A fitness trade-off explains the early fate of yeast aneuploids with chromosome gains

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Abstract

The early development of aneuploidy from an accidental chromosome missegregation shows contrasting effects. On the one hand, it is associated to significant cellular stress and decreased fitness. On the other hand, it often carries a beneficial effect and provides a quick (but typically transient) solution to external stress. These apparently controversial trends emerge in several experimental contexts, particularly in the presence of duplicated chromosomes. However, we lack a mathematical evolutionary modeling framework that comprehensively captures these trends from the mutational dynamics and the trade-offs involved in the early stages of aneuploidy. Here, focusing on chromosome gains, we address this point by introducing a fitness model where a fitness cost of chromosome duplications is contrasted by a fitness advantage from the dosage of specific genes. The model successfully captures the experimentally measured probability of emergence of extra chromosomes in a laboratory evolution setup. Additionally, using phenotypic data collected in rich media, we explored the fitness landscape, finding evidence supporting the existence of a per-gene cost of extra chromosomes. Finally, we show that the substitution dynamics of our model, evaluated in the empirical fitness landscape, explains the relative abundance of duplicated chromosomes observed in yeast population genomics data. These findings lay a firm framework for the understanding of the establishment of newly duplicated chromosomes, providing testable quantitative predictions for future observations.

Introduction

Aneuploidy, a deviation from the normal chromosome number, is a form of large-scale genomic variation, involving changes both at the genotypic and at the phenotypic level, and one of the hallmarks of cancer [1]. In cancer genomes, aneuploidy correlates with important genomic changes, such as TP53 mutation and expression of proliferation genes [2] and drug resistance mutations leading to treatment failure [3, 4]. Drugs that disrupt mitotic progression, called antimitotic drugs [5, 6], are widely used for cancer treatment. These drugs cause chromosome missegregation, large genetic rearrangements and aneuploidy. In yeast models, perturbed gene expression due to extra chromosomes can cause stress resulting from the proteome-wide stoichiometric imbalance of protein levels [7, 8]. Moreover, aneuploidy was shown to cause global changes of mRNA and protein expression and to possibly confer condition-dependents fitness advantage [9–11]. Finally, the emergence of yeast mutator strains depends on ploidy levels [12].

The evolutionary dynamics leading to the emergence of aneuploidy is typically investigated with yeast models, because they can be manipulated with advanced genetics and cell- and molecular-biology methods, and hence be used to create isogenic backgrounds that only differ from each other by chromosome ploidy number, offering a direct point of comparison between euploid and aneuploid strains. Moreover, yeast models can be easily investigated with laboratory-evolution experiments, thanks to their short replication time [6, 9, 13, 14].

Several experiments in the last decades have raised apparently controversial evidence for the evo-

lutionary role of aneuploidy [10, 15]. While aneuploidy carries significant cellular stress and decreased fitness [16], measured for example by a reduction of growth rate, it has also been shown to carry a beneficial effect that provides a quick, transient solution to external stress [14, 15]. This quick solution often emerges faster, hence, more frequently, than other evolutionary routes. Intriguingly, cultured human cells show the same contrasting trends: aneuploid cancer cells lines show a reduction of growth rate [17–19], but specific patterns of aneuploidy, particularly in the presence of extra chromosomes, confer a beneficial effect in specific adverse conditions [20, 21].

In the case of yeast, the literature offers extensive phenotypic data, for example growth curves of aneuploids in several environmental conditions as well as in laboratory-evolution experiments [6, 9, 10, 13–15], offering the opportunity to test for unifying trends. The available modelling studies presented so far have focused on the effect of aneuploidy on cell growth and physiology [7, 22–25]. Two interesting recent studies [22, 24] proposed a stochastic model of evolution similar to the classic Fisher's geometrical model [26] to describe the fitness landscape of a set of engineered aneuploid strains in different stress environments. This model explains the observed correlation between the degree of phenotypic variation and the degree of overall growth suppression, measured in [9]. However, this model, and all the approaches presented so far [7, 22–25], are limited by a static description of the genetic and phenotipic architecture of aneuploids, failing to provide a description of the mutational dynamics leading to its emergence.

Here, we develop a theoretical framework to describe such mutational dynamics and to address the cost-benefit trade-offs in early aneuploids. We introduce a fitness model with a per-gene fitness cost of chromosome duplication is counterbalanced by a fitness advantage resulting from the dosage increase of specific genes. Our approach builds on the so called "mutation bias" framework [27–29], a class of evolutionary models used to investigate the role of fast mutational processes in directing evolution, in a scenario where evolutionary routes emerging with a high mutation rate are in evolutionary competition with alternative mutational targets generated with a lower rate, but able to confer higher fitness advantage. Our model makes quantitative predictions that capture the dynamics leading to the emergence aneuploidy. As we will describe in detail, the model captures the probability of the emergence of extra chromosomes in experimental setups [14],and correctly predicts the observed outcomes for the emergence of aneuploidy. We then make use of phenotypic data to isolate the main features contributing to the fitness landscape of aneuploids with extra chromosomes, and show that the dynamics of our model in this landscape captures the relative abundance of aneuploidies observed in population genomics data.

Results

Model and parameters

We develop and analyze an evolutionary model to describe the emergence of aneuploidy carrying extra chromosomes. Fig. 1A describes the key model ingredients. The model considers a population consisting of euploid individuals, which is exposed to an external stress causing a decrease of their growth rate. Individuals in the population can respond to the stress by increasing the expression of a specific target gene, gaining a beneficial effect quantified by the selection coefficient ($\sigma_b > 0$). Individuals can gain fitness by two alternative evolutionary routes: (i) by increasing the target gene expression (for example with mutations on the promoter binding site) or improving its functionality via a set of point mutations (on coding regions adapting protein function), occurring at a total rate μ_m or (ii) via missegregation events, taking place at a higher rate ($\mu_a > \mu_m$) and resulting in the emergence of aneuploid individuals carrying extra chromosomes. Note that route (i) could require several point mutations (modeled here as a one-step process), but the per-base mutation rate is a lower bound for μ_m. Aneuploids with extra chromosomes are less fit than euploids, because the duplication of the non-target genes in the extra chromosome determines a global fitness cost ($\sigma_c > 0$). Hence, the selection coefficient of aneuploids ($\sigma_b - \sigma_c$) is lower than that of euploid mutants (σ_b) and euploid mutants, although generated at a lower rate, have a higher fixation probability than aneuploids ($\phi_m > \phi_a$). Double mutants (individuals carrying both aneuploidy and point mutations) are produced

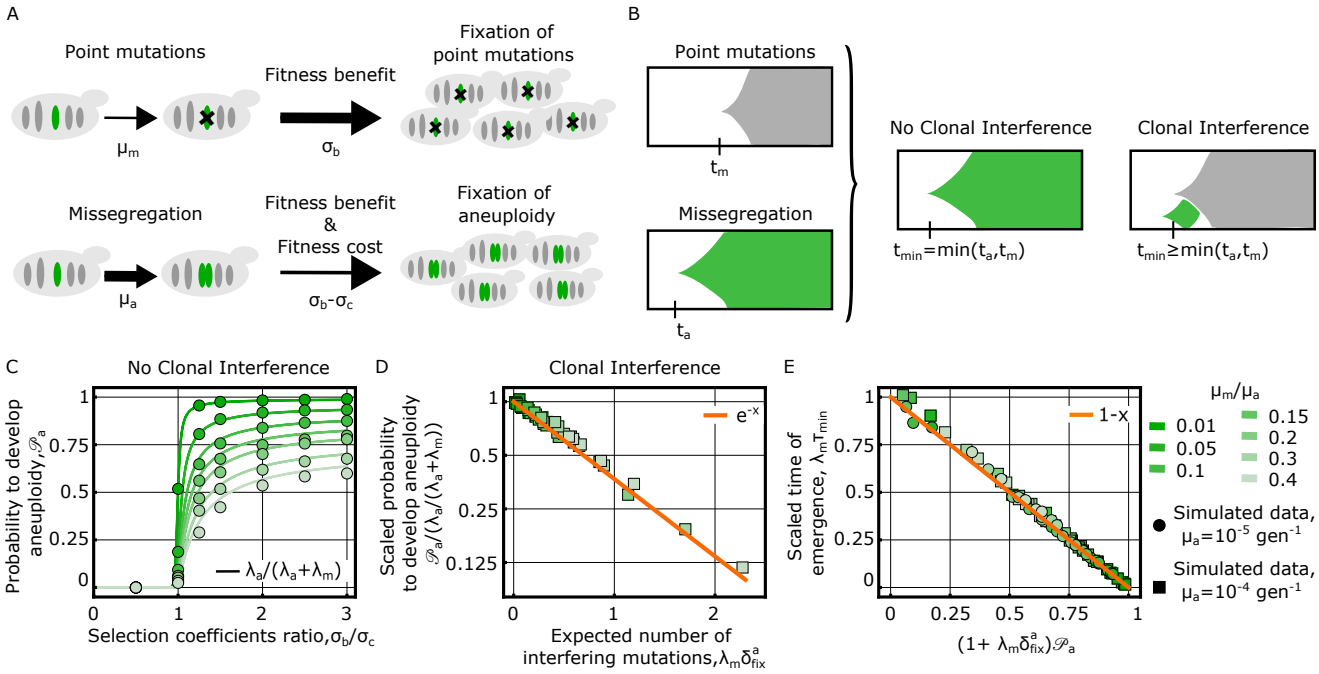

Figure 1: **A trade-off between fitness cost and fitness benefit explains the population dynamics of early aneuploids with extra chromosomes**. A: Schematic illustration of the evolutionary model, which considers a population of euploid individuals exposed to an external stress that reduces its fitness. Individuals can restore their original fitness by increasing the expression of a specific target gene, found on a specific chromosome. Fitness can increase in two distinct ways. Euploid individuals can increase the target gene expression via point mutations, taking place at rate (μ_m), or via duplication of the target chromosome, at a rate related to missegregation. This second evolutionary route takes place at a higher rate ($\mu_a > \mu_m$) and generates aneuploids. Aneuploids with extra chromosomes, however, are less fit than the euploid variant, because they carry the duplication of non-target genes in the extra copy of the chromosome containing the target gene. For this reason, euploids, although emerging at a lower rate, have a higher fixation probability than aneuploids $\phi_m > \phi_a$. B: The dynamics of the two evolutionary routes, here schematically represented with Müller plots, is characterized by the time of emergence of the successful mutant (the mutant whose descendants will eventually take over the population). In the model, both evolutionary routes are attainable and only the fastest of the two mutants, emerging at a time $t_{\min} = \min(t_a, t_m)$, will reach fixation. Clonal interference, occurring for example when a euploid mutant emerges during the fixation dynamics of an aneuploid individual, will disfavour the emergence of aneuploidy and delay the emergence of the successful mutant ($t_{\min} \geq \min(t_a, t_m)$). C: Fixation probability of aneuploids with extra chromosomes in a regime with no clonal interference ($\lambda_m \delta^a_{\text{fix}} \simeq 0$), plotted as a function of the non-dimensional ratios σ_b/σ_c (x axis) and μ_a/μ_m (color coded). Results of simulations (circles) are compared to analytical calculations (solid lines). D-E: Collapse plots of simulated data of the model in the clonal interference regime ($\lambda_m \delta^a_{\text{fix}} \geq 0$) validate the analytical results for the fixation probability of aneuploids with extra chromosomes (Eq. 1, shown in panel D) and for the emergence time of the successful mutant (Eq. 3, shown in panel E). See Material and Methods for details on the numerical simulations of the model. Additional model parameters used for the data shown in panels B,C,D: $N = 1000$, $\sigma_c N = 50$.

at a rate corresponding to the product of the rates ($\mu_m \times \mu_a$) and therefore are very rare and can be neglected. We also assume for simplicity that all mutations other than missegregations and the target point mutations do not contribute to the adaptive dynamics in response to the external stress, hence are neglected. Under these assumptions, the model reduces to the competition between two possible beneficial mutations, aneuploidy *vs* a local mutation.

