Supplementary text and figures

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1 Detailed description of changes in the metabolic profiles

As a result of cold stress several amino acids including alanine, asparagine, lysine, methionine, isoleucine, leucine, as well as organic acids such as 2-aminobutyric acid, or 4-aminobutyric acid increase within the first 40 min post-perturbation. By 50 min post-perturbation the concentration of further amino acids and carboxylic acids (aspartic acid, glutamic acid, phenylalanie, homoserine, threonic acid) increases.

A similar response is observed after heat stress. Most amino acids increase within 20 min after heat stress (isoleucine, threonine, phenylalanine, lysine, alanine, asparagine, glutamic acid, homoserine), in addition to trehalose and fumaric acid, which increase 50 min post-perturbation, and malic acid (which increases 150 min post-perturbation). The accumulation of trehalose in response to heat stress has been previously reported and is thought to reduce the deleterious effect of high temperature on the folding and aggregation of proteins [1]. Whereas the majority of amino acids increase after heat stress exposure, glucose-6-phosphate, pyruvic acid, and glyceric acid-3-phosphate rapidly (10 min after stress application) decrease in addition to 2-ketobutyric acid, methionine, GABA, and, with some delay, succinic acid. Only few metabolites recover from initial decreases such as pyruvic acid, erythrose-4-phosphate, ribose-5-phosphate, and glycerol.

Glucose starvation during lactose diauxie displays a large number of transient changes in metabolite concentration. 10 min after the cessation of growth, phosphoenolpyruvate (PEP) and asparagine increase, whereas leucine, valine, homoserine, 2-ketoglutaric acid, and 2-ketobutyric acid transitorily decrease. Since PEP serves as phosphate donor for the phosphotransferase system (PTS) responsible for glucose import, swift accumulation of PEP was

recently proposed to be a direct effect of decreased glucose import caused by low glucose concentration within the medium [2].

Major changes were observed between 90 and 200 min post-perturbation. At the 90 min time point amino acids (alanine, glutamine, glycine, leucine, lysine, phenylalanine, homoserine, threonine, and valine), organic acids acids (2-hydroxyglutaric acid, pyruvic acid, 2-aminobutyric acid, and 4-aminobutyric acid) and isomaltose increase in a transient fashion. At the 150 min time point asparagine, fumaric acid, succinic acid, 2-hydroxybutyric acid, and 6-phosphogluconic acid also increased.

Transient changes at 10 min post-perturbation also characterize the response to oxidative stress. Alanine and asparagine significantly increase whereas aspartic acid, isoleucine, glucose-6-phosphate, and 2-ketoglutaric acid decrease transiently. Similar to the changes observed during the glucose-lactose shift, major metabolic changes occurred 90 min post-perturbation, including increases in the levels of amino acids (alanine, arginine, cysteine, glycine, isoleucine, phenylalanine, proline, threonine and valine), carboxylic acids (isopropylmalic acid, pyruvic acid, succinic acid, 2-ketoglutaric acid and 4-aminobutyric acid), dodecanoic acid, erythrose-4-phosphate, and trehalose. Most of those metabolites continue to increase in the next time point (150 min) with the addition of asparagine, lysine, methionine, and fumaric acid, which also show a significant increase during entry into the stationary phase.

The massive changes at 90 min post-perturbation observed for the glucose-lactose shift and oxidative stress experiments were also observed for the control culture suggesting that they are due to the prevailing growth phase, i.e. the transition between exponential growth and early stationary phase. This is supported by the increase in levels of trehalose (90 min post-oxidative stress) and many amino acids starting 90 min post-perturbation. Elevated trehalose concentrations have been previously associated with a transition between logarithmic growth and stationary phase [3]. The observed increase in amino acids before entry into stationary phase has been interpreted to result from protein degradation thought to increase availability of building blocks for synthesis of proteins important for survival during starvation [4].

The stationary phase in control cultures is characterized by decreases in the levels of 2-ketobutyric acid and gluconic acid whereas trehalose, PEP, oxalic acid, and glycolic acid levels increase. The accumulation of trehalose during stationary phase is in agreement with earlier reports [5]. Furthermore PEP has been reported to accumulate during entry into stationary phase for *E. coli* [6].

2 Discussion of transcriptional changes observed directly after perturbation

Analysis of highly expressed genes under different conditions reveals numerous stress specific responses such as increase of cold shock and cold inducible proteins *(cspB, cspI, cspG, nusA,*

ynfN) under cold stress, heat shock proteins *(ibpB, ibpA, hchA, hslO, hslR)* under heat stress, oxidative response genes including members of oxyR regulon *(oxyS, sulA, trxC, dps, katG)* under oxidative stress, and disaccharide transporters and carbon starvation inducible proteins *(lacZ, csiD, csiE, lacY)* during glucose lactose shift. The induction of the expression of exemplary stress marker genes are indicated in Figure 2A and B.

Analysis of the transcriptome data for the diauxic shift experiment shows that 459 transcripts change already before induction of *lacZ* becomes detectable. Analysis of GO terms indicates that most of these genes are associated with carbon starvation response including genes associated with GO terms: ATP sythesis, biosynthetic processes of nucleotide, ribonucleotide, amino acid and amine, cell motion and proton transport which are all down-regulated. At the same time a number of starvation specific genes are induced e.g. *cstA* [7], *csiD* [8] and *csiE* [9]. As well, this maximum in gene expression is accompanied by a maximum in metabolite changes including significant increases in PEP and 3PGA levels, metabolites which accumulate during carbon starvation [2].

3 Perturbation elicits a specific response both on metabolic and transcript level

To assess the degree of similarity between different experimental conditions and time points we applied HCA (hierarchical clustering algorithm) to all time points from all conditions tested on both the transcript and metabolic level.

On the metabolic level we observed a separation of all time points into two major groups which reflects on the one hand a strong influence of the growth phase (Suppl. Fig. 8) and on the other hand the specific stress (Suppl. Fig. 8A). Here the metabolic profiles of the stationary phase samples of control, diauxic shift, and oxidative stress experiments group together (black colour coding). The same holds true for the samples of late logarithmic growth (blue). The second major group contains post-perturbation time points (red) of cold, heat and oxidative stress experiments together with distinct sub-clusters of prior-perturbation and control samples (green). The two temperature shift experiments are clearly separated, thereby suggesting specific adaptation to heat and cold. Following both temperature stresses due to continued presence of stress no resumption of logarithmic growth was observed within the limits of the experiment, however a separation of late post-perturbation time points (*t8-t12*) is evident within the heat and cold specific clusters. Co-clustering of post-perturbation adaptation phase time points from oxidative (*t4-t7*) and heat (*t3-t7*) stress experiments could indicate similar mechanism of system response to these two perturbations which is evident in all data descried in this work. It is worth mentioning that all control samples except late log phase (*t8-t9*) and stationary phase (*t10-t12*) cluster together with the time points prior to perturbation of all stress experiments (green) except the diauxic shift experiment which forms a cluster of its own.

When next applying HCA separately to these three groups (before perturbation, post-perturbation, and stationary phase time points) both the pre-perturbation and the stationary phase samples showed a high degree of similarity within each of the two groups and could not be ordered according to the stress applied (data not shown). In contrast HCA applied to early post-perturbation samples (10-40min) from different stress conditions and the corresponding time points from control revealed an overall disparity of sample groups based upon the stress applied (Suppl. Fig. 8B). Two main sub clusters can be seen, the first containing heat stress samples and oxidative stress time points and the second the glucose-lactose shift and control time points as well as cold stress experiment.

High similarity between oxidative stress and heat stress is in agreement with previous observations indicating that oxidative stress triggers physiologically similar responses compared to heat stress (for review see [10]). For example, a number of key proteins important for the protection against heat stress including GroEL, GroES, and DnaK, are induced by oxidative stress as well. Also it is suggested that heat stress by disrupting the electron transport chain can generate reactive oxygen species and trigger an oxidative stress response [11].

When applying a similar analysis on the transcriptomic data, taking into account only the post-perturbation time points, a similar picture emerges. All stresses are well separated from each other and form clusters on their own (except one outlier in case of diauxic shift) with the heat cluster being the most different (Suppl. Fig. 8C).

In summary, the response on both the transcriptome and the metabolome level displays a large amount of specificity allowing one to discriminate the different applied stresses.

4 Overlap between heat stress response and stationary phase might be due to shift to anaerobic respiration.

Increase in the temperature and bacterial culture density might lead to shift from aerobic to micro-aerobic (hypoxia) conditions under both heat stress and stationary phase. This is supported by the analysis of transcript data showing significant increase in levels of genes involved in hypoxic metabolism including fumarate reductase (*frdABCD*), *arcA*, pyruvate formate-lyase (*tdcE*), hydrogenases (*hyaBC*, *hycDG*) and a number of stationary phase induced genes (*ugpABC*, *aspA*, *fumB*).

A shift to micro-aerobic conditions is known to have a predominant influence on central metabolism [12], conversion of pyruvic acid to acetyl-CoA is no longer catalyzed by pyruvate dehydrogenase which is partially replaced by pyruvate formate-lyase (PFL). 2-ketoglutarate dehydrogenase is repressed blocking TCA cycle at 2-ketoglutarate, succinate dehydrogenase activity is replaced by fumarate reductase (Frd), while genes coding enzymes catalyzing conversion of oxaloacetate to fumaric acid (*aspAC*) are induced [13]. Similar transcriptional response was observed also in our own data following heat and stationary phase (see above)

but also during glucose-lactose shift, where levels of *aspA* and *frdACD* significantly increase. The explanation why hypoxia related genes are significantly induced under glucose-lactose shift might come from the previous studies showing that the responses triggered by both carbon starvation and hypoxia are physiologically related and were suggested to originated from similar redirection of metabolic pathways under both conditions [12]. However it is intriguing to find that the metabolic profiles of the glucose-lactose shift and the stationary phase are not similar (Fig. 4B), while the only stress condition which is similar to the stationary phase is heat stress.

Increase in levels of fumaric acid is one of the overlapping changes between those two conditions. The accumulation of fumaric acid under hypoxic conditions might be caused by redirection of TCA cycle flux [13]. Fumaric acid levels might be feed by activation of a route from oxaloacetate through aspartic to fumaric acid and by conversion of malic to fumaric acid by fumarase B [14]. Increased fumaric acid levels can be then used as an alternative electron acceptor for anaerobic respiration. High overlap which was observed between stationary phase and stress responses at transcriptional level (Fig. 4C) can at least partially result from a general transcriptional stress response program including repression of genes from aerobic metabolism [15, 16]. At the same time the actual cellular metabolism is much more condition specific (Fig. 4B) however changes in crucial environmental parameters (oxygen concentration) lead to the similar redirection of the metabolism under different experimental conditions such as heat and stationary phase.

5 Significance estimation of co-clustering events via bootstrap sampling

In order to determine the statistical significance of a co-clustering event of genes and metabolites that leads to a pathway enrichment, we employed a non-parametric bootstrap procedure [17] for each set of co-clustered genes and metabolites. Let X denote such a set comprised of at least one gene and at least one metabolite that resulted in a pathway enrichment by membership of the same cluster. For each set X we perform the following steps:
(1) We sample with replacement from the original set of genes and metabolites (containing in total m variables) by randomly selecting m genes and metabolites with equal probability of $\frac{1}{m}$. If necessary, this step is repeated until all elements of X are present in this bootstrap sample.
(2) The bootstrap sample is subjected to k-means clustering as outlined before in the *Materials and Methods* section of the manuscript. Let $\mathcal{P} = \{P_1, \ldots, P_k\}$ be a clustering composed of k clusters. We define the co-clustering indicator function f_{co} for the set X as:

$$f_{co}(X) = \begin{cases} 1 & : \quad if X \subseteq P_i, 1 \leq i \leq k \\ 0 & : \quad else \end{cases}$$

Since the granularity of the clustering (i.e. the choice of parameter k) greatly effects a possible co-clustering, parameter k in this step is set to match the value of k that lead to an enrichment in the original condition-specific clustering.
(3) The bootstrap sampling procedure and subsequent clustering is repeated 1000 times to obtain an empirical probability $p_{observed}$ of the occurrence of the co-clustering event for X.

The outlined approach consisting of steps (1)-(3) is therefor a Bernoulli trial with 1000 independent repetitions and the dichotomous outcome of 1 (= co-clustering) and 0 (= no co-clustering). Furthermore, we assume that the co-clustering of all members of X occurs randomly. Then, the probability p_{random} of such a random co-clustering for set X equals $\frac{k}{k^l}$, where k denotes the number of clusters and l is the size of set X. A binomial expansion with the parameters $n = 1000$ (i.e. the sample size), $p_{random} = \frac{k}{k^l}$ (i.e. the probability of success) and $q = 1 - p$ (i.e. the probability of failure) yields a probability distribution which equals the binomial distribution $\mathbf{B}(n, p_{random})$. Now, we let H_0 denote the null hypothesis that a co-clustering of set X occurs randomly. By application of the binomial test (e.g. the `binom.test()`-function in `R`) using $\mathbf{B}(n, p_{random})$ as the null-distribution, we can decide if the observed probability $p_{observed}$ for a particular co-clustering is in agreement with H_0 or should be rejected in favor of the alternative hypothesis H_1. Rejection of H_0 implies that a co-clustering event is not random and occurs with the probability of $p_{observed}$. Naturally, we only consider the possibility that $p_{observed} \gg p_{random}$ which corresponds to a right-sided test. Finally, we account for the multiple testing of all co-clustering events found in our analysis by Bonferroni-correction and set the significance level to 1%. P-values obtained by the binomial test, as well as the empirically determined co-clustering probabilities, are presented in supplementary table 3 in conjunction with the respective sets of clusters and pathway enrichment.

