ON ADAPTATION, EPISTASIS AND FITNESS LANDSCAPES

CLAUDIA BANK

INSTITUTO GULBENKIAN DE CIÊNCIA

EVOLUTION (& HIGH-SPEED INTRO TO POPULATION GENETICS)

- Change in heritable trait frequencies of a population over time

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Mutation *Genetic drift* *Migration* *Selection*

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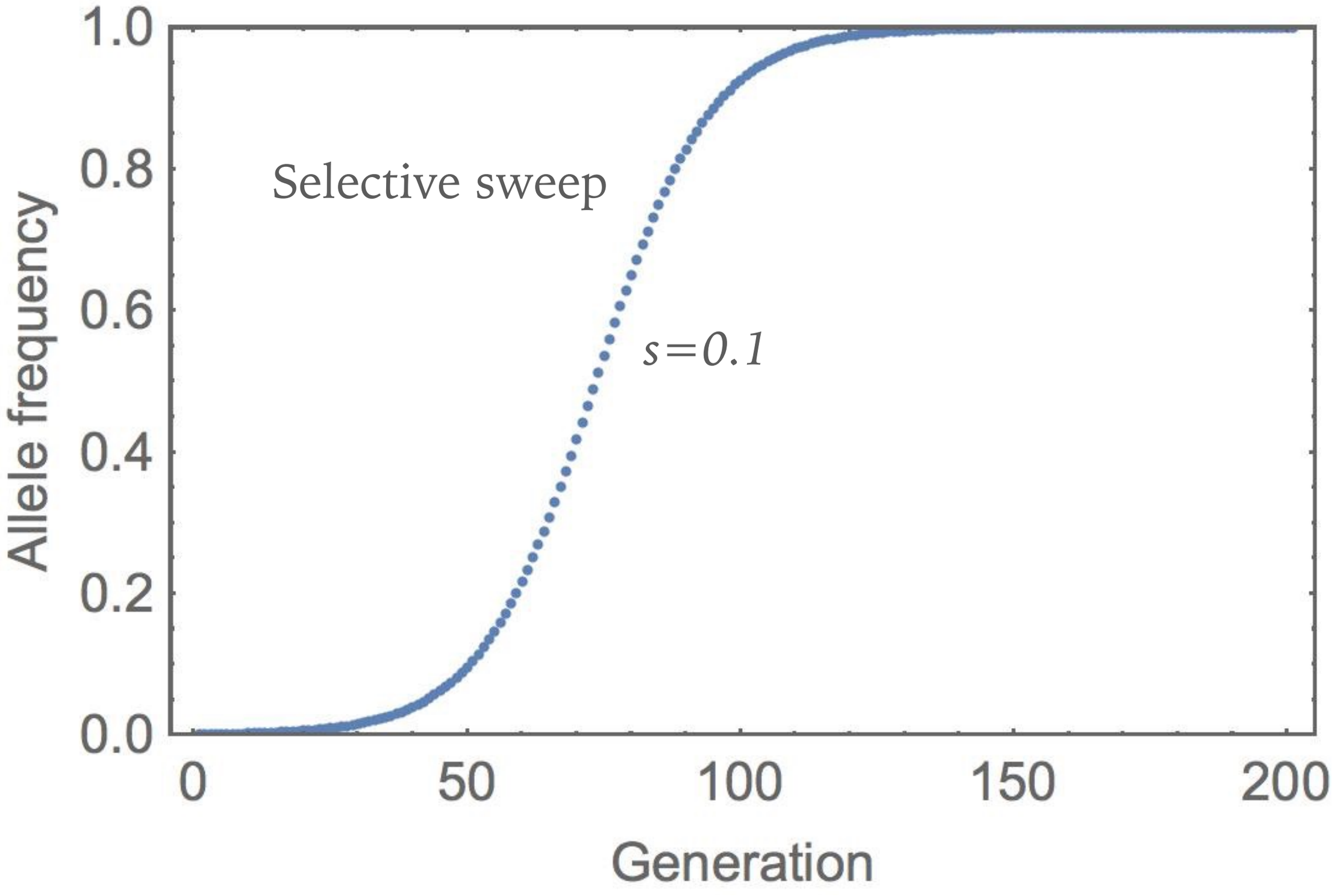
What is your "favorite" evolutionary force, and why?

> Although many processes shape evolution, natural selection is special because it creates complex, functioning organisms. All other processes tend to degrade what has been built up by natural selection, simply because these processes act at random with respect to function.

-Barton et al. , Evolution (textbook)

THEORETICALLY, SELECTION IS THE “EASIEST" EVOLUTIONARY FORCE



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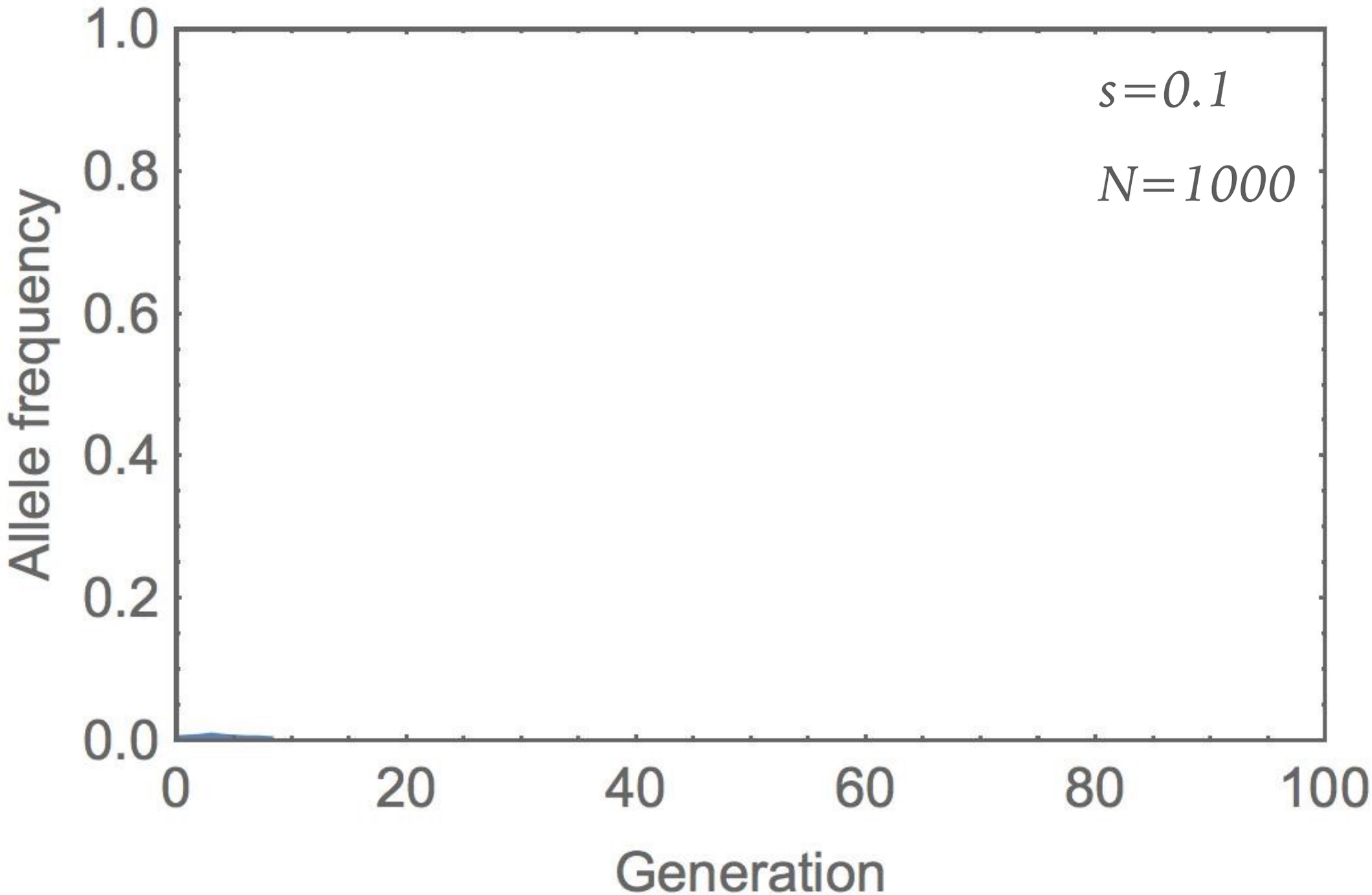

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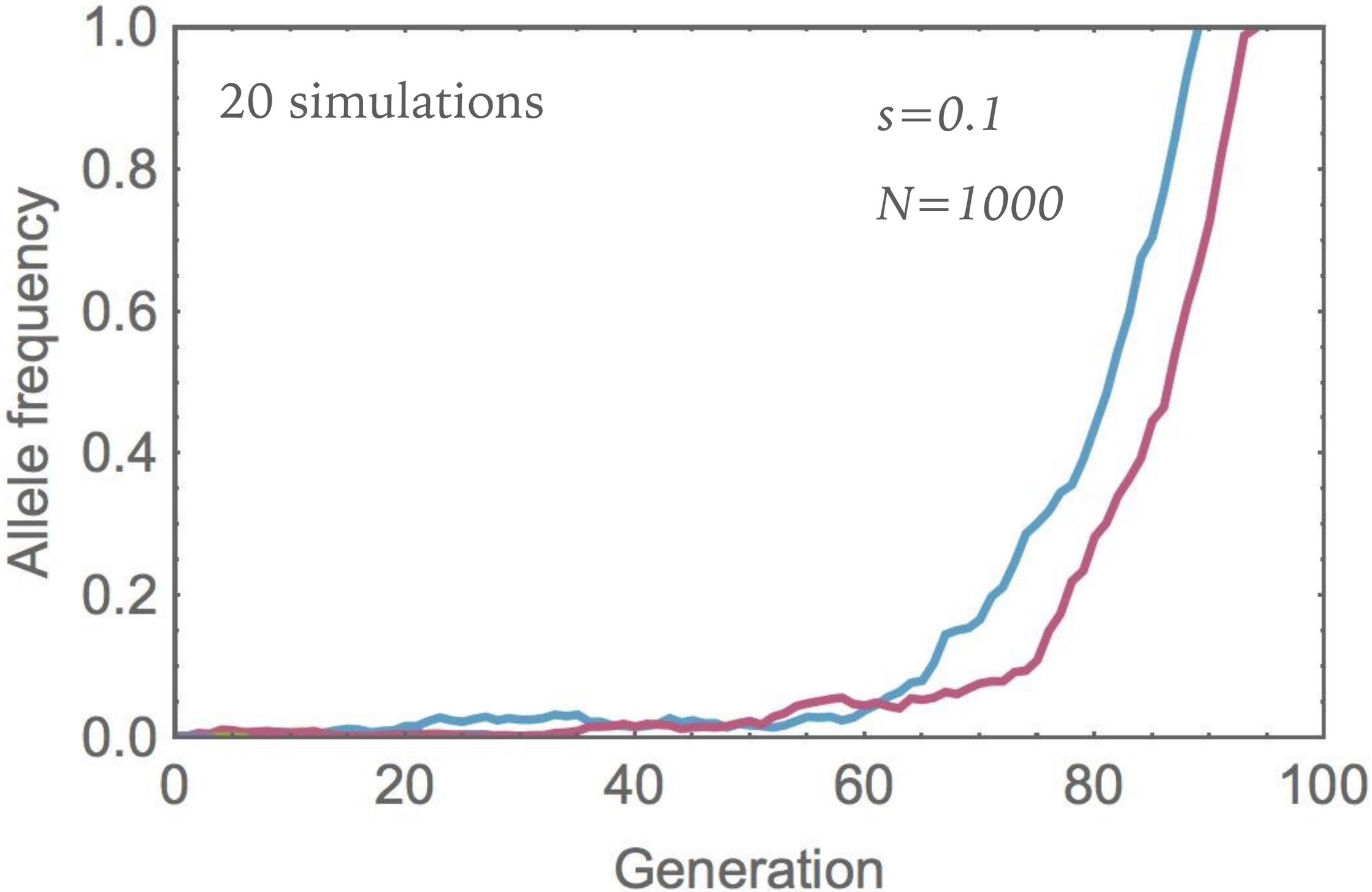

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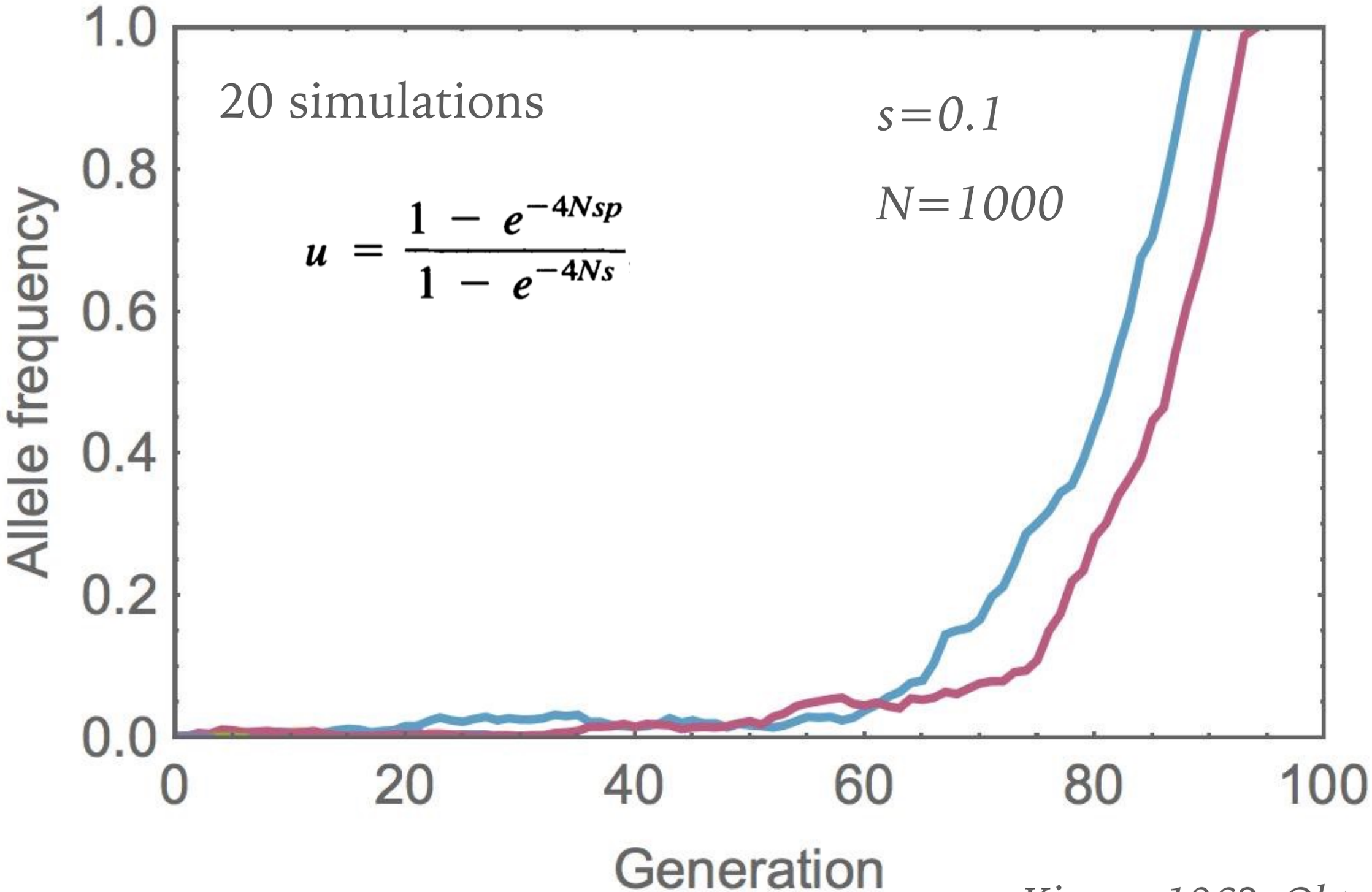

Kimura 1962, Ohta 1973

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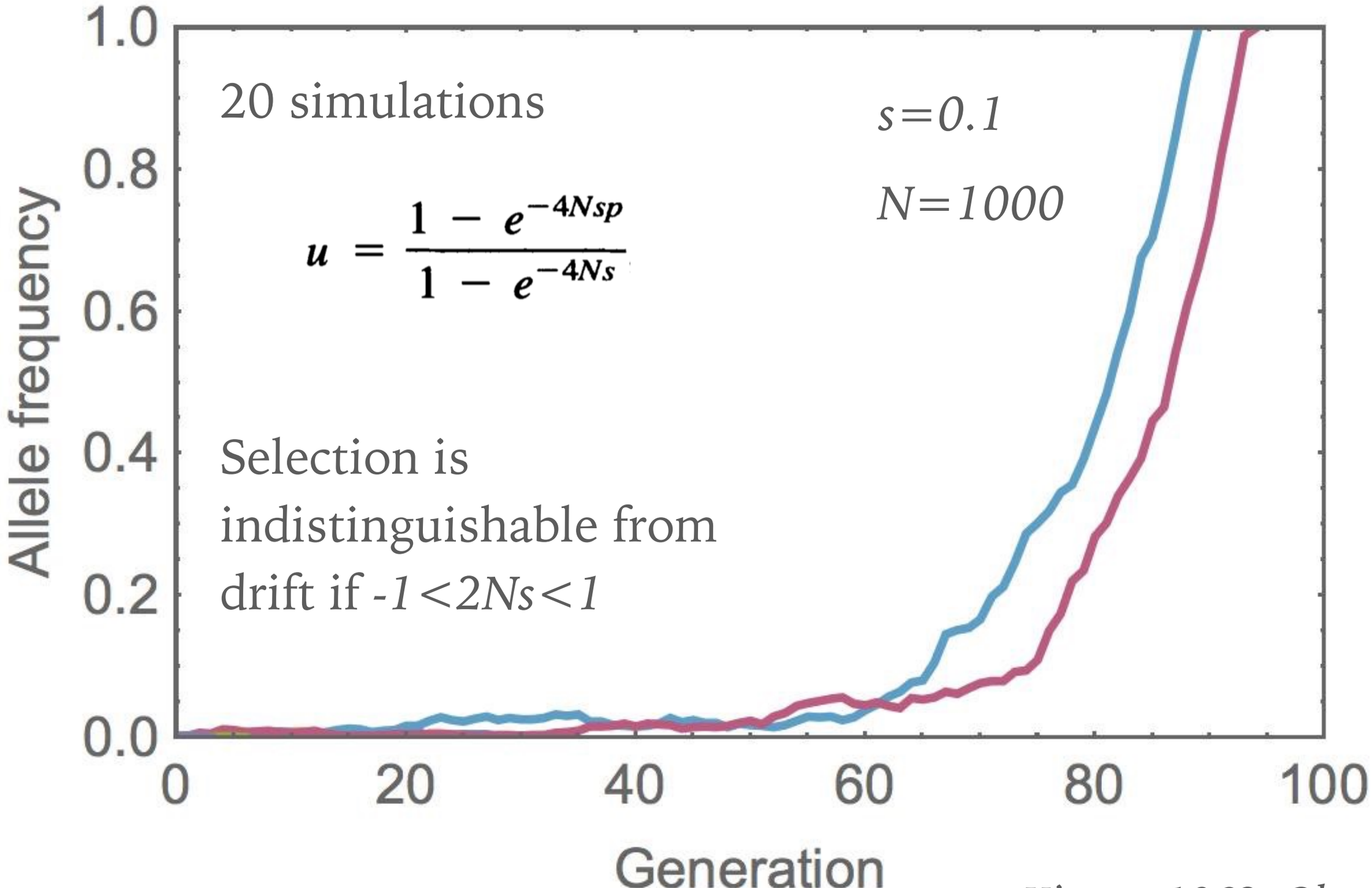

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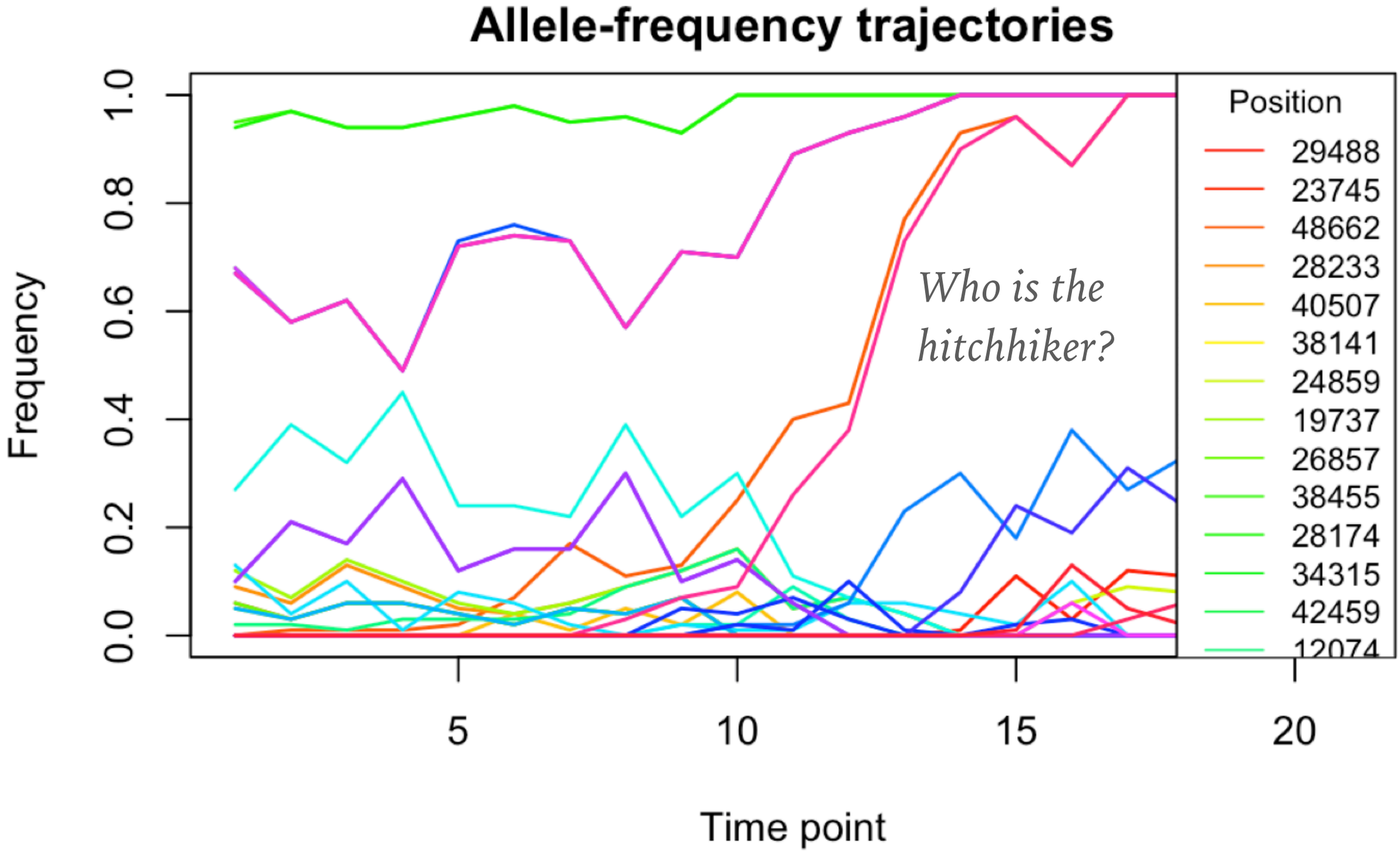
OR LINKAGE


Allele-frequency trajectories
Frequency
0.0
0.2
0.4
0.6
0.8
1.0
5
10
15
20
Time point
Who is the hitchhiker?
Position
29488
23745
48662
28233
40507
38141
24859
19737
26857
38455
28174
34315
42459
12074

OR POPULATION STRUCTURE, OR EPISTASIS, OR [ADD YOUR FAVORITE HERE]

- Keep in mind that selection operates on phenotypic differences among individuals in a population; it does not act on a genotype, much less an allele.

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Evolutionary Dynamics @ IGC:

- How do populations adapt to challenging environments?
  E.g., how does drug resistance evolve?
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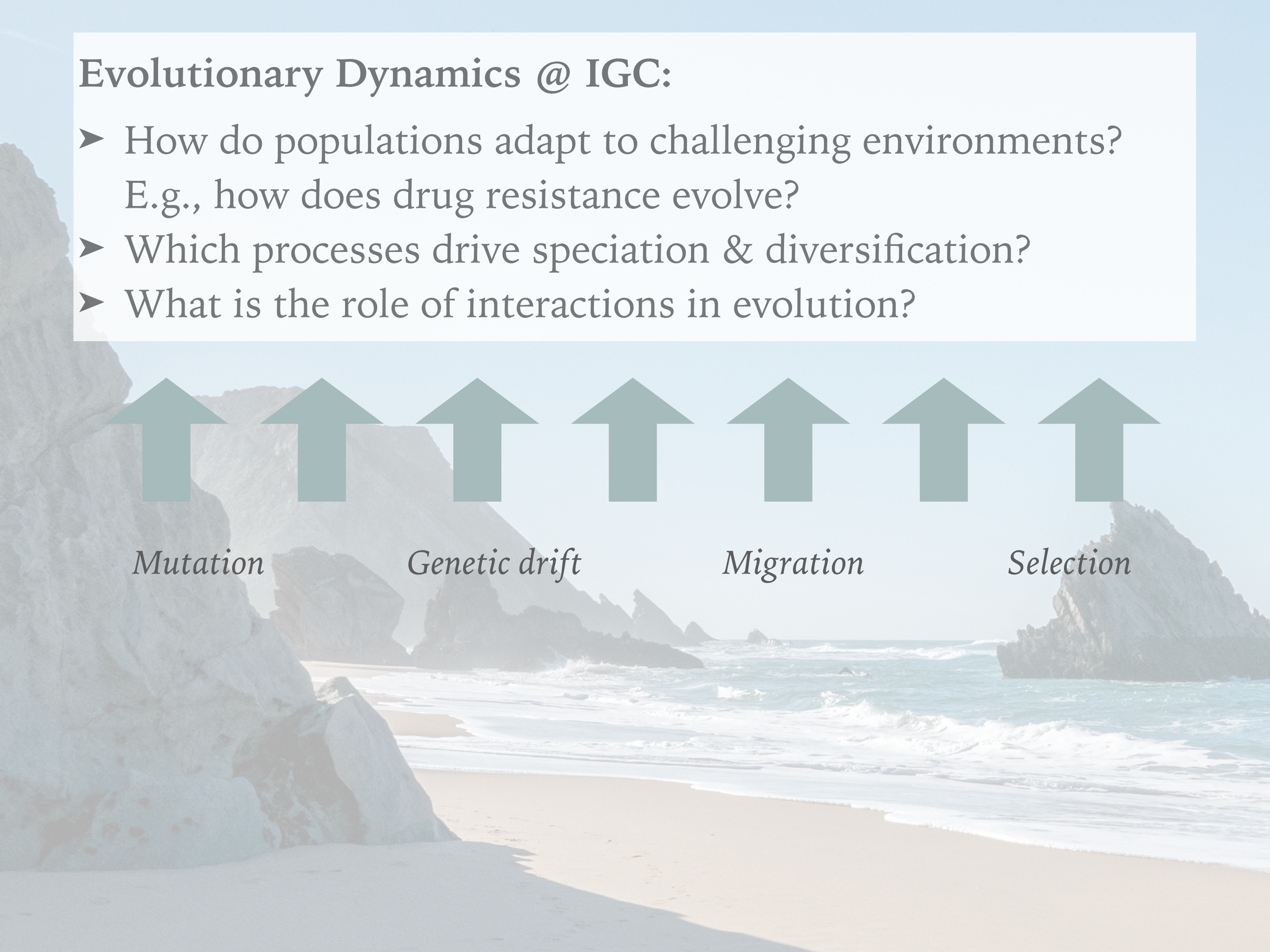

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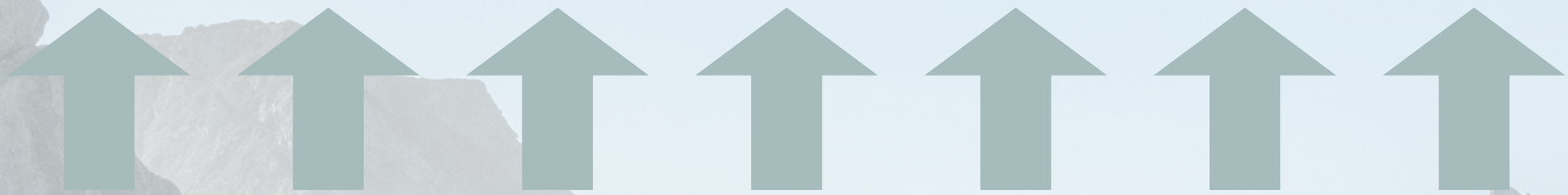

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What we do

- Study evolutionary processes using simple models
- Evaluate these models using empirical and simulated data
- Use modeling to inform experimental design *a priori*

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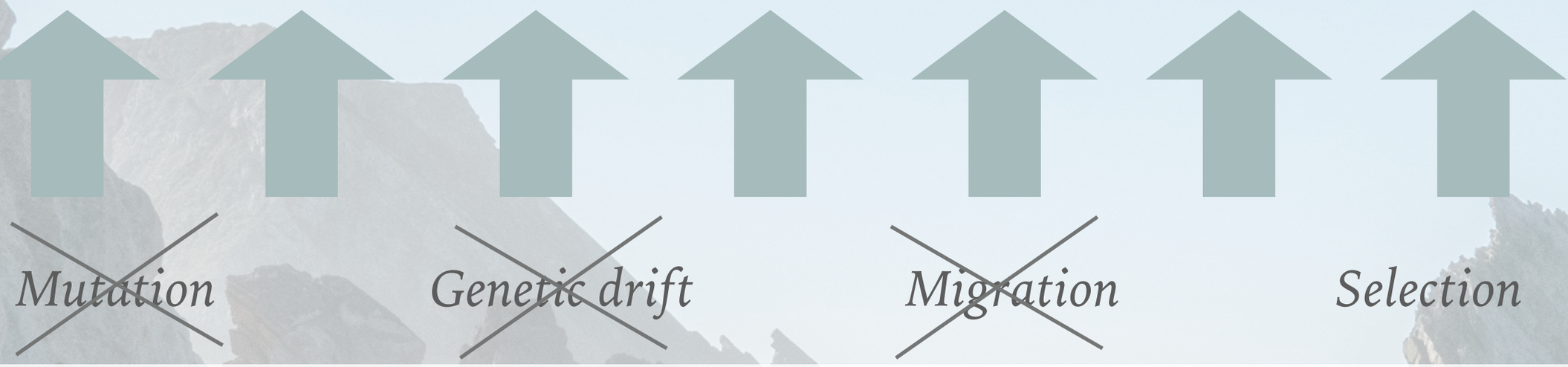

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ADAPTATION VS. "AN ADAPTATION"

- Adaptation: the process of increasing (mean) fitness of a population in a given environment
- An adaptation: a trait that increases its carrier's fitness in a specific environment, and that has spread bc of of the direct action of natural selection for its function

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From Nachmann et al., PNAS, 2003

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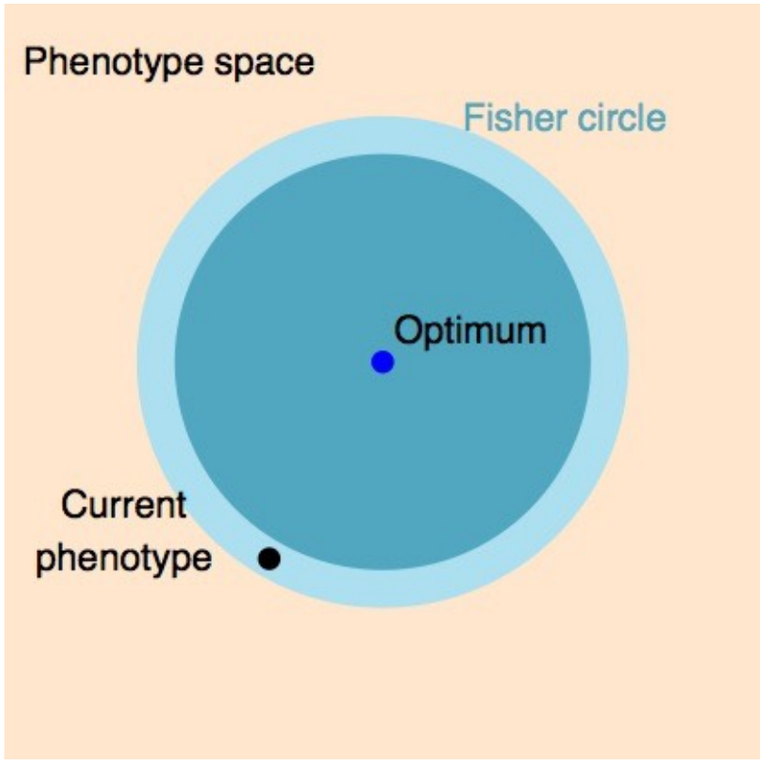
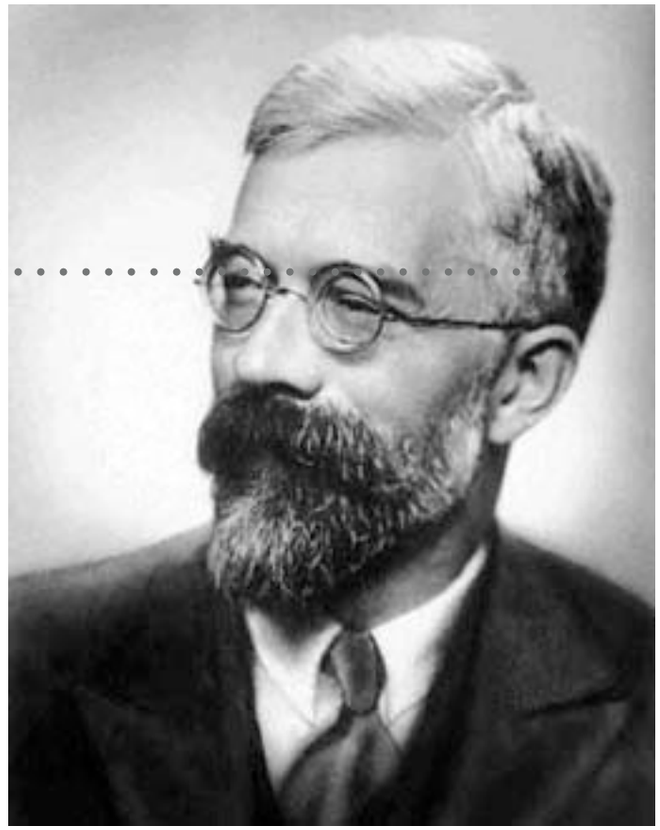
What do we expect adaptation to be like THEORETICALLY?

