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Selection procedure towards genetic improvement of animals: A overview

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Abstract
The present study reviewed the development of different selection method ranging from traditional phenotypic procedure to recent advanced genomic selection technique for improvement of animals from February, 2017 to November, 2017. The different optimal selection procedure focused to combine genetic gain and conserved genetic diversity to reform the selection and breeding procedure for the genetic improvement. Different theorems like natural selection, response to selection based on fitness, multilevel selection, selection method, neutral theory of selection and genomic selection were discussed to explain how the animal has adopted them to evolve better genetic merit. These theorems established to evidence higher accuracy in selection process thereby increasing the chances of success of the breeding programs. However, in future the models for estimation of breeding values and genetic values will be based entirely on DNA markers obtained from genotyping the animal or inferred from other animals.

Keywords: Breeding value, Index Selection, Fitness, Genomic selection, Neutral theory, Selection indices

Introduction
From ancient time along with the development of human civilization, man is trying a lot for improvement of animal productivity to meet the increasing need of growing human population by unknowingly changing its genetic merit [1]. To achieve this various selection procedures had been adapted to different breeds of livestock to increase their performance [2]. But during the starting of the 20th century only and after the discovery of new emerging branch of biological science i.e., Population Genetics it became clear that the selection procedure leads to the improvement of phenotypic value of a trait with the change in the breeding value. According to Ledig [3] during the breeding process, it is foremost important to have a high genetic gain while achieving the genetic diversity. Thereby, genetic gain and conserved genetic diversity are the most active forces that must be combined to reform the selection and breeding procedures [4]. West and Gardner [5] proposed that selection procedure was the process of deciding which animals in a generation will be allowed to become parents of the next generation and how many progenies they will be permitted to leave. Individual merit was the most important basis for selection, although information on ancestors, collateral relatives and the progeny test were valuable aids to individual selection for specific traits [6].

Selection is the means with which all improvement of domesticated animals has been made in terms of economic gain. Thompson [7] established that selective improvement in the quantitative traits was dependent upon the heritability of that trait and the amount of selection practiced i.e., selection differential. The simplest form of selection is to choose individuals on the basis of their own phenotypic values [7]. The net value of an individual depends on several traits. Hence, it is necessary to apply selection simultaneously to all traits of economic importance [8]. For example, in poultry genetic economic value of a layer bird depends on many traits like age at sexual maturity, body weight, number of eggs produced and weight of egg. The traits to be considered for simultaneous selection obviously depend to a large extent, upon their genetic significance and economic values [9]. Hazel [10] discovered that genetic significance of a character means its response to selection which depends on the magnitude of heritability of the character and the genetic association characters with each other. Nevertheless, if several traits are important to the economy of the livestock enterprise, maximum total improvement can be made by using an index which optimally weighs each trait [11]. Simultaneous, selection for several traits reduces the intensity of selection for any one trait.

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According to Price's theorem on selection the difference between two aggregations i.e., selection difference were typically the differences between the two subsequent generations of the same biological population, which leads to evolutionary changes through a long period of time [12]. But Price defined the application of his theorem beyond evolutionary biology [13]. Thus, the present study objective was to review the development of different selection method ranging from traditional phenotypic procedure to recent advanced genomic selection technique for improvement of animals.

2. Price's Theorem on Selection

Price theorem standardized a mapping of 'parents' to 'offspring' between the two generation and described the change in the average of the important quantity into two parts viz. 'selection' being the change due to different parents having different numbers of offspring; and 'transmission' being the change that was due to offsprings not perfectly resembling their parents [8, 14]. However, Price's theorem described about the action of selection in a covariance form:

$\Delta sE_{i \in I}(z_i) = cov_{i \in I}(v_i, z_i)$

Where, v_i denotes the ith parent's relative contribution to the offspring assemblage (i.e. its number of offsprings divided by the average number of offsprings per parent)

z_i denotes this parent's character value

Price's covariance expression represented four important conceptual components of selection [8, 9, 15]. Firstly, the entity upon which the selection acts has been identified here as the holder of the index, i and defines the 'unit of selection'. Secondly, the assemblage within whom selection acts, identified here by the index set I, defines the 'arena of selection' according to Price [9]. Thirdly, the numerical property of the units, identified here as the variable z, whose aggregate change might be driven by selection, defines the 'character under selection' as explained by Price [9]. Lastly, the numerical property of the units identified as the variable v, which provides the measure of a unit's success, defines the 'target of selection' [8]. Price [9] brought all these components of selection together and the action of selection was expressed by the covariance taken over all units within the arena, between the character and the target of selection.

