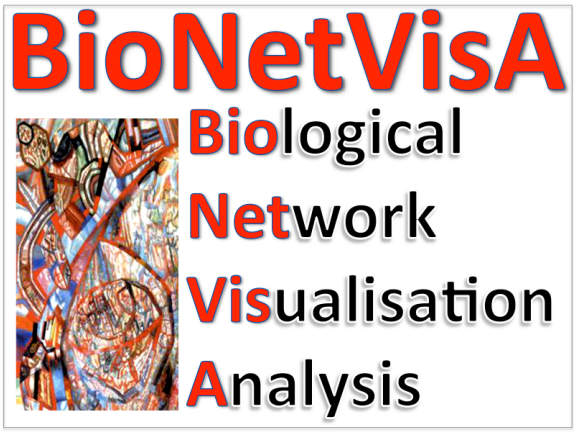

BioNetVisA workshop

From biological network reconstruction to data visualization and analysis in molecular biology and medicine

University of Basel
Kollegienhaus
Petersplatz 1, CH-4001
Basel, Switzerland

12 September 2017

The **BioNetVisA** workshop will bring together different actors of network biology from database providers, networks creators, computational biologists, biotech companies involved in data analysis and modeling to experimental biologists, clinicians that use systems biology approaches. The participants will be exposed to the different paradigms of network biology and the latest achievements in the field.

The goal of **BioNetVisA** workshop is to build a discussion around various approaches for biological knowledge formalisation, data integration and analysis; compatibility between different methods and biological networks resources available the field; applicability for concrete research and clinical projects depending on scientific question and type of high-throughput data.

The **BioNetVisA** workshop aims at identifying bottlenecks and proposing short- and long-term objectives for the community as discussing questions about accessibility of available tools for wide range of user in every-day standalone application in biological and clinical labs. In addition, the possibilities for collective efforts by academic researchers, clinicians, biotech companies and future development directions in the field will be discussed.

Organizers

Inna Kuperstein (Institut Curie, France)
Emmanuel Barillot (Institut Curie, France)
Andrei Zinovyev (Institut Curie, France)
Hiroaki Kitano (Okinawa Institute of Science and Technology Graduate University, RIKEN Center for Integrative Medical Sciences, Japan)
Minoru Kanehisa (Institute for Chemical Research, Kyoto University, Japan)
Samik Ghosh (Systems Biology Institute, Tokyo, Japan)
Nicolas Le Novère (Babraham Institute, UK)
Robin Haw (Ontario Institute for Cancer Research, Canada)
Alfonso Valencia (Spanish National Bioinformatics Institute, Madrid, Stain)
Lodewyk Wessels (Netherlands Cancer Institute, Amsterdam, Netherlands)
Patrick Kemmeren (Princess Maxima Center for Pediatric Oncology, Utrecht, Netherands)

Web site

https://www.bc2.ch/2017/program/workshops/ws2/
http://sysbio.curie.fr/bionetvisa

Venue

https://www.bc2.ch/2017/travel-venue/

Contact

bionetvisa@curie.fr

BioNetVisA workshop program

Session 1: Signaling and metabolic network databases

Chair: Andrei Zinovyev

09.00-09.20 Talk 1
Stephan Gebel (University of Luxembourg, Luxembourg)
A comprehensive map of signalling in Parkinson's disease

09.20-09.35 Talk 2
Konstantinos Sidiropoulos (EMBL-EBI, Hinxton, UK)
Reactome: New features for enhanced pathway visualisation

09.35-10.50 Talk 3
Falk Schreiber (University of Konstanz, Konstanz, Germany)
From static visualisation to immersive analytics of biological networks

10.50-10.05 Talk 4
Björn Sommer (Monash University, Melbourne, Australia)
Multiscale Modeling and 3D Visualization of spatially-embedded Cytological Networks

10.05-10.25 Talk 5
Marcus Krantz (Humboldt-Universität zu Berlin, Berlin, Germany)
Formalisation, visualisation and analysis of signal transduction networks with rxncon

