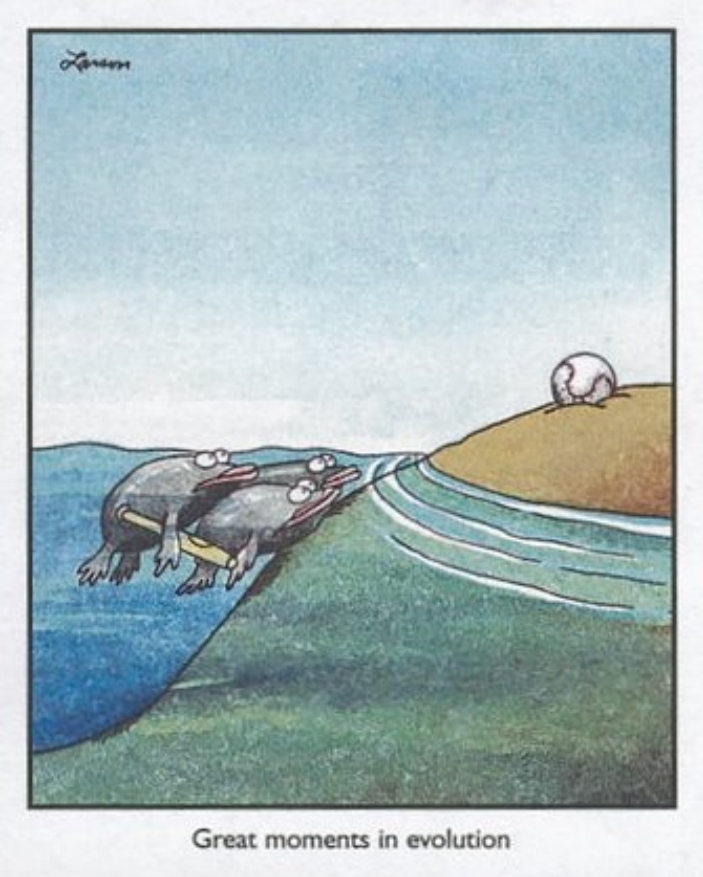
A Characterization of Adaptive Mutations in Yeast



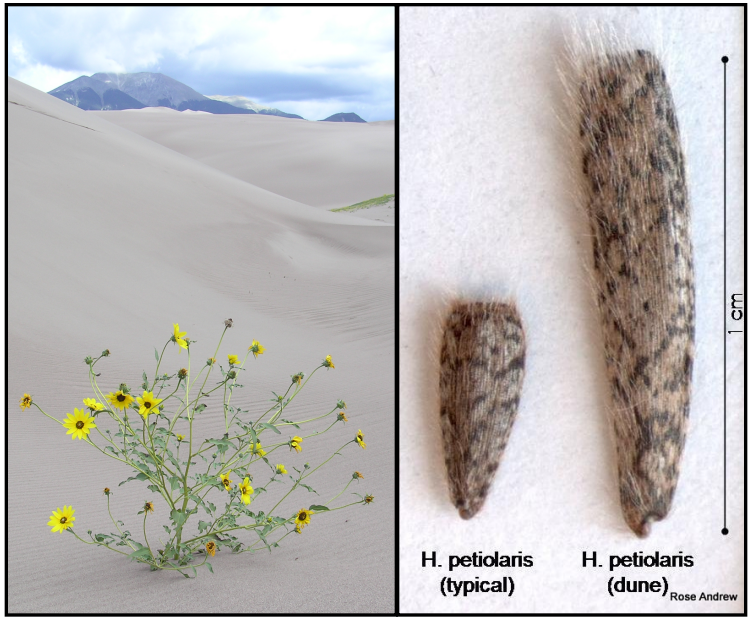
Aleeza Gerstein

Biodiversity Research Centre &
Department of Zoology

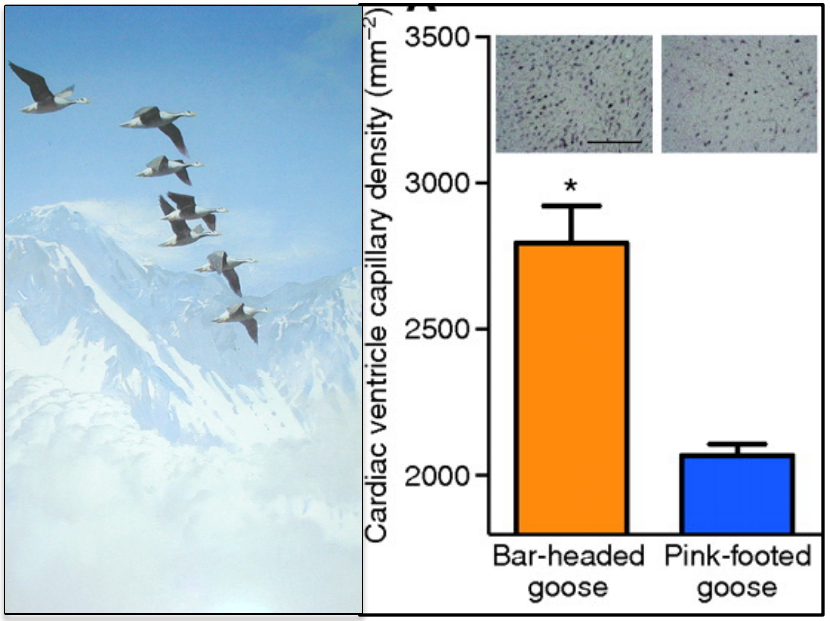
The University of British Columbia

Adaptive traits enable one species/population/individual to outperform another.

We know a lot about some of the traits that enable adaptation.

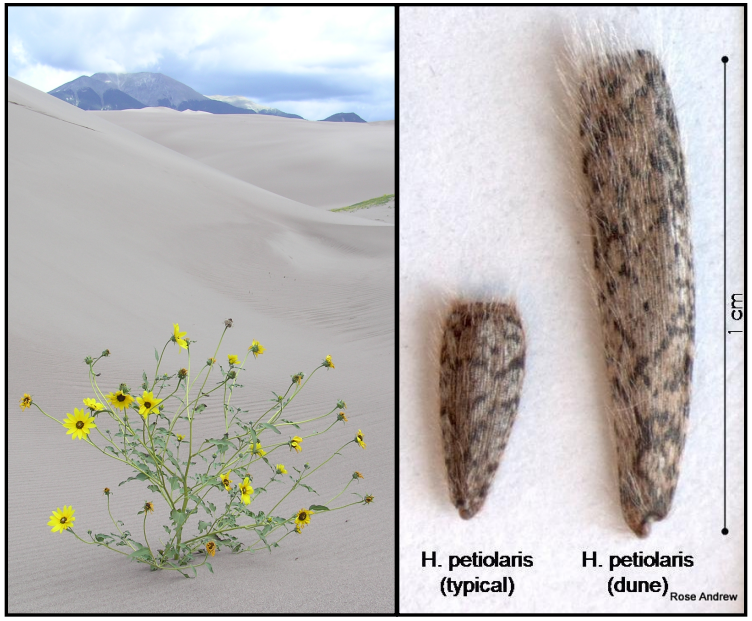


Rose Andrew & Kate Ostevik (Rieseberg/Otto)



Graham Scott (*J Exp Biol*, 2011)

We know a lot about some of the traits that enable adaptation, but much less about the attributes of beneficial mutations.



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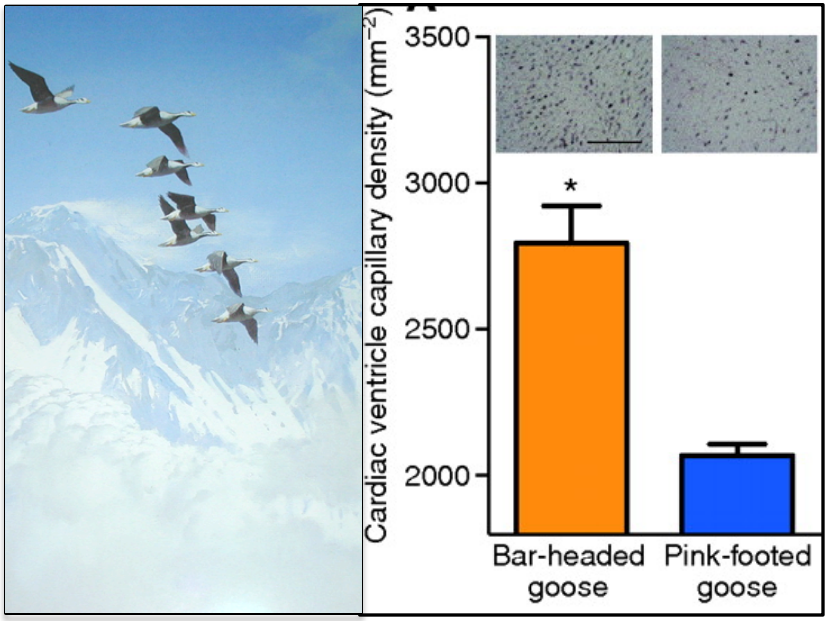
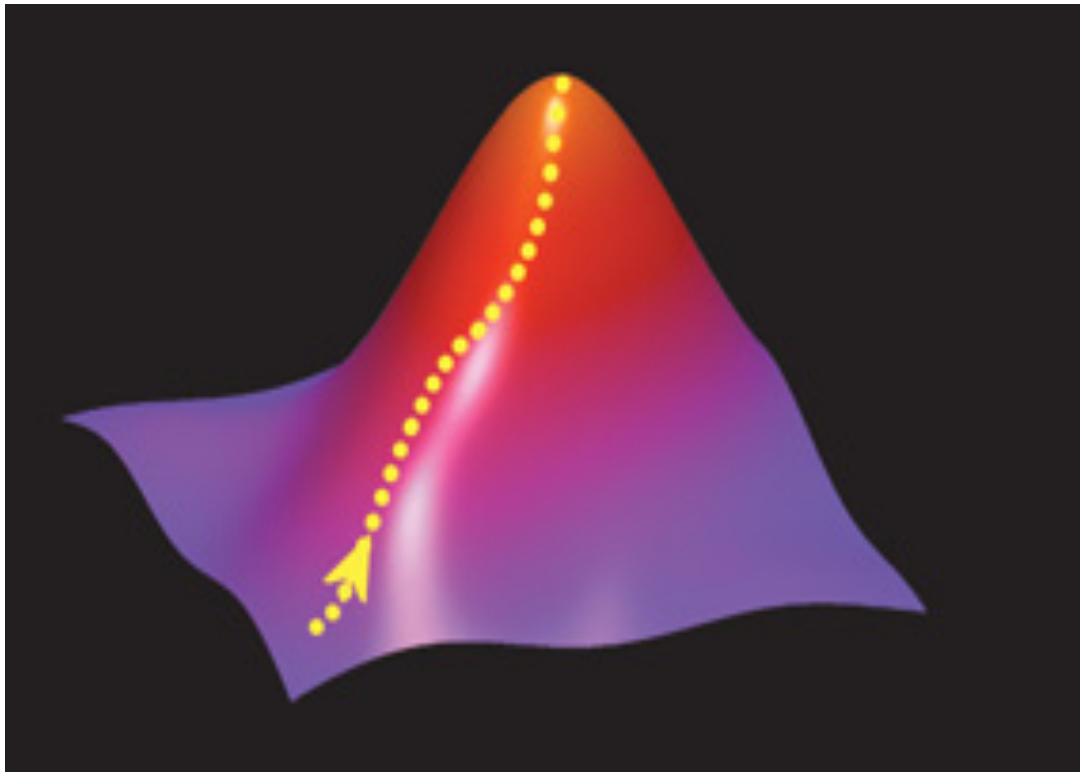


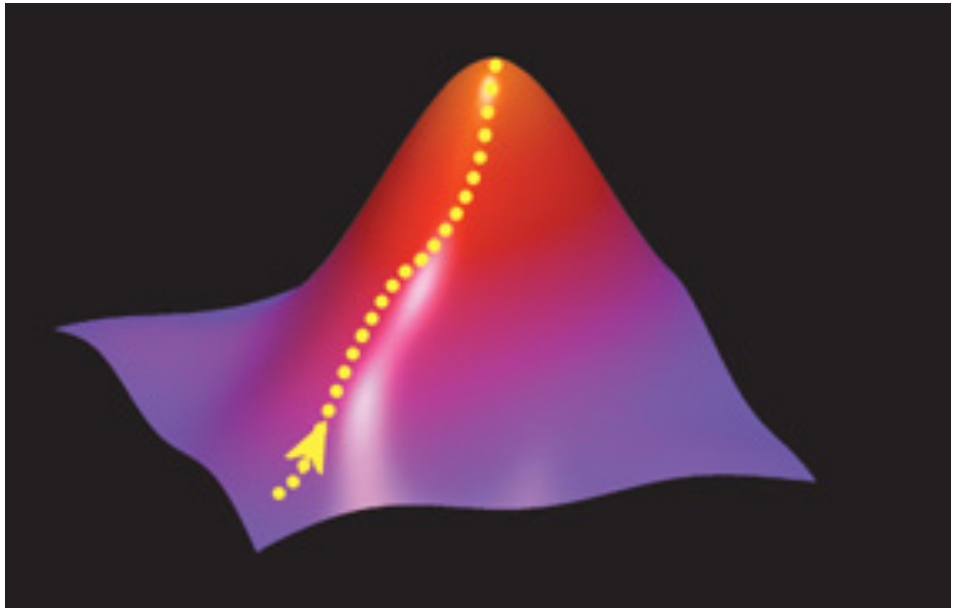
Graham Scott (*J Exp Biol*, 2011)

Many factors affect the appearance and spread of beneficial mutations



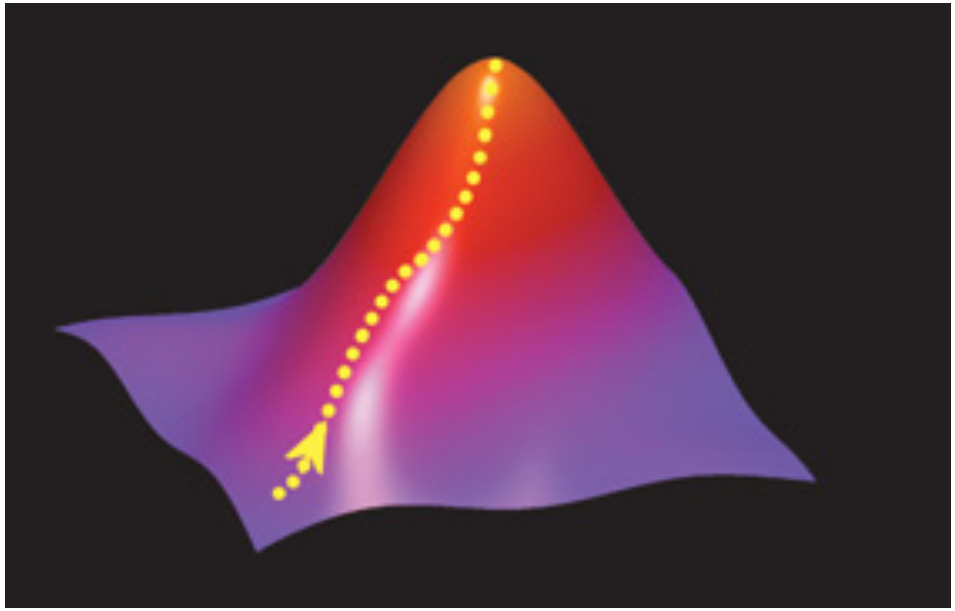
Many factors affect the appearance and spread of beneficial mutations

- Rate new mutations arise
  - Population size (N)
  - Mutation rate (μ)



Many factors affect the appearance and spread of beneficial mutations

- Rate new mutations arise
    - Population size (N)
    - Mutation rate (μ)
- Mutation effect size



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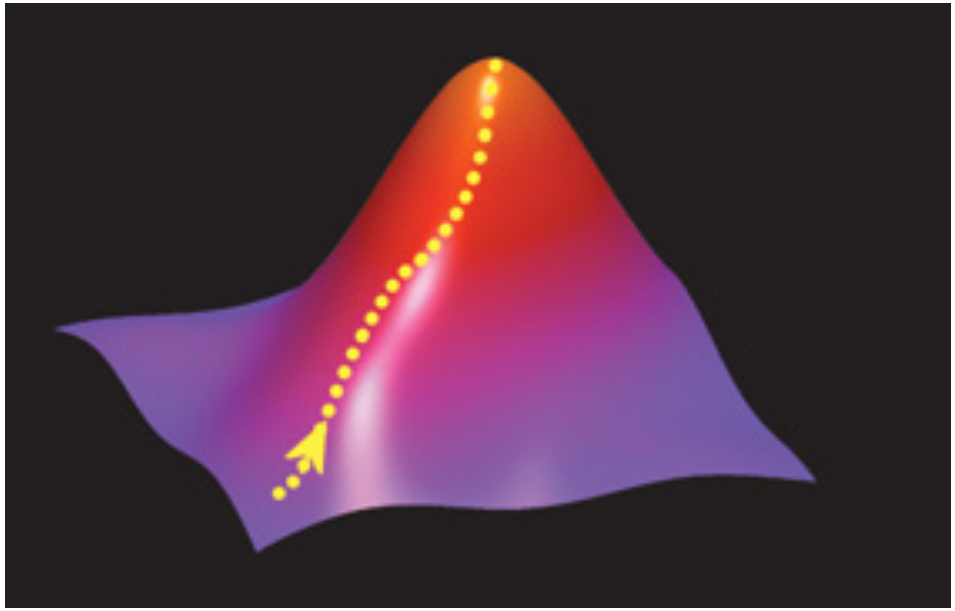
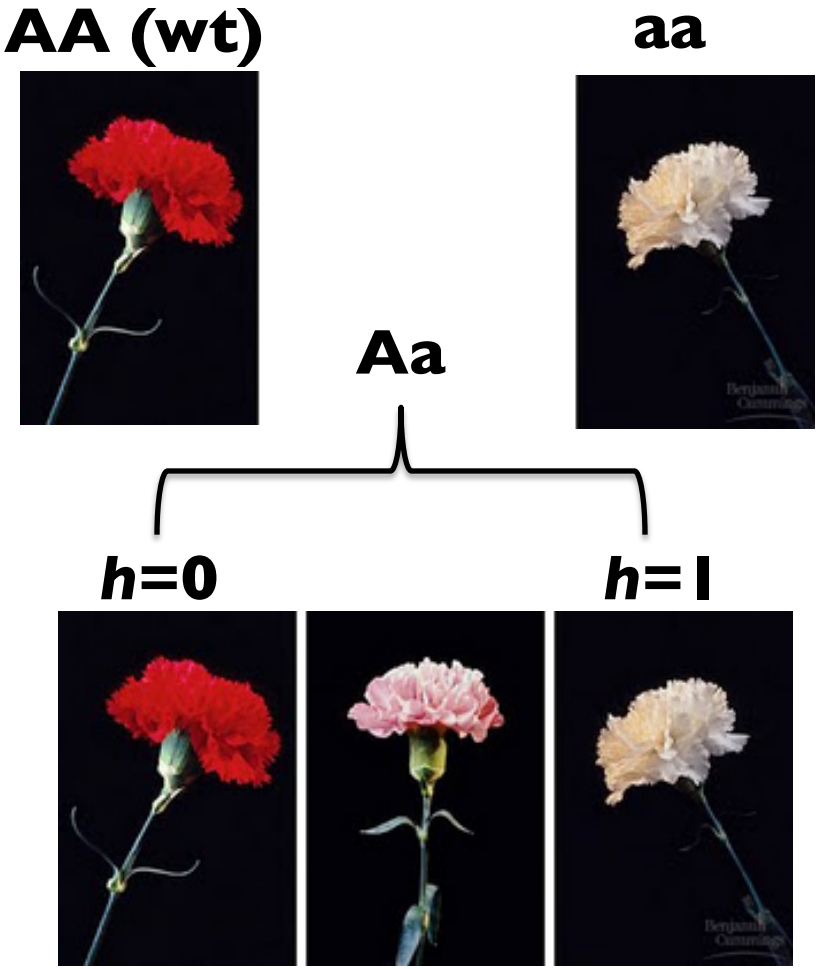


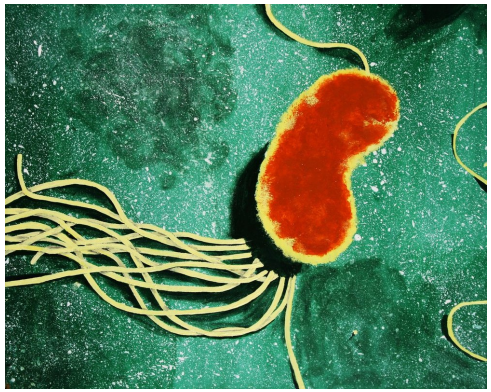
Many factors affect the appearance and spread of beneficial mutations

- Rate new mutations arise
  - Population size (N)
  - Mutation rate (μ)
- Mutation effect size
- Available mutations
- Dominance (*h*)

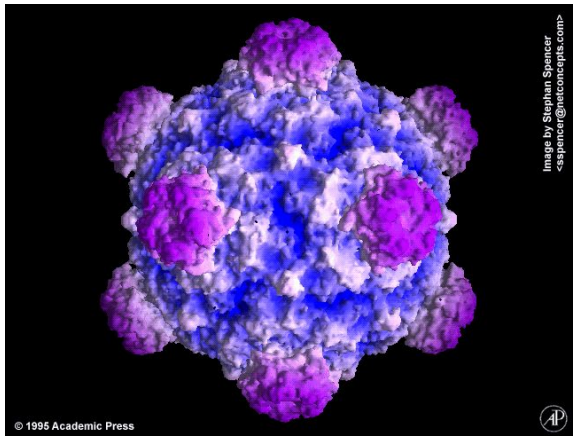


Use microorganisms to study adaption ‘forward’ in time.