TWO MODELS OF ADAPTATION

FISHER'S GEOMETRIC MODEL



Fisher, 1930



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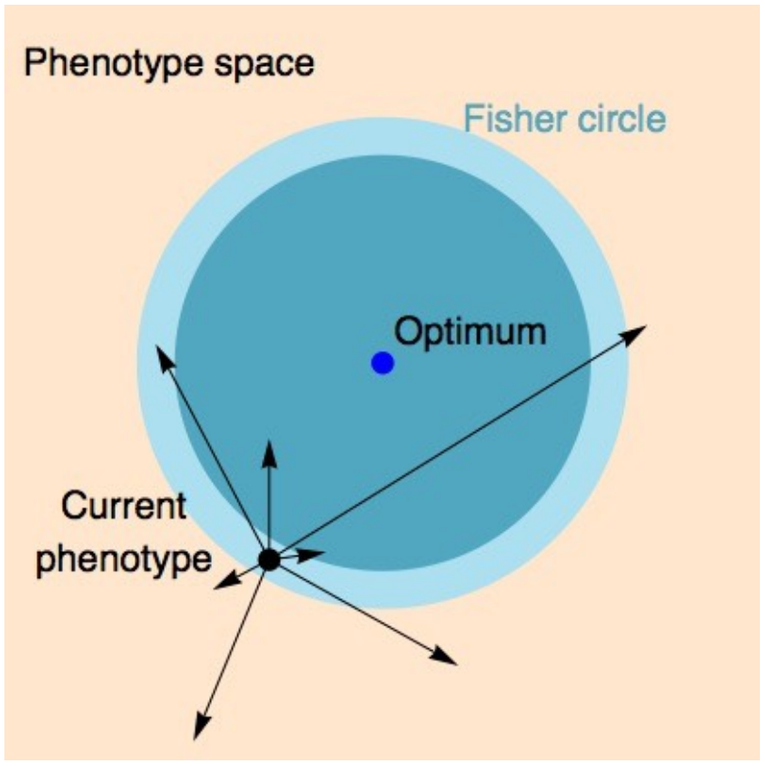

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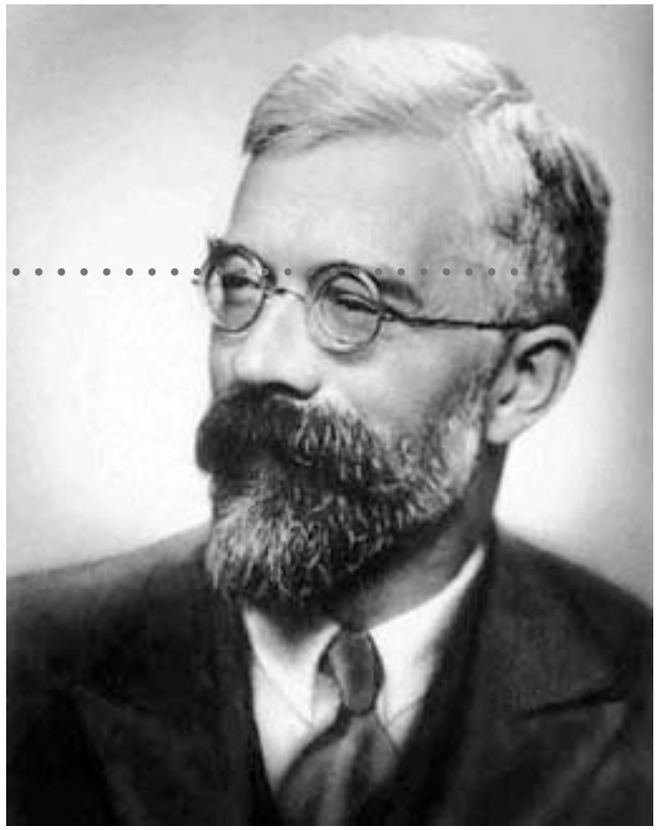

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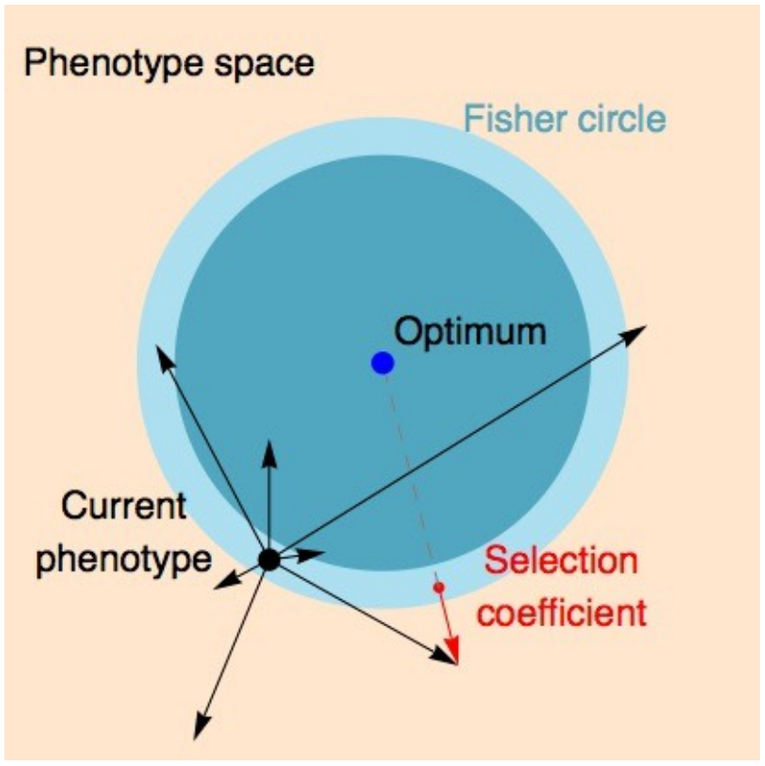

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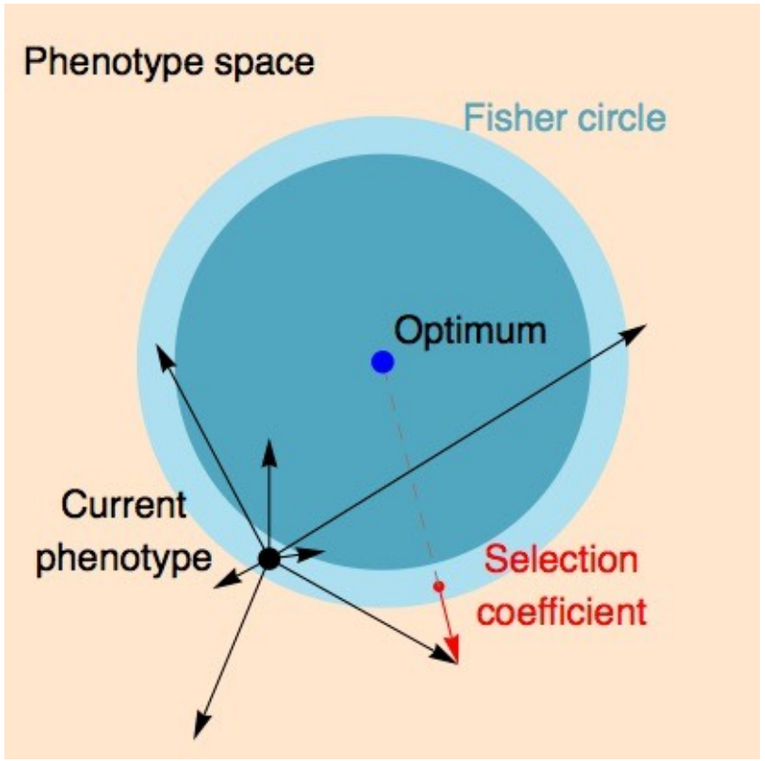

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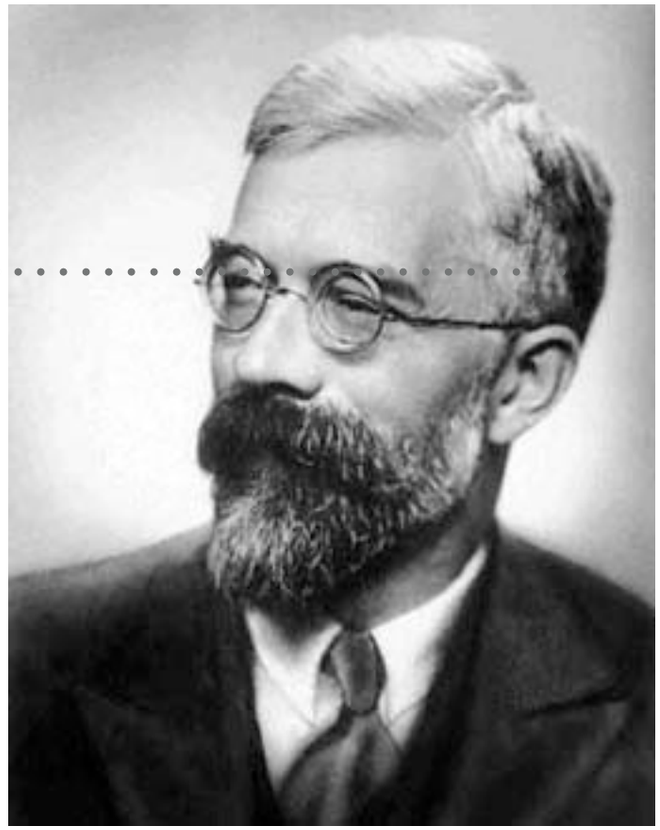
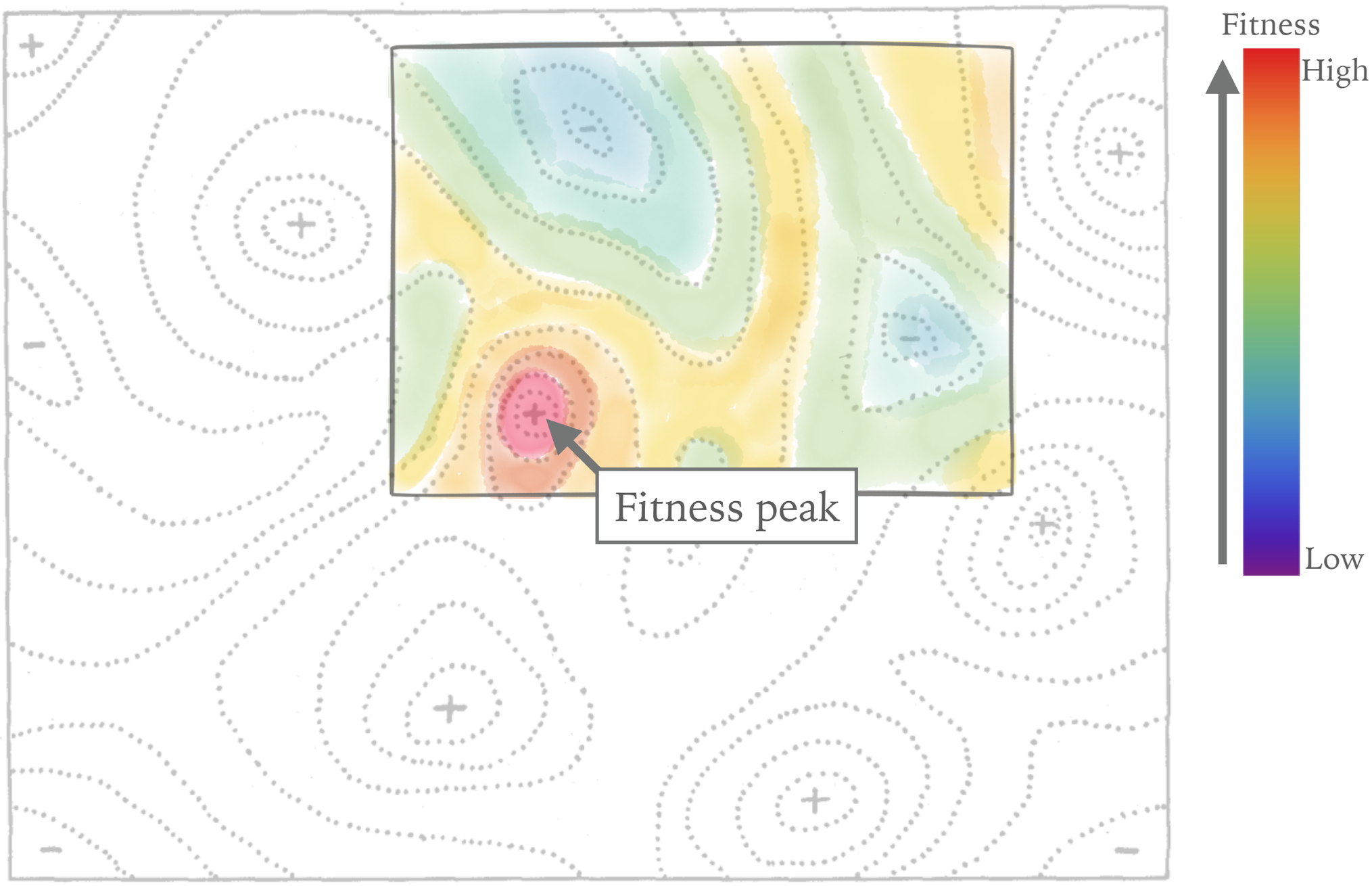


- More challenging environment
  => more beneficial mutations

- Philosophy: Large populations, a single fitness optimum

WRIGHT'S SHIFTING BALANCE



Wright, 1932

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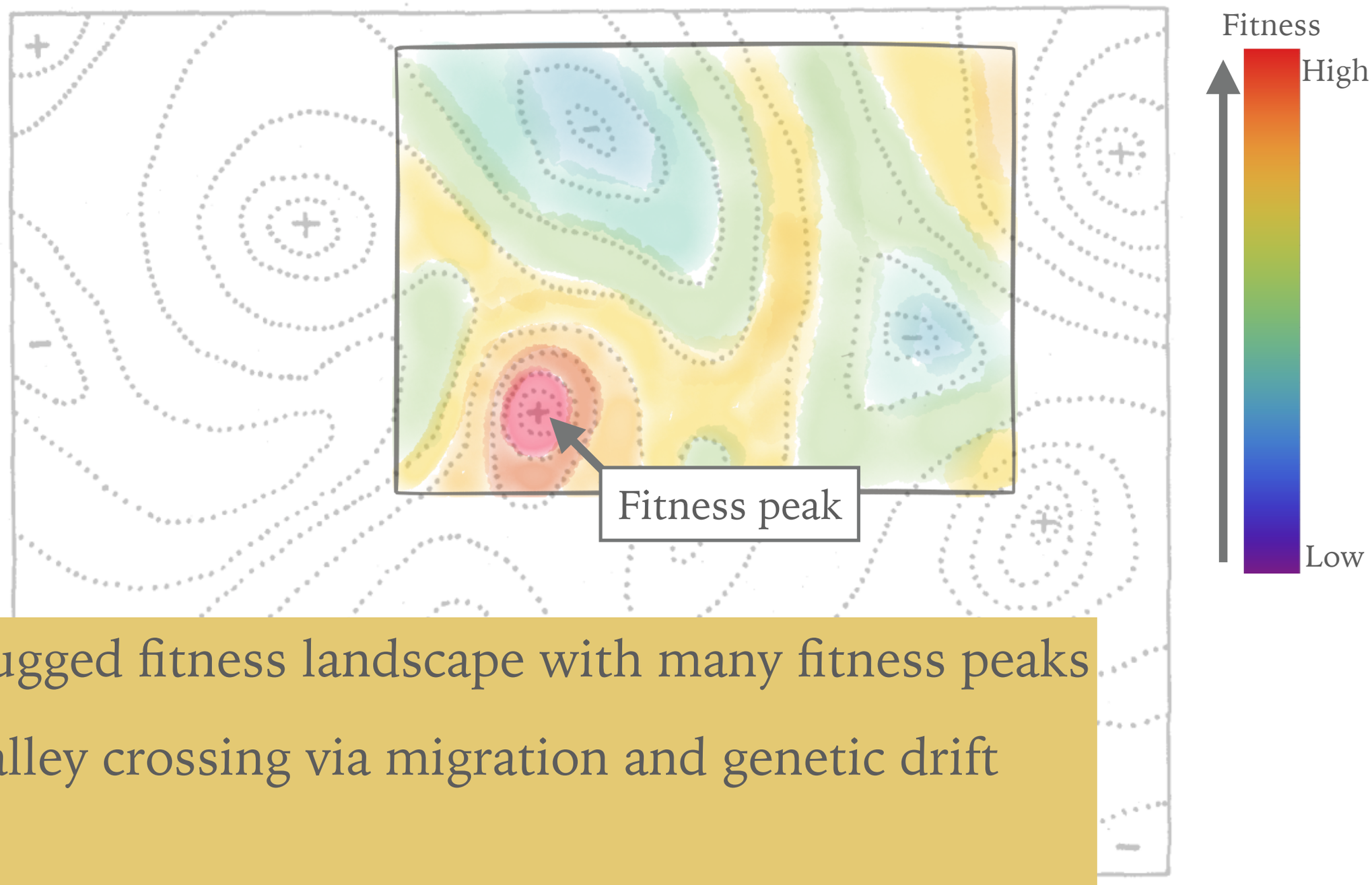

- Rugged fitness landscape with many fitness peaks
- Valley crossing via migration and genetic drift
- Philosophy: Small, structured populations

Wright, 1932

Which team are you on,
Team Fisher or Team Wright, and why?

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- How do mutational effects change dependent on the environment?
- What is the shape of the distribution of fitness effects (DFE)?

ESTIMATES OF MEAN BENEFICIAL EFFECT SIZE FROM POLYMORPHISM DATA

- s=0.002 (Li and Stephan 2006; Jensen et al. 2008)
- s=0.01 (MacPherson et al. 2008)
- s=0.00001 (Andolfatto 2007)

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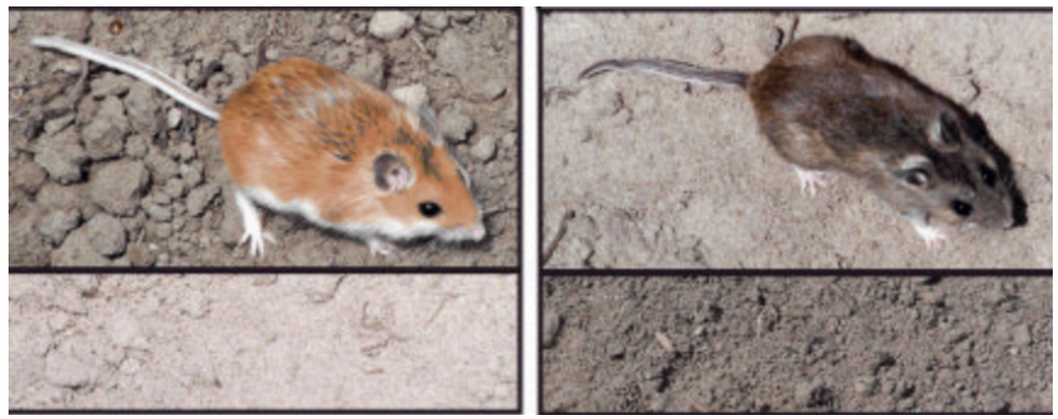

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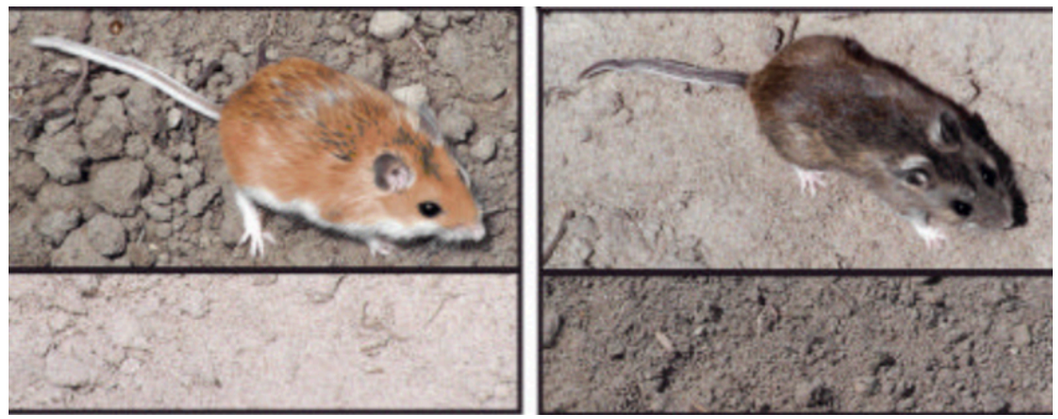


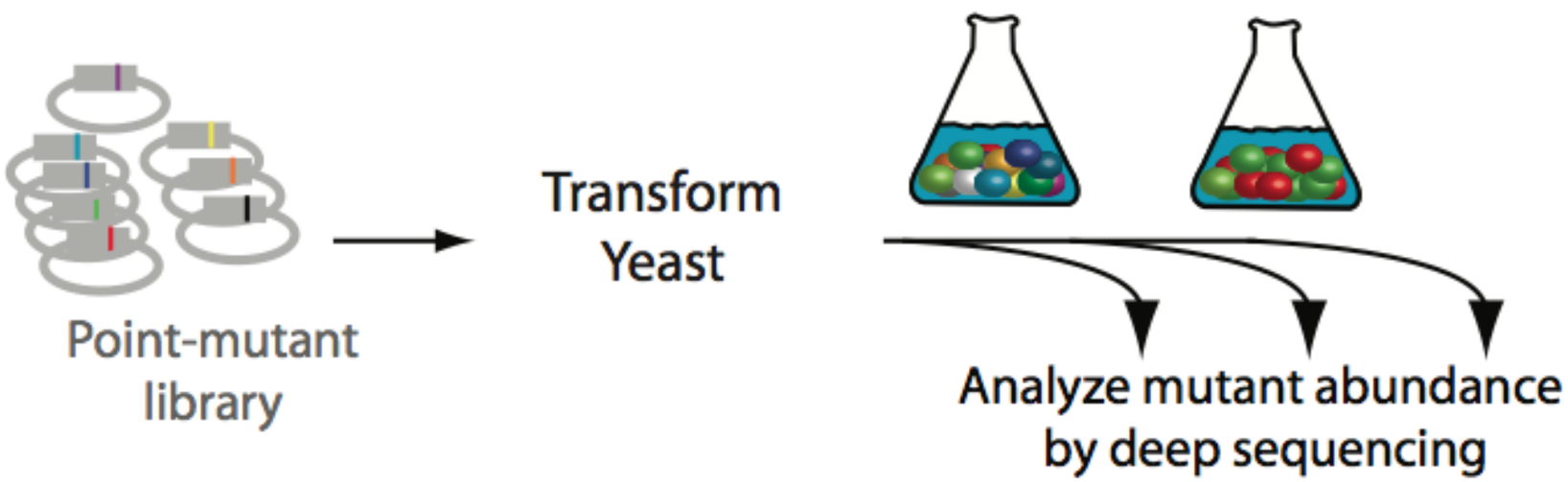
- Example for known phenotype: s=0.102 (Linnen et al. 2009)
- Use experimental approaches to get estimates for whole DFE

AN EXPERIMENTAL APPROACH TO THE DFE: DEEP MUTATIONAL SCANNING

Dan Bolon

Ryan Hietpas

Jeff Jensen



Hietpas, Jensen & Bolon, PNAS, 2011

AN EXPERIMENTAL APPROACH TO THE DFE: DEEP MUTATIONAL SCANNING

- Systematic high-throughout sampling of hundreds of chosen mutations (including those that are strongly deleterious)
- Bulk competitions ensure identical conditions for all mutants
- Genetic background is precisely controlled (minimized potential for secondary mutations)

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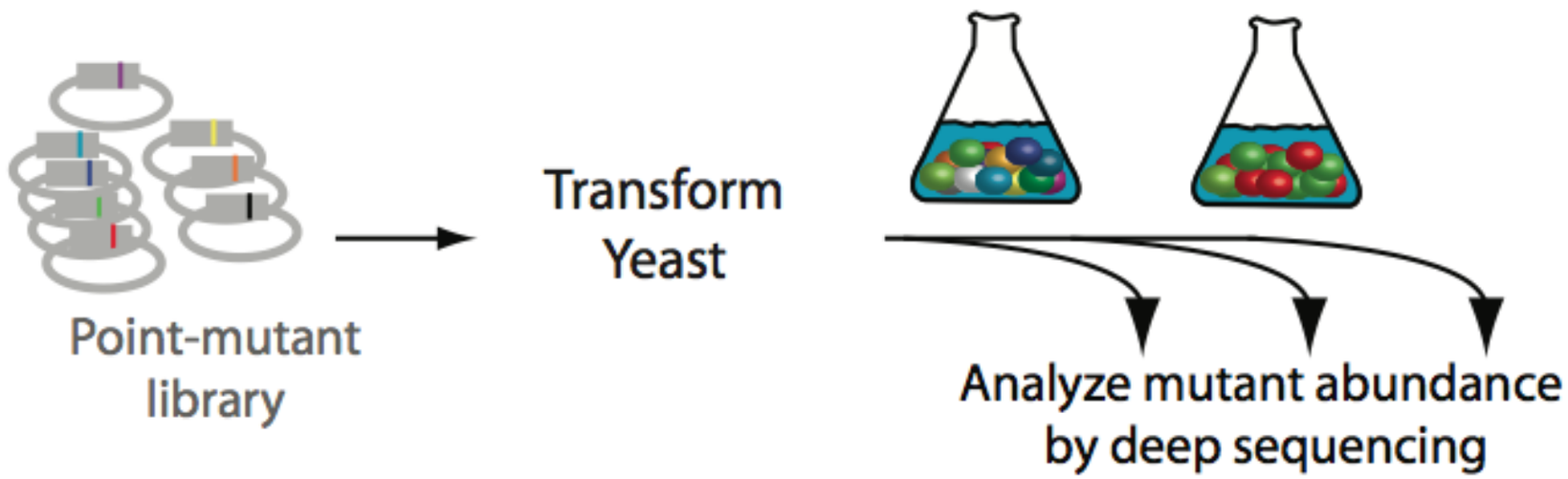

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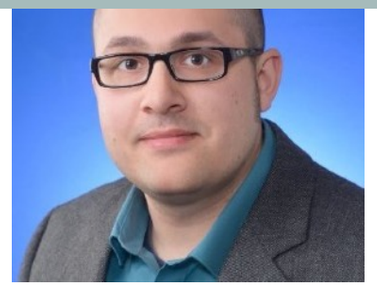
Deep mutational scanning results in a (almost "evolution-free") snapshot of the DFE

- Genetic background is precisely controlled (minimized potential for secondary mutations)



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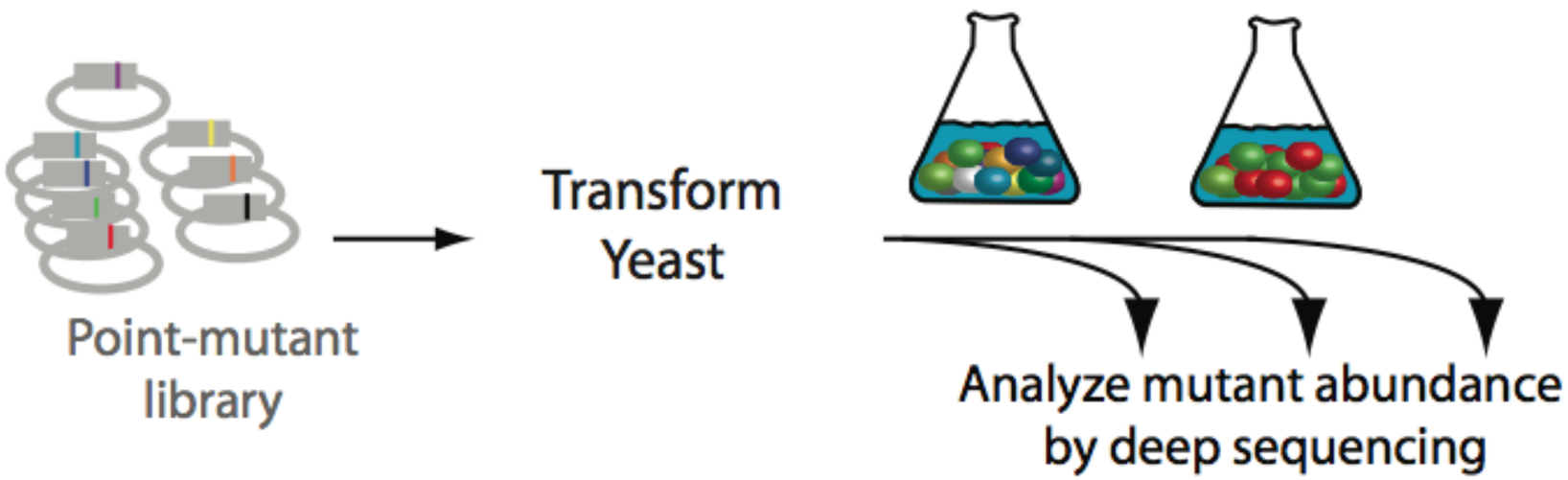

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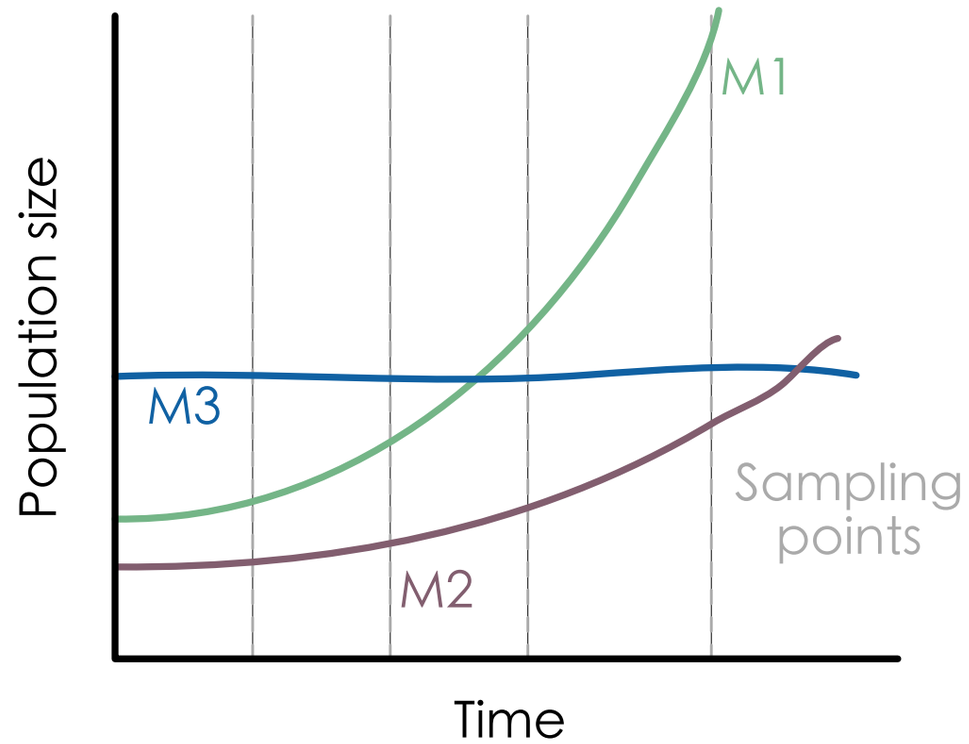
DEEP MUTATIONAL SCANNING FROM A MODELER'S POINT OF VIEW

- Exponential growth of hundreds of mutants, each with its own growth rate/selection coefficient
- Sequencing corresponds to multinomial sampling of mutants independently at each sampling time



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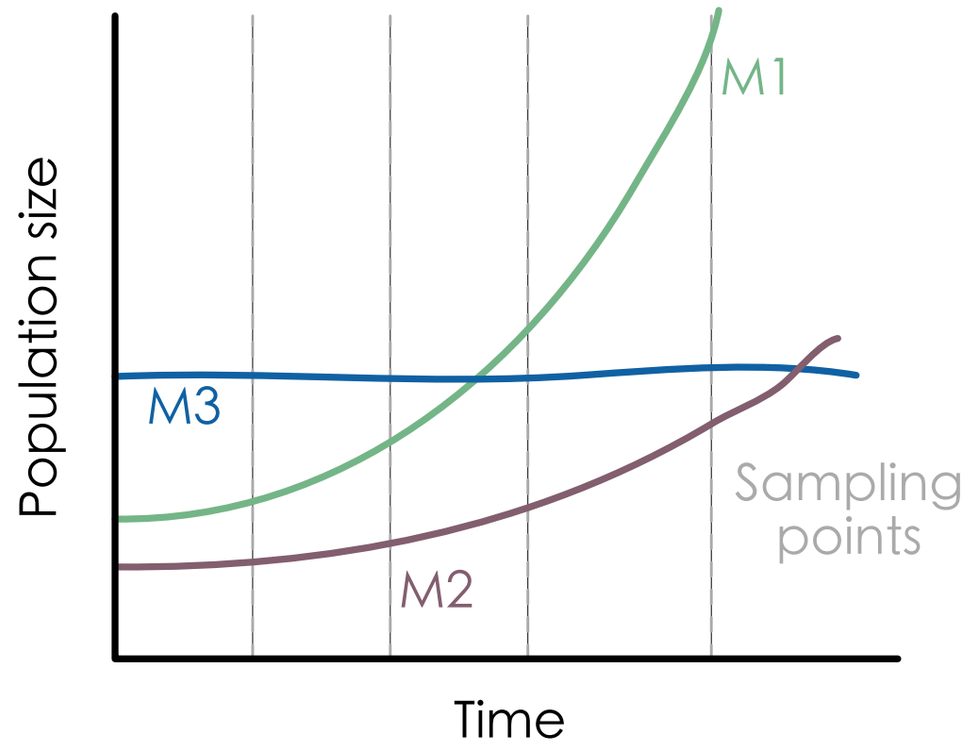

- <1% fitness differences detectable

For the “Fisherians”: the shape of the DFE across environments

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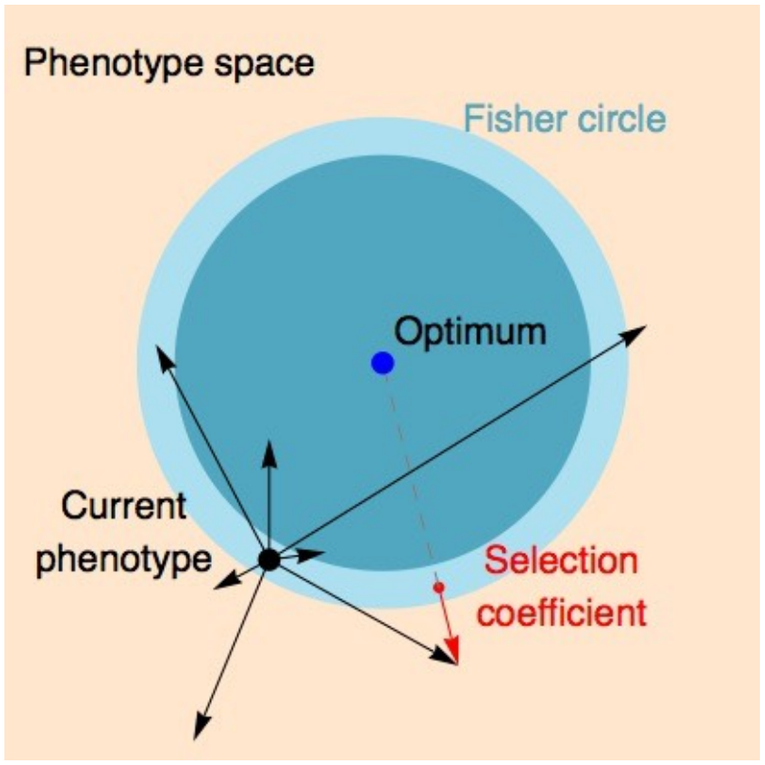

Fisher, 1930

Hypotheses:

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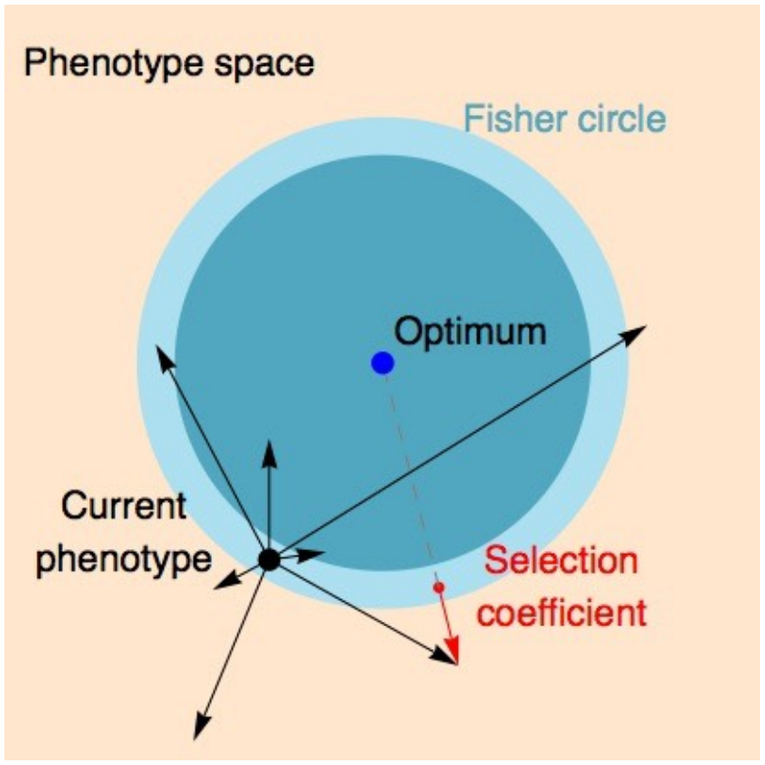

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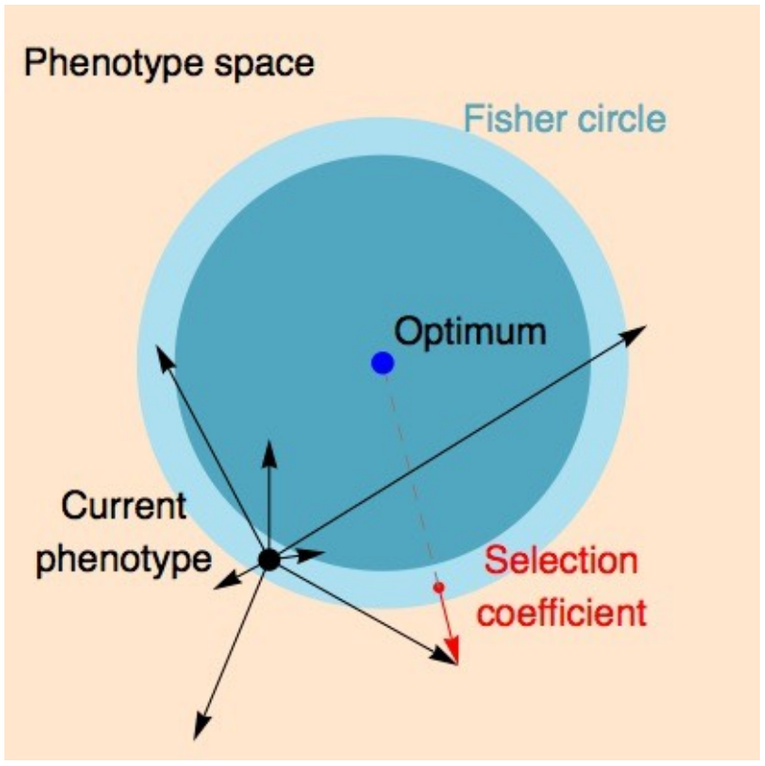

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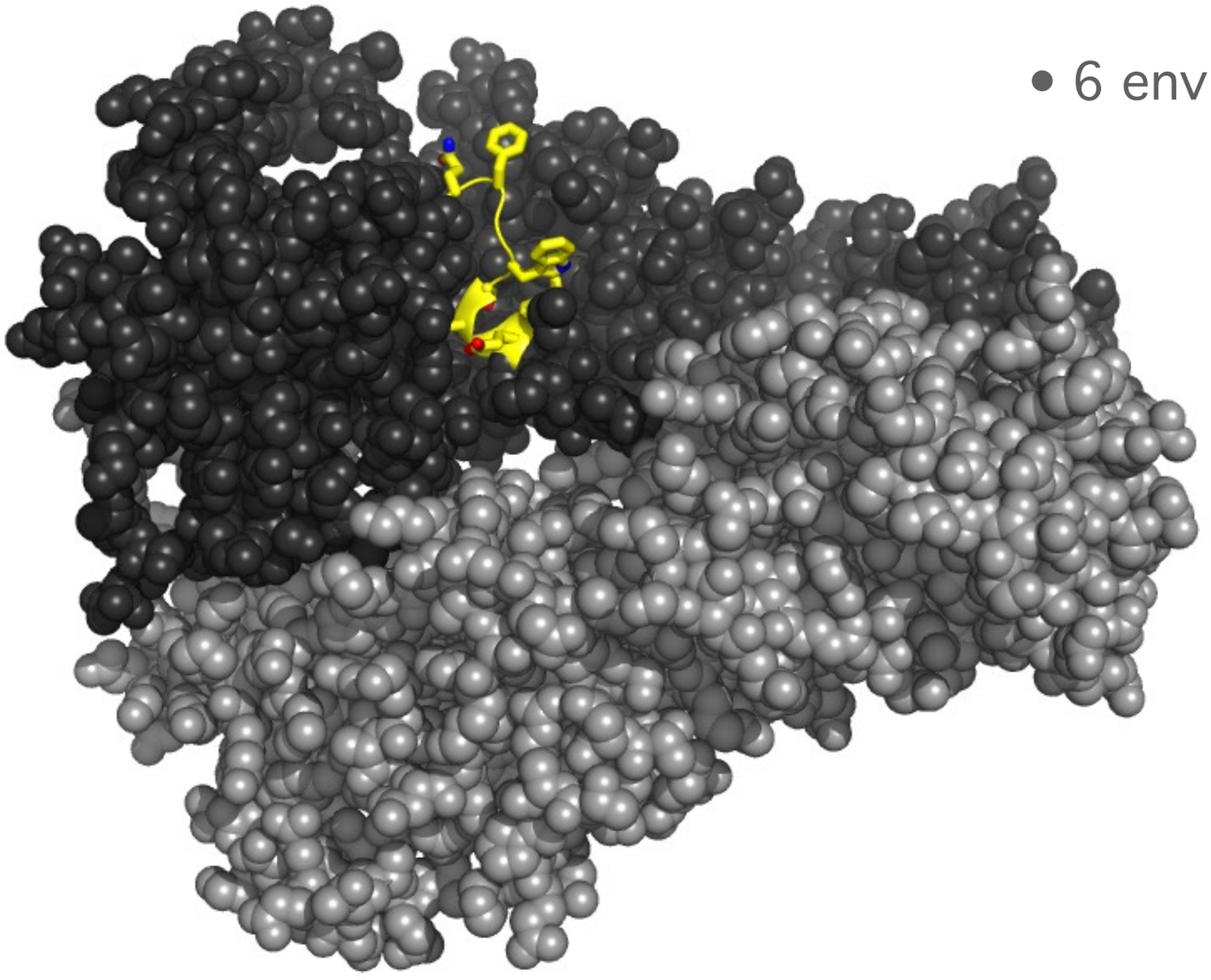
Hypotheses:

- Relocation of the optimum or the current phenotype in a new environment can increase the distance to the optimum and hence the potential for beneficials.
- The distribution of beneficial mutations is bounded or exponential.

THE SHAPE OF THE DFE IN CHALLENGING ENVIRONMENTS

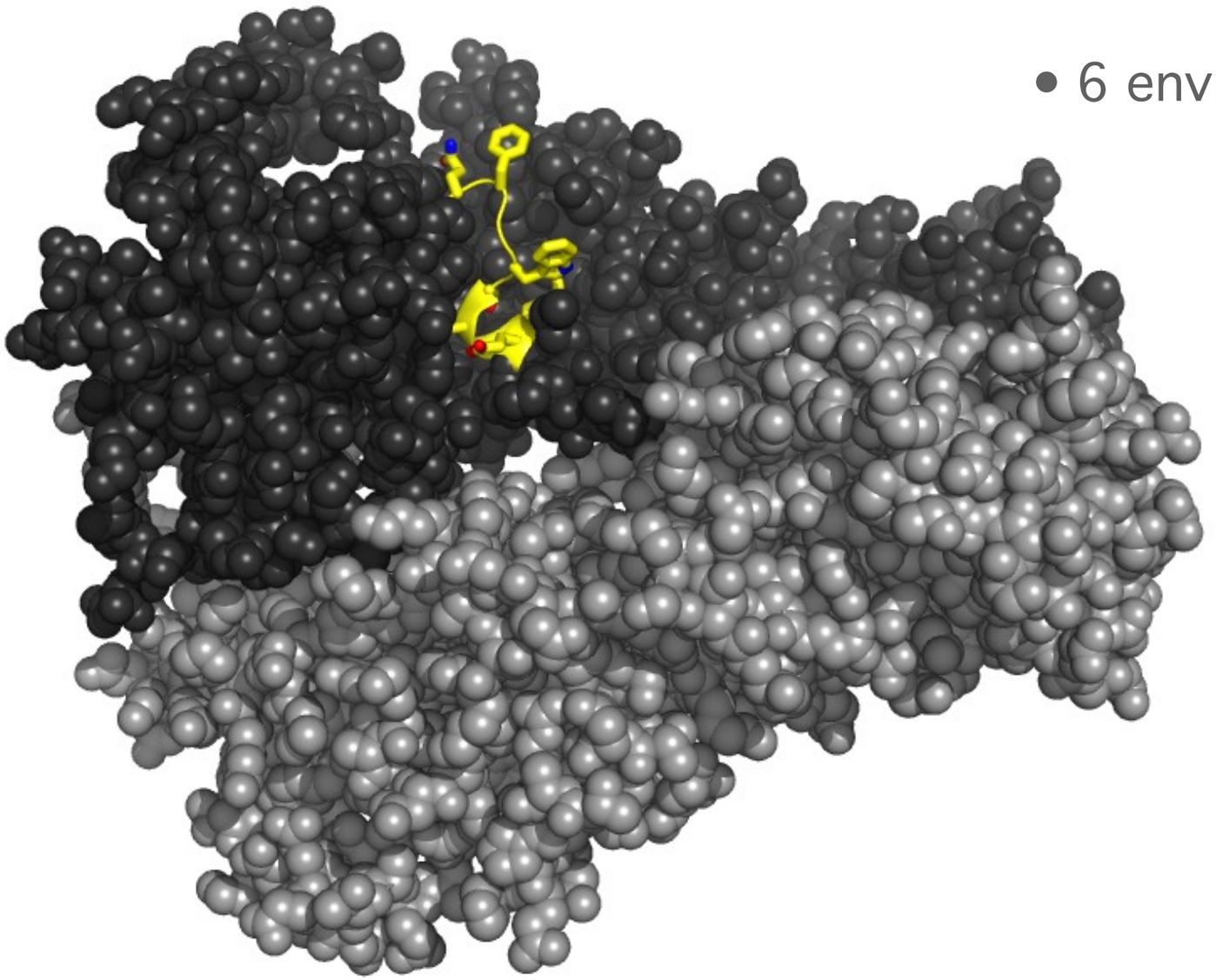
The data set



- 9 aa region from Hsp90 (aa positions 582-590) in Saccharomyces cerevisiae
- 6 environments:

Data obtained by Ryan Hietpas @ UMassMed

The data set



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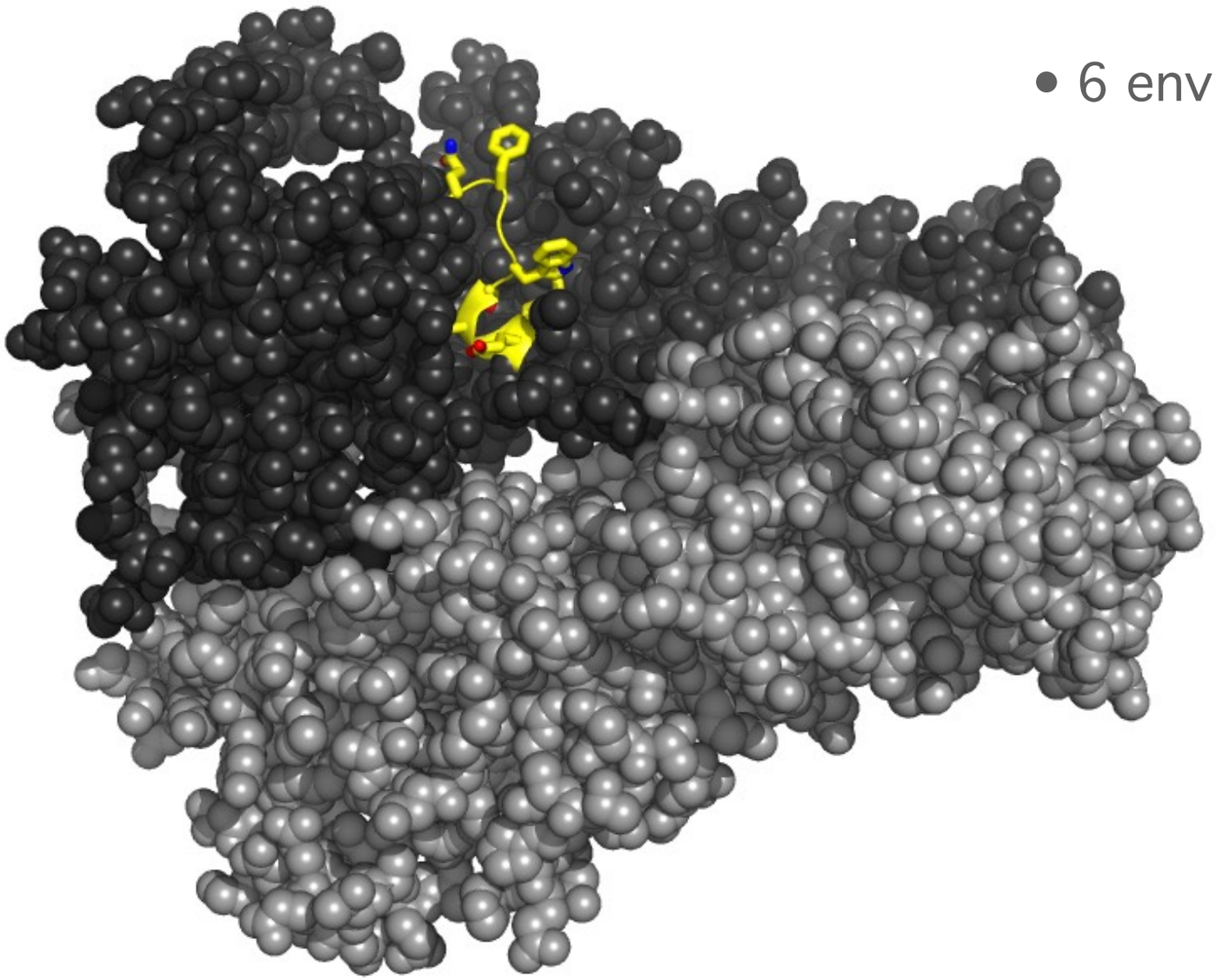

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Relative growth of wt:

1	0,45
0,83	0,33
0,63	0,3

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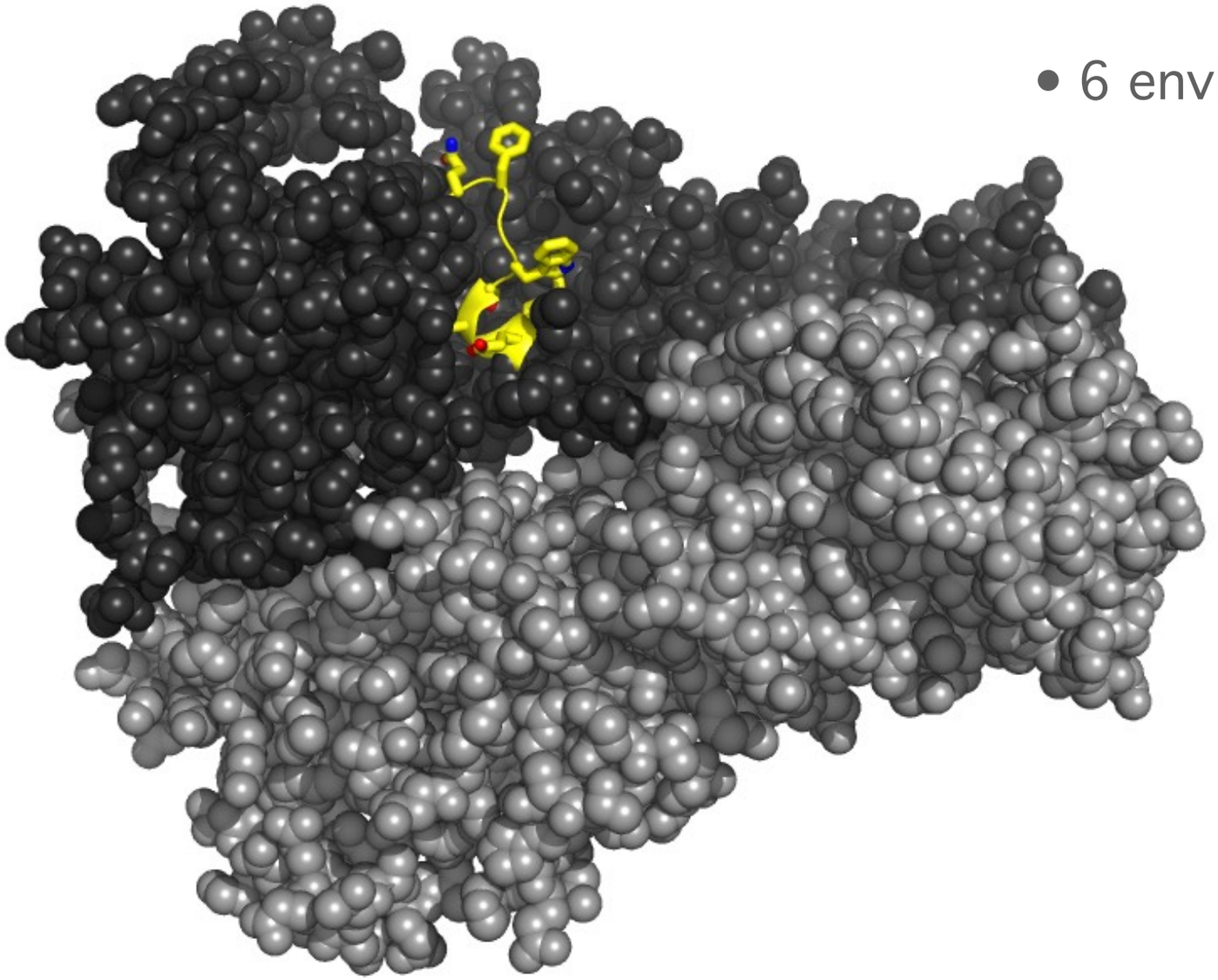

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- Fitness data for every possible codon at each aa position (i.e. the same 560 mutations per environment)

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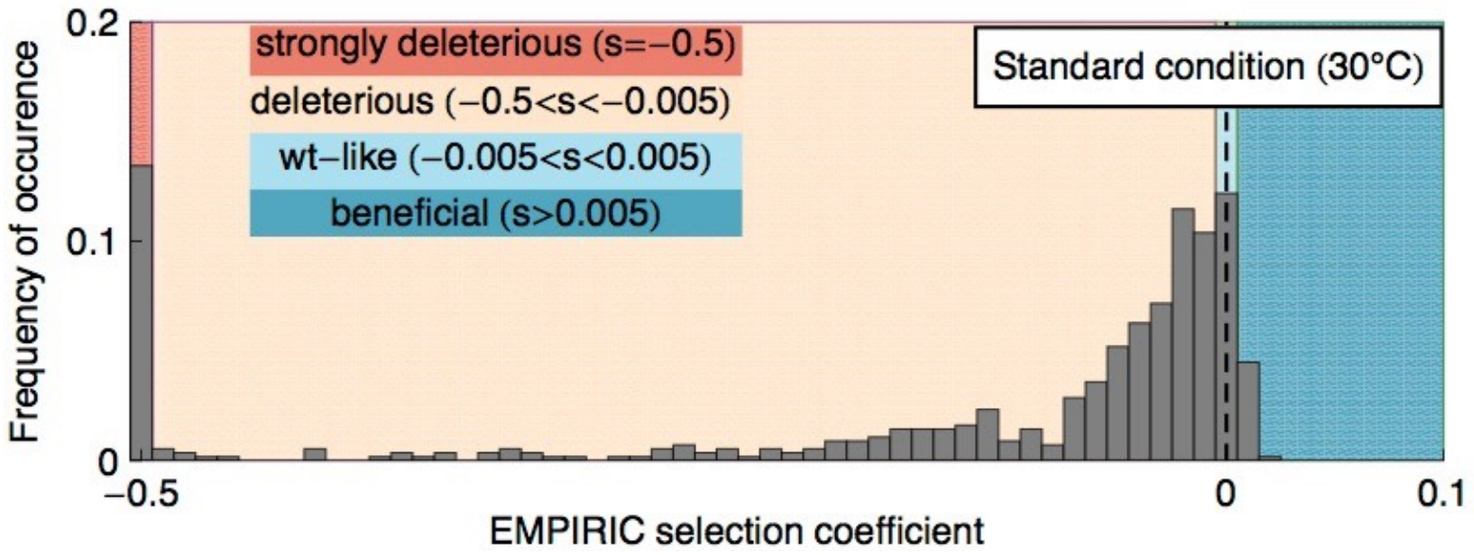
The shape of the full DFE



Hietpas, Bank et al. 2013

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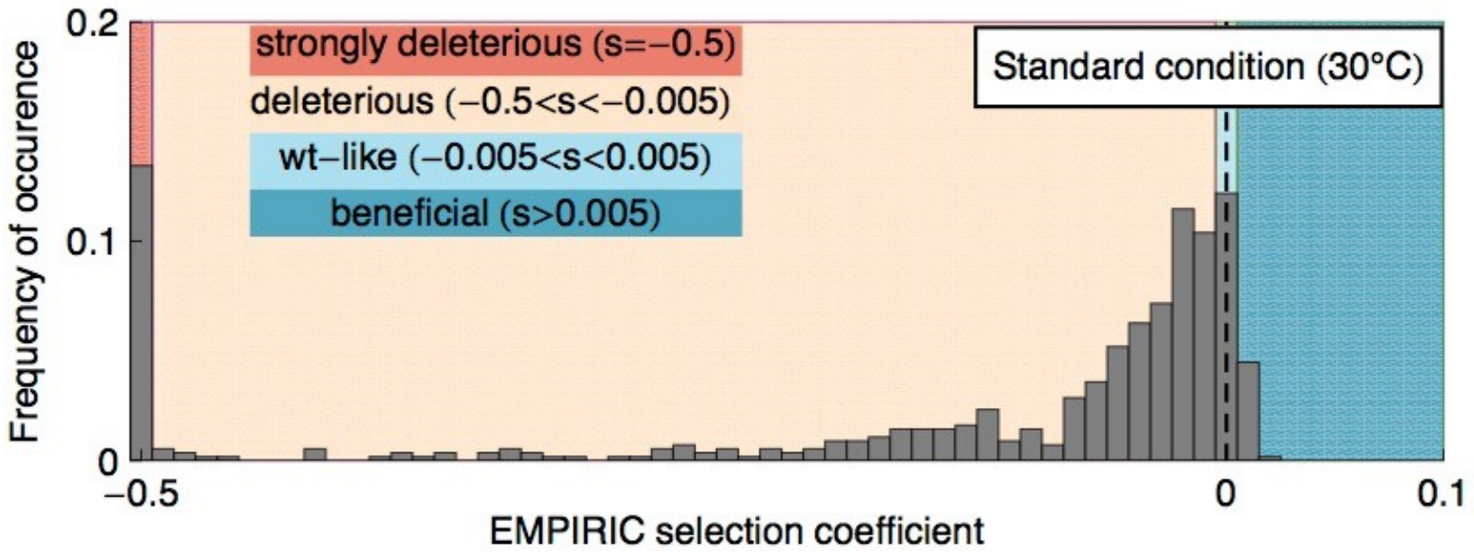
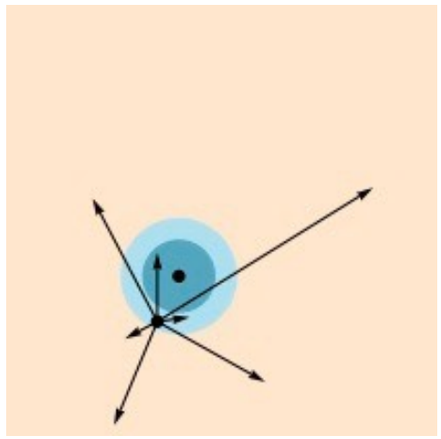
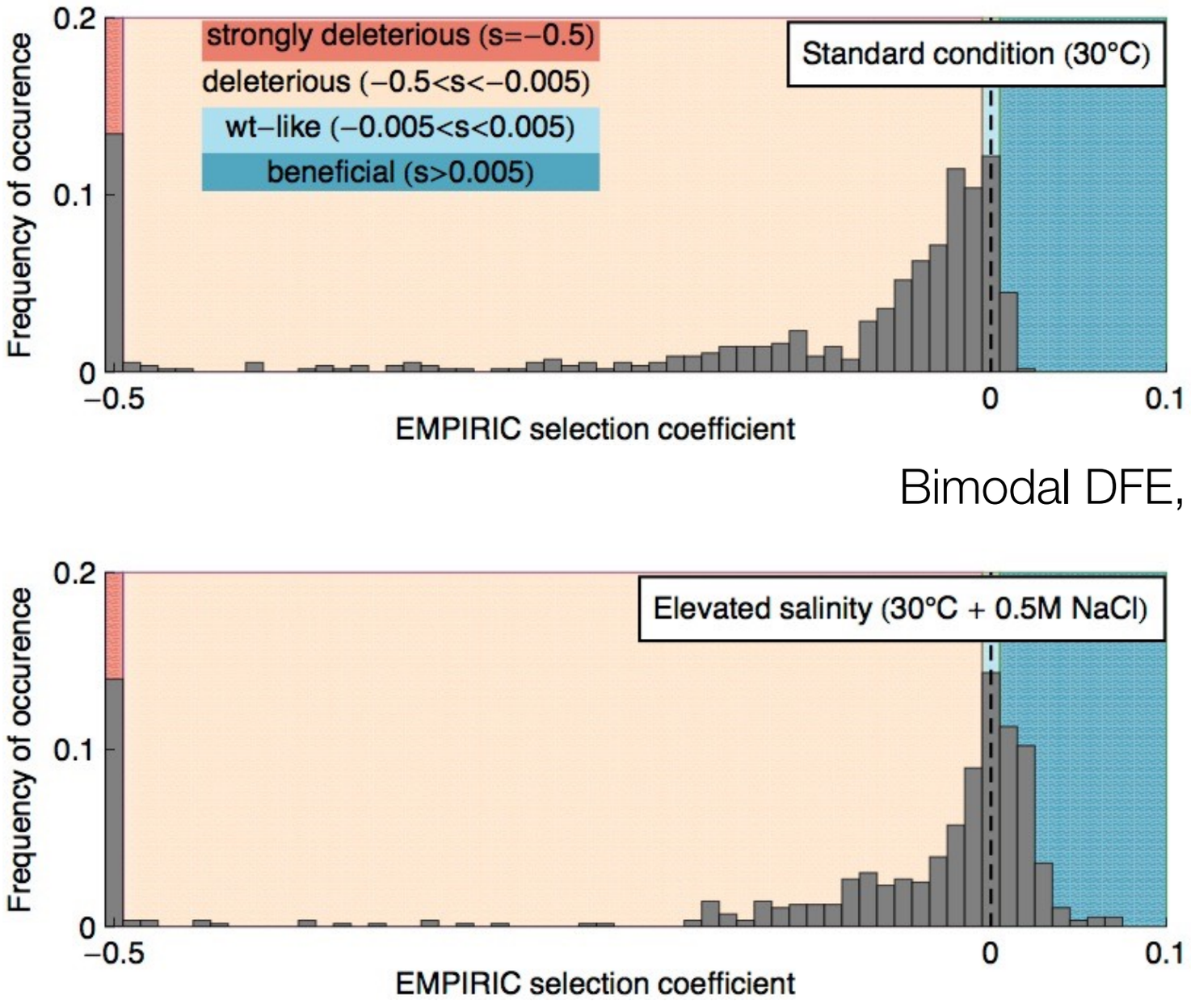


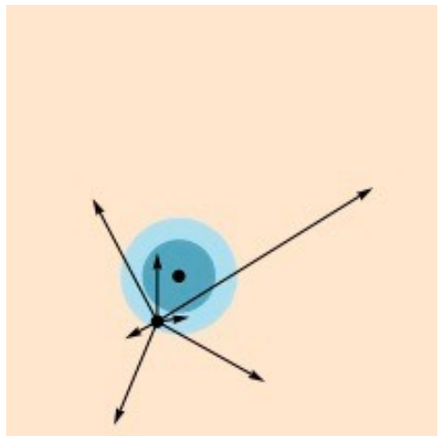


Bimodal DFE, few beneficials - close to optimum

Hietpas, Bank et al. 2013

The shape of the full DFE





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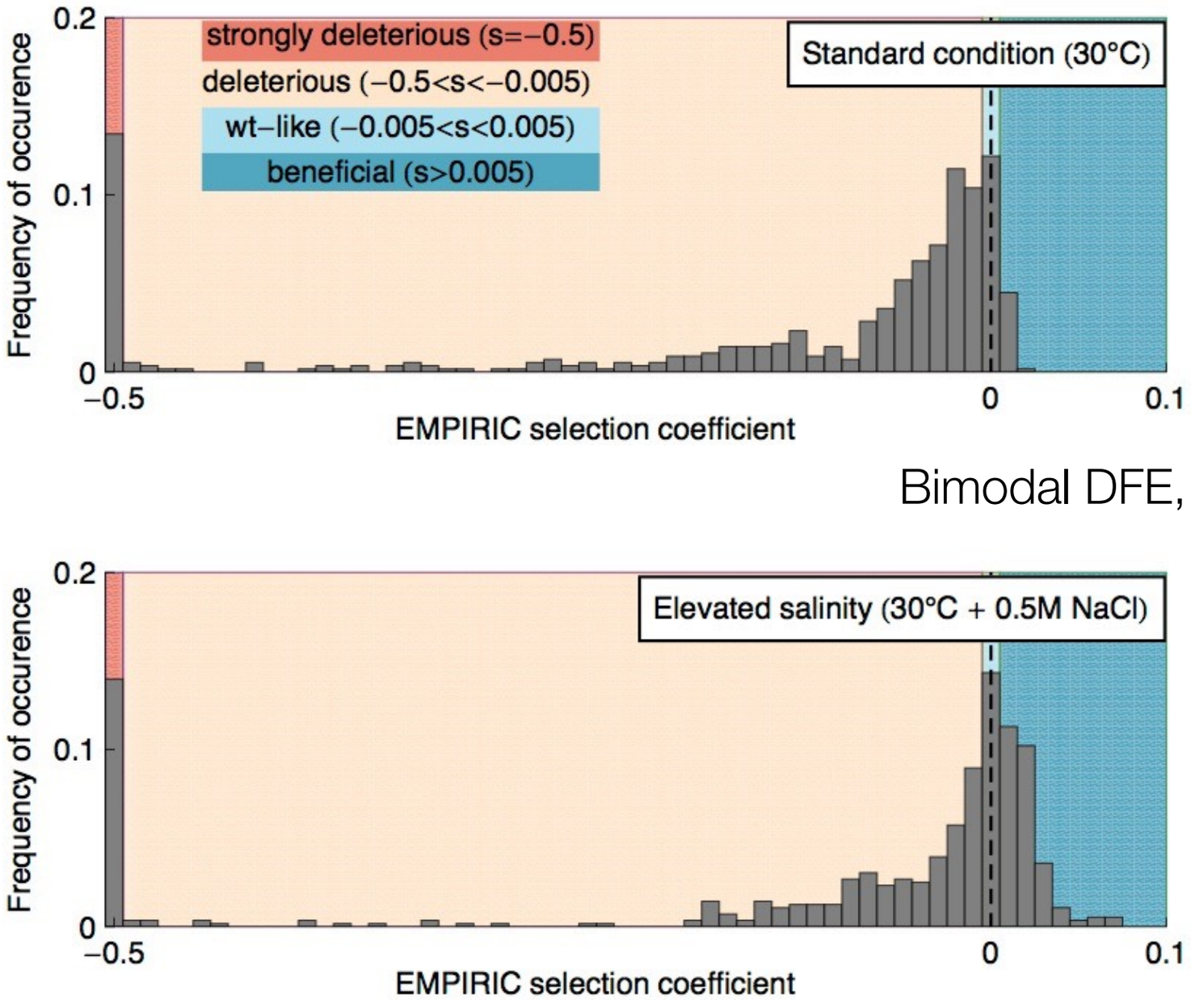

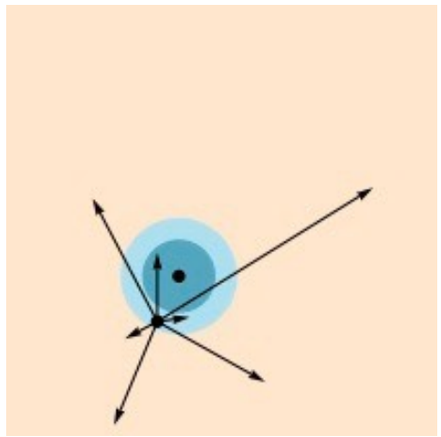

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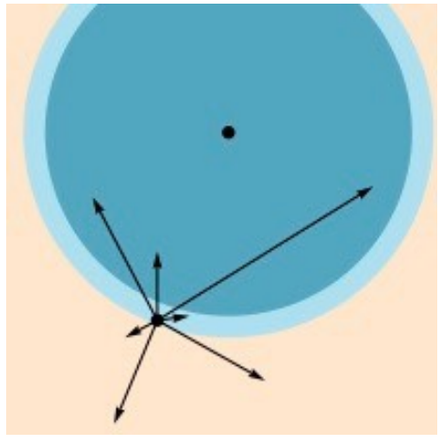
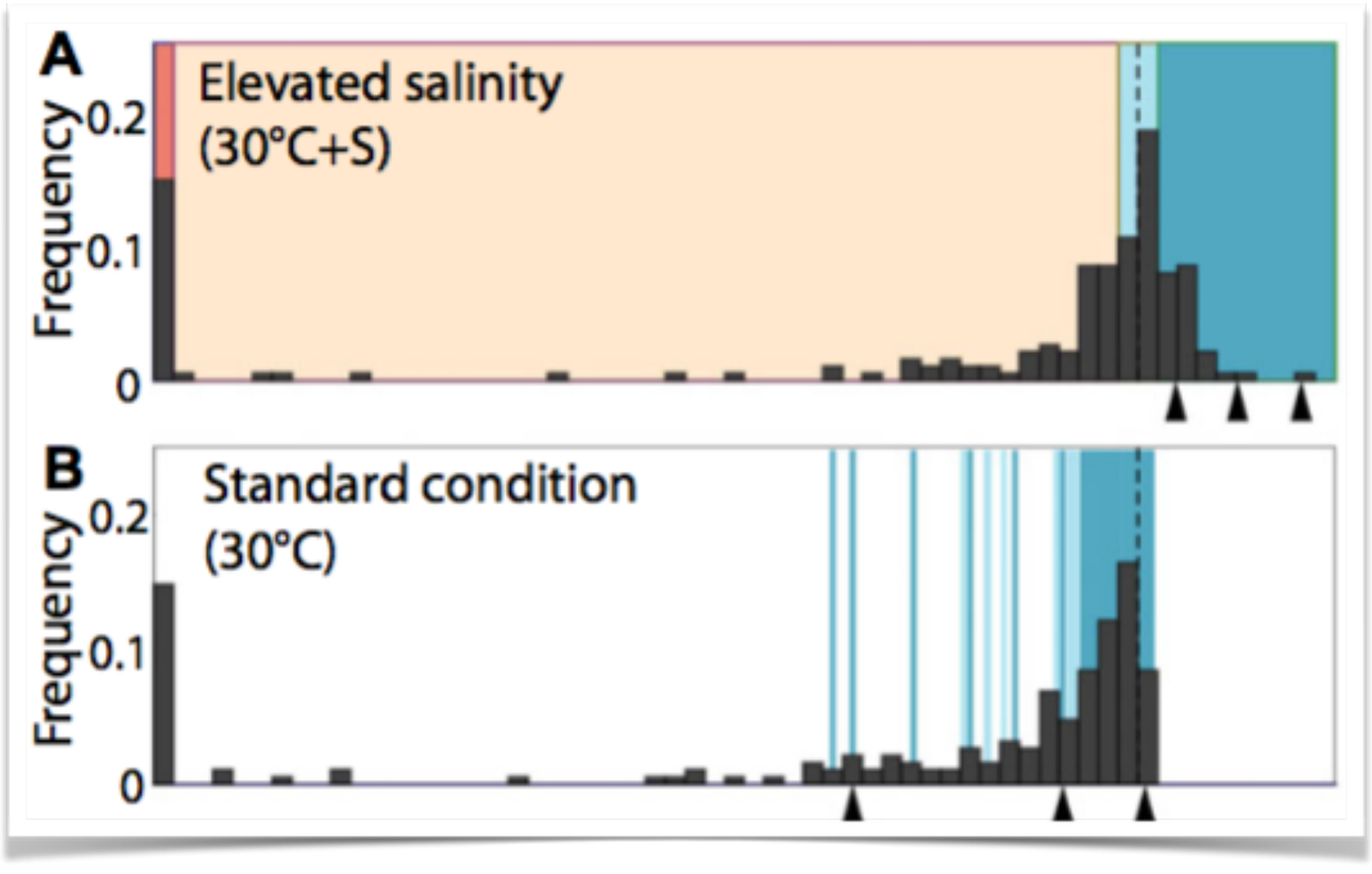


