Bioinformatics III

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Tutorial 8

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Submit your solutions on paper, hand-written or printed, at the beginning of the lecture or in the building E2.1, Room 3.09. Alternatively you may send an email with a single PDF attachment of the solution paper to daria.gaidar@bioinformatik.uni-saarland.de. If requested in the assignment, please forward your source code via mail, too.

Pathways of Metabolic Networks and Rate Equations

Exercise 8.1: Theoretical Drill (15 points)

(a) **Name 3 commercial applications of minimum flux models.** (3)

(b) **Elaborate on advantages and disadvantages of the Flux based analysis?** (4)

(c) **Constraint based modeling.**

(1) Please name the constraints that one can apply on the stoichiometric analysis of the metabolism. (4)

(2) What are the available constraints-based programming packages in Python for running metabolic analysis? (4)

Exercise 8.2: Extreme Pathways and Steady State Flux Distribution. Paper-based (35 points)

For the following network, Figure 1, we want to investigate the steady state properties via the extreme pathways.

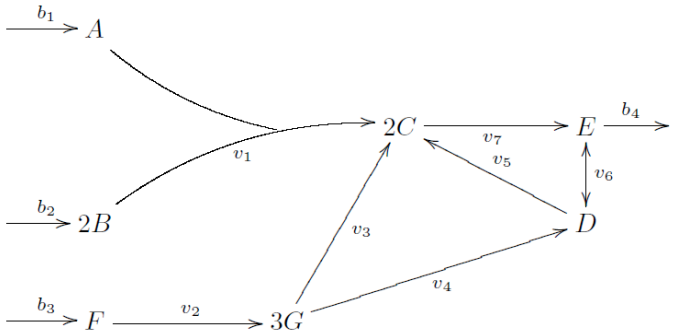

Figure 1: Reaction network to derive extreme pathways from.

Hint: reaction v6 can be split in two.

(a) **Construct the stoichiometric matrix.** (5)

(b) **Calculate from the stoichiometric matrix the extreme pathways. Give the pathways as formulas.** (10)

(c) **Determine the pathway length matrix. Which informations does it provide?** (5)

(d) **Cut-set.** (5)
The output of our network corresponds to the flux through reaction *b4*. A reaction is essential for the network, when there is no output if this reaction is blocked. List all those reactions. *Hint: can you figure out how to determine this cut-set from the extreme pathways?*

(e) **Fluxes.** (10)
For the following steps we will neglect the internal reactions. Then we can see how the (black box) network transforms input through *b1*, *b2* and *b3* into output through *b4* and *b5*. Complete the table given below, which relates the input through *b1*, *b2* and *b3* to the output via *b4* and contains the fluxes through the reactions *v1*, *v2* and *v7*.

Hint: If there are multiple possibilities, list one of them and specify the characteristics of the possibilities.

	I	II	III	IV	V	VI
b_1		1		1		1
b_2		1		2		1
b_3		3		1		0
b_4					3	
v_1	0		1		1	
v_2	1		0		2	
v_7			1			

Figure 2: Table for you to fill-in.

Exercise 8.3: Hands-on with COnstraint-Based Reconstruction and Analysis (COBRA) in Python. (35 points)

Please submit your code via email to get the grade.

