

Table 1. List of essential metabolites and their characteristics. Essential metabolites are identified within nineteen environments specified by combinations of different carbon, phosphate, nitrogen, and sulfate sources, and aerobic/anaerobic conditions (SI Table 2). We present the essential metabolites in the descending order of the number of the participating reactions. Each essential metabolite is characterized as type A, B, C, or D, according to the cell growth profile under attenuation (Note 4).

1-A) Metabolites which are identified as essential for all nineteen growth conditions. The total number of the corresponding metabolites is 231.

Name of metabolite	No. of participating reactions			Growth condition relevant to each type		
	total	incoming	outgoing	A	B	C
H+	497	378	226			1-19
H ₂ O	293	82	231			1-19
ATP	176	38	174			1-19
Phosphate	149	143	35			1-19
ADP	143	141	35			1-19
Nicotinamide adenine dinucleotide	77	42	51		1,3,5-7,9-11,13,15,17	2,4,8,12,14,16,18,19
Nicotinamide adenine dinucleotide - reduced	72	48	40		1,3,5-7,9-11,13,15,17	2,4,8,12,14,16,18,19
CO ₂	60	58	8	2,4,12,14,16,18,19	1,3,9-11,13,15,17	5-8
Nicotinamide adenine dinucleotide phosphate	52	45	20	1-4,7,9,11,12,14-19	5,6,8,10,13	
Pyruvate	51	43	14	5	1,6,8,10,11,13,15,17	2-4,7,9,12,14,16,18,19
Nicotinamide adenine dinucleotide phosphate - reduced	50	18	45	1-4,7,9,11,12,14-19	5,6,8,10,13	
L-Glutamate	46	33	26	1-7,9,11,12,14-19	13	8,10
Coenzyme A	39	24	23		1-4,6-19	5
ammonium	38	34	7	1-7,11,12,14-19	10,13	8,9
AMP	36	33	8	2,4-6,8,10,12,18,19	1,3,7,9,11,13-17	
Acetyl-CoA	26	14	18		1-4,6-19	5
2-Oxoglutarate	25	17	20	2,4,12,14-16,18,19	1,3,5-7,9,11,13,17	8,10
acyl carrier protein	23	18	8	1,2,5,7,9,11-19	3,4,6,8,10	
Phosphoenolpyruvate	23	4	21		1,5-11,13,15,17	2-4,12,14,16,18,19
L-Aspartate	20	8	15	1,3,11,13,15-17	2,4-10,12,14,18,19	
L-Glutamine	15	2	13	1-19		
Glyceraldehyde 3-phosphate	14	13	10	5,6,8,10	7,9	1-4,11-19
CMP	14	12	6	1-19		
Glycerol 3-phosphate	14	10	6	1-19		
GTP	13	2	13	1,3,5,6,8,10,11,15-18	2,4,7,9,12-14,19	
5-Phospho-alpha-D-ribose 1-diphosphate	12	2	12	1-15,17-19	16	
Dihydroxyacetone phosphate	12	10	8	5-10	1-4,11-19	
L-Alanine	12	7	10	1-19		
L-Serine	12	7	9		1-19	
D-Fructose 6-phosphate	12	10	9	5-10	1-4,11-19	
Malonyl-[acyl-carrier protein]	11	1	11	1-19		
D-Glucose 1-phosphate	11	7	10	1-19		
GDP	10	8	5	1,3,5-8,10,11,15-18	2,4,9,12-14,19	
Oxaloacetate	10	7	5	2,4,12-16	1,3,5-11,17-19	
Reduced thioredoxin	10	1	9	5,6,8,10,18	1-4,7,9,11-17,19	
FAD	10	2	9	2,4,12-16,18	1,3,7-11,17,19	5,6
D-Glucose 6-phosphate	10	9	4	4-10	1,3,11,13,15,17	2,12,14,16,18,19
Oxidized thioredoxin	10	9	1	5,6,8,10,18	1-4,7,9,11-17,19	

