Management of lethal recessive alleles while optimizing genetic gain in beef cattle breeding programs

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USDA United States Department of Agriculture National Institute of Food and Agriculture

Project Background

- Tremendous genetic gains in other production traits
  - Haven't seen these same gains in fertility-related traits
- No secret that reproduction is a very important trait in the cowherd
- 2 ways to increase fertility:
  - Maximize number of females that conceive early in the breeding season
  - Maintain pregnancies that are achieved
- **90% fertilization rates but subsequent calving rate is 55%**
  - **~ 35% of embryo/fetal loss**
- Most embryonic mortality between day 12 – 42 of gestation
- Pregnancy failure ~ $165 loss/cow (Lamb, 2008)

What might be causing these early embryonic losses?

Pro-nuclear stage
(hours after fertilization)

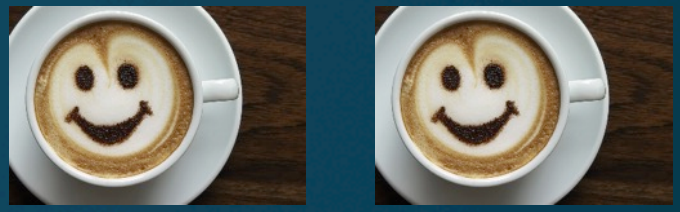
Bovine blastocyst
(day 7)

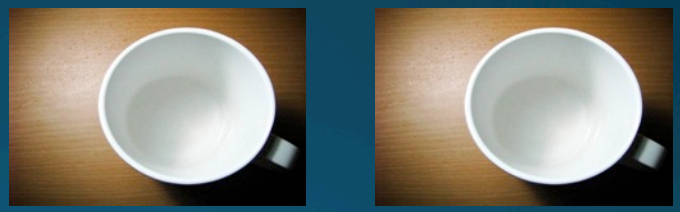
Day 33 bovine embryo

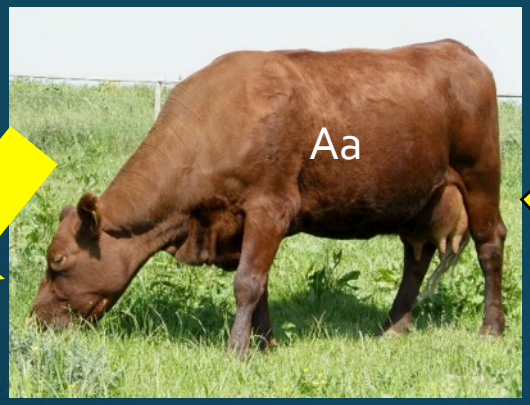
Pictures courtesy of Dr. David Grieger

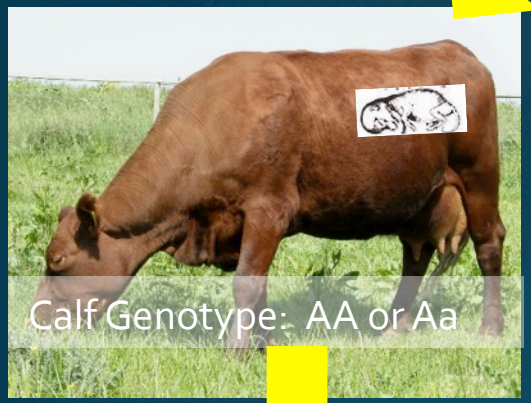
Recessive loss of function (LOF) alleles at essential genes

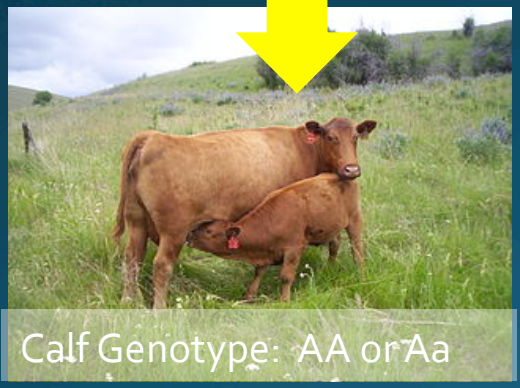
- Some genes are essential for life
  - Basically- if you don't have a functional allele of that gene, you die
    - 2 chances to get a functional copy (♂ and ♀)
    - Lethal phenotype
- Why do lethal alleles matter?
  - All have seen effects of other postpartum lethal alleles (AA, NH, TH, etc.)
  - Managing matings to avoid affected calves is good for profit and good for welfare
- Also have early embryonic lethals
  - Same concept, never see
    - Open cows, slower to breed back, abort and come back into heat
    - When the gene is needed for development, development stops, the cow fails to conceive/ aborts, comes back into heat

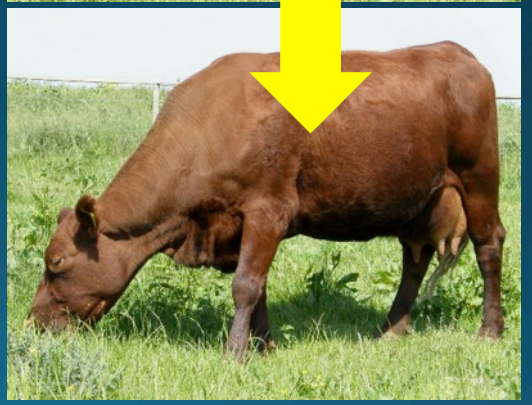










What mutations are never homozygous in living animals?

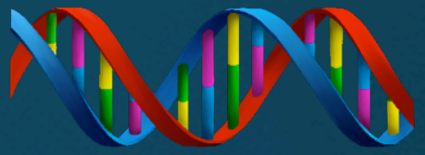
Lethal mutations

★ **Calf was homozygous normal or carrier, calf is born**

• **Calf was homozygous for embryonic lethal, cow is open**

How Do We Detect And Test If Variants Are Lethal?

- 1. Sequence whole genomes of a large number of animals
  - Which mutations are never homozygous in live animals?
  - Which have large predicted changes in protein structure?
  - Which have been shown to be in genes essential for life in other species?

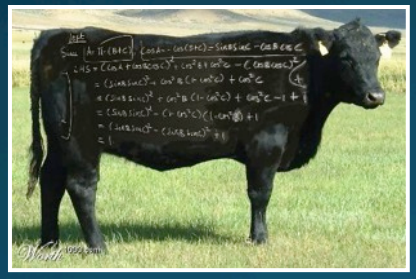


Whole Genome Sequence for 262 taurines

Whole Genome Sequence for 35 indicines/composites

Breed	No. Animals	No. Unique Reads	Total Bases	Av. Raw Coverage
Angus	109	82,263,951,806	8,137,666,488,753	25.74
Hereford	18	15,603,339,064	1,501,290,942,627	28.76
Limousin	12	3,704,169,818	357,264,463,240	10.27
Charolais	14	8,560,329,604	858,471,719,367	21.14
Simmental	11	8,902,705,282	885,698,817,042	27.76
Gelbvieh	8	6,366,906,096	633,479,558,830	27.31
Maine Anjou	5	4,061,220,172	403,867,224,031	27.85
Romagnola	4	901,544,762	89,666,842,589	7.73
Shorthorn	2	1,446,405,682	143,863,277,001	24.80
Red Angus	14	4,430,950,144	441,846,880,499	10.88
Holstein	55	13,650,662,246	1,358,163,462,700	8.52
Jersey	9	1,399,450,902	139,150,036,295	5.33
N'Dama	1	739,233,320	73,483,493,461	25.34
Brahman	11	1,871,667,422	167,772,161,118	5.26
Nelore	8	1,668,006,036	165,728,918,125	7.14
Gir	6	1,583,737,248	157,449,065,756	9.05
Beefmaster	10	8,351,392,646	830,865,082,100	28.65
Canids	132	96,911,894,312	8,634,051,009,336	22.55

The sequencing and genotype development done by Dr. Jerry Taylor et al. at Mizzou



Sequence 100 Angus bulls and identify variants predicted to be deleterious in genes essential for life (in human, mouse, zebra fish)
Make a genotyping chip and put 4K candidates on it

Genotype 10,000 heifers
(Doesn't have to be heifers – but they have reproductive data which can be used for GWAS)

See which alleles NEVER turn up as homozygotes
Impacted by allele frequency if F(D)=0.01 we only expect to see 1 DD individual in 10,000 animals

Place candidates on commercial industry chips (GGP-LD)
Genotype 100K animals/year
Identify causal lethals

How Do We Detect And Test If Variants Are Lethal?

- 2. Take the mutations from step 1 (candidates) and build a genotyping chip

- 3. Validate the candidate mutations
  - Genotype a large number of animals on the chip
  - 11,506 (mostly Angus) heifers genotyped
    - 18,271 animals total on the chip
  - Which candidates are still not seen as homozygous?

