

Thermodynamical Interpretation of an Adaptive Walk on a Mt.
Fuji-type Fitness Landscape: Einstein Relation-like Formula
Holds in a Stochastic Evolution

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Abstract

We have theoretically studied the statistical properties of adaptive walks (or hill-climbing) on a Mt. Fuji-type fitness landscape in the multi-dimensional sequence space through mathematical analysis and computer simulation. The adaptive walk is characterized by the "mutation distance" d as the step-width of the walker and the "population size" N as the number of randomly generated d -fold point mutants to be screened. In addition to the fitness W , we introduced the following quantities analogous to thermodynamical concepts: "free fitness" $G(W) \equiv W + T \times S(W)$, where T is the "evolutionary temperature" $T \propto \sqrt{d/\ln N}$ and $S(W)$ is the entropy as a function of W , and the "evolutionary force" $X \equiv d(G(W)/T)/dW$, that is caused by the mutation and selection pressure. It is known that a single adaptive walker rapidly climbs on the fitness landscape up to the stationary state where a "mutation-selection-random drift balance" is kept. In our interpretation, the walker tends to the maximal free fitness state, driven by the evolutionary force X . Our major findings are as follows: First, near the stationary point W^* , the "climbing rate" J as the expected fitness change per generation is described by $J \approx L \times X$ with $L \approx V/2$, where V is the variance of fitness distribution on a local landscape. This simple relationship is analogous to the well-known Einstein relation in Brownian motion. Second, the "biological information gain" ($\Delta G/T$) through adaptive walk can be described by combining the Shannon's information gain (ΔS) and the "fitness information gain" ($\Delta W/T$).

1 Introduction

The theoretical study on *in vitro* evolution or rational evolutionary design is viewed from an adaptive walk on a fitness landscape in biopolymer sequence space, where the term "fitness" is defined as a quantitative measure of a certain physicochemical property of a biopolymer (i.e. enzymatic activity, affinity to a ligand or structural stability). An additive fitness landscape, called the Mt. Fuji-type landscape, is ideal for stepwise rapid evolution. We have studied the statistical properties of adaptive walks subject to $(1, N)$ -ES or $(1 + N)$ -ES on the Mt. Fuji-type fitness landscape (Aita & Husimi,1998;2000). The $(1, N)$ -ES and $(1 + N)$ -ES are evolution strategies that obey the following simple rule (Rechenberg,1984): a wild-type as a parent produces d -fold point mutants of a population size N as descendants, and subsequently the best mutant among the N mutants (for $(1, N)$ -ES) or among the mixture of the wild-type and N mutants (for $(1 + N)$ -ES) will become a new wild-type in the next generation. This is realized by a cloning-screening type *in vitro* evolution experiment (Yamauchi *et al.*,2002). In the previous study, we found that a single adaptive walker subject to the $(1, N)$ -ES can climb on the landscape rapidly in the initial stage, subsequently in a later stage, the walker reaches a stationary state where a "mutation-selection-random drift balance" is kept. In the stationary state, the walker stagnates around a stationary point with a small fitness fluctuation (here we note that the walker does not stagnate around a particular sequence in the sequence space). In the former half of this paper, we focus on how the stationary point or climbing rate or the mean step number up to the stationary state depends on the search parameter such as the mutation distance d or the population size N .

The evolution can be considered as an analogous system to the nonequilibrium thermodynamic system. That is, the adaptive walker is pushed upward by an "evolutionary force" caused by the mutation and selection pressure. In the evolution process, the mutation rate or finite population size seems to be analogous to the temperature T (Iwasa,1988; Eigen *et al.*,1989). Particularly, the well-known Einstein relation $\mu = D/k_B T$ in Brownian motion seems to be related to the evolution system (Ito *et al.*,2002; Sato *et al.*,2002),

where μ is the mobility or admittance of a particle in nonequilibrium and D is the diffusion constant or fluctuation at equilibrium (Einstein,1905). In the one-dimensional system, the variance V of displacement per unit time is equivalent to $2D$.

Previously, analyzing of evolution from the thermodynamical point of view has been done (Husimi,1988; Iwasa,1988; Eigen *et al.*, 1989; Schuster & Stadler,1994; Wilke *et al.*,2001). However, the evolutionary force or evolutionary temperature remains unclear as well as the relationship between evolutionary dynamics and Einstein relation. In the latter half of this paper, introducing "free fitness", "evolutionary force" and "evolutionary temperature", we take a heuristic approach to interpret the adaptive walks from the thermodynamical point of view and present that the Einstein relation-like formula holds in the evolution system we have studied. In addition, we consider the adaptive walk in terms of three types of "information": one is the "fitness information" as content or meaning of sequences, the second is the "Shannon's information" as extent or degeneracy of sequences with identical fitnesses, the third is the "biological information" as the combination of the two.

In Sections 2, 3 and 4, we focus on the adaptive walk adopting the $(1, N)$ -ES with a random sampling search (stochastic search). The adaptive walk with an exhaustive search (deterministic search) or the walk adopting the $(1 + N)$ -ES is discussed in the Discussion Section (Section 5).

2 Model of Adaptive Walk on Mt. Fuji-type Fitness Landscape

2.1 Mt. Fuji-type Fitness Landscape

We deal with the λ -valued ν -dimensional sequence space of all the possible sequences of biopolymers, where ν represents the chain length of the biopolymer and λ represents the number of available alphabets or letters in each site. We focus on the case of a λ large enough to give $(\lambda - 1)/\lambda \approx 1$. The fitness W for an arbitrary sequence "P" is defined as

follows:

$$W(P) = \sum_{j=1}^{\nu} w_j(\alpha_{P_j}) \leq 0, \quad (1)$$

where $w_j(\alpha_{P_j})$ is the "site-fitness", that is an independent contribution from a particular residue α_{P_j} at the j th site in the sequence P . For a simple mathematical model, the site-fitness contributed from the i -th residue α_i (eg. $(\alpha_0, \alpha_1, \alpha_2, \alpha_3)=(A, T, G, C)$ and $\lambda = 4$ for DNA) at every site is given as follows:

$$w_j(\alpha_i) = \frac{2\varepsilon}{\lambda} i \leq 0 \quad (i = 0, 1, 2, \dots, \lambda - 1). \quad (2)$$

The ε is a negative constant and corresponds to the mean site-fitness over "not optimal" residues ($i = 1, 2, \dots, \lambda - 1$):

$$\varepsilon = \frac{1}{\lambda - 1} \sum_{i=1}^{\lambda-1} w_j(\alpha_i) < 0. \quad (3)$$

The additive fitness landscape defined by eqn. (1) is called the "Mt. Fuji-type" landscape in λ -valued ν -dimensional sequence space. The fitness for the optimal sequence "O" as the peak takes zero and those for all other sequences take negative values. Since the mean fitness over all possible sequences in the defined sequence space is approximately given by $\varepsilon\nu$, the $|\varepsilon\nu|$ corresponds to the height of the landscape (peak), and the measure of the width of the landscape is ν . The probability density of the fitness over all the sequences is approximately given by

$$\mathcal{N}\left(W \left| \varepsilon\nu, \frac{\varepsilon^2\nu}{3} \right.\right) \quad \text{for } W \leq 0, \quad (4)$$

where $\mathcal{N}(W|E, V)$ represents a normal distribution of the variable W with the mean E and variance V .

2.2 Adaptive Walk in a Cloning-Screening Type Evolution System

We consider the adaptive walks on the Mt. Fuji-type fitness landscape. Let P_t be a wild-type in the t -th generation in a single adaptive walk. Thus, the walk process is expressed as a sequential change of P_t :

$$P_0 \xrightarrow{1} P_1 \xrightarrow{2} P_2 \xrightarrow{3} \dots \xrightarrow{t} P_t \xrightarrow{t+1} \dots$$

A "walker" is the general term for these wild-types (P_t corresponds to the internal state of the walker after the t -th step).

A single adaptive walk is performed by repetition of the evolution cycle, which is composed of the following two processes.

1. **Mutagenesis process:** a number of d -fold point mutants of a population size N are randomly generated from the wild-type P_t , where d is the number of mutated sites. The mutation distance d in Hamming distance unit corresponds to the step-width of the walker. The d -fold point mutants are located on the spherical shell with a radius d in the sequence space, where the center of the sphere corresponds to the wild-type P_t . In this paper, we focus on the case where $d \ll \nu$ and

$$N \ll \binom{\nu}{d} (\lambda - 1)^d. \quad (5)$$

The right-hand in the eqn. (5) is the number of all conceivable d -fold point mutants. The search strategy according to eqn. (5) is called the "random sampling search" (or "stochastic search"), which makes the adaptive walk process stochastic (Aita & Husimi,1998;2000).

2. **Selection process:** the fittest mutant R that has the highest fitness among the N mutants is picked out. The wild-type in the $t + 1$ -th generation, P_{t+1} , is determined by

$$P_{t+1} = R. \quad (6)$$

This evolution strategy is called "(1, N)-ES" (Rechenberg,1984).

By describing a single adaptive walk process in the one-dimensional fitness space:

$$W(P_0) \xrightarrow{1} W(P_1) \xrightarrow{2} W(P_2) \xrightarrow{3} \dots \xrightarrow{t} W(P_t) \xrightarrow{t+1} \dots,$$

and by analyzing it mathematically, we examined the statistical properties of the most "expected" or "typical" adaptive walks with a fixed d and N , instead of a particular walk process.

3 Statistical Properties of Adaptive Walk

3.1 Local Fitness Distribution around a Wild-type

As a preliminary study of the adaptive walks, we consider a fitness distribution for a mutant population generated from a wild-type sequence. Consider a wild-type sequence P with a fitness W and a mutant population that consists of all conceivable d -fold point mutants generated from the wild-type P. Let ΔW be a fitness change between the fitness W for the wild-type P and that for an arbitrary d -fold point mutant:

$$\Delta W \equiv W(\text{arbitrary } d\text{-fold point mutant}) - W(\text{wild-type P}),$$

where $W(\text{wild-type P}) = W$. In our previous study, we have derived the local fitness distribution on the Mt. Fuji-type landscape (Aita & Husimi,1996;Aita & Husimi,1998). For a large λ , the probability density of ΔW over the d -fold point mutant population is approximately described by the following truncated normal distribution:

$$\psi(\Delta W|d) \stackrel{\text{def}}{=} \begin{cases} C_1 \mathcal{N}\left(\Delta W \mid E[\Delta W|W], V[\Delta W|W]\right) & \text{for } \Delta W \leq (\Delta W)_u, \\ 0 & \text{otherwise,} \end{cases} \quad (7)$$

where $E[\Delta W|W]$ and $V[\Delta W|W]$ are, respectively, the conditional mean and conditional variance of ΔW with the given W value:

$$E[\Delta W|W] = -(W - \varepsilon\nu)\frac{d}{\nu}, \quad (8)$$

$$V[\Delta W|W] = \left(\frac{W^2}{3\nu} + \frac{\varepsilon^2\nu}{3}\right)\frac{d}{\nu} \quad \text{for } d \ll \nu. \quad (9)$$

In eqn. (8) and (9), the linear contribution of the mutation distance d is originated from the correlated structure of the Mt. Fuji-type landscape. The upper limit of ΔW corresponds to the ΔW of the fittest mutant among all conceivable d -fold point mutants and is given as follows:

$$(\Delta W)_u = |W| \left(2 - \frac{d+1}{\nu+1}\right) \frac{d}{\nu}. \quad (10)$$

In almost cases, the effect of the truncation at $\Delta W = (\Delta W)_u$ is small. The derivation of eqns (7) ~ (9) is shown in Appendix A. The derivation of eqn. (10) is shown in Aita & Husimi (1998).

