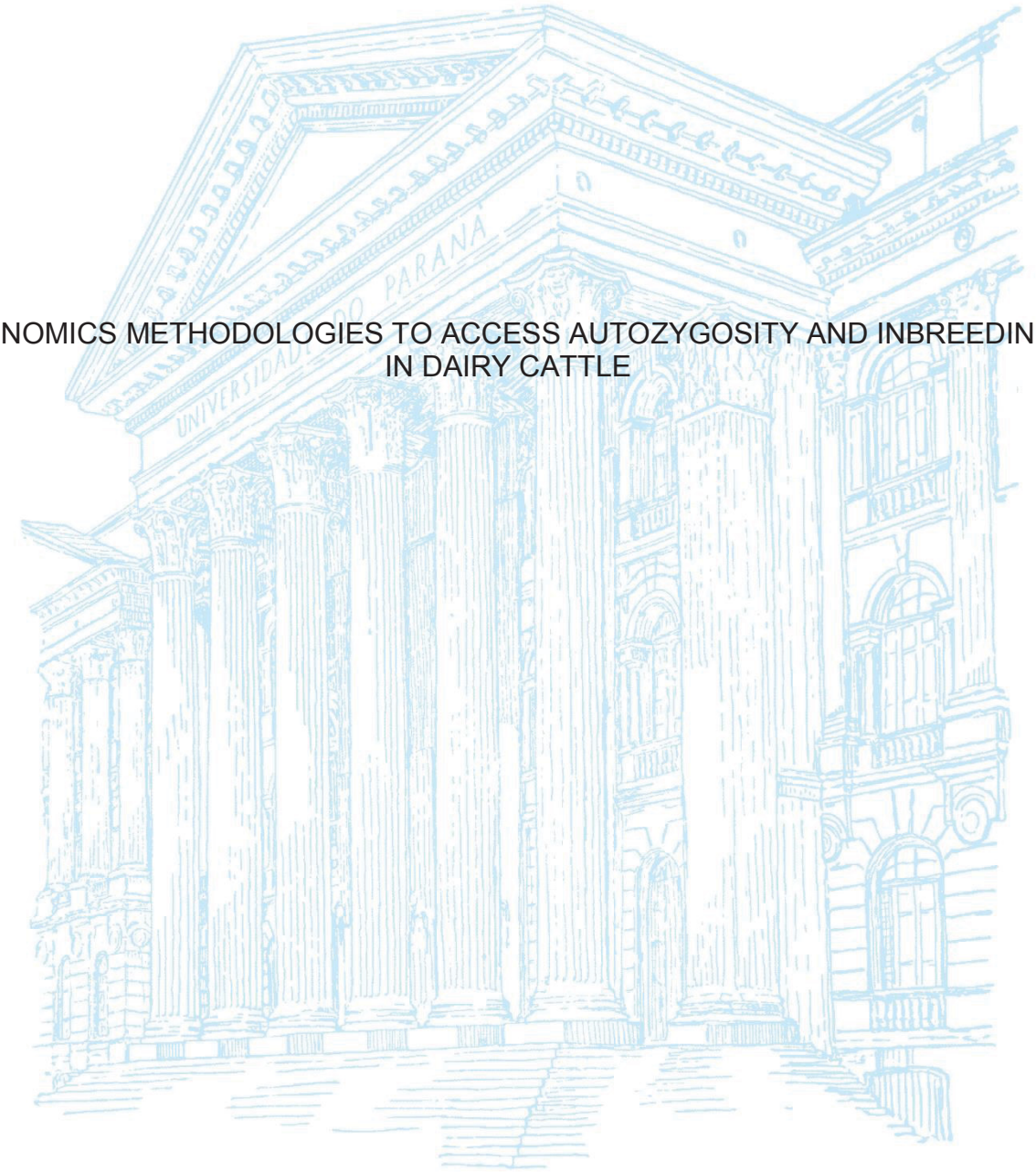
UNIVERSIDADE FEDERAL DO PARANÁ

FRANCISCO ROSA

GENOMICS METHODOLOGIES TO ACCESS AUTOZYGOSITY AND INBREEDING IN DAIRY CATTLE



CURITIBA

2019

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GENOMICS METHODOLOGIES TO ACCESS AUTOZYGOSITY AND INBREEDING IN DAIRY CATTLE

Tese apresentada como requisito parcial à obtenção do grau de Doutor em Zootecnia, no Curso de Pós-Graduação em Zootecnia, Setor de Ciências Agrárias, da Universidade Federal do Paraná.

Orientador: Dr. Rodrigo de Almeida Teixeira

Coorientador: Dr. Roberto Carvalheiro

CURITIBA

2019

R788g

Rosa, Francisco
Genomics methodologies to access autozygosity and inbreeding in dairy cattle / Francisco Rosa. - Curitiba, 2019.
73 p.: il.

Tese (Doutorado) - Universidade Federal do Paraná. Setor de Ciências Agrárias, Programa de Pós-Graduação em Zootecnia.
Orientador: Rodrigo de Almeida Teixeira
Coorientador: Roberto Carvalheiro

1. Holandês (Bovino) - Reprodução. 2. Bovino de leite - Raças. 3. Melhoramento genético. 4. Endogamia. I. Teixeira, Rodrigo de Almeida. II. Carvalheiro, Roberto. III. Título. IV. Universidade Federal do Paraná.

CDU 636.235

Sistema de Bibliotecas/UFPR, Biblioteca de Ciências Agrárias, Douglas Alex Jankoski – CRB 9/1167

MINISTÉRIO DA EDUCAÇÃO
SETOR SETOR DE CIENCIAS AGRARIAS
UNIVERSIDADE FEDERAL DO PARANÁ
PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
PROGRAMA DE PÓS-GRADUAÇÃO ZOOTECNIA - 40001016082P0

TERMO DE APROVAÇÃO

Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em ZOOTECNIA da Universidade Federal do Paraná foram convocados para realizar a arguição da tese de Doutorado de **FRANCISCO ROSA** intitulada: **Genomics methodologies to access autozygosity and inbreeding in dairy cattle**, após terem inquirido o aluno e realizado a avaliação do trabalho, são de parecer pela sua aprovação no rito de defesa.

A outorga do título de doutor está sujeita à homologação pelo colegiado, ao atendimento de todas as indicações e correções solicitadas pela banca e ao pleno atendimento das demandas regimentais do Programa de Pós-Graduação.

CURITIBA, 22 de Fevereiro de 2019.

RODRIGO DE ALMEIDA TEIXEIRA
Presidente da Banca Examinadora (UFPR)

MARSON BRUCK WARRECHOWSKI
Avaliador Interno (UFPR)

ADRIANA LUIZA SOMAVILLA
Avaliador Externo (PE)

LENIRA EL FARO ZADRA
Avaliador Externo (IZ/APTA)

Dedico esta tese à minha mãe, Maria Gorete, por todo seu apoio e amor incondicional.

Agradecimentos

À minha família, que mesmo distante, sempre esteve presente com todo o apoio, carinho e compreensão.

Ao meu orientador, Prof. Dr. Rodrigo de Almeida Teixeira, pela oportunidade, apoio, confiança, e acolhimento das minhas ideias e planos durante essa jornada. Pela atenção e paciência, quando estava em alguns momentos perdido, mas então percebia que estava sempre muito bem orientado.

À Profa. Dra. Laila Talarico Dias, pelo acolhimento no Gama. Com sua atenção, elegância, carinho, e cuidado, sempre manteve e mantém a união de todos os membros da família Gama. Como membro da banca de qualificação e comissão de acompanhamento, pelos apontamentos, conselhos e palavras de apoio.

Ao meu coorientador, Prof. Dr. Roberto Carvalheiro, pelos apontamentos e indicações importantes para a redação da tese.

Aos meus amigos do Gama, por toda a atenção e carinho. Foram vários momentos compartilhando ideias, planos, angústias e dúvidas. Porém, também momentos de descontração, em viagens, churrascos e café com bolo. Tudo isso contribuiu significativamente para o sucesso dessa jornada.

Ao Prof. Dr. Marson Bruck Warpechowski, por todos os apontamentos e conselhos feitos como membro da banca de qualificação, e comissão de acompanhamento.

Aos meus amigos, pelos momentos de descontração, atenção, apoio e carinho. Em especial por compreender a minha ausência, quando precisei lidar com a dupla jornada de trabalho e estudo, e me isolar.

Aos membros da banca de defesa, por todos os apontamentos e sugestões feitas a este trabalho.

"…Understand well as I may, my comprehension can only be an infinitesimal fraction of all I want to understand..." Ada Lovelace

"…I am among those who think that science has great beauty…. Have no fear of perfection; you'll never reach it…." Marie Curie

"…Science, for me, gives a partial explanation for life. In so far as it goes, it is based on fact, experience and experiment..." Rosalind Franklin

"…No matter who you are, no matter what you did, no matter where you've come from, you can always change, become a better version of yourself…" Madonna

RESUMO

Para alcançar a demanda crescente de produtos de origem animal a cadeia de produção de leite tem mudado constantemente nos últimos 20 anos. Por exemplo, o melhoramento genético de bovinos de leite tem aumentado o ganho genético de inúmeras características de qualidade e produtividade. Porém, o intenso uso de um pequeno número de reprodutores e a inseminação artificial nos programas de melhoramento genético tem aumentado também o nível de endogamia dessas populações. Altos índices de endogamia têm sido relacionados com a redução no desempenho produtivo e reprodutivo. Atualmente, em bovinos da raça Holandesa, é praticamente impossível encontrar animais sem algum nível de endogamia. O interesse em estimar coeficientes de endogamia com informação genômica apareceu com o advento da tecnologia de genotipagem utilizando milhares de marcadores. Por exemplo, tem sido aplicada em bovinos de leite a estimativa de endogamia através das corridas de homozigose (ROH). Portanto, o objetivo deste estudo foi avaliar o efeito da seleção com o acasalamento preferencial positivo sobre a depressão endogâmica em diferentes populações simuladas de bovinos leiteiros, diferentes em desequilíbrio de ligação (LD). Além disso, esta tese avaliou o uso de dados genômicos simulados para investigar muitos aspectos e cenários de endogamia e autozigose em populações de bovinos de leite. Portanto, o objetivo também foi em avaliar a habilidade do método da janela de SNPs e do método de SNPs consecutivos para determinação de ROH e o seu acesso à autozigosidade e ao coeficiente de endogamia genômica em populações simuladas de bovinos taurinos e indianos. A avaliação foi aplicada em populações simuladas de bovinos leiteiros diferentes em níveis de desequilíbrio de ligação (LD). Utilizando o software QMSim, as populações foram simuladas pelo processo forward-in-time. Os parâmetros foram escolhidos para gerar populações com características similares às raças leiteiras taurinas e zebuínas. Foram simulados 93 QTLs relacionados à produção de leite, e aleatoriamente distribuídos em 29 autossomos de *Bos taurus*. Para criar alto e baixo desequilíbrio de ligação foi realizado um afunilamento na população histórica, 1.020 ou 2.020 gerações foram simuladas iniciando com um tamanho efetivo de 1.000 e terminando com 200 animais no final do ciclo. Para fundar 20 gerações em 5 cenários diferentes para cada nível de desequilíbrio de ligação, as populações foram simuladas com diferentes sistemas de acasalamento e critérios de seleção. A seleção foi feita baseada nos valores genéticos estimados pelo método BLUP ou pelo valor genético verdadeiro estimado com o efeito dos QTLs. A média de endogamia de cada geração foi estimada pelo próprio QMSim e associado com o nível de depressão endogâmica para produção de leite encontrado na literatura. Da última geração da população histórica, para gerar o genótipo para a seleção, foram aleatoriamente selecionados 50.000 marcadores da população (MAF ≥ 0,02), estes dados imitam os painéis utilizados comumente para genotipar bovinos. As corridas de homozigose foram obtidas por duas diferentes metodologias do pacote detecRUNS do programa R para 1.000 animais nas gerações 1, 5, 10, 15 e 20. O primeiro, o método das janelas consecutivas de SNPs, escaneia cada SNP ao longo do genótipo de cada animal para a detecção de segmentos em homozigose de acordo com um tamanho de corridas de homozigose e um número mínimo de SNPs em homozigose. O segundo, o método consecutivo, não utiliza as janelas para evitar a determinação de falsos ROH, menores que a janela. O coeficiente de endogamia baseado nas corridas de homozigose (F_{ROH}) é definido como a proporção de corridas de homozigose em relação ao genoma total

do indivíduo. Os níveis mais altos de endogamia foram obtidos nos cenários com acasalamento preferencial positivo, e variaram de 0,2 a 0,36 na vigésima geração de seleção. O uso intenso de um pequeno número de touros em vinte gerações de seleção poderia causar perda entre 6,98 e 7,20% na produção de leite nos piores cenários. Em geral, para os cenários imitando o acasalamento dirigido, e minimizando a endogamia, o aumento no nível médio de endogamia de ~3% e ~8% diminui ~0,6 e ~1,8% a produção de leite aos 305 dias respectivamente. A seleção intensa para uma característica pode incrementar rapidamente os níveis do coeficiente de endogamia para valores críticos em populações com baixo e alto desequilíbrio de ligação inicial. Sistemas de acasalamento dirigido podem ser aplicados para a manutenção de baixos níveis de endogamia e consequentemente controlar a depressão endogâmica. Em geral, o maior número de corridas de homozigose nas gerações de 1 a 20 estão na classe com comprimento variando entre 1-2 Mb. A porcentagem de corridas de homozigose diminuíram com o passar das gerações para a classe 1-2 Mb de comprimento. No entanto, a porcentagem de corridas de homozigose aumentou da primeira para a vigésima geração na classe > 8 Mb nas diferentes populações e metodologias utilizadas para a detecção de ROH. A média do comprimento de ROH na classe 1-2 Mb é maior para populações taurinas comparadas às populações indianas. No entanto, para a classe > 8 Mb, a população indiana geralmente possui um média maior no comprimento da corrida de homozigose. O coeficiente de endogamia baseado no pedigree (F_{PED}) aumentou ao longo das 20 gerações simuladas para as populações taurinas e indianas. Porém, os coeficientes de endogamia genômicos baseados nas corridas de homozigose (F_{ROH}), detectados pelas diferentes metodologias, são diferentes entre as populações taurinas e indianas. Estes resultados sugerem que F_{ROH} calculado a partir das corridas de homozigose, obtidas em ambas metodologias, é capaz de acessar a autozigosidade muito antiga. A detecção de corridas de homozigose, pelo método das janelas ou dos SNPs consecutivos, são metodologias importantes para acessar endogamia recente ou mais antiga. A estimativa de endogamia genômica baseada nas corridas de homozigose é capaz de demonstrar eventos evolutivos que diferenciam algumas raças de bovinos.

Palavras-chave: Holandesa, Ligação, Desequilíbrio, QMSim, Simulação, Seleção, ROH, Homozigosidade, SNP.

ABSTRACT

To achieve the livestock products demand, the milk productive chain has been changed constantly over the last 20 years. For instance, dairy cattle's breeding has been improving many milk quality and productivity traits. But, the heavy use of a small number of sires and the artificial insemination practice on breeding programs has been increasing the dairy cattle inbreeding. Besides that, these high levels have been related to reduced fitness and reproductive performance. In Holstein dairy cattle it is almost impossible to find individuals without some level of inbreeding. The interest to estimate inbreeding coefficients with genomic information appears with the advent of high throughput genotyping technologies. For instance, was applied in dairy cattle the estimation of inbreeding coefficient with runs of homozygosity (ROH). Therefore, the aim of this study was to evaluate the effect of selection with assortative positive mating on inbreeding depression considering simulated dairy cattle populations distinguished by linkage disequilibrium (LD). In addition, this thesis evaluated the use of genomic simulated data to investigate many aspects and scenarios of inbreeding and autozygosity under dairy cattle populations. Thus, also the aim of was to evaluate the ability of sliding and consecutive ROH approach to detect and express autozygosity and genomic inbreeding coefficient (F_{ROH}) in taurine and indicine simulated populations with twenty generations of assortative positive mating. The evaluation was applied in dairy cattle populations distinguished by linkage disequilibrium (LD). Using the QMSim software, the populations were simulated based on forward-in-time process. The parameters were chosen to try and generate a population with similar characteristics of taurine and indicine dairy cattle. Were simulated 93 milk yield QTLs randomly distributed on 29 autosomal chromosomes of *Bos taurus.* To create a high and low level of initial linkage disequilibrium were made a bottleneck in the historical population, 1,020 or 2,020 generations were simulated starting from an effective population of 1,000 to 200 animals at the end of the cycle. To found 20 generations of five different scenarios for each level of LD, the populations were simulated with a different mating system and selection criteria. The selection was based on breeding values estimated with BLUP method or, the true breeding value estimated with the effect of QTLs. Each generation inbreeding mean was estimated by QMSim and associated with the level of inbreeding depression of milk yield found in the literature. From the last generation of the historical population, to generate genotypic data for the selection, the individuals were randomly selected with a total of 50,000 markers (MAF ≥ 0.02), these data mimicked the commonly SNP panel used to genotype cattle. The runs of homozygosity were obtained by two different methodologies in the detectRUNS package of R software for 1,000 individuals of generations 1, 5, 10, 15, and 20. At first, the sliding window method scans along everyone's genotype, at each SNP marker position, for detection of homozygous segments with a specified length or number of homozygous SNPs. At second, the consecutive method does not use the sliding windows to avoid the introduction of artificial ROH that are shorter than the window. Inbreeding coefficient based on ROH (F_{ROH}) is a genomic portion of individual autozygosity and defined it as the proportion of the autosomal genome lying in ROH of certain minimal length relative to the overall genome in interest. The highest inbreeding levels, varying from 0.2 to 0.36, in the twentieth generation were obtained for positive assortative mating systems. The intense use of a few numbers of sires in twenty generations of selection may cause a loss between 6.98 and 7.20% on milk yield in the worst scenarios. In general, for minimizing inbreeding scenarios, the average level

inbreeding increasing of ~3 and ~8% in the twenty generations of selection decreases ~0.6 and ~1.8% the milk yield at 305 days respectively. The intensive selection for one trait could rapidly increase the average inbreeding coefficient on critical levels in populations with high and low initial LD. Non-random mating systems must be applied to control inbreeding levels and consequently inbreeding depression. In general, the class of 1-2 Mb length size has the highest number of ROH across all evaluations on generations 1, 5, 10 and 20. The percentage of ROH class 1-2 Mb decreases from generation 1 to 20. Nevertheless, the percentage of ROH class >8 increase across the twenty generations of selection in the distinguished populations and ROH detection methodologies. The mean ROH length in the class 1-2 Mb is higher for taurine than to indicine simulated population. Otherwise, for the class >8 Mb the indicine generally has higher mean ROH length. The inbreeding coefficient level based on pedigree (F_{PED}) increases across the twenty simulated generations for taurine and indicine populations. But, genomic inbreeding coefficients based on ROH detected by sliding approach (F_{ROHs}) and ROH detected with the consecutive approach (F_{ROHc}) are different among these two populations. These results suggest that F_{ROH} from both methods to access ROH can detect ancient and recent autozygosity. Genomic inbreeding estimates based on ROH segments can represent and evolutionary events which distinguish some breeds.