10.30-11.00 Coffee break

Session 2: Platforms and method for analysis of complex biological networks

Chair: Patrick Kemmeren

11.05-11.35 Talk 6
Keynote lecture
Alfonso Valencia (Spanish National Bioinformatics Institute, Madrid, Spain)
Networks and Co-evolution in the Interpretation of Epigenetic Regulation

11.35-11.55 Talk 7
Andrei Zinovyev (Institut Curie, Paris, France)
Application of the reduced Google Matrix approach for the analysis of directed biological networks

11.55-12.15 Talk 8
Ugur Dogrusoz (Bilkent University, Ankara, Turkey)
Interactive web based curation of biological pathways with advanced layout and complexity management support

12.15-12.30 Talk 9
Aura Ileana Moreno-Vega (Institut Curie, Paris, France)
Characterization of the FGFR3 regulatory network in bladder tumors

12.30-13.30 Lunch

Session 3: Biological networks in drug discovery and toxicology studies

Chair: Ugur Dogrusoz

13.30-14.00 Talk 10

Keynote lecture

Minoru Kanehisa (Institute for Chemical Research, Kyoto University)

From gene variants to network variants: a new database for understanding diseases and drugs

14.00-14.20 Talk 11

Mark Ibberson (Swiss Institute of Bioinformatics)

Biomarker discovery in diabetes: A network-based approach

14.20-14.40 Talk 12

Tatyana Doktorova (Douglas Connect GmbH, Basel, Switzerland)

Integrated Modelling and Testing Strategies supporting Systems Toxicology and Evidence-based Safety Assessment

14.40-14.55 Talk 13

Justyna Szostak (Philip Morris International group, Neuchâtel, Switzerland)

Detect Liver Toxicity through Causal Biological Network Model and Computational Algorithm

15.00-15.30 Coffee break

Session 4: Biological networks modelling in medicine

Chair: Matteo Barberis

15.30-15.50 Talk 14

Gregory Batt (Institut Pasteur, Paris, France)

A multi-scale model for investigating TRAIL resistance in multi-cellular tumor spheroids

15.50-16.10 Talk 15

Patrick Kemmeren (Princess Maxima Center for Pediatric Oncology, Utrecht, Netherlands)

Exhaustive Petri net modeling to infer mechanisms of genetic interactions

16.10-16.25 Talk 16

Valeriya Malysheva (Université de Strasbourg, Illkirch, France)

Integration of chromatin structure dynamics in the regulatory network governing cell fate acquisition

16.25-16.45 Talk 17

Matteo Barberis (University of Amsterdam, Amsterdam, The Netherlands)

GEMMER: GEnome-wide software for Multi-scale Modeling data Extraction and Representation

16.45-17.00

Closing remarks and discussion

BioNetVisA workshop abstract

Talk 1

Parkinson's disease map, an interactive map of molecular signaling

Stephan Gebel[1], Marek Ostaszewski[1], Piotr Gawron[1], Reinhard Schneider[1], Rudi Balling[1]

[1]*Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Campus Belval, Luxembourg*

Recent developments in 'omics' technologies allow studying molecular pathogenesis/mechanisms of diseases in great detail. However, comprehensive interpretation of such data requires their integration with the existing body of knowledge on a given disease. The Luxembourg Centre for Systems Biomedicine has established technology and expertise supporting 'molecular disease maps' that allow the upload and interpretation of 'omics' data in the context of existing knowledge. The concept of molecular maps combines manually curated and high-quality knowledge repositories with bioinformatics tools. The new MINERVA platform is tailored for visualization and management of disease and molecular interaction maps. Its integrated tools allow for: automated annotation of elements and verification of the contents, visualisation via embedded Google Map application programming interface, export of the content, as image, network or computational model and combination with biomedical data analysis pipelines. Our pioneering Parkinson's disease (PD) map, developed together with the Systems Biology Institute (SBI) in Tokyo, Japan, makes the information from more than 1500 research articles and public databases available for interpretation in a molecular interaction map. The map is envisaged as a hub for the PD community to deal with rapidly increasing information on PD. To update and refine the map expert knowledge is collected by integrated feedback functions and on frequent workshops with field experts.
The freely accessible (http://pdmap.uni.lu) PD map give valuable insights for fundamental as well as translational researchers in academia, clinics and pharma industry and can be used as a blueprint for the development of other disease maps.

