State of the Art of Genomics for Selection

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After Human (2001) and Mice, WGS of the chicken (2004), the dog (2005), bovine (2006), horse (2007), pig (2009), ...

 Entirely in the public domain

 Sequencing of different individuals => polymorphisms discovery :

  ➢ 3.2 million bovine polymorphisms in dbSNP
  ➢ probably >10 million known today

 New technologies for genotyping and sequencing
SNP : Single Nucleotide Polymorphism

DNA Variation of one base

..GAATCTTATGCTATACATAATTATATACCTAATCGGGTATTGTTCTTAT..  
..GAATCTTATGCTATACATAATTATATACCTAATAGGGTATTGTTCTTAT..
Genotyping chips

- Miniaturized device for the simultaneous genotyping of many SNP
- From few dozens up to several million SNP
- Two main technology providers, Illumina and Affymetrix
- Illumina products in cattle
  - 3000 (6500=LD), **54 000=50k**, 777 000=HD
Exemples of information provided by markers

1) Trace transmissions

2) Measure relationships

3) Measure inbreeding
Example of application: mapping recessive defects

- A defect is rare and originates from one unique mutation
- It is recessive, therefore the affected animals carry two copies of the mutation
- Affected animals are also homozygous for the DNA segment surrounding the mutation
Results based on a few affected animals

BTA13

Log(1/P)

0 1 2 3 4 5

0 20 40 60 80
Genomic selection

Selection based on the prediction of breeding values from the information of dense markers covering the whole genome

Prediction of Total Genetic Value Using Genome-Wide Dense Marker Maps

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How it works?

- **Reference Population**
  - Population with both phenotypes and genotypes
  - Analysis of the genotype – phenotype associations
  - Estimation of marker effects

- **Population of candidates for selection**
  - Population with the same associations
  - Genotypes
  - Prediction of the breeding value by using marker effects estimated in the reference population
Factor of variation of GS efficiency

- Two big factors:
  - Accuracy of SNP effect estimation
    - size of reference population
    - heritability
  - LD between markers and QTL
    - marker density
    - effective size of the population => number of « indépendants » segments
    - Relationship between the candidates and the reference population

- Statistical Methods
A number of methods used

1. G-BLUP: in the conventional BLUP, replace the pedigree based relationships by the marker based relationships

2. Bayesian Methods (Bayes B, C, R …): tries to find the SNP in association with QTL and to give a zero value to most SNP without effect
Comparison of methods

• Marker Density
  • low => little differences between GBLUP and Bayesian methods, accuracy low to moderate
  • high => saturation of efficiency of GBLUP, whereas Bayesian approaches increase in accuracy

• Genetic Determinism
  • polygenic: some advantage to GBLUP
  • at least partially oligogenic: advantage to Bayesian methods
SNP or Haplotypes?

- Most work with individual SNP
- Loss of efficiency due to incomplete Linkage Disequilibrium
- Personal point of view: a haplotype with 8-15 alleles is much more informative
SNP or Haplotypes?

• In France, a method based on haplotypes of 3-6 markers
• 300-700 regions targeted on the genome, for each trait
• QTL-BLUP, including a residual polygenic effect

\[ y_i = \mu + u_i + \sum_j (h_{ij1} + h_{ij2}) + e_i \]

<table>
<thead>
<tr>
<th></th>
<th>Milk</th>
<th>Protein</th>
<th>Fat</th>
<th>Protein content</th>
<th>Fat content</th>
<th>Fertility</th>
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<tbody>
<tr>
<td>BLUP</td>
<td>0.38</td>
<td>0.44</td>
<td>0.40</td>
<td>0.47</td>
<td>0.44</td>
<td>0.29</td>
</tr>
<tr>
<td>GBLUP</td>
<td>0.56</td>
<td>0.55</td>
<td>0.59</td>
<td>0.73</td>
<td>0.72</td>
<td>0.35</td>
</tr>
<tr>
<td>QTL-BLUP</td>
<td>0.60</td>
<td>0.57</td>
<td>0.66</td>
<td>0.73</td>
<td>0.81</td>
<td>0.39</td>
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</table>
Reference populations

- Individuals with performances or EBV
- Focus on progeny tested bulls, because of their high reliability
- Probably more females in the future

- Figures in France
  - 18,300 in Holstein (EuroGenomics Consortium)
  - 1,800 in Montbéliarde
  - 1,300 in Normande
Major consequences of genomic selection

• High reliability ($R^2 = 0.5$ to $0.7$)
• At a early age, before any performance of the candidate
• For all traits (depends only on the reference population)
  => More balanced genetic trend
  A fantastic opportunity to improve functional traits

⇒ Use of bulls without progeny test

  note they will get progeny based EBV, but later
  => Maintaining performance recording is essential !!!
Massive use for females

• Same reliability ($R^2 = 0.5$ to $0.7$) for females as for males
• New possibility for within herd selection, for customized breeding objective
  • use of a wide range of males
  • selection of the best cows + increased prolificacy
  • embryo transfer, sexed semen
• A large proportion of genotyped cows if the cost is reasonable
• A low cost implies 1) large volumes, 2) a low chip (3 -> 6k)
Major consequences of genomic selection

• A nearly doubled potential genetic trend
  • due to a reduced generation interval, combined with a good accuracy and an increased selection intensity

• A more balanced genetic trend
  • due to a rather homogeneous reliability across traits and EBV available for all animals
  • due to an increase in weight for functional traits in the breeding objective (no increased selection pressure for production)

• Possibly, a lower inbreeding trend, if many young bulls are used
Changes in breeding practices

• **REF**: GS for preselection, and progeny test
• **AXMAX**: only young bulls, every young bull also bull sire
• **AXMIX**: 50% AI by young bulls, 50% by older bulls with progeny information

⇒ Stop progeny test
⇒ Don’t use bulls when they have progeny information (in competition with their sons and even grandsons...)

