The Evolution of Mating-Type Switching

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August 11, 2015

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 occuring 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

keywords: epigenetics, sex determination, sexes, yeast, epigenetics, bet hedging, sex ratio, sex allocation

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1 Introduction

ZENA: Bram, In think the intro is a good first draft and has a lot of very good refrences which is great! My view is that it should be more focused on stochastic versus deterministic mechanisms of sex determination. I think that the bipolar/tetrapolar/multiallelic systems in ciliates and fungi are interesting but beyond the scope of this paper. We can discuss how we know that lots of animals have stochastic sex determination and can change their sex during their life time and this has been studied a lot. But fact is many protists have stochastic sex determination and why this is the case has received little attention. Then give some detailed examples of how mating type changes stochastically in paramecium, tetrahemena, yeast (this is important and interesting I think, and you got all the info!). Then give a table of different species, some basic info (e.g. how many mating types) and whether or not stochastic swicthing has been documented. Then we introduce our idea and our modelling effort. I tried to have a go at this but it still needs work and you know

way more than me from your reading. I am open to suggestions of doing this otherwise, so we can chat when we are both back.

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 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).

(THOUGHT: IT MAY BE WORTH TALKING ABOUT SEX CHANGING IN ANIMALS OR EPIGENETIC SEX DETERMINATION IN ANIMALS TO LEAD TO THIS?)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? WE SHOULD MAKE IT CLEAR HERE. MORE INFRO 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 *Kluveromyces*), 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. Naively, one could argue that mating type switching allows a typically outbreeding organism to occasionally mate with their sibling gametes when mates are limited. However several species such as yeasts reproduce largely by selfing (Haber, 2012). The majority of protists reproduce clonaly with sex occuring 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. Something more about the model. We examine the conditions unde which swicthign evolves, specifically the role of the population size, duration of vegetative phase, switching rates and... this allows us to make predictions about when swicthign shoudl evolve and what the rates would be.

I think the following should go in the discussion. This is a really nice model but different to what we are doing. An exception is an evolutionary study by Paixão *et al.* (2011), who showed that pure stochastic types of mating determination

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 $\{M_1, M_2, M_3, \ldots, M_m\}$ where m is the maximum number of different mating types in the population. 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 vegetattive growth with probability p_s. At each vegetative growth step 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 single step meiosis to give rise to the new generation. If the number of mated pairs is less than $N/2$, we sample with replacement from the haploid cells that are produced after meiosis until the population size returns back to N. 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 ti recombine at sex. This life cycle is not meant to represent any particular species but captures general features common amongst protists. We consider several extensions to this simplest framework. The life cycle is illustrated schematically on Fig. 1, and our model parameters are summarized on Table 1.

3 Results

this is a fabulous result $z = \exp$Anthes *et al.* (2008)Anthes *et al.* (2008) What is this?!

3.1 Two mating types

We begin by considering a population with two mating types ($m = 2$). We introduce the switching gene at time t_μ, at low frequency, q_0, and determine the probability of fixation for varying N, g and p_s. In the absence of selection we expect the switching gene to reach fixation with probability equal to q_0 (Wright, 1931; Ewens, 2010).

As the number of vegetative generations between sex increases so does drift on the mating type locus distorting the mating type ratio (Fig.2A). This effect decreases for larger population sizes but

persists even for N=5000. Mating type switching can help restore the mating-type ratio, making the switching gene advantageous. So as g increases from 1 to 500 we see a sharp increase in the fixation probability for the switching gene (Fig.2B). Although the effects of drift 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 proceed by measuring the fixation probability while varying the probability of switching. The same picture emerges for all $N > 100$: changes from $p_s = 0$ to 0.1 result in a significant increase in the fixation probability (Fig. 3A). The fixation probability then plateaus indicating that further increase in p_s provides no additional advantage. Our model therefore suggests that relatively low switching rates can be sufficient to maintain the mating type ratio near 1, particularly for larger populations. For smaller populations (N=100), selection for the switching gene is stronger, the fixation probability is significantly higher and plateaus at a larger value of p_s, closer to 0.5 (Fig. 3A).

