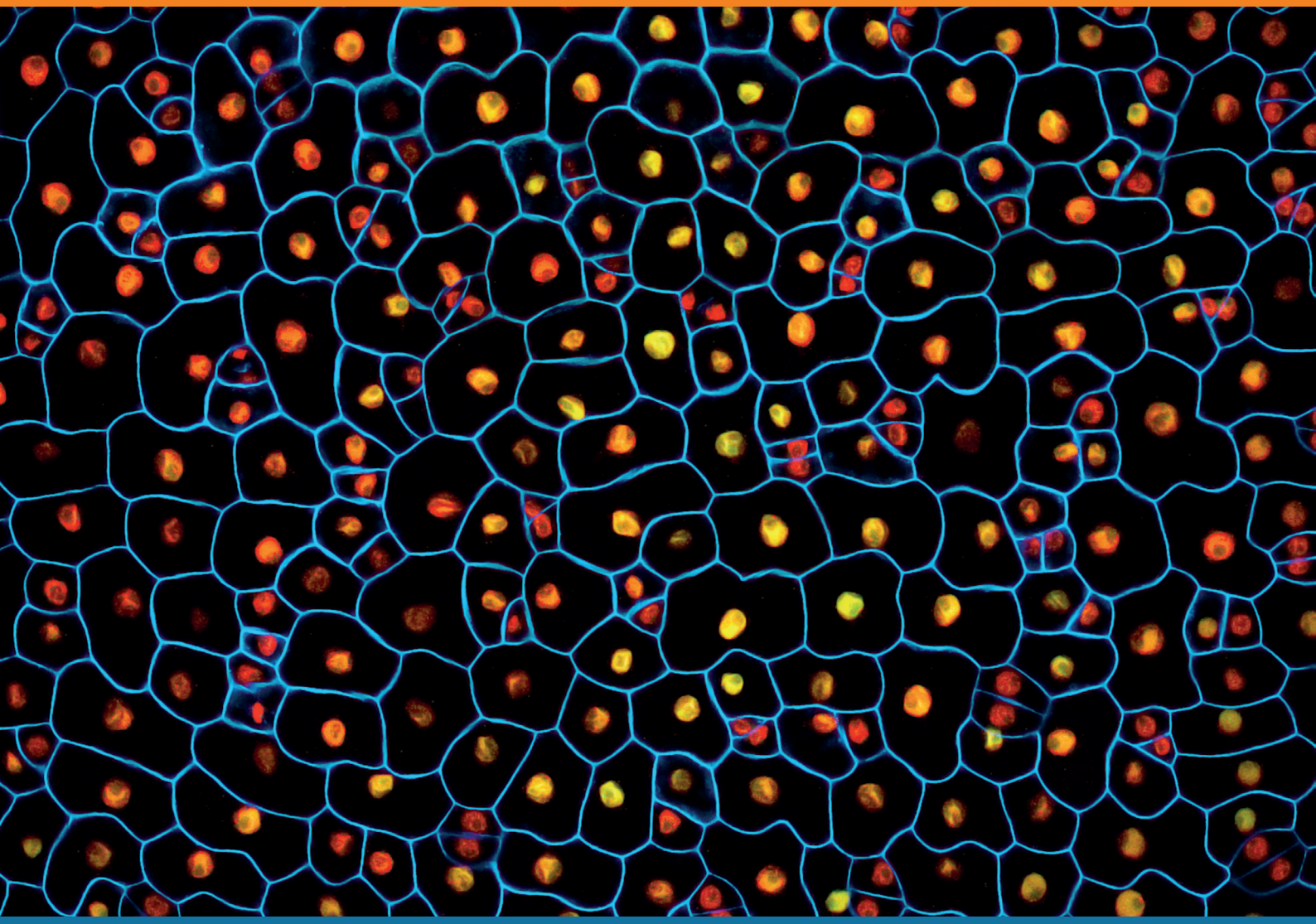
Abstract Book



Quantitative Methods in Gene Regulation III

7–8 December 2015

Corpus Christi College, Cambridge, UK

http://genereg.iopconfs.org

Organised by the IOP Biological Physics Group
Co-sponsored by the Society of Biology

IOP Institute of Physics

INSTITUTE OF PHYSICS
AWARDS 2016

Call for nominations

The awards recognise and reward outstanding achievements by physicists working in industry, business and research as well as contributions made to physics outreach and education, and the application of physics and physics-based technologies.

Deadline

The deadline for nominations is **Friday 29 January 2016**

How to apply

Details of how to apply and an application form can be found by visiting **www.iop.org/about** and selecting “Awards”.

Eligibility

Those eligible for awards should have made a substantial contribution to the development or reputation of physics in the UK or Ireland. The Isaac Newton Medal of the Institute of Physics is open to anyone. Full eligibility criteria can be found at **www.iop.org**.

Our awards are not just for physicists working in academia. Potential nominees might be working in industry, or have a non-physics background, yet may be contributing to the development or reputation of physics. The committee particularly welcomes nominations for women physicists and physicists from ethnic minorities who are often under-represented in the nominations that we receive.

We are seeking nominations for the following medals and prizes:

International award

Isaac Newton Medal of the Institute of Physics
Awarded to any physicist, regardless of subject area, background or nationality, for outstanding contributions to physics.

Gold medals

Dirac Medal of the Institute of Physics
For outstanding contributions to theoretical (including mathematical and computational) physics.

Faraday Medal of the Institute of Physics
For outstanding contributions to experimental physics, to a physicist of international reputation in any sector.

Glazebrook Medal of the Institute of Physics
To reward leadership in a physics context.

Swan Medal of the Institute of Physics
For outstanding contributions to the organisation or application of physics in an industrial or commercial context.

Education and outreach awards

The Bragg Medal and prize
For significant contributions to physics education and to widening participation within it.

The Kelvin Medal and prize
For outstanding contribution to public engagement within physics.

Subject awards

Appleton Medal and prize
For distinguished research in environmental, earth or atmospheric physics.

Franklin Medal and prize
For distinguished research in physics applied to the life sciences, including medical and biological physics.

Gabor Medal and prize
For distinguished work in the application of physics in an industrial, commercial or business context, including work that has enhanced the economic or social wellbeing of the UK or Ireland.

Hoyle Medal and prize
For distinguished research in astrophysics, gravitational physics or cosmology.

Rutherford Medal and prize
For distinguished research in nuclear physics or nuclear technology.

Thomson Medal and prize
For distinguished research in atomic (including quantum optics) or molecular physics.

Early-career awards

These awards are intended for people in the early stages of their career, defined as those individuals in the first 12 years of a research career (allowing for career breaks).

Moseley Medal and prize
For distinguished research in experimental physics.

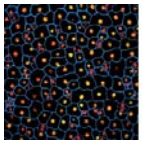
Maxwell Medal and prize
For outstanding contributions to theoretical, mathematical or computational physics.

Paterson Medal and prize
For applied physics, including work that has the potential to enhance economic or social wellbeing.

International bilateral awards

Born Medal and prize
Awarded with the German Physical Society.
For outstanding contributions to physics.

Occhialini Medal and prize
Awarded with the Italian Physical Society.
For distinguished work in any aspect of physics that is ongoing or has been carried out within the 10 years preceding the award.



Quantitative Methods in Gene Regulation III

Programme

Monday 7 December

08:00 Registration and refreshments
Foyer area, *McCrum Lecture Theatre*

(All talks and posters will be in the McCrum Lecture Theatre)

08:50 **Welcome**
Pietro Cicuta, University of Cambridge, UK (Conference Chair)

09:00 **(Invited) Higher-order chromatin and chromosome structure and genome control**
P Fraser, The Babraham Institute, UK

09:35 **Predicting the three-dimensional folding of cis-regulatory regions in mammalian genomes using bioinformatic data and polymer models**
C Brackley, University of Edinburgh, UK

09:55 **The coupling of the circadian clock to dynamic gene circuits**
B Martins, University of Cambridge, UK

10:15 Refreshments

10:45 **(Invited) Dynamics of microbial stress response programs in populations and single cells**
T Bollenbach, Institute of Science and Technology, Austria

11:20 **Cellular systems biology of chromosome dynamics**
K Lipkow, The Babraham Institute, UK

11:40 **Random association of neighbouring replicons creates DNA replication factories**
J Karschau, Max Planck Institute for the Physics of Complex Systems, Germany

12:00 **Live flash poster session 1**

13:00 Lunch
College Dining Hall

14:00 **Live flash poster session 2**

14:30 **(Invited) A bottom-down model for nuclesome mediated epigenetics**
K Sneppen, University of Copenhagen, Denmark

15:05 **(Invited) Epigenetic regulation by MOF containing complexes**
A Ahktar, Max Planck Institute of Immunobiology and Epigenetics, Germany

15:40 Refreshments

16:00 **(Invited) Some statistical aspects of the analysis of expression data**
S Tavare, Cancer Research UK Cambridge Institute, UK

16:35 **Quantitative dissection of the Polcomb target gene FLC by mathematical modelling and experiments**
M Howard, John Innes Centre, UK

16:55 **(Invited) Epigenetic reprogramming in mammalian development**
W Reik, The Babraham Institute, UK

