

Genetic Resilience and the Dynamics of Inbreeding and Diversity in Dairy Breeding

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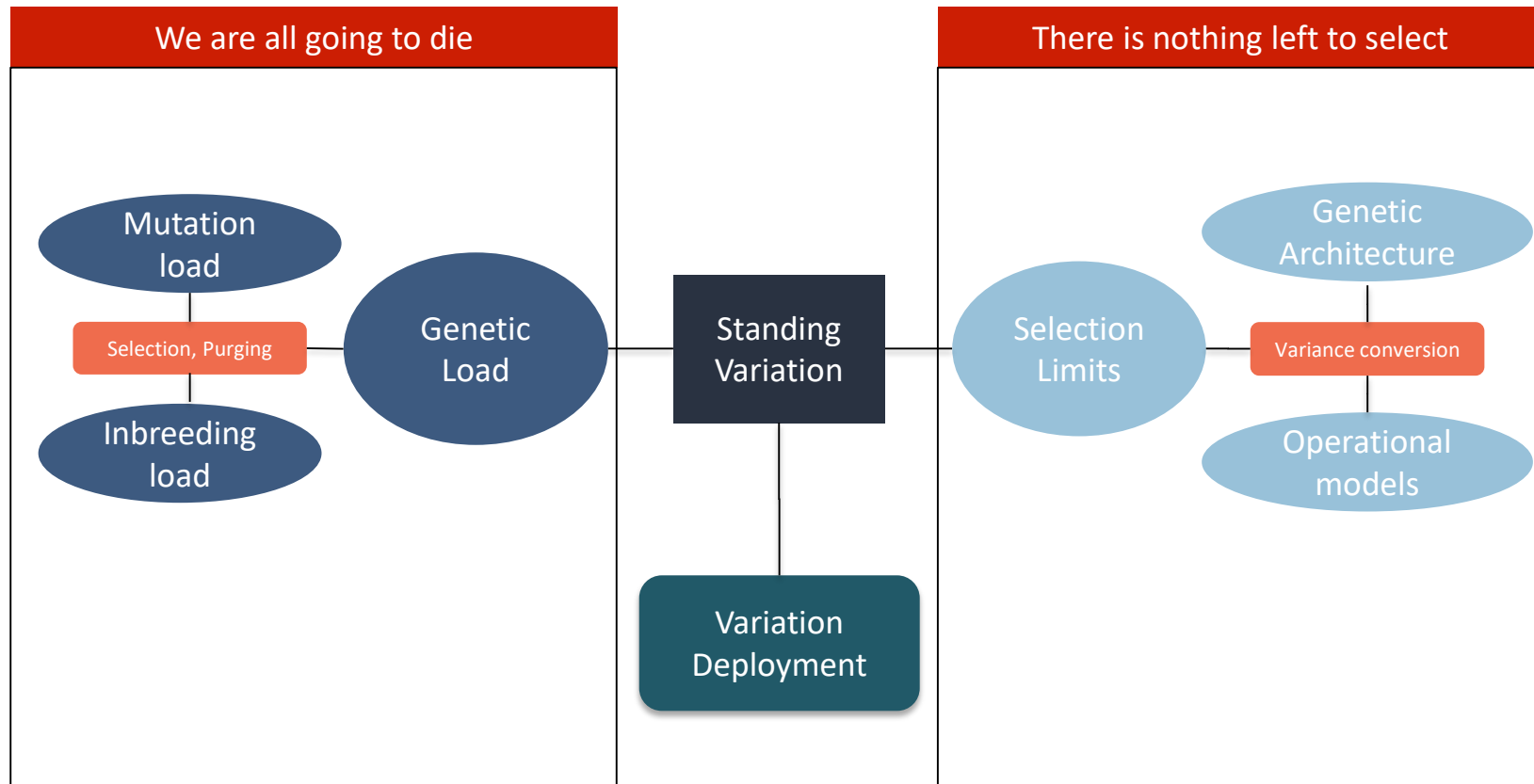
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³Council on Dairy Cattle Breeding, Bowie, MD, USA,

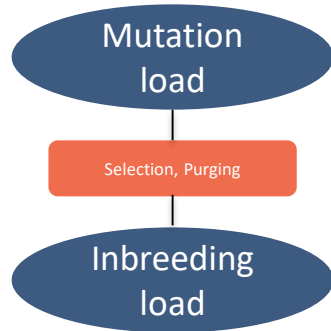
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⁵Centre for Genetic Improvement of Livestock Animal Biosciences, University of Guelph, Guelph, ON, Canada.

MANAGING DIVERSITY (minus the logistics)



GENETIC LOAD



Genome wide homozygosity measures are bad indicators of genetic load

- We use them because we struggle to identify (sublethal) deleterious variants
- Genetic architecture is a direct function of the selection process
 - How much directional dominance there is in dairy cattle is still an open question

We often assume that purging is not happening or not fast enough

- Dairy populations are under strong indirect and direct selection for “functional fitness”
- Fitness is hard to define and quantify in the field

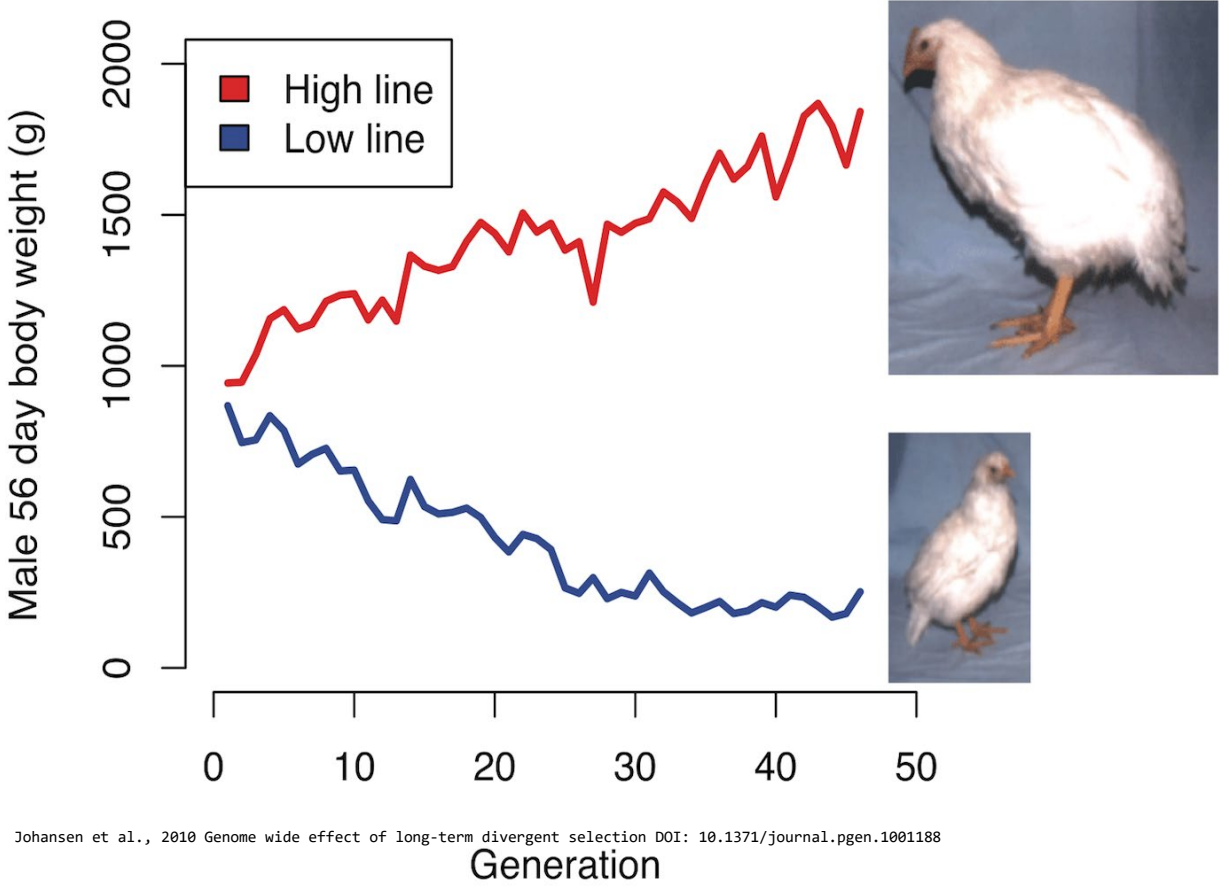
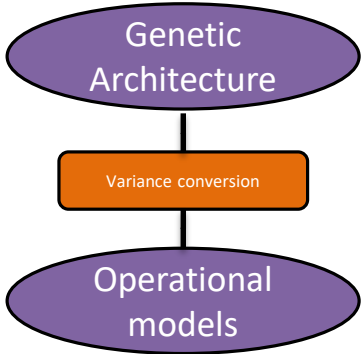
Inferring genomic architecture of inbreeding depression from breeding populations is complicated:

- It is not economically feasible to conduct selection experiments in dairy
- Some of these questions cannot truly be answered retrospectively

- Increase focus on deep phenotyping
- Increase integration of functional annotation
- Increase numbers of genotyped individuals
- Refine analysis tools
- Integrate Model Organism Approaches
- Investigate the potential of advanced technologies
- Data sharing

On the short-term homozygosity will remain an issue best managed through logistic structuring of the breeding process

GENETIC DIVERSITY



Review > J Anim Breed Genet. 2017 Jun;134(3):196-201. doi: 10.1111/jbg.12270.

