Systems Medicine
Volume 2.1, 2019
DOI: 10.1089/sysm.2019.29005.abstracts

The Transformation of Medicine

First International Conference on Network Medicine and Big Data

September 24–26, 2018
Rome, Italy
Abstracts

Systems Medicine
Volume 2.1, 2019
DOI: 10.1089/sysm.2019.29005.abstracts

SYSTEMS MEDICINE
Journal of Medical Systems Biology and Network Medicine

Mary Ann Liebert, Inc. publishers

Open Access

The Transformation of Medicine

Proceedings of the First International Conference on Network Medicine and Big Data

Joseph Loscalzo, MD, PhD

The First International Conference on Network Medicine and Big Data was held in Rome, Italy, on September 24–26, 2018. Cosponsored by the Sapienza University of Rome and Brigham and Women's Hospital, the conference was designed to bring together individuals from many different disciplines to explore novel network science and big data approaches to understanding mechanisms and treatments of complex disease. The fields of network science, physics, applied mathematics and statistics, computer science, biology, and medicine were well represented in this closed meeting among the 120 participants from 24 different institutions and 8 different countries. The ultimate goal of the meeting was to design a strategy by which this interdisciplinary field can truly transform medicine.

The motivation for the development of the field of network medicine is the limitations of reductionist approaches to human biology, disease, and therapeutics. Since the time of Osler, clinicians and biomedical researchers have used reductionism (after Democritus and Descartes) to investigate human pathobiology. Although this strategy has been successful, to be sure, it has clear shortcomings that are becoming ever more apparent largely as a consequence of oversimplification of the complexity of human pathobiology. Until recently, the prospect of unraveling this complexity has been limited by the limited size of data sets and the inadequacy of conventional analytical approaches. Owing to the rapid expansion of large genomic data sets, increasingly detailed quantitative phenotyping, and quantitative approaches to their integrative analysis from the fields of network science, statistics, and machine learning, we are now poised to explore this complexity in all of its dimensions. To do so requires establishing a formalism by which to depict these complex systems, for which network science and graph theory are most suitable. Both static and dynamic network representations of the associations or interactions among many different molecular or phenotypic elements are useful in this regard, and provide clear insights into pathobiology and effective therapies.

The proceedings began with a discussion of network science and its application to biology and medicine in two presentations by Albert Laszlo Barabasi and by Joseph Loscalzo. They reviewed the background to the development of network medicine, a field they helped establish, and highlighted its great potential for dissecting human disease. Principal among their points is the notion that the molecular determinants of disease comprise a subnetwork or disease module within the physical molecular interactome network through which deterministic pathways for disease pathobiology can be discerned, and pathways common to two or more diseases can be identified within regions of module overlap.

These introductory presentations were followed by talks on relevant and evolving methodologies for understanding network topology and dynamics, including synchronization in adaptive networks (G. Caldarelli), graph-based methods for disease gene prediction (P. Velardi), multiscaling in network medicine (J. Baumbach), key nodes in coexpression networks (L. Farina), transitions in regulatory networks and the types of network representations relevant to biology and disease (J. Quackenbush), and articulation points and bridges in complex networks (Y.-Y. Liu). These presentations were notable for their methodological diversity (from applied mathematics to computer science) and their focus on specific network properties or features that are potentially relevant to understanding disease. Presentations on epigenetics in network medicine (C.

Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

Napoli), space technologies and global health with geotracking (A. Geissbuhler), and diet and network medicine in atherogenesis (L. Badimon Maestro) each highlighted different mechanisms by which environmental determinants can affect biological networks, including stochastic post-translational modification through environmental exposures or dietary intake. The first day ended with a presentation on complex antithrombotic regimens tailored to specific patient features (G. DiMinno), highlighting the importance of nuanced phenotyping in precision and network medicine.

The second day of the conference began with two key presentations, one by Joerg Menche that was wide ranging and included network analysis of combinatorial therapeutics, mathematical analysis of circular networks in biological systems and their functional implications, and visual representation and exploration of the physical interactome, enriched by a knowledge graph depiction of information contained within each node and edge. A presentation by Alessandro Vespignani followed, which focused on the use of network dynamics in understanding the spread of epidemics, among the first successful uses of network science in biology. In his presentation, Vespignani highlighted the increased granularity with which contagion can now be assessed, including at the level of individual households.

Machine learning was an important theme of many of the second day's presentations, including its use in emergency medicine and outcomes assessment (Z. Obermeyer), deep learning in lung imaging (G. Washko) and in radiology in general (C. Catalano), and the use of big data in assessing drug risk to the fetus during pregnancy (E. Poluzzi). Disease endophenotypes, that is, well-characterized and universal disease mechanisms such as inflammation, thrombosis, and fibrosis, were presented by B. Maron, with a particular focus on the use of fibrosis networks in identifying a key determinant of pulmonary vascular fibrosis in pulmonary arterial hypertension. Genomics and networks in the characterization of chronic obstructive pulmonary disease (E. Silverman) and the importance of plasticity in the physical interactome in evaluating and treating neurodegenerative disease (M. Papa) explored the application of network medicine to two complex and diverse phenotypes. The use of network medicine in repurposing drugs using a cluster-based algorithm (H. Schmidt) illustrated the power of drug–target networks in assessing drug efficacy and toxicity. Owing to the promiscuity of the great majority of approved drugs ($\sim$32 targets/drug on average), using interaction networks to explore alternative targets and pathways not developed in the original approval process can provide alternative treatment targets for approved drugs, as well as uncover potential toxicities not previously recognized. The formal presentations ended on the second day with a discussion of mobile technology to assess personality traits (J. Stefa) and its potential for guiding psychiatric intervention.

The afternoons of each of the first two days offered a wide range of poster topics to enrich the interdisciplinary experience and encourage growing cross-disciplinary collaboration. Poster sessions were followed on the first day with two working group sessions, on Methods and on Molecular Networks, and on the second day with two additional working group sessions, on Machine Learning in Clinical Medicine and on Phenotypic Networks. On the morning of the last day of the conference, the working group chairs presented the recommendations of each working group on ways by which to advance the field of network medicine and expand the interdisciplinary interactions among participants of the conference as part of an official Consortium of Network Medicine. J. Loscalzo ended the conference with an overview of observations and recommendations for next steps, including a standing set of the four working groups with the development of standards, approaches, interdisciplinary research projects, goals, and training.

Clearly, this new field of network medicine has great potential as an effective strategy for understanding and treating disease. Human disease will be redefined in the process of exploring network-based mechanisms with more specific disease phenotypes, which will lead to improved treatments and outcomes. In this way, network medicine offers a pathway toward true precision medicine and global societal benefit.

Network medicine: from cellular networks to the human diseasome

Albert Laszlo Barbasi[1,2]

[1]*Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.*
[2]*Center of Complex Networks Research, Northeastern University, Boston, Massachusetts.*

Given the functional interdependencies between the molecular components in a human cell, a disease is rarely a consequence of an abnormality in a single gene, but reflects the perturbations of the complex intracellular network. The emerging tools of network medicine offer a platform to explore systematically not only the molecular complexity of a particular disease, leading to the identification of disease modules and pathways, but also the molecular relationships between apparently distinct (patho) phenotypes. Advances in this direction are essential to identify new disease genes, to uncover the biological significance of disease-associated mutations identified by genome-wide association studies and full genome sequencing, and to identify drug targets and biomarkers for complex diseases.

