

Table S4: Growth rates associated with secondary mutations (labeled A) found to interact non-multiplicatively with  $\rho^*$ . Growth rates  $\gamma$  are given in doublings/hour; the absolute epistasis  $\epsilon$  is calculated using Eq. S7, with a 95% confidence interval obtained via resampling of the posterior distribution of model parameters. Concentrations of ethanol, CML (chloramphenicol), and STP (streptomycin) were 5.5% (v/v), 1.875  $\mu\text{g}/\text{mL}$ , and 2.0  $\mu\text{g}/\text{mL}$ , respectively. †: Growth rates calculated using spline-based fitting; see Section 1 for details. ‡: Relative fitnesses obtained from competition experiments (see Section 1.9) thus, growth rates are omitted.

Media	Secondary mutation (A)	$\gamma_{\text{WT}}$	$\gamma_{\rho^*}$	$\gamma_A$	$\gamma_{A,\rho^*}$	$\epsilon_{A,\rho^*}$ (95% CI)
LB+ethanol	<i>rpsL</i> *	(see text)				
LB	<i>rpsL</i> *	2.510	2.640	2.437	2.273	<b>-0.116 (-0.190 – -0.044)</b>
M9t/glucose†	$\Delta visC$	0.951	1.018	0.828	0.704	<b>-0.192 (-0.224 – -0.159)</b>
M9t/ $\alpha$ KG	$\Delta sthA$	0.509	0.525	0.499	0.494	<b>-0.041 (-0.073 – -0.009)</b>
M9t/ $\alpha$ KG†	$\Delta aroM$	0.517	0.527	0.505	0.469	<b>-0.090 (-0.124 – -0.058)</b>
M9t/ $\alpha$ KG	$\Delta yaaI$	0.509	0.525	0.516	0.530	-0.003 (-0.039 – 0.032)
M9t/ $\alpha$ KG	$\Delta ybaM$	0.509	0.525	0.483	0.492	-0.012 (-0.046 – 0.021)
M9t/glucose+CML	$\Delta envZ$	0.379	0.294	0.601	0.455	-0.030 (-0.106 – 0.041)
M9t/glucose+CML	$\Delta yadM$	0.379	0.294	0.373	0.296	0.016 (-0.034 – 0.065)
M9t/glucose+CML	$\Delta iraP$	0.379	0.294	0.376	0.270	<b>-0.056 (-0.105 – -0.009)</b>
M9t/glucose+CML	$\Delta apaH$	0.379	0.294	0.411	0.321	0.007 (-0.050 – 0.062)
M9t/glucose+STP†	$\Delta yagM$	0.660	0.960	0.355	0.924	<b>0.618 (0.495 – 0.737)</b>
M9t/glucose+STP†	$\Delta ykgL$	0.660	0.960	0.581	0.948	<b>0.156 (0.025 – 0.277)</b>
M9t/NADM‡	$\Delta ppdD$			–		<b>-0.359 (-0.518 – -0.212)</b>
M9t/NADM‡	$\Delta yadN$			–		<b>-0.137 (-0.276 – 0.006)</b>