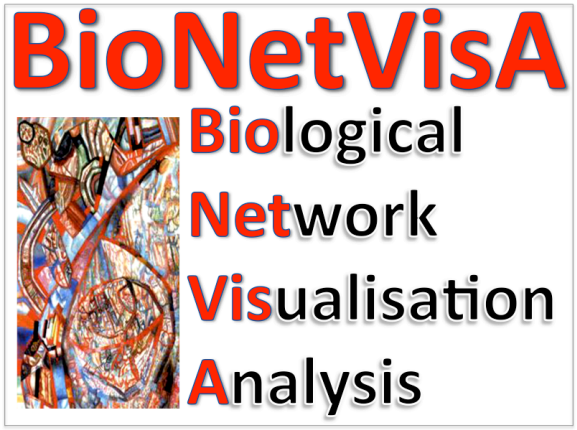

BioNetVisA workshop

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

World Forum Convention Centre
Churchillplein 10
2517 JW The Hague
The Netherlands

Room
Oceania Foyer

4 September 2016

This year **BioNetVisA** and **LogicBio** workshops have been fused. The speakers of the Session 3 entitled 'Modelling of biological networks' were selected from the abstracts submitted to the **LogicBio** workshop.

Organizers and program co-chairs of LogicBio workshop:
Laurence Calzone (Institut Curie, Paris, Fance)
Pedro T. Monteiro (INESC-ID, Lisbon, Portugal)

Visit https://logicbio.sciencesconf.org for full list of the organizing committee members and details on the LogicBio workshop.

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)

Web site

http://www.eccb2016.org/programme/workshops/w10
http://sysbio.curie.fr/bionetvisa

Contact

bionetvisa@curie.fr

BioNetVisA workshop program

Session 1
Development of biological network databases and platforms

Chair: Robin Haw (Ontario Institute for Cancer Research, Toronto, Canada)

09.00-09.25

Comprehensive representation of disease mechanisms
Alexander Mazein (European Institute for Systems Biology and Medicine, Lyon, France)

09.25-09.40

Reactome: a curated knowledgebase of biomolecular pathways
Antonio Fabregat (EMBL_EBI, Germany)

09.40-09.55

Computational reconstruction of NFkB pathway interaction mechanisms during prostate cancer
Daniela Börnigen (Harvard University, Boston, USA)

09.55-10.10

LitPathExplorer: A visual tool for exploring literature-enriched pathway models
Axel J. Soto (University of Manchester, Manchester, UK)

10.10-10.30

Posters flash presentations
Nicolas Alcaraz (University of Southern Denmark, Odense, Denmark)
Markus List (University of Southern Denmark, Odense, Denmark)
Anna Zhukova (Institut Pasteur CNRS – Paris, France)
Åsmund Flobak (Norwegian University of Science and Technology, Trondheim, Norway)
Martina Kutmon (BiGCaT, NUTRIM, Maastricht University, The Netherlands)
Martin Schaefer (The Barcelona Institute of Science and Technology, Barcelona, Spain)
Adrien Fauré (Yamaguchi University, Yamaguchi City, Yamaguchi, Japan)

10.30-11.00 Posters and Coffee break (Foyer, ground floor)

11.00-11.40

Keynote lecture
A systems approach to immune inter-cellular communication: from a cell-centric view to the complexity of the tumor microenvironment
Vassili Soumelis (Institut Curie, Paris, France)

Session 2
Data visualisation and analysis in the context of biological networks in research and medicine

Chair: Lodewyk Wessels (Netherlands Cancer Institute, Amsterdam, Netherlands)

11.40-12.05

Network-based approaches to defeat cancer: quantifying module activity
Emmanuel Barillot (Institut Curie, Paris, France)

12.05-12.30

A refreshing look at Reactome Functional interaction Network
Robin Haw (Ontario Institute for Cancer Research, Toronto, Canada)

12.30-13.30 Lunch (Foyer, ground floor)

13.30-13.55

Metabolic Networks: Visual Analysis of Elementary Flux Modes
Marie Beurton-Aimar (Université Bordeaux 1, Bordeaux, France)

13.55-14.35

Keynote lecture
Integrative network-based analysis for subtyping and cancer driver identification
Kathleen Marchal (Ghent University, Ghent, Belgium)

14.35-15.30 Posters and Coffee break (Foyer, ground floor)

Session3
Modelling of biological networks

Chair: Marie Beurton-Aimar (Université Bordeaux 1, Bordeaux, France)

15.30-15.45

In silico knockout experiments based on Petri net models
Jennifer Scheidel (Johann Wolfgang Goethe-University Frankfurt am Main, Frankfurt am Main, Germany)

15.45-16.00

Modelling of T cell co-inhibitory pathways to predict anti-tumour responses to checkpoint inhibitors
Céline Hernandez (IBENS, Paris, France)

16.00-16.15

Constructing and analyzing disease-specific or developmental stage-specific transcription factor and miRNA co-regulatory networks
Maryam Nazarieh (Saarland University, CBI, Saarbrucken, Germany)

16.15-16.30

Predictive logical modelling of TLR5 and TCR cooperation for CD4 T cell activation
Otoniel Rodríguez-Jorge (CIDC, Mexico and IBENS, Paris, France)

16.30-16.55

Logic models to predict continuous outputs based on binary inputs with an application to personalized cancer therapy
Theo Knijnenburg (Institute for Systems Biology, Seattle, USA)

BioNetVisA workshop abstract

Talk 1
Comprehensive representation of disease mechanisms

Alexander Mazein[1], Marek Ostaszewski[2], Inna Kuperstein[3], Mansoor Saqi[1], Bertrand De Meulder[1], Feng He[4], Irina Balaur[1], Diane Lefaudeux[1], Johann Pellet[1], Piotr Gawron[2], Stephan Gebel[2], Andrew Parton[5], Steven Watterson[5], Nathanaël Lemonnier[6], Pierre Hainaut[6], Markus Ollert[4], Emmanuel Barillot[3], Andrei Zinovyev[3], Rudi Balling[2], Reinhard Schneider[2] and Charles Auffray[1]

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Large amount of high-throughput data become available in the effort to better understand diseases. Despite the availability of various network-based approaches, tools for disease-specific functional analysis are greatly underdeveloped and it becomes increasingly important to advance in systematic data interpretation and hypothesis generation. The direct approach to solve this problem is developing highly accurate comprehensive computerized representations of disease mechanisms on the level of cellular and molecular interactions (Fujita et al., 2013, PMID 23832570; Kuperstein et al., 2015, PMID 26192618; Mizuno et al., 2016, PMID 26849355).