Network medicine: diagnosis and therapy of disease

Joseph Loscalzo[1,2]

[1]*Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts.*
[2]*Harvard Medical School, Boston, Massachusetts.*

Since the time of Osler, clinicians and biomedical researchers have used the conventional reductionist approach to investigate human biology, disease, and therapeutics. While the success of this strategy cannot be disputed, it has major shortcomings including most importantly oversimplification of the complexity of human biology. Until recently, the prospect of unraveling that complexity in a more integrative way has been limited by restricted data sets and inadequate analytical approaches. Biomedicine is now, however, poised to explore rigorously holistic system responses that govern pathophenotype. The rapid growth in large genomic data sets and detailed phenotyping coupled with the rapid expansion of quantitative approaches to their network-based analysis provide a unique opportunity by which to define the dynamic response of biological systems to normal, pathological, and therapeutic perturbations. Put another way, biomedical science is now positioned to explore pathobiological complexity. This new field of network medicine, which applies systems biology and network science approaches to the dissection of molecular pathobiology and treatment, offers a truly novel path toward redefining and treating human disease in the modern genomics era, and facilitates the trajectory of true precision medicine.

Connectivity significance in an expanding universe: DiaBLE(s) and DIAMOnD(s)

Daniele Bizzarri,[1] Manuela Petti,[1] Antonella Verrienti,[2] Rosa Falcone,[2] and Lorenzo Farina[1]

[1]*Dipartimento di Ingegneria Informatica, Automatica e Gestionale "A. Ruberti," Sapienza Università di Roma, Rome, Italy.*
[2]*Dipartimento di Medicina Interna e Specialità Mediche, Sapienza Università di Roma, Rome, Italy.*

Disease genes prediction is a fundamental issue in network medicine. In fact, it is widely recognized that disease is often the result of a complex network of interactions among molecular components and pathways in a cell or tissue. The underlying hypothesis is that disease genes are not randomly scattered on the interactome, but they are organized as "modules" confined in specific regions. Recently, DIAMOnD, a popular algorithm based on connectivity significance, has been presented in the literature. Here, we propose a novel algorithm called DiaBLE (DIAMOnD's Background Local Expansion) which is a modified version of the DIAMOnD algorithm based on a different background model for the hypergeometric test defining the connectivity significance. Precisely, we selected a new "gene universe" at each iteration step, by considering the smallest local expansion of the current seeds set. We show that DiaBLE significantly increases DIAMOnD ranking quality of genes prioritization and provides better performances both in terms of cross-validation and biological consistency. Finally, we briefly discuss the biological and medical insight provided by DiaBLE for the head and neck and kidney cancers.

Multi-Omic data integration in gene regulatory networks

Kimberly Glass

Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

Rapidly evolving Omics technologies are providing unprecedented amounts of Big Data and allowing us to develop a more holistic understanding of disease. We now recognize that disease-related changes often involve simultaneous alterations to the genome, epigenome, transcriptome, and proteome of the cell. Networks provide a powerful approach for identifying disease-related biological mechanisms. In particular, by modeling a cell's *gene regulatory network*, we can gain important insights into the underlying molecular mechanisms influencing disease state. Over the past years, we have developed a suite of methods to effectively integrate multi-Omic data, reconstruct gene regulatory networks, and link regulatory relationships with heterogeneous phenotypes. The basis

of this work is a method we developed, called PANDA (Passing Attributes between Networks for Data Assimilation), that constructs directed genome-wide regulatory networks by using a "message passing" approach to integrate multiple types of genomic data, including protein-protein interaction, gene expression, and predicted transcription factor regulatory relationships. We have applied PANDA to gain mechanistic insights in many human diseases and biological systems, such as multiple tissues in the Genotype-Tissue Expression (GTEx) project. We are now expanding PANDA to integrate micro-RNA regulatory relationships (PUMA: PANDA Using Micro-RNA Associations) and epigenetic information in the form of DNase hypersensitivity data (SPIDER: Seeding PANDA Interactions to Determine Epigenetic Regulation). Together these methods provide a broad-based platform with which to integrate multi-Omics data, infer regulatory networks, and to interrogate those networks to understand alterations in biological processes across heterogeneous disease populations.

Articulation points and bridges in complex networks

Liang Tian,[1,2] Ang-Kun Wu,[1,3,4] Amir Bashan,[1,5] Da-Ning Shi,[2] and Yang-Yu Liu[1,6]

[1]*Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.*
[2]*College of Science, Nanjing University of Aeronautics and Astronautics, Nanjing, China.*
[3]*Department of Physics, Chu Kochen Honors College, Zhejiang University, Hangzhou, Zhejiang, China.*
[4]*Department of Physics and Astronomy, Rutgers University, Piscataway, New Jersey.*
[5]*Physics Department, Bar-Ilan University, Ramat-Gan, Israel.*
[6]*Center for Cancer Systems Biology, Dana-Farber Cancer Institute, Boston, Massachusetts.*

An articulation point (AP) in a network is a node whose removal disconnects the network. Those APs play key roles in ensuring connectivity of real-world networks such as infrastructure networks, protein interaction networks, and terrorist communication networks. Despite their fundamental importance, a general framework of studying APs in complex networks was lacking. We recently developed analytical tools to study key issues pertinent to articulation points, such as the expected number of them and the network vulnerability against their removal, in complex networks with arbitrary degree distributions. We found that a greedy AP removal process provides us a novel perspective on the organizational principles of complex networks. Moreover, this process results in a rich phase diagram with two fundamentally different types of percolation transitions. Our analytical tools can also be used to study bridges—edges in a network whose removal disconnects the network. We found that real networks typically have more bridges than their completely randomized counterparts, but they have a fraction of bridges that is very similar to their degree-preserving randomizations. Our results shed light on the design of more resilient infrastructure networks and the effective destruction of malicious networks.

Leveraging network diffusion for disease gene prioritization

Michele Gentili, Leonardo Martini, Manuela Petti, Lorenzo Farina, and Luca Becchetti

Dipartimento di Ingegneria Informatica, Automatica e Gestionale "A. Ruberti," Sapienza Università di Roma, Rome, Italy.

Graph mining techniques are effective tools in the analysis of the interactome. The focus of our research is on the identification of new properties of "genes and modules that drive disease." We provide an overview of our efforts in the application of state-of-art mining techniques to the problem of disease gene prioritization. We considered two different approaches to gene prioritization, both relying on the use of Protein-Protein Interaction networks to propagate disease information from a seed of known disease proteins: one is the DIAMOnD algorithm, the other is a redesign of the diffusion method based on random walks with restart (RWR). We investigated the role of the restart probability in RWR which, qualitatively speaking, controls the extent to which the random walk is confined within the neighborhood of the seed set. We referred to a well-established and up-to-date interactome built on top of several data sources. We removed disconnected proteins and self-interactions resulting in a network of 13,396 proteins with 138,405 physical interactions. We validated our approach using both gene annotation and miRNA data, for the former extending the validation method proposed in the literature. Our poster presents the results of this exploratory analysis, focusing on and extending state-of-art techniques for experimental validation of results, which allowed us to set up and tune a complete and modular pipeline for analysis and independent result validation. We next plan to apply and/or integrate advanced techniques in the pursuit of more ambitious goals.

