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Pichia pastoris growth rate regulates protein synthesis and secretion, mating, and stress response

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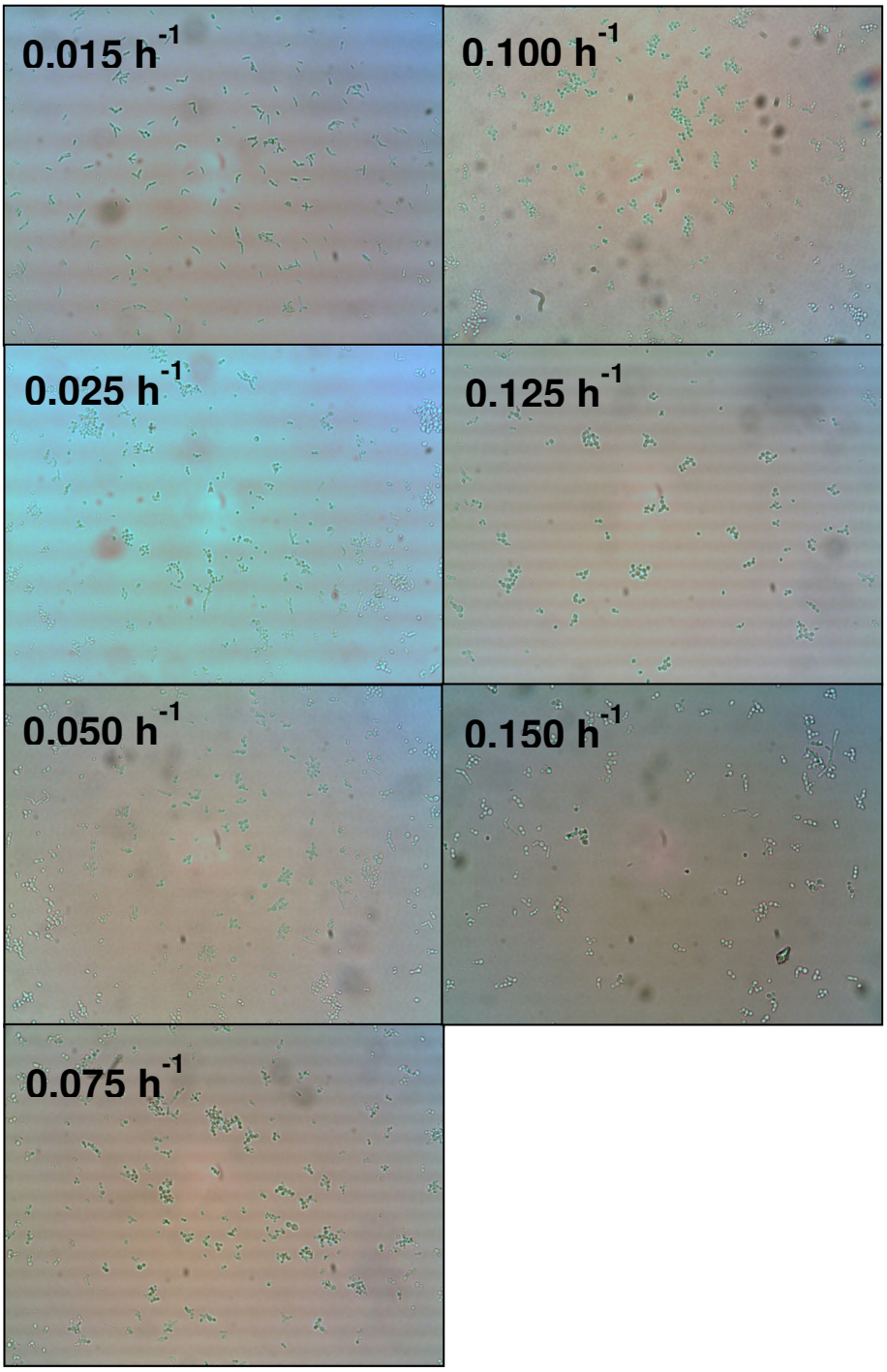
Supplementary Material

Supporting Figures

Figure S1: Morphology of *P. pastoris* grown at different specific growth rates between 0.015 h^{-1} and 0.15 h^{-1}. At the lowest μ most cells have an elongated shape, a phenotype that almost disappears at faster growth.



Supporting Tables

Table S1: Core set of common upregulated genes. A conserved set of genes upregulated with increasing growth in *S. cerevisiae* (Fazio et al. 2008) and regulation of their *P. pastoris* homologs. For references see main manuscript.

