Computation of Large-Scale Genomic Evaluations

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Early genomic theory

- Nejati-Javaremi et al (1997) tested use of genomic relationship matrix in BLUP
- Meuwissen et al (2001) tested linear and nonlinear estimation of haplotype effects
- Both studies assumed that few (<1,000) markers could explain all genetic variance (no polygenic effects in model)
- Polygenic variance was only 5% with 50,000 SNP (VanRaden, 2008), but 50% with 1,000

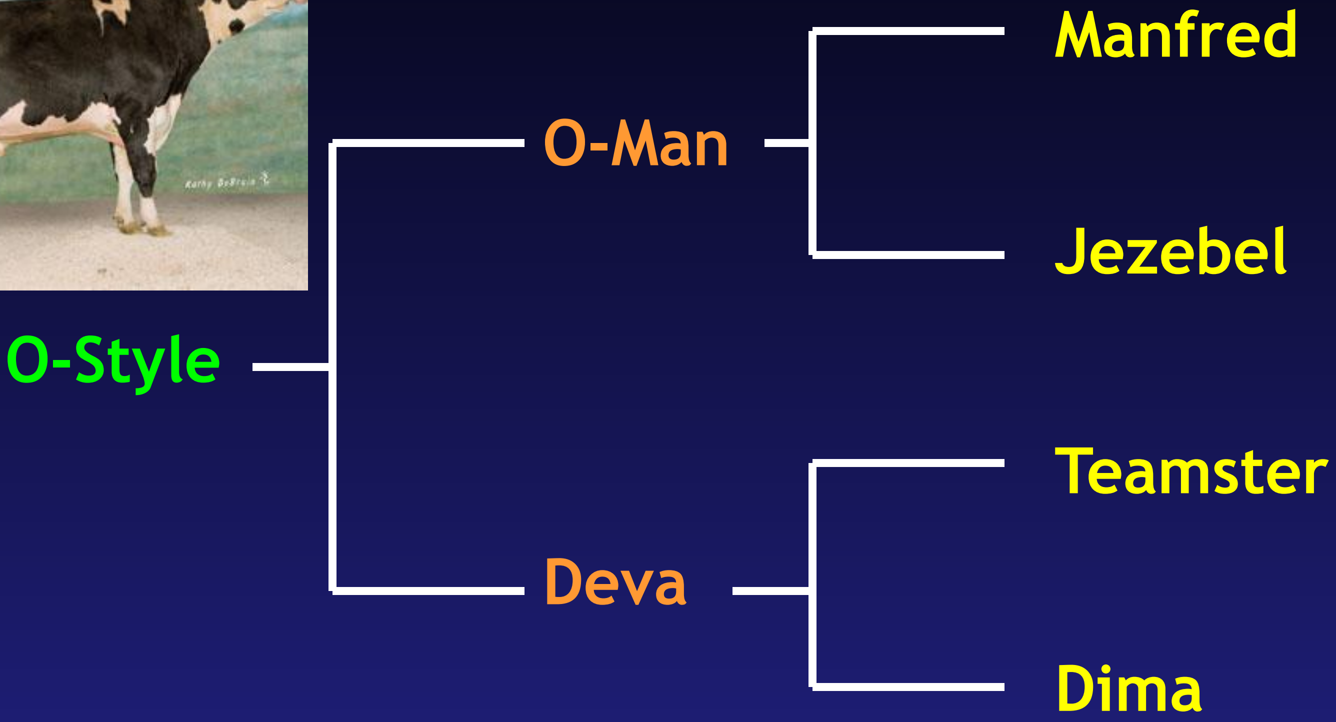
Multi-step genomic evaluations

- Traditional evaluations computed first and used as input data to genomic equations
- Allele effects estimated for 45,187 markers by multiple regression, assuming equal prior variance
- Polygenic effect estimated for genetic variation not captured by markers, assuming pedigree covariance
- Selection index step combines genomic info with traditional info from non-genotyped parents
- Applied to 30 yield, fitness, calving and type traits

