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Statistical Model Derivation and Extension of Hardy – Weinberg Equilibrium

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ABSTRACT

The Hardy-Weinberg equilibrium law states that when a population is in equilibrium, the genotypic frequencies will be in the proportion p^2: 2pq: q^2. In a large random mating hypothetical population where the frequencies of alleles A_1 and A_2 are respectively is p and q, each genotype passes on both alleles with equal frequency over generations in the absence of evolutionary forces (Mutation, migration, and selection). In this paper, the Hardy-Weinberg equilibrium law is derived and extended to the third generation, and the corresponding proportion of frequencies is derived with all mating patterns. The mating frequency matrix is also given. Further, the law is generalized for multiple alleles and generations using binomial expansion.

Introduction

Way back in 1908, a revolutionary contribution has made in genetics and proved statistically by G. H. Hardy and Wilhelm Weinberg, who independently established the principle that the three genotypes A_1A_1, A_1A_2 and A_2A_2 at a bi-allelic locus with allele frequencies p and q = 1 – p are expected to occur in the respective proportions (p2: 2pq: q2) known as Hardy-Weinberg equilibrium (HWE). Some mathematical modeling was formulated based on probability distributions. Fitted models concluded that the gene pool frequencies are inherently stable but that evolutionary forces should be expected in all populations virtually all of the time. Hardy and Weinberg, again they proved the equilibrium stage of a large random mating population. Many geneticists followed them and came to understand that evolution will not occur in a population if the population is large (i.e., there is no genetic drift). All members of the population breed, individuals are mating randomly, and everyone produces the same number of offspring with mutations are negligible, natural selection is not operating in the population, and in the absence of migration in or out of the population. Today, similar studies put forth by many scientists that the HWE is a prevailing hypothesis used in scientific domains (Ward and Carroll, 2013) ranging from botany (Weising, 2005) to forensic science (Council, 1996) and genetic epidemiology (Sham, 2001; Khoury *et al.*, 2004). The formulation of the theorem will be expressed as follows:

Mendel (1865) rules describe how genetic transmission happens between parents and offspring. Consider a monohybrid cross:

A_1A_2 x A_1A_2

¼ A_1A_1 ½ A_1A_2 ¼ A_2A_2

The Hardy-Weinberg Equilibrium principle

A population with random mating results in an equilibrium distribution of genotypes after only one generation, so that the genetic variation is maintained.

When the assumptions are met, the frequency of a genotype is equal to the product of the allele frequencies

The Hardy-Weinberg Law (HWL) states that when a population is in equilibrium state, the genotypic frequencies will be in the proportion p^2, 2pq and q^2. In a theoretical population where the frequency of allele A_1 is *p* and the frequency of allele A_2 is q, each genotype transmit on both alleles that it can posses with equal frequency. Therefore in a population with just two alleles of a gene, the possible combinations as follows:

	Male		Female
Random mating	A_1A_2	x	A_1A_2
Off spring Frequencies	A_1A_1	A_1A_2	A_2A_2
	D	H	R
	$(P + ½\,Q)^2 = p^2$	$2(P + ½\,Q)(½\,Q + R) = 2pq$	$(½\,Q + R)^2 = q^2$

D (Dominant) +H (Heterozygote) + R (Recessive) = 1 and $P^2 + 2pq + q^2 = (p+q)^2 = 1$

The above mating and proportions show the relationship between the allelic frequencies (p and q) and the genotypic frequencies (p^2, 2pq, and q^2), which form the basis of the HWL. For example, the frequency of the genotype A_1A_1 is p^2; the frequency of the genotype A_1A_2 is 2pq.

The HWL states that the allele and genotypic frequencies will remain constant from generation to generation. However, if the population is large, mates randomly, and is free from evolutionary forces (Mutation, migration, and selection). For the above example, it would mean that after taking many generations the frequency of A_1A_1 is still p^2 and the frequency of A_1A_2 is still 2pq.

