APPLICATION OF COMPUTATIONAL SYSTEMS BIOLOGY FOR DISCOVERY OF NEW ANTI-INFLAMMATORY DRUGS

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Two approaches of computational systems biology are presented: pathway reconstruction and kinetic modeling. Pathway reconstruction collects all information about players of interest, processes interconnecting them and their stoichiometry and can be considered as a powerful tool to search for drug targets, discover possible biomarkers and attribute them to particular cell state or phenomenon. In framework of kinetic modeling approach we mine, collect and integrate quantitative *in vitro* and *in vivo* experimental data produced by classical biochemistry, genomics, proteomics and metabolomics and use them to build and verify kinetic models [1,2]. These kinetic models when considered as a repository of all information about the system of interest can be applied to different problems of drug discovery and production such as screening optimization [3], investigation/prediction of drug safety [4] and optimization/maximization of yield of drug precursors.

We have applied these approaches to develop workbench for discovery and safety assessment of anti-inflammatory drugs. All signaling pathways associated with inflammatory processes proceeding in platelets, endothelium cells, neutrophils and macrophages have been reconstructed and annotated. Kinetic models of metabolic pathways involved in synthesis and degradation of arachidonic acid and signaling networks initiated by prostaglandins in platelet and endothelium cells have been developed to understand/predict the mechanism of NSAID-stimulated adverse cardiovascular effects (clot formation). These models quantitatively describe the changes in dynamics and regulations of the pathways caused by the following NSAIDs: aspirin, celecoxib, diclofenac, naproxen, indomethacin, ibuprofen. Experiments assisting modeling efforts have been design to generate data for verification of the models and test model predictions. Software packages based on these kinetic and static models have been developed. This software allows to predict IC50 and clot formation risk for any anti-inflammatory drugs which are able to inhibit prostaglandin H synthetase.

References.

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