21-22 June 2018

3rd Disease Maps Community Meeting (DMCM2018)

Institut Curie

Batiment de biologie du developpement et cancer

BDD building

11 rue Pierre et Marie Curie

Paris

France

institutCurie

systems medicine disease maps

PROGRAMME

21 June - Amphithéâtre BDD

08.30 - 09.00 Arrival and registration

09:00 - 09:05 Opening session and welcome
Emmanuel Barillot, Institute Curie, Paris, France
Reinhard Schneider, Luxembourg Centre for Systems Biomedicine, Belval, Luxembourg

09:05 - 09:15 Aims and perspectives of the DMCM2018 meeting
Alexander Mazein, European Institute for Systems Biology and Medicine, Lyon, France
Inna Kuperstein, Institute Curie, Paris, France

Session 1: Disease maps resources

09:15 - 09:30 Integrating disease maps using a graph database approach
Irina Balaur, European Institute for Systems Biology and Medicine, Lyon, France

09:30 - 09:45 A disease map for the blood pressure and glomerular filtration regulatory network on which antihypertensive and analgesic drugs act
Francisco J. Lopez Hernandez, University of Salamanca, Salamanca, Spain

09:45 - 10:00 Towards a molecular map of cystic fibrosis mechanisms
Catarina Pereira and Andre Falcao, University of Lisbon, Lisbon, Portugal

10:00 - 10:30 Coffee break at BDD Hall

Session 2: Disease maps resources II

10:30 - 10:45 The AsthmaMap: computational representation of disease mechanisms using domain expert knowledge
Alexander Mazein, European Institute for Systems Biology and Medicine, Lyon, France

10:45 - 11:00 A multiscale signalling network map of immune response in cancer reveals signatures of cell heterogeneity and functional polarization
Maria Kondratova, Institute Curie, Paris, France

11:00 - 11:15 Parkinson's disease map facilitated gene expression analysis reveals new insights in PD pathogenesis
Stephan Gebel, Luxembourg Centre for Systems Biomedicine, Belval, Luxembourg

11:15 - 11:30 Computational systems biology approach for the study of rheumatoid arthritis: from a molecular map to a dynamical model
Anna Niarakis, Universite d' Evry Val d' Essonne, Evry Val d' Essonne, France

11:30 - 12:30 Invited talk: WikiPathways: curation, visualization and analysis of biological pathways
Martina-Summer Kutmon Maastricht University, Maastricht, the Netherlands

12:30 - 13:30 Lunch and collaborations discussion at BDD Hall

13:30 - 15:00 Hands-on tutorials: parallel sessions

Time/Place	Amphi BDD	Annexes 1-3 BDD
13:30 - 14:10	Tutorial 1	Tutorial 3

14:10 - 14:15 Break Break
14:15 - 14:55 Tutorial 2 Tutorial 4

Tutorial 1: Constructing and visualizing pathways with web-based SBGN editor Newt
Ugur Dogrusoz, Bilkent University, Ankara, Turkey

Tutorial 2: MINERVA for visualization of disease maps
Piotr Gawron, Marek Ostaszewski, Luxembourg Centre for Systems Biomedicine, Belval, Luxembourg

Tutorial 3: rROMA, a tool for module activity calculation from omics data and networks
Luca Albergante, Urszula Czerwinska, Andrei Zinovyev, Loredana Martignetti, Institute Curie, Paris, France

Tutorial 4: COBRA toolbox for visualisation and map manipulation through CellDesigner and MatLab environment
Jennifer Modamio, Ronan Fleming, Luxembourg Centre for Systems Biomedicine, Belval, Luxembourg
Nicolas Sompairac, Andrei Zinovyev, Inna Kuperstein, Institute Curie, Paris, France

Session 3: Maps of biological processes and disease

15:00 - 15:10 The adult neurogenesis map
Rupert Overall, German Center for Neurodegenerative Diseases, Dresden, Germany

15:10 - 15:20 The Ras/Raf/Mek/Erk Signaling Pathway - Attention to Details
Maria Dost, Humboldt-Universität zu Berlin, Berlin, Germany

15:20 - 15:30 Is cellular senescence a prerequisite for tumor invasion?
Mathieu Boissan, Centre de recherche St-Antoine, Paris, France

15:30 - 16:00 Coffee break at BDD Hall

Session 4: Maps for drug assessment and disease comorbidity

16:00 - 16:10 Comprehensive signaling network of regulated cell death: comparison of cell death modes in Alzheimer's neurodegenerative disease and cancer
Cristobal Monraz, Institute Curie, Paris, France

16:10 - 16:20 Predicting personal activation potential of CD4 T cells
Feng He, Luxembourg Institute of Health, Luxembourg, Luxembourg

16:20 - 16:30 Reconstruction of integrated maps for drug efficacy assessment
Tatiana Serebriyskaya, Moscow Institute of Physics and Technology, Moscow, Russia

16:30- 16:40 Metabolic and signalling network map integration: application to cross-talk studies and omics data analysis in cancer
Nicolas Sompairac, Institute Curie, Paris, France

16:45- 17:00 Group photo
17:00 - 18:15 Marie Curie museum and garden visit

22 June - Amphithéâtre BDD

Session 5: Methods resources and models

09:00 - 09:15 Access and Discover Biological Pathway Information from Pathway Commons
Augustin Luna, Dana-Farber Cancer Institute/Harvard University, Boston, United States

09:15 - 09:30 Community resources connecting chemistry and toxicity knowledge to environmental observations
Emma Schymanski, Luxembourg Centre for Systems Biomedicine, Belval, Luxembourg
Antony Williams, National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Durham,USA

09:30 - 09:45 Differential metabolic activity and discovery of therapeutic targets using summarized metabolic pathway models
Joaquin Dopazo, Fundación Progreso y Salud, Sevilla, Spain

09:45 - 10:00 A computational model of the circadian clock and its application to understanding renal disease
Tom Freeman, The University of Edinburgh, Edinburgh, United Kingdom

10:00 - 10:30 Coffee break at BDD Hall

Session 6: Large Reconstructions and integrations

10:30 - 10:45 Status report: parameter estimation of a large-scale mechanistic model for mast cells in asthma
Thomas S. Ligon, Ludwig-Maximilians-Universitat, Munich, Germany
Jan Hasenauer, Helmholtz Zentrum Munchen, Munich, Germany

10:45 - 11:00 Application of disease maps to rare diseases: as muscular dystrophies
Cecilia Jimenez Mallebrera, Hospital Sant Joan de Deu, Barcelona, Spain

11:00 - 11:15 Maps of influence and interactions of infectious and cancer diseases from Wikipedia networks
Dima Shepelyansky, Laboratoire de Physique Theorique CNRS, Universite Paul Sabatier, Toulouse, France

11:15 - 11:30 Integrating ontological representation and reasoning into a disease map: application to Alzheimer's disease
Vincent Henry, ICM Brain and Spine Institute, Paris, France

11:30 - 12:30 Invited talk: Reactome multi-scale pathway visualization
Henning Hermjakob, Molecular Systems services EMBL-EBI, Cambridge, United Kingdom

12:30 - 13:30 Lunch and collaborations discussion at BDD Hall

13:30 - 15:00 Hands-on tutorials: parallel sessions

Time/Place	Amphi BDD	Annexes 1-3 BDD
13:30 - 14:10	Tutorial 5	Tutorial 7
14:10 - 14:15	Break	Break
14:15 - 14:55	Tutorial 6	

Tutorial 5: From interaction maps to dynamical models with Cell Collective: a hands-on tutorial
Tomas Helikar, University of Nebraska-Lincoln, Lincoln, United States

Tutorial 6: mEPN and yEd: a graphical and computational modelling platform for biological pathways
Tom C. Freeman, University of Edinburgh, Edinburgh, UK

Tutorial 7: A tutorial of hipathia, a mechanistic model of pathway activity
Martha R Hidalgo, Centro de Investigación Principe Felipe, Valencia, Spain
Joaquin Dopazo, Fundación Progreso y Salud, Sevilla, Spain

15:00 - 15:30 Invited talk: Share FAIR – Data management and standards for Systems Medicine
Martin Golebiewski, Heidelberg Institute for Theoretical Studies, Heidelberg, Germany

15:30 - 16:00 Coffee break at BDD Hall

Session 7: Visualization and modeling frameworks

16:00 - 16:10 Instantiation of patient-specific network-based logical models with multi-omics data allows clinical stratification of patients
Jonas Beal, Institute Curie, Paris, France

16:10 - 16:20 Visual analytics of biological networks using VANTED and its SBGN-ED add-on
Hanna Borlinghaus, University of Konstanz, Konstanz, Germany

16:20 - 16:30 MINERVA API and plugin architecture: new data visualization interfaces for disease maps
Piotr Gawron, Luxembourg Centre for Systems Biomedicine, Belval, Luxembourg

16:40 - 17:15 Thematic discussion groups

Integration of maps in a shared repository
Tools for maps generation
Applications of disease maps in research and clinics: what is missing to close the gap?
Maps to models: curation standards to allow easy transformation of networks into executable models
Maps' complexity management approaches
Disease pathways vs. healthy pathways: how different are they?

