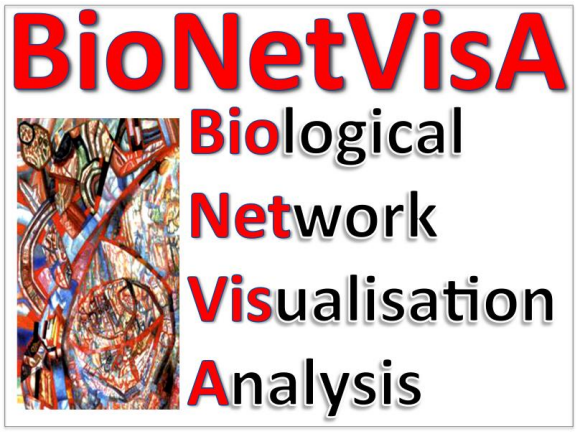


BioNetVisA workshop

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

Stavros Niarchos Foundation Cultural Center (SNFCC)
Leof. Andrea Siggrou 364, Kallithea 176 74
Athens, Greece

9 September 2018

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)
Luis Cristobal Monraz Gomez (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, Netherlands)

Web site

http://eccb18.org/workshop-2/
https://bionetvisa.github.io/

Venue

https://www.snfcc.org/default.aspx

Contact

bionetvisa@curie.fr

Sponsor

ISAC
International Society for Advancement of Cytometry

BioNetVisA workshop program

09:00 - 10:30 Session 1: Signalling and metabolic network resources

Chair: Vassili Soumelis

09.00-09.20 Talk 1
Antonio Fabregat (EMBL-EBI, Hinxton, UK)
The Reactome Pathway Knowledgebase

09.20-09.40 Talk 2
Cristobal Monraz Gomez (Institute Curie, Paris, France)
Atlas of Cancer Signaling Network: a resource of multi-scale biological maps to study disease mechanisms

09.35-10.50 Talk 3
Joaquin Dopazo (Fundación Progreso y Salud, Seville, Spain)
Navigating through disease maps

10.50-10.05 Talk 4
Augustin Luna (Dana-Farber Cancer Institute/Harvard University, Boston, United States)
Access and Discover Biological Pathway Information from Pathway Commons

10.30-11.00 Coffee break

Session 2: Platforms and methods for analysis of complex networks

Chair: Yvan Saeys

11.00-11.25 Talk 5
Georgios Pavlopoulos (Biomedical Sciences Research Center "Alexander Fleming", Athens, Greece)
Using HipMCL, a high-performance parallel implementation of the Markov clustering algorithm, to understand microbial diversity

11.25-11.50 Talk 6
Anna Niarakis (GenHotel EA3886, Univ Evry, Université Paris-Saclay, France)
Disease Networks - Reconstruction, Topology, Dynamics. Towards an automated pipeline from static representations to executable disease models

11.55-12.15 Talk 7
Barbara Shih (The Roslin Institute and Royal (Dick) School of Veterinary Studies, the University of Edinburgh, Easter Bush, Midlothian, Edinburgh, UK)
A platform for the network assembly and visual analysis of transcript isoforms from short-read RNA-sequencing data

12.15-12.30 Talk 8
Warren W. Kretzschmar (KTH Royal Institute of Technology, Stockholm, Sweden)
Multicolored De Bruijn graph visualization of first, second, and third generation RNA-seq offers deeper insight into transcript isoforms in Picea abies

12.30-13.30 Lunch

Session 3: Biological networks in single-cell data analysis

Chair: Augustin Luna

13.30-13.55 Talk 9

Yvan Saeys ISAC Lecture (VIB-Ghent University, Gent, Belgium)

Inferring dynamic regulatory networks from single cell data

13.55-14.20 Talk 10

Andrei Zinovyev (Institute Curie, Paris, France)

Biological networks help unraveling tumoral heterogeneity at single cell level

14.20-14.40 Talk 11

Anirudh Patir (The University of Edinburgh, Edinburgh, UK)

