Genomic BLUP

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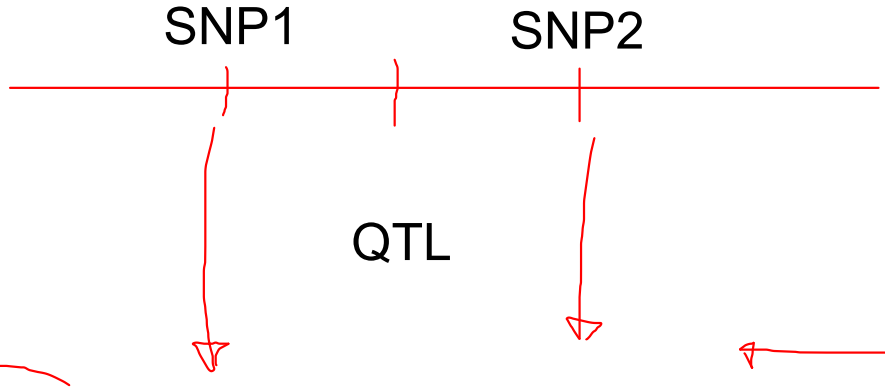
So Far



chromosome

y: phenotypes

N

a1: marker effect for SNP1

- Estimate effect of few SNP loci linked to QTL
- Use parameter estimates to predict genomic breeding values
- **New**: Many SNP, find the important ones

150'000 - 20 Mio

denoted by the variable p

$p \gg N$

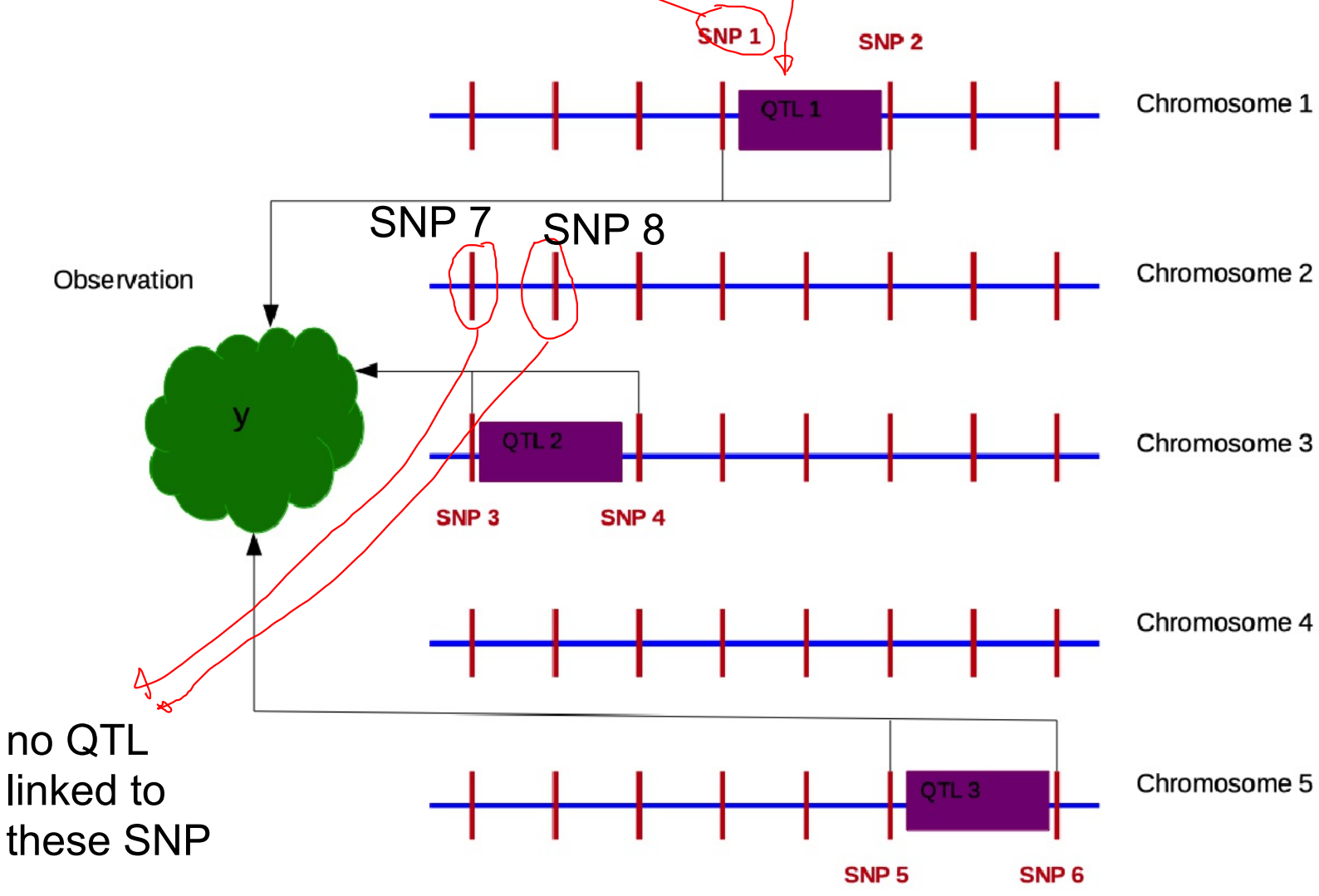
combine estimation of marker effects together with availability of many SNP in the dataset

