A trade-off in the ability of genes to induce phenotypic variability and robustness

Pablo Crotti[1*], Vera Pancaldi[2], and Vahid Shahrezaei[1**]

***Short Abstract* — We quantify genetic determinants of phenotypic variability in *S. cerevisiae* by employing a high-dimensional dataset of morphological phenotypes [1] and based on a comparative analysis of the residuals of the coefficients of variation measured on a wild type strain (HIS3) and 4718 mutants. We show that genes can be categorized into three classes according to their global effect on phenotypic variability: capacitors, inducers and neutrals. We further investigate the biological significance of phenotypic variability inducers that are genes decreasing phenotypic variability in many different phenotypes after deletion.**

***Keywords* — Gene regulation networks, phenotypic variability, cell aging.**

I. Introduction

The 'phenotypic variability' observed in biological systems can be attributed to individual genetic variation, environmental fluctuations and inherent molecular noise within cells [2]. While phenotypic variability can be advantageous to population fitness in certain situations, individuals need reliable and reproducible traits to function properly. Therefore, it is thought that a universal property of biological systems is robustness to perturbations arising from both genetic and non-genetic sources. A recent study suggests that many genes act as 'phenotypic capacitors', buffering against the variations [3]. If these genes are deleted, the underlying hidden phenotypic variability in many traits is revealed. In this study we obtain genes that have the opposite effect, terming them phenotypic variability inducers.

II. Material and Methods

Here, we use the available high-dimensional morphological phenotypic data in *S. cerevisiae* [1] to further investigate the effect of single gene deletions on phenotypic variability. We reorganize the dataset to extract a collection of 4718 non-lethal gene deletions presenting each a set of 501 morphological measures. To study and compare the 4718 available mutants, we introduce a novel score termed Global Phenotypic Variability (GPV). The GPV takes into account 121 representatives of the morphological phenotypes, determined after clustering of the dataset using a k-medoids algorithm [4,5]. An L1-regression between the mean and CV of each representative phenotype is used to produce a mean-corrected measure of CV residuals. The GPV score is defined as the median of the mutant residuals. The GPV is validated as it correlates with other genetic measures, such as the capacitance potential introduced in [3] or the genetic interaction degree [6].

III. Results

We use the GPV measure defined above to segregate genes into three categories labeled *capacitors*, *inducers* and *neutrals*, according to their effect on global phenotypic variability. When removed, the genes labeled as capacitors increase variability in many phenotypes, which were the subject of a recent study [3]. We find that there are few hundred genes, the phenotypic inducers that when removed decrease phenotypic variability in many phenotypes. We also observed that there are some phenotypic capacitors that are also phenotypic inducers. This may seem puzzling as capacitors and inducers are opposite but a closer investigation reveals that these genes, which we call neutrals, increase variability in several phenotypes while decreasing it in a different subset of phenotypes. Neutrals overall effect is a redistribution of variability across phenotypes, while keeping the overall global phenotypic variability unchanged. Increased robustness in some phenotypes results in increased variability in some other phenotypes [7]. A further mapping of the genes using the Gene Ontology (GO) indicates that amongst other GO annotations, replicative cell aging is linked to capacitors whereas chronological cell aging appears to be related to the inducers. The biological significance of the phenotypic variability inducers could be the subject of further investigation.

[1]Department of Mathematics, Imperial College London, South Kensington Campus, London SW7 2AZ, United Kingdom. E-mail: *pablo.crotti@imperial.ac.uk; **v.shahrezaei@imperial.ac.uk

[2]Structural Biology and BioComputing Program, Spanish National Cancer Research Centre, Calle de Melchor Fernandez Almagro, 3, 28029 Madrid, Spain. E-mail: vpancaldi@cnio.es

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