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Inheritance Pattern of Huntington's Disease, a Multiplayer Game

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Evolutionary game theory (EGT) is one of several major developments of game theory. EGT covers ecology and population genetics, among other fields in biology. Most studies in EGT were on a two-player game but non-linearities in biology often occur that need to be considered. Huntington's disease (HD), named after the person who wrote the first detailed description of the disease in 1872, is a neurodegenerative disease that is inherited. This is a case in population genetics, which follows the inheritance pattern called the dominant lethal. In this study, we presented this disease as a multiplayer game among the alleles of the HD gene. We utilized Gokhale and Traulsen's model, wherein a payoff matrix for a four-player game was reduced into a payoff matrix for a two-player game. Depending on the fitness values of each genotype, we have determined that populations consisting of both Huntington and normal alleles may converge to either a purely Huntington, a purely normal, or a mixed composition where both types of genes coexist. If the normal genotype produces more surviving offspring than the other genotypes, then even if a small frequency of normal alleles is injected into a purely Huntington population, the population will be replaced by the normal genotype over time. Such a result was obtained using replicator dynamics and analysis of the stability of equilibrium points. Similar analyses on other genotypes were provided in relation to the inheritance pattern of HD.

Keywords: evolutionarily stable, evolutionary game theory, lethal alleles, population genetics, replicator dynamics, strategies

INTRODUCTION

Game theory is the study of mathematical models of conflict and cooperation between rational intelligent decision-makers. The players are assumed to be perfectly rational and have the same idea of being rational. Rational decision-making in a game means that a player tries to maximize his own profit or payoff based on his own beliefs about how other players are going to play (Aguirre 2008). It was only in the 1990s that the emphasis shifted toward evolutionary models because of the limitations of rationality-based models (Samuelson 2022) and a change in the underlying view of what games represent. Games were previously typically interpreted as a literal description of an idealized interaction with perfect rationality. Now, games are commonly interpreted as just an approximation of an actual interaction. Rubinstein (1991) mentioned that game theory is an analysis of the concepts used in social reasoning and not an attempt to predict behavior. Thus, perfect rationality seems less appropriate (Samuelson 2022).

Evolutionary game theory or EGT is one of several major developments of game theory. It covers ecology and population genetics, among other fields in biology. EGT studies the strategic interactions of individuals in

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a population (Hennes *et al*. 2020). Evolutionary game dynamics can be described in this process: the players of the game can be individuals in a population, and their strategies can be the characteristics or traits they are born with. The probabilities assigned to their strategies are influenced by natural selection, which includes five elements: the multiplication of chances, variation, struggle for existence, heredity, and survival of the fittest (Howerth 1917). Individuals who receive higher payoffs from their strategies are said to be more successful than those who receive lower payoffs (Sandholm 2010).

EGT also discusses the concept of an evolutionarily stable strategy or ESS. In 1973, Maynard Smith and Price introduced this central concept, which is a refinement of Nash equilibrium from classical game theory (Maynard Smith and Price 1973). In a two-person game, a Nash equilibrium is a pair of strategies that are best replies to each other, the best reply being a strategy that maximizes a player's payoff, given the strategy chosen by the other player. On the other hand, a strategy is evolutionarily stable if a population playing that strategy cannot be dominated by a small number of individuals playing another strategy. In 1989, Dawkins suggested that ESS is potentially one of the most important advances in the theory of evolution since Darwin. This is because the concept of ESS is applicable wherever a conflict of interest is involved. He added that through this concept, a collection of individual entities can resemble a single organized whole entity, a development that has the potential to revolutionize ecology (Dawkins 1989).

Both the studies of Taylor and Jonker (1978) and Zeeman (1980) discussed ESS and game dynamics prior to the introduction of the replicator dynamics to EGT. Replicator dynamics illustrate the evolution of behavior in conflicts occurring within a species in a large population (Bomze 1995). Bomze added that population genetics is an important field for the application of replicator dynamics as it describes how frequencies of types in a population change over time. It is a dynamic system that determines the tendency of individuals to play strategies that would give a payoff higher than the average population value (Hennes *et al*. 2020). Replicator dynamics provided a straightforward relationship between classical game theory's Nash equilibrium and EGT's ESS (Hofbauer and Sigmund 1998). Through the replicator dynamics, we know that an ESS is also a Nash equilibrium of the game. This result was also earlier provided by Weibull (1997). He stated that for a strategy to be evolutionarily stable, it must be a Nash equilibrium itself. However, the converse of the statement cannot always be the case. Not all Nash equilibria are evolutionarily stable strategies.

EGT remained confined in the context of two-player analysis and the applications focused on cells (Bach *et al*. 2001; Basanta and Deutsch 2008). However, interactions in biology can be highly non-linear (Shirakihara and Tanaka 1978). Rowe (1998) presented an example of these non-linear interactions through a game theory model for a general diploid system where the strategies are the different genotypes. He considered systems with two alleles and three genotypes and systems with three alleles and six genotypes. This study considers a diploid population with two alleles and three genotypes. In evolutionary games, when strategies are thought of as alleles, analysis is usually restricted to haploid populations (cells with only one set of chromosomes). However, according to Han (2012), it has recently become possible to derive results for equilibrium points, even in the context of diploid populations (cells with two sets of chromosomes). Using replicator dynamics, the equilibrium points of a dynamical system represent the composition of allele frequencies where each allele has the same average fitness. They also help predict a coexistence of these strategies, which is important in the maintenance of polymorphism. In addition, Han (2012) explored the probability of having all strategies present in a system, given a maximal possible number of equilibrium points. This provides an approximation for the maximal level of biodiversity in a biological system.

In population genetics, several comparisons between game theory and some standard models of population genetics were explored (Sigmund 1987a, b). Rowe (1987) derived a model for the average fitness to be the sum of each average payoff multiplied by a corresponding proportion of the total population. Gokhale and Traulsen utilized this sum when they computed the average payoffs of strategies of a multiplayer game, which results in a non-linear interaction (Gokhale and Traulsen 2014). In their paper, they provided a model for a multiple-player game that starts from a symmetric four-player two-strategy game. This kind of game can be reduced into a symmetric two-player two-strategy game in the process of solving for equilibrium points. This model will be applied in this study.

In Gokhale and Traulsen's model, the inheritance pattern of a disease called Huntington's disease (HD) will be treated as a multiplayer game in the context of EGT. Named after the person who wrote the first detailed description of the disease in 1872, HD is a neurodegenerative disease that is inherited. Although it can occur in all racial groups, it is most common among people of northern European origin. On average, the age of onset of its symptoms is around 40 years. Loss of balance and involuntary, irregular, and unpredictable muscle movements, also called chorea, aside from noticeable cognitive or personality changes, are usually the symptoms that appear early. Other symptoms that characterize this disease are progressive motor, cognitive, and psychiatric symptoms. It is an

uncommon disease, but it can be devastating for those who are affected. Following onset, the disease's duration is roughly 10–15 years, although some have been known to survive for 30 years (Stipe *et al*. 1979). HD is not fatal, although secondary complications such as heart failure or pneumonia usually led to the death of someone with the disease. There are no treatments for the disease as of current, but disease-modifying treatments are being tested on animal models (Imarisio *et al*. 2008). Thus, the only treatment available is for managing the symptoms.

