Table 1: Selection

Genotype	Rate of Cell Division	Number of Cells Divisions per Individual Generation	Fitness at the Individual Level	Fitness at the Cellular Level
AA	c_1	$k_1 = c_1\tau$	1	1
Aa	c_2	$k_2 = c_2\tau$	$1 + h_i s_i$	$1 + h_c s_c$
aa	c_3	$k_3 = c_3\tau$	$1 + s_i$	$1 + s_c$

FIGURE 2

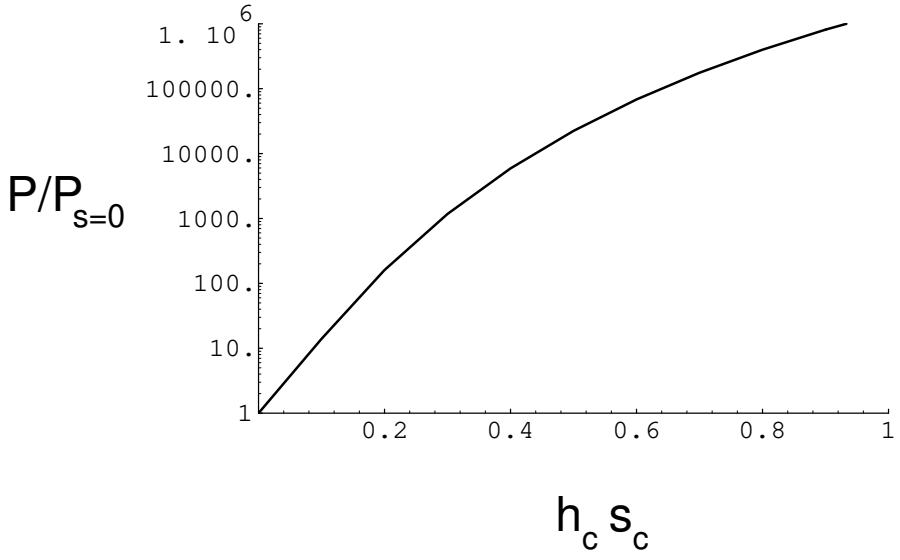
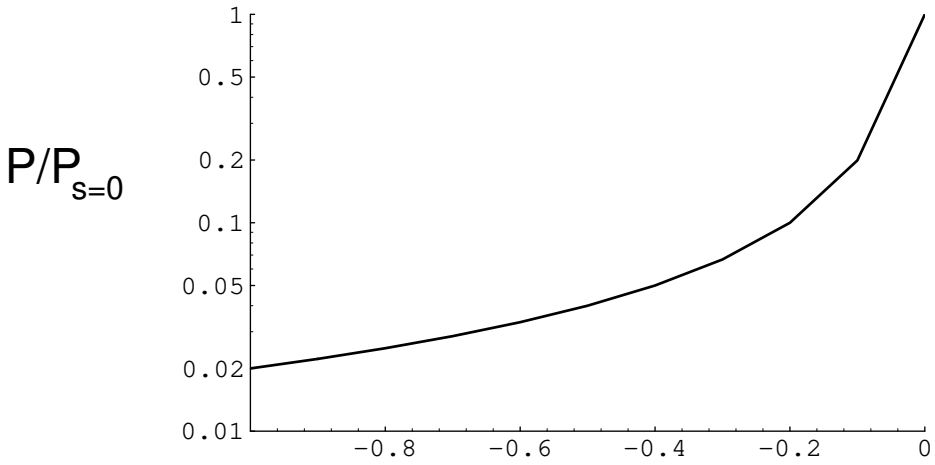


FIGURE 3



the assumption that conversion is unbiased and creates AA cells half of the time. The other half of the time, aa cells are produced leading to a final proportion of aa cells that equals P_{AA} with c_1 replaced by c_3 and k_1 replaced by k_3. Finally, the expected proportion of cells that do not undergo conversion is:

$$P_{Aa} = 2^{k_2}[1 - (1 - X)^{k_2}]. \tag{11}$$

In the presence of mitotic recombination and cell-lineage selection, gametes are not produced in mendelian ratios, instead the expected proportion of a gametes is:

$$P_g = \frac{P_{aa} + P_{Aa}/2}{P_{aa} + P_{Aa} + P_{AA}} \tag{12}$$

will increase the probability of fixation of new beneficial alleles by the amount:

$$\Pi = \frac{e^{h_c s_c k_1} - 1}{h_c s_c k_1}, \tag{9}$$

which rises very rapidly with the strength of cell-lineage selection (figure 1). Therefore the potential impact of cell-lineage selection on the rate at which beneficial alleles fix within a population is tremendous. Strongly selected mutations ($h_c s_c = 1$) can have a chance of fixation that is one million times higher than in the absence of cell-lineage selection with $k_1 = 50$ and 10^12 times higher with $k_1 = 100$. With very weakly selected alleles, the increment is roughly $(h_c s_c k_1)/2$ with cell-lineage selection; with $h_c s_c = 0.01$, this translates into a 25% higher rate of fixation when $k_1 = 50$ and a 50% higher rate when $k_1 = 100$.

Similarly, the probability that a new deleterious mutation will be inherited by at least one member of the population in the next generation is $1 - (1 - p_0)^{2N} \approx 1 - e^{-P} \approx P$. This probability drops dramatically with within-individual selection against mutations (figure 2) as argued by Otto and Orive (1995).

Fate of a mutation in heterozygous offspring – As shown above, selection within an individual can have a major impact on the survival of mutations during the first generation in which a mutation first appears. The mosaicism is then lost as soon as the individual reproduces via single-celled offspring. As argued by Hastings (1989, 1991), however, a major and on-going source of cell-cell variation is mitotic recombination and gene conversion. He cites data that the rate of mitotic crossing over (X) is in the range of $210^{-4} - 10^{-3}$ per individual generation in *Drosophila* and $10^{-7} - 10^{-5}$ per cell generation in yeast.

With mitotic recombination (and all other factors that can convert a heterozygous cell to a homozygous one), the expected proportion of AA cells in an individual that is originally heterozygous is:

$$P_{AA} = \sum_{i=1}^{k_2} 2^i (1 - X)^{(i-1)} \frac{X}{2} 2^{k_1 - c1/c2i}, \tag{10}$$

which sums up over all cell generations the probability that a cell has not undergone conversion before cell generation i then undergoes conversion to AA in cell generation i times the expected number of cells in the adult that will result from the newly converted cell (see Otto and Orive 1995 for a similar derivation for mutation). The 1/2 multiplying X reflects

number of heterozygous cells in the adult will be $2^{c_2(\tau - x/c_1)}$. Similarly, the total number of non-mutant cells will be $(2^x - 1)2^{c_1(\tau - x/c_1)}$. The expected proportion of mutant cells in the adult (P) can thus be calculated as

$$P = \sum_{j=1}^{k_1} \frac{2^x}{\sum_{i=1}^{k_1} 2^i} \frac{2^{c_2(\tau - x/c_1)}}{2^{c_2(\tau - x/c_1)} + (2^x - 1)2^{c_1(\tau - x/c_1)}} \tag{4}$$

When $c_2 = c_1$, equation (4) reduces to

$$\frac{k_1}{2(2^{k_1} - 1)}, \tag{5}$$

which conforms to our expectation that few cells should be mutant since the mutation is likely to occur late in development. With cell-lineage selection ($c_2 \neq c_1$), equation (4) can be evaluated numerically. If, however, we assume that the total number of cells in the adult is relatively unchanged by the processes of cell mutation and selection, then P can be evaluated explicitly and found to equal

$$P \approx \frac{k_1}{2(2^{k_1} - 1)} [\frac{(1 + h_c s_c)^{k_1} - 1}{h_c s_c k_1}] \tag{6}$$

$$\approx \frac{k_1}{2(2^{k_1} - 1)} [\frac{e^{h_c s_c k_1} - 1}{h_c s_c k_1}] \tag{7}$$

This approximation was tested within the range of plausible values for k_1 ($1 - 500$ cell divisions per individual generation) and found to be accurate whenever $-1 \leq h_c s_c < 0.01$.