3. Natural selection

Natural selection follows inevitably from inherited variation in the ability to reproduce to pass their progeny from generation after generation [1, 14]. The systematic accumulation of chance variations are the only process that can lead to biological adaptations and thereby producing organisms that can live in extreme environments and on diverse energy sources [16]. When applied to natural evolution, question arises whether actual rates of adaptation are close to any limitation or whether actual genetic systems have evolved so as to improve the response to selection [15]. Following Darwin and Wallace's proposal of adaptation by natural selection had emphasized that enough time had not been there since the formation of the earth for natural selection to carry out [16]. Thereby, sexual reproduction and blending inheritance would have eliminated the variation on which selection depends. The early Mendelian geneticists explained that natural selection could not generate novelty, since it could only shift amongst genotypes that already existed in the population [16]. However, selection is the accumulation of successive favorable variants that produce genotypes for a long period of time which goes on exceedingly improbable [17]. Wright [18] emphasized that

selection on a single population cannot establish variants that are favorable in combination but individually deleterious. He proposed that this limitation could be circumvented by a "shifting balance" involving selection among populations carrying different gene combinations. The discovery in midcentury of extensive variation in protein and DNA sequence, both within and between species, stimulated Kimura [19] to propose that most of these variations have no effect on fitness that it could not all be maintained by selection.

3.1. Price`s Genetical Theory of Natural Selection

According to Price genetical language i.e. the unit of natural selection is the individual organism and the arena of natural selection is a biological population as explained in a similar manner by Darwin [20]. The character under selection is the heritable portion of the individual's phenotypic trait (g) that is a weighted sum of the frequencies of the alleles which is carried by the individual and the weights are being decided by linear regression analysis [1, 9]. In other words, it is the individual's 'breeding value' [21]. The target of natural selection is the individual's fitness (v) which is an expectation over future uncertainty of number of offspring's expressed relative to the population average [12]. Price [15] illustrated the mathematical statement of natural selection in terms of fitness as

$\Delta_{NS}E_{i \in I}(g_i) = cov_{i \in I}(v_i, g_i)$

It means the action of natural selection is given by the covariance, taken over all the individuals within that population, between the individual's heritable trait and her fitness.

3.2. The fundamental theorem of natural selection

Fisher [22] discovered that the action of natural selection with respect to any genetical character of interest is the heritable component of fitness itself. Fitness may be decomposed into its genetical and environmental components that capture the non-additive genotypic effects (such as dominance, epistasis, synergy and frequency dependence) as well as other more obviously environmental effects [22]. The change in average fitness responsible for the action of natural selection is equal to the additive genetic variance of trait [22, 23]. The significance of this result was that the variances are non-negative and natural selection can only have an improving effect on fitness. Fisher [23] represented the fundamental theorem as an explanation for the idea that individuals will adopt themselves to maximize their fitness [24]. Usually, the fundamental theorem is not concerned with total evolutionary changes that develop due to fitness rather explain only the action of natural selection [25]. Non-selective change in fitness leads to mutation and changing associations between genes and fitness collectively called as deterioration of the environment by Fisher [23] that owing to reduce average fitness [2]. Many evolutionists realized that the fundamental theorem about total evolutionary change in fitness is not totally correct and it is usually applicable under very special conditions [26]. This conceptual confusion realized the importance of being able to mathematically separate the selective versus non-selective components of evolutionary change [27].

Till now, argument persists among geneticists to correct the interpretation of fundamental theorem of Natural Selection. Okasha [28] and Ewens [29] both regarded the theorem as a procedure to the selection of genes particularly concerning to the selection of individuals. As, the genetical character expresses the information carried by genes about the fitness of

individuals was proposed by Okasha [28]. The fundamental theorem was aroused from a selection covariance in which the unit of selection is the individual, the target of selection is the individual's fitness, and the character under selection is the heritable portion of the individual's fitness [29]. Here, genes merely provide a material basis for the inheritance of the individual's character. Gardner [11] revealed that in the fundamental theorem change in a genetical character was driven by the differential fitness of individuals.

4. Conceptual issues on fitness

Fitness is the ability of organisms or species to survive and reproduce in the changing environment by adopting themselves to it [30, 31]. Consequently, the organisms contribute genes to the next generation through the progeny [32]. Fitness is commonly analyzed in two ways. One describes the actual 'components' which give rise to differences in fitness among the individuals, and other by expressing the mathematical measures of fitness to viability [33]. In case of viability, the Fitness is a trait or just called as individual fitness [34]. In terms of viability individual fitness is binary i.e., 0 or 1. That means, the individual is either survives (1) or it does not (0) [34]. In the language of probability theory, viability can be calculated by Bernoulli random variable. If a proportion (P) of zygotes survives, the mean individual fitness in this case, viability [35] is

$P(1) + (1 – P)(0) = P.$

Similarly, we can calculate the variance in individual fitness (viability), which can be expressed in terms of P or (1 – P). Response to natural selection requires that some of the differences in fitness have a genetic basis i.e. fitness must be at least partly heritable [34]. So, fitness was explained in two different forms as absolute fitness and relative fitness.

