Incorporating biological information into genomic prediction models

Andrea Rau, Fanny Mollandin, Pascal Croiseau

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VistaMilk

Artificial Intelligence in Agriculture Masterclass @ Zoom

February 8, 2023

INRAE Research Center @ Jouy en Josas:

- ✓ 1500+ staff
- ✓ Animal biology, microbiology, data science, systems biology

Animal Genetics & Integrative Biology (GABI) unit

- ✓ Understanding & exploiting animal genetic variability
- ✓ Construction of phenotypes and their interaction with microbial ecosystems and environments
- ✓ Agroecological transition

Genomic selection overview

Objective: select the best animals for reproduction to obtain **genetic improvement** of the population on **traits of interest**

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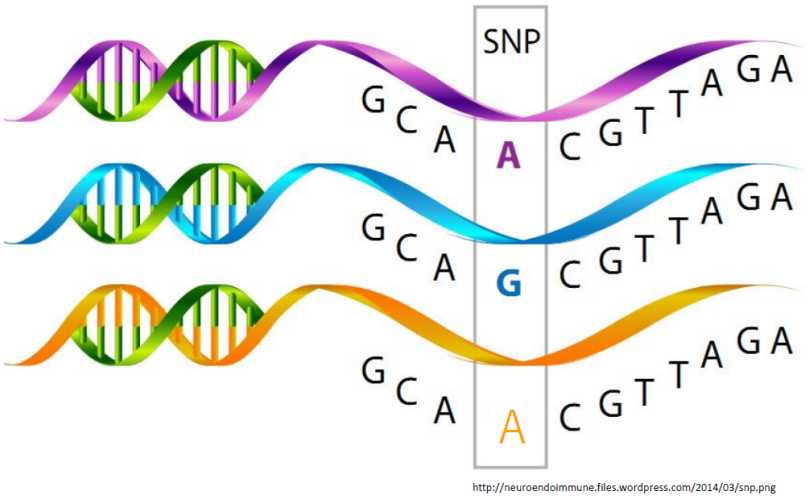

- Low- to high-density genotyping chips (10k-100k SNPs)
  $\rightarrow$ whole genome sequencing (10MM SNPs)

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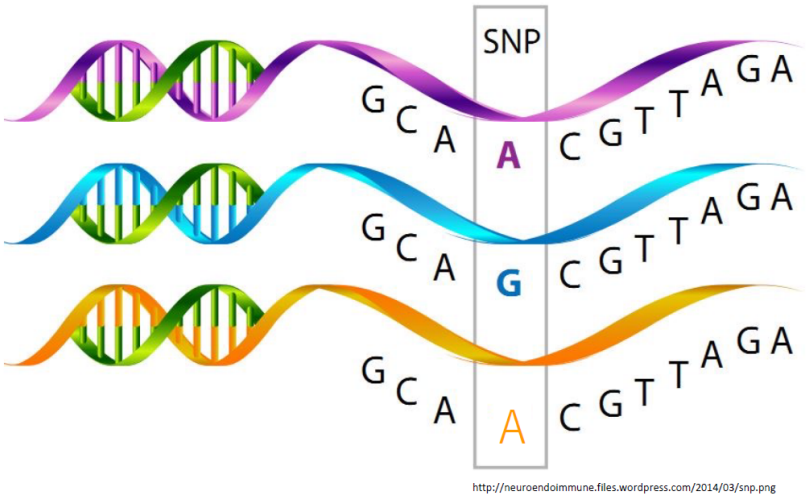

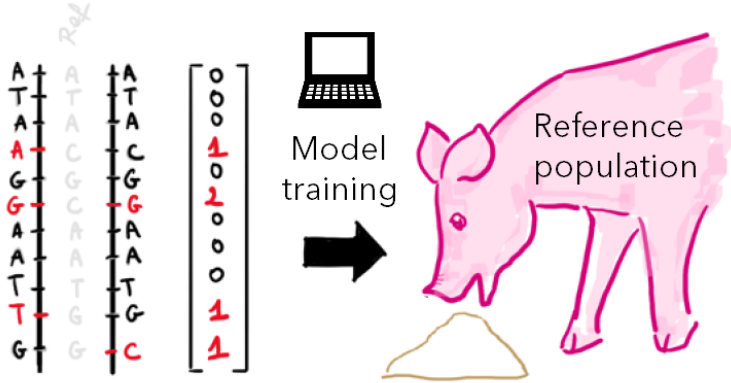

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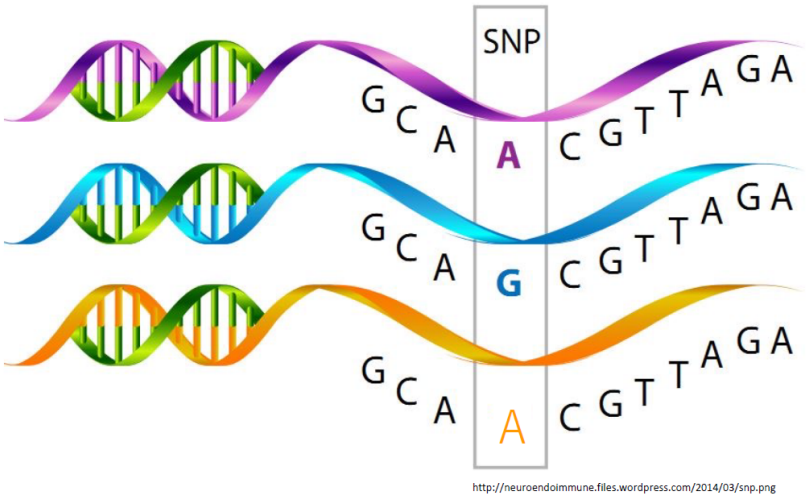

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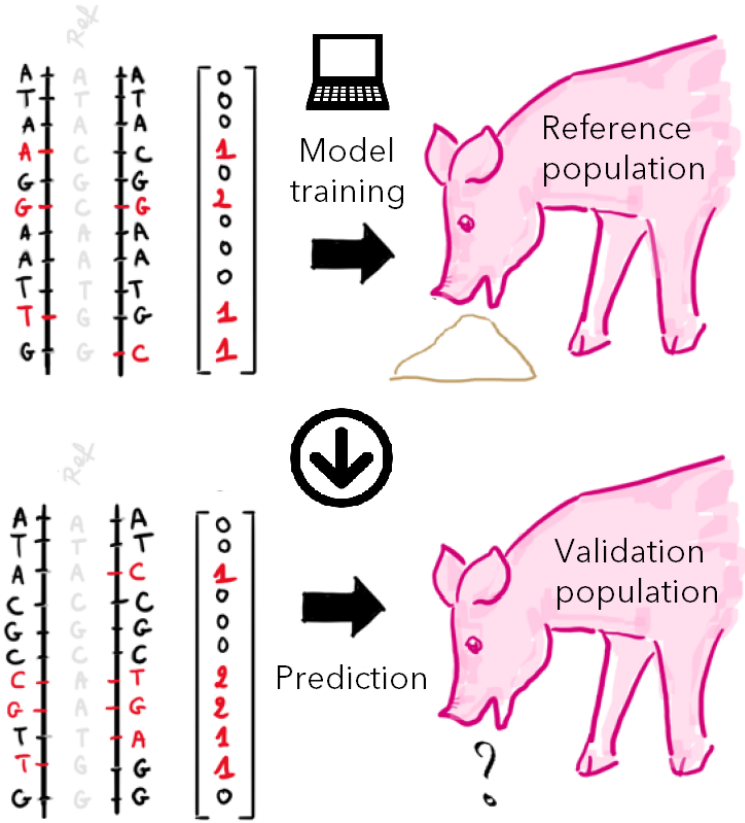

Image: F. Mollandin

Prediction models for genomic selection

Goal: given a **training set** of data (Y_i, X_i, Z_i) for $i = 1, \ldots, n$ individuals

- Y_i = trait
- X_i = vector of (usually genome-wide) genotypes
- Z_i = vector of covariates (age, location, sex, ...)

