

Kinetics of Muller's Ratchet from Adaptive Landscape Viewpoint

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Abstract—Background: The accumulation of deleterious mutations of a population directly contributes to the fate as to how long the population would exist. Muller's ratchet provides a quantitative framework to study the effect of accumulation. Adaptive landscape as a powerful concept in system biology provides a handle to describe complex and rare biological events. In this article we study the evolutionary process of a population exposed to Muller's ratchet from the new viewpoint of adaptive landscape which allows us estimate the single click of the ratchet starting with an intuitive understanding.

Methods: We describe how Wright-Fisher process maps to Muller's ratchet. We analytically construct adaptive landscape from general diffusion equation. It shows that the construction is dynamical and the adaptive landscape is independent of the existence and normalization of the stationary distribution. We generalize the application of diffusion model from adaptive landscape viewpoint.

Results: We develop a novel method to describe the dynamical behavior of the population exposed to Muller's ratchet, and analytically derive the decaying time of the fittest class of populations as a mean first passage time. Most importantly, we describe the absorption phenomenon by adaptive landscape, where the stationary distribution is non-normalizable. These results suggest the method may be used to understand the mechanism of populations evolution and describe the biological processes quantitatively.

Index Terms—Wright-Fisher process, adaptive landscape, stationary distribution, mean first passage time

BACKGROUND

Muller's ratchet is a mechanism that has been suggested as an explanation for the evolution of sex [1]. For asexually reproducing population, without recombination, chromosomes are directly passed down to offsprings, as a consequence the deleterious mutations accumulate so that the fittest class loses. For sexually reproducing population, because of the existence of recombination between parental genomes, a parent carrying high mutational loads can have offspring with fewer deleterious mutations. The high cost of sexual reproduction is thus offset by the benefits of inhibiting the ratchet [2]. Muller predicted ratchet mechanism in 1964. Muller's ratchet has received growing attention recently. Most studies of Muller's ratchet are related to two problems. One major problem is that without recombination, the genetic uniformity of the offspring leads to much lower genetic diversity, which is likely to make it more difficult to

adapt to [3]. The other problem is that population lacking genetic repair should decay with time, due to successive loss of the fittest individuals [4][5]. In addition, Muller's ratchet is relevant to some replicators, endosymbionts and mitochondria. In order to assess the relevance of Muller's ratchet, it is necessary to determine the rate (or the time) for the accumulation of deleterious mutations [6]. It is widely recognized that the rate of deleterious mutations being much higher than that of either reverse or beneficial mutations can be a serious threat to the survival of populations at the molecular level [4]. It would have to be taken into account in any quantitative theory of the ratchet mechanism [7].

Some biologists also have noticed a framework was needed to construct such as [7][6]. The potential evolutionary importance of Muller's ratchet mechanism would make it desirable to carry out careful quantitative studies on its operation [7]. There has been a continuous progress in theory. The simplest and earliest mathematical model is the pioneering work in [8]. The author describes the evolutionary process of asexual population of constant size on the condition of deterministic mutation selection balance according to Wright-Fisher dynamics. And the author finds numerical evidence of relation between the total number of individuals and the average time between clicks of the ratchet. Authors in [9] treat pioneering model as diffusion approximation, they produce more accurate predictions over the relatively slow regime. They note the increasing importance of selection coefficient for the rate of the ratchet for increasing values of the total number of individuals. The author in [10] employs simulation and analytical approaches to Muller's ratchet and estimates how different between the distribution of mutations within a population and a Poisson distribution. The author in [2] obtains diffusion approximations for three different parameter regimes, depending on the speed of the ratchet. The model mathematically embodies as stochastic differential equation and sheds new light on [9]. Authors in [6] also map Muller's ratchet to Wright-Fisher process, and get the prediction of the rate of accumulation of deleterious mutations when parameters lie in the fast and slow regimes of operation of the ratchet. In the present article, inspired by recent works such as [6], we treat the evolutionary process as diffusion Wright-Fisher model, analytically construct

adaptive landscape, where the stationary distribution is non-normalizable. This method extends the application of the model in [6]. The concept of adaptive landscape is proposed by Sewall Wright to quantitatively describe the complex biological phenomena as [11]. Here adaptive landscape is clearly quantified as potential function in [12] from the physical point of view.