Probabilistic mapping of the sub-cellular proteome

Oliver M. Crook,[1] Claire M, Mulvey,[1] Paul D.W. Kirk,[2] Kathryn S. Lilley,[1] and Laurent Gatto[3]

[1]*Cambridge Centre for Proteomics, Department of Biochemistry, University of Cambridge, Cambridge, United Kingdom.*
[2]*MRC Biostatistics Unit, Cambridge Institute for Public Health, Cambridge, United Kingdom.*
[3]*de Duve Institute—UCLouvain, Brussels, Belgium.*

In biology, localization is function—understanding the subcellular localization of proteins is paramount to comprehend the context of their functions. Mass spectrometry-based spatial proteomics and contemporary machine learning enable to build proteome-wide spatial maps, informing us on the location of thousands of proteins. Nevertheless, while some proteins can be found in a single location within a cell, up to half of proteins may reside in multiple locations, can dynamically re-localize, or reside within an unknown functional compartment, leading to considerable uncertainty in associating a protein to their subcellular location. Recent advances enable us to probabilistically model protein localization as well as quantify the uncertainty in the location assignments, thus leading to better and more trustworthy biological interpretation of the data.

Exploring network medicine data with visual analytics

Marco Angelini, Graziano Blasilli, Lorenzo Farina, Simone Lenti, Manuela Petti, and Giuseppe Santucci

Department of Computer, Control and Management Engineering (DIAG)—Sapienza Università di Roma, Rome, Italy.

Visual Analytics (VA) aims at making the best possible use of huge information combining the strengths of automatic data analysis with the visual perception and analysis capabilities of the human user. VA provides powerful means for *analyzing* large and *complex* data set and it performs better than pure automatic analysis when the analysis has the main goal of exploring data or comparing different hypotheses. Visualization is just one component of VA and it is complemented by automated analysis that produces models that drive suitable visualizations that drive further automated computations.

VA is a perfect candidate for network medicine applications that need the integration of large and heterogeneous sources of 'omics' data. Automatic data analysis is not always sufficient to provide *effective* information to the medical user, whereas *visual* representations (just like the "network" representation) are the key to convey *relevant properties* of the complex disease of interest. In other words, VA is both "representation" and "interpretation" of data at the same time.

The DIAG researchers iin VA and bioinformatics have explored this approach with a VA application (awareserver.dis.uniroma1.it:8080/nemesis) that attacks the problem of *exploring* relationships among genes associated with relevant *subsets of diseases*, e.g., cancer diseases or combinations of diseases that maximize ad-hoc objective functions like the cluster of 5 diseases that has the highest proportion of common genes. Currently, the researchers are exploring the possibility of visualizing data coming from a single network (e.g., interactome) and summary data coming from other networks involving diseases, drugs, and biological processes.

Graph-based methods for disease gene prediction

Lorenzo Madeddu,[1] Giovanni Stilo,[1] Paola Bertolazzi,[2] and Paola Velardi[1]

[1]*Dipartimento di Informatica, Sapienza Università di Roma, Rome, Italy.*
[2]*Institute di Analisi dei Sistemi ed Informatica "Antonio Ruberti" Consiglio Nationale delle Ricerche (IASI-CNR), Rome, Italy.*

We predict disease genes using a graph-based methodology which jointly learns functional and connectivity patterns surrounding proteins in the human interactome. We adopt a network model where nodes are proteins, edges are protein-protein interactions, and each node is further described by a multi-dimensional feature vector.

The methodology is in three steps.

1. We collect *network patterns* using a novel method, Double-Random Walks (DRW). In DRW, the walker, when landing on node, selects one feature at random in and then jumps with uniform probability on one of its neighbors. In this way, random walks embody both *pathobiological features* such as related diseases, tissues and pathways, and *connectivity patterns*.
2. Collected patterns are treated as "contexts" for individual features, used to learn *embeddings* ("dense" vector representations of each feature). Embeddings are used to enrich the—otherwise very sparse—multidimensional feature vectors of each node.
3. The network matrix (where each row is the enriched feature vector of a node) is used to train a fully connected neural network for predicting disease-gene associations. The system's output is a *D*-dimensional probability vector, where **D** is the number of considered disease categories.

Our method outperforms i) a baseline method without embeddings, that only captures functional patterns; ii) Node2Vec, a graph embedding algorithm that only captures structural patterns; and iii) Graph Convolutional Networks, a popular deep learning method for graph-based models. Furthermore, we successfully compare with the state of the art system for disease gene prediction, DIAMOND (we use the same dataset and algorithm).

Methods and software tools for in silico clinical trials

Enrico Tronci

Computer Science Department, Sapienza University of Rome, Roma, Italy.

The ever-growing cost of the process of approval for new drugs and treatments along with the high failure rates on humans of drugs that already passed the pre-clinical testing on animal models call for new methods and tools that can reduce time and cost for drug safety and efficacy assessment.

The *In Silico Clinical Trial* (ISCT) approach aims at building computational models accounting for human (patho) physiology and on using them to assess safety and efficacy of new drugs, treatments or biomedical devices. Indeed, development of in silico tools to improve efficiency of clinical trials is among FDA goals, European initiatives such as AVICENNA and Virtual Physiological Human (VPH) as well as of top industries offering modeling and simulation tools for healthcare (e.g., as ANSYS and InSilicoTrials).

Building on our experience on model checking and AI techniques, our main goals in such a setting are: 1) development of methods and software tools for the automatic generation of cohorts of *virtual patients* (VP) to be used within in silico clinical trials; 2) developments of methods and software tools to assess in silico (i.e., by computer simulation) safety and efficacy of drugs, treatments or biomedical devices using virtual patients.

Annotation driven optimized clustering for disease genes batch identification

Federico Francone,[1] Marianna De Santis,[1] Stefano Lucidi,[1] Paolo dell'Olmo,[2] Lorenzo Farina,[1] and Laura Palagi[1]

[1]*Dipartimento di Ingegneria Informatica, Automatica e Gestionale "A. Ruberti," Sapienza Università di Roma, Rome, Italy.*
[2]*Dipartimento di Scienze Statistiche, Sapienza Università di Roma, Rome, Italy.*

It is still uncertain whether disease genes have unique properties that distinguish them from non-disease genes. From a network

perspective, this amounts to asking whether they are randomly localized across the interactome or they show some kind of patterns in the topology, as for instance hubs or modules. We tried to identify such patterns of disease genes using a novel top-down approach. Firstly, we detected gene clusters based on two kinds of annotations: one using GO terms (Gene Ontology—Biological Process) and the other one using KEGG pathways. These two classes of clusters were defined using an optimization procedure aiming at maximizing the number of disease genes within a single cluster. At the end of this procedure we obtained two candidate clusters based on the two kinds of annotations. Secondly, we considered the intersections of such clusters obtaining a batch of known and putative disease genes. Eventually, we selected the final core set of putative new disease genes by considering those that are seed genes' first neighbors on the interactome network. As a preliminary validation, we generated replicates by randomly selecting 70% of the seed genes. We tested our algorithm on a public dataset using a subset of the diseases and invariably obtained consistent results, thus proving robustness of the approach. Further work will be devoted to performing biological validations and in vitro experiments.