Name of metabolite	No. of participating reactions			Growth condition relevant to each type		
	total	incoming	outgoing	A	B	C
UMP	9	8	2	1,3,5-8,10,11,15,17,18	2,4,9,12-14,16,19	
CTP	9	3	8	1-19		
S-Adenosyl-L-methionine	9	3	8	1-19		
L-Cysteine	9	3	7	1-19		
alpha-D-Ribose 5-phosphate	9	9	4	5,6,8,10,18	1-4,7,9,11-17,19	
UDPglucose	8	4	7	1-19		
5,6,7,8-Tetrahydrofolate	8	6	5		1-19	
Acetoacetyl-ACP	8	2	6	1-19		
UDP	8	7	3	1,3,5,6,8,10,11,15,17,18	2,4,7,9,12-14,16,19	
UTP	8	2	8	1,3-6,8,10,11,13-15,17,18	2,7,9,12,16,19	
Succinyl-CoA	8	3	6	2,4,12-16,18,19	1,3,5-11,17	
L-Threonine	8	5	5	1-12,14-19	13	
Putrescine	8	5	5	1-7,9-19	8	
Glycine	8	5	6	5,6,8,10	1-4,7,9,11-19	
GMP	8	6	3	1-19		
Spermidine	7	3	4	1-19		
IMP	7	4	4	1-19		
Phosphatidylglycerol	7	2	6	1-19		
L-Arginine	6	3	5	1-7,9-17,19	18	8
L-Lysine	6	4	3	1-19		
5,10-Methylenetetrahydrofolate	6	3	4		1-19	
Chorismate	6	1	5	1-19		
D-Alanine	6	4	5	1-19		
L-Proline	6	4	3	1-19		
L-Asparagine	6	4	3	1-19		
UDP-N-acetyl-D-glucosamine	6	2	5	1-19		
D-Glucosamine 6-phosphate	5	4	2	1-19		
Nicotinate D-ribonucleotide	5	3	2	1-19		
dGTP	5	2	4	1-19		
Iminoaspartate	5	4	1	1-19		
D-Ribulose 5-phosphate	5	4	4	5,6,8,10,18	1-4,7,9,11-17,19	
Myristoyl-ACP (n-C14:0ACP)	5	2	3	1-19		
3-Methyl-2-oxobutanoate	5	2	4	1-12,14-19	13	
L-Methionine	5	3	2	1-19		
L-Tryptophan	5	4	3	1-8,10-19		9
dTMP	5	4	2	1-19		
phosphatidate	5	4	2	1-19		
L-Valine	5	4	3	1-19		
Bicarbonate	5	2	5	1-19		
dCTP	5	2	4	1-19		
dUMP	5	3	3	1,3,5-8,10,11,15,17,18	2,4,9,12-14,16,19	
L-Glutamate 5-semialdehyde	4	3	1	1-19		
meso-2,6-Diaminoheptanedioate	4	2	3	1-19		
CMP-3-deoxy-D-manno-octulosonate	4	1	3	1-19		
Undecaprenyl diphosphate	4	3	1	1-19		
L-Isoleucine	4	3	3	1-12,14-19	13	
Phosphatidylethanolamine	4	2	3	1-19		

Name of metabolite	No. of participating reactions			Growth condition relevant to each type		
	total	incoming	outgoing	A	B	C
L-Leucine	4	3	2	1-12,14-19	13	
L-Histidine	4	3	2	1-19		
Hexadecenoyl-ACP (n-C16:1ACP)	4	2	2	1-19		
1-Pyrroline-5-carboxylate	4	2	2	1-19		
Sulfite	4	4	1	1-19		
Carbamoyl phosphate	4	3	2	1-19		
D-Erythrose 4-phosphate	4	3	4		1-19	
3-Phospho-D-glycerate	4	3	3		1,3,5-11,13,15,17	2,4,12,14,16,18,19
CDPdiacylglycerol	4	3	4	1-19		
Xanthosine 5'-phosphate	4	2	2	1-19		
dTTP	4	1	4	1-19		
L-Tyrosine	4	2	4	1-19		
L-Homocysteine	4	3	2	1-19		
dATP	4	2	3	2,4-10,12-14,16,18,19	1,3,11,15,17	
10-Formyltetrahydrofolate	4	3	4		1-19	
R-3-hydroxy-myristoyl-ACP	3	2	2	1-19		
Octadecenoyl-ACP (n-C18:1ACP)	3	2	1	1-19		
Palmitoyl-ACP (n-C16:0ACP)	3	2	1	1-19		
(S)-Dihydroorotate	3	1	3	1-19		
Tetradecenoyl-ACP (n-C14:1ACP)	3	2	1	1-19		
2-Oxobutanoate	3	1	2	1-12,14-19	13	
5-Amino-1-(5-Phospho-D-riboseyl)imidazole-4-carboxamide	3	3	2	1-19		
L-Phenylalanine	3	2	3	1-19		
phosphatidylserine	3	1	3	1-19		
UDP-2,3-bis(3-hydroxytetradecanoyl)glucosamine	3	1	2	1-19		
L-Homoserine	3	1	3	1,3,11,13,15-17	2,4-10,12,14,18,19	
Undecaprenyl phosphate	3	1	2	1-19		
(R)-Pantothenate	3	2	1	1-19		
Orotate	3	3	1	1-19		
L-Aspartate 4-semialdehyde	3	2	3	1,3,11,13,15-17	2,4-10,12,14,18,19	
Sedoheptulose 7-phosphate	3	2	3		1-19	
N2-Formyl-N1-(5-phospho-D-riboseyl)glycinamide	3	2	2	1-19		
5-Methyltetrahydrofolate	3	1	2	1-19		
Hydrogen sulfide	3	2	2	1-19		
7,8-Dihydrofolate	3	3	1	1-19		
dTDP	3	3	2	1-19		
glycogen	3	1	2	1-19		
Dodecanoyl-ACP (n-C12:0ACP)	3	1	2	1-19		
4-(1-D-Ribitylamino)-5-aminouracil	3	2	1	1-19		
Prephenate	3	1	2	1-19		

