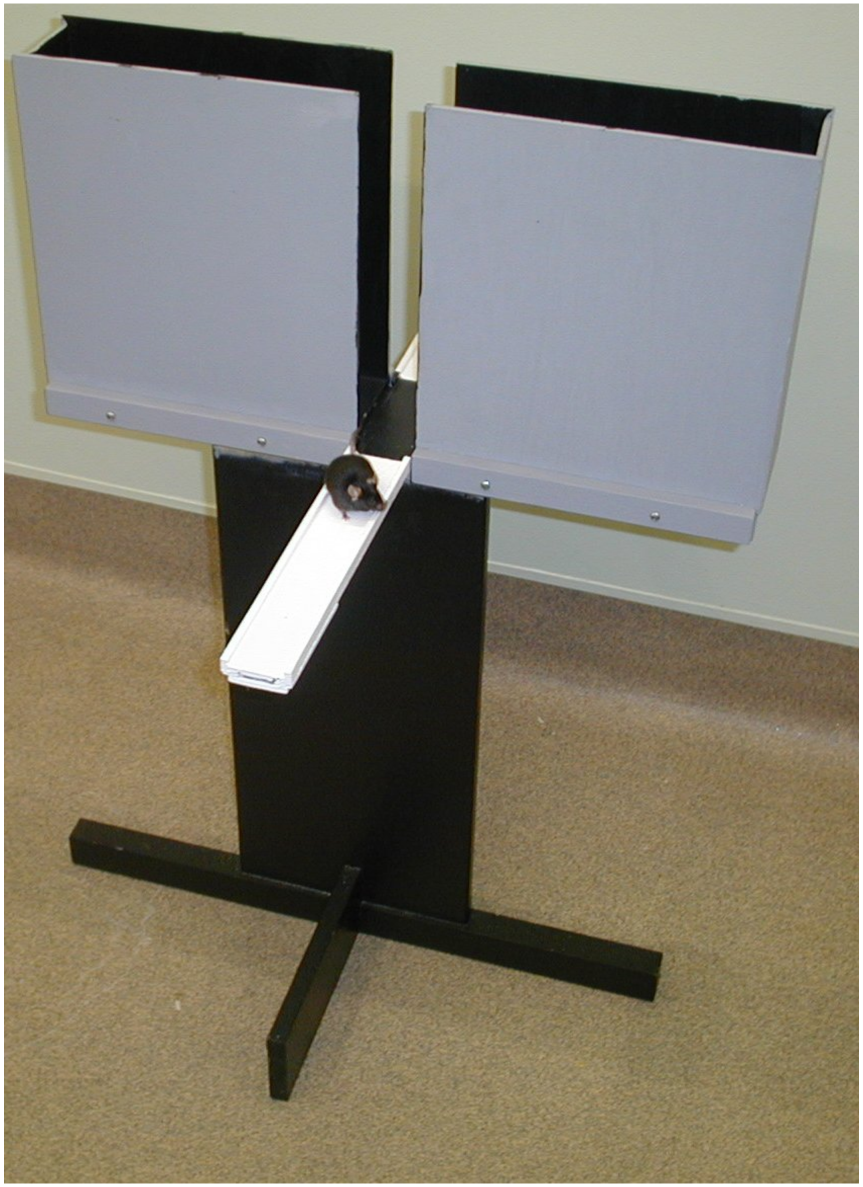
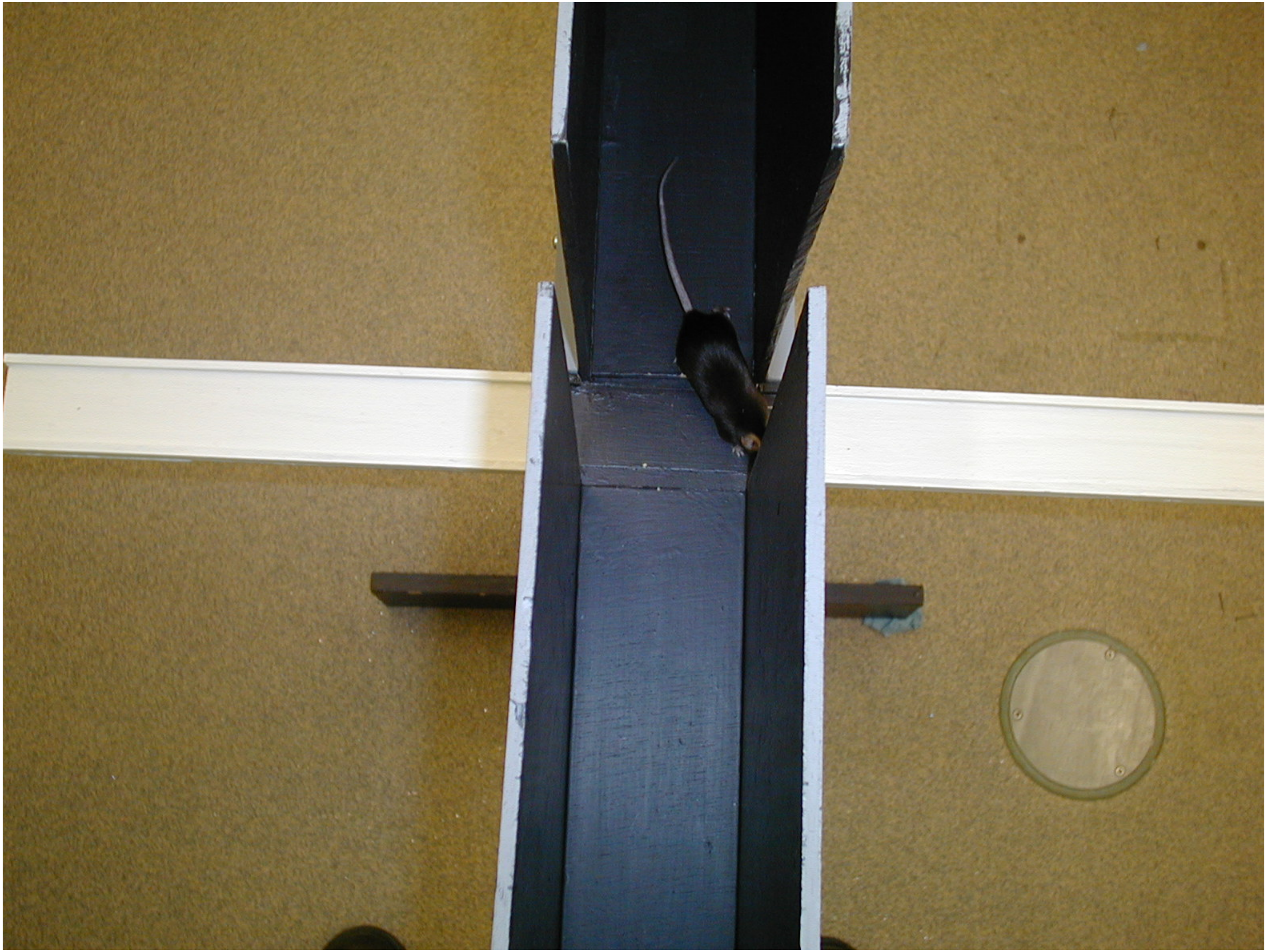
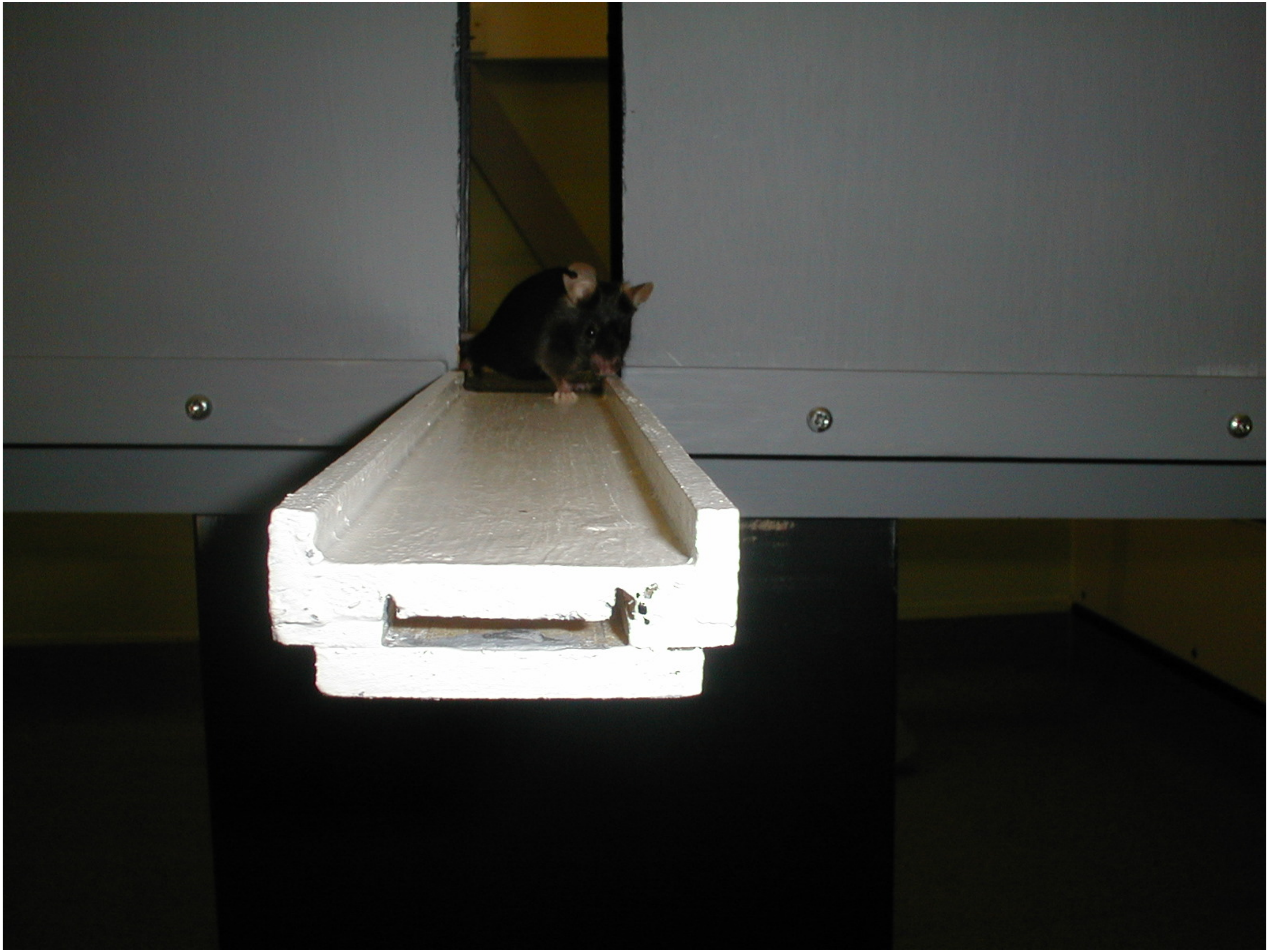
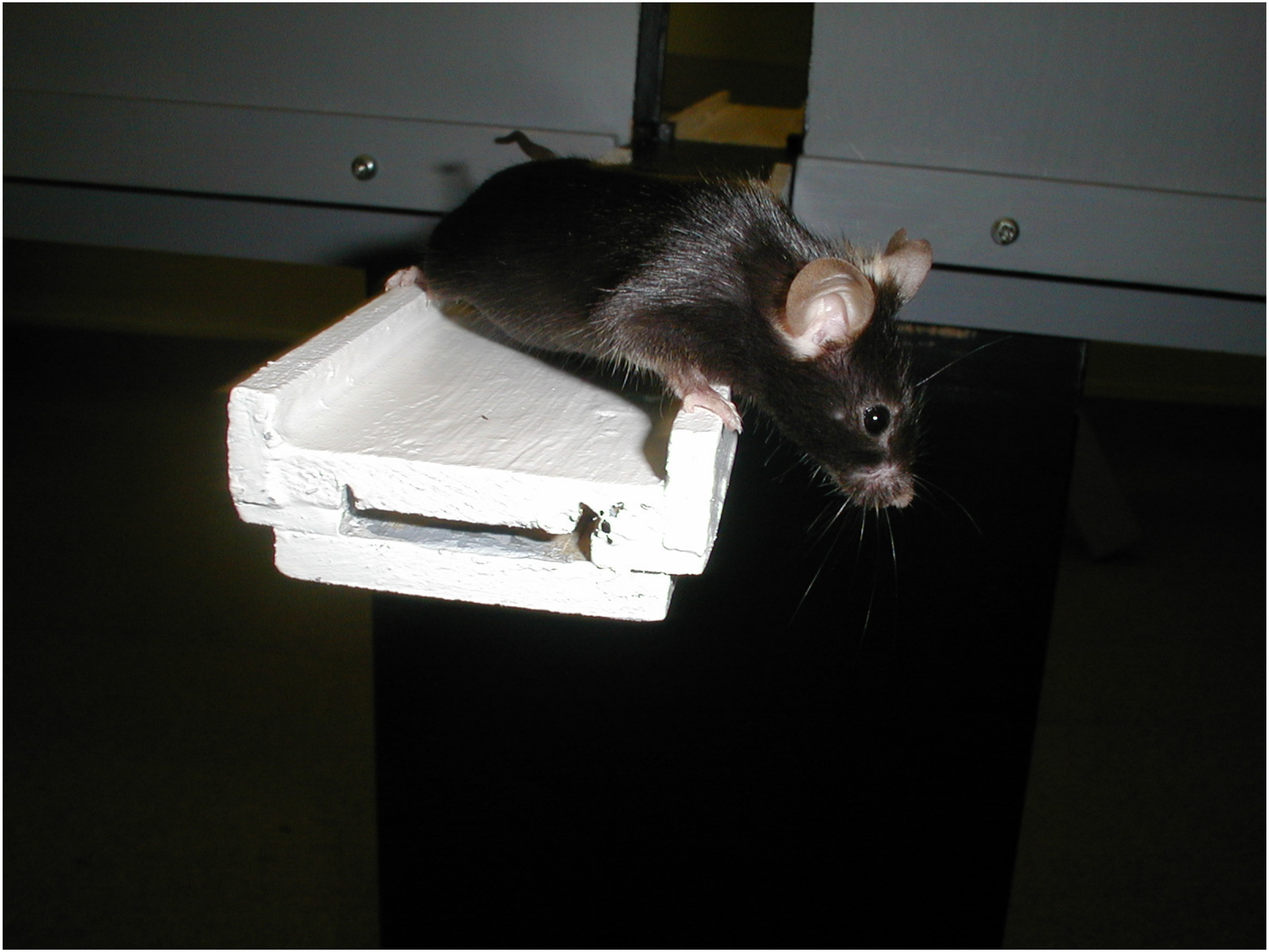
# Gene by environment effects

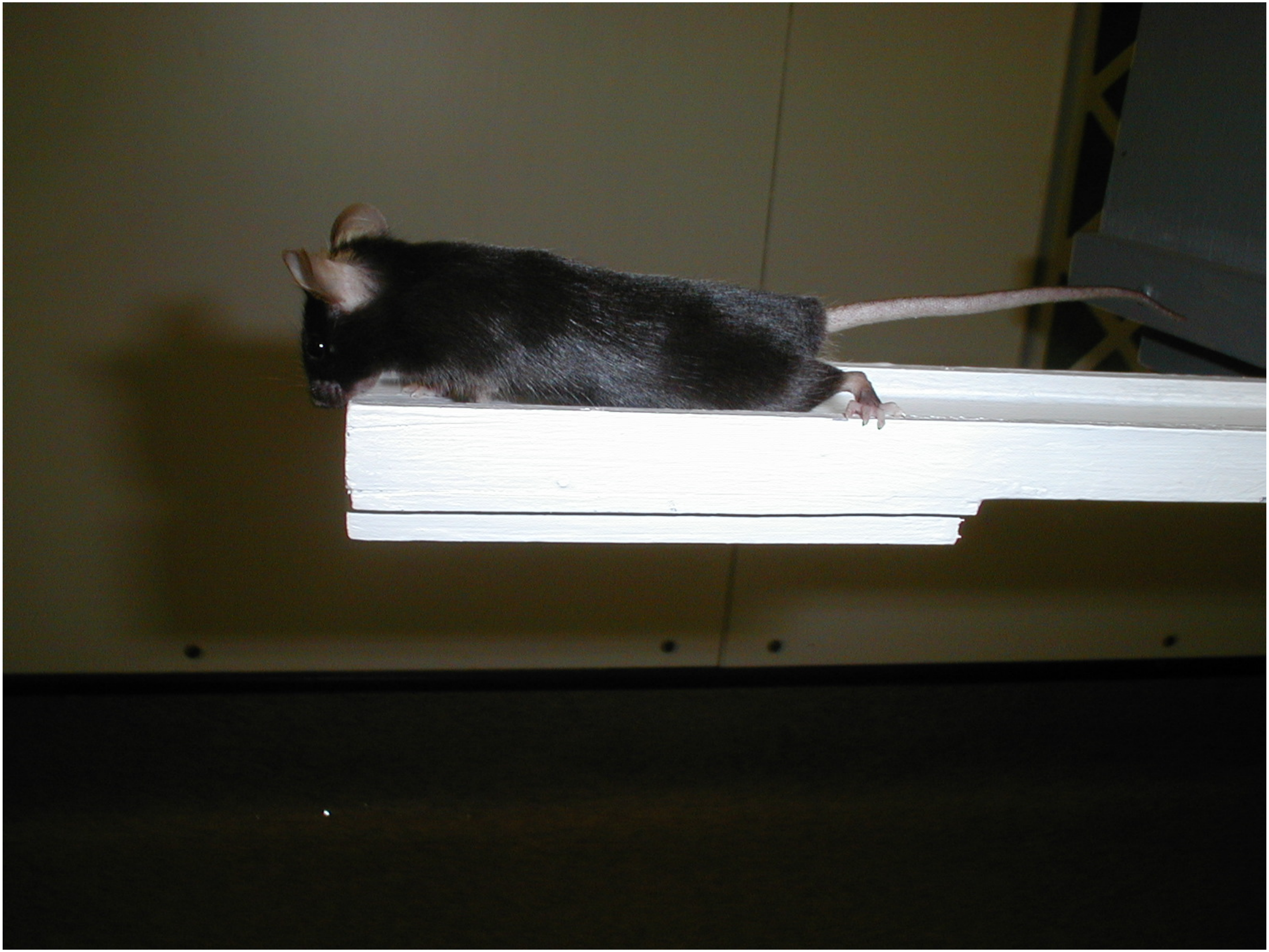
# Elevated Plus Maze (anxiety)

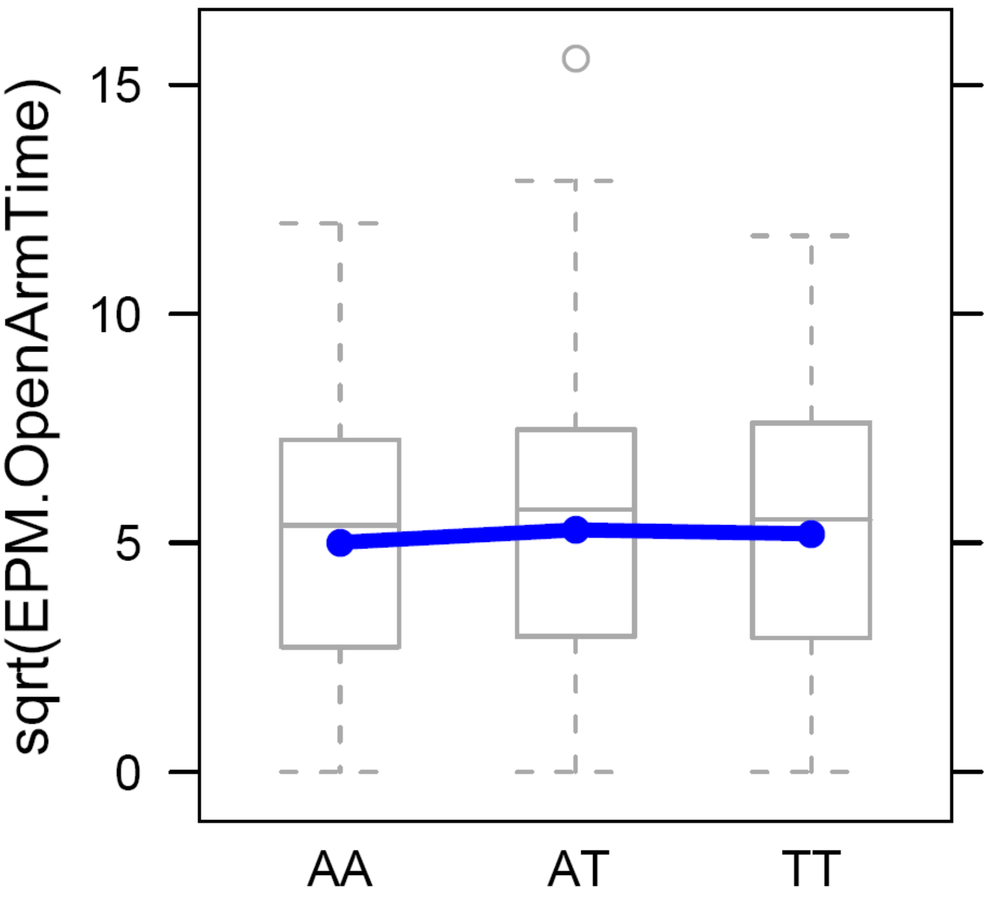


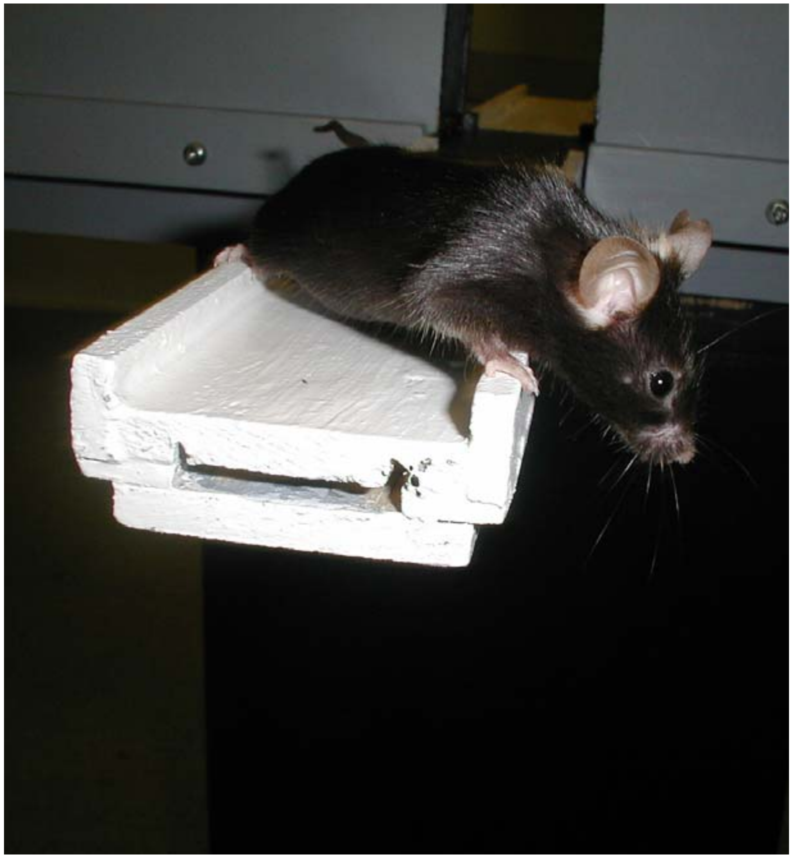


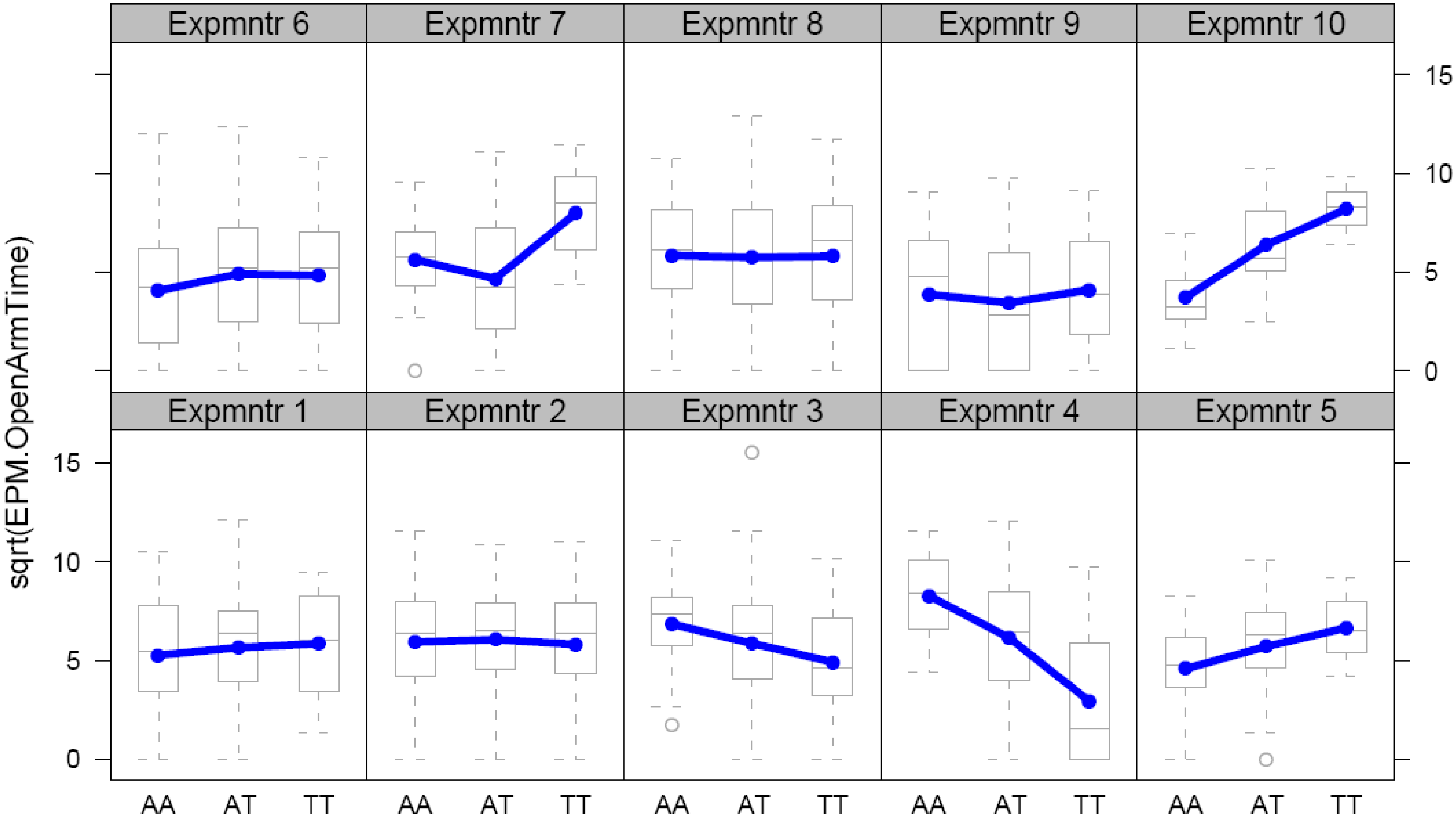







sqrt(EPM.OpenArmTime)
0
5
10
15
AA
AT
TT




Expmntr 6
Expmntr 7
Expmntr 8
Expmntr 9
Expmntr 10
Expmntr 1
Expmntr 2
Expmntr 3
Expmntr 4
Expmntr 5
sqrt(EPM.OpenArmTime)
0
5
10
15
AA
AT
TT

# Modelling E, G and GxE

$H_0$: phenotype ~ 1

$H_1$: phenotype ~ covariate

$H_2$: phenotype ~ covariate + **LocusX**

$H_3$: phenotype ~ covariate + LocusX **+ covariate:LocusX**

# PRACTICAL: Inclusion of gender effects in a genome scan

To start:

1. Copy the folder faculty\valdar\FridayAnimalModelsPractical to your own directory.
2. Start R
3. File -> Change Dir… and change directory to your FridayAnimalModelsPractical directory
4. Open Firefox, then File -> Open File, and open “gxe.R” in the FridayAnimalModelsPractical directory

$H_0$: phenotype ~ sex

$H_1$: phenotype ~ sex + marker

$H_0$: phenotype ~ sex

$H_1$: phenotype ~ sex + marker

```
scan.markers(Phenotype ~ Sex + MARKER,
h0 = Phenotype ~ Sex,
... etc)
```

$H_0$: phenotype ~ sex

$H_1$: phenotype ~ sex + marker

```
scan.markers(Phenotype ~ Sex + MARKER,
h0 = Phenotype ~ Sex,
... etc)
```

$H_0$: phenotype ~ sex

$H_1$: phenotype ~ sex + marker

```
scan.markers(Phenotype ~ Sex + MARKER,
h0 = Phenotype ~ Sex,
... etc)
```

```
head(ped.gender0)
anova(lm(Phenotype ~ Sex + m1 + Sex:m1,
    data=ped.gender0))
```

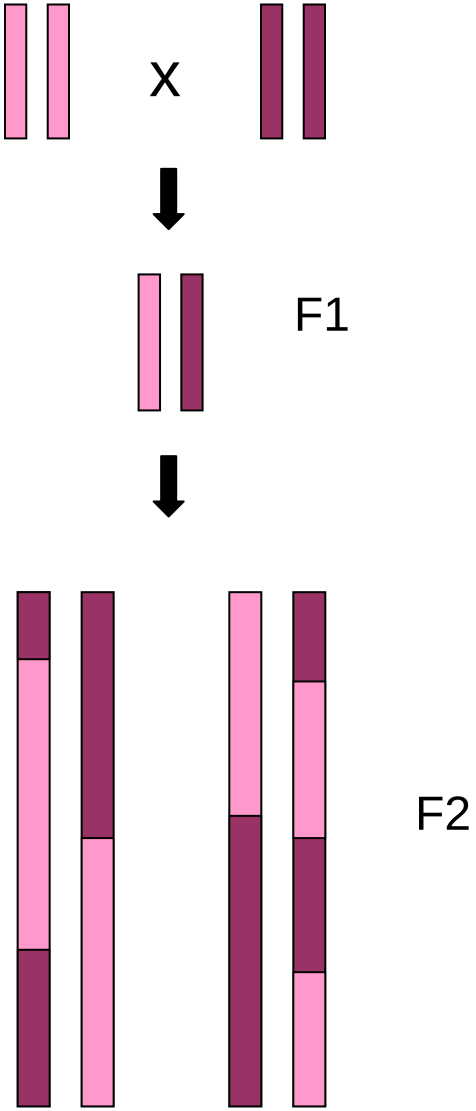
```
head(ped.gender1)
anova(lm(Phenotype ~ Sex + m1 + Sex:m1,
    data=ped.gender1)
```

