Supporting Results for:

A Semi-Supervised Method for Predicting Transcription Factor-Gene Interactions in *Escherichia coli*

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1. GO Analysis of Targets of Global Regulators

In this section we present significant Gene Ontology (GO) categories for the seven transcription factors (TFs) with the largest number of predicted and curated targets. The analysis was done separately on the predicted set and the curated set. The p-value was computed based on the hypergeometric distribution. Only categories with at least 5 genes were included in the analysis. The corrected p-value for testing multiple categories is based on a randomization procedure in which a set of the same size was randomly drawn 500 times from the base set of all genes considered. The corrected p-value is then the proportion of times in which a GO p-value for a random set was more significant than an actual p-value. We observe that in some cases a significant GO category for the predicted targets of a TF is also significant for the curated targets, while in other cases the category is only significant among the predicted targets.

ArcA – predicted

Category ID	Category Name	#Genes Category	#Genes Assigned	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0045333	cellular respiration	30	9.0	0.4	+8.6	1.5E-10	<0.001
GO:0044248	cellular catabolic process	154	15.0	2.2	+12.8	1.9E-9	<0.001
GO:0015980	energy derivation by oxidation of organic com...	43	9.0	0.6	+8.4	5.1E-9	<0.001
GO:0009056	catabolic process	169	15.0	2.4	+12.6	6.8E-9	<0.001
GO:0009109	coenzyme catabolic process	22	6.0	0.3	+5.7	4.1E-7	<0.001
GO:0051187	cofactor catabolic process	22	6.0	0.3	+5.7	4.1E-7	<0.001
GO:0046356	acetyl-CoA catabolic process	22	6.0	0.3	+5.7	4.1E-7	<0.001
GO:0006099	tricarboxylic acid cycle	22	6.0	0.3	+5.7	4.1E-7	<0.001
GO:0009060	aerobic respiration	23	6.0	0.3	+5.7	5.5E-7	<0.001
GO:0006084	acetyl-CoA metabolic process	25	6.0	0.4	+5.6	9.4E-7	<0.001
GO:0009063	amino acid catabolic process	15	5.0	0.2	+4.8	1.3E-6	<0.001
GO:0009310	amine catabolic process	17	5.0	0.2	+4.8	2.7E-6	<0.001
GO:0044270	nitrogen compound catabolic process	17	5.0	0.2	+4.8	2.7E-6	<0.001
GO:0016491	oxidoreductase activity	412	15.0	5.9	+9.1	4.8E-4	0.030
GO:0006732	coenzyme metabolic process	113	7.0	1.6	+5.4	1.0E-3	0.054
GO:0006091	generation of precursor metabolites and ene...	276	11.0	3.9	+7.1	1.5E-3	0.082
GO:0051186	cofactor metabolic process	157	7.0	2.2	+4.8	6.5E-3	0.272
GO:0044262	cellular carbohydrate metabolic process	249	9.0	3.6	+5.4	8.0E-3	0.314
GO:0051539	4 iron, 4 sulfur cluster binding	93	5.0	1.3	+3.7	9.9E-3	0.382
GO:0005506	iron ion binding	219	8.0	3.1	+4.9	0.01	0.416

ArcA – curated

Category ID	Category Name	#Genes Category	#Genes Assigned	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0006091	generation of precursor metabolites and ene...	276	34.0	3.9	+30.1	1.3E-25	<0.001
GO:0048038	quinone binding	14	13.0	0.2	+12.8	3.5E-24	<0.001
GO:0016491	oxidoreductase activity	412	35.0	5.9	+29.1	6.6E-21	<0.001
GO:0050136	NADH dehydrogenase (quinone) activity	24	13.0	0.3	+12.7	5.7E-19	<0.001
GO:0006118	electron transport	236	27.0	3.4	+23.6	6.7E-19	<0.001
GO:0016655	oxidoreductase activity, acting on NADH or N...	25	13.0	0.4	+12.6	1.2E-18	<0.001
GO:0003954	NADH dehydrogenase activity	25	13.0	0.4	+12.6	1.2E-18	<0.001
GO:0009060	aerobic respiration	23	12.0	0.3	+11.7	2.7E-17	<0.001
GO:0016651	oxidoreductase activity, acting on NADH or N...	33	13.0	0.5	+12.5	1.2E-16	<0.001
GO:0048037	cofactor binding	201	23.0	2.9	+20.1	6.1E-16	<0.001
GO:0009109	coenzyme catabolic process	22	11.0	0.3	+10.7	1.2E-15	<0.001
GO:0051187	cofactor catabolic process	22	11.0	0.3	+10.7	1.2E-15	<0.001
GO:0046356	acetyl-CoA catabolic process	22	11.0	0.3	+10.7	1.2E-15	<0.001
GO:0006099	tricarboxylic acid cycle	22	11.0	0.3	+10.7	1.2E-15	<0.001
GO:0045333	cellular respiration	30	12.0	0.4	+11.6	1.6E-15	<0.001
GO:0006084	acetyl-CoA metabolic process	25	11.0	0.4	+10.6	7.3E-15	<0.001
GO:0042773	ATP synthesis coupled electron transport	21	10.0	0.3	+9.7	5.0E-14	<0.001
GO:0008137	NADH dehydrogenase (ubiquinone) activity	21	10.0	0.3	+9.7	5.0E-14	<0.001
GO:0015980	energy derivation by oxidation of organic com...	43	12.0	0.6	+11.4	2.5E-13	<0.001
GO:0009055	electron carrier activity	102	15.0	1.5	+13.5	4.5E-12	<0.001
GO:0006119	oxidative phosphorylation	31	10.0	0.4	+9.6	5.6E-12	<0.001
GO:0009056	catabolic process	169	17.0	2.4	+14.6	7.2E-11	<0.001
GO:0006732	coenzyme metabolic process	113	13.0	1.6	+11.4	3.4E-9	<0.001
GO:0006120	mitochondrial electron transport, NADH to ub...	13	6.0	0.2	+5.8	1.0E-8	<0.001
GO:0042775	organelle ATP synthesis coupled electron tra...	13	6.0	0.2	+5.8	1.0E-8	<0.001
GO:0044248	cellular catabolic process	154	14.0	2.2	+11.8	1.7E-8	<0.001
GO:0051186	cofactor metabolic process	157	14.0	2.2	+11.8	2.2E-8	<0.001
GO:0050662	coenzyme binding	132	13.0	1.9	+11.1	2.3E-8	<0.001
GO:0016310	phosphorylation	75	10.0	1.1	+8.9	6.5E-8	<0.001
GO:0006796	phosphate metabolic process	80	10.0	1.1	+8.9	1.2E-7	<0.001
GO:0006793	phosphorus metabolic process	81	10.0	1.2	+8.8	1.4E-7	<0.001
GO:0044237	cellular metabolic process	1627	41.0	23.2	+17.8	2.7E-6	<0.001
GO:0044262	cellular carbohydrate metabolic process	249	14.0	3.6	+10.4	6.7E-6	<0.001
GO:0006631	fatty acid metabolic process	35	6.0	0.5	+5.5	7.7E-6	<0.001
GO:0032787	monocarboxylic acid metabolic process	92	8.0	1.3	+6.7	3.9E-5	<0.001
GO:0016614	oxidoreductase activity, acting on CH-OH gro...	73	7.0	1.0	+6.0	6.6E-5	0.008
GO:0044464	cell part	2139	45.0	30.5	+14.5	1.0E-4	0.010
GO:0016020	membrane	1134	30.0	16.2	+13.8	1.1E-4	0.010
GO:0005506	iron ion binding	219	11.0	3.1	+7.9	2.1E-4	0.016

CRP – predicted

Category ID	Category Name	#Genes Category	#Genes Assigned	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0008643	carbohydrate transport	107	31.0	6.4	+24.6	2.9E-14	<0.001
GO:0005351	sugar:hydrogen ion symporter activity	106	29.0	6.4	+22.6	1.1E-12	<0.001
GO:0015144	carbohydrate transmembrane transporter ac...	106	29.0	6.4	+22.6	1.1E-12	<0.001
GO:0051119	sugar transmembrane transporter activity	106	29.0	6.4	+22.6	1.1E-12	<0.001
GO:0015293	symporter activity	135	31.0	8.1	+22.9	2.6E-11	<0.001
GO:0009401	phosphoenolpyruvate-dependent sugar pho...	57	20.0	3.4	+16.6	2.8E-11	<0.001
GO:0019751	polyol metabolic process	24	12.0	1.4	+10.6	2.4E-9	<0.001
GO:0015291	secondary active transmembrane transporte...	166	31.0	9.9	+21.1	6.4E-9	<0.001
GO:0006066	alcohol metabolic process	124	26.0	7.4	+18.6	9.5E-9	<0.001
GO:0009065	glutamine family amino acid catabolic proce...	7	6.0	0.4	+5.6	2.9E-7	<0.001
GO:0006059	hexitol metabolic process	7	6.0	0.4	+5.6	2.9E-7	<0.001
GO:0019400	alditol metabolic process	7	6.0	0.4	+5.6	2.9E-7	<0.001
GO:0019402	galactitol metabolic process	7	6.0	0.4	+5.6	2.9E-7	<0.001
GO:0022891	substrate-specific transmembrane transport...	266	37.0	15.9	+21.1	6.8E-7	<0.001
GO:0019544	arginine catabolic process to glutamate	5	5.0	0.3	+4.7	7.4E-7	<0.001
GO:0006536	glutamate metabolic process	12	7.0	0.7	+6.3	1.6E-6	<0.001
GO:0022804	active transmembrane transporter activity	220	32.0	13.2	+18.8	1.6E-6	<0.001
GO:0022857	transmembrane transporter activity	310	40.0	18.6	+21.4	1.7E-6	<0.001
GO:0006527	arginine catabolic process	6	5.0	0.4	+4.6	4.2E-6	0.002
GO:0051234	establishment of localization	782	75.0	46.9	+28.1	6.2E-6	0.002
GO:0006810	transport	772	74.0	46.3	+27.7	7.5E-6	0.006
GO:0007154	cell communication	172	26.0	10.3	+15.7	7.9E-6	0.006
GO:0022892	substrate-specific transporter activity	324	39.0	19.4	+19.6	1.3E-5	0.006
GO:0016616	oxidoreductase activity, acting on the CH-OH ...	65	14.0	3.9	+10.1	2.1E-5	0.008
GO:0007165	signal transduction	150	23.0	9.0	+14.0	2.2E-5	0.008