Stark (2006) demonstrated a model on Clarification of the Hardy–Weinberg Law that HWP can be reached in one round of nonrandom mating with no change in allele frequency.

Stark and Seneta (2012) developed a model which shows that a simple model of non-random mating, which nevertheless embodies a feature of the Hardy-Weinberg Law, can produce Mendelian coefficients of heredity while maintaining the population equilibrium. We can validate this by considering a hypothetical randomly mating population from the table above. To do this, first, consider all the possible matings from every genotypic outcome from table 1.

$D^2 + 4DH(½)(½) + 4H^2(1/4)(1/2) = D^2 + DH + ¼\,D^2 = (D + ½\,H)^2 = p^2$ (1)

Similarly,

$2DH + 2DR + (½)(¼)4H^2 + (½)(½)\,4HR + 2DR + R^2 = 2(D + ½\,H)(½\,H + R) = 2pq$

$(½)(¼)4H^2 + (½)(½)\,4HR + R^2 = R^2 + HR + ¼\,H^2 = (½\,H + R)^2 = q^2$

This is in Hardy–Weinberg equilibrium (HWE) after one generation.

Matrix model

Let the random mating A_1 with A_2 alleles, then from table 1 we have nine mating combinations, from the parental to offspring generation, as identified by the matrix:

$$RM = \begin{bmatrix} A_1A_1 \times A_1A_1 & A_1A_1 \times A_1A_2 & A_1A_1 \times A_2A_2 \\ A_1A_2 \times A_1A_1 & A_1A_2 \times A_1A_2 & A_1A_2 \times A_2A_2 \\ A_2A_2 \times A_1A_1 & A_2A_2 \times A_1A_2 & A_2A_2 \times A_2A_2 \end{bmatrix}$$

Let the initial mating frequencies

$$C = \begin{bmatrix} x_{00} & x_{01} & x_{02} \\ x_{10} & x_{11} & x_{12} \\ x_{20} & x_{21} & x_{22} \end{bmatrix}$$

Where C is the symmetric (Stark and Seneta 2013) i.e., males and females have same frequencies which are denoted by vector $\{x_0, x_1, x_2\}$.

Let C' be the transpose of C, that is putting the column vector in row form

$$C' = \{x_{00}, x_{01}, x_{02}, x_{10}, x_{11}, x_{12}, x_{20}, x_{21}, x_{22}\}$$

Next, we need the Mendel's coefficients of heredity from table 1 in matrix form are:

$$M = \begin{bmatrix} 1 & 1/2 & 0 & 1/2 & 1/4 & 0 & 0 & 0 & 0 \\ 0 & 1/2 & 1 & 1/2 & 1/2 & 1/2 & 1 & 1/2 & 0 \\ 0 & 0 & 0 & 0 & 1/4 & 1/2 & 0 & 1/2 & 1 \end{bmatrix}$$

The composition of the offspring generation is simply given T'= (MC)' …. (1)

$$T' = \{x_{00} + \frac{x_{01}+x_{10}}{2} + \frac{x_{11}}{4}, \frac{x_{01}}{2} + x_{02} + \frac{x_{10}+x_{11}+x_{12}}{2} + x_{20}, \frac{x_{11}}{4} + \frac{x_{12}+x_{21}}{2} + x_{22}\}'$$

If additionally to the conditions of symmetry and sum of all elements equated to unity of *C*, we also assume that the equilibrium H^2=4DR, that is $x_{11}=4x_{02}$ (Stark and Seneta 2013) then the T'=$\{x_0, x_1, x_2\}$.If initial population has frequencies $\{x_0, x_1, x_2\}$, then random mating is expressed as;

$$C_o = \begin{bmatrix} (x_0)^2 & x_0x_1 & x_0x_2 \\ x_1x_0 & (x_1)^2 & x_1x_2 \\ x_2x_0 & x_2x_1 & (x_2)^2 \end{bmatrix}$$

$$C' = \{(x_0)^2, x_0x_1, x_0x_2, x_1x_0, (x_1)^2, x_1x_2, x_2x_0, x_2x_1, (x_2)^2\}'$$

Then, applying T'=(MC)' it will be,

$$T' = \{(x_0 + \tfrac{1}{2}x_1)^2, 2(x_0 + \tfrac{1}{2}x_1)(x_2 + \tfrac{1}{2}x_1), (x_2 + \tfrac{1}{2}x_1)^2\}'$$

Which in equilibrium T' =$\{p^{2'}, 2pq', q^{2'}\}'$.

