

Data simulation (including genomics) QMSim software

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QMSim: why to use it ?

- ✓ To simulate **data** mimicking **livestock species**
 - ✓ **Phenotypes, pedigree, genotypes**
- ✓ A wide variety of genome architectures
 - ✓ From single-locus to infinitesimal model
- ✓ It is a user-friendly tool for simulating data
- ✓ Computationally efficient in terms of time and memory

QMSim[†]: where to find it ?

[†]Sargolzaei & Schenkel (2009), Bioinformatics 25:680-681.

The code is written in C++ language

Executable files are freely available for Windows, Linux, and Mac at: **(Last update: July 12, 2013)**

<http://www.aps.uoguelph.ca/~msargol/qmsim/>

How the simulation is carried out ?

In 2 steps:

✓ *First step:* **Historical Population**

- to create initial LD
- to establish mutation-drift equilibrium
- expansion and contraction of the population

✓ *Second step:* **Recent Population**

- Pedigree
- Phenotypes
- Genotypes

Parameter file

- ✓ It must be in ASCII format
- ✓ It consists of **five** main sections
- ✓ The order of commands within each section is not important
- ✓ All commands end with a semicolon
- ✓ No semicolon → error message and program exits

```
/******  
**      Global parameters      **  
*****/  
title = "Example 1 - 10k SNP panel  
...;  
  
/******  
**      Historical population    **  
*****/  
begin_hp;  
      ....;  
end_hp;  
  
/******  
**      Populations             **  
*****/  
begin_pop = "p1";  
      ....;  
end_pop;  
  
/******  
**      Genome                  **  
*****/  
begin_genome;  
      ....;  
end_genome;  
  
/******  
**      Output options          **  
*****/  
begin_output;  
      ....;  
end_output;
```

1. Global parameters section

```
/******  
**      Global parameters      **  
*****/  
title = "Example 1 - 10k SNP panel";  
seed = "seed.txt";
```

An arbitrary
title

The random number generator (RNG*) requires a **seed file**.

If it is not specified → RNG will be seeded from the system clock

For each run the initial seed numbers will be backed up in
output folder → This allows to repeat the run !

Parameter file: ex01.prm

Output folder: r_ex01/

Example 1 - 10k SNP panel

Output

Initial seed is backed up in [r_ex01/seed].
parameter file is backed up in [r_ex01/ex01.prm].

* Mersenne Twister algorithm (Matsumoto & Nishimura, 1998)

1. Global parameters section

```
/**
**      Global parameters      **
**
title = "Example 1 - 10k SNP panel";
nrep  = 1;           //Number of replicates
h2     = 0.2;        //Heritability
qtlh2  = 0.2;        //QTL heritability
phvar  = 1.0;        //Phenotypic variance
```

QTL effect is
simulated

Range: 0 - 10,000

Overall heritability
(Polygenic + QTL)

```
title = "Example 8"
nrep  = 1;
h2     = 0.2;
qtlh2  = 0.0;
phvar  = 1.0;
```

Only polygenic effect
is simulated

```
title = "Example 11"
nrep  = 1;
h2     = 0.2;
qtlh2  = 0.05;
phvar  = 1.0;
```

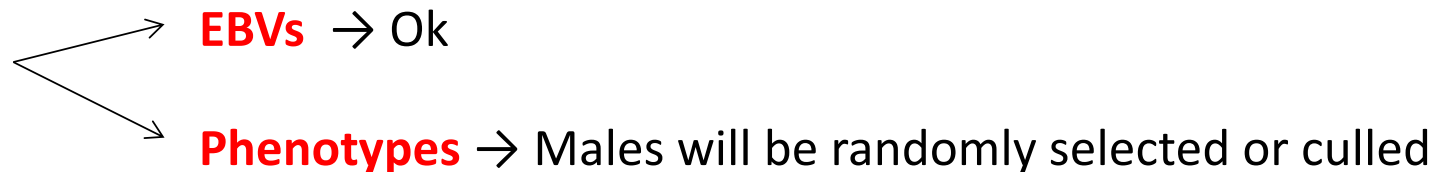
Both, polygenic
and QTL effects
are simulated

