

HOS 6236 Molecular Marker Assisted Plant Breeding

Fall 2017

Last Class:

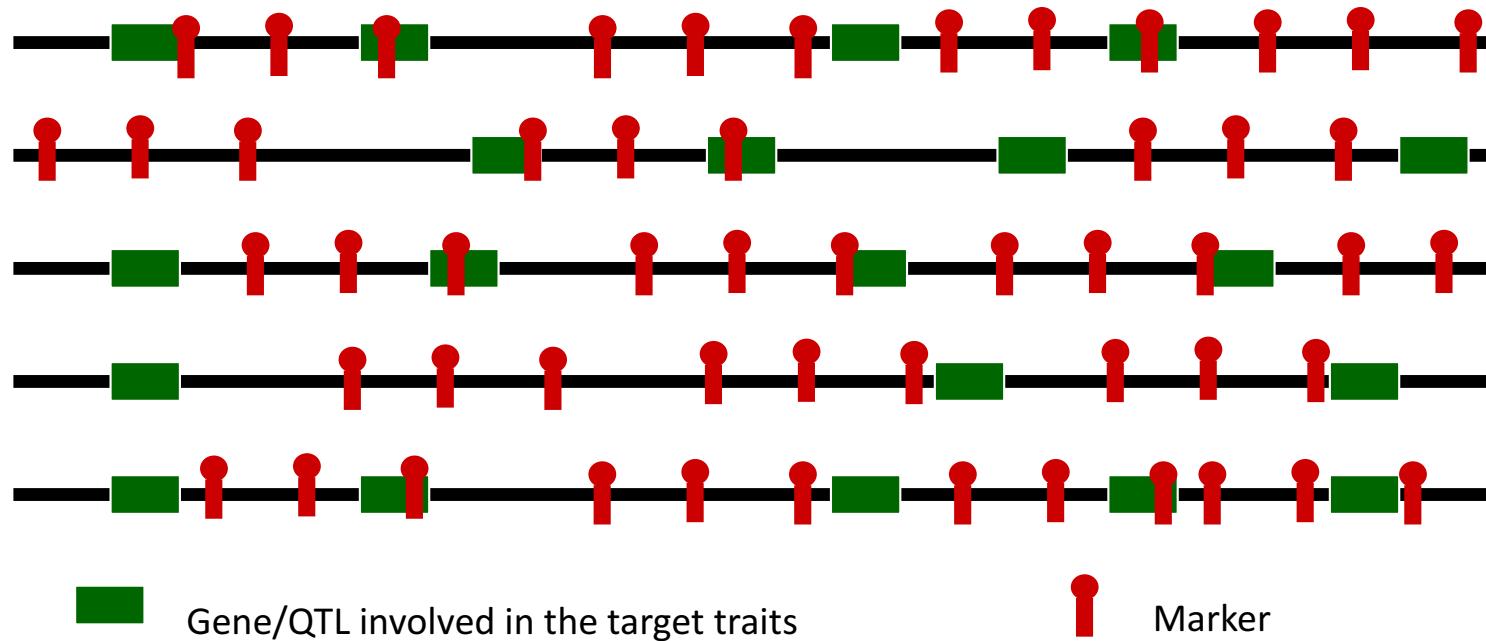
GS - 2

Today's Class:

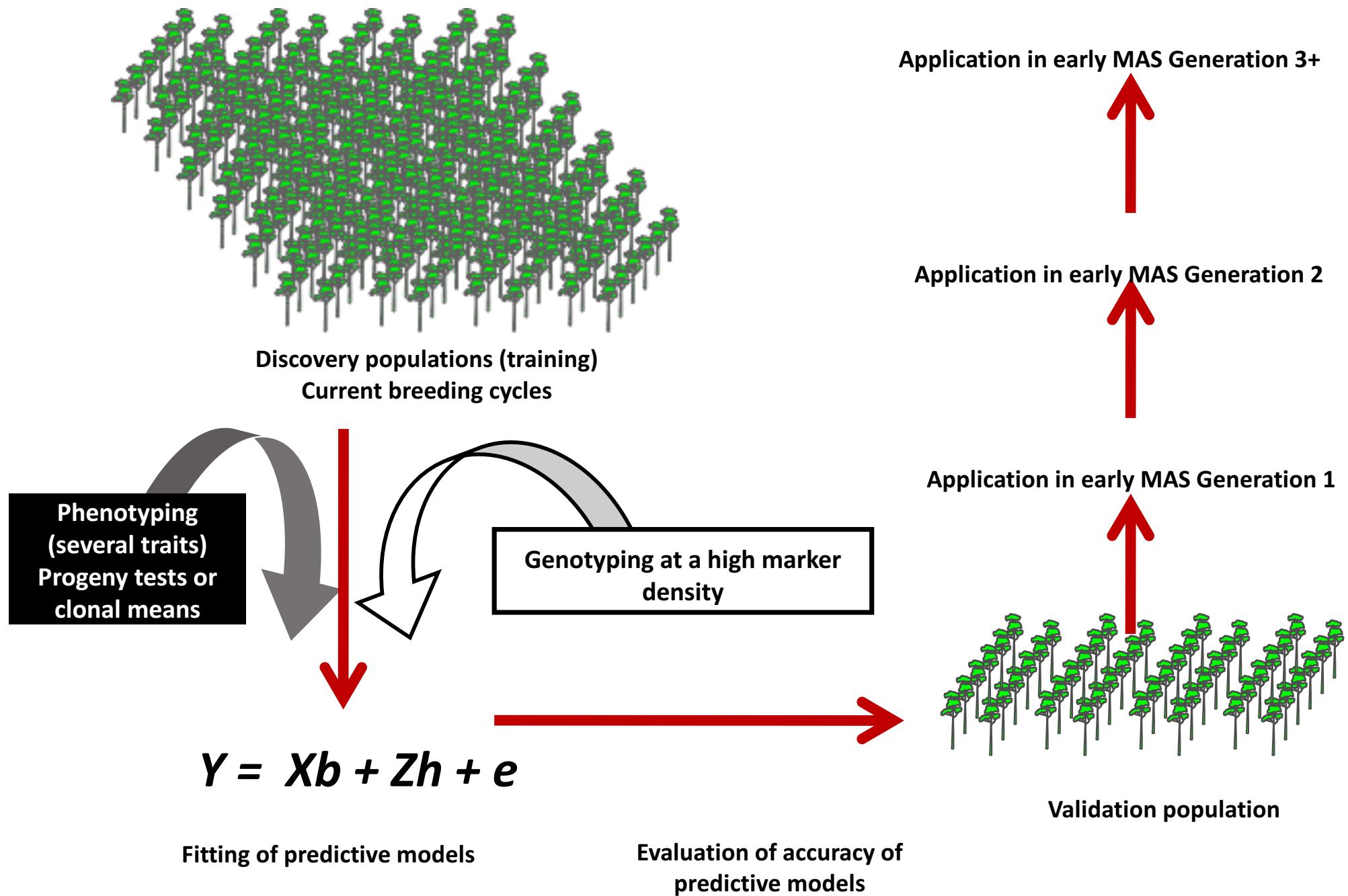
GS - 3

Genome Selection: Principles

1. Identify genetic markers covering most of the genome in the breeding population
2. Develop prediction models that capture most of the quantitative variation of interest.
3. Use prediction models to select superior genotypes in next cycle.



Genome Selection: Principles



Genome Selection: Populations

Training Population

- Individuals have to be genotyped and phenotyped
- Population used to fit the model

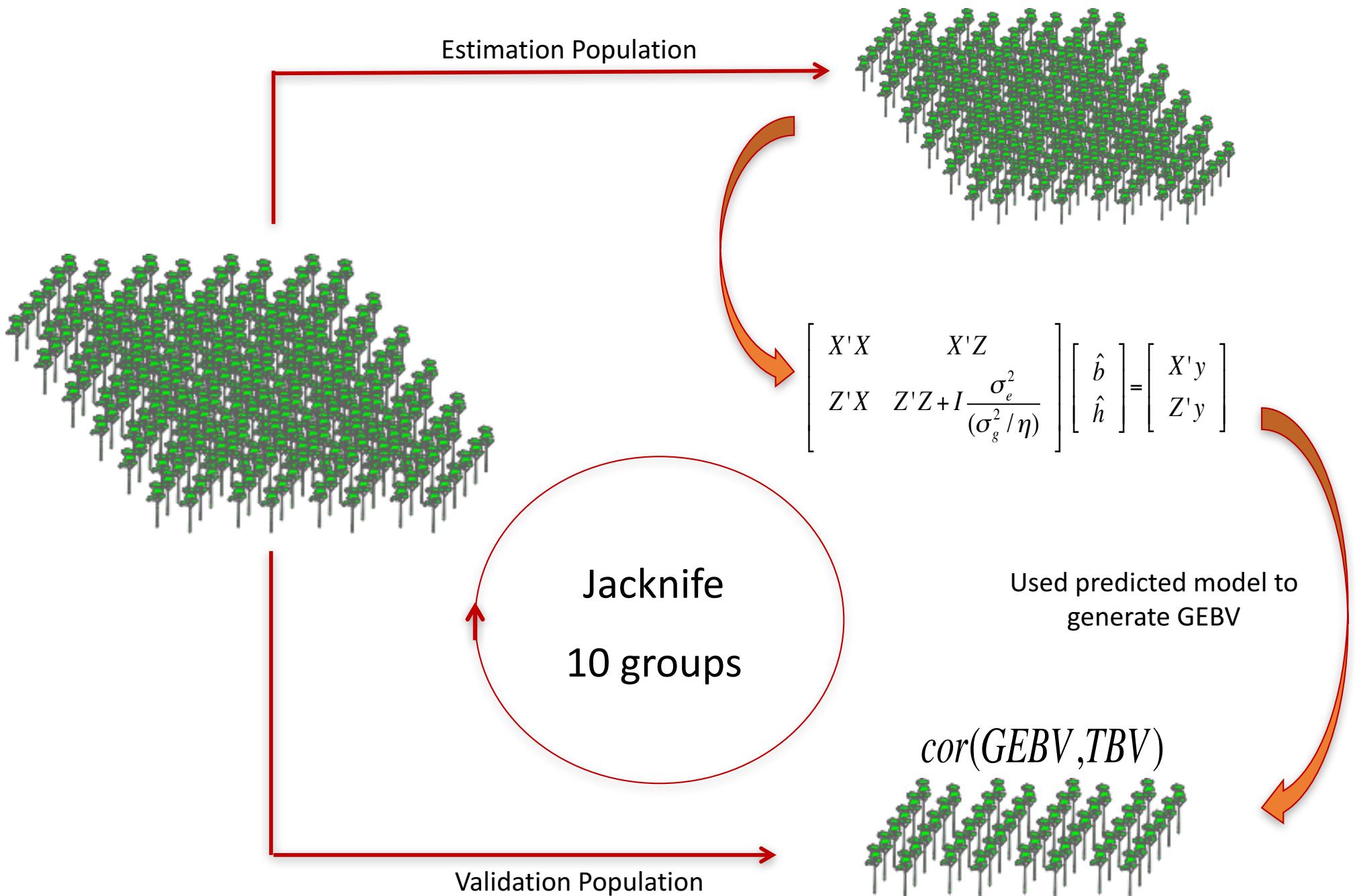
Testing (Validation) Population

- Model is validated
- Evaluates: $\text{cor}(\text{GEBV}, \text{BV})$; $\text{MSE}(\text{GEBV}, \text{BV})$

Selection Population

- Only genotypes; No phenotypic data
- Population where the models are applied

Methods – GS – Cross Validation



Genome Selection: Cross Validation

RAN: random split for training and test sets

GEN: split by generation: older individuals in training

REL: two sets of less related animals

Population	GEN	RAN	REL
Dairy cattle (Protein yield)	0.71	0.82	0.81
Wheat (Grain yield)	--	0.46	0.38

Genome Selection: Cross Validation

Trait Category	Trait	Methods			
		$r_{y\hat{y}}$ - 10-Fold	SE - 10-Fold	$r_{y\hat{y}}$ - L1-Out	SE - L1-Out
Growth	HT	0.39	0.029	0.38	0.029
	HTLC	0.45	0.027	0.46	0.027
	BHLC	0.49	0.026	0.49	0.026
	DBH	0.46	0.027	0.46	0.027
Development	CWAL	0.48	0.029	0.48	0.030
	CWAC	0.38	0.026	0.40	0.027
	BD	0.27	0.032	0.27	0.032
	BA	0.51	0.025	0.52	0.025
	Rootnum_bin	0.28	0.030	0.28	0.030
Disease resistance	Rootnum	0.24	0.031	0.24	0.031
	Rust_bin	0.29	0.032	0.29	0.033
	Rust_gall_vol	0.23	0.033	0.24	0.033
	StiffnessTree	0.43	0.027	0.43	0.028
Wood	Lignin	0.17	0.032	0.17	0.032
	Latewood%4	0.24	0.031	0.25	0.031
	Density	0.20	0.032	0.21	0.032
	C5C6	0.26	0.031	0.27	0.031

Genome Selection: Parameterization

Co-dominant markers

	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
Ind1	CC	CC	GT	GG	AG	CC	CC	AA	TT	TT
Ind2	AC	GG	GG	GG	GG	TT	CG	AA	TT	CC
Ind3	CC	CC	GT	CG	GG	CC	CG	AG	AA	CT
Ind4	AA	CG	TT	CC	AA	CT	GG	GG	AT	CC
Ind5	CC	CG	GG	GG	AG	TT	CC	AA	AA	TT
Ind6	AC	CG	GT	CC	AG	CC	GG	AG	TT	CT

Dominant markers

	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
Ind1	CC	C_	G_	G_	A_	C_	C_	AA	T_	TT
Ind2	A_	GG	G_	G_	GG	TT	C_	AA	T_	C_
Ind3	CC	C_	G_	G_	GG	C_	C_	G_	AA	C_
Ind4	A_	C_	TT	CC	A_	C_	GG	G_	T_	C_
Ind5	CC	C_	G_	G_	A_	TT	C_	AA	AA	TT
Ind6	A_	C_	G_	CC	A_	C_	GG	G_	T_	C_

	Ind1	Ind2	Ind3	Ind4	Ind5	Ind6
Ind1	2	2	1	0	1	0
Ind2	1	0	2	0	2	2
Ind3	2	2	1	1	2	0
Ind4	0	1	0	2	0	1
Ind5	2	1	2	0	1	2
Ind6	1	1	1	2	1	0

