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Technical nuances of machine learning:
Implementation and validation of supervised methods for genomic prediction in plant breeding

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Outline

1. **Introduction**
2. **Machines**
   - Linear models
   - Kernel methods
   - Neural networks
   - Tree ensembles
3. **Validation**
   - Schemes and metrics
   - Information and case of study
4. **Conclusion**

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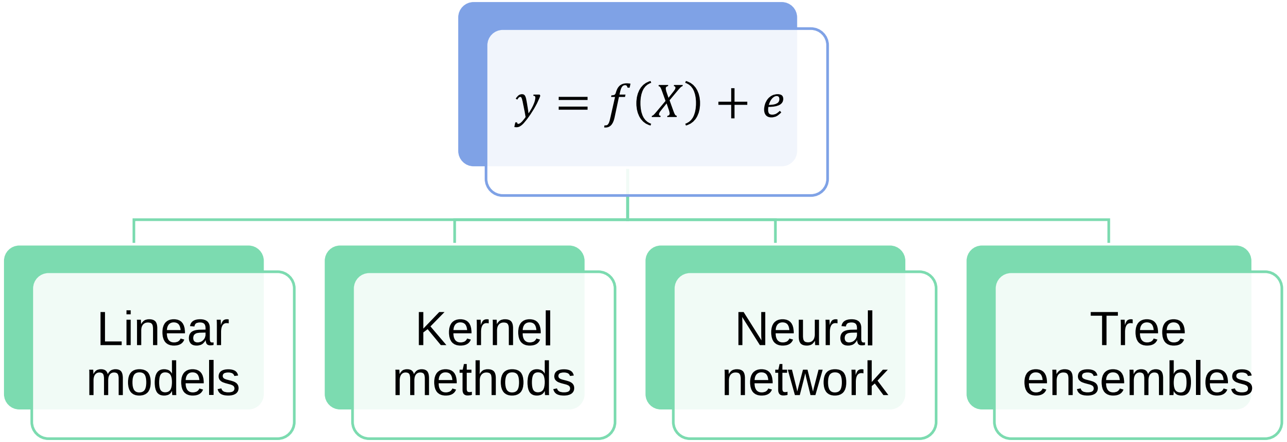
Introduction

Genomic prediction


$$y = f(X) + e$$

Linear models

Kernel methods

Neural network

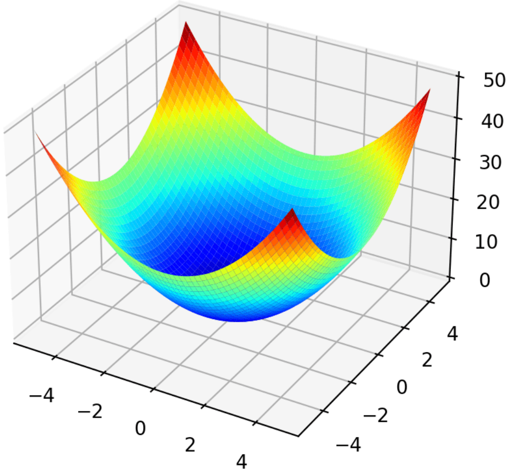
Tree ensembles

Objective of this presentation

- Describe machine learning methods without (too many) jargons
- Review validations strategies to contrast methods

Divergency in philosophy

- In quantitative genetics:
  - Parameters: Variance components + Regression coefficients
  - Function: Likelihood (complex and convex)
  - Tuning: Generally, not needed
  - **Method**: First order (EM, MCMC), second order (AI, MIVQUE)
- In machine learning:
  - Parameters: Regression coefficients (NO VARIANCES!)
  - Function: MSE, L2 (simple)
  - Tuning: Cross validations, need secondary objective function
  - **Method:** First order: coordinate & gradient descent



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Machines

1. Linear methods

$$y = X\beta + e$$

- Phenotype is described as a linear combination of markers
- Easy to compute; easy to store (vector β); easy to interpret
- LMs do not capture any patter that is not explicitly declared in X

Solution for linear models

Conditioning to univariate:
(Coordinate descent)

$$y = Xb + e$$
$$y = X_{-j}b_{-j} + x_j b_j + e$$
$$y - X_{-j}b_{-j} = x_j b_j + e$$
$$y_j = x_j b_j + e,$$

Univariate solutions for b_j

- $b_j(OLS) = \frac{x_j' y_j}{x_j' x_j}$ * Unique solution
  (1722)
- $b_j(RR) = \frac{x_j' y_j}{x_j' x_j + \lambda}$ * Unique solution
  (1970)
- $b_j(EN) = \frac{x_j' y_j - \lambda}{x_j' x_j + \lambda}$
  (2005)
- $b_j(LAR) = \frac{MED(y_j \# x_j)}{Var(x_j)}$
  (1935)
- $b_j(LASSO)_+ = \frac{x_j' y_j - \lambda}{x_j' x_j}$
  (1996)

“Translation” table for geneticists

- Penalization = Shrinkage
- Multiple “penalizations” = Mixed model
- Least squares = Fixed effect
- Ridge regression = Random effect