6 Supplementary Tables

Supplementary Table 1: Metabolites which change significantly ($p < 0.05$, ratios ≥ 2) as ratio between time point of interest and time points before stress are shown. Colours indicate direction of change: purple-increase, blue-decrease.

cold stress	10min	20min	30min	40min	50min	90min	150min	210min	300min	320min
2 aminobutyric acid	5.55	4.93	4.64	4.90	5.33	5.19	4.77		3.56	3.37
2hydroybutyric acid								2.49	3.18	3.22
4Aminobutyric acid			2.16	2.45	3.03	4.58	12.69	25.19	31.07	29.15
Adipic acid	2.27									2.55
Alanine	2.71	2.74	3.09	3.23	3.57	3.19	3.28		2.61	2.51
arginine					2.69				2.80	2.39
asparagine	2.71	2.73	2.66	2.55	2.87	3.56	3.57		4.41	4.09
Aspartic acid					2.45	2.56	2.86	2.46	3.26	3.23
Glutamic acid					2.18	2.37	2.63	2.63	2.97	2.69
Glutamic acid N acetyl					2.16	2.22				
glutamine							3.41	2.81	3.50	3.20
Glutamine N acetyl					2.37	2.28				
Homoserine					2.03	2.62	2.03	2.95		
Isoleucine			2.10	2.30	2.83	2.26	4.12	3.36	5.30	5.04
Leucine		2.07	2.11	2.16	2.38	2.26	2.53	2.03	2.49	2.39
Lysine	2.90	2.61								2.60
Malic acid						0.44	0.45		0.40	0.38
Methionine	2.97	2.38	2.14	2.03	2.36					
Phenylalanine					2.33	2.45	3.20	2.35		3.51
Pyroglutamic acid							2.31	2.55		2.69
ribose5P						0.50	0.44		0.47	0.47
Threonic acid					2.47	2.62	2.93	2.49	3.41	3.29
Tyrosine			0.19							

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Supplementary Table 1 – continued from previous page

glucose-lactose diauxie	10min	20min	30min	40min	90min	140min	210min
Alanine					3.54		
arginine							7.55
asparagine	4.61					7.67	
Benzoic acid 4 hydroy						9.82	
cysteine					4.28	9.38	9.32
Fumaric acid						4.66	
Glucose 6 phosphate							9.29
Glutamine					3.13		
Glutamine N acetyl					10.21		
Glutaric acid 2 hydroy					3.14		
Glycerol 3 phosphate						3.06	
Glycine					3.28		
Isomaltose					9.65		0.23
isopropylmalic acid					3.14	7.58	
Leucine	0.46				2.13		
Lysine					2.90		5.01
Malic acid					4.84	12.15	6.87
Maltose						0.28	0.03
PEP	8.87						
Phenylalanine					3.10		
Homoserine	0.36				4.09		
Proline				2.15	4.62	13.06	
Pyruvic acid					5.37		
ribose 5P						7.39	
Serine major							4.52
Succinic acid						5.48	
Threonine					4.20		
Valine	0.39				3.26		
2 aminobutyric acid					4.59		
2 hydroybutyric acid						4.13	
2 ketobutyric acid	0.34	0.41					
2 ketoglutaric acid	0.32						
4 Aminobutyric acid		2.26	2.95	3.54	4.16		
6 phosphogluconic acid						17.35	9.77

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Supplementary Table 1 – continued from previous page

unperturbed culture	10min	20min	30min	40min	50min	90min	150min	210min	240min	260min
arginine							5.89			
asparagine						3.68	3.67			2.68
Aspartic acid						2.96				
Azelaic acid							0.38	0.27	0.24	0.21
Benzoic acid 4 hydroy						2.72	4.16	4.79	4.88	4.45
cysteine					2.56	5.20	7.70	6.95	7.63	8.10
D erythrose 4 phosphate						3.01				
Fumaric acid						2.56	3.76	3.60	3.88	3.50
Gluconic acid							0.32	0.11	0.07	0.06
Glucose 6 phosphate					2.13	3.85	6.02			
Glutamic acid					2.11	3.24	3.22	2.98	3.32	3.12
Glutamic acid N acetyl						6.42	7.31	4.40	3.28	3.25
Glutamine						2.15				
Glutamine N acetyl						8.34	16.42			6.37
Glutaric acid 2 hydroy						2.67	3.93	4.92	4.90	4.50
Glycerol				0.47						
Glycerol 3 phosphate						2.32	3.45	2.82	3.11	2.50
Glycine						2.16	2.57			
heptadecanoic acid								2.04	2.06	
Isoleucine						2.59		47.16	57.71	52.16
isopropylmalic acid						2.87	4.24	3.33	3.06	2.89
Leucine						2.28		2.54	3.74	3.72
Lysine					2.01	3.13	4.57	5.68	4.54	3.87
Malic acid						2.71	4.28	3.20	4.29	3.24
Maltose										0.26
Methionine						2.90	4.85	5.85	5.74	4.86
oalic acid									10.35	
Pelargonic acid or Nonanoic acid			0.49							
PEP								2.18		
Phenylalanine						2.55	4.67	9.48	10.85	9.86
Homoserine						3.03				
Proline						3.39	5.19	6.36	7.20	5.97
Pyroglutamic acid								2.93	3.20	2.78
Pyruvic acid						3.27	6.22			
ribose 5P						2.86				
Serine major							2.08	2.22	2.53	
Spermidine major										0.41
Succinic acid						2.34	4.35	4.63	4.38	3.60
Threonine						3.29	7.38	7.66	9.78	7.74
Thymine							2.66	2.60	3.21	2.43
Trehalose										321.38
Valine						2.76		2.29	2.73	2.41
2 aminobutyric acid						3.39				
2 hydroybutyric acid							2.65			
2 ketobutyric acid						3.13		0.14	0.13	0.12
2 ketoglutaric acid						2.97		155.91	188.88	164.54
4 Aminobutyric acid						3.07	5.94			3.58
6 phosphogluconic acid					2.22	4.08	7.37			

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Supplementary Table 1 – continued from previous page

heat stress	10min	20min	30min	40min	50min	90min	150min	210min	230min
Alanine		6.05	6.41	7.02	8.42	12.35	14.96	17.89	19.76
arginine				2.39			5.97	8.39	10.28
asparagine		3.31	3.40	3.18	3.80	5.13	6.40	6.86	7.44
Aspartic acid						2.01			
cysteine				2.38					
D erythrose 4 phosphate			0.34						
Fumaric acid					2.47	4.00	5.40	6.81	7.78
Gluconic acid								0.49	
Glucose 6 phosphate	0.39	0.37	0.49	0.35	0.35	0.25	0.34	0.44	0.38
Glutamic acid	2.38	2.59	2.71	2.89	2.90	3.11	3.20	3.59	3.43
Glutamic acid N acetyl			0.47						
Glutamine N acetyl		0.42	0.33	0.32	0.36	0.43	0.42		
glutamine minor									2.15
Glyceric acid 3 phosphate	0.42	0.40	0.39	0.35	0.45	0.50			
Glycerol					0.47				
Isoleucine		22.28	20.31	20.61	23.16		31.82		
Lysine		7.77		7.16			10.16		
Malic acid							2.92	4.27	5.06
Methionine	0.05	0.06	0.05	0.11	0.04	0.06	0.08	0.08	0.08
Phenylalanine		13.31	14.07	14.19	16.54		27.52	40.40	45.39
Homoserine		2.02	2.30	2.52	3.34	5.26	6.35	7.79	8.83
Proline		4.93	5.31	6.16	7.37		12.69		18.34
Pyroglutamic acid							3.12		
Pyruvic acid		0.48	0.42	0.45	0.46			3.39	4.07
ribose 5P				0.43		0.46			
Succinic acid			0.48	0.43	0.43	0.42	0.41		
Threonine		16.11	16.52	17.62	21.96	31.78	38.87	46.83	52.02
Trehalose					2.58		30.99		
ureidopropionic acid								0.44	
2 aminobutyric acid								4.24	
2 ketobutyric acid	0.15	0.14	0.12	0.16	0.15	0.15	0.26	0.37	0.44
4 Aminobutyric acid		0.48	0.47	0.46					
6 phosphogluconic acid						0.48			

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Supplementary Table 1 – continued from previous page

oxidative stress	10min	20min	30min	40min	90min	150min	210min	230min
Alanine	3.75	5.99	6.61	6.44	2.54			
arginine				2.44	2.75	4.56	4.53	
asparagine	2.12	3.52	4.67			4.59		
asparagine minor				3.27				
Aspartic acid	0.36			2.05				
Azelaic acid							0.28	0.18
Benzoic acid 4 hydroy					2.39	3.64	5.79	6.17
cysteine					2.77	5.40	6.02	7.45
D erythrose 4 phosphate					2.16			
dodecanoic acid					2.28			
Fumaric acid						2.58		
Galactonic acid gamma lactone							0.27	
Gluconic acid							0.13	0.07
Glucose 6 phosphate	0.36	0.28	0.39					
Glutamic acid N acetyl					3.82			
Glutamine N acetyl					4.93	12.40	17.72	
Glutaric acid 2 hydroy						9.76	16.77	16.39
Glyceric acid 3 phosphate		0.44						
Glycerol 3 phosphate							3.04	3.24
glycine minor					2.06	2.83		
Glycolic acid							7.27	
Heacosanoic acid							2.12	
Isoleucine	0.38				3.14		42.17	40.44
isopropylmalic acid					2.79	5.92	7.63	7.80
Leucine		0.30				2.05		
Lysine			3.78	4.31		2.95	4.86	3.55
Malic acid	0.27	0.45						
Methionine						3.39	3.79	3.82
Phenylalanine				2.20	2.70	3.63		7.75
Uracil							3.83	4.37
Proline		2.02			2.44			
Pyroglutamic acid				2.48	2.25			2.57
Pyruvic acid				2.58	2.44	4.38		
Serine major								2.77
Succinic acid					3.06			
Threonine					2.80		8.17	11.71
Thymine							2.64	
Trehalose					4.89	9.02		
Valine					2.20			
2 ketobutyric acid						3.72	0.24	0.20
2 ketoglutaric acid	0.30				3.34			
4 Aminobutyric acid					2.16		9.98	12.21
6 phosphogluconic acid		0.36						

Supplementary Table 2: List of 288 genes directly related via biochemical pathway enzymes to analyzed metabolites (based on EcoCyc database).

	gene name	Blatter number	gene product	related metabolite
1	trpB	b1261	tryptophan synthase subunit beta	L-serine
2	ygaF	b2660	predicted enzyme	2-Hydroxyglutarate
3	idnO	b4266	gluconate 5-dehydrogenase	Gluconate
4	tdcE	b3114	pyruvate formate-lyase 4/2-ketobutyrate formate-lyase	2-ketobutyrate
5	pyrC	b1062	dihydroorotase	Dihydroorotate
6	glcD	b2979	glycolate oxidase subunit, FAD-linked	glycolate
7	mhpE	b0352	4-hydroxy-2-ketovalerate aldolase	Ribitol
8	pps	b1702	phosphoenolpyruvate synthase	Phosphoenolpyruvate
9	yhiJ	b3488	hypothetical protein	L-serine
10	thrS	b1719	threonyl-tRNA synthetase	L-threonine
11	cysS	b0526	cysteinyl-tRNA synthetase	L-cysteine
12	pheT	b1713	phenylalanyl-tRNA synthetase beta subunit	L-phenylalanine
13	fadD	b1805	acyl-CoA synthase	2-hexadecenoate
14	idnK	b4268	D-gluconate kinase, thermosensitive	6-phospho-D-gluconate
15	pstS	b3728	phosphate transporter subunit	L-glutamate
16	ugpQ	b3449	cytoplasmic glycerophosphodiester phosphodiesterase	Glycerol
17	hisS	b2514	histidyl-tRNA synthetase	L-histidine
18	lpd	b0116	dihydrolipoamide dehydrogenase	Glycine, Ribitol
19	pyrD	b0945	dihydroorotate dehydrogenase	Dihydroorotate
20	mqo	b2210	malate:quinone oxidoreductase	Malate
21	gnd	b2029	6-phosphogluconate dehydrogenase	6-phospho-D-gluconate
22	folC	b2315	bifunctional folylpolyglutamate synthase/ dihydrofolate synthase	L-glutamate
23	glyA	b2551	serine hydroxymethyltransferase	Glycine
24	purF	b2312	amidophosphoribosyltransferase	L-glutamate
25	gldA	b3945	glycerol dehydrogenase	Glycerol
26	zwf	b1852	glucose-6-phosphate 1-dehydrogenase	beta-D-Glucose 6-phosphate
27	argG	b3172	argininosuccinate synthase	L-aspartate
28	ucpA	b2426	short chain dehydrogenase	D-erythrose-4-phosphate
29	serS	b0893	seryl-tRNA synthetase	L-serine
30	pabC	b1096	4-amino-4-deoxychorismate lyase	Ribitol

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Supplementary Table 2 – continued from previous page