GGPF250

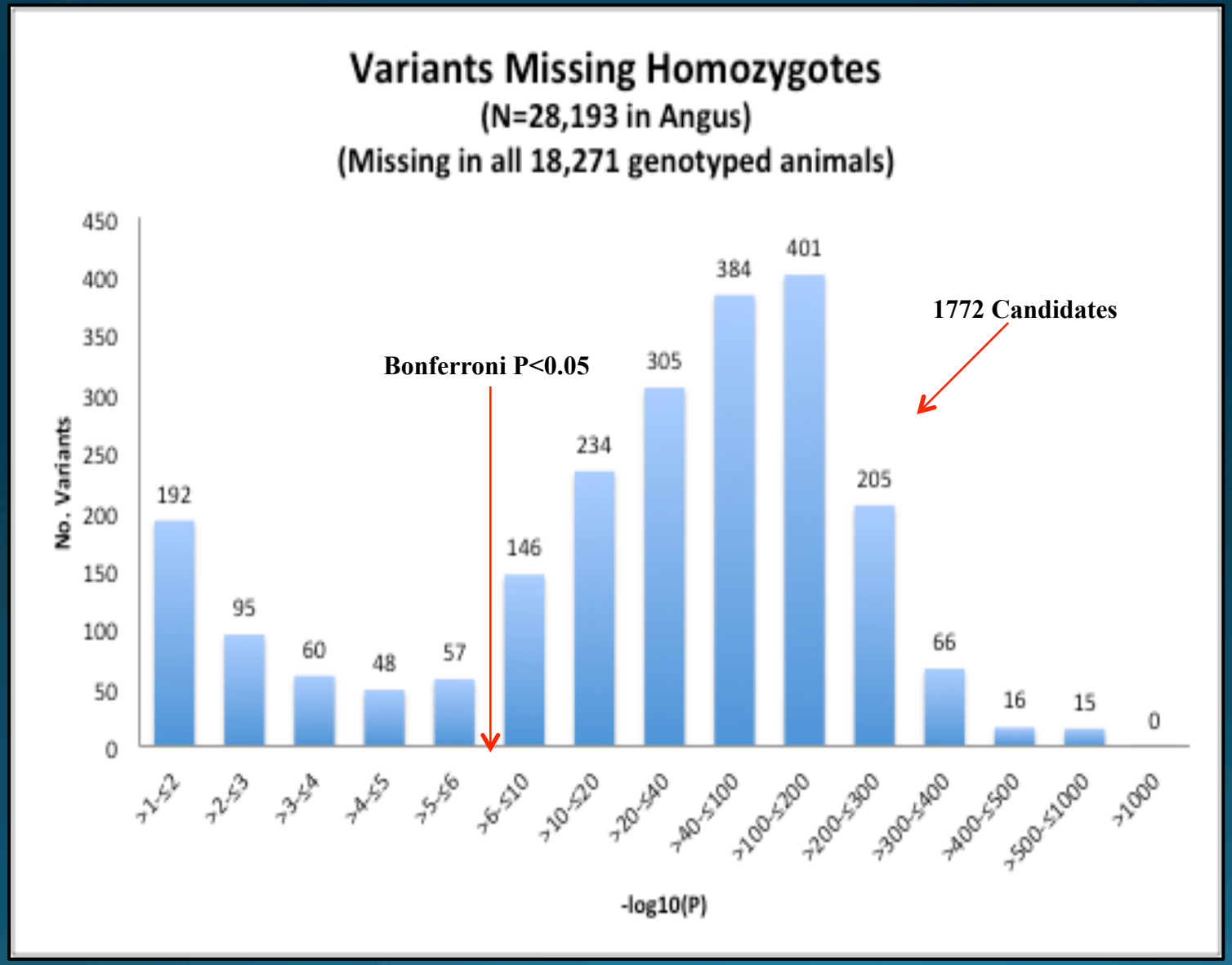
Samples Genotyped on F250

BREED	NO. GENOTYPED	% GENOTYPED
AN	12083	66.13
HFD	945	5.17
LM	219	1.20
CHA	20	0.11
SIM	274	1.50
BRVH	7	0.04
GEL	307	1.68
PIED	9	0.05
RMG	8	0.04
ANR	1255	6.87
CIC	4	0.02
HO	1994	10.91
JER	9	0.05
GNS	7	0.04
NDAM	8	0.04
BR	14	0.08
NEL	8	0.04
GIR	11	0.06
CROS	1073	5.87
BEFM	3	0.02
SGT	11	0.06
SHK	2	0.01
18271/22 Breeds		

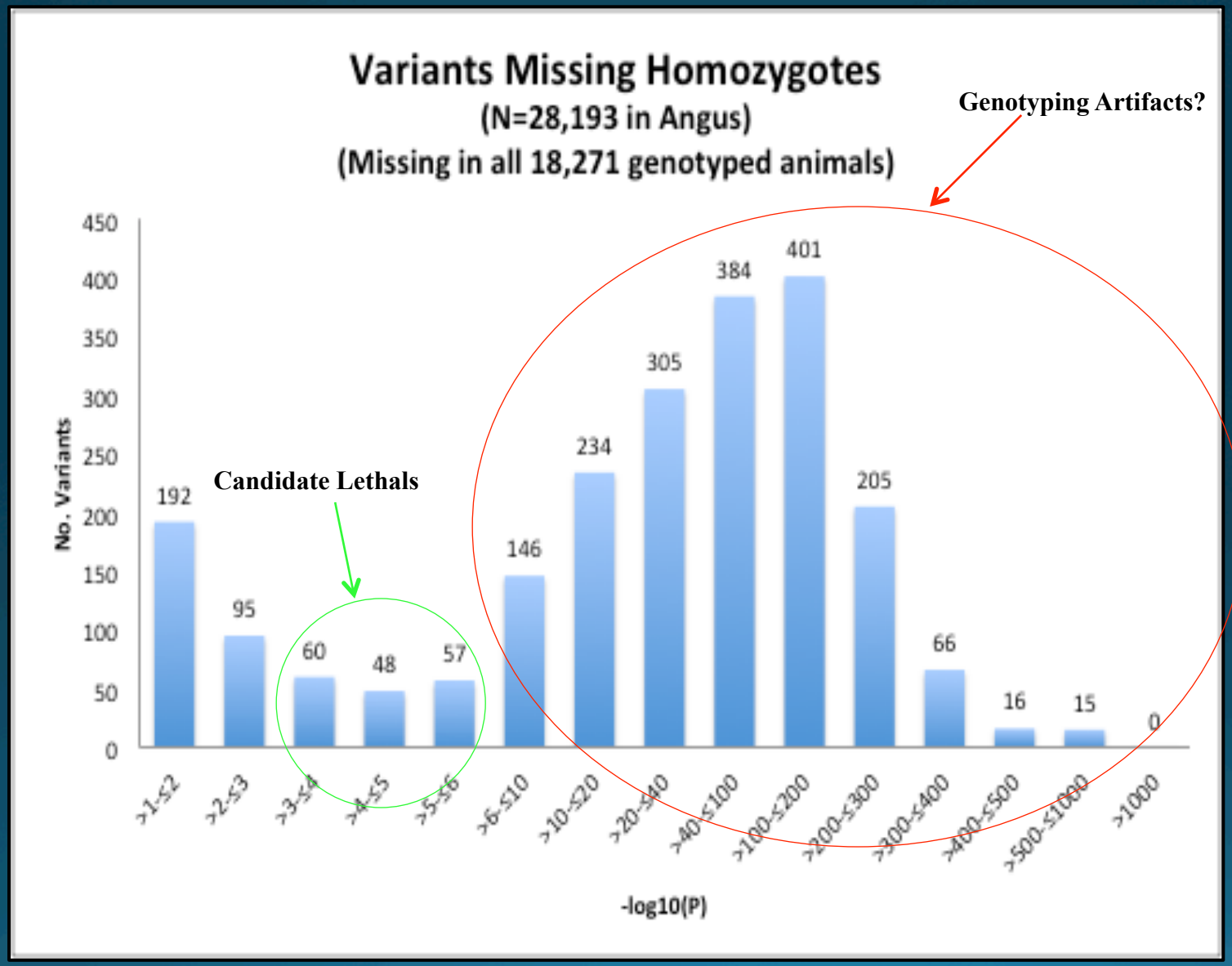
PROJECT	NO. GENOTYPED	% GENOTYPED
Heifer Fertility	11,506	62.97%
Feed Efficiency	4609	25.23%
Bovine Respiratory Disease	1971	10.79%
HapMap/History of Cows	185	1.01%
	18,271	

http://animalgenomics.missouri.edu

Variants With Missing Homozygotes



Mixture Of Two Distributions?



The Future

Narrow down and identify candidate lethal mutations

- Cannot all be lethal
- This sounds like bad news, but it's great news
- You can manage it if you know about it!

