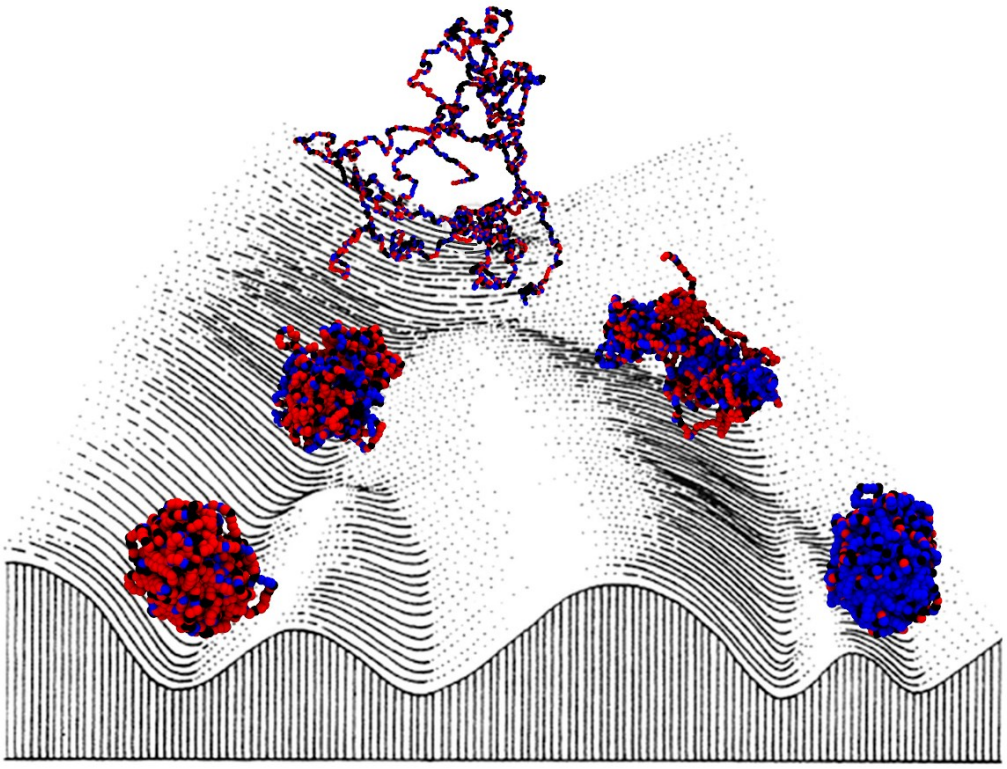
Biophysics of Epigenetic and Chromatin Dynamics

16-17 April 2018

JCMB, University of Edinburgh



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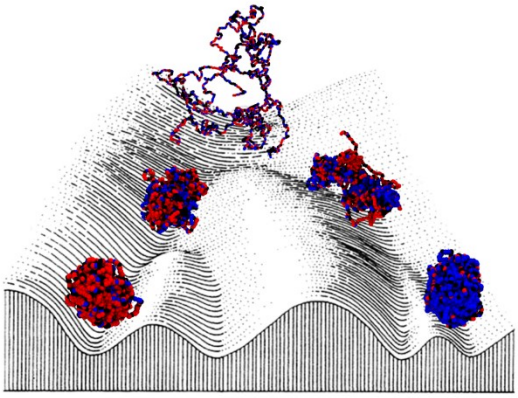


WELCOME

Virtually all cells in our body have the same DNA (hence genetic information), yet a skin, liver and a brain cell all express a very different set of genes. Additionally, when a differentiated cell divides, the daughter has the same set of genes on: a skin cell gives rise to another skin cells, etc. Understanding how cells can establish, maintain and transmit their identity to daughter cells remains a crucial question in biophysics. It is now understood that this process is associated with "epigenetic factors" - such as histone post-translational modifications - which can operate "beyond the genes" and regulate gene expression independently of the underlying genome sequence. In spite of the robustness displayed by cellular identity and memory, the epigenetic factors that are responsible for this stability are highly dynamic and display a fast turn-over. In order to reconcile these two apparently contradictory observations, we need combined experimental and theoretical efforts, involving biologists, physicists and applied mathematicians.

It is also now well established that epigenetic factors are highly correlated with chromatin state, and the folding of chromosomes in three-dimensions within the nucleus. For example, dynamic changes in the distribution of histone modifications are often accompanied by a change in the conformation of chromosomes. A better understanding of the causal relationship between the dynamics of chromatin and that of epigenetic factors should therefore shed light into the biophysics behind cellular differentiation and reprogramming, cellular response to inflammation and external stimuli and cellular ageing.

The goal of the proposed workshop is to bring together leading experts in the field of epigenetic and chromatin dynamics.

In particular, the workshop seeks to:

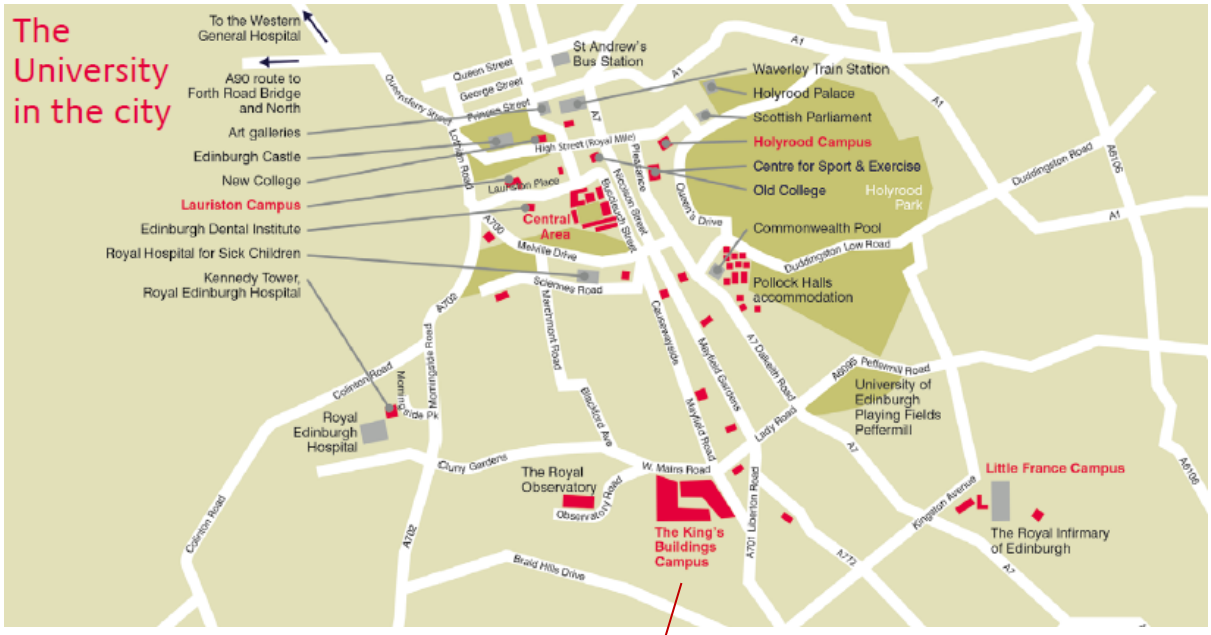
- determine the current state of the art of the field
- foster the exchange of ideas between experiments and theories
- create a fertile ground for the creation of new collaborations between biologists and physicists
- set out the direction for future experiments and modelling efforts.

