

Livestock Biodiversity Workshop, FAO 5-6 May 2010

## Optimal strategies and tools for management of genetic variation

**Asko Mäki-Tanila** MTT Jokioinen Finland

**Miguel Toro** UPM Madrid Spain

Mäki-Tanila Toro

1

**Jesus Fernandez** INIA Madrid, Spain

**Theo Meuwissen** UMB Ås Norway

**Ihab Shaat & Ismo Strandén** / MTT

*Data from FABA Service / Anna Oksa & Jouni Laurila*

Mäki-Tanila Toro

2

Approach in two stages:

**- assessment of the present state (and history)**

useful parameters  
their estimation  
genomic tools

**- management to maintain variation**

methods (optimum contribution)  
cryopreservation

**Genetic variation**

- spectrum of alleles and genotypes in the population
- seen as in morphological, physiological and behavioural differences among the individuals



Most important type is quantitative variation in

- reproduction fitness (ability to evolve)
- production traits (ability to be genetically improved)

## DIRECT MEASURES OF VARIATION WITH GENOMIC TOOLS

1) Frequencies of alleles and genotypes

2) Proportion of polymorphic loci

*sequences: nucleotide diversity (no. SNP per kb)*

**3) OBSERVED HETEROZYGOSITY**

**4) EXPECTED HETEROZYGOSITY** (gene diversity)

*indicator for additive gen var in quantitative traits*

5) Allelic diversity

*determines long-term selection potential*

*sensitive to bottlenecks*

*maximising exp het → max allelic diversity*

*estimates biased by sample size*

### **F – coefficient of inbreeding of an individual**

probability that the two alleles at a locus are identical by descent  
(parents related)

### **f – coancestry coefficient**

probability that alleles from two individuals are identical by descent  
*with random mating*  $F_t = f_{t-1}$

Given different *virtual* alleles over loci in the base generation then  
in any cohort (age group, generation)

$$\text{exp het} = 1 - f$$

$$\text{obs het} = 1 - F$$

**real heterozygosity = (1 – F) x het in founder gen**

Parameters based on *pedigree* give with cheap costs

***Inbreeding coefficient related to mean  
Coancestry measures drift and changes in variance***

Inbreeding is unavoidable.

Populations with many generations of pedigree recording have high estimates for F

BETTER CONCEPT:

Proportional increment or ***rate of inbreeding***  $\Delta F = 1 / 2 N_e$

- stays constant over generations

- useful parameter for comparing populations (or phases in population history)

**Genomic tools provide direct measures on population diversity  
- why to bother about inbreeding and coancestry**

**We would need predictions or answers to questions**

***'what if...'***

***Analysis, predictions and control of changes in coancestry and  
inbreeding would yield holistic answers and tools***

## Reasoning $N_e > 50$ ( $\Delta F < 0.01$ )



### **amount and nature of available variation**

- new variation mutations ( $V_M$ ) vs losses in small populations  
 $h^2 = .33 (.50) \rightarrow N_e = 50 (100)$
- maintaining neutral alleles segregating (potential for future)
- not losing beneficial alleles  
negative pleiotropic effects increases variation
- harmful alleles  
mutation meltdown: fixation reduces overall fitness and repr rate and pop size

### **inbreeding depression**

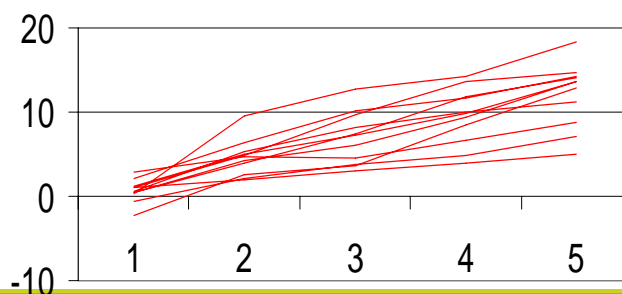
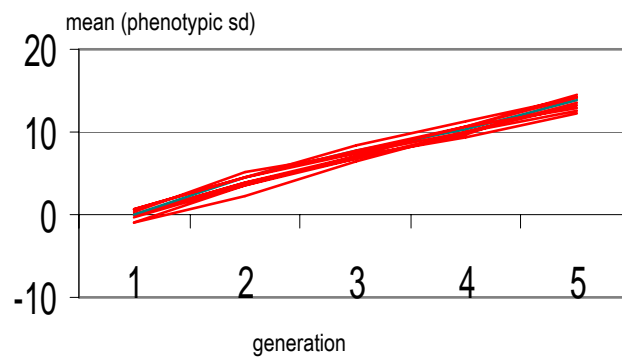
sufficient genetic variation for natural selection to balance reduced performance

