Analyzing the heterogeneous structure of the genes interaction network through the random matrix theory

Nastaran Allahyari¹, Ali Hosseiny¹, Nima Abedpour², and G. Reza Jafari¹*

¹Department of Physics, Shahid Beheshti University, G.C., Evin, Tehran 19839, Iran
²Department of Translational Genomics, University of Cologne, Weyertal 115b, 50931 Cologne, Germany
* g.jafari@sbu.ac.ir

ABSTRACT

There have been massive efforts devoted to understanding the collective behavior of genes. In this regard, a wide range of studies has focused on pairwise interactions. Understanding collective performance beyond pairwise interactions is a great goal in this field of research. In this work, we aim to analyze the structure of the genes interaction network through the random matrix theory. We focus on the Pearson Correlation Coefficient network of about 6000 genes of the yeast Saccharomyces cerevisiae. By comparing the spectrum of the eigenvalues of the interaction networks itself with the spectrum of the shuffled ones, we observe clear evidence that unveils the existence of the structure beyond pairwise interactions in the network of genes. In the global network, we identify 140 eigenvectors that have unnormal large eigenvalues. It is interesting to observe that when the essential genes as the influential and hubs of the network are excluded, still the special spectrum of the eigenvalues is preserved which is quite different from the random networks. In another analysis we derive the spectrum of genes based on the node participation ratio (NPR) index. We again observe noticeable deviation from a random structure. We indicate about 500 genes that have high values of NPR. Comparing with the records of the shuffled network, we present clear pieces of evidence that these high values of NPR are a consequence of the structures of the network. We have tabled the list of such genes.

Introduction

Understanding the pairwise interaction of genes is just the building block to study the heterogeneous structure of the whole gene-gene interaction network. In a gene-gene interaction network, the interaction between two genes is affected by the other interconnections they participate in. The last two decades have witnessed extensive researches concerning the influences of genes on each other¹–⁴. Uncovering the mechanism leading to the collective behavior of genes is considered a significant subject in biology. Here, we explore the weighted signed undirected networks of genetic interaction profile similarities. In this paper, the vital questions that have to be asked are: Do our genetic interaction networks display heterogeneous structures? Regarding the spectrum of eigenvalues and their corresponding eigenvectors, is there some specific evidence to clarify the deviation from randomness? Moreover, we are interested in identifying genes that play a leading role in forming heterogeneities in the network. In the literature, some genes are identified as essential genes against nonessential genes. As a critical question, we are interested to know if we exclude essential genes, is the remained nonessential gene network homogeneous? In other words, do nonessential genes determine their structural role dependent on their interactions with the essential genes, or their interactions have generated a significant nonrandom network. These issues are the basis of this research.

Saccharomyces cerevisiae is a valuable experimental yeast for most aspects of the fundamental study on eukaryotic organisms. Almost all biological processes found in eukaryotes are also existing in Saccharomyces cerevisiae⁵. In this work, we explore its genome as a whole system. All gene interactions should be analyzed together, not separated, to understand the involved complexity. Here, we focus on the gene interaction similarity networks of about 5500 genes belonging to the Saccharomyces cerevisiae. Charles Boone and his colleagues have produced the data. Amongst 5500 genes, about 1000 genes are known as essential genes, and the rest of them as nonessential genes. So, we lead our analysis in three groups of the yeast Saccharomyces cerevisiae’s genes, namely, essential, nonessential, and the combination of these two as global. By considering the threshold taken in⁶ to plot the networks, the essential gene similarity network was more densely connected compared with the corresponding nonessential network. So, it can be deduced that these essential genes play the role of hubs in the global interaction network⁷–¹⁰. Moreover, functional relationships on the gene similarity network for essential genes were stronger. On top of that, their power of function prediction provided higher accuracy⁶,¹¹–¹⁴.

In this study, we explore the weighted, undirected, signed genetic interaction networks compared to shuffled ones in the context of random matrix theory (RMT). We are interested in determining the heterogeneities of our gene interaction networks.
and identifying the genes that play a significant role in this structure. The two characteristics employed from RMT argue that participation of all nodes in each event or participation of each node in all events is hugely affected by the structure. The two features utilized in this analysis are, namely, inverse participation ratio (IPR), node participation ratio (NPR) (equation1, equation2). Such analysis may indicate vectors or genes which play a significant role in the collective behavior of genes. Historically random matrix theory was initially introduced by Eugene Wigner13 to study the spectrum of the nuclei of heavy atoms where a large number of nucleons are interacting. In the last two decades, random matrix theory has provided a valuable framework to study complex biological networks.

Amongst all applications of RMT, we exclusively refer to some successes. Spectral fluctuation of protein interaction and co-expression correlation matrices of yeast have shown to follow the description of the Gaussian orthogonal ensemble (GOE) of RMT16, 17. The overall functioning of altered complex molecules, and predicting the connections among the molecules is one of the main objections in modern biology.18 For co-expression networks through RMT, the cellular roles of some unknown genes are predicted in terms of performance19, 20. Because of inadequacy in the theoretical study to study gene interaction networks in cancer cells, it is crucial to predict the behavior of a large complex interaction network from the behavior of a finite size network21. Furthermore, much information about the structure and dynamics of a network is covered in the eigenvalues of its adjacency matrix. As another application of RMT, the localization properties of the gene co-expression network are followed22. In another work Rai and et al., by considering long-range correlation in cancer network along with the localization properties show important structural patterns including functionally significant proteins23. Also, by analyzing protein-protein interactions in diabetes mellitus II, specific structural patterns important for the occurrence of the disease and the top contributing nodes from localized eigenvectors are revealed24. Meantime, investigating gene interaction networks by spectral analysis of the adjacency matrices has been keeping to be focused on various cancer cells25. RMT has helped solve the challenge of revealing all of the gene-gene interactions that are large in number26. As another application of RMT in biology, in27 the noises in lung cancer gene expression data are removed to construct the gene networks. As a recent application of RMT, we can refer28, by using random matrix theory for the eigenvalues and eigenvectors to denoise single-cell data, which provides the opportunity to identify new cellular states. Also, Margaliot and et al. have developed a new theoretical framework using tools from random matrix theory to analyze the steady-state production rate affected by many stochastic “local” factors29. In addition to the application of RMT mentioned above in biology, the invention of this theory occurs in social, political, ecological, and financial networks too30–40.