ORF	*S.c. Gene Name*	*P.p. Gene Name*	*Short Description*	*Regulation in P.p. (Cluster #)*
YBL039C	URA7	URA7	Major CTP synthase isozyme	Up (11)
YBR189W	RPS9B	RPS9B	Protein component of the small (40S) ribosomal subunit	Up (12)
YBR191W	RPL21A	RPL21B	Protein component of the large (60S) ribosomal subunit	Up (4)
YCR034W	FEN1	FEN1	Fatty acid elongase, involved in sphingolipid biosynthesis	Up (4)
YDL083C	RPS16B	RPS16B	Protein component of the small (40S) ribosomal subunit	Not significant
YDR064W	RPS13	RPS13	Protein component of the small (40S) ribosomal subunit	Not significant
YDR144C	MKC7	MKC7	GPI-anchored aspartyl protease (yapsin) involved in protein processing	Slightly up (1)
YDR321W	ASP1	ASP1	Cytosolic L-asparaginase, involved in asparagine catabolism	Up (6)
YEL040W	UTR2	UTR2	Cell wall protein that functions in the transfer of chitin to beta(1-6)glucan	Up (12)
YER009W	NTF2	NTF2	Nuclear envelope protein	Up (11)
YGL076C	RPL7A	RPL7A	Protein component of the large (60S) ribosomal subunit	Up (6)
YKL081W	TEF4	PAS_chr3_1071	Translation elongation factor EF-1 gamma	Down (9)
YLR186W	EMG1	EMG1	Protein required for the maturation of the 18S rRNA and for 40S ribosome production	Up (6)
YLR325C	RPL38	RPL38	Protein component of the large (60S) ribosomal subunit	Up (6)
YLR372W	SUR4	SUR4	Elongase, involved in fatty acid and sphingolipid biosynthesis	Up (6)
YML036W	CGI121	n.a.	Protein involved in telomere uncapping and elongation	--
YML063W	RPS1B	RPS1B	Ribosomal protein 10 (rp10) of the small (40S) subunit	Up (12)
YMR318C	ADH6	ADH6	NADPH-dependent medium chain alcohol dehydrogenase	Up (6)
YOL040C	RPS15	RPS15	Protein component of the small (40S) ribosomal subunit	Up (4)
YOL120C	RPL18A	RPL18B	Protein component of the large (60S) ribosomal subunit	Up (12)
YPL144W	YPL144W	n.a.	Putative protein of unknown function	--

Table S2: Core set of common downregulated genes. A conserved set of genes downregulated with increasing growth in *S. cerevisiae* (Fazio et al. 2008) and regulation of their *P. pastoris* homologs. For references see main manuscript.

ORF	*S.c. Gene Name*	*P.p. Gene Name*	*Description*	*Regulation in P.p. (Cluster #)*
YOL153C	YOL153C	n.a.	Hypothetical protein	--
YLR345W	YLR345W	PAS_chr4_0266	Similar to 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase	Down (7)
YGR070W	ROM1	PAS_chr3_1175	GDP/GTP exchange protein (GEP) for Rho1p	Down (9)
YMR090W	YMR090W	PAS_FragB_0034	Putative protein of unknown function with similarity to DTDP-glucose 4,6-dehydratases	Down (7)
YDR262W	YDR262W	PAS_chr4_0303	Putative protein of unknown function	Down (5)
YGL121C	GPG1	n.a.	Proposed gamma subunit of the heterotrimeric G protein that interacts with the receptor Grp1p	--
YIL107C	PFK26	PFK26-1	6-phosphofructo-2-kinase	Down (5)
		PFK26-2		slightly up (11)
YGR087C	PDC6	PDC1	Minor isoform of pyruvate decarboxylase, key enzyme in alcoholic fermentation	Slightly up (1)
YIL017C	VID28	VID28	Protein involved in proteasome-dependent catabolite degradation of fructose-1,6-bisphosphatase (FBPase)	unregulated
YGL227W	VID30	n.a.	Protein involved in proteasome-dependent catabolite degradation of fructose-1,6-bisphosphatase (FBPase)	--

Table S3: Reporter metabolites. Reporter metabolites were calculated using the BioMet toolbox. For each condition, adjusted p-values out of the transcriptional comparison (each dilution rate setpoint against the highest specific growth rate of 0.15 h^{-1}) were used for the calculation of Z scores for each reporter metabolite. Additionally reporter metabolites were calculated for the comparisons of μ=0.015 h^{-1} to 0.025 h^{-1} and 0.025 h^{-1} to 0.05 h^{-1}.

Condition 0.015 / 0.15, sorted by descending Z-score and compared with the Z-score of the other conditions

Z-scoresare coloured in light yellow (Z-Score>1) until dark red (Z-Score > 2.5)