A positive predictive or diagnostic result of HD leaves a huge impact on the tested patient. The family members of the said patient may also be a carrier of HD (Novak and Tabrizi 2010). It is believed that most families which have an affected member have more than one affected member, and several more are at risk of manifesting the disease in the future. An affected parent's offspring has a 50% chance of inheriting this abnormality. HD's risk does not skip and continues uninterrupted through generations, and male and female offspring are affected equally (Novak and Tabrizi 2010). HD is a single-gene disease with autosomal dominant inheritance. This means that the gene is located on a chromosome other than the sex chromosome. Hence, it is not sex-linked.

APPLICATION OF GOKHALE AND TRAULSEN'S MODEL

EGT in population genetics begins with a game that can be used as a model of some strategic interaction an organism might participate in. In general, EGT may approach population genetics in two different ways. This can either be with gene dynamics or as dynamics on the phenotypic level, which occurs based on a known genetic setup. This study deals with the latter. Here, the pure strategies will be interpreted as alleles, and the mixed strategy of the players assign the probabilities equal to the respective frequencies of the alleles in the population. The payoffs of these interactions are considered the organism's fitness so that a strategy that receives higher payoffs in the game can be generally expected to increase in frequency. The population is assumed to be infinite and well-mixed. This means that every individual has the same probability to interact with any other individual in the population. Furthermore, there should be no mutations in the population. The model they presented can handle non-linearities and Mendelian inheritance patterns. Mendelian inheritance refers to certain patterns of how traits are passed from parents to offspring. These general patterns were established by Gregor Mendel, who performed experiments with thousands of pea plants in the 19th century (Biology LibreTexts 2022). In his experiments, inherited traits that are unchanged in the breeding process are referred to as dominant traits, whereas recessive traits are those that disappear in the offspring.

We present a game based on Mendelian inheritance starting from the viewpoint of an allele. As part of the mating process, one individual, either paternal or maternal, is characterized by two alleles. Each of the parents contributes one of their alleles, resulting in two alleles transferred to the offspring. However, an allele must first consider the effects of the three other alleles. That is, pairing with one of the three other alleles one at a time may have varying effects on the outcome for each time. Gokhale and Traulsen (2014) provided an arrangement for a four-player game in which the payoffs for the alleles are given. This is shown in the following matrix, where A and a are alleles:

$$\begin{array}{c} \\ A \\ a \end{array} \begin{array}{c} \begin{array}{cccc} AAA & AAa & Aaa & aaa \end{array} \\ \begin{pmatrix} a_3 & a_2 & a_1 & a_0 \\ b_3 & b_2 & b_1 & b_0 \end{pmatrix} \end{array}$$

This arrangement of players takes into consideration mating between two diploid individuals. In EGT, this matrix refers to a multiplayer game with two strategies and four players. The focal player (Player 1) is the row player, and the combination of strategies possible for the remaining three players (Players 2, 3, and 4) is given by the columns. The ordering of the column players does not matter. Thus, playing with AAa will be the same as playing with aAA or AaA, for instance.

Each of Players 1, 2, 3, and 4 can either be an A-type or an a-type. This results to three possible kinds, or genotypes, of parents – namely, AA, Aa, and aa. If the fitness of AA, Aa, and aa are α, β, and γ, respectively, then the values of the payoffs in terms of these fitness were given in the paper as shown:

$$\begin{array}{c} \\ A \\ a \end{array} \begin{array}{c} \begin{array}{cccc} AAA & AAa & Aaa & aaa \end{array} \\ \begin{pmatrix} \alpha & \frac{2\alpha+\beta}{3} & \frac{\alpha+2\beta}{3} & \beta \\ \beta & \frac{2\alpha+\beta}{3} & \frac{\beta+2\gamma}{3} & \gamma \end{pmatrix} \end{array}$$

Given x as the frequency of the A allele, they arrived at the following average payoffs:

$$\pi_A = \alpha x + \beta(1-x) \quad (1)$$
$$\pi_a = \beta x + \gamma(1-x) \quad (2)$$

Hence, the payoff matrix for a two-player two-strategy game given below may be used:

$$\begin{matrix} & A & a \\ A & \alpha & \beta \\ a & \beta & \gamma \end{matrix} \quad (3)$$

Now, we apply this model to HD. HD follows a Mendelian inheritance pattern. The Huntington allele H is the dominant trait. Thus, offspring only need one copy of the allele H to express the disease. The absence of the disease will be denoted by h. If a heterozygous (Hh) man with HD and a normal woman (hh) have children, some of them (about half on average) will have the disease. If we map H to A and h to a, we have a particular application of a Mendelian inheritance pattern in the context of EGT. The detailed computation of the payoff matrix for a symmetric four-player two-strategy game for the inheritance pattern of the HD may be found in the study by Lim and Villamin (2022).

EVOLUTIONARY STABLE STRATEGIES (ESS)

Maynard Smith and Price (1973) introduced the central concept of an evolutionarily stable strategy (ESS). A strategy is evolutionarily stable if a population playing that strategy cannot be dominated by a small number of individuals playing a different strategy. In other words, an ESS is a Nash equilibrium, which is evolutionarily stable (Weibull 1997). Throughout the paper, discussions on ESS are in the context of two players – specifically, a symmetric two-player game following Gokhale and Traulsen's model.

The following proposition from Weibull (1997) will be used for the rest of the paper to compute for the ESS.

Proposition 1. A mixed strategy $x \in \Delta$ is said to be an ESS if and only if the conditions

$$\mathrm{u}(y,x) \leq \mathrm{u}(x,x) \quad \forall \mathrm{y} \in \Delta,$$

$$\mathrm{u}(y,x) = \mathrm{u}(x,x) \Rightarrow \mathrm{u}(y,y) < \mathrm{u}(x,y) \quad \forall \mathrm{y} \neq \mathrm{x}$$

are met.

Suppose we have two players, and Player 2 uses the mixed strategy x. If x is an ESS, then Player 1's payoff when using any mixed strategy y cannot be higher than his payoff when using x. This is the first condition from Proposition 1. If Player 1, when using any mixed strategy $y \neq x$, can earn a payoff equal to his payoff when using x, then Player 1's payoff when using that strategy y must be lower than his payoff when using x, provided Player 2 also uses y.

In this paper, the notion of replicator dynamics will be utilized to determine the possible stable strategy of the game, if any. The replicator equation was introduced by Taylor and Jonker (1978) in their study, "Evolutionarily Stable Strategies and Game Dynamics." It is the first game dynamics studied in connection with EGT. The concept of replicator dynamics is used to express the evolutionary dynamics of an entity called replicator, which has means of making more or less accurate copies of itself. In this study, our replicator is a gene. In EGT, replicators are strategies, which compete for dominance according to the payoff they yield in interaction. The payoffs are interpreted as the replicator's fitness.