Talk 2

Reactome: New features for enhanced pathway visualisation

Konstantinos Sidiropoulos[1], Guilherme Viteri[1], Cristoffer Sevilla[1], Steve Jupe[1], Peter D'Eustachio[3], Lincoln Stein[2,4], Peipei Ping[5], Henning Hermjakob[1,6] and Antonio Fabregat[1,7]

[1]European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Wellcome Genome Campus, Hinxton (UK), [2]Ontario Institute for Cancer Research, Toronto (Canada), [3]NYU Langone Medical Center, New York (USA), [4]Department of Molecular Genetics, University of Toronto,Toronto, (Canada), [5]NIH BD2K Center of Excellence and Department of Physiology, Medicine and Bioinformatics, University of California, Los Angeles, California, [6]State Key Laboratory of ProteomisBeijing Proteome Research Center, Beijing Institute of Radiation Medicine; National Center for Protein Sciences Beijing, 102206, Beijing (China), [7]OpenTargets, Wellcome Genome Campus, Hinxton (UK)

Reactome (http://reactome.org) is a free, open-source, curated and peer-reviewed knowledge base of biomolecular pathways. Pathways in Reactome are organized hierarchically, grouping related detailed pathways (e.g. Translation, Protein folding and Post-translational modification) into larger domains of biological function like Metabolism of proteins. While we provide a hierarchical pathway browser as a key element of the Reactome web interface, the relationships and connectivity between high-level pathways were previously not represented well. In addition, options for re-use of the manually laid out low-level pathway diagrams were limited, as they were only downloadable as PNG images.

Following intensive User Experience testing by external users, we implemented a series of major visual enhancements, to make Reactome more interactive and user-friendly:

1: In the detailed pathway diagrams, sub-pathways are now visually highlighted through shaded boxes.

2: Detailed pathway diagrams are now downloadable as PowerPoint slides, with pathway elements rendered as connected PowerPoint objects, allowing scientists to edit, modify, and re-use them to present their own pathway-related research results in presentations and publications.

3: The relationships between high level nodes in the Reactome hierarchy, for example between Adaptive Immune System, Innate Immune System, and Cytokine Signalling in Immune System, are now visualised through textbook-style diagrams developed by a professional illustrator. However, these diagrams are not static PNG images, but dynamic SVG graphics, allowing fast zooming and navigation, clicking to link to sub-pathways, as well as overlay of aggregated pathway analysis results. Both diagrams and their graphic components are open data and are released as a re-useable library for biomolecular visualisation to the scientific community.

Talk 3

From static visualisation to immersive analytics of biological networks

Falk Schreiber

University of Konstanz, Konstanz, Germany

Modern technologies used in the life sciences produce huge amounts of data about the building blocks of organisms. For an integrative, systems biology directed approach it is not sufficient to consider the biological entities alone but is necessary to study their interactions and to link the experimental data to the underlying biological processes. The key to this integration is biological networks and the development of methods for the modelling, analysis, simulation, and interactive visualisation of these networks and related multimodal data.

This talk presents different aspects of visualising and exploring biological network data, starting with a brief review of biological network visualisation in the past (1), looking at information visualisation approaches for presentation and exploration of biological networks (2-4) as well as standardised visual representations of biological information (5,6), and presenting novel developments for immersive analytics of multimodal biological data including networks (7). The talk will discuss methodological developments and present tools implementing these methods.