Key-words: Holstein, Linkage, Disequilibrium, QMSim, Simulation, Selection, ROH, homozygosity, SNP

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LIST OF ABBREVIATIONS

~ = Approximately

BLUP = Best linear unbiased predictor

EBV = Estimated breeding value

cM = Centimorgan

F_{PED} = Inbreeding coefficient based on pedigree

F_{ROH} = Inbreeding coefficient based on runs of homozygosity

F_{ROHc} = Inbreeding coefficient based on runs of homozygosity – consecutive approach

F_{ROHs} = Inbreeding coefficient based on runs of homozygosity – sliding window approach

GWAS = Genomic-wide association studies

GS = Genomic selection

HLD = High linkage disequilibrium

IBD = Identical by descent

IBS = Identical by state

LD = Linkage disequilibrium

LLD = Low linkage disequilibrium

Mb = Mega pair of bases

MAF = Minor allele frequency

Ne = Effective population size

QTL = Quantitative trait loci

ROH = Runs of homozygosity

SNP = Single nucleotide polymorphism

TBV = True breeding value

YBP = Years before present

SUMMARY

CHAPTER 01. GENERAL THESIS PRESENTATION

1.1 INTRODUCTION

This thesis is organized as follows: Chapter 1 introduces the concepts and shows a review of literature for animal breeding and genetics, since domestication to animal genomics. Chapter 2 shows the paper about the use of QMSim software for simulation of a dairy cattle data set and to evaluate the inbreeding after 20 generations over 10 different scenarios of population parameters. Also, in chapter 2 the results of runs of homozygosity and genomic inbreeding calculation using information of simulated high-density SNP panel.

It is expected demand growth of 70% of livestock products in 2050 (GEORGES; CHARLIER; HAYES, 2018). To achieve this demand, the milk productive chain has been changed constantly over the last 20 years. For instance, the dairy cattle's breeding has been improving, for years, many traits quality and productivity. Furthermore, the main strategy utilized to predict the genetic value of the animals is based on phenotypic and pedigree data. Because of genetics molecular techniques advance, it is possible nowadays to use genotype data in selection.

The sequencing bovine genome generated a big number of SNP (single nucleotide polymorphism) markers. In consequence, it is possible simultaneously to analyze a big loci group. Besides, economic quantitative traits are influenced by many genes. So, this technique increases the chance to identify genomic regions related to quantitative traits. The study with SNP dense panels for identifying genomic regions related to the expression of polygenic traits is called genomic-wide association studies (GWAS). In addition, the selection based on dense markers is called genomic selection (GS).

Currently, the application of GS incremented the genetic gain, because of the genomic evaluation decrease generation interval, with evaluation of animals before reproductive and productive age, and increasing accuracy. However, the spread of this genetic superiority with artificial insemination also promoted the increase of the relatedness among the animals of future generations. The similarity among individuals caused by common ascendance must be correlated with some genetic diseases and productivity loss. The main approach to study the effects of the relationship among

animals is the inbreeding coefficient based on pedigree data. This approach has been used to estimate and control the relatedness in many livestock species. However, the advent of SNP dense panels opened the possibility to investigate the autozygosity of an individual based on runs of homozygosity (ROH). ROH is the continuous stretches of homozygous genotypes without heterozygosity in diploid state. Furthermore, overall, homozygosity is the equal state of a pair of genes, each of them inherited from a parent. Although, autozygosity appears when two identical chromosomal stretches, inherited from each parent, are also inherited from a common ancestor. Thus, ROH has been described as a better indicator of similarity because express identical by descent in the genome and could explain the mechanisms of inbreeding depression in many livestock species.

Even though genotyping has been turning viable and widely applicable, the association studies and ROH determination with many markers are still costly. Nowadays there are many simulation software's well described and constantly improved in the literature. Thus, the population's simulation affords the low cost and fast verifies the effect of different genetic population scenarios for genomic methodologies efficiency. Thus, this thesis evaluated the use of genomic simulated data to investigate many aspects and scenarios of inbreeding and autozygosity under dairy cattle populations.

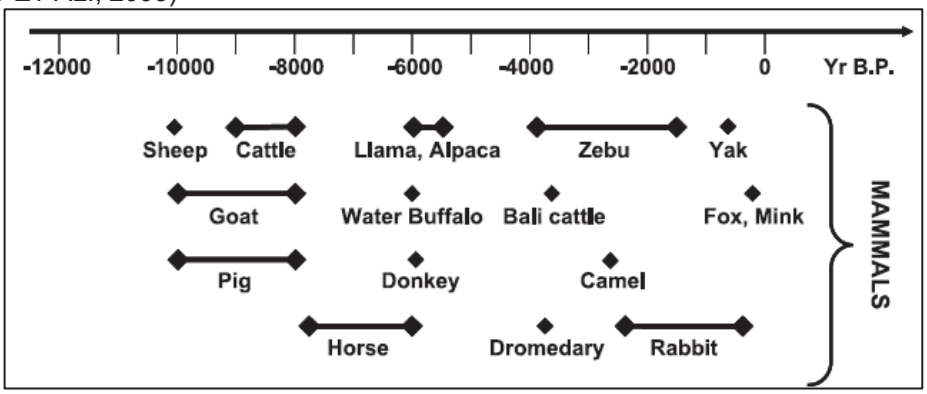
1.2. BIBLIOGRAPHY REVIEW

1.2.1 Animal Breeding, Since Domestication to Genomics

There are some reasons to say that animal breeding starts with the domestication of some livestock species thousands of years ago. Since inbreeding and genetic drift are some uncontrolled process involved in domestication, and, thus controlled process as natural and active selection (MIGNON-GRASTEAU et al., 2005). The domestication starts first with the dogs approximately 20,000 to 40,000 years ago (BOTIGUÉ et al., 2017). After that sheep, taurine cattle, zebu cattle, pigs were domesticated approximately 8,000 to 10,000 YBP (FIGURE 1). Although, other authors consider the work of Robert Bakewell (1725-1795) the start point for animal improvement practice. He was in charge of the breed development and evolution over

cattle, sheep, and horses. Moreover, his work initiated the breeds society formation and creation of herd books (PEREIRA, 2004).

FIGURE 1. DATING OF THE DOMESTICATION OF THE MAJOR LIVESTOCK SPECIES (MIGNON-GRASTEAU ET AL., 2005)



As science, the genetics heredity starts with Gregor Mendel's well-organized peas experiment (MENDEL, 1866). In the aim to elucidate de hybridization, he was successful in the choice of the species and its simple contrasting traits, which are controlled by one pair of genes. The results of his experiment were obscured until other four researchers from different European countries rediscovery and elucidate the laws of heredity in 1,900 (SIMUNEK; HOSSFELD; WISSEMANN, 2011). The English Francis Galton (1822-1911) worked extensively in the measurement of human characteristics and was the first to describe the relationship between statistics and heredity (GALTON, 1872).

The first half of the twenty century was developed the main theories used until nowadays in classical animal breeding. Firstly, in the aim to elucidate Darwin's evolutionary assumptions applying Mendelian approach, the population genetics concepts were introduced by Ronald Fisher and Sewall Wright (HODGE, 1992). Secondly, from 1930 decade, Wright pupil's Jay L. Lush extensively gave over genetics population assumptions to improve livestock (OLLIVIER, 2008). Finally, I.M. Lerner and E. R. Dempster, using poultry data, outlined the population and quantitative genetics knowledge and practice (HILL, 2014).

The further evolution of animal breeding was possible by the use of artificial insemination (AI) and computation development, which contributes to livestock traceability, fast identification, and superior genotypes spread (PEREIRA, 2004). From Edinburgh (Scotland), Rendel and Robertson, using progeny testing bulls data by AI

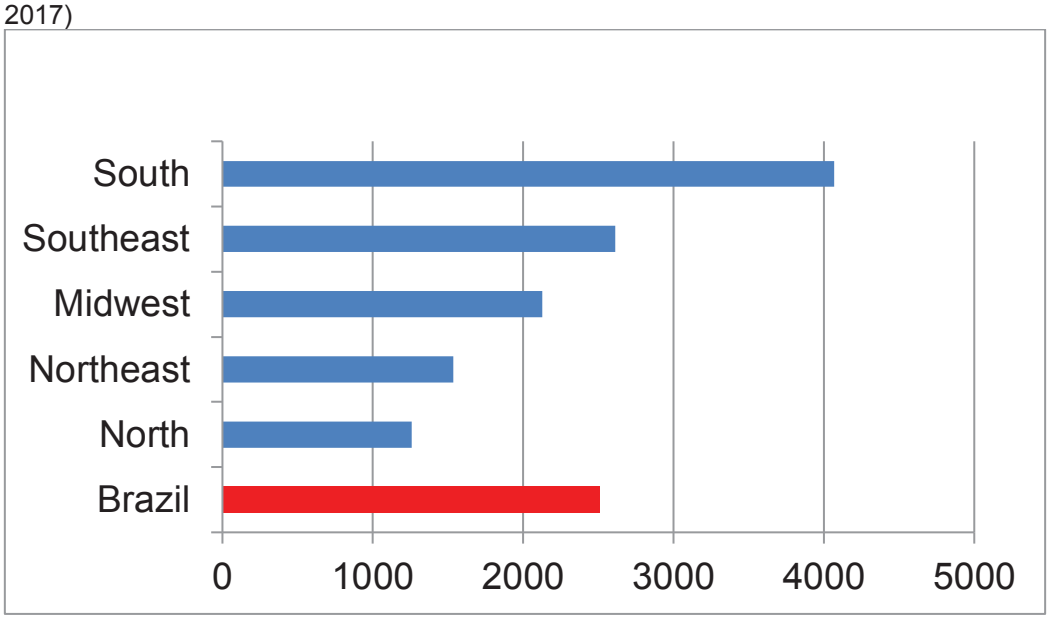
with daughters in many herds, provided a general formula for progress rates (ROBERTSON; RENDEL, 1950). In addition, the “contemporary comparison” method to evaluate sires in AI was developed by Robertson (HILL, 2014). Otherwise, recognizing “fixed and random” effects, which had to be included in the linear model, C. R. Henderson superseded Robertson’s method creating the best linear unbiased predictor (BLUP) (HENDERSON, 1984). These traditional methodologies have been arising considerable genetic gain in different livestock animals in the prediction of genetic value, consequently the recognition of superior genotypes.

Even though the genetic gain with classical animal improvement, the DNA molecule elucidation by Watson and Crick (WATSON; CRICK, 1953) opened up new possibilities in the genomics. In other words, select the animals without the phenotypic records, to locate the loci related to economic traits in the DNA with markers. Therefore, the main DNA markers surged in the 1980 decade with the polymerase chain reaction (PCR) technique (SAIKI et al., 1988). Vignal et al. (2002) classifies DNA markers according to the type of information provided: bi-allelic dominant, bi-allelic co-dominant and multi-allelic co-dominant. About them it is important to cite, RAPDs (random amplification of polymorphic DNA), AFLPs (amplified fragment length polymorphism), RFLPs (restriction fragment length polymorphism), SSCPs (single stranded conformation polymorphism) and microsatellites. Therefore, the revolution in molecular markers came after that with the use of a simple bi-allelic type of marker, the single nucleotide polymorphism (SNP). With these markers, some regions related to quantitative economic traits (QTLs) was discovered and was used to implement marker-assisted selection (MAS) (WILLIAMS, 2005). But the implementation of MAS is limited and the genetic gain was small (DEKKERS, 2004). Despite that, the proposal for utilization of markers covering the whole genome to predict genetic variance brings the new era called genomic selection (GS) (MEUWISSEN; HAYES; GODDARD, 2001). After that, the elucidation of the bovine genome (THE BOVINE HAPMAP CONSORTIUM, 2009), afford the production of SNP chips with millions of markers to extensively genotype dairy cattle. Thus, this genomic information and statistical approach opened the possibility of reducing generation interval, elevate accuracy, and accelerate genetic gain. Consequently, GS more than doubled genetic progress in some livestock species over the past 10 years (GEORGES; CHARLIER; HAYES, 2018).

1.2.2 Brazilian Dairy Cattle Breeding Overview

There is a big heterogeneity in dairy cattle production systems in Brazil, which is caused by differences in environment, livestock system, breeds and also information access to new technologies. For example, the national milk productivity has an average of 2,511 L/cow/year (FIGURE 2). Otherwise, in other technified regions, like Carambeí, Paraná state, the average is 10,278 liters/cow/year, level which is superior of other specialized countries (IBGE, 2017). Argentina, Uruguay and New Zealand produce an average of 3 to 6 thousand kg/cow/year (EMBRAPA, 2018). Furthermore, there is a tendency of decrease in the milk farm number, but at the same time an increase in milk herd in Brazil. Consequently, milk production and productivity are growing as to other countries (IFCN, 2018). It is estimated that 11,990,450 cows were milked in 2017 (IBGE, 2017). Although approximately 6,23% of these dairy cows have been inseminated, 69% of the semen is imported from the Holstein breed, and 31% is Brazilian from Girolando breed (EMBRAPA, 2018). The pure Holstein summarizes 10% of the Brazilian dairy herd and is the base of many crossbreeds (EMBRAPA, 2018). In addition, recently Parana Holstein Breeders Association (APCBRH) has been genetic evaluating dairy cows by selection index, under, for example, group body, milk yield, healthy, and fertility traits (APCBRH, 2017). Also, the Brazilian Agricultural Research Corporation (EMBRAPA) with the Brazilian Association of Holstein Breeders (ABCBRH) has been genetic evaluating Holstein sires since 2003. The most part of evaluated sires used in Brazil came with imported semen from the USA and Europe. Nevertheless, Girolando is another important breed which summarizes 50% of Brazilian dairy herd. Moreover, Girolando is a crossbreed with 5/8 Holstein and 3/8 Gir genetic composition (EMBRAPA; ABCG, 2018). Therefore, this diversity brings the rusticity of indicine with the productivity of taurine in the tropical environment of Brazil. The Girolando breeding program started in 1997 with a partnership between EMBRAPA and the Brazilian Girolando Breeders Association (ABCG) (VERNEQUE et al., 2010). After that the first test was published in 2009 with 32 sires, today the program has 127 sires tested. Consequently, was produced 579,438 semen doses in 2017 and it was observed an increase of 51,29% in milk yield at 305 days from 2000 until 2016 (EMBRAPA; ABCG, 2018).

FIGURE 2. YEAR COW MILK PRODUCTIVITY AVERAGE (L) PER REGION (ADAPTED FROM IBGE, 2017)



1.2.3 Linkage Disequilibrium (LD)

Linkage disequilibrium is a very important concept for genomics, it is influenced by evolutional forces and vary among species and breeds. Linkage disequilibrium is the non-random association among two alleles of two or more loci, not necessary in the same chromosome (FALCONER; MACKAY, 1996). The success of MAS depends on how close the marker and QTL are, in fact, depends on the LD between them. Furthermore, a trait is influenced by many loci in different chromosomes. On that way, when is applied a large number of molecular markers in the animal genome, it is increased the probability of linkage disequilibrium (LD) between markers and some genomic region of interest (HÄSTBACKA et al., 1994). This is the base of GWAS and GS success, which permitted the association of many genomic regions with economic traits and brings high accuracy and low generation interval respectively.

There are different causes which promote LD variation, and these can be measured in different ways. The causes that affect Hardy Weinberg equilibrium affect also LD, so they are, effective size, and events of migration, mutation, and selection (FALCONER; MACKAY, 1996). Moreover, to access the level of LD it is possible to use Lewontin's LD measure (*D'*) (LEWONTIN; JULY, 1964), standardized chi-square (X^2) (YAMAZAKI, 1977) or pooled square of the correlation between loci (r^2) (HILL;

ROBERTSON, 1968). Although, r^2 is the most appropriate measure for estimating LD among SNP markers because *D'* is strongly inflated compared with r^2 (ZHAO; NETTLETON; DEKKERS, 2007). In addition, standardized X^2 correspond to r^2 for biallelic markers (SARGOLZAEI et al., 2008). Therefore, to measure r^2 has used the equation below.

$$r^2 = \frac{D^2}{freq(A1)\ \ freq(A2)\ \ freq(B1)\ \ freq(B2)}$$

Where $freq\ (A1)$ is the population allele $A1$ frequency, the same way for the other alleles in the population and D is $freq(A1\mathrm{A}2) - freq\ (A1)freq(B1)$. Values of r^2 vary between 0, without linkage disequilibrium between loci, until 1 for total linkage disequilibrium between loci. If a marker is in LD with a genomic region of interest, some alleles of these markers will stay positively correlated with some region of interest in all populations (MEUWISSEN; HAYES; GODDARD, 2001). The LD patterns described became well detailed with the use of denser markers panels. Therefore the LD module decreases in function of the distance among markers and with the increase in recombination index between markers (BRITO et al., 2011). Furthermore, the ancestral population of indicine breeds was much larger than that from which taurine cattle were domesticated. Because, indicine breeds have lower r^2 values at short distances and intermediate r^2 values at longer distances (THE BOVINE HAPMAP CONSORTIUM, 2009). For instance, the LD (r^2) decreased from 0.34 for short distance to 0.11 for long distance for an indicine breed (Nelore) (ESPIGOLAN et al., 2013). Otherwise, in taurine cattle (Holstein) was observed a decrease from 0.58 for short distance to 0.08 for long distance (SARGOLZAEI et al., 2008).

1.2.4 Genotyping with Single Nucleotide Polymorphism (SNP)

The base of SNP markers is the elementary variation in the DNA molecule, in other words, a single nucleotide change. In addition, mutation is the main source of variation. Therefore, the punctual dissimilarity is considered SNP if it happens at least 1% of the population (KIRK et al., 2002). Normally, the SNP markers are bi-allelic,

which mean that there are just two different alleles in the same locus (VIGNAL et al., 2002). Moreover, the elucidation of bovine genome (THE BOVINE HAPMAP CONSORTIUM, 2009) afford the production of SNP panels with millions of SNP markers to extensively genotype dairy cattle (MATUKUMALLI et al., 2009). The genotyping with SNP panel cover the whole genome with markers. Consequently, it has been widely used in genetic livestock studies. For instance, to investigate DNA regions related with important quantitative traits (DAETWYLER et al., 2013; HÖGLUND et al., 2014), to predict genetic value with righter accuracy (ERBE et al., 2012; SU et al., 2012; WEIGEL et al., 2009), and to determine autozygosity based in runs of homozygosity (ROH) (HOWRIGAN; SIMONSON; KELLER, 2011; MCQUILLAN et al., 2008; PERIPOLLI et al., 2018; ZAVAREZ et al., 2015).

The density panel is one of the factors which influence genomic livestock studies. On average, higher density panels should lead to better genomic predictions, because they are in strong LD with loci related to quantitative traits (SU et al., 2012). Nowadays, has been used two SNP panel densities; the medium-density with approximately 54,000 markers or 54 K (MATUKUMALLI et al., 2009), and the high-density (HD) SNP chip with approximately 777,000 markers or 777 K (SU et al., 2012). Moreover, there is no significant impact to use HD panel on genomic selection, with a fewer increment on accuracy compared with 50 K panel (ERBE et al., 2012; SU et al., 2012; VANRADEN et al., 2013). Although, to access QTL in cattle it is necessary a panel density of at least 300,000 markers or 300 K (SU et al., 2012). In order to access autozygosity through ROH segments, 50 K panel is efficient to detect segments longer than 4 Mb and not sensitive for the precise determination of small segments compared with HD panel (FERENČAKOVIĆ; SÖLKNER; CURIK, 2013). Consequently, the 54 K panel may provide a satisfactory estimate of inbreeding for populations with high LD and recent inbreeding (MARRAS et al., 2013). Thus, the description of these biases is important to better predict and estimate genetic parameters.