# New approaches

Advanced intercross lines

Genetically heterogeneous stocks

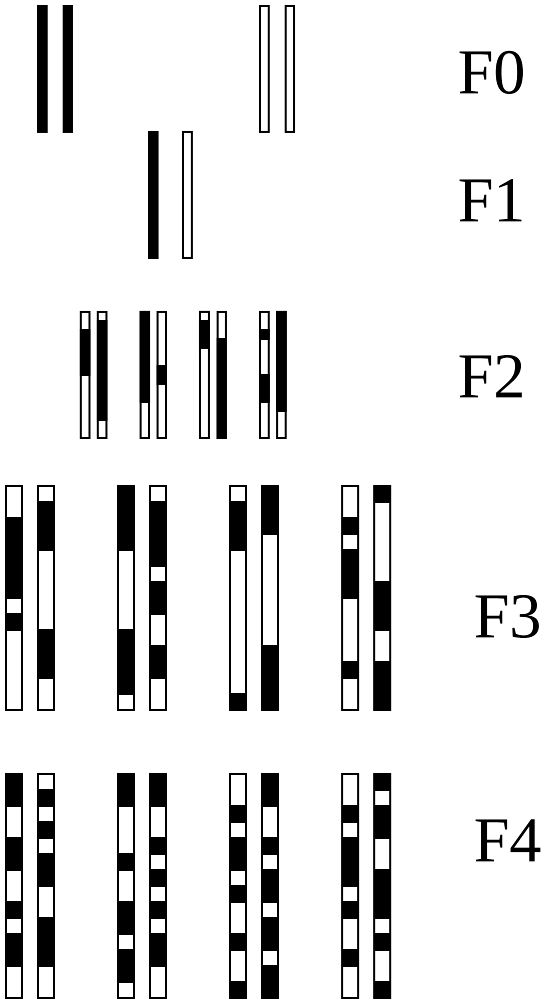
# F2 Intercross



Avg. Distance Between
Recombinations

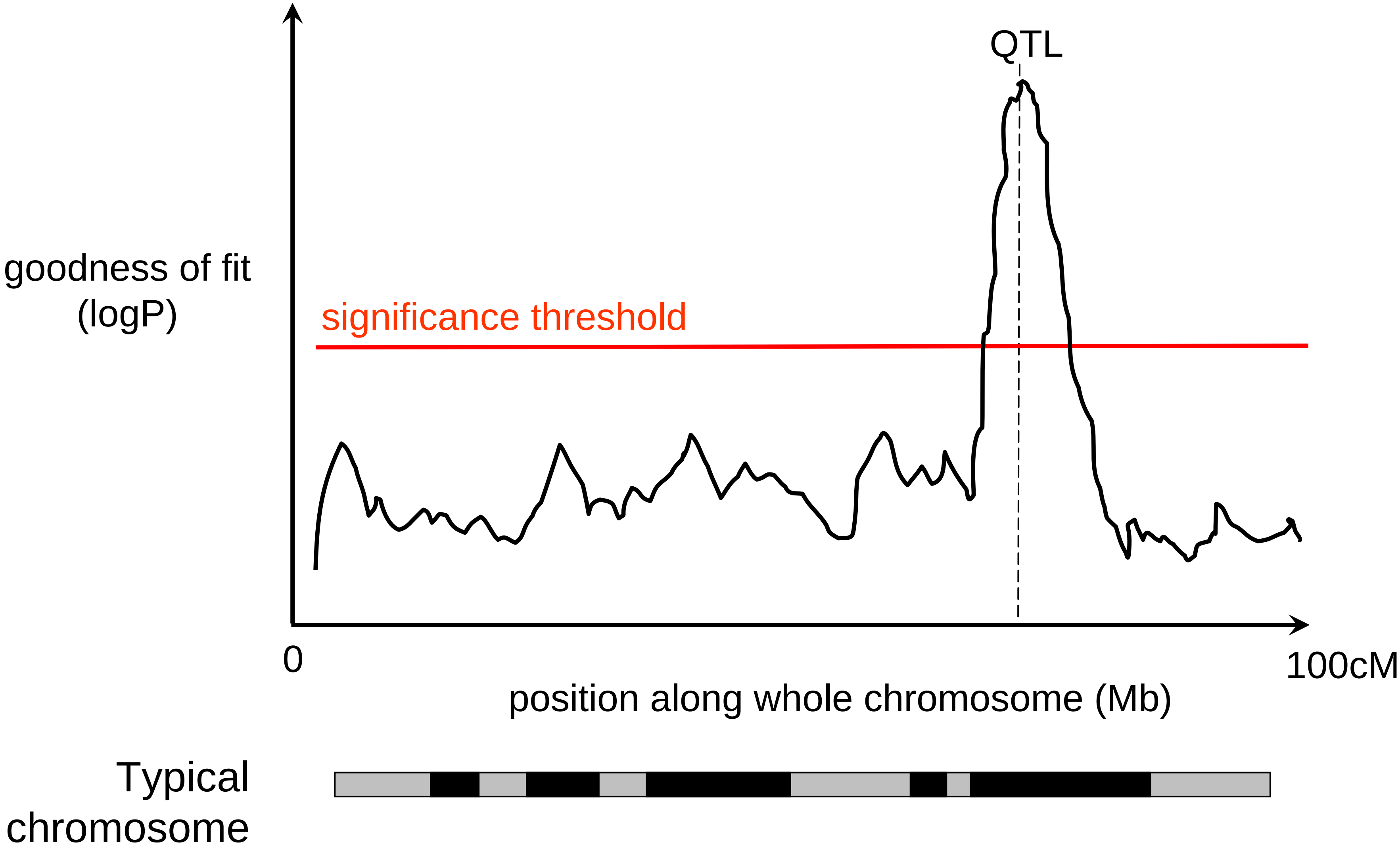
F2 intercross
~30 cM

# Advanced intercross lines (AILs)



Darvasi A, Soller M (1995) Advanced intercross lines, an experimental population for fine genetic mapping. Genetics 141: 1199-1207.

# Chromosome scan for F12



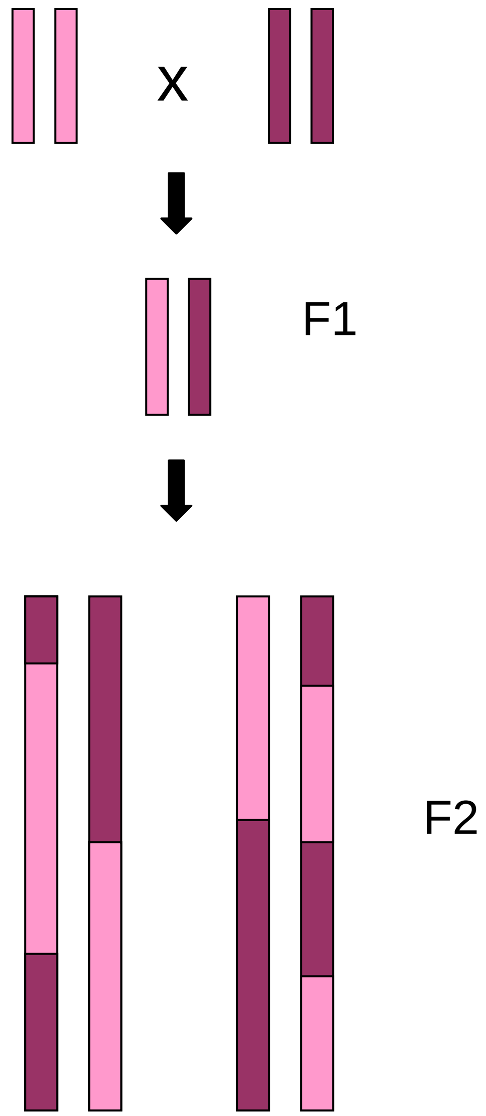
# PRACTICAL: AILs

To start:

1. Open Firefox, then File -> Open File, and open “ail_and_ghosts.R” in the FridayAnimalModelsPractical directory

# Genetically Heterogeneous Mice

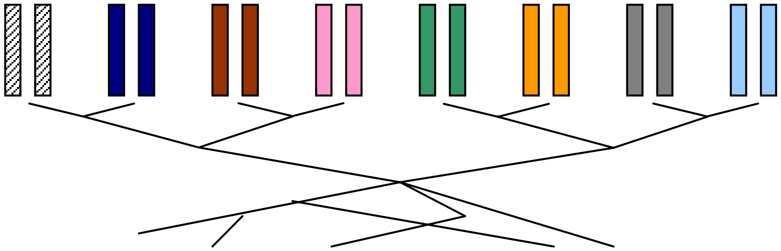
# F2 Intercross



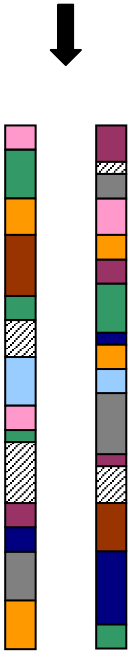
Avg. Distance Between
Recombinations

F2 intercross
~30 cM

## Heterogeneous Stock



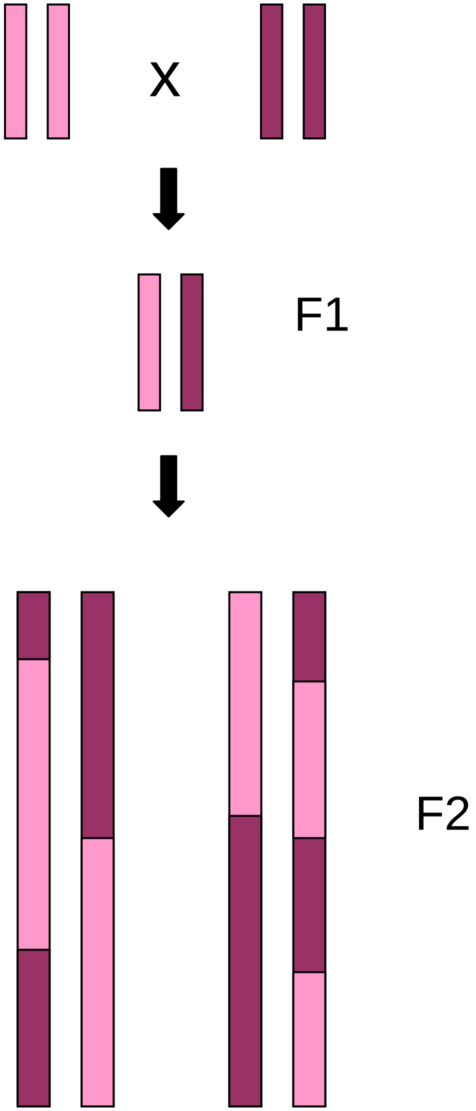
Pseudo-random mating
for 50 generations



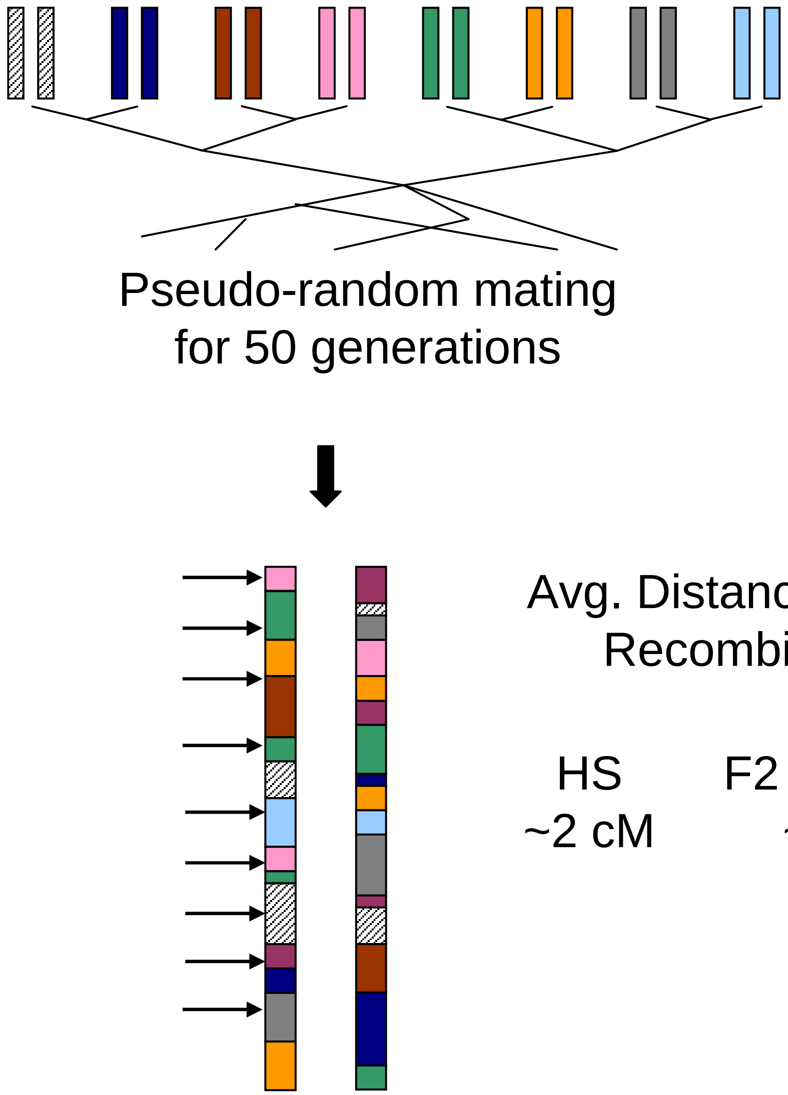
Avg. Distance Between
Recombinations:

| HS | F2 intercross |
|---|---|
| ~2 cM | ~30 cM |

## F2 Intercross

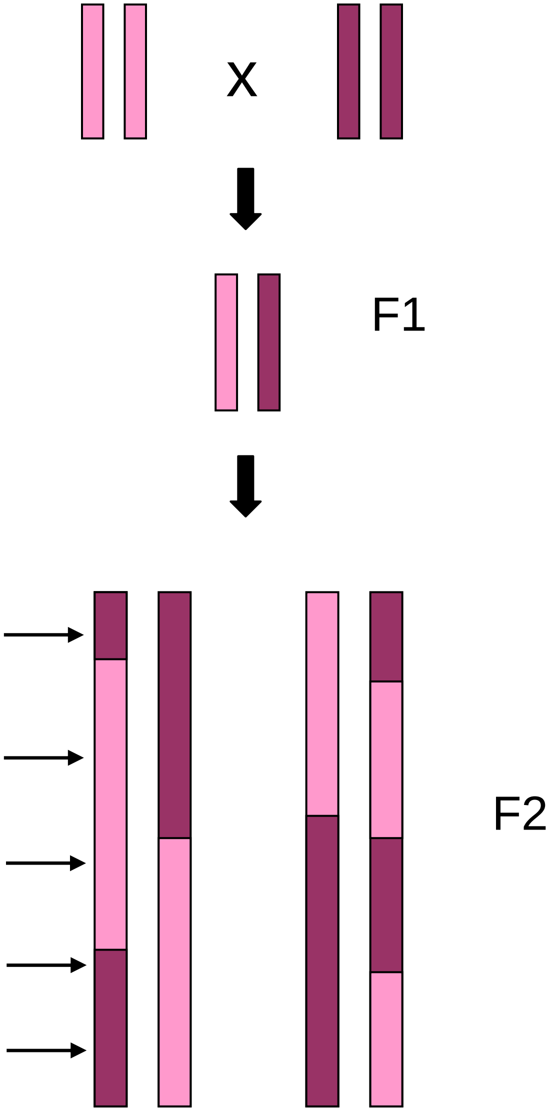


# Heterogeneous Stock



Pseudo-random mating
for 50 generations

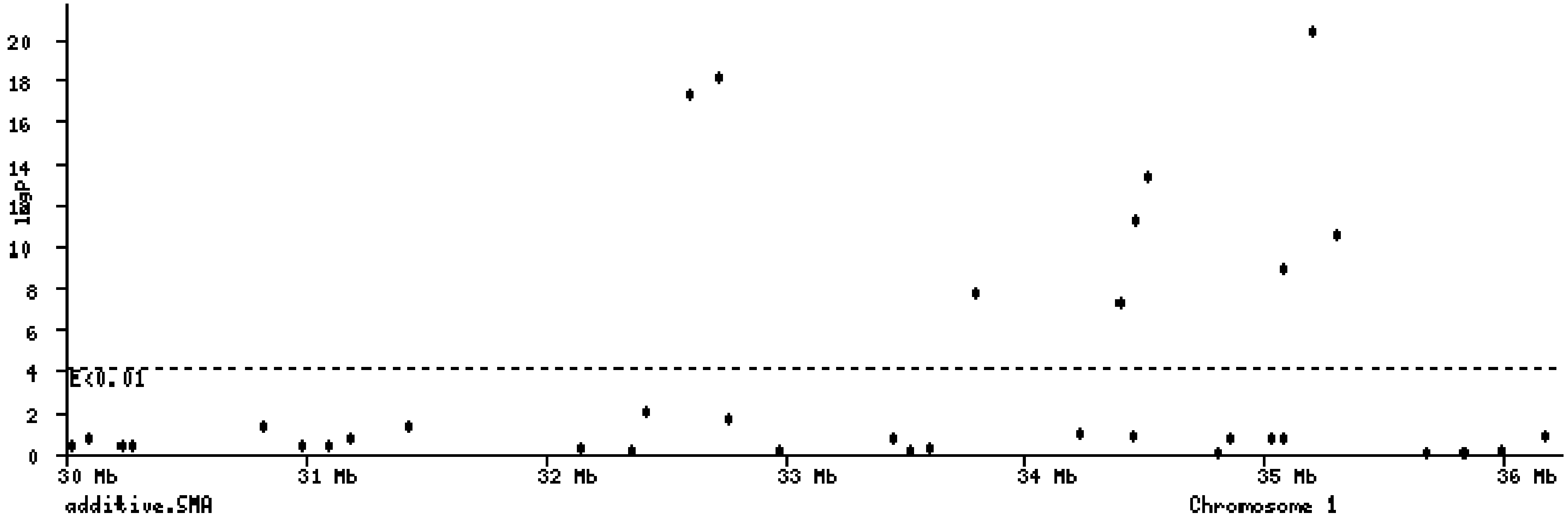
# F2 Intercross



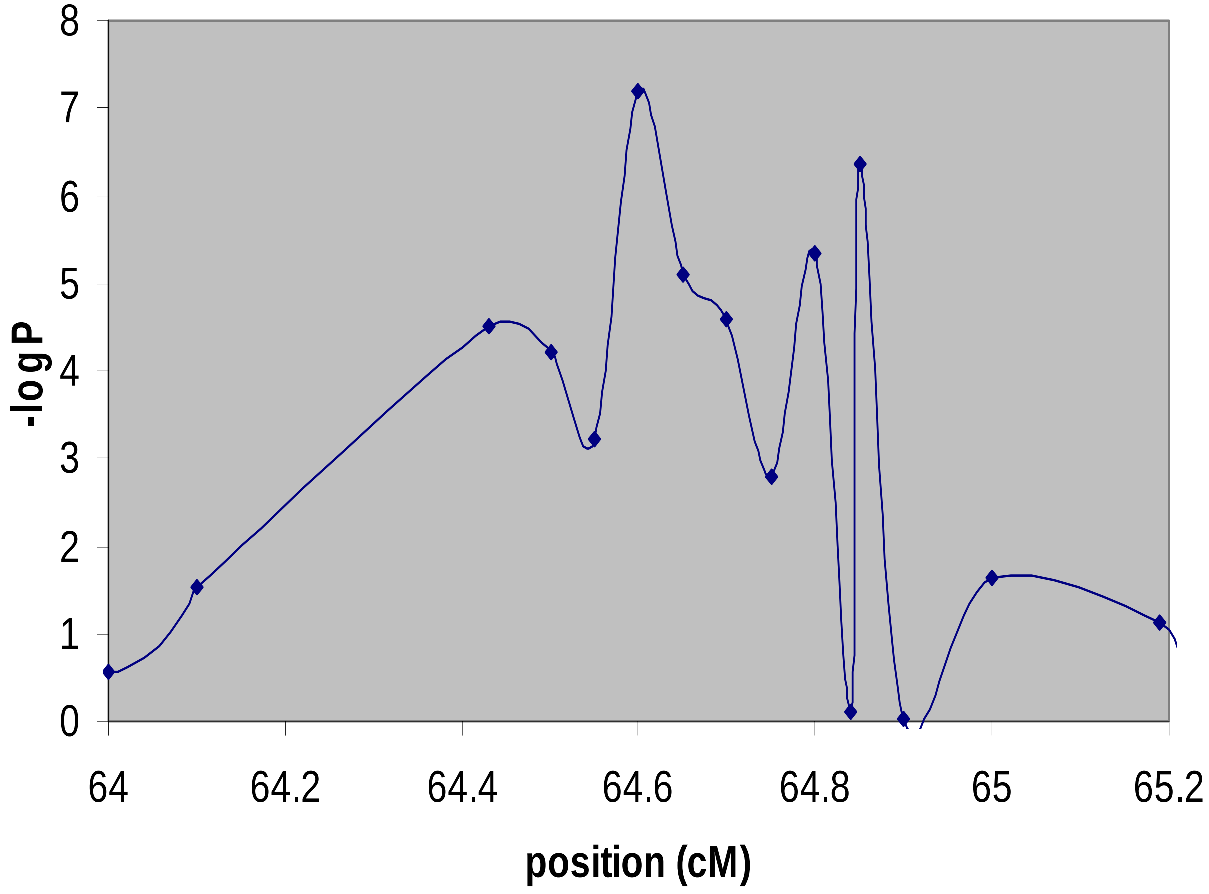
Avg. Distance Between
Recombinations:

| HS | F2 intercross |
|---|---|
| ~2 cM | ~30 cM |

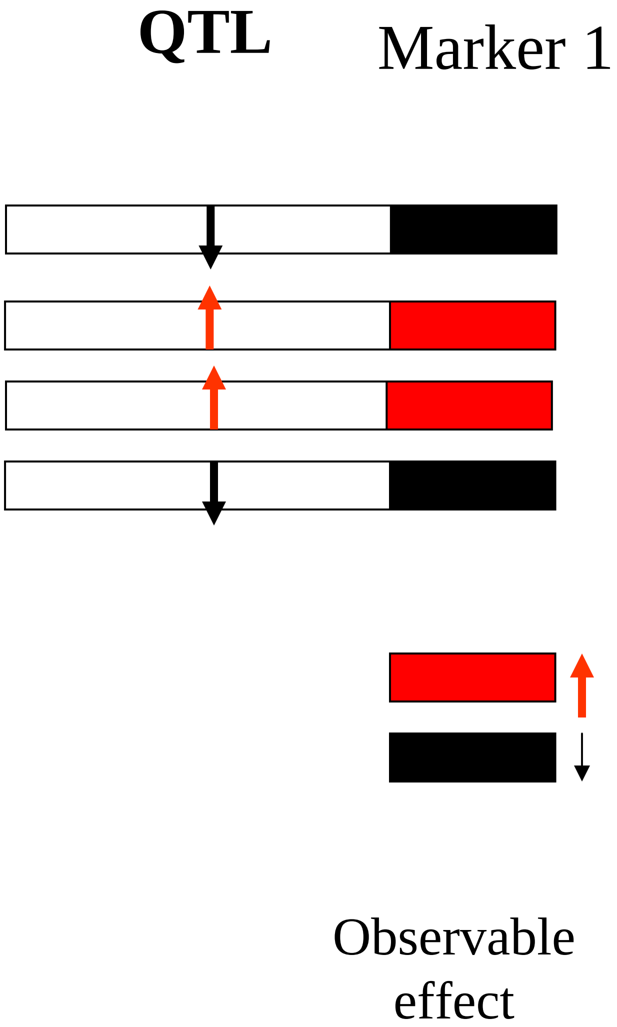
# Genome scans with single marker association



