Computing Life in the dynamic models: From design principles studies to personalised therapy of Parkinson's disease

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Abstract

Following the paradigm that biological function emerges from nonlinear interactions between physical components, we understand how the disturbance of interactions between components leads to the malfunctioning of living systems that are so robust otherwise. This may reveal the essence of the molecular basis of many diseases. However, the millions of interactions make the living organism too complex to be handled intuitively in a human brain or on the back of an envelope. Systems biology developed an approach to reconstruct biological emergence in a computer model in silico, based on realistic component-interaction properties. A whole body model is being developed in the framework of so-called Virtual/Digital/Silicon Human projects. This whole human body model holds great promise for medicine. When it becomes available, it may be parameterized for any patient individually and propel personalized medicine.

We have built and validated experimentally an ODE-based dynamic model of energy metabolism coupled to an intracellular signalling network controlling the response to oxidative stress that is eminently complex. By computational analysis, we disentangle this to various functionalities of Reactive Oxygen Species (ROS) management network. The advantage of mathematical model is that parameters might be kept and the functionality of each module might be checked by just computation. Using a set of dynamic models of different complexity we identified design principles of ROS management that give insight to the relations between ROS management and energy metabolism in the context of ROS-related systems biological diseases, such as Parkinson's disease (PD). We propose a detailed model describing dynamic adaptation to oxidative stress in a short-term, and accumulation of the stress and system's collapse in the long-term. We simulate the effect of PD-related perturbations and search network targets that may delay or avert the collapse, suggesting potential approaches for personalised PD therapy through intervening with ROS management network.

We also propose to consider the model dynamics using model predictive control method – the approach which is widely used in process industries. The method includes transfer of model into Simulink environment and creation of virtual controller which can drive one or several model components (e.g. protein concentration). It can be shown that for every particular type of stress it's possible to choose the best target (protein) to regulate in a special way in order to maintain acceptable level of ROS and to save mitochondria. This provides an opportunity to consider different scenarios of oxidative stress (one-time step, regular, increasing) and suggest the treatment strategy.

About speakers:

Alexey Kolodkin

Ph.D in Systems Biology (2011) and M.Sc in Biomolecular sciences (2008) from VU University of Amsterdam in the Netherlands; M.Sc in Chemical Engineering (2004) from University of Rovira i Virgili in Tarragona, Spain; diploma with honour in Physiology (2000) from Irkutsk State University in Russia. From 2011 works as research associate at the Luxembourg Centre for Systems Biomedicine, University of Luxembourg and have spent two year (2012 –2014) as visiting scholar at the Institute for Systems Biology in Seattle, USA

Research interests: systems biology, biocomplexity, philosophy of systems biology, dynamic network modelling, design principles study, reconstruction of biological emergence in silico, model predictive control, metabolic models, gene regulatory networks, molecular biomedicine, biotechnology, reactive oxygen species (ROS), aging mechanism, neurodegenerative diseases, nuclear receptors, cancer research, stem cells research, toxicology, methods of bio-testing, waste water treatment technology. Author of 9 peer reviewed articles (6 of them as a first or the last author), 8 book chapters, 6 invited lectures and 42 conference participations.

Andrew Ignatenko

B.Sc., Dipl.-Ing. (cum laude) in Electronics (2004) from Belarussian State University in Minsk Belarus. From 2004 to 2012 – researcher in B.I.Stepanov Institute of Physics in Minsk, Belarus. Since 2013 – PhD student at the Faculty of Science, Technology and Communication, University of Luxembourg.

Research interests include computer simulation of complex systems, model control and optimization technics, neural networks, statistical analysis, quantum optics, energy saving technologies.