1.2.5 Inbreeding coefficient

A mating by parents who have some ancestors in common is called inbreeding. Furthermore, it is the result of several different phenomena such as genetic drift, population bottleneck, the mating of close relatives, and natural and artificial selection

(FALCONER; MACKAY, 1996). Moreover, there is an increasing relatedness among bulls in AI service to improve economic traits (HUDSON; VAN VLECK, 1984). Thus, the increase in inbreeding must be caused by the adoption of an animal model for genetic evaluations. In addition, the reduced effective population size is the main cause of genetic diversity loss caused by genetic drift (STACHOWICZ et al., 2011). Also, the number of animals with low inbreeding increases when it is included unknown parent groups (WIGGANS; VANRADEN; ZUURBIER, 1995).

The Wright's work on the coefficient relationship (WRIGHT, 1917, 1921) was the base to the first determination of identical by descent concept (IBD) (MALÉCOT, 1948). Two DNA segments are IBD if they have been inherited from the same ancestral haplotype in a base population, in the absence of crossing over or mutation. But, if the two haplotypes are simple the same, independently of whether they are inherited from a recent ancestor they are identical by state (IBS) (POWELL; VISSCHER; GODDARD, 2010). The probability of two haplotypes at any locus randomly sampled between all loci in the genome is IBD is called inbreeding coefficient (F_{PED}) (MALÉCOT, 1948). Otherwise, the stochastic nature of inheritance resulted from a defined number of chromosomes and a small number of recombination events during meiosis is not considered by F_{PED} (CURIK; FERENČAKOVIĆ; SÖLKNER, 2014). Consequently, there is difficult to compare population inbreeding coefficient measured by averaging the coefficients of the individual pedigree. This occurs because the population pedigrees differ in depth of generation number. Therefore is necessary an adjustment to equate a different number of complete generations between populations (LEROY et al., 2013). Some coefficient inbreeding levels are presented in TABLE 1, which is possible to identify an increase of inbreeding average through generations of selection, and high inbreeding levels for bulls compared with cows.

The inbreeding does not affect gene (allele) frequencies, the genotype changes occur by increasing homozygosity at the cost of decreasing heterozygosity (FALCONER; MACKAY, 1996). This can impact to redistribution of the genetic variations within and among populations (FERNÁNDEZ; ANGEL TORO; LÓPEZ-FANJUL, 1995), reduction in the population fitness (ROKOUEI et al., 2010), the occurrence of homozygous recessive diseases (BENTON et al., 2018; BOSSE et al., 2018). In addition, some studies have been reporting an increase in the genome autozygosity as a consequence of genomic selection (DOEKES et al., 2018;

FORUTAN et al., 2018; KIM et al., 2015, 2013). Thus, the control of autozygosity and inbreeding is necessary for mating decisions (STACHOWICZ et al., 2011) including in genomic selection (DOEKES et al., 2018).

TABLE 1. AVERAGE OF POPULATION INBREEDING COEFFICIENT FOUND IN THE LITERATURE

Autor (year)	Year of birth	Breed	Country	Inbreeding Level
Wiggans et al. (1995)	1990	Holstein	EUA	0.026
Wiggans et al. (1995)	1990	Jersey	EUA	0.033
Queiroz et al. (2000)	1995	Gyr	Brazil	0.029 (cows)
Queiroz et al. (2000)	1995	Gyr	Brazil	0.031 (bulls)
Filho et al. (2010)	2001	Gyr	Brazil	0.028 (cows)
Filho et al. (2010)	2001	Gyr	Brazil	0.078 (bulls)
Rokouei et al. (2010)	2007	Holstein	Iran	0.044 (cows)
Rokouei et al. (2010)	2007	Holstein	Iran	0.052 (bulls)
Stachowicz et al.(2011)	1988	Holstein	Canada	0.022
Stachowicz et al.(2011)	1998	Holstein	Canada	0.048
Stachowicz et al.(2011)	2008	Holstein	Canada	0.060
Stachowicz et al.(2011)	1987	Jersey	Canada	0.030
Stachowicz et al.(2011)	1997	Jersey	Canada	0.040
Stachowicz et al.(2011)	2007	Jersey	Canada	0.055

1.2.6 Inbreeding Depression

The decrease in fitness and reproductive performance has been associated with inbreeding in Holstein cattle (BJELLAND et al., 2013; LEROY, 2014a). This reduction in fitness is defined as inbreeding depression (FALCONER; MACKAY, 1996). Moreover, inbreeding depression has been described for many dairy cattle traits (PANETTO et al., 2010; ROKOUEI et al., 2010; SMITH; CASSELL; PEARSON, 1998; WIGGANS; VANRADEN; ZUURBIER, 1995). TABLE 2 describes some values of inbreeding depression for milk yield in different base populations. In outcrossing species, the inbreeding depression is assessed by measuring the rate with the trait of interest decrease with the inbreeding coefficient (CHARLESWORTH; WILLIS, 2009). Moreover, the standard procedure in livestock species has been to consider a regression of individual performance on the individual pedigree inbreeding coefficient (CURIK; SÖLKNER; STIPIC, 2001).

Inbreeding depression occurs as a consequence of inbreeding association with carrying a large number of deleterious recessive mutations and/or the reduction in the frequency of superior heterozygotes (FALCONER; MACKAY, 1996). For livestock species, it is difficult to access the questions about the genetic basis of inbreeding for different reasons, as ethics and generation interval (LEROY, 2014b).

But, is described that traits with high dominance variance have the largest negative estimates of inbreeding depression (MISZTAL; LAWLOR; GENGLER, 1997).

TABLE 2. AVERAGE OF INBREEDING DEPRESSION (ID) FOR MILK YIELD IN THE FIRST LACTATION (KG/1% INBREEDING) IN DIFFERENTE POPULATIONS FOUND IN THE LITERATURE

Autor (year)	Breed	Country	Trait	ID
Wiggans et al. (1995)	Holstein	EUA	Milk Yield (kg)	-29.60
Wiggans et al. (1995)	Jersey	EUA	Milk Yield (kg)	-21.30
Smith et al. (1998)	Holstein	EUA	First Lactation Milk Yield (kg)	-18.74
Rokouei et al. (2010)	Holstein	Iran	First Lactation Milk Yield (kg)	-18.70
Rokouei et al. (2010)	Holstein	Iran	Third Lactation Milk Yield (kg)	-27,40

The interest to estimate inbreeding coefficients with genomic information appears with the advent of high throughput genotyping technologies (VANRADEN, 2008). Besides, the use of genomic data to determine loci related to inbreeding depression permits to differentiate animals which have the same inbreeding coefficient, but differ in the number of segments that when homozygous cause reduction in fitness (HOWARD et al., 2015). For instance, was applied in Holstein the estimation of inbreeding depression with runs of homozygosity (ROH), which described consistent results with what determined when using pedigree inbreeding (BJELLAND et al., 2013).

1.2.7 Runs of Homozygosity (ROH)

The continuous stretches of homozygous genotypes without heterozygosity in the diploid state is called runs of homozygosity (ROH) (FERENČAKOVIĆ; SÖLKNER; CURIK, 2013). Therefore, among many different mechanisms, inbreeding and LD are the fundamental causes of ROH (BROMAN; WEBER, 1999). Besides that, the runs of homozygosity length explain past evolutionary events. For example, extensive ROH is most likely the consequence of recent inbreeding, where recombination events do not shorten identical haplotypes inherited from a common ancestor. Short ROH, in contrast, propose the earliest inbreeding (FERENČAKOVIĆ; SÖLKNER; CURIK, 2013). Consequently, runs of homozygosity (ROH) has been used for access variability in livestock populations (BOSSE et al., 2012; EUSEBI et al., 2017; SIDLOVA et al., 2015; ZANELLA et al., 2016), to investigate deleterious alleles (SZPIECH et al., 2013), for studies with inbreeding depression (HOWARD et al., 2015; PRYCE et al., 2014; SAURA et al., 2015), and also for estimating genomic inbreeding coefficient

(FERENČAKOVIĆ; SÖLKNER; CURIK, 2013; FORUTAN et al., 2018; PERIPOLLI et al., 2018; ZAVAREZ et al., 2015). Moreover, ROH is considered the best genomic approach to estimate inbreeding, as it allows, different from others, to distinguish between IBD and IBS (HOWARD et al., 2015; KELLER; VISSCHER; GODDARD, 2011; MACLEOD et al., 2009). This occurs because pedigree-based inbreeding coefficients do not contemplate the difference in meiosis, inheritance of segments of chromosomes and LD (FERENČAKOVIĆ; SÖLKNER; CURIK, 2013).

There are different softwares with distinct approaches for detecting runs of homozygosity (ROH), the frequently software used is PLINK v1.07 (PURCELL et al., 2007). PLINK uses a sliding window method to determine an ROH as a DNA section including a minimum specified number of homozygous SNPs within a specified Kb distance (CURIK; FERENČAKOVIĆ; SÖLKNER, 2014). The density of the SNP panel used to determine ROH segments and the population LD average could influence the efficiency of detection. Thus, an SNP panel of 50K is efficient to identify ROH longer than 5 Mb (PURFIELD et al., 2012). In addition, ROH based on these dense panels can overestimate the number of segments shorter than 4 Mb (FERENČAKOVIĆ; SÖLKNER; CURIK, 2013).

1.2.8 ROH-based Inbreeding coefficient (F_{ROH})

Inbreeding coefficient based on ROH (F_{ROH}) is a genomic portion of individual autozygosity and defined it as the proportion of the autosomal genome lying in ROH of certain minimal length relative to the overall genome in interest (MCQUILLAN et al., 2008). The general formula for calculating F_{ROH} panel SNP markers is:

$$F_{ROH} = \frac{\sum L_{ROH}}{L_{AUTOSOME}}$$

Where $\sum L_{ROH}$ is the total extent of all ROH in the genome of an individual, where the regions contain the minimum specified number of successive homozygous SNPs, and $L_{AUTOSOME}$ denotes to the specified extent of the autosomal genome covered by SNPs on the panel.

The biological interpretation of F_{ROH} is easy, it is frequently partitioned into values for specific chromosomes or also for specific chromosomal segments (F_{ROH}> 1Mb, F_{ROH}>4Mb, F_{ROH}>8Mb, F_{ROH}>16Mb) (CURIK; FERENČAKOVIĆ; SÖLKNER, 2014). Consequently, the ROH ability to measure inbreeding from a recent common ancestor (longer ROH) or more distant common ancestor (shorter ROH) (HOWARD et al., 2015) is one of the main advantages comparing with other inbreeding coefficient tools. For instance, in a Holstein dairy cattle study, F_{ROH} for segments longer than 1 Mb and 4 Mb have significantly (P-values<0.001) superior estimates compared with pedigree inbreeding coefficient (F_{PED}) (TABLE 3). Furthermore, there is a positive correlation between F_{ROH} with different segments and F_{PED} (TABLE 4) (MARRAS et al., 2013).

TABLE 3. ESTIMATED MEAN (MIN–MAX) OF PEDIGREE-BASED INBREEDING COEFFICIENTS (F_{PED}) AND ROH-BASED INBREEDING COEFFICIENTS (F_{ROH}), FROH GREATER THAN A SPECIFIC LENGTH CLASS F_{ROH}>CLASS (>1, >4, >8 AND >16 MB)

Coefficient	**Holstein**
F_{PED}	0.044^{A}(0.000 – 0.179)
F_{ROH}>1 Mb	0.116^{B}(0.038 – 0.277)
F_{ROH}>4 Mb	0.073^{C}(0.006 – 0.233)
F_{ROH}>8 Mb	0.051^{A}(0.000 – 0.197)
F_{ROH}>16 Mb	0.026^{D}(0.000 – 0.167)

Estimated means with those that differ significantly within each breed indicated by a different superscript letter, P-values<0.001.
Reference: (MARRAS et al., 2013)

TABLE 4. CORRELATION BETWEEN PEDIGREE-BASED INBREEDING COEFFICIENTS (F_{PED}) AND ROH-BASED INBREEDING COEFFICIENTS, R(F_{PED}, F_{ROH}), CORRESPONDING TO THE MINIMUM SIZE OF THE ROH USED (F_{ROH} > 1, >4, >8, >16 MB).

Correlation	Holstein
r(F_{PED}, F_{ROH})	
F_{ROH} > 1Mb	0.700
F_{ROH} > 4Mb	0.696
F_{ROH} > 8Mb	0.651
F_{ROH} > 16Mb	0.561

Reference: (MARRAS et al., 2013)

1.2.9 Software for Simulation

Linkage disequilibrium (LD) and linkage analyses have been expansively used to recognize quantitative trait loci (QTL) in human and livestock species. Lately, awareness in complete genome fine mapping and particularly genome-wide selection has grown as a result of the dramatic increase in the number of known single

nucleotide polymorphisms (SNP) and the decline in genotyping costs. The contact to dense marker maps has opened up the option for new methods, genotyping costs have substantially decreased, but, large-scale genome-wide association studies are still costly (SARGOLZAEI; SCHENKEL, 2009).

Animal breeding studies have been used both real and simulated genomic data for investigating the power of different statistical methodologies; for evaluating alternative genomic breeding programs; and for the study of the dynamic forces of genomic selection. In general, real data reflect complexity. On the other hand, simulated data permit to explore important breeding characteristics. For instance, the genetic architecture of the trait, size of the dense panel used for analysis and degree of kinship among the training and prediction populations. Also, simulated data gives the opportunity of studying some evolutionary sources of variability, like drift (DAETWYLER et al., 2013). There are three main simulation methods used in literature to simulate livestock genomes: resampling, backward in time and forward in time. For the first, some individual's haplotypes are sampled, in sequence using a real or simulated pedigree, the population genomes are simulated (DAETWYLER et al., 2013). For the second, in backward in time (coalescent theory) is generated a random pedigree of a sample and finally, mutations are randomly located on the genealogy (CARVAJAL-RODRIGUEZ, 2008). Consequently, backward in time simulations, are computationally efficient because they only carry out information for those that are linked to the final sample. However, this approach does not simulate diploid individuals, therefore, it is not applicable selection pressure from dominance (DAETWYLER et al., 2013). For the third methodology, in the forward in time approach the whole history of the simulated individuals is followed from past to present (CARVAJAL-RODRIGUEZ, 2008). The ability to closely mimic the complex evolutionary histories of the real population is the main advantage in forward in time simulations (DAETWYLER et al., 2013). Moreover, in theory, it can simulate genetic samples of any complexity (PENG; AMOS, 2010). For instance, many different forward in time software programs have been taken different mutation rates, a number of generations of burn-in to achieve equilibrium, drift, and linkage disequilibrium as .methodology to initialize the data simulation (DAETWYLER et al., 2013).

There are different forward in time simulation programs available and well described in the literature, like FREGENE (CHADEAU-HYAM et al., 2008), simuPOP

(PENG; KIMMEL, 2005), quantiNemo (NEUENSCHWANDER et al., 2008), and QMSim (SARGOLZAEI; SCHENKEL, 2009). Although, QMSim stands out between them because is a powerful whole-genome stochastic simulation program that was designed to simulate a wide range of genetic and genomic architectures and population structures, particularly in livestock (SARGOLZAEI; SCHENKEL, 2009). Moreover, it is simple to implement and has been used in many different livestock genomic studies (AKANNO et al., 2014; BRITO et al., 2011; DEHNAVI et al., 2018; SENO et al., 2018; YIN et al., 2014).Nonetheless, QMSim is limited to the simulation of a single quantitative trait but includes an interface that can be used for, e.g., the external estimation of breeding values (SCHEPER et al., 2016).

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CHAPTER 02. ACCUMULATED LOSS BY INBREEDING DEPRESSION AND ACCESS OF RUNS OF HOMOZYGOSITY AND GENOMIC INBREEDING COEFFICIENT AFTER TWENTY GENERATIONS ON SIMULATED DAIRY CATTLE POPULATIONS

Rosa, F.[1]; Teixeira, R. A.[2]; Carvalheiro, R.[3]; Dias, L.T.[2]

[1]Programa de Pós-Graduação em Zootecnia, Universidade Federal do Paraná, Curitiba, PR, Brazil.

[2]Departamento de Zootecnia, Universidade Federal do Paraná, Curitiba, PR, Brazil. ZIP 80035-050.

[3]Faculdade de Ciências Agrárias e Veterinárias, Universidade Estadual Paulista "Júlio de Mesquita Filho" (UNESP), Jaboticabal, SP, Brazil. ZIP 14884-900.

*Corresponding author: Francisco Rosa. Email: ffrancisco.rosa@gmail.com - Phone: +55 41 98764-5913

ABSTRACT

The heavy use of a small number of sires and the artificial insemination practice on breeding programs has been increasing the dairy cattle inbreeding. Nevertheless, these high levels have been related to reduced fitness and reproductive performance. Therefore, the aim of this study was to evaluate the effect of selection on inbreeding depression of distinct simulated dairy cow population's scenarios. Using the QMSim software, populations were simulated based on forward-in-time process. The parameters were chosen to try and generate a population with the similar characteristics of taurine and indicine breeds of dairy cattle. Were simulated 93 milk yield QTLs randomly distributed on 29 chromosomes of *Bos taurus.* To create a high and low level of initial linkage disequilibrium were made a bottleneck in the historical population, 1,020 or 2,020 generations were simulated starting from an effective population of 1,000 to 200 animals at the end of the cycle. To found 20 generations of five different scenarios for each level of LD, the populations were simulated with the different mating system and selection criteria. The selection was based on breeding values estimated with BLUP method or a true breeding value estimated with the effect of QTLs. Each generation inbreeding mean was estimated by QMSim and associated with levels of inbreeding depression of milk yield found in the literature. Runs of homozygosity (ROH) were determined in 1,000 animals of generations 1, 5, 10, 15 and 20 by two different methods in the detectRUNS package of R software. The genomic inbreeding coefficients (F_{ROH}) were calculated as the ratio between the sum of all individual ROH segments, where each ROH contains a minimum number of homozygous SNPs, by the total length of their autosomal genome covered by SNPs. The intensive selection for one trait could rapidly increase the average inbreeding coefficient on critical levels in populations with high and low initial LD. The intense use of a few numbers of sires in twenty generations of selection may cause a loss between 6.98 and 7.20% on milk yield in the worst scenarios. Non-random mating systems must be applied to control inbreeding levels and consequently inbreeding depression. In general, the class 1-2 Mb in length has the largest number of ROH in all scenarios. The average number of ROHs in the 1-2 Mb class decreases with the passing of

selection generations in all ROH estimation scenarios and methodologies. However, the number of ROHs in the class greater than 8 Mb increases from generation 1 to 20. Thus, the sliding window and consecutive methodologies are efficient tools for the determination of ROH. The F_{PED} increases with the passing of the twenty selection generations in all scenarios. In addition, the F_{PED} mean level is similar among simulated taurine and indicine populations. However, the inbreeding coefficients based on runs of homozygosity (F_{ROHc} and F_{ROHs}) are different between the two simulated populations. Pearson's correlation between F_{ROHc} or F_{ROHs} with F_{PED} in the twentieth generation of the indicine population was moderately low and positive. Sliding window or consecutive approach are effective tools for accessing simulated populations ancient and recent inbreeding. In addition, genomic inbreeding may identify evolutionary forces, selection and genetic drift, which distinguish some populations.

Keywords: Holstein, Linkage, Disequilibrium, QMSim, Selection.

