Towards accurate imputation of quantitative genetic interactions
Igor Ulitsky*,†, Nevan J Krogan† and Ron Shamir*

Addresses: *Blavatnik School of Computer Science, Tel Aviv University, Tel Aviv 69978, Israel. †Department of Cellular and Molecular Pharmacology, University of California San Francisco, San Francisco, CA 94158, USA. ‡Current address: Whitehead Institute for Biomedical Research, 9 Cambridge Center, Cambridge, MA 02142, USA.

Correspondence: Ron Shamir. Email: rshamir@tau.ac.il

© 2009 Ulitsky et al.; licensee BioMed Central Ltd.
This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited

Published: 10 December 2009
Genome Biology 2009, 10:R140 (doi:10.1186/gb-2009-10-12-r140)
The electronic version of this article is the complete one and can be found online at http://genomebiology.com/2009/10/12/R140

Abstract
Recent technological breakthroughs have enabled high-throughput quantitative measurements of hundreds of thousands of genetic interactions among hundreds of genes in Saccharomyces cerevisiae. However, these assays often fail to measure the genetic interactions among up to 40% of the studied gene pairs. Here we present a novel method, which combines genetic interaction data together with diverse genomic data, to quantitatively impute these missing interactions. We also present data on almost 190,000 novel interactions.

Background
Understanding the interactions between genes and proteins is essential for elucidating their function. Genetic interactions (GIs) describe the phenotype of a double knock-out in comparison to the phenotypes of single mutants, and they can be crudely classified into positive (alleviating), neutral, and negative (aggravating) interactions [1,2]. In a negative GI, the fitness (typically estimated by growth rate) of the double-mutant is lower than expected based on the fitness of single mutants. The most extreme example of a negative interaction is synthetic lethality, in which the joint deletion of two nonessential genes leads to a lethal phenotype. In a positive GI, on the other hand, the double mutant is healthier than expected. The expected fitness is usually defined as the product of the fitnesses of the single mutants [1,3,4].

In a genome of over 6,000 genes, such as that of Saccharomyces cerevisiae, there are some 18 million gene pairs, making the mapping of the complete genetic interactome a formidable challenge. Towards this goal, several techniques for high-throughput GI profiling have been developed. For example, two approaches, systematic genetic analysis (SGA) [5,6] and dSLAM (heterozygote diploid-based synthetic lethality analysis with microarrays) [7,8], have made it possible to screen for negative GIs, namely synthetic sick or synthetic lethal interactions, between a query gene and the collection of all nonessential genes. The recent introduction of E-MAP (epistatic miniarray profile) technology, which is an adaptation of SGA [9-12], has made it possible to quantitatively measure both positive and negative GIs among several hundreds of genes [9-11]. The largest published E-MAP to date [10] covers GIs between 743 S. cerevisiae genes involved in various aspects of chromosome biology. The use of quantitative GIs was shown to significantly improve gene function prediction [10].

Using the E-MAP technology, hundreds of thousands of GIs have been measured in S. cerevisiae. It is therefore appealing to use these data along with other genomic information to predict additional GIs. Wong et al. [13] pioneered the prediction of GIs in S. cerevisiae, using probabilistic decision trees and diverse genomic data, including mRNA expression, functional annotations, subcellular localization, deletion phenotypes and physical interactions. These authors also introduced '2-hop features' for capturing the relationship

Genome Biology 2009, 10:R140
between a gene pair and a third gene. For example, if protein A physically interacts with protein C, and gene B is synthetic lethal with gene C, then the gene pair A-B possesses the characteristic ‘2-hop physical-synthetic lethal’, which was shown to increase the likelihood of a synthetic lethal interaction between A and B. Assessment of the performance on SGA-tested gene pairs revealed sensitivity of 80% at a false positive rate of 18%. The 2-hop features were shown to be the most effective features for prediction of GIs, and omission of other individual features did not significantly hurt the performance. This result suggested that most negative GIs occur between pairs of compensating physical pathways. This phenomenon has since been extensively studied [14-18]. Zhong and Sternberg [19] used similar ideas and combined diverse genomic information from three species to predict synthetic lethal interactions in *Caenorhabditis elegans* using a logistic regression classifier. Paladugu et al. [20] focused on features based on protein-protein interaction (PPI) networks, such as node degree, centrality, and clustering coefficient. Using a support vector machine classifier, they showed that using PPI network information together with 2-hop features is sufficient for predicting synthetic lethality at about 90% accuracy.

Recently, Qi et al. [21] devised the first GI prediction scheme based solely on GI data. Observing that genetically interacting gene pairs are connected by many odd-length paths in the GI network, they developed a graph diffusion kernel that successfully predicts novel GIs. Combining this kernel with kernels based on other genomic data had little effect on prediction accuracy, leading them to conclude that most of the information needed to predict new GIs can be found in the existing GI network. Another method for predicting negative GIs using random walks has been recently proposed by Chipman and Singh [22].

All available methods for predicting GIs were designed and tested on synthetic sick or synthetic lethal GIs obtained with the SGA method [5,6]. SGA differs from E-MAP in two key aspects. First, SGA screens are inherently asymmetrical, as a relatively small set of ‘baits’ are tested against a genome-wide collection of ‘preys’. Using E-MAP, all pairwise interactions among a subset of the genes are tested. Second, E-MAP is quantitative and is capable of capturing both positive and negative GIs. Unfortunately, for technical reasons E-MAPs contain a large number of missing interactions. In the ChromBio E-MAP, for example, over 34% of the interactions were not measured. The fraction of interactions that are missing is higher for essential genes (46% on average), but is similar for genes with reduced fitness in rich media and for other non-essential genes (29% and 33%, respectively). It is logical to surmise that the vast number of interactions measured in the available E-MAPs can be used to predict the unmeasured GIs. The unique features of E-MAPs suggest that a dedicated approach to prediction of missing GIs in E-MAPs may be more powerful than previously suggested techniques for GI prediction. It is this possibility that we address here.

Most of the previous studies on GI prediction were based on a large variety of genomic information available for each gene in *S. cerevisiae*. An exception are the studies by Qi et al. [21] and Chipman and Singh [22], which showed that information about the GI network alone is sufficient for a relatively accurate qualitative prediction of negative GIs. Here we show that by integrating GI information across genes, it is possible to achieve quantitative prediction of both positive and negative GIs that significantly outperforms predictions made by other methods. Furthermore, this prediction can be improved by combining E-MAP-based information with other genomic data, although this improvement is relatively minor. We thus show that the measured gene pairs in the E-MAP are the best source of information for predicting the pairs that could not be measured.

The outline of our study was as follows (Figure 1a). We experimented with a variety of genomic features describing gene pairs, such as the existence of a physical interaction or co-expression, that were used as input to several popular classifiers. Some of the features are akin to previous ones and some are novel. We tested several popular methods that use the features to classify unknown GIs. To evaluate the quality of the combination of a particular feature set and a classifier, we applied a cross-validation procedure in which a fraction of the measurements were hidden and the ability of the classifier to recover them was assessed. The best performing algorithm was linear regression using all the possible features. Using data from three E-MAPs, we predicted 189,985 GIs among 144,498 pairs (some gene pairs appear in more than one E-MAP; see below). For a qualitative prediction of the GI type, we found that the best method was logistic regression using all features: it enabled us to identify over 40% of the missing strong positive and strong negative GIs in the ChromBio E-MAP by testing only 10% of the gene pairs, achieving four-fold improvement over random testing of pairs. The accuracy of our qualitative and quantitative predictions was further assessed with GI information from two additional independent sources.

