The functional transfer of genes from the mitochondria to the nucleus: the effects of selection, mutation, population size and rate of self-fertilization.

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Running head: Simulating gene transfer

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ABSTRACT

The transfer of mitochondrial genes to the nucleus is a recurrent and consistent feature of eukaryotic genome evolution. Although many theories have been proposed to explain such transfers, little relevant data exist. The observation that clonal and self-fertilizing plants transfer more mitochondrial genes to their nuclei than do outcrossing plants contradicts predictions of major theories based on nuclear recombination and leaves a gap in our conceptual understanding how the observed pattern of gene transfer could arise. Here, with a series of deterministic and stochastic simulations, we show how epistatic selection and relative mutation rates of mitochondrial and nuclear genes influence mitochondrial-to-nuclear gene transfer. Specifically, we show that when there is a benefit to having a mitochondrial gene present in the nucleus, but absent in the mitochondria, self-fertilization dramatically increases both the rate and probability of gene transfer. However, absent such a benefit, when mitochondrial mutation rates exceed those of the nucleus, self-fertilization decreases the rate and probability of transfer. This latter effect, however, is much weaker than the former. Our results are relevant to understanding the probabilities of fixation when loci in different genomes interact.

The loss of endosymbiont genes can either be complete, in which lost genes are absent from the host-endosymbiont complex, a substitution, in which a nuclear allele functions in place of the lost symbiont gene, or a functional transfer of an endosymbiont gene to the nucleus, followed by its loss (ADAMS et al. 2003). Such, ‘functional transfer’ involves the relocation of a mitochondrial gene to the nucleus, its acquisition of a promoter, successful targeting to the mitochondria for proper function, and the eventual loss of the gene from the mitochondrial genome altogether. Although this process is probably quite complex and requires numerous evolutionary modifications (MURCHA et al. 2005), there is evidence that some mitochondrial genes are pre-adapted to functional transfer as they contain signals that target them to the mitochondria before functional transfer to the nucleus (UEDA et al. 2008a). The complex evolution of rps16 – is an
illuminating case of both functional gene transfer and substitution. In some lineages, the mitochondrial rps16 is functionally expressed in the nucleus but absent from the mitochondria (functional transfer) while in a subset of taxa, the chloroplast copy is also absent and the nuclear gene is also targeted to the chloroplast (substitution, Ueda et al. 2008b).

A number of evolutionary scenarios have been proposed to account for the massive loss of genes from endosymbionts. A subset of models argues that endosymbiont gene loss is a neutral or nearly neutral process. Since endosymbiosis reduces the strength of selection on genes that are unnecessary or redundant in an obligate intracellular environment, these genes may be quickly lost by the neutral fixation of a deletion or other loss of function mutations. Moreover, even when selection favors the retention of genes in endosymbionts, such selection may be ineffective because of reduction in effective population size due to recurrent bottlenecking (Rispe and Moran 2000). Additionally, frequent input of functional endosymbiont genes into the nucleus makes symbiont genes redundant, exacerbating gene loss via functional transfer (Berg and Kurland 2000).

An alternative class of explanations views the loss of mitochondrial genes (be it complete loss, substitution, or functional transfer) as an adaptive process. The ‘mitochondrial competition theory,’ argues that mitochondrial genomes that either do not contain or do not express a given allele have a replicative advantage over other mitochondria, providing a within-host selective advantage to mitochondrial gene loss (Albert et al. 1996; Selosse et al. 2001; Yamauchi 2005). The ‘benefits of sex’ model posits that the genomic diploid nuclear environment (diploid, sexual) is in some way preferable (e.g. as an escape from Muller’s ratchet or Hill-Robertson Interference) to a
haploid asexual mitochondrial environment (Blanchard and Lynch 2000). The
epiplastic model (Wade and Goodnight 2006) does not advance a specific or consistent
benefit to transfer, but posits that transfer is explicitly a process of co-evolution between
mitochondrial and nuclear genomes where fitness is a function of the gene combination
rather than either gene separately.

Because few species are currently undergoing mitochondrial to nuclear gene
transfer, these alternative hypotheses are difficult to distinguish with direct
experimentation. However the distribution of transferred genes across lineages allows for
evaluation of the alternative hypotheses. For example, self-pollination reduces the rate of
heteroplasmy and consequently the opportunity for competition among genetically
distinct mitochondria. Thus, the mitochondrial competition theory predicts an excess of
transfer events in sexual, outcrossing lineages, with high degrees of ‘paternal leakage.’
Similarly, frequent self-fertilization diminishes the benefits of sex, and thus the benefits
of sex hypothesis predicts fewer transfers in selfing and clonally reproducing plants than
in outcrossing taxa. The epistatic model makes the opposite prediction. Selfing and clonal
reproduction maintain cyto-nuclear gene combinations and increase the response to
selection on epistatic combinations, potentially encouraging transfer. On the other hand,
outcrossing tends to break apart adaptive cyto-nuclear gene combinations, potentially
decreasing the amount of adaptive transfer in outcrossing lineages.

Plant lineages with high levels of self-fertilization or asexual reproduction
transfer more mitochondrial genes to their nuclei than predominantly sexual and
outcrossing lineages (Brandvain et al. 2007). This result is consistent with predictions
of the epistatic model and is contrary to predictions of the mitochondrial competition or
benefits of sex models. More specific predictions allowing further empirical tests require more detailed theoretical investigations of the gene transfer process. Here, we investigate the roles of mutation, selection, and random drift in gene transfer using both deterministic models and stochastic simulations to refine and extend predictions of patterns of functional mitochondrial to nuclear gene transfer.

METHODS

To address the effect of mating system on the probability of functional gene transfer, we simulated a monoecious Fisher-Wright population with two loci – one nuclear and one mitochondrial. At the mitochondrial locus, which is haploid and strictly maternally inherited, $M$ represents a functional copy of an essential mitochondrial gene, while $m$ represents a nonfunctional allele. Initially, the population is fixed for $M$, however, each $M$ allele has a probability, $\mu_m$, of mutating to the nonfunctional allele, $m$, every generation while $m$ alleles cannot revert to their functional progenitor, $M$.

