Simulating experimental designs to compare and select methods based on linkage disequilibrium (LD) and linkage analysis (LDLA) for studying osteochondrosis in horses.

Simon Teyssèdre[1] F. Ytournel[2] M-C. Dupuis[3] J-M. Denoix[3]
G. Guérin[4] A. Ricard[1] J-M. Elsen[1]

[1]INRA (Toulouse), France
[2]University of Goettingen, Germany
[3]ENVA, CIRALE, France
[4]INRA (Jouy en Josas), France

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simon.teyssedre@toulouse.inra.fr

Outline

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Problem

- Objectives of the program GENEQUIN :
  - To Identify the genes underlying the affection of osteochondrosis.
  - To Obtain case/control data on 600 French trotters.
  - Half-sib design with approximately 100 sires.

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  - At the middle of the program, we got some fathers with only 1 offspring and others with a lot of offsprings.
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- Questions about this program :
  - Should we add new sire families or should we increase the size of offsprings in those families with 1 offspring ?
  - Are the associations (LD) and LDLA methods robust for these designs ?

Objectives

Definitions :

- Population structure : Historical structure of the population, can be with low or high inbreeding.
- Design : Recent structure of the population, here we talk about half-sib designs.

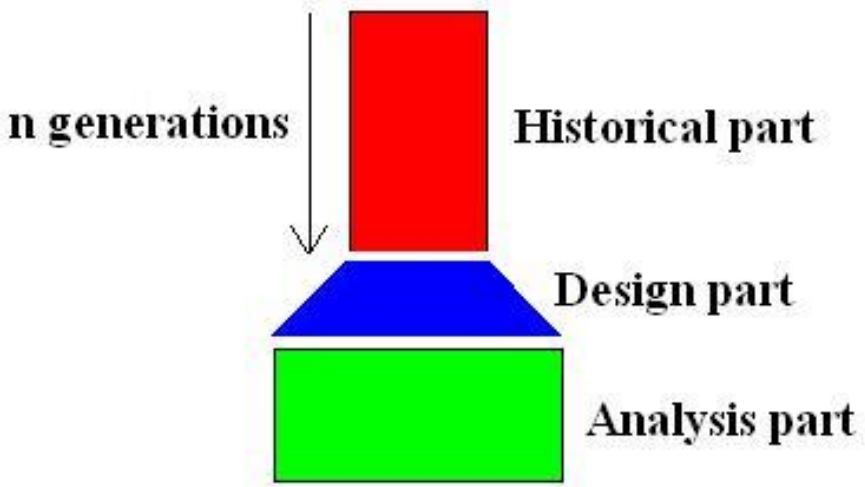
We will run simulations with the following objectives :

- Given a population structure, are LD/LDLA methods robust under different designs ?
- How do methods deal with the problem of population structures ?

Outline

Simulations

- Historical part : 2 different scenarios
  1. Inbreeding $+$, LD $+$.
  2. Inbreeding $-$, LD $-$.



- Number of simulations : 100
- Number of markers : 1000
- Number of QTL : 0
- Chromosome length : 1 Morgan

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- Historical part : 2 different scenarios
  1. Inbreeding $+$, LD $+$.
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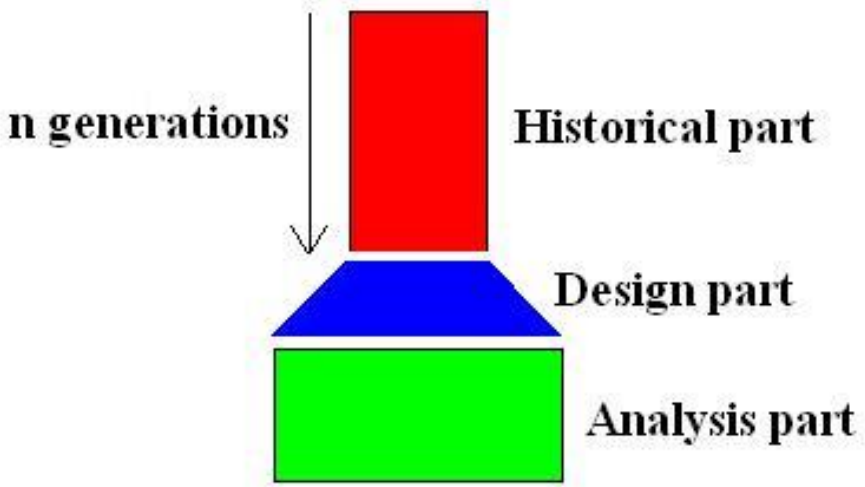
- Design part : 3 different scenarios
  1. Design10 : 600 offsprings born to 10 sires.
  2. Design60 : 600 offsprings born to 60 sires.
  3. Design600 : 600 offsprings born to 600 sires.