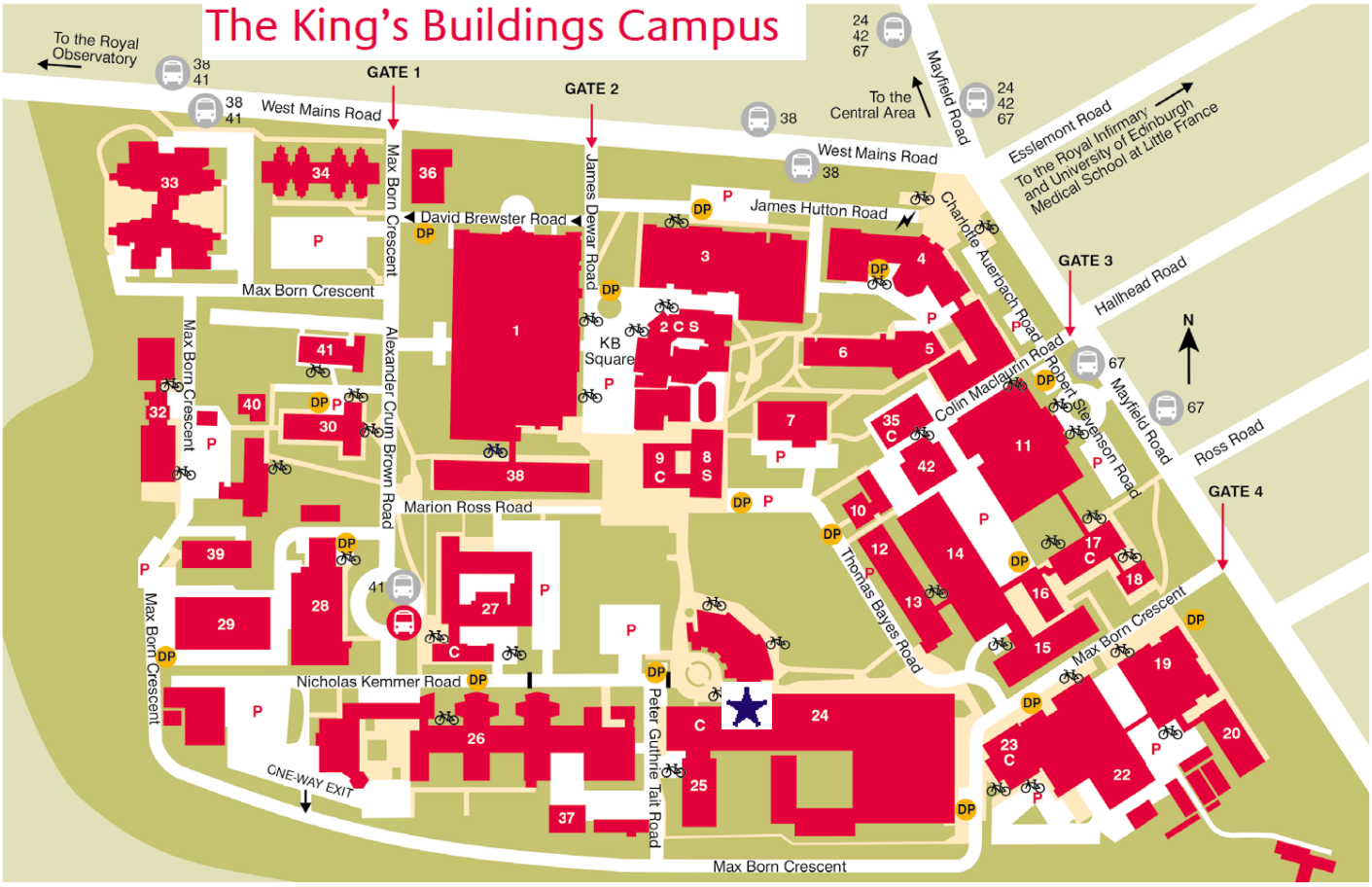
The organising committee:

Davide Michieletto, Chris Brackley and Davide Marenduzzo
University of Edinburgh, School of Physics and Astronomy

VENUE INFORMATION

This workshop will take place at the University of Edinburgh in the James Clerk Maxwell Building, Lecture Theatre A (marked with ★ , building no. 24 on bottom map) on the King's Building campus.





PROGRAMME

Day 1	Monday 16 April
9.15-9.30	Welcome
9.30-10.15	Kim Sneppen (University of Copenhagen) Title TBA
10.15-11.00	Karsten Rippe (Heidelberg University) 'Chromatin in context: integrating protein mobility, the formation of 'chromatin bodies' and gene regulation'
11.00-11.15	Daniel Rico (Newcastle University) 'Identification of epigenomic features linked to 3D interactions using snapshots of chromatin social networks'
11.15-11.45	**Refreshment Break**
11.45-12.30	Cedric Vaillant (CNRS-Ecole Normale Supérieure de Lyon) 'Epigenomics in 3D: modeling the dynamic coupling between epigenome and chromatin organization'
12.30-13.15	Patrick Heun (University of Edinburgh) 'Epigenetic inheritance of centromere identity in a heterologous system'
13.15-13.30	Joshua Moller (University of Chicago) 'The Nucleosome Interaction Landscape Influences Multiscale Modeling of Chromatin'
13.30-14.30	**Lunch**
14.30-14.45	Ruggero Cortini (Centre for Genomic Regulation) 'Principles of transcription factor traffic on a folded chromosome'
14.45-15.30	Enzo Orlandini (University of Padova, Italy) 'The Role of 3D Chromosome Folding in Cellular Identity and HIV Integration'
15.30-16.15	Yuki Ogiyama (CNRS, France) 'Stepwise 3D genome organization during early fly development'
16.30-19.00	Poster Session
Day 2	**Tuesday 17 April**
9.30-10.15	Martin Howard (John Innes Centre, UK) 'Analogue or digital? Bursty or Poissonian? Dissecting the fundamentals of transcriptional regulation'
10.15-11.00	Robin Allshire (University of Edinburgh) 'Can stochastic heterochromatin formation protect cells from external insults?'
11.00-11.20	Discussion session
11.20-11.45	**Refreshment break**
11.45-12.30	Vladimir Teif (University of Essex) 'Microdomain formation in chromatin'
12.30-13.15	Argyris Papantonis (Centre for Molecular Medicine, Cologne) 'Insulating the insulator: 3D genome architecture sustains homeostasis'
13.15-13.30	Rea Kourounioti (John Innes Centre) 'Natural variation identifies specific steps in Polycomb silencing'
13.30-14.30	**Lunch**
14.30-14.45	Sara Buonomo (University of Edinburgh) 'Rif1 a hub connecting nuclear architecture and replication timing'
14.45-15.00	Anagha Joshi (University of Edinburgh) 'Dynamics of promoter bivalency and RNAP II pausing in mouse stem and differentiated cells'
15.00-15.45	Wendy Bickmore (University of Edinburgh) Title TBA
15.45-16.30	Concluding Remarks

TALK ABSTRACTS

Kim Sneppen, University of Copenhagen

TBA

Karsten Rippe, Heidelberg University
Chromatin in context: integrating protein mobility, the formation of 'chromatin bodies' and gene regulation
The cell nucleus lacks internal membrane boundaries and soluble protein factors are rapidly distributed on the 10 µm length scale by free diffusive transport within seconds. Nevertheless, the cell establishes specific patterns of active and silenced genes. The underlying chromatin states are characterized by a distinct composition of chromosomal proteins and RNA, patterns of histone modifications and DNA methylation marks as well as structural features like the position and density of nucleosomes and the 3D folding of the nucleosome chain. To understand the interplay between these features, we investigate the mobility and chromatin interactions of protein factors to dissect the formation of transcriptional active or repressive nuclear subcompartments by a combination of fluorescent microscopy methods in living cells. Based on these measurements biophysical models are derived that address the following questions: (i) How do soluble chromatin modifying enzymes and transcription factors 'search' the nucleus to find their targets? (ii) What mechanisms drive the assembly of chromatin subcompartments like pericentric heterochromatin to form a silenced chromatin state? (iii) How is the induction of gene expression coupled to the chromatin state?