Extension of Hardy Weinberg Equilibrium

If Random Mating is continued, the second generation is mentioned in table 2. We can first consider all the possible matings from every genotypic outcome above. These matings combinations are listed in Column A.

Next, we are assuming that this population is subject to HWL. Many instances, A_1A_1 x A_1A_1 matings do not occur which often to A_2A_2 x A_2A_2 matings. This would be the frequency of mating between any two genotypes is the product T'. Therefore, the mating frequency of A_1A_1 x A_1A_1, will remain in constant state in equilibrium p^2 x p^2 or p^4.

Similar results finding were presented in columns C-E are the genotypic frequencies of the next generation. In our example of A_1A_1 x A_1A_1, is equated to100% of the offspring will have the genotype A_1A_1, so the frequency of that genotype in the next generation is p^4.

If the proven HWE is accurate, then the total in Column B should equal the totals of D, C, and E combined, which should come out the same as the frequencies of the original generation. The combined totals of C, D, and E, which makes up the entire population of the next generation, should still result in the same Hardy-Weinberg equation: $p^2+2pq+q^2=1$.

Let the mating frequency matrix from table 2

$$C_o = \begin{bmatrix} (p^2)^2 & 2p^3q & p^2q^2 \\ 2p^3q & 4p^2q^2 & 2pq^3 \\ p^2q^2 & 2pq^3 & q^4 \end{bmatrix}$$

Let C' be the transpose of C, that is putting the column vector in row form

$C' = \{p^4, 2p^3q, p^2q^2, 2p^3q, 4p^3q^3, 2pq^3, p^2q^2, 2pq^3, q^4\}$

By applying T' = (MC) ' obtained from equation (1), we get

$T' =\{ p^4+ ½\ 2p^3q+ ½\ 2p^3q+ ¼\ 4p^3q^3, ½2p^3q+p^2q^2+½2p^3q+½4p^3q^3+ ½2pq^3 +p^2q^2+½2pq^3, ¼\ 4p^3q^3+ ½\ 2pq^3 + ½\ 2pq^3+q^4 \}$

Then the offspring frequencies which becomes $T' = \{p^{2'}, 2pq', q^{2'}\}'$.

From HWE ($p^2+2pq+q^2 =1$) the above proportions are in HWE of the form $p^2+2pq+q^2 = (p+q)^2$, Which in equilibrium $T'=\{p^2, 2pq,q^2\}'$. Continuation of mating with the offspring of second generation as parent again with A_1A_1 A_1A_2 and A_2A_2 we may get the following 27 combinations of crosses for the third generation offspring frequencies presented in the below table 3. The procedure will be followed as if in second generation.

And, from table 3 we have

Column B: $p^6 + 6p^5q + 15p^4q^2+ 20p^3q^3+ 15p^2q^4 + 6pq^5 + q^6 = (p^2+2pq+q^2)^6 =1$

Column C: $p^6 + 4p^5q + 6p^4q^2+ 4p^3q^3+ p^2q^4$

i.e., $p^2 (p^4 + 4p^3q + 6p^2q^2+ 4p\ q^3+ q^4) = p^2 ((p^2 + 2pq + q^2)^2)^2 = p^2$

Column D: $2p^5q + 8p^4q^2+ 12p^3q^3+ 8p^2q^4 + 2pq^5$

i.e., $2pq (p^4 + 4p^3q+ 6p^2q^2+ 4pq^3 + q^4) = 2pq ((p^2 + 2pq + q^2)^2)^2 = 2pq$

