Supporting Information:

The global *Microcystis* interactome

Cook, K.V.,[1,2] C. Li,[3], H. Cai[1], L.R. Krumholz,[3] K.D. Hambright,[1,2,*] H.W. Paerl,[4] M.M. Steffen,[5] A.E. Wilson,[6] M.A. Burford,[7] H.-P. Grossart,[8] D. P. Hamilton,[7,9] H. Jiang,[10] A. Sukenik,[11] D. Latour,[12] E.I. Meyer,[13] J. Padisák,[14] B. Qin,[10] R.M. Zamor,[15,a] and G. Zhu[10]

Table S1. Summary of metagenome data for each lake.

Lake	category	contigs number	contigs bases(Mbp)	N50(bp)	Max length(bp)	protein-coding gene number
Belső-tó	Bacteria	33496	27.1	765	74324	26699
	Microcystis	890	4.7	16388	81696	4267
Chaohu	Bacteria	23682	19.8	794	36145	18385
	Microcystis	5258	7.8	1944	54606	6268
Clarendon	Bacteria	82636	104.8	1392	321729	102844
	Microcystis	6740	10.9	2336	38246	9427
FP23	Bacteria	155545	19.5	1454	49139	28976
	Microcystis	4816	7.9	2248	35883	6825
Grand	Bacteria	73551	92.3	1418	105344	89141
	Microcystis	9312	11.1	1418	57431	8881
Kinneret	Bacteria	26202	37.0	1817	101729	37307
	Microcystis	4943	9.1	2627	55640	8028
Aasee	Bacteria	36892	57.9	2441	299862	56457
	Microcystis	1122	5.5	19101	77987	5191
Rotoehu	Bacteria	26009	31.1	1368	41132	32313
	Microcystis	503	4.3	16710	49814	4098
Villerest	Bacteria	30454	40.5	1691	97662	36391
	Microcystis	2619	6.7	5702	54900	5927

Table S2. KEGG orthology numbers and functional pathways found in *Microcystis* and the microbiome bacteria, indicating involvement in C, N, P, or S cycling. Complete pathways are indicated by black fill ⬛ , while modules with no more than one pathway missing, are indicated by blue fill 🟦 . Empty cells indicate missing or partial (>1 missing) pathways.

Pathway	*Microcystis*	Bacteria	Biogeo-chemical cycle
Carbohydrate metabolism			
M00001 Glycolysis (Embden-Meyerhof pathway), glucose => pyruvate	⬛	⬛	**C**
M00002 Glycolysis, core module involving three-carbon compounds	⬛	⬛	**C**
M00003 Gluconeogenesis, oxaloacetate => fructose-6P	⬛	⬛	**C, P**
M00307 Pyruvate oxidation, pyruvate => acetyl-CoA	⬛	⬛	**C**
M00009 Citrate cycle (TCA cycle, Krebs cycle)	🟦	⬛	**C**
M00010 Citrate cycle, first carbon oxidation, oxaloacetate => 2-oxoglutarate	⬛	⬛	**C, S**
M00011 Citrate cycle, second carbon oxidation, 2-oxoglutarate => oxaloacetate	🟦	⬛	**C**
M00004 Pentose phosphate pathway (Pentose phosphate cycle)	⬛	⬛	**C, P**
M00006 Pentose phosphate pathway, oxidative phase, glucose 6P => ribulose 5P	⬛	⬛	**C,P**
M00007 Pentose phosphate pathway, non-oxidative phase, fructose 6P => ribose 5P	⬛	⬛	**C,P**
M00580 Pentose phosphate pathway, archaea, fructose 6P => ribose 5P	🟦	⬛	**C,P**
M00005 PRPP biosynthesis, ribose 5P => PRPP	⬛	⬛	**C,P**
M00008 Entner-Doudoroff pathway, glucose-6P => glyceraldehyde-3P + pyruvate		⬛	**C,P**
M00308 Semi-phosphorylative Entner-Doudoroff pathway, gluconate => glycerate-3P		⬛	**C,P**

