What does the dairy industry know about inbreeding that you don't?

John B. Cole, Chief Research & Development Officer
john.cole@uscdcb.com

COUNCIL ON DAIRY CATTLE BREEDING

Outline

- Inbreeding is different things to different people
- New inbreeding matters more than old inbreeding
- We're not alone!
- Inbreeding affects different traits in different ways
- Nobody can agree on what to do about it
- Concluding remarks

We're all running the same race

- AI aims to meet market demands
- High-genetic-merit bulls are very marketable
- Lower inbreeding results in slower rates of genetic gain
- Who's willing to go slower to better manage inbreeding?

Source: Wikimedia Commons.

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Point 1

Inbreeding is different things to different people

Inbreeding arises when related animals are mated

- It's the proportion of the genome that's identical because it came from the same ancestor
- Inbreeding arises when related animals are mated
  - Increased coancestry results in reduced genetic variance
- Inbreeding is inevitable in a finite population
  - It can be managed, but not prevented

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What aspects of selection favor inbreeding?

- Multiple generations of intense directional selection (Robertson, 1961)
- High variance of reproductive success across individuals due to the use of advanced reproductive technologies (Nicholas and Smith, 1983)
- Use of BLUP-based genetic evaluations in combination with truncation selection (Verrier et al., 1993)
- These result in widespread use of related individuals as parents of the next generation (e.g., Howard et al., 2017)

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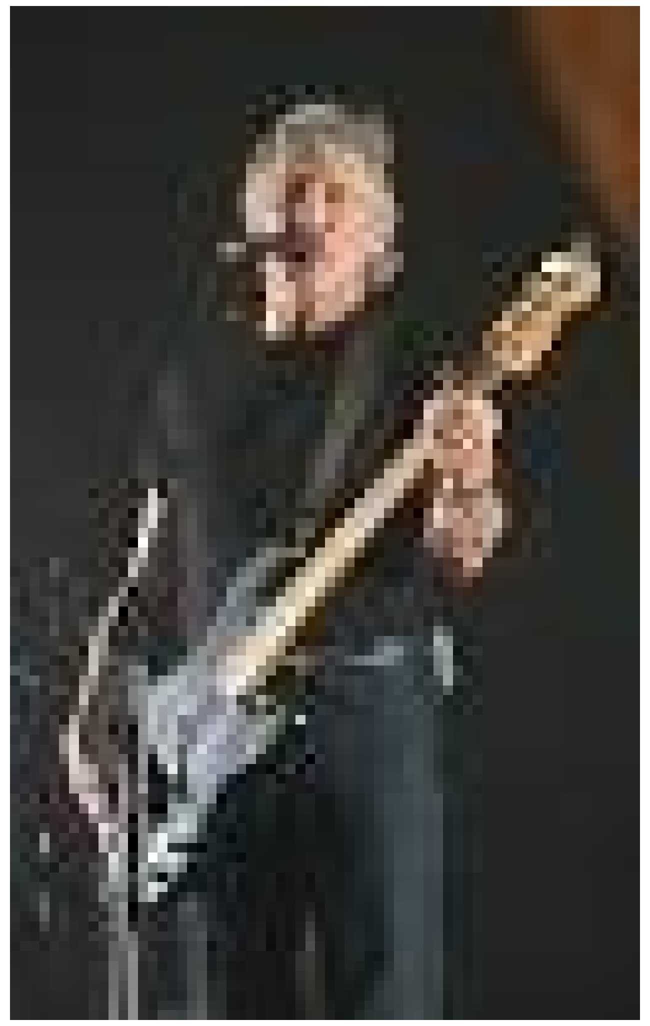
Inbreeding often has undesirable effects

- Harmful loci increase in frequency and are more likely to be paired-up
  - e.g., Haplotypes such as HH1
  - This is thought to account for most inbreeding depression
- Slow inbreeding is more effective at selecting against harmful loci
- Undesirable loci travel along with desirable loci if they're close together ("hitchhiking")



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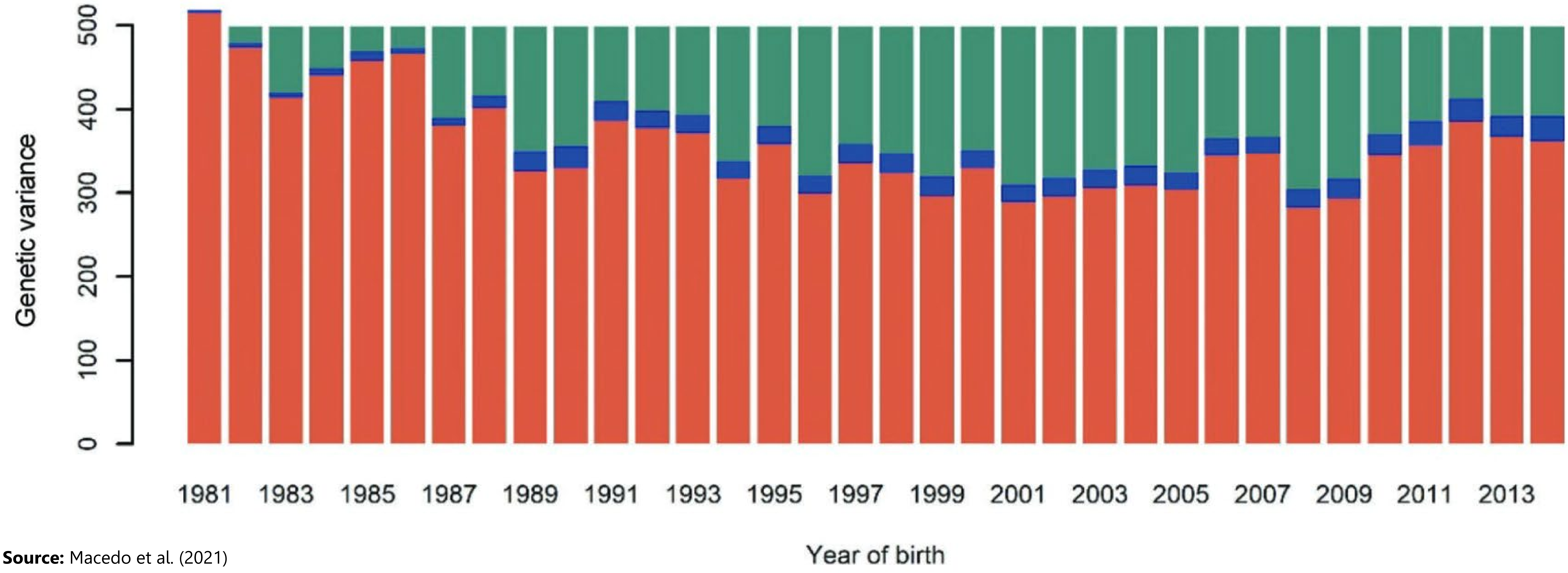
Increased coancestry reduces genetic variance



Source: Macedo et al. (2021)

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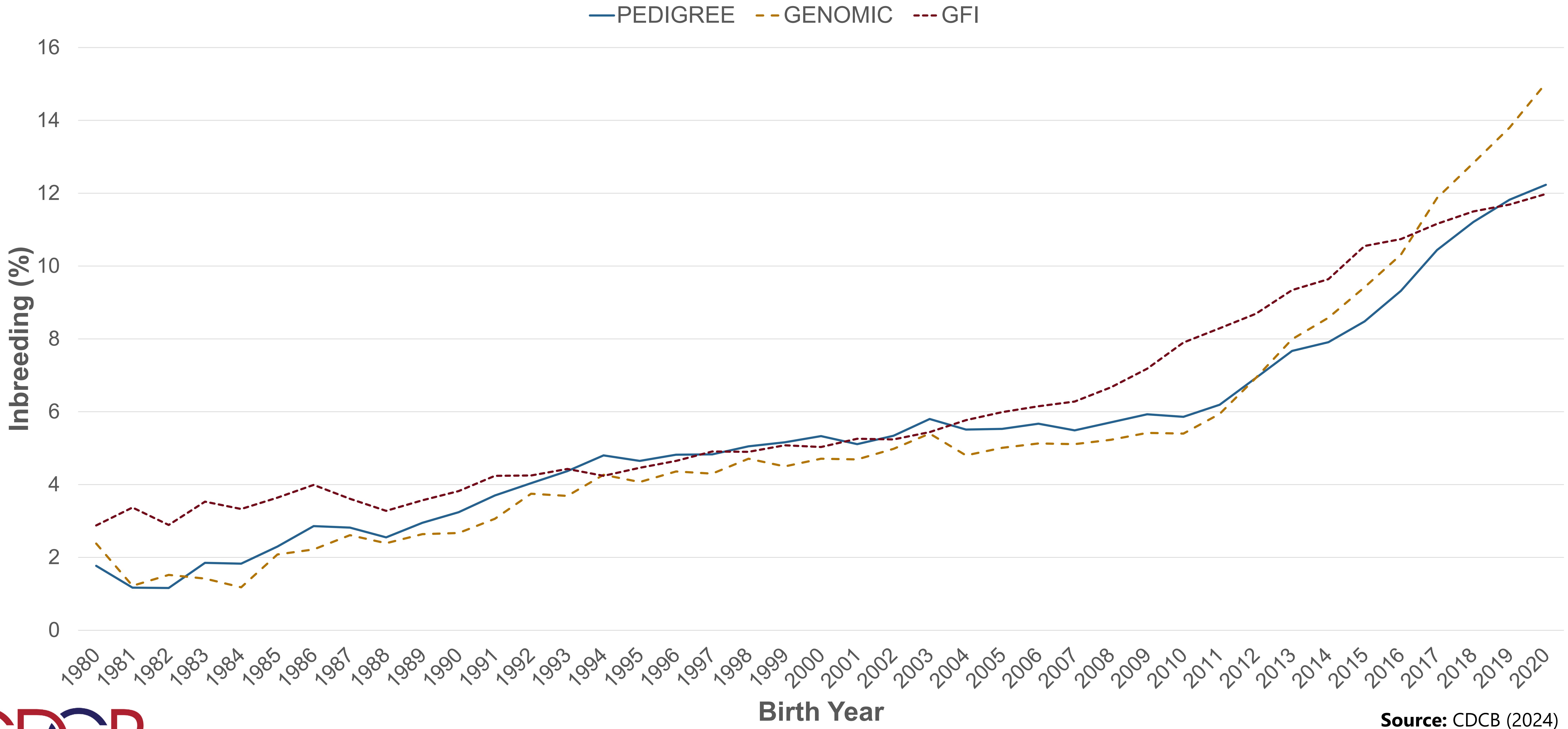
Point 2

