

Aneuploidy can be an evolutionary detour on the path to adaptation

Ilia Kohanovski^{a,b,*}, Martin Pontz^{a,*}, Orna Dahan^c, Yitzhak Pilpel^c, Avihu H.
Yona^d, and Yoav Ram^{a,1}

^aSchool of Zoology, Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel

^bSchool of Computer Science, Reichman University, Herzliya, Israel

^cDepartment of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel

^dInstitute of Biochemistry, Food Science and Nutrition, Robert H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem, Israel

*These authors contributed equally to this work

¹Corresponding author: yoav@yoavram.com

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Abstract

16 Aneuploidy is common in eukaryotes, often leading to decreased growth and fitness. How-
18 ever, evidence from yeast and other fungi, as well as human tumour cells, suggests that specific
20 aneuploidies can be beneficial under stressful conditions and facilitate adaptation. In a prominent
22 example, an evolutionary experiment with yeast, populations evolving under heat stress had be-
come aneuploid (chromosome III), only to later revert back to euploid after genetic mutations have
accumulated. It has therefore been suggested that aneuploidy serves as a "stepping stone" on the
path to adaptation.

24 Here, we test this hypothesis. First, we apply DNA sequencing to show that mutant alleles
common in aneuploid cells are uncommon in the evolved euploid population. Second, we develop
26 an evolutionary model with both aneuploidy and mutation, and fit it to the results of the experiment
using a Bayesian inference framework. We then predict the genotype frequency dynamics during
the experiment, demonstrating that the majority of the evolved euploid population likely did not
28 descend from aneuploid cells, but rather directly from the euploid wild-type population. Our
model shows how the beneficial mutation supply—the product of population size and beneficial
30 mutation rate—determine the evolutionary dynamics: with a low mutation supply, a large fraction
of the evolved population may descend from aneuploid cells; but with a high mutation supply,
32 beneficial mutations are generated before fixation of aneuploidy, and can outcompete aneuploidy
due to the latter's inherent fitness cost.

34 Together, our results suggest that despite its potential fitness benefits under stress, aneuploidy
can be an evolutionary "detour" rather than a "stepping stone": it can delay, rather than facilitate,
36 the adaptation of the population, and cells that become aneuploid may leave less descendants
compared to cells that remain diploid.

38 Introduction

Aneuploidy is an imbalance in the number of chromosomes in the cell: an incorrect karyotype.
40 Evidence suggests aneuploidy is very common in eukaryotes, e.g. animals^{42,33,2}, and fungi^{36,65,40,54}. An euploidy has been implicated in cancer formation, progression, and drug resistance^{4,44,42,21}. It
42 is also common in protozoan pathogens of the *Leishmania* genus, a major global health concern³¹, and contributes to the emergence of drug resistance⁴⁵ and virulence³² in fungal pathogens, which
44 are under-studied⁴¹, despite infecting a billion people per year, causing significant morbidity in >150 million and death in >1.5 million people per year^{45,41}.
46 Experiments with human and mouse embryos found that most germline aneuploidies are lethal. Aneuploidies are also associated with developmental defects and lethality in other multicellular organisms⁴⁸. For example, aneuploid mouse embryonic cells grow slower than euploid cells⁵⁹. Similarly, in unicellular eukaryotes growing in benign conditions, aneuploidy usually leads to slower growth and
50 decreased overall fitness, in part due to proteotoxic stress due to increased expression, gene dosage imbalance, and hypo-osmotic-like stress^{34,57,36,48,43,24,64,58,60}.
52 However, aneuploidy can be beneficial under stressful conditions due to the wide range of phenotypes it can produce, some of which are advantageous^{36,60}. Indeed, in a survey of 1,011 yeast strains,
54 aneuploidy has been detected in about 19%³⁷. Thus, aneuploidy can lead to rapid adaptation in unicellular eukaryotes^{15,56,19,39}, as well as to rapid growth of somatic tumour cells^{44,50}. For example,
56 aneuploidy in *Saccharomyces cerevisiae* facilitates adaptation to a variety of stressful conditions like heat and pH⁶², copper^{7,15}, salt¹⁰, and nutrient limitation^{11,17,1}, with similar results in *Candida albicans*⁶⁰. Importantly, aneuploidy can also lead to drug resistance in pathogenic fungi such as *C. albicans*^{47,46,14} and *Cryptococcus neoformans*⁵¹, which cause candidiasis and meningoencephalitis,
60 respectively.

Yona et al.⁶² demonstrated experimentally the importance of aneuploidy in adaptive evolution. They
62 evolved populations of *S. cerevisiae* under strong heat stress. The populations adapted to the heat stress within 450 generations, and this adaptation was determined to be due a duplication of chromosome III.
64 Later on, after more than 1,500 generations, the populations reverted back to an euploid state, while remaining adapted to the heat stress. Aneuploidy was therefore suggested to be a *transient adaptive solution*, because it can rapidly appear and fixate in the population under stressful conditions, and can then be rapidly lost when the cost of aneuploidy outweighs its benefit—after the stress is removed,
68 or after "refined" beneficial mutations appear and fixate⁶². Furthermore, it has been suggested that aneuploidy is an evolutionary "stepping stone" that facilitates future adaptation by genetic mutations,

70 which require more time to evolve^{62,61}.

Here, we test the hypothesis that aneuploidy is a *an evolutionary stepping stone* that facilitates adaptive evolution by genetic mutations Yona et al.⁶¹. First, we sequenced the genomes of evolved populations reported in⁶² and analyzed their mutant allele frequencies to assess if the evolved euploid cells are descended from aneuploid cells. Second, we develop an evolutionary genetic model and fit it to the experimental results of Yona et al.⁶² in order to predict the genotype frequency dynamics in the experimental populations, thereby estimating the frequency of evolved euploid cells that descended from aneuploid cells. Our results show that aneuploidy reached high frequencies in the experimental populations, but nevertheless, the majority of cells in the evolved euploid population likely did not descend from aneuploid cells, but rather directly from wild-type euploid cells. These results suggest that at the lineage level, aneuploidy may be an evolutionary detour, rather than a stepping stone, on the path to adaptation.

82 Results

In the heat-stress experiment of Yona et al.⁶², four populations of *S. cerevisiae* evolved under 39 °C. Aneuploidy fixed in all four experimental repetitions in the first 450 generations. Two of the repetitions, marked *H2* and *H4*, carried no large-scale duplications other than a chromosome III trisomy. These two repetitions continued to evolve under the same conditions, wherein aneuploidy was eliminated by generation 1,700 and 2,350 in *H4* and *H2*, respectively.

88 **Empirical frequencies of mutant alleles.** For each of two evolved populations (*H2* and *H4*) we sequenced the ancestral diploid population (generation 0), the aneuploid population (generation 450), and the evolved euploid population (generation 1,700 or 2,350) to estimate the mutant allele frequencies (Tables S1 and S2). Overall, between 100 and 173 mutant alleles were detected with at least a single read in the six populations that were sampled. Disregarding 45 and 40 alleles that were present in the ancestral populations at a frequency >10%, the aneuploid and euploid populations carried a large number of mutant alleles: 82 and 95, respectively, in repetition *H2*, and 60 and 66 in repetition *H4*.

96 Surprisingly, out of all these mutant alleles, none was present at a frequency >20% in both the aneuploid and the evolved euploid populations. More importantly, a high mutant allele frequency in the aneuploid population was associated with a low frequency in the evolved euploid population, and vice-versa (Spearman's correlation coefficient $\rho = -0.64$ and -0.66 in the two experimental

100 repetitions; Figure 1), suggesting that mutant alleles frequent in the aneuploid populations decreased
 in frequency when aneuploidy was lost. These results suggest evolved euploid cells are unlikely to
 102 have descended from aneuploid cells.

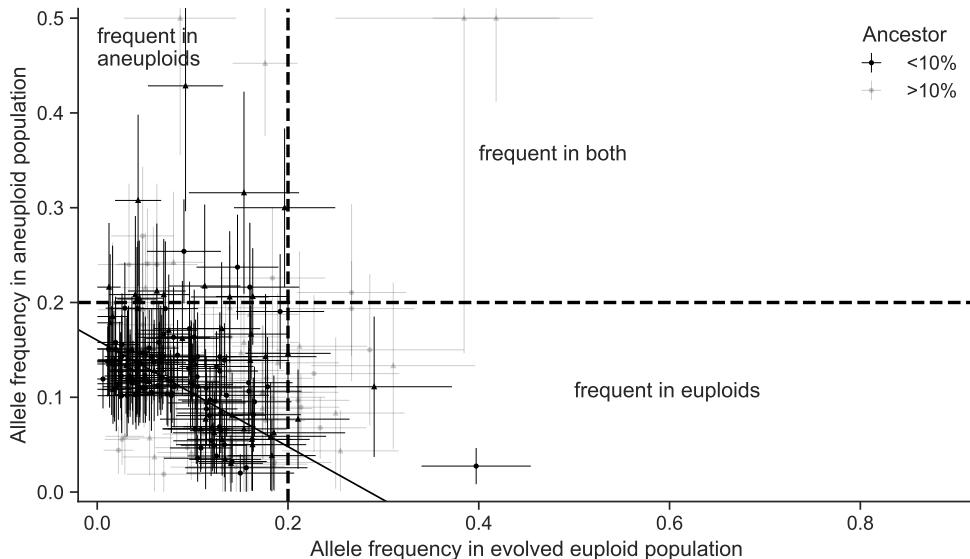


Figure 1: Frequencies of mutant alleles in the experimental populations are negatively correlated. Frequencies of mutant alleles when trisomy was widespread in the population (y-axis) and after it was eliminated (x-axis) in two experimental repetitions (circles for *H2* and triangles for *H4*) from Yona et al.⁶². Mutant alleles with >20% in the aneuploid population were <20% in the euploid population, and vice versa (the upper-right quadrant is empty), suggesting that the majority of evolved euploid cells did not descend from the most common aneuploid genotypes. Alleles with frequency below and above 10% in the ancestral populations are in black and gray, respectively. Solid black line is a linear orthogonal distance regression line (slope=−0.559, intercept=0.164; a regression through alleles that reach at least 20% in one of the populations has slope=−0.645 and intercept=0.297). Dashed vertical and horizontal lines show allele frequencies of 20%. Error bars show SEM (standard error of the mean) assuming the number of reads in Binomially distributed; the SEM may be large when the total number of reads is small. For the 18 mutant alleles with high frequency in the aneuploid populations (>20%), the highest frequencies in the euploid populations were 15.4%, 16%, 16.3% and 19.6% (the rest were below 15%). Similarly, for the 48 mutant alleles with high frequency in the evolved euploid populations, the highest frequencies in the aneuploid populations were 2.7%, 7.7%, and 11.1% (the rest were below 1%).

Evolutionary genetic model. To explore the dynamics during the evolutionary experiments, we
 104 developed an evolutionary genetic model, fitted the model to empirical data, and used it to predict the genotype frequency dynamics, or specifically, the fraction of the evolved euploid population descended

106 from aneuploid cells.

The model includes the effects of natural selection, genetic drift, aneuploidy, and mutation, and follows
108 a population of cells characterized by their genotype: euploid wild-type, $2n$, is the ancestral diploid
genotype; euploid mutant, $2n^*$, has a diploid karyotype and a single beneficial mutation; aneuploid
110 wild-type, $2n+1$, has an extra chromosome due to a chromosome duplication event; and aneuploid
mutant, $2n+1^*$, has an extra chromosome (like $2n+1$) and a beneficial mutation (like $2n^*$). Fitness
112 values of the different genotypes are denoted by w_{2n} , w_{2n^*} , w_{2n+1} , and w_{2n+1^*} , and the rate of mutation
and aneuploidy are denoted by μ and δ , respectively. See Figure 2 for an illustration of the model.

We fitted this model to the experimental results⁶² – time for fixation (>95%) and for loss (<5%) of
114 aneuploidy – using approximate Bayesian computation with sequential Monte Carlo (ABC-SMC)⁵²,
thereby inferring the model parameters: rates aneuploidy and mutation and the fitness of all genotypes.
116 We then sampled posterior predictions for the genotype frequency dynamics using the estimated
parameter values and compared different versions of the model to test additional hypotheses about the
118 evolutionary process.

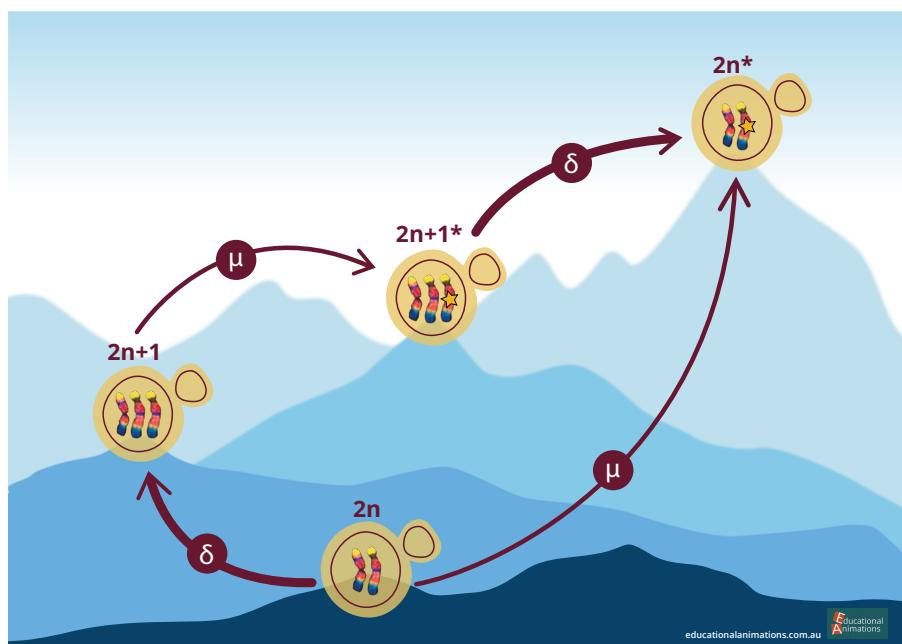


Figure 2: Model Illustration. There are four genotypes in our model: euploid wild-type, $2n$; euploid mutant, $2n^*$; aneuploid wild-type, $2n+1$; and aneuploid mutant, $2n+1^*$. Overall there are two possible trajectories from $2n$ to $2n^*$. Arrows denote transitions between genotypes, with transition rates μ for the beneficial mutation rate and δ for the aneuploidy rate. Elevation differences illustrate the expected, rather than the assumed, fitness differences between the genotypes.

120 **Estimated rates and fitness effects of aneuploidy and mutation.** We inferred the posterior distribution
121 of model parameters (Figure 3). We report parameter estimates using the MAP (maximum a
122 posteriori) and providing the 50% HDI (highest density interval) in square brackets. See Supplementary
123 Material for sensitivity analysis.