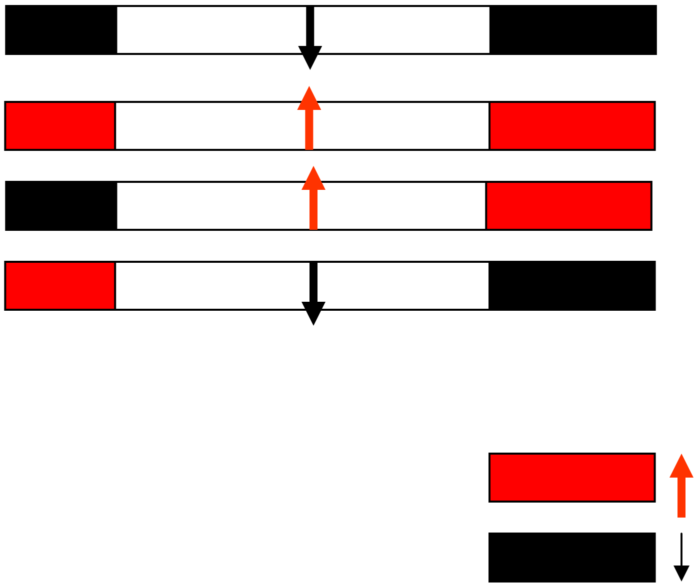
# High resolution mapping



# Relation Between Marker and Genetic Effect



# Relation Between Marker and Genetic Effect



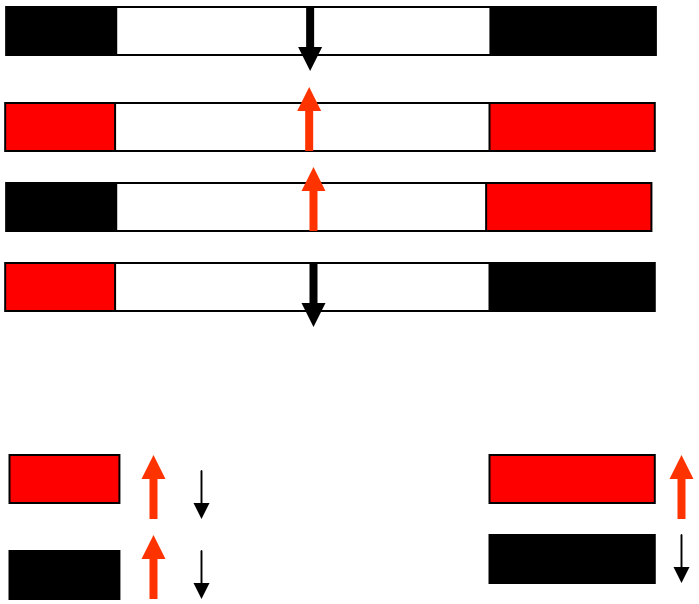
Marker 2

**QTL**

Marker 1

Observable
effect

# Relation Between Marker and Genetic Effect



Marker 2

**QTL**

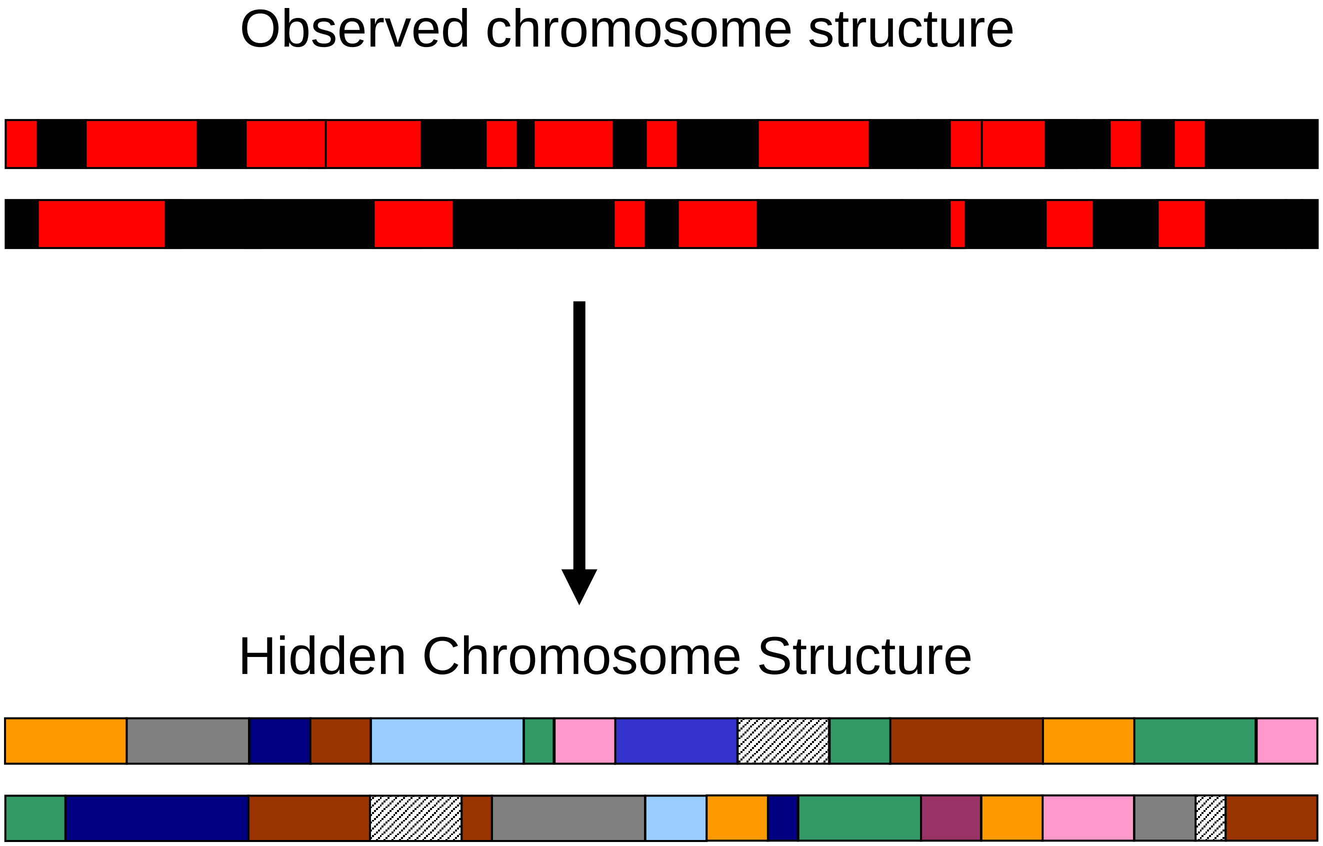
Marker 1

No effect

observable

Observable
effect

# Multipoint method (HAPPY) calculates the probability that an allele descends from a founder using multiple markers



Observed chromosome structure

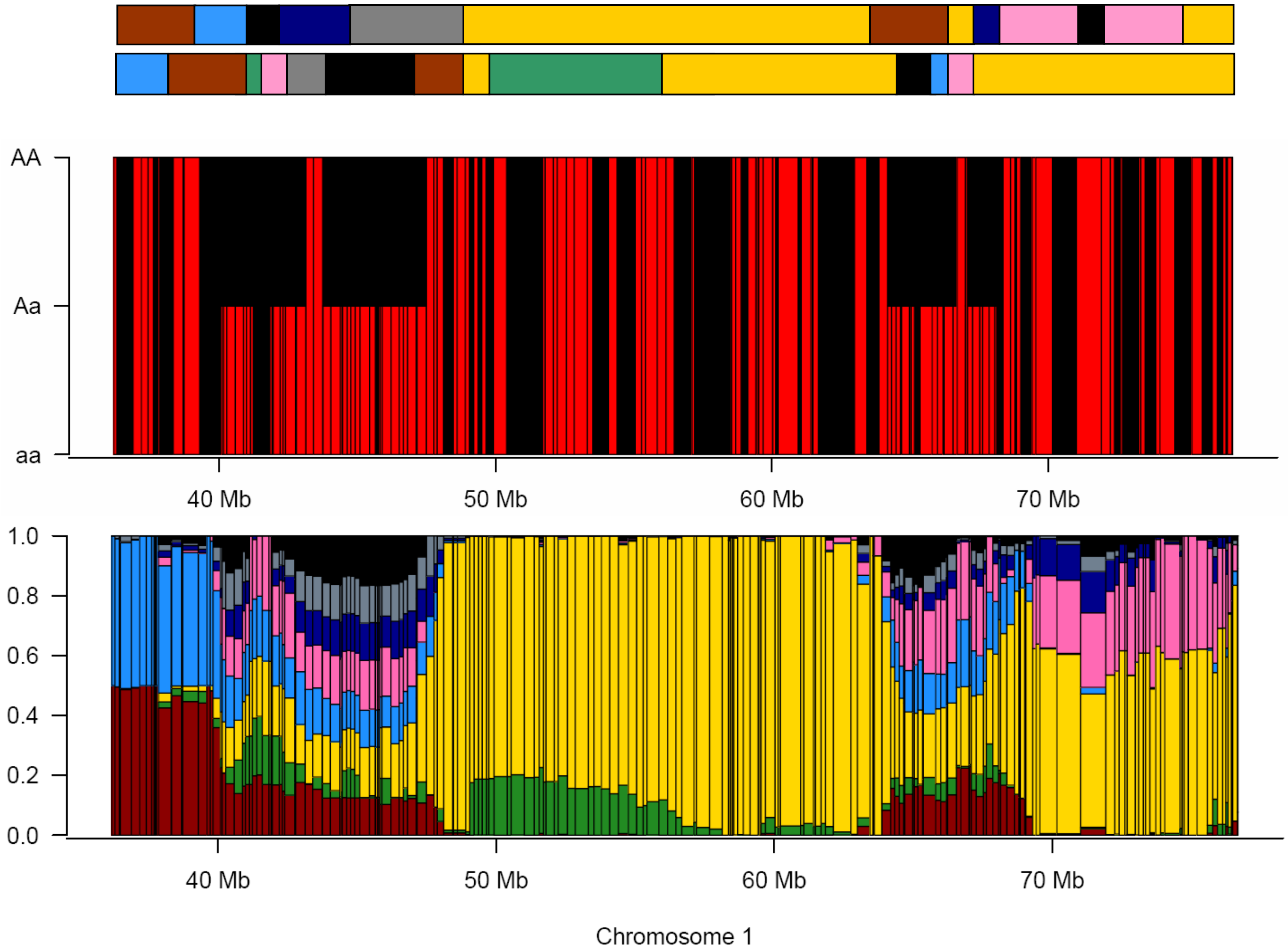
Hidden Chromosome Structure

# Haplotype reconstruction using HAPPY

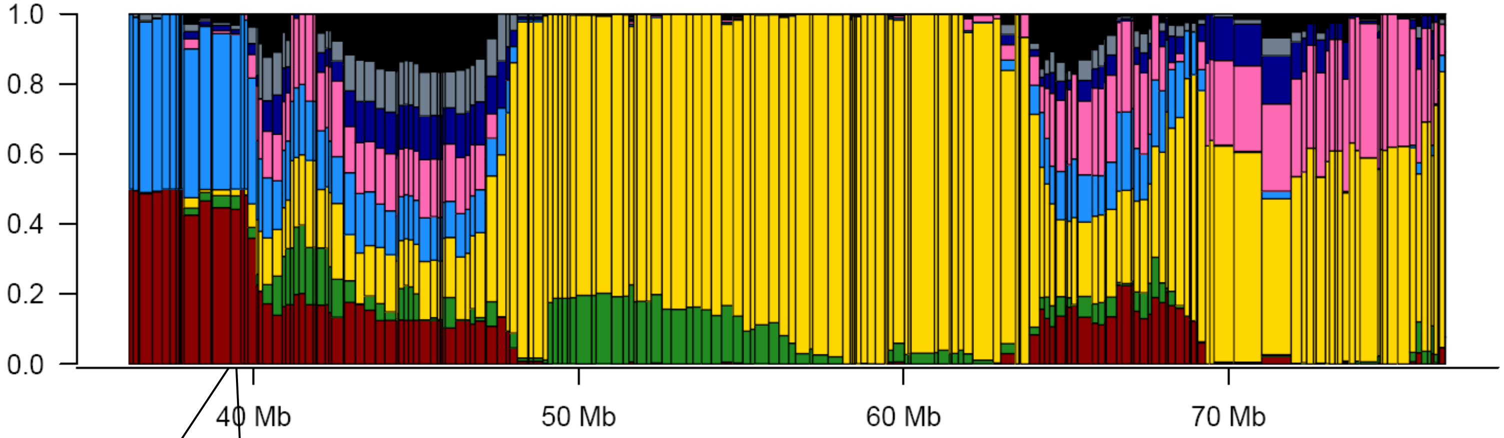
chromosome

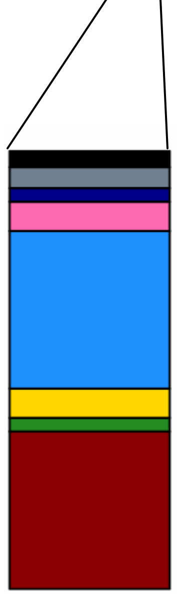
genotypes

haplotype proportions predicted by HAPPY



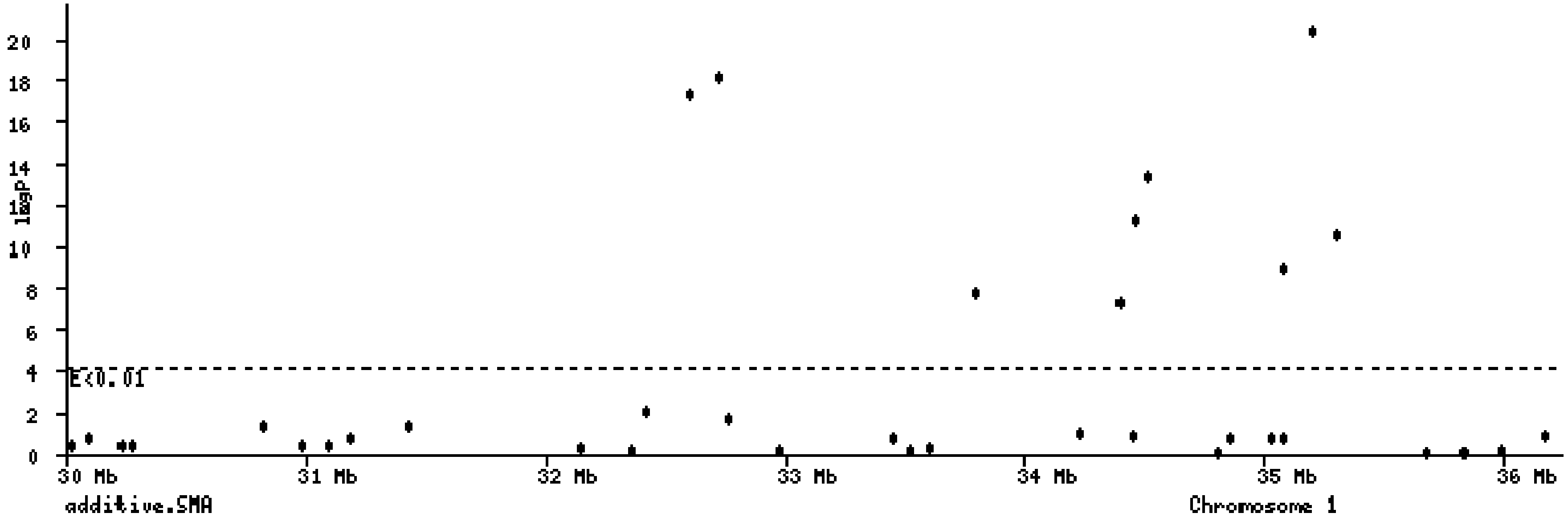
# HAPPY model for additive effects



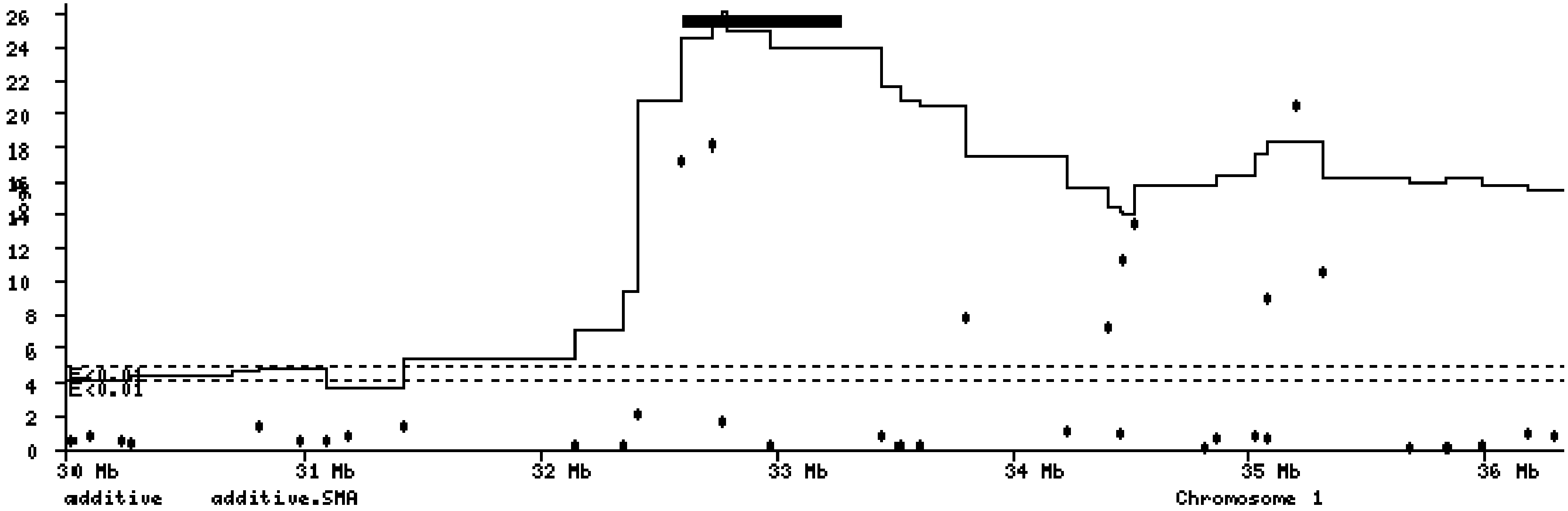


| Strain | *f* (strain) |
|---|---|
| **LP.J** | 0.04 |
| **DBA.2J** | 0.05 |
| **CBA.J** | 0.03 |
| **C57BL.6J** | 0.07 |
| **C3H.HeJ** | 0.36 |
| **BALB.cJ** | 0.07 |
| **AKR.J** | 0.03 |
| **A.J** | 0.36 |

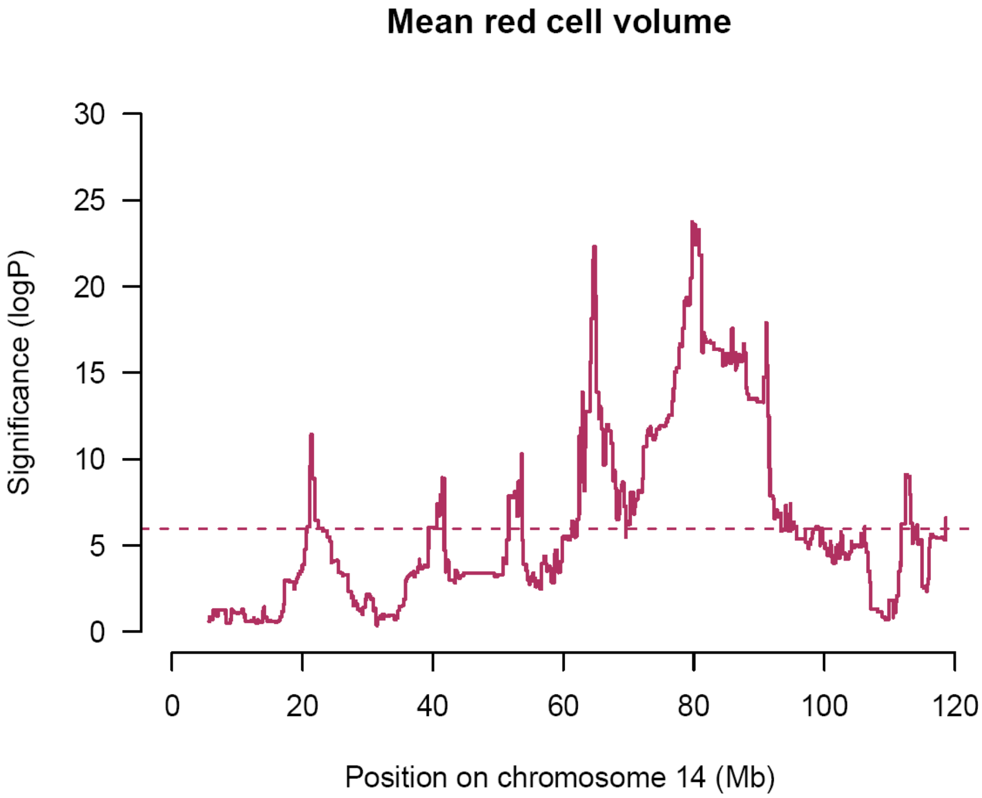
# Genome scans with single marker association



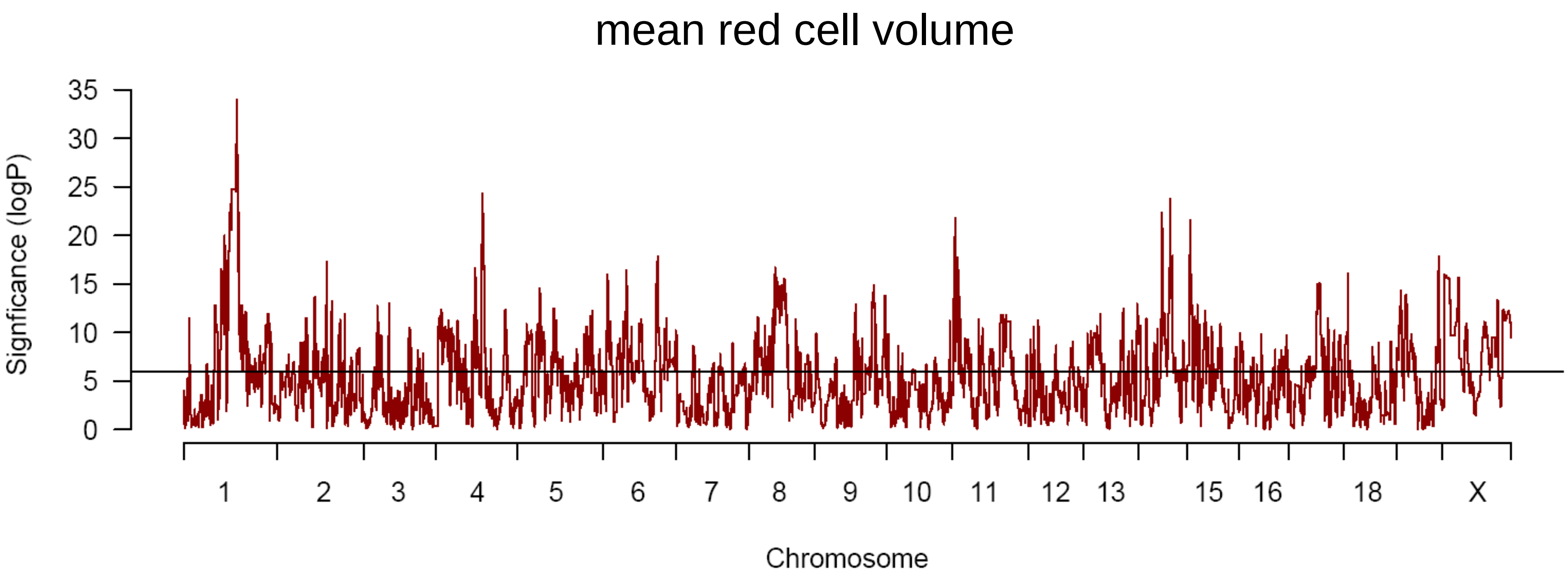
# Genome scans with HAPPY



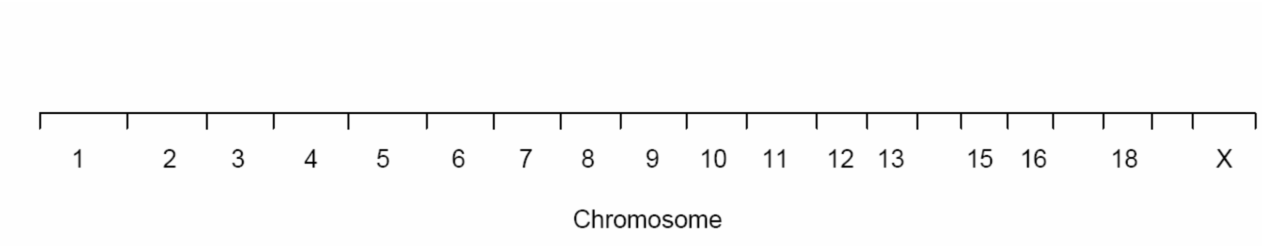
# Results for our HS



# Many peaks


mean red cell volume
Signficance (logP)
0
5
10
15
20
25
30
35
Chromosome
1
2
3
4
5
6
7
8
9
10
11
12
13
15
16
18
X

# How to select peaks: a simulated example



# How to select peaks: a simulated example

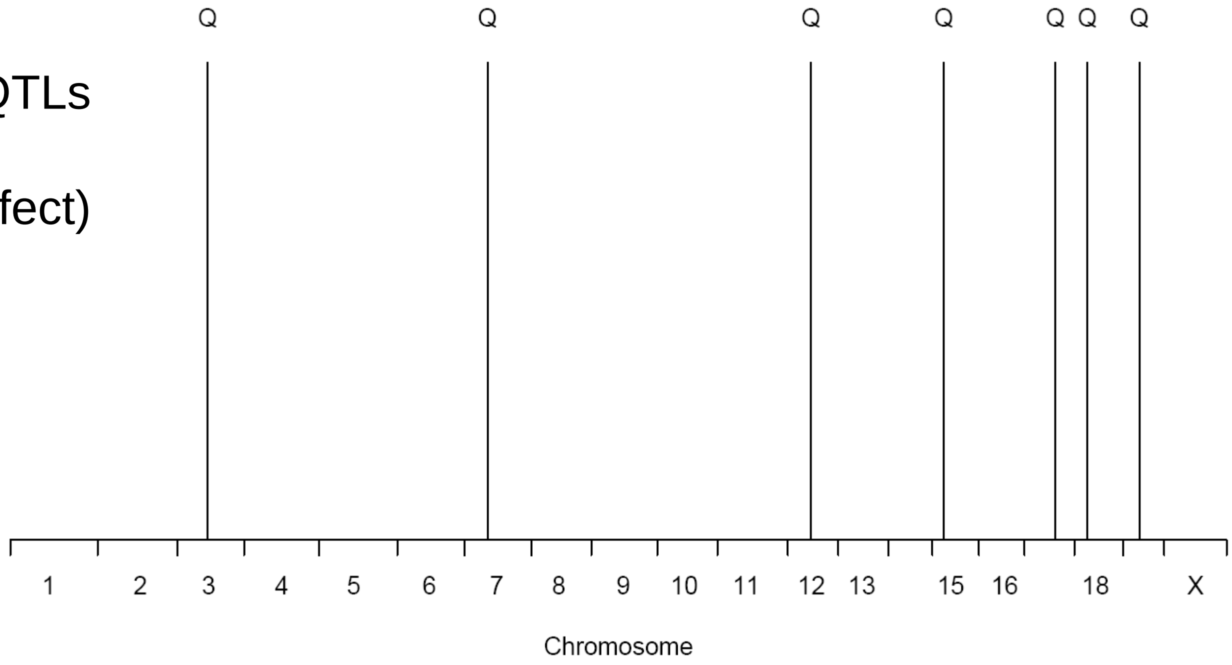
Simulate 7 x  5% QTLs

(ie, 35% genetic effect)

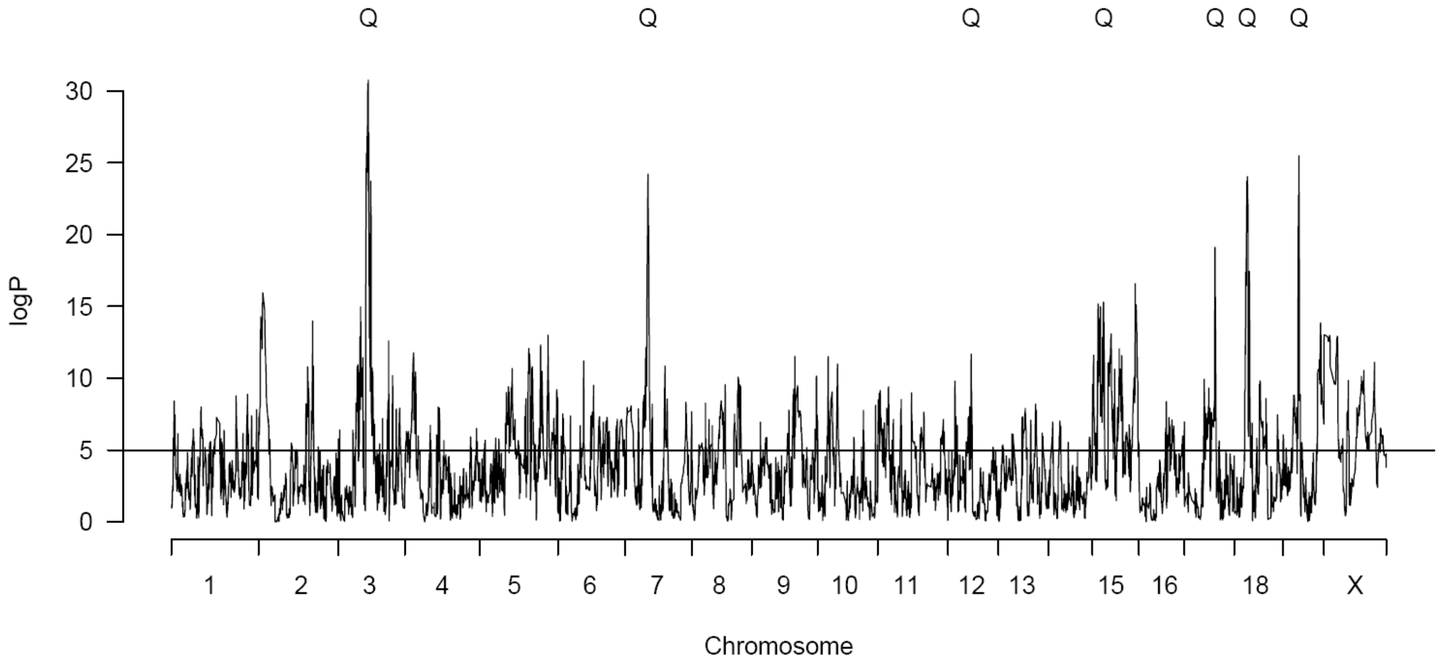
+ 20% shared environment effect

+ 45% noise

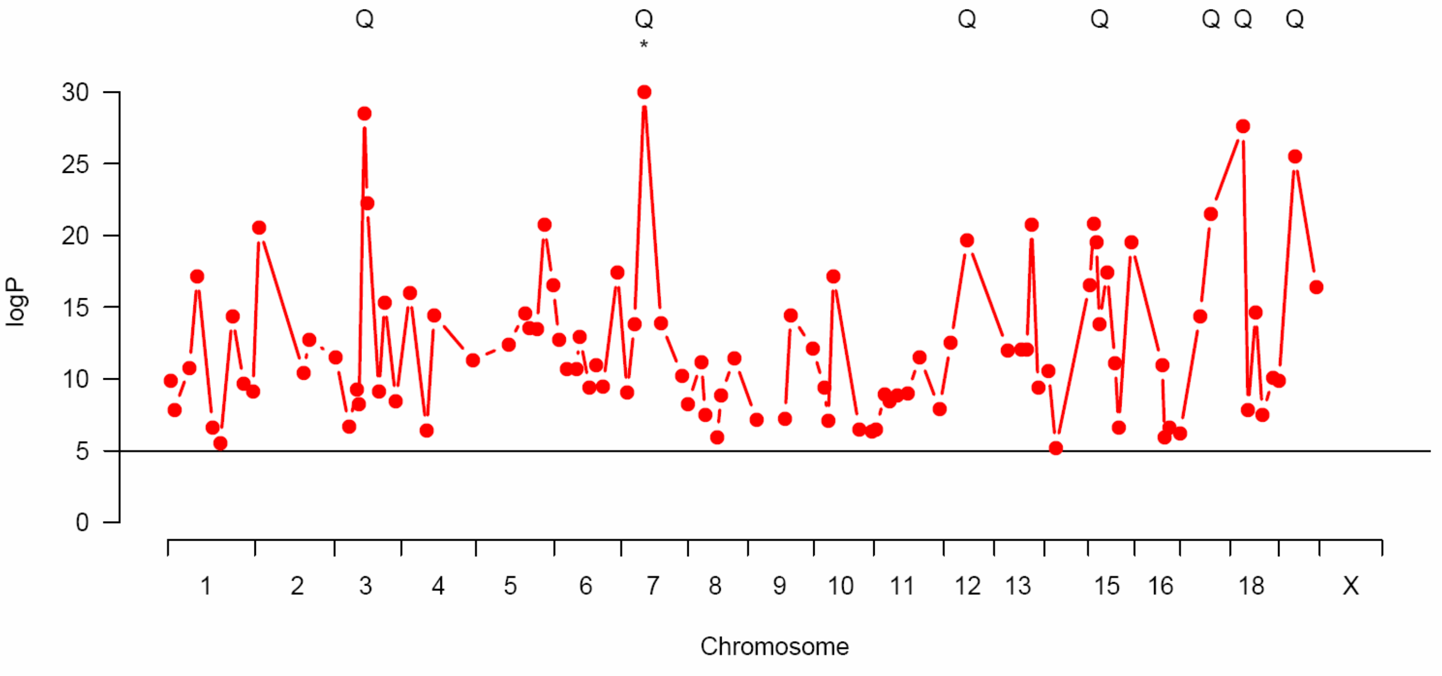
= 100% variance



# Simulated example: 1D scan

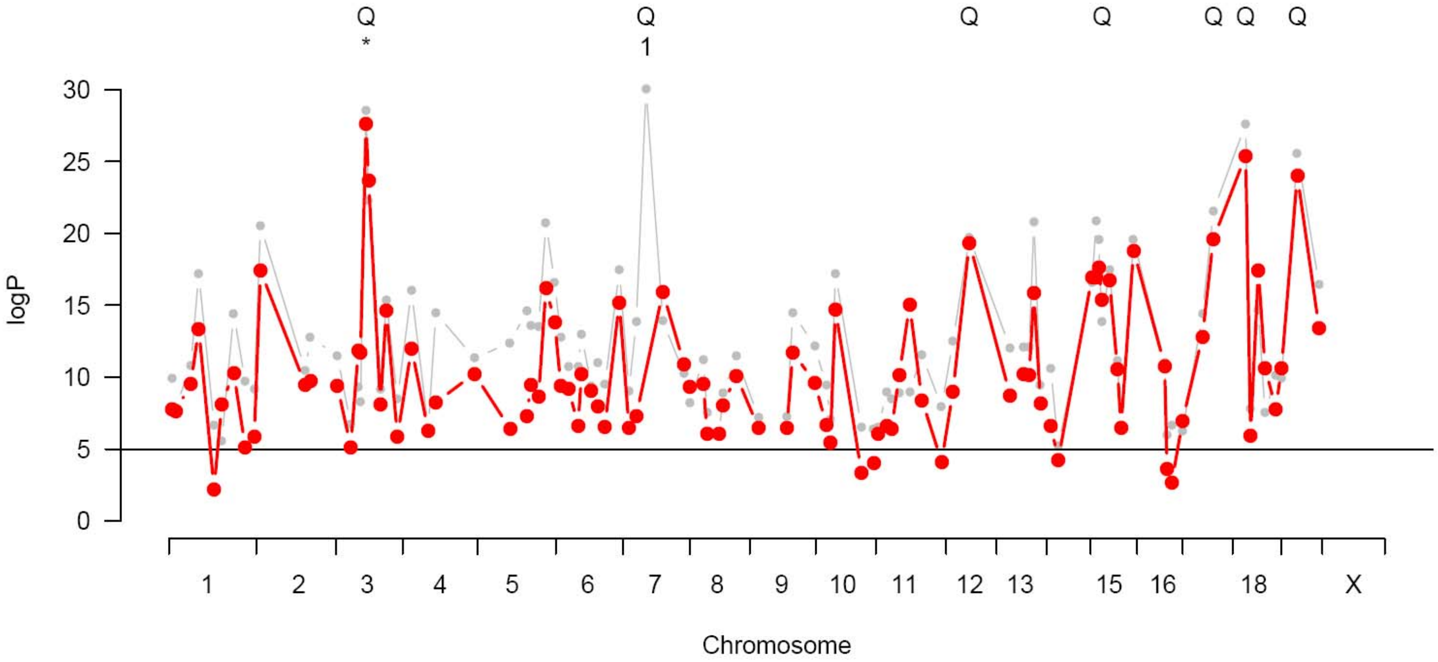


# Peaks from 1D scan



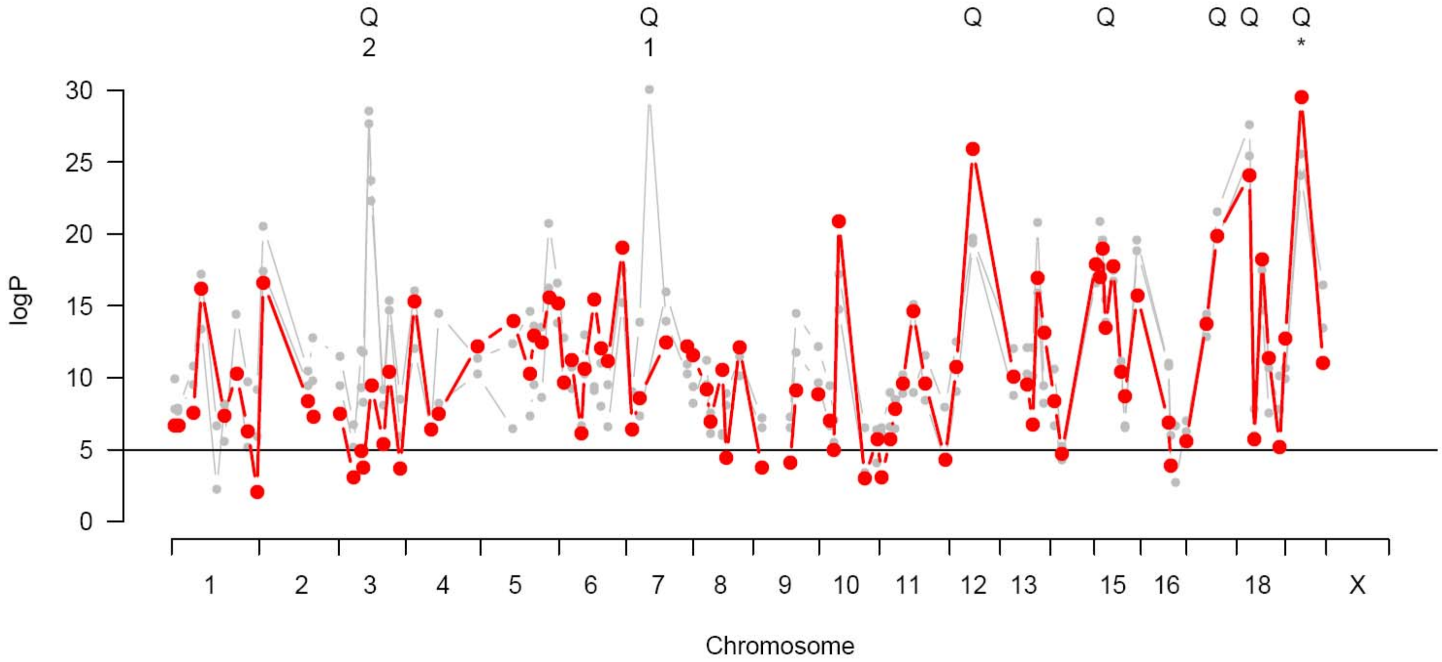
phenotype ~ covariates + ?