2.1 INTRODUCTION

Most individuals in livestock species are related, thus these populations should be considered small with a few numbers of sires and dams in mating systems (ROBERTSON, 2008). In Holstein dairy cattle it is almost impossible to find individuals without some level of inbreeding (CROQUET et al., 2006). Therefore, the effective population sizes are reduced to some hundreds or even less than a hundred animals (LEROY et al., 2013), in which these facts lead to the inbreeding increase over generations of selection. In the whole population of dairy cattle, there are millions of animals, but their Ne is estimated to be less than one hundred (SØRENSEN; SØRENSEN; BERG, 2005; STACHOWICZ et al., 2011). So, there is a concern to increase the critical Ne, as a consequence of the negative results of the correlation between fitness and the artificial selection marks (MEUWISSEN; WOOLLIAMS, 1994). Genetic drift and some loss of alleles during gamete formation are some consequences of small Ne populations (FALCONER; MACKAY, 1996).

Inbreeding is measured through Wright's inbreeding coefficient F (WRIGHT, 1931). The probability that the two alleles at any locus in an individual are identical by descent (IBD) is called inbreeding coefficient (MALÉCOT, 1948). Inbreeding coefficient growing has been reported in different populations of dairy cattle all over the world, Brazil (FILHO et al., 2010; QUEIROZ; ALBUQUERQUE; LANZONI, 2000; SILVA et al., 2016), United States (THOMPSON; EVERETT; HAMMERSCHMIDT, 2000; WIGGANS; VANRADEN; ZUURBIER, 1995), Canada (MIGLIOR; BURNSIDE,

1995), the United Kingdom (KEARNEY et al., 2004) and Denmark (SØRENSEN; SØRENSEN; BERG, 2005).

The decline of economic or reproductive traits average of related animals is called inbreeding depression (FALCONER; MACKAY, 1996). Influenced by recent or past evolutionary events, inbreeding depression is caused partially by the inbreeding load with the expression of deleterious recessive alleles in homozygous individuals (HEDRICK; GARCIA-DORADO, 2016). Furthermore, by the over-dominance hypothesis where the decreasing of heterozygote frequencies by the inbreeding, also reduces also their advantages (LEE et al., 2016). Several studies describe the reduction of the mean on phenotypic value shown by characters connected with reproductive capacity (PARLAND et al., 2007) or physiological efficiency (MC PARLAND; KEARNEY; BERRY, 2009; ROKOUEI et al., 2010; SØRENSEN et al., 2006) of dairy Holstein cattle.

The inbreeding does not affect gene (allele) frequencies, the genotype changes occur by increasing homozygosity at the cost of decreasing heterozygosity (FALCONER; MACKAY, 1996). This can impact to redistribution of the genetic variations within and among populations (FERNÁNDEZ; ANGEL TORO; LÓPEZ-FANJUL, 1995), reduction in the population fitness (ROKOUEI et al., 2010), the occurrence of homozygous recessive diseases (BENTON et al., 2018; BOSSE et al., 2018). In addition, some studies have been reporting an increase in the genome autozygosity as a consequence of genomic selection (DOEKES et al., 2018; FORUTAN et al., 2018; KIM et al., 2015, 2013). The interest to estimate inbreeding coefficients with genomic information appears with the advent of high throughput genotyping technologies (VANRADEN, 2008). Besides, the use of genomic data to determine loci related to inbreeding depression permits to differentiate animals which have the same inbreeding coefficient, but differ in the number of segments that when homozygous cause reduction in fitness (HOWARD et al., 2015). For instance, was applied in Holstein the estimation of inbreeding depression with runs of homozygosity (ROH), which described consistent results with what determined when using pedigree inbreeding (BJELLAND et al., 2013).

The continuous homozygous haplotypes of genotypes without heterozygosity in the diploid state is called runs of homozygosity (ROH) (FERENČAKOVIĆ; SÖLKNER; CURIK, 2013). Therefore, among many different mechanisms, inbreeding

and LD are the fundamental causes of ROH (BROMAN; WEBER, 1999). Therefore, the runs of homozygosity length explain past evolutionary events. For example, extensive ROH is most likely the consequence of recent inbreeding, where recombination events do not shorten identical haplotypes inherited from a common ancestor. Short ROH, in contrast, propose the earliest inbreeding (FERENČAKOVIĆ; SÖLKNER; CURIK, 2013). Consequently, runs of homozygosity (ROH) has been used for access variability in livestock populations (BOSSE et al., 2012; EUSEBI et al., 2017; SIDLOVA et al., 2015; ZANELLA et al., 2016), for investigating deleterious alleles (SZPIECH et al., 2013), for studies with inbreeding depression (HOWARD et al., 2015; PRYCE et al., 2014; SAURA et al., 2015), and also for estimating genomic inbreeding coefficient (FERENČAKOVIĆ; SÖLKNER; CURIK, 2013; FORUTAN et al., 2018; PERIPOLLI et al., 2018; ZAVAREZ et al., 2015). There are different approaches to access runs of homozygosity (ROH), the frequently used is PLINK v1.07 (PURCELL et al., 2007). PLINK uses a sliding window method to determine an ROH as a DNA section including a minimum specified number of homozygous SNPs within a specified distance. The desirable number of SNPs should not be smaller than the window size, although the software will be unsuccessful to determine segments shorter than the window size (CURIK; FERENČAKOVIĆ; SÖLKNER, 2014). Therefore, to solve this bias Marras et al. (2015) proposed the consecutive runs, a window-free method which directly scans the genome SNP by SNP. The density of the SNP panel used to determine ROH segments and the population LD average could influence the efficiency of detection. Has been reported different levels of linkage disequilibrium (r^2) at short and long distances of taurine an indicine breeds (PÉREZ O'BRIEN et al., 2014), which suggest a bigger ancestral population of the last one ("Genome-Wide Survey of SNP Variation Uncovers the Genetic Structure of Cattle Breeds", 2009).

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Investigations on animal breeding studies have been done with real and simulated data (DAETWYLER et al., 2013). Scenarios of genetic data have been suitable to mimic the effect of stochastic events, like selection, drift, and mutation, under sampled genetic data to trial statistic methodologies (CARVAJAL-RODRIGUEZ,

2008; LIU; ATHANASIADIS; WEALE, 2008). Forward-in-time is one of the main methodologies to simulate genomic populations cited in the literature (DAETWYLER et al., 2013), mostly because it can mimic dissimilar populations and genetic architectures (PENG; AMOS, 2010). Amongst several forward in time simulation software, QMSim is highlighted due to its very well described documentation (DAETWYLER et al., 2013). Furthermore, is a powerful whole-genome stochastic simulation program that was designed to simulate a wide range of genetic and genomic architectures and population structures, particularly in livestock (SARGOLZAEI; SCHENKEL, 2009). Dairy cattle populations have been simulated with QMSim in recent studies of genomic selection (SENO et al., 2018), inbreeding (FORUTAN et al., 2018) and genomic prediction (DEHNAVI et al., 2018; NADERI; YIN; KÖNIG, 2016).

Therefore, the aim of this study was to evaluate the effect of selection with assortative positive mating on inbreeding depression considering simulated dairy cattle populations distinguished by selection design and linkage disequilibrium (LD). Furthermore, to evaluate the ability of sliding and consecutive ROH approach to detect and express autozygosity and genomic inbreeding coefficient (F_{ROH}) in taurine and indicine simulated populations with twenty generations of assortative positive mating.

2.2 MATERIAL AND METHODS

2.2.1 Simulation of Populations

The data were simulated with QMSim software (SARGOLZAEI; SCHENKEL, 2009) to generate the phenotypes and inbreeding coefficients in a dairy cattle population in TABLE 5. The software applies a stochastic process to mimic evolutionary events like mutation and drift. Based on the forward-in-time method the simulation was processed in three steps (FIGURE 3). In the first step, a historical population, with a constant size of 1,000 animals, was simulated on 1,000 generations, with the random union of gametes, and an equal number of males and females. In addition, a “bottleneck” was simulated to establish a desired high and low Linkage Disequilibrium (LD), high LD like has been found in taurine (PÉREZ O’BRIEN et al., 2014) and low LD for indicine (ESPIGOLAN et al., 2013) cattle. It was used a distinct number of historical generations in the simulation process to differ the two LD levels. Therefore, this was created with a continuous reduction in the number of animals

(1,000 - 200) from generation 1,001 to 1,020 or 2,020 to obtain high and low LD respectively.

In the second step, to form the expanded population, all animals from the last generation of the historical population were selected (100 males and 100 females). This number of animals is similar to the effective size of the real population (HAYES et al., 2003; SARGOLZAEI et al., 2008). The expanded population was simulated over 6 generations with; a mating system based on the random union of gametes, the absence of selection, exponential growth rate, 5 progenies per dam with equal probability to be male or female, and a replacement rate of 100 % in every generation. Thus, in the last generation of the second step, the population results in 16,000 animals (half females).

TABLE 5. PARAMETERS OF THE SIMULATION PROCESS

Parameters	Indicine	Taurine
Population structure		
Global parameters		
h^2	0.3	0.3
QTL heritability	0.3	0.3
Phenotypic variance	$2.25x10^6$	$2.25x10^6$
Historical population		
Total generations (no.)	2,020	1,020
Number of animals in the first generation	1,000	1,000
Number of animals in the last generation	200[1]	200[1]
Current population		
Generation		20
Number of offspring per mate		1
The probability for sex of the offspring		0.5
Replacement ratios for sires and dams (%)		50 and 20
Culling criteria		Age
Genomic parameters		
Number of chromosomes		29
Length of each chromosome (cM)		60 – 154

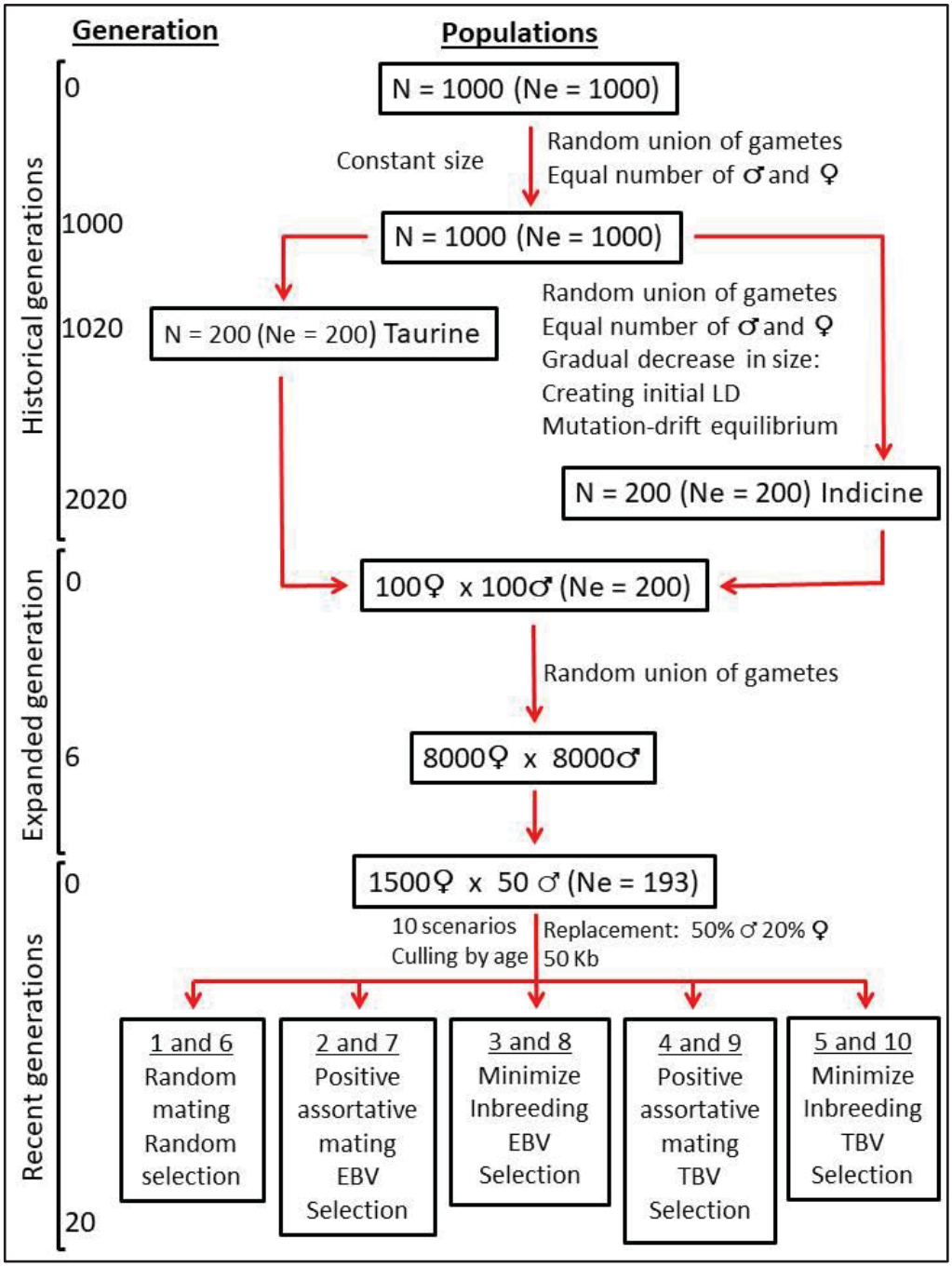
[1]100 males and 100 females

In the third step, to preserve the Ne of a real population (SARGOLZAEI et al., 2008), 50 sires and 1500 dams were selected from the last generation of HLD and LLD populations' second step to form 20 recent generations. To mimic real dairy cattle populations, the age was used as culling criteria, and the replacement rate was 50 % and 20 % for sires and dams respectively. In addition, to mimic real dairy cattle systems, for each population with high and low LD, were created ten discrete scenarios. Thus, all the scenarios were distinguished by mating and selection design (FIGURE 3). The scenarios 1 and 6 with random mating and selection, the scenarios

2 and 7 with positive assortative mating and selection made by estimated breeding value (EBV), the scenarios 3 and 8 with assortative mating minimizing inbreeding and selection made by EBV, the scenarios 4 e 9 with positive assortative mating and selection made by TBV, and for scenarios 5 and 10 assortative mating minimizing inbreeding and selection made by TBV. The prediction of BLUP-EBV was made by QMSim with Henderson´s (HENDERSON, 1975) mixed linear equations. The sum of additive variation of QTL was used for TBV prediction.

The non-random association between alleles in two or more loci, not necessary in the same chromosome, is defined as linkage disequilibrium (FALCONER; MACKAY, 1996). The level and extent of LD in the recent population were estimated as the average correlation between pairs of marker alleles (r^2) (HILL; ROBERTSON, 1968). Markers with minor allele frequency less than 0.1 were excluded.

FIGURE 3. SCHEMATIC REPRESENTATION OF THE SIMULATION SCENARIOS



N: individuals number; Ne: Effective size; ♂: number of males; ♀: number of females; EBV: Estimated breeding value; TBV: True breeding value.

2.2.2 Genome simulation

The genome was simulated with 29 pairs of autosomes with length varied from 60 – 154 cM. The number of bi-allelic markers varied from 2,040 – 5,236 and number of QTLs from 6 – 57, randomly distributed over 29 autosomes. Thus, the simulated genome had a total length of 2,974 cM, with 101,116 bi-allelic markers and 605 QTL

related with milk yield. The QTLs alleles varied randomly between 2 and 4 (DEHNAVI et al., 2018), with initial equal allele frequencies (SARGOLZAEI; SCHENKEL, 2009). In addition, following the simulated genetic variance, a gamma distribution with a shape parameter of 0.4 (HAYES; GODDARD, 2001) and a scale parameter determined inside QMSim was used to determinate the QTL allele effects. Recurrent mutation rates were applied only in historical population generations at a rate of 10^{-4} for markers and QTLs because usually recent populations were simulated with a small number of generations for which the effect of mutation might be ignored (SARGOLZAEI; SCHENKEL, 2009). The Poisson distribution with mean u (u = 2*number of loci*mutation rate) was used to sample the number of mutations. Plus, in the genome, each mutation was allocated in a random locus. From the last generation of the historical population, to generate genotypic data for the selection population it was randomly selected a total of 50,000 markers (MAF ≥ 0.02), these data mimicked the commonly SNP panel used to genotype cattle. The simulation thresholds used in this study intended to mimic a polygenic complex trait affected by many genes of small effects and by few genes with more pronounced effects. Thus, were randomly selected from the last historical generation 93 segregating QTLs (number of QTLs related to milk yield 305)("The Animal Quantitative Trait Loci (QTL) Database (AnimalQTLdb)", [s.d.]). The simulated heritability of 0.3 for milk yield 305 days was a result of the animal's phenotypes. Each phenotype contains the sum of QTL effects plus an error term sampled from a normal distribution with zero mean and variance of $2.25x10^6$, resulting in a trait with a heritability of 0.3.

2.2.3 Inbreeding and inbreeding depression

The mean population inbreeding coefficient (F_i and F_o) at generation **t** were predicted by the following equation:

$$F_t = 1-(1-\frac{1}{2Ne})^t$$

Ne= initial effective population size.

The equation below was used to estimate the milk yield (MY_e) in 305 days on each generation of selection. The mean of first lactation milk yield in the first generation

(8,541 kg) used in the simulation was taken from APCBRH annual report (2017). It was considered -18.7 kg of inbreeding depression with 1% of increase on inbreeding (ROKOUEI et al., 2010).

$$MY_e = MY_m - \left[\left(\frac{F_i - F_0}{10^{-2}}\right).ID\right]$$

MY_e = mean milk yield estimated over inbreeding
MY_m = mean milk yield in the last generation
F_o = mean population inbreeding of the last generation
F_i = mean population inbreeding
ID = inbreeding depression

2.2.4 Genetic similarity and SNP allelic frequencies

In order to verify the genetic similarity among taurine and indicine individuals used in this study, the identity by state (IBS) levels and SNP allelic frequencies were computed by PLINK (PURCELL et al., 2007). This approach was applied among 1,000 individuals of generations 1, 5, 10 and 20, from scenarios 3 and 8 which better mimicked real populations described in the literature. The proportion of genomic segments shared among individuals was estimated through the identity by descent levels (IBD). The allele frequencies averages were calculated for all the markers in the 29 chromosomes.

2.2.5 Runs of homozygosity

The runs of homozygosity were obtained by two different methodologies in the detectRUNS package of R software for 1,000 individuals of generations 1, 5, 10, 15, and 20, from scenarios 3 and 8 which better mimicked real populations described in the literature. At first, the sliding window method (PURCELL et al., 2007) scans along each individual's genotype at each SNP marker position for detection of homozygous segments with a specified length or number of homozygous SNPs (HOWRIGAN; SIMONSON; KELLER, 2011). The parameters and thresholds applied to outline an ROH were:

- A sliding window of 15 SNPs across the genome;

- The proportion of homozygous overlapping windows was 0.05;
- The minimum number of consecutive SNPs included in an ROH was 15;
- The minimum length of an ROH was set to 1 Mb;
- The maximum gap between consecutive homozygous SNPs was 1 Mb;
- The density of one SNP per 50 kb;
- Maximum of four SNPs with missing genotypes and up to on heterozygous genotype were allowed in an ROH.

The ROH was defined by a minimum of 1 Mb in length to avoid short common ROH that occur throughout the genome due to LD. At second, the consecutive method (MARRAS et al., 2015) do not use the sliding windows to avoid the introduction of artificial ROH that are shorter than the window (FERENČAKOVIĆ; SÖLKNER; CURIK, 2013). The parameters and thresholds applied to determine ROH were:

- The minimum number of SNPs included in an ROH was fixed at 15;
- The minimum length of an ROH was set at 1 Mb;
- The maximum distance between adjacent SNPs was 1 Mb;
- One heterozygous and four missing genotypes were allowed in an ROH.