CRP – curated

Category ID	Category Name	#Genes Category	#Genes Assigned	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0008643	carbohydrate transport	107	42.0	6.4	+35.6	5.8E-25	<0.001
GO:0015144	carbohydrate transmembrane transporter ac...	106	41.0	6.4	+34.6	4.5E-24	<0.001
GO:0051119	sugar transmembrane transporter activity	106	41.0	6.4	+34.6	4.5E-24	<0.001
GO:0005351	sugar:hydrogen ion symporter activity	106	41.0	6.4	+34.6	4.5E-24	<0.001
GO:0015293	symporter activity	135	44.0	8.1	+35.9	2.9E-22	<0.001
GO:0015291	secondary active transmembrane transporte...	166	45.0	9.9	+35.1	3.9E-19	<0.001
GO:0044248	cellular catabolic process	154	41.0	9.2	+31.8	3.7E-17	<0.001
GO:0006066	alcohol metabolic process	124	36.0	7.4	+28.6	1.8E-16	<0.001
GO:0009056	catabolic process	169	41.0	10.1	+30.9	1.4E-15	<0.001
GO:0022804	active transmembrane transporter activity	220	45.0	13.2	+31.8	4.4E-14	<0.001
GO:0005975	carbohydrate metabolic process	354	59.0	21.2	+37.8	4.6E-14	<0.001
GO:0022891	substrate-specific transmembrane transport...	266	47.0	15.9	+31.1	3.4E-12	<0.001
GO:0005996	monosaccharide metabolic process	90	26.0	5.4	+20.6	4.4E-12	<0.001
GO:0022857	transmembrane transporter activity	310	50.0	18.6	+31.4	2.2E-11	<0.001
GO:0009401	phosphoenolpyruvate-dependent sugar pho...	57	19.0	3.4	+15.6	2.5E-10	<0.001
GO:0044262	cellular carbohydrate metabolic process	249	42.0	14.9	+27.1	2.7E-10	<0.001
GO:0022892	substrate-specific transporter activity	324	48.0	19.4	+28.6	1.3E-9	<0.001
GO:0019318	hexose metabolic process	80	21.0	4.8	+16.2	3.9E-9	<0.001
GO:0019439	aromatic compound catabolic process	15	8.0	0.9	+7.1	6.6E-7	<0.001
GO:0019299	rhamnose metabolic process	5	5.0	0.3	+4.7	7.4E-7	<0.001
GO:0019323	pentose catabolic process	5	5.0	0.3	+4.7	7.4E-7	<0.001
GO:0019566	arabinose metabolic process	5	5.0	0.3	+4.7	7.4E-7	<0.001
GO:0019568	arabinose catabolic process	5	5.0	0.3	+4.7	7.4E-7	<0.001
GO:0045893	positive regulation of transcription, DNA-dep...	5	5.0	0.3	+4.7	7.4E-7	<0.001
GO:0044237	cellular metabolic process	1627	134.0	97.5	+36.5	1.1E-6	<0.001
GO:0031325	positive regulation of cellular metabolic proc...	8	6.0	0.5	+5.5	1.1E-6	<0.001
GO:0048518	positive regulation of biological process	8	6.0	0.5	+5.5	1.1E-6	<0.001
GO:0048522	positive regulation of cellular process	8	6.0	0.5	+5.5	1.1E-6	<0.001
GO:0009893	positive regulation of metabolic process	8	6.0	0.5	+5.5	1.1E-6	<0.001
GO:0045935	positive regulation of nucleobase, nucleosid...	8	6.0	0.5	+5.5	1.1E-6	<0.001
GO:0045941	positive regulation of transcription	8	6.0	0.5	+5.5	1.1E-6	<0.001
GO:0046164	alcohol catabolic process	47	13.0	2.8	+10.2	2.1E-6	<0.001
GO:0009109	coenzyme catabolic process	22	9.0	1.3	+7.7	2.2E-6	<0.001
GO:0006099	tricarboxylic acid cycle	22	9.0	1.3	+7.7	2.2E-6	<0.001
GO:0051187	cofactor catabolic process	22	9.0	1.3	+7.7	2.2E-6	<0.001
GO:0046356	acetyl-CoA catabolic process	22	9.0	1.3	+7.7	2.2E-6	<0.001
GO:0006071	glycerol metabolic process	17	8.0	1.0	+7.0	2.3E-6	<0.001
GO:0009060	aerobic respiration	23	9.0	1.4	+7.6	3.4E-6	0.002
GO:0044238	primary metabolic process	1500	124.0	89.9	+34.1	3.8E-6	0.002

Fis – predicted

Category ID	Category Name	#Genes Category	#Genes Assigned	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0003735	structural constituent of ribosome	56	31.0	1.8	+29.2	2.4E-33	<0.001
GO:0005840	ribosome	57	31.0	1.8	+29.2	5.2E-33	<0.001
GO:0030529	ribonucleoprotein complex	60	31.0	1.9	+29.1	4.5E-32	<0.001
GO:0044444	cytoplasmic part	85	34.0	2.7	+31.3	2.1E-30	<0.001
GO:0006412	translation	111	37.0	3.5	+33.5	1.0E-29	<0.001
GO:0043228	non-membrane-bound organelle	79	32.0	2.5	+29.5	8.3E-29	<0.001
GO:0043232	intracellular non-membrane-bound organelle	79	32.0	2.5	+29.5	8.3E-29	<0.001
GO:0043229	intracellular organelle	96	34.0	3.0	+31.0	2.8E-28	<0.001
GO:0019843	rRNA binding	37	24.0	1.2	+22.8	3.0E-28	<0.001
GO:0009059	macromolecule biosynthetic process	256	48.0	8.1	+39.9	3.0E-26	<0.001
GO:0003723	RNA binding	111	33.0	3.5	+29.5	1.3E-24	<0.001
GO:0009058	biosynthetic process	617	65.0	19.5	+45.5	1.6E-21	<0.001
GO:0044249	cellular biosynthetic process	441	55.0	13.9	+41.1	3.2E-21	<0.001
GO:0044260	cellular macromolecule metabolic process	381	50.0	12.1	+37.9	4.6E-20	<0.001
GO:0005737	cytoplasm	656	63.0	20.7	+42.3	1.5E-18	<0.001
GO:0044267	cellular protein metabolic process	279	40.0	8.8	+31.2	3.4E-17	<0.001
GO:0044424	intracellular part	697	63.0	22.0	+41.0	3.7E-17	<0.001
GO:0019538	protein metabolic process	285	40.0	9.0	+31.0	7.3E-17	<0.001
GO:0005622	intracellular	835	64.0	26.4	+37.6	8.5E-14	<0.001
GO:0033279	ribosomal subunit	13	9.0	0.4	+8.6	1.6E-11	<0.001
GO:0044422	organelle part	28	11.0	0.9	+10.1	2.8E-10	<0.001
GO:0044446	intracellular organelle part	28	11.0	0.9	+10.1	2.8E-10	<0.001
GO:0000267	cell fraction	62	15.0	2.0	+13.0	3.8E-10	<0.001
GO:0005624	membrane fraction	62	15.0	2.0	+13.0	3.8E-10	<0.001
GO:0044238	primary metabolic process	1500	81.0	47.4	+33.6	1.6E-9	<0.001
GO:0044237	cellular metabolic process	1627	85.0	51.5	+33.5	2.0E-9	<0.001
GO:0043170	macromolecule metabolic process	1177	66.0	37.2	+28.8	6.5E-8	<0.001
GO:0044464	cell part	2139	97.0	67.7	+29.3	1.1E-7	<0.001
GO:0000049	tRNA binding	17	7.0	0.5	+6.5	4.0E-7	<0.001
GO:0015934	large ribosomal subunit	7	5.0	0.2	+4.8	5.9E-7	<0.001
GO:0003676	nucleic acid binding	588	40.0	18.6	+21.4	8.5E-7	<0.001
GO:0008610	lipid biosynthetic process	126	16.0	4.0	+12.0	1.5E-6	<0.001
GO:0044255	cellular lipid metabolic process	148	17.0	4.7	+12.3	2.9E-6	<0.001
GO:0006629	lipid metabolic process	152	17.0	4.8	+12.2	4.2E-6	<0.001
GO:0006633	fatty acid biosynthetic process	18	6.0	0.6	+5.4	1.2E-5	0.002
GO:0009103	lipopolysaccharide biosynthetic process	78	10.0	2.5	+7.5	1.4E-4	0.020
GO:0008653	lipopolysaccharide metabolic process	78	10.0	2.5	+7.5	1.4E-4	0.020
GO:0005515	protein binding	835	44.0	26.4	+17.6	1.8E-4	0.026
GO:0046394	carboxylic acid biosynthetic process	28	6.0	0.9	+5.1	1.9E-4	0.026

Fis – curated

Category ID	Category Name	#Genes Category	#Genes Assigned	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0048038	quinone binding	14	13.0	0.4	+12.6	2.4E-19	<0.001
GO:0003954	NADH dehydrogenase activity	25	14.0	0.8	+13.2	1.7E-15	<0.001
GO:0050136	NADH dehydrogenase (quinone) activity	24	13.0	0.8	+12.2	3.3E-14	<0.001
GO:0016655	oxidoreductase activity, acting on NADH or N...	25	13.0	0.8	+12.2	6.6E-14	<0.001
GO:0016651	oxidoreductase activity, acting on NADH or N...	33	14.0	1.0	+13.0	2.5E-13	<0.001
GO:0042773	ATP synthesis coupled electron transport	21	10.0	0.7	+9.3	1.9E-10	<0.001
GO:0008137	NADH dehydrogenase (ubiquinone) activity	21	10.0	0.7	+9.3	1.9E-10	<0.001
GO:0006119	oxidative phosphorylation	31	10.0	1.0	+9.0	1.8E-8	<0.001
GO:0009055	electron carrier activity	102	16.0	3.2	+12.8	7.6E-8	<0.001
GO:0006120	mitochondrial electron transport, NADH to ub...	13	6.0	0.4	+5.6	1.3E-6	<0.001
GO:0042775	organelle ATP synthesis coupled electron tra...	13	6.0	0.4	+5.6	1.3E-6	<0.001
GO:0016310	phosphorylation	75	11.0	2.4	+8.6	1.8E-5	0.002
GO:0006796	phosphate metabolic process	80	11.0	2.5	+8.5	3.4E-5	0.004
GO:0006793	phosphorus metabolic process	81	11.0	2.6	+8.4	3.8E-5	0.004
GO:0006118	electron transport	236	19.0	7.5	+11.5	1.3E-4	0.022
GO:0048037	cofactor binding	201	17.0	6.4	+10.6	1.6E-4	0.026
GO:0016491	oxidoreductase activity	412	25.0	13.0	+12.0	9.2E-4	0.114
GO:0006091	generation of precursor metabolites and ene...	276	19.0	8.7	+10.3	9.3E-4	0.114

FNR – predicted

Category ID	Category Name	#Genes Category	#Genes Assigned	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0051539	4 iron, 4 sulfur cluster binding	93	7.0	2.0	+5.0	3.8E-3	0.262
GO:0051540	metal cluster binding	126	8.0	2.7	+5.3	5.8E-3	0.354
GO:0051536	iron-sulfur cluster binding	126	8.0	2.7	+5.3	5.8E-3	0.354
GO:0009103	lipopolysaccharide biosynthetic process	83	6.0	1.8	+4.2	8.9E-3	0.470
GO:0008653	lipopolysaccharide metabolic process	83	6.0	1.8	+4.2	8.9E-3	0.470

