Adaptive evolution with aneuploidy and mutation

Ilia Kohanovski[1,*], Martin Pontz[2,*], Avihu H. Yona[3], and Yoav Ram[1,2,†]

[1]School of Computer Sciences, IDC Herzliya, Herzliya, Israel
[2]School of Zoology, Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel
[3]Institute 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
[†]Corresponding author: yoav@yoavram.com

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Abstract

Aneuploidy is common in eukaryotes, often leading to decreased cell growth and fitness. However, evidence from yeast and fungi, as well as human tumour cells, suggests that aneuploidy can be beneficial under stressful conditions and lead to elevated growth rates and adaptation. Because aneuploidy differs from mutation in rate, expected effect, and reversibility, it is crucial to develop a quantitative theory for the role of aneuploidy in adaptive evolution. Here, we develop evolutionary models for adaptive evolution with both mutation and aneuploidy. These models are used within an approximate Bayesian computation framework to estimate the formation rate and fitness effect of aneuploidy and mutation from empirical results of experiments in which *Saccharomyces cerevisiae* adapted to heat stress. The experimental population first acquired chromosome duplications, only to later revert back to a euploid state. We also analyze our models to estimate the effect of the aneuploidy and mutation rates on the expected adaptation time and the probability for adaptation via aneuploidy. Our results suggest that aneuploidy is a transient adaptive solution, which can decelerate adaptation in a non-intuitive manner. By creating an evolutionary conflict between the individual and the population, aneuploidy further complicates the process of adaptation in cell populations.

Introduction

Aneuploidy is common in eukaryotes. Aneuploidy is an imbalance in the number of chromosomes in the cell: an incorrect karyotype. Evidence suggests aneuploidy is very common in eukaryotes, e.g. animals (Santaguida and Amon, 2015; Naylor and van Deursen, 2016; Bakhoum and Landau, 2017), and fungi (Pavelka et al., 2010; Zhu et al., 2016; Robbins et al., 2017; Todd et al., 2017). Aneuploidy has been implicated in cancer formation and progression (Boveri, 2008; Schvartzman et al., 2010): 90% of solid tumours and 50% of blood cancers are aneuploid (Santaguida and Amon, 2015). Aneuploidy is also linked to the emergence of drug resistance (Selmecki et al., 2009) and virulence (Möller et al., 2018) in fungal pathogens, which are under-studied (Rodrigues and Albuquerque, 2018) despite infecting close to a billion people per year, causing serious infections and significant morbidity in >150 million people per year and killing >1.5 million people per year (Selmecki et al., 2009; Rodrigues and Albuquerque, 2018). In addition, aneuploidy is common in protozoan pathogens of the Leishmania genus, a major global health concern (Mannaert et al., 2012).

Aneuploidy is generally deleterious. The molecular and genetic mechanisms involved in aneuploidy have been explored (Musacchio and Salmon, 2007; Sheltzer and Amon, 2011; Chen et al., 2012; Rancati and Pavelka, 2013; Gerstein et al., 2015; Shor and Perlin, 2015). Experiments with human and mouse embryos found that aneuploidy is usually lethal. It is also associated with developmental defects and lethality in other multicellular organisms (Sheltzer and Amon, 2011). For example, aneuploid mouse embryonic cells grow slower than euploid cells (Williams et al., 2008). Similarly, in unicellular eukaryotes growing in benign conditions, aneuploidy usually leads to slower growth and decreased overall fitness (Niwa et al., 2006; Torres et al., 2007; Pavelka et al., 2010; Sheltzer and Amon, 2011; Kasuga et al., 2016), in part due to proteotoxic stress caused by increased expression in aneuploid cells (Pavelka et al., 2010; Santaguida et al., 2015; Zhu et al., 2018) and hypo-osmotic-like stress (Tsai et al., 2019).

Aneuploidy can lead to adaptation. However, aneuploidy can be beneficial under stressful conditions due to the wide range of phenotypes it can produce, some of which are advantageous (Pavelka et al., 2010). Thus, aneuploidy can lead to rapid adaptation in unicellular eukaryotes (Gerstein et al., 2015; Torres et al., 2010; Hong and Gresham, 2014; Rancati et al., 2008), as well as to rapid growth of somatic tumour cells (Schvartzman et al., 2010; Sheltzer et al., 2017). For example, aneuploidy in *S. cerevisiae* facilitates adaptation to a variety of stressful conditions like heat and pH (Yona et al., 2012), copper (Covo et al., 2014; Gerstein et al., 2015), salt (Dhar et al., 2011), and nutrient limitation (Dunham et al., 2002; Gresham et al., 2008). Importantly, aneuploidy can also lead to drug resistance in pathogenic fungi such as *Candida albicans* (Selmecki et al., 2008, 2010; Gerstein and Berman, 2018) and *Cryptococcus neoformans* (Sionov et al., 2010), which cause candidiasis and meningoencephalitis, respectively.