Single-step genomic evaluation

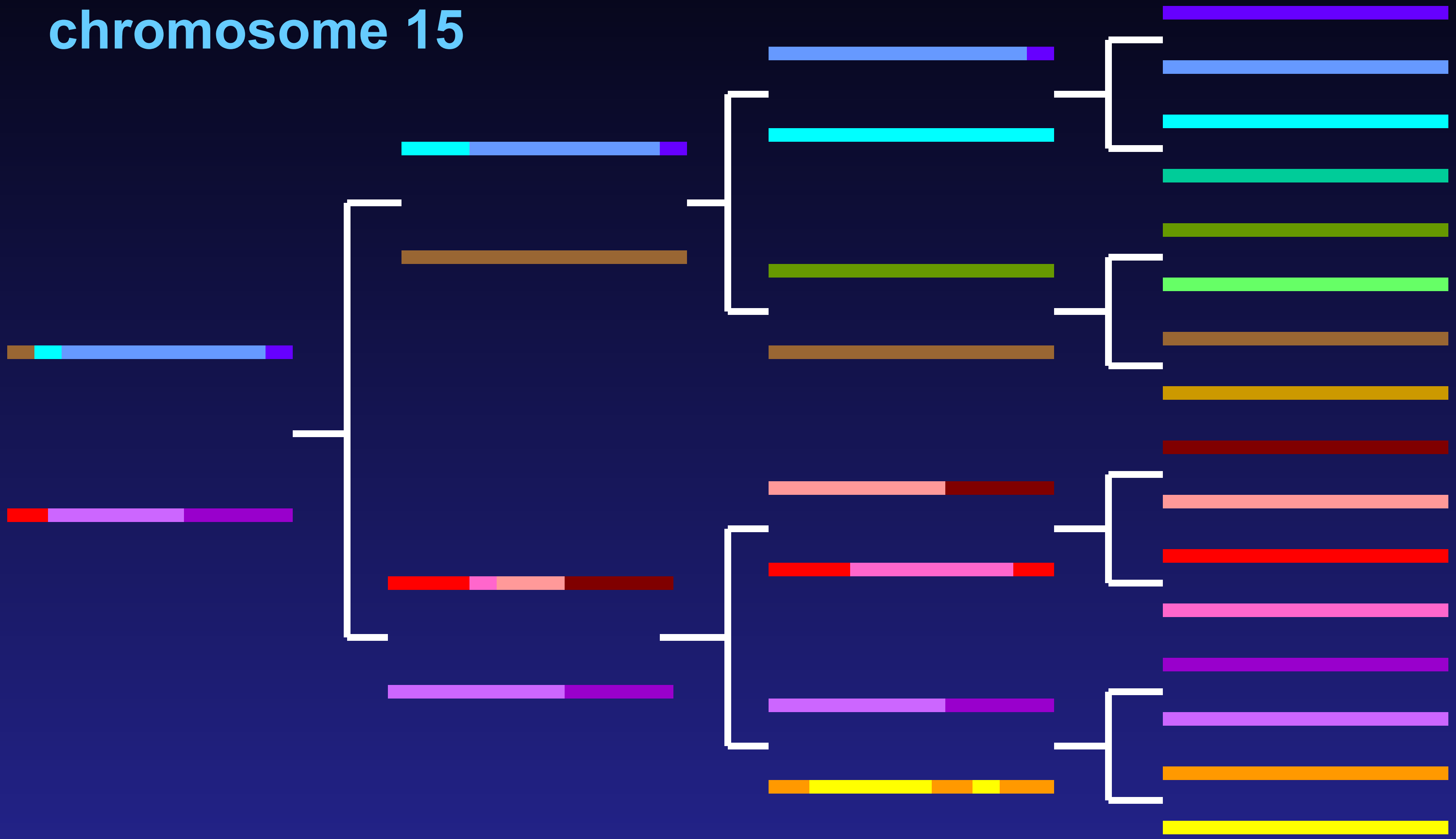
- Benefits of 1-step genomic evaluation
  - Account for genomic pre-selection
  - Expected Mendelian Sampling ≠ 0
  - Improve accuracy and reduce bias
  - Include many genotyped animals
- Redesign animal model software used since 1989

Pedigree: Parents, Grandparents, etc.



O-Style Haplotypes

chromosome 15



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Expected Relationship Matrix[1]

1HO9167 O-Style

	PGS	PGD	MGS	MGD	Sire	Dam	Bull
Manfred	1.0	.0	.0	.0	.5	.0	.25
Jezebel	.0	1.0	.0	.0	.5	.0	.25
Teamster	.0	.0	1.0	. 0	.0	.5	.25
Dima	.0	.0	.0	1.0	.0	.5	.25
O-Man	.5	.5	.0	.0	1.0	.0	.5
Deva	.0	.0	.5	.5	.0	1.0	.5
O-Style	.25	.25	.25	.25	.5	.5	1.0

[1] Calculated assuming that all grandparents are unrelated

Pedigree Relationship Matrix

1HO9167 O-Style

	PGS	PGD	MGS	MGD	Sire	Dam	Bull
Manfred	1.053	.090	.090	.105	.571	.098	.334
Jezebel	.090	1.037	.051	.099	.563	.075	.319
Teamster	.090	.051	1.035	.120	.071	.578	.324
Dima	.105	.099	.120	1.042	.102	.581	.342
O-Man	.571	.563	.071	.102	1.045	.086	.566
Deva	.098	.075	.578	.581	.086	1.060	.573
O-Style	.334	.319	.324	.342	.566	.573	1.043

Genomic Relationship Matrix

1HO9167 O-Style

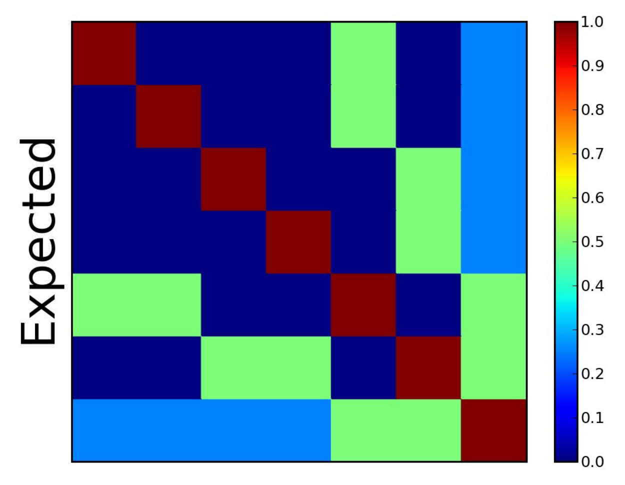
	PGS	PGD	MGS	MGD	Sire	Dam	Bull
Manfred	1.201	.058	.050	.093	.609	.054	.344
Jezebel	.058	1.131	.008	.135	.618	.079	.357
Teamster	.050	.008	1.110	.100	.014	.613	.292
Dima	.093	.135	.100	1.139	.131	.610	.401
O-Man	.609	.618	.014	.131	1.166	.080	.626
Deva	.054	.079	.613	.610	.080	1.148	.613
O-Style	.344	.357	.292	.401	.626	.613	1.157

