

Supplemental File 4: Supplementary *in silico* and *in vivo* information on Yeast 7.11 and CHO 1.2

Table 1. Model modifications from Yeast 7.00 to Yeast 7.11 as reported in sourceforge.net

Model modifications with reaction IDs of Yeast 7.11	References (if any)
<ul style="list-style-type: none"> Aspartate transport r_1117 can only flow in cytoplasm to mitochondria direction, to avoid free generation of proton gradient 	Reported by Hnin Aung
<ul style="list-style-type: none"> Malic enzyme r_0718 is NADP-dependent, not NAD⁺ 	[1], [2], [3]
<ul style="list-style-type: none"> NADH: ubiquinone oxidoreductase r_0773 is not proton translocating 	[4], [5]
<ul style="list-style-type: none"> ATP synthase r_0226 moves 4 cytoplasmic protons 	NA
<ul style="list-style-type: none"> Allow proton leak r_2129 from cytoplasm to mitochondrion 	NA
<ul style="list-style-type: none"> Mitochondrial ADP/ATP transporter r_1110 does not cotransport protons 	[6], [7]
<ul style="list-style-type: none"> Zymesterol intermediate 1c reactions r_0234, r_0240 	[8]
<ul style="list-style-type: none"> GDH2 irreversible 	NA
<ul style="list-style-type: none"> Remove citrate isomerase r_0303 	NA
<ul style="list-style-type: none"> Dihydroorotic acid dehydrogenase r_0453 uses only fumarate as electron donor: Remove r_0338, r_0339, r_2127 	NA
<ul style="list-style-type: none"> Pyruvate can be transported r_1254 out of the cell 	[9]
<ul style="list-style-type: none"> Folic acid is changed to Folate 	NA
<ul style="list-style-type: none"> Heme O monooxygenase r_0530 associated with genes (YPL252C AND YDR376W) or (YPL252C AND YDR376W AND YER141W) 	NA
<ul style="list-style-type: none"> Add chitin and heme a to biomass definition r_4041 with minimal stoichiometry (10⁻⁶) 	NA
<ul style="list-style-type: none"> Allow potassium exchange r_2020 from medium 	NA
<ul style="list-style-type: none"> Extracellular reaction raffinose -> fructose + melibiose is catalysed by gene SUC2 	[10]
<ul style="list-style-type: none"> PHM8 is a 5'-nucleotidase for CMP r_0076, GMP r_1619 and UMP r_0078 	[11]
<ul style="list-style-type: none"> PNP1 phosphorylase activity specific to inosine and guanosine 	[11]
<ul style="list-style-type: none"> URH1 hydrolase activity specific to uridine 	[11]
<ul style="list-style-type: none"> PGM3 is a phosphoribomutase r_0907, not a phosphoglucomutase r_0888 	[11]
<ul style="list-style-type: none"> Metabolite formula, charge and number of carbon atoms added to SBML 	Contributors: Hnin Aung, Kevin Correia, Ben Heavner, Kieran Smallbone, Balázs Szappanos

Table 2. Single gene deletion data sets; one showing *in silico* essential genes, which have been verified *in vivo* and the other showing the ones which are not *in vivo* essentials

Experimentally verified list	<i>in silico</i> essential but non- essential <i>in vivo</i>	Experimentally verified list	<i>in silico</i> essential but non- essential <i>in vivo</i>	Experimentally verified list	<i>in silico</i> essential but non- essential <i>in vivo</i>
YAR015W	YBL076C	YEL058W	YHR208W	YGL245W	
YBL033C	YBR115C	YER003C	YJL167W	YGR060W	
YCL018W	YBR153W	YER014W	YJR148W	YGR264C	
YDL055C	YBR166C	YER052C	YLL018C	YHR007C	
YDL103C	YBR248C	YER055C	YLR060W	YHR019C	
YDL141W	YBR256C	YER090W	YLR359W	YHR025W	
YDL205C	YBR265W	YFR025C	YLR420W	YHR072W	
YDR007W	YCL030C	YGL001C	YMR062C	YIL116W	
YDR037W	YDR044W	YGL009C	YMR300C	YIR034C	
YDR047W	YDR226W	YGL148W	YMR319C	YJL088W	
YDR234W	YER023W	YGL154C	YNL277W	YJL130C	
YDR487C	YFL017C	YGL234W	YOL143C	YJR139C	
YKL104C	YFL022C	YOR095C	YOR130C	YOR335C	
YKL211C	YFL045C	YOR128C	YGL055W	YPL160W	
YKL216W	YGR185C	YOR168W	YPL252C	YPL172C	