least squares cannot be used to estimate marker effects

Situation

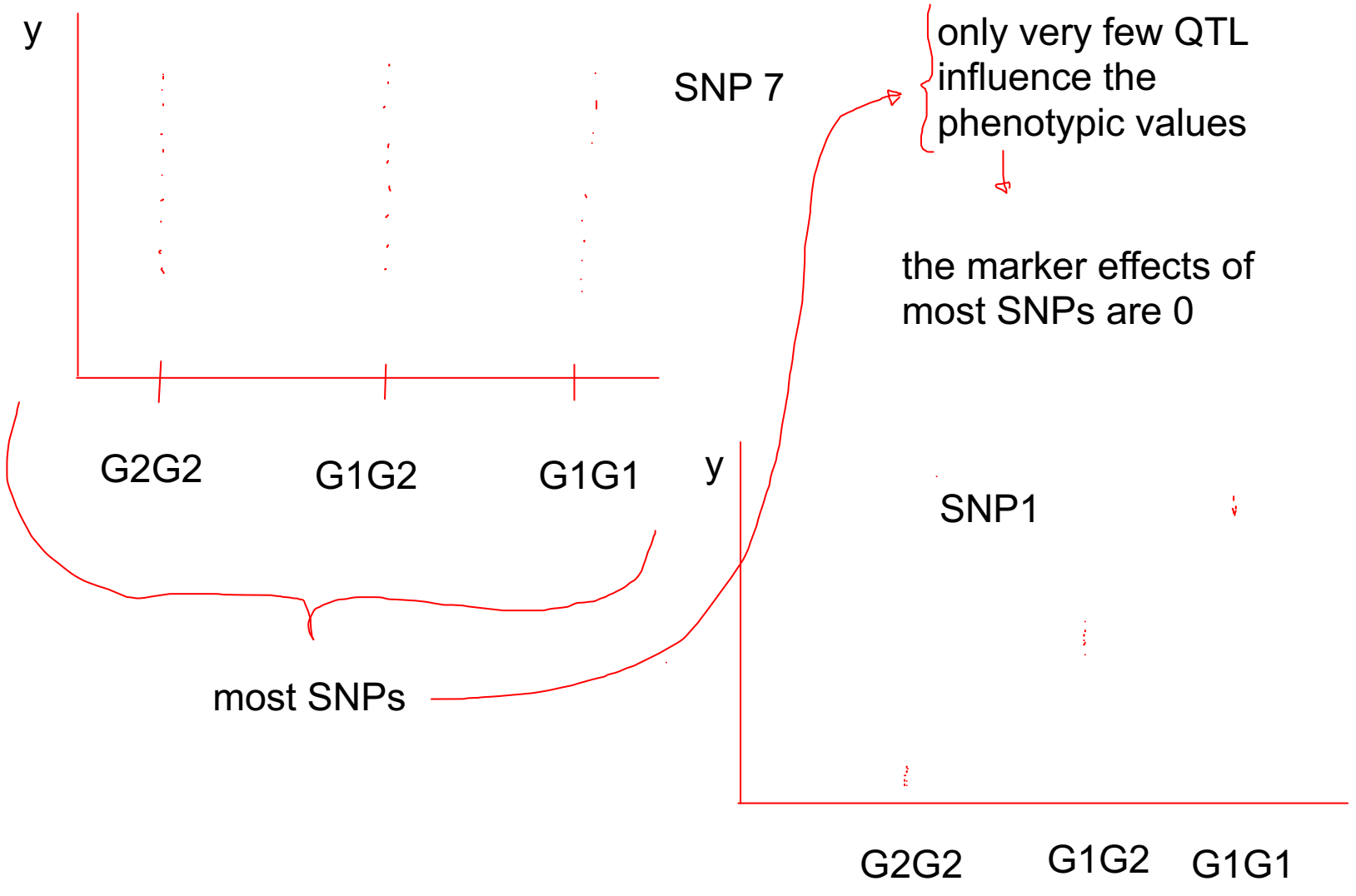
SNP positions is known

Positions of QTLs unknown



Goal: Find SNP 1 – SNP 6 out of the many SNPs

For the two SNPs 7 and 8 that are not linked to a QTL



Summary: 2 Problems

1. if we consider all SNP in our data set, then p>>N
   ==> least squares cannot be used
2. from genetic model: only few QTL for a given trait,
   ==> most SNP have marker effects (a) = 0

because the position of the QTL is unknown, we do not know which SNP have marker effects = 0

Approaches in Fixed Linear Model Framework

Possible solution for problem 2: Model selection to determine which SNP have marker effect that are not 0

