Selection within an individual

Selection among cells during the development of an individual plays only a cameo role in population genetics theory. The most compelling argument for ignoring selection within an individual is that all cells within a multicellular individual are recently derived from a common single-celled ancestor (the zygote or spore) and are hence closely related with little expected variation (Maynard Smith and Szathmary, 1995, p. 244). Mosaicism is, however, commonly observed (Whitham and Slobodchikoff 1981; Gill and Halverson 1984; Klekowski 1988; Gill 1995) and is generated by a number of mechanisms including mitotic mutation, mitotic recombination, and gene conversion (John and Miklos 1988). Together these processes generate the genetic variation that makes possible evolutionary change within an individual. Selection can then act upon differences in cell growth rate and survival due to these genetic changes, leading to gene frequency change within an individual generation (Klekowski and Kazainova-Fukshansky, 1984; Slatkin 1984; Antolin and Strobeck, 1985; Hastings, 1989, 1991; Otto and Orive, 1995).

One of the primary benefits of selection within an individual is that it provides a selective sieve, eliminating deleterious mutations and promoting beneficial ones, with a relatively low fitness cost to the individual. We shall argue that this advantage is substantial and that consequently there must be a fairly large evolutionary cost to organisms that reduce or eliminate selection among the progenitors of reproductive cells. In this section, we first focus on genetic variability generated within an individual by mitotic mutation and examine the effect of cell-lineage selection on the observed mutation rate and on the probability of fixation of a mutation. We then discuss mitotic recombination and gene conversion and their influence on the subsequent dynamics of mutant alleles.

Observed Mutation Rate -- A mitotic mutation that appears during development will be more likely to be transmitted to offspring if it causes cells to survive and replicate at a higher rate and less likely to be transmitted if it impedes cell replication. Consequently, the distribution of mutations that will be observed among the offspring of an individual will be shaped, in part, by the process of cell-lineage selection. We use the term Òunderlying mutation rateÓ to denote the mutation rate per gamete per locus that would be observed in the absence of selection within an individual and Òobserved mutation rateÓ to denote the rate in the presence of within-individual selection. Cell-lineage selection decreases the observed mutation rate for alleles that are deleterious at the cellular level and increases the observed mutation rate for alleles that are beneficial at the cellular level (Figure 1). The distribution of mutations that will be observed among the offspring of an individual will be equal to the product of the underlying distribution of mutations and the function drawn in Figure 1. That is, cell-lineage selection will shift the observed distribution of mutations away from mutations that are deleterious at the cellular level and towards those that are beneficial. [Remove these last sentences?]

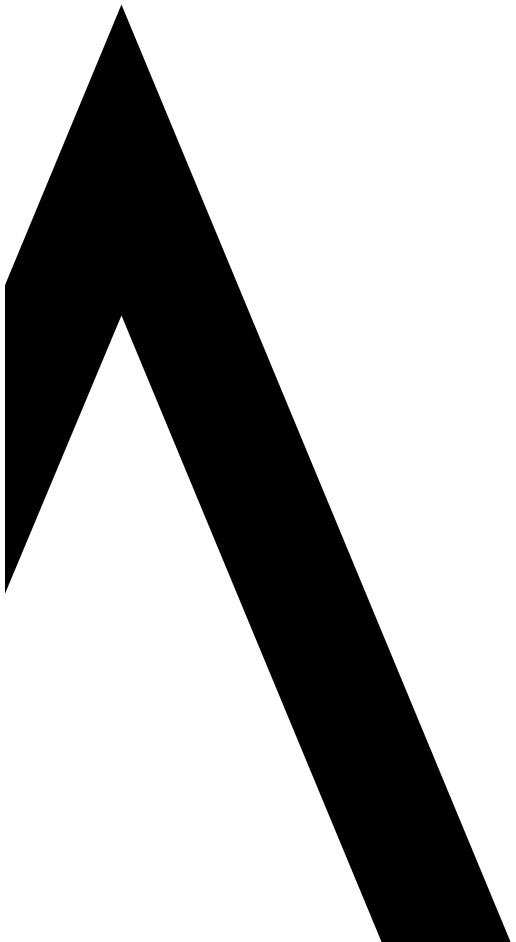
One feature that is evident in this figure is that the observed mutation rate is very sensitive to small changes in the replication rate of cells. This occurs because the effects of cell-lineage selection are compounded over many cell generations, so that small differences in replication rate can cause large changes in the composition of the cell population at the end of development. The cumulative impact of cell-lineage selection is especially pronounced when there are many cell generations during an individual generation.

This phenomenon has been investigated under a variety of assumptions concerning development and selection within an organism. Here we will briefly review these models (more details may be found in GillÕs 1995 review or in the original papers). Luria and Delbruck (1943) were the first to analyse a model of mutation and selection during clonal development. They found that selection

during exponential growth of cells dramatically increased the frequency of beneficial mutations. Although their focus was on an exponentially expanding population of bacteria grown in the presence of a virus, their results are also applicable to any organism with plastic development where growth occurs by nearly equal rates of division among all cells.

Using a developmental model appropriate for seed plants, Klekowski and Kazarinova-Fukshansky (1984) investigated the observed number of mutations in organisms that develop from apical meristems in which at least one cell initially contains a mutation. They concluded that cell-lineage selection has the greatest effect on mutation rates when apical meristems are composed of a large number of cells and when initial cells are chosen infrequently during development to form the next apical meristem. Antolin and Strobeck (1985) studied selection among the buds of a plant and found that positive selection did cause substantial increases in the frequency of mutant buds, especially among long-lived organisms. They stressed, however, that when cellular mutation rates

are low per locus (



), most buds would retain their original genotype even with strong selection.

Hastings (1989) focused on selection among gametic cells produced by animals. These haploid cells express the diploid genotype of parental cells and will express any mutations that have accumulated in the parent cell-lineage. Since selection only occurs at one stage (among the gametes), this form of intra-individual selection had a smaller effect on observed mutation rates. In contrast, Hastings (1991) investigated cell-lineage selection occuring throughout development assuming a deterministic model of replicating cells with different fitnesses, finding that Òunder plausible assumptions of germline molecular biology, the mutation rate per gamete may differ up to 100-fold between loci due to selection within the germlineÓ (p.1171).

Birky (1991) modeled the processes of mutation, selection and drift among the organelles of a cell. Mutations that reduce the replication rate of organelles are unlikely to fix within the cell and tend to be soon lost. Conversely, beneficial mutations are more likely to avoid loss by drift and to fix within the cell. Again these results indicate that seletion within an organism (here among organelles) is likely to alter the observed mutation rate of deleterious and beneficial mutations. Otto and Orive (1995) developed models similar to those of Luria and Delbruck (1943), Klekowski and Kazarinova-Fukshansky (1984), and Birky (1991) to examine the potential influence of somatic selection on the genomic wide mutation rate and deleterious mutation load. The mutation load was found to be very sensitive to changes in the replication rate of cells, especially when many cell divisions occur during development and when development is fairly plastic.