Evolutionary dynamics

Our question concerns the conditions in which chromosomal duplications emerge first. Accordingly, we investigate the "early stage" population defined by the point in time when one of the two mutants, the euploid with point mutations or the aneuploid mutant carrying extra chromosomes, becomes fixed in the population for the first time. This dynamics is described by fixation rates, which are given by the product of the mutation rates, the effective population size N, and the fixation probabilities: $\lambda_m = \mu_m N \phi_m(\sigma_m, N)$ for the euploid mutant and $\lambda_a = \mu_a N \phi_a(\sigma_a, N)$ for the aneuploid one. The fixation probabilities depend on the selection coefficients ($\sigma_a \equiv \sigma_b - \sigma_c$ for the aneuploid, and $\sigma_m \equiv \sigma_b$ for the euploid mutant) and on the effective population size N, as given by Kimura's formula $\phi(\sigma, N) = (1 - e^{-2\sigma})/(1 - e^{-2\sigma N})$ [30].

Analytical expression of the probability to develop aneuploidy with extra chromosomes

In order to characterize the onset of the fastest variant, we focus on the waiting times for the emergence of a successful mutant (defined as the mutant that will eventually reach fixation). The two times, denoted as t_a and t_m for the aneuploid carrying extra chromosomes and the euploid mutant respectively, are stochastic variables, with expected values equal to the inverse of the fixation rates ($\tau_{a,m} \equiv \langle t_{a,m} \rangle = 1/\lambda_{a,m}$), and with exponential probability distribution $t_{a,m} \sim Exp\,(\lambda_{a,m})$.

The statistics of the fastest emerging mutant can be described by the difference of the two times, $t_{\text{diff}} \equiv t_a - t_m$, whose probability density has an analytical expression (see SI appendix). In particular, the problem of computing the probability for the variant carrying extra chromosomes to reach fixation is equivalent to computing the probability for the time difference to be negative ($t_{\text{diff}} < 0$). However, since the selection coefficient of aneuploids carrying extra chromosomes is lower than that of the euploid mutant, individuals of the former class will interfere with the expected progression of the aneuploid mutation to the fixation (see Fig. 1B), by an effect known as "clonal interference" (CI) [31–34].

We find that, to compute the probability to fix extra chromosomes, CI effects are captured by the extended condition $t_{\text{diff}} + \delta_a^{\text{fix}} < 0$, where $\delta_a^{\text{fix}} = \log(2N\sigma_a)/\sigma_a$ is the effective time to fixation of an aneuploid mutant carrying extra chromosomes [34] (see SI appendix). This leads to the expression

$$\mathcal{P}_a \equiv P(t_{\text{diff}} + \delta_a^{\text{fix}} < 0) = \frac{\lambda_a}{\lambda_m + \lambda_a} e^{-\lambda_m \delta_a^{\text{fix}}}, \tag{1}$$

for the fixation probability. This expression is similar to the ones presented in [29, 35]. Consistently with ref. [31], CI effects are related to the expected number of euploid mutations that can emerge during the fixation dynamics of the mutant with extra chromosomes. In the limit $\lambda_m \delta_a^{\text{fix}} \ll 1$, there are no interfering mutations and the probability to develop extra chromosomes is set by the fixation rates alone $\mathcal{P}_a \simeq \frac{\lambda_a}{\lambda_m + \lambda_a}$ (Fig. 1C). In the clonal interference regime $\lambda_m \delta_a^{\text{fix}} > 1$ the emergence of aneuploidy with extra chromosomes is exponentially suppressed to zero ($\mathcal{P}_a \propto e^{-\lambda_m \delta_a^{\text{fix}}}$, Fig.1D).

When $\mathcal{P}_a \geq \frac{1}{2}$, the emergence of aneuploidy dominates over competing beneficial point mutations. Hence, the condition $\mathcal{P}_a = \frac{1}{2}$ sets the a lower critical value for the beneficial selection coefficient

$$\sigma_b^* \simeq \frac{\sigma_c}{1 - r} + \mathcal{O}(\mu_m N \log N). \tag{2}$$

The dominance of the evolutionary route developing extra chromosomes is observed in "stress" conditions where the beneficial effect exceeds the minimal value $\sigma_b \geq \sigma_b^* > \sigma_c$. Here $r = \mu_m/\mu_a < 1$ is the ratio between the mutation μ_m and the missegregation rate μ_a (see SI appendix).

Aneuploidy with extra chromosomes is a "quick fix" in stressful conditions

The dynamics leading to the fixation of one of the two evolutionary routes can also be described in terms of the waiting time before the emergence of the fastest successful mutant. This dynamical quantity is described by the minimum of the two waiting times, $t_{\min} \equiv \min(t_a, t_m)$, and has expected value (Fig.1E, see SI appendix for derivation)

$$\tau_{\min} = \langle t_{\min} \rangle = \tau_m \left(1 - (1 + \lambda_m \delta^a_{\text{fix}}) \mathcal{P}_a \right). \tag{3}$$

Thanks to the possibility of developing extra chromosomes, the waiting time until the emergence of the successful mutant is therefore shorter than the time needed to develop the competing set of point mutations $\tau_m = 1/\lambda_m$, which, in our model, would be attained if the mutational route was the only genomic change offering a solution to the external stress. This evolutionary route is still dynamically selected when $\sigma_b < \sigma_c \rightarrow \tau_{\min} \simeq \tau_m = 1/\lambda_m$, i.e., when the global effect of extra chromosomes (benefit minus cost) is detrimental. Conversely, in the opposite limit $\sigma_b \gg \sigma_c \rightarrow \tau_{\min} \simeq \tau_a = 1/\lambda_a$, the waiting time is dominated by the fixation rate of extra chromosomes alone. Clonal interference effects ($\lambda_m \delta^a_{\text{fix}} > 0$) lead to an increase of the waiting time, i.e., reducing the speed of adaptation in response to the stress, consistently with refs [31–34].

In summary, the model describes in quantitative terms the early-stage evolutionary role of aneuploidy carrying extra chromosomes. According to the predictions, extra chromosomes provide a "quick fix" to the external stress (because $\mathcal{P}_a \simeq 1 \rightarrow \tau_{\min} \simeq \tau_a < \tau_m$). Anaueploidy also has an indirect effect on the mutational dynamics of euploid individuals, by effectively selecting the fast mutants, hence causing a reduction of the waiting time to the emergence of the successful euploid mutant ($1 > \mathcal{P}_a > 0 \rightarrow \tau_{\min} < \tau_m$).

The model correctly predicts the outcome of experimental evolution data from [14]

Our model can be applied to describe the evolutionary dynamics observed in experimental setups akin to ref. [14]. In their experiment, Yona and coworkers exposed four independent yeast populations of diploid strains to a constant heat stress of 39°C. After $\sim$ 450 generations, the duplication of chromosome III (trisomy) was found to have reached fixation in all four populations. The duplication of this chromosome was shown to carry a beneficial effect in response to the applied heat stress and to be the dominant evolutionary solution over an alternative mutational route attained by point mutations inducing the up-regulation of heat-shock genes.

In order to compare the model prediction to the outcome of the experiment, we obtained growth curves from the authors of [14], evaluated for the diploid and aneuploid strain (carrying the trisomy of chromosome III) both in normal conditions (30°C) and in stress conditions (39 °C). We used the growth curves to infer values of the selection coefficients of aneuploid individuals (see Materials and Methods, Fig.S1 and Table S1, the numerical values we obtained are $\sigma_b = 0.17\,\text{gen}^{-1}$ and $\sigma_c = 0.05\,\text{gen}^{-1}$).

Given these values for the selection coefficients, we evaluated the cumulative probability of developing aneuploidy (Eq. 13) *vs* time, according to our model prediction (Eq.s (1,3, see Material and Methods), using an effective population size of $N = 10^6$ individuals, as a function of the missegregation rate (μ_a) and of the total mutation rate (μ_m) (Fig. 2). We find the model predictions Eq.s (1,3) to be in quantitative agreement with the outcome of the experiment, for realistic values of the missegregation rate ($\mu_a \geq 8 * 10^{-7}\text{gen}^{-1}$) and of the total mutation rate ($\mu_m \leq 5 * 10^{-9}$). Similar results are obtained setting a bigger value for the effective population size of ($N = 10^7$, see Fig.S3).

In order to determine realistic ranges of the rates (μ_a, μ_m) in yeast, we reasoned as follows. The total mutation rate is expected to be larger than the yeast per-base spontaneous mutation rate, $\mu_m \geq \mu_{\text{spont.}} = 1.7 * 10^{-10}\text{gen}^{-1}$ [36], since the same phenotypic effect, i.e., the development of resistance to heat by up-regulation of heat-shock genes, can be attained with more than a single point mutation. A conservative estimate the size of this mutational target is no more than 100 bases. Measurements for the missegregation rate exist in the literature.