Evaluation of network methods for the analysis scRNA-seq data and development of a new KNN-based method based on identified caveats

14.40-15.00 Talk 12

Vassili Soumelis (Institute Curie, FR)

Immune cell diversification in response to a single stimulus: from single cells to subsets and back

15.00-15.30 Coffee break

Session 4: Biological networks modelling in drug repositioning and disease comorbidity

Chair: Joaquin Dopazo

15.30-16.15 Talk 13

Alfonso Valencia Keynote Lecturer (Barcelona Supercomputing Center, Barcelona, Spain)

Disease networks for the study of the molecular basis of disease comorbidity

16.15-16.35 Talk 14

Celine Hernandez (Institut de Biologie de l'Ecole Normale Supérieure, Paris, France)

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

16.35-16.55 Talk 15

Sven Bergmann (University of Lausanne & Swiss Institute of Bioinformatics, Switzerland)

Open Community Challenge Reveals Molecular Network Modules with Key Roles in Diseases

16.25-16.45 Talk 16

Josephine Daub (Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands)

Genetic interactions in childhood cancer

BioNetVisA workshop abstracts

Talk 1

The Reactome Pathway Knowledgebase

Antonio Fabregat[1], Konstantinos Sidiropoulos[1], Guilherme Viteri[1], Pascual Lorente[1], Cristoffer Sevilla[1], Thawfeek Varusai[1], Guanming Wu[2], Lincoln Stein[3], Peter D'Eustachio[4] and Henning Hermjakob[1]

[1]EMBL-EBI, Hinxton, UK1, [2]OHSU, Portland, USA , [3]OIRC, Toronto, Canada, [4]NYUMC, New York, USA

The Reactome Knowledgebase (https://reactome.org) provides molecular details of signal transduction, transport, DNA replication, metabolism, and other cellular processes as an ordered network of molecular transformations—an extended version of a classic metabolic map, in a single consistent data model. Reactome functions both as an archive of biological processes and as a tool for discovering unexpected functional relationships in data. To support the continued brisk growth in its size and complexity, we have implemented a series of improvements.

Aiming to reduce the complexity of the represented knowledgebase and to enable a more straightforward access to its content, Reactome provides its data in a Neo4j graph database (available at https://reactome.org/download-data). Neo4j's query language, Cypher, allows queries to be written in a more intuitive way and reduces the average response time per query by 93%.

Additionally, Reactome has improved the performance of its data analysis tools, and adopted new data structures and strategies to boost diagram viewer performance. To make our website more accessible to human users, we have improved our multiscale pathway visualisation by implementing interactive, textbook-style illustrations. To ensure consistency in the visual representation of pathway diagrams we created a freely accessible (under a CC-BY 4.0 licence) Icon Library (https://reactome.org/icon-lib) that includes icons ranging from simple protein labels to representations of organelles, receptors and cell types.

In response to user feedback, the Reactome knowledgebase portal has been simplified and reorganised following a cleaner and responsive design that allows seamless browsing on a variety of portable devices. To encourage re-use of our content, our web service (https://reactome.org/ContentService) allows exporting of pathway diagrams to raster and vector images, as well as to 'PowerPoint' files. Also, analysis results can be downloaded in easy to follow PDF documents.

Talk 2

Atlas of Cancer Signaling Network: a resource of multi-scale biological maps to study disease mechanisms

L. Cristobal Monraz Gomez, Emmanuel Barillot, Andrei Zinovyev and Inna Kuperstein

Institut Curie, Paris, France

We present here the second edition of Atlas of Cancer Signaling Network (ACSN2.0, https://acsn.curie.fr). ACSN is a web-based resource of multi-scale biological maps depicting molecular processes in cancer cell and tumor microenvironment. The core of the Atlas is a set of interconnected cancer-related signaling and metabolic network maps. Molecular mechanisms are depicted on the maps at the level of biochemical interactions, forming a large seamless network of above 8000 reactions covering close to 3000 proteins and 800 genes and based on more than 4500 scientific publications. Constructing and updating ACSN involves careful manual curation of molecular biology literature and the participation of experts in the corresponding fields.

