More dynamic than we think? Conformational averaging in structural biology

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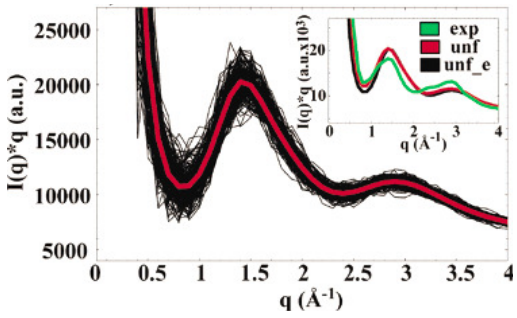
Biomolecules move, fluctuate and change structure. It is a recognized fact that even in their native, functional states they retain significant residual conformational diversity. However, most experimental methods in structural biology provide time- and ensemble-averaged signals and, consequently, molecular structures based upon such signals typically exhibit only idealized, average features. Can it be that in some cases such conformationally-averaged structural models actually misrepresent the underlying microscopic reality? To what extent are the order, symmetry and structure, apparent in such models, simply a direct consequence of the methods that we use to probe the biomolecules in question and the averaging that is inherent in them? Are there some structural motifs that are actually artificially more likely to be "seen" in an experiment simply due to the averaging artifact? Finally, what are the practical consequences of ignoring the averaging effects when it comes to functional and mechanistic implications that we try to glean from the experimentally-based structural models? In this talk, I will attempt to address some of these issues. In particular, I will focus on using molecular dynamics techniques, including distributed computing simulations with the Folding@Home cluster, to address the question of conformational averaging in scattering techniques such as small-angle X-ray scattering and fiber diffraction.



Calculated solution wide-angle X-ray scattering patterns for the simulated unfolded ensemble of villin headpiece (red/unf). A scattering curve based on the experimental structure of villin headpiece is shown in the inset (green/exp) [2].

[1] Zagrovic, B., Snow C.D., Khaliq S., Shirts M.R. & Pande V.S. (2002). *JMB,* **323 (1):**153-164.
[2] Zagrovic, B & Pande, V.S. (2006). *JACS*, **128 (36):** 11742-11743.
[3] Zagrovic, B. (2007). *Mol. Phys.*, **105 (10):** 1299-1306.