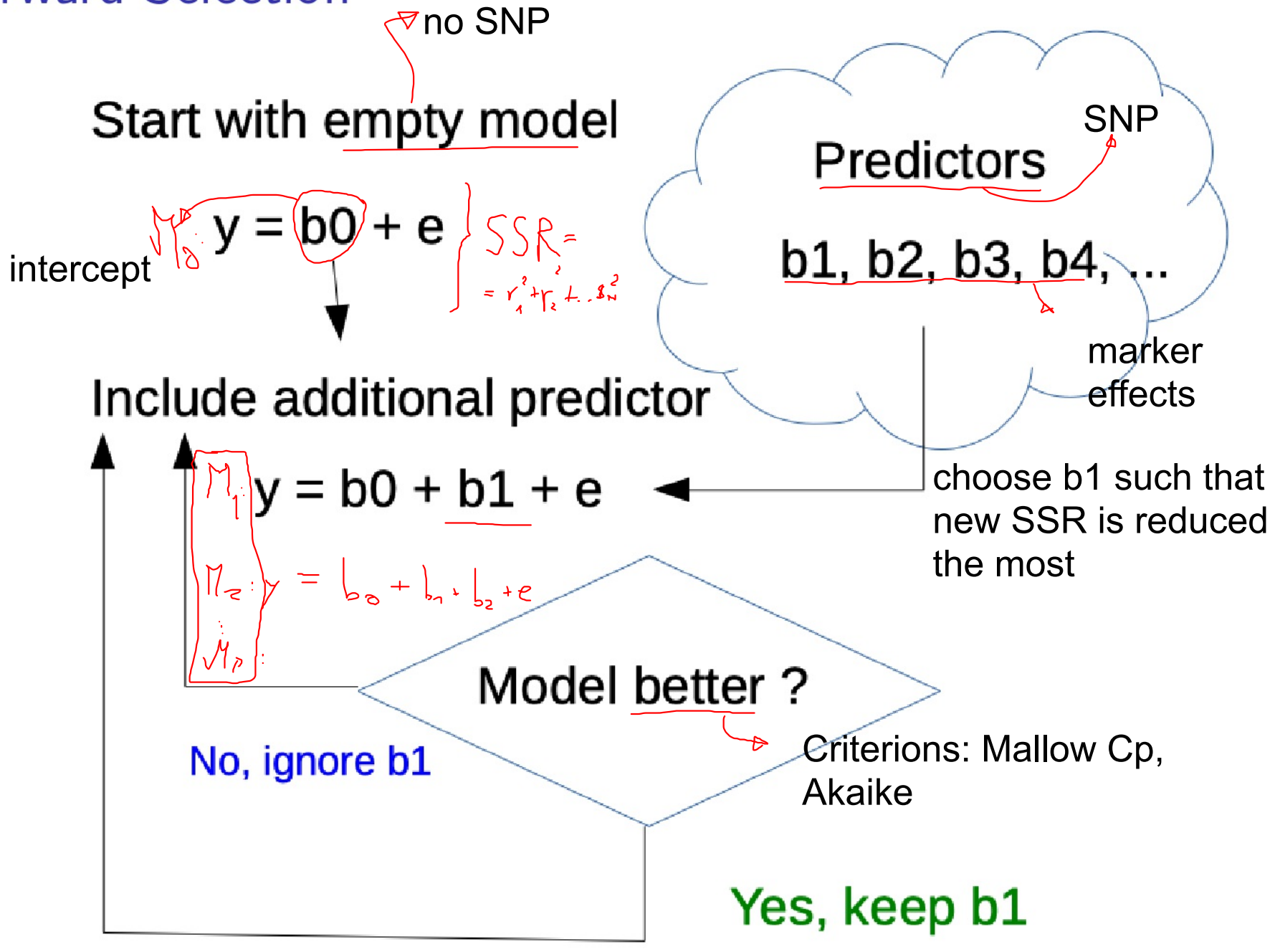
Two Approaches

1. Forward selection: Start with empty model, include predictors that improve model
2. Backward elimination: Start with full model, remove predictors as long as model does not get worse

