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Standing variation of beneficial mutations is sufficient for maintenance of anisogamy

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While the advantages of sexual reproduction for genetic recombination have been studied extensively, the question of emergence and maintenance of asymmetric sexual reproduction (anisogamy) has received much less attention. In the anisogamous case, females are limited in the maximum number of offspring that they can produce, so that the difference in number of offspring for a very fit or moderately fit female is minimal. In contrast, males are far less limited, and a single very fit male can have an enormous number of offspring. We propose that this asymmetry, and specifically the amount by which female fitness is curtailed by the maximum number of offspring she can produce, is what gives rise to evolutionary stability of anisogamy. We show that the variance in fitness for the males (which is related to how much the variance for females is limited) predicts the probability of success of an anisogamous population in competition with an isogamous one. This effect alone is sufficient to explain prevalence of anisogamy in rapidly changing environments, where mutations that had spread through the population as neutral mutations can quickly become beneficial. We end with proposals for experimental verifications of our theory.

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While the advantages of sexual reproduction for genetic recombination have been studied extensively, the question of emergence and maintenance of *asymmetric* sexual reproduction (anisogamy) has received much less attention. In the anisogamous case, females are limited in the maximum number of offspring that they can produce, so that the difference in number of offspring for a very fit or moderately fit female is minimal. In contrast, males are far less limited, and a single very fit male can have an enormous number of offspring. We propose that this asymmetry, and specifically the amount by which female fitness is curtailed by the maximum number of offspring she can produce, is what gives rise to evolutionary stability of anisogamy. We show that the variance in fitness for the males (which is related to how much the variance for females is limited) predicts the probability of success of an anisogamous population in competition with an isogamous one. This effect alone is sufficient to explain prevalence of anisogamy in rapidly changing environments, where mutations that had spread through the population as neutral mutations can quickly become beneficial. We end with proposals for experimental verifications of our theory.

1 Introduction

In many sexually reproducing populations, especially for multicellular organisms, members of the two sexes contribute different amounts of resources to their offspring [1]. This is known as *anisogamy*.[1] In contrast, some species reproduce sexually but isogamously, which means that the two parents give similar amounts of resources to their offspring (for example, α and a yeast mating types contribute equally to the production of tetrads, the spores that will eventually develop into four haploid yeasts [2]). At the extreme, the sperm is so much smaller than the egg that the male contributes virtually no resources to the zygote, and it is the female who invests in the next generation, into both female and *male* offspring. Since the ratio of females to males is often 1:1 (as follows from the famous Fisher's principle [3]) an anisogamous female experiences a fitness cost compared to an isogamous one, as she needs to produce twice as many progeny (females *and* males) to sustain the population. This is generally known as the *two-fold cost of males*. The question then is why a population would reproduce anisogamously rather than isogamously, given that there is such a dramatic cost to doing so.

It is important to distinguish the question of the two-fold cost of males from a better studied question of advantages of sexual vs. asexual reproduction [4]. Sexual reproduction leads to recombination, which is beneficial for a variety of reasons [4, 5, 6, 7]. However, even isogamously reproducing sexual organisms retain the advantages of sex. This means that males are not a necessary cost to pay for the evolutionary advantages of sex, and the advantage males confer must be analyzed against isogamous sexual populations, rather than against asexuals.

One way in which this problem has been approached is by looking at the effects of anisogamous or isogamous reproduction on the size of zygotes. This effect comes into play when we define females as the sex that produces larger (but therefore many fewer) gametes than male., This means that, in an anisogamous pairing, offspring would be smaller than in an isogamous pairing, where both parents would be considered to be essentially females. More specifically, the idea is that each parent has a fixed amount of resources, R, to be divided among their n offspring, and each of the

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[1]We note that anisogamy is usually defined as gametes having different sizes, but parental investment may also extend into rearing, feeding, and protecting the young, and different sexes can contribute differently to all of these. Our use of the term *anisogamy* is broader and encompasses asymmetry in all forms of parental investment.