The shrinkage parameter λ

- Quantitative genetics
  - Analytical solution: $\lambda = \sigma_e^2 \div \sigma_\beta^2$ (only applies to ridge)
  - Variances found via REML, Bayesian, others (MIVQUE, Tilde-Hat)
- Machine learning
  - Run a cross-validation to find λ
  - Secondary criteria to define the best λ… usually some metric of prediction

Solving: $\mathbf{y = Xb + e}$

$Finding \rightarrow argmin(e'e + \lambda b'b)$

- Coordinate descent

(Use diagonals of LHS)

$$\hat{b}_j^{t+1} = \frac{x_j'(y - X_{-j}\hat{b}_{-j})}{x_j'x_j + \lambda}$$

Used for WGR (RR, BayesA)

glmnet, BGLR, bWGR, GS3

- Gradient descent

(Does not build LHS)

$$\hat{b}^{t+1} = b^t - \frac{2r}{n}\left[X'(y - X\hat{b}^t) + \lambda\hat{b}^t\right]$$

Used for Deep Neural Nets

TF/Keras, PyTorch, MXNet, h2o

- Second order

(Builds entire LHS)

$$\hat{b} = (X'X + \lambda)^{-1}(X'y)$$

Used for <u>everything else</u>

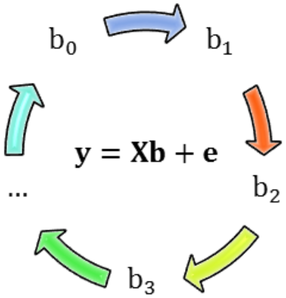
ASREML, lme4, SAS, BLUPF90

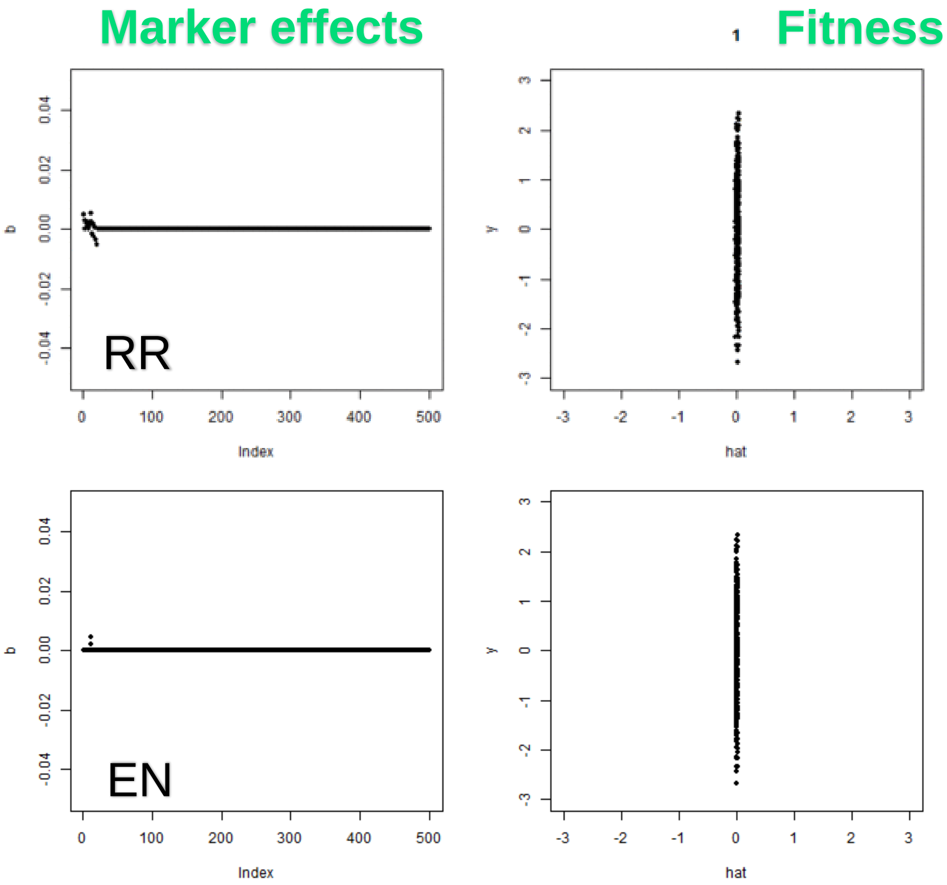
Coordinate descent of ***ridge regression*** (RR) and ***elastic net*** (EN)

CD solved using Gauss-Seidel:

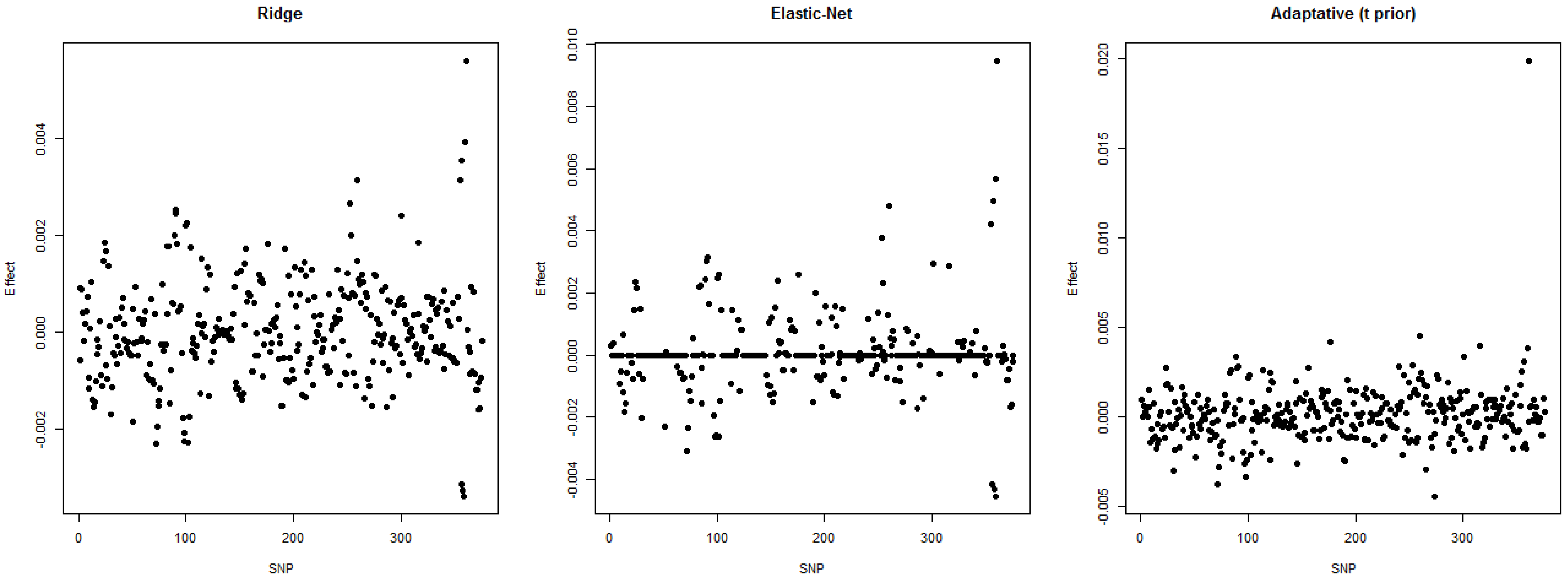
$$\hat{b}_j^{t+1} = \frac{x_j' \hat{e}^t + x_j' x_j \hat{b}_j^t}{x_j' x_j + \lambda}$$

$$\hat{e}^{t+1} = \hat{e}^t - x_j\left(\hat{b}_j^{t+1} - \hat{b}_j^t\right)$$





Impact of different models on the marker effects



Dataset ***tpod*** from bWGR has one QTL on Chr19

2. Kernel methods

$$y = K(X) + e$$

- Markers are used to “map” individuals by similarity / relationship
- Capture complex patterns; Good for P>N and interactions; Solved as LMs;
- Requires factorization; Not possible to store the model from K (“lazy learner”)

Creating kernels

- Kernels (K) are transformations of X
- Before solving the model, we must compute $K = f(X)$

Kernel	Linear	Linear interaction	Gaussian (RBF)	Arccosine
$f(X)$	$K = \alpha XX'$	$K = \alpha(XX')\#(XX')$	$K = \exp(-\alpha D^*)$	$K(i,j) = \pi(x_i'x_i)(x_j'x_j)\sin(\theta_{ij}) + (\pi - \theta_{ij})\cos(\theta_{ij})$
Parameter	$\alpha = n^{-1}tr(XX')$	$\alpha = n^{-1}tr[(XX')\#(XX')]$	$\alpha = median(D)$ Tuning?	$\theta_{ij} = cor^{-1}Corr(x_i, x_j)$
Known as	GBLUP, Kalman filter	Epistatic kernels	RKHS, SVR	“Deep kernel”

* D = Euclidean distance = $\sum(x_i - x_j)^2$

Solution for kernel methods

$y = g + e$
$y \sim N(0, K\sigma_g^2 + I\sigma_e^2)$

$y = g + e$
$y \sim N(0, K\sigma_g^2 + I\sigma_e^2)$

$y = Ua + e$
$y \sim N(0, UDU'\sigma_g^2 + I\sigma_e^2)$

$y = La + e$
$y \sim N(0, LL'\sigma_g^2 + I\sigma_e^2)$

	None	Inversion	Eigen (Spectral)	Cholesky
Factorization	$f(K) = K$	$f(K) = K^{-1}$	$f(K) = UDU'$	$f(K) = LL'$
Solution	$(K + \lambda I)g = Ky$	$(I + \lambda K^{-1})g = y$	$(I + \lambda D^{-1})a = U'y$	$(L'L + \lambda I)a = L'y$
Genomic prediction	$g = g$	$g = g$	$g = Ua$	$g = La$

When K is too big to factorize

K^{-1} sometimes can be estimated directly from data (e.g., pedigree)

1) When K is not inversible;
2) Speed up convergence;
3) Reduction of dimensionality;

Cheaper than Eigen, but K must be inversible

Prediction of new individuals?