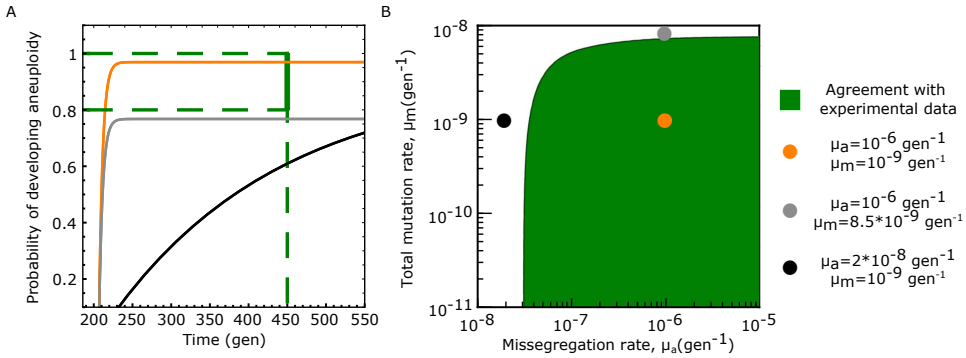

Figure 2: **Model predictions agree with laboratory-evolution data from ref. [14]**. (A) Expected cumulative probability for the emergence of aneuploidy with extra chromosomes *vs* the time to reach fixation (see Material and Methods), computed according to the model prediction (Eqs 1, 3) shown for three combinations of the values of the model parameters (μ_a, μ_m) (color coded, numerical values reported in the legend of the plot). In the experiment, where a yeast population was exposed to stress by increasing the temperature to $39C$, 4 out of 4 yeast populations developed chromosomal duplications ($CI_{66\%} = [0.8, 1]$ for the probability to develop aneuploidy), and all the fixations were reached before 450 generations. Hence, the experimental data fall in region of the plot corresponding to $P_a \in [0.8, 1]$ and $t = 450gen$, marked by a green bar and highlighted by green dashed lines. The trajectories predicted by the model that cross this region are in agreement with the experimental data. Similarly, panel (B) shows the combinations of the numerical values of the model parameters (μ_a, μ_m) that are in agreement with the experimental data, while colored circles mark the values corresponding to the trajectories shown in A. Numerical values of the beneficial selection coefficient ($\sigma_b = 0.17\,\text{gen}^{-1}$) and for the fitness cost of aneuploidy ($\sigma_c = 0.05\,\text{gen}^{-1}$) were obtained from exponential fits of the growth curves of the corresponding yeast strains [14], (see Material and Methods and Fig. S1). The effective population size was set to $N = 10^6$ individuals (Fig. S3 shows results for $N = 10^7$). The data reported here refer to the "High-Temperature" experimental setup. Similar agreement between model prediction and experimental data is observed for the "High-PH" experimental setup (Fig.s S2)

The agreement between model prediction and experimental data is observed yet another independent evolutionary experiment, described in ref.s [14,37], where a diploid yeast population was exposed to a different stressing environment, high PH. This experiment revealed the fixation of strains with the duplication of chromosome V (trisomy, see Supporting Information and Fig.s S1,S2,S3 and Table S1).

The cost of extra chromosomes increases linearly with the number of excess genes

The fitness cost of an aneuploid strain is defined as the reduction of its per-individual offspring. In proliferative conditions, this can be proxied by the growth rate difference with respect to the euploid strain, evaluated in the same environmental conditions. An alternative proxy for fitness is the stationary-phase population size in a given condition. We deduced these proxies from both growth rates [9] and full growth curves [13] collected for yeast aneuploid strains grown in rich media and in the absence of external stress (see Material and Methods).

In both data sets, we found a statistically significant negative linear correlation between the growth rate of aneuploid strains and the total number of genes carried in the exceeding chromosome. This relation is observed (with different slopes) both in strains with disomic chromosomes compared to a haploid (ploidy 1) genomic background (Fig.3 A,B,C) and in strains with trisomic chromosomes compared to a diploid genetic background (Fig. 3 C). Notably the same trend is not only observed in aneuploid strains carrying only a single duplicated chromosome (Fig. 3 A), but also in strains with up to 8 duplicated chromosomes (Fig.3 B-C), suggesting that epistatic interactions between the fitness costs of multiple duplicated chromosomes are small. The data set from ref. [13] also shows a negative correlation between the fitness proxied by stationary-phase population size (optical density, OD) and the total number of genes carried in the excess chromosomes (Fig.3B). Linear negative

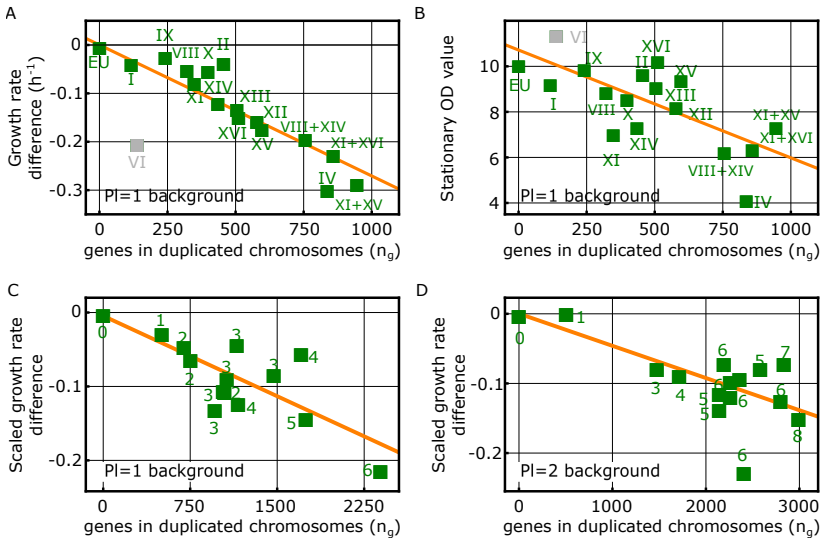

Figure 3: **The fitness cost of extra chromosomes is proportional to the total number of genes present in the excess chromosomes.** A: Plot of the values of the difference between the exponential growth rates of aneuploid strains with extra chromosomes and the exponential growth rate of the euploid strain (squares, labels indicating disomic chromosome numbers) against the number of genes carried in the disomic chromosomes (data from ref. [13], see Materials and Methods for details). The growth rate differences (estimating fitness differences) display a significant negative linear correlation with the number of duplicated genes (red line, Pearsons' r = -0.93, p-value$< 10^{-6}$). B: Values of the stationary-phase optical density (OD, squares, labels indicate disomic chromosomes) shown against the number of genes in the disomic chromosomes (data from ref. [13]). The stationary-phase OD of aneuploid strains, a complementary proxy for the fitness, displays a significant negative linear correlation with the number of duplicated genes (red line, Pearson's r = -0.68, p-value< 0.005). In panels A and B, the data corresponding to the disomy of Chr VI was not included in the statistical evaluation, as this disomy in a euploid background is known to be lethal on its own [13, 15, 38, 39]. C and D: Scaled growth rate differences of aneuploid strains obtained from ref. [9] (see Material and Methods). The plots show scaled growth rates differences (squares) between aneuploid and haploid (C) or diploid strains (D) against the number of genes carried in unbalanced chromosomes (disomic chromosomes for the left plot and trisomic chromosomes in the right plot). Numbers next to the squares indicate the number of unbalanced chromosome carried in each strain. In both panels the proxied fitness difference of aneuploid strains display a significant negative linear correlation with the number of genes carried in extra chromosomes (red lines, Pearson's r = -0.77 (B), -0.69 (C) and p-value≤ 0.001 (B), 0.004 (C).

correlations between growth rates and number of genes in excess chromosomes of aneuploid strains are also coherently observed in all the stress conditions investigated in the data-set from ref. [9] (Fig. S5 A).

Altogether, this experimental body of evidence suggests a general fitness cost for aneuploid individuals with extra chromosomes with respect to a euploid background, of the form

$$\sigma_c = c_0 n_g, \tag{4}$$

where n_g is the total number of genes carried in the extra chromosomes and c_0 is the average cost per gene, which depends on the external condition and on the background. We note that this model considers chromosome copy number and duplication of different chromosomes equivalent in terms of per-gene cost. Specifically, the average fitness costs (c_0) of aneuploid strains with diploid *vs* haploid background display a linear correlation (Fig. S5, B), suggesting the existence of a condition-specific effect on the fitness cost. Values of the fitness cost in the diploid background are found to be about a factor one-half of those observed in the haploid background, indicating that the development of extra chromosomes is suppressed in haploids and is more likely in diploids, an effect that is in agreement with observations based on evolutionary genomics data [15, 40, 41].

Of note, in Fig. 3A , the disomy of Chr VI shows the largest deviation from the linear decreasing trend (similar deviation was observed in [15]). This deviation results from an additional fitness cost that is specific of this disomy, which was reported to be lethal in the ploidy=1 background [13]. This additional cost is due to the two key cytoskeleton genes TUB2 (tubulin) and ACT1 (actin), which reduce cell viability when their expression is increased [38, 39]. Notably, the effect of the disomy of Chr VI is alleviated in combination with other aneuploidies, for example, Chr I and Chr XIII [13].

A minimal fitness model for aneuploid strains with extra chromosomes

The analyses reported in Fig. 2 and 3 suggest that a global effect of extra chromosomes on the growth rate of a strain is recapitulated by a minimal fitness-landscape model, with no epistatic interactions between genes of the extra chromosomes. In this model, fitness is the sum of two contributions: (i) a fitness cost (σ_c) that captures the empirical observation described by Eq.4 and (ii) a chromosome-specific fitness component, which captures the additional beneficial or detrimental effect of excess chromosomes $\sigma_{\mathrm{kar},s}$. Under these assumptions, the selection coefficient of an aneuploid strain (s) in any given growth condition (environment or stress), with respect to the closest euploid background (haploid or diploid) takes the form

$$\begin{aligned} \sigma_s^{\mathrm{cond}} &= -\sigma_{c,s} + \sigma_{\mathrm{kar},s} \\ &= -c_0 \sum_i \chi_s^i n_i + \sum_i \chi_s^i \sigma_i^{\mathrm{cond}}, \end{aligned} \tag{5}$$

where the karyotype of the strain is defined by the characteristic matrix $\chi_{\mathbf{s}}$, where $\chi_s^i = 1$ if, in the strain s, the ith chromosome exceeds the background ploidy number. The fitness cost of the strain is due to the total number of exceeding chromosomes, $\sigma_s^{\mathrm{cond}} = c_0 \sum_i \chi_s^i n_i = c_0 n_s$, where $c_0 > 0$ is the condition-specific average fitness cost per gene, n_i is the number of genes in the ith chromosome and n_s is the total number of extra chromosome of strain s. Each aneuploid chromosome has an effect on the growth rate σ_i^{cond}, which can either be beneficial ($\sigma_i^{\mathrm{cond}} > 0$) or detrimental ($\sigma_i^{\mathrm{cond}} < 0$) and is condition-specific. This results in the kariotype fitness component $\sigma_{\mathrm{kar},s} = \sum_i \chi_s^i \sigma_i^{\mathrm{cond}}$. A condition (environment or stress) is defined by the value c_0 and the set of values $\{\sigma_i^{\mathrm{cond}}\}$.

