Thermodynamical Interpretation of Evolutionary Dynamics on a Fitness Landscape in an Evolution Reactor, II

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Abstract

In our previous report (Aita *et al.*,2004), an analogy between thermodynamics and adaptive walks on a Mt. Fuji-type fitness landscape in an artificial selection system was presented. Introducing the "free fitness" as the sum of a fitness term and an entropy term and "evolutionary force" as the gradient of free fitness on a fitness coordinate, we demonstrated that the adaptive walk (=evolution) is driven by the evolutionary force in the direction in which free fitness increases. In this report, we examined the effect of various modifications of the original model on the properties of adaptive walk. The modifications were as follows: first, mutation distance d was distributed obeying binomial distribution; second, the selection process obeyed the natural selection protocol; third, ruggedness was introduced to the landscape according to the NK model; forth, a noise was included in the fitness measurement. The effect of each modification was described in the same theoretical framework as the original model by introducing "effective" quantities such as the effective mutation distance or the effective screening size.

Notation

ν: Chain length of a biopolymer sequence

λ: Number of available letters, e.g. $\lambda = 20$ for natural proteins

L: Number of blocks (=groups)

ν_l: Chain length of the l-th block, $\sum_{l=1}^{L} \nu_l = \nu$

ε_l: Mean of the site-fitness over λ letters for the l-th block

σ_l: Standard deviation of the site-fitness over λ letters for the l-th block

$\mathcal{N}(x|a, b)$: Normal distribution of a variable x with mean a and variance b.

W: Fitness of a sequence

W_m: Fitness of the m-th fittest among M parents or among N children

$\mathscr{E}$: Mean of the fitness over all possible sequences

$\mathscr{V}$: Variance of the fitness over all possible sequences

M: Number of parents as walkers

N: Number of children (=mutants)

d: Number of mutated sites, Hamming distance between a parent and each of its children

$E[x]$: Expectation of a variable x

$V[x]$: Variance of a variable x

$\mathscr{W}$: Mean fitness over M parents

$\mathscr{U}$: Standard deviation of fitness over M parents

$\Delta\mathscr{W}$: Change of $\mathscr{W}$ after a single generation, climbing rate of M walkers

$\Delta\mathscr{U}$: Change of $\mathscr{U}$ after a single generation

$\mathscr{W}^*, \mathscr{U}^*$: The $\mathscr{W}$ and $\mathscr{U}$ in the stationary state, respectively

$\delta\mathscr{W}, \delta\mathscr{U}$: $\delta\mathscr{W} \equiv \mathscr{W} - \mathscr{W}^*$ and $\delta\mathscr{U} \equiv \mathscr{U} - \mathscr{U}^*$, respectively

ΔW: Change between the mean fitness over M parents ($\mathscr{W}$) and the fitness of their arbitrary mutant

$\widetilde{N}_m$: Expected value of the m-th greatest among N samples from the standard Gaussian

$\langle\widetilde{N}_m\rangle$: Mean of $\widetilde{N}_m$ over M parents, a measure of selection pressure

J: Expectation of climbing rate ($\Delta\mathscr{W}$) when $(\mathscr{W}, \mathscr{U}) = (\mathscr{W}^* + \delta\mathscr{W}, \mathscr{U}^* + \delta\mathscr{U})$

$V[\Delta\mathscr{W}]$: Variance of climbing rate ($\Delta\mathscr{W}$) when $(\mathscr{W}, \mathscr{U}) = (\mathscr{W}^* + \delta\mathscr{W}, \mathscr{U}^* + \delta\mathscr{U})$

D: Diffusion coefficient for a random walk by M walkers

$\Omega(W)$: Number of sequences whose fitnesses range in $W - \Delta \sim W$ ($\Delta > 0$)

$S(W)$: Entropy for a single walker with the fitness W

k: Landscape constant (Boltzmann constant-like quantity)

T: Evolutionary temperature, $T \equiv \sqrt{d}/\langle\widetilde{N}_m\rangle$

$\mathscr{G}(\mathscr{W})$: Evolutionary potential for M walkers with the mean fitness $\mathscr{W}$

$G(\mathscr{W})$: Free fitness for M walkers with the mean fitness $\mathscr{W}$

$X(\mathscr{W})$: Evolutionary force that acts on the M walkers with the mean fitness $\mathscr{W}$

$\mathscr{L}$: Linear transport coefficient or Admittance

μ: Mutation rate per site

$\overline{d}$: Mean of d, $\overline{d} = \mu\nu$

T_c: Critical value of T for phase transition

$d_{\text{eff}}, N_{\text{eff}}, M_{\text{eff}}, T_{\text{eff}}$: Effective values of d, N, M and T, respectively

β: Parameter that governs the strength of natural selection

x_m: The value of the m-th greatest among N samples from the standard Gaussian

$\langle x_m \rangle, Var[x_m\ ]$: the weighted mean and weighted variance of x_m, respectively

K: The number of sites that affect the site-fitness at an arbitrary site

1 Introduction

Darwinian evolution through mutation processes and subsequent selection processes is driven by an entropy force and a selection force. The entropy force drives an evolving population to diverse in the sequence space, whereas the selection force drives the evolving population to converse. This suggests that evolution is analogous to thermodynamics. This analogy has been reported in Iwasa,(1988) and Eigen *et al.*,(1989). The former introduced the idea of "free fitness" and the latter introduced the idea of "quasi-species".

In our previous report (Aita *et al.*,2004), to comprehend the underlying principles of biological evolution, we analyzed an evolution model on a Mt. Fuji-type fitness landscape, in which the mutational effect is additive. In the evolution model, we adopted the (M, N)-Evolutionary Strategy (Rechenberg, 1984). M parents (=wild-types) produce N children (=mutants), and subsequently, the best M individuals among the N children will become new parents in the next generation. The number of mutated sites is fixed at d in a production of every mutant. This is a model of an artificial evolution system directed by engineers (Keefe & Szostak,2001; Yamauchi *et al.*, 2002). As a result from the analysis, we succeeded in quantifying the analogy between evolution and thermodynamics by introducing our original "free fitness" $G = W + TS$, where W, S and T are fitness, entropy and "evolutionary temperature", respectively. The entropy is defined as $S(W) \equiv k \ln \Omega(W)$, where $\Omega(W)$ represents the number of all possible sequences that have the fitness W and k is a "landscape constant". The evolutionary temperature is defined as $T \equiv \sqrt{d/2 \ln(N/M)}$. It contains both of a mutational effect governed by the mutation distance d and a random-drift effect governed by the population size N and M. On the other hand, in Iwasa's definition of free fitness (Iwasa,1988), the temperature-like parameter is $1/2N$, where N is the population size, and it does not contain the mutational effect explicitly. His theory is not based on the structure of fitness landscapes in sequence space. These are the major difference between our definition and Iwasa's one. In the field of evolutionary computation, Maekawa *et al.* applied the concept of free energy minimization principle to the optimization protocol, called "Thermodynamic Genetic Algorithm"

(Maekawa *et al.*,1997). In their protocol, evolving population is selected to minimize free energy (or to maximize free fitness) at each generation. The aim of our study is not to apply thermodynamical concepts to an optimization technique but to find principles underlying in a simplified evolution system.

Our major findings are as follows. An adaptive walk (=evolution) is driven in the direction in which free fitness increases. The walker starting from the foot of the landscape climbs rapidly and then reduces the climbing rate and finally reaches a stationary state, which is the specific region of the "mutation-selection-random drift balance" (Woodcock & Higgs, 1996; Prügel-Bennett, 1997; Lazaro *et al.*,2002) and corresponds to the maximal free fitness state. The walker starting from near top of the landscape descends the landscape to the stationary state. This descending process is called Muller's ratchet (Muller,1964). The stationary point on the fitness coordinate is determined by the evolutionary temperature T. If T is higher (or lower), then the stationary point shifts to a lower (or higher) region on the fitness coordinate. This behavior is analogous to that in thermodynamics, because the highest point of the landscape represents the maximal fitness state and the foot of the landscape is the maximal entropy state.

This behavior has been observed in serial transfer experiments for RNA viruses. Serial transfers with large (or small) populations usually lead to increases (or decreases) in fitness (Novella *et al.*,1995; Escarmis *et al.*,1999; Arias *et al.*,2001). In our interpretation, large (or small) population size N sets the evolutionary temperature T low (or high) values and then pushes the stationary fitness-value upward (or downward). Therefore, the above results of the serial transfer experiments are compatible with our theoretical results.

This report is a sequel of Aita *et al.* (2004). In Section 2, we summarized the previous paper, that is, our original model, definitions and ideas are described. In Section 3, 4, 5 and 6, we introduced various modifications to this original model and examined the effect of each modification on the statistical properties of the adaptive walk. The modifications are as follows. First (in Section 3), it is the case where the mutation distance d is distributed obeying binomial distribution. Second (in Section 4), it is the case where the selection process obeys the natural selection protocol, in which the number of children

generated from a parent depends on the fitness of the parent. Third (in Section 5), it is the case where ruggedness is introduced to the landscape according to the NK model (Kauffman,1993). Fourth (in Section 6), it is the case where a noise is included in the fitness measurement.

As a result, we found that the thermodynamical scheme found in the original model is applicable to various cases by introducing "effective" quantities such as the effective mutation distance or the effective screening size.

