Analyzing subsets of enzymes for the production of Fructose-6-Phosphate in the PPP pathway

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(planning, programming and documentation were all done collaborative)

Introduction

In this exercise we analyze the pentose phosphate pathway (PPP), a well understood metabolic pathway that generates NADPH and pentoses (5-carbon sugars) as well as ribose 5-phosphate, a precursor for the synthesis of nucleotides, among other products. In particular, we are interested in the production of fructose-6-phosphate, a derivative of fructose which has been phosphorylated at the 6-hydroxy group.
In the PPP, it takes 6 enzymes to produce 5 fructose-6-phosphate from 6 ribulose-5-phosphate and water. The goal of this project is to investigate whether subsets of these enzymes are also able to form fructose-6-phosphate from the same educts and analyze their efficiency.

Implementation

We use the MØD software package.

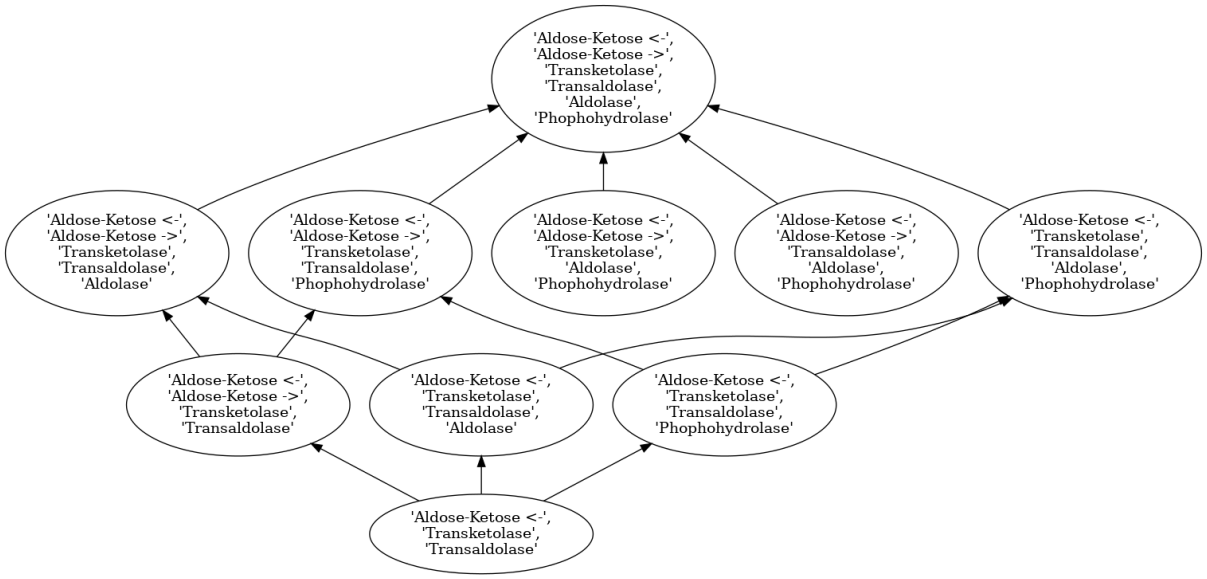
The enzymes in the PPP can be modeled as a set of 6 graph transformation rules. To check which subsets of rules (enzymes) can produce the goal molecule, we try to find an integer hyperflow solution for each subset in the underlying derivation graph that shows a pathway from the educts to the product. We then analyze how efficient the production of each solution is based on a quality measure.

Given an initial set of graphs and transformation rules, the first step is to calculate the powerset of the rules. For each of the subsets, we generate a derivation graph applying the subset of rules with a repeat strategy to the input graphs. This is, the rules are applied until the subset in the state reaches a fixed point or is empty.
Then, we initialize an integer hyperflow model (in MØD simply called flow), with sources water, and ribulose-5-phosphate (we will refer to it just as ribulose), and sink fructose-6-phosphate (referred to as fructose). We constrain the input flow of ribulose to 60, and the output flow of fructose to be greater than 1. The objective function is to maximize the production of fructose (maximum is 50).
Finally, the subsets of enzymes that were able to produce a flow solution can be analyzed.

Further, we implemented a Hasse diagram of the subsets that produce fructose and a table with some quality measures to be generated automatically.

Results

We detected that 10 combinations of enzymes - including the whole set of all 6 enzymes, so 9 alternative combinations of enzymes - are able to also produce fructose from ribulose and water. These are shown in the following Hasse diagram.



The table on the end of this document as well as of summary.pdf visualizes the results in more detail. A solution id, the number of used enzymes and their names are included along with the number of produced fructose and waste (outflow of everything but fructose), their ratio and the number of performed reactions.

The results can be viewed regarding different quality measures like small number of enzymes, high carbon efficiency (high number of fructose produced), small number of waste, small number of reactions.

First of all, *solution 1* stands out by using only 5 enzymes to get the same amount of fructose and waste as 6 enzymes (*solution 0*) while using less reactions (140 instead of 150).
Regarding the small number of enzymes and reactions, interesting results are *solution 5*, *solution 7*, *solution 9* using 5, 4, 3 enzymes and 75, 82, 90 reactions respectively, while still producing 45 of 50 fructose.
Solution 2 and *solution 3* can be considered inefficient since the amount of waste is bigger than the amount of fructose produced, which leaves 7 good alternatives to produce fructose.

id	#enzymes	enzymes	#fructose	#waste	#w/#f	#reactions
0	6	'Aldose-Ketose <-' 'Aldose-Ketose ->' 'Transketolase' 'Transaldolase' 'Aldolase' 'Phophohydrolase'	50	10	0.2	150
1	5	'Aldose-Ketose <-' 'Transketolase' 'Transaldolase' 'Aldolase' 'Phophohydrolase'	50	10	0.2	140
2	5	'Aldose-Ketose <-' 'Aldose-Ketose ->' 'Transaldolase' 'Aldolase' 'Phophohydrolase'	10	50	5.0	150
3	5	'Aldose-Ketose <-' 'Aldose-Ketose ->' 'Transketolase' 'Aldolase' 'Phophohydrolase'	15	45	3.0	135
4	5	'Aldose-Ketose <-' 'Aldose-Ketose ->' 'Transketolase' 'Transaldolase' 'Phophohydrolase'	48	24	0.5	120
5	5	'Aldose-Ketose <-' 'Aldose-Ketose ->' 'Transketolase' 'Transaldolase' 'Aldolase'	45	15	0.3333	75
6	4	'Aldose-Ketose <-' 'Transketolase' 'Transaldolase' 'Phophohydrolase'	48	24	0.5	192
7	4	'Aldose-Ketose <-' 'Transketolase' 'Transaldolase' 'Aldolase'	45	15	0.3333	82
8	4	'Aldose-Ketose <-' 'Aldose-Ketose ->' 'Transketolase' 'Transaldolase'	45	15	0.3333	165
9	3	'Aldose-Ketose <-' 'Transketolase' 'Transaldolase'	45	15	0.3333	90