There are a few assumptions involved in the framework, which led to the replicator equation. The population is assumed to be infinite and well-mixed, *i.e.* every individual has the same probability to interact with any other individual in the population. Furthermore, there should be no mutations in the population. Taking these into account, we consider the alleles H and h of the HD to be the replicators with frequencies x and $1 - x$, respectively. Together with their fitness π_H and π_h, we have the replicator equation (Gokhale and Traulsen 2014):

$$\dot{x} = x(1 - x)(\pi_H - \pi_h) \quad (4)$$

Here, $\dot{x}$ represents the change in x with respect to time. Note that the resulting expansion on the right-hand side is non-linear.

The critical points of the replicator equation are obtained by finding the roots of $\dot{x}$. This gives us $x = 0$, $x = 1$, and solutions to the equation $\pi_H = \pi_h$. Thus, we have these three states: [a] the population consists of only H alleles, [b] the population consists of only h alleles, or [c] alleles H and h have equal fitness. We now solve for the last state.

From Equations 1 and 2 with the payoffs given in Equation 3, we have:

$$x = \frac{-\beta + \gamma}{\alpha - 2\beta + \gamma}.$$

Thus, our candidates for ESS are the pure strategies H and h, which respectively correspond to $\boldsymbol{e}^1 = (1,0)$, $\boldsymbol{e}^2 = (0,1)$, and the mixed strategy $\overline{x} = \left(\frac{-\beta+\gamma}{\alpha-2\beta+\gamma}, \frac{\alpha-\beta}{\alpha-2\beta+\gamma}\right)$. The following theorem gives some parameters for these points to be evolutionary stable.

Theorem 1. Let $G = (H, h)$ be a symmetric two-player game with the payoff matrix given by Matrix 3.

1. If $\alpha \leq \beta$ whenever $\beta < \gamma$ or $\alpha < \beta$ whenever $\beta = \gamma$, then $\boldsymbol{e}^2 \in \Delta^{ESS}$.
2. If $\beta \geq \gamma$ whenever $\alpha > \beta$ or $\beta > \gamma$ whenever $\alpha = \beta$, then $\boldsymbol{e}^1 \in \Delta^{ESS}$.

3. If $\alpha > \beta$ and $\beta < \gamma$, then $\boldsymbol{e}^1, \boldsymbol{e}^2 \in \Delta^{ESS}$.

4. If $\alpha < \beta$ and $\beta > \gamma$, then $\bar{x} = \left(\frac{-\beta+\gamma}{\alpha-2\beta+\gamma}, \frac{\alpha-\beta}{\alpha-2\beta+\gamma}\right) \in \Delta^{ESS}$.

Proof. Consider the payoff matrix given in Matrix 3.

1. Consider the pure strategy $\boldsymbol{e}^2$ and an arbitrary mixed strategy $y = (y_{(1)}, y_{(2)}) \in \Delta$, where $y_{(1)}$ and $y_{(2)}$ are respective proportions of alleles H and h in a population. Suppose $\alpha \leq \beta$ whenever $\beta < \gamma$ or $\alpha < \beta$ whenever $\beta = \gamma$. Let $\beta \leq \gamma$. The first condition from the definition of an ESS in Proposition 1 is $u(y, \boldsymbol{e}^2) \leq u(\boldsymbol{e}^2, \boldsymbol{e}^2)\ \forall y$. We have:

$$u(y, \boldsymbol{e}^2) = y_{(1)}\beta + y_{(2)}\gamma \tag{5}$$

and

$$u(\boldsymbol{e}^2, \boldsymbol{e}^2) = \gamma \tag{6}$$

Observe that for all y, which implies for all $y_{(2)} \in [0,1]$, we have:

$$u(\boldsymbol{e}^2, \boldsymbol{e}^2) - u(y, \boldsymbol{e}^2) = y_{(1)}(-\beta + \gamma) \tag{7}$$

which is always nonnegative because $y_{(1)}$ is nonnegative and $\beta \leq \gamma$. Thus, $u(y, \boldsymbol{e}^2) \leq u(\boldsymbol{e}^2, \boldsymbol{e}^2)\ \forall y$. Hence, the first condition of an ESS is satisfied.

Now suppose $u(y, \boldsymbol{e}^2) \leq u(\boldsymbol{e}^2, \boldsymbol{e}^2)$. From Equation 7, it implies either $y_{(1)} = 0$ or $-\beta + \gamma = 0$, which is equivalent to $y = (0,1) = \boldsymbol{e}^2$ or $\beta = \gamma$, respectively. The second condition from the definition of an ESS is $u(y, y) < u(\boldsymbol{e}^2, y)\ \ \forall y \neq \boldsymbol{e}^2$. Thus, we will not consider $y = \boldsymbol{e}^2$. We then assume that $\beta = \gamma$. Consequently, $\alpha < \beta$.

We then have:

$$u(y,y) = {y_{(1)}}^2(\alpha - \beta) + \beta \tag{8}$$

and

$$u(\boldsymbol{e}^2, y) = \beta \tag{9}$$

Observe that for all y, which implies for all $y_{(1)} \in (0,1]$, we have:

$$u(\boldsymbol{e}^2, y) - u(y, y) = -{y_{(1)}}^2(\alpha - \beta) \tag{10}$$

which is always positive because $\alpha < \beta$. Thus, $u(y, y) < u(\boldsymbol{e}^2, y)\ \forall y \neq \boldsymbol{e}^2$. Hence, the second condition of an ESS is satisfied. Therefore, $\boldsymbol{e}^2 = (0,1)$ is an ESS.

2. Consider the pure strategy $\boldsymbol{e}^1$ and an arbitrary mixed strategy $y = (y_{(1)}, y_{(2)}) \in \Delta$.

Suppose $\beta \geq \gamma$ whenever $\alpha > \beta$ or $\beta > \gamma$ whenever $\alpha = \beta$. Let $\alpha \geq \beta$. We have:

$$u(y, \boldsymbol{e}^1) = y_{(1)}\alpha + y_{(2)}\beta \tag{11}$$

and

$$u(\boldsymbol{e}^1, \boldsymbol{e}^1) = \alpha \tag{12}$$

It can be observed that for all y, where $y_{(2)} \in [0,1]$, we have:

$$u(\boldsymbol{e}^1, \boldsymbol{e}^1) - u(y, \boldsymbol{e}^1) = y_{(2)}(\alpha - \beta) \tag{13}$$

which is always nonnegative, and the first condition of an ESS is satisfied.

