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Huntington's Disease as an Evolutionary Game

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Abstract: Game theory has seen several major developments that proved beneficial even outside economics, where it was originally established for. Evolutionary game theory (EGT) is one development that covers ecology and population genetics, among other fields in biology. Huntingon's disease, named after the person who wrote the first detailed description about the disease in 1872, is a neurodegenerative disease that is inherited. This study aims to present this disease as a multiplayer game and construct its payoff matrix and the average payoffs of each strategy. A payoff matrix is a table in which strategies of one player are listed in rows and those of the other player in columns and the cells show payoffs to each player.

Key Words: evolutionary game theory; population genetics; lethal alleles; payoff matrix

1. INTRODUCTION

The early models used by game theorists were based on rationality. The players were assumed to be perfectly rational and have the same idea of being rational. It was only in the 1990s that the emphasis has shifted toward evolutionary models because of the limitations of rationality-based models (Samuelson, 2022). Another reason is 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. Thus, perfect rationality seems less appropriate (Samuelson, 2022).

In evolutionary games, the players and their strategies are the individuals and the characteristics 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, and evolutionary game dynamics revolves in this process (Sandholm, 2010).

Maynard Smith and Price (Smith & Price, 1973) introduced the central concept of an evolutionarily stable strategy (ESS), which is a refinement of Nash equilibrium from classical game theory. 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 (Dawkins, 1989).

Gokhale and Traulsen (Gokhale & Traulsen, 2014), in their paper entitled "Evolutionary multiplayer games," provided an application of EGT in population genetics, where they dealt with games that included multiple players. This particular inclusion is an example of a non-linear interaction.

Rowe (Rowe, 1988) previously utilized multiple players, where the strategies are the different genotypes.

When strategies in evolutionary games 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 as of recent become possible to derive results for equilibrium points even in the context of diploid populations (cells with two sets of chromosomes). Gokhale and Traulsen provided a model that starts from a symmetric four-player two-strategy game, which can be reduced into a symmetric two-player two-strategy game in the process of solving for equilibrium points. This study will apply the same to the inheritance pattern of the Huntington's Disease.

Huntingon's disease, named after the person who wrote the first detailed description about the disease in 1872, is a neurodegenerative disease that is inherited. It is most common among people of northern European origin, although it can occur in all racial groups. On average, the age of onset of its symptoms is around 40 years (Novak & Tabrizi, 2010). Loss of balance and chorea (involuntary, irregular, and unpredictable muscle movements), 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. Onset is defined as the point at which characteristic motor signs develop (Huntington Study Group, 1996), that is, a person affected by it is no longer a "premanifest gene carrier" but has manifested the disease already. There are also people of age lower than 20 or higher than 70 who start exhibiting symptoms. It is an uncommon disease, but it can be devastating for those who are affected.

Cognitive symptoms include slowing of thought processing, difficulty with multitasking, concentration problems, and short term memory. Individuals affected by this disease also suffer from limb incoordination and impaired hand function. While patients should not be classified as psychiatrically disturbed, psychiatric intervention may be required. As part of the disease, one of the most common psychiatric symptoms is depression. Affected individuals are also more likely to commit suicide compared to the general population.

Following onset, the disease's duration is roughly 10 to 15 years, although some have been known to survive for 30 years (Stipe, et. al, 1979). Huntington's disease is in itself not fatal, although secondary complications such as heart failure or pneumonia usually leads to death of someone with the disease. There are no treatments 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.

Family members of someone diagnosed with the disease also face the prospect of carrying the disease. An affected parent's offspring has a 50% chance of inheriting this abnormality. Huntington's disease's risk does not skip and continues uninterrupted through generations, and male and female offspring are affected equally (Novak & Tabrizi, 2010).

This disease is a single gene disease with autosomal dominant inheritance. That is, the gene is located on a chromosome other than sex chromosome. Hence, it is not sex-linked. Furthermore, the Huntington allele is the dominant trait, thus offspring only need one copy of the allele H to express the disease. Genetic testing can identify the abnormality. In Huntington's disease, the expanded Huntingtin (HTT) gene encodes a mutant form of huntingtin protein, which contributes to the development of the disease. Expanded HTT means that it has at least 36 CAG repeats, whereas a normal HTT gene has fewer than 36. From 36 to 39, some people will develop the disease while some will not. From 40, people will always develop Huntington's disease (Novak & Tabrizi, 2010).

