Imperfect DNA Repair and the Error Catastrophe

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In this Letter, we extend the semiconservative quasispecies equations to incorporate imperfect DNA lesion repair. We study the equilibrium behavior of this model in the limit of infinite sequence length and population size, using a single-fitness-peak landscape for which the master genome can sustain a finite number of lesions and remain viable. We provide a full analytical treatment of the problem, providing a general mathematical framework as well as the full solution for a particular class of fitness landscapes. Stochastic simulations using finite sequence lengths and populations agree well with the analytical results. Applications to biological systems are briefly discussed.

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The quasispecies model of genomic evolution has been used to study a number of problems in evolutionary dynamics. The central result of the theory is the existence of an upper mutational threshold beyond which natural selection can no longer occur. Below this threshold, a replicating population of genomes will eventually produce, over many generations, a “cloud” of closely related genomes clustered about one or a few fast replicating genomes. These “clouds” are termed quasispecies, and are characteristic of the evolutionary dynamics of many viruses, such as HIV.

Above the mutational threshold, natural selection can no longer act to localize the population about the fast replicating genomes, and delocalization occurs over the entire genome space. This localization to delocalization transition is known as the error catastrophe, and it corresponds to the disappearance of any viable strains in the population. The error catastrophe has been observed experimentally, and is believed to form the basis for a number of antiviral therapies.

Because the quasispecies equations were originally developed to deal with single-stranded RNA genomes, the model implicitly assumed a conservative replication mechanism, where the original genome is preserved. However, in order to apply the quasispecies model to living systems, whose genomes are DNA-based, it was necessary to develop the quasispecies equations for semiconservative replication. In semiconservative replication, a double-stranded genome unzips to form two strands, each of which is used as a template for the formation of two new complementary strands by the rules of Watson-Crick base pairing. The original genome is destroyed by this process, and because replication errors can happen in both daughter strand syntheses, it is possible that the two daughter genomes will differ from the parent.

Daughter strand synthesis from the parent template strand is not error-free. Therefore, living systems have evolved a host of mechanisms which correct base-pair mismatches during replication (some of these mechanisms are built into the DNA replicases themselves. Others, such as mismatch repair, occur immediately following daughter strand synthesis). Nevertheless, after replication has occurred, the daughter genomes may still contain mismatched base-pairs. These mismatches result in lesions along the DNA chain, which are repaired by DNA repair and maintenance enzymes present in the cell. Unlike repair that occurs during daughter strand synthesis, during lesion repair the parent and daughter strands are indistinguishable, and hence correct repair occurs with a probability of 1/2.

The semiconservative quasispecies equations were derived under the simplifying assumption that post-replication lesion repair is perfectly efficient. This Letter provides an extension of the original semiconservative quasispecies equations, to account for the case when lesion repair is imperfect (the full details of the solution presented in this work may be found in ). Such an extension is necessary for a proper modeling of many important biological processes. Indeed, imperfect lesion repair was first studied in in the context of modeling cancer. It may also be important for properly modeling asymmetric stem cell kinetics (the so-called “immortal strand” hypothesis).

When lesion repair is perfectly efficient, double-stranded DNA consists of two complementary, antiparallel strands. Each DNA genome is defined by the pair of strands \{σ, σ\} = \{σ, σ\}, where \(σ\) denotes the complement of \(σ\). If each base is drawn from an alphabet of size \(S\) (where \(S = 4\) for known terrestrial life), and if \(b_i\) denotes the complement of a base \(b_i\), then if \(σ = b_1 \ldots b_L\), we have, by the antiparallel nature of DNA, that \(σ = b_L \ldots b_1\).

The replication of a DNA genome \{σ, σ\} may be divided into three stages: (1) Strand separation, where the genome unzips to produce two parent strands, \(σ\) and \(σ\). (2) Daughter strand synthesis, where each parent strand serves as the template for the synthesis of a complementary daughter strand. (3) Lesion repair after cell division.