... **predict the unobserved trait** $Y_\star$ of a future individual with corresponding $X_\star$ and $Z_\star$

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... **predict the unobserved trait** $Y_\star$ of a future individual with corresponding $X_\star$ and $Z_\star$

- Introduced by Meuwissen *et al.* (2001)
- Successfully implemented in many plant/animal breeds for traits related to production, health, climate adaptation, ...
- Modest gains in predictions can have large economic impacts (reduced generation interval, reduced cost and labor for phenotyping)

Challenges of genomic prediction models

- Non-random association between alleles at neighboring loci (aka LD)
- Polygenic nature of complex traits
- Many more SNPs (variables) than individuals (observations) $\Rightarrow$ curse of dimensionality
  - Including too many predictors in a model risks **over-fitting**, **poor generalizability**, and **problems with model estimation**
  - ... but including only a small pre-identified subset of SNPs (e.g., significant GWAS hits) usually leads to **poor predictions**

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Can genomic prediction models be improved by better accounting for our **knowledge** about the **function** of certain regions of the genome?

Context: H2020 GENE-SWitCH project

The regulatory GENomE of Swine & Chicken: functional annotation during development

High-quality richly annotated maps of pig and chicken genomes:

- **Development**: early/late organogenesis, new born/hatched, adult
- **Sexes**: {M,F} $\times$ 3 biological replicates
- **Tissues**: liver, skeletal muscle, small intestine, cerebellum, dorsal epidermis, lung, kidney
- **Assays**: RNA-seq, ATAC-seq, ChIP-seq, smRNA-seq, methylation, Hi-C

Image: http://www.fragencode.org

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Integrate functional information with phenotypic + genotypic data in **genomic prediction models** for greater **power** and **interpretability**

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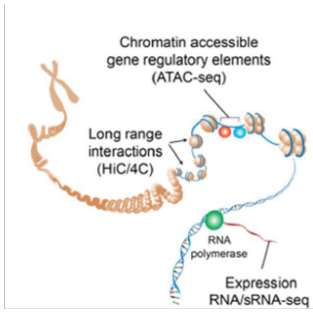

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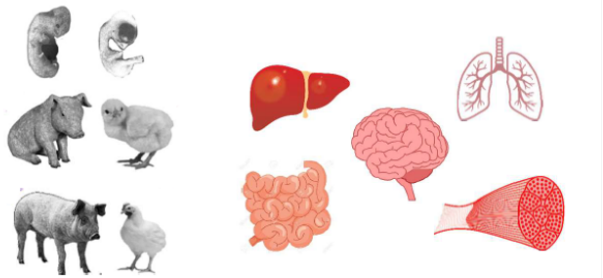

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Integrate functional information with phenotypic + genotypic data in **genomic prediction models** for greater **power** and **interpretability**

But how?

First, back to basics: the linear model

The workhorse of genomic prediction is the multiple linear regression model:

$$Y = \mathbf{Z}\theta + \mathbf{X}\beta + \varepsilon$$

- Y = n-vector of traits
- $\mathbf{Z}$ = $n \times m$ matrix of covariates
- θ = m-vector of covariate effect parameters
- $\mathbf{X}$ = $n \times p$ matrix of (suitably coded) genotypes
- β = p-vector of genetic effect parameters
- ε = n-vector of errors representing noise, assumed to be iid and (usually) normally distributed

Bayesian methods for genomic prediction

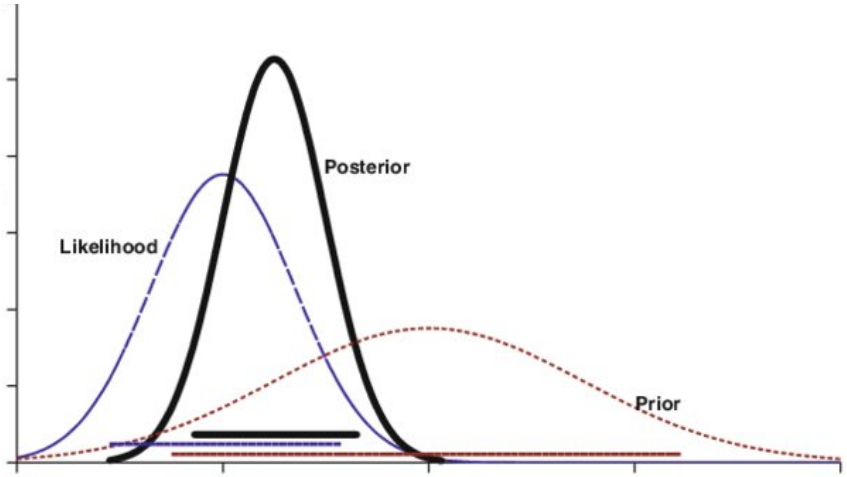
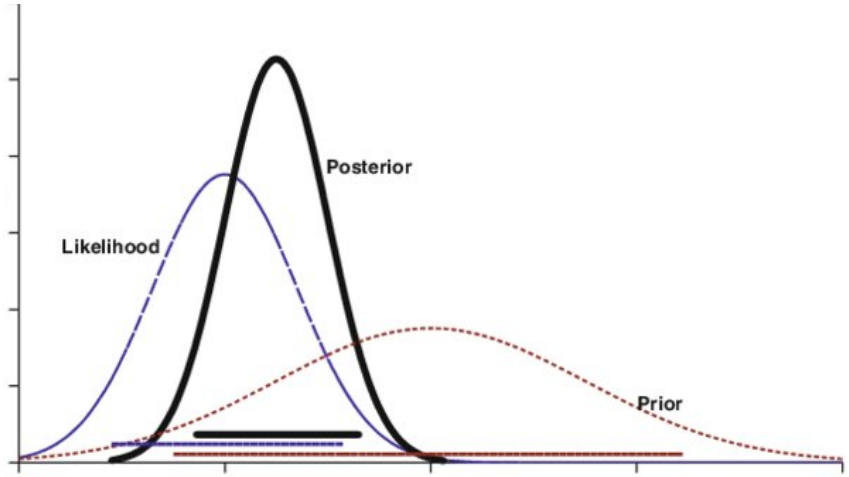