Transient adaptive solution. Aneuploidy differs from mutation due to its distinct properties. Chromosome duplication usually occurs more often than mutation and on average produces larger fitness effects. Yet, because it affects many genes on a whole chromosome or a chromosome fragment, aneuploidy also carries fitness costs. Thus, aneuploidy can be a *transient adaptive solution*: it can rapidly occur and fix in the population under stressful conditions, and can be rapidly lost when the cost outweighs the benefit—when stress is removed or after beneficial mutations occur. Experimental evidence of such a transient role of aneuploidy was demonstrated by Yona et al. (2012). They evolved populations of *S. cerevisiae* under strong heat or pH stress. In these experiments, the populations

adapted to the stress within 450 generations, and this adaptation was determined to be due to chromosome duplications. Much later, after more than 1500 generations, the populations reverted back to an euploid state, while remaining adapted to the stress and accumulating multiple mutations. However, under gradual heat stress, aneuploidy was not observed. Yona et al. (2012) concluded that aneuploidy serves as a transient adaptive solution, or a "quick fix", which is expected to facilitate adaptation.

The present study. Here, we develop evolutionary-genetic models that include the effects of natural selection, genetic drift, aneuploidy, and mutation to examine the role of aneuploidy in adaptive evolution. These models follow a population of cells characterised by both their ploidy and their genotype. We fit these models to the experimental results of Yona et al. (2012) using an *approximate Bayesian computation* framework (Sisson et al., 2007; Klinger et al., 2018) to infer model parameters, including selection coefficients and rates of aneuploidy and mutation, and to perform model selection between different models, thereby testing different hypotheses about the evolutionary process. Furthermore, we analyze these models to estimate the effects of parameters on the adaptation time and the probability for adaptation via aneuploidy. We find that the aneuploidy rate is several orders of magnitude higher than the mutation rate; that a simple model of clonal interference is not enough to explain the transience of aneuploidy; and that aneuploidy is likely to fix in the population and increase its mean fitness, but at the price of delaying further adaptation.

Models and Methods

Evolutionary Models. We developed two models: a single-locus model and a multi-locus model. Both models are based on the Wright-Fisher model (Otto and Day, 2007), assuming a constant population size N with non-overlapping generations and including the effects of natural selection, genetic drift, aneuploidy, and mutation. We focus on beneficial mutations, neglecting the effects of deleterious and neutral mutations. Both models allow for a single aneuploid karyotype (e.g., chromosome III duplication). While the single-locus model allows for only a single mutation to occur, the multi-locus model allows for multiple mutations to accumulate in the genome (Figure 1).

In the following we describe the

Single-locus model. This model follows four genotypes: euploid wild-type, *2n*, the initial genotype; euploid mutant, *2n**, with the standard karyotype and a single beneficial mutation; aneuploid wild-type, *2n+1*, with an extra chromosome, e.g. following chromosome duplication; and aneuploid mutant, *2n+1**, with and extra chromosome and a beneficial mutation.

Beneficial mutations from *2n* to *2n** occur with probability μ, the mutation rate, and from *2n+1* to *2n+1** with probability $\tau\mu$, where τ is the fold-change in the rate of beneficial mutations in aneuploid cells. By default, we assume $\tau = 33/32$, as the wild-type *S. cerevisiae* strains in the experiments by (Yona et al., 2012) are diploid, with 32 chromosomes, and the aneuploid strains are trisomic, with 33