31	aspC	b0928	aspartate aminotransferase, PLP-dependent	2-ketoglutarate
32	treA	b1197	periplasmic trehalase	Trehalose, 2-ketoglutarate
33	serC	b0907	phosphoserine aminotransferase	2-ketoglutarate
34	ydiD	b1701	hypothetical protein	2-hexadecenoate
35	serA	b2913	D-3-phosphoglycerate dehydrogenase	2-Hydroxyglutarate
36	lldD	b3605	L-lactate dehydrogenase, FMN-linked	Ribitol
37	aroA	b0908	3-phosphoshikimate 1-carboxyvinyltransferase	Phosphoenolpyruvate
38	dld	b2133	D-lactate dehydrogenase, FAD-binding, NADH independent	Ribitol
39	glcB	b2976	malate synthase	Malate
40	argA	b2818	N-acetylglutamate synthase	L-glutamate
41	purB	b1131	adenylosuccinate lyase	Fumarate
42	speF	b0693	ornithine decarboxylase isozyme, inducible	L-ornithine
43	pflB	b0903	pyruvate formate lyase I	Ribitol
44	amn	b1982	AMP nucleosidase	D-ribose-5-phosphate
45	lysS	b2890	lysine tRNA synthetase, constitutive	L-lysine
46	pyrG	b2780	CTP synthetase	L-glutamate
47	yidA	b3697	predicted hydrolase	Trehalose
48	metA	b4013	homoserine O-succinyltransferase	Homoserine
49	pgk	b2926	phosphoglycerate kinase	3-phosphoglycerate
50	alr	b4053	alanine racemase	L-alanine
51	gadB	b1493	glutamate decarboxylase B, PLP-dependent	4-aminobutyrate
52	rluD	b2594	23S rRNA pseudouridine synthase	D-ribose-5-phosphate
53	otsB	b1897	trehalose-6-phosphate phosphatase, biosynthetic	Trehalose
54	proS	b0194	prolyl-tRNA synthetase	L-proline
55	pyrE	b3642	orotate phosphoribosyltransferase	Orotate
56	argB	b3959	acetylglutamate kinase	N-Acetyl-L-glutamate
57	ldhA	b1380	D-lactate dehydrogenase	Ribitol
58	panD	b0131	aspartate 1-decarboxylase precursor	beta-Alanine
59	gntK	b3437	gluconate kinase 2	6-phospho-D-gluconate
60	frdB	b4153	fumarate reductase (anaerobic), Fe-S subunit	Fumarate
61	maeB	b2463	malic enzyme	Malate
62	glnS	b0680	glutaminyl-tRNA synthetase	L-Glutamine

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Supplementary Table 2 – continued from previous page

63	metC	b3008	cystathionine beta-lyase	2-ketobutyrate
64	asnS	b0930	asparaginyl-tRNA synthetase	L-asparagine
65	argH	b3960	argininosuccinate lyase	Fumarate
66	fumC	b1611	fumarate hydratase	Fumarate
67	tnaA	b3708	tryptophanase/L-cysteine desulfhydrase, PLP-dependent	2-ketobutyrate
68	gdhA	b1761	glutamate dehydrogenase	2-ketoglutarate
69	leuS	b0642	leucyl-tRNA synthetase	L-leucine
70	ybiV	b0822	predicted hydrolase	Dihydroorotate
71	carA	b0032	carbamoyl-phosphate synthase small subunit	L-glutamate
72	malZ	b0403	maltodextrin glucosidase	Maltose
73	adiA	b4117	biodegradative arginine decarboxylase	L-arginine
74	dapD	b0166	2,3,4,5-tetrahydropyridine-2-carboxylate N-succinyltransferase	2-ketoglutarate
75	murC	b0091	UDP-N-acetylmuramate–L-alanine ligase	L-alanine
76	yeiN	b2165	hypothetical protein	D-ribose-5-phosphate
77	deoA	b4382	thymidine phosphorylase	Thymine
78	eda	b1850	keto-hydroxyglutarate-aldolase/keto-deoxy-phosphogluconate aldolase	Ribitol
79	purA	b4177	adenylosuccinate synthetase	L-aspartate
80	alkB	b2212	oxidative demethylase of N1-methyladenine or N3-methylcytosine DNA lesions	cytosine
81	pykF	b1676	pyruvate kinase	Phosphoenolpyruvate
82	frc	b2374	formyl-coenzyme A transferase	oxalate
83	astA	b1747	arginine succinyltransferase	L-arginine
84	proC	b0386	pyrroline-5-carboxylate reductase	L-proline
85	thrC	b0004	threonine synthase	L-threonine
86	ppc	b3956	phosphoenolpyruvate carboxylase	Phosphoenolpyruvate
87	yjbC	b4022	23S rRNA pseudouridine synthase	D-ribose-5-phosphate
88	aldA	b1415	aldehyde dehydrogenase A, NAD-linked	glycolate
89	talB	b0008	transaldolase B	D-erythrose-4-phosphate
90	menD	b2264	2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylate synthase	2-Hydroxyglutarate
91	frdC	b4152	fumarate reductase subunit C	Fumarate

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Supplementary Table 2 – continued from previous page

92	yghZ	b3001	aldo-keto reductase	Glycerol-3-P
93	puuE	b1302	GABA aminotransferase, PLP-dependent	2-ketoglutarate
94	cls	b1249	cardiolipin synthetase	Glycerol
95	thrA	b0002	bifunctional aspartokinase I/homeserine dehydrogenase I	Homoserine
96	eutI	b2458	predicted phosphotransacetylase subunit	L-valine
97	proB	b0242	gamma-glutamyl kinase	L-glutamate
98	malY	b1622	bifunctional beta-cystathionase, PLP-dependent/ regulator of maltose regulon	2-ketobutyrate
99	metL	b3940	bifunctional aspartate kinase II/homoserine dehydrogenase II	Homoserine
100	lipA	b0628	lipoyl synthase	L-methionine
101	sdhA	b0723	succinate dehydrogenase flavoprotein subunit	Fumarate
102	dgoT	b3691	D-galactonate transporter	Ribitol
103	aspS	b1866	aspartyl-tRNA synthetase	L-aspartate
104	asnB	b0674	asparagine synthetase B	L-asparagine
105	metH	b4019	B12-dependent methionine synthase	L-methionine
106	priA	b3935	primosome assembly protein PriA	D-erythrose-4-phosphate
107	eutC	b2440	ethanolamine ammonia-lyase small subunit	Ethanolamine
108	purL	b2557	phosphoribosylformylglycinamidine synthase	L-glutamate
109	ansA	b1767	cytoplasmic asparaginase I	L-asparagine
110	pck	b3403	phosphoenolpyruvate carboxykinase	Phosphoenolpyruvate
111	ilvI	b0077	acetolactate synthase III large subunit	2-ketobutyrate
112	rffA	b3791	TDP-4-oxo-6-deoxy-D-glucose transaminase	2-ketoglutarate
113	fumA	b1612	fumarate hydratase (fumarase A), aerobic Class I	Fumarate
114	entF	b0586	enterobactin synthase multienzyme complex component, ATP-dependent	L-serine
115	gcvP	b2903	glycine dehydrogenase	Glycine
116	hisF	b2025	imidazole glycerol phosphate synthase subunit HisF	L-glutamate
117	lysC	b4024	aspartate kinase III	L-aspartate

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Supplementary Table 2 – continued from previous page

118	sdhB	b0724	succinate dehydrogenase, FeS subunit	Fumarate
119	gltB	b3212	glutamate synthase, large subunit	2-ketoglutarate
120	yieH	b3715	predicted hydrolase	6-phospho-D-gluconate
121	puuA	b1297	gamma-Glu-putrescine synthase	L-glutamate
122	dxs	b0420	1-deoxy-D-xylulose-5-phosphate synthase	Pyruvate
123	ubiA	b4040	4-hydroxybenzoate octaprenyltransferase	4-Hydroxybenzoate
124	lysU	b4129	lysine tRNA synthetase, inducible	L-lysine
125	aceB	b4014	malate synthase	Malate
126	tyrS	b1637	tyrosyl-tRNA synthetase	L-tyrosine
127	pssA	b2585	phosphatidylserine synthase	L-serine
128	yceQ	b1085	hypothetical protein	D-ribose-5-phosphate
129	avtA	b3572	valine pyruvate transaminase	2-aminobutyrate
130	ilvN	b3670	acetolactate synthase small subunit	2-ketobutyrate
131	entE	b0594	2,3-dihydroxybenzoate-AMP ligase	L-serine
132	prpB	b0331	2-methylisocitrate lyase	Ribitol
133	dapA	b2478	dihydrodipicolinate synthase	Ribitol
134	malQ	b3416	4-alpha-glucanotransferase (amylomaltase)	Maltose
135	nadB	b2574	L-aspartate oxidase	L-aspartate
136	gpmI	b3612	phosphoglyceromutase	3-phosphoglycerate
137	ydcW	b1444	medium chain aldehyde dehydrogenase	4-aminobutyrate
138	ybhE	b0767	6-phosphogluconolactonase	6-phospho-D-gluconate
139	yneI	b1525	predicted aldehyde dehydrogenase	Succinate
140	nudF	b3034	ADP-ribose pyrophosphatase	D-ribose-5-phosphate
141	ldcC	b0186	lysine decarboxylase 2, constitutive	L-lysine
142	sucA	b0726	alpha-ketoglutarate decarboxylase	2-ketoglutarate
143	kdsA	b1215	2-dehydro-3-deoxyphosphooctonate aldolase	Phosphoenolpyruvate
144	rihC	b0030	ribonucleoside hydrolase 3	cytosine
145	rbsK	b3752	ribokinase	D-ribose-5-phosphate
146	poxB	b0871	pyruvate dehydrogenase	Ribitol
147	uidA	b1617	beta-D-glucuronidase	Glycerol
148	tiaE	b3553	2-ketoaldonate reductase/glyoxylate reductase B	Gluconate
149	ymfC	b1135	23S rRNA pseudouridine synthase	D-ribose-5-phosphate
150	astE	b1744	succinylglutamate desuccinylase	L-glutamate

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151	pabB	b1812	para-aminobenzoate synthase component I	L-glutamate
152	glcF	b4467	glycolate oxidase iron-sulfur subunit	glycolate
153	aroF	b2601	3-deoxy-D-arabino-heptulosonate-7-phosphate synthase, tyrosine-repressible	D-erythrose-4-phosphate
154	alaS	b2697	alanyl-tRNA synthetase	L-alanine
155	glk	b2388	glucokinase	beta-D-Glucose 6-phosphate
156	ltaE	b0870	L-allo-threonine aldolase, PLP-dependent	Glycine
157	speA	b2938	arginine decarboxylase	L-arginine
158	gadA	b3517	glutamate decarboxylase A, PLP-dependent	4-aminobutyrate
159	putA	b1014	proline dehydrogenase/pyrroline-5-carboxylate dehydrogenase	L-glutamate
160	pgi	b4025	glucose-6-phosphate isomerase	beta-D-Glucose 6-phosphate
161	eno	b2779	phosphopyruvate hydratase	Phosphoenolpyruvate
162	aceE	b0114	pyruvate dehydrogenase subunit E1	Ribitol
163	ygfH	b2920	propionyl-CoA:succinate-CoA transferase	Succinate
164	metB	b3939	cystathionine gamma-synthase	2-ketobutyrate
165	gshA	b2688	glutamate–cysteine ligase	L-cysteine
166	yjjN	b4358	predicted oxidoreductase, Zn-dependent and NAD(P)-binding	L-Galactonate
167	dapE	b2472	succinyl-diaminopimelate desuccinylase	Succinate
168	frlB	b3371	fructoselysine-6-P-deglycase	beta-D-Glucose 6-phosphate
169	frdD	b4151	fumarate reductase subunit D	Fumarate
170	gabD	b2661	succinate-semialdehyde dehydrogenase I, NADP-dependent	Succinate
171	gcvT	b2905	glycine cleavage system aminomethyltransferase T	Glycine
172	gltD	b3213	glutamate synthase, 4Fe-4S protein, small subunit	2-ketoglutarate
173	treF	b3519	cytoplasmic trehalase	Trehalose
174	tdh	b3616	L-threonine 3-dehydrogenase	L-threonine
175	rihA	b0651	ribonucleoside hydrolase 1	cytosine
176	ybhO	b0789	cardiolipin synthase 2	Glycerol
177	speE	b0121	spermidine synthase	Putrescine
178	mhpC	b0349	2-hydroxy-6-ketonona-2,4-dienedioic acid hydrolase	Succinate

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179	yfbT	b2293	predicted hydrolase or phosphatase	Trehalose
180	icd	b1136	isocitrate dehydrogenase	2-ketoglutarate
181	sucB	b0727	dihydrolipoamide acetyltransferase	2-ketoglutarate
182	cadA	b4131	lysine decarboxylase 1	L-lysine
183	entD	b0583	phosphopantetheinyltransferase	L-serine
184	aroH	b1704	3-deoxy-D-arabino-heptulosonate-7-phosphate synthase	D-erythrose-4-phosphate
185	aceF	b0115	dihydrolipoamide acetyltransferase	Ribitol
186	panC	b0133	pantoate–beta-alanine ligase	beta-Alanine
187	thrB	b0003	homoserine kinase	Homoserine
188	thiH	b3990	thiamine biosynthesis protein ThiH	L-tyrosine
189	tyrB	b4054	tyrosine aminotransferase, tyrosine-repressible, PLP-dependent	2-ketoglutarate
190	nanA	b3225	N-acetylneuraminate lyase	Ribitol
191	mdh	b3236	malate dehydrogenase	Malate
192	cysK	b2414	cysteine synthase A, O-acetylserine sulfhydrolase A subunit	L-cysteine
193	sfcA	b1479	malate dehydrogenase, (decarboxylating, NAD-requiring) (malic enzyme)	Malate
194	yneH	b1524	predicted glutaminase	L-glutamate
195	ilvE	b3770	branched-chain amino acid aminotransferase	2-ketoglutarate
196	yfbB	b2263	predicted peptidase	Ribitol
197	purC	b2476	phosphoribosylaminoimidazole-succinocarboxamide synthase	L-aspartate
198	glpK	b3926	glycerol kinase	Glycerol
199	speB	b2937	agmatinase	Putrescine
200	trpD	b1263	bifunctional indole-3-glycerol-phosphate synthase/anthranilate phosphoribosyltransferase	L-glutamate
201	sdhD	b0722	succinate dehydrogenase cytochrome b556 small membrane subunit	Fumarate
202	fumB	b4122	anaerobic class I fumarate hydratase (fumarase B)	Fumarate
203	aspA	b4139	aspartate ammonia-lyase	Fumarate
204	frdA	b4154	fumarate reductase	Fumarate
205	yfbE	b2253	uridine 5'-(beta-1-threo-pentapyranosyl-4-ulose diphosphate) aminotransferase	2-ketoglutarate
206	argE	b3957	acetylornithine deacetylase	L-ornithine

