**Transcriptional Regulatory Networks**

**Expectations**

**Learning Objectives**

Each student should be able to:

* Explain the purpose of a transcriptional regulatory network.
* Explain the role of a transcription factor.
* Explain dynamic regulatory flux balance analysis.
* Explain the difference between dFBA, dRFBA and PROM regulatory approaches.
* Explain Boolean transcriptional regulation.
* Explain probabilistic transcriptional regulation.
* Describe the difference between the regular constraint-based FBA models and the regulatory FBA model.
* Describe the strengths and limitations of dRFBA analysis.

**Prerequisites**

* Course Introduction
* Matlab Tutorial
* Flux Balance Analysis Overview
* E.coli Core Model
* Cobra Toolbox
* Robustness Analysis & Phenotype Phase Plane Analysis
* Flux Variability Analysis & Parsimonious Analysis
* Gene/Reaction Knockouts
* Randomized Sampling
* Dynamic Flux Balance Analysis

**Resources**

**Required Readings**

1. [Reconstruction and Use of Microbial Metabolic Networks: the Core Escherichia coli Metabolic Model as an Educational Guide by Orth, Fleming, and Palsson (2010) - Sections 5](https://systemsbiology.hi.is/wiki/FurtherReading?action=AttachFile&do=view&target=EcoSal_chapter_revised.pdf)
2. [Covert, M. W., E. M. Knight, et al. (2004). "Integrating high-throughput and computational data elucidates bacterial networks." Nature 429(6987): 92-96.](http://www.ncbi.nlm.nih.gov/pubmed/15129285)
3. Systems Biology: Constraint-based Reconstruction and Analysis, Bernhard O. Palsson, Cambridge University Press, 2015, Chapter 8.

**Recommended Readings**

1. [Chandrasekaran, S (2010). "Probabilistic integrative modeling of genome-scale metabolic and regulatory networks in Escherichia coli and Mycobacterium tuberculosis." Proc Natl Acad Sci U S A 107(41): 17845-17850.](https://www.ncbi.nlm.nih.gov/pubmed/20876091)
2. [Imam, S., S. Schauble, et al. (2015). "Data-driven integration of genome-scale regulatory and metabolic network models." Frontiers in microbiology 6: 409.](https://www.ncbi.nlm.nih.gov/pubmed/25999934)

**Classroom Activities**

**Presentations**

* Lecture Presentation *(“Transcriptional\_Regulatory\_Networks-2021.pdf”)*
* Lecture supporting Matlab Files *(“TRN Matlab Files-2021.zip”)*

**Laboratory**

1. Lab #8 *(“Lab-8.docx”)*

**Reinforcement Activities**

**Examples**

* Related websites
  + - [M. Covert Lab](http://covert.stanford.edu/) (iMC1010)
    - [Tomer Shlomi's Lab](http://www.cs.technion.ac.il/~tomersh/index.html)  (SR-FBA)
    - [Jason Papin Lab](http://bme.virginia.edu/csbl/home.html) (TIGER)
    - [N. Price Lab](https://price.systemsbiology.org/) (PROM)
    - [B. Ø. PalssonLab](http://sbrg.ucsd.edu/)
* Cobra regulatory models
  + - [Yeast](http://genome.cshlp.org/content/16/5/627.long) (Supplementary Material)
* iMC1010 Data
  + - [NCBI GEO Data](https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE1121)
    - [Affymetrix GeneChip Arrays](http://www.ohsu.edu/xd/research/research-cores/gene-profiling-shared-resource/project-design/array-technology/affymetrix-genechip-arrays.cfm)
    - [ASAP database](https://asap.genetics.wisc.edu/asap/experiment_data.php?LocationID=WIS&GenomeID=MG1655)

**Assessment**

**Formative Assessment**

Reflective Questions

1. What is a transcriptional regulatory network?
2. What is a Boolean regulatory network?
3. What is a probabilistic transcriptional regulatory network?
4. What is the relationship between a regulatory network and a metabolic network?
5. What are the key inputs required for dynamic regulatory FBA operation?
6. What is a regulated model? How is it different from a normal FBA model?
7. What is a regulatory rule?
8. What role do the external metabolite inputs play in dRFBA?
9. What role do the internal reaction inputs play in dRFBA?
10. What is the difference between a regulatory gene and a gene that is controlled by regulation?
11. What is catabolite repression?
12. What are some of the differences between the output of dynamicFBA and dynamicRFBA?
13. What is the difference between the iMC1010v1 and iMC1010v2 models?
14. What is the difference between dRFBA and PROM regulatory algorithms?
15. What are the strengths of dynamic regulatory FBA?
16. What are the limitations of dynamic regulatory FBA?

