Simulating Serial-Target Antibacterial Drug Synergies Using Flux Balance Analysis - DTU Orbit (10/03/2019)

**Simulating Serial-Target Antibacterial Drug Synergies Using Flux Balance Analysis**

Flux balance analysis (FBA) is an increasingly useful approach for modeling the behavior of metabolic systems. However, standard FBA modeling of genetic knockouts cannot predict drug combination synergies observed between serial metabolic targets, even though such synergies give rise to some of the most widely used antibiotic treatments. Here we extend FBA modeling to simulate responses to chemical inhibitors at varying concentrations, by diverting enzymatic flux to a waste reaction. This flux diversion yields very similar qualitative predictions to prior methods for single target activity. However, we find very different predictions for combinations, where flux diversion, which mimics the kinetics of competitive metabolic inhibitors, can explain serial target synergies between metabolic enzyme inhibitors that we confirmed in *Escherichia coli* cultures. FBA flux diversion opens the possibility for more accurate genome-scale predictions of drug synergies, which can be used to suggest treatments for infections and other diseases.

**General information**

State: Published  
Organisations: Drug Resistance and Community Dynamics, Novo Nordisk Foundation Center for Biosustainability, Bacterial Synthetic Biology, Boston University, Washington University School of Medicine, Harvard Medical School  
Contributors: Krueger, A. S., Munck, C., Dantas, G., Church, G. M., Galagan, J., Lehár, J., Sommer, M. O. A.  
Number of pages: 18  
Publication date: 2016  
Peer-reviewed: Yes

**Publication information**

Journal: PLoS One  
Volume: 11  
Issue number: 1  
Article number: e0147651  
ISSN (Print): 1932-6203  
Ratings:  
BFI (2019): BFI-level 1  
Web of Science (2019): Indexed yes  
BFI (2018): BFI-level 1  
Web of Science (2018): Indexed yes  
BFI (2017): BFI-level 1  
Scopus rating (2017): CiteScore 3.01 SJR 1.164 SNIP 1.111  
Web of Science (2017): Indexed yes  
BFI (2016): BFI-level 1  
Scopus rating (2016): CiteScore 3.11 SJR 1.236 SNIP 1.101  
Web of Science (2016): Indexed yes  
BFI (2015): BFI-level 1  
Scopus rating (2015): CiteScore 3.32 SJR 1.427 SNIP 1.136  
Web of Science (2015): Indexed yes  
BFI (2014): BFI-level 1  
Scopus rating (2014): CiteScore 3.54 SJR 1.559 SNIP 1.148  
Web of Science (2014): Indexed yes  
BFI (2013): BFI-level 1  
Scopus rating (2013): CiteScore 3.94 SJR 1.772 SNIP 1.153  
ISI indexed (2013): ISI indexed yes  
Web of Science (2013): Indexed yes  
BFI (2012): BFI-level 1  
Scopus rating (2012): CiteScore 4.15 SJR 1.982 SNIP 1.156  
Web of Science (2012): Impact factor 3.73  
ISI indexed (2012): ISI indexed yes  
Web of Science (2012): Indexed yes  
BFI (2011): BFI-level 1  
Scopus rating (2011): CiteScore 4.58 SJR 2.425 SNIP 1.233  
Web of Science (2011): Impact factor 4.092  
ISI indexed (2011): ISI indexed no