

## **Inference of mechanisms regulating chromosome movements**

### **Supervisors:**

Nigel Burroughs (Mathematics Institute/WSBC, [N.J.Burroughs@warwick.ac.uk](mailto:N.J.Burroughs@warwick.ac.uk))  
Andrew McAinsh (Warwick Medical School).

Cell division is a fundamental requirement for life, but its dysregulation or malfunction is a hallmark of diseases such as cancer. In particular the loss of fidelity in accurate division of duplicated chromosomes underpins genetic instability. During cell division, paired chromosomes are observed to perform saw-tooth like oscillations across the cell equator prior to their separation to respective daughter cells, Fig 1A; these oscillations offer a unique opportunity to study the mechanisms driving their movement. Statistical computation methods applied to a vast database of experimental trajectory data (>5000 paired sister trajectories) is giving crucial insight into these processes [1,2]. Our current model consists of two particles (the chromosomes) connected by a weak spring and either particle switching direction with a rate governed by a clock with a spring tension dependent rate, Fig 1B. This coupling allows sister-sister communication, thereby ensuring that the other sister responds by also switching direction when one of them switches - by analogy think of two fast racing cars that are connected by a bungee rope used to detect when the other car switches direction! This system can be modeled as two coupled (Gaussian) random walks with direction (+,-) determined by two hidden Markov chains with position and time since last switch dependent transition rates.

The aim of the project is to extend our current Markov chain Monte Carlo (MCMC) model to incorporate measurement noise, thereby determining how measurement noise degrades our parameter estimates and whether it affects detection of switching events.

**Techniques required:** an understanding of Markov processes and random walks. Familiarity with MCMC methods would be a distinct advantage.

**Deliverables:** software in MatLab, and transferred to C++ if time permits. Testing of your MCMC algorithm on simulated data. Analysis of real data sets (likely ~100 good oscillatory trajectories). Students with prior experience of hidden Markov models in an MCMC context can attempt hierarchical models.

**Beneficiaries:** you would join a large group studying human chromosome organization during cell division, adding to the knowledge base of mechanisms regulating chromosome movements. In the long term we aim to apply these methods to cancerous cells and human meiosis, potentially relating to fertility issues.

**Data:** Available on Figshare, see [2].

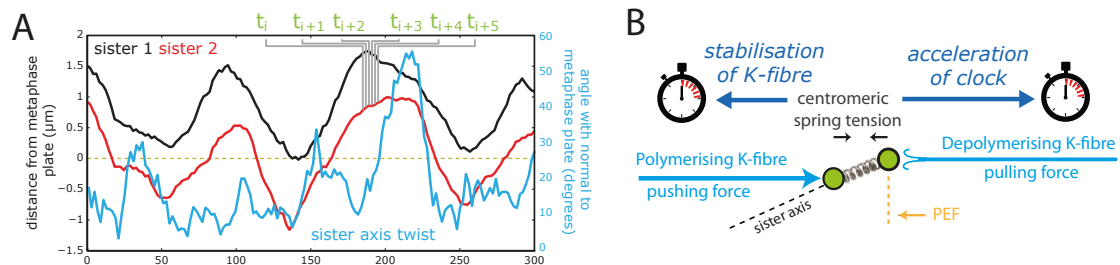
**Prospects of a PhD:** This project could readily be extended to a PhD project; our experimental collaborators in Warwick Medical School are at the forefront of imaging, in fact recently using one of the most advanced microscopes in the world (lattice light sheet microscopy in Janellia Farm, USA). Warwick has its own

light sheet microscope that is just starting to deliver high quality data and this will fundamentally change the acquisition of 3+1D data; in particular the full cell division cycle will be able to be imaged at high time and spatial resolution. Thus, potential projects include modeling of the capture of chromosomes, error correction processes, oscillations, and anaphase and anaphase regulation, whilst also including testing of models with a variety of experimental perturbations. This can also be looked at at a cell level, ie incorporating the spatial variability observed in cells. Funding for experimental work on meiosis and cancer cells is being sort. The PhD would involve analysis of this data using bespoke MCMC algorithms, including model selection techniques (marginal likelihood MCMC simulation) to answer biological hypotheses.

**References:** [1] **Super-resolution kinetochore tracking reveals the mechanisms of human sister kinetochore directional switching.** Nigel J. Burroughs, Edward F. Harry and Andrew D. McAinsh. *eLife* 2015;10.7554/eLife.09500.

[2] **Inferring the Forces Controlling Metaphase Kinetochore Oscillations by Reverse Engineering System Dynamics.** Jonathan W. Armond, Edward F. Harry, Andrew D. McAinsh, Nigel J. Burroughs, *PLoS Comp. Biol.* 2015, DOI: 10.1371/journal.pcbi.1004607.

[3] **SOFTWARE: KiT: A MATLAB package for kinetochore tracking.** Jonathan W. Armond, Elina Vladimirov, Andrew D. McAinsh and Nigel J. Burroughs. *Bioinformatics*, 2016. Advance copy.



**Figure.** **A.** Experimental trajectory showing paired sister oscillations (displacement relative to the equatorial plane (red, black for respective sisters) and twist of sister-sister axis to normal (blue)). **B.** Model schematic of tension-clock model.