Increased number of beneficials, increased variance - far from optimum

Hietpas, Bank et al. 2013

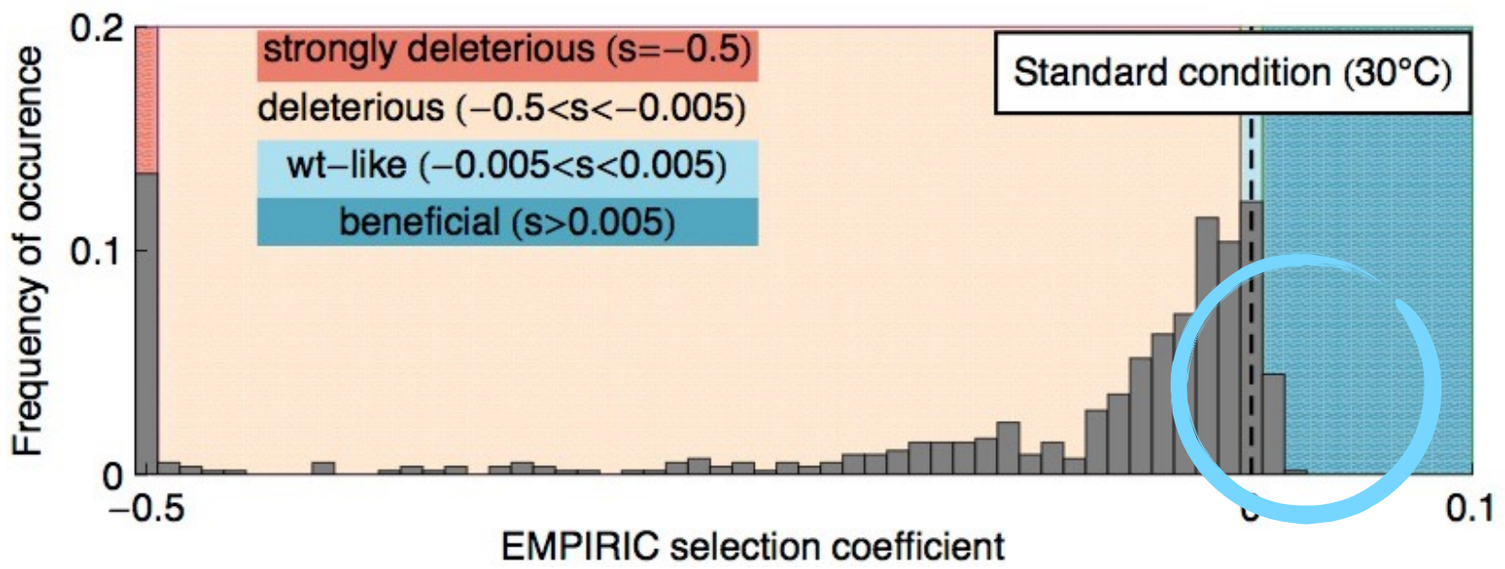
COSTS OF ADAPTATION



THE SHAPE OF THE BENEFICIAL TAIL OF THE DFE

HOW PREDICTABLE IS ADAPTIVE EVOLUTION?

- Fit Generalized Pareto distribution to beneficial tail
- Kappa parameter determines tail shape



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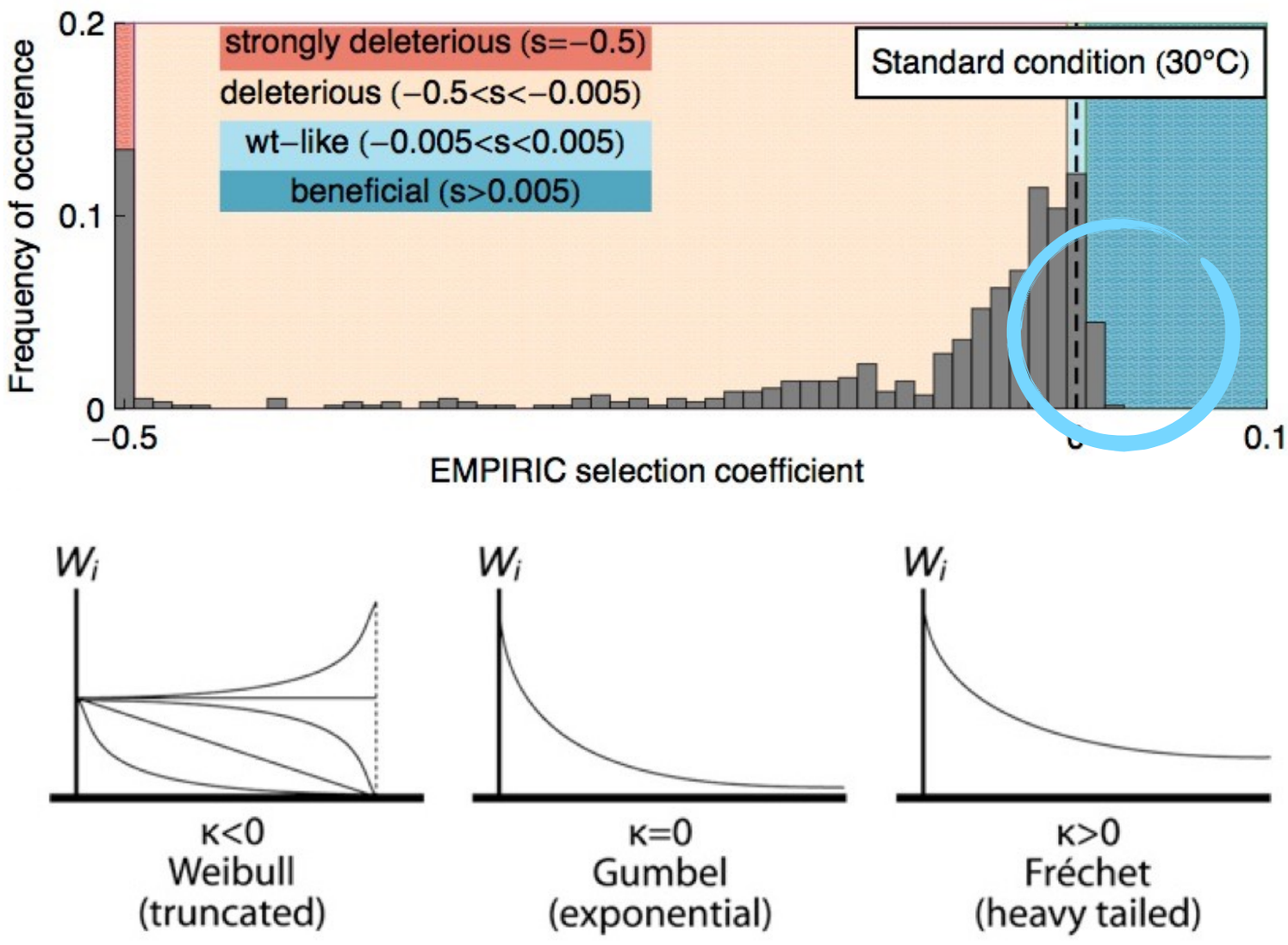

From Beisel et al., Genetics, 2007

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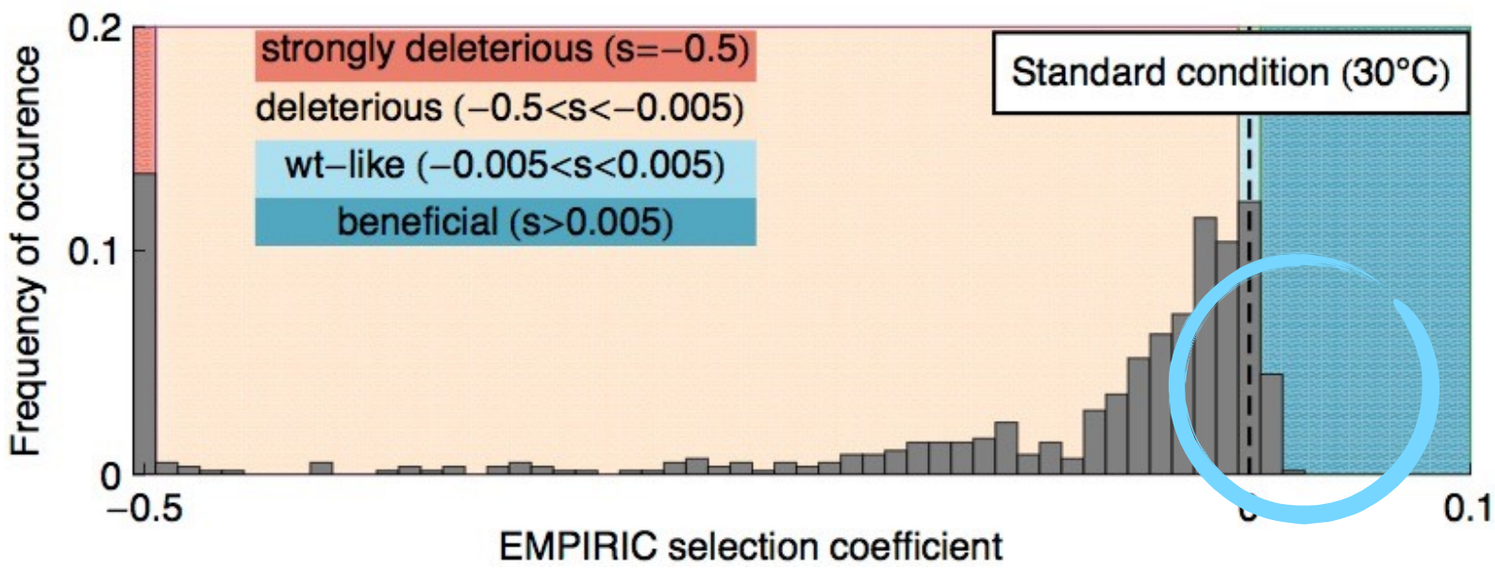
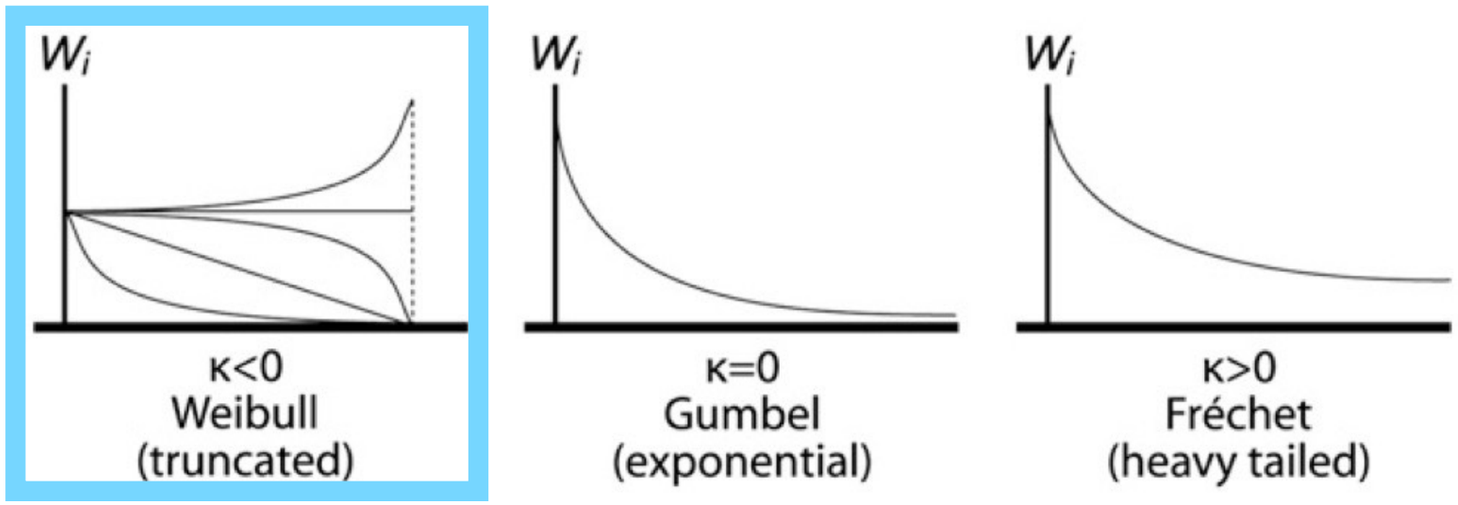


- Bounded DFE, limited potential for adaptation
- Consistent with FGM with close optimum



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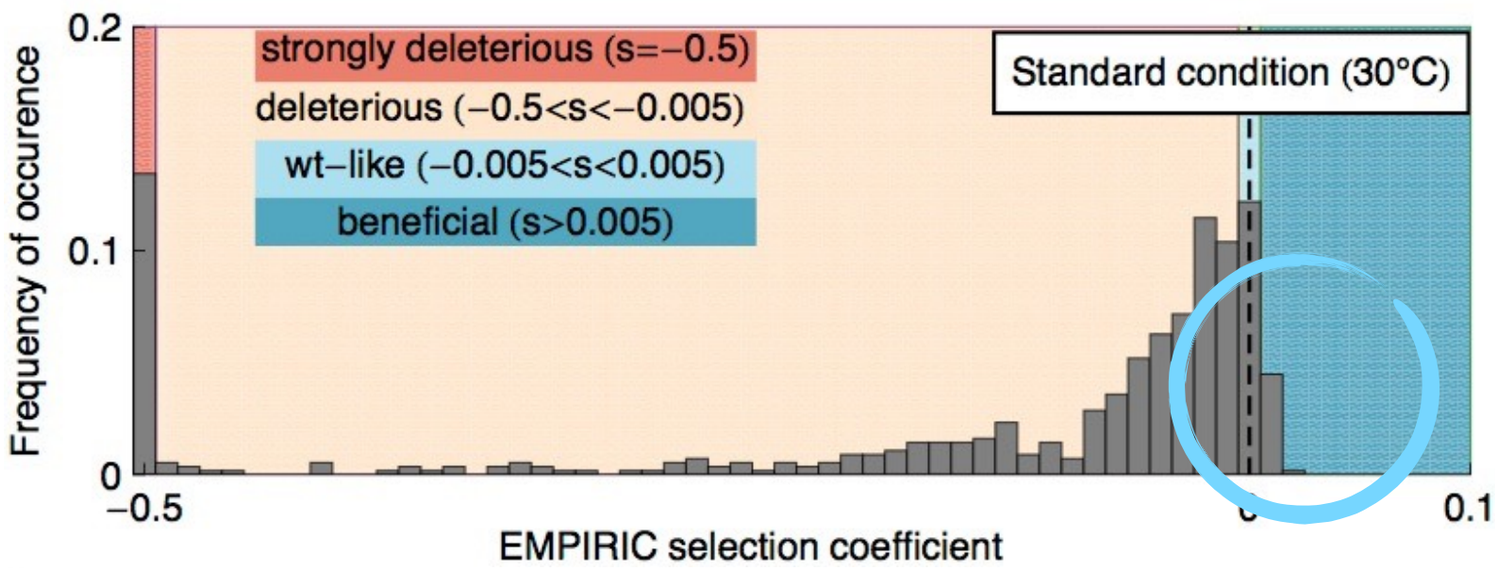

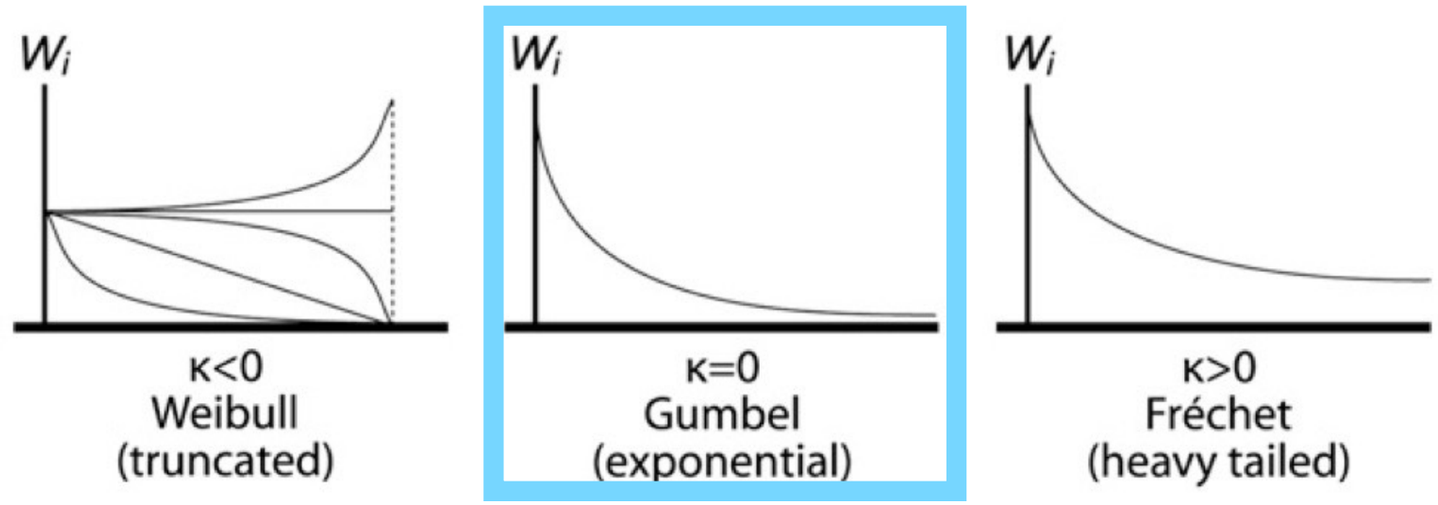

- Unbounded DFE, but low prob. of large-effect mutations
- Consistent with FGM with far optimum

From Beisel et al., Genetics, 2007

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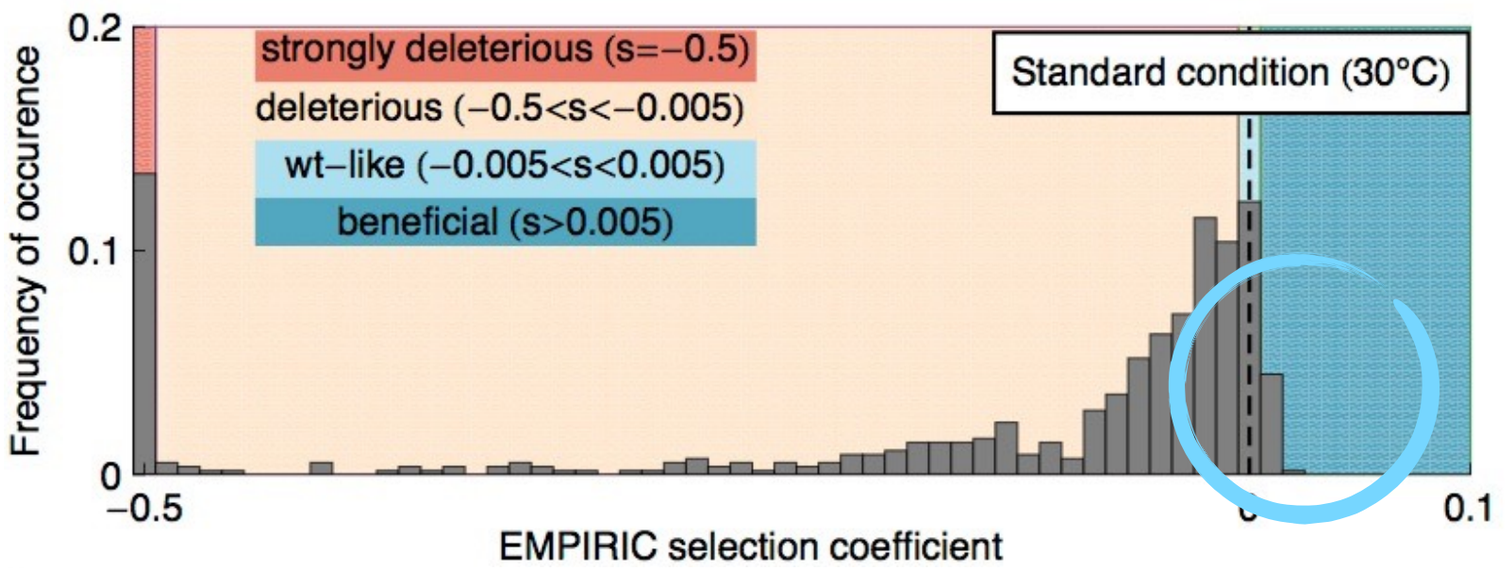
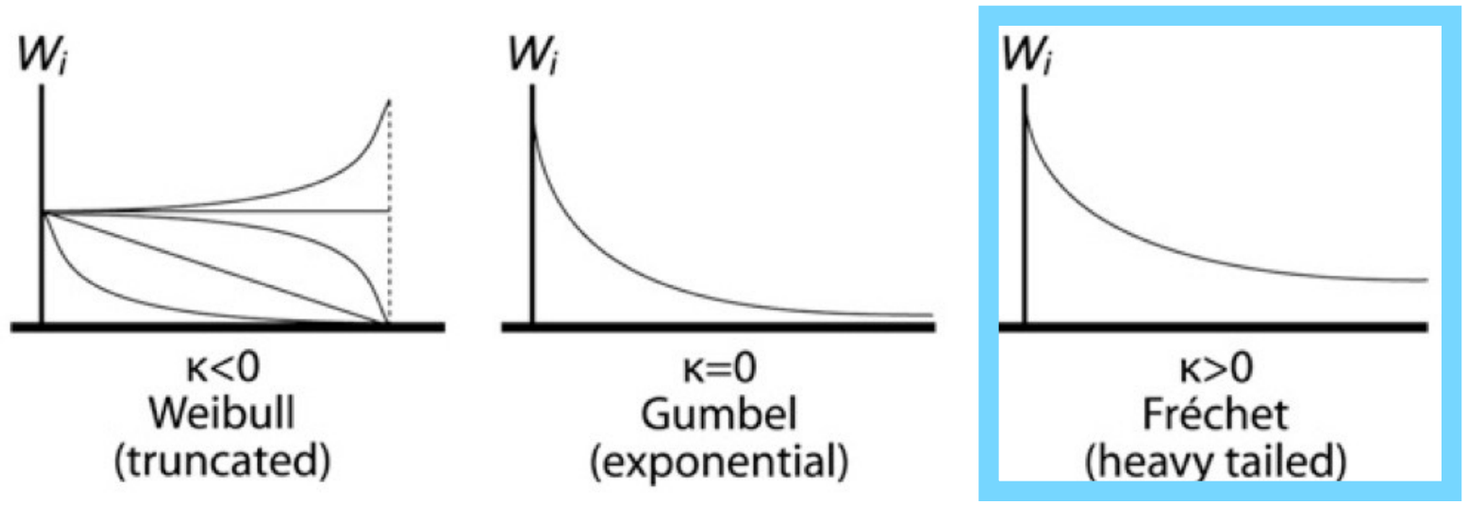


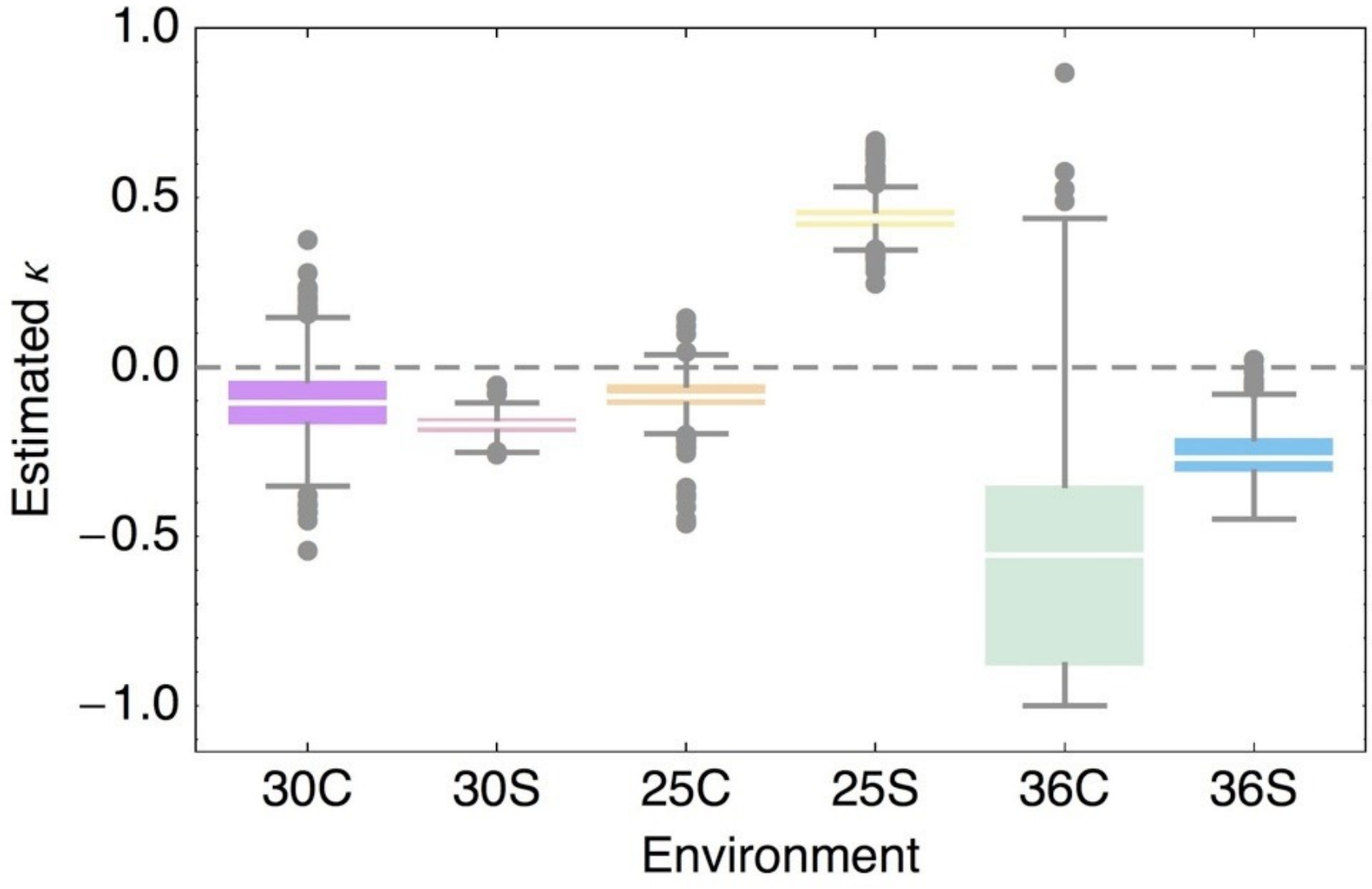


- Unbounded DFE, highly unpredictable mutational effects
- Not captured by FGM

From Beisel et al., Genetics, 2007

TAIL SHAPE PARAMETER IN CHALLENGING ENVIRONMENTS

S. cerevisiae EMPIRIC data from Hsp90



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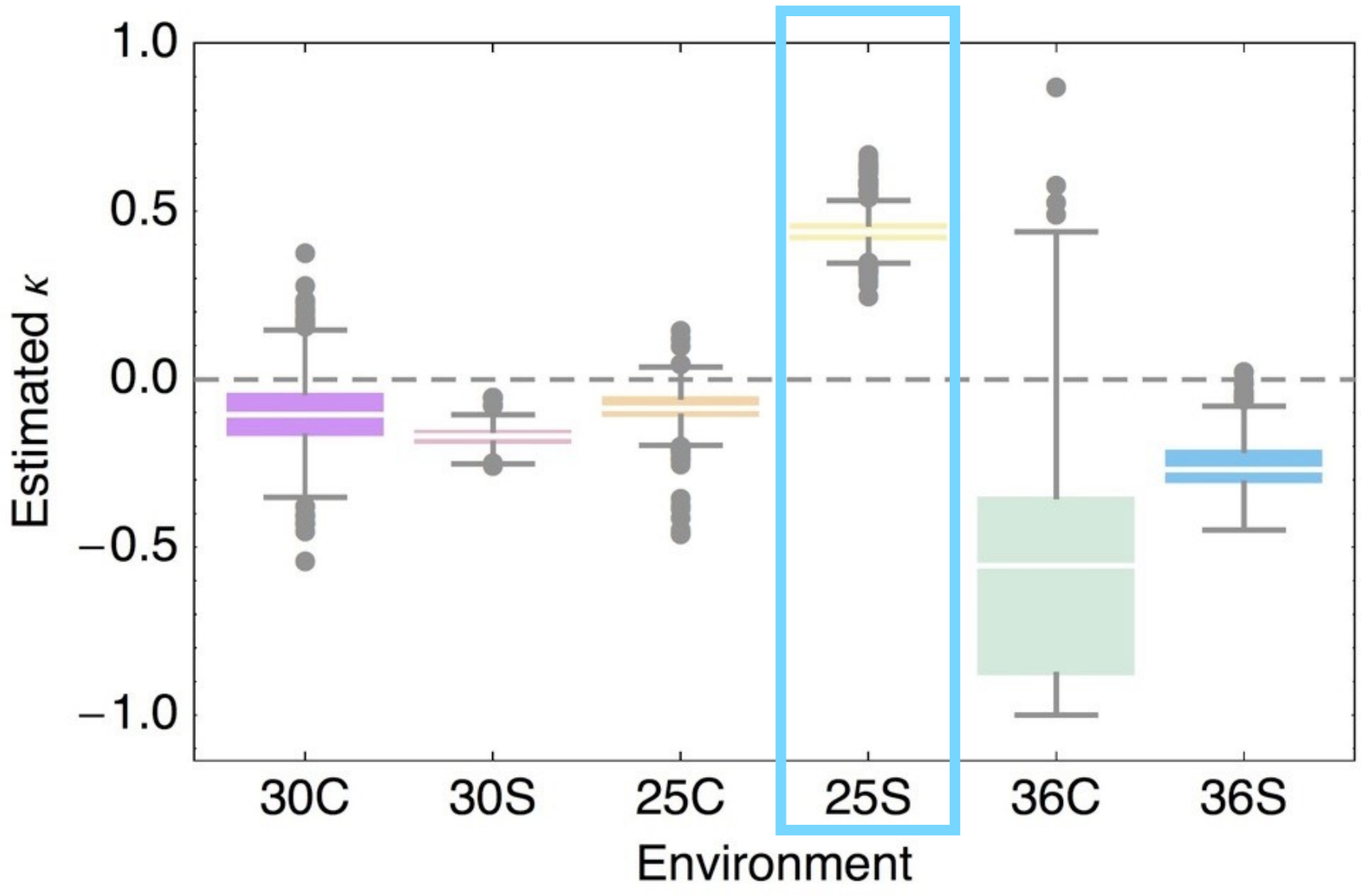


Tail shape parameter in challenging environments

An application to resistance evolution

Influenza H1N1 mutation-accumulation experiment

Tail shape parameter in challenging environments

An application to resistance evolution

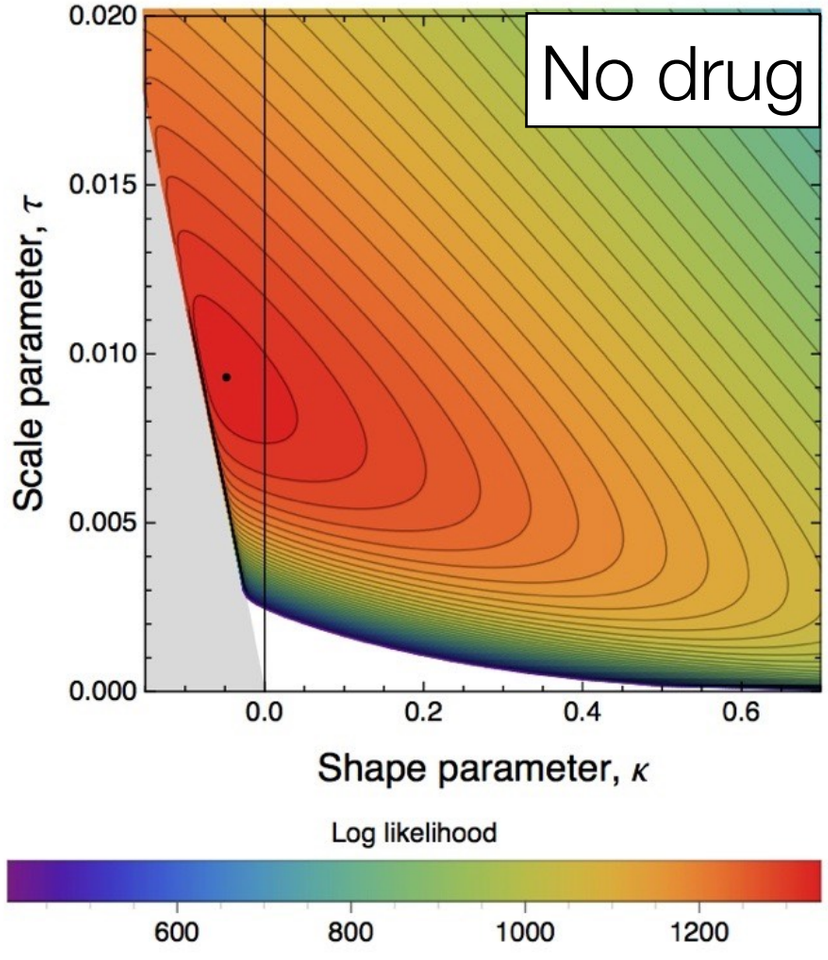
Influenza H1N1 mutation-accumulation experiment