M00309 Non-phosphorylative Entner-Doudoroff pathway, gluconate/galactonate => glycerate		▓	**C**
M00854 Glycogen biosynthesis, glucose-1P => glycogen/starch	▓	▓	**C,P**
M00855 Glycogen degradation, glycogen => glucose-6P	🟦	▓	**C,P**
M00565 Trehalose biosynthesis, D-glucose 1P => trehalose	🟦	🟦	**C,P**
M00549 Nucleotide sugar biosynthesis, glucose => UDP-glucose	🟦	■	**C,P**
M00631 D-Galacturonate degradation, D-galacturonate => pyruvate + D glyceraldehyde 3P		■	**C,P**
M00061 D-Glucuronate degradation, D-glucuronate => pyruvate + D-glyceraldehyde 3P		■	**C,P**
M00632 Galactose degradation, Leloir pathway, galactose => alpha-D-glucose-1P		■	**C,P**
M00552 D-galactonate degradation, De Ley-Doudoroff pathway, D-galactonate => glycerate-3P		■	**C,P**
M00554 Nucleotide sugar biosynthesis, galactose => UDP-galactose		■	**C,P**
M00012 Glyoxylate cycle		■	**C**
M00373 Ethylmalonyl pathway		■	**C**
M00013 Malonate semialdehyde pathway, propanoyl-CoA => acetyl-CoA		■	**C**
M00741 Propanoyl-CoA metabolism, propanoyl-CoA => succinyl-CoA		■	**C**
M00130 Inositol phosphate metabolism, PI=> PIP2 => Ins(1,4,5)P3 => Ins(1,3,4,5)P4		■	**C,P**
M00132 Inositol phosphate metabolism, Ins(1,3,4)P3 => phytate		■	**C**
Energy metabolism			
Carbon fixation			
M00165 Reductive pentose phosphate cycle (Calvin cycle)	■		**C**
M00166 Reductive pentose phosphate cycle, ribulose-5P => glyceraldehyde-3P	■		**C,P**
M00167 Reductive pentose phosphate cycle, glyceraldehyde-3P => ribulose-5P	■		**C,P**

M00168 CAM (Crassulacean acid metabolism), dark	⬛		**C**
M00173 Reductive citrate cycle (Arnon-Buchanan cycle)		⬛	**C**
M00579 Phosphate acetyltransferase-acetate kinase pathway, acetyl-CoA => acetate		⬛	**C,P**
Methane metabolism			
M00345 Formaldehyde assimilation, ribulose monophosphate pathway	🟦	⬛	**C**
M00358 Coenzyme M biosynthesis		🟦	**C**
M00174 Methane oxidation, methanotroph, methane => formaldehyde		🟦	**C**
M00346 Formaldehyde assimilation, serine pathway		⬛	**C**
M00344 Formaldehyde assimilation, xylulose monophosphate pathway		⬛	**C,P**
M00378 F420 biosynthesis		⬛	**C**
Nitrogen metabolism			
M00531 Assimilatory nitrate reduction, nitrate => ammonia	⬛	⬛	**N**
M00175 Nitrogen fixation, nitrogen => ammonia		⬛	**N**
M00530 Dissimilatory nitrate reduction, nitrate => ammonia		⬛	**N**
M00529 Denitrification, nitrate => nitrogen		⬛	**N**
M00528 Nitrification, ammonia => nitrite		🟦	**N**
M00804 Complete nitrification, comammox, ammonia => nitrite => nitrate		🟦	**N**
Sulfur metabolism			
M00176 Assimilatory sulfate reduction, sulfate => H2S	⬛	⬛	S
M00595 Thiosulfate oxidation by SOX complex, thiosulfate => sulfate		⬛	**S**
M00596 Dissimilatory sulfate reduction, sulfate => H2S		🟦	**S**

Photosynthesis			
M00161 Photosystem II	■		C
M00163 Photosystem I	■		C
M00597 Anoxygenic photosystem II		■	**C**
ATP synthesis (Structural complex)			
M00144 NADH:quinone oxidoreductase, prokaryotes	🟦	■	
M00146 NADH dehydrogenase (ubiquinone) 1 alpha subcomplex	🟦	🟦	
M00145 NAD(P)H:quinone oxidoreductase, chloroplasts and cyanobacteria	■		
M00149 Succinate dehydrogenase, prokaryotes	🟦	■	
M00162 Cytochrome b6f complex	🟦		
M00154 Cytochrome c oxidase	🟦		
M00155 Cytochrome c oxidase, prokaryotes	■		
M00153 Cytochrome bd ubiquinol oxidase	🟦		
M00157 F-type ATPase, prokaryotes and chloroplasts	■	■	
M00150 Fumarate reductase, prokaryotes		■	
M00162 Cytochrome b6f complex		■	
M00151 Cytochrome bc1 complex respiratory unit		■	
M00152 Cytochrome bc1 complex		■	
M00154 Cytochrome c oxidase		🟦	
M00155 Cytochrome c oxidase, prokaryotes		■	
M00153 Cytochrome bd ubiquinol oxidase		■	

