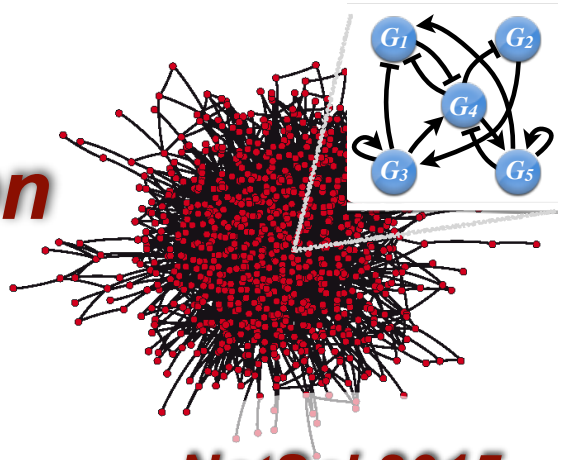
NetSciReg'15

Network Models in Cellular Regulation

http://regan.med.harvard.edu/NetSciReg2015



June 1, 2015
Zaragoza, Spain

NetSci 2015 Satellite

Invited Speakers

- ***Sebastian Ahnert***, Cavendish Lab.
- ***Gábor Balázsi,*** Laufer Center (NY)
- ***Chris Banerji, CoMPLEX, UKL***
- ***Anaïs Baudot,*** Aix-Marseille Univ.
- ***Florian Buettner,*** EMBL-EBI
- ***Guillaume Filion,*** CRG, Barcelona
- ***Benjamin Pfuety, PhLAM***
- ***Daniel Rico,*** CNIO

Organizers

- ***Erzsébet Ravasz Regan,***
  BIDMC / HMS
- **Vera Pancaldi, *CNIO***

Abstracts due: *May 10*

Contact

eregan@bidmc.harvard.edu

Sponsors:

BLUEPRINT epigenome

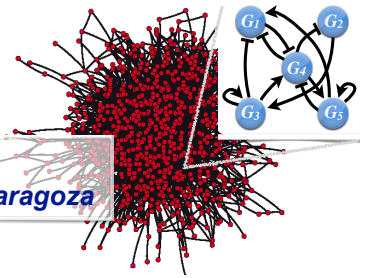
Epigenesys

CVBR Center for Vascular Biology Research
Beth Israel Deaconess Medical Center · Harvard Medical School

Program

NetSciReg'15

Network Models in Cellular Regulation



June 1, 2015
World Trade Center Zaragoza

9:20 - 9:30 Opening remarks (Erzsébet Ravasz Regan & Vera Pancaldi)

Section 1 - Regulatory dynamics and regulatory network evolution

9:30 - 10:10 **Gábor Balázsi** - *How predictable is regulatory network evolution?*
Laufer Center for Physical and Quantitative Biology,
Biomedical Engineering Department, Stony Brook University

10:10 - 10:50 **Sebastian Ahnert** - *Power graph compression reveals the architecture of transcription networks*
Cavendish Laboratory,University of Cambridge, King's College

10:50 - 11:10 **Pan-Jun Kim** - *Deciphering the Kernel Structure in the Regulatory Network of the Plant Circadian System*
(winning contributed talk)
Asia Pacific Center for Theoretical Physics, Pohang

11:10 - 11:30 **Lucia Bandiera** - *In vitro/in silico analysis of phenotypic noise under transcriptional and post-transcriptional control in elementary synthetic gene-circuits*
Laboratory of Cellular and Molecular Engineering "S. Cavalcanti",
University of Bologna

11:30 - 11:50 ***Coffee Break***

Section 2 - Regulatory networks in health and disease

11:50 - 12:30 **Anaïs Baudot** - *Network approaches for human complex diseases*
CNRS - Aix-Marseille Université, Marseilles

12:30 - 1:10 **Christopher Banerji** - *Mapping tissue development and heterogeneity in health and disease with signaling entropy*
Centre for Mathematics and Physics in the Life Sciences and
Experimental Biology (CoMPLEX) University College London

1:10 - 1:30 **Alessandro Rinaldi -** *Reverse Engineering the Multiplexity of Inflammatory Diseases*
Computer Laboratory, University of Cambridge

1:30 - 3:00 ***Lunch Break***

Section 3 - Design principles of regulatory networks

3:00 - 3:40 **Benjamin Pfeuty** - *Design principles of differentiation regulatory networks*
CNRS, Université de Lille Sciences et Technologies, Paris

