

European Association of Animal Science

Lyon, France, August 28-31, 2023

✕ @BaesC1

Practical approaches to managing increased homozygosity caused by genomic selection

CF Baes, C Obari, B Makanjuola, C Rochus, C Maltecca, F Schenkel, F Miglior

Professor and Canada Research Chair in Livestock Genomics, Centre for Genetic Improvement of Livestock, University of Guelph

Chair of the Department of Animal Biosciences, University of Guelph

Adjunct Professor, University of Prince Edward Island

Dozentin, Institut für Genetik, Vetsuisse Fakultät, Universität Bern



IMPROVE LIFE.



Genetic Selection Today

- Genetic selection in the dairy cattle industry has seen dramatic changes in recent decades
 - Introduction of **genomic selection** in 2009
 - Improved and novel technologies
- Increased popularity and usage of **young GPA bulls**
- Broadening of selection goals and number of traits evaluated
- **Accelerated genetic gains** in most traits under selection
- In the genomics era, we also **need strategies and tools to help control some of the negative consequences** to ensure continued genetic progress

Consequences of Genomic Selection

- Increase genetic gain through:
 - Reduced generation interval
 - Increased accuracy
 - Ability to select for traits recorded in only few animals
 - Maintaining herd book integrity
 - Etc., etc., etc...
 - **EVERYTHING IS AWESOME!**

Homozygosity (inbreeding) is increasing at an increased rate

- Homozygous recessives more apparent
- Homozygous recessives with delayed impact (e.g. Cholesterol Deficiency)
- More subtle effects of inbreeding:
 - Reduction in phenotypic mean value
 - Reduction in rate of selection response
- Potential future implications: **unknown**
- Financial economic losses : **unknown**
 - (*\$US 11 million / year, Cole et al.*)
- Social license is eroding

Assessment of Genetic Diversity in Canadian Dairy Cattle



J. Dairy Sci. 103
<https://doi.org/10.3168/jds.2019-18013>
© American Dairy Science Association[®], 2020.

Effect of genomic selection on rate of inbreeding and coancestry and effective population size of Holstein and Jersey cattle populations

Bayode O. Makanjuola,¹ Filippo Miglior,^{1,2} Emhimad A. Abdalla,¹ Christian Maltecca,^{1,3} Flavio S. Schenkel,¹ and Christine F. Baes^{1,4*}

RESEARCH ARTICLE

Open Access

Inbreeding and runs of homozygosity before and after genomic selection in North American Holstein cattle



Mehrnush Forutan^{1,2*}, Saeid Ansari Mahyari^{1*}, Christine Baes², Nina Melzer³, Flavio Schramm Schenkel² and Mehdi Sargolzaei^{2,4,5}

RESEARCH ARTICLE

Open Access

Identification of unique ROH regions with unfavorable effects on production and fertility traits in Canadian Holsteins



Bayode O. Makanjuola^{1*}, Christian Maltecca^{1,2}, Filippo Miglior¹, Gabriele Marras³, Emhimad A. Abdalla¹, Flavio S. Schenkel¹ and Christine F. Baes^{1,4}



J. Dairy Sci. 103:5302–5313
<https://doi.org/10.3168/jds.2019-17846>

© 2020, The Authors. Published by FASS Inc. and Elsevier Inc. on behalf of the American Dairy Science Association[®]. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Symposium review: Exploiting homozygosity in the era of genomics—Selection, inbreeding, and mating programs*

C. Maltecca,^{1†} F. Tiezzi,¹ J. B. Cole,² and C. Baes^{3,4*}



J. Dairy Sci. 102:2807–2817
<https://doi.org/10.3168/jds.2018-15520>
© American Dairy Science Association[®], 2019.

Symposium review: The genomic architecture of inbreeding: How homozygosity affects health and performance*

Christine F. Baes,^{1,2†} Bayode O. Makanjuola,¹ Filippo Miglior,^{1,3} Gabriele Marras,^{1,4} Jeremy T. Howard,^{5,6} Allison Fleming,^{1,3} and Christian Maltecca⁶