The key concept in constructing adaptive landscape is of potential function as a scalar function. There is a long history of definition, interpretation, and generalization of potential. Potential has also been applied to biological systems in various ways. The usefulness of a potential reemerges in the current study of dynamics of gene regulatory networks [13], such as its application in genetic switch [14][15][16]. The role of potential is the same as that of adaptive landscape. In this article, we do not distinct them.

In this article we present an approach to Muller's ratchet, mapping a single click of Muller's ratchet to one dimensional Wright-Fisher model where two allele classes are used to depict all different types of individuals in a population. The Wright-Fisher model predicts the rate of Muller's ratchet and suggests the accurate rate of accumulation of deleterious mutations could be derived more quickly and more convenient by adaptive landscape. In addition we will demonstrate this method is independent of the existence and normalization of stationary distribution. Let us further address one dimensional Wright-Fisher process to make our points more clearer.

METHODS

Model description

We consider here an important and widely applied process-Muller's ratchet which is mapped to Wright-Fisher process. Muller's ratchet is the process by which genomes of a finite population composed of asexual individuals accumulate deleterious mutations in an irreversible manner [17][18]. Consider a population of haploid asexual individuals with discrete generations $t = 0, 1, 2, \dots$. The starting point in a generation is regarded as adult stage, after all selection has occurred and immediately prior to reproduction. New mutations occur at reproduction and all mutations are assumed to deleteriously affect viability but have no effect on fertility. Supposed population size is always fixed each generation, then there are always alleles with constant number in the gene pool. Here we consider one locus with two alleles A and a , that is, there are two classes in the haploid asexual population, one class with allele A while the other with allele a . Supposed mutation from allele A to a is deleterious, we assume population of constant size $N > 1$, generations are non-overlapping. The lifecycle of the individuals in the population is from adults to juveniles, during which we consider the change of allele A in the presence of irreversible mutations, selection and random genetic drift. The change of fittest allele frequency is exposed to Muller's ratchet. Given above assumption, we can study the evolution of allele A . The frequency of allele A in generation t is x_t while that of allele a is $1 - x_t$, $x_t = 0, 1/N, \dots, 1$.

Let μ be the probability that an offspring of an adult with allele A is an individual with allele a . It is labeled by $M_{1,0}$, that is, $M_{1,0} = \mu$. Analogously, $M_{0,0} = 1 - \mu$, $M_{0,1} = 0$, $M_{1,1} = 1$. The relative viability of individuals with allele A is $\nu = 1$ while that of individuals with allele a is $\nu_1 = 1 - \sigma$, where σ can be treated as effective selection rates associated with deleterious mutations. Then in generation $(t + 1)$, the frequency of allele A is

$$x_{t+1} = \frac{(1 - \mu)x_t}{1 - \sigma + \sigma(1 - \mu)x_t}. \quad (1)$$

Under the general diffusion approximation, frequency x_t is treated as continuous quantities x , and this also leads to the distribution of the frequency of allele A being probability density. Let $\rho \equiv \rho(x, t)$ be the probability density of the frequency of allele A being x at time t . The diffusion equation obeys the following formula [19][20]

$$\partial_t \rho = \partial_x^2 [V(x)\rho/2] - \partial_x [M(x)\rho], \quad (2)$$

with

$$M(x) = \frac{x[(\sigma - \mu) - \sigma(1 - \mu)x]}{1 - \sigma + \sigma(1 - \mu)x}, \quad (3)$$

$$V(x) = \frac{x(1 - x)}{N}, \quad (4)$$

where $M(x)$ represents the average transition rate of x or driving force [19][21] and $V(x)$ is the corresponding variance.