Talk 4

Multiscale Modeling and 3D Visualization of spatially-embedded Cytological Networks

Björn Sommer [1,2]

University of Konstanz, Konstanz, Germany[1], *Monash University, Melbourne, Australia*[2]

Since decades, the visualization of cytological networks is an important branch of biological visualization. A famous example is Gerhard Michal's Biochemical Pathways map which was introduced in 1968; its success is today partly reflected by the establishment of databases like KEGG. However, these 2D visualization-based approaches are widely dissociated from the spatial reality of the cell.
Recently, the arrival of stereoscopic 3D visualization in the consumer marked as well as the success of head-mounted displays – such as Oculus Rift – enables immersion into spatial data, with the large advantage to improve the understanding of cellular structures and their functioning.
Over the years, we developed a number of different cell modeling approaches which can be used to embed cytological networks into spatial structures, i.e., combining cell models segmented from 3D tomography with gene/protein-related data derived from databases such as KEGG or UniProt.
Based on the generated models, we created a number of cell visualization approaches which can be explored on multiple scales: from the local computer, to web browsers, to mobile phones and Head-mounted displays, and to large-scale virtual environments like the CAVE2.
In this talk we will give an overview of open source modeling, visualization and human-computer interaction techniques which can be used to create and present spatially-embedded biological networks in scientific as well as educational contexts.

Talk 5

Comprehensive signalling networks, Graphical representation of biological knowledge, Network modelling

Marcus Krantz

Humboldt-Universität zu Berlin, Berlin, Germany

The metabolic modelling community has established the gold standard for bottom-up systems biology with formalisation and analysis of genome-scale models. However, it is difficult to apply these methods to large-scale signalling networks. Signal transduction networks have a key feature that distinguishes them from metabolic networks: Their components can encode information in internal states (e.g. phosphorylation of specific residues) and through complexation. This causes the combinatorial complexity, which leads to severe scalability issues with explicit modelling formalisms. Hence, different tools are needed to formalise, visualise and analyse large-scale signalling networks. We present rxncon, the reaction-contingency language, as a tool to formalise, visualise and analyse large-scale models of signal transduction. The language uses a bipartite definition with reactions and contingencies, where reactions are possible events and contingencies define constraints on these events. By defining elemental reactions and contingencies in terms of elemental states, i.e. states at specific residues and domains, the model definition can be made as complex and precise as the empirical data requires, but not more. Hence, scalability is limited by knowledge rather than by methodological issues. We support the language with a compiler which automates export of a rxncon model to different graphical and executable formats, which enables visualisation and simulation of even large-scale models. In particular, the rxncon regulatory graph makes it possible to visualise large-scale models of signal transduction networks in full mechanistic detail. Most recently, we used rxncon to compile, visualise and analyse a comprehensive model of the cell cycle in budding yeast, encompassing 229 proteins, at full mechanistic detail. Taken together, the rxncon language and toolbox enables the formalisation, visualisation and analysis of large-scale mechanistic models of signal transduction networks.

Talk 6

Networks and Co-evolution in the Interpretation of Epigenetic Regulation

Alfonso Valencia

Barcelona Supercomputing Centre, Barcelona

My lab is interested in the computational developments in the interface of Network Biology and Co-evolution. The description of biological systems in terms of networks offers the possibility of combining complex information to analyse the properties of individual components in relation to their interaction partners. In the other hand, Co-evolution based methods are potentially able to provide additional levels of functional interpretation of the network relations.
I will first present our recent work on the prediction of protein interactions sites to introduce the basic concepts in co-evolution. In the second part of the talk, I will describe the use of co-evolution based approach to complement the information provided by a network of epigenetic components (i.e. chromatin binding proteins, DNA and Histone modifications) related by their co-localization at the genome level. Finally, I will show how the analysis of the network properties can help in the interpretation of complex relations between epigenetic components.