- Approach 1 - **Conditional expectation**
  - $\hat{g}_{\text{new}} = K_{\text{obs,new}} K_{\text{obs}}^{-1} \hat{g}_{\text{obs}}$
  - $\hat{g}_{\text{new}} = K_{\text{obs,new}} \hat{\sigma}_g^2 \left(K_{\text{obs}} \hat{\sigma}_g^2 + I \hat{\sigma}_e^2 \right)^{-1} y_{\text{obs}}$

$$\mathbf{K} = \begin{array}{|c|c|} \hline \mathbf{K}_{\mathbf{obs}} & \mathbf{K}_{\mathbf{obs,new}} \\ \hline \mathbf{K}_{\mathbf{new,obs}} & \mathbf{K}_{\mathbf{new}} \\ \hline \end{array}$$

- Approach 2 - **Missing value**
  - Fit the model where **K** has both observed and new individuals
  - New individuals are fit with weights = 0

3. Neural networks

$$y = \alpha(\alpha(XB_1)B_2)b_3 + e$$

- Markers are used to create non-linear latent spaces
- Can capture complex patterns; Deal with large datasets;
- Requires extensive tuning; Not objectively interpretable;

Progression from LM to Deep Neural Network

Models illustrated without intercept

Linear model

$$y = Xb + e$$

PLS/PCR model

$$y = (XB_1)b_2 + e$$

NN model

$$y = \alpha(XB_1)b_2 + e$$

Deep NN model

$$y = \alpha(\alpha(XB_1)B_2)b_3 + e$$

$\alpha =$ activation function

Solution for neural networks

$$y = Xb + e$$

$$\nabla = \frac{\partial(y - Xb)'(y - Xb) + \lambda b'b}{\partial b}$$

Let's start with Gradient descent for a simple ridge regression

$$\hat{b}^{t+1} = \hat{b}^{t} - r\nabla$$

$$\hat{b}^{t+1} = \hat{b}^{t} - r\left[-2n^{-1}X'\left(y - X\hat{b}^{t}\right) + 2n^{-1}\lambda\hat{b}^{t}\right]$$

$$\hat{b}^{t+1} = \hat{b}^{t} - r\left(-2n^{-1}X'\hat{e} + 2n^{-1}\lambda\hat{b}^{t}\right)$$

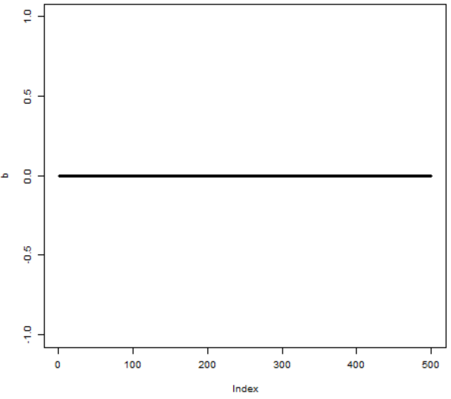
$$\hat{b}^{t+1} = \hat{b}^{t} + 2rn^{-1}X'\hat{e} - 2n^{-1}\lambda\hat{b}^{t}$$

$$\hat{b}^{t+1} = \hat{b}^{t} + 2n^{-1}r\left(X'\hat{e} - \lambda\hat{b}^{t}\right)$$

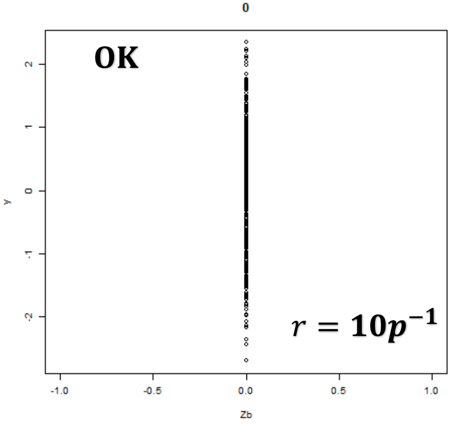
No matrix inversion, just multiplications