The fitness landscape defined by Eq. 5 captures nontrivial behavior of stress phenotypes

The two fitness components of the minimal model, i.e., the fitness costs $\sigma_{c,s}$ and the chromosome specific fitness effects $\sigma_{\mathrm{kar},s}$, can be inferred from large-scale studies of anuploid yeast phenotypes in stressful conditions, such as ref. [9] (see Material and Methods).

The first component captures the global linear decreasing trend of the growth rates of aneuploid strains *vs* the total number of exceeding genes, as discussed above. Interestingly, this component can also explain in quantitative terms the observed linear correlation between the degree of phenotypic variation and the degree of overall growth suppression, observed in the data [9] and modelled in refs [22,24]. In our modelling framework, this correlation corresponds to a linear relationship between the average value ($\overline{\sigma_c}$) and the standard deviation ($\Sigma \equiv (\overline{\sigma_c - (\overline{\sigma_c})^2})^{\frac{1}{2}}$) of the fitness cost evaluated in a cohort of aneuploid strains. Here, we have denoted with $\overline{\cdot}$ averages computed over the cohort of aneuploid strains in a given zgrowth condition. The fitness cost Eq. 4 predicts a linear relationship of the form

$$\overline{\sigma_c} \sim CV(n_g)\ \Sigma, \tag{6}$$

where $CV(n_g) = \frac{\text{St.dev}(n_g)}{\overline{n_g}}$ is the coefficient of variation of the distribution of the number of exceeding chromosomes (the total number of genes contained in aneuploid chromosomes) evaluated in the set of aneuploid strains considered. The quantitative expression Eq. 6 explains about 80% of the observed variability of the growth rates in the data-set of ref. [9], implying that the fitness cost alone cannot explain the whole range of observed phenotypic diversity (Fig. S6).

The deviations from this linear trend are captured by the second (condition- and chromosome-specific) fitness component ($\sigma_{\text{kar},s}$), where the effect of an aneuploid extra chromosome (i) on the growth rate is quantified by a chromosome- and condition-specific fitness effect, σ_i^{cond}. Fig. S7A reports the inferred values of the of the fitness-gain component of each chromosome across stress and control growth conditions for the Pavelka *et al.* data set. These inferred values are net of possible confounding factors due to the per-gene fitness cost highlighted previously. Curiously, the chromosome-specific fitness components in the same environment are generally different (uncorrelated) between the ploidy=1 and ploidy=2 backgrounds (Fig. S7B). This difference could suggest that the effect of chromosome duplication is ploidy-specific, consistently with observations of other ploidy-specific fitness effects [42]. However, since in the Pavelka *et al.* experiments each strain was carrying more than a single aneuploidy, suggesting the presence of epistatic effects between different added chromosomes. Unfortunately, the current data are too sparse to infer such epistatic interactions. Additionally, the difference of the chromosome-specific fitness effect between the ploidy=1 and ploidy=2 background could be related to different physiological constraints seen by haploids and diploids, and to the different relative gene-dosage increase resulting after a duplication in the two different backgrounds.

Looking at Fig. S7A, one clearly sees that adding different specific extra chromosomes can improve or decrease the fitness in a specific environment, but each environment is characterized by the extent of such fitness gains and losses. For example, in stressful environments such 4NQO, adding an extra chromosome to the genetic background could improve or decrease the fitness by a factor that is more than 10-fold larger than performing the same operation in a non-stressful condition such as glycerol media. Because of this property, it is tempting to classify the "harshness" of an environment by the variability in behavior of aneuploids bearing specific extra chromosomes. Indeed, the variability of effects across chromosomes in a fixed given condition is found to be proportional to the fitness cost per gene observed in the same environment (cfr. Fig. S8ABCD), which can be seen as an independent evaluation of the harshness of that environment. Additionally, contrary to the effects of specific chromosomes, the distributions of the fitness components for the ploidy=1 and ploidy=2 backgrounds (shown in Fig. S8CDE) share common properties that are related to the growth condition. In particular, each environment is characterized by distributions of chromosome-specific fitness effects that have a similar width for ploidy=1 and ploidy=2 backgrounds (Fig.S8E).

Expected inter-population dynamics of aneuploids

The minimal fitness-landscape model described by Eq.5 can be used to describe the expected inter-population dynamics of aneuploid strains with a single chromosome gain, by investigating the substitution dynamics associated to Eq. 1 in the landscape (Eq.5) when $\chi_s^i = \delta_{i,j}$, for some $j > 0$, and $\delta_{i,j}$ is the standard Kronecker delta. Following a standard population dynamics approach [43, 44], we can use a probabilistic framework to characterize the selective effects of a generic environment

on the growth rate of a strain with an aneuploid chromosome, by assuming that the beneficial effect (σ_b) is exponentially distributed, $P(\sigma_b) = be^{-b\sigma_b}$. Averages with respect to this distribution, denoted with $\langle\langle\ .\ \rangle\rangle$, quantify the expected dynamics of aneuploid strains with excess chromosomes in a set of conditions. Hence, they can be used to generate predictions on the typical population dynamics of aneuploids. Under these assumptions, the model predicts that the average probability of developing aneuploidy with extra chromosomes,

$$P_a^{\text{inter}} \equiv \langle\langle \mathcal{P}_a \rangle\rangle \simeq e^{-b\sigma_b^*} = e^{-b\frac{c_0 n_g}{1-r}}, \tag{7}$$

decreases exponentially with the number of genes contained in the extra chromosomes, suggesting in particular that the relative abundance of duplicated chromosomes is exponentially suppressed with their length. In addition, the typical selection coefficient of an aneuploid strain that has reached fixation,

$$\sigma_b^{\text{inter}} \equiv \frac{\langle\langle \mathcal{P}_a \sigma_b \rangle\rangle}{\langle\langle \mathcal{P}_a \rangle\rangle} \simeq \frac{1}{b} + \sigma_b^* = \frac{1}{b} + \frac{c_0 n_g}{1-r}\ , \tag{8}$$

is expected to increase linearly with the cost of extra chromosomes, implying in particular that longer chromosomes require higher fitness advantage to reach fixation.

Combined together, the two model predictions (Eq.s 7 and 8), suggest an "equilibrium" distribution of aneuploid strains of the form (see Material and Methods)

$$X_{eq}(n_g) = \frac{1}{Z}\frac{e^{-\kappa n_g}}{n_g}\ , \tag{9}$$

where n_g is the number of genes contained in the aneuploid chromosome, Z is a normalization factor, and κ is an effective fitness cost per gene (see Material and Methods). This prediction is in good agreement with the relative abundances of yeast aneuploid strains observed in evolutionary genomics data (Fig. 4). Interestingly, the numerical values of the effective fitness cost per gene are in agreement with existing experimental evidence [45,46] suggesting a reduced fitness cost for wild strains (collected as "natural strains" in refs. [45, 47] as "wild strains" in ref. [46]). In other words, these strains have a higher propensity to generate aneuploidy, when compared to strains of other kinds, including domesticated, industrial and human-associated strains (cfr. Table S3). We find similar results when comparing the abundance of strains with a ploidy>2 background to that of strains with a lower ploidy background, finding that extra chromosomes are associated to a lower fitness cost in a ploidy>2 background (cfr. Table S3).

Discussion

In yeast, the development of aneuploidy resulting from an accidental chromosome missegregation has been characterized with massive experimental data [3–6, 6–10, 13, 14, 14–16]. As a consequence of this major effort, we are in need of unifying principles to rationalize this wealth of data, and embed the underlying evolutionary dynamics into simple quantitative models. Here we have focused on a specific question, the role of chromosomal duplication with respect to a reference euploid background. Our results show that a simple evolutionary model where a fitness cost of chromosome duplications is counterbalanced by a fitness advantage from the expression of specific genes can explain in quantitative terms two key observations of the emergence dynamics of aneuploidy: (i) chromosome duplications emerge transiently as a "quick fix" to dosage insufficiency of a single gene in stressful environments [11, 13, 48] (ii) depending on the nature of the applied stress, aneuploidy or local mutations may be favored [14].

While traditionally the fitness advantage of a phenotype associated to a certain mutational target was considered to be the primary trait related to its adaptive value, the recent debate has challenged this assumption based on experimental results that highlight an important role of mutational paths and mutation rates. Our analysis of aneuploids with extra chromosomes provides another example where mutational paths with high rates may give a more relevant contribution to adaptation than mutations with large benefits occurring more rarely [27–29].

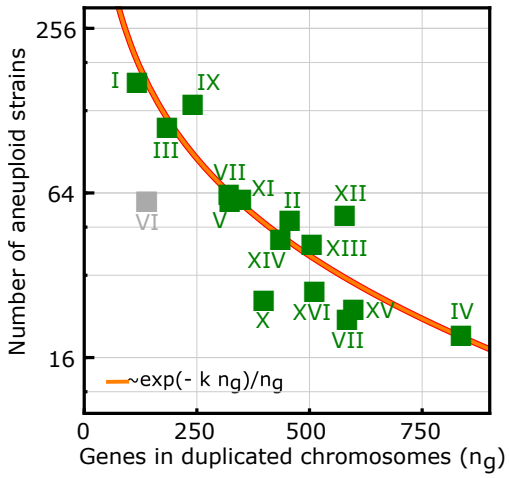

Figure 4: **The fitness landscape derived from phenotypying of laboratory yeast strains explains the relative abundances of yeast aneuploid strains observed in evolutionary genomics data.** Relative abundances of aneuploid strains vs the number of excess genes contained in the aneuploid chromosome (squares). The numbers of aneuploid strains were retrieved from published data collected in eight studies and reported in ref. [15](cfr. Table S3). The orange line shows the fitness model expectation, for the relative equilibrium frequencies set by chromosome acquisition and loss rates of Eq.s (7,8), which predicts a functional dependence of the relative frequencies on the number of excess genes (n_g) of the form $\propto \exp(-\kappa n_g)/n_g$. Numerical values of model parameters are reported in Table S3. Data-count of the duplications of Chr VI (gray square) was not considered in the model fit, since this chromosome is known to be lethal because of the specific effects of the main cytoskeletal genes tubulin and actin [13, 15, 38, 39].

