

Applications of haplotypes in dairy farm management

John B. Cole

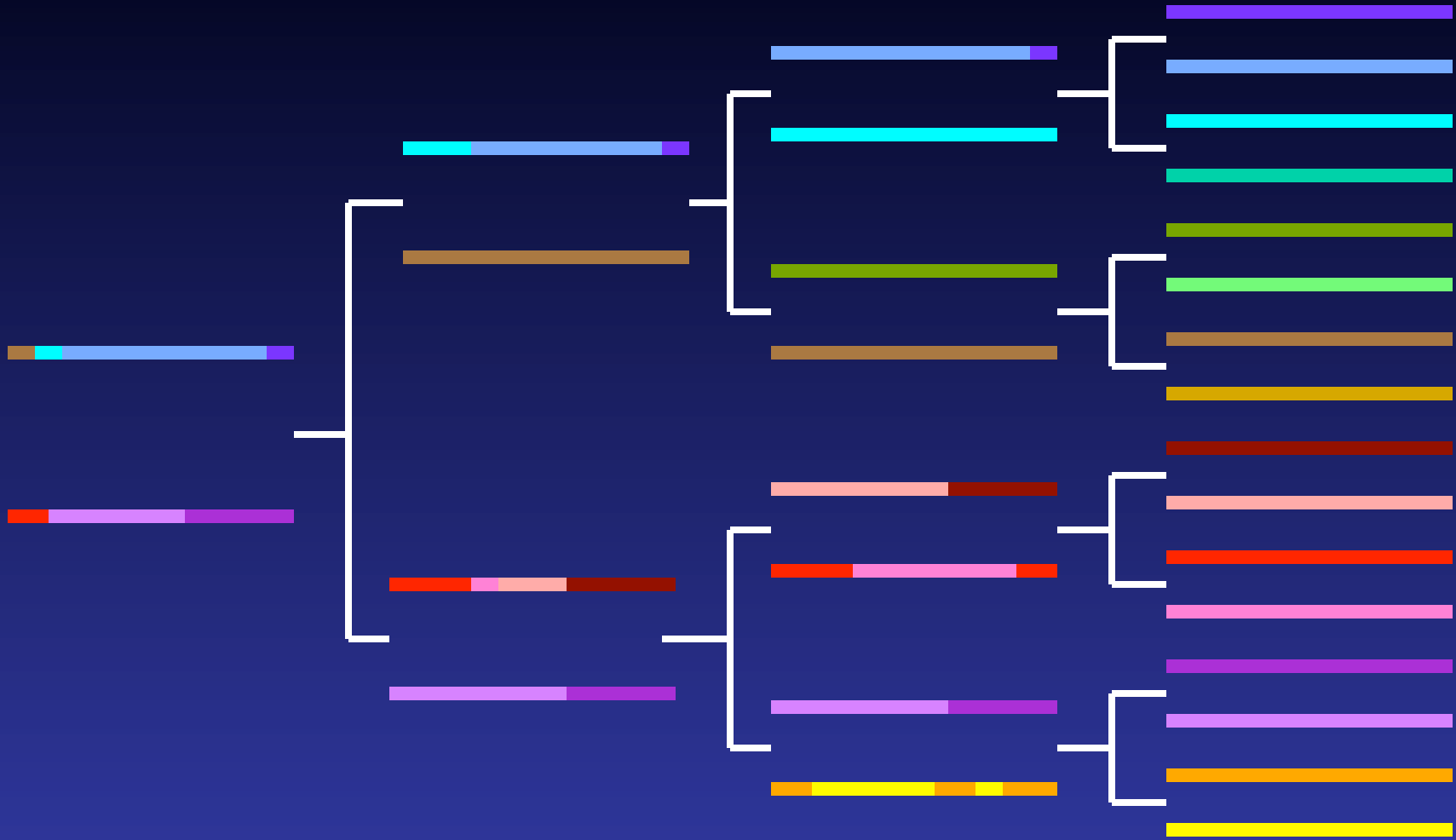
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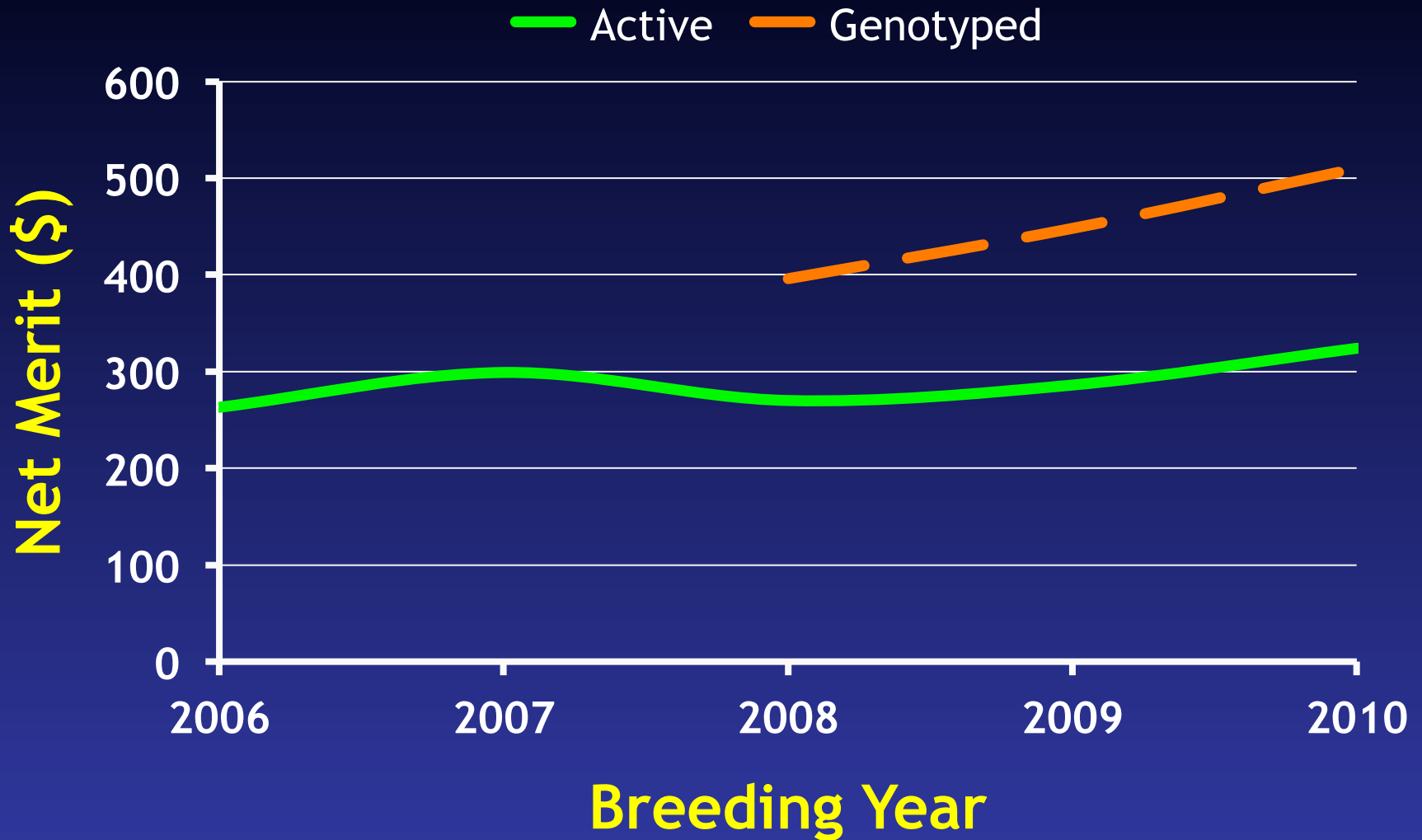
Introduction

