

ADDITIONAL FILE 1: METABOLIC REACTION SET OF *S. CEREVISIAE*

The reaction network contains 55 central metabolic reactions including the secretion & uptake mechanisms (governed by 91 genes), and 25 reactions belonging to the amino acid metabolism (governed by 46 genes). There is one biomass formation reaction additionally. External metabolites were written in bold font in their uptake and secretion reactions. For the simulation of M81 model, reactions 1-79, 80b, and 81b was used. For M57 model, reactions 1-55, 80a and 81a was used.

1. Substrate Uptake

- | | | |
|------|---|---------------------|
| (1a) | 1 GLUC + 1 ATP → 1 GLUC6P + ADP | <i>GLK1, HXK1,2</i> |
| (1b) | 1 ETOH + 1 NAD _{cyt} → 1 ACAL + 1 NADH _{cyt} | <i>ADH2</i> |
| (1c) | → 1 AC | |
| (1d) | 1 ATP + 1 GOH → 1 ADP + 1 GOH3P | |
| (1e) | 1 NAD _{cyt} + 1 LAC → 1 NADH _{cyt} + 1 PYR | |
| (2) | 1 NH₃ → | <i>MEP1,2,3</i> |

2. Glycolysis & Gluconeogenesis^a

- | | | |
|------|---|---|
| (3) | 1 GLUC6P ↔ 1 FRUC6P | <i>PGI1</i> |
| (4) | 1 FRUC6P + 1 ATP → 1 FRUCDP + ADP | <i>PFK1,2</i> |
| (5) | 1 FRUCDP → 1 FRUC6P | <i>FBP1</i> |
| (6) | 1 FRUCDP ↔ 1 GA3P + 1 DHAP | <i>FBA1</i> |
| (7) | 1 DHAP ↔ 1 GA3P | <i>TPI1</i> |
| (8) | 1 GA3P + 1 NAD _{cyt} ↔ 1 P13G + 1 NADH _{cyt} | <i>TDH1,2,3</i> |
| (9) | 1 P13G + 1 ADP ↔ 1 P3G + 1 ATP | <i>PGK1</i> |
| (10) | 1 P3G ↔ 1 P2G | <i>GPM1,2,3</i> |
| (11) | 1 P2G ↔ 1 PEP | <i>ENO1,2,</i>
<i>ERR1,2,3</i> |
| (12) | 1 PEP + 1 ADP → 1 PYR + 1 ATP | <i>PYK1,2</i> |
| (13) | 1 DHAP + 1 NADH _{cyt} → 1 GOH3P + 1 NAD _{cyt} | <i>GPD1,2</i> |
| (14) | 1 GOH3P → 1 GOH | <i>GPP1, HOR2</i> |
| (15) | 1 PYR → 1 ACAL + 1 CO ₂ | <i>PDC1,5,6</i> |
| (16) | 1 ACAL + 1 NADH _{cyt} ↔ 1 ETOH + 1 NAD _{cyt} | <i>ADH1,4,5</i> |
| (17) | 1 ACAL + 1 NADP _{cyt} → 1 AC + 1 NADPH _{cyt} | <i>ALD6</i> |
| (18) | 1 ACAL + 1 NAD _{mit} → 1 AC + 1 NADH _{mit} | <i>ALD4,5</i> |
| (19) | 1 AC + 2 ATP → 1 ACCOA _{cyt} + 2 ADP | <i>ACS1,2</i> |
| (20) | 1 PYR + 1 NAD _{mit} → 1 ACCOA _{mit} + 1 NADH _{mit} + 1 CO ₂ | <i>PDA1,2, PDB1,</i>
<i>PDX1, LPD1</i> |

(21) $1 \text{ PYR} + 1 \text{ ATP} + 1 \text{ CO}_2 \rightarrow 1 \text{ OAC} + 1 \text{ ADP}$ *PYC1,2*

(22) $1 \text{ OAC} + 1 \text{ ATP} \rightarrow 1 \text{ PEP} + 1 \text{ ADP} + 1 \text{ CO}_2$ *PCK1*

3. Pentose Phosphate Pathway

(23) $1 \text{ GLUC6P} + 1 \text{ NADP}_{\text{cyt}} \rightarrow 1 \text{ G15L} + 1 \text{ NADPH}_{\text{cyt}}$ *ZWF1*

