Abstract

In the reproductive process new genetic types arise due to crossing over and recombination at the meiotic stage. A simplified biological model will be developed which incorporates this effect and the effect of selection. Although a chromosome may contain thousands of genes we will consider a simplified model consisting of two genetic loci, each containing two alleles of some gene.

The model will be then turned into a difference equation or mapping model

\[ x^* = G(x, r) \]
where $x$ represents the distribution of genotypes in a certain population, $x^*$ is this distribution one generation later and $r$ is the recombination parameter. For a certain choice of fitness and recombination parameters the mapping exhibits several fixed points. As $r$ is varied one of the fixed points of the mapping loses its stability due to a conjugate pair of eigenvalues of the linearized mapping leaving the unit disk. It is shown that the required non-resonance conditions and “nonlinear damping” condition are satisfied and thus the fixed point undergoes a Neimark-Sacker bifurcation to a cycling or oscillatory state.

Once a cycling orbit is established one can conclude that genetic variation (over time) of the population can be maintained. This work reformulates and proves earlier observations of Alan Hastings in a way that makes the treatment of chromosomes with more genetic loci more straightforward.

**Keywords:** Difference equation, bifurcation, normal form, genetics, recombination, cycling  
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1 Forward

It is the authors’ intention to make this presentation accessible to an audience versed in difference equations while possibly not in the terminology of population genetics. Accordingly all such terminology will be kept to a minimum with only brief explanatory remarks. The main focus will be on the derived equations. We are however dealing with a mathematical model and therefore the simplifying assumptions leading to the model must be exposed. In addition, all references will be made to human reproduction for reasons of familiarity only. This is in spite of the fact that we assume infinite population and random mating in order to arrive at a deterministic model.

2 Introduction

We take as the beginning of reproduction the process known as gametogenesis, the formation of gametes or reproductive cells such as ova or sperm. This takes place during an involved process called meiosis where chromosome pairs (one member from “Mom” the other from “Dad”) replicate themselves. Ignoring other chromosomes (there are 23 distinct types of pairs in a human) and ignoring, only for the moment, crossover, we then have 4 gametes, 2 carrying only genetic information from “Mom”, the other 2 only from ”Dad”.

With this scenario (no crossover) when Mom and Dad become grandparents only one of them will contribute genetic information to their grandchild. Before discussing crossover, which
requires some assumptions as to what exactly a chromosome is, let us carry this scenario to completion of one generational cycle. Upon mating, a gamete (sperm, say) unites with an egg to form a zygote, the earliest form of an embryo. The fitness of this zygote is a number which measures its (a) ability to survive to reproductive age, (b) fertility and (c) ability to successfully mate. The fitness will be a function of the gametes which formed the zygote.

A chromosome is a linear helical chain consisting of thousands of loci, each locus being itself a shorter helical chain of DNA, called a gene which acts as a genetic marker or determining factor for some trait (Rothwell, 1993). Genes come in different forms called alleles and for simplicity we assume just 2 loci. At locus A there are 2 alleles, “A” and “a” and at locus B, “B” and “b”. We shall refer to “A” as the dominant allele and “a”, recessive. Thus a typical chromosome pair before meiosis will be designated by $A^B\ b\ a^A\ B$ giving rise (no crossover) to gametes $A^Bb$ and $ab$. Crossover occurs when this chromosome pair breaks between the A and B loci and recombines to form gametes $AB$ and $ab$.

