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Using Numerical Simulation to Test the "Mutation-Count" Hypothesis

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Abstract

There is now abundant evidence that the continuous accumulation of deleterious mutations within natural populations poses a major problem for neo-Darwinian theory. It has been proposed that a viable evolutionary mechanism for halting the accumulation of deleterious mutations might arise if fitness depends primarily on an individual's "mutation-count". In this paper the hypothetical "mutation-count mechanism" (MCM) is tested using numerical simulation, to determine the viability of the hypothesis and to determine what biological factors affect the relative efficacy of this mechanism.

The MCM is shown to be very strong when given all the following un-natural conditions: all mutations have an equal effect, low environmental variance, and full truncation selection. Conversely, the MCM effect essentially disappears given any of the following natural conditions: asexual reproduction, or probability selection, or accumulating mutations having a natural distribution of fitness effects covering several orders of magnitude. Realistic levels of environmental variance can also abolish or greatly diminish the MCM effect.

Equal mutation effects when combined with partial truncation (quasi-truncation) can create a moderate MCM effect, but this disappears in the presence of less uniform mutation effects and reasonable levels of environmental variance.

MCM does not appear to occur under most biologically realistic conditions, and so is not a generally applicable evolutionary mechanism. MCM is not generally capable of stopping deleterious mutation accumulation in most natural populations.

Key words: mutation count mechanism, mutation accumulation, natural selection, neo-Darwinian theory, numerical simulation, Mendel's Accountant

Introduction

There is a significant body of literature, based upon both logic and mathematical modeling, which indicates that direct selection against deleterious mutations is insufficient to halt deleterious mutation accumulation [1–6]. Recent studies using numerical simulation have demonstrated this point [7–10]. A primary reason for this paradoxical mutation accumulation problem is that most deleterious

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mutations have extremely small biological effects, and thus are essentially invisible to selection [11–16].

It has been argued that this fundamental problem might be resolved by a form of selection not based directly upon the biological effect of each mutation, but instead upon an individual's "mutation count" [17–20]. We term this the "mutation-count mechanism" (MCM). In this paper we use numerical simulation to explore whether the MCM can realistically be expected to stop mutation accumulation. In a companion paper, numerical simulation is used to test a related concept, the synergistic epistasis hypothesis. That more elaborate hypothesis, also attempts to deal with the mutation accumulation problem by focusing selection specifically against high-mutation-count individuals [10].

The concept of selection based upon mutation count was first put forward by Muller [1], but has primarily been developed and expanded by Crow [17–20]. For decades, Crow, Muller, and others have acknowledged that deleterious mutations should logically accumulate continuously in populations, creating an evolutionary paradox. This is especially apparent when mutation rates are higher than one mutation per individual per generation [1]. Even when mutation rates are well below one per individual per generation, Ohta and others [11–16] have shown that most mutations have such small biological effects that they must be "nearly neutral" (effectively neutral), and must routinely escape the influence of selection, leading to continuous accumulation. The problem of continuous accumulation of deleterious mutations creates an evolutionary paradox, wherein populations should logically degenerate continuously, leading inevitably to extinction [1–6].

The idea of selection based upon an individual's mutation count was developed to address this theoretical problem of continuous genetic degeneration. The concept is that, when mutations accumulate to significant levels within a population, some individuals will have substantially more mutations than others due to random statistical fluctuations. If selection is strongly focused against those "high mutation count" individuals, elimination of single individuals might systematically eliminate proportionately more mutations. All this might be feasible if there were a strong correlation between mutation count and phenotypic fitness. Given a strong correlation, the MCM might progressively slow mutation accumulation and eventually even stop it. In such a case, the mean mutation count per individual would increase up to a maximum and then plateau, and mean fitness would cease its decline.