"Conversion" of epistatic into additive genetic variance in finite populations and possible impact on long-term selection response

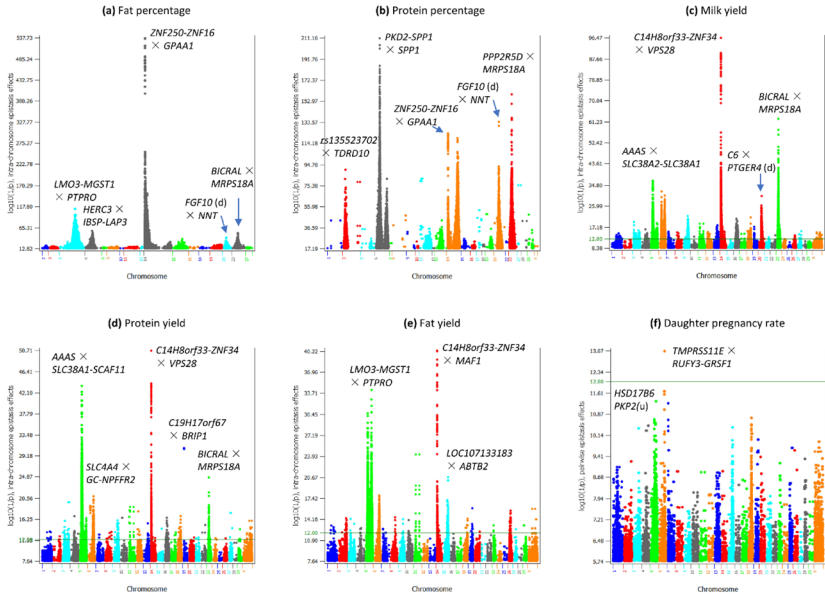
W G Hill¹

Johansen et al., 2010 Genome wide effect of long-term divergent selection DOI: 10.1371/journal.pgen.1001188

Open Access Article

A Large-Scale Genome-Wide Association Study of Epistasis Effects of Production Traits and Daughter Pregnancy Rate in U.S. Holstein Cattle

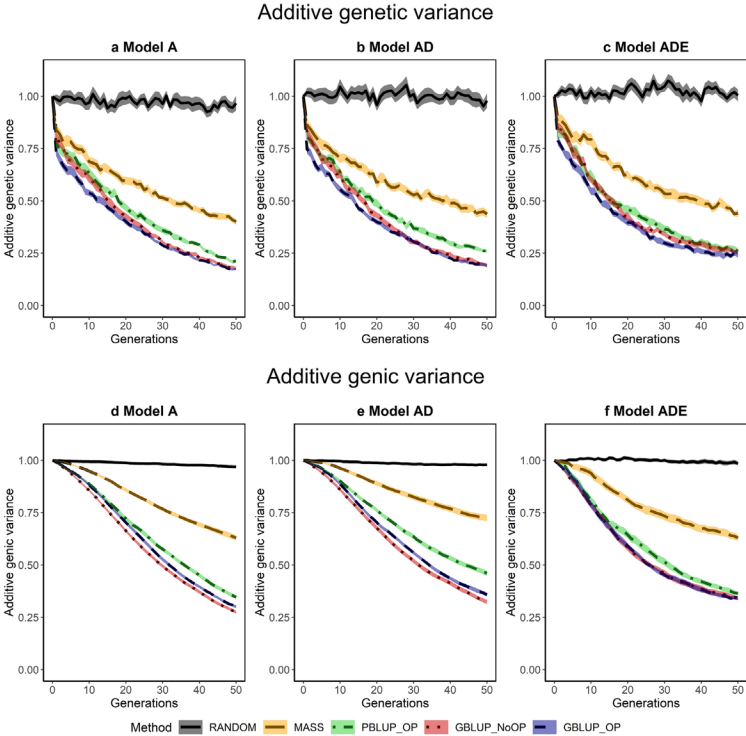
by Dzanis Prakapenka, Zuoxiang Liang, Jicai Jiang, Li Ma and Yang Da



Genet Sel Evol. 2022 Mar 7;54(1):19. doi: 10.1186/s12711-022-00709-7.

The long-term effects of genomic selection: 1. Response to selection, additive genetic variance, and genetic architecture

Yvonne C J Wientjes¹, Piter Bijma², Mario P L Calus², Bas J Zwaan³, Zulma G Vitezica⁴, Joost van den Heuvel³



Research article | [Open Access](#) | [Published: 27 April 2018](#)

Characterization of recombination features and the genetic basis in multiple cattle breeds

[Botong Shen](#), [Jicai Jiang](#), [Eyal Seroussi](#), [George E. Liu](#) & [Li Ma](#) 

BMC Genomics **19**, Article number: 304 (2018) | [Cite this article](#)



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Volume 102, Issue 6, June 2019, Pages 5279-5294



Research

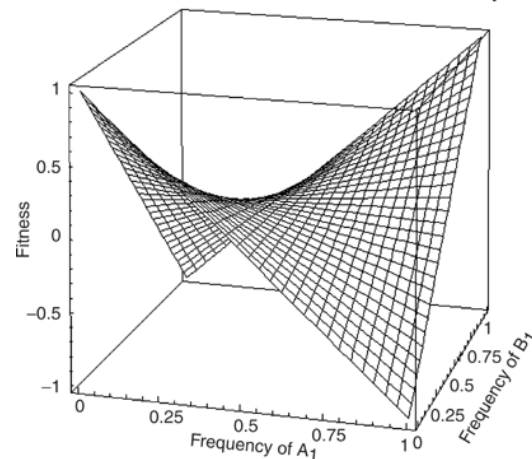
Variance of gametic diversity and its application in selection programs

[D.J.A. Santos](#)^{1,2} , [J.B. Cole](#)³, [T.J. Lawlor Jr.](#)⁴, [P.M. VanRaden](#)³, [H. Tonhati](#)², [L. Ma](#)¹ 

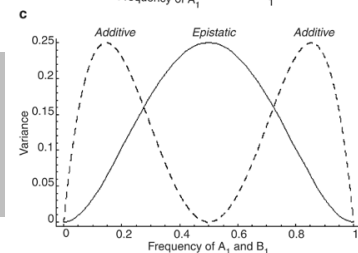
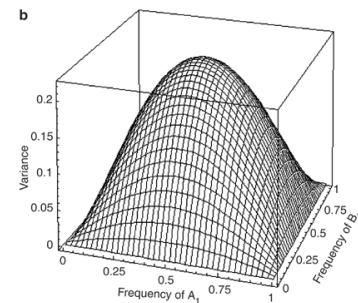
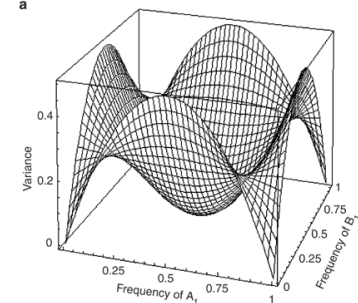
The conversion of variance and the evolutionary potential of restricted recombination ^a

[M. Neiman](#)  & [T.A. Linksvayer](#)

Heredity **96**, 111–121 (2006) | [Cite this article](#)



Genetic recombination is usually considered to facilitate adaptive evolution. However, recombination prevents the reliable co-transmission of interacting gene combinations and can disrupt complexes of coadapted genes. If interactions between genes have important fitness effects, restricted recombination may lead to evolutionary responses that are different from those predicted from a purely additive model and could even aid adaptation.