1. Global parameters section

```
/******  
**      Global parameters      **  
*****/  
title = "Example 1 - 10k SNP panel";  
nrep   = 1;           //Number of replicates  
h2      = 0.2;        //Heritability  
qtlh2   = 0.2;        //QTL heritability  
phvar   = 1.0;        //Phenotypic variance  
no_male_rec;          // No record for males
```

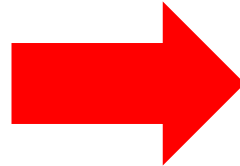
A sex limited trait
like milk yield

When males do not have records, but selection or culling are based on



Parameter file

✓ It consists of **five** main sections



```
/******  
**      Global parameters      **  
*****/  
title = "Example 1 - 10k SNP panel  
...;  
  
/******  
**      Historical population    **  
*****/  
begin_hp;  
    ....;  
end_hp;  
  
/******  
**      Populations             **  
*****/  
begin_pop = "p1";  
    ....;  
end_pop;  
  
/******  
**      Genome                  **  
*****/  
begin_genome;  
    ....;  
end_genome;  
  
/******  
**      Output options          **  
*****/  
begin_output;  
    ....;  
end_output;
```

2. Historical population section

```

/*****
**   Historical population   **
*****/
begin_hp;
  hg_size = 420 [0]           //
           420 [200];
  nmlhg   = 20;               //
end_hp;

```

- ➔ To create initial LD
- ➔ Evolutionary forces: mutation and drift (no selection, no migration)
- ➔ Random mating: union of gametes randomly sampled from the male and female gametic pools
- ➔ Discrete generations
- ➔ Only a single historical population

2. Historical population section

Historical
generation
sizes

```
/******  
**    Historical population    **  
*****  
begin_hp;  
  hg_size = 420 [0]  
           420 [200];  
  nmlhg   = 20;  
end_hp;                                     //
```

Constant size
of 420



hg_size = v1 [v2]

v1 the historical generation **size**
Range: 2 – 100,000

v2 the historical generation **number**
Range: 0 – 150,000

2. Historical population section

Historical **bottleneck** or **expansion** can be simulated

```
/** Historical population **  
begin_hp;  
  hg_size = 2000 [0]  
          200 [1000];  
  nmlhg   = 40;  
end_hp;
```

Gradual decrease in
size from 2000 to 200

```
/** Historical population **  
begin_hp;  
  hg_size = 100 [0]  
          100 [950]  
          3000 [1000];  
  nmlhg   = 200;  
end_hp;
```

Expansion in the last historical
generation from 100 to 3000

LD in livestock extends over longer distances than in humans

2. Historical population section

Number of
males

```
/**
**   Historical population   **
**   *****/
```

```
begin_hp;
```

```
hg_size = 2000 [0]
         200 [1000];
```

```
nmfhg   = 40;
end_hp;
```

Default : equal number of males and females

nmf**h**g → **first** historical generation

Sex ratio will be constant across historical generations. It can be changed in the last generation

```
/**
**   Historical population   **
**   *****/
```

```
begin_hp;
```

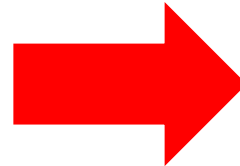
```
hg_size = 2000 [0]
         200 [1000];
```

```
nmlhg   = 40;
end_hp;
```

nm**l**hg → **last** historical generation

Parameter file

- ✓ It consists of **five** main sections



```
/******  
**      Global parameters      **  
*****/  
title = "Example 1 - 10k SNP panel  
...;  
  
/******  
**      Historical population   **  
*****/  
begin_hp;  
    ....;  
end_hp;  
  
/******  
**      Populations            **  
*****/  
begin_pop = "p1";  
    ....;  
end_pop;  
  
/******  
**      Genome                 **  
*****/  
begin_genome;  
    ....;  
end_genome;  
  
/******  
**      Output options         **  
*****/  
begin_output;  
    ....;  
end_output;
```

3. Population section

```
/**
**      Populations      **
**      *****/
```

One or multiple
recent populations

```
begin_pop = "p1";
      ....;
```

For the ***first defined recent population***
(i.e. p1), founders must come
from **the last historical population**

```
begin_pop = "p2";
      ....;
```

For ***subsequent populations*** (i.e. p2),
founders can be chosen from one or more
(up to 10) **previously defined populations** (i.e. p1)

Multiple recent populations can be analyzed
separately (one pedigree for each population) or
jointly (by creating one pedigree for all populations) for inbreeding and EBV

