MODELLING OF CANCER-RELATED SIGNALLING NETWORKS. CHALLENGES, SOLUTIONS AND APPLICATIONS FOR ANTI-CANCER DRUG DEVELOPMENT

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Development of prognostic and predictive models for possible diagnostics and therapeutic applications is one of the major goals of systems biology. Recently network modelling techniques have been increasingly employed to advance our understanding of cancer-related pathways and likely mechanisms of disease.

This presentation will provide an overview of the general pipe-line for the network model development, illustrated with examples. Key challenges will be highlighted, which hamper successful translation of the results of modelling studies into clinical drug development, and potential solutions will be discussed. In particular, the focus will be placed on the problems, caused by a high level of individual variability of the cellular networks involved in seemingly identical cancers, and on the difficulties, arising from a lack of parameter identifiability in large-scale network models. These challenges stimulate a need to develop theoretical approaches capable of addressing individual variability of signalling networks, and drawing valid predictions from the models with uncertain parameters. One suitable framework, offering appropriate mathematical apparatus, is global sensitivity analysis (GSA).

A novel implementation of GSA will be presented [1], specially designed to explore the sensitivity of network model outputs to the perturbation of multiple model parameters within a parameter space, before and after a targeted anti-cancer drug is introduced into a network system. A special emphasis will be placed on identifying a set of critical nodes, controlling the level of cancer-related signal outputs from the network, that provides a basis for generating hypotheses on potential anti-cancer drug targets, biomarkers of drug resistance, and combinatorial therapies. The capabilities of the method will be illustrated via applying it to our previously developed ErbB2/3 network model [2], and exploring the sensitivity profile of its key model readout, phosphorylated Akt (pAkt), in the absence and presence of the ErbB2 inhibitor pertuzumab.

References

1. *Lebedeva et al.* Model-based global sensitivity analysis as applied to identification of anti-cancer drug targets and biomarkers of drug resistance in the ErbB2/3 network // *Eur J Pharm Sci* (2011) doi:10.1016/j.ejps.2011.10.026
2. *Faratian et al.* Systems biology reveals new strategies for personalizing cancer medicine and confirms the role of PTEN in resistance to trastuzumab // *Cancer Res* (2009) 69(16): 6713-20.