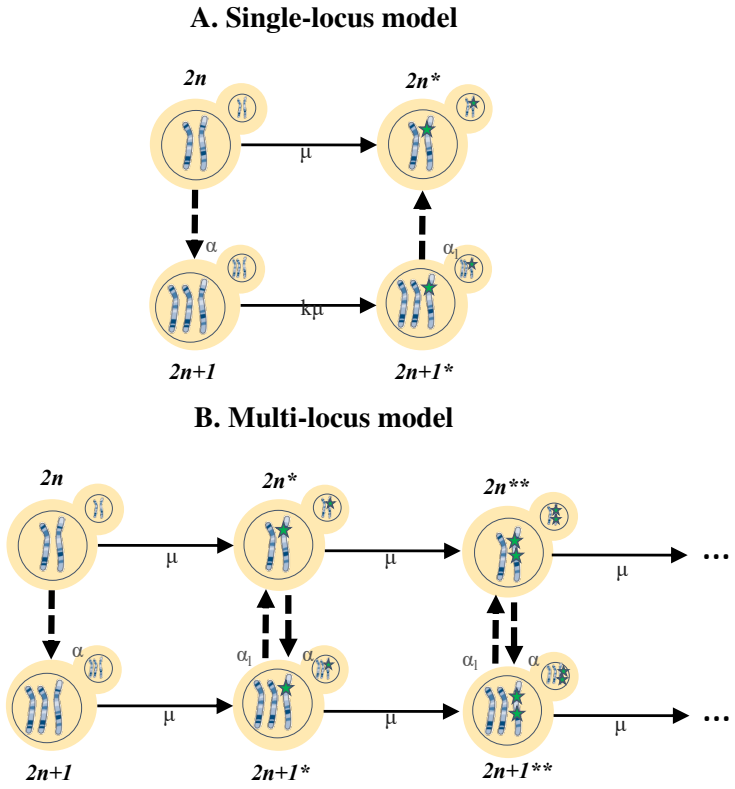

Figure 1: Model illustrations. **(A)** In the single-locus model, the four genotypes are: euploid wild-type, *2n*; euploid mutant, *2n**; aneuploid wild-type, *2n+1*; and aneuploid mutant, *2n+1**. Overall there are two possible trajectories from *2n*to *2n**. **(B)** In the multi-locus model, each genotype is characterized by its karyotype, *2n*or *2n+1*, and the number of accumulated beneficial mutations, denoted by stars. In both panels arrows denote transitions between genotypes, with transitions rates: μ, mutation rate; α, aneuploidy gain rate; α_l, aneuploidy loss rate.

chromosomes. Aneuploidy is formed by chromosome missegregation, so that cells transition from *2n* to *2n+1* or from *2n** to *2n+1** with probability δ, the aneuploidy gain rate. Aneuploidy is lost, transitioning cells from *2n+1* to *2n* or from *2n+1** to *2n** with probability δ_L, the aneuploidy loss rate. The fitness values of the four genotypes are given by

$$\begin{aligned} w_{2n} &= 1 & w_{2n+1} &= 1 - c + \sigma \\ w_{2n+1^*} &= (1-c)(1+s) + \sigma & w_{2n^*} &= 1 + s\,, \end{aligned} \tag{1}$$

such that $s \geq 0$ is the selection coefficient of a beneficial mutation; $\sigma \geq 0$ is the selection coefficient of aneuploidy; and $0 \leq c \leq 1$ is the fitness cost of aneuploidy.

The first generation is initialized with N cells with genotype *2n*. The effect of natural selection on the frequency f_i of genotype $i = 2n, 2n+1, 2n+1^*$, or $2n^*$ is given by

$$f_i^s = \frac{f_i w_i}{\bar{w}}\,, \tag{2}$$

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

$$\begin{aligned} f_{2n}^m &= f_{2n}^s - \delta f_{2n}^s - \mu f_{2n}^s\,, \\ f_{2n+1}^m &= f_{2n+1}^s - \tau\mu f_{2n+1}^s + \delta f_{2n}^s\,, \\ f_{2n+1^*}^m &= f_{2n+1^*}^s - \delta_L f_{2n+1^*}^s + \tau\mu f_{2n+1}^s\,, \\ f_{2n^*}^m &= \mu f_{2n}^s + \delta_L f_{2n+1}^s\,. \end{aligned} \tag{3}$$

Finally, the effect of random genetic drift on genotype frequencies is given by

$$N \cdot (f'_{2n}, f'_{2n+1}, f'_{2n+1^*}, f'_{2n^*}) \sim Mult\Big(N, (f_{2n}, f_{2n+1}, f_{2n+1^*}, f_{2n^*})\Big), \tag{4}$$

where $Mult\Big(N, (f_{2n}, f_{2n+1}, f_{2n+1^*}, f_{2n^*}\Big)$ is a multinomial distribution parameterized by the population size N and the genotype frequencies. Overall, the change in genotype frequencies from one generation to the next is given by the transformation $f_i \rightarrow f'_i$.