### **certainty in achieving the predicted response**

Mäki-Tanila Toro

9

## Realisation of predicted change less certain in a small population



Strandén MTT

## estimation of $N_e$

- formulae are for predictive purposes (asymptotic in a regular system)  
rather than analysing realised genealogies

Estimation of proportional increment of inbreeding level  $F$

$$\Delta F = \frac{F_t - F_{t-1}}{1 - F_{t-1}}$$

or similarly we could compute the changes in coancestry (or  $\frac{1}{2}$  additive relationship)  
(more stable and gives early signals about undesirable trends)

→ we need **pedigree information**

**separation of generations and the intervals between  
inbreeding coefficients  $F$**

(or pairwise coancestry of two individuals or relationship matrix  $A$ )

**lots of methods to compute  $F$**

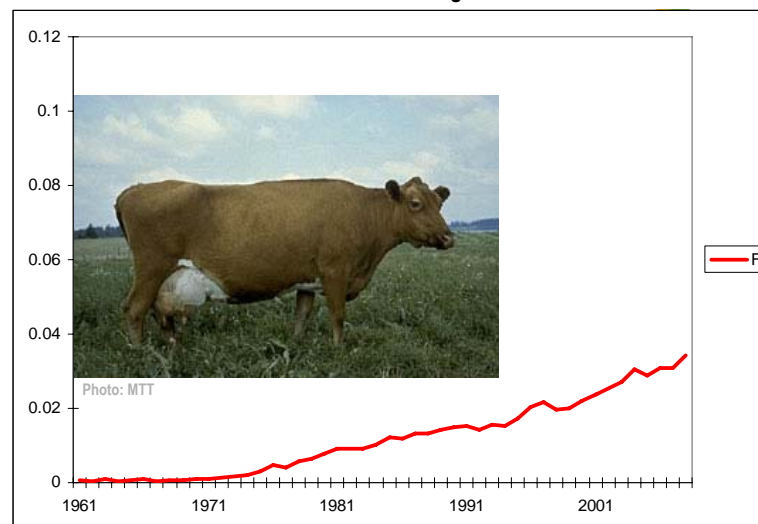
Wright's path method (Colleau, GENUP, PEDIGREEVIEWER)

tabular method (used in BLUP; e.g. Meuwissen;  $A$  given by EVA, ENDOG, PEDIG)

other methods: contribution, gene dropping

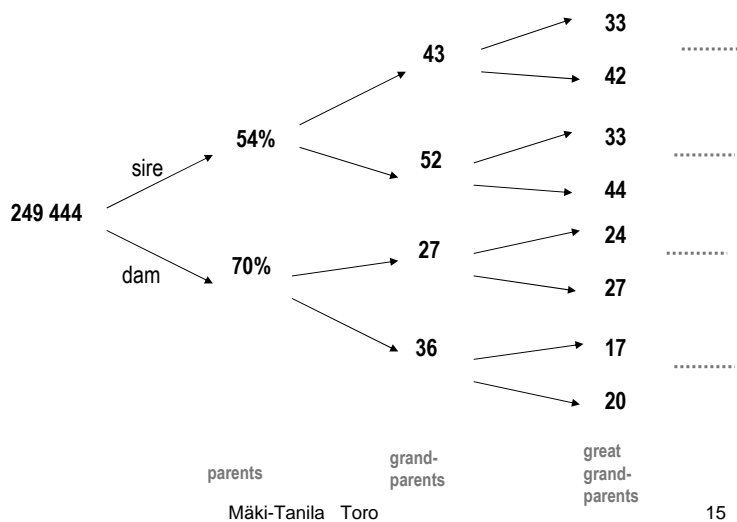
**easy to compute → often the only parameter presented**

**Western Finncattle – level of inbreeding**



information over  $\geq 3$  equivalent generations,  $N_e$  varies 50-1300 – harmonic mean over gen's 171