Adaptive landscape

We can also depict the same evolutionary process by the symmetric equation

$$\partial_t \rho = \partial_x [\epsilon D(x)\partial_x - f(x)]\rho \quad (5)$$

with

$$f(x) = \frac{x[(\sigma - \mu) - \sigma(1 - \mu)x]}{1 - \sigma + \sigma(1 - \mu)x} - \frac{1 - 2x}{2N}, \quad (6)$$

$$\epsilon D(x) = \frac{x(1 - x)}{2N}. \quad (7)$$

Adaptive landscape is directly given by

$$\Phi(x) = \int \frac{f(x)}{D(x)} dx. \quad (8)$$

We are interested in the dynamical property of adaptive landscape, so we treat Φ and Φ/ϵ no different in this respect, that is, for convenience we can take $\epsilon = 1$ of $\epsilon D(x)$.

$$\begin{aligned} \Phi(x) &= \int \frac{f(x)}{\epsilon D(x)} dx \\ &= \frac{2N\mu(1 - \sigma)}{1 - \sigma\mu} \ln(1 - x) - \ln x(1 - x) \\ &\quad + \frac{2N(1 - \mu)}{1 - \sigma\mu} \ln(1 - \sigma + x\sigma(1 - \mu)). \end{aligned} \quad (9)$$

Here the adaptive landscape is composed of three terms. The first term and the third term quantify the irreversible mutation and selection respectively, the second term quantifies random drift.

In addition, the symmetric Eq.(5) has two advantages. On the one hand, the adaptive landscape is directly read out when the detailed balance is satisfied. On the other hand, the constructive method is dynamical, independent of existence and normalization of stationary distribution. We call $f(x)$ directional transition rate, integrating the effects of $M(x)$ and the derivative of $V(x)$. Directional transition rate can give equilibrium states when $f(x)$ is linear form.

Under the very natural boundary condition satisfying the probability flux of the system is zero, we assume the probability flows in $[0, 1]$. The diffusion stationary distribution is given by

$$\rho(x) = \frac{1}{Z} \exp\left(\frac{\Phi(x)}{\epsilon}\right).$$

Stationary distribution can also be expressed as

$$\rho(x) \propto \exp\left(\frac{\sigma\mu - 1 - 2N\mu(\sigma - 1)}{1 - \sigma\mu} \ln(1 - x) - \ln x + \frac{2N(1 - \mu)}{1 - \sigma\mu} \ln(1 - \sigma + x\sigma(1 - \mu))\right) \quad (10)$$

it has the form of Boltzmann-Gibbs distribution [22], so the scalar function $\Phi(x)$ naturally acquires the meaning of potential energy [13]. The value of Z determines the normalization of ρ from the perspective of probability, and the finite value of Z manifests the normalization of ρ . The constant ϵ holds the same position as temperature of Boltzmann-Gibbs distribution in statistical mechanics. From the expression of stationary distribution, it is not the exact Boltzmann-Gibbs distribution. This is because the constant "temperature" does not hold the nature of temperature in Boltzmann-Gibbs distribution.

RESULTS AND DISCUSSION

Previous works mainly focus on the parameter ranges that either lies at the lower mutation rates regime or the higher mutation rates regime based on stochastic differential equations. We analyze the evolutionary process in all parameter regimes based on Fokker-Planck equation by adaptive landscape. We investigate the single click time analytically.

Irreversible mutation, selection and random drift balance

To understand the mechanism of Muller's ratchet, a full characterization of dynamical process is a prerequisite for obtaining more accurate decaying time. Here we study it in the framework of adaptive landscape in detail.

Concretely we divide mutation rates into three regimes. Mutation rates $\mu \in (0, 1/2N - 1]$, selection rates $\sigma \in (\mu, 2\mu/(1 + \mu))$, this condition corresponds to the case that selection rates and mutation rates lie in the lower regime. In the medium regime mutation rates $\mu \in (1/(2N - 1), 1/(2N - 2)]$, selection rates $\sigma \in (\mu, 1)$. In the regime of high mutation rates, it is possible that the number of mutation is greater than one in the process. Concretely, mutation rates $\mu \in (1/(2N - 2), 1)$, selection rates $\sigma \in [\mu, 1)$. The adaptive landscape of full parameter regimes is visualized as Fig.1, From the expression

and visualization of adaptive landscape $\Phi(x)$, we may find there are two singular points 0 and 1 of adaptive landscape, characterized by infinity value in Fig.1. In the low and medium parameters regime, singularity indicates the population stable, but in the high parameters regime, singularity from $x = 0$ indicates the population stable while singularity from $x = 1$ means the population unstable. Fig.1 demonstrates the whole

