf{R}^N, v}$$

### Ex. 1: Actin polymerization

Actin filaments play a crucial role in structural integrity and dynamics of eukaryotic cells. They are key component of the cellular cytoskeleton and are critical for processes such as cell division, cell motility, and intracellular cargo transport. The assembly and dynamics of actin filaments are regulated by various factors, including ATP hydrolysis and other proteins. For instance, the rate of actin polymerization is accelerated and controlled by ATP hydrolysis and interaction with proteins such as profilin and formins, and branched filamentous networks are assembled with the help of Arp2/3 proteins. Many fundamental questions regarding the mechanisms of such regulation remain unanswered and are subject of our ongoing research.

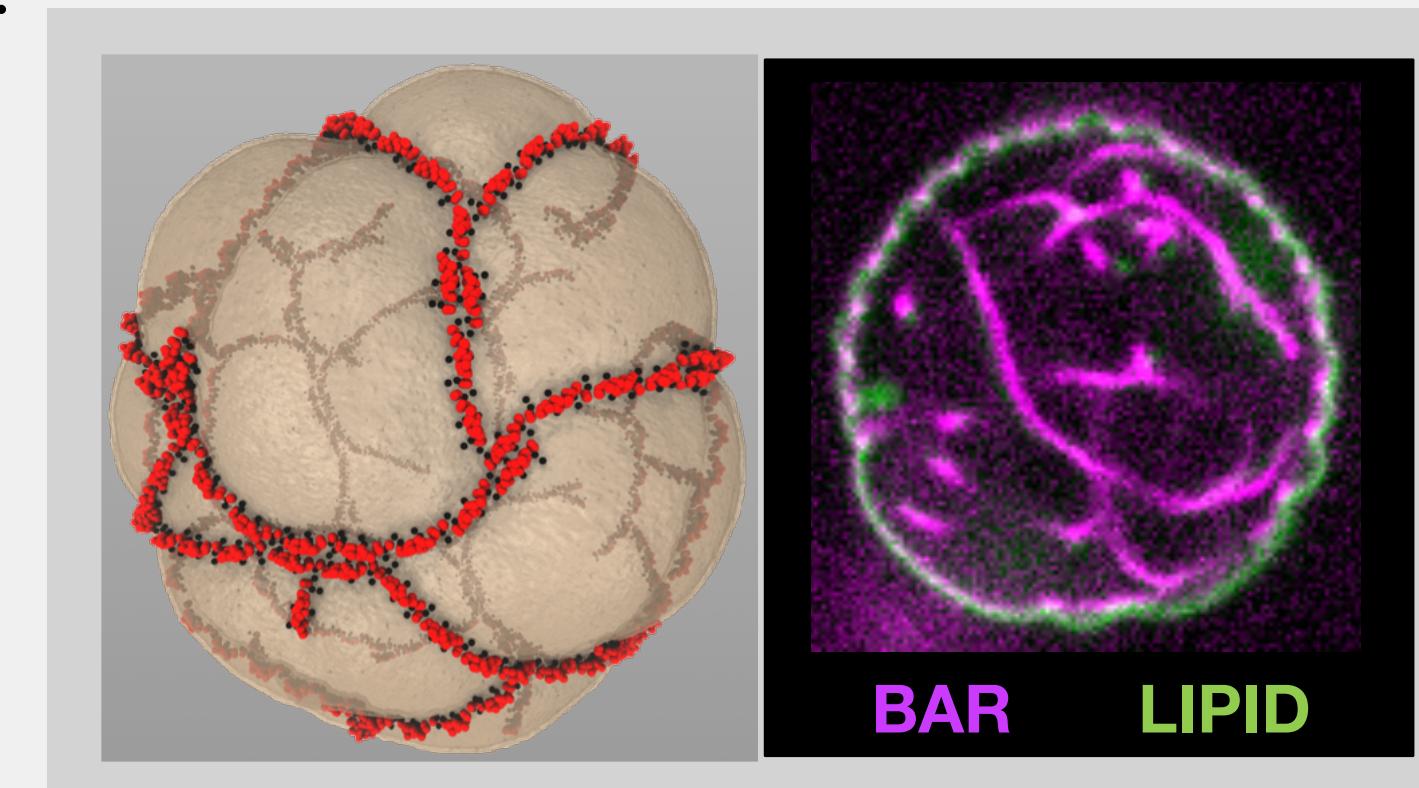


Using all-atom simulations of short fragments of actin filaments, a UCG model of actin was constructed using 12 beads per monomer and one internal variable that can represent nucleotide triphosphate states (ATP, ADP+Pi, or ADP). This allows us to systematically represent heterogeneity critical to actin filament aging and assembly on biologically relevant time and length scales.