Gradient descent of a ridge regression

Marker effects

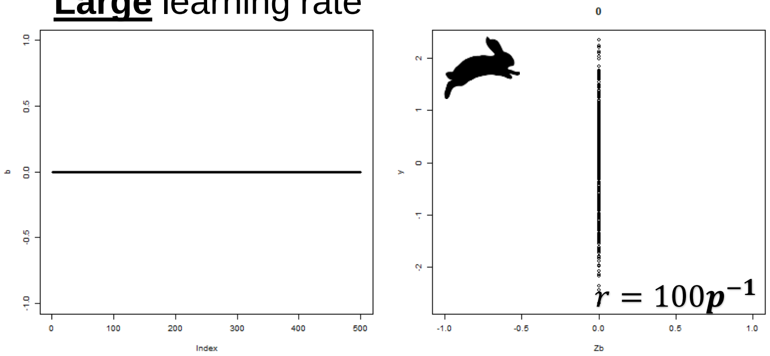


Fitness



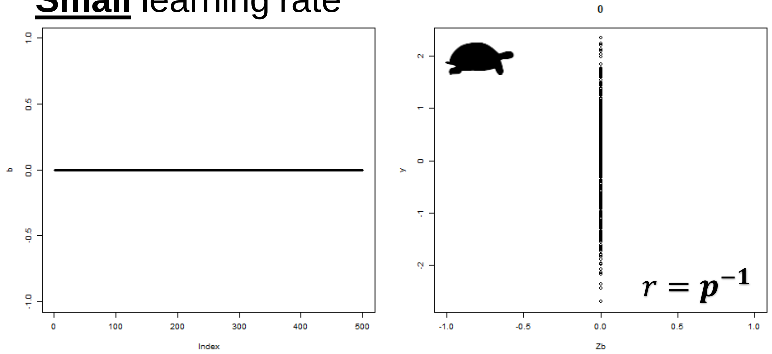
$r = 10p^{-1}$

Large learning rate



$r = 100p^{-1}$

Small learning rate



$r = p^{-1}$

Solution for neural networks

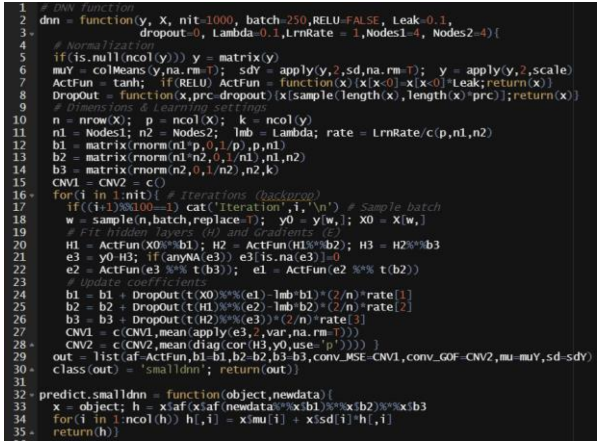
$$y = \underbrace{\alpha(\underbrace{\alpha(\underbrace{XB_1)}_{H_1}B_2)}_{H_2}b_3}_{H_3} + e$$

- Fit layers
  - $H_1 = \alpha(XB_1)$
  - $H_2 = \alpha(H_1B_2)$
  - $h_3 = H_2b_3$

- Compute residuals for gradients
  - $e_3 = y - h3$
  - $E_2 = \alpha(E_3B_3')$
  - $E_1 = \alpha(E_2B_2')$

- Update coefficient
  - $B_1^{t+1} = B_1^t - \gamma\left(\frac{2r_1}{n}[\,X'E_1 - \lambda B_1^t]\right)$
  - $B_2^{t+1} = B_2^t - \gamma\left(\frac{2r_2}{n}[\,H_1'E_2 - \lambda B_2^t]\right)$
  - $b_3^{t+1} = b_3^t - \gamma\left(\frac{2r_3}{n}[\,H_2'e_3 - \lambda b_3^t]\right)$

Scary? Top-to-bottom code ~ 30 lines



```
# DNN function
dnn = function(y, X, nit=1000, batch=250,RELU=FALSE, Leak=0.1,
               dropout=0, Lambda=0.1,LrnRate = 1,Nodes1=4, Nodes2=4){
  # Normalization
  if(is.null(ncol(y))) y = matrix(y)
  muY = colMeans(y,na.rm=T);  sdY = apply(y,2,sd,na.rm=T);  y = apply(y,2,scale)
  ActFun = tanh;  if(RELU) ActFun = function(x){x[x<0]=x[x<0]*Leak;return(x)}
  DropOut = function(x,prc=dropout){x[sample(length(x),length(x)*prc)];return(x)}
  # Dimensions & Learning settings
  n = nrow(X);  p = ncol(X);  k = ncol(y)
  n1 = Nodes1; n2 = Nodes2;  lmb = Lambda; rate = LrnRate/c(p,n1,n2)
  b1 = matrix(rnorm(n1*p,0,1/p),p,n1)
  b2 = matrix(rnorm(n1*n2,0,1/n1),n1,n2)
  b3 = matrix(rnorm(n2,0,1/n2),n2,k)
  CNV1 = CNV2 = c()
  for(i in 1:nit){ # Iterations (backprop)
    if((i+1)%%100==1) cat('Iteration',i,'\n') # Sample batch
    w = sample(n,batch,replace=T);  y0 = y[w,]; X0 = X[w,]
    # Fit hidden layers (H) and Gradients (E)
    H1 = ActFun(X0%*%b1); H2 = ActFun(H1%*%b2); H3 = H2%*%b3
    e3 = y0-H3; if(anyNA(e3)) e3[is.na(e3)]=0
    e2 = ActFun(e3 %*% t(b3));  e1 = ActFun(e2 %*% t(b2))
    # Update coefficients
    b1 = b1 + DropOut(t(X0)%*%(e1)-lmb*b1)*(2/n)*rate[1]
    b2 = b2 + DropOut(t(H1)%*%(e2)-lmb*b2)*(2/n)*rate[2]
    b3 = b3 + DropOut(t(H2)%*%(e3))*(2/n)*rate[3]
    CNV1 = c(CNV1,mean(apply(e3,2,var,na.rm=T)))
    CNV2 = c(CNV2,mean(diag(cor(H3,y0,use='p')))) }
  out = list(af=ActFun,b1=b1,b2=b2,b3=b3,conv_MSE=CNV1,conv_GOF=CNV2,mu=muY,sd=sdY)
  class(out) = 'smalldnn'; return(out)}

predict.smalldnn = function(object,newdata){
  x = object; h = x$af(x$af(newdata%*%x$b1)%*%x$b2)%*%x$b3
  for(i in 1:ncol(h)) h[,i] = x$mu[i] + x$sd[i]*h[,i]
  return(h)}
```