Epigenetics in network medicine

Claudio Napoli

Department of Medical, Surgical, Neurological, Aging and Metabolic Sciences, University of Campania "L. Vanvitelli," Naples, Italy.

Network science offered new tools to study human physiology, pathogenesis of diseases and personalized therapy. Common structural elements, operational patterns and regulatory circuitries investigate pathophysiological adaptation mechanisms. The widely diffusion of the high-throughput systems of analysis highlights the current relevance of epigenomics. Epigenetics investigates the heritable phenotypes resulting from chromatin changes but without major alteration on DNA sequence. Epigenetic-sensitive networks regulate biological processes, and incorrect epigenetic information leading to pathogenesis of cardiovascular diseases, cardiorenal syndrome, stroke, type-1 diabetes, type-2 diabetes, metabolic syndrome and obesity and autoimmune diseases. Bioinformatics and computational epigenomics give a remarkable contribution both in processing and interpreting the large-scale datasets. Systems bioinformatics is the framework in which systems approaches are applied to data, by setting the level of resolution and the boundary of the single system of interest and by studying the properties of the system as a whole rather than the sum of the properties from the single components. Moreover, bioinformatics enhances diagnostic assessment and computational therapeutics, hence paving the way to precision medicine. The clinical utility of epigenetic markers is still limited. Epigenetic mechanisms involved both in primary and in secondary prevention of cardiovascular diseases are mainly represented by circulating miRNAs (miR-122,miR-34a, and miR-24).Metformin and statins are still the major epidrugs studied. Recently, it was proposed an integrated approach to coronary heart disease clinical management involving new imaging techniques coupled to evaluation of epigenetic and markers of the disease. The clinical evaluation and long term follow-up utility of such approach is still under active investigation.

MicroRNA-mRNA network alterations under hypercholesterolemia in rat myocardium

Bence Ágg,[1–3] András Makkos,[1] Tamás Baranyai,[1] Borbála Vető,[4] Nóra Faragó,[5] Ágnes Zvara,[5] Zoltán Giricz,[1] Dániel V. Veres,[6] Péter Csermely,[6] Tamás Arányi,[4] László G. Puskás,[5] Zoltán V. Varga,[1] and Péter Ferdinandy[1,2,7]

[1]*Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary.*
[2]*Pharmahungary Group, Szeged, Hungary.*
[3]*Heart and Vascular Center, Semmelweis University, Budapest, Hungary.*
[4]*Institute of Enzymology, Research Center for Natural Sciences, Hungarian Academy of Sciences, Budapest, Hungary.*
[5]*Institute of Genetics, Biological Research Center of the Hungarian Academy of Sciences, Szeged, Hungary.*
[6]*Department of Medical Chemistry, Semmelweis University, Budapest, Hungary.*
[7]*Cardiovascular Research Group, Department of Biochemistry, University of Szeged, Szeged, Hungary.*

Background: Hypercholesterolemia as a risk factor leads to coronary heart disease and impairs systolic and diastolic cardiac function as an independent factor. We aimed to explore novel hypercholesterolemia-induced microRNA mediated pathway alterations in the heart with an unbiased microRNA-mRNA interaction analysis.
Methods: Male Wistar rats were fed either with or without cholesterol supplemented chow (2% cholesterol and 0.25% cholate, ad libitum) for 12 weeks. Hearts were perfused in a Langendorff system and microRNA was extracted from the myocardium and microRNA microarray analysis was performed. Using microRNA-mRNA interaction database, mRNAs with at least 4 interacting upregulated microRNAs were identified by a network theoretical approach. Selected mRNA targets were validated by qRT-PCR and Western blot analysis. Selected microRNA-mRNA interactions were further validated by luciferase-assay.
Results: 47 microRNAs were up- and 10 microRNAs were downregulated in the hypercholesterolemic rat hearts as compared to the normocholesterolemic control hearts. To find mRNA hubs, a classical microRNA-target network was constructed, in which 11 mRNA target hubs were identified. Adrenoceptor beta 2 (Adrb2) and calcineurin B type 1 (CNB1) showed downregulation at protein level due to hypercholesterolemia. Interaction between two selected targeting microRNAs and the 3′ untranslated region of Adrb2 mRNA was proven by luciferase reporter assay.
Conclusion: According to our results we assume that the downregulation of Adrb2 and the decreased production of the CNB1 protein as product of Ppp3r1 gene, is involved in the mechanism of hypercholesterolemia-induced cardiac dysfunction.

Network analysis identifies microRNAs as mediators of vascular smooth muscle calcification

Amit Jhaveri, Ruisheng Wang, Joseph Loscalzo, and Jane A. Leopold

Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

Vascular calcification is a highly prevalent vascular pathophenotype that is predictive for major adverse cardiovascular events.

Vascular smooth muscle cells (VSMC) mediate vascular calcification via transdifferentiation to osteoblast (bone-forming)-like cells. We hypothesized that a vascular calcification protein-protein interaction network would identify novel microRNAs (miRs) and signaling molecules that regulate this process. The final network included 330 proteins with 756 interactions. A module detection algorithm identified 12 distinct modules based on clustering of protein-protein interactions. Hypergeometric analysis found 10 miRs with overrepresented targets in at least 2 modules ($p < 0.05$). To validate these miRs, human coronary artery VSMC were grown in calcification medium (ß-glycerophosphate, [10 mmol/L]) for 24 h and expression determined via qRT-PCR. There was downregulation of 5 miRs, no change in 3 miRs, and absence of expression of 2 miRs compared to non-calcifying VSMC. MiR-532-5p was selected for further validation. MiR-532-5p expression decreased over time with a concomitant increase in its target protein Ephrin A4 (EphA4), which is involved in bone homeostasis. To confirm that miR-532-5p modulated EphA4 expression, VSMC in normal growth medium were transfected with a miR-532-5p siRNA (60 nM). Compared to negative control-transfected VSMC, inhibition of miR-532-5p increased EphA4 protein expression. EphA4 is postulated to function as a pro-calcification mediator via phosphorylation of the Tyr773 residue of ß3-integrin. Functional analysis of EphA4 in calcifying VSMC demonstrated an increase in phosphorylated Tyr773 compared to non-calcifying VSMC. Taken together, these findings demonstrate that network analysis is a useful tool for identifying novel mediators of vascular calcification, a key cardiovascular endophenotype.