Thus, ROH was classified into four length classes: 1-2, 2-4, 4-8, and >8 Mb, identified as $ROH_{1\text{-}2}$, $ROH_{2\text{-}4}$, $ROH_{4\text{-}8}$ and $ROH_{>8}$, respectively. For generations 1, 5, 10, 15 and 20 of taurine and indicine simulated populations, and for each ROH length category, the total number of ROH detected, the mean length of ROH and the percentage of all ROH segments were calculated.

2.2.6 Genomic inbreeding coefficient (F_{ROH})

Inbreeding coefficient based on ROH (F_{ROH}) is a genomic portion of individual autozygosity and it is defined as the proportion of the autosomal genome lying in ROH of certain minimal length relative to the overall genome in interest (MCQUILLAN et al., 2008). The general formula used for calculating F_{ROH} panel SNP markers was:

$$F_{ROH} = \frac{\sum L_{ROH}}{L_{AUTOSOME}}$$

The $\sum L_{ROH}$ is the total extent of all ROH in the genome of an individual, where the regions contain the minimum specified number of successive homozygous SNPs,

and $L_{AUTOSOME}$ denotes to the specified extent of the autosomal genome covered by SNPs on the panel.

The described statistics of inbreeding coefficients were presented, as well, the Pearson correlation between the inbreeding coefficient based on pedigree (F_{PED}) and genomic inbreeding coefficient based on runs of homozygosity (F_{ROH}).

2.3 RESULTS AND DISCUSSION

2.3.1 Linkage Disequilibrium (LD)

The decrease of linkage disequilibrium (LD) at ten different scenarios from generation zero to twenty is demonstrated in FIGURES 4 to 6. Hight LD in short distances and low LD in long distances among markers was observed at all scenarios throughout twenty generations. For the short distances, the results were high (~0.5) as expected in taurine cattle and low (~0.24) as expected in indicine cattle in the generation zero. For the scenario with random mating, there is a very small increase in LD level between markers throughout generations of selection (FIGURE 4). In addition, in populations with positive assortative mating with EBV or TBV as selection criteria shows an expressive increase in LD from generation zero to twenty (FIGURE 5). Furthermore, in scenarios with minimizing inbreeding parameter the LD level has a small increase throughout generations (FIGURE 6).

FIGURE 4. AVERAGE LINKAGE DISEQUILIBRIUM (LD) AS MEASURED BY r^2 AGAINST DISTANCE (Mb) BETWEEN A PAIR OF MARKERS IN SCENARIOS WITH RANDOM MATING (RND).

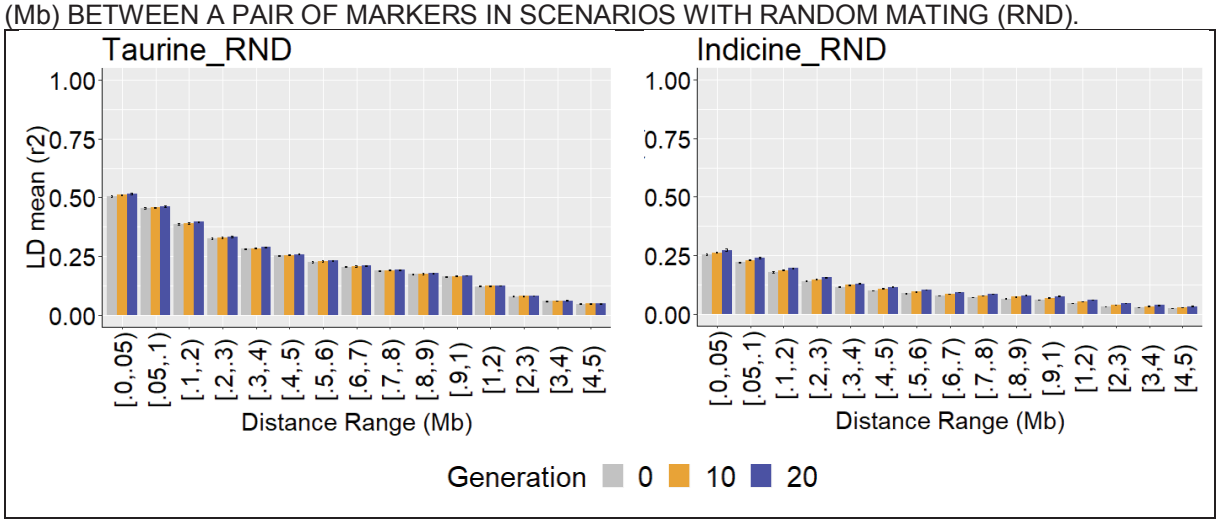
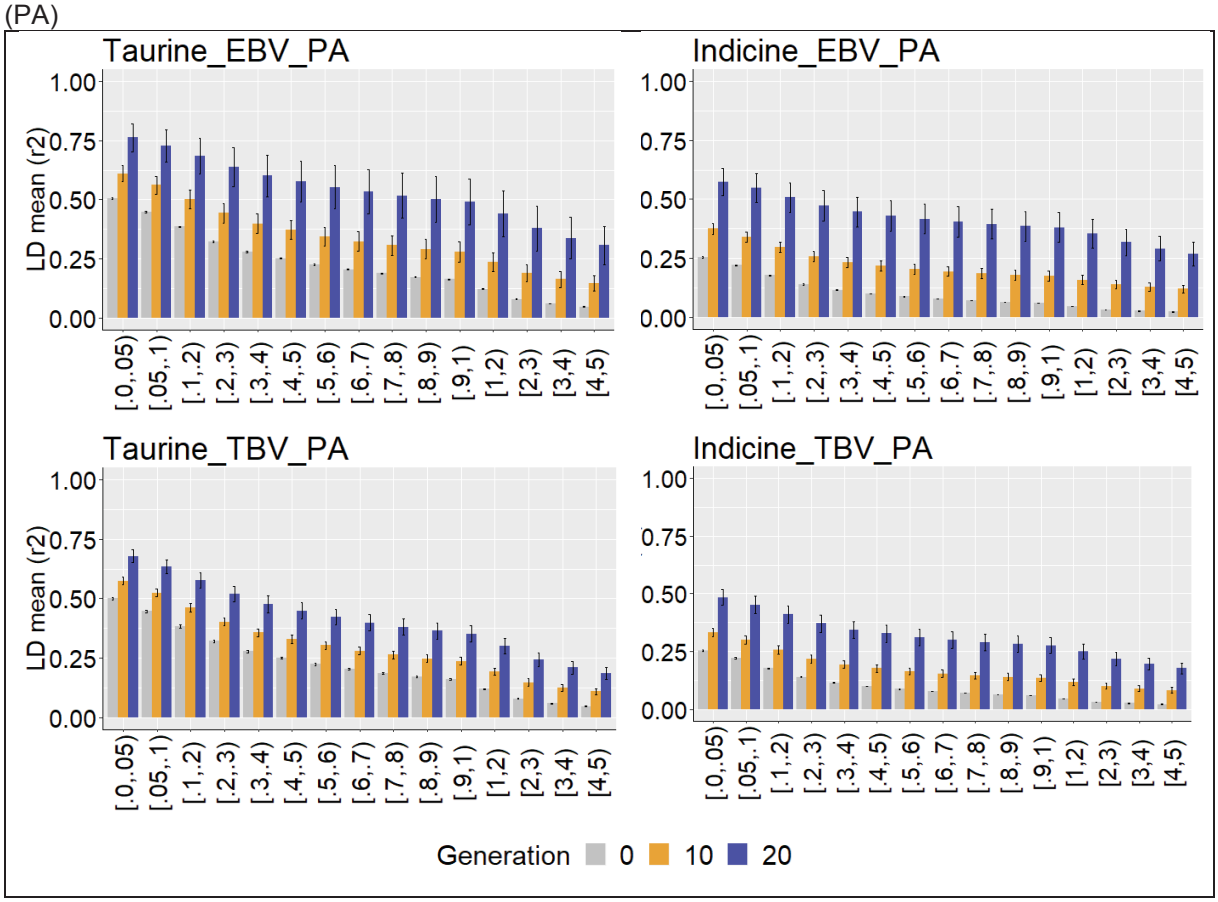
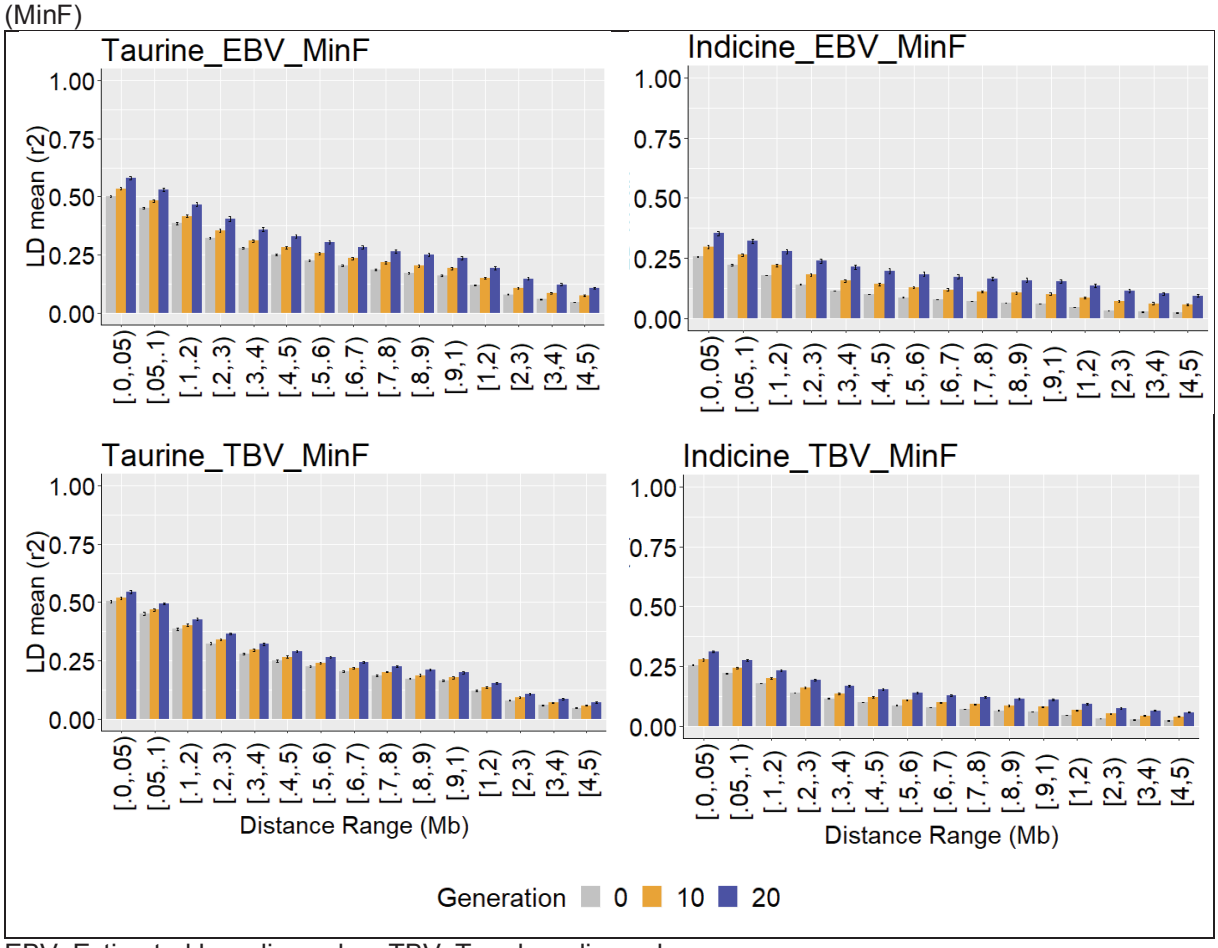


FIGURE 5. AVERAGE LINKAGE DISEQUILIBRIUM (LD) AS MEASURED BY r^2 AGAINST DISTANCE (Mb) BETWEEN A PAIR OF MARKERS IN SCENARIOS WITH POSITIVE ASSORTATIVE MATING (PA)



EBV: Estimated breeding value; TBV: True breeding value

FIGURE 6. AVERAGE LINKAGE DISEQUILIBRIUM (LD) AS MEASURED BY r^2 AGAINST DISTANCE (Mb) BETWEEN A PAIR OF MARKERS IN SCENARIOS WITH MINIMIZING INBREEDING MATING (MinF)



EBV: Estimated breeding value; TBV: True breeding value.

Evolutionary events should influence LD levels among populations or throughout generations. For example, the selection is one of the factors that may influence the level of LD (FALCONER; MACKAY, 1996). Since the intense use of a small number of sires reduces the effective population size (Ne). Thus, high LD at short distances and low LD at long distances of chromosomes is expected in populations with small N_e and bottlenecks in ancestral population (DE ROOS et al., 2008; THE BOVINE HAPMAP CONSORTIUM, 2009). Furthermore, the rapidly decay with increasing in genomic distance for real Holstein cattle suggests one bottleneck first with domestication, and other nowadays with the selection, with less than ~100 animals of the effective population (DE ROOS et al., 2008). The LD decay is faster in real indicine populations in contrast with taurine breeds, which suggests distinct panel density to access some genomic events (PÉREZ O'BRIEN et al., 2014). Otherwise, real Indicine populations showed lower LD between short distances of chromosome compared with taurine breeds (MELO et al., 2016; PÉREZ O'BRIEN et al., 2014). In

order that the LD levels at short distances and the decline observed in the simulated data of this study were the same as found in the literature.

The probability of two alleles at any locus in an individual are identical by descent (IBD) is called inbreeding coefficient (MALÉCOT, 1948). The average levels of inbreeding coefficient in the twentieth generation were similar between taurine and indicine cattle scenarios (TABLE 6). The highest inbreeding levels, varying from 0.2 to 0.36, in the twentieth generation were obtained for positive assortative mating systems. Since, these scenarios mimicked the intensive selection for focusing on just one trait, which the mating occurs between individuals with the highest level of EBV or TBV. Therefore, these highest inbreeding levels occur because the selected individuals with highest EBV or TBV were also related. In addition, the scenarios with minimizing inbreeding showed intermediate inbreeding levels, varying from 0.03 to 0.08, in the twentieth generation of selection, this results are similar as found for real indicine and taurine populations (FILHO et al., 2010; QUEIROZ; ALBUQUERQUE; LANZONI, 2000; STACHOWICZ et al., 2011). Recently, the inbreeding coefficient was estimated between 1989 and 2007 in a Holstein population from Iran, the highest level for the females was 0.31 after 2000 (ROKOUEI et al., 2010). Additionally, the lowest inbreeding level in the twentieth generation was found for scenarios with random mating and random selection, 0.02 for taurine and indicine populations.

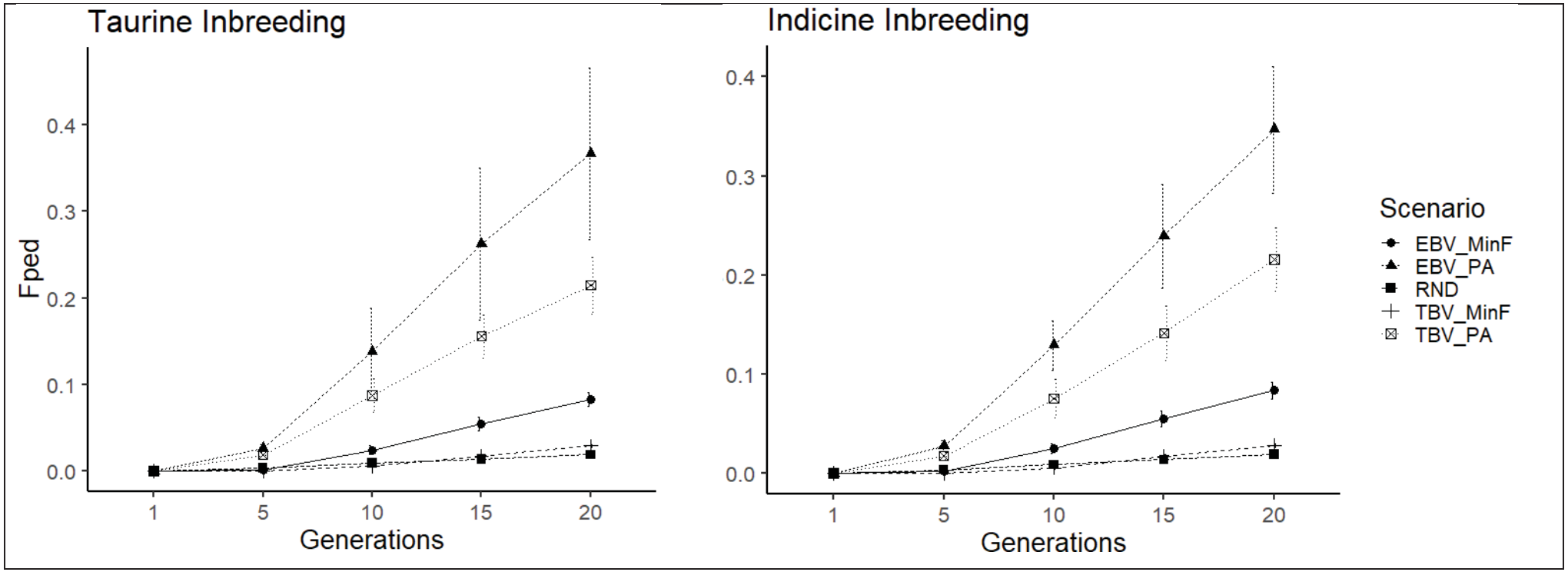
TABLE 6. PERCENTAGE OF LOSS, THE CUMULATED EFFECT OF INBREEDING DEPRESSION (ID), AVERAGE INBREEDING COEFFICIENT (F_{PED}) AND HOMOZYGOSITY LEVELS IN THE TWENTIETH GENERATION OF DIFFERENT MATING AND SELECTION SYSTEMS

		Parameters				
Scenario		**% Loss**	**F_{PED}**	**SD**	**ID***	**SD**
Taurine	**RND**	0.40	0.02	0.001	8,506.78	2.32
	EBV PA	6.98	0.36	0.106	7,944.47	186.06
	EBV MinF	1.81	0.08	0.008	8,386.07	15.03
	TBV PA	4.52	0.20	0.032	8,155.22	61.60
	TBV MinF	0.63	0.03	0.001	8,486.86	2.91
Indicine	**RND**	0.41	0.02	0.001	8,505.47	1.44
	EBV PA	7.20	0.35	0.061	7,926.33	119.80
	EBV MinF	1.83	0.08	0.008	8,384.48	16.30
	TBV PA	4.78	0.22	0.036	8,133.06	60.45
	TBV MinF	0.62	0.03	0.002	8,487.80	3.55

ID*: Milk yield at 305 days of lactation (kg milk/lactation); F_{PED}: Population inbreeding Mean; SD: Standard Deviation; RND: Random mating; EBV PA: Selection based on estimated breeding value and assortative positive mating; EBV MinF: Selection based on estimated breeding value and minimize inbreeding mating; TBV PA: Selection based on true breeding value and assortative positive mating; TBV MinF: Selection based on true breeding value and minimize inbreeding mating.

The inbreeding average levels increasing throughout twenty generations of assortative positive mating is observed for all scenarios showed in FIGURE 7. There is no pedigree information for the individuals of generation 1. Therefore, the average level in generation one is zero for all scenarios. The highest grown of inbreeding occurs for positive assortative mating with an average increase among 1.07 and 1.83% per generation considering both taurine and indicine simulated populations. Smaller results were found in real Holstein dairy cattle population from Iran, which describes an increase of 0.9% per generation (ROKOUEI et al., 2010). These results confirm the influence of reduced Ne, main caused by the use of a few numbers or sires and artificial insemination (AI) (STACHOWICZ et al., 2011). In contrast, an intermediate increase on average levels of inbreeding was obtained for scenarios with minimizes inbreeding parameter, 0.14 and 0.42% in every generation. These results are higher than the increase in twenty generations of random mating and selection, 0.09% in every generation for both taurine and indicine populations.