Recent advances in systems biology made it possible to unambiguously represent biological processes in a consistent way (Le Novère, 2015, PMID 25645874), made this information human- and machine-readable so it can be efficiently explored by computational methods. Disease-specific representations are developed in CellDesigner (www.celldesigner.org) following the Systems Biology Graphical Notation standard (www.sbgn.org). The involvement of domain experts from different groups ensures that different points of view are considered and all the disease hallmarks are covered and adequately represented. We present a concept of the DISEASE MAPS as a community effort and as a collection of reference resources for making sense of omics data in studies focused on a particular disease. Essentially a disease map provides a consensus review on the known disease mechanisms in the format of interconnected metabolic, signalling and gene regulatory pathways, and can be used as the basis for hypothesis generation. We describe our experience on developing disease maps for Parkinson's disease, asthma and cancer, and demonstrate how these resources can be used for data visualisation and interpretation. Because these maps are developed using a strict computational format, they can be used for developing dynamic predictive mathematical models. While being complementary to generic pathway enrichment tools (such as freely available g-Profiler and DAVID, and commercial Ingenuity Pathway Analysis and MetaCore), the disease maps focus on the integration of information into a single hierarchically-organised network, thus enabling analysis using the full power of advanced systems biology approaches in the area of systems medicine. To progress with this approach we propose building on the best practices and lessons learned from previous projects and applying shared standards, tools and protocols for generating high-quality representations and enabling the exchange of reusable pathway modules (e.g. inflammation, central metabolism, etc.). We envision this strategy will facilitate powerful advances in systems medicine for understanding disease mechanisms, cross-disease comparison, finding disease comorbidities, suggesting drug repositioning, generating new hypotheses, and after careful validation, redefining disease ontologies based on their endotypes-confirmed molecular mechanisms.

Talk 2 and Poster 1

Reactome: A curated knowledgebase of biomolecular pathways

Antonio Fabregat

EMBL_EBI, UK

Reactome (http://www.reactome.org) is a free, open-source, curated and peer-reviewed knowledgebase of biomolecular pathways. Its aim is to provide intuitive bioinformatics tools for visualisation, interpretation and analysis of pathway knowledge to support basic research, genome analysis, modeling,
systems biology and education.
Pathways are built from connected “reactions” that encompass many types of biochemical events. Reactions are derived from literature and must cite a publication that experimentally validates them. Pathways are authored by expert biologists and peer reviewed before incorporation into the database. 9,584 reactions in Reactome cover 9,238 human gene products (12,527 including IntAct interactors), supported by 22,838 literature references.
Users can search for proteins or compounds and see details of the complexes, reactions and pathways they participate in. Pathway diagrams allow users to examine the molecular events that constitute the steps in pathways and to view details of the proteins, complexes and compounds involved.
Different forms of pathways analysis can be performed with the Reactome analysis tools. Users can submit a list of identifiers for overrepresentation analysis or submit quantitative datasets, such as microarray data, for expression analysis. Results of these analyses are overlaid onto the Pathways Overview and Diagram Viewer for easy navigation and interpretation.
Interaction data from multiple resources can be used to expand pathways. Interactors from IntAct are included by default in the search feature and can be taken into account in the analysis service. Finally, pathways or all Reactome content can be downloaded in many formats including TSV, CSV, PDF, SBML, BioPax and PSI-MITAB.

Talk 3

Computational reconstruction of NFkB pathway interaction mechanisms during prostate cancer

Daniela Börnigen[126], Svitlana Tyekucheva[3], Xiaodong Wang[5], Jennifer R. Rider[4], Gwo-Shu Lee[5], Lorelei A. Mucci[4], Christopher Sweeney[5], Curtis Huttenhower[12#]

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Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA 02115, USA[3]
Department of Epidemiology, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA 02115, USA[4], Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, USA[5]
Now at: University Heart Center Hamburg-Eppendorf, Clinic for General and Interventional Cardiology, Hamburg, Germany[6]
 # Corresponding author: Tel: +1-617-432-4912; Fax: +1-617-432-5619; Email: chuttenh@hsph.harvard.edu

Molecular research in cancer is one of the largest areas of bioinformatic investigation, but it remains a challenge to understand biomolecular mechanisms in cancer-related pathways from high-throughput genomic data. This includes the Nuclear-factor-kappa-B (NFκB) pathway, which is central to the inflammatory response and cell proliferation in prostate cancer development and progression. Despite close scrutiny and a deep understanding of many of its members' biomolecular activities, the current list of pathway members and a systems-level understanding of their interactions remains incomplete.