		Condition D (h^{-1}) (D (h^{-1}))$^{-1}$	0.015 / 0.15	0.025 / 0.15	0.05 / 0.15	0.075 / 0.15	0.1 / 0.15	0.125 / 0.15
		Number of significantly regulated genes in the metabolic network	330	313	259	175	66	0
Number of neighbors	**Reporter Metabolite**							
10	S-Adenosyl-L-homocysteine[c]		2.71	1.88	0.95	1.32	0.42	-
3	Adenylyl sulfate[c]		2.52	2.11	1.78	2.05	2.35	-
8	L-Methionine[c]		2.36	0.59	1.08	1.63	0.15	-
4	Urea[c]		2.07	1.57	-0.37	0.41	-1.37	-
6	L-Asparagine[c]		2.00	0.91	1.85	2.25	1.51	-
2	3'-Phosphoadenylyl sulfate[c]		1.96	1.41	1.03	1.23	1.47	-
3	2-Oxobutanoate[c]		1.95	2.10	2.12	2.25	2.56	-
10	Succinate[c]		1.94	-0.62	1.02	-0.38	-0.62	-
39	L-Glutamate[c]		1.94	1.76	2.12	2.24	1.81	-
3	Adenosine[c]		1.89	2.27	1.83	1.33	0.96	-
6	L-Homocysteine[c]		1.88	2.47	2.22	1.10	0.91	-
1	Methanol[p]		1.88	1.77	2.03	1.62	2.37	-
14	S-Adenosyl-L-methionine[c]		1.86	2.13	1.56	2.26	1.92	-
9	L-Glutamate[m]		1.84	1.54	2.18	1.87	0.31	-
5	S-Adenosyl-L-methionine[m]		1.78	2.06	1.35	0.84	1.18	-
3	L-Phenylalanine[c]		1.73	1.65	1.89	2.23	1.96	-
5	Phosphatidylcholine[c]		1.72	-0.28	-0.44	0.01	-0.28	-
5	L-Arginine[c]		1.72	1.16	0.49	0.98	0.14	-
5	Ferrocytochrome c[m]		1.70	0.86	0.80	-0.82	-1.01	-
2	(S)-Lactate[c]		1.70	0.67	1.12	1.28	1.89	-
3	Inositol 1-phosphate[c]		1.70	0.01	-0.09	-0.14	-0.19	-
3	Malonyl-CoA[c]		1.69	1.10	0.62	0.63	-0.42	-
2	Putrescine[c]		1.67	1.61	1.69	1.48	2.25	-
2	L-Citrulline[c]		1.67	2.11	2.07	1.98	0.64	-
6	Ferricytochrome c[m]		1.66	1.15	0.66	-0.73	-0.89	-
2	H2O2[m]		1.66	1.48	1.28	1.23	1.05	-
2	1-(5-Phospho-D-ribosyl)-ATP[c]		1.66	1.80	2.07	2.11	2.09	-
2	alpha-D-Glucose[e]		1.65	0.58	0.66	-0.69	-0.03	-
2	H2O[e]		1.61	-0.35	1.27	1.37	1.64	-
2	5-(5-Phospho-D-ribosylaminoformimino)-1-(5-phosphoribosyl)- imidazole-4-carboxamide[c]		1.60	0.80	-0.19	0.11	-0.06	-
2	Cadaverine[c]		1.57	0.49	0.05	0.25	0.77	-
2	Formaldehyde[c]		1.56	0.24	-0.15	0.14	0.28	-
3	Hypoxanthine[c]		1.56	2.00	1.47	1.28	2.24	-
7	L-Ornithine[c]		1.55	1.20	0.82	1.34	0.24	-

Condition 0.025 / 0.15, sorted by descending Z-score and compared with the Z-score of the other conditions

Z-scoresare coloured in light yellow (Z-Score>1) until dark red (Z-Score > 2.5)

	Condition D (h^{-1}) (D (h^{-1}))$^{-1}$	0.015 / 0.15	0.025 / 0.15	0.05 / 0.15	0.075 / 0.15	0.1 / 0.15	0.125 / 0.15
	Number of significantly regulated genes in the metabolic network	330	313	259	175	66	0
Number of neighbors	**Reporter Metabolite**						
6	L-Homocysteine[c]	1.88	2.47	2.22	1.10	0.91	-
3	Adenosine[c]	1.89	2.27	1.83	1.33	0.96	-
14	S-Adenosyl-L-methionine[c]	1.86	2.13	1.56	2.26	1.92	-
2	L-Citrulline[c]	1.67	2.11	2.07	1.98	0.64	-
3	Adenylyl sulfate[c]	2.52	2.11	1.78	2.05	2.35	-
3	2-Oxobutanoate[c]	1.95	2.10	2.12	2.25	2.56	-
5	S-Adenosyl-L-methionine[m]	1.78	2.06	1.35	0.84	1.18	-
3	Hypoxanthine[c]	1.56	2.00	1.47	1.28	2.24	-
2	Urate[c]	1.54	1.98	1.92	1.41	2.26	-
3	Nicotinate[c]	1.41	1.92	2.22	2.47	2.41	-
10	S-Adenosyl-L-homocysteine[c]	2.71	1.88	0.95	1.32	0.42	-
2	1-(5-Phospho-D-ribosyl)-ATP[c]	1.66	1.80	2.07	2.11	2.09	-
1	Methanol[p]	1.88	1.77	2.03	1.62	2.37	-
2	N-(L-Arginino)succinate[c]	0.81	1.76	1.47	1.17	1.88	-
39	L-Glutamate[c]	1.94	1.76	2.12	2.24	1.81	-
2	5-Hydroxyisourate[c]	0.92	1.75	1.94	1.97	1.86	-
2	N-Acetyl-L-glutamate 5-semialdehyde[m]	1.35	1.69	1.23	1.92	2.14	-
2	NH3[m]	1.39	1.69	1.48	1.56	0.85	-
2	4-Phospho-L-aspartate[c]	1.51	1.68	1.77	1.71	2.26	-
2	Acetaldehyde[m]	1.52	1.68	1.52	0.81	-1.32	-
3	L-Phenylalanine[c]	1.73	1.65	1.89	2.23	1.96	-
3	S-Adenosyl-L-homocysteine[m]	1.19	1.64	0.85	0.80	0.97	-
2	alpha-D-Ribose 1-phosphate[c]	1.47	1.63	1.75	1.78	2.08	-
3	5'-Methylthioadenosine[c]	0.44	1.62	1.61	1.90	3.00	-
2	Putrescine[c]	1.67	1.61	1.69	1.48	2.25	-
3	Acyl-carrier protein[c]	1.53	1.61	1.60	1.51	0.77	-
1	Nicotinate[m]	1.09	1.60	1.65	1.85	2.13	-
1	Nicotinamide[c]	1.09	1.60	1.65	1.85	2.13	-
1	Nicotinamide[m]	1.09	1.60	1.65	1.85	2.13	-
2	3-Phosphonooxypyruvate[c]	1.37	1.60	1.73	1.60	2.40	-