17:30 **Using single cell approaches to understand cell fate decisions in early embryo development**
A Scialdone, EMBL-EBI, UK

17:50 **Journal of Physics A: Mathematical and theoretical – a new section in biological modelling**
M Simmons, IOP Publishing, UK
TBC

18:00 **Close and drinks reception**
Old and New Combination Rooms

19:00 Conference dinner
College Dining Hall

Tuesday 8 December

08:30 Arrival refreshments
Foyer area, *McCrum Lecture Theatre*

09:00 **(Invited) Selection on gene expression noise and its role in the evolution of gene regulation**
E Van Nimwegen, University of Basel, Switzerland

09:35 **Stochastic self-assembly of ParB proteins nucleated from the centromere builds bacterial DNA segregation apparatus**
J-C Walter, Université Montpellier, France

09:55 **(Invited) Linking *cis*-regulatory elements**
D Higgs, University of Oxford, UK

10:30 Refreshments

10:50 **(Invited) Models of evolution and population dynamics of bacterial strains**
S Maslov, University of Illinois, USA

11:25 **Impact of cell size and cell cycle on fission yeast transcription in single cells**
V Shahrezaei, Imperial College London, UK

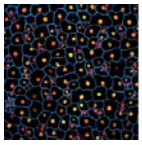
11:45 **(Invited) Small RNA regulators of plant genomes**
D Baulcombe, University of Cambridge, UK

12:20 **(Invited) Mechanical signaling in pluripotency**
K Chalut, University of Cambridge, UK

12:55 Lunch
College Dining Hall

13:55 **(Invited) The large scale features of chromatin 3D organisation**
M Nicodemi, Naples University, Italy

14:30 **The heterodimer auto-repression loop: a robust and flexible pulse-generating genetic module**
E Carlon, KU Leuven, Belgium



Quantitative Methods in Gene Regulation III

14:50	**Delayed self-regulation and time-dependent chemical drive leads to novel states in epigenetic landscapes** B Chakrabarti, Durham University, UK
15:10	Refreshments
15:30	**(Invited) Association of germline chromatin marking and transcription regulatory regions with genome domain boundaries** J Ahringer, University of Cambridge, UK
16:05	**Transcript length as a main determinant of mRNA translation efficiency** L Ciandrini, University of Montpellier, France
16:25	**(Invited) DNA superhelicity shapes genome organisation and chromatin structure** A Travers, University of Cambridge, UK
17:00	Close

Flash poster session 1 – 12:00 – 13:00

FP:01 Quantification of pathway activity in tumour invasiveness and metastasis
L Martignetti, Institut Curie / INSERM U900, France

FP:02 Entropic elasticity and dynamics of bacterial chromosomes: a simulation perspective
M C Pereira, University of Edinburgh, UK

FP:03 M-state cyclic promoter model: exact solution, parameter estimation and model selection
J Dattani, Imperial College London, UK

FP:04 Green auto-fluorescence, a double-edged monitoring tool for bacterial growth and activity in micro-plates
I Mihalcescu, Université Grenoble Alpes, France

FP:05 The change in protein expression from different reporters in *E.coli* points to post-transcriptional physiological feedback under translation limitation
Q Zhang, Université Pierre et Marie Curie, France

FP:06 What determines differential CTCF binding in cell transformation?
V Teif, University of Essex, UK

FP:07 Characterising the epigenetic landscape of breast cancer
R Batra, Cancer Research UK Cambridge Institute, UK

FP:08 Using computational topology to study cell cycle in single-cell RNA-seq data
V Svensson, EMBL-EBI, UK

Flash poster session 2 – 14:00 – 14:30

FP:09 Functional transcription factor target discovery via compendia of binding and expression profiles
A Joshi, The Roslin institute, UK

FP:10 Controllability in non-coding RNA-protein interaction network: Critical control and disease associations
J Nacher, Toho University, Japan

FP:11 An automated single cell imaging platform for tracking the lineages of mouse embryonic stem cells
W Zhai, University of Cambridge, UK

FP:12 Spatiotemporal patterns of gene expression from circadian clocks in the leaves
A Pratap, University of Bristol, UK

FP:13: Using dual-channel fluorescence to study the dynamics of synthetic transcription networks at population level
T Rudge, University of Cambridge, UK

Oral abstracts

Monday 7 December

(Invited) Higher-order chromatin and chromosome structure and genome control

P Fraser, B-M Javierre, S Schoenfelder, J Cairns, W Leung, S Wingett, C Varnai, T Nagano and M Spivakov

The Babraham Institute, UK

Three-dimensional chromatin organisation is thought to play multiple roles in gene regulation, but exactly how this occurs is largely unknown. Cell-type specificity in genome architecture is widely debated as is whether genome architecture is dynamic. We have used Promoter-Capture Hi-C to identify distal sequences interacting with 22,225 annotated promoters in 17 primary human haematopoietic cell types and several mouse cell types. With a total coverage of more than 12 billion unique, promoter contacts we used statistical algorithms to robustly detect 2,816,292 significant long-range, promoter interactions involving 247,962 potential regulatory elements that drive blood cell gene regulatory programs. More than half of the interactions are cell-type or lineage-specific, and preferentially link actively transcribed promoters with active distal enhancers. Clustering patterns of promoter interactions between different blood cell types can be used to reconstruct the hematopoietic lineage tree, demonstrating strong cell-type specific chromatin architecture that reflects cell lineage relationships. These population studies provide useful information on the range of genome interactions with exciting insights into human genetic variation and disease, but mask individual cell variability in genome organization and thus preclude an in-depth analysis of structure as it relates to function. We have developed single cell Hi-C and 3D chromosome and whole genome modeling to attempt to address this deficiency and are presently improving both genomic coverage per cell, and cell throughput to create a tool to understand genome organisation and function at the single cell level.

Predicting the three-dimensional folding of cis-regulatory regions in mammalian genomes using bioinformatic data and polymer models

C A Brackley and D Marenduzzo

University of Edinburgh, UK

The three-dimensional organisation of chromosomes in vivo is of fundamental importance, as it underpins gene regulation in mammalian cells. High-throughput experiments such as Hi-C and Capture-C [1] can now tell us in detail which regions of a genome are spatially proximate in different cell types. However it is difficult to interpret how such population level data is related to the organisation within a single cell, and the mechanisms leading to the observed contact maps are still largely obscure.

There has been much recent interest from physicists, using polymer models to try to understand the folding of chromosomes. A common approach is to use Hi-C data to determine the interactions between different chromosome regions using iterative energy minimisation and fitting. Here we instead start from a simple model based on the assumption that the architecture of eukaryotic chromosomes is maintained by protein bridges, formed by complexes of CTCF or other transcription factors, which form loops in the chromatin fibre [2]. We focus cis-regulation, where in order for transcription to be activated, a gene promoter must be brought into spatial proximity with distant enhancer elements via looping.

As a model system for gene regulation through cis-acting elements we study the folding of several gene loci in mouse erythroid cells [3]. To test the model we perform fluorescence in situ hybridization (FISH) experiments and also compare the results with recent high-resolution Capture-C experiments. Starting merely from the locations of protein binding sites, our model accurately predicts the experimentally observed chromatin interactions, revealing a population of 3-D conformations.

Our model predicts the experimentally observed chromosome interactions at both the population and single cell level. Furthermore, it predicts a high degree of cell-to-cell variability in the folding of the investigated loci. Since the model solely requires protein binding and DNase hypersensitivity data as inputs, it could be applied genome-wide, and to different organisms, to predict the 3-D organisation of different chromosomal regions.

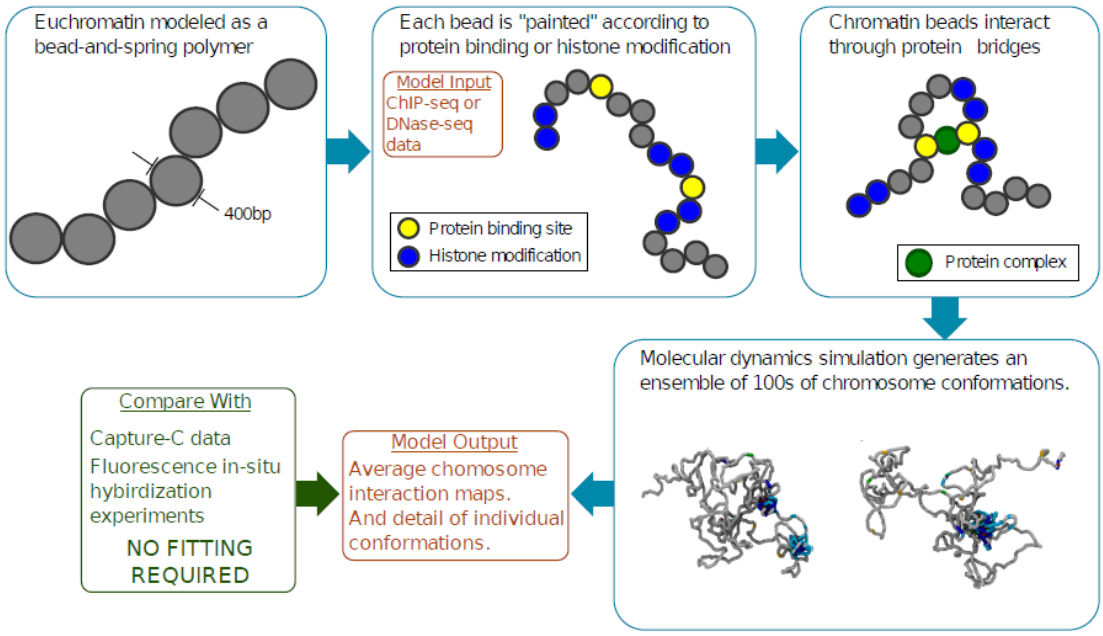


FIG 1: Schematic diagram of the modelling approach.

