# Biological applications of protein dynamics

**Long-range allostery is an essential component of cell signaling.** Protein dynamics on nanoscales, presents us with a novel paradigm for cell signaling: proteins can communicate **within** complexes to effect long-range information transfer, via coupled domains and correlated residue clusters. This idea has been little explored, however, in large part because of a paucity of experimental techniques that can address the necessary questions. Currently, there is a spatial-temporal dynamic gap, on nanosecond-to-microsecond timescale and on nanometer length scales, where it has not been possible to determine the dynamics of proteins and large protein complexes. This gap is particularly amenable to study by neutron spin-echo spectroscopy (**NSE**).

**Neutron spin-echo spectroscopy (NSE)** is unique in its ability to capture these nanoscale motions. NSE is the only technique that can determine protein motion on nano length scale and on nanosecond to microsecond time scales. NSE has the potential to reveal motions in a protein or within a protein complex on length-scales comparable to their overall dimension (Bu et al., 2005; Farago et al., 2010; Bu and Callaway 2011). NSE can determine the correlated domain motion within proteins, and can localize the moving areas of the protein (Callaway et al, 2017).

**This is a problem of great generality.** Protein motion propagates allosteric signals through proteins. In allosteric regulation, information arising from ligand binding can be communicated to a distant site. Multidomain proteins, which contain modular domains, flexible linkers and disordered tails, exist in all forms of life from bacteria to eukaryotes. These multidomain proteins include DNA replication and repair machines, transcription regulators, protein motors, kinases, cell signaling adapters and mechanosensor proteins whose functions require the elaborate coordination of their domains. The available thousands of protein structures have yielded an understanding of many biological processes at atomic resolution. However, protein structure alone is not enough to understand the mechanism of function. During gene replication, the DNA polymerases need to coordinate their different domains in order to add nucleotide precisely and to remove mismatched nucleotides In photosynthetic bacteria, protein vibrational motions promote the energy transfer from the antenna pigments to the sites of photochemical activity. Protein motion controls the gating of membrane transporters, the assembly of cytoskeletal actin and viruses, and influences enzyme catalysis (Bu and Callaway 2011).

**Binding kinetics depends on nanoscale dynamics**. The kinetic association rate constant of the binding of the S339D/S340D mutant in the intrinsically disordered tail of the multi-domain scaffolding protein NHERF1 to the FERM domain of Ezrin is sensitive to buffer salt concentration, correlating with the excited nanoscale dynamics. The results suggest that electrostatics modulates the activation of nanoscale dynamics of an intrinsically disordered protein, controlling the binding kinetics of signaling partners. NSE can pinpoint the nanoscale dynamics changes in a highly specific manner (Callaway et al 2017).

**The possibility of designing biological machines.** Allosteric regulation is a quality that distinguishes biological macromolecules from synthetic polymers. If we could understand and master the principles of protein motions and allosteric regulation that control protein functions, we could make molecular devices inspired by these protein machines in order to perform desired nanoscale functions that are impossible now.

**The need for theoretical physics.** In order to make further progress in this area, it is necessary to develop theoretical tools to interpret NSE data. These will include but not be limited to large scale molecular dynamics simulations. (For example, one can derive simple first cumulant results to test for protein motion that do not require large scale simulation (Bu et al 2005, Farago et al 2010)). What is needed and hoped for is a revolution in protein dynamics that is comparable to that inspired by de Gennes, Edwards, and Doi and their colleagues for polymer dynamics.

## References


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