Talk 7

Application of the reduced Google Matrix approach for the analysis of directed biological networks

José Lages[1], Dima L. Shepelyansky[2] and Andrei Zinovyev[3]

[1]Institut UTINAM, Observatoire des Sciences de l'Univers THETA, CNRS, Université de Franche-Comté, 25030 Besançon, France; [2]Laboratoire de Physique Théorique du CNRS, IRSAMC, Université de Toulouse, CNRS, UPS, 31062 Toulouse, France; [3]Institut Curie, PSL Research University, Mines Paris Tech, Inserm, U900, F-75005, Paris, France

Signaling pathways represent parts of the global biological network which connects them into a seamless whole through complex direct and indirect (hidden) crosstalk whose structure can change during development or in pathological conditions. We suggest a novel methodology, called Googlomics, for the structural analysis of directed biological networks using spectral analysis of their Google matrices, using parallels with quantum scattering theory, developed for nuclear and mesoscopic physics and quantum chaos. We introduce the reduced Google matrix method for the regulatory biological networks and demonstrate how its computation allows inferring hidden causal relations between the members of a signaling pathway or a functionally related group of genes. We investigate how the structure of hidden causal relations can be reprogrammed as the result of changes in the transcriptional network layer during cancerogenesis. The suggested Googlomics approach rigorously characterizes complex systemic changes in the wiring of large causal biological networks.

Talk 8

Interactive web based curation of biological pathways with advanced layout and complexity management support

Ugur Dogrusoz

Bilkent University, Ankara, Turkey

Alterations in human metabolism that we determine again and again in individuals with a certain illness, but not in healthy ones, give us hints about how that illness occurs. With the help of recently developed genomics techniques at a very large scale, one can easily discover such alterations. Even though such discovery is useful in deciding those at risk for the associated disease, it does not help in discovery of the cause of the disease. For exactly this reason, we need to research how our metabolism works and where and why it fails by constructing pathways or maps specific to diseases.

Thus, it is inevitable to develop an interactive web based editor for constructing pathways from scratch or modifying existing ones in a standard notation such as Systems Biology Graphical Notation (SBGN). It needs to feature inspection, search and highlight mechanisms as well as advanced diagramming tools such as grid and alignment guidelines. In addition, the tool should have full support for compound (nested) structures to represent cellular compartments, molecular complexes, and sub-pathways with proper automated layout. Furthermore, operations for hiding or collapsing currently irrelevant parts of a map and then gradually showing or expanding them on demand are especially useful when managing large maps. Finally, ability to overlay experimental data on these maps would be very useful.

Talk 9

Characterization of the FGFR3 regulatory network in bladder tumors

Aura Ileana Moreno-Vega[1], Florent Dufour[1], Mohammed Elati[2], Isabelle Bernard-Pierrot[1], François Radvanyi[1]

[1]Institut Curie, Centre de Recherche, 75248 cedex 05 Paris Cedex, France ; [2] iSSB, CNRS, University of Evry, Genopole, 91030 Evry Cedex, France

Bladder cancer is the fifth most frequently diagnosed cancer in Europe. Fibroblast growth factor receptor 3 (FGFR3) is a tyrosine kinase receptor found frequently altered through mutations or gene fusions in bladder cancer. Much is known about the oncogenic properties of an altered FGFR3 in bladder cancer, yet its regulatory network remains little studied. This project is part of a larger multidisciplinary collaboration group in which bladder cancer regulatory networks have been inferred using the LICORN ("Learning cooperative regulation network) algorithm, as well as web-based functional analysis tools such as IPA and Enrichr. Network reconstruction was carried out using transcriptomic data from human bladder tumors, as well as from in vitro and in vivo models of altered FGFR3 expression and/or activity. Following gene regulatory network reconstruction, our aim is to functionally validate such networks in different bladder cancer cell lines; and thus identify key regulatory elements that could be potential therapeutic targets in the future. The functional validation shall include a small screen using either CRISPR-Cas9 or siRNAs technologies followed by the evaluation of the impact on cell viability and expression of potential target genes. Once the key elements have been identified; their regulatory role in the FGFR3 network shall be confirmed by immunoprecipitation analysis; analysis of post-translational modifications, ChIP-seq etc.