Name of metabolite	No. of participating reactions			Growth condition relevant to each type		
	total	incoming	outgoing	A	B	C
5-amino-1-(5-phospho-D-ribose)imidazole	3	1	2	1-19		
KDO(2)-lipid IV(A)	3	1	2	1-19		
N1-(5-Phospho-D-ribose)glycinamide	3	2	3	1-19		
5-[(5-phospho-1-deoxyribulos-1-ylamino)methylideneamino]-1-(5-phosphoribosyl)imidazole-4-carboxamide	2	1	1	1-19		
Phosphatidylglycerophosphate	2	1	2	1-19		
UDP-N-acetylmuramoyl-L-alanine	2	1	1	1-19		
N-Succinyl-L-2,6-diaminoheptanedioate	2	1	2	1-19		
2-Dehydro-3-deoxy-D-arabino-heptonate 7-phosphate	2	1	1	1-19		
O-Phospho-L-serine	2	1	1		1-19	
UDP-N-acetylmuramate	2	1	1	1-19		
(S)-2-[5-Amino-1-(5-phospho-D-ribose)imidazole-4-carboxamido]succinate	2	2	2	1-19		
UDP-N-acetylmuramoyl-L-alanyl-D-gamma-glutamyl-meso-2,6-diaminopimelate	2	1	1	1-19		
3-Carboxy-3-hydroxy-4-methylpentanoate	2	2	1	1-12,14-19	13	
2,3-Bis(3-hydroxytetradecanoyl)-beta-D-glucosaminyl 1-phosphate	2	1	1	1-19		
3-Deoxy-D-manno-octulosonate 8-phosphate	2	1	1	1-19		
N-((R)-4-Phosphopantothenoyl)-L-cysteine	2	1	1	1-19		
Peptidoglycan subunit of <i>Escherichia coli</i>	2	1	1	1-19		
Adenosine 5'-phosphosulfate	2	1	1	1-19		
Dihydropteroate	2	1	1	1-19		
3-Dehydroshikimate	2	2	2	1-19		
1-(5-Phosphoribosyl)-AMP	2	1	1	1-19		
4-Methyl-2-oxopentanoate	2	1	1	1-12,14-19	13	
D-Glycero-D-manno-heptose 7-phosphate	2	1	1	1-19		
2,3,4,5-Tetrahydrodipicolinate	2	1	1	1-19		
3-Phosphohydroxypyruvate	2	1	1		1-19	