New inbreeding matters more than old inbreeding

US Holstein cattle (proven genotyped bulls)



Source: CDCB (2024)

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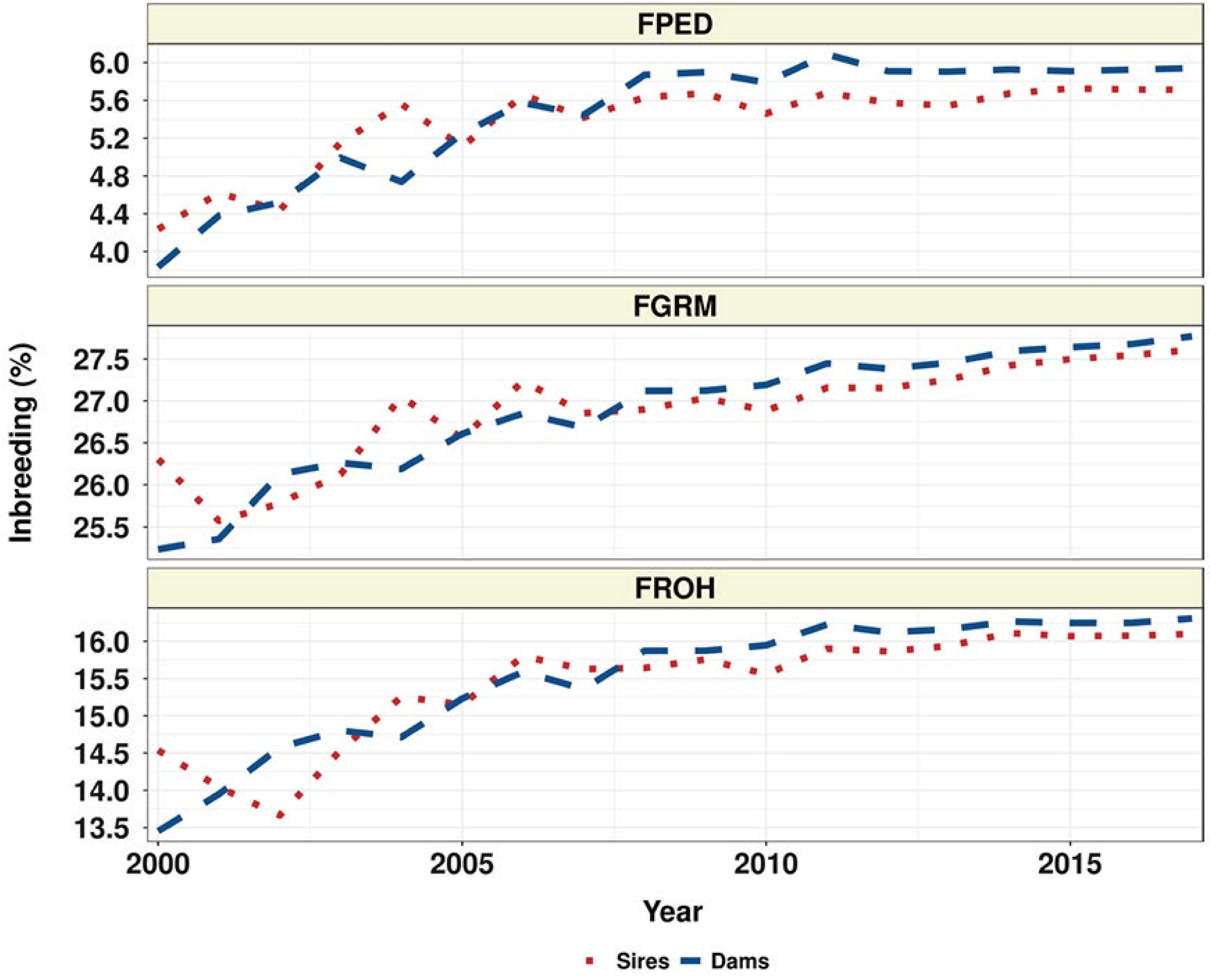
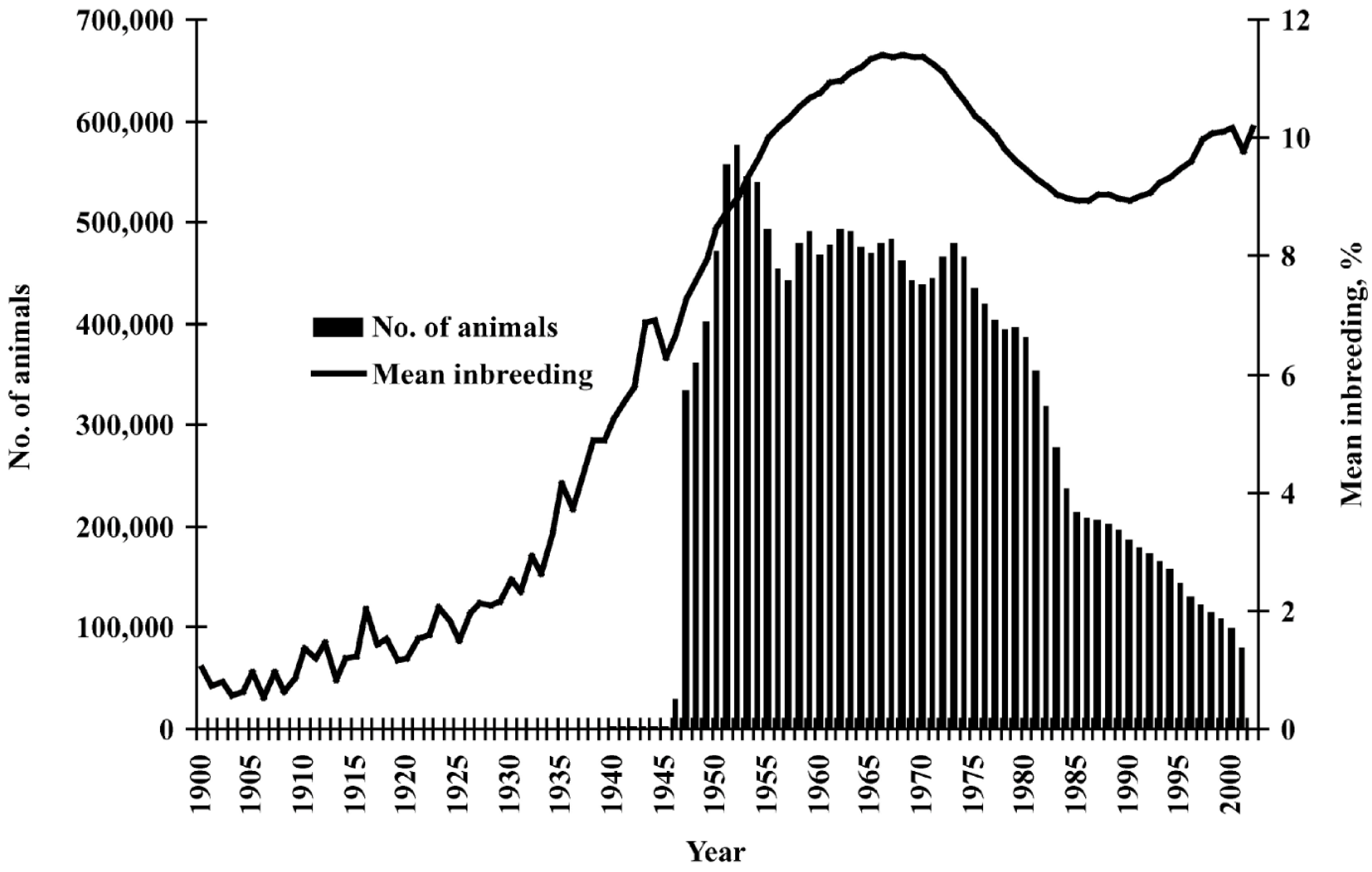
US Angus cattle



Source: Lozada-Soto et al. (2021)

US Hereford cattle



Source: Cleveland et al. (2005)