UNDERSTANDING INBREEDING

- Functional Annotation to Dissect Inbreeding
- Heterogeneity of Inbreeding and Environmental Load
- Inbreeding and Cow Fitness

MANAGING GENETIC DIVERSITY

- Impact of Expected Future Inbreeding Under Varying Scenarios

BONUS

- LLM to identify deleterious variants

Functional Annotation to Dissect Inbreeding



Genomic Partition of Inbreeding Depression in Production Traits of U.S. Jersey Cattle Using Functional Annotations

Chang Xu^{1*}, Christian Maltecca¹, Francesco Tiezzi^{1,2}, John B. Cole^{1,3,4}, Sajjad Toghiani⁵, Li Ma⁶, and Jicai Jiang¹

J. Dairy Sci., under review

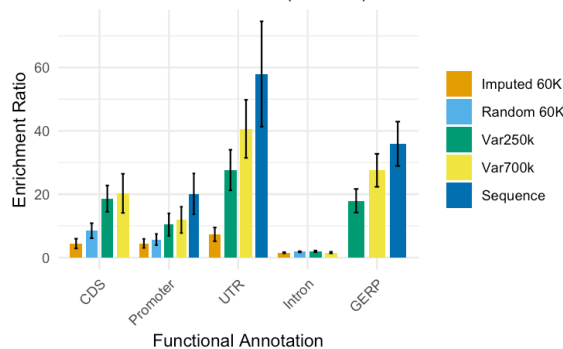
Overview:

- Analyzed 245,517 genotyped Jersey cows using a linear mixed model.
- Mapped 9,532,696 sequence variants into five functional annotations: **Intron**, **Promoter**, **GERP**, **CDS**, **UTR**, and **others**.

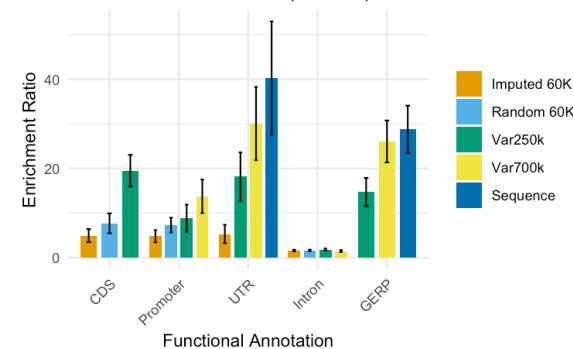
Key Findings:

- Significant enrichment of InD for milk yield in promoter (enrichment ratio = 20.11), UTR (57.96), and GERP regions (35.91).
- Protein yield showed enrichment in promoter (15.25), UTR (46.44), and GERP regions (32.73).
- Fat yield showed enrichment in UTR (40.20) and GERP regions (28.73).

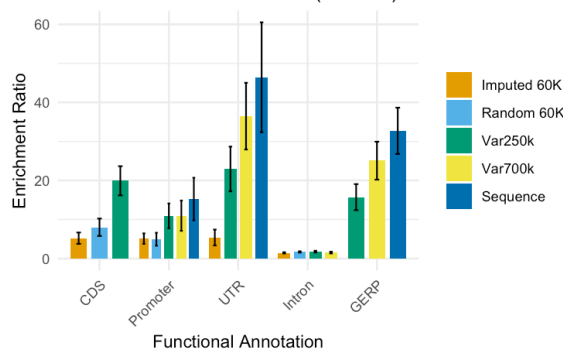
InD Enrichment for Milk (SIPMM)



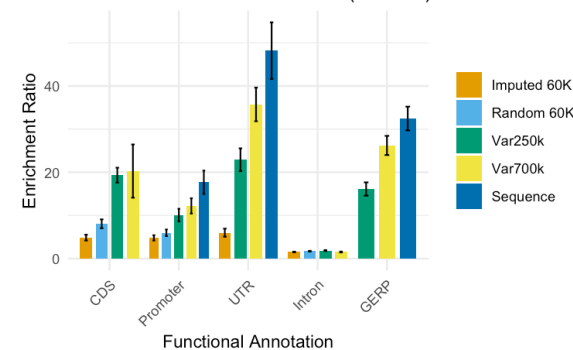
InD Enrichment for Fat (SIPMM)



InD Enrichment for Protein (SIPMM)



InD Enrichment across Traits (SIPMM)

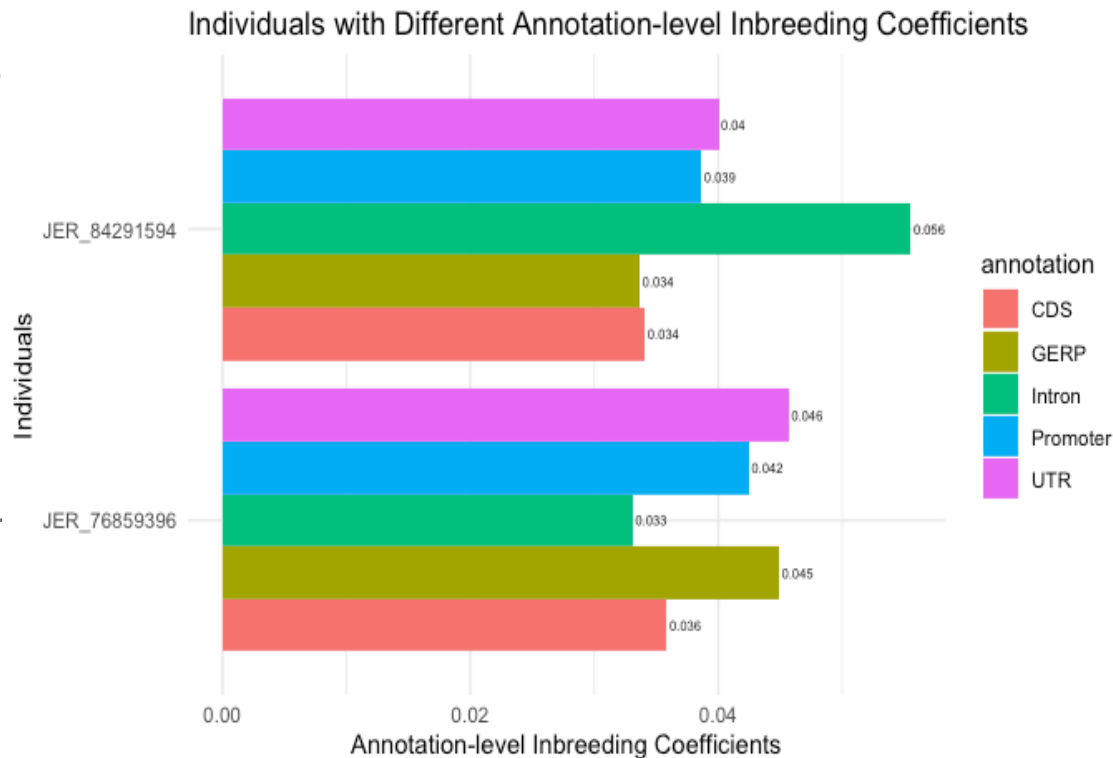


Conclusion:

- Some genome annotations have disproportionate effects on inbreeding depression (InD).
- These regions may be more vulnerable to deleterious mutations.

Implications:

- Enhances understanding of genetic basis of InD.
- Could inform breeding strategies for genomic selection in dairy cattle.



Heterogeneity of Inbreeding and Environmental Load

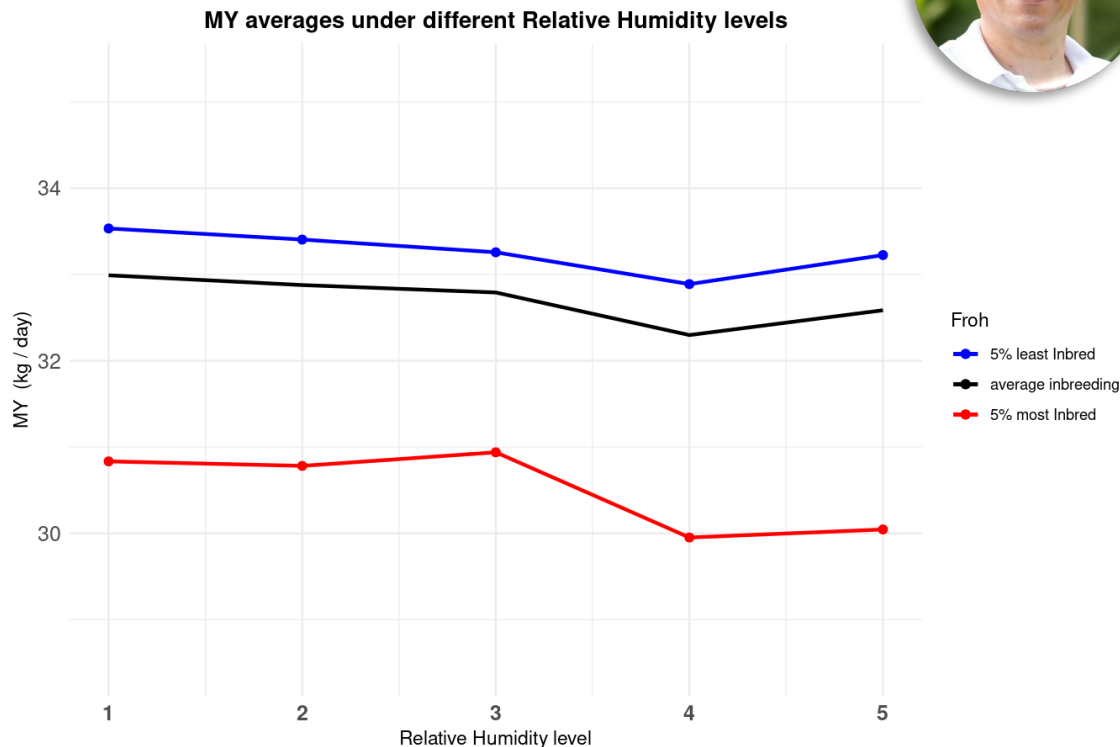
Inbreeding depression for milk yield under environmental stress in Italian Holstein cows

