

Supplementary information

Multi-objective optimization of enzyme manipulations in metabolic networks considering resilience effects

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Results of multi-synthesis maximization by *Escherichia coli* considering energy and redox conservation for co-metabolites

Table S1: The optimal solution for multi-synthesis maximization by *E. coli* considering energy and redox conservation for co-metabolites

ε -value	$\frac{v_{PEPC}^*}{v_{PEPC}^{basal}}$	$\frac{v_{SERS}^*}{v_{SERS}^{basal}}$	$\frac{v_{DAHPS}^*}{v_{DAHPS}^{basal}}$	Modulated enzymes	Optimal objective value η_D^*
1	1.339	1.157	1.144	PK	0.946 ^{†‡}
	1.376	1.165	1.367	G6PDH	0.944
2	1.298	1.611	1.779	G6PDH, SERS	0.827
	1.247	1.506	1.645	PK, SERS	0.856 ^{†‡}
	1.721	1.224	2.142	PK, G6PDH	0.936 [‡]
3	1.587	1.868	2.091	G6PDH, PK, SERS	0.795
	1.439	1.837	2.052	G6PDH, SERS, RPPK	0.802 ^{†‡}
4	1.792	1.966	2.232	G6PDH, PK, SERS, RPPK	0.795
	1.505	2.008	2.247	G6PDH, PK, SERS, DAHPS	0.792
5	1.621	2.280	2.559	G6PDH, PK, SERS, RPPK, DAHPS	0.766
	1.883	2.148	2.398	G6PDH, PK, SERS, RPPK, SYN1	0.790 [‡]

The optimal enzymatic modulation to maximize aromatic amino acid, serine, and oxaloacetate synthesis rates simultaneously by *E. coli* without considering cell viability constraints, but including energy and redox conservation constraints. $\gamma_{x_i}^{LB}$ and $\gamma_{e_i}^{LB}$ are set to 0.2. $\gamma_{x_i}^{UB}$ and $\gamma_{e_i}^{UB}$ are set to 5.0. The superscript * means optimal solution, ε is the number of allowed manipulated genes, superscript † denotes that the solution is not a Pareto optimal solution, and superscript ‡ indicates that the solution is obtained by solving the nonlinear programming problem in which the modulated enzymes are selected in advance.

Table S2: The optimal solution for multi-synthesis maximization by *E. coli* considering resilience effects and energy and redox conservation for co-metabolites

ε -value	$\frac{v_{PEPC}^*}{v_{PEPC}^{basal}}$	$\frac{v_{SERS}^*}{v_{SERS}^{basal}}$	$\frac{v_{DAHPS}^*}{v_{DAHPS}^{basal}}$	Modulated enzymes	Optimal objective value η_D^*
1	1.321	1.150	1.137	PK	0.949 [†]
	1.353	1.157	1.331	G6PDH	0.946
2	1.262	1.538	1.685	G6PDH, SERS	0.847
	1.212	1.436	1.555	PK, SERS	0.876 ^{†‡}
	1.664	1.214	2.047	PK, G6PDH	0.938 [‡]
3	1.467	1.800	2.005	G6PDH, PK, SERS	0.811
	1.363	1.701	1.881	G6PDH, SERS, RPPK	0.834 ^{†‡}
4	1.633	1.903	2.117	G6PDH, PK, SERS, RPPK	0.814
	1.437	1.872	2.079	G6PDH, PK, SERS, DAHPS	0.820 [†]
5	1.538	2.109	2.351	G6PDH, PK, SERS, DAHPS, PEPCxylase	0.797
	1.513	2.057	2.288	G6PDH, PK, SERS, RPPK, DAHPS	0.807 ^{†‡}
	1.779	1.975	2.187	G6PDH, PK, SERS, RPPK, SYN1	0.822 [‡]

The optimal enzymatic modulation to maximize aromatic amino acid, serine, and oxaloacetate synthesis rates simultaneously by *E. coli* considering fuzzy cell viability constraints, fuzzy metabolic and enzyme adjustments, and energy and redox conservation constraints for $[\zeta_{x/e}^{LB}, \zeta_{x/e}^{UB}] = [1.6, 2.0]$. $\gamma_{x_i}^{LB}$ and $\gamma_{e_i}^{LB}$ are set to 0.2. $\gamma_{x_i}^{UB}$ and $\gamma_{e_i}^{UB}$ are set to 5.0. The superscript * means optimal solution, ε is the number of allowed manipulated genes, superscript [†] denotes that the solution is not a Pareto optimal solution, and superscript [‡] indicates that the solution is obtained by solving the nonlinear programming problem in which the modulated enzymes are selected in advance.