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The fastest evolutionary trajectory

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Abstract

Given two mutants, A and B, separated by n mutational steps, what is the evolutionary trajectory which allows a homogeneous population of A to reach B in the shortest time? We show that the optimum evolutionary trajectory (fitness landscape) has the property that the relative fitness increase between any two consecutive steps is constant. Hence, the optimum fitness landscape between A and B is given by an exponential function. Our result is precise for small mutation rates and excluding back mutations. We discuss deviations for large mutation rates and including back mutations. For very large mutation rates, the optimum fitness landscape is flat and has a single peak at type B.

Key words: Evolutionary dynamics, finite populations

1 Introduction

In 1696, the following problem was posed in Acta Eruditorum: *"I, Johann Bernoulli, address the most brilliant mathematicians in the world. Nothing is more attractive to intelligent people than an honest, challenging problem, whose possible solution will bestow fame and remain as a lasting monument [...]. Given two points A and B in a vertical plane, what is the curve traced out by a point acted on only by gravity, which starts at A and reaches B in the shortest time?"* Besides Johann Bernoulli,

his brother Jacob, as well as Gottfried Leibniz, Guillaume de l'Hôpital, and Isaac Newton solved this so called Brachistochrone problem. Newton is said to have found the solution within hours (Rouse Ball, 1960). Four solutions (except the one of de l'Hôpital) were published together. Amazingly, the solution turned out to be the cycloid, which is the position of a point on a circle rolling along a straight line. It has the parametric form

$$x(t) = h(t - \sin t) \qquad y(t) = h(\cos t - 1) \tag{1}$$

To make things even more beautiful, the cycloid is also the curve for which the time of a particle sliding down to the end point is independent of its starting point, as had been shown by Huygens in 1659. Galileo Galilei had addressed the Brachistochrone problem already in 1638 and - wrongly - concluded that the optimum curve would be the arc of a circle.

Here, we address a related problem in biology (see Fig. 1): What is the curve of fitness values on which a population (of constant size) evolves fastest from a fixed starting point to a given end point? Admittedly, this problem is not quite as elegant as the physics problem, since the answer will depend on the population size and the mutation rate. For small mutation rates, we present an analytical solution for a finite number of intermediate states. In this case, the fastest evolutionary trajectory has exponentially increasing fitness values, which means that the relative fitness increase is constant between any two consecutive steps. We discuss extensions of our analysis to higher mutation rates and including back mutation.

2 Small mutation rates

For small mutation rates, u, each mutation either reaches fixation in the population or becomes extinct before the next mutation arises (Crow and Kimura, 1970; Gillespie, 1983; Bürger, 2000). More specifically, this approximation is valid if the average time between two mutations, $1/(Nu)$, is much larger than the average time until a mutant reaches fixation or extinction. The average time to fixation of a neutral mutant in the Moran process is of the order of N generations (Moran, 1962). For frequency independent selection, this is an upper bound for the fixation time. Therefore, we come to the condition