Column E: $p^4q^2+ 4p^3q^3+ 6p^2q^4 + 4pq^5+q^6$

i.e., $q^2 (p^4 + 4p^3q+ 6p^2q^2+ 4pq^3 + q^4) = q^2 ((p^2 + 2pq + q^2)^2)^2 = q^2$

We get 3x5 matrix for third generation combination of HWE i.e.

$$C_o = \begin{bmatrix} p^6 & 4p^5q & 6p^4q^2 & 4p^3q^3 & p^2q^4 \\ 2p^5q & 8p^4q^2 & 12p^3q^3 & 8p^2q^4 & 2pq^5 \\ p^4q^2 & 4p^3q^3 & 6p^2q^4 & 4pq^5 & q^6 \end{bmatrix}$$

From HWE $p^2+2pq+q^2 =1$, the above proportions are in HWE of the form $p^2+2pq+q^2 = (p+q)^2$, Which in equilibrium $\{p^2, 2pq,q^2\}$. Hence the proof.

Generalization of Hardy Weinberg Equilibrium (GHWE)

Ward & Carroll (2013) describes a gene having r alleles $A_1, A_2,..., A_r$ has r(r+1)/2 possible genotypes. These genotypes are naturally indexed over a lower-triangular array as $A_1, A_2,..., A_r$. A population is said to be in Hardy-Weinberg Equilibrium (HWE) the law can assumed the following pdf.

If p_{jk} is the relative proportion of genotype $\{A_j, A_k\}$ in the population, and if θ_k is the proportion of allele A_k in the population, then the system is in HWE if

Table.1 Model derivation of the Hardy-Weinberg proportions

Random Mating	Genotype Frequencies	Mendel's coefficients of heredity/Conditional probabilities			Mating proba-bilities
		A_1A_1	A_1A_2	A_2A_2	
A_1A_1 x A_1A_1	X^2_{11}	1	0	0	D^2
A_1A_2	X_{11} X_{12}	1 /2	1/2	0	4DH
A_2A_2	X_{11} X_{22}	0	1	0	2DR
A_1A_2 x A_1A_1	X_{12} X_{11}	1/2	1/2	0	4HD
A_1A_2	X^2_{12}	1/4	1/2	1/4	$4H^2$
A_2A_2	X_{12} X_{22}	0	1/2	1/2	4HR
A_2A_2 x A_1A_1	X_{22} X_{11}	0	1	0	2HR
A_1A_2	X_{22} X_{12}	0	1/2	1/2	4DR
A_2A_2	X^2_{22}	0	0	1	R^2

Table.2 Mating combination for second generation of HWE

A	**B**	**C**	**D**	**E**
Type of Mating Male x Female	Mating Frequencies	Offspring frequencies		
		A_1A_1	**A_1A_2**	**A_2A_2**
A_1A_1 x A_1A_1	p^2 x p^2 = p^4	p^4	--	--
A_1A_1 x A_1A_2 **A_1A_2 x A_1A_1**	p^2 x 2pq 2pq x p^2 = $4p^3q$	$2p^3q$	$2p^3q$	
A_1A_1 x A_2A_2 **A_2A_2 x A_1A_1**	p^2 x q^2 p^2 x q^2 = 2 p^2q^2	--	2 p^2q^2	--
A_1A_2 x A_1A_2	2pq x 2pq 2pq x 2pq = $4p^2q^2$	p^2q^2	$2p^2q^2$	p^2q^2
A_1A_2 x A_2A_2 **A_2A_2 x A_1A_2**	2pq x q^2 q^2 x 2pq = $4pq^3$	--	$2pq^3$	$2pq^3$
A_2A_2 x A_2A_2	q^2 x q^2 = q^4	--	--	q^4
Total	$(p^2+2pq+q^2)^2$ =1	p^2 $(p^2+ 2pq+q^2)$ =1	2pq $(p^2+2pq+q^2)$ =1	q^2 $(p^2+2pq+q^2)$ =1
	p^2 *AA* +2pq *Aa* + q^2 *aa* = 1			

