

Beyond Recombination: Exploring the Impact of Meiotic Frequency on Genome-wide Genetic Diversity

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JOBIM 2024

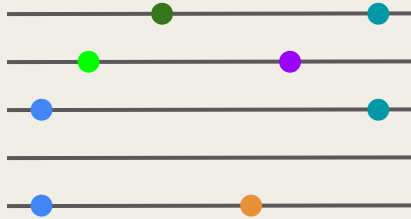
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LCQB

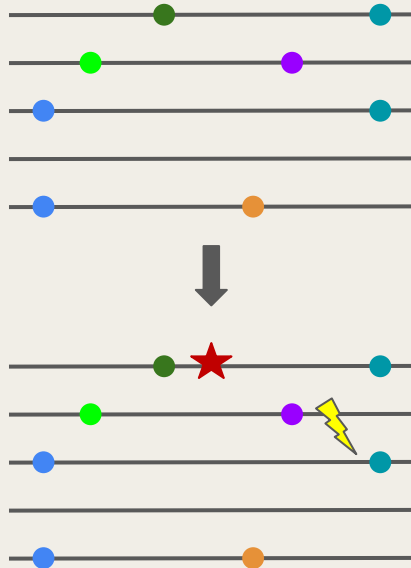
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What is a selective sweep?



● neutral mutation

What is a selective sweep?

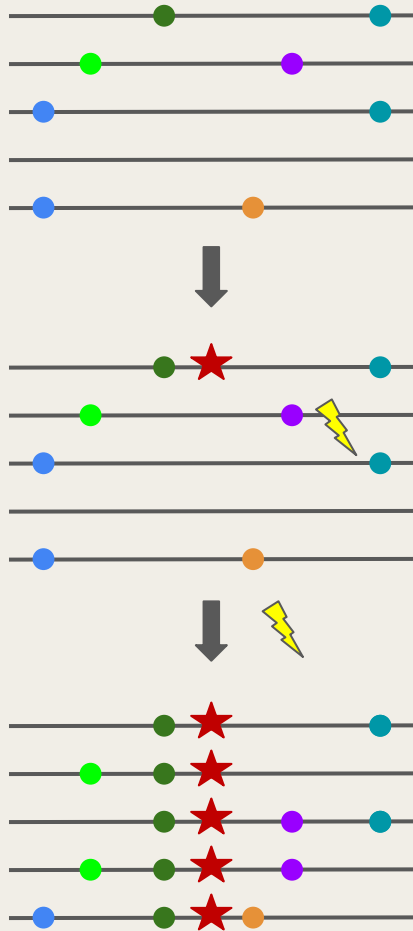


● neutral mutation

★ beneficial mutation

⚡ recombination

What is a selective sweep?

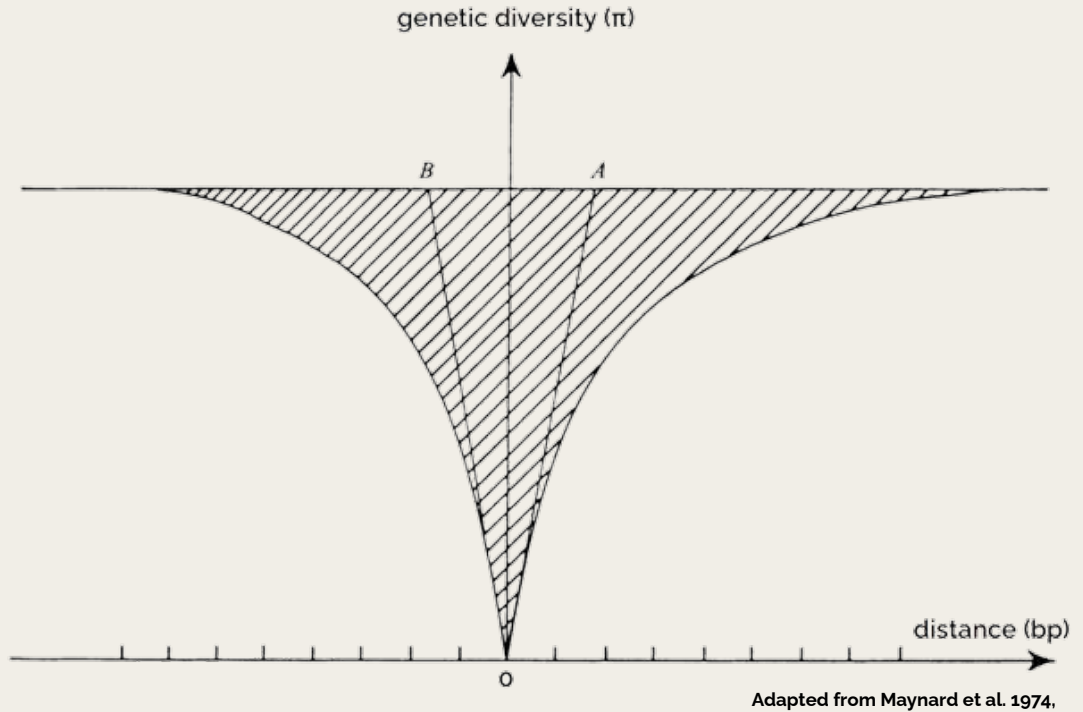
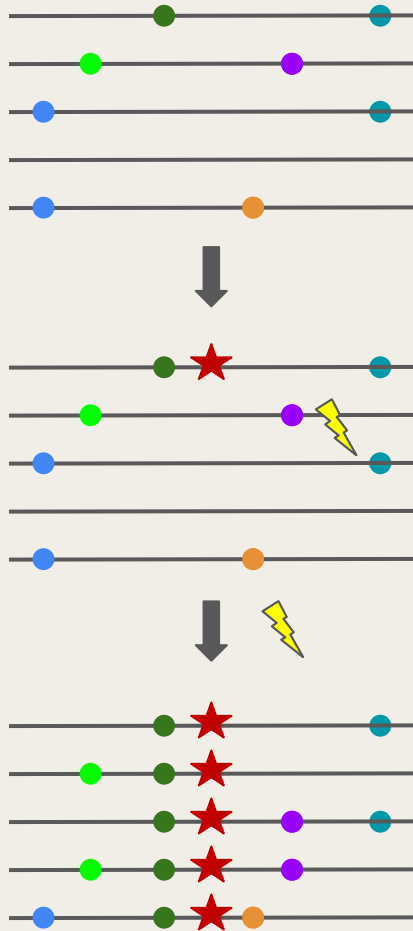


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What is a selective sweep?

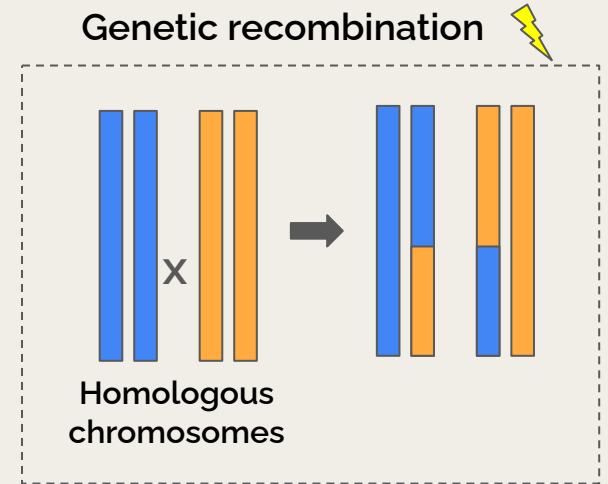
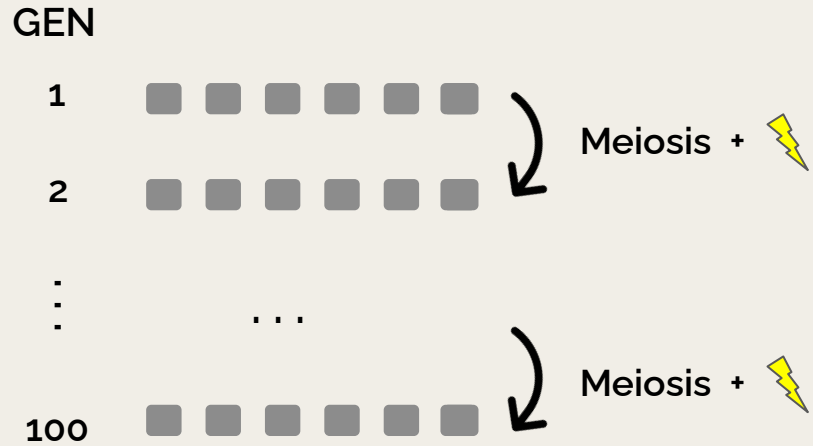


Adapted from Maynard et al. 1974,

genetic diversity (π) : measure of average genetic difference between 2 random individuals (number of sites or branch length)

The underlying reproductive model

Model behind the theory:



⇒ Sexual reproduction (meiosis) between each generation

Facultative sexual reproduction



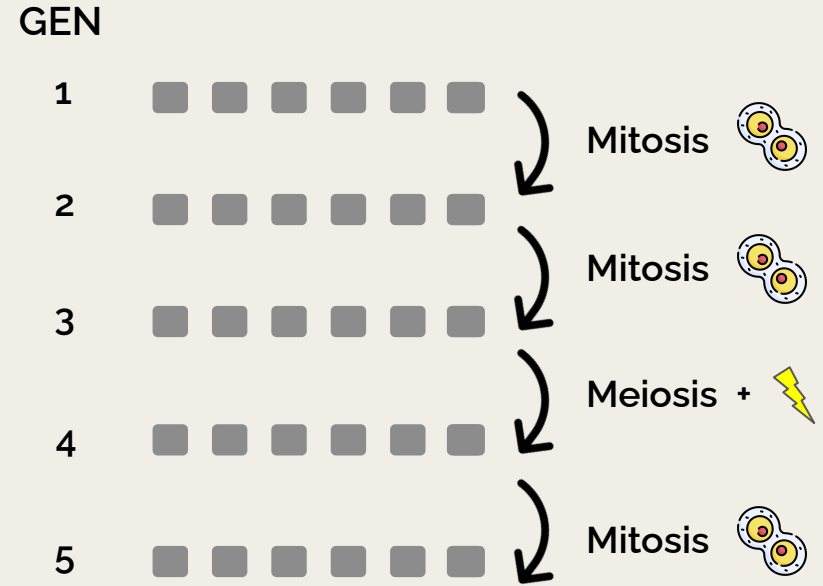
Saccharomyces cerevisiae



Arabidopsis thaliana



Facultative sexual reproduction



⇒ Facultative meiosis

Facultative sexual reproduction

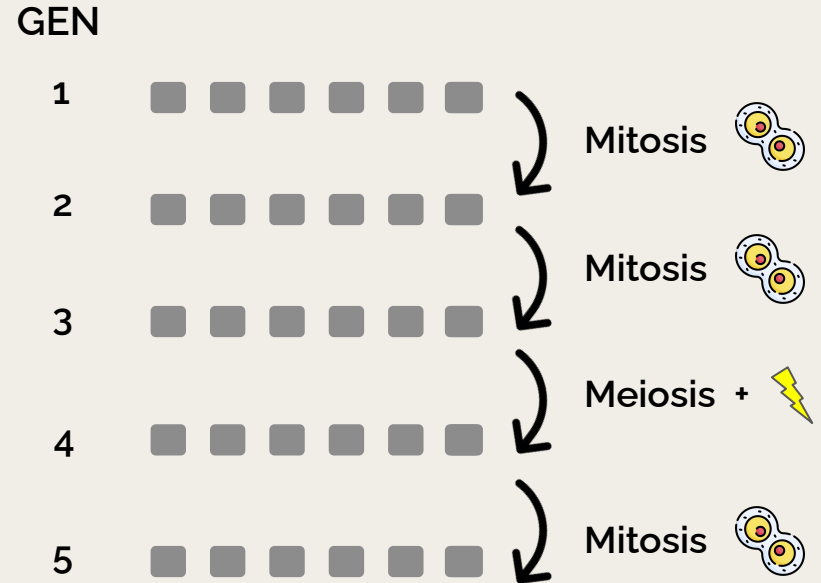


$m = 0.002 - 10e-4$
(1:500-10000 [1])

meiotic frequency
(m)



$m = 0.025$
1:40 [2]



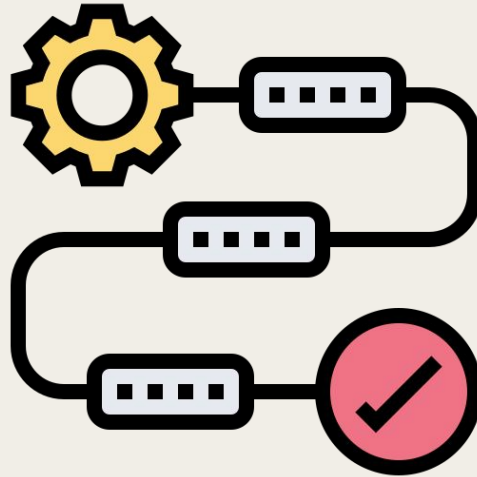
⇒ Facultative meiosis

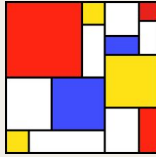
[1] Fischer G, Liti G. The budding yeast life cycle: More complex than anticipated? Yeast. 2020. Available from: <https://onlinelibrary.wiley.com/doi/10.1002/yea.3533>

[2] Hoffman PD, Leonard JM, Lindberg GE, Bollmann SR, Hays JB. Rapid accumulation of mutations during seed-to-seed propagation of mismatch-repair-defective Arabidopsis. Genes & Development. 2004;18(21):2676-85. Available from: <https://genesdev.cshlp.org/content/18/21/2676.abstract>

How does the meiotic frequency (m)
affect the genetic diversity under a
selective sweep ?

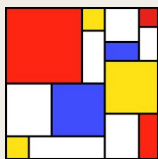
METHODS





SLiM (Selection on Linked Mutations) [1]

The simulation parameters

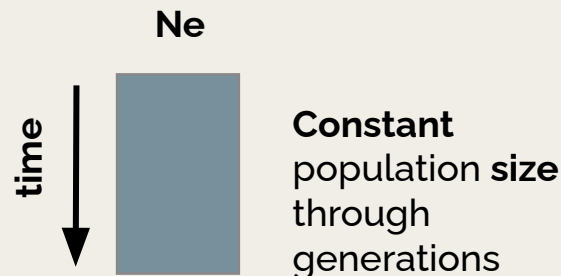


SLiM (Selection on Linked Mutations) [1]

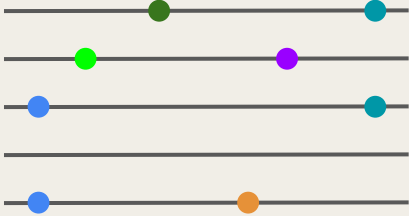
- Population size (N_e) = **1000**
- Mutation rate (μ) = **$1e-8$ mutation/bp**
- Genome size (L) = **1 Mbp**
- Number of generation = $10N_e$ = **10000**
- Frequency of the beneficial mutation (f) = **10%**
- Dominance coefficient (h) = **0.4**

- Meiotic frequency (m) = **0.01 - 1**
- Selection coefficient (s) = **0.1**
- Recombination rate (ρ) = **$5e-8$**

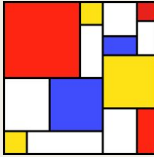
different values will be tested



The simulation model

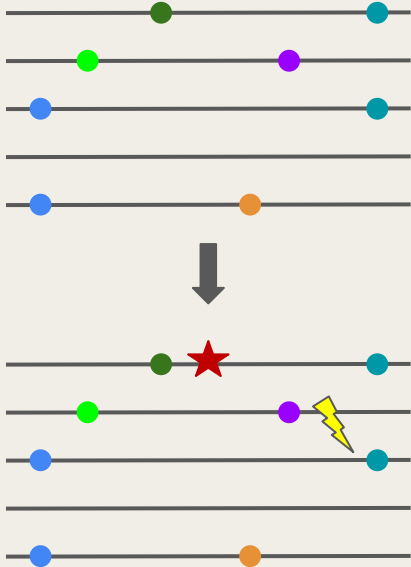


2000 generations
⇒ **standing variation**



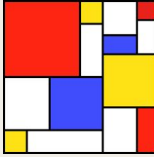
200 replicates

The simulation model



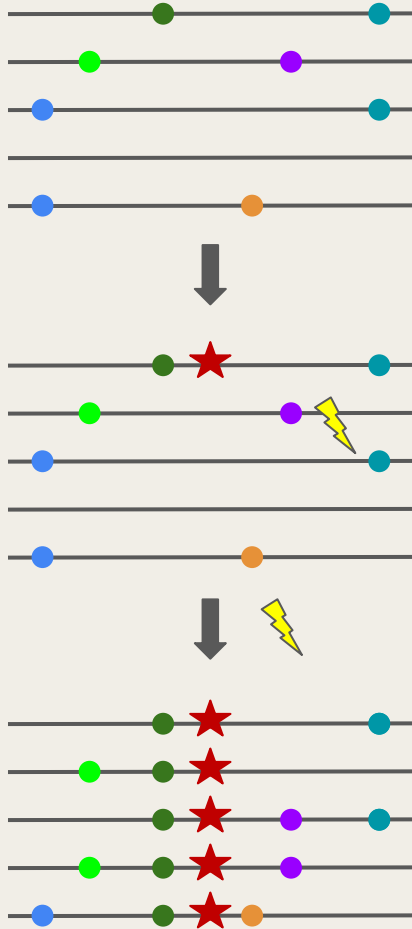
2000 generations
⇒ **standing variation**

