

Changing the pace of evolution

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Abstract

In biological evolution, the rate of mutations is “encoded” by enzymes which can be mutated like any other gene. Inspired by this feature, we present a simple Brownian motion model, in which the temperature itself is a dynamical variable. Intra-well and inter-well relaxations occur at different “temperatures” and have different dynamics, and the Kramers time becomes asymptotically *linear* in the barrier height for large heights.

Living beings possess molecular mechanisms that can change, in a heritable way, both the rate and the kinds of genetic variation that they generate through mutation and recombination [1–6]. In this Letter, we will consider some aspects of what can happen to mathematical formulations of evolutionary theory when this type of genetic alteration is included in the formalism. Because these mechanisms do not encode “traits” in the usual sense of the word, but actually implement the generation of diversity, any model of evolution which takes them into account has some degree of “self-reference”, and we can expect qualitative changes in the behaviour of such models.

An image that has permeated mathematical treatments of evolutionary theory is that of the *adaptive landscape* [7,8]. It was first introduced by Sewall Wright in 1932 [9], in an attempt to illustrate how a random local search could lead to optimization. In this metaphor, the set of all possible combinations of traits in a given species is represented as the coordinates in a cartographic map, with the degree to which that combination is well-adapted being the height on

the map. Mutations would generate random local explorations, the best such mutations would survive and reproduce, and the population would move towards higher ground, clustering on a discrete number of combinations of traits. Dobzhansky [10] furthered the metaphor, so that the ecological niche of an entire species would be represented by a single peak. The original (intra-species) use was refined in microevolutionary theory into the notion of a *fitness landscape* [11].

This image can be interpreted in terms of a Brownian process moving in a potential well, with the wells of the potential representing peaks of adaptation or fitness. Because of this, the metaphor carries with it unwarranted thermodynamic baggage. In actual biological evolution, the mutation rate is not a temperature in any thermodynamically meaningful sense, as we will show below.

If the landscape is static and the mutation rates are constant, then the process through which a population relaxes within a well, and the process through which some individuals undergo a “thermally acti-

vated” jump to a nearby well, are dynamically similar processes; in thermodynamic jargon, we would say that intrawell and interwell relaxations are just two aspects of the same phenomenon, and are linked by detailed balance relations. This view is related to an old, ongoing argument in evolutionary theory, which we could call the “more of the same” argument; it holds that macroevolution is just microevolution seen on a long enough timescale.

Obviously, if a thermodynamic analogy were to go through, we would expect thermally activated jumps to have Arrhenius (exponential) timescales; this poses a deep problem as far as the pace of evolution is concerned. Dobzhansky was the first to posit a “fractal” or “rugged” structure for the adaptive landscape; he wrote, in 1957 [10]:

Thus, the ecological niche occupied by the species “lion” is relatively much closer to those occupied by tiger, puma and leopard than to those occupied by wolf, coyote and jackal. The feline adaptive peaks form a group different from the group of canine peaks. But the feline, canine, ursine [...] peaks form together the adaptive “range” of the carnivores, which is separated by deep adaptive valleys from the “ranges” of rodents, bats, ungulates [...] In turn, these ranges [form] the adaptive system of mammals, which [differs from those of] birds, reptiles, etc.

For Dobzhansky, the hierarchical structure of the adaptive landscape would be reflected in the hierarchical relationships between species. This view was taken further by Kaufmann [12], who argues that landscapes are expected to be rugged, all the way down to the fitness contribution of a single protein.

The problem here is that if landscapes are rugged and we have Arrhenius timescales for jumps, then evolution would probably become a *glassy* problem. The time course of glasses shows *aging*: it slows down, not by not making transitions any more, but by making transitions between set of states which become smaller and smaller all the time. Thus, in a macroscopic sense, they stop evolving: the correlation functions in a glass decay more slowly than exponentially, and sometimes do not decay at all. However, biological evolution has not really slowed down in this sense: for instance, most current mammals evolved in the last two percent of the history of life, even though the mammalian lineage is much older; so a very significant and major addition

occurred in a small fraction of later times.

