Abstract

The cytoskeleton of the cell is a highly complex, dynamic and adaptive system of semiflex- ible filaments with their associated motor proteins and cross-linkers. It generates internal stresses and responds to external ones, intermediates cell signaling, ensures the structural integrity and morphology of the cell and helps in the spatial organization of cellular con- tents. This dynamic regulation is effected by the coordination of the different cytoskeletal components : polymeric filaments such as microtubules, actin and intermediate filaments; cross-linker proteins such as fascin and α-actinin; and motor proteins such as dynein, kinesin and myosin. Much of the physical understanding of the components of cytoskeletal network have been obtained through in-vitro experiments on cytoskeletal extracts. In a bead assay a cy- toskeletal filament is irreversibly attached to a substrate, while the motor proteins moving on the filament are attached to a bead which is optically trapped. On the other hand, in a gliding assay setup, the geometry is inverted. Here, the cargo domains of motor pro- teins are irreversibly adsorbed on a glass substrate, while their filament binding domains attach to the complimentary cytoskeletal filament. In the presence of ATP, the motors move in a directed fashion along the length of the filament before detachment. This re- sults in a gliding movement of the cytoskeletal filament in the opposite direction. Apart from a wealth of information on single motor protein movement and force generation, motility assays have revealed the emergence of collective motion in high densities of such filaments leading to the formation of clusters, swirls and interconnected bands. Within these in-vitro settings, it is possible to ask theoretical questions regarding both the role of individual motor proteins and their cooperative dynamics, in controlling the dynam- ics of the cargo/filament that they bind/unbind to/from and therefore make falsifiable predictions amenable to experimental verifications. In the first problem, we consider an explicit model of a semiflexible filament moving in two dimensions on a gliding assay of motor proteins, which attach to and detach from filament segments stochastically, with a detachment rate that increases with the increase of local load force. Attached motor proteins move along the filament to one of its ends with a velocity that varies nonlinearly with the motor protein extension. The resultant force on the filament drives it out of equilibrium. We characterize the nonequilibrium conforma- tions of the polymer comparing its end-to-end distribution with that of the equilibrium filament. In theoretical studies of active systems, key concepts such as broken detailed balance and entropy production have recently been used to characterize the distance of these systems from their equilibrium counterparts. We show that subtle changes in the local load dependence of detachment rate and active velocity of motor proteins lead to dramatic difference in the end-to-end distribution. With increasing activity, the difference increases, the effective bending stiffness reduces, and the polymer shows a phase coexis- tence between open and spiral chains. The most startling result is seen in the dynamics. The center of mass of the polymer shows a series of crossovers between ballistic and dif- fusive motion, controlled by its inertial, orientational and speed relaxation time scales, a significant result which can be checked in motility assay experiments. In the second problem, we look at the effect of the dynein catch-bond on the intracellu- lar bidirectional transport of cargo on microtubule filaments, achieved by the collective action of oppositely directed dynein and kinesin motors. Experiments have found that in certain cases, inhibiting the activity of one type of motor results in an overall decline in the motility of the cellular cargo in both directions. This counter-intuitive observa- 1tion, referred to as paradox of codependence is inconsistent with the existing paradigm of a mechanistic tug-of-war between oppositely directed motors. Unlike kinesin, dynein motors exhibit catchbonding, wherein the unbinding rates of these motors decrease with increasing force on them. Incorporating this catchbonding behaviour in our theoretical framework, we show that this non-monotonic nature of the detachment kinetics gives rise to extremely non-trivial cooperative effects for bidirectional transport. Using measures like the average processivity, probability distributions of run and pause times and cargo trajectories, we show that in an experimentally viable parameter space, the wide range of results - from those which are in agreement with the

conventional tug-of-war model to the ones which are in contradiction - are all correctly reproduced, therefore providing a plausible resolution of the paradox of codependence. The proposed framework necessi- tates a reassessment of existing experimental data in the light of our predictions, and will enhance the fundamental understanding of intracellular motor- driven processes, which have consequences for the overall spatiotemporal organization within the cell, cellular motility and cell division.