The maps of ACSN2.0 are interconnected, the regulatory loops within cancer cell and between cancer cell and tumor microenvironment are systematically depicted. The cross-talk between signaling mechanisms and metabolic processes in the cancer cells is explicitly depicted thanks to new feature of the Atlas: ACSN2.0 is now connected to RECON metabolic network, the largest graphical representation of human metabolism.

The Atlas is a "geographic-like" interactive "world map" of molecular interactions leading the hallmarks of cancer as described by Hanahan and Weinberg. The Atlas is created with the use of systems biology standards and amenable for computational analysis. As of today, ACSN2.0 is composed of 13 comprehensive maps of molecular interactions. There are six maps covering signalling processes involved in cancer cell and four maps describing tumor microenvironment. In addition, there are 3 cell type-specific maps describing signaling within different cells types frequently surrounding and interacting with cancer cells. This feature of ACSN2.0 reflects the complexity of tumor microenvironment.

The resource includes tools for map navigation, visualization and analysis of molecular data in the context of signaling network maps.

Talk 3

Navigating through disease maps

Joaquín Dopazo

Clinical Bioinformatics Area, Fundacion Progreso y Salud, Seville, Spain

Despite the increasing availability of genomic and transcriptomic data, there is still a gap between the detection of perturbations in gene expression and the understanding of their contribution to the molecular mechanisms that ultimately account for the phenotype studied. Disease maps (http://disease-maps.org/projects) and other generic maps that recapitulate cell signaling, metabolism and functionality (e.g. KEGG, WikiPathways, etc.) offer a detailed picture on the complex network of interrelationships among genes that result in cell activity decisions.

Alterations in the in the functioning of such networks are behind the initiation and progression of many diseases, including cancer. The wealth of available knowledge on biological networks can therefore be used to derive mechanistic models that link gene expression perturbations to changes in metabolic, signaling, etc. activities that provide relevant clues on molecular mechanisms of disease and drug modes of action (MoA).

Here we present simple mechanistic models of signaling (hipathia) and metabolic (Metabolizer) activity based on modules defined as functionally substantiated circuits within pathways. The models have been implemented as web-based applications, which offer intuitive, easy-to-use interactive interfaces to analyze differences in pathway activities that can also be used for class prediction and in silico prediction of Knock-Out (KO) effects. We provide different types of validations of some of the predictions made by the models.

Metabolizer can be found at: http://metabolizer.babelomics.org

Hipathia can be found at: http://hipathia.babelomics.org A Bioconductor/R package can be found at: http://bioconductor.org/packages/devel/bioc/html/hipathia.html

Talk 4

Access and Discover Biological Pathway Information from Pathway Commons

Augustin Luna[1,2], Emek Demir[3], Igor Rodchenkov[4], Özgün Babur[3], Jeffrey V Wong[4], Chris Sander[1,2] and Gary Bader[4]

[1]Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston MA, USA, [2]Cell Biology, Harvard Medical School, Boston MA, USA, [3]Oregon Health & Science University, Portland OR, USA, [4]University of Toronto, Toronto, Canada