Taken together, these studies demonstrate that within-individual selection can have a major impact on the mutation rate that would be observed among the progeny of an individual. In long-lived organisms, the observed mutation rate may be enhanced by orders of magnitude for mutations that are beneficial to cell

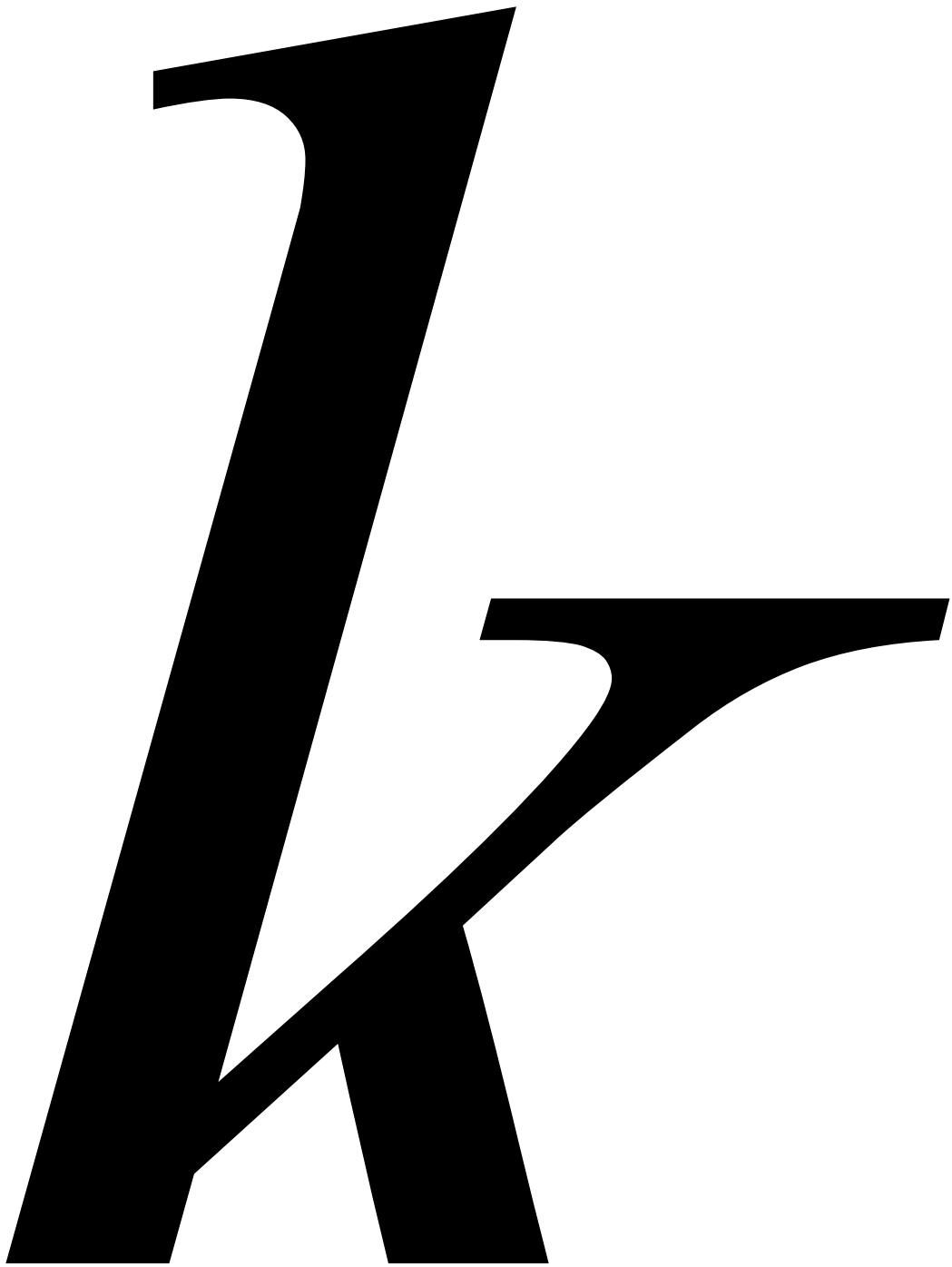
survival and replication and decreased by orders of magnitude for mutations that are deleterious.

Probability of Fixation -- We now consider the fate of those mutations that arise only periodically during the history of a population rather than at a continuous rate. Slatkin (1984) studied the fixation probability of a somatic mutation in trees with multiple branches whose fertility depends on whether or not the mutation is present. He found that such fertility selection among the branches of a tree would increase the probability of fixation of beneficial mutations, especially if the tree is more fertile as a whole due to the presence of the somatic mutation (termed hard selection). Nevertheless, the increase in the probability of fixation is only proportional to the fertility advantage of the mutation, since selection only occurs once during reproduction of the tree.

In the appendix, we use the diffusion results of Kimura (1964) to estimate the probability of fixation of a single mutant that arises during development and which is subject to cell-lineage selection throughout development. This probability is extremely low for a single mutation (equation (A2); see Table 1 for notation). Mutations are most likely to arise fairly late in development when there are already many non-mutant cells, so even if the individual succeeds in producing offspring, it is unlikely that the mutation will be present in the successful gamete. Consequently, the mutation has an extremely high chance of being lost during the first generation. Even if it is transmitted to an offspring, it may still be lost in the first few generations before it becomes established due to sampling error. As shown in Figure 2, the probability of fixation increases sharply when cell-lineage selection favors the mutant allele and decreases sharply when it does not. For weakly selected mutations, cell-lineage selection changes the probability of fixation of a mutation by the factor:

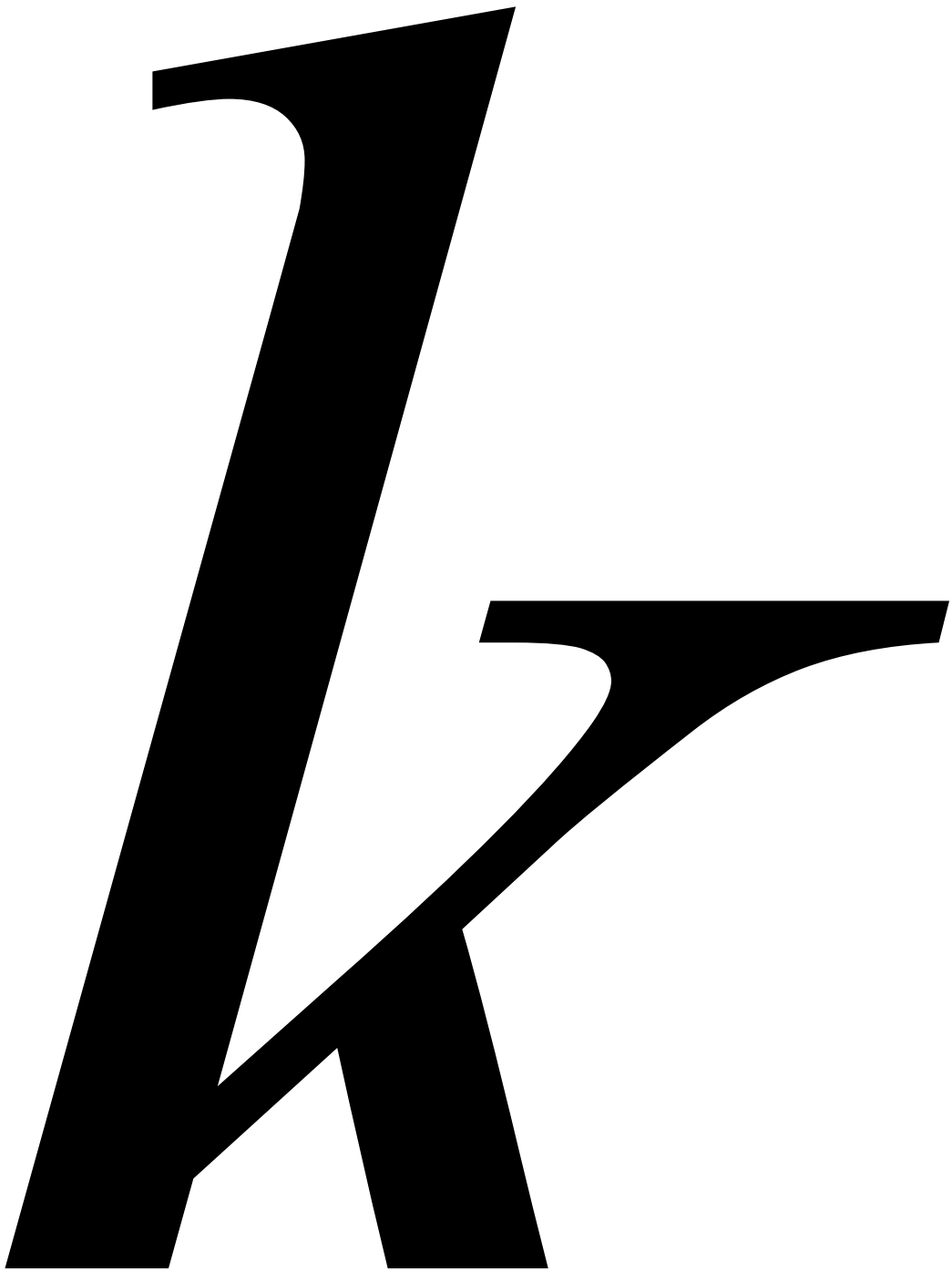
This quantity measures the average amount by which cell-lineage selection changes the proportion of mutant cells during development. When selection is positive, the average probability of fixation rises exponentially with the number of cell divisions per individual generation. Conversely, when selection acts against the mutant allele, its probability of fixation decreases exponentially with the length of the life cycle.

As an example, consider a slightly beneficial mutation which has a cellular selection coefficient of 0.01. With 50 cell divisions per individual generation (



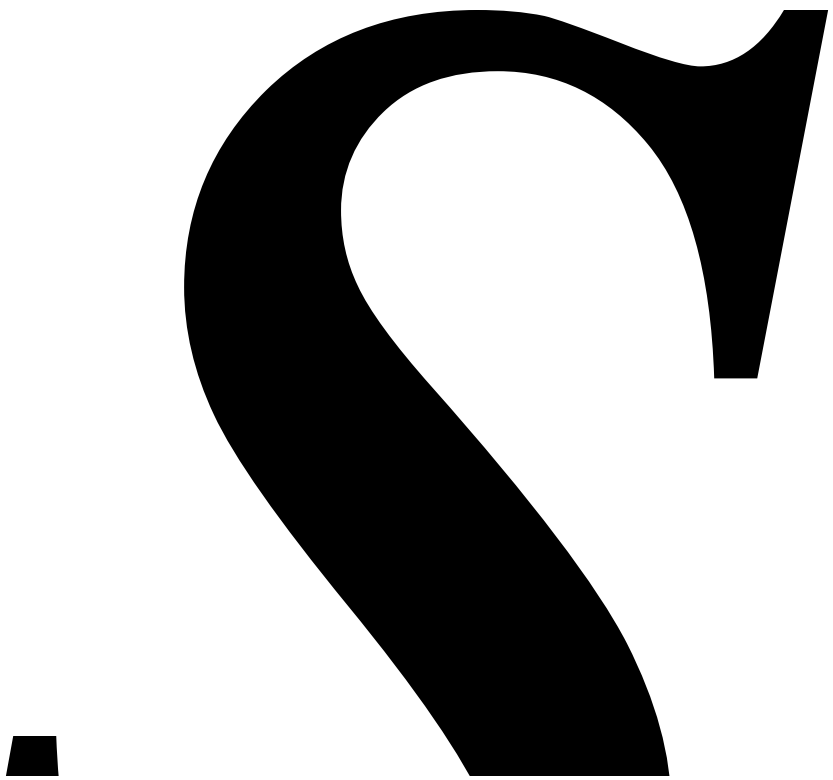
), this mutation will have a 30% higher probability of fixation than if selection

among cells were inoperative. With 100 cell divisions per generation (



), the probability of fixation would rise by 72%. For a strongly selected mutat
on, the more accurate equation (A2) must be evaluated numerically; for mutant

cells twice as fit as non-mutant cells (



), the chance of fixation is one million times higher in the presence of cell-lineage

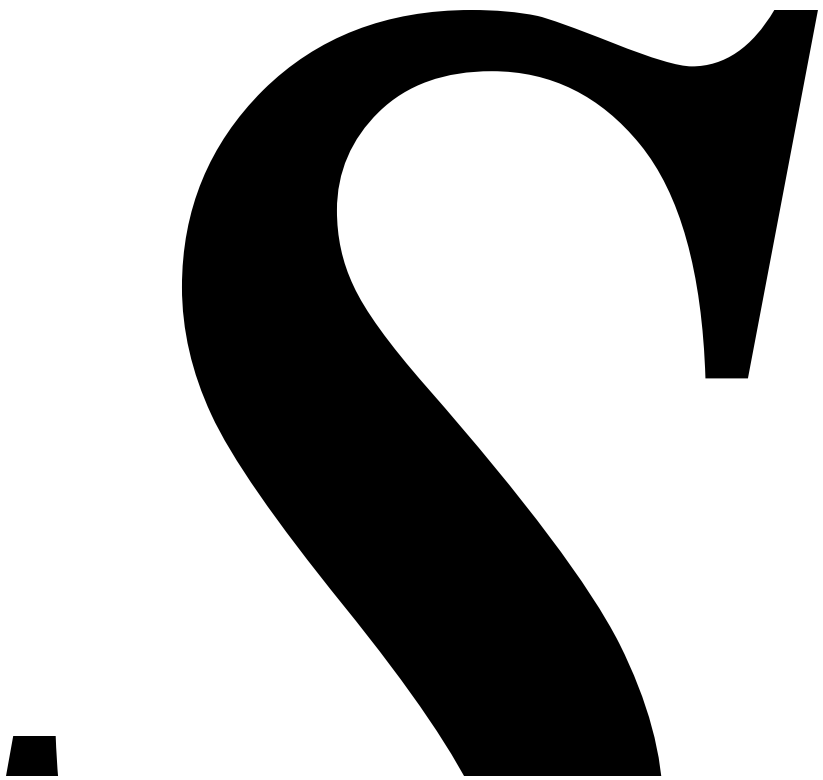
selection with 50 cell divisions per generation and