1 beneficial mutation
appears at **10%** in the pop



200 replicates

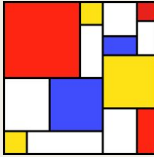
The simulation model



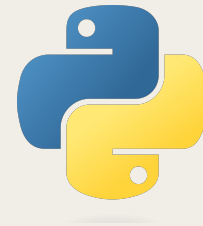
2000 generations
⇒ standing variation

1 beneficial mutation
appears at 10% in the pop

➔ Stop at fixation ➔ π along the genome



200 replicates

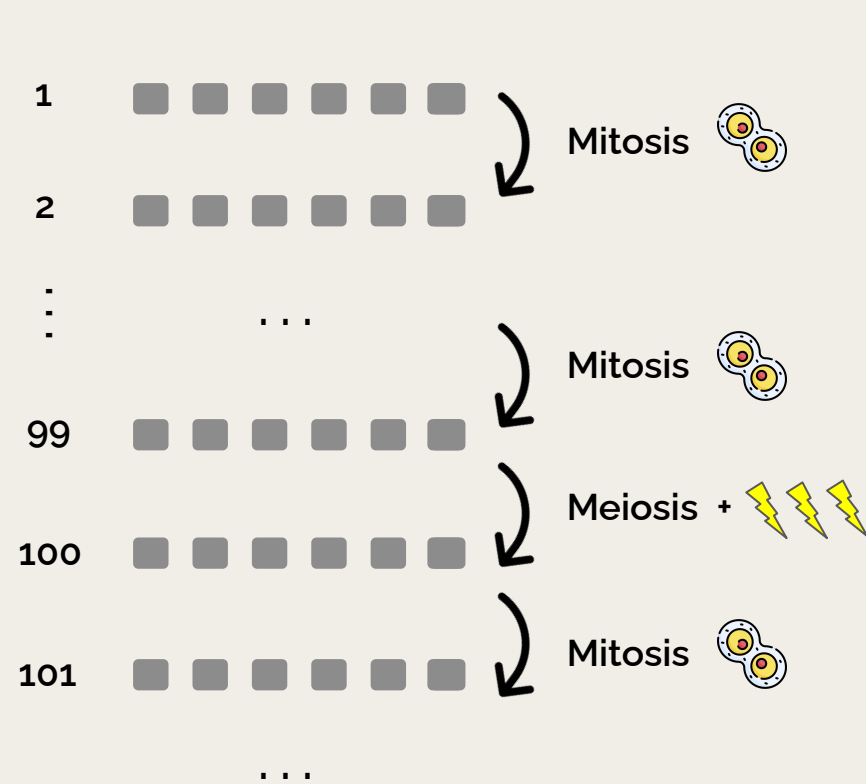


The tested conditions

$m = 1 \Leftrightarrow 1:1 \Rightarrow$ canonical

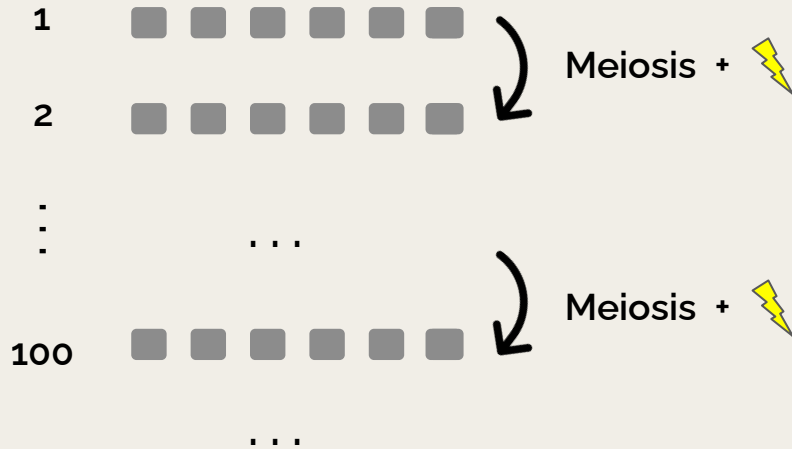


$m = 0.01 \Leftrightarrow 1:100$

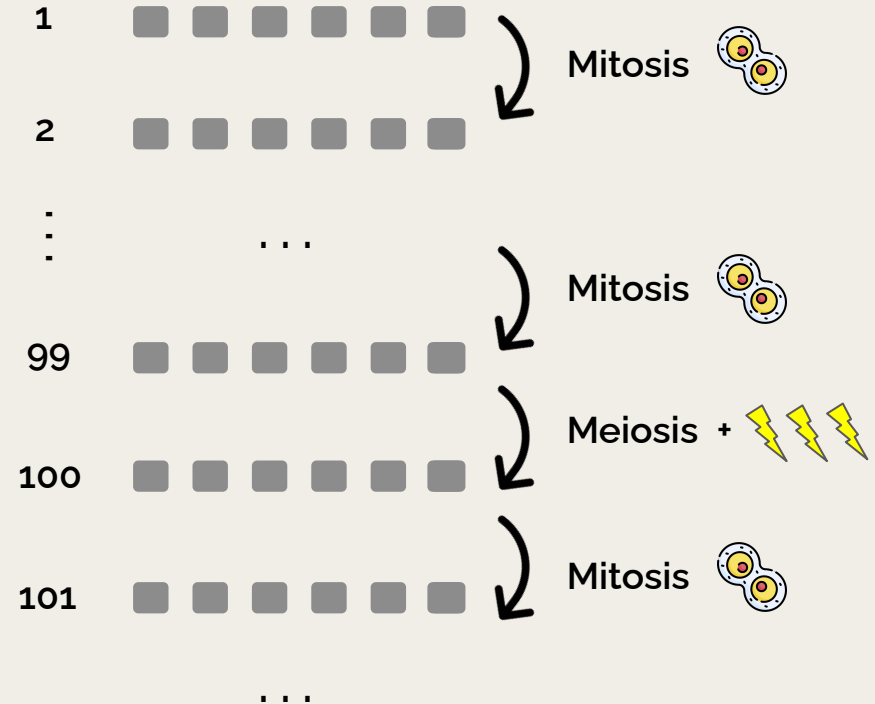


The tested conditions

$m = 1 \Leftrightarrow 1:1 \Rightarrow$ canonical



$m = 0.01 \Leftrightarrow 1:100$