17:15 - 17:30 Conclusions and closing session
Emmanuel Barillot, Institute Curie, Paris, France
Reinhard Schneider, Luxembourg Centre for Systems Biomedicine, Belval, Luxembourg

ABSTRACTS

Session 1: Disease maps resources

Integrating disease maps using a graph database approach

Irina Balaur1, Alexander Mazein1, Charles Auffray1

European Institute for Systems Biology and Medicine (EISBM), Lyon , France1

Background: Disease maps are being developed as comprehensive, highly curated and human-readable resources for describing disease mechanisms. The Disease Maps community is continuously extending and currently includes 14 projects (http://diseasemaps.org/projects). There is a need for integration of disease maps in a common platform in order to facilitate extension, interrogation and visualization of the integrated data. Graph databases are a natural way to represent and manage biological networks (Lysenko et al., 2016, PMID 27462371; Balaur et al., 2016, PMID 27627442; Toure et al., 2016, PMID 27919219; Balaur et al., 2017, PMID: 27993779; Fabregat et al., 2018, PMID 29377902). Objectives: We aim to highlight advantages and comment limitations of using the popular graph database Neo4j (neo4j.com) as a core for the common platform for the management (integration, exploration, visualisation) of biological data available in disease maps. Neo4j facilitates network based data integration and provides functionalities for visual exploration of sub networks of interest via a powerful query language (Cypher). Approach: We discuss several examples where we successfully applied Neo4j for biological knowledge management. Specifically, we first present the Recon2Neo4j framework, which facilitates Recon2 metabolic data exploration using Neo4j (Balaur et al., 2017, PMID: 27993779). Then, we describe a general-purpose UniProt ID-centric framework that has been developed to facilitate exploration of disease context by integrating biological data from major specialized resources on protein-protein interactions, disease-gene associations, drug target relationships, protein-pathway involvement and sequence similarity (Lysenko et al., 2016, PMID 27462371). This resource determined development of specialised Neo4j-based frameworks for asthma and for cardiovascular diseases, to date, by integration of a set of disease-specific implicated genes (denoted here as the “seed genes set”). Finally, we present the STON framework (Toure et al., 2016, PMID 27919219), developed to represent and query information from Systems Biology Graphical Notation (SBGN) diagrams using Neo4j networks. Conclusion: We anticipate that the use of Neo4j would facilitate quick exploration of the integrated data and identification of common/ overlapping modules within disease maps. A common Neo4j-based framework would offer also the possibility to query all disease maps at once and identify those that include, for example, proteins of interest. However, given the complexity of the integrated maps, the development of the graph data model is not trivial and the effort of the framework implementation has to be wellestimated. Acknowledgements: The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking the eTRIKS Project (IMI 1154446) resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.

A disease map for the blood pressure and glomerular filtration regulatory network on which antihypertensive and analgesic drugs act

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Pre-renal acute kidney injury occurs as a result of glomerular hemodynamic alterations resulting in reduced glomerular filtration rate (GFR) with no parenchymal compromise. Renin-angiotensin system inhibitors, such as angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor antagonists (ARAs), non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics are highly prescribed drugs that are frequently administered together. Double and triple associations have been associated with increased pre-renal AKI incidence; which have been termed in the literature as “double whammy” and “triple whammy”, respectively. We have mapped the systemic and renal hemodynamic regulation network to analyze, in an integrative way, the complex interplay among the pathophysiological effects produced by NSAIDs, ACEIs/ARAs and diuretics, when acting alone and also in double and triple therapies altogether. And also, how and to what extent does each of these scenarios alter the physiological equilibrium regulating blood pressure (renal perfusion pressure) and GFR, in order to understand how the additive effect of these drugs increases the odds of inducing AKI by concomitantly reducing blood pressure and distorting renal autoregulation. From this knowledge, a more general model of pre-renal AKI arises, which is based on a multi whammy model whereby several factors are necessary to effectively reduce net filtration. The triple whammy would be only one model leading to pre-renal AKI with the concourse of other risk factors, among numerous potential combinations of clinical circumstances causing hypoperfusion, in which renal autoregulation is not operative or is deregulated. This would lead to uncoupling of the normal BP-GFR relationship, where new (lower) GFR values are obtained at every BP value, or at least in a determined range of BP.

Towards a molecular map of cystic fibrosis mechanisms

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Background. Cystic fibrosis (CF) is a monogenic genetic disease caused by more than 2000 mutations identified in the CF transmembrane conductance regulator (CFTR) gene, although one single mutation -F508del- occurs in ~85% of patients worldwide. This gene encodes CFTR protein, an anion (Cl-/HCO32-) channel which when mutated results in a multi-organ disease that affects mostly the lungs and is ultimately life-shortening. The growing omics studies relative to disease states provide the opportunity to integrate data from different sources and to analyse with a greater context the mechanisms and interactions involved in the development of a disorder like CF (Clarke et al., 2015, PMID 26225835).

Goal and objectives. This work aims to create a disease map for CF describing the existing in an organized way by integrating current data on CF and to use this map as a resource to discover new interactions and new therapeutic targets.

Methods. Data from the literature and pathway databases is used to build a network of interactions for normal (wt) and mutant (F508del) CFTR via the Systems Biology Graphical Notation standard (SBGN, www.sbgn.org). The construction is designed in collaboration with CF domain experts.

Results. MetaCore pathways on wt- and F508del-CFTR were updated by publicly available databases and literature searches for the creation of the CF-MAP. This map represents interactions among more than 300 proteins with focus on the life cycle and the immune response triggered in the lung when the F508del mutation is present.

Conclusion. CF-MAP represents an updated repository containing the current pathways implicated in the pathogenesis of CF. The organized knowledge present in this map may serve as basis for further computational analyses using a transferable and scalable technology that can be applied to different projects do address multiple questions. The CF-MAP thus supports research communities in CF field allowing an easier exploration and analysis of complex data and the identification of key players in the disease, leading to the discovery of new therapeutic targets.

Keywords: CF-MAP; cystic fibrosis; omics; data integration; computational model; SBGN

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Session 2: Disease maps resources II

The AsthmaMap: computational representation of disease mechanisms using domain expert knowledge

Alexander Mazein1,*, Olga Ivanova1,2,3, Irina Balaur1, Valeriya Berzhitskaya4, Tatiana Serebriyskaya4, Bertrand De Meulder1, Richard G. Knowles5, Craig Wheelock6, Sven-Erik Dahlen 6, Kian Fan Chung7, Ian Adcock7, Graham Roberts8,9, Anke-Hilse Maitland-van der Zee3, Josep Roca10, Johann Pellet1, Piotr Gawron10, Stephan Gebel11, Marek Ostaszewski11, Reinhard Schneider11, Rudi Balling11, Peter J. Sterk3, Charles Auffray1,*; U-BIOPRED Study Group; eTRIKS Working Group

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BACKGROUND: Advances in detailed representation of disease mechanisms provide new solutions for the development of personalised medicine. Successful projects have built reference computational resources for cancer, Parkinson's disease, Alzheimer's disease and influenza (Kuperstein et al., 2015, PMID 26192618; Fujita et al., 2014, PMID 23832570; Mizuno et al., 2012, PMID 22647208; Matsuoka et al., 2013, PMID 24088197). These are applied for modelling, advanced hypothesis generation and their subsequent validation in relevant clinical contexts (Chanrion et al., 2014, PMID 25295490; Jdey et al., 2016, PMID 27559053; Kuperstein et al., 2015, PMID 25688112).
OBJECTIVES: In this work we developed a pathway-based representation of asthma mechanisms using literature, databases, inputs from domain experts, combined with the use of a tool for semi-automatic merging of relevant pathways.
METHODS: The overview diagram is designed together by computational biology and asthma domain experts and used to determine the content of the detailed layers. The representation is constructed automatically with a newly developed dedicated pathway merging tool, using the yEd Graph Editor and information from selected MetaCore PathwayMaps converted to the Systems Biology Graphical Notation (SBGN) Activity Flow language (Le Novere et al., 2009, PMID 19668183) for making it both human- and machine-readable.
RESULTS: We introduce the AsthmaMap resource (http://asthma-map.org), a multiscale representation of asthma mechanisms. It is a collection of interconnected asthma-relevant pathways and networks. The Activity Flow layer (http://asthma-map.org/af) consists of 15 cell-specific maps with 2650 nodes and 4716 edges in total and includes 831 unique entities. We discuss the challenges faced in the semi-automatic assembly of such maps. With the proposed technology, the resource becomes highly flexible, less dependent on manual work, and it can be easily updated when new information becomes available.
CONCLUSION: In the context of the Disease Maps Community effort (Mazein et al., 2018, in press; Ostaszewski et al., 2018, PMID 29688273) the development of new technological solutions opens promising possibilities for the efficient construction of new disease maps. While being complementary to other pathway analysis solutions, the AsthmaMap enables 'omics data visualisation and interpretation in the asthma-specific context, thus supporting the process of personalised systems medicine for the understanding and treatment of this complex disease.

