HAZU - Razred za prirodne znanosti – Odbor za primijenjenu genomiku
Znanstveni sastanak: GENOMSKE TEHNOLOGIJE

1995-2019

Genomic dissection of inbreeding depression: a gate to new opportunities

< Genomska disekcija inbriding depresije: nove mogućnosti i izazovi >

Ino Curik

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Quantitative & population genomics

University of Zagreb, Zagreb, Croatia & **BOKU, Vienna, Austria**

23. listopad 2019., HAZU, Strossmayerov trg 14, Zagreb, 12:30-12-50

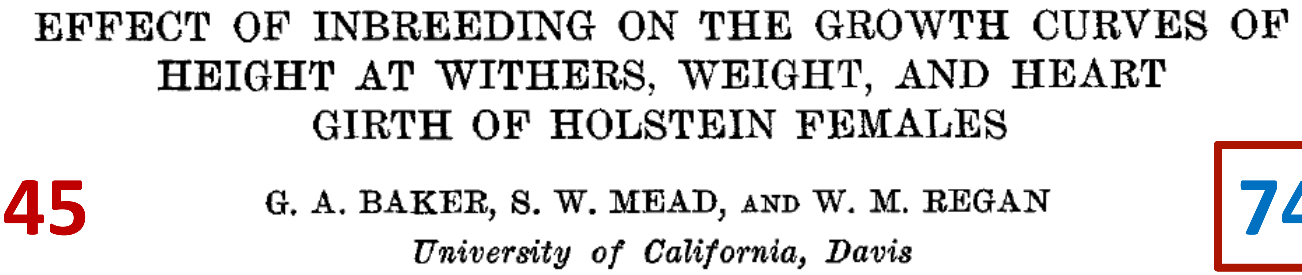
Consequences of inbreeding on the population

Increase in homozygosity ↔ Decrease in heterozygosity

1. **Inbreeding depression***
2. Increase of genetic deffects
3. Redistribution of genetic variances

*The reduction of the population mean for a quantitative trait such as it is size, fertility, vigour, yield, and fitness is an negative consequence of inbreeding known as **inbreeding depression**.

Inbreeding depression: linear regression PHENOTYPE on F_{PED}



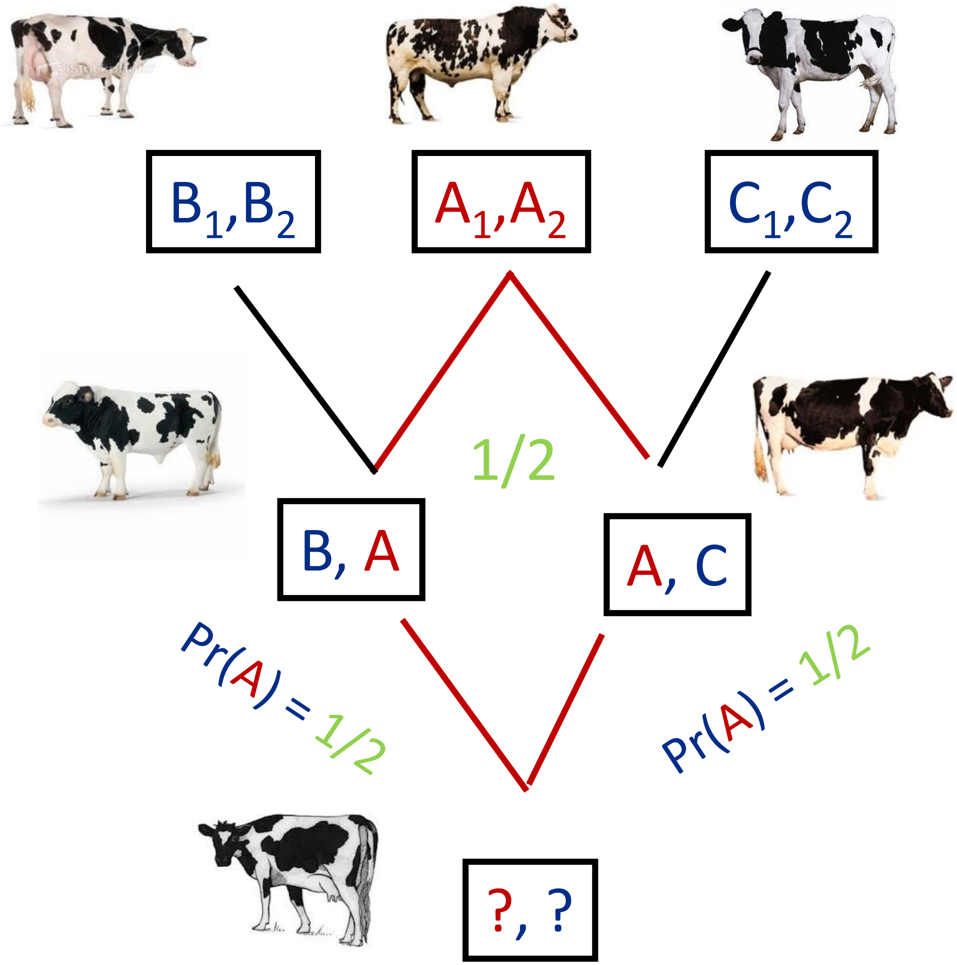
EFFECT OF INBREEDING ON THE GROWTH CURVES OF
HEIGHT AT WITHERS, WEIGHT, AND HEART
GIRTH OF HOLSTEIN FEMALES