**References**

**Dynamic Analysis**

1. [B. Ø. Palsson, “Systems Biology: Properties of Reconstructed Networks,” Cambridge University Press, 2006.](http://www.cambridge.org/us/knowledge/isbn/item6203388/Systems-Biology:-Simulation-of-Dynamic-Network-States/?site_locale=en_US)
2. [Lee, J. M., E. P. Gianchandani, et al. (2008). "Dynamic analysis of integrated signaling, metabolic, and regulatory networks." PLoS computational biology 4(5): e1000086.](http://www.ncbi.nlm.nih.gov/pubmed/18483615)

**Dynamic FBA Growth Simulations**

1. [Becker, S. A., A. M. Feist, et al. (2007). "Quantitative prediction of cellular metabolism with constraint-based models: the COBRA Toolbox." Nature protocols 2(3): 727-738. - See section on Dynamic FBA growth simulations (batch growth simulations)- pp. 731,734](http://www.ncbi.nlm.nih.gov/pubmed/17406635)
2. [Varma, A. and B. O. Palsson (1994). "Stoichiometric flux balance models quantitatively predict growth and metabolic by-product secretion in wild-type Escherichia coli W3110." Applied and Environmental Microbiology 60(10): 3724-3731.](http://www.ncbi.nlm.nih.gov/pubmed/7986045)

**Dynamic Regulatory Flux Balance Analysis**

1. [Feuer, R., K. Gottlieb, et al. (2012). "Model-based analysis of an adaptive evolution experiment with Escherichia coli in a pyruvate limited continuous culture with glycerol." EURASIP J Bioinform Syst Biol 2012(1): 14.](http://www.ncbi.nlm.nih.gov/pubmed/23033959)
2. [Jensen, P. A., K. A. Lutz, et al. (2011). "TIGER: Toolbox for integrating genome-scale metabolic models, expression data, and transcriptional regulatory networks." BMC systems biology 5: 147.](http://www.ncbi.nlm.nih.gov/pubmed/21943338)
3. [Barua, D., J. Kim, et al. (2010). "An automated phenotype-driven approach (GeneForce) for refining metabolic and regulatory models." PLoS computational biology 6(10): e1000970.](https://www.ncbi.nlm.nih.gov/pubmed/21060853)
4. [Gianchandani, E. P., A. R. Joyce, et al. (2009). "Functional states of the genome-scale Escherichia coli transcriptional regulatory system." PLoS computational biology 5(6): e1000403.](https://www.ncbi.nlm.nih.gov/pubmed/19503608)
5. [Gianchandani, E. P., J. A. Papin, et al. (2006). "Matrix formalism to describe functional states of transcriptional regulatory systems." PLoS computational biology 2(8): e101.](https://www.ncbi.nlm.nih.gov/pubmed/16895435)
6. [Barrett, C. L., C. D. Herring, et al. (2005). "The global transcriptional regulatory network for metabolism in Escherichia coli exhibits few dominant functional states." Proceedings of the National Academy of Sciences of the United States of America 102(52): 19103-19108.](http://www.ncbi.nlm.nih.gov/pubmed/16357206)
7. [Herrgard, M. J., M. W. Covert, et al. (2004). "Reconstruction of microbial transcriptional regulatory networks." Current opinion in biotechnology 15(1): 70-77.](http://www.ncbi.nlm.nih.gov/pubmed/15102470)  
   [Covert, M. W., E. M. Knight, et al. (2004). "Integrating high-throughput and computational data elucidates bacterial networks." Nature 429(6987): 92-96.](http://www.ncbi.nlm.nih.gov/pubmed/15129285)
8. [Herrgard, M. J., M. W. Covert, et al. (2003). "Reconciling gene expression data with known genome-scale regulatory network structures." Genome research 13(11): 2423-2434.](https://www.ncbi.nlm.nih.gov/pubmed/14559784)
9. [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.](https://www.ncbi.nlm.nih.gov/pubmed/14708117)
10. [Covert, M. W. and B. O. Palsson (2002). "Transcriptional regulation in constraints-based metabolic models of Escherichia coli." The Journal of biological chemistry 277(31): 28058-28064.](http://www.ncbi.nlm.nih.gov/pubmed/12006566)
11. [Covert, M. W., C. H. Schilling, et al. (2001). "Regulation of gene expression in flux balance models of metabolism." Journal of theoretical biology 213(1): 73-88.](http://www.ncbi.nlm.nih.gov/pubmed/11708855)