## Pedigree completeness in Western Finncattle



## Regression methods

### - overlapping generations and shallow pedigrees

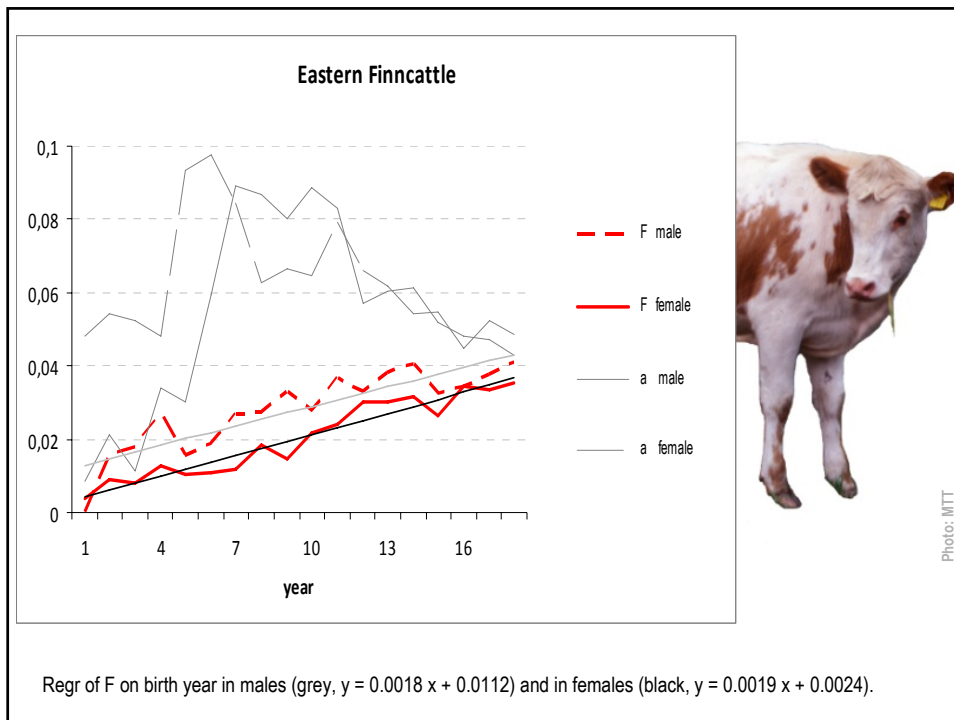
Because at generation  $t$  the level of inbreeding is  $F_t = 1 - (1 - \Delta F)^{t-1} = 1 - (1 - 1/2N_e)^{t-1}$


1)  $N_e$  is log regr of  $(1 - F_t)$  on birth date / generation interval (Perez-Enciso 1995)

2) for individual  $i$  we have  $\Delta F_i = 1 - {}^{t-1}\sqrt{(1 - F_i)}$

and average  $N_e = 1 / 2$  average  $\Delta F$  (González-Recio et al 2007; Gutiérrez et al 2009))

**For Western Finncattle 1)  $N_e = 89$  and 2)  $N_e = 109$**





no genealogical information

*'Tourists cuddle the cows and take photos of the animals;  
the neighbours don't mind our cows running into their backyard'*

Mäki-Tanila Toro

18

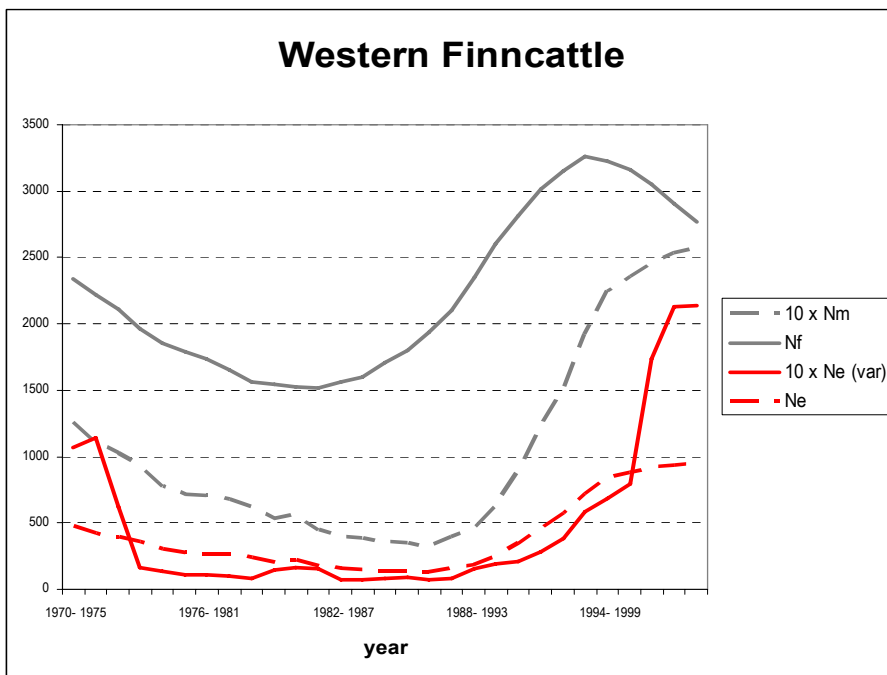
Consider the demographic information  
- number of male ( $N_m$ ) and female ( $N_f$ ) parents