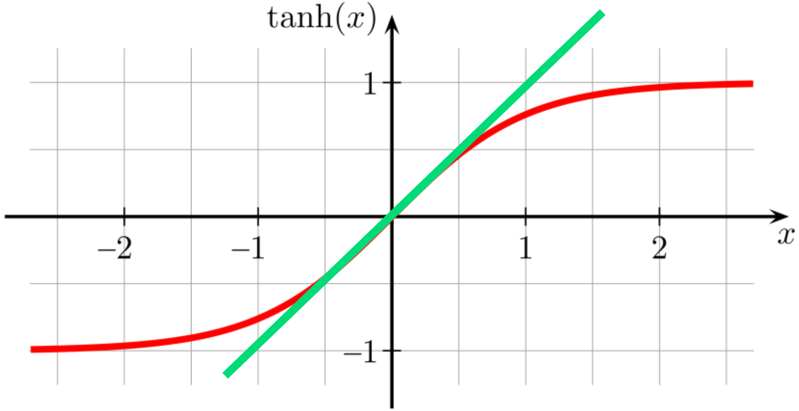
DNN jargons and nuisances

- Latent spaces = non-linear principal components
- “Nodes” = number of PCs = columns of H1 and H2 (driven by the # of columns of B1 and B2)

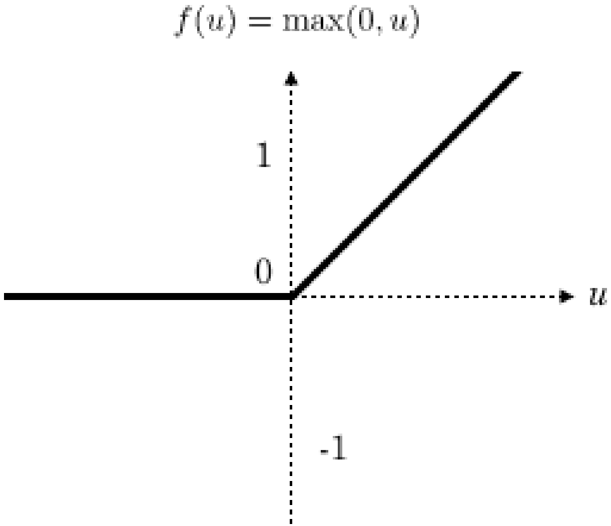
- **Adaptative momentum** speed up convergence: $B^{t+1} = B^{t} - \gamma\nabla^{t} - m\gamma\nabla^{t-t}$
- **Lazy loading**: Each iteration (update of B) uses a different chunk of data
- **Dropoff**: In each iteration, ignore parameters at random to mitigate overfit

- Coefficients **must** start with random values, e.g., $b \sim N(0, p^{-1})$
- **No guarantees** of similar results even if you fit the same model twice on the same data

Activation functions (α)



Linear between -0.5 and 0.5 ?
(most coefficients sit in this intervals)



4. Tree ensembles

$$y = n_t^{-1} \sum T(X) + e$$

- Predictions are averages from several ‘haplotypes’ of random markers
- Can capture complex patterns; Deal with large datasets;
- Requires *some* tuning; Not objectively interpretable;

Solution for tree ensembles

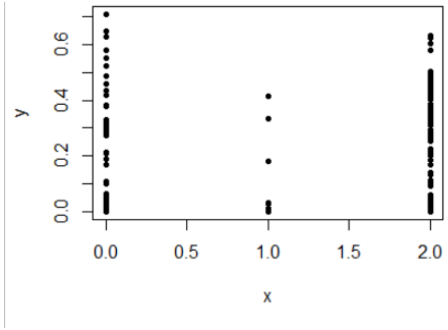
- No algebra. Tree methods are fully algorithmic.

- Three components
  - 1) Recursive partitioning (RP) = Function that splits the data
  - 2) Tree building = Function that runs, organize and store the RPs
  - 3) Ensemble method = Function that runs, organize and store trees

Recursive partitioning

- Univariate operation… $y = f(x)$, where x is a SNP coded as 012

```
data(tpod,bWGR)
x = gen[,100]
plot(x,y,pch=20)
```



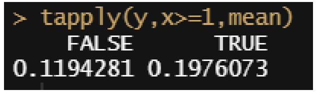
Splits

Get means

Compute error

$x \geq 1$

A/HB

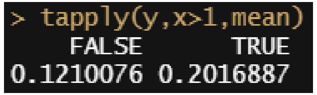


```
> tapply(y,x>=1,mean)
    FALSE      TRUE
0.1194281 0.1976073
```

$(y-\hat{y})'(y-\hat{y}) = 6.9998$

$x > 1$

AH/B



```
> tapply(y,x>1,mean)
    FALSE      TRUE
0.1210076 0.2016887
```

$(y-\hat{y})'(y-\hat{y}) = 6.9801$

Winner!