124 The estimated beneficial mutation rate is $\mu = 2.965 \cdot 10^{-6}$ [$2.718 \cdot 10^{-7} - 3.589 \cdot 10^{-6}$]. From the
125 literature, the mutation rate per base pair is roughly $2 - 3 \cdot 10^{-10}$ (refs.^{66,30}), but it may be higher under
126 heat stress, as several stresses¹⁸, including heat²⁰, may cause hypermutation in yeast. If we assume a
127 10-fold increase over the mutation rate reported in the literature, then the estimated beneficial mutation
128 rate can be explained by a genomic target size of 1,000 base pairs (i.e., 1,000 base pairs across the
129 genome in which a mutation would provide a fitness benefit). Supporting this, Flynn et al.¹² used a
130 deep mutational scan of a single protein, Hsp90, to find 465 amino-acid variants that increased growth
131 rate in 37 °C. Furthermore, Yona et al.⁶² found at least 10 genes on chromosome III that increased
132 heat tolerance when over-expressed. Assuming that other chromosomes also have a similar number of
133 heat-tolerance genes (and even more, as chromosome III is one of the smallest chromosomes¹⁶), we
134 get a total of 160 heat-tolerance genes in the genome. Indeed, mutations were found in 97 genes in an
135 evolutionary experiment with yeast under heat stress²⁰. Thus, to get a genomic target size of 1,000, it is
136 enough that the average gene target size is 6.25 base pairs. For example, Kohn and Anderson²⁷ found
137 a target size of 11 in a proton exporter gene (*PMA1*) that contributes to high-salt adaptation.

138 The estimated aneuploidy rate, $\delta = 1.72 \cdot 10^{-3}$ [$1.47 \cdot 10^{-3} - 2.786 \cdot 10^{-3}$] is higher than in previous
139 studies: for chromosome III in diploid *S. cerevisiae*, Zhu et al.⁶⁶ estimated $6.7 \cdot 10^{-6}$ chromosome
140 gain events per generation, and Kumaran et al.²⁹ estimate $3.0 \cdot 10^{-5} - 4.3 \cdot 10^{-5}$ chromosome loss
141 events per generation (95% confidence interval). However, this difference may be partly explained
142 by an increased aneuploidy rate during heat stress: heat shock can increase the rate of chromosome
143 fragment loss by 2-3 orders of magnitude⁵.

144 The estimated fitness values are $w_{2n+1} = 1.022$ [$1.021 - 1.023$], $w_{2n+1*} = 1.025$ [$1.024 - 1.026$],
145 $w_{2n*} = 1.028$ [$1.026 - 1.029$], all relative to the fitness of $2n$, which is set to $w_{2n} = 1$. Thus, we
146 can infer that the cost of chromosome III trisomy is $c = w_{2n*} - w_{2n+1*} = 0.003$ (or 0.3%) and the
147 benefit of trisomy is $w_{2n+1} - 1 - c = 0.019$ (1.9%), whereas the benefit of the beneficial mutation is
148 $w_{2n*} - 1 = 0.028$ (2.8%).

149 If we allow for transitions (mutation, chromosome loss and gain) to less-fit genotypes (e.g., $2n^*$ to
150 $2n+1^*$), then we infer similar but slightly different values, see Supplementary Material.

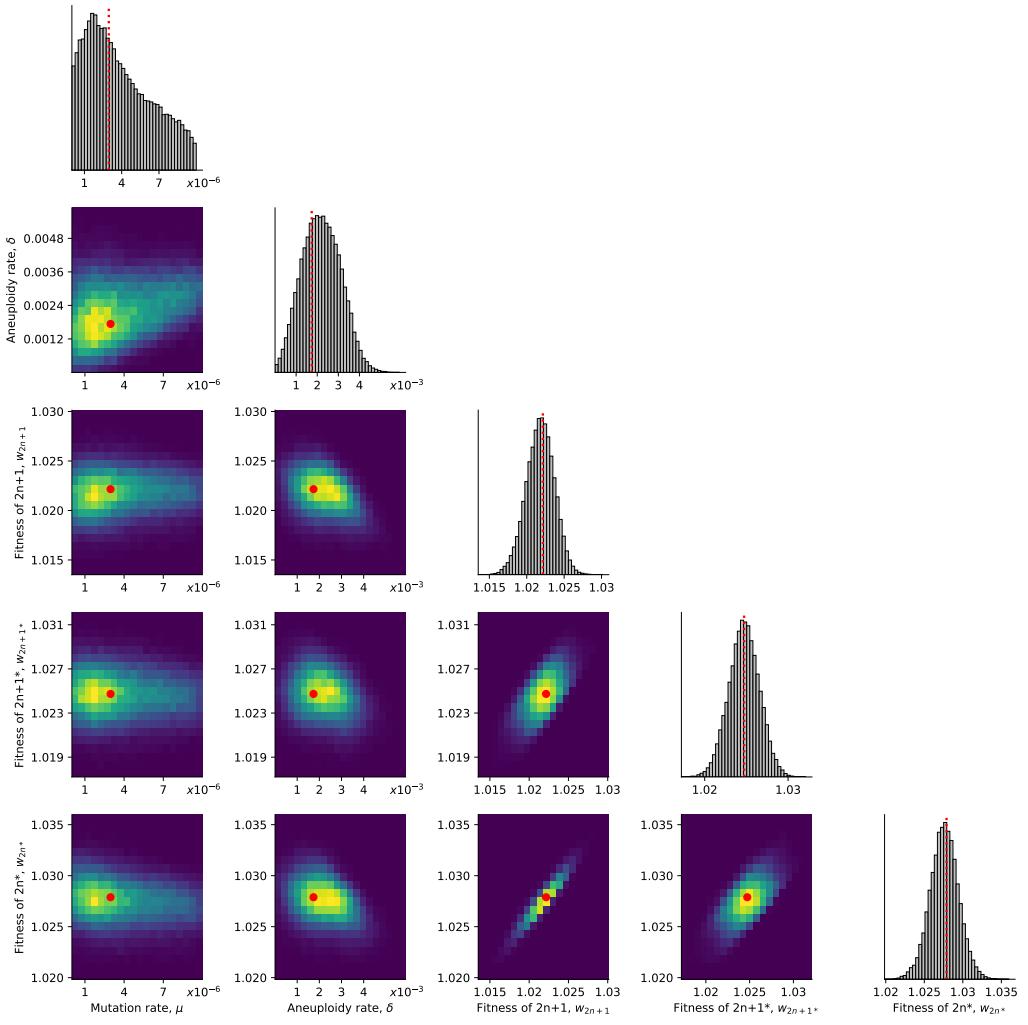


Figure 3: Posterior distribution of model parameters. On the diagonal, the marginal posterior distribution of each model parameter. Below the diagonal, the joint posterior distribution of pairs of model parameters (dark purple and bright yellow for low and high density, respectively). Red markers and orange lines for the joint MAP estimate (which may differ from the marginal MAP, as the marginal distribution integrates over all other parameters).

Model comparison and goodness-of-fit. To assess the fit of our model to the data, we use posterior

152 predictive checks, in which we simulate the frequency dynamics using MAP parameter estimates and
153 compare them to the data. Our model fits the data well: $2n^*$ fixed in 61% of simulations by generation
154 1,700 and in 100% of simulations by generation 2,350 (Figure 4).

However, a model without aneuploidy (where the aneuploidy rate is fixed at zero, $\delta = 0$), fails to

156 explain the experimental observations (Figure 4). The estimated mutation rate without aneuploidy is
157 $\mu = 7.98 \cdot 10^{-9}$ [$7.906 \cdot 10^{-9} - 8.138 \cdot 10^{-9}$], much lower compared to a model with aneuploidy. The
158 fitness of the mutant is also much lower at $w_{2n^*} = 1.013$ [1.012 – 1.013]. This is because, without
aneuploidy, a high mutation rate or fitness effect will lead to faster appearance and fixation of $2n^*$ than

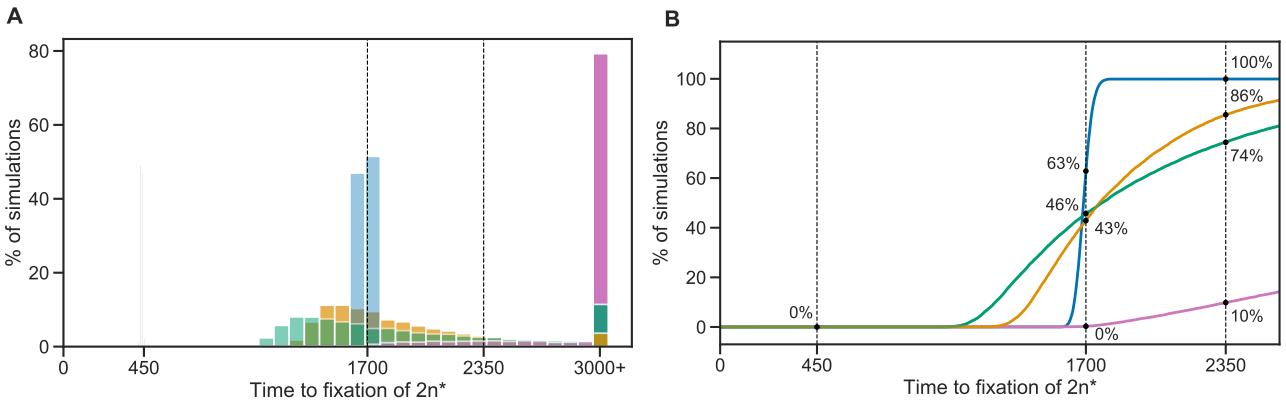


Figure 4: Model fit with and without aneuploidy. The distribution of time to fixation of $2n^*$ (i.e., adaptation time) in 10,000 simulations using MAP parameters of the model with beneficial aneuploidy (blue; $\delta > 0$, $w_{2n} < w_{2n+1} < w_{2n+1^*} < w_{2n^*}$) compared to alternative models: a model with the same parameter values but without aneuploidy (gray, $\delta = 0$, concentrated at $t = 450$); a model fitted to the data assuming no aneuploidy (green, $\delta = 0$); a model fitted to the data assuming neutral aneuploidy (yellow, $\delta > 0$, $w_{2n+1} = w_{2n}$, $w_{2n+1^*} = w_{2n^*}$); and a model with beneficial aneuploidy and an extended prior distribution (pink). In the experiment by Yona et al.⁶², one population lost aneuploidy by generation 1,700 and another by generation 2,350 (dashed lines) but not before generation 450. Thus, the blue distribution has a better fit compared to the other distributions (the gray distribution has a particularly poor fit). The MAP likelihood (eq. (4)) is 0.84, 0.78, 0.67, and 0.14 for the models represented by blue, yellow, green, and pink distributions, respectively. **(A)** Histogram of the time to fixation of $2n^*$. The last bin contains all values equal or greater than 3,000. **(B)** Cumulative distribution of the time to fixation.

160 in the experimental observations.

We also checked a model in which aneuploidy occurs but is adaptively neutral compared to the wild-type, that is, $w_{2n+1} = w_{2n}$ and $w_{2n+1^*} = w_{2n^*}$ but $\delta > 0$. This model fits the data better than the model with no aneuploidy (in which $\delta = 0$), but worse than a model with positive selection for aneuploidy, 164 in which $w_{2n} < w_{2n+1} < w_{2n+1^*} < w_{2n^*}$ (Figure 4).

Model predictions of genotype frequency dynamics. We simulated 50 replicate genotype frequency dynamics using the MAP estimate parameters. Figure 5A shows the simulated frequencies of the four genotypes ($2n$, $2n+1$, $2n+1^*$ and $2n^*$), as well as the frequencies of $2n^*$ cells that arose from either $2n+1$ cells via a sequences of mutation and chromosome loss events ($2n_A^*$), or directly from $2n$ cells via a mutation event ($2n_M^*$). We find that $2n+1^*$ never reaches substantial frequency as it is quickly replaced by $2n^*$ in a process similar to *stochastic tunneling*^{22,28}.

To test the hypothesis that aneuploidy facilitates adaptation, we estimated F_A , the expected frequency
172 of $2n^*$ that arose from $2n+1$, computed as the average frequency of such $2n_A^*$ cells at the end of
simulations using the MAP estimate parameters. Surprisingly, we observe that the majority of $2n^*$
174 cells are $2n_M^*$, a product of a direct mutation in $2n$ cells, rather than descending from $2n+1$ cells
($F_A^{MAP} = 0.106$, average end point of 50 purple lines in Figure 5A). This is despite the fact that the
176 $2n+1$ genotype reaches high frequencies in the population (at least 0.98, Figure 5A).

This result is not unique to the MAP parameter estimate. We simulated genotype frequency dynamics
178 using parameter samples from the posterior distribution, and computed the posterior distribution of F_A
(Figure 5B). The posterior mode F_A was just 0.147 [0.0154-0.370 95% CI] and only in 489 of 100,000
180 posterior samples (0.489%) F_A was larger than 0.5 (see Supporting Material for results when transitions
to less-fit genotypes are allowed, such as $2n^*$ to $2n+1^*$). Thus, if we sample a random cell from the
182 evolved $2n^*$ population, it is more likely to have descended directly from an euploid cell than from
an aneuploid cell. The probability of $2n^*$ descending from $2n+1$ (F_A) increases with the aneuploidy
184 rate, δ , and decreases with both the population size N and the mutation rate, μ (Figure 5C,D). In some
cases it can also be affected by the fitness parameters (Figure S10).

186 **Genetic instability in aneuploid cells.** It has been suggested that aneuploidy increases genetic
instability^{49,21}. Therefore, we inferred model parameters under the assumption that the mutation rate
188 increases in aneuploid cells by a factor $\tau = 1, 33/32$ (due to an additional chromosome), 2, 5, 10, or
100 (due to genetic instability). We found that the posterior distribution was similar for $\tau = 1, 33/32$,
190 2, and 5 (Figure S4). For each τ , we computed the WAIC, a criterion for model selection (lower is
better, see Methods), and found WAIC is lowest for $\tau = 33/32$ and $\tau = 1$ (Table S3).

192 Assuming a strong increase of the mutation rate in aneuploid cells, i.e. $\tau = 100$, the inferred a
mutation rate was $\mu = 4.094 \cdot 10^{-7}$ [$6.252 \cdot 10^{-8} - 6.046 \cdot 10^{-7}$]), and the inferred aneuploidy rate
194 that was $\delta = 0.744 \cdot 10^{-3}$ [$0.506 \cdot 10^{-3} - 1.827 \cdot 10^{-3}$]. Compared to inference made assuming
no effect of aneuploidy on the mutation rate, these rates were about 7-8-fold lower about 2-3-fold
196 lower. Assuming $\tau = 10$, the inferred a mutation rate was only slightly lower compared to $\tau = 1$
($\mu = 1.67 \cdot 10^{-6}$ [$2.836 \cdot 10^{-8} - 2.245 \cdot 10^{-6}$]).