# 1D scan: condition on 1 peak



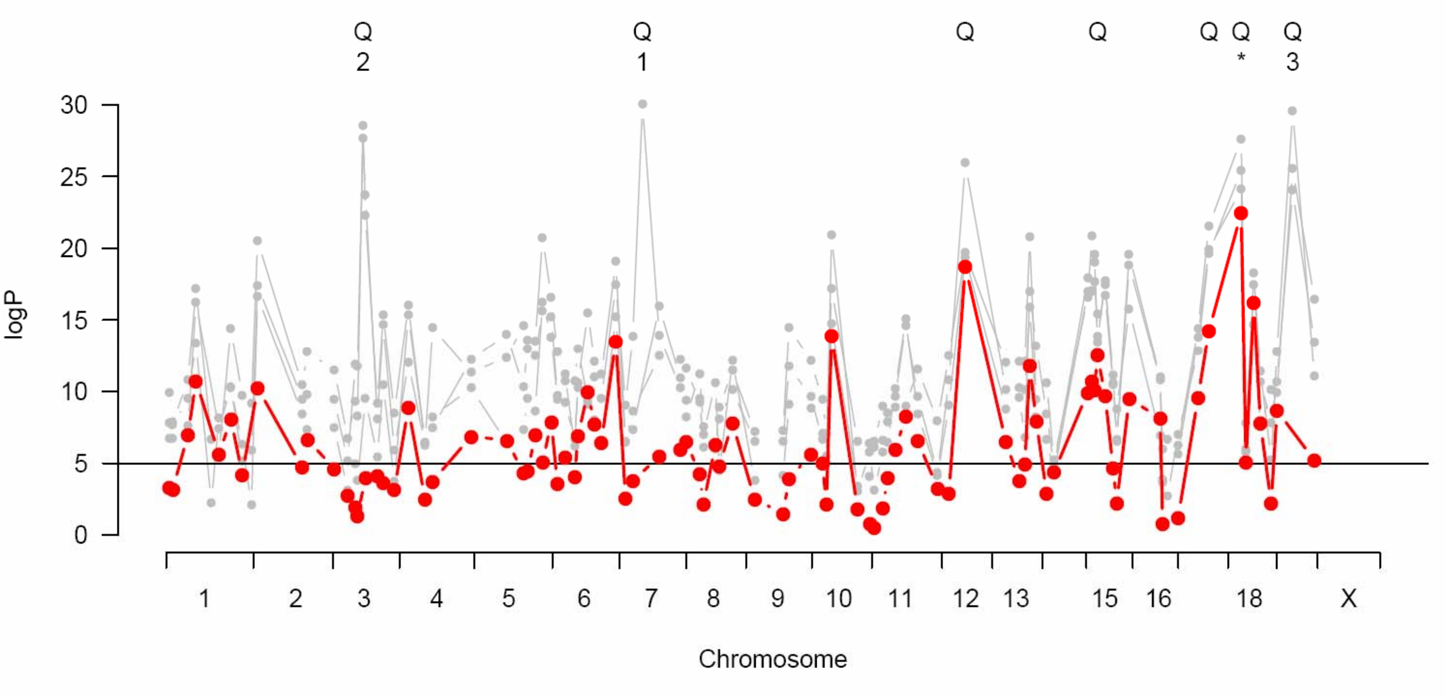
phenotype ~ covariates + peak 1 + ?

# 1D scan: condition on 2 peaks



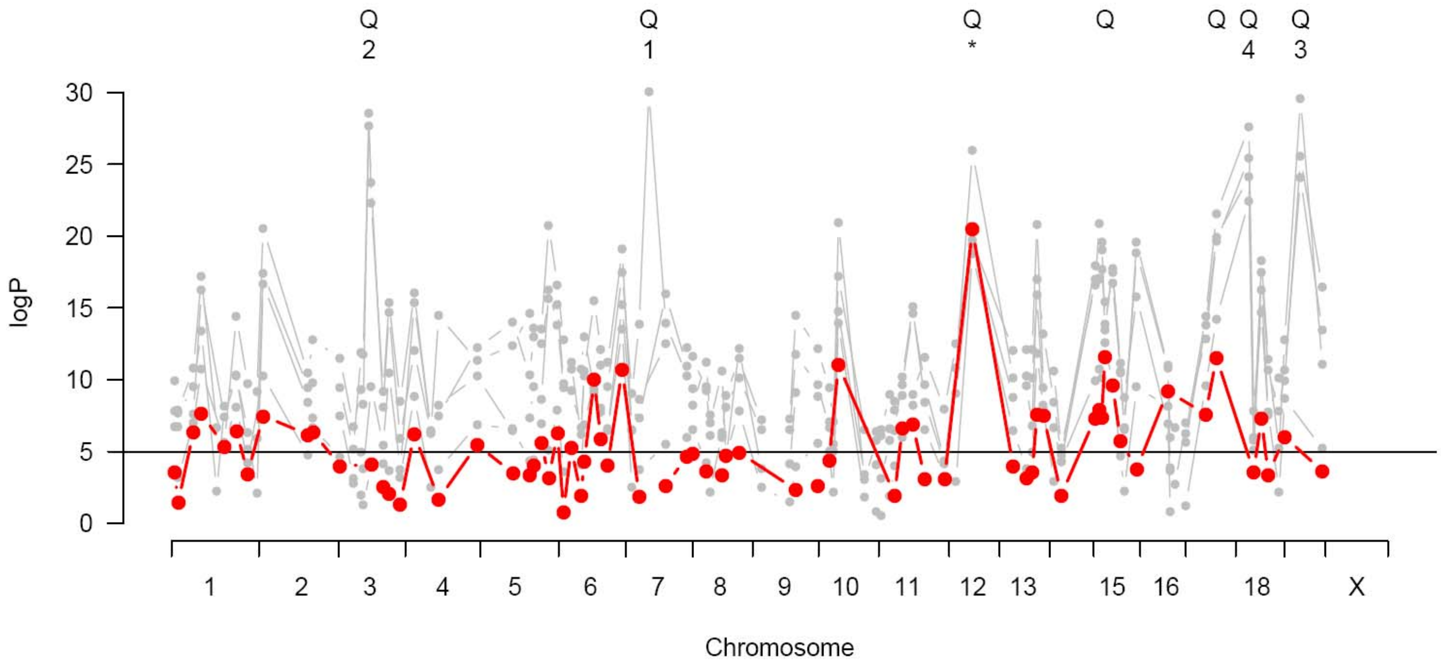
phenotype ~ covariates + peak 1 + peak 2 + ?

# 1D scan: condition on 3 peaks



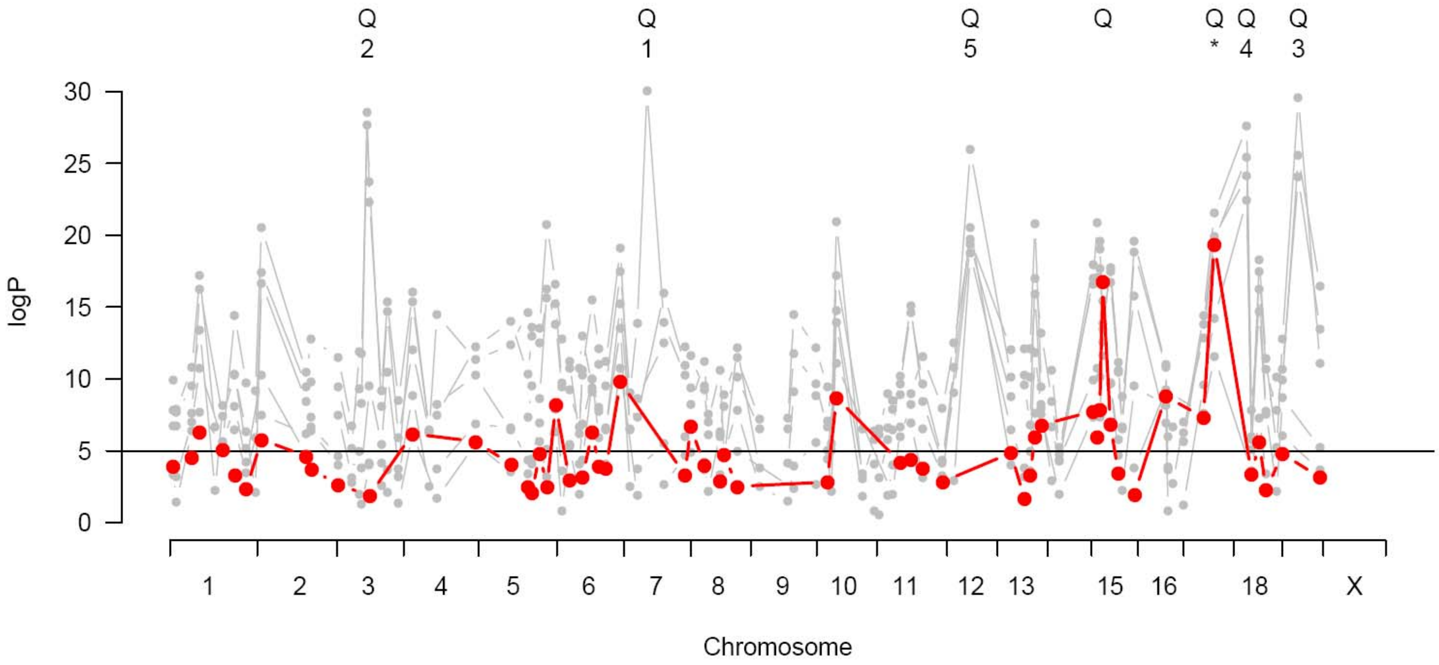
phenotype ~ covariates + peak 1 + peak 2 + peak 3 + ?

# 1D scan: condition on 4 peaks



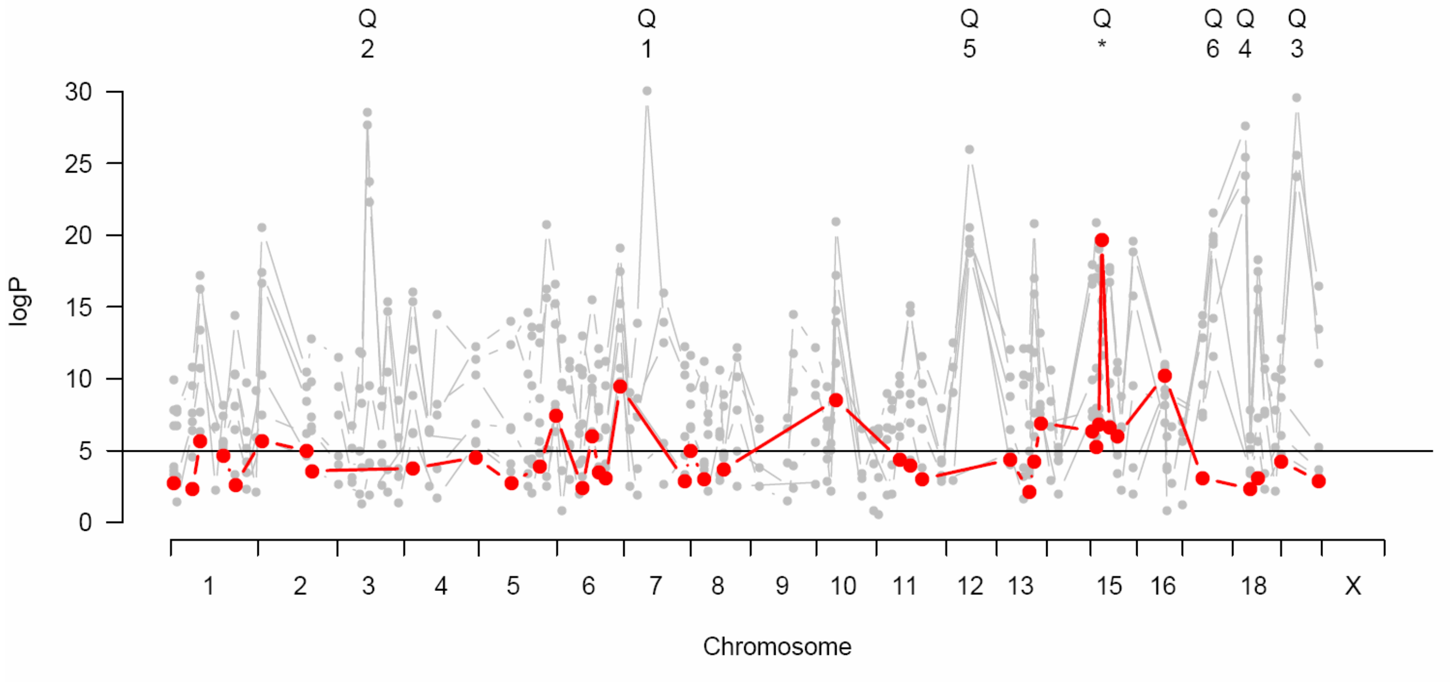
phenotype ~ covariates + peak 1 + peak 2 + peak 3 + peak 4 + ?

# 1D scan: condition on 5 peaks



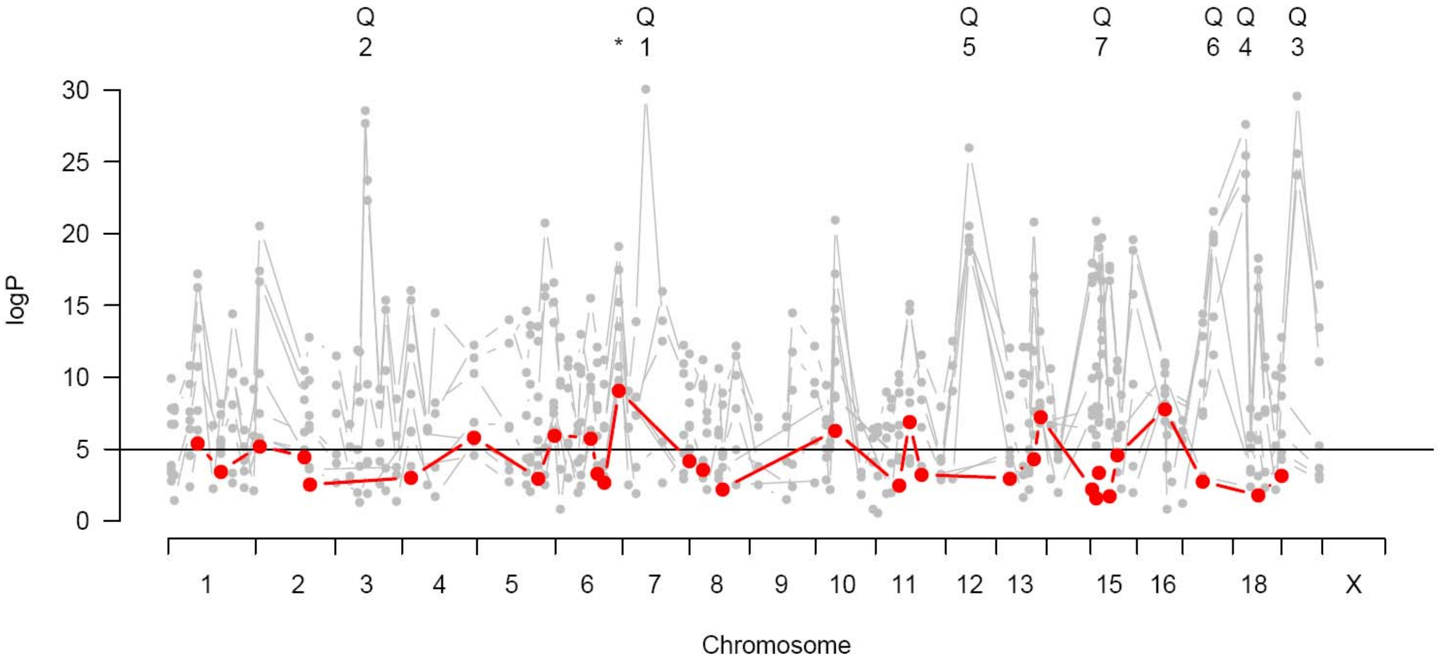
phenotype ~ covariates + peak 1 + peak 2 + peak 3 + peak 4 + peak 5 + ?

# 1D scan: condition on 6 peaks



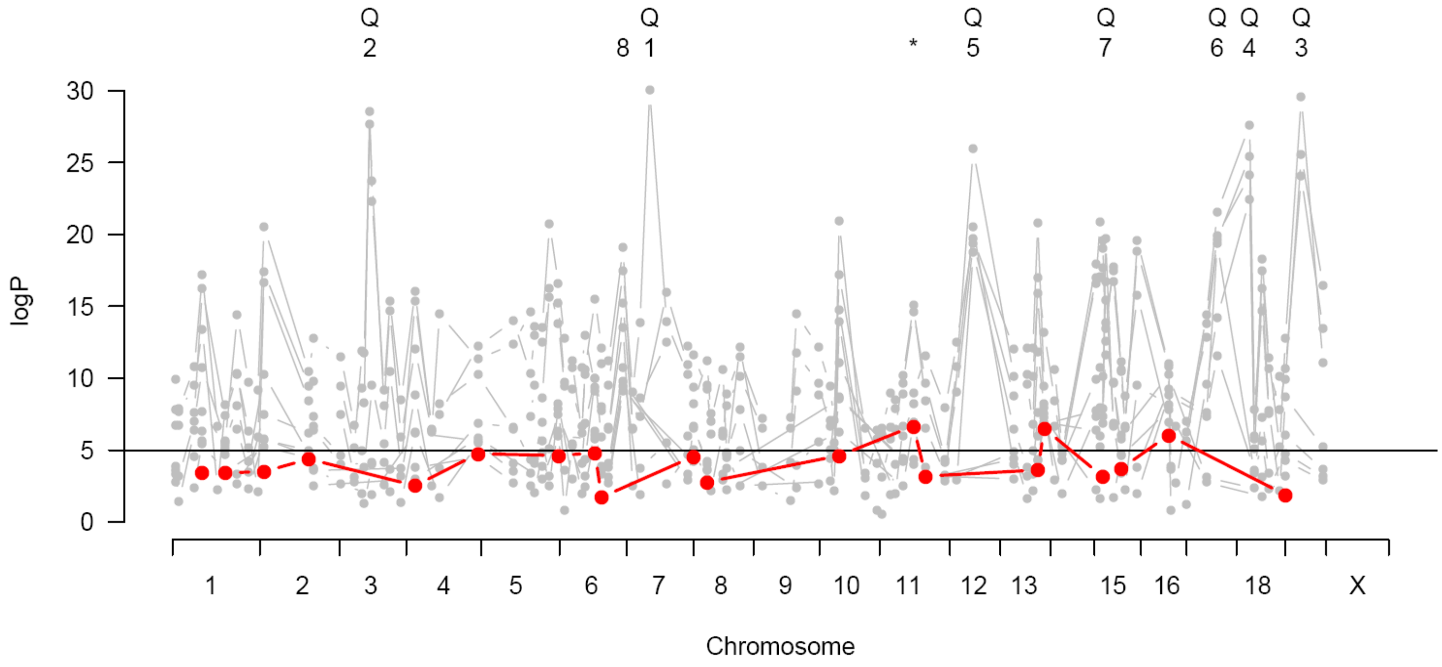
phenotype ~ covariates + peak 1 + peak 2 + peak 3 +
peak 4 + peak 5 + peak 6 + ?

# 1D scan: condition on 7 peaks



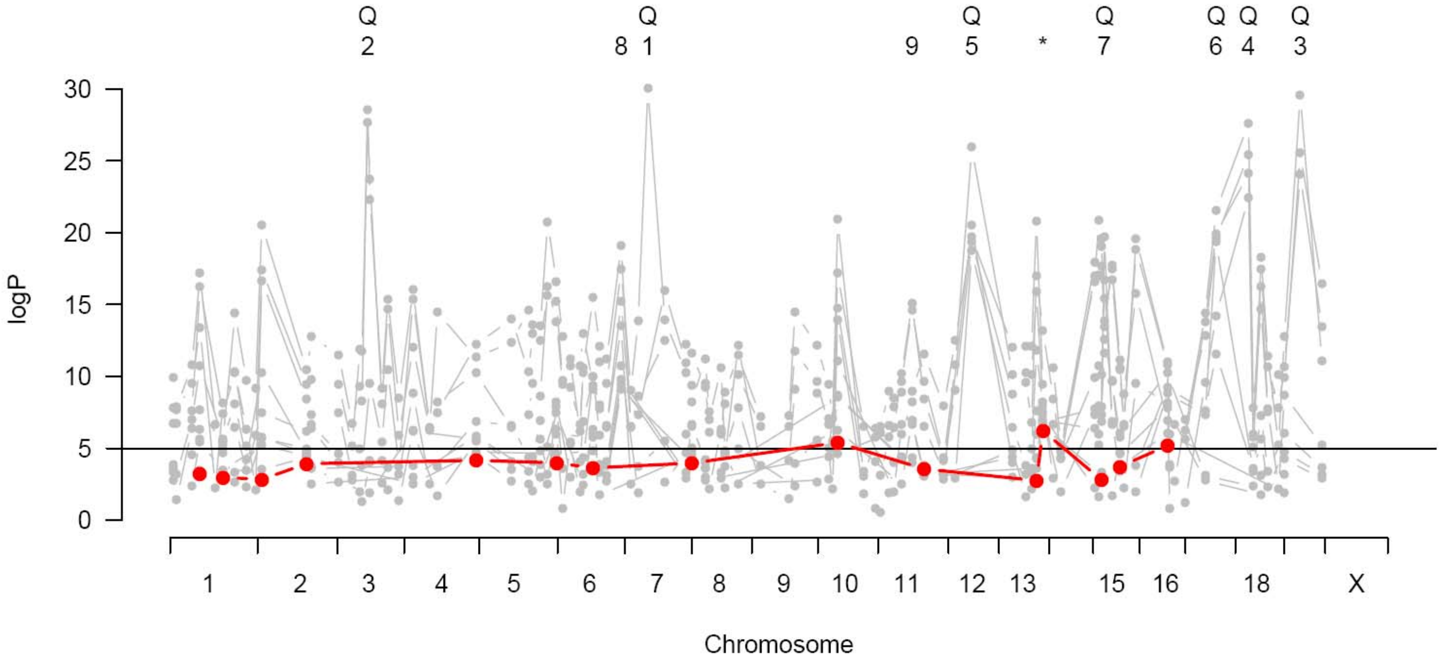
phenotype ~ covariates + peak 1 + peak 2 + peak 3 + peak 4 + peak 5 + peak 6 + peak 7 + ?

# 1D scan: condition on 8 peaks



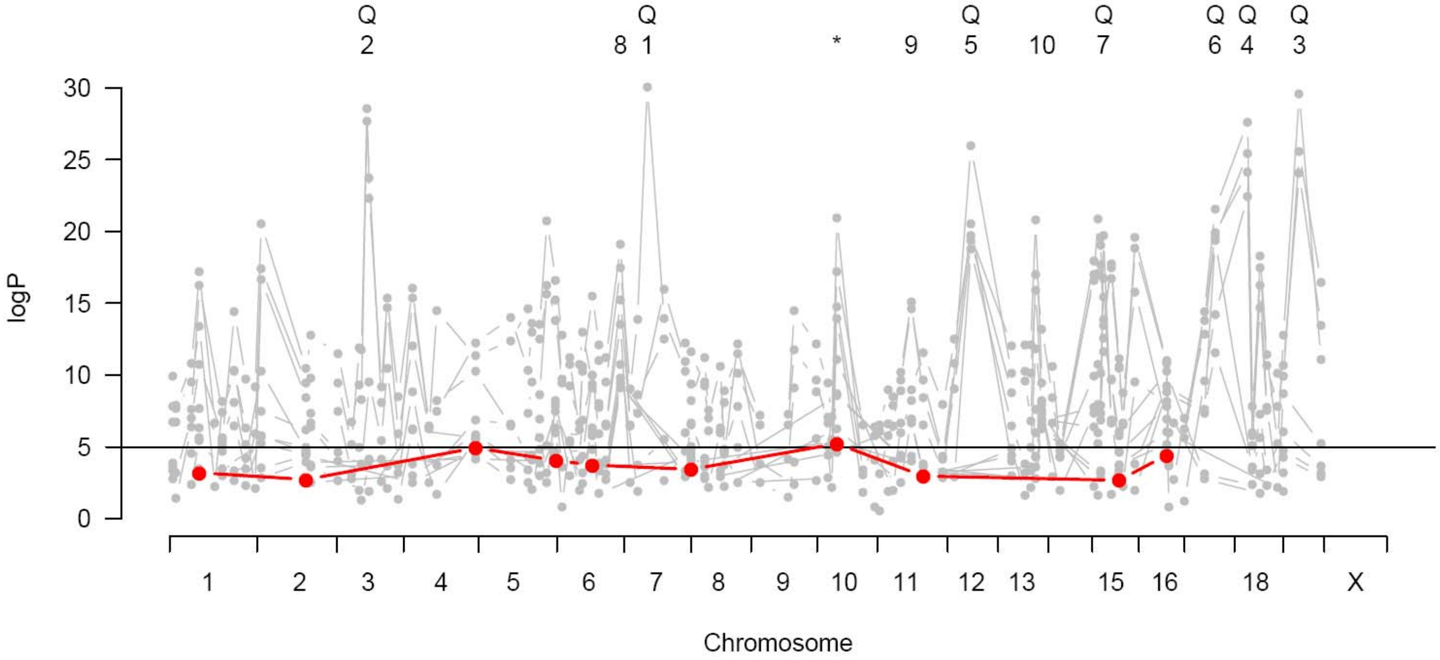
phenotype ~ covariates + peak 1 + peak 2 + peak 3 + peak 4 + peak 5 + peak 6 + peak 7 + peak 8 + ?

# 1D scan: condition on 9 peaks



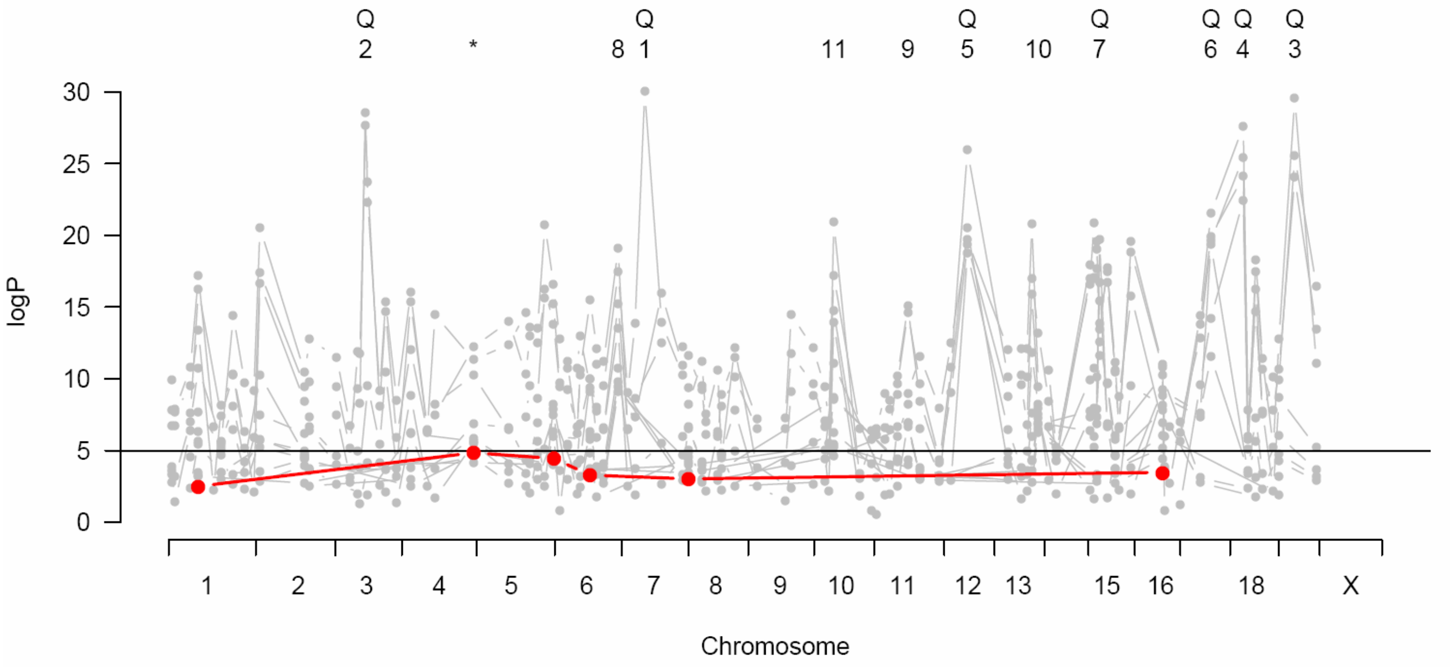
phenotype ~ covariates + peak 1 + peak 2 + peak 3 + peak 4 + peak 5 + peak 6 + peak 7 + peak 8 + peak 9 + ?