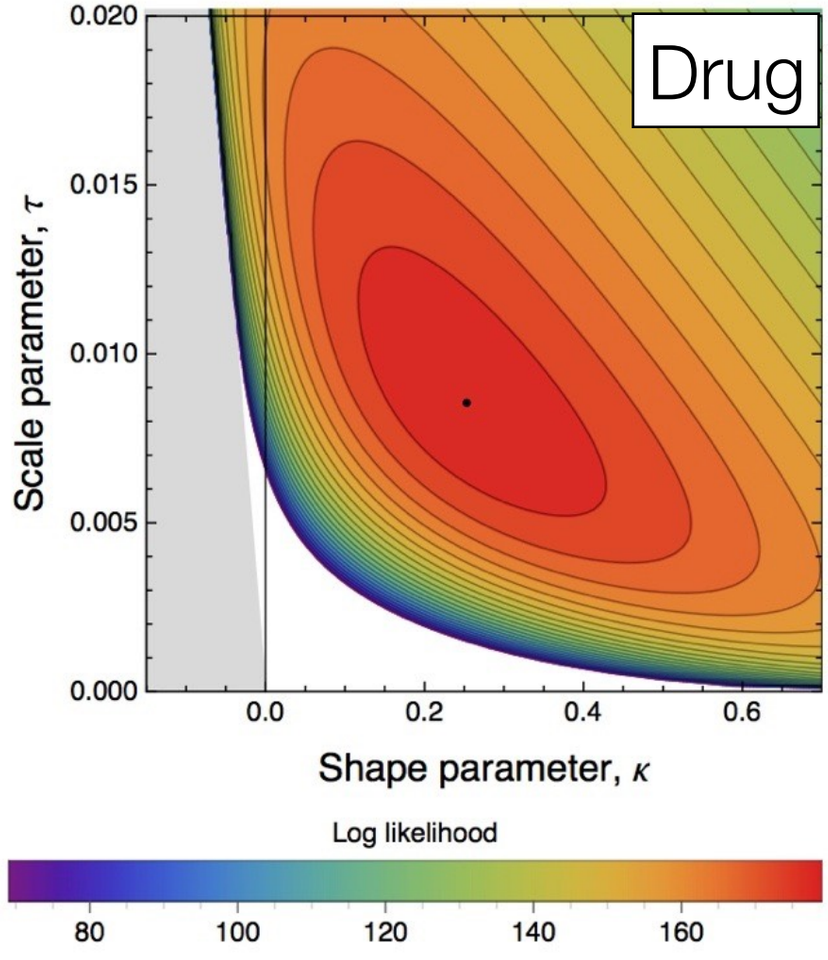
Approach: Serial passaging of influenza H1N1, assayed by time-sampled sequencing and inference via Approximate Bayesian Computation (WFABC; Foll*, Shim* & Jensen, *MER*, 2014)

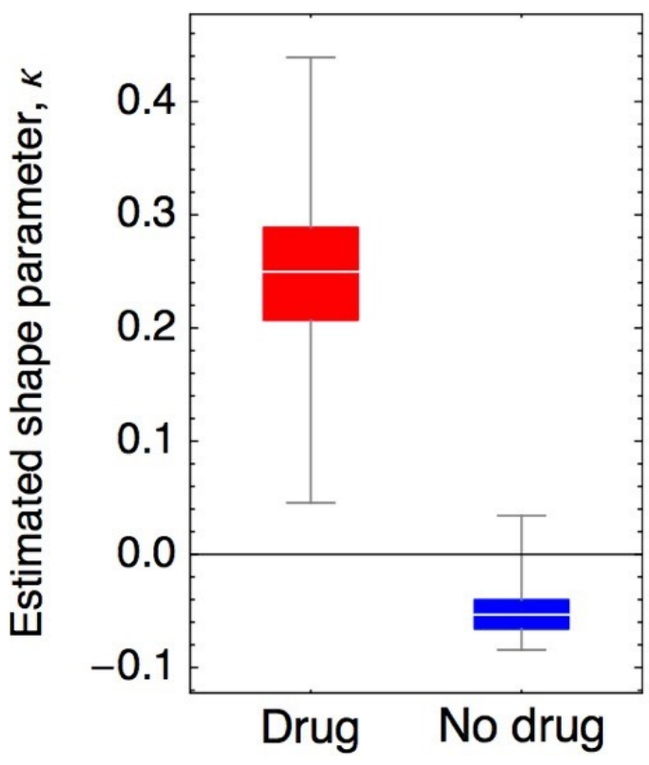
Environments:
MDCK (dog kidney cells) - **'standard' environment**,
MDCK + oseltamivir (Tamiflu) - **severe environmental challenge**

Tail shape parameter in challenging environments

Influenza H1N1 mutation accumulation experiment







Foll, Poh, et al., *PLoS Genetics*, 2014

Tail shape parameter in challenging environments

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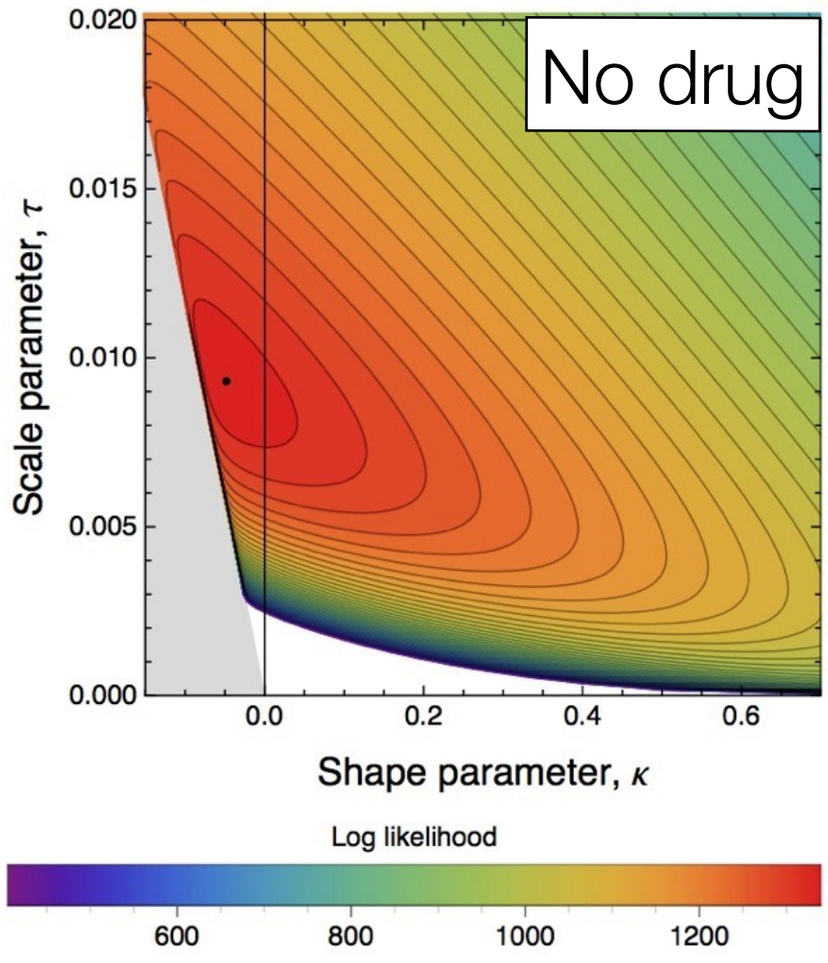

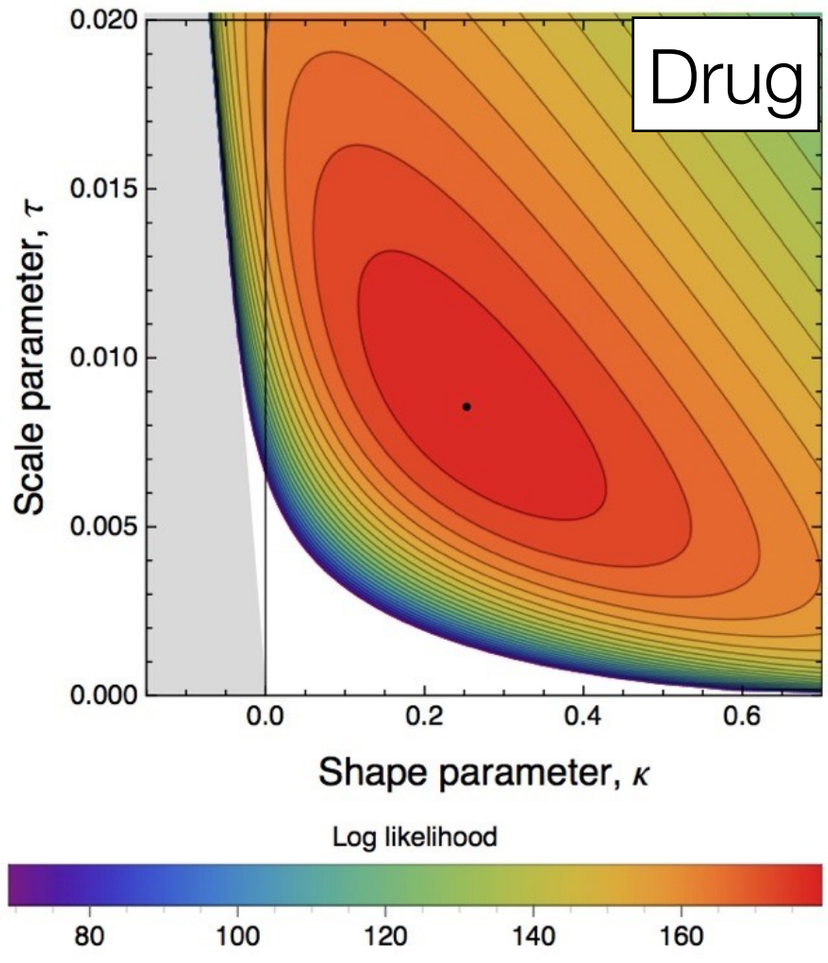

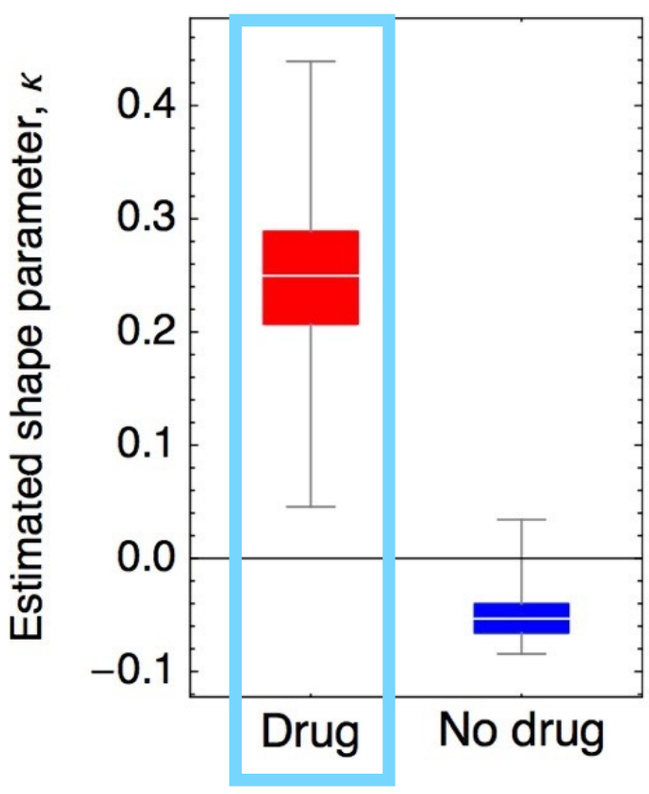

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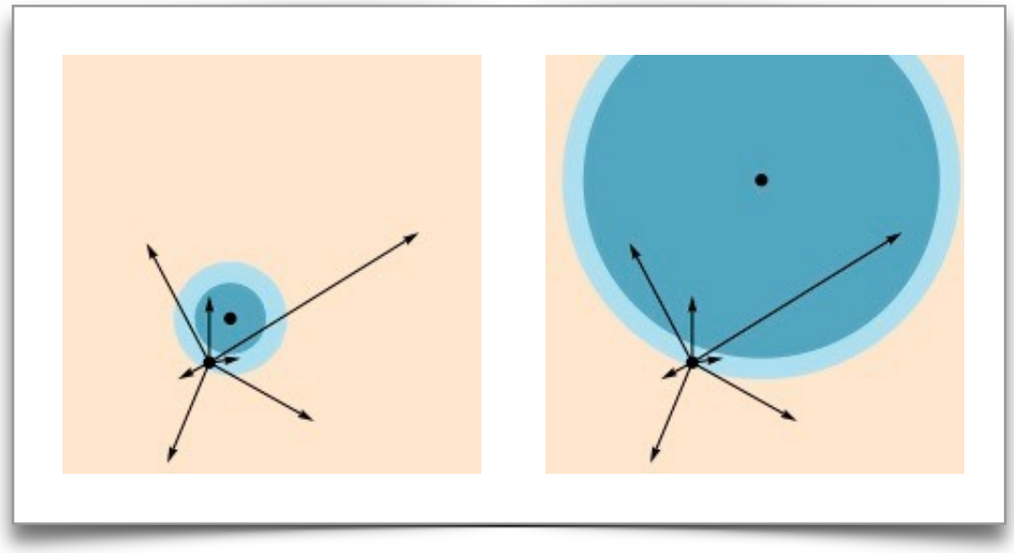
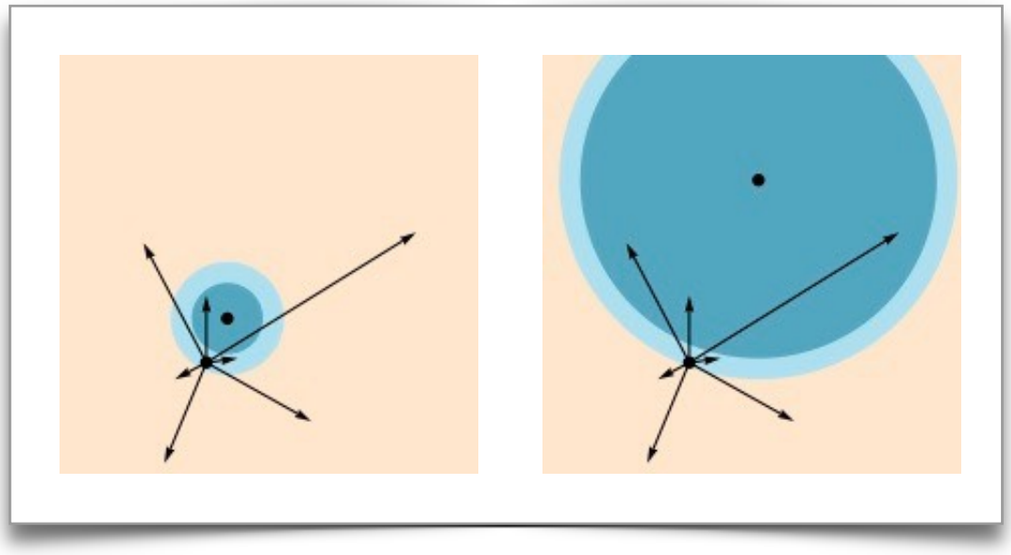
SUMMARY – TEAM FISHER

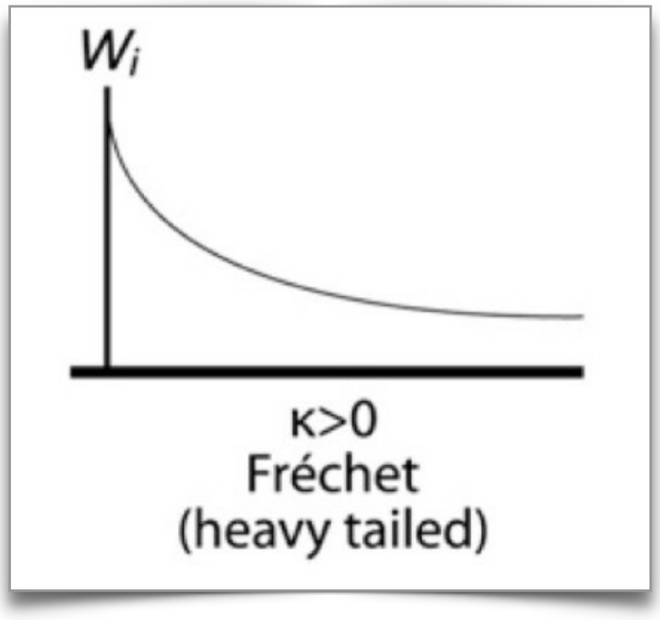
- In response to a novel environmental challenge the number and size of beneficial mutations increases, and costs of adaptation are observed - in agreement with predictions from Fisher's geometric model when the optimum is displaced.



SUMMARY – TEAM FISHER

- In response to a novel environmental challenge the number and size of beneficial mutations increases, and costs of adaptation are observed - in agreement with predictions from Fisher's geometric model when the optimum is displaced.
- Following severe environmental challenges, the step size of adaptive mutations might be highly unpredictable.

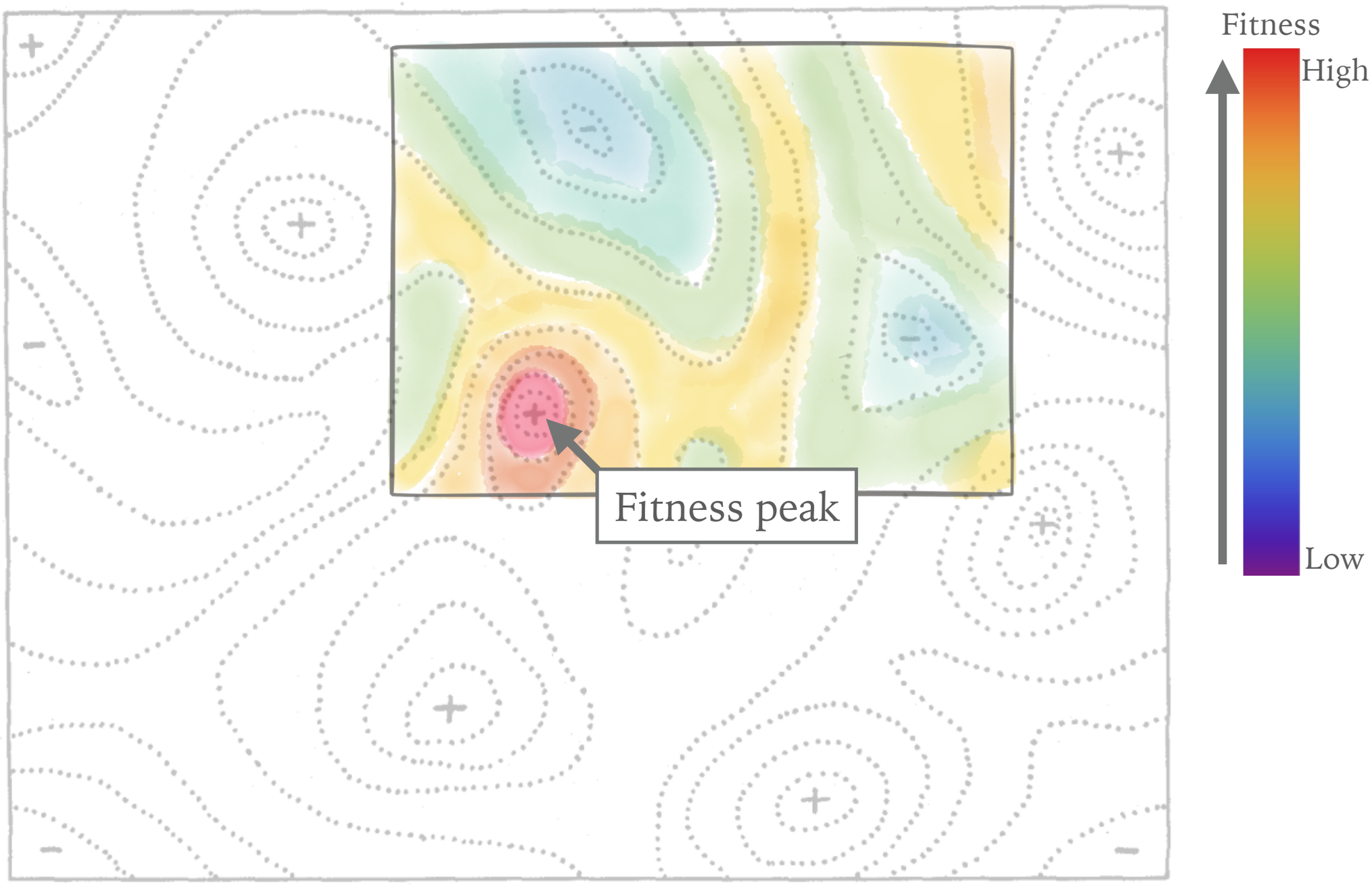




But what about epistasis?

(Spoiler: this is the part for the “Wrightians”)

WRIGHT'S SHIFTING BALANCE



Wright, 1932

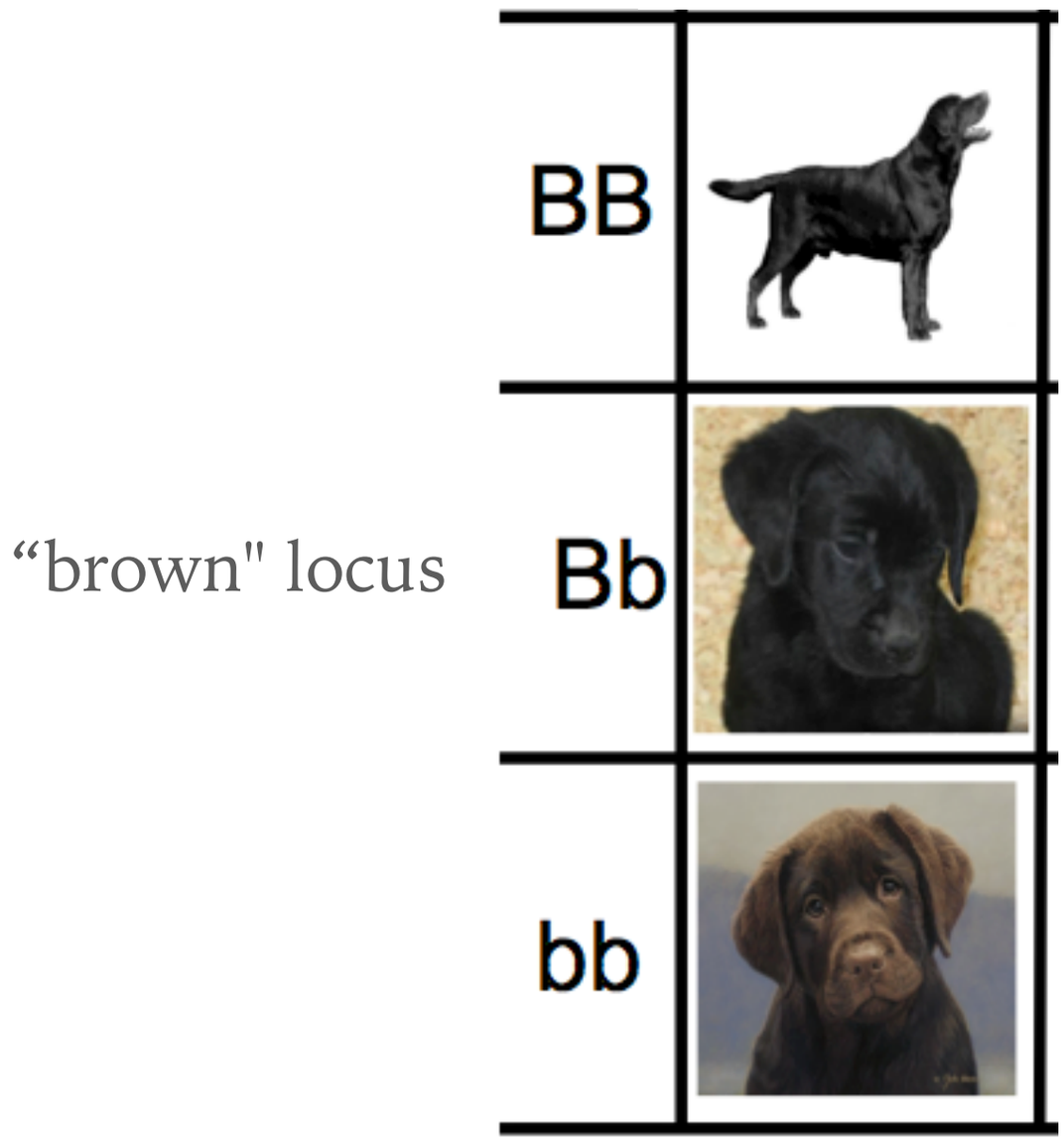
WHAT IS EPISTASIS?

Definition from Nature Reviews Genetics Glossary:

Epistatic interaction: any non-additive interaction between two or more mutations at different loci, such that their combined effect on a phenotype deviates from the sum of their individual effects.

WHAT IS EPISTASIS?

Classical genetics:



(Source: Google image search)

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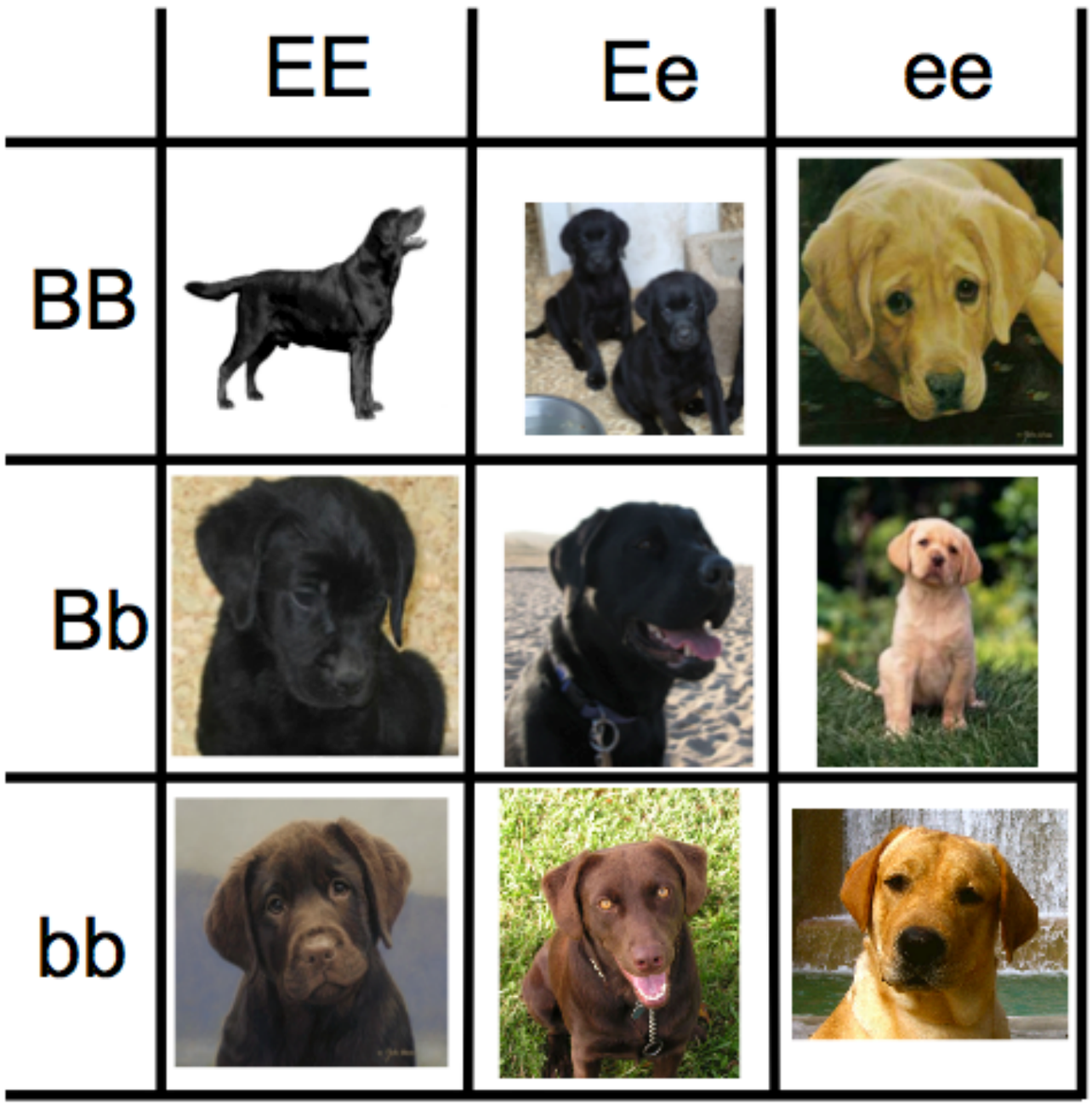


(Source: Google image search)

WHAT IS EPISTASIS?

Classical genetics:

“extension" locus

	EE	Ee	ee
BB			
Bb			
bb			

“brown" locus

This guy should have a brown nose!

(Source: Google image search)

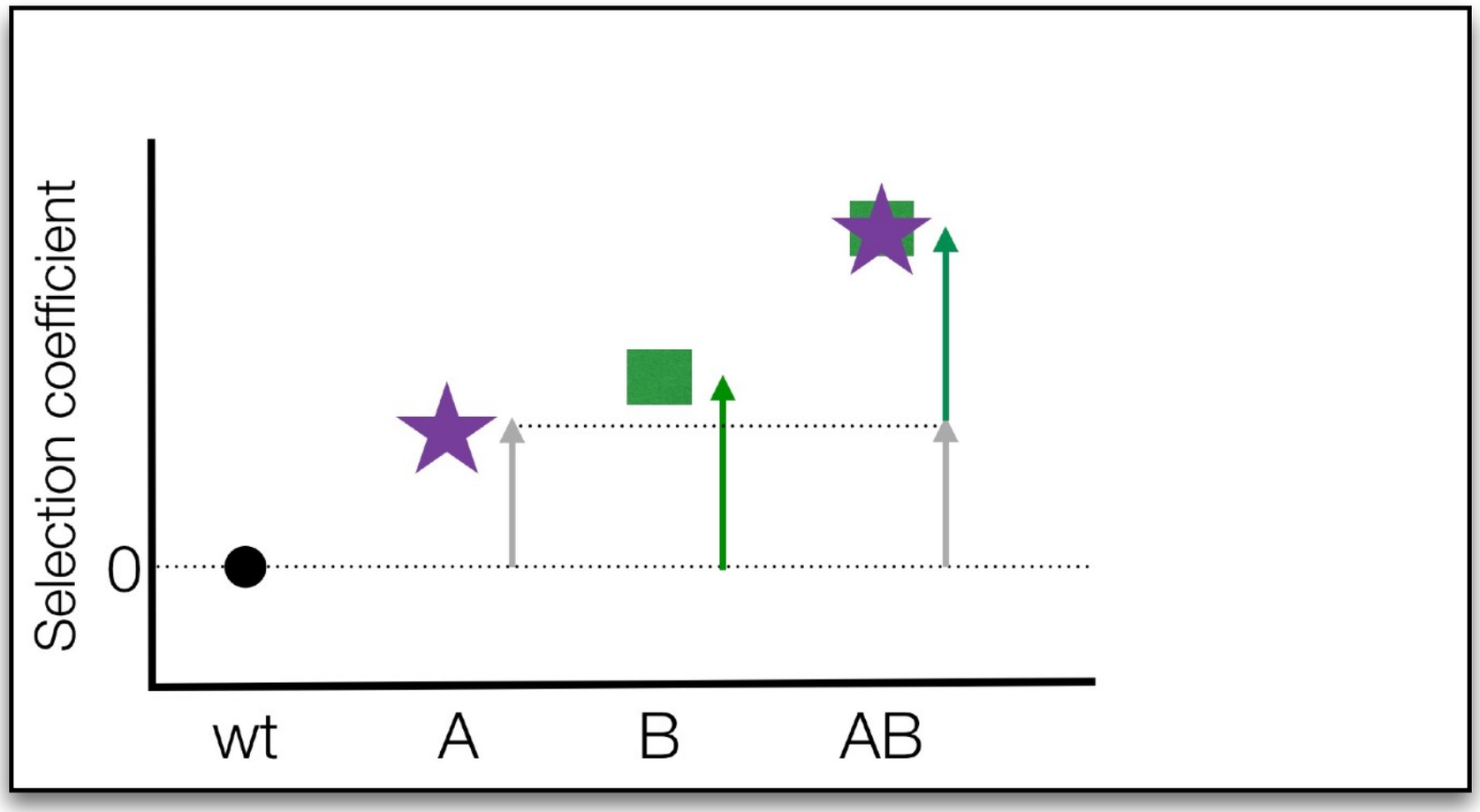
WHAT IS EPISTASIS?

Quantitative Genetics:

Interaction of genetic variants such that the net phenotypic effect of carrying more than one variant is different than would be expected by simply combining the effects of each individual variant.

WHAT IS EPISTASIS?

Phenotype: fitness



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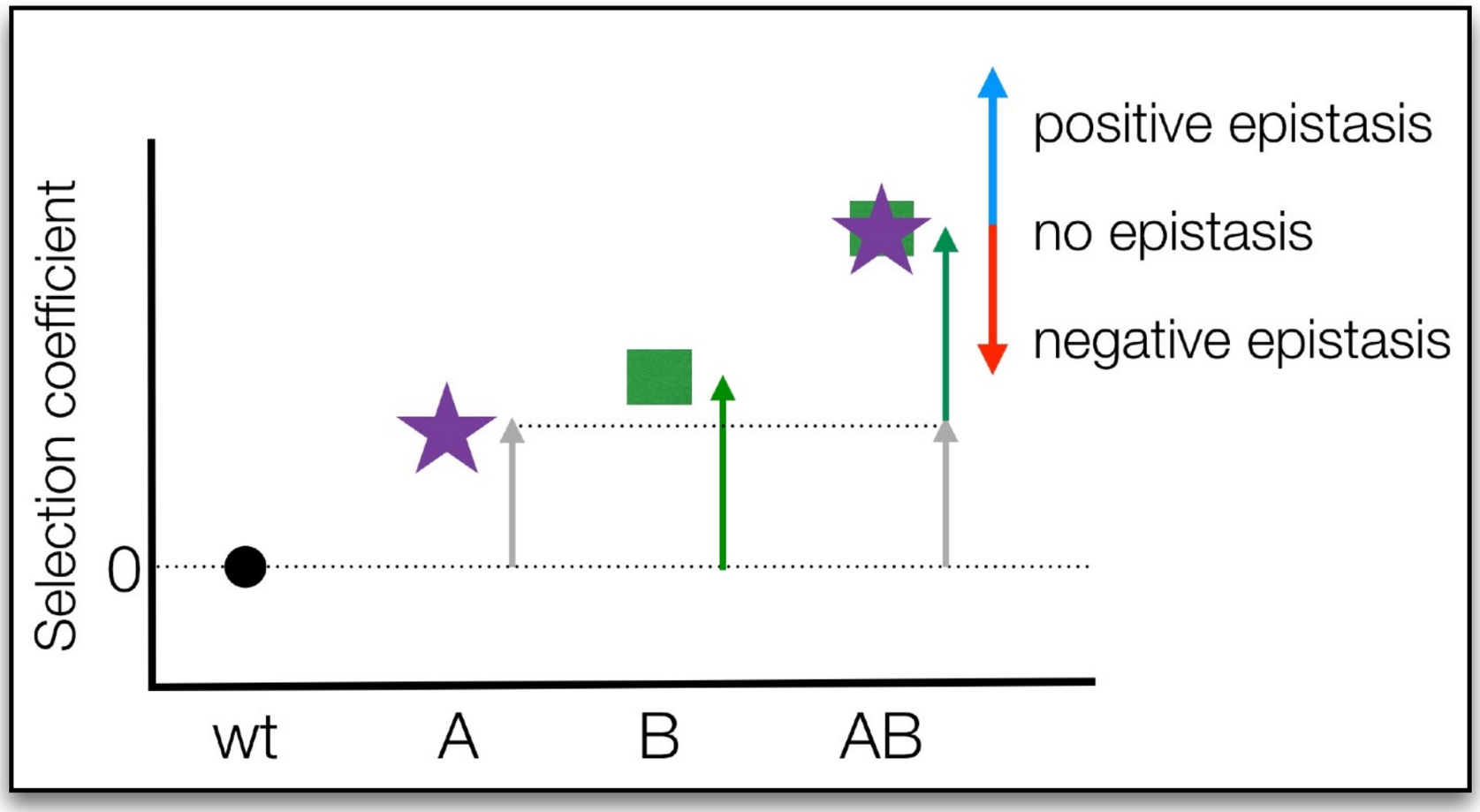

WHY SHOULD WE CARE?