Regarding all these developments of random matrix theory’s perspective, our particular attention has been attracted to investigate whether an inevitable structure exists in the gene-gene interaction network. If there is, which components can be significant elements due to this structure? In this paper, our path is briefly mentioned below: First, we explore the genetic interaction similarity networks to analyze the existence of heterogeneous structures. The distribution functions of eigenvalues in original and shuffled networks are examined. In random networks, the spectrum of eigenvalues fits a semi-circle probability density function (PDF). Deviation from such behaviors is a sign of structure beyond the pairwise interactions. Next, we study the participation of all genes in each eigenvalue in the gene networks. Considering previous results on structured connectivity in the gene networks, it seems that taking into account the IPR of eigenvalues and exploring them in shuffled networks provides us with more insight into particular functional connectivity in the gene network. At last, we illustrate the node participation ratio of each node in all eigenvalues and suppose that there are probably some differences with the NPR of genes in shuffled networks. While comprehending the structure by exploring functional connectivities, our study suggests a new list of genes notable in the structure and their annotation of biological processes.

Data description

We have used the preprocessed data that is provided by Charles Boone and his colleagues and is public at http://boonelab.ccbr.utoronto.ca/supplement/costanzo2016/. Among the all available data files preprocessed, we have used data file S3 "Genetic interaction profile similarity matrices". The following preprocessing steps were performed to provide this data file:

(1) Based on the rate of growth of a colony size including two specific mutated genes, the genetic interaction score of those two mutated genes has been obtained.
(2) Each gene as a query strain is crossed to an ordered array of other strains. Then, a genetic interaction profile for that query gene is achieved.
(3) By calculating the Pearson correlation coefficient, the similarity between each two genetic interaction profiles has been produced. (3-1) In the PCC matrix, the positive value for every two genes means that how much their profiles are functionally similar to each other. Moreover, the larger the PCC value of the two genes, the more similarity between them. On the other hand, the negative value of the PCC matrix for two genes implies contrastingly dissimilarity. Also, elements with zero value say that there is no relation between those two genes functionally. (3-2) There are three PCC matrices. By considering all two essential profiles(essential PCC matrix), and only nonessential strains (nonessential PCC matrix), besides both of them essential
and nonessential strains (global PCC matrix) have been provided. The size of essential, nonessential, and global similarity matrices are ≈1000, 4500, and 5500, respectively. All our matrices here are undirected, signed, and weighted adjacency matrices. The preprocessing procedure on data to reach the networks is algorithmically plotted in Fig.1.

---

**Figure 1.** The algorithmic plot for the procedure of obtaining the genetic networks.
Methods

**Random Matrix Theory: Spectral Analysis.** Our approach to studying the genetic interaction similarity networks is random matrix theory (RMT) that provides a framework to go beyond the assumption that pair interactions are independent of each other in networks. When a large number of elements interact, and a random relation mainly drives the interactions, and the PDF of the components of the interaction matrix is Gaussian, then the PDF of eigenvalues has a semi-circle shape. In a random network with zero mean value of its eigenvalues, all eigenvalues are collected around zero. But in a random network with a nonzero mean value of its eigenvalues, there is an eigenvalue just out of the bulk. In the shuffled network similar to the random ones, the distribution of eigenvalues has the same form. In a heterogeneous structure, the largest eigenvalue plays an outstanding role since it carries data about global structure. Despite the shuffled networks, the original networks have a large class of eigenvalues out of the bulk. To define the boundary of the bulk, we shuffle the matrix, then put the largest eigenvalue aside. This experiment is repeated 100 times. Then the mean value of the borders and the standard variation of them are worked out. When the boundary of the bulk is defined, we reconsider the spectrum of the eigenvalues of the original matrix. All eigenvalues at least three standard variations away from the border are considered as the eigenvalues outside of the bulk. This phenomenon means that these networks have communities. So, the structure of the original networks is not random.