3.2 Stationary Point and Climbing Rate in Adaptive Walk

Consider a sample population of N mutants randomly chosen from among the underlying d -fold point mutant population and the fittest mutant R among the sample population. Let $\widehat{\Delta W}$ be a fitness change between the fitness W for the wild-type P and that for the fittest mutant R:

$$\widehat{\Delta W} \equiv W(\text{the fittest R}) - W(\text{wild-type P}),$$

where $W(\text{wild-type P}) = W$. We note that $\widehat{\cdot}$ (hat) represents a quantity $*$ for the fittest mutant R in this paper. By using eqn. (7), the probability density of $\widehat{\Delta W}$ is described by the following extremal value distribution:

$$\varphi(\widehat{\Delta W}|d, N) \stackrel{def}{=} N \psi(\widehat{\Delta W}|d) \left(\int_{-\infty}^{\widehat{\Delta W}} \psi(\Delta W|d) d\Delta W \right)^{N-1}. \quad (11)$$

For the random sampling search (eqn. (5)), the above density is approximately described by the following truncated normal distribution:

$$\varphi(\widehat{\Delta W}|d, N) \approx \begin{cases} C_2 \mathcal{N}\left(\widehat{\Delta W} \mid E[\widehat{\Delta W}|W], V[\widehat{\Delta W}|W]\right) & \text{for } \widehat{\Delta W} \leq (\Delta W)_u, \\ 0 & \text{otherwise,} \end{cases} \quad (12)$$

where $E[\widehat{\Delta W}|W]$ and $V[\widehat{\Delta W}|W]$ are, respectively, the conditional mean and conditional variance of $\widehat{\Delta W}$ with the given W value:

$$E[\widehat{\Delta W}|W] = E[\Delta W|W] + \sqrt{V[\Delta W|W]} \widetilde{N}, \quad (13)$$

$$V[\widehat{\Delta W}|W] = \frac{V[\Delta W|W]}{\widetilde{N}^2 + 1}. \quad (14)$$

The truncation in eqn. (12) can be neglected for the random sampling search (eqn. (5)). The \widetilde{N} in eqn. (13) and eqn. (14) is defined by transforming the population size N according to

$$\widetilde{N} \exp\left(\frac{\widetilde{N}^2}{2}\right) \int_{-\infty}^{\widetilde{N}} \exp\left(-\frac{s^2}{2}\right) ds = N - 1, \quad (15)$$

with the following limitation:

$$0 \leq \widetilde{N} \leq \frac{(\Delta W)_u - E[\Delta W|W]}{\sqrt{V[\Delta W|W]}}. \quad (16)$$

For a large N , the \widetilde{N} is approximately given by the following form:

$$\widetilde{N} \approx \sqrt{2 \ln \frac{N}{\sqrt{2\pi}}}. \quad (17)$$

The derivation of eqn. (12) \sim eqn. (15) is derived by combining eqn. (11) with eqn. (7) and using the method of steepest descent for the integral (Weinberger,1991).

When $N = 1$, we obtain $\widetilde{N} = 0$ from eqn. (15). In this special case, $E[\widehat{\Delta W}|W] = E[\Delta W|W]$ and $V[\widehat{\Delta W}|W] = V[\Delta W|W]$. This means that the walker performs not an adaptive walk but a random walk on the fitness landscape and the fitness tends to $W = \varepsilon\nu$ which is the maximal entropy state. As N increases, that is, as \widetilde{N} increases, $E[\widehat{\Delta W}|W]$ is larger than $E[\Delta W|W]$. Therefore, the \widetilde{N} can be interpreted as a measure of the selection pressure or a measure of the openness of the system.

We focus on the expectation $E[\widehat{\Delta W}|W]$ hereafter. The $E[\widehat{\Delta W}|W]$ is a monotonously decreasing function of W for $W \leq 0$, and takes zero value when $W = W^* \leq 0$ (proof not shown). In the adaptive walk, a walker starting from around $W = \varepsilon\nu$ moves in the positive direction of the W coordinate, subject to the expected fitness increment $E[\widehat{\Delta W}|W]$, and reaches a stationary point $W = W^*$, in which the walker keeps the "mutation-selection-random drift balance". The stationary point $W = W^*$ satisfies

$$E[\widehat{\Delta W}|W^*] = 0, \quad (18)$$

where $E[\widehat{\Delta W}|W^*]$ is given as a function of W^* by substituting $W = W^*$ into eqn. (13). By substituting eqn. (8) and (9) into eqn. (13) and solving eqn. (18), the W^* is explicitly obtained as follows:

$$W^* = \left(-1 + \frac{\sqrt{2/3}}{\kappa(\tau) \tau} \right) |\varepsilon\nu| \quad \text{for } \tau \geq 1/\sqrt{3}, \quad (19)$$

where τ is the following search parameter:

$$\tau \equiv \frac{\sqrt{d}}{\widetilde{N}} \quad (20)$$

$$\approx 0.71 \sqrt{\frac{d}{\ln N}} \quad \text{for large } N, \quad (21)$$

and $\kappa(\tau)$ is a correction factor as a function of τ :

$$\kappa(\tau) \equiv \frac{1 + \sqrt{6\tau^2 - 1}}{\sqrt{6}\tau} \quad \text{for } \tau \geq 1/\sqrt{3}. \quad (22)$$

We note that the $\kappa(\tau)$ is a monotonously decreasing function of τ and takes the values between 1 and $\sqrt{2}$:

$$1 < \kappa(\tau) \leq \sqrt{2}, \quad (23)$$

where $\kappa(1/\sqrt{3}) = \sqrt{2}$ and $\lim_{\tau \rightarrow \infty} \kappa(\tau) = 1$. In the simulation study, the stationary point $W = W^*$ was obtained numerically. Fig.1 shows the theoretical and numerical values of the stationary point W^* as a function of τ . The resulting W^* -values from the computer simulation are well consistent with the theoretical curve from eqn. (19).

When we put the walker on the point $W = W^* + \delta W$, the expectation of $\widehat{\Delta W}$ after a single step walk from the point $W = W^* + \delta W$ is given by

$$J \equiv E[\widehat{\Delta W} | W^* + \delta W] \approx -\gamma \times \delta W, \quad (24)$$

where

$$\gamma \equiv \left(1 + \left(\frac{\kappa}{\sqrt{6}} - \frac{1}{3\tau} \right) \frac{1}{\tau} \right) \frac{d}{\nu} \quad (25)$$

$$\approx d/\nu \quad \text{for large } \tau. \quad (26)$$

The derivation of eqn. (24) with eqn. (25) is given in the Appendix B. The J is called the "climbing rate" or "evolution rate". It is remarkable that the stationary point W^* is significantly dependent on both of the mutation distance d and the population size N , whereas the climbing rate J around the stationary point is proportional to d but almost independent of N . This theoretical prediction was confirmed through the computer simulation. Fig.2 shows the climbing rate J as a function of δW . The resulting J -values from the simulation are well consistent with the theoretical values from eqn. (24) with eqn. (26).

3.3 Mean Time Course of Fitness and Mean Generation up to the Stationary State

Consider that a single adaptive walker starts at $W = W_0$ and the t -th generation of the walker is located at the point $W = W_t$. The transition probability density for a single step walk is given by eqn. (12). Here we neglect the truncation in eqn. (12), because we

are focusing on the adaptive walk with the random sampling search (eqn. (5)). When the value of W_{t-1} is given, the conditional probability density of W_t is approximately given by

$$\begin{aligned} P(W_t|W_{t-1}) &= \mathcal{N}\left(W_t \middle| W_{t-1} + E[\widehat{\Delta W}|W_{t-1}], V[\widehat{\Delta W}|W_{t-1}]\right) \\ &\approx \mathcal{N}\left(W_t \middle| (1-\gamma)(W_{t-1} - W^*) + W^*, V[\widehat{\Delta W}|W^*]\right). \end{aligned} \quad (27)$$

Using this transition probability density in eqn. (27), we obtain the probability density of W_t by the path integral:

$$\begin{aligned} P(W_t) &= \int_{-\infty}^0 \int_{-\infty}^0 \cdots \int_{-\infty}^0 \prod_{t'=1}^t P(W_{t'}|W_{t'-1}) dW_1 dW_2 \cdots dW_{t-1} \\ &= \mathcal{N}\left(W_t \middle| (1-\gamma)^t(W_0 - W^*) + W^*, \frac{1 - (1-\gamma)^{2t}}{1 - (1-\gamma)^2} V[\widehat{\Delta W}|W^*]\right). \end{aligned} \quad (28)$$

The derivation of eqn. (28) is performed by the mathematical induction. In the case where $W_0 = \varepsilon\nu$, that corresponds to the expected fitness of a random sequence, the expectation of W_t is given by

$$E[W_t] = \left(-1 + (1 - (1-\gamma)^t) \frac{\sqrt{2/3}}{\kappa\tau}\right) |\varepsilon\nu|. \quad (29)$$

Eqn. (29) describes the mean time course of the walker on the W coordinate. Fig.3 shows the mean time course predicted from eqn. (29) and that obtained from the simulation. The theoretical mean time course is approximately consistent with the result from the simulation. The walker with a large (small) step-width d shows a high (low) climbing rate in the initial stage, but reaches a low (high) stationary point W^* .