Daniel Rico, Newcastle University
Identification of epigenomic features linked to 3D interactions using snapshots of chromatin social networks
Chromatin may be envisioned as a complex 3D biological network with connections mediated by proteins and epigenetic marks. Chromatin conformation capture methods are used to assay the 3D interactions present in the chromatin of cells whilst methods such as ChIP-seq may be used to determine the genome wide positions of DNA binding proteins and epigenetic marks. Assortativity is a network property that evaluates how nodes tend to be connected to other nodes with similar properties. For example, in a social network we tend to form connections with people that share common attributes, such as music taste or education level. We apply this network science approach to identify DNA binding proteins and epigenomic modifications that could be mediating different types of genomic 3D interactions.

We have projected over 80 ChIP-seq datasets onto Capture Hi-C, ChIA-PET, HiChIP and single-cell-HiC derived networks in mouse embryonic stem cells (mESCs). We calculated the chromatin assortativity (ChAs) of the ChIP-seq features in these various chromatin networks. ChAs values may be used to infer the importance of a feature in modulating physical interactions of chromatin. Results show that ChIP-seq features may be assortative or not depending on the subnetwork or interaction type. In a DNaseI Capture Hi-C network, we observe H3K9me2 and H3K9me3 histone modifications to be assortative in interactions that connect accessible and inaccessible regions, but they are not assortative in interactions where both regions are accessible. This suggests that these repressive marks might be mediating interactions between closed and open chromatin regions in mESCs. Delving deeper into these integrated networks, we are trying to elucidate the properties of different interaction types by stratifying interactions by cell cycle stage, chromatin state of the interacting regions and their linear distance in chromosomes.

Cedric Vaillant, CNRS-Ecole Normale Supérieure de Lyon

Epigenomics in 3D: modeling the dynamic coupling between epigenome and chromatin organization

Cellular differentiation occurs during the development of multicellular organisms and leads to the formation of many different tissues where gene expression is modulated without modification of the genetic information. These modulations are in part encoded by chromatin-associated proteins or biochemical tags that are set down at the chromatin level directly on DNA or on histone tails. These markers are directly or indirectly involved in the local organization and structure of the chromatin fiber, and therefore may modulate the accessibility of DNA to transcription factors or enzymatic complexes, playing a fundamental role in the transcriptional regulation of gene expression. Statistical analysis of the repartition of this epigenomic information along the chromosomes have shown that genomes of higher eukaryotes are linearly partitioned into domains of functionally distinct chromatin states. In particular, experimental evidence has shown that the pattern of chromatin markers along chromosomes is strongly correlated with the 3D chromatin organization inside the nucleus. This suggests a coupling between epigenomic information and large-scale chromatin structure. Recently, using polymer physics and numerical simulations, we showed that attractive interactions between loci of the same chromatin state might be the driving forces of the folding of chromatin inside the nucleus [1]. In this study, we assumed that the epigenomic information pre-exists to the 3D organization. However, increasing number of experimental results suggests that chromatin marks are themselves highly dynamic during cell cycle or developmental stages and that 3D organization of chromatin might play a key role in the stabilization and function of chromatin markers. We will describe our efforts to better understand the crosstalk between the epigenome and the 3D organization by introducing an original theoretical framework, the so-called "Living Chromatin model" (LC model) where the dynamics of chromatin markers deposition along chromosomes will be coupled to the 3D folding of the chromatin fiber. As a main outcome, we show how the spatial folding of chromatin can indeed strongly influence the establishment and the maintenance of extended epigenomic domains. We discuss the implications of these results in various biological systems like the formation and dynamics of topologically-associated domains in drosophila or the establishment of dosage compensation in worm and mammals.

Patrick Heun, University of Edinburgh

Epigenetic inheritance of centromere identity in a heterologous system

The centromere is an essential chromosomal region required for accurate chromosome segregation. Most eukaryotic centromeres are defined epigenetically by the histone H3 variant, CENP-A, yet how its self-propagation is achieved remains poorly understood. We developed a heterologous system to reconstitute epigenetic inheritance of centromeric chromatin by ectopic targeting of the Drosophila centromere proteins dCENP-A, dCENP-C and CAL1 to LacO arrays in human cells. Dissecting the function of these three components enabled us to close the epigenetic loop of dCENP-C and dCENP-A replenishment during the cell division cycle. Finally, we show that all three Drosophila factors are sufficient for dCENP-A propagation and propose a model for the epigenetic inheritance of centromere identity.

Sara Buonomo, University of Edinburgh

Rif1 a hub connecting nuclear architecture and replication timing

The eukaryotic nucleus is a very busy space, where transcription, DNA replication and DNA repair all take place and influence each other. However, the rules and principles that control these interactions are still unclear. For each of these processes separately, the spatial position of a specific genomic region within the nucleus has been shown to play a role in determining the outcomes. My group is interested in the role that spatial organization plays during the establishment of the replication-timing program that controls the order of activation of the origins of DNA replication. We have identified a protein, Rif1, that acts both helping the spatial organization of the chromatin in the nucleus and delaying origins of replication destined to be activated only late during S-phase. Very intriguingly, we have now discovered that Rif1 also plays a role controlling expression of a subset of genes, modulating the regulatory epigenetic landscape and the contacts between enhancer and promoter. We will present evidences that the consequences of Rif1 deficiency in different processes such as DNA replication and gene expression can be ascribed to deregulated chromatin organization, pointing to nuclear architecture being the master coordinator of nuclear functions.

Ruggero Cortini, Centre for Genomic Regulation

Principles of transcription factor traffic on a folded chromosome

Why do we find transcription factors at many sites that do not contain their corresponding binding motif? And conversely, why are many DNA sequences that contain a binding motif not bound by the transcription factor? I try to shed light on these questions by looking at the role that the three-dimensional structure of the chromosomes plays in shaping the process of transcription factor search in the genome. To do so, I set up molecular dynamics simulations of particles (tracers) that explore the structure of a folded polymer, which represent the process of transcription factors searching for their target sites on a folded chromosome. The results of the simulations show that where a chromosome forms a loop, there will be an increase of binding of all proteins that have a non-specific affinity for chromatin. Conversely, sites that are buried inside a highly compacted region of a chromosome will be excluded from the search process. These results give the first explanation of the puzzling observation that some genomic sites accumulate nonspecific transcription factor binding. Overall, taking into account the structure of the genome has important implications for understanding the distribution of transcription factors.