Letting $x_1, x_2, x_3, x_4$ denote the frequencies (and the names) of the genotypes $AB$, $Ab$, $aB$, $ab$, one readily obtains the recombination mapping (Roughgarden, 1979)

$$ x \rightarrow x^* = R(x) \quad x = (x_1, x_2, x_3, x_4)^T $$

where

$$
\begin{align*}
x_1^* &= x_1 - r(x_1x_4 - x_2x_3) \\
x_2^* &= x_2 + r(x_1x_4 - x_2x_3) \\
x_3^* &= x_3 + r(x_1x_4 - x_2x_3) \\
x_4^* &= x_4 - r(x_1x_4 - x_2x_3)
\end{align*}
$$

and $r$, the recombination coefficient, satisfies $0 \leq r \leq 1/2$. The coefficient $r$ is a measure of the degree to which crossover takes place: $r = 0$ represents tight linkage whereas $r = 1/2$ represents loose linkage between the loci. The quantity in parentheses is called disequilibrium and is a measure of the statistical dependency between the loci. In statistical terms it is the covariance between the loci (Roughgarden, 1979, p.113).

The next mapping to discuss is the selection mapping. After random mating the gametes form zygotes and each zygote is assigned a fitness coefficient $F_{ij} = \text{fitness of } x_i \over x_j$, e.g., $F_{13} = \text{fitness of } A^Bb$. The selection mapping is given by

$$ x \rightarrow x^* = S(x) \quad x = (x_1, x_2, x_3, x_4)^T $$

where

$$
\begin{align*}
x_i^* &= x_i \left( \frac{F_i}{F} \right)
\end{align*}
$$

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and
\[ F_i = \sum_{j=1}^{4} F_{ij} x_j \quad \text{and} \quad \mathcal{F} = \sum_{i,j=1}^{4} F_{ij} x_i x_j = \sum_{i=1}^{4} F_i x_i \]

The quantity \( F_i \) is the \textit{marginal mean fitness} of \( x_i \) and \( \mathcal{F} \) is the \textit{mean fitness} of the population. Dividing by the quantity \( \mathcal{F} \) in (2.2) preserves the relation \( \sum x_i = 1 \). Composing these maps we obtain the \textit{generational map}

\[ x^* = G(x) \quad G = S \circ R. \quad (2.3) \]

It is this mapping that we will study.

A general treatment of the equations of gametic frequency change with linkage and selection in the 2-locus model was given by (Kimura, 1956) in the continuous time case and by (Lewontin and Kojima, 1960) in the discrete time case. In the discrete case they obtain the mapping

\[ x^*_i = \frac{1}{\mathcal{F}} \left\{ x_i F_i + \epsilon_i r (F_{14} x_1 x_4 - F_{23} x_2 x_3) \right\} \quad (2.4) \]

where \( \epsilon_2 = \epsilon_3 = -\epsilon_1 = -\epsilon_4 = 1 \) (\( F_{14} = F_{23} \) in their derivation). Upon close examination of their derivation one can see that (2.4) is just \( x^* = R \circ S(x) \). The difference between this map and \( G \) is minor since if \( x \) is a fixed point for \( R \circ S \) then \( S(x) \) is a fixed point for \( S \circ R \) and similarly for a cycling point–the dynamics are equivalent.

A fixed point of the mapping \( G \) is a distribution of the genotypes that remains the same from one generation to the next. Our interest will be in studying a fixed point which is stable for certain values of \( r \) but loses its stability due to a complex conjugate pair of eigenvalues of the linearized mapping leaving the unit circle as \( r \) increases (or decreases) through some critical value.

Along the lines of an earlier result of (Hopf, 1942) for ordinary differential equations, (Neimark, 1959) conjectured that an invariant curve would bifurcate from the fixed point provided a certain non-linear term has the right sign. Later (Sacker, 1964) independently stated and proved the bifurcation theorem for maps for the first time and discovered that certain low order “resonances” had to be avoided, i.e., the eigenvalues must avoid 3rd and 4th roots of unity as they leave the unit circle. The result has come to be known as the Neimark-Sacker bifurcation theorem (Kuznetsov, 1998). The additional requirement referred to as “nonlinear damping” is needed but its verification depends on first putting the mapping in a certain normal form. See Section 4 for a statement of the theorem using the notation of Section 3. See (Iooss and Joseph, 1990, p.254) for further discussion and references. The result was later rediscovered by (Ruelle and Takens, 1971). Also see (Marsden and McCracken, 1976) and (Hassard et al., 1981).
In the article (Hastings, 1981c) a fixed point for (2.4) with complex eigenvalues is found and “cycling” or recurrence is observed using numerical methods. This was done using a linear programming technique developed in (Hastings, 1981a). The nonlinear damping condition is not verified but rather inferred from the fact that cycling does indeed occur. Although in (Akin, 1982) and (Akin, 1987) the continuous time model is treated and the nonlinear damping is computed using a formula of (Marsden and McCracken, 1976), the discrete time model seems to be the most straightforward to analyze both numerically and analytically.

