S5 Cofactor metabolites

The role of cofactors in the network expansion algorithm is described in detail in [1]. We explain the basic idea with the example of the cofactor ATP. The network expansion algorithm determines which metabolites can be produced if initially only substrates from the seed are available. To include reactions requiring for example ATP as a cofactor, ATP has first to be synthesized *de novo* from the seed. However, this is an unrealistic assumption for any living cell, since it can be assumed that there is always enough ATP present to drive cofactor-dependent reactions. To account for this fact, cofactors are treated specially and are formally represented as two compounds, e. g. ATP/ADP and ATP_{cof}/ADP_{cof}. Those reactions, in which ATP acts as a cofactor, *i.e.* those in which ATP and ADP appear on opposite sides of the reaction equation, are additionally represented in a form in which the compounds ATP and ADP are replaced by their corresponding cofactor compounds ATP_{cof} and ADP_{cof}. For the calculations, the smaller of the two cofactors, ADP_{cof}, is added to the seed. This procedure ensures that reactions with the cofactor pair ATP/ADP may proceed but the actual compound ATP may not be utilized for example by decomposition into building blocks. Why only the smaller cofactor is added, is explained by the following example. Assume, glucose is in the seed. Additionally we have the cofactor ATP_{cof}. Then, glucose may be phosphorylated to glucose-6-phosphate by a cofactor-driven reaction. In a next step, a phosphorylase may yield glucose and orthophosphate, indicating that phosphate can be produced from glucose, which is clearly absurd. This is avoided by adding only ADP_{cof} to the seed.

Cofactors		
Name	MetaCyc-Id	in Seed
N^{10}-formyl-THF	10-FORMYL-THF	
acetyl-CoA	ACETYL-COA	
ADP	ADP	×
AMP	AMP	×
ATP	ATP	
coenzyme A	CO-A	×
GDP	GDP	×
L-glutamine	GLN	×
L-glutamate	GLT	×
GTP	GTP	
NADH	NADH	×
NADPH	NADPH	×
$NADP^+$	NADP	×
NAD^+	NAD	×
phosphoenolpyruvate	PHOSPHO-ENOL-PYRUVATE	×
propionyl-CoA	PROPIONYL-COA	
pyruvate	PYRUVATE	×
succinyl-CoA	SUC-COA	
tetrahydrofolate	THF	×
Acceptor	Acceptor	×
Cytochromes-C-Reduced	Cytochromes-C-Reduced	×
Cytochromes-C	Cytochromes-C	×
Donor-H2	Donor-H2	×
Oxidized-flavodoxins	Oxidized-flavodoxins	×
Reduced-flavodoxins	Reduced-flavodoxins	×

References

[1] T. Handorf and O. Ebenhöh, *Nucleic Acids Res*, 2007, **35**, W613–W618.