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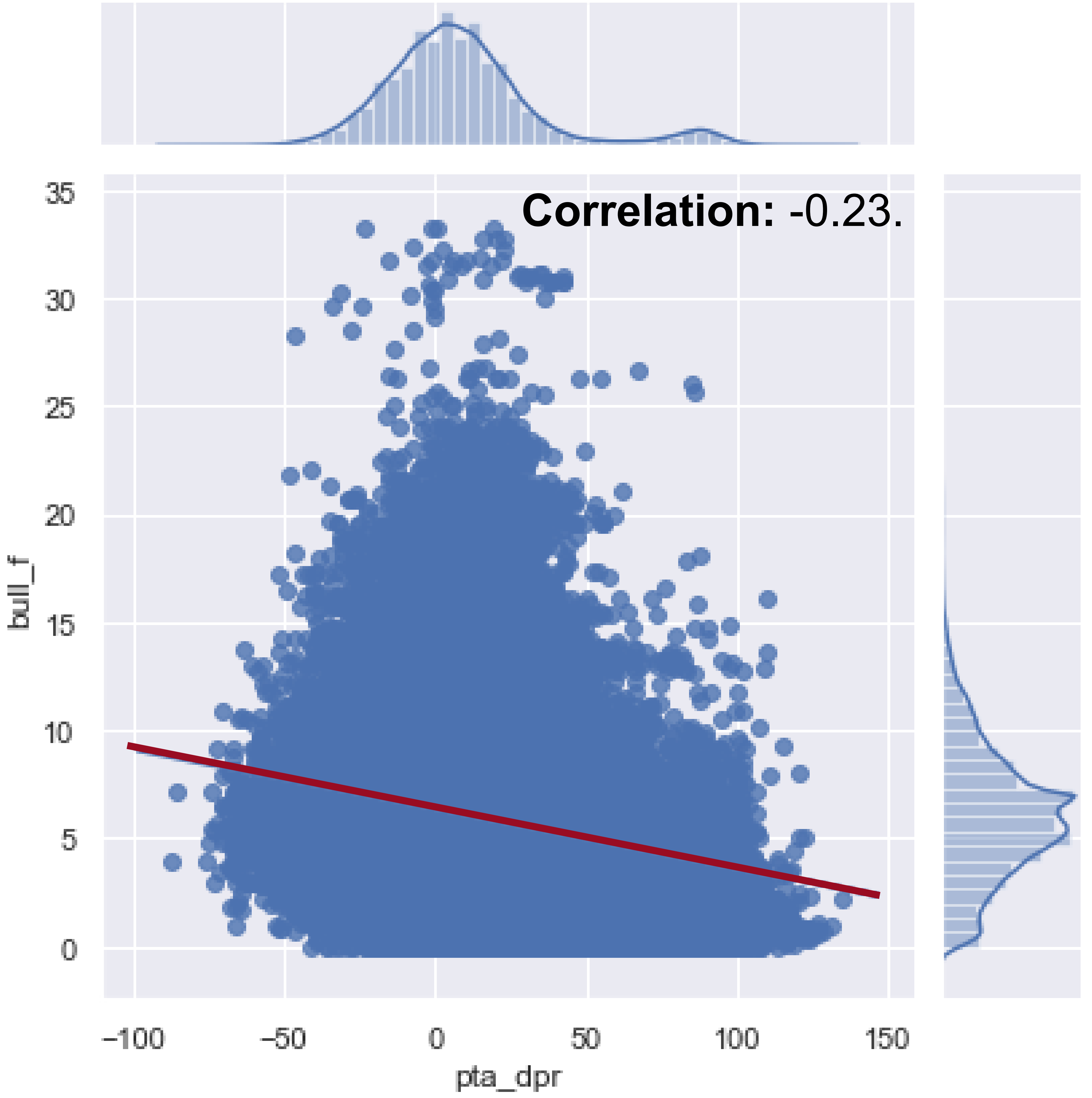
We don't know how much is too much

- Selection is now on indices that include health and fitness data
- This avoids past mistakes from focusing on only one or a few traits
- Will we see genetic merit gradually decrease, or will we cross a threshold and see a sudden crash?
- *Interviewer:* "How did you go bankrupt?"

  Ernest Hemingway: "Two ways. Gradually, then suddenly."



Source: CCDCB (2019).

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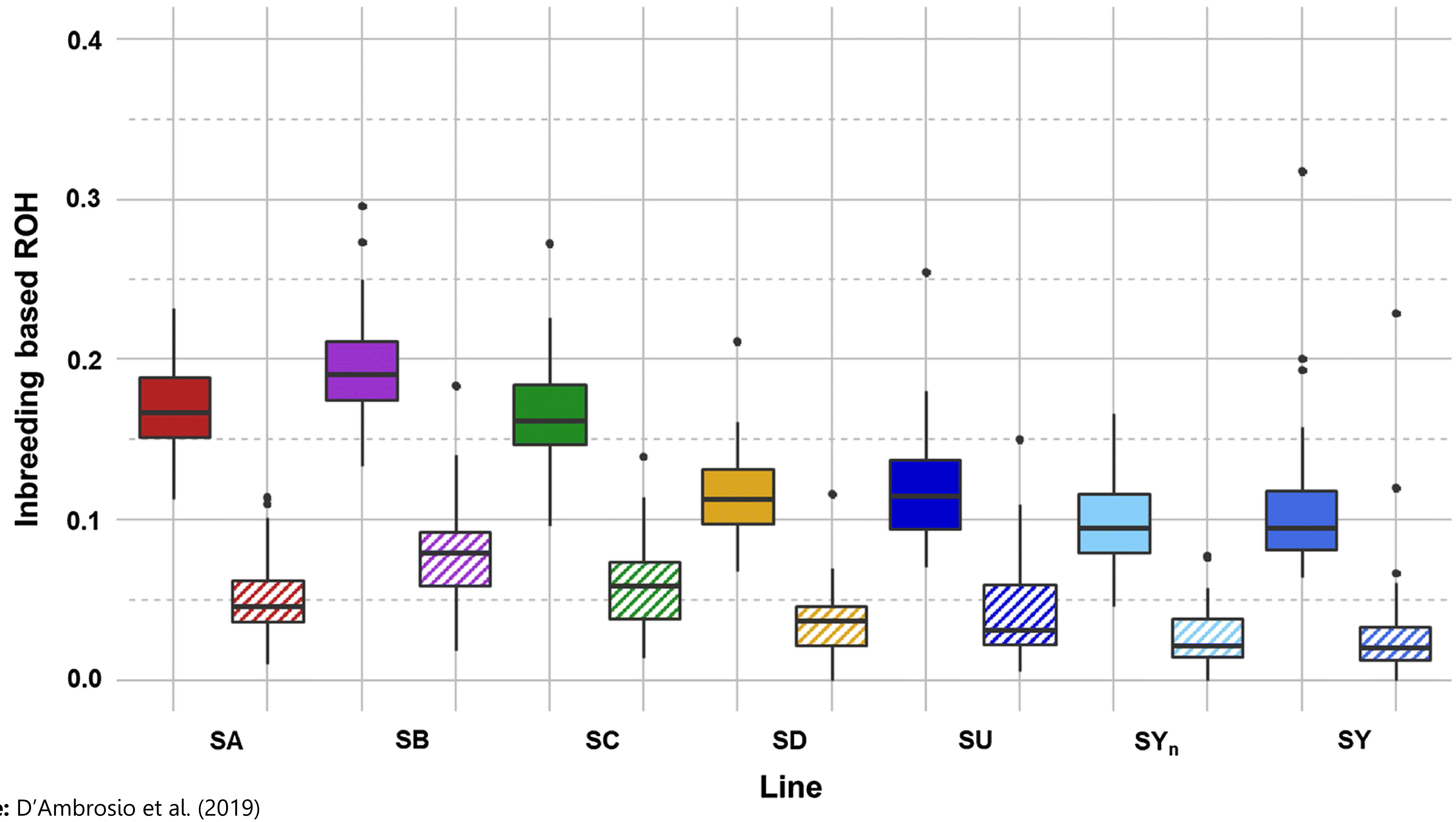
Point 3

We’re not alone!

Commercial rainbow trout lines



Box plots of total inbreeding (FROH) and recent inbreeding (FROH>10) for each rainbow trout line.

Plain box: total inbreeding (FROH).

Hatched box: recent inbreeding (FROH>10).

Source: D'Ambrosio et al. (2019)

