



Inbreeding becomes a serious issue

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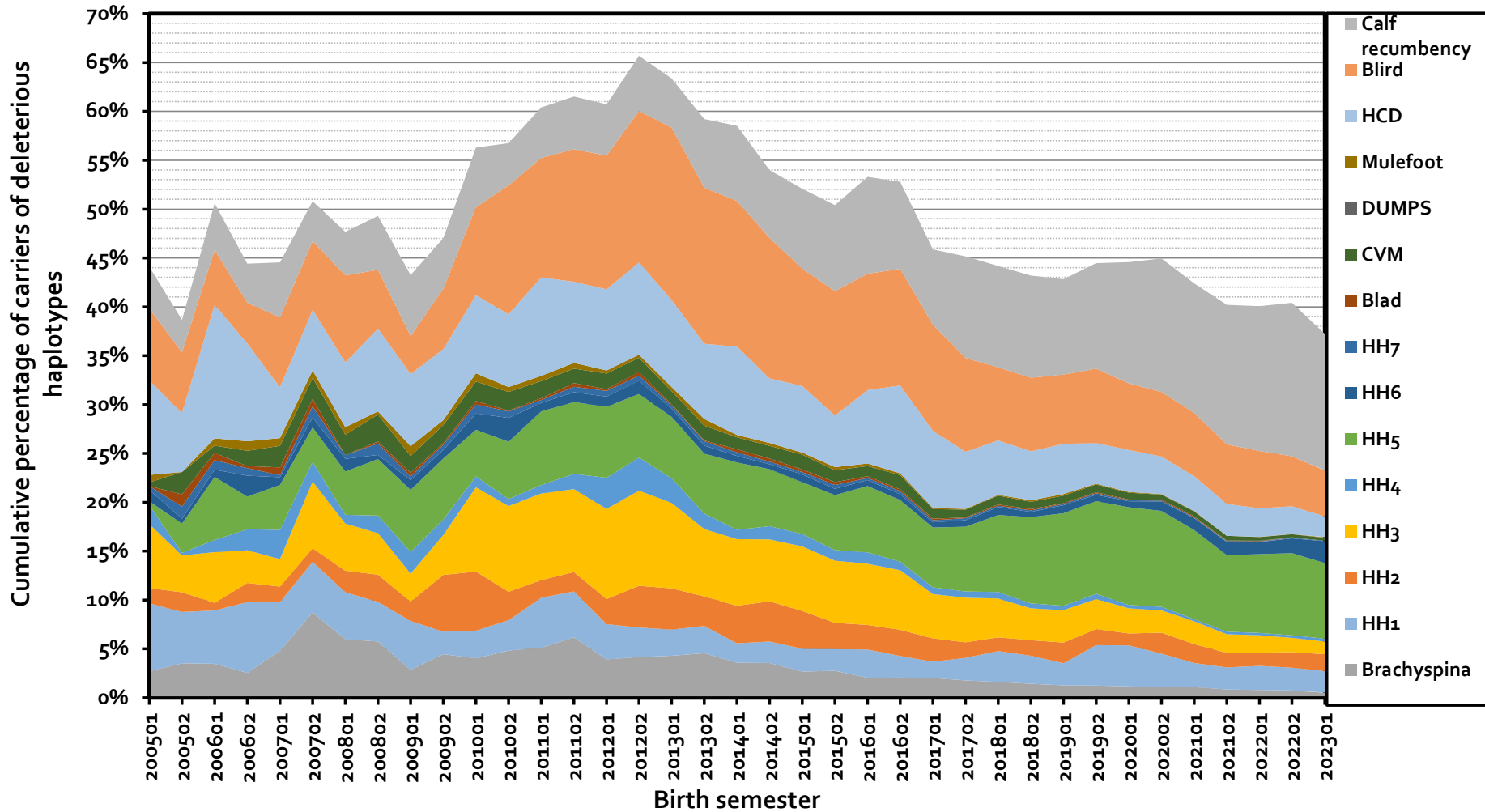


Objective of selection

- We select to eliminate undesirable genetic variants.
- So if we're successful then we get rid of a lot of undesirable genetic variants.
- But then we complain that we lose genetic variation....
- **BUT that is ... what we WANTED!!**
- Losing 'good' variation would be a problem but:
- Is losing 'bad' variation a problem?



Avoiding problems by decreasing deleterious defects...