Here, we provide the first steps toward computational reconstruction of interaction mechanisms of the NFκB pathway in prostate cancer. We identified novel roles for ATF3, CXCL2, DUSP5, JUNB, NEDD9, SELE, TRIB1, and ZFP36 in this pathway, in addition to new mechanistic interactions between these genes and 10 known NFkB pathway members. A newly predicted interaction between NEDD9 and ZFP36 in particular was validated by co-immunoprecipitation, as was NEDD9's potential biological role in prostate cancer cell growth regulation. We combined 653 gene expression datasets with 1.4M gene product interactions to predict the inclusion of 40 additional genes in the pathway. Molecular mechanisms of interaction among pathway members were inferred using recent advances in Bayesian data integration to simultaneously provide information specific to biological contexts and individual biomolecular activities, resulting in a total of 112 interactions in the fully reconstructed NFkB pathway: 13 (11%) previously known, 29 (26%) supported by existing literature, and 70 (63%) novel. This method is generalizable to other tissue types, cancers, and organisms, and this new information about the NFkB pathway will allow us to further understand prostate cancer and to develop more effective prevention and treatment strategies.

Talk 4 and Poster 2 (demo)

LitPathExplorer: A visual tool for exploring literature-enriched pathway models

Axel J. Soto, Chrysoula Zerva, Riza Batista-Navarro and Sophia Ananiadou

National Centre for Text Mining, School of Computer Science, University of Manchester, Manchester, UK

Pathway model curation is a time-consuming, knowledge-intensive task that is often guided by evidence from literature. In order to accelerate curation, a number of text mining-based efforts have sought to provide evidence from scientific literature by extracting information pertaining to biomedical relationships, e.g., protein-protein, drug-target interactions, automatically. Currently, most tools for visualising pathway model reconstructions neither make such literature-based evidence easily accessible to their users, nor do they provide a means for confidence-driven filtering of text-mined interactions. Thus, they often require users to cross-reference external literature sources, consolidate evidence passages, and subsequently assess on their own, the reliability of automatically mined interactions. To address these issues, we developed LitPathExplorer, a tool that provides richer visualisation and exploration of reconstructions by integrating literature-based evidence, thus allowing curators to easily frame a pathway interaction in the context of the source statements they were based on. The tool builds upon the JavaScript-based D3 library and accepts any BioPAX-formatted pathway model. Interactions contained in the model are enriched with literature-derived information, based on the output of our text mining workflows which also provide a consolidated confidence value. The enriched model is displayed as a graph where nodes that correspond to biomolecular events, e.g., phosphorylation, are connected to other nodes representing entities participating in such events, e.g., proteins and small molecules. A key feature of LitPathExplorer is its support for visual exploration and flexible querying. This allows users to filter pathway interactions by specifying event attributes that are of interest to them, or by setting a threshold for literature-based confidence values. By enabling users to focus on interactions with more compelling evidence, the tool aids biologists in identifying interactions to prioritise in their experiments. To facilitate interoperability with other modelling standards, e.g., SBML, we are currently wrapping LitPathExplorer as a Garuda gadget.

Talk 5

A systems approach to immune inter-cellular communication: from a cell-centric view to the complexity of the tumor microenvironment

Vassili Soumelis

Department of immunology, Institut Curie, Paris

Inter-cellular communication is critical to coordinate cellular function in tissue during steady state and inflammation. Few efforts have been done to reconstruct cell communication networks. In addition, the molecular events shaping communication and connectivity within inter-cellular networks are not known. This question is particularly relevant to immune cells during controlled and dysregulated inflammation. We have developed an original systems biology framework to reconstruct cell connectivity networks based on transcriptomics data of purified cell types. In cultured human dendritic cells (DC), we could show that LPS activation promotes an increased cell connectivity, which is controlled by an IL-10 auto-regulatory loop. Blocking endogenous IL-10 increased communication of DC with 12 distinct cell types. Experimental validation was obtained for four communication channels. Results show that a single molecule can control communication of one cell with multiple other cell types. We are now applying this and other strategies to the tumour microenvironment, in order to attempt deciphering the complex cellular networks engaged during tumour inflammation. A combination of molecular and cellular data can be used to infer intercellular communication paths, with the ultimate perspective of reconstructing and modelling complex cell networks. These should be valuable tools to better understand the organisation of anti-tumour immune responses and guide therapeutic manipulations.

Talk 6

Network-based approaches to defeat cancer: quantifying module activity

Emmanuel Barillot

Mines Paris Tech, PSL Research University, Institut Curie, INSERM, U900, F-75005, Paris, France

Four decades of cancer molecular biology research have led to the identification of many molecular determinants of this pathology, and resulted in significant progress in medical treatment. First concepts like magic bullets and oncogene addictions were introduced with the idea that one single gene might have causal role in cancer, or that a strategy of treatment could be focused on one supposedly single gene fragility point. Though it bore fruits in biology and in clinics, this reasoning has shown its limitations when it appeared that the molecular pathways governing tumorigenesis and tumor progression are tightly interconnected in a complex network of interactions which covers essential cell processes named hallmarks of cancer (DNA repair, cell proliferation, cell death, cell differentiation, immune response…), and whose crosstalks, feedbacks and compensatory mechanisms invalidated the former simplistic reasoning and on the clinical side provided a profusion of tumor escape paths to existing treatments. The concept of synthetic pairwise interactions between genes that jointly control phenotypes was then introduced, and shed light on cancer biology as well as it opened perspectives of new therapeutic strategies, that exploits the availability of a growing list of targeted inhibitors which are able to inactivate specifically one given protein. The principle of synthetic pairwise interaction is very fruitful, but also shows limits, and it appears today that the modeling of tumor signaling network is required to explore these interactions, explain the biology of cancer, and design innovative treatment strategies. The talk will present several steps in this direction including the modelling and prediction of synthetic interaction in the context of cancer signalling networks and the predictoin of necessary conditions for the occurrence of metastasis. Consequences in terms of clinical treatment strategies will be discussed.