1

times higher with 100 cell divisions per generation.

For deleterious mutations, equation (1) provides a fairly accurate estimate of the probability of fixation for all selection coefficients. With a cellular selection coefficient of -0.01, the probability of fixation of a deleterious mutation is reduced by 21% with 50 cell divisions per generation and by 37% with 100 cell divisions.

For a strongly deleterious mutation (



), the chance of fixation is reduced by 96% with 50 cell divisions per generation and by 98% with 100 cell divisions.

Selection after initial appearance -- As shown above, selection within an individual can have a major impact on the survival of mutations during the first generation in which a new mitotic mutation occurs. The genetic mosaicism created by mutation is, however, immediately lost as soon as the individual reproduces via single-celled offspring. In diploid populations, genetic variation among cells is regenerated in subsequent generations by mitotic recombination and gene conversion in heterozygous individuals (Hastings, 1989, 1991; Gill

1995). The rate of mitotic crossing-over (*X*) is within the range of

1

to

1

per individual generation in *Drosophila* (Gethmann, 1988) and

1

to

1

per cell generation in yeast (Lichten and Haber, 1989; Yuan and Keil, 1990).

Mitotic recombination or mitotic gene conversion create homozygous regions within the genome. We will assume that there is no bias in which chromosome segment becomes homozygous. The resultant cell may be at an advantage or disadvantage in the face of cell-lineage selection. We shall focus on the effects of selection on a particular locus with two alleles, *A* and *a*. The proportion of *A* alleles among the gametes of a heterozygous individual depends on whether or not by mitotic recombination and gene conversion occur and also on how cell-lineage selection acts upon the *AA* and/or *aa* cells that are produced. In the appendix, we develop an equation that gives the expected proportion of *A* alleles among gametes (see Table 2 for notation). This equation must be evaluated numerically and we do not yet have a satisfactory approximation for it. [CHECK INTEGRAL]

Points for Discussion --

These models demonstrate that selection within an organism can have a major impact on the rate of evolution of a species. Cell-lineage selection can dramatically increase the observed rate of beneficial mutations. Incredibly rare mutations, such as a chromosomal rearrangement or a particular combination of mutations within a gene, may arise only once in a single cell in a single individual and will have very little chance of ultimately fixing within the population even if it confers a major selective advantage. With cell-lineage selection, however, its chances of fixation can be raised by several orders of magnitude.

For deleterious alleles, selection at the level of the cell can eliminate many of the deleterious mutations that arise. Not only will this reduce the mutation load of a population (Otto and Orive, 1995), but it will also reduce the susceptibility of a small population to drift load and mutational meltdown (Berger and Lynch ??). Drift load is caused by the fixation of deleterious alleles in small

populations, but this will occur at a lower rate when somatic selection as well as individual selection acts against the deleterious mutations.

Interestingly, whether or not the rate of evolution is increased by cell-lineage selection depends in part on whether one takes a Fisherian or Wrightian view of evolution. In a Fisherian world, cell-lineage selection will increase the rate of fixation of beneficial mutations and so should hasten the overall rate of evolution of the population. In a Wrightian world, however, populations may be near an adaptive peak with no further benefit possible until drift leads the population across a valley and towards a new peak. Cell-lineage selection will decrease the probability of fixation of deleterious alleles even in very small populations and will therefore decrease the chance that a population will traverse a fitness valley, thereby slowing down the rate of evolutionary change. [BUT should say something about the fact that cell-lineage selection can increase the probability of fixation of a chromosome that bares two mutations that are beneficial in combination...from Hastings 1991.]

Appendix

Fate of a new mutation -- We develop a model to estimate the probability of fixation of a mutation when it is subject to selection at both the individual and cellular levels. We are especially interested in the fate of a rare mutation, such as a rearrangement, deletion, or insertion in the DNA sequence, that does not occur at a continuous rate within the population. For this class of mutations, the probability of fixation of mutant alleles is a major determinant of the rate of evolution of the population. We assume that cell division occurs in a binary fashion, with the rate of cell division depending on the genotype of the cell. (The parameters of the model are described in Table 1).

In the model, within-individual selection acts at the cellular level in tissues leading to reproductive cells (whether confined to a germ-line or not). Selection

depends on whether the cell is wildtype or mutant and acts both at the individual level and at the cellular level. The mutant allele may be either beneficial (s>0) or detrimental (s<0) at either level of selection. The organism may be either haploid or diploid. If diploid, then the fitness of the mutant is assumed to be the heterozygous fitness.

Consider a single mutation that occurs sometime during the development of an individual. The mutation is most likely to occur in later cell divisions since many more cells exist that can potentially mutate. Assuming that the initial cell was non-mutant, the probability that the mutation occurs in one of the 2^x cells present at cell generation x is

$$p_x = \frac{2^x}{\sum_{i=1}^{k_1} 2^i} \qquad \text{(A1)}$$

If the mutation happens in cell generation x (after x/c_1 time units have passed), the resulting number of mutant cells in the adult will be $m_x = 2^{c_2(\tau - x/c_1)}$. Similarly, the total number of non-mutant cells will be $n_x = (2^x - 1)2^{c_1(\tau - x/c_1)}$. The expected proportion of mutant cells in the adult (P) can thus be calculated as