M00417 Cytochrome o ubiquinol oxidase		🟦	
M00156 Cytochrome c oxidase, cbb3-type		⬛	
M00159 V-type ATPase, prokaryotes		🟦	
Lipid metabolism			
Fatty acid metabolism			
M00082 Fatty acid biosynthesis, initiation	⬛	⬛	**C**
M00083 Fatty acid biosynthesis, elongation	⬛	⬛	**C**
M00086 beta-Oxidation, acyl-CoA synthesis	⬛	⬛	**C**
M00087 beta-Oxidation		⬛	**C**
M00861 beta-Oxidation, peroxisome, VLCFA		⬛	**C**
Sterol biosynthesis			
M00862 beta-Oxidation, peroxisome, tri/dihydroxycholestanoyl-CoA => choloyl/chenodeoxycholoyl-CoA		⬛	**C**
M00107 Steroid hormone biosynthesis, cholesterol => prognenolone => progesterone		⬛	**C**
M00110 C19/C18-Steroid hormone biosynthesis, pregnenolone => androstenedione => estrone		🟦	**C**
Lipid metabolism			
M00098 Acylglycerol degradation	🟦	🟦	C
M00088 Ketone body biosynthesis, acetyl-CoA => acetoacetate/3-hydroxybutyrate/acetone		⬛	**C**
M00089 Triacylglycerol biosynthesis		⬛	**C**
M00090 Phosphatidylcholine (PC) biosynthesis, choline => PC		⬛	**C,P**
M00091 Phosphatidylcholine (PC) biosynthesis, PE => PC		⬛	**C,P**

M00092 Phosphatidylethanolamine (PE) biosynthesis, ethanolamine => PE		■	**C,P**
M00093 Phosphatidylethanolamine (PE) biosynthesis, PA => PS => PE		■	**C,P**
M00094 Ceramide biosynthesis		■	**C**
M00066 Lactosylceramide biosynthesis		■	**C**
M00099 Sphingosine biosynthesis		■	**C**
M00100 Sphingosine degradation		■	**C**
Nucleotide metabolism			
Purine metabolism			
M00048 Inosine monophosphate biosynthesis, PRPP + glutamine => IMP	■	■	**C,P**
M00049 Adenine ribonucleotide biosynthesis, IMP => ADP,ATP	■	■	**C,P**
M00050 Guanine ribonucleotide biosynthesis IMP => GDP,GTP	■	■	**C,P**
M00546 Purine degradation, xanthine => urea		■	**C,N**
Pyrimidine metabolism			
M00051 Uridine monophosphate biosynthesis, glutamine (+ PRPP) => UMP	🟦	■	**C,P**
M00052 Pyrimidine ribonucleotide biosynthesis, UMP => UDP/UTP,CDP/CTP	■	■	**C,P**
M00053 Pyrimidine deoxyribonuleotide biosynthesis, CDP/CTP => dCDP/dCTP,dTDP/dTTP		■	**C,P**
M00046 Pyrimidine degradation, uracil => beta-alanine, thymine => 3-aminoisobutanoate		■	**C,P**
Amino acid metabolism			
Serine and threonine metabolism	■	■	
M00018 Threonine biosynthesis, aspartate => homoserine => threonine	🟦	■	**C,N**
M00555 Betaine biosynthesis, choline => betaine		■	**C,N**

M00020 Serine biosynthesis, glycerate-3P => serine		⬛	**C,N**
M00033 Ectoine biosynthesis, aspartate => ectoine		⬛	**C,N**
Cysteine and methionine metabolism			
M00021 Cysteine biosynthesis, serine => cysteine	⬛	⬛	**C,N**
M00338 Cysteine biosynthesis, homocysteine + serine => cysteine	⬛	⬛	**C,N**
M00034 Methionine salvage pathway	🟦	⬛	**C,N**
M00035 Methionine degradation		⬛	**C,N**
M00017 Methionine biosynthesis, apartate => homoserine => methionine		⬛	**C,N**
M00368 Ethylene biosynthesis, methionine => ethylene		🟦	**C,N**
Branched-chain amino acid metabolism			
M00019 Valine/isoleucine biosynthesis, pyruvate => valine / 2-oxobutanoate => isoleucine	⬛	⬛	**C,N**
M00535 Isoleucine biosynthesis, pyruvate => 2-oxobutanoate	🟦	⬛	**C,N**
M00570 Isoleucine biosynthesis, threonine => 2-oxobutanoate => isoleucine	⬛	⬛	**C,N**
M00432 Leucine biosynthesis, 2-oxoisovalerate => 2-oxoisocaproate	⬛	⬛	**C,N**
M00036 Leucine degradation, leucine => acetoacetate + acetyl-CoA		⬛	**C,N**
Lysine metabolism			
M00016 Lysine biosynthesis, succinyl-DAP pathway, aspartate => lysine	🟦	⬛	**C,N**
M00526 Lysine biosynthesis, DAP dehydrogenase pathway, aspartate => lysine	🟦	⬛	**C,N**
M00527 Lysine biosynthesis, DAP aminotransferase pathway, aspartate => lysine	⬛	⬛	**C,N**
M00433 Lysine biosynthesis, 2-oxoglutarate => 2-oxoadipate		🟦	**C,N**
Arginine and proline metabolism			