Talk 7 and Poster 3

A Refreshing Look at the Reactome Functional Interaction Network

Robin Haw

OICR, Toronto, Canada

The Reactome Functional Interaction (FI) network was developed to significantly enlarge protein coverage for high-throughput data analysis by merging curated pathways in Reactome and other reaction-network databases with protein pairwise relationships from other public sources. We have extended the FI network to encompass interactions between transcription factors and their targets from the ENCODE data sets, and miRNAs and their targets from miRecords and miRTarBase. The current version of the FI network contains 327,867 functional interactions, covering over 12,000 SwissProt identifiers (about 60% of total human genes).

ReactomeFIViz, the Cytoscape app based on the Reactome FI network, provides intuitive, user-friendly and rich graphical interfaces for researchers to fulfill pathway and network-based data analysis to discover clinically-relevant disease biomarkers. Using a set of genes, or a gene expression data set, users can carry out network-based analyses by constructing a FI sub-network, search for network modules, and annotate the sub-network or its modules. Users can also visualise Reactome knowledgebase pathways using Cytoscape, either in their native pathway diagram view or expanded FI network view. Using either visualisation approach, users can perform pathway enrichment analysis on a set of genes, and check genes in identified pathways. For prognostic biomarker discovery, users can perform survival analysis using the univariate Cox proportional hazard model using a built-in command. We have recently developed a method to convert Reactome pathways into probabilistic graphical models (PGMs) by adopting the PARADIGM approach to allow users to create predictive models of the effect of perturbing multiple genes on pathway activities.

URL: http://apps.cytoscape.org/apps/reactomefiplugin

Talk 8 and Poster 4

Metabolic Networks: Visual Analysis of Elementary Flux Modes

Marie Beurton-Aimar[1] Joris Sansen[1], Ngoc Tung Nguyen-Vu[2]

LaBRI, CNRS5800, Univ Bordeaux, France[1], EMBL-EBI, Cambridge, UK[2]

Metabolic networks are characterized by their size and the high level of interactions between nodes. Several formalisms can be used to analyze these networks, most of them use tools based on graph theory. Searching Elementary Flux Modes (EFMs) is a way to identify feasible routes through the metabolic networks respecting steady state constraints (Schuster et al. Nat. Biotechnol., 18 (3), 2000). EFMs are useful to find essential metabolites/reactions or to discover alternative process when a gene is knocked-out. Nevertheless, it is well-known that computing EFMs could produce huge results, impracticable to analyze by hands. The lack of user-friendly tools to help biologists to analyze EFMs limits drastically their spread into the community.

We proposed a graphical tool to classify EFMs following shared common set of reactions. This tool, available through a web interface, uses a plot technique based on parallel coordinates (A. Inselberg. The Visual Computer, 1985) to build a diagram of EFMs. It allows the user to visualize associated reactions within different EFMs. A pre-processing step based on K-mean clustering provides a customized view of EFMs as a set of data aggregated by value, depending on if the reaction is present (taking into account the forward or backward direction) or if it is missing. In a second step, editing operations available in the interface allows the user to interact with the representation, making possible to customize the axes order, thus emphazing links between reactions, or to highlight subsets of interest for example, guiding the user for the dataset exploration. To conclude, this editor offers a way to dynamically experiment arrangements between axes, in order to extract new information from EFMs sets.

Talk 9 and Poster 5

Integrative network-based analysis for subtyping and cancer driver identification

Kathleen Marchal[1,2,3,4], Lieven Verbeke[1,2,4], Sergio Pulido-Tamayo[1,2,4], Musthofa Musthofa[1,2,4]

[1] Dept. of Information Technology (INTEC, iMINDS), Ghent University, Belgium
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[4] Department of Genetics, University of Pretoria, South Africa

Inter-cellular communication is critical to coordinate cellular function in tissue during steady state and inflammation. Few efforts have been done to reconstruct cell communication networks. In addition, the molecular events shaping communication and connectivity within inter-cellular networks are not known. This question is particularly relevant to immune cells during controlled and dysregulated inflammation. We have developed an original systems biology framework to reconstruct cell connectivity networks based on transcriptomics data of purified cell types. In cultured human dendritic cells (DC), we could show that LPS activation promotes an increased cell connectivity, which is controlled by an IL-10 auto-regulatory loop. Blocking endogenous IL-10 increased communication of DC with 12 distinct cell types. Experimental validation was obtained for four communication channels. Results show that a single molecule can control communication of one cell with multiple other cell types. We are now applying this and other strategies to the tumour microenvironment, in order to attempt deciphering the complex cellular networks engaged during tumour inflammation. A combination of molecular and cellular data can be used to infer intercellular communication paths, with the ultimate perspective of reconstructing and modelling complex cell networks. These should be valuable tools to better understand the organisation of anti-tumour immune responses and guide therapeutic manipulations.

Talk 10 and Poster 6

In silico knockout experiments based on Petri net models

Jennifer Scheidel, Leonie Amstein, Börje Schweizer, Jörg Ackermann, Ina Koch

Molecular Bioinformatics, LOEWE program Ubiquitin Networks of the State of Hesse, Cluster of Excellence Frankfurt Macromolecular Complexes, Institute of Computer Science, Johann Wolfgang Goethe-University Frankfurt am Main, Frankfurt am Main, Germany

The knockout analysis is a worthwhile method to observe the effect of a specific protein on the systems behavior. Mathematical modeling provides the possibility for *in silico* knockouts. Often only a small fraction of knockout results obtained from a systematical *in silico* knockout analysis was experimentally investigated. Besides the standard Petri net analysis techniques, such as covered by transition invariants, and the biological interpretability of each transition invariant [1], *in silico* knockout experiments are useful for model verification and experiment planning.