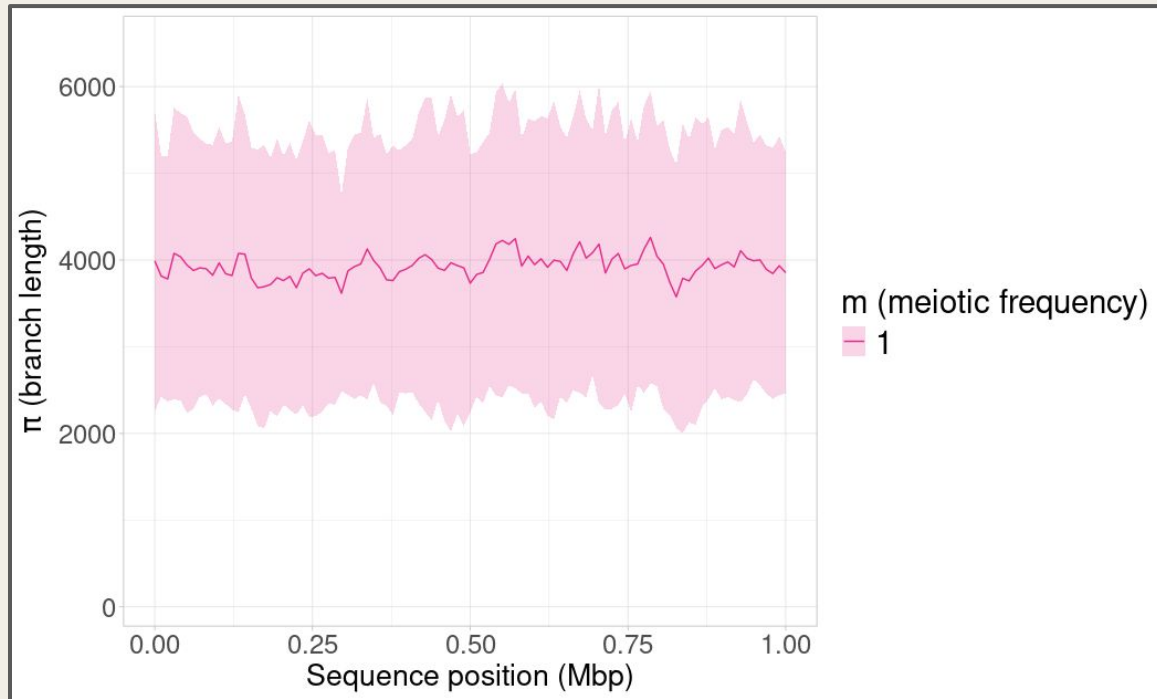


$\rho = m * \rho_m \Rightarrow$ total recombination rate is the same

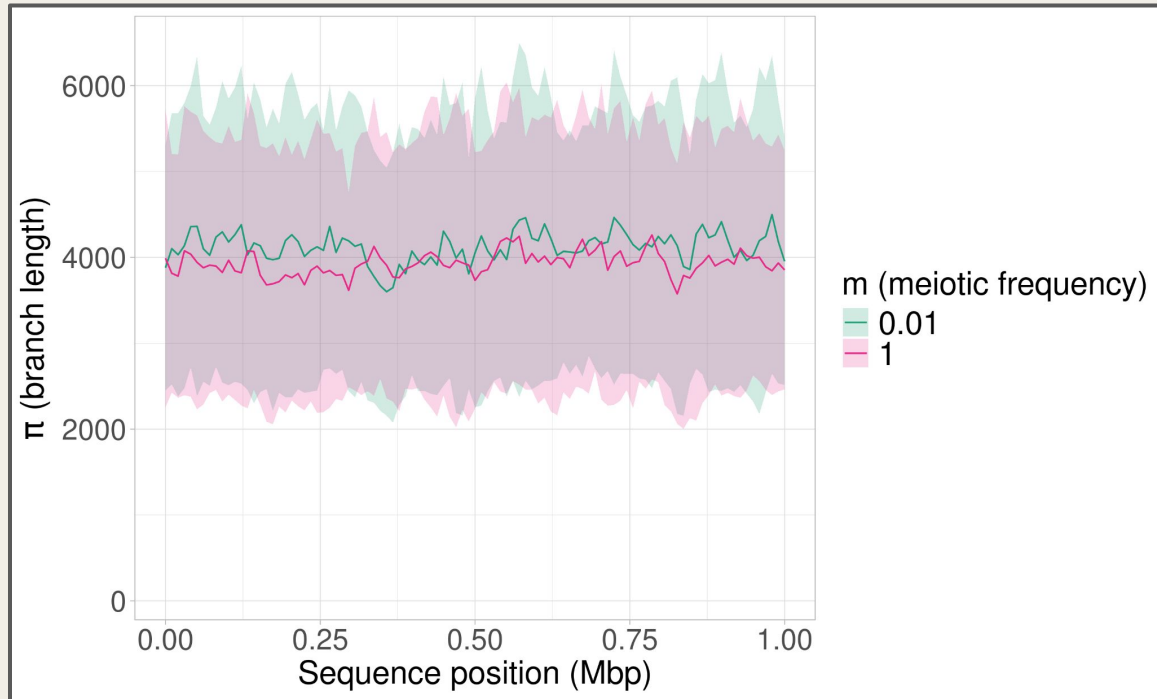
RESULTS



Negative control: effect of m without selective sweep

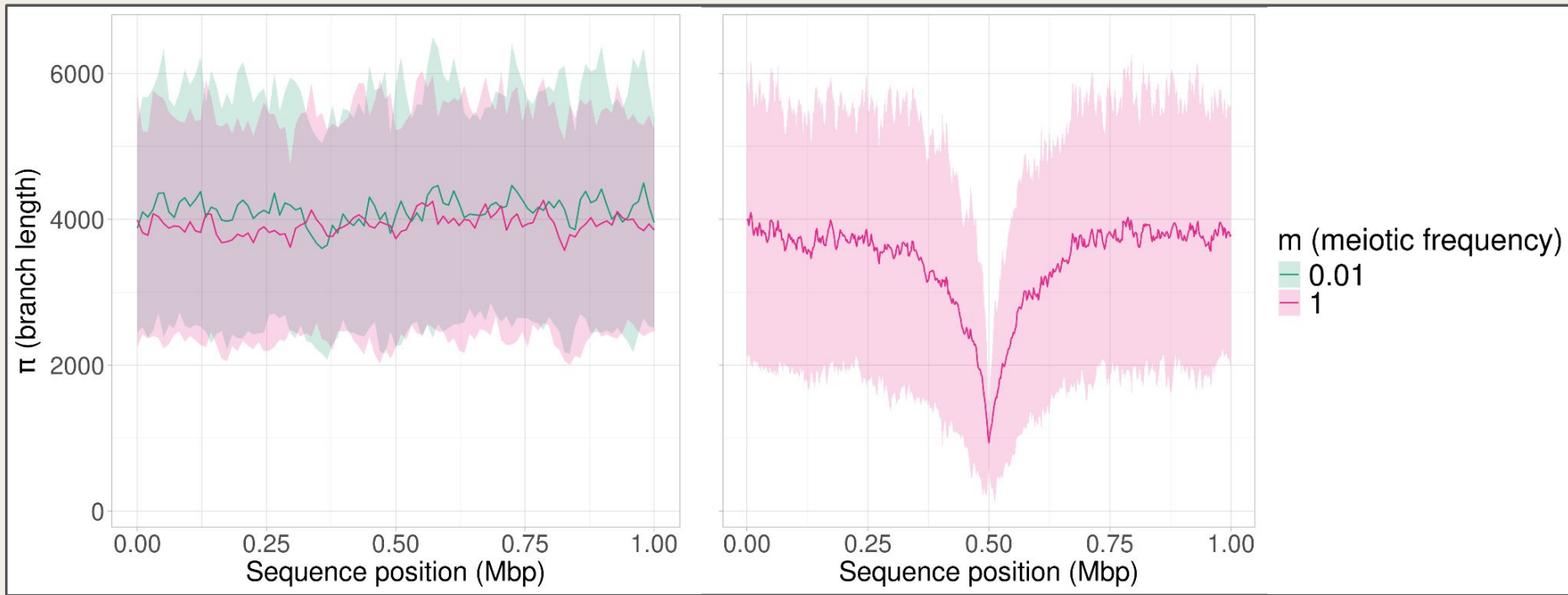


Negative control: effect of m without selective sweep



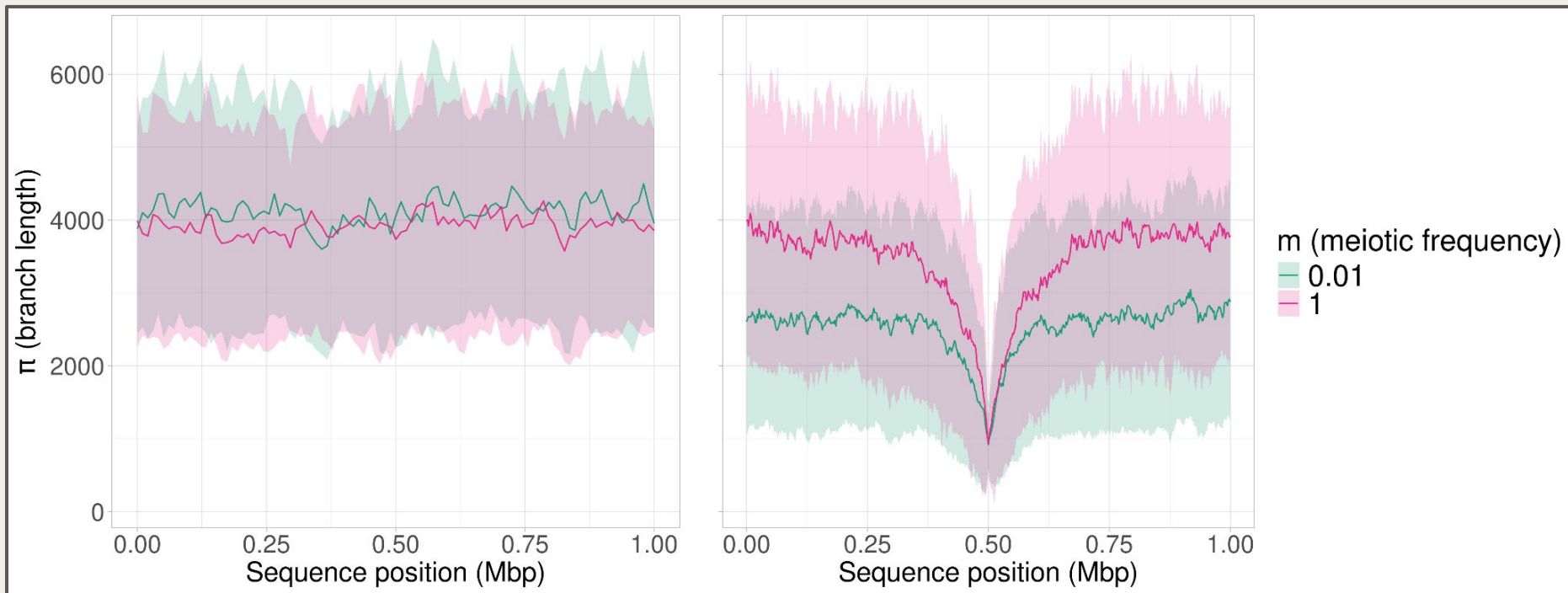
➡ **No major difference in absence of selection**

Meiotic frequency impacts genetic diversity in presence of selection



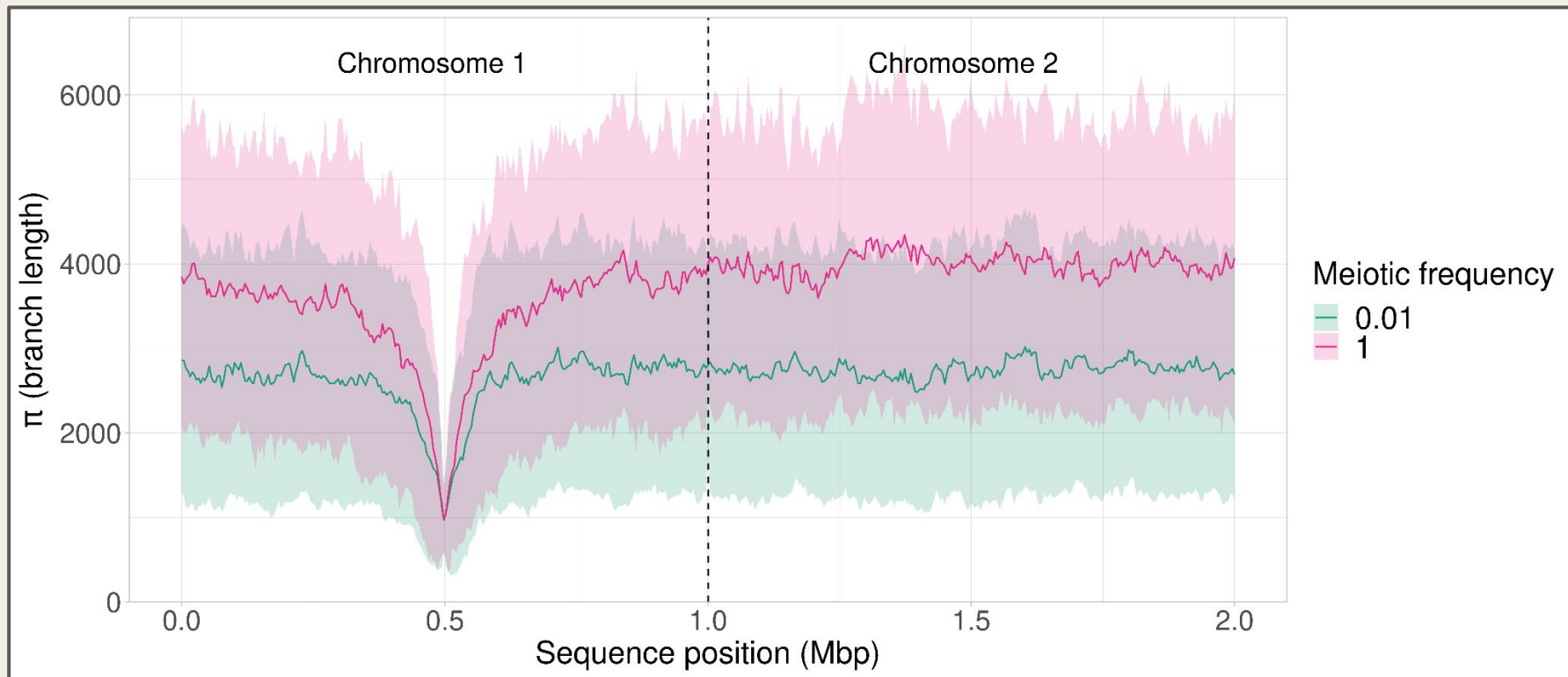
⇒ Hitchhiking valley

Meiotic frequency impacts genetic diversity in presence of selection



➡ Drop in diversity: does it impact the entire genome ?