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We define \( y \) independent, and hence may be denoted by genomes \( \sigma, \sigma' \) where both \( \sigma \) and \( \sigma' \) are arbitrary. Following the derivation in [2], we obtain the quasispecies equations
\[
\frac{dx(\sigma, \sigma')}{dt} = -\left( k(\sigma, \sigma') + \bar{k}(t) \right)x(\sigma, \sigma') + \sum_{(\sigma'', \sigma''')} \kappa(\sigma'', \sigma''')x(\sigma'', \sigma''') \times 
\left[ p((\sigma'', \sigma'''), (\sigma, \sigma')) + p((\sigma'', \sigma'''), (\sigma, \sigma')) \right]
\]
(1)
where \( p((\sigma'', \sigma'''), (\sigma, \sigma')) \) denotes the probability that strand \( \sigma'' \), as part of genome \( \{\sigma'', \sigma''\} \), becomes genome \( \{\sigma, \sigma'\} \) after daughter strand synthesis and lesion repair. Here \( x(\sigma, \sigma') \) denotes the fraction of the population with genome \( \{\sigma, \sigma'\} \), and \( \bar{k}(t) \equiv \sum_{(\sigma, \sigma')} k(\sigma, \sigma')x(\sigma, \sigma') \) is the mean fitness of the population.

In the semiconservative quasispecies equations, the complementarity property allows one to convert the quasispecies dynamics over double-stranded genomes into an equivalent (and considerably simpler) dynamics over single strands [3]. With imperfect lesion repair, the lack of perfect correlation between the two strands in the genome makes a conversion to a single strand model impossible. Nevertheless, we can make an analogous transformation of the dynamics, from double-stranded genomes \( \{\sigma, \sigma'\} \) to ordered pairs of strands, \( (\sigma, \sigma') \), as follows: We define \( y(\sigma, \sigma') = y(\sigma', \sigma) = \frac{1}{2}x(\sigma, \sigma') \) if \( \sigma \neq \sigma' \), and \( y(\sigma, \sigma') = x(\sigma, \sigma') \). Also, we define \( \kappa(\sigma, \sigma') = \kappa(\sigma', \sigma) = \kappa(\sigma, \sigma') \). Finally, we define \( p((\sigma'', \sigma'''), (\sigma, \sigma')) \) to be the probability that \( \sigma'' \), as part of genome \( \{\sigma'', \sigma''\} \), becomes \( \sigma \), with daughter strand \( \sigma' \) (after daughter strand synthesis and lesion repair). Then it follows that
\[
p((\sigma'', \sigma'''), (\sigma, \sigma')) = \begin{cases} 
p((\sigma'', \sigma'''), (\sigma, \sigma')) + p((\sigma'', \sigma'''), (\sigma', \sigma')) & \text{if } \sigma \neq \sigma' \\
p((\sigma'', \sigma'''), (\sigma, \sigma')) & \text{if } \sigma = \sigma'
\end{cases}
\]
(2)
Using these definitions, it is possible to convert the quasispecies equations over the space of double-stranded genomes to the space of ordered sequence pairs. After some manipulation, the final result is,
\[
\frac{dy(\sigma, \sigma')}{dt} = -\left( \kappa(\sigma, \sigma') + \bar{k}(t) \right)y(\sigma, \sigma') + \sum_{(\sigma'', \sigma''')} \kappa(\sigma'', \sigma''')y(\sigma'', \sigma''') \times 
\left[ p((\sigma'', \sigma'''), (\sigma, \sigma')) + p((\sigma'', \sigma'''), (\sigma', \sigma')) \right]
\]
(3)
To determine \( p((\sigma'', \sigma'''), (\sigma, \sigma')) \), we introduce some additional definitions. Define \( \epsilon_\sigma \) to be the subsequence of bases in \( \sigma \) which are complementary with the corresponding bases in \( \sigma' \). That is, suppose \( \sigma = b_1 \ldots b_L \), and suppose for indices \( i_1 < i_2 < \ldots < i_k \) we have that \( b_{i_j} = b'_{L-i_j+1} \). Then \( \epsilon_\sigma = b_{i_1} \ldots b_{i_k} \). We also define \( \epsilon_{\sigma'} \) to be the subsequence of corresponding bases in \( \sigma' \), so that \( \epsilon_{\sigma'} = b'_{i_1} \ldots b'_{i_k} \).

