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Fuzzy Optimization for Identifying Anticancer Targets in Genome-Scale Metabolic Models of Colon Cancer

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Abstract : Developing a drug from conception to launch is costly and time-consuming. Computer-aided methods can reduce research costs and accelerate the development process during the early drug discovery and development stages. This study developed a fuzzy multi-objective hierarchical optimization framework for identifying potential anticancer targets in a metabolic model. First, RNA-seq expression data of colorectal cancer samples and their healthy counterparts were used to reconstruct tissue-specific genome-scale metabolic models. The aim of the optimization framework was to identify anticancer targets that lead to cancer cell death and evaluate metabolic flux perturbations in normal cells that have been caused by cancer treatment. Four objectives were established in the optimization framework to evaluate the mortality of cancer cells for treatment and to minimize side effects causing toxicity-induced tumorigenesis on normal cells and smaller metabolic perturbations. Through fuzzy set theory, a multiobjective optimization problem was converted into a trilevel maximizing decision-making (MDM) problem. The applied nested hybrid differential evolution was applied to solve the trilevel MDM problem using two nutrient media to identify anticancer targets in the genome-scale metabolic model of colorectal cancer, respectively. Using Dulbecco's Modified Eagle Medium (DMEM), the computational results reveal that the identified anticancer targets were mostly involved in cholesterol biosynthesis, pyrimidine and purine metabolisms, glycerophospholipid biosynthetic pathway and sphingolipid pathway. However, using Ham's medium, the genes involved in cholesterol biosynthesis were unidentifiable. A comparison of the uptake reactions for the DMEM and Ham's medium revealed that no cholesterol uptake reaction was included in DMEM. Two additional media, i.e., a cholesterol uptake reaction was included in DMEM and excluded in HAM, were respectively used to investigate the relationship of tumor cell growth with nutrient components and anticancer target genes. The genes involved in the cholesterol biosynthesis were also revealed to be determinable if a cholesterol uptake reaction was not induced when the cells were in the culture medium. However, the genes involved in cholesterol biosynthesis became unidentifiable if such a reaction was induced.

Keywords : Cancer metabolism, genome-scale metabolic model, constraint-based model, multilevel optimization, fuzzy optimization, hybrid differential evolution
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