no SNP

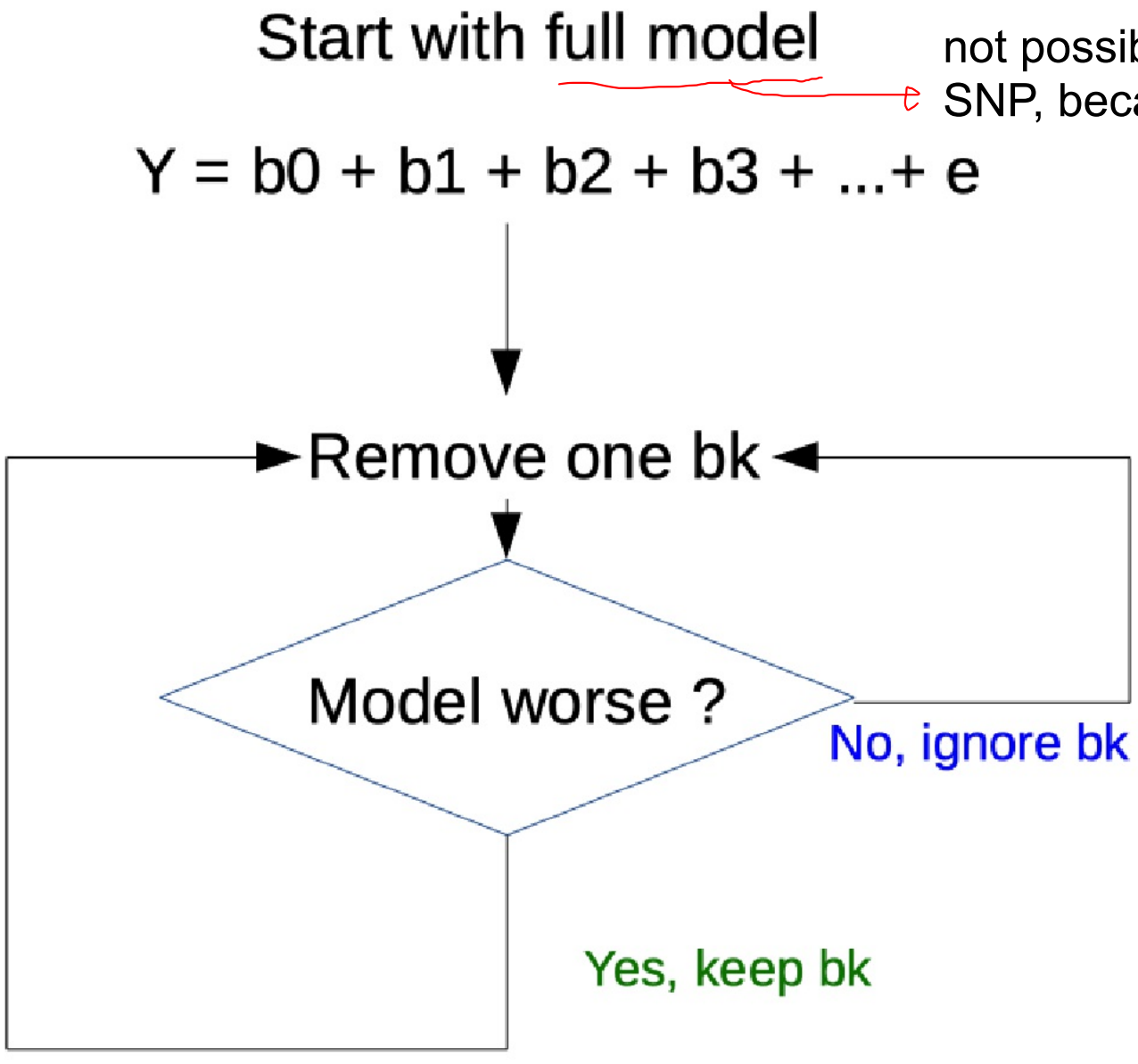
all SNP, not possible due to p>>N

Forward Selection



Backward Elimination

except for SNP data, this is the preferred way



Model Selection With Genomic Data

cannot use backward elimination with genomic data, because parameter estimation in the full model cannot be

- Only backward elimination really works in practical problems
- Large number of predictors ($1.5 * 10^5$)
- How to determine sequence of predictors to eliminate
- Fitting the full model is problematic

Mixed Linear Effect Model

2 Problems:

1. number of parameters p >> number of observations
2. only few SNP are important

- One solution: replace fixed linear effect model by **mixed** linear effect model (mle)
- MLE: additional random effect besides error term
- Random effects are specified by expected value and variance
- In livestock breeding MLE have a good reputation from BLUP animal model

MLE In Genomics

two different types of model are different in their choice of random effects:
1. MEM: marker effects (a-values of the SNP) are taken to be random
2. BVM: genomic breeding value are taken as random