	Ind1	Ind2	Ind3	Ind4	Ind5	Ind6
Ind1	0	1	1	1	1	1
Ind2	1	0	1	1	0	0
Ind3	0	1	1	1	0	1
Ind4	1	1	0	0	1	1
Ind5	0	1	1	1	1	0
Ind6	1	1	1	0	1	1

$$Z = \begin{bmatrix} 2 & 2 & 1 & 0 & 1 & 0 & 0 & 2 & 0 & 0 \\ 1 & 0 & 2 & 0 & 2 & 2 & 1 & 2 & 0 & 2 \\ 2 & 2 & 1 & 1 & 2 & 0 & 1 & 1 & 2 & 1 \\ 0 & 1 & 0 & 2 & 0 & 1 & 2 & 0 & 1 & 2 \\ 2 & 1 & 2 & 0 & 1 & 2 & 0 & 2 & 2 & 0 \\ 1 & 1 & 1 & 2 & 1 & 0 & 2 & 1 & 0 & 1 \end{bmatrix}$$

$$\hat{g} = \begin{bmatrix} 0.23 \\ 0.12 \\ -0.36 \\ 0.02 \\ -0.09 \\ -0.12 \\ 0.34 \\ 0.29 \\ -0.19 \\ -0.13 \end{bmatrix}$$

$$GEBV = \sum_i^n Z_i \hat{g}_i = \begin{bmatrix} 0.83 \\ -0.25 \\ 0.30 \\ 0.27 \\ -0.27 \\ 0.78 \end{bmatrix}$$

Genome Selection: Centering

$Z_{ij} = \frac{(0-2p_i)}{\sqrt{\text{Var}(Z_i)}}$ if the individual is homozygous for the first allele (mm);

$Z_{ij} = \frac{(1-2p_i)}{\sqrt{\text{Var}(Z_i)}}$ if the individual is heterozygous (Mm);

$Z_{ij} = \frac{(2-2p_i)}{\sqrt{\text{Var}(Z_i)}}$ if the individual is homozygous for the second allele (MM) or;

$Z_{ij} = 0$ if the individual is a missing data.

$$Z_{ij} = \frac{Z_{ij} - \mu}{\sigma}$$

$$E(Z) = (2 \times p^2) + (1 \times 2pq) + (0 \times q^2)$$

$$E(Z) = 2p^2 + 2pq$$

$$E(Z) = 2p \times (p + q)$$

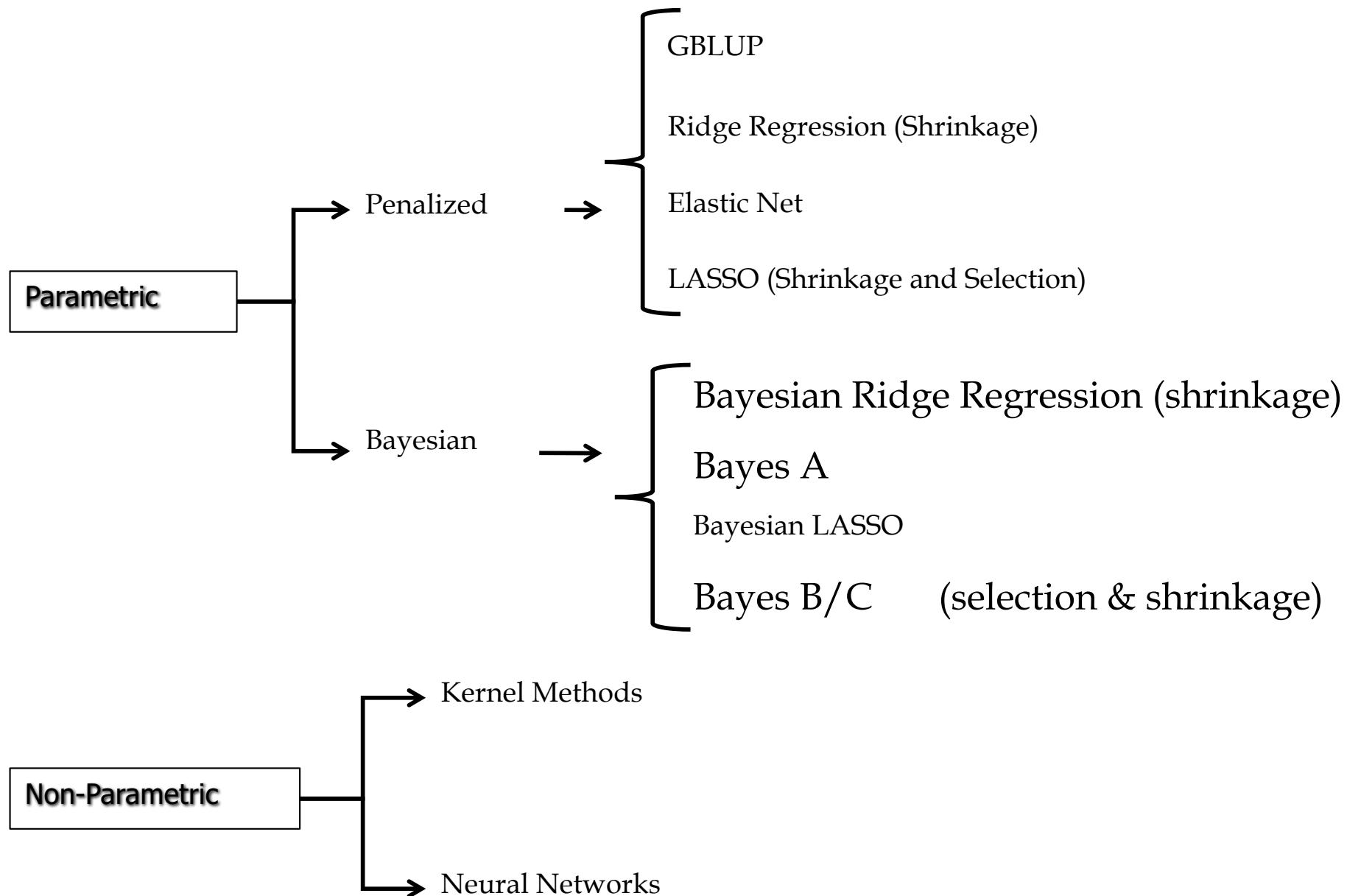
$$E(Z) = 2p$$

$$V(Z) = [(2-2p)^2 \times p^2] + [(1-2p)^2 \times 2pq] + [(0-2p)^2 \times q^2]$$

$$V(Z) = 4p^2 - 8p^3 + 4p^4 + 2pq - 4p^2q + 4p^3q - 4p^2q^2$$

$$V(Z) = 2pq$$

Genome Selection: Methods



GWS

(Additive Genetic Effects)

(Meuwissen et al., 2001)

$$y = \mu + \sum_{j=1}^p X_j g_j + e$$

design matrix (genotypes)

genetic effects of marked genes

- ‘Big p small n paradigm’;
 - Dimension reduction techniques (e.g. SVD and PLS), and stepwise strategies.
 - Alternatively, ridge regression, random effects models, and hierarchical modeling.

Y = Deregressed EBV

- Animal model evaluations by BLUP using the inverse relationship matrix shrink individual and progeny information towards parent average (PA) EBV
- Ideal in the training set is the “true” genetic merit of non-related individuals
- Fitting a model with non-deregressed EBV can lead to estimate of marker effects that are capturing only relatedness rather than the LD with the QTL.
- If parents have an allele of major effect, about half the offspring will inherit the favorable allele and the other half will inherit the unfavorable allele. However, the EBV of both classes of offspring will be shrunk towards the parent average.
- Two regressions, one based in kinship matrix, the other based on the marker data

GWMAS (BLUP)

$$\mathbf{y} = \mathbf{1}\mu + \sum_{j=1}^p \mathbf{X}_j g_j + \mathbf{e}$$



$$\begin{bmatrix} \hat{\mu} \\ \hat{\mathbf{g}} \end{bmatrix} = \begin{bmatrix} \mathbf{1}'\mathbf{1} & \mathbf{1}'\mathbf{X} \\ \mathbf{X}'\mathbf{1} & \mathbf{X}'\mathbf{X} + \mathbf{I}\gamma \end{bmatrix}^{-1} \begin{bmatrix} \mathbf{1}'\mathbf{y} \\ \mathbf{X}'\mathbf{y} \end{bmatrix}$$



$$g_j \sim N(0, \sigma_{gi}^2)$$

$$\gamma = \sigma_e^2 / \sigma_{gi}^2$$

How to choose σ_{gi}^2 ?

- Arbitrary; but σ_{gi}^2 controls amount of shrinkage ;
- Alternative: set $\sigma_{gi}^2 = \sigma_a^2 / \eta$, where σ_a^2 is an estimate (prior) of total additive genetic variance and $\eta = 2 \sum_i^n p_i (1 - p_i)$

Ridge-Regression BLUP

$$X = \begin{bmatrix} 2 & 2 & 1 & 0 & 1 & 0 & 0 & 2 & 0 & 0 \\ 1 & 0 & 2 & 0 & 2 & 2 & 1 & 2 & 0 & 2 \\ 2 & 2 & 1 & 1 & 2 & 0 & 1 & 1 & 2 & 1 \\ 0 & 1 & 0 & 2 & 0 & 1 & 2 & 0 & 1 & 2 \\ 2 & 1 & 2 & 0 & 1 & 2 & 0 & 2 & 2 & 0 \\ 1 & 1 & 1 & 2 & 1 & 0 & 2 & 1 & 0 & 1 \end{bmatrix} \quad y = \begin{bmatrix} 5.23 \\ 5.12 \\ 4.64 \\ 5.02 \\ 4.91 \\ 4.88 \end{bmatrix}$$

$$g = (X'X + I\gamma)^{-1} X'y$$

$$\hat{g} = \begin{bmatrix} 0.04 \\ -0.002 \\ 0.04 \\ -0.07 \\ -0.07 \\ 0.02 \\ 0.05 \\ 0.02 \\ -0.11 \\ 0.007 \end{bmatrix}$$

$$GEBV = \sum_i^n X_i \hat{g}_i = \begin{bmatrix} 0.83 \\ -0.25 \\ 0.30 \\ 0.27 \\ -0.27 \\ 0.78 \end{bmatrix}$$

Analysis: BGLR, rrblup, custom-made scripts

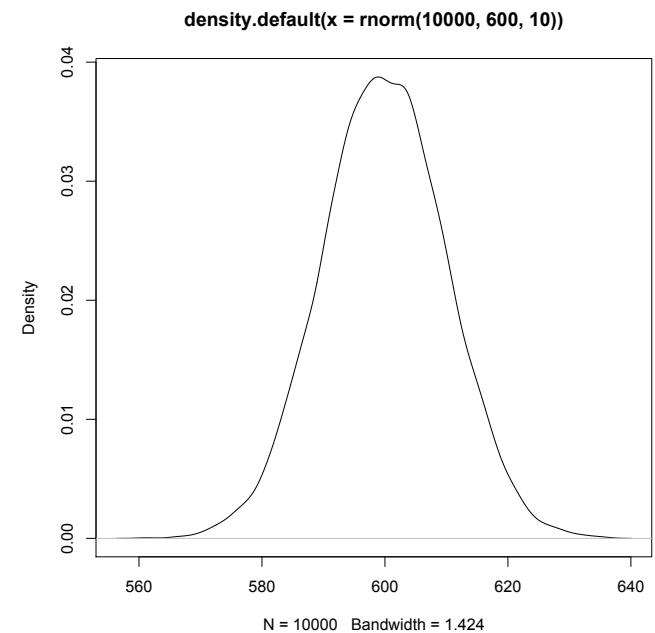
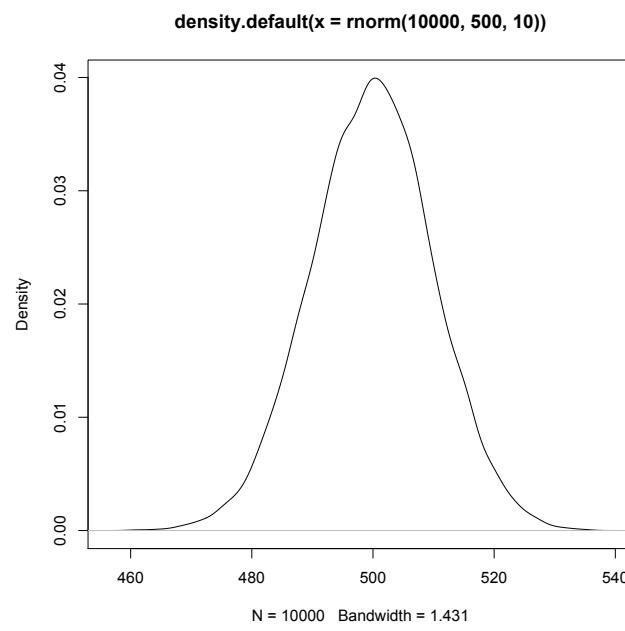
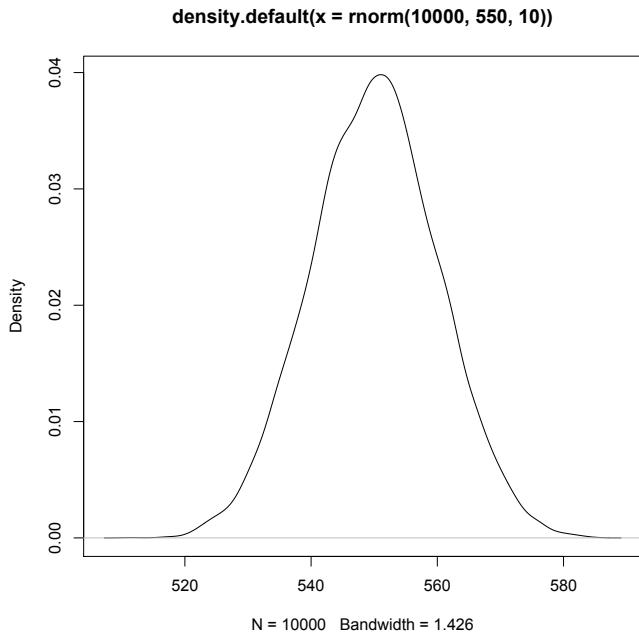
Bayesian methods

$$P(x | y) \propto P(y | x)P(x)$$

Posterior distribution

Probability of y given x

Prior information (prob of x)