Now suppose $u(y, \boldsymbol{e}^1) = u(\boldsymbol{e}^1, \boldsymbol{e}^1)$. Equation 13 implies either $y_{(2)} = 0$ or $\alpha - \beta = 0$. Similar to the proof of Equation 1, we will not consider $y = \boldsymbol{e}^1$. We then assume that $\alpha = \beta$. Consequently, $\beta > \gamma$. We then have:

$$u(y, y) = \beta + {y_{(2)}}^2(-\beta + \gamma) \tag{14}$$

and

$$u(\boldsymbol{e}^1, y) = \beta \tag{15}$$

Observe that for all y:

$$u(\boldsymbol{e}^1, y) - u(y, y) = {y_{(2)}}^2(\beta - \gamma), \tag{16}$$

which is always positive, and the second condition of an ESS is satisfied. Therefore: $\boldsymbol{e}^1 = (1,0)$ is an ESS.

3. Consider the pure strategies $\boldsymbol{e}^1$ and $\boldsymbol{e}^2$ and an arbitrary mixed strategy $y = (y_{(1)}, y_{(2)}) \in \Delta$. Let $\alpha > \beta$ and $\beta < \gamma$. From Equations 7 and 13, the first condition of an ESS in Proposition 1 is satisfied.

For $\boldsymbol{e}^2$, the second condition requires the assumption of $u(y, \boldsymbol{e}^2) = u(\boldsymbol{e}^2, \boldsymbol{e}^2)$. From Equation 7, the previous equation is satisfied only when $y_{(1)} = 0$ because we already assumed $\beta < \gamma$. The equation $y_{(1)} = 0$ is equivalent to $y = (0,1)$. The desired conclusion $u(y, y) < u(\boldsymbol{e}^2, y)\ \forall y \neq \boldsymbol{e}^2$ then becomes vacuously satisfied because there is no other value of y aside from $(0,1) = \boldsymbol{e}^2$.

Similarly, for $\boldsymbol{e}^1$, $u(y, \boldsymbol{e}^1) = u(\boldsymbol{e}^1, \boldsymbol{e}^1)$ is satisfied only when $y_{(2)} = 0$ from Equation (15). Equivalently $y = (1,0)$, because we already assumed $\alpha > \beta$. The desired conclusion $u(y, y) < u(\boldsymbol{e}^1, y)\ \ \forall y \neq \boldsymbol{e}^1$ will also be vacuously satisfied because there is no other value of y aside from $(1,0) = \boldsymbol{e}^1$. Therefore, $\boldsymbol{e}^1$ and $\boldsymbol{e}^2$ are ESS.

4. Consider the mixed strategies

$$\bar{x} = \left(\frac{-\beta+\gamma}{\alpha-2\beta+\gamma}, \frac{\alpha-\beta}{\alpha-2\beta+\gamma}\right), y = (y_{(1)}, y_{(2)}) \in \Delta$$

Then:

$$u(y,x) = \frac{\alpha\gamma - \beta^2}{\alpha - 2\beta + \gamma} \quad (17)$$

and

$$u(x,x) = \frac{\alpha\gamma - \beta^2}{\alpha - 2\beta + \gamma} \quad (18)$$

Since $u(y,x) = u(x,x)\ \ \forall y$, the first condition is satisfied.

Let $\alpha < \beta$ and $\beta > \gamma$. An immediate consequence is $\alpha - 2\beta + \gamma < 0$. For the second condition of an ESS, we have:

$$u(y,y) = (\alpha - 2\beta + \gamma)\left(y_{(1)} - \left(\frac{-\beta + \gamma}{\alpha - 2\beta + \gamma}\right)\right)^2 + \frac{\alpha\gamma - \beta^2}{\alpha - 2\beta + \gamma} \quad (19)$$

and

$$u(x,y) = \frac{\alpha\gamma - \beta^2}{\alpha - 2\beta + \gamma} \quad (20)$$

We consider all possible values of y except $y = x$. Thus, for all $y_{(1)} \in [0,1] \setminus \left\{\frac{-\beta+\gamma}{\alpha-2\beta+\gamma}\right\}$, we have:

$$u(x,y) - u(y,y) = (\alpha - 2\beta + \gamma) - \left(y_{(1)} - \left(\frac{-\beta + \gamma}{\alpha - 2\beta + \gamma}\right)\right)^2 \quad (21)$$

which is always positive. Thus, $u(y, y) < u(x, y)\ \forall y \neq x$ and the second condition is satisfied. Therefore, $\overline{x} = \left(\frac{-\beta+\gamma}{\alpha-2\beta+\gamma}, \frac{\alpha-\beta}{\alpha-2\beta+\gamma}\right)$ is an ESS.

ANALYSIS

Following the model of Gokhale and Traulsen (2014), α, β, and γ are the respective (relative) fitness of the three possible genotypes HH, Hh, and hh. Relative fitness is defined as the average number of surviving offspring of a parent with a corresponding genotype (i.e. the absolute fitness of a genotype) relative to a reference genotype. Hence f_{HH}, f_{Hh}, and f_{hh} are the absolute fitness of HH, Hh, and hh, respectively. We can then assign for instance Hh as a reference genotype and obtain the following equalities:

$$\alpha = \frac{f_{HH}}{f_{Hh}},\ \beta = \frac{f_{Hh}}{f_{Hh}} = 1,\ \text{and}\ \gamma = \frac{f_{hh}}{f_{Hh}}.$$

Throughout the illustrations, we consider the heterozygote genotype, where $\beta = 1$. Consequently, when $\alpha > 1$ (or $\alpha < 1$), the homozygous Huntington class is more (or less) fit than the heterozygous Huntington class. This means that a homozygote parent for HD can produce more (or less) surviving offspring than a heterozygote parent. Similarly, the expression $\beta > \gamma$ is equivalent to saying that the heterozygous Huntington class is more fit than the homozygous normal class. Thus, a heterozygote parent for HD can produce more surviving offspring than a homozygote parent for the normal type. The explanation for the remaining expressions $\alpha = \beta$, $\alpha < \beta$, $\beta = \gamma$, and $\beta < \gamma$ are analogous.

Illustration 1. From Theorem 1 Item 1, we assume $\alpha \leq \beta < \gamma$. This means that hh is the most fit type, and type Hh is at least as fit as type HH. Setting $\alpha = 0.8$, $\beta = 1$, and $\gamma = 1.2$, and substituting to Equation 4 yields the replicator equation:

$$\dot{x} = x(1-x)\big((0)x - 0.2\big)$$

with graph shown in Figure 1.