Talk 10

From gene variants to network variants: a new database for understanding diseases and drugs

Minoru Kanehisa, Mao Tanabe

Institute for Chemical Research, Kyoto University, Uji, Kyoto, Japan

Linking the diversity of genomes to the diversity of organisms in the tree of life has been one of the main objectives of the KEGG database project. We developed the KEGG PATHWAY database as a reference knowledge base for understanding conserved and diverse functions of organisms, which is accomplished by the process of KEGG pathway mapping where genes in the genome are mapped to nodes of molecular networks (KEGG pathway maps). Unfortunately, however, KEGG PATHWAY is not sufficient for understanding the diversity among human genomes, especially in relation to diseases and drugs. KEGG pathway maps for cancers, for example, contain oncogenes and tumor suppressor genes with genetic alterations, which are marked in red but are linked to normal genes. Similarly, gene-disease associations are accumulated in the KEGG DISEASE database, but the details of genetic alterations are not given. Thus, we have started developing a new database named KEGG NETWORK for "perturbed" molecular networks involving human diseases and drugs. KEGG NETWORK is a collection of network elements, which are defined in a way somewhat similar to KEGG modules. Based on published literature we accumulate knowledge on how, for example, signaling pathways in cancer are perturbed by gene variants, viruses and environmental factors. Gene variants are linked to ClinVar, dbSNP, and other databases, so that KEGG NETWORK can be used for interpretation of personal genome sequences.

Talk 11

Biomarker discovery in diabetes: A network-based approach

Mark Ibberson[1]

Vital-IT, SIB Swiss Institute of Bioinformatics, Lausanne, Switzerland[1]

Type 2 diabetes (T2D) is characterized by chronically high blood glucose levels that can lead to serious complications such as cardiovascular disease, kidney failure and blindness. Current treatment strategies rely on a single biomarker: elevated blood glucose (or surrogate markers such as HbA1c) and glucose intolerance, which is elevated when the disease has often already progressed to a stage where beta cell damage has occurred. The hope is that in the future new biomarkers will be available to detect high-risk individuals earlier and adapt treatment strategies to provide better long-term management of the disease.
In this seminar I will describe a recent large European study seeking to bridge the gap between mouse models of T2D and human disease to try to find biomarkers for early disease detection. In this study, metabolically challenged mice were followed over time and various measurements including plasma lipidomics and islet gene expression were taken. A second study was subsequently performed aimed at trying to validate the main findings of the mouse experiment using two independent human cohorts. I will discuss the methodology and results from these studies from a network biology perspective. One of the outcomes of the studies was the discovery that a particular class of lipid was elevated in the plasma of individuals several years before T2D diagnosis. Lipids of this class may therefore represent prognostic biomarkers for early detection of T2D.

Talk 12

Integrated Modelling and Testing Strategies supporting Systems Toxicology and Evidence-based Safety Assessment

Tatyana Doktorova, Barry Hardy, Ahmed Abdelaziz, Maja Brajnik, Joh Dokler, Daniel Bachler, Johan Nystrom, Noffisat Oki, Oana Florean, Lucian Farcal, Thomas Exner

Douglas Connect GmbH, Basel, Switzerland

In this presentation we discuss using case study examples critical ingredients for the robust implementation of integrated modelling and testing strategies supporting systems toxicology and evidence-based safety assessment. We will focus on the following ingredients:

a) Defining the information requirements and knowledge framework for safety assessment of a chemical ingredient or mixture;
b) Using existing information in an evidence-based approach against a knowledge framework including molecular and adverse outcome pathways;
c) Using modelling to fill information gaps and to extrapolate between different contexts of key biological events;
d) Guiding experimental design for generating maximum value information for key biological events in a systems modelling approach and integrated testing strategy;
e) Integrating data and modelling results in reproducible workflows supporting evidence and its judgement.

Talk 13

Detect Liver Toxicity through Causal Biological Network Model and Computational Algorithm.