We developed a new tool called SiKnock to perform and visualize *in silico* knockout experiments. Based on Petri net models we introduce a new concept of *in silico* knockout analysis to ensure the correct prediction of the systems behavior. SiKnock provides single, double, and multi knockout analysis, visualizes the results as a knockout matrix and provides a graphical user interface. We applied the method to study the autophagic degradation pathway of the pathogen Salmonella Typhimurium. We compared the knockout results with published knockout or knockdown experiments and ensured the biological correctness of the model structure. We found knockout behavior known in literature and generated new hypotheses for experiments, for example, knocking out the autophagy receptor NDP52 (nuclear dot protein 52 kDa) predicted no influence on the recruitment of OPTN (optineurin) to ubiquitinated Salmonella Typhimurium.

Talk 11 and Poster 7

Modelling of T cell co-inhibitory pathways to predict anti-tumour responses to checkpoint inhibitors

Céline Hernandez[1], Wassim Abou-Jaoudé[1], Romain Roncagalli[2], Bernard Malissen[2], Morgane Thomas-Chollier[1], Denis Thieffry[1]

Computational Systems Biology team, Institut de Biologie de l'Ecole Normale Supérieure (IBENS), CNRS UMR8197, INSERM U1024, Ecole Normale Supérieure, PSL Research University, F-75005 Paris, France[1]
Centre d'Immunologie de Marseille-Luminy, UM2 Aix Marseille Université, INSERM U1104, CNRS UMR7280, 13288 Marseille, France[2]

In recent years, it has been recognized that T cells have a reduced ability to eliminate cancer cells and that expression of co-inhibitors at their surface accounts for their compromised function. By blocking the functions of these co-inhibitors, therapeutic antibodies (checkpoint inhibitors) have become standard treatment for metastatic melanoma, leading to a revival in the study of T cell co-inhibitors. However, our understanding of the immunobiology of T cell co-inhibitors and of their harmful role during anti-tumour responses is incomplete. Despite a few biochemical studies, a mechanistic understanding at the system-level of the modulation of T cell function by co-inhibitors has remained elusive.

To overcome these limitations, we aim at defining at the system-level the mechanisms through which co-inhibitory molecules such as PD-1 and CTLA-4 impede T cell functions. To reach our goal, we combine high-throughput analysis with computational methods in order to map TCR co-signalling pathways and predict cell responses to perturbations. First, we focus on the development of comprehensive annotated molecular maps through both manual curation of scientific literature and automated queries to public databases. These maps will be used as a support to analyse high throughput data (proteomics, epigenomics, ...), which will be in turn used to refine them. Next, these maps will be translated into a sophisticated logical model recapitulating the observed cellular behaviour. Finally, this model will be used to predict cell response to single or multiple perturbations, and thereby pave the way to the delineation of novel experiments.

This integrated system-level view of the mechanisms of action of key T cell co-inhibitors in cancer will further provide a rationale for designing and evaluating drugs targeting T cell co-inhibitory pathways in anti-cancer immunotherapy.

Talk 12 and Poster 8

Constructing and analyzing disease-specific or developmental stage-specific transcription factor and miRNA co-regulatory networks

Maryam Nazarieh[1,2] Thorsten Will[1,2], Mohamed Hamed[1,2,3] Christian Spaniol [1], Volkhard Helms[1]*

Center for Bioinformatics (CBI) Saarbruecken - Germany[1]
Graduate School of Computer Science Saarbruecken - Germany[2]
Institute for Biostatistics and Informatics in Medicine and Ageing Research Rostock - Germany[3]

TFmiR is a freely available web server for integrative analysis of combinatorial regulatory interactions between transcription factors, miRNAs and target genes that are involved in disease processes in human [1]. To better characterize the differential cellular processes at molecular level from a network perspective in normal and disease conditions in human and now also in mouse, we have extended the published version by various new features such as the construction of tissue-specific networks. Besides disease processes, the successor of TFmiR can now also be applied to identify regulatory motifs associated with the transitions between different developmental stages from the sets of genes and miRNAs provided by the user. One particular challenge in studying gene regulatory networks is to identify the main drivers and master regulatory genes that control such cell fate transitions. In addition to common topological measures and by considering tissue-exclusive genes, we reformulate this problem as an optimization problem of computing a Minimum Connected Dominating Set (MCDS) for directed graphs. MCDS is applied to the well-studied gene regulatory networks of E. coli and S. cerevisiae and to a pluripotency network for mouse embryonic stem cells. The results show that the MCDS captures most of the known key player genes identified so far in the model organisms. Moreover, this method suggests an additional small set of transcription factors as novel key players for governing cell-specific gene regulatory networks. This set can also be investigated with regard to diseases. [1] Mohamed Hamed, Christian Spaniol, Maryam Nazarieh and Volkhard Helms, Nucleic Acids Res. 43: W283-W288 (2015).

Talk 13 and Poster 9

Predictive logical modelling of TLR5 and TCR cooperation for CD4 T cell activation.

Rodríguez-Jorge, O.[1], Kempis-Calanis, L. A. [1], Gutiérrez-Reyna, D. Y. [1], Ramirez-Pliego, O.[1], Abou-Jaoudé, W.[2], Thomas-Chollier, M.[2] Santana, M. A.[1,*], Thieffry, D.[2,*].

Centro de Investigación en Dinámica Celular (CIDC). Instituto de Investigación en Ciencias Básicas y Aplicadas. Universidad Autónoma del Estado de Morelos. Cuernavaca, México[1]
Institut de Biologie de L'Ecole Normale Supérieure (IBENS - CNRS UMR 8197 - INSERM U 1024). Paris, France[2]

Toll-Like Receptor 5 (TLR5) recognises the flagellin monomer, a component of the flagella of many bacteria. Flagellin is being evaluated as a vaccine adjuvant given its ability to induce pro-inflammatory signalling cascades in a variety of cell types. In T cells, flagellin directly provides a co-stimulatory signal to the T cell receptor-mediated (TCR) signals leading to proliferation and IFN-γ production. This study aim to model the cross-talk between TLR5 and TCR signalling pathways leading to CD4 T cell activation. We used the software GINsim to generate and analyse the models. First, we constructed distinct logical models for TCR and TLR5 signalling pathways based on published information and high-throughput data. Next, we validated these models using experimental data obtained in our lab. Then, we reduced these models and merged the reduced versions to obtain a model accounting for the cross-talk between the two pathways. We perform a dynamical analysis of these different models to delineate the specific effects of the cross-talk between TLR5 and TCR pathways on CD4 T cell activation. We then stimulated highly purified naïve CD4 T cells by cross-linking the CD3 molecule, in the presence or absence of flagellin, and evaluated the activation of IKKαβ, c-JUN and CREB by flow cytometry. Experimental data was used to further improve our merged model. The resulting model provides novel insights in the effects of flagellin co-stimulatory signals on CD4 T cell activation.