Numerical simulations using biologically reasonable parameters have consistently failed to show any evidence of the MCM, when using natural mutation distributions [8, 9]. This is most readily seen by plotting mean mutation count per individual over time. Using natural mutation distributions (wherein mutational effects vary over a wide range), the mutation count per individual consistently

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increases over time in a linear manner. This is seen even given intense selection, large populations, and many generations. In such experiments, no stabilization of mutation count is observed, and fitness declines continuously. This is because individuals are being selected based upon phenotypic fitness, as in nature, not based upon a contrived parameter such as an individual's "mutation count". Under realistic conditions, phenotypic fitness should have a weak correlation to mutation count within a natural population. Random sampling of gametes from within the same breeding population will have a strong statistical tendency toward producing similar mutation counts among all the progeny. Individual mutation counts will consistently track closely the population's mean mutation count. Not only will all individuals have approximately the same mutation count, the vast majority of the mutations within any individual will be nearly-neutral. Any meaningful genetic differences between individuals will be due to relatively few higher-impact mutations. These non-trivial mutations should strongly dominate the selection process, largely negating any correlation between an individual's mutation count and that individual's fitness. The correlation between an individual's mutation count and total fitness should logically be weak in most biological situations. This is exactly what is seen in careful numerical simulations; deleterious mutations invariably increase continuously at a constant rate.

Because the MCM hypothesis is a primary rationale for discounting pervasive genetic degeneration in nature, we desired to more carefully explore experimentally the potential for MCM using numerical simulation. For this purpose we employed the numerical forward-time population genetics program, *Mendel's Accountant* [7]. We modified this program so that selection could be based directly upon an individual's mutation count. This was achieved by specifying that all deleterious mutations have exactly the same fitness effect. The result is that an individual's reduction in genotypic fitness can correlate perfectly with its deleterious mutation count. This provided us with a research tool for evaluating the potential of MCM and allowed us to study various factors that affect the efficacy of this mechanism.

Methods

We apply the program *Mendel's Accountant* [7] (henceforth, 'MENDEL') to study the influence of MCM on mutation accumulation and genetic degeneration. This program was designed to study mutation accumulation [8–10], and we believe it is the first biologically-realistic population genetics program [7–10].

It is known that mutation accumulation is affected by many parameters. No set of equations solvable by hand can simultaneously account for all these interacting factors without introducing major simplifying assumptions. Of course, this limits

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both the scope and generality of such analyses. There is enormous biological complexity inherent in the mutation/selection process, especially when it is considered at the level of the whole genome and the whole population. Therefore it cannot be assumed that traditional analytical approaches are adequate for studying the consequences of hypotheses such as MCM. However, thanks to modern advances in scientific computing, complex systems of this type can now be analyzed reliably using numerical simulation. MENDEL tracks a complete biological system, starting with individual mutations, mutation-mutation interactions, linkage blocks, chromosomes, genotypes, phenotypes, mating/recombination events, sub-populations, and whole populations. Using MENDEL, all the primary known parameters that affect the selection/mutation process are accounted for, and can be specified by the program user, and so the computational processing can be faithful to our understanding of how genetic systems operate.

MENDEL can incorporate beneficial mutations, but for the sake of clarity in this paper we include only deleterious mutations. Except where indicated, we use MENDEL's human default parameters, as might reflect a small human population after a population bottleneck, with very intense selection (67% of progeny selected away every generation). Unless otherwise indicated, the most fundamental parameters were as follows: ploidy = diploid; reproduction = sexual; mating = random; linkage = dynamic recombination; new mutations per individual = 10; offspring per female = 6; mode of combining mutation effects = additive; population size = 1000; generations = 500; gene expression = co-dominance; fitness heritability = 1.0.

In these experiments we sometimes used "partial truncation", where selection was intermediate between full truncation selection and full probability selection. Mendel allows the user to specify the degree of partial truncation, with 0.1 specifying 10% truncation and 90% probability selection, while 0.5 specifies 50% truncation and 50% probability selection.

When either truncation or partial truncation selection are employed in our simulations, we have seen that it can result in un-naturally narrow genetic variance, and since we normally scale environmental variance to genetic variance (to specify a given heritability), this can result in a population that has an unreasonable narrow range of phenotypic variance. For this reason we established a non-scaling noise parameter where we can specify a minimal level of phenotypic variance, by adding some non-scaling environmental variance, to generate a reasonably heterogeneous phenotypic population even under truncation selection. In this study, whenever we select a heritability value less than one, we set the non-scaling noise at 0.05 (creating a minimum standard deviation of 0.05 for phenotypic fitness).

We begin by modeling the MCM using idealized conditions for optimal selection efficiency, and then investigate MCM in more depth by introducing more and more elements of realism.