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Working dogs

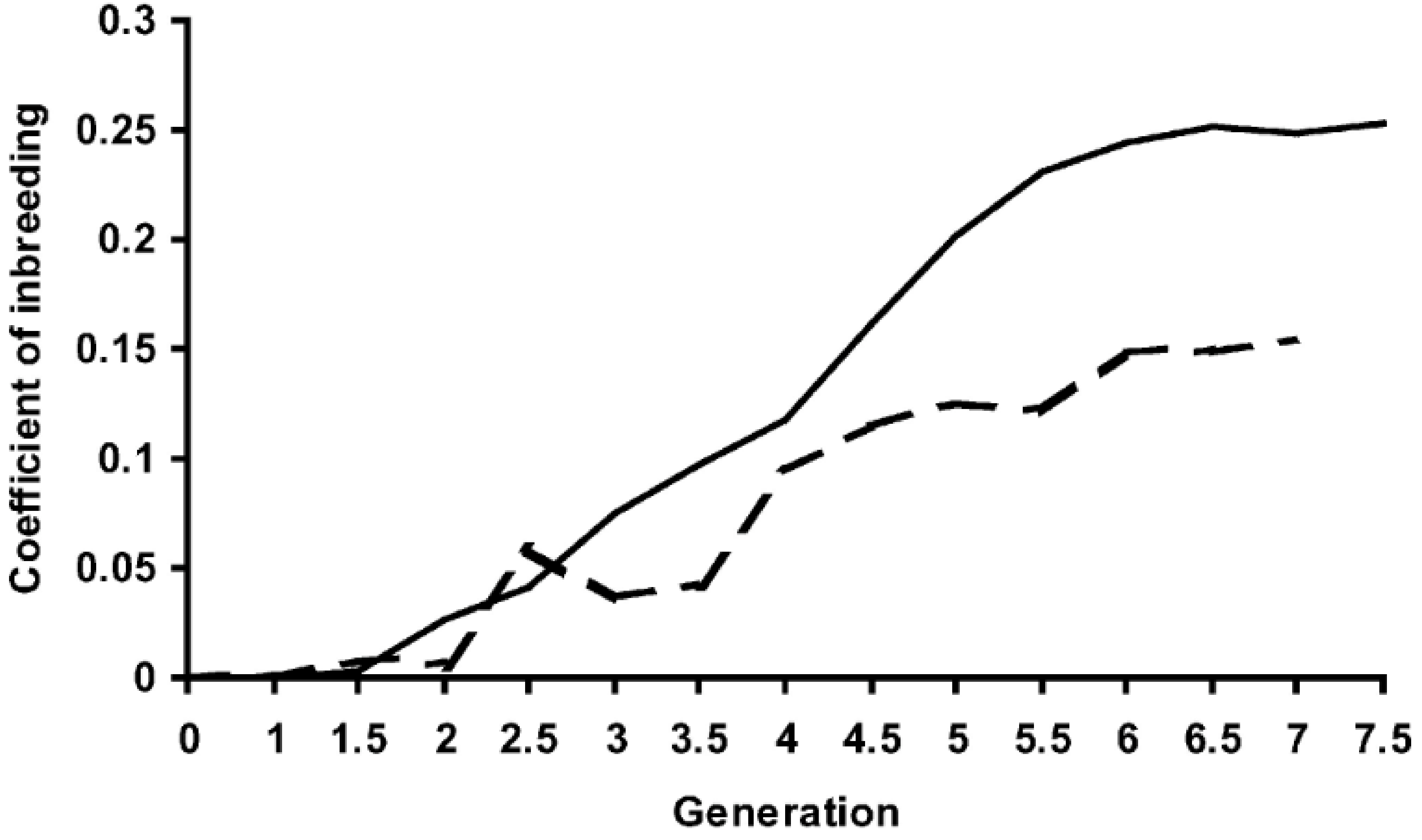


Figure 1. Average coefficients of inbreeding for German Shepherds (—) and Labrador Retrievers (— —).

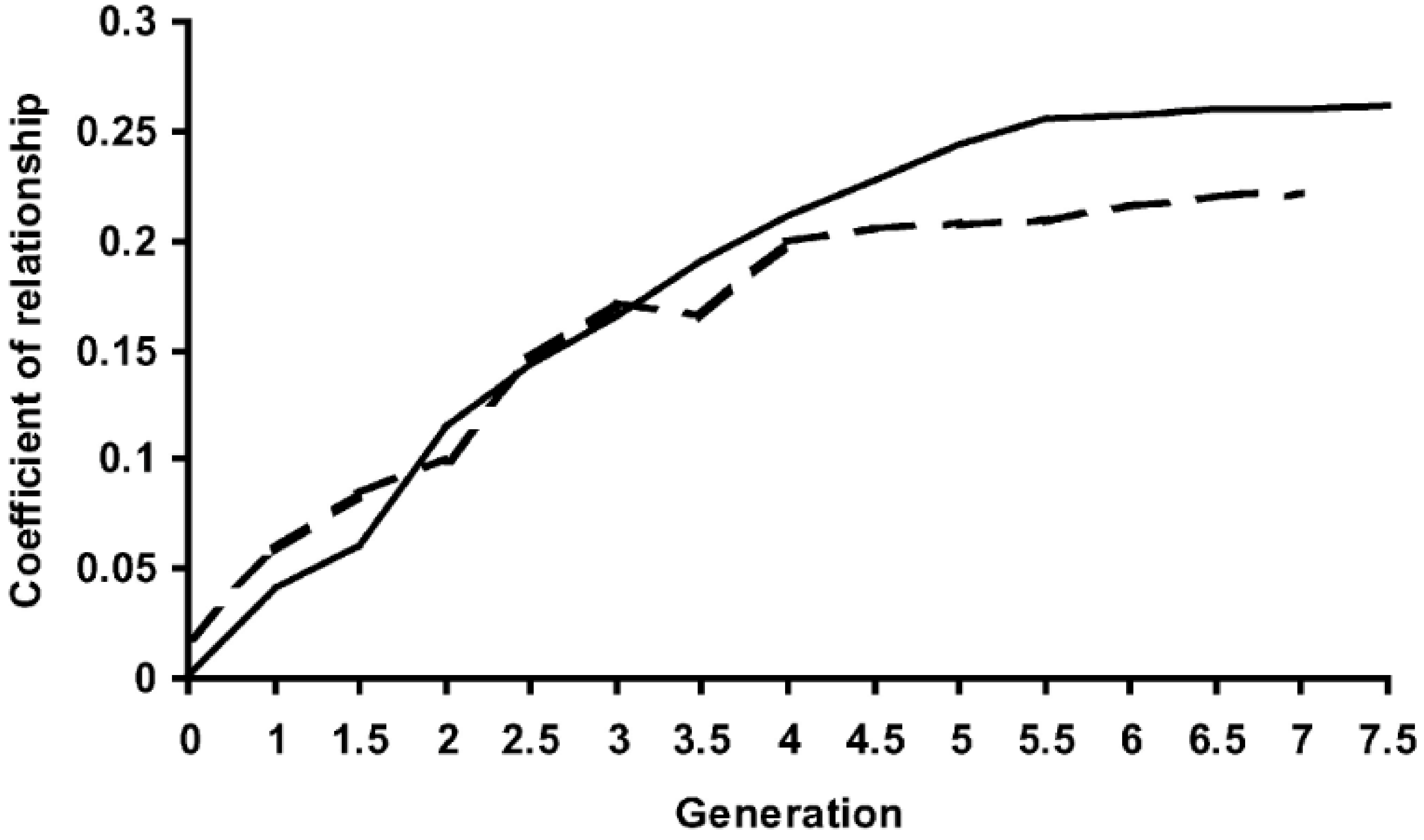
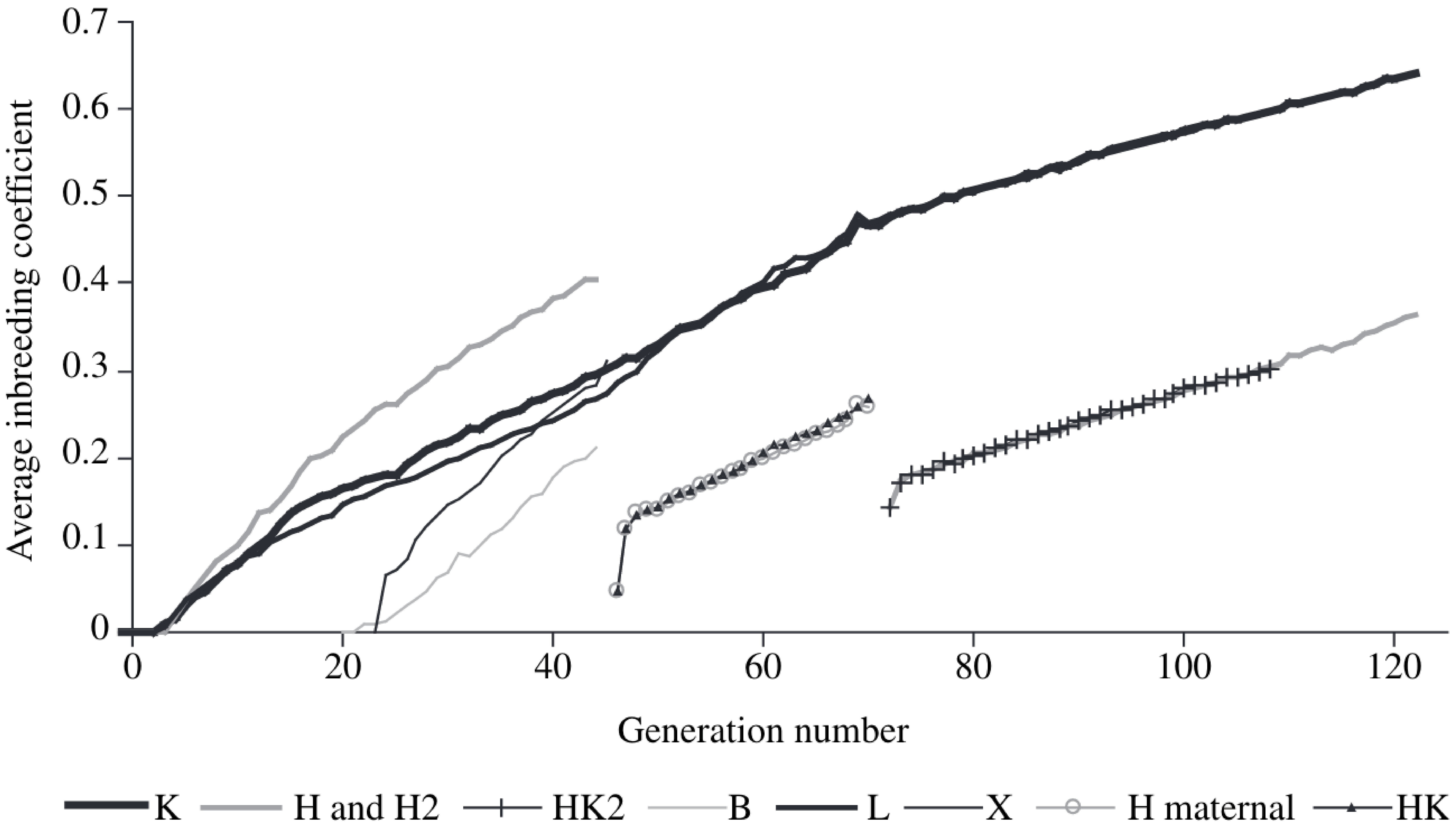


Figure 2. Average pairwise numerator relationships for German Shepherds (—) and Labrador Retrievers (— —).

