

The Evolution of Mating-Type Switching

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Abstract

Predictions about evolutionary transitions in sex-determination mechanisms have been mainly formulated in animals and plants, whereas the evolution of sex-determining mechanisms in groups such as algae, fungi and ciliates is still poorly understood. One remarkable means of sex-determination occurring in these groups is mating-type switching, in which a haploid parent attains a different mating type than its offspring or later genetic descendants. Here we study

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1 Introduction

Explaining the remarkable diversity in sex-determining mechanisms has been a long-standing question in evolutionary biology (Bull, 1983; Uller & Helanterä, 2011; Beukeboom & Perrin, 2014; Bachtrog *et al.*, 2014). Indeed, numerous models have been developed to explain transitions between different sex-determining mechanisms in animals and plants (e.g., Bull, 1981; Bulmer & Bull, 1982; Pomiankowski *et al.*, 2004; Van Doorn & Kirkpatrick, 2007; Kuijper & Pen, 2010, 2014, reviewed in Van Doorn, 2014). By contrast, groups like fungi, ciliates or slime molds have received much less attention: existing models exclusively focus on the evolution of gametic dimorphism [refs], and the number of sexes, or ‘mating types’ (e.g., Charlesworth & Charlesworth, 1979; Iwasa & Sasaki, 1987; Hurst, 1996; Perrin, 2012; reviewed in Billiard *et al.*, 2011), whereas few predictions exist about evolutionary transitions between different forms of mating-type determination (Paixão *et al.*, 2011).

Particularly interesting is the repeated evolution of non-Mendelian forms of mating-type determination, where the mating type identity switches between parents and their offspring or later descendants. For example, in a number of ciliates such as *Paramecium*, an individual's mating type is epigenetically determined by the macronucleus in the parent (Phadke & Zufall, 2009; Sawka, 2012; Bloomfield, 2014), and can be modulated dependent on the parental environment (IS THIS DURING CLONAL GOWTH? WHAT IS THE MECHANISM? WE SHOULD MAKE IT CLEAR HERE. MORE INFO WOULD BE USEFUL...) (Sawka, 2012). In the ciliate *Tetrahymena*, mating type is determined stochastically at sex, so that mating types switch between one of 7 adjacent mating type alleles through recombination each generation (Paixão *et al.*, 2011; Cervantes *et al.*, 2013). Finally, in several distantly related species of ascomycete yeasts (e.g., *Saccharomyces*, *Schizosaccharomyces* and *Kluyveromyces*), individuals contain at least one copy of both mating type alleles, but only express one of both through different mechanisms including epigenetic silencing or ectopic recombination (Klar, 2007; Haber, 2012; Hanson *et al.*, 2014).

Why has mating-type switching repeatedly evolved? Despite numerous studies focusing on the molecular mechanisms underlying switching, few hypotheses exist about its evolutionary origins. An exception is an evolutionary study by Paixão *et al.* (2011), who studied the evolution of stochastic mating type determination following sex and recombination. This work shows that species with multiple mating type would benefit from stochastically switching their mating type following sex so that the mating type of the offspring is randomized. Such a mechanism counters a distortion in the sex ratio due to mating between multiple types and can explain sex determination mechanisms such as those seen in *Tetrahymena*. Many other ciliates and fungi however switch their mating type during vegetative growth which can last for several to hundreds of generations. In addition, mating type switching is common in species such as yeasts that have only two mating types. Naively, one could argue that mating type switching allows a normally outbreeding organism to occasionally mate with their sibling gametes when mates are limited. However several species such as yeasts (and other fungi?? Bram? We keep bringing yeast up, may be good to add some other examples too) reproduce largely by selfing (Haber, 2012).

The majority of protists reproduce clonally with sex occurring rarely following internal or external cues (pnas 2015). Even if a population initially has an even sex or mating type ratio, repeated rounds of vegetative growth are likely to distort the proportion of different mating types. Here we propose that mating type switching is important because it helps maintain an even mating-type ratio in finite populations. By switching their sex or mating type stochastically during their vegetative growth cells can ensure that they find themselves in the presence of compatible partners at the next sexual cycle. In this work, we develop a finite population model to study the evolution of alleles imposing stochastic mating type switching during clonal growth. By explicitly modeling both the asexual and sexual phases of protists' life cycles, we examine the conditions under which switching evolves. Specifically the role of the population size, duration of asexual reproduction, switching rates and other possible sources of stochasticity that may distort the sex ratio. This allows us to make predictions about when switching should evolve and what the expected switching rates would be in real populations.

2 The model

We model a population of N haploid cells, where each cell is characterized by a mating type locus \mathcal{M} , harboring alleles $\{M_1, M_2, M_3, \dots, M_m\}$ where m is the maximum number of different mating types. An individual with allele M_i cannot mate with other individuals bearing the same allele.