Name of metabolite	No. of participating reactions			Growth condition relevant to each type		
	total	incoming	outgoing	A	B	C
D-Glycero-D-manno-heptose 1-phosphate	2	1	1	1-19		
D-erythro-1-(Imidazol-4-yl)glycerol 3-phosphate Sulfate	2	1	1	1-19		
UDP-3-O-(3-hydroxytetradecanoyl)-N-acetylglucosamine	2	1	2	1-19		
2-Amino-4-hydroxy-6-(D-erythro-1,2,3-trihydroxypropyl)-7,8-dihydropteridine	2	1	1	1-19		
UDP-3-O-(3-hydroxytetradecanoyl)-D-glucosamine	2	1	1	1-19		
Orotidine 5'-phosphate	2	1	2	1-19		
UDP-N-acetyl-3-O-(1-carboxyvinyl)-D-glucosamine	2	1	1	1-19		
6-hydroxymethyl dihydropterin	2	1	1	1-19		
O-Acetyl-L-serine	2	1	2	1-19		
UDP-N-acetylmuramoyl-L-alanyl-D-glutamyl-meso-2,6-diaminopimeloyl-D-alanyl-D-alanine	2	1	1	1-19		
UDP-N-acetylmuramoyl-L-alanyl-D-glutamate	2	1	1	1-19		
Cardiolipin	2	1	2	1-19		
(R)-2,3-Dihydroxy-3-methylbutanoate	2	1	1	1-12,14-19	13	
(S)-2-Acetolactate	2	1	1	1-12,14-19	13	
3'-Phosphoadenylyl sulfate	2	1	1	1-19		
1-(5-Phosphoribosyl)-ATP	2	1	1	1-19		
2,3,2'3'-Tetrakis(beta-hydroxymyristoyl)-D-glucosaminyl-1,6-beta-D-glucosamine 1,4'-bisphosphate	2	1	1	1-19		
Shikimate 5-phosphate	2	2	1	1-19		
(R)-Pantoate	2	1	1	1-19		
2-Dehydropantoate	2	1	1	1-19		
CDPethanolamine	2	1	2	1-19		
5-amino-1-(5-phospho-D-ribosyl)imidazole-4-carboxylate	2	2	2	1-19		
5-Phospho-beta-D-ribosylamine	2	2	1	1-19		
N-Succinyl-2-L-amino-6-oxoheptanedioate	2	2	1	1-19		
D-4'-Phosphopantothenate	2	1	1	1-19		

Name of metabolite	No. of participating reactions			Growth condition relevant to each type		
	total	incoming	outgoing	A	B	C
3-Deoxy-D-manno-2-octulosonate	2	1	1	1-19		
ADP-L-glycero-D-manno-heptose	2	1	1	1-19		
beta-Alanine	2	1	1	1-19		
D-Alanyl-D-alanine	2	1	2	1-19		
O-Succinyl-L-homoserine	2	1	1	1-19		
Quinolinate	2	1	1	1-19		
2-(Formamido)-N1-(5-phospho-D-ribosyl)acetamide	2	1	1	1-19		
D-Arabinose 5-phosphate	2	1	2	1-19		
1-(5-Phosphoribosyl)-5-[(5-phosphoribosylamino)methylideneamino]imidazole-4-carboxamide	2	1	1	1-19		
lipopolysaccharide	2	1	1	1-19		
6-hydroxymethyl-dihydropterin pyrophosphate	2	1	1	1-19		
Shikimate	2	1	2	1-19		
Undecaprenyl-diphospho-N-acetylmuramoyl-L-alanyl-D-glutamyl-meso-2,6-diaminopimeloyl-D-alanyl-D-alanine	2	1	1	1-19		
Undecaprenyl-diphospho-N-acetylmuramoyl-(N-acetylglucosamine)-L-ala-D-glu-meso-2,6-diaminopimeloyl-D-ala-D-ala	2	1	1	1-19		
5-phosphoribosyl-5-carboxyaminoimidazole	2	2	1	1-19		
3-Carboxy-2-hydroxy-4-methylpentanoate	2	1	2	1-12,14-19	13	
N-Acetyl-D-glucosamine 1-phosphate	2	1	1	1-19		
L-Cystathionine	2	1	1	1-19		
(S)-3-Methyl-2-oxopentanoate	2	2	1	1-12,14-19	13	
5-O-(1-Carboxyvinyl)-3-phosphoshikimate	2	1	2	1-19		
2-Amino-4-hydroxy-6-(erythro-1,2,3-trihydroxypropyl)dihydropteridine triphosphate	2	1	1	1-19		
D-Glycero-D-manno-heptose 1,7-bisphosphate	2	1	1	1-19		
3-(Imidazol-4-yl)-2-oxopropyl phosphate	2	1	1	1-19		