4.1. Absolute fitness

Absolute fitness is a statistical representation to a genotype that refers to a complex mixture of viability, mating success, fecundity and so on [32]. As such, absolute fitness (W) is a quantity that can be greater than or equal to zero [33]. According to viability selection, individuals of a given genotype have some probability of surviving if all absolute fitness quantities are always kept equal. If only two genotypes segregate in a haploid population, mean absolute fitness is

$W = pW_1 + qW_2$

Where, p is the frequency of genotype 1.

q is the frequency of genotype 2.

(p + q = 1).

W_1 and W_2 are the absolute fitness of genotypes 1 and 2.

It is easy to show mathematically that mean absolute fitness equals to the mean individual fitness. The mean absolute viability is the chance that an individual having a randomly chosen genotype survives; but this must be the same as the probability that a randomly chosen individual survives regardless of information on genotype [32].

4.2 Relative fitness

The relative fitness of a genotype (w) equals to its absolute fitness when get normalized [36]. Barton and Turelli [33] illustrated that in the normalization process, the absolute fitness of each genotype is divided by the absolute fitness of the fittest genotype, such that the fittest genotype has a relative fitness of one. We can also define a selection coefficient (s), a measure of how much 'worse' the A_2 allele is than A_1. Mathematically,

$W_2 = 1 – s$

Although the definition of relative fitness is simple, the mathematical relationship between absolute and relative fitness is distinct [35, 37]. Increasing the absolute fitness of a genotype by some amount has less effect on relative fitness than does decreasing the relative fitness of that genotype by the same amount [31].

The importance of mathematical implication of fitness is straight forward i.e., when zygotes attempt to become mature, selection acts by killing someone. Because a proportion (W_1) of A_1 individuals and a proportion (W_2) of A_2 individuals survive, Bazykin [37] and Beatty [35] enumerated that the proportion of individuals that carry A_1 after selection acts is

$pW_1 / (pW_1 + qW_2)$

It expresses that selection will increase the frequency of the fit A_1 allele from one generation to the next. This increase (Δp) can be calculated as

$\Delta p = pqs/(1 – qs)$ (1)

It was considered that species should have discrete generations, however, if populations or genotypes grow continuously over time. The population geneticists have also generalized measures of fitness and have derived selection model for it [38].

5. Analysis of simple models
5.1. Direct responses to selection

Thompson [7] analyzed the selection response in a univariate model in which the fixed effects are nested within generations and common to all generations. In both cases, he assured that the generations were not overlapping [39]. It was also assumed that males and females were measured for one single trait and the best of each sex then selected as parent for the next generation. Thus, selection operates simultaneously in both sexes. The initial group of animals of first generation was unrelated with some unknown parents. When the selection experiment was completed, all the data were analyzed with an animal model [40]. The breeding value solutions for each generation were averaged and these averages were considered as estimates of selection response [40]. The cause of responses to directional selection with recurrent mutation could be generally divided into two phases [40]. In the first phase, the response to selection is rapid and mostly due to genetic variance existing in the base population [40]. However, when the genes in the initial population approaches to fixation, gradually more response to selection comes from new genetic variation introduced by mutation and the process of response is transformed into the second phase [41]. The second phase of selection response largely rely on new genetic variation which covers a much longer time scale to develop a relatively small response per generation [40]. But, sooner or later, the response will reach a plateau balanced by mutation and directional selection because the potential genetic variance accessible by mutation in a locus must be finite [39]. The analysis is directly related to the evaluation of mutation effects on the long-term response of population to artificial selection [41].

5.2. Potential of selection methods

In artificial selection the main aim is to increase the animal performance in terms of its productivity [42]. So, when the decision is taken to improve the traits to meet the economic importance, the next problem is how the selection should be applied on these traits in order to achieve the maximum improvement of overall economic value [42]. For improvement of livestock common selection methods developed by the animal breeders are-

- Tandem selection [43]
- Independent Culling levels [43]
- Selection Index [10, 44]

5.2.1. Tandem selection
Selection is practiced for one trait at a time until satisfactory improvement has been achieved in this trait [21]. Then, selection efforts for this trait are relaxed and efforts are directed towards the improvement of a second, then for a third and so on, until finally each trait has been improved to the desired level [43]. This method is the least efficient of all the three methods as the amount of genetic progress made by the breeder is too time consuming and effortful [43]. Efficiency of tandem selection depends upon the genetic correlation between the traits selected for [45]. If the genetic correlation is positive and desirable, improvement in one trait by selection would automatically improve the other trait not selected for and then the method could be quite efficient [45]. Otherwise, if there were little or no genetic correlation between the traits, which means that they are inherited independently, the efficiency would be less [43]. Adverse condition arises when the two traits are negatively correlated; improvement in one trait gets nullified or neutralized by the regression in the other [21]. For example, in dairy cattle, selection for milk yield will result in reduction in fat percentage as they are negatively correlated [43].

