# Example Bottom-Up Metabolic Model Construction Process

## 1. The Basics

Starting from glucose-6-phosphate in a glycolytic organism:

# sanity check that one reaction can happen

FRUCTOSE-6-P[CCO-CYTOSOL]

# complete glycolysis and get to pyruvate (alanine, serine, glycerol-3P)

PYRUVATE[CCO-CYTOSOL]

# reach acetyl-CoA after pyruvate (TCA cycle, fatty acids, acetate, IPP, etc)

ACETYL-COA[CCO-CYTOSOL]

# accomplish anaplerosis in the TCA cycle before asking for any products from it

# and reach the carbon skeleton of aspartate

OXALACETIC\_ACID[CCO-CYTOSOL]

# reach the a-ketoglutarate skeleton of glutamate

2-KETOGLUTARATE[CCO-CYTOSOL]

# the glutamate + oxaloacetate <-> 2-ketoglutarate + aspartate reaction

# allows recharging of glutamate used in transamination

# produce glutamate for half of transamination

GLT[CCO-CYTOSOL]

# produce aspartate for the other half of transamination

L-ASPARTATE[CCO-CYTOSOL]

# homoserine is an important amino acid intermediate

HOMO-SER[CCO-CYTOSOL]

# PRPP is required in nucleic acids and in histidine

# be sure that pentose phosphate transaldolases & transketolases

# are appropriately reversible

PRPP[CCO-CYTOSOL]

# GLYCEROL-3P is required in fatty acid head groups

GLYCEROL-3P[CCO-CYTOSOL]

# CARBAMOYL-P is a common metabolic intermediate

CARBAMOYL-P[CCO-CYTOSOL]

# CHORISMATE is a starting point for aromatic amino acid synthesis

CHORISMATE[CCO-CYTOSOL]

# 5-PHOSPHORIBOSYL-5-AMINOIMIDAZOLE is the intermediate between

# PRPP and IMP in purine synthesis

5-PHOSPHORIBOSYL-5-AMINOIMIDAZOLE[CCO-CYTOSOL]

# IMP is a starting point for purine biosynthesis

# it requires folates, 5-PHOSPHORIBOSYL-5-AMINOIMIDAZOLE, HCO3

# and produces fumarate as a byproduct

IMP[CCO-CYTOSOL]

# OROTATE is a precursor to UMP

# it is produced from carbamoyl-phosphate and aspartate

OROTATE[CCO-CYTOSOL]

# UMP is the precursor of pyrimidine biosynthesis

# it is produced from PRPP and OROTATE

UMP[CCO-CYTOSOL]

## 2. The Amino Acids

# NOTE: Sometimes amino acids are synthesized on the tRNA by modification of other amino acids. If you’re lacking a tRNA for a given amino acid in the genome annotation and you don’t see a traditional synthesis pathway for the amino acid, consider this possibility.

# alanine from transamination of pyruvate

L-ALPHA-ALANINE[CCO-CYTOSOL]

# arginine is complex

# argininosuccinate requires AMP recycling (accomplish with an NDP kinase)

# and PPI recycling (accomplish with an inorganic pyrophosphatase)

ARG[CCO-CYTOSOL]

# aspartate has already been done in the basics

L-ASPARTATE[CCO-CYTOSOL]

# asparagine requires AMP/PPI recycling and transamination plus aspartate

ASN[CCO-CYTOSOL]

# cysteine and methionine require sulfur handling; if it is not clear

# how to start from SULFATE, try starting from HS (hydrogen sulfide) instead

# sulfur bearing amino acids can generally be saved for last

# requires serine, acetyl-CoA, and hydrogen sulfide

CYS[CCO-CYTOSOL]