# 1D scan: condition on 10 peaks



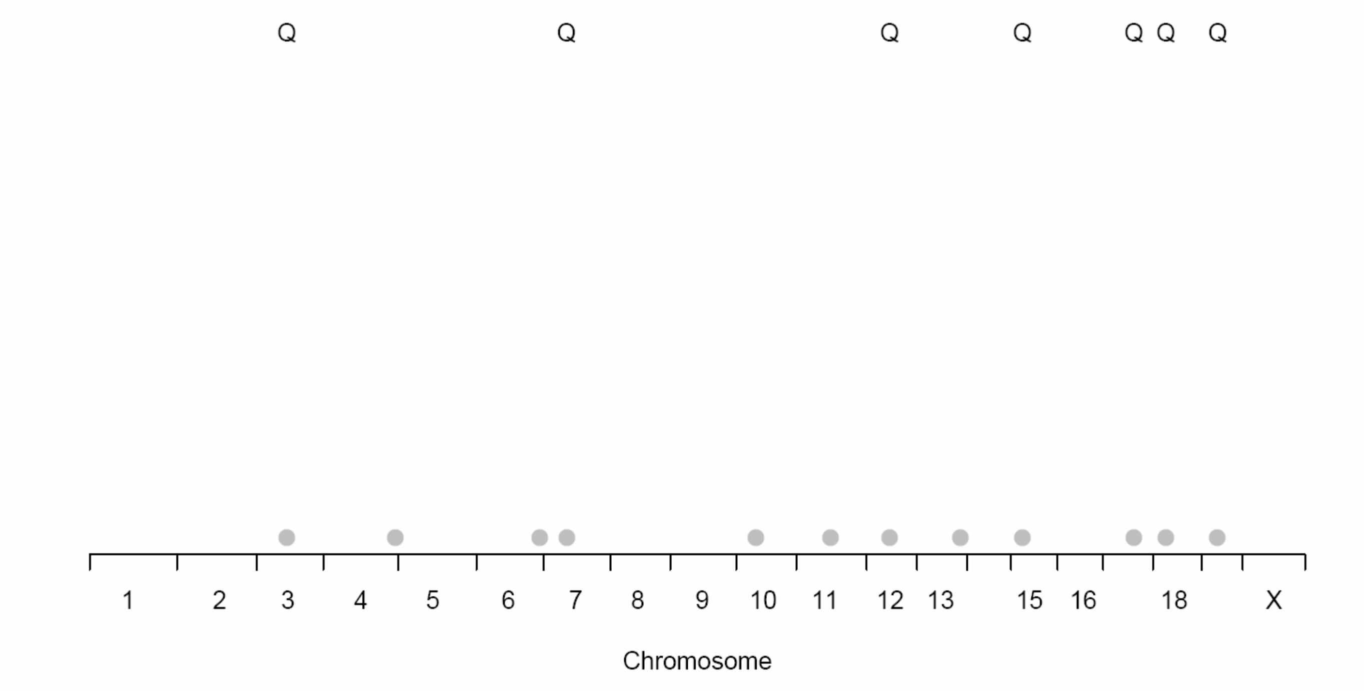
phenotype ~ covariates + peak 1 + peak 2 + peak 3 + peak 4 + peak 5 + peak 6 + peak 7 + peak 8 + peak 9 + peak 10 + ?

# 1D scan: condition on 11 peaks



phenotype ~ covariates + peak 1 + peak 2 + peak 3 + peak 4 + peak 5 + peak 6 + peak 7 + peak 8 + peak 9 + peak 10 + peak 11 + ?

# Peaks chosen by forward selection

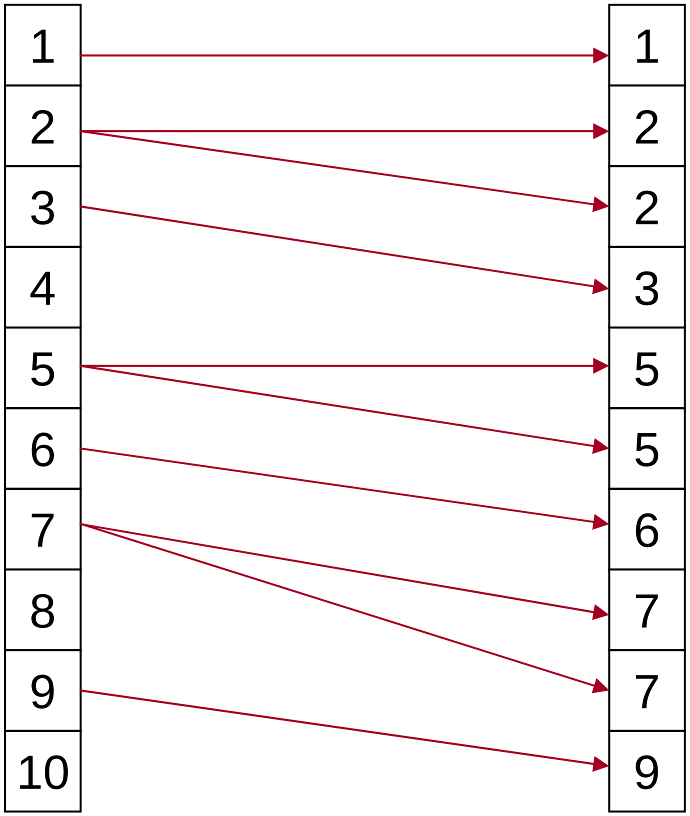


# Bootstrap sampling

10 subjects

1
2
3
4
5
6
7
8
9
10

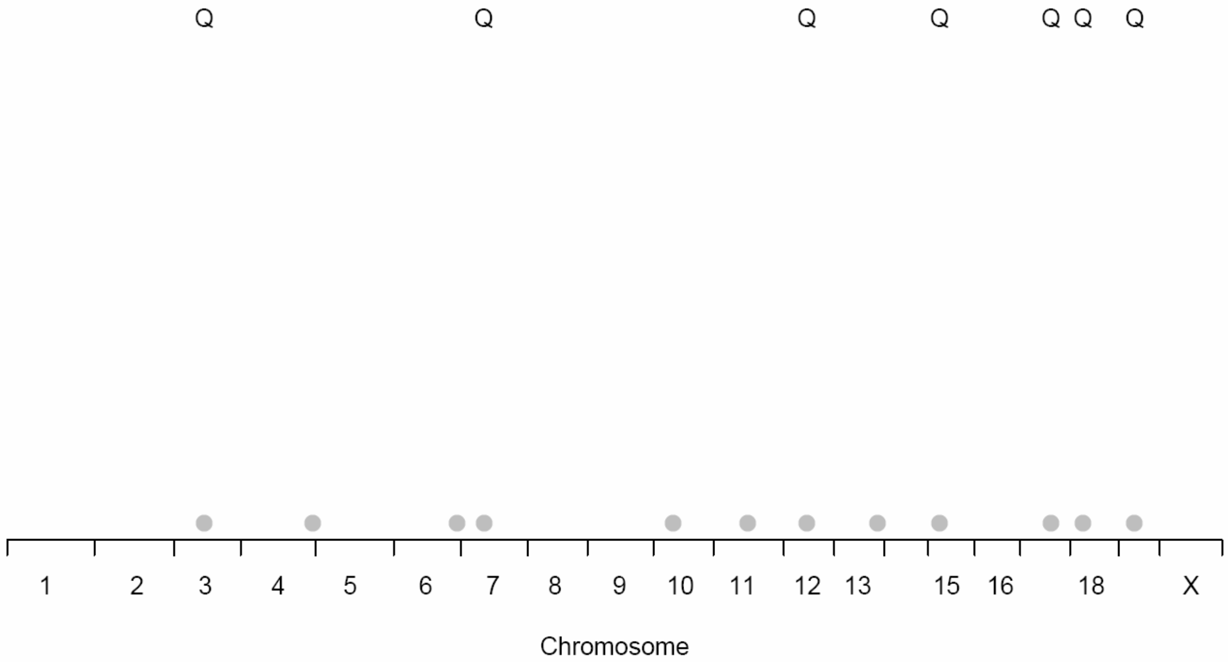
# Bootstrap sampling



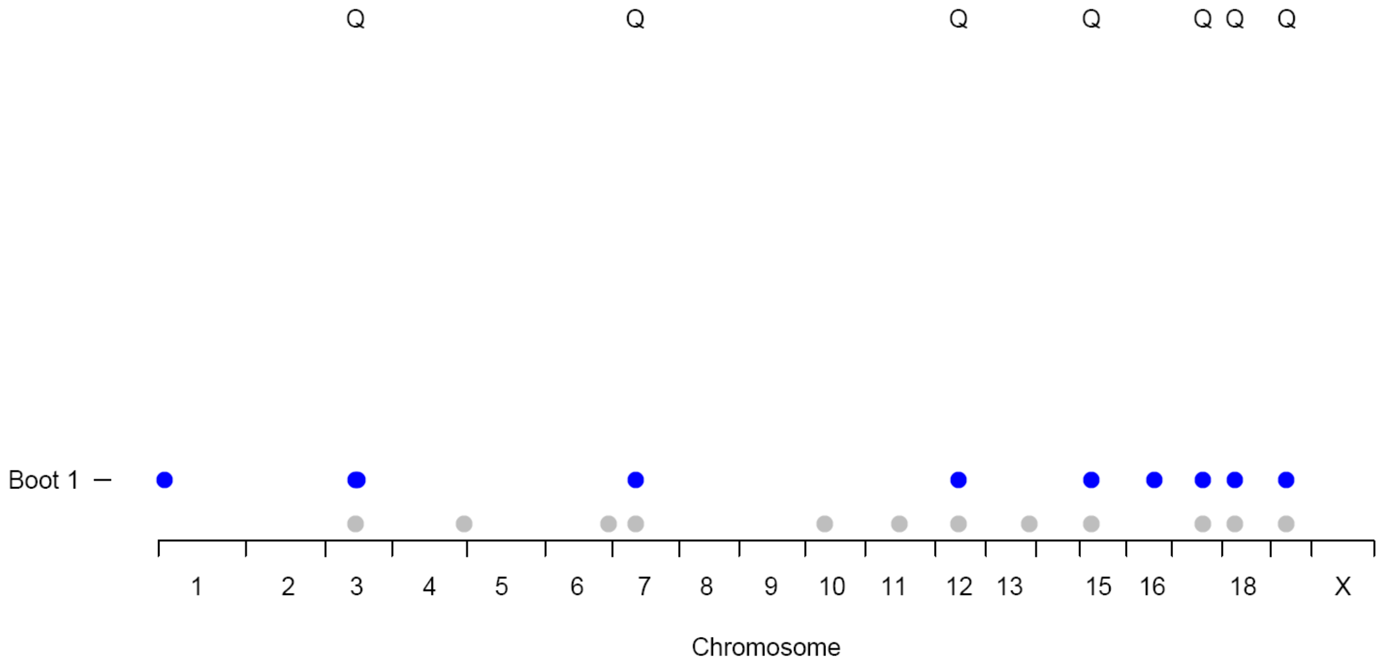
sample with
replacement

10 subjects

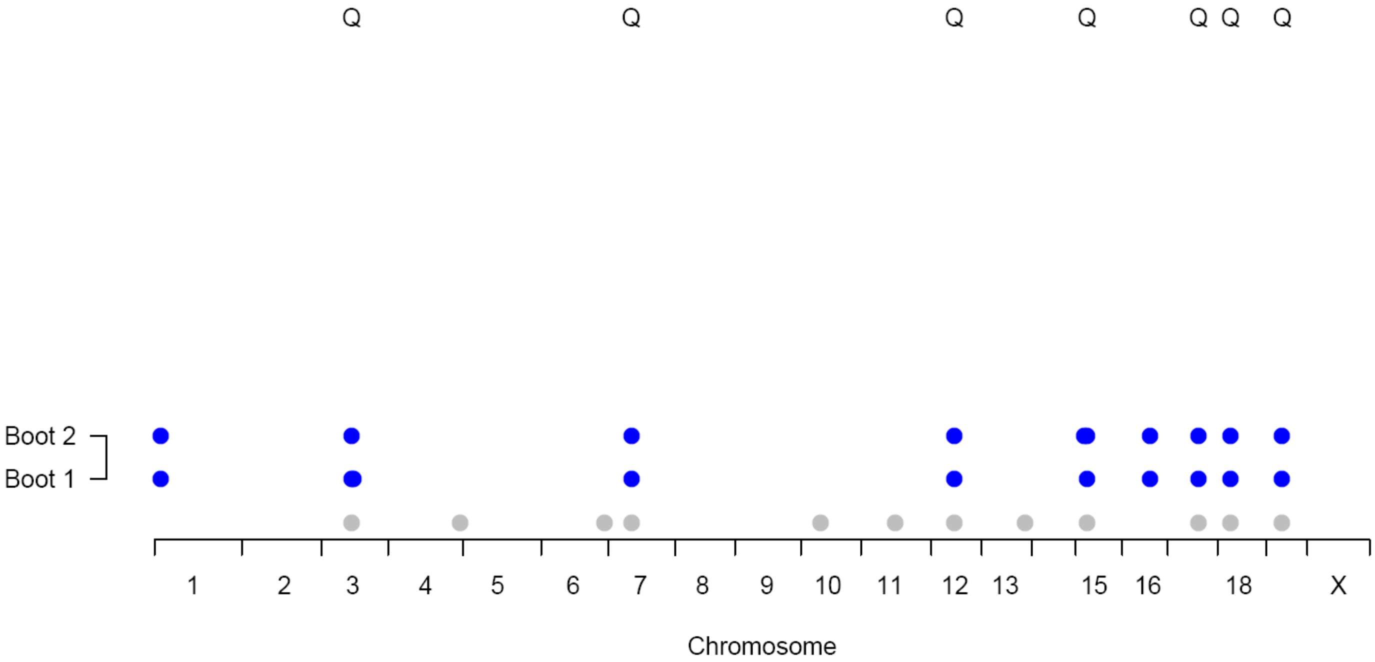
bootstrap sample
from
10 subjects


Q
Q
Q
Q
Q
Q
Q
1
2
3
4
5
6
7
8
9
10
11
12
13
15
16
18
X
Chromosome

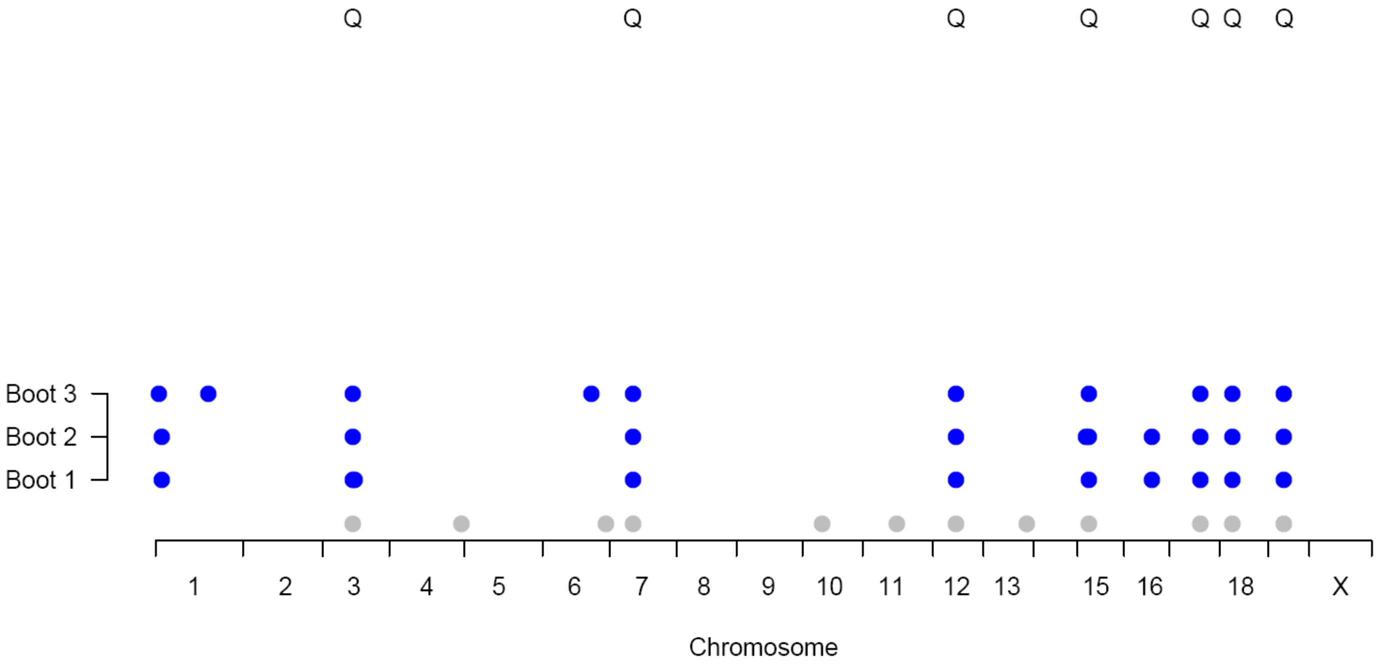
# Forward selection on a bootstrap sample



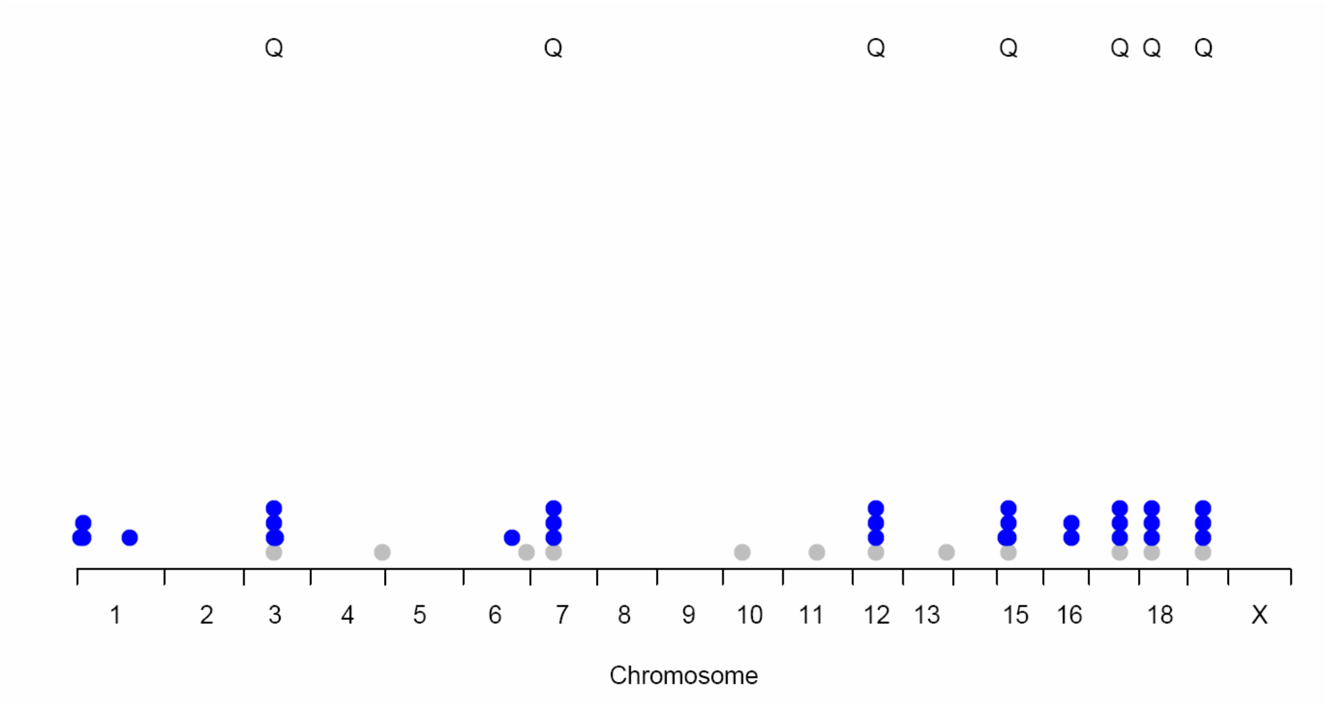
# Forward selection on a bootstrap sample



# Forward selection on a bootstrap sample

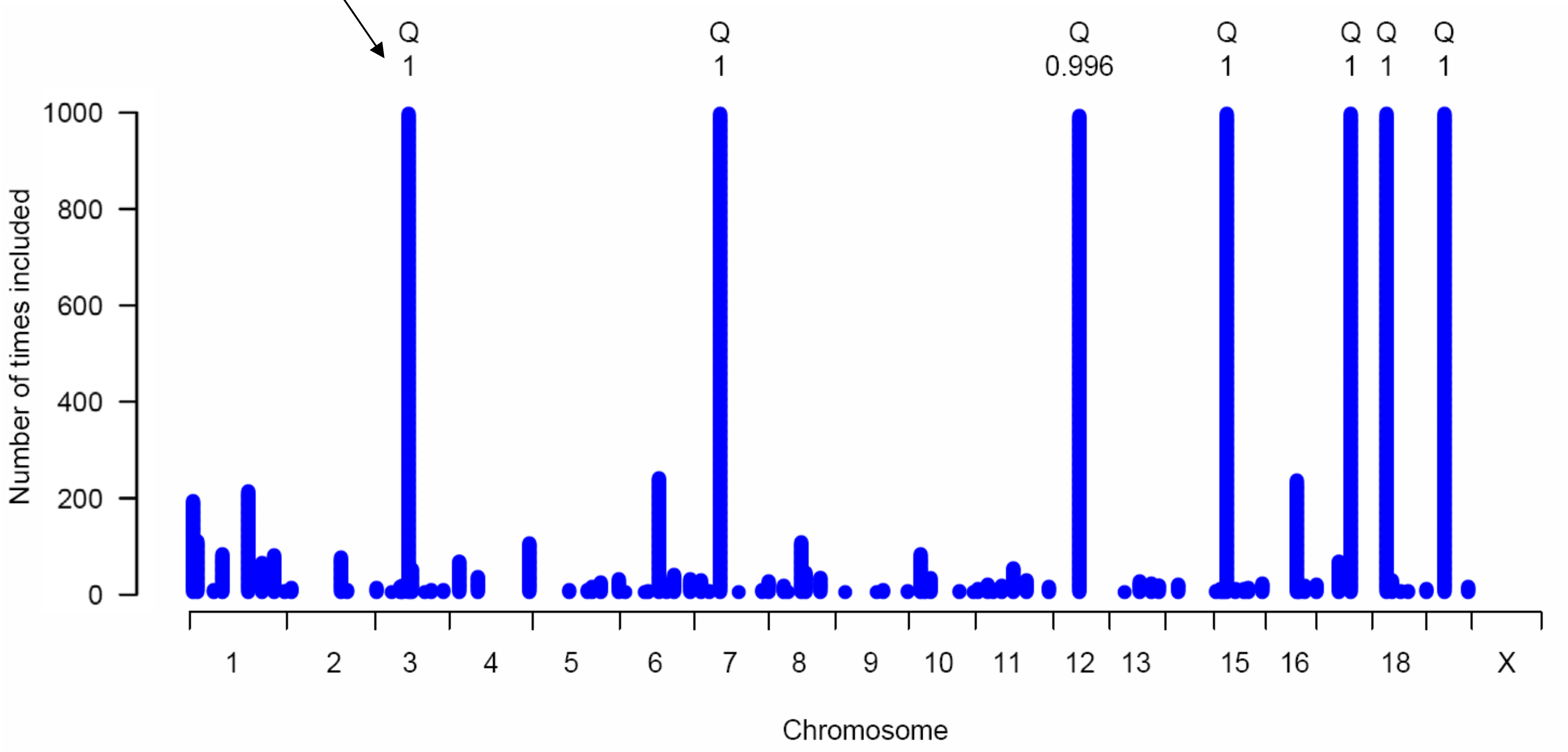


# Bootstrap evidence mounts up…

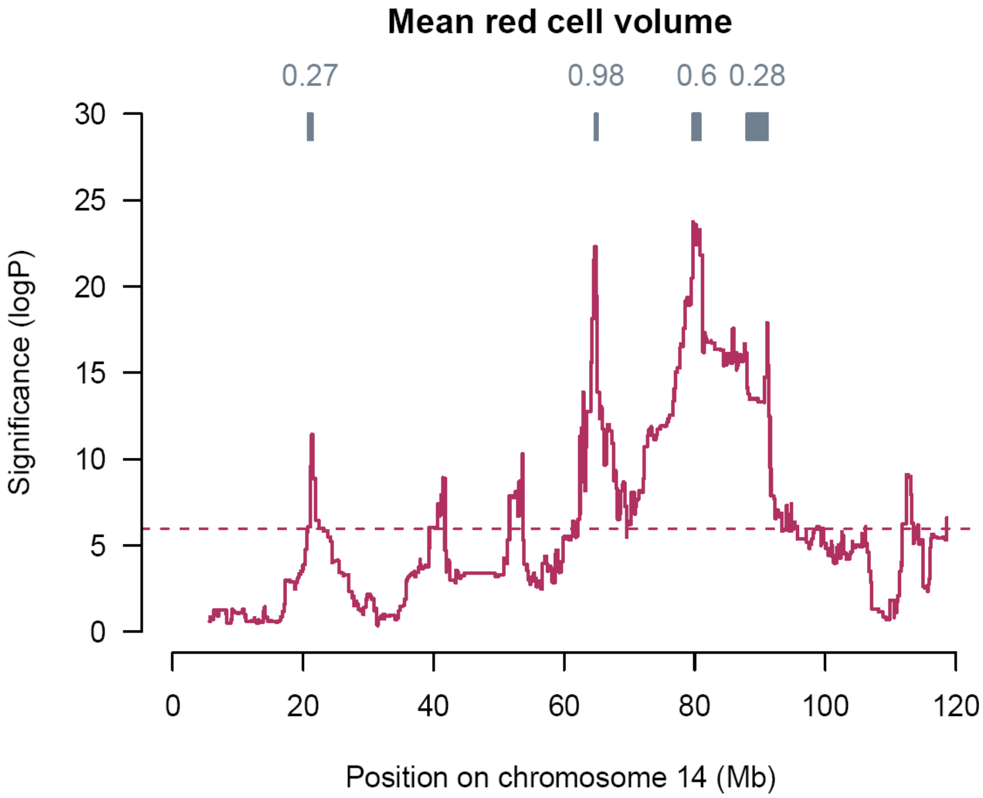


# In 1000 bootstraps…

Bootstrap Posterior Probability
(BPP)



# Results


Mean red cell volume
0.27
0.98
0.6
0.28
Significance (logP)
30
25
20
15
10
5
0
0
20
40
60
80
100
120
Position on chromosome 14 (Mb)

# Tea Break

# Study design

2,000 mice

15,000 diallelic markers

More than 100 phenotypes

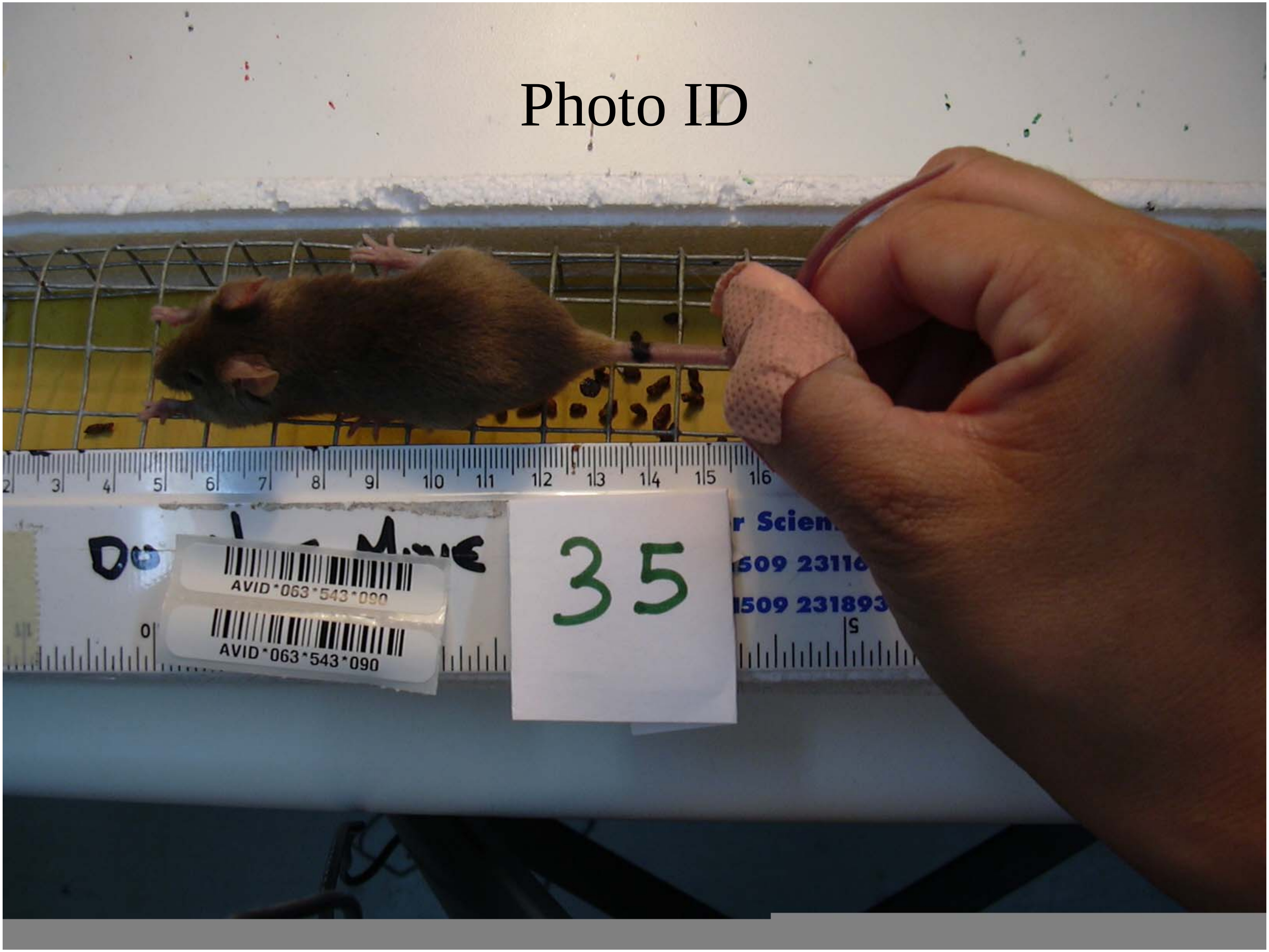
each mouse subject to a battery of tests spread over weeks 5-9 of the animal's life

# 101 Phenotypes

Anxiety (conditioned and unconditioned tasks) [24]
Asthma (plethysmography) [13]
Biochemistry [15]
Diabetes (glucose tolerance test) [16]
Haematology [15]
Immunology [9]
Weight/size related [8]
Wound Healing [1]