RESEARCH ARTICLE

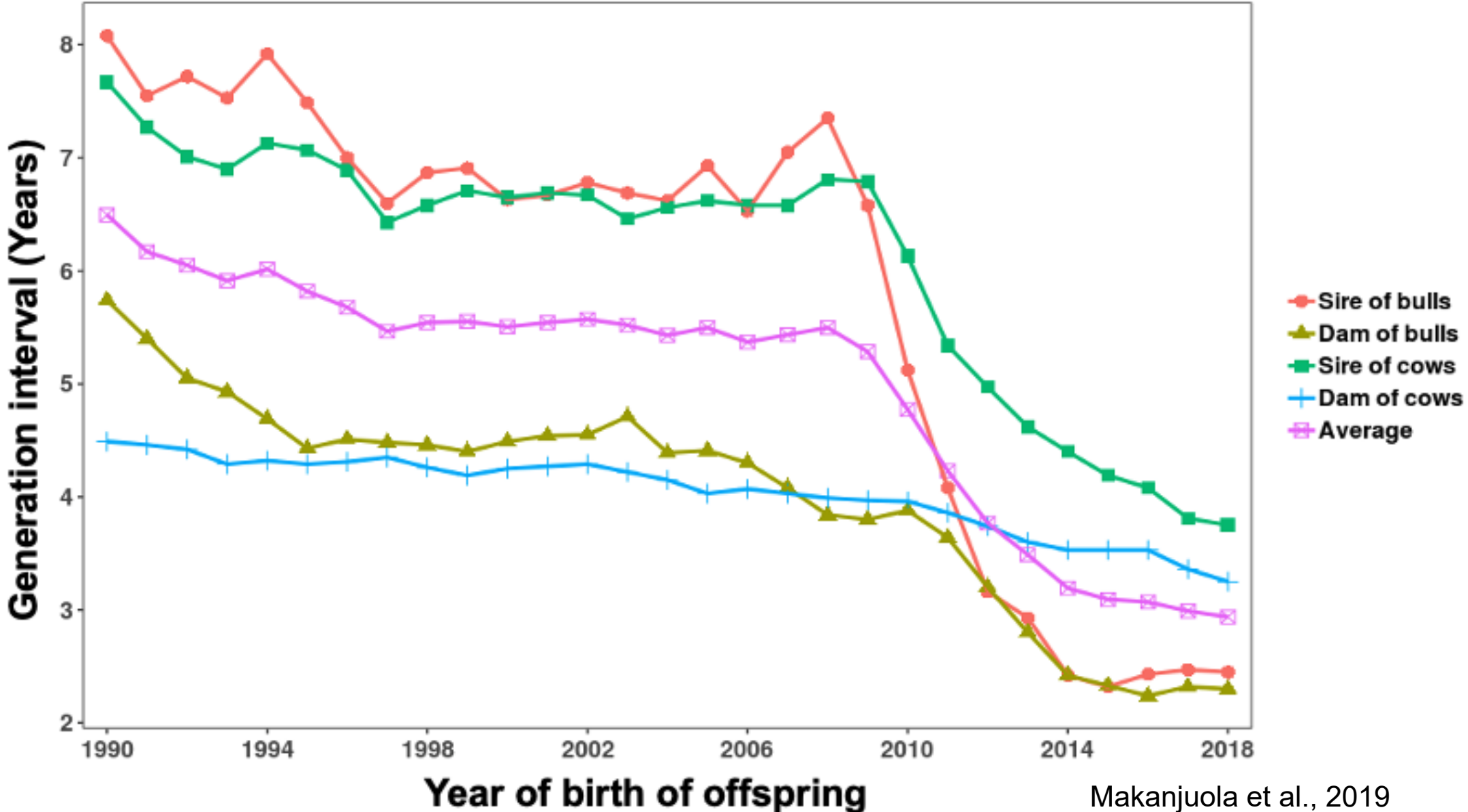
Open Access

Effect of recent and ancient inbreeding on production and fertility traits in Canadian Holsteins



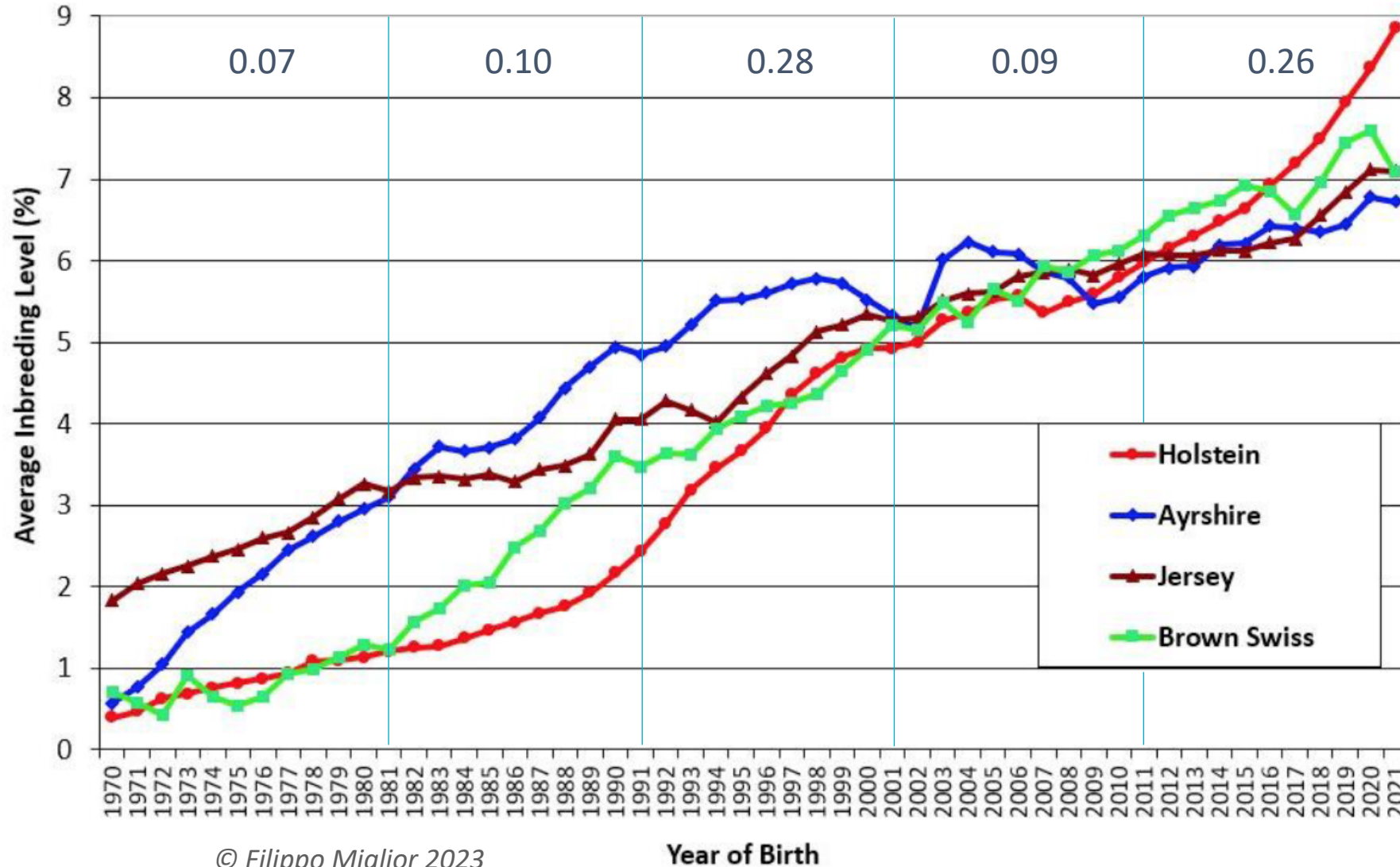
Bayode O. Makanjuola^{1*}, Christian Maltecca^{1,2}, Filippo Miglior¹, Flavio S. Schenkel¹ and Christine F. Baes^{1,3}