We define the "mean generation" or "mean step number", t^* , up to the stationary state as

$$(1-\gamma)^{t^*} = e^{-2}. \quad (30)$$

Therefore, we obtain

$$\begin{aligned} t^* &= \frac{-2}{\ln(1-\gamma)} \approx 2/\gamma \\ &\approx 2\nu/d \quad \text{for a large } \tau. \end{aligned} \quad (31)$$

4 Thermodynamical Interpretation of Adaptive Walk

In this section, we take a heuristic approach to interpret the dynamics of the adaptive walk from a thermodynamical point of view, considering that the adaptive walk is driven by an "evolutionary force". The evolutionary force consists of the "fitness force" and "entropy force". The entropy force is originated from the fitness distribution. We use two different definitions of the entropy force: one is from the fitness distribution over the global landscape (Section 4.1), the other is from the fitness distribution over the local landscape around the walker (Section 4.2).

4.1 Approach from the Global Fitness Distribution

4.1.1 Evolutionary Temperature and Evolutionary Force

According to eqn. (4), the number of sequences whose fitnesses range in $W - \Delta \sim W$ ($\Delta > 0$) is given by

$$\Omega(W) = \lambda^\nu \times \mathcal{N}\left(W \middle| \varepsilon\nu, \frac{\varepsilon^2\nu}{3}\right) \times \Delta \quad \text{for } W \leq 0, \quad (32)$$

where Δ is determined to satisfy $\Omega(0) = 1$. The "entropy" as a function of fitness W is defined by

$$S(W) \equiv |\varepsilon| \times \ln \Omega(W) \quad (33)$$

$$= -\frac{3}{2|\varepsilon\nu|}(W - \varepsilon\nu)^2 + \frac{3}{2}|\varepsilon\nu|. \quad (34)$$

Introducing a parameter T , we define the "free fitness" G as follows:

$$G(W) \equiv W + T \times S(W) \quad (35)$$

$$= -\frac{3T}{2|\varepsilon\nu|} \left(W - \left(-1 + \frac{1}{3T} \right) |\varepsilon\nu| \right)^2 + \frac{3T}{2} \left(-1 + \frac{1}{3T} \right)^2 |\varepsilon\nu|. \quad (36)$$

The parameter T is determined from the postulate that the maximal free fitness state is realized at the point $W = W^*$, that is, the point of the mutation-selection-random drift balance. According to the above postulate, the T is related with W^* by

$$W^* = \left(-1 + \frac{1}{3T} \right) |\varepsilon\nu|. \quad (37)$$

From eqn. (19) and eqn. (37), the T is determined as

$$T \equiv \frac{\kappa}{\sqrt{6}} \tau, \quad (38)$$

and we designate the T as the "evolutionary temperature". It is remarkable that the evolutionary temperature T is roughly proportional to the search parameter τ . In the case where the population size N is large enough to give $\tilde{N} \approx \sqrt{2 \ln N}$ under the condition $\kappa \approx 1$,

$$T \propto \sqrt{\frac{d}{\ln N}}. \quad (39)$$

If $T = \infty$ ($N = 1$), then $W^* = \varepsilon\nu$, which is the maximal entropy state and corresponds to the foot of the landscape. As T moves closer to zero (as N moves closer to ∞), W^* moves closer to zero, which is the maximal fitness state and corresponds to the peak.

The "evolutionary force" $X(W)$ that acts on the walker located at the point W is defined by

$$X(W) \equiv \frac{d}{dW} \frac{G(W)}{T} \quad (40)$$

$$= X_{\text{fit}} + X_{\text{ent}}, \quad (41)$$

where

$$X_{\text{fit}} \equiv \frac{1}{T} \quad \text{and} \quad X_{\text{ent}} \equiv \frac{dS(W)}{dW} \quad (42)$$

are the fitness force and entropy force, respectively. By substituting eqn. (36) into eqn. (40), the evolutionary force is given by

$$X(W) = -\frac{3}{|\varepsilon\nu|} (W - W^*). \quad (43)$$

In the thermodynamical interpretation, the walker approaches the maximal free fitness state, driven by the evolutionary force X . The evolutionary force $X(W)$, that acts on a walker at the point W , depends on the search parameter τ or the evolutionary temperature T . If τ or T is small (large) enough to set W^* greater (less) than W , a positive force $X > 0$ (negative force $X < 0$) acts on the walker and then the walker is pushed upward (downward). We summarized the thermodynamical interpretation by the schematic representation in Fig.4.

4.1.2 Einstein Relation-like Formula in Adaptive Walk

From eqn. (43), the evolutionary force X that acts on the walker located at the point $W = W^* + \delta W$ is given by

$$X = X(W^* + \delta W) = -\frac{3}{|\varepsilon\nu|}\delta W. \quad (44)$$

Substituting eqn. (44) into eqn. (24) and adopting eqn. (26) for γ , we obtain

$$J \approx \frac{|\varepsilon d|}{3} \times X. \quad (45)$$

Meanwhile, we consider a random walk with a step-width d in the Mt. Fuji-type fitness landscape without selection pressure ($\widetilde{N} = 0$). This random walk is carried out in a special condition where $N = 1$. The variance of the fitness change ΔW after a single step walk from a certain point W is equal to $V[\Delta W|W]$ in eqn. (9). Then, the variance at the point $W = W^* + \delta W$ is given by

$$\begin{aligned} V \equiv V[\Delta W|W^* + \delta W] &\approx V[\Delta W|W^*] = \left(\frac{W^{*2}}{3\nu} + \frac{\varepsilon^2\nu}{3} \right) \frac{d}{\nu} \\ &= \frac{2\varepsilon^2 d}{3\kappa^2}. \end{aligned} \quad (46)$$

In the derivation of eqn. (46), we adopted eqn. (91) in Appendix B. Substituting $|\varepsilon d|/3 = \kappa^2 V/2|\varepsilon|$, that is derived from eqn. (46), into eqn. (45), we obtain the following simple linear relationship between J and X :

$$J \approx L \times X, \quad (47)$$

where L is the linear transport coefficient and

$$L = \frac{\kappa^2 V}{2|\varepsilon|}. \quad (48)$$

According to the linear nonequilibrium thermodynamics, we interpret the meaning of each term in eqn. (47) with eqn. (48) as follows:

J = "Generalized flux" as the expected fitness change per generation,

X = "Generalized force" caused by the mutation and selection pressure,

L = "Linear transport coefficient" or "Admittance",

V = "Fluctuation" of the fitness change per generation without the selection pressure,

$|\varepsilon|$ = "Boltzmann constant"-like quantity,

εT = "Mean thermal energy (of a particle)"-like quantity.

Then we can regard eqn. (47) with eqn. (48) as Einstein relation-like formula in adaptive walks on the Mt. Fuji-type fitness landscape.

This theoretical prediction, that is eqn. (47) with eqn. (48), was confirmed through the computer simulation. When a mutation distance d and screening size N are given, T is determined from eqn. (38). The values of J and V were obtained at each point W numerically, while the values of X were calculated from eqn. (44) mathematically. Fig.2 shows the climbing rate J as a function of X . We observed a linear relationship between J and X in a wide range of X . The "admittance" L was calculated as the slope of the regression line for the X - J plots in the range from $X = 0$ through $X = 0.3$. The value of V was averaged over 400 generations in the stationary state. Fig.5 shows the comparison between L and $\kappa^2 V/2|\varepsilon|$. As a result, there was excellent agreement between the two quantities, verifying that the Einstein relation-like formula holds in adaptive walks on the Mt. Fuji-type fitness landscape.

4.1.3 Entropy Change and Information Gain through Adaptive Walk

In the previous Section 4.1.2, we suggested that the εT is considered as a "mean thermal energy (of a particle)"-like quantity. Here we consider the physical meaning of εT in our evolution system. Substituting eqn. (46) into eqn. (14) and adopting $\widetilde{N}^2 + 1 \approx \widetilde{N}^2$, we obtain

$$\begin{aligned} \sqrt{V[\Delta\widehat{W}|W^*]} &\approx \frac{\sqrt{2/3}}{\kappa} |\varepsilon T| && \text{for large } N \\ &= \frac{2}{\kappa^2} |\varepsilon T|. \end{aligned} \quad (49)$$

Through the adaptive walk simulation, we confirmed that eqn. (49) approximately holds when the parameters $(\lambda, \nu, \varepsilon, d, N)$ are the same as those in Fig.5 (data not shown). The

approximation $2/\kappa^2 \approx 2$ holds when the τ is large (eqn. (23)). Substituting $2/\kappa^2 \approx 2$ into eqn. (49), we obtain

$$|\varepsilon T| \approx \frac{\sqrt{V[\widehat{\Delta W}|W^*]}}{2}. \quad (50)$$

This equation means that the mean thermal energy-like quantity corresponds to the uncertainty of the fitness change for a single step walk.

Next, we consider the adaptive walk in terms of entropy and information (Eigen,2000). The change of the fitness, entropy and free fitness per generation are related by the following equation:

$$\frac{\widehat{\Delta G}}{T} = \frac{\widehat{\Delta W}}{T} + \widehat{\Delta S}. \quad (51)$$

The expectation of the fitness change divided by temperature ($\widehat{\Delta W}/T$), entropy change ($\widehat{\Delta S}$) and the free fitness change divided by temperature ($\widehat{\Delta G}/T$), after a single step walk from the point $W = W^* + \delta W$ are given by the following simple formulae, respectively:

$$E\left[\frac{\widehat{\Delta W}}{T} | W^* + \delta W\right] = J/T = J X_{\text{fit}} \quad (52)$$

$$E[\widehat{\Delta S} | W^* + \delta W] = J \left. \frac{dS}{dW} \right|_{W=W^*+\delta W} = J X_{\text{ent}} \quad (53)$$

$$E\left[\frac{\widehat{\Delta G}}{T} | W^* + \delta W\right] = JX \approx LX^2 \geq 0. \quad (54)$$

From eqn. (54), we can confirm that the free fitness is likely to monotonously increase through the walk, and that the function $-G(W)/T$ corresponds to the Lyapunov function of the system:

$$Lyap(W) = -\frac{G(W)}{T} + const. \quad (55)$$

By using the relation

$$\sqrt{V[\widehat{\Delta W}|W^* + \delta W]} \approx \sqrt{V[\widehat{\Delta W}|W^*]} \approx 2|\varepsilon T|, \quad (56)$$

the meaning of eqn. (52) is given as follows:

$$\frac{J}{T} \approx 2|\varepsilon| \times \frac{E[\widehat{\Delta W}|W^* + \delta W]}{\sqrt{V[\widehat{\Delta W}|W^* + \delta W]}}. \quad (57)$$

According to the analogy of thermodynamics, we can interpret that the term J/T in eqn. (52) shows the negative entropy the evolution system absorbs from the surroundings. And eqn. (57) shows that this negative entropy change is interpreted as the "fitness

information gain" absorbed from the surroundings per generation corrected by the "resolution" or "uncertainty" determined by the random sampling protocol. Eqn. (53) shows the negative entropy (=Shannon's information $\times |\varepsilon|$) that is produced per generation in the evolution system. Eqn. (54) shows the total negative entropy change per generation and is interpreted as the "biological information gain". In other description, eqn. (53) and eqn. (52) represent the "extent" change and "content" change of the biological information, respectively (Eigen,2000). We summarized the relationship between fitness information gain, Shannon's information gain and biological information gain by the schematic representation in Fig.6.

