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47 The energy landscape for protein folding and biomolecular machines

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It is amazing how cells have created a number of molecular machines specialized for undertaking tasks needed to control and maintain cellular functions with exquisite precision. Due to fact that biomolecules fluctuate via thermal motion and their dynamics is diffusive, biological machines are fundamentally different from those experienced by conventional heat engines or machines in the macroscopic world. One of the key features of biological machines is the conformational changes triggered by the thermal noise under weak environmental perturbation. Therefore we can explain how they behave using ideas borrowed from the energy landscape theory of protein folding and polymer dynamics. This "new view" allows us to envisage the dynamics of molecular motors from the structural perspective and it provides the means to make several quantitative predictions that can be tested by experiments. For the kinesin motor, a prototype of the biological machines in the cell, molecular simulations of an explicit kinesin and microtubule structures show that fluctuations and flexibility inherent to the structure leads to versatile adaptation of the molecular structure, allosteric communication controlled by internal mechanics, and large amplitude stepping motion harnessing the thermal fluctuation.

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48 Design principles governing the motility of myosin motors

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Myosin V, two-headed motor protein and a member of the myosin super family, ferries cellular cargo by walking hand-over-hand on actin filaments. Interplay between ATD-driven conformational changes in the motor head and stress due to load produces a variety of stepping dynamics: the motor can step forward or backward, or "stomp", where one of the heads detaches and rebinds to the same site. I will present theory that captures all these behaviors, quantitatively matching a wide array of single molecule experiments. The theory lays out the structural and chemical design principles underlying the motor's robust function, which provides a guide for how bioengineering might alter its dynamics (Hinczewski, Tehver, & Thirumalai, 2013). The theoretical results will be complemented with simulations describing the role the internal dynamics of the motor domain plays in motility (Tehver & Thirumalai, 2010).

References

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49 Structure and energetics of the pumping mechanism of membrane ATPase

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P-class (or E1–E2-type) ATPases constitute a superfamily of cation transport enzymes, present both in prokaryote and eukaryote, whose members mediate membrane flux of all common biologically relevant cations (Berg, Tymoczko, & Stryer, 2002). P-class pumps use ATP to transport ions against a gradient. The sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) pumps 2 Ca^{2+} from the cytosol of muscle cells to the sarcoplasmic reticulum by exchanging H^+. In each normal cycle, the Na/K pump transports 3 Na^+ out of the cell by 2 K^+ into the cell at the expense of the hydrolysis of one molecule of ATP. From crystallography, we now dispose of a remarkable series of snapshots showing how these enzymes look at different states of their transport cycle (Kanai, Ogawa, Vilsen, Cornelius, & Toyoshima, 2003; Nyblom et al., 2013; Toyoshima & Cornelius, 2013). SERCA is now by far the membrane protein where the most functionally different conformations have been described in precise structural detail. Using molecular dynamics simulation and the string method with swarms-of-trajectories (Pan, Sezer, & Roux, 2008), we seek to understand the conformational dynamics involved as the pump transits through conformational states revealed by X-ray crystallography, the nature of the coupling between the binding of ATP, phosphorylation, and the movements of charged species across the core of the protein, the stepwise voltage-sensitive steps, and the origin of the ion binding specificity associated with different conformational states. A special attention is given to the protonation state of