FNR – curated

Category ID	Category Name	#Genes Category	#Genes Assigned	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0006118	electron transport	236	45.0	5.2	+39.8	3.4E-33	<0.001
GO:0006091	generation of precursor metabolites and ene...	276	46.0	6.0	+40.0	2.9E-31	<0.001
GO:0016491	oxidoreductase activity	412	46.0	9.0	+37.0	2.4E-23	<0.001
GO:0009055	electron carrier activity	102	27.0	2.2	+24.8	2.7E-23	<0.001
GO:0005506	iron ion binding	219	35.0	4.8	+30.2	1.9E-22	<0.001
GO:0048038	quinone binding	14	13.0	0.3	+12.7	1.5E-21	<0.001
GO:0046914	transition metal ion binding	458	43.0	10.0	+33.0	1.4E-18	<0.001
GO:0003954	NADH dehydrogenase activity	25	14.0	0.5	+13.5	7.6E-18	<0.001
GO:0043169	cation binding	511	43.0	11.2	+31.8	9.7E-17	<0.001
GO:0050136	NADH dehydrogenase (quinone) activity	24	13.0	0.5	+12.5	2.3E-16	<0.001
GO:0046872	metal ion binding	606	46.0	13.3	+32.7	2.7E-16	<0.001
GO:0016655	oxidoreductase activity, acting on NADH or N...	25	13.0	0.5	+12.5	4.6E-16	<0.001
GO:0043167	ion binding	622	46.0	13.6	+32.4	7.6E-16	<0.001
GO:0016651	oxidoreductase activity, acting on NADH or N...	33	14.0	0.7	+13.3	1.2E-15	<0.001
GO:0017004	cytochrome complex assembly	10	9.0	0.2	+8.8	7.6E-15	<0.001
GO:0051540	metal cluster binding	126	22.0	2.8	+19.2	7.8E-15	<0.001
GO:0051536	iron-sulfur cluster binding	126	22.0	2.8	+19.2	7.8E-15	<0.001
GO:0006461	protein complex assembly	14	10.0	0.3	+9.7	1.4E-14	<0.001
GO:0042126	nitrate metabolic process	19	11.0	0.4	+10.6	2.0E-14	<0.001
GO:0042128	nitrate assimilation	19	11.0	0.4	+10.6	2.0E-14	<0.001
GO:0051539	4 iron, 4 sulfur cluster binding	93	19.0	2.0	+17.0	3.4E-14	<0.001
GO:0043623	cellular protein complex assembly	11	9.0	0.2	+8.8	4.1E-14	<0.001
GO:0042773	ATP synthesis coupled electron transport	21	10.0	0.5	+9.5	4.4E-12	<0.001
GO:0008137	NADH dehydrogenase (ubiquinone) activity	21	10.0	0.5	+9.5	4.4E-12	<0.001
GO:0016661	oxidoreductase activity, acting on other nitrog...	16	9.0	0.4	+8.6	7.8E-12	<0.001
GO:0065003	macromolecular complex assembly	26	10.0	0.6	+9.4	6.1E-11	<0.001
GO:0022607	cellular component assembly	27	10.0	0.6	+9.4	9.5E-11	<0.001
GO:0006119	oxidative phosphorylation	31	10.0	0.7	+9.3	4.7E-10	<0.001
GO:0015232	heme transporter activity	5	5.0	0.1	+4.9	4.5E-9	<0.001
GO:0051184	cofactor transporter activity	6	5.0	0.1	+4.9	2.7E-8	<0.001
GO:0006120	mitochondrial electron transport, NADH to ub...	13	6.0	0.3	+5.7	1.4E-7	<0.001
GO:0042775	organelle ATP synthesis coupled electron tra...	13	6.0	0.3	+5.7	1.4E-7	<0.001
GO:0048037	cofactor binding	201	18.0	4.4	+13.6	2.0E-7	<0.001
GO:0016310	phosphorylation	75	11.0	1.6	+9.4	4.7E-7	<0.001
GO:0008940	nitrate reductase activity	9	5.0	0.2	+4.8	5.3E-7	<0.001
GO:0006810	transport	772	37.0	16.9	+20.1	6.3E-7	<0.001
GO:0016151	nickel ion binding	25	7.0	0.5	+6.5	6.7E-7	<0.001
GO:0051234	establishment of localization	782	37.0	17.1	+19.9	8.7E-7	<0.001
GO:0006796	phosphate metabolic process	80	11.0	1.8	+9.2	9.1E-7	<0.001

H-NS – predicted

Category ID	Category Name	#Genes Category	#Genes Assigned	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0032196	transposition	42	5.0	0.6	+4.4	2.4E-4	0.024
GO:0006313	transposition, DNA-mediated	42	5.0	0.6	+4.4	2.4E-4	0.024
GO:0043565	sequence-specific DNA binding	74	6.0	1.0	+5.0	4.7E-4	0.042
GO:0003677	DNA binding	443	15.0	6.1	+8.9	7.1E-4	0.050
GO:0006310	DNA recombination	66	5.0	0.9	+4.1	2.0E-3	0.120
GO:0003676	nucleic acid binding	588	16.0	8.1	+7.9	4.7E-3	0.250

H-NS – curated

Category ID	Category Name	#Genes Category	#Genes Assigned	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0015628	protein secretion by the type II secretion syst...	12	8.0	0.2	+7.8	3.8E-13	<0.001
GO:0015627	type II protein secretion system complex	12	8.0	0.2	+7.8	3.8E-13	<0.001
GO:0009306	protein secretion	40	9.0	0.6	+8.4	1.9E-9	<0.001
GO:0008565	protein transporter activity	41	9.0	0.6	+8.4	2.4E-9	<0.001
GO:0046903	secretion	42	9.0	0.6	+8.4	3.0E-9	<0.001
GO:0032940	secretion by cell	42	9.0	0.6	+8.4	3.0E-9	<0.001
GO:0051649	establishment of cellular localization	46	9.0	0.6	+8.4	7.1E-9	<0.001
GO:0051641	cellular localization	47	9.0	0.6	+8.4	8.6E-9	<0.001
GO:0009289	fimbrium	52	9.0	0.7	+8.3	2.2E-8	<0.001
GO:0042995	cell projection	92	11.0	1.3	+9.7	2.9E-8	<0.001
GO:0033036	macromolecule localization	79	10.0	1.1	+8.9	7.7E-8	<0.001
GO:0008104	protein localization	79	10.0	1.1	+8.9	7.7E-8	<0.001
GO:0045184	establishment of protein localization	79	10.0	1.1	+8.9	7.7E-8	<0.001
GO:0043234	protein complex	110	9.0	1.5	+7.5	1.5E-5	<0.001
GO:0016043	cellular component organization and biogen...	205	12.0	2.8	+9.2	1.6E-5	<0.001
GO:0007155	cell adhesion	31	5.0	0.4	+4.6	5.4E-5	0.002
GO:0044464	cell part	2139	43.0	29.5	+13.5	2.3E-4	0.016
GO:0006810	transport	772	22.0	10.6	+11.4	3.3E-4	0.026
GO:0051234	establishment of localization	782	22.0	10.8	+11.2	4.0E-4	0.034
GO:0022892	substrate-specific transporter activity	324	12.0	4.5	+7.5	1.3E-3	0.096

IHF - predicted

Category ID	Category Name	#Genes Category	#Genes Assigned	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0009103	lipopolysaccharide biosynthetic process	78	19.0	3.0	+16.0	4.0E-11	<0.001
GO:0008653	lipopolysaccharide metabolic process	78	19.0	3.0	+16.0	4.0E-11	<0.001
GO:0000271	polysaccharide biosynthetic process	99	19.0	3.8	+15.2	3.2E-9	<0.001
GO:0005976	polysaccharide metabolic process	105	19.0	4.0	+15.0	8.9E-9	<0.001
GO:0044264	cellular polysaccharide metabolic process	105	19.0	4.0	+15.0	8.9E-9	<0.001
GO:0043284	biopolymer biosynthetic process	108	19.0	4.1	+14.9	1.4E-8	<0.001
GO:0044255	cellular lipid metabolic process	148	22.0	5.7	+16.3	2.5E-8	<0.001
GO:0006091	generation of precursor metabolites and ene...	276	31.0	10.6	+20.4	2.7E-8	<0.001
GO:0006629	lipid metabolic process	152	22.0	5.8	+16.2	4.1E-8	<0.001
GO:0006536	glutamate metabolic process	12	7.0	0.5	+6.5	7.1E-8	<0.001
GO:0009060	aerobic respiration	23	9.0	0.9	+8.1	7.3E-8	<0.001
GO:0019544	arginine catabolic process to glutamate	5	5.0	0.2	+4.8	7.7E-8	<0.001
GO:0045333	cellular respiration	30	10.0	1.1	+8.9	8.0E-8	<0.001
GO:0044262	cellular carbohydrate metabolic process	249	28.0	9.5	+18.5	1.4E-7	<0.001
GO:0006118	electron transport	236	27.0	9.0	+18.0	1.7E-7	<0.001
GO:0008610	lipid biosynthetic process	126	19.0	4.8	+14.2	1.9E-7	<0.001
GO:0006527	arginine catabolic process	6	5.0	0.2	+4.8	4.5E-7	<0.001
GO:0009109	coenzyme catabolic process	22	8.0	0.8	+7.2	7.9E-7	<0.001
GO:0051187	cofactor catabolic process	22	8.0	0.8	+7.2	7.9E-7	<0.001
GO:0006099	tricarboxylic acid cycle	22	8.0	0.8	+7.2	7.9E-7	<0.001
GO:0046356	acetyl-CoA catabolic process	22	8.0	0.8	+7.2	7.9E-7	<0.001
GO:0016051	carbohydrate biosynthetic process	140	19.0	5.4	+13.6	1.0E-6	<0.001
GO:0009065	glutamine family amino acid catabolic proce...	7	5.0	0.3	+4.7	1.5E-6	<0.001
GO:0009288	flagellin-based flagellum	24	8.0	0.9	+7.1	1.7E-6	<0.001
GO:0006084	acetyl-CoA metabolic process	25	8.0	1.0	+7.0	2.4E-6	<0.001
GO:0015980	energy derivation by oxidation of organic com...	43	10.0	1.6	+8.4	3.3E-6	<0.001
GO:0016491	oxidoreductase activity	412	34.0	15.8	+18.2	9.0E-6	0.002
GO:0009063	amino acid catabolic process	15	6.0	0.6	+5.4	1.1E-5	0.002
GO:0019861	flagellum	40	9.0	1.5	+7.5	1.4E-5	0.002
GO:0009310	amine catabolic process	17	6.0	0.7	+5.3	2.5E-5	0.004
GO:0044270	nitrogen compound catabolic process	17	6.0	0.7	+5.3	2.5E-5	0.004