**IPR and NPR.** We used the inverse participation ratio (IPR) to analyze the localization properties of the eigenvectors. Bell and Dean introduced IPR initially in the context of atomic physics. Throughout this study, we have conducted the eigenvectors and eigenvectors to determine the IPR which tries to provide a measure for participation rates of all nodes in each eigenvalue. IPR of each eigenvalue \( \lambda_k \) is given by

\[
IPR_k = \sum_{n=1}^{N} (u_n^k)^4
\]  

The \( u_n^k \) stands for components of the related eigenvector, and \( N \) is the number of nodes. The summation is over all elements in each eigenvector. The IPR shows two extreme cases: 1) a vector with equal elements \( (u_n^k = 1/\sqrt{N}) \) has \( IPR_k = 1/N \), though 2) a vector, with one element \( (u_n^k = 1) \) and the remainders zero has \( IPR_k = 1 \). Thus, the IPR expresses the reciprocal of the number of eigenvector elements that contribute remarkably. Despite the IPR that is a characteristic of each eigenvector, the Node Participation Ratio (NPR) is a characteristic of each node. To find it out, we calculate the sum of its role in all eigenvectors as

\[
NPR_n = \sum_{k=1}^{N} (u_n^k)^4
\]

The summation is over the participation of a node in all eigenvalues. If a node has a random performance in all eigenvalues, then its NPR is small in extreme case equal to \( 1/N \). If, however, a node has unique roles in a few numbers of eigenvectors, then its NPR is high that at extreme equals one. So the great value of NPR means that a node plays a critical role in a specific biological process. To identify genes that have irregular large values of NPR, we shuffle the network. When the network is shuffled, we consider the largest value of NPR. We provide an ensemble of 100 iterations. The mean value plus three standard variations of the largest NRPs of the shuffled matrices is the bound. The original matrix however has a tail of genes that have higher values of the bound.

Data availability

Data is publicly available at [http://boonelab.ccb.r.utoronto.ca/supplement/costanzo2016/](http://boonelab.ccb.r.utoronto.ca/supplement/costanzo2016/). From the SupplementaryOnlineMaterialpackage, the "Data File S3_Genetic interaction profile similarity matrices" has been used.

Results

At first, a brief explanation of the data should be mentioned. The data studied is related to the essential and nonessential genes of the yeast *Saccharomyces cerevisiae*. Functionally, essential genes play a vital role in the bioprocesses. Locally, by applying the same threshold taken in, essential genes display 25 times as many interactions as nonessential genes. When two genes are mutated, in terms of the size of the colony including them, the genetic interaction score between them is obtained. Each gene as a query is crossed to a set of genes as an array. So each gene has an interaction profile with the other genes. By calculating the Pearson correlation coefficient of these genetic interaction scores, the genetic interaction similarity matrices have been provided. There are three genetic interaction similarity matrices. For all pairs of essential genes, for all pairs of nonessential genes, and all possible pairs of strains (essential-essential, nonessential-nonessential, and essential-nonessential) similarity matrices have been calculated. The positive (negative) sign in the PCC matrix for two genes \( i \) and \( j \) clarify their genetic interaction profiles are functionally similar (dissimilar) to each other. Also, the weight of this quantity shows the strength of this similarity. Moreover, when the value of PCC for two genes is zero, it means there is no relation between those two genes functionally.
**An overview of the gene interaction networks.** First, to have a vision of the construction of the genetic interaction similarity networks, we reconstructed and depicted them in Fig. 2 previously presented by Costanzo et al.\(^6\). The genetic interaction similarity networks are constructed by PCC matrices. Since a threshold is taken in their study to plot the similarity networks, if the genetic interaction profile similarity of the two strains is more than 0.2, they are connected, otherwise, there is no connection between them. It should be mentioned that this threshold has only been used to plot the networks, not in all other parts of our analysis. These networks are graphed using a spring-embedded layout algorithm in the Cytoscape software\(^47\). Whatever two genes share more similar genetic interaction profiles, they are positioned closer to each other. Otherwise, genes with smaller similar genetic interaction profiles are positioned farther from each other. The genetic profile similarity network for the essential genes, for nonessential genes, and global genetic profile similarity network including all nonessential and essential genes is constructed. By looking at Fig. 2, some results are inferred. First of all, as we expect, degrees of essential genes are distinguishably higher than nonessential ones. In the global network, the existence of hubs is apparent\(^48-55\). A quantitative analysis, however, is needed for a concrete conclusion.

![Networks of genetic interaction profile similarities](image)

**Figure 2. Networks of genetic interaction profile similarities.** From left to right: Essential similarity network, Nonessential similarity network, Global similarity network.

**Eigenvalues distribution of networks.** Now, a couple of questions arise: How do we evaluate the heterogeneities of the structures of the network? What happens if we analyze the nonessential gene interaction network individually and separated it from the essential genes as hubs? Are we left with a homogenous network with a random structure, then? To answer these questions, we can use spectral methods to look over its spectrum of eigenvalues\(^56\). If the pairwise interaction of genes does not have a higher level of structure, then its matrix should have properties of random matrices. From random matrix theory, we know that for a system that consists of a large number of elements, if the structure is limited to the pairwise level without a higher scale structure and if the probability density function (PDF) of the pairwise interactions comes from a Gaussian distribution then the PDF of eigenvalues has a semi-circle shape that centers around zero. In some systems, heterogeneities relate to the tail of the network. In other words, heterogeneities mainly belong to the hubs of the network. In economics, for example, when we draw the wealth distribution, the main body is log-normal. The tail, however, is power-law. In this work, we first work out the distribution of eigenvalues of the genetic interaction similarity networks depicted in Fig. 3 in green bars. We then shuffle the adjacency matrix. In the shuffling process, two elements of the matrix are chosen randomly and are exchanged. As a result, neither the value of links nor their PDF is modified. But, the correlation between links dissolves. As a result, when the process is complete, the shuffled network has random connections with no specific structure\(^57\). If we recalculate the spectrum of the eigenvalues we end up with a distribution of eigenvalues depicted in purple bars in Fig. 3. As can be seen, the spectrum of the eigenvalues has a nice semi-circle bulk. This analysis has been performed on the essential gene network, nonessential gene network, and global gene network. The serious difference between the spectrum of the genetic interaction similarity networks and their shuffled networks leads us to a clear conclusion that the genetic interaction similarity networks have a structure far from randomness. So, significant information should be carried by the structure of the genetic interaction similarity networks beyond the local pairwise interactions. About the second question, the role of essential genes is so important in the network that their sole annihilation leaves a phenotype footprint in the reproduction process. In our work, however, we are interested in genes whose sole role is not so important that leave a phenotype footprint but play role in shaping the heterogeneities of the network from a random matrix theory perspective. Extracting information from the rich pairwise interaction network will remain a hot topic in the field. In this work, however, we emphasize that in the dynamics of systems, the eigenvectors with the largest eigenvalues carry important information about the outcome of the dynamics. For example, it has been shown that the largest eigenvalue addresses the stability of the large interacting systems such as ecosystems\(^41\). For more information about the role of the largest eigenvalue see\(^42,58\) and references therein. In random
matrices, the largest eigenvalue could in general have a value much larger than the other eigenvalues. Despite the shuffled network, the genetic interaction similarity networks possess a large number of eigenvalues that have large values\textsuperscript{59}. Actually, despite the shuffled network, the global network of genetic interaction similarity has 140 eigenvalues out of the bulk of the shuffled network. Though this number is small in comparison to all its eigenvalues(∼5500), their related eigenvectors can carry meaningful information concerning the system.