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207	rpiA	b2914	ribose-5-phosphate isomerase A	D-ribose-5-phosphate
208	ansB	b2957	periplasmic L-asparaginase II	L-asparagine
209	dfp	b3639	bifunctional phosphopantothenoylcysteine decarboxylase/phosphopantothenate synthase	L-cysteine
210	metG	b2114	methionyl-tRNA synthetase	L-methionine
211	edd	b1851	phosphogluconate dehydratase	6-phospho-D-gluconate
212	trpE	b1264	anthranilate synthase component I	L-glutamate
213	pyrB	b4245	aspartate carbamoyltransferase catalytic subunit	L-aspartate
214	sdhC	b0721	succinate dehydrogenase cytochrome b556 large membrane subunit	Fumarate
215	glnA	b3870	glutamine synthetase	L-glutamate
216	garL	b3126	alpha-dehydro-beta-deoxy-D-glucarate aldolase	Ribitol
217	iscS	b2530	cysteine desulfurase	L-alanine
218	nadE	b1740	NAD synthetase	L-glutamate
219	treC	b4239	trehalose-6-P hydrolase	beta-D-Glucose 6-phosphate
220	yigL	b3826	predicted hydrolase	D-erythrose-4-phosphate
221	tauD	b0368	taurine dioxygenase	2-ketoglutarate
222	cysE	b3607	serine acetyltransferase	L-serine
223	iaaA	b0828	L-asparaginase	L-asparagine
224	rluC	b1086	23S rRNA pseudouridylate synthase	D-ribose-5-phosphate
225	argI	b4254	ornithine carbamoyltransferase 1	L-ornithine
226	udp	b3831	uridine phosphorylase	Uracil
227	gltX	b2400	glutamyl-tRNA synthetase	L-glutamate
228	upp	b2498	uracil phosphoribosyltransferase	Uracil
229	glpQ	b2239	periplasmic glycerophosphodiester phosphodiesterase	Glycerol
230	deoB	b4383	phosphopentomutase	D-ribose-5-phosphate
231	gshB	b2947	glutathione synthetase	Glycine
232	speC	b2965	ornithine decarboxylase, constitutive	L-ornithine
233	hemN	b3867	coproporphyrinogen III oxidase	L-methionine
234	ubiC	b4039	chorismate pyruvate lyase	4-Hydroxybenzoate
235	bioB	b0775	biotin synthase	L-methionine
236	argD	b3359	bifunctional acetylornithine aminotransferase/ succinyldiaminopimelate aminotransferase	2-ketoglutarate
237	carB	b0033	carbamoyl-phosphate synthase large subunit	L-glutamate
238	pykA	b1854	pyruvate kinase	Phosphoenolpyruvate

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239	glyS	b3559	glycyl-tRNA synthetase subunit beta	Glycine
240	epd	b2927	D-erythrose 4-phosphate dehydrogenase	D-erythrose-4-phosphate
241	puuD	b1298	gamma-Glu-GABA hydrolase	4-aminobutyrate
242	glxK	b0514	glycerate kinase II	3-phosphoglycerate
243	lysA	b2838	diaminopimelate decarboxylase, PLP-binding	L-lysine
244	rsuA	b2183	16S rRNA pseudouridylate 516 synthase	D-ribose-5-phosphate
245	glcE	b4468	glycolate oxidase FAD binding subunit	glycolate
246	asnA	b3744	asparagine synthetase AsnA	L-asparagine
247	argS	b1876	arginyl-tRNA synthetase	L-arginine
248	rluB	b1269	23S rRNA pseudouridylate synthase	D-ribose-5-phosphate
249	ilvH	b0078	acetolactate synthase small subunit	2-ketobutyrate
250	rpiB	b4090	ribose-5-phosphate isomerase B	D-ribose-5-phosphate
251	ilvB	b3671	acetolactate synthase large subunit	2-ketobutyrate
252	aroG	b0754	3-deoxy-D-arabino-heptulosonate-7-phosphate synthase	D-erythrose-4-phosphate
253	guaA	b2507	bifunctional GMP synthase/glutamine amidotransferase protein	L-glutamate
254	entB	b0595	isochorismatase	L-serine
255	eutB	b2441	ethanolamine ammonia-lyase, large subunit, heavy chain	Ethanolamine
256	pheS	b1714	phenylalanyl-tRNA synthetase alpha subunit	L-phenylalanine
257	astC	b1748	succinylornithine transaminase, PLP-dependent	2-ketoglutarate
258	pyrI	b4244	aspartate carbamoyltransferase regulatory subunit	L-aspartate
259	metK	b2942	S-adenosylmethionine synthetase	L-methionine
260	ytjC	b4395	phosphoglycerate mutase	3-phosphoglycerate
261	pabA	b3360	para-aminobenzoate synthase component II	L-glutamate
262	sucC	b0728	succinyl-CoA synthetase subunit beta	Succinate
263	tktB	b2465	transketolase 2, thiamin-binding	D-erythrose-4-phosphate
264	ilvA	b3772	threonine dehydratase	2-ketobutyrate

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265	ygjG	b3073	putrescine:2-oxoglutaric acid aminotransferase, PLP-dependent	2-ketoglutarate
266	metE	b3829	5-methyltetrahydropteroyltriglutamate–homocysteine methyltransferase	L-methionine
267	gcvH	b2904	glycine cleavage system protein H	Glycine
268	prsA	b1207	ribose-phosphate pyrophosphokinase	D-ribose-5-phosphate
269	argF	b0273	ornithine carbamoyltransferase 2, chain F	L-ornithine
270	codA	b0337	cytosine deaminase	cytosine
271	ilvM	b3769	acetolactate synthase II, small subunit	2-ketobutyrate
272	purD	b4005	phosphoribosylamine–glycine ligase	Glycine
273	hisH	b2023	imidazole glycerol phosphate synthase subunit HisH	L-glutamate
274	tdcB	b3117	threonine dehydratase	2-ketobutyrate
275	glyQ	b3560	glycyl-tRNA synthetase subunit alpha	Glycine
276	gpmA	b0755	phosphoglyceromutase	3-phosphoglycerate
277	ybaS	b0485	predicted glutaminase	L-glutamate
278	aceA	b4015	isocitrate lyase	Succinate
279	dadA	b1189	D-amino acid dehydrogenase small subunit	Ribitol
280	sucD	b0729	succinyl-CoA synthetase subunit alpha	Succinate
281	dadX	b1190	alanine racemase	L-alanine
282	thiG	b3991	thiazole synthase	L-tyrosine
283	kbl	b3617	2-amino-3-ketobutyrate coenzyme A ligase	Glycine
284	murA	b3189	UDP-N-acetylglucosamine 1-carboxyvinyltransferase	Phosphoenolpyruvate
285	bioF	b0776	8-amino-7-oxononanoate synthase	L-alanine
286	tktA	b2935	transketolase 1, thiamin-binding	D-ribose-5-phosphate
287	gabT	b2662	4-aminobutyrate aminotransferase	2-ketoglutarate
288	hisC	b2021	histidinol-phosphate aminotransferase	2-ketoglutarate

Supplementary Table 3: Metabolites and transcripts co-clustering results. The list includes all metabolites and transcripts which co-cluster across different conditions, clusters with pathway's over-enrichment are shown.

STATIONARY PHASE				
ALL CLUSTERS				
CLUSTER NO	TOTAL NO	METABOLITES NO	TRANSCRIPTS NO	pathway enrichment
1	65	4	61	no
2	63	5	58	no
3	**68**	**2**	**66**	**yes**
4	103	0	103	no
5	69	1	68	no
6	35	14	21	no
7	37	37	0	no
8	74	5	69	no
9	78	1	77	no
10	116	0	116	no
11	141	1	140	no
12	61	1	60	no
13	119	0	119	no
14	59	4	55	no
15	53	21	32	no
16	69	0	69	no
17	**57**	**3**	**54**	**yes**
18	103	2	101	no
19	160	0	160	no
20	99	0	99	no

CLUSTERS WITH PATHWAYS ENRICHMENT

STATIONARY PHASE CLUSTER 3
all cluster members
Trehalose, oxamic acid, b0581, b3093, b4167, b1003, b2662, b1010, b4124, b1836, b1197, b1454, b1256, b4271, b1577, b2332, b4230, b4304, b1188, b4127, b0510, b2405, b2015, b2305, b2665, b1515, b2137, b2535, b4298, b4529, b4269, b1514, b1428, b1297, b2881, b0508, b1784, b1300, b4119, b1440, b1728, b0286, b1442, b2659, b2936, b0812, b0507, b1441, b0304, b4051, b4212, b1467, b2781, b2664, b2310, b4126, b0865, b1512, b2375, b1298, b2172, b3073, b0979, b1675, b4214, b3362, b4128, b1007.
enriched pathway; p-value (enrich.); # of genes; # of metabolites; prob. of co-clust.; p-value (co-clust.)
putrescine degradation II 0.00015 3 0 superpathway of arginine and ornithine degradation; 2.55e-06; 5; 0; superpathway of arginine, putrescine, and 4-aminobutyrate degradation; 2.37e-06; 5; 0; superpathway of ornithine degradation; 8.66e-06; 4; 0; trehalose degradation II trehalase; 0.0018; 1; 1; 4.40e-16; 0.14
enriched GO term_p-value_number of genes_term
GO:0006575 0.0011 5 amino acid derivative metabolic process GO:0006576 0.0093 4 biogenic amine metabolic process GO:0006595 0.00038 4 polyamine metabolic process GO:0006598 4.05e-05 4 polyamine catabolic process GO:0009445 0.0001 4 putrescine metabolic process GO:0009447 4.05e-05 4 putrescine catabolic process GO:0042219 3.44e-05 5 amino acid derivative catabolic process GO:0042402 0.0001 4 biogenic amine catabolic process

STATIONARY PHASE CLUSTER 17

all cluster members
Glycericacid-3-phosphate, histidine, palmitoleic acid, b2341, b1426, b1725, b2148, b2426, b3605, b4512, b0346, b1593, b1376, b2151, b4208, b1415, b0307, b2149, b2537, b2702, b3845, b1205, b0598, b0064, b2243, b3846, b1384, b2597, b1660, b3430, b2869, b2875, b2799, b4151, b4033, b4032, b2242, b2022, b4118, b4037, b4122, b0228, b2147, b4322, b4216, b0306, b2239, b0162, b2241, b4487, b0308, b2146, b2703, b3885, b2342, b3081, b2021
enriched pathway; p-value (enrich.); # of genes; # of metabolites; prob. of co-clust.; p-value (co-clust.)
ethylene glycol degradation; 0.0032; 2; 0;
glycerol degradation I; 0.00037; 4; 0;
histidine biosynthesis; 0.0043; 2; 1; 4.40e-16; 0.54
L-lactaldehyde degradation aerobic; 0.0032; 2; 0;
methylglyoxal degradation IV; 0.0027; 2; 0;
superpathway of fucose and rhamnose degradation; 0.0027; 3; 0;
enriched GO term_p-value_number of genes_term
GO:0006575 0.0011 5 amino acid derivative metabolic process
GO:0006004 0.0048 3 fucose metabolic process
GO:0009056 0.0061 12 catabolic process
GO:0016042 0.0019 4 lipid catabolic process
GO:0019317 0.0019 3 fucose catabolic process
GO:0042354 0.0025 3 L-fucose metabolic process
GO:0042355 0.0019 3 L-fucose catabolic process

OXIDATIVE STRESS				
ALL CLUSTERS				
CLUSTER NO	TOTAL NO	METABOLITES NO	TRANSCRIPTS NO	pathway enrichment
1	21	21	0	no
2	23	3	20	no
3	**36**	**3**	**33**	**yes**
4	38	0	38	no
5	**46**	**9**	**37**	**yes**
6	16	2	14	no
7	59	1	58	no
8	5	5	0	no
9	23	2	21	no
10	**23**	**4**	**19**	**yes**
11	16	14	2	no
12	43	0	43	no
13	44	1	43	no
14	57	0	57	no
15	**41**	**9**	**32**	**yes**
16	41	1	40	no
17	24	2	22	no
18	21	1	20	no
19	16	3	13	no
20	20	20	0	no