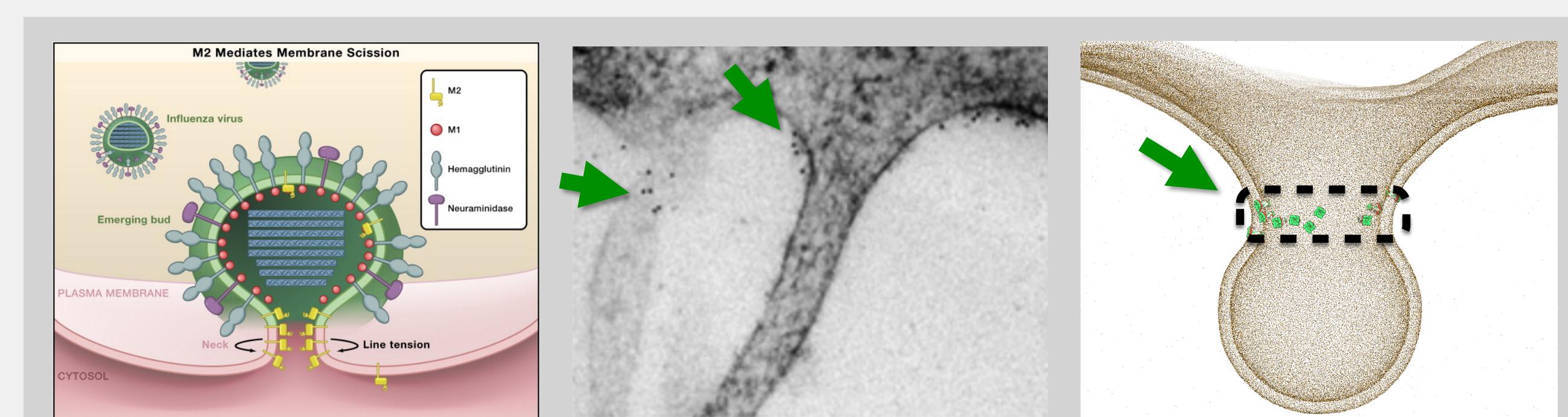


### Ex. 2: Large-scale membrane remodeling

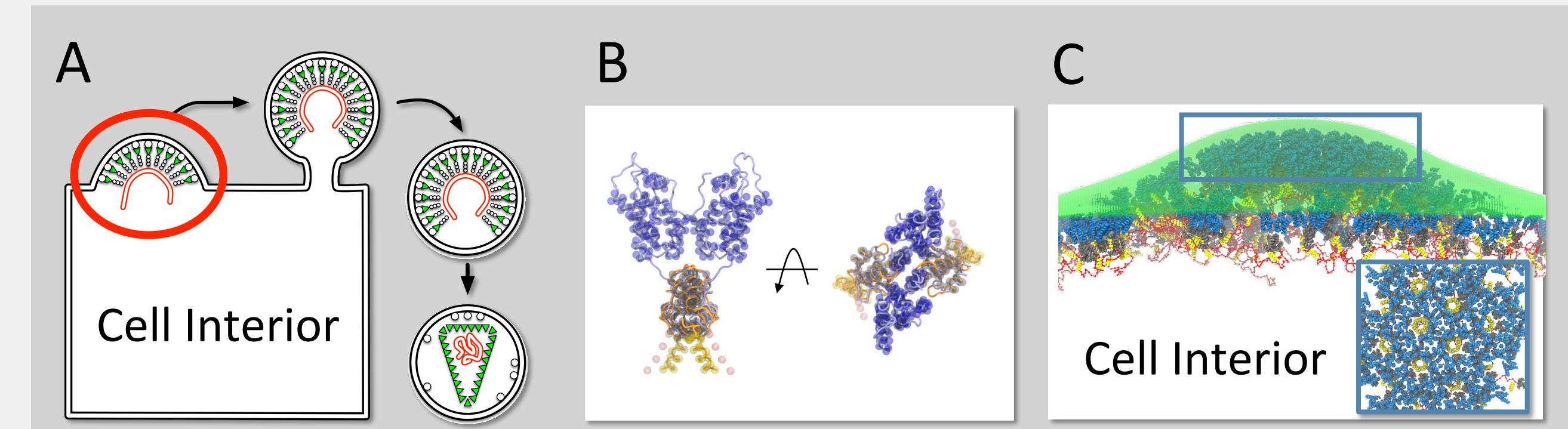
N-BAR family proteins contain two or more amphipathic helix structures at their N-termini. The insertion of these helices into a membrane is thought to be a key mechanism in generating membrane curvature, and CG simulations were used to examine the effect of protein concentration. At low coverage (4-30%) N-BAR aggregates in linear mesh-like structures (**below, left**), a feature validated by electron microscopy (**below, right**). These constructs act as precursors to budding and membrane remodeling.



The influenza A virus M2 protein drives and stabilizes membrane budding during the replication lifecycle. The M2 protein stabilizes negative Gaussian curvature and aggregates in the neck region of the budding virion. Using highly coarse-grained lipid and protein models, we can simulate a budding influenza virion using a polymer brush model in place of the viral RNA and study M2 aggregation in the highly-curved neck region of a budding virion.