5.2.2. Independent culling levels
Hazel and Lush [43] defined if selection was applied simultaneously for all the characters but, independently, rejecting all individuals that fail to meet the minimum standard for any one trait. This method is more efficient than tandem method and has an important advantage over it that selection is practiced for more than one trait at a time [42]. It is never more efficient than the selection index method. But in some cases especially when the traits under consideration are manifested at different ages it offers the practical advantage of disposing a proportion of inferior individuals earlier [43]. It does not permit superiority in some traits to compensate for deficiencies in the other [43]. Characters measured early in life are likely to be overemphasized at the expense of selection for important traits measured later [21]. Determination of optimum culling levels is important when the traits are correlated [21].

5.2.3. Selection index
Selection is made for all traits simultaneously by constructing an index accounting for the net merit of an individual by combining together the scores for component characters was proposed by Smith [44] and Hazel [10]. The individuals with highest score are selected for the breeding purpose [21]. Unless appropriate weighing is adopted some traits will receive too much and others too little attention [46]. The amount of weight given to each trait depends on its relative economic values, its heritability and the genetic and phenotypic correlations between the different traits [47]. Selection index method is more efficient than above two methods because it results in more genetic improvement for the time and effort expended in its use [47].

Taking these advantages selection indices was first proposed by Smith [44] in order to improve the plants. Hazel [10] extended the index procedure for the selection of individuals in animal populations. They made use of the idea by Fisher [48], which had been suggested the concept of discrimination function and said that since genetic values cannot be determined, but it is possible to approximate its values using a linear function of observable phenotypic values. This method was afterwards developed by Baker [42] and widely used in different breeding programs. Williams [47] labeled the Smith-Hazel index as an estimated index since phenotypic and genetic parameters are never known and thus the index has to be derived by use of sample estimates. Sampling errors associated with estimation from a small data set could affect the reliability of the index [46]. Brim *et al*. [6] pointed out that inaccurate estimation of population parameters could bias estimates of theoretical gains. They suggested an alternative index such that each trait is weighted according to its relative economic value. Williams [47] called this as the base index.

5.2.3.1. Combined-Index selection (CI)
When two or more criteria of selection are used to estimate an individual's true breeding value (B.V) it is called as the combined selection. In other words, the selection of an individual on the basis of two or more sources of information is called as the combined selection of index selection [21]. This means to supplement the individual's performance records with those of its relatives. This gives more accurate estimate of B.V. of the individual [49]. It is better to select on the basis of an index combining information from various relatives (dam, sibs and or progeny) with or without individual's own record. This is done by the technique of multiple regressions. These multiple regression coefficients are used as the weighting factors [49]. All information available about individual's breeding value combined into an index of merit is the optimal procedure for selection. It is based on an individual index value formed from within and between family heritability's and to maximize the gain [21]. In phenotypic selection the individuals are ranked and the best are chosen on the basis of their phenotypic behavior irrespective of their relationship to other individuals. Phenotypic selection is a classical method and can be considered as simple and most efficient [45]. Genetic diversity explained as effective population size is affected by sib type, heritability, selection intensity, family number and family size [21]. To maintain genetic diversity at a desired level, it is important to restrict the number of progeny of certain selected parents should be allowed to pass to the next generation [21, 49]. Thereby, the loss of effective number is decreased at the cost of prospective gain. Wei and Lindgren [50] described that the combined index selection was inferior to phenotypic selection if compared at the same effective population size where selection intensity was considered to vary. Comparisons have also been applied to infinite populations [51]. By restricting the family size the methods can be compared at the same effective population size. Wei [49] made such a comparison for one generation of selective breeding, but calculations in most cases assumed families of infinite number and size.

The additive variance maintained for a trait or index of several traits is subjected to selection is one of the great measure of genetic diversity, while the effective population size is a measure of the overall diversity [50]. The effective population size is expressed as status number that can be seen as the number of unrelated, non-inbred genomes in the assessed population at a specific moment, thus the genetic status of that population [52]. In breeding this is a measure for the genetic variability, which is randomly subjected to the breeding efforts and represents the overall genetic variability [52]. Each source of information is assigned a weighting coefficient whose value depends on

- Heritability of the trait (h^2)
- Coefficient of relationship among family members (R)

- Phenotypic correlation among family members (t) and
- Family size (n).

