

1995-2019

# Genomic dissection of inbreeding depression: a gate to new opportunities

< Genomska disekcija inbriding depresije: nove mogućnosti i izazovi >

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**Quantitative & population genomics**



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# Consequences of inbreeding on the population

Increase in homozygosity  $\leftrightarrow$  Decrease in heterozygosity

1. **Inbreeding depression\***
2. Increase of genetic defects
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 a negative consequence of inbreeding known as **inbreeding depression**.

Inbreeding depression: linear regression PHENOTYPE on  $F_{PED}$

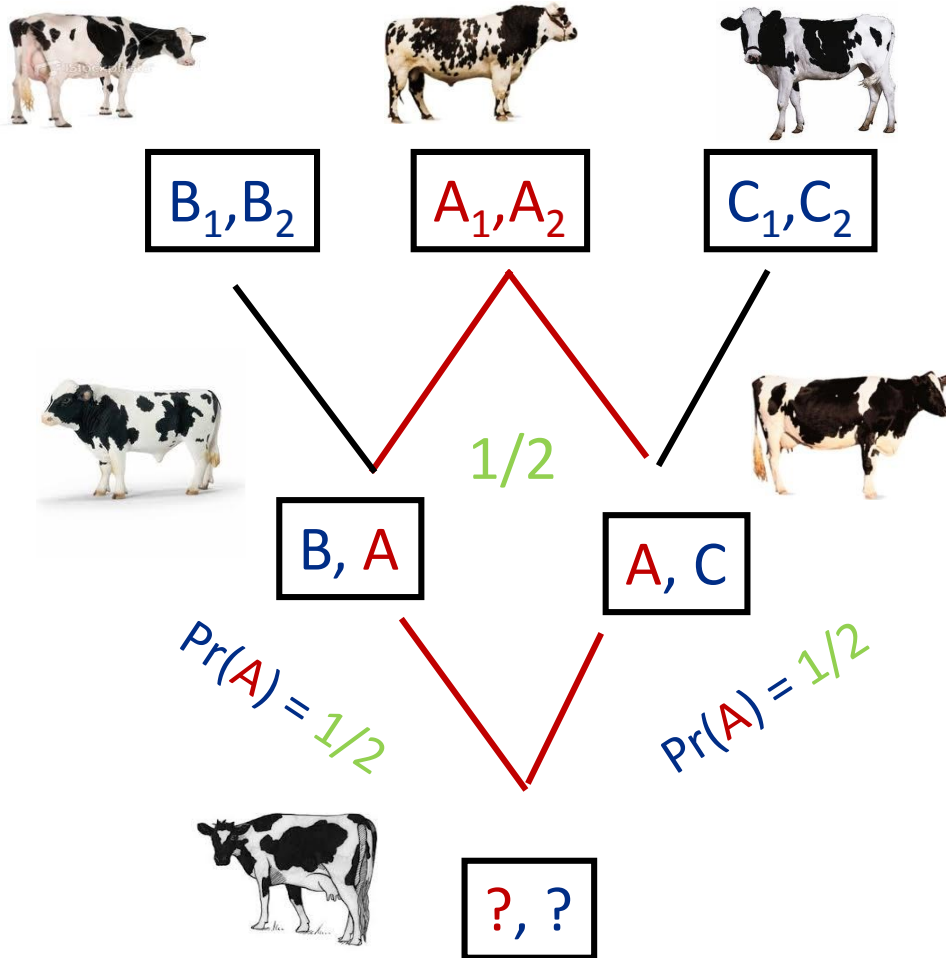
EFFECT OF INBREEDING ON THE GROWTH CURVES OF  
HEIGHT AT WITHERS, WEIGHT, AND HEART  
GIRTH OF HOLSTEIN FEMALES

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

**JDS, 1945**

**74 years**

# Wright, 1922 (path analysis, correlations)



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).