IHF – curated

Category ID	Category Name	#Genes Category	#Genes Assigned	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0003954	NADH dehydrogenase activity	25	17.0	1.0	+16.0	2.9E-19	<0.001
GO:0048038	quinone binding	14	13.0	0.5	+12.5	3.2E-18	<0.001
GO:0050136	NADH dehydrogenase (quinone) activity	24	16.0	0.9	+15.1	5.7E-18	<0.001
GO:0016655	oxidoreductase activity, acting on NADH or N...	25	16.0	1.0	+15.0	1.5E-17	<0.001
GO:0006091	generation of precursor metabolites and ene...	276	43.0	10.6	+32.4	1.7E-16	<0.001
GO:0016651	oxidoreductase activity, acting on NADH or N...	33	17.0	1.3	+15.7	2.4E-16	<0.001
GO:0009055	electron carrier activity	102	26.0	3.9	+22.1	2.1E-15	<0.001
GO:0016491	oxidoreductase activity	412	51.0	15.8	+35.2	2.9E-15	<0.001
GO:0006118	electron transport	236	38.0	9.0	+29.0	4.8E-15	<0.001
GO:0042773	ATP synthesis coupled electron transport	21	13.0	0.8	+12.2	3.7E-14	<0.001
GO:0008137	NADH dehydrogenase (ubiquinone) activity	21	13.0	0.8	+12.2	3.7E-14	<0.001
GO:0006119	oxidative phosphorylation	31	13.0	1.2	+11.8	2.7E-11	<0.001
GO:0048037	cofactor binding	201	28.0	7.7	+20.3	1.1E-9	<0.001
GO:0042775	organelle ATP synthesis coupled electron tra...	13	8.0	0.5	+7.5	4.3E-9	<0.001
GO:0006120	mitochondrial electron transport, NADH to ub...	13	8.0	0.5	+7.5	4.3E-9	<0.001
GO:0051540	metal cluster binding	126	20.0	4.8	+15.2	3.7E-8	<0.001
GO:0051536	iron-sulfur cluster binding	126	20.0	4.8	+15.2	3.7E-8	<0.001
GO:0051539	4 iron, 4 sulfur cluster binding	93	17.0	3.6	+13.4	4.9E-8	<0.001
GO:0016310	phosphorylation	75	15.0	2.9	+12.1	9.0E-8	<0.001
GO:0005506	iron ion binding	219	26.0	8.4	+17.6	1.4E-7	<0.001
GO:0042126	nitrate metabolic process	19	8.0	0.7	+7.3	2.1E-7	<0.001
GO:0042128	nitrate assimilation	19	8.0	0.7	+7.3	2.1E-7	<0.001
GO:0006796	phosphate metabolic process	80	15.0	3.1	+11.9	2.2E-7	<0.001
GO:0006793	phosphorus metabolic process	81	15.0	3.1	+11.9	2.6E-7	<0.001
GO:0016661	oxidoreductase activity, acting on other nitrog...	16	7.0	0.6	+6.4	9.1E-7	<0.001
GO:0006082	organic acid metabolic process	312	28.0	11.9	+16.1	1.4E-5	0.004
GO:0046914	transition metal ion binding	458	36.0	17.5	+18.5	1.4E-5	0.004
GO:0006817	phosphate transport	10	5.0	0.4	+4.6	1.7E-5	0.004
GO:0046872	metal ion binding	606	43.0	23.2	+19.8	2.3E-5	0.004
GO:0019752	carboxylic acid metabolic process	307	27.0	11.8	+15.2	2.9E-5	0.006
GO:0043167	ion binding	622	43.0	23.8	+19.2	4.4E-5	0.008
GO:0006807	nitrogen compound metabolic process	266	24.0	10.2	+13.8	5.6E-5	0.010
GO:0043169	cation binding	511	37.0	19.6	+17.4	6.6E-5	0.012
GO:0009082	branched chain family amino acid biosynthet...	17	5.0	0.7	+4.3	3.3E-4	0.038
GO:0015198	oligopeptide transporter activity	17	5.0	0.7	+4.3	3.3E-4	0.038
GO:0006810	transport	772	47.0	29.6	+17.4	4.2E-4	0.052
GO:0050662	coenzyme binding	132	14.0	5.1	+8.9	4.4E-4	0.060
GO:0015698	inorganic anion transport	28	6.0	1.1	+4.9	5.4E-4	0.066
GO:0051234	establishment of localization	782	47.0	29.9	+17.1	5.7E-4	0.068

NarL - predicted

Category ID	Category Name	#Genes Category	#Genes Assigned	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0016151	nickel ion binding	25	6.0	0.3	+5.7	3.1E-7	<0.001
GO:0006812	cation transport	113	9.0	1.3	+7.7	5.3E-6	<0.001
GO:0042625	ATPase activity, coupled to transmembrane ...	28	5.0	0.3	+4.7	1.6E-5	0.002
GO:0046872	metal ion binding	606	19.0	7.2	+11.8	3.0E-5	0.006
GO:0043167	ion binding	622	19.0	7.4	+11.6	4.3E-5	0.006
GO:0042626	ATPase activity, coupled to transmembrane ...	58	6.0	0.7	+5.3	5.3E-5	0.006
GO:0043492	ATPase activity, coupled to movement of sub...	58	6.0	0.7	+5.3	5.3E-5	0.006
GO:0016820	hydrolase activity, acting on acid anhydrides, ...	60	6.0	0.7	+5.3	6.4E-5	0.006
GO:0015399	primary active transmembrane transporter a...	64	6.0	0.8	+5.2	9.2E-5	0.008
GO:0015405	P-P-bond-hydrolysis-driven transmembrane ...	64	6.0	0.8	+5.2	9.2E-5	0.008
GO:0030001	metal ion transport	97	7.0	1.2	+5.8	1.2E-4	0.010
GO:0006811	ion transport	171	9.0	2.0	+7.0	1.5E-4	0.012
GO:0043169	cation binding	511	16.0	6.1	+9.9	1.7E-4	0.016
GO:0022890	inorganic cation transmembrane transporter...	48	5.0	0.6	+4.4	2.3E-4	0.016
GO:0042623	ATPase activity, coupled	79	6.0	0.9	+5.1	3.0E-4	0.020
GO:0000041	transition metal ion transport	56	5.0	0.7	+4.3	4.7E-4	0.030
GO:0046914	transition metal ion binding	458	14.0	5.4	+8.6	6.3E-4	0.040
GO:0051540	metal cluster binding	126	7.0	1.5	+5.5	6.3E-4	0.042
GO:0051536	iron-sulfur cluster binding	126	7.0	1.5	+5.5	6.3E-4	0.042
GO:0051539	4 iron, 4 sulfur cluster binding	93	6.0	1.1	+4.9	7.2E-4	0.054
GO:0022891	substrate-specific transmembrane transport...	266	10.0	3.2	+6.8	9.3E-4	0.064
GO:0006091	generation of precursor metabolites and ene...	276	10.0	3.3	+6.7	1.2E-3	0.080
GO:0043565	sequence-specific DNA binding	74	5.0	0.9	+4.1	1.7E-3	0.104
GO:0016310	phosphorylation	75	5.0	0.9	+4.1	1.8E-3	0.112
GO:0015075	ion transmembrane transporter activity	111	6.0	1.3	+4.7	1.8E-3	0.112
GO:0005524	ATP binding	347	11.0	4.1	+6.9	2.0E-3	0.120
GO:0000160	two-component signal transduction system (...	78	5.0	0.9	+4.1	2.1E-3	0.128
GO:0032559	adenyl ribonucleotide binding	349	11.0	4.1	+6.9	2.1E-3	0.130
GO:0008324	cation transmembrane transporter activity	79	5.0	0.9	+4.1	2.3E-3	0.134
GO:0006796	phosphate metabolic process	80	5.0	1.0	+4.0	2.4E-3	0.146
GO:0006793	phosphorus metabolic process	81	5.0	1.0	+4.0	2.5E-3	0.152
GO:0022857	transmembrane transporter activity	310	10.0	3.7	+6.3	3.0E-3	0.160
GO:0022804	active transmembrane transporter activity	220	8.0	2.6	+5.4	3.9E-3	0.192
GO:0022892	substrate-specific transporter activity	324	10.0	3.9	+6.1	4.1E-3	0.194
GO:0032555	purine ribonucleotide binding	380	11.0	4.5	+6.5	4.2E-3	0.198
GO:0032553	ribonucleotide binding	380	11.0	4.5	+6.5	4.2E-3	0.198
GO:0004871	signal transducer activity	92	5.0	1.1	+3.9	4.4E-3	0.216
GO:0016887	ATPase activity	133	6.0	1.6	+4.4	4.5E-3	0.218
GO:0030554	adenyl nucleotide binding	390	11.0	4.6	+6.4	5.1E-3	0.228

NarL - curated

Category ID	Category Name	#Genes Category	#Genes Assigned	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0006118	electron transport	236	27.0	2.8	+24.2	1.4E-21	<0.001
GO:0005506	iron ion binding	219	25.0	2.6	+22.4	8.6E-20	<0.001
GO:0006091	generation of precursor metabolites and ene...	276	27.0	3.3	+23.7	9.3E-20	<0.001
GO:0017004	cytochrome complex assembly	10	9.0	0.1	+8.9	2.2E-17	<0.001
GO:0043623	cellular protein complex assembly	11	9.0	0.1	+8.9	1.2E-16	<0.001
GO:0006461	protein complex assembly	14	9.0	0.2	+8.8	4.3E-15	<0.001
GO:0016661	oxidoreductase activity, acting on other nitrog...	16	9.0	0.2	+8.8	2.4E-14	<0.001
GO:0042126	nitrate metabolic process	19	9.0	0.2	+8.8	1.9E-13	<0.001
GO:0042128	nitrate assimilation	19	9.0	0.2	+8.8	1.9E-13	<0.001
GO:0051540	metal cluster binding	126	16.0	1.5	+14.5	3.4E-13	<0.001
GO:0051536	iron-sulfur cluster binding	126	16.0	1.5	+14.5	3.4E-13	<0.001
GO:0016491	oxidoreductase activity	412	25.0	4.9	+20.1	3.8E-13	<0.001
GO:0051539	4 iron, 4 sulfur cluster binding	93	14.0	1.1	+12.9	1.2E-12	<0.001
GO:0046914	transition metal ion binding	458	25.0	5.4	+19.6	4.3E-12	<0.001
GO:0065003	macromolecular complex assembly	26	9.0	0.3	+8.7	6.0E-12	<0.001
GO:0022607	cellular component assembly	27	9.0	0.3	+8.7	8.9E-12	<0.001
GO:0043169	cation binding	511	25.0	6.1	+18.9	5.0E-11	<0.001
GO:0015232	heme transporter activity	5	5.0	0.1	+4.9	1.9E-10	<0.001
GO:0051184	cofactor transporter activity	6	5.0	0.1	+4.9	1.2E-9	<0.001
GO:0046872	metal ion binding	606	25.0	7.2	+17.8	2.1E-9	<0.001
GO:0006810	transport	772	28.0	9.2	+18.8	2.3E-9	<0.001
GO:0051234	establishment of localization	782	28.0	9.3	+18.7	3.1E-9	<0.001
GO:0043167	ion binding	622	25.0	7.4	+17.6	3.7E-9	<0.001
GO:0009055	electron carrier activity	102	11.0	1.2	+9.8	1.7E-8	<0.001
GO:0008940	nitrate reductase activity	9	5.0	0.1	+4.9	2.4E-8	<0.001
GO:0030151	molybdenum ion binding	23	5.0	0.3	+4.7	5.6E-6	<0.001
GO:0042597	periplasmic space	168	10.0	2.0	+8.0	2.0E-5	0.002
GO:0045333	cellular respiration	30	5.0	0.4	+4.6	2.2E-5	0.002
GO:0044464	cell part	2139	39.0	25.4	+13.6	6.8E-5	0.002
GO:0015980	energy derivation by oxidation of organic com...	43	5.0	0.5	+4.5	1.3E-4	0.006
GO:0016020	membrane	1134	26.0	13.5	+12.5	1.4E-4	0.006
GO:0016021	integral to membrane	882	22.0	10.5	+11.5	1.9E-4	0.008
GO:0031224	intrinsic to membrane	882	22.0	10.5	+11.5	1.9E-4	0.008
GO:0006807	nitrogen compound metabolic process	266	11.0	3.2	+7.8	2.2E-4	0.008
GO:0044425	membrane part	945	22.0	11.2	+10.8	5.4E-4	0.030
GO:0016043	cellular component organization and biogen...	205	9.0	2.4	+6.6	5.7E-4	0.030
GO:0044267	cellular protein metabolic process	279	10.0	3.3	+6.7	1.3E-3	0.064
GO:0019538	protein metabolic process	285	10.0	3.4	+6.6	1.6E-3	0.074
GO:0043234	protein complex	110	6.0	1.3	+4.7	1.7E-3	0.090

2. GO Analysis Results of Splits in DREM Map

In this section we present significant GO enrichments for the sets of genes assigned to the same path out of splits conditional on the set of genes going into the split. The split number and the path (i.e. whether it was the low, middle, or high path) is indicated above each table and corresponds to Figure 5A in the main manuscript.

Conditional on the set of genes passing the filtering criteria, the upregulated genes at the first split were most enriched for carbohydrate transport (p-val $<10^{-8}$), while the downregulated genes were most enriched for biosynthetic process genes (p-val $<10^{-30}$) including translation genes (p-val $<10^{-24}$). The most enriched biological process for the highest activated path conditioned on the set of genes going into split 2 was oxidoreductase activity (p-val $<8\times10^{-6}$). The lower path out of split 6 was enriched for genes related to the ribosome (p-val$< 10^{-11}$) and aerobic respiration (p-val $<4\times10^{-7}$). Genes on the lower path out of split 9, were enriched for genes known to be involved in aerobic and cellular respiration (p-val $< 2\times10^{-5}$), TCA cycle (p-val $< 4\times10^{-5}$), and coenzyme catabolic processes (p-val $< 4\times10^{-5}$). Additional GO category enrichments can be found in the tables below. Overall the GO categories found here among activated and repressed genes are consistent with the previously known literature on *E. coli* anaerobic response [1,2,3,4].

