The Impact of Systems Biology on the Digital Patient

by Martin Reczko, Panayiota Poirazi, Anastasis Oulas, Eleftheria Tzamali, Maria Manioudaki, Vassilis Tsiaras and Ioannis Tollis

Substantial advances in predictive, preventive and personalized (PPP) medicine are starting to emerge from computational simulations of complex networked models of metabolism ranging to the molecular level of detail. From the systems biology perspective of the digital patient, diseases are perturbations of biological networks through defective genes or environmental stimuli, and therapies are the interventions needed to restore these networks to their normal states. The Bioinformatics group at FORTH Heraklion is developing novel computational methods for identifying new parts of these networks both from genomic sequences and from metabolite time-series, and to generate meaningful visualizations of them.

Our bioinformatics activities are collaborations between the Biomedical Informatics Lab of the Institute of Computer Science and the Computational Biology Lab of the Institute of Molecular Biology and Biotechnology. The common goal is the data-driven discovery of novel regulatory networks. In most cases, these networks are related to various diseases. One specific focus is the study of the interferon signalling network and its interplay with clinically relevant pathogens such as Cytomegalovirus. In particular, we are developing computational methods to investigate the role in various diseases of a novel class of small regulatory genes called microRNA (miRNA).

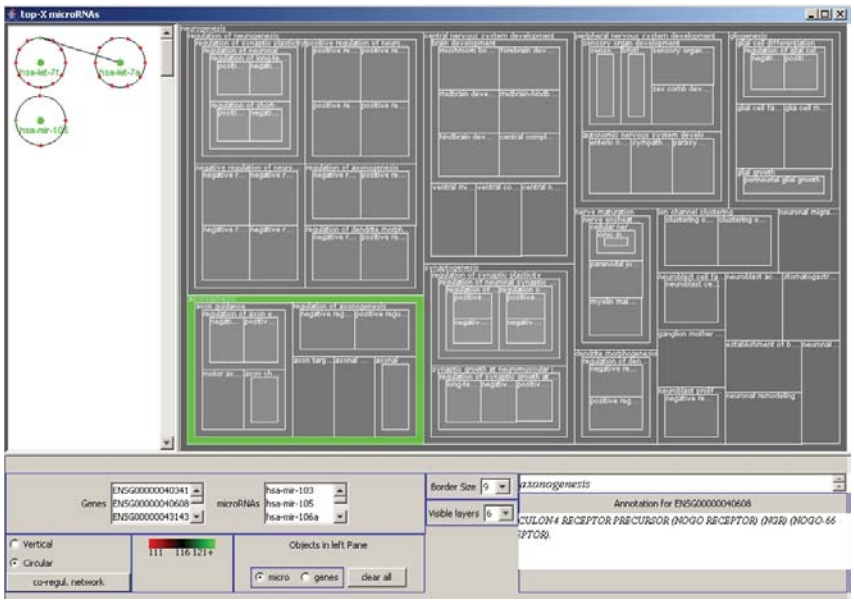

Figure 1: Circular drawing of genes regulated by microRNAs (left) and treemap visualization of the Gene Ontology categories of these genes (right).

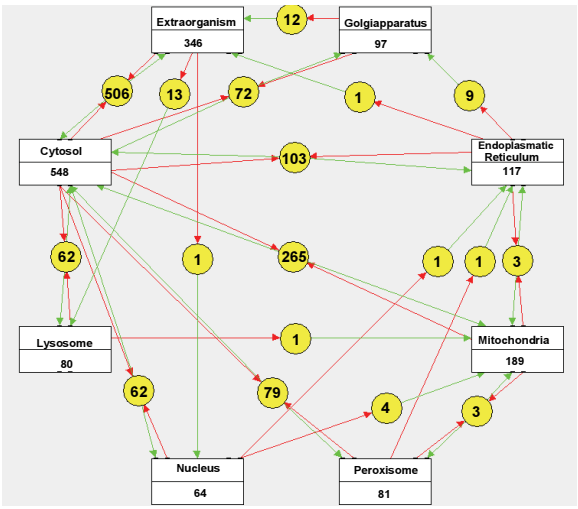

Figure 2: A visualization of the reactions between subcellular compartments of the first global reconstruction of the human metabolic network from the BIGG database (bigg.ucsd.edu). The number of chemical substances are specified in each the compartment box and the number of reactions between compartments are given in the circles. Reactant edges are shown in red and product edges in green.