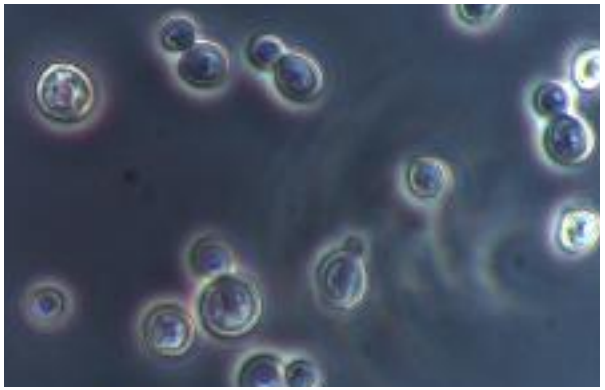
Pseudomonas

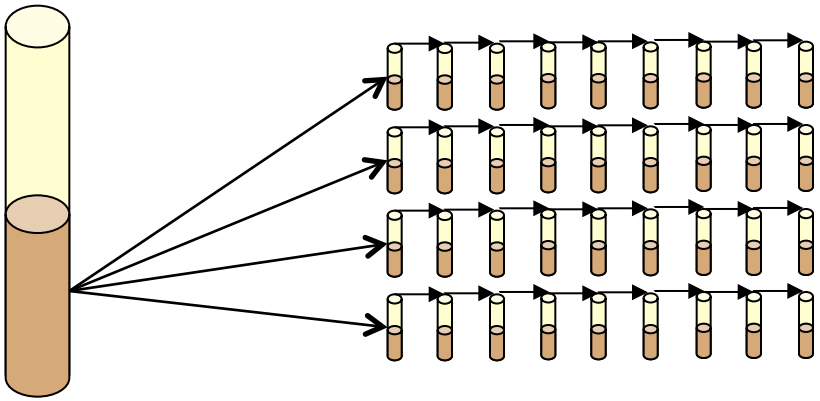


ΦX174 (phage)



Saccharomyces





Research Theme 1: The effect of ploidy on adaptation

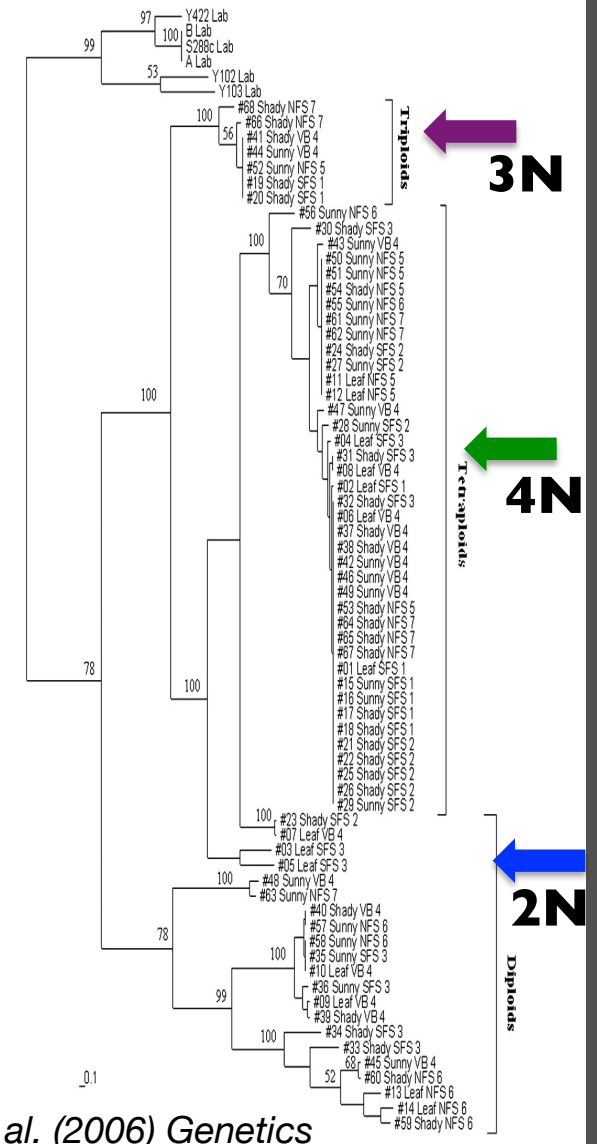
Haploid – Male honey bee

Diploid– Female honey bee

Haploid/Diploid – *Ulva lactuca*

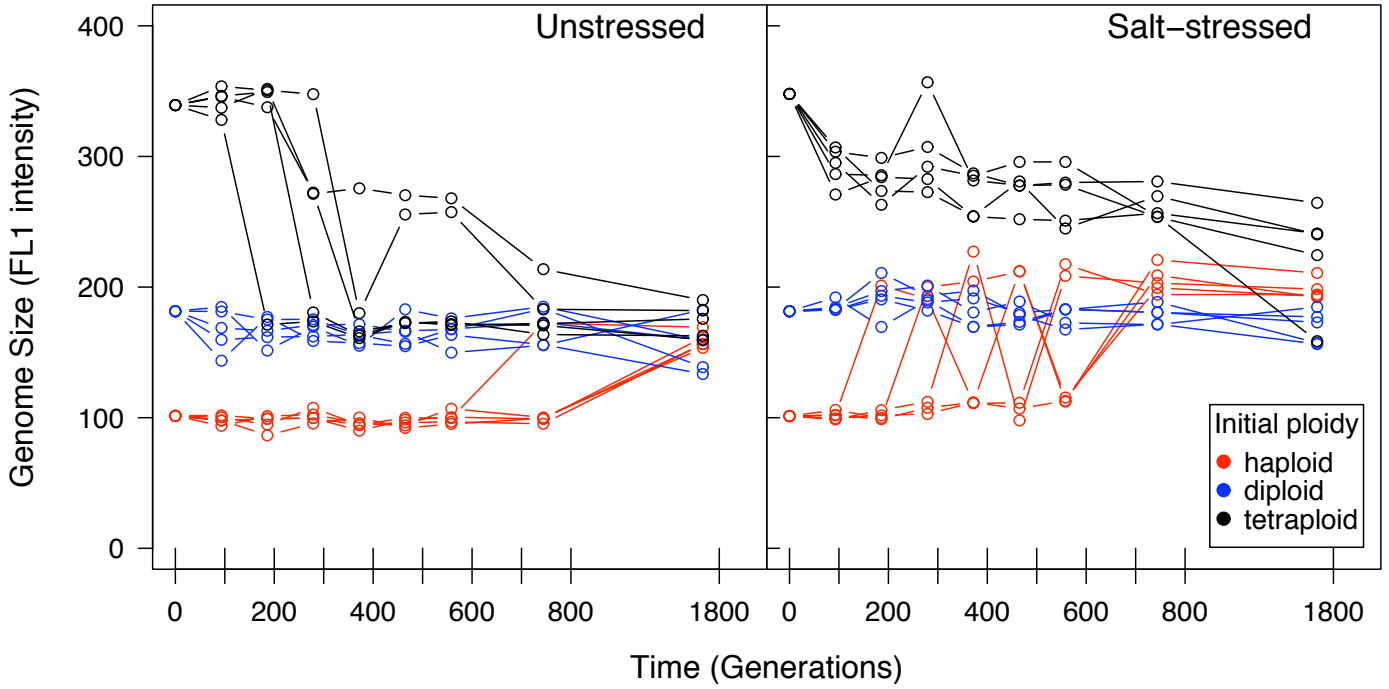
Haploid – *Mastocarpus papillatus* (gametophyte)

Diploid– *Mastocarpus papillatus* (sporophyte)



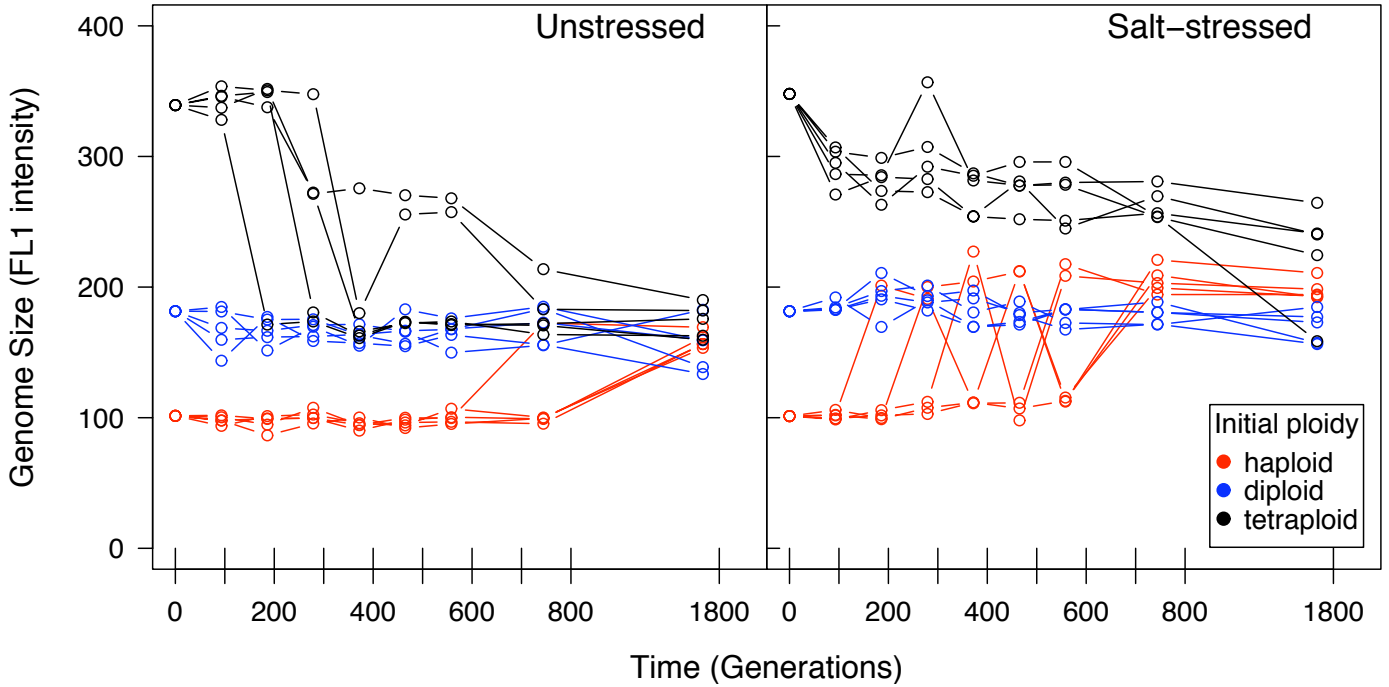
Ezov et al. (2006) Genetics

Theme 1: The effect of ploidy on adaptation



MSc.: *PLoS Genetics (2006)*

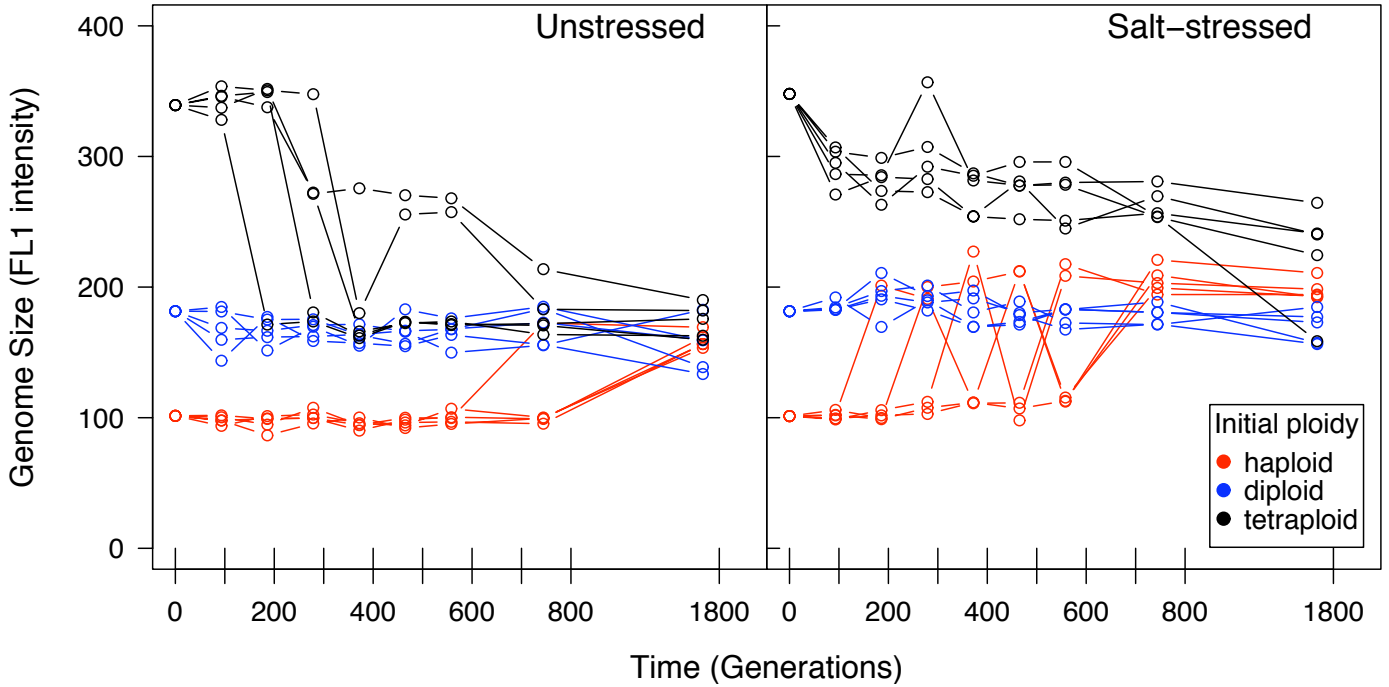
Theme 1: The effect of ploidy on adaptation



What factor(s) allowed diploid mutants to repeatedly invade haploid populations? [*Chapter 2*]

Do haploids or diploids adapt faster to mildly stressful environments? [*Chapter 3*]

Theme 1: The effect of ploidy on adaptation



What factor(s) allowed diploid mutants to repeatedly invade haploid populations? [*Chapter 2*]

Do haploids or diploids adapt faster to mildly stressful environments? [*Chapter 3*]

Do haploids or diploids adapt faster to mildly stressful environments?

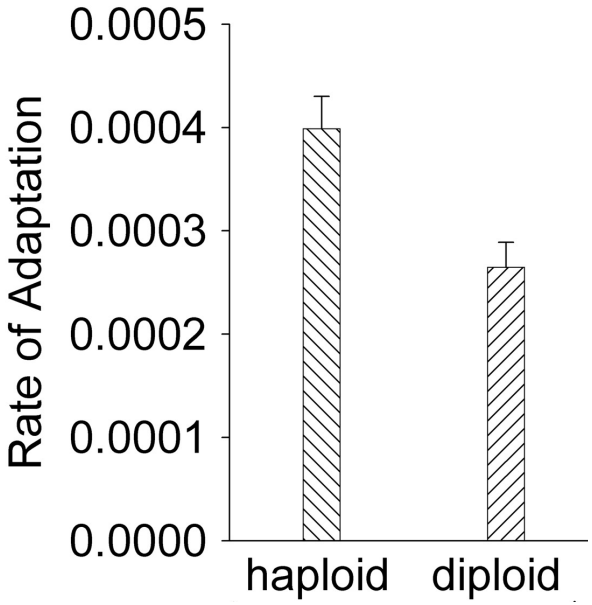
HAPLOIDS (one set of chromosomes):

All mutations immediately "seen" = shorter fixation time.

DIPLOIDS (two sets):

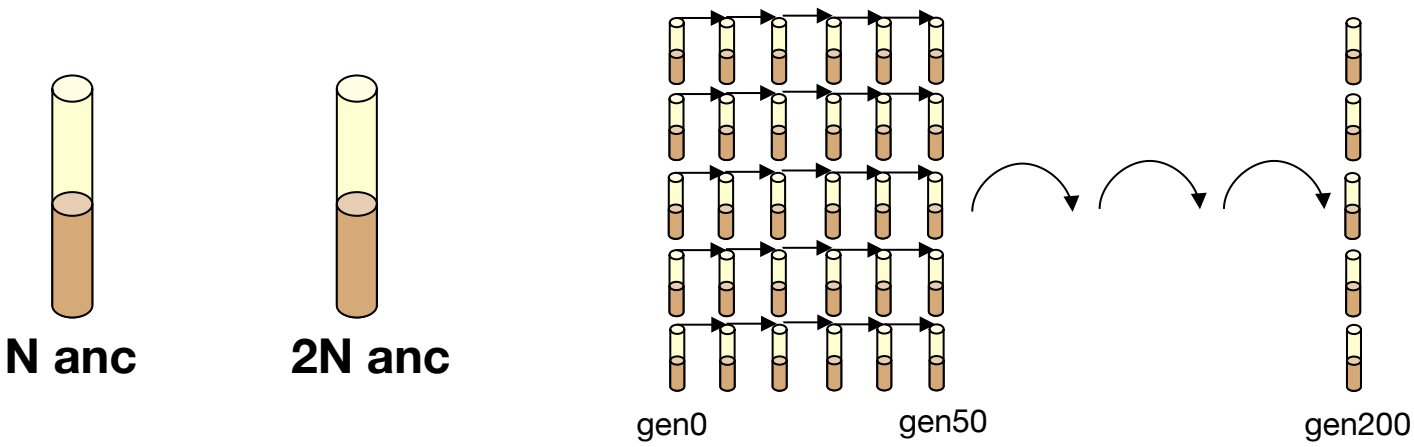
Theoretically twice the mutations rate = shorter waiting time for mutations.

Most mutations at least partially masked (i.e., recessive) = longer fixation time.