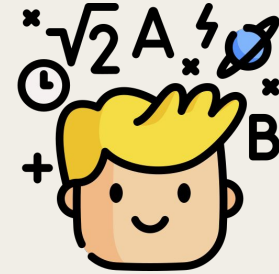
Meiotic frequency leaves its footprint on the entire genome



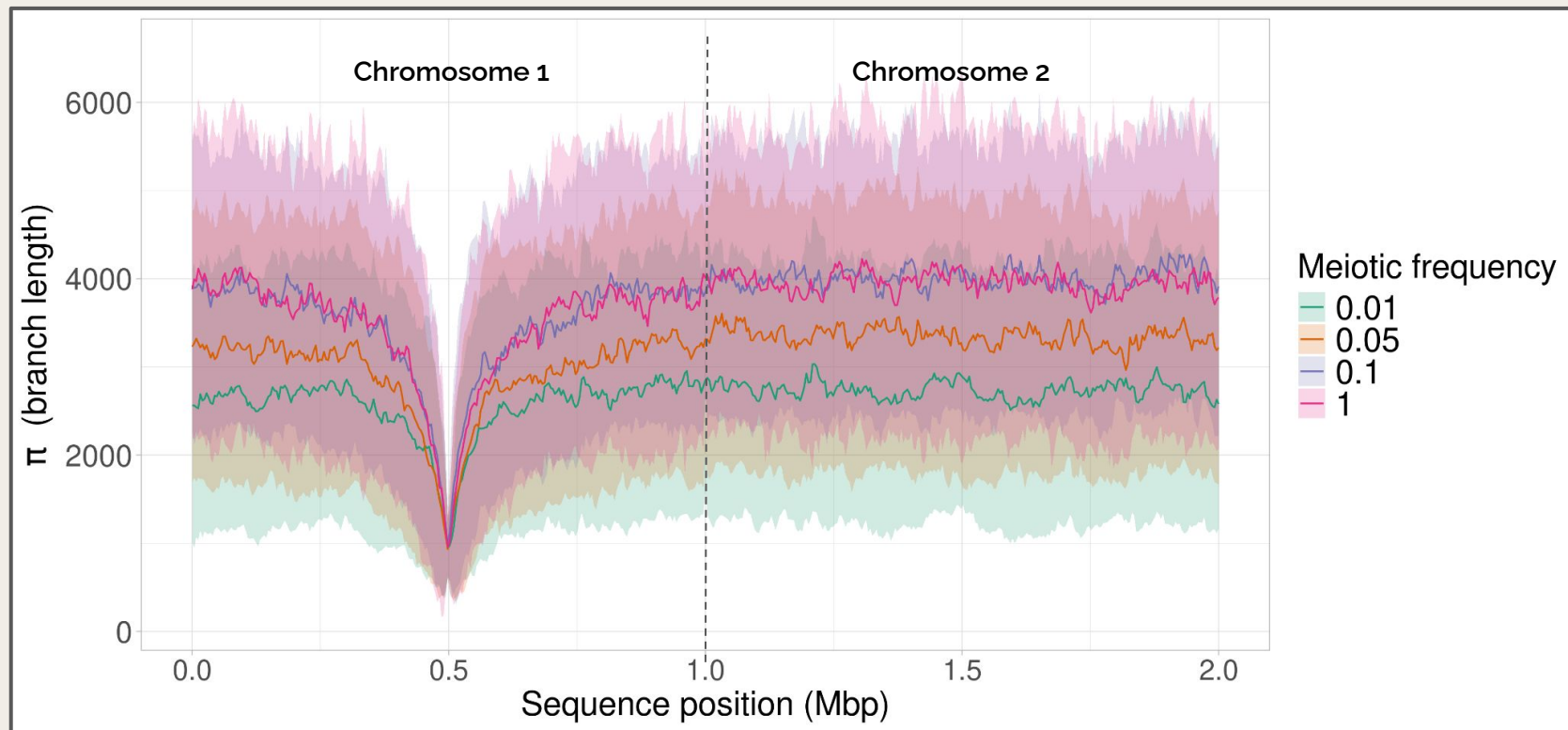
➔ **Genome-wide effect**

⇒ **Genome-wide drop in diversity for rare (but strong) meiosis**

- To assess:
- gradual effect of m ?
 - effect of ρ (recombination rate)?
 - effect of s (selection coefficient)?



Gradual effect of meiotic frequency on genetic diversity



➡ Gradual effect visible for $m < 0.1$

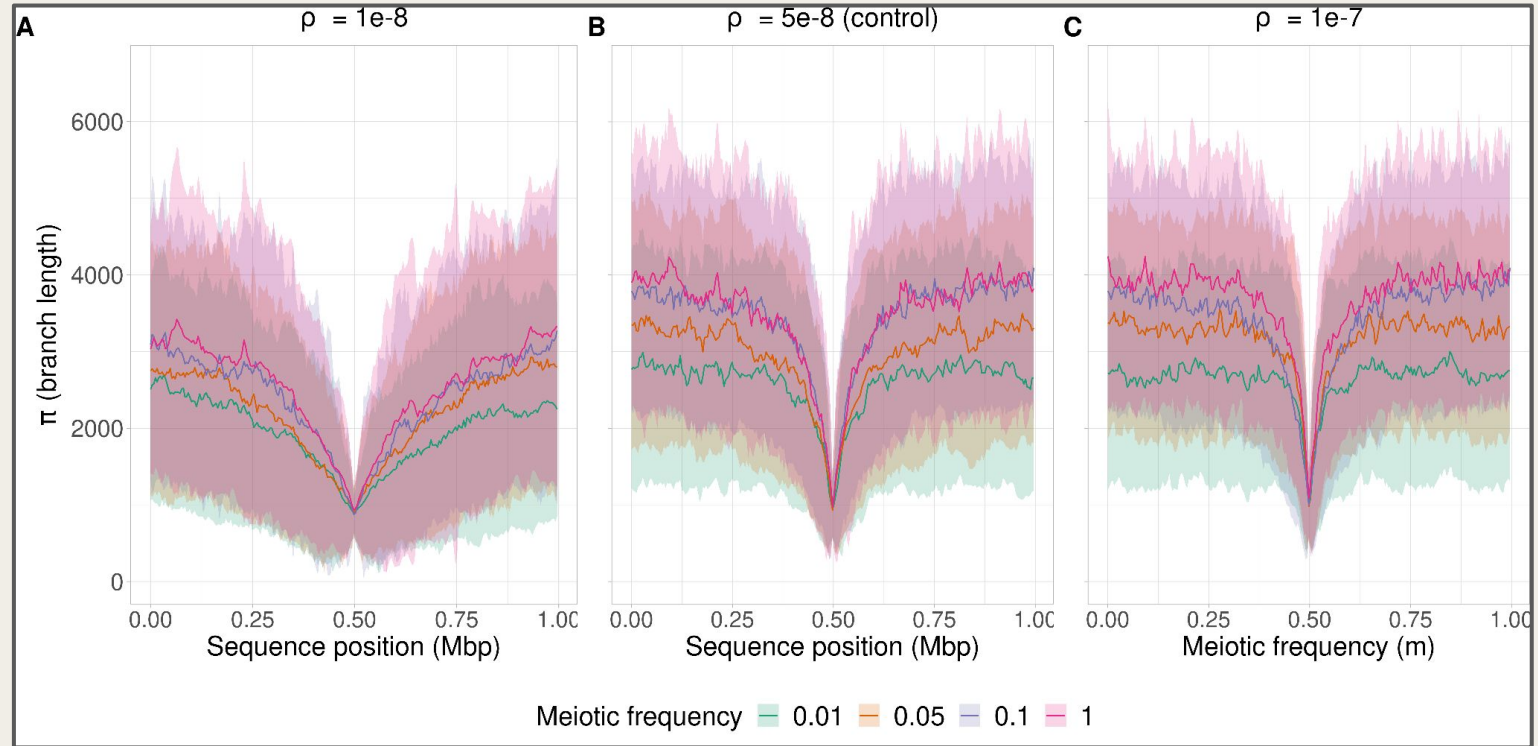
Recombination rate shapes the width of the valley