**Integrated Dynamic Regulatory Flux Balance Analysis**

1. [Imam, S., S. Schauble, et al. (2015). "Data-driven integration of genome-scale regulatory and metabolic network models." Frontiers in microbiology 6: 409.](https://www.ncbi.nlm.nih.gov/pubmed/25999934)
2. [Carrera, J., R. Estrela, et al. (2014). "An integrative, multi-scale, genome-wide model reveals the phenotypic landscape of Escherichia coli." Molecular Systems Biology 10: 735.](https://www.ncbi.nlm.nih.gov/pubmed/24987114)
3. [Covert, M. W., N. Xiao, et al. (2008). "Integrating metabolic, transcriptional regulatory and signal transduction models in Escherichia coli." Bioinformatics 24(18): 2044-2050.](http://www.ncbi.nlm.nih.gov/pubmed/18621757) (iFBA)
4. [Shlomi, T., Y. Eisenberg, et al. (2007). "A genome-scale computational study of the interplay between transcriptional regulation and metabolism." Molecular Systems Biology 3: 101.](http://www.ncbi.nlm.nih.gov/pubmed/17437026)

**Probabilistic Regulation**

1. [Chandrasekaran, S. and N. D. Price (2013). "Metabolic constraint-based refinement of transcriptional regulatory networks." PLoS computational biology 9(12): e1003370.](https://www.ncbi.nlm.nih.gov/pubmed/24348226)
2. [Simeonidis, E., S. Chandrasekaran, et al. (2013). "A guide to integrating transcriptional regulatory and metabolic networks using PROM (probabilistic regulation of metabolism)." Methods in molecular biology 985: 103-112](https://www.ncbi.nlm.nih.gov/pubmed/23417801)
3. [Chandrasekaran, S (2010). "Probabilistic integrative modeling of genome-scale metabolic and regulatory networks in Escherichia coli and Mycobacterium tuberculosis." Proc Natl Acad Sci U S A 107(41): 17845-17850.](https://www.ncbi.nlm.nih.gov/pubmed/20876091)
4. [Shmulevich, I., E. R. Dougherty, et al. (2002). "Probabilistic Boolean Networks: a rule-based uncertainty model for gene regulatory networks." Bioinformatics 18(2): 261-274.](https://www.ncbi.nlm.nih.gov/pubmed/11847074)
5. [Shmulevich, I., E. R. Dougherty, et al. (2002). "Gene perturbation and intervention in probabilistic Boolean networks." Bioinformatics 18(10): 1319-1331.](https://www.ncbi.nlm.nih.gov/pubmed/12376376)

**General Transcriptional Regulation**

1. [Cho, B. K., S. Federowicz, et al. (2012). "Deciphering the transcriptional regulatory logic of amino acid metabolism." Nature chemical biology 8(1): 65-71.](http://www.ncbi.nlm.nih.gov/pubmed/22082910)
2. [Thiele, I., R. M. Fleming, et al. (2010). "Functional characterization of alternate optimal solutions of Escherichia coli's transcriptional and translational machinery." Biophysical journal 98(10): 2072-2081.](http://www.ncbi.nlm.nih.gov/pubmed/20483314)
3. [Thiele, I., N. Jamshidi, et al. (2009). "Genome-scale reconstruction of Escherichia coli's transcriptional and translational machinery: a knowledge base, its mathematical formulation, and its functional characterization." PLoS computational biology 5(3): e1000312.](http://www.ncbi.nlm.nih.gov/pubmed/19282977)
4. [Shlomi, T., O. Berkman, et al. (2005). "Regulatory on/off minimization of metabolic flux changes after genetic perturbations." Proceedings of the National Academy of Sciences of the United States of America 102(21): 7695-7700.](http://www.ncbi.nlm.nih.gov/pubmed/15897462)
5. [Gutierrez-Rios, R. M., D. A. Rosenblueth, et al. (2003). "Regulatory network of Escherichia coli: consistency between literature knowledge and microarray profiles." Genome research 13(11): 2435-2443.](https://www.ncbi.nlm.nih.gov/pubmed/14597655)
6. [Shen-Orr, S. S., R. Milo, et al. (2002). "Network motifs in the transcriptional regulation network of Escherichia coli." Nature genetics 31(1): 64-68.](https://www.ncbi.nlm.nih.gov/pubmed/11967538)