Zeyl et. al (2003)

Method: evolve haploids and diploids for 200 generations in seven mildly stressful environments



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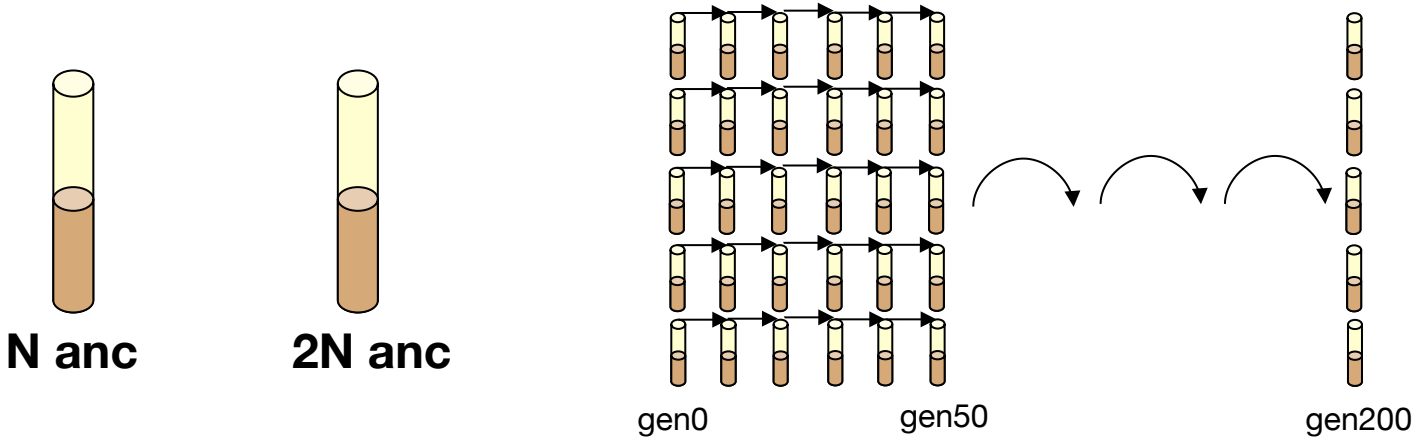
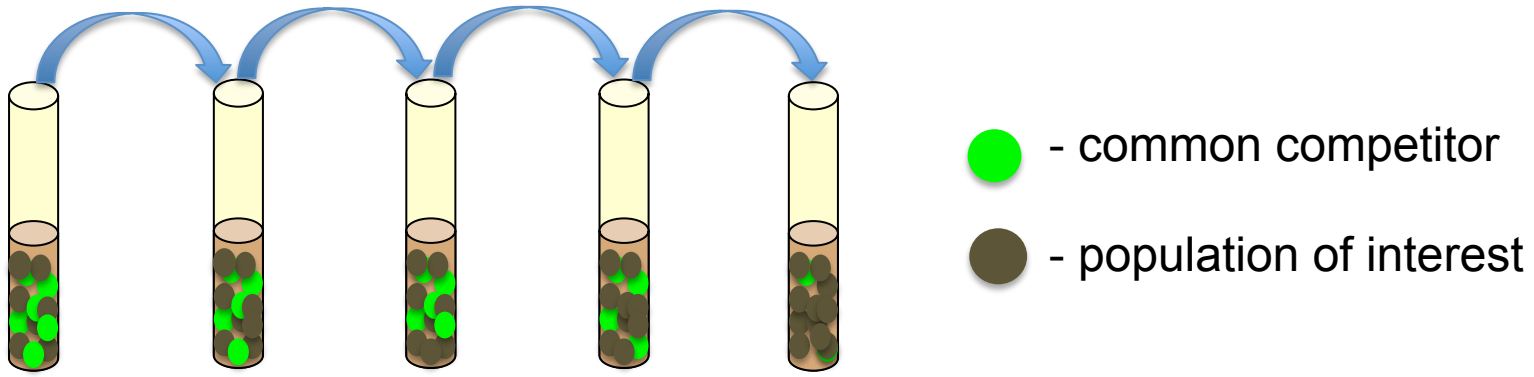
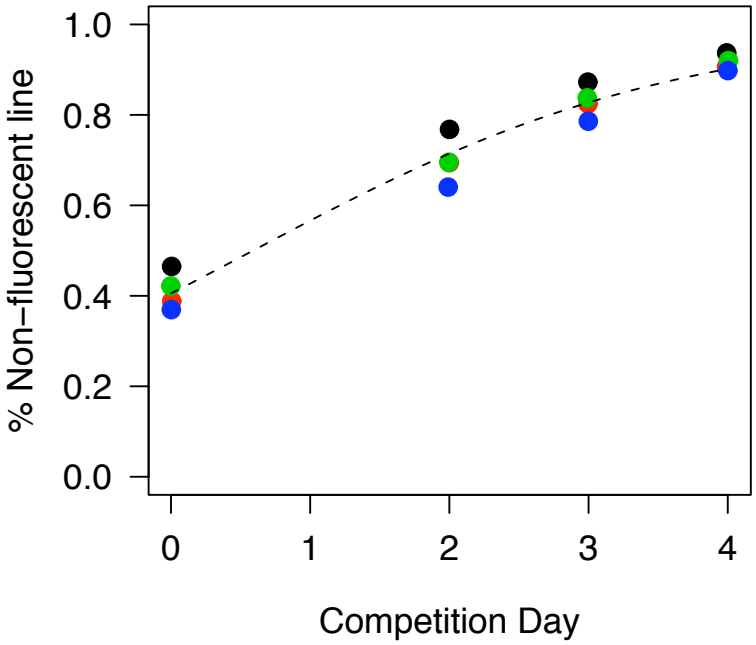


Measure competitive fitness at 50 and 200 generations

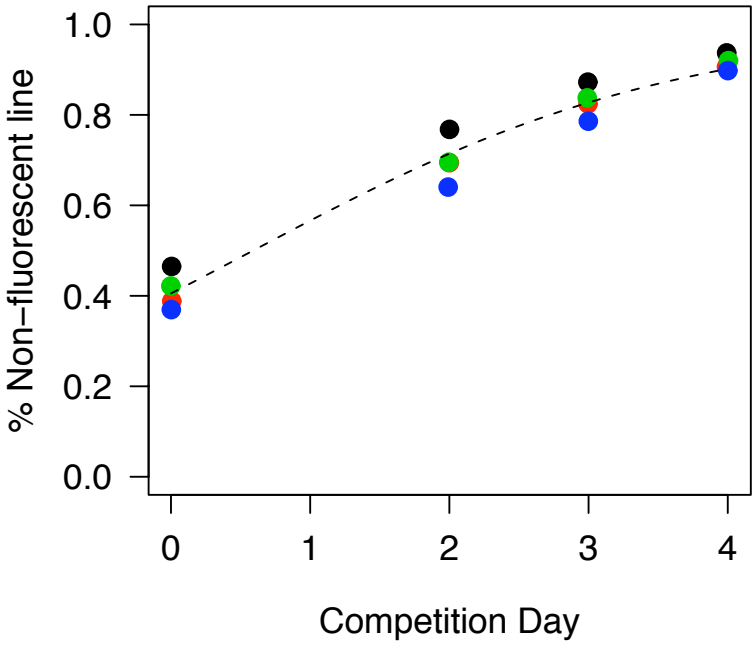


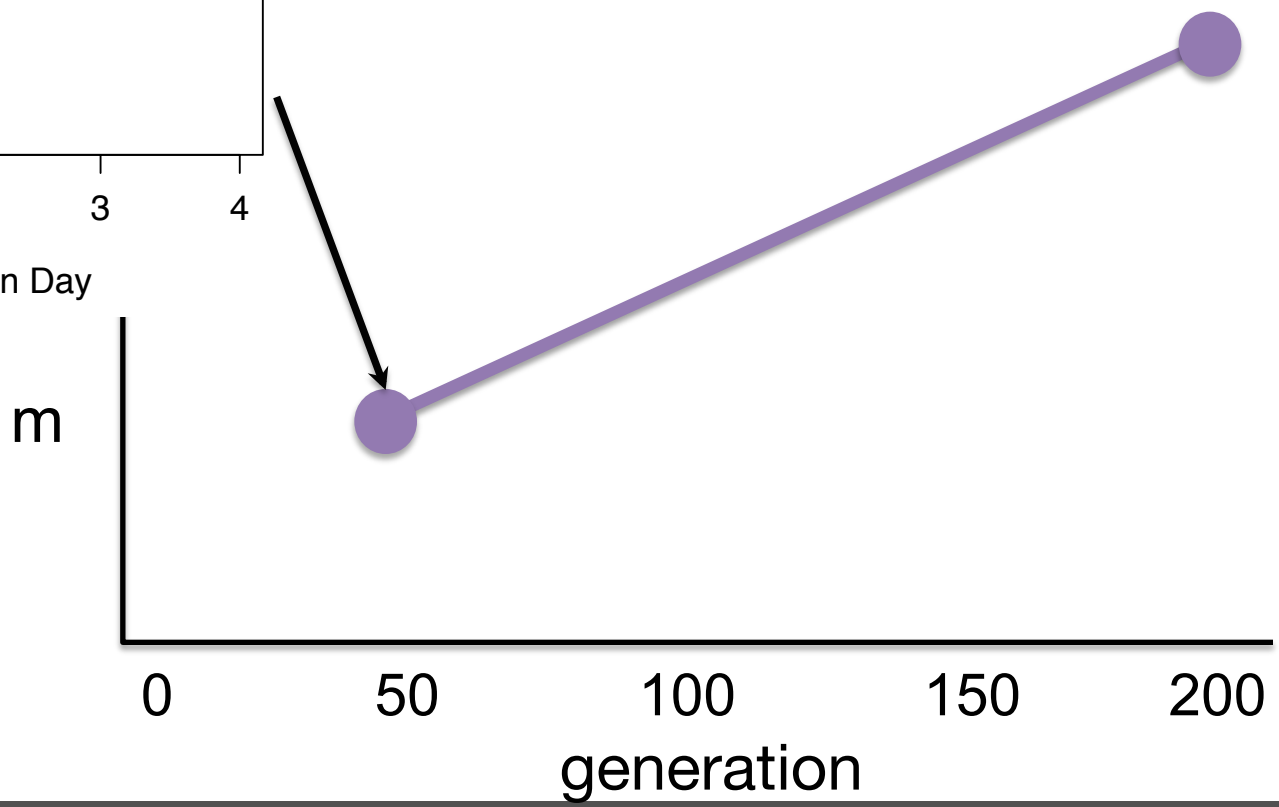
Measure the **rate of adaptation** for each ploidy × environment population.



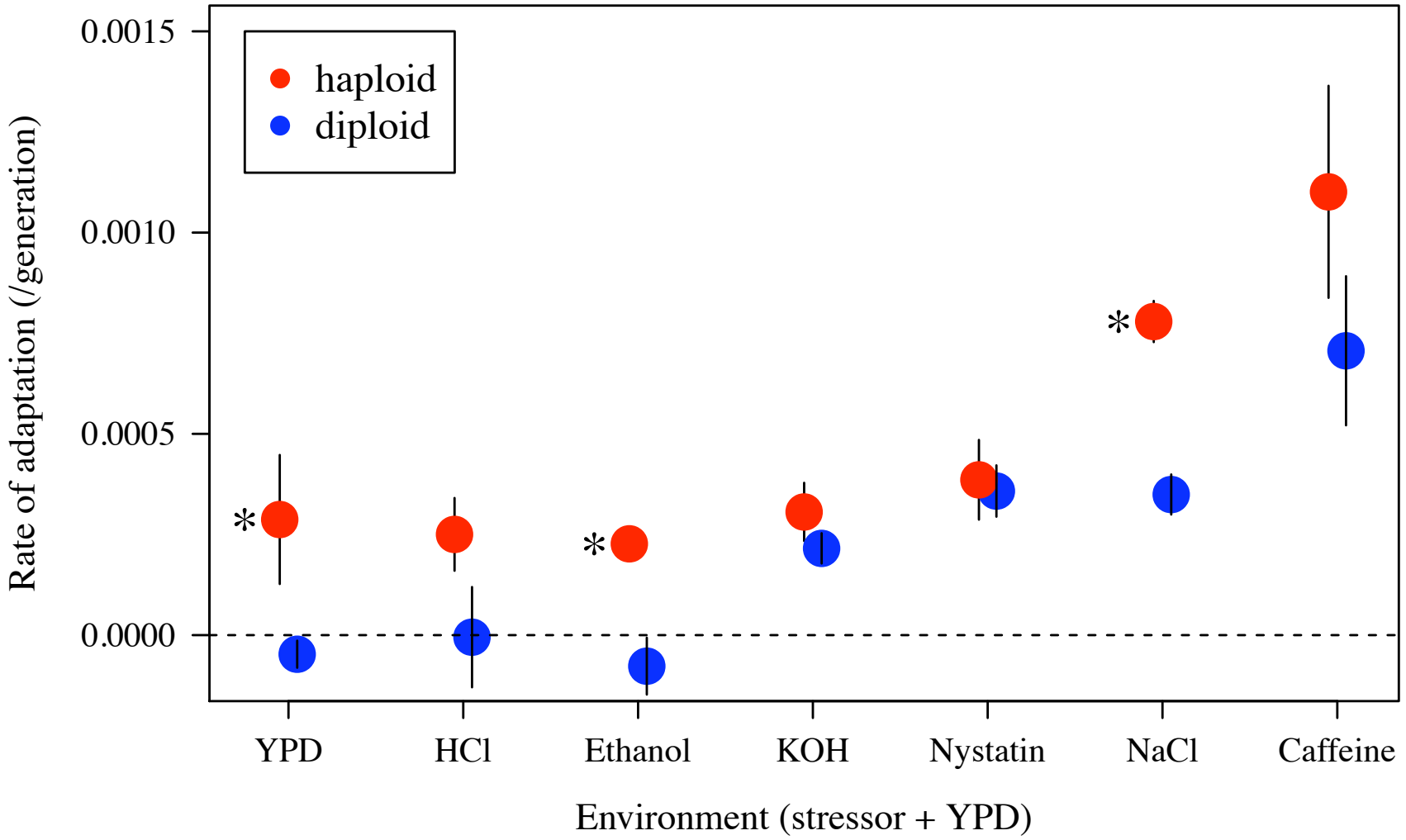
$$\frac{p_0 e^{mt}}{1 - p_0 + p_0 e^{mt}}$$

Measure the **rate of adaptation** for each ploidy × environment population





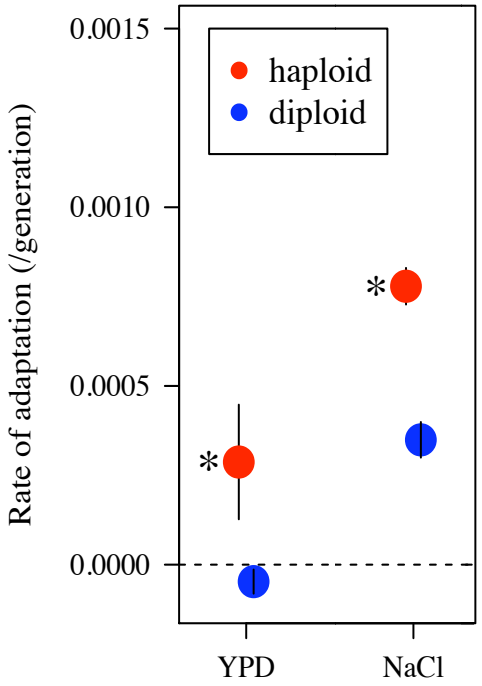
In all environments, haploids adapted faster than diploids.



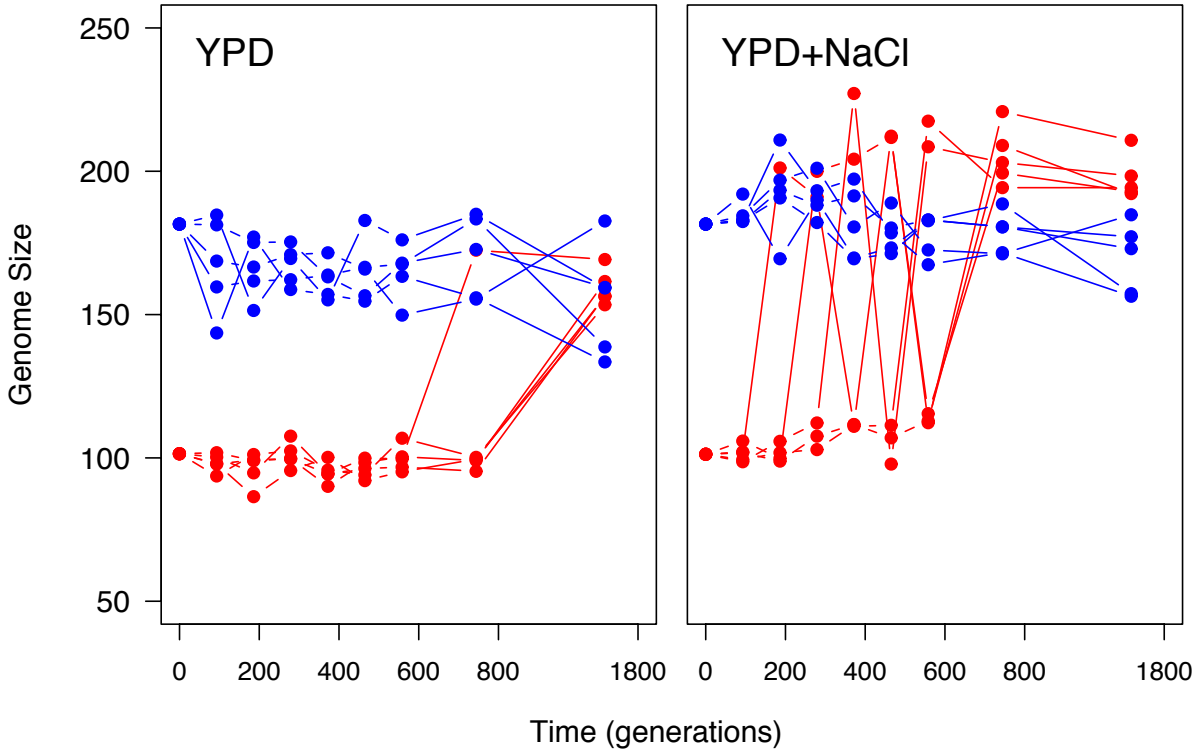
***Chapter 3**: Gerstein et al. J Evol Biol (2011)*

A mystery:

200 generations



1800 generations



Haploids adapt faster . . . but diploids take over haploid populations

MSc.: *Gerstein et al. PLoS Genetics (2006),*
Chapter 2: *Gerstein & Otto PLoS One (2011)*

Why do haploids adapt faster, and why so much variation?

- Initial fitness
- Population size (N)
- Mutation rate (μ)
- Mutation effect size
- Mutation availability
- Dominance

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- **Initial fitness**
- Population size (N)
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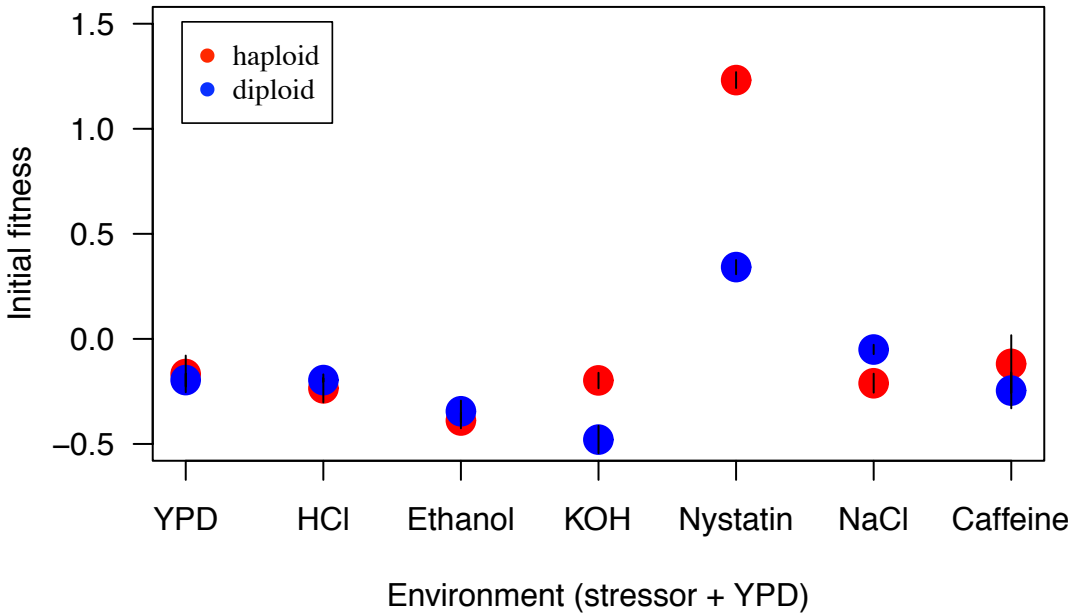

Why do haploids adapt faster, and why so much variation?

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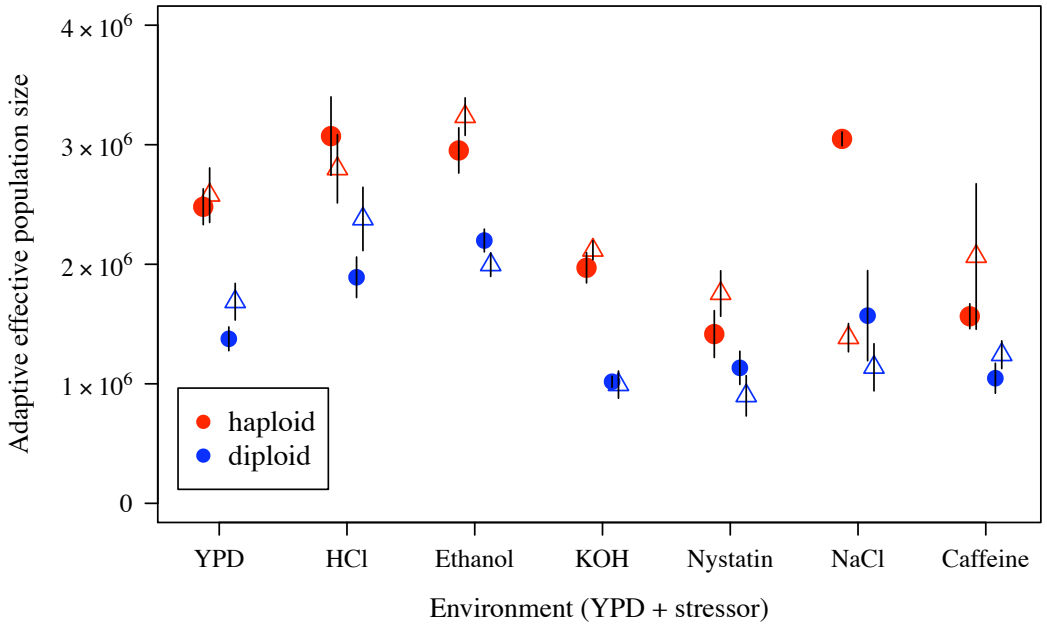

Why do haploids adapt faster, and why so much variation?

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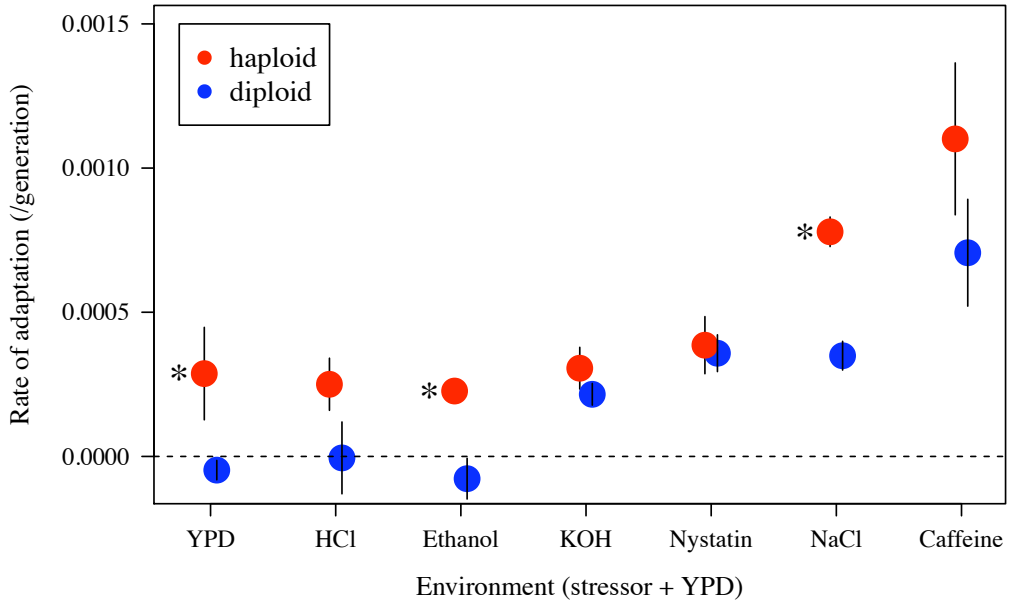
- **Mutation rate (μ)**
- **Mutation effect size**
- **Mutation availability**
- **Dominance**



Why do haploids adapt faster, and why so much variation?