2   Summary of our previous report

2.1   Original model of fitness landscape and evolving population

We deal with the λ-valued ν-dimensional sequence space of all possible sequences of biopolymers, where ν represents the chain length of a biopolymer sequence and λ represents the number of available letters at each site. We focus on cases where λ is large enough to give $(\lambda - 1)/\lambda \approx 1$. Consider individual ν sites classified by tolerance against mutations into L groups, $l = 1, 2, \cdots, L$. Let ν_l be the number of sites belonging to the l-th group. Thus, $\sum_{l=1}^{L} \nu_l = \nu$. We introduced "site-fitness", which is an independent contribution from a particular letter at each site in a given sequence, and assumed that the site-fitness for the i-th letter a_i located at the j-th site in the l-th group is given by the following "comb-type" function :

$$w_{lj}(a_i) = \frac{2\varepsilon_l}{\lambda} i \ \le 0 \qquad (i = 0, 1, 2, \cdots, \lambda - 1), \tag{1}$$

where $\varepsilon_l \le 0$ is a constant equivalent to the mean of the site-fitness over all available letters. The variance of the site-fitness, σ_l^2, plays a key-role in this theory and is given by

$$\sigma_l^2 = \frac{1}{\lambda} \sum_{i=0}^{\lambda-1} (w_{lj}(a_i) - \varepsilon_l)^2 \approx \frac{\varepsilon_l^2}{3}. \tag{2}$$

The fitness W for a given sequence is defined as follows:

$$W = \sum_{l=1}^{L} \sum_{j=1}^{\nu_l} w_{lj}(\alpha_{lj}), \tag{3}$$

where $\alpha_{lj} \in \{a_0, a_1, \cdots, a_{\lambda-1}\}$ represents a particular letter at the j-th site in the l-th group in a given sequence. The fitness landscape resulting from this model is the "anisotropic" Mt. Fuji-type landscape in the λ-valued ν-dimensional sequence space. Let $\mathscr{E}$ and $\mathscr{V}$ be the mean and variance of fitness W over all possible sequences, respectively. The number of sequences whose fitnesses range between $W - \Delta$ and W ($\Delta > 0$) is given by

$$\Omega(W) = \frac{\lambda^\nu}{\sqrt{2\pi\mathscr{V}}} \exp\left(-\frac{(W - \mathscr{E})^2}{2\mathscr{V}}\right) \times \Delta \qquad \text{for } W \leq 0, \tag{4}$$

where Δ is determined to satisfy $\Omega(0) = 1$.

We adopted the (M, N)-Evolutionary Strategy as the hill-climbing protocol: M parents (=wild-types) generate N children (=mutants), and subsequently, the best M individuals among the N children will become new parents in the next generation (Rechenberg, 1984). The Hamming distance between a parent and each of its children is a constant d, that is, d is the number of mutated sites. We dealt with cases where $M \ll N$ and $d \ll \nu_l$ for all l's. This is a model of an artificial evolution system directed by engineers (Keefe & Szostak,2001; Yamauchi *et al.*, 2002).

2.2 Evolutionary dynamics on a fitness landscape

Let $\mathscr{W}$ and $\mathscr{U}$ be the mean fitness and standard deviation of fitness over M parents, respectively. The dynamics of an adaptive walk is described with mean fitness $\mathscr{W}$ and deviation $\mathscr{U}$. The walkers starting from the foot of the landscape climb rapidly and then reduce the climbing rate and finally reach a stationary state, $\mathscr{W} = \mathscr{W}^*$, which is the specific region of the "mutation-selection-random drift balance" (Woodcock & Higgs, 1996; Prügel-Bennett, 1997; Lazaro *et al.*,2002). Meanwhile, the $\mathscr{U}$-value rapidly tends to the stationary value $\mathscr{U}^*$ at the initial stage.

First, we will begin by considering the underlying mutant population, that consists of all conceivable d-fold point mutants generated from the M parents. Let ΔW be the change between the mean fitness $\mathscr{W}$ over M parents and a fitness of their arbitrary mutant. The expectation and variance of ΔW over the underlying mutant population are respectively

given as follows:

$$E[\Delta W] = -(\mathscr{W} - \mathscr{E})\frac{d}{\nu}, \tag{5}$$

$$V[\Delta W] = \left(2\mathscr{V} + c_1(\mathscr{U}^2 + (\mathscr{W} - \mathscr{E})^2) + c_2(\mathscr{W} - \mathscr{E})\right)\frac{d}{\nu} + \left(1 - \frac{d}{\nu}\right)^2 \mathscr{U}^2, \tag{6}$$

where c_1 and c_2 are constants dependent on the landscape properties. The details are described in eqn.(18) and (19) in Aita *et al.*,(2004).

Let $\Delta\mathscr{W}$ be the change of the mean fitness after a single generation, that is the "climbing rate" of the evolving population. By using the extremal value statistics, the expectation of the climbing rate is given by

$$J \equiv E[\Delta\mathscr{W}] = E[\Delta W] + \sqrt{V[\Delta W]}\,\langle\widetilde{N}_m\rangle, \tag{7}$$

where $\langle\widetilde{N}_m\rangle$ is defined as follows. Consider that N samples are randomly chosen according to the standard Gaussian probability density $\mathscr{N}(x|0,1)$, and let x_m be the value for the m-th greatest among the N samples. We denoted the expectation of x_m by $\widetilde{N}_m\ (\equiv E[x_m])$. The mean of $\widetilde{N}_m$ from $m = 1$ through $m = M$ is given by

$$\langle\widetilde{N}_m\rangle \equiv \frac{1}{M}\sum_{m=1}^{M}\widetilde{N}_m \approx \sqrt{2\ln\frac{(N/M)}{\sqrt{2\pi}}}. \tag{8}$$

In eqn. (7), $\langle\widetilde{N}_m\rangle$ governs the climbing rate, then we designate $\langle\widetilde{N}_m\rangle$ as a measure of selection pressure.

From $J = 0$ and $E[\Delta\mathscr{U}] = 0$, the stationary point $(\mathscr{W}^*, \mathscr{U}^*)$ is determined as follows:

$$\mathscr{W}^* \approx \mathscr{E} + \frac{\sqrt{2\mathscr{V}\nu}}{T} \tag{9}$$

$$\mathscr{U}^* \approx 2k\sqrt{d\,Var[\widetilde{N}_m]}, \tag{10}$$

where $Var[\widetilde{N}_m]$ is the variance of $\widetilde{N}_m$ from $m = 1$ through $m = M$. k and T were defined as follows:

$$k \equiv \sqrt{\frac{\mathscr{V}}{2\nu}} = \sqrt{\frac{\sum_{l=1}^{L}\sigma_l^2\,\nu_l}{2\nu}} = \sqrt{\frac{\langle\sigma_l^2\rangle}{2}}, \tag{11}$$

$$T \equiv \frac{\sqrt{d}}{\langle\widetilde{N}_m\rangle} \approx \sqrt{\frac{d}{2\ln(N/M\sqrt{2\pi})}}. \tag{12}$$

σ_l in eqn. (11) is defined in eqn. (2). The meaning of k is the standard deviation of a fitness change for a unit Hamming distance, then we designated k as the "landscape constant". T works just like thermodynamic temperature, then we designated T as the "evolutionary temperature". In our original model, T is constant through the walk process.

For the special case of $N = M$, that is the case of $\langle \widetilde{N}_m \rangle = 0$, since the selection pressure does not act on the walkers, the walkers perform a random walk with a step-width d on the landscape. In this case, the variance of $\Delta \mathcal{W}$ is given by $V[\Delta W]/M$. Then, we introduced a diffusion coefficient D in a random walk on the one-dimensional fitness space as follows.

$$D \equiv \frac{V[\Delta W]}{2M} \tag{13}$$

$$\approx \frac{\mathcal{V}d}{\nu M}. \tag{14}$$

2.3 Thermodynamical interpretation of the evolutionary dynamics

Defining the "entropy" S, with Ω in eqn. (4), as

$$S(W) \equiv k \times \ln \Omega(W) \tag{15}$$

$$= -\frac{k}{2\mathcal{V}}(W - \mathscr{E})^2 + \frac{k\mathscr{E}^2}{2\mathcal{V}}, \tag{16}$$

we defined the "evolutionary potential" $\mathscr{G}$ for M walkers ($m = 1, 2, \cdots, M$) as follows:

$$\mathscr{G}(\mathcal{W}) \equiv \mathcal{W} + T \times S(\mathcal{W}) \tag{17}$$

$$= -\frac{kT}{2\mathcal{V}}\left(\mathcal{W} - \left(\mathscr{E} + \frac{\mathcal{V}}{kT}\right)\right)^2 + const. \tag{18}$$

And we defined the "free fitness": $G(\mathcal{W}) \equiv \mathscr{G}(\mathcal{W}) \times M$. We note that the evolutionary potential $\mathscr{G}$ and free fitness G are the Lyapunov function of the evolution process ($\mathscr{G}$ and G take the maximal values at $\mathcal{W} = \mathcal{W}^*$), if kT in eqn. (18) satisfies the following relationship:

$$kT = \frac{1}{\langle \widetilde{N}_m \rangle}\sqrt{\frac{\mathcal{V}d}{2\nu}}. \tag{19}$$

k defined in eqn. (11) and T defined in eqn. (12) satisfy this relationship. Therefore, $\mathcal{W}^*$ is related with kT by

$$\mathcal{W}^* = \mathscr{E} + \frac{\mathcal{V}}{kT}. \tag{20}$$

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In addition, we defined the "evolutionary force" X that acts on the M walkers:

$$X(\mathscr{W}) \equiv \frac{d}{d\mathscr{W}} \frac{\mathscr{G}(\mathscr{W})}{T} \tag{21}$$

$$= -\frac{k}{\mathscr{V}} (\mathscr{W} - \mathscr{W}^*). \tag{22}$$

The expectation of the climbing rate at $(\mathscr{W}, \mathscr{U}) = (\mathscr{W}^* + \delta\mathscr{W}, \mathscr{U}^*)$ is given by

$$J \approx -\frac{d}{\nu} \times \delta\mathscr{W}. \tag{23}$$

By combining eqn. (23) with eqn. (22) and eqn. (14), we deduced that the expected climbing rate, J, obeys the following simple linear relation with X:

$$J \approx \mathscr{L} \times X \quad \text{with} \quad \mathscr{L} = \frac{MD}{k}, \tag{24}$$

where $\mathscr{L}$ is the linear transport coefficient or admittance. The relation $\mathscr{L} = MD/k$ is analogous to the Einstein relation in Brownian motion (Einstein, 1905). By using this relation, the expected change of $\mathscr{G}/T$ for a single generation is given by

$$E[\frac{\Delta\mathscr{G}}{T}] = JX \approx \mathscr{L} X^2 \geq 0. \tag{25}$$

This shows that $\mathscr{G}$ is the Lyapunov function of the evolution process. Note that many other studies on maximized quantities through evolution have been reported (Iwasa,1988; Weinberger, 2002; Garske & Grimm,2004).

