Title of Project:	3D modelling of changes in genome architecture in development and disease
Cell Mechanism Supervisor Name	Eric Schirmer
Quantitative Supervisor Name	Davide Marenduzzo

Summary of project
Genome organisation changes during differentiation generate tissue-specific spatial patterns of gene positioning important for gene regulation. Schirmer identified tissue-specific nuclear envelope transmembrane proteins (NETs) directing gene repositioning and mapped peripheral genome regions during lymphocyte activation, myogenesis, adipogenesis, and in liver. In each system, important differentiation/metabolic genes fail to reposition/regulate expression upon NET knockdown/knockout yielding inhibition of tissue differentiation/function. Nuclear envelope tethering of regions flanking and slightly distal to genes can also influence the gene's ability to associate with superenhancers. Schirmer found NET mutations in Emery-Dreifuss muscular dystrophy (EDMD) patients and has mouse models for these and for adipogenesis/lipodystrophy. Marenduzzo has used modeling approaches to investigate mechanisms underlying genome organisation. He has also performed simulations informed by bioinformatic data to predict Hi-C contact maps, and has developed force fields to include the effect of the nuclear lamina. This project will use radial and chromosome conformation capture genome organisation data together with RNA-DNA FISH, RNA-Seq, BioID, and 3C performed by the student in Schirmer's lab to inform large scale coarse-grained molecular-dynamics simulations of genome reorganisation in Marenduzzo's lab. The resulting 3D trajectories will be used to shed light on the biophysical mechanism of genomic tethering at the envelope: for instance, we can predict the force required to recruit/maintain a gene at the nuclear envelope, and the extent to which tethering inhibits transcriptional activity. The student could work on any of the experimental systems for which we have existing data (adipogenesis, myogenesis, liver, lymphocyte activation, and ESC pluripotency withdrawal).

What quantitative skills will the student acquire or develop during their PhD project?
The student will learn to produce and analyse genome-wide DamID, Hi-C and RNA-Seq data through supervision from the Schirmer lab bioinformatician, the Wellcome Centre Bioinformatics Core, and our collaborator Job Dekker (University of Massachussetts, USA), while confirming specific results through fluorescence in situ hybridisation and 3C. The student will also learn CRISPR/Cas9 genome editing approaches in association with the post-doc and technician on the MRC grant and with use of the CRISPR users groups. The student will ideally also get their personal animal license (PIL) to assist in mouse studies. From the modelling point of view, the student will learn state-of-the-art techniques to model 4D genome organization maps via coarse-grained molecular dynamics simulations with collaborator Marenduzzo. The models to be used will be based on polymer physics, and build on previous work in Marenduzzo's lab, see e.g. M. Chiang et al., Cell Reports 28, 3212 (2019); A. Buckle et al., Mol. Cell 72, 786 (2018); C. A. Brackley et al., Nucleic Acids Res. 44, 3503 (2016). The student will learn how to compare the population of 3D structures generated by simulations with Hi-C and DamID data from Schirmer's lab, whilst the single conformations will be used to predict the extent of the genome which is associated to the lamina in single cells, and to predict single cell Hi-C contact maps. The BioID data generated in Schirmer's lab will be used to also investigate modelling of protein complexes and force generation on the nuclear envelope from chromatin contacts in Marenduzzo's lab.