For a discussion of bifurcations (not including cycling) in the case in which the coupling (cis) and repulsion (trans) double heterozygotes have different fitness, i.e., $F_{14} \neq F_{23}$, see (Nordborg et al., 1995). Also see (Hoppensteadt, 1976) for a “slow selection” analysis using multitime techniques of (Hoppensteadt and Miranker, 1977). For a thorough discussion giving necessary conditions ensuring the disequilibrium $D = x_1x_4 - x_2x_3$ vanishes at an equilibrium see (Bodmer and Felsenstein, 1967). See also (Hastings, 1981b).

3 Discussion of Mapping

It is clear from the previous discussion that the map $G$ preserves the unit simplicial face in $R^4$:

$$\sum_{i=1}^{4} x_i = 1, \quad x_i \geq 0.$$ 

One of the four equations in (2.3) is therefore redundant and can be ignored. We take the first three equations and make the obvious substitution $x_4 = 1 - x_1 - x_2 - x_3$ in the remaining equations. We then obtain a mapping $T : \Delta \rightarrow \Delta$ where $\Delta$ is the unit simplex in $R^3$

$$\Delta : \sum_{i=1}^{3} x_i \leq 1, \quad x_i \geq 0.$$ 

We now make the following choice of fitness coefficients and recombination coefficient:

$$F_{11} = 0.83301, \quad F_{12} = 0.6585664, \quad F_{13} = 0.5057075, \quad F_{14} = 1.000,$$

$$F_{22} = 1.33068, \quad F_{23} = 1.000, \quad F_{24} = 0.22458, \quad F_{33} = 0.80724, \quad F_{34} = 0.46357, \quad F_{44} = 1.41881,$$

$$r_0 = 0.180223678355.$$  

(3.1)

For these choices, closely related to those studied by (Hastings, 1981c), we find (using MATLAB) one fixed point (out of the 13 found) which is of particular interest:

$$x_{fix} : \quad x_1 = 0.797844, \quad x_2 = 0.0883542, \quad x_3 = 0.0280991 \quad (3.2)$$
For the values (3.1) the linearized mapping at the fixed point (3.2) has eigenvalues:

\[ \lambda = 0.999578 + 0.0290354i, \quad \bar{\lambda} \]
\[ \sigma = 0.695037 \]

The eigenvalue \( \lambda \) lies on the unit circle and since \( \Im \lambda \neq 0 \), the implicit function theorem guarantees the fixed point will vary smoothly as \( r \) varies on a small neighborhood of \( r_0 \). Thus if we let \( r = r_0 - \mu \) and denote the smooth family of fixed points by \( x_{fix}(\mu) \) we have \( x_{fix}(0) \) given by (3.2). Let \( v \) and \( w \) be eigenvectors (columns) corresponding to \( \lambda(\mu) \) and \( \sigma(\mu) \) respectively and define

\[ M(\mu) = [\Re v, \Im v, w] \]

Then the change of variables

\[ x = x_{fix}(\mu) + M(\mu)y, \quad r = r_0 - \mu \]

reduces the mapping to

\[ y^* = \begin{bmatrix} \Re \lambda(\mu) & \Im \lambda(\mu) & 0 \\ -\Im \lambda(\mu) & \Re \lambda(\mu) & 0 \\ 0 & 0 & \sigma(\mu) \end{bmatrix} y + f(y, \mu). \]  