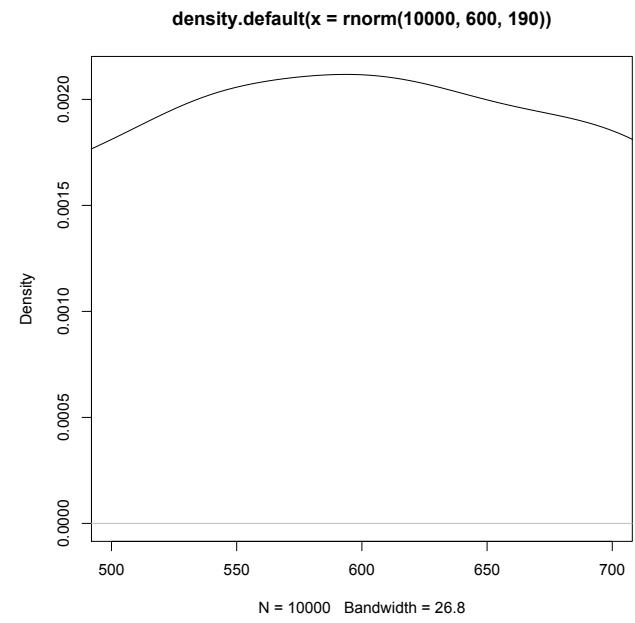
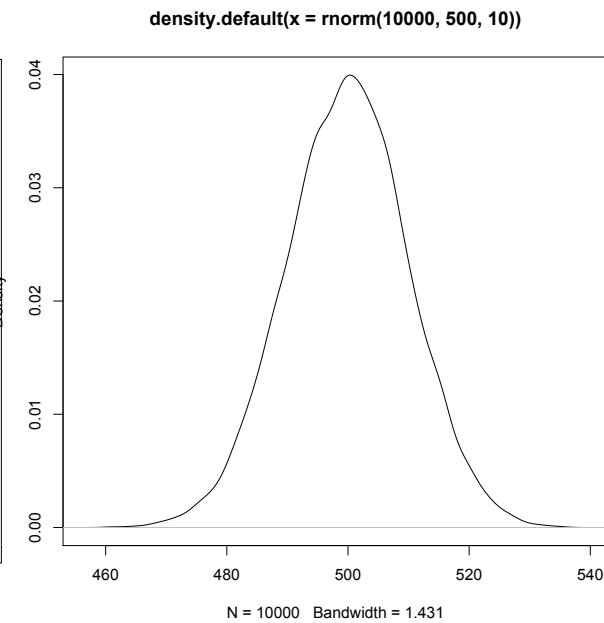
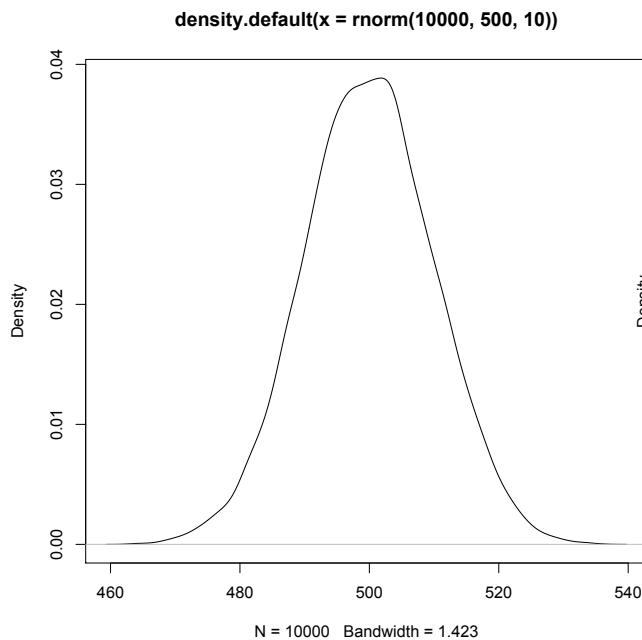
Bayesian methods

$$P(x | y) \propto P(y | x)P(x)$$

Posterior distribution

Probability of y given x

Prior information (prob of x)



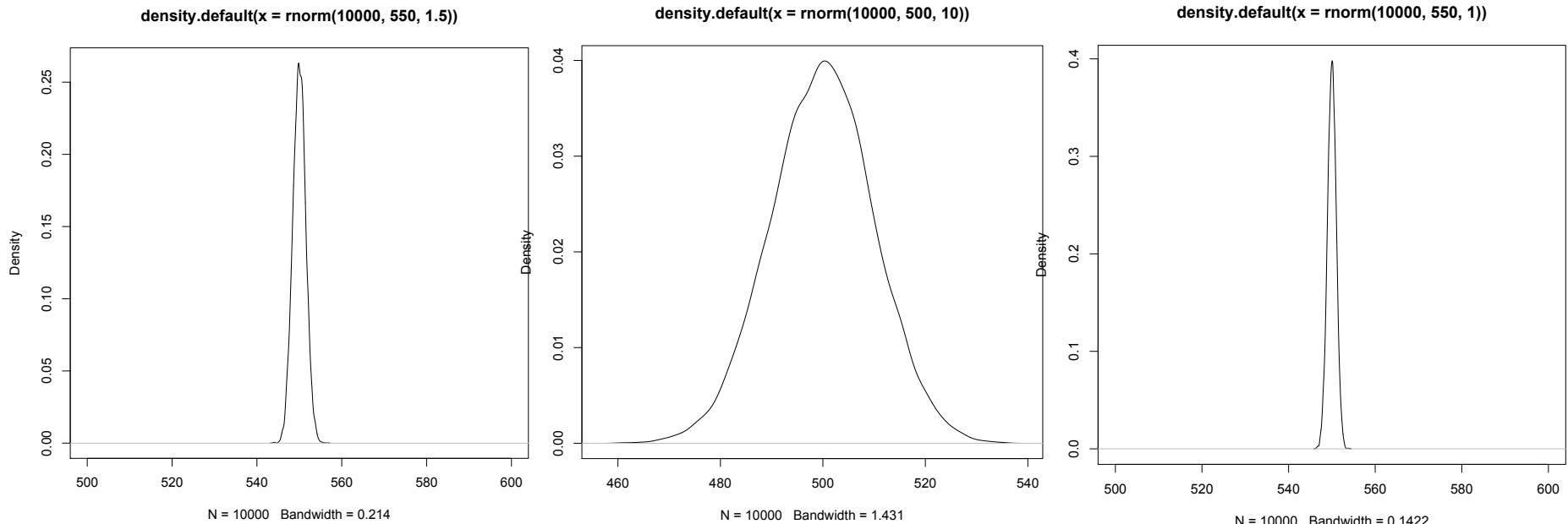
Bayesian methods

$$P(x | y) \propto P(y | x)P(x)$$

Posterior
distribution

Probability of y
given x

Prior information (prob of x)



BAYES A

(Meuwissen et al. 2001)

$$\mathbf{y} = \mathbf{1}\mu + \sum_{j=1}^p \mathbf{X}_j \mathbf{g}_j + \mathbf{e} \quad \rightarrow \quad \mathbf{y} | \mu, \mathbf{g}_j, \sigma_e^2 \sim N(\mathbf{1}\mu + \sum_{j=1}^p \mathbf{X}_j \mathbf{g}_j, \mathbf{I}\sigma_e^2)$$

$$P(g, \mu | y) \propto P(y | g, \mu) P(g, \mu)$$

Prior distributions: $\left\{ \begin{array}{l} \mathbf{g}_j | \sigma_j^2 \sim N(0, \sigma_j^2) \\ \sigma_j^2 \sim \chi^{-2}(v, S) \\ \text{(scaled inverted chi-square distribution with scale parameter } S \text{ and } v \text{ degrees of freedom)} \\ \sigma_e^2 \sim \chi^{-2}(-2, 0) \end{array} \right.$

BAYES B

(Meuwissen et al. 2001)

$$\mathbf{y} = \mathbf{1}\mu + \sum_{j=1}^p \mathbf{X}_j \mathbf{g}_j + \mathbf{e} \quad \rightarrow \quad \mathbf{y} | \mu, \mathbf{g}_j, \sigma_e^2 \sim N(\mathbf{1}\mu + \sum_{j=1}^p \mathbf{X}_j \mathbf{g}_j, \mathbf{I}\sigma_e^2)$$

Prior distributions:

$$\left\{ \begin{array}{l} \mathbf{g}_j | \sigma_j^2 \sim N(0, \sigma_j^2) \\ \\ \sigma_j^2 = 0 \quad \text{with probability } \pi \\ \sigma_j^2 \sim \chi^{-2}(v, S) \quad \text{with probability } (1 - \pi) \\ \\ \sigma_e^2 \sim \chi^{-2}(-2, 0) \end{array} \right.$$

Comparison of different GWMAS Methodologies

(Hayes et al., 2009)

Data

- Reference Population
1098 Holstein bulls progeny tests < 2003.
- Validation
400 Holstein bulls progeny tests > 2003.
- Phenotype
Deregressed EBV for prot, fat, milk volume, prot%, fat%.
- Bulls genotype for 39048 markers.
- Evaluation of methods
 $r(\text{GEBV}, \text{GBV})$.

Comparison of different GWMAS methodologies

(Hayes et al., 2009)

Methods

- BLUP
 - Individual SNP effects;
 - Genomic relationship matrix.
- Bayesian approaches
 - Bayes A
 - Bayesian LASSO
 - Bayes C (mixture)
- Least Angle Shrinkage Selection Operator (LASSO).
- Partial Least Squares (PLS).
- Support Vector Machine (SMV).

Comparison of different GWMAS methodologies

(Hayes et al., 2009)

Results: $r(\text{GEBV}, \text{GBV})$

	Protein	Fat	Milk	Prot%	Fat%	Average
SNP_BLUP	0.59	0.48	0.64	0.65	0.65	0.60
GBLUP	0.60	0.48	0.65	0.64	0.65	0.60
BayesA	0.55	0.48	0.61	0.64	0.71	0.60
Bayes C	0.57	0.51	0.63	0.67	0.74	0.62
Bayesian Lasso	0.56	0.47	0.62	0.62	0.64	0.58
LASSO	0.52	0.51	0.62	0.67	0.74	0.61
PLS	0.60	0.48	0.63	0.65	0.64	0.60
SVM	0.60	0.48	0.64	0.65	0.62	0.60

Comparison of different GS methodologies

(Resende *et. al* 2012)

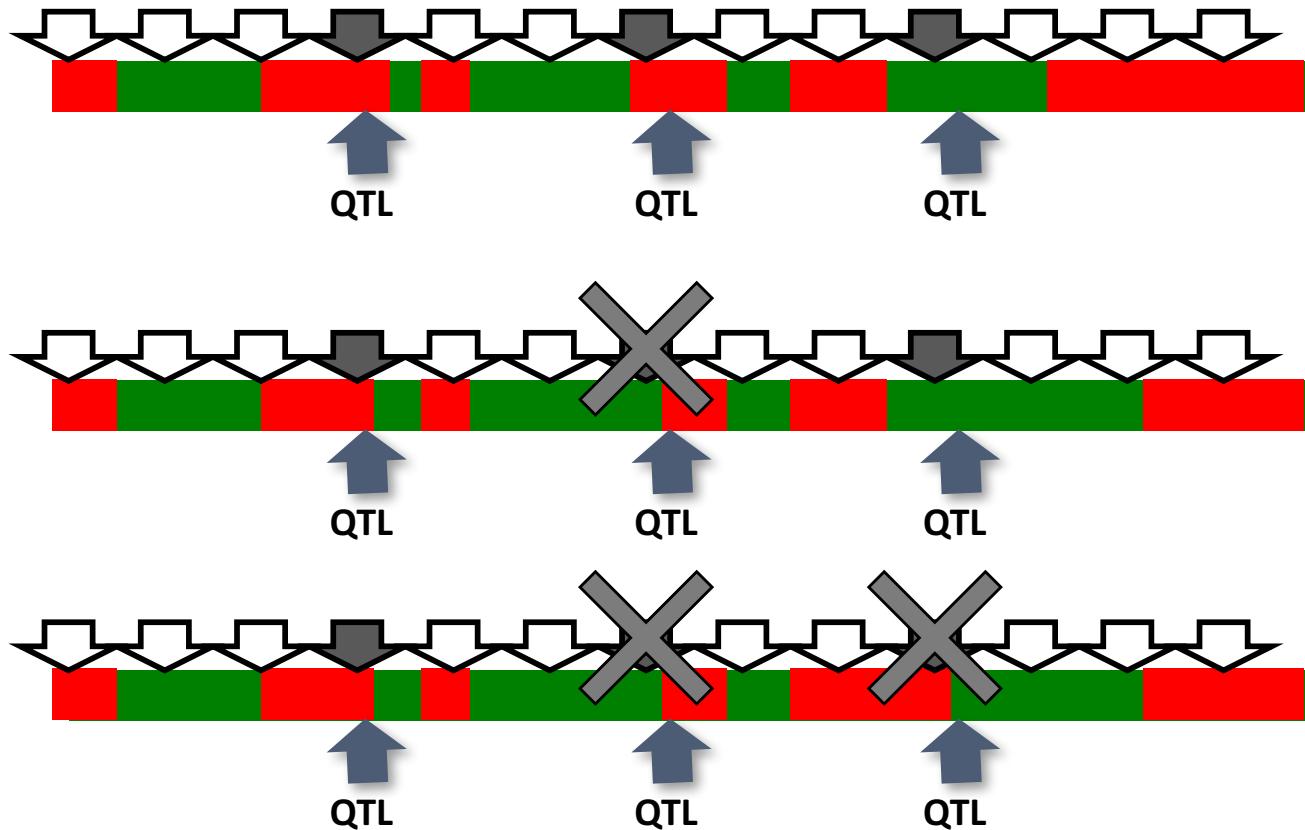
Trait Category	Trait	h^2_m	Methods			
			RR-BLUP	BLASSO	Bayes A	Bayes C π
Growth	HT	0.66	0.48	0.47	0.47	0.47
	HTLC	0.53	0.62	0.60	0.60	0.60
	BHLC	0.52	0.68	0.68	0.68	0.68
	DBH	0.66	0.57	0.57	0.57	0.57
Development	CWAL	0.43	0.58	0.55	0.55	0.55
	CWAC	0.63	0.60	0.58	0.59	0.59
	BD	0.26	0.53	0.49	0.53	0.53
	BA	0.5	0.72	0.72	0.72	0.72
	Rootnum_bin	0.5	0.40	0.40	0.38	0.40
	Rootnum	0.43	0.37	0.40	0.38	0.37
Disease resistance	Rust_bin	0.21	0.63	0.61	0.74	0.74
	Rust_gall_vol	0.18	0.57	0.57	0.66	0.68
Wood	StiffnessTree	0.37	0.71	0.64	0.69	0.69
	Lignin	0.11	0.51	0.51	0.51	0.51
	Latewood%4	0.17	0.58	0.58	0.56	0.58
	Density	0.09	0.67	0.73	0.77	0.73
	C5C6	0.14	0.69	0.67	0.67	0.67

Genomic Selection - Accuracy depends on:

- The level of linkage disequilibrium (LD) between the markers and the QTL (**Effective population size & genotyping density**);
- The number of individuals with phenotypes and genotypes in the reference population (training set) from which the marker effects are estimated (**adjustable**);
- The heritability of the trait in question, or, if deregressed breeding values are used (clonal means or progeny testing), the reliability of these breeding values;
- The distribution of QTL effects – # of loci involved

Genome Wide Selection: Stability of the prediction model

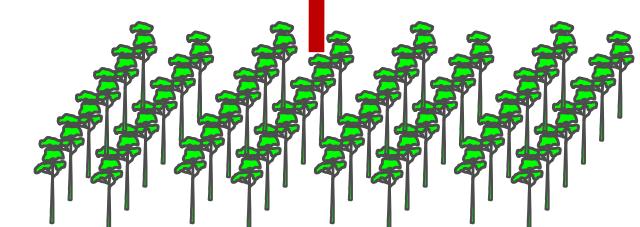
The number of generations that a prediction model can be used depends primarily on the number of markers used to develop the model initially.