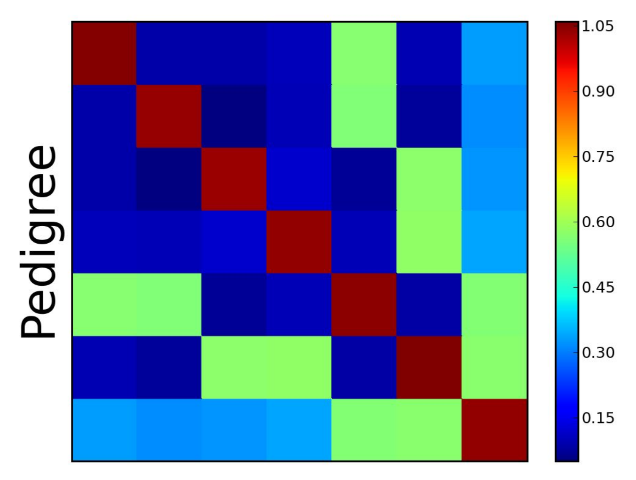
Difference (Genomic – Pedigree)

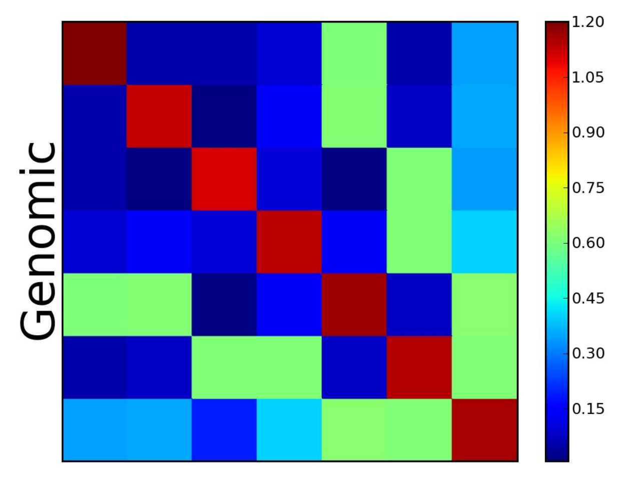
1HO9167 O-Style

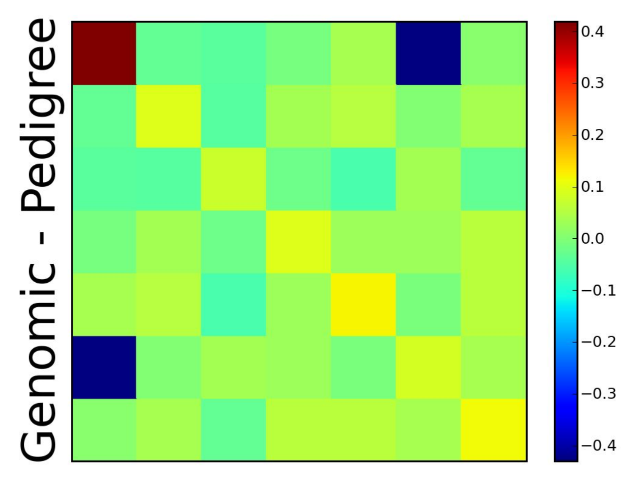
	PGS	PGD	MGS	MGD	Sire	Dam	Bull
Manfred	.149	-.032	-.040	-.012	.038	-.043	.010
Jezebel	-.032	.095	-.043	.036	.055	.004	.038
Teamster	-.040	-.043	.075	-.021	-.057	.035	-.032
Dima	-.012	.036	-.021	.097	.029	.029	.059
O-Man	.038	.055	-.057	.029	.121	-.006	.060
Deva	-.043	.004	.035	.029	-.006	.087	.040
O-Style	.010	.038	-.032	.059	.060	.040	.114

Pseudocolor Plots — O-Style









1 – Step Equations

Aguilar et al., 2010

Model: $y = X\,b + W\,u + e$

\+ other random effects not shown

$$\begin{bmatrix} X' R^{-1} X & X' R^{-1} W \\ W' R^{-1} X & W' R^{-1} W + H^{-1} k \end{bmatrix} \begin{bmatrix} b \\ u \end{bmatrix} = \begin{bmatrix} X' R^{-1} y \\ W' R^{-1} y \end{bmatrix}$$

$$H^{-1} = A^{-1} + \begin{bmatrix} 0 & 0 \\ 0 & G^{-1} - A_{22}^{-1} \end{bmatrix}$$

Size of G and A_{22} >300,000 and doubling each year

Size of A is 60 million animals

Modified 1-Step Equations

Legarra and Ducrocq, 2011

To avoid inverses, add equations for γ, φ

Use math opposite of absorbing effects

$$\begin{bmatrix} X'R^{-1}X & X'R^{-1}W & 0 & 0 \\ W'R^{-1}X & W'R^{-1}W+A^{-1}k & Q & Q \\ 0 & Q' & -G/k & 0 \\ 0 & Q' & 0 & A_{22}/k \end{bmatrix} \begin{bmatrix} b \\ u \\ \gamma \\ \varphi \end{bmatrix} = \begin{bmatrix} X'R^{-1}y \\ W'R^{-1}y \\ 0 \\ 0 \end{bmatrix}$$

Iterate for γ using $G = Z Z' / [\, 2\, \Sigma p(1-p)]$

Iterate for φ using A_{22} multiply (Colleau)

$Q' = [\ 0\ \ I\ ]$ (I for genotyped animals)

Genomic Algorithms Tested

- 1-step genomic model
  - Add extra equations for γ and φ (Legarra and Ducrocq)
  - Converged ok for JE, bad for HO
  - Extended to MT using block diagonal
  - Invert 3x3 $A^{-1}u$, $G\gamma$, $-A_{22}\varphi$ blocks? NO
  - PCG iteration (hard to debug) Maybe