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Results

Our previous studies have clearly shown that given a natural distribution of mutational effects, mutations will accumulate continuously and at a constant rate [7–10]. Therefore, we already knew at the on-set of this research that one essential requirement for activation of MCM is some type of very narrow distribution of mutation fitness effects. For this reason all of the experiments done in this study employed either uniform mutations affects, or a relatively narrow range of fitness effects. This makes these experiments generally unrealistic biologically — yet we needed to make this concession to the MCM hypothesis in order to examine it more closely.

We first examined the MCM using highly idealized conditions. We caused all mutations to affect fitness in an equally deleterious way (each mutation, when in the homozygous form, reduced fitness by 0.001, relative to a reference genotype with a fitness of 1.0). We combined the fitness effects of such mutations additively within individuals. In this way we created a perfect correlation between genotypic fitness reduction and the individual's mutation count. We then applied zero environmental variation (heritability = 1.0), such that phenotypic fitness and genotypic fitness were identical. We then applied artificial truncation (wherein reproduction by a given individual depends exclusively on whether its phenotypic fitness is greater than an arbitrary fitness threshold).

Under these highly artificial conditions we found that MCM was indeed able to very effectively halt both mutation accumulation and fitness decline, as seen in Figure 1. However, using all the same parameters, but suspending sexual recombination (as would apply to any asexual species), completely abolished the MCM effect (Figure 1). Mutation accumulation and fitness decline were both perfectly linear without sexual recombination. Likewise, we found that using the original parameter settings and simply switching to probability selection essentially abolished the MCM effect (Figure 1), except as the population approached zero mean fitness (extinction). This extinction-related MCM effect must be seen as an artifact. As a population approaches a zero mean fitness, mutational load is so high that many individuals have a fitness of zero or less. These individuals are automatically and unconditionally removed from the population, forcing the population from probability selection into an artificially-induced form of truncation selection. However, in the natural world, a population would normally go extinct long before a large fraction of that population had zero biological functionality (for many reasons, including fertility decline and population collapse). Thus this type of MCM effect near the very end of our runs, whenever probability selection is in effect, must be viewed as an artifact of the simulation process which allows mean fitness to approach zero. Apart from this extinction-induced truncation phenomenon, we consistently see that mutation accumulation is essentially linear,

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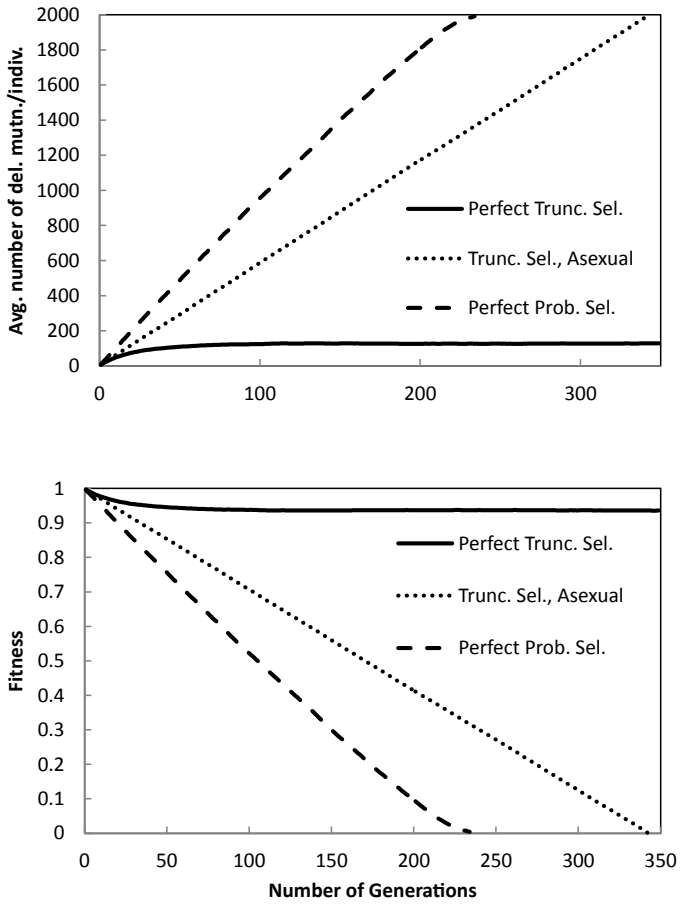