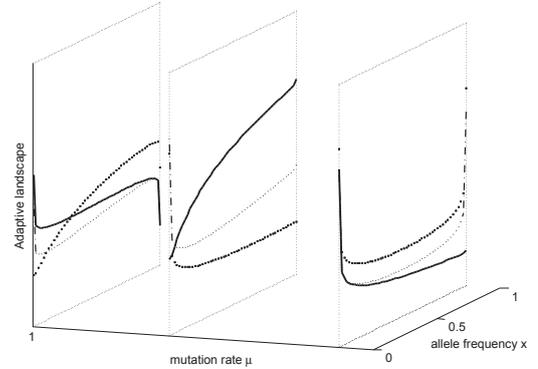


Fig. 1. Adaptive landscape against allele frequency x with mutation rates and selection rates in all regimes. x label represents allele frequency, μ label represents mutation rates while vertical label is corresponding value of Φ . According to order of mutation rates from low to high. Assume population size is constant $N=50$. In the lower regime, dashed dotline represents $\mu=0.000005$, $\sigma=0.00005$, black dotline stands for $\mu=0.000005$, $\sigma=0.019$, black line represents $\mu=0.01$, $\sigma=0.019$. In the medium mutation rates regime, black dotline represents $\mu=0.01015$, $\sigma=0.015$, dashed dotline stands for $\mu=0.01015$, $\sigma=0.05$, black line investigates $\mu=0.01015$, $\sigma=0.9$. In the higher mutation rates regime, black dotline represents $\mu=0.4$, $\sigma=0.9$, dashed dotline stands for $\mu=0.02$, $\sigma=0.1$, black line describes the case for $\mu=0.02$, $\sigma=0.05$.

process of the population evolution including the forming and losing the fittest class. With increasing selection rates the fittest class A is forming quickly while with increasing mutation rates the fittest class A loses easily. In the lower mutation rates regime black dotline describes the population is likely to move to the fittest class with increasing selection rates, the process is dominated by selection. Dashed dotline and black line manifest the losing process of allele A with accumulation of irreversible mutations. Because the mutation rates are lower, selection rates dependent of mutation rates are lower, these factors result in the change of fittest class is not easy. In the end there are two stable states in the process intuitively. In the middle mutation rate regime, it demonstrates the transition process between lower and higher mutation rates. The number of mutations is also fewer than one in one generation in the process. In the higher irreversible mutation rates, Dashed dotline and black line describe the population is likely to move to the fittest class so that the population exists in the form of coexistence of A and a . Black dotline manifests the losing process with accumulation of irreversible mutations. Because mutation rates are higher, as a consequence allele a occurs. Selection rates dependent of mutation rates tends to survive allele A . There are two stable states in the process under the balance of

irreversible mutation and selection. The evolutionary process is dominated by the irreversible mutations, the fittest class A loses. So we can draw the conclusion that the click process occurs when there are two stable states in the process.

The single click time for Muller's ratchet

We visualize adaptive landscape, then one may wonder about how the population moves from one peak to another and how long it might be to move from one maximum to another. The process was first visualized by Wright in 1932. In addition, the problem of transition from metastable states is ubiquitous in almost all scientific areas. Most of previous works encounter finite potential barriers from the physical point of view. Interesting issue here is that we touch upon infinite potential barriers under the circumstance of well defined two stable states. Then we manifest the derivation of a single click time. The time of a click of the ratchet is recognized as the random time of loss of the fittest class as [6].

The single click time occurs when the allele A is lost. The corresponding processes are that there are two well-defined stable states in the system. Corresponding graphs of adaptive landscape is the following:

To evaluate the single click time and show the further power

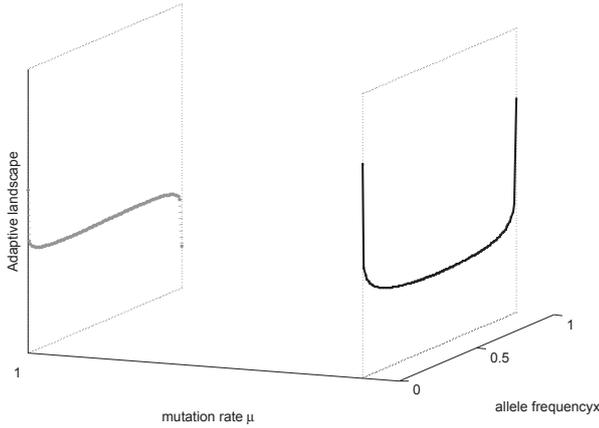


Fig. 2. Adaptive landscape with two stable states in the low and high mutation rates. $N=50$, dashed line represents $\mu=0.02, \sigma=0.05$ while black line stands for $\mu = 0.000005, \sigma=0.00005$.