Application in early MAS
Generation 3+

Application in early MAS
Generation 2

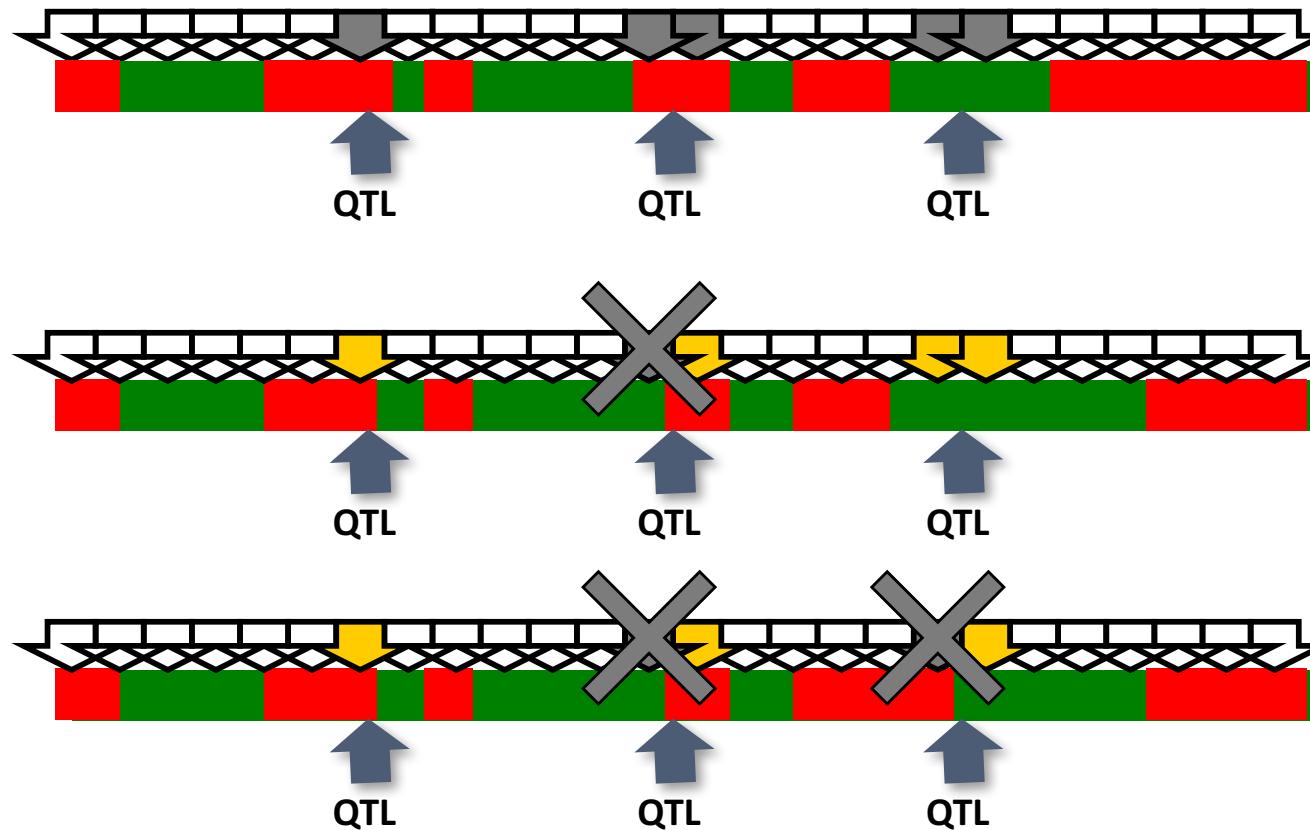
Application in early MAS
Generation 1



Validation population

Genome Wide Selection: Stability of the prediction model

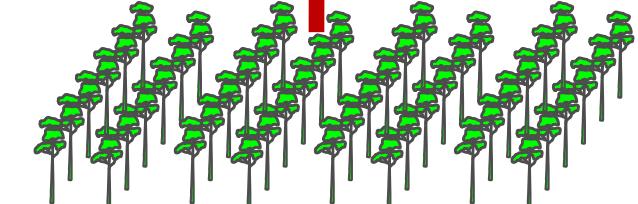
The number of generations that a prediction model can be used depends primarily on the number of markers used to develop the model initially.



Application in early MAS
Generation 3+

Application in early MAS
Generation 2

Application in early MAS
Generation 1



Validation population

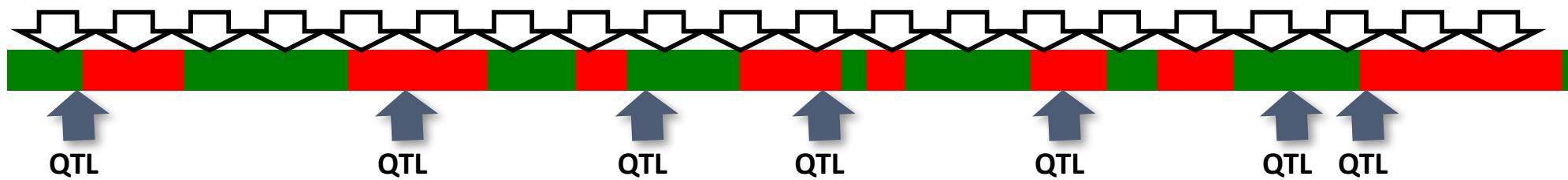
Genomic Selection - Accuracy depends on:

- The number of individuals with phenotypes and genotypes in the reference population (training set) from which the marker effects are estimated (**adjustable**);

A few common questions:

Can I can use my prediction models in unrelated populations?

Training population



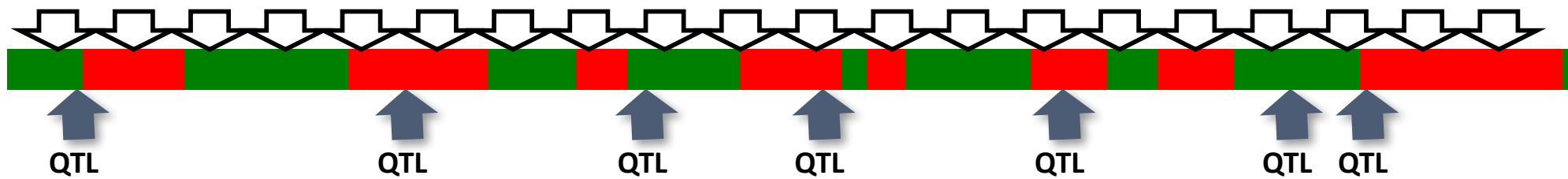
Genomic Selection - Accuracy depends on:

- The number of individuals with phenotypes and genotypes in the reference population (training set) from which the marker effects are estimated (**adjustable**);

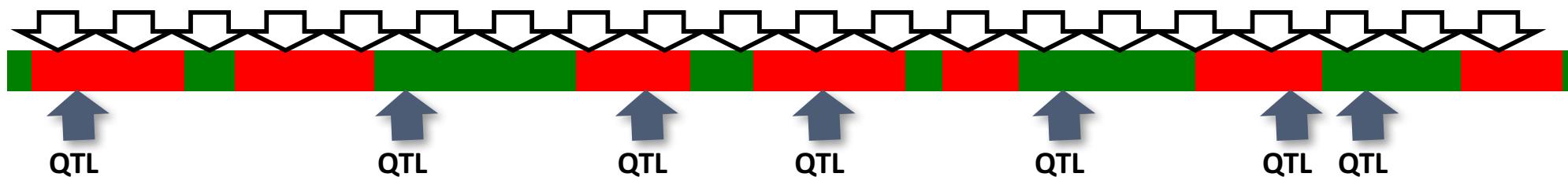
A few common questions:

Can I can use my prediction models in unrelated populations? NO!