The adaptive walker climbs in reducing entropy S , in other words, in getting the Shannon's information up to the maximum free fitness state ($W = W^*$), in which the equality

$$dS = -\frac{dW}{T} \approx -2|\varepsilon| \frac{dW}{\sqrt{V[\widehat{\Delta W}|W^*]}} \quad (58)$$

is satisfied. Eqn. (58) is derived by substituting $X = 0$ into eqn. (41). Eqn. (58) represents the balance between the fitness force X_{fit} and the entropy force X_{ent} . That is, between the information gain by the selection and the information loss by the mutation.

The system gets the biological information through the adaptive walk from $W = \varepsilon\nu$ up to $W = W^*$ by

$$\begin{aligned} \frac{G(W^*)}{T} - \frac{G(\varepsilon\nu)}{T} &= \frac{|\varepsilon\nu|}{\kappa^2 \tau^2} \approx \frac{2\nu |\varepsilon| \ln N}{\kappa^2 d} \\ &= \kappa^{-2} t^* |\varepsilon| \ln N. \end{aligned} \quad (59)$$

This result is reasonable because it shows that the increase of the biological information is approximately equivalent to the product of the information gain at each step (that is, $\ln N$) and the step number up to the stationary state.

In conclusion, an analogy between the thermodynamical system and the evolution system is summarized in Table 1.

4.2 Approach from the Local Fitness Distribution

4.2.1 Evolutionary Temperature and Evolutionary Force

Consider a wild-type with a fitness W and an arbitrary d -fold point mutant generated from the wild-type. Let W' be the fitness for the mutant: $W' = W + \Delta W$. Assuming that the entropy force is originated from the fitness distribution for all d -fold point mutants, we define a "local free fitness" $\mathcal{G}(W')$ as follows:

$$\mathcal{G}(W') \equiv W' + \mathcal{T} \times |\varepsilon| \ln \mathcal{N}(W'|W + E[\Delta W|W], V[\Delta W|W]) \quad (60)$$

$$= W' - \frac{|\varepsilon| \mathcal{T}}{2V[\Delta W|W]} (W' - (W + E[\Delta W|W]))^2 + \text{const}, \quad (61)$$

where \mathcal{T} is the evolutionary temperature and the logarithm in the second term in eqn. (60) is the entropy for the d -fold point mutant spectrum. We define the evolutionary force $\mathcal{X}(W)$ that acts on the walker located at the point W as follows:

$$\mathcal{X}(W) \equiv \left. \frac{d}{dW'} \frac{\mathcal{G}(W')}{\mathcal{T}} \right|_{W'=W} = \frac{1}{\mathcal{T}} + \frac{|\varepsilon| E[\Delta W|W]}{V[\Delta W|W]}. \quad (62)$$

The $\mathcal{X}(W)$ is a monotonously decreasing function of W for $W \leq 0$, and takes zero value when $W = W^* \leq 0$, in the case of $\mathcal{T} > 1/3$ (random sampling search). The proof is not shown. We postulate that this particular point W^* is equivalent to W^* in eqn. (19). Therefore by substituting eqn. (19) into $\mathcal{X}(W^*) = 0$, \mathcal{T} is defined by

$$\mathcal{T} \equiv \frac{\sqrt{2/3}}{\kappa} \tau. \quad (63)$$

4.2.2 Einstein Relation-like Formula in Adaptive Walk

The evolutionary force \mathcal{X} that acts on the walker located at the point $W = W^* + \delta W$ is given by

$$\mathcal{X} \equiv \mathcal{X}(W^* + \delta W) \approx -\frac{3\kappa^2}{2|\varepsilon\nu|} \delta W \quad \text{for large } \tau. \quad (64)$$

Substituting eqn. (64) into eqn. (24) and adopting eqn. (26) for γ , we obtain

$$J \approx \frac{2|\varepsilon d|}{3\kappa^2} \times \mathcal{X}. \quad (65)$$

Substituting $2|\varepsilon d|/3\kappa^2 = V/|\varepsilon|$, that is derived from eqn. (46), into eqn. (65), we obtain the following simple linear relationship between J and \mathcal{X} :

$$J \approx \mathcal{L} \times \mathcal{X} \quad (66)$$

with the admittance

$$\mathcal{L} = V/|\varepsilon|. \quad (67)$$

We obtain the Lyapunov function of the system as follows:

$$\begin{aligned} Lyap(W) &\equiv - \int \mathcal{X}(W) dW \\ &= - \left(\frac{W}{\mathcal{T}} - 3|\varepsilon\nu| \left(\frac{1}{2} \ln \left(\frac{W^2}{3\nu} + \frac{\varepsilon^2\nu}{3} \right) + \tan^{-1} \frac{W}{|\varepsilon\nu|} \right) \right). \end{aligned} \quad (68)$$

The function $Lyap(W)$ ($W \leq 0$) is a concave function of W and takes the minimum value at $W = W^*$.

5 Discussion

The discrepancy is small between the case where the entropy force is derived from the global fitness distribution (Section 4.1) and the other case from the local fitness distribution (Section 4.2). The thermodynamical quantities for the two cases are mutually related as follows: $\mathcal{T}/T = 2/\kappa^2$, $\mathcal{X}/X = \kappa^2/2$, and $\mathcal{L}/L = 2/\kappa^2$. The mathematical definition and formulation in the former is much simpler than the latter. However, from the stand point of kinetics, the latter approach seems to be more reasonable than the former, on the grounds that the adaptive walker climbs searching not globally but locally around him. The small discrepancy suggests the former approach is phenomenologically almost the same as the latter. According to the mathematical definition and formulation in the former, we discuss several issues below.

We focused mainly on the climbing process of the adaptive walker, who is pushed upward by the evolutionary force. Here we mention about the probability distribution of the fitness W_∞ in the stationary state. By combining eqn. (28) at $t = \infty$ with eqn. (14), (26) and (46), the probability distribution at $t = \infty$ is given by $\mathcal{N}\left(W_\infty \middle| W^*, \varepsilon^2 \nu / 3\kappa^2 (\widetilde{N}^2 + 1)\right)$. The distribution becomes more sharp as the selection pressure \widetilde{N} (or population size N) is larger. We note that this distribution represents the fluctuation effect due to finite mutant population.

In this paper, we focused on the adaptive walk adopting the $(1, N)$ -ES with the random sampling search (stochastic search). Here, we mention about the properties of the walk with the exhaustive search (deterministic search), and the walk adopting the $(1 + N)$ -ES.

The exhaustive search is conducted with the condition that the population size N is much larger than the number of all conceivable d -fold point mutants, that is $N \gg \binom{\nu}{d}(\lambda - 1)^d$. The properties for this case are summarized in the following. The evolutionary temperature T is zero ($T = 0$), then the walker reaches the optimum ($W^* = 0$). The time course of the walker is deterministically given by $W_t = -((d/\nu)t - 1)^2 |\varepsilon \nu|$. The flux of the fitness change per generation is given by $J \propto \sqrt{X}$. Therefore, Einstein relation-like formula does not hold in this case.

The properties of the adaptive walk adopting the $(1 + N)$ -ES, which is defined in the Introduction, is understood as follows; If the fitness W of a walker is less than the stationary point W^* ($W < W^*$), the properties for the $(1 + N)$ -ES is almost the same as those for the $(1, N)$ -ES. However, in every case where $W > W^*$, $G(W) = G(W^*) = \text{const}$ and then $X = 0$ and $J = 0$. That is, the walker is trapped at the point W . For the walker to continue climbing upward, the search parameter τ must become small enough to move W^* higher than the walker's fitness W . As a conclusion, Einstein relation-like formula holds in this case.

Our evolution system is based on the *in vitro* evolution system, in which the engineers can control the mutation distance d and population size N and the selection of the fittest mutant from among a sample population is deterministic (Yamauchi *et al.*,2002). In Nature, the number of mutated sites is expected to obey Poisson distribution around the mean d , and the selection is stochastic. Although we did not examine these natural situation, similar results may be expected except that the fluctuation of fitness change in a single step walk becomes larger.

Einstein relation is known as a special case of "fluctuation-dissipation theorem (F-D theorem)" (Kubo,1957). The theorem for the non-zero frequency case is relevant to the evolution in a periodically changing environment. Consider that a walker is located at the middle point of the landscape, and that the alternating evolutionary force ($X > 0$ and $X < 0$) acts on the walker periodically. This situation is realized, for example, by alternating the screening size N between a large value and a small value. The frequency dependence of the admittance may obey the F-D theorem.

In this paper, we proposed several novel quantities analogous to thermodynamical concepts, such as the free fitness, evolutionary temperature and evolutionary force. Similar concepts have been discussed by many researchers. For example, Iwasa regarded the reciprocal of the population size as the evolutionary temperature and defined the free fitness as the sum of the fitness and entropy indicating the population diversity. He stressed that the selection-random drift balance is kept in the maximal free fitness state (Iwasa,1988). However, it seems that his formula does not include the mutational effect explicitly. Eigen

et al. proposed a theory of quasispecies for self-replicators in the infinite population. In their system, the deterministic mutation-selection balance is kept in the stationary state. The mutation rate corresponds to the evolutionary temperature and the eigenvalue of the "replication-mutation rate matrix" in Eigen's equation seems to correspond to the free fitness (Eigen *et al.*,1989; Eigen,2000). In our original definition, the evolutionary temperature includes both the mutational effect and random-drift effect, although our definition is based on the Mt. Fuji-type landscape.

There is a question of whether the thermodynamical interpretation of the adaptive walk on the Mt. Fuji-type landscape can be applied to other landscapes in general. Although we can not answer this question for general cases, we confirmed Einstein relation-like formula holds in the adaptive walk on a spin-glass-like rugged fitness landscape when a walker adopts the random sampling search (data not shown). In this case, X is the same as eqn. (44), and the "admittance" L is equivalent to the variance of fitness over the sequence space (divided by $|\varepsilon|$). This result suggests that the formula may hold in a general case in a stochastic evolution system.

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6 Appendix A: The derivation of eqns (7) ~ (9)

This appendix is a synopsis of the theory developed in Aita & Husimi (1996;1998) (Section 3.1 in Aita & Husimi (1996) and Appendix A.2 in Aita & Husimi (1998)). Variables used here, ΔW , $W(P)$ and D correspond to W , W_P and d_P , respectively, in Aita & Husimi (1996;1998). Variables used here, S , G , X , Ω and γ , are the same as in these references.