Enzo Orlandini, University of Padova, Italy

The Role of 3D Chromosome Folding in Cellular Identity and HIV Integration

Understanding how the three-dimensional (3D) organisation of the genome affects its function is one of the biggest challenges in biophysics. Models that describe the genome as a polymer can dissect the physical principles that guide its 3D folding. For instance, it is now well accepted that epigenetic marks pattern the genome and play a role in determining its organisation. This can be understood via a generic co-polymer model in which transcription factors and bridge proteins bring together distant, but equally marked, chromatin segments. At the same time, it is also well-known that these patterns are formed by factors that are highly dynamic. In this talk I will present polymer models of chromatin that aim to reconcile the stability of the epigenetic landscape with the fast turnover times of the underlying epigenetic marks. We find that the 3D folding of chromosomes is a crucial element that confers stability to the epigenome and, in turn, to cellular identity. The 3D architecture of the genome is also relevant in other situations such as the process of retroviral infection. Specifically, it is now well established that some classes of retroviruses such as HIV, display highly non-random integration patterns along the genome, yet the underlying mechanisms driving this selection are poorly understood. Here I will present a recent effort to rationalise these observations via a generic multi-scale physical framework where HIV integration is modelled as a stochastic "reconnection" between polymeric strands. Stochastic simulations show that the large-scale 3D chromatin folding is one of the main physical drivers biasing the distribution of HIV integration sites towards euchromatic regions. Furthermore, a simple reaction-diffusion model explains the distribution of HIV hot-spots in human T-cells. These results are in very good agreement with experiments on HIV integration and strongly support the importance of physics-based models in understanding the role of 3D genome organisation in many biological processes in the cell.

Yuki Ogiyama, CNRS, France

Stepwise 3D genome organization during early fly development

Nuclear architecture plays an important role in genome function. Although eukaryotic chromosomes fold in a hierarchy of structures, such as loops, TADs and compartments, recent reports suggest that they might change depending on developmental and regulatory cues. Since the epigenetic context changes during development, it is important to understand how these changes relate to chromosome architecture. To understand 3D chromosome organization during early embryogenesis, we performed in situ Hi-C with staged fly embryos. While embryos just after fertilization display a monotonous pattern of chromatin interaction and show only few faint boundary-like structures, embryos in cycles 9-13 showed sizeable boundary formation and long-range interactions. These early preferential structures are associated with histone acetylation and transcription. We also found active and repressive loops between some of the developmental gene loci. Active loops are related to pol II binding loci and can form more than 1Mb genomic distance in pre-MBT (mid-blastula transition) embryos. In contrast, repressive loops form between polycomb response elements (PREs) within TADs domains only after MBT, concomitant with the appearance of PcG foci. FISH experiments combined with PRE deletion by CRISPR/Cas9 system confirm the involvement of PRE loci in repressive loop formation and indicate that PcG loops contribute to the regulation of nearby genes. In summary, our data show that the Drosophila genome acquires its 3D architecture in a multistep manner and each of these organizational layers contributes to establish appropriate gene expression patterns.

Martin Howard, John Innes Centre

Analogue or digital? Bursty or Poissonian? Dissecting the fundamentals of transcriptional regulation

The fundamental nature of transcriptional regulation has been much studied by both biologists and now by physicists over decades. Nevertheless, much remains to be learned about how transcription is quantitatively controlled and whether such regulation is significantly noisy. Here, I will present recent results on this topic from a highly focused study of a single gene, the floral repressor FLC in Arabidopsis, using mathematical modelling, genetics and single cell imaging. FLC is an attractive target for study as it combines several modes of regulation that are environmentally regulated by temperature. I will show that FLC transcription can be modulated in either an analogue, continuously varying fashion or in a digital, on/off mode. For analogue regulation, transcription appears at first sight to be highly noisy. However, this appearance is illusory: once cell size is factored in, transcriptional dynamics become almost entirely Poissonian. For digital regulation, I will present simple models for how such on/off states can be established and maintained locally in the chromatin, showing that an all-or-nothing nature is vital for long-term (epigenetic) memory storage. I will also show results from experimental tests of the digital model for FLC, confirming the presence of chromatin-based digital epigenetic memory, but revealing that there must be additional factors responsible for epigenetic memory storage beyond histone modifications.

Robin Allshire, University of Edinburgh

Can stochastic heterochromatin formation protect cells from external insults?

Fungal pathogens pose an overlooked burden for human health and food security. Fungi cause ~1.6M deaths/year and 30% food crop loss, while anti-fungal resistance is an increasing problem. Environmental conditions are well known to modulate eukaryotic cell transcriptional programs, optimizing survival and often inducing cell cycle arrest. How do fungal cells adapt and develop resistance in response to external insults? Fission yeast, Schizosaccharomyces pombe, lacks DNA methylation. Heterochromatin is formed in fission yeast by methylation of histone H3 on lysine 9, this attracts repressive activities through the direct binding of chromo-domain proteins. Consequently, the expression of genes embedded in heterochromatin is silenced. Normally, heterochromatin is mainly formed on repetitive elements at centromeres, telomeres and the mating type locus. The artificial tethering of the H3 K9 methyltransferase to a euchromatic locus forces the assembly of ‘synthetic’ heterochromatin over a sizable (~15kb) domain and the silencing underlying genes. We previously showed that H3K9- methylation can act as a transmissible epigenetic mark. A read-write mechanism permits inheritance of ‘synthetic’ ectopic heterochromatin domains through multiple mitotic cell divisions. However, the transmission of synthetic ectopic heterochromatin and associated gene silencing is only observed in cells lacking an H3K9 demethylase which usually mediates its erasure. Nevertheless, heterochromatin heritability may provide an epigenetic bet-hedging strategy that permits wild-type cells to adapt to external insults without fixing resistance phenotypes. We are therefore exploring if wild-type cells can utilize the innate transmissible properties of heterochromatin to pass information to progeny cells. It is conceivable that the stochastic assembly of atypical heterochromatin domains might be utilised to prime resistance to anti-fungal agents.

Vladimir B. Teif, University of Essex

Microdomain formation in chromatin

Epigenetic regulation in chromatin is responsible for a large degree of variation in gene expression. However, the understanding of the underlying molecular mechanisms is still far from being complete. One of the outstanding challenges is predicting the locations and boundaries of chromatin domains, with one particular example being the heterochromatin marked by histone H3 lysine 9 methylation. In this talk I will present our new theoretical model and experimental data for the formation of several distinct types of heterochromatin domains in mouse embryonic stem cells. Our model takes into account that chromatin states can be distinguished not only by covalent epigenetic modifications but also by physical structure (an assumption which is supported by the experimental studies). A biophysical lattice model for microdomain formation in chromatin is parameterized using ChIP-seq experiments in cell lines with knock outs of proteins involved in heterochromatin formation, such as Suv39 and Atrx. The model takes into account physical interaction between neighbouring chromatin elements and considers the conversion of nucleosomal arrays between different states of compaction through nucleoprotein assembly governed by architectural proteins such as HP1 and CTCF, as well as heterochromatin-initiating transcription factors. According to our predictions a locally introduced heterochromatic state would spread only to a finite microdomain with well-defined boundary locations – a prediction which we verify using experimental data for mouse embryonic stem cells.

Argyris Papantonis, Centre for Molecular Medicine, Cologne

Insulating the insulator: 3D genome architecture sustains homeostasis

Cellular ageing, as achieved via replicative senescence, is marked by complex events giving rise to heterogeneous cell populations. However, the early molecular events that drive such cascades remain elusive. We hypothesized that primary human cells enter senescence due to the early reorganization of the cells' three-dimensional genome organization. To test this, we applied Hi-C, single-cell and population transcriptomics, and super-resolution imaging on proliferating and replicatively-senescent cells from three distinct lineages. We uncovered a set of genes involved in DNA conformation maintenance that are suppressed upon senescence entry across all cell types. Of these, the abundant HMGB2 chromatin-binder is depleted from nuclei before typical senescence markers appear. Surprisingly, HMGB2 is directly involved in loop formation, and its depletion drives the dramatic spatial clustering of CTCF loops in a "phase separation" manner. Finally, knockdown and rescue experiments combined with in silico modeling and CTCF HiChIP are in line with an "insulating-the-insulator" model, whereby HMGB2-bound chromatin positions, both at TAD boundaries and within TADs, deter the collapse of flanking CTCF loops into large clusters. And this HMGB-mediated deregulation of genomic organization constitutes a primer for the ensuing senescent program across cell lineages.