Table.3 Mating combination for third generation of HWE

A	B		C	D	E
Type of Mating Male x Female	Mating Frequencies		Offspring frequencies		
			A_1A_1	**A_1A_2**	**A_2A_2**
A_1A_1 x A_1A_1 x A_1A_1	p^4 x p^2	p^6	p^6	--	--
A_1A_1 x A_1A_1 x A_1A_2 A_1A_2 x A_1A_2 x A_1A_1 A_1A_1 x A_1A_2 x A_1A_1	p^4 x 2pq 2pq x p^2 x p^2 p^2 x 2pq x p^2	$6p^5q$	$4p^5q$	$2p^5q$	
A_1A_1 x A_1A_1 x A_2A_2 A_1A_1 x A_1A_2 x A_1A_2 A_1A_1 x A_2A_2 x A_1A_1 A_1A_2 x A_1A_1 x A_1A_2 A_1A_2 x A_1A_2 x A_1A_1 A_2A_2 x A_1A_1 x A_1A_1	p^4 x q^2 p^2 x 2pq x 2pq p^2 x q^2 x p^2 2pq x p^2 x 2pq 2pq x 2pq x p^2 q^2 x p^2 x p^2	$15p^4q^2$	$6p^4 q^2$	$8p^4 q^2$	$p^4 q^2$
A_1A_1 x A_1A_2 x A_2A_2 A_1A_1 x A_2A_2 x A_1A_2 A_1A_2 x A_1A_1 x A_2A_2 A_1A_2 x A_1A_2 x A_1A_2 A_1A_2 x A_2A_2 x A_1A_1 A_2A_2 x A_1A_1 x A_1A_2 A_2A_2 x A_1A_2 x A_1A_1	p^2 x 2pq x q^2 p^2 x q^2 x 2pq 2pq x p^2 x q^2 2pq x 2pq x 2pq 2pq x q^2 x p^2 q^2 x p^2 x 2pq q^2 x 2pq x p^2	$20p^3q^3$	$4p^3q^3$	$12p^3q^3$	$4p^3q^3$
A_1A_2 x A_1A_2 x A_2A_2 A_1A_2 x A_2A_2 x A_1A_2 A_2A_2 x A_1A_1 x A_2A_2 A_2A_2 x A_1A_2 x A_1A_2 A_2A_2 x A_2A_2 x A_1A_1 A_1A_1 x A_2A_2 x A_2A_2	2pq x 2pq xq^2 2pq x q^2 x 2pq q^2 x p^2 x q^2 q^2 x 2pq x2pq q^2 x q^2 x p^2 p^2 x q^2 x q^2	$15p^2q^4$	p^2q^4	$8p^2q^4$	$6p^2q^4$
A_1A_2 x A_2A_2 x A_2A_2 A_2A_2 x A_1A_2 x A_2A_2 A_2A_2 x A_2A_2 x A_1A_2	2pq x q^2 x q^2 q^2 x 2pq x q^2 q^2 x q^2 x 2pq	$6pq^5$	--	$2pq^5$	$4pq^5$
A_2A_2 x A_2A_2 x A_2A_2	q^2 x q^2 x q^2	q^6	--	--	q^6
$p^6 + 6p^5q + 15p^4q^2 + 20p^3q^3 + 15p^2q^4 + 6pq^5 + q^6 = (p+q)^6 = 1$					

$$p_{j,k} = p_{j,k}(\theta_j, \theta_k) = \begin{cases} 2\theta_j\theta_k, & j > k \\ \theta_k^2, & j = k \end{cases}$$

Where p_{ik} is the i^{th} parent in j^{th} generation. θ_j & θ_k are the constant of i^{th} parent in j^{th} generation.

