

Supplementary Data

1. Chinese Hamster Ovary (CHO)

The model and reported flux distribution are cited from Llaneras and Pico (2007).

Llaneras, F. Pico, J. An interval approach for dealing with flux distributions and elementary modes activity patterns. *J. Theor. Biol.* 2007, 246, 290-308.

Table S1 Prediction results for the flux distribution of CHO cells by Quadratic programming (QP), the maximum entropy principle (MEP), and Linear Programming in Enzyme Control Flux (ECFLP)

| No | Reactions | Exp | QP | MEP | ECFLP |
|-----|---------------------------------------|------|------|------|-------|
| R1 | G ==> G6P | 4.05 | 4.05 | 4.05 | 4.05 |
| R2 | G6P ==> DAP + G3P | 3.76 | 4.05 | 3.92 | 3.93 |
| R3 | G6P ==> R5P + CO ₂ | 0.28 | 0.00 | 0.13 | 0.12 |
| R4 | DAP ==> G3P | 3.76 | 4.05 | 3.92 | 3.93 |
| R5 | G3P ==> PYR | 7.53 | 8.10 | 7.84 | 7.87 |
| R6 | PYR ==> L | 7.39 | 7.39 | 7.39 | 7.39 |
| R7 | PYR + GLU ==> A + AKG | 0.26 | 0.26 | 0.26 | 0.26 |
| R8 | PYR ==> CO ₂ + ACA | 0.34 | 1.63 | 1.06 | 1.12 |
| R9 | ACA + OXA ==> CIT | 0.34 | 1.63 | 1.06 | 1.12 |
| R10 | CIT ==> CO ₂ + AKG | 0.34 | 1.63 | 1.06 | 1.12 |
| R11 | AKG ==> CO ₂ + MAL | 1.10 | 2.81 | 2.06 | 2.14 |
| R12 | MAL ==> OXA | 0.63 | 1.63 | 1.19 | 1.24 |
| R13 | MAL ==> CO ₂ + PYR | 0.47 | 1.18 | 0.87 | 0.9 |
| R14 | GLU + OXA ==> ASP + AKG | 0.28 | 0.00 | 0.13 | 0.12 |
| R15 | GLU ==> NH ₄ + AKG | 0.20 | 0.92 | 0.61 | 0.64 |
| R16 | Q ==> GLU + NH ₄ | 0.75 | 1.18 | 1.00 | 1.02 |
| R17 | R5P + ASP + Q ==> PU | 0.14 | 0.00 | 0.08 | 0.07 |
| R18 | R5P + ASP + 2 Q ==> PY | 0.14 | 0.00 | 0.05 | 0.05 |
| R19 | GX ==> G | 4.05 | 4.05 | 4.05 | 4.05 |
| R20 | L ==> LX | 7.39 | 7.39 | 7.39 | 7.39 |
| R21 | NH ₄ ==> NH ₄ X | 0.96 | 2.10 | 1.61 | 1.66 |
| R22 | PU ==> PUX | 0.14 | 0.00 | 0.08 | 0.07 |
| R23 | QX ==> Q | 1.18 | 1.18 | 1.18 | 1.18 |
| R24 | A ==> AX | 0.26 | 0.26 | 0.26 | 0.26 |
| R25 | CO ₂ ==> CO ₂ X | 2.61 | 7.25 | 5.19 | 5.4 |
| R26 | PY ==> PYX | 0.14 | 0.00 | 0.05 | 0.05 |

<=> reversible reaction; => irreversible reaction. Exp: Experimental fluxes.

Metabolites:

G, Glucose; L, Lactate; NH₄, Ammonia; PU, Purine; Q, Glutamine; A, Alanine; CO₂, Carbon Dioxide; PY, Pyrimidine; G6P, Glucose-6-phosphate; DAP, Dihydroxy-acetone Phosphate; R5P, Ribose-5-Phosphate; Cit, Citrate; Mal, Malate; Glu, Glutamate; G3P, Glyceraldehyde-3-phosphate; PYR, pyruvate; ACA, acetyl-coenzyme A; OXA, Oxaloacetate; AKG, α -ketoglutarate; ASP, Aspartate; GX, extracellular glucose; LX, extracellular lactate; NH₄X, extracellular ammonia; PUX, product purine; QX, extracellular glutamine; AX, extracellular alanine; CO₂X, extracellular carbon dioxide; PYX, product pyrimidine.