2. EVOLUTIONARY GAME THEORY IN POPULATION GENETICS

Evolutionary game theory in population genetics begins with a game that can be used as a model of some strategic interaction an organism might

participate in. The payoffs of these interactions are considered the organism's fitness, so that a strategy which receives higher payoffs in the game can be generally expected to increase in frequency. Generally, EGT may approach population genetics in two different ways, either with gene dynamics or as dynamics on the phenotypic level which occurs based on a known genetic setup.

In Gokhale and Traulsen's model, pure strategies are thought of as alleles, and the mixed strategy of the players assign the probabilities equal to the respective frequencies of the alleles in the population. The population is assumed to be infinite and well-mixed, that is 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 is an application of EGT in population genetics which can handle non-linearities and Mendelian inheritance patterns.

A game based on Mendelian inheritance starting from the viewpoint of an allele will be constructed. As part of the mating process, one individual, either the paternal or maternal, is characterized by two alleles. Each of the parents contributes one of their alleles resulting to two alleles transferred to the offspring. But 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.

This study will focus on the construction of the payoff matrix of the Mendelian inheritance pattern of the Huntington's Disease, a multiplayer game. This is an example of how non-linear interactions may be introduced in evolutionary games.

3. PAYOFF MATRIX

We now construct the payoff matrix for a symmetric four-player game for the inheritance pattern of the Huntington's Disease following Gokhale and Traulsen's model. The two pure strategies are H and h, where H represents the presence of Huntington disease and h the absence of the disease, with respective probabilities p and $1-p$ assigned by the mixed strategy x.

We will construct the payoff matrix of a four-player two-strategy game. The four players represent four alleles, and each of those alleles can either be H-type or h-type. Matrix (1) below is a player's payoff matrix in a symmetric four-player game. The ordering of the column players does not matter as long as the players are correctly labeled. Thus, playing with HHh will be the same as playing with hHH or HhH, for instance. However, for convenience, we will hide the columns HhH and hHH, which are similar to HHh; and hHh and hhH, which are similar to Hhh. Thus, the cardinality of each of the columns HHh and Hhh is 3.

$$\begin{array}{c} \\ H \\ h \end{array} \begin{array}{c} \begin{array}{cccc} HHH & HHh^{(3)} & Hhh^{(3)} & hhh \end{array} \\ \begin{pmatrix} a_3 & a_2 & a_1 & a_0 \\ b_3 & b_2 & b_1 & b_0 \end{pmatrix} \end{array} \quad (1)$$

Heterozygotes, in simple dominance, have the same phenotype as one of the homozygotes. In terms of disease-producing autosomal dominant genes, however, the homozygotes have been reported to be more severely afflicted. In a study of four possible homozygotes for Huntington's disease, one was assessed to have a 95% likelihood to be homozygous [35]. Interestingly, the age at onset and symptoms were like those of other affected members of the extended family, confirming the observation (Stipe, et. al, 1979) that homozygotes for Huntington's disease are not more severely afflicted than heterozygotes. Thus, there are still three possible genotypes of parents, namely $HH, Hh,$ and hh. Let the fitness of HH, Hh, and hh be α, β, and γ, respectively.

We solve for the values of each entry in the matrix starting with a_3, the payoff received by player H when interacting with the players HHH. The only possible distinct mating that we can have is $HH \times HH$.

We take a look at the Punnett square for $HH \times HH$ shown in Table 1. A Punnett square is a table in which all the possible outcomes for a genetic cross between two individuals with known genotypes are given.

	H	H
H	HH	HH
H	HH	HH

Table 1. Punnett square for $HH \times HH$

To calculate the fitness of the H allele, for each genotype we first multiply the number of H alleles present in that genotype with the number of entries of that genotype in the Punnett square. Then, we multiply it with the fitness of that genotype. For instance, the genotype HH consists of two H alleles and there are four HH entries in the Punnett square. That gives us $2 \cdot 4 = 8$, which we then multiply with the fitness of HH which is α to get 8α. We repeat the same process for genotypes Hh and hh. But both Hh and hh genotypes are not found in the Punnett square. Consequently, we have 0β and 0γ respectively.

We add $8\alpha, 0\beta$, and 0γ, and divide the sum by the total number of H alleles in the Punnett square. There is a total of eight H alleles in the Punnett square. Hence, the fitness of the H allele is

$$a_3 = \frac{8\alpha + 0\beta + 0\gamma}{8} = \frac{8\alpha}{8} = \alpha.$$

Next, we proceed with a_2, the payoff received by player H when interacting with the players HHh. The only possible distinct mating that we can have is $HH \times Hh$. We take a look at the Punnett square for $HH \times Hh$.