Large parts of the general regulatory network operating with miRNAs are not yet known. We have therefore developed a computational pipeline to extract novel miRNAs from the human genome, using support vector machines trained on features of known miRNAs as the central classification method. In collaboration with the Universities of Pennsylvania and Toronto, we experimentally verified the actual expression of a large number of these miRNAs in many different human tissues. Subsequently, the regulatory function of these miRNAs can be partially predicted by computational methods in order to unfold the underlying regulatory network. To visualize these and other types of regulatory networks that contain genes annotated by the Gene Ontology project, we developed a visualization tool using circular drawings and treemaps (see Figure 1).

In developing methods to identify regulatory networks, we use time series of metabolite concentrations in yeast cells exposed to various types of environmental stress. At a higher level of detail we aim to identify the static modular organization of these networks, where the modules are defined as groups of co-regulated genes contributing to one specific biological function. We try to detect the kind of interrelations that govern each module, and the rules for interactions between modules. Initially we use gene expression data in conjunction with several statistical approaches, such as linear and higher-order correlation functions.

More accurate network models emulate the dynamic behaviour of all observable metabolites and have already been used to predict the presence of as yet unknown biological elements; for example, an unknown activating 'modifier' in human colon carcinoma cells that might act as a novel therapeutic target. To derive these types of networks from time series we employ evolutionary optimization methods.

An example of the most successful multilevel model with a wide temporal and spatial range is the virtual heart that recently extended the spatiotemporal detail of the simulations to the level of fixed subcellular modules. Now the first in silico reconstructions of the complete human metabolic network have become available for this and many other predictive models for human diseases.

Figure 2 shows one possible visualization of the reactions in this network; we designed this using the Cytoscape tool. Apart from leading to fundamental advances in biology, these models will have a direct practical value in future medicine for the integration, analysis and classification of data.

This work is supported by the EU-funded projects INFOBIOMED and ACGT, and by the action 8.3.1 (Reinforcement Programme of Human Research Manpower). It is also assisted by the project PrognoChip, which is itself funded by the operational programme 'competitiveness' of the Greek General Secretariat for Research and Technology.

Links:
http://www.ics.forth.gr/bmi
http://www.imbb.forth.gr/groups/computational.html
http://infobiomed.org

Please contact:
Martin Reczko
ICS-FORTH, Greece
E-mail: reczko@ics.forth.gr

Digital Human Modeling and Perception-Based Safety Design

by Vincent G. Duffy

The 'Digital Human Modeling and Perception-Based Safety Design' project is intended to minimize or reduce the need for physical prototyping in design. Researchers at Purdue University from across different colleges have the opportunity to work collaboratively on projects in this area through the Regenstrief Center for Healthcare Engineering and Discovery Park. The work has origins in automotive, aerospace and military vehicle design.

A digital human model is created by inserting a digital representation of the human into a simulation or virtual environment; this is then used to explore issues of safety and/or performance. The model enables researchers to visualize situations of interest, and the virtual environment incorporates all of the necessary mathematics or science to ensure rigour. Perception-based safety design applies fundamentals of human factors and ergonomics to the optimal design of products and processes in various application domains, including manufacturing, automotive, military and healthcare.

This work began in 1996 as an extension of research in virtual environments. Later, results on digital human modeling (DHM) were presented by Purdue researchers at the IIE Applied Ergonomics Conference and the Society of Automotive Engineers Conference on Digital Human Modeling for Design in 2004 and 2005. Some early fundamental research can be found in papers presented at the international conference on Computer-Aided Ergonomics and Safety and at the Human Factors and Ergonomics Society annual conference.

These recent projects on virtual interactive design, which began in 2003, give consideration to both cognitive and physical aspects of the virtual interaction. Motion capture is integrated with virtual reality as an input to some commercially available computer-aided ergonomics models. Additional research leading to new models will provide more robust predictions, including consideration of the dynamic aspects of work for improved safety and risk predictions.

Successes in DHM-related research led to funding from UGS, Nissan, General Motors and the U.S. Army. The current affiliation with the Regenstrief Center for Healthcare Engineering at Purdue University is driving a number of new research initiatives and academic endeavours, including editing the forthcoming Handbook of Digital Human Modeling and organizing the 1st International Conference on Digital Human Modeling, to be held in Beijing, China in July '07.

Opportunities for the systematic application of engineering principles to healthcare delivery include simulations and predictions of healthcare outcomes. By considering human physiological and psychological factors during virtual interactive design, we can determine the likelihood of injury or error given certain workplace conditions and task requirements. Future activities and cooperation with ERCIM will provide opportunities for larger-scale Digital Patient models. Informed by molecular and genetic data, these will provide better predictions and thus have a positive impact on the clinical outcomes of individuals.

Links:
https://engineering.purdue.edu/IE
http://discoverypark.purdue.edu/wps/portal/rchedev

Please contact:
Vincent G. Duffy
Purdue University, USA
Tel: +1 765 496 6658
E-mail: duffy@purdue.edu