The standard deviation of the climbing rate is proportional to kT as follows:

$$\sqrt{V[\Delta\mathscr{W}]} \approx kT \times \frac{4}{\sqrt{M}+1}. \tag{26}$$

$\sqrt{V[\Delta\mathscr{W}]}$ represents "uncertainty" of the mean-fitness change for a single generation. Then, eqn. (26) suggests that the uncertainty corresponds to the mean thermal energy-like quantity kT ($\times 4/(\sqrt{M}+1)$). Then, the quantity $\Delta\mathscr{W}/kT$ is the digitized mean-fitness change by the unit of uncertainty $\sqrt{V[\Delta\mathscr{W}]}$ (because $kT \approx \sqrt{V[\Delta\mathscr{W}]} \times \sqrt{M}/4$). We designated $\Delta\mathscr{W}/T$ as the "fitness information" because it is interpreted as the negative entropy the walkers absorb from the "surroundings". Here, the surroundings consist of the experimental setup.

These results lead to the following interpretation. Driven by the evolutionary force X, the walkers climb the landscape to the maximal free fitness state, through absorbing the fitness information $\Delta \mathscr{W}/T$ from the surroundings. Further consideration from the informational view point is described in Section 4.3 in Aita et $al.$, (2004).

3 Effect of distributed mutation distance

In the original model, we set the mutation distance d constant through a walk process. In this section, we examine a case where the mutation distance d is stochastically distributed obeying binomial distribution. Consider that, in the mutagenesis process, a residue substitution occurs with the probability of μ for each site. The μ is called "mutation rate". Then, the mole fraction of the d-fold point mutants generated from a wild-type obeys

$$B(d) = \binom{\nu}{d} \mu^d (1-\mu)^{\nu-d}. \tag{27}$$

Since d is distributed around its mean $\overline{d} = \mu\nu$, we apply our scheme shown in Section 2 to this case by substituting $d = \overline{d} = \mu\nu$. We confirmed the effectiveness of this approach through computer simulation. Fig.1 shows the theoretical and numerical values of $\mathscr{W}^*$ as a function of T. The resulting $\mathscr{W}^*$-values from the computer simulation agree well with the theoretical ones from eqn. (9). It is remarkable that there are two phases for the stationary state, $\mathscr{W}^* < 0$ when $T > T_c$ and $\mathscr{W}^* = 0$ when $T < T_c$. The latter phase, $\mathscr{W}^* = 0$, is realized in the situation where the replication of sequences is so accurate that a population of N children includes non-mutated sequences identical to their parents. In this case, the walkers never descend the landscape and can reach the peak ultimately. The condition in which the latter phase, $\mathscr{W}^* = 0$, occurs is

$$B(0) \times \frac{N}{M} = (1-\mu)^\nu \times \frac{N}{M} \geq 1. \tag{28}$$

Then, by substituting $d = \overline{d} = \mu\nu$ and $N/M = (1-\mu)^{-\nu}$ into eqn. (12) and using $\ln(1-\mu) \approx -\mu$, the critical T-value for the phase transition is given by

$$T_c \approx \sqrt{\frac{\mu}{-2\ln(1-\mu)}} \approx \sqrt{\frac{1}{2}} = 0.71. \tag{29}$$

Taking an analogy to the phase diagram of the water, we can interpret that the T_c is analogous to the triple point, $T_3 = 273.16\text{K}$, in the phase diagram, in which the degree of freedom for the observer is zero according to the phase rule. The thermodynamic (or absolute) temperature is scaled by T_3. In the same way, the evolutionary temperature T can be scaled by the setup-independent constant T_c as follows:

$$T \approx T_c \times \sqrt{\frac{d}{\ln(N/M\sqrt{2\pi})}}. \tag{30}$$

The mean d-value over selected M mutants as new parents in each generation is denoted by d_{eff}, where the subscript "eff" means an effective quantity. In addition, we introduce the effective screening size, $N_{\text{eff}} = N \times B(d_{\text{eff}})$. Fig.2(a) shows the d_{eff}-values against $\delta\mathscr{W} = \mathscr{W} - \mathscr{W}^*$, where $\mathscr{W}$ is the mean fitness over M parents. In the early stage of the walk, d_{eff} is larger than $\overline{d} = \mu\nu$, whereas in the later stage, d_{eff} is smaller than $\overline{d} = \mu\nu$. At the foot of the landscape, mutants with large d-values have the possibility of jumping to higher regions. As the walkers climb the landscape, the relative number of ascending paths against descending paths decreases, and then mutants with small d-values have the possibility of finding ascending paths, efficiently. This works just like an auto-tuning system in an optimization process. According to eqn. (23), the expectation of the climbing rate, J, is predicted by $J = -d_{\text{eff}}/\nu \times \delta\mathscr{W}$. Fig.2(b)(c) shows the predicted J-values and the J-values obtained by computer simulation. The good agreement between them suggests that the introduction of d_{eff} and N_{eff} is effective to understand the property of the adaptive walks in the theoretical framework of the original model.

In conclusion in this section, our original scheme (mentioned in Section 2) is applied to this case when $T > T_c$, by adopting $d = \overline{d} = \mu\nu$. Moreover, the dynamics in details is described by introducing the effective mutation distance d_{eff} and effective screening size $N_{\text{eff}} = N \times B(d_{\text{eff}})$.

4   Effect of natural selection

In the original model, we dealt with an artificial evolution, in which engineers direct the evolution according to their sense of values. In this section, we examine a case

where evolution is driven by natural selection according to the Darwinian principle, and moreover the selection is frequency independent (Husimi,1989; Novella *et al.*,1995). Since we consider the evolution system in an evolution reactor in which environmental conditions are controlled, the frequency independent selection is easily realized.

Let W_m be the fitness of the m-th fittest among N parents ($m = 1, 2, \cdots, N$), and consider that the m-th parent produces

$$N \times \frac{\exp(\beta W_m)}{\sum_{m=1}^{N} \exp(\beta W_m)} \tag{31}$$

children (=mutants), where β is a parameter that governs the strength of natural selection. The generated N children become new N parents in the next generation. The weight, $\exp(\beta W_m)$, in eqn. (31) is used frequently in the selection protocol in the genetic algorithm (Prügel-Bennett,1997). The use of the weight seems practically effective in handling of the selection of self-replicators (such as viruses or microbes) according to their growth rate in a fixed environment (Husimi,1989; Novella *et al.*,1995; Escarmis *et al.*,1999), or effective in handling of the selection of ligand molecules according to their affinity to a target receptor (Mandecki *et al.*,1995; Sun *et al.*,1996; Yang *et al.*,2003).

First, we will begin by considering the underlying biased mutant population, that consists of d-fold point mutants generated from the N parents with the production bias shown in eqn. (31). The probability density of fitness over the biased mutant population is described in Appendix A. Let ΔW be the change between the mean fitness $\mathscr{W}$ over the N parents and the fitness of their arbitrary mutant. The expectation and variance of ΔW over the biased mutant population, $\widetilde{E}[\Delta W]$ and $\widetilde{V}[\Delta W]$, are respectively related to $E[\Delta W]$ and $V[\Delta W]$, which are the expectation and variance over the non-biased mutant population (see eqn. (5) and (6)), by

$$\widetilde{E}[\Delta W] = E[\Delta W] + \mathscr{U} \langle x_m \rangle (1 - d/\nu) \tag{32}$$

$$\widetilde{V}[\Delta W] \approx V[\Delta W] - \mathscr{U}^2 (1 - Var[x_m])(1 - d/\nu)^2, \tag{33}$$

where x_m is defined below eqn. (7). $\langle x_m \rangle$ and $Var[x_m]$ are respectively the weighted mean

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and weighted variance of x_m as follows:

$$\langle x_m \rangle \quad \equiv \quad \frac{\sum_{m=1}^{N} x_m \exp(\beta \mathscr{U} x_m)}{\sum_{m=1}^{N} \exp(\beta \mathscr{U} x_m)} \tag{34}$$

$$Var[x_m] \quad \equiv \quad \frac{\sum_{m=1}^{N} x_m{}^2 \exp(\beta \mathscr{U} x_m)}{\sum_{m=1}^{N} \exp(\beta \mathscr{U} x_m)} - \langle x_m \rangle^2. \tag{35}$$

$\langle x_m \rangle$ and $Var[x_m]$ play key roles in this model. We obtained numerical values of the expectation $E[*]$ and variance $V[*]$ of $\langle x_m \rangle$ and those of $Var[x_m]$. Fig.3 shows them as functions of $\beta \mathscr{U}$. The approximate forms of them are derived in Appendix B. If $\beta = 0$, $\langle x_m \rangle$ and $Var[x_m]$ take around 0 and 1, respectively, and then $\widetilde{E}[\Delta W]$ and $\widetilde{V}[\Delta W]$ are equivalent to $E[\Delta W]$ and $V[\Delta W]$, respectively. As β becomes higher, $\langle x_m \rangle$ and $Var[x_m]$ tend toward x_1 and 0, respectively, and then $\widetilde{E}[\Delta W]$ becomes greater than $E[\Delta W]$ and $\widetilde{V}[\Delta W]$ becomes less than $V[\Delta W]$.

Since N parents in the next generation are chosen randomly according to the probability density with mean $\widetilde{E}[\Delta W]$ and variance $\widetilde{V}[\Delta W]$, the expectation of climbing rate $\Delta \mathscr{W}$ and that of $\Delta \mathscr{U}$ are given by

$$E[\Delta \mathscr{W}] \quad = \quad \widetilde{E}[\Delta W] \tag{36}$$

$$E[\Delta \mathscr{U}] \quad = \quad \sqrt{\widetilde{V}[\Delta W]} - \mathscr{U}, \tag{37}$$

respectively. Substituting eqn. (32) into eqn. (36), we can see that $\langle x_m \rangle$ works as a selection pressure. By solving equations $E[\Delta \mathscr{W}] = 0$ and $E[\Delta \mathscr{U}] = 0$, the $\mathscr{W}$-value and $\mathscr{U}$-value at the stationary state are determined as follows:

$$\mathscr{W}^* \quad \approx \quad \mathscr{E} + \frac{\sqrt{2 \mathscr{V} \, \nu}}{\widetilde{T}} \tag{38}$$

$$\mathscr{U}^* \quad \approx \quad 2k\sqrt{d}, \tag{39}$$

where k is the landscape constant defined in eqn. (11) and $\widetilde{T}$ is the evolutionary temperature in this natural selection model:

$$\widetilde{T} \equiv \frac{\sqrt{d}}{E[\langle x_m \rangle]}. \tag{40}$$

The derivation of eqns (38) and (39) is shown in Appendix C. Note that eqns (38) and (39) are valid when $\beta \gg \beta_c$. β_c is defined as follows:

$$\beta_c \equiv \frac{E[x_1]}{2k\sqrt{d}} = \frac{1}{2k\widetilde{T_1}}, \tag{41}$$

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where $E[x_1] \approx \sqrt{2\ln(N/2\pi)}$ and $\widetilde{T_1} \equiv \sqrt{d}/E[x_1]$. To verify the effectiveness of eqns (38) and (39), we carried out a computer simulation of adaptive walk by N walkers in this natural selection model. In this simulation, the mutation process obeyed the mutagenesis protocol mentioned in the previous section. That is, the mutation distance d is distributed obeying binomial distribution shown in eqn. (27). Fig.4 shows the theoretical and numerical values of $\mathscr{W}^*$ as a function of $\widetilde{T}$. The resulting $\mathscr{W}^*$-values from the computer simulation agree well with the theoretical ones from eqn. (38), when $\beta \geq \beta_c$. When $\beta < \beta_c$, eqn. (67) is effective (data not shown) instead of eqn. (38).