Condition 0.05 / 0.15, sorted by descending Z-score and compared with the Z-score of the other conditions

Z-scores are coloured in light yellow (Z-Score>1) until dark red (Z-Score > 2.5)

		Condition D (h^{-1}) (D (h^{-1}))$^{-1}$	0.015 / 0.15	0.025 / 0.15	0.05 / 0.15	0.075 / 0.15	0.1 / 0.15	0.125 / 0.15
		Number of significantly regulated genes in the metabolic network	330	313	259	175	66	0
Number of neighbors	**Reporter Metabolite**							
6	UDP-glucose[c]		1.11	1.46	2.26	2.51	2.57	-
3	Nicotinate[c]		1.41	1.92	2.22	2.47	2.41	-
6	L-Homocysteine[c]		1.88	2.47	2.22	1.10	0.91	-
9	L-Glutamate[m]		1.84	1.54	2.18	1.87	0.31	-
39	L-Glutamate[c]		1.94	1.76	2.12	2.24	1.81	-
3	2-Oxobutanoate[c]		1.95	2.10	2.12	2.25	2.56	-
2	1-(5-Phospho-D-ribosyl)-ATP[c]		1.66	1.80	2.07	2.11	2.09	-
2	L-Citrulline[c]		1.67	2.11	2.07	1.98	0.64	-
1	Methanol[p]		1.88	1.77	2.03	1.62	2.37	-
2	5-Hydroxyisourate[c]		0.92	1.75	1.94	1.97	1.86	-
5	L-Valine[c]		1.28	0.28	1.94	2.51	0.49	-
2	Urate[c]		1.54	1.98	1.92	1.41	2.26	-
3	L-Phenylalanine[c]		1.73	1.65	1.89	2.23	1.96	-
5	L-Isoleucine[c]		1.19	0.23	1.88	2.15	0.44	-
6	L-Asparagine[c]		2.00	0.91	1.85	2.25	1.51	-
3	Adenosine[c]		1.89	2.27	1.83	1.33	0.96	-
2	Allantoate[c]		1.39	1.55	1.83	1.46	-1.32	-
3	S-Adenosylmethioninamine[c]		0.44	1.41	1.83	1.98	2.78	-
4	L-Leucine[c]		0.70	0.72	1.79	1.92	0.99	-
3	Adenylyl sulfate[c]		2.52	2.11	1.78	2.05	2.35	-
4	H+[p]		-0.51	0.86	1.77	2.01	1.06	-
2	4-Phospho-L-aspartate[c]		1.51	1.68	1.77	1.71	2.26	-
2	Acetate[e]		1.45	-0.07	1.77	2.28	2.35	-
2	alpha-D-Ribose 1-phosphate[c]		1.47	1.63	1.75	1.78	2.08	-
6	L-Threonine[c]		0.60	0.42	1.73	2.68	-0.58	-
2	3-Phosphonooxypyruvate[c]		1.37	1.60	1.73	1.60	2.40	-
4	L-Histidine[c]		0.71	1.30	1.71	2.23	1.39	-
1	(R)-Lactate[e]		1.43	1.34	1.70	1.68	2.07	-
1	(S)-Lactate[e]		1.43	1.34	1.70	1.68	2.07	-
1	Pyruvate[e]		1.43	1.34	1.70	1.68	2.07	-
2	Putrescine[c]		1.67	1.61	1.69	1.48	2.25	-
6	L-Tyrosine[c]		1.54	0.57	1.69	1.98	1.13	-
1	Dethiobiotin[c]		0.73	1.19	1.68	2.04	2.20	-
1	Sulfur[c]		0.73	1.19	1.68	2.04	2.20	-
1	5'-Deoxyadenosine[c]		0.73	1.19	1.68	2.04	2.20	-
1	Nicotinate[m]		1.09	1.60	1.65	1.85	2.13	-
1	Nicotinamide[c]		1.09	1.60	1.65	1.85	2.13	-
1	Nicotinamide[m]		1.09	1.60	1.65	1.85	2.13	-
10	L-Serine[c]		1.06	1.24	1.61	1.43	0.40	-
3	5'-Methylthioadenosine[c]		0.44	1.62	1.61	1.90	3.00	-
72	Diphosphate[c]		1.40	1.09	1.60	1.54	1.44	-
3	Acyl-carrier protein[c]		1.53	1.61	1.60	1.51	0.77	-

Condition 0.075 / 0.15, sorted by descending Z-score and compared with the Z-score of the other conditions

Z-scores are coloured in light yellow (Z-Score>1) until dark red (Z-Score > 2.5)