We demonstrate the utility of the imputed E-MAP values for two tasks: to improve the ability to detect functionally similar genes using either predicted interactions or correlations of imputed GI profiles; and to more fully inspect the landscape of GIs among co-complexed genes. Finally, we address three scenarios that give rise to missing values in E-MAPs and discuss the ability of our method to predict a substantial number of new interactions through a combination of E-MAPs.

Results and Discussion

Construction of gene-pair feature sets

We analyzed three publicly available E-MAP datasets: the ChromBio dataset [10] containing GIs among 743 genes involved in chromosome biology; the endoplasmic reticulum (ER) dataset [9] containing GIs among 423 genes involved in
the early secretory pathway; and the RNA dataset [12] containing GIs among 552 genes involved in RNA processing. We report mainly on the results from the ChromBio E-MAP, since it is the largest. Results on the two other E-MAPs are presented in Additional file 1. We computed a large number of features for each pair of genes in the E-MAP (Table 1; see Materials and methods for a description of how each feature was computed). These features can be crudely divided into four groups.

The first two groups contain features that were used in previous studies [13,20]: the NETWORK group, which includes features based on the physical and GI networks, and the GENOMIC group, which includes features based on various genomic characteristics. Unlike previous studies, we defined separate individual features for each protein complex, phenotype and localization, whereas others used a single feature, encoding whether the gene pair shares any complex, phenotype or localization. This change stemmed from observations that some complexes tend to take part in a large number of GIs [15,16].

The third and fourth groups constitute the main innovation in our feature set compared to previous works - the use of information on genetically similar genes (GSGs; Figure 1b; Materials and methods). The GI profile of a gene is a vector representing the scores of its GIs with other genes that took part in the GI screen. Previous studies have shown that similarity of GI profiles is a powerful indicator of functional similarity between genes [9,10,18,23]. Following this reasoning, we hypothesized that when predicting the GI between genes A and B, it would be useful to detect genes with GI profiles similar to those of A and B and to check the GIs among them (Figure 1b). We call a set of genes GSGs of gene A if their GI profiles are the most similar to those of A among all the genes in the E-MAP. The third group is called the GSG feature set. When we wish to predict the GI between genes A and B, it contains the GI scores (which, following [24], we call S-scores) between A and the GSGs of B and vice versa (see Materials and methods).

Recent studies have shown that many GIs occur between pairs of functional modules [15-18]. If A and B belong to distinct functional modules, it is reasonable that the S-scores between other members of the same module will be indicative of the S-score between A and B. This is the rationale behind the fourth group, called GSG-MATRIX, which contains S-scores between GSGs of A and GSGs of B (see Materials and methods).

Figure 1
Study outline and new features used. (a) Study outline. Diverse features of gene pairs were computed and used to predict GIs using various classifiers. Performance was assessed by ten-fold cross-validation and the best combination of feature groups and classifier was selected. This combination was used to predict new GIs, which were subsequently tested against an independent E-MAP and negative interactions reported in the BioGrid database. In addition, we tested the correlation between the new GIs with functional similarity based on Gene Ontology. (b) Illustration of the GSG and GSG-MATRIX features. We were interested in predicting the GI between genes A and B. GSG features capture measured GIs between A and genes similar to B and vice versa. GSG-MATRIX features capture measured GIs between genes similar to A and genes similar to B.
Comparison of feature sets and classifiers for prediction of quantitative GIs

We distinguish between two tasks of GI prediction: estimation of the quantitative S-scores between genes; and discrete classification of GIs as positive, negative or neutral. The former task requires a classifier capable of predicting a numeric value for a gene pair, sometimes referred to as a regressor. We compared four regressors (Table 2). The performance was tested using: GSG features only; GSG and GSG-MATRIX features (called GSG+MATRIX); NETWORK and GENOMIC features (both used in previous studies); and all four groups of features. We determined the utility of using complex machine learning algorithms by testing $k$-nearest-neighbor-like classifiers, which estimated the GI between A and B as the average of their GSG features. Finally, we tested a 'blind' classifier that predicts all GIs to be completely neutral (that is, with S-score 0). Using ten-fold cross-validation, we computed the correlation between the predicted and the actual S-scores, and the mean square error of each combination of a classifier and a feature set. The results are presented in Figure 2. We obtained the best performance when using linear regression together with all the features, with similar results obtained using the more computationally intensive M5' (a decision tree with regression models at its leaves [25]). Using M5' or linear regression with GSG+MATRIX features yielded near-optimal results. Overall, these features showed great advantage over those in the NETWORK or GENOMIC groups. The GSGs - that is, the genes with the most similar GI profile to the tested genes - were ranked according to the similarity values. In the linear regression model for GSG features, as expected, features corresponding to GSGs of higher rank were given a higher weight (Figure S1 in Additional file 1). The results show that this weighting gives a clear advantage over using unweighted $k$-nearest-neighbors classifiers (Figure 2). The utility of the GSG features did not depend heavily of the number of GSGs used, as GSGs of order >5 consistently

Table 1

| Feature group | Characteristic | Number of features | Data source | Previous use for GI prediction |
|---------------|----------------|--------------------|-------------|-------------------------------|
| NETWORK       | Physical interaction | 1                  | BioGrid [28] | [13,20]                       |
|               | Shortest physical path | 1                  | BioGrid [28] | [13,20]                       |
|               | Mutual clustering coefficient | 1              | BioGrid [28] | [13,20]                       |
|               | Network degree        | 6                  | BioGrid [28] and E-MAP | [20]                     |
|               | 2-hop                  | 6                  | BioGrid [28] and the E-MAP | [13]                     |
| GENOMIC       | Sequence similarity (BLAST E-value) | 1              | [45]         | [13]                         |
|               | Occurrence in a specific protein complex | 32            | MIPS [42]    | -                             |
|               | Co-occurrence in any protein complex | 1              | MIPS [42]    | [13]                         |
|               | Deletion phenotype     | 53                 | MIPS [42]    | -                             |
|               | A common deletion phenotype | 1              | MIPS [42]    | [13]                         |
|               | Correlation of quantitative phenotype profiles | 1              | [44]         | -                             |
|               | Gene Ontology semantic similarity | 3              | GO [58]      | [13]                         |
|               | Subcellular localization | 17             | [46]         | -                             |
|               | A common subcellular localization | 1              | [46]         | [13]                         |
|               | S-score in S. pombe    | 1                  | [11]         | -                             |
|               | mRNA expression (correlation) | 7              | [47-53]      | [13]                         |
| GSG           | S-score between A and genes similar to B (or vice versa) | 10             | E-MAP        | -                             |
| GSG-MATRIX    | S-scores among genes similar to A and to genes similar to B | 25             | E-MAP        | -                             |

The features are computed for every pair (A-B) of genes. Numbers of certain features depend on the E-MAP and are reported for the ChromBio E-MAP. SL, synthetic lethal; SS, synthetic sick.
attained low weights (Figure S2 in Additional file 1). We got very similar results with the same analysis using the ER and the RNA E-MAPs (Figure S3 in Additional file 1). Imputed versions of all three E-MAPs obtained using linear regression with all features are available in Additional file 2. Due to its superiority over other methods, we used linear regression with all the features in all further experiments (unless indicated otherwise).