Most beneficial mutations are lost soon after they arise. In a large population, the probability of fixation of a mutation at initial frequency p_0 is

$$u = \frac{1 - e^{-4Ns_i p_0}}{1 - e^{-4Ns_i}} \tag{8}$$

(Crow and Kimura, 1970, p. 426), assuming a Poisson distribution of offspring and a census population size near the effective population size. When a mutation first appears as a heterozygote in a fraction (P) of gametes of a single individual, $p_0 = 1/(2NP)$ and the probability of fixation of the mutation is approximately $2sP$. Therefore, cell-lineage selection

level (Table 1). I consider the fate of the mutant allele a which can either be beneficial ($s > 0$) or detrimental ($s < 0$) at either level of selection. Organisms are diploid which develop for a fixed amount of time, τ, irrespective of genotype and then produce haploid gametes. Cell division occurs in a binary fashion, with the rate of cell division, c_i depending on the genotype of the cell (Table 1). c_i is measured as the number of cell divisions that occur for a cell type i during the development of the individual divided by τ.

The rates of cell division and selection at the cellular level are related to one another as follows. The relative fitness of a cell is measured by the expected number of daughter cells produced in the amount of time that it takes a reference genotype (here, AA) to produce two daughter cells. For Aa cells, there are on average $2^{c_2/c_1}$ offspring cells in the time it takes AA cells to produce two cells. Hence, we can equate

$$1 + h_C s_C = \frac{2^{c_2/c_1}}{2}. \tag{1}$$

Similarly,

$$1 + s_C = \frac{2^{c_3/c_1}}{2}. \tag{2}$$

These equations can be used to evaluate the change in gene frequency during growth.

The rate of mitotic recombination or gene conversion is X_c per cell generation. These events lead a heterozygous parental cell to produce a homozygous daughter cell. We assume that there is no bias in conversion so that aa and AA homozygotes occur with equatl frequency.

Fate of a new mutation within the individual in which it first arises – Consider a single mutation that occurs randomly during development, converting a AA genotype to a Aa genotype. It is most likely to occur in later cell divisions since many more cells exist that can potentially mutate. The probability that the mutation occurs in one of the 2^x cells present at cell generation x is

$$\frac{2^x}{\sum_{i=1}^{k_1} 2^i} \tag{3}$$

If the mutation happens in cell generation x (after x/c_1 time has passed), the resulting

Introduction

Population genetics theory is built largely on the assumption that selection acts among individuals; the mutation and selective processes that occur within an individual are, for the most part, ignored. The most compelling argument for ignoring selection within individuals is that all cells within a multicellular individual are recently derived from a common cellular ancestor (the zygote or spore) and hence are closely related with little expected variation (Maynard Smith and Szathmary, 1995, p. 244). Mosaicism is, however, commonly observed and has several sources including mutation, mitotic recombination, and gene conversion. The variation that is generated can then lead to differences in cell growth rates and survival, with the consequence that gene frequencies change within an individual generation (studied by Klekowski and Kazainova-Fukshansky, 1984; Antolin and Strobeck, 1985; Hastings, 1989, 1991; and Otto and Orive, 1995; among others).

Cell-lineage selection acting upon newly arisen mutations can have a major effect on the mutation rate, decreasing the frequency of mutations that are deleterious at the cell level and increasing those that are advantageous (see e.g. Otto and Orive 1995). Although the magnitude of this effect can be large when there are many cell divisions per individual generation, the effect ends upon the death of the individual in which the mutation arises, unless asexual reproduction occurs through multiple cells. In essence, cell-lineage selection simply changes the effective or observed mutation rate (Maynard Smith and Szathmary, 1995, p. 246; Otto and Orive, 1995). In contrast, with mitotic recombination and gene conversion, mosaicism can result whenever an individual is heterozygous, not just when mutations first arise (see Figure 1). Cell-lineage selection acting upon this variation can also have a large impact on evolutionary change (Hastings, 1989, 1991), an effect that mimics meiotic drive in heterozygotes. In this note, we build upon the work of Otto and Orive (1995) and Hastings (1989, 1991) to derive simple formulae that approximate change in gene frequency over time with selection within an individual. These formulae can be used, for example, to estimate the probability of fixation of beneficial mutations or the probability of observing a deleterious mutation.

Model In the model, selection acts at the cellular level (cell-lineage selection) in tissues leading to reproductive cells (whether confined to a germ-line or not). Selection depends on the genotype of a single locus (A/a) and acts both at the individual level and at the cellular

The fate of a mutation with selection within an individual

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March 8, 1996

Running head– Within individual selection.