We assume a life cycle in which cells undergo g rounds of vegetative growth. During each round of vegetative growth, each cell produces two daughter cells and so the population sizes grows from N to $2N$. We assume that the carrying capacity of the population is fixed and sample without replacement to return to a population size equal to N . In addition, we also consider a mating type switching locus \mathcal{S} which modifies the action of the mating type alleles during vegetative growth with probability p_s . At each vegetative generation we assume that the two daughter cells inherit their parent's switching genotype. If the mother cell has the switching allele, one daughter will inherit the maternal mating type and the other daughter cell will switch its mating type from with probability p_s . We assume that a switching cell can switch its mating type to any other type in the population with equal probability. Following the vegetative stage, cells are allowed to mate with one another at random. Only cells that are heterotypic at the mating type locus can mate. It follows that we end up with a maximum of $N/2$ diploid cells, which then undergo meiosis to give rise to the new generation. If the number of mated pairs is less than $N/2$, the population is allowed to grow back to carrying capacity. No switching occurs at the meiotic step. We assume no linkage between the mating type locus and the switching gene so \mathcal{M} and \mathcal{S} are free to recombine at sex. This life cycle encompasses alternating clonal and sexual phases, universal amongst protists. We also consider several extensions to this simplest framework. The life cycle is illustrated schematically on Fig. ??, and our model parameters are summarized on Table 1.

3 Results

3.1 Two mating types

We begin by considering a population with two mating types ($m = 2$). As the number of vegetative generations between sex increases so does drift on the mating type locus distorting the mating type ratio (Fig. ??A). This effect decreases for larger population sizes but persists even for $N=5000$. Mating type switching can help restore the mating-type ratio, deeming the switching gene advantageous. We introduce the switching gene at time t_μ , at low frequency, q_0 , and determine the probability of fixation for varying N and g . In the absence of selection we expect the switching gene to reach fixation with probability equal to q_0 (Wright, 1931; Ewens, 2010). The fixation probability is a good measure of selection against drift in a finite population; the difference between q_{fix} , and q_0 is indicative of the strength of selection. As anticipated, as g increases from 1 to 500 we see a sharp increase in the fixation probability for the switching gene (Fig. ??B). Although the effects of drift on the mating type ratio are more pronounced for smaller populations and larger g , the probability of fixation is doubled contrasted to that expected under drift even for larger populations ($N > 500$) and small g .

We next asked how the switching rate itself, p_s , affects the evolution of the switching locus.

We gradually introduced mutations conferring an incrementally higher switching probability in a quantitative manner (Fig. ??). The selection gradient is steep as p_s rises from 0 and plateaus with larger p_s . Interestingly, the value of p_s at which this occurs, p_s^* , is lower for larger g . This initially appears counter to Fig. ??B. Although a prolonged period of vegetative growth increases selection for the switching gene it also provides a larger time window for restoration of the sex ratio. So despite large values of g correlating with stronger selection for p_s (also indicated by the steep selection gradient for smaller g ; blue and red versus black curve in Fig. ??) they are linked to lower p_s . Furthermore, the effect of the population size on the value of p_s^* is minimal compared to that of g (Fig. SI). Only for low g do we see a distinction due to N : smaller populations require larger p_s , when g is small. For larger g even small populations can maintain a reasonable mating-type ratio with low p_s (Fig. SI). Our model therefore suggests that relatively low switching rates can be sufficient to maintain the mating type ratio near 1 in species with two mating types, particularly for populations that live in consistently larger populations and have prolonged asexual life cycles.

3.2 Introducing a switching cost

Switching is likely to come at a cost. This could be due to the time or energy required for the switching itself (e.g. for gene deletion and duplication [ref]), or due to an increased chance of inbreeding. We ask what are the effects of a switching cost on our findings. We define a cost function,

$$f(p; c, k) = 1 - cp^k \quad (1)$$

where c is the cost of switching and k determines the shape of $f(\cdot)$. A cost dictated by $f(\cdot)$ is imposed on cells carrying the switching gene so that the probability of a cell being sampled at each vegetative step (Fig. ??) is equal to the cost function.

We plotted the difference between the initial frequency of the mutant q_0 and its fixation probability against (c, p_s) for different N and k (Fig. ??). Positive values indicate a selective advantage. When the cost function is concave ($k=2.0$), and $N=100$ we found that the switching gene is advantageous for a large range of (c, p_s) . This becomes more restricted for larger populations and a convex cost function ($k=0.5$). It follows that in situations with low selection for the switching gene (e.g. large populations with frequent sex), a sharp cost for mating type switching is likely to either compromise switching rates or impede the spread of the switching gene all together.

