

RESEARCH SUMMARY

My current area of research lies mainly in *non-equilibrium statistical mechanics, stochastic processes and their application in understanding the dynamics and mechanochemical coupling of various motor proteins* (especially Kinesins, Myosins).

(1) Motor proteins are active enzyme molecules that perform various biologically important processes by converting chemical energy into their mechanical work. They move unidirectionally along the linear helical tracks. Single-molecule experiments suggest that motor proteins, consisting of two motor domains, move in an asymmetric hand-over-hand mechanism. Each subunit plays the role of leading head and trailing head alternatively in two consecutive steps and they do not interact with each other. However recent single-molecule investigations [1] on the dynamics of kinesin do not support the independence of two motor domains. In these experiments force-velocity curves and enzymatic activities were measured for different homodimeric and heterodimeric kinesins. Had the heterodimeric kinesin (in which one of the head is mutated: the microtubule gliding velocity of the homodimeric mutated kinesin is zero) followed the non-interacting hand-over-hand mechanism, then its velocity would also have been zero. But, surprisingly, the velocity of the heterodimeric kinesin was found to be non-zero, indicating that there is some kind of interactions present between the two motor domains. We use a **simple discrete stochastic model** that might explain several aspects of the complex dynamics of both the homodimeric and heterodimeric kinesins. **We argue that interactions between motor domains modify the free energy landscapes and mechanical processivity of each motor subunit.** The motor proteins still move via the hand-over-hand mechanism but **with different transitions rates.** Our calculations of biophysical properties agree very well with the experimental observations. We propose several ways to test our theoretical model. Our work is to appear on *New. J. Phys* (2007).

(2) Many single-molecule experiments on motor proteins measure the **fractions of forward and backward steps and dwell times** between the consecutive events. We use multistate periodic discrete stochastic chemical kinetic models to study the mechanochemical coupling and dynamics of motor proteins. According to this approach, *the experimentally fractions of forward or backward steps and dwell times can be correlated with the so-called splitting probabilities and mean-first-passage times respectively.* The expressions for these quantities are already known for sequential single-chain pathways, and for the biochemical pathways with irreversible detachments. We are interested in deriving the expressions for both the splitting probabilities and the mean-first passage times for:

- **The parallel-chain pathways:** Recent experiments on the processivity of single-headed kinesins and dyneins affirm the existence of a second, ATP-independent biochemical pathway in addition to the ATP dependent pathway. Furthermore, the possibility of parallel biochemical pathways have been approved experimentally for translocating RNA polymerases.
- **The lattices with finite, periodically arranged branched states** at each site to lead off the main processive sequence: It is observed very often in the motion of processive kinesin molecule across microtubule.
- **Periodic parallel lattices with coupling:** This model is very useful for analyzing the dynamics of RNA polymerases or for describing the dynamic instability of microtubules and ParM proteins.

(3) Myosin-V is a two-headed, actin-based processive motor protein that is crucial in organelle and vesicle transport. It has a step size distribution around the mean value of 36 nm (36 ± 5.5 nm). **We are interested in evaluating the effects of the fluctuations in the step size towards the overall dynamics (velocity, dispersion, randomness) of myosin –V.** We plan to follow Derrida's [2] approach but incorporate a dependence of probability density $\rho(d)$, the probability of being in sites with step size d , into the overall probability $P_j(l,t)$ of being in state j of site l at time t . We also argue that contribution of randomness derived from variability of step size and variability of step times towards overall randomness is not simply additive, which was reported earlier by [3], but there might be some coupling also.

References:

- [1] Kaseda, K, Higuchi, H, & Hirose, K. (2002). Coordination of kinesin's two heads studied with mutant heterodimers. *Proc. Natl. Acad. Sci. USA* 99, 16058-16063.
- [2] Derrida, B. (1983). Velocity and Diffusion Constant of a Periodic One-Dimensional Hopping Model. *Journal of Statistical Physics* 31, 433-450.
- [3] Shaevitz, J.W., Block, S.M. and Schnitzer, M.J. (2005). Statistical Kinetics of Macromolecular Dynamics. *Biophysical Journal* 89, 2277-2285.