Now, define \( \sigma_{NC} \) to be the subsequence of bases in \( \sigma \) which are not complementary with the corresponding bases in \( \sigma' \). That is, given the complementary indices \( i_1 < i_2 < \ldots < i_k \) defined above, let \( i'_1 < i'_2 < \ldots < i'_{L-k} \) be the remaining indices. Then \( \sigma_{NC} = b_{i_1} \ldots b_{i_{L-k}} \). We define \( \sigma'_{NC} \) to be the subsequence of corresponding bases in \( \sigma' \), so that \( \sigma'_{NC} = b'_{i'_1} \ldots b'_{i'_{L-k}} \).

We also assume that daughter strand synthesis during replication of the genome \( \{\sigma', \sigma''\} \) is characterized by a per base-pair mismatch probability of \( \epsilon(\sigma', \sigma'') \), and we define \( \epsilon(\sigma', \sigma'') = \epsilon(\sigma', \sigma'') = \epsilon(\sigma', \sigma'') \). Finally, we define \( \lambda \) to be the probability that a post-replicative lesion is repaired. This gives,
\[
p((\sigma'', \sigma'''), (\sigma, \sigma')) = \delta_{\sigma_{NC}, \sigma_{NC}} \left( \frac{\lambda \epsilon(\sigma'', \sigma''')}{2(S-1)} \right)^{D_H(\sigma''', \sigma') + \left( 1 - \epsilon(\sigma'', \sigma''') \right) \frac{1}{S-1} - \left( 1 - \frac{\lambda}{2} \right) \frac{D_H(\sigma', \sigma'') - D_H(\sigma', \sigma')}{S-1}}
\]
(4)
For \( \lambda = 1 \) (all lesions are repaired), our equations reduce to the ordinary semiconservative quasispecies equations [3].

In the simplest case, we assume that \( \epsilon(\sigma, \sigma') \) is genome-independent, and hence may be denoted by \( \epsilon \). We also define \( \mu = L \epsilon \), and consider the quasispecies dynamics at fixed \( \mu \) in the limit of \( L \to \infty \). Note that \( \lim_{L \to \infty} L \epsilon = \mu \) is \( e^{-\mu} \), so fixing \( \mu \) is equivalent to holding the correct daughter strand synthesis probability constant in the limit of infinite sequence length.
We now consider a generalized “single-fitness peak” landscape, characterized by a “master” genome \( \{\sigma_0, \bar{\sigma}_0\} \). A given genome \( \{\sigma, \sigma'\} \) is viable, with a first-order growth rate constant \( k > 1 \), if it is equal to the master genome, differing by at most \( l \) lesions. Otherwise, the genome is unviable, with a growth rate constant of 1.

In the limit of infinite sequence length, it may be shown that, with probability one, the Hamming distance between \( \sigma_0 \) and \( \bar{\sigma}_0 \) is infinite \[4\]. Therefore, we may regard \( (\sigma_0, \bar{\sigma}_0) \) and \( (\bar{\sigma}_0, \sigma_0) \) as infinitely separated in the sequence-pair space, and so, by an appropriate transformation of Eq. (3), we may consider the local dynamics about each sequence pair independently of the other. Thus, we consider the dynamics of the \( x(\sigma,\sigma') \) for two types of \( (\sigma, \sigma') \): First, we consider \( (\sigma, \sigma') \) such that \( D_H(\sigma, \sigma_0) \) and \( D_H(\sigma', \bar{\sigma}_0) \) are finite, and second, we consider \( (\sigma, \sigma') \) such that \( D_H(\sigma, \bar{\sigma}_0) \) and \( D_H(\sigma', \sigma_0) \) are finite. If \( (\sigma, \sigma') \) belongs to the first type of sequence pairs, then it is clear that \( (\sigma', \sigma) \) belongs to the second type. The symmetry of the landscape means that the dynamics about one sequence pair completely determines the dynamics about the other.

