

# Kramers rates in Fisher-Eigen processes. 8.592 final project

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## Abstract

In this project we consider a Darwinian motivated Fisher-Eigen process on a continuous phenotype space. After introducing the system, we reproduce the calculations of [1], to find the rate at which a Fisher-Eigen process can find a nearby maxima in a fitness landscape. We derive an asymptotic formula for the rate with strong noise that differs from the formula in [1]; we have reason to believe that our formula is accurate. Finally we verify the asymptotic rate by numerical simulations.

## Introduction

In this class we have examined simple models for how population genetics change in time due to selection and mutation. We considered a discrete description, so a member of a population is in one of a number of discrete genetic states. This is an effective description for many cases, in particular an organisms genetic information is formed by a discrete number of DNA base pairs. However, it is useful to consider a continuum description instead [2]. Consider the phenotype as being characterised by some vector of continuous variables

$$\mathbf{q} = (q_1, \dots, q_n),$$

which describes somehow an individual organism. We also assume that there is some fitness function  $E(q_1, \dots, q_n; t)$ . In the limit of a large population, we can introduce a population density  $n(\mathbf{q}, t)$  so that there are  $n(\mathbf{q}, t)d\mathbf{q}$  individuals in a volume  $d\mathbf{q}$  of phenotype space. The total population is then

$$\mathcal{N} = \int d\mathbf{q} n(\mathbf{q}, t),$$

from which we can normalise and work with probabilities,

$$p(\mathbf{q}, t) = n(\mathbf{q}, t)/\mathcal{N}, \quad 1 = \int d\mathbf{q} p(\mathbf{q}, t).$$

The probability density then evolves according to a global fitness selection rule [3, 1]

$$\frac{\partial p(\mathbf{q}, t)}{\partial t} = r(E(\mathbf{q}, t) - \langle E \rangle)p(\mathbf{q}, t) + D\nabla^2 p(\mathbf{q}, t), \quad (1)$$

where  $\langle E \rangle = \int d\mathbf{q} E(\mathbf{q}, t)p(\mathbf{q}, t)$ .  $r > 0$  represents a coupling constant, which we will absorb into the definition of  $E$ . The probability density at a point in phenotype space increases if that point is at a fitness higher than the global average fitness. There

is also diffusion, with diffusion constant,  $D$ , due to random mutations. In this project we examine the effectiveness of such an evolutionary strategy at finding a maxima in an energy landscape, in particular with respect to crossing an energy barrier.

## General solution

In general terms, equation 1 is a non-linear PDE. However, an ansatz can transform it into a linear PDE,

$$p(\mathbf{q}, t) = \rho(\mathbf{q}, t) \exp \left[ - \int_0^t \langle E \rangle(s) ds \right],$$

for some function  $\rho(\mathbf{q})$  (which will not stay normalised in general). This leads to the equation

$$\frac{\partial \rho(\mathbf{q}, t)}{\partial t} = E(\mathbf{q}, t)\rho(\mathbf{q}, t) + D\nabla^2 \rho(\mathbf{q}, t).$$

Since this equation is linear, we can solve it by using a separation of variables method, and write the solution as

$$p(\mathbf{q}, t) = \exp \left[ - \int_0^t \langle E \rangle(s) ds \right] \sum_{n=0}^{\infty} c_n \phi_n(\mathbf{q}) e^{-\lambda_n t}.$$

The  $\phi_n$  are eigenfunctions of the operator

$$\hat{H} = -D\nabla^2 - E(\mathbf{q}, t) = -D\nabla^2 + U(\mathbf{q}, t),$$

where we have introduced the potential  $U = -E$  to emphasise the mathematical similarities to the time independent Schrödinger equation. Maximising the average fitness is then equivalent to minimising the average potential energy. The  $\lambda_n$  are eigenvalues, so that  $\hat{H}\phi_n = \lambda_n\phi_n$ , and ordered so that  $\lambda_0 < \lambda_1 < \dots < \lambda_n$ . The coefficients  $c_n$  are determined from initial conditions, and assuming that the  $\phi_n$  are normalised, an expression for them is