3. Population section

Choosing founders for a population

```
/******  
**           Populations           **  
*****  
begin_pop = "line1";  
begin_founder;  
    male    [n = 20,   pop = "hp", select = tbv /h];  
    female  [n = 400, pop = "hp", select = tbv /h];  
end_founder;
```

Parameters for the
founders

Number of
male/female
to be selected

It indicates from
which population the
base animals must
be selected

Type of selection

select: rnd (default),
phen, tbv and ebv
/l : to select low values
/h : to select high values

hp: historical population (last historical generation)

Choosing founders for a population for F2 design

```
/**
**      Populations
**
***/
begin_pop = "line1";
begin_founder;
    male    [n = 20,   pop = "hp", select = tbv /h];
    female  [n = 400,  pop = "hp", select = tbv /h];
end_founder;
ng = 20;           //Number of generations
end_pop;
```

```
begin_pop = "line2";
begin_founder;
    male    [n = 20,   pop = "hp", select = tbv /l];
    female  [n = 400,  pop = "hp", select = tbv /l];
end_founder;
ng = 20;           //Number of generations
end_pop;
```

Crossing between
populations/lines
is allowed

```
//Cross between line1 and line 2 to generate F2
begin_pop = "cross";
begin_founder;
    male    [n = 20,   pop = "line1", gen = 20];
    female  [n = 400,  pop = "line2", gen = 20];
end_founder;
ng = 2;           //Number of generations
```

Choosing founders for a population for migration

```
/******  
**      Populations      **  
******/
```

```
begin_pop = "line1";  
begin_founder;  
    male [n = 20, pop = "hp", select = tbv /h];  
    female [n = 400, pop = "hp", select = tbv /h];  
end_founder;  
ng = 20;           //Number of generations  
end_pop;
```

```
begin_pop = "line2";  
begin_founder;  
    male [n = 20, pop = "hp", select = tbv /l];  
    female [n = 400, pop = "hp", select = tbv /l];  
end_founder;  
ng = 20;           //Number of generations  
end_pop;
```

Migration can be simulated

```
//2 males and 10 females from line 2 immigrate to line 1
```

```
begin_pop = "line1_c";  
begin_founder;  
    male [n = 8, pop = "line1", gen = 10];  
    male [n = 2, pop = "line2", gen = 10]; //2 male immigrants  
    female [n = 90, pop = "line1", gen = 10];  
    female [n = 10, pop = "line2", gen = 10]; //10 female immigrants  
end_founder;  
ng = 5;           //Number of generations
```

3. Population section

Litter size

```
/******  
**                Populations                **  
******/
```

```
begin_pop = "p1";  
begin_founder;  
male [n =  
female [n = 2500; pop = np ];  
end_founder;
```

ls: number of
progeny per dam

ls: Probability of
the litter sizes

```
ls = 1 2 [0.2];
```

//Litter size

```
pmp = 0.5;
```

//Proportion of male progeny

```
ng = 10;
```

//Number of generations

```
md = p_assort/ebv;
```

//Mating design

```
sr = 0.4;
```

//Replacement ratio for sires

```
dr = 0.2;
```

//Replacement ratio for dams

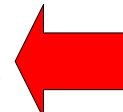
```
sd = ebv /h;
```

//Selection design

```
cd = phen/l;
```

//Culling design

```
ebv_est = blup;
```



3. Population section

Sex ratio

```
/******  
**           Populations           **  
*****
```

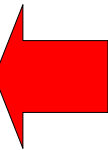
```
begin_pop = "p1";  
begin_founder;  
    male    [n = 50,  
    female  [n = 2500, pop = 1,  
end_founder;
```

```
ls  = 1 2 [0.2];  
pmp = 0.5;  
ng  = 10;  
md  = p_assort/ebv;  
sr  = 0.4;  
dr  = 0.2;  
sd  = ebv /h;  
cd  = phen/l;  
ebv_est = blup;
```

pmp: range
0-1, default is
equal to 0.5

pmp: 0.5 /fix_litter
Sex ratio will be fixed within
litters (progeny of a dam)

```
//Litter size  
//Proportion of male progeny  
//Number of generations  
//Mating design  
//Replacement ratio for sires  
//Replacement ratio for dams  
//Selection design  
//Culling design
```