Our results support the existence of a per-gene cost of single-chromosome duplications, which is not trivially expected, due to the numerous documented complex physiological changes that emerge with aneuploidies, such as dosage imbalance, effects on interaction networks, and consequent osmotic effects [7, 49]. An interesting interpretation of this form of the fitness cost is that the reduction of the growth rate of aneuploid strains may be the result of the interdependence between growth rate and gene expression, in accordance to the one described by phenomenological laws first observed in bacteria [50], and more recently also in yeast [51]. Genes contained in an extra chromosome are unnecessary for the survival and their expression induce a reduction of the growth rate by effectively decreasing the fraction of resources allocated to the ribosomal and housekeeping protein sectors, leading to a decrease in growth rate. This connection holds only if the genetic gene dosage is proportional to gene expression, an effect experimentally observed in for yeast [9, 13, 52]. Interestingly, the connection between the fitness cost and gene dosage is coherent with our analysis, since we observe that values of the fitness cost in the diploid background are close to one-half than of those observed in the haploid background, suggesting a connection of the fitness cost per gene to the relative extra gene dosage. Importantly, the linear (per-gene) cost of duplicated chromosomes is a common unifying feature of the fitness landscape in different conditions and environments. The imbalance in protein-ineraction networks caused by extra chromosomes is also expected to be proportional to their gene content (roughly, multiplied by the average number of interactions that each gene participates into and by the average stoichiometric imbalance caused by each dosage change).

The formulation of a minimal fitness-landscape model (Eq.5) informed by data allows for the inference of chromosome-specific fitness effects. Such effects are only related to the dosage increase of genes contained in specific duplicated chromosomes, offering a quantiative framework for the inference of fitness components of early aneuploids. In addition, we have shown that a simple description of the longer-term evolutionary dynamics of our model (Eq.s1,3) in this landscape captures the relative abundance of aneuploidies observed in yeast population genomics data. Hence, this model can be used to investigate both the intra-population dynamics of aneuploidy individuals within an evolving population (cfr. Fig.2) and the substitution dynamics at the inter-population population level (cfr.

Fig.4).

The model introduced here can be extended to describe more complex scenarios. First, it can be applied to investigate the evolutionary consequences of a sudden increase of the mis-segregation rate [6], which can result from the usage of anti-mitotic drugs. Second, it can be used as an ingredient to build models of chromosomal instability, with a clear interest for cancer development [53]. For the latter aspect, it would be important to clarify to what extent the increase of gene dosage translates into protein production in human cells [16].

Simulations of the evolutionary model. We performed numerical simulations of a standard Wright-Fisher model with mutations and selection, with constant population size N. Individuals of the populations are grouped into three distinct and non-overlapping classes: (a) euploid individuals, (b) aneuploid individuals and (c) euploid individuals with point mutations. Class (b) is generated from class (a) with a rate μ_a (per individual, per generation) and its members have a selection coefficient $\sigma_b - \sigma_c$. Similarly, individuals of class (c), characterized by a selection coefficient σ_b, are generated from individuals of class (a) with a rate μ_m (per individual, per generation). The simulation is initialized with all individuals assigned to class (a) and it is stopped when either class (b) or class (c) reaches a frequency $x \geq 0.95$. At the end of each simulation, we recorded the successful class (either (b) or (c)) and the time of appearance (measured in generations) of the first mutant whose descendants took over the whole population (i.e., the emergence time of the their last common ancestor $t_{\min}$).

Evolutionary parameters for the experimental data [14]. To quantify the fitness cost of the aneuploid strain investigated in [14], we made use of growth curves of the aneuploid and the euploid strains, evaluated at permissive conditions, i.e., without stress. We then inferred the growth rates $f_{eu}^{30°C}$ and $f_{an}^{30°C}$ with an exponential fit of the corresponding growth curves (Fig. S1 A). Similarly, for evaluation of the fitness benefit of the anuploid strain in presence of a heat stress (39°C), we inferred the growth rates $f_{eu}^{39°C}$ and $f_{an}^{39°C}$ (Fig. S1 B). The two selection coefficients were then computed from the following set of equations

$$\sigma_c = 1 - \frac{f_{an}^{30°C}}{f_{eu}^{30°C}} \qquad \sigma_b - \sigma_c = \frac{f_{an}^{39°C}}{f_{eu}^{39°C}} - 1. \tag{10}$$

Selection coefficients of the aneuploid strain for the experiment performed in high pH were computed analogously, using growth curves of the aneuploid and euploid strain evaluated in permissive (Fig. S1 C) and stress condition (Fig. S1 D). Numerical values for the inferred growth rates are shown in Tab.S1.

To estimate the effective population size of the wells used during the evolution experiment, we used the following argument. The experiment in [14] was performed in 96 well plates, with a max volume per well $\simeq 0.4ml$. During the experiment, cell density in liquid cultures was monitored by optical density at 600 nm, reached a maximum value $\sim 1\ OD_{600}$. Since the value $OD_{600} = 1$ corresponds to approximately 10^7 cells per ml [54], we estimated the effective population size to be $10^7 \gtrapprox N \gtrapprox 10^6$. In Fig.2 and Fig.S2 we show results obtained with $N = 10^6$ while in Fig. S3 we show equivalent results computed for $N = 10^7$.

The expected cumulative probability for the emergence of aneuploidy with extra chromosomes was computed as using two model ingredient. First, the cumulative distribution describing the probability to have a successful aneuploid mutant (i.e., a mutant that eventually will reach fixation) emerging before time t, which reads

$$\mathcal{C}_a(t) \equiv P(t_{\text{emergence}} \leq t) = \mathcal{P}_a(1 - e^{-(\lambda_a + \lambda_b)t}), \tag{11}$$

where $\mathcal{P}_a$ is the aneuploidy fixation probability (Eq.1), while $\lambda_m = \mu_m N \phi(\sigma_b, N)$ and $\lambda_a = \mu_a N \phi(\sigma_b - \sigma_c, N)$ are the fixation rates for the euploid and the aneuploid mutant. The fixation probabilities are computed according to Kimura's expression $\phi(\sigma, N) = (1 - e^{-2\sigma})/(1 - e^{-2\sigma N})$ [30]. Second, the time to fixation of the anuploid mutant, which reads (see SI and ref [34])

$$t_{\text{fix}}^a = \frac{2\log(2N(\sigma_b - \sigma_c))}{\sigma_b - \sigma_c} \tag{12}$$

Finally, the expected cumulative probability for the emergence of aneuploidy reads

$$\mathcal{C}_a^{\exp}(t) \equiv \mathcal{C}_a(t - t_{\text{fix}}^a) \tag{13}$$

Growth curves data from [13] and inference of growth rates In the data-set collected by [13] yeast strains were grown in liquid cultures, and OD_{600} measurements were taken for several time points. Aneuploidy strains were engineered to harbour two specific genes (HIS3 and KAN), integrated in the two copies of the disomic chromosomes (one per copy). The two genes were also integrated in two chromosomes of the euploid strain. Growth curves were evaluated in media that is selective for the two genes (–His+G418 medium), therefore preventing the loss of one of the two disomic chromosome in the aneuploid strans, but is otherwise be neutral for other traits and does not induce a fitness difference between euploid and aneuploid strains.

Growth rates were then inferred fitting the growth curves to a logistic model

$$Y(t) = \frac{be^{ft}}{1 + a(e^{ft} - 1)}, \tag{14}$$

where f is the growth rate of the exponential phase, b sets the initial condition $Y(0) = b$, and $\frac{b}{a}$ quantifies the fitness in the stationary phase of the growth (max OD value). We have fitted the data with a parametric Bayesian Model $\log(Y(t)) \sim \mathcal{N}((\log(b) + f\,t - \log(1 + a(e^{ft} - 1)), \sigma_Y)$, choosing priors $a \sim \mathcal{U}(0,1)$, $b \sim \mathcal{U}(0,1)$, $f \sim \mathcal{U}(0.1, 1.1)$ and , $1/\sigma_Y^2 \sim \Gamma(0.01, 0.01)$, where $\sim$ stands for distributed as, and $\mathcal{N}$, $\mathcal{U}$, and Γ stand for normal, uniform, and gamma distribution. Model fits to the data are shown in Fig.S4and inferred model parameters are summarized in Table S2.

Data-set from ref. [9] and evaluation of growth rate differences. Yeast strains in the data-set collected by [9] were grown on solid media plates and growth data were obtained by automated spot detection and intensity measurements. The data-set consisted in 38 fully isogenic aneuploid yeast strains with distinct karyotypes and genome contents between $1N$ and $3N$, and 3 strains euploid strains (one for each ploidy). In our analysis, we retained strains whose karyotype can be identified as an aneuploid resulting from chromosome gain, hence, we required the total number of gene contained in the excess chromosomes to be about one half of the total number (≤ 3200 genes). Aneuploidy strains of this form included the majority of the strains of the original dataset (14 strains with a ploidy=1 background and 15 strains with a ploidy=2 background). Since our analysis involved a stratification of the data according to the closest euploid strains, aneuploid strains with a ploidy=3 were discarded as too few for a statistical investigation (less than 5 strains).

Growth rates differences were evaluated as follow. The data-set consisted of values of the Optical Density (OD) of growth assays, evaluated at the same time (t_{max}), of a set of strains with a similar initial number of cells (N_0). Assuming exponential growth (growth assays that reached saturation were excluded from the analysis by the authors), the OD of a specific strain (s), at a given growth condition (c), can be modelled as

$$O_s^c = N_0\, e^{f_s^c t_{\max}}, \tag{15}$$

where f_s^c is the growth rate of strain s in the growth condition c. OD Values were then normalized to the value observed for the euploid strain with a ploidy=1 background, and in the same growing condition, obtaining transformed values

$$\hat{O}_s^c \simeq e^{(f_s^c - f_{EU_1}^c)t_{\max}}, \tag{16}$$

which we have log-transformed to get

$$\hat{\Delta}_s^c \equiv \log(\hat{O}_s^c) \simeq (f_s^c - f_{EU_1}^c)t_{\max}, \tag{17}$$

which are scaled (a-dimensional) growth rate differences between a given strain s and the euploid (pl=1) controll strain, evaluated in the growth condition c. Scaled growth differences w.r.t. the

closest strains were then obtained by difference

$$\Delta_s^c = \hat{\Delta}_s^c - \hat{\Delta}_{EU_1}^c = (f_s^c - f_{EU_1}^c)t_{\max} \quad \text{pl=1 background} \tag{18}$$

$$\Delta_s^c = \hat{\Delta}_s^c - \hat{\Delta}_{EU_2}^c = (f_s^c - f_{EU_2}^c)t_{\max} \quad \text{pl=2 background.} \tag{19}$$

These values were used to evaluate statistics related to the fitness cost component shown in Fig.2 and Fig.s S5 andS6, as well as for the inference of the chromosome fitness components shown in S7 andS8.