CLUSTERS WITH PATHWAYS ENRICHMENT

OXIDATIVE STRESS CLUSTER 3
all cluster members
Succinic acid, Glutamine, trimethyl lysine, b0704, b2675, b2660, b3221, b0946, b4364, b3172, b1454, b2818, b2676, b3959, b0860, b4127, b3960, b1611, b1956, b0233, b1428, b2999, b3958, b2112, b0789, b3957, b4126, b2209, b3359, b4511, b3361, b2441, b0753, b4128, b4094, b4451
enriched pathway; *p*-value (enrich.); # of genes; # of metabolites; prob. of co-clust.; *p*-value (co-clust.)
adenosine nucleotides biosynthesis; 0.0026; 2; 1; 1.10e-15; 0.41 arginine biosynthesis I; 8.90e-12; 7; 2; 1.10e-15;0.32 guanosine nucleotides biosynthesis; 0.0025; 2; 1; 1.10e-15; 0.22 ornithine biosynthesis 3.36e-07 5 0 superpathway of arginine and polyamine biosynthesis 4.67e-08 7 0
enriched GO term_p-value_number of genes_term
GO:0006082 6.24e-05 9 organic acid metabolic process GO:0006519 3.75e-05 8 cellular amino acid and derivative metabolic process GO:0006520 2.38e-05 8 amino acid metabolic process GO:0006525 1.10e-10 7 arginine metabolic process GO:0006526 1.68e-12 7 arginine biosynthetic process GO:0006807 7.64e-05 8 nitrogen compound metabolic process GO:0008652 1.16e-05 7 amino acid biosynthetic process GO:0009064 2.57e-08 7 glutamine family amino acid metabolic process GO:0009084 1.10e-10 7 glutamine family amino acid biosynthetic process GO:0009262 0.005 2 deoxyribonucleotide metabolic process GO:0009263 0.003 2 deoxyribonucleotide biosynthetic process GO:0009308 3.83e-05 8 cellular amine metabolic process GO:0009309 1.34e-05 7 amine biosynthetic process GO:0015949 0.005 2 nucleobase, nucleoside and nucleotide interconversion GO:0019752 6.24e-05 9 carboxylic acid metabolic process GO:0034641 3.83e-05 8 cellular nitrogen compound metabolic process GO:0044249 0.006 11 cellular biosynthetic process GO:0044271 1.34e-05 7 nitrogen compound biosynthetic process

OXIDATIVE STRESS CLUSTER 5

all cluster members

Alanine, Pyruvic acid, Threonine, Aspartic acid, Glutaric acid, 2-hydroxy, Pyroglutamic acid(oxoproline), Glutamic acid, cysteine, 3-deoxy-D-arabinoheptulosonic acid, b1183, b1102, b0232, b1634, b3161, b1188, b2542, b0585, b0192, b4460, b0401, b2155, b1225, b0594, b2698, b4043, b4256, b1184, b1660, b1060, b2135, b4051, b4293, b3494, b4458, b2008, b4406, b0589, b0592, b1226, b1957, b4367, b0595, b2673, b1743

enriched pathway; p-value (enrich.); # of genes; # of metabolites; prob. of co-clust.; p-value (co-clust.)

2, 3-dihydroxybenzoate biosynthesis; 0.0031; 1; 1; 1.10e-15; 0.37
alanine biosynthesis I; 0.00065; 0; 3;
alanine biosynthesis II; 3.61e-05; 0; 3;
alanine biosynthesis III; 0.0017; 0; 2;
alanine degradation I; 0.00282; 0; 2;
asparagine biosynthesis I; 0.0031; 0; 2;
aspartate biosynthesis; 0.0017; 0; 2;
enterobactin biosynthesis; 0.0075; 2; 0;
glutamate degradation II; 0.0028; 0; 2;
glutathione biosynthesis; 0.0031; 0; 2;
isoleucine biosynthesis I from threonine; 0.0017; 0; 3;
L-cysteine degradation II; 0.0020; 0; 2;
lysine biosynthesis I; 0.0020; 0; 3;
methionine biosynthesis I; 0.0017; 0; 3;
NAD biosynthesis I from aspartate; 0.0075; 0; 2;
peptidoglycan biosynthesis III; 0.0020; 0; 3;
phenylalanine biosynthesis I; 0.004; 0; 2;
pyridoxal 5'-phosphate biosynthesis; 0.0080; 0; 2;
serine biosynthesis; 0.005; 0; 2;
thiamin biosynthesis I; 0.0020; 0; 3;
tRNA charging pathway; 0.0006; 0; 5;
tryptophan biosynthesis; 0.008; 0; 2;
tyrosine biosynthesis I; 0.0031; 0; 2;
valine biosynthesis; 0.008; 0; 2;

enriched GO term_p-value_number of genes_term

GO:0000041 3.40e-07 8 transition metal ion transport
GO:0006281 0.009 4 DNA repair
GO:0006518 0.008 2 peptide metabolic process
GO:0006810 0.004 15 transport
GO:0006811 0.0009 8 ion transport
GO:0006812 5.27e-05 8 cation transport
GO:0006826 6.30e-08 8 iron ion transport
GO:0006974 0.009 4 response to DNA damage stimulus
GO:0009237 0.0053 2 siderophore metabolic process
GO:0009238 0.0053 2 enterobactin metabolic process
GO:0009239 0.0053 2 enterobactin biosynthetic process
GO:0009432 0.0004 4 SOS response
GO:0009605 0.0053 4 response to external stimulus
GO:0009712 0.0053 2 catechol metabolic process
GO:0009991 0.001 4 response to extracellular stimulus
GO:0015674 8.004e-08 8 di-, tri-valent inorganic cation transport
GO:0018958 0.0053 2 phenol metabolic process
GO:0019184 0.0053 2 nonribosomal peptide biosynthetic process
GO:0019290 0.005 2 siderophore biosynthetic process
GO:0019540 0.005 2 siderophore biosynthetic process from catechol
GO:0030001 1.91e-05 8 metal ion transport
GO:0031668 0.001 4 cellular response to extracellular stimulus
GO:0034984 0.0093 4 cellular response to DNA damage stimulus
GO:0043043 0.005 2 peptide biosynthetic process
GO:0051179 0.005 15 localization
GO:0051234 0.0047 15 establishment of localization

OXIDATIVE STRESS CLUSTER 10

all cluster members

Valine, Hexacosanoic acid, cytosine, Linolenic acid, b1900, b2394, b1901, b3774, b0582, b0016, b1987, b3686, b1518, b2788, b4030, b2804, b0355, b3727, b4326, b2012, b2142, b3091, b3497

enriched pathway; *p*-value (enrich.); # of genes; # of metabolites; prob. of co-clust.; *p*-value (co-clust.)

valine biosynthesis; 0.0015; 1; 1; 1.10e-15; 0.53

enriched GO term_p-value_number of genes_term

OXIDATIVE STRESS CLUSTER 15

all cluster members

Isoleucine, Proline, Benzoic acid, 4-hydroxy, Lysine, Trehalose, norvaline, glutamine , arginine, asparagine, b1042, b0872, b3434, b1598, b2074, b1758, b1463, b1195, b3159, b4269, b0752, b2366, b3549, b4366, b1728, b0286, b4546, b0349, b1227, b3441, b2447, b1736, b2957, b4553, b0998, b2730, b0551, b2384, b1512, b0384, b0235, b3408,

enriched pathway; *p*-value (enrich.); # of genes; # of metabolites; prob. of co-clust.; *p*-value (co-clust.)

superpathway of aspartate and asparagine biosynthesis 0.0036; 1; 1; 1.10e-15; 0.53
tRNA charging pathway; 6.62e-05; 0; 5;

enriched GO term_p-value_number of genes_term

GLUCOSE-LACTOSE SHIFT				
ALL CLUSTERS				
CLUSTER NO	TOTAL NO	METABOLITES NO	TRANSCRIPTS NO	pathway enrichment
1	42	11	31	no
2	25	1	24	no
3	12	5	7	no
4	41	0	41	no
5	**12**	**6**	**6**	**yes**
6	38	5	33	no
7	20	1	19	no
8	11	0	11	no
9	29	29	0	no
10	26	4	22	no
11	27	0	27	no
12	23	0	23	no
13	13	4	9	no
14	44	0	44	no
15	26	1	25	no
16	38	0	38	no
17	7	3	4	no
18	22	22	0	no
19	31	7	24	no
20	15	2	13	no

CLUSTERS WITH PATHWAYS ENRICHMENT

GLUCOSE-LACTOSE SHIFT CLUSTER 5
all cluster members
glycine, Threonine, Aspartic acid, Threonic acid, Adipic acid, asparagine, b3375, b2448, b0965, b2807, b3617, b2159
enriched pathway; *p*-value (enrich.); # of genes; # of metabolites; prob. of co-clust.; *p*-value (co-clust.)
asparagine biosynthesis I; 0.00043; 0; 2; asparagine biosynthesis II; 0.00043; 0; 2; superpathway of aspartate and asparagine biosynthesis; 0.0006; 0; 2; threonine degradation II 0.00043; 1; 1; 2.20e-16; 0.25 tRNA charging pathway; 0.00062; 0; 3;
enriched GO term_p-value_number of genes_term

HEAT STRESS				
ALL CLUSTERS				
CLUSTER NO	TOTAL NO	METABOLITES NO	TRANSCRIPTS NO	pathway enrichment
1	120	8	112	no
2	124	3	121	no
3	105	1	104	no
4	52	2	50	no
5	112	1	111	no
6	124	14	110	no
7	51	51	0	no
8	120	9	111	no
9	233	3	230	no
10	60	0	60	no
11	91	0	91	no
12	**57**	**2**	**55**	**yes**
13	164	0	164	no
14	108	3	105	no
15	50	1	49	no
16	39	2	37	no
17	193	0	193	no
18	91	0	91	no
19	81	1	80	no
20	213	0	213	no

CLUSTERS WITH PATHWAYS ENRICHMENT

HEAT STRESS CLUSTER 12
all cluster members
Glutamicacid, heptadecanoicacid, b2230, b0900, b2427, b4268, b0208, b2452, b1598, b2548, b1900, b0982, b2870, b0457, b4186, b2407, b4286, b0877, b1323, b1798, b0130, b4478, b0601, b1250, b2201, b4460, b2546, b2831, b1803, b0987, b1312, b1218, b1525, b4528, b0106, b3891, b0340, b1562, b1217, b3718, b4479, b4424, b4415, b4518, b1196, b0227, b4422, b3130, b4326, b0561, b0048, b1429, b0773, b0802, b1793, b0560, b1999
enriched pathway; *p*-value (enrich.); # of genes; # of metabolites; prob. of co-clust.; *p*-value (co-clust.)
formylTHF biosynthesis I; 0.0071; 1; 1; 4.40e-16; 0.33 tetrahydrofolate biosynthesis; 0.007; 1; 1; 4.40e-16; 0.33
enriched GO term_p-value_number of genes_term

CONTROL				
ALL CLUSTERS				
CLUSTER NO	TOTAL NO	METABOLITES NO	TRANSCRIPTS NO	pathway enrichment
1	**54**	**45**	**9**	**yes**
2	13	11	2	no
3	26	26	0	no
4	21	12	9	no
5	9	5	4	no
6	28	2	26	no

CLUSTERS WITH PATHWAYS ENRICHMENT

CONTROL CLUSTER 1

all cluster members

Alanine, Glycolic acid, Pyruvic acid, Valine Ethanolamine, Leucine, Isoleucine, Glycine, Proline, Urea, Serine (major), Succinic acid Threonine, Fumaric acid, beta-Alanine, Homoserine Malic acid, 4-Aminobutyric acid, Aspartic acid, Threonic acid, Methionine, Glutaric acid (2-hydroxy), Pyroglutamic acid (oxoproline), Glutamic acid Putrescine, Phenylalanine, Benzoic acid (4-hydroxy), Glutamine (N-acetyl), Orotic acid, Lysine, Oleic acid, 2-hydroxybutyric acid, 2-aminobutyric acid, 2-ketoglutaric acid, 2-ketobutyric acid, norvaline, norleucine, glutamine minor, isopropylmalic acid, cysteine, arginine, trimethyl, lysine, shikimic acid-3-phosphate, dihydroorotic acid, 3-deoxy-D-arabinoheptulosonic acid, b2252, b0647, b4113, b2408, b4467, b2254, b2253, b2256, b4112

enriched pathway; *p*-value (enrich.); # of genes; # of metabolites; prob. of co-clust.; *p*-value (co-clust.)

4-aminobutyrate degradation I; 0; 0; 4;
alanine biosynthesis I; 0; 0; 5;
alanine biosynthesis II; 4.76E-005; 0; 4;
arginine biosynthesis I 0; 0; 5;
arginine degradation II AST pathway; 0; 0; 4;
arginine degradation III; arginine; decarboxylase/agmatinase; pathway; 0; 0; 3;
aspartate biosynthesis; 0; 0; 3;
BasSR Two-Component Signal Transduction System; 0.01; 2; 0;
folate polyglutamylation I; 0; 0; 3;
glutamate degradation II; 0; 0; 4;
glutathione biosynthesis; 0; 0; 3;
glycolate and glyoxylate degradation II; 0.01; 1; 2; 2.20e-16; 0.39;
isoleucine biosynthesis I from threonine; 0; 0; 5;
leucine biosynthesis; 4.76E-005; 0; 6;
lysine biosynthesis I; 0; 0; 6;
methionine biosynthesis I; 4.76E-005; 0; 6;
phenylalanine biosynthesis I; 0; 0; 4;
putrescine biosynthesis I; 0; 0; 3;
putrescine degradation I; 0; 0; 4;
putrescine degradation II; 0.01; 0; 3;
serine biosynthesis; 0; 0; 4;
tRNA charging pathway; 3.09E-010; 0; 15;
tyrosine biosynthesis I; 0.01; 0; 3;
uridine-5'-phosphate biosynthesis; 0.01; 0; 4;
valine biosynthesis; 0; 0; 4;

enriched GO term_p-value_number of genes_term

GO:0009245 0.0025 2 lipid A biosynthetic process
GO:0010035 0.0002 3 response to inorganic substance
GO:0010038 0.0001 3 response to metal ion
GO:0010039 4.38e-06 3 response to iron ion
GO:0010041 4.38e-06 3 response to iron(III) ion
GO:0042221 0.0001 5 response to chemical stimulus
GO:0046493 0.002 2 lipid A metabolic process
GO:0046677 0.002 3 response to antibiotic
GO:0050896 0.004 5 response to stimulus