2. *Escherichia coli*

The experimental flux distribution is cited from Burgard and Maranas (2003)

Burgard, A.P., Maranas, C.D. Optimization-based framework for inferring and testing hypothesized metabolic objective functions. *Biotechnol. Bioeng.* 2003, 82, 670-677.

The external flux for acetate is set to be 0 and glucose uptake is set to be 115 under aerobic conditions. The prediction results are shown in Table S2. Under anaerobic conditions, the external fluxes for acetate, ethanol, lactate and succinate are set to be 34.1, 65.3, 69.8 and 3.9, respectively. The uptake of glucose is set to be 115. The prediction results are shown in Table S3.

Table S2 Prediction results for the flux distribution of *E. coli* under aerobic conditions by Quadratic programming (QP), Linear programming (LP), the maximum entropy principle (MEP) and Linear Programming in Enzyme Control Flux (ECFLP)

| Genes | Reactions | Exp | QP | LP | MEP | ECFLP |
|---------------------|---|--------|--------|--------|--------|--------|
| TKTA | 2 P5P \rightleftharpoons GAP + S7P | 18.90 | -0.21 | -2.51 | 28.14 | 29.76 |
| TKTB | P5P + E4P \rightleftharpoons GAP + F6P | 9.60 | -6.23 | -8.59 | 24.13 | 26.26 |
| PCK | CO ₂ + PEP \rightleftharpoons OAA | 21.40 | 43.67 | 44.13 | 29.14 | 25.36 |
| MDH | MAL \rightleftharpoons OAA | 45.00 | 0.21 | 0.00 | 48.34 | 66.66 |
| PYK | PEP \rightleftharpoons PYR | 26.60 | -0.25 | 0.78 | 9.79 | 18.18 |
| CO ₂ EXT | CO ₂ \rightleftharpoons CO ₂ EXT | 254.90 | 75.94 | 69.24 | 280.13 | 333.34 |
| PGI | G6P \rightleftharpoons F6P | 61.00 | 105.22 | 111.96 | 23.61 | 19.67 |
| FUM | FUM \rightleftharpoons MAL | 45.00 | 0.21 | 0.00 | 48.34 | 66.66 |
| TAL | GAP + S7P \rightleftharpoons F6P + E4P | 18.90 | -0.21 | -2.51 | 28.14 | 29.76 |
| GLCEXT | GLCXT \Rightarrow GLC | 115.00 | 115.02 | 115.00 | 115.00 | 115.00 |
| PDH | PYR \Rightarrow ACCOA + CO ₂ | 126.10 | 72.85 | 73.42 | 96.82 | 108.84 |
| ENO | P3G \Rightarrow PEP | 181.20 | 165.79 | 167.35 | 158.84 | 162.81 |
| SDH | SUC \Rightarrow FUM | 45.00 | 0.21 | 0.00 | 48.34 | 66.66 |
| GND | D6PGL \Rightarrow CO ₂ + P5P | 53.10 | 6.80 | 0.00 | 89.39 | 93.59 |
| CS | ACCOA + OAA \Rightarrow ICIT | 52.00 | 16.76 | 16.72 | 59.38 | 76.26 |
| GAP | GAP \Rightarrow P3G | 193.00 | 186.15 | 187.93 | 172.43 | 174.63 |
| ACEXT | AC \Rightarrow ACEXT | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| ZWF | G6P \Rightarrow D6PGL | 53.10 | 6.80 | 0.00 | 89.39 | 93.59 |
| ICDH | ICIT \Rightarrow CO ₂ + AKG | 52.00 | 16.76 | 16.72 | 59.38 | 76.26 |
| ACK | ACCOA \Rightarrow AC | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| GROWTH | 3.058 PYR + 0.219 G6P + 4.093 ACCOA + 0.165 GAP + 0.537 PEP + 0.982 P5P + 0.106 F6P + 1.979 OAA + 0.439 E4P + 1.207 AKG + 1.485 P3G \Rightarrow 1.677 CO ₂ + BIOMASS | 7.00 | 13.71 | 13.85 | 9.15 | 7.96 |
| AKD | AKG \Rightarrow CO ₂ + SUC | 45.00 | 0.21 | 0.00 | 48.34 | 66.66 |
| PFK | F6P \Rightarrow 2 GAP | 89.10 | 97.32 | 99.40 | 74.90 | 74.84 |
| PTS | PEP + GLC \Rightarrow PYR + G6P | 115.00 | 115.02 | 115.00 | 115.00 | 115.00 |