To gauge how the optimal value of p_s changes with g we simulated the evolution of the switching gene quantitatively for varying g. Because our model operates within a finite population scheme, we do this as follows. We assume that the population is initially at a state where the switching probability, p_s , is equal to 0 for all individuals. We then introduce a mutant at low frequency so that mutant individuals have $p_s' = p_s + \varepsilon$, and measure the selection advantage. We repeat this iteration from $p_s = 0$ to $p_s = 1$. We define the optimal p_s^* where selection from p_s to p_s' vanishes. Further details are provided in the Methods section. Fig. 3B shows the value for p_s^* for varying g and N: p_s^* decreases with g. This initially appears counter to Fig.2A. Although a prolonged period of vegetative growth increases selection for the switching gene it also provides a longer period for restoration of the sex ratio. So dispite large values of g correlating with stronger selection for ps they are also linked to lower ps (see Appendix A1 for a quantitative account). The change in p_s^* with N is as expected: smaller populations require larger p_s, particularly when g is small . For larger g even small populations can maintain a reasonable mating-type ratio with low p_s (Fig. 3).

To better understand the evolutionary dynamics of this system, we fixed the frequency of the switching gene at different values and estimated the selective advantage of the mutant over a single round of the life cycle (Fig. 4). Our findings indicate strong frequency dependent selection. The selective advantage for the mutant is higher when it is rare and decreases sharply as its frequency increases. Furthermore, the selection coefficient when rare is higher for mutants that confer a higher switching probability (Fig. 4). As the frequency of the switching gene increases the advantage it confers decreases. This decrease is steeper when the switching probability is higher. The mutant eventually becomes neutral when its frequency reaches 0.9 for all p_s. When at low frequency the mutant has a large advantage as the sex ratio before sex 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 (or for higher p_s), the sex ratio during the vegetative growth becomes more even and the relative advantage of the mutant declines.

3.2 Introducing a switching cost

Switching is likely to be costly. 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,

$$f(p;c,k) = 1 - cp^k \tag{1}$$

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. 1) 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. 5). Positive values indicate a selective advantage. When the cost functiuon 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 high 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. 6A shows the fixation probability of the switching gene for N=5000, 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. 6B shows the frequencies of each of the mating types for m=10 during vegetative growth. Although gworth starts with nearly all mating types at equal numbers, after 100 divisions the mating type ratio is distroted significantly and following 500 divisions some mating types are lost all together (this is for a large population, N=10000). A low swithcing rate, p_s=0.1, is sufficient to maintain the mating type ratio through multiple rounds of growth (Fig. 6B).

[NOTE: I am not sure why there is a decline in pfix for larger m here, it may have to do with the population size as we see less of a drop for a larger population, perhaps it has to do with 30 mating types not being that much better than 20. If you have 30 mating types and 4 are lost by drift is not that much of a deal as if you had 20 types and lost 4. I need to check this. How does m affect ps*?]

3.4 Fluctuating population size

We have so far asummed that the population size is fixed. In reality the size of a colony of protists may vary substantially. For example, a sudden abandance of food may result in an increase in the population size, and invation by pradators or dispersal can lead to a deacre in N. These processes are likely to be sources of additional variation impacting the mating type ratio. Here we extend our model and consider a population that periodically goes through a change in size. At any given step

in the life cycle we allow the population size to change from N to N' with probability r. The initial population size is then resotred by sampling without replacement. N' can be larger or smaller than N and is drawn from a normal distirbution with mean μ and variance σ^2. We plotted the fixation probability of the switching gene aagainst the switching rate for different r and (μ, σ^2), and a large population (N=1000). The fixation probability is now higher than that see for $N = 1000$ in Fig. 3A. In addition, qfix increases for values beyond ps=0.1 suggesting that frequent changes in the ppu;ation size would require higher swithcing rates to maintain an even sex ratio. The value of qfix is larger when r increases, i.e. more frequent changes in the population size lead to stronger selection for switching. Finally, frequent changes to larger rather than smaller populations are expected to generate more variation in the mating type ratio (Fig. SI) and so result in stronger selection for stochastic switching (Fig.).

4 Discussion

- we show that various aspects of an organisms ecology can be sources of drift and distort mating type ratio. This can drive selection for mating type switching. Low rates often satisfactory to restore ratio, this may be more frequenct to what we actually think.

-Relate to what we know from reality

-testing the theory? Suggestions for comparative analyses in yeast. Discuss some of the mechanisms, h90 versus h40 strains read

-we predict low swithcing probabilities for species with a long vegetative growth. Ciliates have this, is their swicthing rate lower than yeast?