AVAILABILITY: All relevant data are available at http://asthma-map.org. The code of the yEd-specific GraphML-SBGN converter is written in Java and available at https://github.com/eisbm/ySBGN.
ACKNOWLEDGEMENTS: Funded in part by the Innovative Medicines Initiative (U-BIOPRED n°115010, eTRIKS n°115446).

A multiscale signalling network map of immune response in cancer reveals signatures of cell heterogeneity and functional polarization

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To describe the balance between components of tumor microenvironment (TME) and to analyse impact of both non-immune and immune cells, we systematically collected information on related molecular mechanisms and represented in a form of comprehensive network maps. The modular map of cancer associated fibroblasts (CAF), the non-immune component of TME, is composed of 681 objects and 585 reactions. The map is covering the main functions of CAFs in tumor among others, interactions with extracellular matrix components, signalling coordinating involvement of CAFs in tumor growth and interactions of CAFs with immune system. There are two types of functional modules on the CAF maps, modules responsible for CAFs activation are associated with protumor activity and modules involved in CAFs inhibition, therefore contributing to anti-tumor activity. In addition, we constructed signalling maps of macrophages, dendritic cells, myeloid-derived suppressor cells, natural killers, neutrophils and mast cells. These cell type-specific maps integrated together and updated by interactions and crosstalks between them and the map of tumor cell, gave rise to a seamless comprehensive meta-map of innate immune response in cancer. The meta-map contains 1466 objects and 1084 reactions and depicts signaling responsible for anti- and pro-tumor activities of innate immunity system as a whole. The meta-map is represented in a geographical-like manner, possessing a hierarchical structure with two functional zones, each divided into meta-modules and smaller sub-modules. The network maps were applied for identification of possible molecular mechanisms regulating CAF and innate immune cells reprogramming in TME in metastatic melanoma. Unsupervised statistical methods were applied for decomposition of single cell RNASeq data of CAF, natural killers and macrophages. Analysis and interpretation of expression patterns in the context of the network maps demonstrated existence of numerous sub-populations within each cell type characterized by different anti- and pro-tumor functional properties. These network-based polarization signatures correlated with the survival status of patients. We concluded that tumor microenvironment may contain a range of CAF and innate immune cells, varying in their polarization status. The fine-tuned balance between the sub-populations will dictate the overall impact of TME onto tumor evolution in each given case.

Parkinson's disease map facilitated gene expression analysis reveals new insights in PD pathogenesis

Stephan Gebel1, Marek Ostaszewski1, Piotr Gawron1, Amer Ashrafi1, Pierre Garcia1, Reinhard Schneider1, Rudi Balling1

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Recent developments in 'omics' technologies allow studying molecular pathogenesis/mechanisms of diseases in great detail. However, comprehensive interpretation of such data requires their integration with the existing body of knowledge on a given disease. The Parkinson's disease (PD) map, developed by the Luxembourg Centre of Systems Biomedicine (LCSB) together with the Systems Biology Institute, Tokyo, Japan, makes the information from more than 1500 research articles and public databases available for interpretation in a molecular interaction map. The MINERVA platform, developed at LCSB, which is tailored for visualization and management of disease maps, allows for overlay of experimental data from 'omics' studies, thereby enabling an interpretation of the data in the context of disease related cellular compartments and molecular processes. PD map platform was successfully applied in the past for the interpretation of transcriptomic data from animal models of PD. The objective of the study was to identify early disease marker for PD, which is essential, since the disease is already in an advanced state when motor symptoms become obvious. The transgenic mouse model used shows a moderate overexpression of mutated human alpha-synuclein. This protein can form aggregates and fibers, resembling contents of Lewy bodies that are supposed to be involved in human PD pathology. Consequently, the mouse line shows mild PD-like pathology starting at 9 months of age. Transcriptomic data were generated from ventral midbrain tissue samples, of 3, 9 and 13 months-old mice, to identify perturbations in relevant molecular pathways before neurodegenerative or behavioral changes appear. Analysis of differential gene expression using the PD map reveals early molecular changes in PD-related processes such as dopamine metabolism and calcium signaling. In addition, the system provides hypotheses on perturbations of regulatory elements, such as transcription factors, that may trigger the disease progression. Furthermore, PD map tools enable translation of the results to human by direct comparisons with data from human studies. Finally, by overlaying gene variants data from NGS studies in humans and linkage out to drug databases PD map will support patient stratification in precision medicine and the identification of potential drug targets.

Computational systems biology approach for the study of rheumatoid arthritis: from a molecular map to a dynamical model

Anna Niarakis1

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In this talk I will present a systematic effort to summarize and code current biological pathway knowledge concerning Rheumatoid Arthritis (RA), in a way that is both human and machine readable, facilitating the use of a molecular map as an analytical tool, as well as the extraction of an executable logic-based dynamical model. A detailed molecular map, based on exhaustive literature scanning, strict curation criteria, re-evaluation of previously published attempts and most importantly experts' advice is being constructed using the software CellDesigner. This RA map will be webpublished in the form of an interactive google map, using the software MINERVA, allowing for easy access, navigation and search of all molecular pathways implicated in RA. The user will have access to all literature used, with detailed annotations for every component and reaction, including PubMed IDs, and a list of identifiers such as Uniprot, EntrezGene, Ensembl, HGNC and RefSeq. As the map is constructed using information from various experimental studies, the user will also be able to opt for visualization of data with specific cell origin, highlighting cell-specific sub-networks within the global one. Moreover, the user will have the possibility to spot all known drug targets, and the corresponding drugs up to date for RA. Detailed view of an element will allow the search for drugs, chemicals and miRNAs targeting this particular element. Additionally, userprovided Omic datasets could be displayed as overlay, giving a first estimation of affected pathways and components. Static representations of molecular networks can provide useful but relatively limited understanding, if one wishes to test more complicated scenarios. A dynamical study can reveal information about the system's behavior under different conditions by in silico simulations, perturbations, complex hypotheses testing and predictions. A detailed molecular map can serve as an excellent basis for a dynamical model, providing a template for the building of a regulatory graph. Leaning on the RA map and using the web platform Cell Collective, a platform that supports annotation and real time simulation and analysis for large scale networks, we are currently working towards the semi- automated inference of a logical (Boolean) model, with a set of preliminary logical rules based on the topology of the network. One of the main objectives of this collaborative and interdisciplinary work is to facilitate the transition from static representations of biological knowledge to executable dynamical models, addressing among others, issues of interoperability between tools widely used by the systems biology community.

Invited talk:

WikiPathways: Curation, Visualization and Analysis of Biological Pathways

Martina-Summer Kutmon1, Kristina Hanspers2, Jonathan Melius1, Ryan Miller1, Nuno Nunes1, Anders Riutta2, Denise Slenter1, Andra Waagmeester3, Egon Willighagen1, Chris T. Evelo1, Alexander Pico2

Maastricht University, Maastricht, the Netherlands1, Gladstone Institutes, San Francisco, CA, USA2, Micelio, Antwerp, Belgium3

WikiPathways (www.wikipathways.org) is a community curated pathway databases that enables researchers to capture rich, intuitive models of pathways. In this talk, I will highlight the latest developments, newest features and ongoing projects of WikiPathways and the associated tools pathvisio.js, PathVisio and the WikiPathways app for Cytoscape. The database and the associated tools are developed as open source projects with a lot of community engagement.

Tools: The interactive JavaScript-based pathway viewer, pathvisio.js, is integrated in the WikiPathways website and enables users to zoom in and click on pathway elements to show links to other databases. The standalone pathway editor, analysis and visualization tool, PathVisio provides easy-to-use drawing and annotation tools to capture identities, relationships, comments and literature references for each pathway element and interaction. The WikiPathways app for Cytoscape can be used to import biological pathways in Cytoscape for data visualization and network analysis.

Data: The WikiPathways database is improved by continuous data curation and updates through an expanding community: more than 630 individual contributors and more than 2,500 edits on nearly 900 pathways in 2017. In February 2018, we have reached a total number of pathways of 2,652 for 27 different species. Recently, we have decided to adopt the Creative Commons CC0 waiver for our content on WikiPathways. Our data is available for download from our website, through our REST webservice or in RDF format from our SPARQL endpoint. We are also in the progress of importing our content into WikiData.

Hands-on tutorials: parallel sessions

Tutorial 1: **Tutorial: Constructing and visualizing pathways with web-based SBGN editor Newt**

Ugur Dugrosoz1

Bilkent University, Bilkent, Ankara, Turkey1

Aim of the tutorial This tutorial aims to introduce the free, open-source pathway editor Newt (http://newteditor.org). Basics of the tool will be demonstrated and the attendees will be asked to reproduce parts of some demos. In addition, an exercise is to be provided for each attendee to construct a simple map from scratch.