- Initial fitness x
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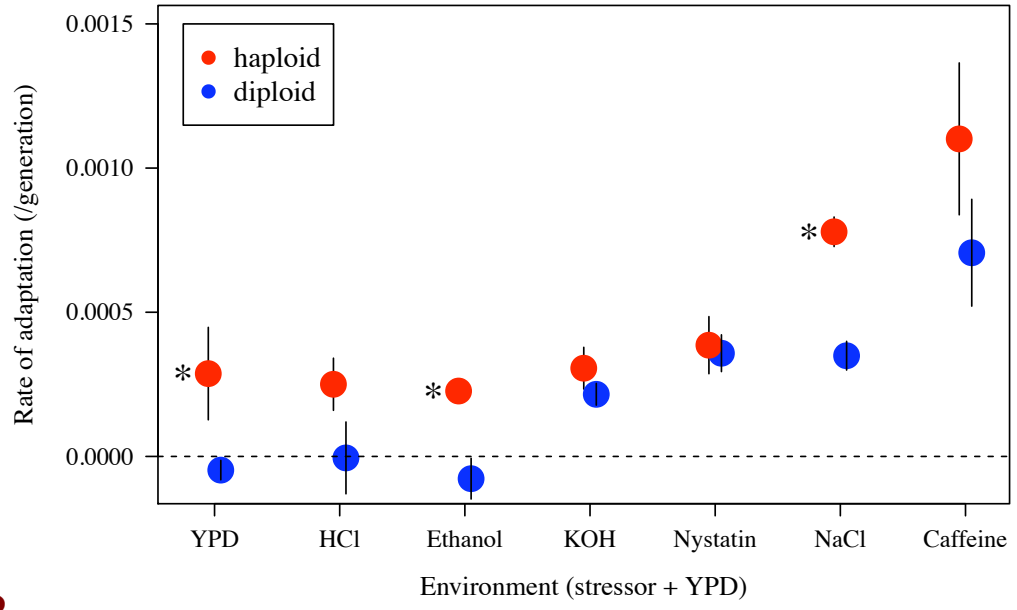
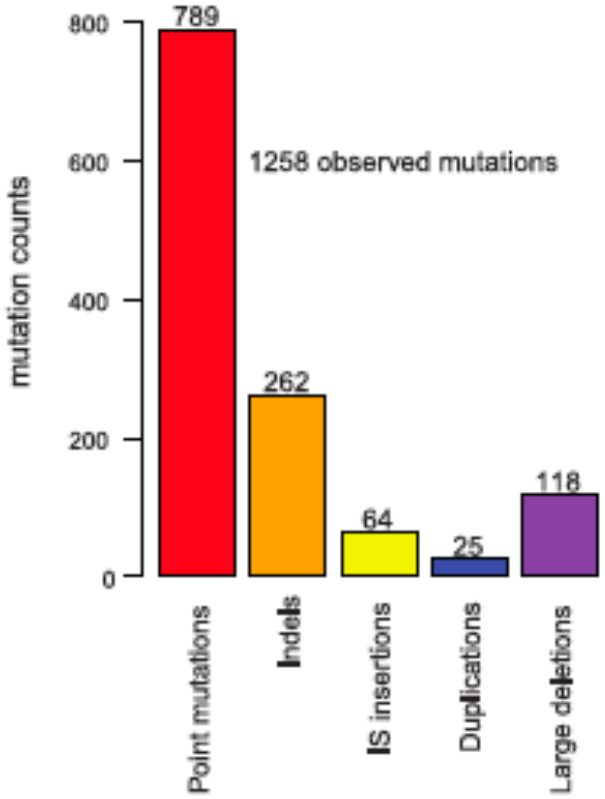
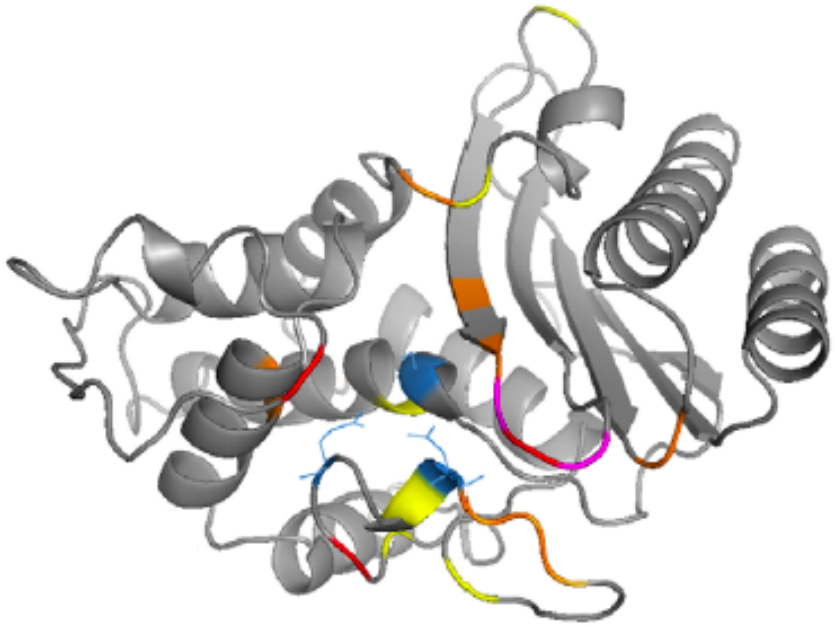
- Dominance ?



Research Theme 2: Characterizing single adaptive mutations in a eukaryote

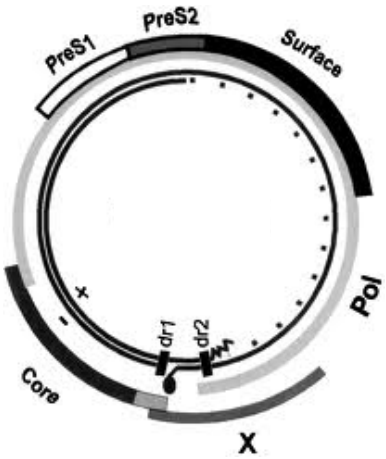


Tenaillon *et. al* 2012
Escherichia coli
115 lines, 2000 generations

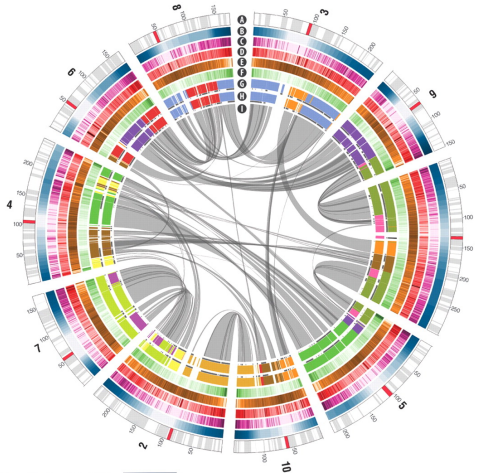


Schenk *et. al* 2012
TEM-1 β-lactamase
48 mutations (mutagenesis)

Theme 2: Characterizing single adaptive mutations

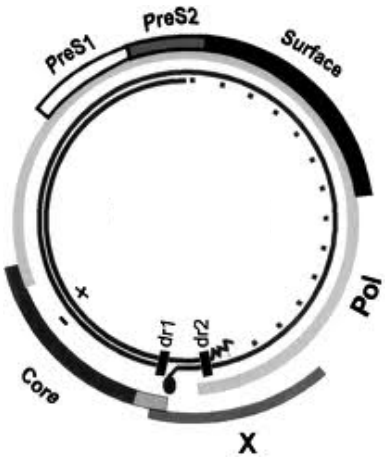


virus (too simple)

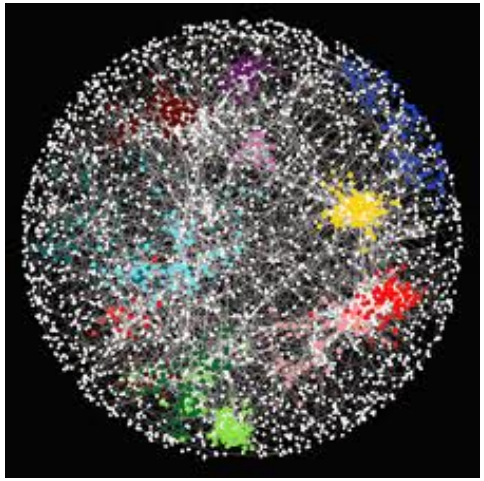


maize (too complex)

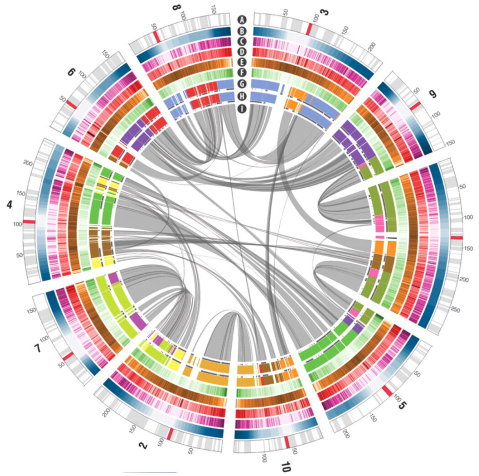
Theme 2: Characterizing single adaptive mutations



virus (too simple)

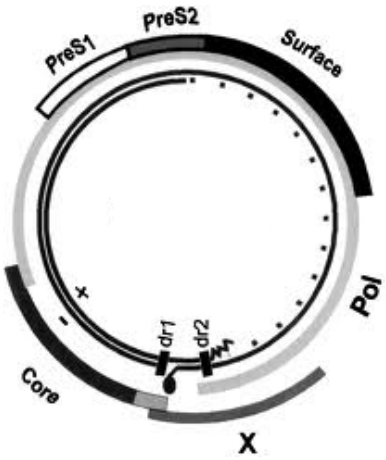


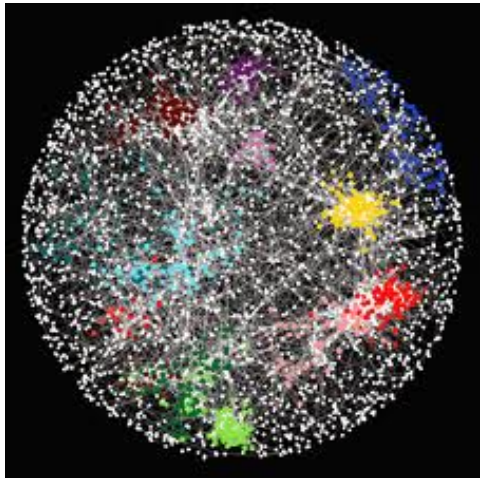
yeast (just right)

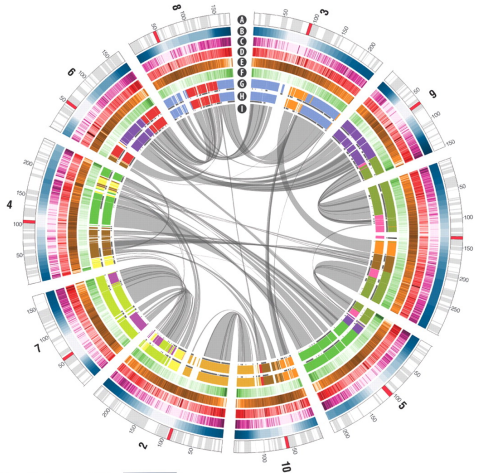


maize (too complex)

Theme 2: Characterizing single adaptive mutations

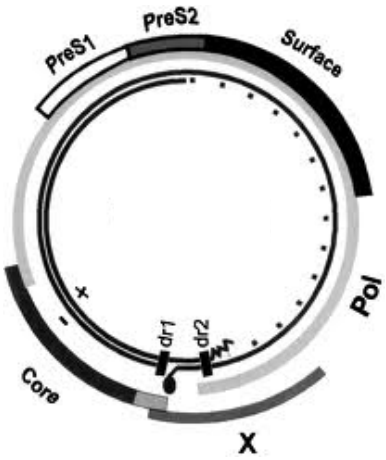


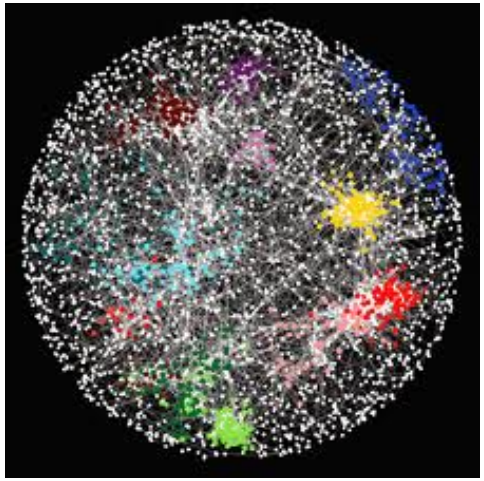


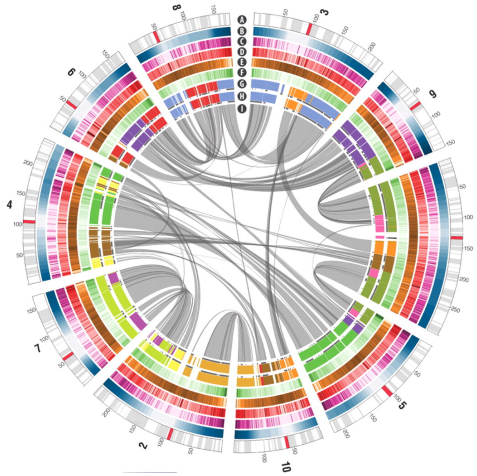


What is the genomic and phenotypic breadth of the first adaptive mutations acquired in response to a novel stressor? [*Chapter 4*]

Theme 2: Characterizing single adaptive mutations



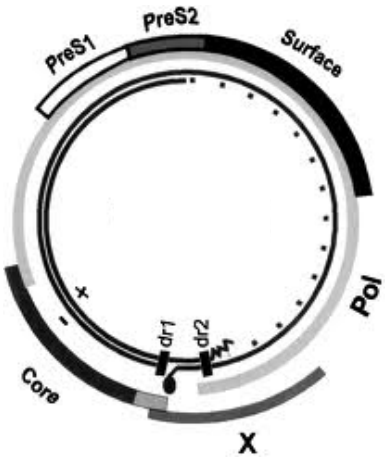


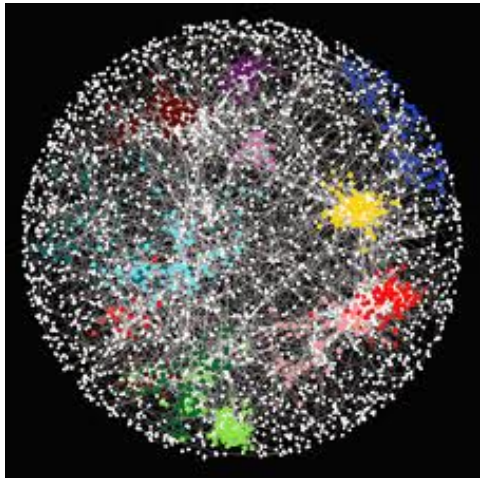


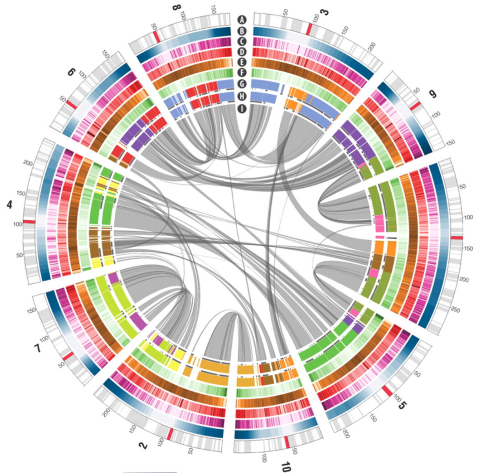
What is the genomic and phenotypic breadth of the first adaptive mutations acquired in response to a novel stressor? [*Chapter 4*]

Do adaptive mutations have the same effect size in haploids and homozygous diploids? [*Chapter 5*]

Theme 2: Characterizing single adaptive mutations





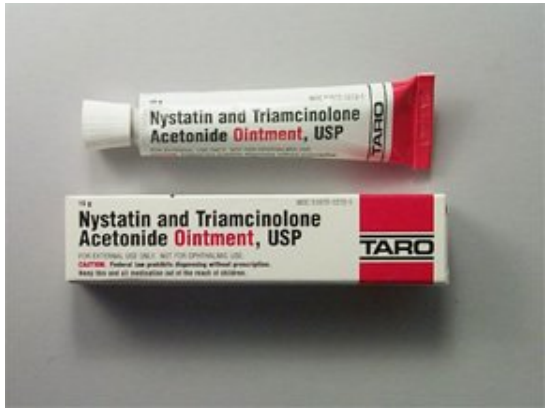


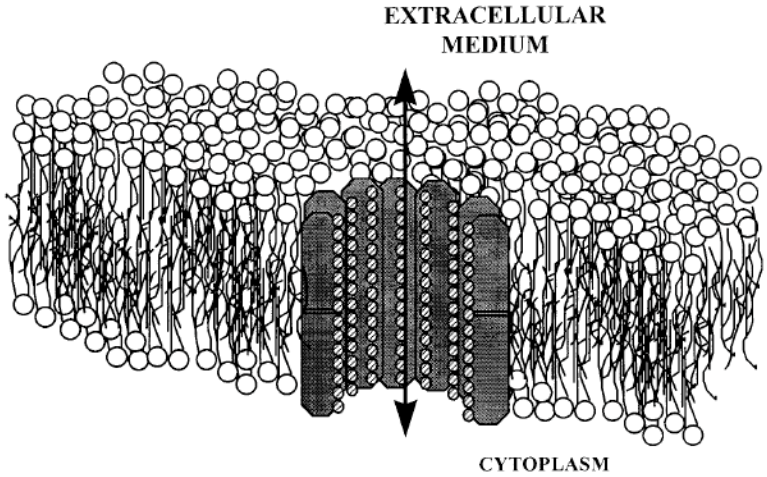
What is the genomic and phenotypic breadth of the first adaptive mutations acquired in response to a novel stressor? [*Chapter 4*]

Do adaptive mutations have the same effect size in haploids and homozygous diploids? [*Chapter 5*]

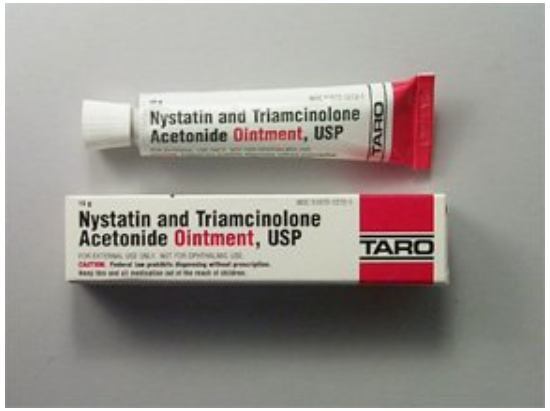
What is the effect of zygosity on adaptive mutations? [*Chapter 6*]

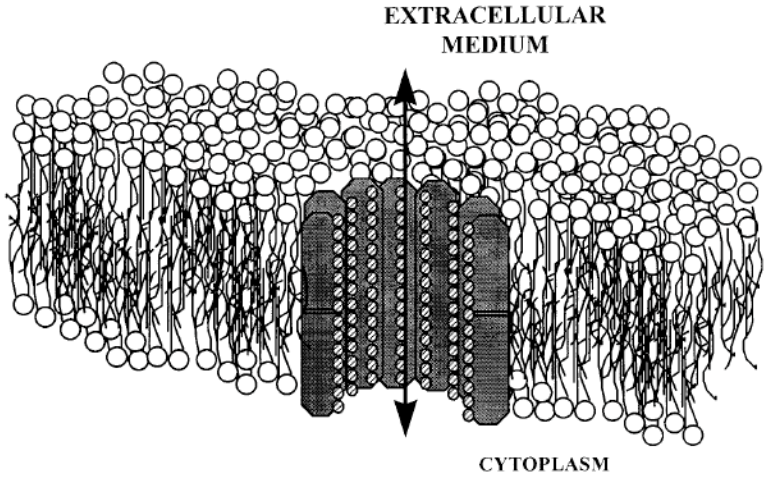
Method: Isolate the first-step mutations that arise in response to nystatin stress.