One way out of this problem is *catastrophism*: large-scale natural catastrophes upset ecosystems, which forces major rearrangements in the relations between species, thus violently changing the landscapes. It could be argued that the later evolution of mammals is a direct result of the demise of *Dinosauria*, which upset ecosystems rather violently. In this view, evolution keeps going because natural catastrophes keep occurring.

We will show that a different, and complementary way to break out of the glassy predicament would be to have an inheritable way to change, for instance, mutation rates. We do know that such mechanisms exist. Taq DNA polymerase during *in vitro* synthesis (without any proofreading mechanism) has a misinsertion rate between 10^{-2} and 10^{-5} , depending on incubation conditions [13,14]. *In vivo* rates are much lower, about 10^{-10} in mammals; but still the average mutation rate per base per replication varies by more than 16 000-fold between different organisms with different genome sizes, though it is relatively constant when measured per genome per replication [15]. There are even variations *within* the same species: Sturtevant [1] noted that different strains of *Drosophila* vary in their mutation rate by sixfold. More spectacularly, the dynamic range of genetically determined spontaneous mutation in *E. coli* is approximately 10^4 [16–18]; most wild-type strains have the lowest mutation rates, while “mutator” strains (with thousandfold higher rates) appear routinely in mutagenesis experiments in bacteria, and in some types of cancerous cells [19–21]. Proofreading can even be turned on and off *within* an organism, through genetic control: the first 12 rounds of cell division in the *Xenopus laevis* egg are performed without some proofreading mechanisms to speed up development [22].

So, it is clear that the actual error rate is eminently a function of the genotype, in particular of the genes encoding the enzymes of DNA metabolism, such as proofreading, mismatch correction and DNA repair [23]. The genes for these enzymes are, like any other gene, subject to mutation and inheritance; so that the error rate is not “given” (as a temperature would be) but a function of the genotype; furthermore, this error rate can change, across species and even transiently within species, by *decades*. Notice that in a usual thermodynamical system, changing “temperature” by four

decades (as mentioned for *E. coli*) is a violent action: just compare that with changing 300 K (room temp.) to 3 000 000 K (the Sun). It is by no means a small effect, and it has been observed reliably and repeatably, at least in bacteria.

We will render this in the most trivial of settings, that of a random walker (representing a single line of descent) and the associated Fokker–Planck equation for populations. This is not a correct rendering from a population genetics point of view; our intention here is only to point out the type of features that mathematical formalisms might develop, and our model should *not* be construed as anything other than an illustration of thermodynamic analogies going wrong. A more accurate, (and more intricate) depiction will be given elsewhere. We will keep (maybe paradoxically) the thermodynamic language throughout, so we will refer to the fitness landscape as (minus) the potential, mutation rates as temperature, and so forth.

We will collect all genotypic degrees of freedom which encode the structure and function of the organism in a variable x , while keeping the degrees of freedom that encode mutation rate in a variable y . To zeroth order, mutation rate does not affect the viability or fitness of *this* organism, only the probability that the offspring will mutate; hence we will assume the potential to be a function of x alone and the temperature to be a function of y alone. We can add a penalty for the mutation rate becoming too high, to reflect the fact that high mutation rates might be deleterious even in a single organism (i.e., cancer or lethal DNA damage). So we write down the Langevin equations for our model:

$$\begin{aligned} \dot{x} &= -\partial_x V(x) + g(y) \xi_1(t), \\ \dot{y} &= -\beta y + g(y) \xi_2(t), \end{aligned} \quad (1)$$

where $\langle \xi_i(t) \xi_j(s) \rangle = \delta_{ij} \delta(t - s)$, $V(x)$ is the potential, $g^2(y)/2 \equiv T(y)$ is the mutation rate, and we imply the Itô convention. We will also have to decide on some $T(y)$; we choose $T(y) = T_0 + (\alpha/2)y^2$.