Image: 10.1007/s10681-007-9516-1

Bayesian methods for genomic prediction



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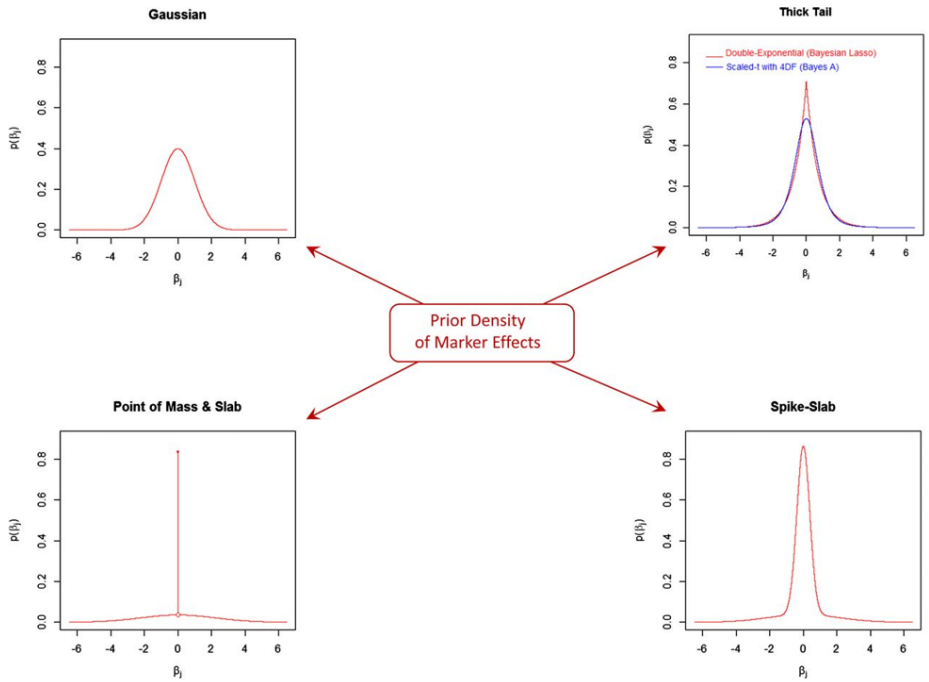
$$\underbrace{\prod_{i=1}^{n} N\left(Y_i \middle| \left(\mu + \sum_{j=1}^{p} X_{ij}\beta_j\right), \sigma^2\right)}_{\text{likelihood}} \times \underbrace{p(\sigma^2)\prod_{j=1}^{p} p(\beta_j|\Psi)}_{\text{prior}}$$

- σ^2 often assigned a χ^{-2} prior distribution
- Choice of prior for β_j should ideally reflect a trait's genetic architecture (and be computationally feasible...)

Which prior to use for β_j?



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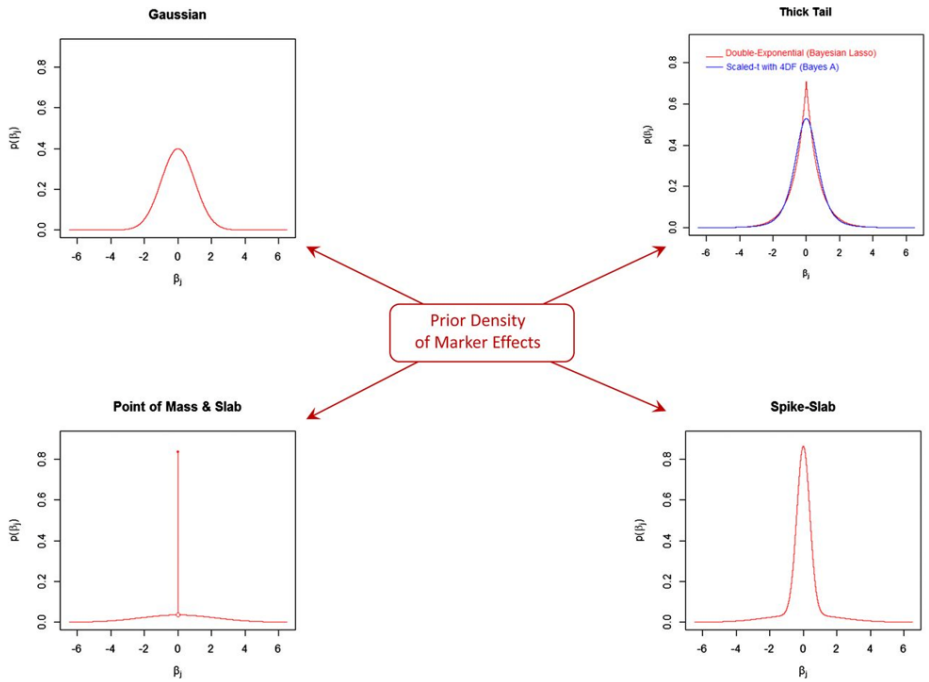

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GBLUP: $\beta_i \sim N(0, \sigma^2_\beta)$

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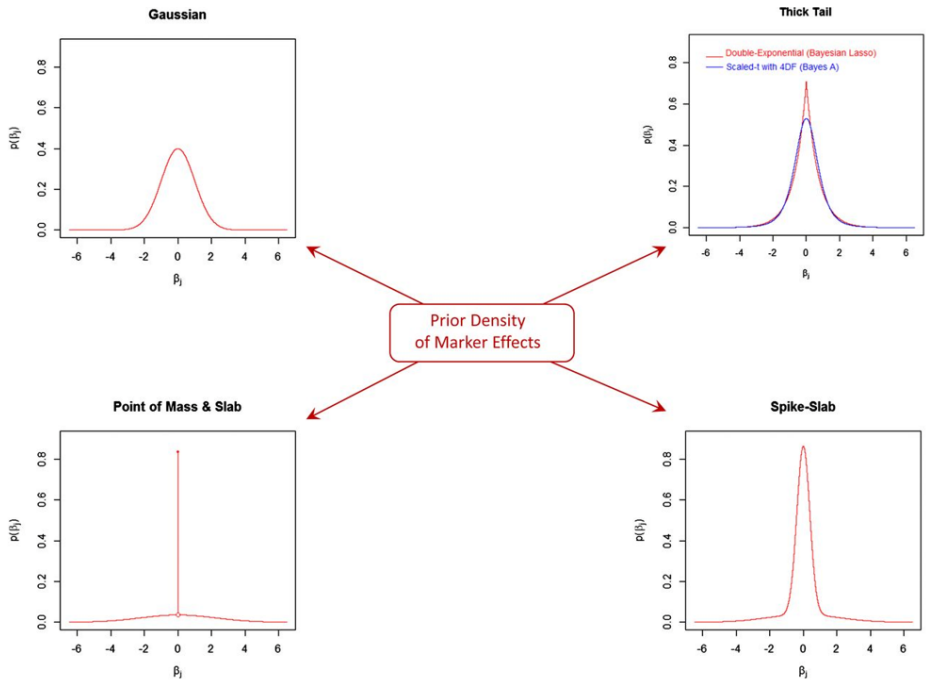

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BayesA: $\beta_i \sim N(0, \sigma^2_{\beta_i}), \sigma^2_{\beta_i} \sim \text{Inv } \chi^2(\nu, S^2)$

BayesB: $\beta_i \sim N(0, \sigma^2_{\beta_i}), \sigma^2_{\beta_i} \sim \pi\delta(0) + (1-\pi)\text{Inv } \chi^2(\nu, S^2)$, π fixed