Pathway Commons (pathwaycommons.org) serves researchers by integrating data from public pathway and interaction databases and disseminating this data in a uniform fashion. The knowledge base is comprised of metabolic pathways, genetic interactions, gene regulatory networks and physical interactions involving proteins, nucleic acids, small molecules and drugs. Alongside attempts to increase the scope and types of data, a major focus has been the creation of user-focused tools and resources that facilitate access, discovery and application of existing pathway information to aid day-to-day activities of biological researchers. Pathway Commons offers a number of tools for accessing and searching the integrated datasets. File downloads are available in Biological Pathway Exchange (BioPAX), Simple Interaction Format (SIF) and gene set (GMT) formats. Provided web services allow for integration with external tools and support full-text search of available data. Results from the web services is provided in the aforementioned formats, as well as, the Systems Biology Graphical Notation Markup Language (SBGNML) and Javascript Object Notation for Linked Data (JSON-LD) formats. Pathway Commons is also accessible via a number of web applications built on reusable Javascript components, including: 1) PCViz that allows the visualization of interaction data as simplified binary interaction networks from input gene names and 2) a web-based 'Search' application that enables users to query pathways by keyword and visualize returned pathways using SBGN with an automated layout. These web applications complement existing desktop software add-ons linking Pathway Commons to the Cytoscape (CyPath2) network analysis tool and the R (paxtoolsr) programming language. We additionally provide an online guide for those wishing to learn more about pathway resources and analysis with published case studies and guided workflows. Ongoing development of web applications will enhance the accessibility to pathways and integrate support for visualization and interpretation of experimental data.

Talk 5

Using HipMCL, a high-performance parallel implementation of the Markov clustering algorithm, to understand microbial diversity

Georgios A. Pavlopoulos

Biomedical Sciences Research Center "Alexander Fleming", Athens, Greece

While various clustering algorithms have been proposed to find highly connected regions within a biological network, Markov Clustering (MCL) has been one of the most successful approaches. Despite its popularity, MCL's scalability suffers from high running times and memory demands. Here, we present the High-performance MCL (HipMCL), a parallel implementation of the original MCL algorithm that can run on distributed-memory computers. HipMCL can efficiently utilize 2000 compute nodes and cluster a network of ∼70 million nodes with ∼68 billion edges in ∼2.4 h. To demonstrate its capabilities, we show how we use HipMCL to understand the biological diversity and discover novel protein clusters.

Talk 6

Disease Networks - Reconstruction, Topology, Dynamics. Towards an automated pipeline from static representations to executable disease models.

Anna Niarakis

GenHotel EA3886, Univ Evry, Université Paris-Saclay, France

Disease maps have been an emerging concept as a useful and intuitive way of describing disease mechanisms in a systematic fashion. Based on information mining, human curation and experts' advice, they summarize current biological pathway knowledge in a standard, comprehensive representation that is both human and machine readable. Disease maps can serve as templates for visualization and analysis of *omic* datasets, or they can be analyzed in terms of their underlying network structure. However, their static nature provides relatively limited understanding concerning the emerging behavior of the system under different conditions. Computational modelling can reveal dynamical properties of the network by *in silico* simulations and perturbations and can be further used for hypotheses testing and predictions. In order to address the lack of kinetic data and the large size of the biological pathways described in a Disease map, Boolean modelling can be employed to study the system's qualitative dynamic behavior.

In this talk I will present our efforts to establish an automated pipeline starting from a fully detailed Disease map and its analysis as a complex network, all the way to the automated inference of a dynamical (Boolean) model, based on network topology and semantics, creating thus "executable" disease networks. I will use Rheumatoid Arthritis as case study.

Talk 7

A platform for the network assembly and visual analysis of transcript isoforms from short-read RNA-sequencing data

Barbara Shih[1], Neil A. Mabbott[1], Tom C. Freeman[1,2]

[1]The Roslin Institute and Royal (Dick) School of Veterinary Studies, the University of Edinburgh, Easter Bush, Midlothian, Edinburgh EH25 9RG, UK, [2]Kajeka Ltd., Roslin Innovation Building, Easter Bush, Midlothian, Edinburgh EH25 9RG, UK

RNA-sequencing (RNA-seq) data describes both transcript abundance and exon usage. However, splicing events can be complex, and therefore difficult to visualise and interpret.