3. Population section

Matting design

rnd (default), **rnd_ug** (a dam can mate with more than one sire in each generation), **p_assort** (similarity), **n_assort** (dissimilarity), **minf** and **maxf** (inbreeding is minimized in the next generation)

```
*****
populations
*****/
l";
er;
n = 50, pop = "hp";
n = 2500, pop = "hp";
r;
2 [0.2]; //Litter size
pmp = 5; //Proportion of male progeny
ng = 10; //Number of generations
md = p_assort/ebv; //Mating design
sr = 0.4; //Replacement ratio for sires
dr = 0.2; //Replacement ratio for dams
sd = ebv /h; //Selection design
cd = phen/l;
ebv_est = blup;
```

Assortative mating base
on **phen**, **ebv** or **tbv**

3. Population section

Replacement

```
/******  
**          Populations          **  
*****/  
begin pop = "p1";  
  founder;  
  le [n = 50, pop = "hp"];  
  male [n = 2500, pop = "hp"];  
  founder;  
  = 1 2 [0.2]; //Litter size  
  p = 0.5; //Proportion of male progeny  
  ng = 10; //Number of generations  
  md = p_assort/ebv; //Mating design  
  sr = 0.4; //Replacement ratio for sires  
  dr = 0.2; //Replacement ratio for dams  
  sd = ebv /h; //Selection design  
  cd = phen/l; //Culling design  
  ebv_est = blup
```

sr : 40% of sires
will be replaced in
all generations

sr : 1, discrete
generations (default)

sr : 0.4 [1] 0.5 [5]
40% of sires will be culled for generation 1 to 5, and
50% from generation 5 to last generation

3. Population section

Selection and culling designs

```

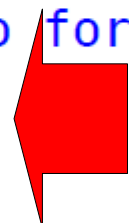
/*****
**          Populations          **
*****/
begin_pop = "p1";
begin_founder;
    male    [n = 50, pop = "hp"];
    female  [n = 2500, pop = "hp"];
end_founder;
ls = 1 2 [0.2];           //Litter size
pmp = 0.5;                //Proportion of male progeny
ng = 10;                  //Number of generations
md = p_assort/ebv;        //Mating design
sr = 0.4;                 //Replacement ratio for sires
dr = 0.2;                 //Replacement ratio for dams
sd = ebv /h;              //Selection design
cd = phen/l;              //Culling design
ebv_est = blup;

```

rnd, phen, tbv ebv
and age (only for
culling)

Breeding value
estimation method

/l or /h to
select low or
high values



```

/*****
**                Populations                **
*****/
begin_pop = "p1";
begin_founder;
    male    [n = 20, pop = "hp"];
    female  [n = 400, pop = "hp"];
end_founder;
ls = 2;
pmp = 0.5 /fix;
ng = 10;
begin_popoutput;
    data;
    stat;
    genotype /snp_code /gen 8 9 10;
end_popoutput;
end_pop;

```

**Population specific
parameters for
saving outputs**

p1_mrk_007.txt

p1_qtl_007.txt

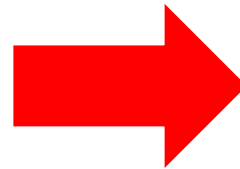
data: save individual's data except their genotype
(File name: 'population name'_data_'replicate number'.txt)

stat: save brief statistic on simulated data

genotype: save genotype data

Parameter file

- ✓ It consists of **five** main sections



```
/******  
**      Global parameters      **  
*****/  
title = "Example 1 - 10k SNP panel  
...;  
  
/******  
**      Historical population   **  
*****/  
begin_hp;  
    ....;  
end_hp;  
  
/******  
**      Populations            **  
*****/  
begin_pop = "p1";  
    ....;  
end_pop;  
  
/******  
**      Genome                 **  
*****/  
begin_genome;  
    ....;  
end_genome;  
  
/******  
**      Output options         **  
*****/  
begin_output;  
    ....;  
end_output;
```