3.3 Multiple mating types

Many species have multiple mating types ($m > 2$) [refs]. How does the number of mating types affect our findings? In this section we vary m from 2 up to 30. Fig. ?? shows the fixation probability of the switching gene for $N=10000$ and varying m . We find that selection on the switching allele increases as the number of mating types increases. Maintaining equal frequencies of all mating types in a population harboring multiple mating types becomes challenging for higher m : the larger the value of m the stronger drift on each mating type [ref]. For example, Fig. ?? shows the frequencies of each of the mating types for $m=10$ during vegetative growth. Although growth

starts with nearly all mating types at equal numbers, after 100 divisions the mating type ratio is distorted significantly and following 500 divisions some mating types are lost all together (this is for a large population, $N=10000$).

A low switching rate, $p_s=0.1$, is sufficient to maintain the mating type ratio through multiple rounds of growth (Fig. ??B). Furthermore, the optimal switching rate does not depend on the number of mating types (Fig. SI). Although the fixation probability initially increases with the number of mating types we see a decrease in q_{fix} when m increases beyond 10. This is due to the relative advantage of an increased number of mating types [ref] which is likely to be higher for small and intermediate values of m . As m becomes large, additional mating types confer a smaller advantage. Therefore, the loss of some mating types is less costly for very large m explaining why the fixation probability for the switching gene, maintaining more mating types in a given the population, is lower (Fig. SI).

3.4 The switching locus over time

In order to make predictions about the distribution of potential switching rates in real populations we developed our model further to consider continuous mutation in an agent based manner. We allow cells to mutate at a low mutation rate ν and in an incremental manner so that a cell's switching ratio mutates to $p'_s = p_s \pm \epsilon$, where ϵ is a small positive number.

We measured the population average switching rate (\bar{p}_s) over time for multiple experiments. This provides an estimate for expected switching rates in real populations. The value of \bar{p}_s increases over time and becomes noisier for larger g (Fig.). Switching is neutrally adaptive during asexual reproduction and so its value is likely to fluctuate in these periods. The trajectories of p_s for individual experiments confirm this: the switching rate is subject to large fluctuations, especially if g is large (Fig. SI). In addition, switching rates above a threshold value are selectively neutral (Fig. 2C), explaining in part why the value of \bar{p}_s is subject to such high fluctuations over time. When a low cost is introduced, \bar{p}_s remains lower (around 0.2), fluctuates on a narrower window and is subject to more frequent loss because it is mildly deleterious during asexual growth. Interestingly, the value of \bar{p}_s when a low cost is assumed for switching is near the expected optimal switching rate as predicted by our previous analysis (Fig. 2C; blue line). Note that the value of p_s within a single population is highly uniform, with most individuals having the same p_s . Our results taken together suggest that the capacity to switch may be occasionally lost and regained over evolutionary time, particularly if switching comes at a cost.

Finally these observations can be understood in light of negatively frequency dependent evolution: the selective advantage for the mutant is higher when it is rare and decreases sharply as its frequency increases (Fig. SI). When at low frequency the mutant has a large advantage as the sex ratio is largely distorted and cells having the capacity to produce offspring of both mating type will have an advantage. As the frequency of the mutant increases (and for higher p_s), the sex ratio during the vegetative growth becomes more even and the relative advantage of the mutant declines [add a reference, Pom said this links back to a known result?]. This is an additional reason why we see such noise/fluctuations in these simulations. [Do we want this last paragraph?].

4 Discussion

In this work we consider the evolution and consequences of stochastic sex determination in protists, where the mating type of individuals can change probabilistically during vegetative growth. This has been well documented in yeasts and ciliates but no theory to date explains its function and evolution. Our work indicates that several aspects of an organism's ecology, such as the duration of asexual reproduction, the size of the population and the number of mating types can result in the distortion of the mating type ratio, even if the different mating types were at equal frequencies immediately sex. Our findings suggest that stochastic mating type switching during the asexual phase can serve to maintain an even mating type ratio in a population, thereby increasing the probability of finding compatible partners at the sexual phase for cells with switching capacity.