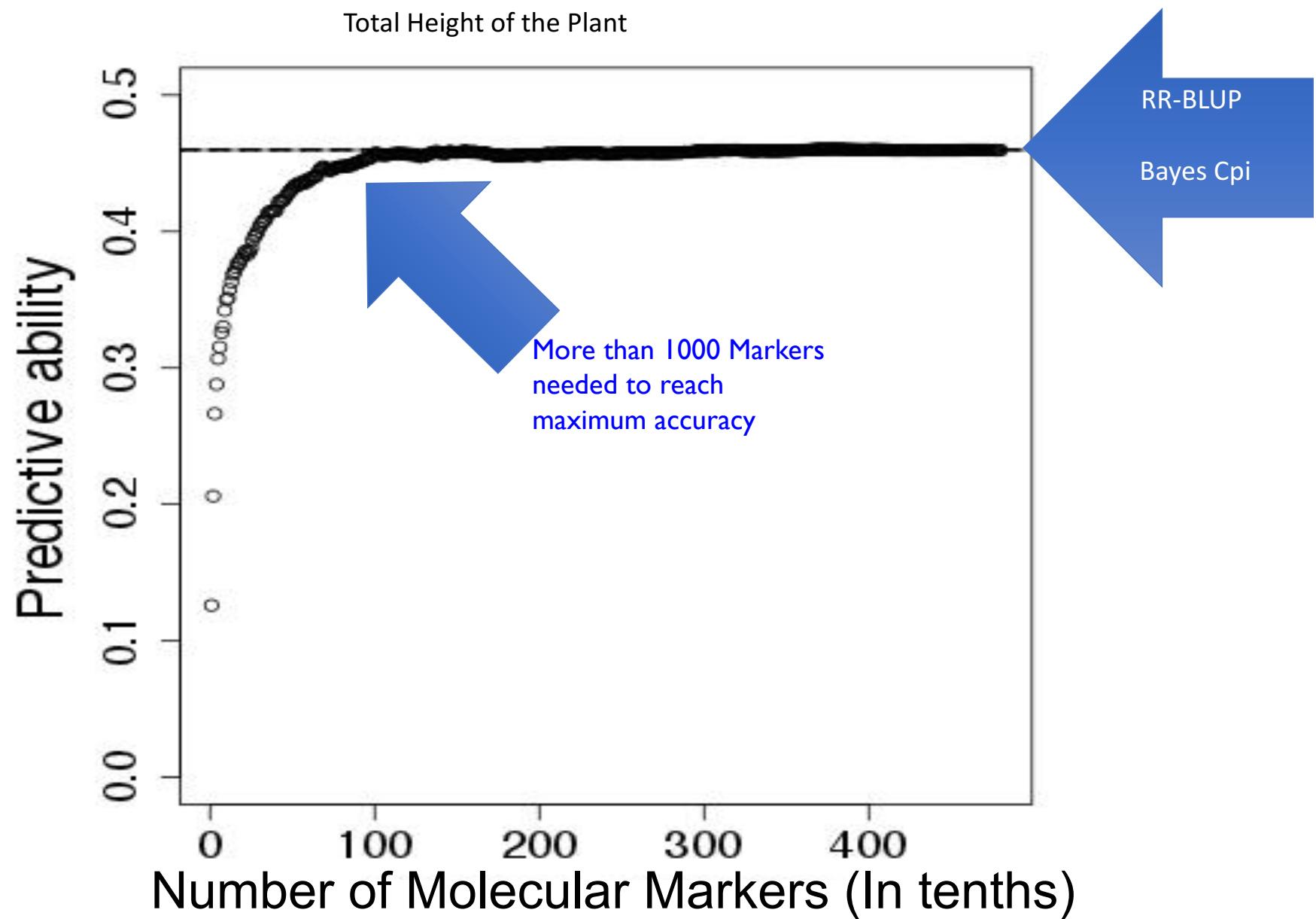
Training population



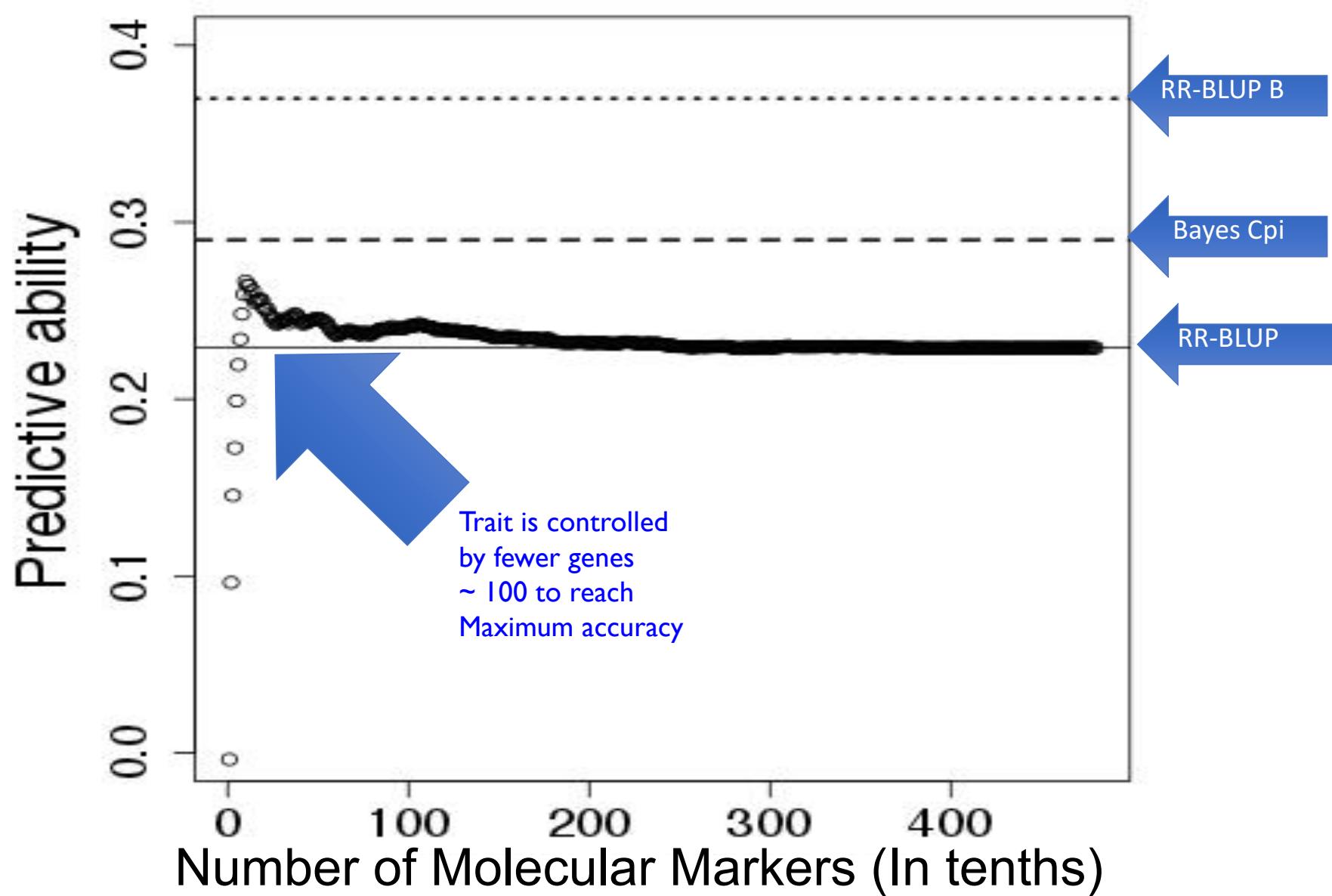
Unrelated population



Genomic Selection- Quantitative traits trend

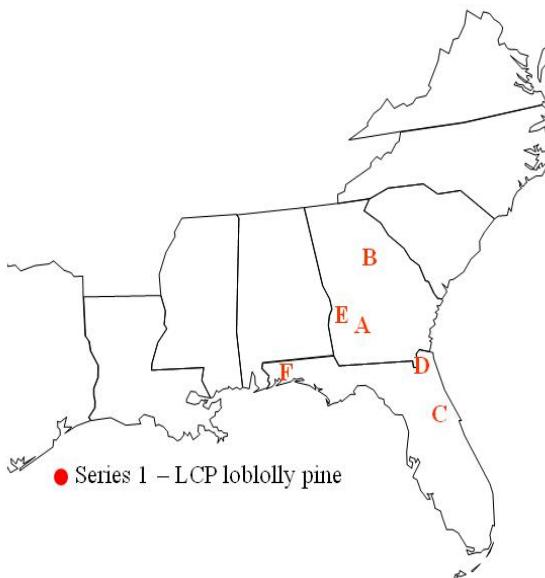


Genomic Selection-RR-BLUP_B on oligogenic traits



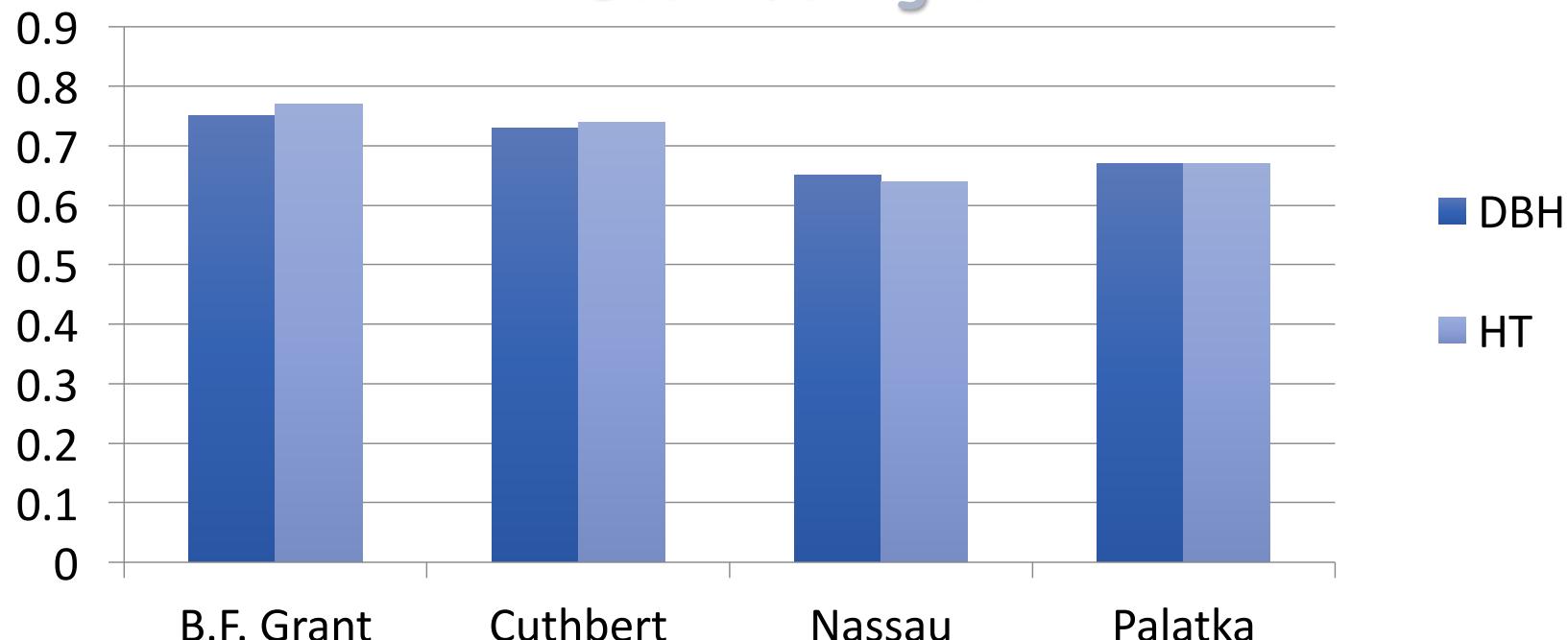
Genomics Selection in CCLONES

- "Comparing Clonal Lines on Experimental Sites = CCLONES"
 - Currently ~3 SNP markers/cM from unique Pine ESTs (Eckert *et. al.*, 2010)
 - Clonal Populations with high quality phenotypic data readily available
 - Parents = 32
 - Four different sites:
 - BFGrant , Cuthbert (Georgia)
 - Nassau, Palatka (Florida)



GWS Accuracies in CCLONES

DBH & Height



$$SR_{GS} = \frac{r_{GS}}{C_{GS}}$$

$$SR_{PS} = \frac{r_{PS}}{C_{PS}}$$

$$R_{GS:PH} = \frac{(r_{GS} \times C_{PH})}{(r_{PS} \times C_{GS})}$$

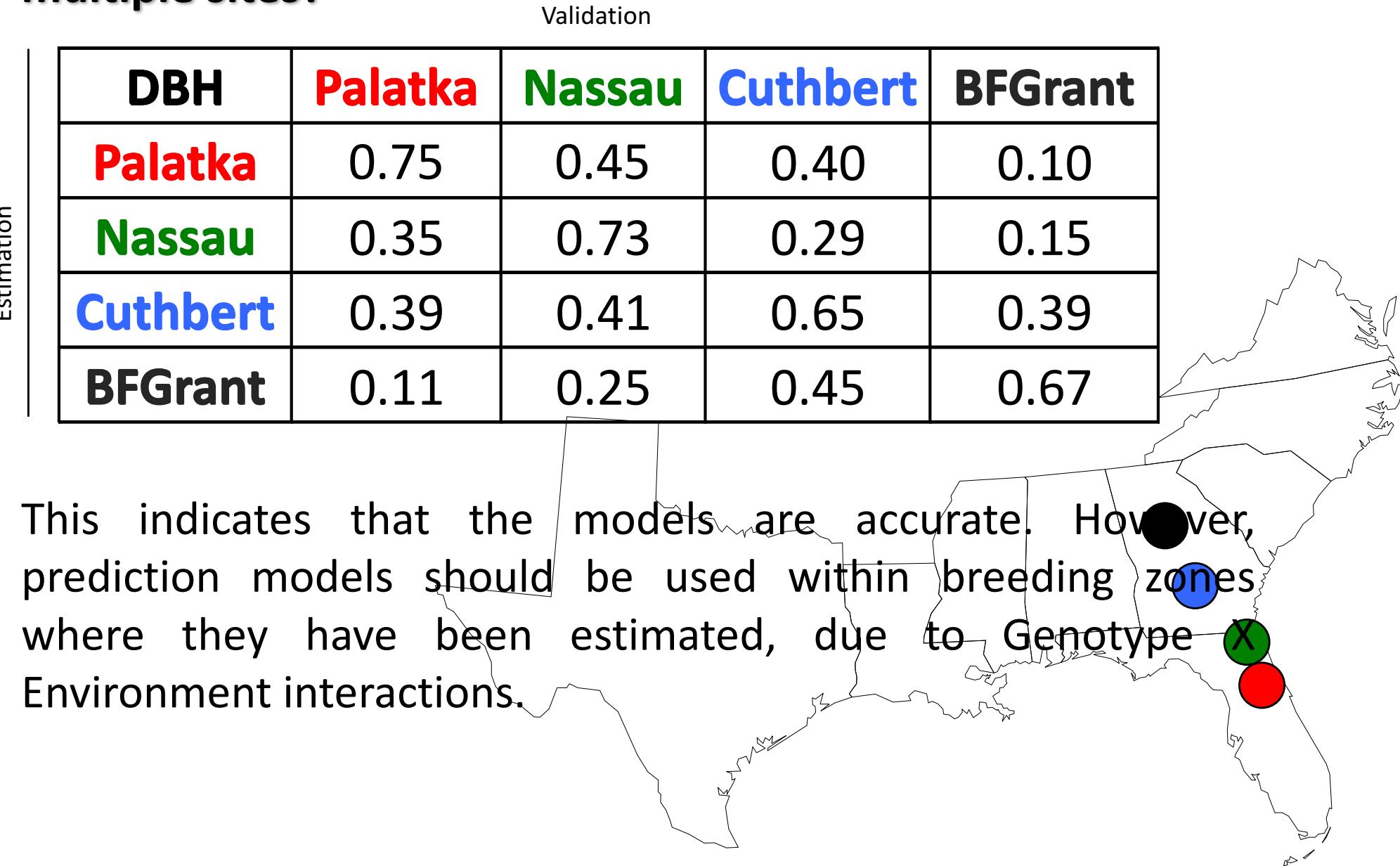
Trait	Site	h (BLUP)	h (GS)	Efficiency	Increase relative to phenotypic selection (%)
DBH	B.F. Grant	0.79	0.75	1.90	90
	Cuthbert	0.75	0.73	1.95	95
	Nassau	0.85	0.65	1.53	53
	Palatka	0.81	0.67	1.65	65
HT	B.F. Grant	0.74	0.77	1.03	108
	Cuthbert	0.68	0.74	2.18	118
	Nassau	0.80	0.64	1.60	60
	Palatka	0.85	0.67	1.58	58

Accuracy × Intensity × Variation
 $\Delta BV / Yr$

Generation Interval

GWS Accuracies in CCLONES

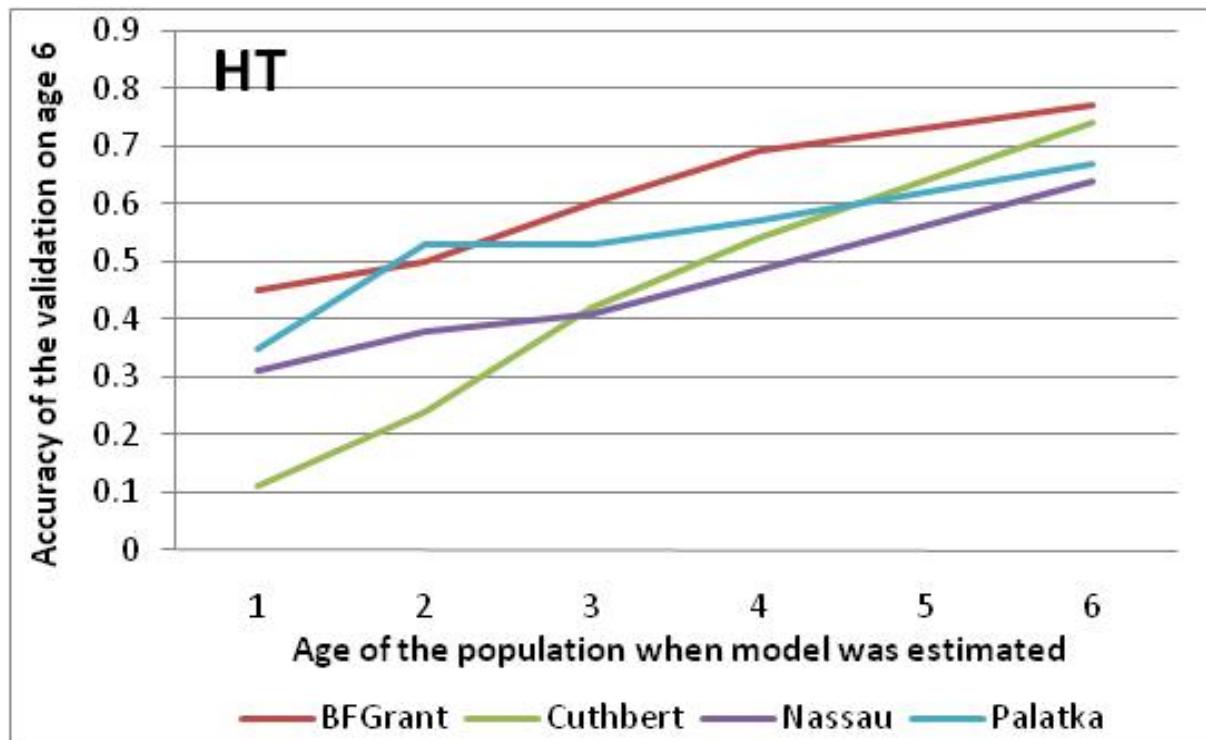
Can breeders use the model developed in one site across multiple sites?



GWS Accuracies in CCLONES

Issue: Stability of the prediction model

The prediction models fall apart after multiple generations



Want model to be accurate for the larger number of generations as possible

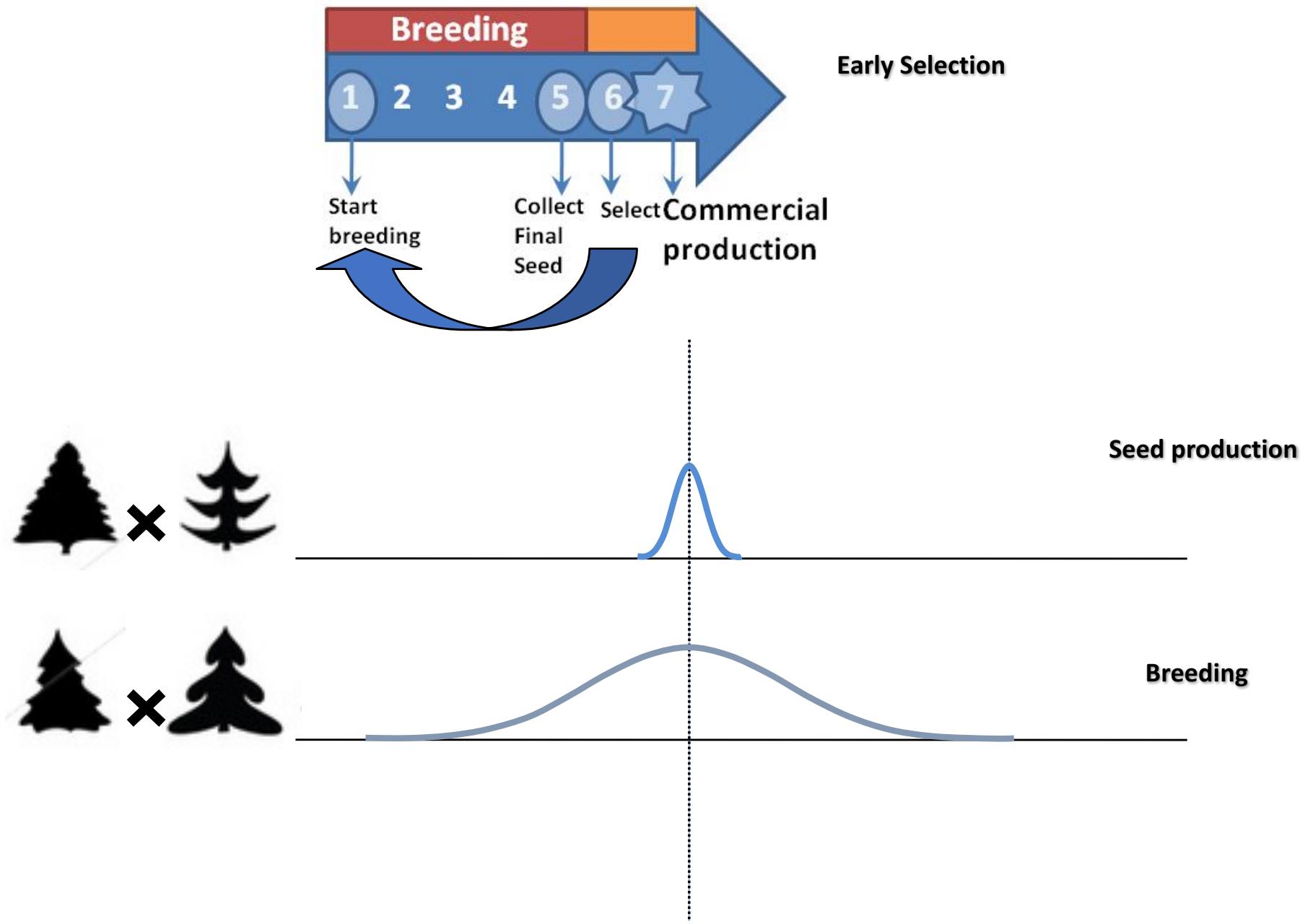
Solution:

Larger number of markers: Model holds for longer;

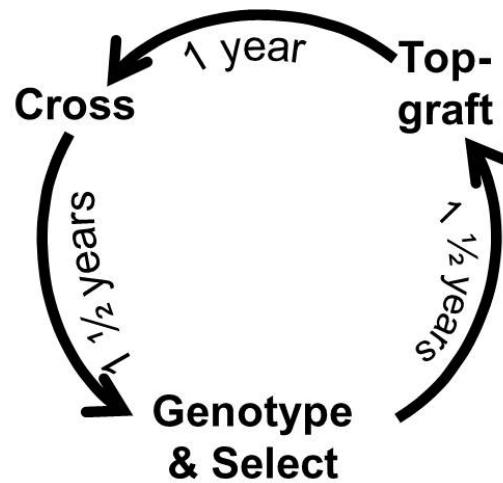
CCLONES: What should you cross?