Inference of fitness components from data-set from ref. [9] We consider a minimal fitness model, where the growth rate f_s^c of an aneuploid strains s in the growth condition c reads

$$\begin{aligned} f_s^c &= f_{EU}^c - f_{\text{cost},s}^c + f_{\text{kar},s}^c \\ &= f_{EU}^c - c_0 \sum_i \chi_s^i n_i + \sum_i \chi_s^i f_i^c, \end{aligned} \tag{20}$$

where f_{EU}^c is the growth rate of the closest euploid strains to s in the same condition. The karyotype of the strain is defined by the matrix χ, where $\chi_s^i = 1$ if, in the strain s, the ith chromosome exceeds the background ploidy number. The fitness cost of the strain is due to the total number of exceeding chromosomes, $f_{\text{cost},s}^c = c_0 \sum_i \chi_s^i n_i = c_0 n_s$, where $c_0 > 0$ is the condition specific average fitness cost per gene, n_i is the number of genes in the ith chromosome and n_s is the total number of exceeding chromosome of strain s. Each aneuploid chromosome has an effect on the growth rate f_i^c, which can either be beneficial ($f_i^c > 0$) or detrimental ($f_i^c < 0$) and is condition specific, that results in the kariotype fitness component $f_{\text{kar},s}^c = \sum_i \chi_s^i f_i^c$. In the minimal model Eq.21 epistatic interactions between chromosomes are not considered.

For each growth condition of the data-set of Pavelka et al, we have inferred the model parameters c_0 and the chromosome fitness effects $\{f_i^c\}$ as follows. It should be noted that, while Eq.21 requires growth rates (in units $[\text{time}]^{-1}$), the data-set by Pavelka et al consisted of scaled, a-dimensional values $f_s^c\ t_{max}$, where t_{max} is a value that is constant for all the strains considered (the time duration of the growth assay). The model Eq.21 can therefore be inferred with the considered data-sets, since all the growth rates are scaled by the same value, and the inferred model parameters of Eq.21 will be expressed in a-dimensional units.

To estimate the value c_0 we performed a linear fit of the data Δ_c^s (Eq.11, Matherial and Methods) vs n_s, inferring the linear model

$$\Delta_c^{\text{linear},s} = \Delta_c^0 - c_0 n_s. \tag{21}$$

The value of Δ_c^0 is a correction to the fitness of the euploid strain. Since the data was normalized to the growth of the euploid strain with pl=1, in the pl=1 data set we imposed $\Delta_c^0 = 0$ while in the pl=2 the parameter was set free.

Deviations of the data from the linear model were then used to infer the chromosome fitness effects. We first subtracted the linear model contribution, obtaining the detrended data

$$\begin{aligned} \Delta_c^{\text{detrended},s} &\equiv \Delta_s^c - \Delta_c^{\text{linear},s} \\ &= \Delta_s^c - \Delta_c^0 + c_0 n_s. \end{aligned} \tag{22}$$

The chromosome fitness component are the solution of the linear system

$$\vec{\Delta}_c^{\text{detrended}} = \chi \vec{f^c}. \tag{23}$$

Since the matrix χ is sparse, the system of equations Eq.23 can not be solved exactly . Hence, we use the approximated Least Square solution of Eq.23

$$\vec{f^c} = \chi^+ \vec{\tilde{\Delta}}^c \tag{24}$$

where χ^+ is the pseudo-inverse of χ, the matrix that specify the kariotypes of the strains considered. Inferred values of the chromosome fitness components are shown in S7 andS8 (see SI appendix).

Fitness-landscape prediction for the relative abundances of aneuploid strains We computed the equilibrium distribution for the relative abundances of aneuploidy strains as the ratio between the onset rate (r), i.e., at which aneuploid strains reach fixation, and the loss rate (l), i.e., the rate at which a aneuploidy is lost because euploid individuals reach fixation,

$$X_{eq} \propto \frac{r}{l}. \tag{25}$$

In this context, aneuploidy strains are identified by the number of genes that are contained in the duplicated chromosome, hence the only dependence on the chrosomome identity is via its gene content (n_g). The two rates corresponding to the model considered here (see Fig.1) are defined in terms of the model predictions Eq.s (78) as follows.

The onset rate can be written as the product of P_a^{inter}, the intra population fixation probability (Eq.7), and an effective rate μ_{stress}, describing the rate at which yeast population are exposed to stress conditions that can promote the emergence of aneuploidy

$$r(n_g) \quad = \quad \mu_{\text{stress}} P_a^{\text{inter}} \propto e^{-\frac{c_0}{1-r} n_g}. \tag{26}$$

The loss rate rate depends on the environmental condition. If the stress condition that promoted the emergence of aneuploidy is no longer in action, then the population will restore the original euploid strain by losing the duplicated chromsome. In this case the euploid strain, generated with a missegragation rate per individual μ_a^{off}, has a beneficial selection coefficient $\sigma_{eu} = \sigma_c$(computed w.r.t. the anuploidy individual) and the loss rate will equal the substitution rate

$$l^{\text{no stress}}(n_g) = \mu_a^{\text{off}} N \phi(\sigma_e u, N) \simeq 2N\mu_a^{\text{off}} \sigma_c \propto c_0 n_g \tag{27}$$

while $\phi(\sigma, N) = (1-e^{-2\sigma})/(1-e^{-2\sigma N})$ is the Kimura's fixation probability [30]. If the stress condition persists, then in the long term the population will substitute aneuploids with euploid with point mutations, i.e., the second mutational channel considered in our model. In the case the loss of aneuploidy would be attained by the sequential generation of an euploid individual, with a missegragation rate per individual μ_a^{off} and selection coefficient $\sigma_{eu} = \sigma_c - \sigma_b^{\text{intra}} < 0$, which then generates a mutant with a mutation rate individual μ_m and selection coefficient $\sigma_m = \sigma_c > 0$.Note that selection coefficients are now computed w.r.t. the anuploidy individual. These two sequential events are known to take place through the so called "stochastic tunneling" process [55, 56], that makes possible progression through intermediate deleterious alleles without the population ever experiencing the transient decline in fitness that would necessarily occur with sequential fixation. Hence, in presence of stress, the offset rate is equal to the tunneling rate [55–58]

$$l^{\text{stress}}(n_g) \simeq 2N\mu_a^{\text{off}} \mu_m \frac{\sigma_c}{\sigma_b^{\text{intra}} - \sigma_c} \propto c_0 n_g + \mathcal{O}(c_0^2), \tag{28}$$

where we used the expression σ_b^{intra} as in Eq.(8).

While the exact form of the equilibrium distribution will differ if considering persisting/non persisting stress conditions after the fixation of aneuploidy, it can be expressed in general terms as a scaling law (*vs* s the number of genes contained in the aneuploid chromosome n_g) that is valid in both conditions, and takes the form

$$X_{eq}(n_g, k) \propto \frac{e^{-k\, n_g}}{n_g}, \tag{29}$$

where $k \equiv \frac{c_0}{1-r}$ is defined in terms of the condition-specific fitness cost per gene (c_0) and the mutational bias towards the generation of anuploidy individuals $r = \mu_m/\mu_a$ (see Main Text). To account for the variability of the growing conditions, which reflects in the variability of the parameter k, we assume the set of environmental stresses to be described by a uniform distribution in for $k \in [0, 2\kappa]$, where 2κ is an upper bound for k. By averaging Eq. 29 over this distribution we find

$$X_{eq}(n_g) \propto \frac{e^{-\kappa\, n_g}}{n_g} + \mathcal{O}(\kappa^2), \tag{30}$$

whose normalized form corresponds to Eq. 9. The value of the parameter κ is an effective fitness cost per gene, which is proportional to the max value of c_0 of the set of growing conditions considered. We note that the numerical value of c_0 is expected to be lower than the inverse of the typical chromosome size (the longest chromosome in yeast has $n_g \simeq 600$ genes), supporting the approximations taken in Eq.s (28,29). This approximation is also validated a-posteriori, by the numerical values obtained in the model fit (cfr. Tab.S3).

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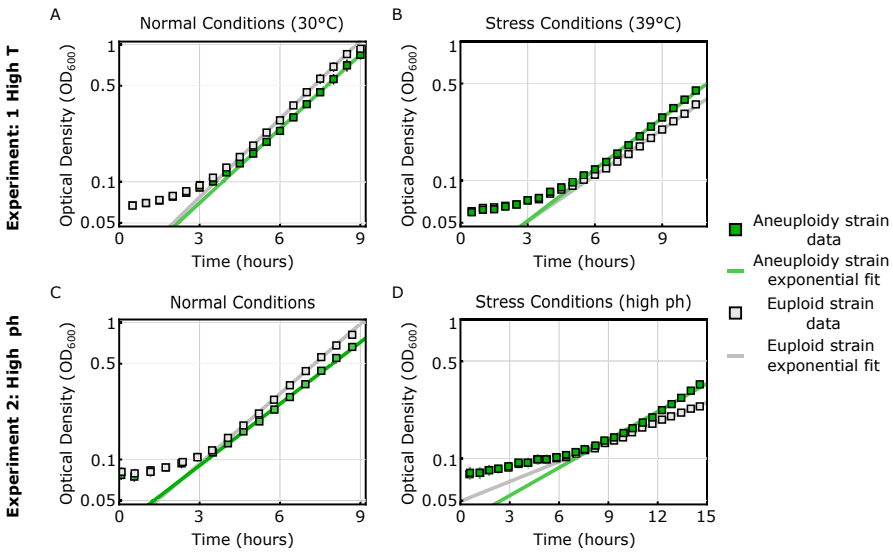

Figure S1: **Growth rates describing of the aneuploid and euploid strain from ref. [14] are inferred from growth curves.** Shown here are growth curves (Optical Density vs time) of the aneuploid strain (diploid strain with the trisomy of chromosome III) and of the diploid strain with the same genetic background evaluated both in normal conditions (30°C, A) and in stress conditions (39 °C, B). Similarly, in C and D we show the growth curves of the aneuploid strain aneuploid strain (diploid strain with the trisomy of chromosome IV) and of the diploid strain with the same genetic background evaluated both in normal conditions (C) and in stress conditions (high ph, D) The experimental data (squares + bars, showing mean and standard deviation evaluated over a set of $\sim$ 35 replicates) is shown together with an exponential fit (solid lines), evaluated neglecting the lag phase ($\sim$ 4 hours in A, $\sim$ 5.5 hours in B ,$\sim$ 4 hours in C and $\sim$ 7.5 hours in D). Values of the inferred growth rates are reported in Table S1.