- **Genomic selection increases selection response by reducing generation interval**
- **Bulls were genotyped first due to cost**
- **Now we have genotypes for many cows**
- **What can we do with those data that we couldn't do before?**

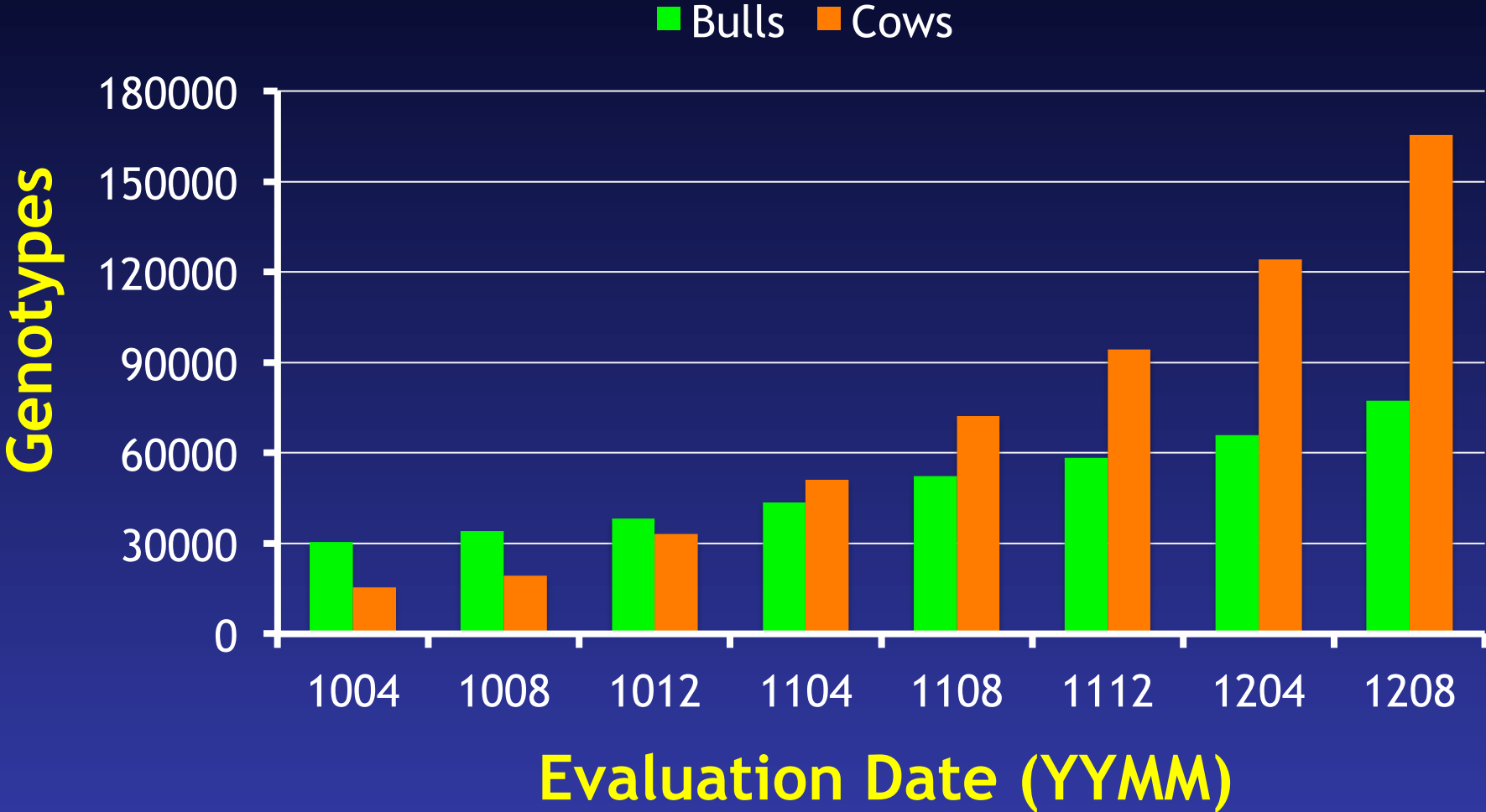
O-Style Haplotypes Chromosome 15



Genetic merit of Jersey bulls



Many cows have been genotyped



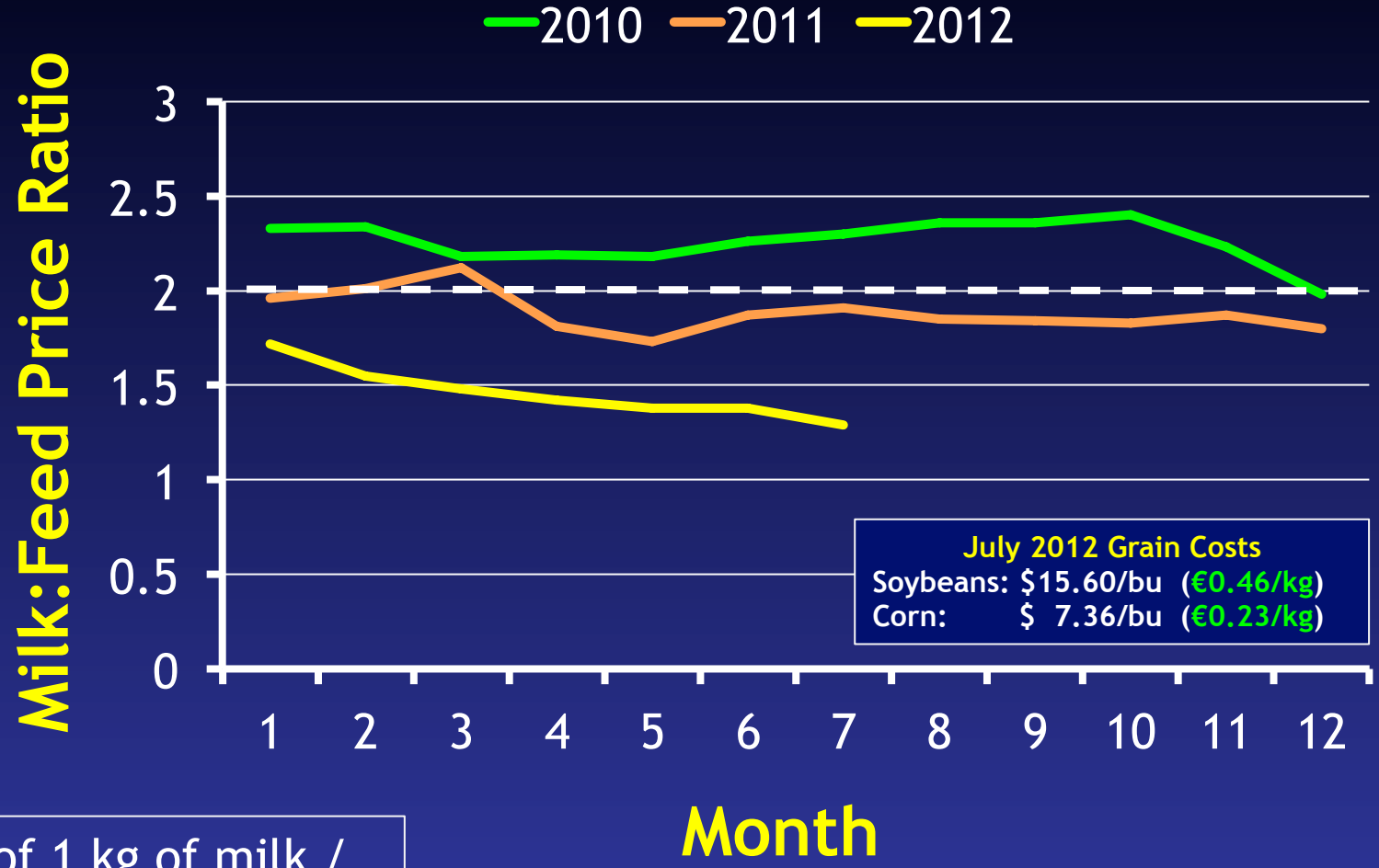
Haplotypes for farm management

- Many uses other than genetic evaluation
 - Culling decisions
 - Mating strategies
 - Identification of new recessive defects
 - Phenotypic prediction



ARS Image Number K7964-1

Input costs are rising quickly



M:FP = price of 1 kg of milk / price of 1 kg of a 16% protein ration

Optimal culling decisions

- Low density genotypes on females can be used to guide early culling decisions
 - **165,526** genotyped cows in August 2012
- Sexed semen increases heifer population from which to select
- What animals should be retained and what animals culled?

Testing and selecting heifer calves

Calves selected	EBV selected calves (pre-ranked, 35% rel.)	Optimal fraction calves tested with genomic test (65% rel.)	EBV selected calves (after genomic testing)	Cost of genomic testing per selected calf	NPV of selected calves
100%	€0	-	-	€0	€0
90%	€31	70-100	€46	€13	€52
80%	€64	60-90	€78	€14	€94
70%	€87	50-90	€113	€22	€136
60%	€112	40-80	€145	€25	€176
50%	€139	30-70	€179	€30	€218

EBV = estimated breeding value, NPV = net present value

Bottom line economics

	No sexed	2x sexed	No sexed	2x sexed
Pre-ranking calf reliability	0%	0%	35%	35%
Genomic testing policy ¹	20-100	0-100	70-90	50-90
Statistics (€/cow/year):				
Profit without heifer calf value	381	378	381	378
