Title of Project:	Decoding mechanical tension at centromeres during chromosome segregation
Cell Mechanism Supervisor Name	Adele Marston
Quantitative Supervisor Name	Andrew Goryachev

Summary of project

During mitosis and meiosis, chromosomes must attach to microtubules from opposite poles, a state known as biorientation. The site of attachment on chromosomes – the centromere – is a complex chromatin structure that performs both biomechanical and signalling functions. This project aims to understand how these two functions are linked together using the budding yeast centromere as a model. The major unsolved problem of chromosome biology and cell cycle regulation is how the centromere decodes mechanical tension generated by the mitotic spindle into a chemical signal that permits segregation of chromosomes. Work in the Marston lab (eLife 2014, Genes Dev 2014) demonstrated that the conserved protein shugoshin is responsible for sensing centromere tension in budding yeast. Shugoshin associates with chromosomes that are not under tension, but dissociates upon tension establishment. While it has been shown that association of shugoshin with kinases and phosphatases is important for its function, the mechanism of conversion of mechanical tension into chemical signal remains unknown. This project will address this question by combining genetics and cell biology with mathematical modelling to gain mechanistic insight into how kinases and phosphatases control shugoshin localization and how this, in turn influences the response to tension.

The project will use state of the art live cell imaging and quantitative genomic methods, together with mathematical modelling to (1) measure the abundance and dynamics of shugoshin and its multiple molecular interactors (kinases, phosphatases); (2) determine how these parameters are altered by perturbation of the regulators and (3) define thresholds and triggers for the tension response.

What quantitative skills will the student acquire or develop during their PhD project?

- Measurement of protein abundance and complex stoichiometry in single cells
- State of the art live cell time-lapse fluorescence imaging
- Development of chemical kinetics models of intracellular dynamics using differential equations
- Elements of spatial modelling of intracellular dynamics using reaction-diffusion equations
- script-writing for automated imaging workflows
- bioinformatics analysis of quantitative genomic data (e.g. calibrated ChIP-seq).