Multi-locus model. This model expands the single-locus model by allowing for the accumulation of beneficial mutations in the genome. Thus, a genotype is characterized by its karyotype, *2n* or *2n+1*, and the number of accumulated beneficial mutations, which can be zero or more. The selection coefficient of the i-th mutation, s_i, is drawn from an exponential distribution with expected value s, $s_i \sim Exp(s)$. The rest of the parameters (N, μ, τ, δ, δ_L, σ, c) are the same as in the single-locus model. The fitness of the different genotypes is the same as in the single-locus model (Equation 1, except that the fitness contribution of beneficial mutations is the product of all accumulated mutations, $\prod_{i\geq 0}(1+s_i)$, instead of the contribution of the single mutation allowed in the single-locus model, $(1+s)$.

Therefore, aneuploidy loss would be favored by selection only if there are enough beneficial mutations or/and the mutation selection coefficients s_i are large enough. The intuition is as follows: when the benefit of the accumulated beneficial mutations is small, then the benefit of aneuploidy has a large effect; when the benefit of the accumulated beneficial mutations benefit is large, then aneuploidy doesnâĂŹt add much, and its cost becomes significant.

Unlike the single-locus model, the population size for the multiple-locus model is not constant. Indeed, a serial-transfer protocol (**?**) is simulated, where the population is repeatedly diluted by transfer to a fresh medium, starting a new growth cycle, similar to the original experiment. In the model the

population initial size is N, then it is doubled every iteration till reaching $8 \cdot N$, then it is diluted back to N.

Denote by n_g be the number of cells of genotype g in the population. At each generation, genotypes frequencies are changed by the following steps:

1. Selection step:
$$n_g \leftarrow n_g \cdot w_g \tag{5}$$

2. Random drift step:
$$f \sim Mult(N', (\frac{n_1}{N'}, \frac{n_2}{N'}, ...)) \text{ where } N' = n_1 + n_2 + ... \tag{6}$$

3. Normalization after population size N change (growth or dilution):
$$n_g \leftarrow f_g \cdot N \tag{7}$$

4. Mutation step:
For each genotype g, draw the number of mutant cells from a binomial distribution $Bin(n_g, \mu)$, and subtract that number from n_g. For each mutant cell, generate a new genotype and add one cell of this genotype to the population. The newly created genotype inherits mutations and ploidy karyotype from the parent genotype g, and in addition gains one more mutation, with the selected coefficient drawn from the exponential distribution $Exp(\lambda)$. The fitness of the newly created genotype is assigned according to the Formula **??**.

5. Aneuploidy gain step:
For each genotype g that doesnâĂŹt already have an aneuploid chromosome, draw the number of new cells that gain aneuploidy from a binomial distribution $z \sim Bin(n_g, \alpha)$. If $z > 0$, then subtract it from n_g and create a new genotype and add to the population with z cells of this genotype. The genotype inherits all the mutations of genotype g and in addition gains aneuploidy. The fitness is calculated appropriately by the Formula **??**.

6. Aneuploidy loss step:
It is similar to the aneuploidy step. For each genotype g that has aneuploidy, draw the number of new cells that lose aneuploidy from the binomial distribution $z \sim Bin(n_g, \alpha_l)$. If $z > 0$, subtract z from n_g, then create new genotype, and add to the population z cells of this genotype. The genotype inherits all the mutations of g and in addition gains aneuploidy. The fitness is calculated appropriately by the Formula **??**.

Data. We inference parameters of the models based on the data of the experiments of Yona at al Yona et al. (2012). In *heat-stress* experiment four populations of *S. cerevisiae* were evolved under 39° heat-stress and developed aneuploidy till 450 generations (here and further by development/loss of genotype trait we mean that 95% of the population are the carriers of the genotype). Then, two populations were checked at generations 1700 and 2350, and for one population the aneuploidy were eliminated and has not observed allready at generation 1700 and for the second at generation 2350. Similarly, in *ph-stress* experiment four populations were evolved unde high-ph stress conditions and developed aneuploidy during 150 generations. At generation 750 aneuploidy fully eliminated for two populations, and only partly for another two.