$$F_x = \Pr(A_1 \equiv A_1) \text{ or } \Pr(A_2 \equiv A_2) = ?$$

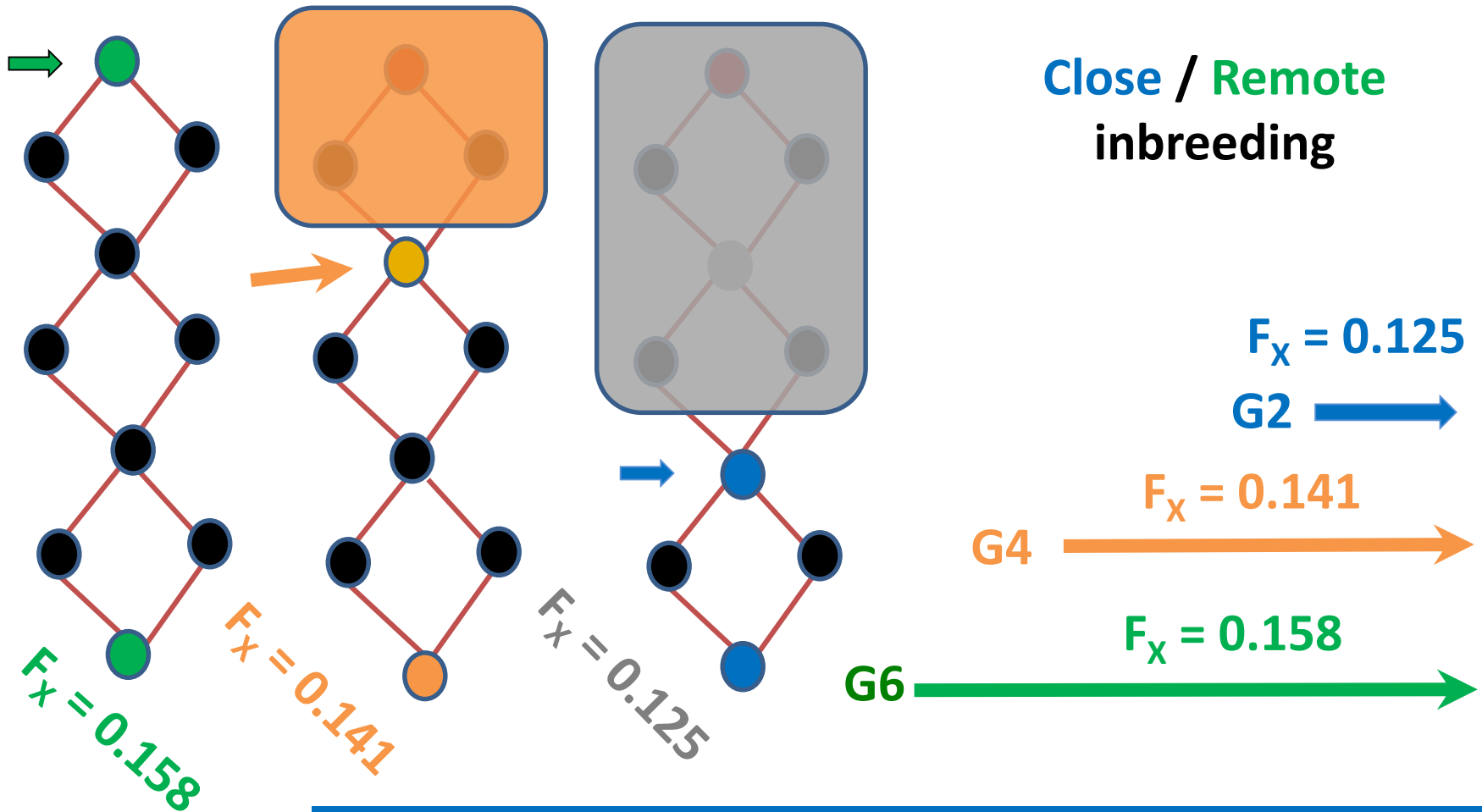
$$F_x = 0.125 (1/8)$$

$F_{PED}$

without sampling variation ( $F_{litter} = \text{constant}$ )

equal for all loci ( $F_{\text{neutral loci}} = F_{\text{selected loci}}$ )

