Objectives

1. Perform synthetic reaction and gene lethality analysis for genome-scale metabolic networks of *E. coli*, *S. enterica*, and *Mycobacterium tuberculosis*.
2. Characterize synthetic lethal gene deletions for these networks.
3. Improve on the Flux Balance Analysis (FBA) predictions using quadratic programming. Characterize the improvement via public domain data on the transcription factor (TF) knock-out experiments.

Introduction

Synthetic lethality arises when a combination of deficiencies in the expression of two or more genes leads to cell death, whereas a deficiency in only one of these genes does not. The deficiencies can arise through mutations, epigenetic alterations or inhibitors of one of the genes.

The phenotype resulting from a gene/reaction deletion is termed a lethal phenotype, if the maximum growth-rate predicted by FBA is less than a cut-off, typically 1% of the maximum *in silico* wild-type growth rate.

FBA [1] solves a Linear Programming (LP) problem in which, typically, flux through a set of biomass reactions is to be maximized subject to the constraints obtained from the stoichiometry of the metabolic network.

Materials

1. SBML models of the organisms:* E. coli*: iAF1260 [2]; *S. enterica Typhimurium*: LT2 STM v1.0 [3]; *M. tuberculosis*: iNJ661 [4].
2. MATLAB (R2015b) interfaced with COBRA Toolbox v2.X.
3. A desktop: 2.4GHz Intel Xeon E5645 processor with 16 GB DDR3 RAM running Windows 8.1 using the IBM CPLEX v12.5.1 solver.

Methods

Mathematical Section

Solve the problem of minimizing the $\ell_1$ norm of the fluxes subject to the FBA constraints such that the biomass produced is the same as the wild type. Let $J_{nz}$ denote the set of reactions that have non-zero flux.

Results: Synthetic Lethal Discovery and Speed-Up

Figure 3: Our algorithms significantly speed up the synthetic lethal identification process.

Results: Quadratic Programming for Growth Predictions

Figure 4: Our quadratic programming solution outperforms other algorithms.

Conclusion and Future Directions

- We have extended the scope of FBA for a more comprehensive and more efficient determination of synthetic lethals.
- Our quadratic programming algorithms predict growth better than other algorithms but require more data.
- We aim to conduct more TF-knock out experiments and develop techniques to include miRNA datasets.

References


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We are looking to work with additional datasets. Do contact us if you have omics data to share!