The choice of $T(y)$ is crucial enough for the outcome that we should clarify some rationale for the choice, other than its obvious simplicity. First, $T(y)$ should be positive and bounded by below. Second, according to Refs. [16–18], “mutator strains” have been observed in *E. coli* with as much as 10^4 higher mutation rates than the wild-type. Hence, our $T(y)$ should

be a function with the potential to span a few decades; an easy way to make it so is to use a $T(y)$ which is unbounded. Finally, how fast $T(y)$ is allowed to grow as y increases reflects a choice of a parametrization; so, it affects all the y terms, in particular the “restoring force” along y (in our case, $-\beta y$). From our assumptions, this restoring force reflects changes in fitness due to T , so it should be of the form $-\partial_y f(T(y))$. We have taken the simplest choice, $f(T) \approx T$. The qualitative results are not changed dramatically by changing the detailed parametrization of $T(y)$ under a fixed choice of f , but are much more susceptible to changes in f , so the exact choice of parametrization is not terribly important. Since the “mutator strains” mentioned above do not seem to be seriously handicapped in any way, we believe that $f(T) \approx T$ is a reasonable choice within the range of our model.

The Fokker–Planck equation for this system reads

$$\begin{aligned} \dot{P}(x, y, t) &+ \left(\frac{\partial_x}{\partial_y} \right) \cdot \left\{ \left(\begin{array}{c} -\partial_x V \\ -\beta y \end{array} \right) P - \left(\frac{\partial_x}{\partial_y} \right) T(y) P \right\} \\ &= 0. \end{aligned}$$

The term inside curly brackets is the *probability current*; the detailed balance condition implies that in the stationary state, the current vanishes identically. In this equation the current can only vanish identically if either V or T is a constant, and so the system cannot have detailed balance. Even if a stationary state is achieved, there will be currents of circulating probability in our system.

The y equation is decoupled from x in Eq. (1), so the stationary distribution for the marginal distribution of y may be found by direct integration,

$$\begin{aligned} P(y) &\equiv \int P(x, y) dx \\ &= \sqrt{\frac{2a}{T_0\pi}} \frac{\Gamma(1 + \beta/\alpha)}{\Gamma(\frac{1}{2} + \beta/\alpha)} \left(\frac{T_0}{T_0 + \frac{1}{2}\alpha y^2} \right)^{1+\beta/\alpha}, \end{aligned} \quad (2)$$

$$\langle T \rangle = \frac{2\beta}{2\beta - \alpha} T_0.$$

Hence $P(y)$ has algebraic tails; it is normalizable for $2\beta > -\alpha$ and has finite average temperature for $2\beta > +\alpha$. Furthermore, this function converges to the expected Gaussian distribution when $\alpha \rightarrow 0$, where the

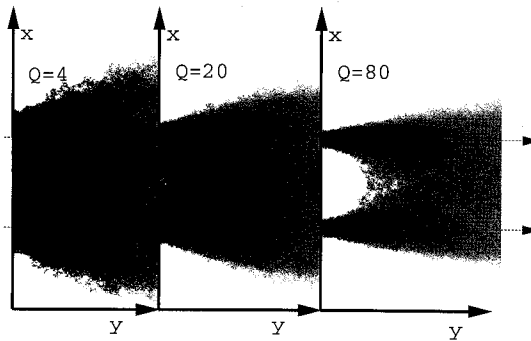


Fig. 1. Numerically obtained histograms as a function of x and y . The density is encoded logarithmically onto gray scales.

y equation becomes an Ornstein–Uhlenbeck process. From the viewpoint of the x variable, our problem here is one of fixed barrier heights with fluctuating temperatures; there have been several studies of fluctuating barriers at constant temperature [24–26], an obviously close setup.

To perform numerical simulations, we have chosen $\alpha = 0.1$, $\beta = 0.06$, $T_0 = 1$, $\langle T \rangle = 6$, and $V(x) = Q(x^2/100 - 1)^2$ a double-well quartic, with wells at $x = \pm 10$, and barrier height equal to Q . For all values of Q , the peaks of the population lie at the bottom of the potential wells, at the lowest available temperature. At very low values of Q/T_0 , the probability has a saddle point between the two peaks, at $x = 0$ (top of the barrier) and $y = 0$ ($T = T_0$). However, as Q increases, there is a bifurcation, and this point becomes a local minimum of probability. There is an arc of probability joining the two wells, but it goes at a temperature different from the minimum. As the value of Q is increased, this arc separates itself further and further from the $y = 0$ axis as shown in Fig. 1.