Heifer calves sold	14	31	14	31
NPV calves before pre-ranking	99	101	99	101
NPV calves due to pre-ranking	0	0	30	51
Added NPV from genomic testing	38	71	7	16
Cost of genomic testing	7	23	4	9
Heifer calf value	146	180	148	191
Profit with heifer calf value	527	558	529	569
			¹ 7K test (€36.50, 65% reliability)	

Farmers want new genomic tools



The screenshot shows the AGWEB website interface. At the top left is the logo "AGWEB POWERED BY FARM JOURNAL". To the right of the logo is the date "Apr 5, 2012" and a navigation menu with links for "Home", "Tools", "Events", "Blogs", and "Discussions". Below this is a red navigation bar with buttons for "News", "Weather", "Markets", "Crops", "Livestock", and "Business". Underneath the navigation bar are social media sharing options: "Facebook | Twitter | Share | Email | Print". The main content area features a large orange headline: "StrataGEN, new inbreeding management program, introduced". Below the headline, it says "APRIL 3, 2012" and "By: Dairy Today Editors". Further down, it lists the source as "Source: Select Sires". The article text begins with "Select Sires Inc. announces the debut of StrataGEN™, a unique, sequential breeding system that offers optimal use of genomic insights to help dairy producers achieve individual breeding goals while also minimizing inbreeding." The text continues with "StrataGEN uses genomic insights to categorize both daughter-proven sires and young sires into one".

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StrataGEN, new inbreeding management program, introduced

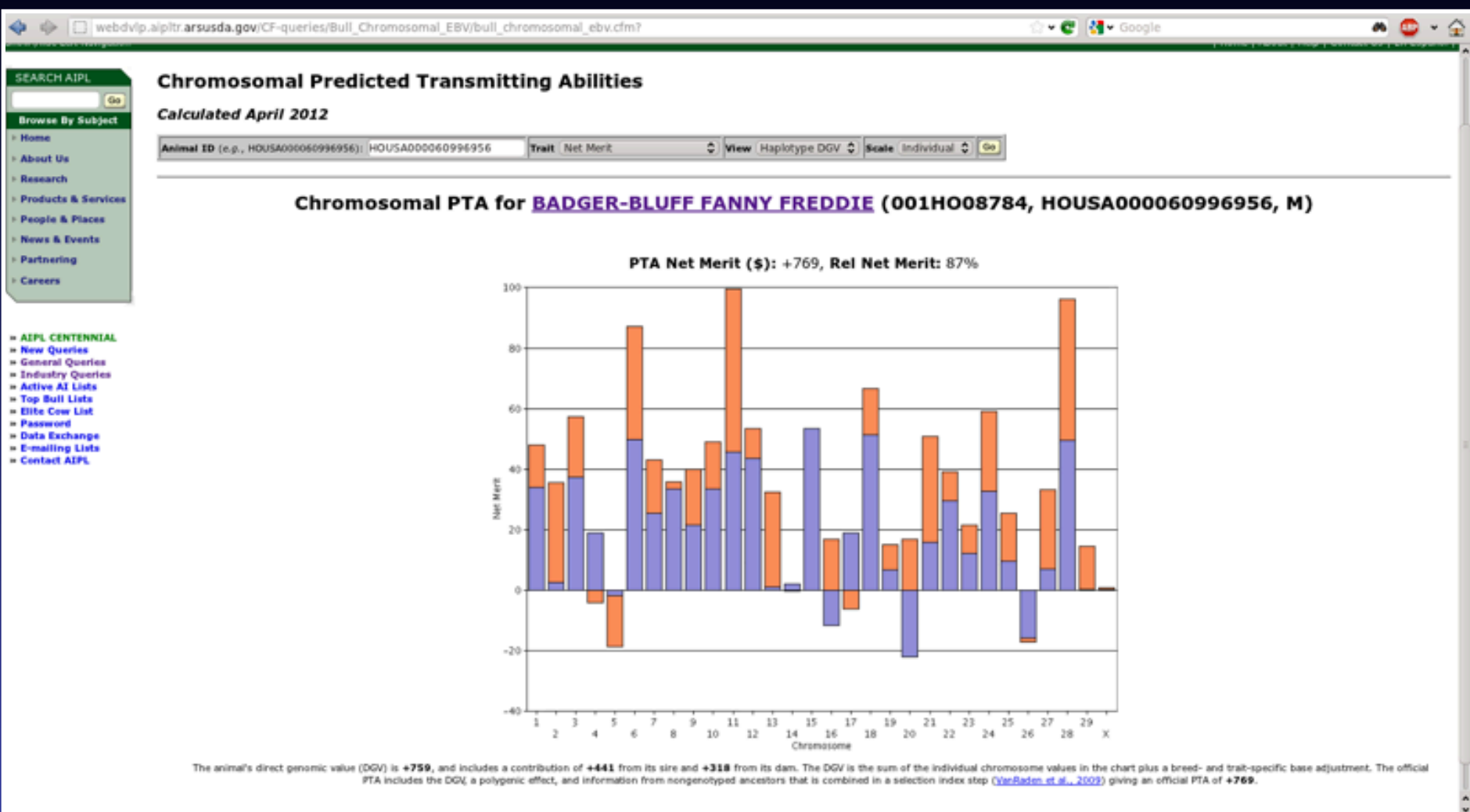
APRIL 3, 2012
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Source: Select Sires

