EVOLUTION AS OPTIMIZATION

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Introduction and Motivation

The purpose of this talk is to present a realistic problem from biology which requires very little background. We take our example from population genetics and will need nothing more than the first and second derivative tests for a complete analysis. Calculus will lead to a biological property and, in turn, interpretation of this biological situation will lead to the mathematical topic of stability.

Vocabulary and Background

A *locus* is a position in genetic material where a gene resides. An *allele* is a particular form of a gene. We consider the case of *diploid* organisms in which each locus contains two (not necessarily distinct) alleles. Most of the organisms with which we are familiar are diploid, including humans. We inherit one allele from each parent. Bacteria are *monoploid*, having only one allele at each locus, and several groups of plants are *polyploid*, having three or more alleles at each locus.

We will concentrate on a single locus and assume this locus can contain the alleles A and/or a, but no others. This is called the "one locus–two alleles model." This leads to three distinct *genotypes*: AA, Aa, and aa. Genotype Aa is said to be *heterozygous* and genotypes AA and aa are *homozygous*. We represent the frequency of the A allele as p (that is, $p \times 100$)% of the alleles at the given locus in the population are the A allele). Therefore, the frequency of the a allele is $1 - p$. We assume random mating (or the so called *Hardy-Weinberg equilibrium*) and therefore the frequencies of the three possible genotypes are

genotype	**frequency**	**fitness**
AA	p^2	w_1
Aa	$2p(1-p)$	w_2
aa	$(1-p)^2$	w_3

In the case that A determines a dominant trait and a a recessive trait, the genotypes AA and Aa are indistinguishable to the "naked eye" (they are said to yield the same *phenotype*) — they both determine the dominant trait. We do not make such a restrictive assumption. We assume that all three genotypes are distinguishable.

Expected Value

Definition. If an experiment has n different numerical outcomes, $x_1, x_2, \ldots, x_n$, each with probability $p_1, p_2, \ldots, p_n$, respectively, then the *expected value* of the experiment is

$$\sum_{i=1}^{n} p_i x_i = p_1 x_1 + p_2 x_2 + \cdots + p_n x_n.$$

Example. If a 6-sided die is rolled, then we have the following outcomes and probabilities:

x_i	y_i
1	1/6
2	1/6
3	1/6
4	1/6
5	1/6
6	1/6

The expected value of this experiment is

$$(1)(1/6) + (2)(1/6) + (3)(1/6) + (4)(1/6) + (5)(1/6) + (6)(1/6) = 3.5.$$

Note. With each genotype, we associate a *fitness*, as above. Fitness represents, in a sense, a genotype's reproductive contribution to future generations. In a population in which the frequency of allele A is p, define the *average fitness* of this population as

$$\begin{aligned}\overline{w} &= p^2 w_1 + 2p(1-p)w_2 + (1-p)^2 w_3 \\ &= (w_1 - 2w_2 + w_3)p^2 + (2w_2 - 2w_3)p + w_3\end{aligned}$$

where w_1, w_2, and w_3 are as given above. Notice that $\overline{w}$ is a second degree polynomial in p. Natural selection will act in such a way as to force $\overline{w}$ to increase with time ("survival of the fittest"). Therefore, we can determine what frequency that allele A will approach as time increases, since it will simply be the value of p that maximizes $\overline{w}$. The result, of course, will depend on w_1, w_2 and w_3.

Computations

Note. We want to maximize $\overline{w}$ for $p \in [0,1]$. Differentiating $\overline{w}$ with respect to p yields

$$\frac{d\overline{w}}{dp} = 2(w_1 - 2w_2 + w_3)p + (2w_2 - 2w_3).$$

If $w_1 - 2w_2 + w_3 = 0$, then $\frac{d\overline{w}}{dp}$ is constant and either

1. $\overline{w}$ has a maximum at $p = 1$ if $w_1 > w_2$ and $w_1 > w_3$, or

2. $\overline{w}$ has a maximum at $p = 0$ if $w_3 > w_1$ and $w_3 > w_2$, or

3. $\overline{w}$ is constant if $w_1 = w_2 = w_3$.

If $w_1 - 2w_2 + w_3 \neq 0$, then $\overline{w}$ has a critical point at

$$p = \frac{w_3 - w_2}{w_1 - 2w_2 + w_3} \equiv c.$$

If $c \notin (0,1)$, then the maximum of $\overline{w}$ on $p \in [0,1]$ will occur at either $p = 0$ or $p = 1$, that is when $\overline{w} = w_1$ or $\overline{w} = w_3$, whichever is larger. If $c \in (0,1)$ then the maximum of $\overline{w}$ on $p \in [0,1]$ will occur at either $p = 0$, $p = c$, or $p = 1$, whichever yields the largest $\overline{w}$. Also, with $c \in (0,1)$, $\overline{w}$ will have a minimum at one of these three points. In fact, under these conditions, $\overline{w}$ must have an extremum at $p = c$. Therefore, the concavity of the graph of $\overline{w}$ is of particular interest.