Generation Interval in North American Holsteins



Inbreeding Trends

The rate of increase and not the absolute value is relevant



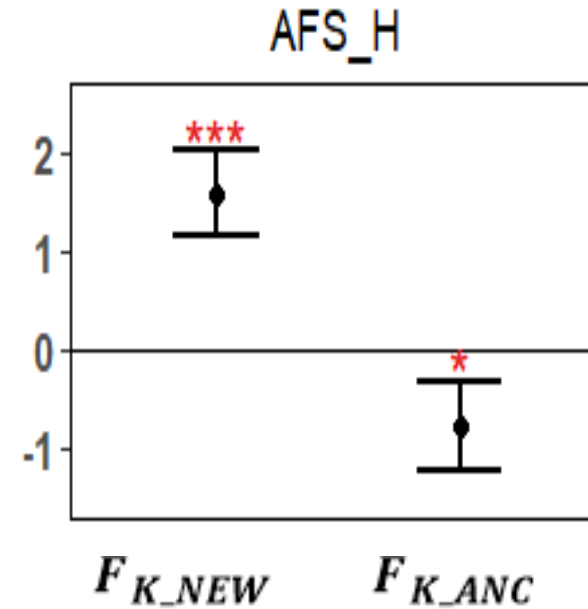
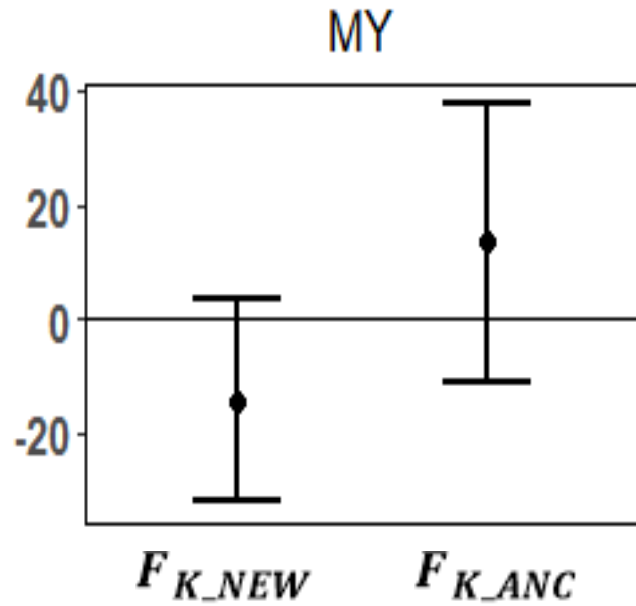
➔ For Holstein

Effective Population Size

Effective population size	Estimated values (Holstein)
Pedigree (Ne_{PED})	66
Runs of Homozygosity ($Ne_{ROH_SNP1101}$)	46
Runs of Homozygosity (Ne_{ROH_PLINK})	43
Genomic Relationship Matrix (Ne_{GRM})	49
Pedigree coancestry (Ne_f)	51
Genomic coancestry (Ne_{fSEG})	51

Effects of Recent vs. Old Homozygosity

Effect of 1% increase in
new and ancient
inbreeding



Pedigree vs Genomic Inbreeding

The ***coefficient of inbreeding*** (Sewall Wright, 1922) is the probability that two base pairs at a randomly chosen position in the genome (*locus*) are *identical by descent*

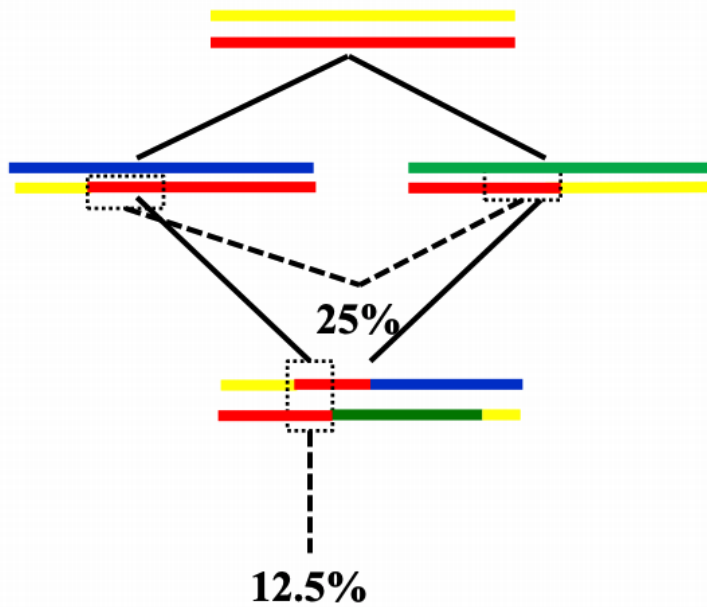
Pedigree Inbreeding

- Classical measure of inbreeding, uses pedigree data and tracing it back to identify common ancestors between the sire and dam
- Formed on averages and are expectations
- Highly dependent upon completeness, depth, and integrity of available pedigree