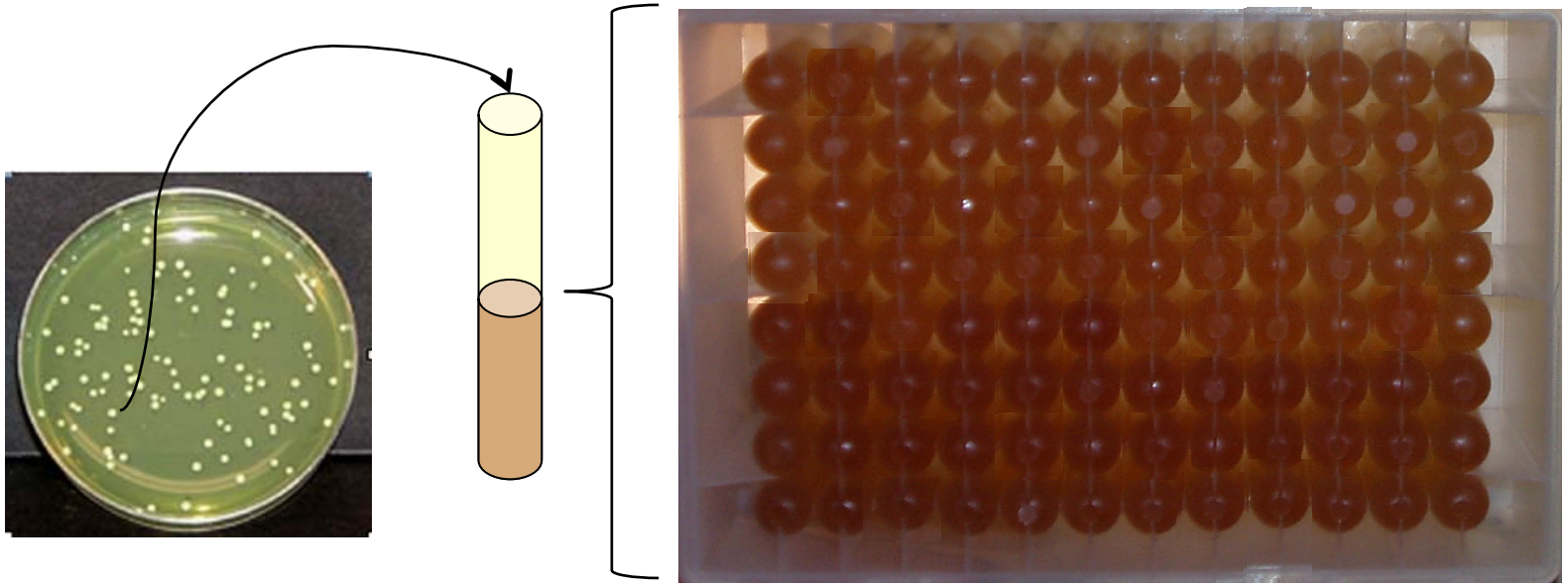




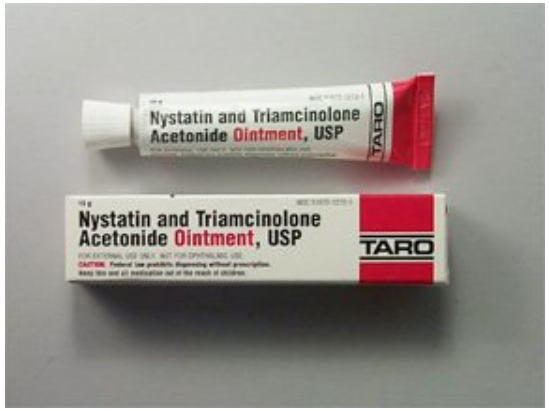
Method: Isolate the first-step mutations that arise in response to nystatin stress.

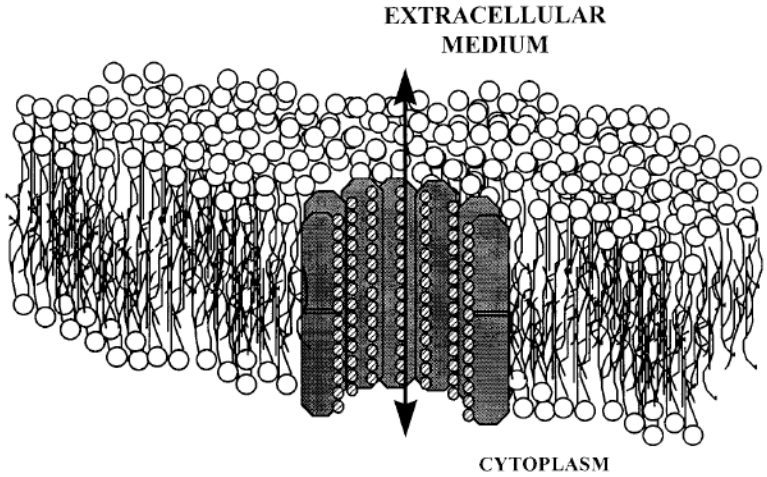


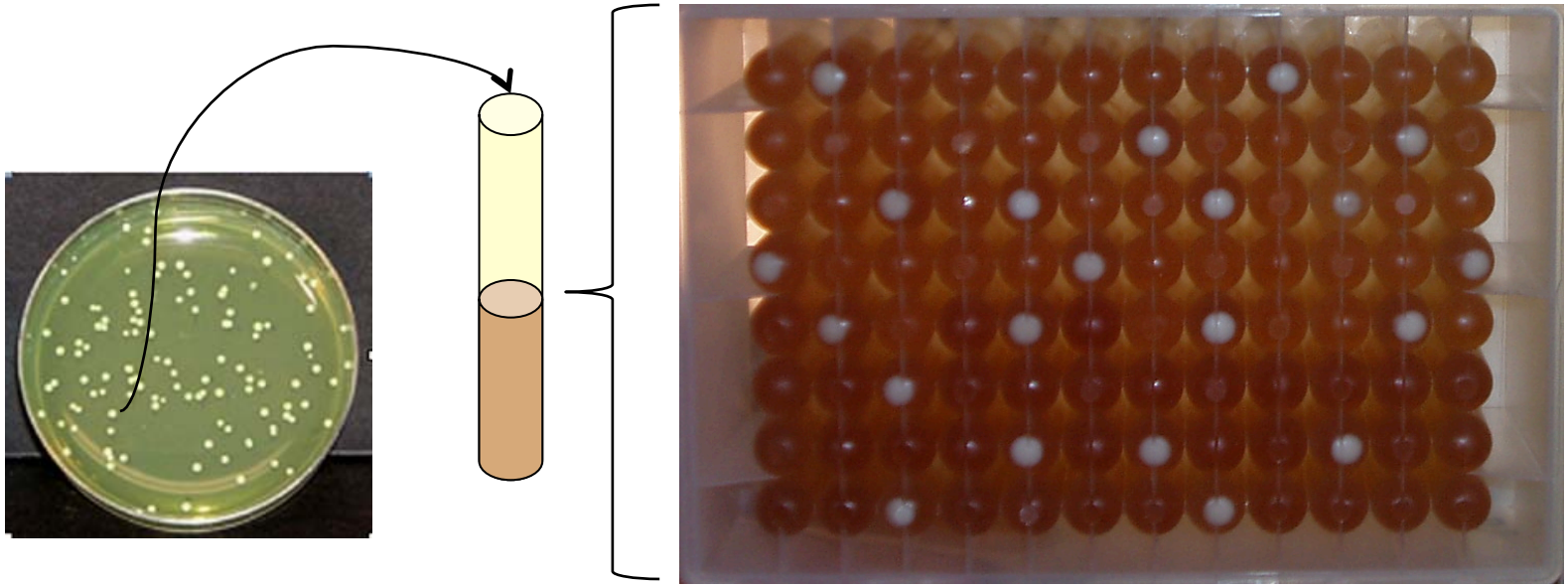




Method: Isolate the first-step mutations that arise in response to nystatin stress.

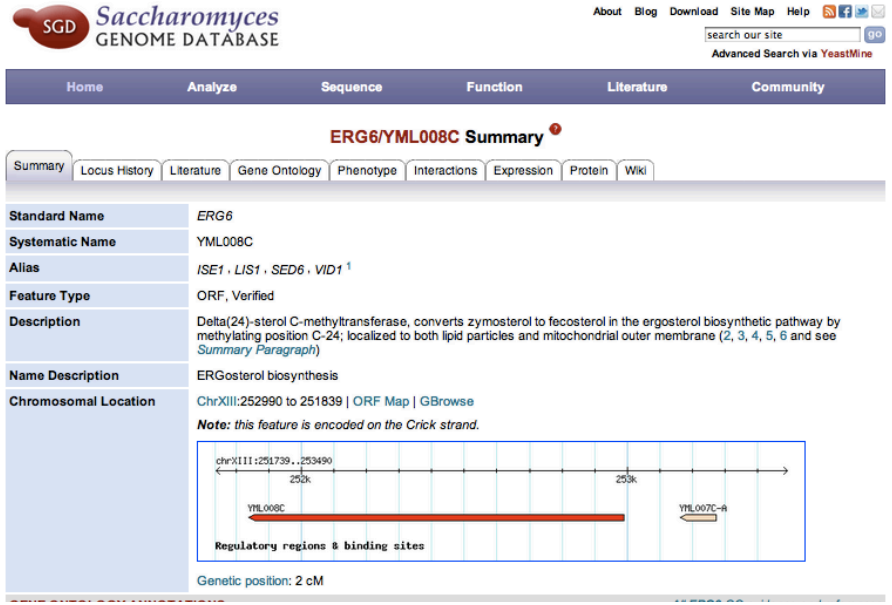






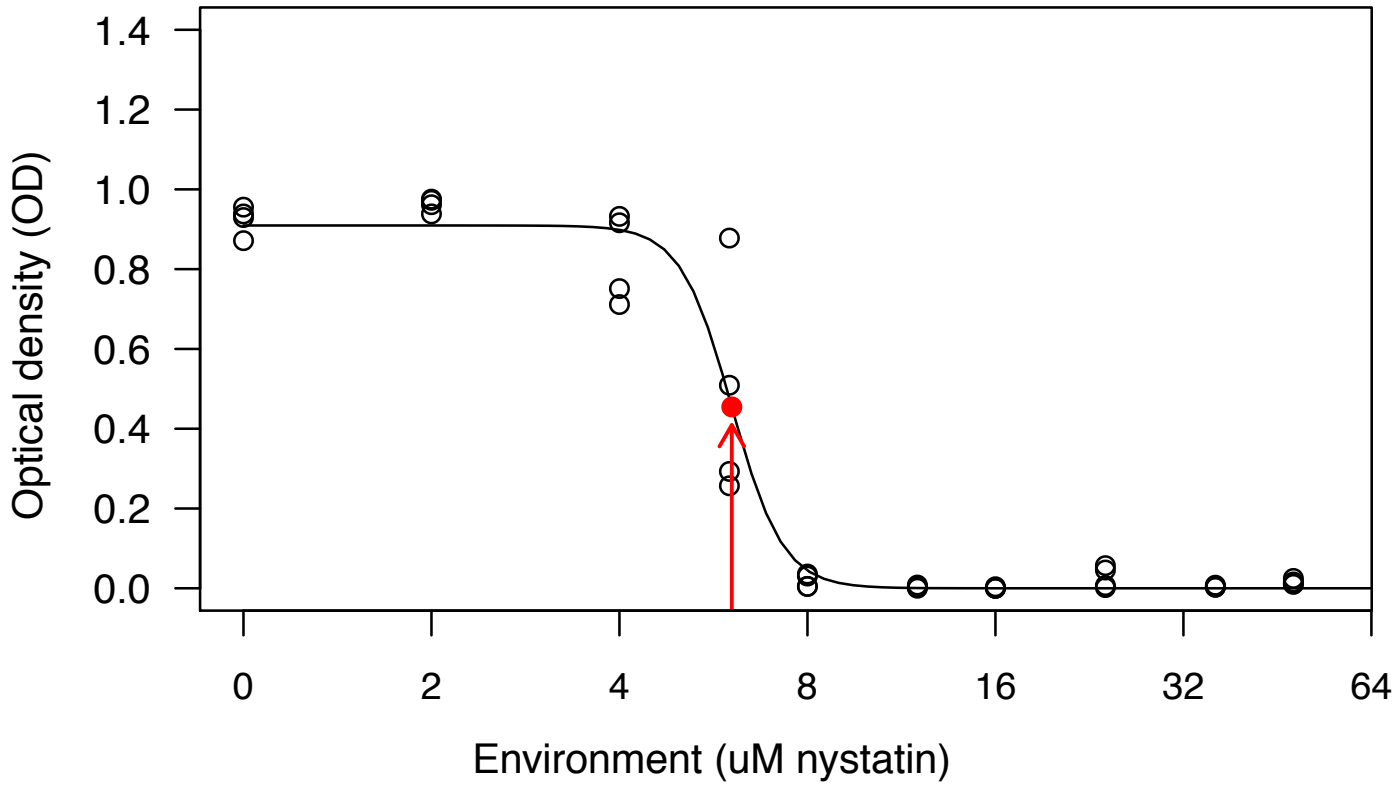
1) What is the genomic and phenotypic breadth of the first adaptive mutations?

Characterize **genomic breadth** by having a really small & well-annotated genome, luck, and magic.

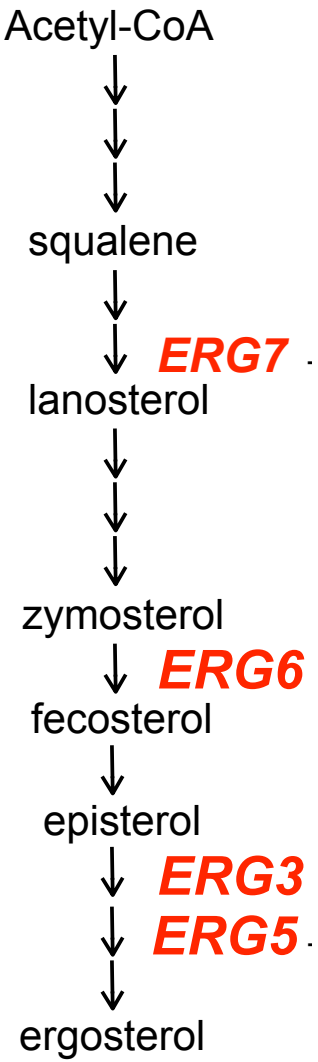


1) What is the genomic and phenotypic breadth of the first adaptive mutations?

Characterize **phenotypic breadth** as tolerance to the stressor (IC_{50}).

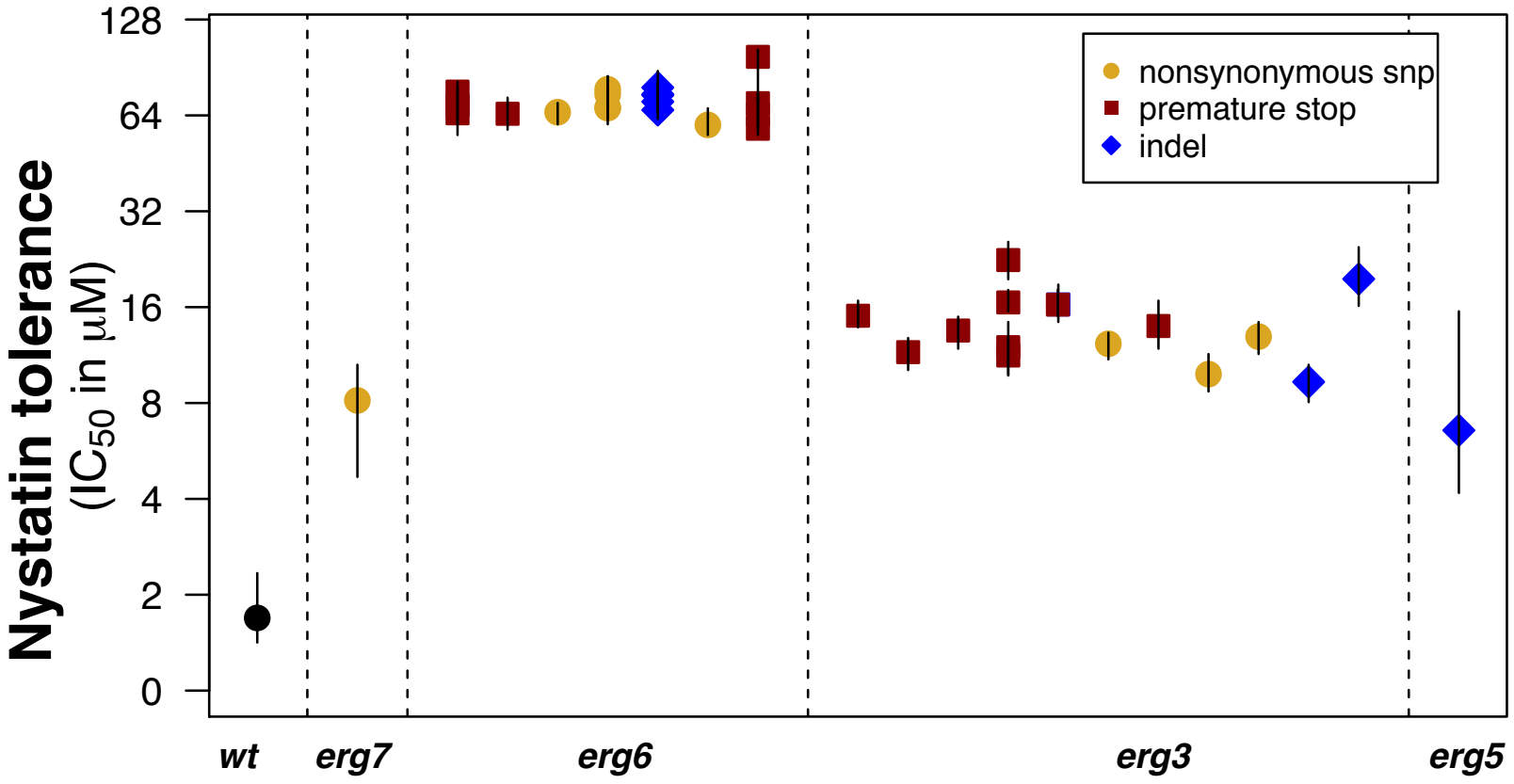


Genomic breadth – Every single line has a mutation in the ergosterol biosynthesis pathway.



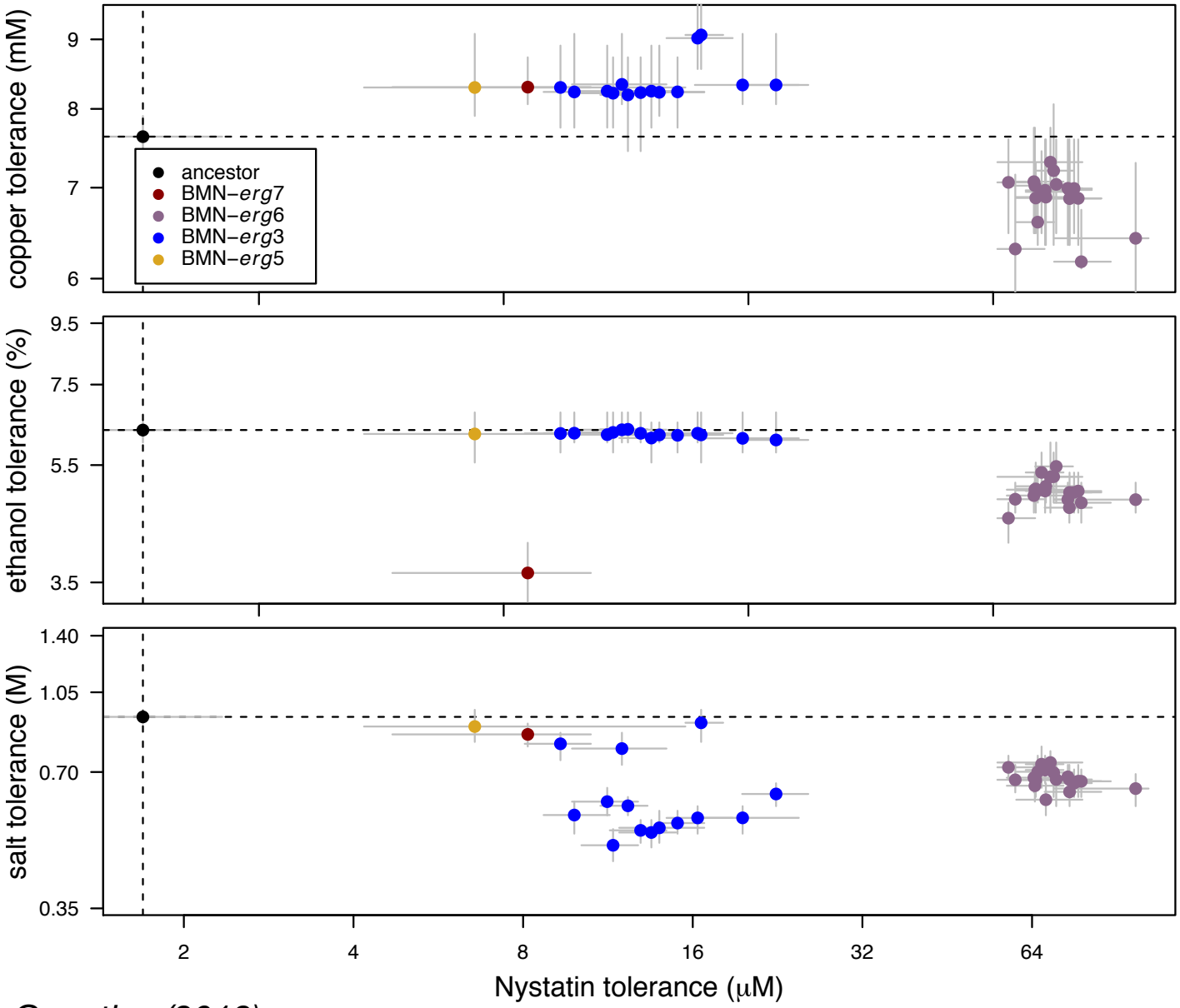
***Chapter 4**: Genetics (2012)*

Phenotypic breadth – Tolerance is similar among different mutations within an *ERG* gene, but different among mutations in different genes.