Tools/methods planned to be presented We plan to have short demos followed by small exercises for the attendees. Tutorials include: - Basics of editing with Newt: creating map entities, creating relations between, aligning entities, annotating entities, export and import facilities, launching Newt with a URL - Automatic layout capabilities in Newt: re-calculating layout and modifying settings for layout - Complexity management with Newt: how to create submaps, how to collapse-expand submaps, compartments, and complexes, how to hide-show parts of a map - [For tool builders] Customizing Newt: how to change look & feel and functionality in the Newt application Exercises include: - Creating simple Process Description and Activity Flow maps from scratch using basic Newt functionality

Technical requirements for attendees: software installation, data downloading Newt is a web based tool and works on all modern browsers with recent versions. Sample data is available within the tool. Attendees are not required to have any prior knowledge of using a similar editor as both there is plenty of online documentation and quick help available within and outside the tool.

Expected take-home message, learning objectives At the end of the tutorial, attendees are expected to be able to: - draw both process description and activity flow maps from scratch - interactively modify both topology and geometry of existing maps - manage complexity of maps through expand-collapse and hide-show operations - persist maps on disk as SBGN-ML or static images - embed their maps in their web pages for convenient editing with Newt - perform live queries to the Pathway Commons database - [for tool builders] modify Newt for building custom applications with specific functionality

Tutorial 2: MINERVA for visualization of disease maps

Piotr Gawron1, Marek Ostaszewski1

Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Luxembourg, Luxembour1

The MINERVA platform (http://r3lab.uni.lu/web/minerva-website/) is used for visual exploration of molecular interaction diagrams and displaying them together with experimental data for interpretation. MINERVA supports several disease maps, including the Parkinson's disease map (pdmap.uni.lu). The functionalities of the platform allow for advanced annotation of uploaded diagrams, configuration of submaps or management of comments to hosted content. This tutorial will teach you how to upload and manage maps in MINERVA.

Tools to be presented: You will be working with a running instance of MINERVA platform to upload your maps, learn how to: - configure an advanced map (with submaps, graphical illustrations and pre-loaded datasets) - configure automated annotators and verifications of the content - manage users and their access to the platform - manage comments to content on the map - (for bioinformaticians) how to use MINERVA REST API and how to configure your own plugin

Technical requirements: We will set up a sandbox instance of MINERVA for the needs of the tutorial. You will need: - A laptop with access to the web and Chrome or Firefox browsers - A CellDesigner software installed (http://celldesigner.org) - Access to Newt Editor (http://newteditor.org)

After the tutorial, you will become familiar with the MINERVA platform and be able to use it for hosting and exploration of various molecular interaction networks. This may become useful not only for supporting disease maps, but other molecular maps you may want to construct and share.

Tutorial 3: rROMA, a tool for module activity calculation from omics data and networks

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In many analysis of high-throughput data in systems biology, the focus has shifted from single gene to the gene-set level. This important change has been motivated biologically, as many diseases are believed to be associated with modest regulation in a set of related genes rather than a strong increase in a single gene. ROMA can be applied in many contexts, from estimating differential activities of transcriptional factors and for finding deregulated pathways in omics data from patients, single-cells and beyond.

The tutorial aims to explain and disseminate this method within the community of researchers involved in high-throughput genomic data analysis in health and disease.

In this tutorial, we present the ROMA (Representation and quantification Of Module Activities) software and the associated rROMA R interface, designed for fast and robust computation of the activity of gene sets (or modules) with coordinated expression. ROMA is a software package written in Java for the quantification and representation of biological module activity using expression data and calculation of the individual gene contribution to the module activity level. ROMA is using the first principal component of a PCA analysis to summarize the coexpression of a group of genes in the gene set. ROMA is also accessible via ROMA Dashboard: complete R shiny interface providing a set of analysis and visualization tools for overdispersion, overcoordination, overexpression analysis of gene signatures and scoring sample-wise, using transcriptomics and quantitative proteomics data.

More information is available at: https://github.com/sysbio-curie/Roma https://github.com/Albluca/rRoma https://github.com/sysbio-curie/rRomaDash https://doi.org/10.3389/fgene.2016.00018

Tutorial 4: The COBRA Toolbox for visualisation and map manipulation through CellDesigner and MatLab environment

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Visualisation of data on top of biochemical pathways is an important tool for interpreting constrained-based modelling results. Biochemical network maps permit the visual integration of model predictions with the underlying biochemical context. Patterns that are very difficult to appreciate in a simple vector can be better appreciated by studying a generic map contextualised with model predictions. No currently available software satisfies all the requirements that might be desired for visualisation of predictions from genome-scale models. Here we present a tool for the visualisation of computational predictions from The Constraint-based Reconstruction and Analysis Toolbox (COBRA Toolbox) to available metabolic maps developed in Cell Designer (CD). Furthermore, online visualization is also possible in ReconMap3.0, a virtual visualisation of human metabolism derived from Recon3D. In this tutorial, basic map manipulations and data visualisation in the context of a metabolic network will be explained. Furthermore, visualisation of some common COBRA methods such as Flux Balance Analysis (FBA) and Flux Variability Analysis (FVA) would be also approached.

The COBRA Toolbox is a MATLAB software suite for quantitative prediction of cellular and multicellular biochemical networks with constraint-based modelling. The COBRA Toolbox can be freely downloaded from (https://opencobra.github.io/). MATLAB environment would be therefore required; a trial can be freely downloaded from (https://nl.mathworks.com/downloads/). If you are already familiarized with MATLAB and you want to test some analyses like FBA on your own, you will need a mathematical solver such as the GUROBI Optimizer solver (http://www.gurobi.com). However, during this workshop, we will provide you with some examples. For map visualisation, the diagram editor for drawing gene-regulatory and biochemical networks Cell Designer would be required, which is also freely available at (http://www.celldesigner.org). The latest version of ReconMap3 and Recon3.0 model can be found and downloaded from (VMH.uni.lu). At last, online visualisation trough the VMH website would be also approached.

After this tutorial, you would be able to understand the structure of a constraint-based model, the structure of a CD metabolic map parsed to MATLAB environment, and more important the crosslink between both structures. Furthermore, you will be able to automatically manipulate CD metabolic maps through MATLAB environment and visualise the output of some COBRA methods in Cell Designer. As for last, you will also visualise these outputs in an online version of the map through VMH website.

Session 3: Maps of biological processes and disease

The Adult Neurogenesis Map

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The hippocampus is a key brain structure for learning and memory. It not only processes input from the environment, but also fundamentally influences behaviour. This means that the neural network in the hippocampus is a core part of an information loop connecting environmental stimulus and response. It is particularly intriguing that this special brain region is also home to a population of neural stem cells which allow the environmentally-regulated creation of new neurons, throughout the life of the organism, that add an extra level of flexibility to hippocampal performance. We have previously shown that the regulation of the stem cell pool and the generation of new neurons are under complex genetic control. We also maintain a structured database of all genes reported to affect adult hippocampal neurogenesis in some way. We now aim to extend this effort to encompass behavioural phenotypes and environmental stimuli. The resulting information is being organised into a structured map to enable interactive browsing and complex searching of the knowledgebase, as well as to provide a platform for predictive modelling. We present here a working draft of the Adult Neurogenesis Map and look forward to community feedback as the project expands.

The Ras/Raf/Mek/Erk Signaling Pathway - Attention to Details

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Cancer is caused by aberrant signaling in cells. Often mutations in important signaling pathways lead to faulty transmission of signals and cause cells to divide uncontrolled. The Ras/Raf/Mek/Erk pathway is one of the important pathways for the cell to relay signals from the plasma membrane to the nucleus and cytosolic targets. It is also frequently involved in the development of cancer. Through years of research an extensive amount of data and knowledge about this pathway has been obtained, but we still find that key elements of our understanding are missing. To address this problem, we assembled a Boolean model of the pathway, to be able to simulate its behavior without making assumptions about rates and concentrations. During the assembly of the model we found a lack of data on short timescales, from the moment of stimulation of the pathway to about 30 minutes. We therefore performed an experiment with nine cell lines and four input stimuli to observe the behavior of phosphorylated Mek and Erk in this timespan. The data showed a marked difference between cell lines carrying a NRasQ61R mutation and those with a NRasQ61L mutation. Using our Boolean Model of the pathway, we propose a possible explanation for the observed behavior. The NRasQ61 site is known to play a role in the binding of GAP and the deactivation of NRas. Analogous to scaffold binding in kinases, the binding site for GAP could be shielded by a scaffold to protect it from premature deactivation. The Q61 residue could therefore play a role in binding the scaffold. The mutations would then affect not only the binding of GAP to NRas, but also the recruitment and binding of a possible scaffold protein.

Is cellular senescence a prerequisite for tumor invasion?