Fig. 1. Mean mutation accumulation per individual (top) and fitness history (bottom) for three experiments. Phenotypic fitness depended solely upon mutation count, that is, mutations all had the same effect (-0.001), and no environmental noise was added. Selection modes were: a) perfect truncation selection; b) perfect probability selection, and truncation selection without sexual recombination. Mutation count and fitness stabilized quickly when truncation selection was applied, due to the MCM effect. Either probability selection or asexual reproduction abolished the MCM effect.

even given idealized conditions, whenever probability selection is employed. In summary, Figure 1 shows us that the MCM can be effective, given equal mutation effects, zero environmental variance, and truncation selection. However, even with all mutation effects being equal, the MCM effect disappears whenever there is either asexual reproduction or probability selection.

We next examined the effect of partial truncation and environmental variance. We repeated the idealized experiment as described above with all mutations being equal, but instead employed partial truncation. We then did a series of runs where we studied the effect of environmental variance, and let the runs go longer (1000

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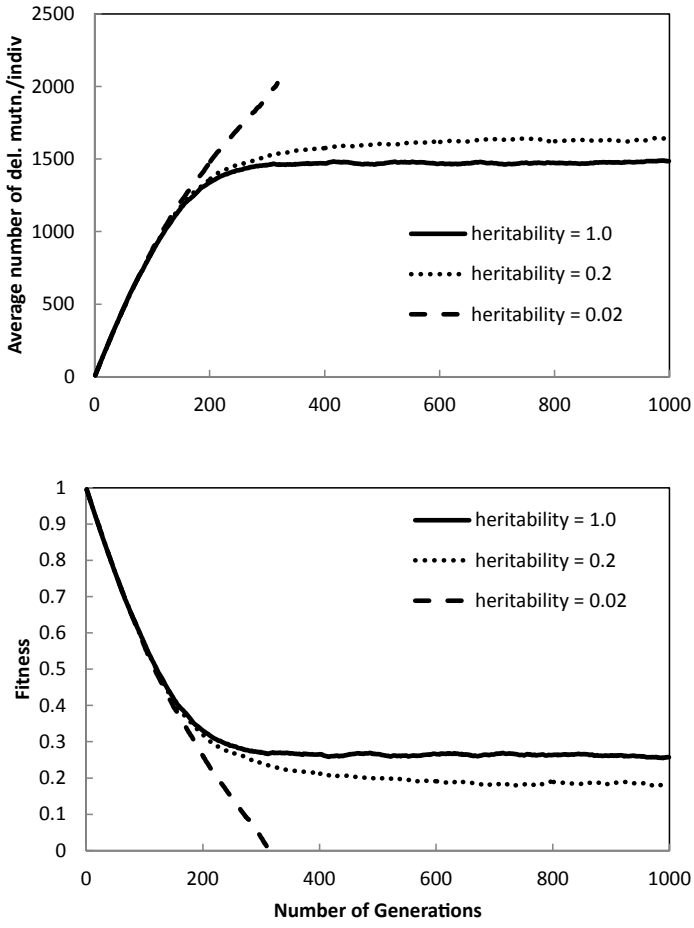

Fig. 2. Mean mutation accumulation per individual (top) and fitness history (bottom) for three experiments involving partial truncation (0.5) with varying amounts of environmental variance: zero environmental variance (heritability = 1.00), low environmental variance (heritability = 0.2), and high environmental variance (heritability = 0.02).

generations). Figure 2 shows that partial truncation (set at 0.5 – a selection mode halfway between perfect truncation and perfect probability selection), when combined with zero environmental variance, still produced a delayed, but still strong MCM effect. We then did experiments that added a low level of environmental variance and a high level of environmental variance. When we combine partial truncation with a low level of environmental noise (fitness heritability = 0.2), we saw that the MCM effect became somewhat weaker (Figure 2). When we combined partial truncation with a high level of environmental noise (fitness heritability = 0.02), we saw that the MCM effect was greatly reduced, becoming insufficient to prevent extinction under those settings (Figure 2).

