Monday June 11th 2018

in the Ecole de Musique – République
8 bis rue de la Fontaine au Roi, 75011 Paris, France

9:00 AM – 9:10 AM Welcome and introduction

Session 1 - Chair: Vera Pancaldi

9:10 AM – 9:55 AM **Keynote 1 - Luis Rocha**
Center for Complex Networks and Systems Research School of Informatics, Computing, and Engineering Indiana University, USA Instituto Gulbenkian de Ciencia, Portugal
Towards understanding biosocial complexity in human health: from control of biochemical regulation of disease to social factors in drug-interaction and human reproduction

9:55 AM – 10:25 AM **Andrei Zynoviev**
Bioinformatics, biostatistics, epidemiology and computational systems biology of cancer, Institut Curie, France
Use of network propagation methods in cancer data analysis

10:25 AM – 10:55 AM **Danielle Bassett**
Complex systems, Department of Bioengineering Pennsylvania University, USA
TBD

10:55 AM – 11:30 AM Coffee and Posters

Session 2 – Chair: Thomas Rolland

11:30 AM – 12:00 PM **Benno Schwikowski**
Systems Biology, Institut Pasteur, France
LEAN discovery of hot spots in networks

12:00 PM – 12:15 PM **Chenyue Wendy Hu**
Department of Bioengineering, RICE University, USA
Leukemia Protein Atlases: Discovering How Molecular Networks of Acute Leukemias Map to Clinical Outcomes

12:15 PM – 12:30 PM **Jon Sánchez Valle**
Barcelona Supercomputing Center - Centro Nacional de Supercomputación, Spain
Stratified co-morbidity networks: Inferring patient-specific comorbidities from transcriptomic data

12:30 PM – 12:45 PM **Kimberly Glass**
DFCI Biostatistics and Computational Biology, USA
Quantifying the Impact of GWAS variants on Gene Regulatory Networks

12:45 PM – 2:00 PM Lunch and Posters

Session 3 – Chair: Amitabh Sharma

2:00 PM – 2:45 PM **Keynote 2 - Natasa Przulj**
University College London, Computer Science Department, UK
Mining the Integrated Connectedness of Biomedical Systems

2:45 PM – 3:15 PM **Maria Rodriguez Martinez**
Zurich Research Laboratory, IBM, Switzerland
Artificial Intelligence approaches for personalized medicine

3:15 PM – 4:00 PM Coffee and Posters

Session 4 – Chair: Marc Santolini

4:00 PM – 4:15 PM **Claudio Duran**
Biomedical Cybernetics, BIOTEC, TU Dresden, Germany
Machine intelligence driven design of genomic combinatorial biomarkers for Parkinson Disease

4:15 PM – 4:30 PM **Tarik Altuncu**
Department of Mathematics, Imperial College London, UK
From free text to clusters of content in health records: an unsupervised graph partitioning approach

4:30 PM – 4:45 PM **Franziska Härtner**
Computational Biology and Data Mining, Johannes Gutenberg Universität, Germany
Geometric characterisation of disease modules

4:45 PM – 5:00 PM **e-Therapeutics**

5:00 PM – 5:15 PM **C4XDiscovery**

5:15 PM – 6:00 PM **Discussion/Debate with Marie Darrason**
Assistance Publique des Hôpitaux de Paris, France
Precision oncology, targeted therapies and network medicine

6:00 PM – 6:45 PM Poster awards & Close

A satellite symposium at

NetSci
International School and Conference on Network Science
11 - 15 June 2018 | Paris, France

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C4X Discovery
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e-therapeutics

KEYNOTE ABSTRACTS

Luis Rocha – Towards understanding biosocial complexity in human health: from control of biochemical regulation of disease to social factors in drug-interaction and human reproduction

Network Science has provided predictive models of many complex systems from molecular biology to social interactions. Most of this success is achieved by reducing multivariate dynamics to a graph of static interactions. Such network structure approach has provided many insights about the organization of complex systems. However, there is also a need to understand how to control them; for example, to revert a diseased cell to a healthy state in systems biology models of biochemical regulation. Based on recent work [1,2] we show that the control of complex networks crucially depends on redundancy that exists at the level of variable dynamics. We present several network methods developed in our group to predict controllability of biochemical regulation, including the effective graph [3] and the dynamics canalization map [2]. We demonstrate their utility with the analysis of various systems biology models, including subsystems involved in leukemia and breast cancer, as well as other biochemical networks available in the Cell Collective.

Network Science has also given us tools to understand higher levels of organization involved in human health, including individual and population-level response to drugs and social factors present in health-care systems. Social media, electronic health records and mobile application data enable population-level observation tools with the potential to speed translational research. I will discuss ongoing work in our group on this front, including the importance of Twitter, Instagram and Facebook for public surveillance of drug interactions in depression, epilepsy and opioid abuse [4], as well as for quantifying the emotional states associated with collective social behavior in phenomena of interest to public health, such as human reproductive behavior [5]. Finally, I will discuss the results of a large-scale longitudinal analysis of electronic health records from the entire city of Blumenau, in southern Brazil [6]. We uncovered significant gender and age biases in the prevalence of known---and thus preventable---drug interactions. Specifically, the risk of drug interactions grows quadratically with age and women are at 60% risk increase when compared to men. Moreover, this risk is much higher than what is expected by increased polypharmacy associated with age or pregnancy. On the positive side, we show that the risk of drug interactions can be predicted with very good accuracy with machine learning methods, thus offering a means to increase the quality of life and substantially reduce the costs of adverse drug reactions to public health systems.