Rea Kourounioti, John Innes Centre

Natural variation identifies specific steps in Polycomb silencing

A need for overwintering allows plants to align their sensitive flowering with the favourable conditions of spring. This vernalization process involves cold-induced Polycomb Repressive Complex 2 (PRC2) silencing of FLOWERING LOCUS C (FLC). Through a combination of experiments and modelling we have dissected the silencing mechanism and shown it consists of multiple steps that switch an actively expressed locus to a fully epigenetically silenced state. Evolutionary changes in vernalization have allowed Arabidopsis genotypes to adapt to very different winter climates and we are currently analysing how these influence the silencing mechanism. Here, we focus on an Arabidopsis accession adapted to Northern Sweden, which needs much longer cold to silence FLC. Short cold leads to re-activation of the gene and delayed flowering, a phenotype caused by 4 non-coding SNPs. Using expression and ChIP data we developed a mathematical model to quantitatively describe the dynamics of FLC reactivation in this genotype. In doing so, we predicted the existence of an additional step in the mechanism, which we then validated experimentally and found to be a general feature in the sequence of events of Polycomb silencing.

Joshua Moller, University of Chicago

The Nucleosome Interaction Landscape Influences Multiscale Modeling of Chromatin

The supramolecular structure of chromatin is influenced by inter- and intra-nucleosome interactions. Central to these interactions, the flexible N-terminal domain histone tails have positively-charged sites that facilitate nucleosome interactions. Recent experiments have quantified inter-nucleosome interactions, but have yet to understand the landscape of resulting anisotropic and chiral interactions. With this work, we utilize coarse-grained brownian dynamics simulations and enhanced sampling techniques to understand how inter-nucleosome interactions influence chromatin structure. We quantify the anisotropic interaction energy landscape and highlight the discrepancy between prior results through varying salt concentrations and counter-ion condensation effects. To examine the effect of epigenetic modifications, we introduce acetylations to the H4 tail and assess the resulting energetic landscape. We then demonstrate how all calculated energetic landscapes can be incorporated into a single rigid body element, creating a new, faster coarse-grained model of chromatin. This novel model presents an opportunity for faster calculations, while still capturing the energetic and dynamic subtleties of the detailed scale.

Anagha Joshi, University of Edinburgh

Dynamics of promoter bivalency and RNAP II pausing in mouse stem and differentiated cells

Mammalian embryonic stem cells display a unique epigenetic and transcriptional state to facilitate pluripotency by maintaining lineage-specification genes in a poised state. Two epigenetic and transcription processes involved in maintaining poised state are bivalent chromatin, characterized by the simultaneous presence of activating and repressive histone methylation marks, and RNA polymerase II (RNAPII) promoter proximal pausing. However, the dynamics of histone modifications and RNAPII at promoters in diverse cellular contexts remains underexplored. We collected genome wide data for bivalent chromatin marks H3K4me3 and H3K27me3, and RNAPII (8WG16) occupancy together with expression profiling in eight different cell types, including ESCs, in mouse. The epigenetic and transcription profiles at promoters grouped in over thirty clusters with distinct functional identities and transcription control. The clustering analysis identified distinct bivalent clusters where genes in one cluster retained bivalency across cell types while in the other were mostly cell type specific, but neither showed a high RNAPII pausing. We noted that RNAPII pausing is more associated with active genes than bivalent genes in a cell type, and was globally reduced in differentiated cell types compared to multipotent.

Wendy Bickmore, University of Edinburgh

Mechanisms of long-range gene control – hints of a role for phase transition

Long-range enhancers - found as far away as 1 megabase from their target gene are key in controlling precise spatial and temporal gene expression in mammals. In contrast to the 20,000 or so genes in our genome, there may be hundreds of thousands, or even millions, of enhancers. Deletion, translocation or point mutations can abrogate the function of these elements in Mendelian diseases associated with severe phenotypes. Moreover, the majority of human genetic variation associated with common disease and quantitative traits also map to enhancers. I will describe our work probing how high-order three-dimensional chromatin structure relates to how enhancers work from a distance. I will present data consistent with the popular chromatin-looping mechanism for enhancer action. However, using a synthetic biology approach, I will also present data inconsistent with a ‘looping’ mechanism at other enhancers and suggesting that poly (ADP- ribosylation)-mediated chromatin decompaction is linked to enhancer activation. These data will be placed in the context of recent models that implicate liquid de-mixing/phase transitions in chromatin-mediated gene regulation.

Tracy Ballinger, University of Edinburgh

Modelling double strand break hotspots to interrogate structural variation in cancer

Structural variants (SVs) are known to play important roles in a wide variety of cancers, but their mutational origins and functional consequences are still poorly understood. The highly nonrandom distributions of these variants across tumour genomes are often assumed to reflect selective processes, but mutation rates can vary by orders of magnitude and often reflect the underlying chromatin structure at a locus. The inference of SVs under selection for enhanced tumourigenesis therefore remains challenging, though identifying such variants may lead to new diagnostic and therapeutic targets. Here we exploit experimentally derived mutation data from NHEK keratinocyte (Lensing et al, 2016) and K562 erythroleukemia cells to derive quantitative models of double strand break (DSB) susceptibility across the human genome, based upon underlying chromatin (ENCODE, 2012) and sequence features. We then use these models to explore SV breakpoint hotspots from tumour sequencing datasets (ICGC, 2010; Hoadley et al, 2014; Beroukhim et al, 2010).

Justyna Cholewa-Waclaw, University of Edinburgh

Mathematical modelling reveals the mechanisms of transcription regulation by MeCP2

Mutations in the gene encoding MeCP2, a protein highly expressed in neurons, cause Rett syndrome, a debilitating neurological disease. Despite decades of research, the mechanism by which mutations in MeCP2 affect transcription remains enigmatic. Here, we combine computer modeling, molecular genetics and statistical analysis to demonstrate that MeCP2 regulates gene expression globally, and that this effect depends on the CpG methylation density in the bodies of genes. To experimentally test the hypothesis, we utilised *in vitro* cultured human dopaminergic neurons (LUHMES cells) which have high levels of methylated CGs. This feature enabled us to investigate the role of mCG alone in mediating MeCP2 function by varying the concentration of the protein by more than an order of magnitude. We show that gene expression negatively correlates with methylated CG density in the gene bodies at a variety of different levels of MeCP2. This relationship is not seen in the case of promoter methylation. Our mathematical modelling approach verified the hypothesis that MeCP2 impedes elongating RNA polymerase II, whereas other models were not compatible with experimental data. Thus, interwoven mathematical and experimental approaches provide quantitative *in vivo* evidence that MeCP2 binding to methylated CpGs globally restrains transcription by slowing polymerization of RNA.