$$N_e = \frac{4 N_m N_f}{N_m + N_f}$$

The small male number determines the effective size  
- *especially number of AI bulls*

Some parents have more offspring than others because of better performance (selection) or popular breed features, etc. Essentially we have less parents and have to consider **variation in progeny number**

### Western Finncattle



In **selected populations**, effective population size is further reduced because superior parents contribute more offspring to the next generation than average parents and a part of the effect of selection persists in the subsequent generations.

Robertson (1961)  
recent review by Nomura (2005).

Gutierrez & Goyache (2005) JABG 122: 172-176 **ENDOG**  
[http://www.ucm.es/info/prodanim/html/JP\\_Web\\_archivos/endog45.zip](http://www.ucm.es/info/prodanim/html/JP_Web_archivos/endog45.zip)

Groeneveld et al EAAP Barcelona Session 13, Poster 22 **POPREP**  
<http://poprep.tzv.fal.de/cgi-bin/entry.pl>

Strandén & Vuori (2006) 8th WCGALP **RelaX2**  
[lsmo.Stranden@mtt.fi](mailto:lsmo.Stranden@mtt.fi)

## Genomic tools

### 1) estimation of $N_e$

- measures of heterozygosity at two time points
- changes of allele frequencies over time (drift)
- linkage disequilibrium (drift)

### 2) molecular vs genealogical analysis

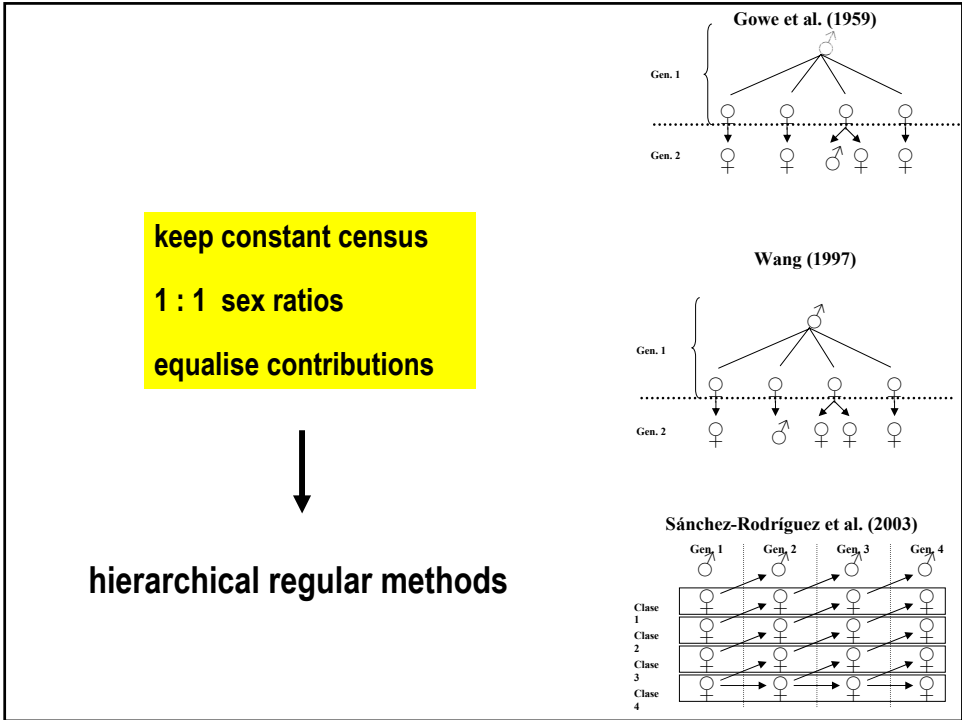
- paternity analysis (few markers)
  - coancestry for individuals without pedigree information
  - genomic relationship matrix
- hundreds or thousands of markers