Romero & Harnold, 2009

WHY SHOULD WE CARE?

- epistasis creates non-random associations between loci (linkage disequilibrium; LD)

Romero & Harnold, 2009

WHY SHOULD WE CARE?

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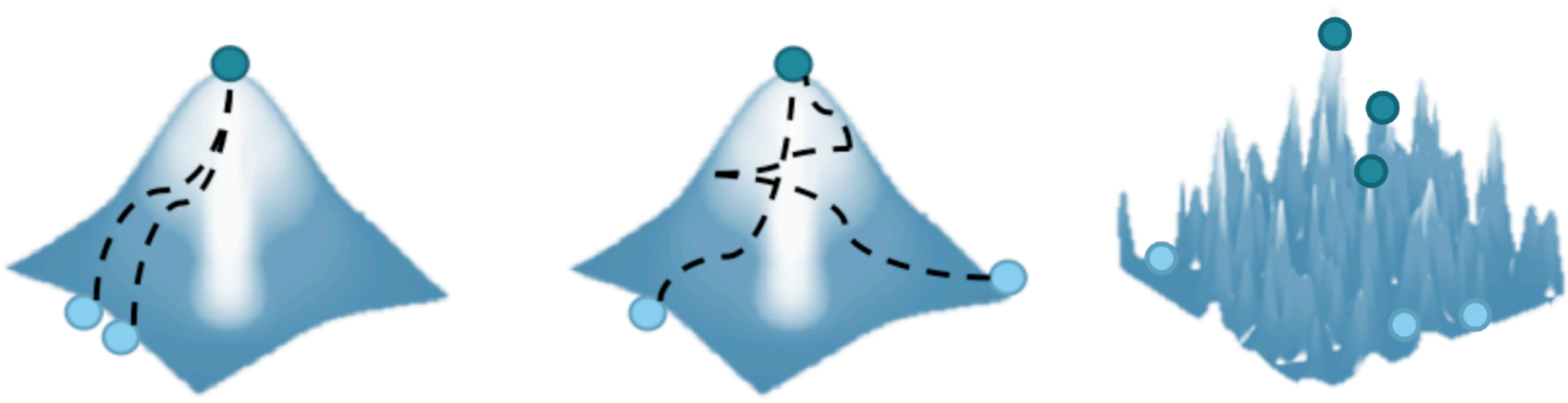
- Ruggedness of fitness landscape is a determinant of predictability/repeatability of evolution



Predictable and Repeatable

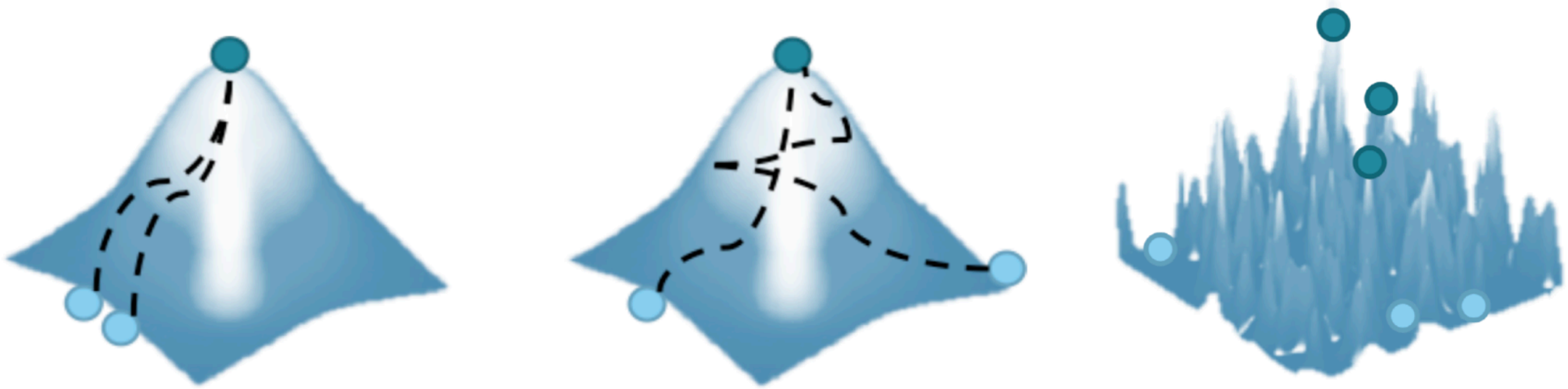
Predictable and Non-repeatable

Non-Predictable

Romero & Harnold, 2009

WHY SHOULD WE CARE?

- epistasis creates non-random associations between loci (linkage disequilibrium; LD)
- Ruggedness of fitness landscape is a determinant of predictability/repeatability of evolution
- accumulation of epistatic alleles is basis of the most widely accepted model for allopatric speciation



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Predictable and Non-repeatable

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WHERE DO WE EXPECT TO SEE EPISTASIS?

- Within proteins
- Between genomic regions involved in biological pathways
- Between species

WHERE DO WE EXPECT TO SEE EPISTASIS?

- Within proteins
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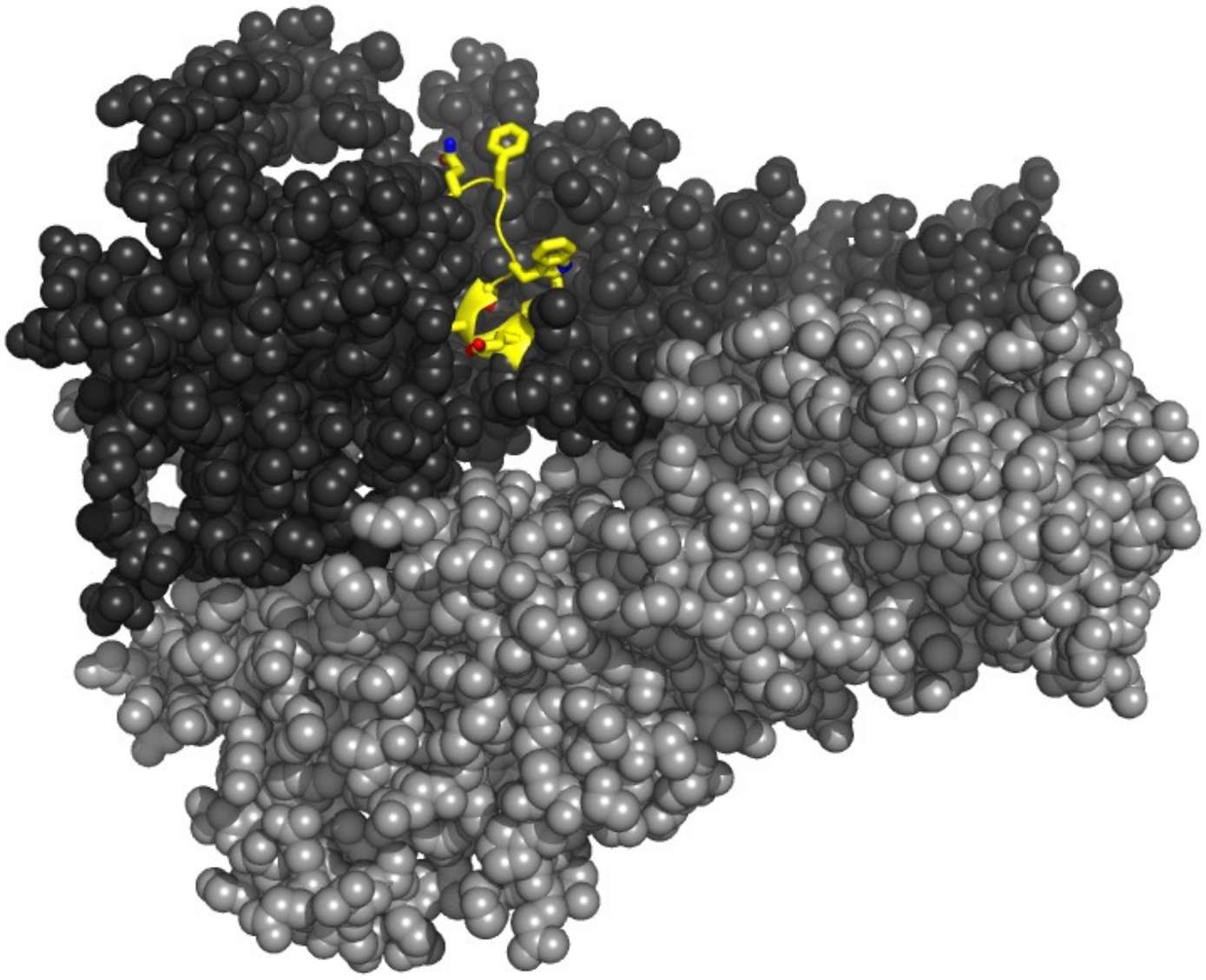
Where do you expect to see the most epistasis, and why?

AN INTRAGENIC EPISTATIC LANDSCAPE

DATA SET

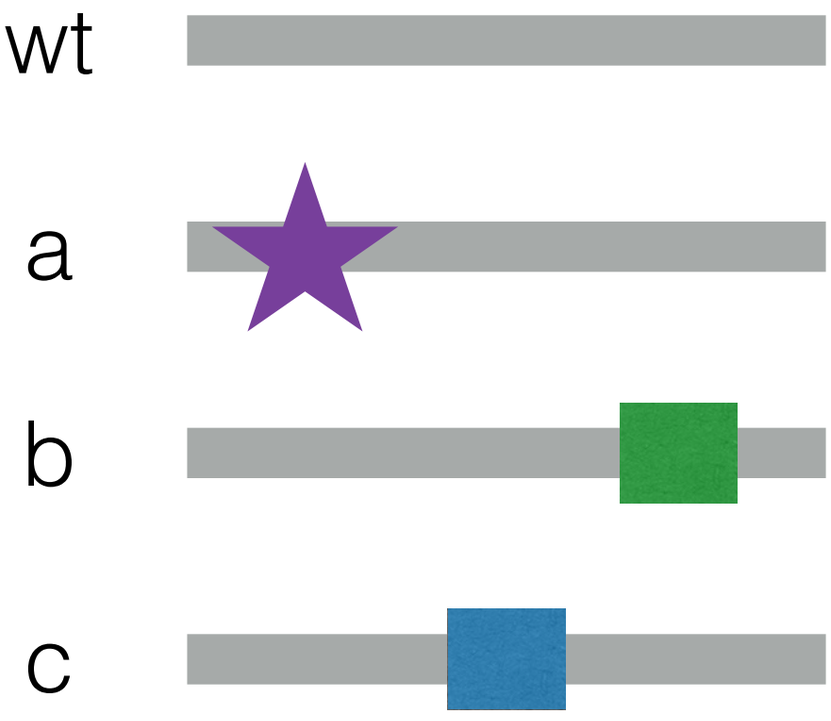
- 9 aa region from Hsp90 (aa positions 582-590) in Saccharomyces cerevisiae



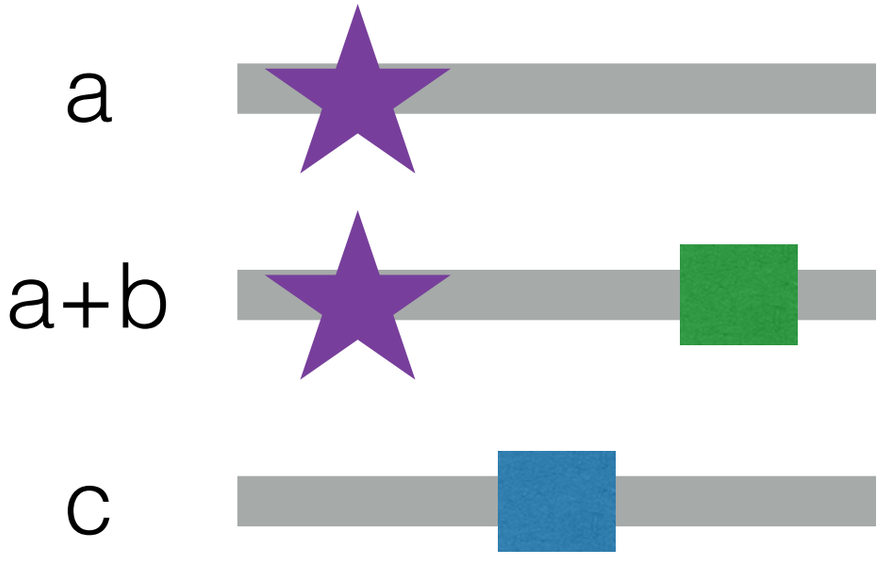
Data obtained by Ryan Hietpas @ UMassMed

Data set

3x 180 1-step mutations



7 anchors, each with
≈140 2nd steps,
≈20 1-step controls



Anchor fitness between 97.5% and 100% of wt

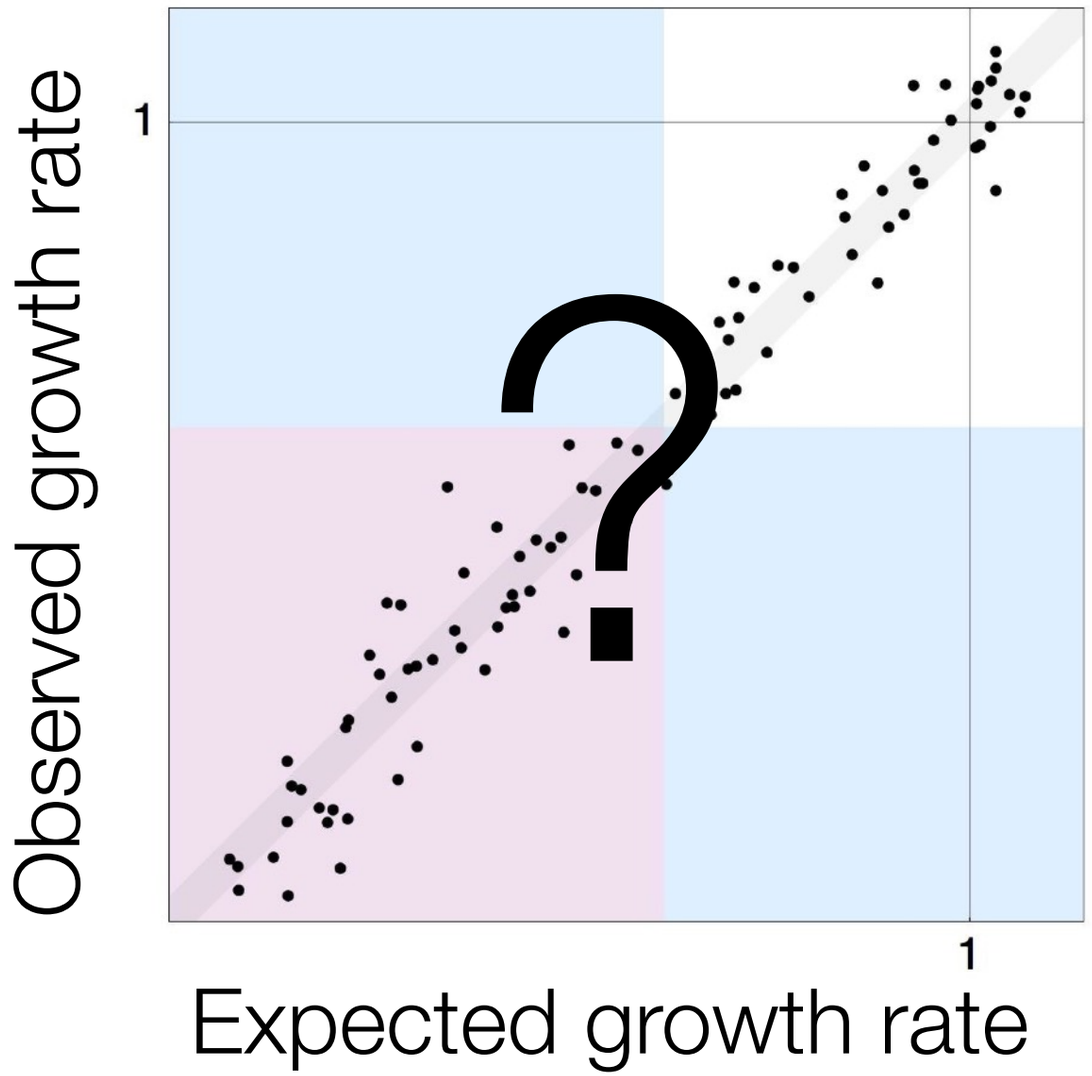
Data obtained by Ryan Hietpas @ UMassMed

Questions

- **What is the general pattern of epistasis?**

- How does “a step away” change the distribution of fitness effects?

- What is the shape of the local fitness landscape?



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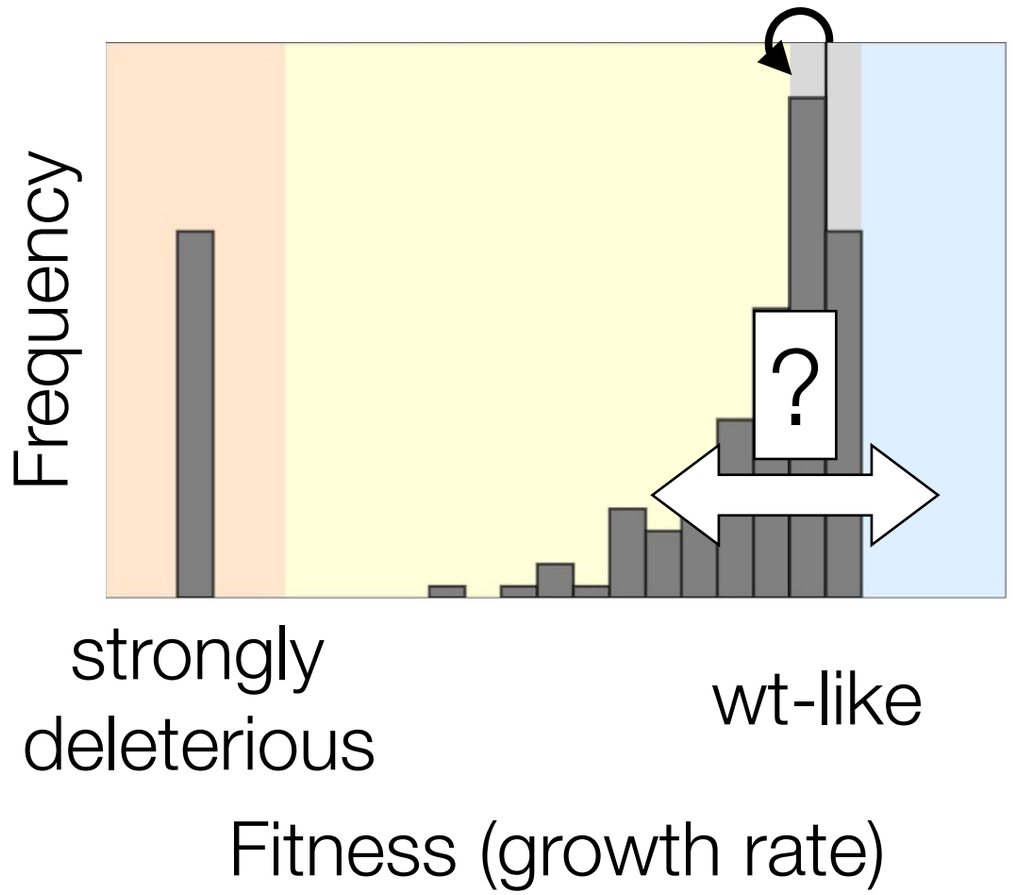
The distribution of fitness effects (DFE)



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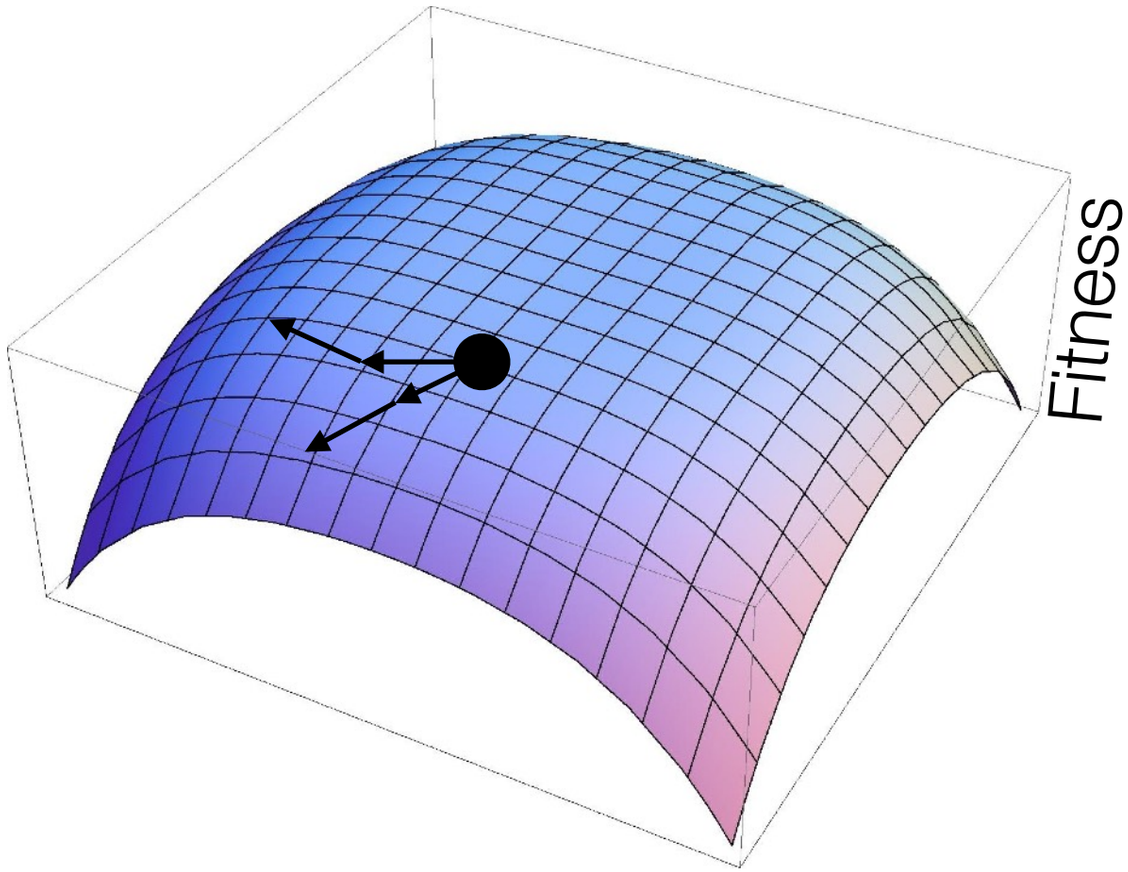
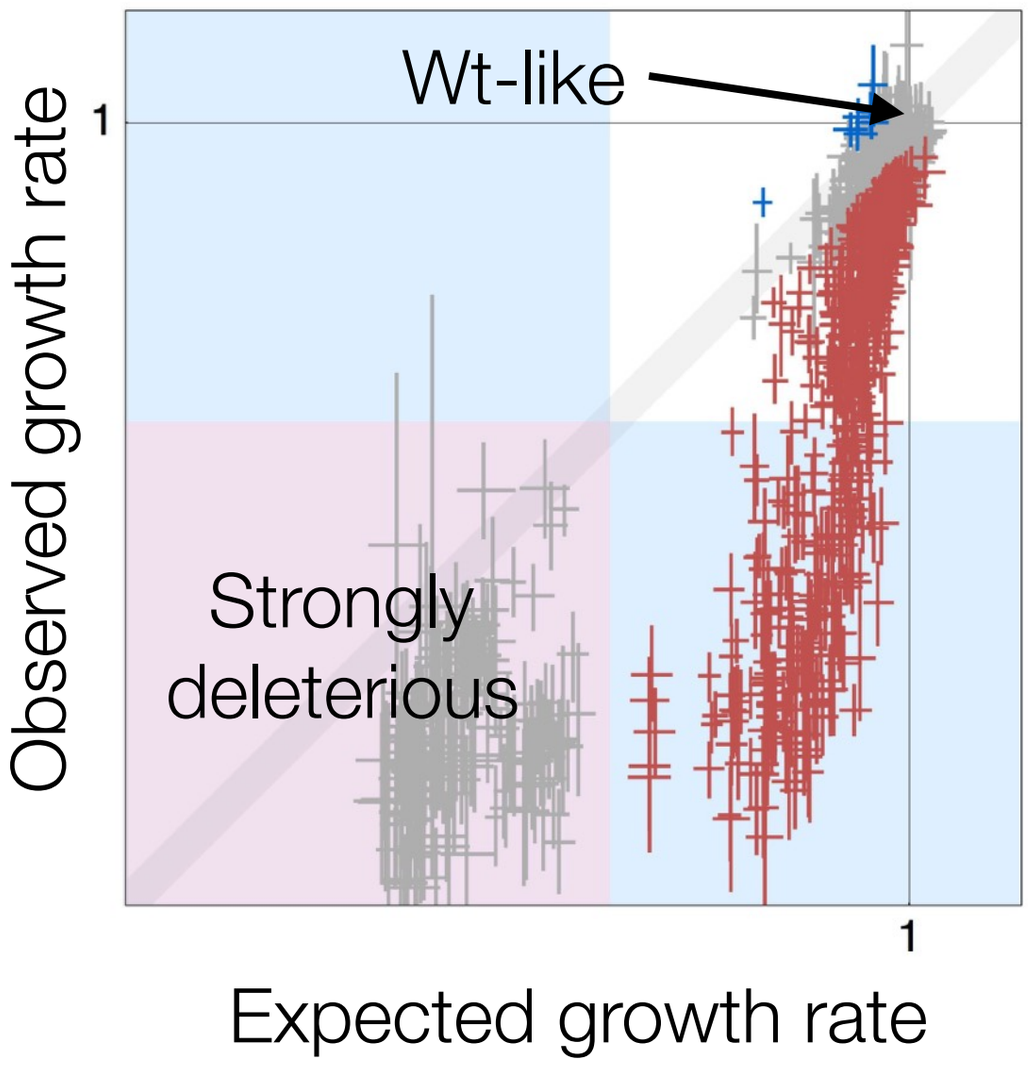
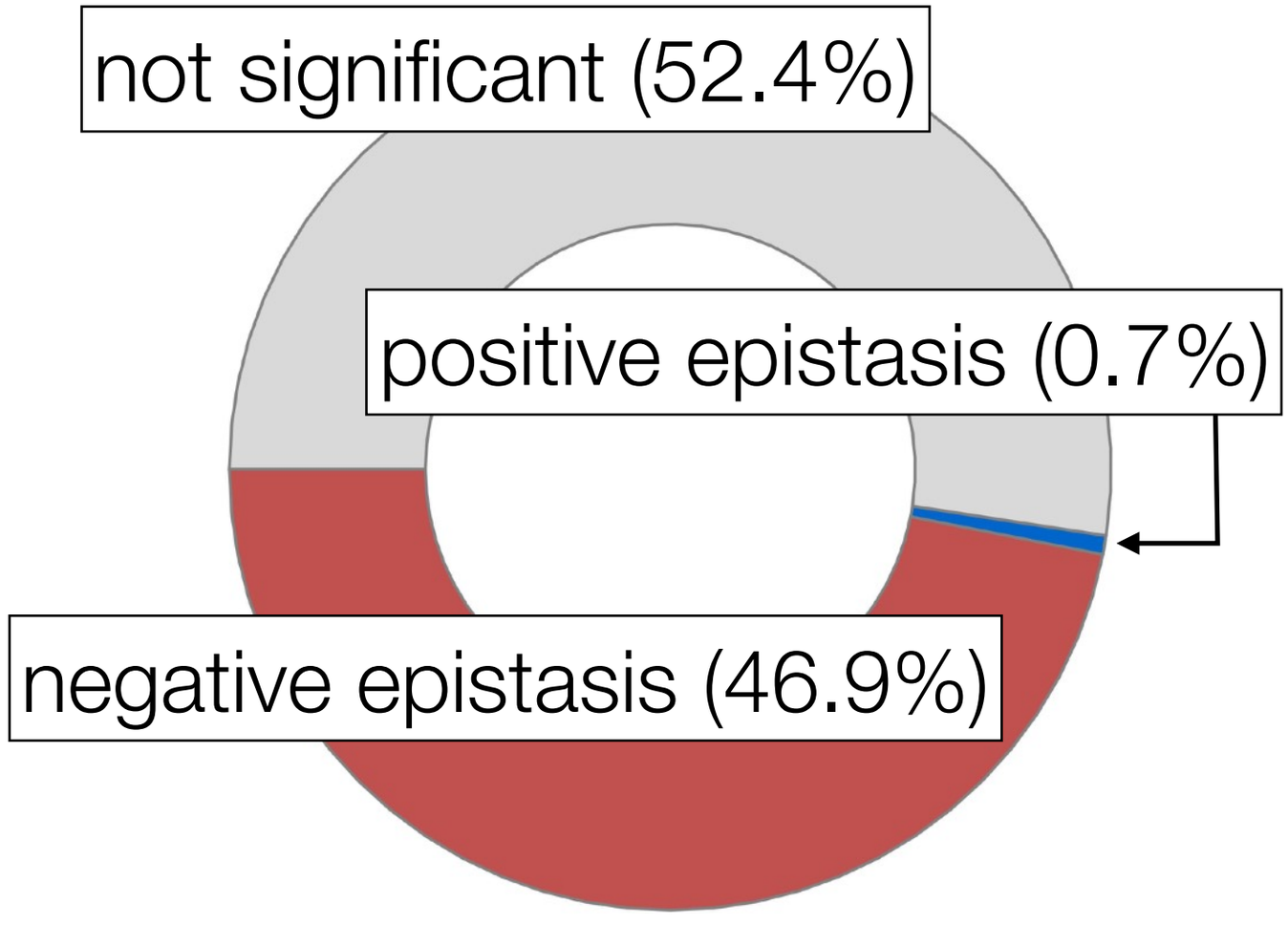
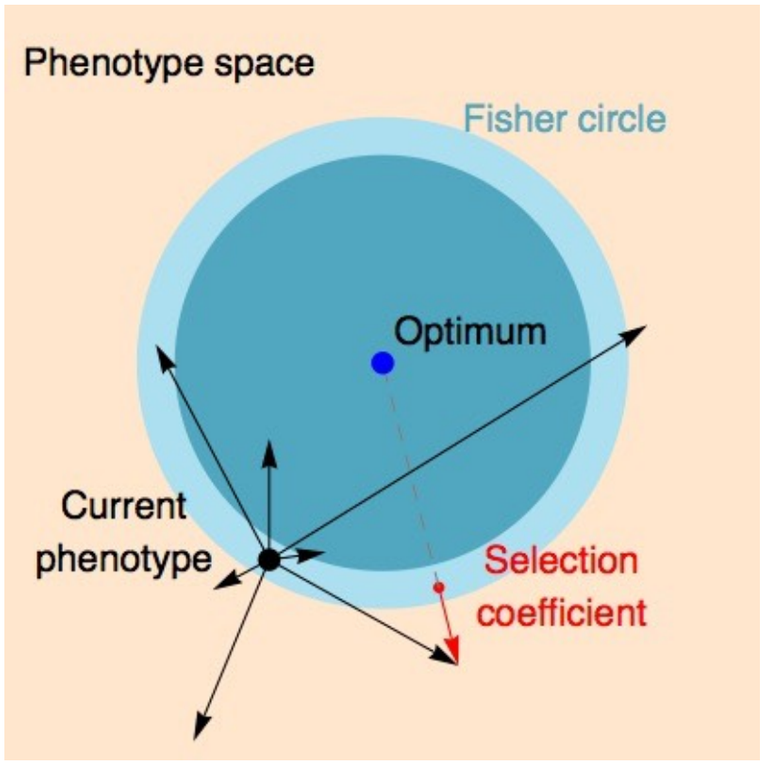


The pattern of epistasis for 1015 2-step mutations





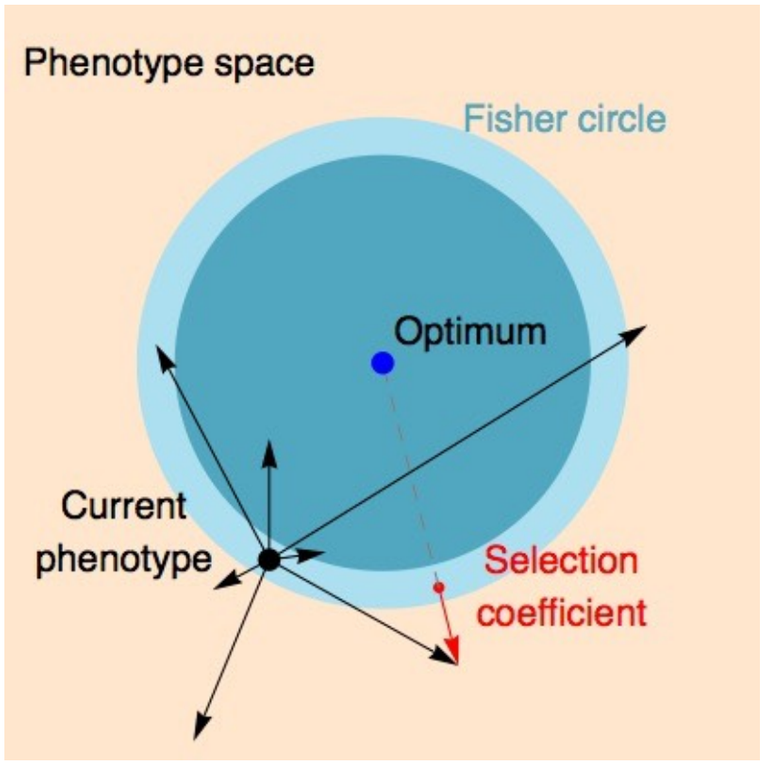
FISHER'S GEOMETRIC MODEL



Fisher, 1930

Hypothesis:

FISHER'S GEOMETRIC MODEL

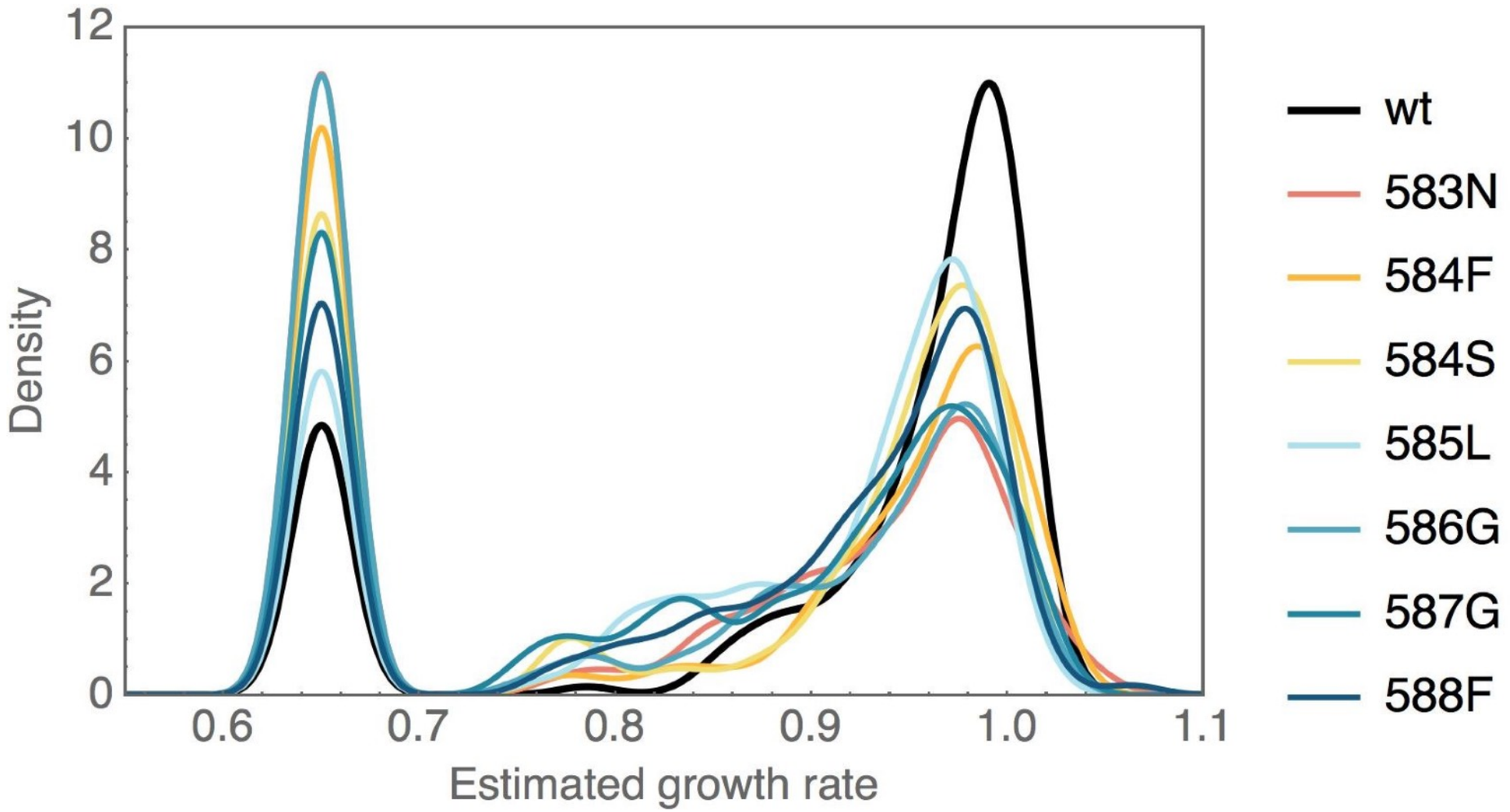


Fisher, 1930

Hypothesis:

- Relocation of the phenotype can increase the distance to the optimum and hence the potential for beneficials.

