**Robustness Analysis & Phenotype Phase Plane Analysis**

**Expectations**

**Learning Objectives**

Each student should be able to:

* Explain the capabilities of robustness analysis
* Explain how shadow prices can be used in metabolic modeling
* Explain how reduced costs can be used in metabolic modeling
* Explain the capabilities of phenotype phase plane analysis

**Prerequisites**

* Course Introduction
* Matlab Tutorial
* Flux Balance Analysis Overview
* *E.coli* Metabolic Core Model
* Cobra Toolbox

**Resources**

**Required Readings**

1. [Orth, J. D., I. Thiele, et al. (2010). "What is flux balance analysis?" Supplementary Tutorial, Nature biotechnology 28(3): 245-248.](http://www.ncbi.nlm.nih.gov/pubmed/20212490) (Supplementary Examples 4 & 5)
2. Systems Biology: Constraint-based Reconstruction and Analysis, Bernhard O. Palsson, Cambridge University Press, 2015, Chapter 21, 22

**Recommended Readings**

1. [Shellenberger, J., R. Que, et al. (2011). "Quantitative prediction of cellular metabolism with constraint-based models: the COBRA Toolbox v2.0." Nature protocols 6(9): 1290-1307.](https://www.ncbi.nlm.nih.gov/pubmed/21886097)
2. [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): pp. 731, 734.](http://www.ncbi.nlm.nih.gov/pubmed/17406635)
3. [Edwards, J. S. and B. O. Palsson (2000). "Robustness analysis of the Escherichia coli metabolic network." Biotechnology progress 16(6): 927-939](http://www.ncbi.nlm.nih.gov/pubmed/11101318).

**Classroom Activities**

**Presentations**

* Lecture Presentation *(“Robustness Analysis & Phenotype Phase Plane Analysis-2021.pdf”)*
* Supporting Matlab Files *(“RA-PPPA Matlab FIles-2021.zip”)*

**Laboratory**

* Lab #3 *(“Lab-3.docx”)*

**Reinforcement Activities**

**Examples**

1. [Orth, J. D., I. Thiele, et al. (2010). "What is flux balance analysis?" Supplementary Tutorial, Nature biotechnology 28(3): 245-248.](http://www.ncbi.nlm.nih.gov/pubmed/20212490) (Supplementary Examples 4 & 5).
2. [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.](http://www.ncbi.nlm.nih.gov/pubmed/17406635)

**Assessment**

**Formative Assessment**

* Reflective Questions
  1. What is the purpose of robustness analysis?
  2. What do the kinks in the robustness analysis represent?
  3. What are shadow prices?
  4. How are shadow prices related to the objective function?
  5. What are reduced costs?
  6. How are reduced costs related to the objective function?
  7. What is the difference between shadow prices and reduced costs?
  8. What should you use to predict the impact of a metabolite on the objective function, shadow prices or reduced costs?
  9. What should you use to predict the impact of a reaction on the objective function, shadow prices or reduced costs
  10. What is the purpose of phenotype phase plane analysis?
  11. How is robustness analysis related to phenotype phase plane analysis?
  12. What is the relationship between shadow prices and phenotype phase plane analysis?
  13. What is the purpose of the variable alpha?
  14. What is the line of optimality?
  15. How do the different phases created in the phenotype phase plane analysis relate to the physiology of a cell?

**References**

**Robustness Analysis**

1. [Edwards, J. S. and B. O. Palsson (2000). "Robustness analysis of the Escherichia coli metabolic network." Biotechnology progress 16(6): 927-939.](http://www.ncbi.nlm.nih.gov/pubmed/11101318)
2. [Orth, J. D., I. Thiele, et al. (2010). "What is flux balance analysis?" Nature biotechnology 28(3): 245-248.](http://www.ncbi.nlm.nih.gov/pubmed/20212490) (Supplementary Tutorial)
3. [Price, N. D., J. A. Papin, et al. (2003). "Genome-scale microbial in silico models: the constraints-based approach." Trends in biotechnology 21(4): 162-169](http://www.ncbi.nlm.nih.gov/pubmed/15494745)

**Phenotype PhasePlane Analysis**

1. [Bell, S. L. and B. O. Palsson (2005). "Phenotype phase plane analysis using interior point methods." Computers & Chemical Engineering 29(3): 481-486](http://apps.webofknowledge.com/InboundService.do?SID=3Ca8xg8H9yui1e4vnRe&product=WOS&UT=WOS%3A000228431500008&SrcApp=EndNote&DestFail=http%3A%2F%2Fwww.webofknowledge.com&action=retrieve&Init=Yes&SrcAuth=ResearchSoft&customersID=ResearchSoft&Func=Frame&IsProductCode=Yes&mode=FullRecord).
2. [Edwards, J.S., R. Ramakrishna, et al. (2002). "Characterizing the metabolic phenotype: a phenotype phase plane analysis." Biotechnology and bioengineering 77(1): 27-36.](http://www.ncbi.nlm.nih.gov/pubmed/11745171)
3. [Ibarra, R. U., J. S. Edwards, et al. (2002). "Escherichia coli K-12 undergoes adaptive evolution to achieve in silico](http://www.ncbi.nlm.nih.gov/pubmed/12432395)  
   [predicted optimal growth." Nature 420(6912): 186-189](http://www.ncbi.nlm.nih.gov/pubmed/12432395)
4. [Kauffman, K. J., J. D. Pajerowski, et al. (2002). "Description and analysis of metabolic connectivity and dynamics in the human red blood cell." Biophysical journal 83(2): 646-662](http://www.ncbi.nlm.nih.gov/pubmed/12124254).
5. [Edwards, J. S., R. U. Ibarra, et al. (2001). "In silico predictions of Escherichia coli metabolic capabilities are consistent with experimental data." Nat Biotechnol 19(2): 125-130](http://www.ncbi.nlm.nih.gov/pubmed/11175725).
6. [Edwards, J. S. and B. O. Palsson (2000). "Robustness analysis of the Escherichia coli metabolic network." Biotechnology progress 16(6): 927-939.](http://www.ncbi.nlm.nih.gov/pubmed/11101318)
7. [Orth, J. D., I. Thiele, et al. (2010). "What is flux balance analysis?" Nature biotechnology 28(3): 245-248.](http://www.ncbi.nlm.nih.gov/pubmed/20212490) (Supplementary Tutorial)
8. [Price, N. D., J. A. Papin, et al. (2003). "Genome-scale microbial in silico models: the constraints-based approach." Trends in biotechnology 21(4): 162-169](http://www.ncbi.nlm.nih.gov/pubmed/15494745)