

**Dynamics of Multiprotein Assemblies: Application to Bacteriophage HK97 Viral Capsid**Vlad, Daniel<sup>1</sup>, Bahar, Ivet<sup>2</sup><sup>1</sup>Department of Molecular Genetics and Biochemistry, School of Medicine, and <sup>2</sup>Center for Computational Biology and Bioinformatics, University of Pittsburgh, Pittsburgh, PA, USA

With advances in structural genomics and the rapid accumulation of protein structures, new questions arise. Knowledge of *structure* is insufficient for predicting or controlling *function*. Function is a *dynamic* property. Efficient methods for predicting *dynamics* at multiple scales are needed. Advanced methods currently exist for examining dynamics at two distinct levels, atomic and systems, based on fundamentally different approaches driven by different disciplines. It is a challenge, however, to develop computationally efficient and physically realistic approaches for modeling the dynamics at intermediate levels, ranging from supramolecular structures to subcellular networks of interacting biomolecules. We focus here on the dynamics of supramolecular structures.

We developed a structure-based computational approach to predict the dynamics of large multiprotein complexes, based on the Gaussian Network Model (GNM) originally introduced in our group. We first validate the approach by comparison with experiments and simulations for well-studied systems (e.g. hemoglobin and a series of protein-inhibitor complexes). These studies show that: (i) each structure has *unique global dynamics*, which primarily depends on its *topology of intramolecular and intermolecular interactions*, (ii) the predicted global dynamics is robust, i.e. insensitive to the details of the selected model and parameters, and hence can be described to a good approximation by coarse-grained models, the appropriate degree of coarse-graining scaling with the size of the system, (iii) there is a correlation between global dynamics and molecular mechanisms of function, and (iv) residues located at *mechanically* constrained loci on protein architecture play a critical (hinge) role in coordinating the collective dynamics, while the most flexible regions act as substrate-specific recognition sites. The analysis suggests that it is possible to interfere with the mechanics and/or biochemistry of the molecule by targeting these key sites.

Extension to bacteriophage HK97 viral capsid shows that the procapsid (ProheadII) is significantly more flexible than the capsid (Head II), and the pentamers are distinguished by their high mobility before maturation. A closer look at the global mode shape of the pentamer chains shows that the major difference between the dynamics of the procapsid and mature capsid resides near the E-loop (residues 148-181). This loop contains the residue Lys<sup>169</sup> that forms an isopeptide bond with the Asn<sup>356</sup> of the neighboring unit in the mature form. The formation of 420 such cross-links is known to lead to the catenation of the adjacent rings into a protein chainmail. Lys<sup>169</sup> enjoys a significant mobility in the Prohead II. This high mobility is expected to facilitate its conformation change to form a cross-link during capsid maturation. Its mobility is almost completely suppressed in the mature form. Asn<sup>356</sup> on the other hand acts as a hinge center, both in the Prohead II and the Head II. It is conceivable that the isopeptide bond formed with Lys<sup>169</sup> would not be functional if Asn<sup>356</sup> were not already playing a key mechanical role before maturation.