Comparison of feature sets and classifiers for prediction of GI class
We also tested different combinations of feature sets and classifiers for qualitative prediction of GIs. The GIs in the training set were assigned to be positive, negative or neutral (see Materials and methods), and the classifiers were trained to predict the three classes. We compared five classifiers (Table 2), including those used in previous GI prediction studies [13,19]. We also compared our approach to the diffusion kernel method recently proposed by Qi et al. [21] (using the original implementation provided by the authors, which we applied to the same dataset; see Materials and methods). We used the G^- diffusion kernel (based on the number of odd-length paths between the two genes) for prediction of negative interactions, and the G^+ kernel (based on the number of even-length paths) for prediction of positive interactions (see Materials and methods). An implementation of the random walk method of Chipman and Singh [22] was not available for comparison. Classifier performance was evaluated separately for prediction of positive and negative interactions, using two criteria. First, as in previous studies, we computed the area under the curve (AUC) score; this is the area under the receiver operating characteristic (ROC) curve, which plots the fraction of true positives as a function of the false positive rate, as the prediction threshold varies [26]. Although widely used, the AUC criterion is not very informative in our case because the dataset is skewed: there are many more negative than positive examples (the ratio between negative, positive and neutral interactions is approximately 6:3:91 in the ChromBio E-MAP and 3:2:95 in the ER and RNA E-MAPs). In the case of GI prediction, it is especially important that there be a sufficient fraction of true positives among the best-ranked predictions that could potentially be experimentally tested. One way to quantify this is to look at the precision-recall curve, which plots the fraction of the predictions that are correct as a function of the true positive rate (the fraction of true pairs that were predicted correctly) [27]. The area under the precision-recall curve (AUPR) provides a better quantitative assessment of the performance when the dataset is skewed. A method with perfect classification accuracy has an AUC of 1 and an AUPR of 1, while a random classifier would have an AUC of 0.5 and (for data with a low fraction of positive examples) an AUPR close to 0.

The results are presented in Figure 3. The best performance was achieved using all the features with the logistic regression or Naïve Bayes classifiers. Using GSG or GSG+MATRIX features, it was possible to obtain near-optimal classification accuracy, and these features significantly outperformed classifiers using only network or genomic properties, which were used in previous studies. The G^- diffusion kernel was indeed very powerful in predicting negative interactions, especially given the amount of information it used (only the synthetic lethal interactions). However, the G^+ kernel performed rather poorly in predicting positive interactions. In general, the prediction of negative GIs appears to be easier than the prediction of positive GIs, since most methods fared much better on the former task. The higher difficulty of predicting positive interactions was manifested for a variety of S-score thresholds used to define those interactions, as the AUPR for predic-

---

Table 2

| Task                                | Classifier                        | Reference         |
|-------------------------------------|-----------------------------------|-------------------|
| Quantitative GI prediction          | Linear regression                 | [59]              |
|                                     | MS'                               | [60]              |
|                                     | Least median squared linear regression | [61]          |
|                                     | Gaussian radial basis function network | [62]          |
|                                     | k nearest neighbors               | [59]              |
| GI class prediction                 | Naïve Bayes                       | [59]              |
|                                     | Random Forest                     | [63]              |
|                                     | J48 decision tree                  | [59]              |
|                                     | Logistic regression                | [64]              |
|                                     | Discretized linear regression      | See Materials and methods |
|                                     | Diffusion kernel                   | [21]              |
tion of positive interactions did not exceed 0.25 for any threshold (Figure S4 in Additional file 1).

Using logistic regression with all features, we find that we can obtain a recall of 40% of negative interactions by testing roughly 4.2% of the interactions at a precision of 61% (Figure 4), a significant improvement over the 45% precision for the same recall reported in [20]. Prediction of positive interactions is significantly more difficult, and recall of 40% requires testing 5.3% of the interactions at 20% precision. Thus, testing about 10% of the top predictions (9,300 gene pairs overall in the ChromBio E-MAP) is enough to discover over 40% of the significant positive and negative GIs that are missing.

Accurate imputation of negative GIs not measured in the E-MAP

As an additional test for the accuracy of our method in prediction of negative GIs, we looked for pairs of genes from the ChromBio set with reported GIs that were not measured in the ChromBio E-MAP. We found 376 (279) synthetic lethal (sick) pairs with these properties in the BioGrid database [28]. The distribution of S-scores predicted for these pairs using linear regression and GSG+MATRIX features is shown in Figure 5. Note that here all the GI information originated from the E-MAP, and no information from BioGrid was used to construct the GSG+MATRIX features. Gene pairs marked as synthetic lethal in BioGrid had lower predicted S-scores (average = -1.81) than those marked as synthetic sick (average = -0.82, t-test P-value = $4.7 \times 10^{-9}$) and than all other gene pairs in the ChromBio E-MAP (average = -0.14, t-test P-value <10^{-200}). We also tested a discrete classifier, the Naïve Bayes classifier, and found that 174 (47.4%) of the gene pairs marked as synthetic lethal in BioGrid were predicted to be negative by our method. This fraction is likely to be an underestimate for the sensitivity of our method, as GIs in BioGrid were obtained in a variety of strains and conditions that were not necessarily the same as those used for the ChromBio E-MAP. Note that it is not possible to use BioGrid to estimate the specificity of our method, as it aggregates only successful negative GI detections from many high- and low-throughput studies, and it is not known which gene pairs were actually tested unsuccessfully in each study. Unfortunately, we could not use BioGrid to validate our positive interaction prediction accuracy: BioGrid contained only 76 pairs with unambiguous positive interactions that were not measured in the E-MAP, and this number was too small for evaluating our prediction accuracy (results not shown).

Validation of quantitative predictions of GIs

While the comparison with BioGrid shows that our method is capable of predicting strong negative GIs, our main goals are to predict positive GIs and to make quantitative predictions. To test our ability to accomplish these goals, we used the RNA E-MAP, which shares 127 genes with the ChromBio E-MAP.
Among these genes, we found 779 gene pairs for which GIs were measured only in the RNA E-MAP. These pairs could be effectively used as an independent test of our ability to predict quantitative GIs. When we imputed the missing values in the ChromBio E-MAP using linear regression with all the features, the correlation between the predicted values and the S-scores in the RNA E-MAP was 0.452 (Pearson correlation P-value = 2.2 × 10^{-16}). While highly significant, this correlation is lower than that of positive interactions (52.5% versus 37.5%).