4. Genome section

Marker information

Example – 10k SNP panel

```
/******  
**                               Genome                                 
*****  
begin_genome;  
  begin_chr = 10;  
  chrlen = 100; //Chromosome length  
  nmloci = 1000; //Number of markers  
  mpos = rnd; //Marker positions  
  nma = all 2; //Number of marker alleles  
  maf = eql; //Marker allele frequencies  
  nqloci = 25; //Number of QTL  
  qpos = rnd; //QTL positions  
  nqa = all 2; //Number of QTL alleles  
  qaf = eql; //QTL allele frequencies  
  qae = rndg 0.4; //QTL allele effects  
end_chr;  
mmutr = 2.5e-5 /recurrent; //Marker mutation rate  
qmutr = 2.5e-5; //QTL mutation rate  
r_mpos_g; // Randomize marker positions across genome  
r_qpos_g; // Randomize QTL positions across genome  
end_genome;
```

Number of chromosomes: 10
chrlen : range 1-5,000 cM

Samples from
uniform distribution
in each replicate

All marker loci will
have 2 alleles

In the first historical
generation, then drift
and mutation

4. Genome section

QTL information

Example – 10k SNP panel

```
/******
```

```
**          Genome          **
```

nqloci: range 1-50,000 on the chromosome

Samples from uniform distribution in each replicate

Nb of QTL alleles in the first historical generation (all: same number)

Equal allele frequencies in the first historical generation

It will be sampled from gamma distribution with shape 0.4

```
chrLen = 100000000; //Chromosome length
nmloci = 10000; //Number of markers
mpos = rnd; //Marker positions
nma = all 2; //Number of marker alleles
maf = eql; //Marker allele frequencies
nqloci = 25; //Number of QTL
qpos = rnd; //QTL positions
nqa = all 2; //Number of QTL alleles
qaf = eql; //QTL allele frequencies
qae = rndg 0.4; //QTL allele effects
end_chr;
mmutr = 2.5e-5; //Mutation rate
qmutr = 2.5e-5; //QTL mutation rate
r_mpos_g; // Random marker positions genome
r_qpos_g; // Random QTL positions genome
end_genome;
```

More genome information

Example – 10k SNP panel

```
/*  
**  
** Genome  
**  
***/
```

```
begin_genome;  
begin_chr = 10;
```

In recurrent mutation, no new allele is generated.
Default: infinite-allele model

```
    chromosome length  
    number of markers  
    number of positions  
    number of  
maf = eql; //Marker al  
nqloci = 25; //Number of  
qpos = rnd; //QTL posit  
nqa = all 2; //Number of QTL a  
qaf = eql; //QTL allele fr  
qae = rndg 0.4; //QTL allele effe
```

SNP recurrent mutations are generally very rare and no evidence that mutation contributes to erosion of LD between SNP (Ardlie et al., 2002)

```
end_chr;  
mmutr = 2.5e-5 /recurrent; //Marker mutation rate  
qmutr = 2.5e-5; //QTL mutation rate  
r_mpos_g; // Randomize marker positions across genome  
r_qpos_g; // Randomize QTL positions across genome  
end_genome;
```

Other possibilities :

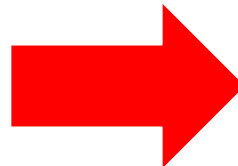
Missing marker/QTL genotypes

Genotyping errors can be simulated (marker/QTL)

Parameter file

- ✓ It consists of **five** main sections

```
/******  
**      Global parameters      **  
*****/  
title = "Example 1 - 10k SNP panel  
...;  
  
/******  
**      Historical population   **  
*****/  
begin_hp;  
    ....;  
end_hp;  
  
/******  
**      Populations            **  
*****/  
begin_pop = "p1";  
    ....;  
end_pop;  
  
/******  
**      Genome                 **  
*****/  
begin_genome;  
    ....;  
end_genome;  
  
/******  
**      Output options         **  
*****/  
begin_output;  
    ....;  
end_output;
```



5. Output section

```
/******  
**          Output options          **  
******/
```

```
begin_output;
```

```
    linkage_map;
```

Marker and QTL linkage map (GWAS)

```
    hp_stat;
```

```
end_output;
```

Save brief statistics on historical population

```
/******  
**          Output options          **  
******/
```

```
begin_output;
```

```
    linkage_map;
```

```
    allele_effect;
```

Save allele effects

```
end_output;
```

QMSim outputs

p1_data_001.txt

```

/*****
**                               **
*****

begin_pop = "p1";
begin_founder;
    male    [n = 20, pop = "hp"];
    female  [n = 400, pop = "hp"];
end_founder;
ls = 2;
pmp = 0.5 /fix;
ng = 10;
begin_popoutput;
    data;
    stat;
    genotype /snp_code /gen 8 9 10;
end_popoutput;
end_pop;