- ~950 individuals
 - ~450,000 possible crosses
 - Mating allocation under a whole genome evaluation scenario (including dominance) – (Toro and Varona, 2010)
 - Estimate of the variance of the future progeny of a given cross

Pine breeding to seed production:

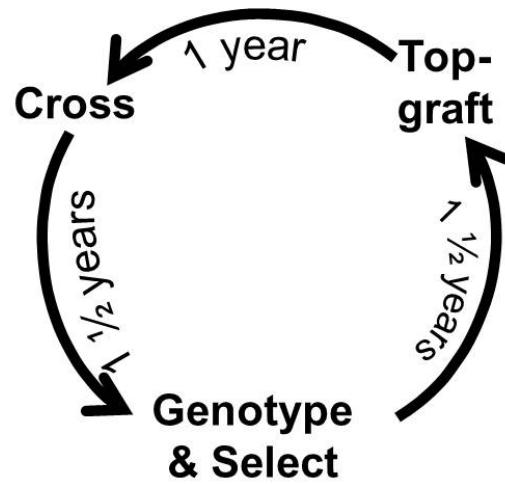


Genomics Selection Guided Crosses



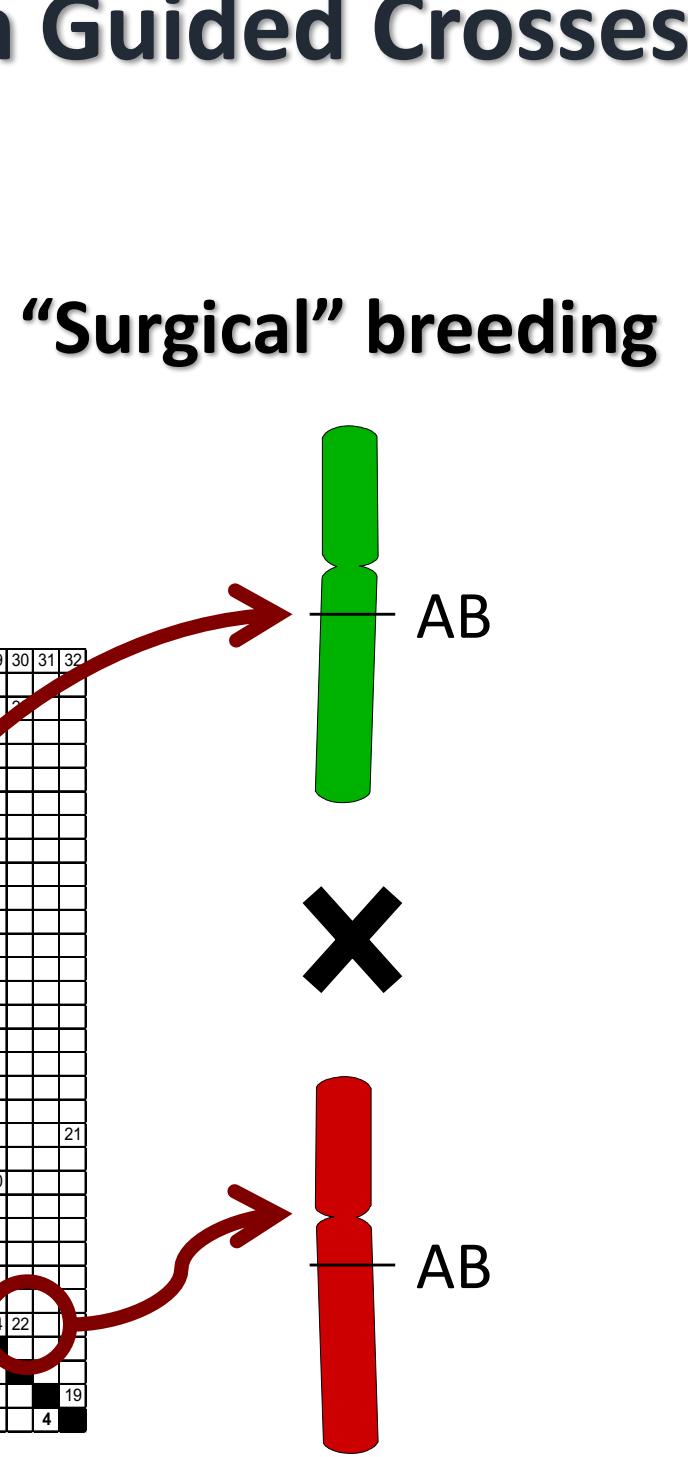
“Surgical” breeding

Genomics Selection Guided Crosses

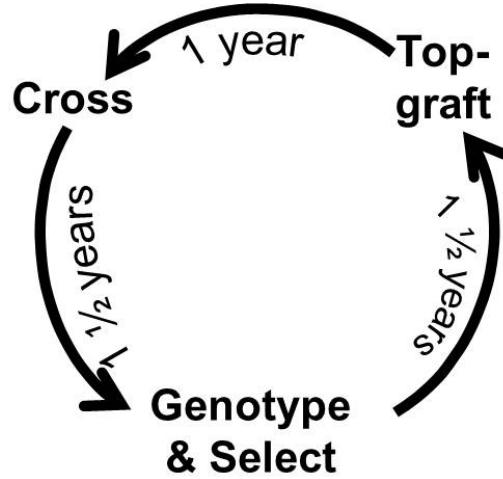


"Surgical" breeding

ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	
1		16	17				18																										
2	6		18	17																													
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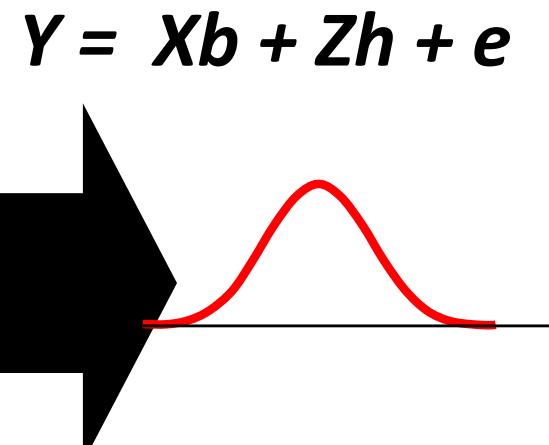
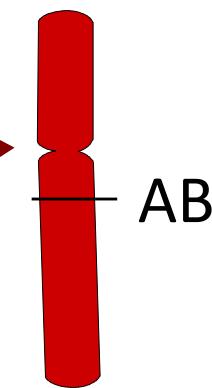
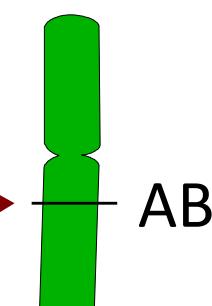


Genomics Selection Guided Crosses

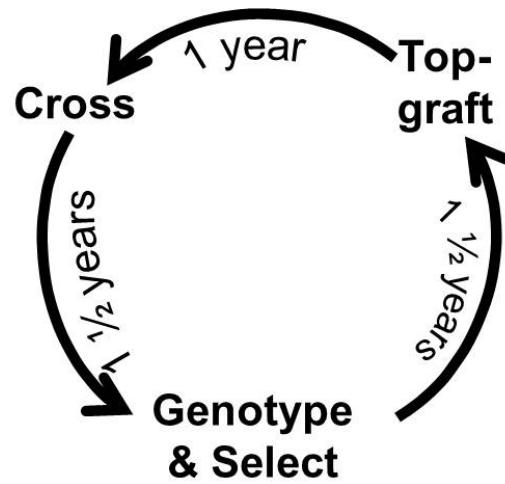


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“Surgical” breeding

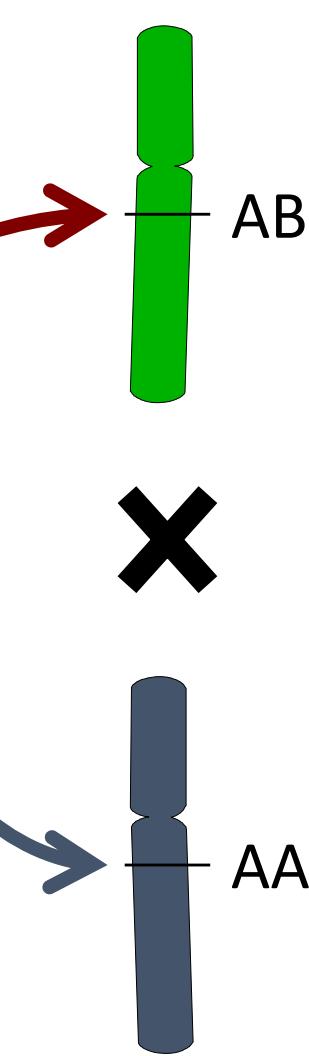


Genomics Selection Guided Crosses

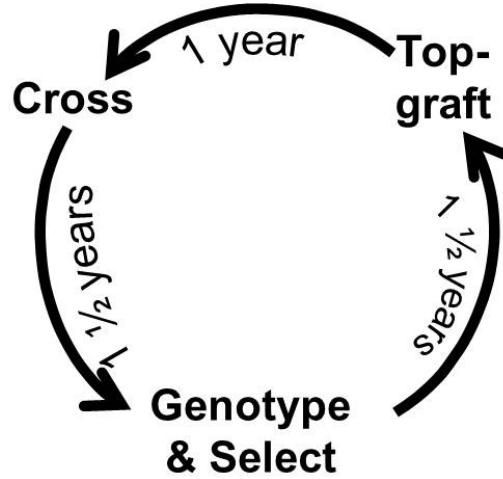


"Surgical" breeding

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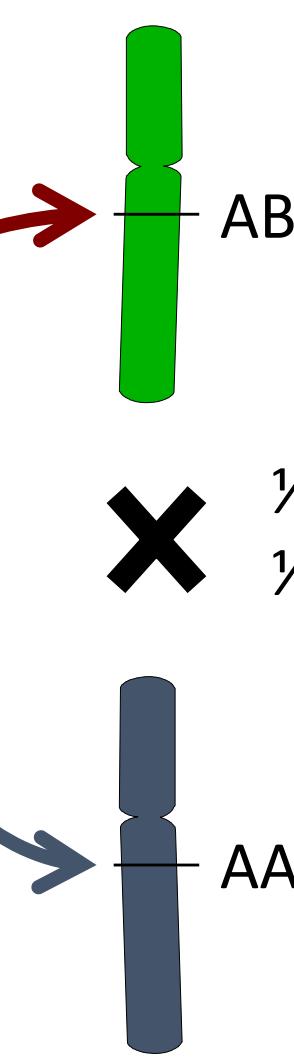


Genomics Selection Guided Crosses

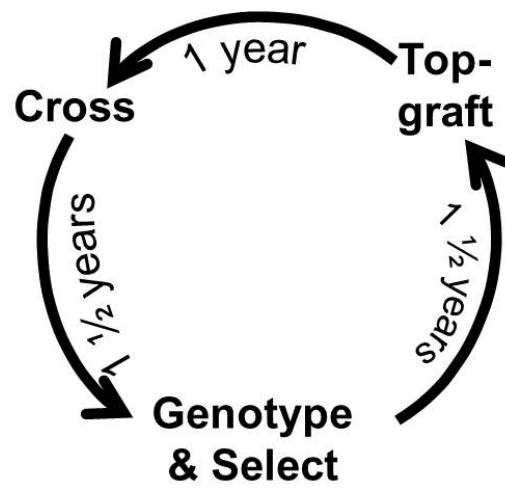


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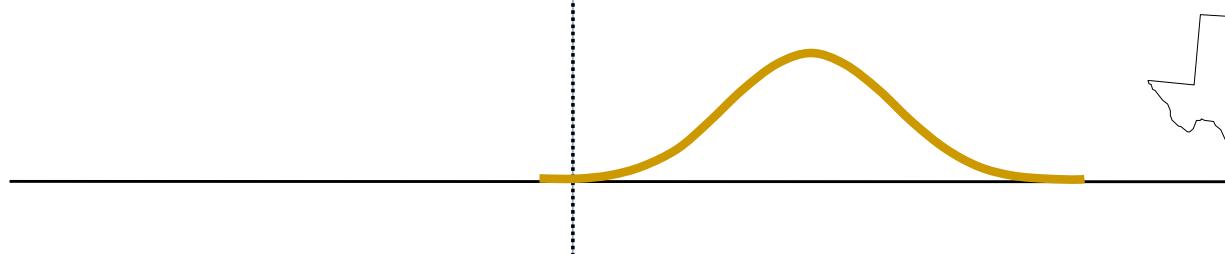
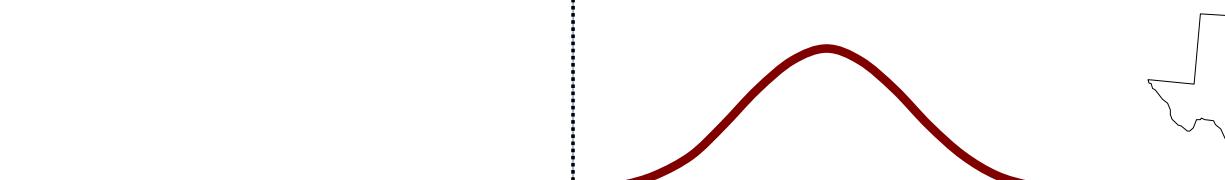
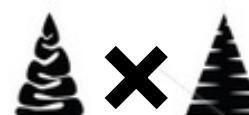
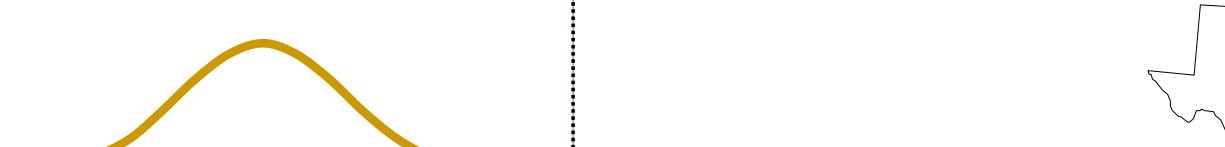
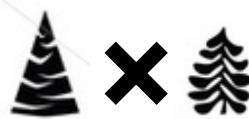
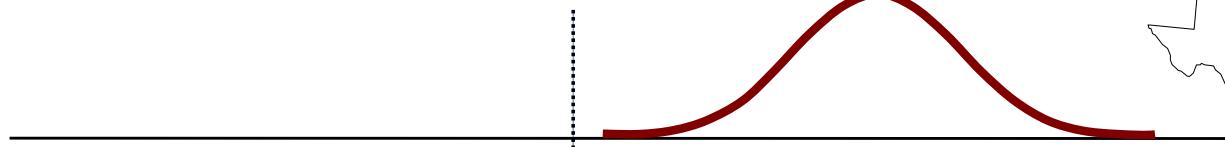
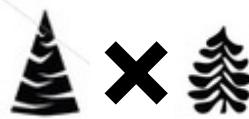
"Surgical" breeding