Consider an arbitrary d -fold point mutant Q generated from a particular wild-type P. The P is fixed in the sequence space and Q is located at an arbitrary point on the condition of $d(P, Q) = d$, where $d(P, Q)$ represents the Hamming distance between P and Q. The Hamming distance between the optimum O and P is denoted by $D \equiv d(O, P)$. Let α_{Pj} be a residue at the j -th site in the sequence P. In the mutation from P to Q, the number of outgoing residues α_{Pj} that satisfy $\alpha_{Pj} \neq \alpha_{Qj}$ is denoted by m , and the number of incoming residues α_{Qj} that satisfy $\alpha_{Qj} \neq \alpha_{Oj}$ is denoted by n .

The m and n satisfy the following condition

$$\begin{aligned}
0 \leq m \leq d & \quad \text{for } d \leq D, \nu - D \\
0 \leq m \leq D & \quad \text{for } D \leq d \leq \nu - D \\
D + d - \nu \leq m \leq d & \quad \text{for } \nu - D \leq d \leq D \\
D + d - \nu \leq m \leq D & \quad \text{for } D, \nu - D \leq d
\end{aligned} \tag{69}$$

$$d - m \leq n \leq d. \tag{70}$$

Since the D and d are fixed, the number of sequences taking m and n is given by

$$\Omega(m, n) = \binom{\nu - D}{d - m} (\lambda - 1)^{d - m} \frac{D!}{(d - n)!(D - m)!(m + n - d)!} (\lambda - 2)^{m + n - d}. \tag{71}$$

Therefore, the probability that these sequences are generated in the mutation is given by

$$\begin{aligned}
\chi(m, n) &= \frac{\Omega(m, n)}{\binom{\nu}{d} (\lambda - 1)^d} \\
&= \frac{\binom{D}{m} \binom{\nu - D}{d - m}}{\binom{\nu}{d}} \times \binom{m}{d - n} \left(\frac{1}{\lambda - 1}\right)^{d - n} \left(\frac{\lambda - 2}{\lambda - 1}\right)^{m - (d - n)} \\
&\quad \text{for } \max(0, d - (\nu - D)) \leq m \leq \min(d, D) \text{ and } d - m \leq n \leq d \\
&= 0 \quad \text{otherwise.}
\end{aligned} \tag{72}$$

In the case where $d \ll \nu$ and $D + d - \nu \ll m \ll D$, eqn (72) is approximated to

$$\chi(m, n) \approx \frac{d!}{(d - m)!(d - n)!(m + n - d)!} \left(1 - \frac{D}{\nu}\right)^{d - m} \left(\frac{D}{\nu(\lambda - 1)}\right)^{d - n} \left(\frac{D(\lambda - 2)}{\nu(\lambda - 1)}\right)^{m + n - d}. \tag{73}$$

In the meanwhile, the fitness change ΔW in the mutation from P to Q corresponds to the difference between the fitness income ΔW^{in} and fitness outgo ΔW^{out} :

$$\begin{aligned}
\Delta W &= \Delta W^{in} - \Delta W^{out}, \\
\Delta W^{out} &= W(\text{P}) - \sum_{\alpha_{Pj} = \alpha_{Qj}} w_j(\alpha_{Pj}) \\
&= \sum_{\alpha_{Oj} \neq \alpha_{Pj} \neq \alpha_{Qj}} w_j(\alpha_{Pj}),
\end{aligned} \tag{74}$$

$$\begin{aligned}
\Delta W^{in} &= W(\text{Q}) - \sum_{\alpha_{Qj} = \alpha_{Pj}} w_j(\alpha_{Qj}) \\
&= \sum_{\alpha_{Oj} = \alpha_{Pj} \neq \alpha_{Qj}} w_j(\alpha_{Qj}) + \sum_{\alpha_{Oj} \neq \alpha_{Pj} \neq \alpha_{Qj} \neq \alpha_{Oj}} w_j(\alpha_{Qj}).
\end{aligned} \tag{75}$$

Here we note that the number of terms in the summation in eqn. (74) and that in eqn. (75) are m and n , respectively.

The underlying probability density of site-fitness w in each site is given by

$$f(w) \equiv \frac{1}{\lambda - 1} \sum_{i=1}^{\lambda-1} \delta(w - \frac{2\varepsilon}{\lambda} i) \approx \begin{cases} 1/|2\varepsilon| & \text{for } 2\varepsilon \leq w \leq 0 \\ 0 & \text{otherwise,} \end{cases} \quad (76)$$

where $\delta(x)$ is the Dirac's delta function. The probability density of ΔW^{in} with a given n is denoted by $\xi^{in}(\Delta W^{in}|n)$ and is given by

$$\xi^{in}(\Delta W^{in}|n) = \begin{cases} \binom{n}{*} f(\Delta W^{in}), & \text{for } n \neq 0 \\ \delta(\Delta W^{in}), & \text{for } n = 0. \end{cases} \quad (77)$$

Using eqn. (76), we obtain

$$\xi^{in}(\Delta W^{in}|n) = \frac{1}{|2\varepsilon|(n-1)!} \sum_{l=0}^{int(\Delta W^{in}/2\varepsilon)} (-1)^l \binom{n}{l} \left(\frac{\Delta W^{in}}{2\varepsilon} - l\right)^{n-1} \approx \mathcal{N}(\Delta W^{in}|\varepsilon n, \frac{\varepsilon^2}{3}n), \quad \text{for large } n.$$

On the other hand, the distribution of site-fitness except zero in the sequence P is described as

$$h_P(w) = \frac{1}{D} \sum_{i=1}^D \delta(w - w_i), \quad (78)$$

where $w_i \leq w_{i+1}$ and w_i 's correspond to $w_j(\alpha_{P_j})$'s ($\neq 0$). The fitness of P is described as $W(P) = \sum_{i=1}^D w_i$. The probability density of ΔW^{out} with a given m is denoted by $\xi^{out}(\Delta W^{out}|m)$ and is given by the following function as the discrete distribution of $S \equiv \sum_{k=1}^m w_{i_k}$:

$$\begin{aligned} \xi^{out}(\Delta W^{out}|m) &= \frac{1}{\binom{D}{m}} \sum_{i_1 < i_2 < \dots < i_m} \delta(\Delta W^{out} - \sum_{k=1}^m w_{i_k}) \\ &= \sum_S A_{m,S} \delta(\Delta W^{out} - S), \end{aligned} \quad (79)$$

where $A_{m,S} \equiv g_{m,S}/\binom{D}{m}$ and the $g_{m,S}$ is defined as the coefficient in the following generating function:

$$\begin{aligned} G(X, Z) &= (1 + X^{w_1} Z)(1 + X^{w_2} Z)(1 + X^{w_3} Z) \dots (1 + X^{w_D} Z) \\ &= \sum_m \left(\sum_S g_{m,S} X^S \right) Z^m. \end{aligned} \quad (80)$$

The probability density of ΔW with a given m and n is denoted by $\xi(\Delta W|m, n)$. From eqn. (77) and (79), we obtain

$$\begin{aligned}\xi(\Delta W|m, n) &= \int_{-\infty}^0 \xi^{out}(\Delta W^{in} - \Delta W|m) \xi^{in}(\Delta W^{in}|n) d\Delta W^{in} \\ &= \frac{1}{\binom{D}{m}} \sum_{i_1 < i_2 < \dots < i_m} \xi^{in}(\Delta W + \sum_{k=1}^m w_{i_k}|n) \\ &= \sum_S A_{m,S} \xi^{in}(\Delta W + S|n).\end{aligned}\quad (81)$$

The ΔW satisfies $-\infty \leq \Delta W \leq -W(P) = -\sum_{i=1}^D w_i$. Additionally, we set $\xi(\Delta W|m, n) = 0$ when $\Delta W > -W(P)$. Combining eqn. (72) and eqn. (81) and considering all possible combination of m and n (eqn. (69) and (70)), we obtain the probability density of ΔW with a given d as follows:

$$\psi(\Delta W|d) = \sum_{m=0}^d \sum_{n=d-m}^d \chi(m, n) \xi(\Delta W|m, n).\quad (82)$$

For a simple description, by using $x \equiv D/\nu$, $y \equiv W(P)/|\varepsilon\nu|$, the mean and variance of ΔW with a given $W(P) = W$ are obtained as follows:

$$E[\Delta W|W] = \left(1 + y - \frac{x}{\lambda - 1}\right) \varepsilon d \quad (83)$$

$$\approx (1 + y) \varepsilon d \quad \text{for large } \lambda \quad (84)$$

$$\begin{aligned}V[\Delta W|W] &= \left(\gamma^2 \left(\frac{1}{x} - \frac{1}{\lambda - 1}\right) + (1 + \gamma_P^2) \left(\frac{y}{x}\right)^2 + \frac{1 - 2y/x}{\lambda - 1}\right. \\ &\quad \left. + \left(\left(\frac{1}{\lambda - 1} - \frac{y}{x}\right)^2 - \frac{\gamma_P^2}{d_P - 1} \left(\frac{y}{x}\right)^2\right) \frac{(d_P - 1)(d - 1)}{(\nu - 1)} - \left(\frac{1}{\lambda - 1} - \frac{y}{x}\right)^2 x d\right) x \varepsilon^2 d\end{aligned}$$

$$\approx \left(\gamma^2 + (1 + \gamma_P^2 + (d_P - 1 - \gamma_P^2) \left(\frac{d - 1}{\nu - 1} - x d\right) \frac{y^2}{x})\right) \varepsilon^2 d \quad \text{for large } \lambda \quad (85)$$

$$\approx \left(\gamma^2 + \left(\frac{1 + \gamma_P^2}{x} - 1\right) y^2\right) \varepsilon^2 d, \quad \text{for large } \lambda \text{ and } d \ll \nu, \quad (86)$$

where $\gamma^2 = \gamma_P^2 = 1/3$ (Aita & Husimi, 1998).

In the case where λ is large, the value of $D \equiv d(O, P)$ for the adaptive walker P, that adopts the $(1, N)$ -ES with the random sampling search (stochastic search), is expected to be ν . Then, substituting $x = 1$ and $y = W/|\varepsilon\nu|$ into eqn. (84) and eqn. (86), we obtain eqns (8) and (9). Since $\xi(\Delta W|m, n)$ in eqn. (82) is Gaussian-like distribution of which the mean is linear against m and n , and $\chi(m, n)$ in eqn. (82) is also Gaussian-like distribution for m and n , we approximate $\psi(\Delta W|d)$ in eqn. (82) by the Gaussian shown in eqn. (7).

