The role of hydrolysis kinetics on the collective performance of single-headed kinesins

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Intracellular traffic is mainly enabled by molecular motors that transport a large variety of organelles along microtubule filaments. One of the most remarkable examples of intracellular transport is found in neurons. Large vesicles that contain synaptic precursors need to be carried from the cell body over long distances along the axon in order to supply dendrites. The collective performance of these motors is essential for the proper transport in the axon since intracellular traffic disorders have been associated to neurodegenerative diseases such as Alzheimer. Kinesins are a large family of processive molecular motors which play a fundamental role in anterograde transport in the axon. Most of them are dimeric motors composed of two motor "heads" which walk in a hand-over-hand fashion by alternating sequentially the motor domains attached to a microtubule filament. However, this model fails to describe the dynamics of KIF1A[1], a monomeric kinesin motor which moves processively by "hopping" along the microtubule track and it is able to freely diffuse while still weakly bound to the filament, without detaching during many steps. Strikingly, *in-vitro* experiments have shown KIF1A is very inefficient acting individually compared to conventional dimeric kinesins. The current open question is why KIF1A is specific of such a demanding task in spite of its clear inefficiency acting individually. We propose KIF1A motors could have an unusual and remarkable adaptation to cooperative action, which could largely compensate their individual inefficiency.

Recent studies on Brownian ratchets have revealed non-trivial dynamics leading to a dramatic enhancement of the efficiency of motor clusters with respect to the expected behaviour of a pure superposition of individual motors[2,3]. We develop a quantitatively realistic model by performing Langevin dynamics of KIF1A motors on a two-state noise-driven ratchet. We find a surprising enhancement on the stall force of the system which is mediated by hydrolysis kinetics. Moreover, the effect becomes more dramatic as the number of motors increases (Fig 1). This mechanism could be of special importance in the axon in order to overcome possible traffic jams and ensuring the proper transport of large vesicles against large forces. The underlying cooperativity which triggers the growth of the stall force relies on the presence of the weakly bound state which allows force transmission between motors. This state is a hallmark of KIF1A which differentiates this motor from its dimeric counterpart. Hence, single-headed kinesins could cooperate achieving much larger forces than dimeric kinesins. Also, we develop a simplified version of the model on a lattice by taking into account the main ingredients used in the previous description. The lattice description successfully describes the main phenomenology found in the Langevin description and it can be specially useful on the study of density waves, traffic jams and non-equilibrium phase transitions. Finally, simple experiments could be proposed to study the cooperative action of small groups of motors and test the previous results. Some examples could be membrane tube extraction experiments[4], long-range transport of vesicles along microtubule networks[5] or gliding assay experiments[6].

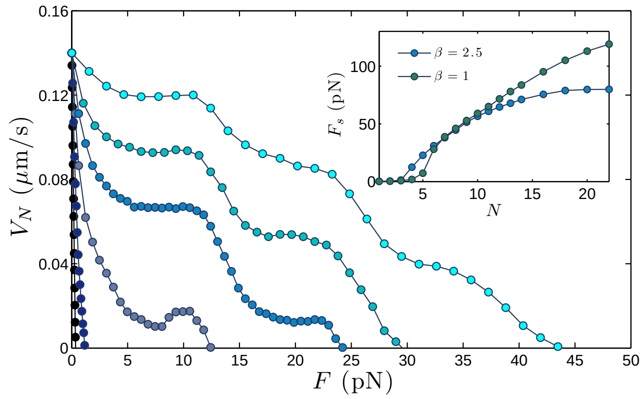

FIG. 1. Velocity-force curves for $N = 2, 3, 4, 5, 6$ and 8 motors (from left to right). We notice the remarkable enhancement of the stall force of the system when the number of motors is increased. Inset: stall force evolution versus the number of motors for two different ratios between the de-excitation rate (ω) and the hydrolysis rate ($\omega^\star$) of motors ($\beta = \omega/\omega^\star$).

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