		Condition D (h^{-1}) (D (h^{-1}))$^{-1}$	0.015 / 0.15	0.025 / 0.15	0.05 / 0.15	0.075 / 0.15	0.1 / 0.15	0.125 / 0.15
	Number of significantly regulated genes in the metabolic network		330	313	259	175	66	0
#Feature	Reporter Metabolite							
L-Threonine[c]	6		0.60	0.42	1.73	2.68	-0.58	-
L-Valine[c]	5		1.28	0.28	1.94	2.51	0.49	-
UDP-glucose[c]	6		1.11	1.46	2.26	2.51	2.57	-
Nicotinate[c]	3		1.41	1.92	2.22	2.47	2.41	-
L-Glutamine[c]	18		0.73	0.57	1.53	2.31	1.21	-
Acetate[e]	2		1.45	-0.07	1.77	2.28	2.35	-
S-Adenosyl-L-methionine	14		1.86	2.13	1.56	2.26	1.92	-
L-Asparagine[c]	6		2.00	0.91	1.85	2.25	1.51	-
2-Oxobutanoate[c]	3		1.95	2.10	2.12	2.25	2.56	-
L-Glutamate[c]	39		1.94	1.76	2.12	2.24	1.81	-
L-Phenylalanine[c]	3		1.73	1.65	1.89	2.23	1.96	-
L-Histidine[c]	4		0.71	1.30	1.71	2.23	1.39	-
L-Isoleucine[c]	5		1.19	0.23	1.88	2.15	0.44	-
1-(5-Phospho-D-ribosyl)-A	2		1.66	1.80	2.07	2.11	2.09	-
Adenylyl sulfate[c]	3		2.52	2.11	1.78	2.05	2.35	-
Dethiobiotin[c]	1		0.73	1.19	1.68	2.04	2.20	-
Sulfur[c]	1		0.73	1.19	1.68	2.04	2.20	-
5'-Deoxyadenosine[c]	1		0.73	1.19	1.68	2.04	2.20	-
H+[p]	4		-0.51	0.86	1.77	2.01	1.06	-
L-Tyrosine[c]	6		1.54	0.57	1.69	1.98	1.13	-
S-Adenosylmethioninami	3		0.44	1.41	1.83	1.98	2.78	-
L-Citrulline[c]	2		1.67	2.11	2.07	1.98	0.64	-
5-Hydroxyisourate[c]	2		0.92	1.75	1.94	1.97	1.86	-
L-Leucine[c]	4		0.70	0.72	1.79	1.92	0.99	-
N-Acetyl-L-glutamate 5-s	2		1.35	1.69	1.23	1.92	2.14	-
5'-Methylthioadenosine[c]	3		0.44	1.62	1.61	1.90	3.00	-
L-Serine[m]	3		0.55	-1.51	1.57	1.89	-0.24	-
L-Glutamate[m]	9		1.84	1.54	2.18	1.87	0.31	-
Nicotinate[m]	1		1.09	1.60	1.65	1.85	2.13	-
Nicotinamide[c]	1		1.09	1.60	1.65	1.85	2.13	-
Nicotinamide[m]	1		1.09	1.60	1.65	1.85	2.13	-
L-Lysine[c]	4		-0.05	-0.02	1.21	1.84	0.27	-
L-Glutamine[m]	2		0.94	-0.35	1.39	1.79	0.52	-
alpha-D-Ribose 1-phosph	2		1.47	1.63	1.75	1.78	2.08	-
(2S)-2-Isopropylmalate[c]	2		1.09	0.86	1.33	1.78	1.44	-
L-Proline[m]	3		0.80	0.03	1.55	1.77	-1.62	-
Uracil[c]	3		-0.88	-1.13	1.59	1.75	-0.15	-
L-Threonine[m]	2		0.80	-0.59	1.44	1.74	-0.40	-
tRNA(Tyr)[c]	1		1.24	1.26	1.37	1.72	1.87	-
L-Tyrosyl-tRNA(Tyr)[c]	1		1.24	1.26	1.37	1.72	1.87	-
4-Phospho-L-aspartate[c]	2		1.51	1.68	1.77	1.71	2.26	-
Chitosan[e]	1		0.79	-1.59	1.03	1.71	1.42	-
3-Methyl-2-oxobutanoic a	4		1.19	1.12	1.58	1.70	1.99	-
(R)-Lactate[e]	1		1.43	1.34	1.70	1.68	2.07	-
(S)-Lactate[e]	1		1.43	1.34	1.70	1.68	2.07	-
Pyruvate[e]	1		1.43	1.34	1.70	1.68	2.07	-
1,3-beta-D-Glucan[c]	2		-1.25	0.16	1.14	1.66	1.62	-
L-Methionine[c]	8		2.36	0.59	1.08	1.63	0.15	-
Fatty acid[r]	1		0.49	1.31	1.25	1.62	1.52	-
Dihydroceramide[r]	1		0.49	1.31	1.25	1.62	1.52	-
(2R,3S)-3-Isopropylmalat	2		1.31	1.08	1.08	1.62	1.67	-
L-Lysine[e]	1		0.45	0.77	1.35	1.62	1.28	-
L-Asparagine[e]	1		1.00	0.83	1.29	1.62	0.97	-
L-Cysteine[e]	1		1.00	0.83	1.29	1.62	0.97	-
L-Glutamine[e]	1		1.00	0.83	1.29	1.62	0.97	-
L-Glutamate[e]	1		1.00	0.83	1.29	1.62	0.97	-
Glycine[e]	1		1.00	0.83	1.29	1.62	0.97	-
L-Histidine[e]	1		1.00	0.83	1.29	1.62	0.97	-
L-Isoleucine[e]	1		1.00	0.83	1.29	1.62	0.97	-
L-Leucine[e]	1		1.00	0.83	1.29	1.62	0.97	-
L-Ornithine[e]	1		1.00	0.83	1.29	1.62	0.97	-
L-Phenylalanine[e]	1		1.00	0.83	1.29	1.62	0.97	-
L-Serine[e]	1		1.00	0.83	1.29	1.62	0.97	-
L-Threonine[e]	1		1.00	0.83	1.29	1.62	0.97	-
L-Tryptophan[e]	1		1.00	0.83	1.29	1.62	0.97	-
L-Tyrosine[e]	1		1.00	0.83	1.29	1.62	0.97	-
L-Valine[e]	1		1.00	0.83	1.29	1.62	0.97	-
Methanol[p]	1		1.88	1.77	2.03	1.62	2.37	-
2-Amino-4-hydroxy-6-(ery	1		1.01	0.96	1.36	1.62	1.73	-
Formamidopyrimidine nu	1		1.01	0.96	1.36	1.62	1.73	-
2,5-Diamino-6-(5'-triphos	1		1.01	0.96	1.36	1.62	1.73	-
2,5-Diaminopyrimidine nu	1		1.01	0.96	1.36	1.62	1.73	-
AMP[c]	44		0.61	0.21	0.78	1.61	1.36	-
tRNA(Glu)[c]	1		1.30	1.26	1.20	1.61	1.70	-
L-Glutamyl-tRNA(Glu)[c]	1		1.30	1.26	1.20	1.61	1.70	-
Spermine[c]	1		1.22	1.30	1.47	1.60	2.10	-
Spermidine[c]	1		1.22	1.30	1.47	1.60	2.10	-
H2O2[p]	5		1.49	0.94	1.14	1.60	1.94	-
3-Phosphonooxypyruvate	2		1.37	1.60	1.73	1.60	2.40	-