Genetic predisposition to systemic sclerosis

Nisha Limaye,[1] Marie Vanthuyne,[2] Frédéric Houssiau,[2,3] Vanessa Smith,[4] and Bernard Lauwerys[2,3]

[1]*de Duve Institute, UCLouvain, Brussels, Belgium.*
[2]*Department of Rheumatology, Cliniques Universitaires St Luc, Brussels, Belgium.*
[3]*Institute of Experimental and Clinical Research, UCLouvain, Brussels, Belgium.*
[4]*Department of Rheumatology, Ghent University Hospital, Ghent, Belgium.*

Systemic sclerosis (SSc) is a multi-system disease of unknown cause, characterized by vascular and immune dysregulation that results in progressive fibrosis of the skin and other organs. While rare, it can be lethal, and there are currently no treatments. SSc is typically sporadic; familial forms are extremely rare. By applying genome-wide Next Generation Sequencing (NGS) to such families, we aim to identify genetic "drivers," i.e., disease-causative or strongly-predisposing alleles. We hypothesize that these genes may also contribute to sporadic disease, when they carry strong *de novo* mutations, weak inherited variants (that cause disease only in combination with other genetic and environmental factors), or somatic mutations in affected tissues.

We performed whole exome sequencing (WES) on blood-DNA from two affected first-degree relatives each from five families, and filtered for genes with missense or nonsense variants that (i) co-segregate with disease, (ii) are rare in public sequence databases and an in-house WES database, and (iii) predicted to affect protein function *in silico*. Between 18 and 40 such genes were identified per family, five of which (*COL12A1, LAMB2, LRP1B, MDN1* and *TSC2*) were common to two. To prioritize among candidates, we will intersect our gene-lists with RNASeq data from sporadic SSc cutaneous tissue biopsies, to earmark genes that are transcriptionally dysregulated, or participate in significantly dysregulated molecular pathways. Candidates implicated in familial SSc will be deep-sequenced in samples from patients with sporadic SSc. Ultimately, these studies will provide insights into the causes of SSc, and may also allow for patient-stratification and targeted therapies.

Neuro-immune hemostasis: homeostasis and diseases in the central nervous system

Ciro De Luca,[1] Anna M. Colangelo,[2] Assunta Virtuoso,[1] Giovanni Cirillo,[1] Lilia Alberghina,[2] and Michele Papa[1]

[1]*Dipartimento di Salute Mentale e Fisica e Medicina Preventiva, Università degli Studi della Campania, Luigi Vanvitelli, Italy.*
[2]*Dipartimento di Biotecnologie e Bioscienze, Università degli Studi Milano-Bicocca, Italy.*

Coagulation and complement cascades interact in several physiological and pathological conditions, including tissue repair and immune responses. This network plays a key role in diseases of the Central Nervous System (CNS) by involving cells and molecular pathways. Endothelial damage prompts platelet activation and the coagulation cascade to support the rescue of damaged tissues, ultimately producing neuroinflammation. Platelets, indeed, can release chemokines and cytokines, and growth factors including PDGF, VEGF, and BDNF. Thrombin, plasmin, and matrix metalloproteinase-1, furthermore, activate intracellular transduction through protease-activated receptors. We aim to reconstruct the complement cascade, which sustains the cellular response to insults by activating the innate immune system and guiding leukocytes migration or differentiation. Impairment of the neuro-immune hemostasis network induces acute or chronic CNS pathologies related to the neurovascular unit, either directly or by the systemic activation of its main steps. Glial cells and the extracellular matrix play a crucial function in a "pentapartite" synaptic model, which we firstly described herein. We thoroughly analyzed the influence of neuro-immune hemostasis on these five elements acting as a functional unit (synapse) in the adaptive and maladaptive plasticity and discuss the relevance of these events in CNS diseases. Taken together the results show a solid neuro-immune hemostatic network (NIH) based on protein-protein interactions. It is of interest to define how the nodes of the NIH network interact in a genome-wide protein-protein interaction map with basic cellular functions. The availability of metabolic constraint-based models may allow to better understanding the events underlying the NIH response.

Comprehensive kinase profiling by open reading frame screen identifies FGFR1 as mechanism of resistance to CDK4/6 inhibitors therapy in ER+ breast cancer

Luigi Formisano, Marcelo Rocha Cruz, Amir Behdad, Massimo Cristofanilli, Aditya Bardia, Joyce O'shaughnessy, Rebecca J. Nagy, Richard B. Lanman, Nadia Solovieff, Michelle Miller, Fei Su, Yu Shyr, Roberto Bianco, Carmine De Angelis, Mario Giuliano, Carlos L. Arteaga, and Sabino De Placido

[1]*Università' degli Studi di Napoli "Federico II," Naples, Italy.*
[2]*Vanderbilt University Medical Center, Nashville, Tennessee.*

[3]*Robert H. Lurie Comprehensive Cancer Center, Chicago, Illinois.*
[4]*Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts.*
[5]*Baylor University Medical Center, Dallas, Texas.*
[6]*Guardant Health, Redwood City, California.*
[7]*Novartis Institutes for Biomedical Research, Cambridge, Massachusetts.*
[8]*Novartis Pharmaceuticals Corporation, East Hanover, New Jersey.*

Approximately 70% of breast cancers (BC) express estrogen receptor (ER). Standard approved therapy for ER+ BC include endocrine therapies (aromatase inhibitors, tamoxifen and fulvestrant), in combination with CDK 4/6 inhibitors (ribociclib, palbociclib, abemaciclib). Despite the remarkable efficacy of these combinations, a significant fraction of patients develops treatment resistance. In order to discover new mechanisms of resistance, we expressed 559 kinase open reading frames (ORFs) in estrogen receptor positive (ER+) MCF-7 cells treated with fulvestrant ± the CDK4/6 inhibitor ribociclib. Eleven kinases induced a >30% increase in viability in cells treated with this combination and five of these (FGFR1, FRK, HCK, FGR, CRKL) also induced resistance in secondary screens. *FGFR1*-amplified ER+ breast cancer cells as well as MCF-7 and T47D cells transduced with FGFR1 were resistant to fulvestrant ± ribociclib or palbociclib. This resistance was abrogated by the adding the FGFR tyrosine kinase inhibitor (TKI) lucitanib. Next generation sequencing of circulating tumor DNA (ctDNA) in 34 patients pre- and post-progression on CDK4/6 inhibitors identified *FGFR1/2* amplification or activating mutations in 14/34 (41%) post-progression specimens. Finally, ctDNA analysis in MONALEESA-2, the registration trial of ribociclib, showed that patients with *FGFR1* amplification exhibit a progression free survival of 10.61 months vs. 24.84 months in patients with wild type *FGFR1*. In sum, aberrant FGFR signaling is associated with resistance to the combination of CDK4/6 inhibitors and antiestrogens. Breast cancers with FGFR pathway alterations should be considered for trials using combinations of ER, CDK4/6 and FGFR antagonists.

Computational systems medicine—what we can learn from Arnold Schwarzenegger about breast cancer survival

Jan Baumbach

Chair of Experimental Bioinformatics, TUM School of Life Sciences Weihenstephan, Technical University of Munich, Germany.