Talk 14 and Poster 10

Logic models to predict continuous outputs based on binary inputs with an application to personalized cancer therapy

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A central challenge in modern biology is to create models that bridge the gap between the molecular level on which interventions can be designed and the cellular and tissue levels on which the biological phenotypes are manifested. Because of the interaction between biological components, single-predictor models are generally not accurate enough to model a biological phenotype. On the other hand, machine learning approaches, such as Elastic Net and Random Forests produce complex multi-predictor models that are hard to interpret and not amenable to the generation of hypotheses that can be experimentally tested. As a consequence, such models are not likely to further our understanding of biology. There is an urgent need for approaches that build small, interpretable, yet accurate models that capture the interplay between biological components and explain the phenotype of interest.

We present 'Logic Optimization for Binary Input to Continuous Output' (LOBICO), a computational approach that infers small and easily interpretable logic models of binary input features that explain a continuous output variable. LOBICO has several unique features that sets it apart from competing approaches: 1) while the continuous output is binarized, the continuous information is retained to find the optimal logic model; 2) LOBICO identifies logic models around predefined operating points in terms of sensitivity and specificity allowing tailoring to, for example, clinical applications; and 3) by employing an integer linear optimization and industry standard solvers, LOBICO rapidly finds optimal solutions without the need of parameter tuning.

Applying LOBICO to the Genomics of Drug Sensitivity in Cancer (GDSC) cell line panel (714 cell lines screened against 142 anticancer drugs), we find that logic combinations of multiple gene mutations are more predictive of drug response than single gene predictors, for more than 85% of the drugs. We show that the use of the continuous output information leads to robust and more accurate logic models. Finally, we show how LOBICO can uncover logic models around predefined operating points in terms of statistical specificity and sensitivity. To the best of our knowledge, LOBICO is the first method to provide this important capability, which is a requirement towards practical application of such models

Poster 11

Robust and on-line multi-omics *de novo* pathway enrichment with KeyPathwayMiner

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Exploiting current biological interaction databases has led to the development of pathway-level enrichment methods for downstream analyses in biological and biomedical settings. Classical pathway enrichment methods rely on a pre-defined list of pathways of known biological processes, which may bias the search towards known pathways and overlook unknown, yet important functional modules. To overcome this limitation, so-called "*de novo*" pathway enrichment approaches have emerged that extract novel pathways from a large interactome and given a series of OMICs studies.

KeyPathwayMiner, available since 2011 as a Cytoscape App, is the most feature-rich and user-friendly tool for *de novo* pathway enrichment available. In addition to existing features such as batch runs and multi-omics integration, we present the latest version of the Cytoscape App that includes support for robustness and validation analyses. Users can evaluate how results change after perturbing the network using one of several network perturbation strategies, or assess how enriched extracted pathways are for genes from a given gold-standard set.

KeyPathwayMinerWeb is a novel web service built on top of KeyPathwayMiner. It is primarily targeted at researchers with little to no experience in Cytoscape. No installation is necessary and convenience features, such as an intuitive web interface and the mapping of identifiers are included. Web application developers may also utilize a RESTful interface to integrate KeyPathwayMinerWeb seamlessly into their own applications.

We will present two use cases that demonstrate how KeyPathwayMiner may be used to fully exploit *de novo* pathway enrichment in different contexts: (1) extraction of de-regulated pathways in Huntington disease, (2) extraction of cancer-relevant pathways given multi-OMICs (mRNA, DNA methylation).

Poster 12

Comprehensive analysis of high-throughput screens with HiTSeekR – From RNAi, CRISPR/Cas9, miRNA and small compound screens to targeted signalling pathways

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High-throughput screening (HTS) is an indispensable tool for drug (target) discovery that currently lacks user-friendly software tools for the robust identification of putative hits from HTS experiments and for the interpretation of these findings in the context of systems biology.

Limited resources only allow for a few putative hits (active samples) to be considered for follow-up experiments. In contrast, systems biomedicine analysis is suited to identify targeted pathways more efficiently based on the entire data set. We developed HiTSeekR as a one-stop solution for chemical compound screens, siRNA knock-down and CRISPR/Cas9 knock-out screens, as well as microRNA inhibitor and -mimics screens. For each screen type, HiTSeekR enables the user to extract a list of (putative) target genes that can be subjected to gene set and network enrichment analysis. The latter is particularly suited for drug target discovery as it allows for extracting novel and disease related functional modules from biological interaction networks.

We will present three use cases that demonstrate how HiTSeekR may be used to fully exploit HTS screening data in quite heterogeneous contexts to generate novel hypotheses for follow-up experiments: (1) a genome-wide RNAi screen to uncover modulators of TNF-alpha, (2) a combined siRNA and miRNA mimics screen on vorinostat resistance and (3) a small compound screen on KRAS synthetic lethality.

HiTSeekR is the first approach to close the gap between raw data processing, network enrichment and wet lab target generation for various HTS screen types.