M00028 Ornithine biosynthesis, glutamate => ornithine	■	■	**C,N**
M00844 Arginine biosynthesis, ornithine => arginine	■	■	**C,N**
M00015 Proline biosynthesis, glutamate => proline	■	■	**C,N**
M00845 Arginine biosynthesis, glutamate => acetylcitrulline => arginine		■	**C,N**
M00047 Creatine pathway		■	**C,N**
Polyamine biosynthesis			
M00133 Polyamine biosynthesis, arginine => agmatine => putrescine => spermidine	■	■	**C,N**
M00134 Polyamine biosynthesis, arginine => ornithine => putrescine		■	**C,N**
M00136 GABA biosynthesis, prokaryotes, putrescine => GABA		🟦	**C,N**
Aromatic amino acid metabolism			
M00022 Shikimate pathway, phosphoenolpyruvate + erythrose-4P => chorismate	■	■	**C,N**
M00023 Tryptophan biosynthesis, chorismate => tryptophan	■	■	**C,N**
M00024 Phenylalanine biosynthesis, chorismate => phenylalanine	🟦	■	**C,N**
M00040 Tyrosine biosynthesis, prephanate => pretyrosine => tyrosine	🟦	■	**C,N**
M00025 Tyrosine biosynthesis, chorismate => tyrosine		■	**C,N**
M00042 Catecholamine biosynthesis, tyrosine => dopamine => noradrenaline => adrenaline		■	**C,N**
M00044 Tyrosine degradation, tyrosine => homogentisate		■	**C,N**
M00533 Homoprotocatechuate degradation, homoprotocatechuate => 2-oxohept-3-enedioate		■	**C,N**
M00545 Trans-cinnamate degradation, trans-cinnamate => acetyl-CoA		■	**C,N**
M00038 Tryptophan metabolism, tryptophan => kynurenine => 2-aminomuconate		■	**C,N**
Glycan metabolism			

Lipopolysaccharide metabolism			
M00064 ADP-L-glycero-D-manno-heptose biosynthesis		⬛	**C**
M00072 N-glycosylation by oligosaccharyltransferase		🟦	**C**
M00073 N-glycan precursor trimming		🟦	**C**
M00056 O-glycan biosynthesis, mucin type core		🟦	**C**
M00070 Glycosphingolipid biosynthesis, lacto-series, LacCer => Lc4Cer		🟦	**C**
M00068 Glycosphingolipid biosynthesis, globo-series, LacCer => Gb4Cer		🟦	**C**
M00060 KDO2-lipid A biosynthesis, Raetz pathway, LpxL-LpxM type		🟦	**C**
M00866 KDO2-lipid A biosynthesis, Raetz pathway, non-LpxL-LpxM type		⬛	**C**
M00063 CMP-KDO biosynthesis		⬛	**C**
M00064 ADP-L-glycero-D-manno-heptose biosynthesis		⬛	**C**
Metabolism of cofactors and vitamins			
Cofactor and vitamin metabolism			**C,P**
M00127 Thiamine biosynthesis, AIR => thiamine-P/thiamine-2P	🟦	⬛	**C,P**
M00125 Riboflavin biosynthesis, GTP => riboflavin/FMN/FAD	🟦	⬛	**C,P**
M00115 NAD biosynthesis, aspartate => NAD	⬛	⬛	**C,N**
M00119 Pantothenate biosynthesis, valine/L-aspartate => pantothenate	🟦	⬛	**C**
M00120 Coenzyme A biosynthesis, pantothenate => CoA	⬛	⬛	**C**
M00123 Biotin biosynthesis, pimeloyl-ACP/CoA => biotin	🟦	⬛	**C**
M00842 Tetrahydrobiopterin biosynthesis, GTP => BH4	🟦	🟦	**C**
M00843 L-threo-Tetrahydrobiopterin biosynthesis, GTP => L-threo-BH4	🟦	🟦	**C**