$$u \ll \frac{1}{N^2}. \tag{2}$$

Often, however, the approximation is valid for much higher mutation rates of the order of $1/N$. This is the case if selection is stronger or if one considers the time in which a small fraction of the population takes over most of the population instead of the time in which a single mutant takes over the whole population.
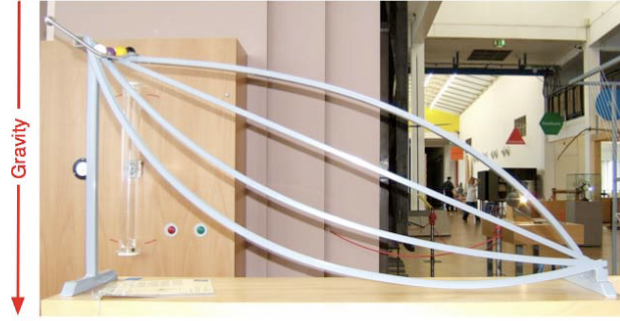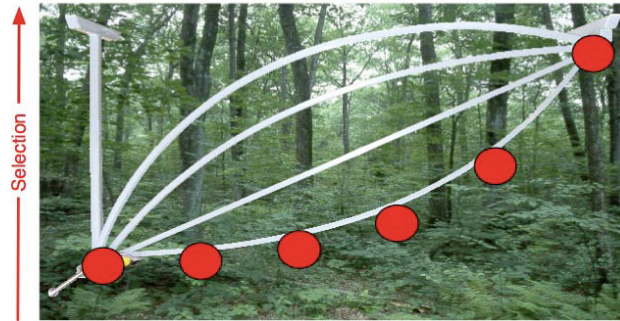
Fig. 1. The classical brachistochrone problem in physics determines the curve of fastest decent of an object that is only affected by gravity. The figure shows a typical experimental setup with four different curves. The fastest decent occurs on the third curve from the top, which has the form described in Eq. 1. (b) To address a similar problem in biology, we invert the y-axis of the setup. The force that leads to higher fitness values is now selection instead of gravity. We consider the problem of a finite number of states (red circles). How do we have to choose the fitness values on this curve to obtain the fastest fixation in the terminal state?

Without loss of generality, we set the initial fitness to $r_0 = 1$ (type A) and the fitness of the final mutant (type B) to $r_n = R$, where n is the number of steps on the evolutionary trajectory. Mutations can only lead from type i to $i + 1$. Later, we will discuss the case of back mutations from $i + 1$ to i. Our goal is to determine the fitness values r_i of the intermediate states $i = 1, \ldots, n - 1$ such that the time from the initial state $i = 0$ to fixation in the final state $i = n$ is minimized.

We assume a Moran process (Moran, 1962; Ewens, 2004; Lieberman et al., 2005; Nowak, 2006), but other processes with the same fixation probability will lead to the same analytical results. We restrict ourselves to birth death processes. With probability T_j^+ the number of mutants increases from j to $j+1$ and with probability T_j^- it decreases from j to $j - 1$. The probability that a single mutant will take over a population of size N and thus reach fixation is given by

$$\rho = \frac{1}{\sum_{j=0}^{N-1} \prod_{k=1}^{j} \frac{T_j^-}{T_j^+}}. \tag{3}$$

3

Obviously, any birth-death process in which the ratio T_j^-/T_j^+ is the same has the same fixation probability. This holds for the frequency independent case as well as for the frequency dependent case (Nowak et al., 2004b; Traulsen et al., 2007). In the Moran process, one individual is selected proportional to its fitness and produces identical offspring, which replaces a randomly chosen individual. Mutants have fitness r, while the wild type has fitness 1. This leads to $T_j^-/T_j^+ = 1/r$. Another possibility to obtain the same ratio is the following: Choose two individuals at random. If the two individuals are different, one of them replaces the other with probability proportional to his payoff. In other words, a mutant would replace a wild type individual with probability $r/(1+r)$. This again leads to $T_j^-/T_j^+ = 1/r$.

However, the ratio T_j^-/T_j^+ is not always $1/r$. If we select one individual to produce identical offspring proportional to its fitness and one individual for death proportional to the inverse fitness, the we obtain $T_j^-/T_j^+ = 1/r^2$. This implies a different form of the optimal trajectory.

For any process with $T_j^-/T_j^+ = 1/r$, the fixation probability of a mutant with fitness r_j in a population with fitness r_i is given by

$$\rho(r_j/r_i) = \frac{1 - r_i/r_j}{1 - (r_i/r_j)^N}. \tag{4}$$

Here, N is the constant size of the population. Due to the small mutation rate, the population will most of the time consist of a single type. Occasionally, a mutation occurs and two types are present for a short time. If the resident has fitness r_i and the mutant has fitness r_j, then the latter becomes extinct with probability $1 - \rho(r_j/r_i)$. The mutant reaches fixation with probability $\rho(r_j/r_i)$. The rate of evolution that takes the population from state i with fitness r_i to state $i+1$ with fitness r_{i+1} is given by the product of the mutation rate per generation, Nu, and the fixation probability. This constant rate leads to an exponential distribution of the time until a successful mutant arises that reaches fixation (note that the average time of the process of fixation itself can be neglected due to the small mutation rates). The average of this distribution is given by