F. Tiezzi, C. Maltecca, J.C.C. Panetto, J.-T. van Kaam, M. Cassandro, C. Cipolat-Gotet, M. Ablondi, A. Zanotti, R. Finocchiario

POSTER Abstract #2049



- 414,514 milk yield records 24,395 cows, 703 herds, 25,001 HTD.
- For each herd-test date, (THI) for the week before the visit were available.
- Inbreeding estimates were assessed via 3 methods:
 - FPED, FGRM, FROH
- Environmental stress-related covariates (temperature, relative humidity, or THI) fitted in the model as cross-classified effects with 5 levels.
- Inbreeding caused **significant depression across all the environmental conditions** observed.
- Extent Inbreeding depression was **dependent on environmental load**.



Inbreeding and Cow Fitness

Assessment of inbreeding depression on stayability of Italian Holstein cows

F. Tiezzi, C. Maltecca, J.C.C. Panetto, J.-T. van Kaam, M. Cassandro, C. Cipolat-Gotet, M. Ablondi, A. Zanotti, R. Finocchiario

J. Dairy Science submitted

POSTER Abstract #2342



Stayability:

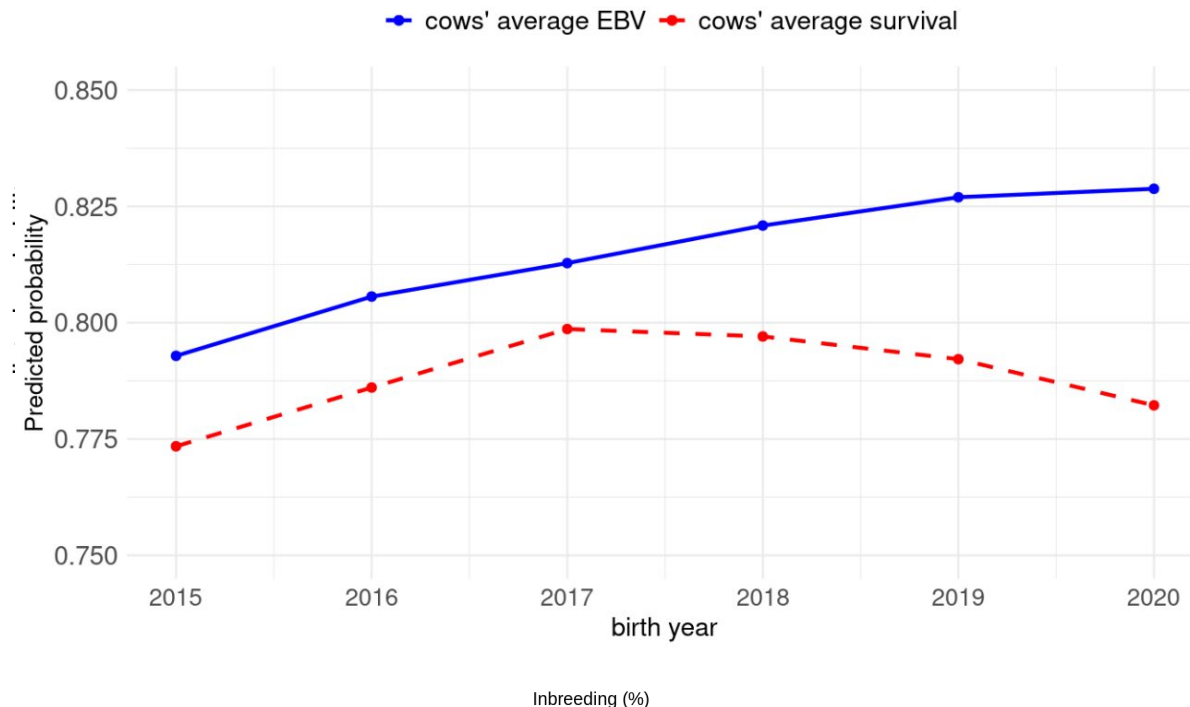
- Defines female survival ability across calving intervals.
- Evaluated through three intervals:
 - **STAY12:** 1st to 2nd calving
 - **STAY23:** 2nd to 3rd calving
 - **STAY34:** 3rd to 4th calving

Study Data:

- Utilized data from up to 48,000 cows with genotype and phenotype records.

Inbreeding Estimation Approaches:

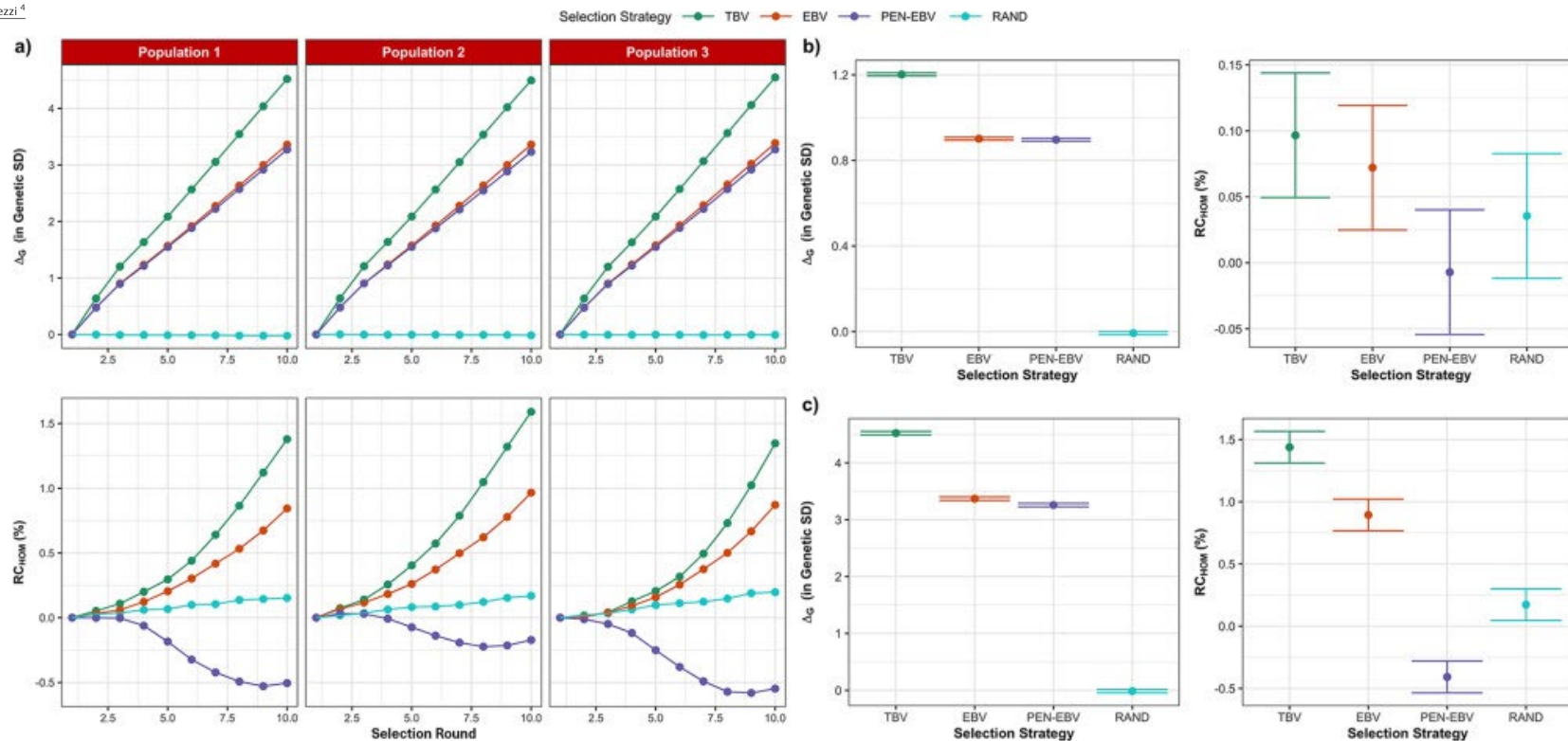
- **FPED FGRM FROH_GENOME FROH_CLASS**



Impact of Expected Future Inbreeding Under Varying Scenarios

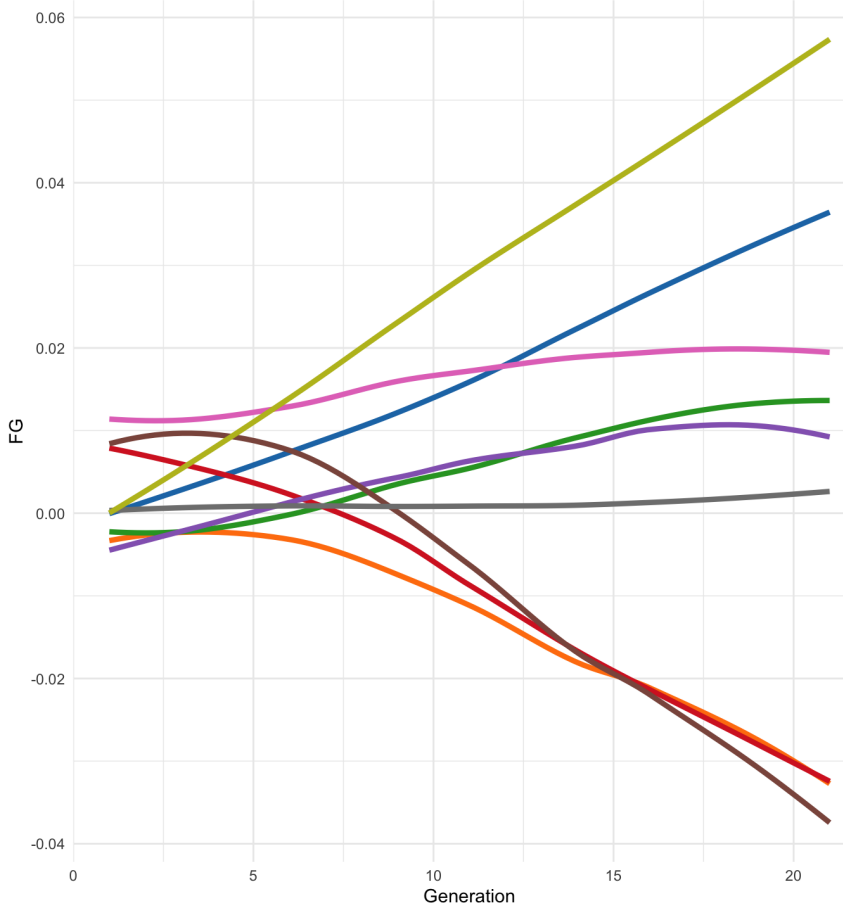
Effects of germplasm exchange strategies on genetic gain, homozygosity, and genetic diversity in dairy stud populations: A simulation study

Emmanuel A. Lozada-Soto¹, ✉, Christian Maltecca¹, Jicai Jiang¹, John B. Cole²,
Paul M. VanRaden³, Francesco Tiezzi⁴

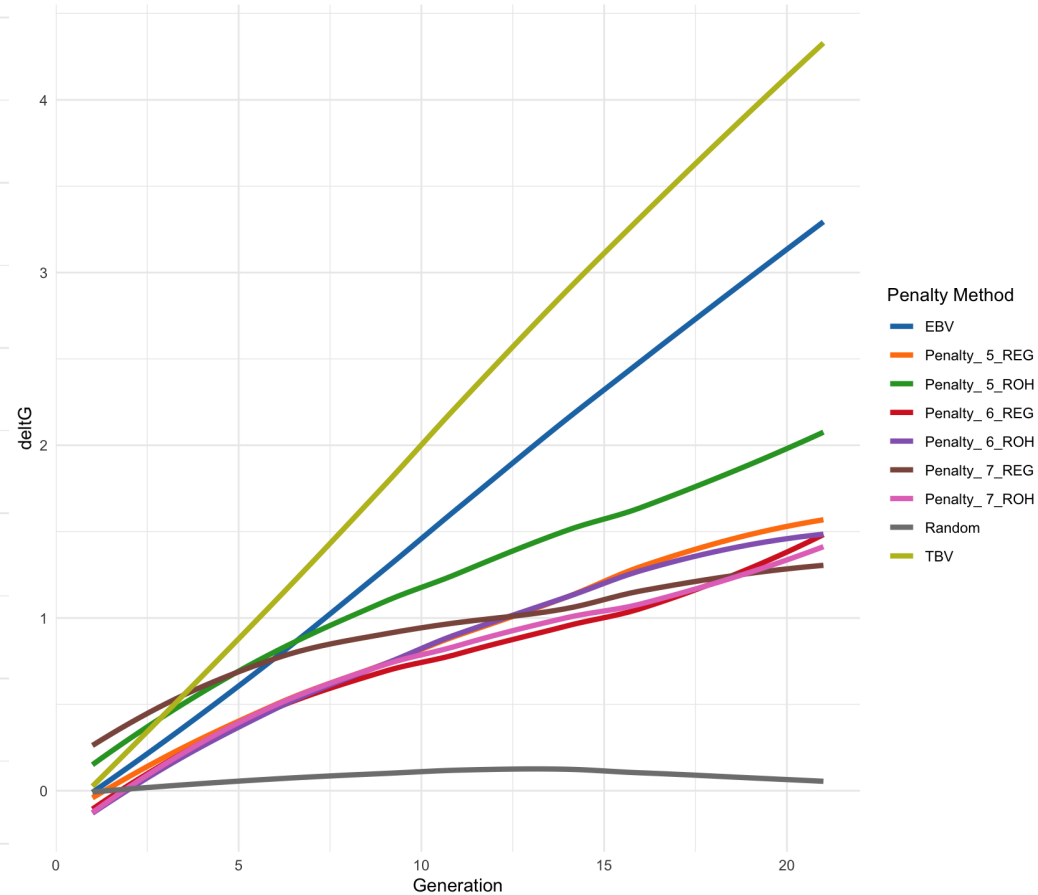




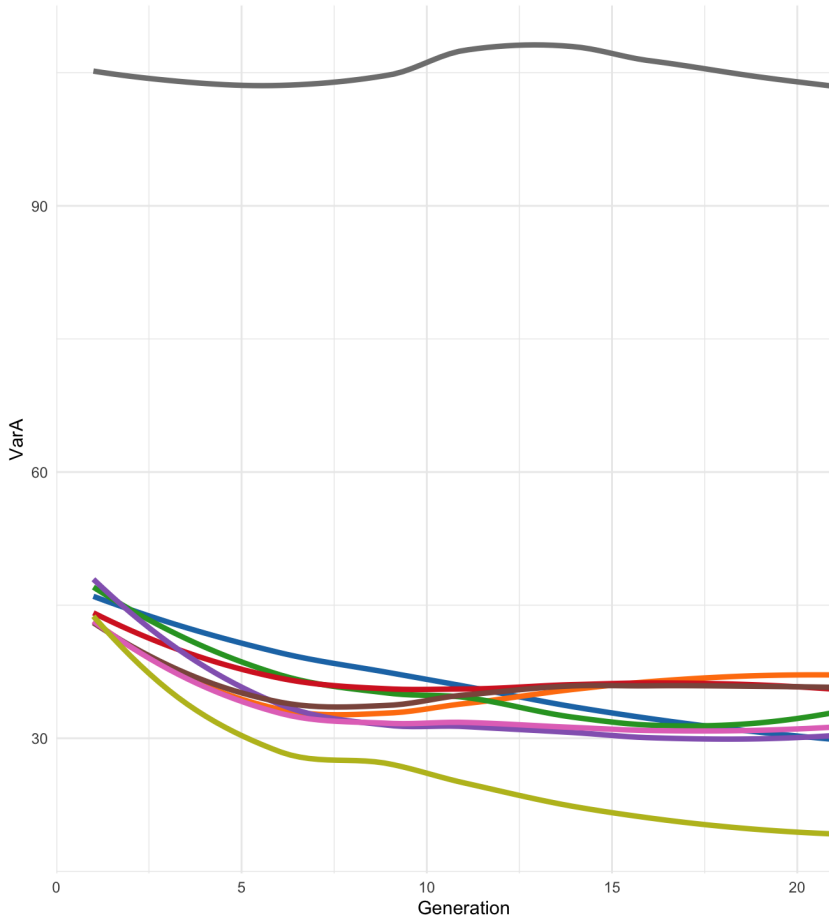
FG vs. Generation Stratified by Penalty Method VD9%



