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Much of a modern person’s day is spent trying to get from point A to point B. So, too, in the cell, much time and energy is expended on shuttling organelles, protein complexes, and mRNA, called “cargo,” from point A to point B. We know that vehicle traffic slows down when roads get jammed with high-volume congestion. The traffic analogy begs the question: Do cellular highways get jammed? This is the question being probed by Leduc et al. in PNAS (1).

Efficient cellular transport is made along “cellular highways” in the form of a cytoskeletal network of proteinaceous filaments called microtubules (2, 3). The microtubules crisscross the cell in a radial array to connect distal regions. The cell has “motor proteins” to traverse the highways and carry cargos. Motor proteins are nanoscale machines made from two polypeptide chains folded and wound together (Fig. 1A). These protein dimers have enzymatic feet (called “motor heads”) that bind to the microtubule filament and use ATP to cause alternative stepping in a hand-over-hand style (Fig. 1A) (4–5). Numerous biophysical studies have discovered a number of amazing properties about motor proteins, including their step size, their maximum force, their off-rate. This is because motor neurons that connect the cell body in the spinal cord to the muscles of the body can be up to a meter in length. Without proper intracellular transport, goods and supplies cannot get from the cell body, where they are produced, to the tip of the axon, where they are needed to maintain the neuromuscular junction connecting nerve to muscle. Without replenishment of supplies, the tip of the axon begins to retract, and the muscle can no longer be controlled, resulting in paralysis. The most identifiable modern case of ALS is distinguished physicist Dr. Stephen Hawking.

The report by Leduc et al. in PNAS demonstrates that motor protein traffic jams can exist, given the right conditions (1). For this demonstration, the authors use Kip3, a yeast kinesin-8 family motor. Kip3 not only walks but is also known to destroy microtubules from their ends (depolymerization) in cells (11). The Kip3 used in this assay was not able to destroy the microtubules because the filaments were doubly stabilized, so the motors only walked along microtubules.

Kip3 kinesins were picked for this study for a number of properties that were likely to result in traffic jams. (i) They are highly processive, meaning they take many steps (more than 2,000 of 8 nm each) before they fall off (dissociate from) the filament (Fig. 1B). This means they get stuck on the microtubule filament. (ii) Kip3 motors also dissociate from the microtubule faster both from the middle of the track and at the end, giving them more exit ramps along the filament and a smaller “construction zone” at the end of the filament.

With these tunable attributes, Leduc et al. demonstrate and measure the evolution of a nanoscale traffic jam (1). Kip3 traffic jams along the microtubule built from the end (construction zone) and caused a buildup that grows in size (Fig. 1). Before hitting the jam, kinesin motors moved at top speed, but once hitting the jam the motors slowed down, just as cars do in a vehicular traffic jam (Fig. 1).

In addition to the slow-down, motor proteins also dissociated from the

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microtubule earlier in a traffic jam. Much like drivers, Kip3 motors opted to exit instead of staying stuck in traffic. Unlike human motorists that become tired of waiting and leave the highway, Kip3 dissociated faster because it was bumping into its neighbors, and those neighbors caused it to fall off the track. It has been shown that kinesin-family proteins are more susceptible to dissociation when their pathway is blocked (12, 13). Unlike kinesin-1, Kip3 still holds on for 1 μm (125 steps), even in highly crowded conditions.

Another interesting difference between the nanoscale Kip3 motors and vehicle traffic is that the motor protein traffic jams depend on the length of the microtubule filament (1). Short microtubule tracks were not long enough to attract and bind a large number of Kip3 motors from solution. Thus, short microtubules were never able to reach the high density of motors needed to jam. Long microtubules, on the other hand, were able to bind a large number of kinesins that associated from solution along the entire length. The longer the length, the more motors could bind. The authors refer to this effect as the “antenna effect” because the microtubule length acts to attract the motors. After associating, the motors walked and began to build up a high density as they approached the impassible end. Because longer microtubules could attract more motors, the longer the microtubule, the bigger the traffic jam. To relate back to our motor vehicle analogy again, this is equivalent to longer roads having more on-ramps but keeping the same number of off-ramps. If more cars can enter the highway but no extra cars can leave, that increases the density of motors that jam.

So, what does this all mean for motor transport inside cells, such as long nerve cells? Will jams hurt us? The good news is that the motors performing long-range transport in long axons have motile properties that inhibit jamming. They have shorter run lengths of 1 to 2 μm, and then dissociate, so they exit before jamming. Further, they are more sensitive to dissociation at obstacles. In analogy, they exit immediately when there is construction.

We may want to believe that we are safe from life-threatening jams in our axons, but motors often work as teams attached to cargos. Teams of motors stay bound longer, walk farther, and do not dissociate as easily at obstacles. Should we worry about cargo jams? Future experiments using cargos with high numbers of motors are needed to test these questions.

Leduc et al. demonstrate and measure the evolution of a nanoscale traffic jam.