![Diagram showing the spectrum of eigenvalues for different networks](image)

**Figure 3.** The spectrum of the eigenvalues of the genetic interaction profile similarities matrices are in green and of their shuffled counterpart are in purple. From left to right: Essential gene network, Nonessential gene network, Global gene network.

**Inverse Participation Ratio (IPR) and Node Participation Ratio (NPR) analysis.** Now a question arises: whether some few nodes have a critical role in shaping the structure of large eigenvalues or a relatively high number of nodes take part there. To answer this question, we calculate the inverse participation ratio (IPR) of eigenvalues. The IPR of the eigenvalues of the networks and their shuffled ones have been depicted in the first row of Fig.4. As can be seen for all of them, i.e., essential gene network, nonessential gene network, and global gene network, the IPR of eigenvectors have a moderate value. In other words, neither it can be claimed all nodes have taken part, nor a small portion of them have taken part to form regular eigenvectors. In all three cases, as we expect in the shuffled network, almost all nodes take part in the eigenvector related to the greatest eigenvalue. In the original networks, the IPR of the greatest eigenvalue is not noticeably more than the other eigenvalues. This issue is another evidence that for this interacting system, no special eigenvector can lead the trend of the network. Though no eigenvalue significantly outpaces the other eigenvalues, still, we expect some genes to play a more critical role.

To indicate significant genes in the collective behaviors, we calculate the node participation ratio (NPR) of each gene. NPR designates to identify if a gene has randomly taken part in a large number of eigenvectors, or has played a significant role in a small portion of eigenvectors. We calculated the NPR of all genes and depicted the spectrum in the second row in Fig.4. As can be seen for all the networks, i.e., essential gene network, nonessential gene network, and global gene network, the NPR of genes have been sorted based on the NPR value in the original networks in green. As can be seen in this sorted spectrum, NPR grows very smoothly for the dominant part of the genes and soars sharply in the tail of it. The end of the spectrum indicates few genes which have significant values for NPR and thereby have information about the structure of the networks. In other words, tail indicates genes that have selected relatively a small portion of eigenvectors to take part. So, these genes have a critical influence on forming heterogeneity of the network. We depicted the NPR of each gene in the shuffled one in purple color. As can be seen, despite the PCC network, in the shuffled one, the NPR of nodes fluctuates around a mean value. This issue proves that genes that have high amounts of NPR in the tail of the spectrum have information about the structure of the network that is lost when shuffled. We indicated 493 genes including both essential and nonessential allele names that have the highest values of NPR and have inserted them in two tables in the supplementary file. Besides that their gene ontology has been checked through the Saccharomyces Genome Database (SGD) there. The high NPR genes and the corresponding bioprocesses performed by them based on data files published by Charles Boone’s lab are presented at the end of the paper in a table.1. Through the pie chart in Fig.5, the percentage of high NPR essential genes and nonessential genes annotating corresponding bioprocesses is represented. It is observable that in both gene networks, the highest percentage of high NPR genes are related to mitosis and chromosome segregation bioprocess.
Discussion

This study has analyzed the undirected weighted signed networks of genetic interaction of Saccharomyces cerevisiae. We followed our questions in the context of random matrix theory (RMT). In the last decades, network analysis to study collective behaviors in biological systems\textsuperscript{60, 61} has questioned the unavoidable impact of the genes on each other through the structure constructed. Here, the vital role that the structure beyond pairwise interactions plays in real-world complex networks is a worthy analysis. Subsequently, our study has shown the following results:

**The heterogeneous structure of our gene interaction similarity networks.** In this work, we analyzed the pairwise interaction network by focusing on its eigenvalues and eigenvectors. Our results interestingly suggest a clear difference between the spectrum of the eigenvalues of the interaction matrices for the essential, nonessential, and the global network with their shuffled counterparts. So, the networks have structures far beyond a random pairwise interaction. We identified 140 eigenvalues that are out of the bulk. They are out of the hands of the shuffled network. So, their existence is a direct consequence of the structures of the network beyond local pairwise interactions. Therefore, our gene interaction networks owe their beautiful complexity. The consequent collective behavior capacities are not only to the number of genes but also the interactions between them. The eigenvectors of the matrix are orthogonal. So one may expect they are related to the distinct multifactorial bioprocesses. Hence, we leave it as an open question whether eigenvectors with large eigenvalues correspond to some multifactorial biological processes. Answering such a question needs extensive studies in the future.