Likelihood function. Denote by A_t the event of aneuploidy observation at generation t; by L_t the event of aneuploidy loss observation at generation t; and by L_{2350^*} the event of aneuploidy loss observation at generation 2350 while there's no loss in generation 1700. The likelihood function of the model with parameter set θ for *heat-stress* experiment is:

$$L(\theta|A_{450}, L_{1700}, L_{2350^*}) = \\ P^4(A_{450}) \cdot (1 - P^4(\neg L_{1700}|A_{450}) - P^4(\neg L_{2350^*}|A_{450}) + P^4(\neg L_{1700} \wedge \neg L_{2350^*}|A_{450})) \quad (8)$$

The likelihood function of the model with parameter set θ for *ph-stress* experiment is:

$$L(\theta|A_{150}, L_{750}) = P^4(L_{450}) \cdot 6 \cdot P^4(L_{750}|A_{150}) \cdot P^4(\neg L_{750}|A_{150}) \quad (9)$$

Parameter inference. To estimate the parameters of the models we apply approximate Bayesian computation with a sequential Monte-Carlo scheme (ABC-SMC), employing pyabc Python package (Klinger et al., 2018)

Results

Discussion

Aneuploidy is not just another type of mutation. The published data indicate that, like mutation, aneuploidy can be both deleterious and beneficial (Pavelka et al., 2010; Sheltzer and Amon, 2011). Nevertheless, there are important and fundamental differences between adaptation by aneuploidy and adaptation by beneficial mutations (Yona et al., 2015), which make aneuploidy a unique mechanism for generating genetic variation. First, the aneuploidy rate (i.e. the frequency of mis-segregation events) is significantly higher than the mutation rate (Santaguida and Amon, 2015). Thus, everything else being equal, adaptation by aneuploidy will be faster and more frequent. Second, fitness effects of aneuploidy are larger than those of the majority of mutations, on average, and are rarely neutral (Pavelka et al., 2010; Yona et al., 2012; Sunshine et al., 2015), allowing selection to quickly sort deleterious and beneficial genotypes. Third, the number of different karyotypes is considerably smaller than the number of different genotypes, and different karyotypes are likely to have different phenotypes (Pavelka et al., 2010). Therefore, exploration of the phenotype space by aneuploidy requires smaller populations and a shorter time span. Fourth, aneuploidy is a reversible state, as the rate of chromosome loss is high and the cost of aneuploidy is significant (Niwa et al., 2006). Indeed, aneuploidy often provides a transient solution: under short-term stress conditions, aneuploidy reverts (chromosome number returns to normal) when the stress subsides; under long-term stress conditions, aneuploidy reverts when refined solutions, generated by beneficial mutations, take over (Yona et al., 2012). Finally, aneuploidy results in increased genome instability, potentially increasing genetic variation by a positive feedback loop (Rancati and Pavelka, 2013; Bouchonville et al., 2009; Zhu et al., 2012), while also increasing its own transience.

Evolutionary theory of aneuploidy. The role of aneuploidy in adaptation has only recently been observed (Sionov et al., 2010; Yona et al., 2012; Gerstein et al., 2015), and is largely missing from the literature on evolution and adaptation: the introductory textbook *Evolution* by Bergstrom and Dugatkin (2012) does not mention the word aneuploidy, and the graduate-level book *Mutation-Driven Evolution* by Nei (2013) only briefly mentions aneuploidy in the context of speciation, but not adaptation. In recent reviews of the literature, aneuploidy is suggested to play an important role in fungal adaptation (Robbins et al., 2017; Todd et al., 2017) and cancer evolution (Santaguida and Amon, 2015; Naylor and van Deursen, 2016; Sansregret and Swanton, 2017), yet these reviews cite no theoretical studies nor any quantitative models. Indeed, evolutionary, ecological, and epidemiological studies mostly assume adaptation occurs via beneficial mutations, recombination, and sex. Therefore, there is a critical need to develop an evolutionary theory of aneuploidy like the evolutionary theories of other mechanisms for generation of genetic variation, e.g. mutation (Lynch, 2010), recombination (Hartfield and Keightley, 2012), and sex (Otto, 2009). An evolutionary theory of aneuploidy will be central to the interpretation of experimental and clinical observations and design of new hypotheses, experiments, and treatments (Carja et al., 2014). For example, despite the lack of theoretical models, aneuploidy has been invoked in a new strategy to combat pathogens and tumour cells by setting âĂIJevolutionary trapsâĂİ (Gerstein et al., 2015; Chen et al., 2015), in which a condition that predictably leads to emergence of aneuploidy is applied, followed by a condition that specifically selects against aneuploid cells.

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