Controlling the self-organisation of chromosomes during cell division
Supervisor: Burroughs (Mathematics). Second supervisor: McAinsh (Medical School).

Background. During cell division both daughter cells must inherit a complete copy of the genome; errors in this process can lead to cancer or conditions such as Down's syndrome. Cell division thus involves duplicating the chromosomes (called sister chromatids), holding the duplicates together until all pairs are self-organised into a holding pattern in the middle of the cell (in a process called chromosome congression), each sister being attached to respective poles, then dissolving the attachments and moving the sisters to opposite poles. This is acheived through a self-assembling machine called the spindle that is comprised of polymerising filaments called microtubules that facilitate attchments between the spindle poles and the chromatids. The mechanics of this self-organisation is fairly well understood, see Figure, but how it is controlled and the sensory signals used for that control are poorly understood.

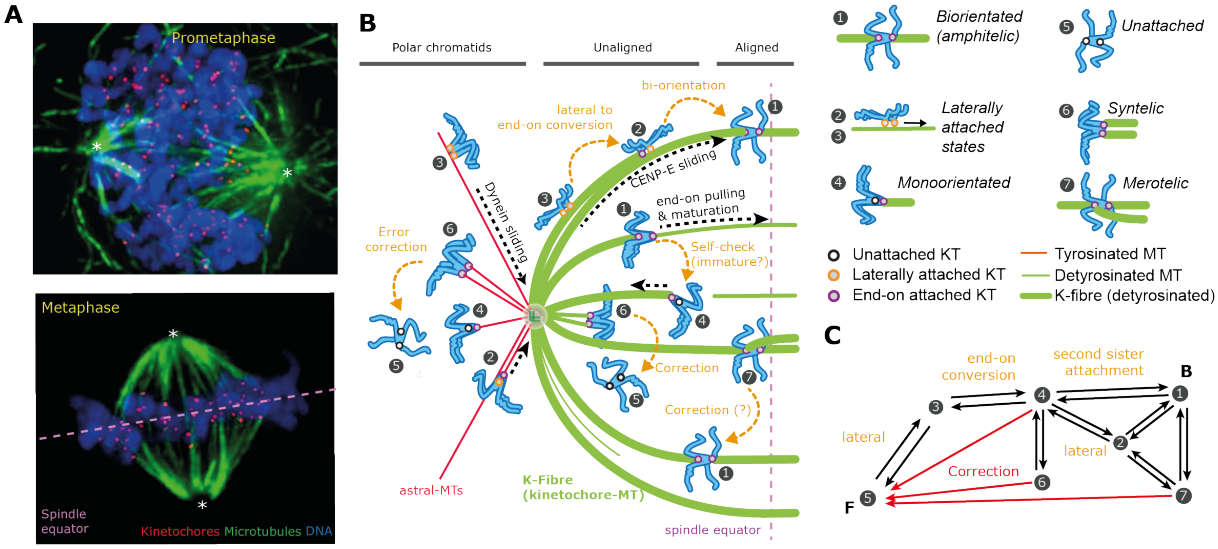

Figure 1: **Chromosome self-organisation.** **A**. Immunofluorescence image of a developing spindle in prometaphase (upper) and a mature spindle with chromosomes held near mid-plane of the cell in metaphase; microtubules (green) emanate from the two spindle poles (asterisks) that capture the chromosomes (blue) through attachment to the middle of each sister chromatid (red). Chromosomes are distributed randomly early on (prometaphase), and self-organise into a holding pattern forming the metaphase plate mid-way between the two poles (dotted line). **B**. Schematic of the self-organisation mechanisms. Paired chromatid (blue) transport mechanisms are indicated with dotted black lines, showing molecular motor driven motion and microtubule (de)polymerisation forces at end-on attached MTs. Orientation in the spindle (biasing chomosome movement towards the cell middle or towards the pole) is acheived by modification of the microtubules behind the spindles (red). Polar ejection forces (PEF) push all chromosomes away from the pole. The attachment state switches as indicated with dotted orange lines. **C**. An attachment graph showing state conversions and detachment by error correction mechanisms (red). F, unattached, B biorientated. Panels A, B modified from [1].

The Project. The key focus will be how attachment errors are corrected during the self-organisation process. The only attachment state that gives rise to the correct separation of chromatids, one to each daughter cell, is the attachment of each sister to separate poles (biorientated, state 1 in Figure). However, attachment is random, the spindle poles initially 'fishing' for chromosomes with their microtubules. Thus, erroneous attachments can occur, in particular a chromatid can attach to both poles (state 7), and both chromatids can attach to the same pole (state 6). Such erroroneous attachments need to be corrected.

We have a relatively simple 1D congression model (a stochastic differential equation) that performs error correction using force sensitive breaking of attachments. Biorentated chromosomes are under tension from their microtobule attachments; hence if the spring force is too low the attachments are broken. The project will have 3 components:

a) Perform an optimisation and robustness analysis of this model to determine optimal parameters for error correction and how sensitive error correction is to those parameters. Characterise the error rates of this model using Monte carlo simulations. The observed error rate in humans is $< 10^{-4}$.

b) Extend the model to 3D. This will alter in particular the 'fishing' process because of the 3D geometry and entail allowance for microtubules to move laterally under forces as the chromosomes congress.

c) If time permits, repeat (a) for the 3D model.

Desirable skills Programming is essential, likely in MatLab but other languages acceptable if preferred, e.g. C++, python. An understanding of the basics of probability theory and Markov processes is required, whilst understanding the basics of stochastic differential equations would be helpful.

Opportunities for a PhD. This mini-project can lead to a PhD with Burroughs and McAinsh (joining their joint lab meetings (3 theory and 4 experimental PDRAs)), and a suitable external partner. The focus of the PhD could be:

(i) Optimal control analysis of congression models. Since these models are stochastic, stochastic control methods can be used to determine the optimal control (feedback) processes. This would likely involve using the latest sequential Monte carlo techniques of optimal control theory.

(ii) Bayesian model inference of congression models fitting to state of the art (lightsheet) tracking data of chromosome congression. You would develop Markov chain Monte carlo algorithms to fit the models to data. The model can then be developed in a data driven manner to generate the first model of mammalian chromosome self-organisation able to describe congression.

Other possible directions can be discussed.

References:

[1] Building an integrated model of chromosome congression. P. Auckland and A.D. McAinsh. 2015, *J Cell Sci.* 128:3363-74