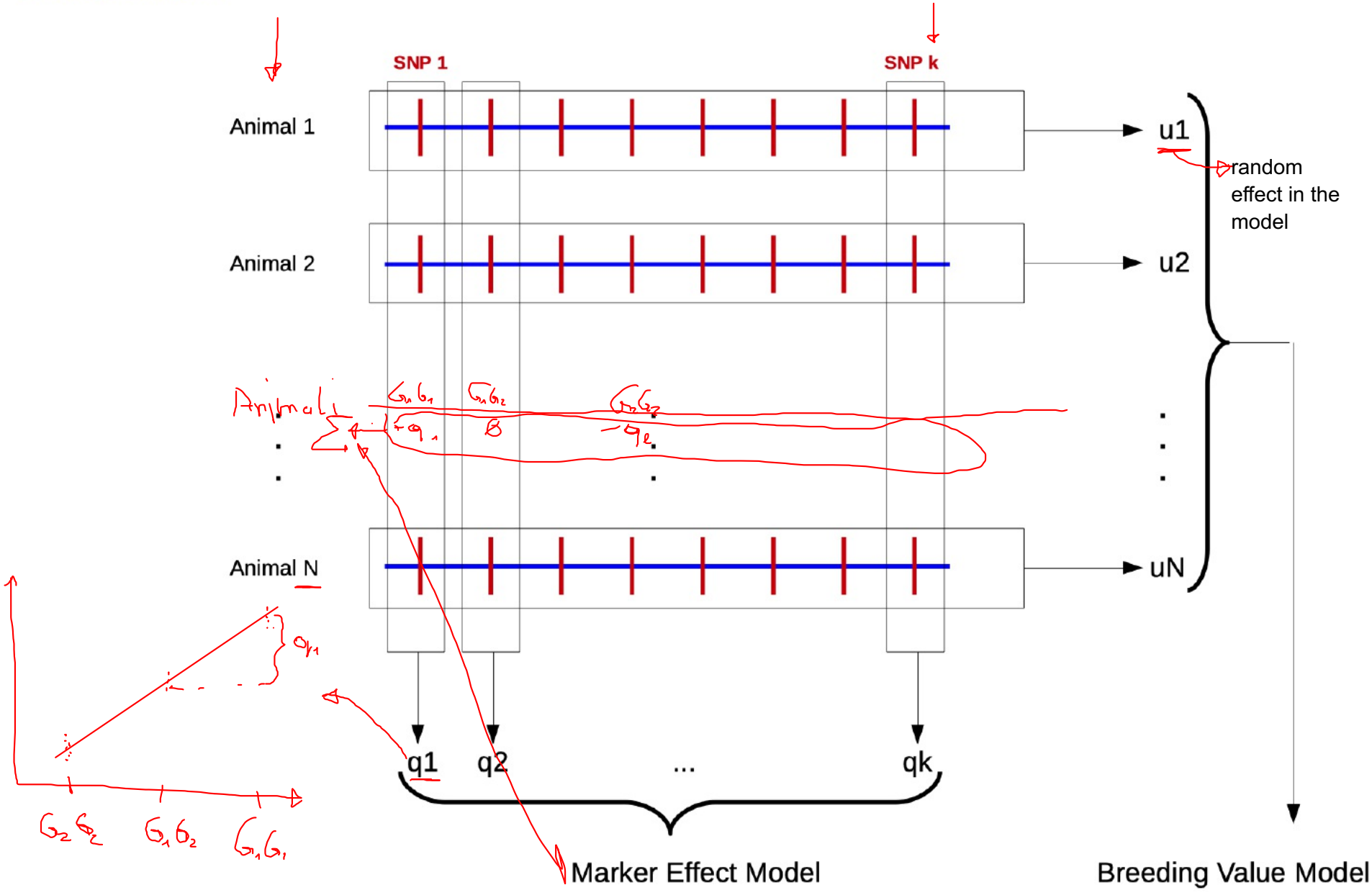
direct prediction of genomic breeding values
without estimating marker effects

similar to the FLEM:
1. estimate marker effects
2. compute genomic breeding based on the estimated marker effects

- Two different parametrizations

1. Marker Effect Model (MEM)
2. Breeding Value Model (BVM)

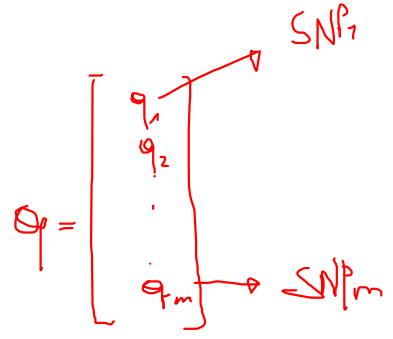
Overview


SNP 1
SNP k
Animal 1
Animal 2
Animal N
u1
u2
uN
random effect in the model
q1
q2
...
qk
Marker Effect Model
Breeding Value Model

Marker Effect Model

In MEM random effects of markers are directly included in the model. For an idealized data set we can write

$$y = 1_n\mu + Wq + e$$



where

y	vector of length n with observations
μ	general mean denoting fixed effects
1_n	vector of length n of all ones
q	vector of length m of random SNP effects
W	design matrix relating SNP-genotypes to observations
e	vector of length n of random error terms

$E(q) = 0$; $var(q) = I \cdot \sigma_q^2$

Breeding Value Model

$E[g] = 0$

$var(g) = G \cdot \sigma_g^2$

genomic relationship matrix

$$y = Xb + Zg + e$$

where

y	vector of length n with observations
b	vector of length r with fixed effects
X	incidence matrix linking elements in b to observations
g	vector of length t with random genomic breeding values
Z	incidence matrix linking elements in g to observations
e	vector of length n of random error terms