Genome-Scale Modelling of Chinese Hamster Ovary Cells by Hybrid Semi-Parametric Flux Balance Analysis

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Abstract

Flux balance analysis is currently the standard method to compute metabolic fluxes in genome-scale networks. Several variations employing diverse objective functions and/or constraints have been published. Here we propose a hybrid semi-parametric version of flux balance analysis that combines mechanistic-level constraints (parametric) with empirical constraints (non-parametric), at the genome-scale. A CHO dataset with 27 measured exchange fluxes obtained from 21 reactor experiments served to evaluate the method. The reduced CHO genome-scale model comprehended 686 metabolites, 788 reactions and 210 degrees of freedom. The experimental flux dataset could be compressed to 6 principal components retaining 93.7% of explained variance. The conjugation of both types of constraints is coded as a linear program with comparable computational cost as standard flux balance analysis. The hybrid flux balance analysis showed a significant reduction in the specific growth rate prediction error in comparison to the non-hybrid version. The hybrid method was eventually used to design a metabolically efficient feed to extend cell expansion from 9.87 Mcell/ml to 22.48 Mcell/ml at the point of induction with minimal accumulation of byproducts. It is concluded that the predictive advantage of the hybrid method resulted from the statistical abstraction of regulatory mechanisms, which were absent in the standard flux balance analysis.

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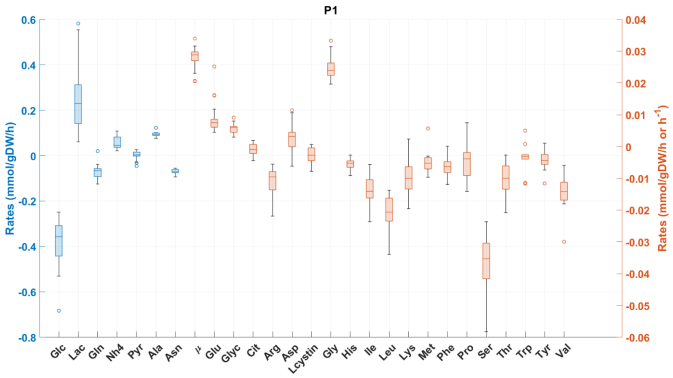

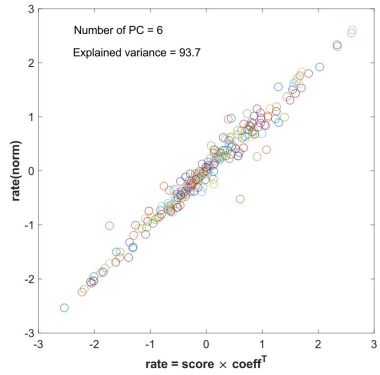

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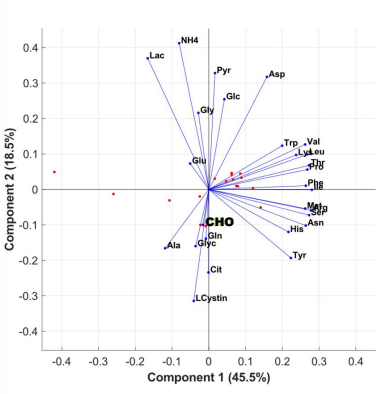

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