Shape of the DFE one step away



- No higher potential for beneficial mutations one step away from the wild type
- 2nd step much more likely to be deleterious

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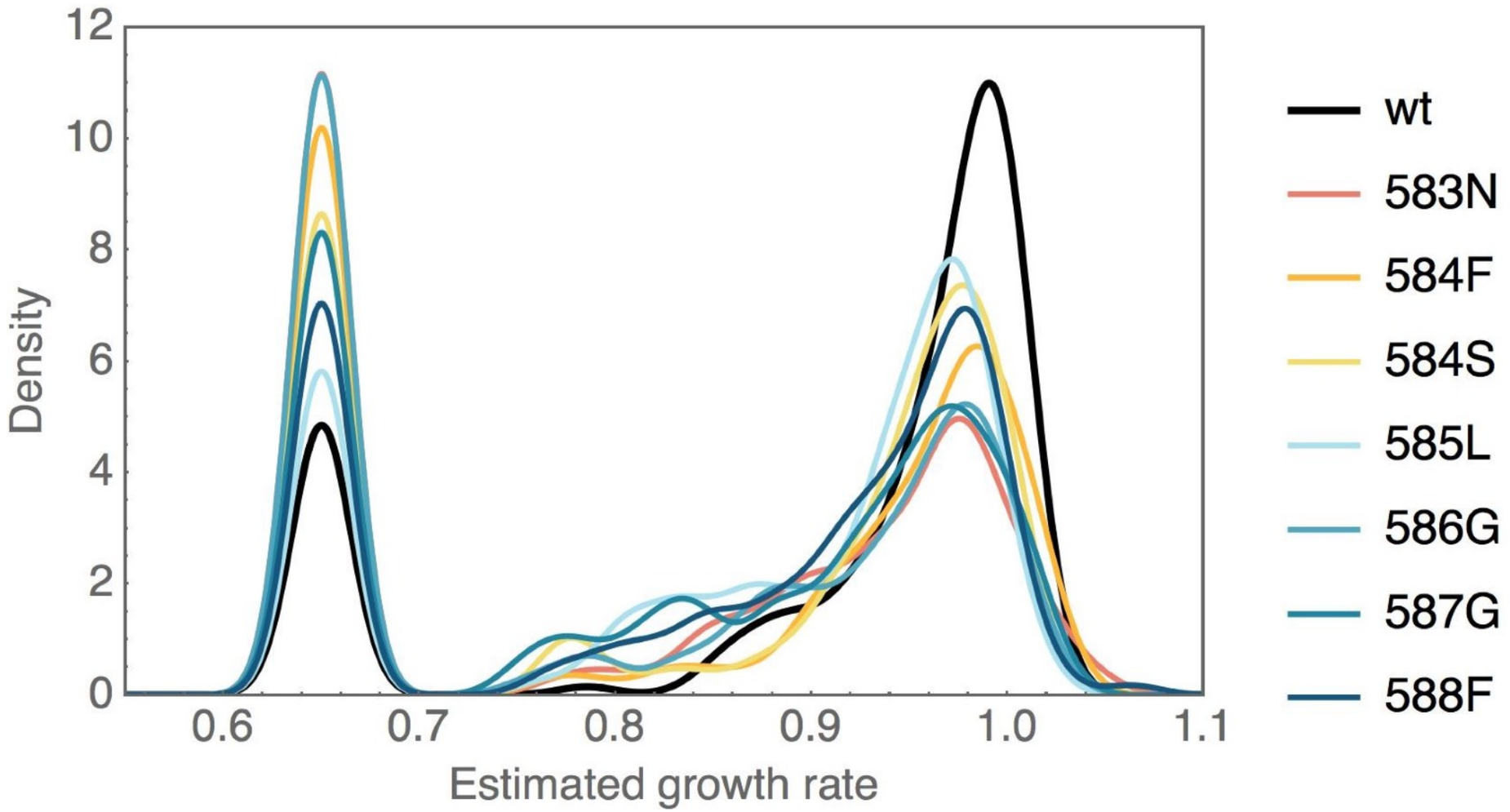

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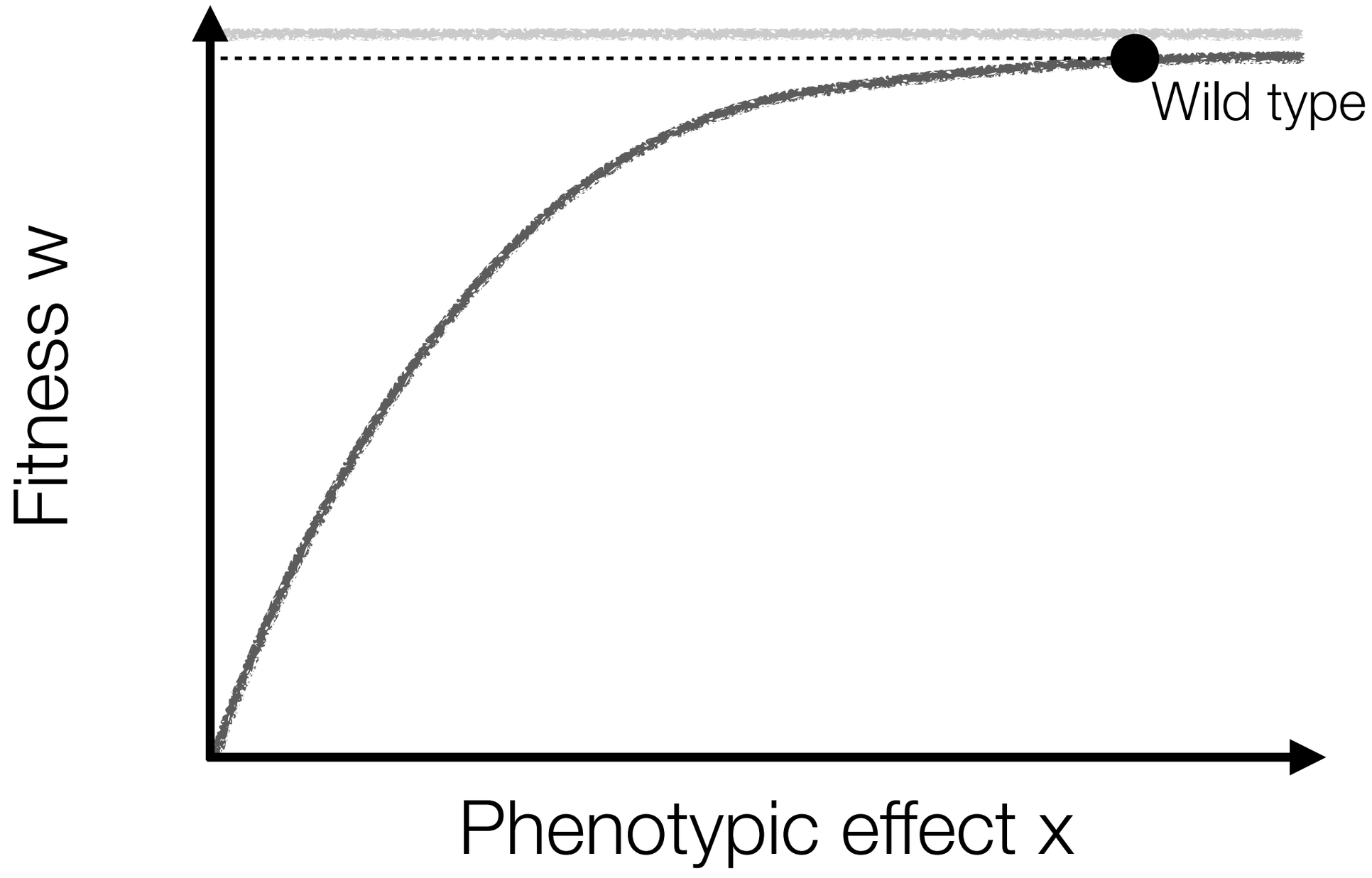
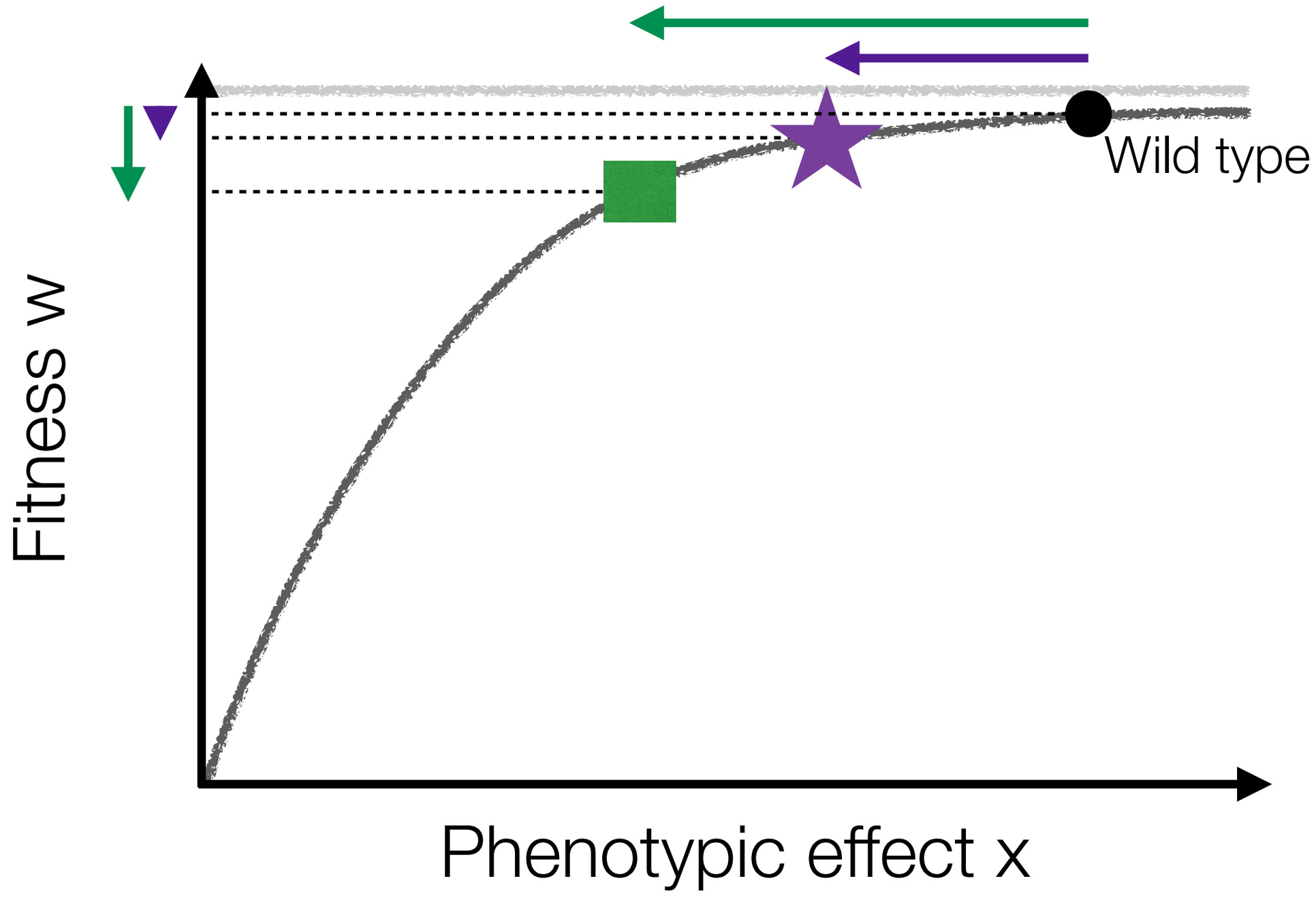
Robustness? - Concave fitness landscape?

Characterizing the shape of the epistatic landscape



Characterizing the shape of the epistatic landscape



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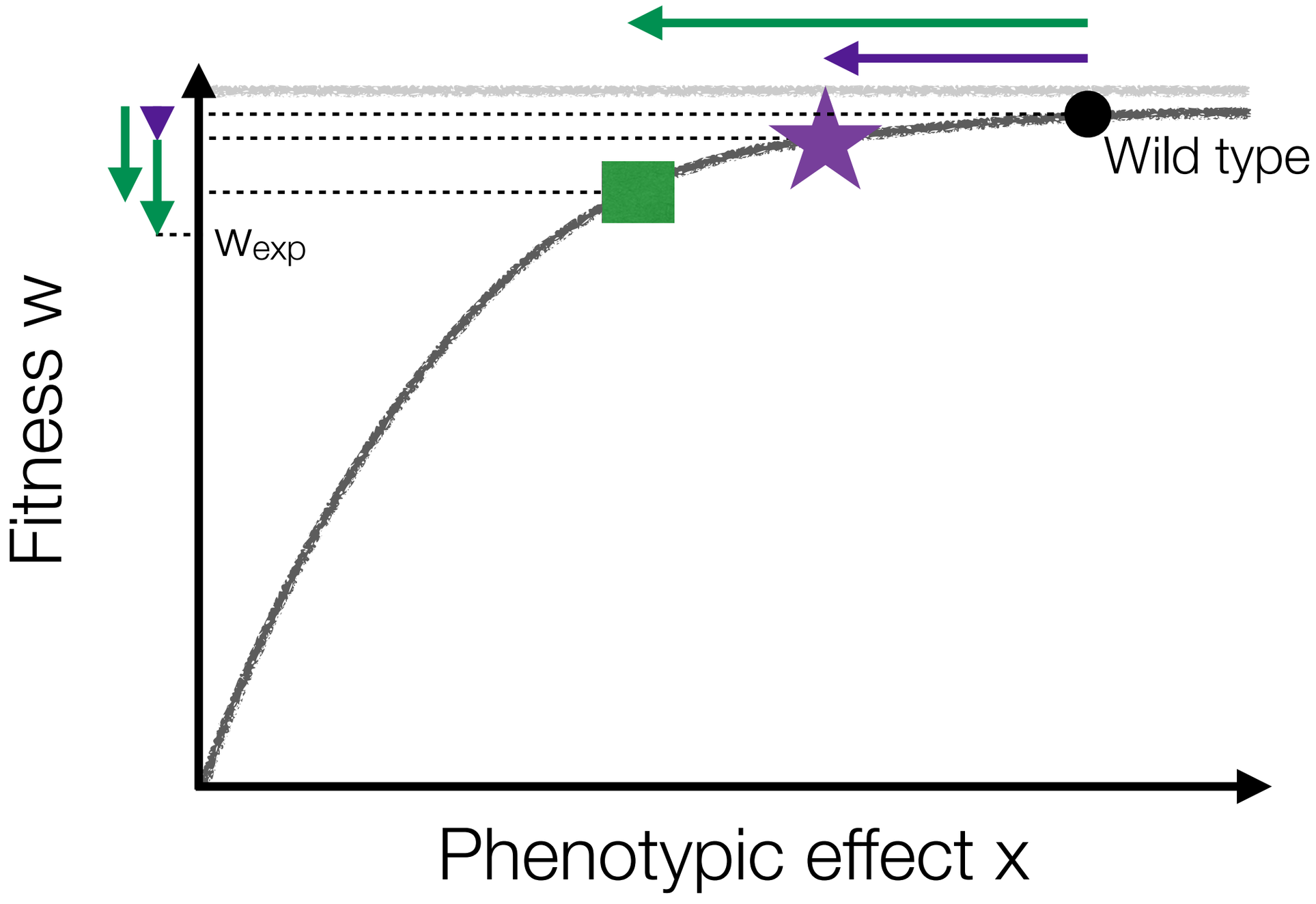

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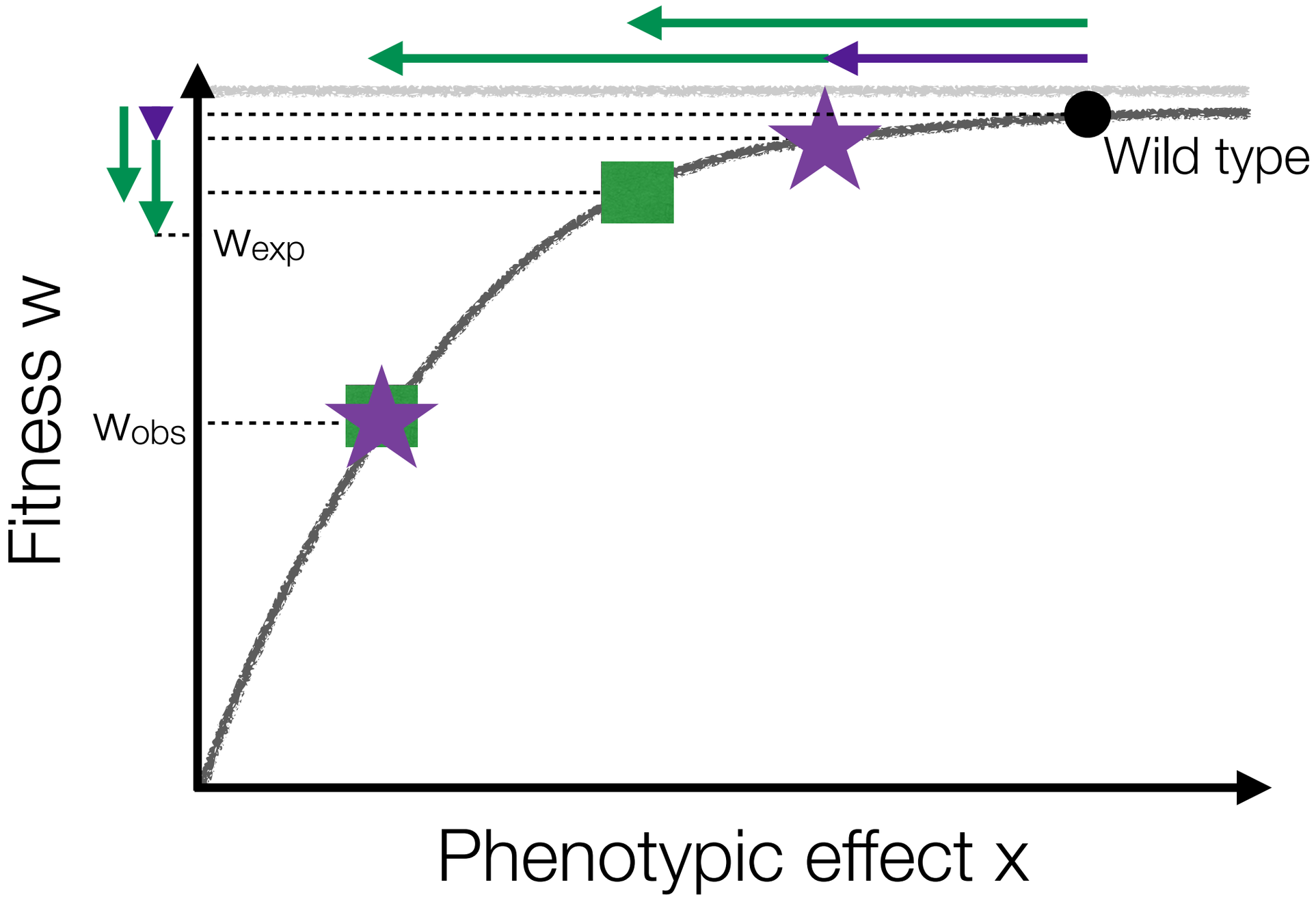

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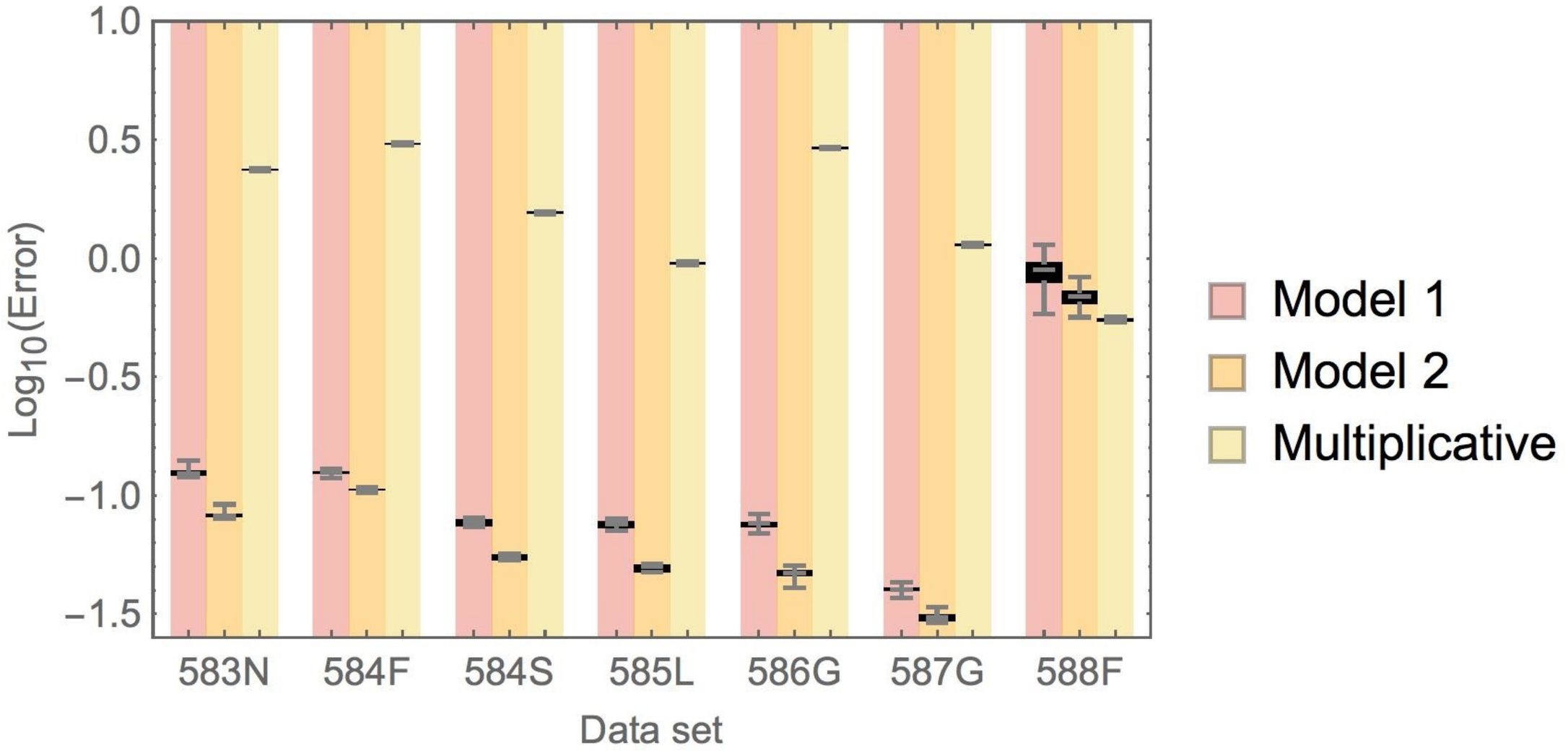

Bank, Hietpas, Jensen & Bolon, *MBE*, 2015

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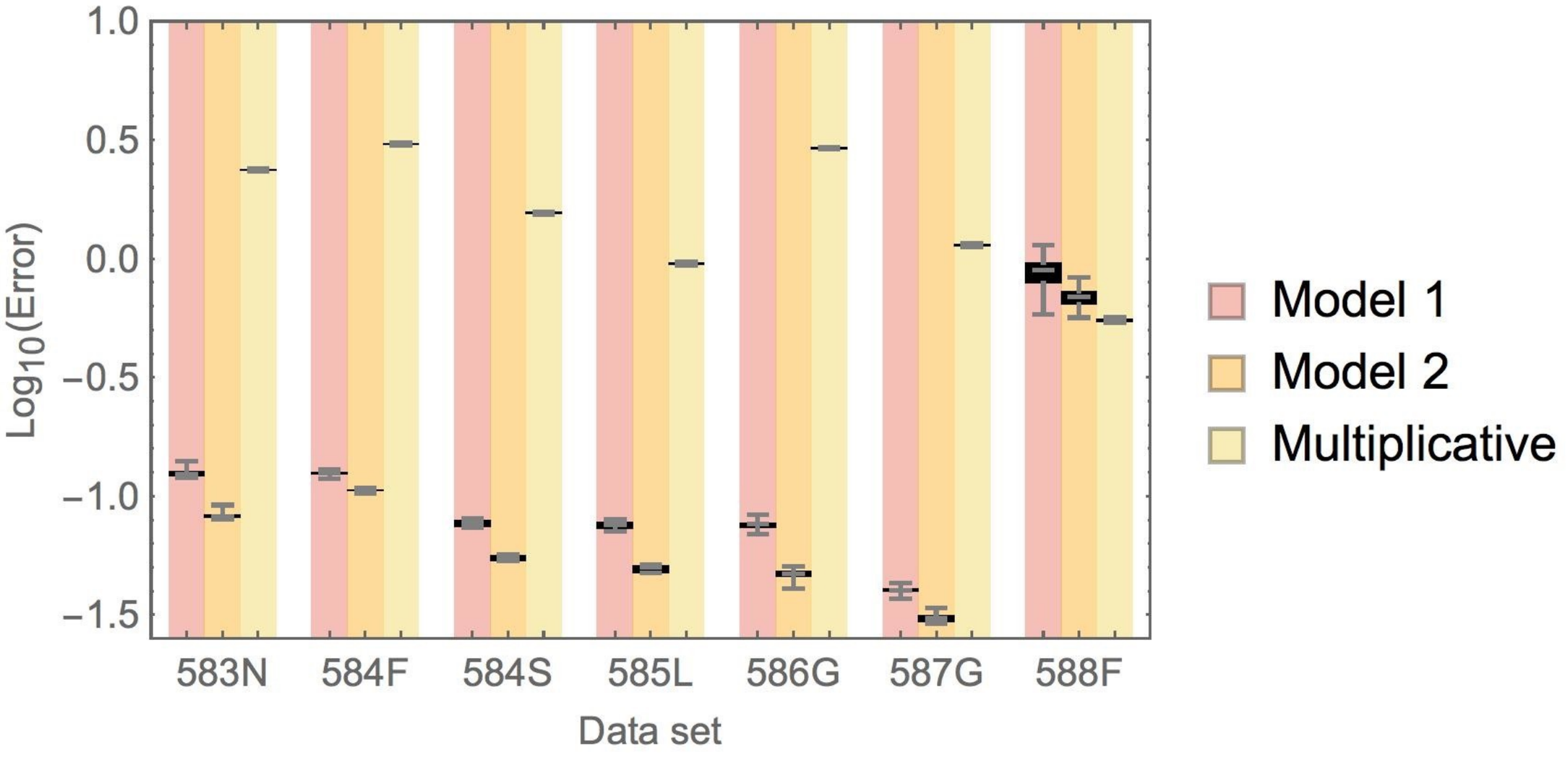
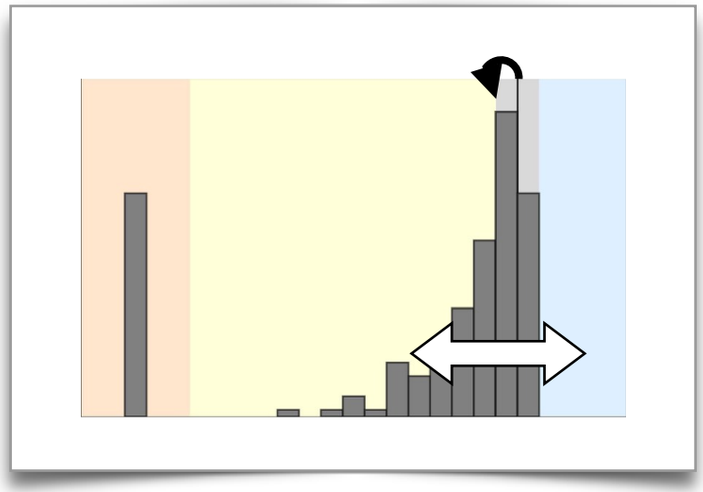


Models of concave fitness landscapes can explain the observed pattern of ubiquitous negative epistasis.

Bank, Hietpas, Jensen & Bolon, *MBE*, 2015

SUMMARY

- Intragenic epistasis is frequent. Changing the genetic background (i.e., dislocating the population from its current state) does not result in a higher potential for beneficial mutations.



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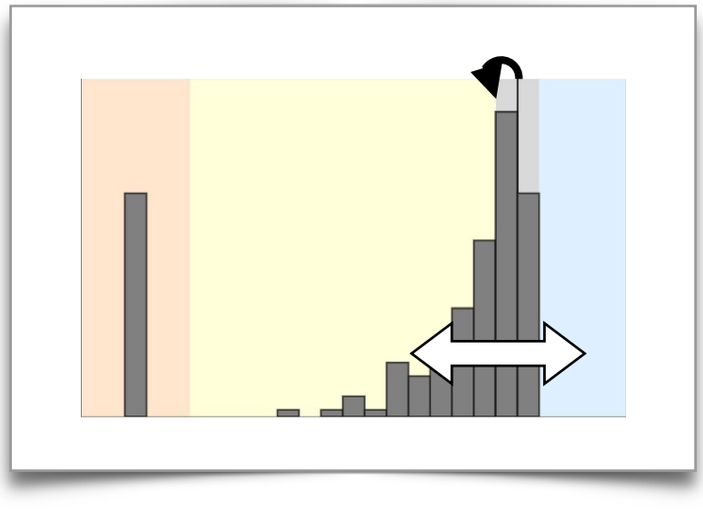
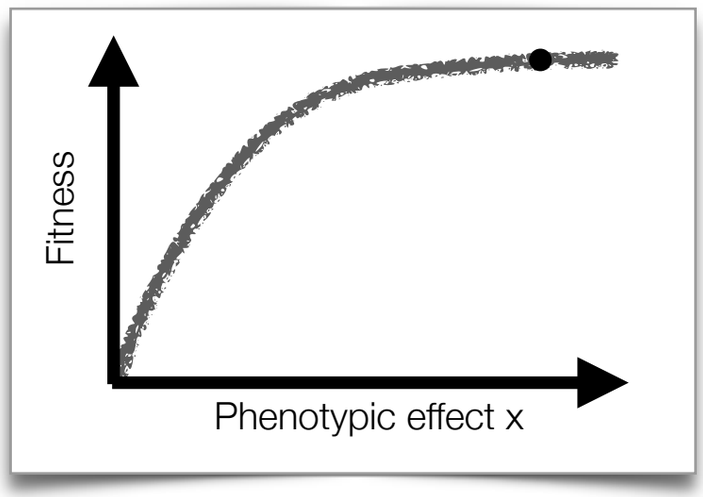
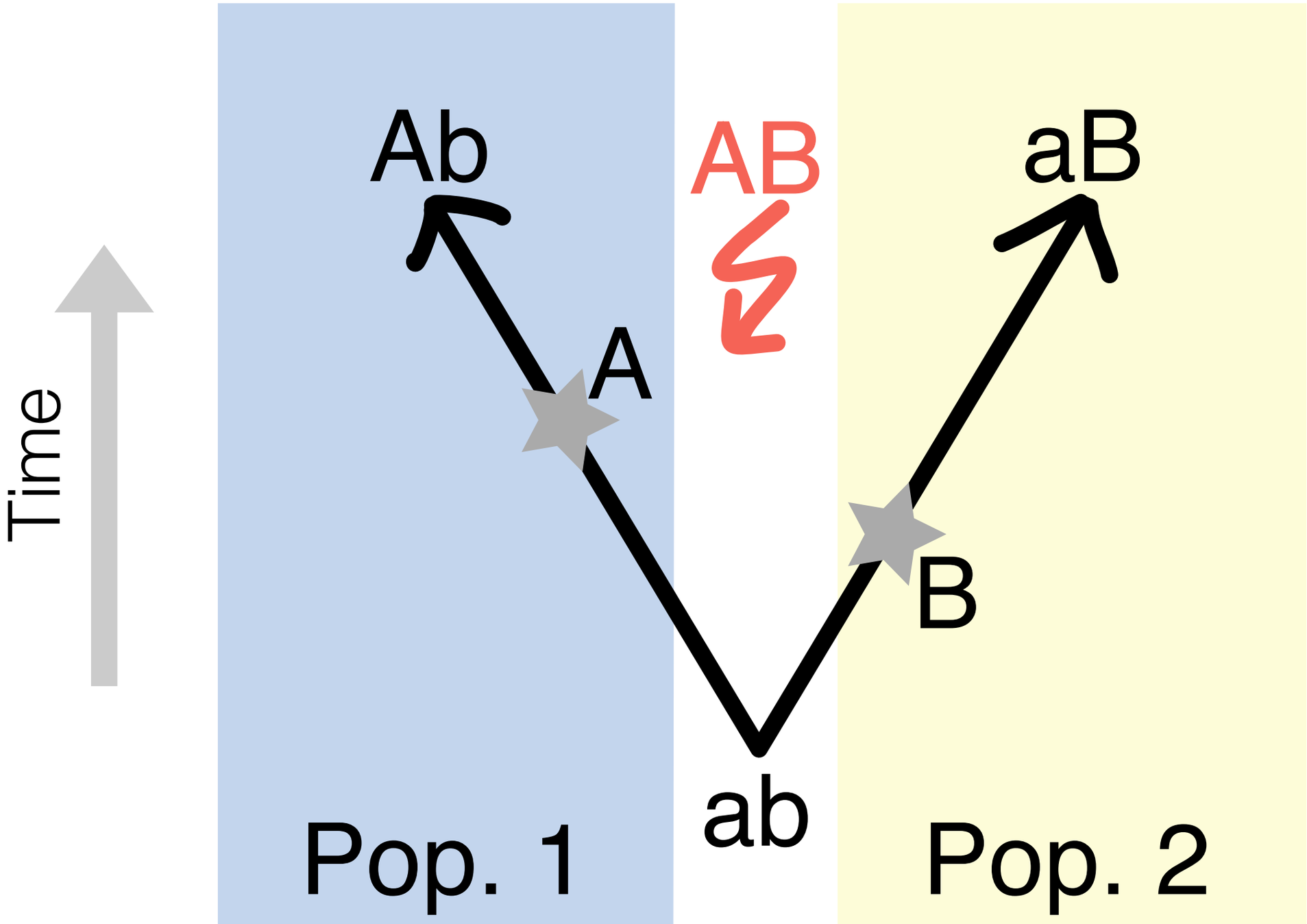


- Models of concave fitness landscape motivated by biophysical properties can explain the observed pattern of epistasis in the standard environment, supporting the idea of mutational robustness.