Source: Cole et al. (2004)

122 generations of mice



Source: Holt et al. (2005)

Point 4

Inbreeding affects different traits in different ways

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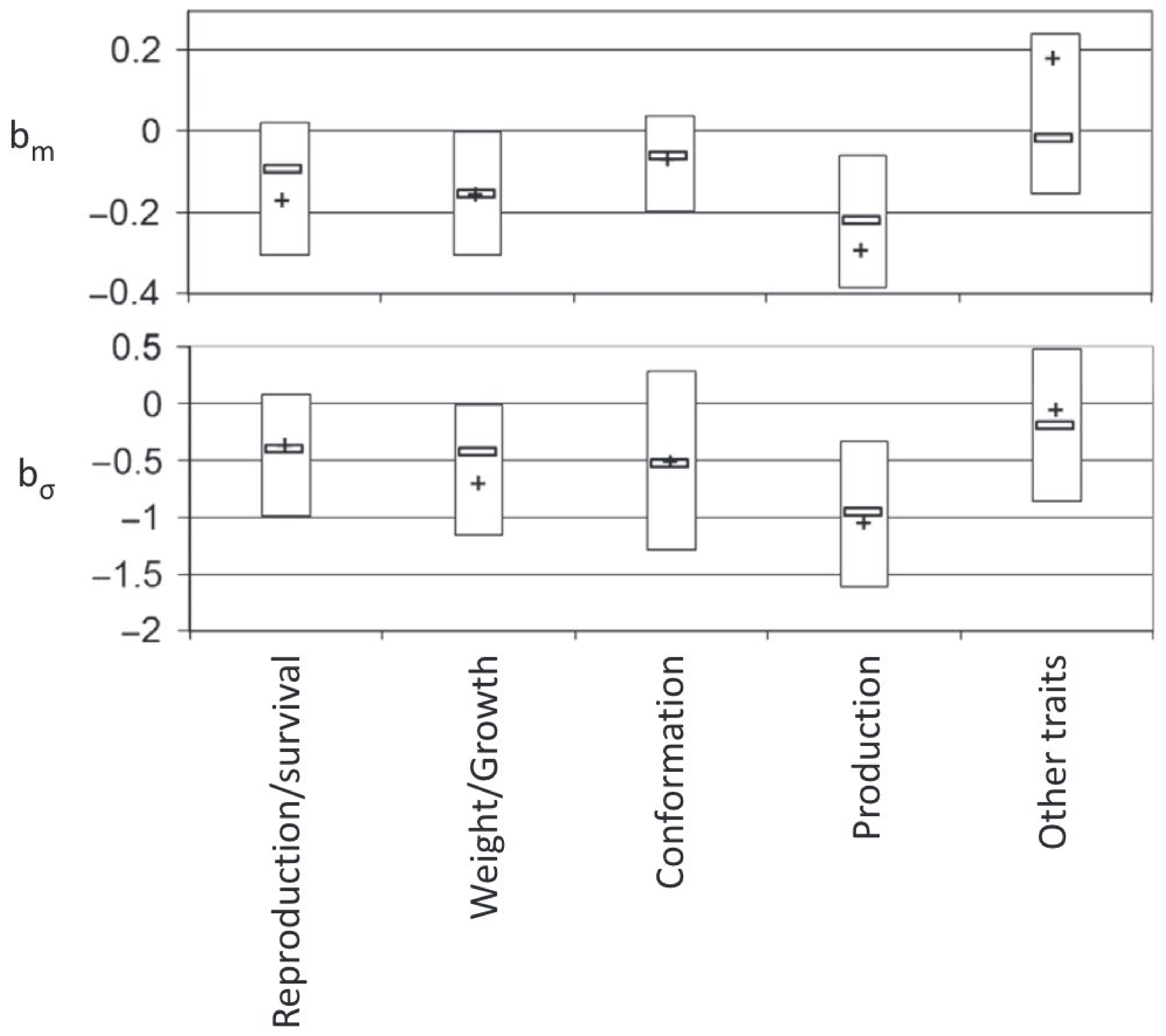
Inbreeding can be depressing



Source: Leroy (2014)

Table 1 Least square means for inbreeding depression over the different traits scaled on mean (b_m) and standard deviation (b_σ).

Trait category	Trait	b_m	b_σ
Reproduction/survival	Age at first egg or weaning	−0.117^{NS} (0.118)	−0.691* (0.35)
	Fertility	−0.191* (0.082)	−0.414^{NS} (0.262)
	Calving ease	0.322* (0.135)	0.713^{NS} (0.396)
	Gestation length	−0.021^{NS} (0.119)	0.039^{NS} (0.328)
	Fecundity	−0.309*** (0.067)	−0.227^{NS} (0.198)
	Litter size	−0.182^{NS} (0.105)	−0.384^{NS} (0.301)
	Litter size (maternal)	−0.254* (0.112)	−0.28^{NS} (0.321)
	Number offspring weaned	−0.686*** (0.146)	−1.092** (0.396)
	Number offspring weaned (maternal)	−0.462** (0.169)	−0.4^{NS} (0.461)
	Offspring survival	−0.322** (0.099)	−0.431^{NS} (0.281)
	Offspring survival (maternal)	0.002^{NS} (0.123)	0.147^{NS} (0.345)
	Adult Survival	−0.489** (0.151)	−1.047* (0.412)
	Functional longevity	−0.19^{NS} (0.104)	−0.299^{NS} (0.329)
Weight/growth	Birth weight	−0.195** (0.074)	−0.429^{NS} (0.23)
	Body weight	−0.29*** (0.06)	−0.771*** (0.191)
	Weight (maternal)	−0.253* (0.111)	−0.384^{NS} (0.325)
	Growth	−0.299*** (0.089)	−0.741* (0.347)
	Growth (maternal)	−0.163^{NS} (0.171)	−0.489^{NS} (0.552)
Conformation	Body dimensions	−0.171** (0.059)	−0.707*** (0.177)
	Body condition score	−0.113^{NS} (0.145)	−0.235^{NS} (0.399)
	Bone quality	−0.038^{NS} (0.137)	−0.201^{NS} (0.38)
	Carcass/meat quality	−0.023^{NS} (0.095)	−0.667^{NS} (0.383)
	Conformation dairy	0.093^{NS} (0.06)	0.074^{NS} (0.182)
	Conformation other	−0.079^{NS} (0.059)	−0.383* (0.174)
	Scrotal circumference	−0.31* (0.129)	−1.194* (0.488)
Production	Milk yield	−0.367*** (0.092)	−1.277*** (0.278)
	Protein yield	−0.225* (0.093)	−1.144*** (0.284)
	Fat yield	−0.249** (0.093)	−1.049*** (0.284)
	SCC	−0.414*** (0.125)	−0.205^{NS} (0.353)
	Milk others	−0.155^{NS} (0.15)	−0.461^{NS} (0.411)
	Egg number	−0.235^{NS} (0.334)	
	Egg weight	−0.301^{NS} (0.196)	
	Litter weight	−0.853*** (0.15)	−1.144** (0.409)
	Litter weight (maternal)	−0.34* (0.166)	−0.259^{NS} (0.452)
	Production fleece	−0.369* (0.151)	−0.996* (0.435)
Other traits	Locomotion	−0.215^{NS} (0.146)	−1.009* (0.402)
	Behavior	0.029^{NS} (0.137)	0.032^{NS} (0.443)

^{NS}non significant, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

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Should dairy farmers worry about inbreeding?

Change in phenotypic performance per 1% (0.25%) increase in inbreeding

Milk	Fat	Protein	PL	SCS	DPR	HCR	CCR	LIV
-73.6	-2.70	-2.10	-0.28	0.01	-0.22	-0.22	-0.31	-0.11
-18.4	-0.67	-0.52	-0.07	0.0025	-0.05	-0.05	-0.08	-0.03

Source: CDCB (https://webconnect.uscdcb.com/#/summary-stats/breed-means-bases-heterosis-inbreeding-regressions).

Change in genetic potential per year when selecting on NM$

Milk	Fat	Protein	PL	SCS	DPR	HCR	CCR	LIV
+126.9	+7.7	+4.4	+0.49	-0.02	+0.03	+0.15	+0.15	+0.25

Source: AGIL, ARS, USDA (https://www.ars.usda.gov/ARSUserFiles/80420530/Publications/ARR/nmcalc-2021_ARR-NM8.pdf).

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Should cattle ranchers worry about inbreeding?

Table 3 Inbreeding depression estimates for growth and heifer pregnancy expressed as change in the phenotype per 1% increase in inbreeding and as a percentage of the trait mean (% of $\bar{x}$)

Trait	Group	F_{PED}			F_{GRM}			F_{ROH}		
		Estimate	95% HPDI	% of $\bar{x}$	Estimate	95% HPDI	% of $\bar{x}$	Estimate	95% HPDI	% of $\bar{x}$
HP[a]		−0.001	(−0.01, 0.01)		−0.002	(−0.01, 0.004)		−0.002	(−0.007, 0.004)	
BiW (kg)	Males	−0.03	(−0.04, −0.03)	−0.09	−0.04	(−0.05, −0.03)	−0.11	−0.04	(−0.04, −0.03)	−0.10
	Females	−0.03	(−0.04, −0.02)	−0.09	−0.05	(−0.05, −0.04)	−0.14	−0.04	(−0.05, −0.03)	−0.11
WW (kg)	Males	−0.50	(−0.55, −0.44)	−0.16	−0.61	(−0.66, −0.57)	−0.20	−0.51	(−0.55, −0.48)	−0.17
	Females	−0.47	(−0.55, −0.40)	−0.17	−0.59	(−0.65, −0.53)	−0.21	−0.49	(−0.54, −0.44)	−0.18
PWG (kg)	Males	−0.64	(−0.71, −0.57)	−0.28	−0.72	(−0.77, −0.67)	−0.32	−0.59	(−0.63, −0.54)	−0.26
	Females	−0.34	(−0.42, −0.25)	−0.30	−0.42	(−0.49, −0.36)	−0.37	−0.35	(−0.41, −0.28)	−0.31

HP heifer pregnancy, *BiW* birth weight, *WW* weaning weight, *PWG* post-weaning gain, F_{PED} total pedigree inbreeding, F_{GRM} genomic relationship matrix derived inbreeding, F_{ROH} inbreeding based on runs of homozygosity

[a] Estimates for heifer pregnancy are given in the liability scale

Source: Lozada-Soto et al. (2021)

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Point 5

Nobody can agree on what to do about it

Can we adjust PTAs to account for inbreeding?