```

Example 1

Progeny	Sire	Dam	G	Sex	MPrg	NFPrg	F	Homo	Phen	Res	Polygene	QTL
1	0	0	0	M	33	27	0.000000	0.696797	+1.323314	+0.331291	-0.000000	+0.992023
2	0	0	0	M	21	19	0.000000	0.695996	+0.933861	+1.323803	-0.000000	-0.389942
3	0	0	0	M	9	11	0.000000	0.673574	+0.903691	-0.106867	-0.000000	+1.010557
4	0	0	0	M	20	20	0.000000	0.685385	+0.502346	+0.068033	-0.000000	+0.434313
5	0	0	0	M	18	22	0.000000	0.696096	-0.038755	+0.870122	+0.000000	-0.908877
6	0	0	0	M	11	9	0.000000	0.692092	+2.246078	+1.202401	+0.000000	+1.043677
7	0	0	0	M	34	26	0.000000	0.704304	+1.312932	+1.393522	+0.000000	-0.080591
8	0	0	0	M	22	18	0.000000	0.692793	+1.375544	+1.060612	+0.000000	+0.314932

p1_stat_001.txt

Example 1

```
begin_popoutput;  
  data;  
  stat;  
  genotype /gen 8 9 10;  
end_popoutput;  
end_pop;
```

```
----- Inbreeding -----  
              Inbred              All  
Gen.      No.      Mean      SD      Mean      SD  
0          0      0.0000 0.0000  0.0000 0.0000  
1          0      0.0000 0.0000  0.0000 0.0000
```

```
----- Homozygosity -----  
Gen.      Mean      SD  
0          0.68254159 0.01207245  
1          0.68200626 0.01103250
```

```
----- Phenotype -----  
Gen.      Mean      SD  
0          0.08440969 1.01093563  
1          0.04504056 1.02152016
```

```
----- QTL -----  
Gen.      Mean      SD  
0          0.04889285 0.56092140  
1          -0.00533798 0.55392545
```

```
----- Brief structure -----  
Gen.      Progeny      Male%      Male Selected      Female Selected      Sire      Culled      Dam      Culled  
0          420 0.047619      20      0      400      0      0      0      0  
1          400 0.500000      200      8      200      80      20      8      400      80  
2          400 0.500000      200      8      200      80      20      8      400      80  
3          400 0.500000      200      8      200      80      20      8      400      80  
4          400 0.500000      200      8      200      80      20      8      400      80  
5          400 0.500000      200      0      200      0      20      0      400      0  
Overall    2420 0.421488      1020      32      1400      320      100      32      2000      320
```


p1_mrk_001.txt

```
begin_popoutput;  
  data;  
  stat;  
  genotype /snp_code /gen 4 5;  
end_popoutput;  
end_pop;
```

ID Genotypes (0 = a1,a1; 2 = a2,a2; 3 = a1,a2; 4 = a2,a1; 5 = missing; The first allele is paternal and the second allele is maternal) ...

10601

23433322330334300430040400330302000200202222000200232330330000002044430204040234040300222020220000200002
2200022222200020020022222002020200020220220220220303320244402330204342243042302320004022020002324044323032
00042043343402340404223432443000220040433000440033400202432402430444243300440220022002220202020000222000
4304402030220002244232032000000022043443443432403022400024000220420022220000232002020002002203020220202
20200200224302302032342334442300020002000202022220220020202200032020004320420442034243404302022202022000
0000222022020402020000343324434444030000002002200004304004304022332244200400432222202220000020200000020

```

/*****
**      Output options      **
*****/

```

```

begin_output;
  linkage_map;
  hp_stat;
end_output;

```

Marker and QTL linkage map

```

.------.
| Example 1 |
|-----|

```

```

----- QTL linkage map -----
ID          Chr      Position
-----
Q1           1       8.88876
Q2           1      13.35024
Q3           1      17.76099
Q4           1      22.12918
Q5           1      29.68482
Q6           1      37.76335
Q7           1      43.84122
Q8           1      46.93041
Q9           1      47.16755
Q10          1      48.56634

```

```

/*****
**      Output options      **
*****/

```

```
begin_output;
```

```
  linkage_map;
```

```
  allele_effect;
```

```
end_output;
```