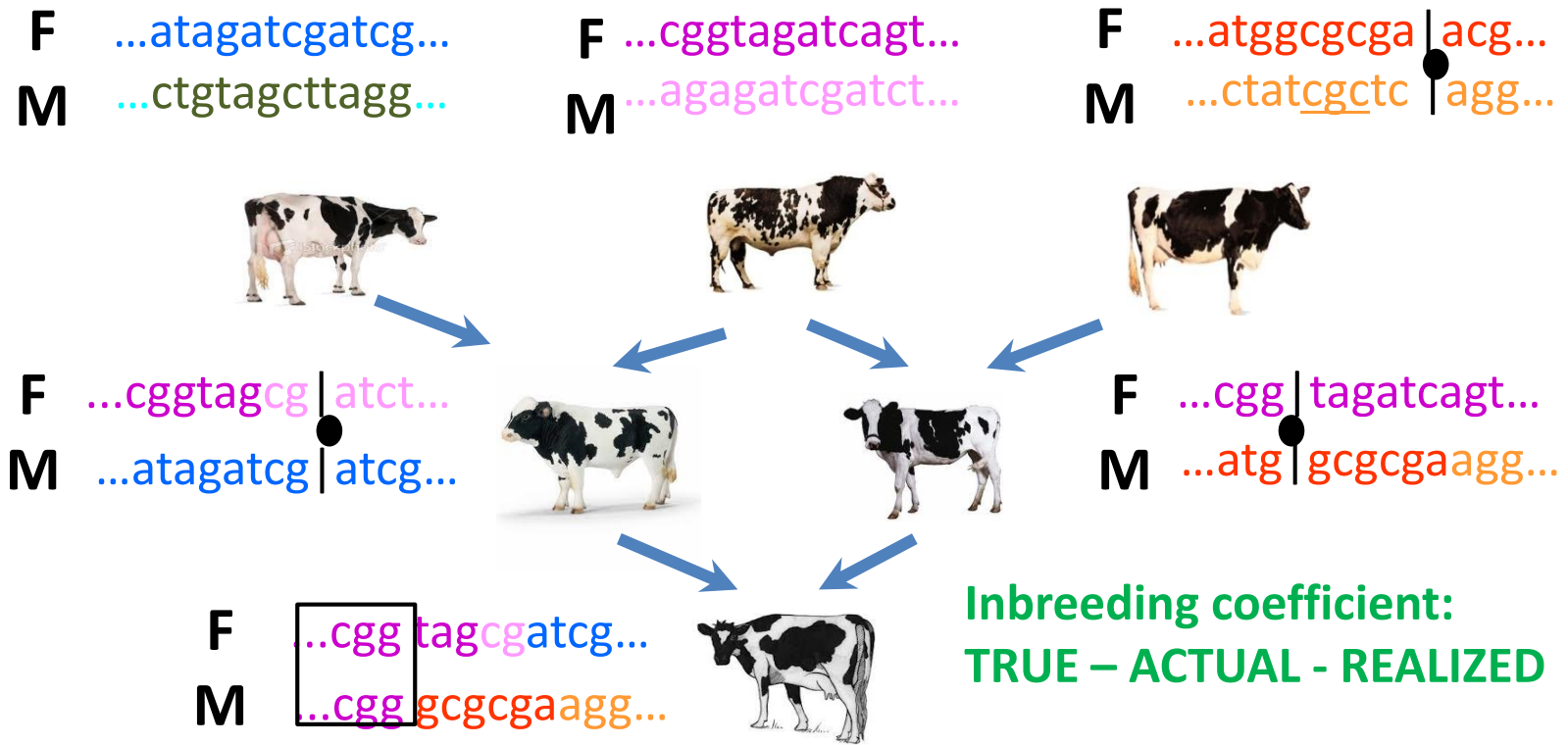
evenly distributed autozygosity across the genome