Holstein origins

- 1870_s-1880_s: ~9000 Dutch animals imported in North-America
- 1880: Two bulls, **Hulleman** and **Neptune H**, are the origin of all modern AI bulls
- Neptune was in uterus when imported from North-Holland to USA
- Conquerer (sire of Hulleman) was imported from North-Holland to USA
- 1920_s-1930_s: **Johanna Rag Apple Pabst** (**Neptune** line) and **Wisconsin Admiral Burke Lad** (**Hulleman** line) as leading foundation sires.
- 1960_s: Pawnee Farm Arlinda **Chief** (**Neptune** line) and Round Oak Rag Apple **Elevation** (**Hulleman** line) as leading sires.
- So Holsteins already had several **population bottlenecks: 3 times 2 leading bulls!**



Y-Chromosome

From Two Bulls, 9 Million Dairy Cows
In the U.S., just two Y chromosomes exist within a population of 9 million Holsteins. Researchers want to know what traits have been lost over time.

O'Hagan 2019

- **>99%** of the Y chromosomes: **Chief** (Neptune line) & **Elevation** (Hulleman line)
- **~1%** of the Y chromosomes: **Ivanhoe** (Neptune line)
- All Holsteins come from **3** sires (**2** paternal lines)!



Use the whole Holstein population

- Americanism of Italian farmers is a **boomerang**.

Average increase in inbreeding per year

Birth Year	1980 to 1990	1990 to 2000	2000 to 2010	2010 to 2019
ITA	0,02	0,18	0,14	0,26
USA	0,19	0,19	0,11	0,26
CAN	0,10	0,26	0,08	0,23
FIN	0,06	0,09	0,19	0,20
POL	0,20	0,10	0,16	0,20
HUN	0,04	0,15	0,13	0,20
ESP	0,13	0,24	0,13	0,20
CHE	0,10	0,13	0,09	0,19
SLO	0,06	0,12	0,11	0,18
NLD	0,24	0,17	0,03	0,16
FRA	0,10	0,20	0,10	0,15
DEU	0,11	0,16	0,08	0,15
IRL	0,10	0,21	0,06	0,15
GBR	-0,02	0,19	0,12	0,14
AUT	0,00	0,09	0,10	0,14
JPN	0,09	0,26	0,13	0,13
SWE	0,06	0,19	0,13	0,12
LUX	0,13	0,13	0,07	0,12
NZL	0,02	0,09	0,03	0,11
DNK	0,11	0,18	0,12	0,10