Here, we interpret this natural selection scheme by the theoretical framework of the original model in Section 2. Comparing eqn. (38) and (40) with eqn. (9) and (12), we can see that $E[\langle x_m \rangle]$ plays the same role as $\langle \widetilde{N_m} \rangle$. $\langle \widetilde{N_m} \rangle$ works as the artificial selection pressure, which is caused by the selection of M individuals from among N candidates, whereas $E[\langle x_m \rangle]$ works as the natural selection pressure, which is caused by the production bias of N individuals. We introduce an effective M-value, M_{eff}, that satisfies $E[\langle x_m \rangle] = \langle \widetilde{N_m} \rangle$. By using eqn. (8), M_{eff} is approximately given by

$$M_{\text{eff}} \approx \frac{N}{\sqrt{2\pi}} \exp\left(-\frac{E[\langle x_m \rangle]^2}{2}\right). \tag{42}$$

If $\beta = 0$, $E[\langle x_m \rangle] = 0$ and then $M_{\text{eff}} = N$, while if $\beta = \infty$, $E[\langle x_m \rangle] = E[x_1]$ and then $M_{\text{eff}} = 1$. Note that the evolutionary temperature $\widetilde{T}$ in the natural selection model is equivalent to T in the artificial selection model with $M = M_{\text{eff}}$.

The expectation of the climbing rate at $(\mathscr{W}, \mathscr{U}) = (\mathscr{W}^* + \delta\mathscr{W}, \mathscr{U}^*)$ is given by

$$J \equiv E[\Delta\mathscr{W}] \approx -\frac{d}{\nu} \times \delta\mathscr{W}. \tag{43}$$

According to eqn. (13), we introduce a diffusion coefficient D in a random walk on the one-dimensional fitness space:

$$D \equiv \frac{V[\Delta W]}{2N} \tag{44}$$

$$\approx \frac{2\mathscr{V}d}{N\nu}. \tag{45}$$

In the derivation of eqn. (45) from eqn. (44), we used the stationary value of $V[\Delta W]$. By combining eqn. (43) with eqn. (22) and eqn. (45), we deduce that the expected climbing

rate, J, obeys the following simple linear relation with X:

$$J \approx \mathscr{L} \times X \quad \text{with} \quad \mathscr{L} = \frac{ND}{2k}. \tag{46}$$

This equation is almost the same as eqn. (24).

The variance of the climbing rate is given by

$$V[\Delta \mathscr{W}] \approx \frac{\widetilde{V}[\Delta W]}{N} + V[\widetilde{E}[\Delta W]] \tag{47}$$

$$\approx \mathscr{U}^{*2}\left(\frac{1}{N} + V[\langle x_m \rangle]\right). \tag{48}$$

$V[\langle x_m \rangle]$ and $E[\langle x_m \rangle]^{-2}$ are plotted against $\beta \mathscr{U}$ in Fig.3(b). It suggests that, for large $\beta \mathscr{U}$, these two quantities become closer to each other. This tendency becomes more conspicuous as N becomes greater. We can theoretically derive the following:

$$\lim_{\beta \to \infty} V[\langle x_m \rangle] = V[x_1] \approx \frac{1}{E[x_1]^2} = \lim_{\beta \to \infty} \frac{1}{E[\langle x_m \rangle]^2}. \tag{49}$$

This means that, when β grows toward ∞, only the children of the fittest parent ($m = 1$) can survive. Then, regarding that $V[\langle x_m \rangle]$ is approximately equal to $E[\langle x_m \rangle]^{-2}$, we obtain the standard deviation of the climbing rate as follows:

$$\sqrt{V[\Delta \mathscr{W}]} \approx \frac{\mathscr{U}^*}{E[\langle x_m \rangle]} = \frac{\sqrt{ND}}{E[\langle x_m \rangle]} = 2k\widetilde{T}, \tag{50}$$

for $\beta \gg \beta_{\mathrm{c}}$. Eqn. (50) is derived by using eqn. (39) and eqn. (45).

In conclusion, by identifying $E[\langle x_m \rangle]$ with $\langle \widetilde{N}_m \rangle$, or by introducing M_{eff}, the natural selection model is comprehended in the similar theoretical scheme of the artificial selection model. If this equivalence is satisfied, the evolutionary temperature, the stationary point $\mathscr{W}^*$ and the expected climbing rate J take identical values between these models. However, several properties remain slightly different from each other.

5   Effect of ruggedness: application to NK landscape

In this section, we examine the effect of ruggedness on a fitness surface by adopting the NK model (Kauffman,1993). The fitness W for a sequence "$\alpha_1 \alpha_2 \cdots \alpha_\nu$" is defined by

$$W = \sum_{j=1}^{\nu} w_j(\alpha_j | \alpha_{j_1}, \alpha_{j_2}, \cdots, \alpha_{j_K}), \tag{51}$$

where the "site-fitness" $w_j(\alpha_j|\alpha_{j_1}, \alpha_{j_2}, \cdots, \alpha_{j_K})$ is a fitness contribution from a particular letter α_j at the jth site when the K sites $\{j_1, j_2, \cdots, j_K\}$ are occupied by the particular letters $\{\alpha_{j_1}, \alpha_{j_2}, \cdots, \alpha_{j_K}\}$. The K sites $\{j_1, j_2, \cdots, j_K\}$ are randomly chosen from the whole $\nu - 1$ sites except the j-th site. The assignment of site-fitness values is modeled as follows. With a set of letters $\{\alpha_{j_1}, \alpha_{j_2}, \cdots, \alpha_{j_K}\}$ given, the site-fitness for an arbitrary letter a_i $(i = 0, 1, 2, \cdots, \lambda - 1)$ at each site is randomly assigned from the following set of λ values, but the degeneracy of assignment is not allowed:

$$w_j(a_i|\alpha_{j_1}, \alpha_{j_2}, \cdots, \alpha_{j_K}) \in \left\{\frac{2\varepsilon}{\lambda} h \middle| h = 0, 1, 2, \cdots, \lambda - 1\right\} \tag{52}$$

under the condition that $w_j(a_i) \neq w_j(a_{i'})$ for $i \neq i'$, where $\varepsilon \leq 0$ is a constant. The resulting fitness landscape is called the "NK landscape", although the original NK landscape was defined in the binary sequence space (Kauffman,1993).

Consider that a single mutation occurs in the j-th site. Let $\widetilde{K}$ be the number of affected sites and let $\{i_1, i_2, \cdots, i_{\widetilde{K}}\}$ be the $\widetilde{K}$ sites affected by the single mutation. The value of site-fitness w_j at the mutated site is re-assigned from eqn. (52). In addition, the values of site-fitnesses, $\{w_{i_1}, w_{i_2}, \cdots, w_{i_{\widetilde{K}}}\}$, for the affected sites are also re-assigned from eqn. (52) randomly. Then, the single mutation causes the change of site-fitnesses for the $(1 + \widetilde{K})$ sites. We can estimate that $\widetilde{K}$ is distributed obeying binomial distribution with mean K and variance $K(1 - K/(\nu - 1))$. Then, we use $\widetilde{K} = K$ for simplicity. Let d_{eff} be the number of sites where site-fitnesses change as results of the d-fold point mutations. d_{eff} is given by

$$d_{\text{eff}} = d + c \sum_{j \in \{\text{mutated sites}\}}^{d} \widetilde{K}, \tag{53}$$

where the sum is taken over the d mutated sites and c is the correction factor to avoid multiplication of counting affected sites and then $c \leq 1$. Therefore, the statistical effect of the d-fold point mutations on the fitness in the NK model is equivalent to the statistical effect of the d_{eff}-fold point mutations on the fitness in the Mt. Fuji-type model ($K = 0$). Therefore, d_{eff} can be called the "effective mutation distance". The mean of d_{eff} is approximately given by

$$\overline{d_{\text{eff}}} \approx d(1 + \widetilde{K}) \approx d(1 + K), \qquad \text{when } d(1 + K) \ll \nu. \tag{54}$$

If $d(1+K)$ is large and comparable to ν, $\overline{d_{\text{eff}}}$ does not show such a linear response against $d(1+K)$. As a result, by replacing the mutation distance d in Section 2 with the mean effective mutation distance $\overline{d_{\text{eff}}}$, we can apply our original scheme shown in Section 2 to this case of NK landscapes. Fig.5(a) shows the theoretical and numerical values of $\mathscr{W}^*$ as a function of T_{eff}, where T_{eff} is given by substituting $\overline{d_{\text{eff}}}$ in eqn. (54) into d in eqn. (12). The resulting $\mathscr{W}^*$-values from the computer simulation agree well with the theoretical ones from eqn. (9). The result suggests that the introduction of $\overline{d_{\text{eff}}}$ is effective in cases where $\overline{d_{\text{eff}}} \ll \nu$.