(24) $1 \text{ G15L} \rightarrow 1 \text{ P6G}$ *SOL3,4*

(25) $1 \text{ P6G} + 1 \text{ NADP}_{\text{cyt}} \rightarrow 1 \text{ RIBL5P} + 1 \text{ NADPH}_{\text{cyt}} + 1 \text{ CO}_2$ *GND1,2*

(26) $1 \text{ RIBL5P} \leftrightarrow 1 \text{ RIB5P}$ *RKI1*

(27) $1 \text{ RIBL5P} \leftrightarrow 1 \text{ XYL5P}$ *RPE1*

(28) $1 \text{ RIB5P} + 1 \text{ XYL5P} \leftrightarrow 1 \text{ SED7P} + 1 \text{ GA3P}$ *TKL1,2*

(29) $1 \text{ SED7P} + 1 \text{ GA3P} \leftrightarrow 1 \text{ FRUC6P} + 1 \text{ E4P}$ *TAL1, YGR043C*

(30) $1 \text{ XYL5P} + 1 \text{ E4P} \leftrightarrow 1 \text{ FRUC6P} + 1 \text{ GA3P}$ *TKL1,2*

4. Citric Acid Cycle

(31) $1 \text{ OAC} + 1 \text{ ACCOA}_{\text{mit}} \rightarrow 1 \text{ CIT}$ *CIT1,3*

(32) $1 \text{ CIT} \leftrightarrow 1 \text{ ISOCIT}$ *ACO1,2*

(33) $1 \text{ ISOCIT} + 1 \text{ NAD}_{\text{mit}} \rightarrow 1 \text{ AKG} + 1 \text{ NADH}_{\text{mit}} + 1 \text{ CO}_2$ *IDH1,2*

(34) $1 \text{ ISOCIT} + 1 \text{ NADP}_{\text{mit}} \rightarrow 1 \text{ AKG} + 1 \text{ NADPH}_{\text{mit}} + 1 \text{ CO}_2$ *IDP1*

(35) $1 \text{ ISOCIT} + 1 \text{ NADP}_{\text{cyt}} \rightarrow 1 \text{ AKG} + 1 \text{ NADPH}_{\text{cyt}} + 1 \text{ CO}_2$ *IDP2,3*

(36) $1 \text{ AKG} + 1 \text{ NAD}_{\text{mit}} \rightarrow 1 \text{ SUCCOA} + 1 \text{ NADH}_{\text{mit}} + 1 \text{ CO}_2$ *KGD1,2, LPD1*

(37) $1 \text{ SUCCOA} + 1 \text{ ADP} \leftrightarrow 1 \text{ SUC} + 1 \text{ ATP}$ *LSC1,2*

(38) $1 \text{ SUC} + 1 \text{ FAD} \rightarrow 1 \text{ FUM} + 1 \text{ FADH}_2$ *SDH1,2,3,4*

(39) $1 \text{ FUM} + 1 \text{ FADH}_2 \rightarrow 1 \text{ SUC} + 1 \text{ FAD}$ *OSM1*

(40) $1 \text{ FUM} \leftrightarrow 1 \text{ MAL}$ *FUM1*

(41) $1 \text{ MAL} + 1 \text{ NAD}_{\text{mit}} \leftrightarrow 1 \text{ OAC} + 1 \text{ NADH}_{\text{mit}}$ *MDH1*

(42) $1 \text{ MAL} + 1 \text{ NADP}_{\text{mit}} \rightarrow 1 \text{ PYR} + 1 \text{ CO}_2 + 1 \text{ NADPH}_{\text{mit}}$ *MAE1*

(43) $1 \text{ ACCOA}_{\text{cyt}} \rightarrow 1 \text{ ACCOA}_{\text{mit}}$ *CAT2, YAT1*

(44) $1 \text{ ACAL} + 1 \text{ NADH}_{\text{mit}} \leftrightarrow 1 \text{ ETOH} + 1 \text{ NAD}_{\text{mit}}$ *ADH3*

5. Glyoxylate Shunt

(45) $1 \text{ OAC} + 1 \text{ ACCOA}_{\text{cyt}} \rightarrow 1 \text{ CIT}$ *CIT2*

(46) $1 \text{ ISOCIT} \rightarrow 1 \text{ GLYO} + 1 \text{ SUC}$ *ICL1,2*

(47) $1 \text{ GLYO} + 1 \text{ ACCOA}_{\text{cyt}} \rightarrow 1 \text{ MAL}$ *MLS1,2*

(48) $1 \text{ MAL} + 1 \text{ NAD}_{\text{mit}} \leftrightarrow 1 \text{ OAC} + 1 \text{ NADH}_{\text{cyt}}$ *MDH2,3*