[1] Hughes, J R. et al, "Analysis of hundreds of *cis*-regulatory landscapes at high resolution in a single,

high-throughput experiment." *Nat. Genet.* 46, 205212 (2014)
[2] Brackley, C A et al, "Nonspecific bridging-induced attraction drives clustering of dna-binding proteins and genome organization." *Proc. Natl. Acad. Sci. USA* 110, 36053611 (2013)
[3] Brackley, C A et al, "Predicting the three-dimensional folding of *cis*-regulatory regions in mammalian genomes using bioinformatic data and polymer models." *Under review* (2015)

The coupling of the circadian clock to dynamic gene circuits

B M C Martins, A K Das and J C W Locke

University of Cambridge, UK

Circadian clocks are an important class of networks that evolved to regulate cycles of gene expression in response to daily cycles of sunlight. The oldest and simplest clocks are found in photosynthetic cyanobacteria, which utilise sunlight to harvest carbon from atmospheric CO_2. By conservative estimates, at least one third of the genome of the cyanobacterium *Synechococcus elongatus* is under circadian control. However, how the clock interacts with other dynamic gene circuits – in cyanobacteria or in other organisms – has not yet been systematically addressed. Here we used quantitative single cell time-lapse microscopy and mathematical modelling to study the coupling of the clock to other gene circuits. Their dynamics were tracked by measuring the activity of promoters fused to fluorescent reporters. We characterised how the periodic signal of the circadian oscillator is modified when processed by gene circuits that are dynamically coupled to the clock. Using genetic perturbations, we uncovered the core features of the underlying network. We then used mathematical modelling to show these circuits can indeed generate the types of dynamics we observed. This iteration of theory and experiment allowed us to identify and understand the design principles that generate those dynamics. This work shows how coupling between gene circuits enables the cyanobacterial clock to drive complex downstream gene expression.

(Invited) Dynamics of microbial stress response programs in populations and single cells

T Bollenbach

Institute of Science and Technology, Austria

Microbial responses to antibiotics and other stressors are a powerful model system for revealing general principles and fundamental limits of global gene regulation. In this talk, I will briefly discuss quantitative principles that capture the resolution of gene regulatory conflicts in the genome-wide bacterial response to antibiotic combinations. Such regulatory conflicts occur when the two antibiotics individually trigger opposite gene expression responses. I will then present our ongoing work on the global dynamics of bacterial stress response programs. In this project, we ask how changes in global cell physiology are coupled to gene expression responses and to what extent stress response programs are synchronized between cells. We address these questions using fluorescent reporters for multiple genes in the same cell combined with robotic high-throughput measurements and time-lapse imaging in microfluidics devices. Our genome-wide data from *Escherichia coli* show that different genes respond on considerably different time scales ranging from less than one to several generation times. Some genes show pulse-like transient and others lasting activity changes. Further, certain responses are highly synchronous among cells while others have more variable timing. We identified examples where such response heterogeneity among clonal cells can predict cell survival when two different stressors are applied consecutively. Overall, our approach yields insight into the dynamics of bacterial stress response programs, its dependence on physiological changes, and its role in phenotypic diversification.

Cellular systems biology of chromosome dynamics

S Sewitz[1,2], Z Fahmi[1,2], L Aljebali[1,2], J Bancroft[2], O J B Brustolini[2,4], H Saad[5], I Goiffon[5], C Varnai[1], B-M Javierre[1], S Schoenfelder[1], A Javer[2], J Kotar[2], M M Babu[6], P Cicuta[2], S G Oliver[2], P Fraser[1], K Bystricky[5] and K Lipkow[1,2]

[1]The Babraham Institute, UK, [2]University of Cambridge, UK, [3]King Saud University, Saudi Arabia, [4]Federal University of Viçosa-MG, Brazil, [5]Université de Toulouse, France, [6]MRC Laboratory of Molecular Biology, UK

The questions of how genes are regulated remains fundamental even after many decades of intense study. Rather than just studying the linear, one-dimensional sequence of DNA to inform us about regulatory mechanisms, we can now investigate the complex 3-dimensional organisation of whole genomes. It has become clear that this organisation is non-random and highly dynamic. To address new questions in genome architecture, we are taking a systems biology approach, combining the bioinformatic determination of chromatin states with quantitative experiments and dynamic, stochastic models of whole genome organisation. Comparing these results with our experimental data, this has led us to understand how biophysical properties of the chromatin fibre lead to significant and biologically relevant self-organisation of the genome.

Random association of neighbouring replicons creates DNA replication factories

J Karschau[1,2], N Saner[3], T Natsume[3], R Retkute[4], C A Nieduszynski[5], J J Blow[3], A P S De Moura[2] and T U Tanaka[3]

[1]Max Planck Institute for the Physics of Complex Systems, Germany, [2]University of Aberdeen, UK, [3]University of Dundee, UK, [4]University of Nottingham, UK, [5]University of Oxford, UK

For simplicity, cartoons often depict DNA replication on a straight 1D line. In fact, we deal with a polymer that is packaged and modified on different levels yielding higher order structures of organisation. Processing a DNA piece (as for example during DNA synthesis in clusters of replication factories) requires proper coordination amongst all individual machines (replicons) that interact with it. However, it remains unknown how such replicons are organised at each replication factory.

We apply a model of two beads connected to a string to mimic the behaviour of two neighbouring replicons (the set of replication machinery). We calculate analytically the probability for replicons to meet using Boltzmann statistics and then fit this with experimental data of replicon association in yeast to determine binding energies. This suffices to link our model to the dynamics of replicon activation and movement along DNA during the synthesis phase. We then extrapolate from our two-neighbour interaction model to the whole yeastgenome nearest neighbour interaction; where there are up to 300 replicons at the peak of the DNA synthesis phase.

Our model describes the properties of the measured experimental distribution of replicon numbers per cluster for an entire yeast cell. This can be readily done without any further parameter fitting and shows the true predictive power from a simple model. Moreover, our model yields a near perfect match with the data suggesting that actively replicating units of DNA randomly associate with each other to form replication factories rather than being controlled by the cell. This provides a new way of thinking about how the apparent order of DNA replication sites in eukaryotes can arise from random events.

(Invited) A bottom-down model for nucleosome mediated epigenetics

K Sneppen

University of Copenhagen, Denmark

Cells can be in different states of gene expression states. These States are universally maintained dynamically by positive feedback mechanisms. A subset of these states are formed by nucleosomes that recruit “read-write" enzymes which in turn modify other nucleosomes. This opens for a level of local genetic regulation which can maintain genes primed for regulation by external factors. We explore simple examples of such systems, emphasizing the minimal requirements for histone mediated epigenetics. Possible generalization of the methodology to include epigentics associated to CpG islands are also discussed. The developed models inspire new perspectives on a variety of developmental systems, including in particular the differentiation of olfactoric neuronal cells. A system where one and only one of 1000 genes are expressed in each cell.

(Invited) Epigenetic regulation by MOF containing complexes

A Ahktar

Max Planck Institute of Immunobiology and Epigenetics, Germany

Our lab is studying the chromatin and epigenetic mechanisms regulated by histone acetylation using evolutionary conserved complexes associated with MOF, a MYST family of histone acetyl transferase. In files and mammals MOF is associated with the MSL and NSL complexes, which are important regulators of gene expression. In flies the MSL complex is well known for regulation of the X chromosome by the process of dosage compensation, while the NSL complex regulates expression of housekeeping genes. In mammals, both complexes appear to be involved in regulating diverse cellular processes. The recent progress of our work will be presented.