Multiple alleles

The expected genotypic array under Hardy-Weinberg equilibrium for two alleles say A_1A_1 and A_2A_2 is p^2, $2pq$, and q^2, which form the terms of the binomial expansion $(p+ q)^2$. To generalize to more than two alleles, one need only add terms to the binomial expansion and thus create a multinomial expansion. For example, with alleles A_1, A_2, and A_3 with frequencies *p*, *q*, and *r*, the genotypic distribution should be $(p+ q + r)^2$, or homozygote will occur with frequencies p^2, q^2, and r^2, and heterozygote will occur with frequencies 2*pq*, 2*pr*, and 2*qr*. Further, if we have multiple alleles A_1, A_2,..., A_k with genotype probability frequencies $x_1, x_2..., x_k$ such that $\Sigma\ x_k = 1$. then the multinomial expansion is given as

$$(x_1 + x_2 + \cdots, x_k)^2 = \sum_{x_1+x_2+\cdots,x_k=k}^{2} \binom{2}{k_1, k_2 \dots, k_n} x_1^{k_1} x_2^{k_2} \dots, x_k^{k_n}$$

Multiple generation / loci

If males and females each have the same two alleles in the proportions of p and q, then genotypes will be distributed as a binomial expansion in the frequencies p^2, 2*pq*, and q^2. From the above derivations the Hardy-Weinberg equilibrium can be extended to include, among other cases, multiple alleles and multiple generations. i.e., for the first generation with probabilities p and q it is $(p+q)^2= p^2+2pq+ q^2 = 1$ with four genotypes. At second generation it is $((p+q)^2)^2 = (p+q)^4= p^4+ 4p^3q+6p^2q^2+ 4\ pq^3+ q^4$ with mating combination of $3^2=9$ genotypes for third generation it is $((p+q)^4)^2= (p+q)^6= p^6 + 6p^5q + 15p^4q^2+ 20p^3q^3+ 15p^2q^4 + 6pq^5 +q^6 = 1$ with mating combination $3^3=27$ genotypes and therefore for the n^th^ generation we generalize using binomial distribution with 3^n Combination genotypes and the distribution pattern of F_2 genotypes is $((p+q)^2)^n$:

$$(p+q)^{2n} = \sum_{k=0}^{2n} \binom{2n}{k} q^k p^{2n-k}$$

$$= \binom{2n}{0} q^0 p^{2n-0} + \binom{2n}{1} q^1 p^{2n-1} + \dots + \binom{2n}{k} q^k p^{2n-k} + \dots + \binom{2n}{2n} q^{2n} p^{2n-2n}$$

With matrix of size 3 x (2n-1) rank.

Edwards (2008) accounted G. H. Hardy's role in establishing in the existence of ''Hardy–Weinberg equilibrium,''. Stark A E (2006) demonstrated a model on Clarification of the Edwards (2008) accounted G. H. Hardy's role in establishing in the existence of ''Hardy–Weinberg equilibrium,''. Stark A E (2006) demonstrated a model on Clarification of the Hardy–Weinberg Law that HWP can be reached in one round of nonrandom mating with no change in allele frequency. Crow (1988) made remarks that ever since its discovery in the early 1900s, the Hardy-Weinberg law has been a subject of intense consideration and a powerful research tool in population genetics. Stark (2006) reviewed the most basic law of population genetics, which is attributed to Hardy (1908) and Weinberg (1908), which is poorly understood by many scientists who use it routinely. As per the present study, HWE derived and extended from the second generation to the third generation with all possible mating including matrix form. Further, the law is generalized for multiple alleles and multiple generations using binomial expansion. At second generation it is $((p+q)^2)^2 = (p+q)^4= p^4+ 4p^3q+6p^2q^2+ 4\ pq^3+ q^4$ with mating combination of $3^2=9$ genotypes for third generation it is $((p+q)^4)^2= (p+q)^6= p^6 + 6p^5q + 15p^4q^2+ 20p^3q^3+ 15p^2q^4 + 6pq^5 +q^6 = 1$ with mating combination $3^3=27$ genotypes and therefore for the n^{th} generation we generalize using binomial distribution with 3^n Combination genotypes and the distribution pattern of F_2 genotypes is $((p+q)^2)^n$ With matrix of size 3 x (2n-1) rank.

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