3:40 - 4:20 **Florian Buettner** - *Unravelling gene regulatory networks for differentiating stem cells*
The EMBL-European Bioinformatics Institute (EMBL-EBI), Cambridge

4:20 - 4:40 ***Coffee Break***

Section 4 - Epigenetics mechanisms in cellular regulation

4:40 - 5:20 **Daniel Rico** - *Network approaches to decipher epigenetic communication in embryonic stem cells*
Spanish National Cancer Research Centre (CNIO), Madrid

5:20 - 6:00 **Guillaume Filion** - *Integrated reporters reveal distinct pathways of gene silencing in Drosophila*
Centre of Genomic Regulation (CRG), Barcelona

6:00 - 6:20 **Krzysztof Poterlowicz -** *Modelling of Carbon Copy Chromatin Conformation Capture(5C) and ChIP-Seq profiles reveal a high-resolution spatial genomic proximity network controlling epidermal keratinocyte differentiation*
University of Bradford, Bradford

6:20 - 6:40 **Biola-Maria Javierre -** *High-resolution analysis of genomic regulatory architecture in multiple human cell types with Promoter-Capture HiC*
Babraham Institute, Nuclear Dynamics Programme, Cambridge

Panel Discussion

6:40 - 7:00 *The future of mechanistic modeling in biology*
Theme: What is missing from our conceptual or technical repertoire?

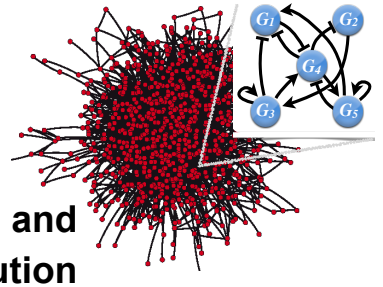
BLUEPRINT epigenome

Epigenesys

CVBR Center for Vascular Biology Research
Beth Israel Deaconess Medical Center · Harvard Medical School

NetSciReg'15

Network Models in Cellular Regulation



How predictable is regulatory network evolution?

Gábor Balázsi

Time: 9:30 - 10:10 AM

Type: Invited presentation

Affiliation: Laufer Center for Physical and Quantitative Biology, Biomedical Engineering Department, Stony Brook University

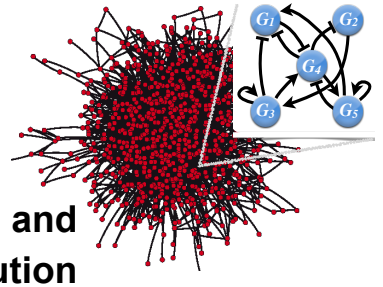
Abstract

The evolution of gene regulatory networks is poorly understood, partly because we lack appropriate model systems that allow the development of quantitative, experimentally testable predictions. To address this problem, we inserted a synthetic gene network module into the budding yeast genome and followed its evolution in various environments that affected its costs and benefits to the host. In agreement with computational predictions, we found that mutations: (i) target and eliminate the module if it has only cost; (ii) activate the module if it is potentially beneficial and carries no cost; and (iii) fine-tune the module's response if it has excessive cost and/or insufficient benefit. These results suggest that gene network evolution may be predictable from the interplay of environment-dependent costs and benefits with network dynamics, all of which in principle can be determined prior to evolution.

Section 1 - Regulatory dynamics and regulatory network evolution

NetSciReg'15

Network Models in Cellular Regulation



Section 1 - Regulatory dynamics and regulatory network evolution

Power graph compression reveals the architecture of transcription networks

Sebastian Ahnert

Time: 10:10 - 10:50 AM

Type: Invited presentation

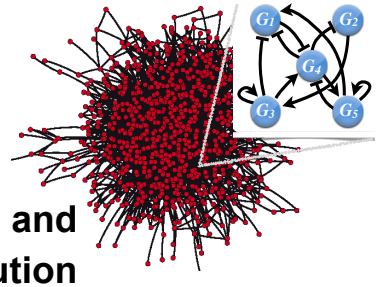
Affiliation: Cavendish Laboratory at the University of Cambridge, King's College, Cambridge

Abstract

We introduce a framework for the discovery of dominant relationship patterns in transcription networks, by compressing the network into a power graph with overlapping power nodes. We apply this approach to the transcription networks of *S. cerevisiae, E. coli*, and *A. thaliana*. This analysis, paired with GO term enrichment analysis, provides a highly informative overview of the most prominent relationships in the gene regulatory networks of these three organisms. We will also discuss extensions of the current algorithm to enable the analysis of larger networks.

