**Flux Balance Analysis**

**Expectations**

*Learning Objectives*

Each student should be able to:

* Explain flux balance analysis (FBA).
* Explain the stoichiometric reactions and metabolites.
* Explain mass balanced linear equations.
* Explain the biomass reaction.
* Explain how to create a stoichiometric matrix from reactions and metabolites.
* Explain gene-protein-reaction associations
* Explain the constraint-based modeling.

*Prerequisites*

* Course Introduction

**Resources**

*Presentations/Tutorials*

* None

*Required Readings*

1. Orth, J. D., I. Thiele, et al. (2010). "What is flux balance analysis?" Nature biotechnology 28(3): 245-248.
2. Orth, J. D., I. Thiele, et al. (2010). "What is flux balance analysis?" Supplementary Tutorial, Nature biotechnology 28(3): 245-248.
3. Oberhardt, M. A., B. O. Palsson, et al. (2009). "Applications of genome-scale metabolic reconstructions." Molecular Systems Biology 5: 320.
4. Price, N. D., J. L. Reed, et al. (2004). "Genome-scale models of microbial cells: evaluating the consequences of constraints." Nature reviews. Microbiology 2(11): 886-897.

**Classroom Activities**

*Presentations*

* Lecture Presentation (“*Flux Balance Analysis Overview - 2021.pdf”*)

*Laboratory*

* None

**Reinforcement Activities**

*Examples*

* External Lectures/Tutorials
  + Eran Eden lecture on "Flux Balance Analysis in Metabolic Networks.

*Videos*

* None

**Assessment**

*Formative Assessment*

* Reflective Questions
  1. What does steady state mean in flux balance analysis (FBA)?
  2. What are genome-scale metabolic network reconstruction?
  3. What is the purpose of biomass objective function?
  4. What phase of growth does FBA assume (lag, exponential, stationary, death)?
  5. What is the purpose of constraints in FBA?
  6. What are the limits of FBA?
  7. What role does the stoichiometric matrix play in FBA?
  8. Why are visualization tools needed?

**References**

*Flux Balance Analysis Overview*

1. Monk, J., J. Nogales, et al. (2014). "Optimizing genome-scale network reconstructions." Nature biotechnology 32(5): 447-452.
2. Monk, J. and B. O. Palsson (2014). "Genetics. Predicting microbial growth." Science 344(6191): 1448-1449.
3. McCloskey, D., B. O. Palsson, et al. (2013). "Basic and applied uses of genome-scale metabolic network reconstructions of Escherichia coli." Molecular Systems Biology 9: 661.
4. Orth, J. D., I. Thiele, et al. (2010). "What is flux balance analysis?" Nature biotechnology 28(3): 245-248.
5. Reconstruction and Use of Microbial Metabolic Networks: the Core Escherichia coli Metabolic Model as an Educational Guide by Orth, Fleming, and Palsson (2010)
6. Oberhardt, M. A., B. O. Palsson, et al. (2009). "Applications of genome-scale metabolic reconstructions." Molecular Systems Biology 5: 320.
7. Palsson, B. (2009). "Metabolic systems biology." FEBS letters 583(24): 3900-3904.
8. Adam M. Feist, Ines Thiele, and Bernhard Ø. Palsson, Chapter 9: Genome-Scale Reconstruction, Modeling,and Simulation of E. coli’s Metabolic Network, S.Y. Lee (ed.), Systems Biology and Biotechnology of Escherichia coli, DOI 10.1007/978-1-4020-9394-4\_9, Springer Science+Business Media B.V. 2009.
9. Feist, A. M. and B. O. Palsson (2008). "The growing scope of applications of genome-scale metabolic reconstructions using Escherichia coli." Nature biotechnology 26(6): 659-667.
10. Reed, J. L., I. Famili, et al. (2006). "Towards multidimensional genome annotation." Nature reviews. Genetics 7(2): 130-141.
11. Price, N. D., J. L. Reed, et al. (2004). "Genome-scale models of microbial cells: evaluating the consequences of constraints." Nature reviews. Microbiology 2(11): 886-897.
12. Price, N. D., J. A. Papin, et al. (2003). "Genome-scale microbial in silico models: the constraintsbased approach." Trends in biotechnology 21(4): 162-169
13. Reed, J. L. and B. O. Palsson (2003). "Thirteen years of building constraint-based in silico models of Escherichia coli." Journal of Bacteriology 185(9): 2692-2699.
14. Covert, M. W., I. Famili, et al. (2003). "Identifying constraints that govern cell behavior: a key to converting conceptual to computational models in biology?" Biotechnology and bioengineering 84(7): 763-772.