The individual's own performance and the average performance of the family are commonly used sources of information for estimating the breeding value of the individual using combined selection [49]. The breeding value of the individual is estimated using the following equation:

E.B.V. = $P + b_1 (P_1 - P) + b_2$ (Family Av.- P)

Where, P = population average

b_1= weighing coefficient for the individuals own performance

b_2= weighing coefficient for the family average

The b_1 and b_2 are calculated by using the following formula

$b_1 = h^2 \frac{1-R}{1-t}$ and $b_2 = h^2 \frac{1+(n-1)R}{1+(n-1)t}$

where, R= coefficient of relationship among family members (R=0.5 for full-sib family and R=0.25 for half-sib family)

t=phenotypic correlation among family members (t=R h^2)

n=number of family members (family size)

5.2.3.2. Individual selection by combining all sorts of relatives

There are situations when information from the individual, its parents, FS, HS etc. are available and the characters such as sex limited traits which cannot be measured on the individual [15]. The individual can be selected to combine all information with an index. This involves the matrix method and takes the form of a multiple regression of B.V. on all the sources of information [53]. The index so constructed is the best linear prediction of an individual's B.V [54]. The index can be represented as:

I = $b_1P_1 + b_2P_2 + b_3P_3+....+ b_nP_n$

Where b_1, b_2, ... b_n are the weighting factors whose values are to be estimated as there is maximum correlation between index and B.V (R_{IA}). P's are the phenotypic values of different selection criteria [47]. The maximization of R_{IA} means to minimize the sum of squared deviations of index value from linear regression of I and A like $\sum(I-A)2$. The b's values so obtained are the partial regression coefficients of individual's B.V [47]. The maximization leads to a set of simultaneous equations equal to the number of sources of information [44]. If the sources of information are three *viz*. the individual, the parents (dam) and paternal half sibs, then three simultaneous equations will be as follows

b1Vp1 + b2CovP12 + B3CovP13 =VA1

b1CovP21 + B2VP2 +b3CovP25 =Cov21

bCovP31 +b2 CovP32 + b3VP3 =CovA31

Where, I =Individual, 2=Parents and 3 =PHS

The b's can be estimated after putting the values of variances and covariances.

5.2.3.3. Family selection by combining within and between families

The family selection may be used to support individual selection when h^2 of a trait is low. It is better to select an individual with better record belonging to a superior family compared to an individual with similar performance belonging to a mediocre or inferior family [21, 49]. Considering the family mean and within family deviation of the phenotypic value of an individual it is obvious that the phenotypic value of an individual (P) is composed of two parts *viz*. P_f which is the deviation of its family mean from the population mean and Pw which is the deviation of the individual from the family mean called as the within family

deviation [21, 49]. Thus,

P = $P_f + P_w$

The weight given to these two parts decides the procedure of selection. When equal weight is given to both the parts it is known as individual selection [55]. When family mean is considered as a basis of selection giving no weight to the within family deviation (Pw), it is known as family selection whereas the selection, on the basis of the within family deviation (Pw) along giving no weight to the family mean (P_f), is known as within family selection and the best individual from each family is selected [53]. Lastly, when the two components (P_f and Pw) are given different weights, the selection is known as combined selection. The best estimate of an individual's breeding value on the basis of its phenotypic value is h^2P where h^2 is the regression of breeding value on phenotypic value. Gardner and Grafen [56] postulated that the two parts of the phenotypic value (P_f and Pw) which are uncorrelated and give independent information about the breeding value of an individual can be estimated from multiple regression equation as follows

E.B.V. = $h^2_f P_f + h^2_w P_w$

Where, the two heritabilities (h^2_f and h^2_w) are the weighting factors (partial regression coefficients of family mean and within family mean deviation). Now substituting the values of two heritabilities Sober [57] formulated the E.B.V. equation as follows

E.B.V. = $[(1-r)/(1-t)]*Pw + [(1+(n-1)r)/(1+(n-1)t]*Pf$.

After omitting the term h^2 which is common to both the weighing factors will not affect the relative weighing. Sorensen and Kennedy [58] proposed the following index of merit after rearrangement of the appropriate weighing factors and taking the individual values in place of within family deviations (which is more convenient) after assigning them a weight of 1 :

I = $P + [(r-1)/(1-r) \times n/(1+(n-1)t)]P_f$

Where, P is the value of the individual.

The expected response to this combined selection is generally 10-20% higher than individual selection, family selection and within family selection.

$R_c = i\delta_p h^2 \sqrt{1 + (r - t)2/(1 - t) X (n - 1)/(1 + (n - 1)t}$

The quantity under the under root is the combined efficiency of family average and individual mean.