# glutamate has already been done in the basics

GLT[CCO-CYTOSOL] 1.0 ## L-glutamate

# glutamine from ammonium assimilation or transamination of glutamate

GLN[CCO-CYTOSOL] 1.0 ## L-glutamine

# there are 3-ish routes to glycine:

# serine hydroxymethyltransferase (C1 pathway / folate transformation)

# glycine cleavage system

# threonine aldolase

# make sure that you do not add more glycine manipulation than you need

# the folates are complicated and involve considerable instantiation

# be sure that folates are

# glycine can be complicated so don’t let its smallness fool you!

GLY[CCO-CYTOSOL] 1.0 ## glycine

# histidine synthesis requires PRPP and PPI recycling

# it also produces AICAR as a byproduct

# AICAR is transformed to IMP and is generally employed in nucleotide synthesis

# but it can also be degraded; so, if HIS synthesis is not working

# make sure you are dealing with the AICAR produced

HIS[CCO-CYTOSOL] 1.0 ## L-histidine

# isolecuine comes from threonine and pyruvate

ILE[CCO-CYTOSOL] 1.0 ## L-isoleucine

# leucine comes from valine and acetyl-CoA

LEU[CCO-CYTOSOL] 1.0 ## L-leucine

# lysine has a long biosynthetic pathway and produces succinate (SUC)

# as a byproduct

LYS[CCO-CYTOSOL] 1.0 ## L-lysine

# methionine is another sulfur bearer

# it produces succinate as a byproduct and requires the participation of folates

MET[CCO-CYTOSOL] 1.0 ## L-methionine

# phenylalanine requires chorismate

PHE[CCO-CYTOSOL] 1.0 ## L-phenylalanine

# proline comes from glutamate

PRO[CCO-CYTOSOL] 1.0 ## L-proline

# serine has three routes:

# comes from 3-phosphoglycerate in glycolysis

# can be produced by serine hydroxymethyltransferase

# can be produced in some degradation reactions

SER[CCO-CYTOSOL] 1.0 ## L-serine

# threonine comes from aspartate via homo-serine

THR[CCO-CYTOSOL] 1.0 ## L-threonine

# tryptophan comes from serine and chorismate

TRP[CCO-CYTOSOL] 1.0 ## L-tryptophan

# tyrosine comes from chorismate

TYR[CCO-CYTOSOL] 1.0 ## L-tyrosine

# valine comes directly from pyruvate

VAL[CCO-CYTOSOL] 1.0 ## L-valine

## 3. The Ribonucleic Acids

# NOTE: GTP and ATP require each other. In order to overcome this impasse, just make sure that you have NDP kinases and can rephosphorylate ADP. Then, you can produce GTP from ATP and then use it to make ATP de novo. Start with GTP.

# NOTE: Be sure to remove ATP as a prop nutrient/secretion! You are now producing

# ATP de novo, as opposed to simply rephosphorylating it

# NOTE: You should implement CMP & CDP salvage after building ribonucleic acids

# This is because direct production of CTP does not include rephosphorylation

# of CMP to CDP and then CTP, but this is necessary to recycle from e.g.

# CDP-diacylglycerol.

# GTP is produced from IMP and requires ATP

GTP[CCO-CYTOSOL]

# ATP is produced from aspartate and IMP, requires folates/GTP, produces fumarate

ATP[CCO-CYTOSOL]

# UTP is produced from UMP and requires ATP

UTP[CCO-CYTOSOL]

# CTP is produced directly from UTP

CTP[CCO-CYTOSOL]

## 4. The Deoxyribonucleic Acids

# These are usually produced by a reduction step mediated by iron-sulfur or

# thiol proteins.

# Most organisms carry out the reduction at the NDP step (NDP -> dNDP -> dNTP)

# Some carry it out at the NTP step (NDP -> NTP -> dNTP)

# DATP is produced from ATP

DATP[CCO-CYTOSOL]

# DGTP is produced from GTP

DATP[CCO-CYTOSOL]

# DCTP is produced from CTP

DCTP[CCO-CYTOSOL]

# TTP (dTTP, really) is produced from dUMP + folate

TTP[CCO-CYTOSOL]

## 5. Phospholipids

# Phospholipids can get complicated when you start getting into

# unsaturated compounds. Only assemble the phospholipids you need.

# The following covers only the process up to CDP-diacylglycerol &

# you will want to