## Management of genetic variation

- maximising effective population size  $N_e$

*'Farmers with real passion for the breed choose to support biodiversity and opt for high-quality products and low environmental impact'*



**let us minimise coancestry !!!**

⇒ from pedigrees or from markers

Mäki-Tanila Toro 26

OPTIMAL  
CONTRIBUTIONS  $c_i$

- overrepresented individuals are penalised
- loosely related individuals are favoured

Ballou & Lacy (1995)

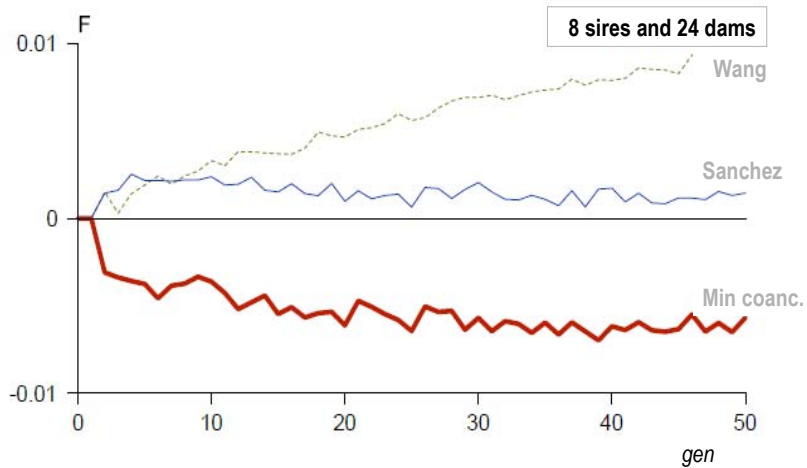
$$\min \sum_{i=1}^N \sum_{j=1}^N c_i c_j f_{ij}$$

- equalises ancestral contributions
- maximises  $N_e$  (minimises  $\Delta F$ )
- maximises gene diversity (exp. het.)
- flexible and robust

deviations

- in mating scheme
- no. progeny

(Fernandez et al 2003)



## Selection to maintain/improve the performance

*'I don't want to live like Robinson Crusoe; my cows are production animals, not pets'*

## OPTIMAL CONTRIBUTIONS $c_i$ (Wray & Goddard 1994, Meuwissen 1997)

For breeding values  $\max \left( \sum_{i=1}^N c_i EBV_i \right)$

and constraining the increases in average coancestry ...

$$\min \left( \sum_{i=1}^N \sum_{j=1}^N c_i c_j f_{ij} \right)$$

*How much genetic gain does it cost: none - can achieve >30% more gain at equal  $\Delta F$*