**The existence of sub structures: Inverse Participation Ratio, a measurement for participation rates of all nodes in each eigenvalue (The first row in Figure.4).** Regarding the IPR of original networks, we have observed the following result: In the analysis of the inverse participation ratio, we observed that averagely the inverse participation ratio of the genes in the eigenvalues of the networks is larger than the shuffled ones. This result supports the fact that the networks have a substructure. The IPR of the largest eigenvalue of the global network is 0.00120. Such a number means that 83 nodes have taken part in forming the largest eigenvalue. In comparison, the participation ratio for the largest eigenvalue of the shuffled global network is around 0.00018. Such behavior is observed in both essential and nonessential sub-networks. Higher values for the inverse participation ratio are another sign of structure and heterogeneities of the network.

**The significant genes: Node Participation Ratio, a measurement for participation rates of each node in all eigenvalues (The second row in Figure.4).** The existence of structure in the scales higher than pairwise gene interaction suggests further analysis to identify genes that play a significant role in the higher structure of the interaction network. In our last analysis (NPR), we indicated a method that is new in this field. NPR identifies nodes that play an important role in a small portion of the

---

**Figure 4.** First row: Inverse participation ratio (IPR) of eigenvalues of the matrices themselves are in green, and their shuffled counterparts are in purple. From left to right: Essential gene network, Nonessential gene network, Global gene network. Second row: Node participation ratio (NPR) of genes for the original networks are in green, and their shuffled counterparts are in purple. From left to right: Essential gene network, Nonessential gene network, Global gene network.
Figure 5. Pie chart. Each slice illustrates the percentage of high NPR genes in each bioprocess. From up to down:
Essential gene network, Nonessential gene network.

eigenvectors. We observed that similar to the spectrum of eigenvalues, in the spectrum of NPR, a set of genes carry such large values that cannot be seen in the shuffled network. So, these genes have properties that are lost when we shuffle their networks. These genes play an outstanding role in forming a few eigenvectors (Figure 5). It was observable that essential genes have a structure. It was, however, interesting to observe that the nonessential genes as well carry structure. This evidence may lead us to the effect of the structure created by these genes compared to their functional role isolated. A more interesting observation is that the spectrum of both networks is similar. This consideration means that the same biological properties that have led to the special structure of the essential genes have extended its effect to the nonessential ones.

References

1. Szappanos, B. et al. An integrated approach to characterize genetic interaction networks in yeast metabolism. Nat. Gen. 43, 656-662 https://doi.org/10.1038/ng.846 (2011).
2. Cordell, H. J. Detecting gene–gene interactions that underlie human diseases. Nat. Rev. Gen. 10, 6, 392-404. https://doi.org/10.1038/nrg2579 (2009).
3. Tong, A. H. Y., et al. Global mapping of the yeast genetic interaction network. Sci. 303, 5659, 808-813. https://doi.org/10.1126/science.1091317 (2004).
4. Marbach, D., et al. Wisdom of crowds for robust gene network inference. Nat. Meth. 9, 8, 796-804. https://doi.org/10.1038/nmeth.2016 (2012).
5. Parapouli, M., Vasileiadis, A., Afendra, A. S., Hatziloukas, E. Saccharomyces cerevisiae and its industrial applications. AIMS Microbiol. 6, 1,1-31. https://doi.org/10.3934/microbiol.2020001(2006).
6. Costanzo, M., et al. A global genetic interaction network maps a wiring diagram of cellular function Sci. 353, 6306. https://doi.org/10.1126/science.aaf1420 (2016).
7. Blomenand, V. A., et al. Gene essentiality and synthetic lethality in haploid human cells. Sci. 350, 1092-1096 https://doi.org/10.1126/science.aac7557 (2015).
8. Winzeler, E. A., et al. Functional characterization of the S. cerevisiae genome by gene deletion and parallel analysis. Sci. 7, 901–906 https://doi.org/10.1126/science.285.5429.901 (1999).
9. Giaever, G., et al. Functional profiling of the Saccharomyces cerevisiae genome. *Nat.* **418**, 387–391. https://doi.org/10.1038/nature00935 (2002).

10. Wang, T., et al. Identification and characterization of essential genes in the human genome. *Sci.* **350**, 1096-1101. https://doi.org/10.1126/science.aac7041 (2015).

11. Costanzo, M., et al. The Genetic Landscape of a Cell. *Sci.* **327**, 425-431. https://doi.org/10.1126/science.1180823 (2010).

12. Baryshnikova, A., et al. Quantitative analysis of fitness and genetic interactions in yeast on a genome scale. *Nat. Met.* **7**, 1017–1024. https://doi.org/10.1038/nmeth.1534 (2010).

13. Deshpande, R., et al. A comparative genomic approach for identifying synthetic lethal interactions in human cancer. *AACR.* **73**, 20. https://doi.org/10.1158/0008-5472.CAN-12-3956 (2013).

14. Li, Z., et al. Systematic exploration of essential yeast gene function with temperature-sensitive mutants. *Nat. Bio.* **29**, 361-367. https://doi.org/10.1038/nbt.1832 (2011).