G. A. BAKER, S. W. MEAD, AND W. M. REGAN
University of California, Davis

JDS, 1945

74 years

Wright, 1922 (path analysis, correlations)



B_1,B_2

A_1,A_2

C_1,C_2

1/2

B, A

A, C

Pr(A) = 1/2

Pr(A) = 1/2

?, ?

$F_X = Pr(A_1 \equiv A_1)$ or $Pr(A_2 \equiv A_2) = ?$

$F_X = 0.125$ (1/8)

The individual inbreeding coefficient (F_X) is defined as:

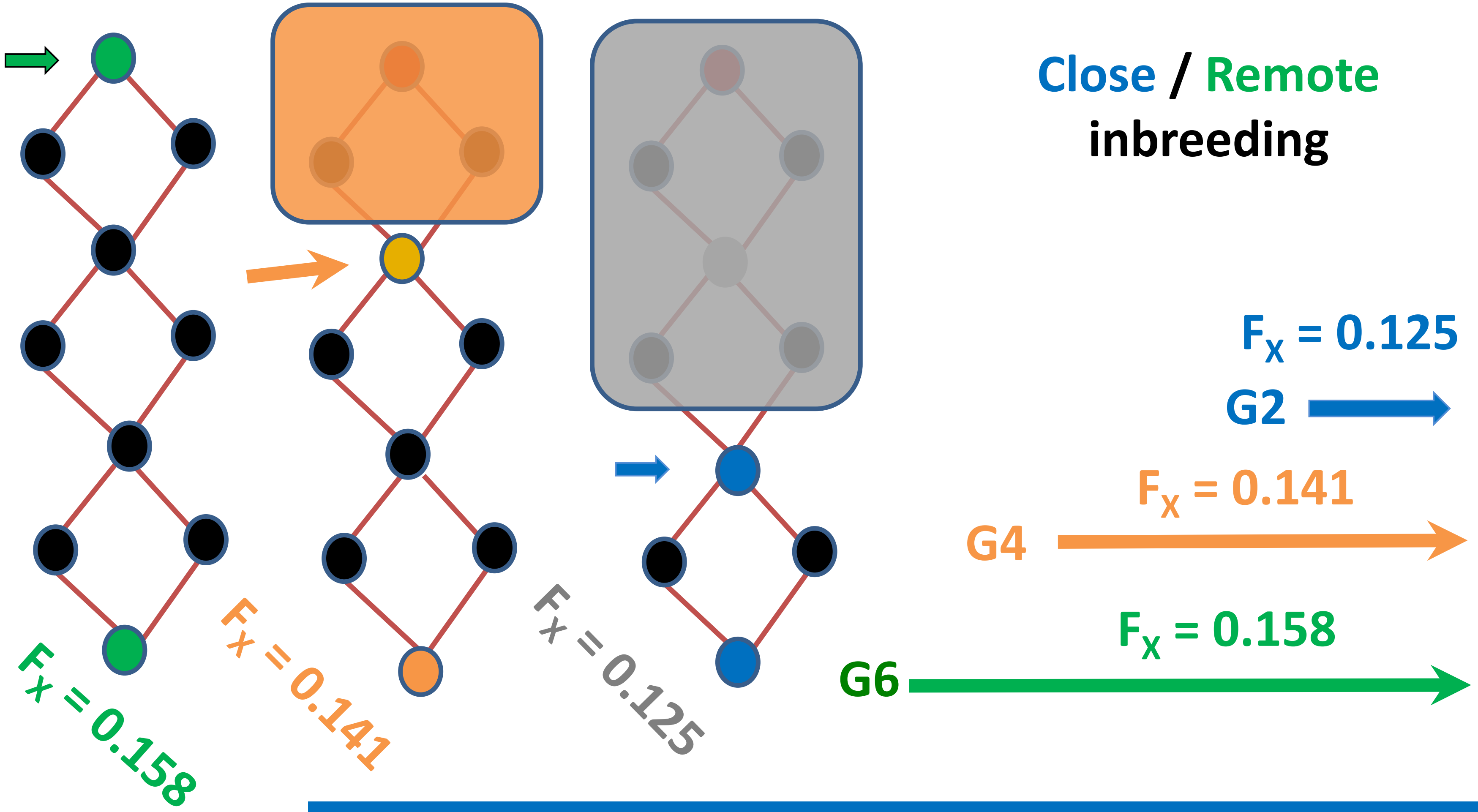
Malécot G (1948),

1. The probability of a randomly sampled locus in the genome to be autozygous (IBD).

2. The proportion of an individual´s genome that is autozygous (IBD).

F_{PED}

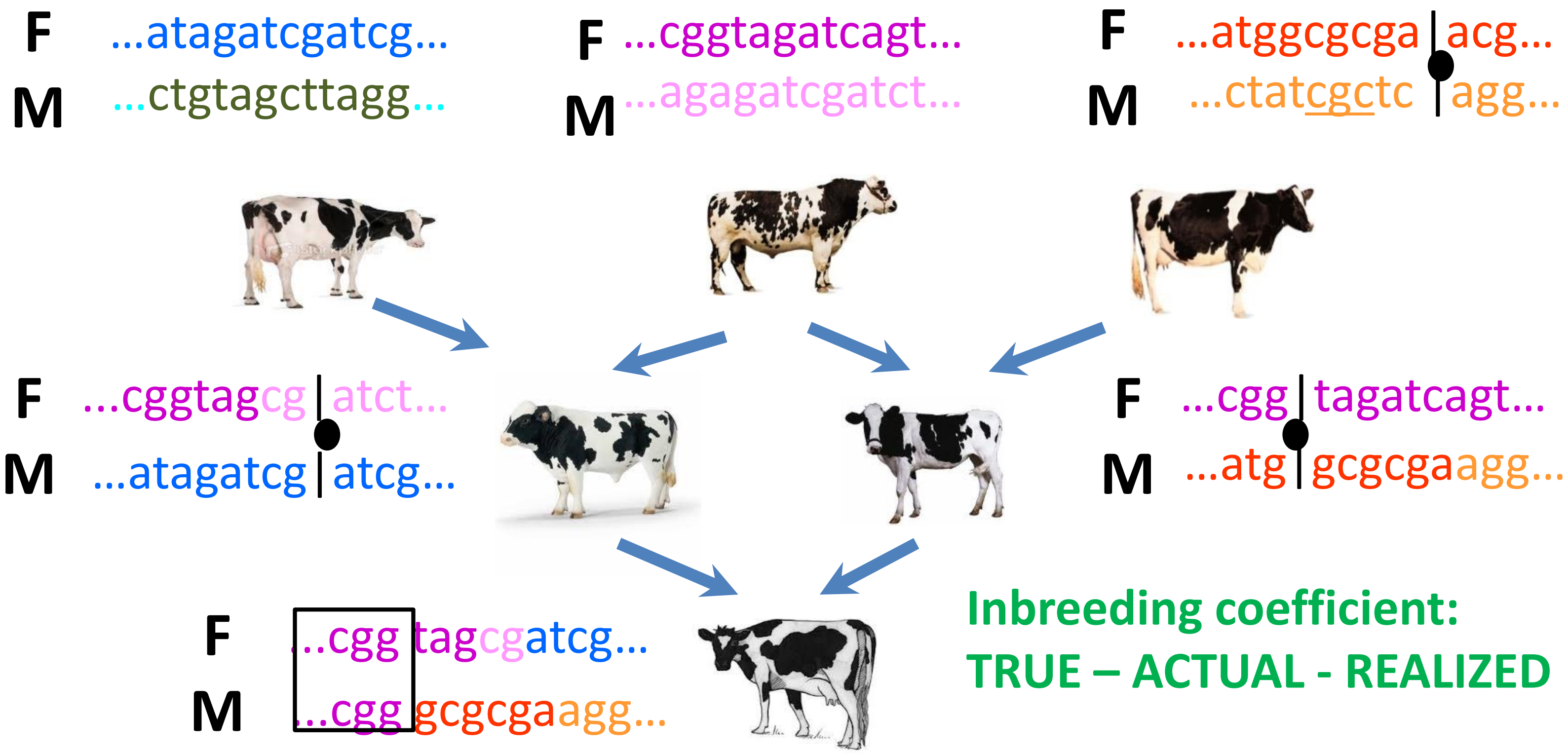
- without sampling variation (F_{litter} = constant)
- equal for all loci ($F_{neutral\ loci} = F_{selected\ loci}$)
- **evenly distributed autozygosity across the genome**



Relative measure with respect to the base generation

ROH based inbreeding coefficient

- **Humans** (McQuillan et al., 2008; Nalls et al., 2009)
- **Cattle** (Ferenčaković et al., 2011; Purfield et al., 2012; Ferenčaković et al., 2013)
- **Pig** (Bosse et al., 2012; Silio et al., 2013)



F ...atagatcgatcg...
M ...ctgtagcttagg...

F ...cggtagatcagt...
M ...agagatcgatct...

F ...atggcgcga|acg...
M ...ctatcgctc|agg...

F ...cggtagcg|atct...
M ...atagatcg|atcg...

F ...cgg|tagatcagt...
M ...atg|gcgcgaagg...

F ..cgg tagcgatcg...
M ..cgg gcgcgaagg...