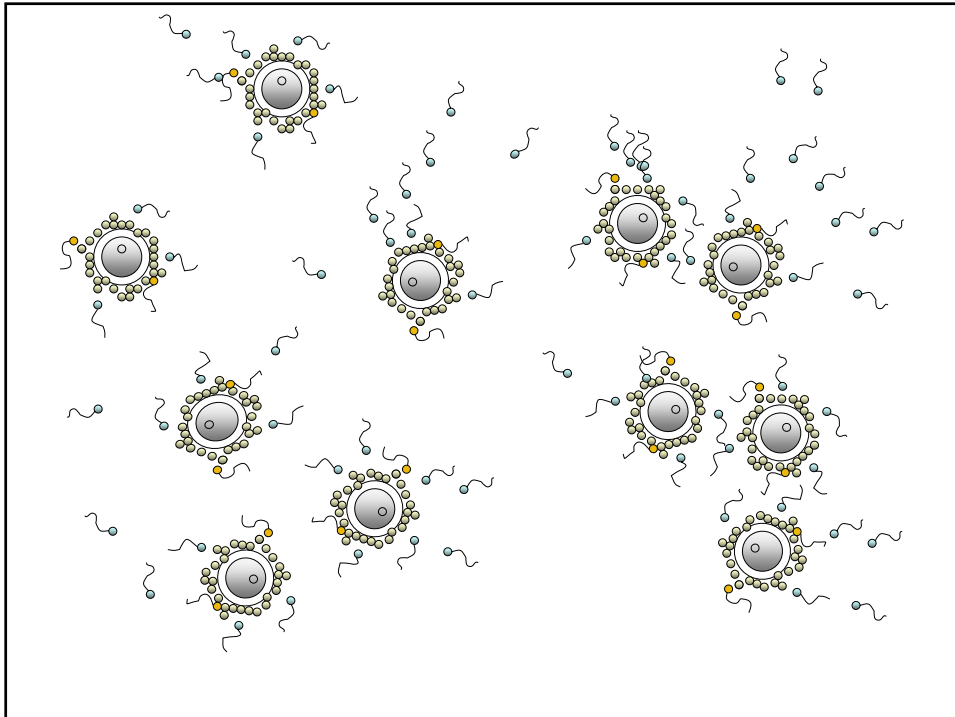
## Genetic management

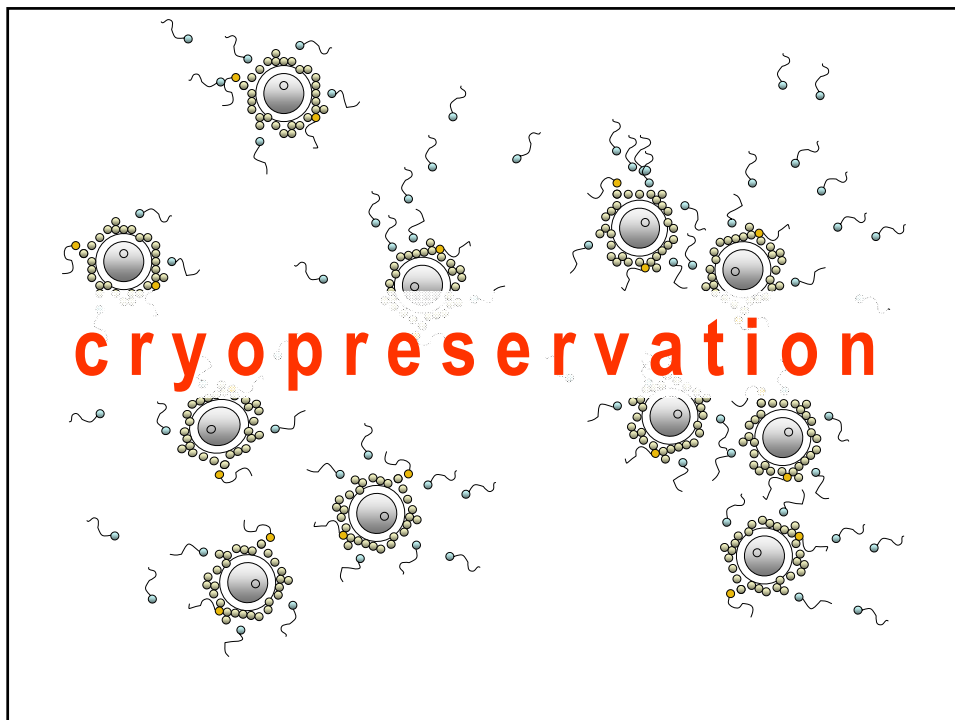
two decisions to take:

- *which individuals reproduce?*
- *how they mate?*

mating less important than selection

*little margin for improvement*





Cryopreservation is a very useful tool in the management of genetic variability, and has several advantages:

- 1) enlarges the population size – use of post-reproductive individual animals
- 2) reduces drift
- 3) longer generation interval - undesirable effect on annual genetic gain
- 4) 'back-up' for the genetic constitution (after some catastrophic events)

## Aim of semen bank

- Store a back-up population that conserves ancestral variation as much as possible



- Using **optimum contribution** language:
  - **consider only males as candidates**
  - **minimise A of stored semen**
  - **add to existing contributions of males to bank**  
*adapt current contribution to existing bank*
  - **no overlapping gen's: set up one back-up population**

## RECAPITULATING



- understanding and management of genetic variation should be integrated in the development and utilisation of breed diversity.
- census and pedigree recording are important.
- state of genetic variation is best expressed by the *rate of inbreeding* ( $\Delta F$ ) rather than the level of inbreeding.
- when molecular and genomic information is compared with genealogical information, it turns out that:
  - small number molecular markers are not very useful (only for paternity);
  - genomic information may soon replace pedigree information;
  - genomic and pedigree analyses have different time perspectives.



## RECAPITULATING ...



Management of genetic variation aims to maximise  $N_e$  (minimise rate of inbreeding)

- choosing parents is more important than mating strategies
- optimal methods, such as OC selection, are the best tools for management of genetic variation, but require expertise - *simple hierarchical methods could be used first*
- cryopreservation is a cost-efficient back-up for genetic variation.
- software exists for analysis and management of genetic diversity