-yeats can exist as dormant spore for a long time and so fall under the fluctuating environment types, predict higher switching rates.

-Relate this to the Paixao paper, how are they similar and how are they different.

5 Figures and Tables

6 Appendix

Some analytic derivations to complement results.

Give more details on methods

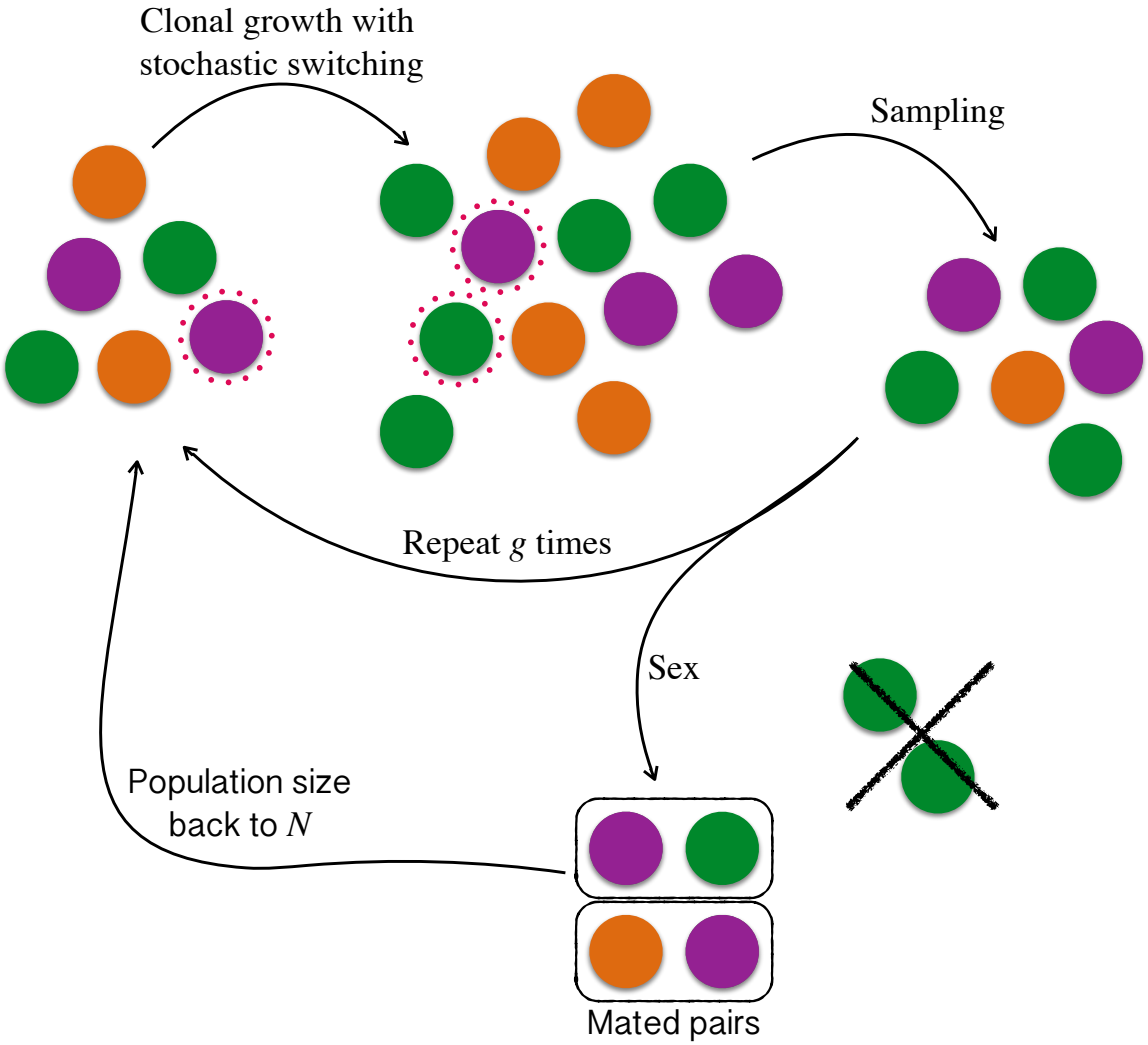

Figure 1: The life cycle begins with N individuals of m mating types at equal rates 1/m. All individuals grow and divide mitotically to produce two daughters of the same mating type as the parent cell. Individuals that posses the mating type switching gene can produce one daughter with mating type that differs from their own. For example, the purple cells produced one purple and one orange cell inidcating a mating type swithcing 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.