In a physical sense, the ruggedness should affect not the evolutionary temperature but the landscape constant k. Therefore, we redefine k and T as follows. Substituting $\overline{d_{\text{eff}}}$ in eqn. (54) into d in eqn. (19), we define the landscape constant k as

$$k \equiv \sqrt{\frac{\mathscr{V}(1+K)}{2\nu}} = \sqrt{\frac{\langle \sigma_l^2 \rangle (1+K)}{2}},\tag{55}$$

while the evolutionary temperature T is defined as it is in eqn. (12). In this interpretation, k is $\sqrt{1+K}$ times greater than the k in eqn. (11) for the Mt. Fuji-type landscape. This is reasonable because the landscape constant k represents a standard deviation of a fitness change for a unit Hamming distance and the ruggedness enlarges the standard deviation. Fig.5(b) shows the theoretical and numerical values of $\mathscr{W}^*$ as a function of T, for various k-values. It is demonstrated that the redefinition of k is effective for interpretation of the properties of the NK landscape.

Next, we consider cases where the mutagenesis protocol is the same as that in Section 3, that is, cases where the mutation distance d is distributed according to the binomial distribution shown in eqn. (27). Under a low evolutionary temperature, the walker has the problem of getting trapped at the local optima (Amitrano et $al.$,1989). According to Section 3, we can expect that the walker is likely to get trapped at the local optima when $T \leq T_{\text{c}}$, where T_{c} is shown in eqn. (29). We verified this prediction by the computer simulation. Fig.6 shows the theoretical and numerical values of $\mathscr{W}^*$ as a function of T, for various K-values. We can confirm that the phase transition occurs around $T = T_{\text{c}}$, for every K-value (see Fig.1 for comparison). In conclusion, when $T > T_{\text{c}}$, the adaptive walk

is ergodic and our original scheme is applicable, while when $T < T_c$, the system settles in a glass-like state (Stellinger & Weber,1984), the adaptive walk is not ergodic and our original scheme is not applicable.

6 Effect of noise in the fitness measurements

In this section, we examine the effect of noise in the fitness measurements (Levitan & Kauffman,1995). For simplicity, we deal with the case of $M = 1$, that is the adaptive walk by the fittest. Consider that a random noise obeying Gaussian density with standard deviation ϱ is added to the fitness values. The fitness measurements with large noise is likely to select the second- or third- or m-th fittest mutant as the "pseudo-fittest" instead of the fittest mutant. From a statistical view point, the expected fitness of the m-th fittest among N mutants is equivalent to that of the fittest among N/m mutants (see eqn.(21) in Aita *et al.*,(2004)). Therefore, we introduce $N_{\text{eff}} = N/m$ as the "effective screening size". We estimated the probability $p(m)$ that the m-th fittest mutant is selected as the pseudo-fittest by the fitness measurements with the resolution ϱ. The mean value of N_{eff} is given by

$$\overline{N_{\text{eff}}} = \sum_{m=1}^{N} N_{\text{eff}}\, p(m) = \sum_{m=1}^{N} \frac{N}{m} p(m) \tag{56}$$
$$\approx N^{(1-0.21\varrho/\sqrt{V})}, \tag{57}$$

where V represents the variance of mutant's fitness, $V[\Delta W]$ in eqn. (6). As a result, by replacing the population size N in Section 2 with the mean effective population size $\overline{N_{\text{eff}}}$, we can apply our original scheme shown in Section 2 to this case.

7 Conclusion

Introducing various modifications to the original evolution model, that is based on the adaptive walk adopting (M, N)-ES on the Mt. Fuji-type fitness landscape, we examined the effect of the modification on the properties of adaptive walk. We introduced "effective" quantities such as the effective mutation distance d_{eff} or effective screening size N_{eff}. By

applying these effective quantities to the original model, the effect of each modification is systematically described in the theoretical framework of the original model. Then, the thermodynamical scheme mentioned in Section 2 is almost applicable by modifying the evolutionary temperature T shown in eqn. (12) to the effective one:

$$T_{\text{eff}} = \sqrt{\frac{d_{\text{eff}}}{2\ln(N_{\text{eff}}/M_{\text{eff}}\sqrt{2\pi})}}. \tag{58}$$

The effective quantities are as follows. (1) In the case where the mutation distance d is distributed obeying binomial distribution $B(d)$ with mean $\overline{d}$, the effective mutation distance $d_{\text{eff}} = \overline{d}$ and effective screening size $N_{\text{eff}} = N \times B(d_{\text{eff}})$ should be applied. (2) In the case where the selection process obeys the natural selection protocol (the number of children generated from a parent depends on the fitness of the parent), we interpret that M_{eff} parents produce N children and the best M_{eff} individuals among the N children will become new parents in the next generation. M_{eff} is given by $M_{\text{eff}} \approx \frac{N}{\sqrt{2\pi}}\exp\left(-E[\langle x_m\rangle]^2/2\right)$, where $E[\langle x_m\rangle]$ is a measure of the selection pressure. (3) In the case where ruggedness is introduced to the landscape according to the NK model, the landscape constant k (= standard deviation of a fitness change for a unit Hamming distance) is $\sqrt{1+K}$ times greater than the k-value for the Mt. Fuji-type fitness landscape. It is reasonable that ruggedness enlarges the landscape constant k. (4) In the case where a noise is included in the fitness measurement, we interpret that the screening size is reduced to $N_{\text{eff}} \approx N^{(1-0.21\varrho/\sqrt{V})}$, where $\sqrt{V}/\varrho$ represents Signal/Noise ratio in the fitness measurement.

In addition, we found that there are two different phases in cases where the mutation distance d is distributed according to the binomial distribution. When $T > T_{\text{c}} \approx 0.71$, the adaptive walk is ergodic and the thermodynamical scheme holds, while when $T < T_{\text{c}}$, the adaptive walk is not ergodic and thermodynamical scheme is not applicable. The reason is as follows: when $T < T_{\text{c}}$, the replication of sequences is so accurate that a population of N children includes non-mutated sequences identical to their parents. In this case, the walkers never descend the landscape. This leads to the problem of getting trapped at the local optima on rugged fitness landsacpe.

8 Appendix

8.1 A: Probability density of fitness over the biased mutant population

Let ΔW_m be the fitness change from the m-th parent to its arbitrary mutant. We denoted the probability density of ΔW_m over all conceivable mutants generated from the m-th parent by $\psi_m(\Delta W_m)$ (eqn.(16) in Aita $et\ al.$,2004). Let ΔW be the change between the mean fitness $\mathscr{W}$ over the N parents and the fitness of their arbitrary mutant. That is, these variables are related by $\mathscr{W} + \Delta W = W_m + \Delta W_m$. The probability density of ΔW over the biased mutant population is described by

$$\widetilde{\Psi}(\Delta W) = \sum_{m=1}^{N} \frac{\exp(\beta\,W_m)}{\sum_{m=1}^{N} \exp(\beta\,W_m)} \psi_m(\Delta W + \mathscr{W} - W_m). \tag{59}$$

Here, we assume that W_m's are randomly chosen according to the Gaussian density $\mathscr{N}(x|\mathscr{W}, \mathscr{U}^2)$. Then, we assume

$$W_m = \mathscr{W} + \mathscr{U}\,x_m. \tag{60}$$

The expectation and variance of ΔW_m based on the density $\psi_m(\Delta W_m)$ are respectively given by eqn.(11) and eqn.(13) in Aita $et\ al.$,(2004). Then, by substituting eqn. (60) into eqn. (59), the expectation and variance of ΔW based on $\widetilde{\Psi}(\Delta W)$ are, respectively, given by

$$\widetilde{E}[\Delta W] = -(\mathscr{W} - \mathscr{E})\frac{d}{\nu} + \mathscr{U}\langle x_m\rangle\left(1 - \frac{d}{\nu}\right), \tag{61}$$

$$\widetilde{V}[\Delta W] = \left(2\mathscr{V} + c_1(\mathscr{U}^2 Var[x_m] + (\mathscr{W} + \mathscr{U}\langle x_m\rangle - \mathscr{E})^2) + c_2(\mathscr{W} + \mathscr{U}\langle x_m\rangle - \mathscr{E})\right)\frac{d}{\nu}$$

$$+ \left(1 - \frac{d}{\nu}\right)^2 Var[x_m]\,\mathscr{U}^2, \tag{62}$$

where $\langle x_m\rangle$ and $Var[x_m]$ are defined in eqns (34) and (35), respectively.

8.2 B: Analytical forms for the expectations of eqns (34) and (35)

We define the following generating function:

$$Z(\beta\mathscr{U}) \equiv \ln \sum_{m=1}^{N} e^{\beta\mathscr{U}\,x_m}.$$

The expectations of eqns (34) and (35) are respectively given by

$$
\begin{aligned}
E[\langle x_m \rangle] &= E\left[\frac{\mathrm{d}Z}{\mathrm{d}(\beta\mathscr{U})}\right] = \frac{\mathrm{d}E[Z]}{\mathrm{d}(\beta\mathscr{U})} \\
E[Var[x_m]] &= E\left[\frac{\mathrm{d}^2 Z}{\mathrm{d}(\beta\mathscr{U})^2}\right] = \frac{\mathrm{d}^2 E[Z]}{\mathrm{d}(\beta\mathscr{U})^2}.
\end{aligned}
$$

Since x_m's are Gaussian random variables according to the standard Gaussian $\mathscr{N}(x|0,1)$, the probability density of $\sum_{m=1}^{N} \exp(\beta\mathscr{U} x_m)$ can be calculated by the N-fold convolution of the logarithmic Gaussian distribution $\mathscr{N}(\ln y|0,(\beta\mathscr{U})^2)/y$. This convolution is however complicated. Here, we use the following approximation:

$$
\begin{aligned}
E\left[\frac{1}{N}\sum_{m=1}^{N} e^{\beta\mathscr{U} x_m}\right] &\approx \int_{-\infty}^{E[x_1]} e^{\beta\mathscr{U} x} \mathscr{N}(x|0,1)\mathrm{d}x \\
&= e^{(\beta\mathscr{U})^2/2} \int_{-\infty}^{E[x_1]-\beta\mathscr{U}} \mathscr{N}(x|0,1)\mathrm{d}x.
\end{aligned}
$$

Then, we obtain the approximate form of $E[Z]$ as follows:

$$
\begin{aligned}
E[Z] &\approx \ln E\left[\sum_{m=1}^{N} e^{\beta\mathscr{U} x_m}\right] \\
&\approx \frac{(\beta\mathscr{U})^2}{2} + \ln \int_{-\infty}^{E[x_1]-\beta\mathscr{U}} \mathscr{N}(x|0,1)\mathrm{d}x,
\end{aligned}
$$

where we drop a constant term.