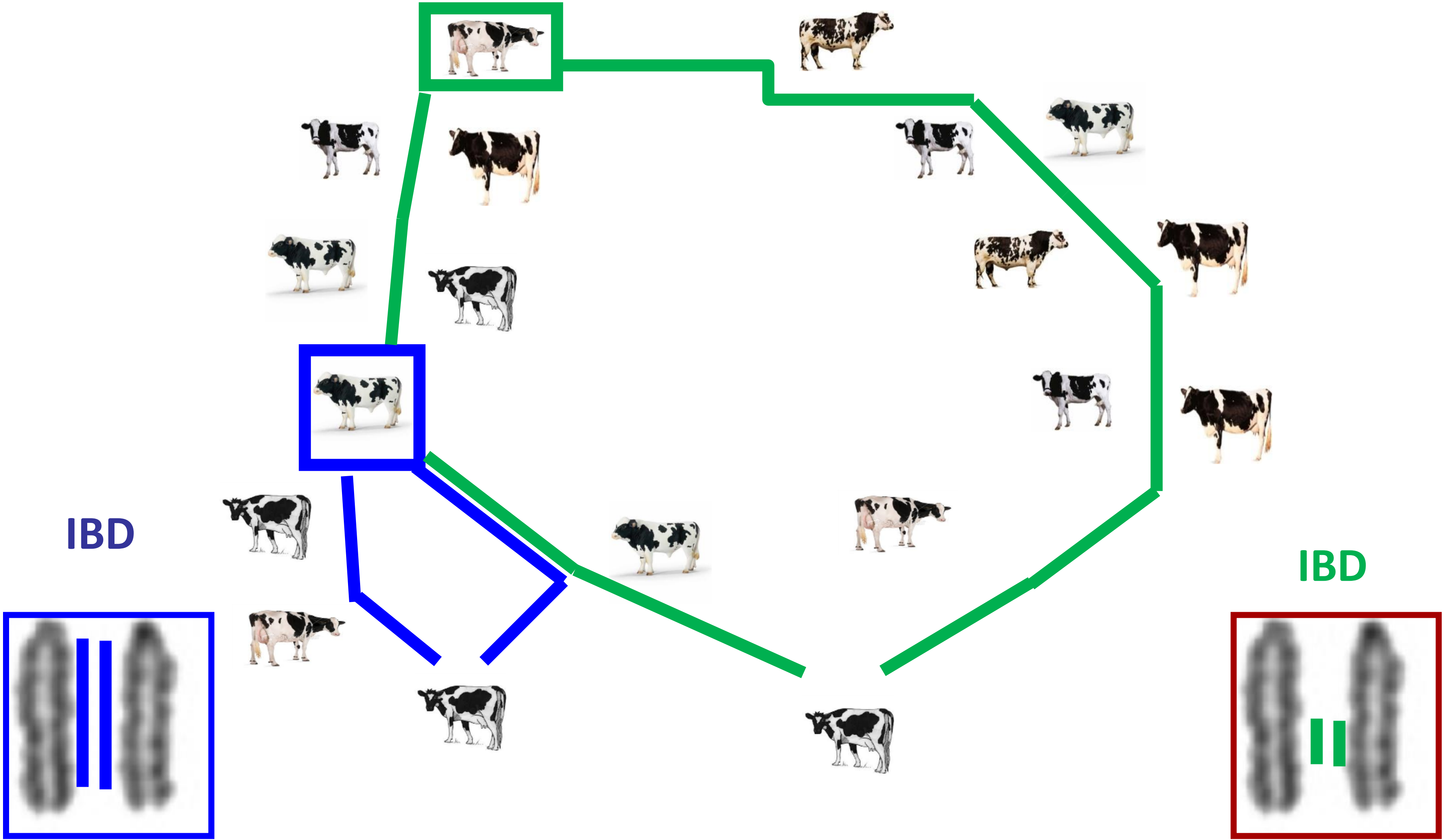
Inbreeding coefficient:
TRUE – ACTUAL - REALIZED

IBD ...022 112022112...

