In an exponential growth model, the frequency of a double mutant strain in a given condition at a time represents its total growth from an initial number as a proportion of the total growth of all other strains in the pool:

(x,y index instead of i,j to denote the double mutant, but keep i,j in the sum)

Here, is inversely related to the doubling time of strain . A frequency at t=0 therefore represents:

To remove the unknown term, we define

To remove the unknown and terms, we can normalize this score by of a reference “wildtype” strain,

For , we use the median score for all neutral-neutral pairs measured in the assay. We can take the log of this ratio to obtain a relative score compared to wildtype:

To obtain , which represents the number of doublings of the wildtype strain, we use the median of all well-measured same-same pairs (arbitrarily set to >100 counts in the heterozygous diploid state), assuming that for this strain:

To estimate , which represents the number of doublings of the wildtype strain, we use the number of doublings of the pool as a whole.

After having obtained this number, we can obtain , the number of doublings, for all strains:

We then obtain the relative growth rate of each strain compared to the wild type by dividing their number of doublings. If assuming constant exponential growth, this metric is independent of time. In reality, represents the average growth rate over the measured time period.

To estimate the single mutant fitness and for a given pair, we use the mean estimate of or combined with neutral genes, excluding all pairs with <100 counts in the heterozygous diploid condition.

We then definite the genetic interaction score (GIS) as the difference between and the product of with :

When calculating this score, we have uncertainty in and as any combination with neutral genes could represent the single-mutant fitness:

We combine these uncertainties into uncertainty about

We define as divided by the standard deviations of uncertainty in the multiplicative score. Thus represents the number of standard deviations from 0 (in either the positive or negative direction).

To choose negative and positive cutoffs for for each condition (, we analyze the distribution of in all neutral-neutral and neutral-DNA damage pairs (abbreviated to ), as few or no genetic interactions are expected to take place between these pairs. We use this distribution to estimate the number of false positives amongst the DNA-DNA damage pairs (abbrediated ).

We then use the estimated number of positives to estimate an ‘internal’ False Discovery rate for a given cutoff:

and are then chosen such that and . An internal estimated for each interaction in each condition is stated so that other cutoffs may be chosen.