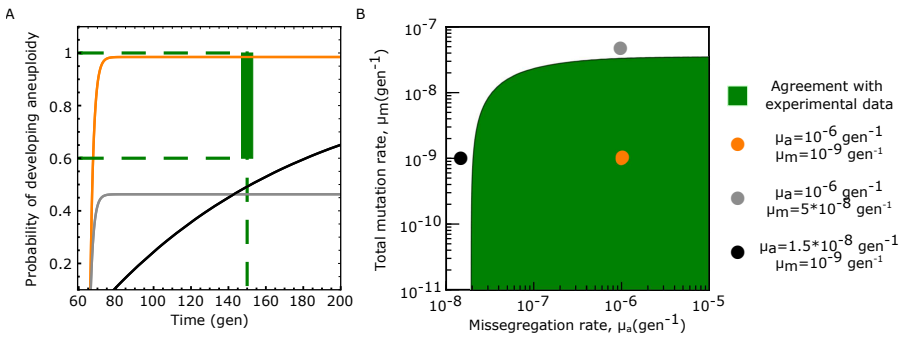

Figure S2: **Model predictions agree with laboratory-evolution data from ref. [14] (High ph experimental setup)**. (A) Expected cumulative probability for the emergence of aneuploidy with extra chromosomes vs the time to reach fixation (see Material and Methods), computed according to the model prediction (Eqs 1, 3) shown for three combinations of the values of the model parameters (μ_a, μ_m) (color coded, numerical values reported in the legend of the plot). In the experiment, where a yeast population was exposed to stress by increasing the temperature to $39C$, 1 out of 1 yeast population developed chromosomal duplications ($CI_{66\%} = [0.6, 1]$ for the probability to develop aneuploidy), and the fixation wes reached before 150 generations. Hence, the experimental data fall in region of the plot corresponding to $P_a \in [0.6, 1]$ and $t = 150gen$, marked in green, delineate. Trajectories predicted by the model that cross this region are in agreement with the experimental data. Similarly, in (B) we show the combinations of the numerical values of the model parameters (μ_a, μ_m) that are in agreement with the experimental data, while coloured dots marks the values corresponding to the trajectories shown in A. Numerical values of the beneficial selection coefficient ($\sigma_b = 0.29\,\text{gen}^{-1}$) and for the fitness cost of aneuploidy ($\sigma_c = 0.12\,\text{gen}^{-1}$) were obtained from exponential fits of the growth curves of the corresponding yeast strains [14], (see Material and Methods and Fig. S1). The effective population size was set to $N = 10^6$ individuals (Fig. S3 shows results for $N = 10^7$).

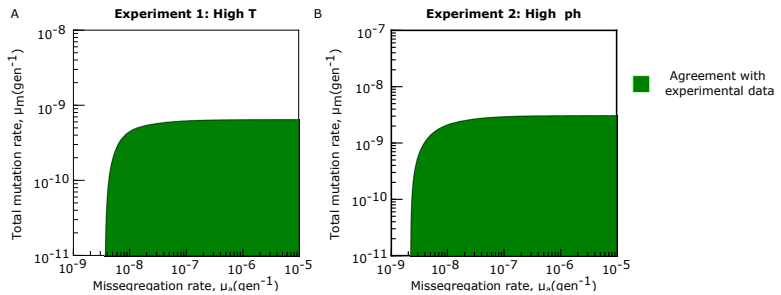

Figure S3: **Quantitative model predictions agree with the laboratory evolutionary experiment from ref. [14] for** $N = 10^7$. Values of the model parameters (μ_a, μ_b) for which the model prediction is in agreement with the experimental data of ref [14] when assuming a population size of $N = 10^7$ individuals, for the experimental setup at high temperature (A) and high ph(B) of agreement b as Fig.**??**B

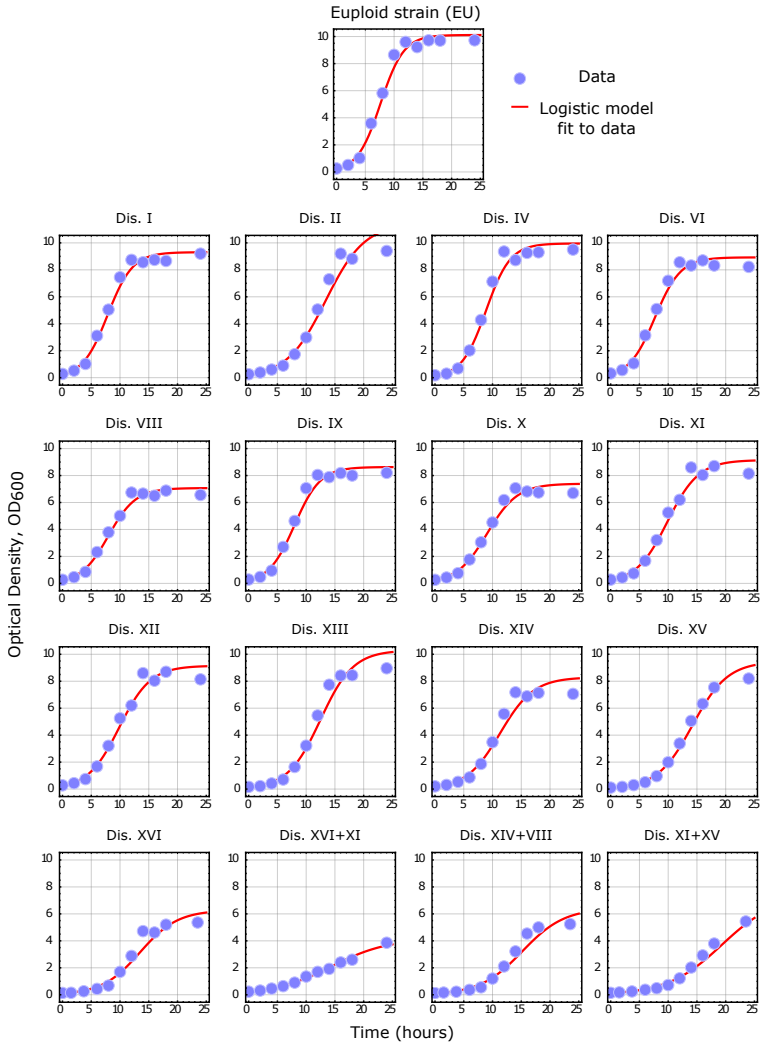

Figure S4: **Growth rates of aneuploid strains from ref. [13] are inferred with a logistic fit of growth curves.** Shown here are growth curves (Optical Density vs time) of the aneuploid strain and of the euploid strains with the same genetic background taken form Torres at al. The experimental data (circles) are shown together with a logistic fit (solid red lines). Model parameters were inferred with a Bayesian framework (see Material and Methods). Values of the posterior mean values are reported in Table S2.

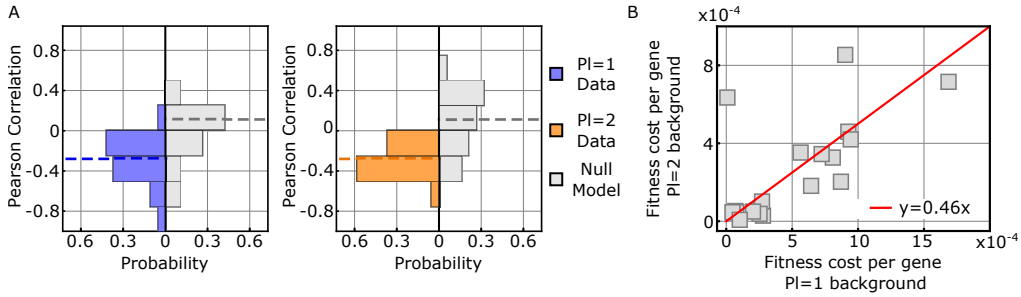

Figure S5: **Linear negative correlations between growth rates and number of genes in exceeding chromosomes of aneuploid strains are coherently observed in all growth conditions.**A: Histograms of the values of the Pearson's correlation coefficients of aneuploidy strains with a Ploidy=1 (Left) and a Ploidy=2 background (Right, for the data-set from ref. [9]. In each condition, the Pearson coefficient was evaluated between the values of strain growth rates and the corresponding total number of genes contained in the aneuploidy chromosomes. The null model was obtained with a randomization test, where, in each conditions, growth rates and number of exceeding genes were randomly shuffled and the Pearson correlation coefficient was evaluated for the shuffled data. Dashed lines mark the mean value of each histogram. The difference between the null model distribution and the corresponding distributions of Pl=1 and Pl=2 background are statistically significant ($p_{val} = 0.00003, 0.005$ respectively, Mann Whitney U test). B: Scatter plot for the fitness cost per gene (c_0) evaluated for Pl=1 and Pl=2 strains (each data-point correspond to the same condition). The values of the fitness cost display a statistically significant linear correlation (Pearson Correaltion coefficient 0.68, $p_{val} < 0.002$). The red line show the best linear fit of the data-points.

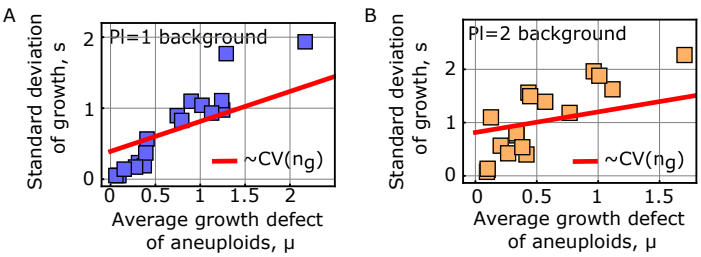

Figure S6: **The fitness cost model predicts a linear relationship between the average fitness defect of aneuploids and standard deviation of growth rates, and explains about** 80% **of the observed dispersion.** A and B: Model predictions capture large-scale phenotype data from ref. [22]. The scatter plots of the average growth rate defect (μ) of an aneuploid strain across several conditions (environments and stresses) versus its standard deviation across the same set of conditions (s). Each square represents a strain of the aneuploid collection of ref. [9] (see Materials and Methods for description of the data-set). Panel A refers to a haploid background, whereas panel B refers to a diploid background. Our form of the fitness cost predicts a linear relation between μ and s, with a slope equal to the coefficient of variation (CV) of the distribution of the number of excess genes (n_g) contained in the aneuploid chromosomes across the set of strains (see Materials and Methods). The red lines show that the this model components alone can describe the observed linear trend and explain the data only partially, with values of the R^2 statistics: $0.84, 0.80$ for panel A and B respectively,