Individual features most useful for prediction of GI type
In order to assess the features most useful for prediction of GIs, we ranked the features based on the absolute value of their correlation with the S-scores across the 182,057 gene pairs measured in the ChromBio E-MAP. The top 50 features are listed in Table 3 and the full list appears in Table S1 in Additional file 1. The comparison further emphasizes the high utility of the GSG features. Consistent with our findings in comparing different feature sets, the 29 top ranked features are all GSG and GSG-MATRIX features, and all 35 GSG+MATRIX features appear in the top 36 features. Not surprisingly, the three top features are the GIs between GSG(A) and GSG(B), A and GSG(B), and B and GSG(A) (GSG(X) is the gene ranked i by GI profile similarity to X). As for other feature types, consistent with the results of [13], we found that among the features based on network and genomic information, the 2-hop features are very powerful, with five such features ranked in the top 50. We found ‘2-hop physical-synthetic lethal’ the most useful 2-hop feature, consistent with the dominant role of GIs as bridging physical pathways [14-16]. Other high-ranking features include the average degrees of the gene pair in the synthetic lethal (ranked 29th), synthetic sick (37th) and physical (88th) networks. The physical and the genetic degree of a gene were shown to be correlated in *S. cerevisiae* [29]. The high ranks of these features indicate that genes already established to be involved in many genetic and physical interactions are likely to be involved in
Figure 4

Qualitative GI prediction using logistic regression and all the features. Performance was evaluated by ten-fold cross-validation on the ChromBio E-MAP. (a) Receiver operating characteristic (ROC) plot. (b) Precision-recall plot.
additional GIs. However, the presence of a physical interaction was only very weakly correlated with the measured S-scores (ranked 162nd), consistent with the observation that both strongly positive and strongly negative S-scores frequently correspond to physical interactions (see below). The highest ranking phenotype feature (ranked 46th) was 'slow growth', indicating that genes whose deletion limits the growth of the cell are likely to cause strong phenotypes when their deletion is accompanied by an additional knockout.

Our feature set contained separate features representing individual complexes, phenotypes or localizations. This information was summarized using a single feature in [13]. Thirteen individual complex features were ranked higher than the 'same MIPS complex' feature; 25 individual phenotype features were ranked higher than 'same MIPS phenotype'; and two localizations were ranked higher than 'same localization'. Hence, using individual features is indeed beneficial, as their information content frequently exceeds that of 'summary' features.

Finally, we compared the performance of each of the four groups of features separately with linear regression (Figure S5 in Additional file 1) and found that the performance of the GSG features alone was best, followed, in decreasing order, by GSG_MATRIX, NETWORK and GENOMIC groups. Note that this order is reversed to the number of features in each group, indicating that the quality of the features is much more important than their number.

**Gene pairs predicted to genetically interact are functionally related**
Pairs of genes exhibiting positive or negative GIs were previously shown to be functionally related and likely to physically interact [10,12,18]. We therefore examined whether the GIs we predicted shared the same characteristics. To test this, we predicted the 93,596 missing values in the ChromBio E-MAP using linear regression and the GSG+MATRIX features. When predicted positive and negative GIs were tested separately, their absolute values were significantly correlated with an increasing functional similarity ($P = 1.2 \times 10^{-7}$ and $P < 2.2 \times 10^{-16}$ using Pearson correlation, for positive and negative interactions, respectively; functional similarity was measured using Gene Ontology (GO) semantic similarity [30], using the Resnik similarity measure [31]) and an increasing propensity for physical interactions (defined by the fraction of gene pairs reported to physically interact in the BioGrid database, $P = 0.041$ and $P < 2.2 \times 10^{-16}$; Figure 6).

**Imputation improves correspondence between genetic and functional similarity**
The results in the previous sections show that our method is capable of improving the accuracy of predicting GIs. One potential use of such prediction is to elucidate the functional relationship between two genes based on the prediction of the
Table 3

The features with the highest correlation to measured S-scores

| Number | Group          | Feature                  | Correlation |
|--------|----------------|--------------------------|-------------|
| 1      | GSG-MATRIX     | GSG-MATRIX #1            | 0.505       |
| 2      | GSG            | GSG #1 for A             | 0.501       |
| 3      | GSG            | GSG #1 for B             | 0.491       |
| 4      | GSG-MATRIX     | GSG-MATRIX #2            | 0.489       |
| 5      | GSG-MATRIX     | GSG-MATRIX #3            | 0.419       |
| 6      | GSG            | GSG #2 for A             | 0.417       |
| 7      | GSG            | GSG #2 for B             | 0.412       |
| 8      | GSG-MATRIX     | GSG-MATRIX #4            | 0.403       |
| 9      | GSG            | GSG #3 for A             | 0.366       |
| 10     | GSG-MATRIX     | GSG-MATRIX #7            | 0.364       |
| 11     | GSG            | GSG #3 for B             | 0.358       |
| 12     | GSG-MATRIX     | GSG-MATRIX #8            | 0.341       |
| 13     | GSG-MATRIX     | GSG-MATRIX #6            | 0.329       |
| 14     | GSG            | GSG #4 for A             | 0.328       |
| 15     | GSG-MATRIX     | GSG-MATRIX #5            | 0.321       |
| 16     | GSG-MATRIX     | GSG-MATRIX #13           | 0.319       |
| 17     | GSG            | GSG #4 for B             | 0.310       |
| 18     | GSG-MATRIX     | GSG-MATRIX #9            | 0.294       |
| 19     | GSG-MATRIX     | GSG-MATRIX #14           | 0.293       |
| 20     | GSG            | GSG #5 for A             | 0.280       |
| 21     | GSG            | GSG #5 for B             | 0.280       |
| 22     | GSG-MATRIX     | GSG-MATRIX #12           | 0.271       |
| 23     | GSG-MATRIX     | GSG-MATRIX #10           | 0.270       |
| 24     | GSG-MATRIX     | GSG-MATRIX #21           | 0.270       |
| 25     | GSG-MATRIX     | GSG-MATRIX #11           | 0.264       |
| 26     | GSG-MATRIX     | GSG-MATRIX #15           | 0.257       |
| 27     | GSG-MATRIX     | GSG-MATRIX #22           | 0.248       |
| 28     | GSG-MATRIX     | GSG-MATRIX #16           | 0.242       |
| 29     | GSG-MATRIX     | GSG-MATRIX #20           | 0.235       |
| 30     | NETWORK        | SL degree (average of A and B) | -0.232 |
| 31     | GSG-MATRIX     | GSG-MATRIX #17           | 0.231       |
| 32     | GSG-MATRIX     | GSG-MATRIX #23           | 0.227       |
| 33     | GSG-MATRIX     | GSG-MATRIX #18           | 0.226       |
| 34     | GSG-MATRIX     | GSG-MATRIX #19           | 0.221       |
| 35     | GSG-MATRIX     | GSG-MATRIX #24           | 0.207       |
| 36     | GSG-MATRIX     | GSG-MATRIX #25           | 0.205       |
| 37     | NETWORK        | 2-hop physical-SL        | 0.186       |
| 38     | NETWORK        | SS degree (average of A and B) | -0.164 |
| 39     | GENOMIC        | S-score in S. pombe      | 0.145       |
| 40     | NETWORK        | 2-hop SL-SL              | 0.130       |
| 41     | NETWORK        | 2-hop physical-SS        | 0.128       |
| 42     | NETWORK        | 2-hop SS-SS              | 0.100       |
single GI between them. Another is through the use of GI profile similarity. We tested whether the imputation of missing values improves the ability to detect functionally similar genes using GI profile similarity. We used GO Resnik semantic similarity [31] to compute the functional similarity between every pair of genes in the E-MAP and then tested the correlation between functional similarity and GI profile similarity before and after the imputation. Imputation was performed using linear regression and GSG features (excluding features related to functional annotations in order to avoid bias). The results are presented in Figure 7. The imputation improves the correspondence between similarity of GI profiles and functional similarity by 27.6% on average. Interestingly, the difference was most profound in the ER E-MAP.

