

Modelling the interactions of DNA-associated proteins that determine cell type

Supervisors: Wolfram Moebius and Brian Hendrich

As organisms develop, cells take on specific identities, such as becoming nerve, muscle, or skin cells. To become a particular cell type, genes linked to that identity must be activated, while genes linked to other cell types must be switched off. You will use physical modelling to understand the intricate interplay of proteins bound to DNA just after the cell receives an external signal to commit to a specific cell type.

Specifically, you will build on biophysical principles and experimental data to develop a model that integrates enhancers (regulatory DNA regions that control which genes are transcribed), transcription factors (proteins that control transcription), RNA polymerase II (the enzyme that transcribes genes), and finally nucleosomes (complexes responsible for packaging DNA). At first, the model will be one-dimensional, where proteins bind to, unbind from, and move along a lattice representing DNA. Later, this may be complemented by a three-dimensional model, which may describe more aspects at the cost of higher complexity and computational demands.

You will use this model to develop a mechanistic understanding of a recent discovery by the Hendrich Lab: When a cell receives an external signal, paused RNA polymerase II at enhancers is immediately released. This interferes with multiple aspects of the enhancers themselves – transcription factor binding is disrupted, becoming more dynamic and the density of nucleosomes at enhancers is reduced, making these regions much more accessible. This creates an opportunity for transcription factors to exchange places, allowing new genes to be turned on while others are turned off.

The project will be supervised by a team dedicated to interdisciplinary research: Wolfram Moebius, a physicist with experience in modelling a range of biological systems, and Brian Hendrich, a stem cell biologist whose lab made the discovery motivating this project. Throughout your research, you will develop sought-after skills, specifically modelling biological systems, simulating highly stochastic systems, and – depending on your interest – performing experiments to test your own predictions. The host institution, the Living Systems Institute at the University of Exeter, will provide both a stimulating atmosphere and plenty of scope for interactions for additional input and advice.