References

[1] A. Gates and L.M. Rocha. [2016]. Scientific Reports 6, 24456. (PMC4834509.)
[2] M. Marques-Pita and L.M.Rocha [2013]. PLOS One, 8(3): e55946. (PMC3592869.)
[3] R.B. Correia, A. Gates, X. Wang, L.M. Rocha [2018].]. Frontiers in Physiology: Systems Biology. In Press. arXiv:1803.04774.
[4] R.B. Correia, L. Li, L.M. Rocha [2016]. Pac. Symp. Biocomp. 21:492-503. (PMC4720984)
[5] I.B Wood, P.L. Varela, J. Bollen, L.M. Rocha, J. Gonçalves-Sá [2017]. Scientific reports 7(1): 17973. (PMC5740080.)
[6] R.B. Correia, L.P. de Araújo, M.M. Mattos, D. Wild and L.M. Rocha [2018]. arXiv:1803.03571.

Natasa Przulj – Mining the integrated connectedness of biomedical systems

We are faced with a flood of molecular and clinical data. Various bio-molecules interact in a cell to perform biological function, forming large, complex systems. Large-scale patient-specific omics datasets are increasingly becoming available, providing heterogeneous, but complementary information about cells, tissues and diseases. The challenge is how to mine these interacting, complex, complementary data systems to answer fundamental biological and medical questions. Dealing with them is nontrivial, because many questions we ask to answer from them fall into the category of computationally intractable problems, necessitating the development of heuristic methods for finding approximate solutions.

We develop methods for extracting new biomedical knowledge from the wiring patterns of systems-level, heterogeneous, networked biomedical data. Our methods link the patterns in molecular networks and the multi-scale network organization with biological function. In this way, we translate the

information hidden in the wiring patterns into domain-specific knowledge. In addition, we introduce a versatile data fusion (integration) framework that can effectively integrate the information obtained from mining molecular networks with patient-specific somatic mutation data and drug chemical data to address key challenges in precision medicine: stratification of patients, prediction of driver genes in cancer, and re-purposing of approved drugs to particular patients and patient groups. Our new methods stem from novel network science approaches coupled with graph-regularized non-negative matrix tri-factorization, a machine learning technique for dimensionality reduction and co-clustering of heterogeneous datasets. We utilize our new framework to develop methodologies for performing other related tasks, including disease re-classification from modern, heterogeneous molecular level data, inferring new Gene Ontology relationships, and aligning multiple molecular networks.

INVITED TALKS ABSTRACTS

Andrei Zinovyev - Use of network propagation methods in cancer data analysis

Biological networks reflecting our state-of-the-art knowledge of molecular interactions implicated in normal physiology and diseases are resources routinely used in the analysis of cancer data. Fundamental to network-based data analysis is the concept that functionally related genes have smaller distance in the network than unrelated ones, where this distance can be formally defined in a number of ways. In the last decade, a family of bioinformatics methods was introduced exploiting the idea of network propagation, based on metaphors of heat or information diffusion or random walks in order to formally describe how a potential perturbation (such as mutation) spread over the complex network landscape. In this talk, I will present two recently developed methods exploiting the network propagation paradigm, in order to obtain insights into cancer biology. The first one is based on applying the reduced Google Matrix method in order to quantify indirect oriented connections between members of a related set of proteins through a global network of oriented interactions (influences). This allows to infer hidden causal relation which, for example, has to be taken into account when creating a mechanistic model of a pathway. With few examples, we show how the structure of a signalling pathway can be effectively rewired as a consequence of changes in the structure of the underlying transcriptional regulation network. In the second part, a popular network-based stratification method for the analysis of mutations in cancer will be revised. Based on this analysis, a novel method for network-based pre-processing of cancer mutation data (NetNorm) is suggested, which increases the predictive power of mutational profiles and ameliorates the unsupervised patient stratification. Using data from 8 cancer types from The Cancer Genome Atlas (TCGA), we show that NetNorm improves over the raw binary mutation data and network diffusion. In doing so, we also provide a thorough assessment of somatic mutations prognostic power which has been overlooked by previous studies because of the sparse and binary nature of cancer mutation profiles.

References:

J Lages, DL Shepelyansky, A Zinovyev. Inferring hidden causal relations between pathway members using reduced Google matrix of directed biological networks. 2018. PloS One 13 (1), e0190812.

M Le Morvan, A Zinovyev, JP Vert. NetNorM: capturing cancer-relevant information in somatic exome mutation data with gene networks for cancer stratification and prognosis. 2017. PloS Computational Biology 13 (6), e1005573.