Here, we describe a new data pipeline/visualisation platform developed to support the representation of RNA-seq data as networks (RNA-assembly graphs), thereby providing a visual representation of data structure that facilitates interpretation of exon/intron use. The pipeline requires the following files: input BAM files, the corresponding GTF file, and genes of interest. Two approaches are available within the pipeline for the graph generation. The first is based on comparing sequence similarity, e.g. by Blast, whereby the similarity scores are used to define edges between reads (nodes). However, generation of graphs using this approach can be computationally expensive (due to the blast step) and graphs can be very large. In order to circumvent these issues, a second approach is based on mapping reads to specific loci, i.e. regions of the genome, which are represented as nodes, and edges are defined by the number of reads spanning across regions. To visualise both RNA-assembly graph types we have also been developing a new network analysis platform, called Graphia (Kajeka Ltd). This platform not only supports the visualisation of massive graphs (millions of nodes of edges), but supports the overlay of other information, e.g. gene or exon IDs, dynamic filtering on edge weight or source as well as a range of other functionalities.

Using real and simulated short-read RNA-seq data we have demonstrated that different splicing events (alternative start/end, exon skipping and mutually exclusive exons) produce distinct network structures by both approaches. However, the implementation of the loci-based approach drastically simplifies the graphs, enabling direct comparison of exon usage across different samples. We believe this approach significantly improves our ability to interpret the often complex splicing captured by RNA-seq analysis.

Talk 8

Multicolored De Bruijn graph visualization of first, second, and third generation RNA-seq offers deeper insight into transcript isoforms in Picea abies

Warren W. Kretzschmar[1], Shirin Akhter[2], Veronika Nordal[2], Nicolas Delhomme[2], Nathaniel R. Street[2], Ove Nilsson[3], Olof Emanuelsson[1], Jens F. Sundström[2]

[1]KTH Royal Institute of Technology, Stockholm, Sweden, [2]Swedish University of Agricultural Sciences, Sweden, [3]Umeå University, Umeå, Sweden

Third-generation sequencing technologies offer cheap, long reads, but with higher error rates than reads from first or second generation technologies. In transcriptome assembly, these technologies are complementary. However, useful approaches to combining data from all these technologies are needed. De Bruijn graphs, a staple of transcriptome assemblers, offer a natural way of combining low-error reads into a graph. Multicolored De Bruijn graphs allow the joint representation of read information from multiple sequencing technologies.

We present a visualization of Picea abies transcript isoforms assembled from Sanger, Illumina, and PacBio IsoSeq reads based on a multicolored De Bruijn graph. This visualization allows close assessment of read support for transcript isoforms from all three technologies simultaneously.

Talk 9

Inferring dynamic regulatory networks from single cell data

Yvan Sayes

VIB-Ghent University, Gent, Belgium

High-throughput methods for measuring proteins and RNA at the single-cell level are currently revolutionizing the life sciences. Examples include multicolor flow cytometry, mass cytometry, imaging flow/mass cytometry and single-cell transcriptomics. However, the success of these novel technologies crucially depends on computational methods to interpret, visualize, and model these novel data types.

In this talk, I will present a novel class of techniques to infer dynamic regulatory networks from single-cell data, as well as a novel benchmarking framework that can be used to evaluate dynamic regulatory networks and stimulate their further developments. Case studies will be presented on immune cell differentiation.

Talk 10

Biological networks help unraveling tumoral heterogeneity at single cell level

Andrei Zinovyev

Institut Curie, Paris, France

TBA

Talk 11

Evaluation of network methods for the analysis scRNA-seq data and development of a new KNN-based method based on identified caveats