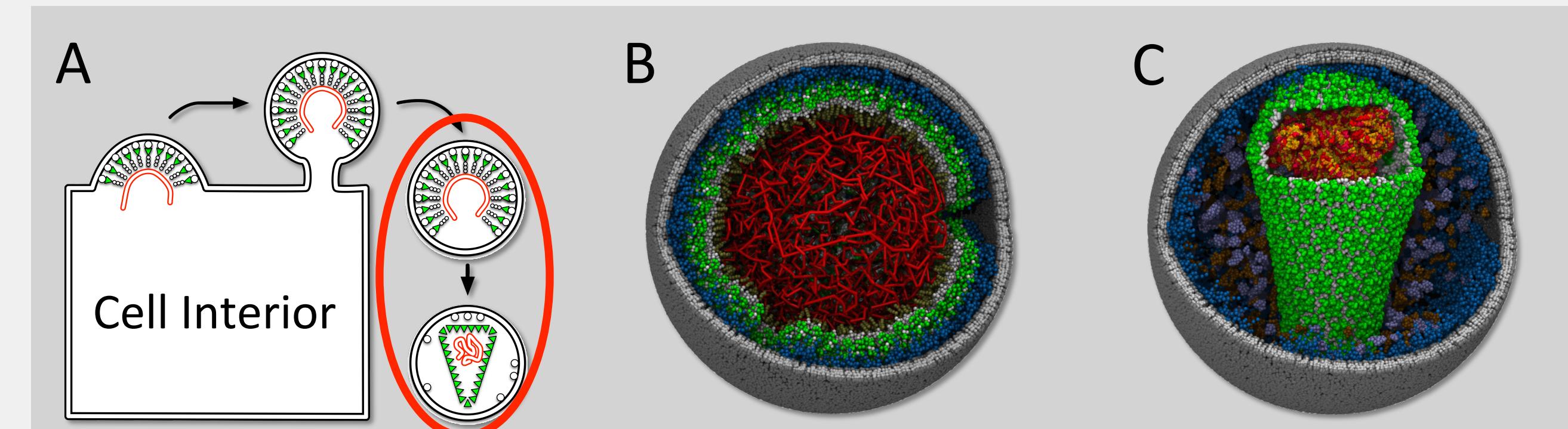


### Ex. 3: HIV-1 viral particle budding

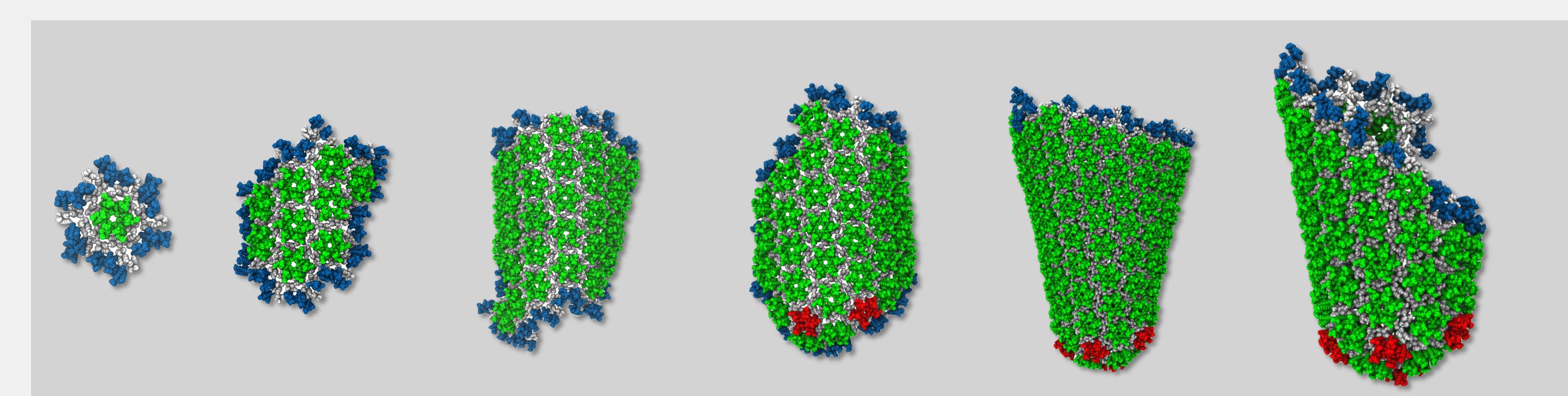


The viral lifecycle of HIV-1 requires the release and subsequent “maturation” of a membrane-bound viral particle from an infected cell (A). To assemble a viral particle, many copies of the HIV-1 “Gag” molecule must aggregate at the surface of an infected cell, sequestering viral RNA and forming a characteristic lattice packing morphology (A, red oval). The self-assembly of Gag lattice is associated with membrane deformations in the infected cell, eventually leading to the production of a viral particle. To investigate this process, we have created CG models of key components of this system (membrane, Gag (B), and viral RNA) which self-assemble to reproduce not only the Gag-associated membrane deformation (C) but also the detailed structural morphology of the Gag lattice (C, inset).

### Ex. 4: HIV-1 viral particle maturation



Subsequent to budding and release, HIV-1 viral particles undergo a process of “maturation” (A, red oval): significant internal changes must occur inside an initially non-infectious viral particle (B) to produce a mature and infectious form (C). A crucial aspect of viral maturation is the enzymatic cleavage of Gag molecules to release several thousand copies of the HIV-1 capsid protein (CA). Approximately 1,500 CA molecules then self-assemble into a cone-shaped “capsid” structure that encloses the viral RNA. The capsid is composed of quasi-equivalent hexagon and pentagon structures in a fullerene cone motif. We have created UCG models of the conformationally dynamic HIV-1 capsid protein in order to better understand the important early stages of capsid self-assembly, with particular attention paid to the initial nucleation and growth of CA lattice structures in crowded environments.



Once a hexagon surrounded by triangles has spontaneously assembled, this structure acts as a stable nucleating factor for large-scale CA lattice growth (**above**). As the region of CA lattice grows, pentamers are occasionally incorporated into the structure, producing regions of higher local curvature in e.g. the ends of a capsid (red, **above**).