Incorporate candidate lethal variants on commercially utilized chips

- GeneSeek GGP products
- Zoetis i50K, GeneMax® Advantage™
- Irish Cattle Breeding Federation IBD chip

- Ongoing process
  - New candidate mutations discovered and added to genotyping assays as more animals sequenced
  - Old candidates eliminated as more animals are genotyped
    - Find a homozygote
    - Hard to find homozygous animals for mutations at very low frequency in the population

Limitations of this Approach

- **Limited by the number of animals that have been sequenced**
  - If no sequence, may miss rare variants they possess
- **Looking for variations in genes**
  - Miss anything that may be important but not in a gene (the majority of the genome)
    - Regulate gene expression
- **Dependent on the quality of the genome sequence**
  - Missing genes or portions of genes
  - Improving the sequence assembly improves ability to ID variants in genes/ functional variants

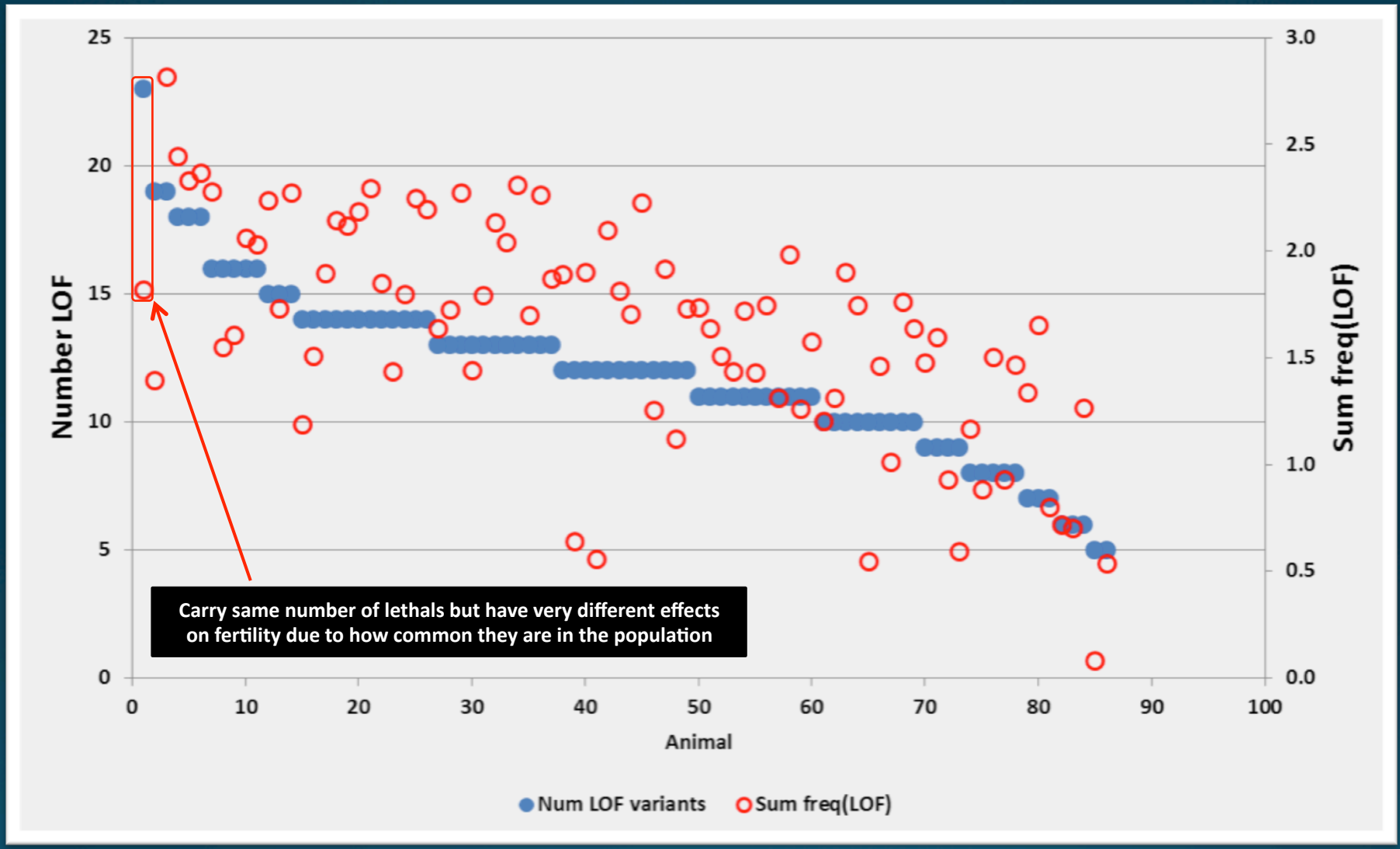
Genetic implications of recessive genetic factors

"Carrier animals….their overall breeding value worth may outweigh the economic value of carrier status"

Chalier C. et al. (2008) Highly effective SNP-based association mapping and management of recessive defects in livestock. Nature Genetics 40:449-454

Need to penalize carrier animals appropriately (*not prohibit their use entirely*) and let mate selection software optimize their use in the breeding programs

How Important is a Mutation? Depends on frequency

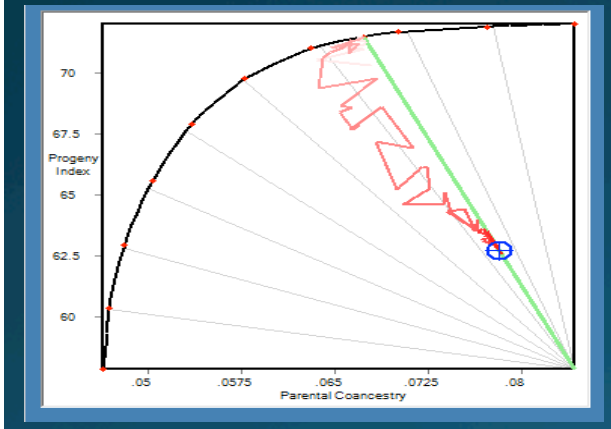


Range 5 to 23

How Does The Beef Industry Use This Information?

- **Develop decision support software to optimize breeding schemes via implementation of selection indexes and mate selection based on sire and dam recessive lethal genotypes**
  - Develop software to handle the mutations discovered in this project, and deliver selection and mating recommendations to US beef breeders that exploit this information optimally in competition with other factors of importance (e.g. trait merit, genetic diversity (inbreeding), genetic defects and recessive lethals, logistics, semen costs, etc.)

MATESEL



Management of lethal recessive alleles while optimizing genetic gain in beef cattle

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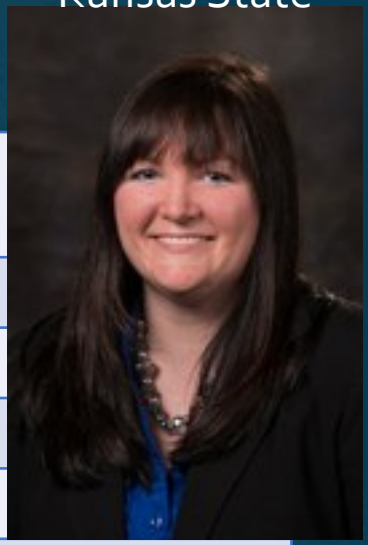
2017 Proceedings, Western Section, American Society of Animal Science

How Does The Beef Industry Use This Information?

Dr. Megan Rolf
Kansas State



Develop a web-based educational training program

Educational website launched early 2016, http://beefreproduction.org **Megan Rolf, Kansas State University**	
Module 1. Genetic correlations and antagonisms	
Module 2. What is the genome?	
Module 3. What is an EPD?	
Module 4. History of Selection and Genetic Change in Beef Cattle	
Additional topics: Introduction to the Central Dogma of Biology Mendelian Inheritance Risk management of genetic defects LOF Mutations Parentage testing Selection indexes Recombination Genome sequencing, annotation, and assembly	Use of DGVs and Genomic-Enhanced EPDs EPD Accuracy Formulating breeding objectives Optimizing vs maximizing for trait selection Heterosis and mating systems Fitting to the environment Use of MateSel in multi-trait selection

Conclusions

- **GGP-F250 was designed as a research tool to meet needs of Heifer Fertility, Respiratory Disease and Feed Efficiency Projects**
  - Gene centric but designed to allow genotype imputation into datasets genotyped with BovineSNP50, BovineHD, GGP-HD, GGP-LD, etc
  - Only ~50% of variants detected by sequencing are designable
  - Contains every designable AA substitution discovered in sequence data!
  - Useful research tool e.g. to explore basis of heterosis, inbreeding depression
  - Publicly available now through GeneSeek
- **Lethal Variants**
  - 2,224 candidates
  - Cannot all be lethal
  - Multiple approaches now required to filter data for genotyping artifacts and identification of true lethals (gene essential for life, lack of homozygous haplotypes in large industry datasets)
- **Delivery to Industry**
  - Requires selection indexes
  - Mate selection