(Invited) Some statistical aspects of the analysis of expression data

S Tavaré[1], J Marioni[2] and A Touloumis[1]

[1]Cancer Research UK Cambridge Institute, UK, [2]EMBL-EBI, UK

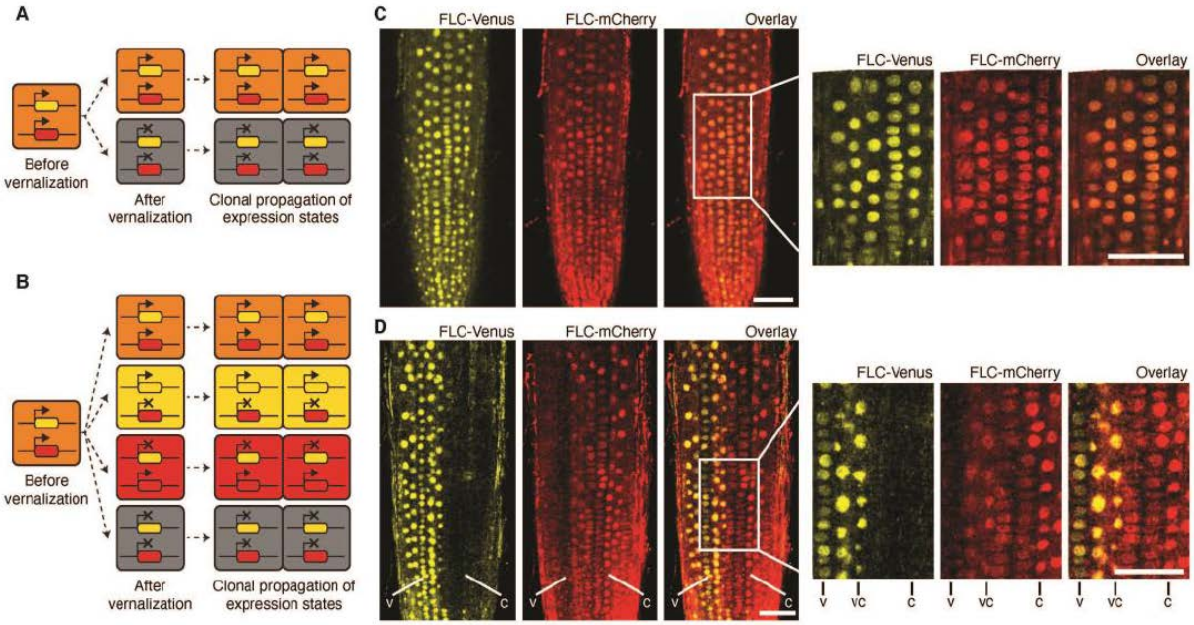
By collecting multiple samples per subject, researchers can characterise intra-subject variation using, for example, gene expression profiling from each sample. This can yield important insights into fundamental biological questions ranging from cell type identity to tumour development. For each subject, the data measurements can be written as a matrix with the different subsamples (e.g. multiple tissues) indexing the columns and the genes indexing the rows. In this context, neither the genes nor the tissues are expected to be independent and straightforward application of traditional statistical methods that ignore this two-way dependence might lead to erroneous conclusions. I will describe one approach to modeling this dependence, motivated by the matrix-valued normal distribution. I will describe a suite of tools, available in the R/Bioconductor package HDTD, for robustly estimating and performing hypothesis tests about the mean relationship and the covariance structure within the rows and columns, and will illustrate their utility by applying them to analyze data generated by the Genotype-Tissue Expression project.

Quantitative dissection of the Polycomb target gene FLC by mathematical modelling and experiments

S Berry, C Dean and M Howard

John Innes Centre, UK

Vernalization, the perception and memory of winter cold in plants, is a classic epigenetic process that involves epigenetic silencing of the floral repressor gene FLC. The slow dynamics of vernalization, taking place over weeks in the cold, generate a level of stable silencing of FLC in the subsequent warm that depends quantitatively on the length of the prior cold. The silencing is believed to be mediated by the addition of covalent modifications to histones, in this case trimethylation of histone 3 lysine 27 (H3K27me3). Using mathematical modelling, chromatin immunoprecipitation and fluorescent imaging, we have shown that the quantitative nature of vernalization is generated by H3K27me3-mediated FLC silencing in the warm in a subpopulation of cells whose number depends on the length of the prior cold. During the cold, H3K27me3 levels progressively increase at a tightly localized nucleation region within FLC. At the end of the cold, numerical simulations predict that such a nucleation region is capable of switching the bistable (digital) epigenetic state of an individual locus, with the probability of overall FLC coverage by silencing H3K27me3 marks depending on the length of cold exposure. Thus, the model predicts a digital, on or off pattern of FLC gene expression in individual cells, a prediction we verified using a fluorescent FLC-Venus reporter. I will also present new results demonstrating that Polycomb-based epigenetic memory is indeed stored in cis (see figure below) and that the nature of temperature registration during cold exposure is itself digital inside individual cells. The consequences of these results for epigenetic regulation generally will be briefly discussed.



Berry et al, eLife (2015)

(Invited) Epigenetic reprogramming in mammalian development

W Reik[1,2,3], H Lee[1,3], I Milagre[1], S Patalano[1], C Krueger[1], M Iurlaro[1], F von Meyenn[1], R Berrens[1], M King[1], S Clark[1], T Chandra[1,3], F Krueger[1], S Andrews[1], F Santos[1] and W Dean[1]

[1]The Babraham Institute, UK, [2]University of Cambridge, UK, [3]Wellcome Trust Sanger Institute, UK

Epigenetic information is relatively stable in somatic cells but is reprogrammed on a genome wide level in germ cells and early embryos. Epigenetic reprogramming appears to be conserved in mammals including humans. This reprogramming is essential for imprinting, and important for the return to pluripotency including the generation of iPS cells, the erasure of epimutations, and perhaps for the control of transposons in the genome. Following reprogramming, epigenetic marking occurs during lineage commitment in the embryo in order to ensure the stability of the differentiated state in adult tissues. Signalling and cell interactions that occur during these sensitive periods in development may have an impact on the epigenome with potentially long-lasting effects.

A key component of reprogramming is the erasure of DNA methylation which probably involves an intricate combination of passive (DNA replication without maintaining methylation) and active mechanisms. We have identified signalling events which regulate DNA methylation dynamics during early development, and which connect reprogramming firmly with naïve pluripotency. This is probably important in order to disable epigenetic memory in pluripotent cells. Altered reprogramming may also result in transgenerational epigenetic inheritance. A recently developed method for single cell whole genome bisulfite sequencing (scBS-seq) reveals extensive heterogeneity of DNA methylation especially in enhancers at the exit of pluripotency. It is possible that such epigenetic heterogeneity could help with key cell fate decisions during gastrulation.

Using single cell approaches to understand cell fate decisions in early embryo development

A Scialdone[1], W Jawaid[2], V Moignard[2], Y Tanaka[2], N Wilson[2], J Marioni[1,2,3] and B Göttgens[2]

[1]EMBL-EBI, UK, [2]University of Cambridge, UK, [3]Cancer Research UK Cambridge Institute, UK

In most early metazoan embryos progenitor cells differentiate into precursor cells of major organ systems (blood, heart, etc.) through a process called gastrulation. During gastrulation, pluripotent cells migrate through the primitive streak in a complex spatio-temporal pattern to form the three germ layers (mesoderm, endoderm and ectoderm) that lay the foundation of the basic body plan.

Given the inaccessibility and the extremely limiting number of cells in the embryo, traditional experimental approaches for transcriptome analysis cannot be applied to study the diversification of cells during early gastrulation directly in the embryo. Hence, the attention has been focussed on *in vitro* systems that, however, cannot recapitulate the dynamic of developmental processes *in vivo*.

We used single-cell RNA-sequencing to investigate mesodermal lineage development from hundreds of single cell transcriptomes, covering a developmental time-course from early gastrulation to the generation of primitive red blood cells.

For the first time, we characterised mesoderm formation *in vivo* with the identification and the description of multiple new cell subpopulations. Moreover, we computationally reconstructed the developmental trajectory leading to embryonic blood formation, in the first *in vivo* study of primitive erythropoiesis at the single cell level. This data will allow us to investigate the mechanisms underlying the cell fate decisions that generate the diverse cell types during gastrulation, in particular during key events that accompany the initiation of gastrulation like the migration of cells through the primitive streak.

Journal of Physics A: Mathematical and theoretical – a new section in biological modelling

M Simmons

IOP Publishing, UK

Journal of Physics A: Mathematical and Theoretical, is a major journal of theoretical physics reporting research on the mathematical structures that describe fundamental processes of the physical world and on the analytical, computational and numerical methods for exploring these structures. With a recently launched section in Biological Modelling, it now offers a dedicated publishing venue to those researchers working in the interdisciplinary field connecting biology and biochemistry with the underlying physical and mathematical models. Recognising that theoretical models are not usually allowed to take centre-stage when published in biological journals and are often relegated to the supplementary information, *JPhysA* provides a forum to put those models and the analysis of them in the limelight. Here, we give an overview of the journal, introduce the new section and highlight the ways that publishing with *JPhysA* can make your research more visible.

Tuesday 8 December

(Invited) Selection on gene expression noise and its role in the evolution of gene regulation

E van Nimwegen

University of Basel, Switzerland

Over the last years, several large-scale studies on gene expression noise have shown that the transcriptional noise of a gene is to a large extent encoded in its promoter sequence. Consequently, transcriptional noise is subject to natural selection. I will discuss a recent project in which we studied how natural selection has acted on transcriptional noise in *E. coli* by evolving a large collection of synthetic *E. coli* promoters in the lab de novo, and comparing their noise properties with those of native promoters. Surprisingly, we find *E. coli's* native promoters have not been selected for minimizing noise, but promoters that are highly transcriptionally regulated show evidence of having been selected for increasing their noise levels. To explain these observations, we developed a general theory for the interplay between gene regulation and gene expression noise in the evolution of gene regulation. This theory shows that noise propagation from regulators to their targets is often beneficial and can be considered a rudimentary form of gene regulation. Importantly, the theory explains how gene expression noise helps gene regulation to evolve de novo.