offspring gets R/n resources from each of their parents. The fitness of the offspring (either the zygote or the gametes) is then assumed to be a function of the resources received from its parents, and these functions take various forms but generally fitness increases with R/n for gametes and $R_1/n_1 + R_2/n_2$ for zygotes, where subscripts refer to the two parents. It has been shown that, given some reasonable fitness functions, there are possible stable states for both anisogamy and/or isogamy [8, 9, 6, 10]. Although these studies do allow for direct comparison between the fitness of anisogamous and isogamous populations, they require making assumptions about how fitness depends on size of the gamete or zygote, and how the size of the gamete or zygote depends on whether it was created anisogamously or isogamously. All of the analyses also require specific choices of functions for the relationship between fitness and size off offspring, which may or may not be representative of the actual biological systems, and which add another layer of complexity to the problem.

Alternatively, the benefits of anisogamy have also been analyzed in terms of how it speeds the clearance of deleterious mutations from a population: under certain conditions, anisogamous populations clear a mutational load much more quickly than asexual populations [11, 12, 13, 14]. These results, however, tend to depend on different particular assumptions about gene action (such as epistasis) or on how selection would act on the two sexes in anisogamy (sexual selection). Sexual selection in particular was shown to significantly reduce mutational load at a single locus [15], and was expanded to different realizations for anisogamous populations, where sexual selection would be strong [16]. However, these comparisons are generally not done between anisogamous and isogamous populations, but instead compare the fitness of an anisogamous and an asexual population, which again conflates sexual reproduction and anisogamy. It is also unclear that the assumptions underlying these analyses are biologically realistic, especially across the large spectrum of existing anisogamous populations. For example, the common explanation for anisogamy in terms of a strong sexual selection on males seems intuitive, but strong sexual selection also exists in populations that reproduce isogamously [17], and it is not clear why similar benefits from selection could not arise in isogamous populations as well. Similarly, other assumptions often made (such as reasonably strong synergistic epistasis between deleterious mutations) lack evidence of their presence in many biological systems [18].

We propose that the benefits of anisogamy (and the reason it could be beneficial despite the two-fold cost) arise exactly because of the differences in possible numbers of offspring. If each adult has limited resources (and therefore is only capable of investing a limited amount into its offspring), adults who invest more in their offspring/gametes are *necessarily* limited to a smaller number of possible offspring. That means that a female whose fitness is several standard deviations above the mean still cannot produce many more offspring than females of average or slightly above average fitness – she is limited by other factors. In other words, her *reproductive rate* deviates from her *fitness* due to basic physiology. Isogamous adults, who only have to contribute half of the needed resources for their offspring, are somewhat less limited. Crucially, however, in the limit where males produce an infinite number of gametes each of which gives no resource contribution to the zygote, anisogamous males do not face this limitation, so that a single very fit male can sire a very large number of offspring. Given that selection favors individuals at the far tail of high fitness, we here focus on the effects of the spread of beneficial mutations in this setup.

Unlike in previous analyses [11, 12, 13, 14, 19, 16, 20, 15], here the advantage of males is not in clearing deleterious mutations from a population, but rather facilitating a rapid spread of advantageous mutation. This requires a large supply of beneficial mutations, such as would exist after a rapid environmental change. Existence of such supply is an emerging consensus in laboratory evolution experiments [21, 22, 23, 24, 25], especially in changing environments (e.g., during host-pathogen co-evolution [26, 27, 28], where many previously neutral mutations may simultaneously gain fitness effects.

The fact that the fastest way of spreading beneficial mutations is to have a single male with the sought-after phenotype to sire all of the next generation offspring has been known in animal breeding since pre-historic times. However, surprisingly, we have not discovered quantitative analysis of this phenomenon in the literature, and specifically under which conditions this effect alone is sufficient to stabilize anisogamy in sexual reproduction in natural populations. Some analyses have been done on the role of the spread of beneficial mutations [29, 30], but these papers also focused on the role of sexual selection. Interestingly, however, previous work [30] does show a similar scenario to our expectation of the role of the standing variation — the effects of anisogamy (or sexual selection) on the spread of beneficial alleles is shown to be the most dramatic in the

nonequilibrium period, immediately after the environment changes.