5.3. Multilevel selection (MLS)

Presently, the interest for selection of animal has been rejuvenated towards the theory of multilevel selection [54, 56, 59]. From time being debate has been going on to whether or not selection can operate at multiple levels because of the confusion that arises due to the presence of weak individuals at the group levels but with respect to time the individual might show much stronger notion of adaptation at the different level [56, 60, 61]. Although, now the social evolution theorists had also widely accepted that a covariance between group trait and fitness may arise due to response to group selection in the natural environment. However, MLS theory continues to be beset by conceptual difficulties [62, 63]. Initially, obscurity developed over the precise meaning of group trait. Animal breeder has considered it as a simple 'aggregate' of the traits of the group's that is constituent by individuals, nevertheless some other scholars had imagination that group traits were often 'emergent' and might be undefined at the individual level [64, 65]. Secondly, a similar type of ambiguity arises over the actual concept of group fitness. Typically, it has been defined that the group with greater number of daughter individuals would considered as most fittest group,

however, an alternative approach clearly disagree the concept in the context of variable group size [57, 62, 66]. Lastly, there was a doubt regarding how to carry out the multilevel selection analysis, as multilevel selection 1 (MLS-1) was mostly responsible for describing the change in the frequencies of different types of individual and multilevel selection 2 (MLS-2) explained about the change in the frequencies of different types of groups [67, 68]. Moreover, MLS theory did not take care of the problems engaged with class structure, i.e., when different groups differ from others in terms of non-genetic reasons [5, 56, 59]. Many solution has been proposed by the scientists to solve the problem (i) the classes should consist of separate individuals, such that the only differences arises within classes were genetically [59]; (ii) the role of natural selection had been described separately for each classes [59]; and (iii) the overall value of natural selection was calculated as a sum of all classes, where each classes were given a weightage according its long-term genetic 'reproductive value' that contributes to its future generations [23, 69]. Simultaneously, if at all the natural selection was playing a divine role in driving the allele frequency change; it might not be responsible for all of these changes [70]. And so, to describe properly the action of natural selection in terms of genetical point of view, it is important to consider the alleles are neutral and remains unchanged till the end of time [70]. In order to determine the corresponding changes in the genetic frequencies under neutrality, it was subtracted from the actual allele frequency changes that occur in the real-world scenario in which natural selection is operating [71]. These developed class reproductive values explained well about the expected genetic contribution that each class contributes to the distant future in the neutral counterfactual scenario [61].

6. The Neutral Theory

The innovative animal models that describe about the dynamics of genetic variance of a population but having no effect on fitness are so called neutral models [18, 72]. Kimura [38] described the dynamics of neutral mutations in finite populations applying mathematical formulas based on particle physics concept. However, Kimura's postulate on neutral theory remain uncontested its applicability to data analysis was not understood properly until when it was discovered that enormous amounts of molecular genetic variation exit in both within and between species [73, 74]. The observed levels of variation was appeared inconsistent with animal models that described selective effects for all or most mutations known as the Neutral Theory that leads to the discovery of Molecular Evolution [19, 75, 76]. Regardless on the doubt for the validity of the Neutral Theory [39, 77], it has become the predominant framework for research in population genetics and molecular evolution for almost 40 years. Enormous complex models had been discovered to describe the expected patterns of variation within and between species [76]. That made the researchers to reveal that the evolutionary processes acting in nature because of single loci as well as due to all genes in a genome [78]. Actually, the neutral theory explained clearly about the theoretical information about the DNA variation and an array of statistical tools that distinguish natural selection from random genetic drift [79, 80]. According, to the first population genomic dataset, it was ensured that the central predictions of the neutral theory do not hold in natural populations [80]. So, for better understanding of neutral theory two points that taken into consideration were that the increasing amounts of data and their attendant predictions do not hold for the vast majority of genes and species [79].