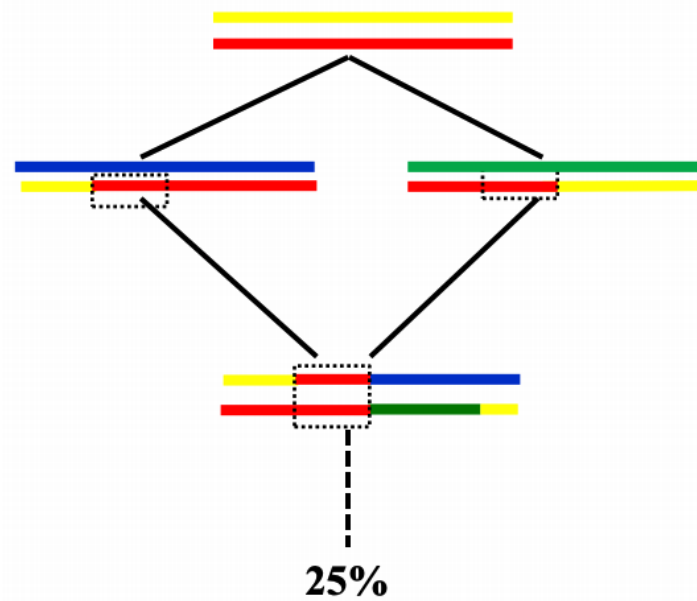
Genomic Inbreeding

- Accounts for Mendelian sampling (chance factor in distributing half the genetic material) between individuals
- Captures realized inbreeding

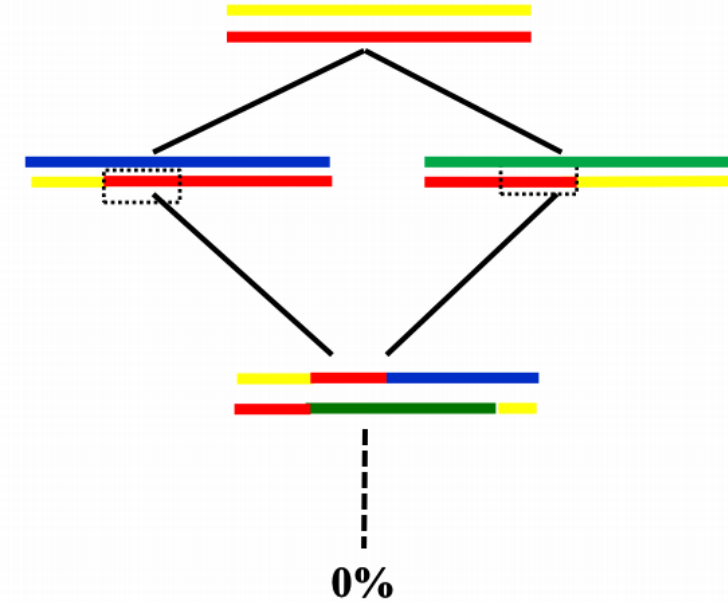
Pedigree vs Genomic Inbreeding



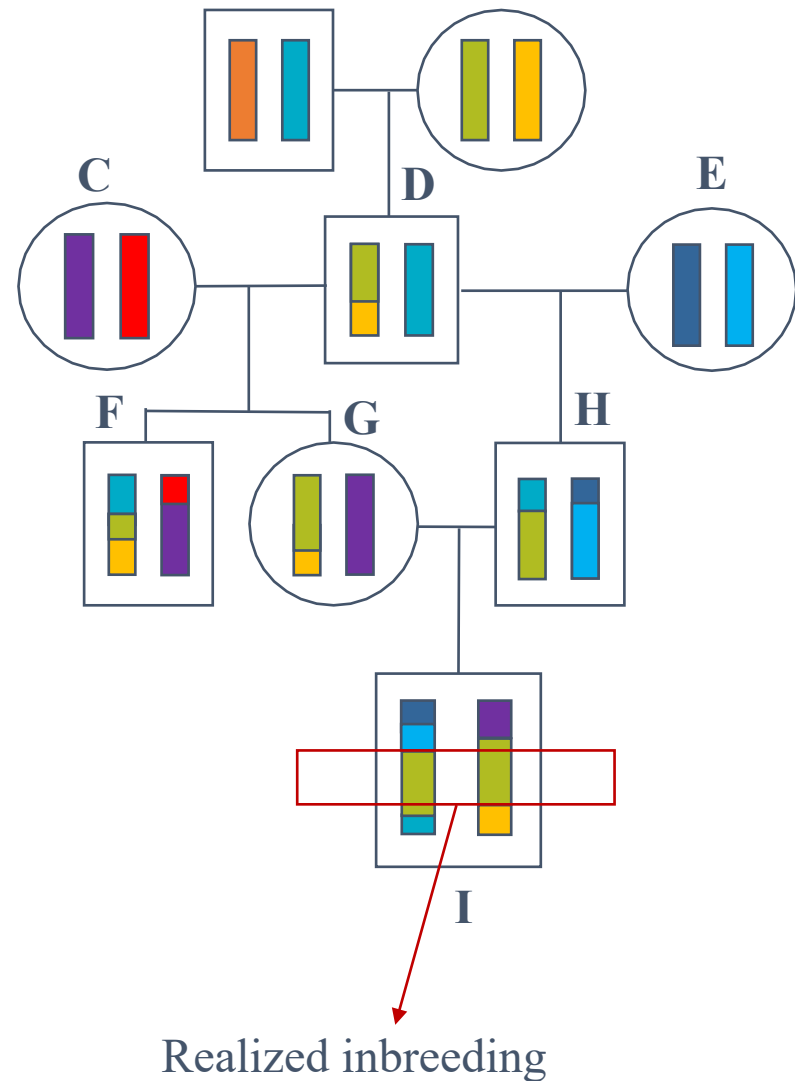
(Expectation)