NetSciReg'15

Network Models in Cellular Regulation



Deciphering the Kernel Structure in the Regulatory Network of the Plant Circadian System

Mathias Foo[1], David E. Somers[3]
Pan-Jun Kim[1, 3]

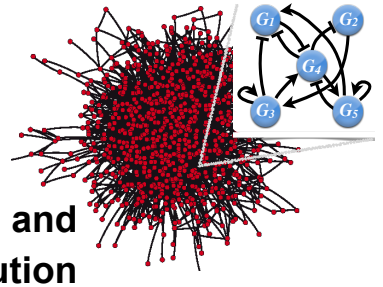
Time: 10:50 - 11:10 AM
Type: Winning Contributed Talk
Affiliation: [1] Asia Pacific Center for Theoretical Physics, Pohang (Republic of Korea); [3] Department of Molecular Genetics, The Ohio State University (USA); [3] Department of Physics, Pohang University of Science and Technology, Pohang, (Republic of Korea)

Abstract
The circadian system generates an endogenous oscillatory rhythm that offers adaptive advantages to organisms through a coordination of their biological functions with the optimal time of day. Owing to the advancement in molecular biology techniques, many plant circadian genes have been recently identified, forming much complex regulatory interactions compared to the animal cases. With such complexity of the plant circadian interactions, a natural question arises: are all these interactions equally significant to generate the circadian rhythm? To address this question, we first constructed the full mathematical model of the circadian system in plant *Arabidopsis thaliana*. The model consists of the most up-to-date, experimentally-verified transcriptional regulations and post-translational modifications among the genes and proteins in the plant circadian system. Using this model, we systematically discovered the 'kernel' structure of this system, which is defined as the minimal or core interaction sets necessary for the generation of the clock oscillatory behaviors. The kernel structure successfully reveals a set of essential feedback loops responsible for the circadian rhythms and clearly distinguishes endogenous oscillation generator components and environment-responsive components. Surprisingly, both the full regulatory network and the kernel structure were found to be overwhelmed by inhibitory interactions among the genes, while there exist only few activatory interactions. We here elucidate the dynamical and functional origin of the prevalence of such inhibitory interactions, and our suggested mechanism turns out to be supported by the analysis of animal circadian systems as well. Together, our systematic approach provides the fundamental mechanistic understanding of this important genetic circuitry, highlighting the design principle of the circadian system with implications for synthetic biology.

Section 1 - Regulatory dynamics and regulatory network evolution

NetSciReg'15

Network Models in Cellular Regulation



In vitro/in silico analysis of phenotypic noise under transcriptional and post-transcriptional control in elementary synthetic gene-circuits

Lucia Bandiera[1],
A. Pasini[1], M. Cortesi[1], E. Giordano[1,2] & S. Furini[3]

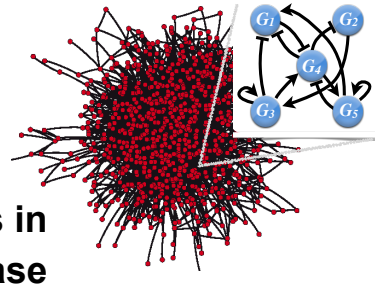
Time: 11:10 - 11:30 AM
Type: Contributed Talk
Affiliation: [1] Laboratory of Cellular and Molecular Engineering "S. Cavalcanti", Department of Electrical, Electronic and Information Engineering "G. Marconi" (DEI), University of Bologna (Italy); [2] BioEngLab, Health Science and Technology, Interdepartmental Center for Industrial Research (HST-CIRI), University of Bologna (Italy); [3] Department of Medical Biotechnology, University of Siena (Italy)