Select Sires Inc. announces the debut of StrataGEN™, a unique, sequential breeding system that offers optimal use of genomic insights to help dairy producers achieve individual breeding goals while also minimizing inbreeding.

StrataGEN uses genomic insights to categorize both daughter-proven sires and young sires into one

New haplotype query

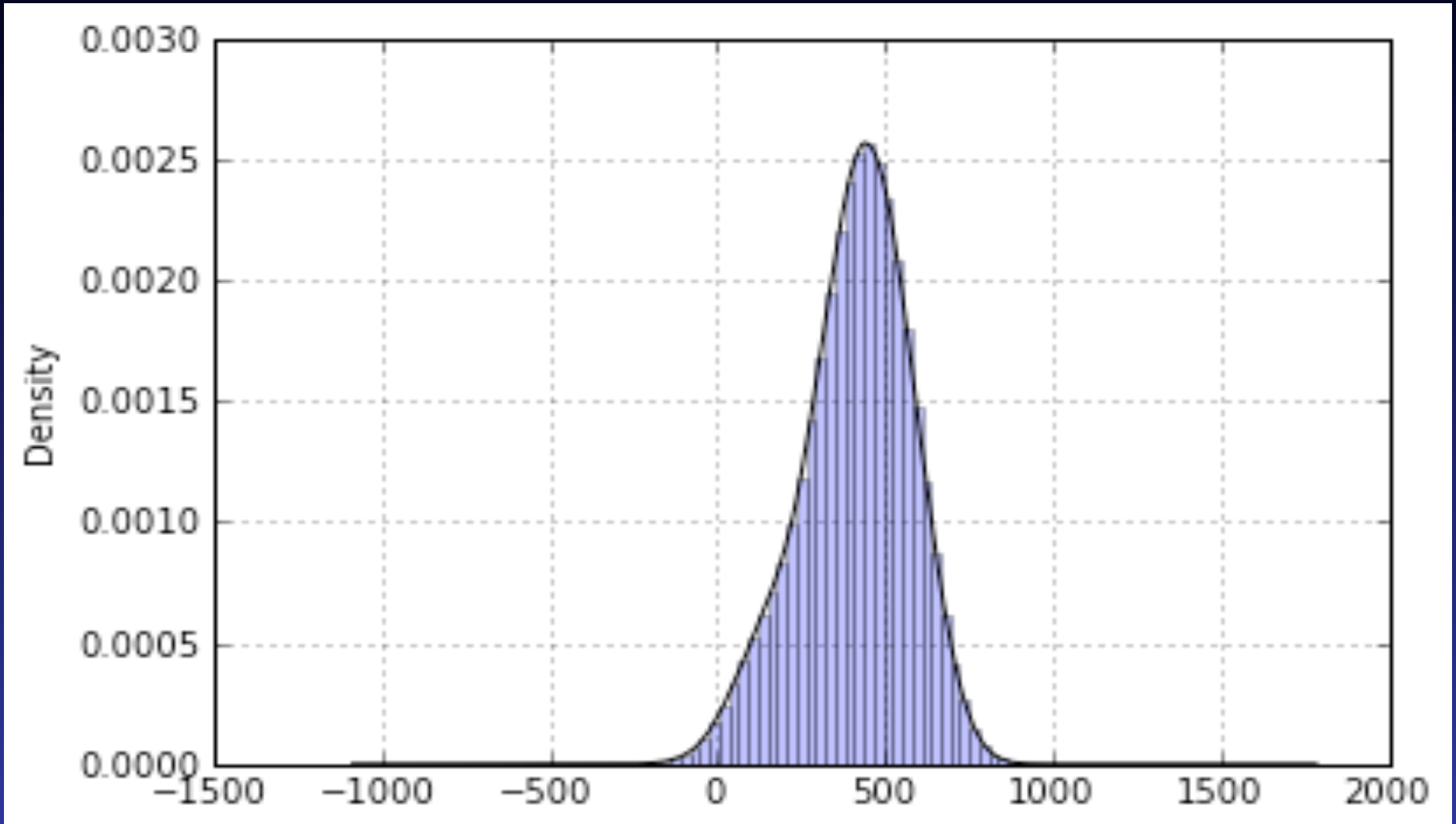


Cole, J.B., and Null, D.J. 2012. AIPL Research Report GENOMIC2: Use of chromosomal predicted transmitting abilities. Available: http://aipr.arsusda.gov/reference/chromosomal_pta_query.html.