One major obstacle in current medicine and drug development is inherent in the way we define and approach diseases. We discussed the diagnostic and prognostic value of (multi-)omics panels in general. We had a closer look at breast cancer survival and treatment outcome, as case example, using gene expression panels—and we discussed the current "best practice" in the light of critical statistical considerations. We found that randomly generated gene panels of the same size have a similar chance of significantly predicting treatment outcome as the real panels (e.g., PAM50, MammaPrint). We also demonstrate this effect for other diseases using the MSigDB database. It emerges because we have a high number of features (>22K genes) and usually a small number of samples (<1K patients), which leads to model overfitting and a lack of statistical robustness. To address this problem we introduce computational approaches for network-based medicine. We present novel developments in graph-based machine learning using examples ranging from Huntington's disease mechanisms via Alzheimer's drug target discovery back to where we started, i.e., breast cancer treatment optimization—but now from a systems medicine point of view. These approaches are way more robust in their statistics and prediction power, as can be demonstrated e.g., by a drop in performance when applying permutation tests. We conclude that multi-scale network medicine and modern artificial intelligence open new avenues to shape future medicine. The following online available tools were introduced: KeyPathwayMiner (https://keypathwayminer.compbio.sdu.dk) and GrandForest (https://grandforest.compbio.sdu.dk).

Using networks to link genotype to phenotype: a bioinformatics approach

John Quackenbush

Harvard TH Chan School of Public Health and Dana-Farber Cancer Institute, Boston, Massachusetts.

One of the central tenants of biology is that our genetics—our genotype—influences the physical characteristics we manifest—our phenotype. But with more than 25,000 human genes and more than 6,000,000 common genetic variants mapped in our genome, finding associations between our genotype and phenotype is an ongoing challenge. Indeed, genome-wide association studies have found thousands of small effect size genetic variants that are associated with phenotypic traits and disease. The simplest explanation is that these genetic variants work synergistically to help define phenotype and to regulate processes that are responsible for phenotypic state transitions. We will use gene expression and genetic data to explore gene regulatory networks, to study phenotypic state transitions, and to analyze the connections between genotype, gene expression, and phenotyope. We have found that the networks, and their structure, provide unique insight into how genetic elements interact with each other and the structure of the network has predictive power for identifying SNPs likely to be associated with phenotype through genome wide association studies. I will show multiple examples, drawing on my work in cancer, in chronic obstructive pulmonary disease, and in the analysis of data from thirty-eight tissues provided by the Genotype-Tissue Expression (GTEx) project.

Deep learning and imaging

George Washko, and Raúl San José Estépar

Brigham and Women's Hospital, Boston, Massachusetts.

Medical imaging is a highly standardized tool for data acquisition and there has been a remarkable evolution in the utilization of such information for patient care as well as clinical, epidemiologic and genetic investigation. These advances are due to a combination of improved computational capacity and the application of advanced analytic techniques including deep learning. The impacts of these are most evident when examining research performed over the past 15 years. Deep learning has enabled new

ways to navigate and synthesize imaging data, extract biomarkers and predict clinical outcomes. Because of the added flexibility in image analytics afforded by these approaches, efforts focused on building highly curated cohorts of research subjects are being replaced by the aggregation and examination of real world clinical data. Hospital systems can now navigate their data archives to identify previously undiagnosed disease and predict clinical outcomes. Finally, deep learning is enabling the development of virtual imaging modalities that integrate data from CT, PET and MRI as well as the extraction of new information from standard chest X-rays.

Genomics and networks in COPD

Edwin K. Silverman

Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

Although genetic association studies have provided important insights into many complex diseases, most of the genetic variation remains unexplained. Single genetic variants are unlikely to explain complex diseases, because perturbations of biological networks, not isolated genes, confer disease risk. We studied gene expression levels in lung tissue samples from 111 COPD cases and 40 control subjects (J. Morrow et al., Scientific Reports 2017; 7: 44232). Although none of the top COPD GWAS loci were differentially expressed, genes that interacted with HHIP, FAM13A, and IREB2 based on protein-protein interactions and cell-based models were often differentially expressed in these lung tissues. Weighted gene coexpression network analysis implicated B cell proliferation and signaling differences between COPD cases and controls.

We also used COPD GWAS genes as seed genes for random walk analysis to identify a disease module of connected proteins within the protein-protein interaction network (A. Sharma et al., Scientific Reports 2018; 8: 14439). FAM13A was not included in the disease module, because it was missing from the reference protein-protein interaction network. Affinity purification assays were used to identify protein interacting partners with FAM13A. By adding FAM13A and its connecting proteins, a COPD disease network module of 163 genes was created that had significant differences in gene expression between COPD cases and controls in alveolar macrophages, sputum, blood, lung tissue, and bronchial brushing samples. Thus, correlation-based networks, gene regulatory networks, and protein-protein interaction networks provide complementary information regarding complex diseases like COPD.

Plasticity interactome: the necessary network for the development of a predictive and personalized medicine for neurodegenerative diseases

Fivos Panetsos[1,2], Giovanni Cirillo[3], Ciro De Luca[3], Assunta Virtuoso[3], Julio Mayol[4], and Michele Papa[3]

[1]*Neuro-computing and Neuro-robotics Research Group, Complutense University of Madrid, Spain.*
[2]*Neural Plasticity Research Group, Institute for Health Research, San Carlos Clínical Hospital (IdISSC), Madrid, Spain.*
[3]*Department of Mental and Physical Health and Preventive Medicine, University of Campania "Luigi Vanvitelli," Naples, Italy.*
[4]*Technology, Design and Medical Innovation Research Group, Institute for Health Research, San Carlos Clínical Hospital (IdISSC), Madrid, Spain.*

Seminal work has been carried out on the integration of interactome networks and the identification of emergent properties defining different phenotypes of complex organisms. Several approaches have been proposed to relay such properties to human diseases and to develop predictive and personalized medicine. Protein-protein interactions, transcriptional regulatory, gene expression, metabolic networks have been developed and used to characterize complex cellular organisms and identify diseases.

In this context, neurodegenerative pathologies represent a major challenge since brain is a continuously evolving system, with adaptivity, memory and learning. Such properties are emergent properties of a peculiar interactome, the "plasticity interactome," exclusively present in the nervous system, which works in a tight integration with all above-mentioned networks. In plasticity interactome play important role cells, circuits, synaptic strengths, connections, injuries, potentiation, stimulations and many other objects, structures and processes, that have to be rigorously defined and organized in an interactome structure according to their functional interrelations.

Here we briefly present two sub-networks of the plasticity interactome: the "pentapartite" synaptic network involving the neural and glial cells, the extracellular matrix and the neurovascular units together with the influence of the neuro-immune hemostasis on these five elements in the adaptive and maladaptive plasticity, and the plastic changes of cortical and subcortical maps in their anatomy, energetic level, protein synthesis and functional activity as well as of their modulation by manipulation of the external inputs. We discuss the relevance of these events in inflammatory, cerebrovascular, Alzheimer, neoplastic and psychiatric diseases.