198 Therefore, we do not find any evidence of an increase in mutation rate in aneuploid cells. This may
be because, unless the increase is strong ($\tau \geq 10$), it does not seem to affect our inference; or because
200 chromosome III is one of the smallest chromosomes¹⁶. We also checked the differences in genotype
frequency dynamics for different τ values. We observe $\tau = 100$ could be distinguished if accurate

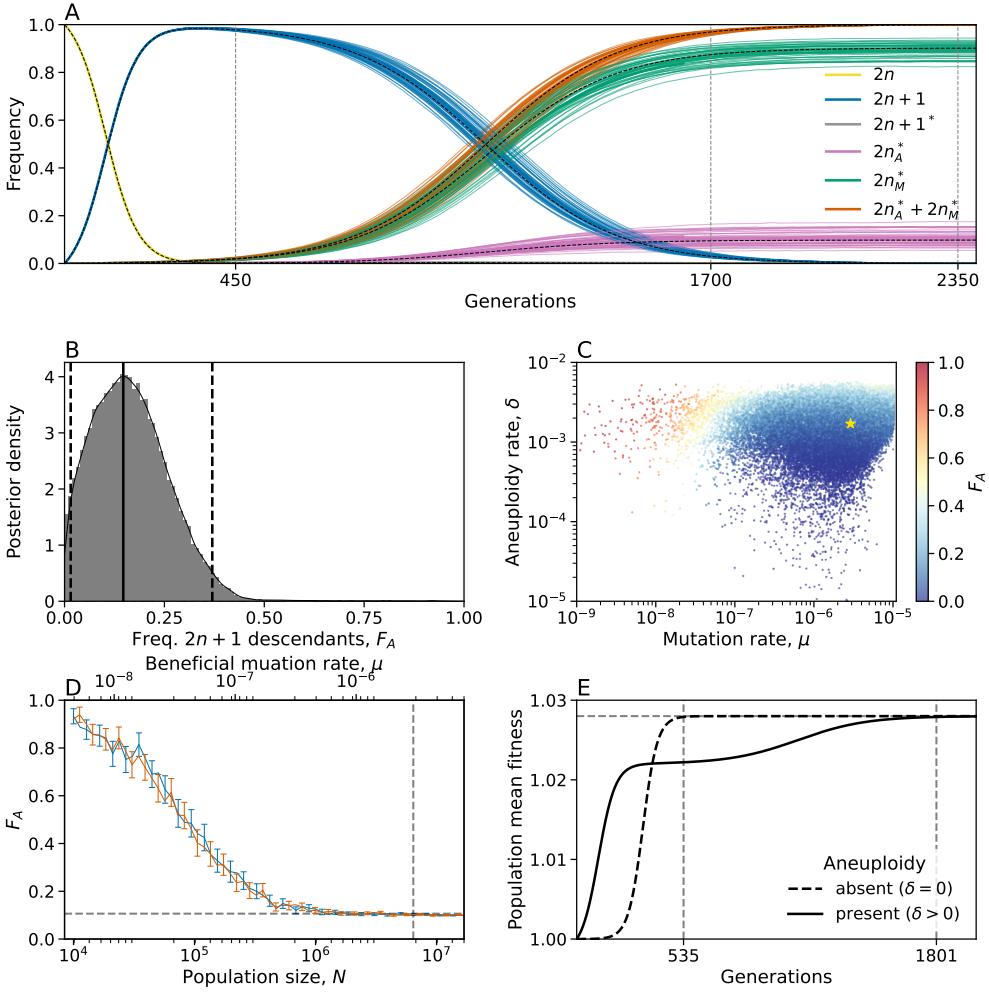


Figure 5: Predicted frequency of aneuploid-descended cells. **(A)** Posterior predicted genotype frequencies over time, including the source of $2n^*$: $2n_A^*$ arose from $2n+1$, whereas $2n_M^*$ arose directly from $2n$. Colored curves are 50 simulations using the MAP estimate parameters. Black dashed curves are the expected genotype frequencies without genetic drift (from a deterministic model). See Figure S9 for log-log scale, in which the sequence of events is easier to observe. **(B)** Posterior distribution of F_A , the expected frequency of $2n^*$ cells descended from $2n+1$ cells, computed as the average frequency at the end of 100 simulations for 100,000 samples from the parameter posterior distribution. Solid and dashed lines show the mode and 95% CI. **(C)** F_A values (color coded) from panel B, with their corresponding mutation rate μ on x-axis and aneuploidy rate δ on the y-axis. Yellow star shows the MAP estimate. See also Figure S10. **(D)** F_A as a function of the population size (N , bottom x-axis) and the beneficial mutation rate (μ , top x-axis) in posterior predictions with MAP parameters. Markers show F_A in 250 simulations per population size or mutation rate value. Error bars show mean F_A with 95% CI (bootstrap, $n = 10,000$). Blue and red bars for varying population size and mutation rate, respectively. Vertical dashed line for population size in the experiment, $6.425 \cdot 10^6$, and the MAP mutation rate, $2.965 \cdot 10^{-6}$. Horizontal line for $F_A^{MAP} = 0.106$. **(E)** Population mean fitness in a model without drift using MAP estimate parameters. Solid lines for mean fitness with aneuploidy ($\delta > 0$), where the population reaches adaptation (mean fitness at 99.99% of maximum value) at generation 1,802. Dashed lines for mean fitness without aneuploidy ($\delta = 0$), where the population adapts much earlier, at generation 535.

202 data was available for the waiting time until the frequency of $2n$ to decrease below 95% (Figure S5A)
203 or for waiting time for the frequency of $2n+1$ to either reach or go below 95% (Figure S5B). We also
204 did not find evidence for an increase in the aneuploidy rate in aneuploid cells (data not shown).

Discussion

206 In a study on the role of chromosome duplication in adaptive evolution, Yona et al.⁶² found that a
207 chromosome III trisomy was acquired by *S. cerevisiae* populations evolving under heat stress, only
208 to be later replaced by euploid mutant cells that carry "refined" solutions to the stress. Additionally,
209 such a replacement also occurred when they initiated evolutionary experiments with a population in
210 which all cells carry a chromosome III trisomy. They hypothesized that aneuploidy is a "useful yet
211 short-lived intermediate that facilitates further adaptation", suggesting that the euploid mutant cells
212 evolved by heat-resistance mutations in aneuploid cells followed by reversion of trisomy due to a
213 chromosome loss event.

214 If indeed the evolved euploid population is descended from the aneuploid population, then mutant
215 alleles that were common in the aneuploid populations should also be common in the evolved euploid
216 population. However, we found that this is not the case (Figure 1): mutant allele frequencies in the
217 aneuploid and euploid populations are negatively correlated, such that common alleles in the former
218 are rare in the latter. Furthermore, we developed an evolutionary genetic model of adaptive evolution
219 by aneuploidy and mutation (Figure 2), fitted it to the experimental results of Yona et al.⁶², and
220 used it to predict the genotype frequency dynamics. The model predicted that only about 10-15% of
221 the evolved euploid population descended from aneuploid cells—that is, the majority of the euploid
222 population are not descended from aneuploid cells, but rather are direct descendants of the ancestral
223 wild-type population (Figure 5).

224 This happens despite aneuploidy reaching a high frequency in the population (>95%). Conventional
225 wisdom might suggest that once the aneuploid genotype $2n+1$ reaches high frequency, it will have a
226 better chance at producing "refined" solutions via mutations, and its descendants will come to dominate
227 the population: the frequency of $2n_A^*$ (which arises from $2n+1^*$) will be higher than the frequency of
228 $2n_M^*$ (which arises directly from $2n$).

So how does $2n_M^*$ prevail? Initially, the supply rates of $2n+1$ and $2n_M^*$ are $N\delta \approx 11,000$ and $N\mu \approx 19$,
230 respectively (assuming MAP parameter estimates). Therefore, both genotypes are expected to appear
immediately at the beginning of the experiment (Figure S9). However, $2n+1$ appears at a much higher

frequency as $\delta \gg \mu$ by 2-3 orders of magnitude. After they first appear, $2n_M^*$ has higher fitness. But as long as the frequency of $2n$ is high, the supply rate of $2n+1$ is higher than that of $2n_M^*$, again due to $\delta \gg \mu$. However, supply rates of both genotypes decreases with the frequency of $2n$. Therefore, when the latter decreases, mainly due to the increase in the frequency of $2n+1$, both supply rates diminish. At this stage, the higher fitness of $2n_M^*$ comes into play and it starts to take over the population, which is mainly composed of $2n+1$. For the aneuploid lineage to compete with the mutant lineage, it must produce $2n_A^*$ via a mutation followed by chromosome loss. Although this is a stochastic process (due to drift), our results show that the time until $2n_A^*$ reaches a frequency of 0.1% is roughly 450 generations, without much variation (intersection of purple lines and vertical dashed line in Figure S9). However, by that time $2n_M^*$ is already at a roughly 10-fold higher frequency (1.86%), and since both mutants have the same fitness, their relative frequency remains roughly the same until the end of the experiment.

Predictions for small populations and low mutation rates. We examined the effect of the population size, N , and the beneficial mutation rate, μ , on the frequency of $2n+1$ descendants in the evolved population, F_A . We found that F_A is expected to decrease as the population size or mutation rate increase (Figure 5D), ranging from >90% when the population size is 10,000 or the mutation rate is $6 \cdot 10^{-9}$, to about 10% when the population size is above 1,000,000 (less than the experimental population size, which was 6,425,000) or the mutation rate is above $2 \cdot 10^{-6}$ (less than the inferred mutation rate, which is $2.965 \cdot 10^{-6}$). Thus, our model provides a testable prediction: if the experiment was repeated under a lower population size (via stronger daily dilutions or in a smaller volume) or a lower mutation rate (via a non-mutagenic stress or stress with a smaller target size such as drug resistance), then the fraction of the population descending from aneuploid cells would be much higher.

Aneuploidy delays rather than facilitates adaptation. An additional interesting result of our study is that aneuploidy increases, rather than decreases, the adaptation time (Figure 5E). This happens despite the fact that the mean fitness initially increases faster in the presence of aneuploidy (Figure 5E). This is because once $2n+1$ is common, selection for the mutant strain ($2n+1^*$ or $2n^*$) is weaker compared to when $2n^*$ competes directly with $2n$.

Rate and fitness effect of aneuploidy and mutation. We inferred the rates of aneuploidy and mutation and their effects on fitness. We estimate that the aneuploidy rate (i.e., number of chromosome gains per generation) is $1.7 \cdot 10^{-3}$, higher than a previous estimate of $6.7 \cdot 10^{-6}$ (ref 65). This may be due

262 to genetic instability caused by heat stress⁵. In addition, we find no evidence for increased mutation
264 rates in aneuploid cells. Previous empirical studies have suggested that genetic instability (e.g.,
266 elevated mutation rates) in aneuploid cells is due to stress associated with the aneuploid state^{3,6,63,21}.
However, in the experiment of Yona et al.⁶², both the wild-type and the aneuploid were under heat
268 stress, which may explain why we did not find evidence for an increased mutation rate specifically in
aneuploid cells.

268 **Conclusions.** Here, we tested the hypothesis that aneuploidy cells are an evolutionary "stepping
stone", or adaptive intermediate, between wild-type euploid cells and mutant euploid cells⁶¹. Our
270 results suggest that, although it seems the population goes from euploid to aneuploid and back, this is
not the case at the individual level. We estimate that only about 10-15% of the euploid cells descended
272 from aneuploid cells, whereas the rest are direct descendants of the wild-type euploid cells. Thus,
aneuploidy can delay, rather than accelerate, adaptation, and cells that become aneuploid may leave
274 less descendants than cells that remain euploid. This surprising result reinforces the importance of
mathematical models when interpreting evolutionary dynamics. Moreover, our study emphasizes the
276 unintuitive outcomes of clonal interference between mechanisms for generation of variation that differ
in their rate of formation and distribution of fitness effects, including mutation, copy number variation,
278 horizontal gene transfer, and epigenetic modifications.

Models and Methods

280 **DNA sequencing.** Whole-genome sequencing of the ancestral diploid strain ($2n$) was performed
on a single colony of the ancestor. Whole-genome sequencing of the four evolving populations ($H2$
282 after 450 and 2,350 generations, and $H4$ after 450 and 1,700 generations) was performed on a sample
from these populations (rather than from single colonies) in order to maintain the population diversity.
284 Cells were grown in 5ml of YPD medium, either at 30 °C (ancestral diploid) or 39 °C (evolved
populations) in shaking conditions (200rpm) until reaching stationary phase. Following growth,
286 3ml of each culture were centrifuge (14,000rpm) and cell pellets were used for DNA extraction.
Genomic DNA was extracted using "MasterPure Yeast DNA Purification Kit" (Lucigen) according to
288 the manufacture instructions. Following extraction, DNA concentrations were determined by Qubit
assay (Thermo Fisher) and ~ 1 μ g DNA was used for library preparation using Illumina sample
290 preparation kit (Illumina). Samples were sequenced using a 100 bp pair end read output run using
Illumina HiSeq2500.

292 **Evolutionary genetic model.** We model the evolution of a population of cells using a Wright-Fisher
 293 model³⁵, assuming a constant effective population size N , non-overlapping generations, and including
 294 the effects of natural selection, genetic drift, aneuploidy, and mutation. We focus on beneficial genetic
 295 modifications, neglecting the effects of deleterious and neutral mutations or karyotypic changes. The
 296 model allows for a single aneuploid karyotype (e.g., chromosome III duplication) and a single mutation
 297 to accumulate in the genotype. Thus, the model follows four genotypes (Figure 2): euploid wild-type,
 298 $2n$, the initial genotype; euploid mutant, $2n^*$, with the standard karyotype and a single beneficial mutation;
 300 and aneuploid mutant, $2n+1^*$, with an extra chromosome, i.e., following chromosome duplication.

Transitions between the genotypes occur as follows (Figure 2): Beneficial mutations from $2n$ to $2n^*$
 302 and from $2n+1$ to $2n+1^*$ occur with probability μ , the mutation rate. We neglect back-mutations (i.e.,
 303 from $2n^*$ to $2n$ and from $2n+1^*$ to $2n+1$). Aneuploidy is formed by chromosome mis-segregation,
 304 so that cells transition from $2n$ to $2n+1$ and from $2n+1^*$ to $2n^*$ with probability δ , the aneuploidy
 306 rate. That is, we assume chromosomes are gained and lost at the same rate, and we neglect events
 308 that form a less-fit genotype (i.e., $2n+1$ to $2n$ and $2n^*$ to $2n+1^*$). A model that assumed increased
 310 aneuploidy rates in aneuploid cells did not perform well and was abandoned.