M00140 C1-unit interconversion, prokaryotes	🟦	⬛	**C**
M00121 Heme biosynthesis, plants and bacteria, glutamate => heme	🟦	⬛	**C, Fe**
M00846 Siroheme biosynthesis, glutamate => siroheme	🟦	⬛	**C,N,Fe**
M00112 Tocopherol/tocotorienol biosynthesis	⬛	⬛	**C**
M00124 Pyridoxal biosynthesis, erythrose-4P => pyridoxal-5P		🟦	**C,P**
M00572 Pimeloyl-ACP biosynthesis, BioC-BioH pathway, malonyl-ACP => pimeloyl-ACP		⬛	**C,P**
M00573 Biotin biosynthesis, BioI pathway, long-chain-acyl-ACP => pimeloyl-ACP => biotin		🟦	**C,P**
M00577 Biotin biosynthesis, BioW pathway, pimelate => pimeloyl-CoA => biotin		🟦	**C**
M00126 Tetrahydrofolate biosynthesis, GTP => THF		⬛	**C**
M00841 Tetrahydrofolate biosynthesis, mediated by PTPS, GTP => THF		🟦	**C**
M00122 Cobalamin biosynthesis, cobinamide => cobalamin		⬛	**C,Co**
M00117 Ubiquinone biosynthesis, prokaryotes, chorismate => ubiquinone		🟦	**C**
M00116 Menaquinone biosynthesis, chorismate => menaquinol		⬛	**C**
Biosynthesis of terpenoids and polyketides			
Terpenoid backbone biosynthesis			
M00096 C5 isoprenoid biosynthesis, non-mevalonate pathway	⬛	⬛	**C**
M00364 C10-C20 isoprenoid biosynthesis, bacteria	⬛	⬛	**C**
M00365 C10-C20 isoprenoid biosynthesis, archaea	🟦	🟦	**C**
M00095 C5 isoprenoid biosynthesis, mevalonate pathway		🟦	**C**
Xenobiotics biodegradation			
Aromatics degradation			

M00538 Toluene degradation, toluene => benzoate	⬛	**C**
M00537 Xylene degradation, xylene => methylbenzoate	⬛	**C**
M00551 Benzoate degradation, benzoate => catechol / methylbenzoate => methylcatechol lete)	⬛	**C**
M00637 Anthranilate degradation, anthranilate => catechol	⬛	**C**
M00568 Catechol ortho-cleavage, catechol => 3-oxoadipate	⬛	**C**
M00569 Catechol meta-cleavage, catechol => acetyl-CoA / 4-methylcatechol => propanoyl-CoA	⬛	**C**
M00540 Benzoate degradation, cyclohexanecarboxylic acid =>pimeloyl-CoA	⬛	**C**
M00638 Salicylate degradation, salicylate => gentisate	⬛	**C**
M00623 Phthalate degradation, phthalate => protocatechuate	⬛	**C**
Drug resistance		
M00627 beta-Lactam resistance, Bla system		
M00745 Imipenem resistance, repression of porin OprD (13)	⬛	
M00651 Vancomycin resistance, D-Ala-D-Lac type	🟦	
M00726 Cationic antimicrobial peptide (CAMP) resistance, lysyl-phosphatidylglycerol (L-PG) synthase MprF	🟦	
M00744 Cationic antimicrobial peptide (CAMP) resistance, protease PgtE	⬛	
M00718 Multidrug resistance, efflux pump MexAB-OprM	⬛	
M00642 Multidrug resistance, efflux pump MexJK-OprM	⬛	
M00643 Multidrug resistance, efflux pump MexXY-OprM	🟦	
M00769 Multidrug resistance, efflux pump MexPQ-OpmE	🟦	
M00649 Multidrug resistance, efflux pump AdeABC	⬛	

M00696 Multidrug resistance, efflux pump AcrEF-TolC	🟦
M00697 Multidrug resistance, efflux pump MdtEF-TolC	🟦
M00698 Multidrug resistance, efflux pump BpeEF-OprC	🟦
M00700 Multidrug resistance, efflux pump AbcA	⬛
M00714 Multidrug resistance, efflux pump QacA	⬛