To Learn More:

- Beefreproduction.org

Videos


Impact of Genetic
Correlations on Beef
CATTLE SELECTION
09:24
HD vimeo

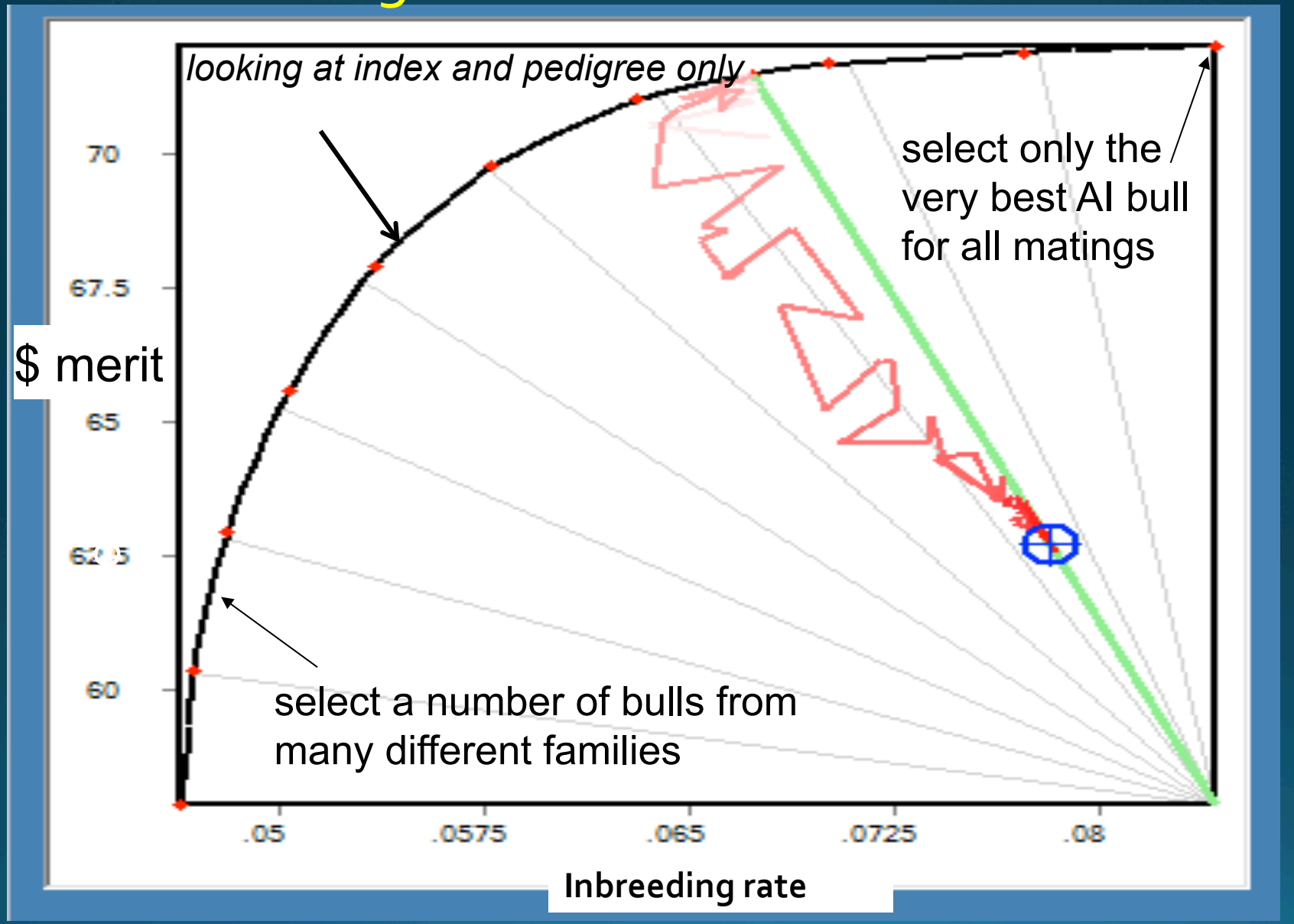

Understanding
GENOMICS
09:28
HD vimeo

MateSel Demonstration

Lindsay Upperman
Animal Biology Master's Student
University of California, Davis

UCDAVIS
ANIMAL SCIENCE

Mate Sel: Balancing inbreeding and genetic merit – the frontier gives the unconstrained solution



Finding the right balance

- **The formal breeding objective ($Index)**
- **Inbreeding**
- **Additional constraints e.g. use no carrier animal with a genetic defect in pedigree**

Mate selection tool shows you the 'opportunity cost' of imposing non –optimal constraints on mate selection

Background of what was simulated

- The base scenario
  - Need to make 125 matings in a herd
  - No sire can be used more than 50 times
  - The selection index being modeled is $B
  - There are 50 hypothetical recessive lethal loci – some are common, some are rare
  - All animals have been genotyped – none are "aa"
  - MateSel is a mate allocation program that calculates which are the best bulls to mate to each of the 125 cows to maximize progress towards your selection objective

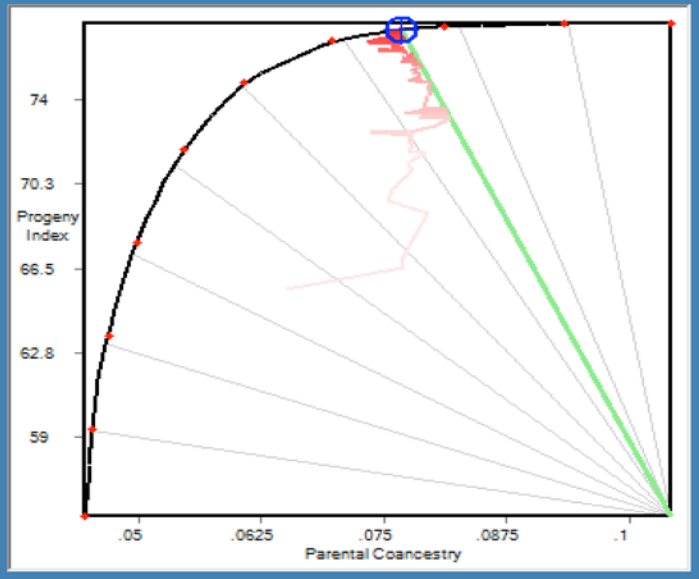
In the absence of any other consideration or lethal recessive alleles – the baseline value is that these 5 sires are selected

Direction | Frontier | Convergence | Grouping | NRM

Balance strategy: 3. Hard constraint on Target Degrees

Weight on coancestry	0	Weight on progeny F	0
Max permissable coan.	.075	Progeny F threshold	.24
Target Degrees	25	Weight on F threshold	0

Run | Update | Pause | Print Matings | Stop | Close



Console for FortranDLL.dll | Progeny Inbreeding | Trait management | Marker management | Mate selections