(Colleau et al, 2009)
### The French situation in 2010

#### 669 young bulls marketed in 2010

<table>
<thead>
<tr>
<th>Breed</th>
<th>Bull category</th>
<th>Number</th>
<th>Doses par bull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montbéliarde</td>
<td>Young</td>
<td>141</td>
<td>1600</td>
</tr>
<tr>
<td></td>
<td>Progeny tested</td>
<td>35</td>
<td>14000</td>
</tr>
<tr>
<td>Normande</td>
<td>Young</td>
<td>161</td>
<td>1200</td>
</tr>
<tr>
<td></td>
<td>Progeny tested</td>
<td>25</td>
<td>12700</td>
</tr>
<tr>
<td>Holstein</td>
<td>Young</td>
<td>367</td>
<td>2330</td>
</tr>
<tr>
<td></td>
<td>Progeny tested</td>
<td>107</td>
<td>15800</td>
</tr>
</tbody>
</table>

(Institut de l’Elevage)
## Mean EBV (genetic standard deviations)

<table>
<thead>
<tr>
<th>Breed</th>
<th>Bull category</th>
<th>Total merit</th>
<th>Dairy traits</th>
<th>SCC</th>
<th>Fertility</th>
<th>Longevity</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montbéliarde</td>
<td>Young</td>
<td>1,8</td>
<td>1,4</td>
<td>0,3</td>
<td>-0,1</td>
<td>0,7</td>
<td>0,8</td>
</tr>
<tr>
<td></td>
<td>Progeny tested</td>
<td>1,7</td>
<td>1,4</td>
<td>0,2</td>
<td>0,1</td>
<td>0,3</td>
<td>0,9</td>
</tr>
<tr>
<td>Normande</td>
<td>Young</td>
<td>1,5</td>
<td>1,5</td>
<td>0,2</td>
<td>0,1</td>
<td>0,6</td>
<td>0,3</td>
</tr>
<tr>
<td></td>
<td>Progeny tested</td>
<td>1,8</td>
<td>1,4</td>
<td>0,8</td>
<td>0</td>
<td>0,4</td>
<td>0,6</td>
</tr>
<tr>
<td>Holstein</td>
<td>Young</td>
<td>2,7</td>
<td>1,8</td>
<td>0,6</td>
<td>0,2</td>
<td>1,2</td>
<td>1,8</td>
</tr>
<tr>
<td></td>
<td>Progeny tested</td>
<td>2,2</td>
<td>1,8</td>
<td>0,5</td>
<td>-0,1</td>
<td>0,3</td>
<td>1,3</td>
</tr>
</tbody>
</table>

(INRA - Institut de l’Elevage)
A challenge for the short term: combine breeds

• Share reference populations
• Share cost, solution for smaller breeds, increase overall efficiency, maintain solidarity, only solution for new traits difficult to record
• The trick: adapt the marker density to across breed LD, by using a High Density chip

⇒ A third kind of population for imputation, in addition to candidates and reference populations
A challenge for the short term: combine breeds

Within breed:
- Long segments (300-400kb)
- Medium marker density

Across breeds:
- Short segments (10-20kb)
- High marker density
Multi breed evaluation

Gembal project: 5000 animals genotyped in HD (beef and dairy)

- Breed A
  - Reference Population
  - Candidates

- Breed B
  - Reference Population
  - Candidates

- Breed C
  - Reference Population
  - Candidates

- 777k (or sequencing)
- 54k
- 50k or lower density
And about sequencing?

- Very rapid technological developments!
- Sequencing corresponds to the complete genotyping of all mutations (5 to 10 million?)
- Use with the same principles as HD chip: sequence a limited number of animals, impute missing information in the rest of the population

- What evolution if sequencing is as cheap as genotyping?
Another challenge: select for new traits

- Generate the corresponding reference populations
- Several (tens of) thousand animals
- Female population, with own performances
- Taking advantage of the large scale genotyping
- Economic model: who pays for these data?
- New consortia: breeding company – performance recording organizations - farmers
Another challenge: select for new traits

- New phenotypes:
  - animal health: metabolic diseases, trimming data, paratuberculosis
  - milk quality: fatty acids, individual proteins
  - carcass quality: data from slaughterhouse
  - meat quality,
  - environmental footprint (methane emission), feed efficiency
  - heat detection,
  - behaviour....
In conclusion

• A revolution for dairy cattle !!!
• Potential genetic trend nearly doubled !
• Need to revisit completely the management of selection
   => large scale genotyping for a strong selection pressure
   => stop progeny test, use of many young bulls and bull sires
• An opportunity for functional traits, with a good reliability in spite of their low heritability
• An opportunity for new traits (milk composition, health…), as far as the phenotypes are collected for several thousand of cows
• A possibility of within herd cow selection and the only way to replace the reference populations
Collaborators and sponsors

<table>
<thead>
<tr>
<th>INRA</th>
<th>UNCEIA</th>
<th>LABOGENA</th>
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<tbody>
<tr>
<td>J.J. Colleau</td>
<td>A. Baur</td>
<td>M.N. Rossignol</td>
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<td>P. Croiseau</td>
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<td>T. Druet (^{(1)})</td>
<td>C. Hoze</td>
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<td>D. Boichard</td>
<td>L. Journaux</td>
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</table>

(1) Now at Liège
(2) Now at Illumina
(3) INRA & Institut de L'Elevage