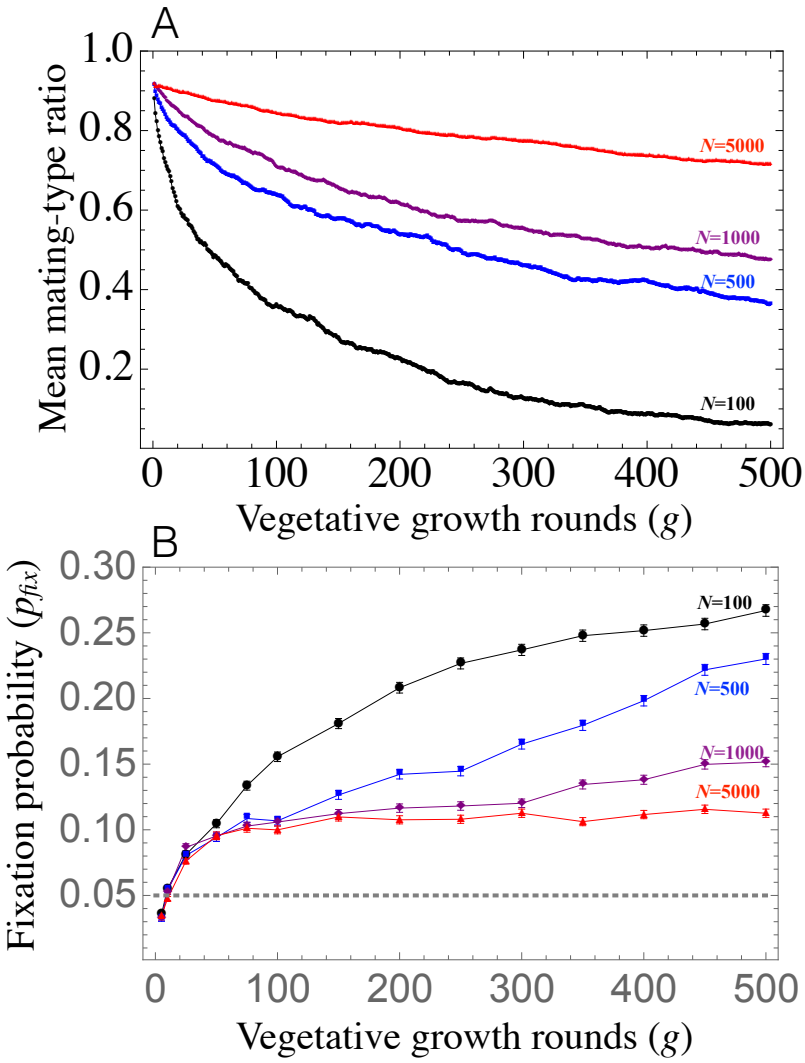

Figure 2: Text

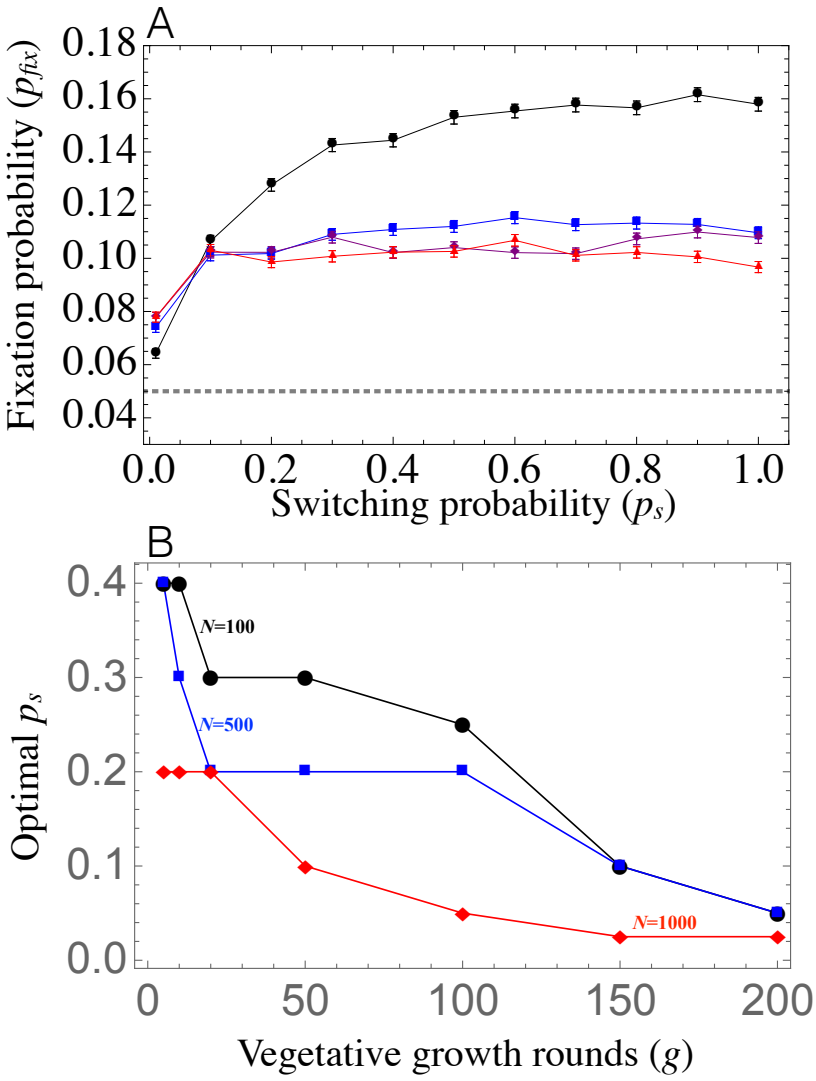

Figure 3: Text

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