COLD STRESS				
ALL CLUSTERS				
CLUSTER NO	TOTAL NO	METABOLITES NO	TRANSCRIPTS NO	pathway enrichment
1	93	5	88	no
2	**117**	**21**	**96**	**yes**
3	101	4	97	no
4	59	1	58	no
5	126	2	124	no
6	160	6	154	no
7	116	1	115	no
8	**193**	**7**	**186**	**yes**
9	56	0	56	no
10	134	1	133	no
11	147	2	145	no
12	**128**	**13**	**115**	**yes**
13	239	2	237	no
14	151	0	151	no
15	147	1	146	no
16	51	28	23	no
17	247	4	243	no
18	132	3	129	no
19	129	0	129	no
20	117	0	117	no

CLUSTERS WITH PATHWAYS ENRICHMENT

COLD STRESS CLUSTER 2
all cluster members
Pyridine3-hydroxy, phosphoric acid, Phosphate, Benzoic acid, Serine(major), Uracil, Glutaric acid, 2-hydroxy, Ribose, Orotic acid, Gluconic acid, Oleic acid, Glucose6-phosphate;Lactitol, D-erythrose-4-phosphate, choline chloride;oxamic acid, shikimic acid-3-phosphate, tyramine histidine, ribose5P, Spermidine(major), b0805, b0034, b3723b0807, b1755, b0272, b0908, b4512, b3751, b3669, b3869, b1877, b3745b0238, b1940, b1593, b3431, b0778, b2306, b0166, b3613, b1987, b3538b0599, b0524, b0749, b0469, b0147, b2627, b2155, b0833, b0675, b4541, b4369, b4367, b1682, b4368, b0745, b1975, b1230, b1757, b3606, b0885, b2858, b2421, b3937, b1446, b3978, b1821, b0748, b1756, b2404, b4541, b4369, b4367, b1682, b4368, b0745, b1975, b1230, b1757, b3606, b0885, b2858, b2421, b3937, b1446, b3978, b1821, b0748, b1756, b2404, b2026, b0640, b0743, b3416, b3752, b3337, b0747, b1945, b3976, b1730, b0381, b2784, b1910, b2153, b1944, b3064, b0788, b2092, b0133, b4207, b4037, b2204, b4378, b3798, b1467, b4390, b1989, b0803, b1835, b1960, b1019, b1939, b3977, b3925, b0804, b1074, b1382, b0666, b3590, b4370, b4541, b4369, b2025, b0724, b1681, b1231, b1231.
enriched pathway; p-value (enrich.); # of genes; # of metabolites; prob. of co-clust.; p-value (co-clust.)
degradation of pyrimidine ribonucleosides; 0.001; 0; 4; histidine biosynthesis; 0.009; 2; 2; 1.54e-15; 0.019 pentose phosphate pathway non-oxidative branch; 0.006; 0; 4; PRPP biosynthesis I; 0.001; 0; 3; PRPP biosynthesis II 0.006; 0; 3; ribose degradation 0.0006; 1; 3; 1.54e-15; 0.021; salvage pathways of adenine, hypoxanthine, and their nucleosides; 0.0013; 2; 3; 1.54e-15; 0.006 superpathway of gluconate degradation; 0.007; 0; 4;
enriched GO term_p-value_number of genes_term

COLD STRESS CLUSTER 8

all cluster members

4-Aminobutyric acid, Pyroglutamic acid(oxoproline), Glutamine, 2-hydroxybutyric acid, norvaline, norleucine, arginine, b2157, b1958, b0167, b2979, b3512, b3886, b1719, b2009, b2587, b4020, b0882, b1841, b3244, b4396, b0686, b3164, b0610, b1278, b1663, b0290, b0800, b2467, b3910, b0489, b4467, b2317, b0490, b3243, b0114, b0494, b4340, b4012, b4294, b0881, b0845, b4468, b1299, b1839, b2020, b2699, b4059, b1781, b0195, b2369, b0478, b0932, b3804, b3699, b3434, b2795, b4109, b0200, b0730, b2133, b3496, b1164, b1489, b1206, b2063, b0693, b1981, b1083, b1657, b1860, b1464, b4234, b3350, b1542, b0959, b3499, b1328, b2071, b0763, b3648, b0516, b3021, b1777, b1322, b4551, b3625, b0759, b1302, b1249, b3847, b0958, b3585, b0953, b1840, b0628, b1271, b0391, b0127, b4296, b1020, b2678, b3178, b1625, b1482, b1325, b1297, b2522, b4014, b1921, b0110, b1490, b1301, b2217, b2292, b0190, b1300, b2574, b2677, b3034, b2943, b3549, b1215, b2837, b1398, b0968, b2616, b1165, b1778, b4030, b0848, b0779, b0109, b0495, b1764, b1192, b4077, b1326, b1167, b1321, b0438, b0437, b0764, b0213, b0866, b0115, b2893, b1279, b0392, b2392, b2679, b0111, b3805, b3426, b1447, b4212, b3649, b3888, b1448, b2249, b0683, b2530, b2016, b3554, b2620, b2549, b3773, b1748, b2529, b4210, b3284, b0761, b4355, b0024, b2007, b0481, b0488, b1782, b2696, b1189, b1190, b1992, b3279, b4430, b4360, b4403, b3040, b3602, b3351,

enriched pathway; *p*-value (enrich.); # of genes; # of metabolites; prob. of co-clust.; *p*-value (co-clust.)
glycolate and glyoxylate degradation II; 0.001 4; 0;
putrescine degradation II; 0.0002; 4; 1; 1.54e-15; 0.618;
superpathway of arginine and ornithine degradation; 0.0002; 6; 1; 1.54e-15; 0.702;
superpathway of arginine, putrescine, and 4-aminobutyrate degradation; 0.0003; 5; 1; 1.54e-15; 0.36;
superpathway of glycol metabolism and degradation; 0.009; 4; 0;
superpathway of ornithine degradation; 0.0005; 5; 0;

enriched GO term_p-value_number of genes_term

COLD STRESS CLUSTER 12

all cluster members

Alanine, Leucine, Isoleucine, Threonine, Homoserine, Aspartic acid, Threonic acid, Glutamic acid, Phenylalanine, Glutamine N-acetyl, 2-aminobutyric acid glutamine, asparagine, b4356, b2046, b2210, b1706, b3627, b0453, b1522, b0019, b1082, b1634, b3632, b2594, b3210, b1894, b4048, b2105, b1620, b0476, b0155, b2123, b1432, b1845, b3629, b4516, b0786, b0038, b3293, b0275, b3716, b1747, b0925, b4172, b3743, b0119, b2435, b4361, b2572, b2577, b3631, b2382, b3711, b0401, b0265, b3101, b0705, b1741, b1829, b0706, b3179, b1789, b2501, b1085, b4394, b2531, b2698, b4043, b0439, b3292, b2010, b3347, b0122, b1617, b0944, b0124, b4313, b3086, b2593, b3444, b4058, b3194, b3207, b3616, b0927, b3894, b4424, b3834, b2331, b0128, b2910, b1296, b0022, b1254, b2301, b1688, b1848, b2008, b3662, b3193, b4422, b0891, b2640, b3163, b4175, b0388, b3895, b4447, b1957, b3802, b2101, b2560, b0942, b2949, b1335, b3848, b0214, b0926, b3195, b2106, b4140, b3162, b4420, b3181, b1295, b3036, b3617

enriched pathway; *p*-value (enrich.); # of genes; # of metabolites; prob. of co-clust.; *p*-value (co-clust.)
alanine biosynthesis II; 0.0065; 0; 2;
aminopropanol biosynthesis; 0.0065; 1; 1; 3.24e-6; 0.003;
asparagine biosynthesis I; 0.0027; 0; 3;
threonine degradation II; 0.00084; 2; 1; 1.54e-15; 0.653;
threonine degradation III to methylglyoxal; 0.0065; 1; 1; 1.54e-15; 0.234
tRNA charging pathway; 0.0001; 0; 8;
aspartate biosynthesis; 0.0065; 0; 2;
Lipid A-core biosynthesis; 0.0065; 3; 0;

enriched GO term_p-value_number of genes_term

GO:0006259 0.0076 13 DANN metabolic process
GO:0006950 0.0060 15 response to stress
GO:0009432 0.0063 5 SOS response
GO:0034960 0.0063 39 cellular biopolymer metabolic process
GO:0043170 0.0063 41 macromolecule metabolic process
GO:0043283 0.0063 39 biopolymer metabolic process
GO:0044260 0.0063 40 cellular macromolecule metabolic process

Supplementary Table 4: List of all metabolites and transcripts used for CCA analysis.

metabolites	**genes**				
	ppp	**glycolysis**	**TCA cycle**	**transcriptional regulators**	**anaerobic respiration**
Succinic acid	tktA	glpX	sdhA	arcA	frdA
Fumaric acid	tktB	eno	sdhB	arcB	frdB
Malic acid	talA	gpmA	sdhC	crp	frdC
6-phosphogluconic acid	talB	fbaA	sdhD	fnr	frdD
D-erythrose-4-phosphate	zwf	fbaB	gltA	fruR	hycB
ribose 5P	gnd	fbp	acnA	dgsA	hycC
Glucose 6-phosphate	rpiA	pfkA	acnB	dcuB	hycD
Glyceric acid-3-phosphate	rpiB	pfkB	icd	cyaA	hycE
PEP	rpe	pgi	lpd		hycF
Pyruvic acid	ybhE	tpiA	sucB		hycG
2-ketoglutaric acid		pgk	sucA		pflB
		pykA	sucC		tdcE
		pykF	sucD		poxB
		pps	fumA		fdhF
		ytjC	fumB		
		yggF	fumC		
		ybhA	mqo		
		gpmI	mdh		
		gapA			

	x = G6P	x = PEP	x = pps	canon. corr. $x = V_i$,$1 \leq i \leq 11$
$cor(x, U_1)$	**-0.80**	**-0.57**	**-0.65**	**0.97**
$cor(x, U_2)$	**-0.36**	**-0.39**	**-0.40**	**0.96**
$cor(x, U_3)$	0.35	0.60	-0.41	0.94
$cor(x, U_4)$	-0.23	0.12	-0.00	0.81
$cor(x, U_5)$	0.03	0.07	-0.17	0.76
$cor(x, U_6)$	-0.11	-0.22	-0.29	0.71
$cor(x, U_7)$	0.01	0.12	-0.13	0.68
$cor(x, U_8)$	0.06	0.25	0.00	0.64
$cor(x, U_9)$	-0.06	0.12	0.05	0.59
$cor(x, U_{10})$	0.04	-0.11	-0.10	0.35
$cor(x, U_{11})$	-0.01	-0.01	0.17	0.34

Supplementary Table 5: Example of canonical structure correlations of two metabolites and the pps gene under control condition. This table shows the canonical structure correlations of glucose 6-phosphate (G6P), phosphoenolpyruvate (PEP) and the pps gene encoding phosphoenolpyruvate synthase. Each row corresponds to the respective Pearson correlation of the original representation of a variable (a column vector in X or Y) and the respective canonical variate U_i, $1 \leq i \leq 11$. Note, as the dimension of the metabolite matrix Y is 21×11 and the dimension of the gene matrix X is 21×69, we can determine 11 linear combinations of X and Y resulting in 11 cononical correlations of the respective canonical variates U_i and V_i (as shown in column 4). As a result of the restriction on succesive higher-order canonical variates to be orthogonal, the canonical correlation decreases. The scatter plots in the manuscript use the first and second canonical structure correlations, marked in bold.

7 Supplementary Figures

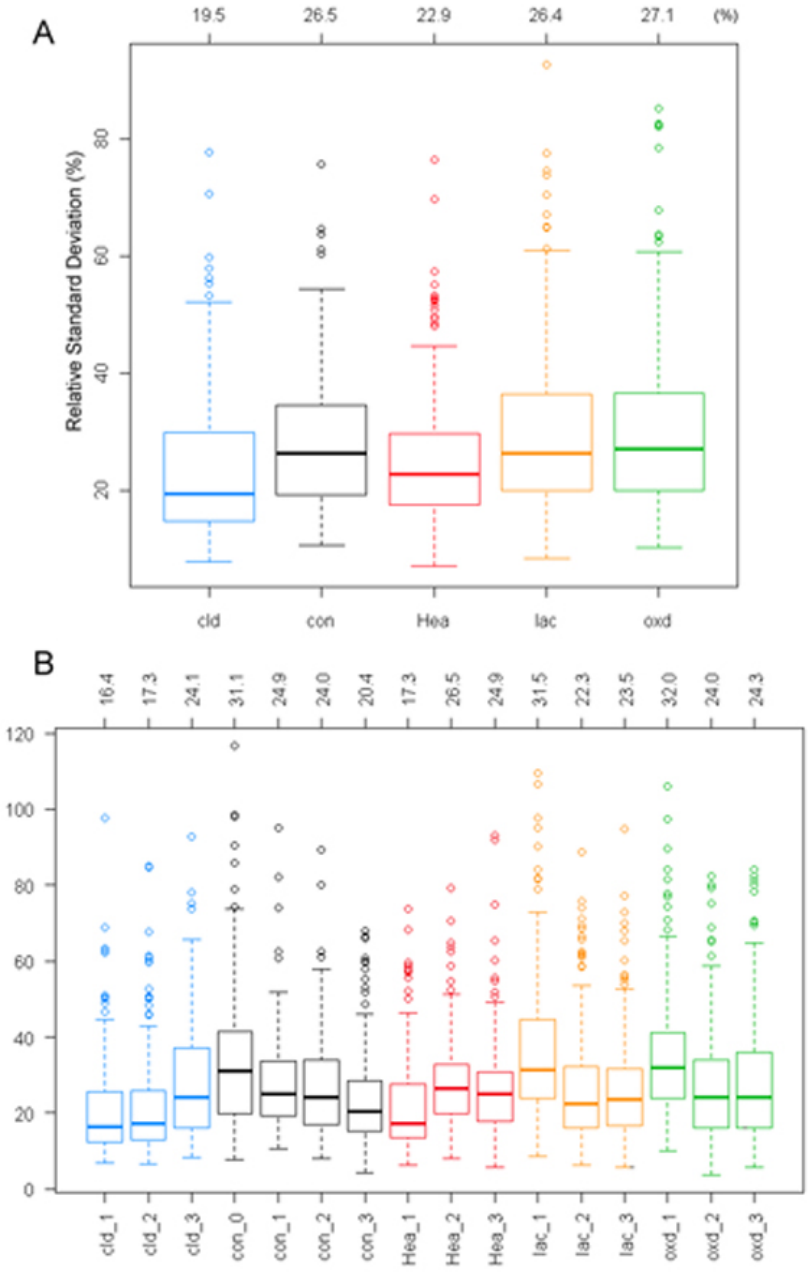

Figure 1: Relative standard deviation (RSD) of metabolite data of all biological and technical replicates. A: Box plots show RSD averages for all time points and all technical replicates within individual conditions. B: Box plots show RSD for the three technical replicates averaged independently for all biological replicates. Different conditions are indicated on the figure and additionally colour coded: blue-cold, black-control, red-heat, orange-lactose shift, green-oxidative stress.