\rightleftharpoons reversible reaction; \Rightarrow irreversible reaction. Exp: Experimental fluxes;

Metabolites:

G6P, glucose-6-phosphate; ACCOA, acetyl-coenzyme A; CO₂, carbon dioxide; S7P, sedoheptulose-7-phosphate; PEP, phosphoenolpyruvate; P5P, pentose-5-phosphate; SUC, succinate; OAA, oxaloacetate; ICIT, isocitrate; P3G, 3-phosphoglycerate; LAC, lactate; PYR, pyruvate; ETH, ethanol; GAP, glyceraldehydes-3-phosphate; D6PGL, d-6-phosphate gluconate; MAL, malate; F6P, fructose-6-phosphate; AC, acetate; GLC, glucose; FUM, fumarate; E4P, erythrose-4-phosphate; AKG, α -ketoglutarate; ACEXT, external acetate; BIOMASS, biomass; GLCXT, external glucose; CO₂EXT, external carbon dioxide.

Table S3 Prediction results for the flux distribution of *Escherichia coli* under anaerobic conditions by Quadratic programming (QP), Linear programming (LP), the maximum entropy principle (MEP), and Linear Programming in Enzyme Control Flux (ECFLP)

| Genes | Reactions | Exp | QP | LP | MEP | ECFLP |
|---------|--|--------|--------|--------|--------|--------|
| MDH | MAL <=> OAA | 0.80 | 0.00 | 0.00 | 3.44 | 4.91 |
| PCK | CO ₂ + PEP <=> OAA | 6.10 | 6.88 | 14.07 | 8.33 | 10.31 |
| PGI | G6P <=> F6P | 30.00 | 2.40 | 114.30 | 35.27 | 70.43 |
| TAL | S7P + GAP <=> F6P + E4P | 28.20 | 37.29 | -0.58 | 26.22 | 14.35 |
| TKTA | 2 P5P <=> S7P + GAP | 28.20 | 37.29 | -0.58 | 26.22 | 14.35 |
| TKTB | P5P + E4P <=> GAP + F6P | 26.90 | 36.88 | -1.98 | 25.61 | 13.46 |
| PYK | PEP <=> PYR | 69.10 | 65.92 | 84.78 | 73.16 | 79.81 |
| CO2EXT | CO ₂ <=> CO ₂ EXT | 199.60 | 224.27 | 123.15 | 203.91 | 176.11 |
| FUM | FUM <=> MAL | 0.80 | 0.00 | 0.00 | 3.44 | 4.91 |
| ENO | P3G ==> PEP | 194.60 | 188.31 | 215.56 | 197.24 | 206.20 |
| SDH | SUC ==> FUM | 0.80 | 0.00 | 0.00 | 3.44 | 4.91 |
| GND | D6PGL ==> CO ₂ + P5P | 84.90 | 112.39 | 0.00 | 79.43 | 44.13 |
| SUCCEXT | SUC ==> SUCEXT | 3.90 | 3.90 | 3.90 | 3.90 | 3.90 |
| ACEXT | AC ==> ACEXT | 34.10 | 34.10 | 34.10 | 34.10 | 34.10 |
| ICDH | ICIT ==> CO ₂ + AKG | 4.80 | 5.03 | 7.75 | 9.02 | 11.24 |
| ZWF | G6P ==> D6PGL | 84.90 | 112.39 | 0.00 | 79.43 | 44.13 |
| LDH | PYR ==> LAC | 69.80 | 69.80 | 69.80 | 69.80 | 69.80 |
| ACK | ACCOA ==> AC | 34.10 | 34.10 | 34.10 | 34.10 | 34.10 |
| PTS | PEP + GLC ==> G6P + PYR | 115.00 | 115.00 | 115.00 | 115.00 | 115.00 |
| GLCEXT | GLCXT ==> GLC | 115.00 | 115.00 | 115.00 | 115.00 | 115.00 |
| PDH | PYR ==> ACCOA + CO ₂ | 111.40 | 108.26 | 120.22 | 114.11 | 118.86 |
| CS | ACCOA + OAA ==> ICIT | 4.80 | 5.03 | 7.75 | 9.02 | 11.24 |
| GAP | GAP ==> P3G | 205.00 | 189.70 | 220.31 | 199.30 | 209.18 |
| ETHEXT | ETH ==> ETHEXT | 65.30 | 65.30 | 65.30 | 65.30 | 65.30 |
| LACEXT | LAC ==> LACEXT | 69.80 | 69.80 | 69.80 | 69.80 | 69.80 |
| GROWTH | 0.219 G6P + 4.093 ACCOA + 0.537 PEP + 0.982 P5P + 1.979 OAA + 1.485 P3G + 3.058 PYR + 0.165 GAP + 0.106 F6P + 0.439 E4P + 1.207 AKG ==> 1.677 CO ₂ + BIOMASS | 2.00 | 0.94 | 3.19 | 1.39 | 2.01 |
| AKD | AKG ==> CO ₂ + SUC | 4.70 | 3.90 | 3.90 | 7.34 | 8.81 |
| ADH | ACCOA ==> ETH | 65.30 | 65.30 | 65.30 | 65.30 | 65.30 |
| PFK | F6P ==> 2 GAP | 84.90 | 76.48 | 111.41 | 86.96 | 98.03 |

<=> reversible reaction; ==> irreversible reaction. Exp: Experimental fluxes;

Metabolites:

G6P, glucose-6-phosphate; ACCOA, acetyl-coenzyme A; CO₂, carbon dioxide; S7P, sedoheptulose-7-phosphate; PEP, phosphoenolpyruvate; P5P, pentose-5-phosphate; SUC, succinate; OAA, oxaloacetate; ICIT, isocitrate; P3G, 3-phosphoglycerate; LAC, lactate; PYR, pyruvate; ETH, ethanol; GAP, glyceraldehydes-3-phosphate; D6PGL, d-6-phosphate gluconate; MAL, malate; F6P, fructose-6-phosphate; AC, acetate; GLC, glucose; FUM, fumarate; E4P, erythrose-4-phosphate; AKG, α -ketoglutarate; ACEXT, external acetate; BIOMASS, biomass; SUCEXT, external succinate; ETHEXT, external ethanol; GLCXT, external glucose; LACEXT, external lactate; CO₂EXT, external carbon dioxide.

3. *Saccharomyces cerevisiae*

The experimental flux distribution is cited from Frick and Wittmann (2005).

Frick, O., Wittmann, C. Characterization of the metabolic shift between oxidative and fermentative growth in *Saccharomyces cerevisiae* by comparative ¹³C flux analysis, *Microb Cell Fact*, 2005, 4, 30.

The external fluxes of glucose, acetate, ethanol and glycerol are set to be the same value as the experimental data.

Metabolites (Table S4-S6):

R5P, ribose-5-phosphate; G6P, glucose-6-phosphate; CO₂, carbon dioxide; S7P, sedoheptulose-7-phosphate; PEP, phosphoenolpyruvate; ACE, acetate; ACCOACYT, cytosolic acetyl-coenzyme A; SUC, succinate; DHAP, dihydroxyacetone phosphate; SUCCOA, succinyl-coenzyme A; OAA, cytosolic oxaloacetate; P3G, 3-phosphoglycerate; PYR, cytosolic pyruvate; P6G, 6-phospho-gluconate; GA3P, glyceraldehydes-3-phosphate; MAL, malate; G15L, 6-phospho-glucono-1,5-lactone; RU5P, ribulose-5-phosphate; ACA, acetate; ICI, isocitrate; OAAMIT, mitochondrial oxaloacetate ; F6P, fructose-6-phosphate; ACCOAMIT, mitochondrial acetyl-coenzyme A; PYRMIT, mitochondrial pyruvate; X5P, xylulose-5-phosphate; GP, glycerone-3-phosphate; E4P, erythrose-4-phosphate; FUM, fumarate; AKG, α-ketoglutarate; ACEX, external acetate; CO₂EX, external carbon dioxide; BIOMASS, biomass; ETH, ethanol; GLYC, glycerol; GLC, glucose; ETHEXT, external ethanol; GLCEXT, external glucose; GLYCEXT, external glycerol.

<=> reversible reaction;

=> irreversible reaction.

Exp: Experimental fluxes;

Table S4. Prediction results for the flux distribution of *Saccharomyces cerevisiae* ($\mu=0.15 \text{ h}^{-1}$) by Quadratic programming (QP), Linear programming (LP), the maximum entropy principle (MEP), and Linear Programming in Enzyme Control Flux (ECFLP)

| Genes | Reactions | Exp | QP | LP | MEP | ECFLP |
|---------|---|--------|--------|--------|--------|--------|
| ENO | P3G \rightleftharpoons PEP | 128.70 | 107.54 | 110.48 | 124.78 | 132.21 |
| SDH | SUC \rightleftharpoons FUM | 63.40 | 4.84 | 0.00 | 44.56 | 61.83 |
| TPI | DHAP \rightleftharpoons GA3P | 58.30 | 53.19 | 59.60 | 60.41 | 63.45 |
| MDH | MAL \rightleftharpoons OAAMIT | 56.20 | -12.06 | -16.59 | 17.75 | 30.75 |
| RKI | RU5P \rightleftharpoons R5P | 20.00 | 12.83 | 3.98 | 12.66 | 12.70 |
| TAL | S7P + GA3P \rightleftharpoons F6P + E4P | 18.70 | 9.13 | 0.00 | 9.77 | 10.17 |
| TKL | R5P + X5P \rightleftharpoons S7P + GA3P | 18.70 | 9.13 | 0.00 | 9.77 | 10.17 |
| TKI | X5P + E4P \rightleftharpoons GA3P + F6P | 16.30 | 5.43 | -3.98 | 6.88 | 7.63 |
| RPE | RU5P \rightleftharpoons X5P | 30.00 | 14.55 | -3.98 | 16.65 | 17.80 |
| TDH | GA3P \rightleftharpoons P3G | 134.10 | 114.94 | 118.45 | 130.56 | 137.28 |
| LSC | SUCCOA \rightleftharpoons SUC | 63.40 | 4.84 | 0.00 | 44.56 | 61.83 |
| FUM | FUM \rightleftharpoons MAL | 63.40 | 4.84 | 0.00 | 44.56 | 61.83 |
| FBA | F6P \rightleftharpoons DHAP + GA3P | 60.20 | 56.33 | 62.83 | 63.27 | 66.19 |
| ACS | ACE \Rightarrow ACCOACYT | 73.60 | 44.93 | 41.15 | 48.03 | 49.67 |
| GPD | DHAP \Rightarrow GP | 2.20 | 3.14 | 3.23 | 2.86 | 2.74 |
| ACEX | ACE \Rightarrow ACEX | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| GND | P6G \Rightarrow CO ₂ + RU5P | 54.70 | 27.38 | 0.00 | 29.31 | 30.50 |
| HXK | GLC \Rightarrow G6P | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 |
| CO2EX | CO ₂ \Rightarrow CO ₂ EX | 270.00 | 76.76 | 37.47 | 190.24 | 239.94 |
| ZWF | G6P \Rightarrow G15L | 54.70 | 27.38 | 0.00 | 29.31 | 30.50 |
| BIOMASS | 3 R5P + 25 G6P + 6 PEP + 24 ACCOACYT + 10 OAA + 6 P3G + 3 ACCOAMIT + 18 PYRMIT + GP + 3 E4P + 11 AKG \Rightarrow 100 BIOMASS | 0.60 | 1.23 | 1.33 | 0.96 | 0.84 |
| PYC | CO ₂ + PYR \Rightarrow OAA | 23.80 | 42.81 | 44.47 | 47.02 | 48.82 |
| PGI | G6P \Rightarrow F6P | 25.20 | 41.77 | 66.81 | 46.62 | 48.40 |
| KGD | AKG \Rightarrow CO ₂ + SUCCOA | 63.40 | 4.84 | 0.00 | 44.56 | 61.83 |
| IDP | ICI \Rightarrow CO ₂ + AKG | 73.10 | 18.41 | 14.60 | 55.15 | 71.12 |
| CAT | ACCOACYT \Rightarrow ACCOAMIT | 53.40 | 15.32 | 9.29 | 24.92 | 29.41 |
| ALD | ACA \Rightarrow ACE | 73.60 | 44.93 | 41.15 | 48.03 | 49.67 |
| MAE | MAL \Rightarrow CO ₂ + PYRMIT | 7.20 | 16.90 | 16.59 | 26.80 | 31.09 |
| PYK | PEP \Rightarrow PYR | 124.30 | 100.14 | 102.52 | 119.00 | 127.15 |
| SOL | G15L \Rightarrow P6G | 54.70 | 27.38 | 0.00 | 29.31 | 30.50 |
| GPP | GP \Rightarrow GLYC | 1.90 | 1.91 | 1.90 | 1.90 | 1.90 |
| PDC | PYR \Rightarrow CO ₂ + ACA | 73.30 | 45.23 | 41.45 | 48.33 | 49.97 |
| PDB | PYRMIT \Rightarrow CO ₂ + ACCOAMIT | 21.80 | 6.79 | 9.29 | 33.12 | 44.25 |
| OAAT | OAA \Rightarrow OAAMIT | 16.80 | 30.47 | 31.20 | 37.39 | 40.38 |
| ADH | ACA \Rightarrow ETH | 0.30 | 0.30 | 0.30 | 0.30 | 0.30 |
| CIT | OAAMIT + ACCOAMIT \Rightarrow ICI | 73.10 | 18.41 | 14.60 | 55.15 | 71.12 |
| YEL006W | PYR \Rightarrow PYRMIT | 27.00 | 12.10 | 16.59 | 23.65 | 28.35 |
| GLCup | GLCEXT \Rightarrow GLC | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 |
| ETHEXT | ETH \Rightarrow ETHEXT | 0.30 | 0.30 | 0.30 | 0.30 | 0.30 |
| GLYCEXT | GLYC \Rightarrow GLYCEXT | 1.90 | 1.91 | 1.90 | 1.90 | 1.90 |

Table S5. Prediction results for the flux distribution of *Saccharomyces cerevisiae* ($\mu=0.30 \text{ h}^{-1}$) by Quadratic programming (QP), Linear programming (LP), the maximum entropy principle (MEP), and Linear Programming in Enzyme Control Flux (ECFLP)

| Genes | Reaction | Exp | QP | LP | MEP | ECFLP |
|---------|---|--------|--------|--------|--------|--------|
| ENO | P3G \rightleftharpoons PEP | 156.90 | 128.60 | 136.87 | 150.53 | 147.52 |
| SDH | SUC \rightleftharpoons FUM | 47.20 | 2.93 | 0.00 | 43.87 | 35.75 |
| TPI | DHAP \rightleftharpoons GA3P | 73.10 | 55.92 | 69.18 | 69.37 | 68.64 |
| MDH | MAL \rightleftharpoons OAAMIT | 22.70 | -7.19 | -10.91 | 22.76 | 16.75 |
| RKI | RU5P \rightleftharpoons R5P | 16.00 | 19.38 | 2.62 | 11.90 | 11.03 |
| TAL | S7P + GA3P \rightleftharpoons F6P + E4P | 10.20 | 17.17 | 0.00 | 10.37 | 9.31 |
| TKL | R5P + X5P \rightleftharpoons S7P + GA3P | 10.20 | 17.17 | 0.00 | 10.37 | 9.31 |
| TKI | X5P + E4P \rightleftharpoons GA3P + F6P | 8.50 | 14.95 | -2.62 | 8.84 | 7.60 |
| RPE | RU5P \rightleftharpoons X5P | 14.00 | 32.12 | -2.62 | 19.21 | 16.92 |
| TDH | GA3P \rightleftharpoons P3G | 159.80 | 133.03 | 142.11 | 153.58 | 150.94 |
| LSC | SUCCOA \rightleftharpoons SUC | 47.20 | 2.93 | 0.00 | 43.87 | 35.75 |
| FUM | FUM \rightleftharpoons MAL | 47.20 | 2.93 | 0.00 | 43.87 | 35.75 |
| FBA | F6P \rightleftharpoons DHAP + GA3P | 78.70 | 62.15 | 75.55 | 75.37 | 74.71 |
| ACS | ACE \Rightarrow ACCOACYT | 19.50 | 26.93 | 27.07 | 31.27 | 31.59 |
| GPD | DHAP \Rightarrow GP | 6.00 | 6.24 | 6.37 | 6.01 | 6.07 |
| ACEX | ACE \Rightarrow ACEX | 14.70 | 14.70 | 14.70 | 14.70 | 14.70 |
| GND | P6G \Rightarrow CO ₂ + RU5P | 29.60 | 51.50 | 0.00 | 31.11 | 27.94 |
| HXK | GLC \Rightarrow G6P | 100.00 | 99.99 | 100.00 | 100.00 | 100.00 |