Relative measure with respect to the base generation

# ROH based inbreeding coefficient

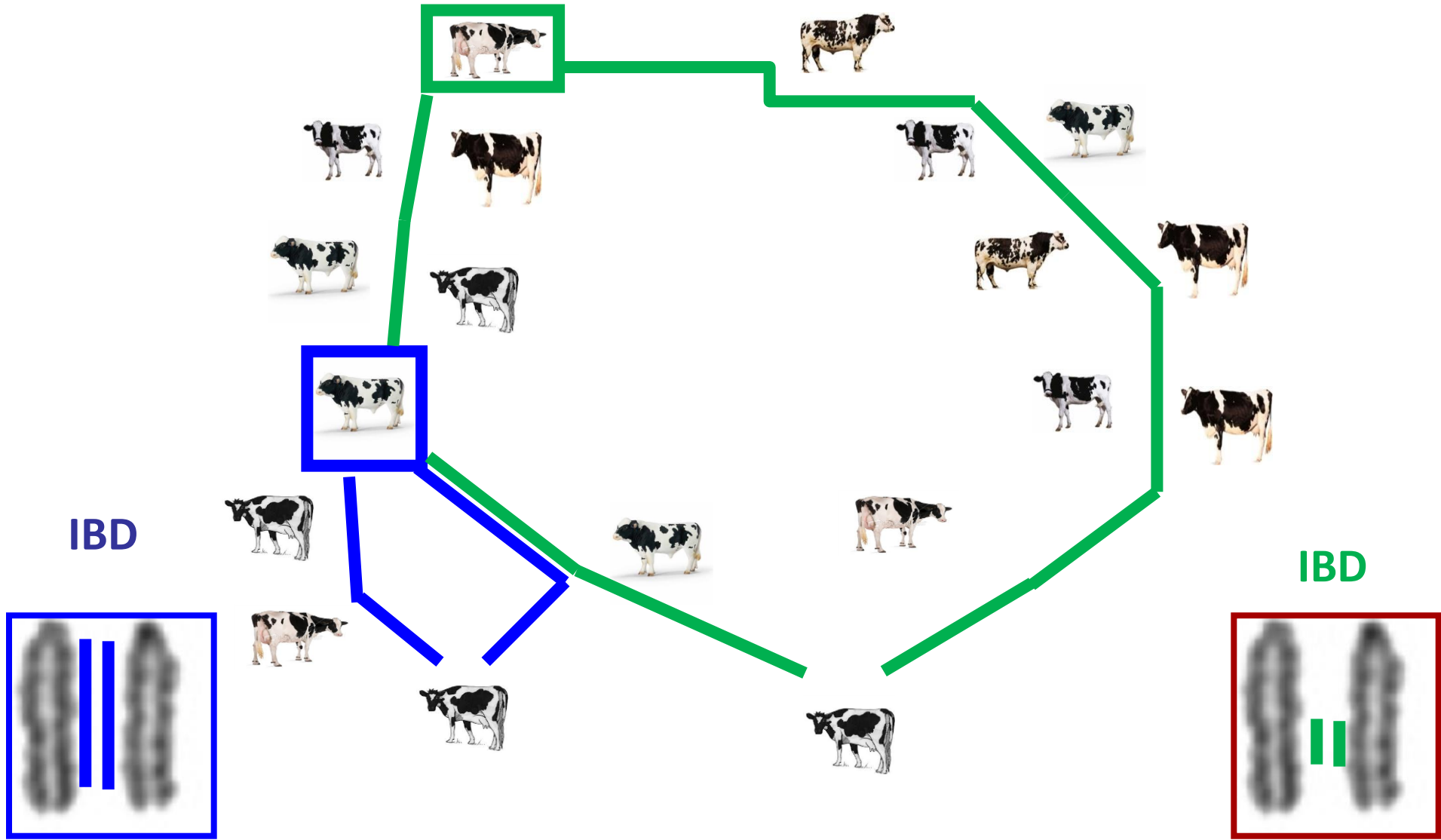
- **Humans** (McQuillan et al., 2008; Nalls et al., 2009)
- **Cattle** (Ferenčaković et al., 2011; Purfield et al., 2012; Ferenčaković et al., 2013)
- **Pig** (Bosse et al., 2012; Silio et al., 2013)