Jekaterina Erenpreisa, Latvian Biomedical Research and Study Centre

Epichromatin: DNA B-A transition, supranucleosomal packaging, and nuclear traffic

The chromatin fraction ('epichromatin') directly attached to the inner nuclear membrane has a peculiar structure – on conventional EM representating the rows of tightly apposed 30nm granules, are composed of short ~ 1Kb domains, enriched in GC-stretches, and ALU, 'dashed' along the chromosomal DNA [1,2]. In our recent work [3], probing conformation of the epichromatin by the DNA structural test with Acridine orange staining, we came to the conclusion that it preferently assumes the hydrophobic A-DNA form, favoured by the juxta-vicinity of the lipid membrane. We also suggested that the epichromatin forms superbeads of about 6 nucleosomes per domain. These appear to be stacked together and apposed to the inner nuclear membrane by hydrophobic forces and counteraction from more hydrated lamin associated chromatin domains. Together, with the inner nuclear membrane, the epichromatin can form the nuclear envelope limited chromatin sheets (ELCS) and participates in nuclear rotation by intruding into the perinuclear space, forming projections (particularly including perinucleolar material) as well as producing 'nuclear pockets' (NP) for autophagic degradation of excessive ELCS material [4,5]. Our preliminary data suggest that ELCS may transfer the circular transposon-excised DNA of the perinucleolar origin in senescing cells [5]. We suggest that vimentin attaching to circular extrachromosomal DNA is putting a brake on nuclear rotation [6] of ELCS facilitating their looping and capture of extrachromosomal DNA in NP for autophagic clearance. I also shall discuss several hypotheses on the physical mechanisms of ELCS traffic.

References:

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[6]Gerashchenko et al., Cell Biol Int. 2009, 33:1057-64. doi: 10.1016/j.cellbi.2009.06.020.

Ilya Flyamer, University of Edinburgh

Polycomb-dependent 3D chromatin organisation is independent of RING1B catalytic activity but requires genome-wide DNA methylation

The Polycomb complexes form an epigenetic system that is essential to silence developmentally regulated genes. One proposed mechanism for this function is the modulation of chromatin structure, both through local compaction of chromatin, and by bringing distal Polycomb targets together in the nuclear space. To investigate the contribution of Polycomb activity in regulating nuclear architecture we have used both molecular approaches (Hi-C) and microscopy (FISH) in mouse ES cells (ESCs). Mammalian cells generally have two Polycomb Repressive Complexes with distinct activities: PRC1 and PRC2. RING1B is a core component of the PRC1 complex, often implicated in compacting chromatin. It is an E3 ubiquitin ligase whose main known substrate is the lysine 119 residue of histone H2A. Mice deficient for RING1B do not complete gastrulation, in contrast to mice carrying a catalytically dead version of RING1B (RING1BI53A/I53A) who are viable until the later stages of embryonic development. By comparing RING1B-/- and RING1BI53A/I53A ESCs, we find that the E3 ubiquitin ligase activity is dispensable for chromatin compaction at Polycomb target loci, and for their long-range clustering.The factors involved in targeting the Polycomb system to the correct genomic targets remains controversial, however, it has been shown that loss of DNA methylation leads to the redistribution of Polycomb across the genome – likely through Polycomb being titrated away to the newly exposed unmethylated genomic regions. To investigate the impact of this on 3D chromatin organisation, we cultured ES cells in 2i conditions (serum-free medium with small-molecule inhibitors of Mek and GSK3) to induce a cell-state reminiscent of the inner cell mass (ICM) of the blastocyst where DNA methylation levels are significantly reduced. We show that the consequent DNA hypomethylation leads to partial dissolution of local chromatin compaction and distal looping of Polycomb target loci. To disentangle the changes in DNA methylation in 2i culture conditions from altered signalling, we compared constitutively methylated cells (overexpressing DNMT3B and DNMT3L) grown in 2i conditions, with inducible DNA methylation-deficient ES cells grown in normal serum. We show that it is changes in DNA methylation, not 2i conditions per se, that drive loss of Polycomb-associated compaction and looping through redistribution of PcG binding. Our data show the inter-dependencies of two major epigenetic regulators and how changes in the 2D epigenome can lead to altered 3D chromatin organisation.

Dave Gerrard, University of Manchester

GenomicLayers - Simple, sequence-based simulation of epi-genomes

I recently developed GenomicLayers, a prototype R package that serves as a common framework within which to simulate temporary marks on whole genome sequence. Arbitrary layers can represent a wide range of marks or events and can be deposited or erased by binding factors that recognise DNA sequence motifs and/or regulatory states. My aim is to demonstrate the utility of the framework as a common environment in which multiple researchers can build, test, share and compete alternative or overlapping models of epigenetic processes. Collaborators will publish the model components as digital reagents, freely available to quickly and easily exchange and incorporate into their models. I will focus on a simulation using the mouse X chromosome in activation, as a stepping stone towards better understanding of human development.

Eamon Fitzgerald, University of Edinburgh

Transcriptomic and Epigenetic Examination of the Mouse Brain after Preterm Birth Related Brain Insults

Preterm birth (PTB) is clinically defined as birth prior to 37 weeks of gestation and is a leading cause of neurodevelopmental disorders. The mechanistic underpinnings of this is largely unknown. One potential process which may be involved is epigenetic dysregulation resulting from PTB related brain insults such as inflammation, hypoxia or glucocorticoid alterations (endogenous or synthetic). In a recent study from Sparrow et al, babies born preterm were seen to have many differentially methylated loci at key neurodevelopmental genes in buccal swabs taken at term equivalent age when compared to term control babies. To investigate possible mechanisms of altered DNA methylation/hydroxymethylation we are using the neonatal mouse brain in a slice culture paradigm. A mouse on its day of birth is at equivalent brain development to a human at 24 weeks of gestation, and at postnatal day 10, the mouse is equivalent in brain development to a term baby (40 weeks). We are using this postnatal window of mouse brain development to model insults to the brain commonly seen in prematurity at neurodevelopmentally relevant timepoints and the impact these have with respect to DNA methylation and hydroxymethylation. Here we show that PTB related insults to the brain produce differential expression of the TET enzymes and use hydroxymethylated DNA immunoprecipitations to assess the impact of these alterations on 5hmC deposition at candidate loci.

Stefano Gnan, University of Edinburgh

Can We Untangle Replication Timing And Chromatin Architecture?

Topological associated domains (TADs) are the fundamental units of genome three-dimensional (3D) organization (Dixon, et al. 2012). TADs, and more broadly chromatin 3D structure, are re-established every cell cycle in early G1 simultaneously with the establishment of the Replication-Timing (RT) program that regulates the order of replication of TADs during S-phase (Dimitrova, et al. 1999; Dileep, et al. 2015).The temporal coincidence between the establishment of RT and chromatin 3D organization suggests a need for global control defining the order of replication of different genomic regions as well as fine tuning at the origins' level during the executions of the program in S-phase. Rif1 is a conserved protein that regulates both the establishment and the execution of RT as well as nuclear 3D organization (Cornacchia, et al. 2012; Foti, et al 2016). However, it is not known if these are two independent functions or if Rif1-dependent control of nuclear architecture contributes to RT establishment. The role of Rif1 at the origins is at least partially mediated through its interactions with protein phosphatase 1 (PP1)(Davé, et al. 2014; Mattarocci et. al 2014; Poh et al. 2014; Hiraga et al. 2017). The aim of this project is to investigate whether Rif1/PP1 interaction plays a role in the control of the nuclear 3D organization. To this end, we created a Rif1 mutant that abolishes the interaction with PP1 and investigated whether it leads to a separation of Rif1 functions.