FIGURE 7. AVERAGE PEDIGREE INBREEDING (FPED) OVER 20 GENERATIONS OF DIFFERENT MATING AND SELECTION SYSTEM FOR SIMULATED TAURINE AND INDICINE POPULATIONS



RND: Random mating;
EBV PA: Selection based on estimated breeding value and assortative positive mating;
EBV MinF: Selection based on estimated breeding value and minimizes inbreeding mating;
TBV PA: Selection based on true breeding value and assortative positive mating;
TBV MinF: Selection based on true breeding value and minimizes inbreeding mating.

The decline of economic or reproductive traits mean of related animals is called inbreeding depression (FALCONER; MACKAY, 1996). The inbreeding depression was estimated through the production decay of -18.7 kg on milk yield with 1% of inbreeding increasing (ROKOUEI et al., 2010). Thus, the results of inbreeding depression throughout twenty generations in dairy cattle populations are shown in FIGURES 8 to 10. The average level inbreeding increase of ~1.8% in the population with random selection and mating reduces in 0.4% the milk yield at 305 days after twenty generations (FIGURE 8). Otherwise, highest losses on milk yield were obtained for populations with assortative positive mating with 6.98 and 7.20% with selection based on EBV in both taurine and indicine scenarios respectively (FIGURE 9). In addition, for the cumulated effect of inbreeding depression in the twentieth generation of assortative positive mating for milk yield in populations simulated with selection based on EBV (7,944.74 and 7,926.33) was higher than based in TBV (8,155.22 and 8,133.06). After all, the means of coefficient inbreeding are the highest for scenarios with positive assortative mating and selection based in EBV in the twentieth generation (0.36 and 0.35) showed in TABLE 6.

FIGURE 8. INBREEDING DEPRESSION OVER TWENTY GENERATIONS OF RANDOM MATING

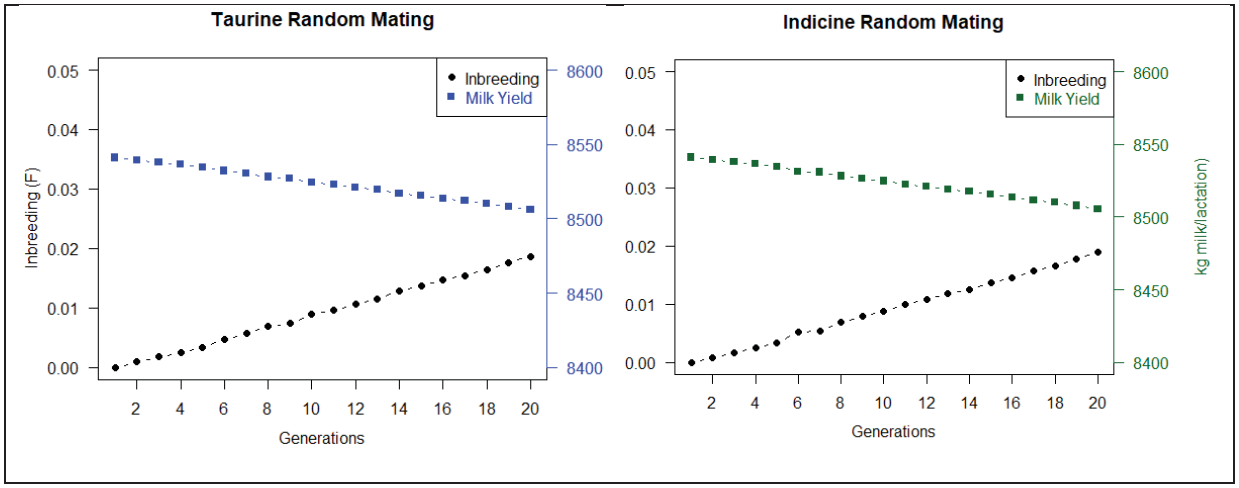
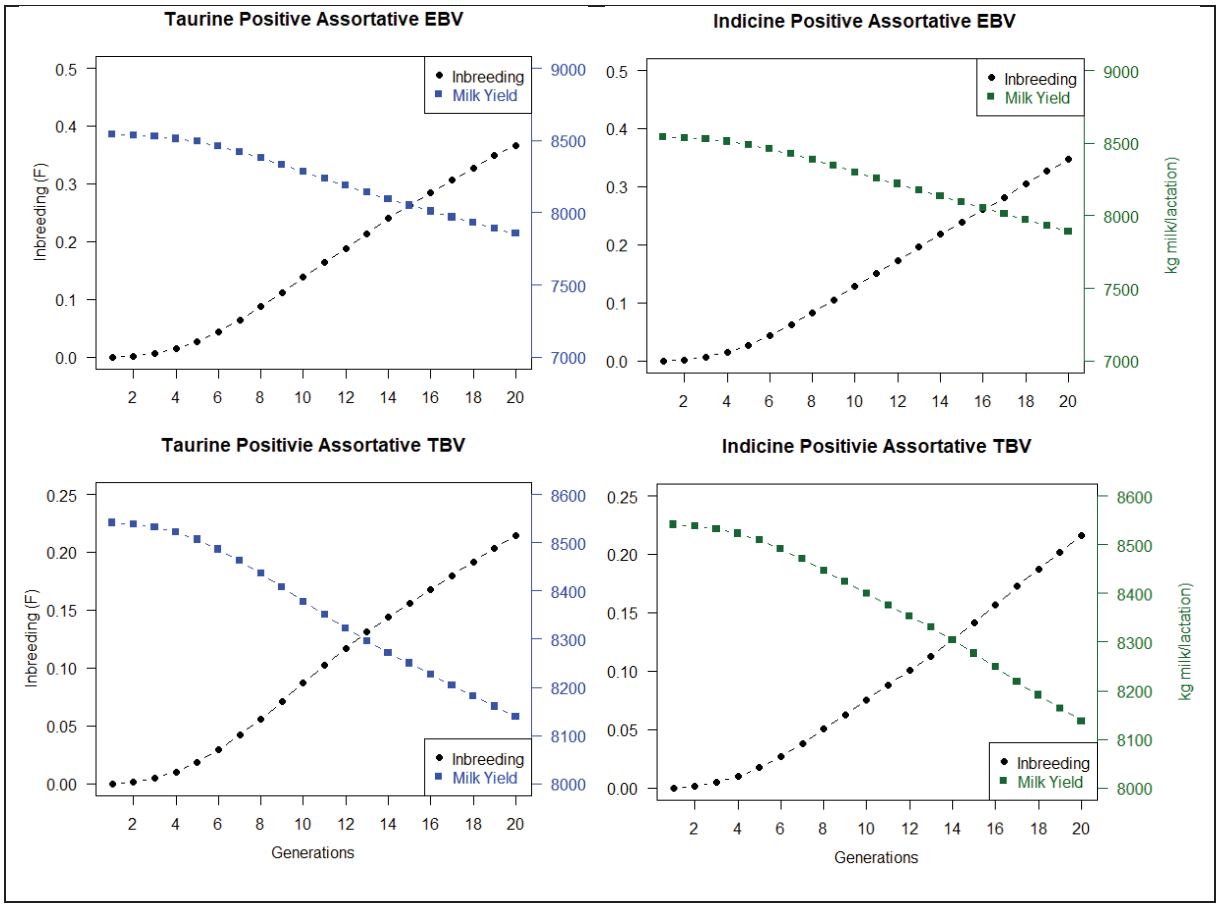
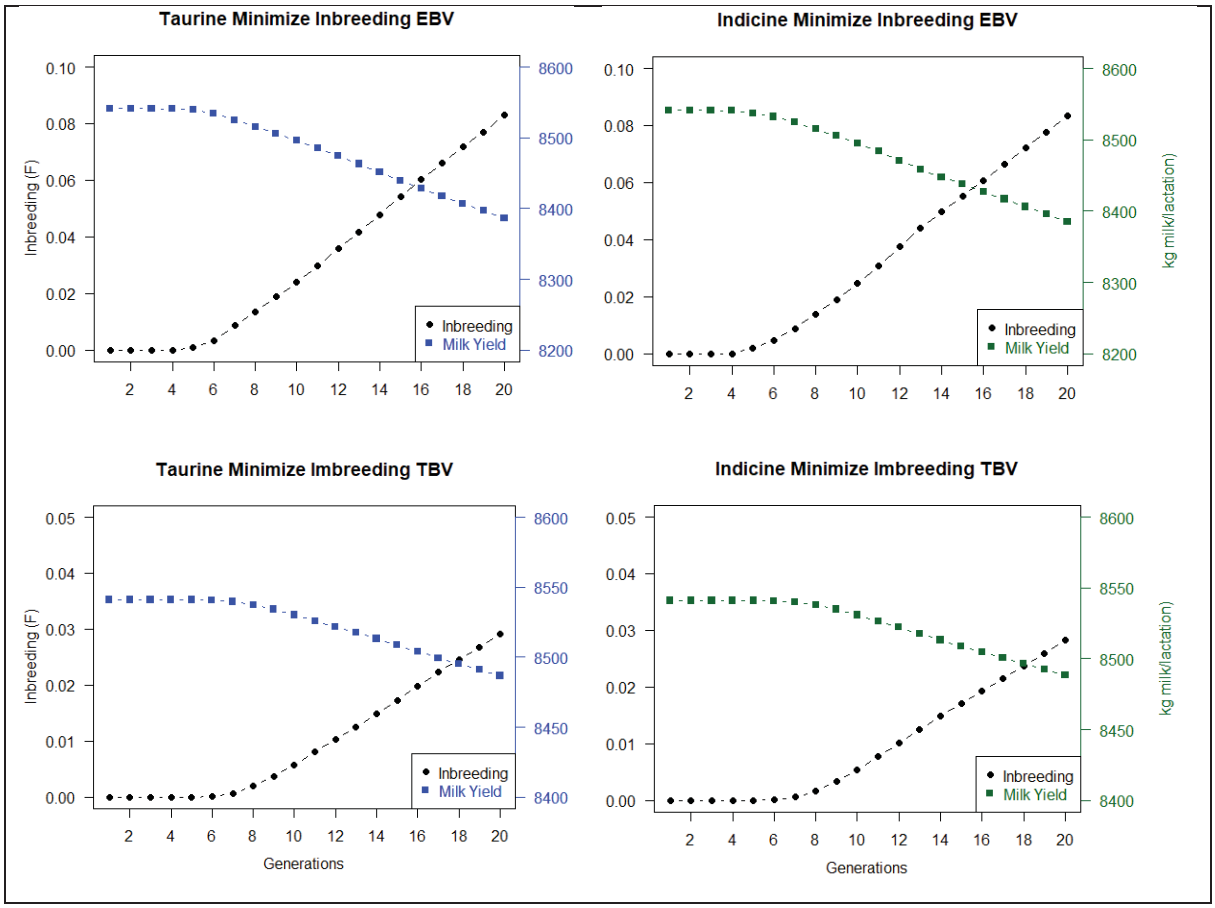


FIGURE 9. INBREEDING DEPRESSION THROUGHOUT TWENTY GENERATIONS OF SELECTION BASED ON ESTIMATED BREEDING VALUE (EBV) OR TRUE BREEDING VALUE (TBV) IN POPULATIONS WITH POSITIVE ASSORTATIVE MATING



For minimizing the increase of inbreeding throughout generations mimicking a non-random mating system, the QMSim program applies the annealing method (SONESSON; MEUWISSEN, 2001). The results of populations applying to minimize inbreeding are shown in FIGURE 10. In general, for minimizing inbreeding scenarios, the average level inbreeding increase of ~3 and ~8% in the twenty generations of selection decreases ~0.6 and ~1.8% the milk yield at 305 days respectively. These results are lower than found in populations with assortative positive mating and higher than random mating.

FIGURE 10. INBREEDING DEPRESSION OVER 20 GENERATIONS OF SELECTION BASED ON ESTIMATED BREEDING VALUE (EBV) OR TRUE BREEDING VALUE (TBV) IN POPULATIONS WITH MINIMIZING INBREEDING MATING



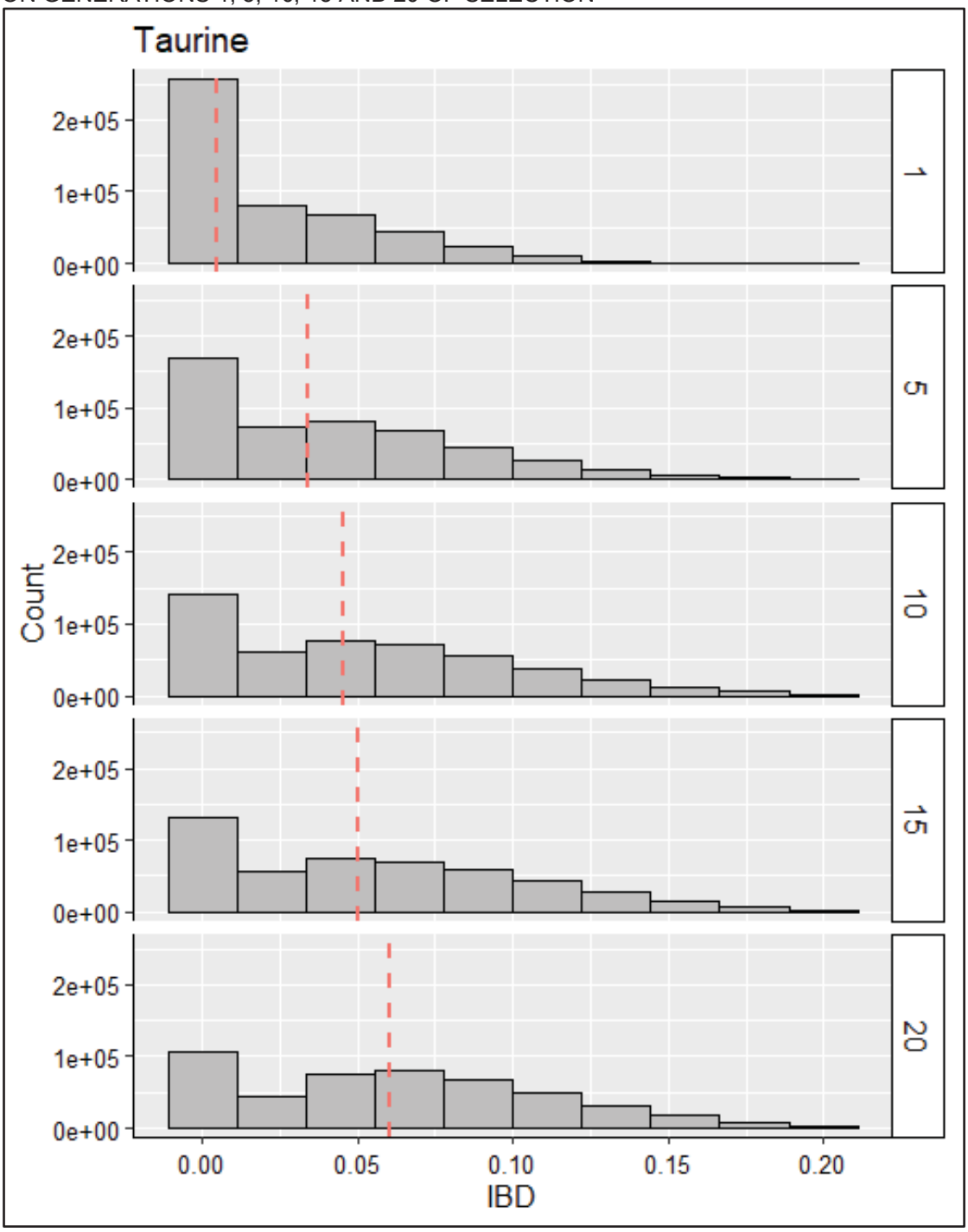
For real Holstein populations, it was obtained an inbreeding depression of -15.28 kg for milk yield in inbreed cows in populations with an inbreeding coefficient of 4.9 and 0.04% respectively (ALLAIRE; HENDERSON, 1965). Additionally, other research in the same breed found inbreeding depression of -21.1 kg in populations with 0.09% of inbreeding coefficient mean (HUDSON; VAN VLECK, 1984). Furthermore, comparing the reduction of different traits, inbreeding depression shows more effect on production traits, which means a superior economic income impact over breeding decisions (LEROY, 2014). One of the main causes of inbreeding depression is the expression of deleterious recessive alleles (HEDRICK; GARCIA-DORADO, 2016). Since the homozygous loci are increased by inbreeding, which is closely related with the expression of a lethal recessive mutation in dairy cattle populations (AGERHOLM et al., 2001; SHANKS; ROBINSON, 1989; SHUSTER et al., 1992; VANRADEN et al., 2011). Therefore, it is necessary to include the trial for deleterious recessive alleles in bulls at progeny test for milk yield (ROBERTSON; RENDEL, 1950). Nevertheless, Genomic brought others perspectives to control inbreeding in selection

schemes, most because it is possible to take into account different genetic mechanisms involved in inbreeding depression (LEROY, 2014).

2.3.3 IBD and allelic frequency levels

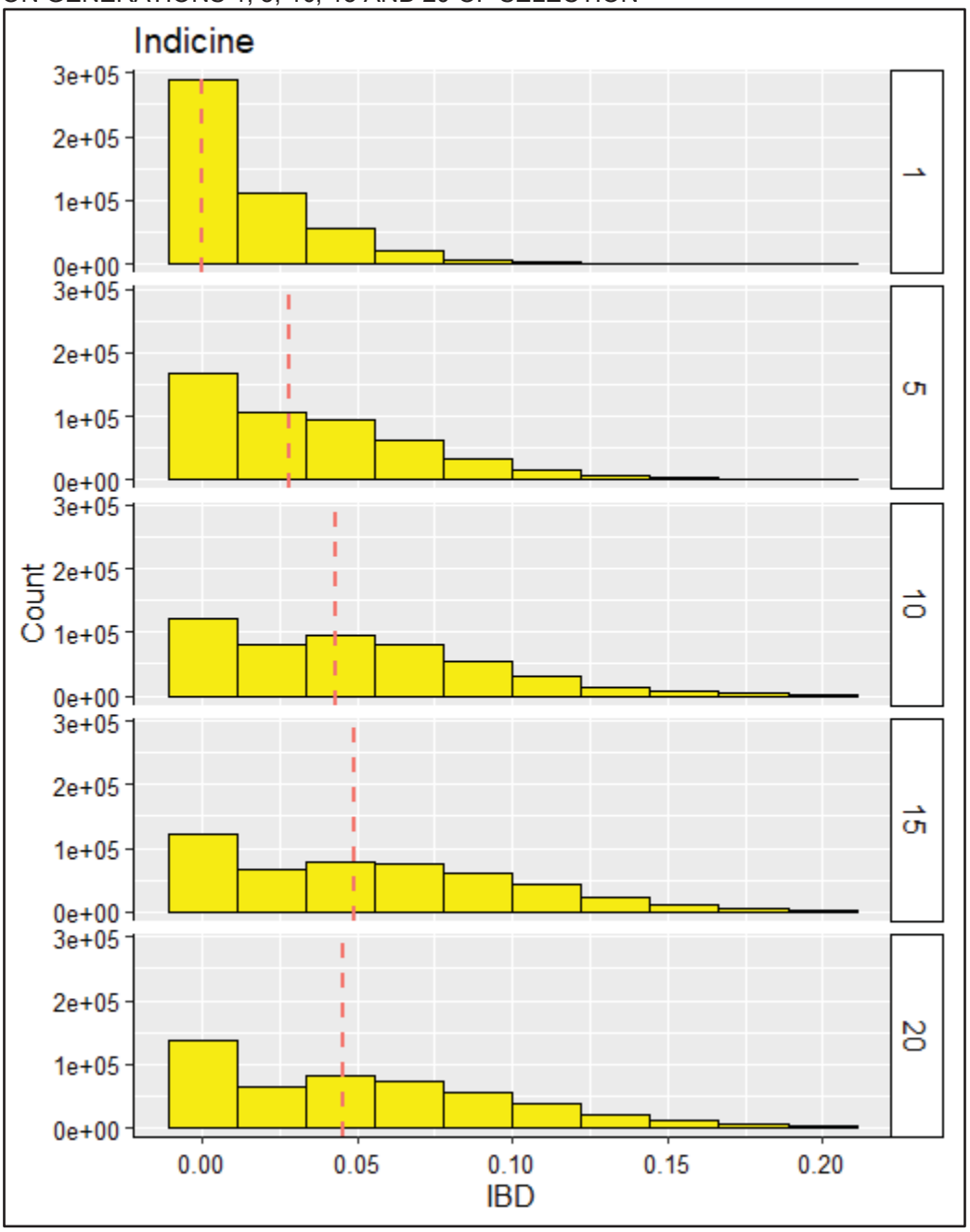
The median IBD levels between all the simulated animals increase from 0.005 to 0.06 upon the twenty generations of selection for taurine population (FIGURE 11). In addition the increase from 0.00 to 0.04 for the indicine population. These results suggest a decrease in variability among the individuals until generation fifteen on both taurine and indicine populations (FIGURE 12). In generation twenty of Indicine, there is a short decrease in the median IBD level from 0.049 to 0.045. This decrease occurs since the mating system adopted by simulation control the levels of inbreeding.