F Rapaport, A Zinovyev, M Dutreix, E Barillot, JP Vert. Classification of microarray data using gene networks. 2007. BMC bioinformatics 8 (1), 35.

Danielle Bassett – TBD

Benno Schwikowski - LEAN discovery of hot spots in networks

“Everything should be made as simple as possible but not simpler,” said Einstein. But what does this mean for new computational models that link complex disease ‘omics data with relevant phenotypes? To be useful in practice, new models need to be simple enough to be computationally tractable, and yield biologically interpretable outcomes. Yet, models also need to be complex enough to allow the

discovery of new, non-classical relationships between molecular and clinical measurements and disease phenotypes.

In my talk, I will discuss a simple subnetwork model for identifying 'hot spots' in interaction networks. Methods based on the classical subnetwork model tend to imply enormous computational effort, provide single or partial, often heuristic, solutions, contain user-tuneable parameters, and lead to solutions that are difficult to interpret. An alternate approach (termed Local enrichment analysis, or LEAN) substitutes the general model by simpler model. The simpler model is more constrained, but, in return, allows exact, parameter-free, efficient, and exhaustive identification of local subnetworks that are statistically dysregulated, and directly implicates single genes for follow-up experiments.

A first empirical evaluation on simulated and biological data suggests that LEAN detects dysregulated subnetworks, and reflects biological similarity between experiments better than standard approaches. A strong signal for the local subnetwork around Von Willebrand Factor (VWF), a gene which showed no change on the mRNA level, was identified by LEAN in transcriptome data in the context of a genetic disorder, Cerebral Cavernous Malformations (CCM). Targeted follow-up experiments revealed an unexpected strong cellular phenomenon around VFW. The LEAN method can be used to pinpoint statistically significant local subnetworks in any genome-scale data set.

Maria Rogriguez Martinez - Artificial Intelligence approaches for personalized medicine

In recent years, deep learning has become one of most active fields in machine learning with astounding performances in a broad area of applications such as computer vision, speech recognition and natural language processing. In computational biology, the recent availability of large amounts of data generated by word-wide consortia together with technical developments facilitating the implementation and training of more performant models have made possible the broad application of deep learning to a vast set of problems.

In this talk, I will present current activities at the Computational Systems Biology group in IBM Research, Zurich, that illustrate the application of AI approaches to integrate disparate data types with the goal of unraveling disease mechanisms and develop personalized patient models. Specifically, I will show two examples. First, I will demonstrate how state-of-the-art text ingestion and analysis can be used to automatically extract knowledge from text sources and obtain comprehensive maps of molecular interactions. Second, I will explain how deep learning can be used to identify the map of molecular alterations induced by cancer and support the development of personalized patient models.

SELECTED TALKS FULL AUTHOR LIST

Chenyue Wendy Hu, Andrew Ligeralde, David Noren, Byron Long, Jennifer Dawkins, YiHua Qiu, Fieke Hoff, Terzah Horton, Steven M. Kornblau, Amina Ann Qutub
Leukemia Protein Atlases: Discovering How Molecular Networks of Acute Leukemias Map to Clinical Outcomes

Jon Sánchez Valle, Vera Pancaldi and Alfonso Valencia.
Stratified co-morbidity networks: Inferring patient-specific comorbidities from transcriptomic data

Kimberly Glass, John Platig, Damien Croteau-Chonka, Marieke Kuijjer and Benjamin Raby
Quantifying the Impact of GWAS variants on Gene Regulatory Networks

Claudio Duran, Matthew Valentine, Kosuke Hashimoto, Shinji Saiki, Hattori Nobuta, Stefano Gustincich, Piero Carninci and Carlo Vittorio Cannistraci
Machine intelligence driven design of genomic combinatorial biomarkers for Parkinson Disease

Tarik Altuncu, Erik Mayer, Sophia N. Yaliraki and Mauricio Barahona
From free text to clusters of content in health records: an unsupervised graph partitioning approach

Franziska Härtner, Miguel Andrade-Navarro and Gregorio Alanis-Lobato
Geometric characterisation of disease modules

SELECTED POSTERS FULL AUTHOR LIST

Shawn Gu, John Johnson, Fazle Faisal and Tijana Milenkovic
From homogeneous to heterogeneous network alignment

Sam Greenbury, Mauricio Barahona and Iain Johnston
HyperTraPS: an efficient framework for inference of dynamics in disease and beyond

Ilyes Abdelhamid, Alessandro Muscoloni, Amitabh Sharma and Carlo Vittorio Cannistraci
Prediction of candidate genes for disease modules in human interactomes by network similarities based on local topology

Joana Gonçalves-Sá and Cláudio Vieira
Identifying and tracking non-infectious disease: using influenza to study anxiety

Yang-Min Kim
Genetic stratification based on Protein-Protein Interaction (PPI) networks in cancer and autisms

Noël Malod-Dognin, Thomas Gaudelet, Sam Windels and Natasa Przulj
Higher-order modelling and integration of biological data for precision medicine