Abstract
Phenotypic noise is defined as the cell-to-cell variability in gene expression within an isogenic population. Despite the detrimental consequences on cellular events that require a fine control of information flow, this variability has also been exploited during evolution providing advantages to cells in dynamically changing environments. Beyond the natural context, the control of noise on gene expression represents a pivotal requirement for the design of gene-circuits with well-defined functionalities in synthetic biology. The overall phenotypical noise arises from the inherent stochasticity of biochemical reactions occurring within the cellular compartment (intrinsic noise) and differences in status among individual cells (extrinsic noise), e.g. numbers of RNA-polymerases or ribosomes, local environmental conditions, or concentration of transcription factors. The interplay between the gene network architecture and stochasticity in gene expression has been the subject of intense research in recent years, under the dual perspective of shedding light into how naturally occurring pathways evolved to counteract or amplify noise amplitude and defining design requirements for synthetic gene circuits with reliable functions. In this study, we compared phenotypic noise within an isogenic population of bacterial cells transformed with elementary synthetic circuits implementing either a transcriptional or a post-transcriptional control of gene expression. The circuit design aimed at the implementation of both control mechanisms by similar molecular architectures, in order to evaluate transcriptional and post-transcription control in two comparable systems. Gene synthesis was controlled by a promoter regulated by an exogenous signal in both gene circuits. Experimental measurements and mathematical models provided a consistent description of the differences on protein variability resulting from the two control mechanisms. Specifically, our results highlight that noise is lower for the gene-circuit with post-transcription control, and that the difference in protein variability between the two circuits increases when the post-transcription control on gene-expression is more efficient. These experimental results were correctly reproduced by stochastic simulations based on mathematical models that explicitly described cell-divisions events and did not include transcriptional burst. The data presented in this study support the hypothesis that post-transcriptional control might have been naturally selected for decreasing the noise on protein expression. Finally post-transcriptional control, although metabolically more demanding, proves to be a plausible tool for reducing phenotypic variability in synthetic biology applications.

Section 1 - Regulatory dynamics and regulatory network evolution

NetSciReg'15

Network Models in Cellular Regulation



Network approaches for human complex diseases

Anaïs Baudot

Section 2 - Regulatory networks in heath and disease

Time: 11:50 AM - 12:30 PM

Type: Invited presentation

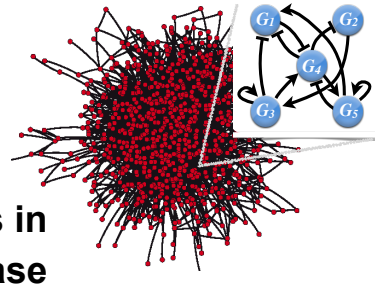
Affiliation: CNRS - Aix-Marseille Université, Marseilles, France

Abstract

Networks are scaling-up the analysis of gene and protein functions, hence offering new avenues to study the complex diseases in which these genes and proteins are involved. In the first part of my talk, I will focus on the exploration of interactome networks containing thousands of physical and functional interactions between proteins. We develop partitioning algorithms to recover community - or functional modules - from these large-scale networks, and use them to study the cellular functions of proteins of interest. We proposed for instance the involvement of Hsp27, a key stress-response protein, in DNA repair and splicing. We have recently extended the community detection to multiplex networks, i.e., networks containing different layers representing different interaction categories, such as protein-protein interaction or gene co-expression. In the second part of my talk, I will present our ongoing work, which aims to contextualize networks and set up dynamic analyses to study prostate cancer progression to resistance. We proceed through proteomics data integration into large-scale static networks and dynamic models. Finally, I will describe how network models of cell signaling can be used to predict relevant drug synergies in gastric cancers.

NetSciReg'15

Network Models in Cellular Regulation



Mapping tissue development and heterogeneity in health and disease with signaling entropy

Christopher Banerji

Time: 12:30 - 1:10 PM

Type: Invited presentation

Affiliation: Centre for Mathematics and Physics in the Life Sciences and Experimental Biology (CoMPLEX), University College London, UK