Simulated matings

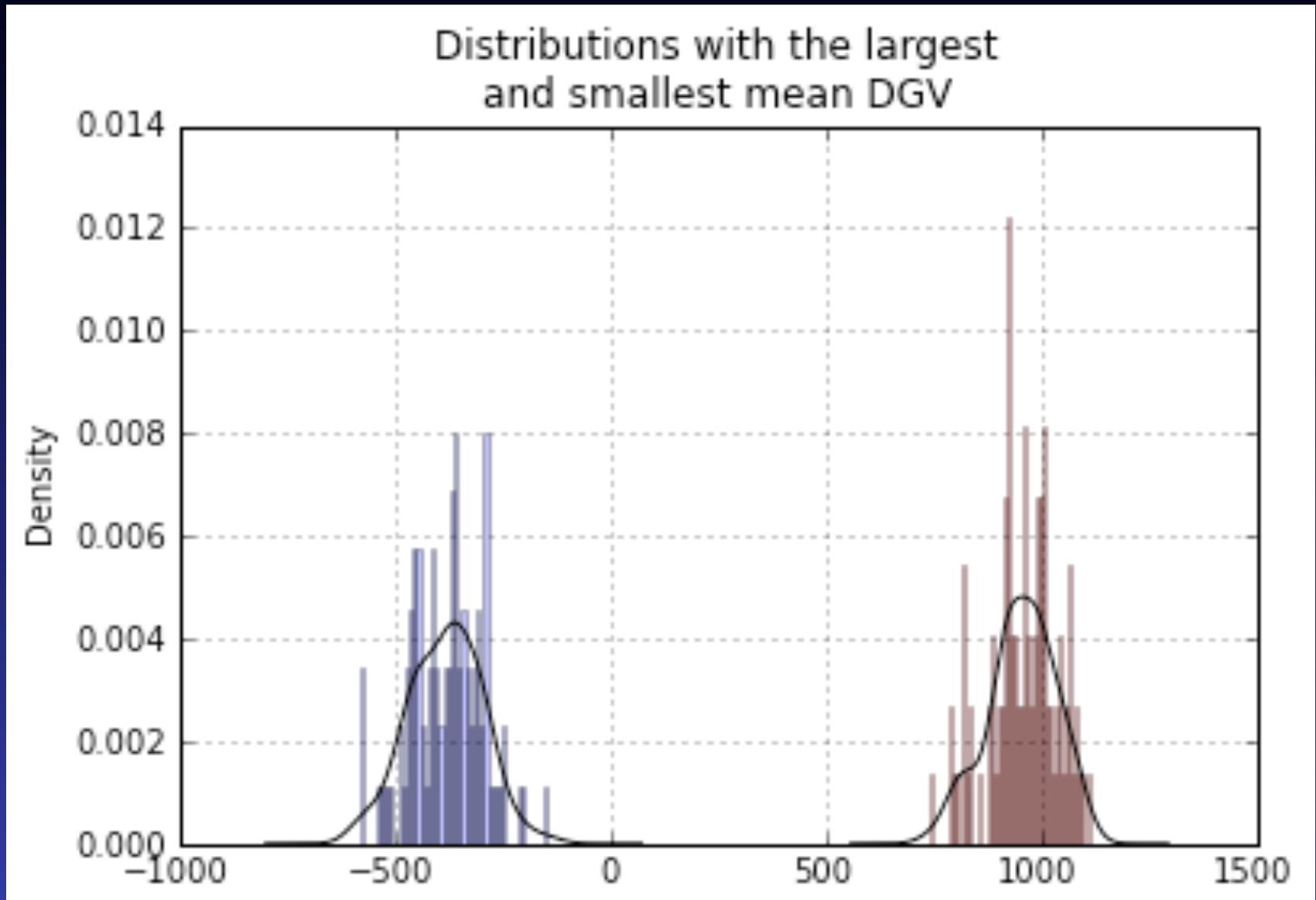
- Mated all genotyped Jersey bulls and cows in a fully cross-classified design
 - 5,877 bulls and 15,553 cows
 - 91,404,981 matings
 - Crossovers, independent assortment
 - 100 replicates per mate pair
- Mean, variance, skewness, and kurtosis

Distribution of progeny DGV

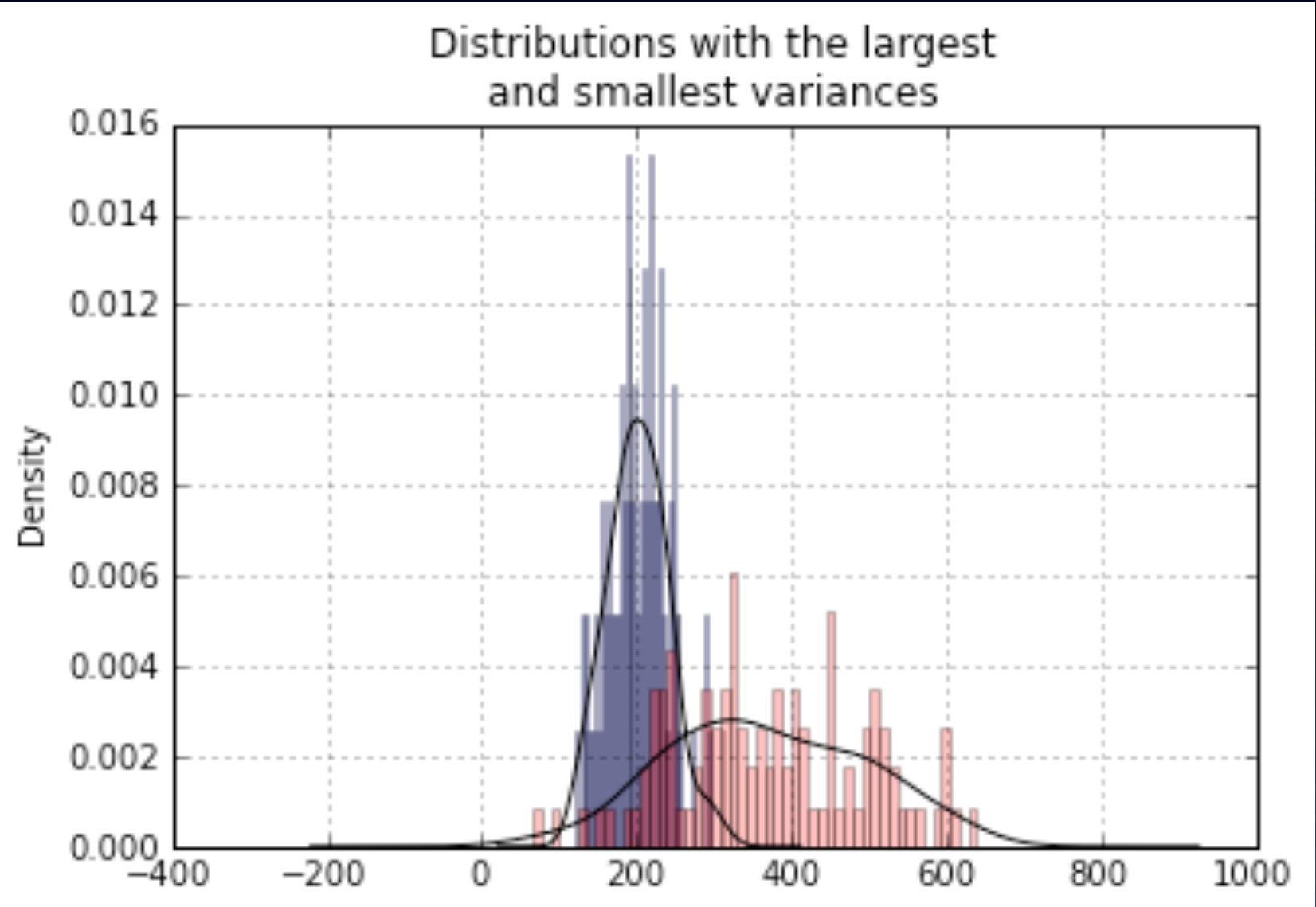


Distribution of 6,000,000 randomly sampled simulated matings.