FIGURE 11. SHARED ALLELE'S PERCENTAGE BETWEEN SIMULATED TAURINE ANIMALS (IBD) ON GENERATIONS 1, 5, 10, 15 AND 20 OF SELECTION



The dashed line on each grafic indicates the median of the IBD distribution

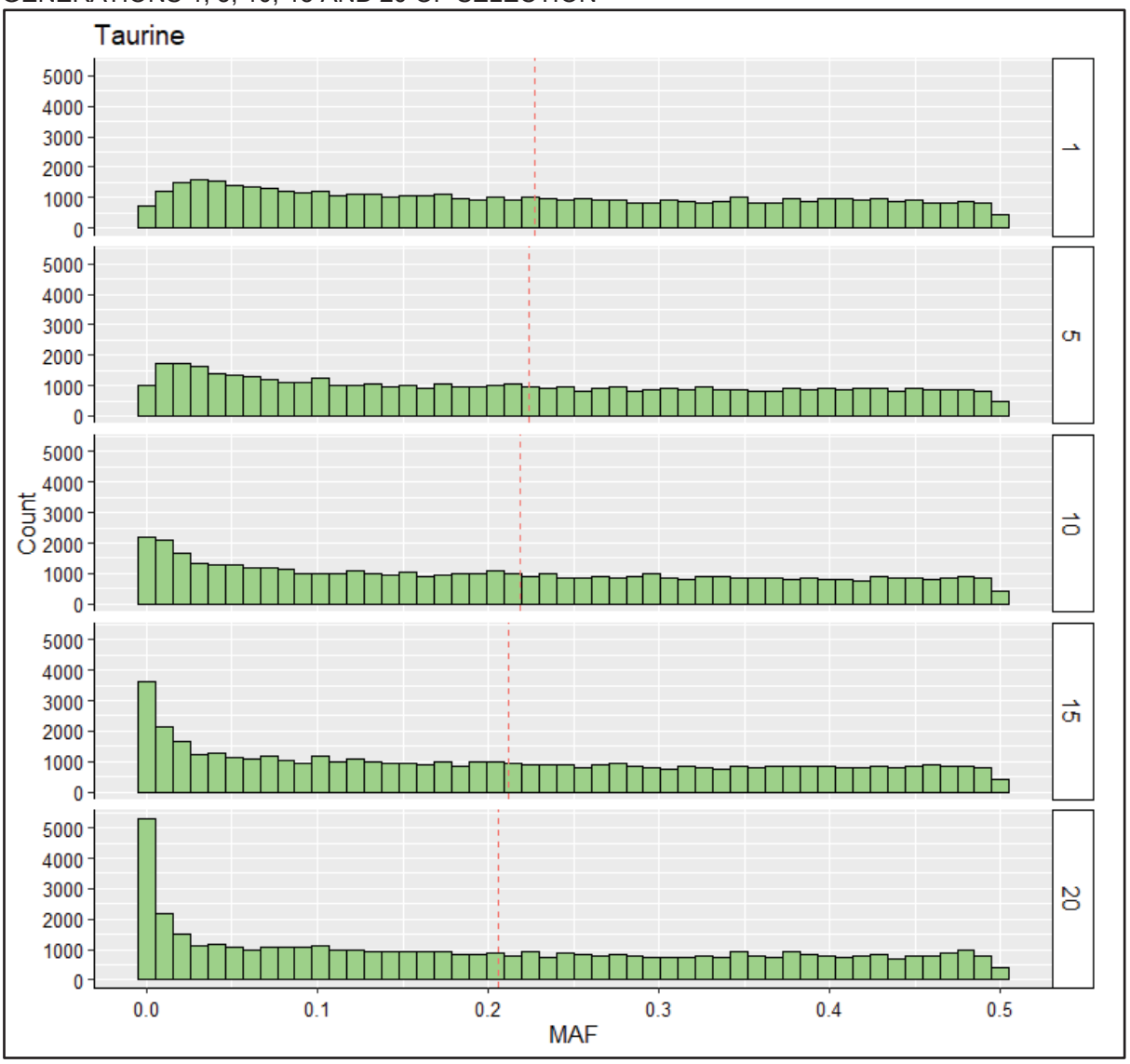
FIGURE 12. SHARED ALLELE'S PERCENTAGE BETWEEN SIMULATED TAURINE ANIMALS (IBD) ON GENERATIONS 1, 5, 10, 15 AND 20 OF SELECTION



The dashed line on each graphic indicates the median of the IBD distribution

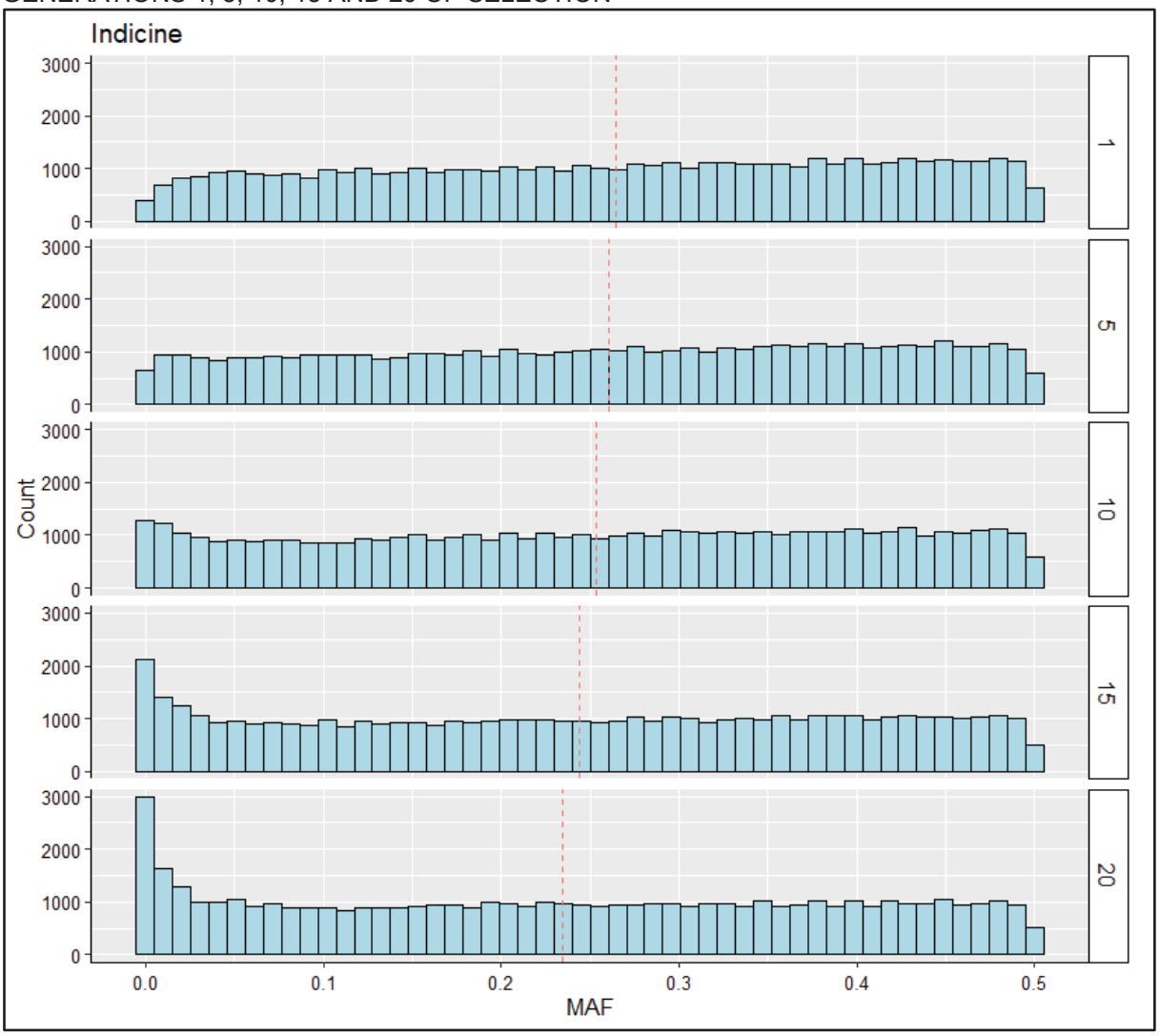
In relation to the minor allelic frequencies (MAF) of all 50,000 SNP markers analyzed, the average frequency level decreases from 0.22 to 0.20 for taurine, and from 0.26 to 0.23 for indicine population over twenty generations of selection (FIGURE 13 and 14). Therefore, it is also evidence of variability of autosomal markers decrease in consequence of simultaneously drift and selection pressure. In addition, the variability of the indicine population is higher than taurine in all generation analyzed. Furthermore, MAF of 0.29 in animals genotyped with a 49 Kb panel is described for a real Holstein population (HE et al., 2018).

FIGURE 13. ALLELIC FREQUENCIES AMONG THE SIMULATED TAURINE CHROMOSOMES ON GENERATIONS 1, 5, 10, 15 AND 20 OF SELECTION



The dashed line on each graphic indicates the average level of the MAF distribution

FIGURE 14. ALLELIC FREQUENCY AMONG THE SIMULATED INDICINE CHROMOSOMES ON GENERATIONS 1, 5, 10, 15 AND 20 OF SELECTION



The dashed line on each graphic indicates the average level of the MAF distribution

2.3.4 Runs of homozygosity detection and distributions

The average number of ROH per different class length sizes (1–2, 2–4, 4–8, and >8 Mb) considering sliding window and consecutive methodology to access ROH, in both taurine and indicine simulated populations is shown in TABLE 7. In general, the class of 1-2 Mb length size has the highest number of ROH across all evaluations on generations 1, 5, 10 and 20. Similarly, high frequency for ROH 1-2 Mb was found in five different cattle breeds farmed in Italy with (MARRAS et al., 2015). Moreover, most of the total length of ROH for a real Gyr cattle population, approximately 60%, is composed of short segments (PERIPOLLI et al., 2018). Furthermore, the number of ROH in the class of 1-2 Mb length size decreases across the generations in all

evaluations. On the other hand, the number of ROH in the class >8 Mb increases. Given that repeated meiosis broken down ROH segments throughout generations, small ROH tends to reflect ancient inbreeding while long ROH represents recent inbreeding since recombination did not have enough time to short IBD segments (FERENČAKOVIĆ; SÖLKNER; CURIK, 2013; KIRIN et al., 2010).

TABLE 7. AVERAGE NUMBER OF ROH PER CLASS FOLLOWED BY STANDARD DEVIATION ESTIMATED FROM SLIDING WINDOW AND CONSECUTIVE METHODS IN TAURINE AND INDICINE SIMULATED POPULATIONS ON GENERATION 01 AND 20.

[2]ROH class	**Taurine Population**			
	Sliding Method		**Consecutive Method**	
	Generation 01	**Generation 20**	**Generation 01**	**Generation 20**
$ROH_{1\text{-}2\ Mb}$	2.16 ±0.200	2.01 ±0.030	2.59 ±0.030	2.41 ±0.030
$ROH_{2\text{-}4\ Mb}$	1.27 ±0.170	1.22 ±0.020	1.14 ±0.020	1.11 ±0.020
$ROH_{4\text{-}8\ Mb}$	0.50 ±0.010	0.51 ±0.010	0.34 ±0.008	0.37 ±0.010
$ROH_{>8\ Mb}$	0.17 ±0.003	0.26 ±0.010	0.11 ±0.002	0.21±0.010
[2]ROH class	**Indicine Population**			
	Sliding Method		**Consecutive Method**	
	Generation 01	**Generation 20**	**Generation 01**	**Generation 20**
$ROH_{1\text{-}2\ Mb}$	2.16 ±0.020	1.98 ±0.040	2.04 ±0.550	1.88 ±0.030
$ROH_{2\text{-}4\ Mb}$	0.63 ±0.010	0.62 ±0.010	0.43 ±0.007	0.43 ±0.010
$ROH_{4\text{-}8\ Mb}$	0.13 ±0.002	0.18 ±0.007	0.09 ±0.002	0.14 ±0.007
$ROH_{>8\ Mb}$	0.05 ±0.002	0.17 ±0.010	0.04 ±0.001	0.16 ±0.010

$ROH_{1\text{-}2\ Mb}$: average runs of homozygosity number in the length class between 1 and 2 Mb; $ROH_{2\text{-}4\ Mb}$: average runs of homozygosity number in the length class between 2 and 4 Mb; $ROH_{4\text{-}8\ Mb}$: average runs of homozygosity number in the length class between 4 and 8 Mb; $ROH_{>8\ Mb}$: average runs of homozygosity number in the length class higher than 8 Mb; [2]values followed by 10^5.

The evolutionary forces influence on ROH length segments is also visualized on the percentage of ROH per class length size (1–2, 2–4, 4–8, and >8 Mb) considering sliding window and consecutive methodology to access ROH, in both taurine and indicine simulated populations is showed in TABLE 8. In general, the percentage of ROH class 1-2 Mb decrease from generation 1 to 20. Moreover, the percentage of ROH class >8 increase across the twenty generations of selection in the distinguished populations and ROH detection methodologies. Furthermore, the indicine population has a higher percentage of ROH class 1-2 Mb compared with the taurine population between the two ROH detection methods. These results suggest what was described before by Mészáros et al. (2015), animals with the same genome length covered by distinguished numbers of ROH segments is a consequence of the distinct distances from the common ancestor. Recalling that continuous reduction in the number of animals (bottleneck) was made from generation 1,001 to 1,020 or 2,020 to obtain taurine and indicine simulated populations respectively.

TABLE 8. PERCENTAGE OF ROH PER CLASS FOLLOWED BY STANDARD DEVIATION ESTIMATED FROM SLIDING WINDOW AND CONSECUTIVE METHODS IN TAURINE AND INDICINE SIMULATED POPULATIONS ON GENERATION 01 AND 20.

	Taurine Population			
	Sliding Method		**Consecutive Method**	
ROH class	**Generation 01**	**Generation 20**	**Generation 01**	**Generation 20**
$ROH_{1\text{-}2\ Mb}$	0.53 ±0.005	0.50 ±0.008	0.62 ±0.005	0.59 ±0.007
$ROH_{2\text{-}4\ Mb}$	0.31 ±0.003	0.30 ±0.006	0.27 ±0.003	0.27 ±0.004
$ROH_{4\text{-}8\ Mb}$	0.12 ±0.002	0.13 ±0.003	0.09 ±0.002	0.12 ±0.003
$ROH_{>8\ Mb}$	0.04 ±0.001	0.07 ±0.004	0.05 ±0.000	0.05 ±0.003
	Indicine Population			
	Sliding Method		**Consecutive Method**	
ROH class	**Generation 01**	**Generation 20**	**Generation 01**	**Generation 20**
$ROH_{1\text{-}2\ Mb}$	0.73 ±0.003	0.67 ±0.008	0.78 ±0.003	0.72 ±0.009
$ROH_{2\text{-}4\ Mb}$	0.21 ±0.002	0.21 ±0.005	0.16 ±0.002	0.17 ±0.005
$ROH_{4\text{-}8\ Mb}$	0.04 ±0.001	0.06 ±0.002	0.03 ±0.001	0.05 ±0.002
$ROH_{>8\ Mb}$	0.02 ±0.000	0.06 ±0.003	0.02 ±0.000	0.06 ±0.004

$ROH_{1\text{-}2\ Mb}$: average runs of homozygosity percentage in the length class between 1 and 2 Mb; $ROH_{2\text{-}4\ Mb}$: average runs of homozygosity percentage in the length class between 2 and 4 Mb; $ROH_{4\text{-}8\ Mb}$: average runs of homozygosity percentage in the length class between 4 and 8 Mb; $ROH_{>8\ Mb}$: average runs of homozygosity percentage in the length class higher than 8 Mb.

The average segment ROH length per class length size (1–2, 2–4, 4–8, and >8 Mb) showed in TABLE 9 was also affected across the generations evaluated. Higher average ROH length was found in the twentieth generation of selection in both approaches and breeds. Therefore, these results suggest the ability to access ancient and recent autozygosity. Since inbreeding from recent common ancestors that occurred only five generations ago is associated with ROH longer than 10 Mb (HOWRIGAN; SIMONSON; KELLER, 2011). Generally, the mean ROH length in the class 1-2 Mb is higher for taurine than to indicine simulated population. Otherwise, considering the class >8 Mb the indicine generally has a higher mean ROH length.

TABLE 9. ROH LENGTH MEAN (MB) PER CLASS FOLLOWED BY STANDARD DEVIATION ESTIMATED FROM SLIDING WINDOW AND CONSECUTIVE METHODS IN TAURINE AND INDICINE SIMULATED POPULATIONS ON GENERATION 01 AND 20.