Concerning the expectations,

$$
\lim_{\beta\mathscr{U}\to 0} E[\langle x_m \rangle] = \beta\mathscr{U} \qquad \lim_{\beta\mathscr{U}\to\infty} E[\langle x_m \rangle] = E[x_1], \tag{63}
$$

$$
\lim_{\beta\mathscr{U}\to 0} E[Var[x_m]] = 1 \qquad \lim_{\beta\mathscr{U}\to\infty} E[Var[x_m]] = 0. \tag{64}
$$

Concerning the variances,

$$
\lim_{\beta\mathscr{U}\to 0} V[\langle x_m \rangle] = 1/N \qquad \lim_{\beta\mathscr{U}\to\infty} V[\langle x_m \rangle] = V[x_1], \tag{65}
$$

where $V[x_1]$ is the variance of x_1 and is approximately given by $V[x_1] \approx 1/(E[x_1]^2 + 1)$. We neglect $V[Var[x_m]]$ because of its smallness.

8.3 C: Derivation of eqns (38) and (39)

The $\mathscr{W}$-value and $\mathscr{U}$-value at the stationary state, $\mathscr{W}^*$ and $\mathscr{U}^*$, are determined by solving equations $E[\Delta\mathscr{W}] = 0$ (eqn. (36)) and $E[\Delta\mathscr{U}] = 0$ (eqn. (37)). The procedure of solving

the equations is similar to the way that is shown in Appendix C in Aita *et al.*,(2004). As a result, the $\mathscr{U}^*$-value is given by solving the following equation of $\mathscr{U}^*$:

$$\mathscr{U}^* = \sqrt{\frac{2\mathscr{V}d}{\nu(1 - (1 - 2d/\nu)Var[x_m])}}, \tag{66}$$

where $Var[x_m]$ is the function of $\mathscr{U}^*$ (eqn. (64)). By using the resulting $\mathscr{U}^*$-value, we can determine the $\mathscr{W}^*$-value as follows:

$$\mathscr{W}^* = \mathscr{E} + \sqrt{\frac{2\mathscr{V}\nu}{1 - (1 - 2d/\nu)Var[x_m]}} \times \frac{1}{\widetilde{T}}, \tag{67}$$

where $\widetilde{T}$ is the following "search parameter" defined in eqn. (40). In this study, we deal with cases where β is large enough to satisfy $\beta\mathscr{U}^* \gg E[x_1]$ and then $Var[x_m] \approx 0$. In addition, by using eqn. (11), we obtain eqns (38) and (39).