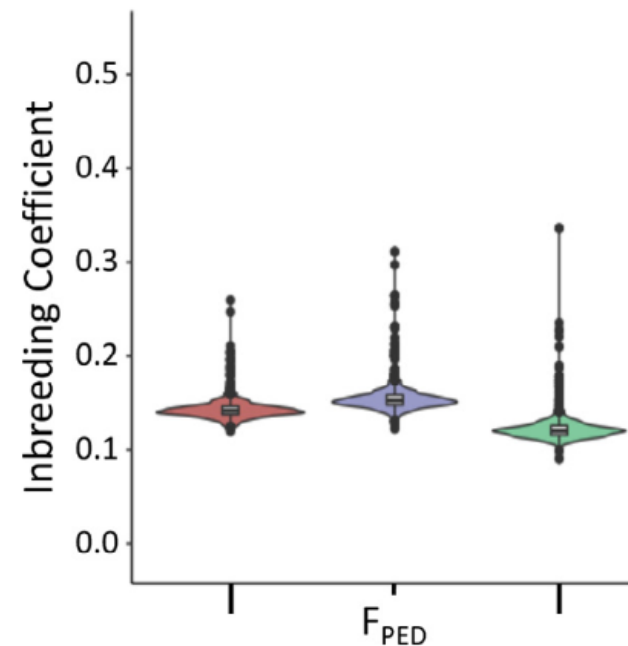
(Mendelian Sampling)



Runs of Homozygosity: Improved Measure of Inbreeding



- **ROH** = unbroken homozygous chromosomal regions present on homologous chromosomes of a specific animal



Perspectives

Industry Perspective:

- a) I do everything I can to avoid inbreeding at all costs
- b) I don't like the increase in inbreeding, but I can't change it.
- c) If it ain't broke, don't fix it.

Public Perspective:

“...the gene pool is about as deep as a pie-plate”



Academic Perspective:

The benefits of intense directional selection currently outweigh the detrimental effects of inbreeding, but there could be a threshold at which lack of genetic diversity causes serious problems.

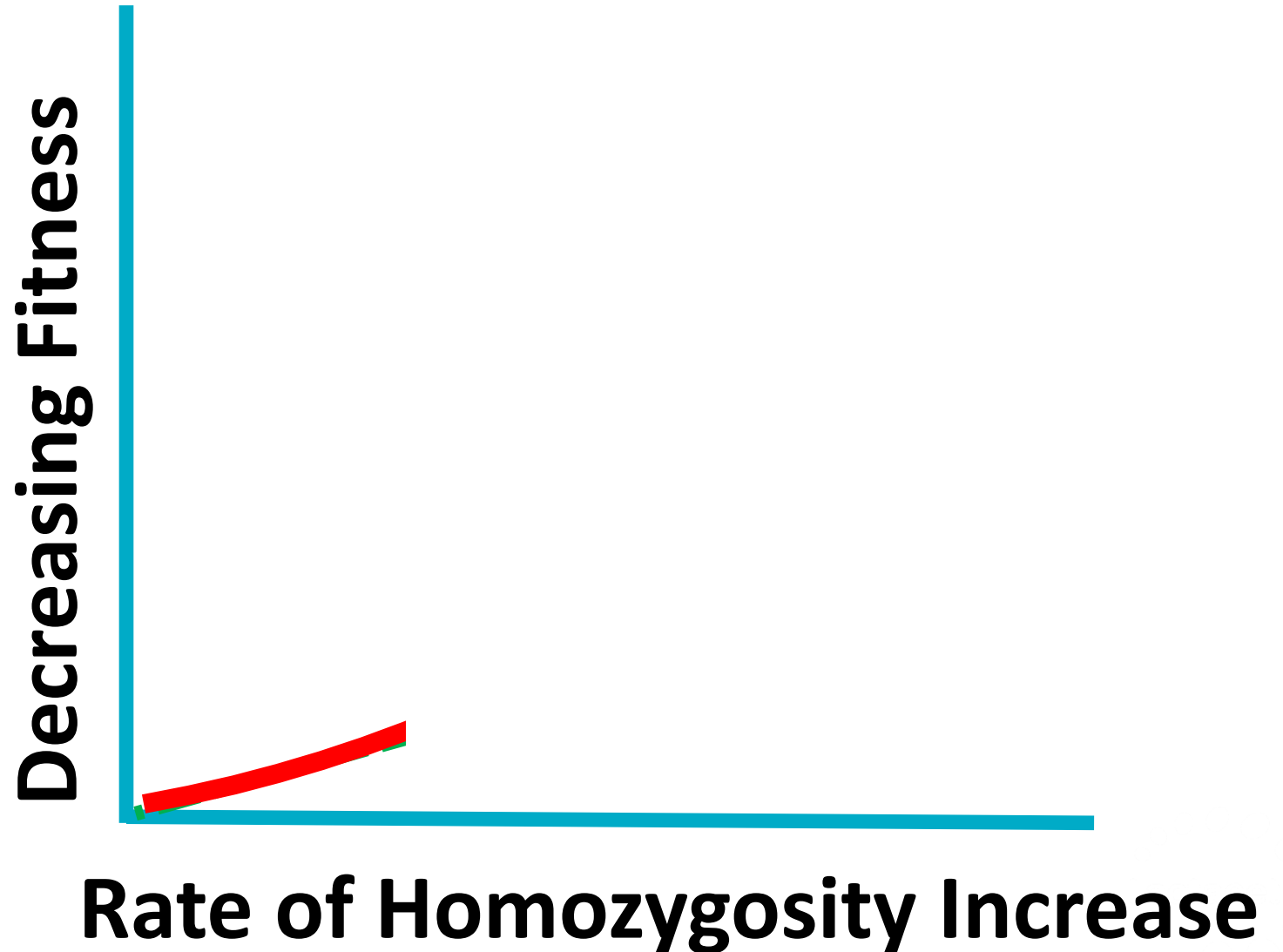
We don't know when/if that would happen.