$F_{GENOMIC}$ = 0.25 (0,0 to 1,0); $F_{PEDIGREE}$ = 0.125

Longer IBD haplotypes → more recent ancestors

Longer homozygous haplotypes → higher IBD probability



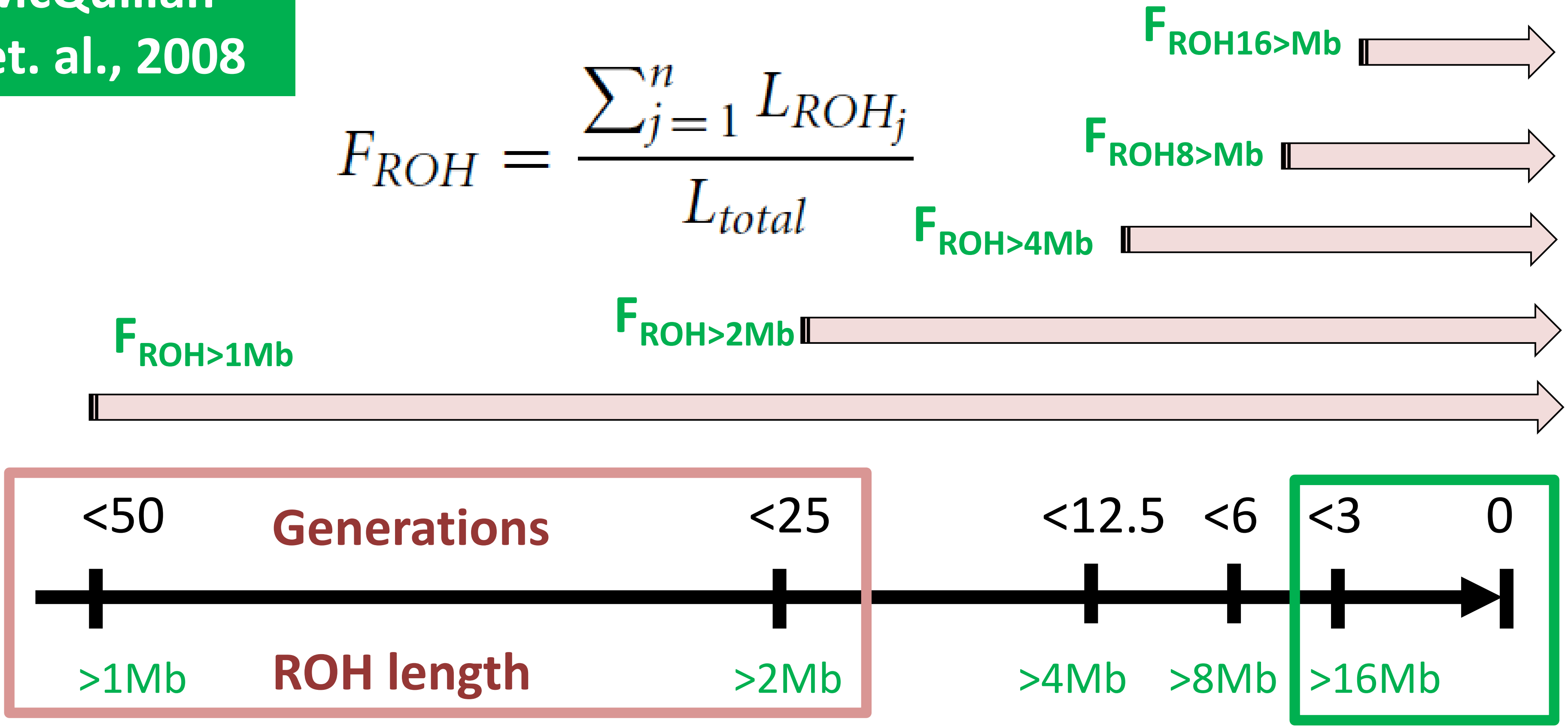
F_{ROH}

- with sampling variation ($F_{litter} \neq$ constant)
- not equal for all loci ($F_{neutral\ loci} \neq F_{selected\ loci}$)
- **unevenly distributed autozygosity across the genome**

→ opportunity to provide regional estimates

McQuillan et. al., 2008

$$F_{ROH} = \frac{\sum_{j=1}^{n} L_{ROH_j}}{L_{total}}$$



Relative measure with respect to the base generation

Inbreeding depression: linear regression PHENOTYPE on F_{ROH}

Simulation: Keller et al., 2011

3-8 years

Cattle: Bjelland et al., 2013; Pryce 2014; Howard et al., 2015

Curik et al., 2012 (4thICQG, Edinburgh) → 2011-2016

Maja Ferenčaković, Johann Sölkner, Miroslav Kapš & Ino Curik

Genome-wide mapping and estimation of inbreeding depression of semen quality traits in a cattle population

J. Dairy Sci. 100:1–10
https://doi.org/10.3168/jds.2016-12164
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Austrian
Simmental
bull
Austria

2017

Univariate mixed models:

- total number of spermatozoa (10^9): BOXCOX→ $[(TNS^{0.3}-1)/0.3]$
- percent of live spermatozoa (%)

Illumina Bovine SNP50 Beadchip

19,720 ejaculates from 554 bulls

Random effect: bulls

Fixed effects: age of bull

month of collection

year of collection

days between successive ejaculates

semen collector

AI station

Covariates: **Inbreeding coefficients:**

- F_{PED}, F_{PED5},
- F_{HOM} (F_{IS}),
- $F_{ROH2\text{-}4Mb}$, $F_{ROH>2Mb}$, $F_{ROH>4Mb}$, $F_{ROH>8Mb}$, $F_{ROH>16Mb}$