308 In the experiment by Yona et al.⁶², the population was grown every day from $1.6 \cdot 10^6$ cells until
 310 reaching stationary phase and then diluted 1:120. Thus, we set the population size to $N = 6.425 \cdot 10^6$,
 312 the harmonic mean of $\{2^k \cdot 1.6 \cdot 10^6\}_{k=0}^7$ ⁹. The initial population has N cells with genotype $2n$. The
 314 effect of natural selection on the frequency f_i of genotype $i = 2n, 2n + 1, 2n + 1^*$, or $2n^*$ is given
 316 by

$$f_i^s = \frac{f_i w_i}{\bar{w}}, \quad (1)$$

314 where w_i is the fitness of genotype i and $\bar{w} = \sum_j f_j w_j$ is the population mean fitness. The effect of
 316 mutation and aneuploidy on genotype frequencies is given by

$$\begin{aligned} f_{2n}^m &= (1 - \delta - \mu)f_{2n}^s, \\ f_{2n+1}^m &= \delta f_{2n}^s + (1 - \mu)f_{2n+1}^s, \\ f_{2n+1^*}^m &= \mu f_{2n+1}^s + (1 - \delta)f_{2n+1^*}^s, \\ f_{2n^*}^m &= \mu f_{2n}^s + \delta f_{2n+1}^s + f_{2n^*}^s. \end{aligned} \quad (2)$$

Finally, random genetic drift is modeled using a multinomial distribution³⁵,

$$318 \quad \mathbf{f}' \sim \frac{1}{N} \cdot \text{Mult}(N, \mathbf{f}^m), \quad (3)$$

318 where $\mathbf{f}^m = (f_{2n}^m, f_{2n+1}^m, f_{2n+1^*}^m, f_{2n^*}^m)$ are the frequencies of the genotypes after mutation and
 320 aneuploidy, \mathbf{f}' are the genotype frequencies in the next generation, and $\text{Mult}(N, \mathbf{f})$ is a multinomial

distribution parameterized by the population size N and the genotype frequencies \mathbf{f} . Overall, the change
 322 in genotype frequencies from one generation to the next is given by the transformation $f_i \rightarrow f'_i$.

Empirical data for model inference. We use the results of evolutionary experiments reported by
 324 Yona et al.⁶². In their heat-stress experiment, four populations of *S. cerevisiae* evolved under 39 °C.
 Aneuploidy fixed in all four population in the first 450 generations. Hereafter, fixation or elimination
 326 of a genotype by *generation t* means that more than 95% or less than 5% of the population carry the
 genotype at generation t , and possibly earlier. From re-analysis of data not published in the original
 328 paper, aneuploidy did not fix before at least 200 generations elapsed. The experiment continued with
 two populations, in which aneuploidy was eliminated by generation 1,700 and 2,350 while still under
 330 the same conditions of elevated heat (39 °C).

Likelihood function. Because our model, just like the Wright-Fisher model, is non-linear and
 332 stochastic, computing the distribution of fixation time $T(g)$ of genotype g for use in the likelihood
 function is intractable (it is even hard to use a diffusion-equation approximation due to the model having
 334 multiple genotypes, rather than just two). We overcome this problem by approximating the likelihood
 using simulations. We simulate 1,000 experiments per parameter vector $\theta = (\mu, \delta, s, b, c)$, resulting in
 336 a set of simulated observations $\tilde{\mathbf{X}} = \{\tilde{X}_i\}_{i=1}^{1000}$. We then compute the approximate likelihood,

$$\begin{aligned} \mathcal{L}(\theta) = P^4(200 \leq T(2n+1) \leq 450) \cdot & \left[1 - \right. \\ & P_{\tilde{\mathbf{X}}}^4(\{T(2n^*) < 1700\} \mid 200 \leq T(2n+1) \leq 450) - \\ & P_{\tilde{\mathbf{X}}}^4(\{1700 < T(2n^*) < 2350\} \mid 200 \leq T(2n+1) \leq 450) + \\ & \left. P_{\tilde{\mathbf{X}}}^4(\{T(2n^*) < 1700\} \wedge \{1700 < T(2n^*) < 2350\} \mid 200 \leq T(2n+1) \leq 450) \right], \end{aligned} \quad (4)$$

338 where $\{ \dots \}$ is the "logical not" operator, $P^4(\dots)$ is the 4th power of $P(\dots)$, and all probabilities
 $P_{\tilde{\mathbf{X}}}(\dots)$ are approximated from the results of the simulations $\tilde{\mathbf{X}}$. For example, $P_{\tilde{\mathbf{X}}}(\{T(2n^*) < 1700\} \mid$
 340 $200 \leq T(2n+1) \leq 450)$ is approximated by taking simulations in which $2n+1$ fixed before generation
 450 but not before generation 200, and computing the fraction of such simulations in which $2n^*$ did
 342 not fix by generation 1,700, and hence aneuploidy did not extinct before generation 1,700. Figure S1
 compares results with less and more simulated experiments, demonstrating that 1,000 simulations are
 344 likely sufficient.

For a model without aneuploidy (that is, when the aneuploidy rate is fixed at zero, $\delta = 0$), we disregard
 346 the increased expression in chromosome III and the growth advantage measured in generation 450, and
 focus on the growth advantage measured in later generations, presumably due to a beneficial mutation.

348 Therefore, the likelihood is approximated by

$$\begin{aligned}\mathcal{L}_!(\theta) = 1 - P_{\tilde{\mathbf{X}}}^4(\{T(2n^*) < 1700\}) - \\ P_{\tilde{\mathbf{X}}}^4(\{1700 < T(2n^*) < 2350\}) + \\ P_{\tilde{\mathbf{X}}}^4(\{T(2n^*) < 1700\} \wedge \{1700 < T(2n^*) < 2350\}).\end{aligned}\quad (5)$$

350 **Parameter inference.** To infer model parameters, we use approximate Bayesian computation with
 a sequential Monte-Carlo scheme, or ABC-SMC⁵², implemented in the pyABC Python package²⁶
 352 [pyabc.readthedocs.io](#). This approach uses numerical stochastic simulations of the model to infer
 a posterior distribution over the model parameters. It is a method of likelihood-free, simulation-
 354 based inference⁸, that is, for estimating a posterior distribution when a likelihood function cannot be
 directly computed. It is therefore suitable in our case, in which the likelihood function can only be
 356 approximated from simulations, and cannot be directly computed.

The ABC-SMC algorithm employs sequential importance sampling over multiple iterations^{55,25,53}. In
 358 iteration t of the algorithm, a set of parameter vectors, $\{\theta_{i,t}\}_{i=1}^{n_t}$, also called *particles*, are constructed
 in the following way. A proposal particle, θ^* , is sampled from a proposal distribution, and is either
 360 accepted or rejected, until n_t particles are accepted. The number of particles, n_t , is adapted at every
 362 iteration t using the adaptive population strategy²⁶ [pyabc.readthedocs.io](#). For $t = 0$, the proposal
 364 particle is sampled from the prior distribution, $p(\theta)$. For $t > 0$, the proposal particle is sampled from
 the particles accepted in the previous iteration, $\{\theta_{i,t-1}\}_{i=1}^{n_{t-1}}$, each with a probability relative to its weight
 366 $W_{t-1}(\theta_{i,t-1})$ (see below). The proposal particle is then perturbed using a kernel perturbation kernel,
 368 $K_t(\theta^* | \theta)$ where θ is the sample from the previous iteration. Then, a set of synthetic observations
 370 $\tilde{\mathbf{X}}^*$ is simulated, and the proposal particle θ^* is accepted if its approximate likelihood (eq. (4)) is high
 enough, $\mathcal{L}(\theta^*) > 1 - \epsilon_t$ (or more commonly, if $1 - \mathcal{L}(\theta^*) < \epsilon_t$), where $\epsilon_t > 0$ is the *acceptance*
 372 *threshold*, as higher values of ϵ_t allow more particles to be accepted. The acceptance threshold ϵ_t
 374 is chosen as the median of the $1 - \mathcal{L}(\theta)$ of the particles accepted in the previous iteration, $t - 1$,
 and $\epsilon_0 = 0.01$. For each accepted particle $\theta_{i,t}$ a weight $W_t(\theta_{i,t})$ is assigned: for $t = 0$, $W_0(\theta_{i,0}) = 1$,
 and for $t > 0$, $W_t(\theta_{i,t}) = p(\theta_{i,t}) / \sum_{i=1}^{n_{t-1}} W_{t-1}(\theta_{i,t-1}) K_t(\theta_{i,t}, \theta_{i,t-1})$, where $p(\theta)$ is the prior density of θ
 376 and $K_t(\theta', \theta)$ is the probability of a perturbation from θ to θ' . $K_t(\theta' | \theta)$ is a multivariate normal
 378 distribution, fitted at iteration t to the particles from the previous iteration, $\{\theta_{i,t-1}\}_{i=1}^{n_{t-1}}$, and their
 380 weights, $\{W(\theta_{i,t-1})\}_{i=1}^{n_{t-1}}$.

Acceptance is determined according to the approximate likelihood (eq. (4)), which has a maximum
 382 value of $\mathcal{L}_{max} = 0.875$ (giving a minimal value of $\epsilon_{min} = 0.125$). We terminated the inference
 384 iterations when the change in ϵ value from one iteration to the next was small. With our standard prior

378 and model, we reached $\epsilon = 0.13$ (or $\mathcal{L} = 0.87$) after six iterations, with $n_6 = 982$ accepted parameter
379 vectors and effective sample size ESS=651 (Figure S2). Running the inference algorithm with different
380 initialization seeds and less or more simulations for approximating the likelihood produced similar
381 posterior distributions (Figure S1).

382 After producing a set of weighted particles from the the posterior distribution using the above ABC-
383 SMC algorithm, we approximate the posterior using kernel density estimation (KDE) with Gaussian
384 kernels. We truncate the estimated posterior to avoid positive posterior density for values with zero
385 prior density. The MAP (maximum a posteriori) estimate is computed as the the maximum of the
386 estimated joint posterior density. We then draw 5,000,000 samples from the posterior distribution
387 to compute the HDI (highest density interval) and draw 50,000 samples to visualize the posterior
388 distribution with histograms.

Model comparison. We examine several versions of our evolutionary models, e.g. without aneuploidy or with increased mutation rate in aneuploid cells, as well as several different prior distributions (see below). To compare these, we plot posterior predictions: for each model we execute 10,000
390 simulations using the MAP parameter estimates and plot the distributions of time to fixation of $2n^*$,
391 one of key properties of the model likelihood. These plots visualize the fit of each model to the
392 data. Also, for similar models we plot the marginal and joint posterior distributions of the parameters;
393 if these are similar, we consider the models interchangeable. We validate this by comparing HDI
394 (highest density interval) of posterior distributions.

Where posterior plots are very similar and the number of parameters is the same, we use WAIC, or
395 the widely applicable information criterion ¹³, defined as

$$WAIC(\theta) = -2 \log \mathbb{E}[\mathcal{L}(\theta)] + 2\mathbb{V}[\log \mathcal{L}(\theta)] \quad (6)$$

400 where θ is a parameter vector, and $\mathbb{E}[\cdot]$ and $\mathbb{V}[\cdot]$ are the expectation and variance taken over the
401 posterior distribution, which in practice are approximated using 50,000 samples from the posterior
402 KDE. We validated that upon resampling WAIC values do not significantly change and that differences
403 in WAIC between models are preserved. WAIC values are scaled as a deviance measure: lower values
404 imply higher predictive accuracy²³.

Prior distributions. We used informative prior distributions for $w_{2n+1} = 1 - c + b$, $w_{2n+1^*} =$
405 $(1+s)(1-c)+b$ and $w_{2n^*} = 1+s$, which we estimated from growth curves data from mono-culture growth
406 experiments previously reported by Yona et al.⁶², Figs. 3C, 4A, and S2. We used Curveball, a method

408 for predicting results of competition experiments from growth curve data³⁸ curveball.yoavram.com.
Briefly, Curveball takes growth curves of two strains growing separately in mono-culture and predicts
410 how they would grow in a mixed culture, that is, it predicts the results of a competition assay. From these
predictions, relative fitness values can be computed. Because Curveball uses a maximum-likelihood
412 approach to estimate model parameters, we were able to estimate a distribution of relative fitness
values to be used as a prior distribution by sampling 10,000 samples from a truncated multivariate
414 normal distribution defined by the maximum-likelihood covariance matrix (Figure S3).

We used growth curves of $2n$ and $2n+1$ in 39 °C to estimate an informative prior distribution for
416 w_{2n+1} (Figure S3-D, assuming $w_{2n} = 1$). In this prior distribution, we used the same prior for w_{2n+1*}
and w_{2n*} . To increase computational efficiency, we also assumed $w_{2n*} > w_{2n+1*} > w_{2n+1} > w_{2n}$;
418 running the inference without this assumption produced similar results. See *supporting material* for
an extended informative prior distribution that uses growth curves of $2n^*$ and $2n+1$ growing in 39 °C;
420 this prior distribution proved to be less useful.

As a control, we tested an uninformative uniform prior with $U(1, 6)$, for (i) all w_{2n+1} , w_{2n+1*} , w_{2n*} , or
422 (ii) only for w_{2n+1*} , w_{2n*} , using the above informative prior for w_{2n+1} . In these cases the inference
algorithm failed to converge.

424 For the mutation rate, μ , and aneuploidy rate, δ , we used uninformative uniform priors, $\mu \sim U(10^{-9}, 10^{-5})$ and $\delta \sim U(10^{-6}, 10^{-2})$. A wider mutation rate prior, $\mu \sim U(10^{-9}, 10^{-3})$, produced
426 similar results.

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References

434 [1] Avecilla, G., Chuong, J. N., Li, F., Sherlock, G., Gresham, D. and Ram, Y. 2022, ‘Neural
networks enable efficient and accurate simulation-based inference of evolutionary parameters
436 from adaptation dynamics’, *PLOS Biology* **20**(5), e3001633.