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Epithelial-mesenchymal transition (EMT) and tumor invasion allowing cancer cells to degrade extracellular matrices are crucial events in metastasis dissemination, yet poorly understood. Premature senescence, defined as a stable G1 cell cycle arrest within oxidative stress, the main inducer, is often considered as a mechanism of protection against cancer. Nothing is presently known about how senescence could be linked to tumor invasion and senescence pathways activation has not been reported yet as a prerequisite to cancer invasion. Metastatic and invasive programs are limited by NM23H1/NME1, the first discovered metastasis suppressor but the mechanisms involved remain unknown. The general goal of this project is to combine experimental and computational approaches to establish and understand the link between senescence and tumor invasion in cancer cells, while highlighting the role of NM23-H1/NME1 in this process. By using human tumoral cell lines endowed with different invasive properties and tumor samples, we show that genetic modulations of NM23-H1 (overexpression/depletion) regulate mitochondrial production of the reactive oxygen species (ROS) and the resulting cellular senescence process. In addition, we have observed that the invasive program of low NM23-H1 cells is significantly reduced in the presence of ROS scavenger. Strikingly, in samples of human colorectal tumors, we observed a senescent phenotype in the tumor budding region i.e a dedifferentiated region with EMT characteristics as compared to the well-differentiated central area. Accordingly, samples of human colorectal cancer of high grade (grade IV) strongly expressed senescence markers as compared to low grade (grade I), associated with a dramatic downregulation of NM23-H1. We constructed a comprehensive signaling network map to systematically represent the knowledge from the scientific literature about these molecular mechanisms and retrieve an explanation for the experimental observations as above and decipher the role of NM23-H1 with respect to senescence and invasion. In particular, we depicted the pathways involved in oxidative stress, senescence, EMT and invasion while focusing on NM23-H1 impact. The map contains around 700 proteins, 1500 reactions, 11 functional modules and it is based on approximately 1400 scientific papers. We performed structural analysis of the network to retrieve models explaining the interplay between oxidative stress, senescence and invasion with respect to the NM23-H1 protein. This work will help to a better understanding of the molecular bases of the invasive program and will permit to design new diagnosis or treatment strategies against metastatic spread. We could indeed give some new answers regarding the possibility to kill senescent cells using senolytic molecules in case of a cancer in order to improve current cancer treatment.

Session 4: Maps for drug assessment and disease comorbidity

Comprehensive signaling network of regulated cell death: comparison of cell death modes in Alzheimer's neurodegenerative disease and cancer

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Based on experimental data retrieved from literature, an integrated signalling network of Regulated Cell Death (RCD map) has been constructed. The RCD map is composed of three layers; the "Initiation" layer covers biochemical triggers, input signals and mechanisms that initiate RCD. The "Signalling" layer, recipient of inputs, is the level where the decision about cell death mode is made choosing among Apoptosis, Necroprosis, Ferroptosis and Parthanatos and Pyroptosis. The "Execution" layer depicts the mechanisms activated by one of the five signalling RCD modes and represents the decomposition and degradation mechanisms of the cell. The RCD map is divided into 26 functional modules that can be visualized in the context of the whole map or as individual diagrams. The map contains about 1200 proteins and genes, 2020 biochemical reactions and is based on 600 scientific papers. The map is an open source platform facilitated by the NaviCell web-tool (https://navicell.curie.fr/pages/maps_rcd.html). The RCD map was applied to explore and interpret the differences in cell death regulation between Alzheimer's disease and lung cancer, diseases that have been suggested to have inverse comorbidity. Enrichment analysis of RCD map modules using gene expression data from each disease was performed using the ROMA algorithm; deregulated molecular functions as well as the main players were compared. Mostly, the activation of stress response and metabolic functional modules was observed in lung cancer; whereas the modules of cell death initiation, especially ligand-receptor pathways leading to apoptosis and necroptosis were less active. Alzheimer's disease data analysis revealed that the majority of regulated cell death modes are actually not completely present, except of pyroptosis, in agreement with previous studies showing an active pyroptosis key player in the betaamyloid plaque development. We observed that metabolism-related modules are less active in the Alzheimer's disease, in opposite to lung cancer. We concluded that the inverse comorbidity between these diseases implicates rather metabolic pathways.

Predicting personal activation potential of CD4 T cells

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Human individuals show great variance in both innate and adaptive immune responses following immune stimuli. However, little is known about which and how molecular subnetworks quantitatively control the immune response potential. Such knowledge would generate a huge impact and have far-reaching consequences for shaping individual immune responses to vaccinations, antigen-specific immunotherapies (IT), anti-cancer immunotherapies and others. Here we used machine learning approaches to infer gene subnetworks that could quantitatively predict activation potential of different individuals using transcriptome of baseline CD4+CD25- effector T cells (Teffs) sorted from peripheral blood mononuclear cells (PBMC) of distinct donors. The top-ranked candidate genes were further tested using siRNA knockdown methods and indeed showed a significant effect on the activation potential of human Teffs. The in-vitro results will be further validated in a clinical trial using multi-layer 'Omics' analysis on various subsets of CD4 T cells sorted from time-series blood samples of allergy patients following antigen-specific IT. The resulted subnetworks before the commencement of IT could be used as valuable predictive biomarkers to support clinical decisions on tailored immunotherapies of different patients.

Reconstruction of integrated maps for drug efficacy assessment

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Background. Analysis of biological network and signaling pathways is widely used for investigation of cell processes, mechanisms of disease, drug development and analysis of drug repurposing perspectives. Different scientific groups develop similar conceptions of biological networks and pathways that represent processes in norm , but conceptions of disease-specific pathways and drug mechanism of action pathways can differ significantly amoung researchers. Previously, we've developed the conception of disease-specific pathway maps that show affected normal processes in pathology and some steps that newer have been detected in norm. The disease maps show enhanced and weakened interactions or reactions under pathological conditions resulting from mutations or abberant gene expression. Another conceptions was compillation of disease-specific pathways with drug, xenobiotic or another enviromental factor action in one mapthat represent both disease-specificity and drug-induced perturbations. Research objective. The aim of research was to elucidate mechanisms of acquired or hereditary drug resistance for small group of patients suffering from breast cancer with triple negative phenotype (TNBC). Materials and methods. Group of 10 patients suffered from TNBC has been enrolled in study. All patients have got similar antitumor therapy. Whole exome sequencing and whole transcriptome analysis ware performed for the genomic DNA and RNA obtained from tumor samples . DAVID and MetaCorehave been used for functional and integrated analysis. Reconstruction of integrated maps of tumor processes has been performed in Cytoscape APP. Results. Whole exome sequence showed high heterogeneity of tumor samples. Several hereditary risk factors (mutations in TP 53/ Li-Fraumeni syndrome, mutation in MSH6 / Lynch syndrome) and damaging mutations in well- known driver genes were detected in patient samples. Analysis of tumor gene expression data allowed to reveal the concordance of patient data with different subtypes of Lehmann's classification of TNBC. Pathway analysis by MetaCore and David wasn't capable to explain tumor drug resistance in patients. So for the aims of this project we've combined conceptions of disease-specific and drug mechanism of action maps and reconstructed integrated models using Cytoscape. Compilation of different types of data in these maps allowed to clearly define differences between Lehmann's subtype patients and explain possible drug resistance mechanisms in each subtype. Conclusion. Compilation of disease-specific pathways and mechanisms of drug action with genetic, farmacogenomic and expression data allows to build comprehensive models that reflect processes of tumor progression and in some cases explain the drug resistance.

Metabolic and signalling network map integration: application to crosstalk studies and omics data analysis in cancer

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The interplay between metabolic processes and signalling pathways remains poorly understood. Global, detailed and comprehensive reconstructions of human metabolism and signalling pathways exist in the form of molecular maps, but they have never been integrated together. We aim at filling in this gap by creating an integrated resource of both signalling and metabolic pathways allowing a visual exploration of multi-level omics data and study of cross-regulatory circuits between these processes in health and in disease. We combined two comprehensive manually curated network maps. Atlas of Cancer Signalling Network (ACSN), containing mechanisms frequently implicated in cancer; and ReconMap 2.0, a comprehensive reconstruction of human metabolic network. We linked ACSN and ReconMap 2.0 maps via common players and represented the two maps as interconnected layers using the NaviCell platform for maps exploration. In addition, proteins catalysing metabolic reactions in ReconMap 2.0 were not previously visually represented on the map canvas. This precluded visualisation of omics data in the context of ReconMap 2.0. We suggested a solution for displaying protein nodes on the ReconMap 2.0 map in the vicinity of the corresponding reaction or process nodes. This permits multi-omics data visualisation in the context of both map layers. Exploration and shuttling between the two map layers is possible using Google Maps-like features of NaviCell. The integrated ACSN-ReconMap 2.0 resource is accessible online and allows data visualisation through various modes such as markers, heat maps, bar-plots, glyphs and map staining. The integrated resource was applied for comparison of immunoreactive and proliferative ovarian cancer subtypes using transcriptomic, copy number and mutation multi-omics data. A certain number of metabolic and signalling processes specifically deregulated in each of the ovarian cancer sub-types were identified. As knowledge evolves and new omics data becomes more heterogeneous, gathering together existing domains of biology under common platforms is essential. We believe that an integrated ACSN-ReconMap 2.0 resource will help in understanding various disease mechanisms and discovery of new interactions at the intersection of cell signalling and metabolism. In addition, the successful integration of metabolic and signalling networks allows broader systems biology approach application for data interpretation and retrieval of intervention points to tackle simultaneously the key players coordinating signalling and metabolism in human diseases. The manuscript is available at BioRxiv (https://www.biorxiv.org/content/early/2018/03/03/274902).

