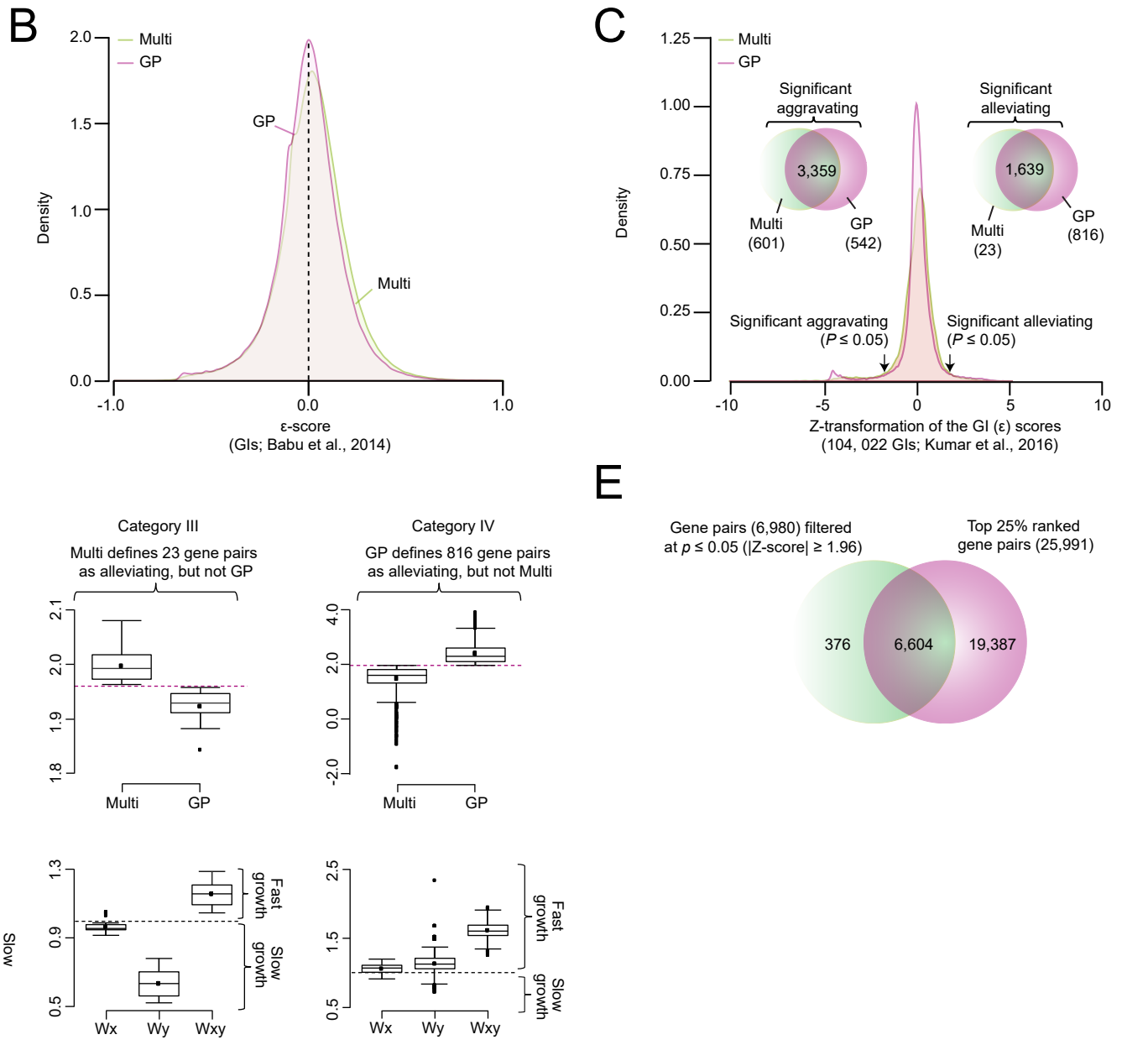
A

Testing of selected definition (or model)	Training gene pairs	
	RMSE	MAE
A. Predefined models		
Multiplicative (Multi)	0.171	0.106
Minimum (Min)	0.067	0.051
Logarithimic (Log)	0.174	0.109
Additive (Add)	0.186	0.123
B. Machine learning models		
Gaussian process (GP)	0.061	0.049
Linear regression (LR)	0.135	0.106
Neural network (NN)	0.090	0.072
Support vector regression (SVR)	0.142	0.100

RMSE: root mean square error; MAE:mean absolute error



Supplementary Fig. 1. Comparison of error metrics, and distributions of GI score for gene pairs between GP and multiplicative models. (**A**) Error metrics shown for indicated definition is evaluated using the non-interacting training pairs from a genome-wide GI study (Babu et al., 2014). (**B, C**) Histogram of *E. coli* GI ε-scores (Babu et al., 2014; panel B) or Z-transformation of GI (ε) score distribution (panel C) for gene pairs from GP and multiplicative models showing a normal Gaussian distribution centered on zero (dotted line), and arrows (panel C) indicate statistical thresholds (corresponding to two standard deviations; |Z-score| ≥ 1.96; $p \leq 0.05$) to define significant GI pairs. The overlap of aggravating or alleviating GIs between GP and the multiplicative model is shown as a Venn diagram (C) in the inset. (**D**) Box plots showing the distribution of Z-transformed GI (ε) scores (dotted line shows the |Z-score| ≥1.96 cut-off) for disagreement gene pairs (grouped under various categories) between GP and the multiplicative definitions, and their respective normalized single (Wx: donor; Wy: recipient) and double (Wxy) mutant colony sizes that exhibit slow (< 1.0), normal (1.0), and fast (>1.0) growth. (**E**) Venn diagram showing the overlap between the significant Z-transformed GI pairs in the 95th percentile ($p \leq 0.05$) and in the top 25% of the ranked GI pairs.