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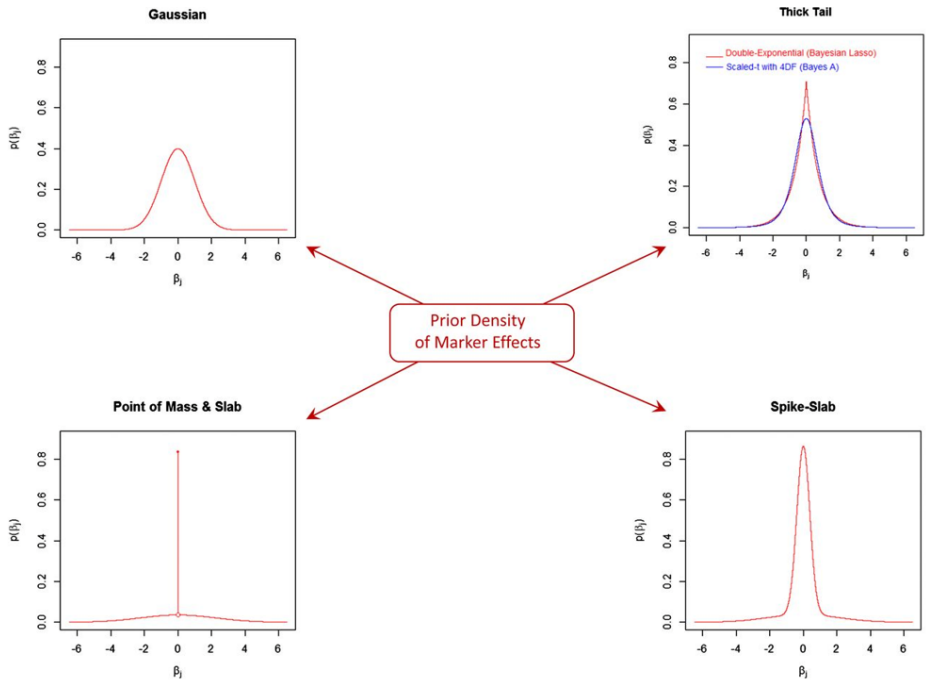

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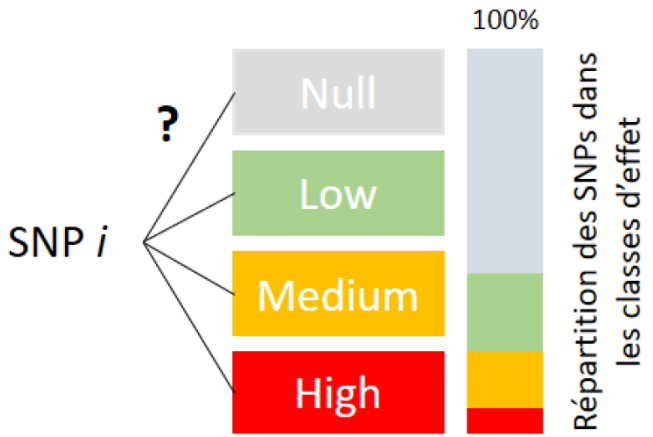
BayesC: $\beta_i \sim \pi\delta(0) + (1-\pi)N(0, \sigma^2_\beta), \sigma^2_\beta \sim \text{Inv } \chi^2(\nu, S^2)$, π fixed

BayesCπ: BayesC with $\pi \sim \text{Unif}(0, 1)$

BayesR (Erbe *et al.*, 2012)

$$\beta_i \sim \pi_1 \underbrace{\delta(0)}_{\text{null}} + \pi_2 \underbrace{N(0, 0.0001\sigma_g^2)}_{\text{small}} + \pi_3 \underbrace{N(0, 0.001\sigma_g^2)}_{\text{medium}} + \pi_4 \underbrace{N(0, 0.01\sigma_g^2)}_{\text{large}}$$

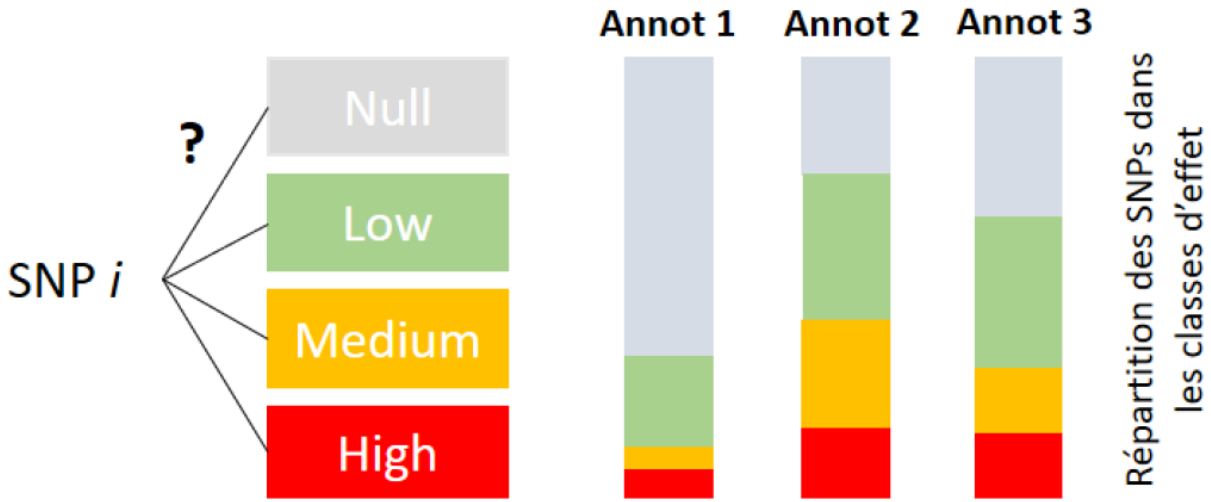
- $\pi \sim \text{Dirichlet}(\alpha)$, with $\alpha = (1, 1, 1, 1)$
- Gibbs sampler for estimation



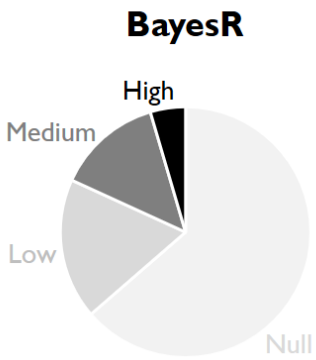
Back to annotations: BayesRC (MacLeod *et al.*, 2016)

$$f(\beta_i|C_i = c) = \sum_{k=1}^{4} \pi_{c,k} f_k(\cdot|\theta_k)$$

- SNPs assigned to disjoint **"annotations"**, model is a factorized BayesR
- $\pi_c \sim$ Dirichlet(α), with $\alpha = (1, 1, 1, 1)$
- Gibbs sampler for estimation



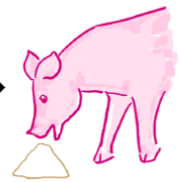
From BayesR to BayesRC ... and beyond



Genotype ...0000010012010021002000101000010110010111110...

...ACTCCGTAACTAGCCTACAAAGGCTAACTTACAAAAGATTTA...

Predict



GBV

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GENE-SWitCH

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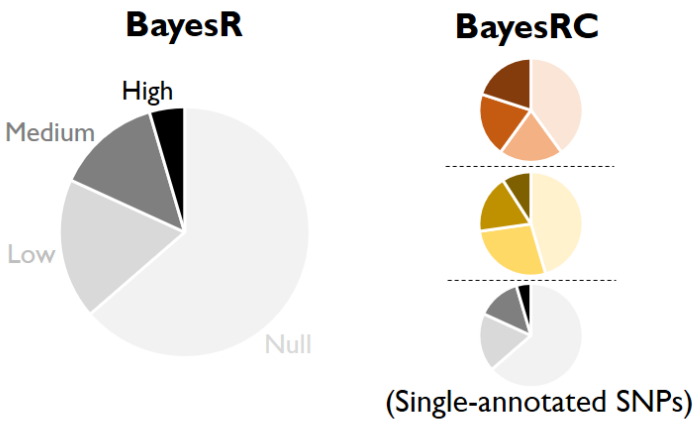