Poster 13

Mimoza: a user-centric tool for zoomable navigation and knowledge-based exploration of metabolic networks

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Large-scale metabolic networks include thousands of reactions needed for accurate computer simulation. However this abundance of details is difficult for a human: it can mask errors and important organism-specific adaptations. It is therefore important to find the right levels of abstraction that are comfortable for human experts. Interestingly, hidden similarities between groups of reactions can be discovered, and generalized to reveal higher-level patterns.

The web-based navigation system Mimoza combines the model generalization method with the zooming user interface (ZUI) paradigm and allows a human expert to explore metabolic network models in a semantically zoomable manner. Mimoza takes a metabolic model in SBML format and automatically creates a 3-level representation for it:

1. the full-model level represents the initial network with the generalization-based layout (where similar metabolites and reactions are placed next to each other);
2. the generalized level shows the generalized versions of reactions and metabolites in each compartment;
3. the compartment level represents the compartments of the model and transport between them.

Mimoza highlight the general model structure and the divergences from it, such as alternative paths or missing reactions, and allows a user to analyse it in a top-down manner.

Mimoza can be installed standalone, or used on-line at mimoza.bordeaux.inria.fr. Mimoza views can be embedded in web pages, or downloaded as COMBINE archives.

Poster 14

DrugLogics: Logical models for drug screen prioritization

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Multi-drug precision oncology is in need of approaches that enable drug combination prioritization, since the combinatorial explosion renders traditional trial-and-error screening approaches ineffective. Our computation-assisted approach contributes by highly efficient prediction of drug responses while relying only on characterizing the experimental system (cell line, tumor) at baseline conditions.
Logical models are derived from cancer signaling topologies, calibrated to particular cell types or tumors by steady state biomarkers from unperturbed cells. Based on a proof-of-concept model (Flobak *et al PLoS Comp Biol*, 2015) we now explore a pipeline for automated causal network topology assembly, logical model parameterization and model ensemble evaluation. Prior knowledge is integrated from databases on cell signaling (Reactome, Signor, SignaLink etc), and multi-omic data is integrated to describe patterns of signaling entity activities characterizing a given experimental system. While parameterization constraints are traditionally obtained from drug response experiments, we explore self-contained topologies as a means of constraining possible parameterizations. Genetic algorithms are employed to optimize logical equations to obtain models where the attractor recapitulates steady state biomarkers from biological assays. Model simulations suggest prioritization of drugs that targets proteins to disrupt disease phenotypes, leading to restoration and activation of regulatory anti-survival phenotypes present in healthy cells.
The pipeline correctly classified 20 of 21 combinations as synergistic or non-synergistic (Flobak 2015), with one novel synergy validated in vivo. When applied to a manually curated topology, models automatically parameterized predicted five synergies (four true positives, no false negatives) when normalized to topology-intrinsic synergies. A Reactome-topology-derived model predicted five synergies (three true positives). In ongoing work, model predictions are challenged with a dataset of 171 drug combinations (19 individual drugs) across 8 cell lines.
Our prototype computational-experimental pipeline demonstrates the potential to economize pre-clinical drug combination synergy discovery and to provide clinical decision support for personalized therapy.

Poster 15

WikiPathways: Curation, Visualization and Analysis of Biological Pathways

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Pathway diagrams are found everywhere: in textbooks, in review articles, on posters and on whiteboards. Their utility to biologists as conceptual models is obvious. They have also become immensely useful for computational analysis and interpretation of large-scale experimental data when properly modeled. We will highlight the latest developments and newest features of WikiPathways (www.wikipathways.org), a community curated pathway database that enables researchers to capture rich, intuitive models of pathways. WikiPathways and the associated tools PathVisio and pvjs are developed as open source projects with a lot of community engagement.

The new interactive JavaScript-based pathway viewer, pvjs (https://github.com/wikipathways/pvjs/), is integrated in the WikiPathways website and enables users to zoom in and click on pathway elements to show linkouts to other databases.

The standalone pathway editor and analysis and visualization tool, PathVisio (www.pathvisio.org), was refactored with the goal to achieve a better, modular system that can be easily extended with plugins. Plugins are accessible through the new plugin repository and can be installed through the plugin manager from within the application. This is an important aspect of usability that will allow users to build an application with all the necessary modules relevant for their work. The WikiPathways plugin of PathVisio allows searching and browsing WikiPathways from within PathVisio. Furthermore users can upload new pathways or update existing pathways.

The WikiPathways app for Cytoscape (http://apps.cytoscape.org/apps/wikipathways) enables the use of WikiPathways pathways in network visualization and analysis approaches.

Poster 16

HIPPIE v2.0: enhancing meaningfulness and reliability of human PPI networks

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The large-scale experimental detection of human protein-protein interactions (PPI) needs to be accompanied by bioinformatics strategies to filter and interpret these PPIs: the increasing knowledge of interaction partners for most human proteins makes it difficult for researchers to extract the relevant information when proteins are studied under specific conditions. To this end we generated the Human Integrated Protein-Protein Interaction rEference or HIPPIE [http://cbdm.uni-mainz.de/hippie/]. HIPPIE is a one-stop resource for the generation of meaningful PPI networks relevant to a specific research question and the interpretation of the resulting networks. We provide highly reliable, context-specific PPI networks and guide their interpretation. We just released the second major update of HIPPIE implementing various new features. HIPPIE now contains more than 270,000 confidence scored and annotated PPIs.

HIPPIE's confidence scoring scheme has been designed by human experts and computationally optimized to reflect the amount and quality of evidence for a given PPI. We use different types of experimental information to allow for the construction of context-specific networks. For example, we recently integrated GTEx RNAseq data from 53 human tissues for the generation of tissue-specific networks. We implemented basic graph algorithms that highlight important proteins and interactions. Specifically, HIPPIE infers signal flow, effect and directionality from network properties and phenotypic data.

