COMP 572 Bioinformatics: Network Analysis
Homework Assignment #4
Fall 2009
Due Date: Dec 3, 2009 (in class).

1 Analyzing Stoichiometric Matrices

Consider a simple reaction system composed of the following reactions.

$$
\begin{aligned}
R1: &\quad A_{\text{External}} \to A \\
R2: &\quad B_{\text{External}} \leftrightarrow B \\
R3: &\quad P \to P_{\text{External}} \\
R4: &\quad A \to B \\
R5: &\quad A \to C \\
R6: &\quad A \to D \\
R7: &\quad B \leftrightarrow C \\
R8: &\quad B \to P \\
R9: &\quad C + D \to P
\end{aligned}
$$

"$\to$" denotes irreversible reactions (rightward) and "$\leftrightarrow$" denotes reversible reactions.

(a) In class, we discussed two configurations of metabolic networks, i.e.,

  I distinguish between irreversible reactions and reversible reactions in additional information

  II use two opposite irreversible reactions to reversible *internal* reactions

  Draw simple network diagrams of this reaction system under the two configurations. Delineate the boundary of the system on your diagram.

(b) Write down the stoichiometric matrices of the system under the two configurations. (Hint: do not distinguish between A_{External} and A.)

(c) Under the first configuration, compute the left and null space of the system. What is the dimension of these two spaces? The columns of your null space correspond to one of the many linear basis that spans the space. How many elements in your basis are biochemically feasible? (10 bonus points for numerically finding the leading singular value and its corresponding eigen-reactions and eigen-connectivities in SVD. Please feel free to use Matlab or Mathematica or whatever software you like.)

(d) Under the second configuration, compute the *complete* set of extremal pathways of the system using the algorithm we discussed in class. (Hint: map the extremal pathways onto your network diagram and make sure they make sense.)

(e) Under the second configuration, compute the *complete* set of elementary flux modes of the system by treating reversible reactions as separate. Compare the set of extremal pathways and the set of elementary flux mode. Do they coincide? If not, what single constraint on the reaction system would you suggest to make the set of extremal pathways coincide with the set of elementary flux mode? (Hint: In class, we discussed the conditions for the equivalence of elementary mode and extremal pathways)

(f) Under the first configuration, can you compute the elementary flux modes? Is the result the same as what you got under the second configuration? If not how would you interpret the difference? Is the number of elementary modes sensitive to the choice of configurations?

2 Flux Balance Analysis

Consider the previous reaction system. Suppose the system is under the environment condition where it can gain no B from outside (i.e., reaction R_2 is constrained to move leftward), we want to know which route the system take at steady state to produce P given A. The more production of P given certain amount of A (or equivalently, the less consumption of A given certain production of P), the fitter the system.

(a) How would you set the constraint (i.e., the upper and lower bound) for the flux of each reaction (Hint: . Since we want to compare the optimal yield of A, we can set $0 \leq v_1 \leq 1$, or arbitrary interval with continous and finite support).

(b) What is your objective function? (Hint: It is a linear transformation, you can express it into a vector $s = (s_1, s_2, \ldots, s_9)$ such that $[P] = s \cdot v$ where v is some flux mode.)

(c) Perform linear programming on the problem setup above. What is the optimal flux v_{optimal}? How much is the optimal yield over input $[P]/[A]$ corresponding to v_{optimal}? Is the v_{optimal} one of the extremal pathways? Is it one of the elementary modes? Can you generalize your observation. (Please feel free to use Matlab or whatever software you like to do the linear programming) (Hint: simplex algorithm suffices.)

3 Integrating Metabolic and Regulatory Networks

Read the paper

> T. Shlomi, Y. Eisenberg, R. Sharan, and E. Ruppin, "A genome-scale computational study of the interplay between transcriptional regulation and metabolism", Molecular Systems Biology, 3:101, 2007

and (1) write down four questions you have about the paper (approach, data, conclusions, assumptions, etc.), and (2) propose brief answers or ideas to these questions (these can be in the form of hypotheses).

4 Network Dynamics

Read the paper

> G. Chechik, E. Oh, O. Rando, J. Weissman, A. Regev, and D. Koller, "Activity motifs reveal principles of timing in transcriptional control of the yeast metabolic network", Nature Biotechnology, 26:1251-1259, 2008

and (1) write down four questions you have about the paper (approach, data, conclusions, assumptions, etc.), and (2) propose brief answers or ideas to these questions (these can be in the form of hypotheses).