sas

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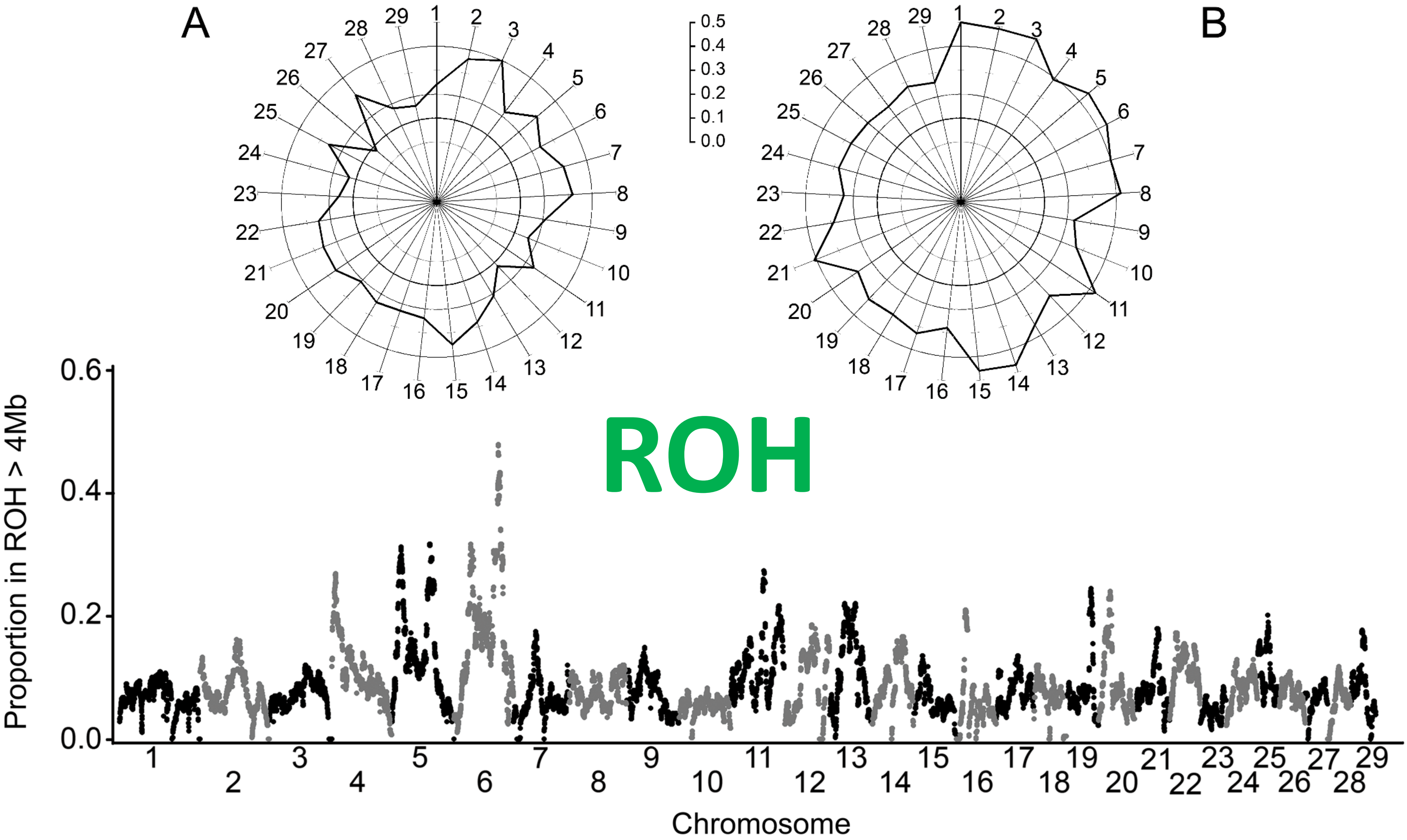
Accelerating the Quest for Significance™

“Global” inbreeding depression: total number of spermatozoa

Inbreeding coefficient	Regression coefficient^{REML} (SE)	ΔAIC^{ML} (43907.5)
F_{PED}	****-5.80 (1.94)**	**0.0**
$F_{ROH2\text{-}4\ Mb}$	****-11.40 (4.00)**	**0.8**
$F_{ROH>2\ Mb}$	*-2.72 (1.22)	3.9
$F_{ROH>4\ Mb}$	-1.91 (1.31)	6.5
F_{PED5}	-2.81 (2.03)	7.0
$F_{ROH>8\ Mb}$	-1.91 (1.51)	7.3
F_{IS}	**-0.49 (0.77)**	**8.5**
$F_{ROH>16\ Mb}$	-0.78 (2.16)	8.8

Modeling: “remote inbreeding” > “close inbreeding”

Correlations of chromosomal $F_{ROH>4Mb}$ with F_{PED} (A) & $F_{ROH>4Mb}$ (B)



ROH

Curik et al., 2018, RBZ

ROH-based mapping of regions contributing to inbreeding depression

Univariate mixed models:

- total number of spermatozoa (10^9): BOXCOX→ [($TNS^{0.3}$-1)/0.3]
- percent of live spermatozoa (%)