Figure 1 shows various curves for selected values of α and γ such that $\alpha \leq \beta = 1 < \gamma$. Curves similar to blue ($\alpha = 0.2$, $\gamma = 1.8$), orange ($\alpha = 0.4$, $\gamma = 1.6$), gray ($\alpha = 0.6$, $\gamma = 1.4$), and yellow ($\alpha = 0.8$, $\gamma = 1.2$), which are symmetric with respect to $x = 0.5$, are obtained when the difference between the fitness values of types HH and Hh is the same as the difference between the fitness values of types Hh and hh. Curves similar to light blue ($\alpha = 0.2$, $\gamma = 1.2$ and green ($\alpha = 0.4$, $\gamma = 1.4$), which are skewed closer to $x = 1$, are obtained when the difference between the fitness values of types HH and Hh is more than the difference between the fitness values of types Hh and hh. Curves similar to dark blue ($\alpha = 0.6$, $\gamma = 1.6$) and maroon

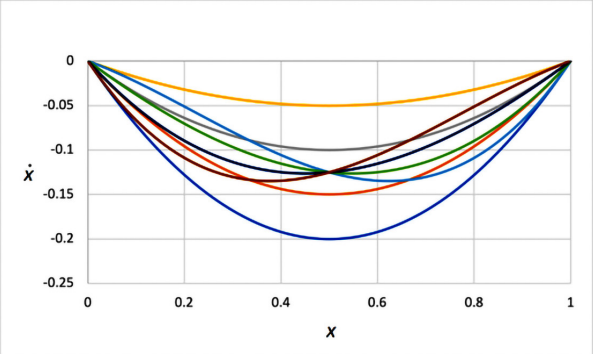

Figure 1. Illustration of Theorem 1 Item 1, $\alpha \leq \beta$ whenever $\beta < \gamma$ for different values of α and γ, with $\beta = 1$.

($\alpha = 0.8$, $\gamma = 1.8$), which are skewed closer to $x = 0$, are obtained when the difference between the fitness values of types HH and Hh is less than the difference between the fitness values of types Hh and hh.

Since $\dot{x}$ represents the change in x over time, a zero $\dot{x}$ implies an equilibrium point, whereas a positive (negative) value of $\dot{x}$ means that x will increase (decrease). In Figure

1, the value of $\dot{x}$ is 0 when $x = 0$ or $x = 1$ and negative for any value of x in between. This implies $x = 0$ and $x = 1$ are equilibrium points. There will be no change in the frequency of H alleles if the entire population consists of only H alleles, i.e. all Huntington, or only h, i.e. all normal.

To further explain, suppose we have a purely Huntington population at the parental generation, i.e. $x = 1$. Since all players of the game are H alleles, then the only possible mating that we can generate is between two homozygote parents for the Huntington gene, i.e. $HH \times HH$. This mating will always produce offspring of the same genotype. Hence, at the first generation of offspring, no h alleles are produced and so the frequency of H remains at $x = 1$. Repeating this over time will yield the same result for the second, third (and so on) generations of offspring. The same thing happens for the other equilibrium point $x = 0$, which represents a purely normal population, i.e. all players of the game are h alleles.

On the other hand, if we have any mixed population (we will use the term "mixed population" throughout these illustrations to refer to mixed strategy) $(x, 1 - x)$, where $x \in (0,1)$, the frequency of H alleles will decrease.

Suppose we start with the mixed population $(0.4, 0.6)$ at the parental generation. This means that the proportion of Huntington allelles in the population is $x = 0.4$, whereas the proportion of normal alleles is $1 - x = 0.6$. Since both players are present in the game, there is now a possibility for heterozygous offspring to be produced and for both alleles to be preserved in the population for another generation. This can happen when HH parents interact with hh parents or when Hh parents are formed and interact with parents of any genotype. We compute for the change on the frequency of H after one generation. Substituting $x = 0.4$ to Equation 4 gives us $\dot{x} = -0.048$, which means a negative change on the frequency of H. Consequently, the frequency of H alleles decreases to $x = 0.352$ at the first generation of offspring. Another iteration of the same process with $x = 0.352$ gives us $\dot{x} = -0.0456192$, and the frequency of H decreases further to $x = 0.3063808$ at the second generation of offspring. Repeating this process over time eventually pushes the frequency x of Huntington alleles to the equilibrium point $x = 0$. This is shown by the yellow curve in Figure 2. Similar results can be observed if we start with any value of $x \in (0,1)$, in particular, with $x = 0.5$ (light blue) or $x = 0.8$ (maroon). Hence, the population would eventually be completely dominated by normal alleles, and the Huntington alleles would become extinct.

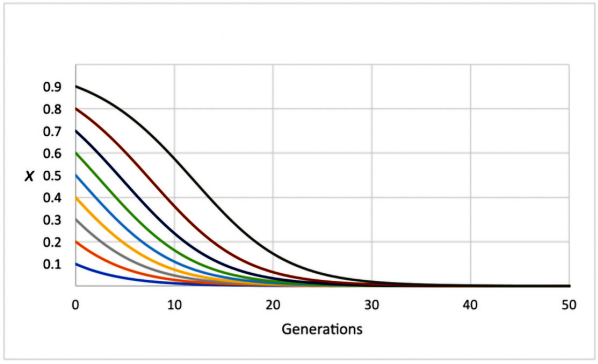

Figure 2. Trajectories of x with $\alpha = 0.8$, $\beta = 1$, and $\gamma = 1.2$.

On the other hand, small disturbances at $x = 1$ – specifically, a decrease – cause the frequency of H to continue decreasing and not return to the original state $x = 1$. This is because $\dot{x}$ will then become negative. For example, suppose we have a purely Huntington population at $x = 1$. If even a small frequency of normal alleles is injected into this large population of Huntington alleles, then we now have $x < 1$. By Equation 4, this value will generate a negative $\dot{x}$, which means a decrease in the population frequency. Over time, this frequency will continue to decrease until it reaches $x = 0$, or when all Huntington alleles have now become extinct, and the population is replaced by normal alleles.

Illustration 2. The second part in the first item of Theorem 1 will be illustrated here. We consider $\alpha < \beta = \gamma$. We set

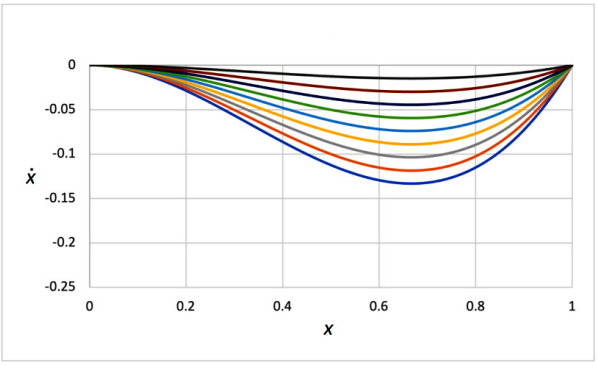

Figure 3. Illustration of Theorem 1 Item 1, $\alpha < \beta$ whenever $\beta = \gamma$ for different values of α, with $\beta = \gamma = 1$.

$\alpha = 0.8$, $\beta = \gamma = 1$ as an example, and this gives us the replicator equation:

$$\dot{x} = x(1 - x)\big((-0.2)x\big)$$

with graph shown in Figure 3.