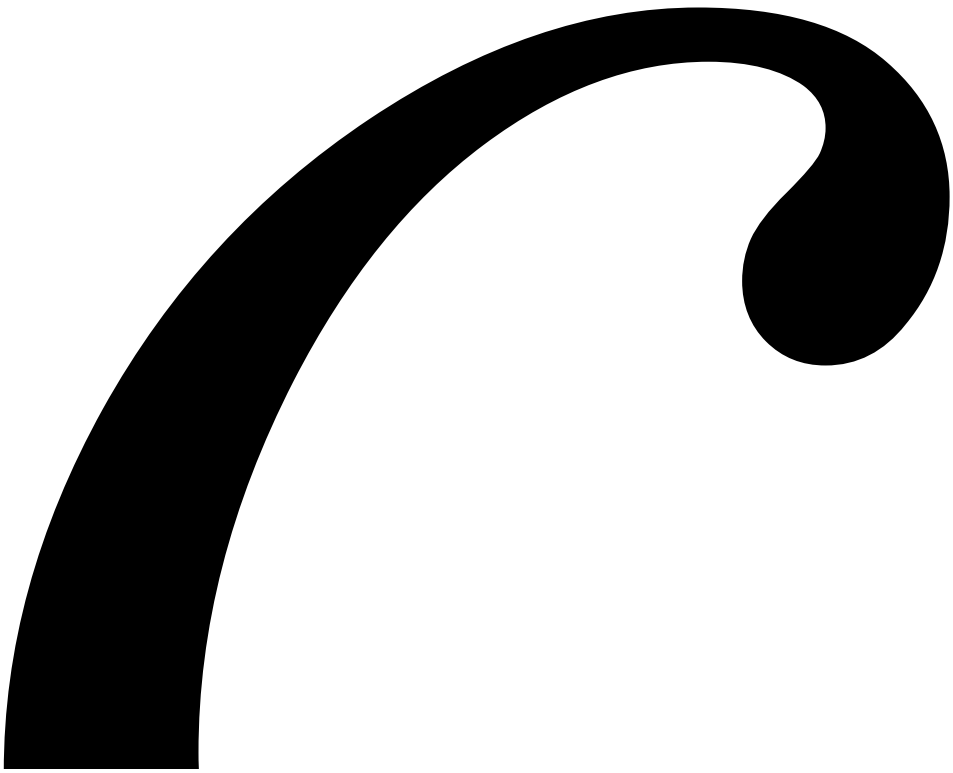
$$P = \sum_{x=1}^{k_1} p_x \frac{m_x}{n_x + m_x}$$

(A2)

The actual distribution of mutant cells in models such as this one is extremely skewed (Luria and Delbruck, 1948; Lea and Coulson 1949). Mutations are unlikely to occur early in development, but when they do the proportion of mutants is very high. More often, mutations happen late in development leading to a very small proportion of mutant cells. We are interested, however, in the

average probability of fixation and so the expected value of P given by (A2) will serve our purposes.

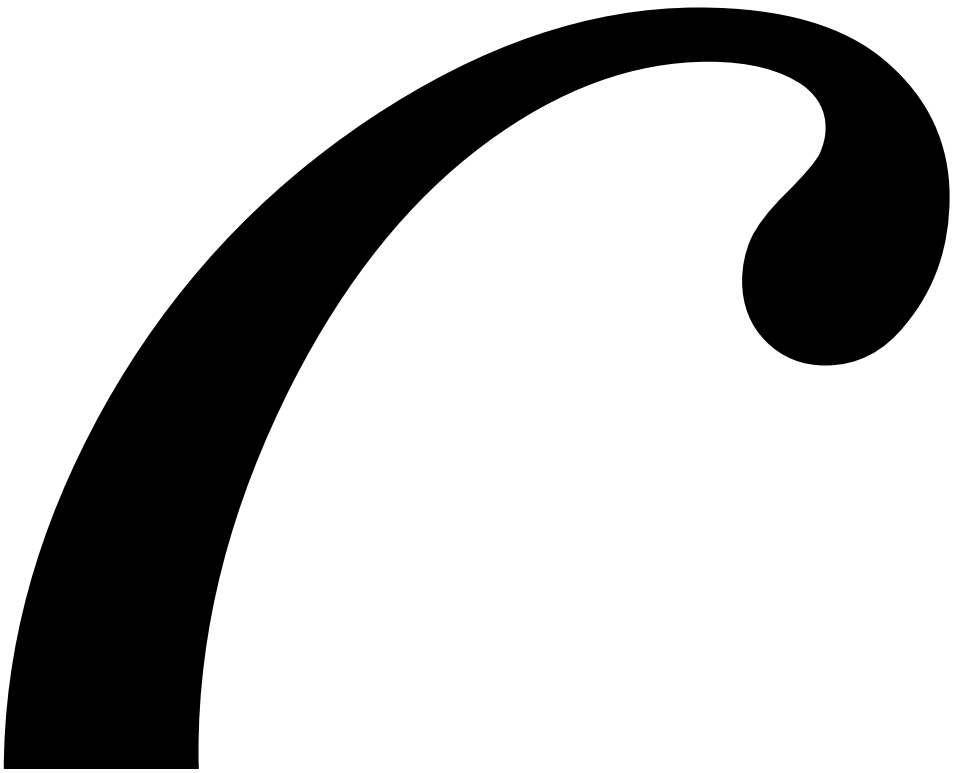
When



, equation (A2) reduces to

which conforms to our expectation that extremely few cells should be mutant since the mutation is likely to occur late in development. With cell-lineage