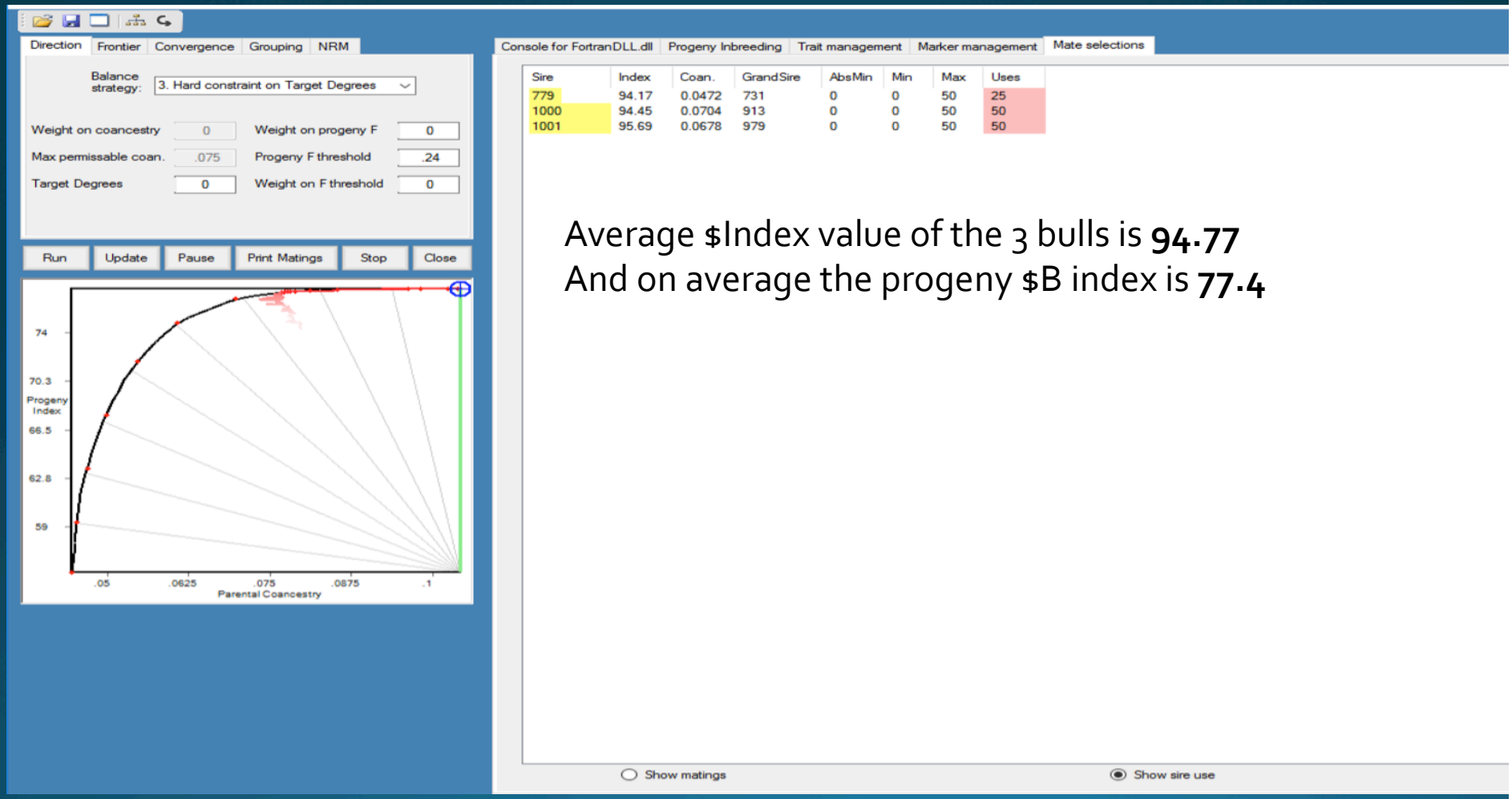
Sire	Index	Coan.	GrandSire	AbsMin	Min	Max	Uses
779	94.17	0.0472	731	0	0	50	26
785	93.89	0.0455	760	0	0	50	26
983	93.13	0.0343	888	0	0	50	24
1000	94.45	0.0704	913	0	0	50	19
1001	95.69	0.0678	979	0	0	50	30

BASELINE

Average $B Index value of the 5 bulls is **94.3**
And on average the progeny $B index is **77.1**

○ Show matings ◉ Show sire use ○ Show dam use Update

If all of the emphasis is placed on selecting the best bulls without regard for inbreeding these are the 3 sires that are selected



Average $Index value of the 3 bulls is **94.77**
And on average the progeny $B index is **77.4**

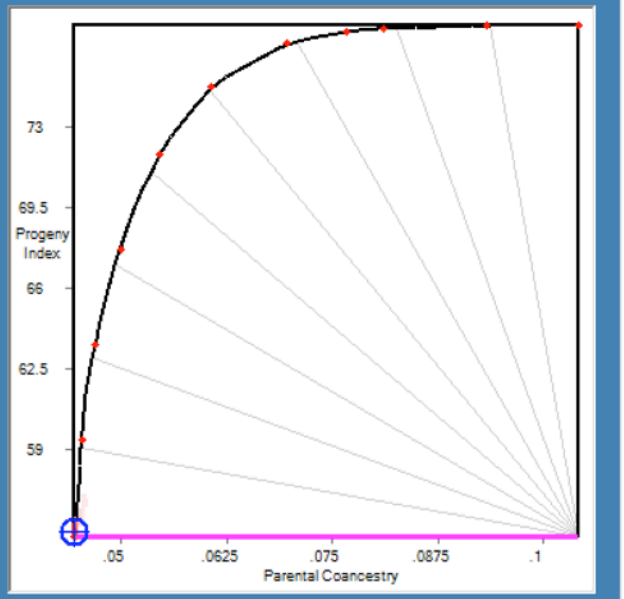
If all of the emphasis is placed on avoiding inbreeding without regard for genetic progress these are the 33 sires that are selected

Direction | Frontier | Convergence | Grouping | NRM

Balance strategy: 3. Hard constraint on Target Degrees

Weight on coancestry	0	Weight on progeny F	0
Max permissable coan.	.075	Progeny F threshold	.24
Target Degrees	90	Weight on F threshold	0

Run | Update | Pause | Print Matings | Stop | Close

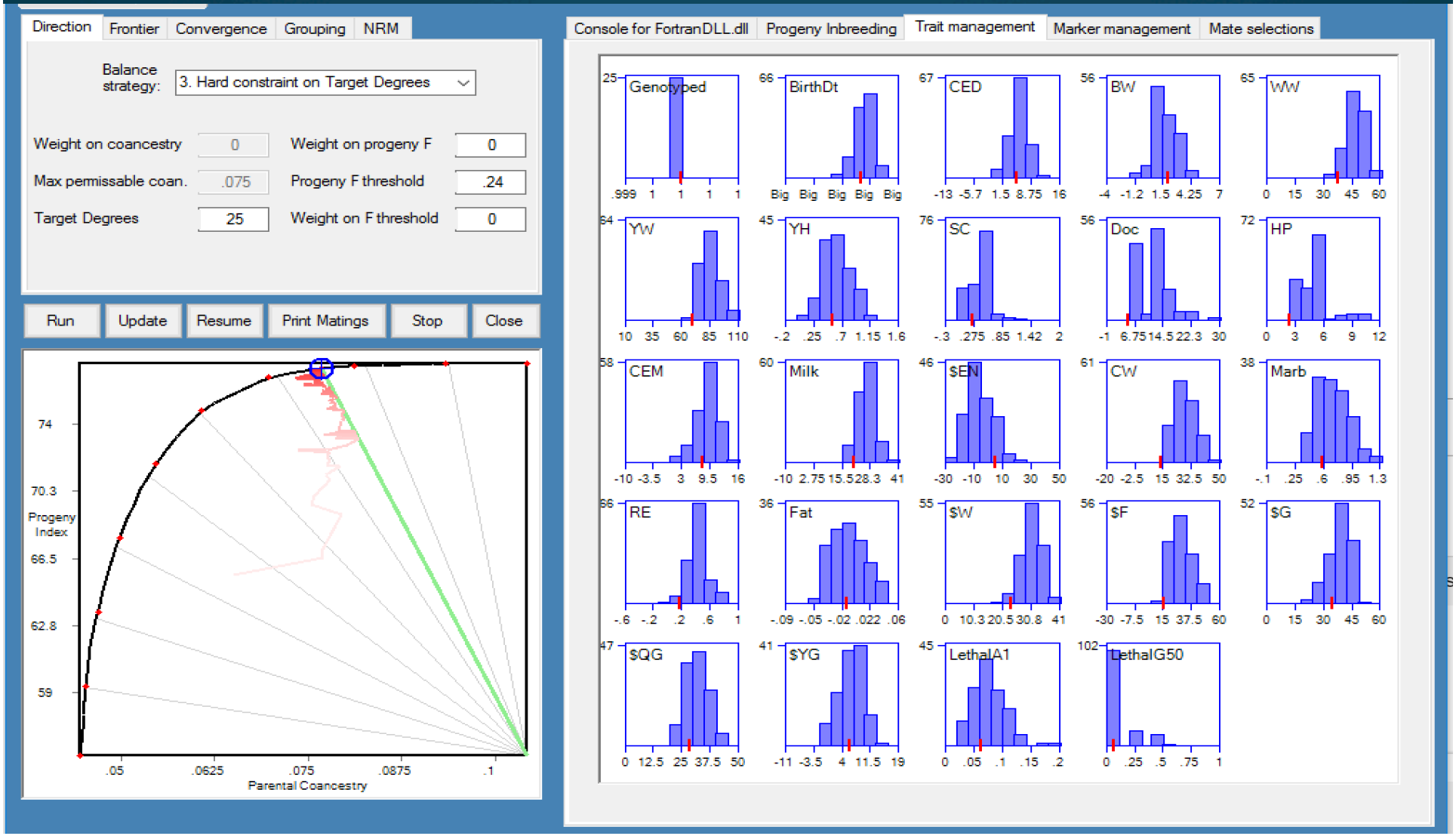


Console for FortranDLL.dll | Progeny Inbreeding | Trait management | Marker management | Mate selections