Condition 0.1 / 0.15, sorted by descending Z-score and compared with the Z-score of the other conditions

Z-scores are coloured in light yellow (Z-Score>1) until dark red (Z-Score > 2.5)

		Condition D (h^{-1}) (D (h^{-1}))$^{-1}$	0.015 / 0.15	0.025 / 0.15	0.05 / 0.15	0.075 / 0.15	0.1 / 0.15	0.125 / 0.15
	Number of significantly regulated genes in the metabolic network		330	313	259	175	66	0
#Feature	Reporter Metabolite							
5'-Methylthioadenosine[c]	3		0.44	1.62	1.61	1.90	3.00	-
S-Adenosylmethioninami	3		0.44	1.41	1.83	1.98	2.78	-
UDP-glucose[c]	6		1.11	1.46	2.26	2.51	2.57	-
2-Oxobutanoate[c]	3		1.95	2.10	2.12	2.25	2.56	-
Phenylpyruvate[c]	3		-0.52	0.72	0.93	0.90	2.47	-
Nicotinate[c]	3		1.41	1.92	2.22	2.47	2.41	-
3-Phosphonooxypyruvate	2		1.37	1.60	1.73	1.60	2.40	-
Methanol[p]	1		1.88	1.77	2.03	1.62	2.37	-
Adenylyl sulfate[c]	3		2.52	2.11	1.78	2.05	2.35	-
Acetate[e]	2		1.45	-0.07	1.77	2.28	2.35	-
Urate[c]	2		1.54	1.98	1.92	1.41	2.26	-
4-Phospho-L-aspartate[c]	2		1.51	1.68	1.77	1.71	2.26	-
Putrescine[c]	2		1.67	1.61	1.69	1.48	2.25	-
Hypoxanthine[c]	3		1.56	2.00	1.47	1.28	2.24	-
Dethiobiotin[c]	1		0.73	1.19	1.68	2.04	2.20	-
Sulfur[c]	1		0.73	1.19	1.68	2.04	2.20	-
5'-Deoxyadenosine[c]	1		0.73	1.19	1.68	2.04	2.20	-
Triacylglycerol[c]	3		0.75	1.51	1.39	1.46	2.18	-
Peptide 2-(3-carboxy-3-a	1		1.26	1.21	1.49	1.59	2.18	-
Peptide 2-[3-carboxy-3-(r	1		1.26	1.21	1.49	1.59	2.18	-
L-Histidinol phosphate[c]	2		0.99	1.20	1.35	1.20	2.15	-
N-Acetyl-L-glutamate 5-s	2		1.35	1.69	1.23	1.92	2.14	-
Nicotinate[m]	1		1.09	1.60	1.65	1.85	2.13	-
Nicotinamide[c]	1		1.09	1.60	1.65	1.85	2.13	-
Nicotinamide[m]	1		1.09	1.60	1.65	1.85	2.13	-
1,2-Diacyl-sn-glycerol 3-p	5		1.25	1.03	0.61	0.19	2.12	-
Spermine[c]	1		1.22	1.30	1.47	1.60	2.10	-
Spermidine[c]	1		1.22	1.30	1.47	1.60	2.10	-
1-(5-Phospho-D-ribosyl)-A	2		1.66	1.80	2.07	2.11	2.09	-
alpha-D-Ribose 1-phosph	2		1.47	1.63	1.75	1.78	2.08	-
Phenylacetaldehyde[c]	1		-0.25	-0.27	-0.23	-0.10	2.08	-
(R)-Lactate[e]	1		1.43	1.34	1.70	1.68	2.07	-
(S)-Lactate[e]	1		1.43	1.34	1.70	1.68	2.07	-
Pyruvate[e]	1		1.43	1.34	1.70	1.68	2.07	-
Pyruvate[c]	14		-0.27	0.16	0.27	1.43	2.05	-
Aminopropylcadaverine[c	1		1.23	1.31	1.53	1.56	2.02	-
3-Methyl-2-oxobutanoic a	4		1.19	1.12	1.58	1.70	1.99	-
Peptide[c]	2		0.24	1.31	1.57	1.41	1.98	-
L-Phenylalanine[c]	3		1.73	1.65	1.89	2.23	1.96	-
L-Cystathionine[c]	4		0.32	1.35	0.76	0.86	1.95	-
H2O2[p]	5		1.49	0.94	1.14	1.60	1.94	-
(S)-Dihydroorotate[c]	1		0.81	1.23	1.21	1.42	1.93	-
S-Adenosyl-L-methionine	14		1.86	2.13	1.56	2.26	1.92	-
tRNA(His)[c]	1		1.20	1.22	1.23	1.20	1.91	-
L-Histidyl-tRNA(His)[c]	1		1.20	1.22	1.23	1.20	1.91	-
L-Histidine[m]	1		1.20	1.22	1.23	1.20	1.91	-
tRNA(His)[m]	1		1.20	1.22	1.23	1.20	1.91	-
L-Histidyl-tRNA(His)[m]	1		1.20	1.22	1.23	1.20	1.91	-
(S)-Lactate[c]	2		1.70	0.67	1.12	1.28	1.89	-
O-Phospho-L-serine[c]	2		0.65	1.36	1.44	1.32	1.88	-
