Metabolic modeling, Spring 07, Exercise 4, Thursday, 19.4.2007, 14.15 – 16.00 C222

1. Consider an organism $\mathcal{O}$ with the metabolic network consisting of the following enzymatic reactions: $\rightarrow M_1, M_1 \rightarrow M_2, M_1 \rightarrow M_3 + M_4, M_2 \rightarrow M_5 + M_8, M_3 \rightarrow M_8, M_4 \rightarrow, M_5 + M_8 \rightarrow M_6, M_7 \rightarrow M_6, M_6 \rightarrow , \rightarrow M_7, M_8 \rightarrow$ where M_1 and M_7 are external substrates and M_4, M_6 and M_8 are external products.

   (a) Draw a bipartite graph representing the metabolic network of $\mathcal{O}$.

   (b) Compute the enzyme subsets of $\mathcal{O}$. Explain the results.

2. Assume that we are able to measure that the flux of external reaction $\rightarrow M_1$ equals 3 mmol/s in steady state C. Add this information to the stoichiometric constraints of $\mathcal{O}$ and compute the rank of the resulting linear equation system. Is the system of full rank?

3. Let M_1, M_2, M_6 and M_7 of $\mathcal{O}$ contain two carbons and the rest of the metabolites of $\mathcal{O}$ one carbon. Let the carbon mapping λ_i of reaction $M_5 + M_8 \rightarrow M_6$ be: $\lambda_i(M_5) = M_6|C_1$, $\lambda_i(M_8) = M_6|C_2$, where $M_6|C_i$ denotes i'th carbon of M_6. Let the carbon mapping λ_j of reaction $M_1 \rightarrow M_3 + M_4$ be: $\lambda_j(M_1|C_1) = M_3$, $\lambda_j(M_1|C_2) = M_4$. Let the carbon mapping λ_k of reaction $M_2 \rightarrow M_5 + M_8$ be: $\lambda_j(M_2|C_1) = M_5$, $\lambda_j(M_2|C_2) = M_8$. Let the carbon mappings of the other reactions be trivial, that is, carbon 1 of a substrate is always mapped to carbon 1 of a product. Draw a bipartite graph of the metabolism. Model metabolites as sets of carbon atoms. Draw also carbon mappings (See slide 6 of 13C metabolic flux analysis lecture).

4. Enumerate the fragment equivalence sets in the metabolic network of the previous assignment.

5. Let us assume that we were able to measure the following constraints to the isotopomer distributions for the metabolites of $\mathcal{O}$ in steady state C: $P(^{00}M_1) = 0.6, P(^{01}M_1) = 0.2, P(^{10}M_1) = 0.15, P(^{11}M_1) = 0.05; P(^{0}M_7|C_1) = 0.6, P(^{0}M_7|C_1) = 0.4; P(^{00}M_6) = 0.475, P(^{01}M_6) = 0.225, P(^{10}M_6) = 0.15, P(^{11}M_6) = 0.15; P(^{0}M_8) = 0.7833, P(^{1}M_8) = 0.2166$. Propagate the measurement information inside equivalence sets, that is, by applying the carbon mappings of the reactions, compute

constraints to the isotopomer distributions of unmeasured metabolites from the measured ones. It is enough to compute the isotopomer distribution $D(M_2)$ of M_2 from the isotopomer distribution $D(M_1)$ of M_1, $D(M_5)$ from $D(M_2)$ and $D(M_3)$ from $D(M_1)$. (Hint: slides 5, 10 – 15.)

6. Based on the propagated isotopomer information, form generalized isotopomer balances for M_8 and for $M_6|C_1$. Add these balances to the linear equation system of assignment 2 and solve the system in MATLAB (hint: operator \ or function *pinv*).