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

Longer IBD haplotypes  $\rightarrow$  more recent ancestors

Longer homozygous haplotypes  $\rightarrow$  higher IBD probability



# $F_{ROH}$

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

McQuillan  
et. al., 2008

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

$F_{ROH16>Mb}$

$F_{ROH8>Mb}$

$F_{ROH>4Mb}$

$F_{ROH>1Mb}$

$F_{ROH>2Mb}$

<50

**Generations**

<25

<12.5

<6

<3

0



>1Mb

**ROH length**

>2Mb

>4Mb

>8Mb

>16Mb

Relative measure with respect to the base generation

**Simulation:** Keller et al., 2011

**3-8 years**

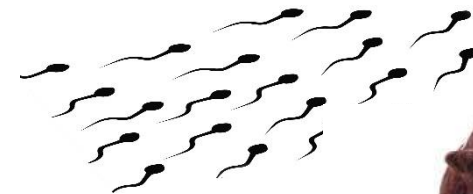
**Cattle:** Bjelland et al., 2013; Pryce 2014; Howard et al., 2015  
Curik et al., 2012 (4<sup>th</sup> ICQG, Edinburgh) → 2011-2016

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>  
© American Dairy Science Association®, 2017.



Austrian  
Simmental  
bull  
Austria

**2017**



# Univariate mixed models:

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



**Random effect:** bulls

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

Illumina Bovine SNP50 Beadchip  
19,720 ejaculates from 554 bulls



**Covariates:** **Inbreeding coefficients:**

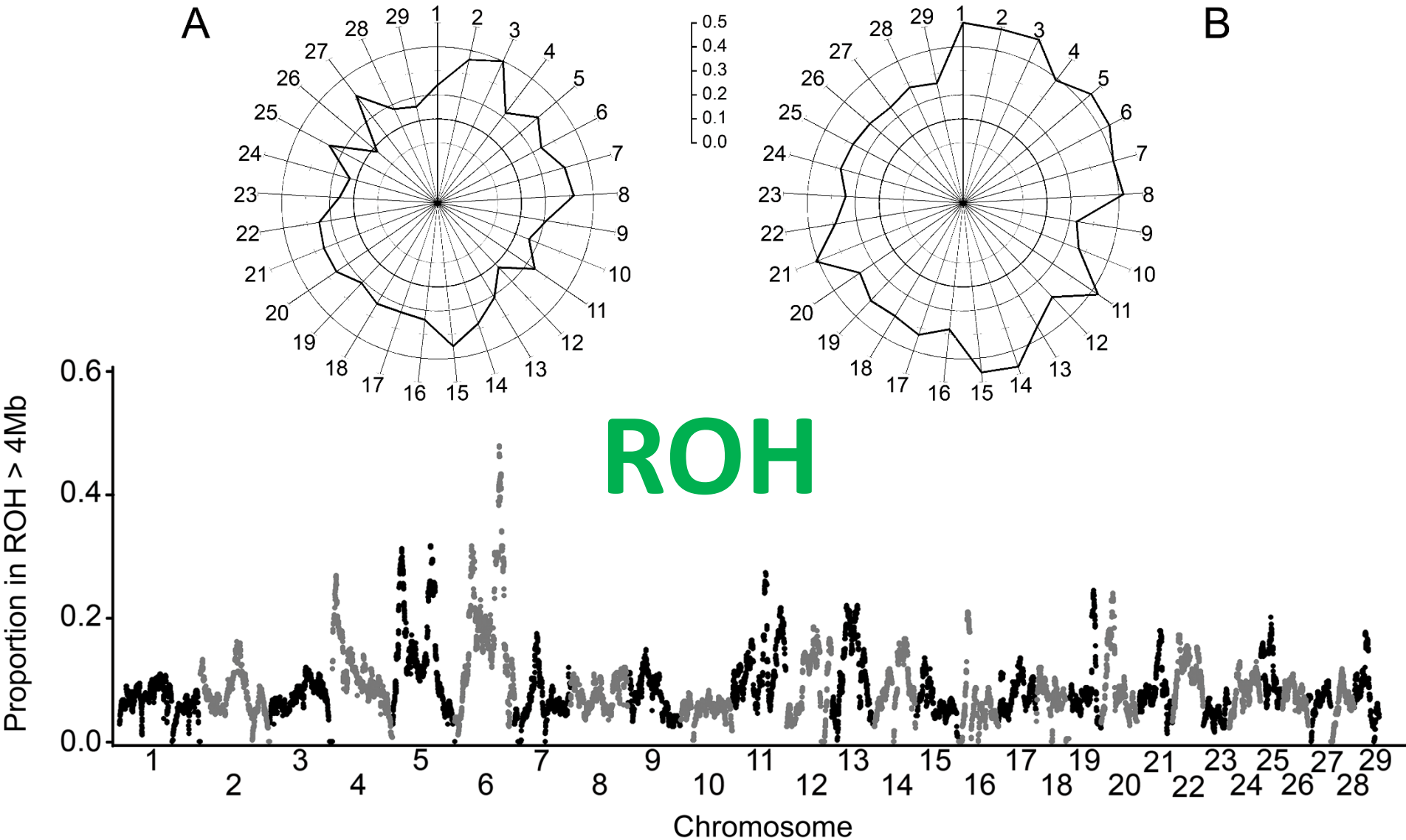
- $F_{PED}$ ,  $F_{PED5}$
- $F_{HOM}$  ( $F_{IS}$ ),
- $F_{ROH2-4Mb}$ ,  $F_{ROH>2Mb}$ ,  $F_{ROH>4Mb}$ ,  $F_{ROH>8Mb}$ ,  $F_{ROH>16Mb}$