$$c_n = \int d\mathbf{q} \phi_n^*(\mathbf{q}) p(\mathbf{q}, 0).$$

From equation 1 and initial conditions, we know that the probability remains normalised for all time. But then it must hold that

$$1 = \exp \left[ - \int_0^t \langle E \rangle (s) ds \right] \sum_{n=0}^{\infty} c_n l_n e^{-\lambda_n t},$$

with

$$l_n = \int d\mathbf{q} \phi_n(\mathbf{q}).$$

One can therefore write an expression for the probability density

$$p(\mathbf{q}, t) = \frac{\int_{n=0}^{\infty} c_n \phi_n(\mathbf{q}) e^{-\lambda_n t}}{\int_{n=0}^{\infty} c_n l_n e^{-\lambda_n t}}.$$

For any generic initial condition, one expects all of the  $c_n$  to be non-zero (If  $c_n = 0$  exactly, then there must be some symmetry based reason why this would be true, else  $c_n$  could be small, but non-zero). Then in the long time limit,

$$p(\mathbf{q}, t) \rightarrow \frac{\phi_0(\mathbf{q})}{l_0}, \quad \langle U \rangle \rightarrow \lambda_0,$$

## Kramers rates

The idea of Kramers rates comes from reaction rate theory [4]. Consider a particle sitting at a local minima of a potential,  $U$ . We assume that the particle obeys a Langevin equation of the form

$$\frac{dx}{dt} = -\nabla U(x) + \xi(t),$$

where  $\xi(t)$  is Gaussian white noise. One then wonders how long will it take for the particle to overcome an energy barrier to find the global minimum of the potential, or another local minima. Kramers rate theory can provide (approximate) answers to this problem. In this project we will do the same, but instead of an ensemble of particles obeying a Langevin equation, we consider a population evolving under a Fisher-Eigen process. Consider a population initially at a local maxima of a fitness landscape. We want to know how long it takes for this population to explore the global fitness landscape and find the global fitness maximum. It is also an interesting question to ask what are the transition rates in equilibrium between clusters of the population at different fitness maxima.

In general, we expect the phenotype space to be very high dimensional. The dynamics of searching

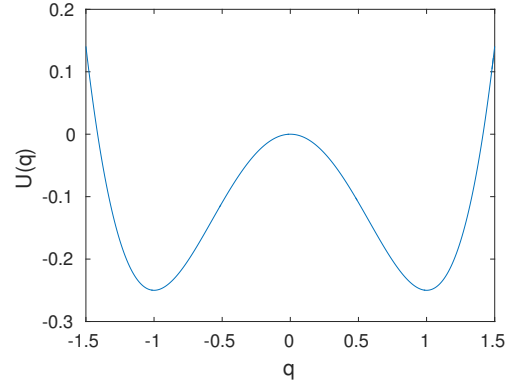


Figure 1: Plot of the double-welled potential

for a fitness maxima are influenced by the fact that the underlying space is high dimensional [3]. In such a space, one expects to find many more saddle points than maxima, and while progress has been made, the question of how a Fisher-Eigen process searches such a landscape is still somewhat unresolved [3]. Here, we make the questionable, but simplifying assumption that the typical path taken between two minima will be the most likely (or instanton) path. Thus the space reduces to a single variable,  $q$ . When a specific potential is needed, we will follow [1] and use

$$U(q) = \frac{1}{4}q^4 - \frac{1}{2}q^2,$$

which is shown in figure 1.

Suppose at time  $t = 0$ , we start the entire population in the left well, say  $p(q, 0) = \delta(q + 1)$ , and then let the system evolve. We want to calculate the rate at which the population crosses to the right well. One can approximate the system by the master equations,

$$p_-(t) = \int_{-\infty}^0 dq p(q, t), \quad p_+(t) = \int_0^{\infty} dq p(q, t).$$

$$\begin{aligned} \dot{p}_- &= -k_+ p_- + k_- p_+ \\ \dot{p}_+ &= k_+ p_- - k_- p_+, \end{aligned}$$

where since the chosen potential is symmetric,  $k_+ = k_- = k$ , and the solution is

$$p_{\pm} = \frac{1}{2} \mp \frac{1}{2} \exp(-2kt).$$

Thus by finding  $k$ , we know how fast the population can cross the barrier and discover the minimum on the other side.

