Tracking molecular motors and intracellular cargo transport

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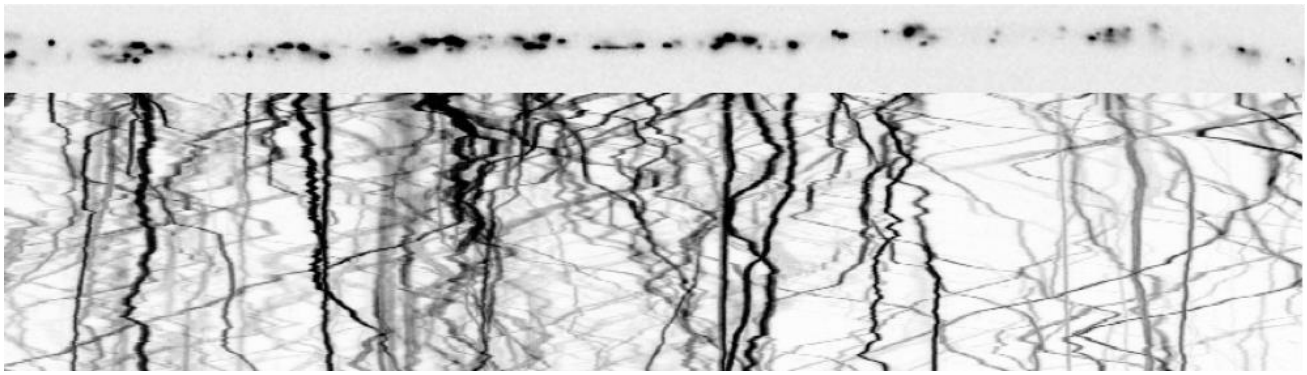

Figure 1: Vesicles labelled with NPY-RFP in a human cell. Lower panel shows space-time plot of the region above visualising the motion of vesicles in both directions.

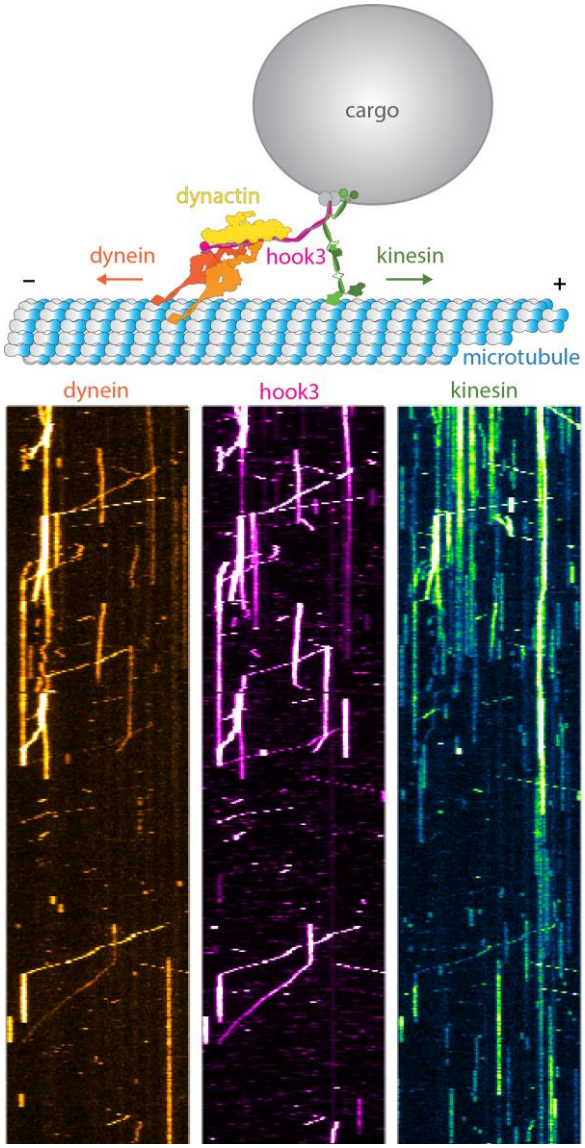

Figure 2: Schematic of bidirectional complex of dynein/dynactin and kinesin, mediated by cargo adapter hook3. Lower panel shows motility of complex in kymographs.

Inside living cells, tiny machines transport cargo along filamentous polymers. This is important to deliver cellular components to the edges of the cell, which can be a very long distance in the case of neurons reaching from the spine to the tip of your toes. These tiny machines undertake directional stepping powered by chemical energy in the form of ATP, which is consumed at the rate of 1 ATP per step. Different kinds of motors walk towards opposite ends of microtubules filaments and it has been recognised that cellular cargo recruits motors of opposite polarity to undergo bidirectional motion. This is useful if the cargo needs to be distributed equally in the cell, but probably also to navigate roadblocks. To test this idea directly, we analyse the behaviour of bidirectional cargo vesicles in cells (Figure 1) and reconstitute bidirectional motor complexes from purified components (Figure 2). Both approaches result in timelapse imaging data in which we need to track moving objects to determine motile properties (speed and run length in each direction) and the frequency and location of directional switch events.

To track bidirectional motor complexes in timelapse images, you will use information of intensity values in three channels to identify and track kinesin only, dynein only and bidirectional complexes. In order to track these proteins and estimate the underlying properties of interest, modern target-tracking algorithms will be used, which enable the modelling of all the aspects of the problem: (i) the number of proteins in the images might be unknown and time-dependent, (ii) some of the proteins in the field of view might not appear in every frame (false negative) and (iii) there might be background noise in the

acquisition so that not all bright area in the image corresponds to actual proteins. The motion and observation of each protein will be modelled in a probabilistic way using hidden Markov models (also known as state space models), allowing for a range of different behaviour to be represented.

The project is suitable as a PhD project to expand tracking problems to 3D non-point objects such as microtubule end markers for which information of shape, intensity distribution and correlation of speed and intensity need to be integrated to optimise tracking. Potential project partners are LUMICKS, an academic spin-off company developing single-molecule imaging and force measurement instruments and 3i, a manufacturer of high-end microscopes and imaging software.