YLR100W

YOR176W

YPR033C

YLR304C

YOR236W

YPR035W

YLR355C

YOR278W

YPR060C

YMR220W

YPR183W

YNL220W

YPL231W

YNL280C

YLR303W

YNR016C

YGR204W

YMR202W

YBR126C

YMR217W

YDR074W

YNR050C

YJR109C

YOL140W

YOR303W

YOR074C

YPR167C

Table 3. Double gene deletion data sets; one showing *in silico* SL gene pairs, which have been verified *in vivo* and the other showing the ones which have not been tested *in vivo*

Experimentally verified list	<i>in silico</i> predictions not tested <i>in vivo</i>
YBR117C, YPR074C	YAL054C, YLR153C
YBR249C, YDR035W	YBR294W, YLR092W
YGL125W, YPL023C	YDL131W, YDL182W
YGR143W, YPR159W	YML106W, YMR271C
YGR209C, YLR043C	YOR222W, YPL134C
YGL202W, YHR137W	YBR121C, YPR081C
YJL121C, YNL241C	YDR035W, YKL029C
YBL039C, YJR103W	YCL050C, YJR010W
YKL181W, YOL061W	YMR170C, YPL061W
YDR502C, YLR180W	YDR300C, YLR438W
YGR032W, YLR342W	YBR291C, YKL029C
YCR034W, YLR372W	YNL104C, YOR108W
YLR450W, YML075C	
YLR028C, YMR120C	
YGR124W, YPR145W	

Table 4. Higher order gene deletion data sets; one showing *in silico* SL gene sets, which have been verified *in vivo* and the other showing the ones which have not been tested *in vivo*

	Experimentally verified list	<i>in silico</i> predictions not tested <i>in vivo</i>
SL Triplets	YER099C, YHL011C, YBL068W	YCL040W, YFR053C, YGL253W
	YDL095W, YAL023C, YJR143C	YHR216W, YLR432W, YML056C
		YGR254W, YHR174W, YKR097W
		YAL062W, YDL171C, YOR375C
		YDR497C, YJL153C, YOL103W
SL Quadruplets	No information	YDR287W, YDR497C, YHR046C, YOL103W
	No information	YEL046C, YGR087C, YLR044C, YLR134W

Table 5. List of essential genes for the CHO 1.2 model along with auxotrophy information