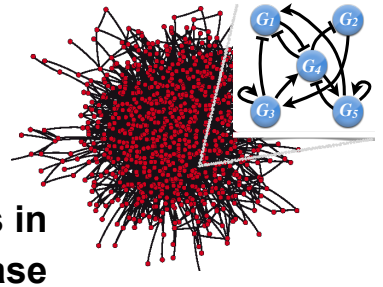
Abstract

Cellular differentiation is a fundamental biological process, essential for the development and maintenance of multicellular life; conversely, the subversion of this process is the foundation for some of the most devastating human pathologies, notably cancer. Recently, certain global principles of what characterises pluripotent stem cell populations have emerged, positing a strong role for gene expression heterogeneity. We postulated that signalling entropy, a single sample, network theoretic measure of interactome signalling promiscuity and intra-sample heterogeneity, derived from genome wide gene expression data, may prove a unifying quantification of a cells position in the global differentiation hierarchy. By analysing over 1,000 healthy tissue samples we demonstrated that signalling entropy correlates with cell potency across multiple lineages, being highest in embryonic stem cells and decreasing systematically over differentiation time courses. We also revealed that our measure is elevated in cancerous as opposed to healthy tissue, and in cancer stem cells as opposed to the tumour bulk. We next considered our measure as a prognostic indicator in epithelial cancer, analysing over 5,000 primary tumour samples. We demonstrated the signalling entropy is strongly prognostic in both breast and lung adenocarcinoma, out-performing current prognostic indicators. Our measure is found to be a robustly prognostic, valid regardless of oestrogen-receptor status in breast cancer and within the stage I stratum in lung adenocarcinoma. We thus present signalling entropy as a means to chart the differentiation landscape, providing insight into regenerative medicine and disorders of development.

Section 2 - Regulatory networks in heath and disease

NetSciReg'15

Network Models in Cellular Regulation



Reverse Engineering the Multiplexity of Inflammatory Diseases

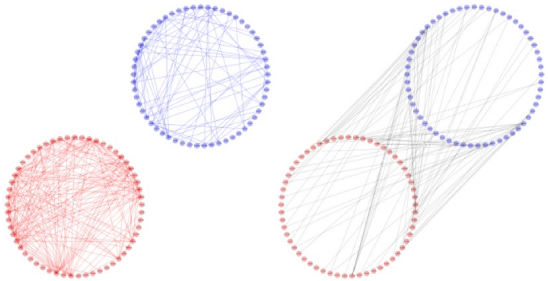
Alessandro Rinaldi , Pietro Liò

Time: 1:10 - 1:30 PM
Type: Contributed presentation
Affiliation: Computer Laboratory, University of Cambridge

Abstract

In the last two decades the emergence of high-throughput technologies has made available huge amounts of high-dimensional multi-omic data sets, revealing the multifaceted nature of most biological processes in living organisms [1]. Despite this abundance of data, our comprehension of structural patterns, functional prin- ciples, and systemic behaviours in complex systems is still approximate. A clear example of this gap between richness in data and poverty in knowledge is the difficulty in uncovering the relational structure between molecules within a living cell [2]. Genes, for instance, interact in a complex web of relations that or-chestrate various functions in response to both endogenous and exogenous stimuli. Traditional methods to reverse-engineering gene networks from measured expres- sion data include graphical Gaussian modeling (GGM) [3], Bayesian networks [4], relevance networks [5], and Pearson correlation networks [6], just to name a few. In this paper we propose a new approach to infer and study gene networks, com- bining methylation and gene expression data in a multilayer network [7, 8]. In- stead of using standard co-expression measures, such as Pearson's correlation co- efficient, mutual information, or Spearman's rank correlation coefficient, we build a multilayer network (Figure 1) computing a pairwise similarity between genes within each layer and between the layers by means of a Gaussian kernel. In par- ticular, we associate to each gene a feature vector consisting of three elements: the mean value of its expression/methylation level for healthy subjects, the mean value for patients, and a normalized value resulting from the t-test for the two populations (healthy subjects and patients). Our formulation implicitly embodies a plurality of relationships and functional roles between genes, making it possible to elucidate the dynamical mechanism of aggregation and disruption of connectivity structures across multiple omic layers. We analyze the role played by methylation in regulating gene expression for ten inflammatory diseases by considering traditional descriptive measures at both lo- cal and global scale and providing a Bayesian nonparametric generative model based to investigate the formation of mesoscopic structures.

Section 2 - Regulatory networks in heath and disease



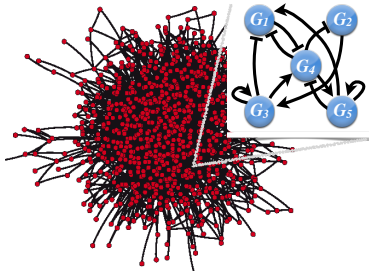
(a) Intralayer structure. (b) Interlayer structure

References

[1] A. R. Joyce and B. O. Palsson, Mol Cell Bio 7:198-210, 2006.
[2] A. L. Barabasi and Z. N. Oltvai, Nat Gen 5:101-114, 2004.
[3] A. Wille et al., Genome Biol 5(11):R92+, 2004.
[4] N. Friedman, M. Linial, I. Nachman, D. Pe'er, J Comp Biol 7:601-620, 2000.
[5] A. J. Butte and I. S. Kohane, AMIA Ann Symp Proc Arch 711-715, 1999.
[6] B. Zhang and S. Horvath, Stat Applic Gen Mol Biol 4(1):17+, 2005.
[7] S. Boccaletti et al., Phys Rep 544(1):1-122, 2014.
[8] M. Kivela et al, J Complex Networks 2:203-271, 2014.