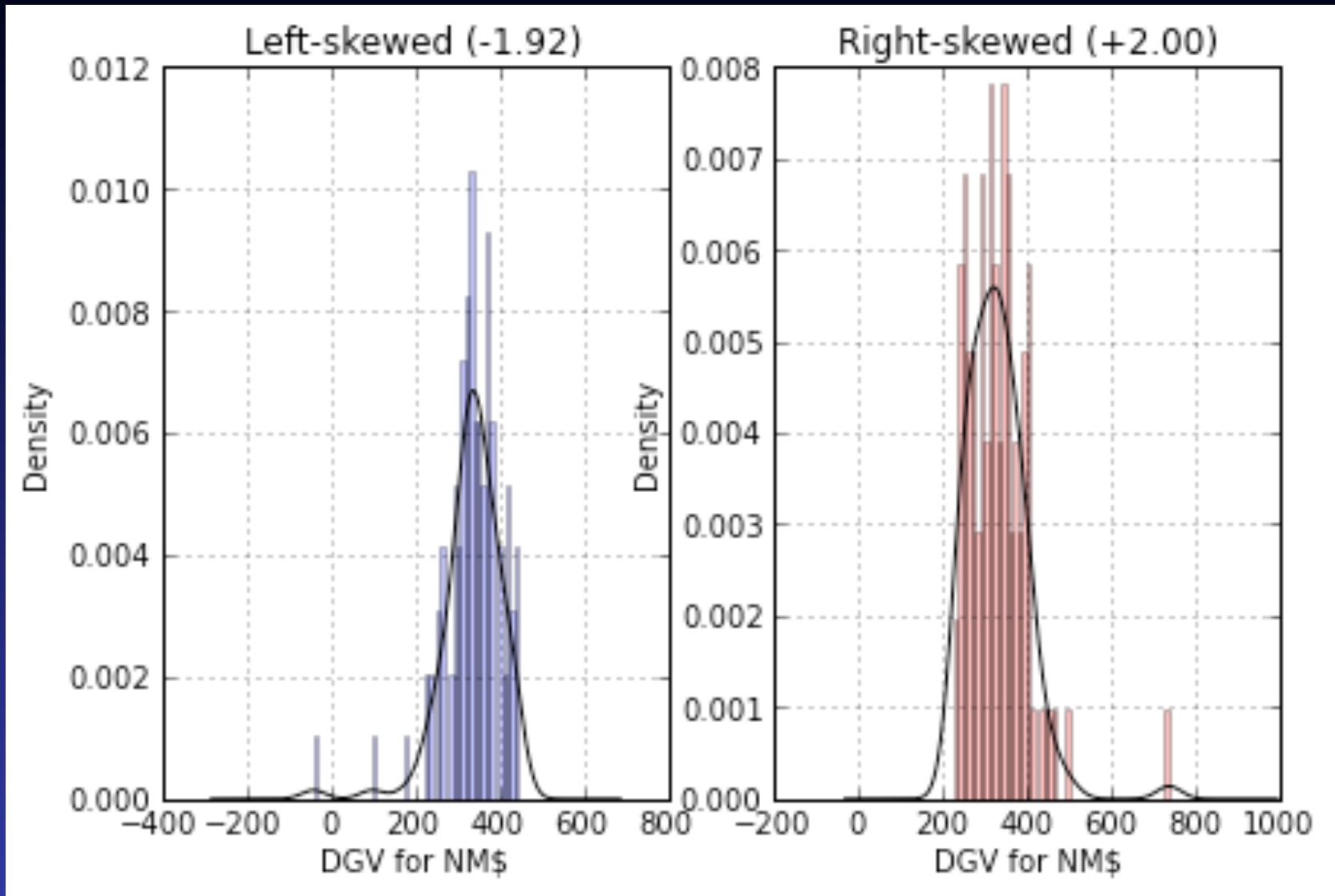
Most extreme groups for progeny DGV



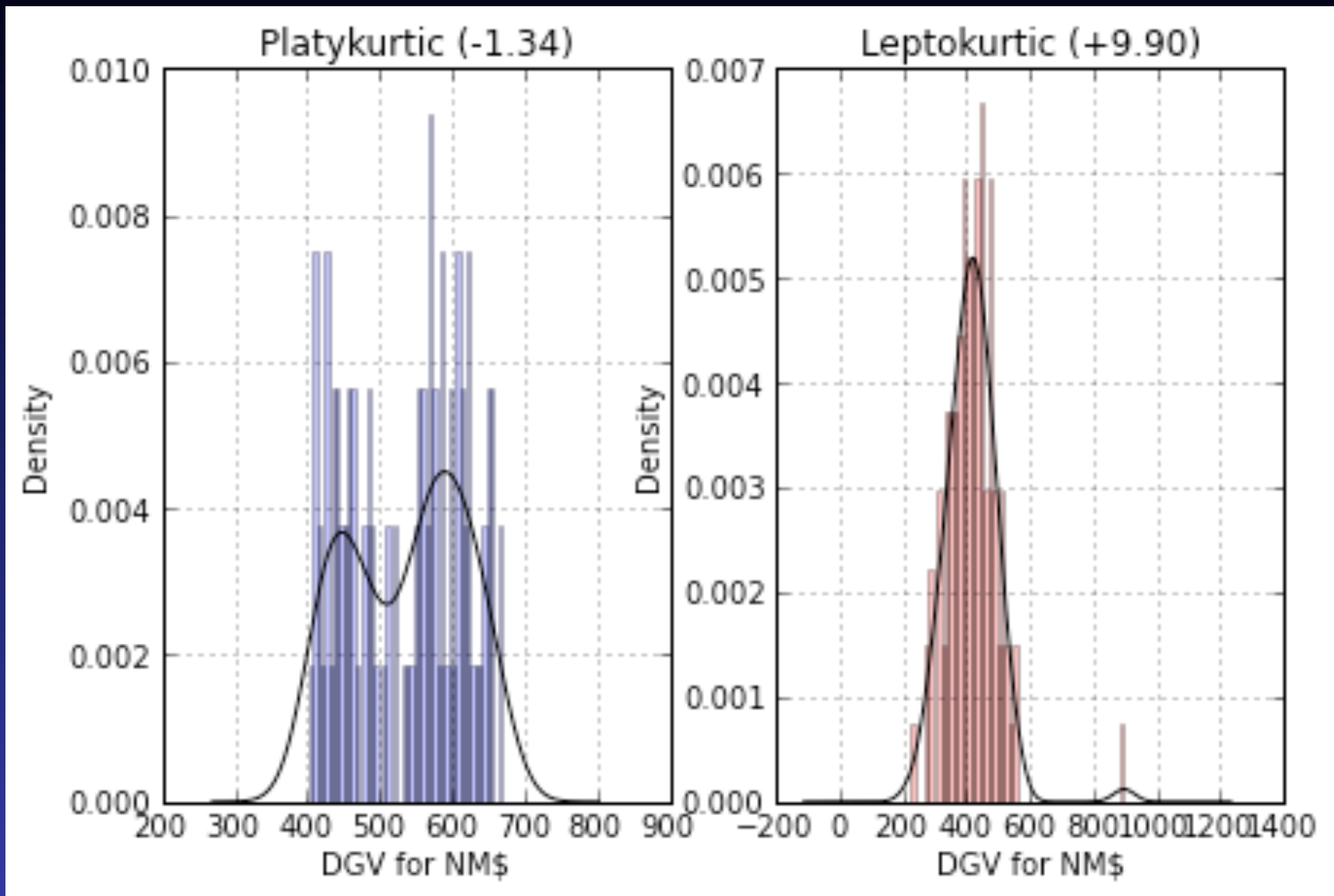
Most extreme groups for DGV variance



Most- and least-skewed progeny groups



Most- and least-kurtotic progeny groups



Within-herd analysis

- Selected **3** Jersey herds
 - Ranked by number of genotyped animals and percentage of 50K genotypes
- Compared actual with possible matings
- Could the herd manager have selected better mate pairs?