Figure 3 shows various curves for select values of α and γ such that $\alpha < \beta = \gamma$. We still have $\beta = 1$. Observe that all curves are skewed closer to $x = 1$. The blue curve is obtained when $\alpha = 0.1$, while the following curves are obtained respectively as α increases in 0.1 increments:

orange, gray, yellow, light blue, green, dark blue, maroon, dark gray. Notice that the smaller α is, and consequently the wider its gap is with β and γ, the lower value of $\dot{x}$ is generated. In other words, the frequency of Huntington alleles always decreases but accomplishes it faster when homozygotes parents for HD are unable to produce more offspring than heterozygotes and normal parents.

Since the value of $\dot{x}$ is also 0 when $x = 0$ or $x = 1$, there will be no change in the frequency of H alleles throughout generations if the entire parental population consists of either only Huntington alleles or only normal alleles. On the other hand, the value of $\dot{x}$ is negative for any value of x in between; hence, x in any mixed population is going to decrease due to a negative $\dot{x}$.

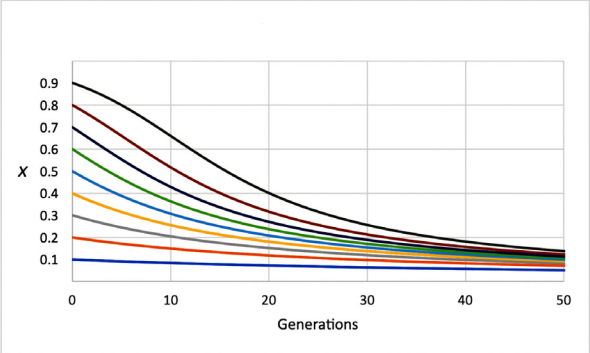

Figure 4. Trajectories of x with $\alpha = 0.8$, $\beta = 1$, and $\gamma = 1$.

We illustrate in Figure 4 the trajectory of x in mixed populations with different starting points. We see that over time, x continues to decrease until it converges to the equilibrium point $x = 0$. Although it will take a longer time as compared to the Illustration 1, the population would eventually still be completely dominated by normal alleles, and Huntington alleles would become extinct.

On the other hand, small disturbances at $x = 1$ – specifically, a decrease – cause the frequency of H to continue decreasing and not return to the original state $x = 1$. This is because $\dot{x}$ will then become negative.

Illustration 3. From Theorem 1 Item 2, we first assumed $\beta \geq \gamma$ whenever $\alpha > \beta$, i.e. HH is the most fit type and type Hh is at least as fit as type hh, by setting $\alpha = 1.2$, $\beta = 1$, and $\gamma = 0.8$ as an example. This gives us the replicator equation:

$$\dot{x} = x(1-x)\big((0)x + 0.2\big)$$

with graph shown in Figure 5.

Figure 5 shows various curves for select values of α and γ such that $\alpha > \beta \geq \gamma$ with $\beta = 1$ since it is our reference

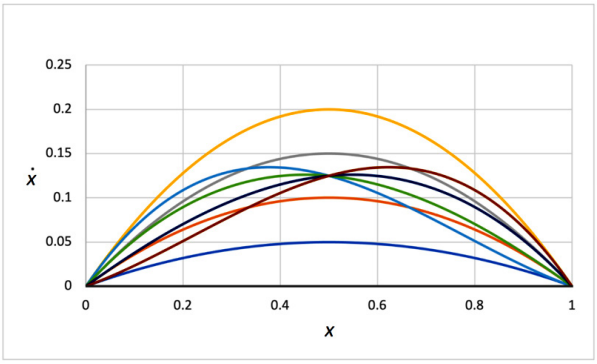

Figure 5. Various curves for different values of α and γ, with $\beta = 1$.

genotype. Curves similar to blue ($\alpha = 1.2, \gamma = 0.8$), orange ($\alpha = 1.4, \gamma = 0.6$), gray ($\alpha = 1.6, \gamma = 0.4$), and yellow ($\alpha = 1.8, \gamma = 0.2$), which are symmetric with respect to $x = 0.5$, are obtained when the difference between the fitness values of types HH and Hh is the same as the difference between the fitness values of types Hh and hh. Curves like the light blue ($\alpha = 1.2, \gamma = 0.2$) and green ($\alpha = 1.4, \gamma = 0.4$, which are skewed closer to $x = 0$, are obtained when the difference between the fitness values of types HH and Hh is less than the difference between the fitness values of types Hh and hh. Curves like the dark blue ($\alpha = 1.6, \gamma = 0.6$) and maroon ($\alpha = 1.8, \gamma = 0.8$), which are skewed closer to $x = 1$, are obtained when the difference between the fitness values of types HH and Hh is more than the difference between the fitness values of types Hh and hh. The value of $\dot{x}$ this time is positive for any value of x in between; hence, x in any mixed population

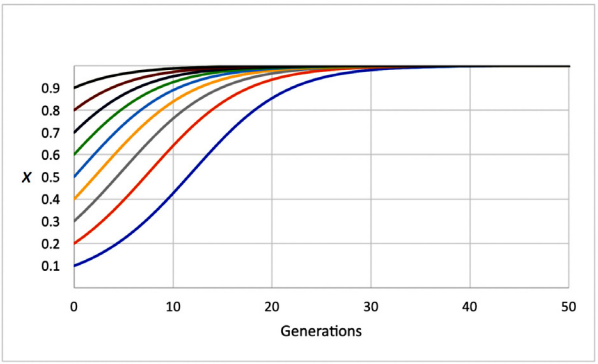

Figure 6. Trajectories of x with $\alpha = 1.2$, $\beta = 1$, and $\gamma = 0.8$.

is going to increase due to a positive $\dot{x}$.

Similarly, we illustrate in Figure 6 the trajectory of x in mixed populations with different starting points. We see that over time, x continues to increase until it converges to the equilibrium point $x = 1$. Hence, the population would eventually be completely dominated by Huntington alleles, and normal alleles would become extinct.

Small disturbances at $x = 0$ – specifically, an increase – cause the frequency of H to continue increasing and not return to the original state $x = 0$. This is because $\dot{x}$ will then become positive. For example, suppose we have a purely normal population $x = 0$. If even a small frequency of Huntington alleles is injected into this large population of normal alleles, then we now have $x > 0$. This value will generate a positive $\dot{x}$, which means an increase in the population frequency. Over time, this frequency will continue to increase until it reaches $x = 1$, or when all normal alleles have now become extinct, and the population is replaced by Huntington alleles.

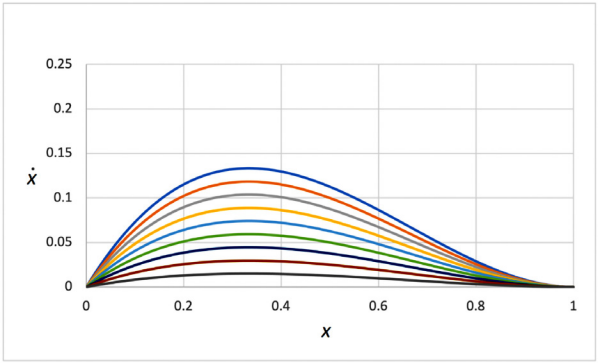

Figure 7. Various curves for different values of α and γ, with $\beta = 1$.

