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First passage times: A common theme in the kinetics of macromolecular motors

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A molecular motor is made of either a single macromolecule or a macromolecular complex. Just like their macroscopic counterparts, molecular motors "transduce" input energy into mechanical work. Their diffusion is biased by the energy pumped in by the "burning fuel". In this talk I'll begin by giving an elementary introduction to the most essential and relevant features of molecular motors [1, 2] and then present three sets of examples to establish the ubiquity of first-passage times in intracellular processes. Some motors walk along filamentous proteins carrying molecular cargo. The stochastic pause-and-translocation of such a porter is characterized by the distribution of the times of its dwell at the successive positions on its track. The dwell times are essentially first-passage times and their fluctuation provides a lower bound on the number of kinetic states of the motor. For a motor that can step both forward and backward the kinetics of translocation is characterized by the distributions of four distinct conditional dwell times. DNA polymerase is a motor that can not only step forward and backward mechanically, but also step backward by catalyzing a different chemical reaction; its stepping kinetics is characterized by nine distinct conditional dwell times. As the first example of first passage times, I'll define these conditional dwell times and summarize our analytical results as well as their physical implications [1, 2]. In the nucleus DNA is stored in a hierarchical structure called chromatin. The basic unit of chromatin consists of 146 base pairs of a double stranded DNA (dsDNA) wrapped around a spool formed by proteins. The helical path of the dsDNA on a spool is also called its "footprint". We have investigated the mechanism of footprint traversal by a chromatin-remodeling enzyme (CRE), a motor that translocates along the dsDNA thereby unwrapping it from the spool. A CRE-induced biased diffusion of a small DNA loop along the footprint can lead to the sliding of the spool along the DNA. The average time needed for the traversal of the footprint, for the first time, by sliding is essentially the corresponding mean first passage time. As an example of second class of first-passage problems, I'll present our model and fuel-dependence of the mean foot-print traversal time [3]. The third type of example I'll present occurs in chromosome segregation before cell division. Each of the sister chromatids, that result from chromosome replication, is bound to a structure, called kinetochore (kt) that, in turn, is coupled to the plus ends of stiff protein filaments called microtubules (MT). The lifetime of a kt-MT attachment is also a first-passage time. I'll present our recent results that explain the experimentally observed, apparently counter-intuitive, dependence of the mean lifetime on the externally applied tension that tends to detach MT from the kinetochore [4, 5].

References

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