$$T_i = \frac{1}{Nu\rho(\gamma_i)}. \tag{5}$$

We use the abbreviation $\gamma_i = r_{i+1}/r_i$ for the fitness ratio between state i and $i+1$. The average time to reach fixation in $i = n$ starting from $i = 0$ is the sum of the waiting times in the intermediate states,

$$T = \frac{1}{Nu} \sum_{i=0}^{n-1} \frac{1}{\rho(\gamma_i)}. \tag{6}$$

How do we have to choose the fitness ratios, γ_i, to minimize this time? We can solve this problem using Lagrange multipliers. The details of this calculation are

4

shown in the Appendix. It turns out that the unique fastest evolutionary path has exponentially increasing fitness given by

$$r_i = R^{i/n} \qquad \text{for} \qquad i = 0, \ldots, n. \qquad (7)$$

This exponential path is the fastest evolutionary path for an arbitrary number of states, n, if the mutation rate, u, is smaller than the inverse of the squared population size, $u \ll N^{-2}$. The exponential path results from the fact that $1/\rho(x)$ is a strictly convex function, see Appendix.

The exponential path is in line with the observation of Orr (2003) that the distribution of fitness effects among beneficial mutations is independent of the fitness of the wild type allele. This means that natural selection chooses from the same distribution of fitness values regardless of the initial configuration. The same is true for the optimal evolutionary trajectories calculated here: no matter where the system starts, the relative fitness of the next mutant has the same value.

Interestingly, the result of an exponential path is also valid for $R < 1$, i.e. a path with decreasing fitness values. The fastest way to reach a fitness minimum is given by a decreasing fitness landscape with $r_i = R^{i/d}$. However, the question how long it takes to decrease the fitness to a minimum is usually of minor interest.

Note that we do not ask for the fastest way to reach a certain fitness value (this would of course be a single mutation with this fitness), but for the fastest way to reach a mutant which is n steps away.

3   Extensions of the analytical theory

Here, we present various possibilities to extend the analytical theory presented above. Most extensions lead to some deviations from the simple exponential path. In the Appendix, we discuss the case where different mutants have different mutation rates. In the following, we discuss the effect of large mutation rates and back mutations.

3.1   High mutation rates

The optimum path with exponentially increasing fitness has been derived for small mutation rates. For larger mutations rates, the population usually consists of a mixture of the different mutants. In this case, our analytical approach is no longer valid and one has to resort to numerical simulations.

Once the mutation rates become so high that all states are reached within a short

time, then a single individual will reach type B (state n) fast. In this case, a deterministic framework based on the quasispecies equation can be used to describe the dynamics (Eigen and Schuster, 1977; Eigen et al., 1989; Nowak, 1992, 2006; Jain and Krug, 2007). We observe that some mutants of type B are present after a very short time. To minimize their time to fixation, every other type should have fitness 1, such that the relative fitness advantage of the final state is maximized compared to all other states. Thus, higher mutation rates lead to smaller fitness in the intermediate states compared to the exponential path that is optimal in the limit of small mutation rates, see Figs. 2-4 for numerical examples.

In Fig. 2, we show how the time to fixation in the final state for a system with a single intermediate state depends on the fitness in this state. For small mutation rates, the simulations agree well with our analytical theory. As expected, the deviations become larger when the mutation rates increase. For high mutation rates, the fastest fixation occurs when the intermediate fitness is minimized, as discussed above. The fitness landscape is flat and has a single peak for mutant n. Fig. 3 shows how the optimal fitness of the intermediate state depends on the mutation rate, u, and on the population size, N. Fig. 4 addresses numerical simulations of trajectories with two intermediate steps. Again, for low mutation rates the fastest path has exponentially increasing fitness. For high mutation rates, a flat fitness landscape with a single peak in the final state leads to the fastest fixation.