	H	h
H	HH	Hh
H	HH	Hh

Table 2. Punnett square for $HH \times Hh$

Following the same procedure in computing the H allele, we add 4α, 2β, and 0γ, and divide the sum by the total number of H alleles in the Punnett square. Hence, the fitness of the H allele is

$$a_2 = \frac{4\alpha + 2\beta + 0\gamma}{6} = \frac{2\alpha + \beta}{3}$$

Next, we proceed with a_1, the payoff received by player H when interacting with the players Hhh. The possible distinct matings that we can have are $HH \times hh$ and $Hh \times Hh$ with cardinality 2 because we can pair our focal player H either with Hhh or Hhh. We will take the average fitness from the three possible matings. The Punnett square for the first mating is given in Table 3.

	h	h
H	Hh	Hh
H	Hh	Hh

Table 3. Punnett square for $HH \times hh$

Following the same procedure as the previous computations, we add $0\alpha, 4\beta$, and 0γ, and divide the sum by the total number of H alleles in the Punnett square. Hence, the fitness of the H allele for the first mating, given by a_1^1, is

$$a_1^1 = \frac{0\alpha + 4\beta + 0\gamma}{4} = \beta$$

The second mating, $Hh \times Hh$, gives us the Punnett square in Table 4.

	H	h
H	HH	Hh
H	Hh	hh

Table 4. Punnett square for $Hh \times Hh$

Adding $2\alpha, 2\beta$, and 0γ, and dividing the sum by the total number of H alleles in the Punnett square, the fitness a_1^2 of the H allele for the second mating is

$$a_1^2 = \frac{2\alpha + 2\beta + 0\gamma}{4} = \frac{\alpha + \beta}{2}$$

Taking the average fitness from the three possible matings finally gives us

$$a_1 = \frac{\alpha + 2\beta}{3}$$

Next, we proceed with a_0, the payoff received by player H when interacting with the players hhh. The only possible distinct mating that we can have is $Hh \times hh$ with the Punnett square in Table 5.

	h	h
H	HH	Hh
h	Hh	hh

Table 5. Punnett square for $Hh \times hh$

Similarly, to find the fitness of the H allele, we add $0\alpha, 2\beta$, and 0γ, and divide the sum by the total number of H alleles in the Punnett square. Hence, the fitness of the H allele is

$$a_0 = \frac{0\alpha + 2\beta + 0\gamma}{2} = \beta$$

Next, we proceed with b_3, the payoff received by player h when interacting with the players HHH. The only possible distinct mating that we can have is $Hh \times HH$. The Punnett square is given in Table 6.

	H	H
H	HH	HH
h	Hh	Hh

Table 6. Punnett square for $Hh \times HH$

To calculate the fitness of the h allele, we add $0\alpha, 2\beta$, and 0γ, and divide the sum by the total number of h alleles in the Punnett square. Hence, the fitness of the h allele is

$$b_3 = \frac{0\alpha + 2\beta + 0\gamma}{2} = \beta$$

Next, we proceed to compute b_2, the payoff received by player h when interacting with the players HHh. The possible distinct matings that we can have are $Hh \times Hh$, with cardinality 2 because we can pair our focal player h either with HHh or HHh, and $hh \times HH$. We will take the average fitness from the three possible matings.

	H	h
H	HH	Hh
h	Hh	hh

Table 7. Punnett square for $Hh \times Hh$

The fitness of the h allele will be the sum of $0\alpha, 2\beta$, and 2γ divided by the sum of the total number of h alleles in the Punnett square. The fitness of the h allele for the first mating is given by b_2^1,

$$b_2^1 = \frac{0\alpha + 2\beta + 2\gamma}{4} = \frac{\beta + \gamma}{2}$$

Because the first mating has cardinality 2, we proceed with the third mating. The third mating, $hh \times HH$, gives us the Punnett square in Table 8.

	H	H
h	Hh	Hh
h	Hh	Hh

Table 8. Punnett square for $hh \times HH$

For the third mating, the fitness of the h allele, represented by b_2^3 is given by

$$b_2^3 = \frac{0\alpha + 4\beta + 0\gamma}{4} = \beta$$

Taking the average fitness from the three possible matings finally gives us

$$b_2 = \frac{2\beta + \gamma}{3}$$

Next, we proceed with b_1, the payoff received by player h when interacting with the players Hhh. The only possible distinct mating that we can have is $Hh \times hh$ given in Table 9.