7 Appendix B: Derivation of eqn. (24) with eqn. (25)

Expanding the Taylor series for the following function of W (eqn. (9)),

$$\sqrt{V[\Delta W|W]} = \sqrt{\left(\frac{W^2}{3\nu} + \frac{\varepsilon^2\nu}{3}\right) \frac{d}{\nu}}, \quad (87)$$

around $W = W^*$ and adopting the first-order term, we obtain

$$\sqrt{V[\Delta W|W^* + \delta W]} \approx \sqrt{V[\Delta W|W^*]} + \sqrt{\frac{d}{\nu} \frac{W^*}{3\nu}} \left(\frac{W^{*2}}{3\nu} + \frac{\varepsilon^2\nu}{3}\right)^{-\frac{1}{2}} \delta W. \quad (88)$$

Using this equation, we obtain the expectation of the fitness change $\widehat{\Delta W}$ after a single step walk from the point $W = W^* + \delta W$ as follows:

$$\begin{aligned} J \equiv E[\widehat{\Delta W}|W^* + \delta W] &\approx E[\widehat{\Delta W}|W^*] + \left(-1 + \frac{W^*}{3\sqrt{\nu\tau}} \left(\frac{W^{*2}}{3\nu} + \frac{\varepsilon^2\nu}{3}\right)^{-\frac{1}{2}}\right) \frac{d}{\nu} \delta W \\ &= \left(-1 + \frac{W^*}{3\sqrt{\nu\tau}} \left(\frac{W^{*2}}{3\nu} + \frac{\varepsilon^2\nu}{3}\right)^{-\frac{1}{2}}\right) \frac{d}{\nu} \delta W. \end{aligned} \quad (89)$$

From eqn. (19),

$$W^* - \varepsilon\nu = \frac{\sqrt{2/3}}{\kappa\tau} |\varepsilon\nu|. \quad (90)$$

Substituting eqn. (90) into eqn. (18), we obtain

$$\sqrt{\frac{W^{*2}}{3\nu} + \frac{\varepsilon^2\nu}{3}} = \frac{\sqrt{2/3}|\varepsilon|\sqrt{\nu}}{\kappa}. \quad (91)$$

Substituting eqn. (19) and eqn. (91) into eqn. (89), we obtain eqn. (24) with eqn. (25).

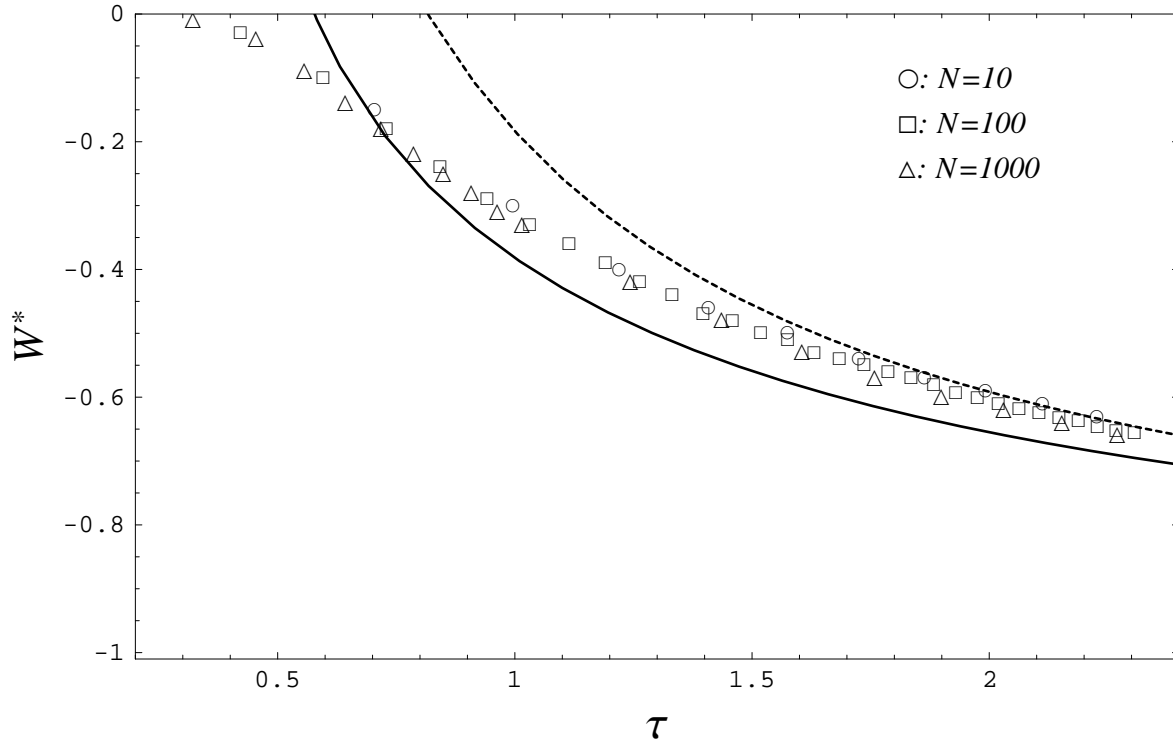


Figure 1: **The stationary point W^* as a function of τ .** The ordinate represents W^* normalized by $|\varepsilon\nu|$. The solid line represents the theoretical curve described in eqn. (19). The dashed line represents the approximate curve described in eqn. (19) with $\kappa = 1$. The plots of each symbol ($\circ, \square, \triangle$) represent the resulting values from the adaptive walk simulation by using the Monte Carlo method. Adaptive walks were carried out starting from randomly generated sequences up to the stationary state, with various search parameters (d, N). The numerical W^* -values were obtained as the average of the fitness W over 3000 generations in the stationary state. The mutation distance d is as follows: $d = 1, 2, \dots, 10$ for $N = 10$ (\circ), $d = 1, 2, \dots, 30$ for $N = 10^2$ (\square), $d = 1, 2, \dots, 10, 15, 20, 25, 30, 35, 40, 45, 50$ for $N = 10^3$ (\triangle). $(\lambda, \nu) = (200, 300)$. $\varepsilon = -1$.

8 定常状態における適応度分布

定常状態の適応度を y_∞ とすると、その分布は式 (28) より、

$$\rho(y_\infty) = \mathcal{N}\left(y_\infty \middle| y^*, \frac{V[\widehat{\Delta y}|y^*]}{2\gamma}\right) \quad (92)$$

Thermodynamics	Evolution
Energy, Enthalpy: H	Fitness: W
Boltzmann constant: k_B	Mean site-fitness: $ \varepsilon $
Entropy: S	Entropy: $S \equiv \varepsilon \ln \Omega$
Temperature: T	Evolutionary temperature: $T \propto \sqrt{d/\ln N}$
Free energy: $G \equiv H - TS$	Free fitness: $G \equiv W + TS$
Mean thermal energy of a particle: $k_B T$	Uncertainty of fitness change per generation: $ \varepsilon T \approx \sqrt{V[\widehat{\Delta W} W^*]}/2$
Diffusion constant: D	A half of variance of fitness distribution on a local landscape: $V/2$
Generalized flux: J	Expected fitness change per generation: $J \equiv E[\widehat{\Delta W} W]$
Generalized force: X	Evolutionary force: $X \equiv d(G/T)/dW$
Einstein relation: $\mu T = D/k_B$	$L(\equiv J/X) \approx V/2 \varepsilon $
$\Delta S_{\text{system}} = \Delta S$	Shannon's information gain ($\times \varepsilon $): $-\widehat{\Delta S}$
$\Delta S_{\text{surroundings}} = -\Delta H/T$	Fitness information gain: $\widehat{\Delta W}/T$
$\Delta S_{\text{universe}} = -\Delta G/T$	Biological information gain: $\widehat{\Delta G}/T$

Table 1: **An analogy between the thermodynamical system and our evolution system.**

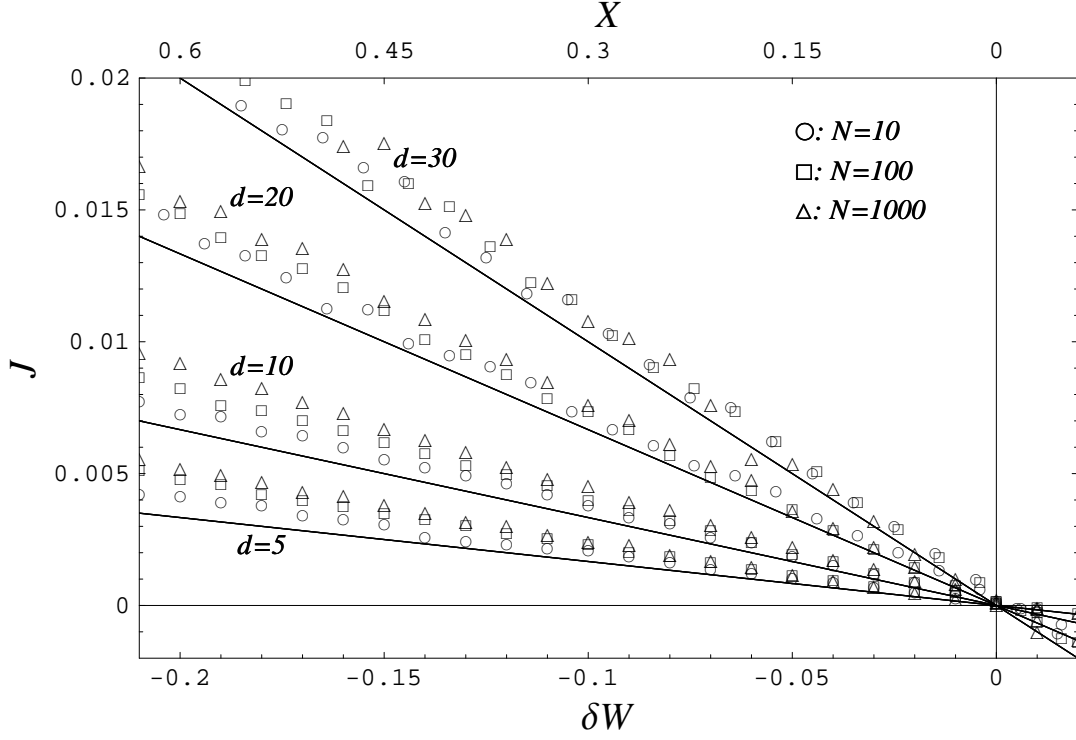


Figure 2: **The climbing rate J as a function of δW or X .** The ordinate represents J normalized by $|\varepsilon\nu|$. The abscissa (bottom) represents δW normalized by $|\varepsilon\nu|$. The resulting J -values from the computer simulation are represented by symbols (the details are described in the text). The values of $\delta W = W - W^*$ were calculated from the numerical W^* -values from the simulation (Fig.1). The X -values were calculated from eqn. (44). The solid straight lines are the theoretically predicted values described in eqn. (24) with eqn. (26). The population size N is $N = 10$ (\circ), $N = 10^2$ (\square) and $N = 10^3$ (\triangle). For each N -value, the mutation distance d is 5, 10, 20 and 30. $(\lambda, \nu) = (200, 300)$. $\varepsilon = -1$.