N-(L-Arginino)succinate[c	2		0.81	1.76	1.47	1.17	1.88	-
tRNA(Tyr)[c]	1		1.24	1.26	1.37	1.72	1.87	-
L-Tyrosyl-tRNA(Tyr)[c]	1		1.24	1.26	1.37	1.72	1.87	-
(S)-Methylmalonate semi	1		1.34	0.82	1.01	0.85	1.86	-
5-Hydroxyisourate[c]	2		0.92	1.75	1.94	1.97	1.86	-
Palmitoyl-CoA[r]	1		1.19	1.18	0.84	1.22	1.84	-
CoA[r]	1		1.19	1.18	0.84	1.22	1.84	-
(R)-Lactate[c]	3		0.42	0.46	0.07	0.76	1.83	-
(GlcNAc)2(Man)2(Asn)1[r	1		1.11	1.15	1.25	1.38	1.83	-
(GlcNAc)2(Man)1(Asn)1[r	1		1.11	1.15	1.25	1.38	1.83	-
G00309[v]	1		1.11	1.15	1.25	1.38	1.83	-
G00319[v]	1		1.11	1.15	1.25	1.38	1.83	-
D-Mannose[v]	1		1.11	1.15	1.25	1.38	1.83	-
L-Glutamate[c]	39		1.94	1.76	2.12	2.24	1.81	-
tRNA[c]	1		0.70	0.76	0.95	1.36	1.77	-
tRNA containing 6-isoper	1		0.70	0.76	0.95	1.36	1.77	-
tRNA uridine[c]	1		1.04	1.11	1.17	1.35	1.74	-
tRNA pseudouridine[c]	1		1.04	1.11	1.17	1.35	1.74	-
2-Amino-4-hydroxy-6-(ery	1		1.01	0.96	1.36	1.62	1.73	-
Formamidopyrimidine nu	1		1.01	0.96	1.36	1.62	1.73	-
2,5-Diamino-6-(5'-triphos	1		1.01	0.96	1.36	1.62	1.73	-
2,5-Diaminopyrimidine nu	1		1.01	0.96	1.36	1.62	1.73	-
O-Acetyl-L-homoserine[c]	3		-0.85	-0.33	-0.98	0.59	1.71	-
beta-D-Glucose[c]	1		1.39	1.35	1.58	1.46	1.71	-
Cellobiose[c]	1		1.39	1.35	1.58	1.46	1.71	-
Xanthosine 5'-phosphate[	1		1.12	1.15	0.83	0.84	1.70	-
tRNA(Glu)[c]	1		1.30	1.26	1.20	1.61	1.70	-
L-Glutamyl-tRNA(Glu)[c]	1		1.30	1.26	1.20	1.61	1.70	-
Glutaminyl-tRNA[m]	1		0.71	1.09	1.02	1.12	1.67	-
L-Aspartyl-tRNA(Asn)[m]	1		0.71	1.09	1.02	1.12	1.67	-
L-Glutamyl-tRNA(Gln)[m]	1		0.71	1.09	1.02	1.12	1.67	-
Palmitoyl-CoA[p]	3		0.26	0.83	-0.02	0.97	1.67	-
Tetradecanoyl-CoA[p]	3		0.26	0.83	-0.02	0.97	1.67	-
Dodecanoyl-CoA[p]	3		0.26	0.83	-0.02	0.97	1.67	-
Amylose[c]	2		0.94	-0.39	1.19	1.36	1.67	-
(2R,3S)-3-Isopropylmalat	2		1.31	1.08	1.08	1.62	1.67	-
RNA[c]	4		1.29	1.32	1.45	1.23	1.66	-
2,3-Diketo-5-methylthiope	2		1.17	0.99	1.11	1.45	1.66	-
H2O[e]	2		1.61	-0.35	1.27	1.37	1.64	-
5-Phosphoribosylamine[c	1		0.74	1.05	0.03	1.25	1.63	-
1,3-beta-D-Glucan[c]	2		-1.25	0.16	1.14	1.66	1.62	-
N-Acetyl-L-glutamate 5-p	1		0.79	1.34	0.87	1.35	1.62	-
L-Asparaginyl-tRNA(Asn)	2		0.84	1.00	1.21	1.37	1.61	-
3-Oxooctadecanoyl-CoA[	2		-0.48	-0.38	0.60	1.04	1.60	-
3-Oxopalmitoyl-CoA[p]	2		-0.48	-0.38	0.60	1.04	1.60	-
3-Oxotetradecanoyl-CoA[	2		-0.48	-0.38	0.60	1.04	1.60	-
3-Oxodecanoyl-CoA[p]	2		-0.48	-0.38	0.60	1.04	1.60	-
3-Oxododecanoyl-CoA[p]	2		-0.48	-0.38	0.60	1.04	1.60	-
3-Oxooctanoyl-CoA[p]	2		-0.48	-0.38	0.60	1.04	1.60	-
Inosine[c]	1		0.78	1.23	1.37	1.40	1.60	-
Deoxyguanosine[c]	1		0.78	1.23	1.37	1.40	1.60	-
2-Deoxy-D-ribose 1-phos	1		0.78	1.23	1.37	1.40	1.60	-
Guanosine[c]	1		0.78	1.23	1.37	1.40	1.60	-
Deoxyadenosine[c]	1		0.78	1.23	1.37	1.40	1.60	-
Deoxyinosine[c]	1		0.78	1.23	1.37	1.40	1.60	-
Deoxyuridine[c]	1		0.78	1.23	1.37	1.40	1.60	-
tRNA(Met)[m]	1		0.59	0.64	0.66	0.90	1.60	-