Diet and network medicine in atherogenesis

L. Badimon,[1–3] T. Padro,[1,2] and G. Vilahur[1,2]

[1]*Cardiovascular Program-ICCC, Research Institute-Hospital de la Santa Creu i Sant Pau, IIB-Sant Pau, Barcelona, Spain.*
[2]*Centro de Investigación Biomédica en Red Cardiovascular (CIBERCV) Instituto de Salud Carlos III, Madrid, Spain.*
[3]*Cardiovascular Research Chair, Universidad Autónoma Barcelona (UAB), Barcelona, Spain.*

Diet is the most important life-style and environmental factor for maintaining health and preventing disease. Interventions to improve nutritional habits have shown to produce good results in quality of life and disease prevention but have proven difficult to implement. During the last years there have been initiatives to develop and implement systems biology approaches to improve nutritional research and applications. The availability and progress of transcriptomic, proteomic and metabolomic platforms have opened up new opportunities to build up network models with accurate predictive value in nutrition-related disease, to decipher the health promoting properties of functional foods and to design dietary interventions for healthy aging. Oxidative stress is strongly implicated in aging and in the pathophysiology of numerous diseases including neurodegenerative disease, cancers, metabolic disorders and cardiovascular diseases. Atherosclerosis

progression and complications, the underlying cause of clinical cardiovascular disease, is in particular clearly dependent on dietary trends and life-style. Exploiting systems biology approaches in nutrition and medicine may provide new opportunities oriented toward reducing atherosclerosis and promoting personalized nutrition and medical treatment.

Key nodes' role in co-expression networks: from grapevine to cancer

Lorenzo Farina

Department of Computer, Control and Management Engineering "A. Ruberti," Sapienza University of Rome, Rome, Italy.

A gene co-expression network (GCN) is an undirected network, where to each node is associated a gene, and two genes are linked if they show a "similar" transcription profile across samples. We measured co-expression similarity of genes using the "1 minus Pearson correlation coefficient" and obtained a GCN using the minimal threshold resulting in a single connected component. Then, for each node of the network, we considered the average Pearson correlation coefficient (APCC) of its "interacting" partners (first neighbors) and used initially gene expression profiles from grapevine [1]. We found a significant peak located at negative values of the hubs APCC distribution diagram. We termed these genes "fight-club hubs." We also considered two further parameters: Z_g to measure within-module connections and K_π to measure between-module connections. Surprisingly, we found that most of the fight-club hubs had low values of Z_g and high values of K_π. Such topological characterization suggests the intriguing possibility that they could be enriched with "key global regulators" of the entire network. Indeed, we found that this is very likely to be the case for many different "biological programs" such as the grapevine maturation program or cancerogenesis. Recently, a software package (called SWIM–SWItch Miner) has been developed for finding "switch genes" directly from gene expression profiles. In conclusion, although our study can be considered in its infancy and *in vitro* experimentation of predictions is needed, we believe that it can improve our knowledge of the cellular events in many organisms both in physiological and pathological conditions.

A network approach to investigate the impact of genetic modifiers on driver-guided carcinogenesis

Lorenzo Farina[1] and Sebastiano Filetti[2]

[1]*Department of Computer, Control and Management Engineering "A. Ruberti," Sapienza University of Rome, Rome, Italy.*
[2]*Department of Internal Medicine and Medical Specialties, "Sapienza" University of Rome, Rome, Italy.*

Driver mutations promote cancer development by providing a selective growth advantage. However, cancer is a complex network of molecular alterations and signaling pathways influenced by genetic and epigenetic modifiers. This phenomenon becomes evident in simple genetic models, such as Mendelian diseases, where family members carrying the same driver germ-line mutation may have different disease-phenotypes. An emblematic example is in families with hereditary medullary thyroid cancer (MTC) induced by the driver mutation V804M/L in the RET (rearranged during transfection) gene. It is not rare to find families in which, among members carrying the same mutation, some never show clinical evidence of MTC, others develop a mild disease, and yet others develop an aggressive disease. One explanation may be the segregation of RET germline polymorphisms that could influence the behavior of the driver mutation. If this is true, we would expect the evolution of cells carrying the driver RET mutation alone or in combination with one or more polymorphisms to be different and to be led by a specific complex network of molecular alterations and signaling pathways. In order to understand how the driver-guided carcinogenic process may be modulated by other genetic factors including polymorphisms, a network medicine approach, using the SWIM software to identify switch genes, and based on omics data and their interaction topology, may provide an accurate and complete picture of cancer evolution.

SWIM tool identifies specific genes controlling glioblastoma stem-like cells fate

Paola Paci,[1] Giulia Fiscon,[1,2] Federica Conte,[1,2] and Lorenzo Farina[3]

[1]*Institute for Systems Analysis and Computer Science "Antonio Ruberti," National Research Council, Rome, Italy.*
[2]*SysBio Centre for Systems Biology, Milan, Italy.*
[3]*Department of Computer, Control, and Management Engineering Antonio Ruberti (DIAG), Sapienza University of Rome, Rome, Italy.*

Glioblastoma multiforme, the most malignant brain cancer, contains self-renewing, stem-like cells that sustain tumor growth and therapeutic resistance. Identifying genes promoting stem-like cell differentiation might unveil targets for novel treatments. To detect them, we applied SWIM—a software able to unveil genes (switch genes) involved in drastic changes of cell phenotype—to two public datasets of gene expression profiles from human glioblastoma cells: i) RNA-sequencing data from stem-like and differentiated glioblastoma cells; ii) microarray data from glioblastoma stem-like cells, the corresponding primary tumors, and conventional glioma cells. By analyzing both datasets, we found that switch genes resulting down-regulated in stem-like cells are enriched in cell-cell communication pathways and their expression in differentiated cells highly correlates with the depletion of genes related to neural development and differentiation, such as the 4-core of transcription factors (TFs)—OLIG2, POU3F2, SALL2, SOX2—whose induction is sufficient to reprogram differentiated glioblastoma into stem-like cells. These findings suggest a potential involvement of switch genes in controlling the stem-like phenotype of glioblastoma cells by direct repression of the 4-core TFs. Searching for switch genes shared by both datasets, FOSL1 drew our attention since it appeared down-regulated in stem-like cells, positively correlated with genes encoded for proteins crucial for cell-matrix adhesion and cell motility, negatively correlated with the 4-core TFs and with a consensus binding motif in their regulatory regions. Therefore, we suggest FOSL1 as promising candidate to orchestrate the differentiation of cancer stem-like cells by repressing the 4-core TFs expression, which severely halts cancer growth.