Gene	Auxotrophy	Gene	Auxotrophy
<i>acaCb</i>	sphingomyelin	<i>lysXt</i>	L-lysine
<i>acsL1</i>	sphingomyelin	<i>metXt</i>	L-methionine
<i>acsL2</i>	sphingomyelin	<i>mthFr</i>	5-Methyltetrahydrofolate
<i>acsL3</i>	sphingomyelin	<i>mvd</i>	cholesterol
<i>acsL4</i>	sphingomyelin	<i>mvk</i>	cholesterol
<i>akrLa4</i>	sphingomyelin	<i>nadS</i>	NAD ⁺
<i>aldOa1</i>	phosphatidylglycerol phosphatidylserine phosphatidylethanolamine phosphatidylcholine cardiolipin 1Phosphatidyl-D-myoinositol	<i>nmnAt</i>	NAD ⁺ , NADH, NADP ⁺
<i>arg1</i>	spermidine putrescine	<i>odc1</i>	Spermidine putrescine
<i>argXt</i>	L-arginine spermidine putrescine	<i>otrA41</i>	spermidine
<i>cds1</i>	L-arginine spermidine putrescine	<i>pinS</i>	1Phosphatidyl-D-myoinositol
<i>crIS1</i>	phosphatidylglycerol 1Phosphatidyl-D-myoinositol cardiolipin	<i>pisD</i>	phosphotidylethanolamine
<i>fasN</i>	cholesterol	<i>pmvK</i>	cholesterol
<i>ffa10</i>	cholesterol	<i>qprT</i>	NAD ⁺ , NADH, NADP ⁺ , NADPH
<i>ffa11</i>	cholesterol	<i>sgmS1</i>	glycogen
<i>ffa12</i>	cholesterol	<i>sptLc1</i>	sphingomyelin
<i>ffa7</i>	cholesterol	<i>sptLc2</i>	sphingomyelin
<i>ffa9</i>	cholesterol	<i>sptLc3</i>	sphingomyelin
<i>fvt1</i>	sphingomyelin	<i>sqlE</i>	cholesterol
<i>ggpS1</i>	cholesterol	<i>srm</i>	spermidine
<i>gys1</i>	glycogen	<i>thrXt</i>	L-threonine
<i>gys2</i>	glycogen	<i>trpXt</i>	L-tryptophan
<i>haaO</i>	NAD ⁺ , NADH, NADP ⁺ , NADPH	<i>ugp2</i>	glycogen
<i>hisXt</i>	histidine	<i>valXt</i>	valine
<i>hmgCr</i>	cholesterol	<i>fdtT1</i>	sphingomyelin
<i>idi1</i>	cholesterol	<i>ebp</i>	cardiolipin
<i>ileXt</i>	L-isoleucine	<i>afmId</i>	sphingomyelin
<i>khh</i>	phosphatidylglycerol phosphatidylserine phosphatidylethanolamine phosphatidylcholine cardiolipin 1Phosphatidyl-D-myoinositol		

Table 6. List of SL gene pairs for the CHO 1.2 model along with auxotrophy information

Gene Pair	Auxotrophy	Gene Pair	Auxotrophy
<i>asnS, asnXt</i>	L-asparagine	<i>pemT, slc5a7</i>	sphingomyeline phosphatidylcholine cholesterol
<i>pbeF1, prpS2</i>	NAD ⁺ , NADP ⁺ , NADPH	<i>dhcR24, sc5D</i>	1Phosphatidyl-D-myoinositol
<i>pc3, ahcY11</i>	phosphatidylcholine	<i>isyNa1, ugtLa2</i>	sphingomyelin phosphatidylserine phosphatidylethanolamine phosphatidylcholine phosphatidylserine phosphatidylethanolamine phosphatidylserine phosphatidylethanolamine phosphatidylcholine 1Phosphatidyl-D-myoinositol
<i>pc4, slc5a7</i>	sphingomyeline, phosphatidylcholine	<i>chkB, ptdSs1</i>	1Phosphatidyl-D-myoinositol
<i>ahcY11, slc5a7</i>	sphingomyeline, phosphatidylcholine	<i>pc3, pc2</i>	dTTP
<i>pc3, pc4</i>	phosphatidylcholine	<i>impA2, mioX</i>	1Phosphatidyl-D-myoinositol
<i>txnd2, tr3</i>	dATP, dGTP, dCTP, dTTP	<i>isyNa1, gusB</i>	1Phosphatidyl-D-myoinositol
<i>pc3, pcyT2</i>	phosphatidylcholine phosphatidylethanolamine phosphatidylserine	<i>polA1, tymS</i>	1Phosphatidyl-D-myoinositol
<i>pheXt, tyrXt</i>	L-phenylalanine, L-tyrosine	<i>impA2, ugtLa2</i>	1Phosphatidyl-D-myoinositol
<i>pah, pheXt</i>	L-phenylalanine	<i>isyNa1, mioX</i>	1Phosphatidyl-D-myoinositol
<i>slc14a2, slc14a1</i>	spermidine, putrescine	<i>isyNa1, ugdH</i>	sphingomyelin, phosphatidylcholine 1Phosphatidyl-D-myoinositol
<i>dhcR24, choL4</i>	cholesterol	<i>pc5, slc5a7</i>	phosphatidylcholine
<i>qdpR, pheXt</i>	L-phenylalanine	<i>impA2, ugdH</i>	cholesterol
<i>pc3, chkB</i>	phosphatidylcholine phosphatidylethanolamine phosphatidylserine phosphatidylethanolamine sphingomyeline	<i>pc3, pc5</i>	phosphatidylcholine
<i>pc2, ptdSs1</i>	sphingomyelin phosphatidylserine phosphatidylethanolamine phosphatidylcholine	<i>choL4, sc5D</i>	phosphatidylcholine
<i>fh1, sdhc</i>	sphingomyelin	<i>pc3, pemT</i>	phosphatidylglycerol phosphatidylserine phosphatidylethanolamine phosphatidylcholine cardiolipin 1Phosphatidyl-D-myoinositol NAD ⁺ , NADP ⁺ , NADPH
<i>chkA, chkB</i>		<i>cel, lpl</i>	
<i>sdhD, sdhc</i>		<i>indOl, tdo2</i>	
<i>ptdSs1, ptdSs2</i>	phosphatidylserine phosphatidylethanolamine dTTP	<i>pcyT1a, pcyT1b</i>	sphingomyelin
<i>dtyMk, polA1</i>	1Phosphatidyl-D-myoinositol	<i>pgm1, pgm2</i>	glycogen
<i>gusB, impA2</i>	phosphatidylserine phosphatidylethanolamine phosphatidylcholine		
<i>pc3, ptdSs2</i>			