	h	h
H	Hh	Hh
h	hh	hh

Table 9. Punnett square for $Hh \times hh$

Following the same procedure as the previous computations, the fitness b_1 of the h allele is given by

$$b_1 = \frac{0\alpha + 2\beta + 4\gamma}{6} = \frac{\beta + 2\gamma}{3}$$

Finally, we proceed with b_0, the payoff received by player h when interacting with the players hhh. The only possible distinct mating that we can have is $hh \times hh$.

	h	h
h	hh	hh
h	hh	hh

Table 10. Punnett square for $hh \times hh$

There is a total of eight h alleles in the Punnett square. Hence, the fitness b_0 of the h allele is

$$b_0 = \frac{0\alpha + 0\beta + 8\gamma}{8} = \gamma$$

Now that we have found the value of each entry, we end up with the final payoff matrix below.

$$\begin{array}{c} \\ H_p \\ H_{1-p} \end{array} \begin{array}{c} \begin{array}{cccc} HHH_{p^3} & HHh^{(3)}_{p^2(1-p)} & Hhh^{(3)}_{p(1-p)^2} & hhh_{(1-p)^3} \end{array} \\ \begin{pmatrix} \alpha & \frac{2\alpha+\beta}{3} & \frac{\alpha+2\beta}{3} & \beta \\ \beta & \frac{2\alpha+\beta}{3} & \frac{\beta+2\gamma}{3} & \gamma \end{pmatrix} \end{array}$$

We then proceed with calculating the average payoff for each strategy. The average payoff for H is denoted by u_H, while the average payoff for h is denoted by u_h.

$$u_H = \alpha p^3 + 3\left(\frac{2\alpha+\beta}{3}\right)p^2(1-p) + 3\left(\frac{\alpha+2\beta}{3}\right)p(1-p)^2 + \beta(1-p)^3$$
$$= \alpha p^3 + (2\alpha+\beta)(p^2-p^3) + (\alpha+2\beta)(p-2p^2+p^3) + \beta(1-3p+3p^2-p^3)$$
$$= \alpha p^3 + 2\alpha p^2 - 2\alpha p^3 + \beta p^2 - \beta p^3 + \alpha p - 2\alpha p^2 + \alpha p^3 + 2\beta p - 4\beta p^2 + 2\beta p^3 + \beta - 3\beta p + 3\beta p^2 - \beta p^3$$
$$= \alpha p + \beta(1-p)$$

$$u_h = \beta p^3 + 3\left(\frac{2\beta+\gamma}{3}\right)p^2(1-p) + 3\left(\frac{\beta+2\gamma}{3}\right)p(1-p)^2 + \gamma(1-p)^3$$
$$= \beta p^3 + (2\beta+\gamma)(p^2-p^3) + (\beta+2\gamma)(p-2p^2+p^3) + \gamma(1-3p+3p^2-p^3)$$
$$= \beta p^3 + 2\beta p^2 - 2\beta p^3 + \gamma p^2 - \gamma p^3 + \beta p - 2\beta p^2 + \beta p^3 + 2\gamma p - 4\gamma p^2 + 2\gamma p^3 + \gamma - 3\gamma p + 3\gamma p^2 - \gamma p^3$$
$$= \beta p + \gamma(1-p)$$

For comparison, let $x' = (p, 1-p)$ be a mixed strategy, in another symmetric game, of players 1 and 2 whose sets of strategies consist of H' and h'. Suppose this game has the payoff matrix

$$\begin{array}{c} \\ H' \\ h' \end{array}\begin{array}{c} \begin{array}{cc} H'_p & h'_{1-p} \end{array} \\ \begin{pmatrix} \alpha & \beta \\ \beta & \gamma \end{pmatrix} \end{array}$$

The average payoff for H' is denoted by $u_{H'}$, while the average payoff for h' is denoted by $u_{h'}$.

$$u_{H'} = \alpha p + \beta(1-p)$$
$$u_{h'} = \beta p + \gamma(1-p)$$

Then, $u_H = u_{H'}$ and $u_h = u_{h'}$, which implies that we could have in hindsight just made use of the payoff matrix for a two-player two-strategy game, where H' corresponds to the pure strategy H, and h' corresponds to the pure strategy h of the original four-player two-strategy game.

4. CONCLUSIONS

The study presented the payoff matrix for a symmetric four-player game for the Huntington's disease following Gokhale and Traulsen's model. The two pure strategies are H and h, where H represents the presence of Huntington disease and h the absence of the disease. with respective probabilities p and $1 - p$ assigned by the mixed strategy x.

We have also computed the average payoff of each strategy and use these to show that the payoff matrix of this four-player two-strategy game may be reduced to a two-player two-strategy game.

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