of adaptive landscape, in the following we will demonstrate how the single click time from one stable state to another is derived in this framework. After easily calculating, backward Fokker-Planck corresponding to Eq.(5) can be expressed with the property of time homogeneous in the following form [23][24]

$$\partial_t \rho = (f(x) + \epsilon D'(x)) \partial_x \rho + \epsilon D(x) \partial_x^2 \rho, \quad (11)$$

general single click time dependent on initial Dirac function satisfies

$$(f(x) + \epsilon D'(x)) \partial_x T(x) + \epsilon D(x) \partial_x^2 T(x) = -1. \quad (12)$$

With boundary condition

$$T'(1) = T(0) = 0. \quad (13)$$

The general solution corresponding to Eq.(12) is

$$T(x) = \int_x^0 \frac{1}{\epsilon D(y)} \exp(-\Phi(y)) dy \int_1^y \exp(\Phi(z)) dz, \quad (14)$$

here $\Phi(x) = \int^x f(x')/\epsilon D(x') dx' (\epsilon = 1)$.

Here the evolutionary process naturally occurs when $x \in [0, 1]$. We are more interested in the transition time between the two stable states $x = 0$ and $x = 1$. In the process, there are two important states x^*, x_3^* . Interval $(0, 1)$ contains an potential well at $x^*, f(x^*) = 0, f'(x^*) < 0$, and an potential barrier at $x_3^*, f(x_3^*) = 0, f'(x_3^*) > 0$. Then one can use Laplace's methods to simplify the transition time to

$$\begin{aligned} T_{1 \rightarrow 0} &= \lim_{x \rightarrow 1} T(x) \\ &\approx \frac{2\pi \exp(\Phi(x_3^*) - \Phi(x^*))}{D(x^*) \sqrt{\Phi''(x^*) \Phi''(x_3^*)}} \\ &\quad + \int_{x_3^*}^1 \frac{1}{f(x)} dx. \end{aligned} \quad (15)$$

The second term is for downhill relaxation. The first term is the time for barrier crossing. This method for mean first passage time is consistent with [25].

In the high mutation rate regime, where x_3^* approximates to a stable state which is near enough to 1, x^* corresponds to the saddle point that the population lies between the two stable states 0 and x_3^* . The single click time approximates to

$$\begin{aligned} T_{1 \rightarrow 0} &= \lim_{x \rightarrow 1} T(x) \\ &= \lim_{x \rightarrow 1} \int_0^x \frac{1}{\epsilon D(y)} \exp(-\Phi(y)) dy \int_y^1 \exp(\Phi(z)) dz \\ &= \lim_{x \rightarrow 1} 2N \int_0^x \frac{(1-y)^{\frac{2N\mu(\sigma-1)}{1-\sigma\mu}}}{(1-\sigma+y\sigma(1-\mu))^{\frac{2N(1-\mu)}{1-\sigma\mu}}} dy \\ &\quad \times \int_y^1 z^{-1} (1-z)^{\frac{\sigma\mu-1-2N\mu(\sigma-1)}{1-\sigma\mu}} \\ &\quad \times (1-\sigma+\sigma z(1-\mu))^{\frac{2N(1-\mu)}{1-\sigma\mu}} dz \\ &\approx \frac{2\pi \exp(\Phi(x_3^*) - \Phi(x^*))}{D(x^*) \sqrt{\Phi''(x^*) \Phi''(x_3^*)}} \\ &\approx \frac{N}{3} 2^{5-2N} \frac{(4-\sigma+3\sigma\mu)^{\frac{2N(1-\mu)}{1-\sigma\mu}}}{(2-\sigma\mu+3\sigma)} \mathcal{O}(1) \end{aligned} \quad (16)$$

Here x_3^* and x^* are the zero points of $f(x)$ respectively. For the lower mutation rate regime, the single click time can be calculated similarly, where x_3^* approximates to 1, x^* corresponds to the saddle point that the population lies at the lowest potential.

