AISP - 36th National Congress. **Bologna, Italy. October 4-6, 2012**

Inference and Modelling of the Gemcitabine Pharmacokinetics and Resistance

Paola Lecca[1], Corrado Priami[1,2]

[1]The "Microsoft Research-University of Trento" Centre for Computational and Systems Biology. Rovereto, TN, Italy. [2]University of Trento. Trento, Italy

Context Integrative network inference methods and modelling approaches could support the experimental activity devoted to the identification of mechanisms of action of oncological drugs as well as the identification of pathways entailing with the chemoresistance. Network inference is a branch of computational systems biology that deals with the deduction of interaction network among the systems components from experimental data recording the behaviour - in time or at steady state - of the abundance of the components themselves (e.g., molecules, proteins, metabolites, enzymes). Metabolic reactome data, measurements of the metabolites concentration and rate of drug influx and efflux, as well as gene expression data are the input of the advanced integrative techniques of network inference applied to pharmacology. The outcome of the network inference procedures is the set of interactions composing the network of drug metabolism, drug mechanisms of action, and chemoresistance. Once this network is inferred we dispose of a pharmacokinetics model deeply rooted in real *in vivo* or *in vitro* experimental data. The network is a model that can be specified in a mechanistic way and whose dynamic can be simulated through algorithms implementing the physics of biochemical interactions. **Objective** The first goal of our study was to infer the metabolic network and the mechanisms of action and resistance to gemcitabine from time-series experimental data regarding the concentration of the main drug metabolites and the recent experimental data about gemcitabine uptake and efflux in and out the cell. Our second objective was to simulate the inferred network in a stochastic mechanistic framework to better reproduce the behavior of the molecular interactions at the micro- and nano-scale. **Methods** We used a time-lagged correlation network inference approach to infer the pharmacokinetics model from time-series data of the concentration of gemcitabine metabolites. We then used time-series gene expression data to infer the interactions between genes capable of determining the sensitivity to gemcitabine, recently identified and reported in literature. We finally, merged the gene regulatory network with the metabolic network. **Results** We obtained the regulatory interaction of the chemoresistance assembled into metabolic pathways, and we simulated the dynamics of this network to monitor the time-behavior of its components and to analyse its structural and parametric sensitivity. We obtained a good agreement with the experimental observations that makes us confident in the usefulness of this model to explore the a range of variability of the parameters characterizing each patient. **Conclusion** Integrative network inference from different types of data can support the development of targeted therapies taking into account the differences among patients expressing different levels of chemoresistance and different drug kinetics.