3.2 Back mutations

So far, we have neglected mutations that lead from type i back to type $i-1$. Such back mutations might alter our result of an exponential path. If back mutations are included, the time until the population reaches fixation in state d for the first time is obtained by solving a random walk, which leads to

$$T = \frac{1}{Nu} \sum_{i=0}^{n-1} \sum_{k=0}^{i} \frac{1}{\rho(\gamma_k)} \prod_{j=k+1}^{i} \frac{\rho\left(1/\gamma_{j-1}\right)}{\rho(\gamma_j)} \tag{8}$$

If the fitness is increasing along the trajectory and selection is strong, which means $N(r_{j+1} - r_j) \gg 1$ for all j, then the fixation probability of a mutant with lower fitness is very small, $\rho(1/\gamma_{j-1}) \ll 1$. The product in Eq. (8) is then very small except when $k = i$, where it is 1 by definition. Hence, we can neglect all terms except those in which $k = i$. This allows us to remove one sum, and we return to Eq. (6). Hence, for strong selection, even for the process with back mutations the fastest evolutionary path has exponentially increasing fitness.

For weak selection and back mutations, however, the problem becomes different. Weak selection means that the fitness difference between the states is small, $R - 1 \ll 1$ (Ohta, 2002). As weak selection is closely related to an undirected random walk, one has to reduce the time that the population spends far away from the final
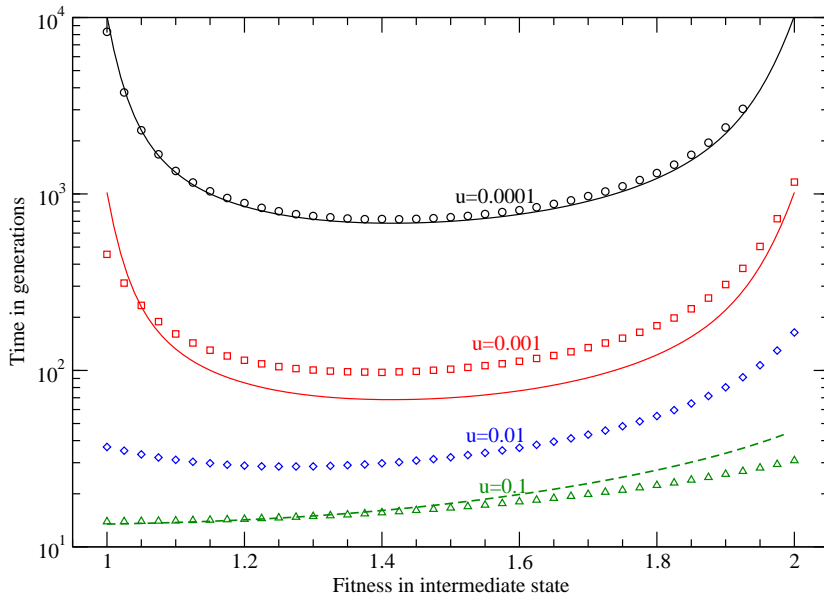
6

Fig. 2. Fixation times depending on the fitness in the intermediate state for a system with $n = 2$. For small mutation rates ($u = 0.0001$), the approximation from Eq. 5 (full lines) agrees well with numerical simulations (symbols). For larger u, the fixation times are not longer described well by the approximation in the limit of $u \ll N^{-2}$, but the minimum might still occur at the same point. For very large mutation rates ($u = 0.1$), a deterministic limit of the process can be used to describe the fixation times (dashed line), see Appendix. The dependence of the minimum on the mutation rate is shown in Fig. 3 (parameters $N = 100$, $r_0 = 1$, $R = 2$, averages over 10^5 independent realizations of the process).

state rather than optimize the time in each intermediate state. The fastest path can be determined from a numerical optimization of Eq. (8). For example, with $n = 2$, $R = 1.01$, and $N = 100$, we obtain for the intermediate fitness $r_1 = 1.0056 > \sqrt{R}$. Hence, the time for the first step is shorter than on an exponential path. If the path has more than one intermediate step, the optimal path can even have highest fitness in state $n-1$. For instance, $n = 3$, $R = 1.01$, and $N = 100$ leads to an optimal path with $r_1 = 1.0035 < \sqrt{R}$ and $r_2 = 1.0155 > R$. In this case, the time is minimized if one secures first that the whole population reaches fixation near the final state.