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Numerical simulations as described above, revealed evidence for a very significant MCM effect when mutation effects were perfectly uniform, and when selection was either full truncation or strong partial truncation. Addition of substantial environmental variation could greatly reduce the MCM, but did not entirely negate it. We therefore wished to examine how a moderate amount of variation in mutation effects might influence the efficacy of the MCM. Instead of using entirely uniform mutation fitness effects, we truncated our normal Weibull distribution of mutational effects so that the smallest mutational effect reduced fitness one part in 100,000 (3000-fold less than the Mendel default value). We then tested the four selection modes: full truncation, strong partial truncation (0.5), weak partial truncation (0.1), and probability selection. We let these experiments run 10,000 generations, introducing a modest amount of environmental variance (heritability = 0.2). The results of these experiments are shown in Figure 3. Given

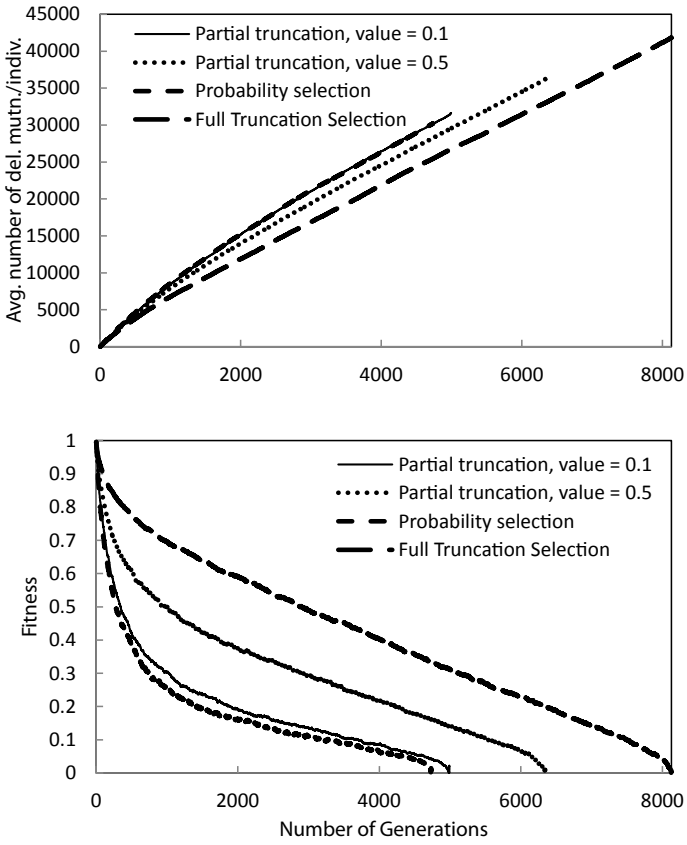

Fig. 3. Mean mutation accumulation per individual (top) and fitness history (bottom) for four experiments involving four modes of selection, given modest a amount of environmental variation (heritability = 0.2), and a relatively narrow range of fitness effects (lower limit = .00001). Selection modes were: full truncation, strong partial truncation selection (0.5), weak truncation selection (0.10), and probability selection.

these very favorable parameter settings, selection effectively removed all mutations with fitness effects of 0.001 or more (data not shown), and also removed most mutations with fitness effects between 0.0001 and 0.001. Therefore the accumulating mutations in these experiments were primarily in the range of 0.00001 to 0.0001 (varying across just over one order of magnitude). Despite this relatively narrow range of fitness effects, mutation accumulation eventually became essentially linear — regardless of whether selection mode was truncation, strong partial truncation (0.5), weak partial truncation (0.1), or probability selection. In the same way, fitness decline also became essentially linear regardless of selection mode, until population colapse occurred (mutational meltdown), as zero mean fitness was approached.

Discussion

Crow [19] recognized that if the deleterious mutation rate approached even one per generation, selective removal would fail and then de-evolution would logically result. Trying to escape this problem, he went back to the logic of Muller [1]. To quote Crow [19], "There is a way out, however. In stating his genetic death principle, Muller stated, 'For each mutation, then, a genetic death — except in so far as, by judicious choosing, several mutations may be picked off in the same victim.' Thus, natural selection… can indeed pick off several mutations at once…".

This is the essence of the mutation count mechanism — selecting away the highest mutation-count individuals by "judicious choosing", such that one death can remove more than one deleterious mutation. Our numerical simulations vividly illustrate the power of the MCM mechanism under ideal conditions (Figure 1). When all deleterious mutations have equal fitness effects, with no environmental variance, and with artificial truncation selection, mutation accumulation can be halted in very few generations.