# “Global” inbreeding depression: total number of spermatozoa

Inbreeding coefficient	Regression coefficient <sup>REML</sup> (SE)	$\Delta\text{AIC}^{\text{ML}}$ (43907.5)
$F_{\text{PED}}$	** <b>-5.80 (1.94)</b>	<b>0.0</b>
$F_{\text{ROH}2-4 \text{ Mb}}$	** <b>-11.40 (4.00)</b>	<b>0.8</b>
$F_{\text{ROH}>2 \text{ Mb}}$	* <b>-2.72 (1.22)</b>	<b>3.9</b>
<hr style="border-top: 1px dashed black;"/>		
$F_{\text{ROH}>4 \text{ Mb}}$	-1.91 (1.31)	6.5
$F_{\text{PED5}}$	-2.81 (2.03)	7.0
$F_{\text{ROH}>8 \text{ Mb}}$	-1.91 (1.51)	7.3
$F_{\text{IS}}$	<b>-0.49 (0.77)</b>	<b>8.5</b>
$F_{\text{ROH}>16 \text{ Mb}}$	-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)



## Univariate mixed models:

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

- percent of live spermatozoa (%)



**Random effect:** bull

**Fixed effects:** age of bull

month of collection

year of collection

days between successive ejaculates

semen collector

AI station

Illumina Bovine SNP50 Beadchip

19,720 ejaculates from 554 bulls

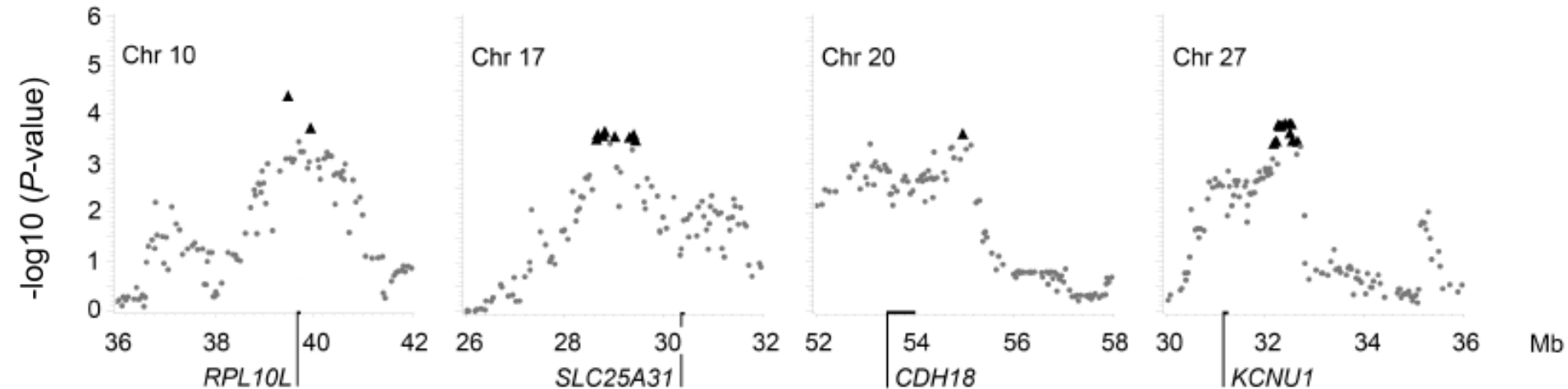


**Covariates:** **Additive effects; SNP (0, 1, 2)**

**ROH > 2 Mb effects; SNP (0, 1)**

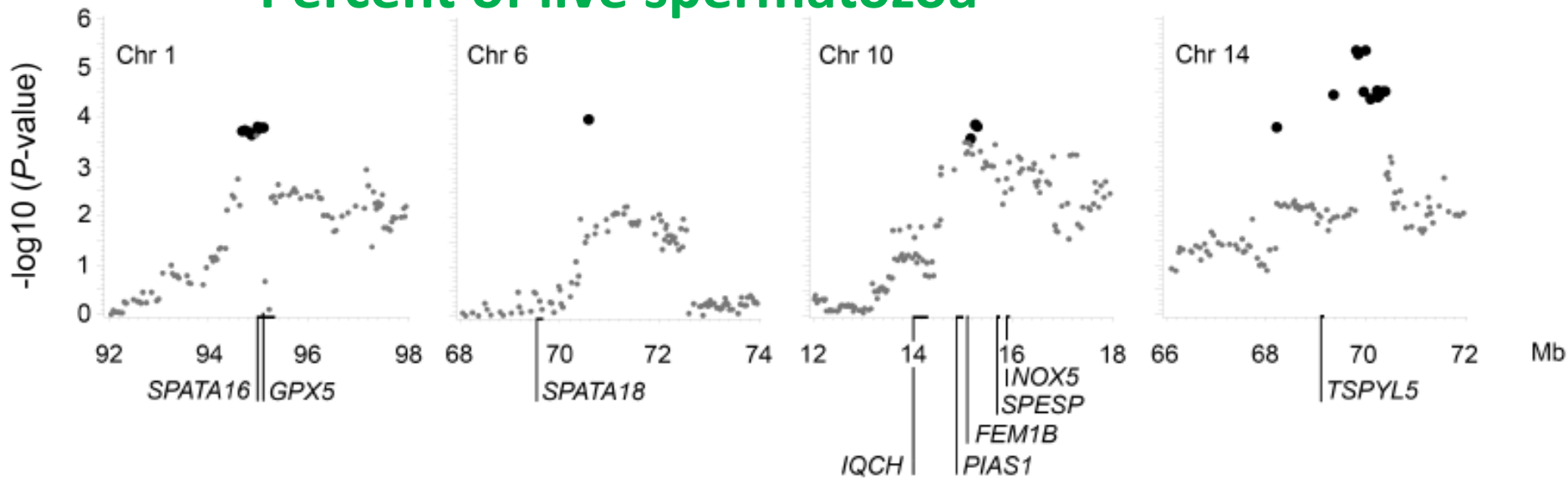
**Adjustment for multiple comparisons: Gao et al., 2008**