Split 1 - Low

Category ID	Category Name	#Genes Split in	#Genes on Path	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0009058	biosynthetic process	358	246.0	146.8	+99.2	8.8E-31	<0.001
GO:0044249	cellular biosynthetic process	259	189.0	106.2	+82.8	1.9E-28	<0.001
GO:0044424	intracellular part	430	276.0	176.3	+99.7	4.8E-27	<0.001
GO:0006412	translation	94	86.0	38.5	+47.5	1.1E-25	<0.001
GO:0005737	cytoplasm	410	260.0	168.1	+91.9	4.9E-24	<0.001
GO:0009059	macromolecule biosynthetic process	179	137.0	73.4	+63.6	8.5E-24	<0.001
GO:0005622	intracellular	501	302.0	205.4	+96.6	6.1E-23	<0.001
GO:0043228	non-membrane-bound organelle	69	66.0	28.3	+37.7	8.5E-23	<0.001
GO:0043232	intracellular non-membrane-bound organelle	69	66.0	28.3	+37.7	8.5E-23	<0.001
GO:0043229	intracellular organelle	76	71.0	31.2	+39.8	1.0E-22	<0.001
GO:0030529	ribonucleoprotein complex	57	56.0	23.4	+32.6	2.7E-21	<0.001
GO:0044237	cellular metabolic process	922	487.0	378.0	+109.0	4.3E-21	<0.001
GO:0005840	ribosome	56	55.0	23.0	+32.0	6.7E-21	<0.001
GO:0003735	structural constituent of ribosome	55	54.0	22.6	+31.4	1.7E-20	<0.001
GO:0044238	primary metabolic process	862	459.0	353.4	+105.6	2.5E-20	<0.001
GO:0003723	RNA binding	82	72.0	33.6	+38.4	4.1E-19	<0.001
GO:0044444	cytoplasmic part	74	65.0	30.3	+34.7	2.4E-17	<0.001
GO:0044260	cellular macromolecule metabolic process	265	170.0	108.7	+61.3	5.8E-16	<0.001
GO:0019843	rRNA binding	36	36.0	14.8	+21.2	7.7E-15	<0.001
GO:0044267	cellular protein metabolic process	200	132.0	82.0	+50.0	7.7E-14	<0.001
GO:0043170	macromolecule metabolic process	683	360.0	280.0	+80.0	1.2E-13	<0.001
GO:0019538	protein metabolic process	204	132.0	83.6	+48.4	7.6E-13	<0.001
GO:0003676	nucleic acid binding	311	179.0	127.5	+51.5	1.9E-10	<0.001
GO:0006399	tRNA metabolic process	39	35.0	16.0	+19.0	2.2E-10	<0.001
GO:0006396	RNA processing	39	34.0	16.0	+18.0	2.3E-9	<0.001
GO:0044464	cell part	1241	578.0	508.8	+69.2	2.8E-9	<0.001
GO:0006139	nucleobase, nucleoside, nucleotide and nuc...	377	204.0	154.6	+49.4	1.4E-8	<0.001
GO:0008610	lipid biosynthetic process	82	58.0	33.6	+24.4	2.9E-8	<0.001
GO:0044422	organelle part	19	19.0	7.8	+11.2	4.0E-8	<0.001
GO:0044446	intracellular organelle part	19	19.0	7.8	+11.2	4.0E-8	<0.001
GO:0043283	biopolymer metabolic process	398	210.0	163.2	+46.8	1.3E-7	<0.001
GO:0006629	lipid metabolic process	94	62.0	38.5	+23.5	5.5E-7	<0.001
GO:0044255	cellular lipid metabolic process	93	61.0	38.1	+22.9	9.2E-7	<0.001
GO:0016874	ligase activity	53	39.0	21.7	+17.3	1.2E-6	<0.001
GO:0005515	protein binding	471	237.0	193.1	+43.9	3.0E-6	0.002
GO:0006732	coenzyme metabolic process	62	43.0	25.4	+17.6	4.5E-6	0.004

Split 1 - High

Category ID	Category Name	#Genes Split in	#Genes on Path	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0008643	carbohydrate transport	79	70.0	46.6	+23.4	4.5E-9	<0.001
GO:0015144	carbohydrate transmembrane transporter ac...	77	68.0	45.4	+22.6	1.1E-8	<0.001
GO:0051119	sugar transmembrane transporter activity	77	68.0	45.4	+22.6	1.1E-8	<0.001
GO:0005351	sugar:hydrogen ion symporter activity	77	68.0	45.4	+22.6	1.1E-8	<0.001
GO:0009401	phosphoenolpyruvate-dependent sugar pho...	42	40.0	24.8	+15.2	8.6E-8	<0.001
GO:0015293	symporter activity	91	76.0	53.7	+22.3	2.8E-7	<0.001
GO:0007165	signal transduction	88	73.0	51.9	+21.1	8.5E-7	<0.001
GO:0015291	secondary active transmembrane transporte...	109	86.0	64.3	+21.7	5.7E-6	<0.001
GO:0007154	cell communication	95	76.0	56.0	+20.0	8.0E-6	<0.001
GO:0008982	protein-N(PI)-phosphohistidine-sugar phosp...	22	22.0	13.0	+9.0	8.5E-6	0.002
GO:0006810	transport	469	317.0	276.7	+40.3	1.2E-5	0.002
GO:0031224	intrinsic to membrane	487	327.0	287.3	+39.7	2.1E-5	0.006
GO:0016021	integral to membrane	487	327.0	287.3	+39.7	2.1E-5	0.006
GO:0051234	establishment of localization	471	317.0	277.9	+39.1	2.2E-5	0.008
GO:0044425	membrane part	531	349.0	313.3	+35.7	1.8E-4	0.036

Split 2 - Low

Category ID	Category Name	#Genes Split in	#Genes on Path	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0009289	fimbrium	23	18.0	8.3	+9.7	4.1E-5	0.002

Split 2 - Middle

Category ID	Category Name	#Genes Split in	#Genes on Path	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0043167	ion binding	226	154.0	131.1	+22.9	4.2E-4	0.020
GO:0006811	ion transport	54	43.0	31.3	+11.7	5.6E-4	0.030
GO:0046872	metal ion binding	216	147.0	125.3	+21.7	6.4E-4	0.036

Split 2 - High

Category ID	Category Name	#Genes Split in	#Genes on Path	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0016491	oxidoreductase activity	156	23.0	9.0	+14.0	7.7E-6	<0.001
GO:0042126	nitrate metabolic process	12	6.0	0.7	+5.3	2.2E-5	0.002
GO:0042128	nitrate assimilation	12	6.0	0.7	+5.3	2.2E-5	0.002
GO:0006091	generation of precursor metabolites and ene...	111	17.0	6.4	+10.6	9.8E-5	0.008
GO:0006950	response to stress	44	10.0	2.5	+7.5	1.2E-4	0.008
GO:0006118	electron transport	102	16.0	5.9	+10.1	1.2E-4	0.010
GO:0016661	oxidoreductase activity, acting on other nitrog...	13	5.0	0.8	+4.2	5.1E-4	0.032
GO:0016614	oxidoreductase activity, acting on CH-OH gro...	21	6.0	1.2	+4.8	8.3E-4	0.046

Split 3 - High

Category ID	Category Name	#Genes Split in	#Genes on Path	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0006091	generation of precursor metabolites and ene...	73	47.0	30.3	+16.7	3.0E-5	0.002
GO:0051540	metal cluster binding	35	26.0	14.5	+11.5	6.0E-5	0.004
GO:0051536	iron-sulfur cluster binding	35	26.0	14.5	+11.5	6.0E-5	0.004
GO:0006118	electron transport	67	43.0	27.8	+15.2	7.8E-5	0.004
GO:0051539	4 iron, 4 sulfur cluster binding	27	21.0	11.2	+9.8	1.1E-4	0.006

Split 5- High

Category ID	Category Name	#Genes Split in	#Genes on Path	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0016020	membrane	142	116.0	99.5	+16.5	1.9E-4	0.002

Split 6 - Low

Category ID	Category Name	#Genes Split in	#Genes on Path	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0044444	cytoplasmic part	65	37.0	12.5	+24.5	1.9E-12	<0.001
GO:0019843	rRNA binding	36	26.0	6.9	+19.1	2.0E-12	<0.001
GO:0003735	structural constituent of ribosome	54	33.0	10.3	+22.7	2.3E-12	<0.001
GO:0005840	ribosome	55	33.0	10.5	+22.5	4.8E-12	<0.001
GO:0030529	ribonucleoprotein complex	56	33.0	10.7	+22.3	9.7E-12	<0.001
GO:0043229	intracellular organelle	71	37.0	13.6	+23.4	7.0E-11	<0.001
GO:0044424	intracellular part	276	88.0	52.9	+35.1	5.8E-10	<0.001
GO:0043228	non-membrane-bound organelle	66	34.0	12.6	+21.4	7.4E-10	<0.001
GO:0043232	intracellular non-membrane-bound organelle	66	34.0	12.6	+21.4	7.4E-10	<0.001
GO:0006412	translation	86	39.0	16.5	+22.5	4.3E-9	<0.001
GO:0006091	generation of precursor metabolites and ene...	69	33.0	13.2	+19.8	1.6E-8	<0.001
GO:0005737	cytoplasm	260	81.0	49.8	+31.2	2.0E-8	<0.001
GO:0005622	intracellular	302	90.0	57.9	+32.1	2.3E-8	<0.001
GO:0015078	hydrogen ion transmembrane transporter ac...	15	13.0	2.9	+10.1	2.4E-8	<0.001
GO:0006732	coenzyme metabolic process	43	24.0	8.2	+15.8	4.3E-8	<0.001
GO:0044464	cell part	578	142.0	110.7	+31.3	4.3E-8	<0.001
GO:0009059	macromolecule biosynthetic process	137	51.0	26.2	+24.8	5.1E-8	<0.001
GO:0051186	cofactor metabolic process	53	27.0	10.2	+16.8	7.5E-8	<0.001
GO:0015077	monovalent inorganic cation transmembran...	16	13.0	3.1	+9.9	1.1E-7	<0.001
GO:0044237	cellular metabolic process	487	124.0	93.3	+30.7	2.5E-7	<0.001
GO:0003723	RNA binding	72	32.0	13.8	+18.2	2.6E-7	<0.001
GO:0009060	aerobic respiration	17	13.0	3.3	+9.7	3.7E-7	<0.001
GO:0009201	ribonucleoside triphosphate biosynthetic pro...	11	10.0	2.1	+7.9	5.0E-7	<0.001
GO:0009206	purine ribonucleoside triphosphate biosynth...	11	10.0	2.1	+7.9	5.0E-7	<0.001
GO:0009145	purine nucleoside triphosphate biosynthetic ...	11	10.0	2.1	+7.9	5.0E-7	<0.001
GO:0009142	nucleoside triphosphate biosynthetic process	11	10.0	2.1	+7.9	5.0E-7	<0.001
GO:0022890	inorganic cation transmembrane transporter...	22	15.0	4.2	+10.8	5.0E-7	<0.001
GO:0044260	cellular macromolecule metabolic process	170	57.0	32.6	+24.4	5.1E-7	<0.001
GO:0006818	hydrogen transport	13	11.0	2.5	+8.5	5.4E-7	<0.001
GO:0009141	nucleoside triphosphate metabolic process	13	11.0	2.5	+8.5	5.4E-7	<0.001
GO:0015992	proton transport	13	11.0	2.5	+8.5	5.4E-7	<0.001
GO:0044267	cellular protein metabolic process	132	47.0	25.3	+21.7	1.0E-6	<0.001
GO:0019538	protein metabolic process	132	47.0	25.3	+21.7	1.0E-6	<0.001
GO:0044238	primary metabolic process	459	117.0	87.9	+29.1	1.1E-6	<0.001
GO:0045333	cellular respiration	18	13.0	3.4	+9.6	1.1E-6	<0.001