A given sequence pair \( (\sigma, \sigma') \) of the first type can be characterized by the four parameters \( l_C, l_L, l_R, \) and \( l_B \). The first parameter, \( l_C \), denotes the number of positions where \( \sigma, \sigma' \) are complementary, yet differ from the corresponding positions in \( \sigma_0, \bar{\sigma}_0 \), respectively. The second parameter, \( l_L \), denotes the number of positions where \( \sigma \) differs from \( \sigma_0 \), but the complementary positions in \( \sigma' \) are equal to the corresponding ones in \( \bar{\sigma}_0 \). The third parameter, \( l_R \), denotes the number of positions where \( \sigma \) is equal to the ones in \( \sigma_0 \), but the complementary positions in \( \sigma' \) differ from the corresponding ones in \( \bar{\sigma}_0 \). Finally, the fourth parameter, \( l_B \), denotes the number of positions where \( \sigma, \sigma' \) are not complementary, and also differ from the corresponding positions in \( \sigma_0 \) and \( \bar{\sigma}_0 \), respectively.

For our generalized single-fitness peak model, the fitness of a given sequence pair \( (\sigma, \sigma') \) of the first type is determined by \( l_C, l_L, l_R, l_B \), hence we may write \( \kappa_{(\sigma,\sigma')} = \kappa_{(l_C,l_L,l_R,l_B)} \). Specifically, \( \kappa_{(l_C,l_L,l_R,l_B)} = k > 1 \) if \( l_C = 0 \), and if \( l_L + l_R + l_B \leq \ell \). Otherwise, \( \kappa_{(l_C,l_L,l_R,l_B)} = 1 \).

We define \( z_{(l_C,l_L,l_R,l_B)} \) to be the total fraction of the population whose genomes are characterized by the parameters \( l_C, l_L, l_R, \) and \( l_B \). Note that we can consider these same parameters as characterizing genomes of the second type (i.e., defined by the ordered pair \( (\bar{\sigma}_0, \sigma_0) \)), and consider the corresponding population fraction \( \bar{z}_{(l_C,l_L,l_R,l_B)} \).

Because the fitness is only determined by \( l_C, l_L, l_R, \) and \( l_B \), it follows that we may presymmetrize our population and reexpress the quasispecies dynamics in terms of the \( z_{(l_C,l_L,l_R,l_B)} \). In [11], we show that the neglect of backmutations in the limit of infinite sequence length implies that we may set \( \bar{z}_{(l_C,l_L,l_R,l_B)} = 0 \) when \( l_B \neq 0 \), and when \( l_L, l_R \) are simultaneously nonzero. Therefore, the relevant equations are

\[
\begin{align*}
\frac{dz_{(l_C,0,0,0)}}{dt} &= -(\kappa_{(l_C,0,0,0)} + \bar{\kappa}(t))z_{(l_C,0,0,0)} + 2e^{-\mu(1-\lambda/2)} \sum_{l'_C=0}^{l_C} \frac{1}{l'_C!} \left( \frac{\lambda}{2} \right)^{l'_C} \sum_{l'_L=0}^{l_C-l'_C} \sum_{l'_R=0}^{\infty} \kappa(l'_C-l'_C, l'_L, l'_R, 0) z(l'_C-l'_C-l'_L, 0) \\
\frac{dz_{(l_C,l_L,0,0)}}{dt} &= -(\kappa_{(l_C,l_L,0,0)} + \bar{\kappa}(t))z_{(l_C,l_L,0,0)} + \frac{1}{l_C!} (\mu(1-\lambda))^{1+e^{-\mu(1-\lambda/2)}} \sum_{l'_C=0}^{l_C} \frac{1}{l'_C!} \left( \frac{\lambda}{2} \right)^{l'_C} \sum_{l'_L=0}^{l_C-l'_C} \sum_{l'_R=0}^{\infty} \kappa(l'_C-l'_C-l'_L, 0) z(l'_C-l'_C-l'_L, 0) \\
\frac{dz_{(l_C,0,l_R,0)}}{dt} &= -(\kappa_{(l_C,0,l_R,0)} + \bar{\kappa}(t))z_{(l_C,0,l_R,0)} + \frac{1}{l_R!} (\mu(1-\lambda))^{1+e^{-\mu(1-\lambda/2)}} \sum_{l'_C=0}^{l_C} \frac{1}{l'_C!} \left( \frac{\lambda}{2} \right)^{l'_C} \sum_{l'_L=0}^{\infty} \sum_{l'_R=0}^{l_C-l'_C} \kappa(l'_C-l'_C-l'_L, 0) z(l'_C-l'_C-l'_L, 0)
\end{align*}
\]