Crow goes on to say "…such an efficient way of removal of mutations at small cost is strictly a consequence of sexual reproduction. An asexual species must either have a much lower mutation rate or suffer a large number of genetic deaths." Our numerical simulations also vividly confirm Crow's second assertion. Given the same idealized conditions as produced extremely effective halting of mutation accumulation, but excluding sexual recombination, the MCM effect vanishes completely (Figure 1). Genetic degeneration progresses like clockwork when we model asexual species, even given equal mutation effects, no environmental variance, and full truncation selection. Therefore the MCM mechanism does not appear to apply to dandelions, viruses, most bacteria, and innumerable other microbes. This means that the MCM mechanism is not generically applicable in the biological realm, and cannot be a generalized solution to the problem of

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mutation accumulation. The balance of this study has focused on populations having regular sexual recombination.

Even given normal sexual recombination combined with uniform mutation effects and zero environmental noise, the MCM effect essentially disappears given natural probability selection (Figure 1). It is widely understood that probability selection is what is generally happening in nature. Truncation selection is the type of artificial selection employed consciously by plant and animal breeders, and is not generally applicable to natural populations (truncation selection seems to primarily be invoked for natural populations only when the MCM is deemed desirable). However, it is significant to note that given uniform mutation effects and probability selection, as the population approaches zero mean fitness (extinction), we often observe clear evidence of the MCM effect, and this can slow or even stop mutation accumulation. This effect is weakly evident in Figure 2. But this special phenomenon actually helps prove the point, because what is happening as the population approaches extinction is that selection is forced from probability selection into a type of truncation selection. This actually helps demonstrate that some form of truncation is required to activate the MCM. In this particular case, as the population's mean fitness approaches zero, many individuals have a fitness of zero or less, and they are hence unconditionally removed from the population (truncation).

When selection regimes are employed that are intermediate between probability selection and truncation selection (partial truncation), with mutation effects still being equal and with no environmental variance, there is still a strong MCM effect — which can either slow or halt mutation accumulation (Figure 2). Low levels of environmental variation can interfere with the MCM effect under partial truncation, but cannot by itself negate it (Figure 2). However, higher levels of environmental variation can strongly interfere with the MCM effect (Figure 2), most especially in the case of full truncation selection (not shown).

Although it is instructive to model uniform mutation effects on fitness, we know that mutation fitness effects are never uniform, and are actually extremely variable in all living systems. Therefore we tested how effective the MCM might be, given a distribution of mutation effects which was intermediate between a totally uniform fitness effect and a realistic distribution for higher organisms. We did this by doing experiments using a Weibull distribution of mutation fitness effects having a higher than normal minimal fitness effect (.00001). This is 3,000 times greater than what we consider reasonable (i.e., the inverse of the functional genome size). In a large genome, there should be many mutation effects smaller than one is a million or even one in a billion. Even in free-living bacteria, deleterious mutation effects should minimally range down to .00001. We did a series of experiments using this more limited range of mutation effects. Given this distribution, the

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mutations that were accumulating only ranged from .001 to .00001 (just one to two orders of magnitude). We found that even given this relatively narrow range of accumulating fitness effects, mutation accumulation and fitness decline could not be halted, even under full truncation selection (Figure 3). Some non-linearity of mutation accumulation and fitness decline is evident early in these runs, but in all four experiments these rates eventually became very linear. Mutation accumulation and fitness decline then progressed at constant rates all the way to population collapse just prior to extinction, regardless of whether selection was full truncation, strong truncation, weak truncation, or probability selection. The selection mode merely affected the time to extinction (Figure 3).

We also experimented with an even narrower Weibull mutation distribution, with a lower limit of .001 (data not shown). When we combined this distribution with partial truncation selection (0.1), low environmental variance (heritability = 0.2), and a high mutation rate (10) the population went to extinction very rapidly, due to the high mean mutation effect. However if the mutation rate was reduced to 5, then there was sufficient time for the MCM mechanism to operate, and the population stabilized prior to extinction. This is hardly surprising when we consider that under those favorable conditions, the selection threshold was below .001, making the range of accumulation mutations extremely narrow (less than one order of magnitude). Because high-impact deleterious mutations (i.e., with fitness effects above .001) are rare, and because the few that do arise are rapidly removed from the population, the mutation accumulation problem is largely confined to low-impact mutations. To the extent that we can define conditions where there are no low-impact mutations, the mutation accumulation problem largely goes away. However, this is not realistic, especially for organisms with large functional genomes, where most mutations should have extremely subtle effects.