Illustration 4. The second part in the second item of Theorem 1 will be illustrated here. We consider $\alpha = \beta > \gamma$. We set $\alpha = \beta = 1$ and $\gamma = 0.8$ as an example, and this gives us the replicator equation:

$$\dot{x} = x(1 - x)\big((-0.2)x + 0.2\big)$$

with graph shown in Figure 7.

Figure 7 shows various curves for select values of α and γ such that $\alpha = \beta > \gamma$. Observe that all curves are skewed closer to $x = 0$. The blue curve is obtained when $\gamma = 0.1$, whereas the following curves are obtained respectively as γ increases in 0.1 increments: orange, gray, yellow, light blue, green, dark blue, maroon, dark gray. Notice that the smaller γ is – and, consequently, the wider its gap is with α and β – the higher value of $\dot{x}$ is generated. In other words, the frequency of Huntington alleles always increases but accomplishes it faster when homozygote normal parents are unable to produce more offspring than HD parents. The value of $\dot{x}$ is positive for any value of $x \in (0,1)$; hence, x in any mixed population is going to increase due to a positive $\dot{x}$.

For this case, Figure 8 shows the trajectory of x in mixed populations with various starting points. Over time, x continues to increase until it converges to the

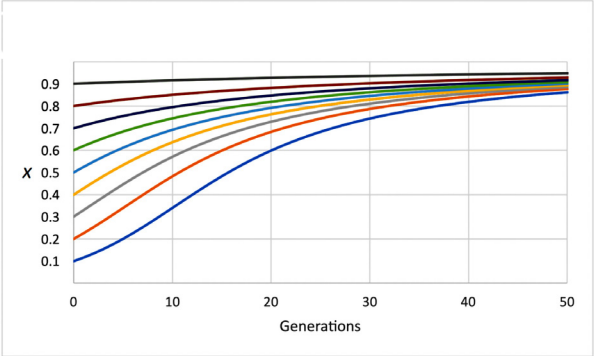

Figure 8. Trajectories of x with $\alpha = 1$, $\beta = 1$, $\gamma = 0.8$.

equilibrium point $x = 1$. Although it will take a longer time as compared to the previous example, the population would eventually be completely dominated by Huntington alleles, and normal alleles would become extinct. Small disturbances at $x = 0$, specifically an increase, cause the frequency of H to continue increasing.

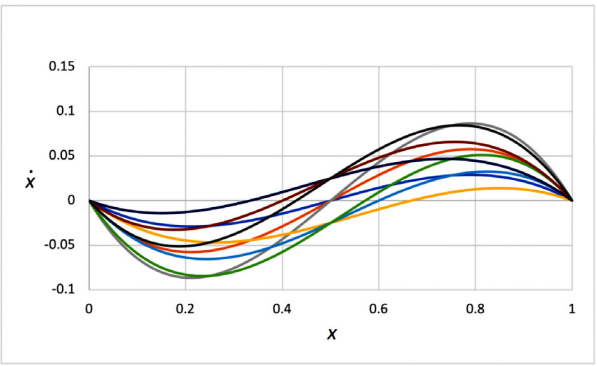

Figure 9. Various curves for different values of α and γ, with $\beta = 1$.

Illustration 5. From Theorem 1 Item 3, we assume $\alpha > \beta$ and $\beta < \gamma$, i.e. Hh is the least fit type, by setting $\alpha = \gamma = 1.3$ and $\beta = 1$ as an example. This gives us the replicator equation:

$$\dot{x} = x(1 - x)\big((0.6)x - 0.3\big)$$

with graph shown in Figure 9.

Figure 9 shows various curves for select values of α and γ such that $\alpha > \beta$ and $\beta < \gamma$. Observe that values of $\dot{x}$ in every curve is negative from $x = 0$ up to a corresponding $\bar{x}$ and positive for some $\bar{x}$ to $x = 1$. Curves similar to blue ($\alpha = \gamma = 1.3$), orange ($\alpha = \gamma = 1.6$), and gray ($\alpha = \gamma = 1.9$), which have another equilibrium point at $\bar{x} = 0.5$, are obtained when the fitness values of types HH and hh are equal. Curves similar to yellow ($\alpha = 1.2$, $\gamma = 1.4$), light blue ($\alpha = 1.4$, $\gamma = 1.6$), and green ($\alpha = 1.6$, $\gamma = 1.8$), which have another equilibrium point at $\bar{x} > 0.5$, are obtained when the fitness value of HH is less than

that of hh. Otherwise, if HH parents are more fit than hh parents, we obtain curves similar to dark blue ($\alpha = 1.4$, $\gamma = 1.2$), maroon ($\alpha = 1.6$, $\gamma = 1.4$), and gray ($\alpha = 1.8$, $\gamma = 1.6$), which have another equilibrium point at $\bar{x} < 0.5$.

From the blue curve, the value of $\dot{x}$ is also 0 when $x = 0$ or $x = 1$. But this time, we have another intercept at $\bar{x} = \frac{-\beta+\gamma}{\alpha-2\beta+\gamma} = 0.5$. Thus, there are three equilibrium states: [a] if the entire parental population consists of only Huntington alleles, [b] if the entire parental population consists of only normal alleles, or [c] if the population is a composition of Huntington and normal alleles, with equal probabilities of 0.5. There will still be no change in the frequency of H alelles throughout generations if the parental population consists of either only Huntington alleles, only normal alleles, or a mix of both alleles with equal probabilities of 0.5. On the other hand, the value of $\dot{x}$ is nonzero for any value of $x \in (0,1)\backslash\{0.5\}$. That is, if we have a mixed population $(x, 1-x)$, where $x \in (0,1)\backslash\{0.5\}$, the frequency of H either increases or decreases.

The trajectory of x in mixed populations with starting points $x = 0.2$ (orange) and $x = 0.4$ (yellow) is shown in Figure 10. We see that over time, x continues to decrease until it converges to the equilibrium point $x = 0$. On the

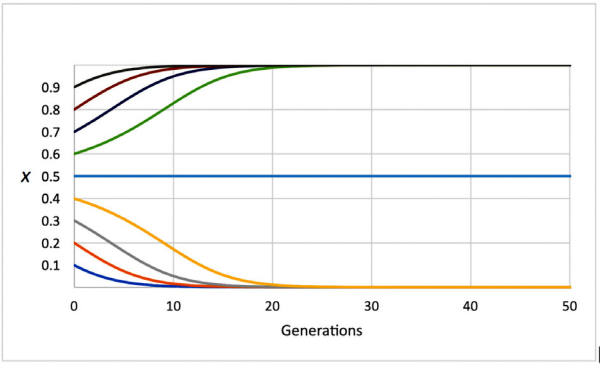

Figure 10. Trajectories of x with $\alpha = 1.3$, $\beta = 1$, and $\gamma = 1.3$.

other hand, with starting points $x = 0.6$ (green) and $x = 0.8$ (maroon), we see that over time, x continues to increase until it converges to the equilibrium point $x = 1$. Hence, the two pure strategies dominate the population, and the population stabilizes with either of Huntington or normal alleles, depending on the initial frequency of Huntington alleles. Small disturbances at $x = 0.5$ cause the frequency of H to either increase or decrease.