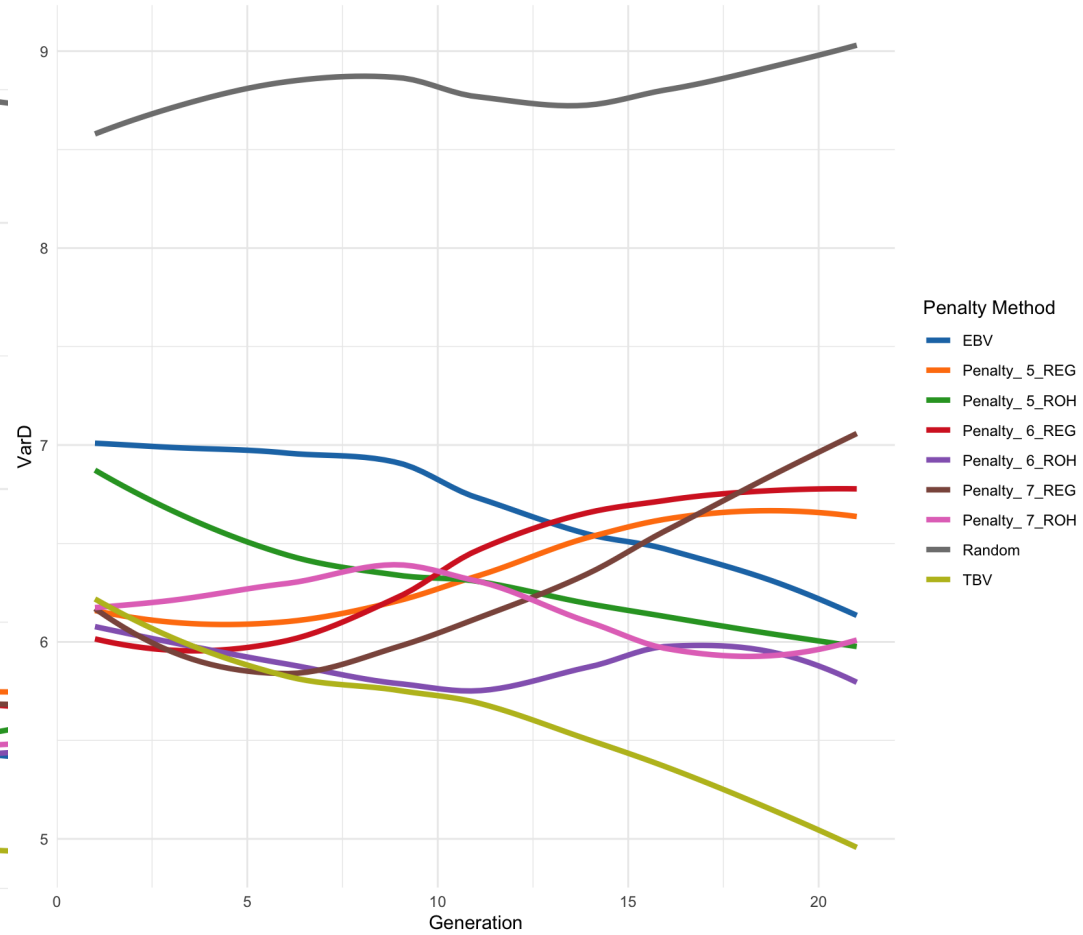
deltG vs. Generation Stratified by Penalty Method VD9%



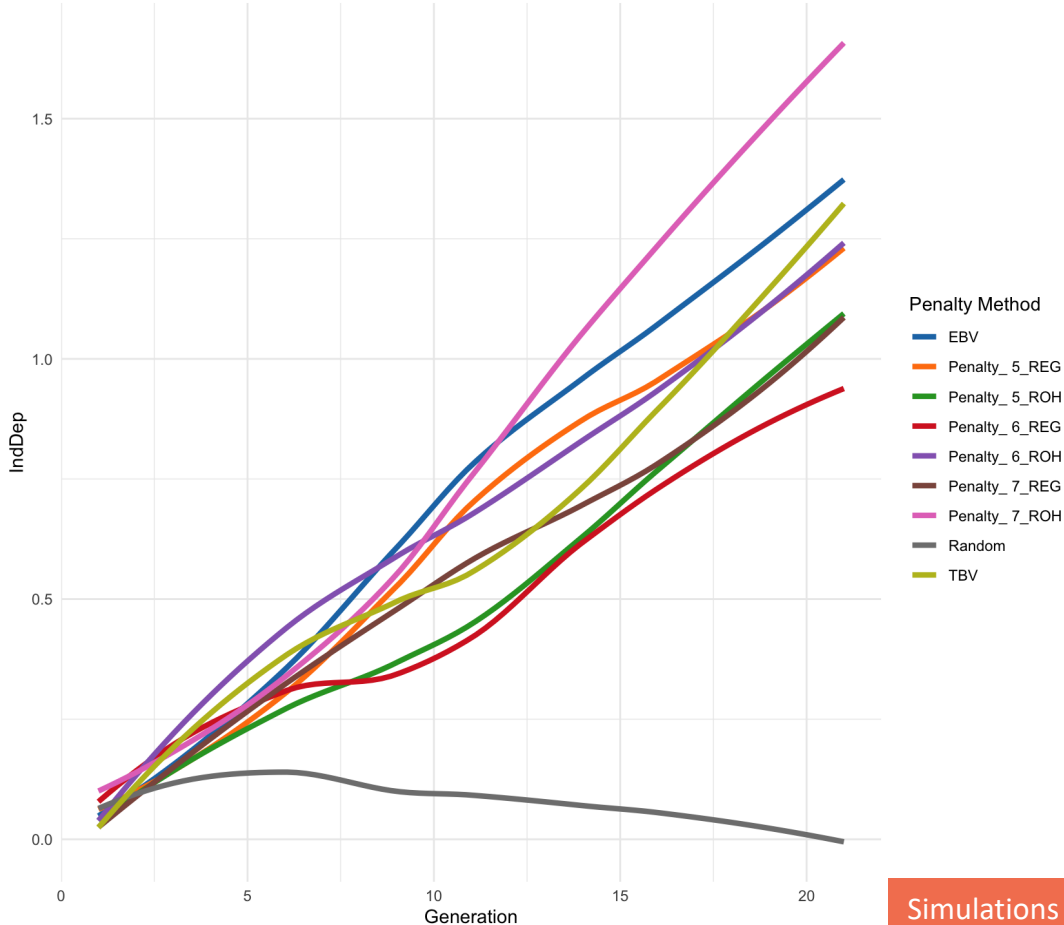
VarA vs. Generation Stratified by Penalty Method VD9%



VarD vs. Generation Stratified by Penalty Method VD9%



IndDep vs. Generation Stratified by Penalty Method VD9%



Conclusions:

- Penalizing Future Inbreeding effective at constraining accumulation of inbreeding in population
 - Both GFI and ROHFI work
 - ROH penalize less genetic gain
 - Similar level of VA after 20 Gen
- Penalizing FI helps maintain higher level of VD in the population
 - Stronger penalty work better
 - ROH and G based similar results
- Inbreeding depression does accumulate regardless of methods
- Some aggressive penalty might actually prevent purging from pop?

