The complex internal structure of cells depends to a large extent on the targeted transport of vesicles, organelles and other types of cargo. This traffic is powered by molecular motor proteins that can be thought of as cellular ‘nano-trucks’ and transport cargo along cytoskeletal filaments, the cellular ‘roads’. These filaments possess an intrinsic direction: they have a ‘plus’ and a ‘minus’ end. Some motors such as kinesin-1 walk to the plus end, while others such as cytoplasmic dynein walk to the minus end. Unlike trucks, however, the molecular motors constantly undergo thermal collisions with water molecules and therefore fall off their track after a certain distance. This run length is typically of the order of 1 µm.

Motors Team up to Pull a Cargo

In the cell, molecular motors work in teams, i.e. a single cargo is usually transported by more than one motor. For example, a cargo may be transported by several kinesin motors as depicted in Fig. 1(a). Because of thermal collisions with water molecules, the motors unbind from and rebind to the filament in a stochastic manner. This means that the number of motors pulling the cargo fluctuates in time. We have studied the transport of a cargo pulled by several motors both theoretically and experimentally [1, 2]. In a biomimetic in vitro experiment, we monitored beads pulled by several kinesins. The number of kinesins on the beads was changed in a controlled manner by incubating the beads in solutions with varying kinesin concentration c, which is directly proportional to the average number of kinesin on the bead.

The main effect of a larger number of motors is an increase in the run length of the cargo, see Fig. 1(b)-(h). The intuitive reason for this increase is that, when one motor unbinds from the track, the other bound motors still provide a connection between the cargo and the filament, and give the unbound motor a chance to rebind to this filament. We have successfully fitted our experimental results with our theoretical model, see the lines in Fig. 1(b)-(h). This allowed us to determine the maximal number of motors pulling the beads to vary between two and seven motors for the concentrations shown in Fig. 1.

Motors Play Tug-of-War

In the cell, many cargoes travel back and forth along cytoskeletal filaments, changing direction every few seconds. Since one type of motor can walk only into one direction, two types of motors must be present on such bidirectional cargoes. Indeed, cellular cargoes are often transported by several plus-end moving kinesins and several minus-end moving dyneins. This leads to the problem of coordinating motors that walk into opposite directions, see Fig. 2(a). Naively, one would expect that the motors should block each other, leading to almost no cargo motion as depicted in Fig. 2(d). However, cellular cargoes are observed to move rapidly back and forth as shown in Fig. 2(e). This transport pattern implies that during plus motion, only plus motors are active (Fig. 2(b)) and during minus motion, only minus motors are active (Fig. 2(c)). How is this cooperation accomplished?

In order to explain the observed bi-directional transport, several groups have postulated a coordination machinery that organizes the motors into states (b) and (c) and prevents state (a) in Fig. 2. However, we have recently developed a model which can explain the experimental observations without such an extra machinery [3, 4]. In our model, the motors manage to organize themselves by playing tug-of-war: the plus motors pull on the minus motors and vice versa. This force leads to an increased tendency of the motors to drop off the filament.
If, for example, more plus than minus motors are bound to the filament, the force on each minus motor is higher than the force on each plus motor. This higher force increases the probability for a minus motor to unbind from the filament. As soon as one minus motor has unbound, the remaining bound minus motors have to sustain the plus motor’s force alone. This increases the unbinding probability of the minus motors even further and leads to a cascade of minus motor unbinding events until no minus motor is left – the cargo ends up in a state with only plus motors bound, as shown in Fig. 2(b), and quickly moves into the plus direction. This plus motion persists until the stochastic unbinding and binding events of the motors lead to a cargo state for which more minus than plus motors are bound to the filament. Then an unbinding cascade of the plus motors leads to a state with only minus motors bound, see Fig. 2(c) and therefore to fast minus motion. In total, the cargo stochastically switches between fast plus and minus motion, see Fig. 2(e). Our tug-of-war model can thus explain the experimentally observed bi-directional motion without postulating an unknown coordination machinery.

We have compared the results of our model to experiments on the transport of lipid droplets in fly embryos performed by Steven Gross and co-workers from the University of California in Irvine, USA. Our model was able to explain their experimental observations quantitatively.

Motor Traffic with Internal States
If many molecular motors walk along the same filament, the traffic may become congested. We have studied this situation theoretically, taking into account that stepping of a molecular motor is a complex process which consists of a series of transitions between different motor states [5]. We have considered the simplest case of two internal states.

We have found that even for only two internal states, some properties of the motor traffic exhibit a strong and surprising dependence on the detailed kinetics of the step. For example, the effective unbinding rate of the motors may both increase and decrease with increasing motor density, see Fig. 3(a). Likewise, the run length either exhibits a strong decrease or almost no dependence on the motor density, see Fig. 3(b). These results may help to clarify controversial experimental results on motor unbinding rates and run lengths for high motor densities.

References: