Supplementary Material (ESI) for Molecular BioSystems

Supplementary material

The kinetic reactions of the HOG network shown in Fig. 1 in the main text are listed below:

Upstream of Sho1 branch

$$msb2 \underset{b_{-1}}{\overset{b_0*(1\div V_{tot})^m}{\rightleftharpoons}} msb2_{active}$$

$$msb2_{active} + sho1 \underset{b_{-2}}{\overset{b_2}{\rightleftharpoons}} msb2_{active}sho1 \xrightarrow{a_2} msb2_{active} + sho1_{active}$$

$$sho1_{active} + pbs2 \underset{b_{-3}}{\overset{b_3}{\rightleftharpoons}} sho1_{active}\,pbs2$$

$$cdc42 + ste20 \underset{c_{-1}}{\overset{c_0*(1\div V_{tot})^{m2}}{\rightleftharpoons}} cdc42_{active}\,ste20$$

$$cdc42_{active}\,ste20 + ste11ste50 \underset{c_{-2}}{\overset{c_2}{\rightleftharpoons}} cdc42_{active}\,ste20ste11ste50 \xrightarrow{c_3} cdc42 + ste20 + ste11ppste50$$

$$sho1_{active}\,pbs2 + ste11ppste50 \xrightarrow{b_5} sho1_{active}\,pbs2ste11ppste50$$

$$sho1_{active}\,pbs2ste11ppste50 \xrightarrow{b_6} sho1_{active}\,pbs2\,ppste11ppste50$$

$$sho1_{active}\,pbs2\,ppste11ppste50 \xrightarrow{b_7} sho1_{active} + pbs2\,pp + ste11ppste50$$

$$ste11ppste50 \xrightarrow{b_8} ste11pp + ste50$$

$$ste11pp + MAPPP\_P \underset{d_7}{\overset{a_7}{\rightleftharpoons}} ste11ppMAPPP\_P \xrightarrow{p_7} ste11p + MAPPP\_P$$

$$ste11p + MAPPP\_P \underset{d_8}{\overset{a_8}{\rightleftharpoons}} ste11pMAPPP\_P \xrightarrow{p_8} ste11 + MAPPP\_P$$

$$sho1_{active} \xrightarrow[\left(hog1\,pp_{cyt}{}^{r} \div (q + hog1\,pp_{cyt}{}^{r})\right)]{ksho1hog1} sho1P$$

$$sho1P \xrightarrow{kd\_sho1} sho1$$

$$ste50 \xrightarrow[\left(hog1\,pp_{cyt}{}^{r2} \div (q2 + hog1pp_{cyt}{}^{r2})\right)]{kste50hog1} ste50P$$

$$ste50P \xrightarrow{kdste50} ste50$$

Upstream of Sln1 branch

$$s\ln 1 \xrightarrow{k_0(\pi_t \div \pi_t^0)^n} s\ln 1p$$

$$s\ln 1p + ypd1 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} s\ln 1pypd1 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} s\ln 1ypdp \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} s\ln 1 + ypdp$$

$$ssk1p \xrightarrow{k_7} ssk1$$

$$ssk1 + ssk2 \underset{k_{-8}}{\overset{k_8}{\rightleftharpoons}} ssk1ssk2 \xrightarrow{m_8} ssk1 + ssk2p$$

$$ssk2p + MAPKKK\_p \underset{k_{-9}}{\overset{k_9}{\rightleftharpoons}} ssk2pMAPKKK\_p \xrightarrow{m_9} ssk2 + MAPKKK\_p$$

$$ssk2p + pbs2 \underset{k_{-10}}{\overset{k_{10}}{\rightleftharpoons}} ssk2ppbs2 \xrightarrow{m_{10}} ssk2p + pbs2p$$

$$ssk2p + pbs2p \underset{k_{-11}}{\overset{k_{11}}{\rightleftharpoons}} ssk2ppbs2p \xrightarrow{m_{11}} ssk2p + pbs2pp$$

Dephosphorylation reactions of Pbs2pp and Hog1pp

$$hog1_{cyt} + pbs2pp \underset{d_{11}}{\overset{a_{11}}{\rightleftharpoons}} hog1_{cyt}pbs2pp \xrightarrow{p_{11}} hog1p_{cyt} + pbs2pp$$

$$hog1p_{cyt} + pbs2pp \underset{d_{12}}{\overset{a_{12}}{\rightleftharpoons}} hog1p_{cyt}pbs2pp \xrightarrow{p_{12}} hog1pp_{cyt} + pbs2pp$$

$$hog1pp_{cyt} \xrightarrow{k\_hog1pp\_nuc} hog1pp_{nuc}$$

$$hog1_{cyt} \underset{k_{trans2}}{\overset{k_{trans2}}{\rightleftharpoons}} hog1_{nuc}$$

$$pbs2pp + MAKP\_P \underset{d_9}{\overset{a_9}{\rightleftharpoons}} pbs2ppMAKP\_P \xrightarrow{p_9} pbs2p + MAKP\_P$$

$$pbs2p + MAKP\_P \underset{d_{10}}{\overset{a_{10}}{\rightleftharpoons}} pbs2pMAKP\_P \xrightarrow{p_{10}} pbs2 + MAKP\_P$$

$$hog1pp_{cyt} + PTP_{cyt} \underset{d_{13}}{\overset{a_{13}}{\rightleftharpoons}} hog1pp_{cyt}PTP_{cyt} \xrightarrow{p_{13}} hog1p_{cyt} + PTP_{cyt}$$

$$hog1p_{cyt} + PTP_{cyt} \underset{d_{14}}{\overset{a_{14}}{\rightleftharpoons}} hog1p_{cyt}PTP_{cyt} \xrightarrow{p_{14}} hog1_{cyt} + PTP_{cyt}$$

$$hog1pp_{nuc} + PTP_{nuc} \underset{d_{15}}{\overset{a_{15}}{\rightleftharpoons}} hog1pp_{nuc}PTP_{nuc} \xrightarrow{p_{15}} hog1p_{nuc} + PTP_{nuc}$$

$$hog1p_{nuc} + PTP_{nuc} \underset{d_{16}}{\overset{a_{16}}{\rightleftharpoons}} hog1p_{nuc}PTP_{nuc} \xrightarrow{p_{16}} hog1_{nuc} + PTP_{nuc}$$

Reactions for mRNAs and proteins

$$\xrightarrow[kts_i]{Hog1pp\_nuc} mRNA_{nuc,i}$$

$$mRNA_{nuc,i} \xrightarrow{kex_i} mRNA_{cyt,i}$$

$$mRNA_{cyt,i} \xrightarrow[\deg radation]{krd_i}$$

$$mRNA_{cyt,i} \xrightarrow{ktl_i} Protein_i$$

$$protein_i \xrightarrow[degradation]{kpd_i}$$

The above reactions can be translated into a set of ordinary differential equations (ODE):

ODEs for upstream part of the Sho1 branch

$$\frac{d}{dt}[sho1] = - b_1 * [sho1] + b_{-1} * [sho1_{active}] + k\_d\_sho1 * [sho1\_p]$$

$$\frac{d}{dt}[sho1\_active] = b_1 * [sho1] - b_{-1} * [sho1_{active}] - b_2 * [sho1\_active] * [pbs2] + b_{-2} * [sho1\_pbs2] + b_7 * [sho1\_pbs2pp\_ste11pp\_ste20] - k\_sho1\_hog1 * [sho1\_active] * [hog1pp] + b1 * [sho1];$$

$$\frac{d}{dt}[sho1\_p] = k\_sho1\_hog1 * [sho1\_active] * [hog1pp] - k\_d\_sho1 * [sho1\_p];$$

$$\frac{d}{dt}[ste20] = - b_4 * [sho1\_pbs2\_ste11] * [ste20] + b_{-4} * [sho1\_pbs2\_ste11\_ste20] + b_7 * [sho1\_pbs2pp\_ste11pp\_ste20];$$

$$\frac{d}{dt}[ste11] = - b_3 * [sho1\_pbs2] * [ste11] + b_{-3} * [sho1\_pbs2\_ste11] + p_8 * [ste11p\_MAPKKK\_p];$$

$$\frac{d}{dt}[sho1\_pbs2] = b_2 * [sho1\_active * pbs2] - b_{-2} * [sho1\_pbs2] - b_3 * [sho1\_pbs2] * [ste11] + b_{-3} * [sho1\_pbs2\_ste11];$$

$$\frac{d}{dt}[sho1\_pbs2\_ste11] = b_3 * [sho1\_pbs2] * [ste11] - b_{-3} * [sho1\_pbs2\_ste11] - b_4 * [sho1\_pbs2\_ste11] * [ste20] + b_{-4} * [sho1\_pbs2\_ste11\_ste20];$$

$$\frac{d}{dt}[sho1\_pbs2\_ste11\_ste20] = b_4 * [sho1\_pbs2\_ste11] * [ste20] - b_{-4} * [sho1\_pbs2\_ste11\_ste20] - b_5 * [sho1\_pbs2\_ste11\_ste20] ;$$

$$\frac{d}{dt}[sho1\_pbs2\_ste11pp\_ste20] = b_5 * [sho1\_pbs2\_ste11\_ste20] - b_6 * [sho1\_pbs2\_ste11pp\_ste20];$$

$$\frac{d}{dt}[sho1\_pbs2pp\_ste11pp\_ste20] = b_6 * [sho1\_pbs2\_ste11pp\_ste20] - b_7 * [sho1\_pbs2pp\_ste11pp\_ste20];$$

$$\frac{d}{dt}[ste11p] = p_7 * [ste11pp\_MAPKKK\_p] - a_8 * [ste11p] * [m\_p\_tot - ste11p\_MAPKKK\_p - ste11pp\_MAPKKK\_p] + d_8 * [ste11p\_MAPKKK\_p];$$

$$\frac{d}{dt}[ste11pp] = b_7 * [sho1\_pbs2pp\_ste11pp\_ste20] - a_7 * [ste11pp] * [m\_p\_tot - ste11p\_MAPKKK\_p - ste11pp\_MAPKKK\_p] + d7 * [ste11pp\_MAPKKK\_p];$$

$$\frac{d}{dt}[ste11pp\_MAPKKK\_p] = a7 * [ste11pp] * [m\_p\_tot - ste11p\_MAPKKK\_p - ste11pp\_MAPKKK\_p] - (d_7 + p_7) * [ste11pp\_MAPKKK\_p];$$

$$\frac{d}{dt}[ste11p\_MAPKKK\_p] = a_8 * [ste11p] * [m\_p\_tot - ste11p\_MAPKKK\_p - ste11pp\_MAPKKK\_p] - (d_8 + p_8) * [ste11p\_MAPKKK\_p];$$

ODEs for upstream part of the Sln1 branch

$$\frac{d}{dt}[sln1] = k_3 * [sln1\_ypd1p] - k_{-3} * [sln1] * [ypd1p] - k * [sln1] - [sln1] * v_r - [sln1] * \mu$$

$$\frac{d}{dt}[sln1p] = -k_1 * [sln1p] * [ypd1] + k_{-1} * [sln1p\_ypd1] + k * [sln1] - [sln1p] * v_r - [sln1p] * \mu$$

$$\frac{d}{dt}[sln1p\_ypd1] = k_1 * [sln1p] * [ypd1] - (k_{-1} + k_2) * [sln1p\_ypd1] + k_{-2} * [sln1\_ypd1p] - [sln1p\_ypd1] * v_r - [sln1p\_ypd1] * \mu$$

$$\frac{d}{dt}[sln1\_ypd1p] = k_2 * sln1p\_ypd1 - (k_{-2} + k_3) * sln1\_ypd1p + k_{-3} * [sln1] * [ypd1p] - [sln1\_ypd1p] * v_r - [sln1p\_ypd1p] * \mu$$

$$\frac{d}{dt}[ypd1p] = k_3 * [sln1\_ypd1p] - k_{-3} * [sln1] * [ypd1p] - k_4 * [ypd1p] * [ssk1] + k_{-4} * [ypd1p\_ssk1] - [ypd1p] * v_r - [ypd1p] * \mu$$

$$\frac{d}{dt}[ypd1] = -k_1 * [sln1p] * [ypd1] + k_{-1} * [sln1p\_ypd1] + k_6 * [ypd1\_ssk1p] - [ypd1] * v_r - [ypd1] * \mu$$

$$\frac{d}{dt}[ypd1p\_ssk1] = k_4 * [ypd1p] * [ssk1] - (k_{-4} + k_5) * [ypd1p\_ssk1] + k_{-5} * [ypd1\_ssk1p] - [ypd1p\_ssk1] * \mu - [ypd1p\_ssk1] * v_r$$

$$\frac{d}{dt}[ypd1\_ssk1p] = k_5 * [ypd1p\_ssk1] - (k_{-5} + k_6) * [ypd1\_ssk1p] - [ypd1\_ssk1p] * v_r - [ypd1\_ssk1p] * \mu$$

$$\frac{d}{dt}[ssk1p] = k_6 * [ypd1\_ssk1p] - k_7 * [ssk1p] - [ssk1p] * v_r - [ssk1p] * \mu$$

$$\frac{d}{dt}[ssk1] = - k_4 * [ypd1p] * [ssk1] + k_{-4} * [ypd1p\_ssk1] + k_7 * [ssk1p] - k_8 * [ssk1] * [ssk2] + (k_{-8} + m_8) * [ssk1\_ssk2] - [ssk1] * v_r - [ssk1] * \mu$$

Supplementary Material (ESI) for Molecular BioSystems
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$$\frac{d}{dt}[ssk2] = - k_8 * [ssk1] * [ssk2] + k_{-8} * [ssk1\_ssk2] + m_9 * [ssk2p\_pase] - [ssk2] * v_r - [ssk2] * \mu$$

$$\frac{d}{dt}[ssk2p] = m_8 * [ssk1\_ssk2] - k_9 * [ssk2p] * [pase\_total - ssk2p\_pase] + k_{-9} * [ssk2p\_pase]$$
$$- k_{10} * [ssk2p] * [pbs2] + (k_{-10} + m_{10}) * [ssk2p\_pbs2] - k_{11} * [ssk2p] * [pbs2p]$$
$$+ (k_{-11} + m_{11}) * [ssk2p\_pbs2p] - [ssk2p] * v_r - [ssk2p] * \mu$$

$$\frac{d}{dt}[ssk1\_ssk2] = k_8 * [ssk1] * [ssk2] - (k_{-8} + m_8) * [ssk1\_ssk2] - [ssk1\_ssk2] * v_r - [ssk1\_ssk2] * \mu$$

$$\frac{d}{dt}[ssk2p\_pase] = k_9 * [ssk2p] * [pase\_total - ssk2p\_pase] - (k_{-9} + m_9) *$$
$$[ssk2p\_pase] - [ssk2p\_pase] * v_r - [ssk2p\_pase] * \mu$$

$$\frac{d}{dt}[ssk2p\_pbs2] = k_{10} * [ssk2p] * [pbs2] - (k_{-10} + m_{10}) * [ssk2p\_pbs2] - [ssk2p\_pbs2] * v_r - [ssk2p\_pbs2] * \mu$$

$$\frac{d}{dt}[ssk2p\_pbs2p] = k_{11} * [ssk2p] * [pbs2p] - (k_{-11} + m_{11}) * [ssk2p\_pbs2p] - [ssk2p\_pbs2p] * v_r - [ssk2p\_pbs2p] * \mu$$

ODEs for MAPKK Pbs2 and MAPK Hog1 phosphorylation and dephosphorylation:

$$\frac{d}{dt}[pbs2] = -k_{10} * [ssk2p] * [pbs2] + k_{-10} * [ssk2p\_pbs2] + p_{10} * [pbs2p\_E] - b_2 * [sho1\_active] *$$
$$[pbs2] + b_{-2} * [sho1\_pbs2] - [pbs2] * v_r - [pbs2] * \mu$$

$$\frac{d}{dt}[pbs2p] = m_{10} * [ssk2p\_pbs2] - k_{11} * [ssk2p] * [pbs2p] + k_{-11} * [ssk2p\_pbs2p] + p_9 * [pbs2pp\_E]$$
$$- a_{10} * [pbs2p] * [E\_total - pbs2p\_E - pbs2pp\_E] + d_{10} * [pbs2p\_E] - [pbs2p] * v_r - [pbs2p] * \mu$$

$$\frac{d}{dt}[pbs2pp] = m_{11} * [ssk2p\_pbs2p] - a_9 * [pbs2pp] * [E\_total - pbs2p\_E - pbs2pp\_E]$$
$$+ d_9 * [pbs2pp\_E] - a_{11} * [hog1\_cyt] * [pbs2pp] + (d_{11} + p_{11}) * [hog1\_cyt\_pbs2pp]$$
$$- a_{12} * [hog1p\_cyt] * [pbs2pp] + (d_{12} + p_{12}) * [hog1p\_cyt\_pbs2pp]$$
$$+ b_9 * [sho1\_pbs2pp\_ste11pp\_ste20] - [pbs2pp] * v_r - [pbs2pp] * \mu$$

$$\frac{d}{dt}[pbs2pp\_E] = a_9 * [pbs2pp] * [E\_total - pbs2p\_E - pbs2pp\_E] - (d_9 + p_9) * [pbs2pp\_E]$$
$$- [pbs2pp\_E] * v_r - [pbs2pp\_E] * \mu$$

$$\frac{d}{dt}[pbs2p\_E] = a_{10} * [pbs2p] * [E\_total - pbs2p\_E - pbs2pp\_E] - (d_{10} + p_{10}) * [pbs2p\_E]$$
$$- [pbs2p\_E] * v_r - [pbs2p\_E] * \mu$$

$$\frac{d}{dt}[hog1\_cyt] = -a_{11} * [hog1\_cyt] * [pbs2pp] + d_{11} * [hog1\_cyt\_pbs2pp]$$
$$+ p_{14} * [hog1p\_cyt\_ptp\_cyt] - (k\_hog1\_trans2) * [hog1\_cyt]$$
$$+ (k\_hog1\_trans1) * [hog1\_nuc] * (v\_nuc/v\_cyt) - [hog1\_cyt] * v_r - [hog1\_cyt] * \mu$$

$$\frac{d}{dt}[hog1p\_cyt] = p_{11} * [hog1\_cyt\_pbs2pp] - a_{12} * [hog1p\_cyt]*[pbs2pp] + p_{13} * [hog1pp\_cyt\_ptp\_cyt] - a_{14} * [hog1p\_cyt] * [ptp\_cyt\_total - hog1p\_cyt\_ptp\_cyt-hog1pp\_cyt\_ptp\_cyt] + d_{12} * [hog1p\_cyt\_pbs2pp] + d_{14} * [hog1p\_cyt\_ptp\_cyt] - [hog1p\_cyt] * v_r - [hog1p\_cyt] * \mu$$

$$\frac{d}{dt}[hog1pp\_cyt] = p_{12} * [hog1p\_cyt\_pbs2pp] - a_{13} * [hog1pp\_cyt]*[ptp\_cyt\_total - hog1p\_cyt\_ptp\_cyt - hog1pp\_cyt\_ptp\_cyt] + d_{13} * [hog1pp\_cyt\_ptp\_cyt] - [k\_hog1pp\_trans] * [hog1pp\_cyt] - [hog1pp\_cyt] * v_r - [hog1pp\_cyt] * \mu$$

$$\frac{d}{dt}[hog1pp\_nuc] = (k\_hog1pp\_trans) * [hog1pp\_cyt] * (v\_cyt/v\_nuc) - a_{15} * [hog1pp\_nuc] * [p\_n\_total - hog1p\_ptp\_nuc - hog1pp\_ptp\_nuc] + d_{15} * [hog1pp\_ptp\_nuc];$$

$$\frac{d}{dt}[hog1p\_nuc] = p_{15} * [hog1pp\_ptp\_nuc] - a_{16} * [hog1p\_nuc] * [p\_n\_total - hog1p\_ptp\_nuc - hog1pp\_ptp\_nuc] + d_{16} * [hog1p\_ptp\_nuc];$$

$$\frac{d}{dt}[hog1\_nuc] = p_{16} * [hog1p\_ptp\_nuc] + (k\_hog1\_trans2) * [hog1\_cyt] * (v\_cyt/v\_nuc) - (k\_hog1\_trans1) * [hog1\_nuc];$$

$$\frac{d}{dt}[hog1\_cyt\_pbs2pp] = a_{11} * [hog1\_cyt] * [pbs2pp] - (d_{11}+p_{11}) * [hog1\_cyt\_pbs2pp] - [hog1\_cyt\_pbs2pp] * v_r - [hog1\_cyt\_pbs2pp] * \mu$$

$$\frac{d}{dt}[hog1p\_cyt\_pbs2pp] = a_{12} * [hog1p\_cyt] * [pbs2pp] - (d_{12}+p_{12}) * [hog1p\_cyt\_pbs2pp] - [hog1p\_cyt\_pbs2pp] * v_r - [hog1p\_cyt\_pbs2pp] * \mu$$

$$\frac{d}{dt}[hog1pp\_cyt\_ptp\_cyt] = a_{13} * [hog1pp\_cyt] * [ptp\_cyt\_total - hog1p\_cyt\_ptp\_cyt -hog1pp\_cyt\_ptp\_cyt] - (d_{13}+p_{13}) * [hog1pp\_cyt\_ptp\_cyt] - [hog1pp\_cyt\_ptp\_cyt] * v_r - [hog1pp\_cyt\_ptp\_cyt] * \mu$$

$$\frac{d}{dt}[hog1p\_cyt\_ptp\_cyt] = a_{14} * [hog1p\_cyt] * [ptp\_cyt\_total - hog1p\_cyt\_ptp\_cyt -hog1pp\_cyt\_ptp\_cyt] - (d_{14}+p_{14}) * [hog1p\_cyt\_ptp\_cyt] - [hog1p\_cyt\_ptp\_cyt] * v_r - [hog1p\_cyt\_ptp\_cyt] * \mu$$

$$\frac{d}{dt}[hog1pp\_ptp\_nuc] = a_{15} * [hog1pp\_nuc] * [p\_n\_total - hog1p\_ptp\_nuc - hog1pp\_ptp\_nuc] - (d_{15}+p_{15}) * [hog1pp\_ptp\_nuc];$$

$$\frac{d}{dt}[hog1p\_ptp\_nuc] = a_{16} * [hog1p\_nuc] * [p\_n\_total - hog1p\_ptp\_nuc - hog1pp\_ptp\_nuc] - (d_{16}+p_{16}) * [hog1p\_ptp\_nuc];$$

Supplementary Material (ESI) for Molecular BioSystems

ODEs for mRNAs and proteins induction:

$$\frac{d}{dt}[mRNA\_nuc_i] = kts_i * [hog1pp\_nuc] - kex_i * [mRNA\_nuc_i]$$
$$\frac{d}{dt}[mRNA\_cyt_i] = kex_i * [mRNA\_nuc_i] * (v\_nuc/v\_cyt) - krd_i * [mRNA\_cyt_i] - [mRNA\_cyt_i] * v_r$$
$$\frac{d}{dt}[protein_i] = ktl_i * [mRNA\_cyt_i] - kpd_i * [protein_i] - [protein_i] * v_r;$$

(i = 1 for genes responsible for glycerol production, i= 2 for genes responsible for phosphatases and i=3 for genes PYK and PDC1)

ODEs for metabolic reactions:

v2=h2/(1+((h21/(ATP)) * (1+(ADP/h22))) +
(h23/(gluc))+((h21/(ATP)) * (h23/(gluc)) * (1+(ADP/h22))));
v3=(protein1/protein10)^w1 * h3 * ATP * G6P/((h31+ATP) * (h32+(G6P)));
v4=h4 * (FBP-(GAP * DHAP/Keq4))/(kFBP4+FBP+kDHAP4 * GAP/(Keq4 * vbf4)+
kGAP4/(Keq4 * vbf4)+FBP * GAP/(KIGAP4)+GAP * DHAP/(Keq4 * vbf4));
v5=h5 * (DHAP-GAP/Keq5)/(KDHAP5 * (1+GAP/KGAP5)+DHAP);
v6=h6 * GAP * NAD * ADP;
v7=h7 * ADP * Pyr * NAD/(KNAD7 * Pyr+KPyr7 * NAD+KI7 * NADH);
v8=h8 * Pyr * NAD/((k81+Pyr) * (k82+NAD));
v9=h9 * Pyr * ATP/((KPyr9+Pyr) * (KATP9+ATP));
v10=h10 * G6P * ATP/((KG6P10+G6P) * (KATP10+ATP));
v11=h11 * (protein1/protein10)^w4 * (DHAP * NADH-G3P * NAD/Keq11)/
(1+DHAP/kd11+NADH/kn11+G3P * NAD/kh11);
v12=h12 * G3P * (protein1/protein10)^w5;
v13= h130 * (glyc-glycex); h130 = h13*KIhog/(KIhog + *Hog*1*pp*);
v14=h14 * NADH * ADP/(KADP14+ADP);
v15=h15 * NAD;
v16=h16 * ATP/(KATP16+ATP);
r_{PDC} = ((protein3/protein30)^bm) * r_{PADmax} * (Pyr^n9)/(ka9 + kpyr9 + kpyr9 * Pyr + Pyr^n9);
r_{ADH} = (vfw * ALD * NADH/(kp * kiq) - vnw * (EtOH * NAD)/(kia * kb))/(1+EtOH/kia
+ ka * NAD/(kia * kb) + kq * ALD/(kp * kiq) + NADH/kiq + EtOH * NAD/(kia * kb)
+ kq * EtOH * ALD/(kia * kp * kiq) + ka * NAD * NADH/(kia * kb * kiq)
+ ALD * NADH/(kp * kiq) + EtOH * NAD * ALD/(kia * kb * kip)
+ NAD * ALD * NADH/(kia * kb * kiq));
r_{Aldh} = (protein1/protein10)^w2 * $r_{Aldhmax}$ * ALD/(kAlde11 + ALD + ALD^2/kIAlde11);

Supplementary Material (ESI) for Molecular BioSystems
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$$\frac{d}{dt}[\text{gluc\_ext}]=v1*x/\rho;$$

$$\frac{d}{dt}[\text{gluc}]=v1-v2-\text{gluc}*v_r-\text{gluc}*\mu;$$

$$\frac{d}{dt}[\text{G6P}]=v2-v3-v10-\text{G6P}*v_r-\text{G6P}*\mu;$$

$$\frac{d}{dt}[\text{FBP}]=v3-v4-\text{FBP}*v_r-\text{FBP}*\mu;$$

$$\frac{d}{dt}[\text{GAP}]=v4+v5-v6-\text{GAP}*v_r-\text{GAP}*\mu;$$

$$\frac{d}{dt}[\text{DHAP}]=v4-v5-v11-\text{DHAP}*v_r-\text{DHAP}*\mu;$$

$$\frac{d}{dt}[\text{Pyr}]=v6-v7-v8-v9-Y_{p/x}\mu x-\text{Pyr}*v_r-\text{Pyr}*\mu;$$

$$\frac{d}{dt}[\text{G3P}]=v11-v12-\text{G3P}*v_r-\text{G3P}*\mu;$$

$$\frac{d}{dt}[\text{glyc}]=v12-v13-\text{glyc}*v_r-\text{glyc}*\mu;$$

$$\frac{d}{dt}[\text{glycex}]=(v13*x/\rho);$$

$$\frac{d}{dt}[\text{NADH}]=v6+4*v7-v8-v11-v14+v15-\text{NADH}*v_r-\text{NADH}*\mu;$$

$$\frac{d}{dt}[\text{NAD}]=-v6-4*v7+v8+v11+v14-v15-\text{NAD}*v_r-\text{NAD}*\mu;$$

$$\frac{d}{dt}[\text{ATP}]=-v2-v3+2*v6+v7-v9-v10+3*v14-v16-\text{ATP}*v_r-\text{ATP}*\mu;$$

$$\frac{d}{dt}[\text{ADP}]=v2+v3-2*v6-v7+v9+v10-3*v14+v16-\text{ADP}*v_r-\text{ADP}*\mu;$$

$$\frac{dE_{ext}}{dt}=(V_{total})^{w_6}\left(K_{Etoh1}E_{int}-K_{Etoh2}*E_{ext}*k_{1glu}/(k_{1glu}+Glu_{ext})\right)\frac{\rho}{X}$$

$$\frac{dALD}{dt}=r_{PDC}-r_{ADH}-r_{Aldh}*KIG2/(KIG2+\text{gluc\_ext})-ALD*\mu-ALD*v_r$$

$$\frac{dE_{int}}{dt}=r_{ADH}-K_{Etoh1}*E_{int}+K_{Etoh2}*E_{ext}*k_{1glu}/(k_{1glu}+Glu_{ext})-E_{int}*v_r-E_{int}*\mu$$

$$\frac{dX}{dt}=\left(\mu_1+\mu_2\right)X$$

where ,

$$\mu_1=\mu_{1\max}\frac{pyr}{k_{pyr}+pyr} \text{ and } \mu_2=\mu_{2\max}\frac{Acet}{k_{Acet}+Acet}$$

Supplementary Material (ESI) for Molecular BioSystems

Equations for external and internal osmotic pressure, turgor pressure and volume regulation (Klipp *et al* 2005)

$$\pi_e = \pi_e^f (1 - \exp[-t/\lambda_m]) + \pi_e^0 \cdot \exp[-t/\lambda_m]$$

$$\pi_t = \pi_t^0 \cdot \left(1 - \frac{\mathrm{V}_{os}^0 - \mathrm{V}_{os}}{\mathrm{V}_{os}^0 - \mathrm{V}^{\pi=0}}\right)$$

$$\frac{d}{dt}\pi_i = \pi_i \cdot \frac{dc}{c \cdot dt}$$

$$\frac{d}{dt}c = v_{12} - v_{13} - c \cdot \mathrm{V}_r$$

$$\frac{d}{dt}\mathrm{V}_{os} = kp \cdot (\pi_i - \pi_e + \pi_t)$$

$$\frac{d}{dt}\mathrm{V}_{total} = \frac{d}{dt}\mathrm{V}_{cyt} = \frac{d}{dt}\mathrm{V}_{os}$$

$$\mathrm{V}_{os} = \mathrm{V}_{total} - \mathrm{V}_b$$

$$\mathrm{V}_r = \frac{d\mathrm{V}_{os}}{\mathrm{V}_{os} \cdot dt}$$

Supplementary Material (ESI) for Molecular BioSystems

The present model includes 188 parameters which are listed in Table S1 below:

Table S1. Parameters.

Parameters from (Parmar *et al* 2009)

$k_1 = 27\ \mu M\ s^{-1}$	$k_{-1} = 31.5\ s^{-1}$	$k_2 = 34.7\ s^{-1}$
$k_{-2} = 220\ s^{-1}$	$k_3 = 5680\ s^{-1}$	$k_{-3} = 787\ \mu M\ s^{-1}$
$k_4 = 5674\ \mu M\ s^{-1}$	$k_{-4} = 4.8\ s^{-1}$	$k_5 = 150\ s^{-1}$
$k_7 = 0.4079$	$v0 = 1.296\ mM\ s^{-1}$	$h_2 = 1.777\ mM\ s^{-1}$
$h3 = 0.895\ mM\ s^{-1}$	$h4 = 1.8764e6\ mM\ s^{-1}$	$h_5 = 190\ mM\ s^{-1}$
$h_6 = 45.127\ mM^{-2}\ s^{-1}$	$h_7 = 639.137\ s^{-1}$	$h_8 = 5.6425\ mM\ s^{-1}$
$h_9 = 0.8090\ mM\ s^{-1}$	$h_{10} = 1.9377\ mM\ s^{-1}$	$h_{11} = 7.1507\ (mM\ s)^{-1}$
$h_{12} = .0162\ s^{-1}$	$h_{130} = 0.005\ s^{-1}$	$h_{14} = 384.024\ s^{-1}$
$h_{15 =}\ 1.1235\ s^{-1}$	$h_{16} = 99.887\ mM\ s^{-1}$	$h_{21} = 0.2\ mM$
$h_{31} = 0.01\ mM$	$h_{22} = 1.2\ mM$	$h_{32}=0.012\ mM$
$h_{23}=.2\ mM$	$K_{eq4} = .81\ mM$	kFBP4=0.054 mM
kDHAP4 = 2.0 mM	kGAP4 = 2.0 mM	$vbf4 = 5\ mM^{-1}$
KIGAP4 = 10 mM	Keq5 = 0.045 mM	KDHAP5 = 0.38 mM
KGAP5 = 0.064 mM	KPyr7 = 70 mM	KNAD7 = 160 mM
KI7=20 mM	$k_{81} = 1.2\ mM$	$k_{82} = .6\ mM$
KPyr9 = 0.92 mM	KATP9 = 13.2 mM	KG6P10 = 2.7 mM
KATP10 = 0.4 mM	kd11 = .37 mM	kn11 = 0.6 mM
kh11 = .2 mM	Keq11 = 37	kx = 6.67e1
n13 = 4	KADP14 = 0.42 mM	KATP16 = 5 mM;
$kts2 = 0.00045\ s^{-1}$	$kex2 = 4.9129e\text{-}5\ s^{-1}$	$krd2 = 0.0337\ s^{-1}$
$ktl2 = 0.00125\ s^{-1}$	$kpd2 =1.4e\text{-}4\ s^{-1}$	$kts1 = 0.0005\ s^{-1}$
$kex1 = 0.0037\ s^{-1}$	$krd1 = 3.4165\ s^{-1}$	$ktl1 = 0.0205\ s^{-1}$

Supplementary Material (ESI) for Molecular BioSystems

kpd1 = 0.000219 s^{-1}

a7 = 12.3228 $\mu M^{-1}s^{-1}$	a8 = 16.4983 $\mu M^{-1}s^{-1}$	a9 = 20 $\mu M^{-1}s^{-1}$
a10 = 20 $\mu M^{-1}s^{-1}$	a11 = 5.3950 $\mu M^{-1}s^{-1}$	a12 = 5 $\mu M^{-1}s^{-1}$
a13 =5.3730 $\mu M^{-1}s^{-1}$	a14 = 3.2143 $\mu M^{-1}s^{-1}$	a15 = 8.3071 $\mu M^{-1}s^{-1}$
a16 =17.3685 $\mu M^{-1}s^{-1}$	d7 = 8.2082 s^{-1}	d8 = 4.2664 s^{-1}
d9 = 0.5000 s^{-1}	d10 = 0.1000 s^{-1}	d11 = 4.5230 s^{-1}
d12 = 3.1302 s^{-1}	d13 =2.7054 s^{-1}	d14 = 4.1749 s^{-1}
d15 =1.1399 s^{-1}	d16 = 0.6163 s^{-1}	p7 = 2.3822 s^{-1}
p8 = 1.6055 s^{-1}	p9 = 0.1145 s^{-1}	p10 = 0.5337 s^{-1}
p11 = 0.8843 s^{-1}	p12 = 4.8499 s^{-1}	p13 =4.3871 s^{-1}
p14 =3.6934 s^{-1}	p15 =5 s^{-1}	p16 =1 s^{-1}
b0 = 6.4749e-005 s^{-1}	b_{-1} = 0.9294 s^{-1}	b_2 = 0.2253 $\mu M\ s^{-1}$
b_{-2} = 0.9316 $\mu M\ s^{-1}$	a_2 = 1.2466 s^{-1}	b3 = 21.9422 $\mu M\ s^{-1}$
b3m = 6.1490 s^{-1}	b4 = 19.9717 $\mu M\ s^{-1}$	b4m = 1.0000e-010 s^{-1}
b5 = 9.9375 s^{-1}	b6 = 9.9990 s^{-1}	b7 = 10.0065 s^{-1}
b8 = 0.0228	c0 = 0.8660 s^{-1}	c_{-1} = 1.0019 s^{-1}
c_2 =7.0577 $\mu M\ s^{-1}$	c_{-2} = 5.4609	c_3 = 5.2990 s^{-1}
ksho1hog1 = 0.0054 $\mu M\ s^{-1}$	kdsho1 = 7.9829e-006 s^{-1}	kste50hog1 = 1.0296 $\mu M\ s^{-1}$
m = 26.7	q = 11	r = 1
r_2 = 2	q_2 = 80	ms = 16.0638
kdste50 = 2.4152e-004 s^{-1}	k_6 = 1.5936	k_hog1_trans1 = 0.11 s^{-1}
k_hog1_trans2 = 0.091 s^{-1}		

Parameters obtained from Hynne *et al.* (2001)

Vm = 16.9160 mM s^{-1}	k2glc = 1.1034 mM	k21G6P = 1.2 mM
k211G6P = 7.2 mM	kIAlde11 = 0.19 mM^2	kAlde11 = 0.10

mM K2ATP = 0.0880 mM	K2Glc = 0.0139 mM	ka = 17 mM
kpyr9 = 4.93 mM	vfw = 700 mM s^{-1}	rAldhmax = 0.98 mM s^{-1}
vnw = 10 mM s^{-1}	rPADmax = 2.62 mM s^{-1}	kb = 0.17 mM
kp = 0.11 mM	kq = 1.11 mM	kia = 90
kib = 2.92 mM	kip = 10.5 mM	kiq = 1.1 mM

Parameters fitted to experimental data

kn = 0.6985	cm = 311	an = 0.2735
dm = 1.2	cnn = 149	w4 = 0.4;
w5 = 0.4;	am = 0.2688	bm = 0.0428
w2 = 0.0483	gn = 14	kts3 = 0.0032
kex3 = 0.0251	krd3 = 2.8063	ktl3 = 1.7186e-007
kpd3 = 2.6962e-004	bn = 2.3816	e1 = 3.4743
KIG2 = 0.0813 mM	kTCA 0.373 mM	w1 = 0.01
kETH1= 0.4 mM	kETH2 = 0.2 mM	kACET = 350 mM
kTCAC = 0.04 mM	kpy = 40 mM	KIhog = .001;
phog = 0.3;	KIhog = 0.12;	phog = 2;
w3 = 4.6;	kn = 0.8;	

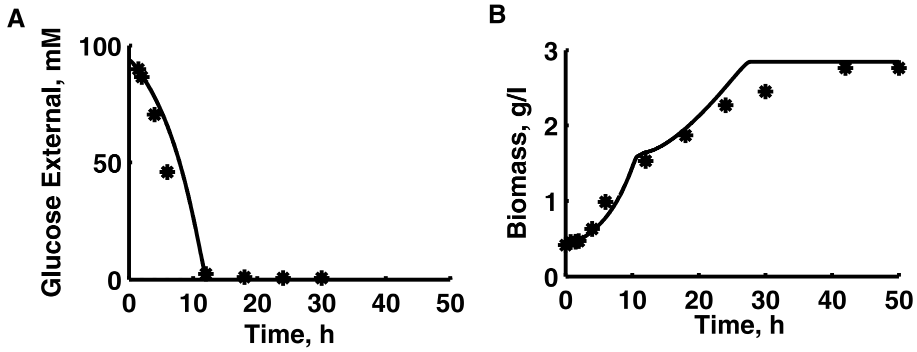

Figure S1: Comparison of the model simulation with experimental data for a wild-type strain for 0.8 M NaCl concentration depicted in (A) glucose and (B) biomass. Model simulations are depicted by solid line and experimental data are represented by symbol.

As discussed in the method section in the main text, we used the metric *I* for biomass and activated Hog1 for global sensitivity analysis. For each case, based on the K-S value (see main text), we ranked 188 parameters which are shown in Table S2 and Table S3 for biomass and activated Hog1, respectively.

Table S2. Parameters ranking based on the *I* metric used for biomass.

rank	0.5 M NaCl	1 M NaCl
1	'am Pyk regulation'	'w3 Glucose ihnibition'
2	'kpd3 Pyk regulation '	'kpd3 Pyk regulation '
3	'h11 DHAP --> G3P '	'w5 Gpd1 regulation '
4	'd13 <-- hog1pp_cyt_ptp_cyt '	'kip ALD --> Ethanol'
5	'K2Glc GLU --> G6P '	'bn Specific growth Inhibition'
6	'b1m msb2a --> msb2'	'w4 Gpd1 regulation '
7	'kn glycerol --> DHA '	'am Pyk regulation'
8	'w4 Gpd1 regulation '	'km8 <-- ssk1_ssk2 '
9	'w2 ALD6 regulation'	'kia ALD --> Ethanol'
10	'cm glycerol --> DHA '	'k7 ssk1p --> '
11	'lemda2 Glycerol --> DHA'	'm11 ssk2p_pbs2p -->'
12	'd9 <-- pbs2pp_E '	'a13 hog1pp_cyt + ptp -->'
13	'km1 <-- sln1p_ypd1'	'a11 hog1_cyt + pbs2pp --> '
14	'h32 G6P --> FBP '	'Vm max glucose uptake'
15	'km11 <-- ssk2p_pbs2p'	'kpd2 PTP regulation '
16	'a11 hog1_cyt + pbs2pp --> '	'k10 ssk2p + pbs2 --> '
17	'kETH1 Ethanol export'	'bm Pdc1 regulation'
18	'k211G6P Glucose uptake'	'km11 <-- ssk2p_pbs2p'
19	'krd1 Gpd1 regulation '	'an DHA --> DHAP '
20	'bm Pdc1 regulation'	'a7 ste11pp + MAPKKK_p --> ste11pp_MAPKKK_p'
21	'Keq5 DHAP --> GAP '	'p9 pbs2pp_E -->'
22	'd11 <-- hog1_cyt_pbs2pp '	'ka9 PYR --> ALD '
23	'd16 <-- hog1p_ptp_nuc '	'c1m cdc42ste20 -->'
24	'a13 hog1pp_cyt + ptp -->'	'kts2 PTP regulation '
25	'kex2 PTP regulation '	'c2m cdc42ste20ste11ste50 -->'
26	'h130 glycerol transport '	'vfw ALD --> Ethanol '
27	'kFBP4 FBP --> GAP + DHAP '	'w2 ALD6 regulation'
28	'kpd2 PTP regulation '	'KNAD7 PYR --> CO2 '
29	'KPyr9 PYR --> BIOM'	'kTCA Acetate to TCA cycle'
30	'r sho1 deactivation'	'ktl1 Gpd1 regulation '
31	'e1 Ethanol uptake regulation'	'vbf4 FBP --> GAP + DHAP '
32	'a2 msb2asho1 --> msb2a + sho1_active'	'kste50hog1 ste50 + hog1pp --> '
33	'KATP9 PYR --> BIOM'	'h32 G6P --> FBP '
34	'h15 NAD --> NADH '	'lemda2 Glycerol --> DHA'

35	'b2 msb2a + sho1 --> msb2asho1'	'h130 glycerol transport '
36	'b0 msb2 --> msb2a'	'b2m msb2a + sho1 <-- msb2asho1'
37	'q2 ste50 phosphorylation'	'h7 PYR --> CO2 '
38	'KIG1 Glucose inhibition to ethano upatke'	'rAldhmax ALD to Acetate'
39	'an DHA --> DHAP '	'a12 hog1p_cyt + pbs2pp --> '
40	'K2ATP GLU --> G6P '	'K2Glc GLU --> G6P '
41	'kpyr9 PYR --> ALD '	'b7 sho1apbs2ppste11ppste50 dissociation'
42	'd14 <-- hog1p_cyt_ptp_cyt '	'm msb2 activation'
43	'n Sln1 activation'	'h3 G6P --> FBP '
44	'kp ALD --> Ethanol'	'kTCAC Acetate to TCA cycle'
45	'kACET Acetate --> BIOM '	'km3 sln1 + ypd1p --> '
46	'b2m msb2a + sho1 <-- msb2asho1'	'k2glc Glucose uptake'
47	'kd11 DHAP --> G3P '	'h15 NAD --> NADH '
48	'm10 ssk2p_pbs2 --> '	'q2 ste50 phosphorylation'
49	'km8 <-- ssk1_ssk2 '	'k21G6P Glucose uptake'
50	'k1 sln1p + ypd1 -->'	'p7 ste11pp_MAPKKK_p --> '
51	'c0 Cdc42 + Ste20 -->'	'a9 pbs2pp + E_total --> '
52	'kq ALD --> Ethanol'	'km9 <-- ssk2p_pase'
53	'b3 sho1a + pbs2 --> '	'm10 ssk2p_pbs2 --> '
54	'kTCAC Acetate to TCA cycle'	'KATP10 G6P --> FBP '
55	'a10 pbs2p + E_total --> '	'kp ALD --> Ethanol'
56	'd12 <-- hog1p_cyt_pbs2pp'	'krd1 Gpd1 regulation '
57	'km3 sln1 + ypd1p --> '	'k1 sln1p + ypd1 -->'
58	'p13 hog1pp_cyt_ptp_cyt --> '	'p10 pbs2p_E --> '
59	'kdsho1 sho1p --> sho1'	'km2 <-- sln1_ypd1p'
60	'k2 sln1p_ypd1 -->'	'KATP16 ATP --> ADP '
61	'b4 ste11 + ste50 --> '	'b2 msb2a + sho1 --> msb2asho1'
62	'km4 <-- ypd1p_ssk1 '	'h6 GAP --> PYR '
63	'kste50hog1 ste50 + hog1pp --> '	'p15 hog1pp_ptp_nuc --> '
64	'h7 PYR --> CO2 '	'kiq ALD --> Ethanol'
65	'k2glc Glucose uptake'	'cnn DHA --> DHAP '
66	'ka ALD --> Ethanol'	'h10 G6P --> FBP '
67	'h4 FBP --> GAP + DHAP '	'vnw ALD --> Ethanol '
68	'km9 <-- ssk2p_pase'	'kFBP4 FBP --> GAP + DHAP '
69	'p9 pbs2pp_E -->'	'w1 PFK regulation'
70	'h5 DHAP --> GAP '	'p14 hog1p_cyt_ptp_cyt --> '
71	'h12 G3P --> Glycerol'	'krd3 Pyk regulation '
72	'vbf4 FBP --> GAP + DHAP '	'kn glycerol --> DHA '
73	'KATP10 G6P --> FBP '	'k6 ypd1_ssk1p --> '
74	'h3 G6P --> FBP '	'c0 Cdc42 + Ste20 -->'
75	'ktl2 PTP regulation '	'kGAP4 FBP --> GAP + DHAP '
76	'k8 ssk1 + ssk2 --> '	'kpyr9 PYR --> ALD '
77	'k7 ssk1p --> '	'kDHAP4 FBP --> GAP + DHAP '
78	'kpy PYR --> BIOM'	'k_hog1pp_trans hog1pp_cyt --> hog1pp_nuc

		'
79	'KGAP5 DHAP --> GAP '	'd11 <-- hog1_cyt_pbs2pp '
80	'k10 ssk2p + pbs2 --> '	'b5 sho1apbs2 --> sho1a + pbs2_active'
81	'k6 ypd1_ssk1p --> '	'n9 PYR --> ALD '
82	'a7 ste11pp + MAPKKK_p --> ste11pp_MAPKKK_p'	'a8 ste11p + MAPKKK_p --> ste11p_MAPKKK_p '
83	'bn Specific growth Inhibition'	'r sho1 deactivation'
84	'kex1 Gpd1 regulation '	'KIG1 Glucose inhibition to ethano upatke'
85	'kb ALD --> Ethanol'	'Keq11 DHAP --> G3P '
86	'q sho1 deactivation'	'Keq5 DHAP --> GAP '
87	'p16 hog1p_ptp_nuc --> '	'kq ALD --> Ethanol'
88	'km2 <-- sln1_ypd1p'	'k2 sln1p_ypd1 -->'
89	'Vm max glucose uptake'	'a10 pbs2p + E_total --> '
90	'vfw ALD --> Ethanol '	'KPyr7 PYR --> CO2 '
91	'kpd1 Gpd1 regulation '	'phog glycerol transport '
92	'ktl1 Gpd1 regulation '	'a2 msb2asho1 --> msb2a + sho1_active'
93	'ksho1hog1 sho1a + hog1pp --> '	'd8 <-- ste11pp_MAPKKK_p'
94	'w3 Glucose ihnibition'	'kIAlde11 ALD --> Acetate'
95	'kts2 PTP regulation '	'ktl2 PTP regulation '
96	'cnn DHA --> DHAP '	'n Sln1 activation'
97	'kDHAP4 FBP --> GAP + DHAP '	'e1 Ethanol uptake regulation'
98	'KDHAP5 DHAP --> GAP '	'h14 NADH --> NAD '
99	'h9 PYR --> BIOM'	'b4m ste11ste50 --> ste11 + ste50'
100	'p11 hog1_cyt_pbs2pp --> '	'd14 <-- hog1p_cyt_ptp_cyt '
101	'k9 ssk2p + pase_total --> '	'p16 hog1p_ptp_nuc --> '
102	'kiq ALD --> Ethanol'	'kex3 Pyk regulation '
103	'm11 ssk2p_pbs2p -->'	'h12 G3P --> Glycerol'
104	'k_hog1pp_trans hog1pp_cyt --> hog1pp_nuc '	'k5 ypd1p_ssk1 --> '
105	'KG6P10 G6P --> FBP '	'h9 PYR --> BIOM'
106	'gn DHA --> DHAP '	'kAlde11 ALD --> Acetate'
107	'Keq4 FBP --> GAP + DHAP '	'krd2 PTP regulation '
108	'k21G6P Glucose uptake'	'KIGAP4 FBP --> GAP + DHAP '
109	'm9 ssk2p_pase --> '	'kts3 Pyk regulation '
110	'KATP16 ATP --> ADP '	'q sho1 deactivation'
111	'kts1 Gpd1 regulation '	'kdsho1 sho1p --> sho1'
112	'c2'	'd13 <-- hog1pp_cyt_ptp_cyt '
113	'k11 ssk2p + pbs2p --> '	'kts1 Gpd1 regulation '
114	'h31 G6P --> FBP '	'p11 hog1_cyt_pbs2pp --> '
115	'd8 <-- ste11pp_MAPKKK_p'	'k11 ssk2p + pbs2p --> '
116	'kIAlde11 ALD --> Acetate'	'd9 <-- pbs2pp_E '
117	'rPADmax PYR --> ALD '	'h2 GLC --> G6P'
118	'KADP14 NADH --> NAD '	'b0 msb2 --> msb2a'
119	'krd3 Pyk regulation '	'km1 <-- sln1p_ypd1'
120	'KIhog glycerol transport '	'k4 ypd1p + ssk1 --> '

121	'k5 ypd1p_ssk1 --> '	'k9 ssk2p + pase_total --> '
122	'd7 <-- ste11pp_MAPKKK_p'	'vn glycerol --> DHA '
123	'a9 pbs2pp + E_total --> '	'r2 ste50 phosphorylation'
124	'h6 GAP --> PYR '	'd15 <-- hog1pp_ptp_nuc '
125	'kip ALD --> Ethanol'	'KPyr9 PYR --> BIOM'
126	'kGAP4 FBP --> GAP + DHAP '	'KG6P10 G6P --> FBP '
127	'kh11 DHAP --> G3P '	'kdste50 ste50p --> '
128	'kAlde11 ALD --> Acetate'	'b4 ste11 + ste50 --> '
129	'K1 Sln1 activation'	'd16 <-- hog1p_ptp_nuc '
130	'p7 ste11pp_MAPKKK_p --> '	'K1 Sln1 activation'
131	'dm DHA --> DHAP '	'rPADmax PYR --> ALD '
132	'km10 <-- ssk2p_pbs2'	'ksho1hog1 sho1a + hog1pp --> '
133	'Keq11 DHAP --> G3P '	'd12 <-- hog1p_cyt_pbs2pp'
134	'krd2 PTP regulation '	'kACET Acetate --> BIOM '
135	'ms cdc42 + ste20 -->'	'a15 hog1pp_nuc + ptp_nuc -->'
136	'rAldhmax ALD to Acetate'	'k_hog1_trans1 hog1_nuc --> hog1_cyt '
137	'm8 ssk1_ssk2 --> '	'p12 hog1p_cyt_pbs2pp --> '
138	'ka9 PYR --> ALD '	'kETH1 Ethanol export'
139	'n9 PYR --> ALD '	'b1m msb2a --> msb2'
140	'vnw ALD --> Ethanol '	'KADP14 NADH --> NAD '
141	'm msb2 activation'	'kpy PYR --> BIOM'
142	'kia ALD --> Ethanol'	'c2'
143	'h14 NADH --> NAD '	'h5 DHAP --> GAP '
144	'b7 sho1apbs2ppste11ppste50 dissociation'	'a14 hog1p_cyt + ptp '
145	'a12 hog1p_cyt + pbs2pp --> '	'd7 <-- ste11pp_MAPKKK_p'
146	'b8 ste11ppste50 --> ste11pp + ste50'	'm9 ssk2p_pase --> '
147	'p12 hog1p_cyt_pbs2pp --> '	'k211G6P Glucose uptake'
148	'd15 <-- hog1pp_ptp_nuc '	'KDHAP5 DHAP --> GAP '
149	'h10 G6P --> FBP '	'b3m sho1a + pbs2 <-- sho1apbs2'
150	'KNAD7 PYR --> CO2 '	'KIG2 Glucose inhibition to Acetate prodctn'
151	'h16 ATP --> ADP '	'b8 ste11ppste50 --> ste11pp + ste50'
152	'kETH2 Ethanol import'	'Keq4 FBP --> GAP + DHAP '
153	'kn11 DHAP --> G3P '	'K2ATP GLU --> G6P '
154	'r2 ste50 phosphorylation'	'c3 cdc42ste20ste11ste50 -->'
155	'p15 hog1pp_ptp_nuc --> '	'kex2 PTP regulation '
156	'b4m ste11ste50 --> ste11 + ste50'	'ms cdc42 + ste20 -->'
157	'k4 ypd1p + ssk1 --> '	'b6 sho1apbs2ste11ppste50 --> sho1apbs2PPste11ppste50'
158	'KIG2 Glucose inhibition to Acetate prodctn'	'd10 <-- pbs2p_E '
159	'b5 sho1apbs2 --> sho1a + pbs2_active'	'h11 DHAP --> G3P '
160	'b3m sho1a + pbs2 <-- sho1apbs2'	'kpd1 Gpd1 regulation '
161	'h2 GLC --> G6P'	'KGAP5 DHAP --> GAP '
162	'ktl3 Pyk regulation '	'KATP9 PYR --> BIOM'

163	'kTCA Acetate to TCA cycle'	'KI7 PYR --> CO2 '
164	'KIGAP4 FBP --> GAP + DHAP '	'km10 <-- ssk2p_pbs2'
165	'c1m cdc42ste20 -->'	'ktl3 Pyk regulation '
166	'p10 pbs2p_E --> '	'kn11 DHAP --> G3P '
167	'c2m cdc42ste20ste11ste50 -->'	'k3 sln1_ypd1p --> '
168	'w5 Gpd1 regulation '	'kb ALD --> Ethanol'
169	'phog glycerol transport '	'km4 <-- ypd1p_ssk1 '
170	'KI7 PYR --> CO2 '	'm8 ssk1_ssk2 --> '
171	'd10 <-- pbs2p_E '	'h4 FBP --> GAP + DHAP '
172	'c3 cdc42ste20ste11ste50 -->'	'a16 hog1p_nuc + ptp_nuc --> '
173	'w1 PFK regulation'	'kd11 DHAP --> G3P '
174	'KPyr7 PYR --> CO2 '	'kh11 DHAP --> G3P '
175	'k_hog1_trans1 hog1_nuc --> hog1_cyt '	'k_hog1_trans2 hog1_cyt --> hog1_nuc '
176	'k_hog1_trans2 hog1_cyt --> hog1_nuc '	'ka ALD --> Ethanol'
177	'k3 sln1_ypd1p --> '	'kex1 Gpd1 regulation '
178	'p8 ste11pp_MAPKKK_p --> '	'p13 hog1pp_cyt_ptp_cyt --> '
179	'b6 sho1apbs2ste11ppste50 --> sho1apbs2PPste11ppste50'	'p8 ste11pp_MAPKKK_p --> '
180	'kdste50 ste50p --> '	'gn DHA --> DHAP '
181	'a15 hog1pp_nuc + ptp_nuc -->'	'kETH2 Ethanol import'
182	'kex3 Pyk regulation '	'k8 ssk1 + ssk2 --> '
183	'a8 ste11p + MAPKKK_p --> ste11p_MAPKKK_p '	'KIhog glycerol transport '
184	'a16 hog1p_nuc + ptp_nuc --> '	'cm glycerol --> DHA '
185	'kts3 Pyk regulation '	'dm DHA --> DHAP '
186	'p14 hog1p_cyt_ptp_cyt --> '	'b3 sho1a + pbs2 --> '
187	'vn glycerol --> DHA '	'h16 ATP --> ADP '
188	'a14 hog1p_cyt + ptp '	'h31 G6P --> FBP '

Table S3. Parameter ranking based on the *I* metric used for activated Hog1.

rank	0.5 M	1 M
1	'kpd3 Pyk regulation '	'w3 Glucose ihnibition'
2	'am Pyk regulation'	'lemda2 Glycerol --> DHA'
3	'k10 ssk2p + pbs2 --> '	'kn glycerol --> DHA '
4	'k11 ssk2p + pbs2p --> '	'w5 Gpd1 regulation '
5	'a11 hog1_cyt + pbs2pp --> '	'p10 pbs2p_E --> '
6	'cm glycerol --> DHA '	'a11 hog1_cyt + pbs2pp --> '
7	'ktl2 PTP regulation '	'a10 pbs2p + E_total --> '
8	'kts2 PTP regulation '	'km11 <-- ssk2p_pbs2p'
9	'kpd2 PTP regulation '	'a9 pbs2pp + E_total --> '
10	'a10 pbs2p + E_total --> '	'k10 ssk2p + pbs2 --> '
11	'a15 hog1pp_nuc + ptp_nuc -->'	'p11 hog1_cyt_pbs2pp --> '
12	'd11 <-- hog1_cyt_pbs2pp '	'k11 ssk2p + pbs2p --> '
13	'km11 <-- ssk2p_pbs2p'	'p9 pbs2pp_E -->'
14	'm10 ssk2p_pbs2 --> '	'c0 Cdc42 + Ste20 -->'
15	'kn glycerol --> DHA '	'w4 Gpd1 regulation '
16	'p9 pbs2pp_E -->'	'd11 <-- hog1_cyt_pbs2pp '
17	'bn Specific growth Inhibition'	'h9 PYR --> BIOM'
18	'p11 hog1_cyt_pbs2pp --> '	'k_hog1_trans1 hog1_nuc --> hog1_cyt '
19	'a9 pbs2pp + E_total --> '	'c2m cdc42ste20ste11ste50 -->'
20	'k_hog1_trans2 hog1_cyt --> hog1_nuc '	'r sho1 deactivation'
21	'krd2 PTP regulation '	'b1m msb2a --> msb2'
22	'ka9 PYR --> ALD '	'kDHAP4 FBP --> GAP + DHAP '
23	'p10 pbs2p_E --> '	'kETH2 Ethanol import'
24	'd9 <-- pbs2pp_E '	'b6 sho1apbs2ste11ppste50 --> sho1apbs2PPste11ppste50'
25	'm11 ssk2p_pbs2p -->'	'k9 ssk2p + pase_total --> '
26	'km10 <-- ssk2p_pbs2'	'dm DHA --> DHAP '
27	'kpyr9 PYR --> ALD '	'h15 NAD --> NADH '
28	'w1 PFK regulation'	'ktl1 Gpd1 regulation '
29	'h5 DHAP --> GAP '	'm9 ssk2p_pase --> '
30	'h3 G6P --> FBP '	'm10 ssk2p_pbs2 --> '
31	'n Sln1 activation'	'h12 G3P --> Glycerol'
32	'kn11 DHAP --> G3P '	'k211G6P Glucose uptake'
33	'd8 <-- ste11pp_MAPKKK_p'	'km3 sln1 + ypd1p --> '
34	'kACET Acetate --> BIOM '	'b3m sho1a + pbs2 <-- sho1apbs2'
35	'vfw ALD --> Ethanol '	'Keq4 FBP --> GAP + DHAP '
36	'p16 hog1p_ptp_nuc --> '	'KIG1 Glucose inhibition to ethano upatke'
37	'b2m msb2a + sho1 <-- msb2asho1'	'c2'
38	'kDHAP4 FBP --> GAP + DHAP '	'w1 PFK regulation'

39	'kETH2 Ethanol import'	'd10 <-- pbs2p_E '
40	'w4 Gpd1 regulation '	'kIAlde11 ALD --> Acetate'
41	'kq ALD --> Ethanol'	'h4 FBP --> GAP + DHAP '
42	'kIAlde11 ALD --> Acetate'	'k2 sln1p_ypd1 -->'
43	'w5 Gpd1 regulation '	'kn11 DHAP --> G3P '
44	'd15 <-- hog1pp_ptp_nuc '	'vn glycerol --> DHA '
45	'k9 ssk2p + pase_total --> '	'a15 hog1pp_nuc + ptp_nuc -->'
46	'kste50hog1 ste50 + hog1pp --> '	'kpd1 Gpd1 regulation '
47	'd12 <-- hog1p_cyt_pbs2pp'	'p15 hog1pp_ptp_nuc --> '
48	'k1 sln1p + ypd1 -->'	'kts1 Gpd1 regulation '
49	'Keq5 DHAP --> GAP '	'kFBP4 FBP --> GAP + DHAP '
50	'b4 ste11 + ste50 --> '	'p12 hog1p_cyt_pbs2pp --> '
51	'k_hog1_trans1 hog1_nuc --> hog1_cyt '	'kex1 Gpd1 regulation '
52	'kip ALD --> Ethanol'	'h31 G6P --> FBP '
53	'KIG2 Glucose inhibition to Acetate prodctn'	'rPADmax PYR --> ALD '
54	'p14 hog1p_cyt_ptp_cyt --> '	'e1 Ethanol uptake regulation'
55	'a16 hog1p_nuc + ptp_nuc --> '	'd14 <-- hog1p_cyt_ptp_cyt '
56	'n9 PYR --> ALD '	'kAlde11 ALD --> Acetate'
57	'kdsho1 sho1p --> sho1'	'km10 <-- ssk2p_pbs2'
58	'p13 hog1pp_cyt_ptp_cyt --> '	'k2glc Glucose uptake'
59	'p15 hog1pp_ptp_nuc --> '	'ka ALD --> Ethanol'
60	'kts3 Pyk regulation '	'h16 ATP --> ADP '
61	'ms cdc42 + ste20 -->'	'KPyr7 PYR --> CO2 '
62	'lemda2 Glycerol --> DHA'	'k4 ypd1p + ssk1 --> '
63	'd13 <-- hog1pp_cyt_ptp_cyt '	'vnw ALD --> Ethanol '
64	'a13 hog1pp_cyt + ptp -->'	'kdsho1 sho1p --> sho1'
65	'c2m cdc42ste20ste11ste50 -->'	'h2 GLC --> G6P'
66	'KATP9 PYR --> BIOM'	'b8 ste11ppste50 --> ste11pp + ste50'
67	'Keq11 DHAP --> G3P '	'h3 G6P --> FBP '
68	'h31 G6P --> FBP '	'KGAP5 DHAP --> GAP '
69	'KIhog glycerol transport '	'h14 NADH --> NAD '
70	'rPADmax PYR --> ALD '	'KIhog glycerol transport '
71	'K1 Sln1 activation'	'ksho1hog1 sho1a + hog1pp --> '
72	'd14 <-- hog1p_cyt_ptp_cyt '	'kia ALD --> Ethanol'
73	'km9 <-- ssk2p_pase'	'b2 msb2a + sho1 --> msb2asho1'
74	'km8 <-- ssk1_ssk2 '	'b2m msb2a + sho1 <-- msb2asho1'
75	'm msb2 activation'	'd16 <-- hog1p_ptp_nuc '
76	'dm DHA --> DHAP '	'KIGAP4 FBP --> GAP + DHAP '
77	'k6 ypd1_ssk1p --> '	'm8 ssk1_ssk2 --> '
78	'q sho1 deactivation'	'k21G6P Glucose uptake'
79	'K2Glc GLU --> G6P '	'd7 <-- ste11pp_MAPKKK_p'
80	'KPyr7 PYR --> CO2 '	'ka9 PYR --> ALD '
81	'b7 sho1apbs2ppste11ppste50 dissociation'	'b4 ste11 + ste50 --> '

82	'bm Pdc1 regulation'	'p13 hog1pp_cyt_ptp_cyt --> '
83	'kAlde11 ALD --> Acetate'	'ms cdc42 + ste20 -->'
84	'ksho1hog1 sho1a + hog1pp --> '	'k_hog1pp_trans hog1pp_cyt --> hog1pp_nuc '
85	'kd11 DHAP --> G3P '	'k3 sln1_ypd1p --> '
86	'c0 Cdc42 + Ste20 -->'	'm11 ssk2p_pbs2p -->'
87	'w2 ALD6 regulation'	'KNAD7 PYR --> CO2 '
88	'h12 G3P --> Glycerol'	'd9 <-- pbs2pp_E '
89	'r sho1 deactivation'	'k1 sln1p + ypd1 -->'
90	'k2 sln1p_ypd1 -->'	'c3 cdc42ste20ste11ste50 -->'
91	'a12 hog1p_cyt + pbs2pp --> '	'kts2 PTP regulation '
92	'ka ALD --> Ethanol'	'kdste50 ste50p --> '
93	'kdste50 ste50p --> '	'a2 msb2asho1 --> msb2a + sho1_active'
94	'KPyr9 PYR --> BIOM'	'b7 sho1apbs2ppste11ppste50 dissociation'
95	'p12 hog1p_cyt_pbs2pp --> '	'K1 Sln1 activation'
96	'krd1 Gpd1 regulation '	'a13 hog1pp_cyt + ptp -->'
97	'h32 G6P --> FBP '	'K2Glc GLU --> G6P '
98	'b4m ste11ste50 --> ste11 + ste50'	'a14 hog1p_cyt + ptp '
99	'kex2 PTP regulation '	'km1 <-- sln1p_ypd1'
100	'b3m sho1a + pbs2 <-- sho1apbs2'	'kTCAC Acetate to TCA cycle'
101	'k7 ssk1p --> '	'n9 PYR --> ALD '
102	'h9 PYR --> BIOM'	'vbf4 FBP --> GAP + DHAP '
103	'b5 sho1apbs2 --> sho1a + pbs2_active'	'gn DHA --> DHAP '
104	'd16 <-- hog1p_ptp_nuc '	'k8 ssk1 + ssk2 --> '
105	'KDHAP5 DHAP --> GAP '	'a16 hog1p_nuc + ptp_nuc --> '
106	'k21G6P Glucose uptake'	'kiq ALD --> Ethanol'
107	'kex1 Gpd1 regulation '	'bn Specific growth Inhibition'
108	'cnn DHA --> DHAP '	'd15 <-- hog1pp_ptp_nuc '
109	'K2ATP GLU --> G6P '	'KIG2 Glucose inhibition to Acetate prodctn'
110	'h10 G6P --> FBP '	'a12 hog1p_cyt + pbs2pp --> '
111	'w3 Glucose ihnibition'	'p16 hog1p_ptp_nuc --> '
112	'kiq ALD --> Ethanol'	'h130 glycerol transport '
113	'k2glc Glucose uptake'	'b4m ste11ste50 --> ste11 + ste50'
114	'krd3 Pyk regulation '	'kpyr9 PYR --> ALD '
115	'r2 ste50 phosphorylation'	'kex2 PTP regulation '
116	'kia ALD --> Ethanol'	'kACET Acetate --> BIOM '
117	'k4 ypd1p + ssk1 --> '	'r2 ste50 phosphorylation'
118	'h4 FBP --> GAP + DHAP '	'd13 <-- hog1pp_cyt_ptp_cyt '
119	'c2'	'h7 PYR --> CO2 '
120	'h130 glycerol transport '	'p8 ste11pp_MAPKKK_p --> '
121	'a2 msb2asho1 --> msb2a + sho1_active'	'krd2 PTP regulation '
122	'kb ALD --> Ethanol'	'b5 sho1apbs2 --> sho1a +

		pbs2_active'
123	'kpy PYR --> BIOM'	'bm Pdc1 regulation'
124	'e1 Ethanol uptake regulation'	'kpd2 PTP regulation '
125	'h11 DHAP --> G3P '	'KATP10 G6P --> FBP '
126	'kTCAC Acetate to TCA cycle'	'kb ALD --> Ethanol'
127	'a14 hog1p_cyt + ptp '	'n Sln1 activation'
128	'ktl3 Pyk regulation '	'KG6P10 G6P --> FBP '
129	'kp ALD --> Ethanol'	'kts3 Pyk regulation '
130	'k5 ypd1p_ssk1 --> '	'am Pyk regulation'
131	'p7 ste11pp_MAPKKK_p --> '	'kq ALD --> Ethanol'
132	'd10 <-- pbs2p_E '	'KI7 PYR --> CO2 '
133	'm9 ssk2p_pase --> '	'cm glycerol --> DHA '
134	'ktl1 Gpd1 regulation '	'ktl2 PTP regulation '
135	'kGAP4 FBP --> GAP + DHAP '	'q sho1 deactivation'
136	'a7 ste11pp + MAPKKK_p --> ste11pp_MAPKKK_p'	'KPyr9 PYR --> BIOM'
137	'KGAP5 DHAP --> GAP '	'kGAP4 FBP --> GAP + DHAP '
138	'KG6P10 G6P --> FBP '	'h10 G6P --> FBP '
139	'a8 ste11p + MAPKKK_p --> ste11p_MAPKKK_p '	'w2 ALD6 regulation'
140	'phog glycerol transport '	'd12 <-- hog1p_cyt_pbs2pp'
141	'h14 NADH --> NAD '	'krd3 Pyk regulation '
142	'vnw ALD --> Ethanol '	'km9 <-- ssk2p_pase'
143	'd7 <-- ste11pp_MAPKKK_p'	'Keq11 DHAP --> G3P '
144	'KADP14 NADH --> NAD '	'c1m cdc42ste20 -->'
145	'b6 sho1apbs2ste11ppste50 --> sho1apbs2PPste11ppste50'	'k7 ssk1p --> '
146	'KNAD7 PYR --> CO2 '	'Keq5 DHAP --> GAP '
147	'kex3 Pyk regulation '	'b3 sho1a + pbs2 --> '
148	'k211G6P Glucose uptake'	'kETH1 Ethanol export'
149	'KI7 PYR --> CO2 '	'h11 DHAP --> G3P '
150	'h7 PYR --> CO2 '	'm msb2 activation'
151	'h15 NAD --> NADH '	'rAldhmax ALD to Acetate'
152	'kTCA Acetate to TCA cycle'	'kex3 Pyk regulation '
153	'an DHA --> DHAP '	'Vm max glucose uptake'
154	'KATP10 G6P --> FBP '	'K2ATP GLU --> G6P '
155	'kpd1 Gpd1 regulation '	'vfw ALD --> Ethanol '
156	'k_hog1pp_trans hog1pp_cyt --> hog1pp_nuc '	'kpy PYR --> BIOM'
157	'c3 cdc42ste20ste11ste50 -->'	'phog glycerol transport '
158	'vn glycerol --> DHA '	'h5 DHAP --> GAP '
159	'c1m cdc42ste20 -->'	'km2 <-- sln1_ypd1p'
160	'kFBP4 FBP --> GAP + DHAP '	'kTCA Acetate to TCA cycle'
161	'KIG1 Glucose inhibition to ethano upatke'	'km8 <-- ssk1_ssk2 '
162	'KIGAP4 FBP --> GAP + DHAP '	'h6 GAP --> PYR '
163	'h6 GAP --> PYR '	'krd1 Gpd1 regulation '

164	'vbf4 FBP --> GAP + DHAP '	'd8 <-- ste11pp_MAPKKK_p'
165	'KATP16 ATP --> ADP '	'kpd3 Pyk regulation '
166	'km1 <-- sln1p_ypd1'	'kh11 DHAP --> G3P '
167	'kh11 DHAP --> G3P '	'kp ALD --> Ethanol'
168	'b2 msb2a + sho1 --> msb2asho1'	'h32 G6P --> FBP '
169	'rAldhmax ALD to Acetate'	'q2 ste50 phosphorylation'
170	'b0 msb2 --> msb2a'	'km4 <-- ypd1p_ssk1 '
171	'kETH1 Ethanol export'	'k_hog1_trans2 hog1_cyt --> hog1_nuc '
172	'b1m msb2a --> msb2'	'ktl3 Pyk regulation '
173	'h16 ATP --> ADP '	'k5 ypd1p_ssk1 --> '
174	'k3 sln1_ypd1p --> '	'KATP9 PYR --> BIOM'
175	'km2 <-- sln1_ypd1p'	'an DHA --> DHAP '
176	'k8 ssk1 + ssk2 --> '	'b0 msb2 --> msb2a'
177	'gn DHA --> DHAP '	'KADP14 NADH --> NAD '
178	'km3 sln1 + ypd1p --> '	'cnn DHA --> DHAP '
179	'q2 ste50 phosphorylation'	'kd11 DHAP --> G3P '
180	'kts1 Gpd1 regulation '	'KDHAP5 DHAP --> GAP '
181	'p8 ste11pp_MAPKKK_p --> '	'kste50hog1 ste50 + hog1pp --> '
182	'Vm max glucose uptake'	'p7 ste11pp_MAPKKK_p --> '
183	'km4 <-- ypd1p_ssk1 '	'a7 ste11pp + MAPKKK_p --> ste11pp_MAPKKK_p'
184	'Keq4 FBP --> GAP + DHAP '	'p14 hog1p_cyt_ptp_cyt --> '
185	'h2 GLC --> G6P'	'k6 ypd1_ssk1p --> '
186	'b8 ste11ppste50 --> ste11pp + ste50'	'kip ALD --> Ethanol'
187	'b3 sho1a + pbs2 --> '	'a8 ste11p + MAPKKK_p --> ste11p_MAPKKK_p '
188	'm8 ssk1_ssk2 --> '	'KATP16 ATP --> ADP '