

S1. Methods

Determination of inhibitory concentrations (IC).

IC (inhibitory concentration) values of the three phenol derivatives were determined by measuring optical densities (usually $OD_{595\text{ nm}} - OD_{600\text{ nm}}$) of *wt* cell growth in medium without and with various concentrations of the phenol compounds at 30 °C for 17-20 hr. At least duplicates were performed in each experiment and average cell densities were used to generate a dose-response curve for *S. cerevisiae* cells (Negritto et al., 2017). Similar methods were used to determine the IC values of BHA, BHT, and BPA for *S. pombe* cells (S4). The IC_{50} is the concentration of phenol derivative, which results in a 50% growth inhibition compared to the growth of cells in the absence of the compound. To prepare the stock solutions, the phenol compounds were dissolved in 100% Dimethyl sulfoxide (DMSO). The stock solutions were at least 100X so that the final concentration of DMSO did not exceed 1% in the medium for cell growth tests. BHA, BHT, and BPA were purchased from Sigma-Aldrich.

Table 1. IC values of BHA, BHT and BPA for *S. pombe* wild-type cells

IC Values	BHA	BHT	BPA
IC₅₀ (mM)	0.3	0.4	0.38
IC₇₀ (mM)	0.4	0.6	0.63
IC₈₀ (mM)	0.5	0.8	0.75

Table 2. IC values of BHA, BHT and BPA for wt *S. cerevisiae* cells

IC Values	BHA	BHT	BPA
IC ₅₀ (mM)	0.19	0.13	0.68
IC ₇₀ (mM)	0.33	0.20	0.77
IC ₈₀ (mM)	0.43	0.25	0.82

Digitization of the cell growth data

In addition to identifying sensitive strains by visual inspection after screening the *S. pombe* genomic deletion strains, quantitative analysis was used to confirm the list of mutants responsive to the phenolic treatment. The cell growth data is in image format of an 8 by 12 array of 96 colonies from different strains. The digitization of the images was a two-step process. First, the image was automatically subdivided into 96 regions, one for each of the grown colonies. In case the colony array was not regular, the subdivision was manually adjusted to ensure that each colony was completely covered and separated from the neighboring ones. Second, for each of the 96 regions a local threshold was defined to separate cell growth from background. This operation was adaptive as the threshold values for different regions might be different, depending on the local lighting condition during the imaging process.

The goal of the threshold operation was to separate the colony composed of brighter pixels from the background composed of darker pixels by an optimal threshold value. The optimality was achieved by maximizing certain distance between the colony and the background, treated as two different classes of pixels. In other words, the thresholding was carried out as a two-class classifier.

The distance between the two groups of pixels is defined based on the mean μ_i and variance σ_i ($i=1, 2$) of each of the two groups of pixels. Specifically, we define the following:

1. Between-class scatteredness

$$S_b = p_1(m_1 - m)^2 + p_2(m_2 - m)^2$$

where m_1 and m_2 are the means of the two classes while m is the total mean of all pixels, and $p_i = n_i / (n_1 + n_2)$ ($i=1, 2$) with n_1 and n_2 being the number of pixels in each of the two classes.

2. Within-class scatteredness:

$$S_w = p_1\sigma_1 + p_2\sigma_2$$

3. Total scatteredness, which is simply the variance $S_t = \sigma$ of all pixels in the region independent of the two classes

The three variables defined above are related by $S_t = S_b + S_w$, indicating that the total scatteredness (independent of the two classes) is due to the contributions of both within-class scatteredness and between-class scatteredness. Our goal is to find the optimal threshold value in the range between zero (black) and 255 (white) that maximizes S_b and minimizes S_w . The threshold algorithm simply exhausts all 255 possible threshold values to find the optimal one that maximizes S_b / S_w or equivalently S_b / S_t . Some manual post-processing was performed if needed after automatic thresholding to individually adjust the threshold value in case of no growth, severe noise, or contamination. The sum of all pixels above the optimal threshold value, representing both the size (number of pixels) and quality (brightness of pixels), was used as the numerical representation of the level of cell growth for each colony and used in the subsequent analysis.

For Figure 3A, after cells were grown for 3 days at 30 °C, the density of individual colonies on plates were scanned or imaged with Carestream Image Station 4000R. Tiff images were then analyzed using IQTL software to determine pixel intensity of each colony, followed by array analysis to digitize colony density through defining boundary of a colony and subtracting background.

To analyze the data quantitatively, the growth score values (GSV) of the mutant (*mt*) strains to BHA, BHT, or BPA were calculated, which is defined as the ratio of the growth score for a treated (T) sample over its corresponding untreated (UT) sample divided by the ratio of the *wt* treated over the *wt* untreated (ratio of ratio): $GSV = (mtT/mtUT)/(wtT/wtUT)$. This method allows us to identify abnormal growth specifically due to the response of a deletion strain to the

environment but not simply a growth defect as a result of the deletion. A deletion strain is defined as sensitive when $GSV < 0.5$; as resistant when $GSV > 2$; and no growth phenotype when the ratio $0.5 < GSV < 2$.

Clustering analysis of growth fitness data

After digitization of the growth fitness data to identify the deletion mutants sensitive to BHA, BHT, or BPA, the response properties of corresponding genes were further analyzed by a clustering analysis through applying a top-down algorithm described in (Wang et al., 2003) with modifications. This clustering process was carried out recursively so that all genes are organized in a hierarchical tree. The branches separate the relevant genes into groups of similar response to the testing phenolic compounds.