Justyna Szostak, Marja Talikka, Florian Martin, Iro Oikonomidi, Giuseppe Lo Sasso, Manuel C. Peitsch, and Julia Hoeng

Philip Morris Products S.A. (part of Philip Morris International group of companies), Quai Jeanrenaud 5, 2000 Neuchâtel, Switzerland

With the progression of omics technologies, we have developed Causal Biological Network Models that use high-throughput data to predict early toxicity. Previously developed network models, focused on pulmonary and cardiovascular disease, demonstrated the relevance of the network approach in the quantification of the impact of exposures on biological processes. Recently we have focused on modelling the xenobiotic metabolism process that results in the elimination of chemical or xenobiotic substances (i.e. compounds foreign to the body). The enzymes involved in this process convert xenobiotics into hydrophilic derivatives that are then eliminated through excretion into the aqueous compartments of the tissues. Since the liver is the primary site of xenobiotic metabolism in mammals, we built a new suite of network models that represent biotransformation and chemical elimination involved in Phase I, Phase II and Phase III xenobiotic metabolism in the liver.
Nuclear receptors such as the aryl hydrocarbon receptor (AR), orphan nuclear receptors, and nuclear factor-erythroid two p45-related factor 2 (Nrf2) play a critical role in all phases of xenobiotic metabolism. While Phase I and II xenobiotic metabolism network models largely describe the transformation of xenobiotic into hydrophilic product, Phase III model focuses on the xenobiotic transport and excretion. The combination of the network models with transcriptomics data and computational scoring algorithms could be a valuable approach for the pharmacological industry to predict early drug toxicity.

Talk 14

A multi-scale model for investigating TRAIL resistance in multi-cellular tumor spheroids

François Bertaux[1], Dirk Drasdo[2] and Gregory Batt[3,4]

[1] *Imperial College, London, UK,* [2]*Inria and Sorbonne Universités, Paris, France,* [3]*Inria and Université Paris-Saclay, Palaiseau, France, and* [4] *Institut Pasteur, Paris, France*

TRAIL is an anti-cancer drug that induces apoptosis selectively in cancer cells. Unfortunately even high doses of TRAIL do not kill all cells and subsequent TRAIL treatments are transiently less effective. Despite extensive studies, a mechanistic understanding of these phenomena is still lacking. In this talk, I will present an extension of a previously-proposed model describing TRAIL signal transduction in Hela cells (Spencer et al, Nature 2011) with simple models accounting for the turnover of the proteins involved in the pathway at the cell level and the dynamics (growth and death) of the cell population in monolayers and in 3D spheroids. This model is minimalistic in the sense that it uses default values from the literature for all but two parameters. Yet, it explains the existence of survivors (fractional killing), the increased resistance of the surviving population and its transient aspect. The analysis of model predictions calls into question the importance of survival pathways and highlights the critical role of the stochastic turnover of proteins in zymogen-based pathways in which activated forms are rapidly degraded.

Talk 15

Exhaustive Petri net modeling to infer mechanisms of genetic interactions

Patrick Kemmeren[1], Saman Amini[1], Frank Holstege[1]

Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

Understanding the molecular mechanisms of genetic interactions and their relation to various biological processes is crucial to decipher pathway organization, cellular organization and disease progression. Several potential mechanisms have been suggested before. Many of these however lack systematic and exhaustive exploration of the complete modeling space. Here, an exhaustive petri net modeling approach is presented to systematically investigate and infer mechanisms of genetic interactions. Using twenty-six gene pairs between signaling proteins and gene-specific transcription factors all genetic interaction patterns are first grouped in different types. Inversion is a genetic interaction type primarily associated with gene-specific transcription factors and investigated further. Exhaustive petri net modeling is then employed to simulate over nine million four node models with two regulatory nodes, two downstream nodes and quantitative edges. This demonstrates that inversion can be explained using a minimum of three nodes and that a quantitatively regulatory difference is a mechanistic requirement when observing inversion. In combination with a fourth node, buffering is the most frequently observed genetic interaction pattern together with inversion. Taken together these results show that the petri net modeling approach can be successfully applied to systematically infer mechanisms of genetic interactions and that this approach is useful to infer common patterns underlying genetic interactions.