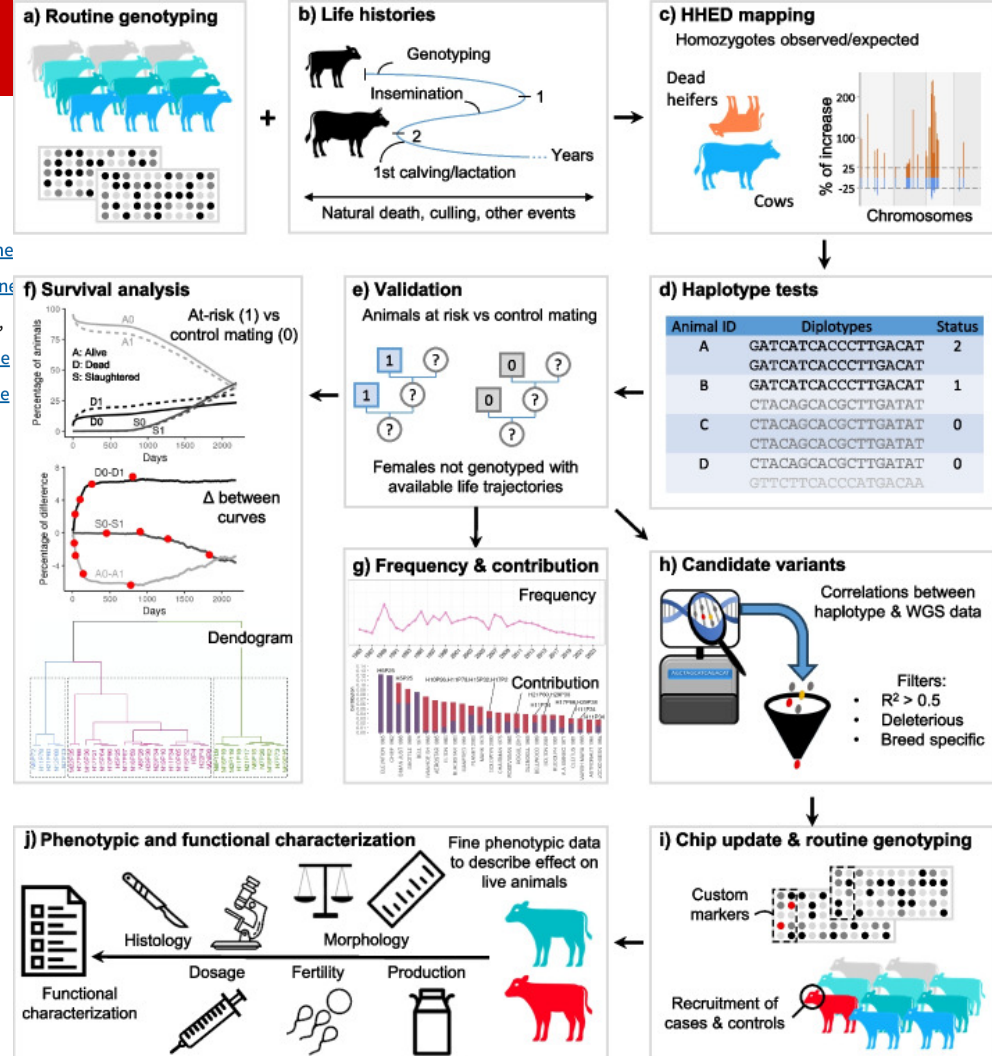
LLM to identify deleterious variants

Massive detection of cryptic recessive genetic defects in dairy cattle mining millions of life histories

[Florian Besnard](#)^{1,2,✉}, [Ana Guintard](#)^{1,3}, [Cécile Grohs](#)¹, [Laurence Guzylack-Piriou](#)⁴, [Margarita Cano](#)¹, [Clémentine Escoufflaire](#)^{1,3}, [Chris Hozé](#)^{1,3}, [Hélène Leclerc](#)^{1,3}, [Thierry Buronfosse](#)⁵, [Lucie Dutheil](#)⁴, [Jeanlin Jourdain](#)^{1,3}, [Anne Barbat](#)¹, [Sébastien Fritz](#)^{1,3}, [Marie-Christine Deloche](#)^{1,3}, [Aude Remot](#)⁶, [Blandine Gaussières](#)⁴, [Adèle Clément](#)⁴, [Marion Bouchier](#)⁵, [Elise Contat](#)⁵, [Anne Relun](#)⁷, [Vincent Plassard](#)⁸, [Julie Rivière](#)^{1,9}, [Christine Péchoux](#)¹, [Marthe Vilotte](#)¹, [Camille Eche](#)¹⁰, [Claire Kuchly](#)¹⁰, [Mathieu Charles](#)¹, [Arnaud Boulling](#)¹, [Guillaume Viard](#)^{3,11}, [Stéphanie Minéry](#)², [Sarah Barbey](#)¹², [Clément Birbes](#)¹³, [Coralie Danchin-Burge](#)², [Frédéric Launay](#)¹², [Sophie Mattalia](#)², [Aurélien Allais-Bonnet](#)^{3,11}, [Bérangère Ravary](#)⁸, [Yves Millemann](#)⁸, [Raphaël Guatteo](#)⁷, [Christophe Klopp](#)¹³, [Christine Gaspin](#)¹³, [Carole Iampietro](#)¹⁰, [Cécile Donnadié](#)¹⁰, [Denis Milan](#)¹⁴, [Marie-Anne Arcangoli](#)⁵, [Mekki Boussaha](#)¹, [Gilles Foucras](#)⁴, [Didier Boichard](#)¹, [Aurélien Capitan](#)^{1,3,✉}

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PMCID: PMC11441225 PMID: 39343954

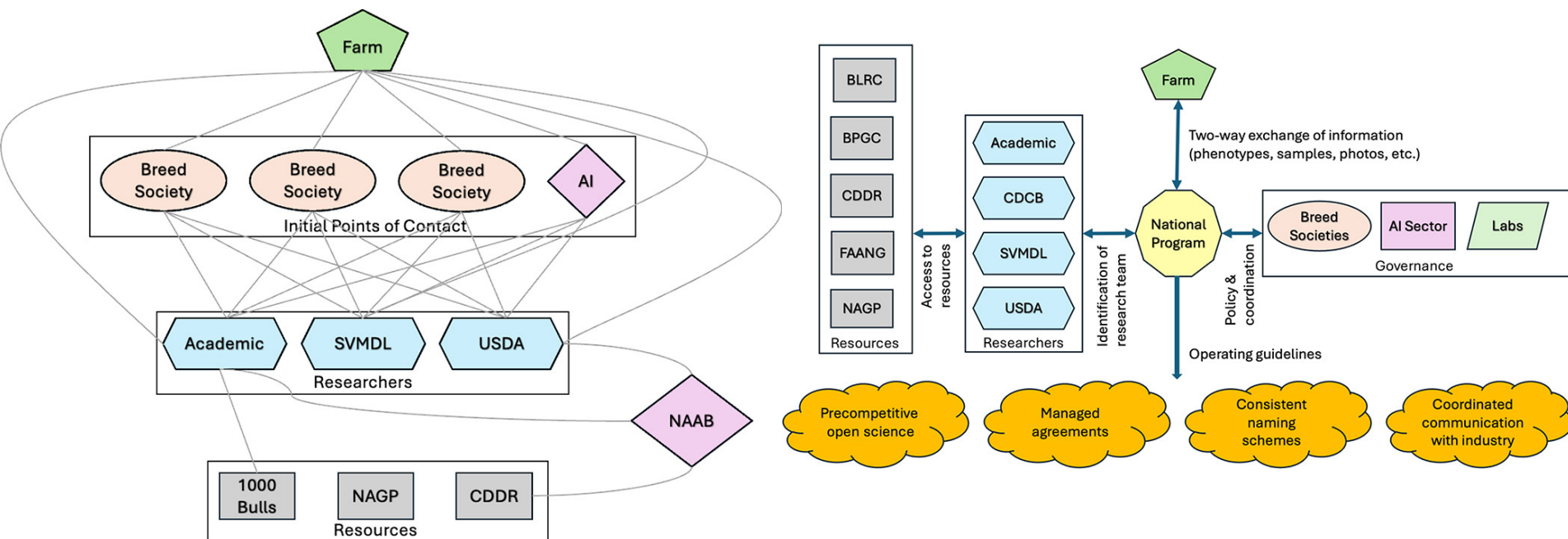


Invited review: Management of genetic defects in dairy cattle populations

[John B. Cole](#)^{1,2,3} [✉](#) · [Christine F. Baes](#)^{4,5} · [Sophie A.E. Eaglen](#)⁶ · [Thomas J. Lawlor](#)⁷ · [Christian Maltecca](#)³ · [M. Sofia Ortega](#)⁸ ·

[Paul M. VanRaden](#)⁹ [Show less](#)

[Affiliations & Notes](#) [Article Info](#)



Evo 2: DNA Foundation Model

Evo 2 is a genomic foundation model capable of generalist prediction and design tasks across DNA, RNA, and proteins. It uses a frontier deep learning architecture to enable modeling of biological sequences at single-nucleotide resolution with near-linear scaling of compute and memory relative to context length.

Evo 2 is trained with 40 billion parameters and 1 megabase context length on over 9 trillion nucleotides of diverse eukaryotic and prokaryotic genomes. (<https://arcinstitute.org/tools/evo>)

Sequence modeling and design from molecular to genome scale with Evo

ERIC NGUYEN  MICHAEL POLI MATTHEW G. DURRANT BRIAN KANG OMBIVA KATHEKAD  DAVID D. LI  LIAM J. BARTIS ARMIN W. THOMAS SAMUEL H. KING 
[...], AND BRIAN L. HEE  [+10 authors](#) [Authors Info & Affiliations](#)

SCIENCE • 15 Nov 2024 • Vol 386, Issue 6723 • DOI: 10.1126/science.adr3236

Can We Effectively Predict Deleterious Variants in Bulls Based on LLM?