Outputs for SNP x:

Split rule: x>1

MSE: 6.9801

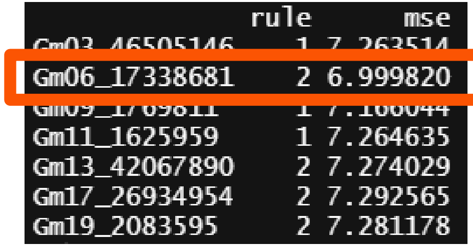
RP function:

- **Inputs**: x, y
- **Output**: best split rule, MSE

Tree-building

- Multiple responses… $y = f(x_1, x_2, x_3, \dots, x_p)$

1) Run RP for all SNPs



```
                  rule      mse
Gm03_46505146        1 7.263514
Gm06_17338681        2 6.999820
Gm09_1769811         1 7.100044
Gm11_1625959         1 7.264635
Gm13_42067890        2 7.274029
Gm17_26934954        2 7.292565
Gm19_2083595         2 7.281178
```

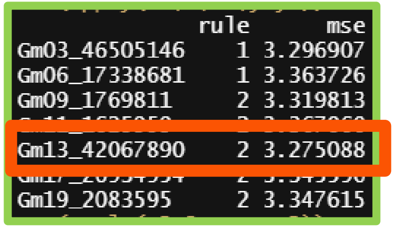
Rule 1 (A/HB): $x \geq 1$
Rule 2 (AH/B): $x > 1$

2) Identify winner, split y

Y1 = Y[$x \leq 1$]
Y2 = Y[$x > 1$]

3) Until reach stopping criteria:
Repeat 1 and 2 for each branch

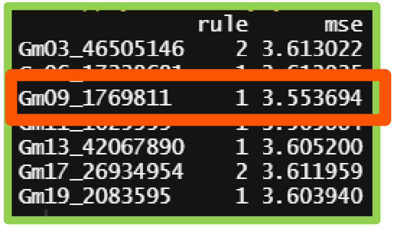
Y1)



```
                  rule      mse
Gm03_46505146        1 3.296907
Gm06_17338681        1 3.363726
Gm09_1769811         2 3.319813
Gm11_1625959         2 [illegible]
Gm13_42067890        2 3.275088
Gm17_26934954        2 [illegible]
Gm19_2083595         2 3.347615
```

Y1.1 = Y[$x \leq 1$]
Y1.2 = Y[$x > 1$]

Y2)



```
                  rule      mse
Gm03_46505146        2 3.613022
Gm06_17338681        1 [illegible]
Gm09_1769811         1 3.553694
Gm11_1625959         1 [illegible]
Gm13_42067890        1 3.605200
Gm17_26934954        2 3.611959
Gm19_2083595         1 3.603940
```

Y2.1 = Y[$x < 1$]
Y2.2 = Y[$x \geq 1$]

(...)

Tree function:
- **Inputs**: X, y
- **Output**: Store splits rules, averages of branches

Ensemble methods

- Trees are known as “weak learners”… addressed by averaging many trees

1) Bagging (*e.g.*, random forest) = multiple **independent** trees

- Fit multiple trees (~ 500) using random samples of observations (bootstrapping or subsampling) and markers ($\sqrt{p}$ or $p/3$). The final predictor is the average of all trees.

2) Boosting (*e.g.*, xgboost, adaboost) = multiple **sequential** trees

- Boosting/Stacking: Fit a tree, use residuals to fit the next, and then next, and so on. Each tree may be fit different observations and markers. Final predictor is the sum of all trees.

- Partial Boosting: Fit a tree, reweight observations based on residuals (learning rate defines reweighting), fit the next tree, reweight, and so on. Final predictor is the average of all trees.

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Validation

CV schemes

- **Random CV** = Upper-bound predictive potential
- **Leave-one-out** = Assess structured scenarios (e.g., geography-out, year-out)
- **Holdout** = Reproduce true applications (e.g., predict individuals from upcoming)

	Genotype	Environment	Difficulty
CV00	New	New	*****
CV0	Observed	New	***
CV1	New	Observed	***
CV2	Observed	Observed	*

Adapted from Crossa et al. (2017) doi.org/10.1016/j.tplants.2017.08.011

Validation metrics

- **Correlations**
  - Most common metrics in breeding (e.g., predictability, accuracy when possible)
  - Pertinent to ranking and selection of complex traits
- **Prediction error**
  - Utilized when the predicted values must be as close as possible to original scale
  - Pertinent to risk prediction (e.g., disease risk)
- **Success**
  - Accommodate complex or subjective criteria, independent or otherwise
  - Pertinent to decision involving data from multiple sources (e.g., advancement)

Information

Information carried by each marker:

- ***Linkage disequilibrium (LD)***: Marker proximity to a causative locus or regions, irrespective of population source.
- ***Linkage:*** Marker inherited from a specific source or parents. Also referred to as: co-segregation, haplotype, short-term LD.
- ***Relationship***: Marker information attributed to population structure. Captures differences among families and populations.

NOTE: Whether allelic information is additive, dominant or epistatic depends on parametrization and coding.