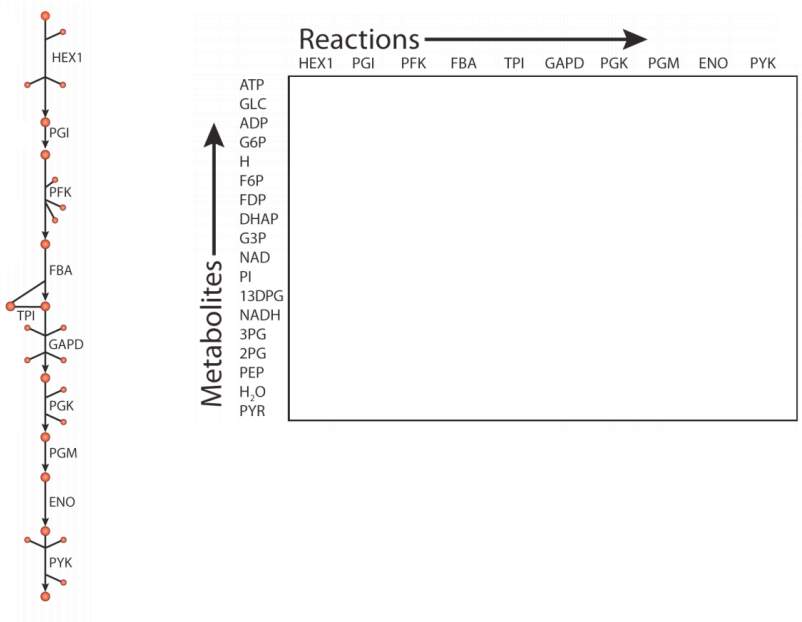

Figure 3: Fragment of the *E.coli* metabolic network (left). The template of the stoichiometry matrix for you to fill-in. Plots are adapted from (1) and (2).

Get yourself comfortable with COBRA package for Python. Go through the docs sections 1 to 4.

To get the reactions and their stoichiometry you can query the BiGG Knowledge base. But the docs will teach you a shorter way.

(a) **Provide formulas of the reactions participating in the chain given on the Figure 3.** (10)

(b) **Fill in the stoichiometry matrix, Figure 3.** (10)

(c) **Create the model for the given chain of reactions. Provide the number of reactions, metabolites and genes in it.** (10)

(d) **Which tool(s) would you use to visualise the results of the COBRA analysis?** (5)

Exercise 8.4: Drug Design: Identifying Targets (15 points)

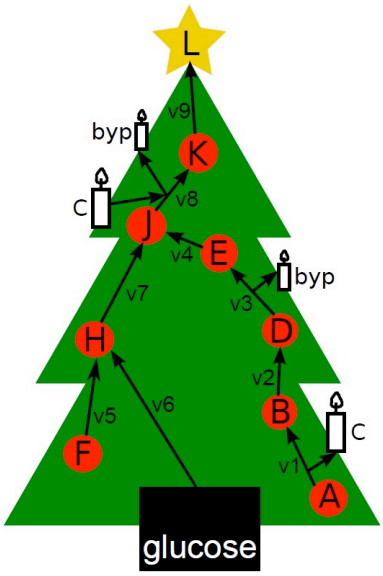

Figure 4: The Christmas tree shown produces light (in its star) from glucose. In various intermediate steps, accessory Christmas balls and candles are involved.

(a) **Essential substrates.** (3)
Consider all pathways in the tree. Identify without calculation the important Christmas balls that are essential to light up the star. Explain your findings.

(b) **Inhibition of biomass production.** (9)
Now assume that this Christmas tree is the central part of the metabolism of a dangerous bacterium and you want to develop an eficient drug.

(1) On which reactions (enzymes) would you concentrate when searching for an inhibitor? Explain your answer.

(2) Would you change your strategy, if you knew that high concentrations of *byp* slow down or even reverse reactions *v3* and *v8*?

(3) Would you change your strategy, if you knew that high concentrations of J were lethal for the host? What would then be a suitable inhibitor?

(c) **Inhibitor = drug?** (3)
Let us assume that you find a suitable inhibitor for one or several reactions mentioned above. Does it mean you have a potent therapeutic drug or which other problems you might encounter.

As now You got the methodology of Flux Based Analyis, You also got closer to be called a modern alchemist. Have a look on how the modern Alchemy works.

References

[1] Reed, Jennifer L., et al. "Towards multidimensional genome annotation." Nature Reviews Genetics 7.2 (2006): 130-141.

[2] Schellenberger, Jan, et al. "Quantitative prediction of cellular metabolism with constraint-based models: the COBRA Toolbox v2. 0." Nature protocols 6.9 (2011): 1290-1307.