We created a graphical interface that allows wet lab and computational scientists alike to access the data and implements several ways to query and browse human PPIs. Visualization of the output facilitates easy inspection of relevant parts of the human interactome. Integrating and interfacing external tools allow to interpret the results of HIPPIE queries and to pass them on for subsequent analyses.

Poster 17

PheNetic2.0: Integrated multi-omics data interpretation and analysis

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As more and more data is gathered from experimental biology, functional interpretation and analysis from these results becomes harder and harder. This not only because of the vast size of the generated data but also the generation of parallel data sets and the integration of multi omics data sets. Analyzing these data requires combining these results in the light of public knowledge of the molecular mechanisms observed in the experiment. To this end biological networks pose ample opportunities for integrating not only parallel results but also multi omics datasets. To this end we have developed and successfully applied the PheNetic framework over the last years which we made available as a web server (De Maeyer, 2015).

Here we want to give a preview of the new version of the PheNetic web server we are currently working on where we extend the previous version with the ability of integrating multiple experimental results from multiple omics sources. A practical usable web server requires visualization and interactive representation of the initial and analysis results. To this end we give an overview of the visualization and interpretation of multi-omics experimental results on interaction networks, the abilities of our network integration platform PheNetic in integrating these datasets and the resulting visualization we have developed in d3js and cytoscapejs allowing for an easy and practical interpretation of the experimental results by biologists.

Poster 18

Towards a new definition of circuit functionality

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In the wake of the seminal work of René Thomas, the notion of functionality in a regulatory network has focused on the asymptotic behavior "generated" by simple positive and negative circuits: Thomas' conjectures state that a positive circuit is necessary for multistationarity; a negative circuit, for sustained oscillations; and functionality has been loosely defined as the property of a positive or negative circuit that produces the corresponding behavior.

More precisely, in the logical formalism, a circuit is said to be functional when all its arcs are functional, and its sign is the product of the signs of the arcs. Different definitions of circuit functionality then arise depending on the region of the state space where the arcs are required to be functional (1). Unfortunately, current definitions only allow proof of Thomas conjectures for very restricted conditions, if at all. Moreover, major questions remain unanswered, including the full decomposition of a network into functional modules and the very definition of what "generate" exactly means.

In an attempt to clarify those issues we are currently investigating the possible role of symmetry in the dynamics of a model as a marker of functionality. Focusing on the behavior of a circuit in pairs of mirror states, we introduce new definitions and conjectures to connect the presence of circuits in a logical regulatory graph with symmetric patterns in the state transition graph.

Poster 19

MGVizNet: Importance of graph databases in curation of biological networks

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Biological processes such as gene regulation or metabolic pathways are often represented in the form of biological networks. Their modelling, analysis and visualisation are essential to reveal important properties of the underlying biological system. It is very important to identify the most appropriate generic data model to aggregate data from several resources, enabling the creation of efficient algorithms and making possible the management and integration of complex datasets.

Only graph databases such as Reactome or BioNetDB, that embraces relationships as a core aspect of its data model, are able to store, process, and query connections in a network proficiently. Data integration using graph databases allows an efficient traversing of the network through different data resources. As they are fast for retrieving information on large numbers of associative data elements, graph databases may allow an interactive and dynamic visualisation. Also, their schemaless nature allows the data model to evolve and expand without sacrificing the speed of access or adding significant and costly overhead to development cycles.

We are providing tools to improve curation of biological pathways and allow researchers to curate data more efficiently. Using a schemaless database and the possibility of creating dynamic visualisations of the stored data, curators can explore biological relationships and add new data more easily and quickly. Our current implementation creates customizable visualisations that allow researchers to focus on specific segments of the network. This allows highlighting the connections with other modules of data and changing quickly to any of the new connections, retaining the visualisation of the desired elements of different interconnected pathways.

To sum up, modelling biological networks with graph databases provides us the opportunity to explore a network of thousands of interacting components and gives us clues about how their organisation and connection influences their function and dynamic responses.

Poster 20

Atlas of Cancer Signaling Network and NaviCell: systems biology resources for studying cancer biology

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Studying reciprocal regulations between cancer-related pathways is essential for understanding signaling rewiring during cancer evolution and in response to treatments. With this aim we have constructed the Atlas of Cancer Signaling Network (ACSN), a resource of cancer signaling maps and tools with interactive web-based environment for navigation, curation and data visualization. The content of ACSN is represented as a seamless 'geographic-like' map browsable using the Google Maps engine and semantic zooming. The associated blog provides a forum for commenting and curating the ACSN maps content. The integrated NaviCell web-based tool box allows to import and visualize heterogeneous omics data on top of the ACSN maps and to perform functional analysis of the maps. The tool contains standard heatmaps, barplots and glyphs as well as the novel map staining technique for grasping large-scale trends in numerical values projected onto a pathway map. To demonstrate applications of ACSN and NaviCell we show a study on drug sensitivity prediction using the networks. We performed a structural analysis of Cell Cycle and DNA repair signaling network together with omics data from ovary cancer patients resistant to genotoxic treatment. Following this study we retrieved synthetic lethal gene sets and suggested intervention gene combinations to restore sensitivity to the treatment. In additional study we show how epithelial to mesenchymal transition (EMT) signaling network from the ACSN collection has been used for finding metastasis inducers in colon cancer through network analysis. We performed structural analysis of EMT signaling network that allowed highlighting the network organization principles and complexity reduction up to core regulatory routs. Using the reduced network we modeled single and double mutants for achieving the metastasis phenotype. We predicted that a combination of p53 knock-out and overexpression of Notch would induce metastasis and suggested the molecular mechanism. This prediction lead to generation of colon cancer mice model with metastases in distant organs. We confirmed in invasive human colon cancer samples the modulation of Notch and p53 gene expression in similar manner as in the mice model, supporting a synergy between these genes to permit metastasis induction in colon.