Numerical simulations of the system with back mutations for high mutation rates raise another problem: the definition of the 'final state' of the evolutionary process is no longer clear. For high mutation rates and allowing back mutations, it might (almost) never happen that the entire population is of type B. One could ask for the time it takes until the first mutant reaches type B, but this time does no longer depend on the fitness in the final state. Thus, the fitness in state $n - 1$ could be arbitrarily high and even higher than R. With the restriction $r_{n-1} \leq r_n = R$,
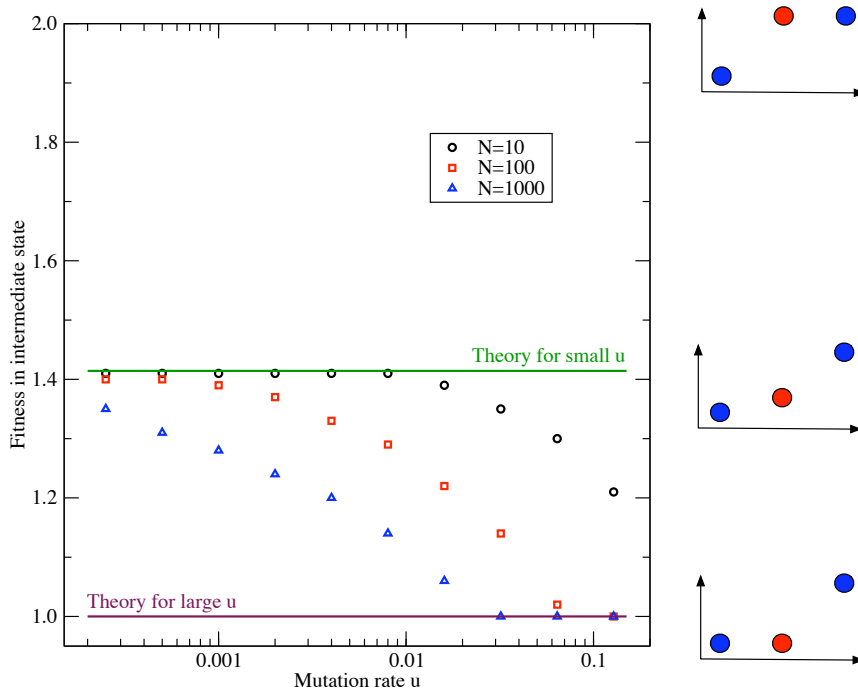
Fig. 3. Dependence of the optimal path with a single intermediate state on the mutation rate for population sizes $N = 10$, $N = 100$, and $N = 1000$ from simulations. For $u \ll N^{-2}$, we find the exponential path predicted by the theory (full line). For high mutation rates, the optimal path becomes close to a neutral path. On the right hand side, the different paths are drawn schematically: If the intermediate fitness is equal to the initial fitness (bottom), the path is neutral. For an intermediate fitness of $\sqrt{R}$, the path is exponential (middle). For intermediate fitness equal to R, the whole fitness difference occurs between the initial and the first state (parameters $r_0 = 1$, $R = 2$, averages over 10^5 independent realizations of the process)

we find that the time until the first mutant reaches the final state is minimized for $r_{n-1} = R$. Similar problems arise if one asks for a concentration of 50% of the individuals in the final state. Instead, one could ask for the time it takes until the stationary distribution is reached, starting from an initial population in state 0 (type A). However, this question is far from our original goal to address the problem of evolutionary brachistochrones.