Reality:

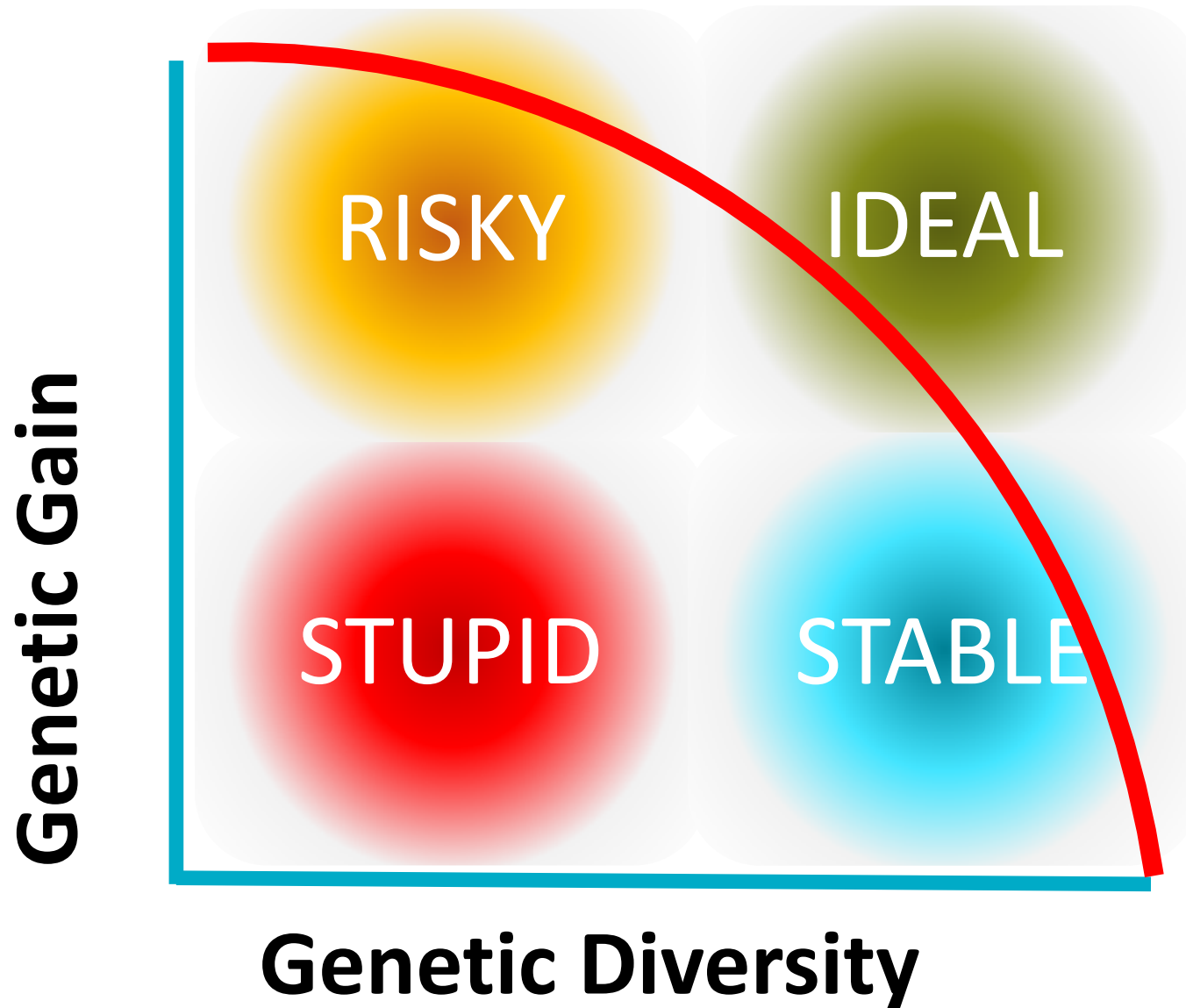
- Inbreeding is an unavoidable in intense directional selection programs
- At best, we can **manage and monitor** the **loss** of diversity

Why should we care?

- **Short-term consequences:** smaller, less diverse population = , decreased relative fitness (i.e., survival and fertility)
- **Long-term consequences:** lower gene diversity means less raw material for adaptations to changing environments, which may affect long-term survival



“The Breeders Dilemma”



Current Farmers Priorities

- Average inbreeding levels continue to rise in each breed
- Difficult to find outcross sires of interest with high genetic merit

Realities

- Knowing the inbreeding level of a female and of potential mating sires contributes little to controlling the rate of inbreeding in your herd
- Two important decision points for maintaining genetic diversity in a dairy population:
 - The genetic diversity of young bulls purchased by AI companies
 - The selection of sires when mating a female in your herd