NetSciReg'15

Network Models in Cellular Regulation



Design principles of differentiation regulatory networks

Benjamin Pfeuty

Time: 3:00 - 3:40 PM

Type: Invited presentation

Affiliation: CNRS, Université de Lille Sciences et Technologies

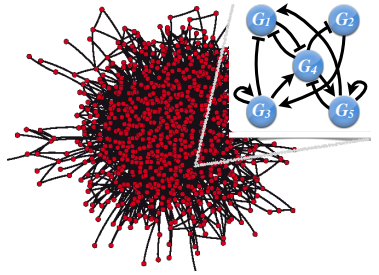
Abstract

Cellular regulatory networks often exhibit a sophisticated architecture made of many interlocked feedback loops operating at multiple timescales, even in the case of an a priori simple cellular function: a differentiation decision switch. In this presentation, I wish to discuss the notion that the complex design of differentiation regulatory network reflects various requirements, most likely related to the fact that the differentiation process competes or cooperates with other cellular processes (e.g.,alternative differentiation fates, proliferation, metabolism, cell-cell communication etc...). This discussion will draw upon recent theoretical studies based on abstract and detailed network models,with special emphasis on the issue of how the differentiation process is intimately linked to the cell-cycle and intercellular signaling processes.

Section 3 - Design principles of regulatory networks

NetSciReg'15

Network Models in Cellular Regulation



Unravelling gene regulatory networks for differentiating stem cells

Florian Buettner

Time: 3:40 - 4:20 PM

Type: Invited presentation

Affiliation: The EMBL-European Bioinformatics Institute (EMBL-EBI), Cambridge

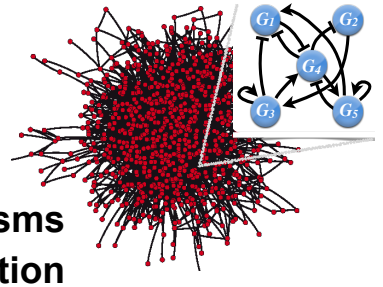
Abstract

Reconstruction of gene regulatory networks form of experimental data is an important challenge in computational biology as it allows to gain deeper insights in how genes interact on different molecular levels in order to execute specific biological functions. This in turn, is crucial for understanding complex processes such as cell differentiation and disease. In recent years, technological advances allow us to measure gene expression at the level of single cells, which are often being regarded as the fundamental unit in biology. The availability of experimental data at this unprecedented resolution gives rise to new opportunities and challenges for reconstructing regulatory network dynamics. Here, I will illustrate current approaches for network reconstruction based on single-cell gene expression data at the example of early blood development. In addition to these standard methods, which are usually based on the application of network reconstruction methods for static bulk data, I will present our recent efforts on unravelling the dynamics of such networks. In contrast to previously developed methods, our approach allows for the accurate reconstruction of Boolean logic gates and presence/absence of regulatory edges by leveraging the rich information inherent in the single-cell data. This resulted in a computationally executable transcriptional regulatory network model of blood development that revealed new insights in the transcriptional programs that underlie organogenesis.