4 Discussion

Evolutionary biology often assumes that natural selection has already maximized fitness. Thus, what we observe in nature is close to the genotype with the maximum fitness or the ESS. Underlying this view is the assumption that the organism we observe is an outcome of a long evolutionary process over many generations.
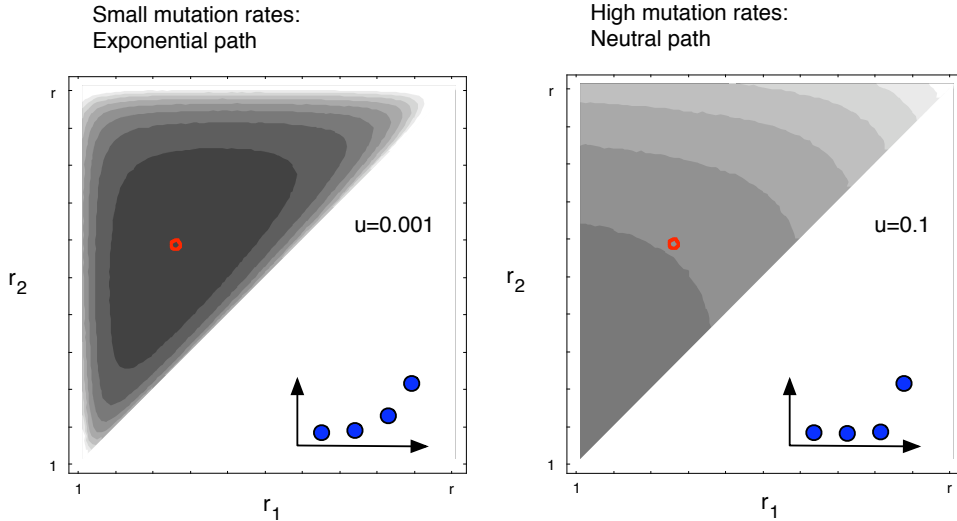
Fig. 4. Fixation times on a path with two intermediate steps, $n = 3$. The figure shows a contour plot of the times on the path, where darker colors indicate shorter fixation times. For $u = 10^{-3}$ (left), the system can be described by a stochastic framework. In this case, the optimal path is exponential with fitness values $1, R^{1/3}, R^{2/3}, R$, indicated by the red circle. For $u = 10^{-1}$ (right), a deterministic framework is more appropriate due to the high mutation rate. The fastest path is neutral with fitness values $1, 1, 1, R$ (population size $N = 100$, fitness in end state $R = 2$).

However, when evolution occurs for a limited time only, the time required for the evolutionary realization might sometimes determine what we observe. Then, a particular state might be realized in nature not because it has the highest fitness, but because there is a sequence of intermediate evolutionary states which realize the path connecting these states with the fastest rate.

In this paper, we discuss the rate of the evolution along a chain of evolutionary states. We show that even if the fitness of the final state is exactly the same, the rate of evolution through the chain greatly differ between paths depending on the fitness of the intermediate states.

Such rate of evolution along different evolutionary paths can be important in a variety of contexts. For example, affinity selection of antibodies during immune responses occurs by the clonal expansion of B cells expressing a surface immunoglobulin with a higher affinity for antigen compared to their competitors (Gram et al., 1992; Maclennan, 1994). It is quite important to achieve the fastest evolution through somatic mutation and selection of B cells in germinal centers (Kepler and Perelson, 1993). In another example, the cancer initiation of colon cancer occurs through the inactivation of two copies of a tumor suppressor gene in each stem cell (Nowak et al., 2004a). The time until the cancer initiation is exactly the problem of speed along the chain of mutations. Similarly, pathogens may reach escape states after multiple mutations within the host body (Nowak et al., 1991; Sasaki, 1994; Iwasa et al., 2003). Still another important implication could arise in the context of the

9

origin of life, where the time to reach an important intermediate state can become important if multiple attempts to create this intermediate state compete. In all of these examples, fixation in the end state can be some important prerequisite for further evolution or be associated with an important new property of the system.

