MathSys Project: Modelling information propagation through the microtubule lattice.
Supervisors: Burroughs (Mathematics Institute) & Cross (Medical School)

Background: Microtubules are bistable polymers that spontaneously switch between polymerisation (lengthening) and depolymerisation (shortening), a behaviour called dynamic instability. Microtubules comprise 13 protofilaments that are arranged in a tube, see Figure 1. It was until recently believed that once assembled, the microtubule tube was static, but recent evidence reveals that its lattice of subunits is highly dynamic and plastic and that it can sense, integrate and transmit mechanical signals (information). We now know for example that microtubules can self-repair and that the binding of interacting proteins to the lattice modulates its spacing, its curvature, its stability and its tendency to bind further proteins and drugs [1,2]. We hypothesise that protein binding exerts its effects by generating mechanical stress in the lattice. This stress then propagates through the lattice, changing its properties. As a result, microtubule mechanics, microtubule dynamic instability and the modulation of the lattice by protein binding are intertwined, having a common dependence on lattice stress.

This project will construct a 3D simulation of microtubules informed by experimental data, and develop a deep understanding of microtubule lattice modulation and signal propagation.

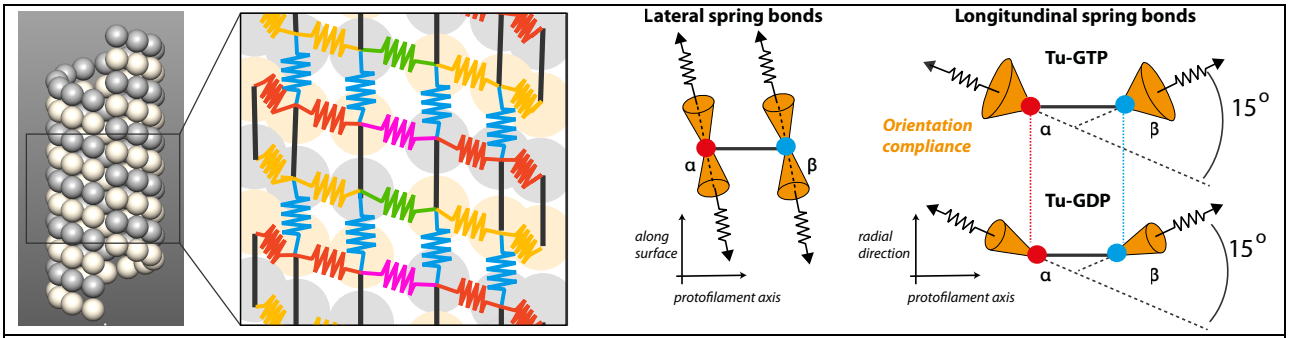

Fig.1 *Lattice of spring-bonds model. Left: a microtubule composed of tubulin dimers organised into 13 protofilaments; the pitch of the spiral is such that there is a seam on one side. The panel shows the six bonds between dimers. Right: sketch of the bonds for Tu-GDP and Tu-GTP $\alpha\beta$ dimers which have characteristically different spring bonds. Each bond has a length, a stiffness, a 3D directional preference (cones) and a strain-dependent breaking rate.*

The project: You will build a simulation model of a microtubule, modelling the microtubule tube by a network of springs connecting the Tubulin dimers (the subunits that form the microtubule lattice), Figure 1. Such models are called bead-spring models. Key will be capturing the microtubule's natural anisotropy in the model, i.e. distinguishing the longitudinal protofilament bonds and the lateral bonds between protofilaments to form an *orthotropic tube model*. The elasticity of an orthotropic tube depends on the direction of stretch. Tubulin dimers also have a natural bend, Figure 1, so protofilaments are curved when not part of the microtubule, and generate internal stress within the tube. Your model will comprise beads (Tubulin dimers) connected by 6 springs with spring constants, orientation potentials that constrain the spring direction and force dependent bond breaking rates, Figure 1. Parameters will be determined from experimental data where available, and otherwise determined from qualitative comparison to observed behaviour.