Save allele effects

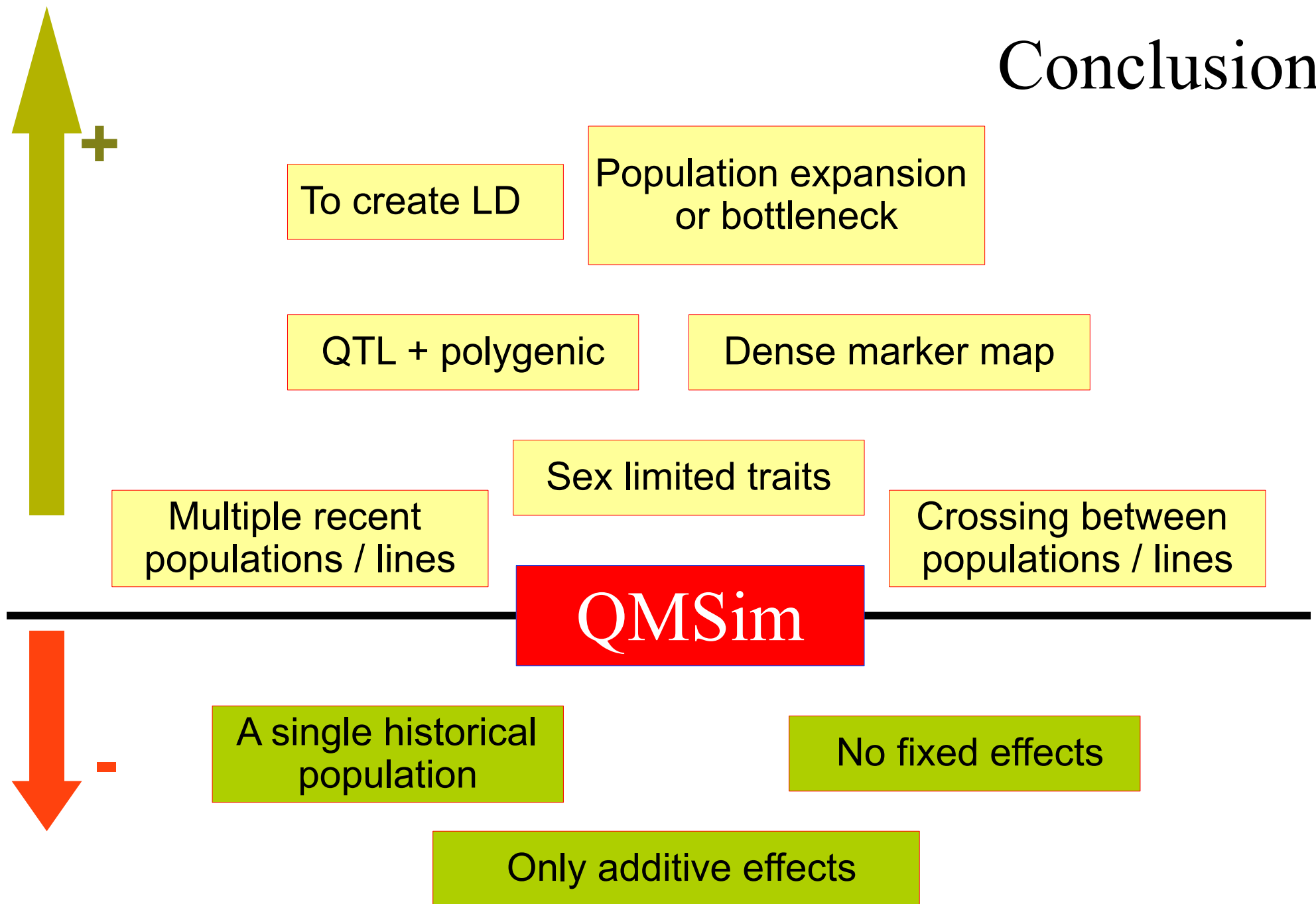
```

.------.
| Example 1 |
|-----|

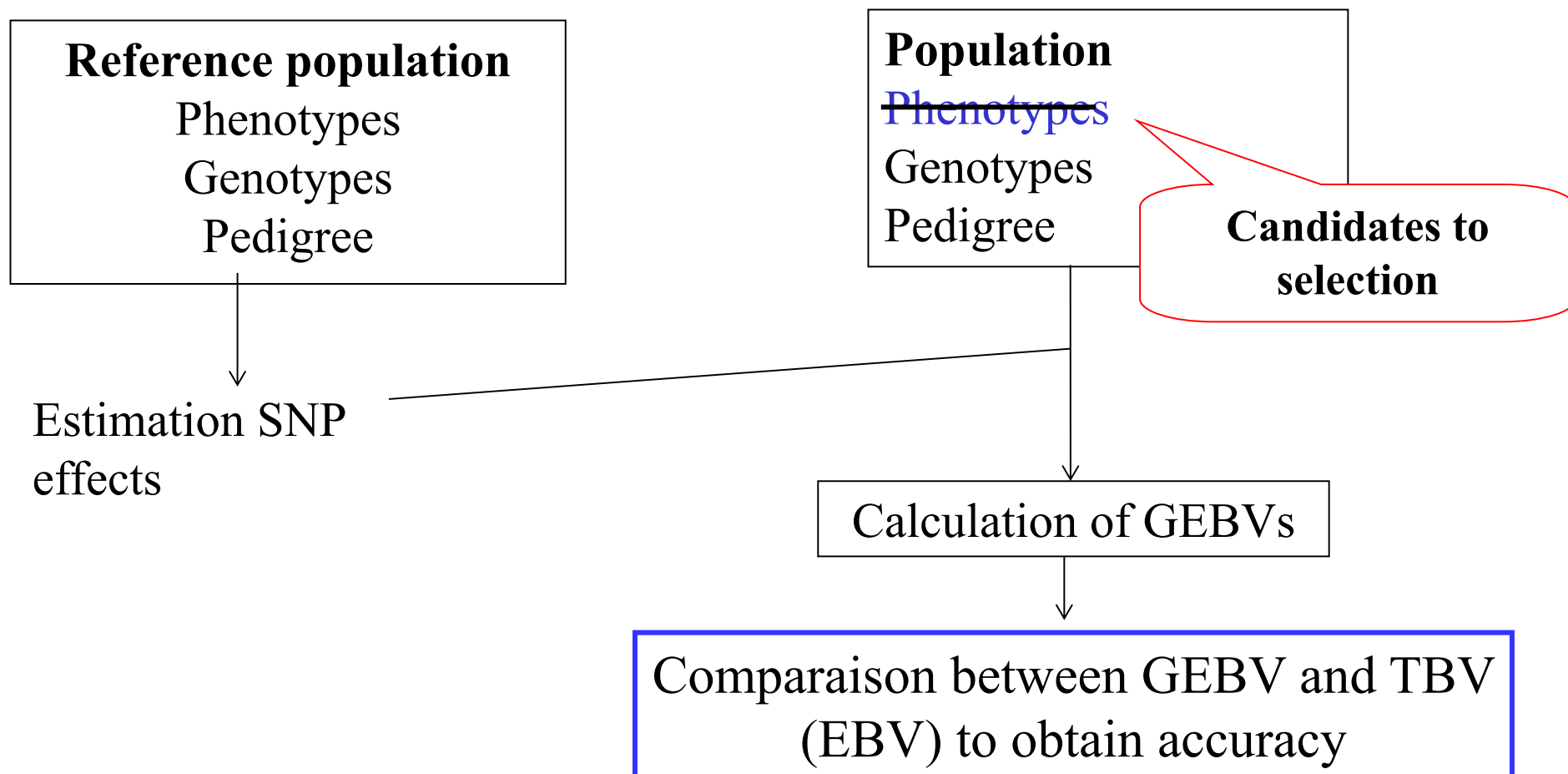
```

ID	Chr	Allele:Effect ...
Q1	1	1: 0.066403 2: -0.001068
Q2	1	1: -0.050405 2: 0.031267
Q3	1	1: -0.006917 2: 0.009631
Q4	1	1: -0.000543 2: 0.000171
Q5	1	1: -0.001498 2: 0.004858
Q6	1	1: 0.001299 2: -0.000535
Q7	1	2: 0.000000
Q8	1	1: -0.004849 2: 0.003374
Q9	1	1: -0.014103 2: 0.018606
Q10	1	1: 0.048198 2: -0.006161
Q11	1	1: 0.000189 2: -0.001423

Conclusion



Genomic selection : validation



Example of simulation