At the nuclear locus, $I$ represents a functioning, transferred copy of the essential mitochondrial gene, while allele $0$ represents a nonfunctional (or absent) allele. The nuclear locus is diploid, and bi-parentally inherited, with Mendelian meiosis. Like the mitochondrial allele, each $I$ allele has a probability, $\mu_n$, of mutating to the nonfunctional allele, $0$, and there is no back mutation.

Allele $I$ begins at a low frequency (5%), i.e., rare physical transfer has occurred, but the evolutionary resolution of this transfer event is uncertain and may be affected by the nature of selection, the mating system, the effective population size, and the relative
mutation rates of the two genomes. Genotypic frequencies in the population in the first
generation equal the values expected given the selfing rate (Table 1). We then make new
generations by the processes of mutation, reproduction and selection.

Although interesting evolutionary dynamics may occur in between the
introduction of a new mutation (at frequency 1/2N) and the initiation of our simulation
(5%), much of this initial process will be characterized by neutral evolutionary processes
because the nuclear gene is unlikely to have accumulated a substantial amount of loss of
function mutations, and therefore should be unaffected by the parameters investigated
below.

**Deterministic Simulations**

We begin at generation zero with a vector of genotypic frequencies, \((F_t, t = 0,\)
Table 1). Genotypic frequencies after selection, \(F'_t\), equal the product of the relative
fitness matrix, \(\tilde{W}\), in which all values on the main diagonal are the genotypic relative
fitnesses, while all values off the main diagonal equal 0 (Appendix 1) and \(F_t\), the vector
of initial allele frequencies.

\[
F'_t = \tilde{W} \cdot F_t
\]  

[1]

Multiplying the reproduction matrix, \(R\), by \(F'_t\) yields \(F''_t\) – the vector of expected
genotypic frequencies after selection. We complete the transition from genotypes \((F_t)\) at
one generation to the next \((F_{t+1}\), note that \(F''_t = F'_{t+1}\)) by multiplication of the mutation
matrix \((\mu)\) and \(F''_t\).

Because loss of the functional mitochondrial allele is approached asymptotically,
and because the functional nuclear allele attains different frequencies at mutation-
selection balance across fitness functions and selfing rates, we iterate these matrices until
the frequency of the functional nuclear allele is common (i.e. > 95%) and report the number of generations needed for the population to reach this frequency.

Parameters: In our deterministic models of infinitely large populations with discrete, non-overlapping generations, we investigate the effects of mutation by factorially combining mitochondrial and nuclear mutation rates ($\mu_m$ and $\mu_n$, respectively) in increments of an order of magnitude from $10^{-3}$ to $10^{-6}$. We examine the influence of selfing by varying selfing rate from zero to one in 0.001 increments.

We examine a wide array of selection regimes (Table 1). For all selection regimes, all genotypes containing a functional mitochondrial gene has a fitness of one – that is, $w_{M11} = w_{M10} = w_{M00} = 1.00$. Because we assume that the $M$ allele is essential for survival, we set the fitness of individuals entirely lacking a functional copy of this allele to zero (i.e. $w_{m00} = 0$). We vary the fitness of heterozygotes lacking a functional mitochondrial allele from 0.90 to 1.10 in 0.05 increments (i.e. $0.90 \leq w_{m10} \leq 1.10$) in order to explore transfer with ($w_{m10} < 1.00$) and without ($w_{m10} \geq 1.00$) heterozygote fitness valleys. We vary the fitness of the genotype homozygous for the functional nuclear allele but with a nonfunctional mitochondrial allele from 1.00 to 1.10 in 0.05 increments (i.e. $1.00 \leq w_{m11} \leq 1.10$). Because nuclear overdominance will maintain the system at an intermediate equilibrium, we excluded cases in which $w_{m10} > w_{m11}$.

Stochastic simulations

From initial genotypic frequencies (Table 1), we create the next generation one individual at a time until the population consists of $N$ individuals. Each genotype in the parental generation ($t$), has an $f_j w_i / \bar{w}$ probability of being the mother of an individual in the offspring of generation ($t + 1$). This mother is also the father with probability, $S$,
where $S$ is the selfing rate. With probability $1 - S$, that mother is not the father and a new parent is chosen (with replacement) where each genotype has a probability, $f_i w_i / \bar{w}$, of being the father. One nuclear allele is chosen at random from each parent, while the mitochondrial allele is maternally inherited. Each allele is then subject to a risk of mutation according to the rate appropriate for the genome of origin. We iterate this sampling scheme until we create $N$ offspring. Then, we repeat this process until either the mitochondrial gene is lost (transfer) or the nuclear gene is lost (retention), and repeat this algorithm 1,000 times for each set of parameters.

**Parameters:** In our stochastic simulations, generations are discrete and non-overlapping, and population sizes are stationary. We investigate factorial combinations of three population sizes, $N$, (100, 500, and 1000) and eleven selfing rates, $S$, (0-1 in 0.10 increments). All other parameters (i.e., selective regimes and mutation rates) match those of the deterministic model.

Since nuclear overdominance can maintain the system at an intermediate equilibrium, we exclude fitness combinations in which $w_{m10} > w_{m11}$ and lack a fully balanced design. To create a balanced analysis we comparison the influence of homozygote fitness keeping heterozygote fitness constant. Turning our attention to the effect of heterozygote fitness, we compare across heterozygote fitnesses holding homozygote fitness constant.

**RESULTS**

**Deterministic simulations**
The number of generations necessary for a functional nuclear allele to increase from rarity \((f_0 = 0.05)\) to commonness \((f_t = 0.95)\) is determined by an interaction of the selfing rate, relative mutation rates \((\mu_m \text{ vs } \mu_n)\), and the selection scenario. Here we discuss each of the three different classes of mutational parameters: (A) \(\mu_m << \mu_n\); (B) \(\mu_m = \mu_n\); and, (C) \(\mu_m >> \mu_n\) (see Figures 1A, B, and C, respectively).