ρ = recombination rate

lower ρ

higher ρ

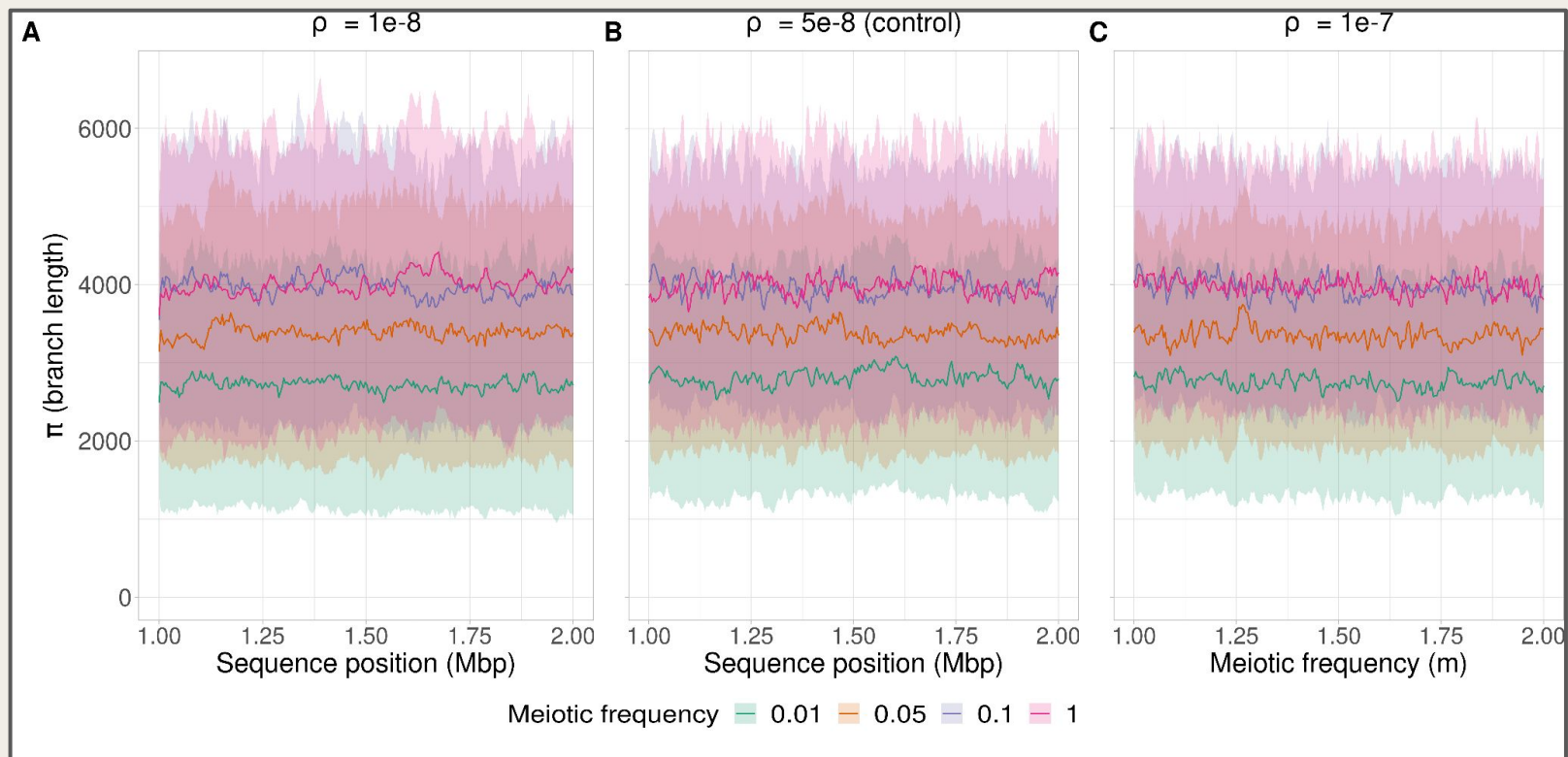
Chromosome 1



➡ Genetic linkage valley widen as ρ decreases \Rightarrow effect on chr 2 ?

Recombination rate shapes the width of the valley

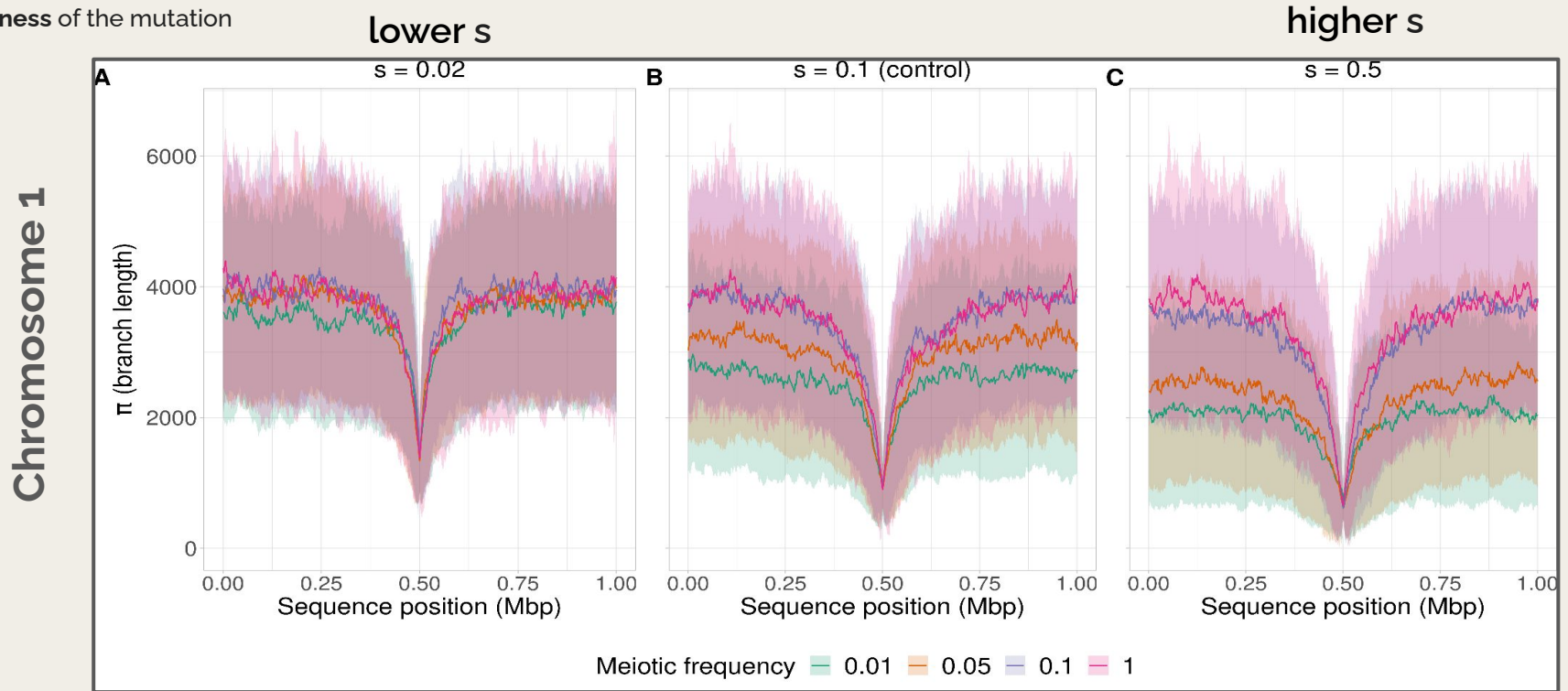
Chromosome 2



⇒ ρ does not influence the plateau

Selection coefficient shapes genome-wide genetic diversity

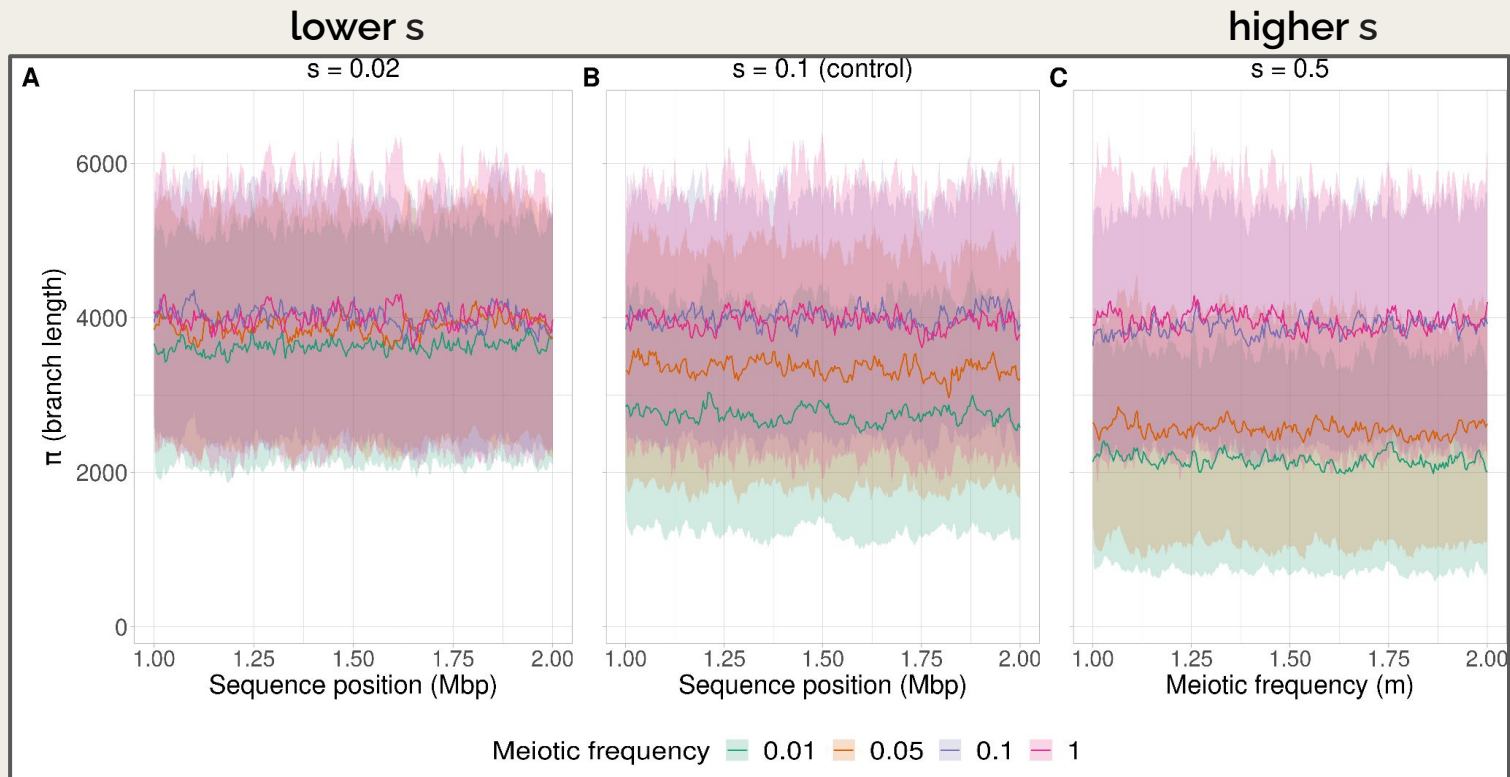
s = selection coefficient
⇒ fitness of the mutation



⇒ Difference in π between m increases with s ⇒ effect on chr 2 ?