Split 7 - Low

Category ID	Category Name	#Genes Split in	#Genes on Path	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0006412	translation	47	30.0	17.0	+13.0	6.1E-5	0.006
GO:0003735	structural constituent of ribosome	21	16.0	7.6	+8.4	1.7E-4	0.008
GO:0009059	macromolecule biosynthetic process	86	46.0	31.0	+15.0	3.5E-4	0.022
GO:0005840	ribosome	22	16.0	7.9	+8.1	4.3E-4	0.026
GO:0030529	ribonucleoprotein complex	23	16.0	8.3	+7.7	9.6E-4	0.074

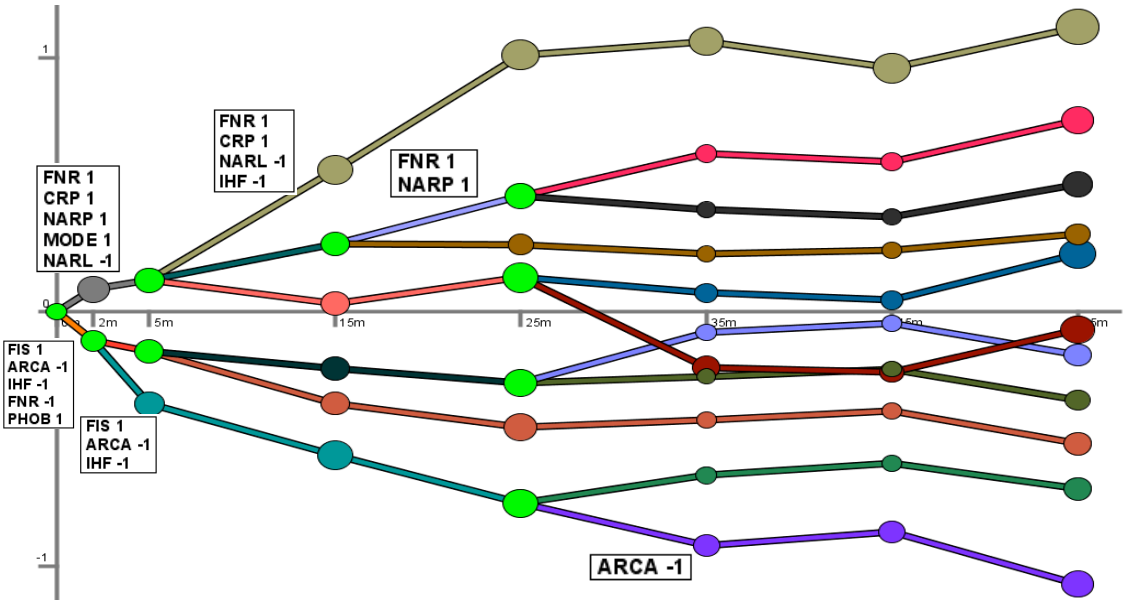
Split 9 - Low

Category ID	Category Name	#Genes Split in	#Genes on Path	#Genes Expected	#Genes Enriched	p-value	Corrected p-value
GO:0045333	cellular respiration	13	12.0	4.4	+7.6	1.1E-5	<0.001
GO:0009060	aerobic respiration	13	12.0	4.4	+7.6	1.1E-5	<0.001
GO:0015980	energy derivation by oxidation of organic com...	13	12.0	4.4	+7.6	1.1E-5	<0.001
GO:0009109	coenzyme catabolic process	12	11.0	4.1	+6.9	3.3E-5	<0.001
GO:0051187	cofactor catabolic process	12	11.0	4.1	+6.9	3.3E-5	<0.001
GO:0006099	tricarboxylic acid cycle	12	11.0	4.1	+6.9	3.3E-5	<0.001
GO:0006084	acetyl-CoA metabolic process	12	11.0	4.1	+6.9	3.3E-5	<0.001
GO:0046356	acetyl-CoA catabolic process	12	11.0	4.1	+6.9	3.3E-5	<0.001
GO:0046872	metal ion binding	30	20.0	10.2	+9.8	6.8E-5	<0.001
GO:0043167	ion binding	30	20.0	10.2	+9.8	6.8E-5	<0.001
GO:0044248	cellular catabolic process	20	15.0	6.8	+8.2	9.1E-5	0.002
GO:0006091	generation of precursor metabolites and ene...	33	21.0	11.2	+9.8	1.2E-4	0.002
GO:0009056	catabolic process	21	15.0	7.2	+7.8	2.3E-4	0.004
GO:0006732	coenzyme metabolic process	24	16.0	8.2	+7.8	4.9E-4	0.014
GO:0043169	cation binding	18	13.0	6.1	+6.9	5.9E-4	0.014
GO:0051186	cofactor metabolic process	27	17.0	9.2	+7.8	8.6E-4	0.020
GO:0046914	transition metal ion binding	17	12.0	5.8	+6.2	1.4E-3	0.046

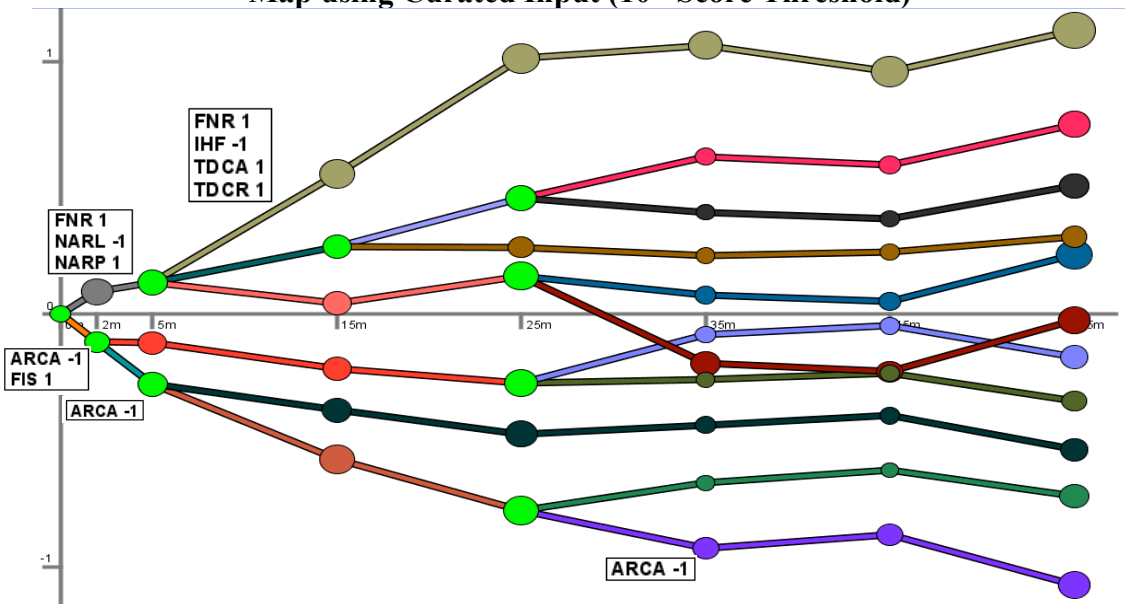
3. Dynamic Regulatory Maps at Different Score Thresholds

The following two maps are based on the same input data as the maps shown in Figure 5A and 5C of the main manuscript, but with a stricter score requirement of (10^{-5}) for a TF and regulatory mode label (1 activator; -1 repressor) to appear on a path out of a split. The split score is computed based on the hypergeometric distribution (see Supporting Methods).

Map using Prediction Extended Input (10^{-5} Score Threshold)

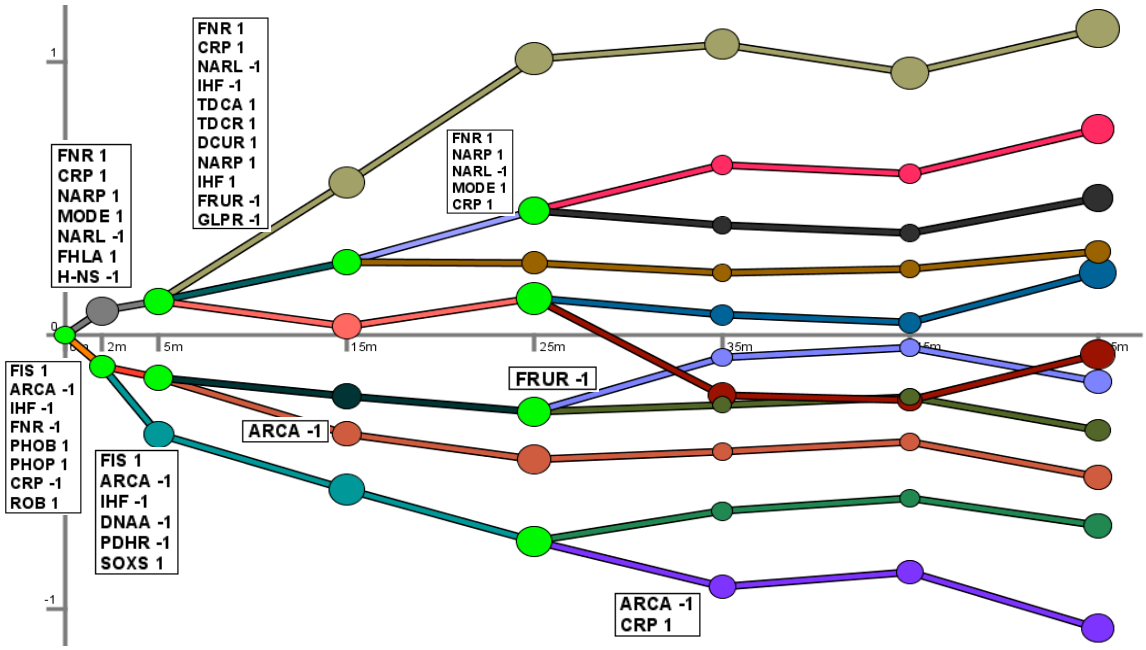


Map using Curated Input (10^{-5} Score Threshold)

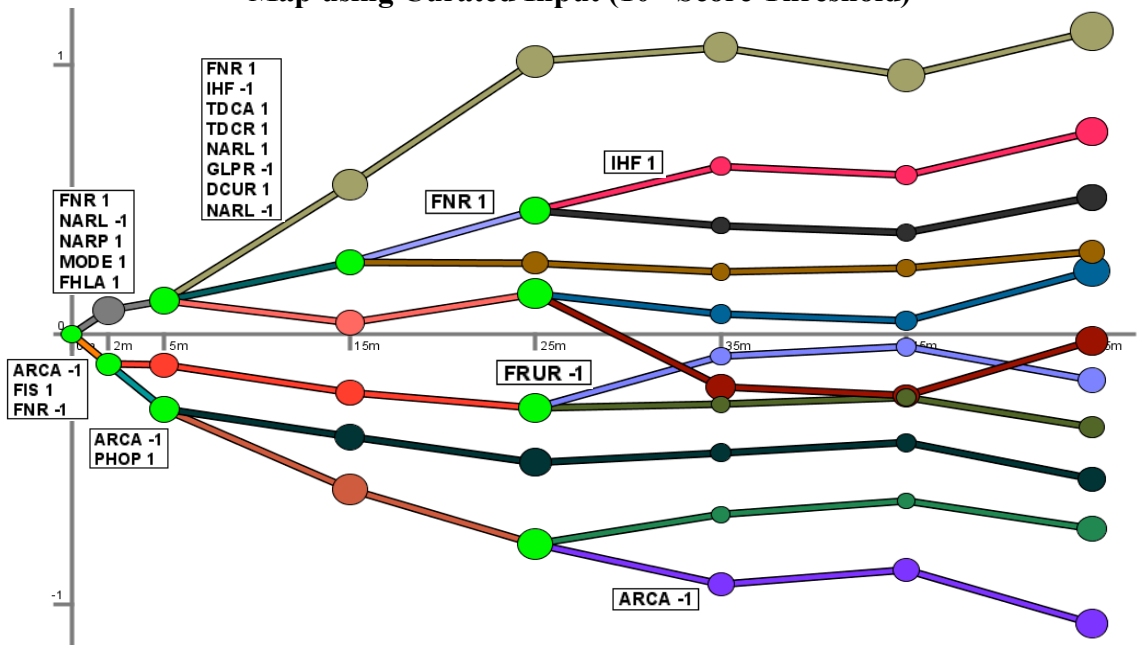


The following maps are based on the same input data as the maps shown in Figure 5A and 5C of the main text, but with a looser score requirement of (10^{-3}) for a TF label to appear on a path out of a split.