- 438 [2] Bakhoum, S. F. and Landau, D. A. 2017, ‘Chromosomal instability as a driver of tumor heterogeneity and evolution’, *Cold Spring Harb. Perspect. Med.* **7**(6), 1–14.
- 440 [3] Bouchonville, K., Forche, A., Tang, K. E. S., Semple, C. a. M. and Berman, J. 2009, ‘Aneuploid chromosomes are highly unstable during dna transformation of *Candida albicans*.’, *Eukaryot. Cell* **8**(10), 1554–66.
- 442 [4] Boveri, T. 2008, ‘Concerning the origin of malignant tumours’, *J. Cell Sci.* **121**(Supplement 1), 1–84.
- 444 [5] Chen, G., Bradford, W. D., Seidel, C. W. and Li, R. 2012, ‘Hsp90 stress potentiates rapid cellular adaptation through induction of aneuploidy.’, *Nature* **482**(7384), 246–50.
- 446 [6] Chen, G., Rubinstein, B. and Li, R. 2012, ‘Whole chromosome aneuploidy: Big mutations drive adaptation by phenotypic leap’, *BioEssays* **34**(10), 893–900.
- 448 [7] Covo, S., Puccia, C. M., Argueso, J. L., Gordenin, D. A. and Resnick, M. A. 2014, ‘The sister chromatid cohesion pathway suppresses multiple chromosome gain and chromosome amplification.’, *Genetics* **196**(2), 373–384.
- 450
- 452 [8] Cranmer, K., Brehmer, J. and Louppe, G. 2020, ‘The frontier of simulation-based inference’, *Proceedings of the National Academy of Sciences* p. 201912789.
- 454 [9] Crow, J. F. and Kimura, M. 1970, *An introduction to population genetics theory*, Burgess Pub. Co., Minneapolis.
- 456 [10] Dhar, R. and Sägesser, R and Weikert, C and Yuan, J and Wagner, Andreas, doi = 10.1111/j.1420-9101.2011.02249.x, i . . j . . J. m . . m. n . . p . . p . . t . . A. v . . y . . n.d..
- 458 [11] Dunham, M. J., Badrane, H., Ferea, T., Adams, J., Brown, P. O., Rosenzweig, F. and Botstein, D. 2002, ‘Characteristic genome rearrangements in experimental evolution of *Saccharomyces cerevisiae*’, *Proc. Natl. Acad. Sci.* **99**(25), 16144–16149.
- 460 [12] Flynn, J. M., Rossouw, A., Cote-Hammarlof, P., Fragata, I., Mavor, D., Hollins, C., Bank, C. and Bolon, D. N. 2020, ‘Comprehensive fitness maps of hsp90 show widespread environmental dependence’, *Elife* **9**, 1–25.
- 462
- 464 [13] Gelman, A., Carlin, J. B., Stern, H. S., Dunson, D. B., Vehtari, A. and Rubin, D. B. 2013, *Bayesian Data Analysis, Third Edition*, Chapman & Hall/CRC Texts in Statistical Science, Taylor & Francis.

- 466 [14] Gerstein, A. C. and Berman, J. 2018, ‘Diversity of acquired adaptation to fluconazole is influenced
by genetic background and ancestral fitness in *Candida albicans*’, *bioRxiv* p. 360347.
- 468 [15] Gerstein, A. C., Ono, J., Lo, D. S., Campbell, M. L., Kuzmin, A. and Otto, S. P. 2015, ‘Too
much of a good thing: the unique and repeated paths toward copper adaptation.’, *Genetics*
470 **199**(2), 555–71.
- 472 [16] Gilchrist, C. and Stelkens, R. 2019, ‘Aneuploidy in yeast: Segregation error or adaptation
mechanism?’, *Yeast* **36**(9), 525–539.
- 474 [17] Gresham, D., Desai, M. M., Tucker, C. M., Jenq, H. T., Pai, D. A., Ward, A., DeSevo, C. G.,
Botstein, D. and Dunham, M. J. 2008, ‘The repertoire and dynamics of evolutionary adaptations
to controlled nutrient-limited environments in yeast’, *PLoS Genet.* **4**(12).
- 476 [18] Heidenreich, E. 2007, ‘Adaptive Mutation in *< i>Saccharomyces cerevisiae</i>*’, *Crit. Rev.
Biochem. Mol. Biol.* **42**(4), 285–311.
- 478 [19] Hong, J. and Gresham, D. 2014, ‘Molecular specificity, convergence and constraint shape adap-
tive evolution in nutrient-poor environments’, *PLoS Genet.* **10**(1).
- 480 [20] Huang, C. J., Lu, M. Y., Chang, Y. W. and Li, W. H. 2018, ‘Experimental Evolution of Yeast for
High-Temperature Tolerance’, *Mol. Biol. Evol.* **35**(8), 1823–1839.
- 482 [21] Ippolito, M. R., Martis, V., Martin, S., Tijhuis, A. E., Hong, C., Wardenaar, R., Dumont,
M., Zerbib, J., Spierings, D. C., Fachinetti, D., Ben-David, U., Fojer, F. and Santaguida, S.
484 2021, ‘Gene copy-number changes and chromosomal instability induced by aneuploidy confer
resistance to chemotherapy’, *Dev. Cell* **56**(17), 2440–2454.e6.
- 486 [22] Iwasa, Y., Michor, F. and Nowak, M. A. 2004, ‘Stochastic tunnels in evolutionary dynamics’,
Genetics **166**(3), 1571–1579.
- 488 [23] Kass, R. E. and Raftery, A. E. 1995, ‘Bayes factors’, *J. Am. Stat. Assoc.* **90**(430), 773.
- 490 [24] Kasuga, T., Bui, M., Bernhardt, E., Swiecki, T., Aram, K., Cano, L. M., Webber, J., Brasier,
C., Press, C. and Grünwald, Niklaus J. and Rizzo, David M. and Garbelotto, Matteo, doi
= 10.1186/s12864-016-2717-z, i . . . i . . . j . . B. n . . . p . . . p . . . p . . B. t . . H. v . . . y . . . n.d..
- 492 [25] Klinger, E. and Hasenauer, J. 2017, A scheme for adaptive selection of population sizes in
approximate bayesian computation - sequential monte carlo, *in* J. Feret and H. Koepll, eds,
494 ‘Computational Methods in Systems Biology’, Vol. 10545, Springer International Publishing,
pp. 128–144. Series Title: Lecture Notes in Computer Science.

- 496 [26] Klinger, E., Rickert, D. and Hasenauer, J. 2018, ‘pyabc: distributed, likelihood-free inference’,
Bioinformatics (May), 1–3.
- 498 [27] Kohn, L. M. and Anderson, J. B. 2014, ‘The underlying structure of adaptation under strong
selection in 12 experimental yeast populations’, *Eukaryot. Cell* **13**(9), 1200–1206.
- 500 [28] Komarova, N. L., Sengupta, A. and Nowak, M. A. 2003, ‘Mutation-selection networks of cancer
initiation: Tumor suppressor genes and chromosomal instability’, *J. Theor. Biol.* **223**(4), 433–
502 450.
- 504 [29] Kumaran, R., Yang, S.-Y. and Leu, J.-Y. n.d., ‘Characterization of chromosome stability in
diploid, polyploid and hybrid yeast cells’, *8*(7), e68094.
- 506 [30] Lynch, M., Sung, W., Morris, K., Coffey, N., Landry, C. R., Dopman, E. B., Dickinson, W. J.,
Okamoto, K., Kulkarni, S., Hartl, D. L. and Thomas, W. K. 2008, ‘A genome-wide view of the
spectrum of spontaneous mutations in yeast’, *Proceedings of the National Academy of Sciences*
508 **105**(27), 9272–9277.
- 510 [31] Mannaert, A., Downing, T., Imamura, H. and Dujardin, J. C. 2012, ‘Adaptive mechanisms in
pathogens: Universal aneuploidy in *Leishmania*’, *Trends Parasitol.* **28**(9), 370–376.
- 512 [32] Möller, M., Habig, M., Freitag, M. and Stukenbrock, E. H. 2018, ‘Extraordinary genome
instability and widespread chromosome rearrangements during vegetative growth’, *Genetics*
210(2), 517–529.
- 514 [33] Naylor, R. M. and van Deursen, J. M. 2016, ‘Aneuploidy in cancer and aging’, *Annu. Rev. Genet.*
50(1), 45–66.
- 516 [34] Niwa, O., Tange, Y. and Kurabayashi, A. 2006, ‘Growth arrest and chromosome instability in
aneuploid yeast’, *Yeast* **23**(13), 937–950.
- 518 [35] Otto, S. P. and Day, T. 2007, *A biologist’s guide to mathematical modeling in ecology and
evolution*, Princeton University Press.
- 520 [36] Pavelka, N., Rancati, G., Zhu, J., Bradford, W. D., Saraf, A., Florens, L., Sanderson, B. W., Hat-
tem, G. L. and Li, R. 2010, ‘Aneuploidy confers quantitative proteome changes and phenotypic
522 variation in budding yeast.’, *Nature* **468**(7321), 321–5.
- 524 [37] Peter, J., De Chiara, M., Friedrich, A., Yue, J. X., Pflieger, D., Bergström, A., Sigwalt, A., Barre,
B., Freel, K., Llored, A., Cruaud, C., Labadie, K., Aury, J. M., Istace, B., Lebrigand, K., Barbry,

- P., Engelen, S., Lemainque, A., Wincker, P., Liti, G. and Schacherer, J. 2018, ‘Genome evolution across 1,011 <i>Saccharomyces cerevisiae</i> isolates’, *Nature* **556**(7701), 339–344.
- 526
- [38] Ram, Y., Dellus-Gur, E., Bibi, M., Karkare, K., Obolski, U., Feldman, M. W., Cooper, T. F.,
528 Berman, J. and Hadany, L. 2019, ‘Predicting microbial growth in a mixed culture from growth curve data’, *Proceedings of the National Academy of Sciences* **116**(29), 14698–14707.
- 530 [39] Rancati, G., Pavelka, N., Fleharty, B., Noll, A., Trimble, R., Walton, K., Perera, A., Staehling-
532 Hampton, K., Seidel, C. W. and Li, R. 2008, ‘Aneuploidy underlies rapid adaptive evolution of yeast cells deprived of a conserved cytokinesis motor’, *Cell* **135**(5), 879–893.
- [40] Robbins, N., Caplan, T. and Cowen, L. E. 2017, ‘Molecular evolution of antifungal drug resistance’, *Annu. Rev. Microbiol.* **71**(1), 753–775.
- 534
- [41] Rodrigues, M. L. and Albuquerque, P. C. 2018, ‘Searching for a change: The need for increased support for public health and research on fungal diseases’, *PLoS Negl. Trop. Dis.* **12**(6), 1–5.
- 536
- [42] Santaguida, S. and Amon, A. 2015, ‘Short- and long-term effects of chromosome mis-segregation and aneuploidy’, *Nat. Rev. Mol. Cell Biol.* **16**(8), 473–485.
- 538
- [43] Santaguida, S., Vasile, E., White, E. and Amon, A. 2015, ‘Aneuploidy-induced cellular stresses limit autophagic degradation’, *Genes Dev.* **29**(19), 2010–2021.
- 540
- [44] Schwartzman, J. M., Sotillo, R. and Benezra, R. 2010, ‘Mitotic chromosomal instability and cancer: Mouse modelling of the human disease’, *Nat. Rev. Cancer* **10**(2), 102–115.
- 542
- [45] Selmecki, A. M., Dulmage, K., Cowen, L. E., Anderson, J. B. and Berman, J. 2009, ‘Acquisition of aneuploidy provides increased fitness during the evolution of antifungal drug resistance’, *PLoS Genet.* **5**(10), e1000705.
- 544
- [46] Selmecki, A. M., Forche, A. and Berman, J. 2010, ‘Genomic plasticity of the human fungal pathogen *Candida albicans*’, *Eukaryot. Cell* **9**(7), 991–1008.
- 546
- [47] Selmecki, A. M., Gerami-Nejad, M., Paulson, C., Forche, A. and Berman, J. 2008, ‘An isochromosome confers drug resistance in vivo by amplification of two genes, erg11 and tac1’, *Mol. Microbiol.* **68**(3), 624–641.
- 548
- [48] Sheltzer, J. M. and Amon, A. 2011, ‘The aneuploidy paradox: Costs and benefits of an incorrect karyotype’, *Trends Genet.* **27**(11), 446–453.
- 550
- [49] Sheltzer, J. M., Blank, H. M., Pfau, S. J., Tange, Y., George, B. M., Humpton, T. J., Brito, I. L.,

- 554 Hiraoka, Y., Niwa, O. and Amon, A. 2011, ‘Aneuploidy drives genomic instability in yeast’,
Science **333**(6045), 1026–1030.
- 556 [50] Sheltzer, J. M., Ko, J. H., Replogle, J. M., Habibe Burgos, N. C., Chung, E. S., Meehl, C. M.,
Sayles, N. M., Passerini, V., Storchova, Z. and Amon, A. 2017, ‘Single-chromosome gains
558 commonly function as tumor suppressors’, *Cancer Cell* **31**(2), 240–255.
- 560 [51] Sionov, E., Lee, H., Chang, Y. C. and Kwon-Chung, K. J. 2010, ‘*Cryptococcus neoformans*
overcomes stress of azole drugs by formation of disomy in specific multiple chromosomes’,
PLoS Pathog. **6**(4), e1000848.
- 562 [52] Sisson, S. A., Fan, Y. and Tanaka, M. M. 2007, ‘Sequential monte carlo without likelihoods’,
Proceedings of the National Academy of Sciences **104**(6), 1760–1765.
- 564 [53] Syga, S., David-Rus, D. and Schälte, Yannik and Hatzikirou, Haralampos and Deutsch, Andreas,
doi = 10.1038/s41598-021-01407-y, j. . S. n. . p. . t. . I. v. . y. . n.d..
- 566 [54] Todd, R. T., Forche, A. and Selmecki, A. M. 2017, ‘Ploidy variation in fungi: Polyploidy,
aneuploidy, and genome evolution’, *Microbiol. Spectr.* **5**(4), 1–20.
- 568 [55] Toni, T., Welch, D., Strelkowa, N., Ipsen, A. and Stumpf, M. P. 2009, ‘Approximate bayesian
computation scheme for parameter inference and model selection in dynamical systems’, *J. R.
570 Soc. Interface* **6**(31), 187–202.
- 572 [56] Torres, E. M., Dephoure, N., Panneerselvam, A., Tucker, C. M., Whittaker, C. A., Gygi, S. P.,
Dunham, M. J. and Amon, A. 2010, ‘Identification of aneuploidy-tolerating mutations’, *Cell*
143(1), 71–83.
- 574 [57] Torres, E. M., Sokolsky, T., Tucker, C. M., Chan, L. Y., Boselli, M., Dunham, M. J. and Amon,
A. 2007, ‘Effects of aneuploidy on cellular physiology and cell division in haploid yeast’, *Science*
576 (80-.). **317**(5840), 916–924.
- 578 [58] Tsai, H. J., Nelliat, A. R., Choudhury, M. I., Kucharavy, A., Bradford, W. D., Cook, M. E., Kim,
J., Mair, D. B., Sun, S. X., Schatz, M. C. and Li, R. 2019, ‘Hypo-osmotic-like stress underlies
general cellular defects of aneuploidy’, *Nature* .
- 580 [59] Williams, B. R., Prabhu, V. R., Hunter, K. E., Glazier, C. M., Whittaker, C. a., Housman,
D. E. and Amon, A. 2008, ‘Aneuploidy affects proliferation and spontaneous immortalization in
582 mammalian cells’, *Science* **322**(5902), 703–709.