We have analyzed the speed of the simplest possible situation, which is a single trajectory of sequential mutations between an initial genotype A and a final genotype B. From this analysis, we can obtain important insights in the problem of evolutionary speed. We have discovered that there exists a best choice of fitness values for the intermediate states. The fastest fitness landscape depends on the relative magnitude of the mutation rate (compared to the inverse of the population size).

For small populations and low mutation rates, the population is monomorphic most of the time. In this case, a continuous improvement, i.e. each mutational step increases the fitness by the same factor, leads to the fastest evolutionary trajectory. On all other trajectories, it will take longer to reach the end state. For example, one could consider a path in which the fitness of the end state is immediately reached. Then, there are no longer any selective differences to the end state available and this neutral evolution would take a much longer time than the path with improvement by the same factor.

In contrast for large populations and high mutation rates, the system can be described by a deterministic approach based on quasi-species dynamics. In this case, the result is completely different. Now, the fastest evolutionary trajectory is given by neutral (or even slightly deleterious) intermediate states and only the last step leads to a fitness advantage. In this way, the selective advantage of individuals in the end state (which appear after a very short time) is maximized compared to all other types and fixation occurs fastest.

These findings may also have implications for understanding cancer progression via the inactivation of tumor suppressor genes (Knudson, 1971; Nowak et al., 2004a; Iwasa et al., 2004a,b; Michor et al., 2004). For small mutation rates (and small populations of cells), the fastest progression would occur if inactivating each allele leads to the same relative fitness increase (i.e. an exponentially trajectory). For large mutation rates (and large population sizes), the fastest progression occurs if inactivating the first allele of the tumor suppressor gene is neutral, and inactivating the second allele leads to a large fitness increase of the (pre-) cancer cell.

To address some of those applications in more detail, the theoretical framework presented here might have to be extended, for example to include multiple different paths leading from A to B (Weinreich, 2005; Weinreich et al., 2006; Poelwijk et al., 2007).

Evolutionary trajectories through a discrete phenotype space are characterized by a time-scale on which mutations accumulate. Here, we have addressed the question for which fitness values evolution proceeds fastest, and we have calculated the

resulting fitness values in some simple cases.

A Appendix

A.1 The fastest trajectory for small mutation rates

Any solution for the fitness ratios γ_i has to fulfill $r_0 = 1$ and $r_n = R$, i.e. $r = \prod_{i=0}^{n-1} \gamma_i$. In order to optimize the time T in Eq. (6) with this side condition, we introduce the Lagrange function

$$L = \sum_{i=0}^{n-1} \frac{1}{Nu} \frac{1}{\rho(\gamma_i)} + \lambda \left(R - \prod_{i=0}^{n-1} \gamma_i \right). \tag{A.1}$$

Here, $\lambda \neq 0$ is the Lagrangian multiplier which guarantees that the side condition is fulfilled. For the optimum trajectory, L has an extremum. A necessary condition for this is

$$\frac{\partial}{\partial \gamma_j} L = -\lambda \frac{R}{\gamma_j} + \frac{1}{Nu} \frac{\partial}{\partial \gamma_j} \frac{1}{\rho(\gamma_j)} = 0 \tag{A.2}$$

for all γ_j. Hence, the following equation has to be fulfilled for $j = 1, \ldots, n-1$

$$\gamma_j \frac{\partial}{\partial \gamma_j} \frac{1}{\rho(\gamma_j)} = \text{const.} \tag{A.3}$$

One possibility is to choose a constant fitness ratio γ_j between adjacent states. Hence, the optimal path has exponentially increasing fitness given by

$$r_i = R^{i/n} \qquad \text{for} \qquad i = 0, \ldots, n. \tag{A.4}$$

In the more general case of different mutation rates, $u_i \neq u_j$, the Lagrange function reads

$$L = \sum_{i=0}^{n-1} \frac{1}{Nu_i} \frac{1}{\rho(\gamma_i)} + \lambda \left(R - \prod_{i=0}^{n-1} \gamma_i \right), \tag{A.5}$$

and the condition for the optimal path becomes

$$\frac{\gamma_j}{u_j} \frac{\partial}{\partial \gamma_j} \frac{1}{\rho(\gamma_j)} = \text{const.} \tag{A.6}$$