| CO2EX | CO ₂ \Rightarrow CO ₂ EX | 250.00 | 145.37 | 88.85 | 241.38 | 215.58 |
| ZWF | G6P \Rightarrow G15L | 29.60 | 51.50 | 0.00 | 31.11 | 27.94 |
| BIOMASS | 3 R5P + 25 G6P + 6 PEP + 24 ACCOACYT + 10 OAA + 6 P3G + 3 ACCOAMIT + 18 PYRMIT + GP + 3 E4P + 11 AKG \Rightarrow 100 BIOMASS | 0.40 | 0.74 | 0.87 | 0.51 | 0.57 |
| PYC | CO ₂ + PYR \Rightarrow OAA | 27.40 | 25.62 | 29.25 | 31.80 | 30.98 |
| PGI | G6P \Rightarrow F6P | 60.00 | 30.03 | 78.17 | 56.16 | 57.79 |
| KGD | AKG \Rightarrow CO ₂ + SUCCOA | 47.10 | 2.93 | 0.00 | 43.87 | 35.75 |
| IDP | ICI \Rightarrow CO ₂ + AKG | 54.40 | 11.05 | 9.60 | 49.47 | 42.03 |
| CAT | ACCOACYT \Rightarrow ACCOAMIT | 6.40 | 9.22 | 6.11 | 19.06 | 17.89 |
| ALD | ACA \Rightarrow ACE | 34.20 | 41.63 | 41.77 | 45.97 | 46.29 |
| MAE | MAL \Rightarrow CO ₂ + PYRMIT | 14.50 | 10.12 | 10.91 | 21.11 | 19.00 |
| PYK | PEP \Rightarrow PYR | 153.20 | 124.17 | 131.63 | 147.47 | 144.10 |
| SOL | G15L \Rightarrow P6G | 29.60 | 51.50 | 0.00 | 31.11 | 27.94 |
| GPP | GP \Rightarrow GLYC | 5.50 | 5.50 | 5.50 | 5.50 | 5.50 |
| PDC | PYR \Rightarrow CO ₂ + ACA | 82.90 | 91.33 | 91.47 | 95.67 | 95.99 |
| PDB | PYRMIT \Rightarrow CO ₂ + ACCOAMIT | 49.50 | 4.05 | 6.11 | 31.94 | 25.85 |
| OAAT | OAA \Rightarrow OAAMIT | 21.70 | 18.24 | 20.52 | 26.71 | 25.28 |
| ADH | ACA \Rightarrow ETH | 49.70 | 49.70 | 49.70 | 49.70 | 49.70 |
| CIT | OAAMIT + ACCOAMIT \Rightarrow ICI | 54.40 | 11.05 | 9.60 | 49.47 | 42.03 |
| YEL006W | PYR \Rightarrow PYRMIT | 42.80 | 7.21 | 10.91 | 20.00 | 17.12 |
| GLCup | GLCEXT \Rightarrow GLC | 100.00 | 99.99 | 100.00 | 100.00 | 100.00 |
| ETHEXT | ETH \Rightarrow ETHEXT | 49.70 | 49.70 | 49.70 | 49.70 | 49.70 |
| GLYCEXT | GLYC \Rightarrow GLYCEXT | 5.50 | 5.50 | 5.50 | 5.50 | 5.50 |