So, intrawell relaxation is carried out primarily at $T_{<} \approx T_0$, while interwell transitions occur at a larger temperature $T_K \gg T_0$. The main effect of intrawell relaxation is the lowering of the average potential energy for the population within one well; the fundamental interwell timescale is the average time it takes the system to jump over a barrier into an adjacent well, usually called the Kramers time. These two processes, which we can loosely associate to microevolution and macroevolution, have become dynamically distinct, and data on one of them does not allow us to infer the parameters of the other. In particular, measuring the mutation rate of one population within one

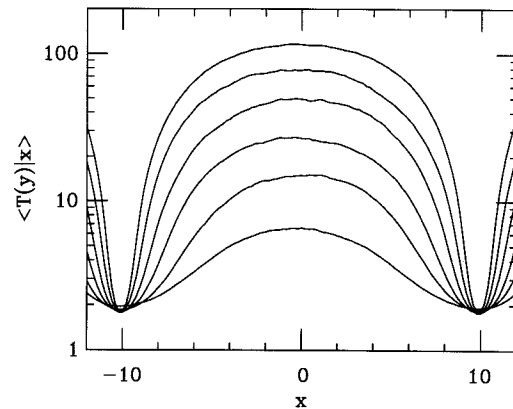


Fig. 2. Average temperature as a function of position: $\langle T(y)|x \rangle$. The curves correspond to $Q = 5$ (bottom curve), 10, 20, 40, 80 and 160 (top).

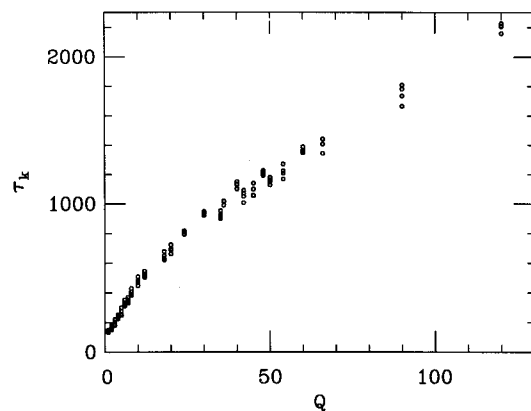


Fig. 3. Kramers time τ_K as a function of barrier height Q . $T_0 = 1$, and $\langle T \rangle = 6$. There is an inflection point in the vicinity of $Q = \langle T \rangle$: for Q below this value, the transitions between wells do not need to go through higher temperatures.

well does not allow us to estimate the Kramers rate, because the average temperature within the well can be decades smaller than the temperature at the top of the barrier. This is shown explicitly on Fig. 2, where the average temperature as a function of x is shown. (Notice that, while T is a function of y alone, $\langle T|x \rangle \equiv \int T(y) P(x, y) dy$ is indeed a function of x).

Fig. 3 shows the Kramers time τ_K as a function of Q . It is definitely not an exponential. Actually, it looks like, for large Q , τ_K is *linear* in Q . We submit to the reader that this type of behaviour will effectively *de-glass* a glassy potential, unlocking its time evolution.

We can argue that in our case the Kramers rate should be asymptotically linear as $Q \rightarrow \infty$ through the following (quite crude) argument. We can estimate that the rate for crossing the barrier at a given y goes as $\exp[-Q/T(y)]$. Since we know the chances of being at any given y are $P(y)$, the average rate for crossing can be estimated as

$$\frac{1}{\tau_K} \approx \int P(y) e^{-Q/T(y)} dy,$$

wherefrom τ_K becomes asymptotically linear in Q as $Q \rightarrow \infty$. We have to note that this linearity is linked both to the particular form of $T(y)$ we chose, and, more fundamentally, to the dimensionality of the space. In detailed balance, the Boltzmann factors are independent of dimensionality, but in our system, which lacks detailed balance, we have no such guarantee. In particular, the bulk of the dependence would be on the number of the y variables (if we had more than one), because the algebraic tails would be particularly sensitive to entropic pressure effects.