The strength of selection increases when the mating type ratio fluctuates more, namely in smaller populations with long periods of vegetative growth, high probability of dispersal or multiple mating types. Selection on the switching gene only acts at sex. The switching gene is in fact selectively neutral during the vegetative phase and could be subject to perpetual loss and evolution particularly in species with long vegetative phases and consistently large population size, or if switching itself comes at a cost (e.g. by delaying mitosis). {{So we expect this to be very unstable – we can recommend some experiments here. Bram what does your biology knowledge tell you?! I think that the experiments you described to me with loss and regain of the capacity to switch would go nicely here but I don't know if Bart has actually published these? We can make interesting predictions either way....}}

We predict higher switching rates in small populations or in species with frequent population size changes and dispersal (NOTE: Bram, I know yeast has high dispersal, do we know anything about switching rates in yeast compared to paramecium for example? I'd say our model predicts lower switching rates for paramecium than yeast. Paramecium has large g.). Generally, our findings suggest that low switching rates (of the order of 0.1 per generation) are sufficient to preserve a nearly even mating type ratio. Although long vegetative phases can distort the mating type ratio more, they also provide more time for switching to occur, countering the effects of drift. So even though long vegetative growth is linked to higher selection pressure for switching, it should also be associated with lower switching rates. Finally, we predict switching rates to be as high as 0.5 in small populations. NOTE: We should discuss what we know about different species and make predictions here. Do we know any actual rates?

Discuss dispersal and relate to our model. We do not explicitly model dispersal here but frequent dispersal may account for additional variation and so equivalent to smaller populations. For example yeast spores can even be found on their own before they are in growth conditions so important to be able to regain ability to mate. yeast can exist as dormant spore for a long time and so fall under the fluctuating environment types, predict higher switching rates.

The presence of multiple mating types is common amongst protists [ref]. The amount of drift on the mating type locus increases with the number of mating types, and so switching becomes more favorable as the number of mating types increases. This echoes the findings of Paixao et al who showed that stochastic sex determination following recombination is adaptive in species with multiple mating types. This study, however did not consider the role of clonal growth, arguably the most prominent phase in most protists life cycles. Here we find that even if each sexual cycle

starts off with all mating types possible, some are likely to be lost through asexual phase. So vegetative growth additional problem. It explains the mechanism in *Tetrahymena* but not other ciliates and yeasts where switching happens during the growth phase. So our work complements that work.

-low switching rate that could be good enough+loss/regain may explain why not observed this vary much. specially in lab strains that are likely to be under little selection for this. so may be worth looking at new strains...

-testing the theory? Suggestions for comparative analyses in yeast. Discuss some of the mechanisms, h90 versus h40 strains read. Bram, this was your note! Thoughts?! It sounds interesting!

Our study highlights the importance of drift on the sex ratio and suggests that mechanisms such as switching are in place to control it in protists that reproduce mainly asexually. We modeled a number of different ecological parameters that can be sources of variation in the mating type ratio. These are not exclusive and other things may come in.

not a response to not finding a partner but a provisional mechanism that ensures drift does not mess things up for when it's time for sex. why not all switch at once with high prob and have small probs continuously?! because then you get total inbreeding all the time!

5 Figures and Tables

5.1 Figure Legends

Fig. 1 The life cycle begins with N individuals of m mating types at equal rates $1/m$. All individuals grow and divide mitotically to produce two daughters of the same mating type as the parent cell. Individuals that possess the mating type switching gene can produce one daughter with mating type that differs from their own. For example, the purple cells produced one purple and one orange cell indicating a mating type switching event. After growth the population returns to its initial size. This is repeated g times. At the end of the vegetative growth cells enter the sexual phase where they form pairs of different mating type until no more heterotypic pairs are possible. The population size then returns to N and the new vegetative round begins.

Fig. 2 The duration of the vegetative growth dictates the adaptive benefit of switching and the optimal switching rate.

A: The mating type ratio (for $m=2$) against the duration of the asexual phase for varying population size (N). The population is assumed to enter the asexual phase with both mating types at equal frequencies. Results were averaged over X repetitions. **B:** The fixation probability of the switching gene against the duration of the vegetative growth for varying population size. The switching gene was introduced at $q_0=0.05$. **C.** Selection against the switching rate, ps . The dotted lines mark the optimal switching rate for each parameter set.

Fig. 3 Title

Table 1: Explanations of the symbols used in the description of the model.

Symbol	Explanation
N	Population size
m	Number of mating types
g	Number of vegetative
p_s	The probability that a cell carrying the switching gene will produce one daughter of the opposite mating type
\mathcal{S}	Switching gene locus
q	Frequency of the mutant switching allele
q_0	Initial frequency of the switching gene
q_{fix}	Probability that the mutant switching allele goes to fixation

The selection coefficient (defined as $q_{\text{fix}} - q_0$) for mutants with different switching rates and switching cost. A, B: concave and convex for $N=100$. C, D:... The dotted lines depicts neutrality. Above this... below this...

Fig. 4 Species with multiple mating types can suffer mating type loss if long asexual phase and no switching

The frequency of each mating type in a population with $m=10$ mating types over vegetative time, without switching (top row) and in a population with switching rate (p_s) set to 0.1. Without any switching the frequency of all mating types is distorted after 100 generations and some mating types are extinct after 500 generations.

Fig. 5 multiple mating types

Fig. 6 The expected value of p_s over

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