Tools / strategies Available

Google

software for preventing inbreeding in livestock

x

🔍

🔍

All

Images

News

Videos

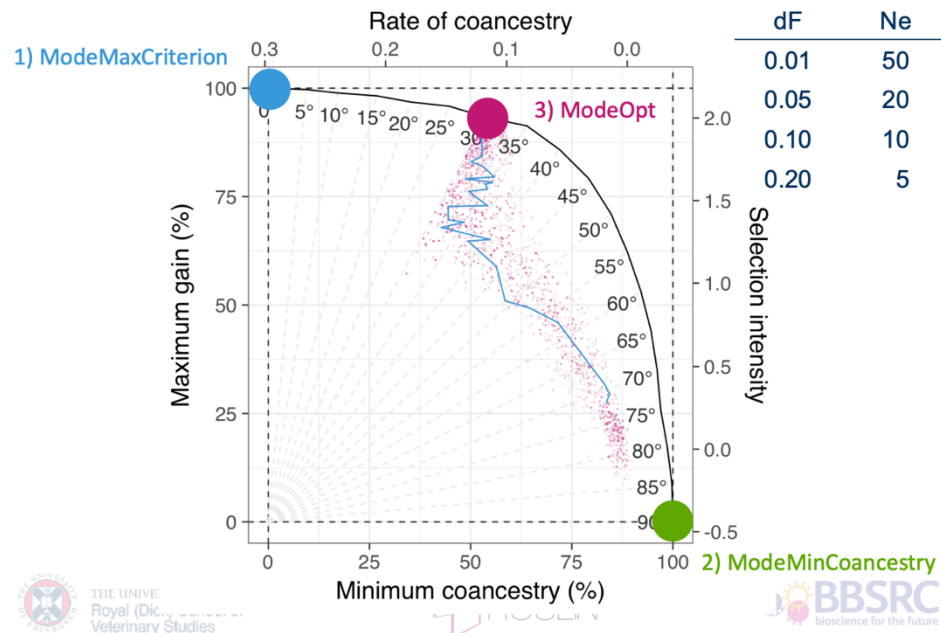
Shopping

More

Tools

About 127,000 results (0.47 seconds)

AlphaMate – evolutionary optimization



Reality:

- Optimal Contribution Selection / other approaches rarely used in dairy
- Top lists dominate conversations / decisions / semen tanks
- “Outcrosses” interesting, but generally unpopular
- Experiments (cross breeding, etc.)

Example: Lactanet Inbreeding Calculator

Know the potential inbreeding for specific matings and avoid those above a tolerable level

- E.g. maintain current inbreeding

POTENTIAL MATES	Potential Progeny's Inbreeding and Parent Averages														
	LPI Code	%INB	LPI	Pro\$	MILK	FAT	PROT	%F	%P	SCS	Conf	MS	F&L	DS	RP
PEAK ALTAHOTHAND-ET	GEBV	9.99	3604	3027	1775	93	80	+0.20	+0.16	108	9	7	5	5	7
WESTCOAST ALCOVE	GEBV	10.62	3596	2848	2008	116	85	+0.31	+0.13	101	7	3	6	9	5
FARNEAR DELTA-LAMBDA-ET	GEBV	10.69	3584	2789	1404	74	65	+0.16	+0.14	106	10	7	8	5	6
NO-FLA CAPITAL 45499-ET	GEBV	9.98	3575	2719	1066	73	72	+0.27	+0.29	105	8	8	4	4	2
S-S-I PR RENEGADE-ET	GEBV	9.46	3570	2775	1306	95	74	+0.37	+0.24	103	6	4	5	5	3
PINE-TREE-I PURSUIT	GEBV	10.32	3560	2937	1440	96	71	+0.34	+0.18	103	7	4	8	5	4
OCD BANDARES CABERNET-ET	GEBV	10.48	3550	2919	847	94	62	+0.52	+0.26	105	8	6	6	5	2