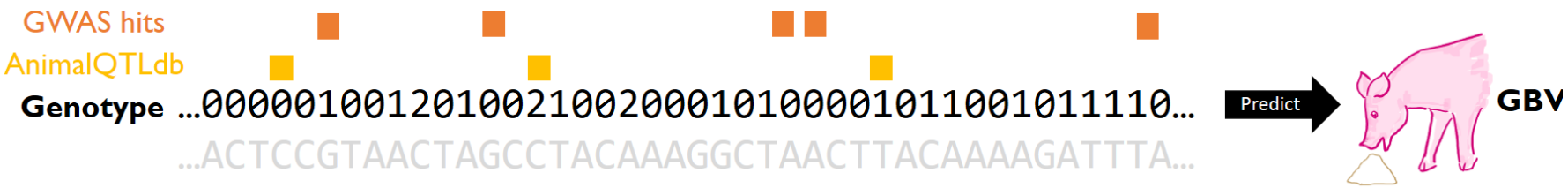

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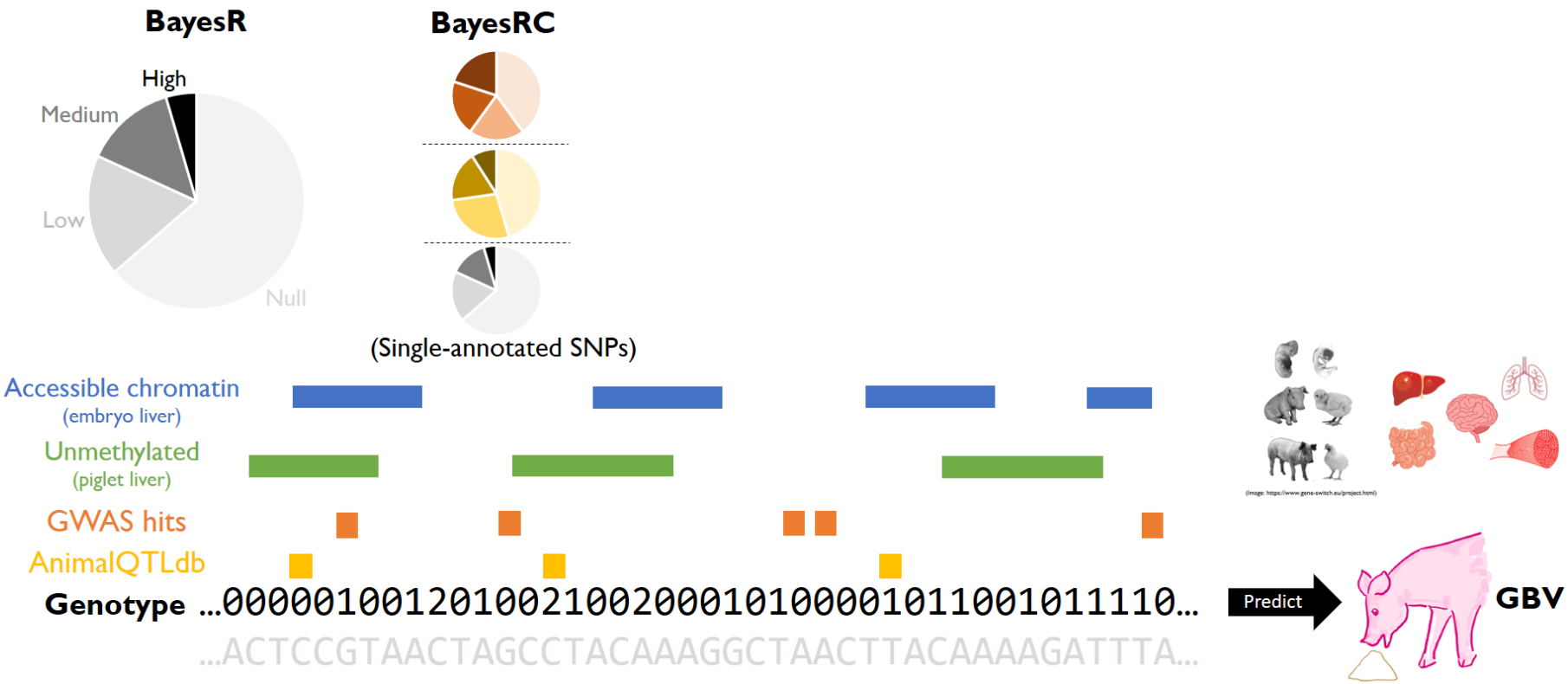

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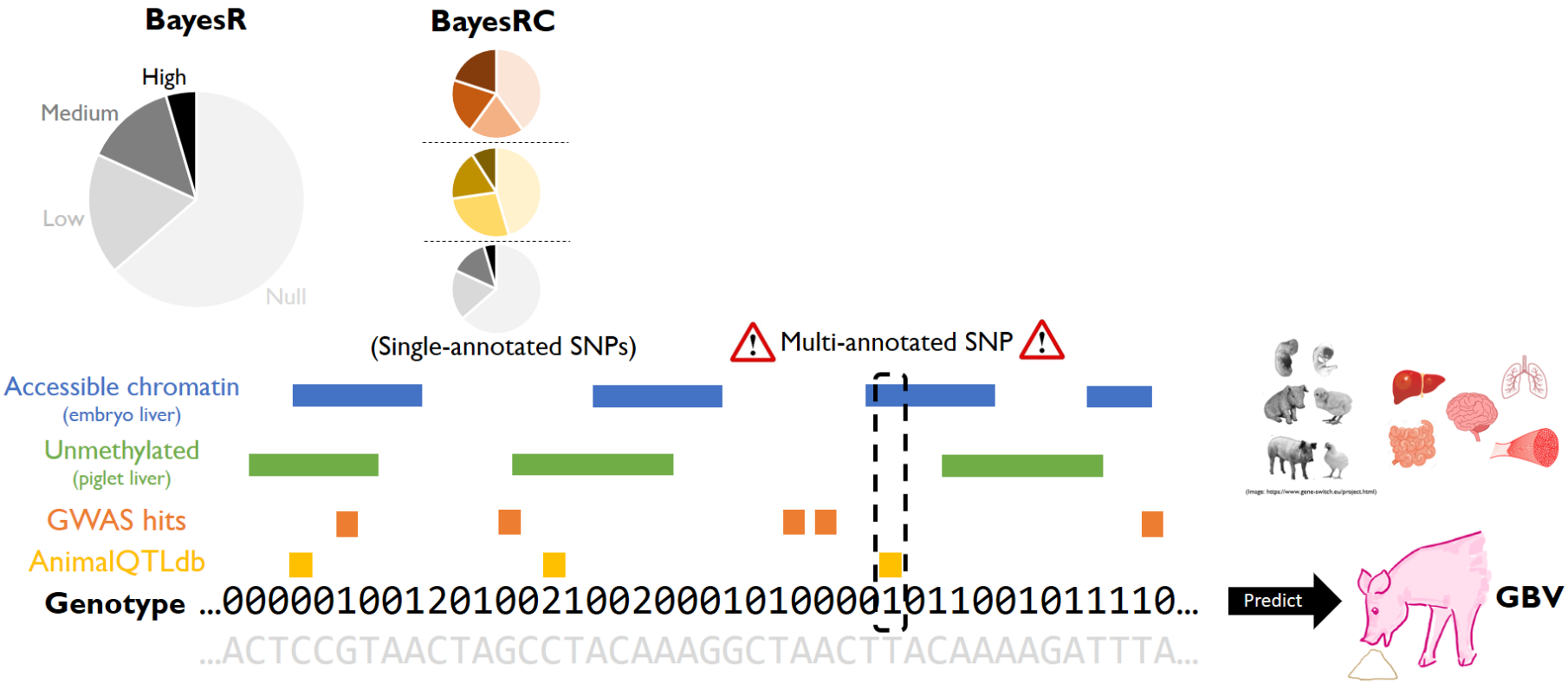