Analogous to the derivation of $T_{1 \rightarrow 0}$, we can calculate

$$\begin{aligned}
T_{0 \rightarrow 1} &= \lim_{x \rightarrow 0} \int_1^x \frac{1}{\epsilon D(y)} \exp(-\Phi(y)) dy \int_y^0 \exp(\Phi(z)) dz \\
&= \lim_{x \rightarrow 0} 2N \int_1^x \frac{(1-y)^{\frac{2N\mu(\sigma-1)}{1-\sigma\mu}}}{(1-\sigma+y\sigma(1-\mu))^{\frac{2N(1-\mu)}{1-\sigma\mu}}} dy \\
&\quad \times \int_y^0 z^{-1}(1-z)^{\frac{\sigma\mu-1-2N\mu(\sigma-1)}{1-\sigma\mu}} \\
&\quad \times (1-\sigma+\sigma z(1-\mu))^{\frac{2N(1-\mu)}{1-\sigma\mu}} dz \\
&= \infty.
\end{aligned} \tag{17}$$

Here the single click time asymptotically conforms to exponential form according to Eq.(15), though the shapes of adaptive landscape are different. And once the population arrives at the stable state $x = 0$, the population is absorbed as Eq.(17) describes. The accurate graph of single click time $T_{1 \rightarrow 0}$ is the following:

Fig.3 describes the single click time increases with increasing

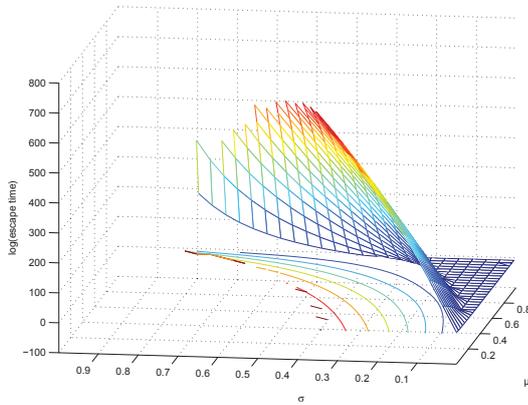


Fig. 3. Exact numerical results about the single click time corresponding to Eq.(15). Horizontal coordinates represent selection rates σ and mutation rates μ , vertical coordinate corresponds to the value of the click time $T_{1 \rightarrow 0}$.

mutation rates and decreases with increasing selection rates. This is consistent with adaptive landscape in the lower and higher regimes in Fig.1. Asymptotic results corresponds to formula (16).

The estimated results are more accurate when the parameters lie in the high regime.

Discussion

The present article presents a new approach to estimate the single click time of Muller's ratchet. Inspired by a recent work as [6], we connect it to one locus Wright-Fisher model with asexual population including N haploid individuals. Direct classical diffusion approximation of Wright-Fisher model can reduce complex calculation to solve matrix equations, this method is functional especially when the dimension of the matrix is higher. Our theoretical results generalize the application of the model proposed in [6]. Our method doesn't

need the existence and normalization of stationary distribution. Our dynamical constructive method is independent of the stationary distribution. Compared with the method based on the diffusion approximation, mathematically it embodies as stochastic differential equations such as [10][2], our method investigates the global dynamical property of the system more directly than theirs, and reduces the complex of calculating stochastic differential equations. In addition, our results demonstrate the dynamical process of Muller's ratchet and the single click time is approximately exponentially distributed. Most importantly, we depict the absorption phenomena from the adaptive landscape viewpoint.

To summarize, we have obtained two main sets of results in the present work. First, we demonstrate a transformation of a simple Fokker-Planck equation so that the adaptive landscape can be explicitly read out as a potential function. Such demonstration suggests this concept applicable to all levels of systems biology. This not only allows computing click time of Muller's ratchet straightforward, but also makes the stability analysis of the ratchet system intuitive. Second, in this framework the derivation of single click time is easy even for situations that steady state distribution is nonnormalizable. Hence it allows us another way to handle absorbing boundary condition. In this perspective our work may be a starting point for estimating the click time for Muller's ratchet in more general situations.

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