Using the procedure introduced in (Sacker, 1964) we define \( z = y_1 + iy_2 \) and \( W = y_3 \). Then the mapping takes the form

\[ z^* = \lambda(\mu)z + P(z, \bar{z}, W, \mu) \]
\[ W^* = \sigma W + Q(z, \bar{z}, W, \mu). \]

where \( P \) and \( Q \) are rational functions in \( z, \bar{z} \) and \( W \) whose power series begin with quadratic terms while \( P \) and \( Q(0, 0, 0, \mu) = 0 \) identically for \( \mu \) in some small neighborhood of zero. Since all the conditions for bifurcation are verified at \( \mu = 0 \) we shall suppress the \( \mu \) dependence until it is actually needed. Thus we consider

\[ z^* = \lambda z + P(z, \bar{z}, W) \]
\[ W^* = \sigma W + Q(z, \bar{z}, W) \]

and proceed to put this into the desired canonical where the bifurcation conditions can be verified.

The first step is to “remove”, from the first equation of (3.7), all the quadratic terms of the form \( z^k \bar{z}^l \), \( k + l = 2 \) by means of the transformation

\[ z = \zeta + a\zeta^2 + b\zeta\bar{\zeta} + c\bar{\zeta}^2. \]

in a sufficiently small neighborhood of the origin. If \( \lambda^3 \neq 1 \), \( a, b \) and \( c \) can be uniquely chosen so that in the new mapping

\[ \zeta^* = \lambda \zeta + \ldots \]
\[ W^* = \sigma W + \ldots \]

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the first equation is devoid of these specific quadratic terms.

The next step is to “remove” the same type quadratic terms from the second equation of (3.8) by means of the transformation

\[ W = Y + \alpha \zeta^2 + \beta \zeta \bar{\zeta} + \gamma \bar{\zeta}^2. \]

The fact that \(|\sigma| < 1\) guarantees that \(\alpha, \beta\) and \(\gamma\) can be uniquely chosen so that in the new mapping

\[ \zeta^* = \lambda \zeta + \ldots \]
\[ Y^* = \sigma Y + \ldots \] (3.9)

the second equation is devoid of these specific quadratic terms. The others can stay.

In the proof of the bifurcation theorem it is assumed that \(\lambda^\nu \neq 1\) for \(\nu = 1, 2, 3, 4\). The exclusion of the fourth roots of unity (together with \(|\sigma| < 1\)) is needed to remove terms of the form

\[ \zeta^k \bar{\zeta}^l, \quad k + l = 3, k \neq 2; \quad \zeta Y \text{ and } \bar{\zeta} Y \] (3.10)

from the first equation of (3.9) to obtain the canonical form

\[ \zeta^* = \lambda \zeta + b \zeta^2 \bar{\zeta} + \mathcal{F}_4(\zeta, \bar{\zeta}, Y) \]
\[ Y^* = \sigma Y + \mathcal{F}_3(\zeta, \bar{\zeta}, Y) \] (3.11)

where the Taylor expansion of \(\mathcal{F}_j\) has no monomials of “weight” \(< j\). The weight \(\tau\) of the monomial \(\zeta^k \bar{\zeta}^l Y\) is defined to be \(\tau = 2s + t + u\).

Upon close inspection of the transformations needed to eliminate the terms (3.10), e.g,

\[ \zeta = w + \alpha w^k \bar{w}^l, \quad \zeta = w + \gamma wY \text{ and } \zeta = w + \gamma \bar{w} Y, \]

it is easy to see that the coefficient \(b\) in (3.11) is the same as the coefficient of the same monomial in (3.9) – see (Kuznetsov, 1998), p. 133 for details. Thus in the application (as opposed to the proof) of the bifurcation theorem one may stop at (3.9) and read off the coefficient \(b\) in (3.11).