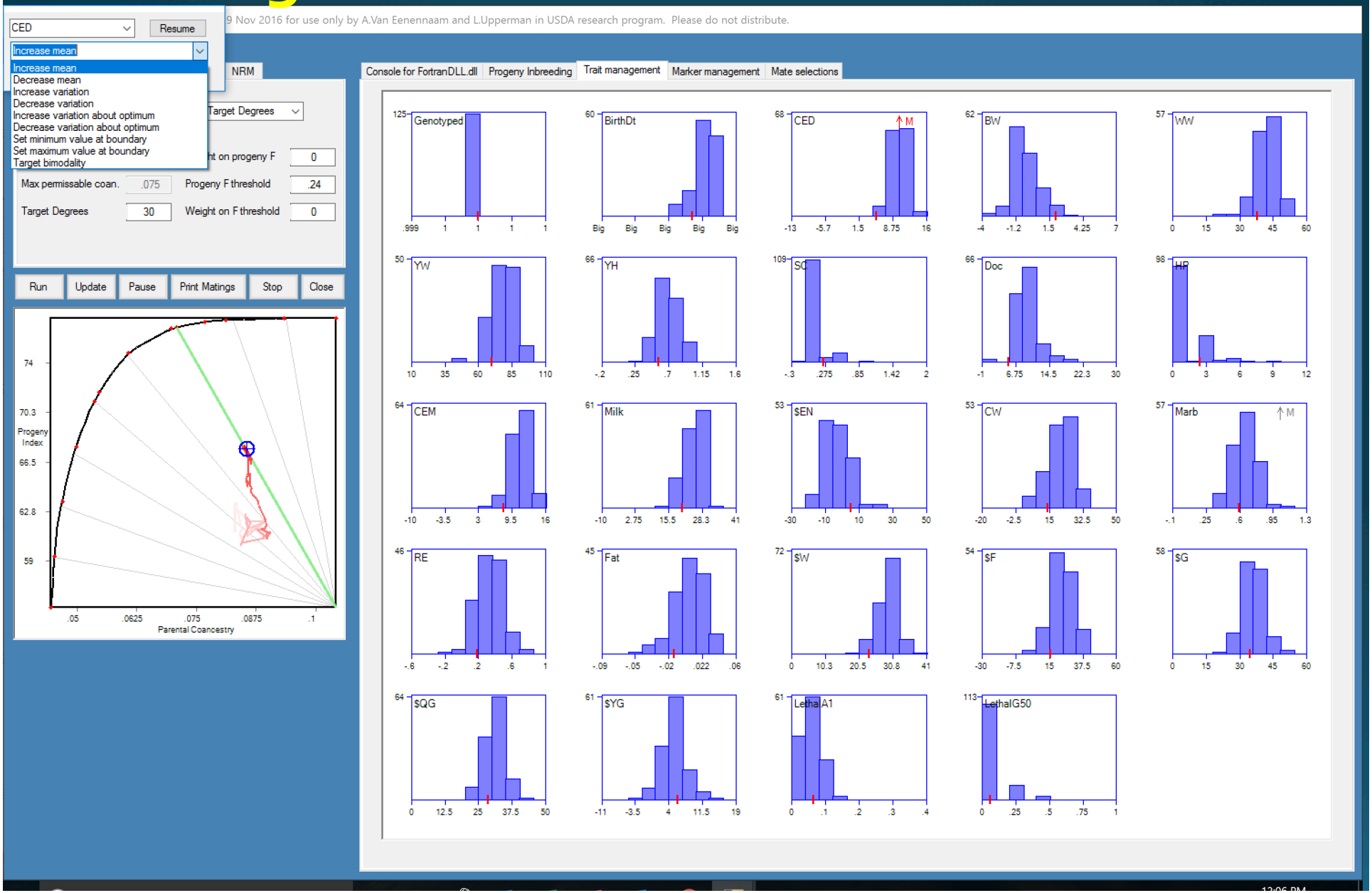
Sire	Index	Coan.	GrandSire	AbsMin	Min	Max	Uses
701	31.57	0.0247	685	0	0	50	11
718	35.68	0.0287	701	0	0	50	7
735	65.33	0.0492	711	0	0	50	2
760	56.19	0.0324	696	0	0	50	10
765	81.32	0.0342	623	0	0	50	9
768	34.57	0.0544	752	0	0	50	1
778	67.01	0.046	733	0	0	50	3
779	94.17	0.0472	731	0	0	50	4
842	66.61	0.05	731	0	0	50	4
858	44.91	0.0515	639	0	0	50	3
874	78.49	0.0508	646	0	0	50	1
910	43.2	0.0481	617	0	0	50	3
916	66.99	0.0453	864	0	0	50	4
929	72.48	0.0595	913	0	0	50	1
930	65.92	0.0465	872	0	0	50	5
979	91.61	0.0504	868	0	0	50	5
981	70.39	0.0469	842	0	0	50	2
982	87.83	0.048	842	0	0	50	1
983	93.13	0.0343	888	0	0	50	7
997	68.84	0.0483	842	0	0	50	2
998	69.46	0.0456	916	0	0	50	3
999	68.86	0.0483	842	0	0	50	1
1012	72.65	0.043	960	0	0	50	7
1013	85.71	0.0547	979	0	0	50	1
1017	85.36	0.0442	980	0	0	50	4
1029	74.69	0.0525	778	0	0	50	1
1030	62.75	0.029	782	0	0	50	11
1042	73.54	0.0655	932	0	0	50	3
1048	64.17	0.0621	1000	0	0	50	1
1072	43.36	0.0704	932	0	0	50	1
1078	82.2	0.0394	983	0	0	50	5
1085	74.06	0.0529	979	0	0	50	1
1111	51.96	0.0551	1062	0	0	50	1

Average Index value of the 33 bulls is **67.42**

In the baseline scenario this is what the trait distribution look like



Now if I go in and increase the mean for CED



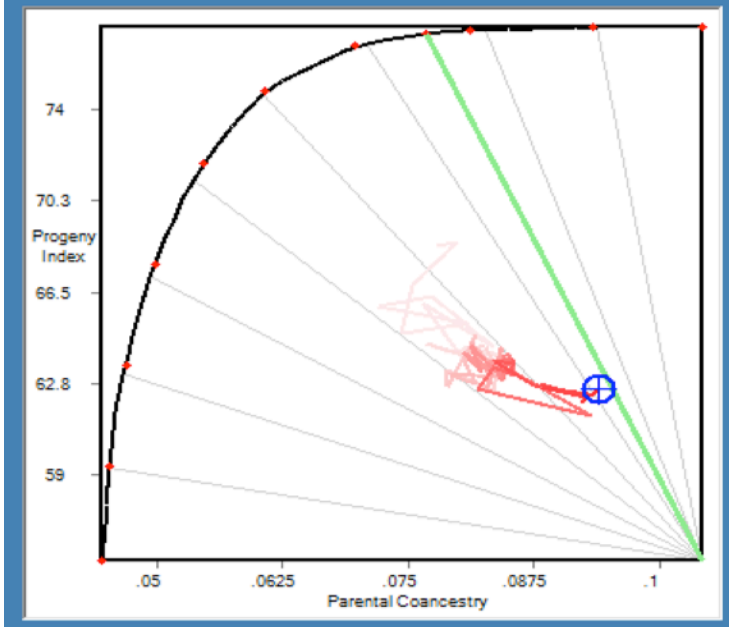
If a -10 emphasis is placed against getting heterozygous offspring (avoid ALL carriers) then 3 sires are selected

Direction | Frontier | Convergence | Grouping | NRM

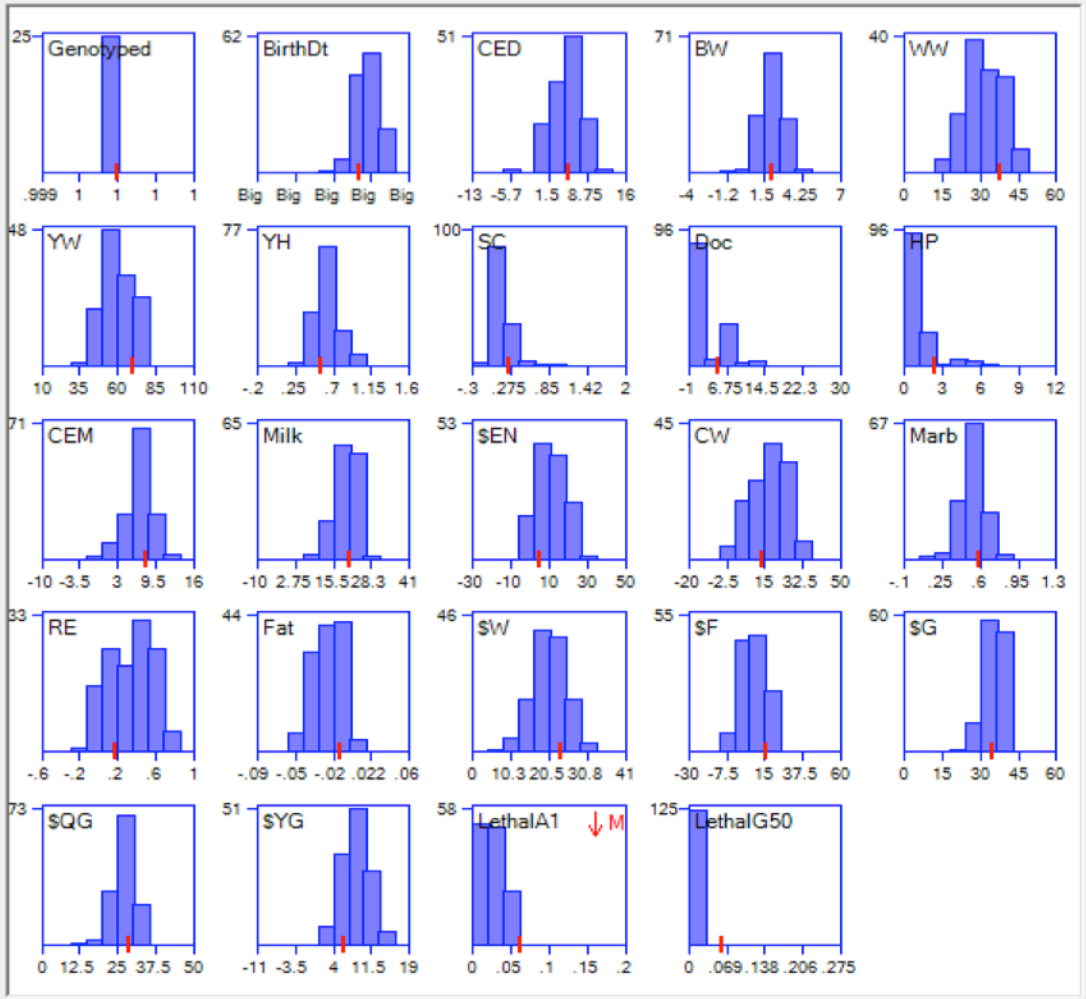
Balance strategy: 3. Hard constraint on Target Degrees