\(\mu_n >> \mu_m\): When the nuclear mutation rate is greater than that of the mitochondria, a fitness benefit of nuclear relocation is a necessary but not sufficient criterion for the spread of the nuclear allele. It is not sufficient, since a benefit to transfer \((w_{M11} > 1.00)\) does not ensure that the nuclear allele becomes common (Figure 1A). Selection cannot increase the frequency of a functional nuclear allele until the selfing rate surpasses a critical threshold. At this point, time to commonness decreases very quickly with increased selfing rates (Figure 1A). The selfing rate plays a role because the benefit to nuclear transfer is dependent on the mitochondrial genotype, and selfing increases the heritability of mito-nuclear gene combinations (Wade and Goodnight 2006). These results are qualitatively consistent across all combinations of mutation rates examined so long as \(\mu_n >> \mu_m\) (not shown).

\(\mu_n = \mu_m\): When nuclear and mitochondrial mutation rates are equal, a fitness benefit is still necessary for deterministic increase in the frequency of a mitochondrial gene transposed to the nucleus; however, the nuclear allele can increase in frequency over a wider region of parameter space than above (where \(\mu_n >> \mu_m\), compare Figures 1A and 1B). Here the time until commonness decreases as selfing rate increases; i.e. the first derivative of the function in Figure 1B is always negative.
Although dy/dx is always negative, the second derivative is always positive and generally decreasing, ultimately approaching zero at extreme rates of self-fertilization. This approach is not smooth, and we use critical points representing local minima and maxima of d²y/dx² (dₘᵢₙ and dₘ₃ₙ corresponding to d³y/dx³ = 0, d⁴y/dx⁴ > 0, and d³y/dx³ = 0, d⁴y/dx⁴ < 0, respectively) to describe and compare the shapes of these functions. Hereafter, we designate these points d₁.₀₅ₘᵢₙ and d₁.₁₀₅ₘᵢₙ and d₁.₀₅₃ₘᵢₙ and d₁.₁₀₃ₘᵢₙ, in which heterozygote fitness, wₘ₁₀, equals one and the numerical subscript following d represents the homozygote fitness, wₘ₁₁.

Regardless of the mutation rate, the shape of this curve is much the same, with d₁.₀₅ₘᵢₙ and d₁.₁₀₅ₘᵢₙ and d₁.₀₅₃ₘᵢₙ and d₁.₁₀₃ₘᵢₙ occurring at nearly equivalent selfing rates (d₁.₀₅ₘᵢₙ ≈ 0.78, d₁.₁₀₅ₘᵣ ≈ 0.69, d₁.₀₅₃ₘᵢₙ ≈ 0.89, d₁.₁₀₃ₘᵢₙ ≈ 0.81). Although the selfing rates at these inflection points are invariant across mutation rates, the corresponding time until commonness at these points differs. For all four cases of μₘ = μₙ examined, dₘᵢₙ is proportional to (1/μ), the inverse of the mutation rate. While dₘ₃ₙ is also inversely related with the mutation rate, the form of this relationship is more complicated (see Table 2).

μₙ ≪ μₘ: When the mitochondrial mutation rate exceeds the nuclear mutation rate, a functional nuclear allele can become common without a direct fitness advantage. However, this mechanism of gene transfer is very slow and varies minimally across selfing rates, until selfing is nearly obligate. By this point (S = 0) the time to commonness is one and a half to two times greater than it is with no selfing at all (S = 0; Figure 1C’).

When transfer is adaptive (wₘ₁₁ > 1.05), the time to commonness decreases with increased selfing (dy/dx < 0). Again, the second derivative is always positive, but
ultimately approaches zero, with a shape similar to that described in the previous section. Table 2 shows that whenever $\mu_n << \mu_m$, the time until commonness at the critical points is very sensitive to changes in nuclear mutation rates but not to changes in the mitochondrial mutation rate. As was the case when mutation rates were equal, time to commonness at $d_{1.05\text{min}}$ and $d_{1.10\text{min}}$ increases by an order of magnitude as mitochondrial mutation rates decrease by an order of magnitude.

**Stochastic simulations:**

Overall, we investigated 6,336 parameter combinations (12 fitness combinations x 4 nuclear mutation rates x 4 mitochondrial mutation rates x 3 population sizes x 11 selfing rates = 6,336) and each was replicated 1,000 times, totaling more than six million independent binomial results. Below, we describe these results with the aid of the applied logistic regression (HOSMER and LEMESHOW 1989). The number of transfers out of 1,000 runs, when $\mu_n = \mu_m = 1 \times 10^{-3}$, and $N = 1,000$, are presented in Figure 2. Results across all population sizes and mutation rates are presented in Electronic Appendix 1. Although we do not correct for multiple comparisons, p-values of significant results are generally very small and supported by greater trends, suggesting that these results are robust to multiple comparisons.

**Main effects**

For all main effects we report results as odds ratios so that factors that enhance the likelihood of gene transfer give a ratio greater than one, while those that reduce the likelihood have a ratio less than one. The denominator of our odds ratios is the case where transfer to the nucleus goes through an unfavorable heterozygous stage ($w_{m10} = 0.90$) with neutral homozygotes ($w_{m11} = 1.00$), very low mutation rates ($\mu_n = \mu_m = 10^{-6}$)
and small population sizes (N = 100). The focal value of the parameter of interest is the numerator.

*Selection:* Increasing the fitness of m11 individuals increases the probability of transfer. The odds of achieving functional transfer were twice as high (OR = 1.97, SE = 0.010, p < 0.001) when \( w_{m11} \) equaled 1.05 relative to the neutral case \( (w_{m11} = 1.00) \) and 2.5 times as high when \( w_{m11} \) was 1.10 (OR = 2.52, SE = 0.012, p < 0.001).

Increasing the fitness of m10 genotypes has similar but much weaker effects (Table 3). Relative to the ‘under-dominant’ heterozygote fitness, \( w_{m10} = 0.90, w_{m10} = 0.95 \) has an OR of 1.03 (SE = 0.011, p = 0.003) and \( w_{m10} \) equal to 1.00 has an OR of 1.09 (SE = 0.011, p < 0.001).