Genomic Algorithms (continued)

- Multi-step insertion of GEBV
  - $[W'R^{-1}W + A^{-1}k]\ u = W'R^{-1}y$ (without G)
  - Previous studies added genomic information to $W'R^{-1}W$ and $W'R^{-1}y$
  - Instead: insert GEBV into u, iterate
- 1-step genomic model using DYD
  - Solve SNP equations from DYD & YD
  - May converge faster, but approximate

Data for 1-Step Test

- National U.S. Jersey data
  - 4.4 million lactation phenotypes
  - 4.1 million animals in pedigree
  - Multi-trait milk, fat, protein yields
  - 5,364 male, 11,488 female genotypes
- Deregressed MACE evaluations for 7,072 bulls with foreign daughters (foreign dams not yet included)

Jersey Results

New = 1-step GPTA milk, Old = multi-step GPTA milk

Statistic	Animals	
Corr(New, Old)	All bulls	0.994
Corr(New, Old)	Genotyped bulls	0.992
Corr(DYD_g, DYD)	Genotyped bulls	0.999
Corr(New, Old)	Young genomic	0.966
SD old PTA milk	Young genomic	540
SD new PTA milk	Young genomic	552
Old milk trend	1995-2005 cows	1644
New milk trend	1995-2005 cows	1430

1-Step vs Multi-Step: Results

Data cutoff in August 2008

Evaluation	Regression	Squared Correlation
Parent Average	.73	.436
Multi-Step GPTA	.75	.520
1-Step GPTA	.85	.520
Expected	.93	

Multi-step regressions also improved by modified selection index weights

Computation Required

- CPU time for 3 trait ST model
  - JE took 11 sec / round including G
  - HO took 1.6 min / round including G
  - JE needed ~1000 rounds (3 hours)
  - HO needed >5000 rounds (>5 days)
- Memory required for HO
  - 30 Gigabytes (256 available)

Remaining Issues

- Difficult to match G and A across breeds
- Nonlinear model (Bayes A) possible with SNP effect algorithm
- Interbull validation not designed for genomic models
- MACE results may become biased

Steps to prepare genotypes

- Nominate animal for genotyping
- Collect blood, hair, semen, nasal swab, or ear punch
  - Blood may not be suitable for twins
- Extract DNA at laboratory
- Prepare DNA and apply to BeadChip
- Do amplification and hybridization, 3-day process
- Read red/green intensities from chip and call genotypes from clusters

Ancestor Validation and Discovery

- Ancestor discovery can accurately confirm, correct, or discover parents and more distant ancestors for most dairy animals because most sires are genotyped.
- Animal checked against all candidates
- SNP test and haplotype test both used
- Parents and MGS are suggested to breed associations and breeders since December 2011 to improve pedigrees.

Ancestor Discovery Results by Breed

	SNP Test	Haplotype Test	
	MGS	MGS	MGGS
Breed	% Confirmed[*]	% Confirmed	% Confirmed
Holstein	95 (98)[†]	97	92
Jersey	91 (92)	95	95
Brown Swiss	94 (95)	97	85

[*] Confirmation = top MGS candidate matched true pedigree MGS.

[†] 50K genotyped animals only.

Data (Yield and Health)

- One step model includes:
  - 72 million lactation phenotypes
  - 50 million animals in pedigree
  - 29 million permanent environment
  - 7 million herd mgmt groups
  - 11 million herd by sire interactions
  - 7 traits: Milk, Fat, Protein, SCS, longevity, fertility
  - Genotypes not yet included

New Features Added

- Model options now include:
  - Multi-trait models
  - Multiple class and regress variables
  - Suppress some factors / each trait
  - Random regressions
  - Foreign data
  - Parallel processing
  - Genomic information
- Renumber factors in same program

Computation Required: Evaluation

- CPU for all-breed model (7 traits)
  - ST: 4 min / round with 7 processors and ~1000 rounds (2.8 days)
  - MT: 15 min / round and ~1000 rounds
  - ~200 rounds for updates using priors
  - Little extra cost to include foreign
- Memory required
  - ST or MT: 32 Gbytes (256 available)

Computation Required: Imputation

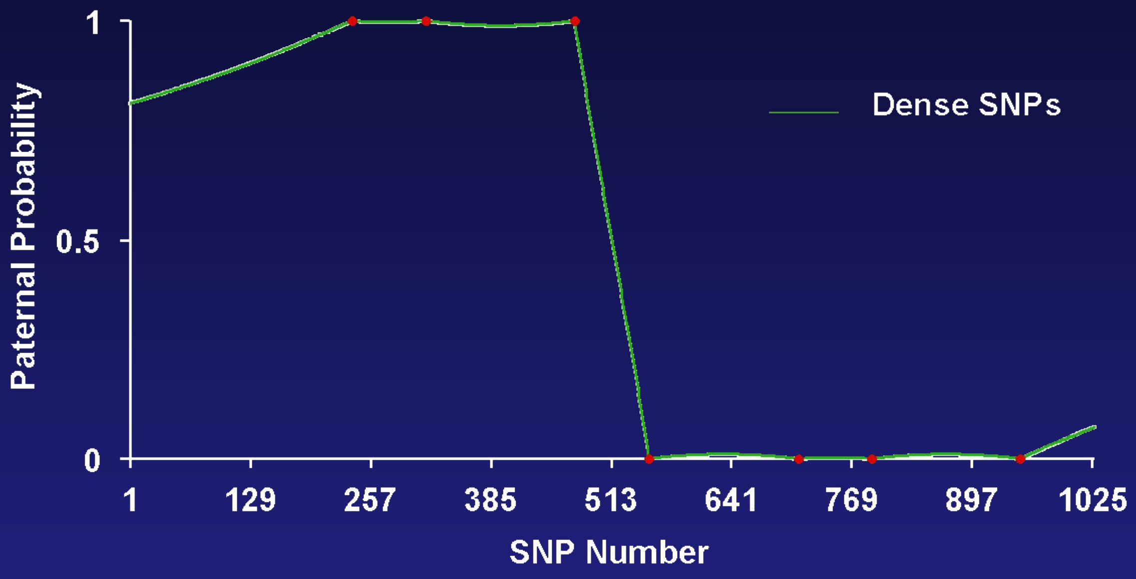
- Impute 636,967 markers for 103,070 animals
  - Required 10 hours with 6 processors (findhap)
  - Required 50 Gbytes memory
  - Program FImpute from U. Guelph slightly better
- Impute 1 million markers on 1 chromosome (sequences) for 1,000 animals
  - Required 15 minutes with 6 processors
  - Required 4 Gbytes memory