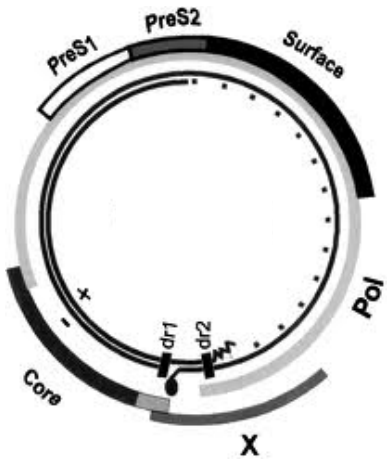
***Chapter 4**: Genetics (2012)*

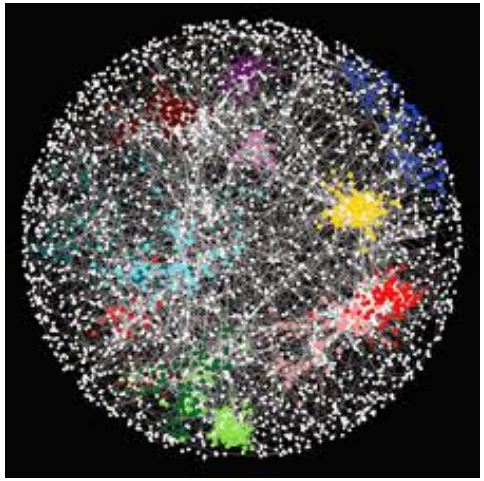
Phenotypic breadth – Gene-environment interactions

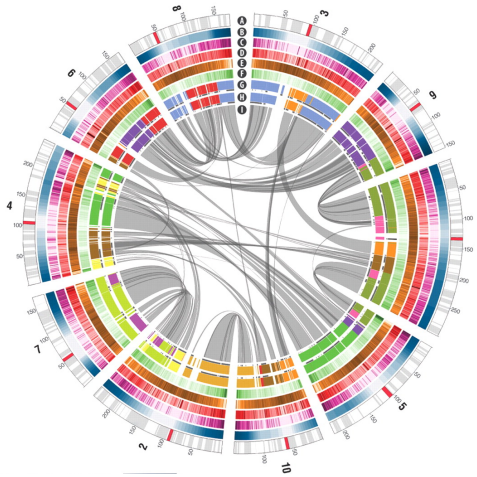


***Chapter 4**: Genetics (2012)*

Theme 2: Characterizing single adaptive mutations



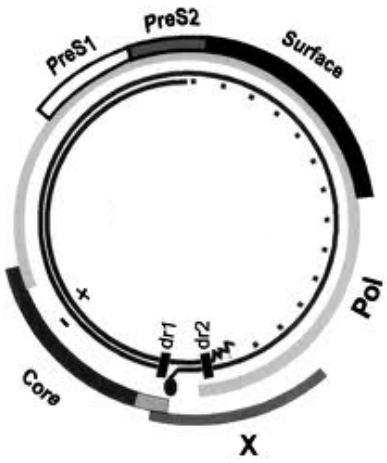


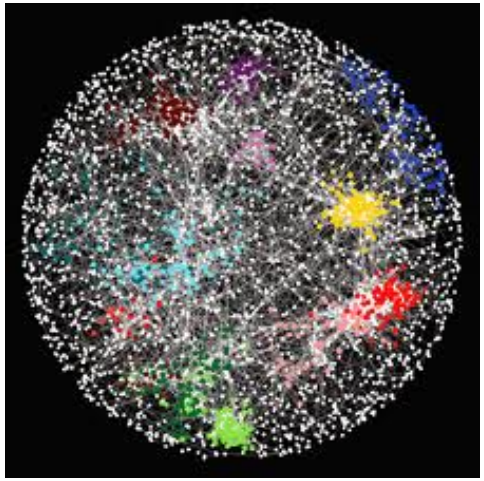


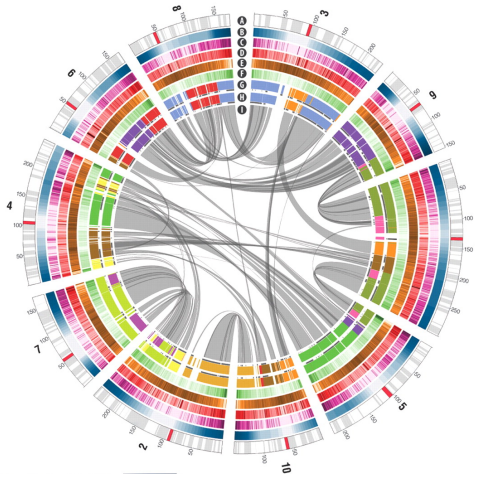
1) What is the genomic and phenotypic breadth of the first adaptive mutations?

- narrow genomic breadth (four genes in one pathway)
- broad phenotypic breadth (large differences in primary environment, gene-environment interactions)

Theme 2: Characterizing single adaptive mutations





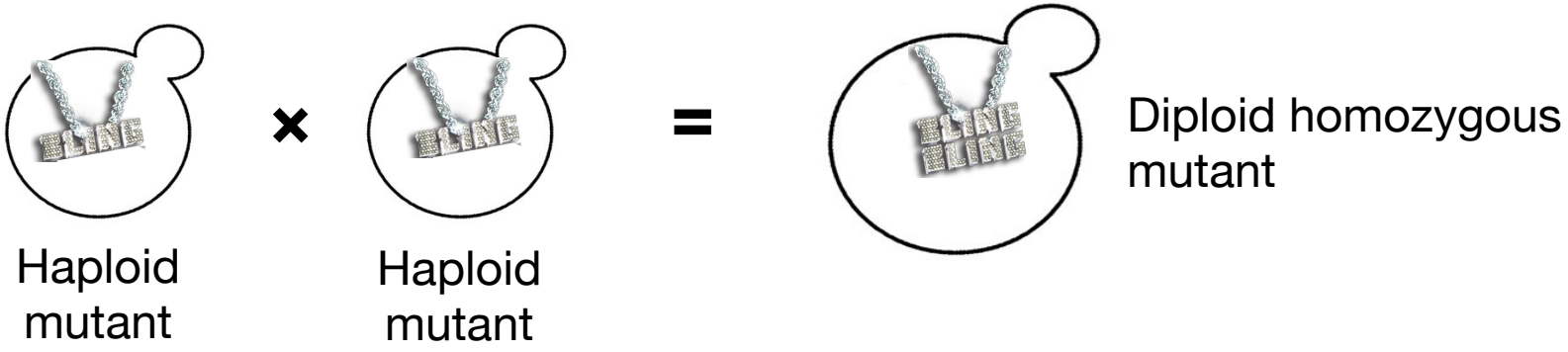


1) What is the genomic and phenotypic breadth of the first adaptive mutations?

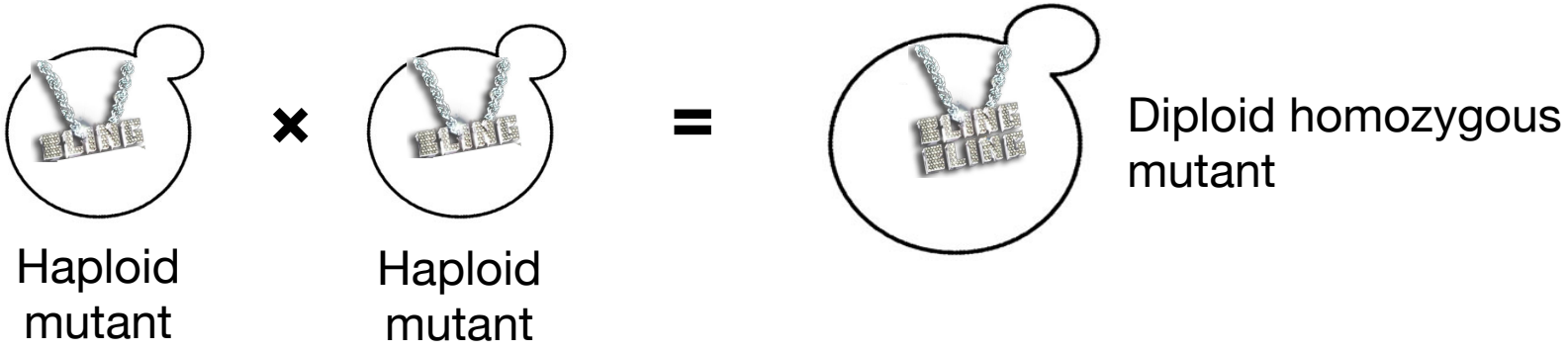
2) Do adaptive mutations have the same effect size in haploids and homozygous diploids?

3) What is the effect of zygosity on adaptive mutations?

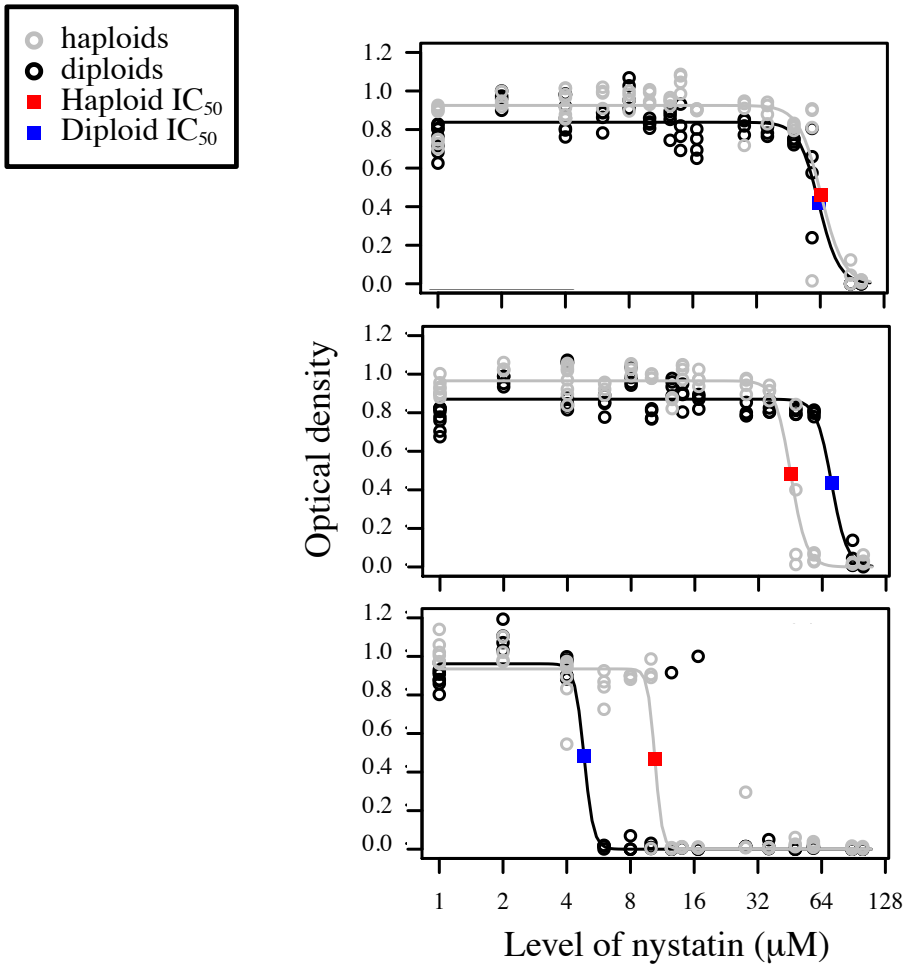
Method: Make heterozygous and homozygous diploids from haploid nystatin mutants.



Method: Make heterozygous and homozygous diploids from haploid nystatin mutants.



2) Do adaptive mutations have the same effect size in haploids and homozygous diploids?

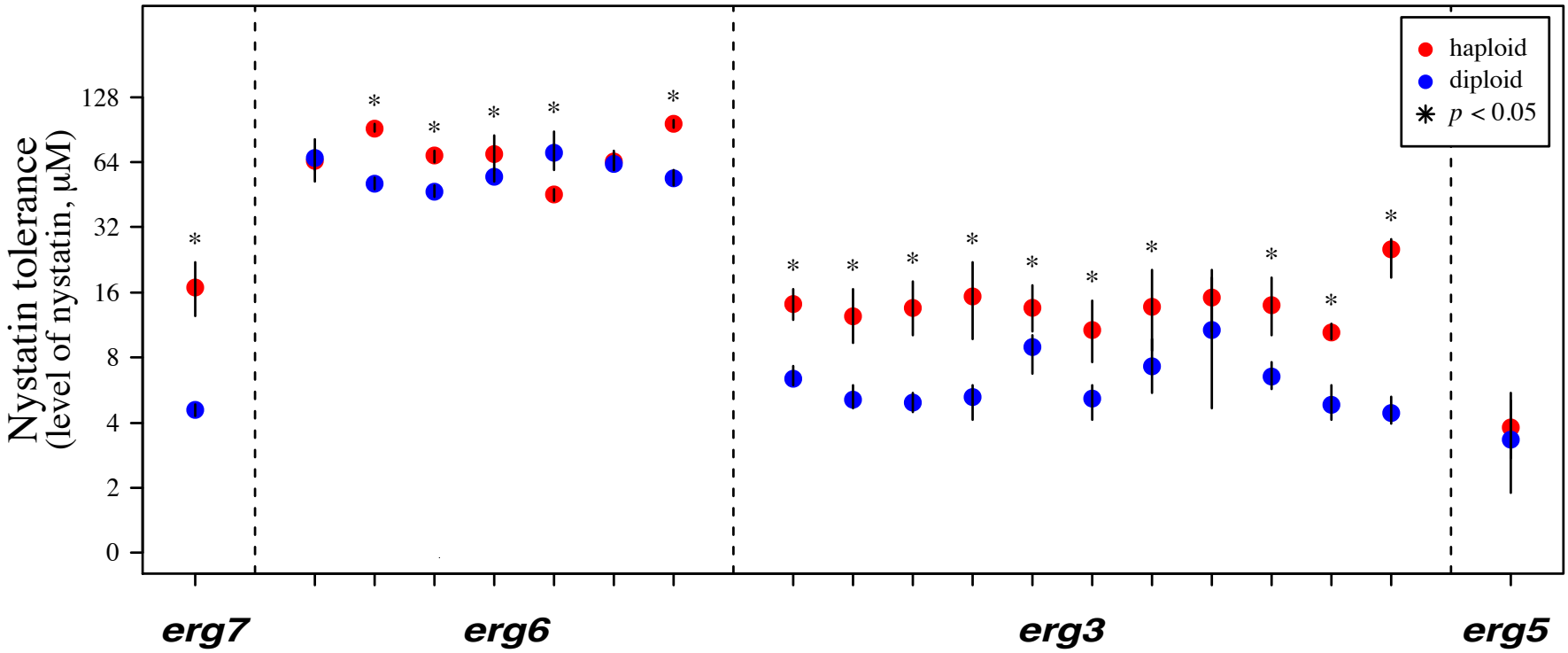


N = 2N

N < 2N

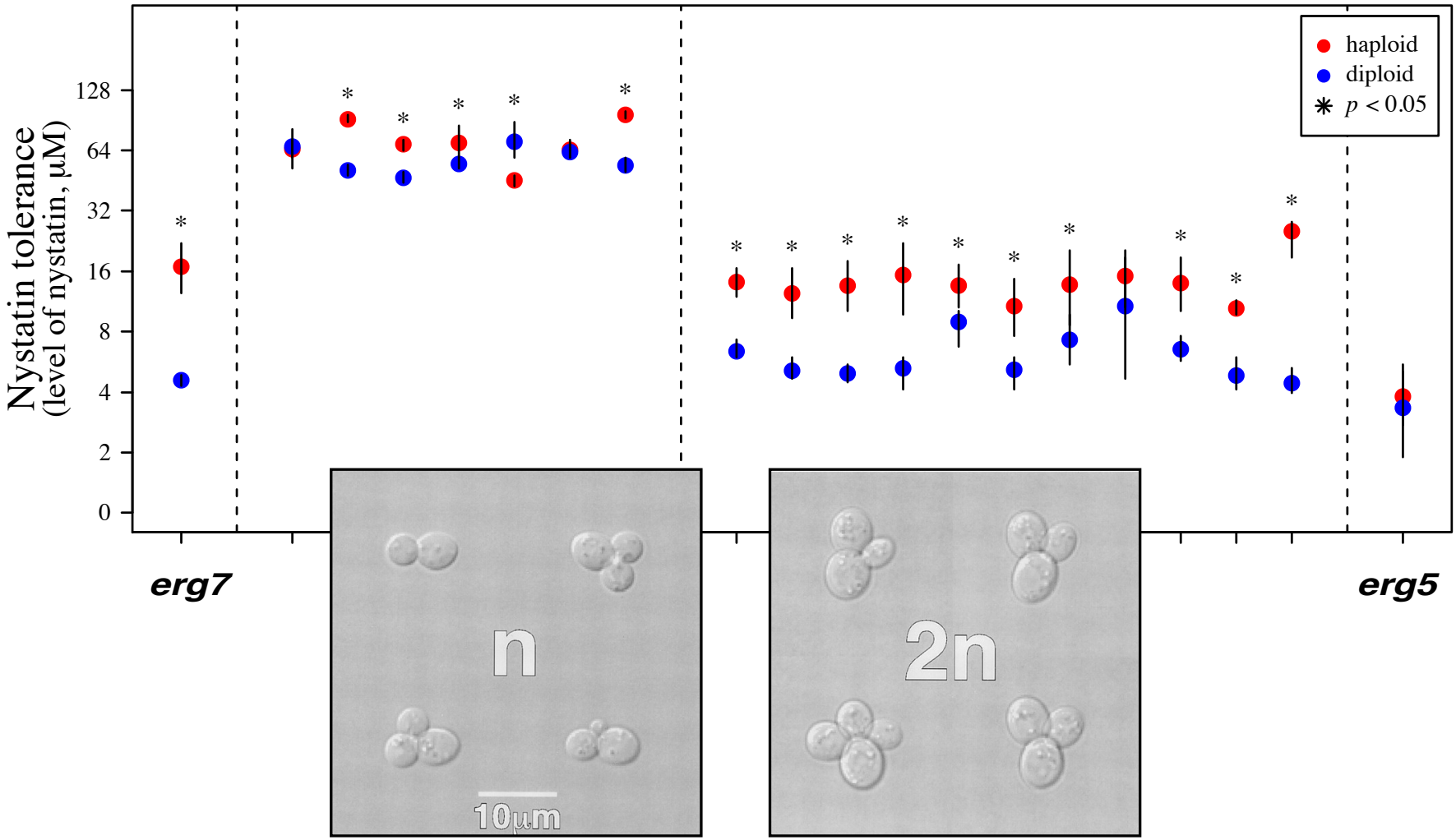
N > 2N

Nystatin adaptive mutations generally confer larger tolerance on haploids than homozyous diploids.

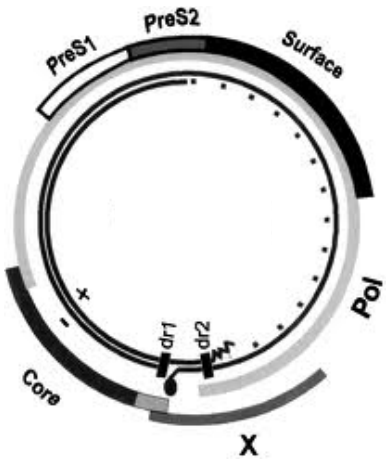


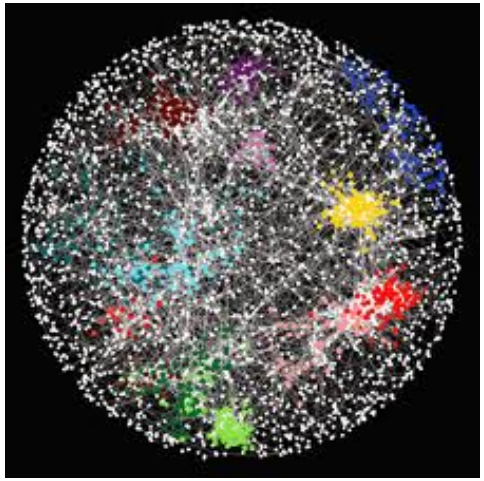
***Chapter 5**: submitted to Biology Letters*

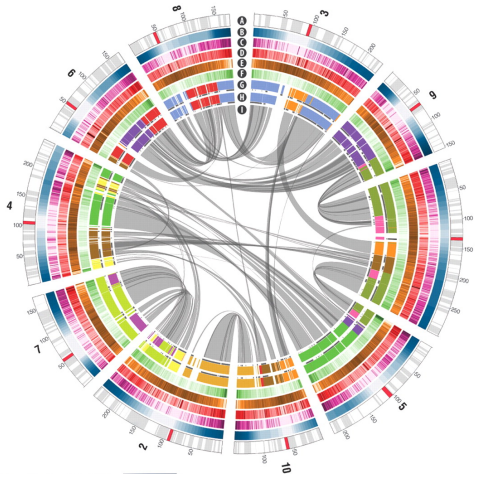
Nystatin adaptive mutations generally confer larger tolerance on haploids than homozygous diploids.