The second derivative of $\overline{w}$ with respect to p is

$$\frac{d^2\overline{w}}{dp^2} = 2(w_1 - 2w_2 + w_3).$$

So if $2w_2 < w_1 + w_3$, then the graph of $\overline{w}$ will be concave up and $\overline{w}$ will have a minimum at $p = c$ (see Figure 1). If $2w_2 > w_1 + w_3$ then the graph of $\overline{w}$ will be concave down and $\overline{w}$ will have a maximum at $p = c$ (see Figure 2). It is this second case which interests the biologist.

Discussion

Note. A single locus in a population may be *monomorphic*, in which case every member of the population has the same type of allele present at that locus, or a locus may be *polymorphic* in which case there is more than one type of allele present in the population at that locus. When molecular methods were introduced into genetics, it was discovered that there is a great deal of polymorphism in most natural populations. It is this diversity that gives the method of "DNA fingerprinting" its power to distinguish between the genetic material of individuals (and in the absence of a reliable database of allele frequencies for different ethnic populations that has led to controversy over the forensic applications of this method). So, we ask the question "What are the possible values of w_1, w_2, and w_3 such that natural selection will maintain polymorphism?"

To maintain polymorphism, $c \in (0,1)$ is necessary and the graph of $\overline{w}$ must be concave down, that is $2w_2 > w_1 + w_3$. Simple algebraic manipulations show that these two conditions imply that $w_2 > w_1$ and $w_2 > w_3$. If we consider what this means biologically, then it is exactly what is expected! This is the so-called *heterozygote advantage* model in which the heterozygote is more fit than either homozygote. In the case that either homozygote is more fit than the heterozygote, genetic diversity is lost and fixation for one of the alleles occurs. Therefore, the only way to preserve polymorphism at a single locus with natural selection is through heterozygote advantage. This is an important *biological* fact which we have discovered from the underlying *mathematics*!

Stability and Equilibria

Note. We have assumed an absence of outside forces in our model. For example, we have ignored random genetic drift (i.e. changes in allele frequencies which result from chance alone; these changes are due to "sampling error" in populations of finite size and is less important in large populations), migration and mutation. All three of these factors can act to perturb allele frequencies from an equilibrium. Additionally, immigration and mutation can introduce new or extinct alleles into a population. Continuing to restrict our model to two alleles, we can view all of these outside forces as perturbations in allele frequencies. This biological interpretation now leads to the mathematical idea of *stability*. In the case of heterozygote advantage, natural selection will push a population to a polymorphic equilibrium (see Figure 2). If the allele frequencies are slightly perturbed, then selection will force the population back to the equilibrium (we can view selection as a force pulling upward on points which are restricted to the $\overline{w}$ curve). Therefore, in this case, the equilibrium at $p = c$ is said to be *stable*. In fact, it is said to be *universally* or *globally* stable, since any initial value of $p \in (0, 1)$ will, with time, be "attracted" to this equilibrium. For this reason, this equilibrium is called an *attractor* or a *sink*. On the other hand, in Figure 2 there are also equilibria at both $p = 0$ and $p = 1$ (at which polymorphism is lost and fixation of the a allele or the A allele occurs, respectively). However, these represent *unstable* equilibria since a slight perturbation (represented by the introduction of the missing allele through mutation or immigration) will have the effect of sending the population (through the force of selection) away from the original equilibrium and towards the polymorphic equilibrium. The idea of stability is very important in mathematics, particularly in differential equations (linear and nonlinear) and dynamical systems. The labeling of equilibrium points as stable, unstable, or semistable gives a fundamental classification of these points and yields important physical information about the underlying dynamical problem. Our application gives insight into this mathematical concept through an intuitive understanding of the underlying biology!

An Example

Note. One of the best such examples for our model is the allele which in the homozygous condition codes for thalassemia, a type of lethal hereditary anemia related to sickle cell anemia. We represent this allele by a and let the alternative allele be represented by A. In the heterozygous state, an individual has a resistance to malaria. In some areas in which malaria is prevelant, the frequency of the thalassemia allele may be as high as 10 percent (see [1]). We now use this data and our model to analyze the fitness values associated with the three different genotypes (namely, the AA or normal genotype, Aa or the malaria resistant genotype, and the aa or thalassemia genotype). First, individuals which have genotype aa have lethal thalessemia, and so $w_3 = 0$. The choice of w_2 is arbitrary, so take $w_2 = 1.0$. The frequency of the a allele is observed to be 0.10, so there is an equilibrium at $c = p = 0.90$. Setting

$$c = \frac{w_3 - w_2}{w_1 - 2w_2 + w_3} = 0.90,$$

gives that $w_1 = 0.89$. Notice that for this population, $\overline{w} = 0.90$ and the average fitness in this population is higher than that in a population without the thalassemia allele. It is this small advantage that keeps the allele present (at the expense, one might observe, of automatically losing one percent of the population to the anemia). This illustrates the strength with which natural selection can act to encourage the presence of traits which may give a slight advantage to individual members of a population (this is, of course, a fundamental property of Darwinian evolution).