Table S6. Prediction results for the flux distribution of *Saccharomyces cerevisiae* ($\mu=0.40 \text{ h}^{-1}$) by Quadratic programming (QP), Linear programming (LP), the maximum entropy principle (MEP), and Linear Programming in Enzyme Control Flux (ECFLP)

| Genes | Reactions | Exp | QP | LP | MEP | ECFLP |
|---------|---|--------|--------|--------|--------|--------|
| ENO | P3G \rightleftharpoons PEP | 167.40 | 145.19 | 157.62 | 159.11 | 162.97 |
| SDH | SUC \rightleftharpoons FUM | 16.80 | 1.49 | 0.00 | 17.78 | 20.49 |
| TPI | DHAP \rightleftharpoons GA3P | 80.50 | 59.10 | 77.73 | 71.97 | 76.33 |
| MDH | MAL \rightleftharpoons OAAMIT | -4.10 | -3.66 | -6.80 | 7.43 | 9.18 |
| RKI | RU5P \rightleftharpoons R5P | 6.00 | 24.62 | 1.63 | 12.50 | 7.77 |
| TAL | S7P + GA3P \rightleftharpoons F6P + E4P | 5.30 | 23.49 | 0.00 | 11.46 | 6.69 |
| TKL | R5P + X5P \rightleftharpoons S7P + GA3P | 5.30 | 23.49 | 0.00 | 11.46 | 6.69 |
| TKI | X5P + E4P \rightleftharpoons GA3P + F6P | 3.80 | 22.36 | -1.63 | 10.41 | 5.61 |
| RPE | RU5P \rightleftharpoons X5P | 10.00 | 45.85 | -1.63 | 21.87 | 12.30 |
| TDH | GA3P \rightleftharpoons P3G | 171.00 | 147.45 | 160.88 | 161.20 | 165.14 |
| LSC | SUCCOA \rightleftharpoons SUC | 16.80 | 1.49 | 0.00 | 17.78 | 20.49 |
| FUM | FUM \rightleftharpoons MAL | 16.80 | 1.49 | 0.00 | 17.78 | 20.49 |
| FBA | F6P \rightleftharpoons DHAP + GA3P | 87.10 | 65.98 | 84.78 | 78.82 | 83.20 |
| ACS | ACE \Rightarrow ACCOACYT | 11.10 | 13.71 | 16.85 | 17.78 | 19.28 |
| GPD | DHAP \Rightarrow GP | 6.80 | 6.88 | 7.04 | 6.85 | 6.86 |
| ACEX | ACE \Rightarrow ACEX | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 |
| GND | P6G \Rightarrow CO ₂ + RU5P | 15.10 | 70.47 | 0.00 | 34.37 | 20.07 |
| HXK | GLC \Rightarrow G6P | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 |
| CO2EX | CO ₂ \Rightarrow CO ₂ EX | 191.60 | 197.98 | 127.72 | 209.93 | 204.14 |
| ZWF | G6P \Rightarrow G15L | 15.10 | 70.47 | 0.00 | 34.37 | 20.07 |
| BIOMASS | 3 R5P + 25 G6P + 6 PEP + 24 ACCOACYT + 10 OAA + 6 P3G + 3 ACCOAMIT + 18 PYRMIT + GP + 3 E4P + 11 AKG \Rightarrow 100 BIOMASS | 0.30 | 0.38 | 0.54 | 0.35 | 0.36 |
| PYC | CO ₂ + PYR \Rightarrow OAA | 31.40 | 13.05 | 18.21 | 17.64 | 18.90 |
| PGI | G6P \Rightarrow F6P | 77.90 | 20.13 | 86.41 | 56.95 | 70.90 |
| KGD | AKG \Rightarrow CO ₂ + SUCCOA | 16.80 | 1.49 | 0.00 | 17.78 | 20.49 |
| IDP | ICI \Rightarrow CO ₂ + AKG | 22.90 | 5.63 | 5.98 | 21.60 | 24.46 |
| CAT | ACCOACYT \Rightarrow ACCOAMIT | 0.60 | 4.69 | 3.81 | 9.44 | 10.61 |
| ALD | ACA \Rightarrow ACE | 16.10 | 18.71 | 21.85 | 22.78 | 24.28 |
| MAE | MAL \Rightarrow CO ₂ + PYRMIT | 20.90 | 5.16 | 6.80 | 10.35 | 11.31 |
| PYK | PEP \Rightarrow PYR | 164.60 | 142.94 | 154.36 | 157.03 | 160.80 |
| SOL | G15L \Rightarrow P6G | 15.10 | 70.47 | 0.00 | 34.37 | 20.07 |
| GPP | GP \Rightarrow GLYC | 6.50 | 6.50 | 6.50 | 6.50 | 6.50 |
| PDC | PYR \Rightarrow CO ₂ + ACA | 123.50 | 126.21 | 129.35 | 130.28 | 131.78 |
| PDB | PYRMIT \Rightarrow CO ₂ + ACCOAMIT | 23.70 | 2.06 | 3.81 | 13.20 | 14.93 |
| OAAT | OAA \Rightarrow OAAMIT | 27.10 | 9.29 | 12.78 | 14.17 | 15.28 |
| ADH | ACA \Rightarrow ETH | 107.50 | 107.50 | 107.50 | 107.50 | 107.50 |
| CIT | OAAMIT + ACCOAMIT \Rightarrow ICI | 22.90 | 5.63 | 5.98 | 21.60 | 24.46 |
| YEL006W | PYR \Rightarrow PYRMIT | 9.70 | 3.67 | 6.80 | 9.10 | 10.12 |
| GLCup | GLCEXT \Rightarrow GLC | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 |
| ETHEXT | ETH \Rightarrow ETHEXT | 107.50 | 107.50 | 107.50 | 107.50 | 107.50 |
| GLYCEXT | GLYC \Rightarrow GLYCEXT | 6.50 | 6.50 | 6.50 | 6.50 | 6.50 |