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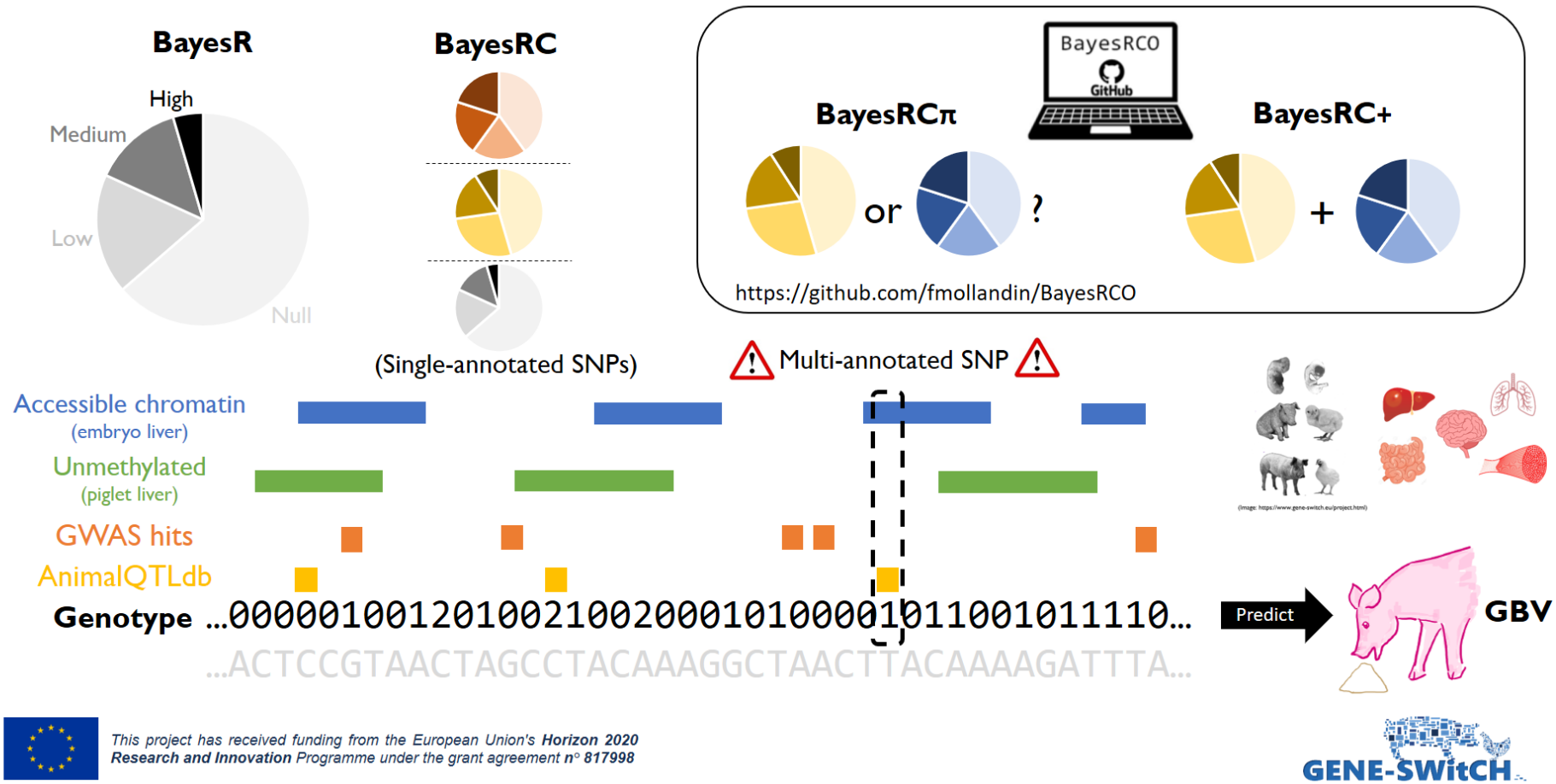

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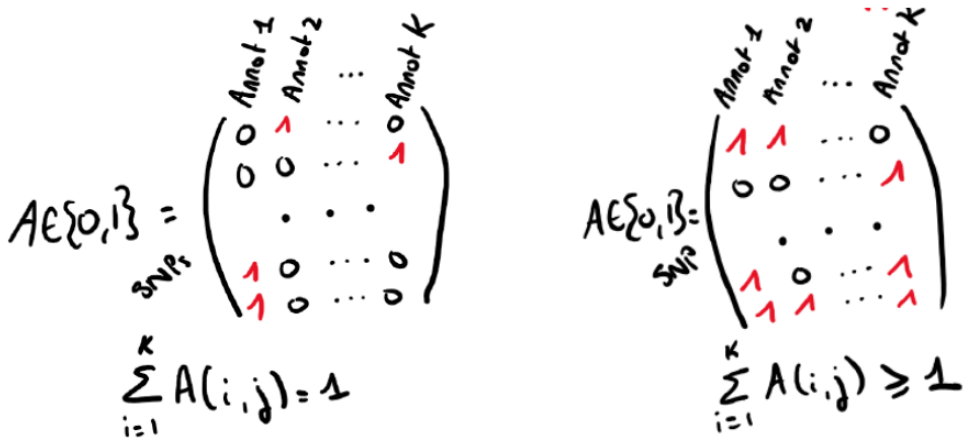
GENE-SWitCH

BayesRCO: BayesRC for Overlapping annotations

Two hypotheses = two models!

1. Multi-annotations represent **added confidence** → BayesRC+
2. Multi-annotations represent **uncertainty** → BayesRCπ



Method	SNP effect prior distribution	Annotations
BayesR	$\beta_i \sim \sum_{K=1}^{4} \pi_K \mathcal{N}(0, k\sigma_g^2)$	No
BayesRC	$\beta_i \vert a = A(i) \sim \sum_{K=1}^{4} \pi_{K,a} \mathcal{N}(0, k\sigma_g^2)$	Yes, disjointed
BayesRC+	$\beta_i \vert a \in A(i) \sim \sum_{a \in A(i)} \sum_{K=1}^{4} \pi_{K,a} N(0, k\sigma_g^2)$	Yes, overlapping
BayesRCπ	$\beta_i \vert a \in A(i) \sim \sum_{a \in A(i)} p_{i,a} \sum_{K=1}^{4} \pi_{K,a} N(0, k\sigma_g^2)$	Yes, overlapping