References

1. W. Bodmer and L. Cavalli-Sforza, *The Genetics of Human Populations*, W.H. Freeman and Co., NY (1971).

2. R. Gardner, "An Application of Differential Calculus to Population Genetics," *Mathematics and Computer Education* **29**(3) (1995), 305–311.

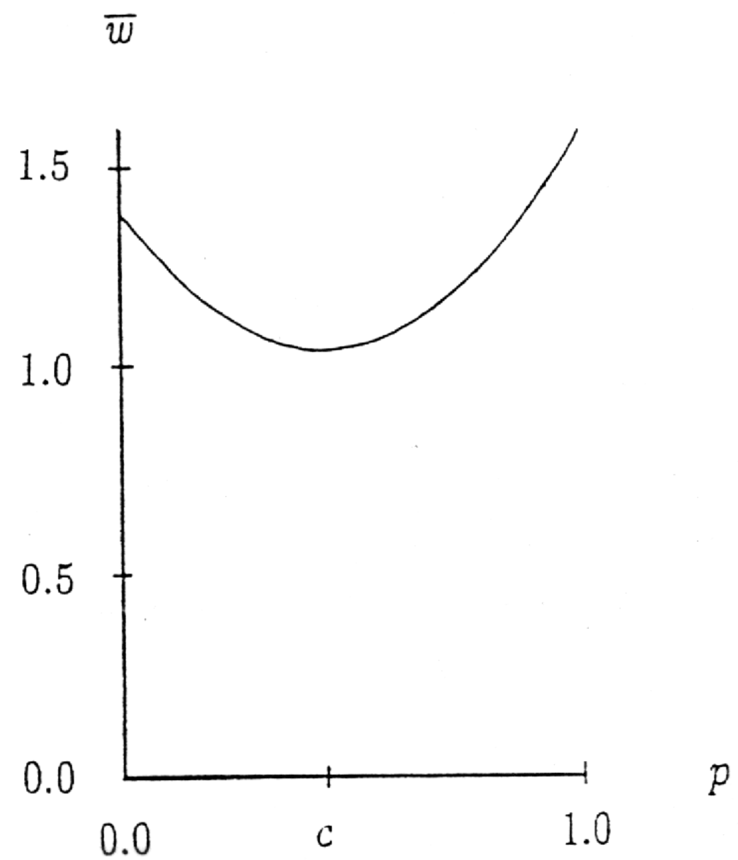

Figure 1. A graph of average fitness $\overline{w}$ for a population in which p represents the frequency of allele A. The graph of $\overline{w}$ is concave up and natural selection will eliminate polymorphism. In this graph, $w_1 = 1.6$, $w_2 = 0.6$ and $w_3 = 1.4$.

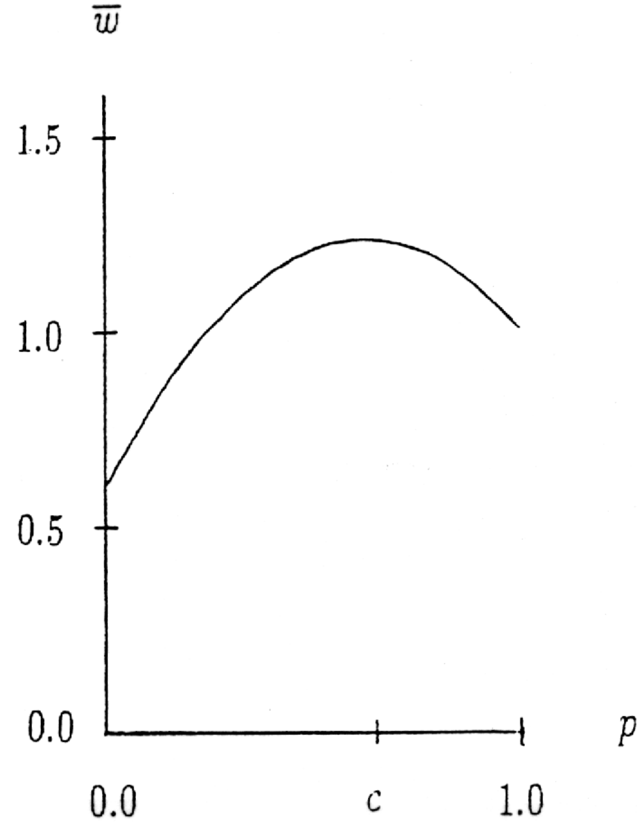

Figure 2. A graph of average fitness $\overline{w}$ for a population in which selection will maintain polymorphism. Again, p is the frequency of allele A. The critical point at $p = c$ gives a stable equilibrium for the model and the points $p = 0$ and $p = 1$ are unstable equilibria. In this graph, $w_1 = 1.0$, $w_2 = 1.6$ and $w_3 = 0.6$.