SUPPLEMENTARY MATERIAL

1. SUPPLEMENTARY TABLES

Supplementary Table S1 - List of gene pairs from the genome integrity study (Kumar et al., 2016; Sheet 1), along with their predicted GI scores by selected models. List of 3,481 gene pairs (category A) defined by the multiplicative model as aggravating, whereas GP classified these interactions as non-interacting (close to neutrality or fell short below the chosen cut-off; Sheet 2). List of 1,614 gene pairs (category B) defined by the multiplicative model as non-interacting (either it was close to neutrality or fell short below the chosen cut-off), whereas GP classified these interactions as aggravating (Sheet 3). List of 592 gene pairs (category C) defined by the multiplicative model as alleviating, whereas GP classified these interactions as non-interacting (either it was close to neutrality or fell short below the chosen cut-off; Sheet 4). List of 2,459 gene pairs (category D) defined by the multiplicative model as aggravating (or close to neutrality), whereas GP classified these interactions as alleviating (Sheet 5). List of GI pairs (14,740) that were alleviating in both GP and multiplicative definitions (Sheet 6). List of GI pairs (7,192) that were aggravating in both GP and multiplicative definitions (Sheet 7).

Supplementary Table S2 – List of training (336; Sheet 1), and test (400 interacting, Sheet 2; 400 non-interacting, Sheet 3) gene pairs and their predicted GI (ε) scores based on observed and expected mutant fitness. Mean and standard deviation from a 5-fold cross validation of the training dataset (Sheet 4) shown for machine learning models in Fig. 1a. Evaluating the performance of GP and NN models (Sheet 5) under different parameter settings by measuring error metrics (RMSE, MAE) using the training set.

Supplementary Table S1 - List of Z-transformed GI scores by selected models (Sheet 1) for gene pairs from the genome integrity study (Kumar et al., 2016; Sheet 1). List of 601 gene pairs (category I) defined by the multiplicative model as aggravating (Sheet 2). List of 542 gene pairs (category II) that GP classified as aggravating (Sheet 3). List of 23 gene pairs (category III) defined by the multiplicative model as alleviating (Sheet 4). List of 816 gene pairs (category IV) that GP classified as alleviating (Sheet 5). List of GI pairs (3,359) that were aggravating in both GP and multiplicative definitions (Sheet 6). List of GI pairs (1,639) that were alleviating in both GP and multiplicative definitions (Sheet 7).

Supplementary Table S4 - Multiplicative model misclassifies 21 alleviating interactions as non-interacting, 2 non-interacting as alleviating, and 2 alleviating as aggravating or non-interacting based on a decision-tree classification score threshold (Sheet 1). Accuracy and error of the GI definitions estimated based on a 5-fold cross validation on 104,022 gene pairs compiled from the genome integrity study (Kumar et al., 2016; Sheet 2). Area under the receiver operating characteristic curve for the interacting and non-interacting test pairs predicted under GP and multiplicative definitions based on the decision-tree classification system (Sheet 3).

Supplementary Table S5 - GI pairs sharing a similar enriched gene ontology (GO) annotation.

2. SUPPLEMENTARY FIGURES

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| $\geq$ 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 (C) in the inset. (**D**) Box plots showing the distribution of Z-transformed GI (ε) scores (dotted line shows the |Z-score| $\geq$ 1.96 cut-off) for disagreement gene pairs (grouped under various categories) between GP and the multiplicative definition, and their resepective normalized single (Wx: donor; Wy: recipient) and double (Wxy) mutant colony sizes that exhibit slow (< 1.0), normal (1.0), and fast (>1.0) in growth. (**E**) Venn 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.

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.

3. SUPPLEMENTARY DATA

The source code, encompassing the algorithm functions and parameters used to generate the machine learning models in WEKA software environment were provided along with the supporting *E. coli* training (336 gene pairs) dataset in WEKA's native format.