Theme 2: Characterizing single adaptive mutations



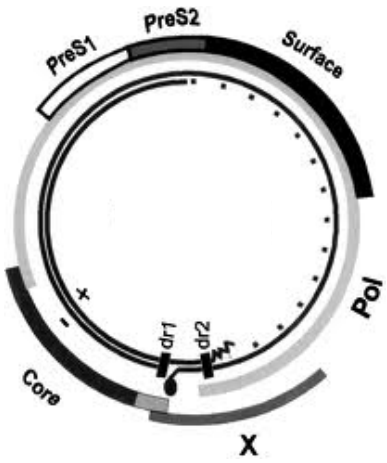


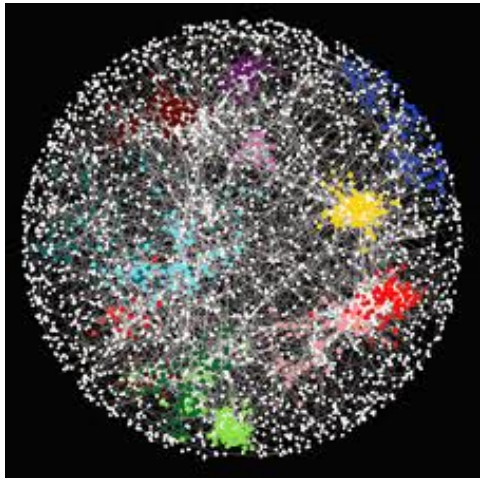


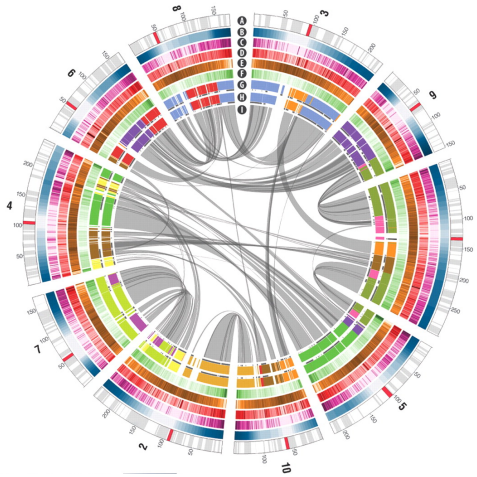
2) Do adaptive mutations have the same effect size in haploids and homozygous diploids?

- not these mutations

Theme 2: Characterizing single adaptive mutations





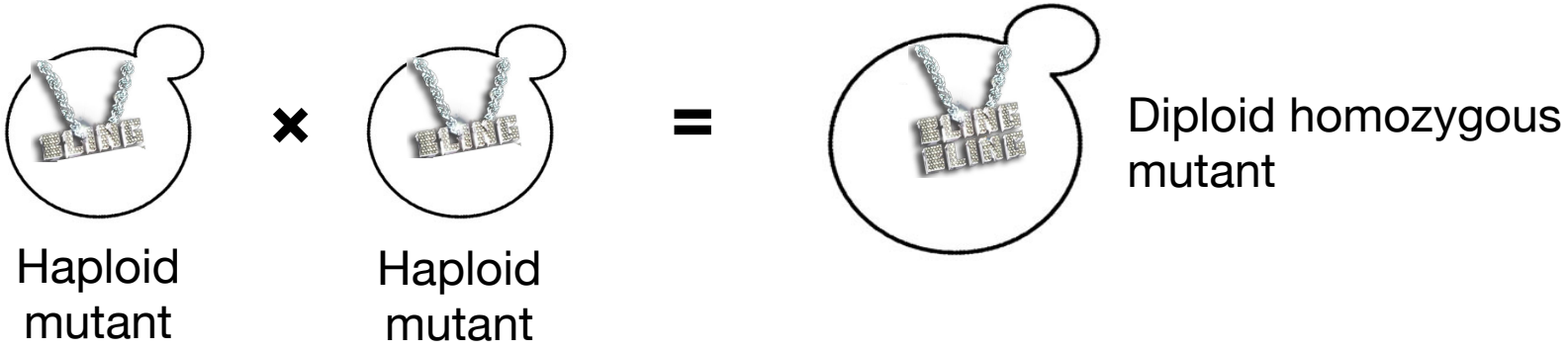


1) What is the genomic and phenotypic scope of the first adaptive mutations?

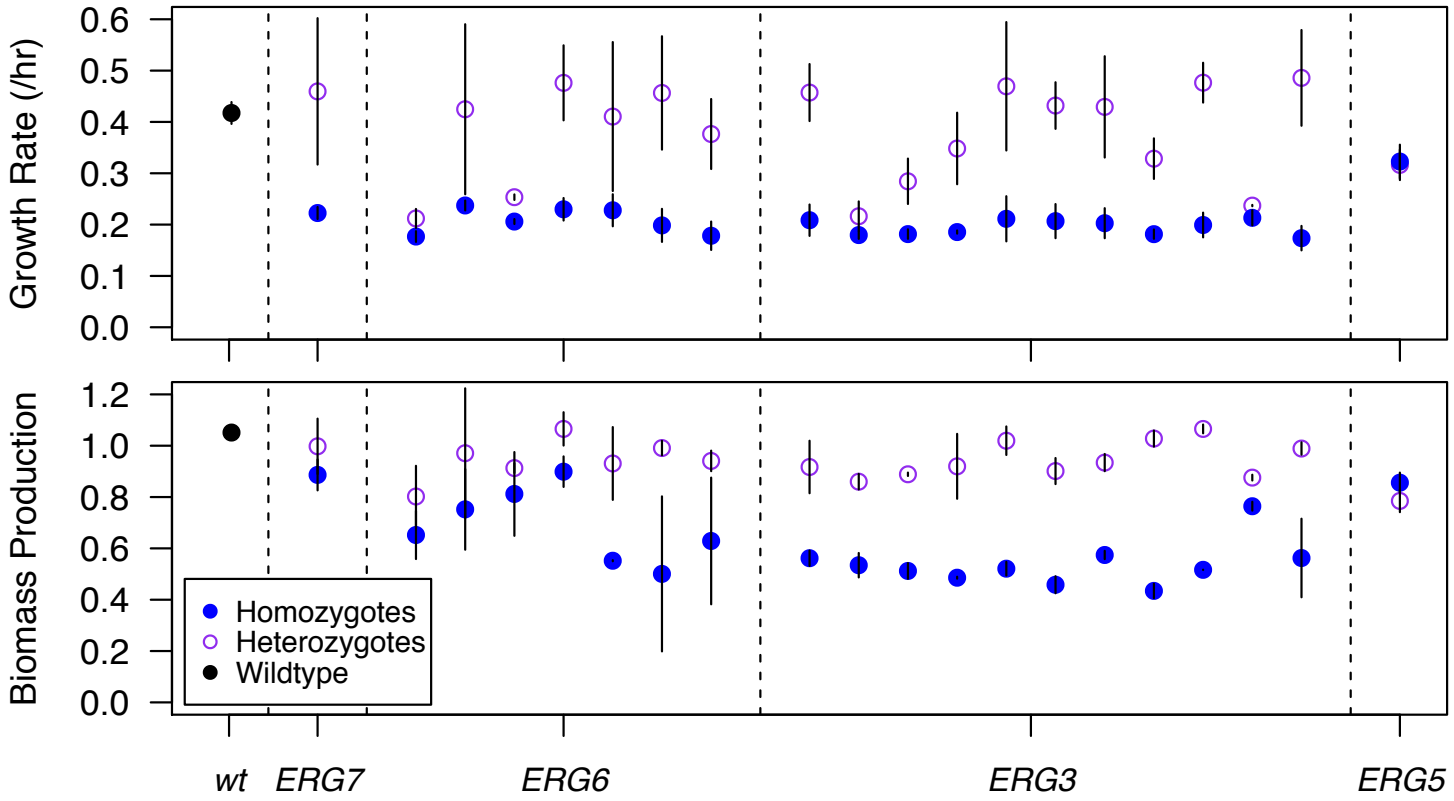
2) Do adaptive mutations have the same effect size in haploids and homozygous diploids?

3) What is the effect of zygosity on adaptive mutations?

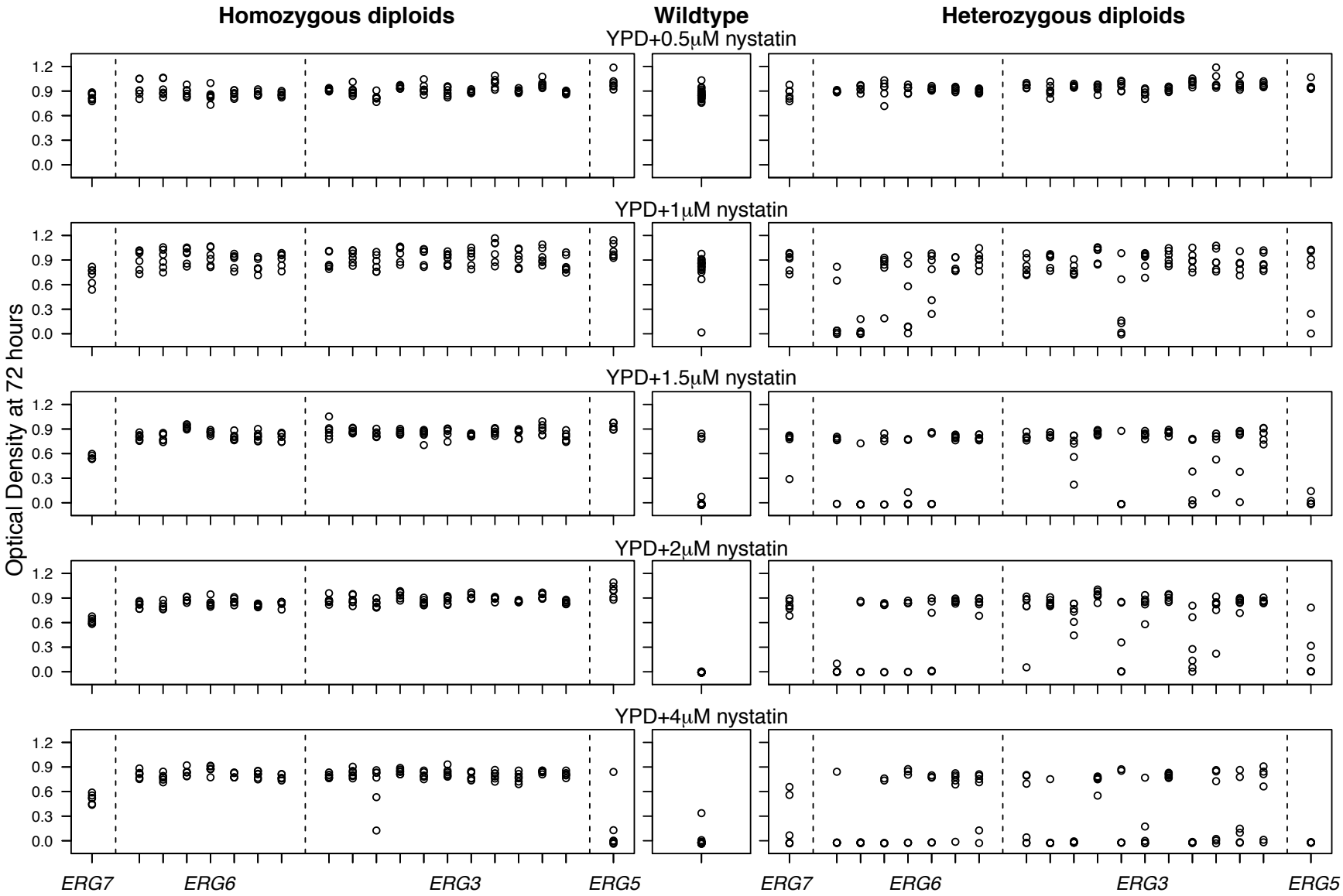
Method: Make heterozygous and homozygous diploids from haploid nystatin mutants.



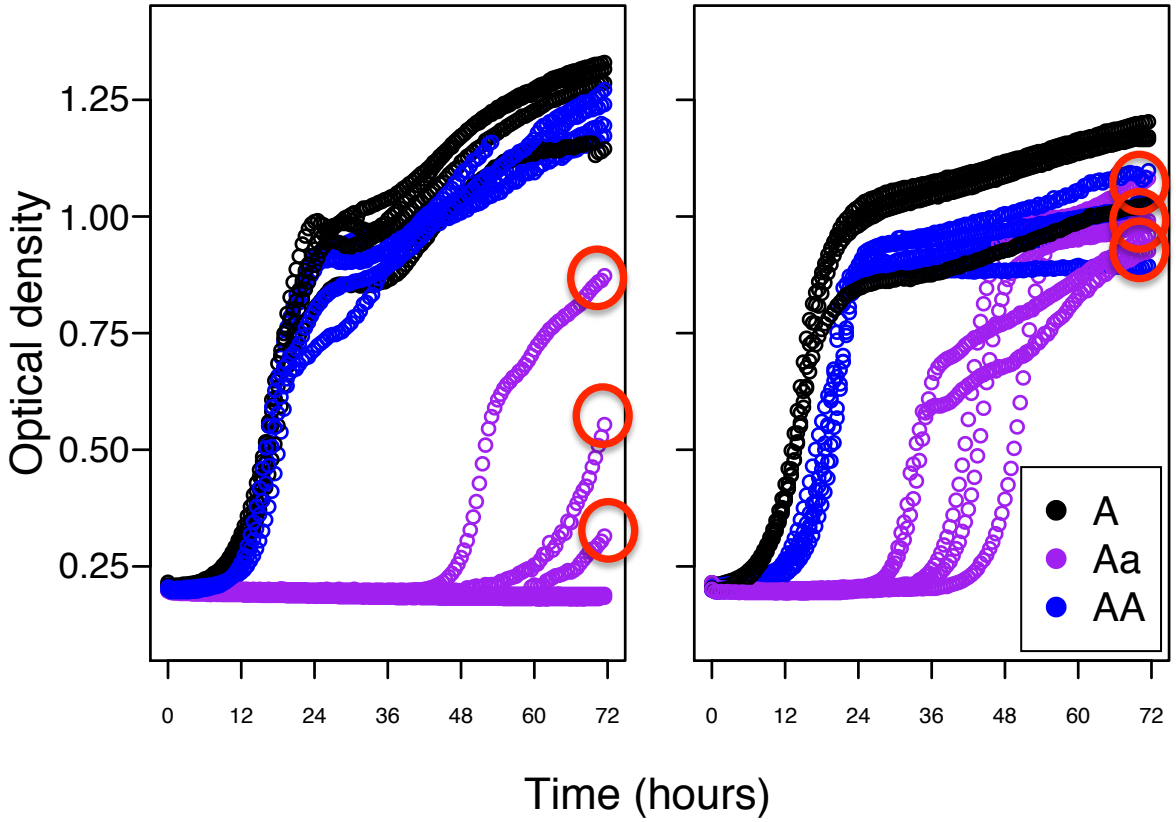
In an unstressful environment, heterozygotes generally grow better than homozygous mutants.



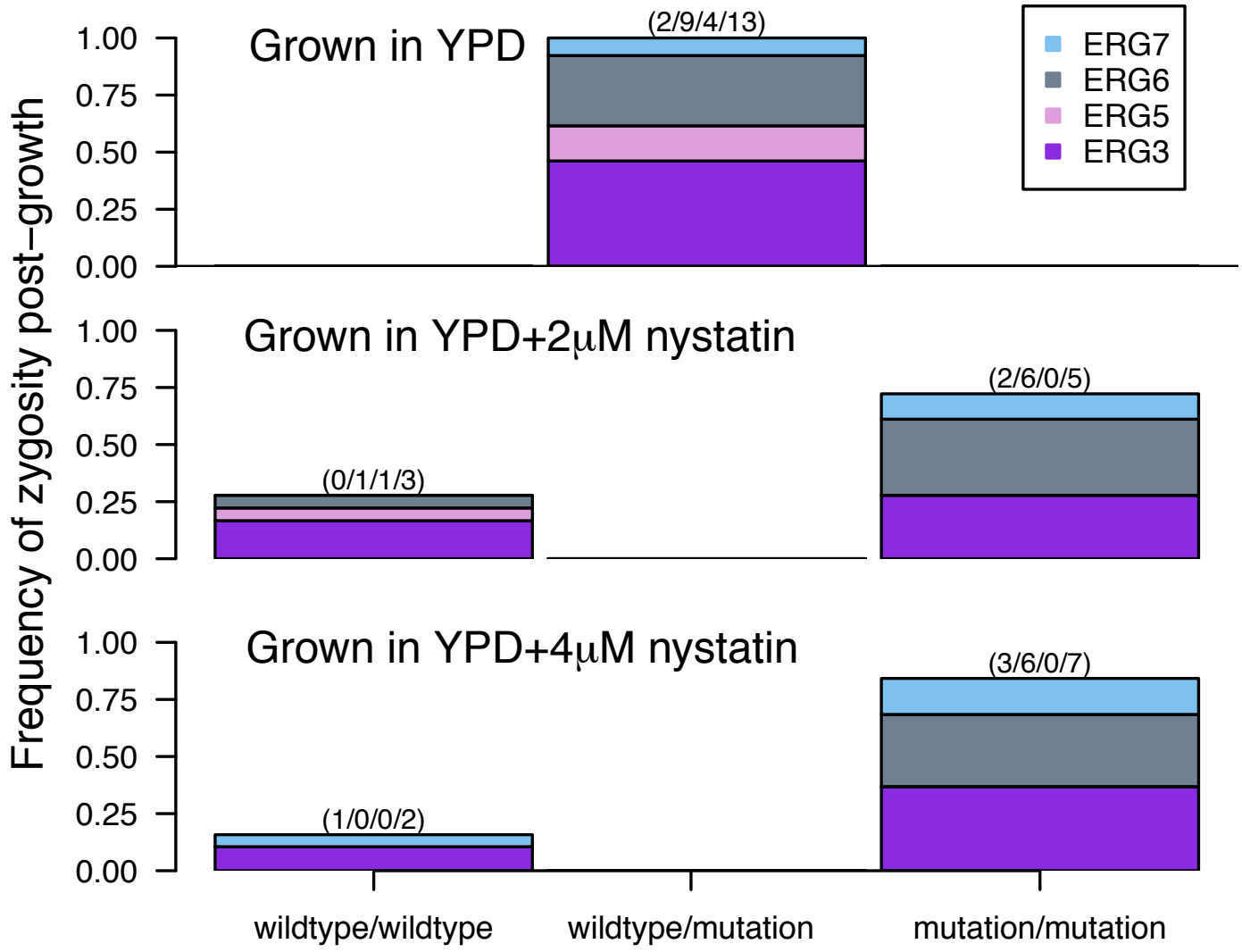
In nystatin, heterozygotes grow stochastically.



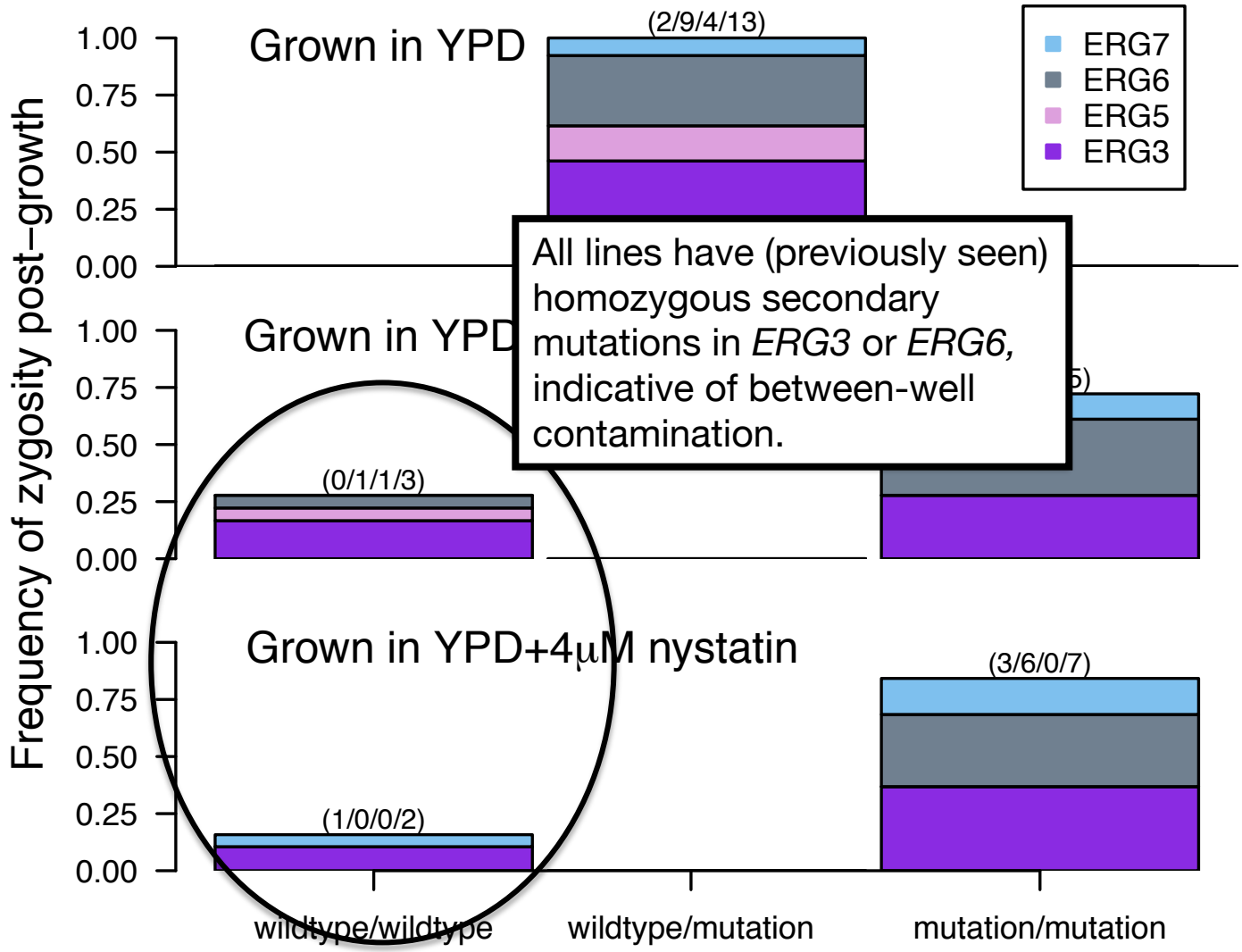
Method: isolate heterozygous replicates that showed growth in nystatin, re-sequence the known mutation locus.