Table 7. List of higher order SL gene sets for the CHO 1.2 model along with auxotrophy information

	Higher order SL-gene sets	Auxotrophy
Synthetic Lethal Triplets	<i>dhoDh , fh1 , cytB</i>	<i>Sphingomyelin</i>
	<i>ggh , pipOx , slc19a1</i>	<i>5Methyltetrahydrofolate</i>
	<i>cox1 , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox2 , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox3 , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox5a , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox5b , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox6c , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox7b , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox8a , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox7c , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox8b , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox6a1 , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox6a2 , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox6b1 , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox7a1 , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox6b2 , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox7a2 , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox7b2 , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
	<i>cox7a2l , dhoDh , sdhD</i>	<i>Sphingomyelin</i>
SL Quadruplets	<i>nanS , npl , st8Sia1 , st8Sia5</i>	<i>N-Acetylneuraminate</i>
	<i>ak1 . ak2 , ak3L1 , cmpK1</i>	<i>Phosphatidylglycerol</i> <i>Phosphatidylserine</i> <i>Phosphatidylethanolamine</i> <i>Phosphatidylcholine</i> <i>Cardiolipin</i> <i>1Phosphatidyl-D-myoinositol</i>
	<i>polA1 , rrm1 , rrm2 , rrm2b</i>	<i>dATP</i>

Table 8. List of gene members for the most important gene-hubs based on node centrality analysis

Genes forming SL2 with <i>pc3</i>	Genes forming SL2 with <i>slc5a7</i>	Genes forming SL2 with <i>ptdSs1</i>	Genes forming SL2 with <i>isyNa1</i>	Genes forming SL2 with <i>chkB</i>	Gene pair forming SL3 with <i>dhoDh</i> only	Genes forming SL3 with <i>sdhD</i> - <i>dhoDh</i> gene pair
<i>ahcY11</i> <i>pc4</i> <i>pc5</i> <i>pemT</i> <i>pcyT2</i> <i>pc2</i> <i>chkB</i> <i>ptdSs2</i>	<i>pc4</i> <i>ahcY11</i> <i>pemT</i> <i>pc5</i>	<i>chkB</i> <i>ptdSs2</i> <i>pcyT2</i> <i>pc2</i>	<i>ugdH</i> <i>gusB</i> <i>mioX</i> <i>ugtLa2</i>	<i>pc3</i> <i>chkA</i> <i>ptdSs1</i>	<i>cytB-fh1</i>	<i>cox1</i> <i>cox2</i> <i>cox3</i> <i>cox5a</i> <i>cox5b</i> <i>cox6c</i> <i>cox7b</i> <i>cox8a</i> <i>cox8b</i> <i>cox7c</i> <i>cox6a1</i> <i>cox6a2</i> <i>cox6b1</i> <i>cox7a1</i> <i>cox6b2</i> <i>cox7a2</i> <i>cox7b2</i> <i>cox7a2l</i>

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