6. Oxidative Phosphorylation

(49) $24 \text{ ADP} + 20 \text{ NADH}_{\text{mit}} + 10 \text{ O}_2 \rightarrow 24 \text{ ATP} + 20 \text{ NAD}_{\text{mit}}$ *NADHX*

(50) $24 \text{ ADP} + 20 \text{ FADH}_2 + 10 \text{ O}_2 \rightarrow 24 \text{ ATP} + 20 \text{ FAD}$ *FADHX*

(51) $1 \text{ ATP} \rightarrow 1 \text{ ADP}$ *MAINT*

7. Product Secretion

(52)	$\rightarrow 1 \text{ GOH}$	<i>FPS1</i>
(53)	$\rightarrow 1 \text{ ETOH}$	
(54)	$\rightarrow 1 \text{ AC}$	<i>BPH1</i>
(55)	$\rightarrow 1 \text{ SUC}$	

8. Glutamate & Glutamine Metabolism

(56)	$1 \text{ AKG} + 1 \text{ NADPH}_{\text{cyt}} + 1 \text{ NH}_3 \rightarrow 1 \text{ GLT} + 1 \text{ NADP}_{\text{cyt}}$	<i>GDH1,3</i>
(57)	$1 \text{ GLT} + 1 \text{ NAD}_{\text{cyt}} \rightarrow 1 \text{ AKG} + 1 \text{ NADH}_{\text{cyt}} + 1 \text{ NH}_3$	<i>GDH2</i>
(58)	$1 \text{ GLT} + 1 \text{ ATP} + 1 \text{ NH}_3 \rightarrow 1 \text{ GLN} + 1 \text{ ADP}$	<i>GLN1</i>
(59)	$1 \text{ AKG} + 1 \text{ GLN} + 1 \text{ NADH}_{\text{cyt}} \rightarrow 2 \text{ GLT} + 1 \text{ NAD}_{\text{cyt}}$	<i>GLT1</i>
(60)	$1 \text{ GLT} \rightarrow 1 \text{ CO}_2 + 1 \text{ GABA}$	<i>GAD1</i>
(61)	$1 \text{ AKG} + 1 \text{ GABA} \rightarrow 1 \text{ GLT} + 1 \text{ SUCSAL}$	<i>UGA1</i>
(62)	$1 \text{ SUCSAL} + 1 \text{ NADP}_{\text{cyt}} \rightarrow 1 \text{ SUC} + 1 \text{ NADPH}_{\text{cyt}}$	<i>UGA2</i>

9. Aspartate & Asparagine & Alanine Metabolism

(63)	$1 \text{ OAC} + 1 \text{ GLT} \leftrightarrow 1 \text{ AKG} + 1 \text{ ASP}$	<i>AAT1,2</i>
(64)	$2 \text{ ATP} + 1 \text{ GLN} + 1 \text{ ASP} \leftrightarrow 2 \text{ ADP} + 1 \text{ GLT} + 1 \text{ ASN}$	<i>ASN1,2</i>
(65)	$1 \text{ ASN} \rightarrow 1 \text{ ASP} + 1 \text{ NH}_3$	<i>ASP3-4,1</i>
(66)	$1 \text{ PYR} + 1 \text{ GLT} \leftrightarrow 1 \text{ AKG} + 1 \text{ ALA}$	<i>ALT1,2</i>

10. Leucine & Valine Metabolism

(67)	$2 \text{ PYR} \rightarrow 1 \text{ CO}_2 + 1 \text{ ACLAC}$	<i>ILV2,6</i>
(68)	$1 \text{ ACLAC} + 1 \text{ NADPH}_{\text{mit}} \rightarrow 1 \text{ NADP}_{\text{mit}} + 1 \text{ DHVAL}$	<i>ILV5</i>
(69)	$1 \text{ DHVAL} \rightarrow 1 \text{ OIVAL}$	<i>ILV3</i>
(70)	$\text{ACCOA}_{\text{mit}} + 1 \text{ OIVAL} \rightarrow 1 \text{ IPPMAL}$	<i>LEU4</i>
(71)	$1 \text{ IPPMAL} + 1 \text{ NAD}_{\text{cyt}} \rightarrow 1 \text{ NADH}_{\text{cyt}} + 1 \text{ OICAP} + 1 \text{ CO}_2$	<i>LEU2</i>
(72)	$1 \text{ OICAP} + 1 \text{ GLT} \leftrightarrow 1 \text{ AKG} + 1 \text{ LEU}$	<i>BAT1,2</i>
(73)	$1 \text{ OIVAL} + 1 \text{ GLT} \leftrightarrow 1 \text{ AKG} + 1 \text{ VAL}$	<i>BAT2</i>