The above equations may be used to solve for the equilibrium mean fitness \( \bar{\kappa}(t = \infty) \) for the generalized single-fitness-peak landscape. Below the error catastrophe, the result is

\[
\bar{\kappa}(t = \infty) = \frac{A(\mu, \lambda) + \sqrt{A(\mu, \lambda)^2 + 4B(\mu, \lambda)}}{2}
\]
where $A(\mu, \lambda) = k((1 + f_1(\mu, \lambda))e^{-\mu(1-\lambda/2)} - 1) - f_1(\mu, \lambda)e^{-\mu(1-\lambda/2)} + e^{-\mu\lambda/2} - 1$, and $B(\mu, \lambda) = k(e^{-\mu\lambda/2} + e^{-\mu(1-\lambda/2)} - 1)$, where we define $f_1(\mu, \lambda) = \sum_{t=0}^{\infty} ((\mu(1-\lambda)))^t$.

The error catastrophe occurs when the mean equilibrium fitness determined by Eq. (8) becomes equal to the growth rate of the unviable genomes. At this point, the selective advantage of the viable genomes is no longer sufficiently strong to localize the population, and delocalization occurs over the entire genome space. The critical $\mu$ is therefore found by setting $\bar{\kappa}(t = \infty) = 1$ in Eq. (8), and solving for $\mu$. The resulting expression is

$$\frac{e^{-\mu(1-\lambda/2)}}{2 - e^{-\mu\lambda/2}} = \frac{k + 1}{k(2 + f_1(\mu, \lambda)) - f_1(\mu, \lambda)}.$$  \hspace{1cm} (9)

It is instructive to study the behavior of $\bar{\kappa}(t = \infty)$ for specific landscapes and values of $\lambda$. First of all, note that $f_1(\mu, 1) = 1$, giving $\bar{\kappa}(t = \infty) = k(2e^{-\mu/2} - 1)$, which is exactly the expected semiconservative result with perfect lesion repair. Also, note that $f_\infty(\mu, \lambda) = e^{(1-\lambda)\mu}$, which gives $\bar{\kappa}(t = \infty) = k(e^{-\mu(1-\lambda/2)} + e^{-\mu\lambda/2} - 1)$. For $\lambda = 1$, we of course recover the semiconservative result. However, for $\lambda = 0$, we obtain $\bar{\kappa}(t = \infty) = k e^{-\mu}$, which is exactly the result expected from conservative replication. Therefore, when only one perfect strand in a double stranded genome is necessary for the organism to remain viable, we recover an effectively conservatively replicating system in the absence of lesion repair (see also [11]).

In Figure 1 we show some results of stochastic simulations of replicating genomes, which corroborate the analytical results obtained from our theory.

The recent incorporation of semiconservative replication into the quasispecies model was an important step toward modeling real systems that revealed a number of important dynamical signatures absent in the original model. However, the initial assumption used in previous semiconservative works, namely that post-replication DNA repair is perfect, is clearly an oversimplification that is particularly poor for some of the most scientifically interesting systems such as cancer and stem cells [10, 11, 12]. This approximation introduces a false symmetry that can drastically alter the evolutionary behavior and equilibria. By providing a full treatment of semiconservative quasispecies dynamics with partially activated lesion repair, we have taken a significant step forward in the modeling of genomic evolution.

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**FIG. 1:** Plots of $\bar{\kappa}(t = \infty)$ versus $\mu$, from both stochastic simulation and theory. We took $l = \infty$. For our stochastic simulations, we averaged our results over 10 runs, using sequence lengths of 20, and a population size of 1,000 organisms.

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