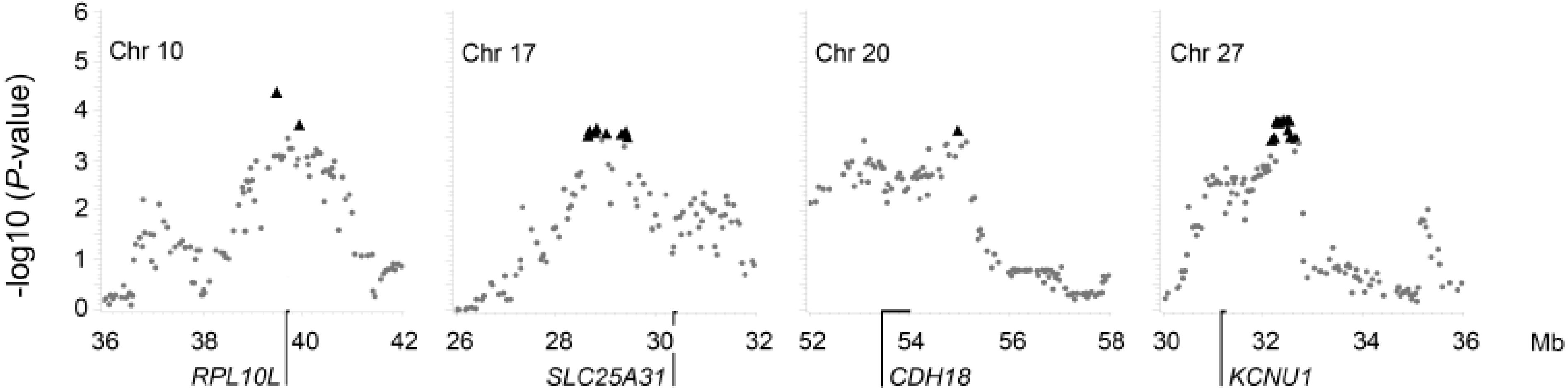
Illumina Bovine SNP50 Beadchip

19,720 ejaculates from 554 bulls

Random effect:	bull
Fixed effects:	age of bull
	month of collection
	year of collection
	days between successive ejaculates
	semen collector
	AI station
Covariates:	**Additive effects; SNP (0, 1, 2)**
	ROH>2 Mb effects; SNP (0, 1)

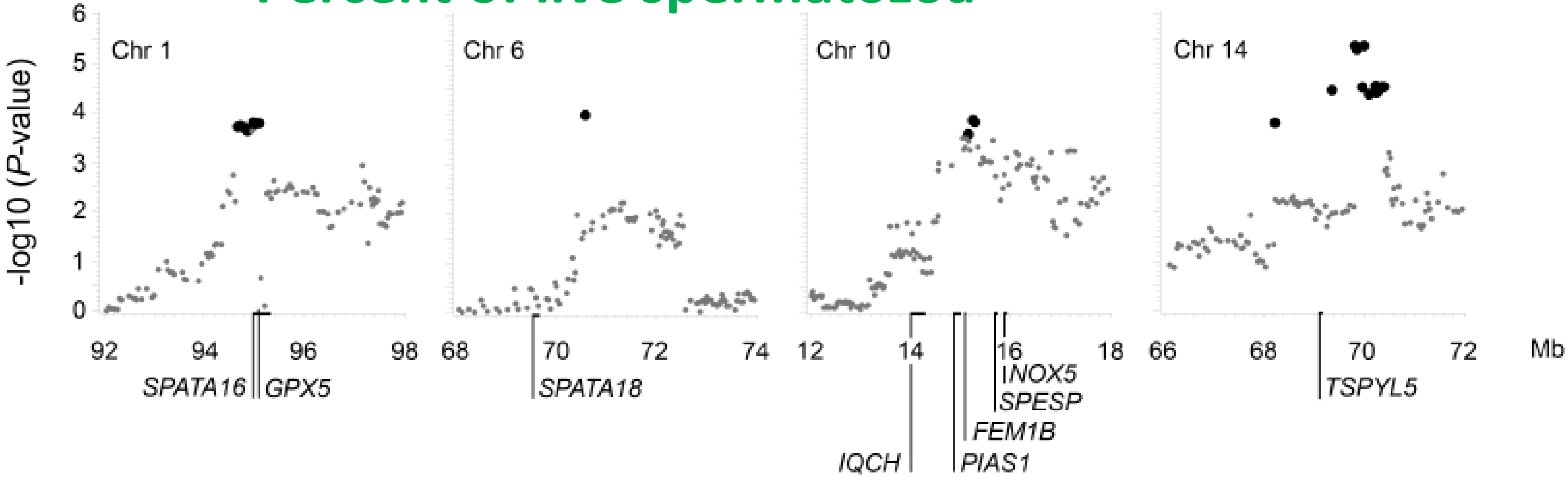
Adjustment for multiple comparisons: Gao et al., 2008

The total number of spermatozoa



- **RPL10L**: helping to inactivated X-linked genes in spermatogenesis
- **SLC25A31**: sperm flagellar energy carrier protein
- **CDH18**: significant influence on sperm motility
- **KCNU1**: codes testis specific potassium channel