### Table 3 (Continued)

| Rank | Feature Type | Feature Description | Correlation |
|------|--------------|---------------------|-------------|
| 43   | NETWORK      | 2-hop SL-SS         | 0.088       |
| 44   | GENOMIC     | GO cellular compartment similarity | -0.064     |
| 45   | GENOMIC     | Localization: Golgi | -0.047      |
| 46   | GENOMIC     | MIPS phenotype: Slow-growth | -0.045     |
| 47   | GENOMIC     | Quantitative phenotype correlation | -0.045     |
| 48   | GENOMIC     | Localization: microtubule | -0.039     |
| 49   | GENOMIC     | GO biological process similarity | -0.039     |
| 50   | GENOMIC     | Co-occurrence in any subcellular localization | 0.038     |

The features are sorted by the absolute value of their correlation with measured S-scores. The features are computed between every pair A-B of genes. SL, synthetic lethal; SS, synthetic sick.

### Figure 6

**Functional similarity for different ranges of predicted S-scores.** All the missing values in the ChromBio E-MAP were imputed using linear regression and GSG+MATRIX features and binned into 11 bins. The percent of protein interactions refers to the fraction of gene pairs that had a physical interaction between them reported in the BioGrid database. The average GO biological process semantic similarity was computed as described in [31].
(Figure 7b), despite the fact that it has relatively few missing values (7.33% compared to 34% in the ChromBio E-MAP). We validated that the improvement occurs also when using Wang semantic similarity [32]. The results are shown in Figure S6 in Additional file 1. The imputation improves the correspondence between similarity of GI profiles and functional similarity in seven out of nine cases. The two exceptions occur with the ‘molecular function’ ontology and GI profile correlations in the ER and RNA E-MAPs.

**Predicted genetic interactions within protein complexes**

We next analyzed the predicted landscape of GIs among genes belonging to the same protein complex. Bandyopadhyay et al. [17] studied the ChromBio E-MAP and found that many protein complexes are enriched with either positive or negative GIs, and that complexes enriched with negative interactions commonly carry out essential functions and thus are more likely to contain essential genes. However, several complexes, such as TFIIID, TFIIIF and Mediator, contained a very large number of missing values and therefore could not be reliably studied using the measured interactions. We performed imputation on the ChromBio E-MAP using linear regression and all the features, and inspected the fraction of positive and negative interactions among genes belonging to the same complex.

We selected all the complexes described in a recent yeast protein complex curation [33] that contained at least three genes in the ChromBio set. Of these complexes, 38 contained at least one positive or negative GI after imputation using linear regression and all the features; and 17 (15) were significantly enriched with positive (negative) GIs (false discovery rate < 0.05; see Materials and methods; Figure 8a, b). Bandyopadhyay et al. [17] identified 19 modules (corresponding to putative complexes or pathways) that were enriched for positive interactions and 9 enriched for negative ones. In contrast, we found that the number of complexes enriched with negative interactions is comparable to that of complexes enriched with positive interactions. This is probably because we were able to analyze additional complexes that are enriched with negative interactions (see below).

We were able to significantly increase the number of complexes that have predominantly negative interactions (Figure 8a). Four such complexes are shown in Figure 8c: DNA replication factor C, TFIIIF, RNA polymerase III and TFIIID. Among protein complexes enriched with positive GIs (Figure 8b), most of the interactions were measured ones, with the exception of the SWI/SNF complex, in which we predicted many positive GIs (Figure 8d). Consistent with the results of Bandyopadhyay et al. [17], in six out of the seven complexes in which the majority of the negative interactions were newly predicted ones, at least two-thirds of the complex members are essential. In contrast, none of the members of the SWI/SNF complex are essential.

We emphasize that gene essentiality was not part of the features used for GI prediction. Our results provide further evidence that complexes enriched with negative GIs are likely to carry out essential functions.

**The effect of missing values abundance and distribution on prediction accuracy**

Three scenarios can cause missing values in E-MAP experiments. In the first (‘Random’ model; Figure 9a), some gene pairs are not measured. In the second (‘Submatrix’ model; Figure 9b), all the interactions among a certain subset of genes (for example, essential genes) are missing. In the third scenario (‘Cross’ model; Figure 9c), all the interactions...
among two disjoint subsets of genes are missing. This last scenario arises, for example, if two E-MAPs that share a subset of their genes are combined into a new large E-MAP: all the interactions between genes that did not appear together in one original E-MAP are missing. The GSG+MATRIX features that we use rely heavily on ‘borrowing’ interaction data from similar genes. Hence, we compared the performance of a linear regression using these features alone or in combination with all other features in the three scenarios: for $X = 5 \sim 90$ we hid $X\%$ of the E-MAP measurements (a) randomly; (b) by first selecting a random subset of the genes and then hiding all the interactions between them; or (c) by first selecting two random disjoint sets of genes of equal size and then hiding all the interactions between them. Note that in the ‘Cross’ model it is not possible to hide more than 50% of the data. The ER E-MAP was used in this test, as it contained the fewest missing values.

The results are presented in Figure 9d, e. Our predictions were reasonably accurate ($r > 0.4$) when up to 50% of the E-
MAP values were hidden for the 'Random' and 'Submatrix' models. For the 'Cross' model, performance already deteriorated when 40% of the data were removed. The performance was better than random (which results in correlation 0) even when up to 90% of the data were missing. As could be expected, when the fraction of hidden interactions was up to 40%, the prediction was more accurate in the 'Random' model than the 'Submatrix' model. Surprisingly, this trend was reversed when 50% or more of the data were hidden. A possible explanation for this phenomenon is that the number of common GI partners scales quadratically with the fraction of missing values for all the gene pairs in the first scenario, and scales linearly for some gene pairs in the second scenario (see Text S1 in Additional file 1 for a detailed explanation).

With regard to the utility of our method for a combination of E-MAPs, we find that missing GIs can be predicted quite accurately ($r > 0.4$) when the two E-MAPs share $\geq 64\%$ of their genes (which leads to $\leq 30\%$ missing values). It is expected that as the percentage of missing GIs increases, the inclusion of NETWORK and GENOMIC features will be more helpful. Indeed, the difference between the performance using the GSG+MATRIX features only (Figure 9d) and using all the features (Figure 9e) was small ($<10\%$) as long as $\leq 40\%$ of the data were removed, but rose to above 20% when $\geq 70\%$ of the data were removed.

**Conclusions**

In this study we investigated prediction of quantitative GIs using data from E-MAP experiments. To the best of our knowledge, this is the first study attempting to address this problem. Our results suggest that such imputation is possible...
with about 60% accuracy by combining information from the available GI maps. Adding genomic data contributes only marginally to the prediction accuracy. This finding has important implications for the study of organisms other than *S. cerevisiae*, such as *Schizosaccharomyces pombe* for which two GI maps are already available [11,34], but other genomic data, such as PPIs, are still scarce. Our results show that imputation of missing values in future studies in such organisms will not be seriously affected by the lack of other genomic data.

The strength of the proposed approach is that it borrows information about GIs from related genes. This also underlines one of its limitations: it can only predict GIs among genes that have been studied genetically (that is, they appear in the same E-MAP). This limitation is shared by other methods utilizing only data about GIs [21], which are restricted to predicting GIs among genes that appear in the GI network.