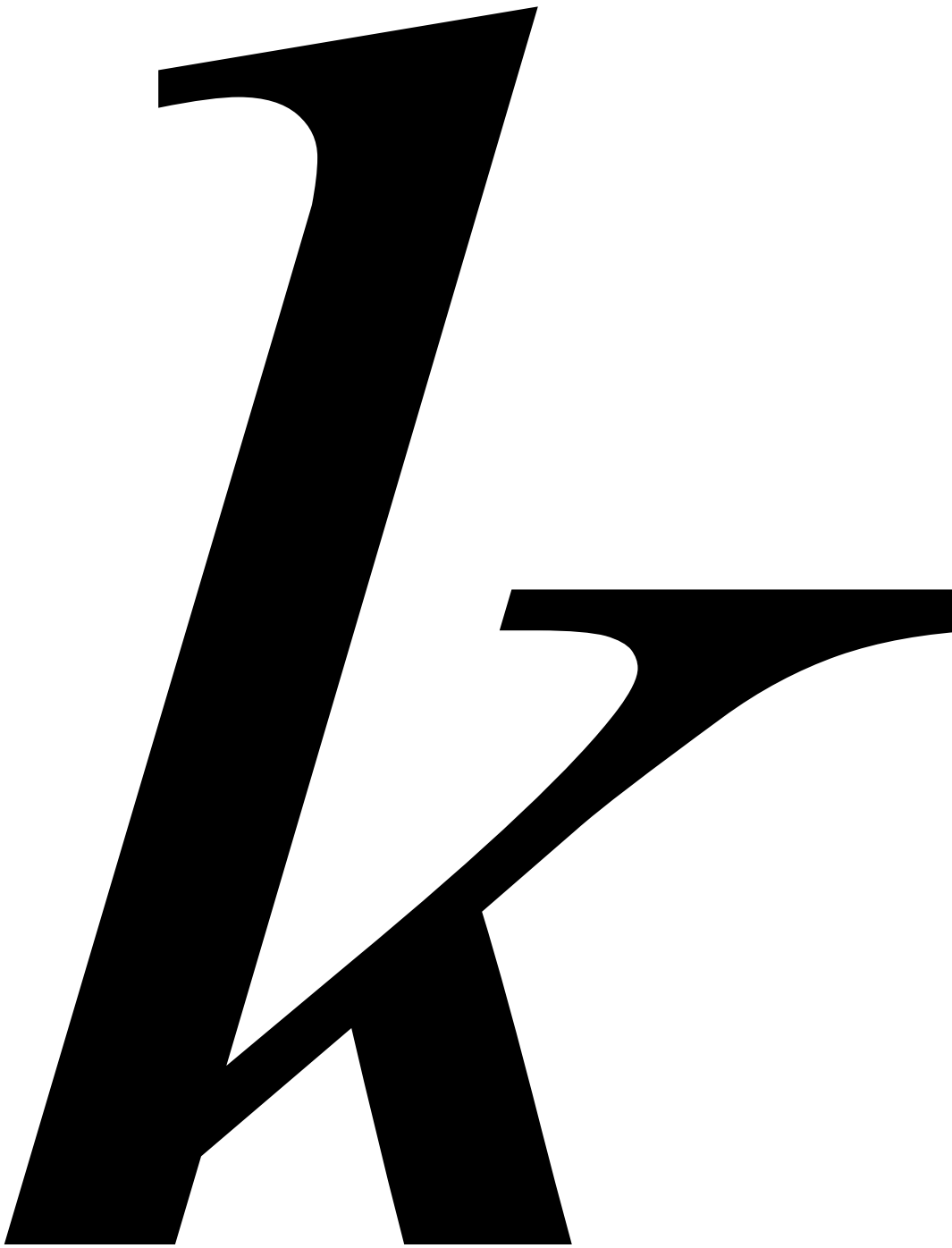
selection (



), equation (A2) can be evaluated numerically. If, however, we assume that the tota l number of cells in the adul t is relatively unchanged by the processes of ce

(A4)

This approximation was tested within the range of plausible values for



(1-500 cell divisions per individual generation) and found to be fairly accurate whenever $-1 \leq s_C \leq 0.01$.

We can use this information about the expected frequency of mutant cells in an individual to calculate the probability of ultimate fixation within the population of a single mutation that occurs during development. We will use the results of Kimura (1964) who determined the probability of fixation of an allele in a finite population based on a diffusion analysis. In a diploid population of size 2*N*, Kimura found that the probability of fixation of a mutation at initial frequency p_0 is

$$u = \frac{1 - e^{-4Ns_I p_0}}{1 - e^{-4Ns_I}} \qquad \text{(A5)}$$

which assumes a Poisson distribution of offspring per parent and a census population size near the effective population size. For a haploid population, *N* must be replaced with *N/2* wherever it appears. When a mutation first appears in a fraction (*P*) of gametes of a single individual, p_0 equals $P/2N$. For a beneficial mutation in a large population, the probability of fixation is then approximately $2 s_I P$. Therefore, cell-lineage selection changes the probability of fixation of a mutant allele by the amount:

$$\Pi = \frac{e^{s_C k_1} - 1}{s_C k_1} \qquad \text{(A6)}$$

For beneficial alleles, the probability of fixation rises rapidly with the strength of cell-lineage selection (Figure 2). For deleterious alleles, the probability of fixation decreases until only those alleles that arise in the last cell generation have any chance of fixing (Figure 2). [CONNECT TO IAN'S SIMULATIONS]

Fate of a mutation in heterozygotes -- 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. With mitotic recombination (and all other factors that can convert a heterozygous cell to a homozygous one), the expected number of *aa* cells in an individual that is originally heterozygous is:

$$N_{aa} = \sum_{i=1}^{k_2} 2^i (1 - X_C)^{i-1} \frac{X_C}{2} 2^{c_1(\tau - i/c_2)} \quad . \qquad \text{(A7a)}$$

$$= \frac{2^{c_1\tau} X_C - 2^{c_2\tau}(1 - X_C)^{c_2\tau} X_C}{2^{c_1 - c_2}} \quad . \qquad \text{(A7b)}$$

Equation (A7a) is calculated as follows (see Otto and Orive 1995 for a similar derivation for mutation). After i mitotic divisions, there will on average be $2^i (1 - X_C)^{i-1} X_C$ cells that have not converted in any of the previous mitoses, but have just converted in the last mitotic division. It is assumed that these newly converted cells have 1/2 chance of being *aa*. Such cells will then divide at rate c_1 for the remainder of the individual generation ($\tau - i/c_1$ time units). Similarly, the expected number of *AA* cells is

$$N_{AA} = \sum_{i=1}^{k_2} 2^i (1 - X_C)^{i-1} \frac{X_C}{2} 2^{c_3(\tau - i/c_2)} . \qquad \text{(A8a)}$$

$$= \frac{2^{c_3\tau} X_C - 2^{c_2\tau}(1 - X_C)^{c_2\tau} X_C}{2^{c_3/c_2} - 2 + 2X_C} \quad . \qquad \text{(A8b)}$$

Finally, the expected number of cells that never undergo conversion and remain heterozygous in the adult is:

$$N_{Aa} = 2^{c_2\tau}(1 - X_C)^{c_2\tau} \quad \text{(A9)}$$

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 approximately:

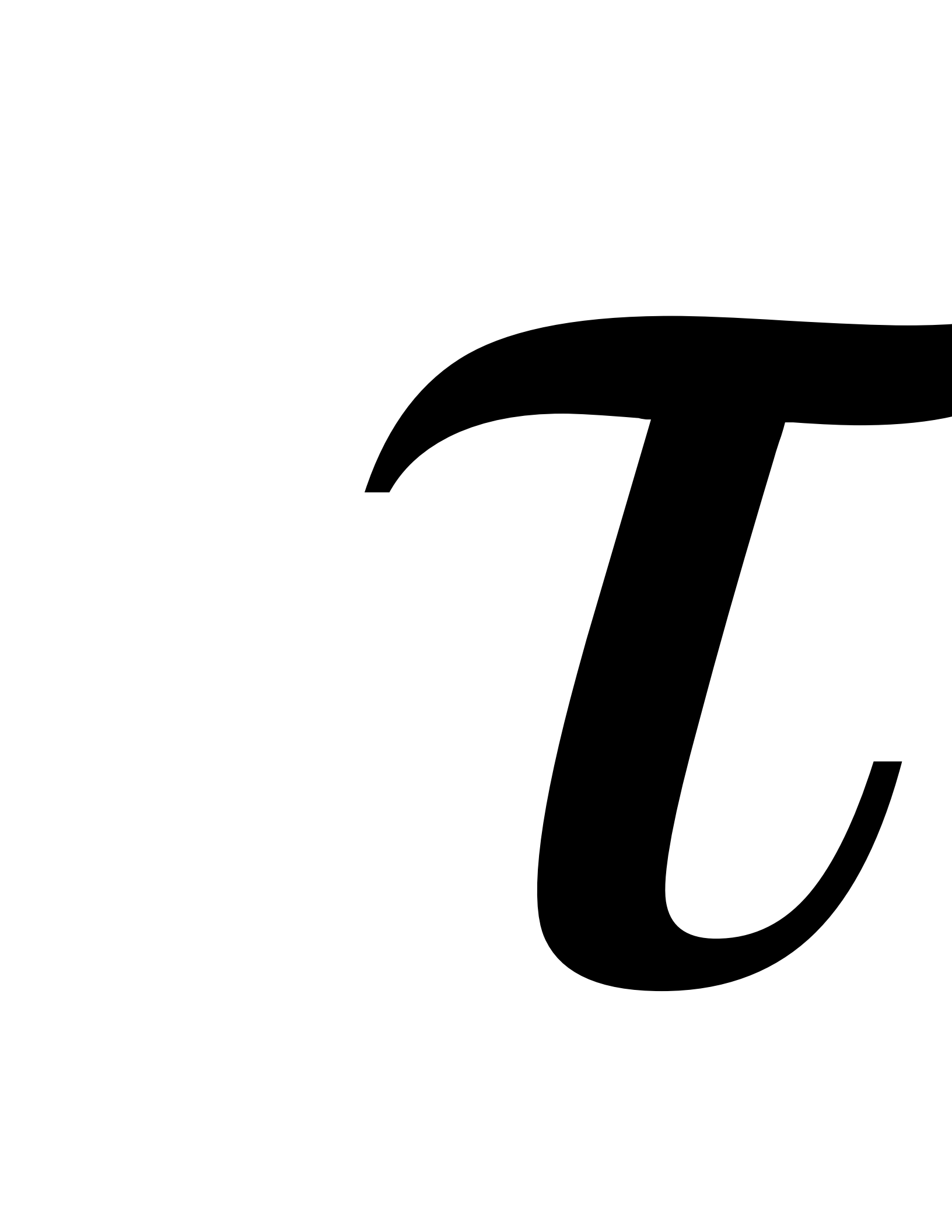
(A9)

Equation (A9) is not technically correct, because the expectation of a ratio is not the ratio of the expected values, but simulations indicate that the error caused by using the approximation (A9) is not large when...[Need to check with simulations]

Equation (A9) can be used to determine the expected amount of segregation distortion that should be observed due to selection among cells within an individual. If cell-lineage selection distorts the gamete frequencies in favor of allele *A* and individual-level selection also favors allele *A*, then the two will act in concert to raise the total fitness advantage of the allele as well as its probability of fixation. In contrast, if the two levels of selection act in opposite directions then the possibility exists for a balance between selection at the different levels, which may be examined using the classical models of meiotic drive. [How should we connect this section in? Do we need a figure or table here?]

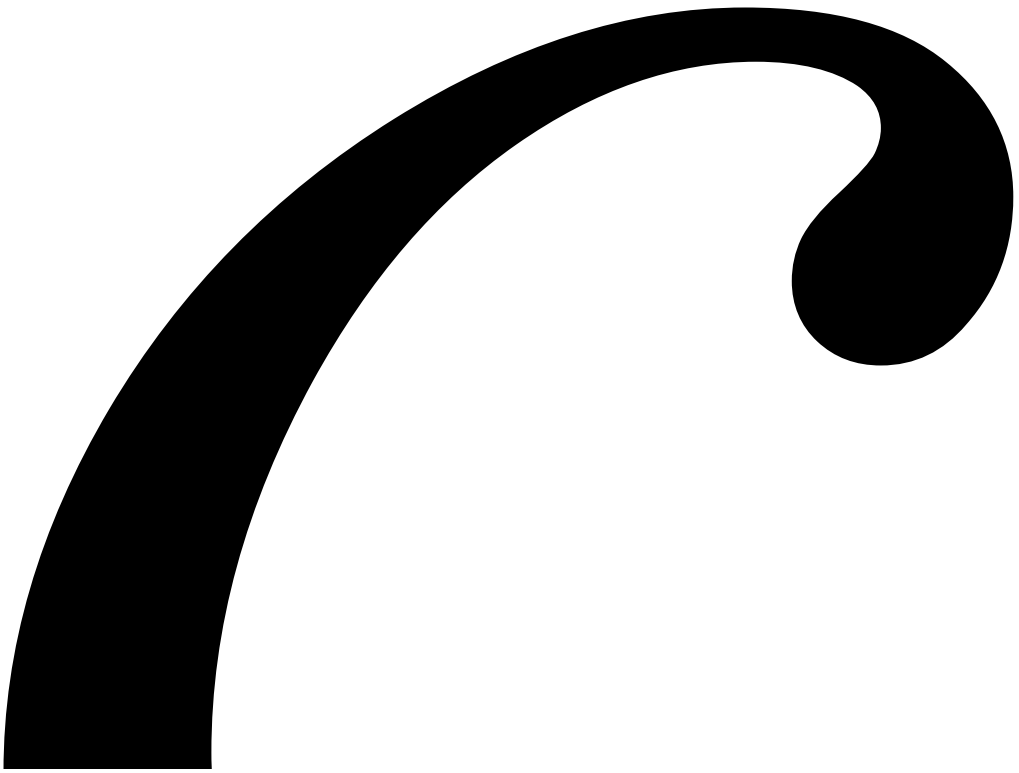
Tables

Table 1: Parameters of the mitotic mutation model. The organism is assumed to grow for a specified amount of time,



. The rates of cell division and fitness at the cellular level are related to one another as follows. The relative fitness of a mutant cell is the expected number of daughter cells produced relative to non-mutant cells during a single cell

