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Systems level metabolic pathway analysis for understanding antibiotic resistance in *Chromobacterium violaceum*

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Antibiotic resistance is a serious threat to public health globally. Altered metabolism, in addition to the pathogenicity islands and virulence factors have been implicated in pathogenesis and antibiotic susceptibility. The systems biology paradigm of integrating heterogeneous data-types with computational metabolic models offers a constraints-based framework to understand connections between growth, metabolism and resistance. *Chromobacterium violaceum* (CV) populations resistant to chloramphenicol (chlR) and streptomycin (streptR) have been evolved under controlled laboratory conditions. A Genome scale metabolic model (GSM) of CV was reconstructed including drug metabolic pathways. Constraint-based flux balance analysis was further used to define resistant and susceptible phenotypes of CV and understand metabolic rewiring in the differential phenotypes. The model constrained using physiological, genomic and metabolic profiling (MALDI) data acquired in-house mimicked the multiple pathogen phenotypes *in silico*. Biolog (TM) data was used to validate the model. The differential growth & respiration profiles on exogenous Carbon & Nitrogen sources were predicted with good accuracy. The Antibiotic sensitivity was also calculated as cfu/ml on 30 different carbon and nitrogen sources and TCA cycle intermediates citrate and succinate allow reversal of antibiotic resistance. Flux variability analysis captured the differential metabolic secretome of susceptible and resistant cells and gave insight into the alternate routes available to the pathogen. Metabolic reprogramming in pathogens as a response to antibiotics may allow development of strategies against the emergence of antibiotic resistance.

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*merlin* latest developments for pathways analysis

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*merlin* is a user-friendly open-source software tool developed for the reconstruction of genome-scale metabolic models. These models are derived from sets of reactions, organised in pathways, which can be used to mimic the behaviour of microorganisms in different genetic and environmental conditions. One of the toughest challenges, when reconstructing models is the identification of gene-protein-reaction associations, a step usually performed by manually searching literature. Thus, a novel approach for automatically predicting, at the genome level, protein subunits using gene association rules retrieved from the KEGG BRITE database was developed and integrated in *merlin*. The presence or absence of the different pathways in the metabolic models may be related with several properties of the microorganism, namely the ability to survive in specific environments. Moreover, the analysis of metabolic pathways is important for finding gaps, which can impair model predictions by blocking the production of a by-product of interest, or a biomass component. Additionally, this analysis may propose more efficient pathways to increase the production of specific metabolites by, for instance, proposing knock-out or knock-in of genes. Therefore, an innovative reactions panel, which organises reactions by pathway allowing the visualisation and analysis of the constructed models’ reactions in KEGG pathways was developed and integrated into *merlin*. 