Section 3 - Design principles of regulatory networks

NetSciReg'15

Network Models in Cellular Regulation



Network approaches to decipher epigenetic communication in embryonic stem cells

Daniel Rico

Time: 4:40 - 5:20 PM

Type: Invited presentation

Affiliation: Spanish National Cancer Research Centre (CNIO), Madrid

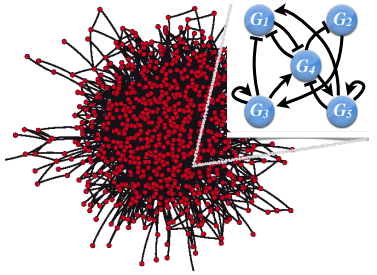
Abstract

Cell identity depends on complex communication networks based on chemical processes that modify the DNA, the histones and other chromatin proteins. It is now clear that the combination of different histone marks and cytosine modifications play an important role in defining epigenomic scaffolds affecting to the binding and function of other epigenetic players (eg. different protein complexes). However, we are yet far from understanding the epigenomic "language" and how the different chromatin components communicate with each other to perform biological functions. Here, we establish a global framework to rationalize and study epigenomic communication. This framework combines network-based analyses and evolutionary characterization of a communication network derived from high- throughput data and literature knowledge. We followed a systems biology approach to investigate the functional interdependence between chromatin components in mouse embryonic stem cells (ESCs). We constructed the epigenetic signaling network in ESCs as a combination of a high quality genomic co-localization network (extracted from 139 ChIP-seq experiments on 77 different epigenomic features) plus edge directionality based on the functional role of the proteins in this network. We defined histone marks and cytosine modifications as signals and classified those proteins co-localizing to them as their emitters or receivers based on the information derived from the literature regarding to the functional role of the proteins. The analysis of this network revealed that cytosine 5-hydroxy-methylation (5hmC) is a key signal for mediating communication among different regions of the network. A more detailed exploration of 5hmC-centered communication shows that it can co-localize independently with several different emitters. Our co- evolutionary analysis of this network points to 5hmC-mediated communication as the major source of co-dependent changes in this system, suggesting an important role of 5hmC-mediated communication in metazoan evolution. Altogether, we propose that 5hmC acts as a central switch between alternative mutually dependent chromatin configurations in ESCs. To our knowledge, this chromatin network is the most complete available global model of the epigenetic signaling and therefore we propose it as a valuable tool for understanding communication processes in ESCs.

Section 4 - Epigenetics mechanisms in cellular regulation

NetSciReg'15

Network Models in Cellular Regulation



Integrated reporters reveal distinct pathways of gene silencing in Drosophila

Guillaume Filion

Section 3 - Design principles of regulatory networks

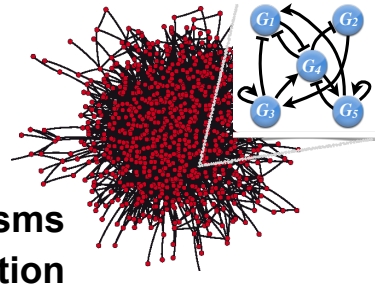
Time: 5:20 - 6:00 PM

Type: Invited presentation
Affiliation: Centre of Genomic Regulation (CRG), Barcelona

Abstract
Recent genome-wide mapping studies in eukaryotes have shown that most transcriptionally silent domains lack repressive histone marks and repressors of transcription, prompting to ask what makes genes of these regions silent. Here we set out to answer this question by assaying position effects genome-wide for several reporters of transcription. To this end, we used a shotgun approach called TRIP (Thousands of Reporters Integrated in Parallel) to insert identical reporter genes at different loci of the Drosophila genome and measure their expression. We obtained expression data for more than 85,000 integrated reporters under eight different promoters, constituting the largest dataset of position effects available to date. We identified 10-100 kb domains of either high or low reporter activity. These domains are similar for different reporter constructs, showing that they correspond to the underlying organization of the genome. We identified novel protein signatures associated to the repression of reporter genes. One of them consists of chromatin proteins associated to transcriptionally active regions with a deficit of DMAP1, which suggests that this protein is critical for the expression of reporters. Overall, our results reveal that the effect of the chromatin context on transcription results from multiple processes at work simultaneously.

NetSciReg'15

Network Models in Cellular Regulation



Modelling of Carbon Copy Chromatin Conformation Capture (5C) and ChIP-Seq profiles reveal a high-resolution spatial genomic proximity network controlling epidermal keratinocyte differentiation

Krzysztof Poterlowicz[1],
J. Yarker[1], N. Naumova[2], B. Lajoie[2], I. Malaschchuk[1],
A. Mardaryev[1], A. Sharov[3], J. Dekker[2], V. Botchkarev[1,3],
and M. Fessing[1]

Time: 6:00 - 6:20 PM
Type: Contributed Talk
Affiliation: [1] University of Bradford; [2] University of Massachusetts Medical School; [3] Boston University School of Medicine

