

Problem Set 8

1 Evolution in Finite Populations (15 points)

In a population of size N , a mutant population of size i with relative growth rate $r = 1 + s$ has a probability x_i of taking over the population,

$$x_i = \frac{1 - 1/r^i}{1 - 1/r^N}$$

- a. [4 points] In a population of a hundred individuals, what is the (approximate) probability that a mutant with a growth advantage of 0.1% will take over given that it starts as,
 1. A single member of the population
 2. A subpopulation of size twenty
- b. [3 points] Consider a population of size $N = 100$ with the three individual mutants with relative growth rate $r_A = 2$, $r_B = 1.01$, and $r_C = 0.99$. What is the probability that each of the three mutants will take over the population?
- c. Distribution of beneficial mutants that take over a population.
 1. [4 points] Consider a population of size N subject to beneficial mutations that are distributed uniformly between $s = 0$ (neutral) and $s_0 = 0.01$ (representing a 1% growth advantage).
 - i. Draw the distribution of beneficial mutations that take over in a population of size ten. (Assume that the mutation rate is very low.)
 - ii. Draw the distribution of beneficial mutations that take over in a population of size one thousand. In particular, what does the region near $s = 0$ look like? (Assume that the mutation rate is very low.)
 2. [4 points] Consider a population of size N subject to beneficial mutations that are distributed exponentially with a characteristic magnitude of $s_0 = 0.01$.
 - i. Draw the distribution of beneficial mutations that take over in a population of size ten. (Assume that the mutation rate is very low.)
 - ii. Draw the distribution of beneficial mutations that take over in a population of size one thousand. In particular, what does the region near $s = 0$ look like? (Assume that the mutation rate is very low.)

2 COMPUTATION Simulation of clonal interference (20 points)

The simulations in this problem take a long time to run. Please plan accordingly.

Consider a population of size N subject to beneficial mutations that are distributed exponentially with a characteristic magnitude of $s_0 = 0.01$.

- [8 points] Simulate Moran process with a single mutant starting in the population. In each run, the selective advantage of this mutant should be sampled from an exponential distribution. For $N = 10$ and $N = 1000$, draw a histogram of the selective advantage of mutants that eventually take over the population, and compare it with your analytical estimation in the previous problem.
- [8 points] When there are multiple mutants competing at the same time, we encounter clonal interference. Now include clonal interference by allowing a probability μ (the mutation rate) of generating a new beneficial mutation. For simplicity, we do not allow mutants to acquire secondary beneficial mutations. Each time when a non-mutant is chosen to divide, there is a probability μ that the daughter cell will gain a beneficial mutation sampled from the exponential distribution. For $N = 10$ and $N = 1000$, draw histograms of the selective advantage of mutants that eventually take over the population with $\mu = 10^{-5}$, 10^{-4} , 10^{-3} , and 10^{-2} .
- [4 points] How is the distribution of fixed beneficial mutations changed in the presence of clonal interference? At what regime is the distribution in part a still a good approximation?

3 The Luria-Delbrück experiment (15 points)

Up to now we have focused on evolutionary dynamics, that is, how deterministic process (selection) and stochastic process (genetic drift, clonal interference) act on genetic variation of a population and influence the outcome of evolution. In this problem, we will look at another important aspect of evolution: mutation. Mutations generate genetic variation in a population and provide the raw materials for selection.

In 1943, Max Delbrück and Salvador E. Luria published a landmark paper¹ for which they were awarded the Nobel Prize. In this paper, they combined experiment and quantitative analysis to address an important question: do genetic mutations arise in the absence of selection, or in response to selection? In their experiment, they created a large collection of replicate cultures of a strain of bacteria *E. coli* which was not resistant to a phage strain they used. Each bacterial culture was allowed to grow for some generations and then challenged by exposure to the phage. The phage would kill all non-resistant bacteria within a generation time of bacteria. In the end, the number of resistant bacteria that survived the phage challenge was counted for each culture, so they arrived at an empirical distribution of the number of resistant bacteria from many replicate cultures.

The goal of their experiment was to find out which of the two competing hypothesis is true: 1) “Mutation”: bacterial cells in the culture spontaneously mutated from “sensitive” to “resistant” with a small probability during their growth, even in the absence of phage. 2) “Acquired hereditary

¹S. E. Luria and M. Delbruck. Mutations of bacteria from virus sensitivity to virus resistance. *Genetics* 28: 491 (1943).

immunity”: after encounter of the phage, bacterial cells have a small probability to survive the phage challenge and the acquired resistance can be inherited by the offsprings. Luria and Delbruck analyzed the distribution of the number of resistant bacteria in their experiment and showed that the data support the “Mutation” hypothesis. Let’s see how this can be done.

- a. [6 points] **COMPUTATION** “Mutation” hypothesis. Imagine a set of C cultures (separate flasks) each containing N_0 bacteria cells initially. Assume that all cells in a culture divide at the same time, and that every time a cell divides there is a small probability $\alpha = 2 \cdot 10^{-9}$ that one of the daughter cells will mutate to become resistant to phage attack. Assume that the initial population has no resistant mutants, and that the progeny of resistant cells are all resistant (no reverse mutation). We also assume that both the mutant and the wild-type bacteria grow at the same rate (no cost for resistance). For $C = 500$ cultures, each with $N_0 = 200$ cells initially, find the number of cultures with m resistant mutant cells after $T = 21$ doublings (generations). Plot a histogram for m . Compute the sample mean and sample variance of the distribution of number of resistant bacteria².

Hint: What is the distribution of number of new mutants that appear at generation k , with population size $N_k = N_0 2^k$? You can draw from this distribution at each generation to decide how many mutants are introduced into the population. The brute force approach of simulating the mutation process by generating a random variable for each cell at each generation is not recommended here because it takes too much time for 21 generations. However, if you are determined to try that you might want to use a higher mutation rate $\alpha = 2 \cdot 10^{-7}$ and stop after $T = 15$ generations.

- b. [6 points] “Acquired hereditary immunity” hypothesis. Now we assume there is no spontaneous “mutation”, instead there is a small probability β that a bacterial cell would acquire resistance after exposure to phage. Starting with $N_0 = 200$ initially, the bacteria are exposed to phage after $T = 21$ doublings. What is the distribution of the number of resistant bacteria m in this case? Express the distribution in terms of the given parameters.
- c. [3 points] Based on the above analysis, how would you use the empirical distribution of number of resistance bacteria in the Luria-Delbruck experiment to distinguish the two hypothesis?

Feedback (+1 Extra Credit)

²The exact distribution, named Luria-Delbruck distribution, was analytically derived in the paper.

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