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Structural basis for dynein motor domain coordination

Dynein motor proteins power cellular processes, such as directed vesicle transport and cilia beating, by converting the chemical energy of Adenosine Triphosphate (ATP) into mechanical work. Cyclic functioning of the motor requires coordination of biochemical and mechanical changes in its catalytic domain. Processive hand-over-hand motion also implies an inter-domain coordination of the two heads. Despite extensive research efforts, a detailed picture of mechanochemical coordination and force generation by dynein remains controversial. One of the main challenges in elucidating a functional mechanism is the large size of the motor. Until recently, only crystal structures of isolated domains have been available. However, even recent crystallization of a full-size dynein did not offer immediate explanation for how the motor operates.

Combining available data from both structural and biochemical studies on dynein, we developed a coarse grained model of the full motor. Stochastic simulations demonstrate that the model is consistent with experimentally observed stepping behavior and suggest answers to a number of fundamental questions about dynein's mechanochemistry. The model demonstrates how a direct physical interaction between dynein's AAA+ rings can occur without disrupting movement of the heads during 8.2 nm stepping. In fact, this interaction facilitates coordination and efficiency of motor function. We demonstrate how and why dynein is capable of switching between processive forward and backward runs while maintaining a directional bias for forward stepping. Finally, we explore sources of dynein's structural flexibility and their effects on the step size distribution. Our model provides a computational framework for studying cooperative multi-motor transport and collective force generation, thus bridging dynamic phenomena on the length scales of nanometers to microns.