Keisuke Kaji, Centre for Regenerative Medicine
Mapping transcription factor occupancy using minimal numbers of cells in vitro and in viv

The identification of transcription factor (TF) binding sites in the genome is critical to understanding gene regulatory networks (GRNs). While ChIP-seq is commonly used to identify TF targets, it requires specific ChIP-grade antibodies and high cell numbers, often limiting its applicability. DNA adenine methyltransferase identification (DamID), developed and widely used in Drosophila, is a distinct technology to investigate protein-DNA interactions. Unlike ChIP-seq, it does not require antibodies, precipitation steps or chemical protein-DNA crosslinking, but to date it has been seldom used in mammalian cells due to technical limitations. Here we describe an optimised DamID method coupled with next generation sequencing (DamID-seq) in mouse cells, and demonstrate the identification of the binding sites of two TFs, POU5F1 (also known as OCT4) and SOX2, in as few as 1,000 embryonic stem cells (ESCs) and neural stem cells (NSCs), respectively. Furthermore, we have applied this technique in vivo for the first time in mammals. POU5F1 DamID-seq in the gastrulating mouse embryo at 7.5 days post coitum (dpc) successfully identified multiple POU5F1 binding sites proximal to genes involved in embryo development, neural tube formation, mesoderm-cardiac tissue development, consistent with the pivotal role of this TF in post-implantation embryo. This technology paves the way to unprecedented investigation of TF-DNA interactions and GRNs in specific cell types of limited availability in mammals, including in vivo samples.

Gabrielle Olley, University of Edinburgh
Defective fine tuning of the DNA damage response by BRD4 in CdLS

Acetylation of lysine residues is a histone modification associated with active chromatin. The modified residues provide docking sites for the epigenetic reader BRD4, which binds to the acetylated lysines via its two bromodomains. BRD4 is known to be involved in RNA polymerase II activation, maintaining the pluripotency of embryonic stem cells and in DNA damage response signalling. Recently, we identified a missense mutation in BRD4 in a patient with a Cornelia de Lange syndrome (CdLS)-like phenotype. CdLS is a neurodevelopmental disorder that can cause a range of symptoms including limb malformations, craniofacial abnormalities and intellectual disability and is usually associated with mutations in components of the cohesin complex and the cohesin loader NIPBL. How these mutations may cause CdLS is currently unknown. Using a mouse embryonic stem cell line, engineered through CRISPR-Cas9 technology to be homozygous for the patient mutation in BRD4, we've shown that the mutation decreases the binding of BRD4 to cis-regulatory elements, without affecting transcription of nearby genes. Instead we observe a decreased binding of the DNA damage protein 53BP1 to CREs and an increase in DNA damage signalling in the mutant cells, resulting in increased cell cycle checkpoint activation and a delay in the cell cycle. These results have lead us to propose defective fine tuning of the DNA damage response (DDR) by BRD4 as the cause of CdLS in this patient. Furthermore, evidence for the roles of NIPBL and cohesin in the DDR and colocalisation of NIPBL with 53BP1 ChIP-seq peaks indicates that this mechanism may be common to CdLS in general.

Cecilia Lövkvist, John Innes Centre
Spatiotemporal modelling of DNA methylation

In mammals, DNA methylation is primarily found on cytosines of CpG sites. CpG sites are rare and normally methylated, however, clusters of CpG sites are usually unmethylated. Occasionally CpG clusters are methylated and interfere with gene expression when located on promoters. In this work, we explore additional features of methylation of CpG sites by investigating the topology of CpG sites in the human genome. We confirm that spacings between CpG sites are far from random, but instead, they are either "long" (~100 bp) or "short" (~ 10 bp). Moreover, we define CpG clusters by requiring short distances between CpG sites inside and long distances outside clusters. Analysing methylation levels of these clusters, we find those with few CpG sites to be predominantly hyper-methylated, while larger clusters are predominantly hypo-methylated. Intermediate clusters, however, are either hyper- or hypo-methylated but are rarely found partly methylated, hence show a strong tendency for bimodality [2]. Furthermore, we explain how our observed methylation patterns of CpG clusters are inherited through cell division. The classical model for inheritance of DNA methylation in mammals, in which individual CpG sites are independent, provides no explanation for the observed non-random methylation patterns. We propose a model where CpG sites collaborate, i.e. the methylation status of a CpG site depends on the status of surrounding CpG sites. The model explains the observed bistable patterns, i.e. a dense cluster of CpG sites near a promoter is either fully methylated or fully unmethylated[1]. Additionally, we explain the inheritance of methylation levels of CpG clusters of various lengths. We incorporate the distances between the CpG sites into our collaborative model [1] : methylated CpGs thereby recruit methylation enzymes that can act on CpGs over an extended local region; unmethylated CpGs, conversely, recruit demethylation enzymes that act more strongly on nearby CpGs. The new model correctly reproduces the effects of CpG clustering on methylation levels and stable inheritance through cell division [2].

[1] Jan O Haerter, Cecilia Lövkvist, Ian B Dodd, and Kim Sneppen. Collaboration between CpG sites is needed for stable somatic inheritance of DNA methylation states. Nucleic Acids Research, 42(4):2235–2244 (2014).

[2] Cecilia Lövkvist, Ian B Dodd, Kim Sneppen, and Jan O Haerter. DNA methylation in human epigenomes depends on local topology of CpG sites. Nucleic Acids Research, 44(11): 5123-5132 (2016).

Manolis Papamichos-Chronakis, Newcastle University

Control of premature termination of mRNA synthesis by INO80 regulates gene expression

RNA quality control is critical to ensure productive gene expression. Eukaryotic mRNAs are subjected to co-transcriptional RNA surveillance and aberrant transcripts are eliminated by premature non-canonical transcriptional termination and subsequent degradation. The Nrd1-Nab3-Sen1 (NNS) RNA binding complex and the nuclear exosome complex contribute to mRNA quality control, leading to transcriptional attenuation of protein coding genes. Elimination of aberrant mRNAs is particularly pronounced during the early steps of transcriptional elongation by RNA Polymerase II. However, the mechanisms regulating removal of prematurely terminated mRNA transcripts from chromatin remain poorly understood. Moreover, the extent to which transcriptional attenuation contributes to the expression of functional mRNAs is unclear. Here we show that, in budding yeast, the evolutionarily conserved ATP-dependent chromatin remodelling complex INO80 promotes the removal of nascent mRNA transcripts from chromatin. In the absence of INO80 aberrant native mRNAs accumulate across the genome. Loss of INO80 leads to increased transcriptional pausing at DNA contact sites for the histone H3 N-terminal tail proximally to promoters, abrogating productive transcription elongation. INO80 interacts with Nrd1 and promotes non-canonical termination and RNA decay. Retention of native mRNAs at promoter-proximal sites is regulated by the Rpd3S Histone Deacetylation complex. We show that inactivation of Rpd3S rescues the defect in expression of functional mRNAs caused by disruption of INO80 during non-canonical transcription termination. Our work suggests that nucleosomal organisation of chromatin regulates an mRNA quality control checkpoint for termination of aberrant mRNAs to control productive gene expression.

Jean-Charles Walter, CNRS, Paris

Surfing on protein waves: proteophoresis as a mechanism for bacterial genome partitioning

Efficient bacterial chromosome segregation typically requires the coordinated action of a three-component, fueled by adenosine triphosphate machinery called the partition complex. We present a phenomenological model accounting for the dynamic activity of this system that is also relevant for the physics of catalytic particles in active environments. The model is obtained by coupling simple linear reaction-diffusion equations with a proteophoresis, or “volumetric” chemophoresis, force field that arises from protein-protein interactions and provides a physically viable mechanism for complex translocation. This minimal description captures most known experimental observations: dynamic oscillations of complex components, complex separation and subsequent symmetrical positioning. The predictions of our model are in phenomenological agreement with and provide substantial insight into recent experiments. From a non-linear physics view point, this system explores the active separation of matter at micrometric scales with a dynamical instability between static positioning and travelling wave regimes triggered by the dynamical spontaneous breaking of rotational symmetry.