11. Serine & Glycine Metabolism

(74)	$1 \text{ P3G} + \text{NAD}_{\text{cyt}} \rightarrow 1 \text{ PHP} + 1 \text{ NADH}_{\text{cyt}}$	<i>SER3,33</i>
(75)	$1 \text{ PHP} + 1 \text{ GLT} \rightarrow 1 \text{ AKG} + 1 \text{ P3SER}$	<i>SER1</i>
(76)	$1 \text{ P3SER} \rightarrow 1 \text{ SER}$	<i>SER2</i>
(77)	$1 \text{ SER} \leftrightarrow 1 \text{ GLY} + 1 \text{ C1}$	<i>SHM1,2</i>
(78)	$1 \text{ ALA} + 1 \text{ GLYO} \leftrightarrow 1 \text{ PYR} + 1 \text{ GLY}$	<i>AGX1</i>
(79)	$1 \text{ GLY} + \text{NAD}_{\text{mit}} \rightarrow 1 \text{ C1} + \text{NADH}_{\text{mit}} + \text{CO}_2 + \text{NH}_3$	<i>GCV1</i>

12. AICAR synthesis

(80a)	$1 \text{ R5P} + 1 \text{ P3G} + 8 \text{ ATP} + 1 \text{ NAD}_{\text{mit}} + 1 \text{ NAD}_{\text{cyt}} + 2 \text{ NADPH}_{\text{cyt}} \rightarrow 1 \text{ NADH}_{\text{mit}} + 1 \text{ NADH}_{\text{cyt}} + 2 \text{ NADP}_{\text{cyt}} + 8 \text{ ADP} + 1 \text{ AICAR}$	<i>ADE4,5,7,8,6,5, 2,1,13- CCM</i>
(80b)	$1 \text{ R5P} + 6 \text{ ATP} + 2 \text{ GLN} + 1 \text{ GLY} + 1 \text{ C1} + 1 \text{ CO}_2 + \text{ASP} \rightarrow 2 \text{ GLU} + 1 \text{ FUM}$	<i>ADE4,5,7,8,6,5,</i>

+ 6 ADP + 1 AICAR

2,1,13 -CCMAA

13. Biomass Formation

(81a) 0.05877 PYR + 0.03293 OAC + 0.03430 AKG + 0.01767 P3G + 0.04302 *BIOMX-CCM*

ACCOA_{cyt} + 0.00996 ACCOA_{mit} + 0.00802 RB5P + 0.00889 E4P + 0.01777 PEP (1 C-mol)

+ 0.04400 G6P + 0.00187 GOH3P + 0.00201 AICAR + 0.28658 NADPH_{cyt} +

0.03080 NADPH_{mit} + 0.05056 NAD_{cyt} + 0.01716 NAD_{mit} + 1.80302 ATP

→

0.05056 NADH_{cyt} + 0.01716 NADH_{mit} + 0.28658 NADP_{cyt} + 0.03080 NADP_{mit} +

1.80302 ADP + 0.05806 CO₂ + 1 BIOM

(81b) 0.00555 PYR + 0.04302 ACCOA_{cyt} + 0 ACCOA_{mit} + 0.00802 RB5P + 0.00889 *BIOMX-*

E4P + 0.01777 PEP + 0.04400 G6P + 0.00187 GOH3P + 0.04485GLT + 0.02116 *CCM-AA*

GLN + 0.01545 ALA + 0.03703 ASP + 0.00343 ASN + 0.00885 SER + 0.00976 (1 C-mol)

GLY + 0.00996 ILE + 0.00892 VAL + 0.00595 C1 + 0.00201 AICAR + 0.12717

NADPH_{cyt} + 0.01192 NADPH_{mit} + 0.02198 NAD_{cyt} + 0.01716 NAD_{mit} + 1.77156

ATP

→

0.02198 NADH_{cyt} + 0.01716 NADH_{mit} + 0.12717 NADP_{cyt} + 0.01192 NADP_{mit} +

1.77156 ADP + 0.02922 CO₂ + 1 **BIOM** + 0.00754 OAC + 0.03171 AKG +

0.00094 P3G + 0.00650 NH₃

^aReversible reactions were written in the direction of their occurrence in glycolysis.