EPSRC DTP PhD Research Project

Project Title: Mathematical modelling of spindle orientation in the fly embryo

Primary Supervisor details:

Dr David Richards, Physics and LSI

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Prof Helen White-Cooper University of Cardiff

Additional Supervisory team details: N/A

Department: Faculty of Environment, Science and Economy

Location: N/A

PhD Programme: PhD Mathematics and Statistics

Project Description:

Despite decades of research, the very earliest stages of animal development are still not well understood. Some of the most fascinating unsolved questions are related to cellular symmetry breaking. How do cells formed from the first few divisions of the fertilised egg orientate themselves? How is cell orientation influenced by the neighbouring cells? And what happens when cell orientation goes wrong?

To answer such questions, it is important to first start with relatively simple cases. For this reason, the organism of choice in the field is the fruit fly, Drosophila melanogaster. Its rapid life cycle and existence of transgenic flies expressing fluorescent proteins important in cell division make it possible to see exactly how cells orientate and to follow this in real time.

Limitations in microscopy have, until now, precluded the high spatial and temporal imaging required to characterise this phenomenon. However, the new Light Sheet Microscopy system the University recently acquired provides the ideal opportunity to fully document these divisions which, when coupled to a physical and mathematical exploration, will allow a full understanding of how spindles are orientated relative to the rest of the embryo.

Traditionally, problems like this have been tackled with a purely experimental approach. However, much quicker progress can be made if instead mathematical modelling and biophysical understanding are intimately combined with experiments. This is the exciting program of this PhD.

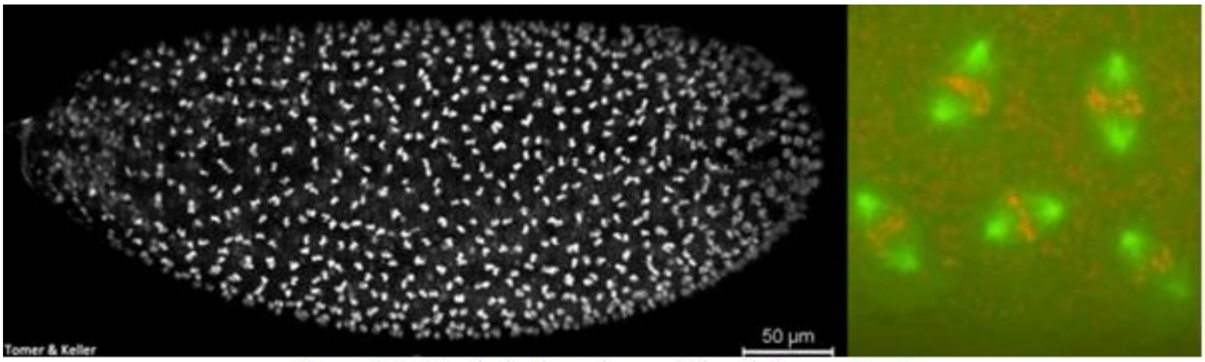

Figure 1: Left: whole fly embryo with spindles marked.
Right: Zoomed in image of spindles showing various orientations.

The PhD will use a truly multidisciplinary approach that combines mathematical modelling, computer simulations, light sheet microscopy and image analysis, allowing the student to learn a wide range of different skills and techniques, ideal for a future career in academia or elsewhere. The project will proceed in four parts:

1. Mathematical modelling and computer simulation. Motivated by the famous Ising model of interacting spins in physics, a three-dimensional mathematical model of mitotic spindle orientation will be developed that includes dependence on spatial position and interaction with neighbouring spindles. These models will be simulated and analysed using MATLAB and/or C++.

2. Light sheet microscopy of developing Drosophila embryos. In the lab, the student will learn how to handle and genetically manipulate fruit flies, and image transgenic embryos expressing a variety of fluorescent proteins using our brand new, state-of-the-art light sheet microscope.

3. Image analysis. Based on existing code within our groups, new image analysis software will be designed that automatically extracts spindle orientation in the developing embryo. This information will then be used to inform, validate and test the mathematical model in part 1 and the experiments in part 2.

4. Applying the model to other oriented cell divisions. Working with the research group of Helen White-Cooper (University of Cardiff), the experimental approach and mathematical model will be applied to the oriented cell divisions of the Drosophila larval testes niche.

Timeline

Years 0-1: Introduction to modelling and lab experiments; initial mathematical model; first modelling paper

Years 1-2: Microscopy and image analysis; model development; visit to Cardiff; experimental paper

Years 2-3: Final experiments and model refinement; third combined modelling-experiment paper

References: N/A

Project specific enquiries:

If you have any general enquiries about the application process please email PGRApplicants@exeter.ac.uk

If you have project specific enquiries please contact the lead supervisor named above.