Selection coefficient shapes genome-wide genetic diversity

Chromosome 2

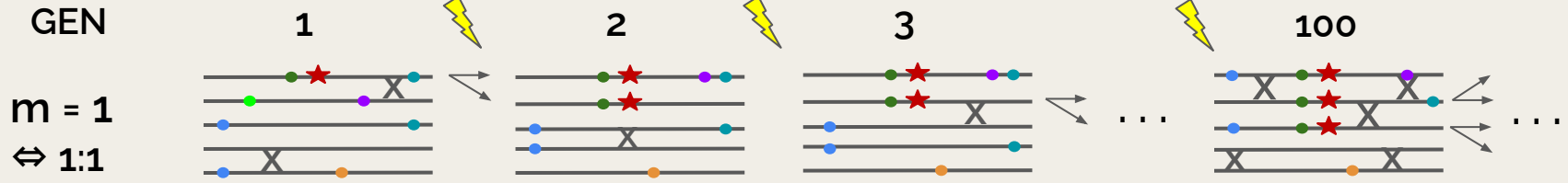


➔ s influences the plateau

DISCUSSION



Why is there a drop in genetic diversity ?

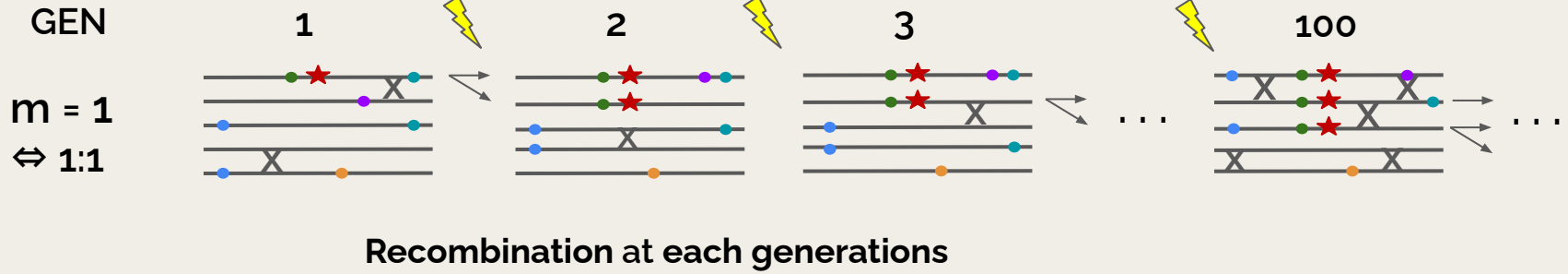


Recombination at each generations

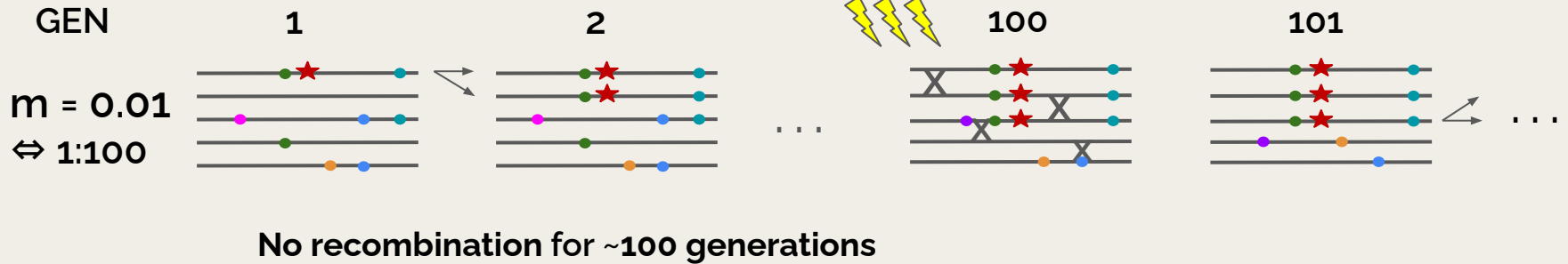


Introduction at 10%
+ neutral mutations

Why is there a drop in genetic diversity ?



 Introduction at 10%
+ neutral mutations

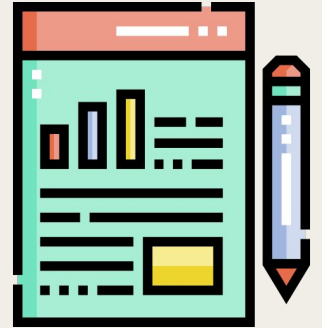


In presence of selective sweep:

⇒ ρ dictates the width

⇒ For low m : m & s dictate the plateau level

⇒ genome-wide linkage on genetic diversity



In presence of selective sweep:

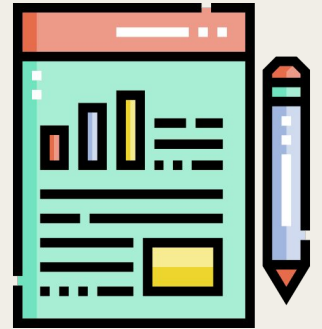
⇒ ρ dictates the width

⇒ For low m : m & s dictate the plateau level

⇒ genome-wide linkage on genetic diversity

Perspectives

- mathematical model
- recurrent selective sweep
- hard sweep
- effect of other parameters (h , N_e)



Acknowledgement

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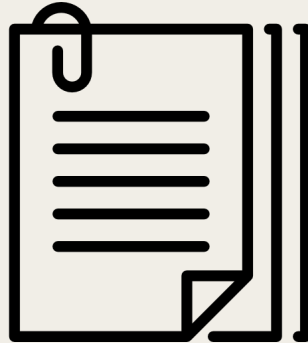
Gilles FISCHER
Zhou Xu

Région
île de France

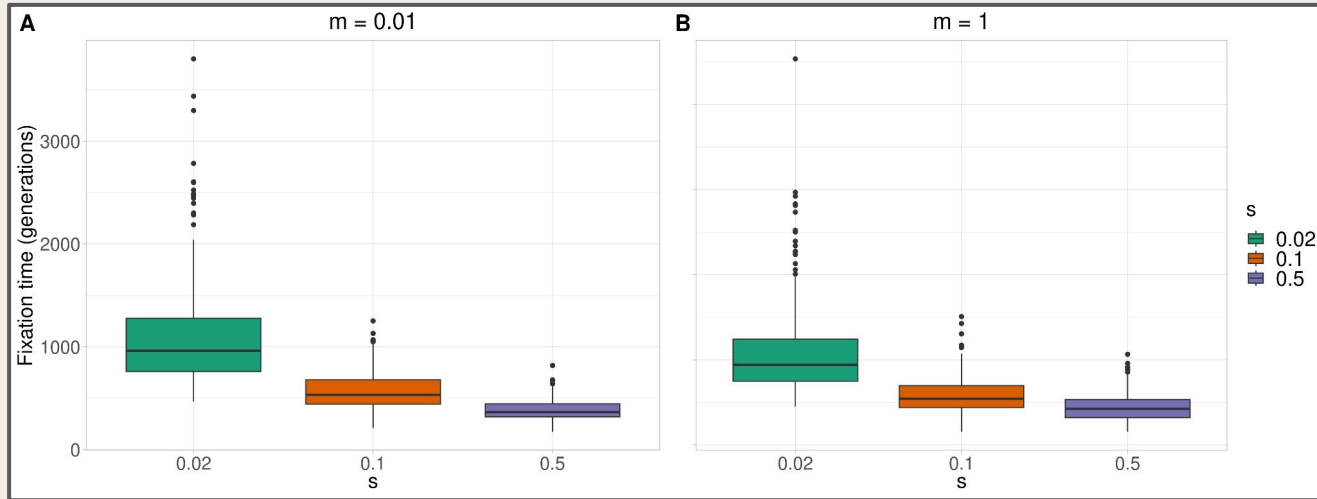


This work has been supported by the Paris Île-de-France Région in the framework of DIM AI4IDF

APPENDIX

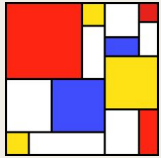


Effect of s



⇒ Faster to reach fixation ⇒ less recombination events

SLiM



[1]

