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Constraint based Analysis of Clostridium Difficile Metabolic Network: FBA and MOMA Approach for Drug Target Identification

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Abstract—*Clostridium difficile, a gram-positive, anaerobic, spore-forming bacillus is a widely distributed cause of nosocomial infections. Deaths related to C. difficile increased to 400% between 2000 and 2007 in United States. Escalating antibiotic resistance due to C. difficile being naturally resistant to a wide range of antibiotics used to treat other infections has aided C. difficile to emerge as a deadly strain resulting in life threatening cases of diarrhea. There is pressing need to reinvigorate the antibiotic pipeline to combat the problem of ever growing antibiotic resistance. Exploiting genome scale metabolic reconstructions using constraint based methods have huge potential to decode the physiological properties which govern the pathophysiological state of an organism. Computational quantification of genome scale metabolic networks open up new avenues for novel drug target identification against ever widening range of infectious diseases. We utilized a combinatorial approach employing a combination of systems biology and bioinformatics approaches. We performed flux balance analysis and minimization of metabolic adjustment studies on genome scale reconstruction model of C. difficile to predict metabolites which can be modeled into potential therapeutic strategies. Constraint based methods predict metabolites critical to bacterial survival by gene knockout studies which were then prioritized based on a set of physiochemical properties. Metabolites involved in peptidoglycan biosynthesis, and fatty acid biosynthesis pathways such as murC, murD, murE, ddl, accA, accB etc. were prioritized as candidate drug targets.*

Keywords*: Clostridium difficile, metabolic networks, FBA, MOMA, drug target, constraint based modeling*