generation for a non-mutant cell. Since the rate of cell replication is



for non-mutant cells, the cell generation time is

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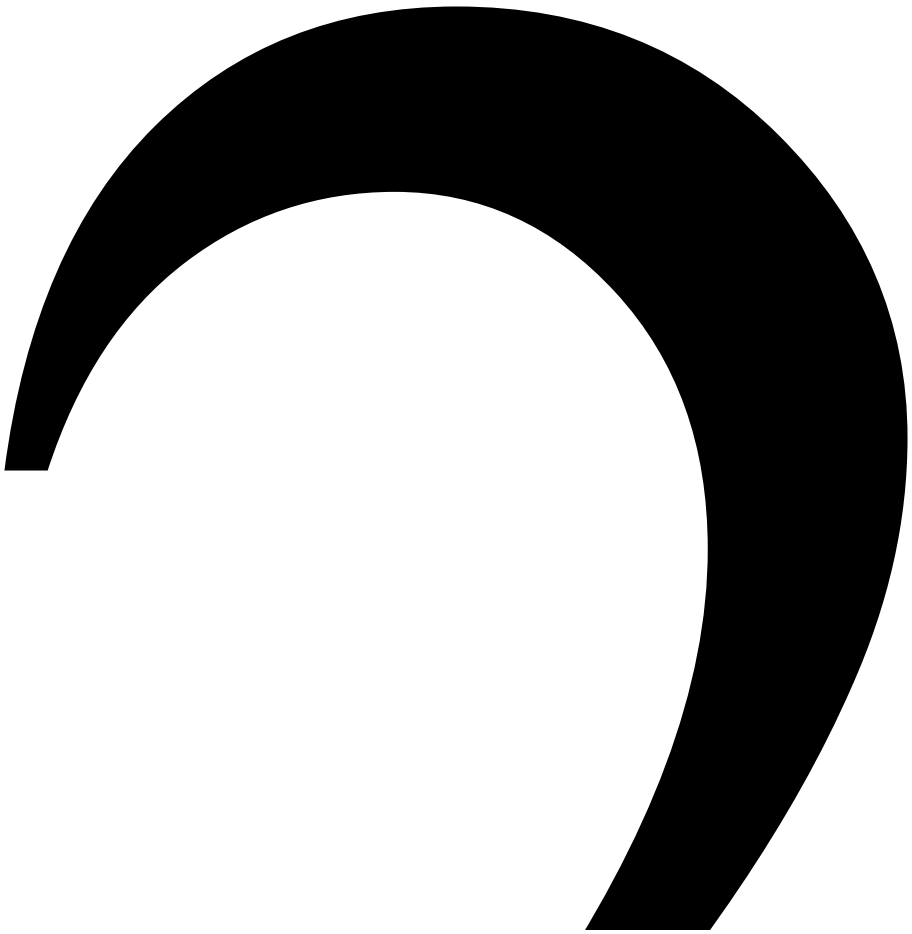
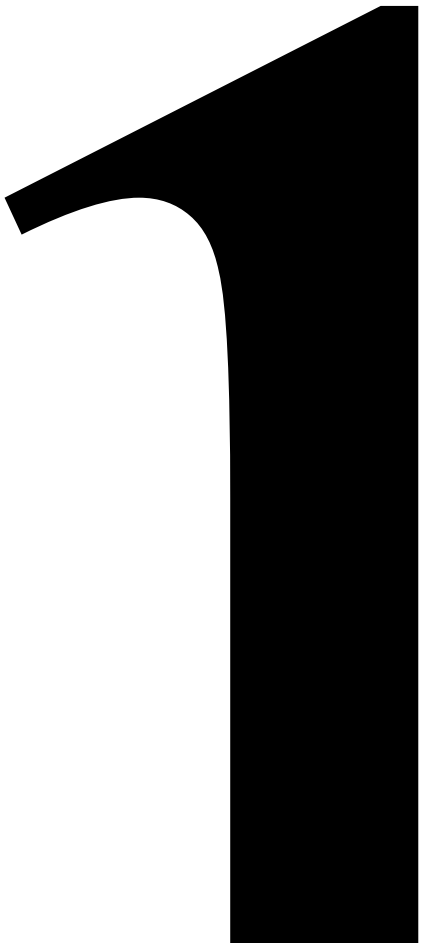
time units, in which time the mutant cells are expected to produce



daughter cells while non-mutant cells produce two daughter cells. Therefore the

relative fitness of mutant cells is given by



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Genotype	Rate of Cell Division	Number of Cell Divisions per Generation	Fitness at the Individual Level	Fitness at the Cellular Level

Non-mutant

Mutant

Table 2: Parameters of the mitotic recombination model. The parameter set defined in Table 1 is extended to an explicitly diploid model (see legend of Table 1 for more details).

Genotype	Rate of Cell Division	Number of Cell Divisions per Generation	Fitness at the Individual Level	Fitness at the Cellular Level
aa	c_1	$k_1 = c_1\tau$	1	1
Aa	c_2	$k_2 = c_2\tau$	$1 + h_I s_I$	$1 + h_C s_C = 2^{c_2 - c_1}$
AA	c_3	$k_3 = c_3\tau$	$1 + s_I$	$1 + s_C = 2^{c_3 - c_1}$

Figures

Figure 1: The effect of cell-lineage selection on mutation rates. The observed mutation rate divided by the underlying mutation is shown as a function of the replication rate of mutant cells relative to that of non-mutant cells. Curves are calculated from equation (4) of Otto and Orive (1995). A mutation rate of 10^{-8} per locus per cell generation was used, although identical curves are obtained for mutation rates above 10^{-4}. *k* is the number of cell divisions per individual generation for non-mutant cells.

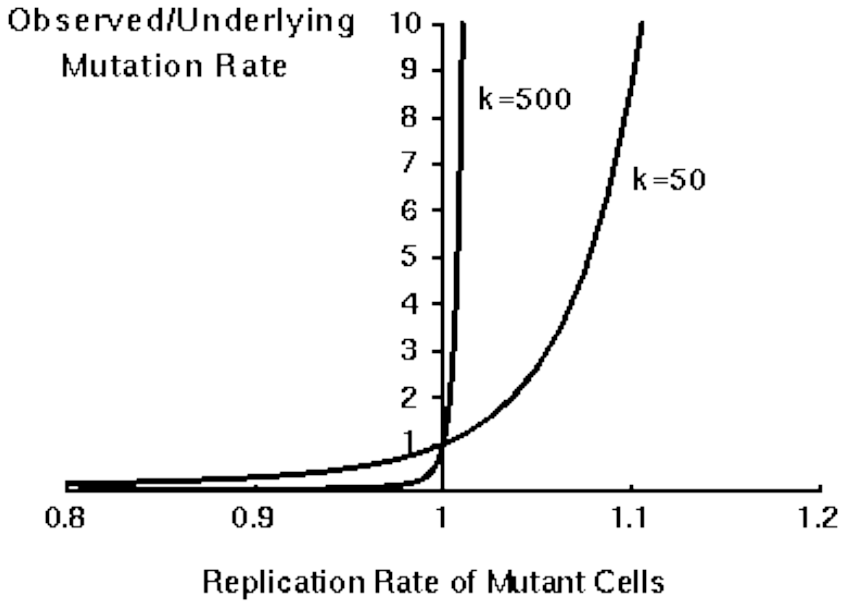

Figure 2: The effect of cell-lineage selection on the probability of fixation of a mutant allele. The observed probability of fixation in the presence of cell-lineage selection divided by the probability of fixation in the absence of cell-lineage selection is graphed as a function of the selection coefficient of the mutant allele. The mutant allele is assumed to occur once during the development of the organism. There are 50 cell divisions per individual generation for non-mutant cells. The bottom curve is based on the more exact equation (A2), while the top curve shows the approximation from (A4).