We believe that the lower limit of mutation effects for a given species can reasonably be approximated to be one over the functional genome size. In this light, a viroid might reasonably have mutation fitness effects that only range down to .001, and a typical virus might reasonably have fitness effects that only range down to .0001. Extremely small genomes of this type might reasonably be subject to the MCM — except for two problems. Firstly, most of these tiny genomes lack sexual recombination, and secondly such organisms should normally be subject to probability selection. Either of these is sufficient to negate the MCM effect. Indeed, even when we model the influenza virus (10,000 bp), which does have some limited recombination, the MCM effect is very weak. In such a case the mutation count increase is not initially strictly linear, yet mutation accumulation is not halted (data not shown). When we model genomes that would reflect any free-living organism (genomes of 10^6 bp or above), under all reasonable parameters settings, MCM very consistently fails and mutation accumulation is linear.

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A possible objection to our methodology might involve the artificiality of defining certain nucleotides to be "mutant", since it might be argued from an evolutionary point of view that *all* nucleotides arose as mutations. This line of thinking would suggest that any hypothetical selection mechanism based upon "mutation count" is inherently contrived and artificial. This objection is reasonable; however it must be addressed to those who developed the MCM model in the first place. We are merely testing the viability of that concept. The MCM hypothesis obviously rests entirely on the idea that individuals within a population can actually have knowable and meaningful differences in their "mutation counts". On a practical level we have simulated this by assuming a genetically uniform population (as mighty arise after an extreme bottleneck), with all individuals initially having the same genotype and the same relative fitness of 1.0. This starting reference genotype then serves as our basis for defining all "new" mutations and for tracking each individual's subsequent "mutation count". All new mutations represent deviations from the starting reference genotype.

Careful numerical simulation reveals that the MCM hypothesis has very limited power to explain how deleterious mutation accumulation can be halted in natural populations. The mechanism works very well under highly unrealistic conditions, but fails when realistic parameters are applied. Previous numerical simulation studies have already clearly demonstrated that mean mutation count per individual consistently increases linearly over time [8, 9], given realistic parameter settings. Whenever there is a realistic distribution of mutation effects, even when all other relevant parameters are optimized, there is no stabilization of mutation count or fitness, indicating that meaningful selection against higher mutation-count individuals is not happening. We conclude that the MCM is not generally operational.

The primary reason MCM fails is because in real populations the distribution of deleterious mutational effects is never uniform, but must vary over many orders of magnitude. Deleterious mutation fitness effects should range from negative one (lethal), down to parts per million or even parts per billion. Therefore there must be a vanishingly small correlation between phenotypic fitness and actual mutation count. This means there can be no mechanism whereby natural selection can do any "judicious choosing" to remove individuals with slightly higher mutation counts, as required by Muller [21] and Crow [19, 22].

In this paper, we effectively falsify the general MCM hypothesis. In a companion paper [10], we falsify the synergistic epistasis hypothesis, which is a more elaborate model, but also employs the concept of focusing selection against high mutation-count individuals. These two hypotheses have been used for several decades, to try to dismiss the mutation accumulation problem. The falsification of both hypotheses leaves modern genetic theory without any credible mechanism that might halt genetic degeneration within natural populations. This strongly

suggests there is a very fundamental flaw in our current understanding of theoretical genetics.

Addendum — *Since the finalization of this chapter, a significant new paper has been published. See: Sanford, J. & Nelson, C. (2012). The Next Step in Understanding Population Dynamics: Comprehensive Numerical Simulation, Studies in Population Genetics, in: M. Carmen Fusté (Ed.), ISBN: 978-953-51-0588-6, InTech, Available from: http://www.intechopen.com/books/studies-in-population-genetics/the-next-step-in-understanding-population-dynamics-comprehensive-numerical-simulation.*

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Acknowledgements

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