# High throughput phenotyping facility

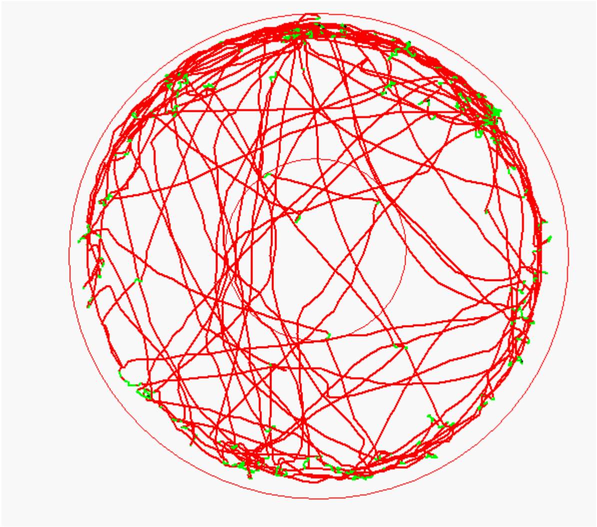
# Photo ID


AVID*063*543*090
AVID*063*543*090
35
r Scien
509 2311
509 231893

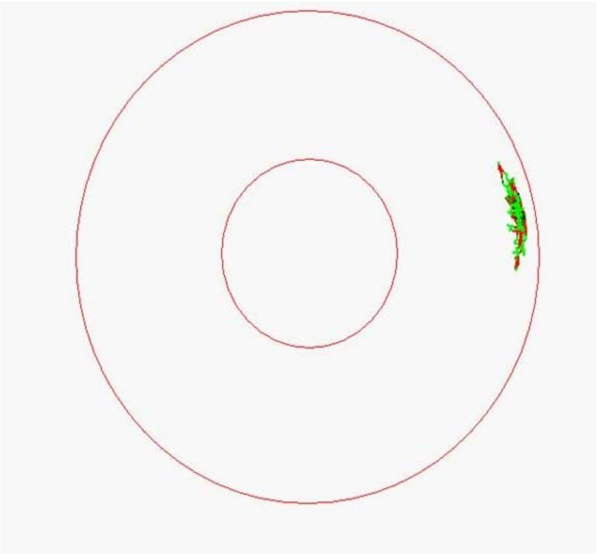
# Open Field

# Open Field

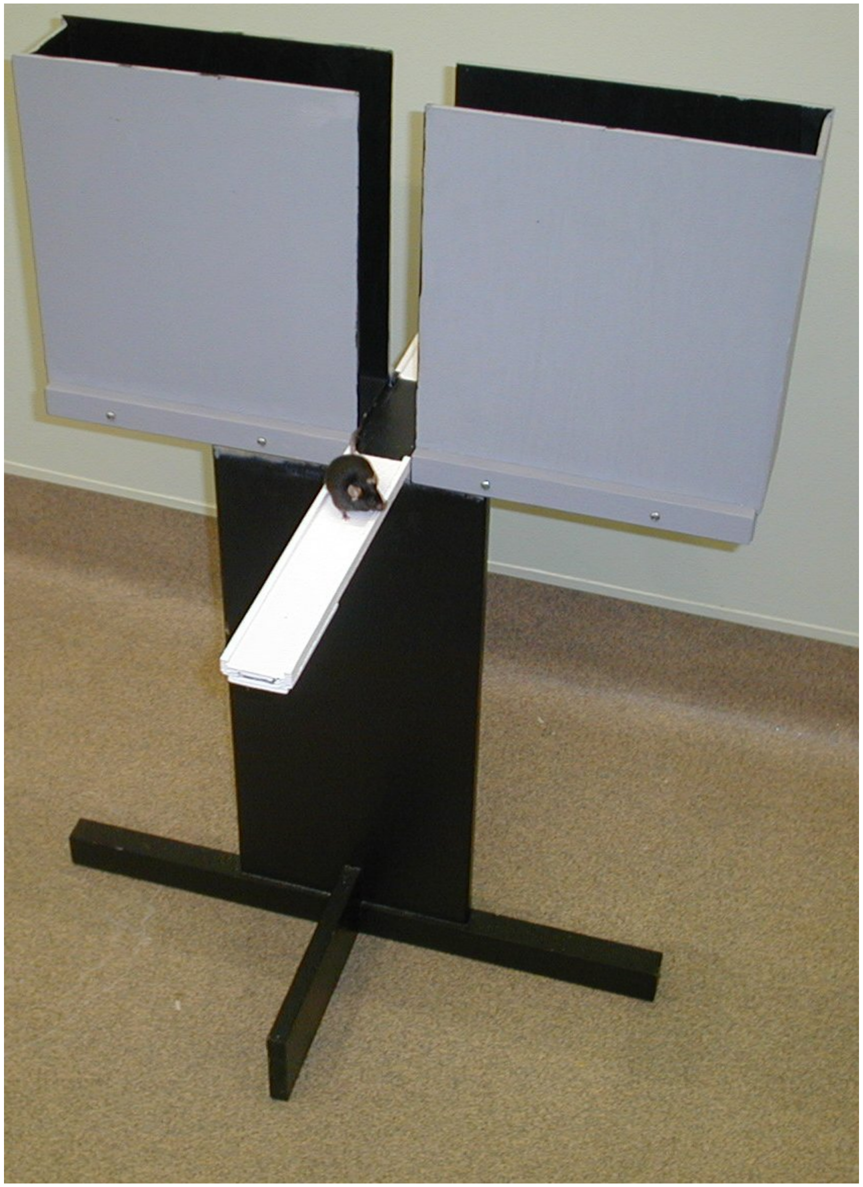
Non anxious mouse

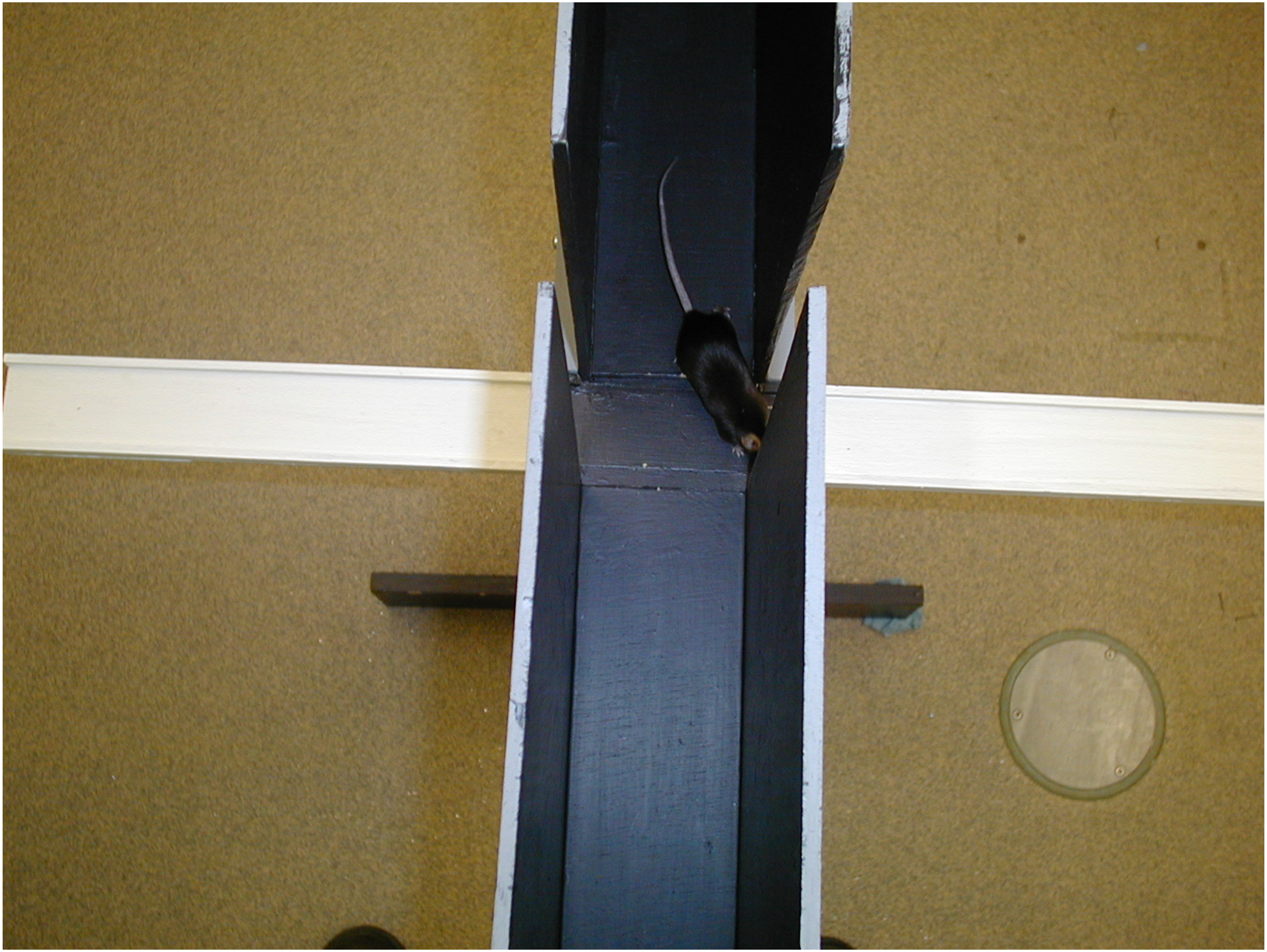


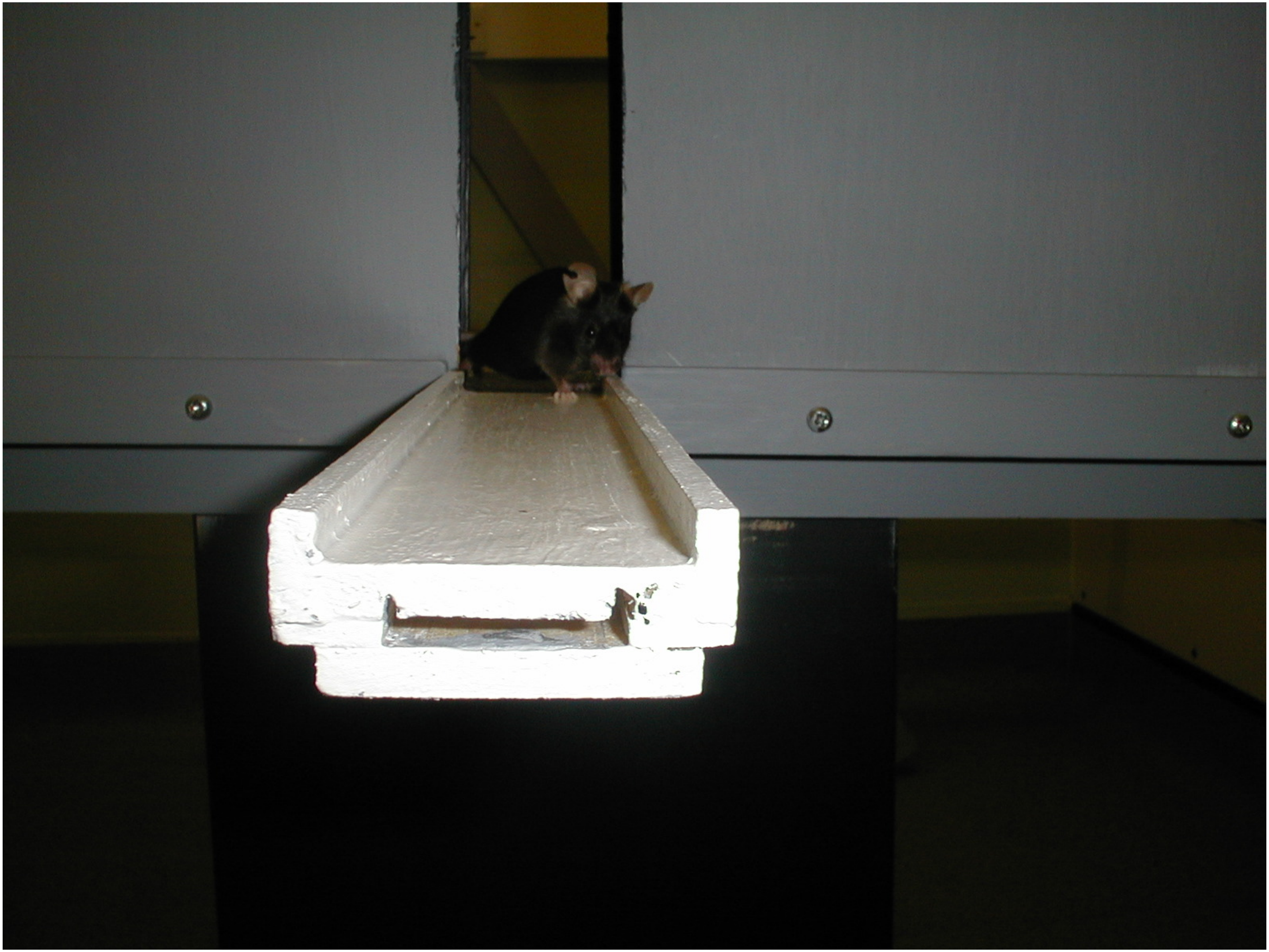
Anxious mouse

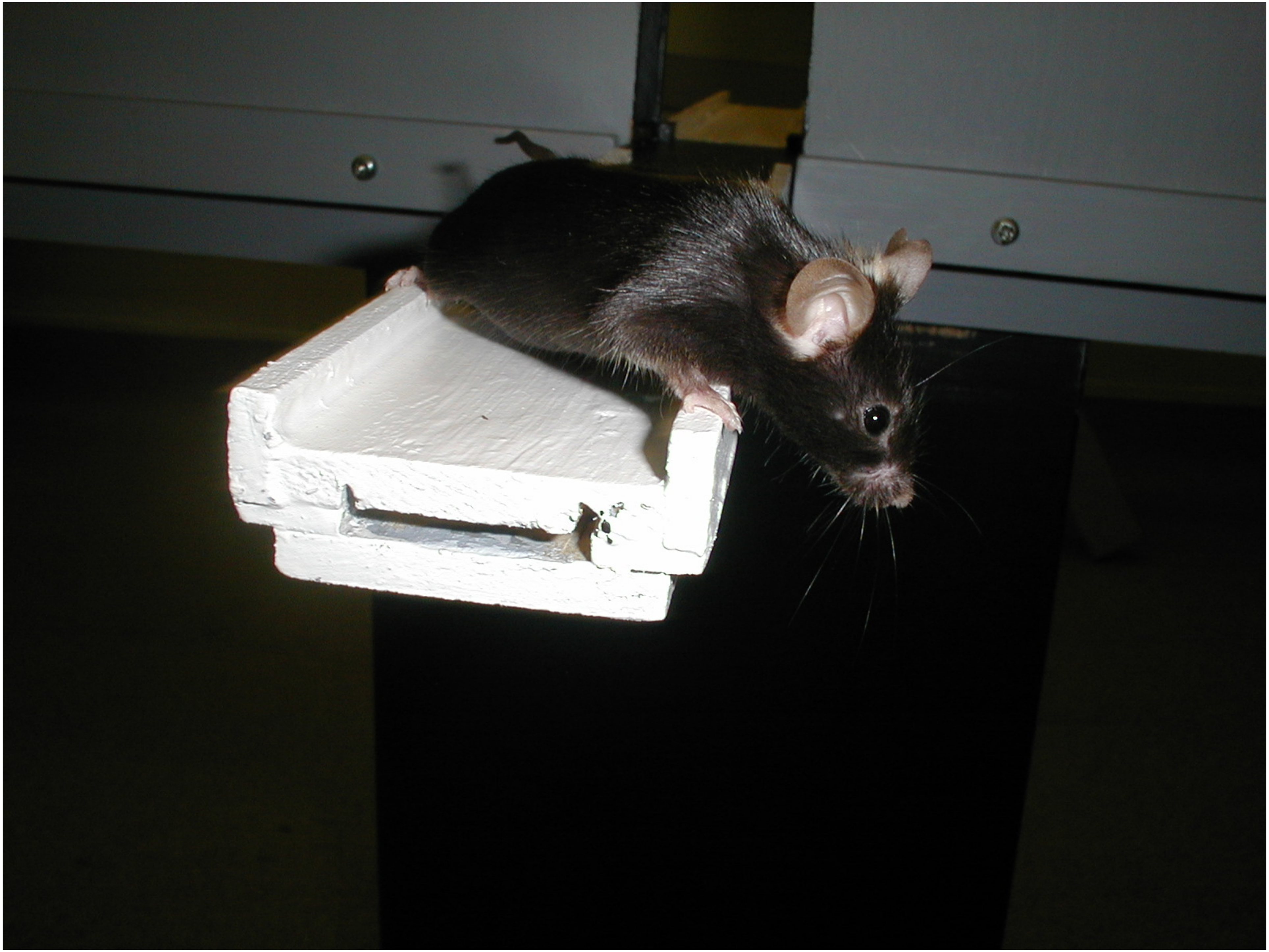


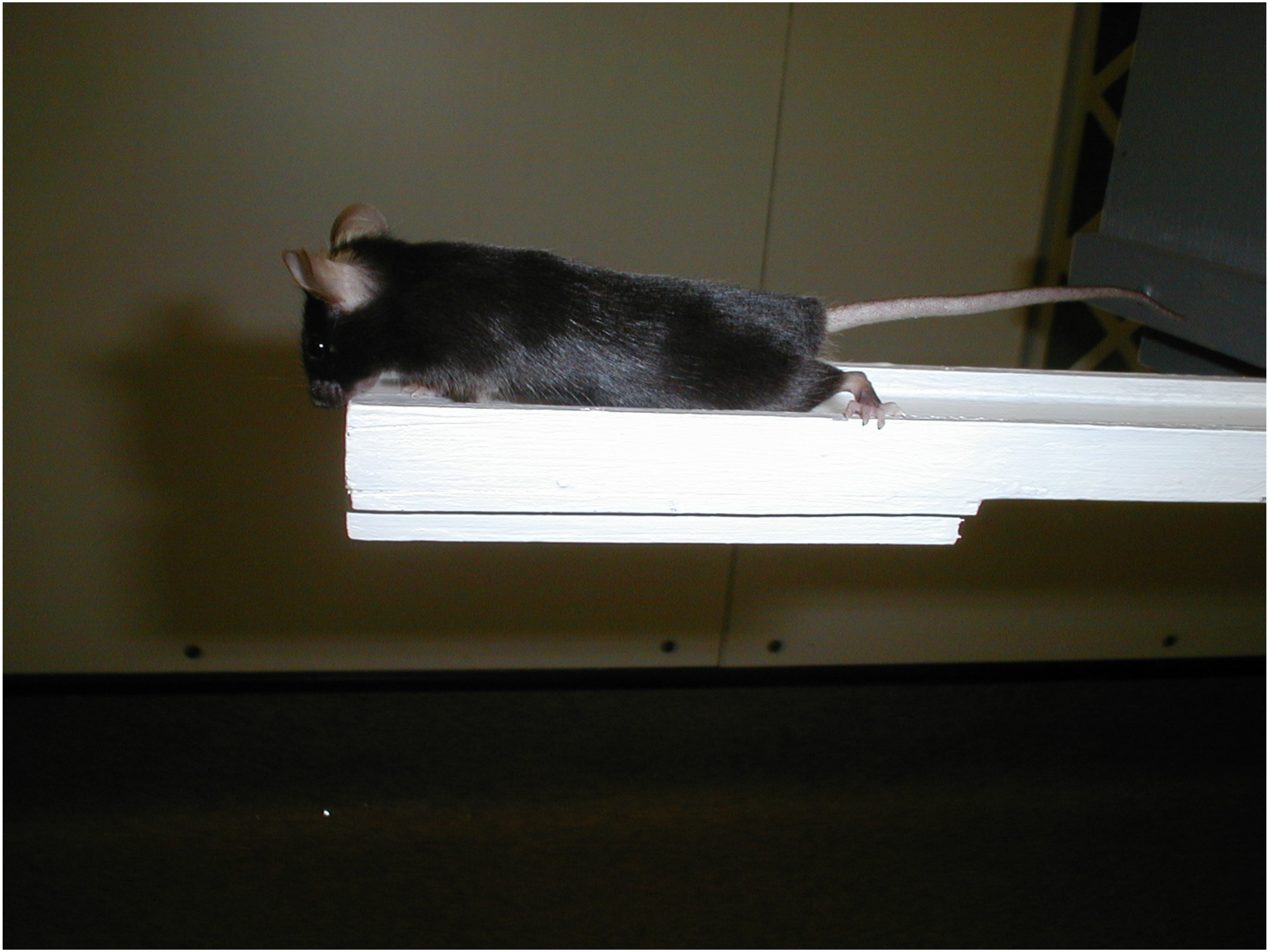
# Elevated Plus Maze (anxiety)





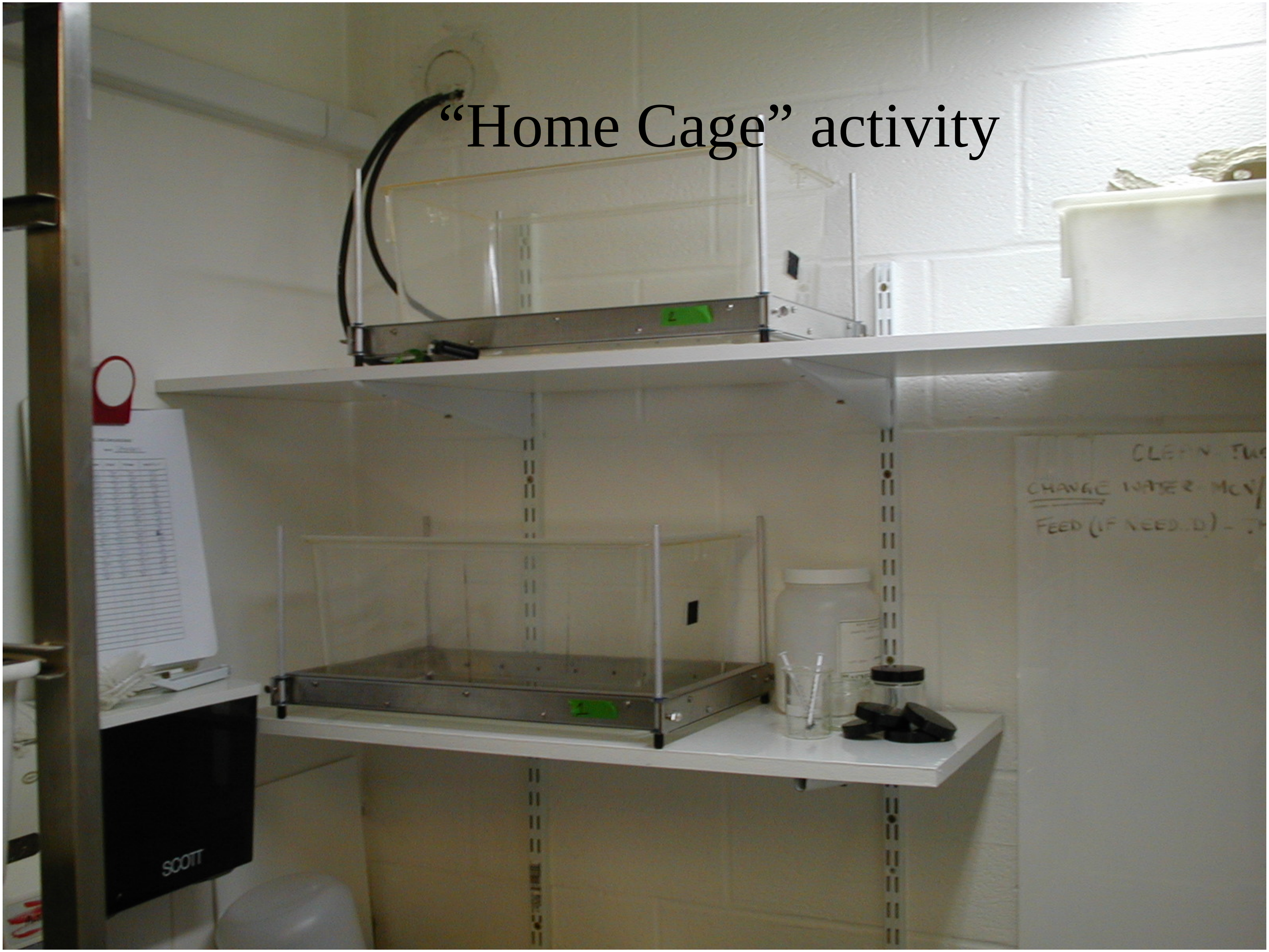




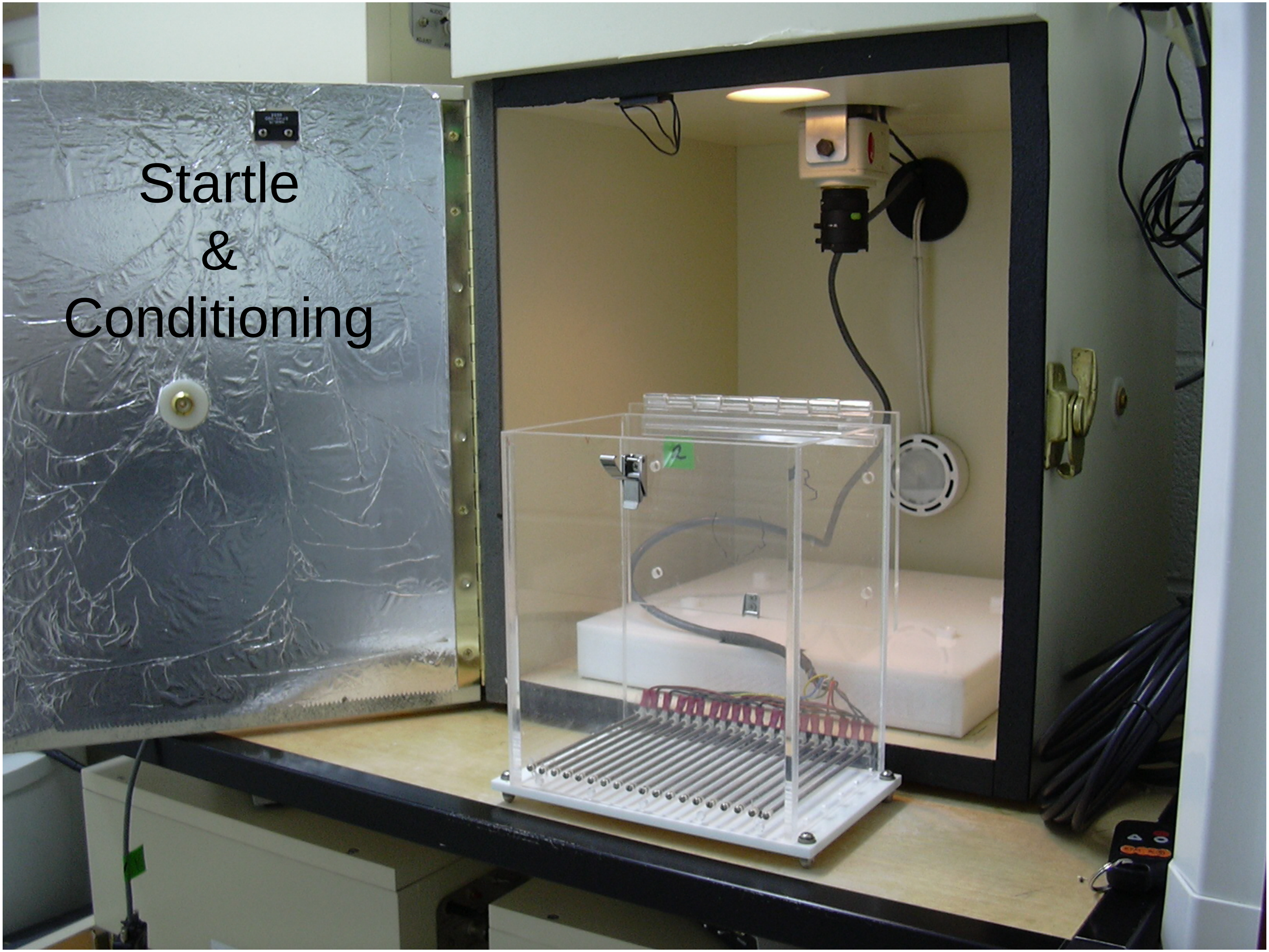


Food hyponeophagia
(reluctance to try new food)