In this thesis, I analyze the effects of readily available beneficial mutations on stability of anisogamous sex using numerical simulations. I show that, without additional assumptions, such as sexual selection, or variable offspring size, anisogamous reproduction is evolutionarily stable when the supply of beneficial mutations in the population is reasonably large. In other words, the two-fold cost of males can be overcome by the males' ability to speed up the spread of plentiful beneficial mutations.

2   The Model

We investigated the fitness effects of anisogamy by numerically competing an anisogamous population and an equivalent, but isogamous population. There are many ways to to set up such competition, and here we view it in terms of females having a limited number of offspring over their lifespan, and isogamous females being less limited in the number of offspring that they can have, which is what establishes the two-fold cost of anisogamous reproduction, or the two-fold cost of males. While the definitions of the sexes are clear in the anisogamous case (by convention, males do not invest in their offspring and instead create many gametes), the two sexes are equivalent in the isogamous case. Nonetheless, throughout the description of our model, we refer to isogamous males or females for consistency, even though these two genders play equivalent roles.

In our simulations, each individual is diploid, with the genome consisting of two copies of L loci each. A locus does not necessarily represent an individual base pair, but rather an independently recombining length of DNA ($L \sim 100$ for a large genome). Each locus is binary (absence of mutation is 0, and presence of an advantageous mutation is 1). ~~In our model~~ Anisogamous and isogamous subpopulations combined make up a population of size N. Generations are discrete, and these two subpopulations compete for space in the next generation for their offspring. In each generation, each female anisogamous adult produces n gametes, where each gamete randomly chooses one of the two available copies of DNA for each of the L loci. Similarly, each anisogamous male produces gametes with independent assortment for each of the loci, but produces infinitely many gametes. In the isogamous case, adults of each sex produce $2n$ gametes, thus explicitly encoding the two fold cost of males. In reality, the cost may be less than a full factor of 2, especially when the males' resource contribution to the zygote is nonzero. However, a smaller relative benefit would only strengthen our arguments as presented here.

We first compete the females of each sex in order to determine how much of the following generation would be made up of anisogamous or isogamous adults chosen to procreate. If we define k as the number of beneficial mutations in the parent of a gamete, and s as the fitness benefit of a mutation at a single locus (which we assume to be constant for simplicity), then the the probability of each female gamete (isogamous or anisogamous) to propagate to the next generation is given by the exponential of the fitness,

$$w = \frac{1}{Z} \exp(sk), \tag{1}$$

where Z is the normalization constant. Note that this way we are selecting on gametes, and not on the parents, although the fitness of a gamete is dependent on the parents' genome rather than the gamete's.

Once the female gametes for the following generation are selected (which determines the number of isogamous and anisogamous adults in the next generation), the male gametes within each subpopulation then compete to be allowed to mate, but no direct competition between isogamous and anisogamous male gametes is modeled. Each mating produces two offspring, one male and female, which means that thee gender ratio is fixed withing each subpopulation. Note that the intra-sex, intra-species competition among the males was entirely to determine which gametes mated with females, and not to determine *which* females the males mated with. In other words, there is no sexual selection, and we model purely effects of anisogamy. If we had additionally allowed for more fit females to choose more fit males, or the other way, we expect that the effects of beneficial mutations on maintenance of anisogamy would have increased. Finally, each individual gets the genomes of each of their constituent gametes (which are recombined genomes of the parents), with no additional mutations.

Importantly, our model does not assume any particular or different selection on either population (the anisogamous or isogamous), and instead we are simply applying the same fitness function.

Further, unlike previous work we also do not assume a stronger selection on males, and instead use the same fitness function for both sexes.

We expect that an isogamous population will initially grow faster than an equivalent anisogamous population because of the two-fold cost to anisogamous sex — even though we expect beneficial mutations to spread more quickly in the anisogamous population, meaning that each individual gamete will have a higher fitness than in the isogamous population, isogamous females have twice as many gametes, meaning that that population can still 'win' even if its fitness is lower. Thus looking at just fitness comparisons is insufficient – we need to see if the fitness gains could be enough to offset the cost in female reproduction.

