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Optimization of an Elastic Network Augmented Coarse Grained Model to Study Ccmv Capsid Deformation
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The major protective coat of most viruses is a highly symmetric protein capsid that forms spontaneously from many copies of identical proteins. Structural and mechanical properties of such capsids, as well as their self-assembly process, have been studied experimentally and theoretically, including modeling efforts by computer simulations on various scales. Atomistic models include specific details of local protein binding but are limited in system size and accessible time, while coarse grained (CG) models do get access to longer time and length scales but often lack the specific local interactions. Multi-scale models aim at bridging this gap by systematically connecting different levels of resolution. A CG model for CCMV (Cowpea Chlorotic Mottle Virus), a virus with an icosahedral shell of 180 identical proteins, is developed, where parameters are derived from atomistic simulations of capsid protein dimers in aqueous solution. In particular, a new method is introduced to combine the MARTINI CG model with a supportive elastic network based on structural fluctuations of individual proteins. In the parametrization process, both network connectivity and strength are optimized. This elastic-network optimized CG model, which solely relies on atomistic data of small units (dimers), is able to correctly predict inter- protein conformational flexibility and properties of larger aggregates. Here, aggregates of 20 and more capsid proteins are chosen that are possible intermediates in the assembly process or otherwise relevant for the mechanical stability of the CCMV virus shell. Furthermore, it is shown that this CG model reproduces experimental (Atomic Force Microscopy) indentation measurements of the entire viral capsid. Thus it is shown that one obvious goal for hierarchical modeling, namely predicting elastic aspects of larger protein complexes from models that are carefully parametrized on smaller units, is achievable.

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Improving Inference of Rate Parameters for Viral Capsid Assembly Systems
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Computational methods have been widely used to infer properties of complex systems that one cannot directly observe experimentally. Viral capsid assembly is a key model system for complex self-assembly for which we lack direct experimental data on critical information, such as kinetic parameters, needed to build models and reveal detailed assembly pathways. We previously sought to learn such hidden parameters with a heuristic optimization approach using gradient and response surface methods applied to the light scattering measurements of three in vitro viral assembly systems: human papillomavirus (HPV), hepatitis B virus (HBV), and cowpea chlorotic mottle virus (CCMV). This method successfully learned plausible kinetic parameters for all the three viruses leading to reconstruction of detailed models of assembly pathways. Significant computational challenges, however, hinder our ability to construct more precise or detailed models and reliably quantify uncertainty in the inferences. First, there is no closed form representation for the quality of fit of models to data, which therefore must be evaluated through computationally costly simulations. Second, the problem requires stochastic simulations, and the resulting simulation trajectories must be averaged over many replicates to suppress noise. Third, optimization of parameters must account for unknown factors and imprecision of experimental measurements. We explore here improvements based on the idea of derivative free optimization (DFO), a class of optimization algorithm that can achieve faster and more accurate fitting, especially on systems characterized by costly, noisy evaluations of quality of fit. Preliminary tests show improvements over our custom gradient-based method using a DFO strategy. Work is continuing on evaluating different DFO methods and customizing them to inference of kinetic parameters in order to determine the best strategies for inferring unobservable physical parameters in complex biological self-assembly systems.

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Molecular Simulations of pH-Dependant Maturation-Associated Structural Changes in Bacteriophage HK97
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Many viruses systems respond to cellular cues by undergoing structural rearrangements. The rearrangements can involve modification of the individual subunit protein configuration and/or large scale changes to the capsid shape, size and morphology. In the latter case, these changes are largely driven by changes to the protein-protein interfaces in capsid. One of the most common cues a virus encounters during its infection process are pH modifications. The manner in which viral systems respond to pH changes is varied, however, by developing robust simulations methods for exploring these changes we will be able to examine a range of systems in the near future. In this work, we have focused on the bacteriophage HK97, as a model system for understanding large-scale, pH-induced conformational changes in virus capsids. HK97 undergoes a maturation process during which the capsid swells and facets, changing it from a spherical to a polyhedral morphology. The in-vivo process involves the packaging of the DNA genome, however, in-vitro, an analogous transformation can be achieved in the absence of DNA, just by means of pH alterations. We have employed constant-pH molecular dynamics along with string-method refinement and umbrella-sampling calculations to estimate the free-energy profiles along the maturation reaction coordinate. We have investigated how pH can influence this energy landscape by calculating pKas of titratable residues in both the mature and immature states, from which $\Delta\Delta G$'s of maturation can be calculated as a function of pH. By correlating key structural rearrangements with residues which have significant pKa shifts we can begin to form a mechanistic picture of how pH can trigger changes to the capsid structure and modulate the free energy landscape.

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Applying Cellular Crowding Models to Simulations of Virus Capsid Assembly In Vitro
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Viral capsid assembly has been widely studied as a biophysical system both for its biological and medical significance and as an important model system for complex self-assembly processes. One important and largely unresolved question is how viruses select among the potential pathways by which a capsid might assemble. Sources of experimental data to resolve assembly pathways are limited in scope to in vitro studies. We have previously applied numerical optimization methods to fit kinetic rate parameters of assembly simulations to light scattering data in order to more accurately model the in vitro viral capsid assembly process, making it possible to predict detailed patterns of interaction and pathways of assembly of specific viruses. There is substantial reason, however, to suspect the interaction patterns inferred in vitro might be altered in a very different in vivo environment. We examine here one aspect of this difference, effects of intracellular molecular crowding on assembly kinetics and pathways. We have applied regression models developed from Green's function reaction dynamic simulations to adjust inferred reaction kinetics of capsid models to reflect likely differences in crowded systems. We then examined how such adjustments affect computer models of the capsid assembly process. We applied these methods to three icosahedral viruses: human papillomavirus (HPV), hepatitis B virus (HBV), and cowpea chlorotic mottle virus (CCMV). Preliminary results show complicated effects on pathway dynamics, with increased cellular crowding increasing the nucleation rate of CCMV and HBV capsids while slowing the nucleation rate for HPV capsids and increasing a propensity to kinetic trapping in all viruses studied. Future work will explore how additional features of the cellular environment may act synergistically to lead to rapid, robust growth in living cells.

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Brownian Dynamics Simulations of Polymer Mediated Capsid Assembly
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Viral capsid assembly consists of hundreds to thousands of protein subunits spontaneously forming an icosahedral shell around the viral nucleic acid genome. We investigate this assembly using Brownian Dynamics simulations of coarse-grained models which include capsid protein cationic tails, or Arginine Rich Motifs (ARMs); a common structural element through which viral capsids interact with their nucleic acid genome or a surrogate polymer cargo. In our simulations, we find that the presence of a polymer greatly enhances the rate of assembly through a disordered mechanism, wherein many capsomers adhere to the polymer before successful capsid assembly occurs. Through these simulations we are able to investigate the role of several variables, including ARM location and length, as well as structural features of the polymer cargo, including the length, stiffness, and secondary structure