	Taurine Population			
	Sliding Method		Consecutive Method	
ROH class	Generation 01	Generation 20	Generation 01	Generation 20
$ROH_{1\text{-}2\ Mb}$	1.41 ±0.003	1.41 ±0.003	1.39 ±0.003	1.39 ±0.006
$ROH_{2\text{-}4\ Mb}$	2.74 ±0.005	2.75 ±0.009	2.69 ±0.003	2.70 ±0.009
$ROH_{4\text{-}8\ Mb}$	5.40 ±0.013	5.43 ±0.017	5.34 ±0.011	5.40 ±0.028
$ROH_{>8\ Mb}$	13.54 ±0.134	16.60 ±0.336	14.16 ±0.149	17.57 ±0.308
	Indicine Population			
	Sliding Method		Consecutive Method	
ROH class	Generation 01	Generation 20	Generation 01	Generation 20
$ROH_{1\text{-}2\ Mb}$	1.36 ±0.001	1.36 ±0.003	1.32 ±0.001	1.33 ±0.003
$ROH_{2\text{-}4\ Mb}$	2.64 ±0.006	2.66 ±0.009	2.61 ±0.005	2.65 ±0.009
$ROH_{4\text{-}8\ Mb}$	5.28 ±0.015	5.47 ±0.047	5.33 ±0.019	5.52 ±0.047
$ROH_{>8\ Mb}$	16.27 ±0.460	19.16 ±0.43	16.79 ±0.531	19.38 ±0.401

$ROH_{1\text{-}2\ Mb}$: average runs of homozygosity length mean in the length class between 1 and 2 Mb; $ROH_{2\text{-}4\ Mb}$: average runs of homozygosity length mean in the length class between 2 and 4 Mb; $ROH_{4\text{-}8\ Mb}$: average runs of homozygosity length mean in the length class between 4 and 8 Mb; $ROH_{>8\ Mb}$: average runs of homozygosity length mean in the length class higher than 8 Mb.

2.3.5 Inbreeding coefficients

Pedigree-based inbreeding coefficients were available for both taurine and indicine simulated populations in the QMSim output. The average inbreeding coefficients estimated using different approaches and their standard deviation in generation 1, 5, 10, 15 and 20 are presented in TABLE 10. The highest average F_{PED} level was observed for the indicine population in generation 20. The inbreeding coefficient level based on pedigree (F_{PED}) increases across the twenty generations of selection in taurine and indicine populations. The generation 10 and 15 F_{PED} average level is similar to which has been described in real Holstein cattle populations farmed in EUA, Iran, and Canada (ROKOUEI et al., 2010; STACHOWICZ et al., 2011; WIGGANS; VANRADEN; ZUURBIER, 1995). Moreover, the F_{PED} average levels are similar among these two populations. Otherwise, genomic inbreeding coefficients based on ROH detected by sliding approach (F_{ROHs}) and ROH detected with the consecutive approach (F_{ROHc}) are different among these two populations (FIGURE 15). These results suggest that F_{ROH} from both methods to access ROH can detect ancient autozygosity. Besides, the use of genomic data to search loci related to inbreeding depression permits to differentiate animals which have the same inbreeding coefficient but differ in the number of segments that when homozygous cause reduction in fitness (HOWARD et al., 2015). For instance, was applied in Holstein the estimation of

inbreeding depression with runs of homozygosity (ROH), which described consistent results with what determined when using pedigree inbreeding (BJELLAND et al., 2013).

The Person correlations between F_{ROHs} or F_{ROHc} and F_{PED} were quite low positive (FIGURE 16 and 17). Otherwise, higher correlations were found between F_{ROH} estimated with ROH segments longer than 16 Mb (0.42 $p<0.01$) in real indicine population genotyped with ~777 kb markers panel (PERIPOLLI et al., 2018). Furthermore, a stronger correlation between F_{PED} and F_{ROH} was observed on Simmental cattle genotyped with ~54 kb markers and using ROH segments longer than 8 Mb to estimate F_{ROH} (MARRAS et al., 2015). These results should be explained since segments longer than 16 Mb represents recent inbreeding (~ 3 generations), thus some of autozygosity that is due to more distant common ancestors is not covered with them (FERENČAKOVIĆ et al., 2013). All ROH segments were used to calculate F_{ROH}, probably the short ones, which represent ancient inbreeding, reduced the correlation to low estimates. Since there is an overestimation of genomic inbreeding with the introduction of ROH <4 Mb in its determination when 54 kb SNP panel is used (MARRAS et al., 2015). In addition, F_{PED} does not take into account the stochastic variations into account to predict the inbreeding level, which does not guarantee precision estimation as ROH based inbreeding does (FERENČAKOVIĆ et al., 2013).

TABLE 10. AVERAGE INBREEDING COEFFICIENT (F_{PED}) AND GENOMIC INBREEDING COEFFICIENTS BASED ON SLIDING WINDOW (F_{ROHS}) AND CONSECUTIVE (F_{ROHC}) ROH DETECTING METHODS FOLLOWED BY STANDARD DEVIATIONS ON GENERATIONS 1, 5, 10, 15 AND 20 OF SELECTION IN TAURINE AND INDICINE SIMULATED POPULATIONS

	Taurine			Indicine		
Generation	**F_{PED}**	**F_{ROHs}**	**F_{ROHc}**	**F_{PED}**	**F_{ROHs}**	**F_{ROHc}**
1	0.00 ±0.000	0.38 ±0.019	0.33 ±0.020	0.00 ±0.000	0.21 ±0.019	0.17 ±0.020
5	0.00 ±0.000	0.40 ±0.017	0.35 ±0.017	0.00 ±0.000	0.20 ±0.015	0.17 ±0.015
10	0.02 ±0.005	0.39 ±0.020	0.34 ±0.020	0.02 ±0.005	0.21 ±0.019	0.18 ±0.019
15	0.05 ±0.007	0.42 ±0.021	0.37 ±0.022	0.05 ±0.008	0.24 ±0.024	0.21 ±0.025
20	0.07 ±0.005	0.44 ±0.022	0.39 ±0.022	0.08 ±0.008	0.27 ±0.027	0.24 ±0.027

FIGURE 15. AVERAGE INBREEDING COEFFICIENT (F_{PED}) AND GENOMIC INBREEDING COEFFICIENTS BASED ON CONSECUTIVE (F_{ROHC}) AND SLIDING WINDOW (F_{ROHS}) ROH DETECTING METHODS ON GENERATIONS 1, 5, 10, 15 AND 20 OF SELECTION IN TAURINE AND INDICINE SIMULATED POPULATIONS

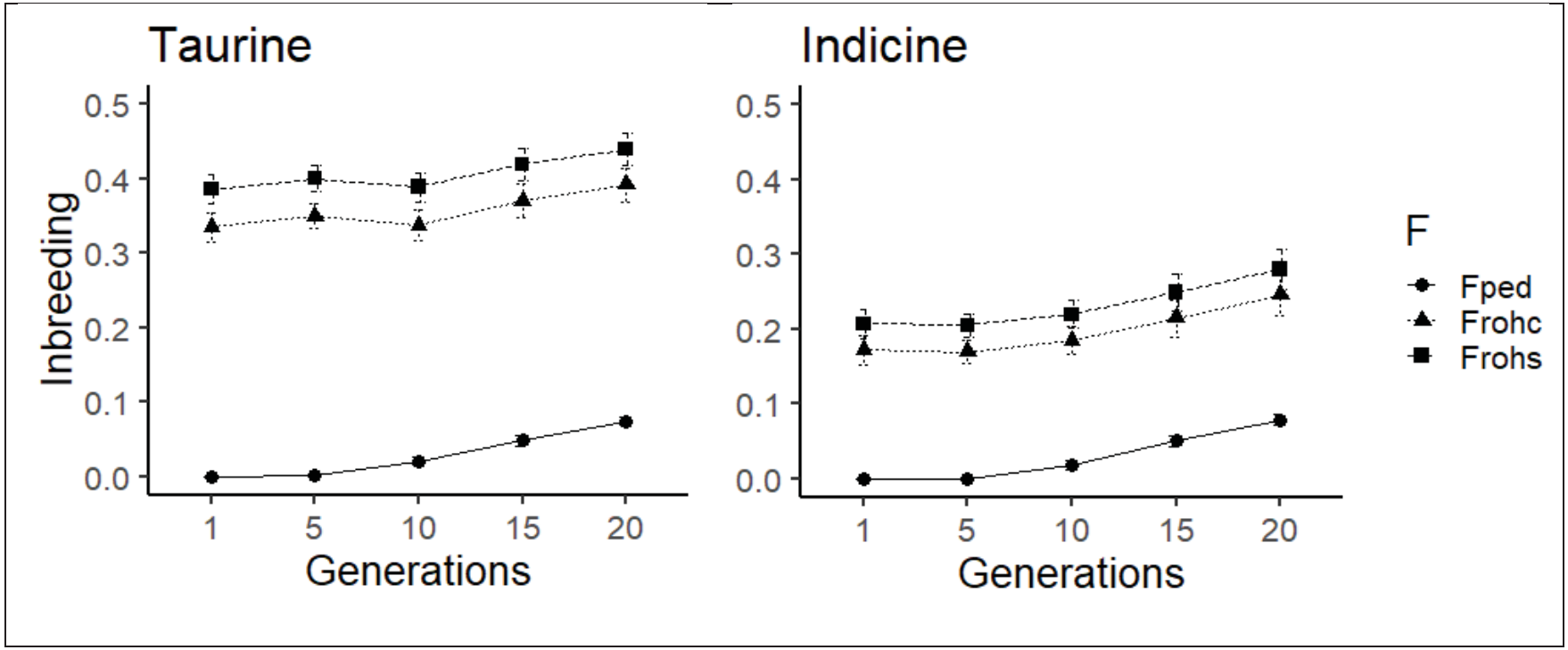


FIGURE 16. PEARSON CORRELATION BETWEEN INBREEDING COEFFICIENT (F_{PED}) AND GENOMIC INBREEDING COEFFICIENT (F_{ROH}) ON GENERATIONS 10, 15 AND 20 OF SELECTION IN TAURINE'S SIMULATED POPULATION

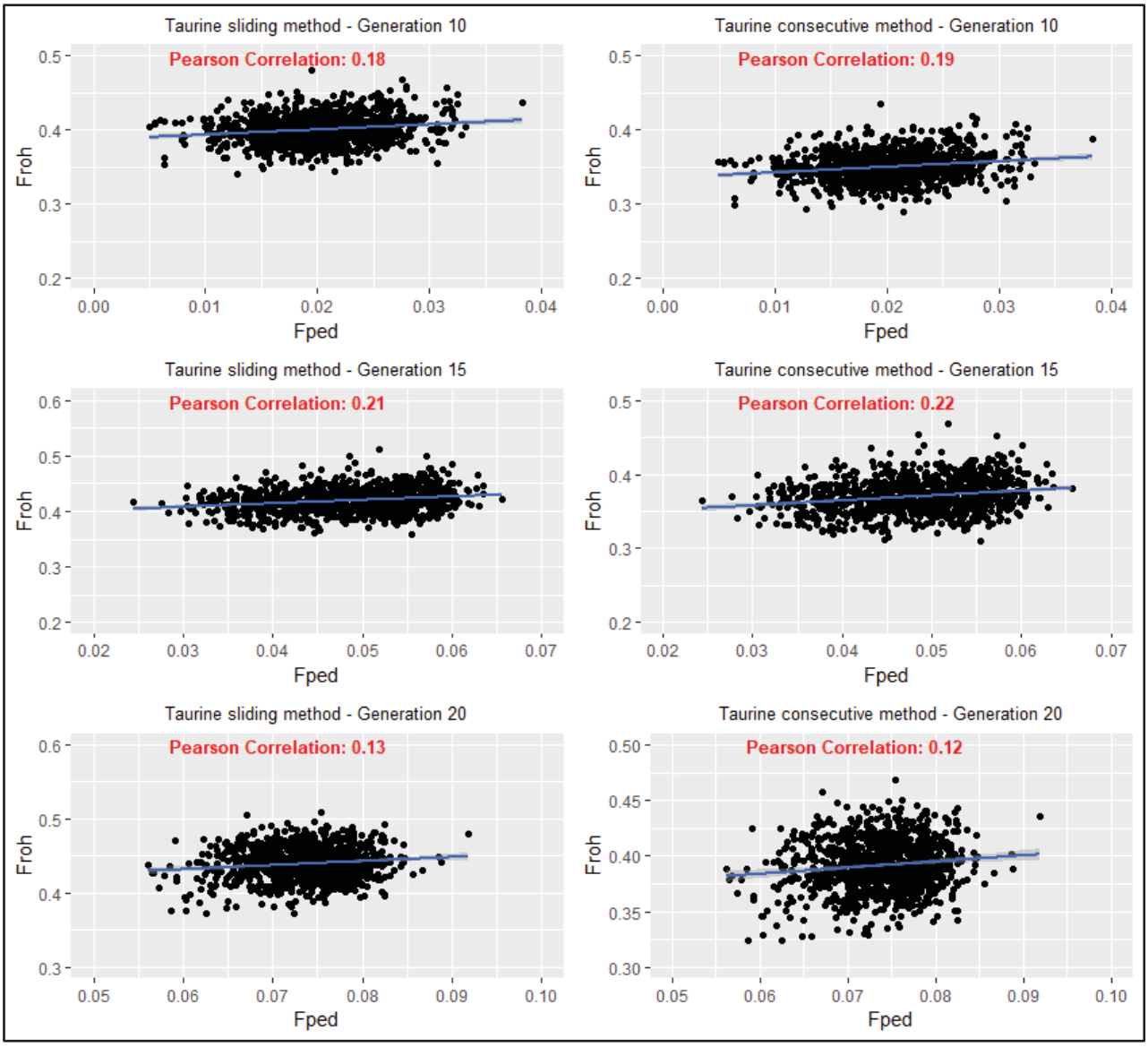
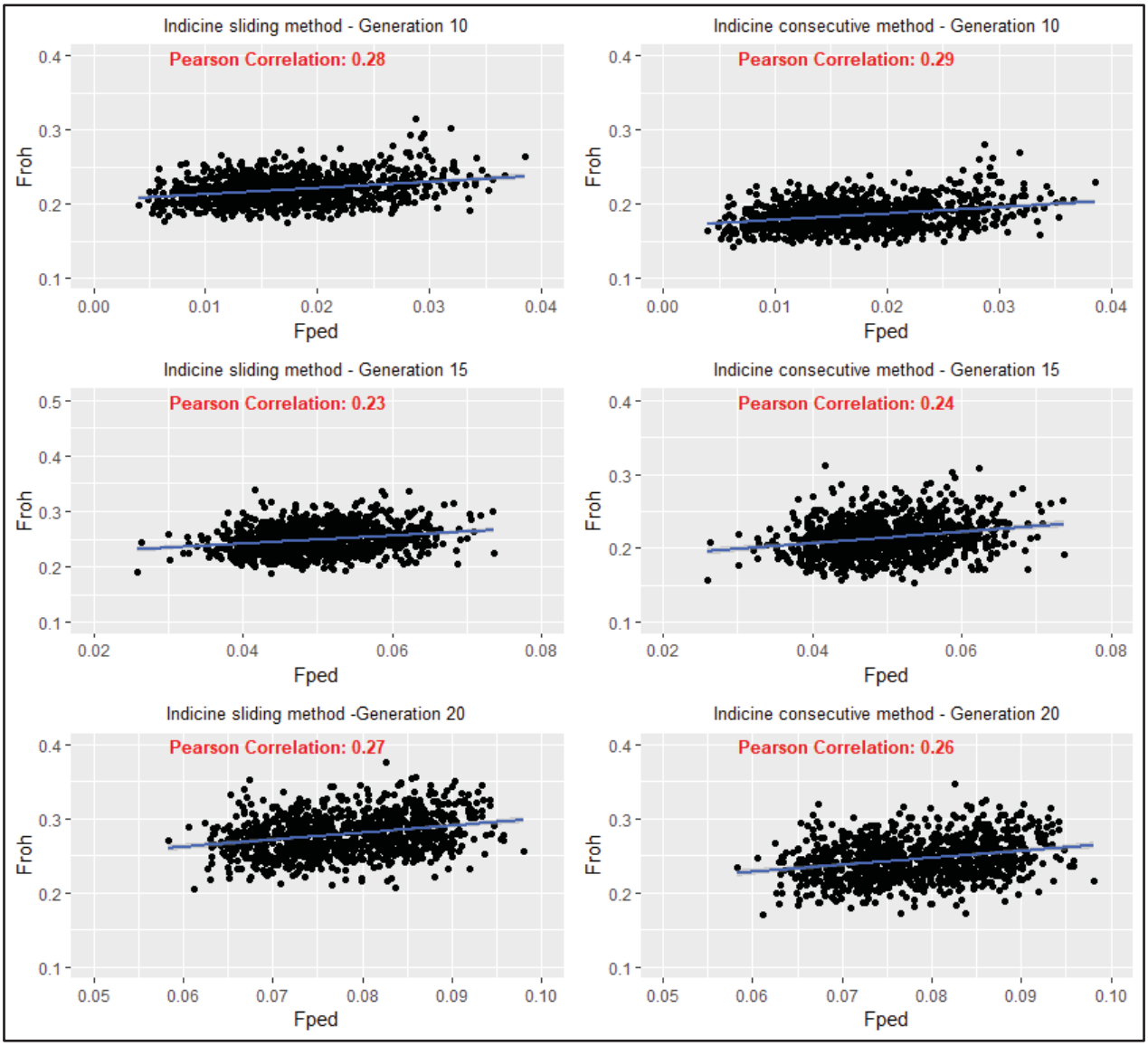


FIGURE 17. CORRELATION BETWEEN INBREEDING COEFFICIENT (F_{PED}) AND GENOMIC INBREEDING COEFFICIENT (F_{ROH}) ON GENERATIONS 10, 15 AND 20 OF SELECTION IN INDICINE'S SIMULATED POPULATION



2.4 CONCLUSIONS

Even in the absence of selection, levels of inbreeding tend to increase over the generations as a function of the effective size decrease in the population. However, this increase is accentuated in scenarios with assortative positive mating, consequently with high levels of inbreeding depression. The intensive selection for one trait could rapidly increase the average inbreeding coefficient on critical levels in populations with high and low initial LD. This inbreeding increment observed in

simulated populations of dairy cattle is related to inbreeding depression and could cause irreversible damages in milk yield. Non-random mating systems must be applied to control inbreeding levels and consequently inbreeding depression. The estimation of inbreeding by the pedigree can not access the difference in inbreeding depression between the zebu and taurine populations.

Inbreeding depression is influenced by many genetic factors. Thus, is necessary to understand the molecular influence of inbreeding on inbreeding depression to better explain acceptable levels of inbreeding coefficient in dairy cattle.

The sliding or consecutive approach are powerful methodologies for detecting runs of homozygosity. These approaches can also access ancestral and recent inbreeding in simulated dairy cattle populations. Besides that, genomic inbreeding should express also evolutionary forces like selection and drift which distinguished some breeds and species.

ACKNOWLEDGMENTS

To the Zootechny Graduate Program PPGZ – UFPR and the Guelph University in Canada for the free availability of QMSim software.

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FINAL CONSIDERATIONS

Animal breeding is an essential tool to increase animal protein production. Important results have been historically shown in milk yield and quality. Otherwise, part of the genetic gain is related to the reduction of effective population size (Ne). Consequently, there is also an increase in animal inbreeding on these dairy cattle populations, which implies inbreeding depression and variability reduction. Therefore, it is necessary to constantly evaluate and follows all the effects of animal breeding goals. In other words, it is important to adjust genetic gain and efficiency of maintaining sustainability.

The advent of high-density SNP panels enabled to speed up the genetic gain of many traits. Furthermore, this approach enabled also to research and follow many evolutive events. For instance, selection and genetic drift are closely linked with variability decrease. Among the distinct available and described methodologies, runs of homozygosity (ROH) stands out. Since ROH allows to identify recent and ancient evolutive events. Therefore, many studies have been applied in associate ROH with diseases and deleterious traits which are commonly expressed in the homozygous state.

There are some different approaches to access ROH, sliding or consecutive methods can both access ancient and recent autozygosity. The different number and runs of homozygosity size between simulated populations explain the importance of applying these methodologies to investigate their relationship with inbreeding depression in real dairy cattle populations. Besides that, the inbreeding coefficient based on ROH provides a different tool to control and follows inbreeding throughout selection schemes for animal breeding.

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