The brain-kidney network

Davide Viggiano,[1] Francesco Trepiccione,[1] Michele Ceccarelli,[2,3] and Giovambattista Capasso[1,2]

[1]*Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli," Naples, Italy.*
[2]*Biogem Scarl, Istituto di Ricerche Gaetano Salvatore, Ariano Irpino, Italy.*
[3]*Department of Science and Technology (DST), University of Sannio, Benevento, Italy.*

The new approach of the "medicine of networks" forces the physician to consider the disease of an organ as part of a system disease, due to the network of interactions among organs. Indeed, in recent years, new horizons have been explored in the case of kidney diseases, such as the pathologic relation between kidney and heart diseases (cardio-nephrology), kidney diseases and gut microbiota (entero-nephrology) and kidney diseases and tumors (onco-nephrology). One field that is still in its infancy is the relation between kidney and brain diseases. The introduction of high throughput techniques (genomics, urine peptidome and metabolome etc), new brain imaging modalities and new animal models opens today an unprecedented opportunity: the possibility to understand the kidney-brain network of diseases. Indeed, kidney diseases are linked to several brain dysfunctions such as mild cognitive impairment, dementia, restless leg syndrome, altered sleep pattern etc. The brain-kidney relation involves the interaction of multiple networks at multiple levels: disease networks, molecular networks, gene networks, drug networks, uremic toxins network, and brain neuronal network. Furthermore, the network of electrolyte imbalances (Na+, K+, Ca+ etc.) induced by kidney diseases may affect the brain network function. The topic is a new challenge and deserves great attention for its potential to uncover phenomena that would shed light on other brain diseases.

Mechanistic disease cluster-based drug repurposing

Harald H.H.W. Schmidt[1,2]

[1]*Department of Pharmacology and Personalized Medicine, Faculty of Health, Medicine and Life Sciences, Maastricht University, the Netherlands.*
[2]*Co-Editor-in-Chief Systems Medicine.*

Since the 50's, the efficacy drug discovery and development is facing a constant decline. One cause of failure is the inconsistency of observed clinical data with previous basic research and pre-clinical evidence. At the basic science level, a predominant focus on (i) high impact, lower quality and irreproducible publications and (ii) acquiring research funding as main career criteria deviate researchers from achieving patient benefit. Stringent statistical thresholds, reporting negative data (pre-clinicaltrials.org), systematic review/meta-analysis to detect positive publication bias, pRCT approaches to increase robustness of findings and different career and funding incentives may enhance biomedical data validity. Another key reason for failure and our current imprecision in medicine are our definitions of diseases, i.e., mostly by organ or symptom, not by mechanism. Systems Medicine will lead to a mechanism-based redefinition of diseases, precision diagnostics and therapies that eliminate both the risk in drug discovery but eventually also the need for further drug discovery. Current diseases will become phenotypes or symptoms of causal signaling networks, i.e., subgraphs of the interactome. Any drug targeting this pathway is a candidate to be repurposed for any other phenotype within the same common mechanism cluster (see repo-trial.eu). We show this for a reactive oxygen-cGMP defined ROCG cluster by repurposing two drugs in development for diabetic nephropathy and heart failure now for ischemic stroke. There may be time point in the not so far future when we will have all the drugs we need.

Big data analytics in healthcare system

R. Verde, A. Irpino, E. Romano, and A. Balzanella

Dipartimento di Matematica e Fisica–Università della Campania "Luigi Vanvitelli," Caserta, Italy.

Big Data analysis requests techniques for extracting, analyzing, and visualizing valuable information from data characterized by a high volume, variability and velocity. The challenge consists in the definition of methods that are scalable, efficient and rapid. These objectives cannot be optimized jointly, so some compromises must be accepted. Recent solutions coming from Symbolic Data Analysis, Functional Data analysis and Data Stream Analysis can be considered.

Store, sketch, or reduce big data stream in a data processing pipeline are among the key challenges. For doing this it is useful to sample or to use summaries of data. Symbolic Data Analysis model is proposed for describing set-valued data with a minimum loss of information in terms of variability. If data are observed in time and/or space; Functional Data approach is useful to modeling spatial or temporal sequences to discovery interactions and patterns.

Data stream techniques allow of produce summaries of subsequences of continuous coming data, usually on fly, without storing data and in one-pass. Data mining techniques are then applied on the summaries of data streams, usually, off line.

Data are today of different and complex types: images, videos, audios, unstructured text, sequence of measurements from sensors. In health care domain, some examples are electronic health records (EHRs). Records are made of texts, images, set of measurements. Summaries or aggregates of the data flows are represented by intervals of values, empirical distributions, and functions.

Our main contributions are in the developing of methods to analyze distributional data, Data stream and Functional analysis.

My-AHA, an ICT platform to detect frailty risk and propose personalized intervention

Alessandro Vercelli and I. Rainero on behalf of the My-AHA Consortium

Department of Neuroscience, University of Torino (I), Torino, Italy.

Stemming from a holistic view of interrelated frailties, cognitive decline, physical frailty, depression and anxiety, social isolation and poor sleep quality, My-AHA proposes an ICT platform for early detection of pre-frailty and intervention to sustain active and healthy aging and slowing or reversing further decline.

The main aim of My-AHA is to reduce frailty risk by improving physical activity and cognitive function, psychological state,

social resources, nutrition, sleep and overall well-being in older adults with pre-frailty symptoms. It will empower older citizens to better manage their own health, providing new ways of health monitoring and disease prevention through individualized profiling and personalized recommendations, feedback and support. An ICT-based platform will detect defined risks in the frailty domains early and accurately via non-stigmatizing embedded sensors and data readily available in the daily living environment of older adults. When risk is detected (pre-frail), My-AHA will provide targeted ICT-based interventions. These interventions will follow an integrated approach to motivate users to participate in physical exercise, cognitively stimulating games and social networking to achieve long-term behavioral change, sustained by continued end user engagement with My-AHA. A randomized controlled study (RCT), involving 300 subjects receiving intervention, and 300 controls from many EU and non-EU countries, is undergoing to evaluate intercultural aspects.

The ultimate aim is to deliver significant innovation in the area of AHA through cooperation between European health care organizations, Small and Medium Enterprises, and Non-Governative Organizations.

Space technologies and global health

Antoine Geissbuhler[1,2]

[1]*Faculty of Medicine, University of Geneva, Geneva, Switzerland.*
[2]*Working Group on Space and Global Health, UN Office for Outer Space Affairs, Vienna, Austria.*

Precision global health aims at improving the effectiveness and relevance of public health interventions at a global level, by leveraging on information-driven approaches. Space technologies can provide useful information sources, through remote sensing, global navigation satellite services (GNSS), and satellite telecommunications.

Parameters that can be derived via remote sensing include land temperature, altitude, humidity, rainfall, cloud coverage, air pollutants, livestock density, vegetation indices, sea temperature, sea salinity, sea nutrient concentration, sea algae concentration, sea bacteria concentration, urbanization, population density, and bare soil coverage. For example, fight against vector-borne diseases can be improved using satellite imaging combined with meteorological data, mathematical modeling of population movements, and socio-economical maps. Remote sensing can also be used to monitor air pollutants, droughts, and to investigate links with non-communicable diseases, premature birth or low-birth weight.

GNSS can be used to track physical activity, identify travel patterns, investigate person-to-person transmission, predict vector-breeding sites, map households or determine population estimates. Geolocation can be used to assess the physical accessibility of healthcare services, thus better informing health system planning activities. Satellite telecommunication enables applications such as telemedicine and distance education in remote and under-served areas.

These various services can be bundled and organized to provide multiple virtuous circles that enable learning health systems. With the adoption of the Sustainable Development Goals by the United Nations, there is a growing interest in considering planet-wide issues and multi-sectoral approaches to global health issues. Approaches and tools such as big data and network-based analysis will be needed to master such complexity.