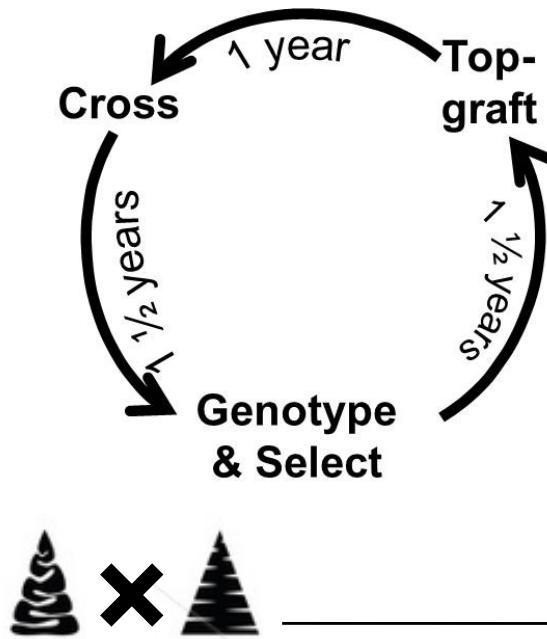
Genomics Selection Guided Crosses



"Surgical" breeding

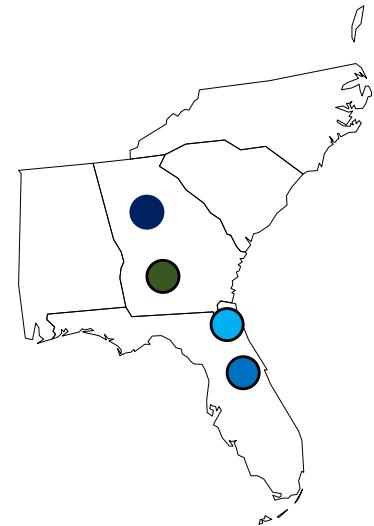
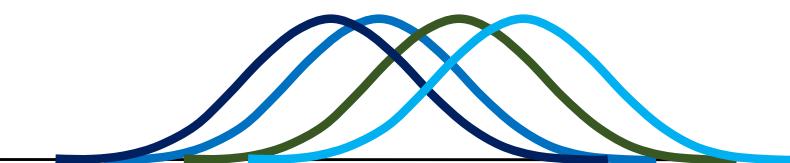


Genomics Selection Guided Crosses

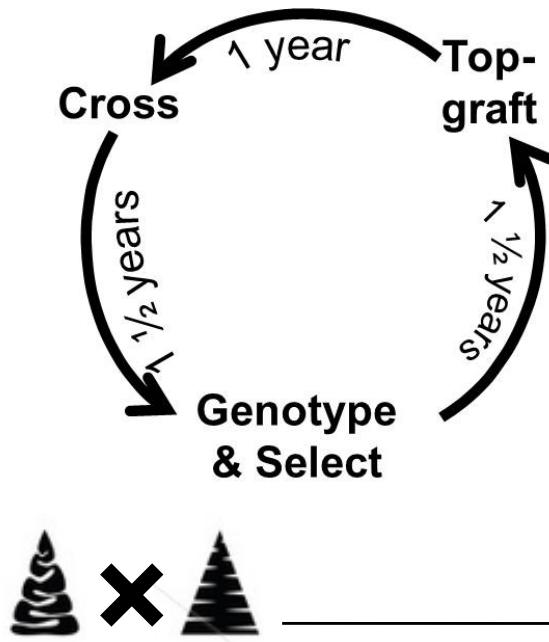


"Surgical" breeding

Height

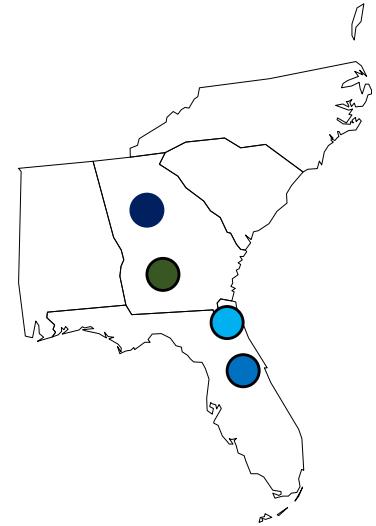


Genomics Selection Guided Crosses

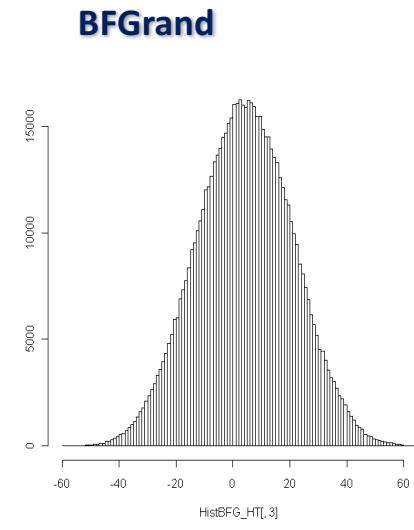
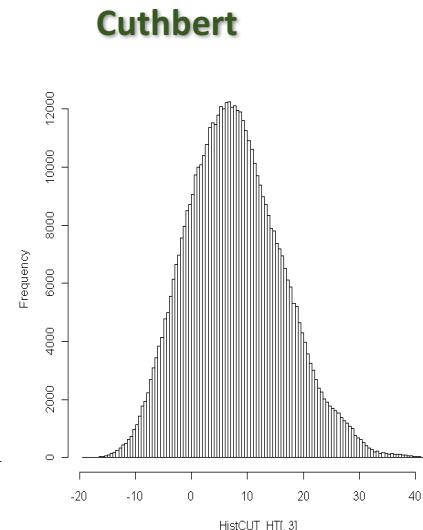
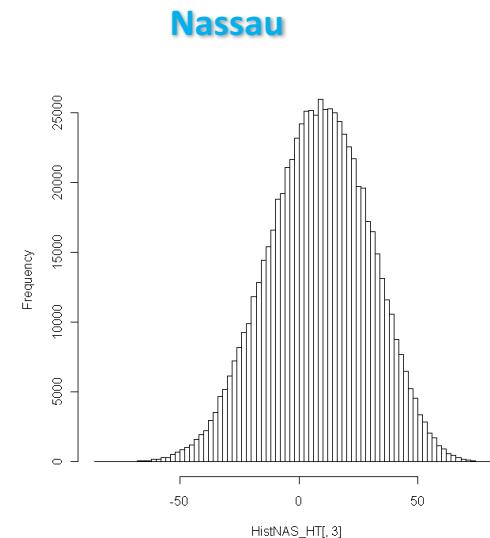
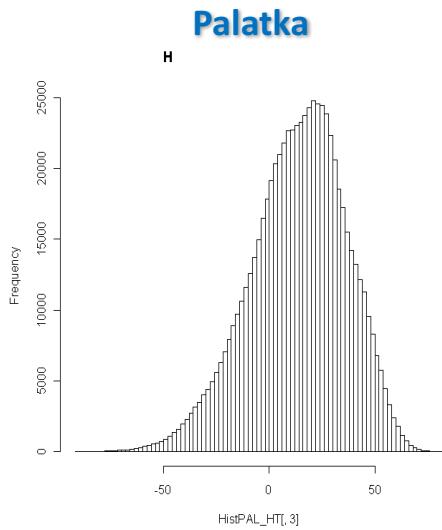


“Surgical” breeding

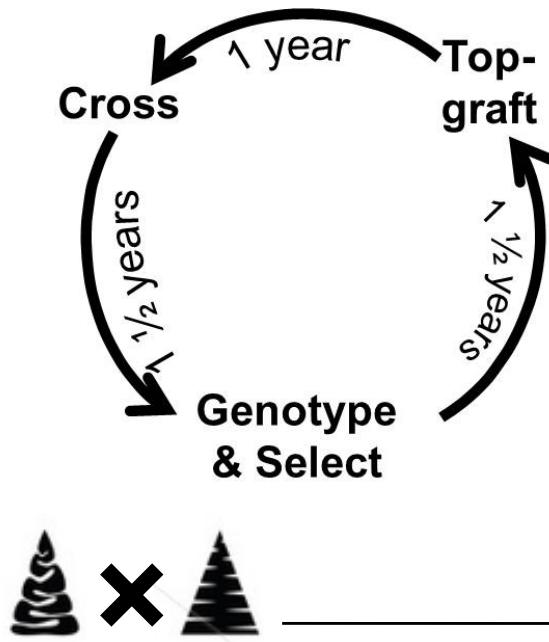
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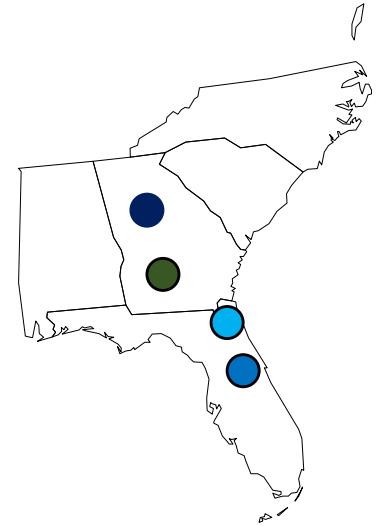


Genomics Selection Guided Crosses



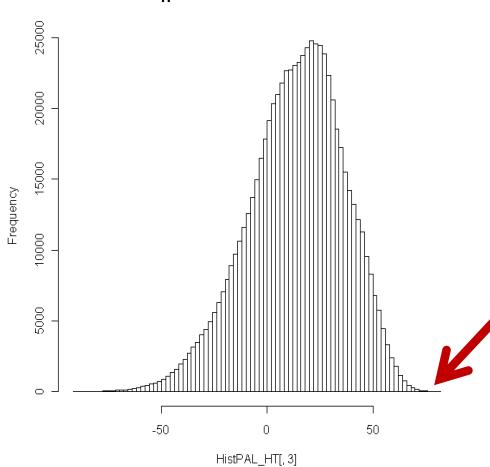
“Surgical” breeding

Height

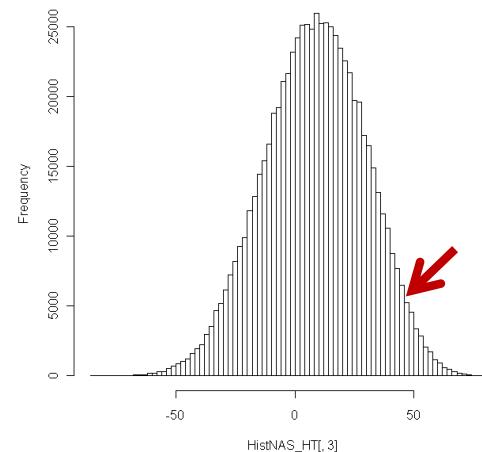


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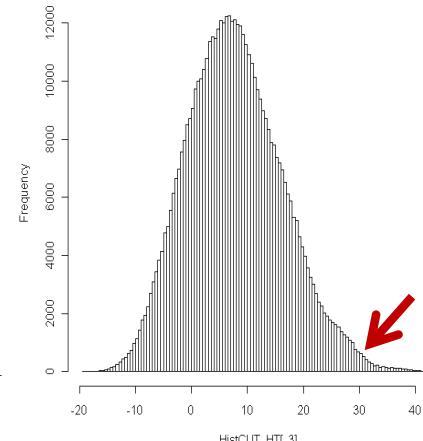
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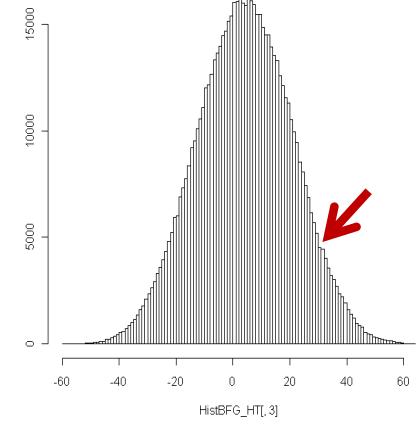
Nassau



Cuthbert



BFGGrand



Detection of candidate genes for Rust resistance in Eucalyptus using Genomic Selection

Marcio Resende Jr.
University of Florida



Picture: *Puccinia psidii* infecting *Eucalyptus grandis*
Credit: Acelino Couto Alfenas.

