Coordination of cell division in space and time: mechanistic modelling of the spindle assembly checkpoint

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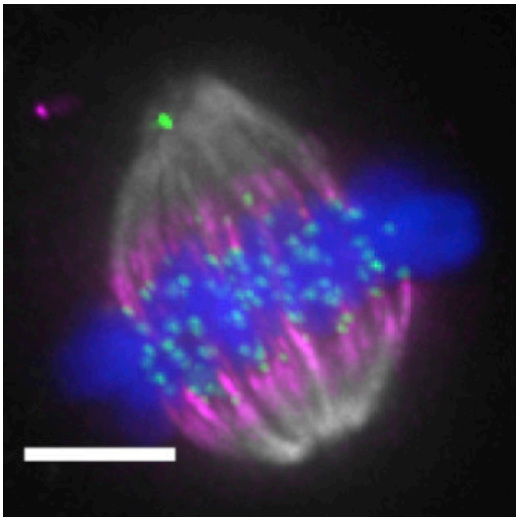

Background
During cell division, chromosome segregation must take place reliably without errors to ensure daughter cells obtain full copies of the genome. Failures of this process are associated with developmental disorders and cancer. A key step in ensuring the fidelity of chromosome segregation is the spindle assembly checkpoint. While the spindle assembly checkpoint is active, a wait signal is provided to the cell to prevent it progressing the division until mechanical feedback is available from the chromosomes. How this process is controlled in space and time is not fully understood, in particular how the process is controlled at a local level (at each chromosome) versus the global cell level. Understanding this coordination is valuable as proteins involved in the spindle assembly checkpoint are targeted in cancer therapies.

Aims and scope of the project
The aim of this project is to build and simulate a mechanistic mathematical model of the spindle assembly checkpoint that incorporates space, and is consistent with recent experimental observations of differences in the timing of separation of sister chromatids in space across the metaphase plate.

A successful model will capture slow chemical and mechanical maturation, leading to fast switch-like behaviour upon silencing of the checkpoint, and spatial differences in the coordination of this switch. This will provide insight into the role of global versus local components of the switch governing separation of chromosomes and to what extent communication between chromosomes occurs.

In this project, the student will consider the existing biological and modelling literature [1-5] to construct a reaction-diffusion model of key proteins involved in the spindle assembly checkpoint, and consider how these interact with mechanical cues from the chromosomes. Continuum reaction-diffusion partial differential equations (PDEs) coupled to a stochastic Markov process to describe the mechanical attachment states of the chromosomes would provide an appropriate framework for the model. This hybrid modelling framework could be further extended to incorporate stochastic effects via a mesoscopic Reaction Diffusion Master Equation (RDME) framework) [6], or by using observed data from tracks of chromosomes to inform the positions of chromosomes in the model.

PhD Projects
1) Further development and application of the hybrid reaction-diffusion model to investigate how chromosomes escape the spindle assembly checkpoint resulting in cell division errors, or modelling correction of errors in cell division.
2) Calibration of the mechanistic model of the spindle assembly checkpoint to experimental data in a Bayesian framework. This is likely to require coarse-graining of the model and interaction with our biological collaborators (McAinsh lab in the CMCB, Warwick Medical School) to inform experimental design.

Keywords
Spindle assembly checkpoint; Partial Differential Equations (PDEs); Reaction Diffusion Master Equation (RMDE); stochastic modelling; hybrid modelling

External partners
Dependent on the direction of the PhD project, there is a possibility of international collaboration with experimental labs.

References:
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[6] Isaacson, 2013, Journal of Chemical Physics, “A convergent reaction-diffusion master equation”