- 584 [60] Yang, F., Todd, R. T., Selmecki, A., Jiang, Y. Y., Cao, Y. B. and Berman, J. 2021, ‘The fitness
costs and benefits of trisomy of each *Candida albicans* chromosome’, *Genetics* **218**(2), 1–7.
- 586 [61] Yona, A. H., Frumkin, I. and Pilpel, Y. 2015, ‘A relay race on the evolutionary adaptation
spectrum’, *Cell* **163**(3), 549–559.
- 588 [62] Yona, A. H., Manor, Y. S., Herbst, R. H., Romano, G. H., Mitchell, A., Kupiec, M., Pilpel, Y.
and Dahan, O. 2012, ‘Chromosomal duplication is a transient evolutionary solution to stress.’,
Proceedings of the National Academy of Sciences **109**(51), 21010–5.
- 590 [63] Zhu, J., Pavelka, N., Bradford, W. D., Rancati, G. and Li, R. 2012, ‘Karyotypic determinants of
chromosome instability in aneuploid budding yeast’, *PLoS Genetics* **8**(5).
- 592 [64] Zhu, J., Tsai, H.-J., Gordon, M. R. and Li, R. 2018, ‘Cellular stress associated with aneuploidy’,
Dev. Cell **44**(4), 420–431.
- 594 [65] Zhu, Y. O., Sherlock, G. and Petrov, D. A. 2016, ‘Whole genome analysis of 132 clinical *Sac-*
charomyces cerevisiae strains reveals extensive ploidy variation’, *G3 Genes, Genomes, Genetics*
596 **6**(8), 2421–2434.
- [66] Zhu, Y. O., Siegal, M. L., Hall, D. W. and Petrov, D. A. 2014, ‘Precise estimates of mutation rate
598 and spectrum in yeast’, *Proceedings of the National Academy of Sciences* **111**(22), E2310–E2318.

Supplementary Material

600 Supplementary Analysis

Sensitivity analysis. Changing a single parameter while keeping the rest fixed at the MAP estimate produces a worse fit to the data (Figure S6). Furthermore, we fitted models with a mutation rate fixed at $\mu = 10^{-5}$, 10^{-6} and 10^{-7} . We inferred similar parameters estimates for the model with $\mu = 10^{-6}$ compared to the model with a free μ parameter, in which the inferred mutation rate is $\mu \approx 3 \cdot 10^{-6}$. Inference assuming $\mu = 10^{-5}$ or $\mu = 10^{-7}$ produced similar estimates except that the estimated aneuploidy rate, δ , was higher, and assuming $\mu = 10^{-7}$, the estimated fitness of $2n+1$ was lower (Figure S7).

608 **Extended informative prior distribution.** In an extended informative prior distribution, we used additional growth curves of $2n^*$ (*refined* strain from Yona et al.⁶²) and $2n+1$ in 39 °C to estimate w_{2n^*}/w_{2n+1} (Figure S3L). The same distribution was used for w_{2n^*}/w_{2n+1*} . Thus, our main informative prior uses a single prior distribution for fitness values of $2n+1$, $2n+1^*$, and $2n^*$, whereas the extended informative prior uses one distribution for $2n+1$, and another distribution for both $2n+1^*$ and $2n^*$.

614 We estimated the parameters under this extended informative prior. Inference took much longer to run but the posterior distribution seemed to converge, as it did not change much in the final 616 iterations. The posterior predictive plot shows that inference with this extended prior produces a posterior distribution that fails to explain the empirical observations (pink in Figure 4). However, 618 the inferred posterior distribution is considerably narrower (compare Figures 3 and S8) and therefore parameter estimates are less variable. The estimated mutation rate was much lower compared to 620 the main informative prior, with $\mu = 2.474 \cdot 10^{-9}$ [$2.423 \cdot 10^{-9} - 2.612 \cdot 10^{-9}$]. Other parameter estimates are: $\delta = 2.705 \cdot 10^{-3}$ [$2.094 \cdot 10^{-3} - 3.094 \cdot 10^{-3}$], $w_{2n+1} = 1.022$ [$1.021 - 1.024$], 622 $w_{2n+1*} = 1.052$ [$1.05 - 1.054$], $w_{2n^*} = 1.053$ [$1.051 - 1.055$], the latter two being much higher compare to the main informative prior. Notably, the mode of the posterior ratio $w_{2n^*}/w_{2n+1} = 1.0009$ 624 is much lower than the mode of the prior ratio of 1.033 (Figure S3H) and closer to the ratio of 1 that we assume in the main informative prior. Together with the posterior predictive results, we conclude 626 that the main informative prior is preferable over the extended informative prior.

Model with transitions to less-fit genotypes We also estimated the parameters of a version of the

628 model that includes transitions (mutation, chromosome loss and gain) to less-fit genotypes (e.g., $2n^*$ to $2n+1^*$),

$$\begin{aligned}
 f_{2n}^m &= (1 - \delta - \mu)f_{2n}^s + \delta f_{2n+1}^s + \mu f_{2n+1}^s, \\
 f_{2n+1}^m &= \delta f_{2n}^s + (1 - \delta - \mu)f_{2n+1}^s + \mu f_{2n+1}^s, \\
 f_{2n+1}^m &= \mu f_{2n+1}^s + (1 - \delta - \mu)f_{2n+1}^s + \delta f_{2n}^s, \\
 f_{2n}^m &= \mu f_{2n}^s + \delta f_{2n+1}^s + (1 - \delta - \mu)f_{2n}^s.
 \end{aligned} \tag{7}$$

The inferred values are slightly different. The estimated mutation rate, $\mu = 1.036 \cdot 10^{-7}$ [8.01 ·

632 $10^{-8} - 1.339 \cdot 10^{-7}$], corresponds to a mutation target size of $\sim 300 - 500$, assuming the mutation
rate per base pair is roughly $2 \cdot 10^{-10}$ (ref.⁶⁶) or $3.3 \cdot 10^{-10}$ (ref.³⁰). The estimated aneuploidy

634 rate, $\delta = 2.358 \cdot 10^{-4}$ [$1.766 \cdot 10^{-4} - 2.837 \cdot 10^{-4}$] is 5-35-fold higher than in previous studies:

for chromosome III in diploid *S. cerevisiae*, Zhu et al.⁶⁶ estimated $6.7 \cdot 10^{-6}$ chromosome gain
636 events per generation, and Kumaran et al.²⁹ estimate $3.0 - 4.3 \cdot 10^{-5}$ chromosome loss events per
generation (95% confidence interval). The estimated fitness values are $w_{2n+1} = 1.024$ [1.023 – 1.025],

638 $w_{2n+1}^* = 1.025$ [1.024 – 1.026], $w_{2n} = 1.032$ [1.031 – 1.033], all relative to the fitness of $2n$, which
is set to $w_{2n} = 1$. Thus, we can infer that the cost of trisomy is $c = w_{2n} - w_{2n+1}^* = 0.007$ (or 0.7%)

640 and the benefit of trisomy is $w_{2n+1} - 1 - c = 0.017$ (1.7%), whereas the benefit of beneficial mutation
is $w_{2n} - 1 = 0.032$ (3.2%).

642 We simulated genotype frequency dynamics using parameter samples from the posterior distribution,
and computed the posterior distribution of F_A . The mean F_A in this case is just 0.0189 [0.0004 - 0.1214
644 95% CI], lower than without the transitions to less-fit genotypes. Here, F_A is the sum of frequencies
of both $2n_A^*$ and $2n + 1_A^*$, which reaches a frequency of 0.0007. Out of 100,000 posterior samples,
646 none had F_A above 0.05 (i.e., 5% of the population).

Supplementary Figures & Tables

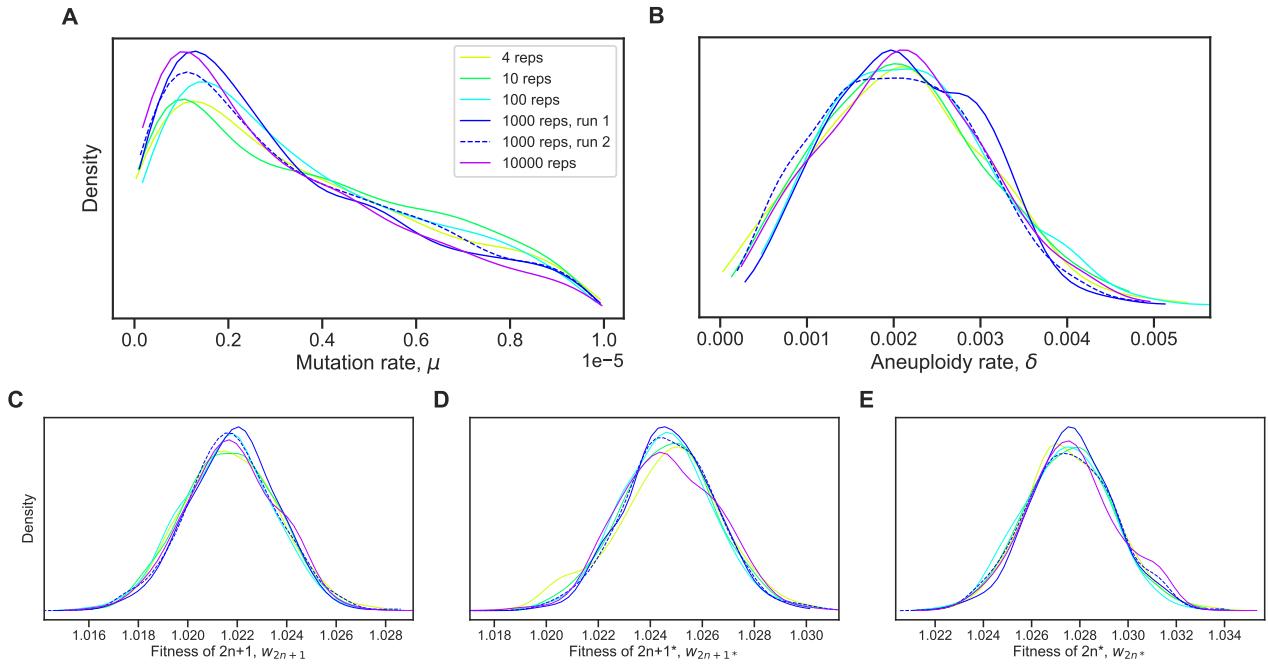


Figure S1: Posterior distribution validation. The posterior distribution of model parameters is roughly the same regardless of the number of simulations (4-10,000 replicates) used to approximate the likelihood (eq. (4)).

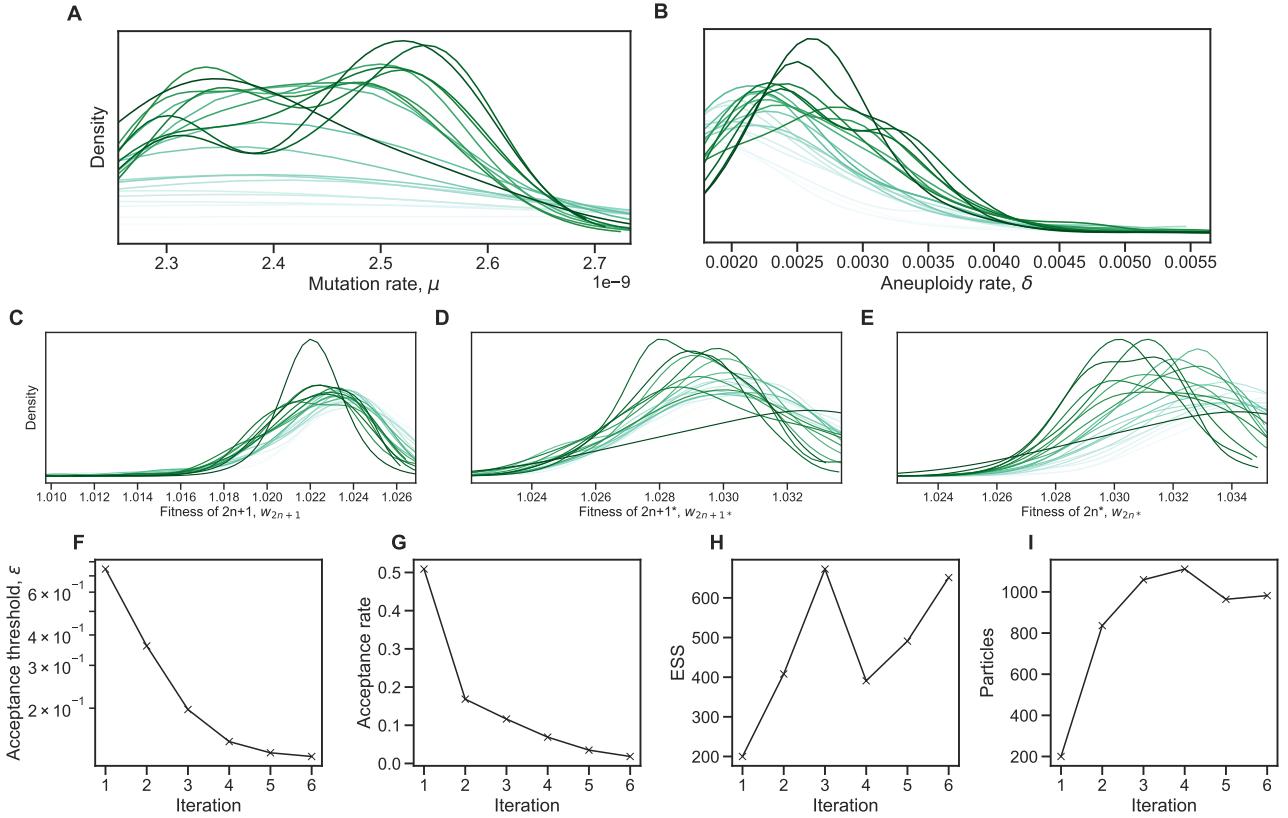


Figure S2: Inference convergence. The ABC-SMC algorithm was used to infer the model parameters. **(A-E)** The approximate posterior distributions of model parameters at each iteration of the ABC-SMC algorithm demonstrates convergence, as the posterior did not significantly change after the first iteration, $t = 1$. **(F-I)** ABC-SMC measures of convergence. After iteration number 6, the acceptance threshold was $\epsilon = 0.13$ (i.e., $\mathcal{L} = 0.87$, eq. (4)), the acceptance rate was 0.018, the number of particles was 982, and the effective sample size ESS=651.