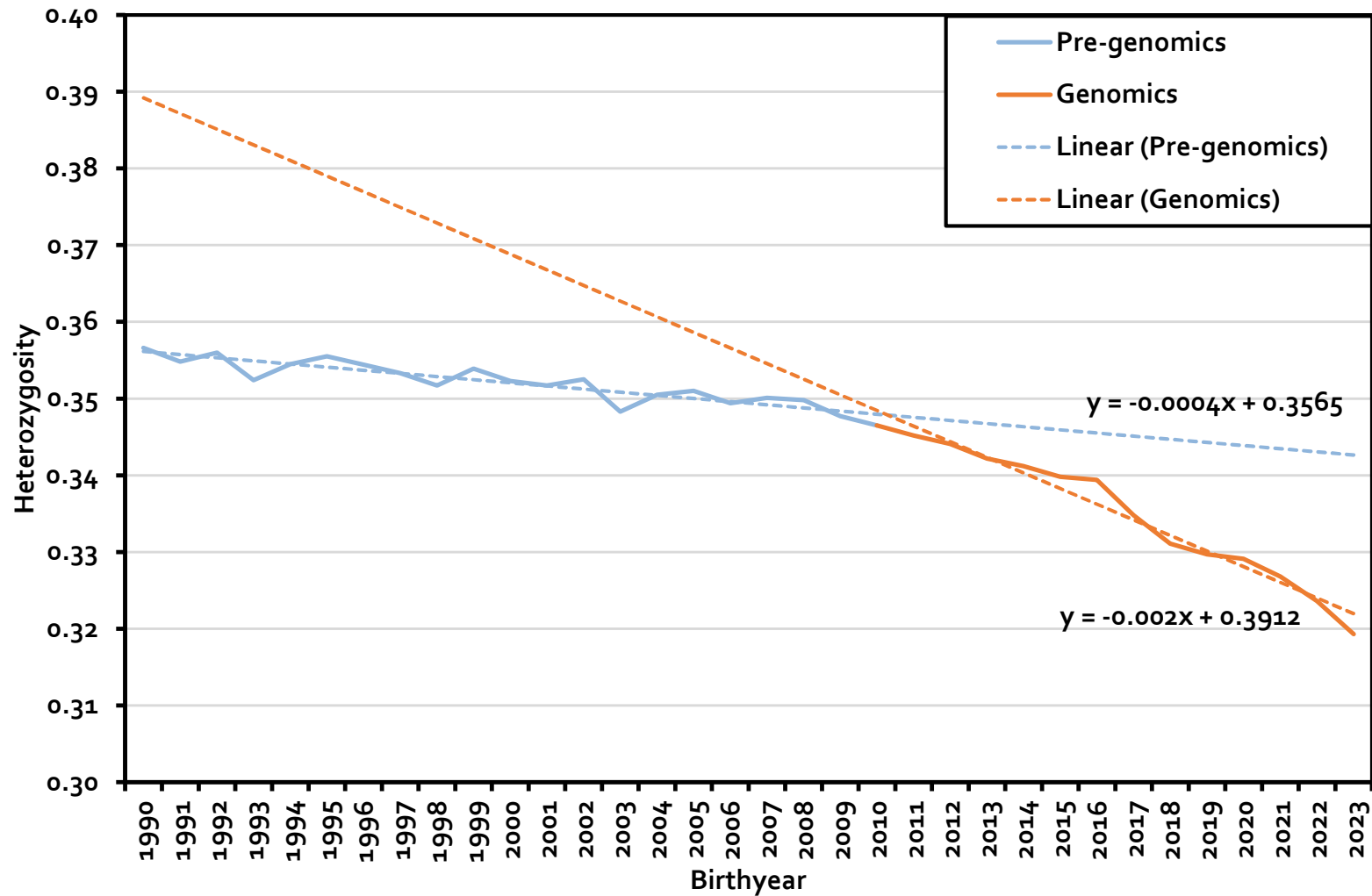
difficult

moderate





Trend of SNP heterozygosity



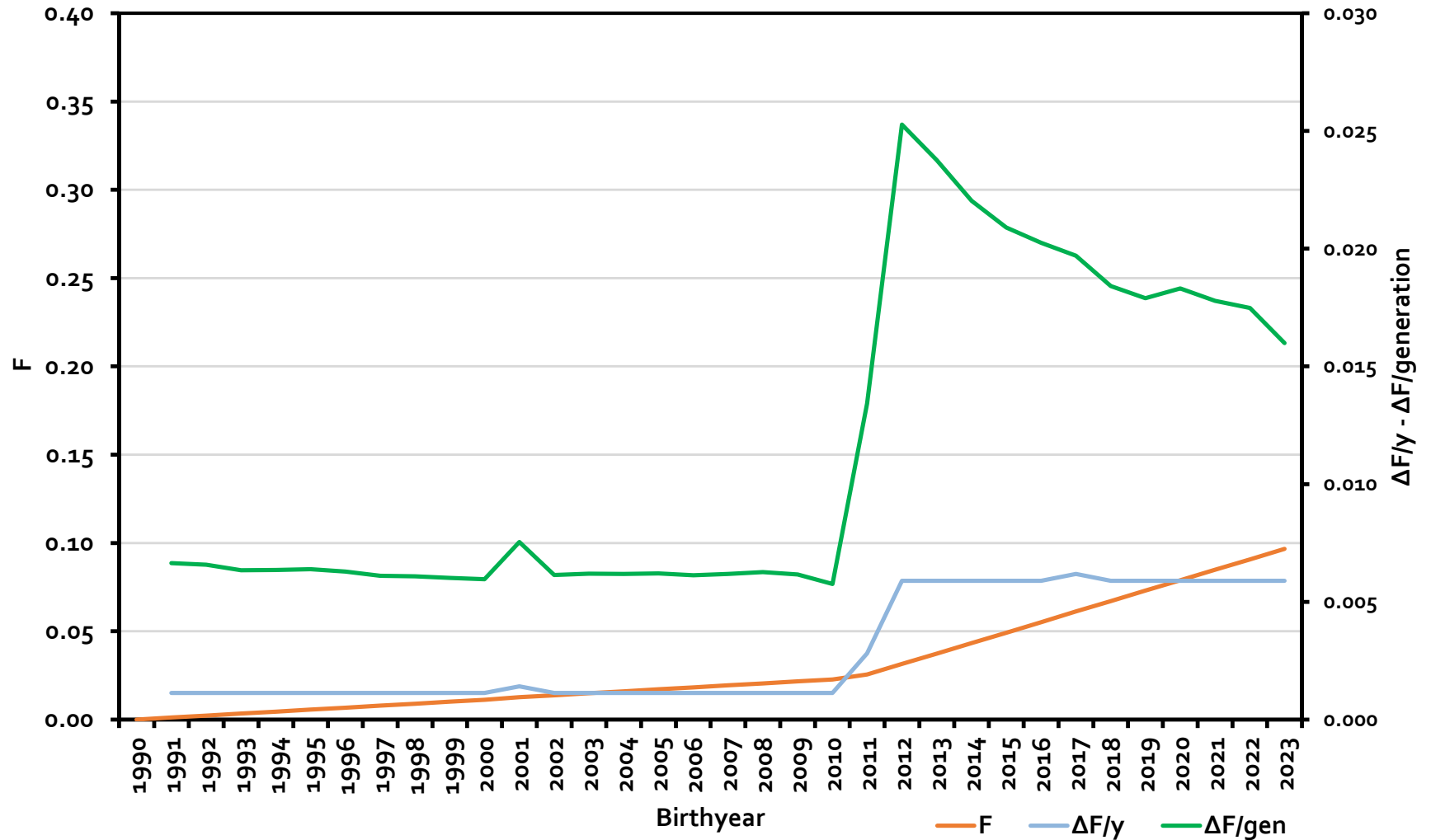


How much time is left?

- If the SNP heterozygosity is 0.32 and the (linear) annual decline is 0.002, then after $0.32 / 0.002 = 160$ years we are at a **heterozygosity of 0.00**.
- North America + Italy: Mostly select North-American
- Europe: Select North-American + European
- Higher inbreeding tendency in countries that primarily limit selection to North America.
- More moderate trend in countries using North America and Europe.
- Convince breeders / AI centers to **look beyond North America**. We need the whole breed.