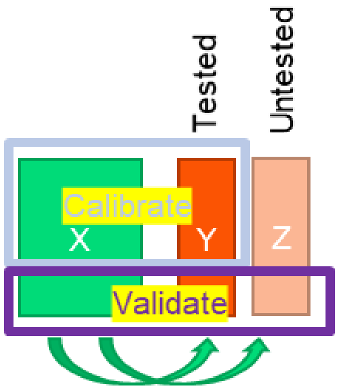
Information

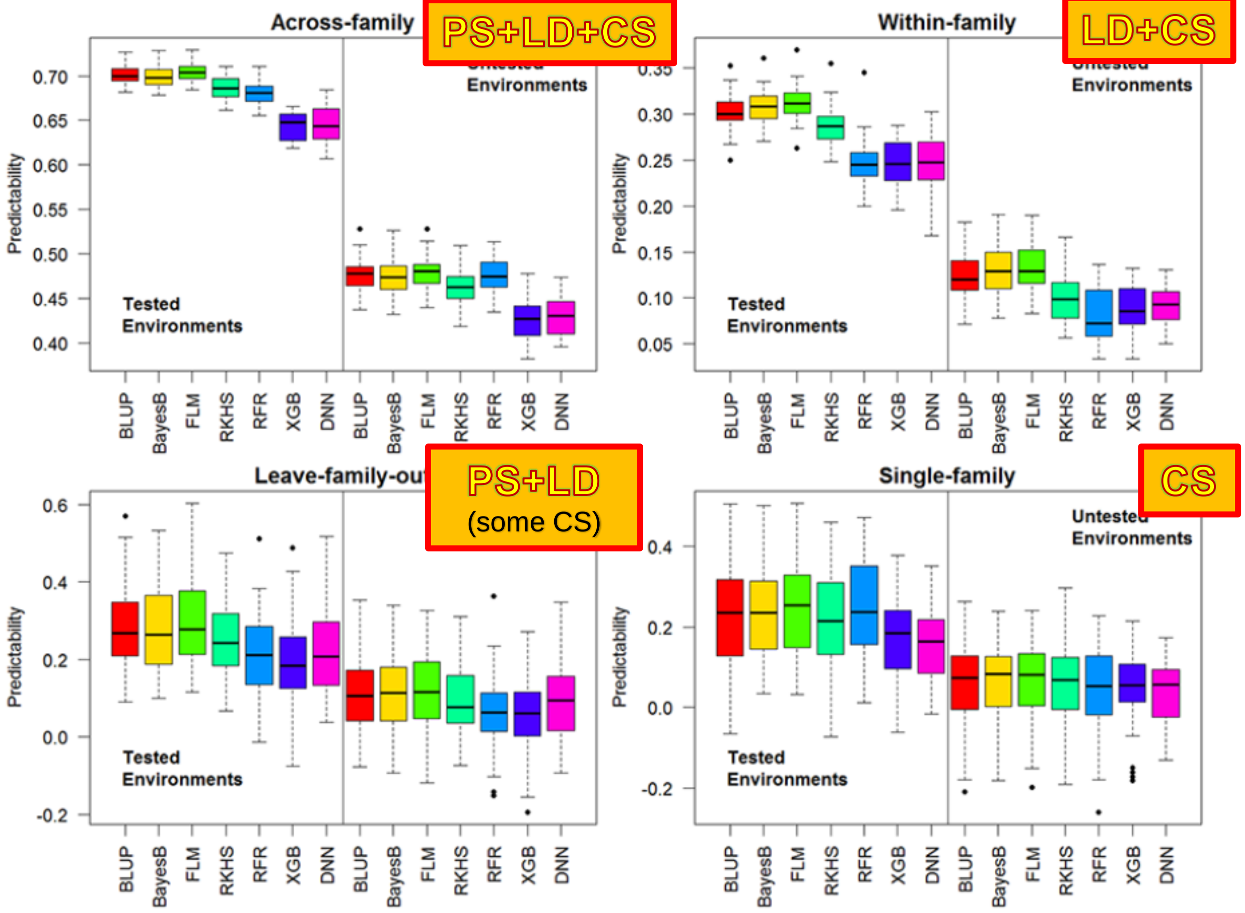
Genetic information assessed by cross-validation setup

- ***Intra-family***: Linkage*
- ***Within-family***: Linkage and LD
- ***Across-family***: Relationships**, Linkage and LD
- ***Leave-family-out***: Relationships and LD

- ***Untested environments***: Same as above + GxE component

CV scheme





SoyNAM data
ES: 2012 (7 loc)
PS: 2013 (4 loc)
#Fam = 40
Genos = 5600
SNPs = 4300
Obs: 3k-5k obs/loc

Figure 1. Four cross-validation schemes illustrating predictability of various methods utilized for genomic prediction. Grain yield models from the SoyNAM population, validated upon unobserved individuals from tested and untested environments.

Type of information captured by SNP

- Population structure (PS)
- Linkage disequilibrium (LD)
- Cosegregation / Haplotype (CS)

1. **Introduction**
2. **Machines**
   - Linear models
   - Kernel methods
   - Neural networks
   - Tree ensembles
3. **Validation**
   - Schemes and metrics
   - Information and case of study
4. **Conclusion**

Conclusion

Thank you for your attention!

Remarks:

1) There are discrepancies in thought and nomenclature between ML and QG
2) We reviewed the 4 major types of machines utilized in genomic predictions
3) Cross-validation help us to understand methods' strengths and limitations

Questions??

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Unnecessarily complex analysis should not be used as a foil to disguise lower quality datasets

Kruuk (2004 *apud* Walsh and Lynch 2018)

Data > Method