Stochastic self-assembly of ParB proteins nucleated from the centromere builds bacterial DNA segregation apparatus

A Sanchez[1,2], D I Cattoni[3], J-C Walter[3], J Rech[1,2], A Parmeggiani[3], M Nollmann[3] and J-Y Bouet[1,2]

[1]CNRS, France, [2]Université de Toulouse, France, [3]Université Montpellier, France

Genome processing relies on the intracellular localization and dynamic assembly of higher-order nucleoprotein complexes. In bacteria, the mechanism of assembly for the most widespread partition systems, ParABS, responsible for active DNA segregation remains elusive. We have combined super-resolution, genome-wide, biochemical and modeling approaches to investigate quantitatively the formation of the nucleoprotein complex organized around the centromere-like sequences, parS. We found that the active confinement of nearly all ParB proteins around parS, observed at the single molecule resolution, relies on a network of synergistic interactions involving protein-protein and protein-DNA interactions. Our physico-mathematical modeling of ParB binding pattern revealed that ParB binds stochastically in the vicinity of parS over long distances. Based on our findings, and consistent with previous data, we propose a new model that relies on a nucleation and looping mechanism leading to the formation of a dynamic lattice for the partition complex assembly. We thus provide new bases to model the DNA segregation process. Our original assembly model may also apply to many unrelated proteins that self-assemble in superstructures through nucleation centers.

(Invited) Linking *cis*-regulatory elements

D Higgs

University of Oxford, UK

Abstract unavailable

(Invited) Models of evolution and population dynamics of bacterial strains

S Maslov

University of Illinois, USA

I will present two recent models my lab has been working on. The first model allowed us to make sense of large collections of bacterial strain genomes in terms of their evolutionary dynamics via point mutations and Horizontal Gene Transfer followed by homologous recombination [1]. For closely related pairs of *E. coli* strains, we identified a patchwork of long (10-100kbp) horizontally transferred (recombined) segments interspersed among vertically inherited (clonal) genomic regions. Once the nucleotide sequence divergence between two *E. coli* strains exceeds ~1.3%, the clonal segments virtually disappear. SNP density in recombined segments follows exponential distribution as expected on both biophysical (requirement of perfectly matched 30-mers in the beginning and the end of a recombined segment) and population genetics (exponential coalescence time distribution) grounds. We show that the transition between mostly clonal and recombinant regimes in our model is metastable and investigate biological significance of this transition in terms of population coherence. The other model [2] describes population dynamics in ecosystems exposed to episodic collapses such as those in which susceptible bacteria are decimated by phages following Kill-the-Winner strategy.

[1] Dixit PD, Pang TY, Studier FW, Maslov S. (2015) Recombinant transfer in the basic genome of Escherichia coli. Proc Natl Acad Sci U S A. 112(29):9070-5.

[2] Maslov S, Sneppen K (2015) Diversity waves in collapse-driven population dynamics, PLoS Comput Biol 11: e1004440.

Impact of Cell size and cell cycle on fission yeast transcription in single cells

X-M Sun, A Bowman, V Shahrezaei and S Marguerat

Imperial College London, UK

Transcriptional output scales genome-wide with cell size and is regulated during cell cycle. As a result, cells of different size and physiological states contain different numbers of mRNAs and proteins. How this remarkably coordinated regulation is achieved, remains largely mysterious. Moreover, little is known about the impact of global changes in molecules numbers on regulatory networks. RNA and protein numbers exhibit cell-to-cell variation due to the stochastic nature of gene expression. Levels of noise in gene expression are linked to molecule numbers, and therefore are connected to cell size. Yet, whether and how these basic features of the cell affect gene expression noise remains vastly unexplored. We have used single-molecule counting of mRNA to explore the relationship of intrinsic and extrinsic noise in gene expression with cell-size during the cell cycle. We find that mRNA numbers are highly correlated with cell size, resulting in an approximately constant mean concentration of mRNA during the cell cycle. We also find cell-size is often the major source of correlation between expression of gene pairs, which is related to extrinsic noise. We use approximate Bayesian computation to infer parameters of a stochastic mathematical model of cell growth, division and transcription to obtain an insight on cell size regulation of gene expression. Our results reveal the importance of mRNA life-time in concentration homeostasis and regulation of extrinsic noise.

(Invited) Small RNA regulators of plant genomes

D Baulcombe

University of Cambridge, UK

Eukaryotes contain small regulatory RNAs that have been referred to as the dark matter of genetics. They are typically 21-24 nucleotides long, associated with Argonaut or Piwi proteins. Some of these small RNAs guide the Argonaut/Piwi protein to a complementary RNA and they are negative regulators of gene expression acting at the level of messenger RNA turnover or translation. Others participate in more complex epigenetic systems affecting chromatin or they act as part of an RNA signal that moves between cells. In plants the posttranscriptional mechanism is involved in defence against RNA viruses. The chromatin effects play a role in defence against DNA viruses and transposable elements and it is associated with the establishment of heritable epigenetic marks.

These small RNA regulators are often considered as negative switches like transcriptional and other repressors. However they are often part of more complex systems with negative feedback, amplification and other nonlinear properties. I will describe examples of such systems from various plant systems.

(Invited) Mechanical signaling in pluripotency

K Chalut

University of Cambridge, UK

Embryonic stem (ES) cells can indefinitely self-renew in a state of naïve pluripotency, in which they are competent to generate all somatic cells. It has been hypothesized that, before irreversibly committing, ES cells pass through at least one transition state. This transition would represent a gateway for differentiation and reprogramming of somatic cells. Using a combination of specially engineered substrates, microfluidics and atomic force microscopy, we are seeking to better understand how the exit from naïve pluripotency is mechanically regulated. Specifically, we have shown that ES cells can be maintained in a state of self-renewing pluripotency using mechanical signaling alone. Furthermore, I will discuss the specific role of nuclear mechanics and shape in the exit from pluripotency. Specifically, we sought a mechanical phenotype of transition by probing the nuclear response to compressive and tensile forces and found that, only during transition, nuclei of ESCs are auxetic: they displayed a cross-sectional expansion when stretched and a cross-sectional contraction when compressed, and their stiffness increased under compression[1]. We showed recently that the auxetic phenotype of transition ESC nuclei is driven at least in part by global chromatin decondensation. Our findings highlight the importance of nuclear structure in the regulation of differentiation and reprogramming. Importantly, there are also significant volume and shape implications we explored for the auxetic phenotype in ESC nuclei during transition. Stretched auxetic nuclei expand significantly in volume, whilst compressed auxetic nuclei condense significantly in volume; this is very unlike most materials, which tend to conserve or lose volume under stress. Therefore, I will discuss how the physical properties of these nuclei in a dynamically remodeling tissue could enhance differentiative capacity by acting as stress-driven auxetic pumps to increase molecular turnover. I will also show that changes in the tension of the actin cortex of the cells are responsible for propagating forces from the substrate to the nucleus. The forces resulting from changes in tension cause substantial changes in nuclear shape during the exit from pluripotency. Taken together, our results suggest a very important role for nuclear mechanics in regulating pluripotency.

[1] Pagliara, S, Franze, K,…, Chalut, K. *Auxetic nuclei in embryonic stem cells exiting pluripotency, Nature Materials,* 2014, 13(6), 638-644.

(Invited) The large scale features of chromatin 3D organisation

M Nicodemi

Naples University, Italy

I discuss the picture emerging from recent experimental data and models of polymer physics of the large scale features of chromosome 3D organisation.

The heterodimer auto-repression loop: a robust and flexible pulse-generating genetic module

E Carlon[1], B Lannoo[1,2] and M Lefranc[2]

[1]KU Leuven, Belgium, [2]Université Lille, France

We investigate the dynamics of the heterodimer autorepression loop (HAL), a small genetic module in which a protein A acts as an auto-repressor and binds to a second protein B to form a AB dimer. For suitable values of the rate constants the HAL produces an oscillatory output in which pulses of A alternate with pulses of B. By means of analytical and numerical calculations, we show that the duration of A-pulses is extremely robust against variation of the rate constants while the duration of the B-pulses can be flexibly adjusted. With these combined properties, the HAL is a minimal genetic module particularly relevant for cellular signaling, with also great potential in synthetic biology.

Delayed self-regulation and time-dependent chemical drive leads to novel states in epigenetic landscapes

M K Mithun[2], P R Taylor[3], T C B McLeish[1] and B Chakrabarti[1]

[1]Durham University, UK, [2]Indian Institute of Technology Bombay, India, [3]Oxford University, UK

The epigenetic pathway of a cell as it differentiates from a stem cell state to a mature lineage committed one has been historically understood in terms of Waddington's landscape, consisting of hills and valleys. The smooth top and valley-strewn bottom of the hill represent their undifferentiated and differentiated states, respectively. Although mathematical ideas rooted in nonlinear dynamics and bifurcation theory have been used to quantify this picture, the importance of time delays arising from multistep chemical reactions or cellular shape transformations have been ignored so far. In this talk we argue that this feature is crucial in understanding cell differentiation and explore the role of time delay in a model of a single-gene regulatory circuit. We show that the interplay of time-dependent drive and delay introduces a new regime where the system shows sustained oscillations between the two admissible steady states. We interpret these results in the light of recent perplexing experiments on inducing the pluripotent state in mouse somatic cells. We also comment on how such an oscillatory state can provide a framework for understanding more general feedback circuits in cell development.