Since the potential is symmetric, if  $\phi_n(q)$  is an eigenfunction, so is  $\phi_n(-q)$ , with the same eigenvalue. Therefore the eigenfunctions are either odd or even. It seems to be generally true for a symmetric potential that  $\phi_0(q)$  is even, and  $\phi_1(q)$  is odd. The author has never seen a formal proof of this, although it is known numerically in the current case.  $\phi_1$  being odd implies that  $l_1 = 0$ . Taking the asymptotic limit of large time, and including the first correction to equilibrium gives that

$$p(q, t) = \frac{\phi_0(q)}{l_0} + \frac{c_1 \phi_1(q)}{c_0 l_0} e^{-(\lambda_1 - \lambda_0)t}.$$

Identifying decay rates with the master equation gives that

$$k = \frac{1}{2}(\lambda_1 - \lambda_0).$$

While it is non-trivial to find such eigenvalues, in particular exact solutions do not exist, the problem is equivalent to finding energy levels in quantum mechanics. There are many ways to obtain approximate solutions to this problem [5]. Here we will use the Rayleigh-Ritz method to derive approximate answers, which are valid in the large noise regime. It is also possible to use a WKB method in the small noise regime [1]. The derivation here is slightly different to [1], but the same in principle.

We use the test function

$$\phi_a(q; c) = (2c/\pi)^{1/4} \exp(-cx^2),$$

so that  $\lambda_0 \lesssim \min_c \langle \phi_a | \hat{H} | \phi_a \rangle$ . Similarly, if

$$\phi_b(q; d) = 2(2d^3/\pi)^{1/4} x \exp(-dx^2),$$

then  $\lambda_1 \lesssim \min_d \langle \phi_b | \hat{H} | \phi_b \rangle$ . Using the fact that

$$\int_{-\infty}^{\infty} q^{2n} e^{-2cq^2} dq = \frac{\Gamma(n + \frac{1}{2})}{(2c)^{n + \frac{1}{2}}},$$

we can calculate that

$$\begin{aligned} \langle \phi_a | \hat{H} | \phi_a \rangle &= D \left[ c + \frac{3}{64Dc^2} - \frac{1}{8Dc} \right] \\ \langle \phi_b | \hat{H} | \phi_b \rangle &= D \left[ 3d + \frac{15}{64Dd^2} - \frac{3}{8Dd} \right]. \end{aligned}$$

To solve for the minimum values, one has to solve the equations

$$\begin{aligned} 0 &= 1 - \frac{3}{32Dc^3} + \frac{1}{8Dc^2} \\ 0 &= 3 - \frac{15}{32Dd^3} + \frac{3}{8Dd^2}. \end{aligned}$$

We find the approximate solutions

$$c = \frac{1}{2} \left( \frac{3}{4D} \right)^{1/3} - \frac{1}{24D} + \dots$$

$$d = \frac{1}{2} \left( \frac{5}{4D} \right)^{1/3} - \frac{1}{24D} + \dots$$

$$\begin{aligned} \min_c \langle \phi_a | \hat{H} | \phi_a \rangle &= D \left[ \frac{3}{4} \left( \frac{3}{4D} \right)^{1/3} - \frac{1}{2} \left( \frac{1}{6D^2} \right)^{1/3} + \dots \right] \\ \min_d \langle \phi_b | \hat{H} | \phi_b \rangle &= D \left[ \frac{9}{4} \left( \frac{5}{4D} \right)^{1/3} - \frac{3}{2} \left( \frac{1}{10D^2} \right)^{1/3} + \dots \right], \end{aligned}$$

$$\begin{aligned} k &= \frac{1}{2}(\lambda_1 - \lambda_0) \approx \frac{3D^{2/3}}{8(4)^{1/3}} \left( 3(5)^{1/3} - 3^{1/3} \right) \\ &\quad - \frac{D^{1/3}}{4} \left( \frac{3}{10^{1/3}} - \frac{1}{(6)^{1/3}} \right). \end{aligned}$$

We respectfully disagree with the algebra in [1]. We note that if we use  $d = \frac{1}{2}(3/4D)^{1/3}$  in our formula for  $\langle \phi_b | \hat{H} | \phi_b \rangle$ , then we get the formula in [1]. However, the minimizations should occur separately, so the values of  $c$ ,  $d$  could and should be different. Of course, one can use this value of  $d$  for an approximation, but then why calculate a higher order term in the expansion if we don't correctly calculate the first? Perhaps there is a reason to set  $c = d$ , but an explanation is not provided in [1].