Illustration 6. Finally, from Theorem 1 Item 4, we assume $\alpha < \beta$ and $\beta > \gamma$, that is, Hh is the most fit type, we set $\alpha = \gamma = 0.7$ and $\beta = 1$ as an example. This gives us the replicator equation:

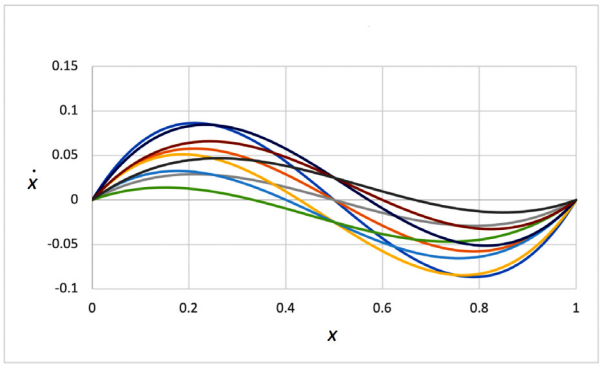

Figure 11. Various curves for different values of α and γ, with $\beta = 1$.

$$\dot{x} = x(1-x)\big((-0.6)x + 0.3\big)$$

with graph shown in Figure 11.

Various curves for select values of α and γ such that $\alpha > \beta$ and $\beta < \gamma$ are shown in Figure 11. Observe that values of $\dot{x}$ in every curve is positive from $x = 0$ up to a corresponding $\bar{x}$ and negative from some $\bar{x}$ to $x = 1$. Curves similar to blue ($\alpha = \gamma = 1.3$), orange ($\alpha = \gamma = 1.6$), and gray ($\alpha = \gamma = 1.9$), which have another equilibrium point at $\bar{x} = 0.5$, are obtained when the fitness values of types HH and hh are equal. Curves similar to yellow ($\alpha = 0.2$, $\gamma = 0.4$), light blue ($\alpha = 0.4$, $\gamma = 0.6$), and green ($\alpha = 0.6$, $\gamma = 0.8$), which have another equilibrium point at $\bar{x} < 0.5$, are obtained when the fitness value of HH is less than that of hh. Otherwise, if HH parents are more fit than hh parents, we obtain curves similar to dark blue ($\alpha = 0.4$, $\gamma = 0.2$), maroon ($\alpha = 0.6$, $\gamma = 0.4$), and gray ($\alpha = 0.8$, $\gamma = 0.6$), which have another equilibrium point at $\bar{x} > 0.5$.

There will also be three equilibrium states: [a] if the entire parental population consists of only Huntington alleles, [b] if the entire parental population consists of only

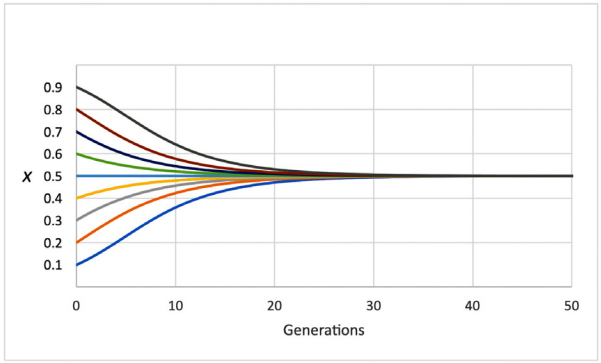

Figure 12. Trajectories of x with $\alpha = 0.7$, $\beta = 1$, and $\gamma = 0.7$..

normal alleles, or [c] if the population is a composition of Huntington and normal alleles, with equal probabilities of 0.5. There will still be no change in the frequency of H alleles throughout generations if the parental population consists of either only Huntington alleles, only normal alleles, or a mix of both alleles with equal probabilities of 0.5. Similarly, the value of $\dot{x}$ is nonzero for any value of $x \in (0,1)\backslash\{0.5\}$. That is, if we have a mixed population $(x, 1-x)$, where $x \in (0,1)\backslash\{0.5\}$, the frequency of H either increases or decreases.

Figure 12 illustrates the trajectory of x in mixed population. We see that over time, x continues to increase until it converges to the equilibrium point $\bar{x} = 0.5$. On the other hand, with the starting points $x = 0.6$ (green) and $x = 0.8$ (maroon), we see that over time, x continues to decrease until it converges to the same equilibrium point $\bar{x} = 0.5$. Hence, no pure strategy dominates the population, and the population stabilizes with the coexistence of both Huntington and normal alleles with equal probabilities of 0.5.

CONCLUSION AND RECOMMENDATION

In this study, we applied EGT in population genetics – specifically, in the case of the inheritance pattern of HD – which was presented as a four-player game. As presented by Gokhale and Traulsen, the payoff matrix of the game was reduced to a symmetric two-player game. Their model served as the payoff matrix employed to determine the evolutionary stable strategies of the game.

Given some parameters, the solutions to the replicator equation were verified to be evolutionary stable strategies. From these results, we have determined when the population compositions for alleles H and h are evolutionarily stable depending on the fitness values of each genotype HH, Hh, and hh. As shown in the illustrations, mixed populations converge to a purely normal composition, that is $x = 0$, if normal parents will produce more offspring than HD parents. Consequently, more h alleles are passed on through generations of offspring compared to H alleles. The opposite applies and mixed populations converge to a purely Huntington composition, that is, $x = 1$, if HD parents will produce more offspring than normal parents. This is because more H alleles are passed on through generations of offspring compared to h alleles. Mixed populations may also converge to either pure composition, depending on the composition of the frequencies of H and h at the parental generation. This happens if homozygotes HH and hh are more fit than heterozygotes. Lastly, it is also possible that a mixed population converges to a composition where both types of genes H and h coexist. This happens if heterozygotes are more fit than homozygotes.

HD falls under the category of Mendelian inheritance. Gokhale and Traulsen's model can also be applied to non-Mendelian inheritance pattern. Studies on the application for such inheritance pattern like the one presented here would further show how EGT may be applied in biology. In addition to this, since infinite population was considered in this paper, potential directions include extensions of the research field by considering spatial structure and finite populations. There have already been numerous studies (Thomas and Pohley 1981; Nowak and May 1992; Ficici and Pollack 2000; Nowak and Sigmund 2004), which took into consideration the aforementioned, and key advances were produced. However, most of the analysis for finite populations, was limited to two-player games (Noe and Hammerstein 1995; Miekisz 2008). Thus, the introduction of various non-linear interactions such as what we did in this study (introducing multiplayer games) would be helpful in furthering the diversity and reach of EGT.

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