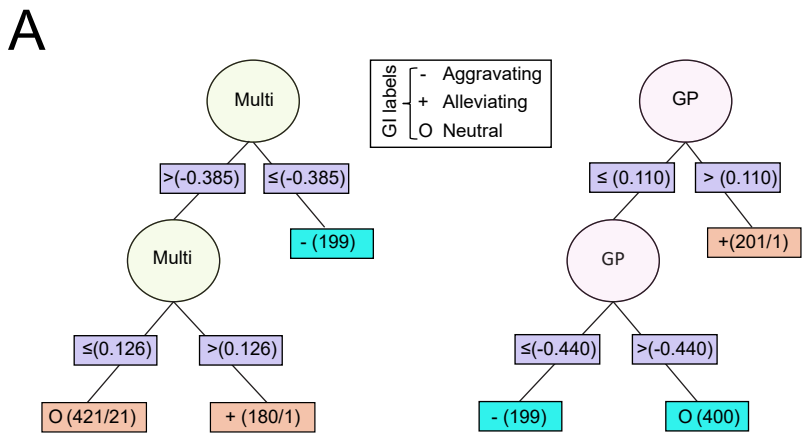
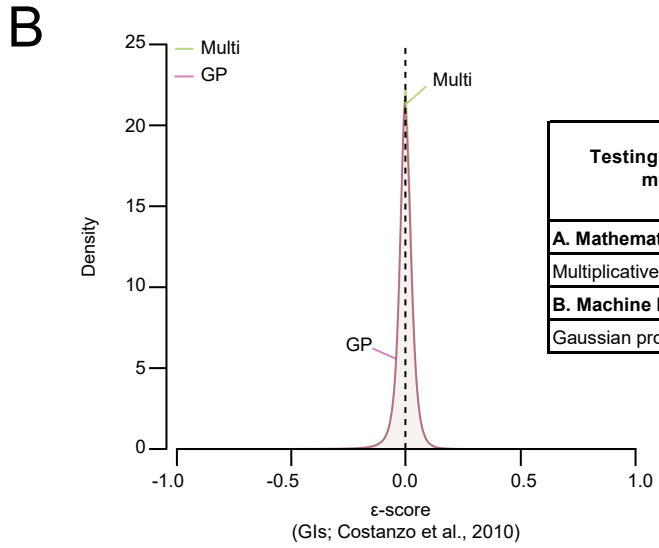
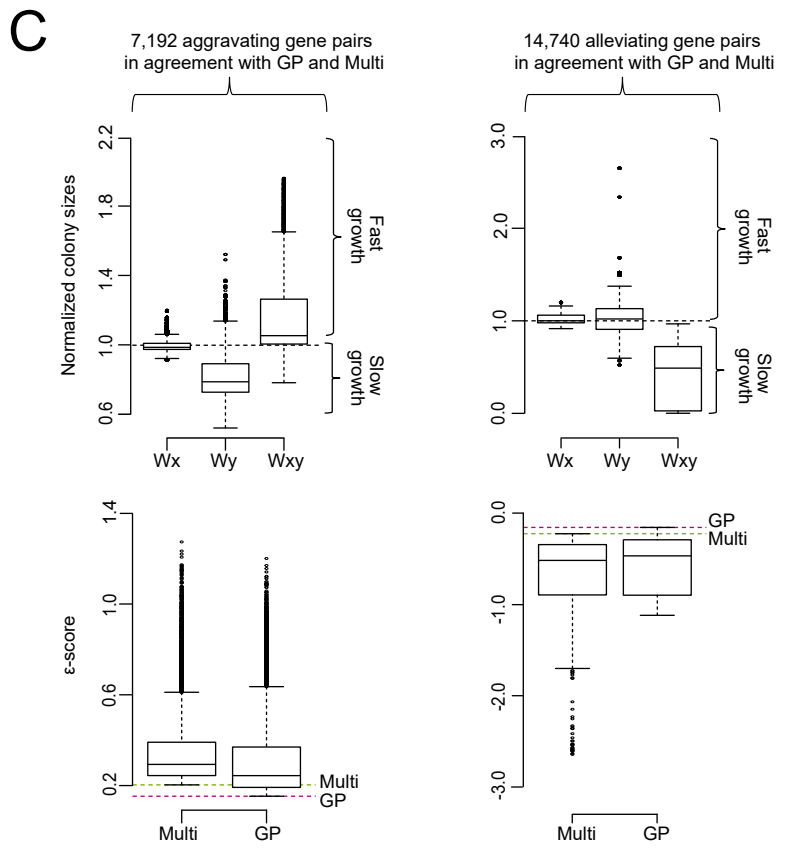




Testing of selected models	Non-interacting training gene pairs	
	RMSE	MAE
A. Mathematic model		
Multiplicative (Multi)	0.052	0.033
B. Machine learning model		
Gaussian process (GP)	0.052	0.034



Supplementary Fig. 2. Probabilistic decision tree-based classification score, ε-score distributions, and other indicated measurements to evaluate the performance of GP and multiplicative models using the dataset compiled from the published *E. coli* (Kumar et al., 2016) and yeast (Costanzo et al., 2010) epistatic interaction studies. (**A**) Threshold selection on the 800 test dataset [200 aggravating (-), 200 alleviating (+), 400 non-interacting (O) pairs] obtained from the genome integrity epistatic screen (Kumar et al., 2016) using a decision-tree classification system. The moon raker color points to the decision-tree classification score cut-off; bright turquoise color represents gene pairs classified to proper GI type labels, whereas mandys pink color indicates the number of pairs classified to a GI type (numerator) and how many of those were misassigned (denominator). For example, in the case of O (421/21), the multiplicative definition miscategorized 21 gene pairs to the 400 non-interacting test pairs as opposed to classifying them under alleviating + (180/1) category. In the latter, 180 were assigned as alleviating by the multiplicative model, and the remaining 20 pairs were misclassified as non-interacting and 1 as aggravating. Likewise, with respect to +(201/1), of the 200 alleviating pairs tested, GP classified 200 pairs to alleviating phenotype with 1 classified inconsistently. (**B**) Histogram of yeast GI (ε) scores from GP and multiplicative models showing a normal distribution centered on zero (dotted line), along with their error values displayed in a Table on the top right corner of the Gaussian distribution. (**C**) Box plots showing the normalized colony size values (Wx: donor mutants; Wy: recipient mutants; Wxy: double mutants) and the GI (ε) score distributions of agreement pairs (i.e. 7,192 aggravating and 14,740 alleviating) for multiplicative and GP definitions.