Anirudh Patir and Tom Freeman

The University of Edinburgh, Edinburgh, UK

Advances in single-cell RNA-seq (scRNA-seq) analyses have revolutionised the ability to characterise cellular heterogeneity and opened up new opportunities to study cell and tissue biology in development or disease, e.g. tracking differentiation trajectories of cells (pseudotime analysis). However, the data generated is large and technically noisy, making several methods for analysing bulk RNA-seq data unsuitable. As a result, a plethora of tools have been developed for the visualisation and analysis of scRNA-seq data, with the lack of a comprehensive comparison. Hence, in this study, we compare the non-stochastic network-based methods that are gaining popularity in the field, including Phenograph, correlation analysis, KNN, and SNN. These methods have been applied to real datasets of variable cell numbers and evaluated for their sensitivity and stability in identifying cell-subtypes of varying proportions, and in detecting outliers. Conventional correlation analysis easily identifies outliers, though unable to distinguish cell-subtypes. In contrast, KNN & SNN based approaches can detect these subtypes, however, without addressing outliers and with the stability of clusters relying on the parameter 'k'. In all methods, datasets containing variable proportions of cell populations resulted in misclassification of subtypes. To address these two limitations, we developed a modified KNN algorithm. Firstly, outliers are revealed, as a variable set of edges are assigned to a node, depending on the respective correlations. This is in contrast to the KNN based algorithms, which does not distinguish between poor and strong correlations considered. Secondly, the current algorithm can identify cell subtypes of variable proportions by constructing the network based on the density of cell-types. Additionally, by visualising the relevant structure of the data, differentiation trajectories can also be described. Together this study identifies the caveats associated with current network approaches and proposes an algorithm to address these limitations, in particular highlighting outliers and distinguishing cell-types of varied proportions.

Talk 12

Immune cell diversification in response to a single stimulus: from single cells to subsets and back

Vassili Soumelis[1], Nathalie Lehmann[2], Morgane Thomas-Chollier[2], Philémon Sirven[1], Denis Thieffry[2]

[1]Institut Curie, Cancer Immunotherapy Center, Paris, France, [2]Institut de Biologie de l'Ecole Normale Supérieure, IBENS, Paris, France

Cells change state in response to environmental stimuli, a process called adjustment. When a seemingly homogeneous cell population receives a stimulus, it collectively and progressively switches to a different state. In a recent study of innate immune cells, i.e plasmacytoid pre-dendritic cells (pDC), we could show that primary human pDC diversify over 24h into three distinct subpopulations (P1, P2, P3) in response to a single microbial stimulus, such as influenza virus or CpG oligonucleotide (Alculumbre et al, Nat Immunol, 2018). This was revealed by single cell analysis using multicolor flow cytometry. P1-, P2-, and P3-pDC harbor distinct morphology, phenotype, transcriptional signatures for coding and non-coding RNA, as well as function. Subsequently, we turned back to single cell RNAseq analysis of pDC diversification in order to precisely quantify transcriptomic level diversity of pDC over time following stimulation, and search for putative molecular mechanisms underlying the stepwise diversification process, helped by pseudo time analysis. We propose that cell diversification may be a general mechanisms generating diversity following cellular adjustment to a single stimulus, driven by stochastic as well as deterministic events characterizing each specific cellular system.

Talk 13

A patient centred disease comorbidity network

Alfonso Valencia

Barcelona Supercomputing Center, Barcelona, Spain

Even if concomitant presence of two or more diseases represent a significant problem in preventive medicine the underlying molecular basis are poorly understood. Based on the analysis of patient specific expression signatures, we have developed a network based approach for the prediction of the risk of developing secondary diseases at the individual level (1).

In the first place, we build a network of patients based on the similarity of their expression profiles and estimate relative disease co-ocurrence risks. The network overlaps and complements the previously general trends detected in EHR by the Barabási and Brunak's groups. In a second step, we include in the network inverse relations between gene expression profiles that correspond to known inverse comorbidity relationships, such as the protection Alzheimer's disease provides to lung cancer patients. Inverse comorbidities add a new orthogonal dimension to the previous disease networks. Third, we deconstruct the network in patient subgroups. Subgroups reflect more accurately the inherent heterogeneity of human diseases and help to explain the differences in tendencies to acquire secondary diseases observed in real clinical cases. Finally, we associate drugs to the patient subgroup to dissect possible molecular causes of comorbidities and to explore possible drug repositioning options.

In the long run, our intention is to explore the use of the patient-to-patient disease networks to prevent the possible incidence of secondary diseases at the personal level in real clinical scenarios.