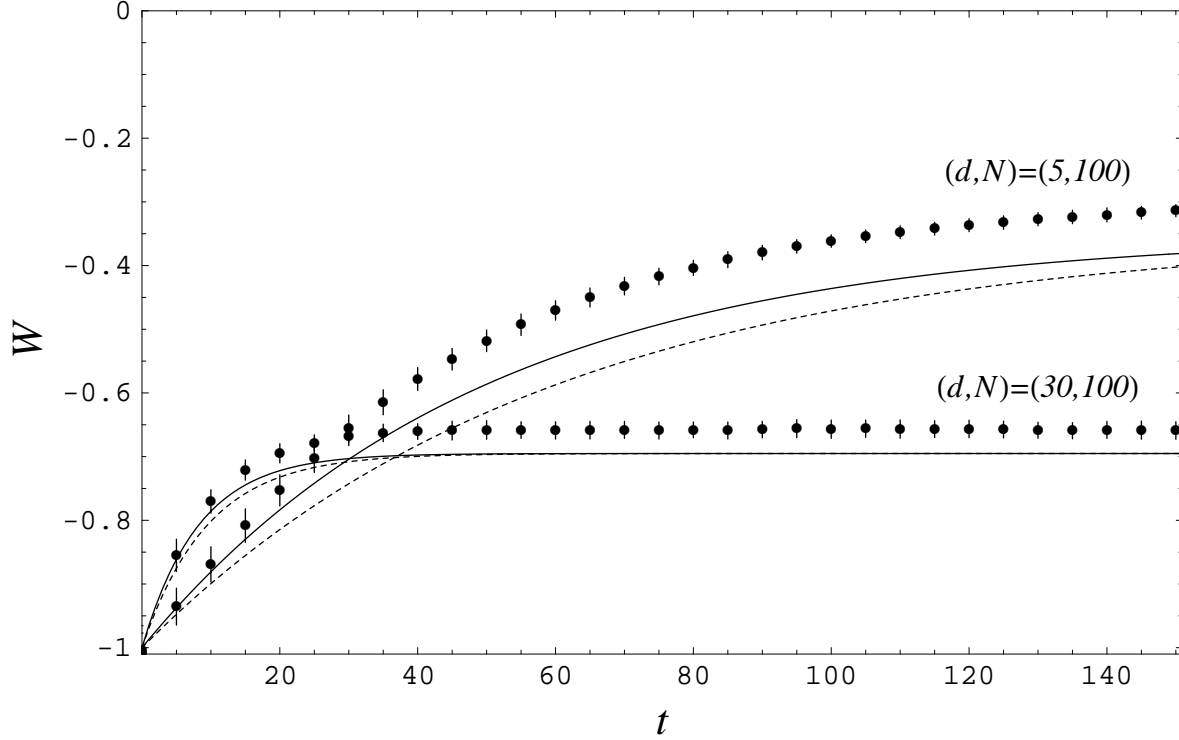


Figure 3: **Mean time course of adaptive walks.** The ordinate represents the fitness W normalized by $|\varepsilon\nu|$. The mean fitness W of the walker at the t -th generation is plotted against each generation t . Each single walk started from randomly chosen sequences and continued up to a stationary state. The resulting mean time course from the simulation is shown by a series of dots. The error bar represents the standard deviation. The theoretical mean time course predicted from eqn. (29) is shown by a solid line and a dashed line. Regarding the γ -value, the solid line and the dashed line adopt eqn. (25) and eqn. (26), respectively. $(d, N) = (5, 100)$ and $(d, N) = (30, 100)$. $(\lambda, \nu) = (200, 300)$. $\varepsilon = -1$.

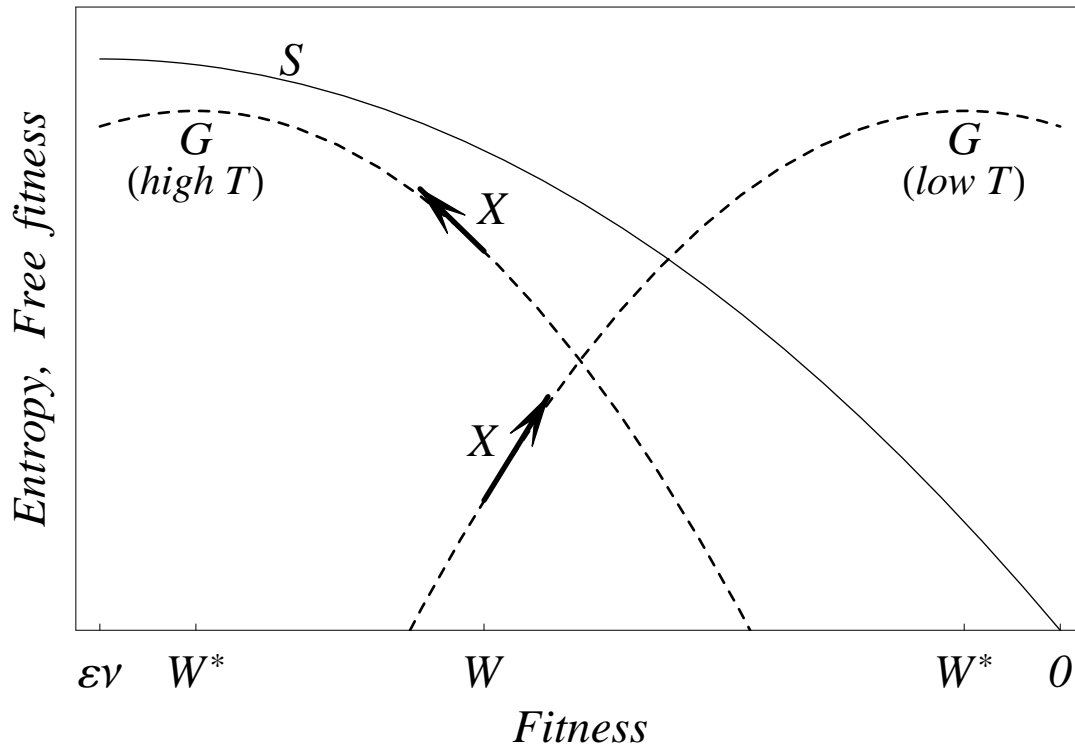


Figure 4: **Schematic representation of thermodynamical interpretation of adaptive walk.** The solid line and dashed line represent the entropy S and free fitness G , respectively, as a function of fitness. The right (left) dashed line is for the case of a low (high) evolutionary temperature T . The W^* represents the stationary point, in which the G takes the maximum. The vector (=arrow) represents the evolutionary force X that acts on a walker at the point W . Details are described in the text.

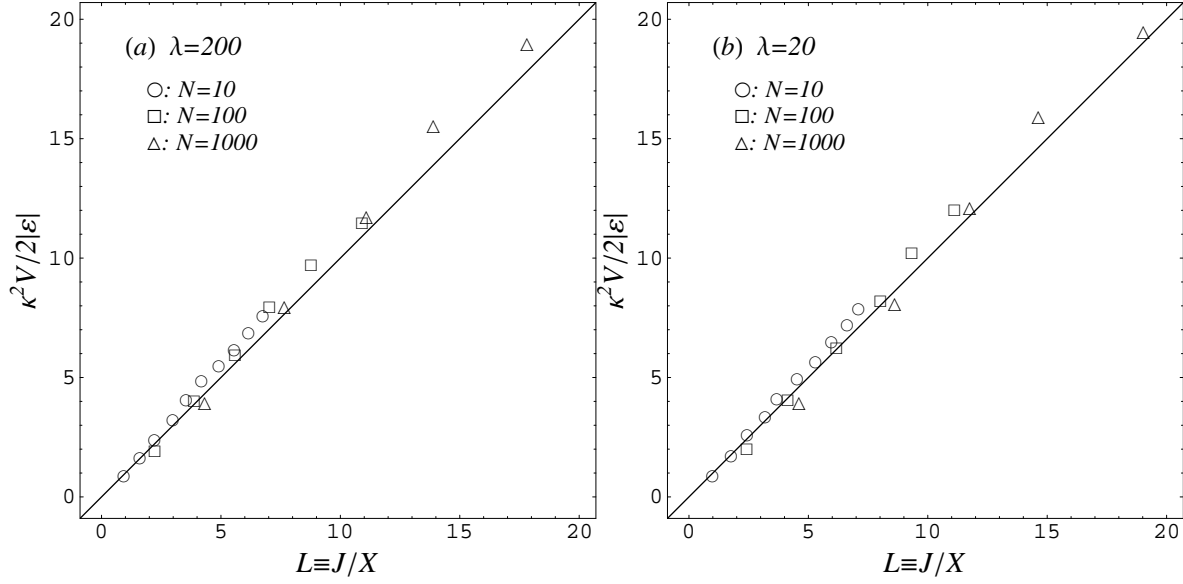


Figure 5: **Comparison between $L \equiv J/X$ and $\kappa^2 V/2|\varepsilon|$.** The numerical values of L were obtained from the slopes of the regression line for the X - J plots (Fig.2). The values of $\kappa^2 V/2|\varepsilon|$ were obtained from the numerical V -values obtained through the simulation. The mutation distance d is as follows: $d = 2, 4, 6, 8, 10, \dots, 20$ for $N = 10$ (\circ), $d = 5, 10, 15, 20, 25, 30$ for $N = 10^2$ (\square), $d = 10, 20, 30, 40, 50$ for $N = 10^3$ (\triangle). (a) $(\lambda, \nu) = (200, 300)$. (b) $(\lambda, \nu) = (20, 300)$. $\varepsilon = -1$.