Map using Prediction Extended Input (10^{-3} Score Threshold)

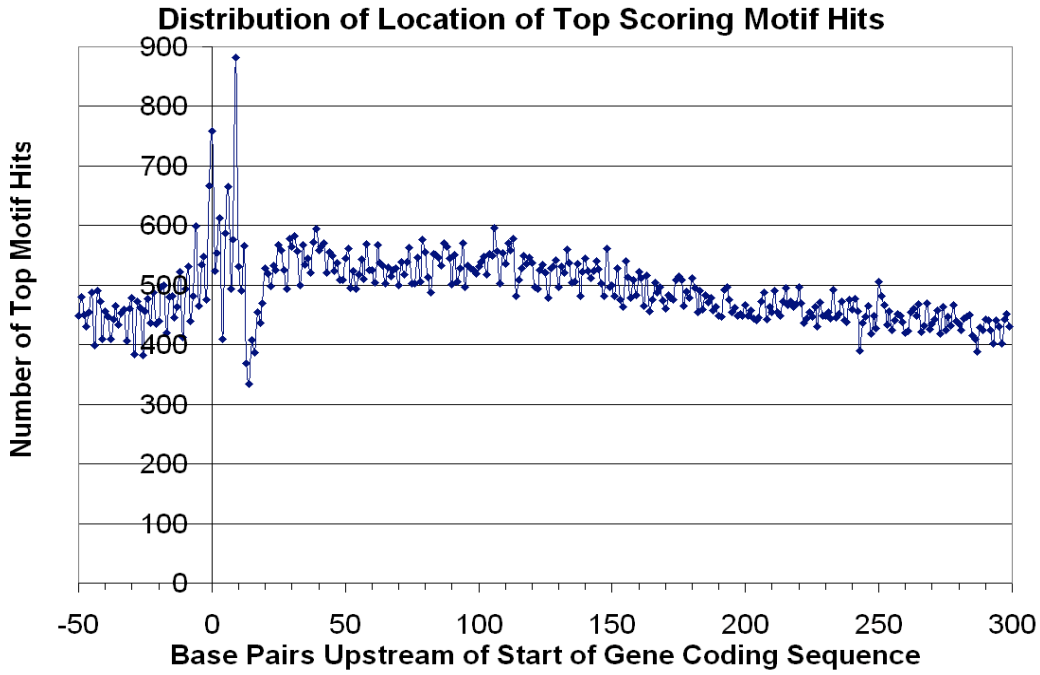


Map using Curated Input (10^{-3} Score Threshold)



4. Motif Scanning Distribution of Location of Sites

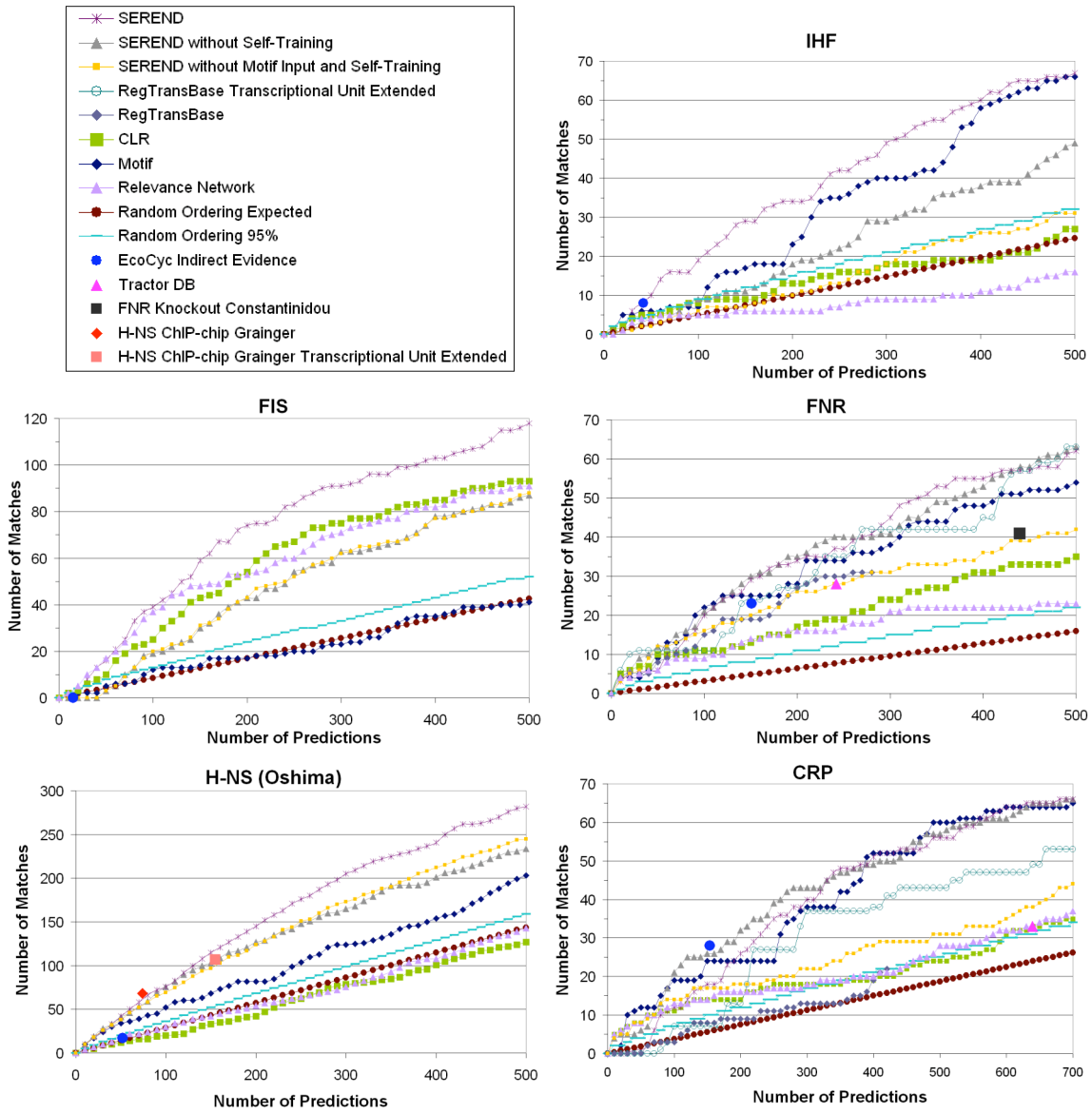
For the 71 TFs with a confirmed target based on direct evidence in EcoCyc [5] and a motif positional weight matrix in RegulonDB, we scanned for binding site motifs on both strands in a 350 base pair region around any gene which was the first gene transcribed in a transcriptional unit based on the RegulonDB list [6]. The 350 base pair region ranged from 50 base pairs downstream of the start of the coding sequence to within 300 base pairs upstream of the start of the coding sequence. The base that was closest to the downstream end of the region determined the position of the motif. Only one base of the motif needed to lie within the upstream boundary, but the entire motif would need to be within the downstream boundary. For a gene we associated its motif score with the score in the region of the first gene transcribed in its transcriptional unit. If the gene belonged to several transcriptional units with different initial genes we used the highest score. Below we plot distribution of the location of highest scoring sites we associated with genes, only counting sites with a positive score and a site once for each TF. The plot is aggregated over all 71 TFs. As can be seen the number of motif hits tended to be lower near the boundaries of the region we consider. One can also observe a positional bias for binding sites immediately upstream of the start of the coding region.



5. Extended Analysis of ChIP-chip Validation

In this section, we present below an extended version of Figure 3 from the main manuscript. In the figure below we have added the following to Figure 3:

1. To all the graphs we added a curve which represents the expected 95th percentile performance of a method that randomly orders genes. This curve was computed based on the hypergeometric distribution.
2. For all graphs we added a curve based on using SEREND on only the expression data and direct targets in EcoCyc without the motif input, and also without using the self-training procedure. The values from this curve corresponds to the expression feature of the meta-classifier during the initial iteration of SEREND, before any labels have changed.
3. For all graphs we added a curve based on the results of the Relevance Network approach [7] using the square of the correlation coefficient which was previously reported to outperform mutual information for network inference on this data [8]. We applied the correlation coefficient on the same normalized and transformed gene expression data as described in the main manuscript.
4. For FNR and CRP we added curves based on the direct set of results returned by RegTransBase [9] without extending the list to include other genes listed in the same transcriptional unit.
5. For FNR case we have add a point corresponding to the set of genes listed in the Supplement of Ref. [10] as being differentially expressed in FNR knockouts.
6. For the H-NS case we extend here the list of the H-NS bound targets listed in Ref. [11] to include any other gene in the same RegulonDB [6] transcriptional unit as a gene from this H-NS bound list.