*Mutation:* Increasing the mitochondrial mutation rate increases the probability of transfer, suggesting that mutation pressure promotes mitochondria-to-nuclear gene transfer. This effect increases nonlinearly with the mitochondrial mutation rate (\( \mu_m = 10^{-5}: \) OR = 1.04, SE = 5.90 X 10^{-3}, p < 0.001. \( \mu_m = 10^{-4}: \) OR = 1.61, SE = 8.38 X 10^{-3}, p < 0.001. \( \mu_m = 10^{-3}: \) OR = 4.32, SE = 1.99 X 10^{-2}, p < 0.001).

Nuclear mutational pressure has an effect similar in magnitude but opposite in direction. Increasing the nuclear mutation rate from 10^{-6} to 10^{-5} has a negligible effect (OR = 1.00, SE = 3.90 X 10^{-3}, p = 0.666), but increasing it to 10^{-4} significantly decreases the probability of functional transfer (OR = 0.84, SE = 3.43 X 10^{-3}, p < 0.001). At the highest nuclear mutation rate examined, \( \mu_n = 10^{-3}, \) the probability of transfer is reduced 60% (OR = 0.41, 2.02 X 10^{-3}, p < 0.001).
*Population size:* Large populations are more likely to successfully transfer mitochondrial genes to the nucleus than small populations (relative to \(N = 100; N = 500: OR = 1.98, SE = 8.65 \times 10^{-3}, p < 0.001. N = 1,000: OR = 2.87, SE = 1.19 \times 10^{-3}, p < 0.001\)). Since much of parameter space examined in this simulation involves a selective benefit to transfer, this is expected as the efficacy of selection is mitigated by random drift, which weakens with increases in \(N\).

*Selfing rate:* For most but not all cases, increasing the selfing rate increases the probability of transfer. Compared to strict outcrossing, low levels of selfing slightly decrease the probability of transfer. As selfing rate increases further, the probability of transfer slowly increases, until the odds ratio is approximately equal to one at a selfing rate of 0.7. At this point, slight increases in selfing rate dramatically increase the probability of transfer (Table 4). This result reflects the findings of *Brandvain et al.* (2007) across plant taxa, where strongly selfing groups were much more likely to transfer mitochondrial genes to their nuclei than outcrossing species or plants with mixed mating systems.

*Interactions among parameters*

From the total of fifty-six interaction terms (15 two-way + 20 three-way + 15 four-way + 6 five-way = 56 total interactions) – we discuss a sub-sample illustrative of the overall trends. In Electronic Appendix 2, we present all pairwise interactions between population size and other parameters. In investigating higher order interactions, we restrict our analysis to large populations (\(N = 1,000\)).

*Interactions with population size:* In large populations, the effect of selection favoring transfer is more pronounced than it is in small populations (Electronic Appendix 2. Table
Similarly, the influence of selfing rate on the probability of transfer is more pronounced in large populations (Electronic Appendix 2, Table 3). By contrast, the influence of mutation rate on the probability of functional transfer is much the same across population sizes (Electronic Appendix 2, Tables 4 and 5, respectively), suggesting no interaction between these parameters.

*Interactions between selfing rate and homozygote fitness:* In large populations (N = 1,000), the influence of selfing rate on the probability of transfer depends on homozygote fitness. When transfer is neutral (i.e. \( w_{m11} = 1.00 \)), odds of transfer steadily decline with increased selfing rates. This pattern is reversed when transfer is adaptive (\( w_{m11} =1.05 \) or \( w_{m11} = 1.10 \)). In these cases, an initial decrease in odds of transfer with slight selfing rapidly disappears, making way for increased odds of transfer with extreme selfing rates.

The increase in odds of transfer with selfing begins at different threshold selfing values depending on homozygote fitness. When homozygote fitness is 1.05, selfing rates \( \geq 0.8 \) have better odds of transfer than obligate outcrossers. When transfer is strongly advantageous (\( w_{m11}=1.10 \)) the increase in odds of transfer with selfing rate begins at lower selfing rates near 0.6. In either case, the probability of transfer greatly increases with selfing rate once the threshold selfing rate is reached (Figure 3).

*Interactions between selfing rate and mutation rates:* Above, we showed that increased selfing decreases the probability of transfer under neutrality. Here we show that this result depends on the *relative rate* of nuclear to mitochondrial mutation. We limit our discussion to large populations (N = 1,000) with no benefit to transfer (\( w_{m11}=1.00 \)).
When the nuclear mutation rate is less than the mitochondrial mutation rate (i.e. $\mu_n << \mu_m$), increasing the selfing rate decreases the odds of transfer. On the other hand, when the nuclear and mitochondrial mutation rates are equal, or when nuclear mutation rates are greater than mitochondrial mutation rates there is no strong association between odds of transfer and selfing rates. This result is consistent across heterozygote fitness, and is thus unlikely due to dominance effects (Table 5).

**DISCUSSION AND CONCLUSIONS**

The transfer of mitochondrial genes to the nucleus has been “*a key step in stabilizing the transition from an autonomous endosymbiont to a host-dependent mitochondrion*” (LYNCH 2007, page 308). Despite the many theories presented to explain this phenomenon, its evolution is not well understood. We explored the interaction of key population-genetic parameters (selection, dominance, mutation rates, and population size) with the rate of self-fertilization to influence the rate and probability of functional transfer of mitochondrial genes to the nucleus. Here, we address points that are not addressed by our model, outline our major findings and relate these findings to the existing literature.

*Input bias and the possibility of functional transfer:* Our model does not address the input of genes to the nucleus or mechanistic factors that may allow or prevent the functional transfer of mitochondrial genes to the nucleus. Nevertheless, these factors could influence phylogenetic patterns. SHEPPARD et al. (2008) have shown that chloroplast genes are more likely join the nucleus via microgametes than macrogametes. This finding
does not influence the input of selfing versus outcrossing species, but may severely reduce the input of endosymbiont genes to the nuclei of asexually reproducing plants. Elucidating other molecular mechanisms, such as the rate of reverse transcription, which could bias the input of mitochondrial genes to the nucleus will further refine our understanding of this process and distribution of transfer events.

