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Mechanistic Understanding of the Difference in two Strains Cholerae Causing Pathogens and Predicting Therapeutic Strategies for Cholera Patients Affected with new Strain Vibrio Cholerae El.tor. Using Constrain-based Modelling

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Abstract : Cholera caused by pathogenic gut bacteria Vibrio Cholerae (VC), is a major health problem in developing countries. Different strains of VC exhibit variable responses subject to different extracellular medium (Nag et al, Infect Immun, 2018). In this study, we present a new approach to model the variable VC responses in mono- and co-cultures, subject to continuously changing growth medium, which is otherwise difficult via simple FBA model. Nine VC strain and seven E. coli (EC) models were assembled and considered. A continuously changing medium is modelled using a new iterative-based controlled medium technique (ITC). The medium is appropriately prefixed with the VC model secretome. As the flux through the bacteria biomass increases secretes certain by-products. These products shall add-on to the medium, either deviating the nutrient potential or block certain metabolic components of the model, effectively forming a controlled feed-back loop. Different VC models were setup as monoculture of VC in glucose enriched medium, and in co-culture with VC strains and EC. Constrained to glucose enriched medium, (i) VC_Classical model resulted in higher flux through acidic secretome suggesting a pH change of the medium, leading to lowering of its biomass. This is in consonance with the literature reports. (ii) When compared for neutral secretome, flux through acetoin exchange was higher in VC_El tor than the classical models, suggesting El tor requires an acidic partner to lower its biomass. (iii) Seven of nine VC models predicted 3-methyl-2-Oxovaleric acid, mysirtic acid, folic acid, and acetate significantly affect corresponding biomass reactions. (iv) V. parhemolyticus and vulnificus were found to be phenotypically similar to VC Classical strain, across the nine VC strains. The work addresses the advantage of the ITC over regular flux balance analysis for modelling varying growth medium. Future expansion to co-cultures, potentiates the identification of novel interacting partners as effective cholera therapeutics.

Keywords : cholera, vibrio cholera El. tor, vibrio cholera classical, acetate
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