To the best of our knowledge, this is also the first attempt to predict positive GIs. Our results show that the available approaches for predicting negative GIs perform poorly for prediction of positive interactions. While our method provides encouraging results in predicting such interactions, this task is evidently much more difficult than prediction of negative interactions. The accuracy of the best method to predict negative interactions is more than double that of the best method for prediction of positive interactions (0.45 versus 0.2 using the AUPR measure). One possible explanation for this difference in performance is that there are fewer positive interactions in the E-MAPs, and therefore less data points to properly train the classifiers. Another possibility is that the nature of these interactions is more complex than that of the negative GIs, making their prediction a more difficult task. Perhaps other, yet to be discovered features can predict these interactions with better accuracy.

The use of GI maps in yeasts has already led to identification of novel complexes and gene functions, some of which were not recovered by other available methods [10,35-40]. It is thus expected that the use of such maps will increase, and large GI maps will be created for other biological systems (for example, mammalian cell lines) in the near future. As long as these maps remain prone to biological and technical noise, imputation of missing data will play a key role in their computational analysis.

**Materials and methods**

**Data preprocessing**

We used the S-scores reported in the original publications [9-12]. To avoid bias due to extreme S-scores, S-scores below -10 were set to -10 and S-scores above 10 were set to 10. When an open reading frame was represented by more than one deletion strain (for example, a knock-out strain and a strain with a DAmP allele [9]), the strain with the least missing values was chosen. When predicting the type of the GI, following [12], we defined a GI as negative if the S-score was below -2.5 and as positive if the S-score was above 2.

**Network and genomic feature sets**

We now describe the features based on network properties and genomic information that we used. Previous studies that employed these features for GI prediction are listed in Table 1. We used three networks: PPI, and synthetic lethal and synthetic sick networks, all taken from BioGrid [28]. We added to the synthetic lethal network interactions between gene pairs from the analyzed E-MAP that had S-scores ≤ -2.5.

**Physical interaction**

Physical interaction is a binary feature indicating if the proteins interact in the physical network.

**Network degree**

Network degree is the number of neighbors in the PPI, synthetic lethal and synthetic sick networks recorded for each gene. Following [20] we used two features for each network and each gene pair with degrees $d_i$ and $d_j$: the average degree $(d_i + d_j)/2$ and the absolute difference between the degrees, $|d_i - d_j|$.

**Shortest physical path**

The shortest physical path is the length of the shortest path between the proteins in the PPI network.

**Mutual clustering coefficient**

Mutual clustering coefficient was computed as described in [41] using the PPI network.

**Z-hop**

The 2-hop feature was computed as described in [13], using the physical, synthetic lethal and synthetic sick networks.

**Protein complexes**

Protein complexes were taken from the MIPS (Munich Information Center for Protein Sequences) database [42]. Only complexes in which at least three proteins appeared in the analyzed E-MAP were used. For each complex we added a ternary feature indicating how many of the proteins in the gene pair (0, 1 or 2) appeared as part of the complex. Using a newer collection of protein complexes [43] did not significantly affect the prediction performance (results not shown).

**MIPS phenotypes**

*S. cerevisiae* single deletion strain phenotypes (for example, sensitivity to DNA damaging agents) were obtained from MIPS [42]. Only phenotypes shared by at least three genes in the analyzed E-MAP were used. As for protein complexes, we
added a ternary feature for each phenotype and a binary feature indicating whether the gene pair shared any phenotype.

**Quantitative phenotype correlation**

We used the quantitative measurements of single deletion phenotypes described in [44]. For each gene pair, we computed the Pearson correlation between the phenotypic profiles of the genes.

**GO semantic similarity**

Semantic similarity between the annotations of the two genes were computed using the method described in [31]. Similarity was computed separately for each part of the GO - 'biological process', 'molecular function' and 'cellular compartment'.

**Protein sequence similarity**

Translated open reading frames obtained from the Saccharomyces Genome Database [45] were BLASTed for quantifying the protein sequence similarity. The feature equals the -log(E-value) for the best local alignment found (if the best E-value was above 5 the feature was set to 0).

**Subcellular localization**

Subcellular localization for *S. cerevisiae* proteins was obtained from [46]. Only localizations shared by at least three genes in the analyzed E-MAP were used.

**S-score in *S. pombe***

For each gene pair this feature contained the S-score between the orthologs of the genes in *S. pombe* (if available in the Pombe E-MAP [11]). Orthology assignments between *S. cerevisiae* and *S. pombe* were taken from [11].

**mRNA expression**

We computed the Pearson correlation between the gene expression profiles of the genes in seven mRNA expression datasets [47-53]. Overall, 811 gene expression profiles were used.

**GSG and GSG-MATRIX features**

For each gene A, we ordered all the other genes based on the similarity between their GI profile and the GI profile of A (using Euclidean distance as a measure of similarity). Gene B is called a GSG of A if it is among the genes most similar to A. A GSG of A is informative about B if the information about its GI with B is available (that is, it is neither missing nor hidden in the cross-validation experiments). The GSG feature set consists of 2 k features: for each gene pair A-B, it contains the S-scores between A and the k highest order GSGs of B that are also informative about A (called GSG #1 through GSG #k for A) and between B and the k top informative GSGs of A (called GSG #1 - k for B; Figure 1b; Figure S7 in Additional file 1). Note that since the gene pairs are not ordered, the k pairs of GSG features are symmetric (that is, GSG #1 for A and GSG #1 for B should be equally informative). Therefore, the small differences we observe between these feature pairs (Table S1 in Additional file 1) probably arise by pure chance. We used k = 5 throughout this study (see Figure S2 in Additional file 1 for the analysis of sensitivity to k).

The GSG-MATRIX feature set contains k² features representing the available S-scores between the top GSGs of A and the top GSGs of B (Figure S7 in Additional file 1). Due to missing values, typically there will be less than k² S-scores available between the top k GSGs of A and the top k GSGs of B. We therefore used the following strategy. Denote by GSGj(A) the i-th GSG of A. In iteration i we added to the feature set the available S-scores between [GSGj(A)] and the i top GSGs of B and between GSGj(B) and the i top GSGs of A. Starting from i = 1, we increased i until k² features were constructed. In each iteration we iteratively increased j from 1 to i - 1 and added the features corresponding to the GIs between [GSGj(A), GSGj(B)] and between [GSGj(B), GSGj(A)]. The iteration was stopped once k² features were obtained. This way, we ensured that the feature set did not contain missing values and preferred features corresponding to genes more similar to A and B.

**Classifiers**

We used the classifiers implemented in Weka [54]. A fast implementation of Random Forest was taken from [55]. All the classifiers were used with default parameters. For GI class prediction, the linear regression predicted values were treated as negative if the predicted score was ≤ -2.5 and positive if it was ≥ 2.

**Prediction of GIs using a diffusion kernel**

We constructed a synthetic lethality network by combining interactions from BioGrid with interactions between genes whose S-score in the E-MAP was ≤ -2.5. The network was analyzed using supplementary MATLAB code from [21]. G* kernel was used to predict negative GIs, and G⁺ to predict positive GIs. Note that the G⁺ was originally proposed for prediction of PPIs, but we found that it performed better than G⁺ for prediction of positive interactions (a task that was not addressed by Qi et al. [21]). We tested different values of the γ parameter between 1 and 40 and selected for each E-MAP the parameter value that obtained the best AUC.