Name of metabolite	No. of participating reactions			Growth condition relevant to each type		
	total	incoming	outgoing	A	B	C
3,4-dihydroxy-2-butanone 4-phosphate	2	1	1	1-19		
KDO(2)-lipid IV(A) with laurate	2	1	1	1-19		
2-Isopropylmalate	2	2	2	1-12,14-19	13	
KDO-lipid IV(A)	2	1	1	1-19		
ADP-D-glycero-D-manno-heptose	2	1	1	1-19		
KDO(2)-lipid (A)	2	1	1	1-19		
N6-(1,2-Dicarboxyethyl)-AMP	2	2	1	1-19		
5-Formamido-1-(5-phospho-D-ribose)imidazole-4-carboxamide	2	2	2	1-19		
Lipid A Disaccharide	2	1	1	1-19		
2,3-Dihydrodipicolinate	2	1	1	1-19		
3-Dehydroquininate	2	2	1	1-19		
4-Phospho-L-aspartate	2	2	2	1,3,11,13,15-17	2,4-10,12,14,18,19	
S-Adenosylmethioninamine	2	1	2	1-19		
3-Carboxy-4-methyl-2-oxopentanoate	2	1	1	1-12,14-19	13	
Phenylpyruvate	2	2	1	1-19		
D-Glucosamine 1-phosphate	2	1	2	1-19		
Dephospho-CoA	2	1	1	1-19		
ADPglucose	2	1	1	1-19		
4-Aminobenzoate	2	1	1	1-19		
L-Histidinol phosphate	2	1	1	1-19		
LL-2,6-Diaminoheptanedioate	2	2	1	1-19		
Dihydroneopterin monophosphate	2	1	1	1-19		
Pantetheine 4'-phosphate	2	1	1	1-19		
N-Carbamoyl-L-aspartate	2	2	1	1-19		
(R)-2,3-Dihydroxy-3-methylpentanoate	2	1	1	1-12,14-19	13	
Malonyl-CoA	2	2	2	1-19		
4-amino-4-deoxychorismate	2	1	1	1-19		
D-Glutamate	2	1	2	1-19		
3-(4-Hydroxyphenyl)pyruvate	2	2	1	1-19		
L-Histidinol	2	1	1	1-19		
Deamino-NAD+	2	1	1	1-19		
(S)-2-Aceto-2-hydroxybutanoate	2	1	1	1-12,14-19	13	

1-B) Essential metabolites which are identified only under specific growth conditions. The total number of the corresponding metabolites is 32. In the following list, we do not include the uptake sources for a given condition.

Name of metabolite	No. of participating reactions			Growth condition relevant to each type			
	total	incoming	outgoing	A	B	C	D
Diphosphate	75	74	8	13,14			
Succinate	22	18	8		8,10	5	
Ubiquinol-8	18	15	4			5-8	1,3,9-11,13,15,17
Menaquinone 8	17	7	10	2,4,12,14,16,18			
Ubiquinone-8	17	4	14			5-8	1,3,9-11,13,15,17
Fumarate	13	10	8	2,4,12,14,16,18		5,6	
L-Malate	9	5	6			5,6	10
Glyoxylate	9	5	4	5			
FADH2	8	8	1			5,6	
Ornithine	7	5	5	1-7,9-19			
Citrate	4	3	2	2,4,12-16,18,19	1,3,6,7,9,11,17	5	
Isocitrate	3	2	3	2,4,12-16,18,19	1,3,6,7,9,11,17	5	
N-Acetyl-L-glutamate 5-semialdehyde	3	2	3	1-7,9-19			
C ³ -(3-Indolyl)-glycerol 3-phosphate	3	1	2	1-8,10-19			
6,7-Dimethyl-8-(1-D-ribityl)lumazine	2	1	1	1-11,13-19			
N-Acetyl-L-glutamyl 5-phosphate	2	2	1	1-7,9-19			
N2-Acetyl-L-ornithine	2	1	2	1-7,9-19			
D-Glycerate 2-phosphate	2	2	2			2,4,12,14,16,18,19	
N-Acetyl-L-glutamate	2	1	1	1-7,9-19			
5-Amino-6-(5'-phosphoribitylamino)uracil	2	1	1	1-11,13-19			
1-(2-Carboxyphenylamino)-1-deoxy-D-ribose 5-phosphate	2	1	1	1-8,10-19			
N-(5-Phospho-D-ribosyl)anthranilate	2	1	1	1-8,10-19			
N(omega)-(L-Arginino)succinate	2	2	1	1-7,9-17,19	18		
2,5-Diamino-6-(ribosylamino)-4-(3H)-pyrimidinone 5'-phosphate	2	1	1	1-11,13-19			
5-Amino-6-(5'-phosphoribosylamino)uracil	2	1	1	1-11,13-19			
Anthranilate	2	1	1	1-8,10-19			
Riboflavin	2	1	1	1-11,13-19			
FMN	2	1	1	1-11,13-19			
L-Citrulline	2	1	2	1-7,9-17,19	18		
3-Phospho-D-glyceroyl phosphate	2	2	2	5-10		2,4,12,14,16,18,19	