contr; cold; heat		1	2	3	4	5	6	7	8	9	10	11	12
lactose; oxidative	1	2	3	4	5	6	7		8	9	10	11	12
	OD 0.3	OD 0.5	OD 0.6	10min	20min	30min	40min	50min	90min	150min	210min	235min	260min
control 1		0.51	0.62	0.68	0.74	0.77	0.88	0.95	1.43	2.15	2.35	2.34	2.35
control 2		0.50	0.59	0.69	0.76	0.83	0.92	1.00	1.42	2.26	2.26	2.26	2.25
control 3		0.53	0.61	0.70	0.75	0.82	0.91	0.99	1.44	2.21	2.43	2.47	2.46
control 4		0.49	0.59	0.71	0.79	0.85	0.92	1.01	1.40	2.16	2.50	2.51	2.47
cold 1		0.50	0.61	0.62	0.62	0.65	0.64	0.67	0.68	0.67	0.71	0.77	0.76
cold 2		0.52	0.63	0.66	0.62	0.64	0.66	0.68	0.72	0.65	0.71	0.79	0.78
cold 3		0.50	0.60	0.64	0.60	0.61	0.64	0.67	0.65	0.68	0.71	0.75	0.74
heat 1		0.49	0.61	0.68	0.73	0.73	0.73	0.75	0.80	0.83	0.86	0.87	NA
heat 2		0.52	0.59	0.64	0.65	0.64	0.68	0.69	0.74	0.79	0.78	0.87	NA
heat 3		0.50	0.58	0.62	0.67	0.68	0.69	0.69	0.73	0.77	0.81	0.86	NA
oxidative 1	NA	0.43	0.67	0.66	0.66	0.67	0.69		0.92	1.53	2.20	2.11	NA
oxidative 2	NA	0.53	0.64	0.64	0.64	0.66	0.67		0.91	1.60	2.24	2.28	2.29
oxidative 3	NA	0.51	0.62	0.67	0.68	0.69	0.72		1.00	1.73	2.21	2.21	2.20
lactose 1	0.36	0.45	0.55	0.61	0.63	0.65	0.67		0.74	0.96	2.30	NA	NA
lactose 2	0.32	0.60	0.66	0.66	0.67	0.70	0.75		1.15	2.02	2.23	2.32	2.28
lactose 3	0.48	0.63	0.69	0.68	0.70	0.72	0.76		1.27	2.01	2.30	2.33	2.29

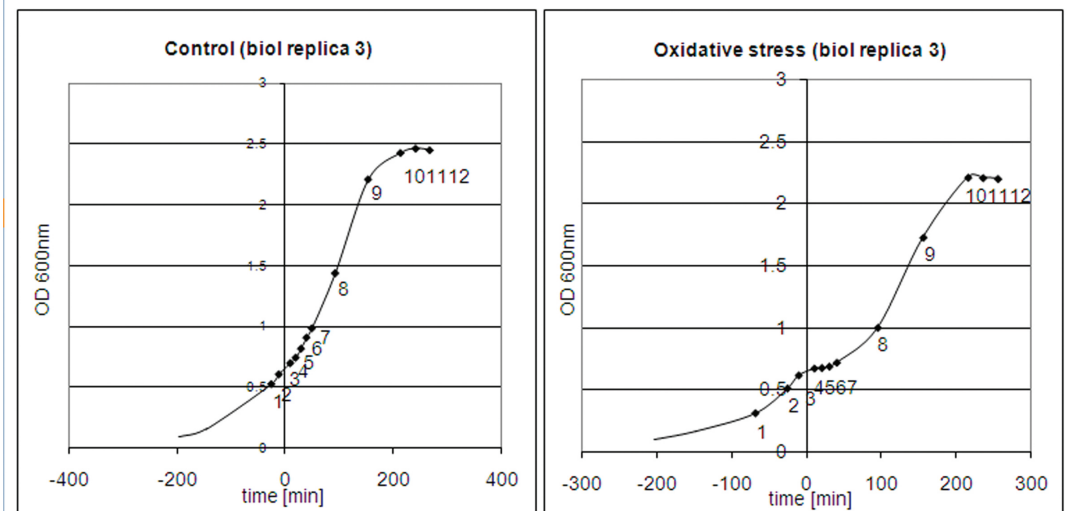

Figure 2: Sampling time of all conditions tested. Time course is represented by 12 time points: 2-3 before stress, 4-5 every 10 min after stress and 5 time points (90-260min) late after stress. Different phases of growth are marked by colours: exponential growth before stress: green, growth arrest after stress: red, resumption of exponential growth after stress and late log growth (90-150min) in control: blue, stationary phase: black. Optical density (600nm) is shown for every time point. pH 7 did not change significantly during culture growth, also temperature (37°C) was kept constant except both temperature stresses. Exemplary growth curves (based on OD 600nm) for a control and the oxidative stress experiment are shown below with depicted time points. The moment of stress (or OD=6 in control) is indicated on the X axis by 0.

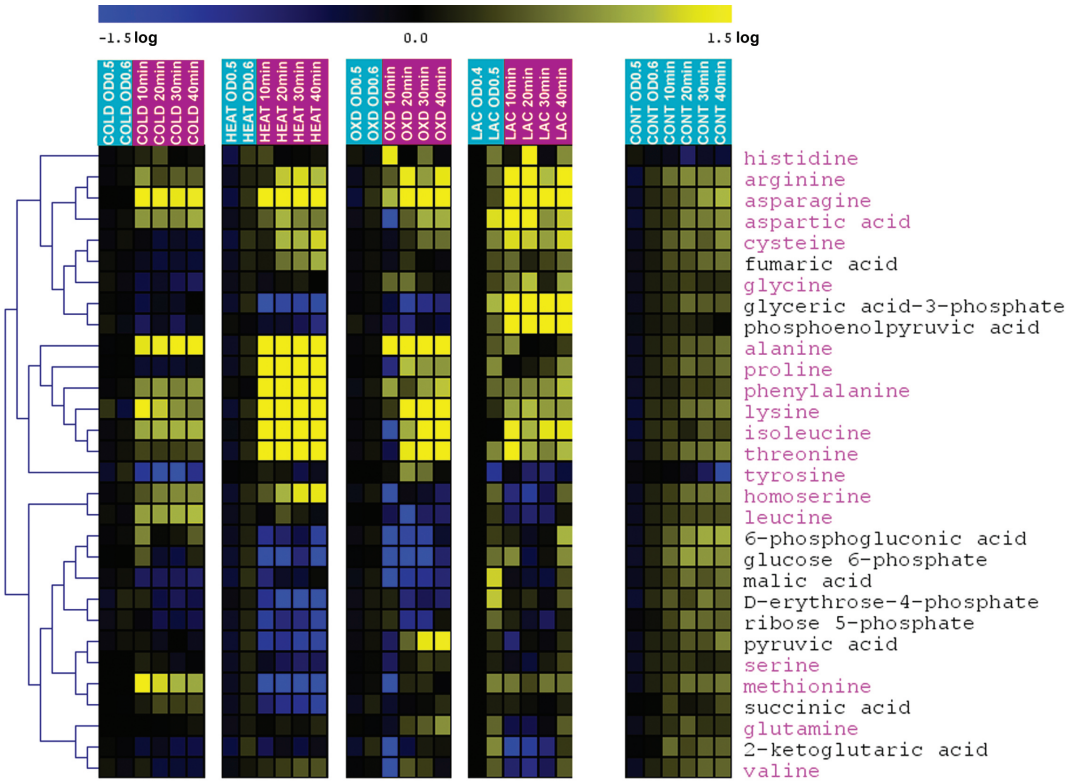

Figure 3: Median metabolite levels from time points up to 40 minutes after applied stress for three independent biological repetitions of each stress condition, plus the controls, relative to time points prior to the perturbation are shown in columns. The color of the panel indicates the growth phase: blue- exponential growth, magenta- growth cessation or reduction. Time points before stress application are indicated by their optical density. Only metabolites described as a part of the general response to perturbation - amino acids (magenta) and metabolites associated with glycolysis, the pentose phosphate pathway, and TCA cycle (black) are shown. The hierarchical clustering (Pearson correlation, average linkage aggregation method) separates these two groups of compounds, illustrating a tendency of amino acids to accumulate while intermediates of central metabolism decrease.

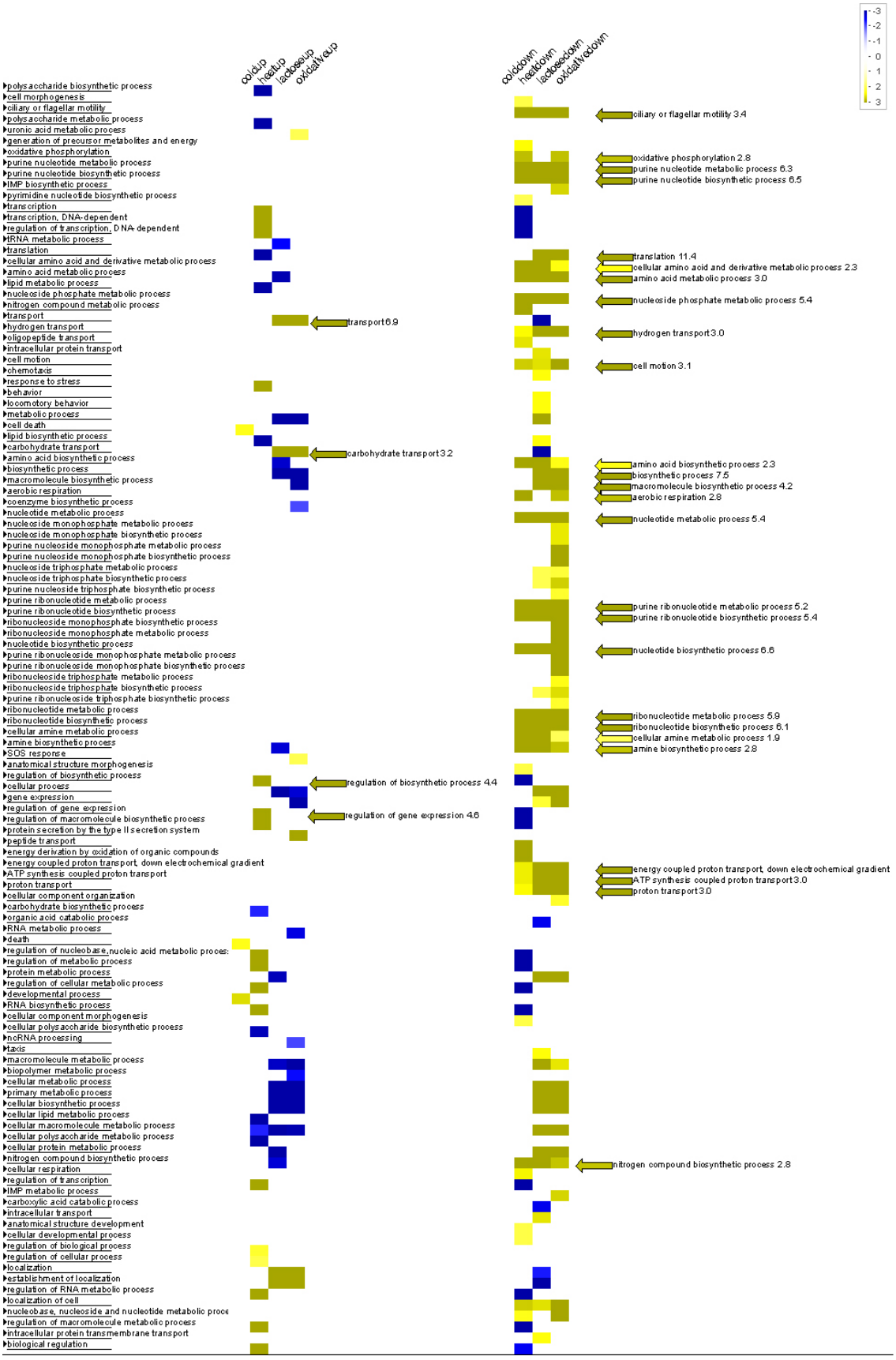

Figure 4: GO over- and underrepresentation analysis of genes changing expression under various environmental conditions. Continued on next page.