A great deal of research has addressed properties that can influence the functional transfer of specific genes from the mitochondria to the nucleus (Daley and Whelan 2005). For example, the hydrophobic hypothesis proposes that hydrophobic proteins cannot easily cross membrane boundaries and are therefore unlikely to be functionally transferred (VON HEIJNE 1986), while the redox-control hypothesis argues that certain genes expressed in the electron transport chain need be expressed within their organelles to maintain redox balance (ALLEN 1993; RACE et al. 1999). Both hypotheses provide important clues as to which genes are likely to be retained in organelles. Our understanding of which genes relocate to the nucleus requires additional information regarding which genes may increase fitness when encoded in the nucleus rather than in an organelle.

Without a direct fitness benefit to gene transfer, selfing does not increase the probability of gene transfer: BRANDVAIN et al, (2007) showed that clonal and selfing plant taxa transferred more mitochondrial genes to their nuclei than outcrossing taxa or those with mixed mating systems. Our model shows that this pattern cannot be due to neutral evolutionary processes. When there is no advantage to transfer (i.e., \( w_{11} = 1.00 \)), the probability of transfer does not increase with selfing rate in any combination of parameters investigated. Thus, the positive association between selfing and transfer
cannot be explained with strict neutrality, but is consistent with the hypothesis of positive
selection (We did not examine the possibility that there is a mechanistic bias favoring the
input of mitochondrial genes to the nucleus in selfing lineages; its existence is an
empirical matter, which is not yet supported by any existing data.)

When transfer is neutral, and nuclear mutation rates are smaller than
mitochondrial mutation rates, mutational pressure drives the transfer mitochondrial
genomes to the nucleus. Although animal mitochondria contain tRNAs and rRNAs, these
mitochonrdria are notable for the few protein coding genes (12-13) they contain, relative
to the greater number (30-40) found in those of plants. This pattern is particularly
extraordinary because the non-standard genetic code of animal mitochondria has
precluded the recent transfer of mitochondrial genes to the nucleus, while the process of
gene transfer is ongoing in plants (ADAMS and PALMER 2003). We suggest that this
disparity can be largely explained by the relative mutation rates of plant and animal
genomes. LYNCH et al. (2006, Table 1) have shown that in animals $\mu_m/\mu_n$ ranges from
8.84 in bilaterian invertebrates to 24.68 in reptiles/amphibians, while in plants $\mu_m/\mu_n$ is
approximately 0.05, three or four orders of magnitude smaller. Assuming the value of
$\mu_m/\mu_n$ of extant animals reflect $\mu_m/\mu_n$ in the lineage leading to animals, which suffered
extreme losses of mitochondrial genes, the difference in the relative mutation rates
between plants and animals is thus consistent with, and may contribute to explaining, the
observed macro-evolutionary pattern of functional gene transfer. Although our model is
consistent with this pattern, there are numerous plausible alternative explanations. One
possible alternative is that the transfer of essential genes from the mitochondrial genome
to the nucleus, relaxes selection on modifiers of the mitochondrial mutation rate.
For neutral transfers, mutational pressure is enhanced by outcrossing and is diminished by frequent selfing. The stochastic results show a slight but significant linear decrease in the probability of transfer with increased selfing when transfer is neutral and $\mu_m/\mu_n >> 1$. In contrast the same conditions produce a nonlinear increase in time to commonness with increased selfing in the deterministic model: for selfing rates between 0 and 0.95, the time to commonness is relatively unaffected by selfing rate, but at extreme selfing rates in excess of 0.95, time to commonness becomes larger. The difference between these results suggests that stochastic processes are important to neutral transfer.

Thus, our results show that with mutational pressure and no other benefit to transfer, the transfer of mitochondrial genes to the nucleus is more likely in predominantly outcrossing species than in highly inbred taxa. Presumably, with outcrossing, functional nuclear alleles can migrate into cytotypes lacking functional mitochondrial alleles and thus rescue these genotypes providing a selective benefit for gene retention.

Elevated mitochondrial mutation rates increase the probability of mitochondrial to nuclear gene transfer. Although plant mitochondrial mutation rates are generally much smaller than those of animals, the rates vary widely across taxa (Mower et al. 2007; Cho et al. 2004; Palmer et al. 2000). If mitochondrial mutational pressure drives the functional transfer of mitochondrial genes to the nucleus, then plants with higher mitochondrial mutation rates are expected to have transferred more mitochondrial genes to their nuclei than plants with lower mitochondrial mutation rates. Existing data (Table
6) are consistent with this prediction. Although current data are clearly incomplete, there is a significant positive correlation between the mitochondrial mutation rate and the frequency of transfers (Spearman’s $\rho = 0.514$, $P = 0.029$; Kendall’s $\tau_a = 0.346$, Kendall’s $\tau_b = 0.397$, Kendall’s score = 53, $P = 0.037$). Although both selfing rate (Brandvain et al 2007) and mitochondrial mutation rate (above) are associated with greater frequencies of functional transfer, these two variables are uncorrelated (Spearman’s $\rho = 3.79$, $P = 0.181$, $N = 14$; Data from above and BRANDVAIN et al. 2007, S2) suggesting that each independently influences the probability of functional gene transfer.

When transfer is adaptive, selfing increases the probability of functional gene transfer. BRANDVAIN et al. (2007) found that selfing and clonal plants transfer functional mitochondrial genes to the nucleus more frequently than outcrossing plants. Our model shows that this pattern cannot arise under neutrality. Thus, it is likely that in extant plant lineages, the transfer of mitochondrial genes to the nucleus is an adaptive process. Although we examined a number of adaptive scenarios that facilitate transfer, we cannot propose a specific fitness advantage to such transfers. This is an empirical question and adaptive explanations must be examined on a case-by-case basis until a general pattern, if one exists, emerges from the data.