Cumulative → BayesRC+

Preferential assignment → BayesRCπ

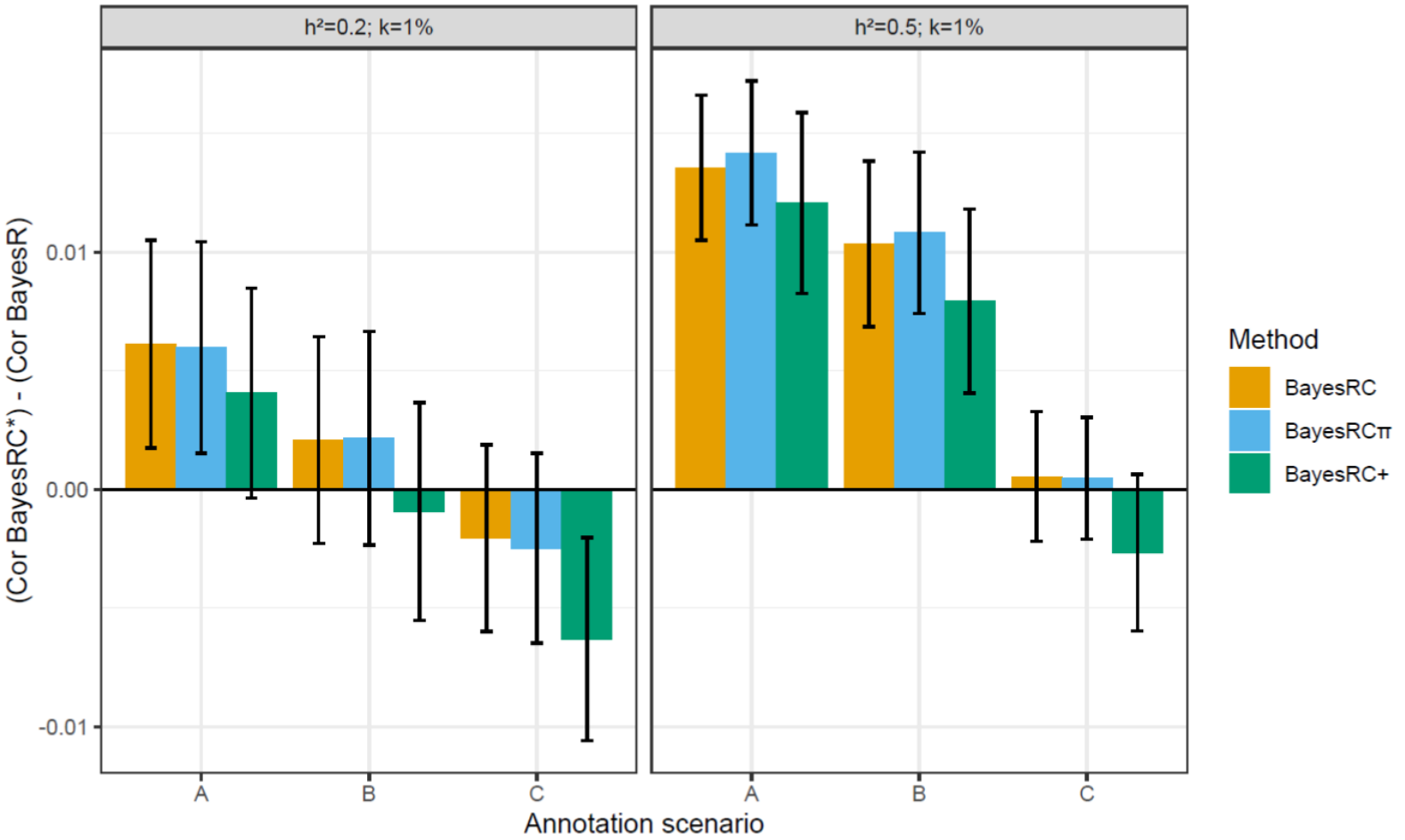
Simulation strategy

Phenotypes simulated from real cattle genotypes, 2500 animals:
- $h^2 = \{0.2, 0.5\}$
- 5 large QTLs representing $k = \{1\%, 2.5\%, 5\%\}$ of total additive variance σ_a^2
- 300 medium QTLs representing 0.1% of σ_a^2
- 4500 to 6500 low effect SNPs representing 0.01% of σ_a^2
- 50 datasets generated for each setting

4 types of annotations possible:

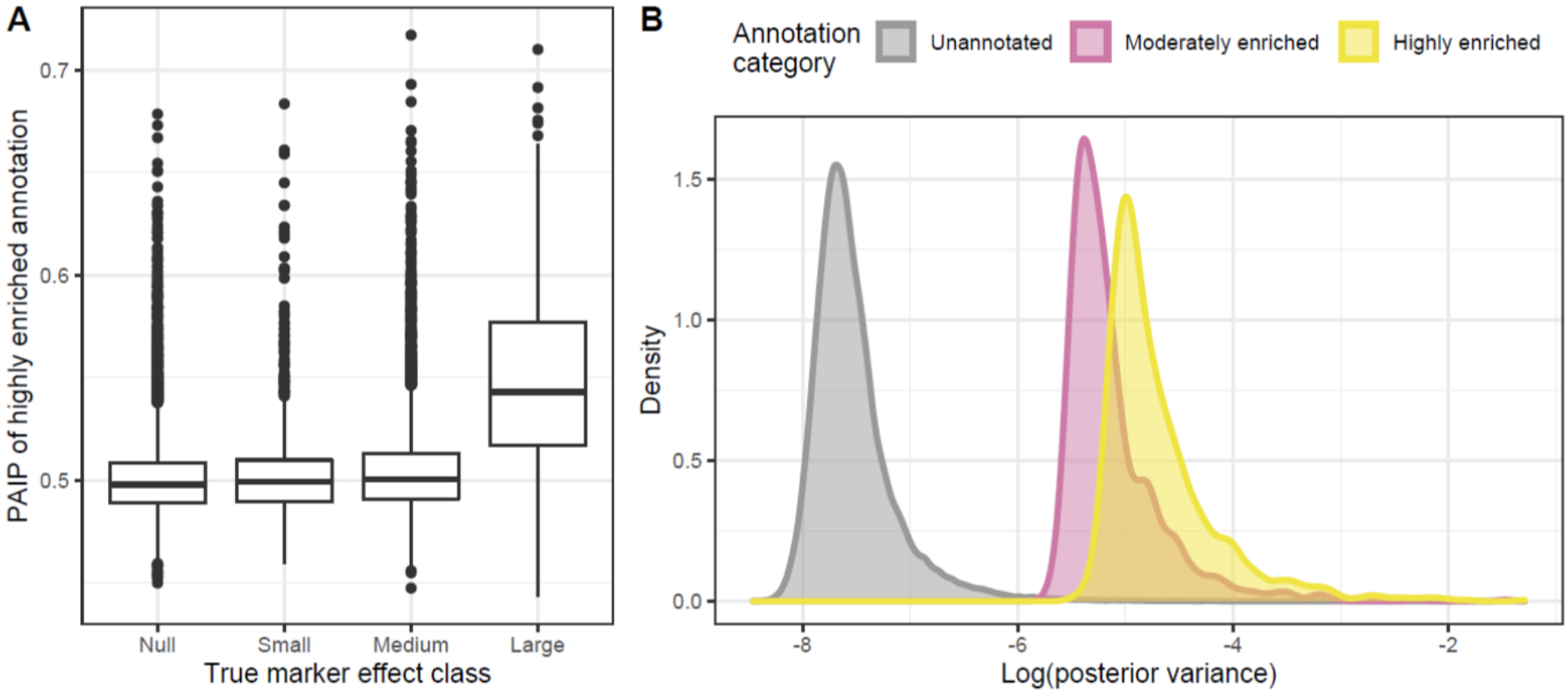
1. **strongly enriched**: 5 large QTLs + 300 medium QTLs + 150 low or null SNPs
2. **moderately enriched**: 2 large QTLs + 100 medium QTLs + 300 low or null SNPs
3. **weakly enriched**: 20 medium QTLs + 400 low or null SNPs
4. **unenriched**: 450 low or null SNPs

Evaluating impact of using annotations on validation data



k= per-large QTL % of additive variance
A= 1 strongly enriched + 1 moderately enriched + unannotated;
B= 1 strongly enriched + 1 moderately enriched + 1 weakly enriched + 1 unenriched + unannotated
C= 2 strongly enriched + 2 moderately enriched + 3 weakly enriched + 2 unenriched + unannotated