An anonymous referee made us aware of the following alternative way to derive our main result, which also allows to show the uniqueness of the solution: Setting $x = -\log \gamma$, the inverse fixation probability can be written as

$$\frac{1}{\rho(\gamma)} = \frac{1 - \gamma^{-N}}{1 - \gamma^{-1}} = \sum_{k=0}^{N-1} \gamma^{-k} = \sum_{k=0}^{N-1} e^{kx} = f(x). \tag{A.7}$$

11

It can be shown that $f(x)$ is a strictly convex function, i.e. $\lambda f(x) + (1 - \lambda)f(y) \geq f\left(\lambda x + (1 - \lambda)y\right)$. In our case, this leads to a lower bound for the time T until the final state is reached,

$$T\,Nu = \sum_{i=0}^{n-1} \frac{1}{\rho(\gamma_i)} = \sum_{i=0}^{n-1} f(x_i) \geq f\left(\sum_{i=0}^{n-1} x_i\right) = f\left(-\log \prod_{i=0}^{n-1} \gamma_i\right) = f\left(-\log R\right).$$
(A.8)

Both sides of the equation are equal if and only if all fitness ratios are equal, $\gamma_i = R^{1/n}$ for all i. Thus, the exponential path is the only path on which evolution occurs fastest.

A.2   The limit of large populations

For large populations, we can approximate the dynamics by a deterministic equation which is obtained from the stochastic dynamics in the limit $N \to \infty$. Since populations are typically mixed in this case, we have to describe the dynamics of selection and mutation in more detail than before. For example, it can make a difference if mutations arise spontaneously or only during reproduction. In every time step, we select an individual proportional to its fitness. With probability $1 - u$, it produces identical offspring. With probability u, it produces a mutant offspring. An individual in state i can only produce a mutant in state $i + 1$. Then, a randomly selected individual is removed from the population. The probability $T_{j \to i}$ that an individual of type i replaces and individual of type j in this process is given by

$$T_{j \to 0} = \frac{x_0 r_0}{\langle r \rangle}(1 - u)x_j$$

$$T_{j \to i} = \left(\frac{x_i r_i}{\langle r \rangle}(1 - u) + \frac{x_{i-1} r_{i-1}}{\langle r \rangle}u\right)x_j \qquad i = 1, \ldots n - 1 \qquad \text{(A.9)}$$

$$T_{j \to n} = \left(\frac{x_n r_n}{\langle r \rangle} + \frac{x_{n-1} r_{n-1}}{\langle r \rangle}u\right)x_j$$

x_j is the now fraction of individuals in state j. The average fitness $\langle r \rangle$ is given by $\langle r \rangle = \sum_{l=0}^{n} x_l r_l$. The rate at which the density of individuals in state i, x_i, changes in the limit $N \to \infty$ is given by $\dot{x}_i = \sum_{j=0}^{n} T_{j \to i} - T_{i \to j}$, see Traulsen et al. (2006) for details. In our case, the system of equations simplifies to

$$\dot{x}_0 = x_0 \frac{r_0(1-u) - \langle r \rangle}{\langle r \rangle}$$

$$\dot{x}_i = x_i \frac{r_i - \langle r \rangle}{\langle r \rangle}(1-u) + \frac{x_{i-1}r_{i-1} - x_i\langle r \rangle}{\langle r \rangle}u \qquad i = 1, \dots n-1 \quad \text{(A.10)}$$

$$\dot{x}_n = x_n \frac{r_n - \langle r \rangle}{\langle r \rangle} + x_{n-1}\frac{r_{n-1}}{\langle r \rangle}u.$$

To compare this to a finite population of size N, we compute numerically the time it takes starting in state $x_i = \delta_{i,0}$ until the population density in state n is $1 - 1/N$. Fig. 2 shows that this approximation works for $N = 100$ and $u = 0.1$ for a single intermediate step, $n = 2$, if the fitness in the intermediate state is sufficiently small.

Acknowledgements

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