Methods to Trace Inheritance

- **Few markers**
  - **Pedigree needed**
  - **Prob (paternal or maternal alleles inherited) computed within families**
- **Many markers**
  - **Can find matching DNA segments without pedigree**
  - **Prob (haplotypes are identical) mostly near 0 or 1 if segments contain many markers**

Haplotype Probabilities

with Few Markers (12 SNP / chromosome)



Haplotype Probabilities

with More Markers (50 SNP / chromosome)

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Haplotyping Program: findhap.f90

- **Population haplotyping**
  - Divide chromosomes into segments
  - List haplotypes by genotype match
  - Similar to FastPhase, IMPUTE, or long range phasing
- **Pedigree haplotyping**
  - Look up parent or grandparent haplotypes
  - Detect crossovers, fix noninheritance
  - Impute nongenotyped ancestors

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2013

Coding of Alleles and Segments

- Genotypes
  - 0 = BB, 1 = AB or BA, 2 = AA, 5 = __ (missing)
  - Allele frequency used for missing
- Haplotypes
  - 0 = B, 1 = not known, 2 = A
- Segment inheritance (example)
  - Son has haplotype numbers 5 and 8
  - Sire has haplotype numbers 8 and 21
  - Son got haplotype number 5 from dam

Population Haplotyping Steps

- Put first genotype into haplotype list
- Check next genotype against list
  - Do any homozygous loci conflict?
    - If haplotype conflicts, continue search
    - If match, fill any unknown SNP with homozygote
    - 2nd haplotype = genotype minus 1st haplotype
    - Search for 2nd haplotype in rest of list
  - If no match in list, add to end of list
- Sort list to put frequent haplotypes 1st

Check New Genotype Against List

1st segment of chromosome 15

Search for 1st haplotype that matches genotype:

022112222011221022021110220010110212202000102020120002021

5.16% 022222222020020022002020200020000200202000022022222202220
4.37% 022020220202200020022022200002200200200000200222200002202
4.36% 022020022202200200022020220000220202200002200222200202220
3.67% 0220202220202220020222022202020000202220000200002020002002
3.66% 0222222220202220222020200220000020222202000002020220002022

Get 2nd haplotype by removing 1st from genotype:

0220022220022200220222020220020200202220200020202002000202
0

3.65%
022020022202200200022020220000220202200002200222200202222
3.51%
0220022220202220222022020202202002220022000000002022220002220
3.42%
02200222200222002202220202200202002022202000202020020002020
3.24%
02222222202020000000220202200202002022202000202020020002020
3.22%

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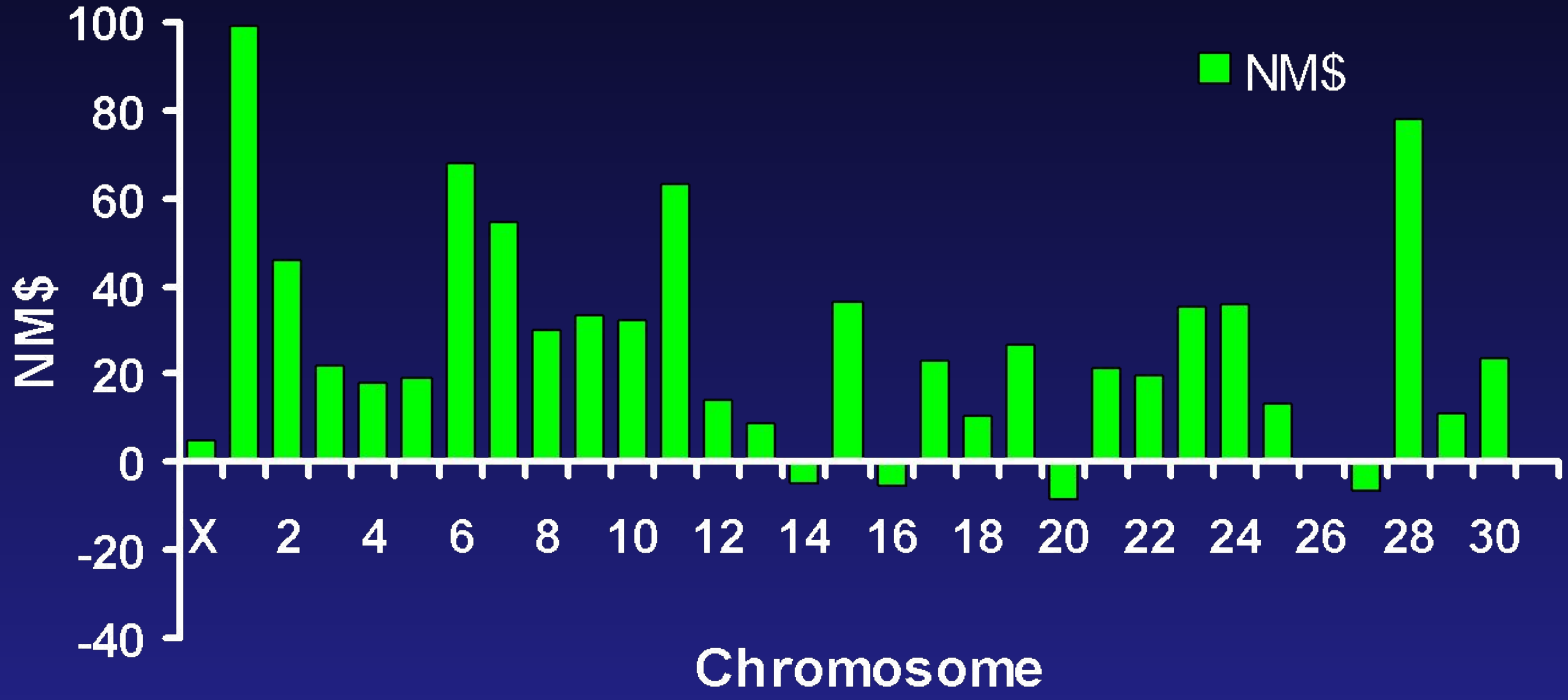
Net Merit by Chromosome

