**COBRA Toolbox**

**Expectations**

*Learning Objectives*

Each student should be able to:

* Explain the purpose of the Cobra Toolbox,
* Demonstrate basic operation of the Cobra Toolbox,
* Explain the of BIGG Database,
* Explain the capabilities of Paint4Net.

*Prerequisites*

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

**Resources**

*Presentations/Tutorials*

* Matlab Tutorials ([Getting Started](https://www.mathworks.com/videos/getting-started-with-matlab-68985.html?s_tid=main_tutorial_ML_rp), [Writing a Matlab Program](https://www.youtube.com/watch?v=pRsGM7H91VY))

*Required Readings*

1. Orth, J. D., I. Thiele, et al. (2010). "What is flux balance analysis?" Supplementary Tutorial, Nature biotechnology 28(3): 245-248. (Read Pages 1-4).
2. Laurent Heirendt et al, Creation and analysis of biochemical constraint-based models: the COBRA Toolbox v3.0, Nature Protocols, volume 14, pages 639–702, 2019.
3. Systems Biology: Constraint-based Reconstruction and Analysis, Bernhard O. Palsson, Cambridge University Press, 2015, Chapter 15, 16.

*Recommended Readings*

1. Palsson, B. (2009). "Metabolic systems biology." FEBS letters 583(24): 3900-3904.
2. [Hyduke, D., J. Schellenberger, et al. (2011). "COBRA Toolbox 2.0.", Protocol Exchange, 11 May 2011.](https://protocolexchange.researchsquare.com/article/nprot-2097/v1)
3. Schellenberger, 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.
4. Zachary A. King, Andreas Dräger, Ali Ebrahim, Nikolaus Sonnenschein, Nathan E. Lewis, and Bernhard O. Palsson (2015) Escher: A web application for building, sharing, and embedding data-rich visualizations of biological pathways, PLOS Computational Biology 11(8): e1004321

**Classroom Activities**

*Presentations*

* Cobra Toolbox Lecture (“*Cobra Toolbox – 2021.pdf”*)
* Supporting Matlab Files *(“Cobra Toolbox Matlab Files-2021.zip”)*

*Laboratory*

* Lab #2 *(“Lab-2.docx”)*

**Reinforcement Activities**

*Examples*

* [Cobra Toolbox Website](https://opencobra.github.io/)
* [Cobra Toolbox Matlab Documentation](https://opencobra.github.io/cobratoolbox/stable/index.html)
* [Matlab Documentation](https://www.mathworks.com/help/matlab/)
* [Google Groups: Cobra Toolbox](https://groups.google.com/g/cobra-toolbox?pli=1)
* [Cobra Methods Wiki](http://cobramethods.wikidot.com/)
* [Paint4Net User Manual & Download](http://biosystems.lv/index.php/software/paint4net/15-paint4net-download-and-installation)
* [Paint4Net:Visualization toolbox for COBRA](https://opencobra.github.io/cobratoolbox/latest/tutorials/tutorialPaint4net.html)

*Videos*

* [Paint4Net tutorial](https://www.youtube.com/watch?v=4hMrLnM4HZw)

**Assessment**

*Formative Assessment*

* Reflective Questions
  1. What is the openCobra Project?
  2. What is the relationship between Matlab and the Cobra Toolbox?
  3. Where can you find the documentation for all the Cobra Toolbox functions?
  4. What is the start-up process that must be followed to use the Cobra Toolbox?
  5. What is the difference between the Cobra Toolbox and a Cobra model?
  6. How is a Cobra model stored in the Cobra Matlab interface?
  7. What Matlab function is used to load a Cobra model?
  8. What location in a Cobra model stores the reactions?
  9. What location in a Cobra model stores the metabolites?
  10. What location in a Cobra model stores the stoichiometric matrix?
  11. What location in a Cobra model stores the objective function?
  12. What Cobra Toolbox function is used to calculate the network fluxes?
  13. What location in a optimized solution struct stores the flux vector?
  14. What location in a optimized solution struct stores the objective function value?
  15. How can you calculate the cell doubling time?
  16. What Cobra Toolbox function is used to read an export map?
  17. What process must be followed to print a Cobra model map using the Cobra Toolbox?
  18. What Cobra Toolbox function is used to write fluxes onto an map?
  19. What is the default file name for maps created by the Cobra Toolbox?
  20. What Cobra Toolbox function is used to change the upper and lower bounds of a reaction?
  21. What Cobra Toolbox function is define the objective function?
  22. Explain the capabilities of the printFluxVector command?
  23. What is the purpose of the BIGG Database?
  24. How do you plot flux on Escher models?
  25. How do you plot flux on legacy COBRA models?
  26. What is the purpose of the COBRA v.3.0 tutorials?

**References**

*Cobra Toolbox*

1. Laurent Heirendt et al, Creation and analysis of biochemical constraint-based models: the COBRA Toolbox v3.0, Nature Protocols, volume 14, pages 639–702, 2019.
2. Daniel Hyduke et al, Protocol Exchange (2011), Published online 11 May 2011
3. Schellenberger, 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.
4. Schellenberger, J., J. O. Park, et al. (2010). "BiGG: a Biochemical Genetic and Genomic knowledgebase of large scale metabolic reconstructions." BMC Bioinformatics 11: 213.
5. Orth, J. D., I. Thiele, et al. (2010). "What is flux balance analysis?" Supplementary Tutorial, Nature biotechnology 28(3): 245-248..
6. Palsson, B. (2009). "Metabolic systems biology." FEBS letters 583(24): 3900-3904.
7. 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.

*Cobra Enhancements*

1. Thorleifsson, S. G. and I. Thiele (2011). "rBioNet: A COBRA toolbox extension for reconstructing high-quality biochemical networks." Bioinformatics.
2. Fleming, R. M. and I. Thiele (2011). "von Bertalanffy 1.0: a COBRA toolbox extension to thermodynamically constrain metabolic models." Bioinformatics 27(1): 142-143.

*Visualization*

1. Laurent Heirendt et al, Creation and analysis of biochemical constraint-based models: the COBRA Toolbox v3.0, Nature Protocols, volume 14, pages 639–702, 2019.
2. Kostromins, A. and E. Stalidzans (2012). "Paint4Net: COBRA Toolbox extension for visualization of stoichiometric models of metabolism." Bio Systems.

*Loop Elimination*

1. Schellenberger, J., N. E. Lewis, et al. (2011). "Elimination of thermodynamically infeasible loops in steady-state metabolic models." Biophysical journal 100(3): 544-553.

*Experimental Verification*

1. Ibarra, R. U., J. S. Edwards, et al. (2002). "Escherichia coli K-12 undergoes adaptive evolution to achieve in silico predicted optimal growth." Nature 420(6912): 186-189.
2. Fong, S. S., J. Y. Marciniak, et al. (2003). "Description and interpretation of adaptive evolution of Escherichia coli K-12 MG1655 by using a genome-scale in silico metabolic model." Journal of Bacteriology 185(21): 6400-6408.