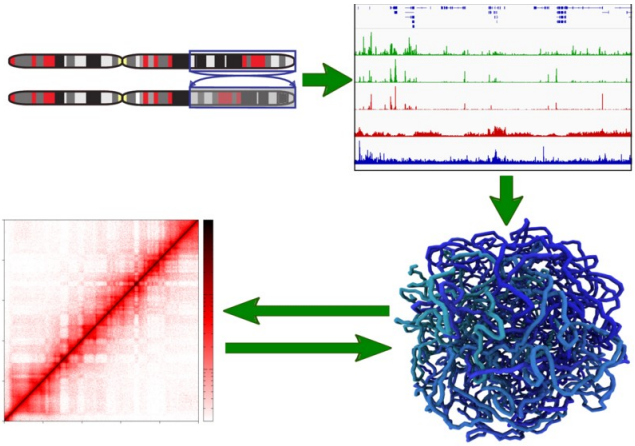
PhD Project : Physical Modelling of Chromosome Organisation in Human Disease

We offer an interdisciplinary PhD project at the **University of Edinburgh** working with Dr Chris Brackley and Prof. Davide Marenduzzo in the School of Physics, and Dr Adam Buckle and Prof. Nick Gilbert at the Institute for Genetics and Molecular Medicine.



This highly interdisciplinary computational project will use polymer physics simulations to understand how the three-dimensional organisation of chromosomes within cell nuclei controls gene expression [1], and how disruption of the organisation can lead to disease.

Recent advances in "chromosome conformation capture" technologies [2] have allowed the 3-D structure of the genome to be probed with greater precision than ever before. Gene regulation by non-coding elements is recognised as a major mechanism for asserting the complex patterns of gene expression in cells [3] and depends strongly on 3-D chromosome organisation [4].

Sequence alterations within the regulatory portion of the genome, and the consequence on 3-D structure is of major importance for human health and disease; well-studied examples include disorders such as *β*-thalassemia, hemophilia and atherosclerosis [3]. Yet understanding the consequences in terms of gene deregulation is a major challenge, requiring detailed molecular and genetic analysis [3].

In this project polymer simulations will be used to predict chromosome folding based on protein binding data [4-6]; then new and existing chromosome folding data will be analysed together with gene expression data to investigate the causal relationship between the two. These two aspects will then be brought together with the aim of using the simulations to predict how chromosome organisation is disrupted in disease, and how this will affect expression.

Candidates should have a background in computational science, be proficient in computer programming, and have, or be about to complete, an undergraduate degree in physics, biophysics, applied maths, or similar. Ideally candidates should have experience of simulations, polymer physics, or biophysical modelling. While prior experience in biology is not necessary, candidates should have a strong interest in building expertise in this area. The project will involve working closely with experimental biologists, and analysing large bioinformatics data sets.

The position is offered as part of the Precision Medicine Doctoral Training Programme funded by the Medical Research Council, the University of Edinburgh and the University of Glasgow; it provides funding for tuition fees and stipend, and is open to UK/EU nationals. This prestigious programme offers PhD with Integrated Study studentships, providing research training alongside taught courses over four years of study.

Further information about the programme is available here:
https://www.ed.ac.uk/usher/precision-medicine
with details of the project here:
https://www.ed.ac.uk/usher/precision-medicine/how-to-apply/18-19-projects/2018-computational-methods-for-predictingchanges

Interested candidates should contact Profs. Marenduzzo [dmarendu@ph.ed.ac.uk] or Gilbert [nick.gilbert@ed.ac.uk] in the first instance. The application deadline is Wed 10th January 2018.

References:

[1] Sazer and Schiessel "The Biology and Polymer Physics Underlying Large Scale Chromosome Organization" *Traffic* (2017)
[2] Schmitt et al., "Genome-wide mapping and analysis of chromosome architecture" *Nat. Rev. Mol. Cell Biol.* **17** (2016) p743-755
[3] Epstein "Cis-regulatory mutations in human disease" *Brief.Func.Genom.* **8** (2009)
[4] Brackley et al., "Nonspecific bridging-induced attraction drives clustering of DNA-binding proteins and genome organization" *Proc. Nat. Acad. Sci.* **110** (2013) pE3605
[5] Brackley et al., "Predicting the three-dimensional folding of cis-regulatory regions in mammalian genomes using bioinformatic data and polymer models" *Genome Biol.* **17** (2016)
[6] Brackley et al., "Binding of bivalent transcription factors to active and inactive regions folds human chromosomes into loops, rosettes and domains" *Nucl. Acids Res.* **44** (2016) p3503