Eucalyptus x *Puccinia psidii*



Picture: Alfenas *et. al.* 2009

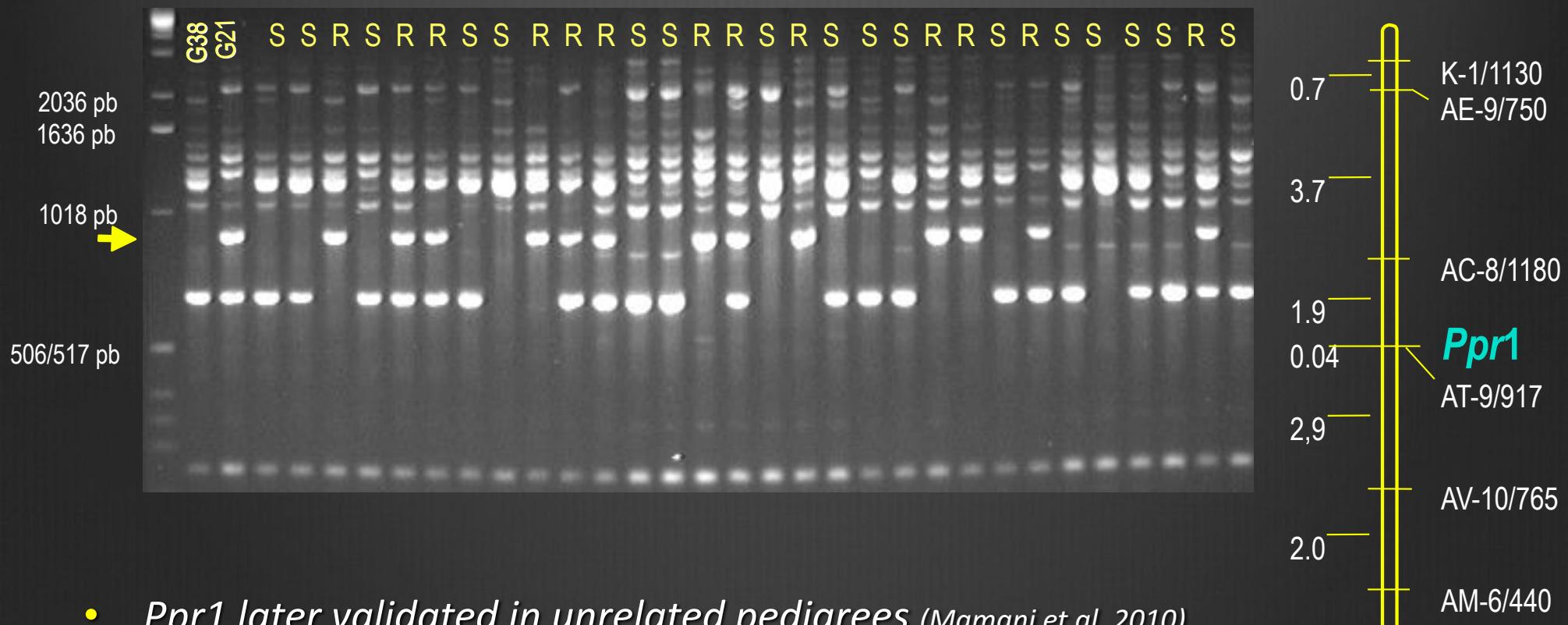
E. grandis:
Largely planted ... and highly susceptible



D. T. Junghans · A. C. Alfenas ·
S. H. Brommonschenkel · S. Oda · E. J. Mello ·
D. Grattapaglia

Resistance to rust (*Puccinia psidii* Winter) in *Eucalyptus*: mode of inheritance and mapping of a major gene with RAPD markers

Received: 19 December 2002 / Accepted: 2 June 2003 / Published online: 19 September 2003
© Springer-Verlag 2003



- *Ppr1* later validated in unrelated pedigrees (Mamani et al. 2010)
- However *Ppr1* resistance was not fully effective in the field (Suzano pers. comm)

Objective of the work

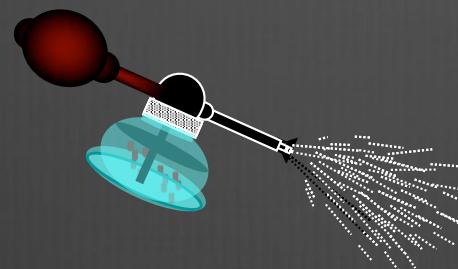
- Evaluate the use of Genomic Selection approach for Rust resistance in Eucalyptus
 - Phenotype prediction
 - Candidate gene detection
- Approach:
 - 482 individuals
 - 2747 DArT markers
 - Bayesian variable selection model (BayesC π – Habier *et. al.* 2009)

BIGS/GenSel

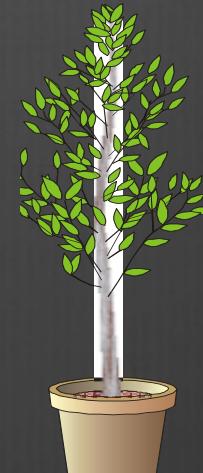
Inoculation method



Syzygium jambos



2×10^4 spores/mL



Phenotyping: 1-5 Scale

Phenotyped 20 D.A.I.



Junghans *et al.* 2003

S0 immune

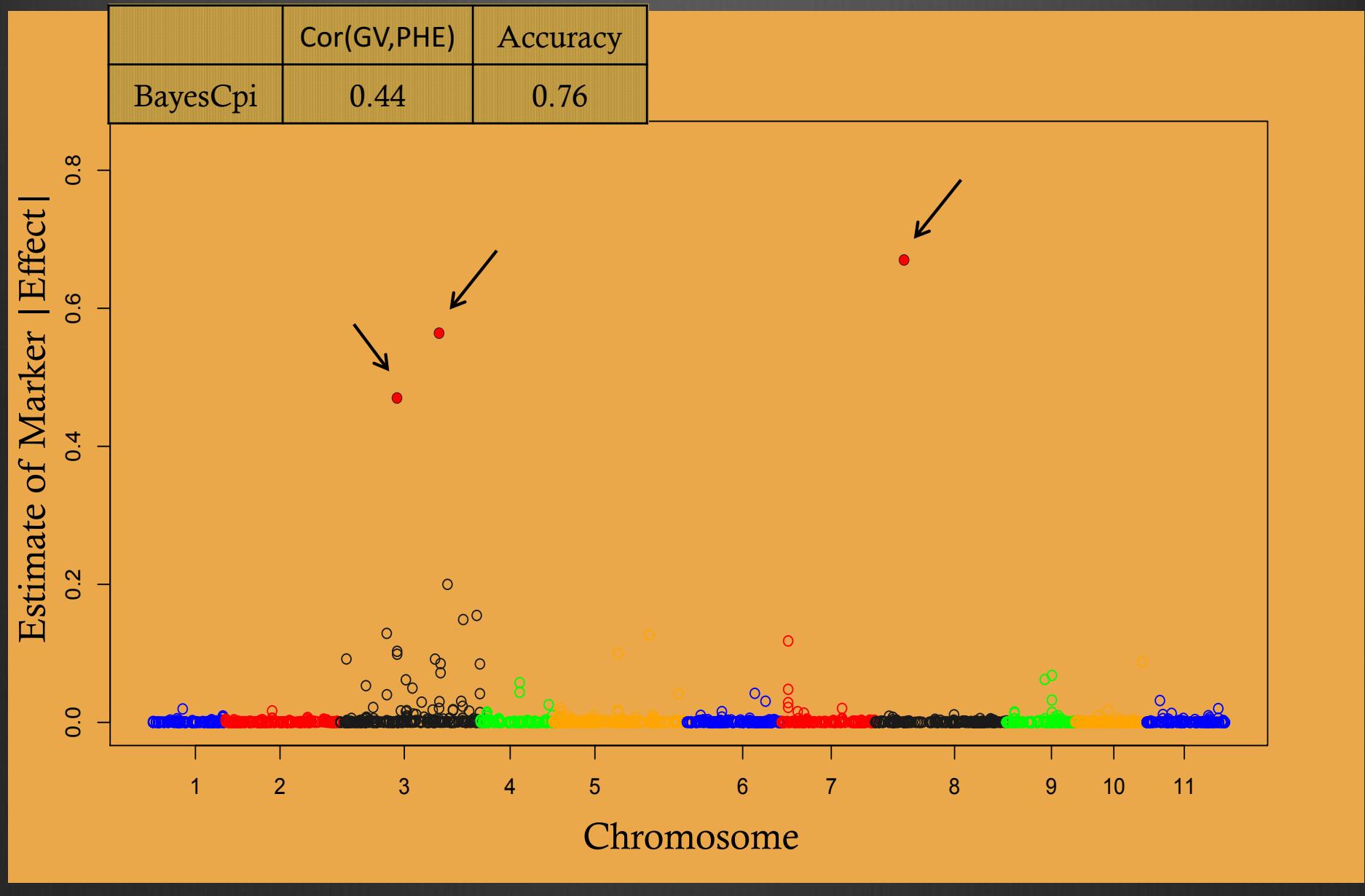
S0 HR

S1

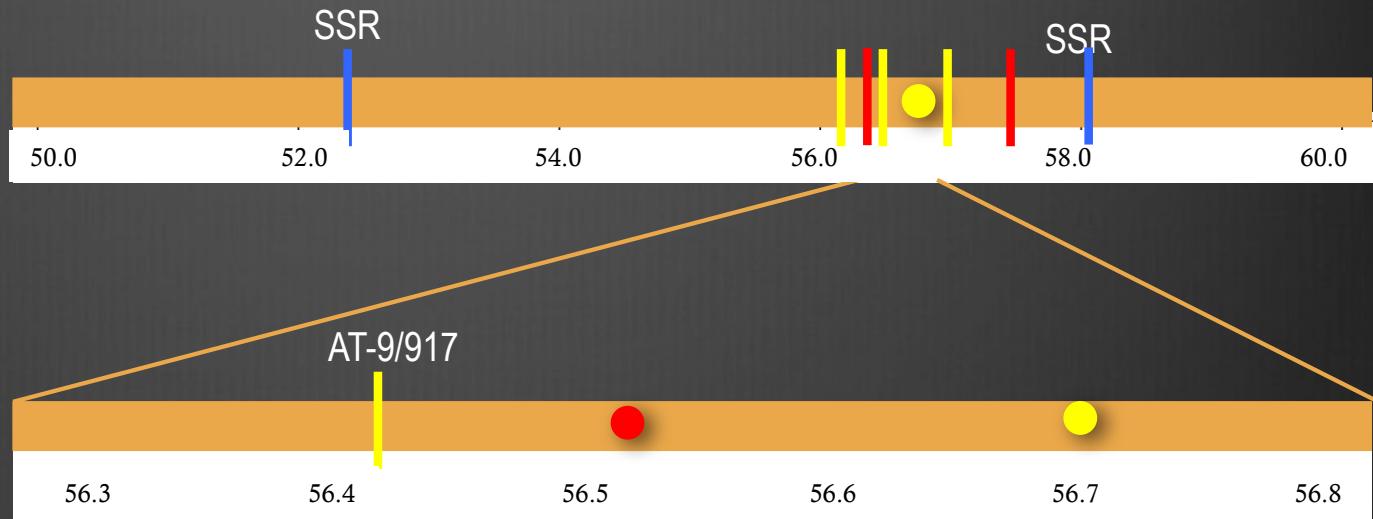
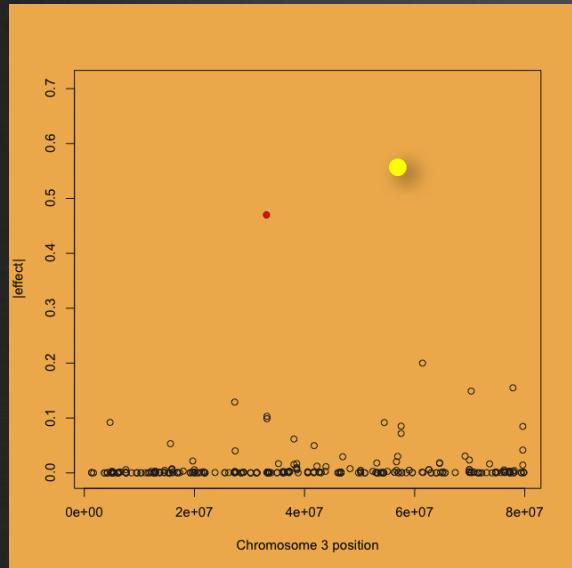
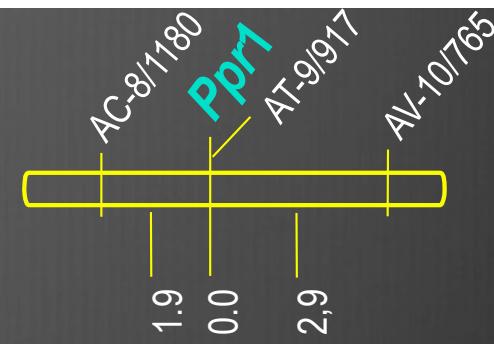
S2

S3

Marker Effects



Zooming in CHR 3



Identification of a novel QTL contributing to rust resistance in *Eucalyptus*



R-NBS-LRR class) family

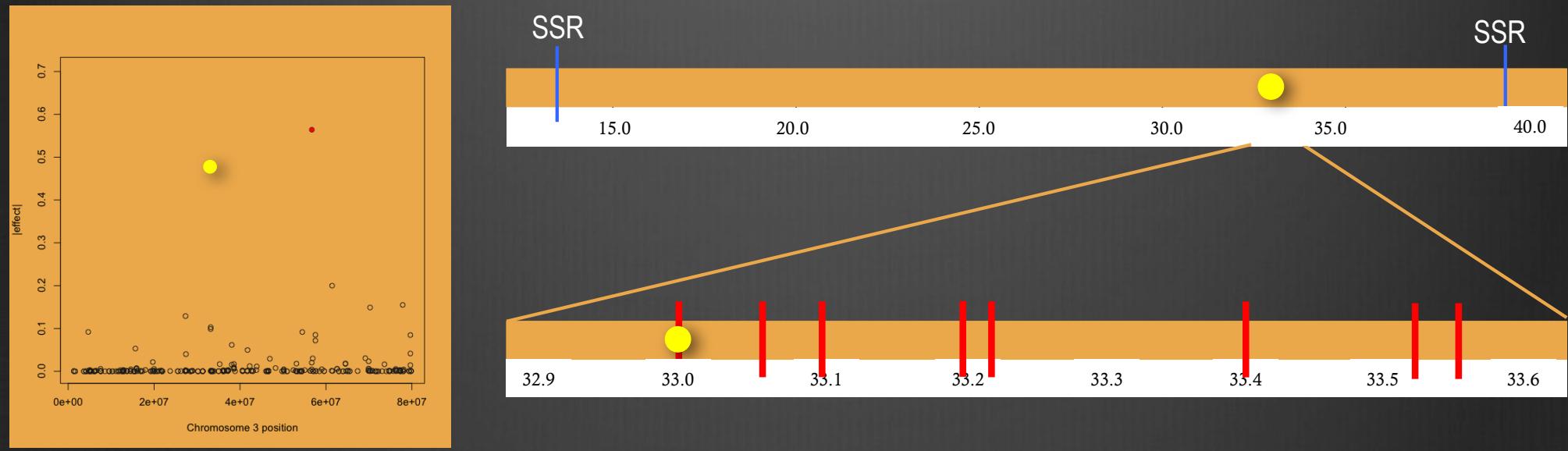
Bruno M Lima^{1*}, Juliana EC Teixeira², Rodrigo Gazaffi¹, Antonio AF Garcia¹, Dario Grattapaglia³, Raphaelle KD Valle⁴, Luis EA Camargo⁴

Genetic mapping provides evidence for the role of additive and non-additive QTLs in the response of inter-specific hybrids of *Eucalyptus* to *Puccinia psidii* rust infection

Alexandre Alonso Alves · Carla Cristina Gonçalves Rosado ·
Danielle Assis Faria · Lúcio Mauro da Silva Guimarães · Douglas Lau ·
Sérgio Hermínio Brommonschenkel · Dario Grattapaglia · Acelino Couto Alfenas



Zooming in CHR 3



Identification of a novel QTL contributing to rust resistance in *Eucalyptus*

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