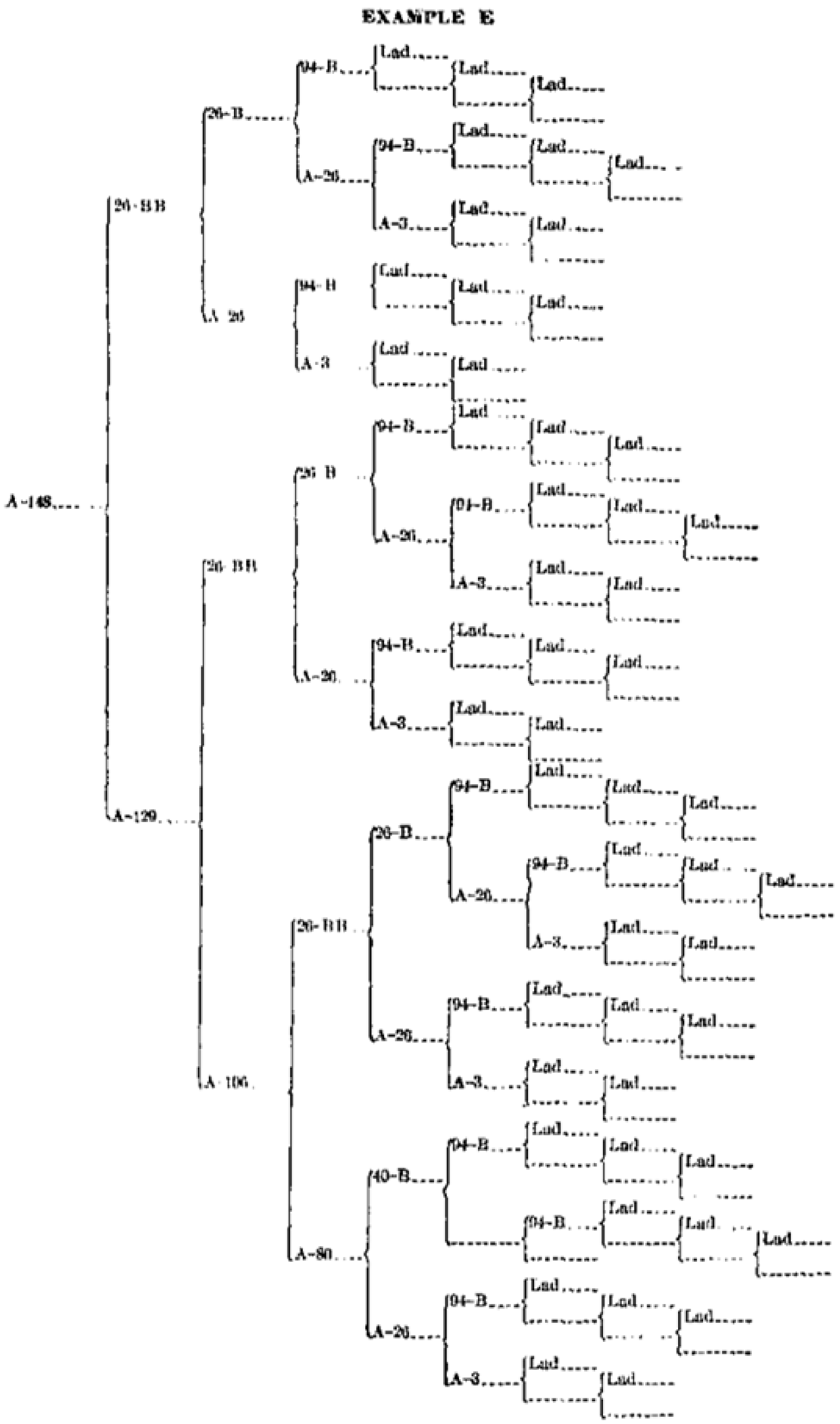
- Penalize bulls whose daughters are more related to the breed?
- Use genomic rather than pedigree inbreeding?
- The US does both!

Source: Alta Genetics

- Limit active bulls from the same sire family?
- What about embryo donors?

Should we trim pedigrees?

- Inbreeding melts away with the touch of a button!
- Reflects the biological impact of new versus old inbreeding
- Some countries already do this
  - Italy (4), Slovak Republic (3), UK (
  - Some countries have more recent “founder” years



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What if we don’t publish PTAs?

- To avoid overuse of bulls, no PTA will be published
- Bulls will be mated at random to cows
- Or, bulls can receive “red”, “yellow”, or “green” badges for each trait to indicate quality
- Or, only the mate selection software knows the PTA

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What if we don't publish PTAs? (cont'd)

Beef cattle breeders appear to be ahead of the dairy sector on alternative ways of ranking bulls

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Could we use terminal dairy embryos?

- Instead of selling semen to farmers, we could sell only embryos that represent the ideal terminal dairy cross
- There would be no inbreeding!
- Who will maintain the purebred lines needed for this program?
- Is the cost of creating and transferring these embryos manageable?

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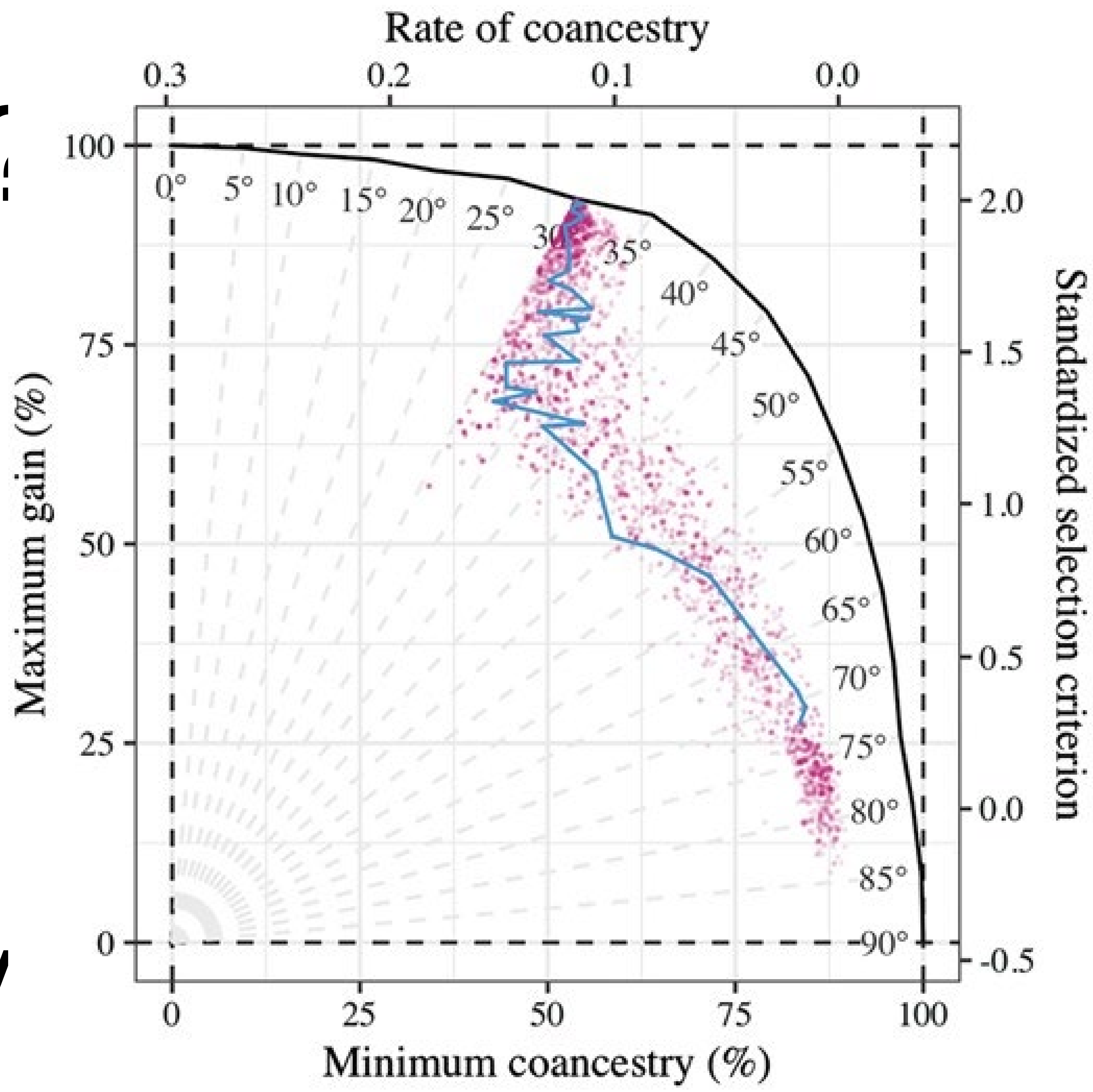
What if we change the index?

- Add some measure of genetic diversity to selection indices
- A possible opportunity to use subpopulation membership
- Isn't this just a lessefficient way optimal contribution theory, which we've all been carefully ignoring?



