The 4th Iranian Conference on Systems Biology

Development of a General Algorithm to Identify n-Tuple Synthetic Lethal Reactions in Genome-Scale Models: A Systematic Approach Based on Fast-SL

Mehdi Dehghan Manshadi, Payam Setoodeh*

School of Chemical and Petroleum Engineering, Shiraz University, Shiraz, Iran

**Corresponding Author's E-mail: payamst@shirazu.ac.ir*

Shiraz University

Abstract

Simultaneous removal of synthetic lethal reactions or genes (SLs) that their simultaneous removal prohibits the growth. These SLs are potential to form drug targets for multi-drug resistance pathogens. Seeking higher-order SLs is a challenging problem, due to the large search space. In this work, a new comprehensive and integrated algorithm is provided based on the main idea of Fast-SL. This novel algorithm is capable to compute higher SLs without limitation on cardinality of the sets. In addition, by making minor revisions on original Fast-SL algorithm, the number of examined cases is reduced 2-fold compared to the original method.

Keywords: Systems biology, Drug target identification, constraint-based modeling

Introduction

Fast-SL (Pratapa et al. 2015) is the most recent and successful method presented to identify different SLs. This technique reduces the number of studied cases by approximately 4000-fold for finding triple SLs, compared to the exhaustive search. However, up to now, no comprehensive algorithms have been reported for this method and consequently computation of higher SLs (n > 4) is not practical using the reported and available approach for Fast-SL, due to the necessity of developing new algorithms for each state. Therefore, devising a new algorithm to overcome these limitations is necessary.

Materials and Methods

We have proposed a two-step procedure to compute all SLs of arbitrary cardinality. In the first step, all possible combinations of reactions up to the desired cardinality are considered. By starting from the cases with only one target, the biomass objective function is evaluated for each case. To prevent the generation of trivial answers, when a lethal set is identified, all of their supersets are omitted from the list of the potential cases. To this end, the main potential targets are computed, and the non-lethal combinations (NLCs), that are the clues for finding the SLs are identified. In the second step, the Depth First Search algorithm (DFS) (Cormen et al. 2009) is applied to identify new SLs. To perform this task, each set of NLC is deleted from the model. When the fluxes for this mutant are computed, the flux-carrying reactions which are not a subset of flux carrying reactions of wild type srain (J_{nz}) are identified. Based on the DFS search, the first newly-found reaction is removed from the model and flux distribution for maximizing the biomass formation is determined. The procedure should be repeated for the new sets, until the maximum cardinality is reached or an SL is identified in the branch.

Results

To test and demonstrate the efficiency of the developed algorithm and make a comparison with that of the original Fast-SL, our approach was applied to iAF1260 model of *E. coli* for finding the quadruple SLs. Successfully, all reported SLs by Fast-SL were identified using the proposed approach. In addition, the number of the studied cases using the presented algorithm was reduced to half, compared to that of Fast-SL for computing quadruple SLs (7,195,825 cases versus 14,529,932 cases). Furthermore, this algorithm makes it possible to compute higher SLs among a set of genes with no limitations in the number of targets in the set. To examine this capability, all octuple SLs (8 reactions in set) contributing only in "Nucleotide salvage pathway" subsystem of iAF1260 were computed. Although this subsystem contains only 95 reactions, examination of about ~10^9 cases is required for applying exhaustive search to identify octuple SLs. However, using the presented algorithm, all octuple SLs in this subsystem were identified by computing only 532538 cases. Based on our knowledge, no octuple SLs have been reported previously.

Discussion, Conclusion and Suggestions

In this work, we developed a new comprehensive and integrated algorithm based on the idea of Fast-SL method to overcome its limitations for computing higher SLs. In contrast to Fast-SL, which uses different algorithms for SLs with different cardinalities, the presented algorithm is capable to compute SLs up to any arbitrary maximum number of targets in a set. By applying this method on E. coli model of iAF1260, all quadruple SLs, which had been found previously by Fast-SL, were successfully reevaluated. However, using the reduced model, prepared based on the defined medium, the number of the studied cases became reduced by 2-fold compared to original Fast-SL technique. Finally, to show the capabilities of the developed approach for computing higher SLs, the whole octuple SLs, which affect only "Nucleotide salvage pathway" subsystem of iAF1260, were identified.

References

26"Fast-Sl: An Efficient Algorithm to Identify Synthetic Lethal Sets in Metabolic Networks." Bioinformatics 31, no. 20 (2015): 3299-305.

Silver, Lynn L. "Multi-Targeting by Monotherapeutic Antibacterials." Nature Reviews Drug Discovery 6, no. 1 (2007): 41.

Tanwar, Jyoti, Shrayanee Das, Zeeshan Fatima, and Saif Hameed. "Multidrug Resistance: An Emerging Crisis." Interdisciplinary perspectives on infectious diseases 2014.