We integrated equation 1 numerically with the same numerical method as [1] and compared it against the theoretical predictions. A verification of the code is shown in figure 2. In figures 3,4, we have compared asymptotic results for strong noise against the numerics. In figure 3 we see that when including both terms, either formula gives good predictions against the data. In figure 4 we see that our leading order term performs fractionally better than the one in [1], but there is not much difference either way.

## Conclusion

In this project we have examined the Fisher-Eigen process as a model for selection in a continuous phenotype space. We acknowledge that the process takes place in a high-dimensional space, and this changes how the process operates in a non-trivial way. However, the process in a high dimensional space is not completely understood. Therefore we restricted ourselves to examining the rate at which this process can surmount a barrier in a one-dimensional space.

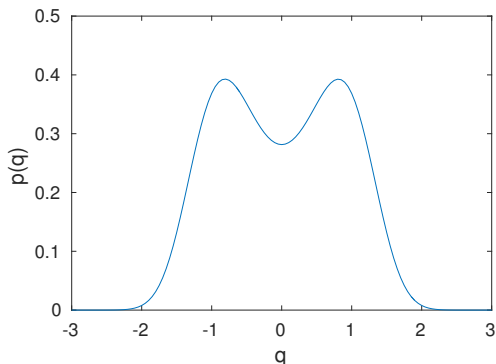


Figure 2: Integration of equation 1 until equilibrium with  $D = 0.04$ . We recover the same distribution found in figure 5 of [1].

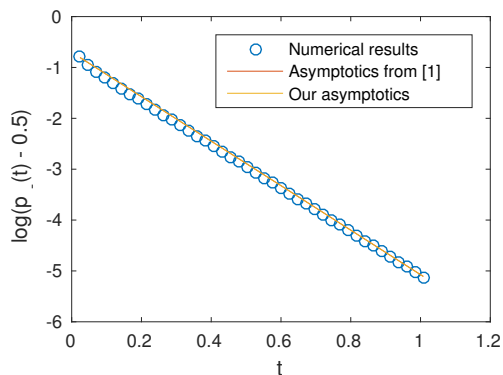


Figure 3: Comparison of strong noise asymptotics to numerical integration for  $D = 5$ . Here we have included the first two terms in the asymptotic formula for  $k$ , both from here and from [1]. When including both terms, both derivations give accurate results.

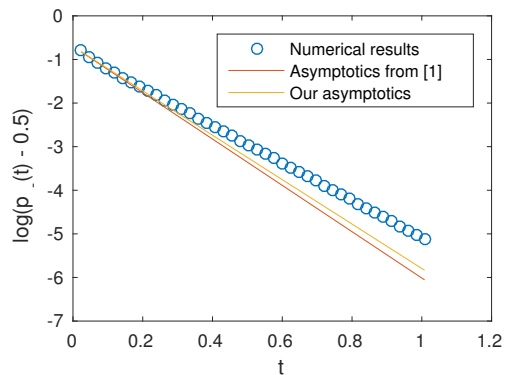


Figure 4: Comparison of strong noise asymptotics to numerical integration for  $D = 5$ . Only the first term in the asymptotics has been used. We see that our formula gives a fractionally better first estimate than [1].

We derived a formula that the Kramers rate was  $k = \frac{1}{2}(\lambda_1 - \lambda_0)$ , where the  $\lambda_i$  are eigenvalues of a Schrödinger like equation. The eigenvalues can only be found numerically, but we derived an approximate formula in the limit of strong noise. Our expression differed from [1], and we have reason to believe our expression was correct, although both are just approximations. Finally, we verified the analytic results with some simple numerical simulations.

## References

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