15. Wigner, E. P. On a class of analytic functions from the quantum theory of collisions. *Annals of mathematics.* **53**, 1,36-67. https://doi.org/10.2307/1969342 (1951).

16. Luo, F., Srimani, P. K., Zhou, J. Application of Random Matrix Theory to Analyze Biological Data (Springer, New York, NY, 2011).

17. Luo, F., Zhong, J., Yang, Y., Zhou, J. Application of random matrix theory to microarray data for discovering functional gene modules. *Phys. Rev. E.* **73**, 031924. https://doi.org/10.1103/PhysRevE.73.031924 (2006).

18. Rai, A., Pawar, A. K., Jalan, S. Network spectra for drug-target identification in complex diseases: new guns against old foes. *Applied Network Science.* **3**, 51. https://doi.org/10.1007/s41109-018-0107-y (2018).

19. Luo, F., Yang, Y., Zhong, J., Gao, H., Khan, L., Thompson, D. K., Zhou, J. Constructing gene co-expression networks and predicting functions of unknown genes by random matrix theory. *BMC Bioinformatics.* **8**, 299. https://doi.org/10.1186/1471-2105-8-299 (2007).

20. Frost, H. R., Amos, C. I., Moore, J. H. A global test for gene-gene interactions based on random matrix theory. *Genetic epidemiology.* **40**, 689-701. https://doi.org/10.1002/gepi.21990 (2016).

21. Kikkawa, A. Random Matrix Analysis for Gene Interaction Networks in Cancer Cells. *Sci. Rep.* **8**, 10607. https://doi.org/10.1038/s41598-018-28954-1 (2018).

22. Jalan, S., Solymosi, N., Vattay, G., Li, B. Random matrix analysis of localization properties of gene coexpression network. *Phys. Rev. E.* **81**, 046118. https://doi.org/10.1103/PhysRevE.81.046118 (2010).

23. Mano, V., Jalan, S. Randomness and preserved patterns in cancer network. *Sci. Rep.* **4**, 6368. https://doi.org/10.1038/srep06368 (2014).

24. Rai, A., Shinde, P., Jalan, S. Prognostic interaction patterns in diabetes mellitus II: A random-matrix-theory relation. *Phys. Rev. E.* **92**, 022806. https://doi.org/10.1103/PhysRevE.92.022806 (2015).

25. Kikkawa, A. Spectral analysis for gene communities in cancer cells. *Complex Networks.* **8**, 1. https://doi.org/10.1093/comnet/cnaa005 (2020).

26. Margaliot, M., Huleihel, W., Tuller, T. Variability in mRNA translation: a random matrix theory approach. *Sci. Rep.* **11**, 5300. https://doi.org/10.1038/s41598-021-84738-0 (2021).

27. Aparicio, L., Bordyuh, M., Blumberg, A. J., Rabadan, R. A Random Matrix Theory Approach to Denoise Single-Cell Data. *Patterns.* **1**, 3-10035. https://doi.org/10.1016/j.patter.2020.10035 (2020).

28. Margaliot, M., Huleihel, W., Tuller, T. Variability in mRNA translation: a random matrix theory approach. *Sci. Rep.* **11**, 5300. https://doi.org/10.1038/s41598-021-84738-0 (2021).

29. Guhr, T., Groeling, A. M., Weidenmueller, H. A. Random matrix theories in quantum physics: Common concepts. *Phys. Rept.* **299**, 189-425. https://doi.org/10.1016/S0370-1573(97)00088-4 (1998).

30. Grilli, J., Rogers, T., Allesina, S. Modularity and stability in ecological communities. *Nat. Com.* **7**, 12031. https://doi.org/10.1038/ncomms12031 (2016).
32. Allesina, S. Grilli, J. Barabási, G. Tang, S. Aljadeff, J. Maritan, A. Predicting the stability of large structured food webs. Nat. Com. 6, 7842. https://doi.org/10.1038/ncomms8842 (2015).
33. Mehta, M. L. Random Matrices. Academic Press. (2004).
34. Stone, L. The stability of mutualism. Nat. Com. 11 2648. https://doi.org/10.1038/s41467-020-16474-4 (2020).
35. Urama, T. C., Ezepue, P.O., Nnanwa,C.P. Analysis of cross-correlations in emerging markets using random matrix theory. Mathematical Finance. 7, 291-307. https://doi.org/10.1023/A:1004879905284 (2001).
36. Jamali, T., Jafari, G. R. Spectra of empirical autocorrelation matrices: A random-matrix-theory–inspired perspective. Epl. 111, 10001 https://doi.org/10.1209/0295-5075/111/10001 (2015).
37. May, R. M. Will a large complex system be stable? Nat. 238, 5364. 10.1038/238413a0 (1972).
38. Pradhan, P., Jalan, S. From Spectra to Localized Networks: A Reverse Engineering Approach. IEEE. 7, 4,3008-3017. https://doi.org/10.1109/TNSE.2020.3008999 (2020).
39. Albert, R., Barabási, A. L. Statistical mechanics of complex networks. Rev. Mod. Phys. 74, 47. https://doi.org/10.1103/RevModPhys.74.47 (2002).
40. Newman, M. E. J Networks An Introduction. (Oxford University Press, 2010)
Author contributions
N.A., A.H., N.A., and G.R.J conceived and designed the study. N.A. analyzed the data, performed the statistical analysis, created the figures, and wrote the first draft of the manuscript. N.A., A.H., and G.R.J analyzed the results. All authors read and approved the final manuscript.