Freddie - highest Net Merit bull



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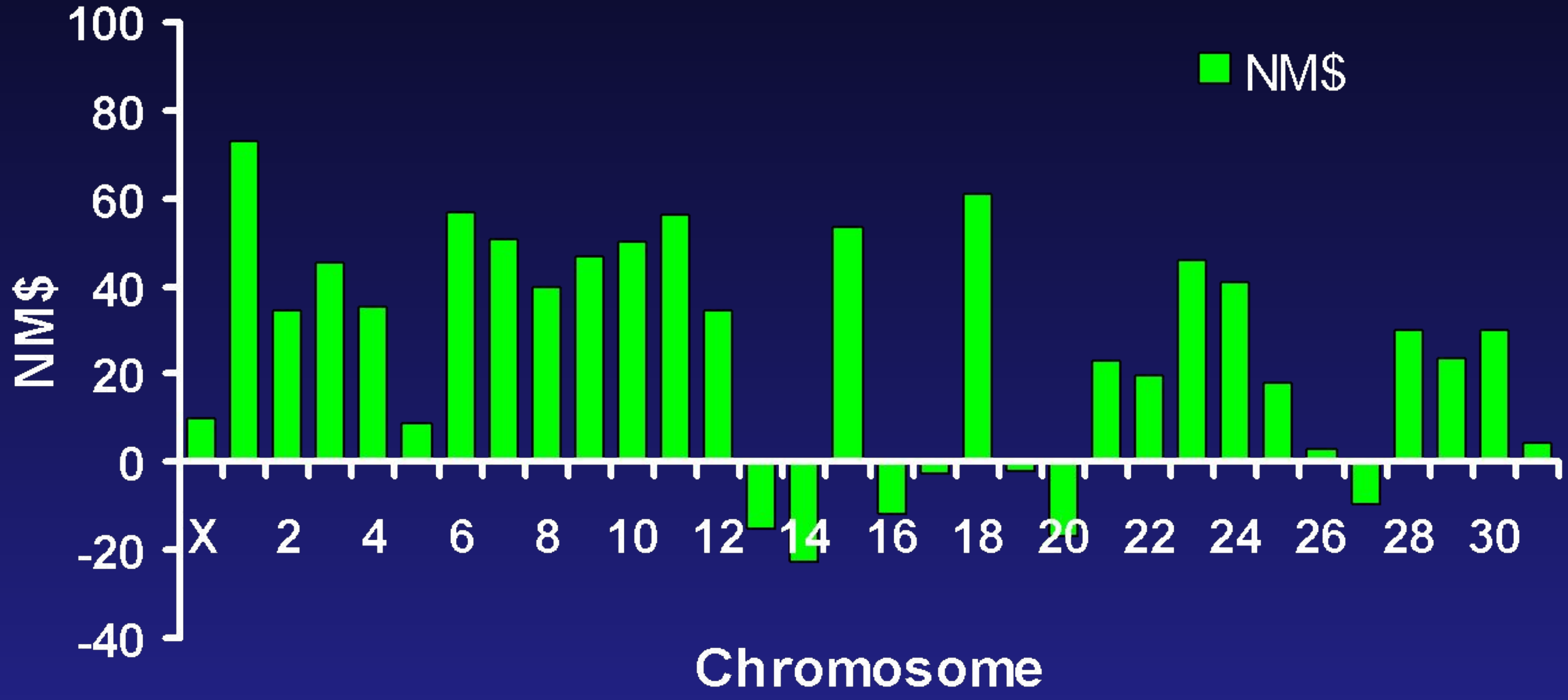
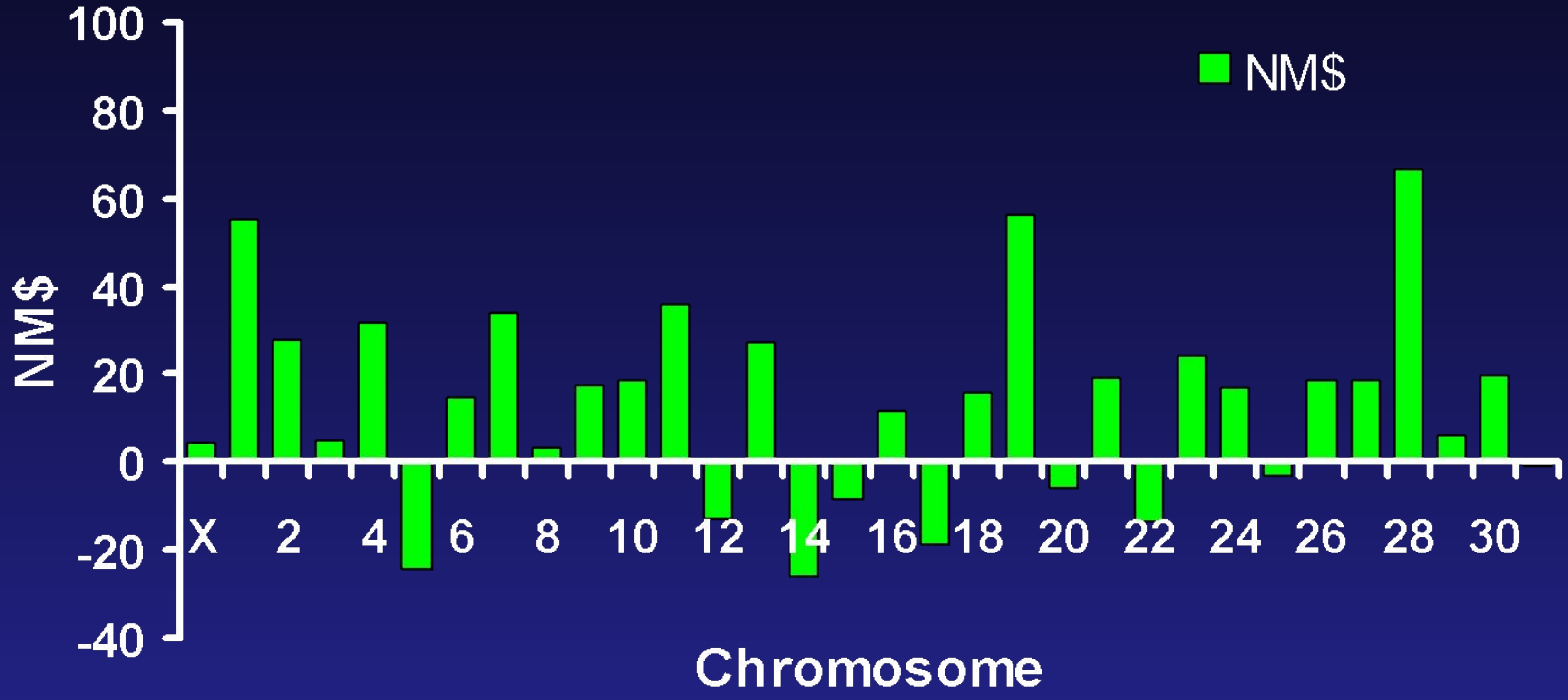
Net Merit by Chromosome