In this scenario, we expect the effects of anisogamy to be most pronounced when there are many beneficial mutations in the population available to be fixed. Thus we focused on cases with a standing supply of beneficial mutations, rather than beneficial mutations that occur via mutation, and then spread. We therefore setup our initial conditions so that at the beginning of each simulation a proportion f of the alleles were mutated, and where the number of mutants per site was set according to known distributions for neutral mutations. This can be views as modeling a sudden environmental change, where many standing neutral mutations suddenly become advantageous and as such our results point to a strong benefit to anisogamy in a rapidly changing environment, where new beneficial mutations with standing variation become available from time to time. For the analysis shown below, we used $f = 0.3$, but the results are consistent across values of f where f and $1 - f$ are limited away from zero.

2.1 Simulation details

For the figures below, we have chosen the following parameter values. We set genome length $L = [10, 1000]$ loci. For fitness of each mutation, we choose $s = [0.01, 0.5]$. We work with $N = 1000$, but other population sizes have been analyzed as well, and the effects described here are consistent across population sizes. Each simulation starts with the equal number of anisogamous and isogamous adults.

With these parameters, we compete the populations until either only isogamous or anisogamous subpopulations remain, updating the populations probabilistically as described above. Since the simulations are probabilistic, we repeat every one of them 200 times, and measure the frequency of the anisogamous population winning the competition. With the usual Bernoulli statistics, for 200 simulations, we expect the relative error of the estimated survival frequencies to be $< 10\%$.

3 Results

We first demonstrated that our intuition was correct, in that the variance in number of offspring for males is larger than that of females for the anisogamous popualtion (at least in certain parameter regimes), and that the variance in the number of offspring of the females is limited. This can be seen in Fig. 1, where the variance in the numbed of offspring of the females is consistently less than that of the males.

We then tested our prediction that the success of anisogamous populations would arise from how much the distribution of numbers of offspring is 'cut off' by n being finite. According to Fisher's fundamental theorem of natural selection, the increase in fitness in a population per generation is proportional to the fitness variance. Thus the fitness of the anisogamous population (whose variance in number offspring is unlimited, at least for males) will grow faster, which may be able to compensate for the two fold cost of males. We note that the variance of fitness of anisogamous males $\mathrm{Var}(\log(w)) \sim Ls^2$, while the variance of the effective fitness of females (either isogamous or anisogamous) is $O(1)$ for small n values. We thus expect that the probability of the anisogamous population to win the competition will scale as Ls^2, which is clearly visible in Fig. 2. Indeed, the equal winning probability curves are fitted by $Ls^2 = $ const nearly perfectly.

Finally, the extent to which the tails of the female's fitness distribution are 'cut off' is dependent both on the location of the 'cutoffs' and the width of the distribution. Therefore we also expect n to be predictive of the probability of the anisogamous population to win the competition. We therefore expect the underlying predictive variable of the success of an anisogamous population to be some combination of Ls^2 and n, and the relationship can be seen in Fig. 3.

4 Discussion

In this work, we discussed a few results addressing the two fold cost of males, one of the oldest questions in evolutionary biology. We argue that the faster spread of beneficial mutations conferred by males can be sufficient for maintenance of the anisogamy.

In our model, the two fold cost of males is overcome due to a large supply of beneficial mutations, which the males help to spread rapidly. We note that, unlike many previous attempts at addressing the problem, we carefully separated the advantage of sex from the effects of anisogamy. Further, we did not have to postulate an explicit stronger selection on males, or sexual selection within the population. Even in such a reduced model, males are advantageous for various parameter values, specifically where the variance of fitness in the population, $\sim Ls^2$, is large. The main reason for this advantage is the difference between the potential (set by w) and the true (set by actual number of offspring) fitness of females, which are incapable of producing a large variation in the number of the offspring due to physiological constraints. In fact, a simple theoretical argument based on this consideration fits our results remarkably well.

The parameters of our model are biologically realistic. For example, the red tailed deer females all produce one offspring per year, while the variation in the number of offspring for the males is much larger [31]. Similarly, a recent series of experiments has shown that a population of nematodes goes from nearly 100% hermaphrodite to almost 50% male when the population is introduced into a new environment, or into a co-evolutionary (and hence rapidly changing) context with a predatory bacterium [27, 26, 28] (though it should be noted that this work has not clearly separated the advantageous effects of males from those of genetic recombination). Some of our parameters are large (such as $s = 0.3$), but a single locus can ave many mutations, and the large s could be a result of their combination.