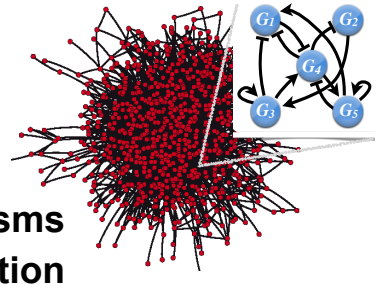
Abstract
During development, the execution of distinct cell differentiation programs is accompanied by establishing specific higher-order chromatin arrangements between the genes and their regulatory elements. The Epidermal Differentiation Complex (EDC) locus contains multiple co-regulated genes involved in the epidermal keratinocyte (KC) differentiation. Here we applied a probabilistic approach for the investigation of properties of chromatin architecture. Furthermore, we characterise the high-resolution spatial genomic proximity network of a 5Mb region containing the EDC and its flanking regions in mouse epidermal KCs. This was done by modelling data obtained from the 5C experiments and a set of eighteen ChIP-Seq profiles for histone modifications, chromatin architectural and remodelling proteins. The analysis reveals that a substantial number of the spatial interactions at the EDC overlap with chromatin states

Section 4 - Epigenetics mechanisms in cellular regulation

involving regulators of gene transcription and chromatin architecture. These include different combinations of transcription factors acting predominantly as a transcription repressors in keratinocyes (Cebpa, Cebpb, Mxi1, Ovol2), co-repressor chromatin remodelers (Sin3a ,Kdm5) and proteins involve in higher order chromatin folding (Ctcf, Rad21,Satb1) We confirmed by using both 5C and 3D FISH that chromatin at the 5Mb genome locus spanning the EDC and its flanking regions form several topologically associated domains (TADs) with similar borders. Moreover, it showed markedly different intra-domain folding in KCs versus thymocytes (TC), e.g. two adjacent TADs at the EDC central part were more condensed and non-randomly folded in KCs versus TCs. In summary, our probabilistic approach allows us to suggest an involvement of the chromatin architecture and remodelling proteins into the spatial interaction network of gene cis-regulatory regions controlling co-ordinated gene expression at the EDC locus. It provides an important platform for further studies of the higher order chromatin folding at KC-specific genomic loci involved in controlling gene expression programmes in skin epithelia in health and disease.

NetSciReg'15

Network Models in Cellular Regulation



High-resolution analysis of genomic regulatory architecture in multiple human cell types with Promoter-Capture HiC

Biola-Maria Javierre[1], J.Cairns[1], O. Burren[2], S. Wilder[3], S. Sewitz[1], S. Wingett[1], F. Wang[4], T. Cutler[3], J. B. Dmitrieva[5], P. Freire-Pritchett[1], S. Hill[4], C. Oury[5], M. Georges[5], D. Zerbino[3], H. Stunnenberg[6], K. Downes[7,8,9], C. Wallace[2], M. Frontini[*,7,8,9], W. Ouwehand[*,7,8,9,10], M. Spivakov[*,1], P. Fraser[*,1]

Time: 6:20 - 6:40 PM
Type: Contributed Talk
Affiliation: [1] Babraham Institute, Nuclear Dynamics Programme, Cambridge, UK; [2] Cambridge Institute for Medical Research, Cambridge, UK;[3] EMBL-European Bioinformatics Institute, Cambridge, UK; [4] MRC Biostatistics Unit, Cambridge, UK; [5] University of Liege, GIGA-Research, Liege, Belgium; [6] Radboud Institute for Molecular Life Sciences, Radboud University, Nijmegen, Netherlands; [7] University of Cambridge, Department of Haematology, Cambridge, UK; [8] Cambridge Biomedical Research Centre, National Institute for Health Research, Cambridge, UK; [9] National Health Service Blood and Transplant , Cambridge, UK; [10] Wellcome Trust Sanger Institute, Cambridge, UK

Abstract
Remote regulatory regions such as enhancers play a key role in metazoan gene regulation. We have coupled HiC technology with sequence capture to enrich HiC material for interactions involving (at least on one end) ~22,000 known promoters in primary human cells. Combining Promoter-Capture HiC with a peak-calling algorithm (CHiCAGO) developed specifically for this data, we detected hundreds of thousands of putative regulatory interactions across ~20 human primary cell types at a single-restriction fragment resolution. Promoter-Capture HiC enriches the material purely based on sequence on one end of an interacting pair of fragments. Therefore, interactions are detected irrespective of target promoter activity, the identity of recruited transcription factors and across the whole range of distances between interacting fragments. Using this approach, we have assessed the diversity of enhancer-promoter and promoter-promoter interactions across cell types, profiled their dynamics upon lineage commitment and detected the interaction "hallmarks" of active, poised and repressed genes. In addition, we take advantage of promoter interactome data to enhance the annotation of genetic variants mapping to non-coding sequences.

Section 4 - Epigenetics mechanisms in cellular regulation