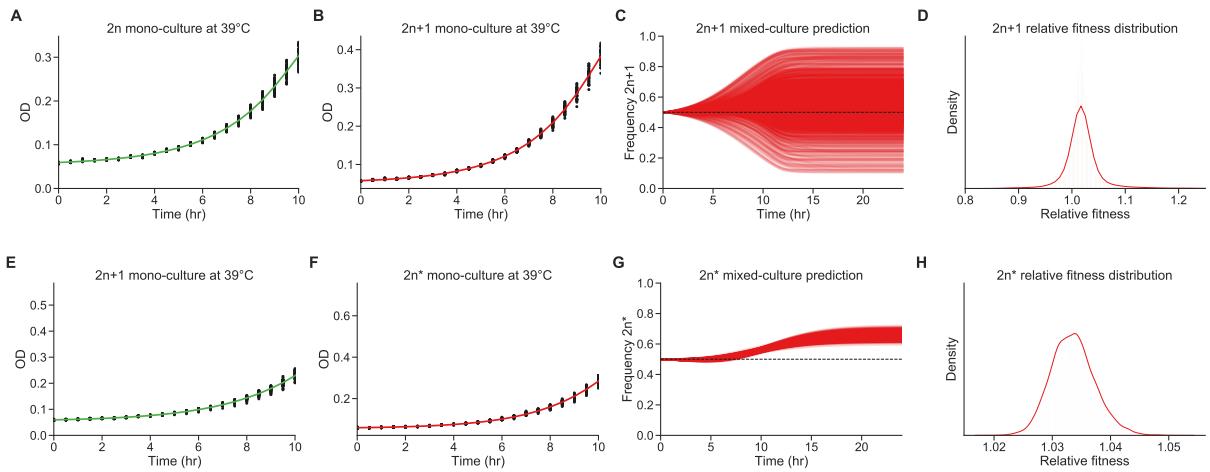


Figure S3: Fitness estimation from growth curves. **(A-D)** Fitness estimation from growth curves of $2n$ and $2n+1$ at 39°C . $w_{2n+1}/w_{2n}=1.024$ (95% CI: 0.959 - 1.115). **Curveball (E-H)** Fitness estimation from growth curves of $2n+1$ and $2n^*$ at 39°C . $w_{2n^*}/w_{2n+1}=1.033$ (95% CI: 1.027 - 1.041). Growth curves previously described in Yona et al.⁶², Figs. 3C, 4A, and S2. Fitness estimated from growth curves using Curveball, a method for predicting results of competition experiments from growth curve data³⁸ curveball.yoavram.com. See *Models and Methods, Prior distributions* for more details. **(A,B;E,F)** Mono-culture growth curve data (markers) and best-fit growth models (lines). **(C,G)** The mixed-culture prediction for the strains from A,B and E,F respectively, 6,375 generated curves. **(D,H)** The relative fitness distribution for $2n+1$ relative to $2n$ (panel D) and $2n^*$ relative to $2n+1$ (panel H). Figures generated by Curveball.

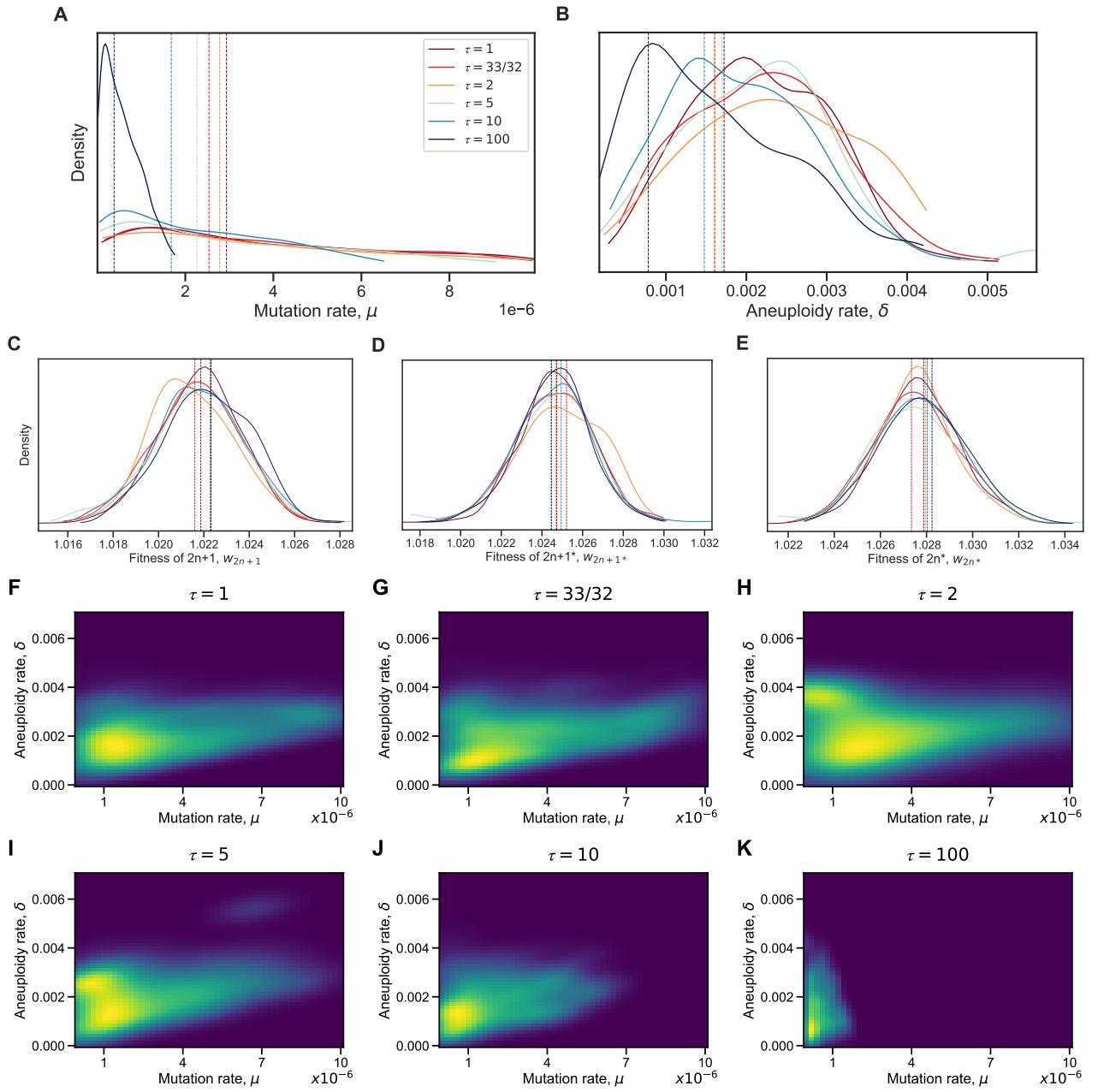


Figure S4: Model with elevated mutation rate in aneuploid cells. (A-E) The inferred posterior distributions for models with different values of τ , the fold-increase in mutation rate in aneuploid cells ($2n+1$ and $2n+1^*$). Vertical dashed lines represent the MAP (maximum a posteriori) of each distribution. When the increase in mutation rate is high, $\tau = 10$ and $\tau = 100$, the inferred mutation (A) and aneuploidy (B) rates tend to be lower. (F-K) The inferred joint posterior distribution of mutation rate (μ) and aneuploidy rate (δ) with different τ values (dark purple and bright yellow for low and high density, respectively).

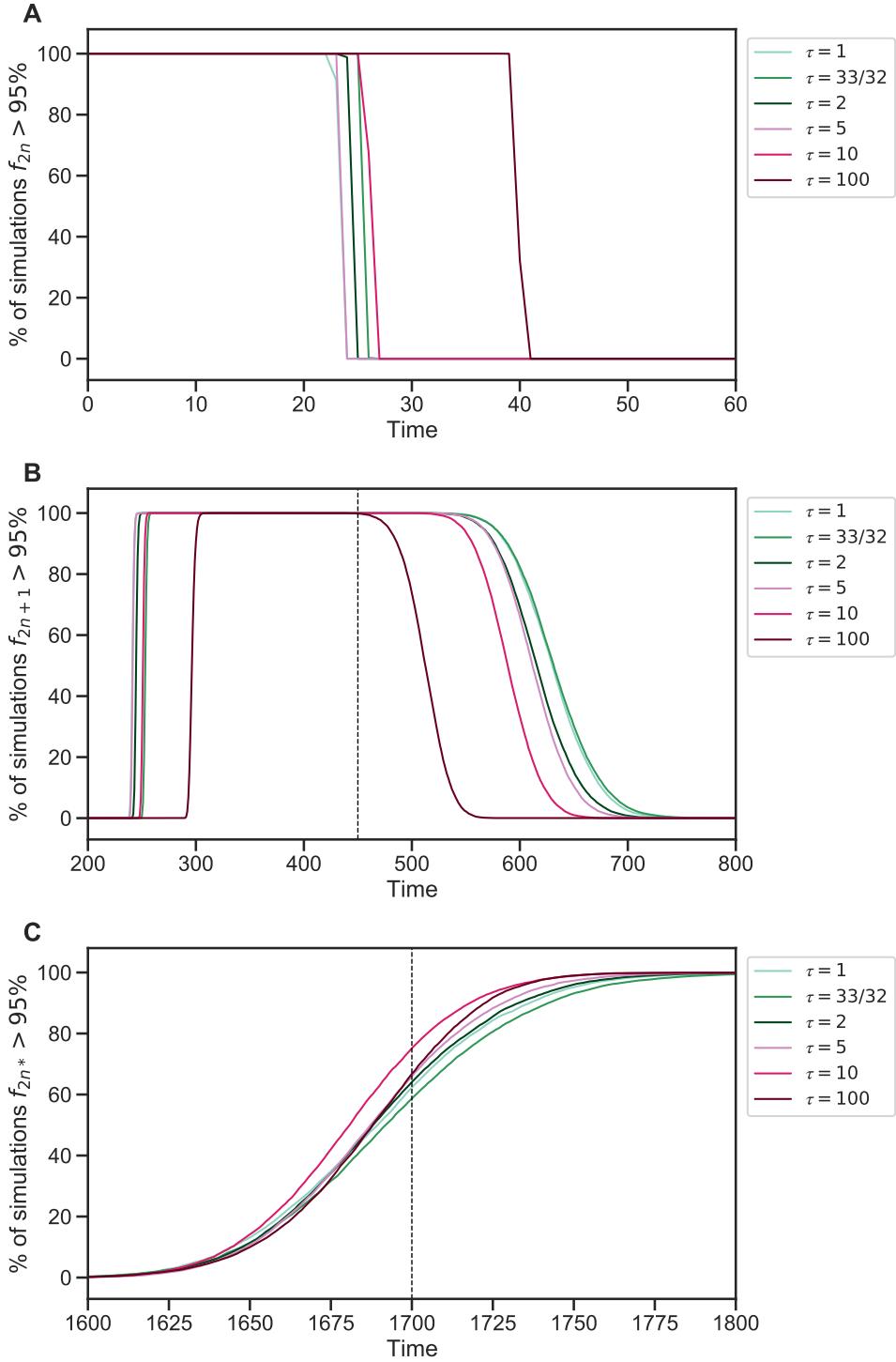


Figure S5: Genotype fixations for models with increased genetic instability. We estimated the parameters for different models, each assuming a different value of τ , the fold-increase in mutation rate in aneuploid cells. We then generated 10,000 simulations using the MAP estimate of each model and evaluated the fraction of simulations in which the frequency of genotype $2n$ (**A**), $2n+1$ (**B**), and $2n^*$ (**C**) is above 95% (y-axis) at each generation (x-axis). Note that $2n+1^*$ did not fix. We can see that $\tau = 100$ can be distinguished if the waiting time for $f_{2n} < 95\%$ is known (panel A) or if the waiting time for $f_{2n+1} > 95\%$ or $f_{2n+1} < 95\%$ is known (panel B). It is harder to distinguish between $1 \leq \tau \leq 10$.

Table S1: Mutant alleles in population $H2$.

Mutant alleles identified in the ancestor (generation 0), aneuploid (generation 450), and evolved (generation 2,350) of population $H2$. See supplementary file.

Table S2: Mutant alleles in population $H4$.

Mutant alleles identified in the ancestor (generation 0), aneuploid (generation 450), and evolved (generation 1,700) of population $H4$. See supplementary file.

Table S3: WAIC values for different τ values.

| Model | WAIC |
|----------------|------|
| $\tau = 1$ | -9 |
| $\tau = 33/32$ | -9 |
| $\tau = 2$ | -8 |
| $\tau = 5$ | -12 |
| $\tau = 10$ | -9 |
| $\tau = 100$ | -12 |

WAIC defined in eq. (6).

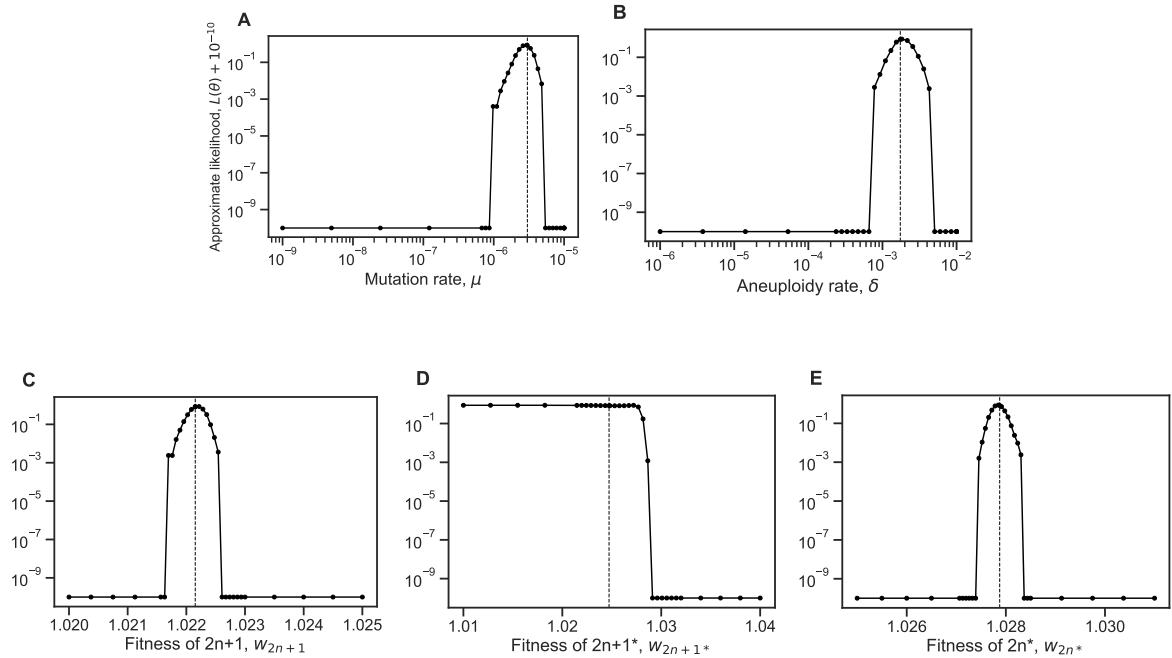


Figure S6: Likelihood profiles. Sensitivity of the model approximate likelihood, $\mathcal{L}(\theta)$, to changing a single parameter while the other parameters remain fixed at their MAP estimates. Dashed vertical line represents the MAP value. The prior distributions for the mutation rate and aneuploidy rate are $\mu \sim U(10^{-9}, 10^{-5})$ and $\delta \sim U(10^{-6}, 10^{-2})$, respectively.