9 Acknowledgements

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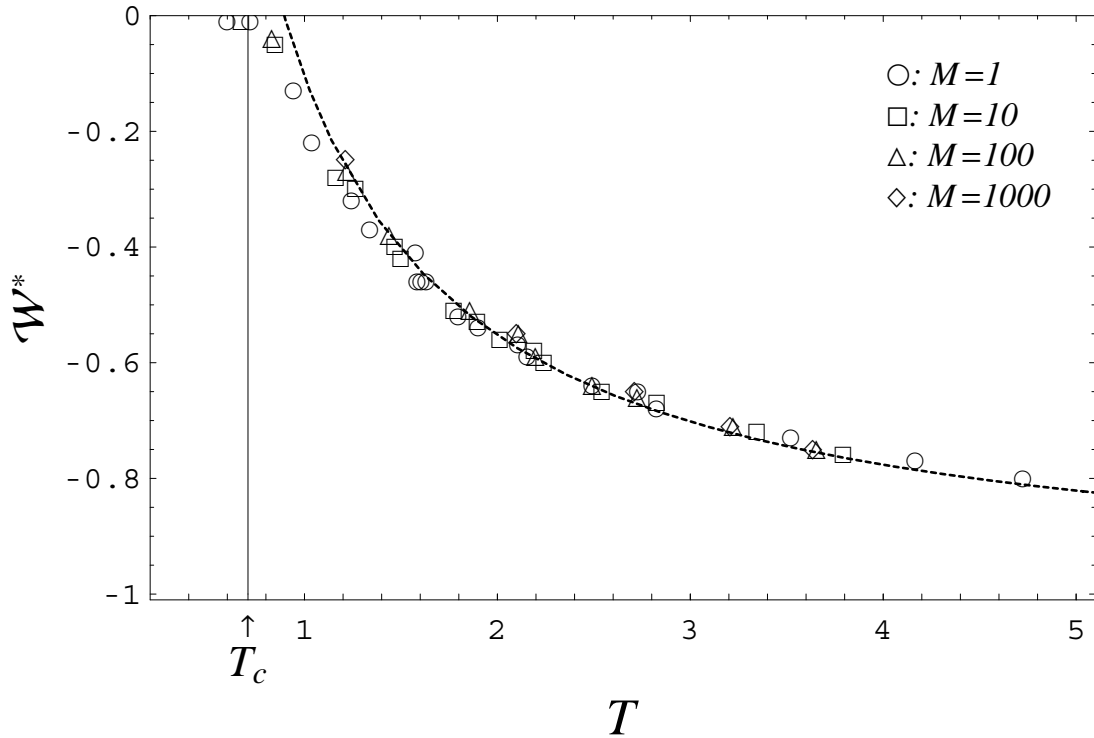
Figure 1: **The stationary point $\mathscr{W}^*$ as a function of T.** The ordinate represents $\mathscr{W}^*$ normalized by $|\mathscr{E}|$, where $\mathscr{E}$ is the mean fitness over all possible sequences. T was calculated by substituting $d = \overline{d} = \mu\nu$ into eqn. (12). The dashed line represents the theoretical values described in eqn. (9). T_c represents the critical point for phase transition and is given in eqn. (29). The plots of each symbol represent the resulting values from an adaptive walk simulation using the Monte Carlo method. N=10, 100, 1000 and 10000 for $M = 1$. N=100, 1000 and 10000 for $M = 10$. N=1000 and 10000 for $M = 100$. N=10000 for $M = 1000$. The μ-values were set as follows: $\overline{d} = \mu\nu = 5, 15, 25, 35, 45$ for each M-value. $(\lambda, \nu, L) = (200, 400, 4)$. $\nu_l = 100$ for all l. $\varepsilon_l = -4/10 \times l$.
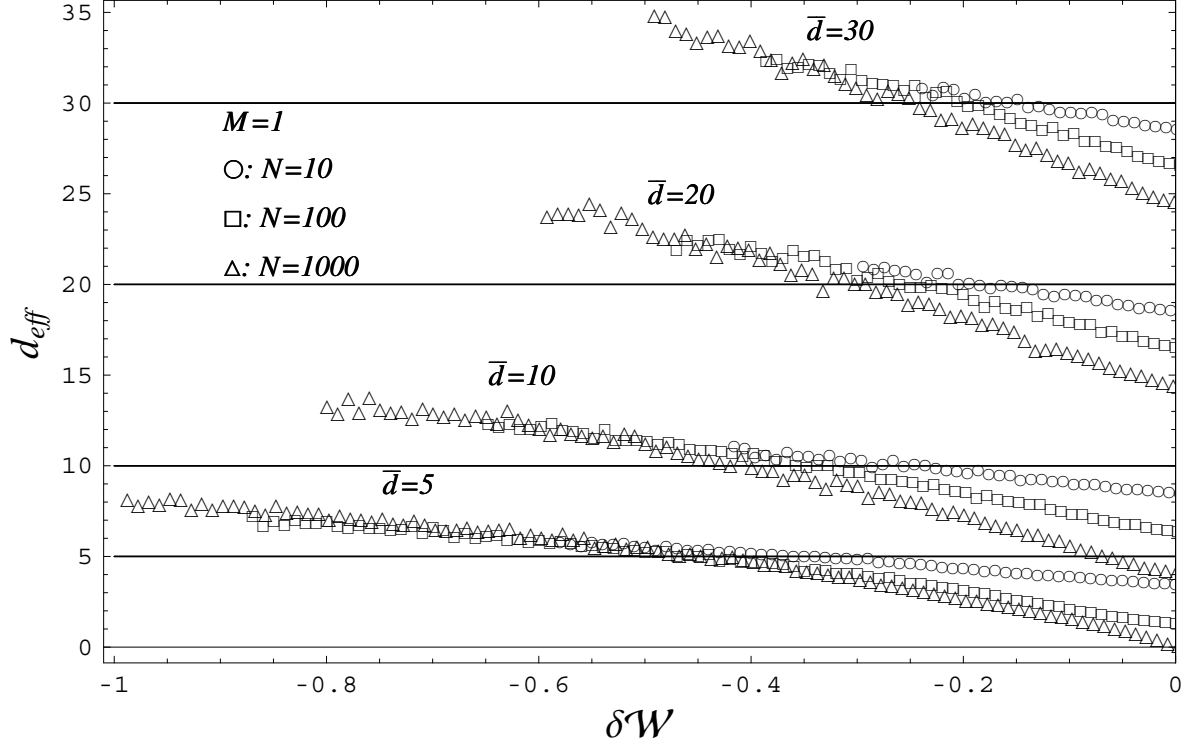
Figure 2: **(a): The effective mutation distance, d_{eff}, as a function of $\delta\mathscr{W}$.** The values of $\delta\mathscr{W} = \mathscr{W} - \mathscr{W}^*$ were calculated from the numerical $\mathscr{W}^*$-values from the simulation (Fig.1). Four horizontal lines represent $\overline{d} = 5$, 10, 20 and 30, from the lower line to the upper line. The values of N, M and $\overline{d} = \mu\nu$ are shown in the Figure. $(\lambda, \nu, L) = (200, 400, 4)$. $\nu_l = 100$ for all l. $\varepsilon_l = -4/10 \times l$. **(b),(c): The expectation of climbing rate, J, as a function of $\delta\mathscr{W}$ or X.** The ordinate and abscissa (bottom) represent J and $\delta\mathscr{W}$, respectively, normalized by $|\mathscr{E}|$. The J-values from the computer simulation are plotted by symbols. The X-values were calculated from eqn. (22). The solid lines are the theoretically predicted values by $J = -d_{\mathrm{eff}}/\nu \times \delta\mathscr{W}$.
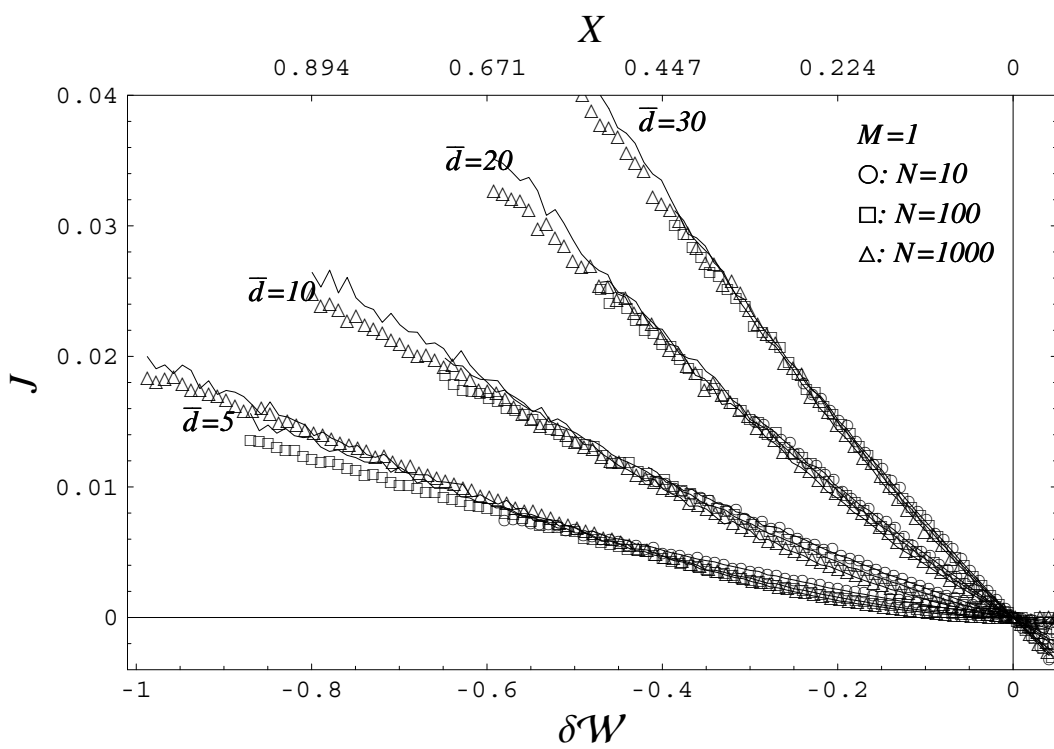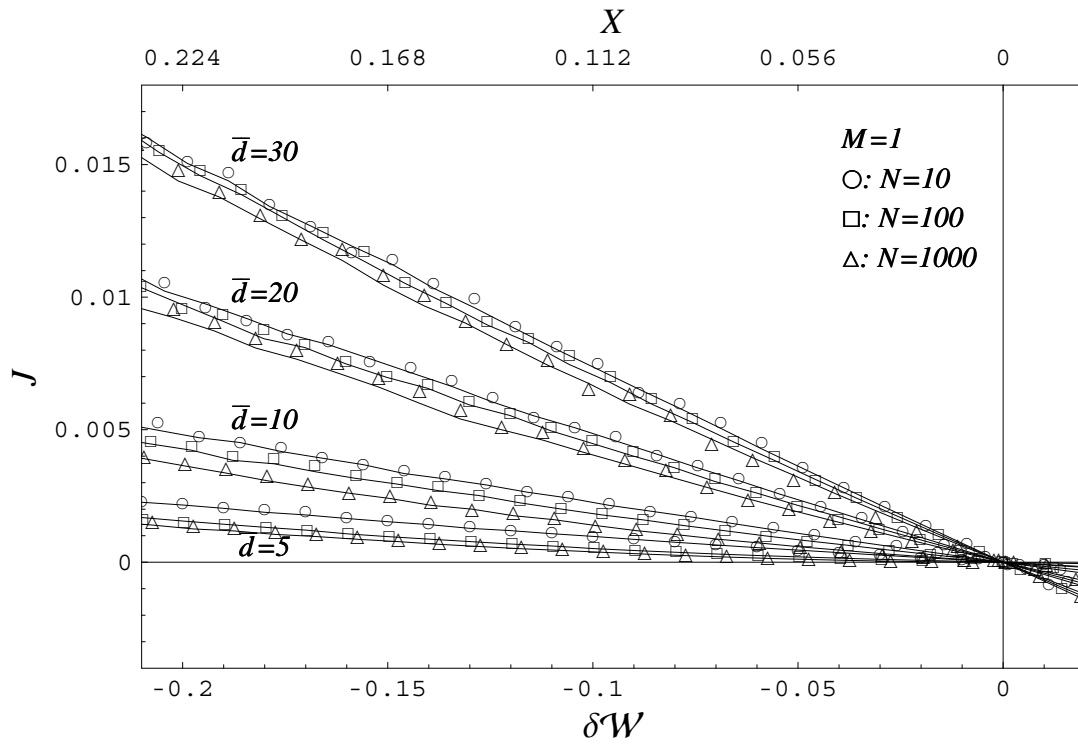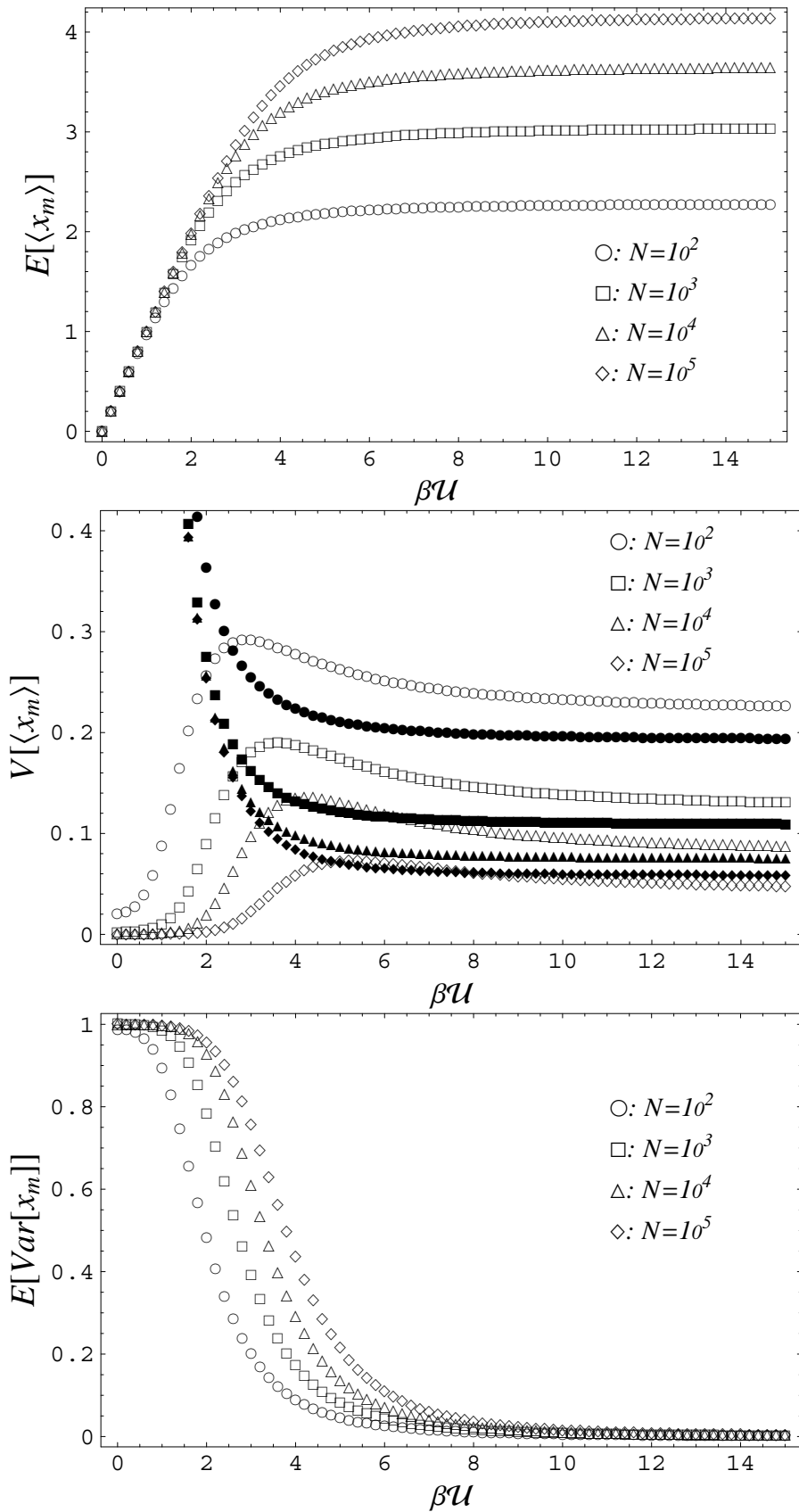
Figure 3: $E[\langle x_m \rangle]$ (upper), $V[\langle x_m \rangle]$ (middle) and $E[Var[x_m]]$ (bottom) against $\beta \mathcal{U}$. The plotted values were obtained through computer simulation. The filled symbols represent the values of $E[\langle x_m \rangle]^{-2}$ for their respective outlined symbols, for comparing with $V[\langle x_m \rangle]$.