But the nonexponential dependence on the barrier height also tells us something else besides the unlocking of the dynamics. Our model displays the *Landauer syndrome*: the relative stability of two different wells can not be computed locally, as a function of the difference in well depth, but is a function of the barrier height, i.e. of the path between the wells [27–29]. Landauer's examples have typically made use of x -dependent temperatures, as in the case of his famous blowtorch [28]; even though in our case the temperature is not a function of x , but of a different variable, the effect remains. For a potential with more than two wells, it is entirely possible to arrange barrier heights so that the maximum probability is concentrated on a well which is not the deepest one, with probability currents going across closed loops of wells.

An intuitive view of why this should be so can be found by realizing the similarities between this dynamics and simulated annealing (SA). SA is a widely used heuristic method for finding the minimum of a glassy potential, by starting at a high temperature and then cooling the system in appropriate fashion. The most important piece of heuristics in applying SA is the *cooling schedule*, which is crucial to the success of the method. In a sense, SA maps all of the complication of the glassy problem into finding the correct cooling schedule. Now, we may argue that the y

equation in (1) is a machine for ergodically generating random cooling schedules; that is the reason why the system can avoid being glassy: because all cooling schedules are tried. But the same equation also generates *heating schedules*, and therefore, even if the absolute minimum of the potential is found, the system will be kicked out of there and into some other well. This is why we cannot guarantee that the populations in the wells have any relationship to the depth of the well.

We can now engage in some further speculation as to what this trivial model tells us we might expect in more detailed models of evolution. First, we can argue that *the ability to change the pace at which evolutionary novelty is created will be used by Darwinian evolution whenever it can confer some type of advantage*. One such advantageous use of changes of pace would be to uncouple macro- and microevolutionary dynamics. Interwell transitions should not be “more of the same” as intrawell relaxations, because they have conflicting requirements on said pace: intrawell relaxation asks for the smallest available mutation rate, so that a set of adaptations might be refined with the utmost care under the minimum possible genetic load, while interwell transitions require much more copious amounts of novelty to be able to make it through the intervening unfavourable terrain in a reasonable time, and genetic load is not an issue during transitions. While in its current form our model uses assumptions that restrict its applicability to higher organisms¹, we believe that the idea transcends these assumptions. We do know of a myriad molecular mechanisms controlling not just mutation rates, but also the processes which are important for the higher taxa, like recombination, chromosome segregation, etc.; all of these can be inheritably affected by mutation, or even genetic regulation.

Secondly, the fact that the Arrhenius-induced slowing down can be avoided by our model tells us that catastrophes may not be a *necessary* agent in the production of new adaptations. They are probably an important evolutionary force, and we do know that nat-

¹ The technical assumption made here is “linkage disequilibrium”: the x and y characters are inherited together without separate dissolution into the gene pool. This assumption holds most strongly for clonal, asexual (or infrequently mating) organisms, such as bacteria and cancerous cells.

ural catastrophes occur with power-law distributions; but they might not necessarily be the *only* way out of the dilemma. The rapid jumping across barriers displayed by our model could be seen as a manifestation of “punctuated equilibrium” [30]. It has been pointed out that the change of a phenotypic character in an interwell transition will have a punctuated character [31,32]; our paper is concerned with the related, but distinct, problem of the timescales between jumps. While our model shows the same punctuated features, it is restricted in applicability (see Footnote 1). We think that models applicable to higher taxa may inherit features of this type, but we cannot assert so at this time.

Finally, and most importantly, any model that incorporates a genome-dependent mutation rate will have the Landauer syndrome. This leads to a view of evolution that differs substantially from “programmatic” evolutions such as genetic algorithms. The dynamics of our model is no longer an optimization dynamics. It definitely optimizes *locally*, within each well, within each set of adaptations; and it does so as carefully as is allowed. But the evolution *across* wells looks much more like a greedy “fill-all-space” algorithm than like an optimization dynamics. Because all interwell equilibrations is carried at a high temperature, all wells are filled with roughly similar populations regardless of their depths. We can argue that this type of dynamics *feels* much more like the dynamics of life as we know it than a plain optimization strategy, since we know life to be adept at filling every available niche and adapting to every single environment, regardless of how hard or desperate it might look on a global scale.

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