Metabolic Modelling, Spring 2009, Exercises
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Solutions

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1. Flux estimation with tree topology. We assume that the tree is turned right, i.e. the leaves are on the left, root is on the right.

   The linear pathway algorithm is trivially:

   1a) if incoming flux for M_i is known, set outgoing flux to the same as incoming
   ..2) next handle M_{i+1}
   1b) otherwise apply the algorithm to the previous metabolite M_{i-1}

   With tree topology, we can use the linear pathway algorithm until a junction is met. A junction is necessarily one where several pathways converge to a single pathway. At junction, we apply the linear pathway algorithm recursively to all incoming pathways with unknown fluxes. This procedure runs until we meet another junction (another recursive call) or an incoming exchange reaction, and the fluxes can be set for that linear pathway. At junctions, the outgoing flux is the sum of incoming fluxes and the linear pathway algorithm is continued.

   This can be seen as a tree traversal method where each node is the sum of its children, and initially only leaves have values.

2. Equivalence sets. There are 5 equivalence sets in total. These can be inferred by looking at all connected components in the graph and deducing if those atoms travel intact to other components. Note that for a component of H to be in any equivalence classes, *all* the reactions producing that component have to have the same isotopomer distribution.

   - $\{C, G, A|3, E|2, H|3\}$
   - $\{A|12, B|12\}$
   - $\{A|23, E\}$
   - $\{A|1, B|1, D|1, F|2\}$
   - $\{A|2, B|2, E|1, F|1\}$

3-4. Isotopomers can be generated by first looking at the isotopomers of the intermediate metabolites and then combining them by multiplying the distributions. E.g. The $P(H|\rho_4)$ comes from distributions $P(B)$ and $P(C)$, where $P(B) = P(^{00}B, ^{01}B, ^{11}B) = (0.5, 0.25, 0.25)$, and $P(C) =$

$P(^0C,^1C) = (0.75, 0.25)$. All combinations of the isotopes produces the table below with multiplication.

Isotopomer	$P(H\|\rho_4)$	$P(H\|\rho_5)$	$P(H\|\rho_6)$	Useful information?	Measured
000	0.375	0.375	0.375	no	0.3750
001	0.125	0	0.125	yes	0.0938
010	0.1875	0.1875	0	yes	0.1406
011	0.0625	0.1875	0	yes	0.0781
100	0	0.125	0.1875	yes	0.0781
101	0	0	0.0625	yes	0.0156
110	0.1875	0.0625	0.1875	yes	0.0156
111	0.0625	0.0625	0.0625	no	0.0625

Table 1: Isotopomer distributions of H based on the producing reaction

The isotopomers (rows in the table) with useful information are those that separate different reaction routes, i.e. have non-uniform probabilities of the isotopomer.

5. The measured isotopomer distribution $P(H)$ for (000,001,010,011,100,101,110,111) is $(0.3750, 0.0938, 0.1406, 0.0781, 0.0781, 0.0156, 0.0156, 0.0625)$. This is consistent with determined isotopomer pattern, as all the values are between the minimum and maximum value of the isotopomers according to reactions (ρ_4, ρ_5, ρ_6).

   We assume that exchange flux consuming H has value 1, thus $v_{\rho_7} = 1$. Now the equation we are interested in is $v_{\rho_4} + v_{\rho_5} + v_{\rho_6} = 1 = v_{\rho_7}$.

   The matrix of coefficients $P(^{xyz}H|\rho_j)$ and measurement vector D_H with this extra constraint are

```
A =

    0.3750    0.3750    0.3750
    0.1250         0    0.1250
    0.1875    0.1875         0
    0.0625    0.1875         0
         0    0.1250    0.1875
         0         0    0.0625
    0.1875    0.0625    0.1875
    0.0625    0.0625    0.0625
    1.0000    1.0000    1.0000

D =

    0.3750
    0.0938
    0.1406
    0.0781
    0.0781
    0.0156
```

```
    0.0156
    0.0625
    1.0000
```

The system $Av = D_H$ with constraint $v_{\rho_4} + v_{\rho_5} + v_{\rho_6} = 1$ can be solved directly with $A \backslash D$. This gives

```
v =

    0.2603
    0.5395
    0.1840
```

Note that the solution is somewhat inaccurate (roughly 5 percent) due to perhaps measurements errors:

```
>> A*v - D

ans =

   -0.0060
   -0.0383
    0.0094
    0.0393
    0.0238
   -0.0041
    0.1014
   -0.0010
   -0.0161
```