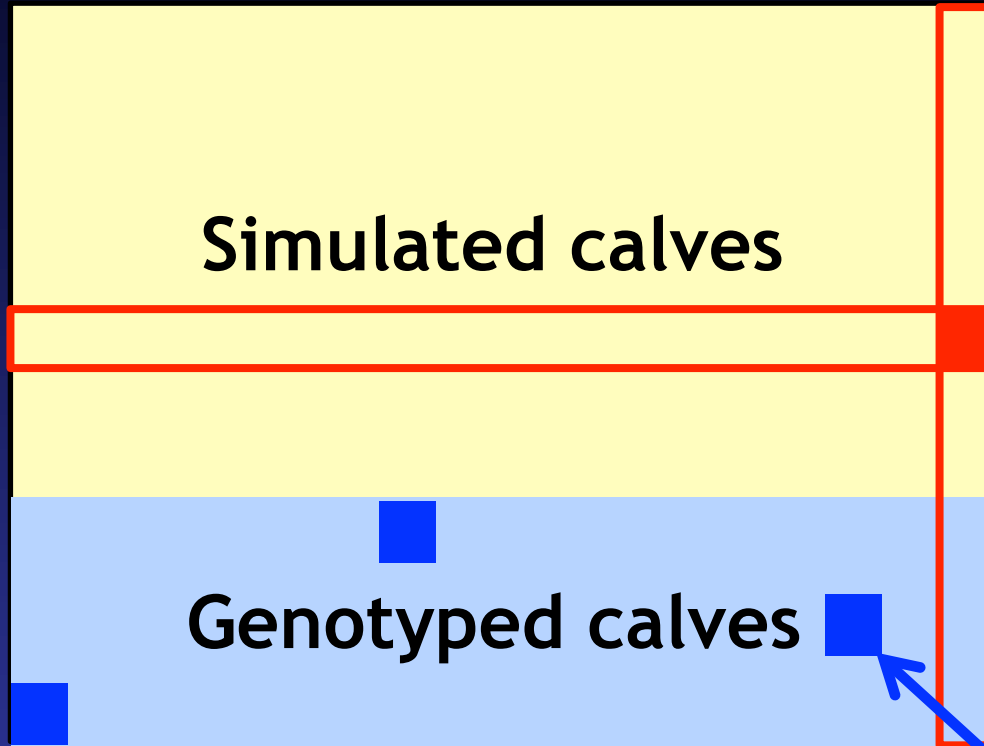
Comparison to actual matings

- Simulated matings were compared to **220** actual matings from **142** mate pairs
- Three strategies tested in simulation
 - Mating plans using traditional and genomic PTA as in Pryce et al. (2012)
 - Selection of mate pairs with greatest mean DGV
 - Bulls limited to **10** matings

Sire portfolios

Cows in herd

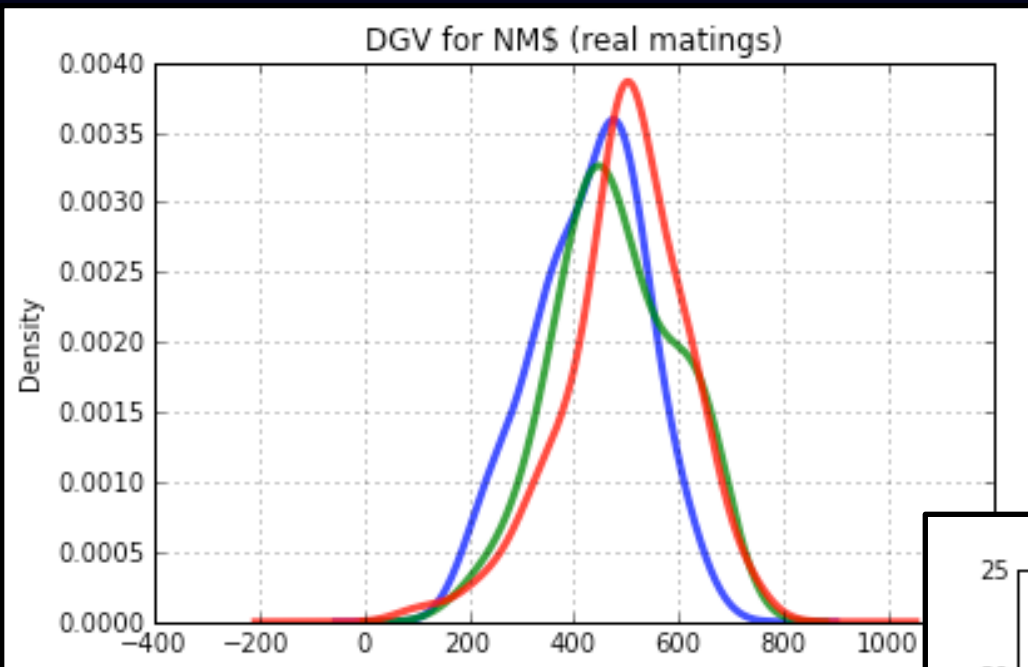
Bulls used in herd



Consider each bull as a mate for each cow using different strategies.

Actual calves born to these parents.

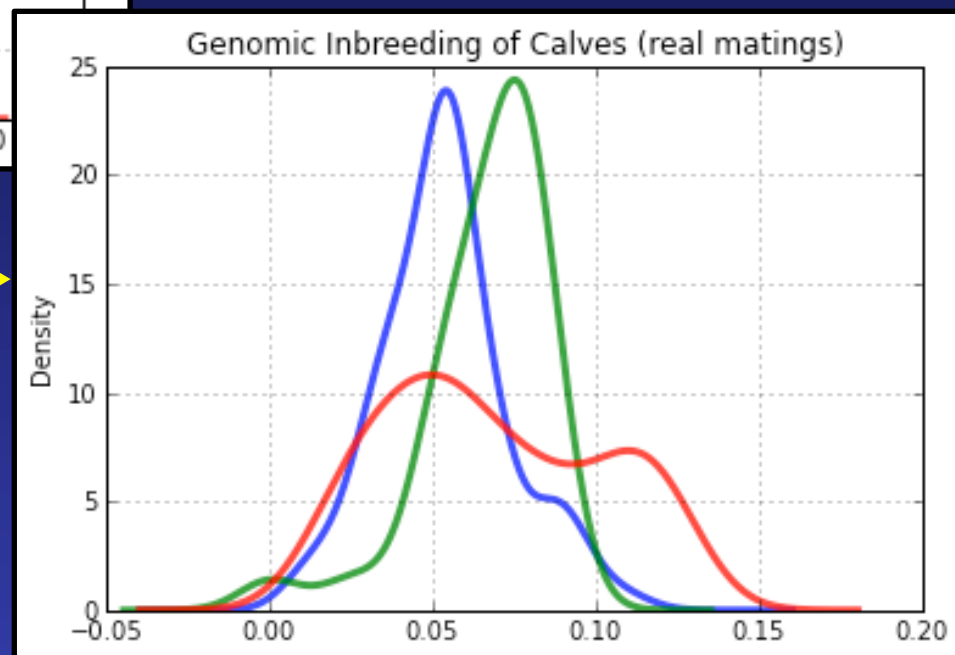
Actual DGV and inbreeding



Similar distribution of DGV



Different distribution of relationships – different sire portfolios



Herd 1 results

	Actual ¹	Best PTA ²	Best gPTA ²	Best DGV ²
Genetic value	416	308	446	452
Difference	–	-108	+28	+36
SE(Genetic)	12	7	11	12
Inbreeding	0.053	0.075	0.083	0.070
Min	0.010	0.005	0.027	<0.001
Max	0.110	0.274	0.145	0.112
Correlation	–	0.443	0.218	0.247

¹Results from 94 genotyped offspring of 62 cows.