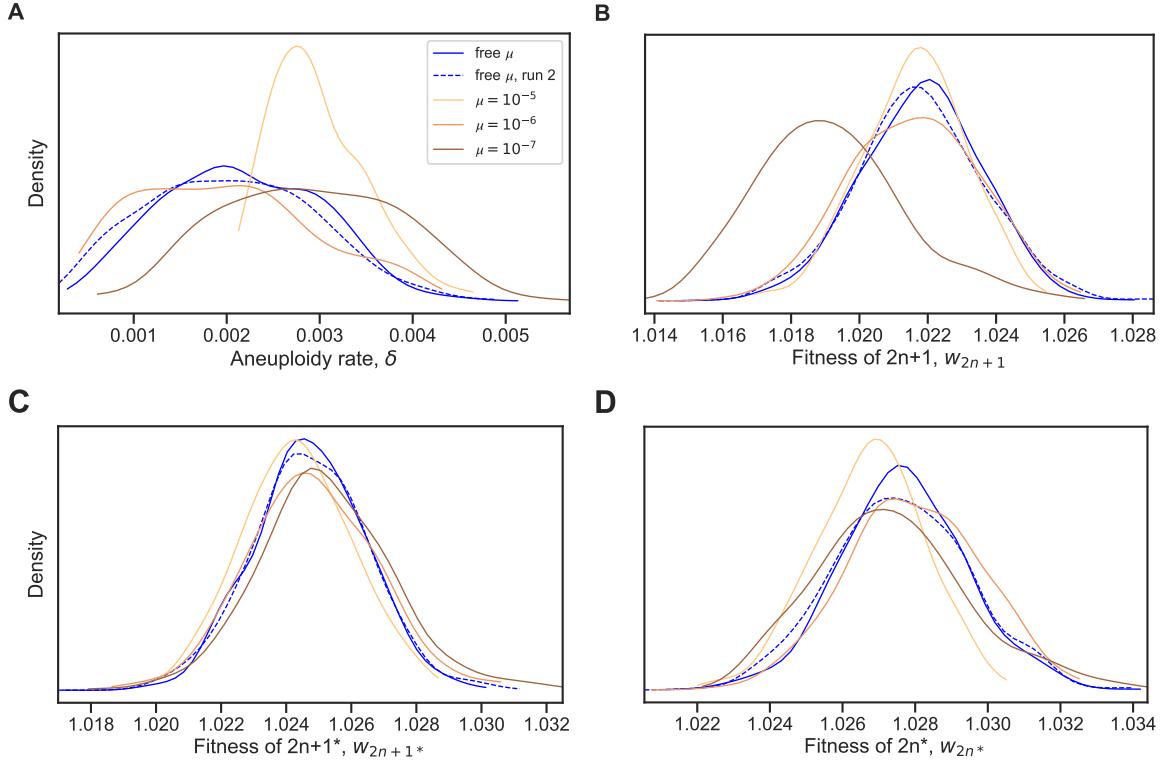


Figure S7: Model with fixed mutation rate. (A-D) The inferred posterior distributions for models with free and fixed mutation rate, μ . The MAP (maximum a posteriori) and 50% HDI (highest density interval) for each model are: **free μ , run 1:** $\delta = 1.720 \cdot 10^{-3}$ [$1.470 \cdot 10^{-3} - 2.786 \cdot 10^{-3}$], $w_{2n+1} = 1.022$ [1.021 – 1.023], $w_{2n+1^*} = 1.025$ [1.024 – 1.026], $w_{2n^*} = 1.028$ [1.026 – 1.029]; **free μ , run 2:** $\delta = 2.129 \cdot 10^{-3}$ [$1.334 \cdot 10^{-3} - 2.695 \cdot 10^{-3}$], $w_{2n+1} = 1.022$ [1.02 – 1.023], $w_{2n+1^*} = 1.025$ [1.023 – 1.026], $w_{2n^*} = 1.028$ [1.026 – 1.029]; **$\mu = 10^{-5}$:** $\delta = 2.903 \cdot 10^{-3}$ [$2.399 \cdot 10^{-3} - 3.156 \cdot 10^{-3}$], $w_{2n+1} = 1.022$ [1.021 – 1.023], $w_{2n+1^*} = 1.024$ [1.023 – 1.025], $w_{2n^*} = 1.027$ [1.026 – 1.028]; **$\mu = 10^{-6}$:** $\delta = 1.917 \cdot 10^{-3}$ [$9.624 \cdot 10^{-4} - 2.447 \cdot 10^{-3}$], $w_{2n+1} = 1.022$ [1.02 – 1.023], $w_{2n+1^*} = 1.025$ [1.023 – 1.026], $w_{2n^*} = 1.028$ [1.027 – 1.029]; **$\mu = 10^{-7}$:** $\delta = 2.901 \cdot 10^{-3}$ [$2.139 \cdot 10^{-3} - 3.671 \cdot 10^{-3}$], $w_{2n+1} = 1.019$ [1.017 – 1.02], $w_{2n+1^*} = 1.025$ [1.024 – 1.026], $w_{2n^*} = 1.027$ [1.026 – 1.029].

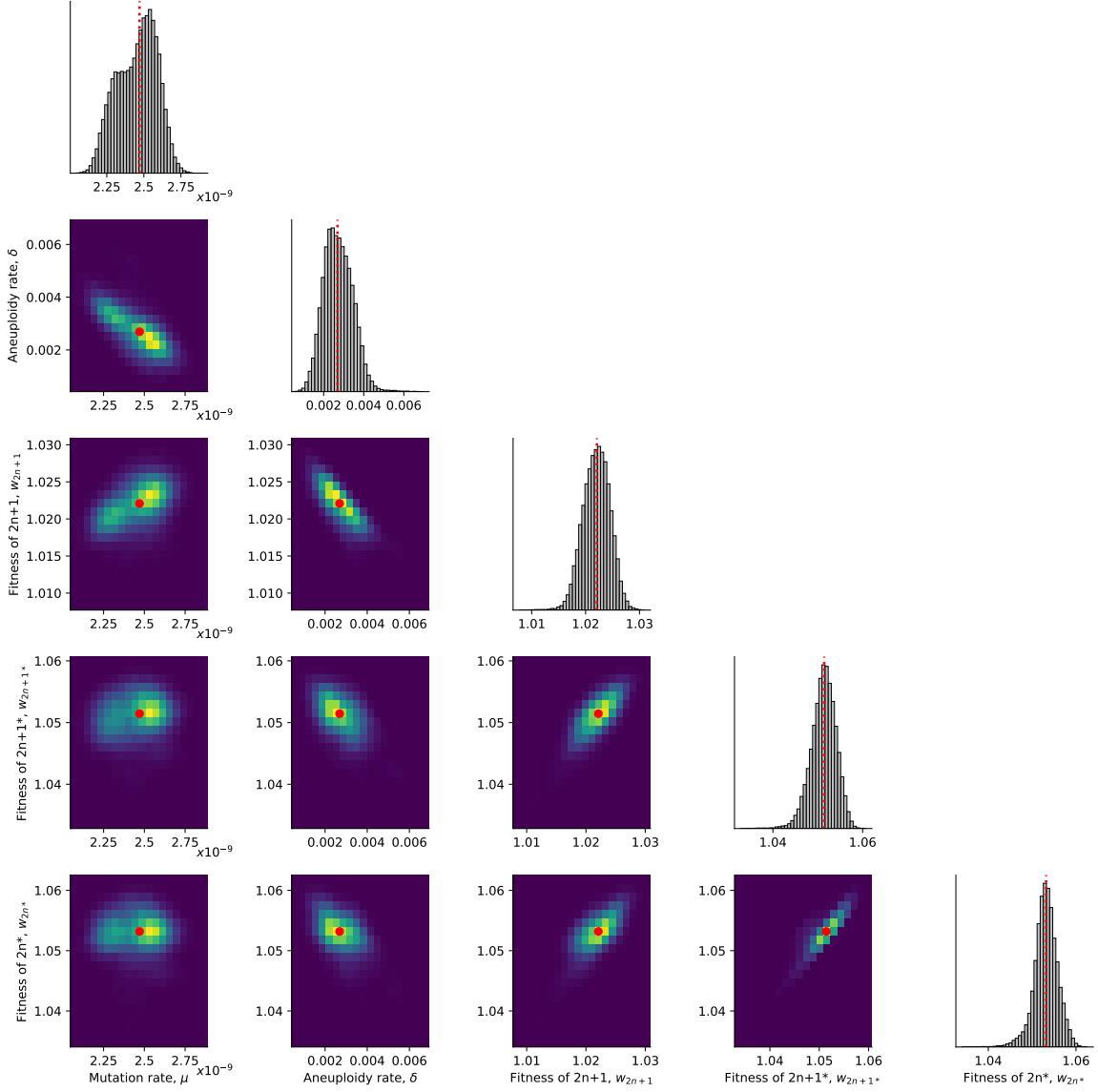


Figure S8: Posterior distribution of parameters inferred with the extended prior distribution. On the diagonal, the inferred posterior distribution of each model parameter. Below the diagonal, the inferred joint posterior distribution of pairs of model parameters (dark purple and bright yellow for low and high density, respectively). Red markers and orange lines for the joint MAP estimate (which may differ from the marginal MAP, as the marginal distribution integrates over all other parameters).

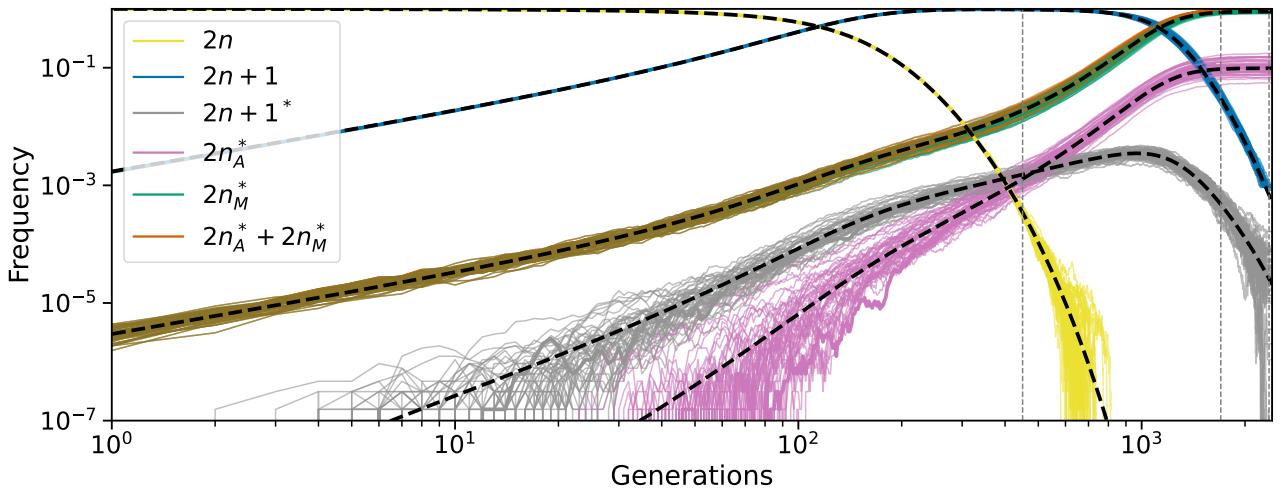


Figure S9: Posterior predicted genotype frequencies in log-log scale. Frequency dynamics of the different genotypes with MAP parameter estimates, same as Figure 5A, but in log-log scale. Black dashed curves for a deterministic model without genetic drift. Clearly, appearance of $2n+1$ and $2n_M^*$ is deterministic. Appearance of $2n+1^*$, and therefore $2n_A^*$, is stochastic, however, the frequency dynamics are deterministic above a frequency of roughly 0.001. Note that the $2n_M^*$ and the $2n_A^* + 2n_M^*$ lines are overlapping for much of their trajectories.

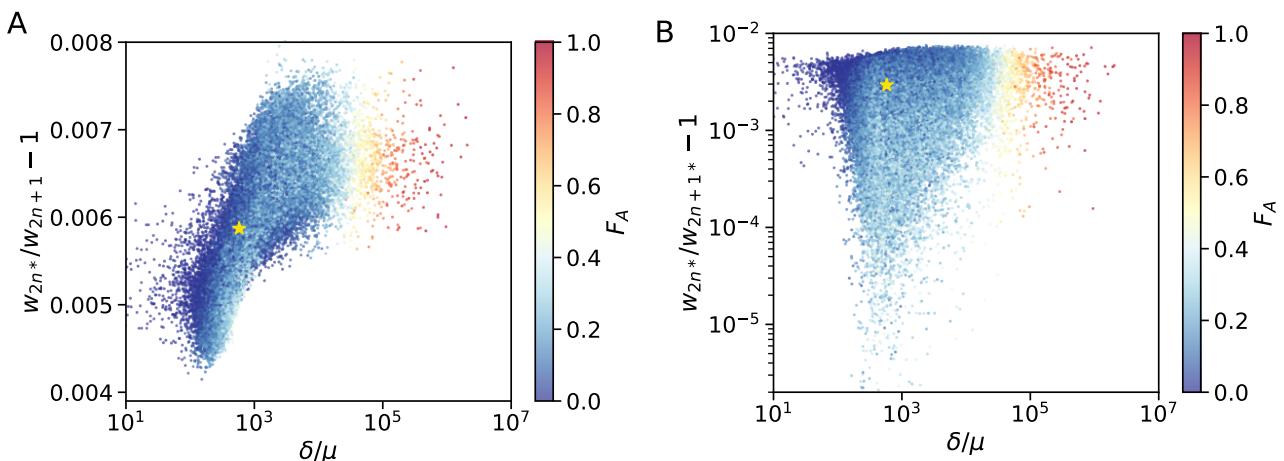


Figure S10: Posterior distribution of F_A . (A,B) F_A values (color coded) as in Figure 5 for different parameter choices on the x- and y-axes. White star denotes the MAP estimate.