6.1. Importance of direct selection on the Neutral Theory

Wilson and Wilson [60] explained about the importance of direct selection on the Neutral Theory that neither the vast majority of polymorphisms within species nor fixed differences between species had any effect on fitness. This did not mean that all possible mutations were neutral rather only the observed mutations were neutral [81]. Strongly deleterious variants were rarely segregating in populations with smaller chance of being fixed so, were not observed. Likewise, adaptive mutations might make up a small fraction of differences between species but were fixed so quickly that they were not sampled when polymorphic. Ohta and Kimura [82] discovered that approximately 8% on the proportion of advantageous substitutions consistent with the Neutral Theory. That synonymous changes in coding sequences or changes in non-functioning non-coding sequences were neutral in nature claimed by Akashi [83] and Resch et al. [81] independently. But, still disagreement continues around the neutrality of mutations that whether it had the capacity to change the phenotype or not [81]. The direct selection claim of the Neutral Theory was also one of the most misunderstood ideas in molecular evolution, as the term "neutral" was always conflated with "unconstrained" as argued by Kimura [77]. The Direct Selection claimed that it provides the fundamental foundation for many tests of selection, against such instances of selection could be evaluated by providing the null neutral hypothesis [81]. The most direct tests of this claim were carried out by comparing the number and frequency of functionally relevant mutations either by coding or regulatory to those which had no effect on function [84]. Polymorphism and divergence data from these classes of sequences could be combined in the McDonald–Kreitman (MK) test [84]. Smith and Eyre-Walker [85] predicted that the neutral model was obtained by the ratio of functional and non-functional polymorphisms (e.g., non-synonymous: synonymous) would be equal to the same ratio among fixed differences. The MK test on hundreds of genes in *Drosophila melanogaster* and *D. simulans* had concluded that anywhere between 30% and 94% of all amino acid substitutions were fixed by adaptive natural selection [85, 86, 87]. Similar studies on the untranslated and regulatory regions upstream of Drosophila genes revealed estimates of adaptive divergence [88, 89, 90], as such studies had been carried out on protein-coding genes in *Escherichia coli* [91]. However, an alternative result was found in both humans and *Arabidopsis thaliana* that an excess of non-synonymous polymorphisms consistent with the non-neutral evolution of segregating variation [92, 93]. As both humans and *A. thaliana* had much smaller population sizes than either Drosophila or *E. coli*, it was believed that the observed excess of variation was largely due to mildly deleterious mutations that were not purged from small populations, however, do not contribute to interspecific divergence [93]. Alternative methods that compare the allele frequencies of non-synonymous polymorphisms and synonymous polymorphisms were always in consistent with a large amount of segregating deleterious polymorphism in both humans and Arabidopsis [94, 95, 96]. It should also be noted that even though the MK test was relatively powerful compared to other tests of molecular evolution, it was still very conservative and likely to misses a large proportion of non-neutral evolution [83]. It might even more conservative if non-synonymous polymorphisms were actually leads to advantageous mutations on their way to fixation [95].

6.2. Importance of linked selection on the Neutral Theory

The linked selection claim of the Neutral Theory explained that the linked selection does not affect a vast majority of loci;

thereby the variation in nature leads to the predictions of neutral models [92]. Population genetics theory provides quantitative explanation of the level and frequencies of polymorphisms under neutrality [92]. However, if selection acts on even a small fraction of mutations, patterns of variation at linked loci would be affected as neutral polymorphisms were dragged along with selected individuals [92]. The effect of selection on mutations linked to neutral polymorphisms, whether advantageous [97] or deleterious [98]. It was believe that the selection on mutation was to lower the level of variation and skew the frequency spectrum of mutations relative to neutral expectations. An alternative way to state this claim was that most loci were expected to be at mutation i.e., drift equilibrium where the number of mutations entering a population was equal to the number being lost due to drift although recent changes in population size might disturb this equilibrium [97]. This means that if either the population size or the mutation rate goes up that leads to increase in the amount of variation within a species and vice versa [99]. Likewise, when all mutations were neutral the average number of nucleotide differences measured between two sequences from different species denoted by the time back to the ancestor of the two sequences and mutations could occur on both lineages. The average number of nucleotide differences was unaffected by population size [19] and was determined solely by the amount of time that had elapsed the mutation rate which also affects the level of polymorphism [97]. In addition, it had been shown theoretically that linked selection does not affect the level of neutral divergence [100], although the selected mutation itself obviously contributes to the number of differences between species. Because the number of differences between single representative sequences from two different species includes both the fixed substitutions that had accumulated and the derived polymorphisms present in those individual samples, it was common to use a corrected distance that represents only fixed divergence [99].

7. Genomic selection

Traditionally, the method of prediction of breeding values for genetic improvement of livestock using information on phenotypes and pedigrees has been a great success story [18]. But predicting the breeding values by using the information on variation in DNA sequence between animals is much more accurate than traditional method Meuwissen et al. [101]. That leads to discovery of new selection method known as Marker Assisted Selection (MAS). Dekkers, [102] found that research on marker assisted selection (MAS) was very extensive with very little increase in genetic gain and limited implementation. Goddard and Hayes [103] showed that the factors governing the additional gains from MAS were the accuracy of the existing estimated breeding values (EBV). If at all, the accuracy was high, there would be little gain. It was observed for the traits where traditional selection process was facing most difficulties for example the traits that only displayed in females [103]. Dekkers [102] illustrated that economic traits were influenced by polygene, so that, tracking a small sequence of these through DNA markers would only be explained by a small proportion of the genetic variance. Moreover, individual genes had little effect on particular economic traits and so a large amount of data was required to accurately predict their effects [102]. This problem could be solved if a haplotype of markers was used to track QTL. So, the foremost important point was to estimate as many as haplotype effects according to Meuwissen et al. [101]. When it was in linkage equilibrium (LD), the MAS markers used to