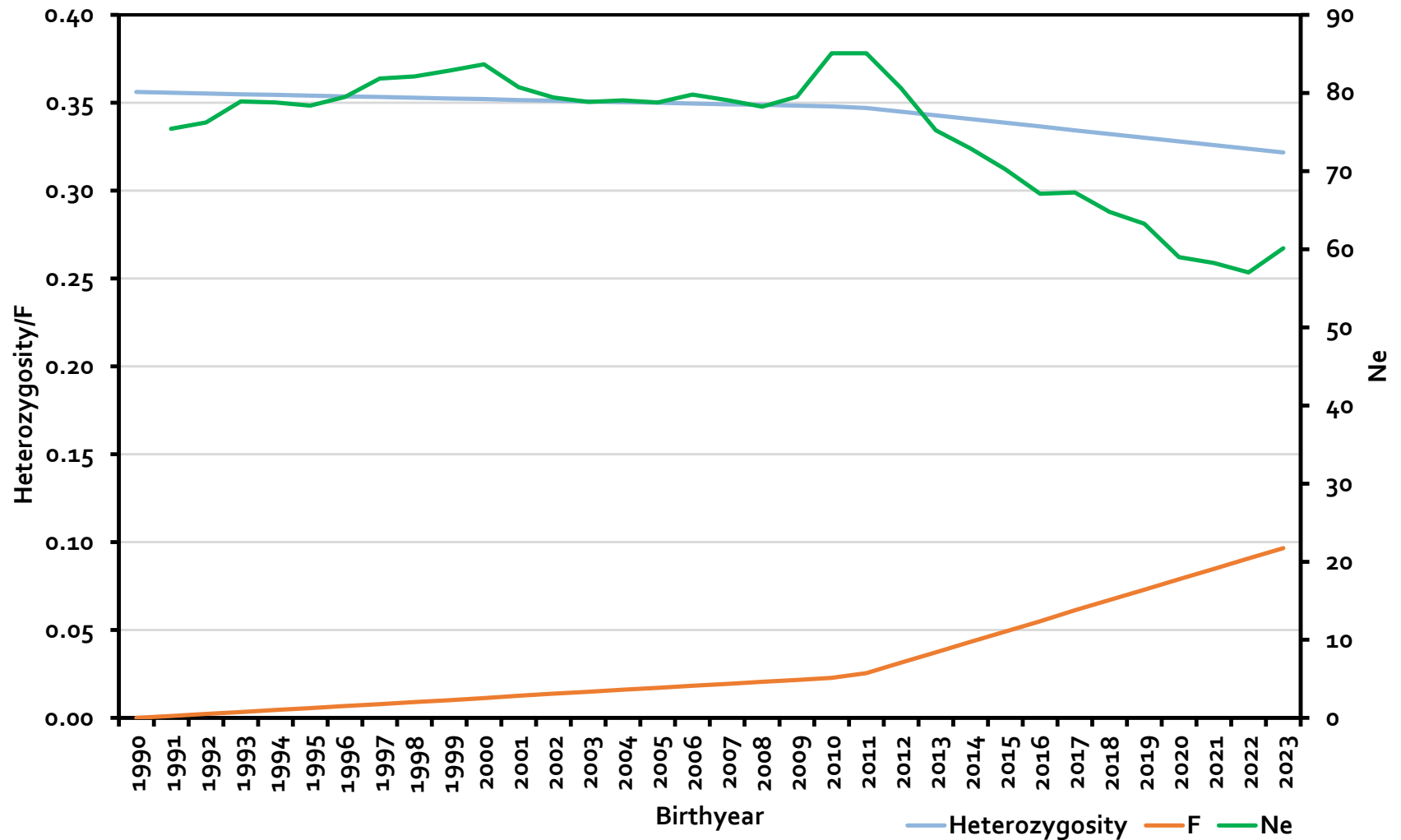


Inbreeding coefficients





Effective population size: Decreasing since genomics





Avoid inbreeding/loss of genetic variation

- At the **population** level: **Selection** is key
- At the **individual** level: **Mating** is key
- For the population the individual matings are irrelevant.
- Most of the selection is done by **AI centers** ... not by farmers.
- Solution therefore has to come mainly from AI centers.
- How to ensure AI centers maintain diversity?
- **Competitive pressure** pushes them to use mainly the elite dams/sires. But they **MUST** use a wide variety of sires and dams of sons.



Within breed solutions

- Premium/Penalize for **(genomic) expected future inbreeding**
- Penalize for inbreeding depression
- Optimum contribution selection
- Create subpopulations



GEFI: Genomic Expected Future Inbreeding (1)

- Genomics: More accurate relationship with future population
- **Expected Future Inbreeding... NOT own inbreeding**
- Expected future inbreeding coefficient: The probability in an autosomal segment that the haplotype transmitted from a random mate is identical in descent to the transmitted haplotype of this individual.



GEFI: Genomic Expected Future Inbreeding (2)

- I take HOLITAF animals in the last 2 years as a reference sample for the future of the population.
- Sample of animals not used as single individuals but for **population haplotype frequencies**. So you don't need the single matings (to take the average later) but you multiply directly with the frequency so we immediately have the average!
- Since segments are numbered by pedimpute.fgo, we don't need to compare if SNPs are identical... just check if **segments** are **numbered identical**. (ROH: Runs Of Homozygosity)
- For all animals, I calculate the average of the expected percentage of segments that are homozygous when matched with the reference population. This is ROH future expected inbreeding.



Ideas behind GEFI

1. SNP-by-SNP comparison... lots of animals... lots of SNPs... very **slow** process. Instead if we use the **numbered segments** and compare: homozygous or not (~**ROH**).
2. Comparing each animal with a reference sample will be very slow. Use the **haplotype frequencies** in the reference sample instead.

GEFI calculation: 597.905 animals in 13 minutes... (in single threaded Python)



Pedimpute: Imputation

- Pedimpute.fgo:
 - Assigns **24 million** alleles/second
 - ~80 SNPs per segment in the last step
 - Different segments have each a unique number
 - If an animal has the same segment on both homolog chromosomes... then we have an ROH!!

Animals	Segments			
	1	2	3	
• 21325480 ...	6	10	440	homolog 1
• 21325480 ...	6	9	184	homolog 2: 1 of 3 segments ROH
• 21367735 ...	6	10	13	homolog 1
• 21367735 ...	6	10	13	homolog 2: 3 of 3 segments ROH



Take home message

- At the **population** level: **Selection** is key.
- At the **individual** level: **Mating** is key, at population level individual matings are irrelevant.
- Most of the selection is done by **AI centers**... not by farmers.
- AI centers **MUST** use a wide variety of sires and dams of sons.
- We need to use the whole Holstein population, rather than just a piece.
- Breeding programs need to be 're'-designed to avoid genetic bottlenecks.
- Select against undesirable alleles.
- **We are working on premium/penalty based on genomic expected future inbreeding**



Thanks for your attention

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