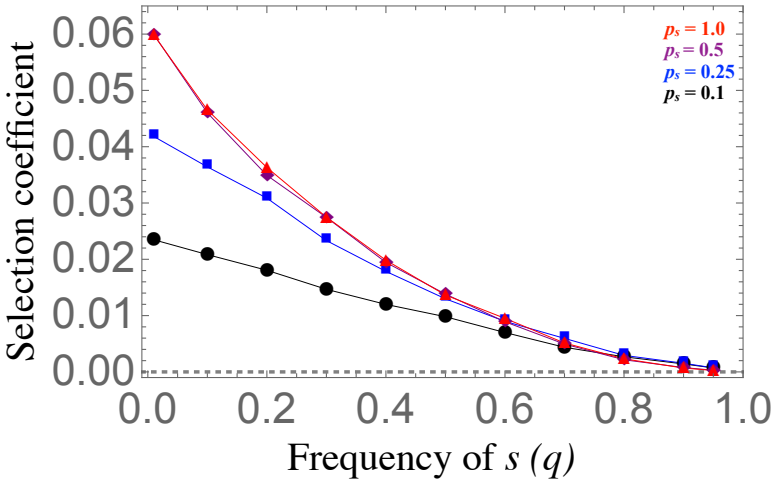

Figure 4: text

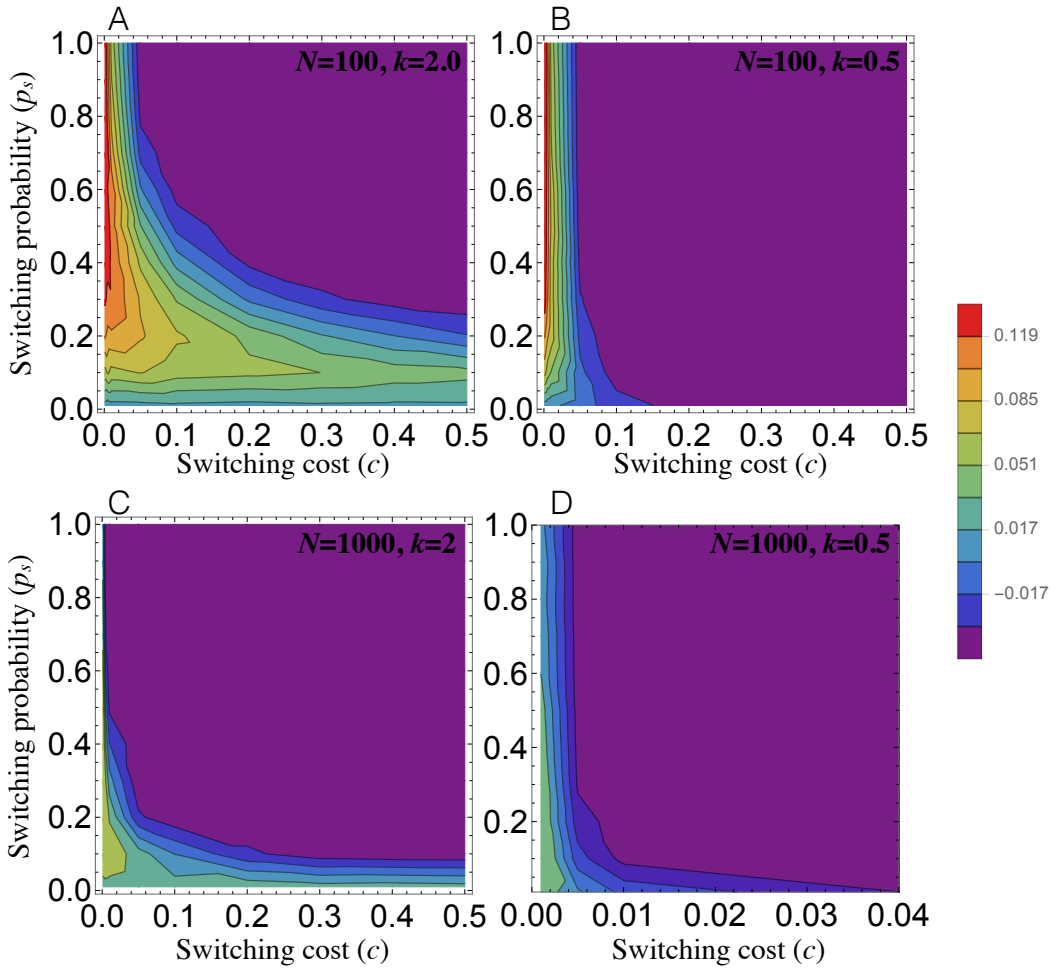

Figure 5:

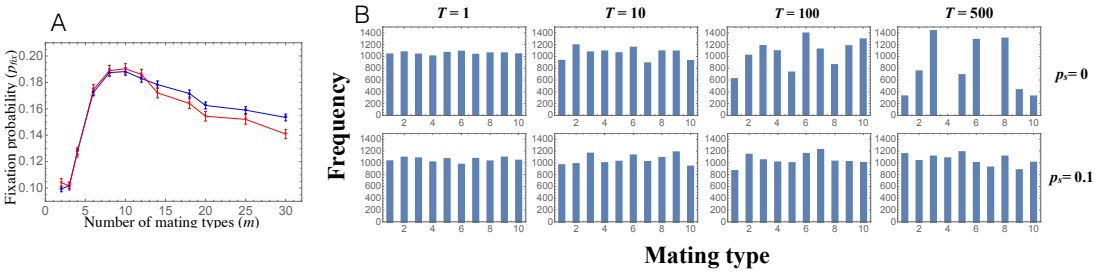

Figure 6:

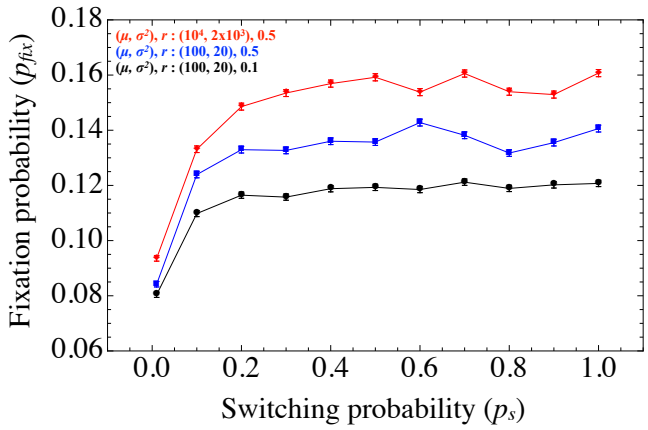

Figure 7: text

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