(1) Unveiling the molecular basis of disease co-occurrence towards personalized comorbidity profiles. by J Sánchez-Valle, H Tejero, JM Fernández, D Juan, S Capella-Gutiérrez, F AlShahrour, R Tabarés-Seisdedos, V Pancaldi and A. Valencia. submitted.

Talk 14

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

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

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

In recent years, T cells were recognized to often display a reduced ability to eliminate cancer cells, caused by the expression of co-inhibitors at their surface. Antibodies blocking these co-inhibitors (checkpoint inhibitors) have become standard treatment for metastatic melanoma (Simpson et al. 2013), thus leading to a revival in the study of T cell co-inhibitors. However, our understanding of their immunobiology and their harmful role during anti-tumour responses remains fragmentary. Particularly, a mechanistic understanding at the systems-level of T cell function modulation by co-inhibitors has remained elusive.

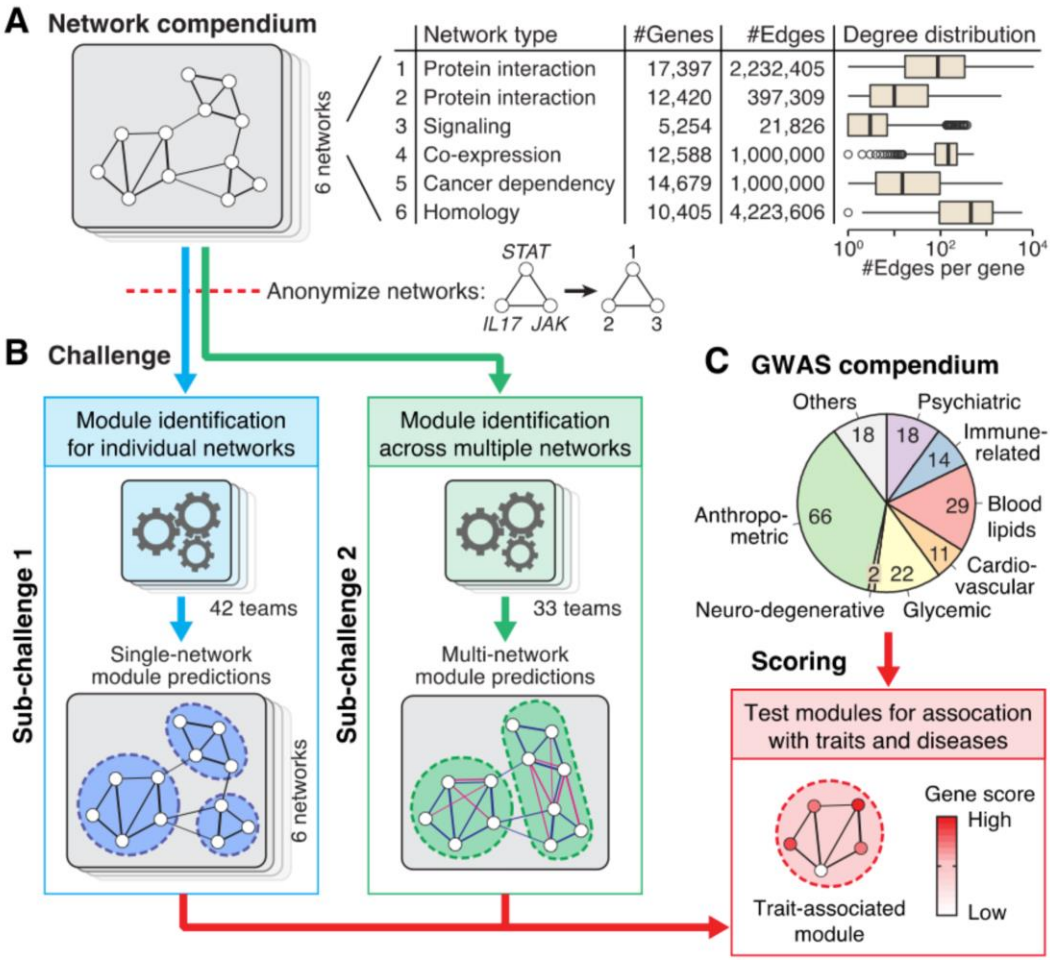
To overcome these limitations, we aim to delineate the mechanisms through which co-inhibitory molecules, such as PD-1 and CTLA-4, impede T cell functions at the systems-level. To reach this goal, we use computational methods to map and model TCR co signalling pathways, and ultimately predict cell responses to perturbations. First, we developed comprehensive annotated molecular maps (using the software CellDesigner, http://www.celldesigner.org) by curated scientific literature, automated queries to public databases and protein-protein graph reconstruction. Next, using the software GINsim (http://www.ginsim.org), these maps and protein networks were translated into a regulatory graph integrating current knowledge. The major challenge was then to properly model concurrent intracellular processes, along with feedback control mechanisms. To cope with this complexity, we explored network modules using a Rule-based formalism (Feret et al. 2009), in order to evaluate concurrent biological hypotheses and specify logical rules that recapitulate observed component behaviour into the logical model. The resulting integrative model will be used to predict cell response to single or multiple perturbations, thus paving the way to delineate novel experiments, which in turn will be used to refine the maps and model. This integrated systems-level view of the action mechanisms of key T cell coinhibitors will provide a further rationale for designing and evaluating drugs targeting T cell co-inhibitory pathways in anti-cancer immunotherapy.