Session 5: Methods resources and models

Access and Discover Biological Pathway Information from Pathway Commons

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Pathway Commons (www.pathwaycommons.org/) serves researchers by integrating data from public pathway and interaction databases and disseminating it 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 facilitate day-today activities of biological researchers. For those wishing to browse and discover pathways within the collection, we offer a web-based 'Search' application that enables users to query by keyword and visualize ranked search results. 'PCViz' is a web tool that accepts gene names and returns a customizable interaction network visualization based upon pathway data resources. These complement existing desktop software add-ons linking Pathway Commons to the Cytoscape (CyPath2) network analysis tool and the R (paxtoolsr) programming language. To facilitate analysis and interpretation of experimental data - for instance, enrichment studies that distill pathway alterations from underlying gene expression changes - pathway data file downloads can be directly used in software tools such as Gene Set Enrichment Analysis. For those wishing to learn more about pathway resources and analysis, an online 'Guide' includes case studies and guided workflows. Ongoing development of web apps will enhance the accessibility to pathways and integrate support for visualization and interpretation of experimental data.

Community Resources Connecting Chemistry and Toxicity Knowledge to Environmental Observations

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Exposure to chemicals may be a causative or contributing factor to the progression of diseases. On the other hand, chemicals such as pharmaceuticals are also used to prevent, treat or alleviate the symptoms of diseases. Considering a far broader range of small molecules than are currently captured in many biological networks is a huge challenge for disease maps. The number of chemicals for consideration is daunting. The largest chemical databases presently available contain ~100 million chemicals (of which many were never produced in significant amounts), while Europe produces or imports >143,000 substances above 1 tonne/yr, and an estimated 70,000 chemicals are used in households. The latest version of the Human Metabolome Database (HMDB) now contains 114,100 metabolites, yet many of these are predicted structures. Smaller resources such as the US EPA's environmentally focused CompTox Dashboard contain >760,000 chemicals, but even this collection includes chemicals such as isotopically labeled compounds and "UVCB chemicals" - unknown or variable composition, complex reaction products or biological materials, which can represent 10s to 100s of individual chemical components. However, all of these chemical databases are inherently incomplete. In high resolution mass spectrometry (HR-MS) measurements, used to measure chemicals in metabolomics, exposomics, foodomics, forensics and personalized medicine, we are confronted with tens of thousands of features, of which only a few percent can be annotated as "known" and confirmed as metabolites or chemicals of interest using all available chemical databases. How can we reconcile our chemical knowledge with our sample observations? This talk will cover European, US and worldwide community initiatives to help connect knowledge on chemistry and toxicity with environmental observations, i.e. helping researchers to find small molecules in big data in smarter ways - from compound databases to spectral libraries and retrospective screening. It will touch on the challenges of standardized structure representations, data curation, deposition and communication between resources. Finally, it will show how interdisciplinary efforts and data sharing can facilitate research in metabolomics, exposomics and beyond, aiming to stimulate discussions on possibilities for integrating these approaches into disease maps. Note: this abstract does not necessarily represent U.S. EPA policy.

Differential metabolic activity and discovery of therapeutic targets using summarized metabolic pathway models

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In spite of 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. Alterations in the metabolism are behind the initiation and progression of many diseases, including cancer. The wealth of available knowledge on metabolic processes can therefore be used to derive mechanistic models that link gene expression perturbations to changes in metabolic activity that provide relevant clues on molecular mechanisms of disease and drug modes of action (MoA). In particular, pathway modules, which recapitulate the main aspects of metabolism, are especially suitable for this type of modeling. Here we present a simple model of metabolic activity based on pathway modules. The model has been implemented in a web-based application, Metabolizer, which offers an intuitive, easy-to-use interactive interface to analyze differences in pathway module metabolic activities that can also be used for class prediction and in silico prediction of Knock-Out (KO) effects. Moreover, Metabolizer can automatically predict the optimal KO intervention for restoring a diseased phenotype. We provide different types of validations of some of the predictions made by Metabolizer. Metabolizer can be found at: http://metabolizer.babelomics.org. Acknowledgements This work is supported by grants SAF2017-88908-R from the Spanish Ministry of Economy and Competitiveness (MINECO), Plataforma de Recursos Biomoleculares y Bioinformáticos PT13/0001/0007 from the ISCIII, co-funded with European Regional Development Funds (ERDF) and EU H2020-INFRADEV-1-2015-1 ELIXIR-EXCELERATE (ref. 676559)

A computational model of the circadian clock and its application to understanding renal disease

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The circadian clock allows an organism to schedule their internal physiology and behaviour to function at the appropriate time of day. The molecular components at the core of the clock and the interactions between them are highly conserved between all tissues and cells, but their phases and the downstream effects are generally tissue- or cell-specific. The renal circadian clock plays a pivotal role in regulating daily fluctuations in blood pressure through the modulation of sodium transport and extra-cellular fluid volume. Perturbations of this rhythm, particularly the nocturnal dip, confer increased risk for cardiovascular and renal disease. In order better understand the circadian biology of the kidney, we decided to construct a model of this system. We first performed an exhaustive search of existing models and the primary literature that described the components of the mammalian circadian clock and the interactions between them. We then employed the modified Edinburgh Pathway Notation (mEPN) modelling language to build a graphical representation of the circadian clock using the principles of bipartite graphs to differentiate between pathway components (places) and processes (transitions). This then allowed us to run Petri net-based stochastic simulations of the system's dynamic activity. To parameterise the model, we used mRNA levels derived from transcriptomics data which describes the diurnal variation in gene expression in the kidney – the expression level of core clock genes in the kidney being used to define starting conditions (expression levels being used as a proxy for protein levels). The transcriptomics data was also used as a target readout of model activity and to achieve this various 'delay motifs' were added to modulate token flow. The result of this work is a detailed network model of the core mammalian circadian clock, which summarises the current literature and understanding on how the circadian clock operates. It contains over 2013 nodes, 2100 edges and represents the interactions between 69 molecular species. The model has also been parameterised for computational modelling using known activity profiles of genes expressed in the kidney. In virtual knock out experiments, the model has been shown to reflect experimental data. It also identifies the points at which canonical clock genes may integrate with downstream processes regulating genes likely to affect blood pressure and other aspects of kidney function.

Session 6: Large Reconstructions and integrations

Status report: parameter estimation of a large-scale mechanistic model for mast cells in asthma

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Background: Asthma is a complex disease involving various heterogeneous mechanisms. A deeper understanding of the heterogeneity of asthma is needed for better diagnosis and therapy. To this end, the development of a mechanistic description of asthma mechanisms was initiated, the AsthmaMap (http://disease-maps.org/projects/asthma). Objective: Our work employs the AsthmaMap to build a mechanistic model of mast cell dynamics, improving our understanding of the disease and offering a tool for predicting the efficacy of medications. Here we aim to develop a predictive model which integrates qualitative knowledge about the pathway topology and quantitative experimental data available in the literature. Methods: We employed the expertise of several domain experts to derive a Systems Biology Markup Language (SBML) model from the mast cell part of the AsthmaMap and additional literature. For the simulation and parameterizations of the SBML model, we used the MATLAB toolboxes AMICI (Fröhlich et al., 2017, PMID 28114351) and PESTO (Stapor et al., 2018, PMID 29069312). Quantitative experimental data were extracted from several published studies (e.g., Parravicini et al., 2002, PMID 12089510). Results: We obtained an SBML model with CellDesigner markup for mast cell signalling, which has more than 300 species and 400 parameters, and includes kinetic laws for all reactions. Additionally, we established a pipeline for building a data repository, which is used for the model parameterization. Preliminary results indicate that the parameterization of the model is challenging, due to nonlinear dynamics. However, the current model already captures several aspects of the mast cell response to allergens. Conclusion: Our study has shown that the translation of a disease map to a mechanistic computational model is a complex process involving a series of steps, among others the establishment of a repository of quantitative experimental data. In the future, this repository might be built alongside the disease map. Overall, we have made substantial progress towards the development of a predictive model for mast cell dynamics. Acknowledgements: Funded in part by the Innovative Medicines Initiative (U-BIOPRED n°115010, eTRIKS n°115446): IB, AM, DL and CA.

Application of disease maps to rare diseases: neuromuscular diseases

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Neuromuscular diseases are a heterogeneous group of neurological conditions. Most of them are inherited, with over 400 genes identified, and rare due to their very low individual prevalence. However, as a whole they are as prevalent as common neurological conditions such as Parkinson´s disease and multiple sclerosis. Based on the anatomical origin of the primary defect they are classified as motor neuron diseases (including spinal muscular atrophy and amyotrophic lateral sclerosis), peripheral neuropathies, myasthenic syndromes (neuromuscular junction) and myopathies and dystrophies (muscle fibre). Although each of them is characterized by a set of clinical and pathological hallmarks, they share some common mechanisms such as fibrosis, inflammation, mitochondrial dysfunction, muscle fibre degeneration and impaired regeneration. In the last few years we have seen a significant development of clinical trials based on molecular therapies or pharmacological modulation of downstream pathways. At present there are two FDA-approved drugs for spinal muscular atrophy and Duchenne muscular dystrophy (DMD). However, a limitation for research and further therapy development in neuromuscular diseases is the fractionation of knowledge and the limited integration between studies, even at the high-throughput data level. Duchenne muscular dystrophy is the most common form of the childhood muscular dystrophies and a paradigm for degenerating muscle diseases. It is caused by mutations in the DMD gene leading to the deficiency of the dystrophin protein from the sarcolemma of muscle fibres. The aim of this project is to generate a repository that describes molecular mechanisms of DMD (the "DMD-map"), and that supports biomarker identification, omics data interpretation, identification of disease types, mapping drug action mechanisms, developing predictive models and suggesting therapeutic strategies. The DMD-map will be the first stage for building a disease map of myopathies (MyoMap) using the information and experience gained in constructing the DMD-map.