Thus we will work with (3.11) which we rewrite

\[ \zeta^* = \lambda \zeta + b \zeta^2 \bar{\zeta} + \mathcal{F}_4(\zeta, \bar{\zeta}, Y) \] (3.12)
\[ = \lambda (1 + \beta |\zeta|^2) \zeta + \mathcal{F}_4 \]
\[ = e^\alpha e^{\beta |\zeta|^2} \zeta + \tilde{\mathcal{F}}_4 \]
\[ = e^{\alpha (\mu) + \beta (\mu)|\zeta|^2} \zeta + \tilde{\mathcal{F}}_4(\zeta, \bar{\zeta}, Y, \mu) \]
\[ Y^* = \sigma Y + \mathcal{F}_3(\zeta, \bar{\zeta}, Y) \]
where in the last two equalities we have returned the \( \mu \) dependence. Note, however, that the \( \mu \) dependence in, e.g., \( \hat{F}_4 \) comes about only through coefficients of monomials of weight 4 and higher.

4 Statement of Bifurcation Theorem

In this section we state the theorem directly from (Sacker, 1964) as it applies to the above equations

\textbf{Theorem 1} In (3.6), viz.,

\[
\begin{align*}
    z^* &= \lambda(\mu)z + P(z, \bar{z}, W, \mu) \\
    W^* &= \sigma(\mu)W + Q(z, \bar{z}, W, \mu).
\end{align*}
\]

where \( P(0, 0, 0, \mu) = Q(0, 0, 0, \mu) = 0 \) identically for \( \mu \) in some small neighborhood of zero. Assume further that

1. \(|\lambda(0)| = 1, \quad \lambda^3(0) \neq 1, \text{and } \lambda^4(0) \neq 1 \quad (\text{non resonance}) \)
2. \( \Re \lambda'(0) > 0 \quad (\text{loss of stability}) \)
3. \(|\sigma(0)| < 0 \quad (\text{stability in } "\text{normal}" \text{ direction}) \) and
4. \( \text{In the normal form (3.12), } \Re \beta(0) < 0 \quad (\text{nonlinear damping}) \)

Then in a sufficiently small \( \mu \) neighborhood, \( 0 < \mu < \mu_* \), (4.1) has an asymptotically stable invariant curve parametrized by \( \theta \), \( 0 \leq \theta \leq 2\pi \)

\[
\begin{align*}
    z &= a_0 \sqrt{\mu} \exp(i\theta) + \mu f(\theta, \mu) \\
    W &= \mu g(\theta, \mu)
\end{align*}
\]

where \( a_0 = \sqrt{-\Re \alpha'(0) / \Re \beta(0)} \).

In (3.12) the pertinent constants are:

\[
\begin{align*}
    \alpha(\mu) &= \ln \lambda(\mu) = \alpha(0) + \alpha'(0)\mu + \ldots \\
    &= -0.0290395i + (10.545392 + 10.718922i)\mu + \ldots \\
    \beta(0) &= b(0)/\lambda(0) = -2.936877 - 6.270699i
\end{align*}
\]
The calculation of \( \alpha'(0) \) is done numerically using MATLAB while the quantity \( b(0) \) is computed using MAPLE by actually transforming the mapping into canonical form subject to the comments preceding (3.12).

Thus the existence of an invariant curve for the generational map (2.3) is established. The curve is most easily seen in the coordinates \( \zeta \) and \( Y \) in which the mapping (3.12), in the first approximation, is

\[
\begin{align*}
\zeta^* &= \zeta \exp[\Re \alpha'(0)\mu + \Re \beta(0)|\zeta|^2] \exp i[\Im \alpha(0) + \Im \beta(0)|\zeta|^2] \\
Y^* &= \sigma Y.
\end{align*}
\] (4.4)

where it is clear that the circle \( |\zeta| = a_0 \sqrt{\mu}, \ Y = 0 \) is invariant. Further it can be seen from (4.4) that on this circle points are moved by the mapping, in the first approximation, by \( \Im \alpha(0) = -0.0290395 \) radians and therefore it takes 217 iterations of the map to return approximately to the initial point. This agrees with numerical simulations to within one iteration.(Bürger, 2000, p.53)

References


