Modelling and analysis of the dynamics of molecular motors and intracellular cargo

Supervisors: Jeremie Houssineau, Statistics, University of Warwick (`https://jeremiehoussineau.com/`)
Anne Straube, Warwick Medical School (`http://mechanochemistry.org/Straube/`)

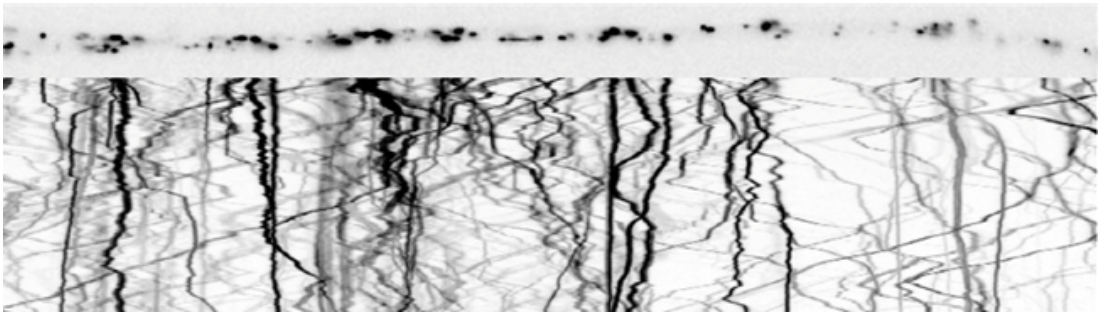

Figure 1: Vesicles labelled with NPY-RFP in a human cell. Lower panel shows space-time plot of the region above visualising the motion of vesicles in both directions.

Project outline

Biologists have been successful in generating parts lists of components involved in most fundamentally important biological processes. However, to understand how these work, we must understand the dynamics of the recruitment and movement of those components. New imaging technology enables the acquisition of large datasets capturing the dynamics of several individually labelled components in 3D over time. These 5D datasets (3D volumes in several channels and many timepoints) are usually too complex to label and track components by hand. Therefore, algorithms have to be developed in order to process it. When imaging proteins inside of a living cell, a number of challenges arise:

i) physical and biological limitations lead to a low signal-to-noise ratio,
ii) the number of proteins inside a diffraction limited spot is unknown a priori and fluctuates in time and
iii) localising the proteins over time is not sufficient and potentially complex behaviours must be accounted for in the modelling.

Due to these factors, a suitable statistical model must be designed in order to capture the uncertainty in the data and to quantify the reliability of the associated outputs. In this project, students will work together with our experimental partner to track molecular motor protein complexes inside living cells. Cargo vesicles and individual motors will be labelled with different fluorescent tags and 3D volumes imaged using lattice light sheet microscopy. The task will be to track the movement of the cargo and the recruitment and release of individual motors to those cargoes. Once the analysis pipeline has been established, human patient mutations will be introduced to the motor and alterations in the behaviour of motors and cargo characterised.

Approach

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.

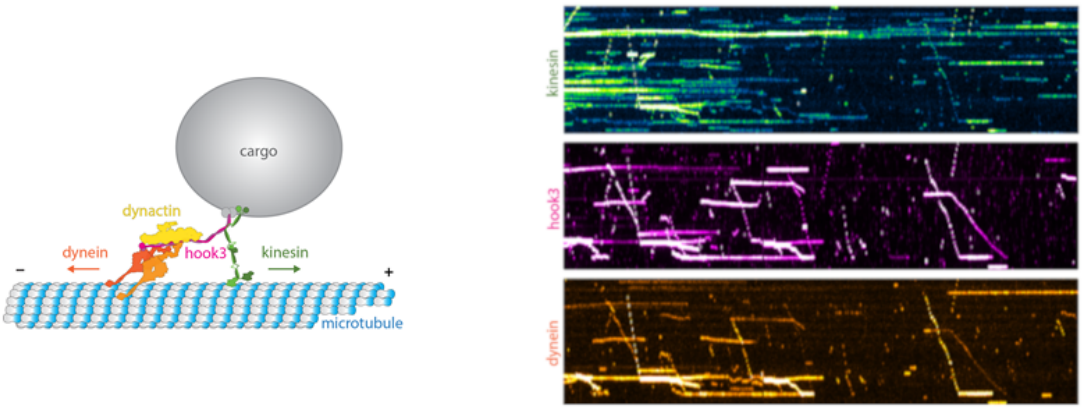

Figure 2: Schematic of bidirectional complex of dynein/dynactin and kinesin, mediated by cargo adapter hook3. Right panel shows motility of complex in kymographs.

Targeted outcomes

1. The introduction of principled algorithms for the detection and the estimation of the behaviour of intra-cellular components from bio-imaging data.

2. The development of a software, e.g. as a MATLAB toolbox or ImageJ plugin, making these algorithms accessible to a general audience.

3. The qualitative and quantitative understanding of some of the biological processes determining intra-cellular mechanisms.

This project could then lead to a PhD for which the objective would be to obtain a comprehensive understanding of cargo movement in a range of model systems (including recycling vesicles in neurons and viral capsids in infected fibroblasts) in addition to the single molecule behaviour of the motors responsible for the cargo transport. This could include: time spent diffusing in 3D, bound on microtubules and undertaking directed runs along microtubules and the frequencies of switching between that behaviour. Another aspect that could be considered is the understanding of the behaviour changes in different places in the cell; differences are indeed expected between behaviour changes near the membrane where material is taken up and delivered to and behaviour changes near the nucleus where the bulk of the recycling and viral capsid maturation happens.

References

[1] N. Siddiqui, A.J. Zwetsloot, A. Bachmann, D. Roth, H. Hussain, J. Brandt, I. Kaverina and A. Straube, "PTPN21 and Hook3 relieve KIF1C autoinhibition and activate intracellular transport." Nature communications, 10(1), 2693, 2019.

[2] U. Theisen, E. Straube, A. Straube, "Directional persistence of migrating cells requires Kif1C-mediated stabilization of trailing adhesions." Developmental cell, 11; 23(6), 1153-66, 2012.

[3] R. Mahler, "Multitarget Bayes filtering via first-order multitarget moments." IEEE Transactions on Aerospace and Electronic systems, 39(4), 1152-1178, 2003.

[4] J. Houssineau and D.E. Clark, "Multi-target filtering with linearized complexity." IEEE Transactions on Signal Processing, 66(18), 4957-4970, 2018.