Weight on coancestry	0	Weight on progeny F	0
Max permissable coan.	.075	Progeny F threshold	.24
Target Degrees	25	Weight on F threshold	0

Run | Update | Resume | Print Matings | Stop | Close



Console for FortranDLL.dll | Progeny Inbreeding | Trait management | Marker management | Mate selections



If a -10 emphasis is placed against getting heterozygous offspring then these 3 sires are selected

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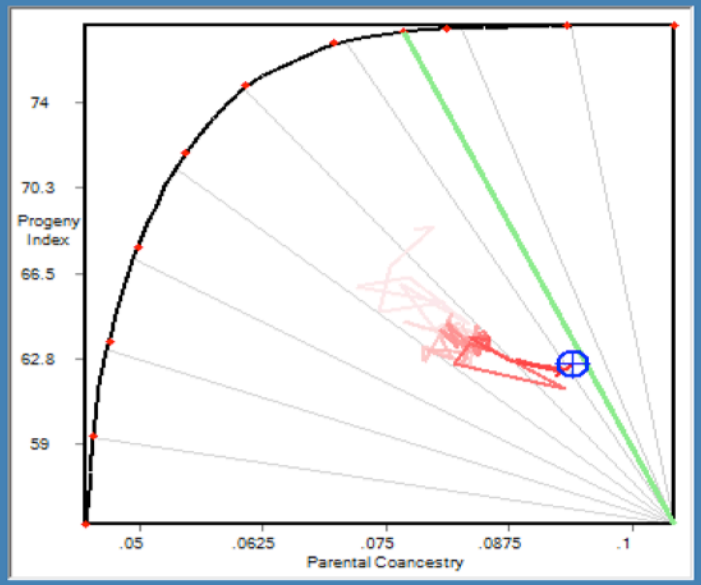
Run | Update | Pause | Print Matings | Stop | Close



Console for FortranDLL.dll | Progeny Inbreeding | Trait management | Marker management | Mate selections

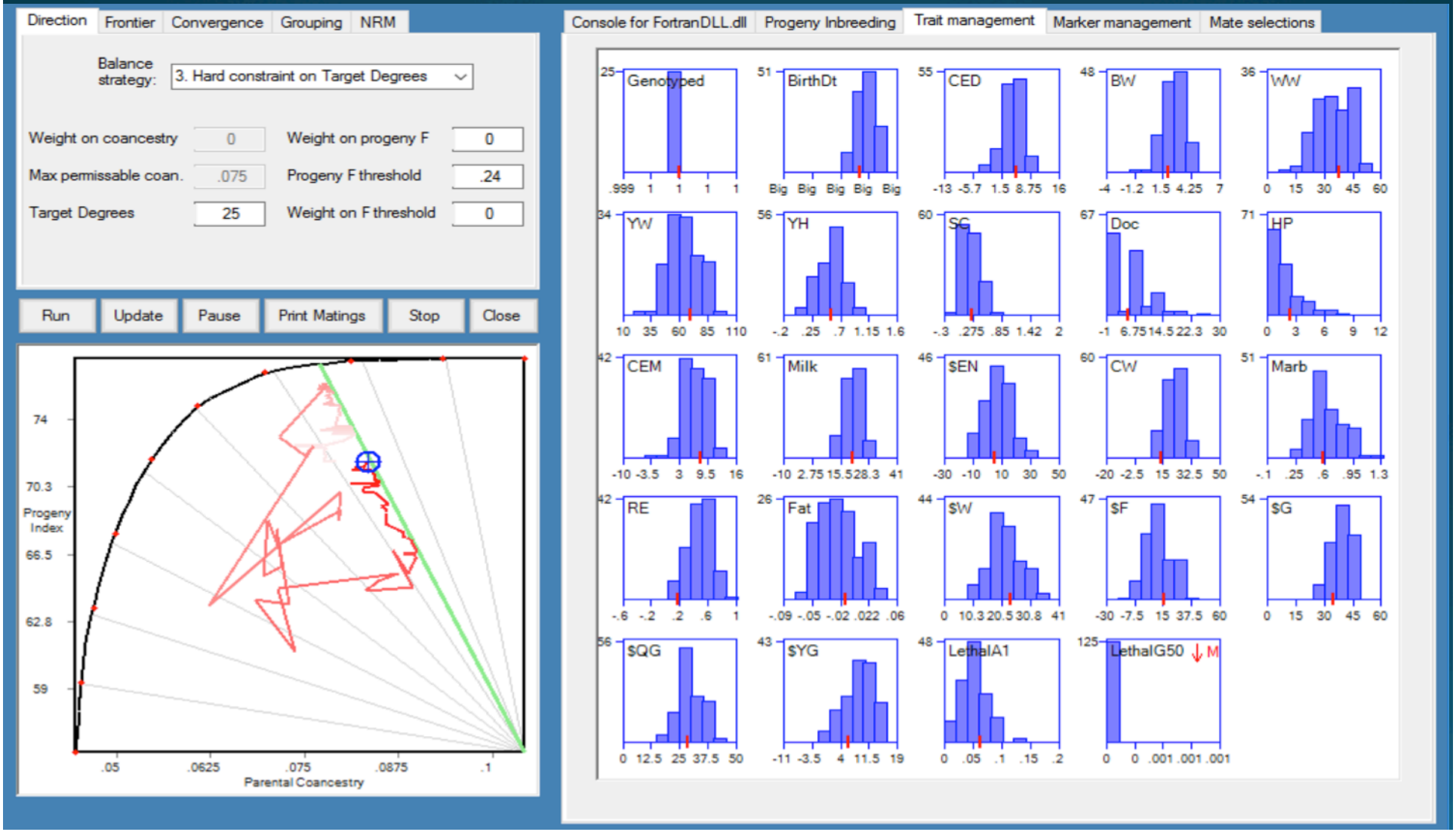
Sire	Index	Coan.	GrandSire	AbsMin	Min	Max	Uses
999	68.86	0.0483	842	0	0	50	25
1017	85.36	0.0442	980	0	0	50	50
1095	67.12	0.0621	1001	0	0	50	50

Average Index value of the 3 bulls is **73.78**

The average of the progeny index is ~ $60 down from ~$77 in unconstrained case so $17/ calf x 125 calves = $2,125 loss in genetic gain but you have been able to avoid all embryonic mortalities (aa) calves which would have otherwise cost ~5.5 x $200 = $1,100

○ Show matings ◉ Show sire use ○ Show dam use Update

If a -10 emphasis is placed against getting affected (aa) calves then 7 sires are selected



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Direction | Frontier | Convergence | Grouping | NRM