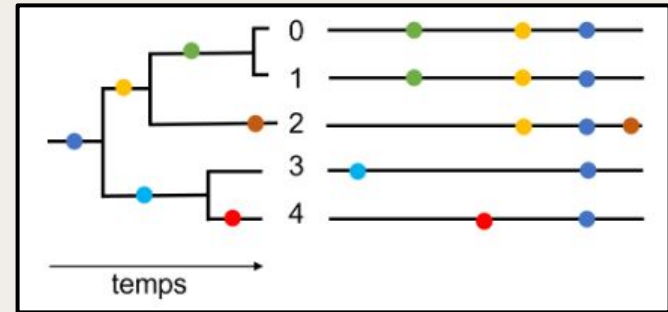
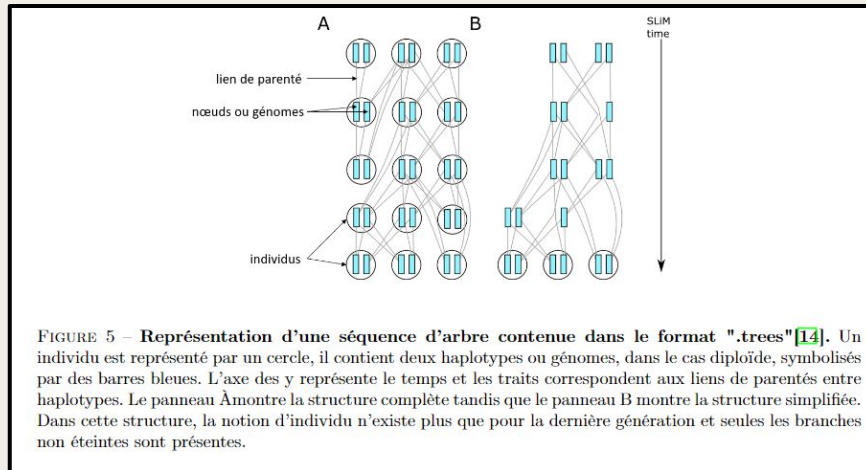
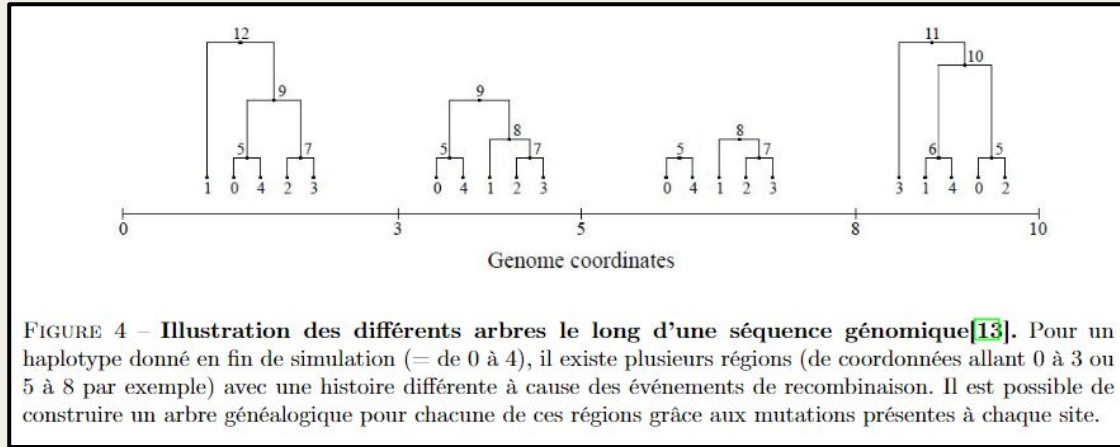
SLiM is an evolutionary simulation framework that combines a powerful engine for population genetic simulations with the capability of modeling arbitrarily complex evolutionary scenarios.

```
1 // set up a simple neutral simulation
2 initialize() {
3     initializeMutationRate(1e-7);
4
5     // m1 mutation type: neutral
6     initializeMutationType("m1", 0.5, "f", 0.0);
7
8     // g1 genomic element type: uses m1 for all mutations
9     initializeGenomicElementType("g1", m1, 1.0);
10
11    // uniform chromosome of length 100 kb with uniform recombination
12    initializeGenomicElement(g1, 0, 99999);
13    initializeRecombinationRate(1e-8);
14 }
15
16 // create a population of 500 individuals
17 1 early() {
18     sim.addSubpop("p1", 500);
19 }
20
21 // output all fixed mutations at end
22 2000 late() { sim.outputFixedMutations(); }
```

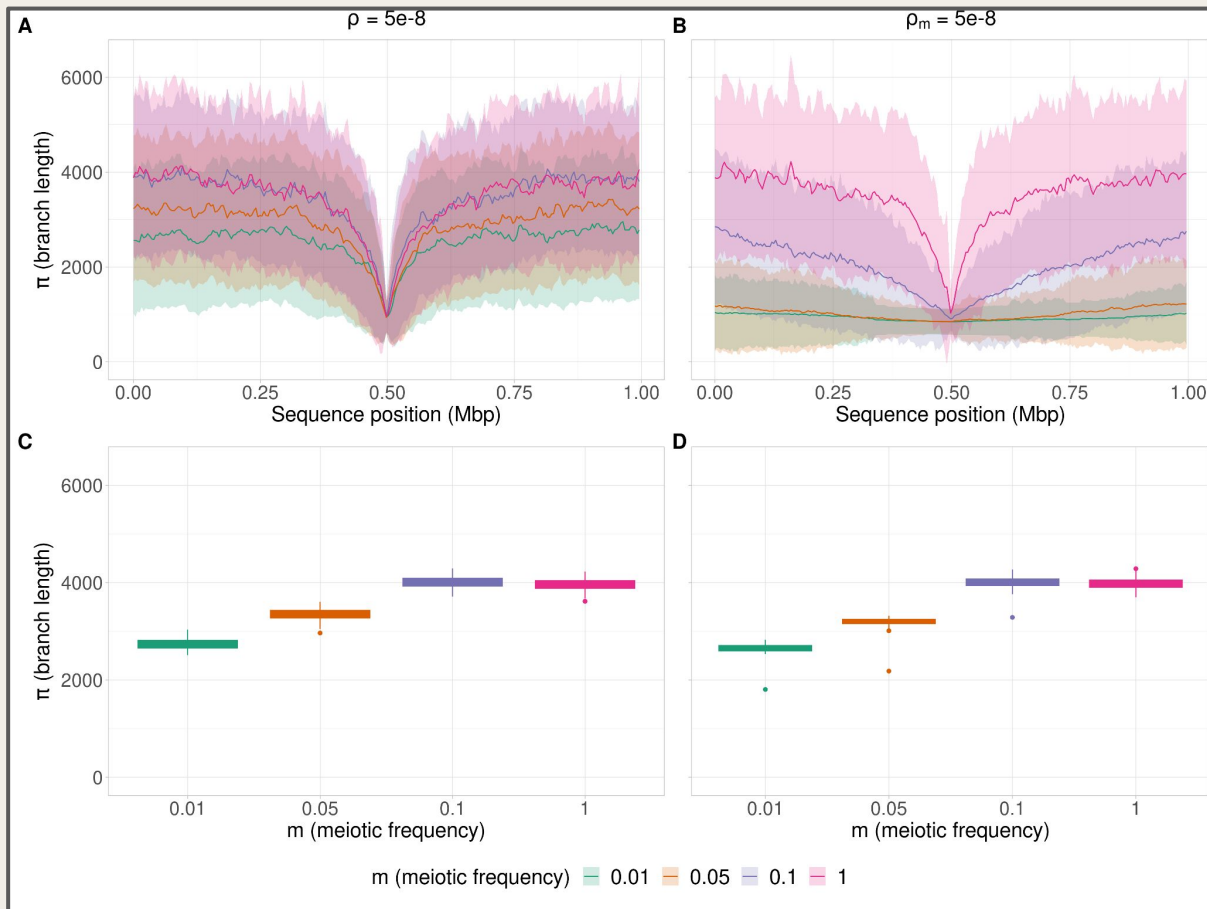


```
44 10024 m1 52555 0 0.5 p1 1911 1
43 18971 m1 20163 0 0.5 p1 1926 1
39 19184 m1 16207 0 0.5 p1 1947 1
48 19244 m1 48776 0 0.5 p1 1953 1
49 19276 m1 51292 0 0.5 p1 1956 1
26 19408 m1 65075 0 0.5 p1 1972 1
37 19450 m1 892 0 0.5 p1 1975 1
32 19650 m1 9360 0 0.5 p1 1994 1
6 19696 m1 45316 0 0.5 p1 1999 1
Genomes:
p1:0 A 0 1 2 3 4 5 6 7 8 9 10 11 12
p1:1 A 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
p1:2 A 32 0 33 1 2 3 4 5 8 9 10 11 34 12
p1:3 A 0 1 2 35 3 4 5 7 8 9 10 11 36 12
p1:4 A 0 33 1 2 3 4 5 8 9 10 11 12
p1:5 A 37 0 33 1 2 3 4 5 8 9 10 11 12
p1:6 A 38 39 40 41 42 3 4 5 27 30
p1:7 A 13 14 15 16 17 18 19 20 43 21 22 23 24 44 45 25 46 27 28 29
30 31
p1:8 A 0 33 1 2 3 4 47 5 48 49 8 9 10 11 12
p1:9 A 0 1 2 35 3 4 5 27 30
#OUT: 2000 2000 F
Mutations:
0 769 m1 60898 0 0.5 p1 78 1212
1 2891 m1 70215 0 0.5 p1 286 1302
```

Tree sequence



Unscaled recombination rate



Fixation time different rho