Percent of live spermatozoa



- **SPATA16**: associated with male infertility in humans
- **GPX5:** marker of boar sperm quality
- **SPESP1 :** involved in the fusion of sperm with the egg plasma membrane
- **SPATA18**: encodes a so-called “mitochondrion-eating protein”
- **TSPYL5:** linked to male idiopathic infertility
- **NOX5:** regulate redox-dependent processes in lymphocytes and spermatozoa
- **PIAS1:** plays a role in maintenance of spermatogenesis
- **IQCH:** play a regulatory role in spermatogenesis
- **FEM1B:** maturation of epithelial cells involved in prostate gland development

Quantitative genomic analyses

Whole Genome Sequence analyses
of the “significant regions - signals” → bulls

Identification of the causative mutations

In process …

Genomic dissection of inbreeding depression (BS)

Genetic architecture of inbreeding depression:

- Oligogenic inheritance
- Mixed inheritance: major genes + polygenic
- **Polygenic inheritance: infinitesimal model with dominance**

- Dominance or over-dominance ?
- Positive vs. negative dominance effects ?
- Is inbreeding depression equally distributed across chromosomes ?
- Are there strong inbreeding depressors (SNP)?

Falconer & Mackay, 1996. Introduction to quantitative genetics
Inbreeding depression - single gene model

Genotype	AA	Aa	aa
HWE - population	p^2	2pq	q^2
F - population	p^2+pqF	2pq-2pqF	q^2+pqF
Genotypic value	a	d	-a

$$\mu_{HWE} = a(p^2) + d(2pq) - a(q^2) = a(p-q) + 2pqd$$

$$\mu_F = a(p^2+pqF) + d(2pq-2pqF) - a(q^2+pqF) = a(p-q) + 2pqd - 2pqdF$$

$$= \mu_{HWE} - \mathbf{2\,pq\,d\,F}$$

- 2 pq d F ↑

$$2\sum pqdF_{ROH} > 0$$

Genomic dissection of inbreeding depression

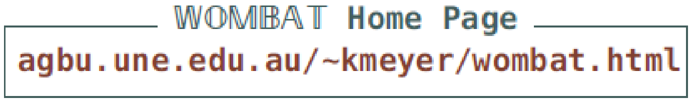
Univariate mixed models: sperm quality

Volume of ejaculate (ml)

Concentration of ejaculate (109/ml)

Illumina Bovine SNP50 Beadchip

8,756 ejaculates from 162 BS bulls



WOMBAT Home Page

agbu.une.edu.au/~kmeyer/wombat.html

Random effect: bull

Fixed effects: age of bull
month of collection
year of collection
period between two successive ejaculates
semen collector
AI station

Covariates: **Additive effects; SNP (0, 1, 2) → a**

Dominance effects; SNP (0, 1, 0) → d

$F_{ROH>4Mb}$ → F

$$2\Sigma pqdF_{ROH>4Mb}$$

Ferenčaković et al., 2014, Cardiff

Single locus (region) contribution to inbreeding depression

$$\frac{pqdF_{ROH}}{\sum pqdF_{ROH}}$$

Volume of ejaculate (ml) => 6%

Concentration of ejaculate (10^9/ml) => 4%

$$\mathbf{2\Sigma pqdF_{ROH>4Mb}}$$

$$\sum ? \quad 2pqdF_{ROH} \quad 2pqdF_{ROH} \quad 2pqdF_{ROH}$$

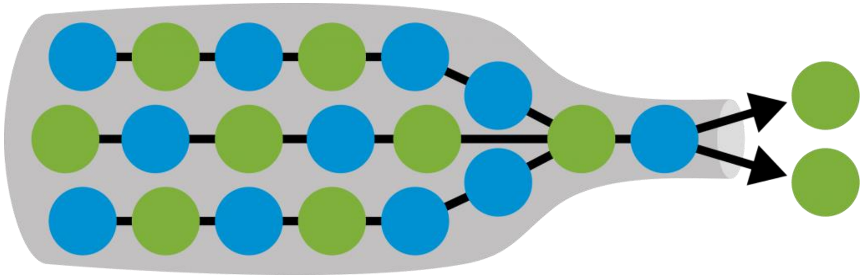
Still a number of problems to solve ...

- Confounding in the estimation of neighbouring loci (pruning ?)
- Covariance between A & D with increase in ROH (inbreeding)
- Separation of selection from inbreeding (mating) effects

The management of detrimental load in genetically small populations

New era

Detrimental load elimination ?!



1. Estimation/Mapping/Dissection of inbreeding depression
2. Prediction of detrimental load from the sequence
3. Gene editing → correction of detrimental mutations
4. Founder partial inbreeding depression (planed mating)
5. Purging mating strategy → genomic revision

Miroslav Kapš, Gabor Mészáros, Yuri Utsunomiya,
Patrik Waldmann, Sophie Eaglen, Roberto Carvalheiro,
Istvan Nagy, Roswitha Baumung, …

Hvala na pozornosti !

Ministry of Science,
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