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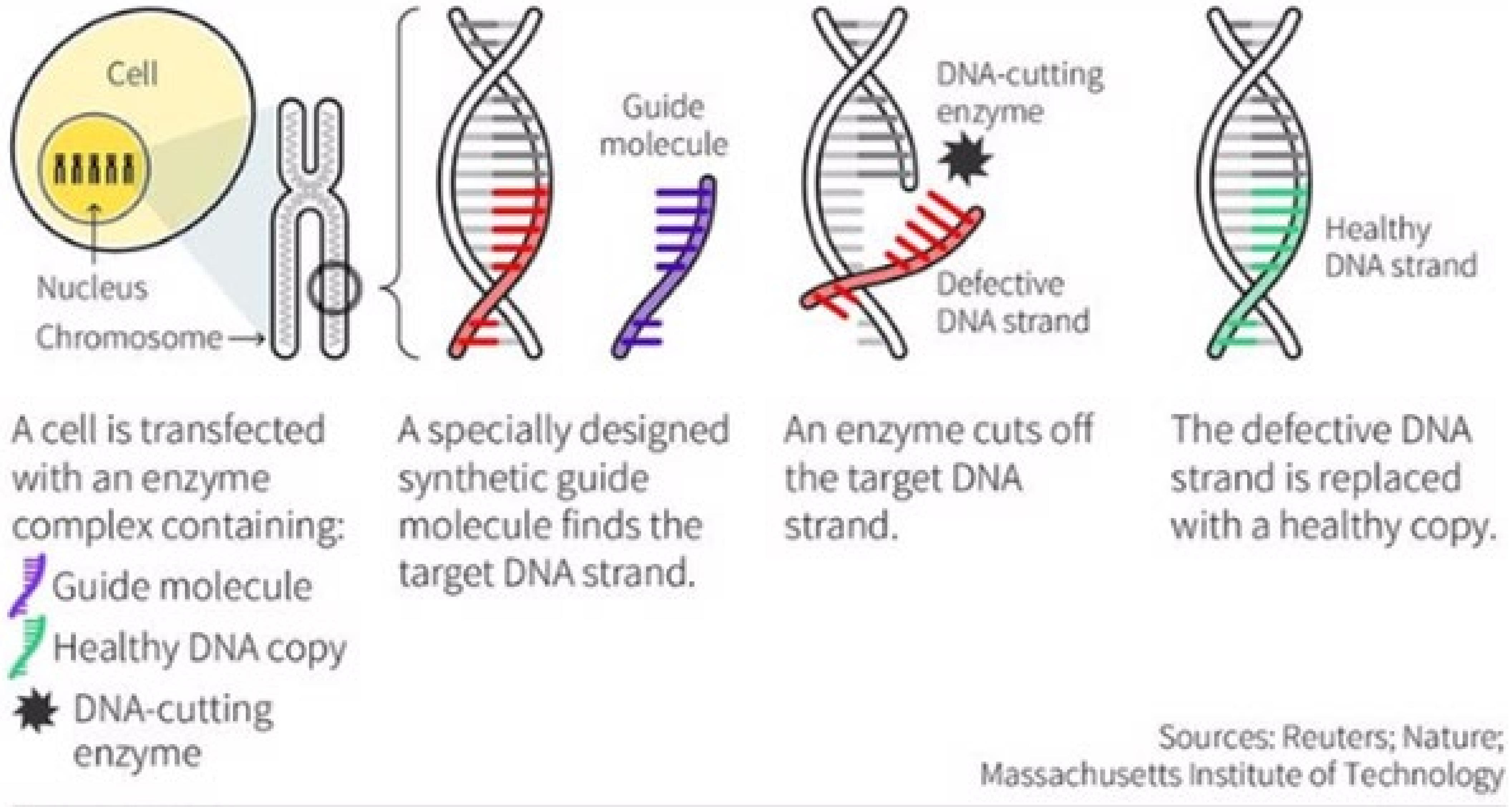
Maybe gene editing is the solution?

- What if we just use gene editing to "fix" defects when we find them (Johnsson et al., 2019)?
  - You only lose a few months with surrogate sires!
- We can get rapid genetic gain without consequences!
- Do we know where it's important to have diversity?



Am I serious about this?

- Genetic evaluation is a tool for ranking animals for selection, not managing genetic diversity
  - We can favor “outcross” animals, if we can find them, and penalize “inbred” animals
  - Such adjustments lack theoretical justification and can’t achieve what we want them to
- Would we rather pretend we’re doing things, or make changes that have real impacts (Cole, 2024)?

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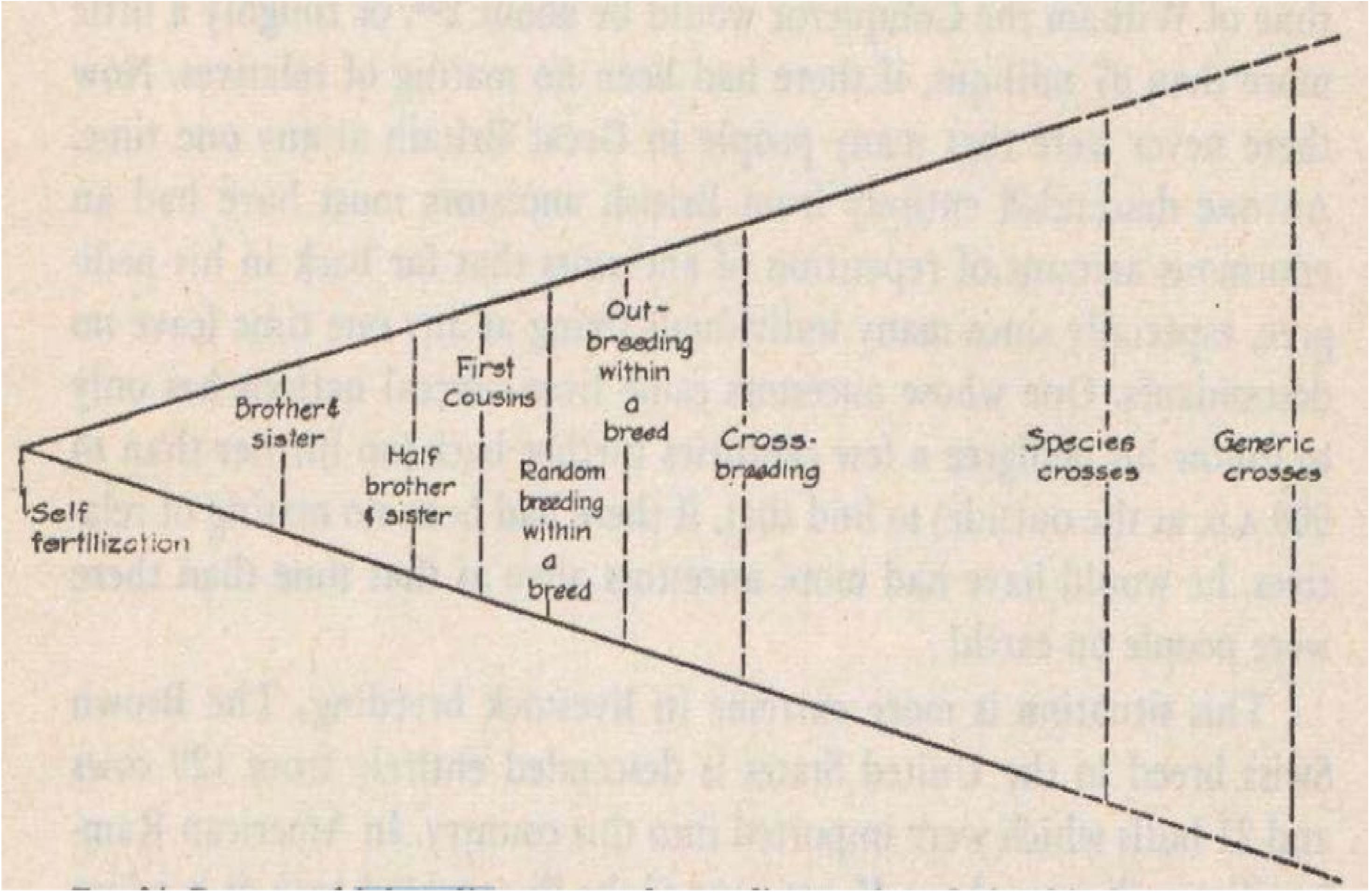
We can outcross between studs



Source: Lush (1945)

- AIs are creating sub-populations within breeds because of genetic protection programs
  - Will this lead to rotational breeding from each stud in turn?
- How much difference should we expect if we're all using similar breeding objectives?