O Man – Sire of Freddie



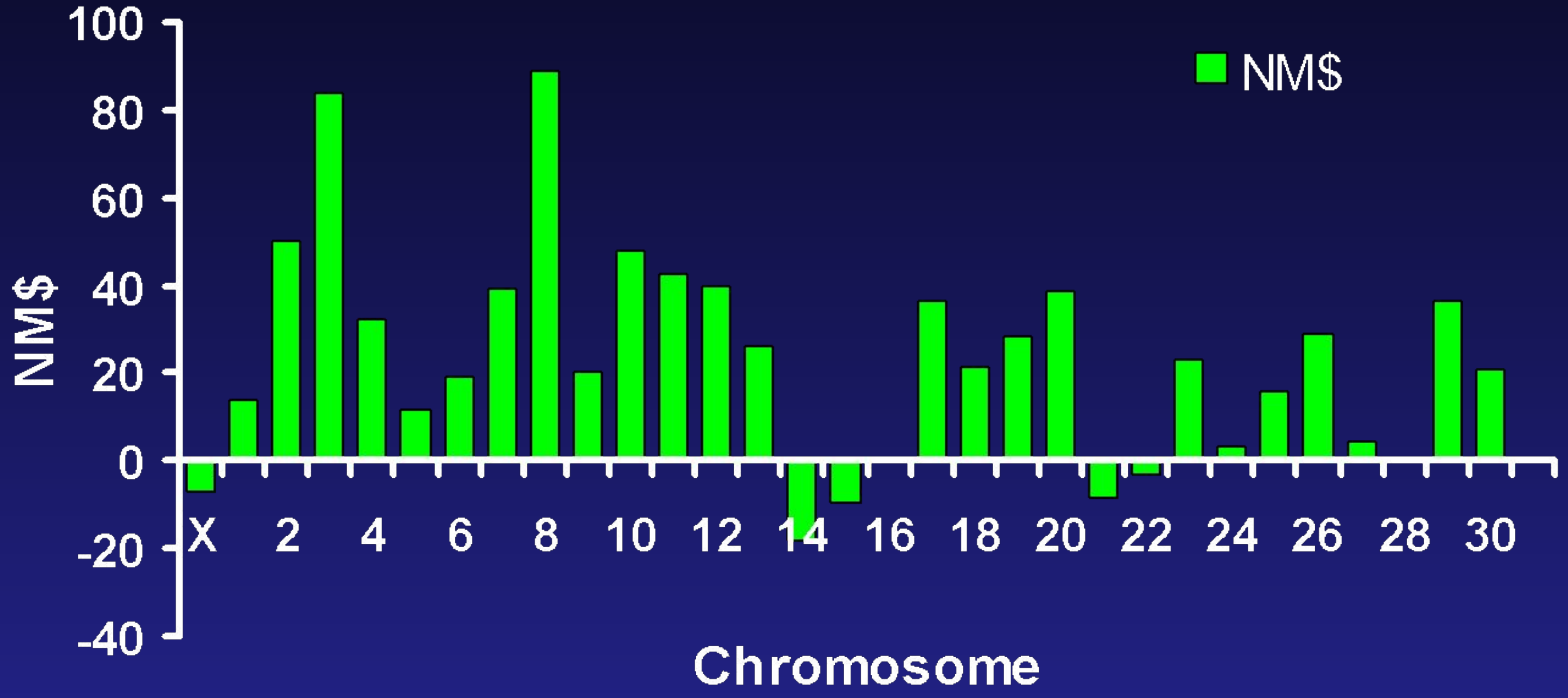
Net Merit by Chromosome

Die-Hard - maternal grandsire

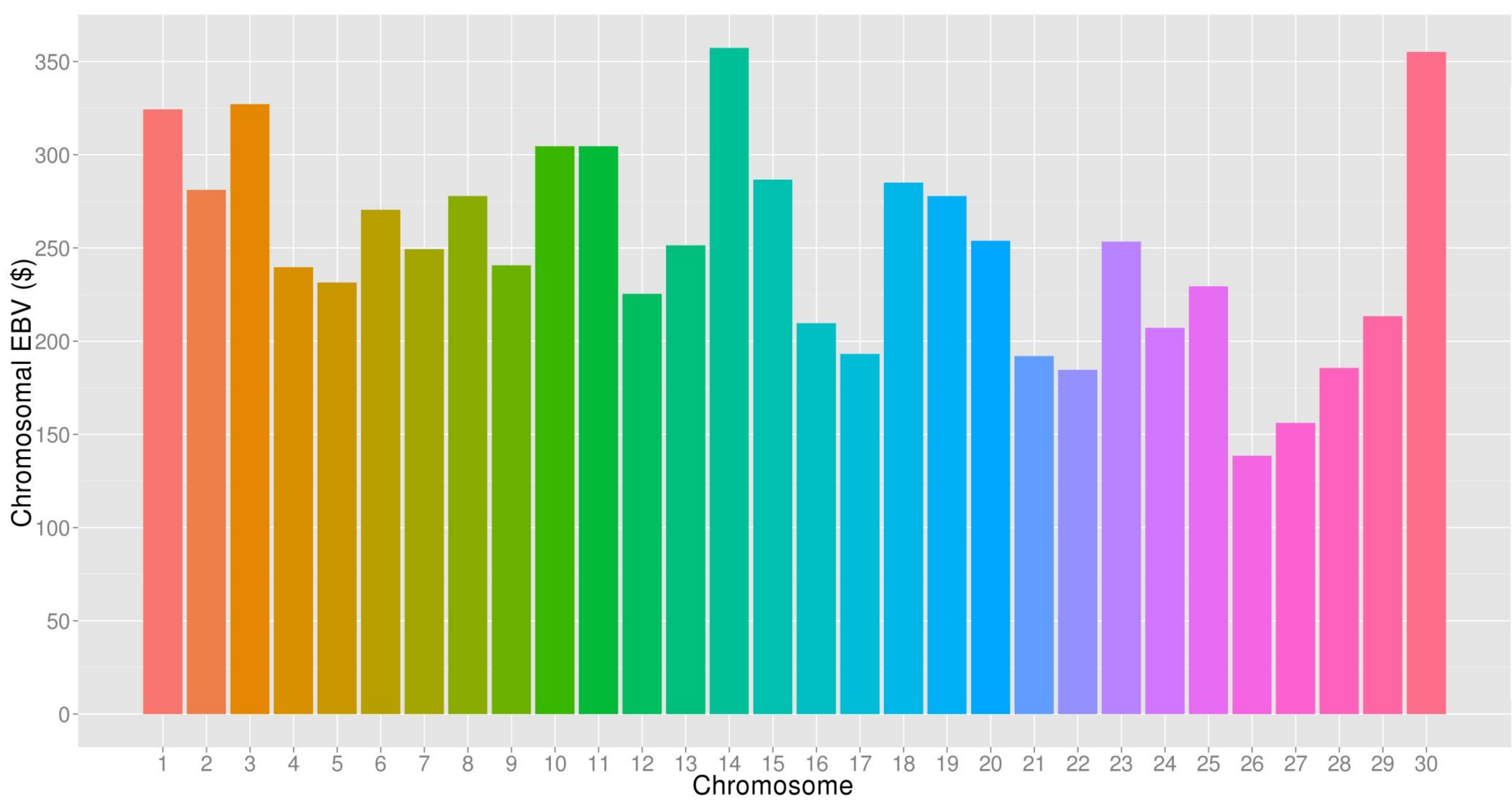


Net Merit by Chromosome

Planet – high Net Merit bull



What's the best cow we can make?



A "Supercow" constructed from the best haplotypes in the Holstein population would have an EBV(NM$) of $7515

Conclusions

- 1-step genomic evaluations tested
  - Inversion avoided using extra equations
  - Converged well for JE but not for HO
  - Same accuracy, less bias than multi-step
  - Foreign data from MACE included
- Further work needed on algorithms
  - Including genomic information
  - Extending to all-breed evaluation

Conclusions

- Foreign data can add to national evaluations
  - In one step model instead of post-process
  - High correlations of national with MACE
- Multi-trait all-breed model developed
  - Replace software used since 1989
  - Many new features added
  - Correlations ~.99 with traditional AM
  - Tested with 7 yield and health traits
  - Also tested with 14 JE conformation traits

Acknowledgments

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