The positive relationship between selfing rate and the probability of adaptive transfer sheds light on the roles of linkage and recombination in the fixation of co-adapted gene combinations (TAKAHASI and TAJIMA 2005; PHILLIPS 1996). Coadaptation of mitochondrial and nuclear genes is well documented (RAND et al. 2004; SACKTON et al. 2003; RAND et al. 2006), and thus our results are likely to be broadly relevant to the
evolution of mitochondrial and nuclear genomes. Moreover, although most relevant data concerning the transfer of mitochondrial genes to the nucleus in plants has been exhausted in this and a previous paper, chloroplast genes also relocate to the nucleus, much of this transfer is recurrent (Martin et al. 1998; 2002), and there is some evidence for genetic interaction between chloroplast and nuclear genes (Grun 1976; Maroof et al. 1992). Thus, the transfer of chloroplast genes to the nucleus provides a unique opportunity for further tests of the epistatic theory of Wade and Goodnight (2006).

The role of gene interactions in the evolutionary process is an historically contentious issue (Coyne et al. 1997; 2000; Goodnight and Wade 2000; Lopez-Fanjul 1999; Wade and Goodnight 1998). Wright’s ‘shifting balance theory’ emphasizes the fixation of adaptive gene combinations in some subpopulations and the exportation of these adaptive combinations across the larger metapopulation by differential migration (Wade and Goodnight 1991). Goodnight (1987; 1988) has shown that fixing one background in an epistatic system ‘converts’ the segregating variation at another, interacting locus into additive variation, which is subsequently available for a response to selection.

In selfing or clonal organisms, each lineage acts as a subpopulation in which the genetic background is fixed, so that epistatic effects of nuclear genes appear additive and selectable when random drift changes cytoplasmic allele frequencies (Wade and Goodnight 2006). Our results and the observed pattern of a positive association between selfing/clonal reproduction and number of gene transfers (Brandvain et al. 2007) together suggest that these forces influence the functional transfer of mitochondrial genes to the nucleus. Moreover, the variation in mating systems among extant plant taxa and the
frequency of cyto-nuclear epistasis for fitness (e.g. GALLOWAY and FENSTER 1999; POLLAK 1991; SAMBATTI et al. 2008) provide fertile grounds for further tests of the role of selection on epistasis in subdivided populations in evolutionary change.
Acknowledgements:

This paper was inspired by an insightful discussion with MW Hahn, and has benefitted from discussions and comments from S Dickinson, MS Barker, LC Moyle, AO Richardson, D van Dyken, T Cruickshank, P Nista, P. Zee, D Drury, D. M. Rand and two anonymous reviewers. This work was made possible by support from the NIH training grant, Common Themes in Reproductive Diversity, and an NSF Predoctoral Fellowship to YB and NIH R01-GM084238 to MJW
APPENDIX 1

Matrices for the deterministic models

Vector of allele frequencies: $F = f_{m00}$

The fitness matrix: $\tilde{W} =
\begin{bmatrix}
\tilde{W}_{m11} & 0 & 0 & 0 & 0 & 0 \\
0 & \tilde{W}_{m10} & 0 & 0 & 0 & 0 \\
0 & 0 & \tilde{W}_{M00} & 0 & 0 & 0 \\
0 & 0 & 0 & \tilde{W}_{M10} & 0 & 0 \\
0 & 0 & 0 & 0 & \tilde{W}_{M00} & 0 \\
\end{bmatrix}$

The recombination matrix $R$: The rows and columns of the transition matrices (below) are labeled with the relevant genotypes. In the reproduction matrix ($R$), values in row $i$, column $j$ represent the frequency with which an individual of genotype $j$ parents an individual of genotype $i$.

\begin{eqnarray*}
m11 & m10 & m00 & M11 & M10 & M00 \\
m11 & S + (1 - S) \frac{f_1 + f_{\text{mu}}}{2} & (1 - S) \frac{f_0 + f_{\text{mu}}}{2} & 0 & (1 - S) \frac{f_{\text{mu}}}{2} & (1 - S) \frac{f_{\text{mu}}}{2} & 0 \\
m10 & \frac{S}{4} + (1 - S) \frac{f_1 + f_{\text{mu}}}{4} & S + (1 - S) \frac{f_0 + f_{\text{mu}}}{4} & (1 - S) \frac{f_{\text{mu}}}{4} & (1 - S) \frac{f_{\text{mu}}}{4} & (1 - S) \frac{f_{\text{mu}}}{4} & 0 \\
M11 & (1 - S) \frac{f_{\text{mu}}}{2} & (1 - S) \frac{f_{\text{mu}}}{2} & 0 & S + (1 - S) \frac{f_1 + f_{\text{mu}}}{2} & (1 - S) \frac{f_{\text{mu}}}{2} & (1 - S) \frac{f_{\text{mu}}}{2} \\
M10 & (1 - S) \frac{f_{\text{mu}}}{4} & (1 - S) \frac{f_{\text{mu}}}{4} & (1 - S) \frac{f_{\text{mu}}}{4} & S + (1 - S) \frac{f_1 + f_{\text{mu}}}{4} & \frac{S}{2} + (1 - S) \frac{f_1 + f_{\text{mu}}}{4} & \frac{S}{4} + (1 - S) \frac{f_1 + f_{\text{mu}}}{4} \\
M00 & 0 & (1 - S) \frac{f_{\text{mu}}}{2} & (1 - S) \frac{f_{\text{mu}}}{2} & 0 & (1 - S) \frac{f_1 + f_{\text{mu}}}{2} & S + (1 - S) \frac{f_1 + f_{\text{mu}}}{2} \\
\end{eqnarray*}
The mutation matrix $\mu$: In the mutation matrix ($\mu$), values in $ij$ represent the frequency with which a zygote of genotype $j$ mutates to genotype $i$.

$$
\mu = \begin{pmatrix}
(1 - \mu_n)^2 & 2\mu_n(1 - \mu_n) & \mu_n^2 & 0 & 0 & 0 \\
0 & 1 - \mu_n & \mu_n & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 \\
\mu_n(1 - \mu_n)^2 & \mu_n^2(1 - \mu_n) & \mu_n^2 & (1 - \mu_n)^2(1 - \mu_n) & (1 - \mu_n)^2\mu_n(1 - \mu_n) & \mu_n^2(1 - \mu_n) \\
0 & \mu_n(1 - \mu_n) & \mu_n & (1 - \mu_n)(1 - \mu_n) & \mu_n(1 - \mu_n) \\
0 & 0 & \mu_n & 0 & (1 - \mu_n) 
\end{pmatrix}
$$


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100: 581-586.