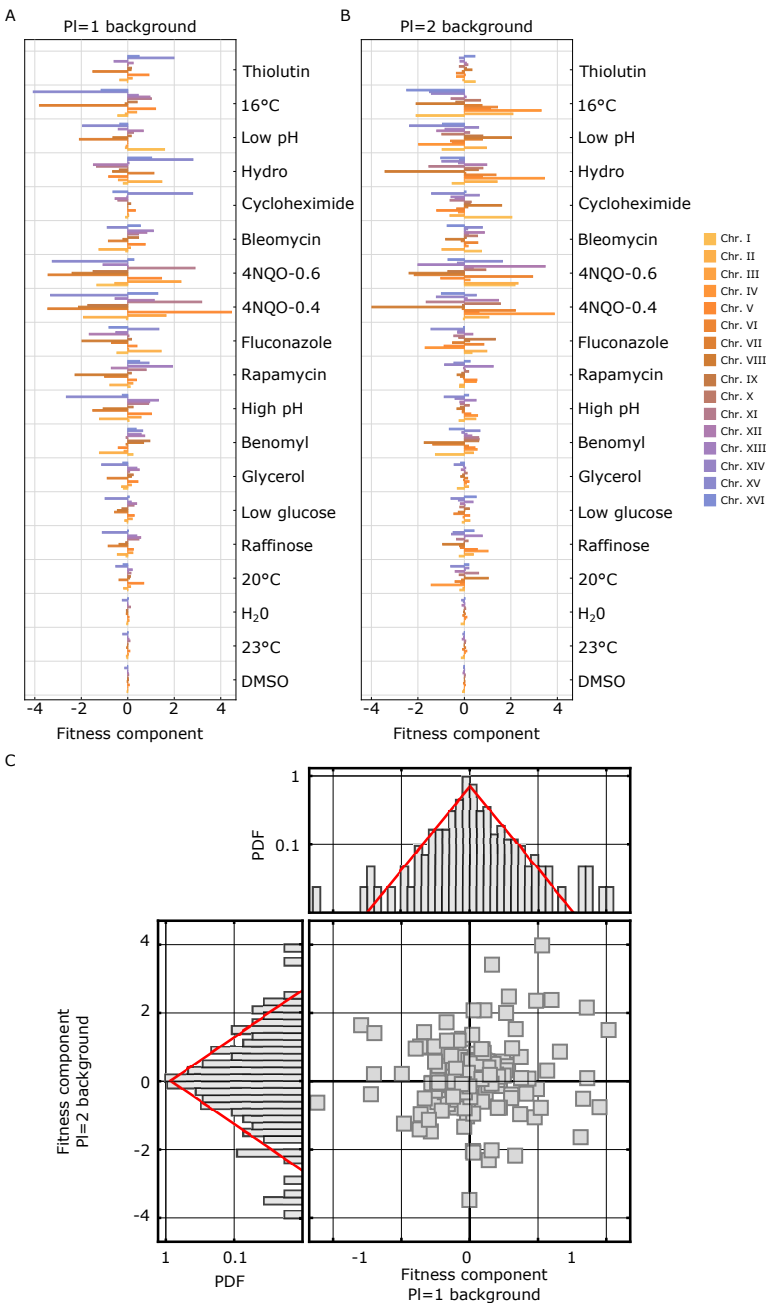

Figure S7: **Chromosome fitness components of aneuploid strains can be inferred from measured growth rates.** The inferred fitness component of A, a disomic chromosome in a ploidy=1 background, and B, a trisomic chromosome in a ploidy=2 background, is shwon here as a function of the stress condition in which growth rates were evaluated (shown in the x axis). In both the two panels, the chromosome-specific component is shown with a bar plot color coded according to the legend shown on the right. Chromosome fitness components were inferred from growth rates obtained from [9]. Details about the inference are given in Materials and Methods.B. Statistics of the inferred values of the selection coefficients of aneuploidy chromosomes, inferred from [9],and evaluated across several stress conditions. The central panel shows the scatter plot for the values of the chromosomal selection coefficient evaluated in strains with ploidy=1 background vs ploidy=2 background (each square correspond to the same condition and the same chromosome). The data does not show statstically significant correlation (Pearson's r=0.11). Left and top panels show the probability distribution density of the chromosomal selection coefficients across all conditions and for all chromosomes together for (Top) ploidy=1 and (Left) ploidy=2 background, respectively (gray boxes). The two distributions are in very good agreement with a Laplace distribution (red lines, mean values $-0.01, 0.02$ and variance $1, 0.7$ respectively). Note that in the central panel we report only components that are present in both data-sets.

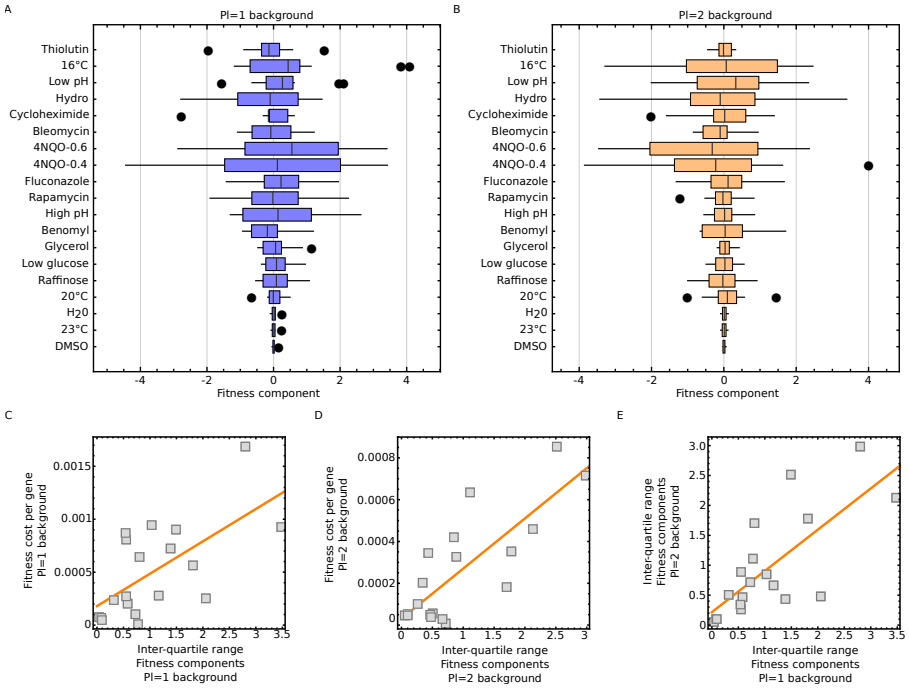

Figure S8: **The statistical properties of the distributions of chromosomal fitness components classify environments by harshness.** Panels A and B show Box-Whisker plots for the distributions of the inferred values of the chromosome-specific fitness components for each environment. Panel A shows the distributions for ploidy=1 background and panel B shows the distributions for ploidy=2 background. In the boxes, the black line marks the mean value of the distribution, the boxes make the lower (Q1) and upper (Q3) quartile. Whiskers mark the minumum-maximum values and circles mark outliers (points beyond the inter-quartile range from the edge of the box). C: Scatter plot of the inter-quartile ranges of the distributions shown in A *vs* fitness cost per gene in the ploidy=1 background, supporting the idea that the environment-specific inter-chromosome variability of fitness effects is a proxy of environmental harshness. D: Scatter plot for the inter-quartile ranges of the distributions shown in B *vs* fitness cost per gene in the pl=2 background. E: Scatter plot between the inter-quartile ranges of the distributions for ploidy=1 and polidy=2 backgrounds, showing that the width of the distributions are correlated. In panels C-D-E we observe a statistically significant linear correlation coefficient, with Pearson's r values= $(0.8, 0.7, 0.6)$ and p-val= $(0.00004, 0.0003, 0.003)$ respectively.

Table S1: **Inferred Values of the growth rates of the aneuploid and euploid strain from ref. [14]**

High Temperature

	Estimate (h^{-1})	Standard Error (h^{-1})
$f_{\text{eu}}^{30°C}$	0.439	0.004
$f_{\text{an}}^{30°C}$	0.415	0.006
$f_{\text{eu}}^{39°C}$	0.253	0.005
$f_{\text{an}}^{39°C}$	0.284	0.003

High Ph

	Estimate (h^{-1})	Standard Error (h^{-1})
$f_{\text{eu}}^{\text{normal ph}}$	0.392	0.005
$f_{\text{an}}^{\text{normal ph}}$	0.345	0.005
$f_{\text{eu}}^{\text{high ph}}$	0.109	0.002
$f_{\text{an}}^{\text{high ph}}$	0.154	0.005

Table S2: **Posterior mean values of the model parameters for the logistic fit** $y(t) = \frac{be^{ft}}{1+a(e^{ft}-1)}$ **of the growth data from ref. [13]**

Strain	# exceeding genes	f (h^{-1})	a	b	inverse variance $1/\sigma_Y^2$
Eu	0	0.5	0.022	0.22	38
Dis. I	117	0.46	0.026	0.25	48
Dis. II	456	0.46	0.025	0.24	48
Dis. IV	836	0.2	0.053	0.22	169
Dis. VI	139	0.29	0.019	0.22	35
Dis. VIII	321	0.45	0.031	0.28	43
Dis. IX	241	0.47	0.015	0.15	35
Dis. X	398	0.44	0.028	0.24	40
Dis. XI	348	0.42	0.033	0.24	51
Dis. XII	578	0.34	0.02	0.17	29
Dis. XIII	505	0.37	0.026	0.24	48
Dis. XIV	435	0.38	0.031	0.23	61
Dis. XV	597	0.33	0.0095	0.09	55
Dis. XVI	511	0.35	0.012	0.13	25.
Dis. XVI+XI	859	0.27	0.016	0.1	19
Dis. XIV+VIII	756	0.3	0.016	0.1	17
Dis. XI+XV	945	0.21	0.016	0.12	33

Table S3: **Best-fit model parameters for the aneuploid strains abundances data ([15])**. Numerical values of the model parameters for the fit of Eq.**??** to aneuploidy strains abundances data. In (i) we considered the full data-set presented in ref. ([15], where authors aggregated data for aneuploidy strains from 8 independent studies. In (ii) we split the data-set into two subsets, the subset of "natural strains" from ref. [47] and its complement set, in order to evaluate differences between model parameters for the two subsets. Similarly, in (iii) we compared the set of "wild strains" from ref. [15] and its complement set. In (iv) we focused on the subset of natural strains only, which we further partitioned into aneuploid strains with a ploidy>2 background and strains with ploidy=1 and ploidy=2 background.

	Dataset	Normalization, $1/Z$	Effective cost per gene, κ	N_{strains}
(i)	All strains (ref.s [40, 47, 59–64])	24000.	5×10^{-4}	936
(ii)	Natural strains (ref.s [47])	6300.	2.1×10^{-4}	295
	Complement set (ref.s [40, 59–64])	17000.	5.7×10^{-4}	641
(iii)	Wild Strains(ref.s [47, 60])	4400.	2.2×10^{-5}	237
	Complement (ref.s [40, 47, 59, 61–64])	20000.	7.4×10^{-4}	699
(iv)	Natural strains, ploidy >2 (ref [47])	1100.	2.5×10^{-7}	63
	Natural strains, ploidy 1 and 2 (ref [47])	5100.	3.7×10^{-4}	232