Competing interests
The authors declare no competing interests.
### Table 1. Classification of highlighted essential and nonessential genes as high NPR ones in terms of the biological process included

| Biological process                                      | Essential gene                                                                 | Nonessential gene                               |
|--------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------|
| Cell polarity and morphogenesis                         | YAL041W, YBL105C, YDR188W, YDR212W, YFL0059, YFL039C, YGL233W, YIL118W,     | YCR009C, YER149C, YLR370C, YOR327C               |
| DNA replication and repair                              | YDL064W, YDL105W, YDR510W, YIL150C, YJL072C, YJR006W                        | YER173W, YOR368W, YPL194W                        |
| Glycosylation protein folding                          | YBL040C, YBR004C, YDR032W, YDR331W, YDR434W, YDL002W, YGL022W, YHR188C,     | YDL095W, YFL031W, YFL032W, YHR030C, YHR078W,    |
| /targeting cell wall biosynthesis                       | YJR118W, YGR113W, YGR140W, YHR172W, YJR191C, YJL060W, YJR008C              | YJR105W, YJR110C, YPL089C, YPL227C               |
| MVB sorting and pH depending signaling                 | YAL073C, YBL036C, YBR135W, YBR160W, YDL003W, YDL008W, YDR180W, YDR356W,     | YMR077C                                         |
| Mitosis and chromosome segregation                     | YER133W, YER147C, YER148W, YFL008W, YFL032C, YFL034C – B, YFR027W, YFR028C, |                                                 |
| Nuclear–cytoplasmic transport                          | YGL093W, YGR092W, YGR113W, YGR140W, YHR172W, YHR191C, YJL060W, YJR008C,     |                                                 |
| Peroxisome                                             | YAL045W, YOL102C, YOR149C, YPL076W, YPR183W                                  |                                                 |
| Respiration oxidative phosphorylation                  | YAR007C, YBL034C, YBR135W, YBR160W, YDL003W, YDL008W, YDR180W, YDR356W,     | YBR268W, YCR046C, YCR071C, YDR337W, YDR350C,    |
| Ribosone biogenesis                                    | YER133W, YER147C, YER148W, YFL008W, YFR027W, YFR028C, YGL093W, YGR092W,     | YDR462W, YER077C, YML129C, YMR257C, YOR201C,    |
| Transcription and chromatin organization               | YBR193C, YBR198C, YBR253W, YDR145W, YDR228C, YGR005C, YIL081C, YJR017C,     | YPL189C – A                                    |
| Vehicle traffic                                        | YJR093C, YML098W, YML114C, YMR005W, YPL228W, YPR086W, YPR161C                 |                                                 |
| mRNA and tRNA processing                               | YBR119W, YBR188C, YGL174W, YOR308C                                        |                                                 |
| rRNA and ncDNA processing                              | YJR014W, YDL148C, YDR060W, YDR449C, YKL021C, YLR222C, YMR093W, YMR309C, YNL061W, YNR053C, YOL144W, YOR272W |                                                 |
| tRNA wobble modification                               | YPL204W                                                                      | YGR200C, YHR187W, YNL119W                      |

**Supplementary**

All our highlighted genes as high NPR ones are represented in the following tables 2 and 3. The gene ontology of them has been explored from [https://www.yeastgenome.org/](https://www.yeastgenome.org/) through this path: function> gene ontology> GO term finder> uploading our file of gene names, then picking component as an ontology aspect, and setting p-value below 0.1. The significant GO terms used to describe our set of essential genes are accessible at [https://www.yeastgenome.org/goTermFinder?genes=&uploadFile=aaallel_new_pcc_ESE_HIGH_NPR.txt&genes4bg=&uploadFile=&pvalue=0.1&FDR=FDR&submit=Submit+Form](https://www.yeastgenome.org/goTermFinder?genes=&uploadFile=aaallel_new_pcc_ESE_HIGH_NPR.txt&genes4bg=&uploadFile=&pvalue=0.1&FDR=FDR&submit=Submit+Form), and for nonessential ones at [https://www.yeastgenome.org/goTermFinder?genes=&uploadFile=aaallel_new_pcc_NON_HIGH_NPR.txt&genes4bg=&uploadFile=&pvalue=0.1&FDR=FDR&submit=Submit+Form](https://www.yeastgenome.org/goTermFinder?genes=&uploadFile=aaallel_new_pcc_NON_HIGH_NPR.txt&genes4bg=&uploadFile=&pvalue=0.1&FDR=FDR&submit=Submit+Form). The annotation of our highlighted genes as high NPR ones mentioned in the main article amongst these genes has been published as data file S5_SAFE analysis_Gene cluster identity and functional enrichments, the fifth sheet by Charles Boone and his colleagues at [http://boonelab.ccbr.utoronto.ca/supplement/costanzo2016/](http://boonelab.ccbr.utoronto.ca/supplement/costanzo2016/).
Table 2. Allele names of essential genes with high NPR