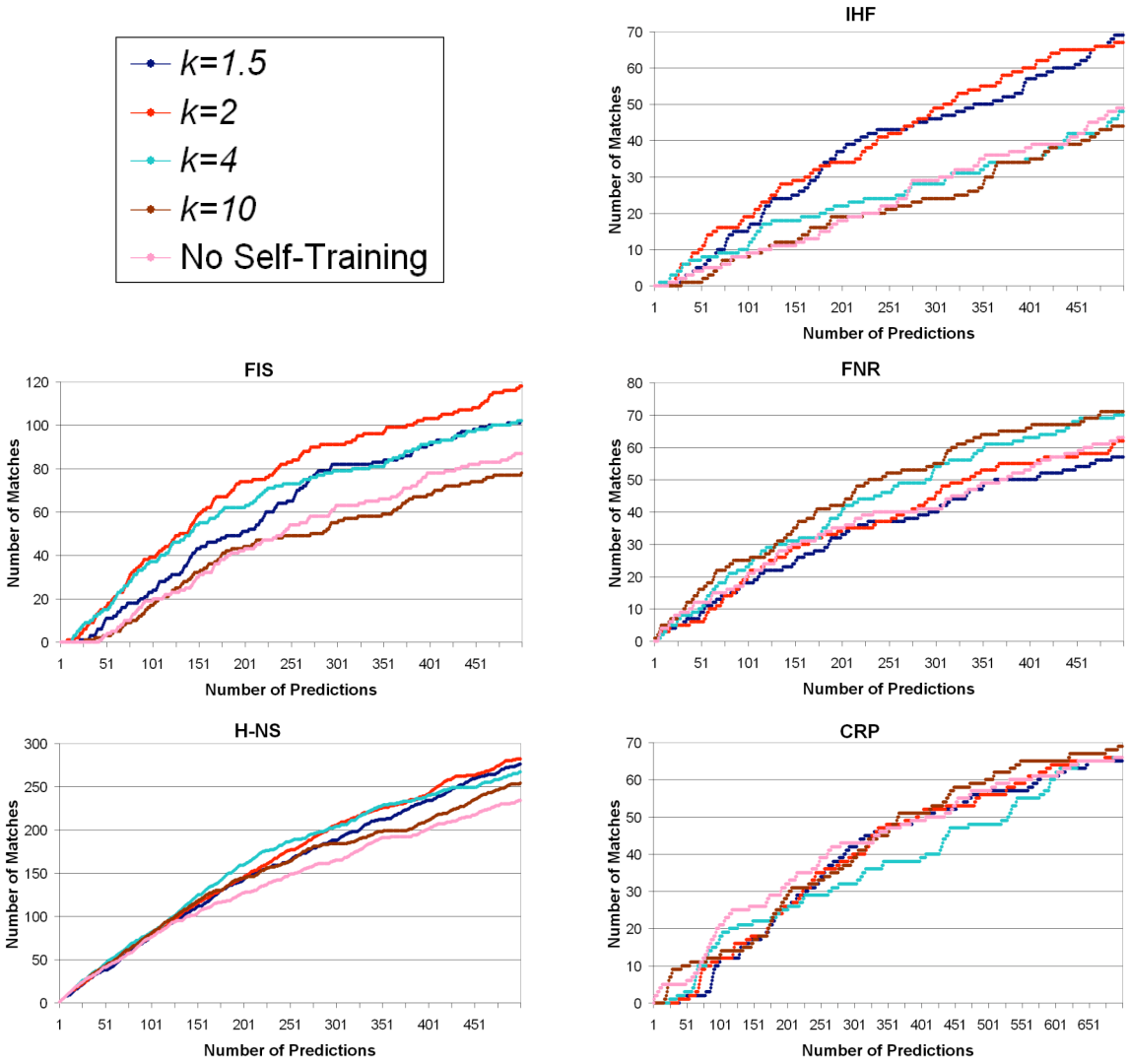

SEREND
SEREND without Self-Training
SEREND without Motif Input and Self-Training
RegTransBase Transcriptional Unit Extended
RegTransBase
CLR
Motif
Relevance Network
Random Ordering Expected
Random Ordering 95%
EcoCyc Indirect Evidence
Tractor DB
FNR Knockout Constantinidou
H-NS ChIP-chip Grainger
H-NS ChIP-chip Grainger Transcriptional Unit Extended
IHF
FIS
FNR
H-NS (Oshima)
CRP
Number of Matches
Number of Predictions

6. Effect of Self-Training Parameter *k*

For the self-training procedure as stated in the main text of the manuscript, SEREND would change the label of a gene *g* based on a formula that depends on a parameter *k*. As *k* increases the self-training method requires greater confidence from the classifier that the gene is actually regulated by the TF before changing its label. When *k* is sufficiently high no gene will be relabeled as a target of the TF making the SEREND method similar to a version that does not use self-training.

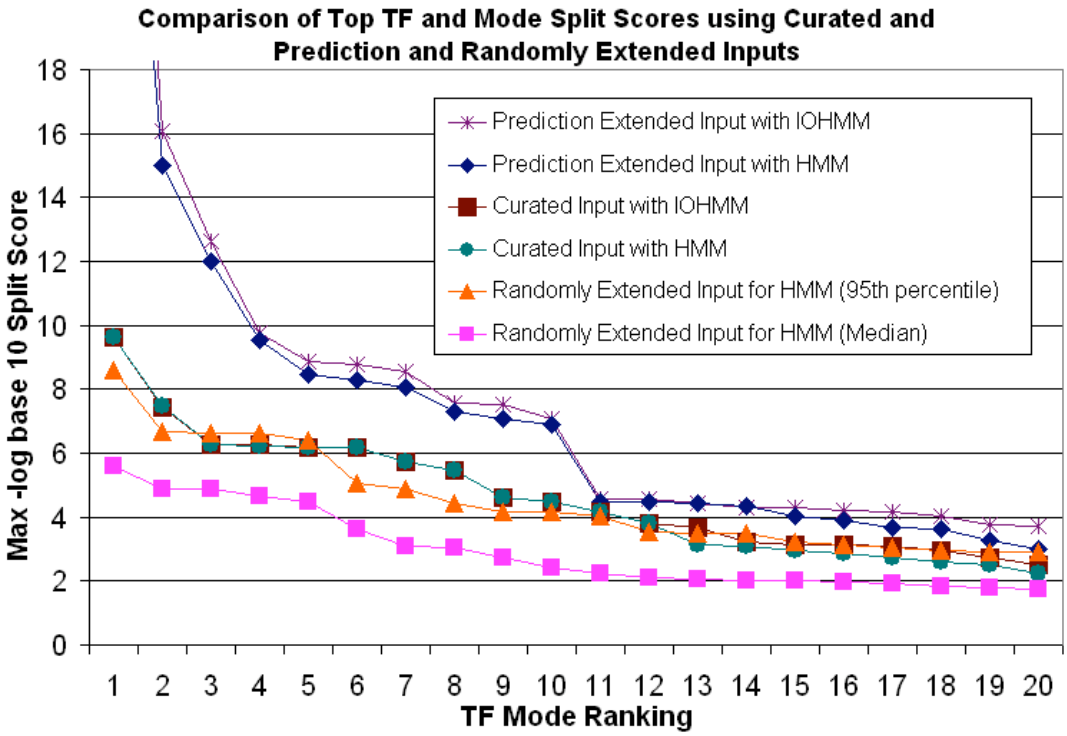
In the figure below we investigate the effect of this choice of parameter value on the results that would be obtained with our ChIP-chip validation for three more values of *k*: 1.5, 4, and 10. We observe from these figures that in the FNR case with values of *k*=4 and *k*=10 we observe an improvement using self-training that we did not observed when *k*=2. However in the IHF case, the results with *k*=4 and *k*=10 are similar to the results when not using self-training, while there is an improvement over self-training for *k*=1.5 and *k*=2.

Analysis on the Effect of the Choice of *k* on Recovering ChIP-chip targets without Direct Evidence



7. Effect of Randomly Extending the Curated Network

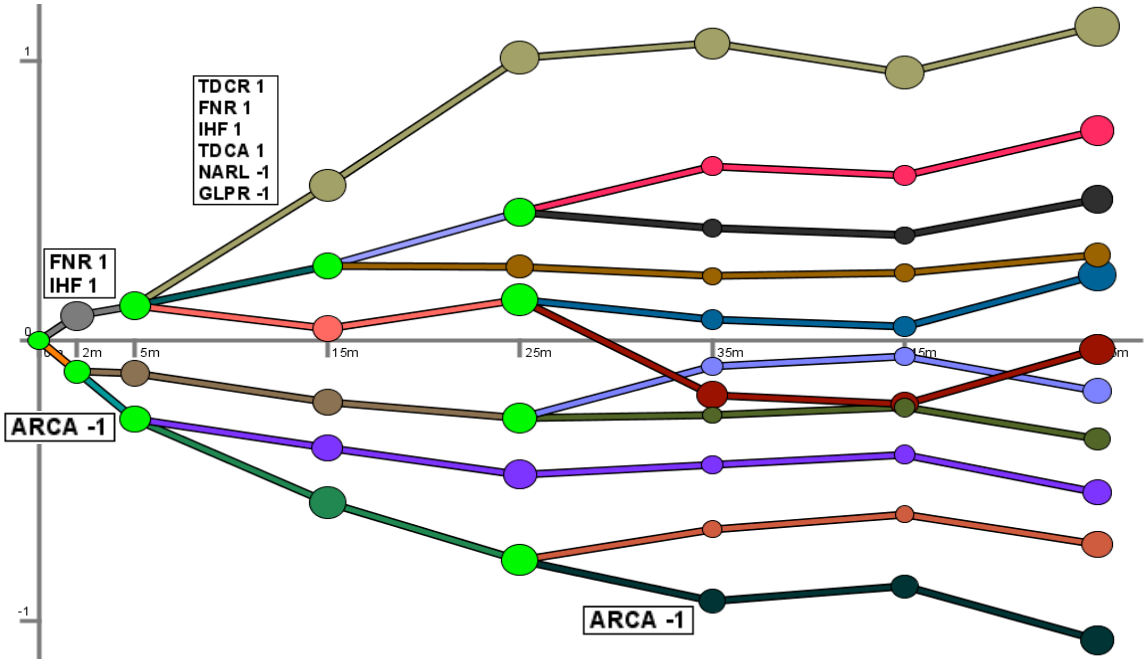
In Figure 6A of the main manuscript, we showed that by extending the curated inputs with additional predictions DREM increased the score significance of most of the key TFs. To investigate whether this could be a result of simply predicting more TF-gene interactions we generated 10,000 sets of randomly extended TF-gene inputs. These randomly extended inputs had the same curated targets as the prediction extended network, additionally among the genes used in the aerobic-anaerobic shift application of DREM we also constrained a random extension to have the same number of predicted targets for each TF and regulatory mode (activator or repressor) as in our prediction extended network. For those genes that were a target of a TF in both the curated and prediction extended network, but had a different regulatory mode annotation, we used the annotation in the prediction extended input. The DREM software [12] contains the option to either use TF-gene input in inferring the model or only as a post-processing step. If the TF-gene input was used to infer the model, then the transition probabilities for a gene between states were based on the specific set of TFs regulating the genes as determined based on an Input-Output Hidden Markov Model (IOHMM). If the option to use TF-gene input only in a post-processing step is selected, then DREM infers the regulatory map using only the time series expression data, and under this option the transition probabilities are the same for each gene and the model is an instance of a Hidden Markov Model (HMM). For both the IOHMM and HMM, the TF-gene inputs were used in a post-processing step to score TFs at splits. While we use the IOHMM to infer the dynamic maps presented in this paper, we observed for this data that the difference in scores given to TFs using the HMM and IOHMM model for both the curated and prediction extended input was minor compared to the difference in scores based on the differences of these input sets (see below). Thus in our evaluation we only inferred a model once based on the time series data using an HMM, which we then in a post-processing step scored using all 10,000 randomly extended input sets sets. As can be seen in the figure below even the 95th percentile of scores resulting from these randomly extended inputs did not improve over just using the curated inputs.



The graph shows the top 20 values of the maximum negative log base 10 scores for a TF and mode (activator or repressor) at any split, only including a TF and mode pair once. We evaluated this for the curated input, as well as the random and prediction extended inputs using a HMM, and also for the curated input and prediction extended input using an IOHMM. To keep the scale of the graph reasonable the highest score with the prediction extended input using an IOHMM (38.2) and using an HMM (33.4) are not shown in the figure.

We also provide in the figure below a dynamic map using the IOHMM model and the first input set that was randomly generated based on a scoring threshold of 10^{-4}. We note that this map has fewer TF-labels at an equivalent scoring threshold than, both the curated input and the prediction extended input shown in Figure 5 of the main text, which were based on the same scoring threshold.

Map using a Randomly Extended Input Set (10^{-4} Score Threshold)



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