Table 1. Initial frequencies and fitnesses of all two-locus genotypes: The initial frequency of nuclear allele 1, $f_1$, equals one. The initial frequency of the nonfunctional nuclear allele, $f_0$, equals 0.05.

<table>
<thead>
<tr>
<th>Cyto-nuclear Genotype</th>
<th>Initial frequency</th>
<th>Fitness</th>
</tr>
</thead>
<tbody>
<tr>
<td>M11</td>
<td>$f_1^2 + Sf_1f_0$</td>
<td>$w_{M11} = 1.00$</td>
</tr>
<tr>
<td>M10</td>
<td>$2f_1f_0(1 - S)$</td>
<td>$w_{M10} = 1.00$</td>
</tr>
<tr>
<td>M00</td>
<td>$f_0^2 + Sf_1f_0$</td>
<td>$w_{M00} = 1.00$</td>
</tr>
<tr>
<td>m11</td>
<td>0</td>
<td>$1.00 \leq w_{m11} \leq w_{m10}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$w_{m10} \leq w_{m11}$</td>
</tr>
<tr>
<td>m10</td>
<td>0</td>
<td>$0.90 \leq w_{m10}$</td>
</tr>
<tr>
<td>m00</td>
<td>0</td>
<td>$w_{m00} = 0.00$</td>
</tr>
</tbody>
</table>
Table 2 – Inflection points describing results from deterministic models across mutation rates and homozygote fitness values are indicated by the subscript immediately following d. $d_{\text{min}}$ and $d_{\text{max}}$ correspond to $\frac{d^3y}{dx^3} = 0, \frac{d^4y}{dx^4} > 0$ and $\frac{d^3y}{dx^3} = 0, \frac{d^4y}{dx^4} < 0$, respectively. $w_{m10} = 1.00$ in all cases.

<table>
<thead>
<tr>
<th>$\mu_m$</th>
<th>$\mu_n$</th>
<th>$d_{1.05\text{min}}$</th>
<th>$d_{1.05\text{max}}$</th>
<th>$d_{1.10\text{min}}$</th>
<th>$d_{1.10\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^{-5}$</td>
<td>$10^{-5}$</td>
<td>$3.4 \times 10^4$</td>
<td>$7.0 \times 10^4$</td>
<td>$2.3 \times 10^4$</td>
<td>$4.2 \times 10^4$</td>
</tr>
<tr>
<td>$10^{-4}$</td>
<td>$10^{-4}$</td>
<td>$3.1 \times 10^4$</td>
<td>$3.1 \times 10^4$</td>
<td>$2.0 \times 10^4$</td>
<td>$1.6 \times 10^4$</td>
</tr>
<tr>
<td>$10^{-5}$</td>
<td>$10^{-5}$</td>
<td>$3.1 \times 10^5$</td>
<td>$2.3 \times 10^5$</td>
<td>$2.0 \times 10^5$</td>
<td>$1.0 \times 10^4$</td>
</tr>
<tr>
<td>$10^{-6}$</td>
<td>$10^{-6}$</td>
<td>$3.0 \times 10^6$</td>
<td>$2.1 \times 10^5$</td>
<td>$2.0 \times 10^6$</td>
<td>$9.1 \times 10^5$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$\mu_m = \mu_n$</th>
<th>$\mu_m &gt; \mu_n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^{-3}$</td>
<td>$10^{-4}$</td>
</tr>
<tr>
<td>$10^{-3}$</td>
<td>$10^{-5}$</td>
</tr>
<tr>
<td>$10^{-3}$</td>
<td>$10^{-6}$</td>
</tr>
<tr>
<td>$10^{-4}$</td>
<td>$10^{-5}$</td>
</tr>
<tr>
<td>$10^{-4}$</td>
<td>$10^{-6}$</td>
</tr>
<tr>
<td>$10^{-5}$</td>
<td>$10^{-6}$</td>
</tr>
</tbody>
</table>
Table 3: Effect of increasing m10 heterozygote fitness on the likelihood of functional transfer from the mitochondria to the nucleus. The odds ratio, OR, measures the likelihood of transfer relative to the case where \( w_{m10} \) is 0.90.

<table>
<thead>
<tr>
<th>( W_{m11} )</th>
<th>( W_{m10} )</th>
<th>OR</th>
<th>SE</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>0.95</td>
<td>1.03</td>
<td>1.05 ( \times 10^{-2} )</td>
<td>0.003</td>
</tr>
<tr>
<td>1.00</td>
<td>1.00</td>
<td>1.10</td>
<td>1.11 ( \times 10^{-2} )</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.05</td>
<td>0.95</td>
<td>1.04</td>
<td>7.89 ( \times 10^{-3} )</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.05</td>
<td>1.00</td>
<td>1.09</td>
<td>8.19 ( \times 10^{-3} )</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.05</td>
<td>1.05</td>
<td>1.16</td>
<td>8.57 ( \times 10^{-3} )</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.10</td>
<td>0.95</td>
<td>1.05</td>
<td>7.12 ( \times 10^{-3} )</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.10</td>
<td>1.00</td>
<td>1.09</td>
<td>7.34 ( \times 10^{-3} )</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.10</td>
<td>1.05</td>
<td>1.15</td>
<td>7.67 ( \times 10^{-3} )</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.10</td>
<td>1.10</td>
<td>1.23</td>
<td>1.23 ( \times 10^{-3} )</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 4. The nonlinear effect of increased selfing on the probability of functional gene transfer.