Reference: Walter J.-C., Dorignac J., Lorman V., Rech J., Bouet J.-Y., Nollmann M., Palmeri J., Parmeggiani A. & Geniet F., Surfing on protein waves: proteophoresis as a mechanism for bacterial genome partitioning, Phys. Rev. Lett. 119, 028101. arXiv:1702.07372 [q-bio.SC]

Chongzhi Zang, University of Virginia
Modeling Functional Enhancers and Transcriptional Regulation Using Epigenomic Profiles

Epigenetic regulation of gene expression plays a critical role in many biological processes including cancer formation and progression. Several experimental techniques including ChIP-seq and DNase/ATAC-seq have been developed to identify genome-wide profiles epigenetic factors, including transcription factors, histone modifications, and chromatin accessibility. Using epigenomic data to predict functional DNA elements and transcription factors regulating gene expression is an essential problem in quantitative modeling of such biological systems. We develop MARGE, a computational method for predicting cis-regulatory profiles to interpret differential expression gene sets by leveraging over 1000 H3K27ac ChIP-seq datasets from the public domain. We introduce a regulatory potential quantity for each gene by summarizing nearby ChIP-seq signals, use logistic regression to retrieve relevant H3K27ac profiles that model gene sets of interest, and adopt a semi-supervised learning approach to identify cis-regulatory elements. We then develop BART, another computational method for further predicting transcription factors associated with MARGE-predicted cis-regulatory profiles using thousands of transcription factor ChIP-seq datasets. Our work demonstrates the power of computational modeling and utilization of public data for quantitative studies in gene regulation research.

Alexey Onufriev, Virginia Tech
Physical epigenetics at the nucleosome level

The nucleosome -- a complex of 147 base-pairs of DNA with eight histone proteins -- is the fundamental unit of chromatin compaction in the living cell, which controls access to its genetic information. The exact mechanism of the control remain unclear.A simplified physical model reveals that while the nucleosome itself is much more stable than a typical protein, its peculiar shape dictates that even slight lowering of the charge of the globular histone core can significantly loosen the core-DNA association, thus increasing the DNA accessibility. The finding hints at a possible general principle of DNA accessibility control at the nucleosome level -- alteration of the nucleosome globular core charge via charge-altering post-translational modifications (PTMs) such as lysine acetylation, which neutralize the charge. A detailed multi-state atomistic model confirms the basic idea, but reveals a much richer and nuanced picture, including counter-intuitive trends such decrease of DNA accessibility for some lysine acetylations in the core. Connection to transcription regulation in-vivo is made, and a model of transcription modulation via charge-altering PTMs in the histone core is proposed.

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UNDERSTANDING THE Physics of Life

Physics of Life is a national network which emerged in 2012 after EPSRC identified Physics of Life as a Physics Grand challenge.

The aim of the network is to foster cross disciplinary scientific particularly focusing on Physics and Biology. The latest network funding has been secured until 2020 from EPSRC/BBSRC. The network is run from Durham University but this welcomes all to get involved with this ever growing community. The community is fostered through a series of core activities organised and funded by Physics of Life including: workshops, sandpits, early career researcher summer schools and town meetings.

To become a member subscribe for **FREE** by email to: physicsoflifenet2@gmail.com

Network members receive quarterly newsletters with latest updates on:

- Funding opportunities
- Events
- Network news
- Opportunities of interest outside of the network community.

Join in on Twitter: @PhysicsofLifeUK

PHYSICS OF LIFE FUNDING OPPORTUNITIES

Funding applications are welcomed from any of our members interested in a topic that crosses the Biology/Physics interface. Our opportunities include:

Over £90k in funding opportunities

Workshop Funds:

- Up to £4k available for 2 day workshops
- A new call will be shortly announced.

Sandpit Funds:

- Small discussion forums for key collaborators to gather and discuss a particular research idea that can be turned into a grant application.
- Up to £5k available for 2 day sandpits.
- This is an **OPEN,** all year call**.**

Pump Priming:

- Usually leading on from PoL sandpits up to £7k is available for research ideas requiring pump priming.
- This is an **OPEN,** all year call**.**

All our funded activities receive administrative support to organise events or facilitate grant submissions.

UPCOMING EVENTS

UNDERSTANDING THE Physics of Life

Biophysical Sciences Institute

BBSRC bioscience for the future

EPSRC Pioneering research and skills

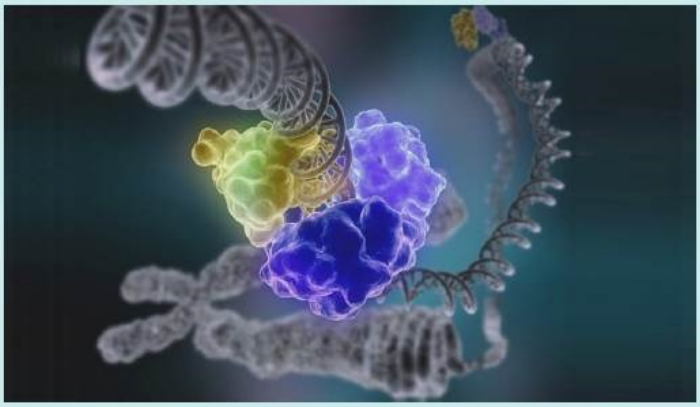
PHYSICS OF LIFE SUMMER SCHOOL:

New Approaches to Biomolecular structure, dynamics and function

16-20 July 2018

Grey College, Durham University

http://www.physicsoflife.org.uk/summer-schools.html



A one week course with 20 hours of lectures for early career research scientists.

Organisers:
Tom McLeish FRS and Martin Cann

This one week summer school will present state-of-the art computational, theoretical and experimental techniques used to explore how biomolecular dynamics depend on molecular structure and connects to and determines biological function. This is a rapidly expanding field which combines many different aspects of biology and physics.

Aimed at early-career researchers from either life-science of physical-science background, it will assist in effective working in the interdisciplinary world that connects them.

Registration deadline: 29 May 2018

Registration fee: £100 (includes Monday to Friday accommodation and meals)

Topics and Speakers:

- X-ray/synchrotron technologies (Martin Walsh, Diamond Light Source and Ehmke Pohl, Durham)
- High resolution microscopies (Robert Pal, Durham)
- Multiscale modelling (Gerhard Gompper, Julich)
- Protein Dynamics (Sarah Harris, Leeds)
- Epigenetic memory (Martin Howard, John Innes)
- NMR (Anastasia Zhuravleva, Leeds)
- Protein Evolution (Bhavin Khatri, Francis Crick Institute)
- Working across disciplines (Tom McLeish FRS, Martin Cann and John Girkin, Durham and Olwyn Byron, Glasgow)

EPSRC Pioneering research and skills

UNDERSTANDING THE Physics of Life

BBSRC bioscience for the future

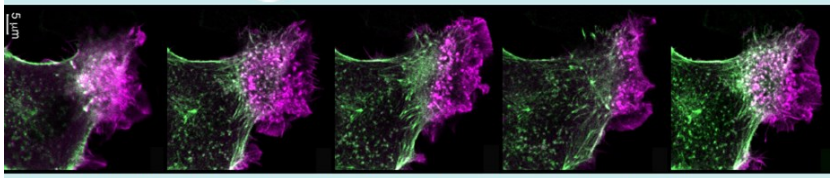


Image: RUFFLING CELL - A melanoma cell expressing a GFP Affimer for actin (green) and mcherry (magenta)
Image Credit: Michelle Peckham (Leeds)

Multi-scale mechanics in biology:

Current Challenges and Potential Solutions for Healthcare Applications

15-16 May, Weetwood House, Leeds

Register here: http://www.physicsoflife.org.uk/multiscale-mechanics-in-biology.html