[1] J Roy. Soc. Interface, 11, 20140706 (2014)

(Invited) Association of germline chromatin marking and transcription regulatory regions with genome domain boundaries

K J Evans, P Stempor, N Huang, M A Chesney, T A Down, and J Ahringer

University of Cambridge, UK

Eukaryotic genomes are organized into domains of differing structure and activity. We investigated genome domain organization in *C. elegans* and identify features associated with domains and borders. We find that the genome is organized into extended active and inactive chromatin domains that correspond with regions of low and high H3K27me3. Germline gene activity and transcription regulatory regions are prominent at or adjacent to domain borders. Notably, a subset of borders associated with germline active chromatin has higher levels of H3K36me3 and MES-4, a germline H3K36 histone methyltransferase. In animals with reduced *mes-4* activity, H3K27me3 spreads across these borders towards active domains, suggesting that germline events contribute to domain definition. We further show that intergenic regions at borders have different properties than those in domains, being longer and more enriched for transcription factor binding. These differences and their location between active and inactive chromatin suggests a possible role in separating chromatin domains.

Transcript length as a main determinant of mRNA translation efficiency

L Dias Fernandes[1], A De Moura[1], L Ciandrini[2,3]

[1]University of Aberdeen, UK, [2]University of Montpellier, France, [3]University of Montpellier, France

Proteins are the basis of cellular functions, yet key parameters regulating protein synthesis remain elusive. Understanding the fine mechanisms of this regulation is a major goal of molecular and systems biology, and this knowledge will support many “synthetic biological” applications. We have the ambitious goal of providing a comprehensive modeling framework of one of the last steps of protein synthesis, namely mRNA translation. In this presentation I will focus from a modeler’s point of view, on the role of translation initiation and how this step is mainly dictated by ribosome abundances, finite size effects and recycling. We propose an approach based on the standard exclusion process, prototypic lattice gas model. This mathematical framework considers long-range dynamical effects often neglected in standard translation models. The model is compared to experimental ribosome density data, which are well reproduced qualitatively and quantitatively. The proposed mathematical framework thus describes the origins of the well-known and yet not understood relation between transcript efficiency and its length. We also speculate on the role of transcript length in the competition for ribosomes among different mRNAs.

(Invited) DNA superhelicity shapes genome organization and chromatin structure

A Travers

University of Cambridge, UK

In a closed topological domain an active DNA translocase, such as RNA polymerase, generates positive and negative DNA superhelicity, respectively preceding and following its passage. The superhelicity so produced is not uniformly distributed along DNA but is likely highest closest to the active enzyme. Importantly some DNA sequences are more sensitive to topological strain than others. Short topologically sensitive sequences if bounded by insensitive sequences, as in some promoter sites, act as sinks for negative superhelicity facilitating local melting while longer sensitive sequences facilitate further coiling of DNA into a superhelix (writhing). The talk will describe how the DNA sequences of yeast and bacterial genes and of bacterial chromosomes functionally reflect varying levels of DNA superhelicity, implying that DNA superhelicity per se is a major determinant of sequence organization in genomes.

Chromatin selectively stores negative, but not positive, supercoils. In eukaryotic chromatin the 30 nm fibre is an iconic structure that constrains negative supercoils. I shall describe a novel structural model for this fibre that reconciles previously contradictory interpretations and is topologically consistent with all published data. I shall argue that this fibre, as is also characteristic of bacterial chromatin, is well suited to maintaining DNA compaction in a torsionally dynamic environment.

Flash poster abstracts

Flash poster session 1

FP:01 Quantification of pathway activity in tumour invasiveness and metastasis

L Martignetti, L Calzone, D Cohen, E Barillot and A Zinovyev

Institut Curie/INSERM U900, France

The rapidly increasing availability of high-throughput transcriptomics data may help to study pathway activity in a context-specific way. Indeed, it is more and more evident that monitoring expression patterns is more informative at the pathway level rather than at the gene level. We developed a method to quantify the activity of signalling pathways included in a regulatory model of tumour invasiveness and metastasis. We computed the activity scores of pathways involved in metastases based on a human colon cancer gene expression dataset [1]. The pathway activity score in tumour samples was defined as the contribution of this sample into the first principal component computed for all samples on the set of the pathway target genes, as it was done in [2]. We revealed that NOTCH and WNT pathways are significantly activated, while P53 pathway is down regulated in the metastatic compared to non-metastatic tumours. These results collectively confirm the major role of these pathways in metastasis development.

To confirm the relevance of this approach, we performed the same analysis on cancer cell lines for which EMT was induced [3]. Quantification of pathway activity allows us to verify the consistency of the mechanisms highlighted by the mathematical model with the transcriptomics data.

[1] Muzny DM, Bainbridge MN, Chang K, Dinh HH, Drummond JA, et al. (2012). Comprehensive molecular characterization of human colon and rectal cancer. Nature 487:330–337.

[2] Bild AH, Yao G, Chang JT, Wang Q, Potti A, et al. (2006) Oncogenic pathway signatures in human cancers as a guide to targeted therapies. Nature 439:353–357.

[3] Sartor MA, Mahavisno V, Keshamouni VG, Cavalcoli J et al. (2010) ConceptGen: a gene set enrichment and gene set relation mapping tool. Bioinformatics 15;26(4):465-6320

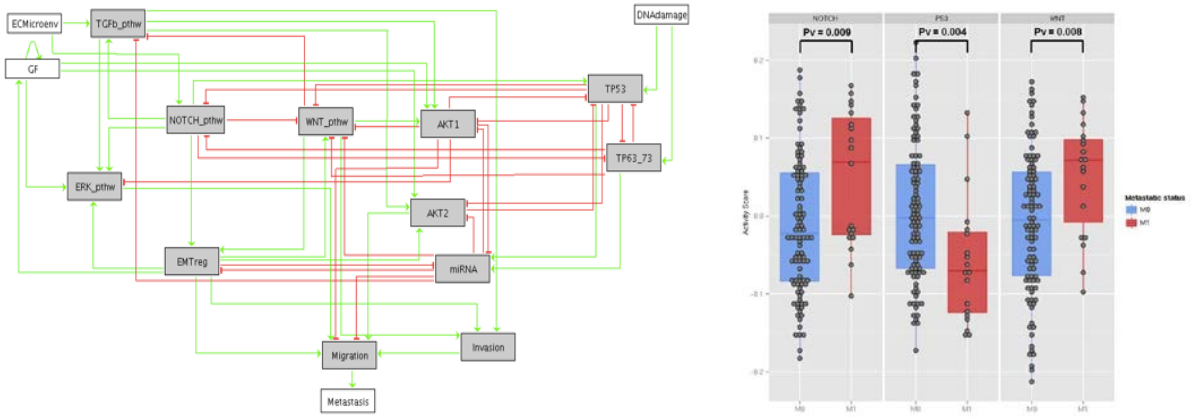


Fig. 1. a) Regulatory network representing the influences of pathways and genes on metastasis process. b) The activity score computed for the NOTCH, P53 and WNT pathways in human colon cancer samples. The data points represent primary tumour samples grouped according to the observation of distant metastases.

FP:02 Entropic elasticity and dynamics of bacterial chromosomes: a simulation perspective

M C Pereira and D Marenduzzo

University of Edinburgh, UK

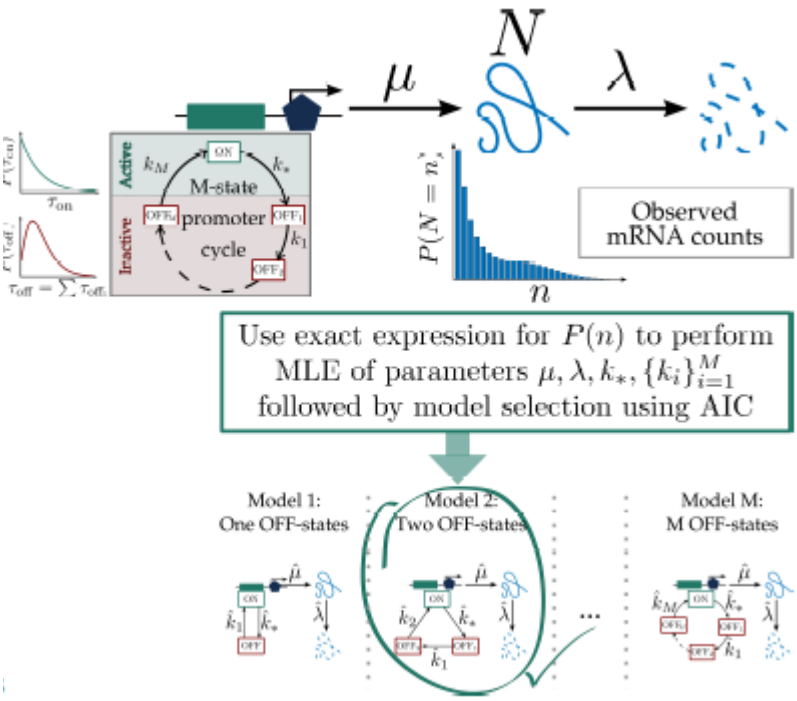
DNA is found in cells organized in compact structures – the chromosomes. This feature allows the bacterial DNA molecule, which can be two to three times longer than the cell where it is embedded, to be compacted in the cell nucleoid. DNA compaction is a result of crowded cellular conditions (entropic forces), binding of the DNA with nucleoid-associated proteins and partition of the DNA molecule into topologically isolated supercoiled domains. Here we model the bacterial DNA molecule as a self-avoiding chain of beads connected by spring bonds to explore the role of proteins, DNA-binding proteins and supercoiling on the elastic response of bacterial DNA under compression. The DNA molecule and the surrounding proteins are compressed using a piston that moves along the cylinder where the system is confined. The relation between the "force applied to the piston" and "extension of the DNA molecule" shows that for large forces the steric effects are dominant and, also, that bacterial proteins are important in determining the entropic force which is exerted against the cell membrane. The curves of the free expansion of the DNA after being compressed show that the DNA's dynamics becomes sluggish in the presence of proteins, and slows even more as DNA-binding proteins interact more and more with the DNA. We also single out the contribution of supercoiling on the dynamics of the DNA.

