MathSys Project: Modelling microtubule lattice modulation by protein binding
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Background: Microtubules are formed by polymerising Tubulin dimers into tubes, tubes comprising 13 protofilaments, protofilaments binding to generate a spiral lattice, see Figure 1. They are a major component of mammalian cells providing structural integrity, an extensive transportation system, and being vital for cell motility and cell division. It was widely believed that once polymerised the microtubule lattice was static, but recent evidence [1,2] demonstrates that proteins that bind to the microtubule surface modulate the lattice spacing which alters the microtubule properties, eg promoting more protein to bind. Underpinning this behaviour is mechanical stress in the microtubule, stress that in fact is pivotal to the phenomena of microtubule dynamic instability - the tendency of microtubules to stochastically switch between growth and retraction. Thus, microtubule mechanics, microtubule dynamic instability and lattice modulation by binding proteins are all intertwined, having a common lattice stress dependence. This project will construct a 3D simulation of microtubules and their interactions with motor proteins to recapitulate upto three key experiments in order to develop understanding of this lattice modulation.

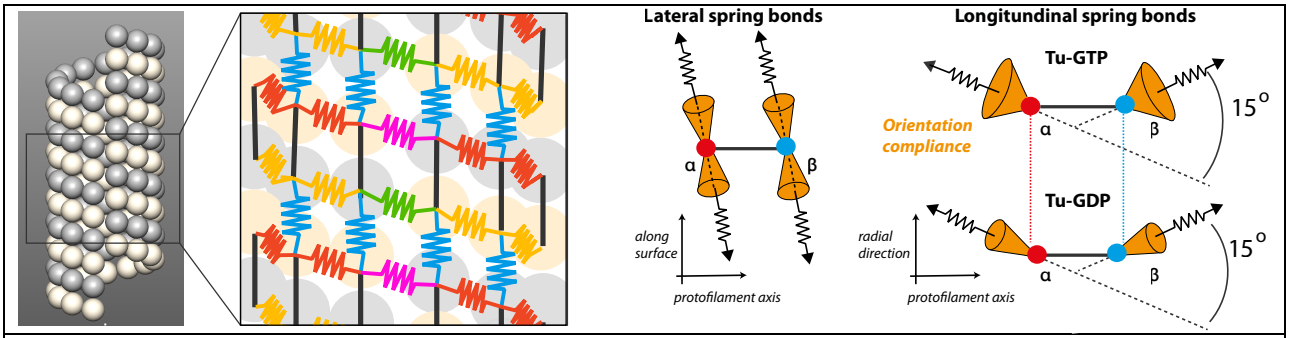

Fig.1 *Lattice of spring-bonds model. Left: a microtubule composed of tubulin dimers organised into 13 protofilaments; the pitch of the spiral is such that there is a seam on one side. The panel shows the six bonds between dimers. Right: sketch of the bonds for Tu-GDP and Tu-GTP $\alpha\beta$ dimers 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: This is a computational project, using ideally MatLab, C++ or python, although molecular dynamics simulators (e.g. LAMMPS) may also be used if desired to simulate coarse grained 3D Brownian dynamics. You will build a simulation of a bead-spring model of a microtubule, Figure 1, capturing the microtubule's natural anisotrophy, i.e. its longitudinal protofilament structure and their lateral binding to form a tube. This is called an orthotropic tube model. The tube's elasticity therefore depends on the direction of stretch (anisotrophy). Tubulin dimers also have a natural bend, Figure 1, so protofilaments are curved when not part of the microtubule, although free protofilaments are unstable. Thus, microtubules are under internal stress. The model will thus comprise bead dimers (Tubulin dimers) connected by 6 springs with spring constants, spring orientation potentials and breaking rates, Figure 1. Parameters will be from literature where available, and otherwise determined from qualitative comparison to observed behaviour. Experiments to be simulated will be:

i) Bending and buckling of microtubules by bending with a dual beam optical trap, Figure 2. The aim will be to reproduce the results of [3] on buckling forces. You will also be able to compare to a simpler elastic rod model of microtubules [4] and determine the error in

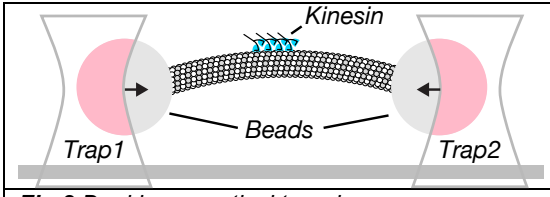

Fig.2 *Dual beam optical trapping*

using the latter. You will then compare mechanical properties between bare microtubules and those coated with binding proteins.

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

iii) Microfluidic bending of microtubules. Microtubules bend under flow in microfluidic chambers. By adding certain 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 elastic rod model [3].

Desirable skills. A keen interest in using high level computation. Experience with Monte carlo methods will be useful. 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. A possible external is in Birbeck College, an expert on MT cryoEM.
ii) A PhD focusing on drug action and how drugs change microtubule behaviour. A possible external is in Geneva, an expert on MT drug action.
iii) A PhD focusing on microtubule lattice defects that underpin microtubule fatigue [5] and possibly rescue events in dynamic instability. A possible external would be 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] Microtubules soften due to cross- sectional flattening. Edvin Memet, Feodor Hilitski, Margaret A Morris *et al*. 2018. *eLife* 2018 7:e346695.
[4] 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.
[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.