Talk 15

Open Community Challenge Reveals Molecular Network Modules with Key Roles in Diseases

Sven Bergmann

Department of Computational Biology, University of Lausanne & Swiss Institute of Bioinformatics, Switzerland



Identification of modules in molecular networks is at the core of many current analysis methods in biomedical research. However, how well different approaches identify disease-relevant modules in different types of networks remains poorly understood. We launched the “Disease Module Identification DREAM Challenge”, an open competition to comprehensively assess module identification methods across diverse gene, protein and signaling networks. Predicted network modules were tested for association with complex traits and diseases using a unique collection of 180 genome-wide association studies (GWAS). While a number of approaches were successful in terms of discovering complementary trait-associated modules, consensus predictions derived from the challenge submissions performed best. We find that most of these modules correspond to core disease-relevant pathways, which often comprise therapeutic targets and correctly prioritize candidate disease genes. This community challenge establishes benchmarks, tools and guidelines for molecular network analysis to study human disease biology.

The full manuscript describing this work is available at:
https://www.biorxiv.org/content/early/2018/02/15/265553

Talk 16

Genetic interactions in childhood cancer

Josephine Daub, Saman Amini, Frank Holstege and Patrick Kemmeren

Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

Even though the survival rate of childhood cancer has increased in the last decades to around 80% today, it is still the major cause of death in children in developed countries. Cancer develops through the acquisition of multiple mutations, and it is assumed that genetic interactions between mutated genes play an important role in cancer onset and progression. One approach to find genetic interactions in cancer is to search for pairs of mutated genes that occur more (or less) often than expected given the frequency of the individual mutated genes. Highly co-occurring mutated genes suggest a cooperative role of these altered genes in cancer development. Mutually exclusive gene pairs can be a signal of synthetic lethality and could therefore point to possible cancer treatments.
We developed a pipeline, based on two genetic interaction tests [1,2], to detect significant cases of co-occurrence and mutual exclusivity in two pediatric cancer data sets [3,4], comprising over 2,500 tumors from 24 cancer types. In total we detect twelve co-occurring and 42 mutually exclusive genetic interactions. We not only confirm previously detected genetic interactions between significantly mutated genes (SMGs), but also find many interactions that involve non-driver genes. This suggests that the inclusion of the whole set of genes instead of the set of SMGs, can lead to novel discoveries.

[1] Park & Lehner. Mol Syst Biol 11, 2015.
[2] Kim, Madan & Przytycka. Bioinformatics 33; 814–821, 2017.
[3] Gröbner et al. Nature 555;321-327, 2018.
[4] Ma et al. Nature 555;317-376, 2018.