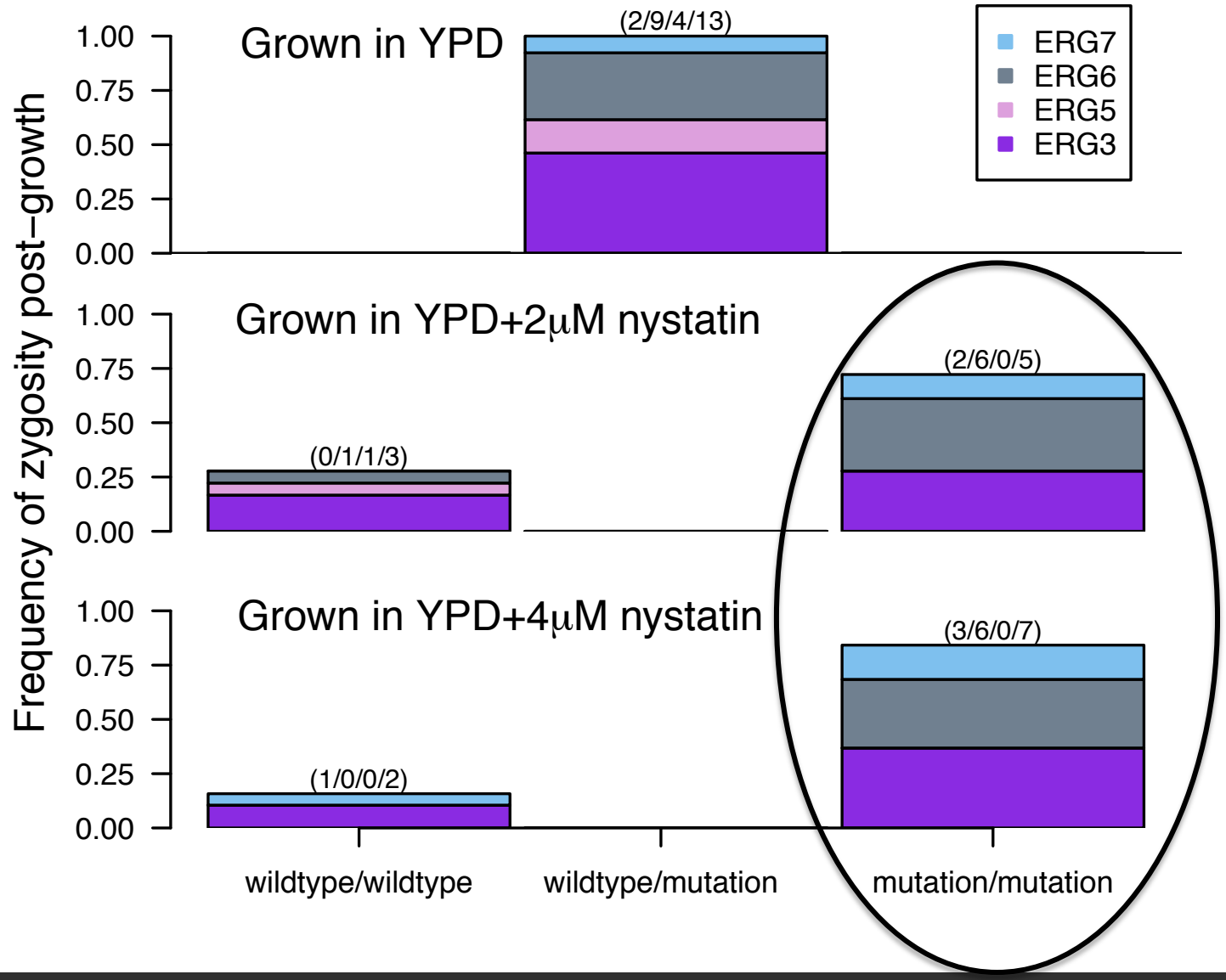
Heterozygotes are not staying heterozygous in nystatin.



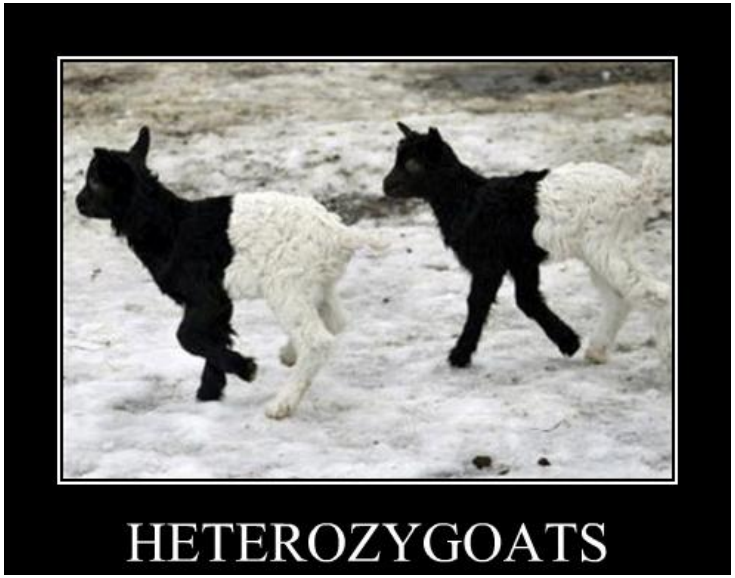
Heterozygotes are not staying heterozygous in nystatin.



Rapid **loss-of-heterozygosity.**



Theme 2: Characterizing single adaptive mutations

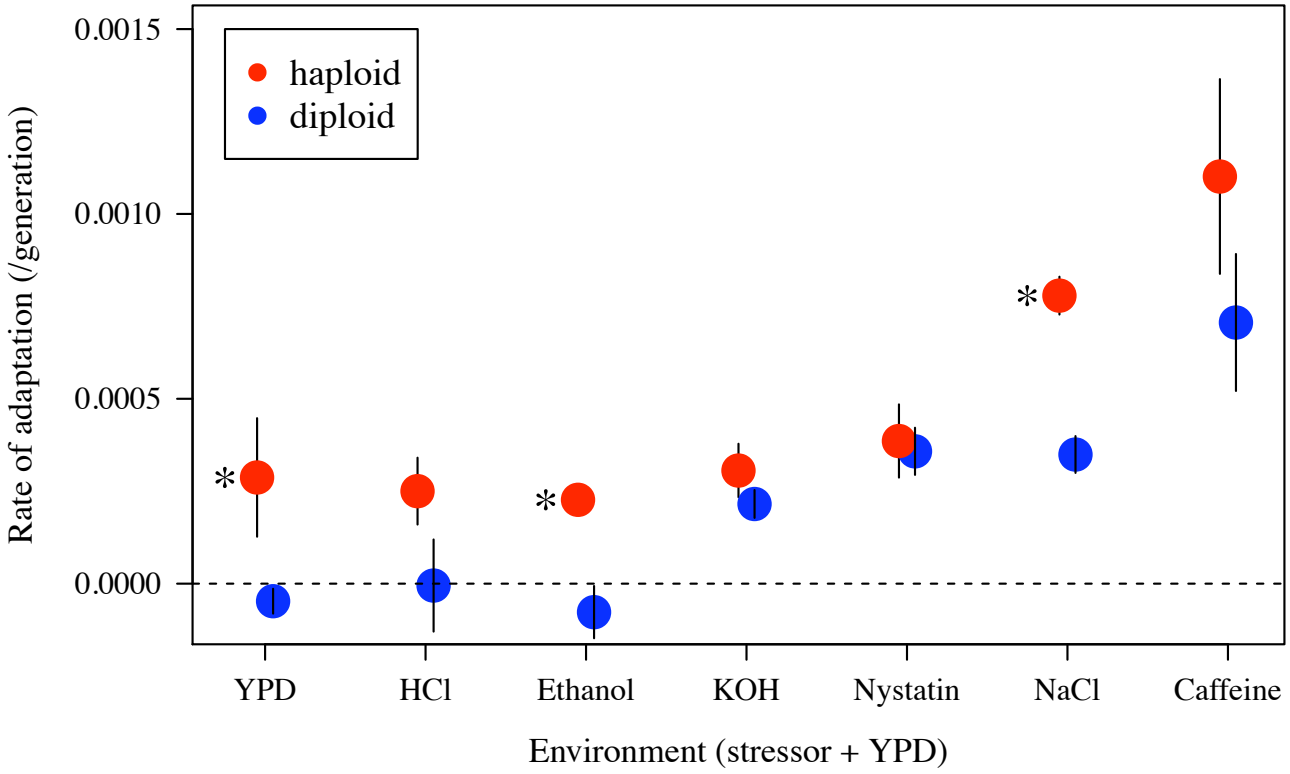


3) What is the effect of zygosity on adaptive mutations?

- Mutations tended to be less deleterious in heterozygotes
- Heterozgyotes grew stochastically under nystatin stress
    - Rapid loss-of-heterozygosity of adaptive mutations
- Dominance of mutations changed between environments

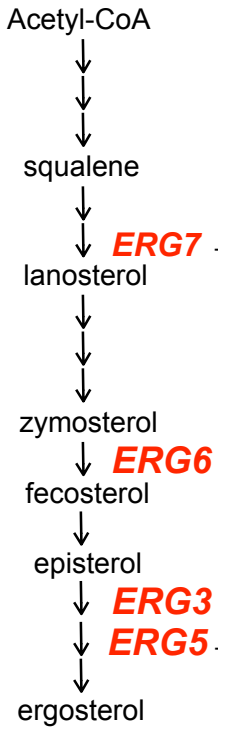
Conclusions

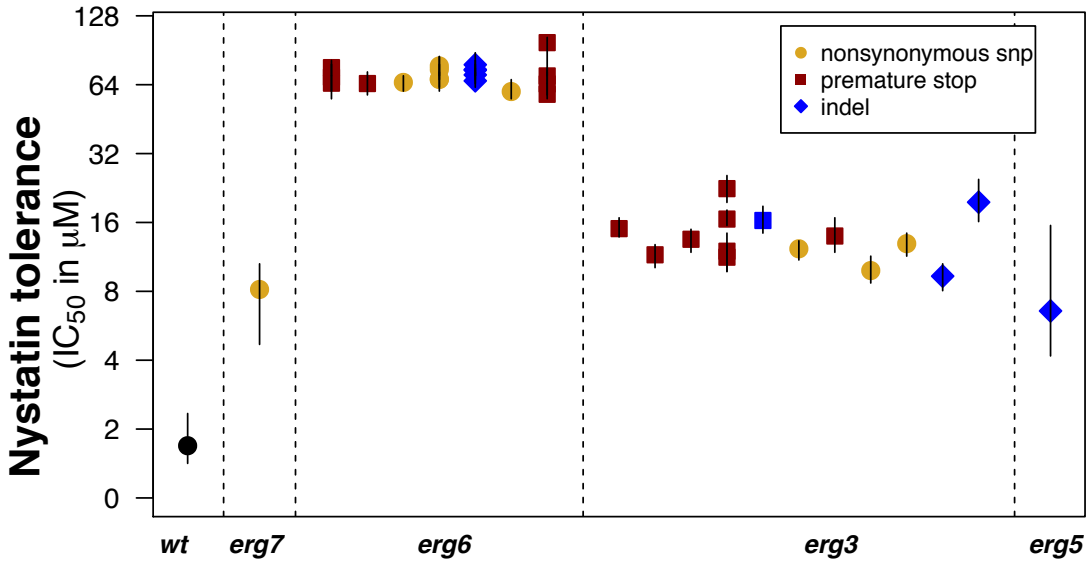
1) Haploids adapted faster than diploids to mildly stressful environments.



Conclusions

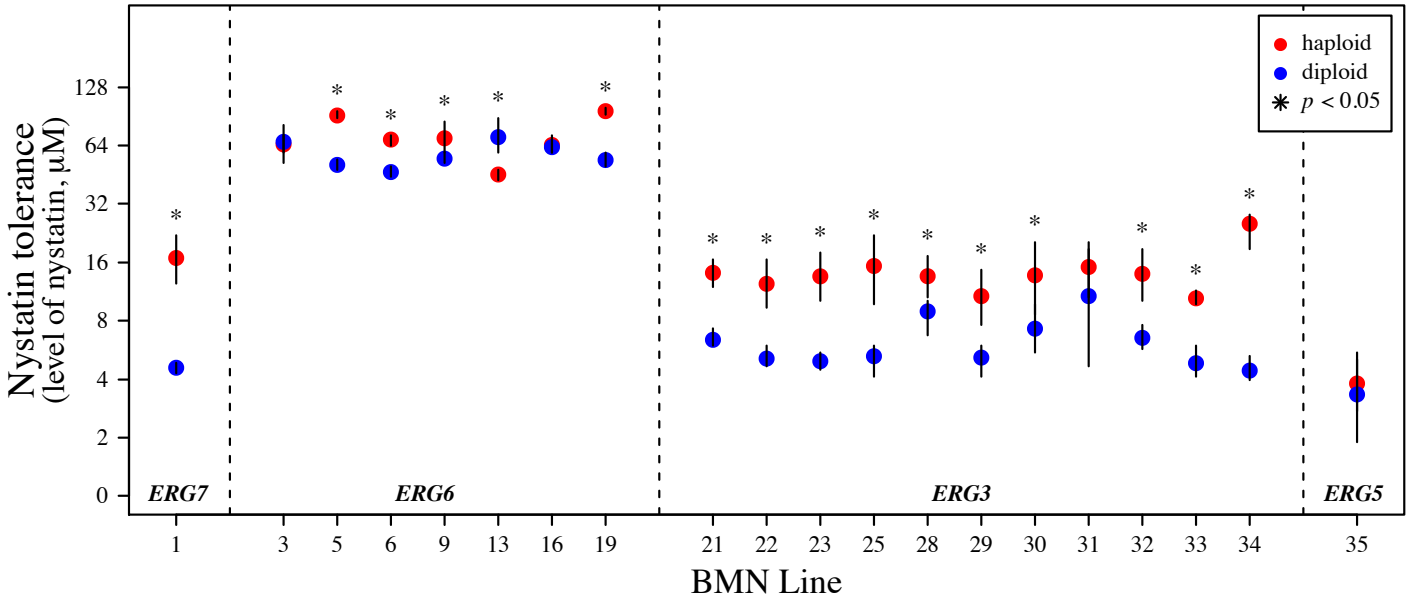
2) The first acquired nystatin adaptive mutations have a narrow genomic breadth and broad phenotypic breadth





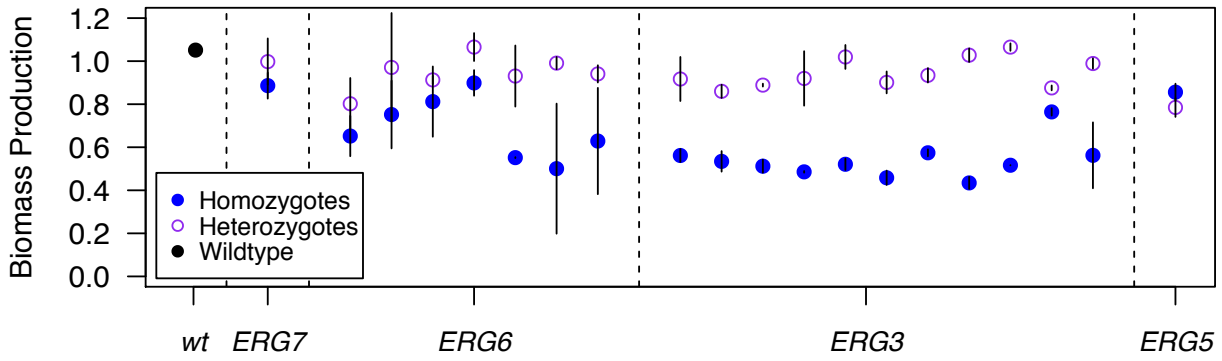
Conclusions

3) The first acquired nystatin adaptive mutations confer a larger tolerance to haploids than homozygous diploids.



Conclusions

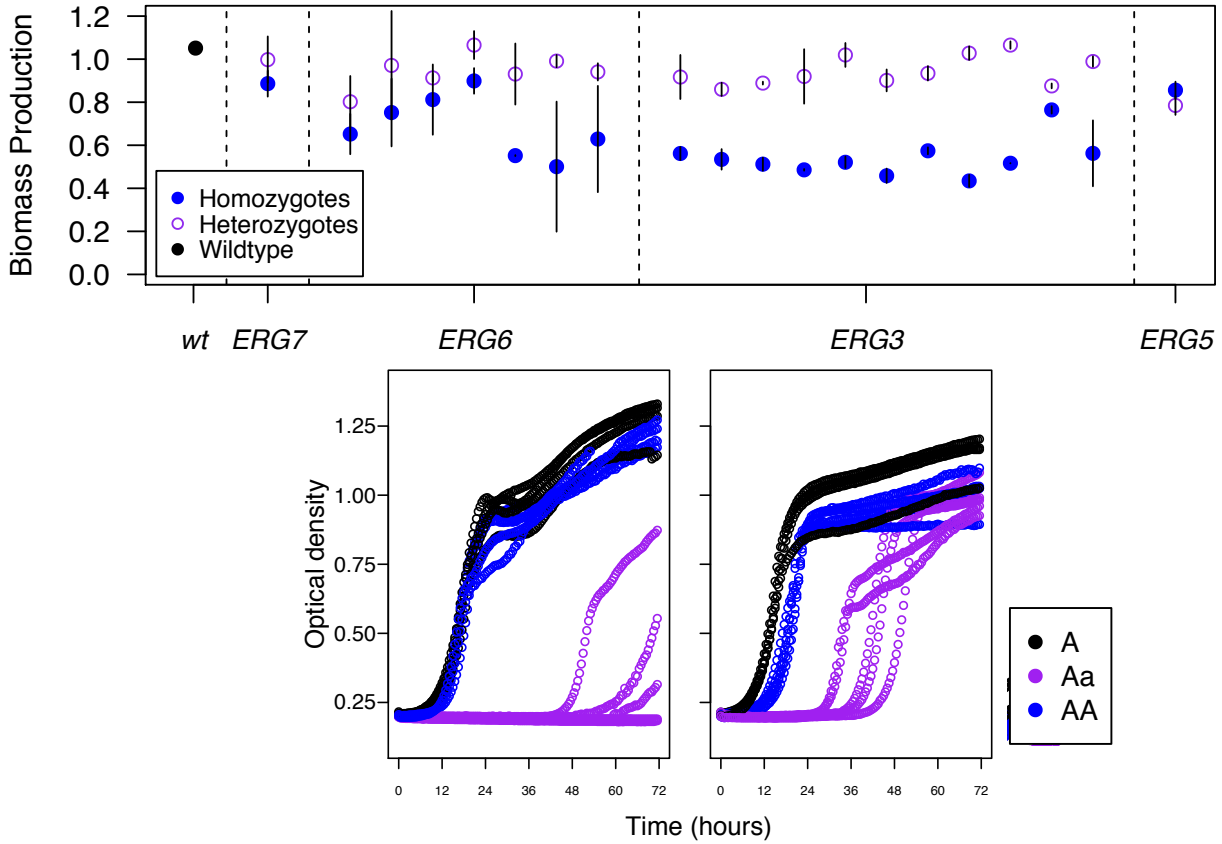
4) Heterozygotes grow better than homozygous mutants in YPD



YPD

Conclusions

4) Heterozygotes grow better than homozygous mutants in YPD, yet must become homozygous to grow under nystatin stress.



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Dara Lo – undergraduate coauthor (nystatin)

Rich Fitzjohn – all things R

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