**Cross-validation**

The gene pairs with measured values in the analyzed E-MAP were divided into ten random groups. In each iteration (fold), nine of the groups were used to train the classifiers and their performance was evaluated using the tenth group. In order to enhance computational efficiency, only 30% of the ChromBio and 50% of the RNA E-MAP measured gene pairs were used as the training set in each fold (the subset used was chosen randomly).
Enrichment of protein complexes with positive or negative interactions

We used the following procedure to evaluate if a protein complex C is enriched with positive (negative) interactions. Suppose C contains k positive interactions. We generated an unweighted graph \(G_p\) in which the nodes are the genes in the E-MAP and an edge connects u and v in \(G_p\) if there is a positive interaction between u and v in the E-MAP. We then generated 1,000 random degree preserving graphs using edge shuffling [56]. The empirical \(P\)-value of the enrichment of C with positive interactions was estimated as the fraction of these graphs that contained at least k edges between the nodes in C. An analogous procedure was used to estimate the significance of the enrichment of C with negative interactions. Complexes enriched with a false discovery rate < 0.05 were selected using the Benjamini-Hochberg procedure [57].

Abbreviations

AUC: area under curve; AUPR: area under the precision-recall curve; E-MAP: epistatic miniarray profile; ER: endoplasmic reticulum; GI: genetic interaction; GO: Gene Ontology; GSG: genetically similar gene; PPI: protein-protein interaction; ROC: receiver operating characteristic; SGA: systematic genetic analysis.

Authors’ contributions

IU, NJK and RS conceived the study, and participated in its design. IU and RS developed the prediction method, analyzed the results and wrote the manuscript. All authors read and approved the final manuscript.

Additional files

The following additional data are available with the online version of this paper: a Word document including Text S1, Figures S1-S7, and Table S1 (Additional file 1); S-scores in ChromBio, ER and RNA E-MAPs after imputation of missing values (Additional file 2).

Acknowledgements

We thank Roye Rozov for comments on an early version of this manuscript. Ron Shamir was supported in part by the Raymond and Beverly Sackler Chair in Bioinformatics and by the Israel Science Foundation (grant no. 802/08). Igor Ulitsky was supported in part by a fellowship from the Edmond J Safra Bioinformatics Program at Tel Aviv University.

References

1. Segre D, Deluna A, Church GM, Kishony R: Modular epistasis in yeast metabolism. Nat Genet 2005, 37:77-83.
2. Beyer A, Bandyopadhyay S, Ideker T: Integrating physical and genetic maps: from genomes to interaction networks. Nat Rev Genet 2007, 8:699-710.
3. Mani R, Sr. Onge RP, Hartman JLT, Giaever G, Roth FP: Defining genetic interaction. Proc Natl Acad Sci USA 2008, 105:3461-3466.
4. Sr Onge RP, Mani R, Oh J, Proctor M, Fung E, Davis RW, Nislow C, Roth FP, Giaever G: Systematic pathway analysis using high-resolution fitness profiling of combinatorial gene deletions. Nat Genet 2007, 39:199-206.
5. Tong AH, Evangelista M, Parsons AB, Xu H, Bader GD, Page N, Robinson M, Raghibizadeh S, Hogue CW, Bussey H, Andrews B, Tyers M, Boone C: Systematic genetic analysis with ordered arrays of yeast deletion mutants. Science 2001, 294:2364-2368.
6. Tong AH, Lesage G, Bader GD, Ding H, Xu H, Xin X, Young J, Berriz GF, Brost RL, Chang M, Chen Y, Cheng X, Chua G, Friesen H, Goldberg DS, Haynes J, Humphries C, He G, Hussein S, Ke L, Krogan N, Li Z, Levinson JN, Lu H, Menard P, Munyana C, Parsons AB, Ryan O, Tonikian R, Roberts T, et al.: Global mapping of the yeast genetic interaction network. Science 2004, 303:808-813.
7. Pan X, Yuan DS, Wang X, Xiong D, Wang X, Sookhai-Mahadeo S, Bader JS, Hieter P, Spencer F, Boeke JD: A robust toolkit for functional profiling of the yeast genome. Mol Cell 2004, 16:497-496.
8. Pan X, Ye P, Yuan DS, Wang X, Bader JS, Boeke JD: A DNA integrity network in the yeast Saccharomyces cerevisiae. Cell 2006, 106:109-118.
9. Schuldiner M, Collins SR, Thompson NJ, Denic V, Bhamidipati A, Punna T, Ihmels J, Andrews B, Boone C, Greenblatt JF, Weissman JS, Krogan NJ: Exploration of the function and organization of the yeast early secretory pathway through an epistatic miniarray profile. Cell 2005, 123:507-519.
10. Collins SR, Miller KM, Maas NL, Rogeu A, Fillingham J, Chu CS, Schuldiner M, Gebbia M, Recht J, Shales M, Ding H, Xu H, Han J, Ingvarsdottir K, Cheng B, Andrews B, Boone C, Berger SL, Hieter P, Zhang Z, Brown GW, Ingles CJ, Emili A, Allis CD, Toczyski DP, Weissman JS, Greenblatt JF, Krogan NJ: Functional dissection of protein complexes involved in yeast chromosome biology using a genetic interaction map. Nature 2007, 446:806-810.
11. Rogeu A, Bandyopadhyay S, Zoffal M, Zhang X, Fischer T, Collins SR, Qu H, Shales M, Park HO, Hayles J, Hoe KL, Kim DJ, Ideker T, Greaves SJ, Weissman JS, Krogan NJ: Conservation and rewiring of functional modules revealed by an epistatic map in fission yeast. Science 2008, 322:405-410.
12. Wilmes GM, Bergkessel M, Bandyopadhyay S, Shales M, Braberg H, Cagney G, Collins SR, Whitworth GB, Kress TL, Weissman JS, Ideker T, Greaves SJ, Weissman JS, Krogan NJ: A genetic interaction map of mRNA processing factors reveals links between Semi1/Dss1-containing complexes and mRNA export and splicing. Mol Cell 2008, 32:735-746.
13. Zhang LV, Wang SL, Zhang LV, Tong AH, Li Z, Goldberg DS, King OD, Lesage G, Vidal M, Andrews B, Bussey H, Boone C, Roth FP: Combining biological networks to predict genetic interactions. Proc Natl Acad Sci USA 2004, 101:15682-15687.
14. Zhang LV, King OD, Wong SL, Goldberg DS, Tong AH, Lesage G, Andrews B, Bussey H, Boone C, Roth FP: Motifs, themes and thematic maps of an integrated Saccharomyces cerevisiae interaction network. J Biol 2005, 4:6.
15. Kelley R, Ideker T: Systematic interpretation of genetic interactions using protein networks. Nat Biotechnol 2005, 23:561-566.
16. Ulitsky I, Shamir R: Pathway redundancy and protein essentiality revealed in the Saccharomyces cerevisiae interaction network. Mol Syst Biol 2007, 3:104.
17. Bandyopadhyay S, Kelley R, Krogan NJ, Ideker T: Functional maps of protein complexes from quantitative genetic interaction data. PLoS Comput Biol 2008, 4:e1000065.
18. Ulitsky I, Shlomi T, Kupiec M, Shamir R: From E-MAPs to module maps: dissecting quantitative genetic interactions using physical interactions. Mol Syst Biol 2008, 4:209.
19. Zhong W, Sreenberg PW: Genome-wide prediction of C. elegans genetic interactions. Genome Res 2007, 17:1481-1484.
20. Paladugu SR, Zhao S, Ray A, Raval A: Mining protein networks for synthetic genetic interactions. BMC Bioinformatics 2008, 9:426.
21. Qi Y, Suhail Y, Lin YY, Boeke JD, Bader JS: Finding friends and enemies in an enemies-only network: a graph diffusion kernel for predicting novel genetic interactions and co-complex membership from yeast genetic interactions. Genome Res 2008, 18:1991-2004.
22. Chipman KC, Singh AK: Predicting genetic interactions with random walks on biological networks. BMC Bioinformatics 2009, 10:17.
23. Ye P, Poyser BD, Pan X, Boeke JD, Spencer FA, Bader JS: Gene function prediction from congruent synthetic lethal interactions in yeast. Mol Syst Biol 2005, 1:2005.0026.
24. Collins SR, Schuldiner M, Krogan NJ, Weissman JS: A strategy for extracting and analyzing large-scale quantitative epistatic interaction data. Genome Biol 2006, 7:R63.
25. Wang Y, Witten I: Induction of model trees for predicting continuous classes. In Induction of Model Trees for Predicting Continuous Classes Handbook. The University of Waikato; 1996.