Talk 16

Integration of chromatin structure dynamics in the regulatory network governing cell fate acquisition

Valeriya Malysheva[1,2], Marco-Antonio Mendoza-Parra[1], Matthias Blum[1,3] and Hinrich Gronemeyer[1]

Equipe Labellisée Ligue Contre le Cancer, Department of Functional Genomics and Cancer, Institut de Génétique et de Biologie Moléculaire et Cellulaire, Centre National de la Recherche Scientifique, UMR7104, Institut National de la Santé et de la Recherche Médicale, U964, Université de Strasbourg, Illkirch, France[1], Nuclear Dynamics Programme, The Babraham Institute, Babraham Research Campus, Cambridge CB22 3AT, UK[2], European Molecular Biology Laboratory, European Bioinformatics Institute, Wellcome Genome Campus, Cambridge CB10 1SD, UK[3]

Cell fate acquisition and transition are fundamental processes in the ontogeny of multicellular organisms and aberrations along these processes can generate pathologies. Previously we have defined the dynamic gene-regulatory networks underlying endodermal and neuronal differentiation induced by the morphogen all-trans retinoic acid (RA). Here we assessed the contribution of the chromatin interactome to commitment and selective acquisition of these two cell fates.

To understand the molecular features of the particular biological system and to predict its response to effectors we have developed a regulatory network approach that integrates transcription factor-target gene (TF-TG) relationships, chromatin states (TF ChIP-seq and FAIRE-seq) and chromatin conformation (HiC) data. Using this approach, we reconstructed Gene Regulatory Network that indicated key regulatory elements responding to the initial signal of RA, driving neuronal and endodermal cell differentiation.

We observed previously unrecognized highly dynamic re-wiring of chromatin interactome during cell differentiation. Long-range chromatin interactions are massively reorganized, erasing the majority of the interactome of undifferentiated cells and establishing new interactions already 6 hours after RA treatment.

Our data reveal an enormous capacity of the morphogen to reorganize long- range chromatin interactions as a means to “read” distant epigenetic signals to drive cell fate acquisition and suggest that the differential establishment of chromatin contacts directs the acquisition of the two cell fates.

Talk 17

GEMMER: GEnome-wide software for Multi-scale Modeling data Extraction and Representation

Matteo Barberis, Thierry D.G.A. Mondeel, Frédéric Crémazy

Synthetic Systems Biology and Nuclear Organization, Swammerdam Institute for Life Sciences, University of Amsterdam, Amsterdam, The Netherlands

Building multi-scale models of biological processes spanning multiple spatial-temporal-functional scales is currently a challenge in computational biology. A critical step in this process is the identification of biological function and spatial localization of interactions that occur among a set of molecules. Several tools to visualize such interactions exist; however, none of these combine the desired properties of: (i) being specific for budding yeast, (ii) allowing simultaneous filtering, clustering and coloring of molecules that are (iii) based on function, abundance and localization.

Here, we present GEMMER (GEnome-wide software for Multi-scale Modeling data Extraction and Representation), a web-based tool that allows to generate a high quality visualization of physical and genetic interactions between proteins/genes in budding yeast. Its novel contribution is to allow for the unification of (i) general and function annotation from Saccharomyces Genome Database (SGD), (ii) localization and abundance data from both CYCLoPs and Yeast GFP Fusion Localization databases. The tool allows for the simultaneous visualization of an interaction network with colors, clustering and size varying across functional, abundance and spatial scales. Specifically, nodes in an interaction network may be clustered and colored based on localization data and abundance measurements. Furthermore, interactions may be filtered out based on number of total number of experiments, of unique experimental methods, or of number of publications revealing an interaction.

GEMMER utilizes the JavaScript library D3js, AJAX, JSON and PHP around a core application written in Python. A user-friendly form on the main web page allows user input, e.g. which molecule(s) to center the visualization around and how to filter, cluster and color the interactors. Visualization and export options are in SVG format and Excel. Furthermore, for each interaction, hyperlinks to the experimental evidence in the literature are provided.

The authors aim for GEMMER to become a go-to tool for the multi-scale modeling community.