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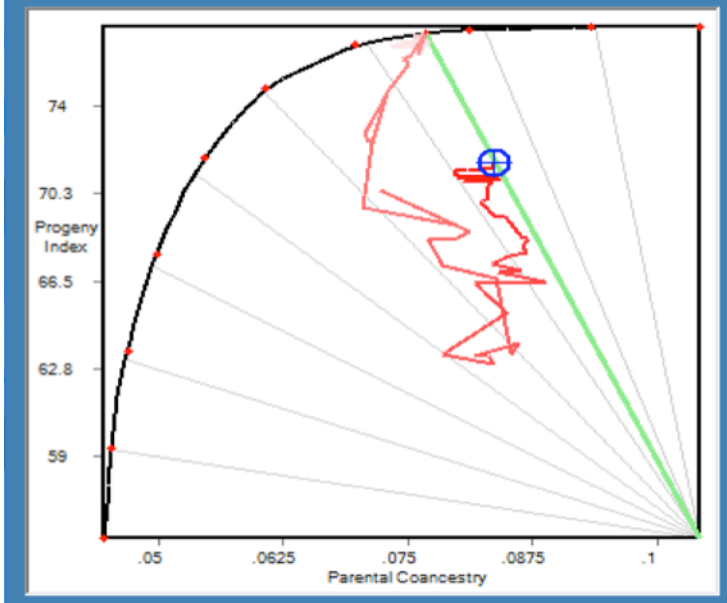
Weight on coancestry	0	Weight on progeny F	0
Max permissable coan.	.075	Progeny F threshold	.24
Target Degrees	25	Weight on F threshold	0

Run | Update | Pause | Print Matings | Stop | Close



Console for FortranDLL.dll | Progeny Inbreeding | Trait management | Marker management | Mate selections

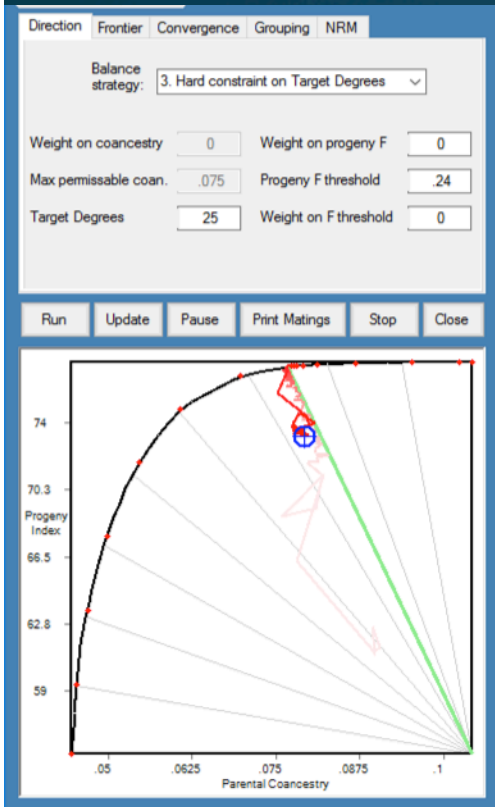
Sire	Index	Coan.	GrandSire	AbsMin	Min	Max	Uses
779	94.17	0.0472	731	0	0	50	27
960	79.43	0.052	868	0	0	50	1
982	87.83	0.048	842	0	0	50	49
1001	95.69	0.0678	979	0	0	50	21
1004	64.16	0.0492	765	0	0	50	2
1124	65.73	0.0622	1062	0	0	50	24
1127	70.15	0.0536	779	0	0	50	1

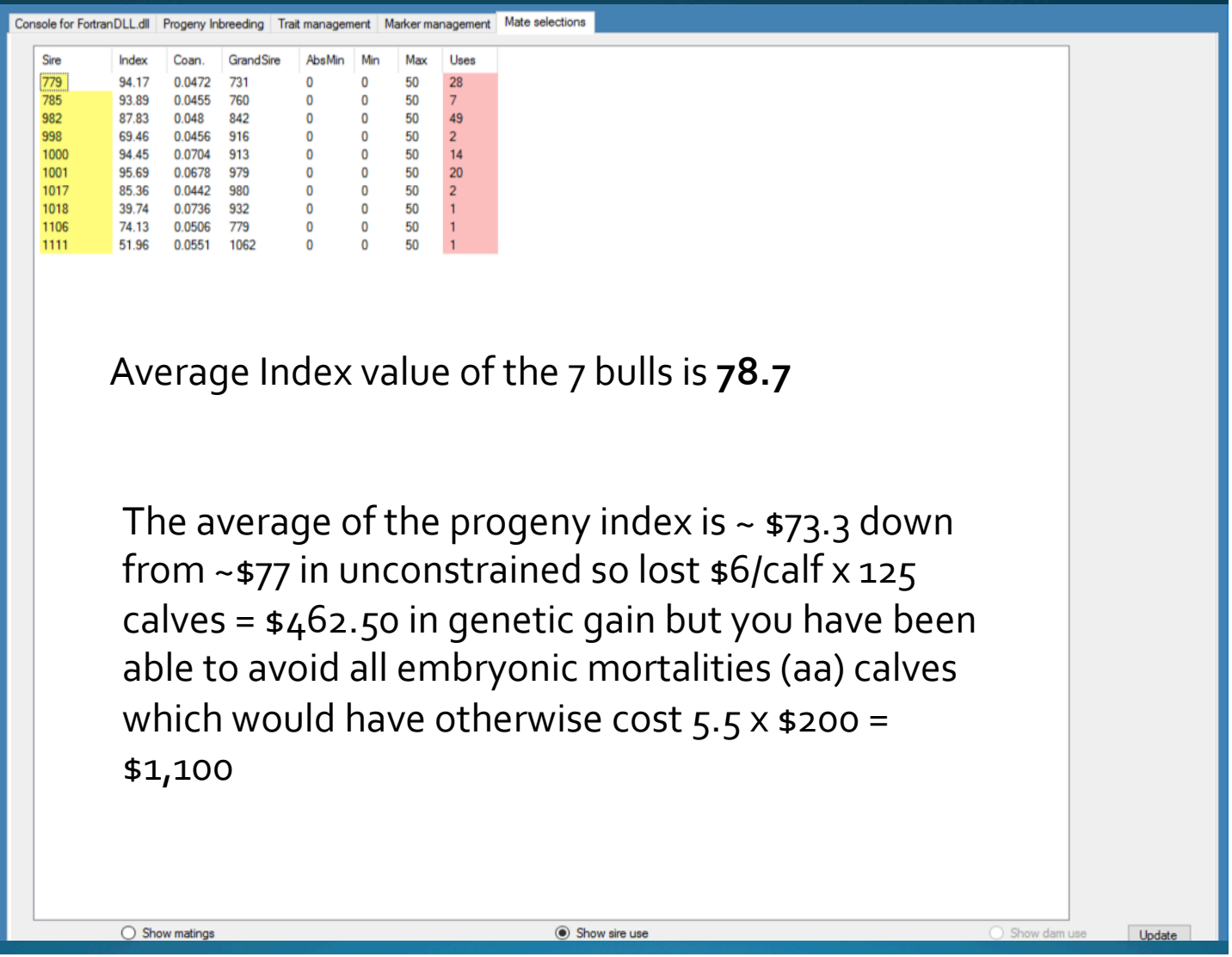
Average Index value of the 7 bulls is **79.60**

The average of the progeny index is ~ $71 down from ~$77 in unconstrained so lost $6/ calf x 125 calves = $750 in genetic gain but you have been able to avoid all embryonic mortalities (aa) calves which would have otherwise cost ~5.5 x $200 = 1,100

○ Show matings ◉ Show sire use ○ Show dam use | Update

If a -1 emphasis is placed against getting affected (aa) calves and let run longer then these 10 sires are selected





Sire	Index	Coan.	GrandSire	AbsMin	Min	Max	Uses
779	94.17	0.0472	731	0	0	50	28
785	93.89	0.0455	760	0	0	50	7
982	87.83	0.048	842	0	0	50	49
998	69.46	0.0456	916	0	0	50	2
1000	94.45	0.0704	913	0	0	50	14
1001	95.69	0.0678	979	0	0	50	20
1017	85.36	0.0442	980	0	0	50	2
1018	39.74	0.0736	932	0	0	50	1
1106	74.13	0.0506	779	0	0	50	1
1111	51.96	0.0551	1062	0	0	50	1

Average Index value of the 7 bulls is **78.7**

The average of the progeny index is ~ $73.3 down from ~$77 in unconstrained so lost $6/calf x 125 calves = $462.50 in genetic gain but you have been able to avoid all embryonic mortalities (aa) calves which would have otherwise cost 5.5 x $200 = $1,100

Summary

- MateSel allocates mates to maximize progress
- Allows user to specify different scenarios and see consequences of different mating strategies
- If this project identifies a large number of recessive loci – this software will enable optimum management
  - Our data indicate that strong selection against carriers (NEVER USE A CARRIER) as a class does result in fewer embryonic deaths but it comes at considerable expense to genetic progress!
  - A better strategy is to select against mating carriers at a given locus to avoid "aa" lethal calves; while still allowing genetic progress towards selection goals ("SMART" MATE ALLOCATION)
- MateSel visually represents tradeoffs of decisions

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  - Australian Angus Association
  - Argentine Angus Association
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  - American International Charolais Association
  - American Simmental Association
  - American Maine-Anjou Association
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  - Missouri Angus Association
  - Circle A Angus
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- **Website:** http://beefreproduction.org