26. Van Rijbergen CJ: Information Retrieval Newton, MA: Butterworth-Heinemann; 1979.

27. Chua HN, Sung WK, Wong L: Exploiting indirect neighbours and topological weight to predict protein function from protein-protein interactions. Bioinformatics 2006, 22:1623-1630.

28. Stark C, Breitkreutz BJ, Reguly T, Boucher L, Breitkreutz A, Tyers M: BioGRID: a general repository for interaction datasets. Nucleic Acids Res 2006, 34:D535-539.

29. Ozier O, Amin N, Ideker T: Global architecture of genetic interactions on the protein network. Nat Biotechnol 2003, 21:490-491.

30. Lord PW, Stevens RD, Brass A, Goble CA: Investigating semantic similarity measures across the Gene Ontology: the relationship between sequence and annotation. Bioinformatics 2003, 19:272-283.

31. Resnik P: Semantic similarity in a taxonomy: An information-based measure and its application to problems of ambiguity in natural language. J Artificial Intelligence Research 1999, 11:95-130.

32. Wang JZ, Du Z, Payatakeel R, Yu FS, Chen CF: A new method to measure in a semantic similarity of GO terms. Bioinformatics 2007, 23:1274-1281.

33. Pu S, Wong J, Turner B, Cho E, Wodak SJ: Up-to-date catalogues of yeast protein complexes. Nucleic Acids Res 2009, 37:825-831.

34. Dixon SJ, Fedyshyn Y, Koh JL, Prasad TS, Chahwan C, Chua G, Toufighi K, Baraychikova A, Hayles J, Hoe KL, Kim DU, Park HO, Myers CL, Pandey A, Durocher D, Andrews BJ, Boone C: Significant conservation of synthetic lethal genetic interaction networks between distantly related eukaryotes. Proc Natl Acad Sci USA 2008, 105:16653-16658.

35. Jonikas MC, Collins SR, Denic V, Oh E, Quan EM, Schmid V, Weibe-Dawson K, Beem KD, Greenblatt JF, Harbeck J, Harte S, Hill DP, Preiss J, Schulze-Eisinger F, Weng S, Botstein D: Global analysis of prote in localization in budding yeast. Cell 2006, 1275-1283.

36. Hamilton: The University of Waikato; 1996.

37. Schuldiner M, Meizel S, Schmid V, Botstein D, Elledge SJ, Brown PO: Genomic expression responses to DNA-damaging agents and the regulatory role of the yeast ATR homolog Meclp. Mol Cell 2001, 12:2987-3003.

38. Gasch AP, Spellman PT, Kao CM, Carmel-Harel O, Eisen MB, Storz G, Botstein D, Brown PO: Genomic expression programs in the response of yeast cells to environmental changes. Mol Cell Biol 2000, 20:4124-4137.

39. Roberts CJ, Nelson B, Marton MJ, Stoughton R, Meyer MR, Bennett HA, He YD, Dai H, Walker WL, Hughes TR, Tyers M, Boone C, Friend SH: Signalling and circuitry of multiple MAPK pathways revealed by a matrix of global gene expression profiles. Science 2000, 287:873-880.

40. Hughes TR, Marton MJ, Jones AR, Roberts CJ, Stoughton R, Armour CD, Bennett HA, Coffey E, Dai H, Ye YD, Kidd MJ, King AM, Meyer MR, Slade D, Lum PY, Stepaniants SB, Shoemaker DD, Gachotte D, Chakraborty K, Simon J, Bard M, Friend SH: Functional discovery via a compendium of expression profiles. Cell 2000, 102:109-126.

41. Spellman PT, Sherlock G, Zhang MQ, Iyer VR, Anders K, Eisen MB, Brown PO, Botstein D, Futcher B: Comprehensive identification of cell cycle-regulated genes of the yeast Saccharomyces cerevisiae by microarray hybridization. Mol Biol Cell 1999, 9:3273-3297.

42. O’Rourke SM, Herskowitz I: Unique and redundant roles for HOG MAPK pathway components as revealed by whole-genome expression analysis. Mol Cell Biol 2004, 15:532-542.

43. Causton HC, Ren B, Koh SS, Harbison CT, Kanin E, Jennings EG, Lee TI, True HL, Lander ES, Young RA: Remodeling of yeast genome expression in response to environmental changes. Mol Cell Biol 2001, 21:323-337.

44. Frank E, Hall M, Trigg L, Holmes G, Witten I: Data mining in bioinformatics using Weka. Bioinformatics 2004, 20:2479-2481.

45. Fast Random Forest Project [http://code.google.com/p/fast-random-forest/]

46. Shen-Or SS, Milo R, Mangan S, Alon U: Network motifs in the transcriptional regulation network of Escherichia coli. Nat Genet 2002, 31:64-68.

47. Benjamini Y, Hochberg Y: Controlling the false discovery rate: a practical and powerful approach to multiple testing. J Roy Stat Soc Methodological 1995, 57:289-300.

48. Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM, Davis AP, Dolinski K, Dwight SS, Eppig JT, Harris MA, Hill DP, Issel-Tarver L, Kasarskis A, Lewis S, Matese JC, Richmond JE, Ringwald M, Rubin GM, Sherlock G: Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. Nat Genet 2000, 25:25-29.

49. Witten I, Frank E: Data mining: practical machine learning tools and techniques with Java implementations. ACM SIGMOD Record 2002, 31:76-77.

50. Wang Y, Witten I: Induction of model trees for predicting continuous classes. J Roy Stat Soc Methodological 1995, 57:289-300.

51. Krogan NJ, Keogh MC, Datta N, Sawa C, Ryan OW, Ding H, Haw RA, Poonootao J, Tong A, Canadien V, Richards DP, Wu X, Emilai A, Hughes TR, Buratowski S, Greenblatt JF: A Snf2 family ATPase complex required for recruitment of the histone H2A variant Htz1. Mol Cell 2003, 12:1565-1576.

52. Cessie SL, Houwelingen JC: Ridge estimators in logistic regression. Applied Statistics 1992, 41:191-201.