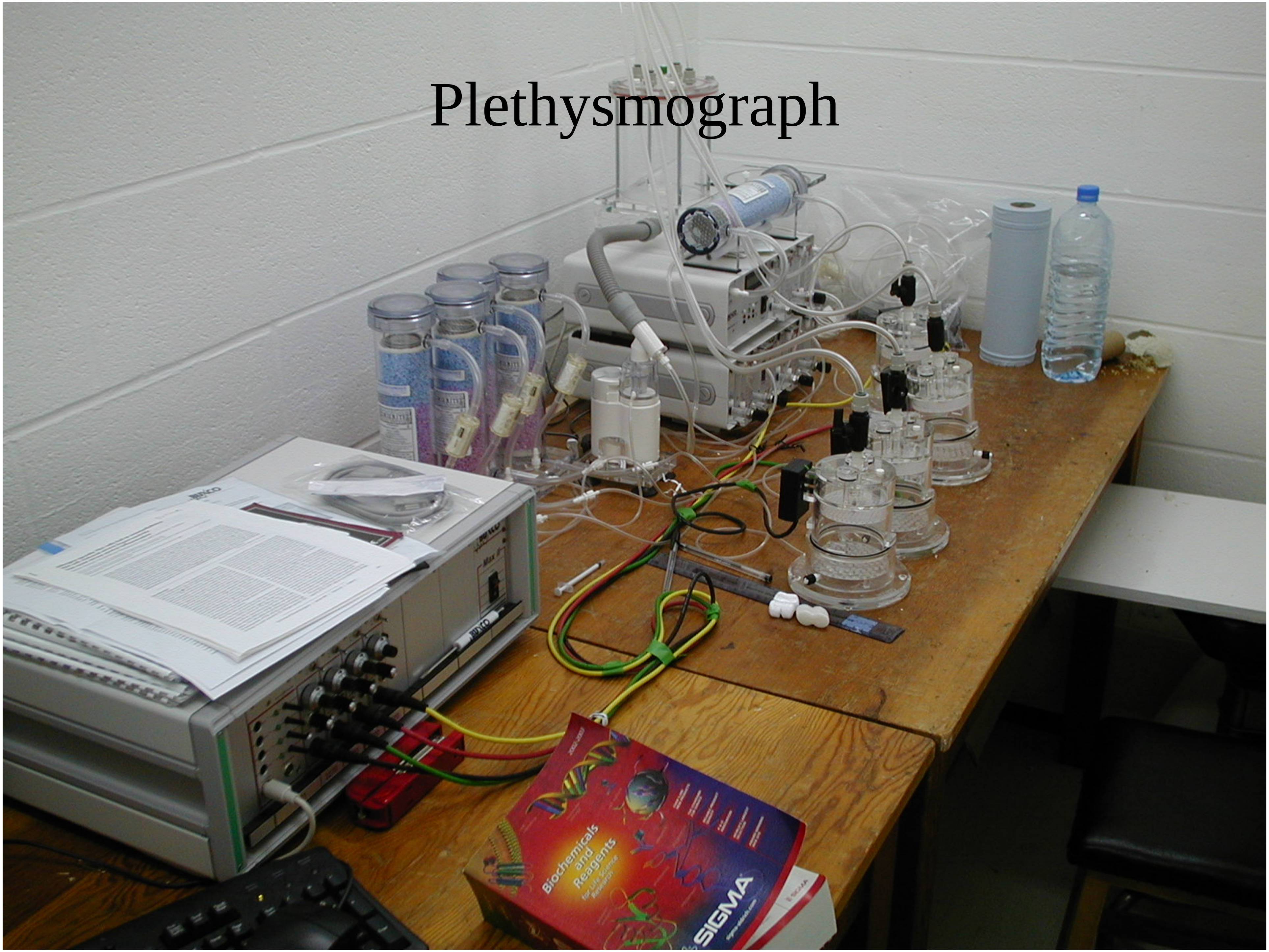
# “Home Cage” activity

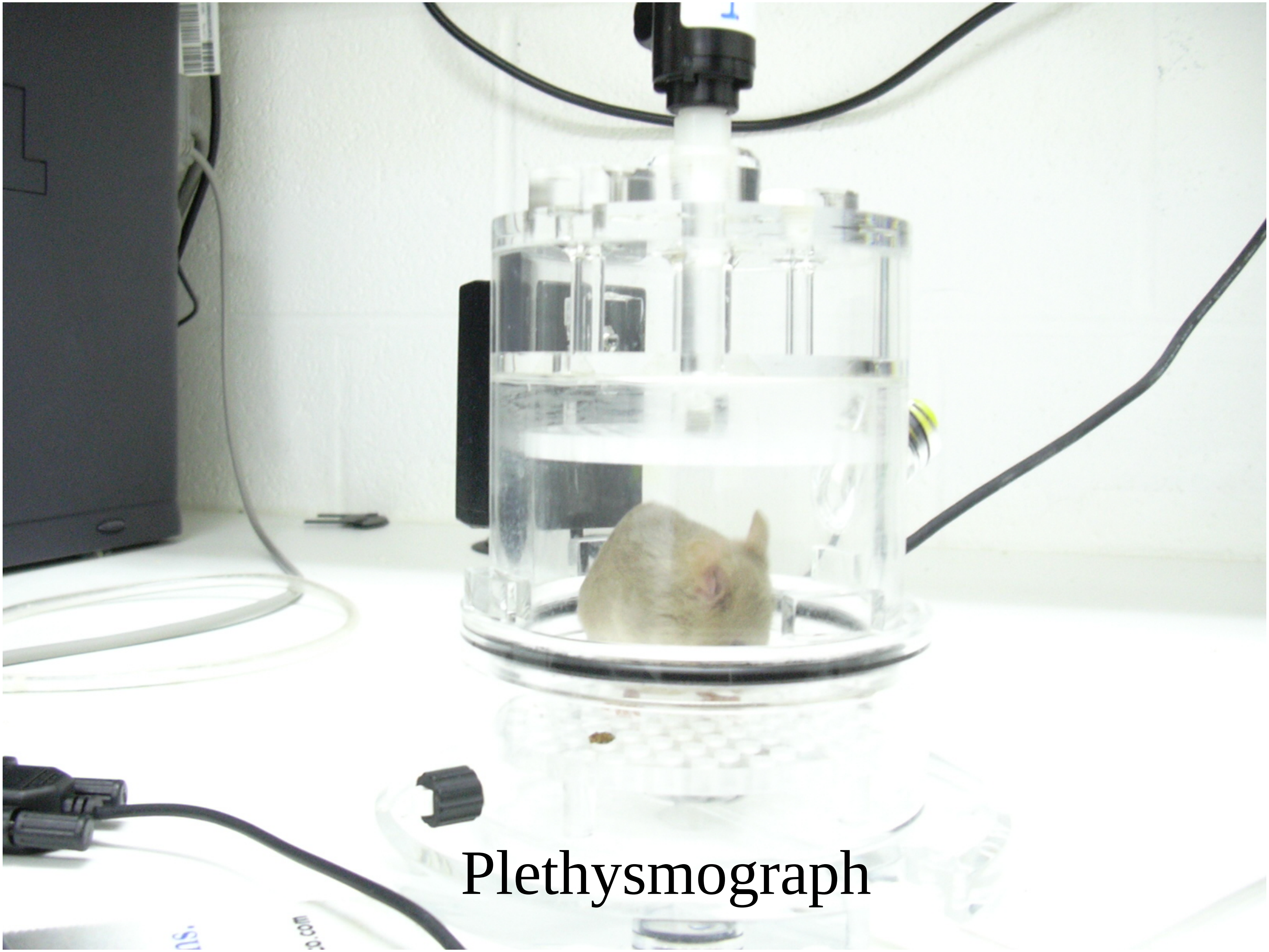


# Startle
# &
# Conditioning



# Plethysmograph

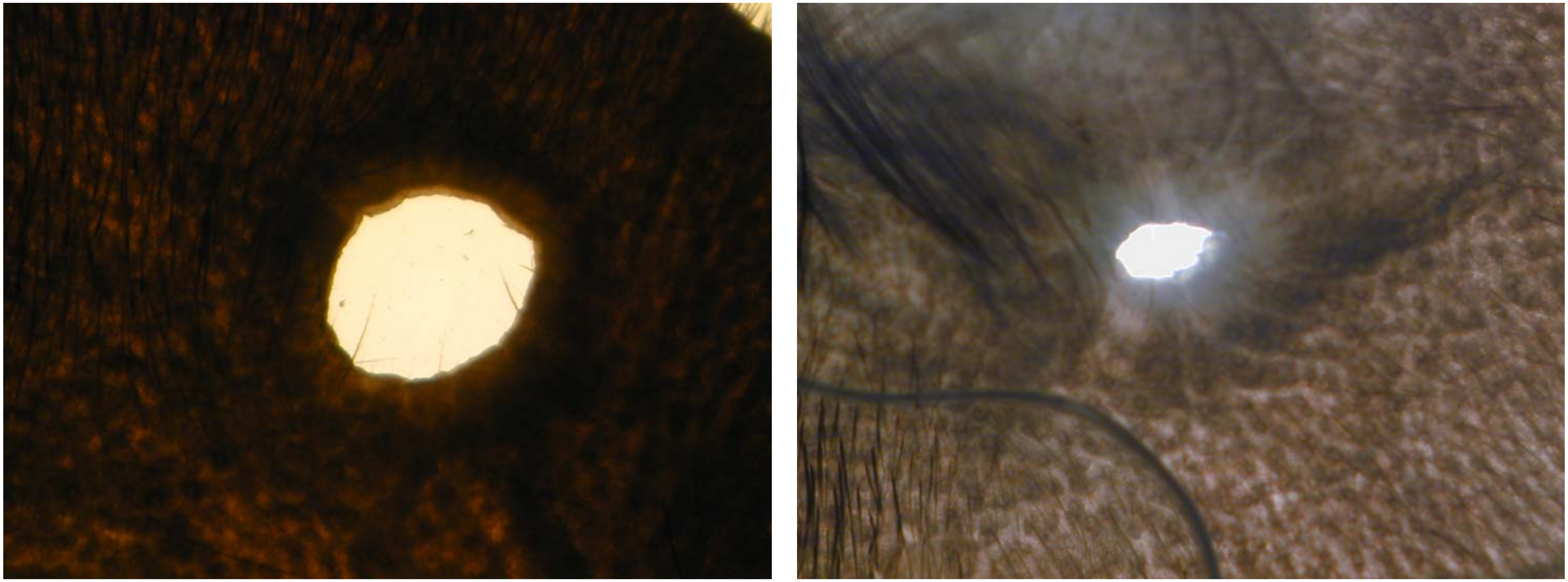




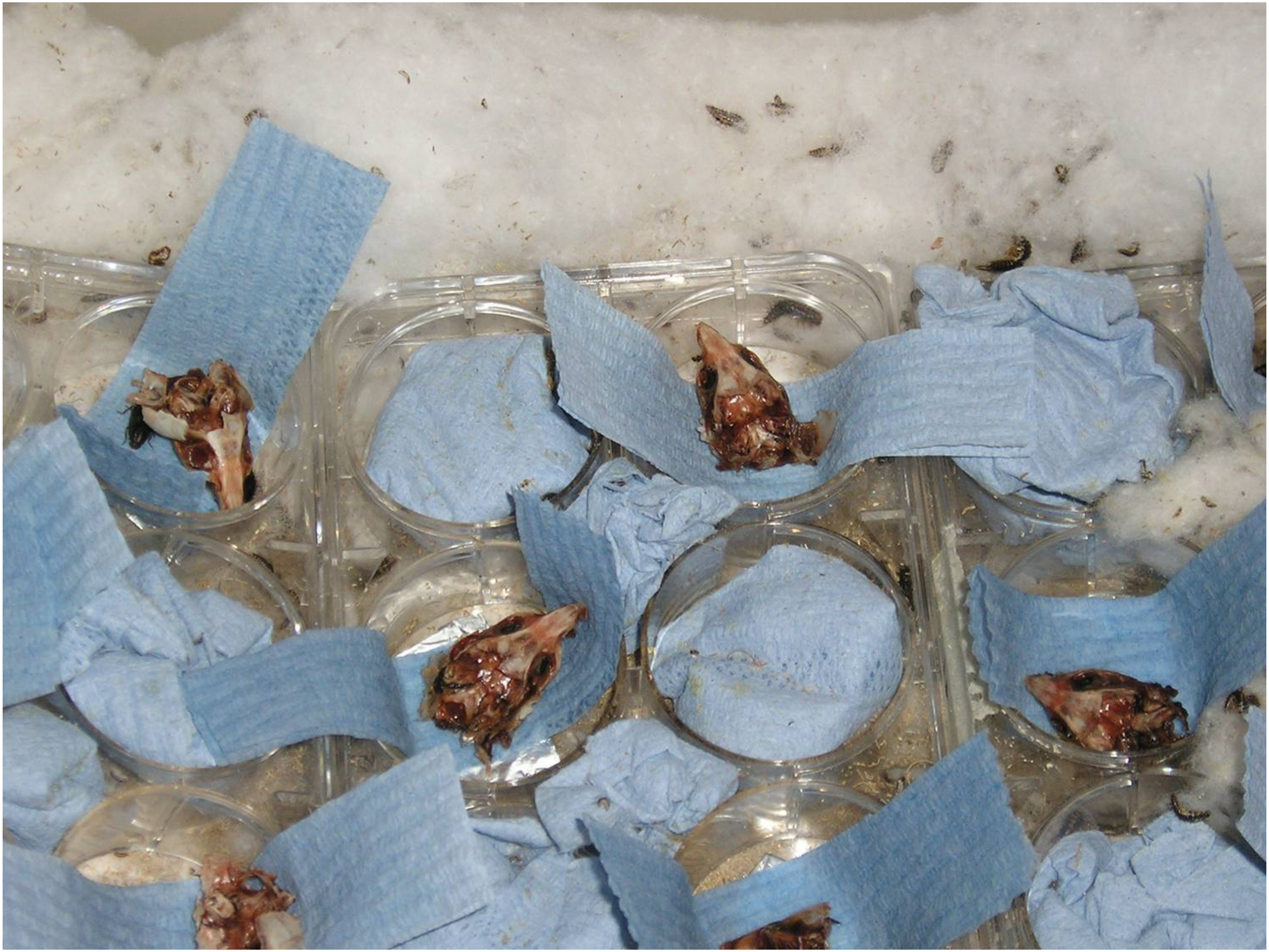
Plethysmograph

Glucose Tolerance Test (diabetes)

# Wound healing




TUNING
PLAY/PAUSE
STOP

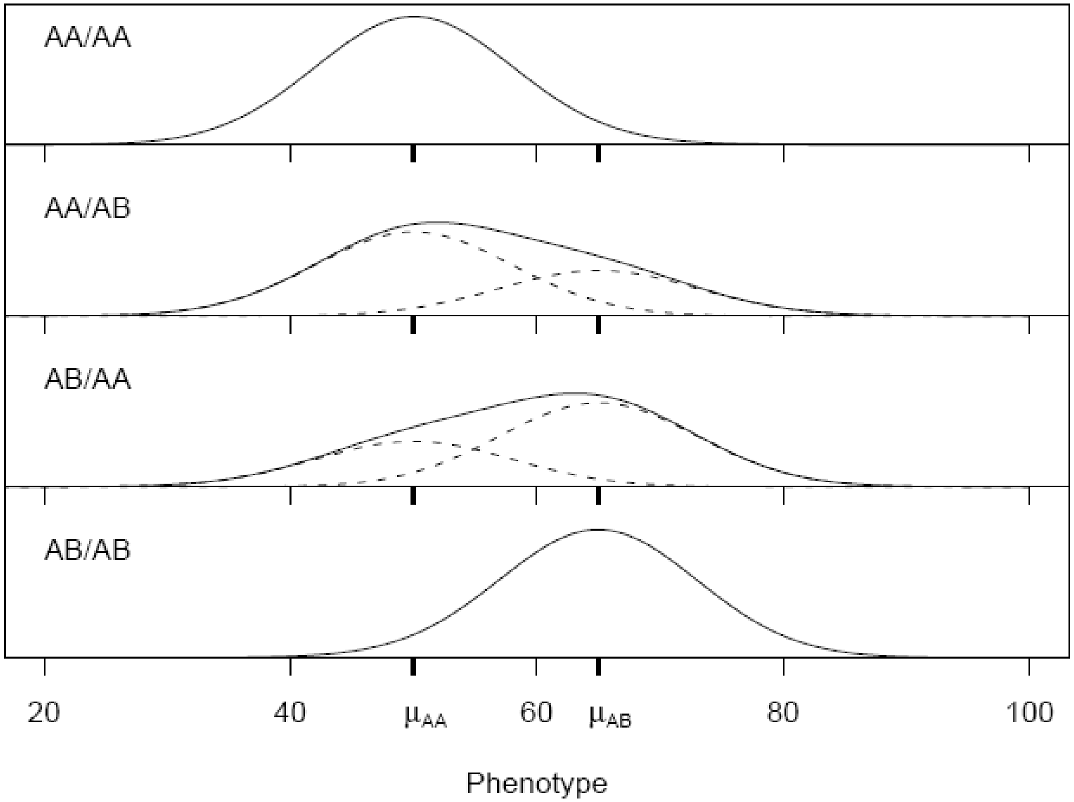


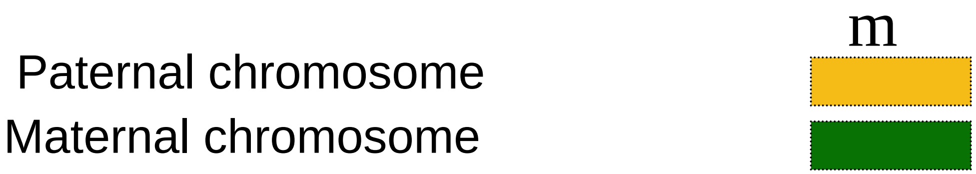

5
2

**PRACTICAL: http://gscan.well.ox.ac.uk**

END

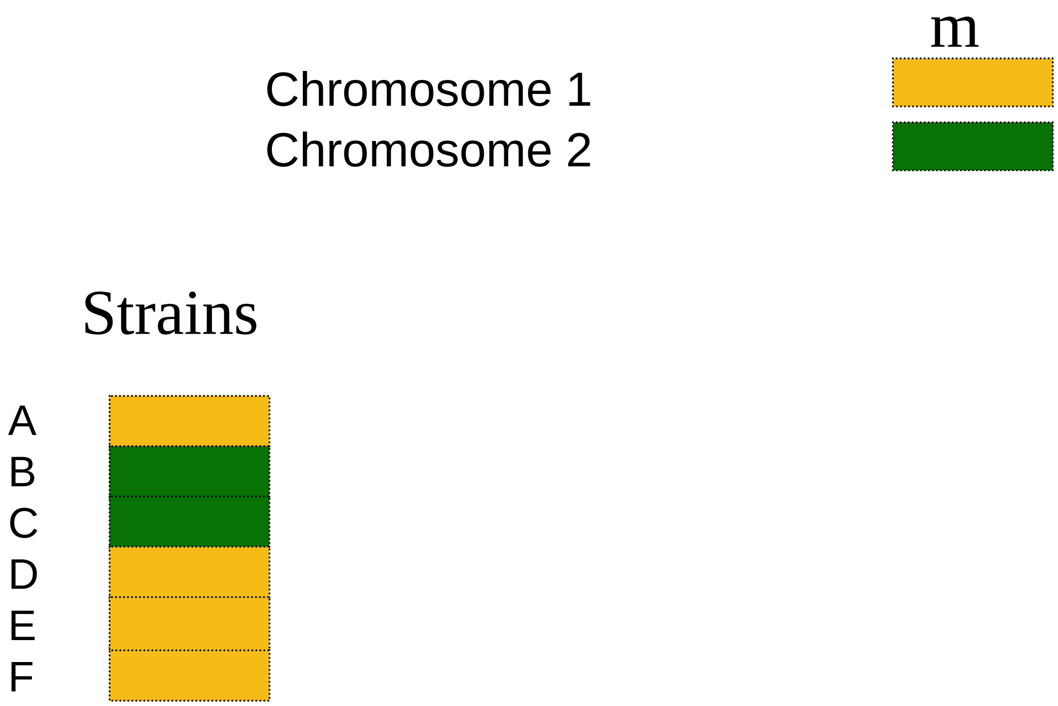
# An individual’s phenotype follows a mixture of normal distributions