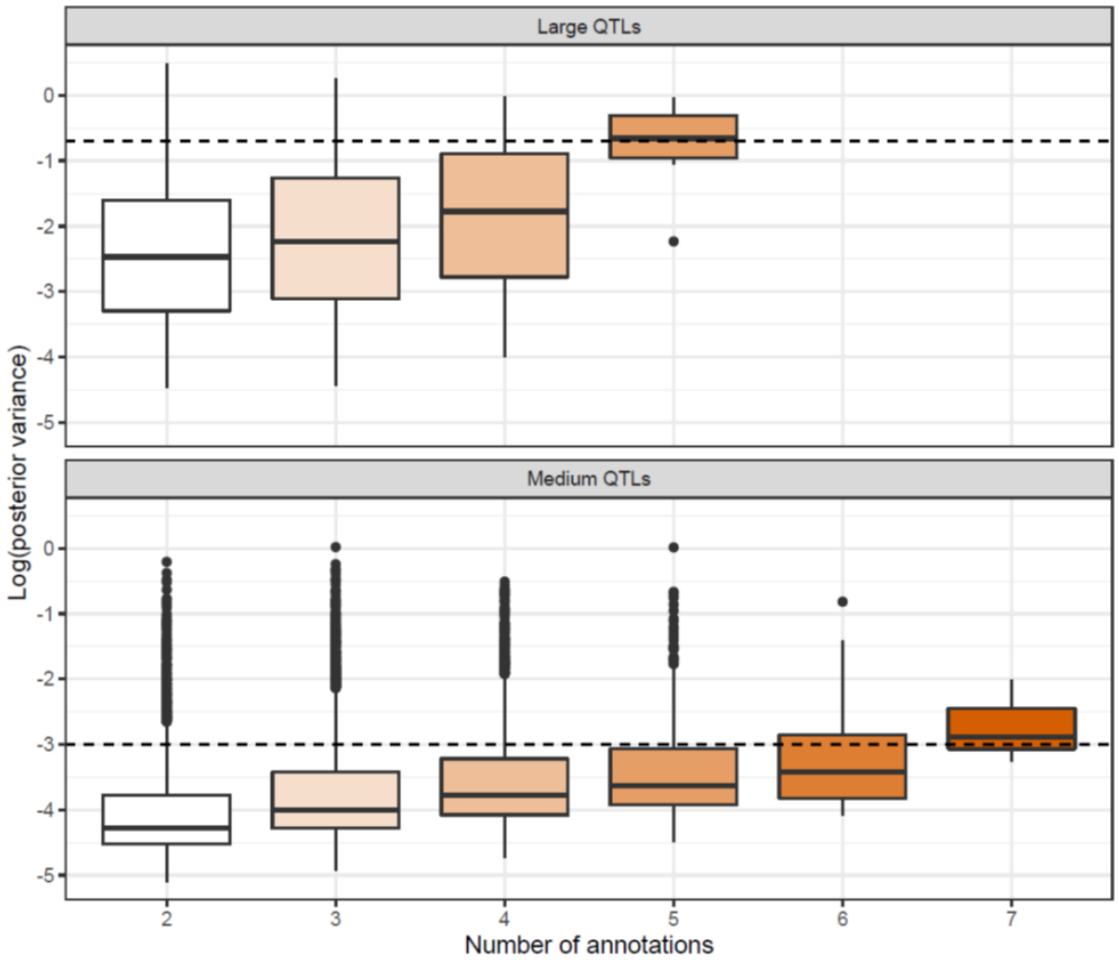
BayesRCπ assigns informative annotations to QTLs



$h^2 = 0.5$, k = 1%, scenario A

PAIP = posterior annotation inclusion probability (BayesRCπ output)

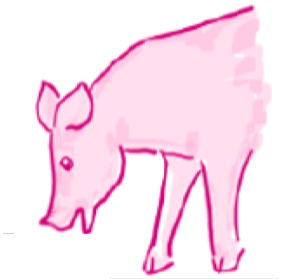
BayesRC+ assigns more weight to multi-annotated variants



$h^2 = 0.5$, k = 1%, scenario C

Application in backcross population of growing pigs

- $n = 1297$ backcross pigs (3/4 Large-White, 1/4 Creole), genetically related sows sired with 10 boars
  - Genotyped with Illumina Porcine 60k BeadChip array
  - Sibling-structured 10-fold cross validation procedure
- Traits pre-corrected for age, sex, farm
- Focus on average daily weight gain (**ADG**) and backfat thickness (**BFT**) at 23 weeks



Correlation of predicted traits in pig validation data

Annotations constructed using pigQTLdb for 11 trait sub-hierarchies

- Anatomy, behavioral, blood parameters, conformation, fatness, fatty acid content, feed conversion, growth, immune capacity, litter, reproductive organs
- Nearest up- and downstream neighboring markers also annotated

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	BayesR	BayesRC	BayesRCπ	BayesRC+
ADG	0.21 (±0.08)	+1.2 pts	+1.7 pts	+1.4 pts
BFT	0.26 (±0.16)	-0.6 pts	-1 pts	+0.6 pts

Interpreting pigQTLdb annotations with BayesRCπ

Conclusions: incorporating annotations with BayesRCO

BayesRCO:

→ **BayesRCπ** can assign informative annotations to multi-annotated SNPs to account for uncertainty in prior knowledge

→ **BayesRC+** upweights multi-annotated SNPs and is robust to various annotation scenarios

- Fairly modest improvements in prediction ($\sim$1-2 points) observed when incorporating biological annotations
  - Improved predictions and rankings of large QTLs in simulations, especially for highly informative annotations
  - Slight improvement in predictions for some traits in real data
  - Strategies for constructing annotation categories impact results

Take home messages

Can genomic prediction models be improved by better accounting for our **knowledge** about the **function** of certain regions of the genome?

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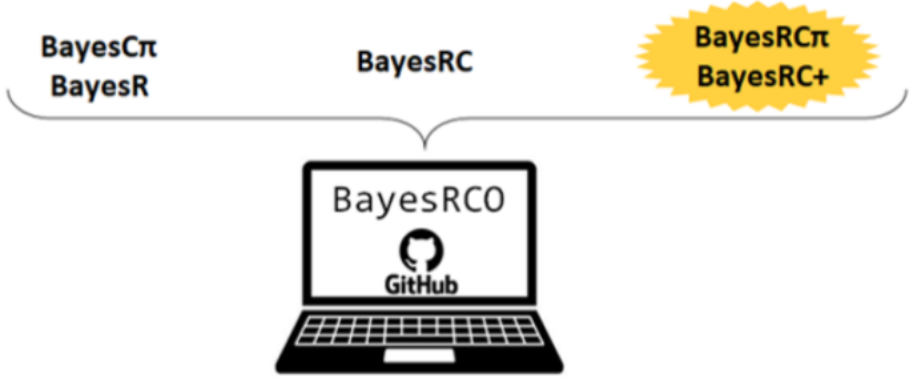
- **Models** → BayesRCO for overlapping annotation categories, extensions in progress to handle quantitative annotations
- **Genotyping data** → Capitalizing on annotation maps likely requires WGS resolution
- **Validation data** → Greater potential gains when prediction is performed on genetically distant populations
- **Traits** → Heritability, genetic architecture, link with annotations, ...
- **Annotations** → Which molecular assays, in which tissues?

Thank you!

Mollandin *et al.* (2022) Accounting for overlapping annotations in genomic prediction models of complex traits, *BMC Bioinformatics*, 23:65.



`https://github.com/FAANG/BayesRCO`