The advantages of anisogamy as predicted by our model can be verified experimentally. For example, Figures 2 and 3 make explicit quantitative predictions about the prevalence of anisogamy as a function of the fitness variance and the maximum number of offspring per female. The former can be measured experimentally in such systems as *C. elegans*. The latter can be manipulated genetically in various organisms, such as the nematode, as well. Then, by changing these factors, one can have competition experiments, were the males are the driving factor.

Our model could be further extended by introducing non-random mating, removing discrete generational constraints, or introducing spatial inhomogeneities leading to compartmentalization. The latter may be able to explain co-existence of both mating modalities as is often observed, such as in the vegetative or sexual reproduction of plants. Here we stress that even the simplest model, accounting only for anisogamy, rather than for other phenomena usually correlated with it, is able to overcome the two fold cost of males, one of the oldest puzzles in evolutionary biology.

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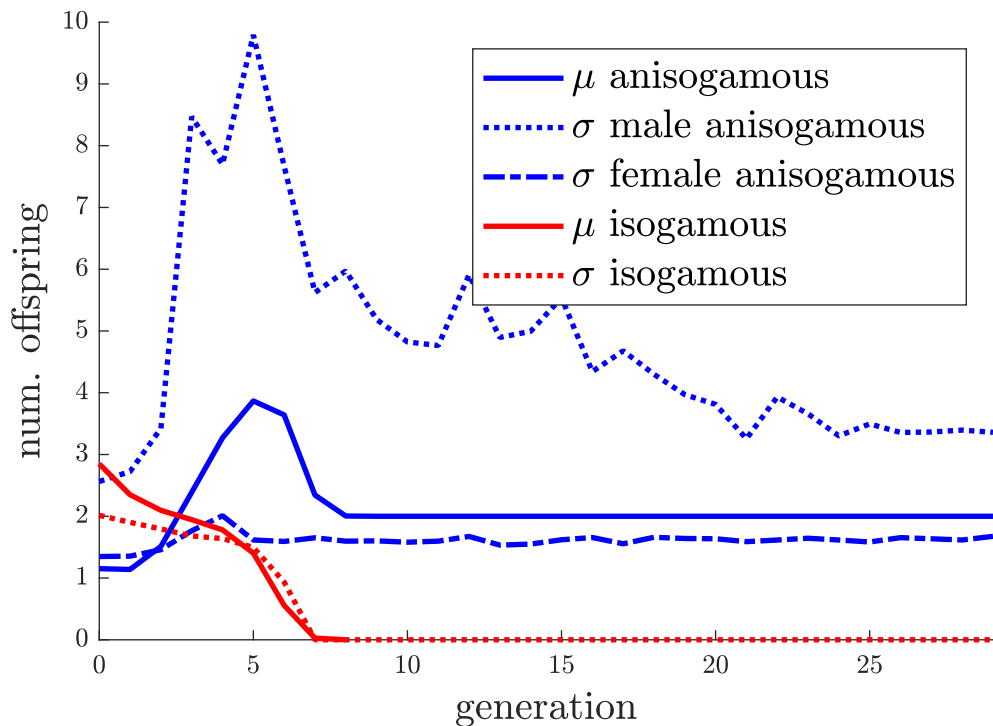
Figure 1: Mean and standard deviation of number of offspring per individual for a single sample run, with parameters $N = 1000$ individuals, $n = 3$ gametes per anisogamous female, $L = 300$ loci in the genome, and a $s = 0.3$ fitness effect of each