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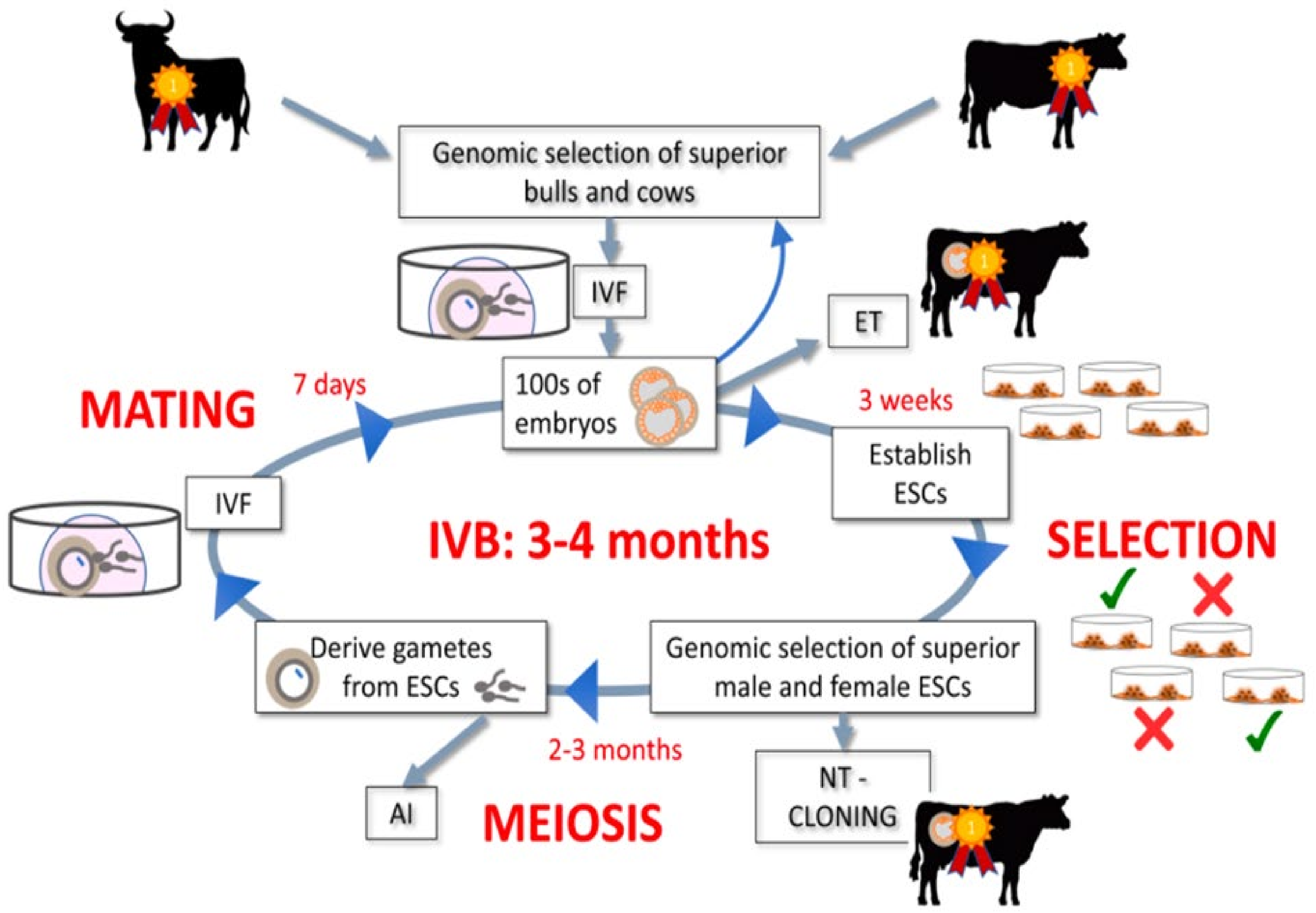
Will *in vitro* breeding ever work?

- Embryonic stem cells can be turned into sperm and eggs and used to create a new generation of embryos (Goszczynski et al., 2018)
- Faster genetic gain because less time is needed to create the next generation
- Live animals eventually needed



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Will we retain license to operate?

- Inbreeding may **impact our social license** more than production economics
- People don't understand the selection on performance practiced by livestock farmers
- What will consumers, retailers, and bankers demand?


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Most Dairy Cows Are Kissing Cousins, and Scientists Are Worried

Selective breeding helps Holsteins produce 94% of the nation's milk, but can also lead to the proliferation of diseases

Nearly all Holsteins in the U.S. and abroad descend from just two bulls.

PHOTO: CINDY SCHULTZ FOR THE WALL STREET JOURNAL

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Are there better solutions to this problem?

- There are many theoretically satisfying ideas that nobody uses
- Geneticists and AI staff don't breed cows, farmers do
- Many cows are now mated at random to a portfolio of bulls
- Everyone's neighbor should use different bulls

Some ways to avoid inbreeding
Optimal contribution theory
Minimization of progeny inbreeding
Linear programming
Look-ahead mate selection
Selection against lethal alleles
Index selection including Mendelian sampling variance
Genomic selection including dominance

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Conclusions

Are we concerned about the wrong thing?

- "Selection, however - in marked contrast to its effectiveness in changing average merit **is a very feeble tool for changing homozygosity**, except under the very simplest genetic situations..." (Lush, 1945)
- "When the pure breeds finally reach equilibrium between the production of heterozygosis by mutations and the loss of heterozygosis because the effective number of animals in the breed is small, it is possible that **the pure breed may support only a few scores of unfixed loci**" (Lush, 1945)

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Closing thoughts

- Homozygosity is bad when there's **inbreeding depression**
- Increased genetic load **compromises animals' adaptability**
- When there is tight control throughout the production chain (as in pork and poultry breeding) **genetic diversity can be managed** effectively

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THANK YOU FOR YOUR ATTENTION!

QUESTIONS?

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References

- Cleveland, M.A., H.D. Blackburn, R.M. Enns, and D.J. Garrick. 2005. Changes in inbreeding of U.S. Herefords during the twentieth century. Journal of Animal Science 83:992–1001. https://doi.org/10.2527/2005.835992x.
- Cole, J.B. 2024. Perspective: Can we actually do anything about inbreeding? J. Dairy Sci. 107:6643–6648. https://doi.org/10.3168/jds.2023-23958.
- Cole, J.B., D.E. Franke, and E.A. Leighton. 2004. Population structure of a colony of dog guides. J. Anim. Sci. 82:2906–2912. https://doi.org/10.2527/2004.82102906x.
- Cole, J.B., and P.M. VanRaden. 2011. Use of haplotypes to estimate Mendelian sampling effects and selection limits. J. Anim. Breed. Genet. https://doi.org/10.1111/j.1439-0388.2011.00922.x.
- D'Ambrosio, J., F. Phocas, P. Haffray, A. Bestin, S. Brard-Fudulea, C. Poncet, E. Quillet, N. Dechamp, C. Fraslin, M. Charles, and M. Dupont-Nivet. 2019. Genome-wide estimates of genetic diversity, inbreeding and effective size of experimental and commercial rainbow trout lines undergoing selective breeding. Genet Sel Evol 51:26. https://doi.org/10.1186/s12711-019-0468-4.

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References (cont'd)

- Goszczynski, D.E., H. Cheng, S. Demyda-Peyrás, J.F. Medrano, J. Wu, and P.J. Ross. 2018. In vitro breeding: application of embryonic stem cells to animal production. Biol. Reprod. https://doi.org/10.1093/biolre/ioy256 .
- Holt, M., T. Meuwissen, and O. Vangen. 2005. Long-term responses, changes in genetic variances and inbreeding depression from 122 generations of selection on increased litter size in mice. J. Anim. Breed. Genet. 122:199–209. https://doi.org/10.1111/j.1439-0388.2005.00526.x.
- Howard, J.T., J.E. Pryce, C. Baes, and C. Maltecca. 2017. Invited review: Inbreeding in the genomics era: Inbreeding, inbreeding depression, and management of genomic variability. Journal of Dairy Science 100:6009–6024. https://doi.org/10.3168/jds.2017-12787.
- Johnsson, M., R.C. Gaynor, J. Jenko, G. Gorjanc, D.-J. de Koning, and J.M. Hickey. 2019. Removal of alleles by genome editing (RAGE) against deleterious load. Genet. Sel. Evol. 51:14. https://doi.org/10.1186/s12711-019-0456-8.
- Macedo, F.L., O.F. Christensen, and A. Legarra. 2021. Selection and drift reduce genetic variation for milk yield in Manech Tête Rousse dairy sheep. JDS Comm. 2:31–34. https://doi.org/10.3168/jdsc.2020-0010.

References (cont'd)

- Leroy, G. 2014. Inbreeding depression in livestock species: review and meta-analysis. Animal Genetics 45:618–628. https://doi.org/10.1111/age.12178.
- Lozada-Soto, Emmanuel A., Christian Maltecca, Jicai Jiang, John B. Cole, Paul VanRaden, and Francesco Tiezzi. 2022. Genomic characterization of autozygosity and recent inbreeding trends in all major breeds of US dairy cattle. J. Dairy Sci. 105:8956-8971. https://doi.org/10.3168/jds.2022-22116.
- Lozada-Soto, E.A., C. Maltecca, D. Lu, S. Miller, J.B. Cole, and F. Tiezzi. 2021. Trends in genetic diversity and the effect of inbreeding in American Angus cattle under genomic selection. Genetics, Selection, Evolution. 53:50. https://doi.org/10.1186/s12711-021-00644-z.
- Lush, J.L. 1945. Animal Breeding Plans. 2nd ed. Iowa State College Press, Ames, IA.
- McParland, S., J.F. Kearney, M. Rath, and D.P. Berry. 2007. Inbreeding trends and pedigree analysis of Irish dairy and beef cattle populations. Journal of Animal Science 85:322–331. https://doi.org/10.2527/jas.2006-367.

References (cont'd)

- Nicholas, F.W., and C. Smith. 1983. Increased rates of genetic change in dairy cattle by embryo transfer and splitting. Anim. Prod. 36:341–353. https://doi.org/10.1017/S0003356100010382.
- Rafter, P., N. McHugh, T. Pabiou, and D.P. Berry. 2022. Inbreeding trends and genetic diversity in purebred sheep populations. animal 16:100604. https://doi.org/10.1016/j.animal.2022.100604.
- Robertson, A. 1961. Inbreeding in artificial selection programmes. Genet.Res. 2:189–194. https://doi.org/10.1017/S0016672300000690.
- Verrier, E., J.J. Colleau, and J.L. Foulley. 1993. Long-term effects of selection based on the animal model BLUP in a finite population. Theoret. Appl. Genetics 87:446–454. https://doi.org/10.1007/BF00215090.
- Villanueva, B., A. Fernández, M. Saura, A. Caballero, J. Fernández, E. Morales-González, M.A. Toro, and R. Pong-Wong. 2021. The value of genomic relationship matrices to estimate levels of inbreeding. Genet. Sel. Evol. 53:42. https://doi.org/10.1186/s12711-021-00635-0.

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