Maps of influence and interactions of infectious and cancer diseases from Wikipedia networks

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We use the Google matrix analysis of the English Wikipedia articles network to infer influence of diseases on countries and to infer interactions between diseases and drugs. Nowadays, the free online encyclopedia supersedes old ones such as Encyclopedia Britanica in volume and in quality of articles devoted to scientific topics [1]. For instance, articles devoted to biomolecules are actively maintained by scholars of the domain [2,3]. The Google matrix analysis, associated to the PageRank algorithm [4] initially invented by Sergey Brin and Larry Page to efficiently rank pages of the WWW, allows to probe the network of Wikipedia articles in order to measure the influence of every articles. Recently, using parallels with quantum scattering in nuclear physics, mesoscopic physics, and quantum chaos, we have suggested a novel methodology, called Googlomics [5], for the structural analysis of directed biological networks using spectral analysis of their Google matrices. Moreover we used the new reduced Google matrix method which allows to infer hidden interactions between a set of nodes selected from a huge network. We successfully applied this method for the regulatory biological networks and demonstrate how its computation allows inferring hidden causal relations between the members of a signaling pathway or a functionally related group of genes [5]. Here we study diseases through their entries in the English Wikipedia edition. In particular we focus: - on the set of articles devoted to infectious diseases and the set of articles devoted to countries, in order to measure the influence of different diseases on different countries. Also the reduced network of infectious diseases is built showing direct and hidden relations between diseases, - on the set of articles devoted to cancer types and the set of articles devoted to drugs for cancer treatment, in order to possibly measure hidden interactions between drugs and cancers.

PageRank sensitivity of countries to the variation of the HIV→country link in 2017 English Wikipedia.
References: [1] J. Giles, Internet encyclopaedias go head to head, Nature 438, 900–901 (2005) [2] D. Butler, Publish in Wikipedia or perish, published online 16 December 2008, Nature [3] E. Callaway, No rest for the bio-wikis, Nature 468, 359-360 (2010)
[4] S. Brin, L. Page, The anatomy of a large-scale hypertextual Web search engine, Computer Networks and ISDN Systems 30, 107 (1998) [5] J. Lages, D. L. Shepelyansky, A. Zinovyev, Inferring hidden causal relations between pathway members using reduced Google matrix of directed biological networks, PLoS ONE 13(1): e0190812 (2018)

Integrating ontological representation and reasoning into a disease map: application to Alzheimer's disease

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Background and Objectives: Systems medicine disease maps are ongoing projects that provide fine curated knowledge on pathophysiology at the molecular and phenotypic level (http://disease-maps.org/projects). They are based on a common framework that includes the use of standards and guidelines for defining biological processes and entities. Despite this standardisation effort, there remains some formal and semantics ambiguities: for instance, processes with unexpected participants (e.g. translation of genes instead of transcripts) or phenotypes named with process names (e.g. apoptosis). Ontologies provide a consistent framework to deal with these issues: axiomatic-based definition and logical reasoning properties allow one to underline formal inconsistencies and refine semantic descriptions. In the present work, we propose to use an ontology in order to increase the consistency of the AlzPathway map [1]. Approach: We first built an ontological model based on the definition and axiomatization of high-level classes offered by the CellDesigner diagram [2] including: -the disjunction of gene, gene product (RNA, protein and complex) and phenotype. -the definition of processes according to their actions (e.g. transcription is a process that has as input at least one gene and as output at least one RNA). -the definition of phenotype naming as a state of the system and not as an action. Then, the knowledge contained in AlzPathway was integrated as subclasses of the previously defined high-level classes. This resulted in 2,429 subclasses. We then performed automatic reasoning. It allowed us to identify 285 redundancies, 53 inconsistent processes and 14 inconsistent participants. Moreover, the fine exploration of the ontology led to the identification of 55 phenotypes that refer to biological aggregated processes. We manually fixed these inconsistencies and validated the correction with automatic reasoning. Finally, we validated the ability of this modified map to manage biomedical data using multiomics data from a clinical study. Conclusions: In conclusion, we integrated ontological properties into AlzPathway. Our model clears out ambiguities in the gene, gene product, metabolite, phenotype and biological process specifications, and thus, facilitates the integration of multiomics data. Furthermore, our work points out the lack of consensual definition of phenotypes and the need to manage process granularity. Interestingly, the integration of ontological standard into AlzPathway opens perspectives to link AlzPathway with the Alzheimer Disease Ontology [3].

References 1. Mizuno et al. BMC Syst Biol, 2012, 30; 6:52 2. Kitano et al. Nat biotechnol, 2005, 23; 961-6 3. Malhotra et al. Alzheimers Dement, 2014, 10; 238-46

Invited talk:

Reactome Multi-Scale Pathway Visualisation

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Reactome (https://reactome.org) [1] is a free, open-source, open-data, curated and peer-reviewed knowledge base of biomolecular pathways, currently covering 2,106 Pathways; 10,712 protein coding genes; 11,302 reactions; 27,452 literature references and 1,800 small molecules. Pathways are arranged in a hierarchical structure, allowing the user to navigate from high level concepts like immune system to detailed pathway diagrams showing biomolecular events like membrane transport or phosphorylation. The Reactome curation strategy focuses on the annotation of “normal” pathways in human. However, we increasingly annotate disease-specific pathway modifications, grouped in three major classes: loss of function (typically metabolic disease phenotypes), gain of function (typically cancer phenotypes), and host-pathogen interactions. Here, we present new developments in the multi-scale Reactome visualization system that facilitate navigation through the pathway hierarchy and enable efficient reuse of Reactome visualizations for users' own research presentations and publications. For the higher levels of the hierarchy, Reactome now provides scalable, interactive textbook-style diagrams in SVG format, which are also freely downloadable and editable (Fig 1). Repeated diagram elements like 'mitochondrion' or 'receptor' are freely available as a library of graphic elements at https://reactome.org/icon-lib. Detailed lower-level diagrams are now downloadable in editable PPTX format as sets of interconnected objects, as well as in standard png format.

[1] Sidiropoulos K, Viteri G, Sevilla C, Jupe S, Webber M, Orlic-Milacic M, Jassal B, May B, Shamovsky V, Duenas C, Rothfels K, Matthews L, Song H, Stein L, Haw R, D'Eustachio P, Ping P, Hermjakob H, Fabregat A. Reactome enhanced pathway visualization. Bioinformatics. 2017 Nov 1;33(21):3461-3467.

Hands-on tutorials: parallel sessions

Tutorial 5: Tutorial: From interaction maps to dynamical models with Cell Collective: A hands-on tutorial

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The tutorial will be hands-on throughout. The first part will comprise of an overview of logical modeling and Cell Collective (and its previous applications). The second (larger) part will be spent by having attendees construct and simulate their own models in Cell Collective. Ideally, attendees come with a disease or biological process that they would like to model -- this way they can leave the tutorial with a starting point of a model. For those who just want to learn about the technology (and don't have a biological system in mind), we have a curriculum that will enable them to get familiar with the technology by constructing and analyzing the dynamics of a model of the lac operon regulatory system.

Tutorial 6: mEPN and yEd: a Graphical and Computational Modelling Platform for Biological Pathways

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Aim of tutorial To introduce our biologist-friendly graphical and computational modelling approach1-3. This combines three elements, a sophisticated but easy to use language for depicting biological events at the molecular level, a Petri net-based flow simulation algorithm, and a powerful visualisation engine with which to observe the dynamics of the system being modelled. The modified Edinburgh Pathway Notation (mEPN) language facilitates the construction of detailed network diagrams, summarising the components of a biological pathway (such as proteins, biochemicals etc.) and how they interact. Once constructed, these diagrams can then be used to simulate activity flow through a pathway, thereby modelling system dynamics.

Tools/methods The workshop will involve discussion and hands on experience of the four stages of modelling using this approach: (1) assembly of network diagrams using the mEPN scheme and yEd network editing software using pathway information obtained from published literature and databases of molecular interaction data; (2) parameterisation of the pathway model within yEd through the placement of 'tokens' based on the known or imputed amount or activity of a component; (3) model testing through visualization and quantitative analysis of the movement of tokens through the pathway using network analysis tool Graphia Professional; (4) optimisation of model parameterisation and experimentation. The tutorial requires no prior experience of modelling.