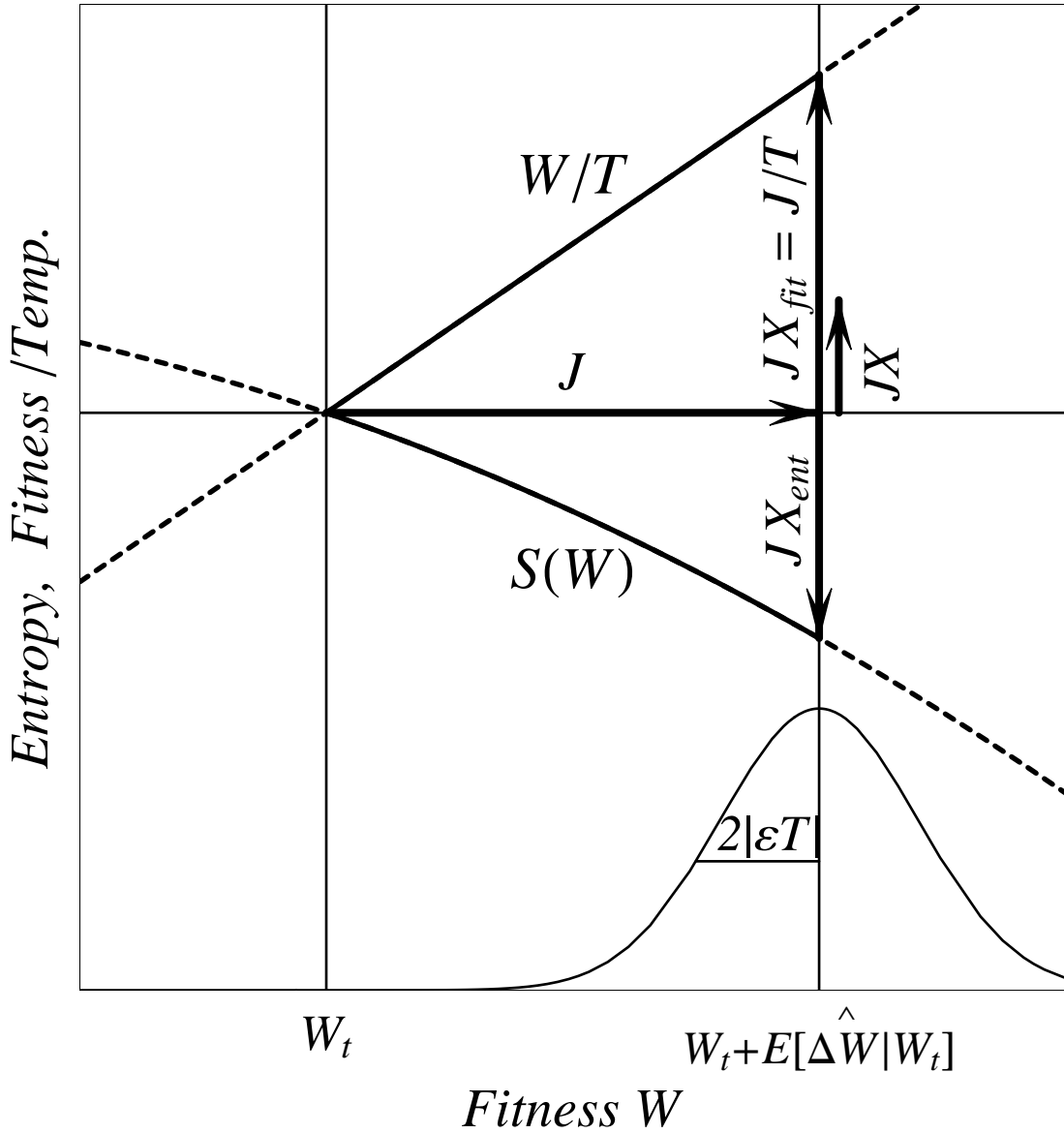


Figure 6: **Schematic representation of the relationship between fitness information gain, Shannon's information gain and biological information gain, for a single step walk.** The abscissa represents the coordinate of fitness W . The W_t represents the fitness of the t -th generation. The probability density of the fitness change after a single step walk (eqn. (12)) is shown as Gaussian form. The ordinate represents W/T or $S(W)$ as a function of W . The four arrows represent the expected changes corresponding to J as the fitness flux, JX_{fit} as the fitness information gain, $-JX_{\text{ent}}$ as the Shannon's information gain ($\times|\varepsilon|$) and JX ($= JX_{\text{fit}} + JX_{\text{ent}}$) as the biological information gain.

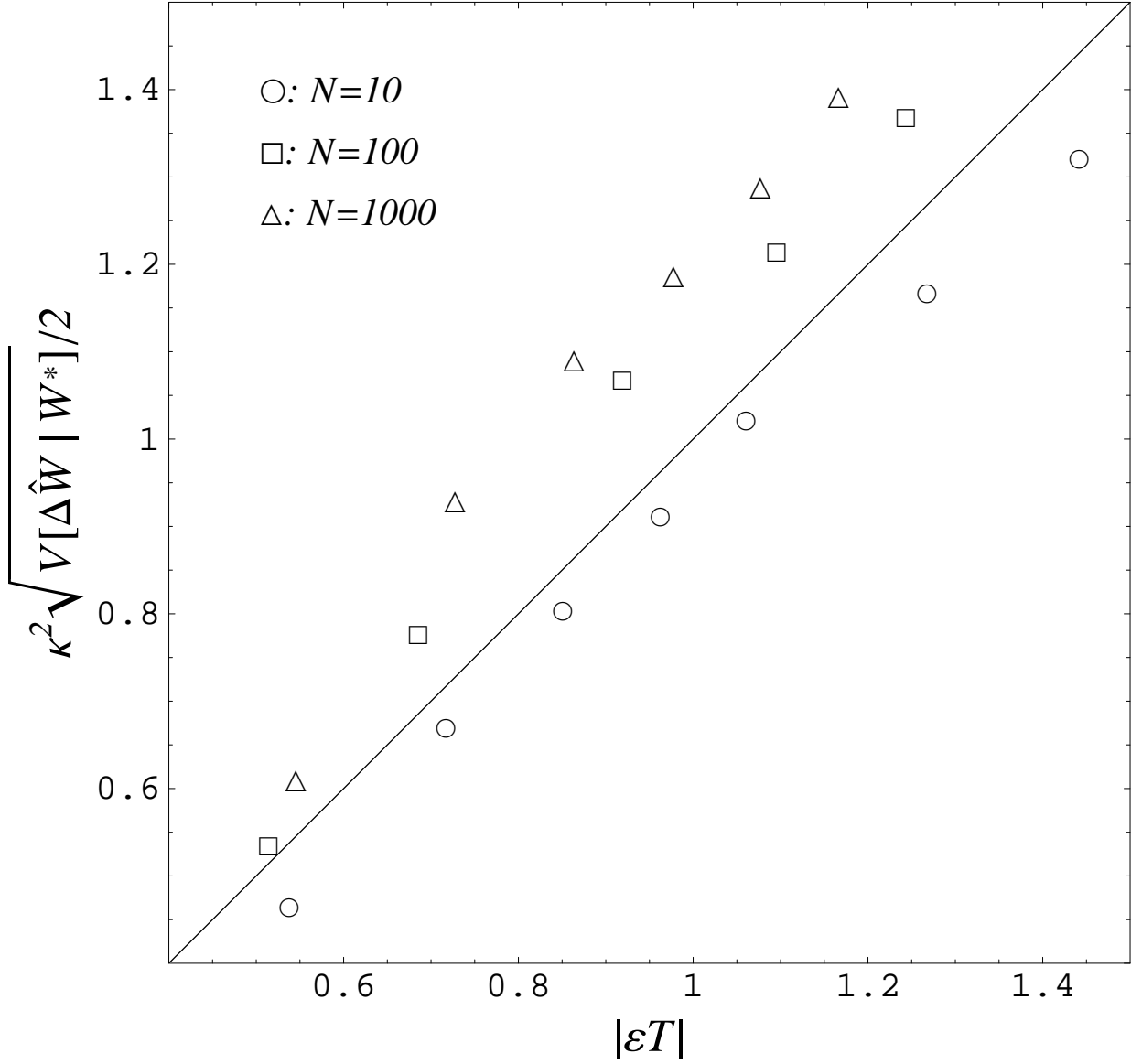


Figure 7: **Comparison between $\kappa^2 \sqrt{V[\widehat{\Delta W} | W^*]}/2$ and $|\varepsilon T|$.** The numerical values of $V[\widehat{\Delta W} | W^*]$ were obtained through the adaptive walk simulation. The mutation distance d is as follows: $d = 2, 4, 6, 8, 10, 15, 20$ for $N = 10$ (\circ), $d = 5, 10, 20, 30, 40$ for $N = 10^2$ (\square), $d = 10, 20, 30, 40, 50, 60$ for $N = 10^3$ (\triangle). $(\lambda, \nu) = (200, 300)$. $\varepsilon = -1$. The quantitatively same result was obtained when $(\lambda, \nu) = (20, 300)$.

である。その分散は式 (14),(46) と (26) を用いて、

$$V[y_\infty] = \frac{V[\widehat{\Delta y}|y^*]}{2\gamma} = \frac{1}{3\nu\kappa^2(\widetilde{N}^2 + 1)} \quad (93)$$

である。よって、自由適応度を用いた、定常状態における適応度分布の表現は

$$\rho(y_\infty) = Z(d, N)^{-1} \exp\left(\frac{G(y_\infty)\kappa^2(\widetilde{N}^2 + 1)}{T}\right) \quad (94)$$

$$Z(d, N) \equiv \int_{-\infty}^0 \exp\left(\frac{G(y_\infty)\kappa^2(\widetilde{N}^2 + 1)}{T}\right) dy_\infty \quad (95)$$

となる。この分布形がボルツマン因子 $\exp(G/T)$ の $\kappa^2(\widetilde{N}^2 + 1)$ 乗になっていることに注目すべきである。

さらに、進化力を

$$\widetilde{X}(y) \equiv \frac{d}{dy} \frac{G(y)\kappa^2(\widetilde{N}^2 + 1)}{T} = \kappa^2(\widetilde{N}^2 + 1) X(y)$$

と再定義した場合、式 (47) と (48) は

$$J \approx \widetilde{L} \times \widetilde{X} \quad (96)$$

$$\widetilde{L} = \frac{V[\widehat{\Delta y}|y^*]}{2} \approx \frac{2}{\kappa^4} T^2 \quad (97)$$

となる。

The quantity $2/\kappa^2$ corresponds to the standard deviation of the entropy change $\widehat{\Delta S}$ after a single step walk from the stationary point $y = y^*$:

$$\begin{aligned} \sqrt{V[\widehat{\Delta S}|y^*]} &\approx \left(\int_{-\infty}^{\infty} \widehat{\Delta S}^2 \mathcal{N}(\widehat{\Delta y}|0, V[\widehat{\Delta y}|y^*]) d\widehat{\Delta y} \right)^{1/2} \\ &= \frac{2}{\kappa^2} \approx 1 \sim 2. \end{aligned} \quad (98)$$