Condition A_B: 0.015/0.025; condition B_C: 0.025/0.05
Sorted for high Z-score in A_B (> 2) and low Z-score in B_C (< 2)

#Feature	Condition: A_B Z-score	Condition: B_C Z-score
Fe2+[c]	3.55237	0.981414
L-Alanine[c]	3.0241	0.682319
alpha-D-Glucose 1-phosphate[c]	2.86158	-0.302103
Fumarate[c]	2.84363	-0.525585
Biotin[c]	2.73901	1.04075
Fe3+[c]	2.67409	1.80295
(Indol-3-yl)acetamide[c]	2.6238	-0.623151
sn-glycero-3-Phosphoethanolamine[c]	2.60404	1.58571
(S)-Malate[c]	2.60377	0.242996
UDP-glucose[c]	2.42272	-1.10989
L-Methionine[c]	2.4199	0.563615
L-Tryptophan[c]	2.41599	1.61105
3-Hexaprenyl-4,5-dihydroxybenzoate[m]	2.36321	-0.623151
3-Hexaprenyl-4-hydroxy-5-methoxybenzoate[m]	2.36321	-0.623151
(S)-3-Hydroxydocosanoyl-CoA[p]	2.34544	0.356819
(S)-3-Hydroxyeicosanoyl-CoA[p]	2.34544	0.356819
(S)-3-Hydroxyoctadecanoyl-CoA[p]	2.34544	0.356819
(S)-3-Hydroxyhexacosanoyl-CoA[p]	2.34544	0.356819
(S)-3-Hydroxytetracosanoyl-CoA[p]	2.34544	0.356819
(S)-3-Hydroxyhexadecanoyl-CoA[p]	2.34544	0.356819
(S)-3-Hydroxytetradecanoyl-CoA[p]	2.34544	0.356819
(S)-Hydroxydecanoyl-CoA[p]	2.34544	0.356819
(S)-Hydroxyhexanoyl-CoA[p]	2.34544	0.356819
(S)-3-Hydroxydodecanoyl-CoA[p]	2.34544	0.356819
(S)-Hydroxyoctanoyl-CoA[p]	2.34544	0.356819
Oxaloacetate[p]	2.33577	1.73205
L-Methionine[e]	2.25872	-0.623151
(S)-Malate[p]	2.22363	0.784573
3-Sulfopyruvate[c]	2.21422	-0.623151
3-Sulfolactate[c]	2.21422	-0.623151
Acetaldehyde[m]	2.18657	1.60275
L-Ornithine[c]	2.1816	1.45438
Sphinganine[c]	2.16153	1.16975
L-Arginine[c]	2.13642	1.54853
Stearidonic acid[c]	2.11356	1.94105
Glyoxylate[c]	2.10833	-0.273315
3-Oxooctadecanoyl-CoA[p]	2.10733	0.356819
3-Oxopalmitoyl-CoA[p]	2.10733	0.356819
3-Oxotetradecanoyl-CoA[p]	2.10733	0.356819
3-Oxodecanoyl-CoA[p]	2.10733	0.356819
3-Oxododecanoyl-CoA[p]	2.10733	0.356819
3-Oxooctanoyl-CoA[p]	2.10733	0.356819
2-Methylbutanal[c]	2.10576	-0.623151
1-Acyl-sn-glycero-3-phosphocholine[c]	2.09105	-0.881201
1-Acyl-sn-glycero-3-phosphoethanolamine[c]	2.09105	-0.881201
4-Fumarylacetoacetate[c]	2.03303	-0.623151
Acetoacetate[c]	2.03303	-0.623151
Dihydroceramide[c]	2.03288	1.62822
O-Acetylcarnitine[m]	2.03007	1.85003
Carnitine[m]	2.03007	1.85003
alpha-D-Glucose[e]	2.02812	1.02054
Carnitine[c]	2.02233	0.81801
H+[p]	2.01327	0.807558
L-Citrulline[c]	2.58043	2.61956
N-(L-Arginino)succinate[c]	2.46255	2.14143

The last two lines were included as they relate to the upregulated part of the arginine pathway