Paternal chromosome

Maternal chromosome



m

Chromosome 1 🟨

Chromosome 2 🟩

Strains

A 🟨

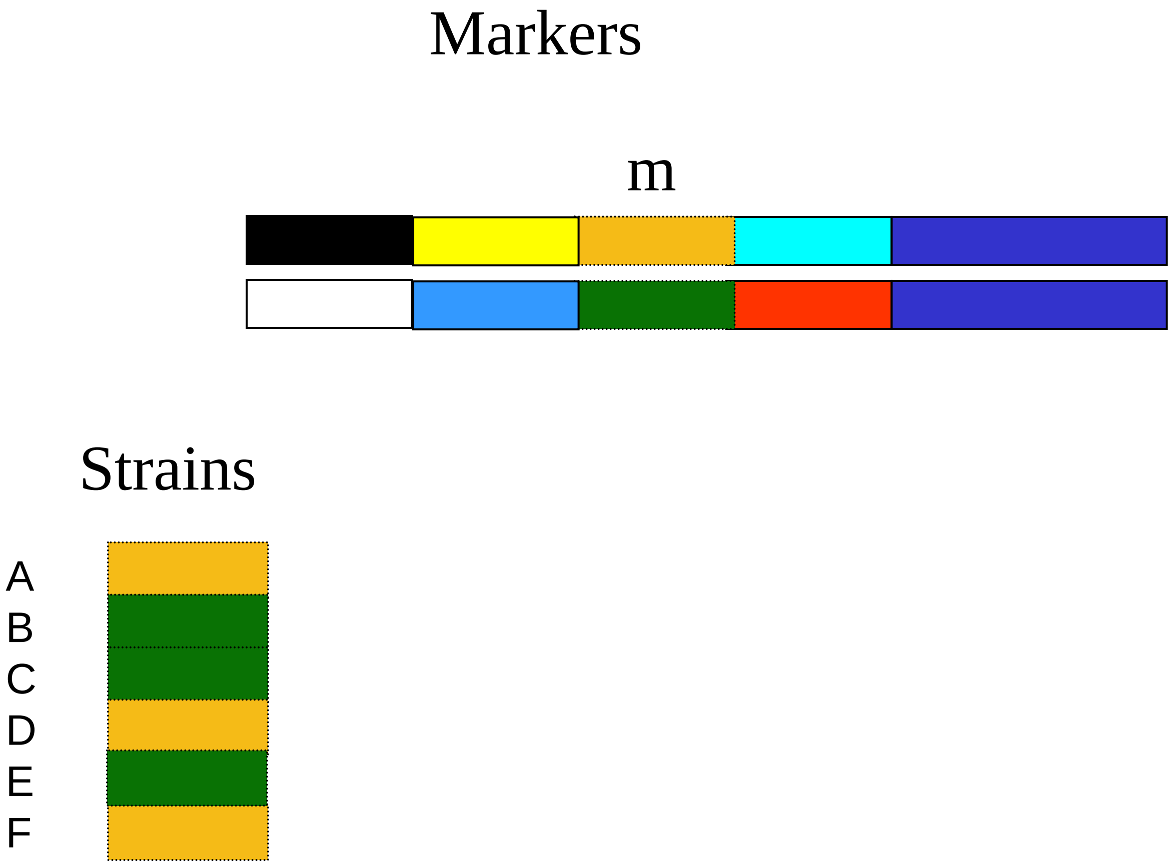
B 🟩

C 🟩

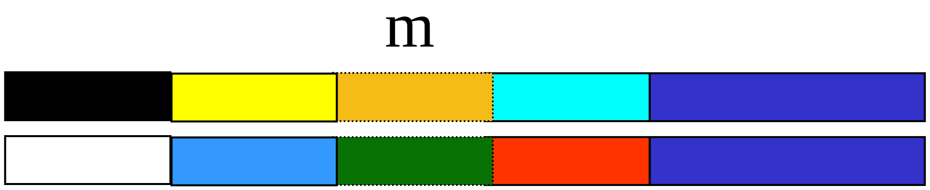
D 🟨

E 🟨

F 🟨

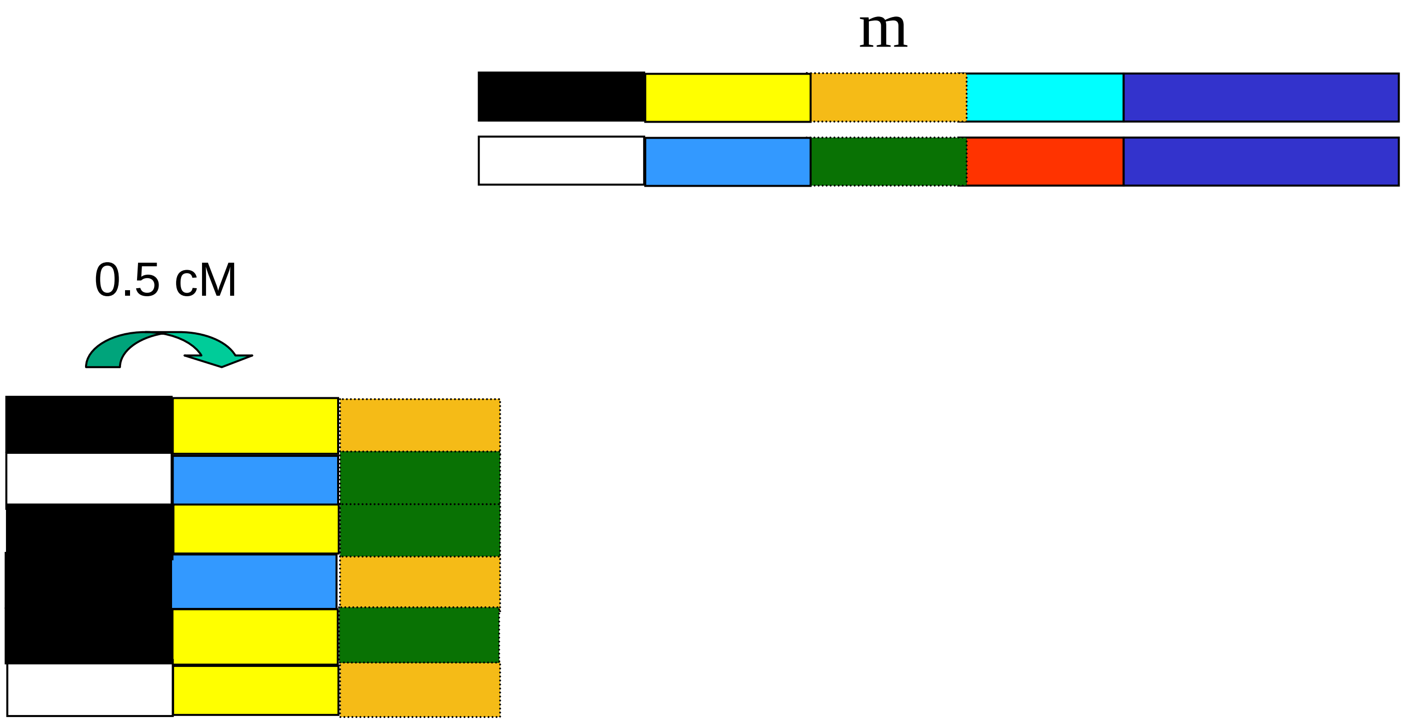

Markers
m
Strains
A
B
C
D
E
F

Markers

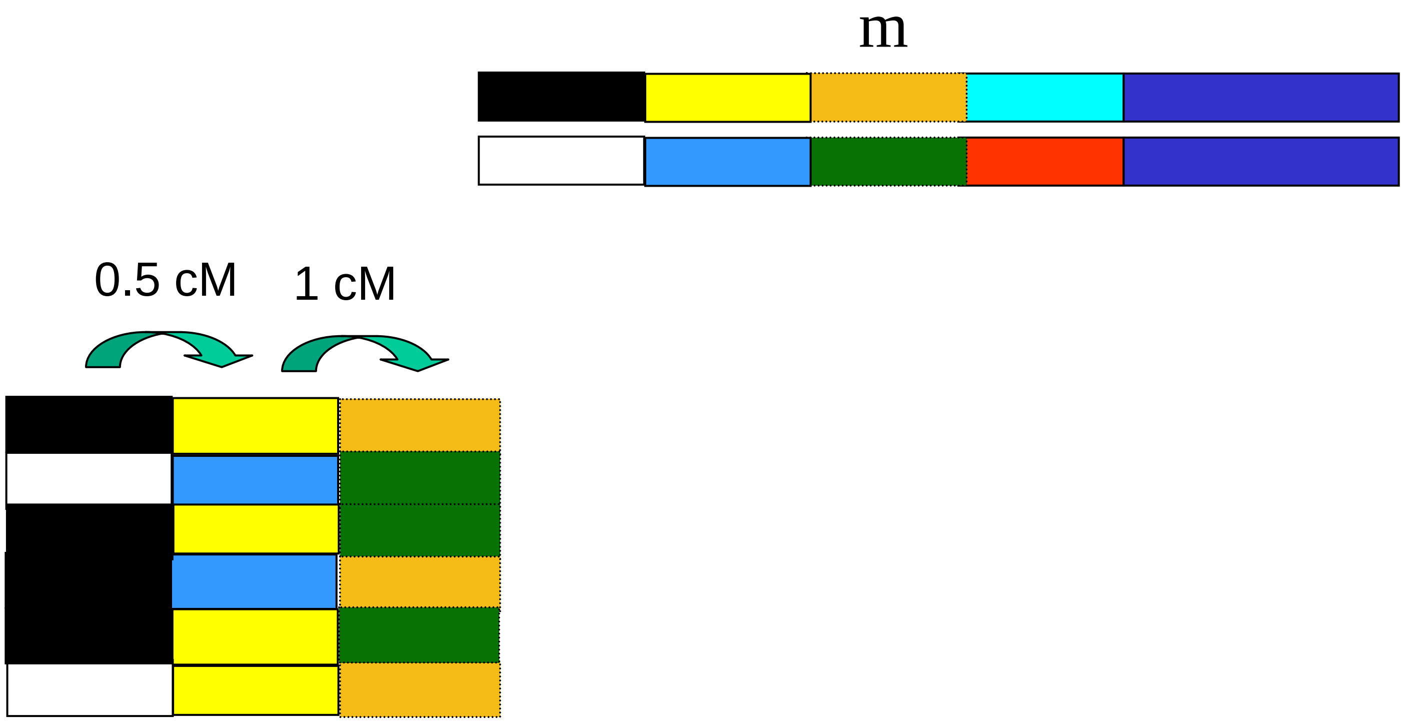


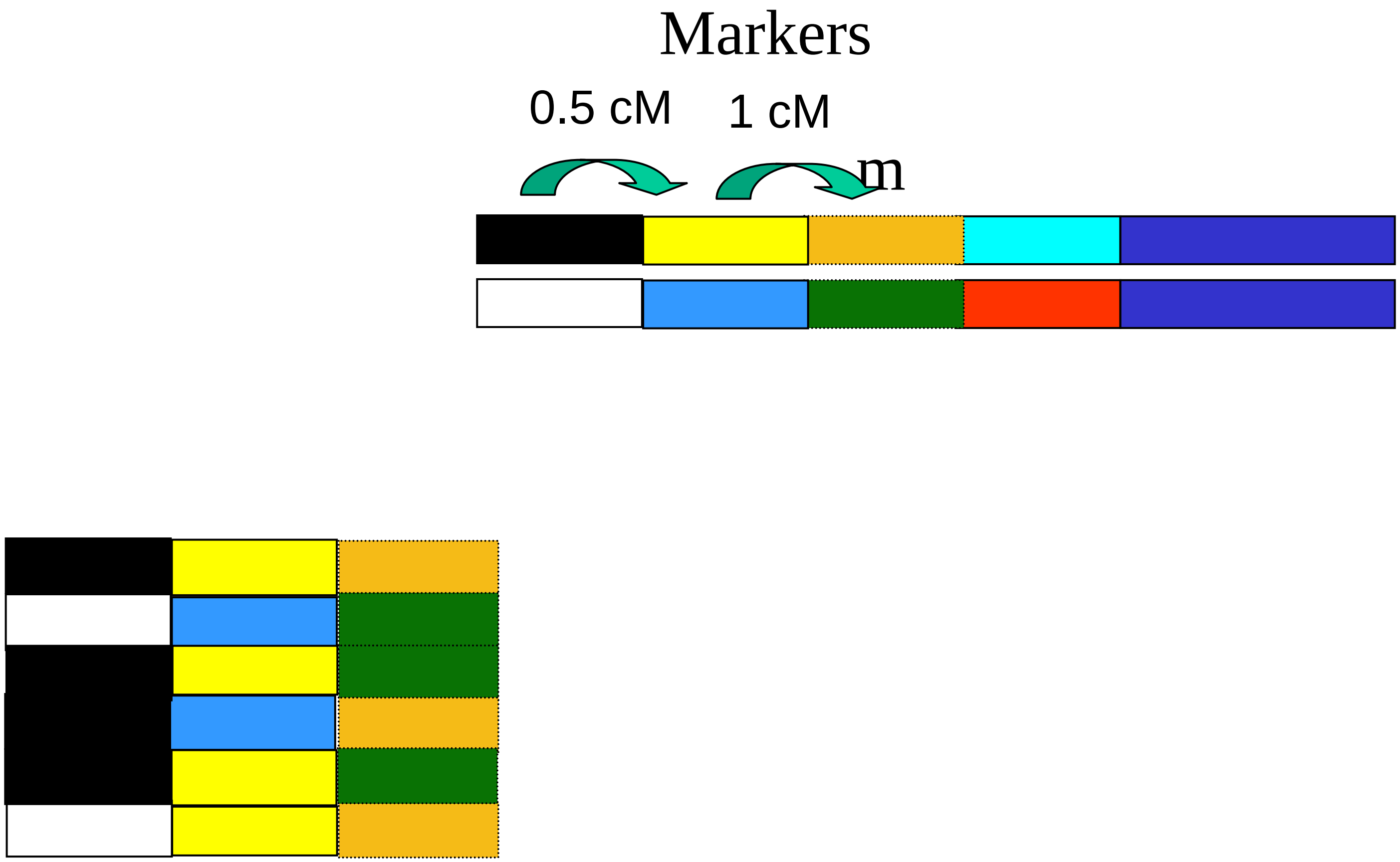
Strains

# Markers



Markers





Markers

0.5 cM

1 cM

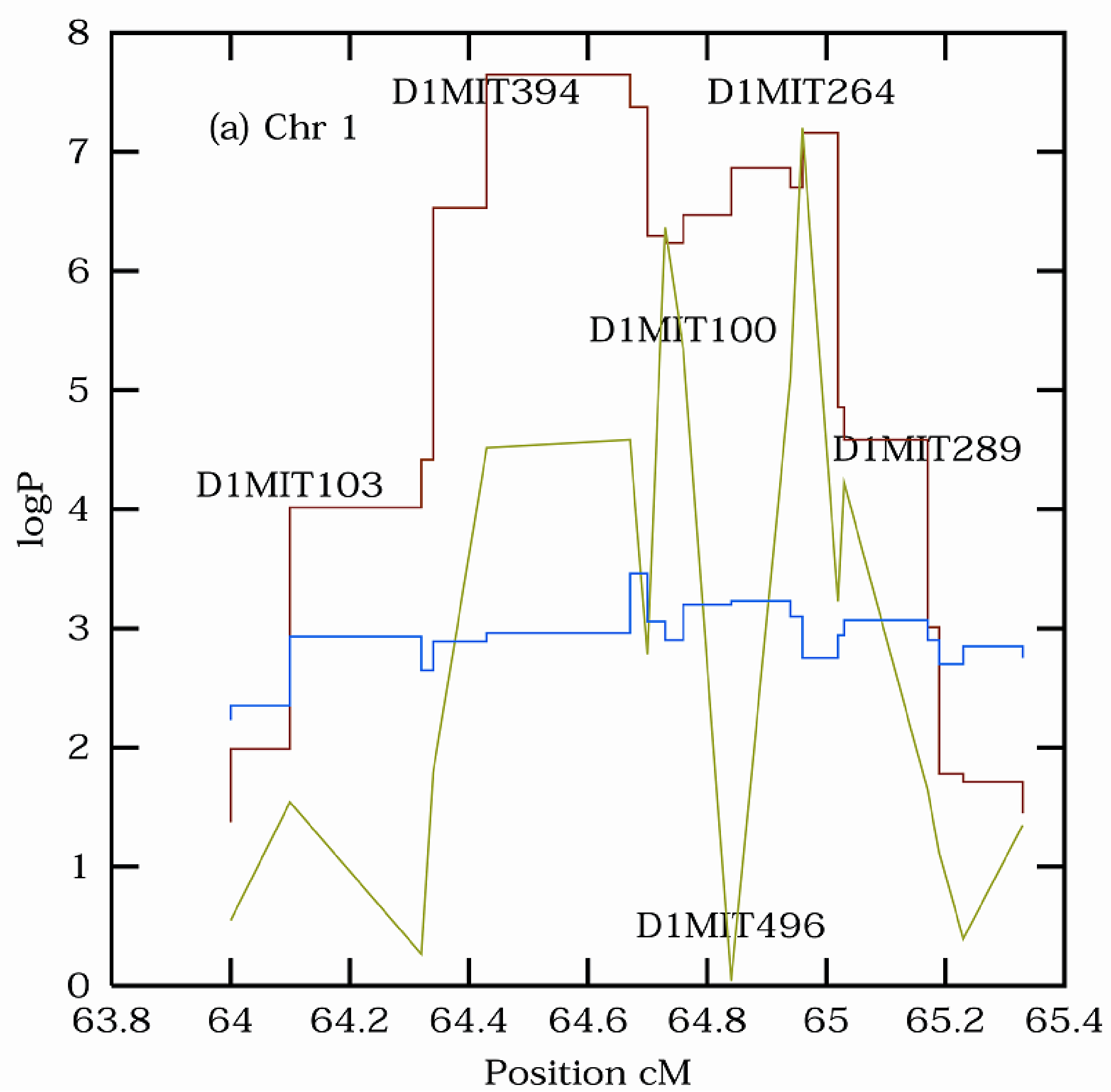
m

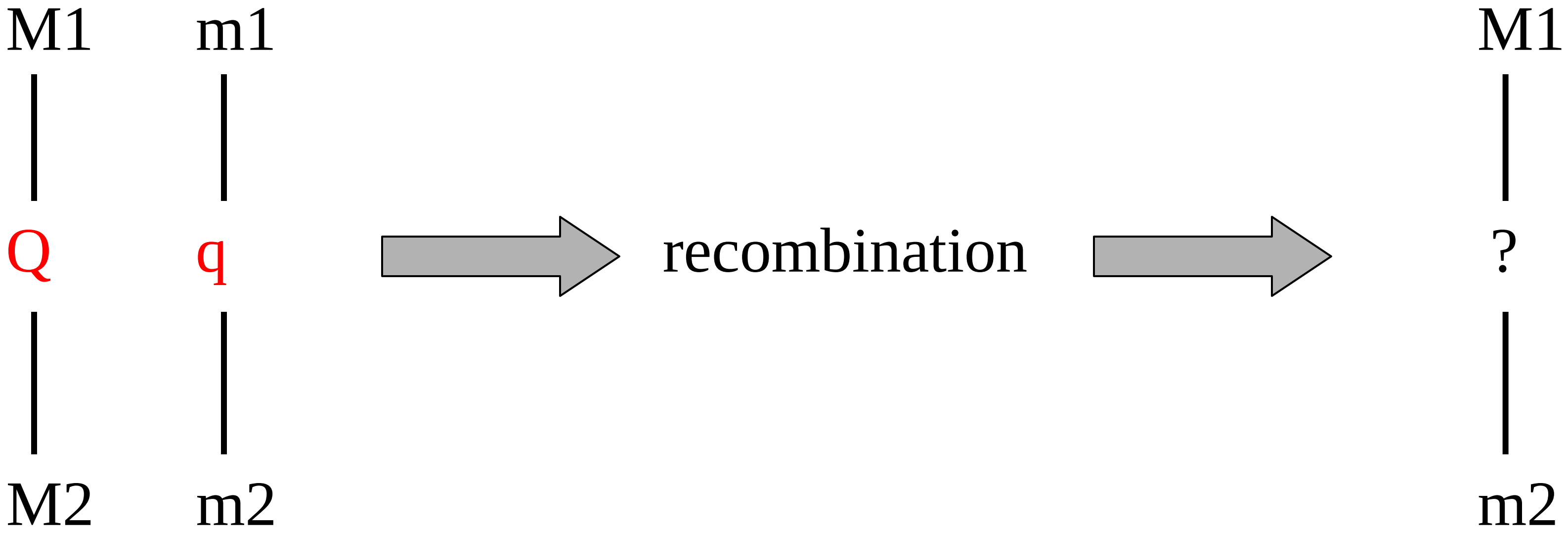
# Analysis

$$x_m(s,t) = \sum_{s',t'} x_{m-1}(s',t')\psi_m(s,t|s',t')$$

Probabilistic Ancestral Haplotype Reconstruction (descent mapping): implemented in HAPPY

http://www.well.ox.ac.uk/~rmott/happy.html


(a) Chr 1
D1MIT394
D1MIT264
D1MIT100
D1MIT289
D1MIT103
D1MIT496
logP
Position cM
0
1
2
3
4
5
6
7
8
63.8
64
64.2
64.4
64.6
64.8
65
65.2
65.4



M1 m1

Q q

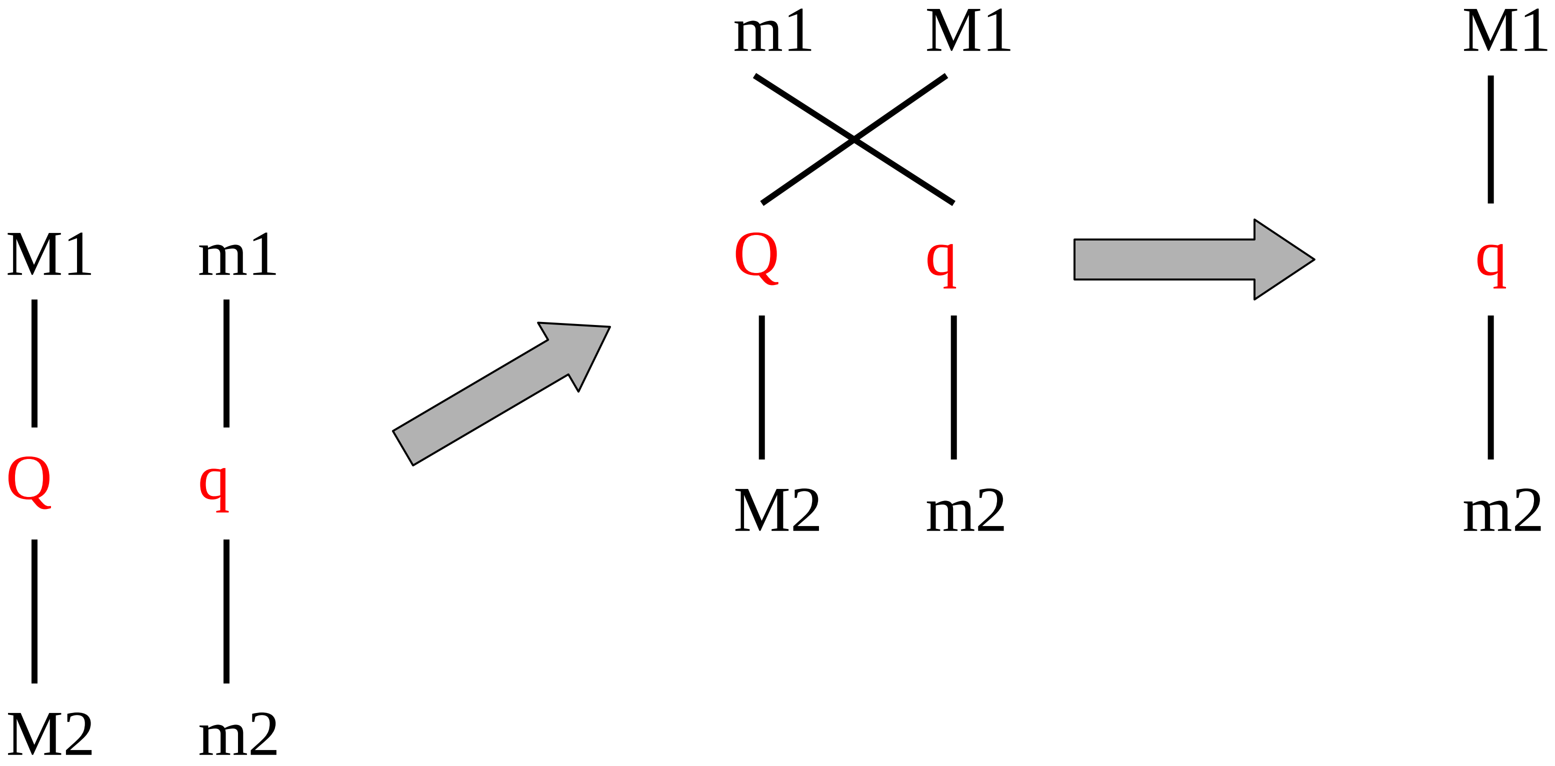
recombination

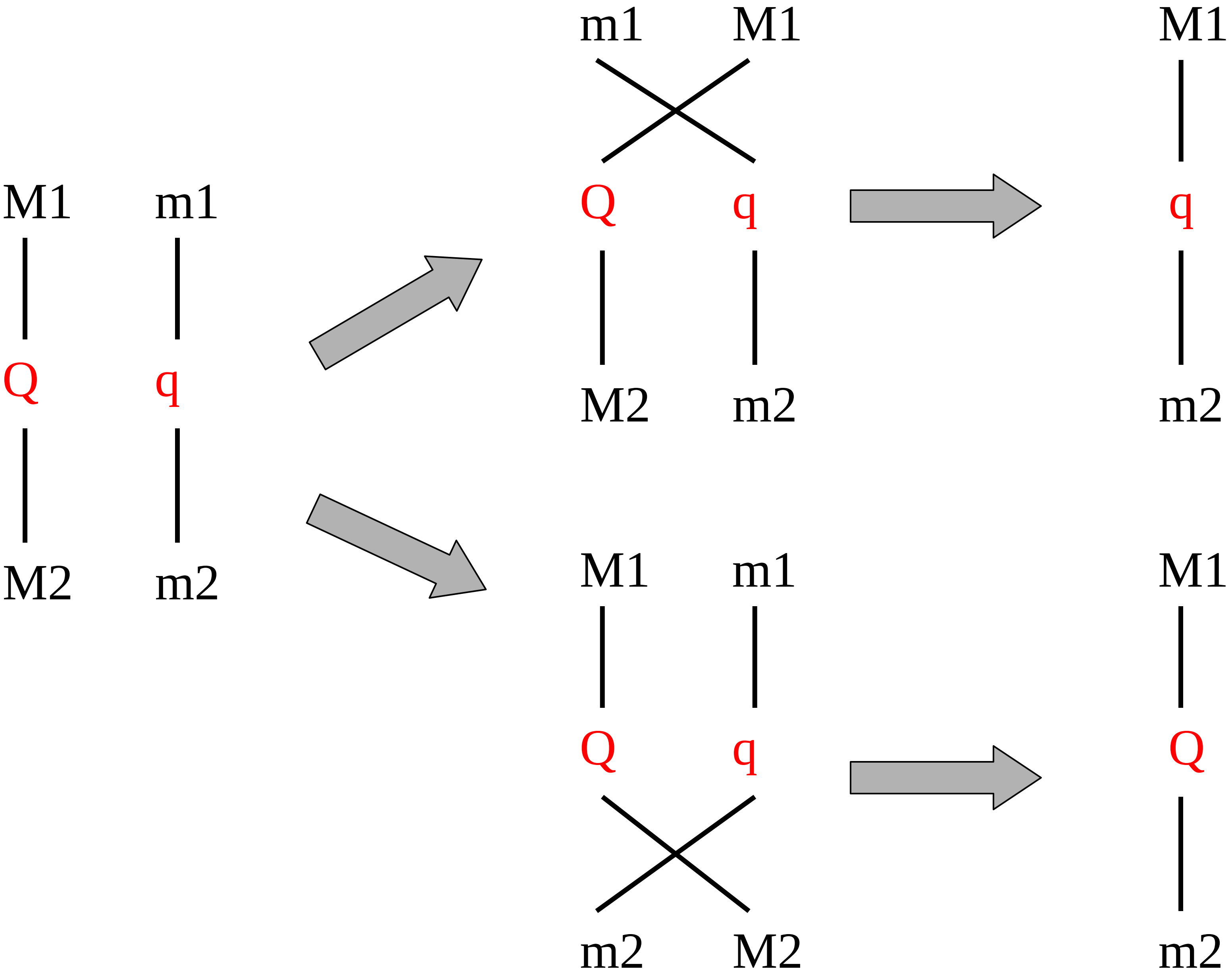
M1

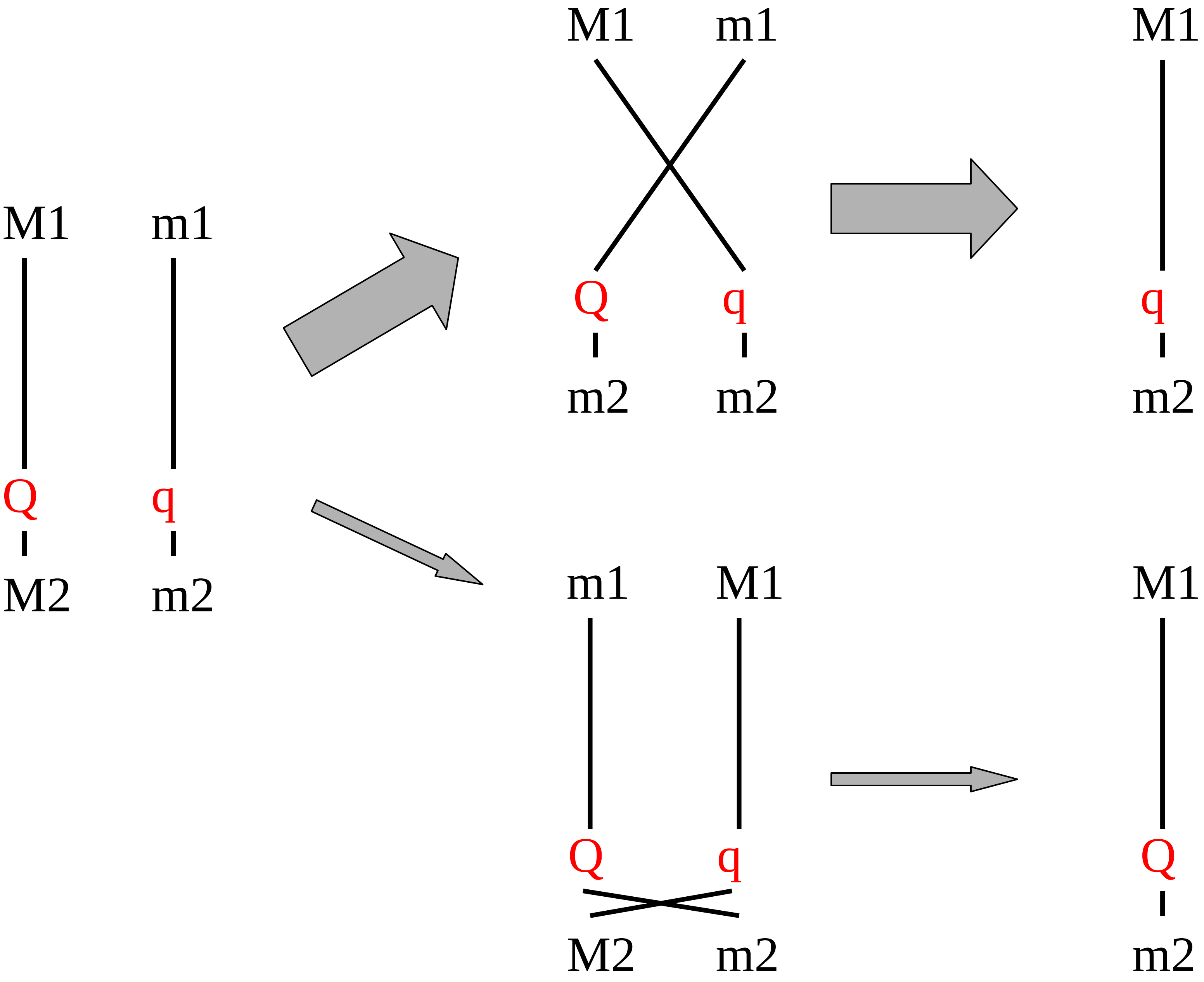
?

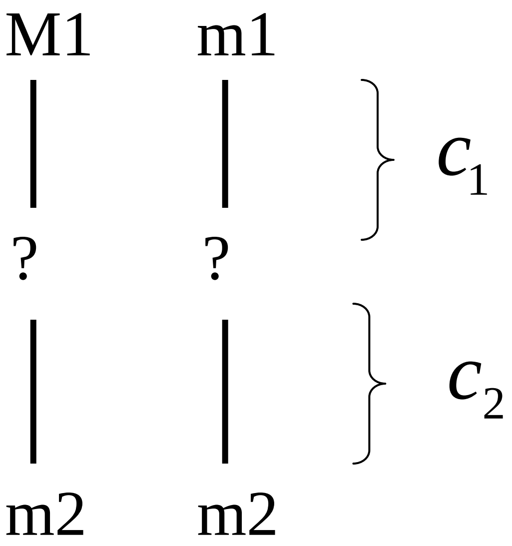
M2 m2

m2


M1
m1
Q
q
M2
m2
m1
M1
Q
q
M2
m2
M1
q
m2


M1
m1
Q
q
M2
m2
m1
M1
Q
q
M2
m2
M1
q
m2
M1
m1
Q
q
m2
M2
M1
Q
m2


M1
m1
Q
q
M2
m2
M1
m1
Q
q
m2
m2
M1
q
m2
m1
M1
Q
q
M2
m2
M1
Q
m2



M1 m1

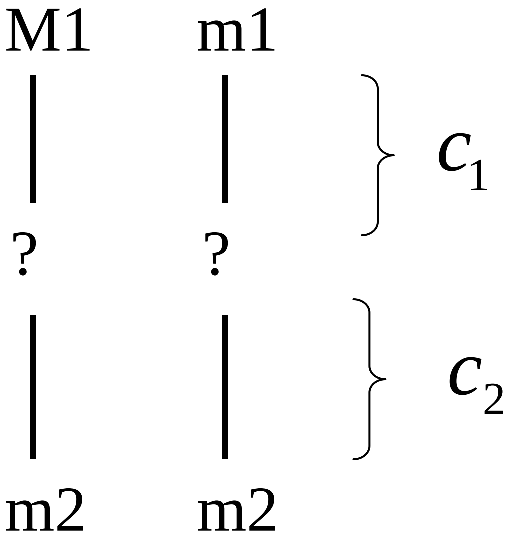
?  ?

$c_1$

$c_2$

m2 m2

cM distances
determine
probabilities



M1 m1

? ?

m2 m2

$c_1$

$c_2$

cM distances
determine
probabilities

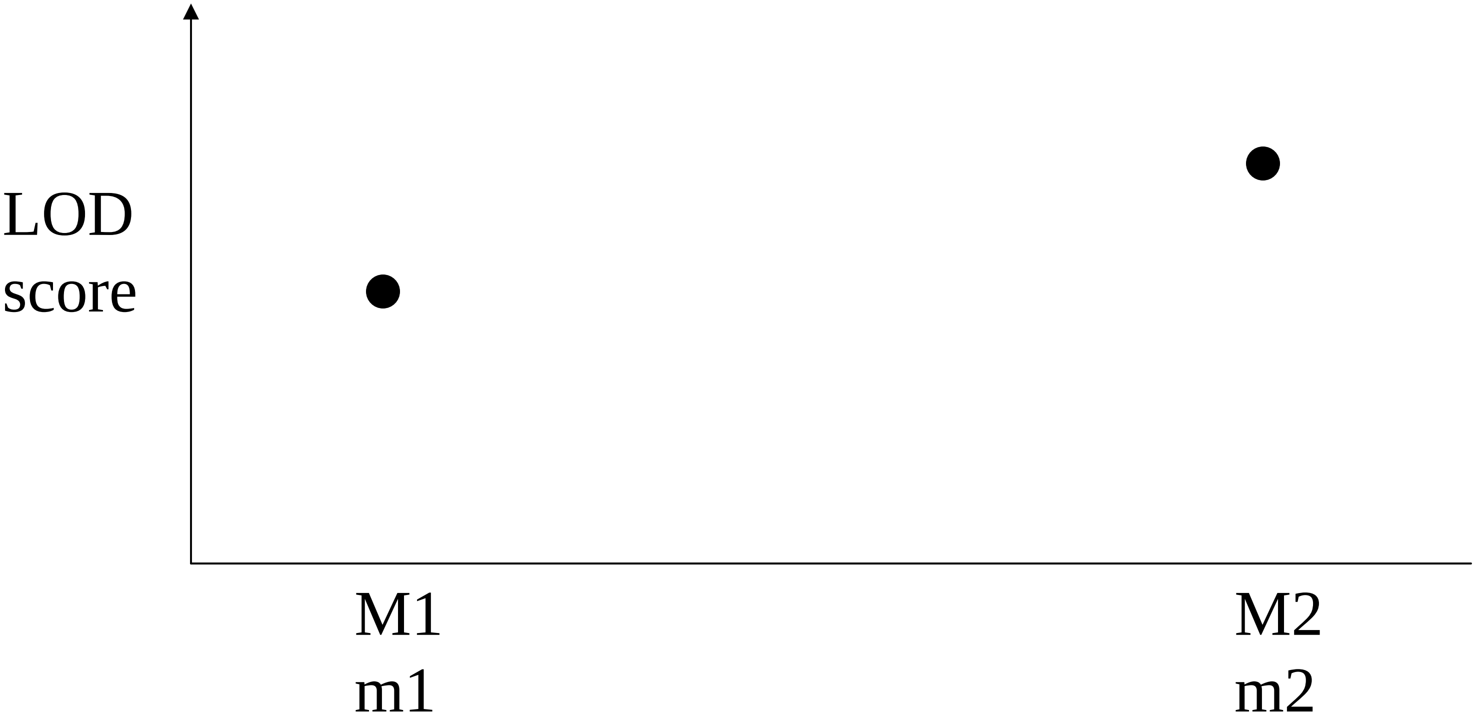
Eg,

$$\Pr\left( qq \mid M_1 m_2 m_1 m_2 \right) = 0.5$$

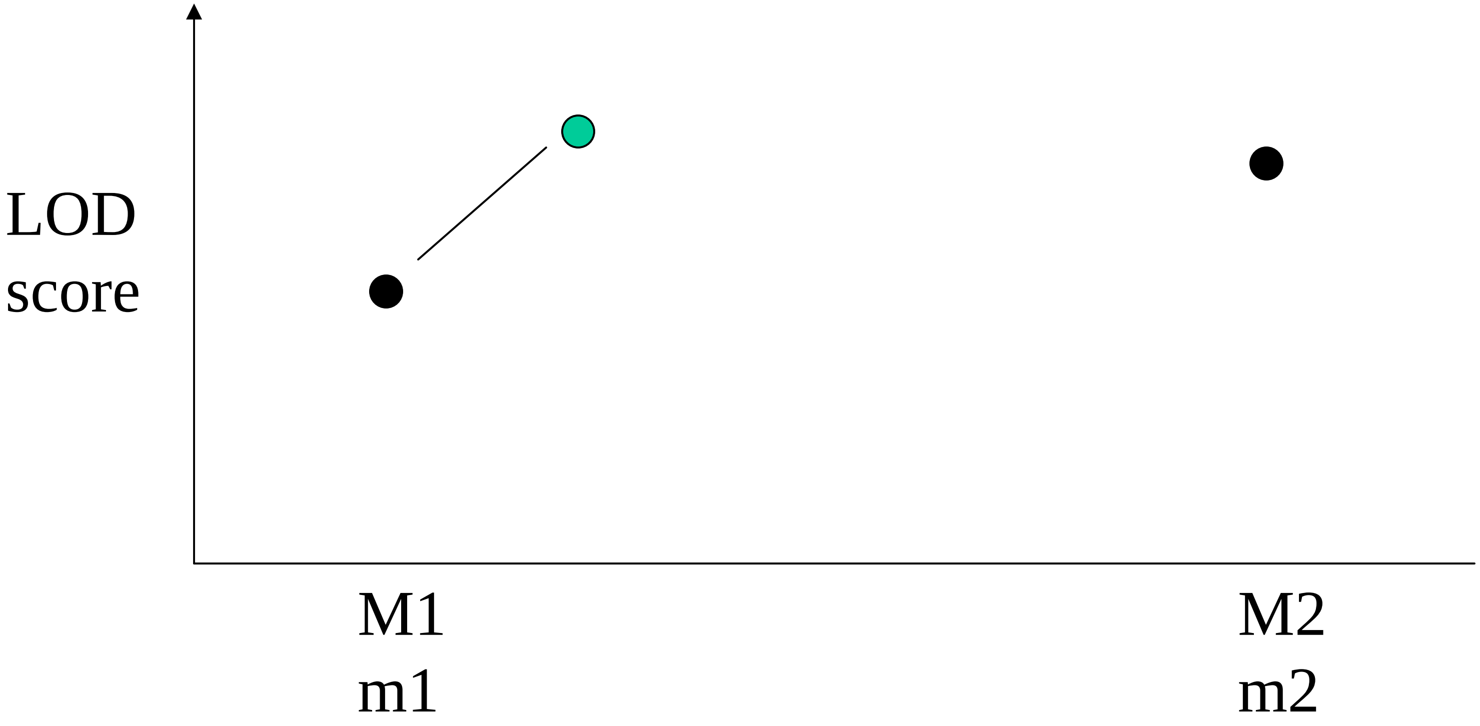
$$\Pr\left( qQ \mid M_1 m_2 m_1 m_2 \right) = 0.5$$

$$\Pr\left( QQ \mid M_1 m_2 m_1 m_2 \right) = 0$$

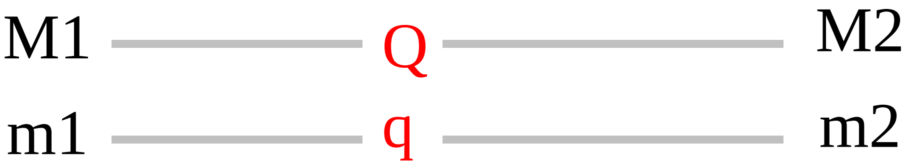
# Interval mapping

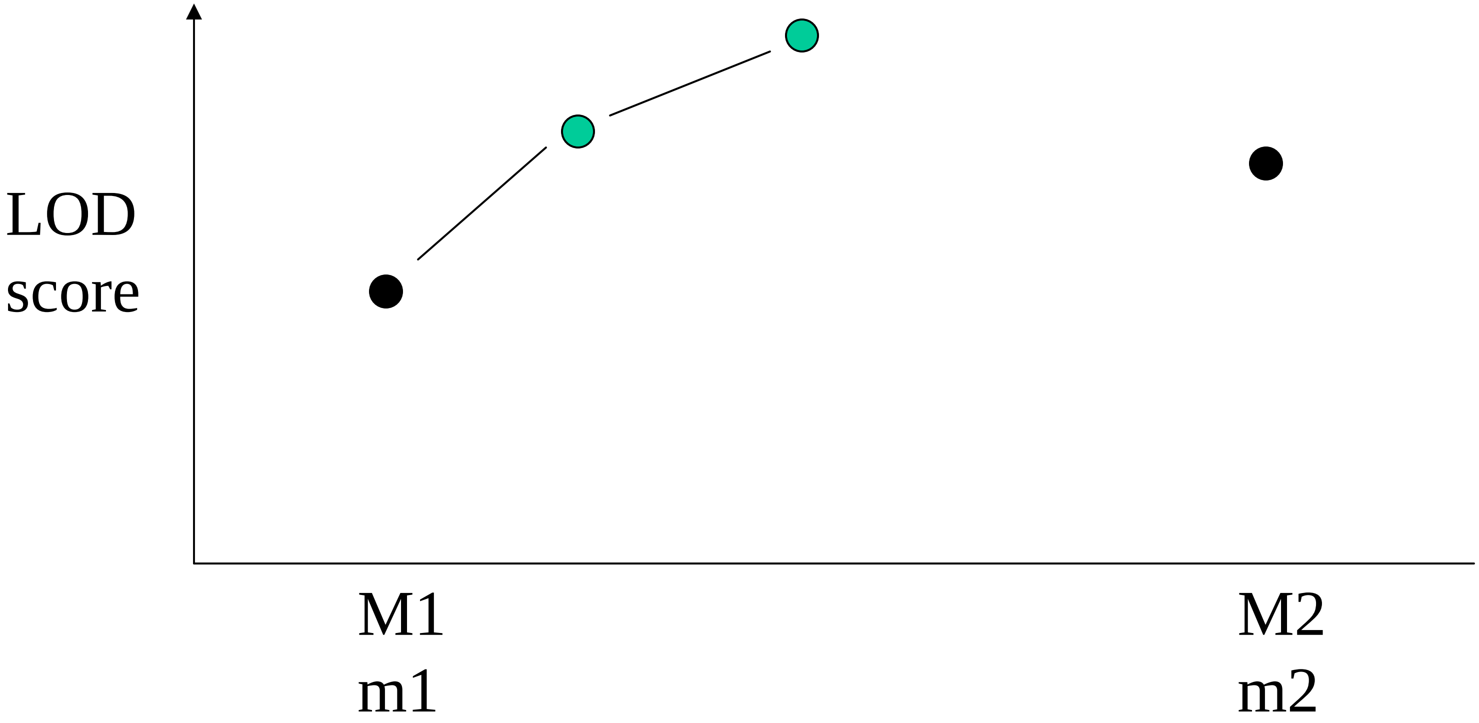


# Interval mapping



# Interval mapping





# Interval mapping


M1 Q M2

m1 q m2