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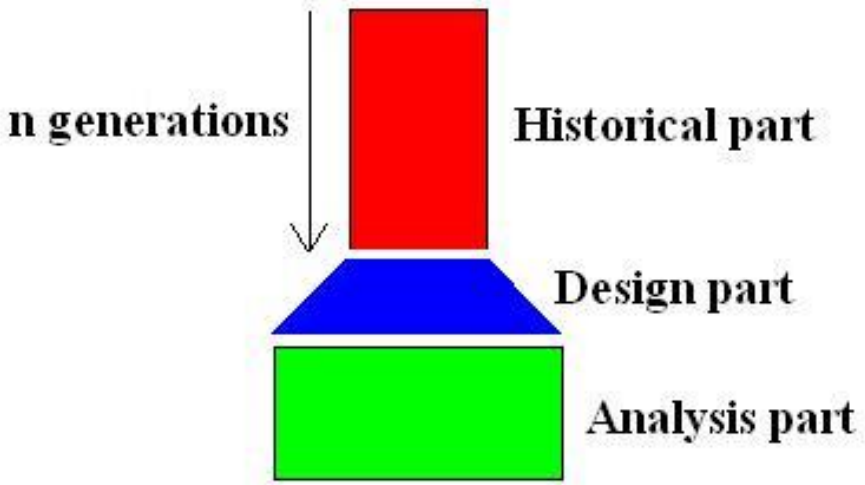
- Analysis part : 4 different methods



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Choice of methods

We tested 4 different methods (all are single SNP analysis) :

1. Simple regression
2. PCA analysis (Price & al, Nature, 2006)
3. QTDT analysis (Abecasis & al, Am J Hum Genet, 2007)
4. GRAMMAR (Aulchenko & al, Genetics, 2007)

Decision rules :

1. Classic (5%), number of p-values $< 5\%$
2. False Discovery rate (FDR,5%), corrected for multiple tests (Benjamini-Hochberg, J.R. Statist. Soc. 1995).

Tools used for the simulations

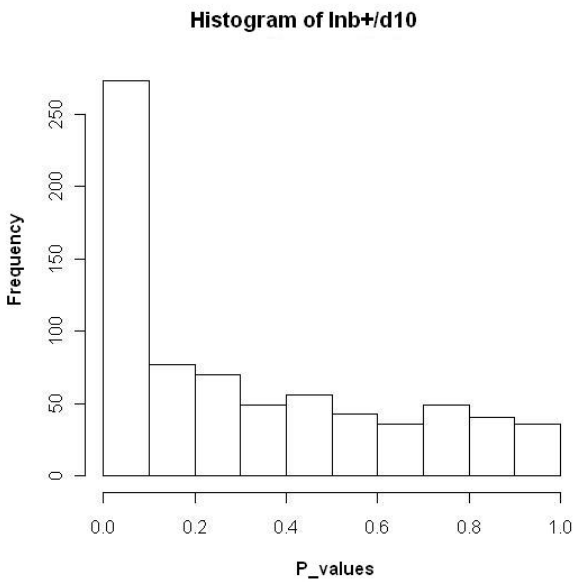
1. Historical part : Linkage Disequilibrium with Several Options (LDSO, F.Ytournel 2008)
   - Developed to generate data for QTL mapping.
   - Simulates the history of a single or two populations.
   - Takes into account the evolutionary forces (mutation, selection and bottleneck).
2. Design part : Extension of LDSO to pedigree
   - Genotypes and phenotypes created (historical part) from LDSO are integrated into the founders of the pedigree.
3. Analysis part : Package GenABEL (R, Y.Aulchenko 2008)
   - Quality check, Genomic relationship matrix, polygenic effect
   - Different methods based on linkage disequilibrium

Outline

What about regression ?

	Inbreeding +			Inbreeding −		
Number of sires	10	60	600	10	60	600
FDR (%)	7.3	3.1	4.0	1.9	0.1	0.1
Classic (%)	25	–	–	–	–	8

- Strong effect of population structure.
- Strong effect of population design for a small number of sires (10 vs 60).



And the others methods...

	Inbreeding $+$, $d10$		Inbreeding $-$, $d600$	
False positives (%)	FDR	Classic	FDR	Classic
Regression	7.3	25	0.1	8
PCA	5.9	23	0.1	8
GRAMMAR	0	0.9	0	1.8
GRAMMAR + GC	0.1	5	0	5
QTDT	0.02	5	0.002	4.9

- PCA : ($\approx$ Regression), number of markers too low to distinguish several groups in the PCA.
- GRAMMAR : The distribution of p-values is not uniform and is very conservative.
- GRAMMAR + GC : Distribution of p-values appears to follow a uniform law after correcting by Genomic control.
- QTDT : Same as GRAMMAR+GC without genomic control.

Outline

Discussion & On going

Discussion :

- Deviation from p-values distribution of a uniforme law appears to be closely related to the occurrence of false positives (the statistical test doesn't follow a χ^2).
- Difficulty of methods to remain robust when there is inbreeding.

On going :

- More simulations with more markers.
- Simulations with QTL(s) to test the power of methods.

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Thank you for your attention !