*E.coli Reconstructions*

1. Monk, J. M., P. Charusanti, et al. (2013). "Genome-scale metabolic reconstructions of multiple Escherichia coli strains highlight strain-specific adaptations to nutritional environments." Proceedings of the National Academy of Sciences of the United States of America 110(50): 20338-20343.
2. McCloskey, D., B. O. Palsson, et al. (2013). "Basic and applied uses of genome-scale metabolic network reconstructions of Escherichia coli." Molecular Systems Biology 9: 661.
3. Orth, J. D. and B. O. Palsson (2012). "Gap-filling analysis of the iJO1366 Escherichia coli metabolic network reconstruction for discovery of metabolic functions." BMC systems biology 6(1): 30.
4. Orth, J. D., T. M. Conrad, et al. (2011). "A comprehensive genome-scale reconstruction of Escherichia coli metabolism--2011." Molecular Systems Biology 7: 535.
5. Orth, J. D., I. Thiele, et al. (2010). "What is flux balance analysis?" Supplementary Tutorial, Nature biotechnology 28(3): 245-248.
6. Orth JD, Fleming RM, Palsson BØ (2010a) 10.2.1 -- Reconstruction and use of microbial metabolic networks: the core Escherichia coli metabolic model as an educational guide. In EcoSal -- Escherichia coli and Salmonella Cellular and Molecular Biology, Karp PD (ed), 10.2.1. Washington DC: ASM Press
7. Feist, A. M., C. S. Henry, et al. (2007). "A genome-scale metabolic reconstruction for Escherichia coli K-12 MG1655 that accounts for 1260 ORFs and thermodynamic information." Molecular Systems Biology 3: 121.
8. Reed, J. L., T. D. Vo, et al. (2003). "An expanded genome-scale model of Escherichia coli K-12 (iJR904 GSM/GPR)." Genome biology 4(9): R54.
9. Edwards, J. S. and B. O. Palsson (2000). "The Escherichia coli MG1655 in silico metabolic genotype: its definition, characteristics, and capabilities." Proceedings of the National Academy of Sciences of the United States of America 97(10): 5528-5533.

*Biomass Composition (Biomass Objective Function)*

1. Feist, A. M. and B. O. Palsson (2010). "The biomass objective function." Current opinion in microbiology 13(3): 344-349.
2. Kumar, V. S. and C. D. Maranas (2009). "GrowMatch: an automated method for reconciling in silico/in vivo growth predictions." PLoS computational biology 5(3): e1000308.
3. Gianchandani, E. P., M. A. Oberhardt, et al. (2008). "Predicting biological system objectives de novo from internal state measurements." BMC Bioinformatics 9: 43.
4. Schuetz, R., L. Kuepfer, et al. (2007). "Systematic evaluation of objective functions for predicting intracellular fluxes in Escherichia coli." Molecular Systems Biology 3: 119.
5. Izard, J. and R. J. Limberger (2003). "Rapid screening method for quantization of bacterial cell lipids from whole cells." Journal of microbiological methods 55(2): 411-418.
6. Burgard, A. P. and C. D. Maranas (2003). "Optimization-based framework for inferring and testing hypothesized metabolic objective functions." Biotechnology and bioengineering 82(6): 670-677.
7. Benthin, S., Nielsen, J. & Villadsen, J. A simple and reliable method for the determination of cellular RNA content. Biotechnol. Tech. 5, 39–42 (1991).
8. Herbert, D., Phipps, P.J. & Strange, R.E. Chemical analysis of microbial cells. Methods Microbiol. 5, 209–344 (1971).