advantageous mutation. Note that the isogamous females start with, on average, twice as many offspring as their anisogamous equivalents, but this does not save their population from going extinct in as little as 7 generations. The variance of the number of offspring for the female anisogamous population is clearly limited throughout the entire run (or else it would align with the males), and most noticeably around five generations, where even though the population is growing quickly, the variance in number of offspring does not increase for the females.
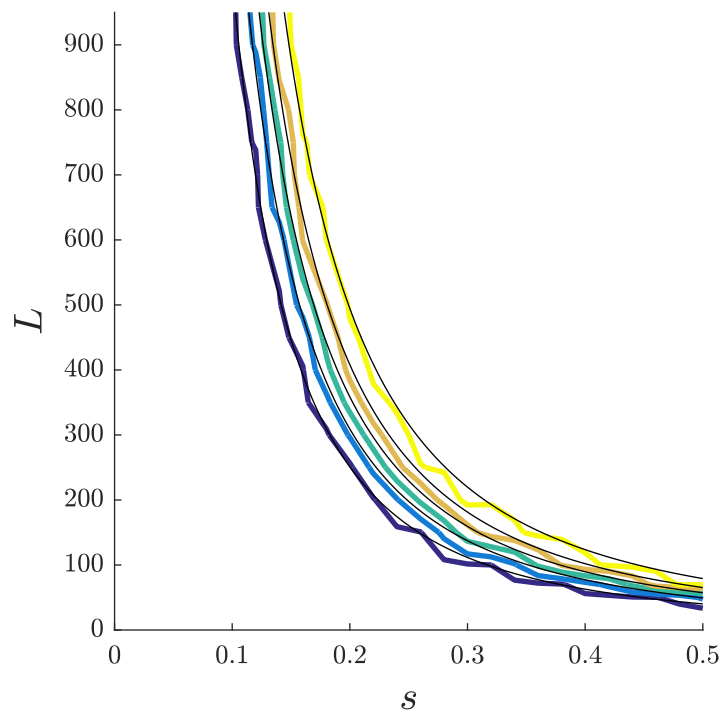
Figure 2: Contours (from dark blue to yellow: 0.05, 0.25, 0.5, 0.75, 0.95) for the frequency of an anisogamous population winning a competition over multiple runs. The black lines are fits to Ls^2, which fits nearly perfectly, and seems to show that the maximum variance in fitness for the population (which is proportional to Ls^2) is nearly perfectly predictive of anisogamous success in our setup.
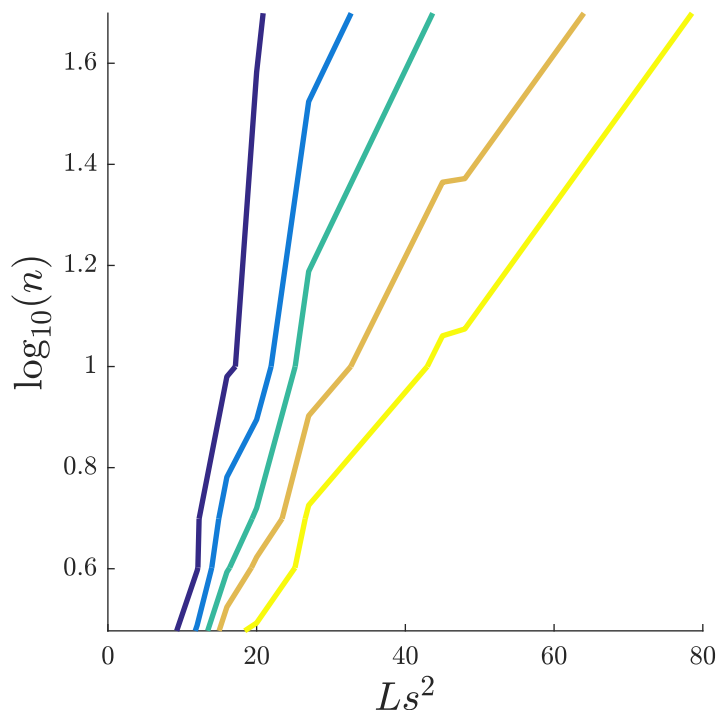
Figure 3: Contours (from dark blue to yellow: 0.05, 0.25, 0.5, 0.75, 0.95) for the frequency of an anisogamous population winning a competition over multiple runs. Here we show that while Ls^2 is predictive for a fixed n value, in truth the success of the anisogamous population depends both on that variance in fitness and the extent to which females' variance in fitness is limited.

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