FP:03 M-state cyclic promoter model: exact solution, parameter estimation, and model selection

J Dattani and M Barahona

Imperial College London, UK

Gene transcription often occurs in discrete burst periods, which are punctuated by intervals of inactivity. Quantitative data analysis for such transcription kinetics commonly uses a 2-state (ON-OFF) model of gene transcription, for which the exact solution is known [1]. However, this model implies that the waiting times in both the ON and OFF states should be exponentially distributed, whereas recent time-lapse recordings show that this is not always the case for the OFF state [2, 3]. Rather, data suggests that a model with several inactive states in sequence could provide a more realistic basis for data analysis [2, 4]. We present the exact solution for the probability distribution of mRNA transcripts under a cyclic promoter with M inactive (OFF) states. The solution is obtained explicitly in terms of standard functions, and we use the solution to perform maximum likelihood estimation (MLE) and model selection using the Akaike Information Criterion (AIC) on in silico generated data. This quantitative data analysis makes full use of the obtained algebraic expression for P(N = n), the probability that a randomly chosen cell in the population has n mRNA transcripts. We use our results: i) to exemplify how the assumption of the minimal 2-state model can lead to gross mis-estimation of the underlying parameters; and ii) to demonstrate that for many parameter regimes snapshot population data cannot be used to infer the underlying time scales, and in those cases single-cell time series analysis is necessary to validate the results



[1] A Raj, C S Peskin, D Tranchina, D Y Vargas, and S Tyagi, PLoS Biol. 4, 1707 (2006).
[2] D M Suter, N Molina, D Gatfield, K Schneider, U Schibler, and F Naef, Science 332, 472 (2011).
[3] M Kandhavelu, A Häkkinen, O Yli-Harja, and A S Ribeiro, Phys. Biol 9, 026004 (2012).
[4] B Zoller, D Nicolas, N Molina, and F Naef, Mol. Syst. Biol 11, 823 (2015).

FP:04 Green auto-fluorescence, a double-edged monitoring tool for bacterial growth and activity in micro-plates

I Mihalcescu, M V-M Gateau, B Chelli, C Pinel and J-L Ravanat

Université Grenoble Alpes / CNRS, France

High throughput experiments of the in vivo gene expression in bacteria are largely based on microplate readers. As the attention of the scientific community increasingly goes now for the quantitative analysis of the gene expression dynamic, the constraints in terms of data acquisition and interpretation raise also. We find that the common bacteria *Escherichia coli* continuously produces and excretes flavins into the medium, with an excretion rate 10 time higher than the growth rate. We use for that HPLC and complementary methods of fluorescence analysis. The accumulated flavins in the supernatant are, then, at the origin of a strong intrinsic green autofluorescence. We show that this can be a help into the correct evaluation of the bacterial cell concentration. At the same time, when green fluorescent reporters are used, the strong fluorescence of the supernatant limits the range of the reporter detectability and can lead to a false interpretation of lower global dynamic range of expression than what really happens.

FP:05 The change in protein expression from different reporters in *E. coli* points to post-transcriptional physiological feedback under translation limitation

Q Zhang[1], E Brambilla[2] B Sclavi[2] and M Cosentino Lagomarsino[1]

[1]Université Pierre et Marie Curie, France, [2]LBPA, France

Escherichia coli growth physiology is primarily governed by the amounts of RNA polymerase and ribosomes available for transcription and translation respectively. For a constitutive (unregulated) promoter, assayed by enzymatic activity of a reporter, a decrease of protein concentration with increased growth rate is observed, due to a constant expression rate and an increased dilution rate. Under translation-limiting conditions a decrease in protein concentration has also been observed, due to a decrease in resources available resulting from more resources being used for the induction of ribosome production. The main proposed explanation of this last effect is a transcriptional feedback by ppGpp resulting in increased transcription of ribosomal genes and reducing the amount of RNA polymerase available for transcription of other genes. In order to investigate this feedback on different kinds of promoters, we assayed expression from chromosomally inserted constitutive and ribosomal-like promoters through both enzymatic (beta-galactosidase) activity and GFP reporters. We found that, while the ribosomal promoter shows the expected behavior, expression of GFP from two different constitutive promoters increases upon translation inhibition by addition of chloramphenicol in a similar fashion to the increase observed for the ribosomal promoter, independently of the growth medium used. Our measurements suggest a role of post-transcriptional initiation processes in regulation of protein expression and pose an important warning regarding gene expression measurements through fluorescent and enzymatic reporters with different characteristics. They also indicate that there may be another level of feedback regulation under translation limitation conditions in addition to ppGpp. A mathematical model is also proposed to quantify our results based on the consideration of the differences of the mRNA of the reporters and in ribosome availability and working efficiency.

FP:06 What determines differential CTCF binding in cell transformations?

V B Teif

University of Essex, UK

Cell fate is controlled by complex networks that link chromatin features like DNA methylation, histone modifications, nucleosome positioning and transcription factor binding. A particular interesting aspect are changes of the competitive binding of the histone octamer and transcription factors during differentiation and resulting effects on the cell's active transcription program. In our recent studies we have combined high-throughput sequencing with theoretical modeling to decipher nucleosome repositioning as a novel mechanism that connects DNA methylation/demethylation with transcription factor binding. As an example of a transcription factor utilizing this mechanism we have specifically investigated the CCCTC-binding factor CTCF. CTCF is becoming increasingly popular in genome-wide studies, because it not only acts as a transcription factor but also has functions in active/inactive chromatin region demarcation, DNA loop formation, maintaining 3D genome structure and its deregulation is a characteristic for many diseases. We found that during differentiation of mouse embryonic stem cells (ESCs) DNA methylation (5mC), hydroxymethylation (5hmC), nucleosome repositioning and CTCF binding are linked in a context-dependent manner. The mostly unmethylated CpG islands displayed reduced nucleosome occupancy and were enriched in cell type-independent binding sites for CTCF. The few remaining methylated CpG dinucleotides were preferentially associated with nucleosomes. In contrast, outside of CpG islands most CpGs were methylated and the average methylation density oscillated so that it was highest in the linker region between nucleosomes. Outside CpG islands binding of TET1, an enzyme that converts 5mC to 5hmC, was associated with labile nucleosomes. Such nucleosomes were poised for eviction in ESCs and became stably bound in differentiated cells upon reduction of TET1 and 5hmC levels. This process regulates a class of CTCF binding sites outside CpG islands that were occupied by CTCF in ESCs but lost the protein during differentiation. This cell type dependent targeting of CTCF can be rationalized with a quantitative biophysical model of competitive binding with the histone octamer in dependence of the TET1, 5hmC and 5mC state. Here new results relating differential CTCF binding to covalent CTCF and DNA modifications will be presented and discussed in the light of a general theory of differential transcription factor binding to chromatin.

[1] Teif V B, Beshnova D A, Marth C, Vainshtein Y, Mallm J-P, Höfer T and Rippe K (2014). Nucleosome repositioning links DNA (de)methylation and differential CTCF binding during stem cell development. Genome Research 24, 1285-1295.

[2] Beshnova D A, Cherstvy A G Vainshtein Y. and Teif V B (2014). Regulation of the nucleosome repeat length in vivo by the DNA sequence, protein concentrations and long-range interactions. PLoS Comput. Biol. 10(7):e1003698.

[3] Teif V B, Erdel F, Beshnova D A, Vainshtein Y, Mallm J-P, Rippe K (2013) Taking into account nucleosomes for predicting gene expression. Methods 62, 26-38.

[4] Teif V B, Vainshtein Y, Caudron-Herger M, Mallm J-P, Marth C, Höfer T, *Rippe K (2012) Genomewide nucleosome positioning during embryonic stem cell development. Nature Struct. Mol. Biol. 19, 1185-92.

FP:07 Characterising the epigenetic landscape of breast cancer

R N Batra, A T Vidakovic, O M Rueda, S F Chin, A Bruna, M Callari and C Caldas

Cancer Research UK Cambridge Institute, UK

Breast cancer is one of the leading causes of cancer death in women, and is unanimously considered a heterogeneous disease displaying distinct therapeutic responses and outcomes. While recent advances have led to the integration of the genomic and transcriptomic architecture of breast cancers to refine the molecular classification of the disease, the epigenetic landscape has received less attention.