| Allele | Genotype   |
|--------|------------|
| cab1   | 5001       |
| stk1   | 6          |
| rpi1   | 5006       |
| rpi6   | 1          |
| act1   | 133        |
| cdc1   | 2          |
| rpn11  | 8          |
| rpn11  | 14         |
| ct8f   | 9          |
| pck1   | 4          |
| nbp1   | 1          |
| prp16  | 2          |
| ct8f   | 162        |
| gsc3   | 5001       |
| med8   | 39         |
| las1   | 17         |
| ntr2   | 5001       |
| rat1   | 1          |
| act1   | 105        |
| spn3   | 2          |
| cct6   | 18         |
| mak11  | 5001       |
| eco1   | 1          |
| srp54  | 5001       |
| rve2   | 5001       |
| str2   | 5001       |
| gsp1   | p162f      |
| scc4   | 5001       |
| utp15  | 5001       |
| gsc1   | 5001       |
| erg27  | 5001       |
| rgr1   | 100        |
| nse4   | 5001       |
| sad1   | 1          |
| tsc3   | 2          |
| tfc8   | 5001       |
| nip1   | 5007       |
| pre2   | 2          |
| gpi16  | 5001       |
| orc1   | 5001       |
| gpi12  | 5001       |
| mob2   | 38         |
| crm1   | 1          |
| nolp1  | 3          |
| gtd14  | 4          |
| gpi11  | 5001       |
| krp33  | 5001       |
| dpm1   | 6          |
| prp9   | 1          |
| gpi8   | 5001       |
| pkg1   | rds3       |
| prp6   | ts         |
| qrl1   | ts1        |
| sec15  | 1          |
| ded1   | f144c      |
| pri1   | m4         |
| scf2   | 1          |
| apc2   | 8          |
| mob2   | 14         |
| mob2   | 2          |
| gpi21  | 5001       |
| gsc1   | 2          |
| act2   | 122        |
| srb6   | 5001       |
| gna1   | 5001       |
| rpb7   | 5001       |
| mes1   | 1          |
| gpi19  | 5001       |
| nup159 | 1          |
| tpr1   | 5001       |
| act1   | 159        |
| rtp6   | 25         |
| nup192 | 5001       |
| yjr141w| 5001       |
| gpi15  | 9          |
| gna1   | 5001       |
| poh3   | q308k      |
| nup2   | 6          |
| cep3   | 1          |
| mob2   | 34         |
| taf5   | 3          |
| stt3   | 7          |
Table 3. Allele names of nonessential genes with high NPR

| arp10 | tmc | bdh2 | est1 | alg5 |
|-------|-----|------|------|------|
| yir044c | chl4 | fdh2 | vps20 | dcc1 |
| ydr444w | yer187w | mch1 | ycr007c | emc34 |
| ybl029c–a | arc18 | ady3 | cin1 | rad17 |
| bud13 | ydr537c | dip5 | swr1 | hxt3 |
| swe3 | ubp13 | ynl234w | tpc1 | sag1 |
| ycr023c | mrx1 | rtx2 | muk1 | jj1 |
| vps71 | ymr181c | ygr125w | heh2 | ynl140c |
| bsc5 | mgr1 | yhr210c | ask10 | rvs161 |
| spo16 | ydr338c | nip100 | gic1 | ysw1 |
| def1 | ssh4 | coa2 | ecl1 | togi |
| cbs2 | map2 | lst4 | ncr1 | sap30 |
| fun19 | rrt13 | td8a | rex3 | mad2 |
| tim18 | cwp1 | ylf089w | dep1 | vps35 |
| cmp2 | ecm27 | mxr2 | ydl199c | ybr071w |
| ybl086c | etf8 | elp2 | yml096w | dot5 |
| ett1 | ylf017w | tax4 | arp6 | alb1 |
| cox14 | fun26 | yjl211c | rad28 | ddc1 |
| mca1 | ydr290w | yer166c | hrr1 | nmd4 |
| iki1 | par1 | pep8 | lam4 | srl1 |
| tho1 | irc10 | bck1 | pmu1 | sys1 |
| kel3 | ids2 | rpl12a | hac1 | las21 |
| chz1 | yor022c | fre5 | htz1 | arp1 |
| mcm21 | yor342c | vma8 | rad24 | cin8 |
| rps7a | mgl1 | rds2 | vba5 | ufo1 |
| mrpl37 | yfl032w | dfb2 | spg3 | cce1 |
| yof019w–a | vel1 | psy4 | mrc1 | fhn1 |
| irc15 | ump1 | ymr102c | yer175w–a | yj144w |
| mpp6 | nth2 | aim33 | ctf3 | nrm1 |
| nat1 | pet111 | ypl216w | ybr255c–a | shy1 |
| yhr078w | trm82 | ecm18 | efml1 | cog6 |
| yhl042w | ygr226c | mlf3 | slr2 | ngl1 |
| pol4 | snu66 | ypk3 | yfr057w | ygl138c |
| pho85 | ybr242w | yor316c–a | ydl038c | ycl060c |
| gat4 | yhr2 | wh4 | ntc20 | yj118w |
| om45 | pmu1 | ldl16 | yhr131c | pea2 |
| ume1 | num1 | ynl050c | ygr177c | ynl194c |
| rps19a | typ18 | dst1 | hif1 | ybr137w |
| gln4 | ybr184w | ldb18 | ncs2 | ydh1 |
| yip3 | hur1 | crg1 | ydl211c | rps9a |
| sdh6 | err1 | sas5 | vps72 | cf19 |
| rlm1 | pdr11 | eaf1 | jnm1 | vki1 |
| pex30 | snn3 | tos2 | pmr1 | ebs1 |
| cog7 | dyn3 | yhr097c | sncc2 | yor997c |
| mrps28 | ccw12 | rpl6a | sk8 | pdp3 |
| gep3 | rmd5 | tda4 | mrm1 | ymr001c–a |
| cog8 | img2 | rps21a | cog5 | nup170 |
| snf8 | mud1 | mit1 | rps4a | doo4 |
| mrpl28 | atp22 | ade3 | ylr466c–b | hit1 |