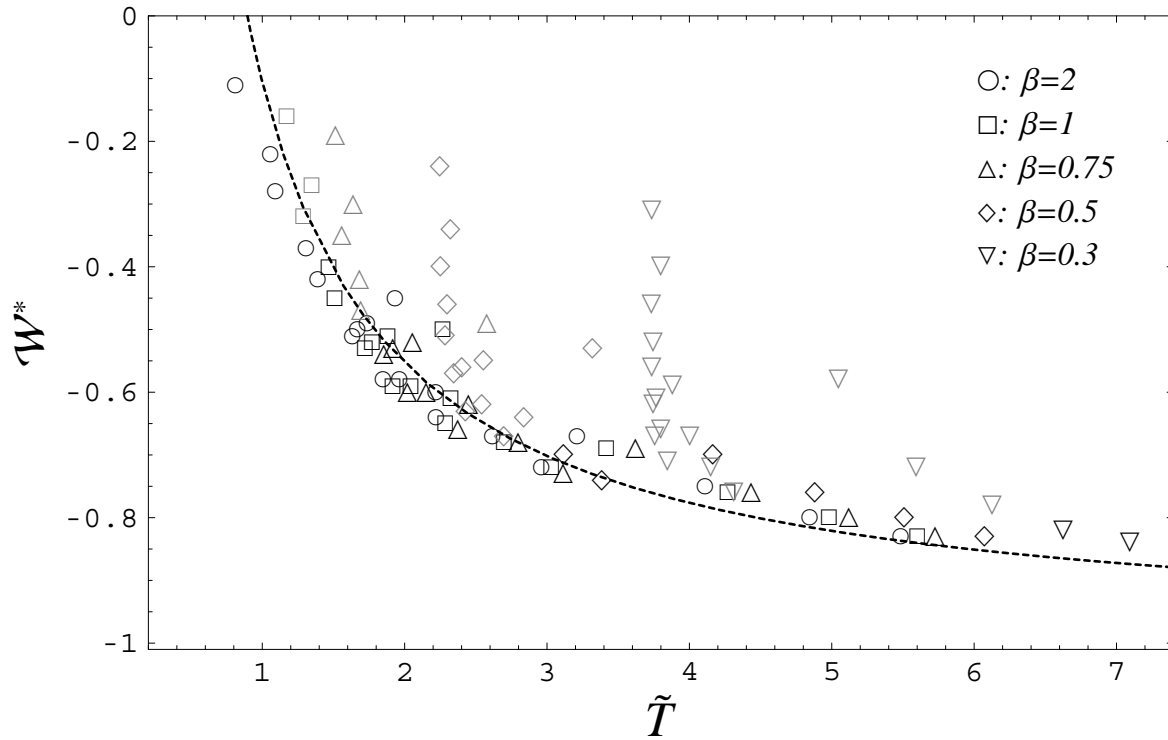
Figure 4: **The stationary point $\mathscr{W}^*$ as a function of $\widetilde{T}$.** The ordinate represents $\mathscr{W}^*$ normalized by $|\mathscr{E}|$. $\widetilde{T}$ was calculated by substituting $d = \overline{d} = \mu\nu$ into eqn. (40). The dashed line represents the theoretical values described in eqn. (38). The plots of each symbol represent the resulting values from an adaptive walk simulation using the Monte Carlo method. The thick symbols and thin ones are for cases where $\beta \geq \beta_c$ and cases where $\beta < \beta_c$, respectively. $N=10$, 100, 1000 and 10000 for each β-value. The μ-values were set as follows: $\overline{d} = \mu\nu = 5, 15, 25, 35, 45$ for each β-value. $(\lambda, \nu, L) = (200, 400, 4)$. $\nu_l = 100$ for all l. $\varepsilon_l = -4/10 \times l$.
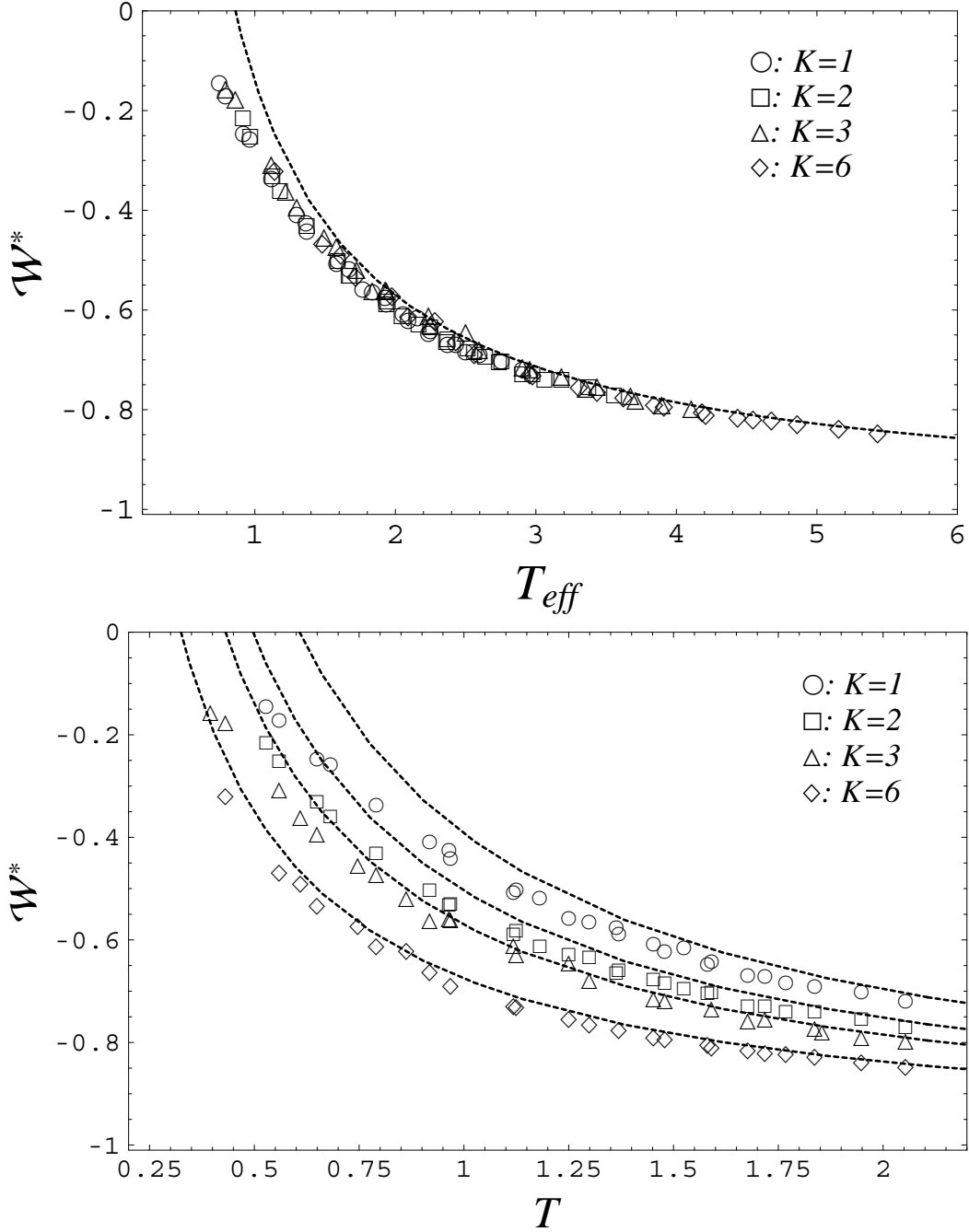
Figure 5: **The stationary point $\mathscr{W}^*$ as a function of T_{eff} (top) or as a function of T (bottom).** The mutation distance d is constant through the walk process. The ordinate represents $\mathscr{W}^*$ normalized by $|\mathscr{E}|$. T_{eff} was calculated by substituting $\overline{d_{\text{eff}}} = d(1 + K)$ into d in eqn. (12). The dashed line represents the theoretical values described in eqn. (20) with $T = T_{\text{eff}}$ (top) or with $k = \sqrt{\mathscr{V}(1 + K)/2\nu}$ (bottom). The plots of each symbol represent the resulting values from an adaptive walk simulation using the Monte Carlo method. Each walk was carried out up to 400 generations. K=1, 2, 3 and 6. $M = 1$. N=10, 100, 1000 and 10000. $d = 1 \sim 30$. $(\lambda, \nu, L) = (20, 100, 1)$. $\varepsilon = -1$.
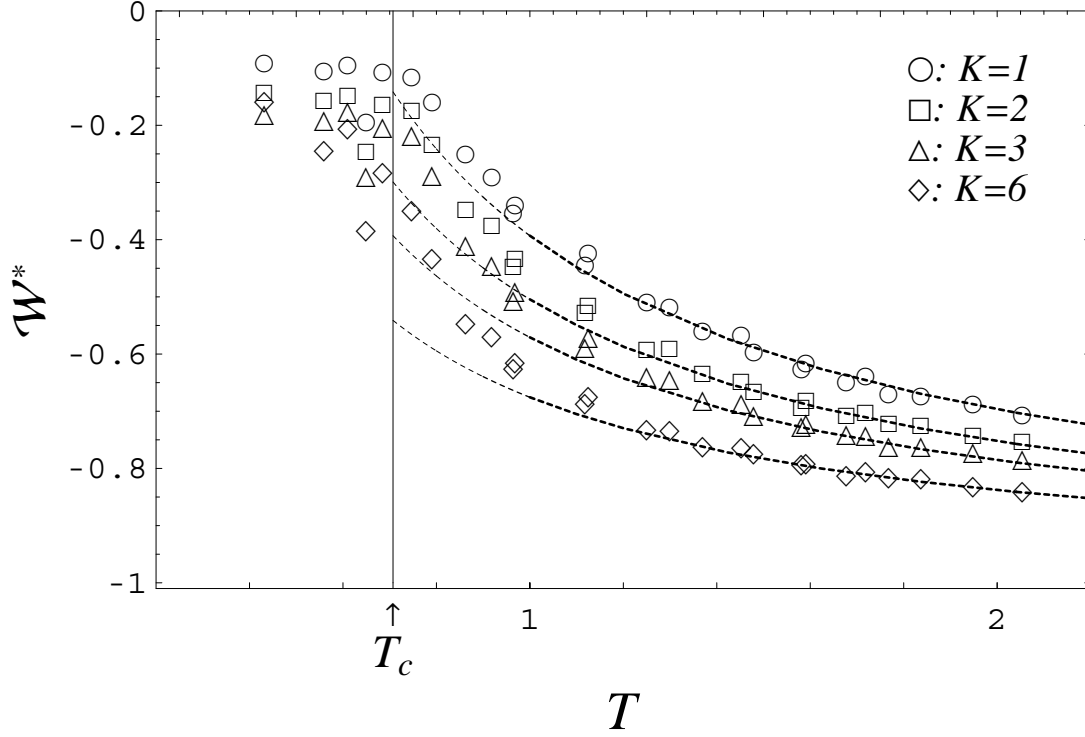
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Figure 6: **The stationary point $\mathscr{W}^*$ as a function of T.** The mutation distance d is distributed according to the binomial distribution shown in eqn. (27). T was calculated by substituting $d = \bar{d} = \mu\nu$ into eqn. (12). The dashed line represents the theoretical values described in eqn. (20) with $k = \sqrt{\mathscr{V}(1+K)/2\nu}$. T_c represents the critical point for phase transition and is given in eqn. (29). Other captions are the same as those in Fig.5.