We are conducting the largest Next-generation sequencing-based breast cancer methylome study of 2000 primary breast cancer tumours (and 500 matched normals) from the METABRIC cohort in order to provide a comprehensive investigation of the DNA methylation landscape of breast cancer. I have designed a robust sequencing and bioinformatics Reduced Representation Bisulphite Sequencing (RRBS) pipeline that is not only suitable for high-throughput, but also maximises the information content yield while keeping in mind feasibility in terms of cost. I also introduce novel methods for statistical analysis and biological interpretation of the observed methylation differences for RRBS analyses. Preliminary findings illuminate the regulatory role of methylation alterations in tumorigenesis in different genomics features such as gene promoters and enhancers, as well its contribution to breast cancer heterogeneity.

Finally, I discuss the investigation of DNA methylation markers using RRBS in a large panel of Patient Derived Tumour Xenografts, that constitute one of the best pre-clinical models available today, and are able to recapitulate inter and intra-tumour heterogeneity observed in patients. Examining the pharmacogenetic associations of these signatures would enable the identification of therapeutically tractable epigenetic targets in breast cancer.

FP:08 Using computational topology to study cell cycle in single-cell RNA-seq data

V Svensson, K Natarajan and S Teichmann

EMBL-EBI, UK

Some processes in cells are inherently cyclical, the most obvious example being the mitotic cell cycle. Cells sampled evenly from a cyclic process will give rise to certain patterns of gene expression regulating the different phases of a cycle. Neither linear projections such as PCA nor most nonlinear methods can faithfully represent cyclic latent variables due to their underlying assumptions. We therefore apply methods from computational topology to study cyclic patterns using persistent cohomology. In the end we arrive at statistical tests for determining the degree of cycling, and a way to sort cells over a cyclic process. We apply the method to investigate cell cycling rates in ESC to NPC differentiation series, and CD4 T-cells from mice during malaria infection, and found that the method can detect changes in cell proliferation rates which we would expect in these experiments.

Flash poster session 2

FP:09 Functional transcription factor target discovery via compendia of binding and expression profiles

A Joshi

The Roslin institute, UK

Genome-wide experiments to map the DNA-binding locations of transcription associated factors (TFs) have shown that the number of genes bound by a TF far exceeds the number of possible direct target genes. Distinguishing functional from non-functional binding is therefore a major challenge in the study of transcriptional regulation. We hypothesized that functional targets can be discovered by correlating binding and expression profiles across multiple experimental conditions.

To test this hypothesis, we obtained ChIP-seq and RNA-seq data from matching cell types from the human ENCODE resource, considered promoter-proximal and distal cumulative regulatory models to map binding sites to genes, and used a combination of linear and non-linear measures to correlate binding and expression data. We found that a high degree of correlation between a gene's TF-binding and expression profiles was significantly more predictive of the gene being differentially expressed upon knockdown of that TF, compared to using binding sites in the cell type of interest only. Remarkably, TF targets predicted from correlation across a compendium of cell types were also predictive of functional targets in other cell types. Finally, correlation across a time course of ChIP-seq and RNA-seq experiments was also predictive of functional TF targets in that tissue.

FP:10 Controllability in non-coding RNA-protein interaction network: Critical control and disease associations

H Kagami[1], T Akutsu[2], S Maegawa[2], H Hosokawa[2] and J C Nacher[1]

[1]Toho University, Japan, [2]Kyoto University, Japan

Network controllability has recently emerged in complex network field (Liu at al., Nature 2011) and various approaches to determine driver nodes (or controllers) in biological networks (Wuchty, PNAS 2014) have been proposed. However, most of the approaches have focused on unipartite networks. On the other hand, there are growing evidences showing that although some RNA molecules are not translated into a protein (non-coding RNA), they can still play key biological regulatory functions in a cell and are potentially linked to diseases. To shed light on this complex biological system, we investigate topological and critical controllability features of the bipartite non-coding RNA-protein interaction network using a new algorithmic approach. First, we mapped the available annotated information of more than 350 human disorders to the largest collection of human ncRNA-protein interactions, which define a bipartite network of almost 93,000 interactions. Second, the application of the novel minimum dominating set algorithmic-based controllability approach to the assembled bipartite network showed that the ncRNAs engaged in critical network control are also statistically linked to human disorders. Our analysis therefore highlights those genes that encode optimized subsets of ncRNAs engaged in critical control as well as the large-scale view of the structural controllability in non-coding RNA interactions.

FP:11 An automated single cell imaging platform for tracking the lineages of mouse embryonic stem cells

W Zhai[1], K Natarajan[2], E Cammarota[1], V Proserpio[2], E Nugent[1], P Cicuta[1] and S Teichmann[2]

[1]University of Cambridge, UK, [2]Wellcome Trust Sanger Institute & EMBL-European Bioinformatics Institute, UK

Previous stem cell research has demonstrated a close association between cell fate decisions and the cell-cycle, which revealed insights in the mechanisms synchronizing differentiation and proliferation in developing tissues[1,2]. In our research, we aim to study the cellular doubling time of mouse embryonic stem (mES) cells cultured in different media conditions, namely 2i-LIF media (2 inhibitors with Leukemia inhibitory factor (LIF)) and Serum-LIF media (serum conditioned media with LIF) [3,4]. We hypothesize that mES cells in different culture conditions across cell cycle stages have different proliferation rates [5] . We aim to simultaneously analyze correlations between cell doubling times, cell cycle stage, and expression of the Zfp42/Rex-1 gene, a pluripotency transcription factor tagged with GFP in our reporter cell line. To further investigate this question, we will also carry out systematic time lapse imaging of hundreds of single cells, with semi-automated custom image analysis for segmentation and measurement of intracellular fluorescence.

[1] S Pauklin and L Vallier, The Cell-Cycle State of Stem Cells Determines Cell Fate Propensity, Cell 155(1), 135-147 (2013)

[2] Q Deng, D Ramsköld, B Reinius and R Sandberg, Single-Cell RNA-Seq Reveals Dynamic, Random Monoallelic Gene Expression in Mammalian Cells, Science 343, 193-196 (2014)

[3] G Guo, M Huss, G Tong et. al., Resolution of Cell Fate Decisions Revealed by SingleCell Gene Expression Analysis from Zygote to Blastocyst, Develop. Cell 18, 675-685(2010)

[4] H Marks, T Kalkan, R Menafra et. al., The Transcriptional and Epigenomic Foundations of Ground State Pluripotency, Cell 149, 590-604 (2012)

[5] J A Hardwick and A Philpott, Nervous decision-making: to divide or differentiate, CellPress, 30(6), 254-261(2014)

FP:12 Spatiotemporal patterns of gene expression from circadian clocks in the leaves

A Pratap[1], B Wenden[2], S Hodge[2] and A Millar[2]

[1]University of Bristol, UK, [2]University of Edinburgh, UK

A remarkable variety of biological oscillatory systems undergo collective synchronisation and display a range of spatio-temporal patterns even when there are large variations in the natural frequencies of the population. In plants, circadian clock in a cell comprises of interacting transcriptional feedback loops giving rise to ~24hr oscillatory gene expression even without the exposure to the day/night light cycle (Pokhilko et al. 2012). Using the luciferase reporter gene, we imaged circadian oscillations in the leaves of *Arabidopsis thaliana* plants exposed to constant light for 4 days. Spatio-temporal quasi regular travelling waves were visible in all of the leaves that were monitored, indicating weak intercellular coupling (Sakaguchi et al. 1988, Wenden et al. 2012). We discover that particular type of the intercellular interaction in concert with high variance in the frequency distribution gives rise to travelling waves. We also find that frequency distribution variance is reduced at later time points indicating collective phase synchronisation of the cells. Furthermore, we incorporate our experimental observations into a mathematical model which approximates the leaf cells as a 2-dimensional grid of weakly coupled limit-cycle oscillators. We use this model to describe the intercellular coupling between circadian clocks in leaves.

FP:13 Using dual-channel fluorescence to study the dynamics of synthetic transcription networks at population level

T Rudge, F Federici, J Kotar, J Haseloff and P Cicuta

University of Cambridge, UK

Synthetic transcription networks have proven useful for both biotechnology applications and systems biology studies. Accurate design of such networks will enable quantitative analysis and control of biological processes such as metabolism, sensing and information processing, and spatio-temporal organisation. Measuring and modelling the regulation of promoters by their transcription factors will be essential in this design process. However, promoter regulation can change significantly in different conditions due to coupling with the host cell. We present dual-channel fluorescence ratiometric characterisation of promoter regulation, in which a reference promoter is used to control for extrinsic variation. This approach is applied to quantitative characterisation of promoter regulation and modelling of small synthetic transcription networks driven by chemical inputs. We measure these networks in cells growing in bulk culture, microfluidic devices, and surface growing microcolonies. From these measurements we parameterise models of the dynamics of promoter activity with respect to the different growth conditions, and examine their effect on overall transcription network behaviour.

Institute of Physics
76 Portland Place, London W1B 1NT, UK
Telephone: +44 (0)20 7470 4800
Fax: +44 (0)20 7470 4848
www.iop.org/conferences

Registered Charity Number: 293851