You will analyse a number of experiments (with potential to constrain model parameters directly from data):

i) Microfluidic bending of microtubules. Microtubules bend under flow in microfluidic chambers. By adding binding proteins, that bend can be fixed-in when the flow is stopped [1].

You will reproduce this behaviour from your simulation and compare to the behaviour of an elastic rod model [3]. A key unknown here is the degree of clustering during binding that may explain the microtubule crinkling observed experimentally.

ii) Shearing of microtubules. By binding microtubules to a surface coated in a microtubule binding protein, it is observed during depolymerisation that the top of the microtubule can shear off leaving a partial tube (tail), about ½ of the tube [1]. You will simulate this and find parameters sets that reproduce the effect with realistic rates (eg match tail and top retraction rates).

iii) Bending and buckling of microtubules by forces in a dual beam optical trap, Figure 2. The aim will be to reproduce the results of [4] on buckling forces. You will compare to a simpler elastic rod model of microtubules [3] and determine the error in using the latter. You will then anlayse mechanical properties of bare microtubules and those coated with binding proteins.

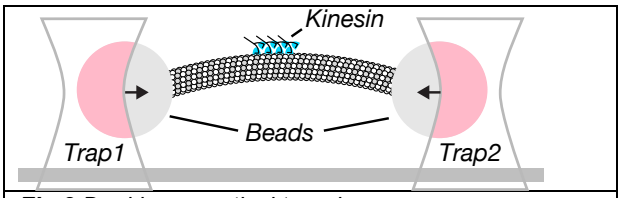

Fig.2 *Dual beam optical trapping*

Desirable skills. You should have a keen interest in using high-level computational methods to solve problems. Programming is essential, ideally MatLab, C++ or python, although molecular dynamics simulators (e.g. LAMMPS) may also be used if desired. Experience with Monte carlo methods and/or an understanding of mechanics will be useful.

Possibilities of a PhD.
This can be extended to a PhD in a number of ways depending on the interests of the student. For instance:
i) A PhD focusing on structural changes in the microtubule through protein binding. External: You would collaborate with an expert on MT cryoEM in Birkbeck College,
ii) A PhD focusing on drug action and how drugs change microtubule behaviour. External: You would collaborate with an expert on MT drug action in Geneva.
iii) A PhD focusing on microtubule lattice defects that underpin microtubule fatigue [5] and possibly rescue events in dynamic instability. External: You would collaborate with an expert on MT repair and fatigue in CNRS, Grenoble, France.
In these PhDs, utilising the latest Monte carlo algorithm protocols, such as multi-level MC, and using parallelisation, either MPI, GPU would be a key focus.

References.
[1] Kinesin expands and stabilizes the GDP-microtubule lattice. R. Peet, Nigel J Burroughs, Robert A. Cross. *Nature Nanotechnology* 2018, 13:386–91.
[2] Kinesin-binding–triggered conformation switching of microtubules contributes to polarized transport. Tomohiro Shima, Manatsu Morikawa, Junichi Kaneshiro et al. 2018. *JCB* 217, 4164-83.
[3] Curvature-Sensitive Kinesin Binding Can Explain Microtubule Ring Formation and Reveals Chaotic Dynamics in a Mathematical Model. Simon P. Pearce, Matthias Heil, Gareth Wyn Jones, Andreas Prokop. Bull Math Biol. 2018.
[4] Microtubules soften due to cross- sectional flattening. Edvin Memet, Feodor Hilitski, Margaret A Morris *et al*. 2018. *eLife* 2018 7:e346695.
[5] Microtubules self-repair in response to mechanical stress. Laura Schaedel, Karin John, Jérémie Gaillard, Maxence V. Nachury, Laurent Blanchoin, and Manuel Théry. 2015. *Nature materials*. 14;1156-63.