Summary Depending on a model's complexity and the availability of information, its construction can take days to months, and, with refinement, possibly years. However, once assembled and parameterised, a simulation run, even on a large model, typically takes only seconds. Models constructed using this approach provide a means of knowledge management, information exchange, and through the computation simulation of their dynamic activity, a means to generate and test hypotheses, and predict a system's behaviour when perturbed.

References: 1. O'Hara et al., Modelling the Structure and Dynamics of Biological Pathways. PLoS Biol. 14(8): e1002530 (2016). 2. Livigni et al., A graphical and computational modelling platform for biological pathways. Nature Protocols 4: 705 (2018). 3. www.virtuallyimmune.org

Tutorial 7: A tutorial of hipathia, a mechanistic model of pathway activity

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Conventional gene-based approaches ignore the modular nature of most human traits, while pathway enrichment methods produce only illustrative results of limited practical utility. Recently, new methods have emerged that change the focus from the whole pathways to the definition of elementary sub-pathways or circuits within them that have any mechanistic significance. In some cases, this involves the recodification of Process Description pathways into Influence Maps that describe hoe proteins interact among them to trigger or carry out cell functionalities. The activity of such circuits defined within Influence Map pathways is expected to be better descriptor of cell functional activity than whole pathways of single genes. Here we present a tutorial on the HiPathia MPA method (1), implemented in a R/Bioconductor package (http://bioconductor.org/packages/devel/bioc/html/hipathia.html) as well as in an interactive web application (http://hipathia.babelomics.org/). This tutorial demonstrates how to transform decontextualized gene expression measurements into highly-informative cell activity quantitative values how and relate them to phenotypes. Different analyses can be carried out using circuit activities that include differential activity analysis when two conditions are compared or relation of circuit activities to a continuous variable. Since circuits modeled have a functional meaning (any of them trigger one or more cell functions, defined by Gene Ontology terms), the results provide direct clues to understand disease mechanisms or drug modes of action. It is also possible to build predictors directly based on circuit activities, which adds an interesting mechanistic dimension to the prediction process. In addition to be used to uncover the molecular basis of phenotypes, mechanistic models can also be used to predict what would be the potential effect of one or several interventions (KOs, inhibitions, over-expressions, drugs, etc.) over the system studied. Thus, the PathAct (2) wen application (http://pathact.babelomics.org/) allows predicting from a holistic perspective what would be the effects of interventions over a specific system. The HiPathia suite provides a friendly environment to use Influence Map pathways as templates of cell functionality to provide a mechanistic interpretation of transcriptomics data.

1. M. R. Hidalgo et al., High throughput estimation of functional cell activities reveals disease mechanisms and predicts relevant clinical outcomes. Oncotarget 8, 5160 (Dec 22, 2017). 2. F. Salavert et al., Actionable pathways: interactive discovery of therapeutic targets using signaling pathway models. Nucleic Acids Res 44, W212 (Jul 08, 2016).

Invited talk:

Share FAIR – Data management and standards for Systems Medicine

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FAIRDOM develops and offers integrated data management support for research in the fields of systems biology and systems medicine within and across research consortia, like the German research network 'Systems Medicine of the Liver' (LiSyM: http://www.lisym.org), or European research networks like ERASysAPP and NMTrypI (New Medicines for Trypanosomatidic Infections). Parts of these solutions are also applied to projects with a local focus as the Synthetic Biology Centres at Manchester (SynBioChem) and Edinburgh (SynthSys).

Our data management concept aims at bundling, storing and integrating research assets like data, models and description of processes and biological samples in a Findable, Accessible, Interoperable and Reusable (FAIR) manner (http://fair-dom.org) and consists of 4 major pillars: 1) Infrastructure backbone: The SEEK software as registry for data, models, samples, processes, publications and presentations, and as yellow pages for projects, people and events. SEEK is either implemented as data management platform that is maintained by the research project itself (e.g. LiSyM SEEK: http://seek.lisym.org) or as hub service maintained by us and spanning different consortia (FAIRDOMhub: https://www.fairdomhub.org). 2) Standardized data description: Data spreadsheet templates and tailored use of controlled vocabularies and ontologies to describe data and metadata 3) Modelling support: Seamless handling and simulation of models by integrated modelling platforms (e.g. JWS-Online or SYCAMORE) 4) Social support: Facilitators (PALs) in the projects for gathering requirements and dissemination

SEEK specifically supports the interaction between modelling and experimentation. Datasets can be associated with models and/or workflows or biological samples, and model simulations can be compared with experimental data.

For their integration into models, standardization of these data is crucial and also comprises the standardized description of applied methods, biological material and workflows for data processing, analysis, exchange and integration (e.g. into computational models), as well as the setup, handling and simulation of the resulting models. Hence, standards for formatting and describing experimental data, applied workflows and computer models have become important, especially for data integration across the biological scales for multiscale approaches. To this end many grassroots standards for data, models and their metadata have been defined by the scientific communities and are driven by standardization initiatives such as the Computational Modeling in Biology Network (COMBINE). With our activities we also aim at enhancing the harmonization of these standards. This is achieved by building a bridge between
stakeholders and developing the means and channels for transferring information about standards between them, such as the NormSys registry for modelling standards (http://normsys.h-its.org).

Session 7: Visualization and modeling frameworks

Instantiation of patient-specific network-based logical models with multiomics data allows clinical stratification of patients

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We present here a novel framework to tailor logical models to a particular biological sample like a patient's tumor. This methodology permits to compare the model simulations to individual clinical data, such as drug response and survival time. Our approach focuses on integrating mutation data, copy number alterations (CNA), and expression data (transcriptomics or proteomics) to logical models. These data need first to be binarized or set between 0 and 1, and can then be incorporated in the logical model by modifying the activity of the node, the initial conditions or the transition rates. The use of MaBoSS, a tool that uses Monte-Carlo kinetic algorithm to perform stochastic simulations on logical models and obtain model state probabilities, allows for a semiquantitative study of the model's phenotypes and perturbations.

As a proof of concept, we use a published generic model of a cancer network and molecular data from 1904 METABRIC breast cancer patients. For this example, we test several combinations of data incorporation and discuss that the most comprehensive METABRIC patient-specific cancer models are obtained by modifying the activity of the nodes of the logical model with mutation and CNA data and altering the transition rates with RNA expression. We conclude that these models' simulations show good results when compared to the clinical data such as patients' Nottingham prognostic index (NPI) subgrouping and survival time. We observe that two highly relevant cancer phenotypes, Proliferation and Apoptosis, exhibit different simulated probabilities across NPI subgroups: patients with low survival show highly proliferative and low apoptotic probabilities, in accordance with biological expectations. Our approach aims to combine the mechanistic insights of logical modeling with multi-omics data integration to provide patient-relevant models. This work leads to the use of logical modeling for precision medicine and will eventually facilitate the choice of patient-specific drug treatments by physicians.

Visual analytics of biological networks using VANTED and its SBGN-ED add-on

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We present methods and algorithms to support working with SBGN maps in systems biology. VANTED (www.vanted.org) is an integrative and extendable framework for systems biology applications which aims at the integration, analysis and visual exploration of experimental data in the context of biological networks as well as the modelling, simulation and analysis of molecular biological processes. The VANTED extension SBGNED (www.sbgn-ed.org) is a SBGN editor which allows creating, editing and exploring all types of SBGN maps. Furthermore, the syntactical and semantical correctness of created or edited maps can be validated. Already existing non-SBGN maps from the KEGG database can be translated into SBGN PD maps including automatic layout. Translation of PD to AF maps and a visualisation of SBML models in SBGN PD is also provided. Additionally, the tool allows exporting of SBGN maps into several file and image formats including the SBGN-ML format.

MINERVA API and plugin architecture: new data visualization interfaces for disease maps

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Disease maps offer contextualized knowledge on disease mechanisms, which is indispensable for proper interpretation of high volumes of data generated by high throughput experiments, and available via numerous bioinformatics databases. Such interpretations become possible with proper data interfaces that allow to construct multiple information layers on top of disease maps. MINERVA (http://r3lab.uni.lu/web/minerva-website/), a standalone platform for web-based visual exploration of molecular diagrams, is developed with this goal in mind.

With the growth of the Disease Maps Community comes the demand for new visualization functionalities. Similarly, additional data interfaces are needed with more and more datasets becoming available, and with the advancing complexity of analysis required for interpretation. To address these needs, the MINERVA platform currently supports the Application Programming Interface (API), enabling automatization of a number of routines that were currently possible only via the user interface. The REST API of MINERVA automates such functionalities as: i) obtain elements and reactions of hosted maps; ii) list drugs, chemicals and miRNA targeting map elements; iii) upload data overlays to a given map. An important extension of the API enables custom JavaScript to interact with the respective MINERVA instance to retrieve its data and modify its visual state. This allows construction of custom plugins for advanced visualization, independent of the core functionality of MINERVA.

In the talk, we will discuss the REST API functionality of MINERVA and will demonstrate two extensions: i) a custom plugin facilitating the traversal of complex maps and ii) a new functionality for the visualization of structural information for the proteins participating in reactions shown via MINERVA. We will discuss future steps, by which the platform may support the Disease Maps Community better.