# The total number of spermatozoa



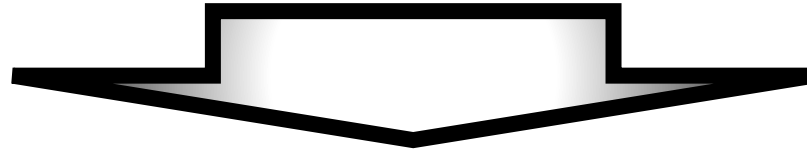
- **RPL10L**: helping to inactivated X-linked genes in spermatogenesis
- **SLC25A31**: sperm flagellar energy carrier protein
- **CDH18**: significant influence on sperm motility
- **KCNU1**: codes testis specific potassium channel

# Percent of live spermatozoa

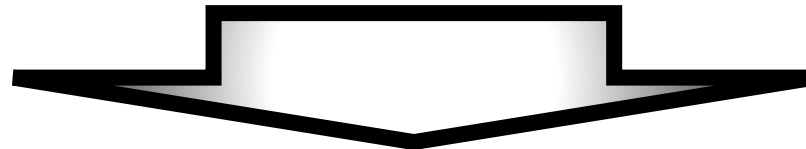


- **SPATA16**: associated with male infertility in humans
- **GPX5**: marker of boar sperm quality
- **SPESP1** : involved in the fusion of sperm with the egg plasma membrane
- **SPATA18**: encodes a so-called “mitochondrion-eating protein”
- **TSPYL5**: linked to male idiopathic infertility
- **NOX5**: 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

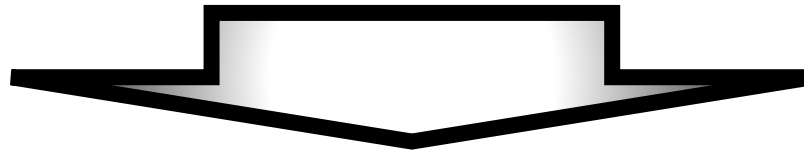


Identification of the causative mutations

In process ...

## 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	$a$	$d$	$-a$

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

$$\begin{aligned} \mu_F &= a(p^2+pqF) + d(2pq-2pqF) - a(q^2+pqF) = a(p-q) + 2pqd - 2pqdF \\ &= \mu_{HWE} - 2pqdF \end{aligned}$$

$$- 2pqdF$$



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

# Genomic dissection of inbreeding depression

Univariate mixed models: sperm quality



**Volume of ejaculate (ml)**

**Concentration of ejaculate (10<sup>9</sup>/ml)**

Illumina Bovine SNP50 Beadchip

8,756 ejaculates from 162 BS bulls

**Random effect:** bull

**Fixed effects:**

age of bull

month of collection  
year of collection

period between two successive ejaculates  
semen collector  
AI station

WOMBAT Home Page

[agbu.une.edu.au/~kmeyer/wombat.html](http://agbu.une.edu.au/~kmeyer/wombat.html)

**Covariates:**

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

**Dominance effects; SNP (0, 1, 0) → d**

$F_{ROH>4Mb} \rightarrow F$

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

# 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%

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

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

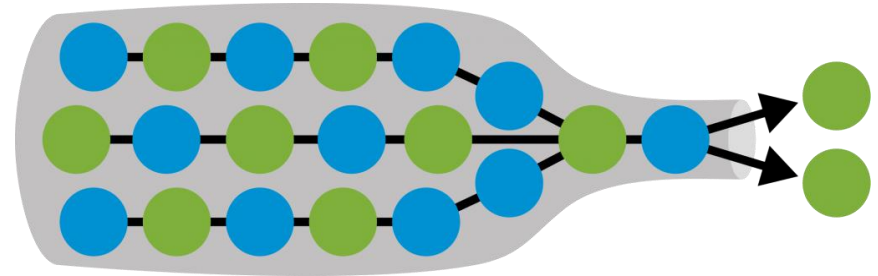
Still a number of problems to solve ...

- 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 (planned mating)
5. Purging mating strategy → genomic revision



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

*Hvala na pozornosti!*



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