<table>
<thead>
<tr>
<th>Selfing Rate</th>
<th>OR</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.90</td>
<td>6.93E-3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.2</td>
<td>0.95</td>
<td>7.22E-3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.3</td>
<td>0.93</td>
<td>7.11E-3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.4</td>
<td>0.95</td>
<td>7.27E-3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.5</td>
<td>1.00</td>
<td>7.55E-3</td>
<td>0.795</td>
</tr>
<tr>
<td>0.6</td>
<td>0.98</td>
<td>7.42E-3</td>
<td>0.007</td>
</tr>
<tr>
<td>0.7</td>
<td>1.07</td>
<td>7.95E-3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.8</td>
<td>1.24</td>
<td>8.93E-3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.9</td>
<td>1.64</td>
<td>1.13E-2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.0</td>
<td>2.14</td>
<td>1.41E-2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 5: Effect of relative mutation rate on the probability of neutral ($w_{m11} = 1.00$) functional transfer of mitochondrial genes to the nucleus in large populations ($N = 1,000$), across heterozygote fitnesses. † $p > 0.10$, * $p < 0.10$, ** $p < 0.05$, *** $p < 0.001$

**Odds Ratio as a linear function of selfing rate**

<table>
<thead>
<tr>
<th>Relative mutation rate</th>
<th>$w_{m10}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>$\mu_n &gt;&gt; \mu_m$</td>
<td>0.98†</td>
</tr>
<tr>
<td>$\mu_n = \mu_m$</td>
<td>0.90†</td>
</tr>
<tr>
<td>$\mu_n &lt;&lt; \mu_m$</td>
<td>0.60***</td>
</tr>
</tbody>
</table>
Table 6) Relationship between mitochondrial mutation rate ($\mu_m$) and the number of mitochondrial genes independently transferred to the nucleus. Spearman’s $\rho = 0.514$, $p = 0.029$. Kendall’s $\tau_a = 0.346$, Kendall’s $\tau_b = 0.397$, Kendall’s score = 53, $p = 0.037$. *$\mu_m$ reported in synonymous substitutions per site per billion years, from MOWER et al. (2007). †Independent transfers reported as the number of inferred phylogenetically independent losses of essential mitochondrial ribosomal protein and $sdh$ genes, from ADAMS et al. 2002.

<table>
<thead>
<tr>
<th>Genus</th>
<th>$\mu_m$</th>
<th>Independent transfers†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platanus</td>
<td>0.08</td>
<td>0</td>
</tr>
<tr>
<td>Liriodendron</td>
<td>0.09</td>
<td>0</td>
</tr>
<tr>
<td>Sambucus</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>Laurus</td>
<td>0.11</td>
<td>0</td>
</tr>
<tr>
<td>Nicotiana</td>
<td>0.19</td>
<td>2</td>
</tr>
<tr>
<td>Philodendron</td>
<td>0.19</td>
<td>2</td>
</tr>
<tr>
<td>Mahonia</td>
<td>0.23</td>
<td>0</td>
</tr>
<tr>
<td>Nymphaea</td>
<td>0.26</td>
<td>0</td>
</tr>
<tr>
<td>Nepenthes</td>
<td>0.29</td>
<td>0</td>
</tr>
<tr>
<td>Eichhornia</td>
<td>0.33</td>
<td>1</td>
</tr>
<tr>
<td>Piper</td>
<td>0.36</td>
<td>0</td>
</tr>
<tr>
<td>Daucus</td>
<td>0.38</td>
<td>5</td>
</tr>
<tr>
<td>Arabidopsis</td>
<td>0.56</td>
<td>0</td>
</tr>
<tr>
<td>Beta</td>
<td>0.56</td>
<td>3</td>
</tr>
<tr>
<td>Plant</td>
<td>Value</td>
<td>Frequency</td>
</tr>
<tr>
<td>-----------</td>
<td>-------</td>
<td>-----------</td>
</tr>
<tr>
<td><em>Stellaria</em></td>
<td>0.59</td>
<td>1</td>
</tr>
<tr>
<td><em>Oenothera</em></td>
<td>0.7</td>
<td>1</td>
</tr>
<tr>
<td><em>Erodium</em></td>
<td>0.79</td>
<td>12</td>
</tr>
<tr>
<td><em>Acorus</em></td>
<td>2.45</td>
<td>4</td>
</tr>
</tbody>
</table>
FIGURE LEGENDS:

Figure 1) Results of deterministic simulation model across mutation rates and fitnesses. A
\( \mu_n = 10^{-3} \gg \mu_m = 10^{-4} \). B, \( \mu_n = 10^{-4} = \mu_m = 10^{-4} \). C, \( \mu_n = 10^{-5} \ll \mu_m = 10^{-4} \). Homozygote
fitness, \( w_{m11} \), is given by symbols (•: \( w_{m11} = 1.00 \). No symbol: \( w_{m11} = 1.05 \). •: \( w_{m11} = 1.10 \)). Heterozygote fitness, \( w_{m10} \) is given by line color (–: \( w_{m10} = 0.90 \). –: \( w_{m10} = 0.95 \). –: \( w_{m10} = 1.00 \). –: \( w_{m10} = 1.05 \). –: \( w_{m10} = 1.10 \)).

Figure 2) Number of functional transfers of mitochondrial genes to the nucleus per 1,000
stochastic simulations. Here, we report results from large populations (N = 1,000) with
high mutation rates (\( \mu_n = 10^{-3} = \mu_m = 10^{-3} \)). Complete results, spanning all mutation rate
and population sizes examined, are presented in Electronic Appendix 1. Homozygote
fitness, \( w_{m11} \), is given by symbols (•: \( w_{m11} = 1.00 \). No symbol: \( w_{m11} = 1.05 \). •: \( w_{m11} = 1.10 \)). Heterozygote fitness, \( w_{m10} \) is given by line color (–: \( w_{m10} = 0.90 \). –: \( w_{m10} = 0.95 \). –: \( w_{m10} = 1.00 \). –: \( w_{m10} = 1.05 \). –: \( w_{m10} = 1.10 \)).

Figure 3) Effects of the interaction between selfing rate and homozygote fitness on the
probability of transfer in a large population (N = 1,000). Homozygote fitness, \( w_{m11} \), is
given by symbols (•: \( w_{m11} = 1.00 \). No symbol: \( w_{m11} = 1.05 \). •: \( w_{m11} = 1.10 \)). To enforce a
balanced design, analysis is limited to \( w_{m10} \leq 1.00 \).