Hybrid approaches to characterize structure and dynamics of biomolecular systems from single molecule experiments

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In recent years, the number of structures solved by cryo-EM methods has considerably increased and more structures are becoming available through the EMDB database. In parallel, numerous computational tools have been developed to interpret cryo-EM data, in particular, to characterize dynamics of biological molecules. These computational tools have shown to be quite reliable in obtaining accurate pseudo-atomic models, but limitations do exist. Studies have shown that for some systems many, if not all, methods may fail to produce accurate models, even though the underlying framework to describe dynamics of biological molecules is rather different. One possible explanation might be a limited conformational sampling with the molecule being trapped in a local minimum during the fitting. To test this theory, multiple flexible fittings were performed using different initial conditions for a protein data set for which two distinct conformation are known. Results show that accurate models could be obtained by performing repeated simulations, however, as such conformation is not always the most dominant in the simulation, in many cases the resulting atomic model has low accuracy. To overcome this problem, flexible fitting with enhanced sampling was introduced and shown to provide more accurate models.