A Proof of Concept



Jicai Jiang



THE UNIVERSITY OF
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OMIA - ONLINE MENDELIAN INHERITANCE IN ANIMALS

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chicken	dog	cat	goat	horse	pig	sheep	cattle
27	248	111	7	71	29	60	168

Single Locus Diseases Variants

Control Variants

Anonymized

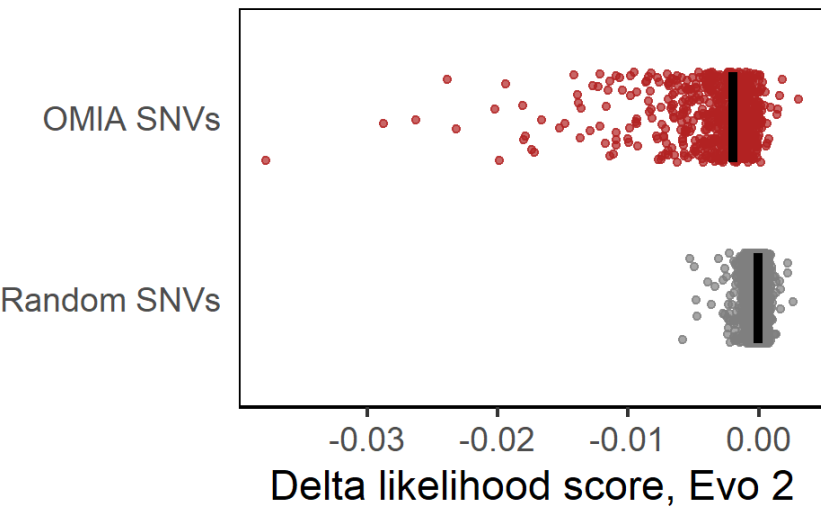
EVO2

Disease

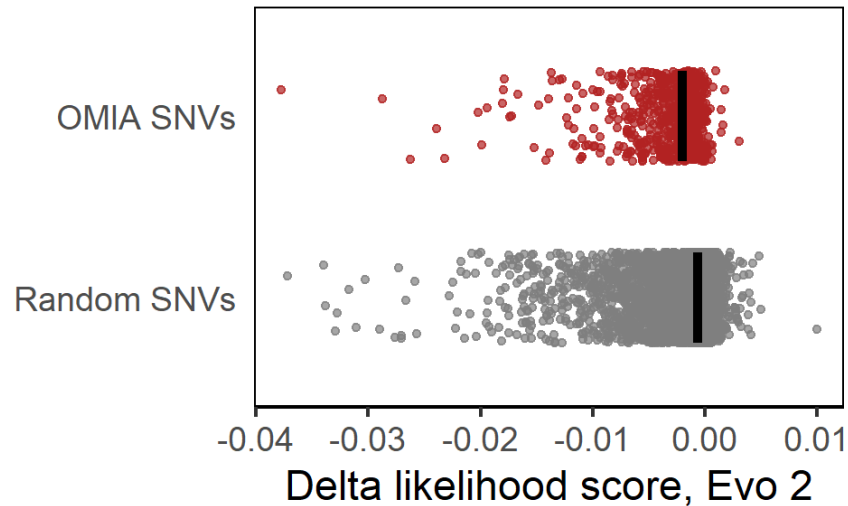
Neutral

Zero-shot classification

Variant-type blind: AUROC = 0.9338 & AUPRC = 0.8315

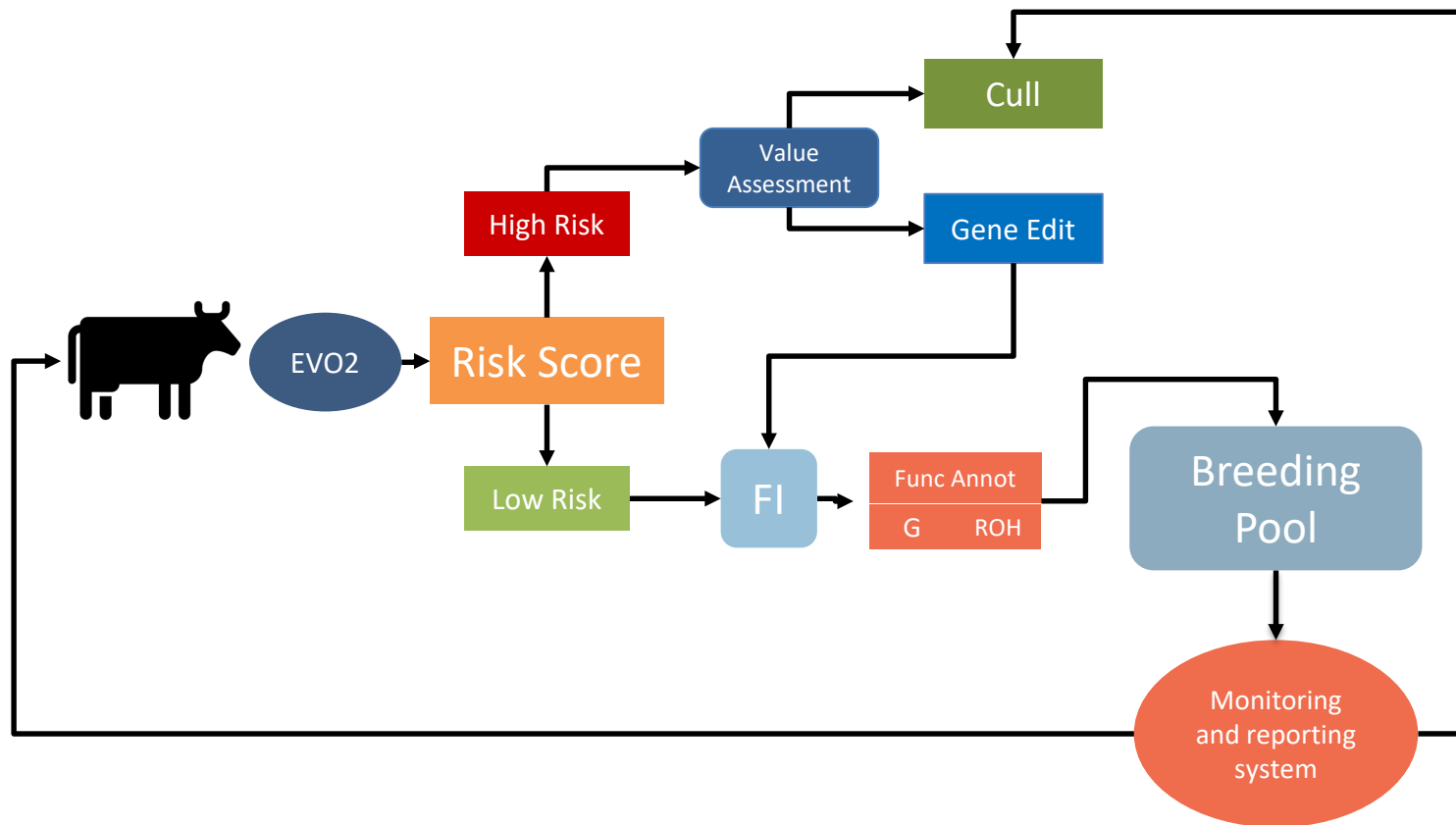


Variant-type matching: AUROC = 0.7174 & AUPRC = 0.1659



test_species	Variant-type blind		Variant-type matching	
	AUROC	AUPRC	AUROC	AUPRC
chicken	0.8438	0.3740	0.6126	0.1645
dog	0.9133	0.5817	0.7738	0.2674
cat	0.8969	0.5518	0.6832	0.2008
goat	0.8714	0.5606	0.6571	0.3557
horse	0.9307	0.5590	0.8276	0.2942
pig	0.9310	0.6070	0.8430	0.3925
sheep	0.8954	0.5574	0.6753	0.2524
cattle	0.8958	0.5077	0.7438	0.2672
AVERAGE	0.8973	0.5374	0.7271	0.2744

A potential framework



- We now have better tools to understand inbreeding and inbreeding depression
 - We do need a better system and a more systematic effort
 - Look beyond algebraic massage of LMM
- Inbreeding load is heterogeneous
 - Based on the definition of “fitness”
 - Based on functional annotation
 - But also based on the environmental load
 - Are we underestimating it in stressful conditions?
- EFI is a valuable tool not only to curb inbreeding accumulation but also to preserve exploit dominance variance
 - G and ROH FI perform similarly
 - Very strong penalty on F might prevent purging of deleterious variance (strong emphasis on might)
 - With availability of producing ability in cows (A+D) possible to re-capture some of VD indirectly in selection process



National Institute of Food and Agriculture
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