link the QTL [102]. If the marker was in linkage equilibrium with the QTL and all QTL alleles in founder animals were considered to be different, then to estimate the effect, the number of QTL alleles had to be further increased. Despite all these difficulties, Boichard et al. [104] described the method to achieve the maximum genetic gain by a very large amount of genotyping data. To overcome these difficulties, Meuwissen et al. [101] proposed a variant of MAS that they called genomic selection. The key features of the new method were that markers covering the whole genome were used [104]. So that, potentially all the genetic variance was explained by the markers and the markers were assumed to be in LD with the QTL thereby, the number of effects per QTL to be estimated was found to be very small [104]. Using simulation, they showed that the breeding value could be predicted with an accuracy of 0.85 from marker data alone [104]. The major limitation to the implementation of genomic selection had been the large number of markers required and the cost of genotyping these markers [105]. Recently, both these limitations have been overcome in most livestock species following the sequencing of the livestock genomes along with the subsequent availability of hundreds of thousands of single nucleotide polymorphisms (SNP). As a result of these developments, there were many livestock breeding companies planning to implement genomic selection in the near future predicted by Grapes et al. [105]. Statistical analysis to calculate EBV from genome-wide DNA markers it was convenient to think of the process in three steps [104]:

- Use the markers to deduce the genotype of each animal at each QTL.
- Estimate the effects of each QTL genotype on the trait.
- Sum all the QTL effects for selection candidates to obtain their genomic EBV (GEBV).

As the markers were unlikely to be evenly spaced, and due to the variable nature of the LD, still, it could not expect that all QTL would had an SNP in complete LD with them. This suggested that there was an immediate need of denser markers than were currently available. The technology to solve the problem was achieved by Parkes et al. [106]. An additional problem arises if the researcher wished to estimate the effect of each marker across more than one breed. Then, it required not only high correlation in each breed but the same linkage phase between the marker and the QTL in each breed. Goddard et al. [107] found that this occurred between Angus and Holstein cattle only for markers <10 kb apart. An alternative to using single marker genotypes was to construct haplotype based on several markers. A QTL that was not in complete LD with any individual marker might be in complete LD with a multimarker haplotype [105]. Using 9323 SNP genotypes from Angus cattle, and considering a randomly chosen SNP as a surrogate for a QTL, Hayes et al. [108] found that the proportion of variance explained by a haplotype of the surrounding markers increased from 0.2 for the nearest marker to 0.58 for a six marker haplotype. The use of multiple marker genotypes but without deducing haplotypes, e.g. with multiple marker regression, would be in between these two extremes [109]. However, Hayes et al. [110] and Grapes et al. [111] independently ensured that the increase in QTL variance explained from using marker haplotype more than compensated for the decrease in accuracy of estimating a greater number of haplotype effects, so that haplotype predicted the effect of the QTL alleles more accurately than a single marker [105]. As the total number of animals with phenotypes and marker genotypes increases, the accuracy of estimating marker genotype effects would approach 1.0 and

so, the accuracy of estimating the haplotype effects [105]. However, the accuracy for the haplotype would approach 1.0 more slowly than the accuracy of estimating SNP effects because there were more than two haplotype effects per QTL to be estimated [106]. Therefore, the advantage of the haplotype over single markers was expected to increase as the amount of data for estimation increases, especially at lower marker densities [110]. The linkage analysis and the LD analysis could be combined to estimate a matrix of IBD probabilities between all QTL alleles and this could be used to estimate the effects of all QTL alleles [111]. Calus *et al*. [112] demonstrated in this situation, that the IBD approach performed better than the haplotype approach, which in turn performed better than the single marker approach.

8. Conclusion
Selection will be based on a prediction equation derived from a reference population that has extensive phenotypic recording and genotype data. For an optimal selection procedure over many generations, a combination of methods, from generation to generation, might prove feasible. For combined objectives, compromising between desired genetic improvement and preservation of genetic diversity, phenotypic selection was proven to be an acceptable option for one generation breeding by introducing animal model. The initial implementation of animal models centered on prediction of additive genetic values to carry out selection decisions, but it has become common practice to plot averages of these predicted additive genetic values across time as estimates of genetic trend by different types of model. Univariate animal model estimates of correlated responses are often biased. An adequate mixed-model analysis of correlated changes requires a multivariate approach, in which genetic and environmental variances and covariances, and additive genetic values, are estimated simultaneously. Considering the purpose of simultaneous selection, we found that the selection index was more consistent both in the indication of the best progenies and in the identification of potential genotypes to form the next breeding generation. The comparison of different selection indices is only possible through their application and their comparison via the calculated criteria is only theoretical and these indices only evaluate the expected values. However, in the long term it was believed that models for estimation of breeding values and genetic values will be based entirely on DNA markers obtained from genotyping the animal or inferred from other animals. The hope is that, because this method will track all the genetic variance, it will yield accurate EBV even without phenotypic measurements on the selection candidates.

9. Acknowledgment

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