Figure 4: Continued from previous page. GO term enrichment analysis was performed for the time point of maximal changes at transcript level (cf. Figure 4). The analysis was performed for both up (left column) and down (right column) regulated genes. GO terms described in the main text are indicated with arrows. The intensity of the colour indicates the significance, with the highest significance for the most intense colour. Different colours indicate if given GO term in under- (blue) or overrepresented (yellow). Since for each Bin p-values are calculated, a transformation has to be made to display them on a linear scale for visualization. PageMan compresses the p-values by converting them into z-scores with a z-score of 1.96 representing a p-value of 0.05. All p-values above 0.05 (Bonferroni corrected) are masked (coloured white).

A

t1 (10min)	cold	heat	lactose	oxidative
cold	12	0/1	3/0.08	1/0.65
heat		10	0/1	7/6.1E-07
lactose			18	1/0.79
oxidative				16

t2 (20min)	cold	heat	lactose	oxidative
cold	7	1/0.68	0/1	4/7.6E-03
heat		29	5/0.02	16/3.3E-09
lactose			12	3/0.21
oxidative				27

t3 (30min)	cold	heat	lactose	oxidative
cold	14	2/0.55	3/0.054	5/0.01
heat		25	1/0.84	12/3.5E-07
lactose			13	3/0.16
oxidative				22

t4 (40min)	cold	heat	lactose	oxidative
cold	14	4/0.2	0/1	4/0.08
heat		34	2/0.69	17/9.1E-10
lactose			13	3/0.22
oxidative				25

B

t1(10min)	cold	heat	lactose	oxidative
cold	6	5/0.04	1/0.71	2/0.11
heat		115	32/1.1E-03	24/8.5E-07
lactose			54	8/0.15
oxidative				29

t2(20min)	cold	heat	lactose	oxidative
cold	40	22/0.09	13/0.02	14/0.01
heat		127	33/6.4E-03	47/4.4E-11
lactose			55	27/2.5E-08
oxidative				57

t3 (30min)	cold	heat	lactose	oxidative
cold	60	32/0.02	3/0.99	13/2.7E-03
heat		118	6/1	24/5.1E-06
lactose			40	2/0.94
oxidative				30

t4 (40min)	cold	heat	lactose	oxidative
cold	61	33/8.6E-03	0/1	8/4.8E-03
heat		115	0/1	11/7.7E-03
lactose			7	0/1
oxidative				15

Figure 5: Similarity between metabolites (a) and transcripts (b) changing in comparison to control condition as a result of the respective stress application Parallel time points post perturbation (t1: 10 min after perturbation; t2: 20 min; t3: 30 min; t4: 40 min) from different experiments were compared against corresponding time points from an unperturbed growth curve (control). The total number of metabolites (A) which differ ($p \leq 0.05$, ratios ≥ 2) between control and the corresponding treatment and genes coding enzymes which could be directly linked to measured metabolites (B) which do likewise ($p \leq 0.05$, ratios ≥ 3) is shown in grey boxes. Lists of significant differences were compared and the number of similarly changing features (in the same direction) following pair wise comparison is displayed in orange boxes. The significance of the overlap was tested using the Fisher exact test, from which respective p-values are shown for each comparison. The significant overlaps are showed in blue boxes.

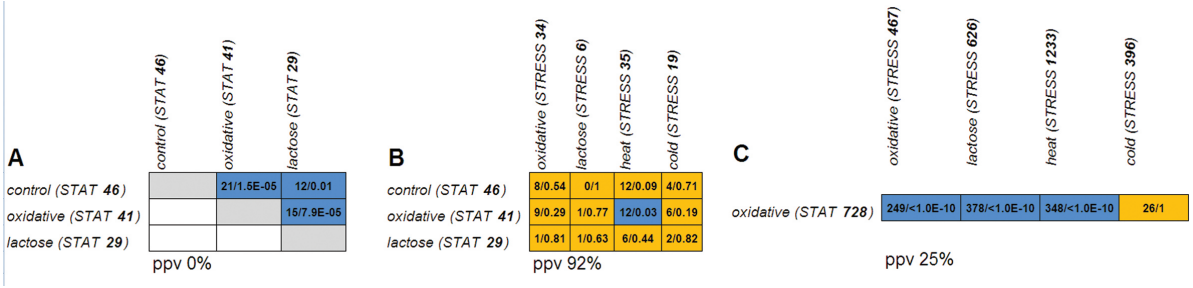

Figure 6: Changes in metabolites during stationary phase are similar between different cultures (A) but different from metabolites changing during post-perturbation phase (B) whereas transcripts changing during stationary phase or during post-perturbation phase are very similar (C). The number of metabolites: A,B ($p \leq 0.05$, ratios ≥ 2) and transcripts: C ($p \leq 0.05$, ratios ≥ 3), which change upon entry into stationary phase (STAT) and post-perturbation changes (STRESS) (numbers are given in parentheses after the respective condition) are compared and number of changing transcripts and metabolites shared between two conditions are displayed. The significance of overlap between different conditions was tested using the Fisher exact test and respective p-values are shown. Significant overlaps are highlighted in blue. A: Comparison of metabolites changing for three different cultures (control conditions; oxidative stress; glucose-lactose shift) upon entering stationary phase. The number in brackets given after the respective condition indicates the number of significantly changing metabolites. B: Comparison of metabolites changing for three different cultures (control conditions; oxidative stress; glucose-lactose shift) upon entering stationary phase with metabolites changing during post-perturbation phase for all four different environmental conditions. The number in brackets given after the respective condition indicates the number of significantly changing metabolites. C: Comparison of transcripts changing upon entering stationary phase (as exemplified for the culture exposed to oxidative stress treatment) with transcripts changing during post-perturbation phase for the four different stress treatments.

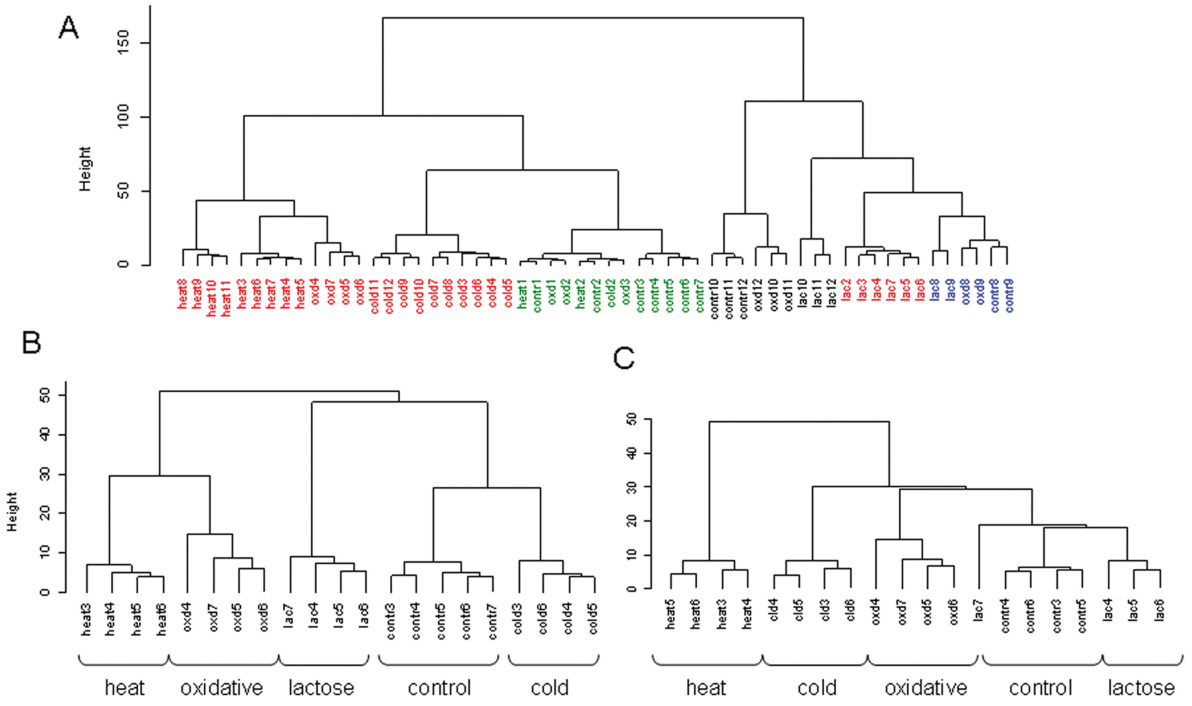

Figure 7: Hierarchical clustering of all samples based on metabolites (Figure 2A, B) and transcripts (Figure 2C). A. HCA of all samples based on metabolite composition. cold: cold treatment; heat: heat treatment; oxd: oxidative stress experiment; lac: glucose-lactose diauxic shift experiment; contr: no stress application. Numbering refers to the numbering given in supplemental figure 1. B. HCA of post-perturbation samples plus control based on metabolite data. Further details are as in figure 2A. C. HCA of post-perturbation samples plus controls based on transcript data. Further details are as in figure 2A.

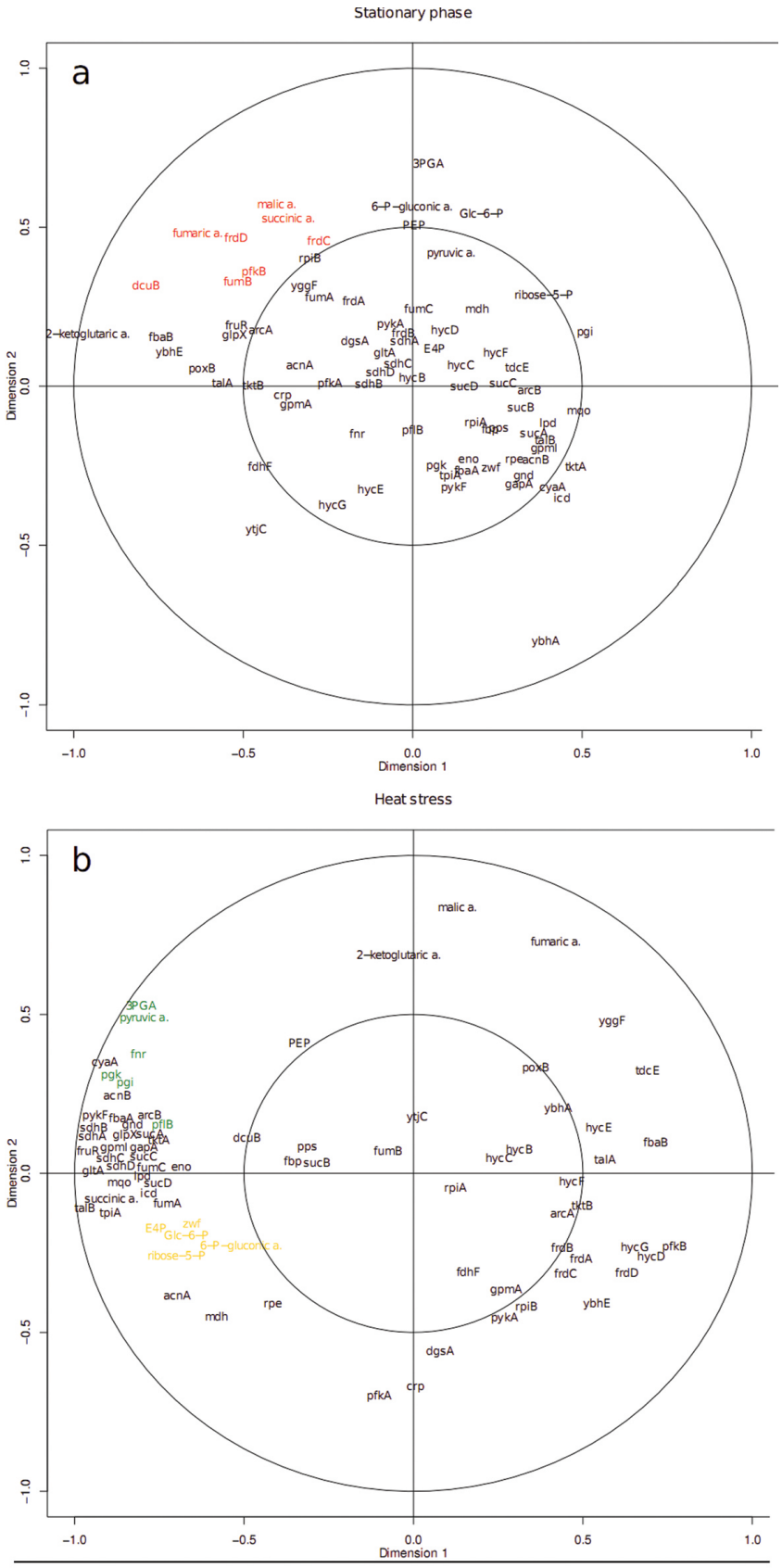

Figure 8: Visualization of the CCA results of metabolites and genes involved in primary metabolism under stationary phase and heat stress. Continued on next page.

Figure 8: Continued from previous page. **(a)** Visualization of the canonical structure correlations with the first two canonical variates under stationary phase: The group of genes colored in red is comprised of three metabolites of the TCA cycle including malic acid, fumarate and succinic acid. Additionally, 4 genes including fumarate reductase (*frd C,D*), fumarase B (*fumB*) and fumarate-succinate antiporter (*dcuB*) are in the close proximity. **(b)** Representation of the CCA result under heat stress: We were able to identify two groups of genes and metabolites. Colored in yellow we find similarity between the *zwf* gene encoding the glucose-6-phosphate dehydrogenase and three intermediates of the ppp, including glucose-6-phosphate (Glc-6-P), 6-phosphogluconic acid (6-P-gluconic a.) and D-erythrose-4-phosphate (E4P). The second group colored in green consists of pyruvic acid, glyceric acid 3-phosphate (3PGA) and the genes *fnr*, *pgk*, *pflB* and *pgi*. For futher details see the main text.

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