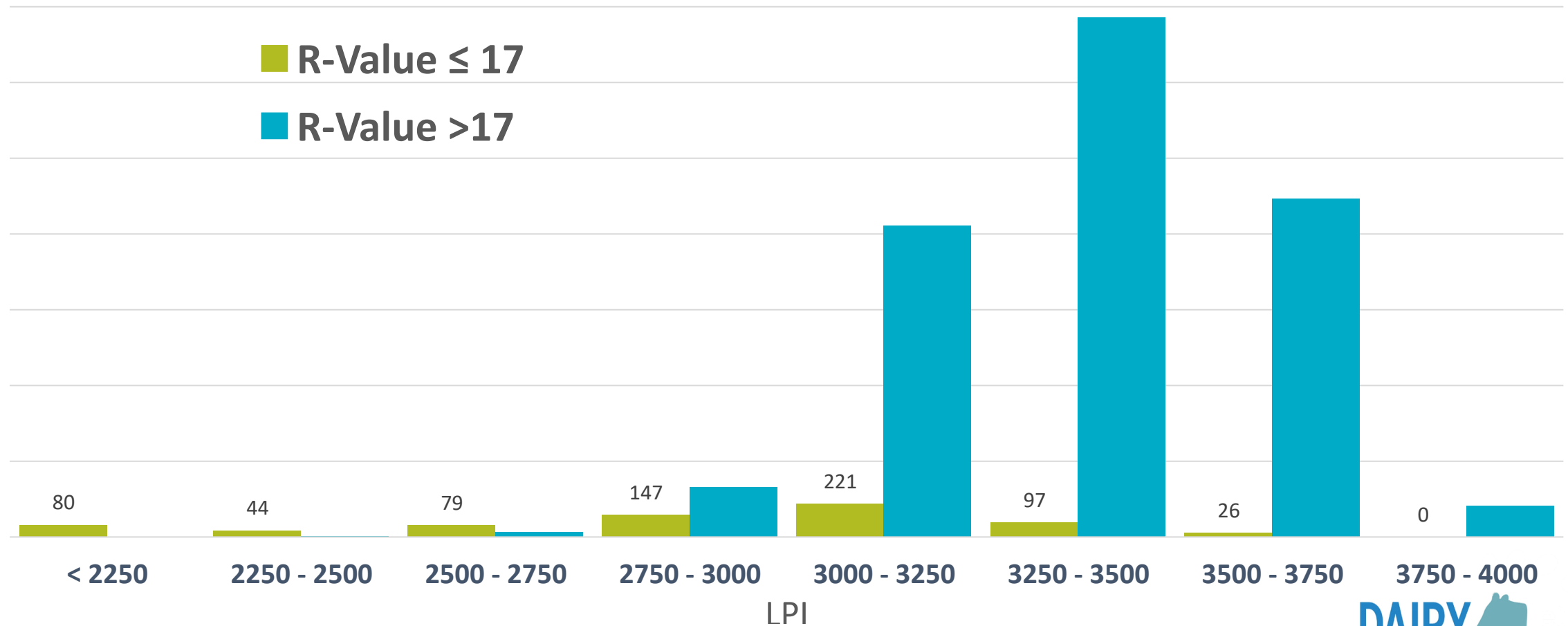
Example: “Outcross” bulls

R-value (Relationship-value)

- Represents the percentage of DNA that the bull has in common (i.e. its average pedigree relationship) with active females of the same breed
- Difficult to find outcross sires of interest with high genetic merit
 - Little advantage for A.I. companies to buy more outcross sires, which normally come with a lower genetic offering
 - Poor demand for their semen

Example: “Outcross” bulls

Actively marketed young GPA Holstein bulls



Improvements: Within-Herd R-Values

- Current R-values are on a population level
 - The relationship with animals in a specific herd could be very different
 - A bull may be outcross to one herd but highly related to another
- Need herd-specific solutions and tools to make it easier to find diverse bulls
- Help farmers identify sires that will add genetic diversity in their herd

★ Working toward **within herd R-values** to provide lists of “**diversity**” bulls specific to individual herds

Second Phase – Breeding Companies

- To-date, there has been little advantage for A.I. companies to buy more outcross sires, which normally come with a lower genetic offering
 - Poor demand for their semen
- Focus continues to be on highest genetic merit
- Still need to develop other tools to help AI companies identify and purchase “Diversity” sires after genotyping new young bull candidates

Genetic Recessives and Abnormalities

- Genomics has aided in the discovery of genetic recessives, but we are also seeing higher occurrences
- **Gene testing and management of genetic recessives**
 - Avoid carrier bulls and never mate two potential carriers
- Need improved reporting of abnormalities and deaths to discover these as early as possible
 - **Will be working with industry partners to develop an improved method for easy reporting and rapid responses**



Genomic Solutions

- Move toward looking at **genomic or realized inbreeding** instead of traditional pedigree-based inbreeding
- Future tools should take advantage of genomic information to identify sires to use within a genotyping herd
 - Where both sire and dam are genotyped, genomic relationships can be used **more accurately** than pedigree relationships
- **Not all inbreeding has a negative effect on performance**
 - Sire selection advice can include genomic information for finding complementary genotypes and avoid negative effects of homozygosity

Future Tools

What future services would help farmers **manage** / **maintain** genetic diversity?

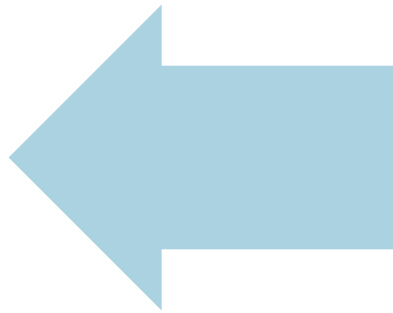
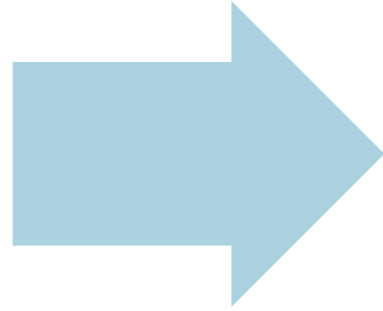
1. Include genomic information where possible for more accurate measures of relatedness
2. Provide a within-herd tool for producers to see which bulls are LEAST related to their herd
3. Develop other tools to help A.I. companies identify and purchase “Diversity” sires after genotyping new young bull candidates
4. Tool to ease the reporting of genetic abnormalities
5. Continue research using new technologies to further understand (biological, economic) impacts of homozygosity

First Steps

- Inbreeding levels are increasing, and that is **unavoidable**
 - Some consequences of inbreeding are still unknown
- Balance genetic gain with increases in inbreeding levels
 - Seek bulls that would be **outcross** to your females
- Do gene testing and manage genetic recessives
- **Genotype females** to also get more information about the current status of inbreeding
- **Continue genomic selection for traits related to health, reproduction, fitness, survival, etc.**

The approach forward involves industry collaboration,
but someone needs to make the first move!

2 Critical Decision points affecting diversity of dairy



Acknowledgements

- Dairy Cattle Genetics Research and Development (DairyGen) Council of Lactanet
- National Science and Engineering Research Council of Canada (NSERC)
- John Cole, Christian Maltecca, Bayode Makanjuola, Holstein Canada Inbreeding Working Group Members, Filippo Miglior, Brian Van Doormaal, Allison Fleming, Pete Sullivan, and many Canadian producers



NSERC
CRSNG

Leveraging Genomics to Achieve Dairy Net-Zero

Recruiting talent for next 4 years:

- PhD students
- Post-docs
- Project manager

Contact: fmiglior@uoguelph.ca or cbaes@uoguelph.ca

Join us for the following American Dairy Science Association Discover Conferences (www.adsa.org):

45th Discover Conference:
Dairy Cattle Lifespan: New Perspectives
October 23-26, 2023, IL, USA

46th Discover Conference:
Milking the Data – Value Driven Dairy Farming
May 6-9, 2024, IL, USA