²Simulated matings of 62 cows to a portfolio of 54 bulls (n=3348 combinations).

Herd 2 results

	Actual ¹	Best PTA ²	Best gPTA ²	Best DGV ²
Genetic value	468	396	534	538
Difference	–	-72	66	70
SE(Genetic)	23	14	13	13
Inbreeding	0.068	0.051	0.077	0.077
Min	0.025	0.001	0.021	0.021
Max	0.090	0.120	0.124	0.106
Correlation	–	0.577	0.735	0.745

¹Results from 31 genotyped offspring of 19 cows.

²Simulated matings of 19 cows to a portfolio of 31 bulls (n=589 combinations).

Herd 3 results

	Actual ¹	Best PTA ²	Best gPTA ²	Best DGV ²
Genetic value	480	342	505	501
Difference	–	-138	25	21
SE(Genetic)	19	8	12	10
Inbreeding	0.068	0.076	0.093	0.068
Min	0.015	0.000	0.045	0.015
Max	0.125	0.183	0.178	0.106
Correlation	–	0.665	0.682	0.495

¹Results from 95 genotyped offspring of 38 cows.

²Simulated matings of 38 cows to a portfolio of 25 bulls (n=950 combinations).

Specific combining ability

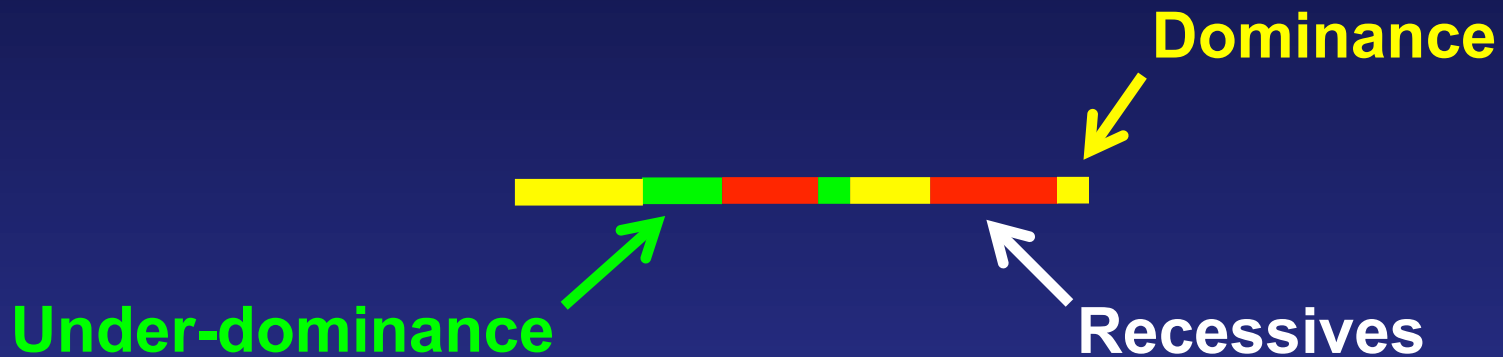
- Quantitative model
 - Must solve equation for each mate pair
- Genomic model
 - Compute dominance for each locus
 - Haplotype the population
 - Simulate matings and compute average dominance

Inbreeding effects

- Are inbreeding effects distributed uniformly across the genome?
 - Where are the recessives and the over- and under-dominant loci?
- Inbreeding changes transcription levels and gene expression profiles in *D. melanogaster* (Kristensen et al., 2005)

Precision inbreeding

- Runs of homozygosity may indicate genomic regions where inbreeding is acceptable



- Can we target those regions by selecting among haplotypes?

Phenotypic prediction

- **Can haplotypes be used to improve phenotypic predictions?**
 - **Models with GxE are better predictors (Bryant et al., 2005)**
 - **Models with A+D better than records from relatives (Lee et al., 2008)**
 - **Disease risk can be predicted even if mechanisms unknown (Wray et al., 2005)**

Unknown phenotypes

- Susceptibility to disease
 - e.g., Johne's is difficult to diagnose
- Differential response to management
 - e.g., Feed conversion efficiency
- Can simulate **more plausible** outcomes with haplotypes than genotypes
 - Chromosome transmitted, not means

Loss-of-function mutations

- At least **100** LoF per human genome surveyed (MacArthur et al., 2010)
 - Of those genes **~20** are completely inactivated
 - Uncharacterized LoF variants likely to have phenotypic effects
- How can mating programs deal with this?

Novel haplotypes affecting fertility

Name	Chromosome	Location	Carrier Freq	Earliest Known Ancestors
HH1	5	62-68	4.5	Pawnee Farm Arlinda Chief
HH2	1	93-98	4.6	Willowholme Mark Anthony
HH3	8	92-97	4.7	Glendell Arlinda Chief, Gray View Skyliner
JH1	15	11-16	23.4	Observer Chocolate Soldier
BH1	7	42-47	14.0	West Lawn Stretch Improver

Precision mating

- Eliminate undesirable haplotypes
 - Detection at low allele frequencies
- Avoid carrier-to-carrier matings
 - Easy with few recessives, difficult with many recessives
- Include in selection indices
 - Requires many inputs

Threats to continued progress

(19) **United States**
(12) **Patent Application Publication** (10) **Pub. No.: US 2012/0151625 A1**
Guo et al. (43) **Pub. Date: Jun. 14, 2012**

(54) **METHODS FOR INCREASING GENETIC GAIN IN A BREEDING POPULATION** *A01H 5/10* (2006.01)
C12N 5/04 (2006.01)

(76) Inventors: **Zhigang Guo**, Champaign, IL (US);
Venkata Krishna Kishore,
Bloomington, IL (US)

(21) Appl. No.: **13/307,733**

(22) Filed: **Nov. 30, 2011**

(52) **U.S. Cl. 800/275; 435/410; 800/260; 800/298**

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Publication Classification

(51) **Int. Cl.**
A01H 1/02 (2006.01)
A01H 5/00 (2006.01)

Provisional US patent filed on **20 NOV 2010** after the 9WCGALP in Leipzig – no disclosure at that time!



This MS with similar ideas was submitted **22 SEP 2010** and published on **12 APR 2011**.



Journal of Animal Breeding and Genetics

ORIGINAL ARTICLE

Use of haplotypes to estimate Mendelian sampling effects and selection limits

J.B. Cole, P.M. VanRaden

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Why share?

Conclusions

- **Selecting calves based on genomic tests can increase farm profitability**
- **Simple mate selection using haplotypes is as good or better than other strategies**
- **We may be able to do interesting things with inbreeding and prediction**
- **Tools for handling many new recessives in breeding programs are needed**

Acknowledgments

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