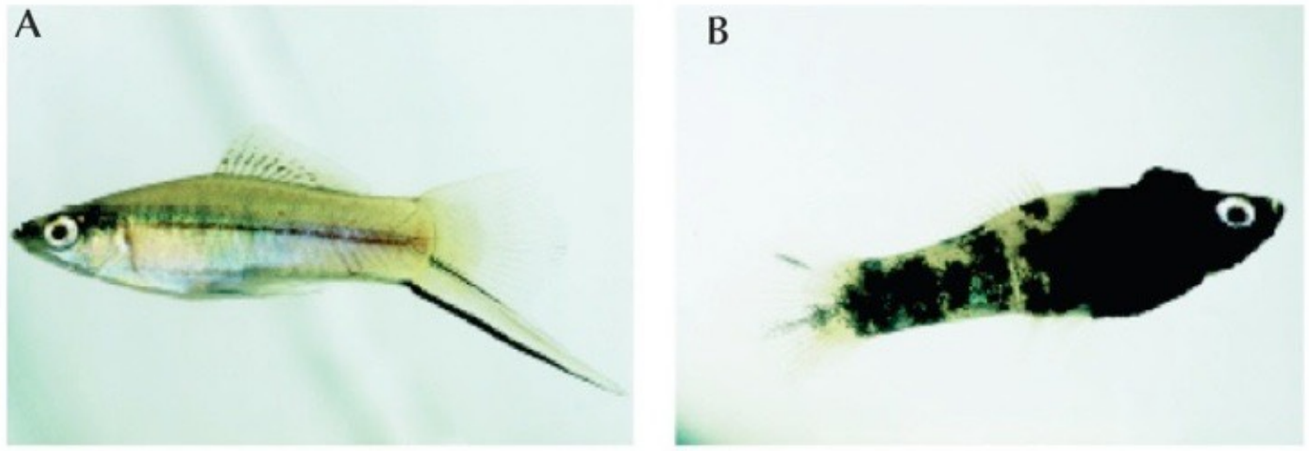


EPISTASIS BETWEEN SPECIES

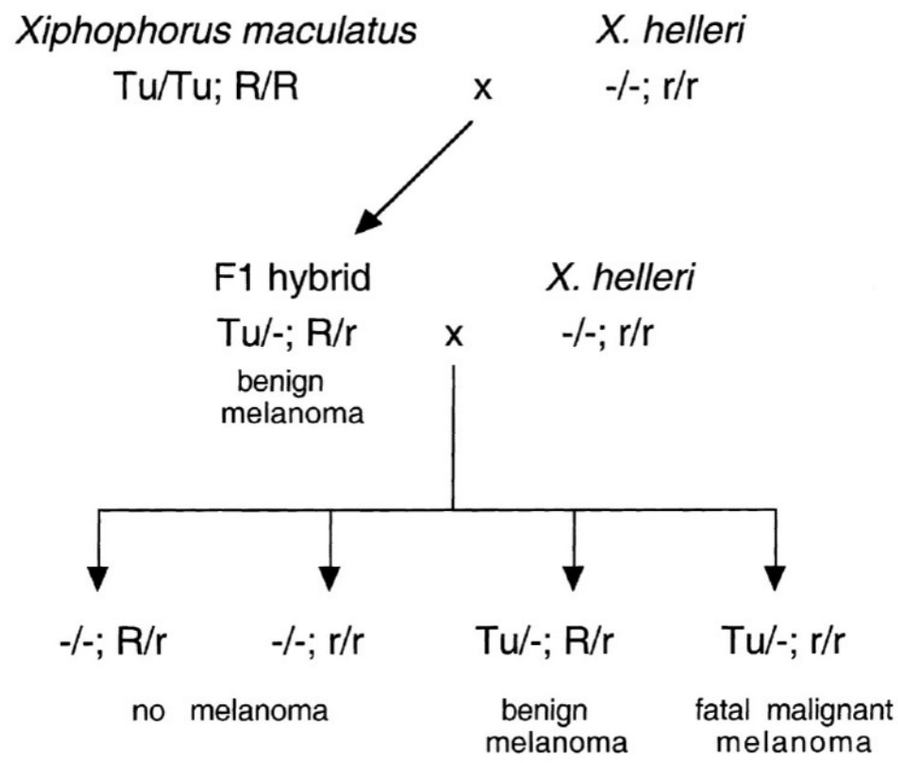
THE DOBZHANSKY-MULLER MODEL



DMIS



Orr & Presgraves, *Bioessays*, 2000



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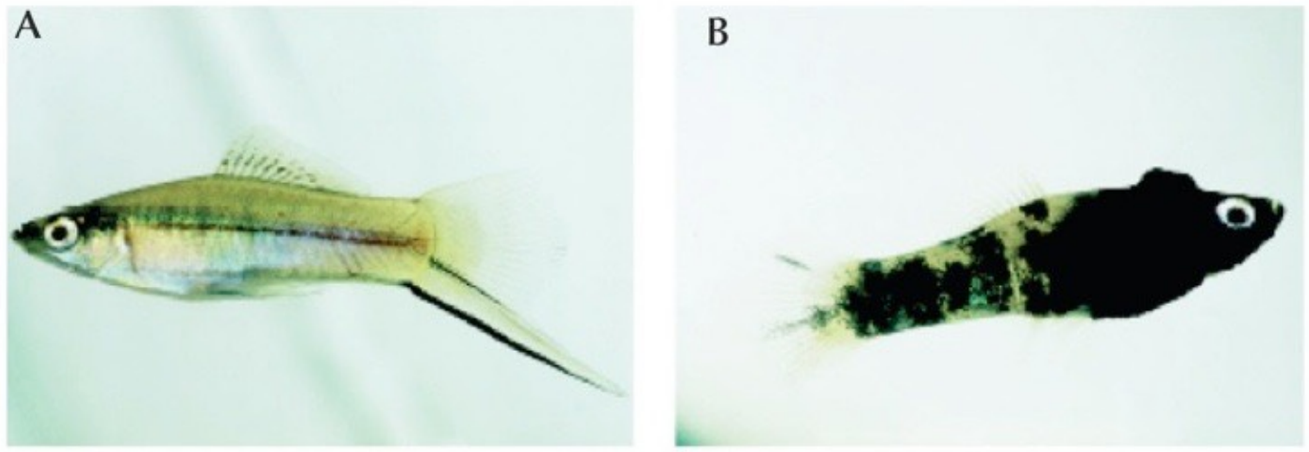

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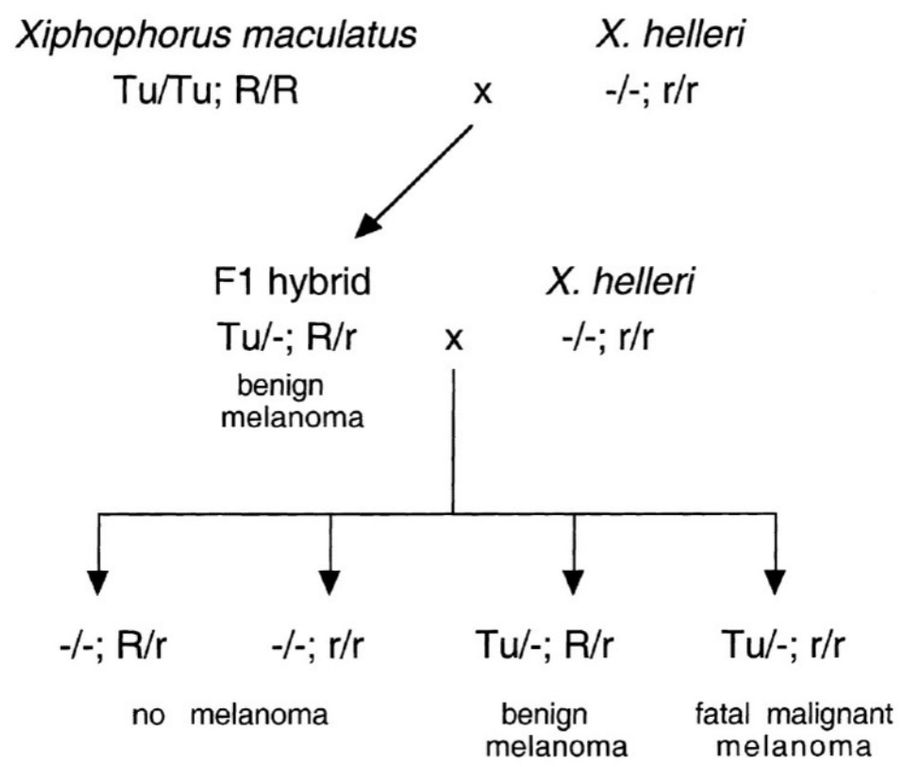
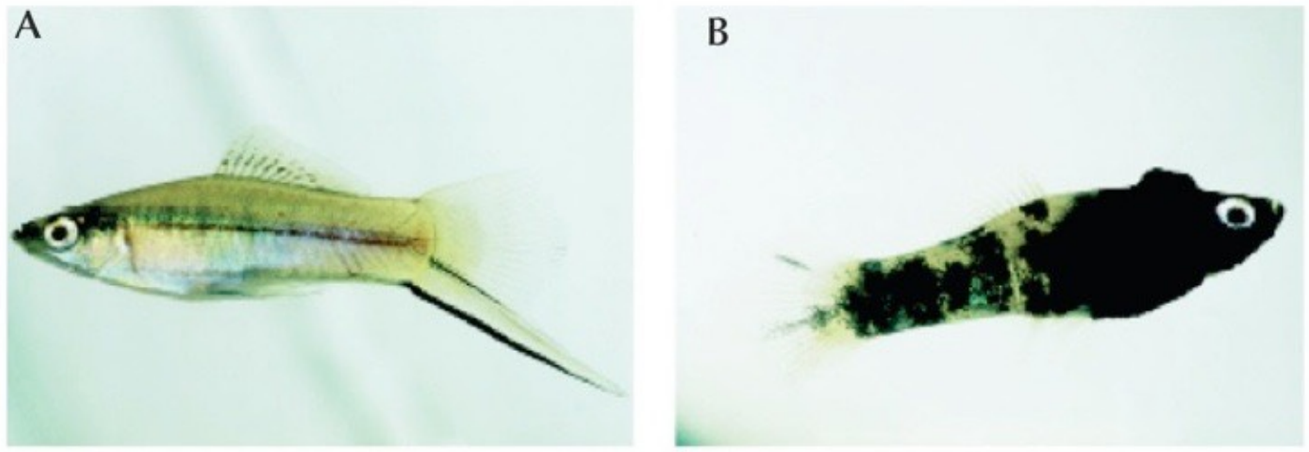


- sexual selection on tumor gene

Scarpino et al., MBE, 2013

DMIS



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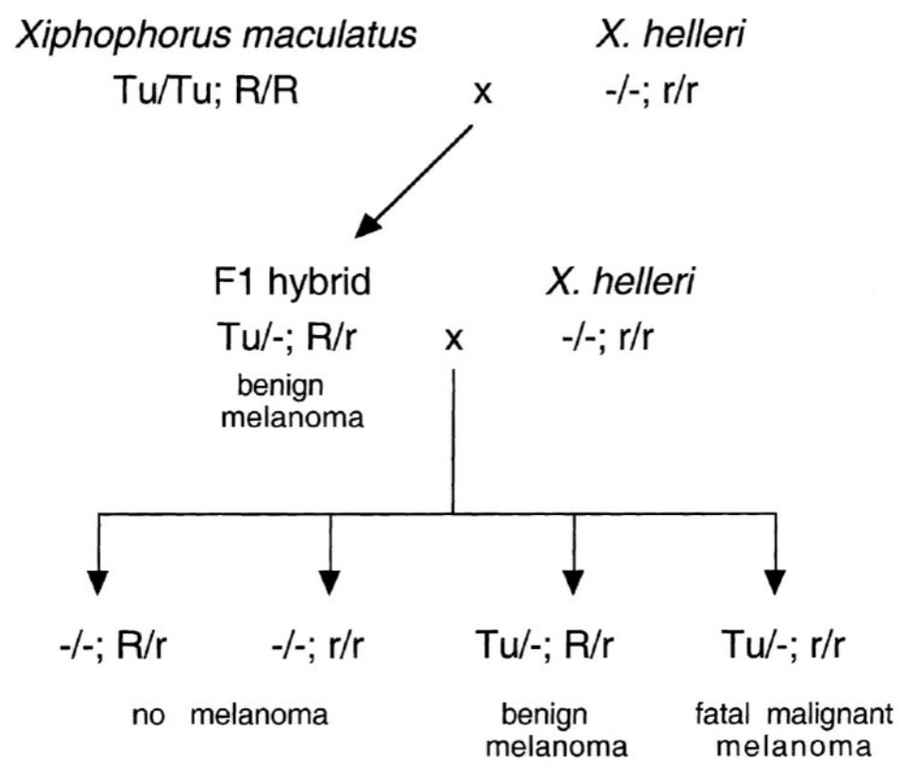

- sexual selection on tumor gene
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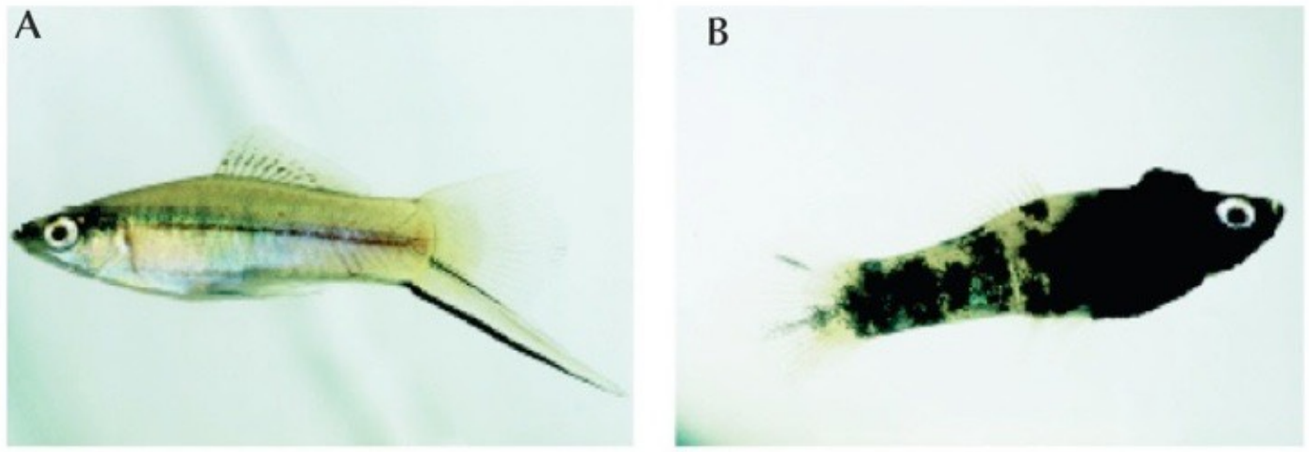

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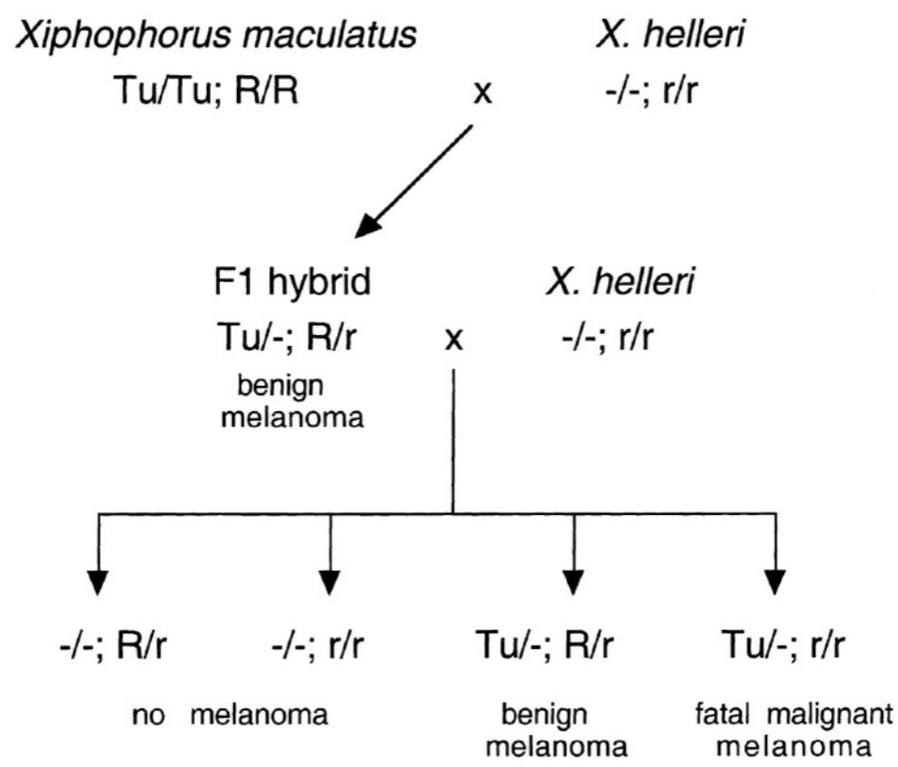

- sexual selection on tumor gene
- interaction with promoter of repressor gene
- ongoing gene flow

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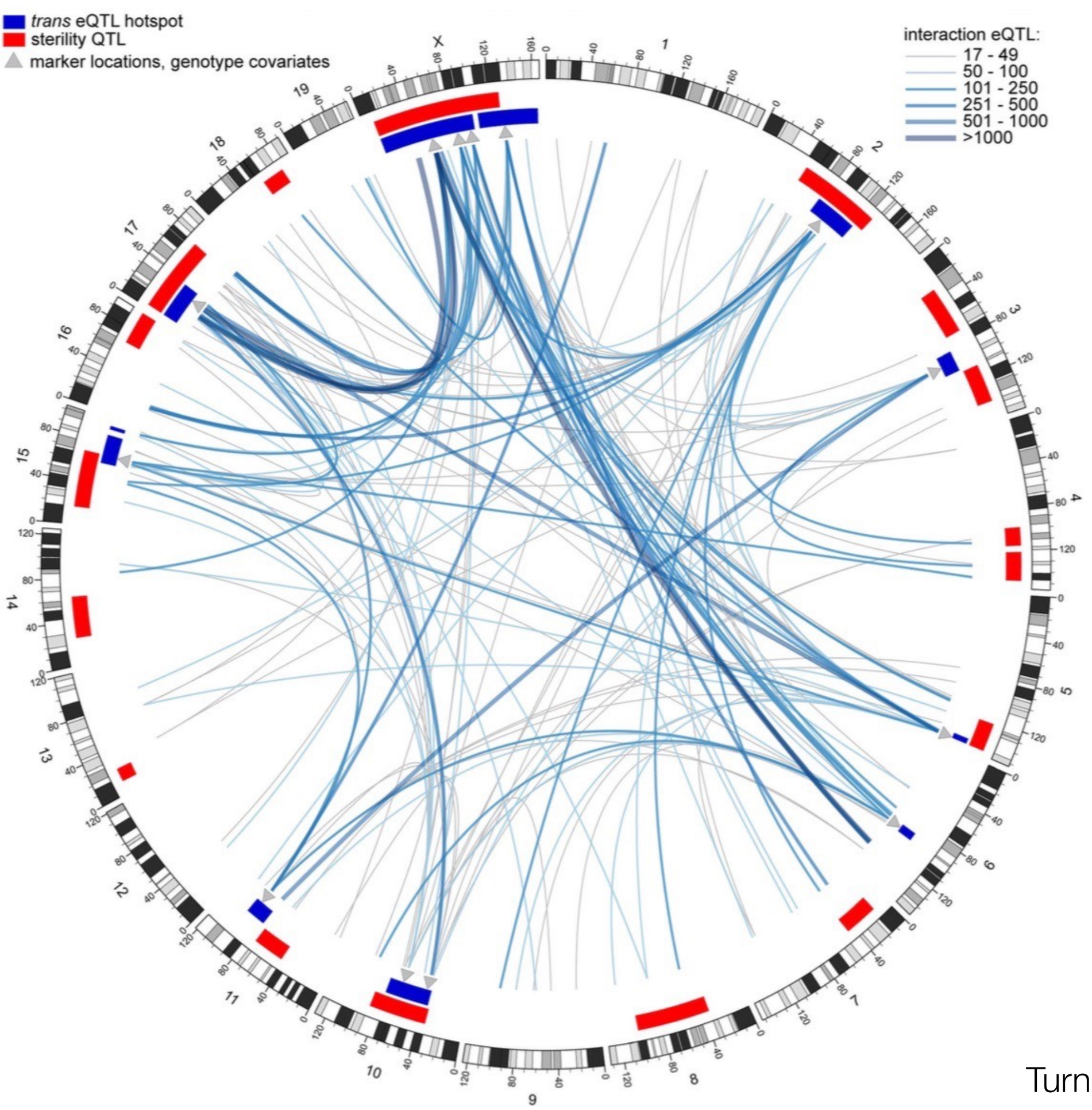
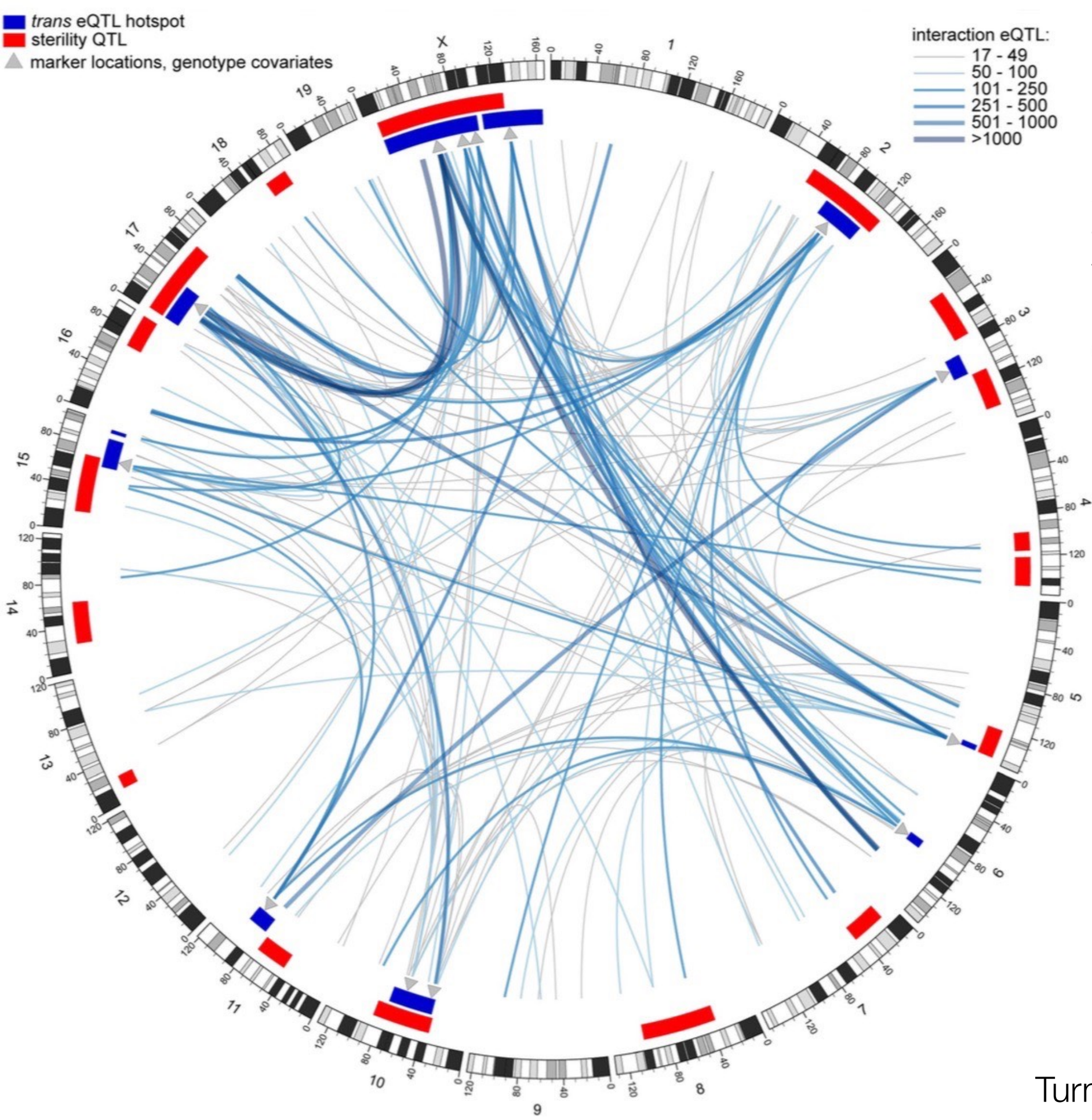


DMIS

Turner et al., *PlosGen*, 2014



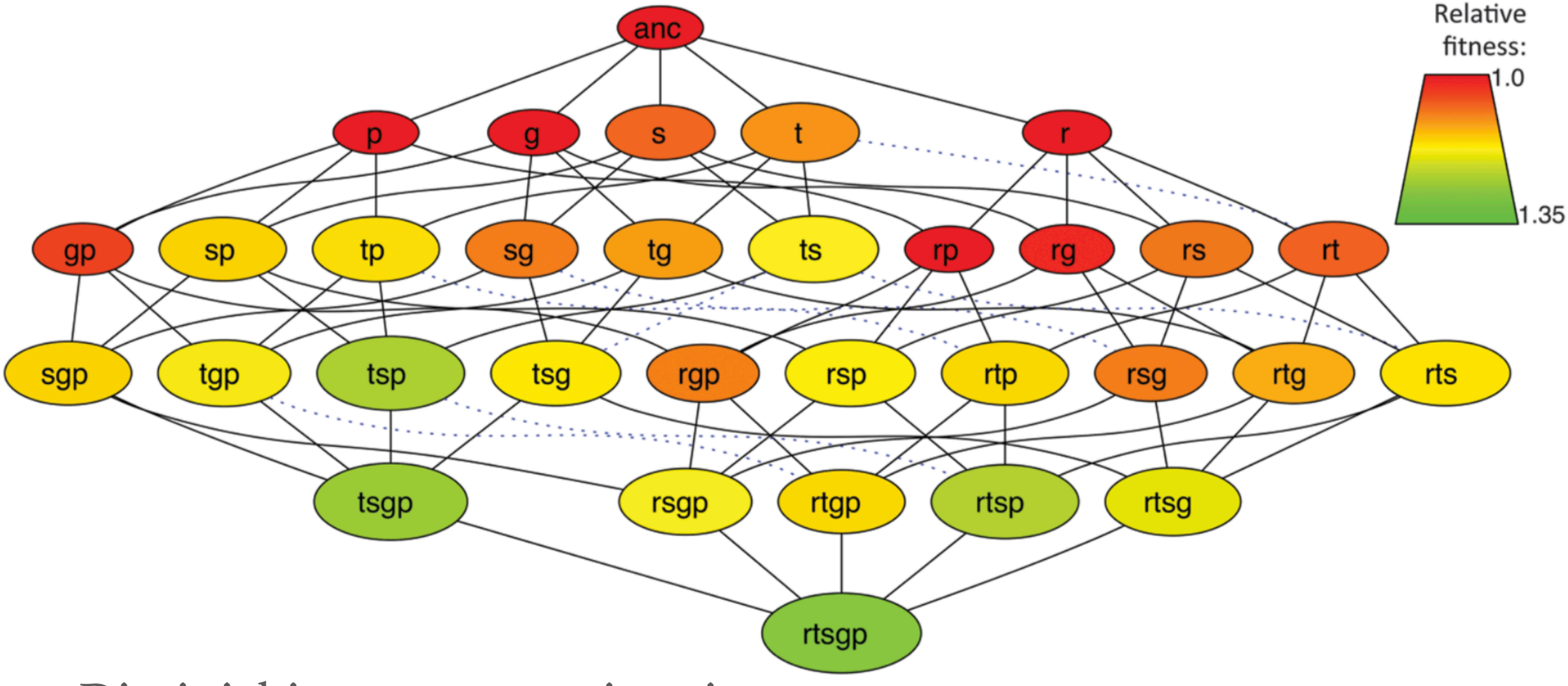
DMIS

In fact these were both "pathway" examples too…

Turner et al., *PlosGen*, 2014

TAKE A LOOK AT THE WHOLE FITNESS LANDSCAPE

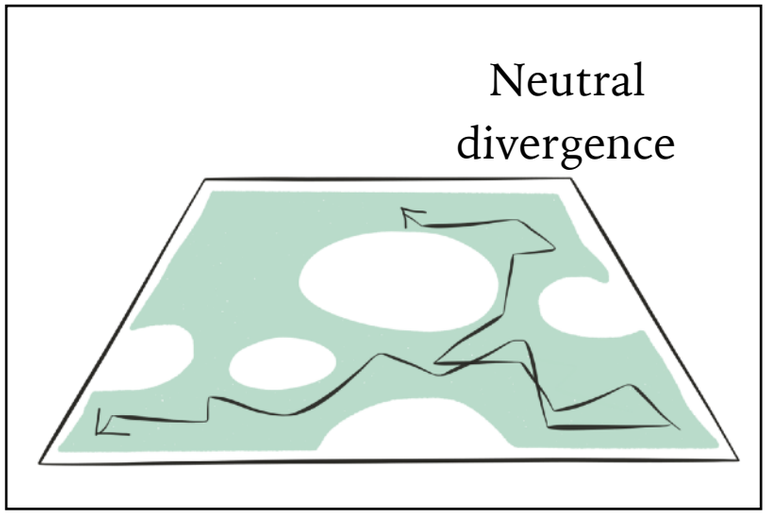
A FAMOUS EXAMPLE

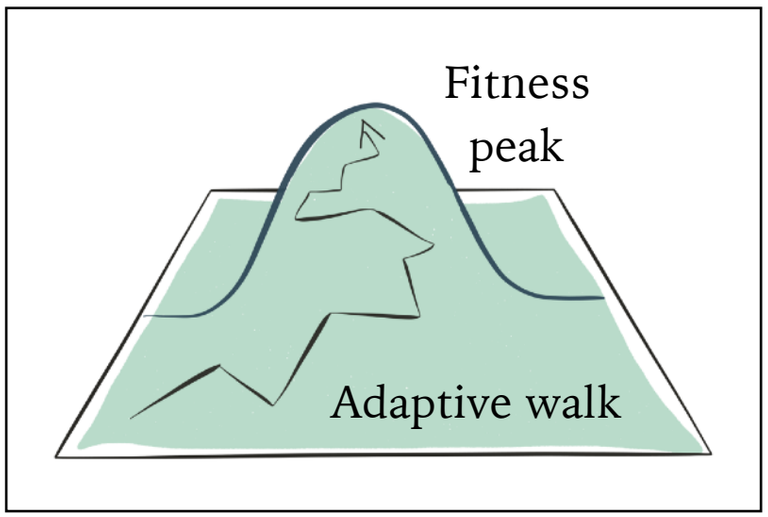


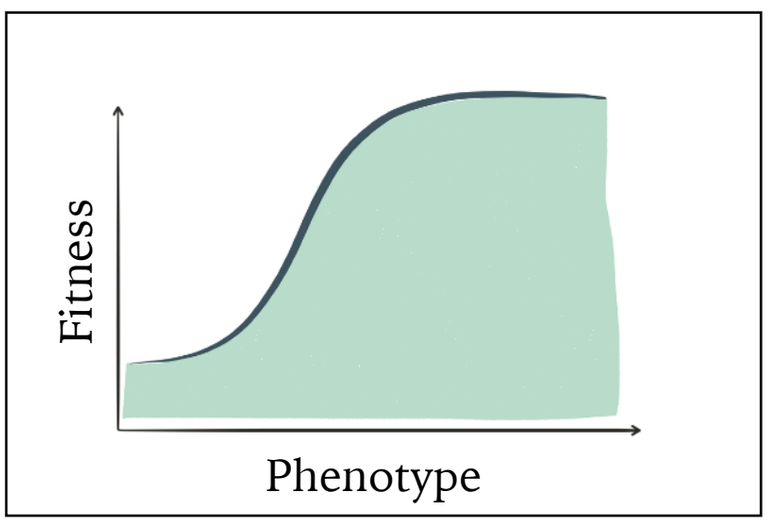
- Diminishing-returns epistasis
- Accessible but epistatic, single-peaked

Khan et al. 2011

WHY FITNESS LANDSCAPES ARE APPEALING







- fitness landscapes yield information on the predictability and repeatability of evolution

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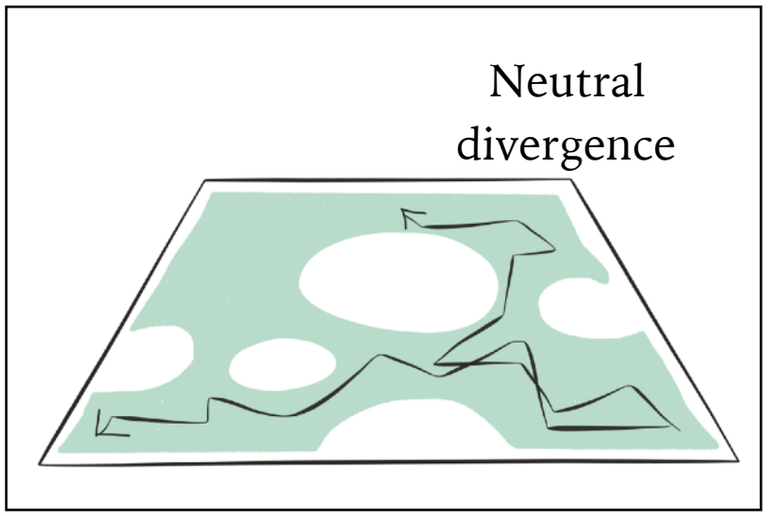
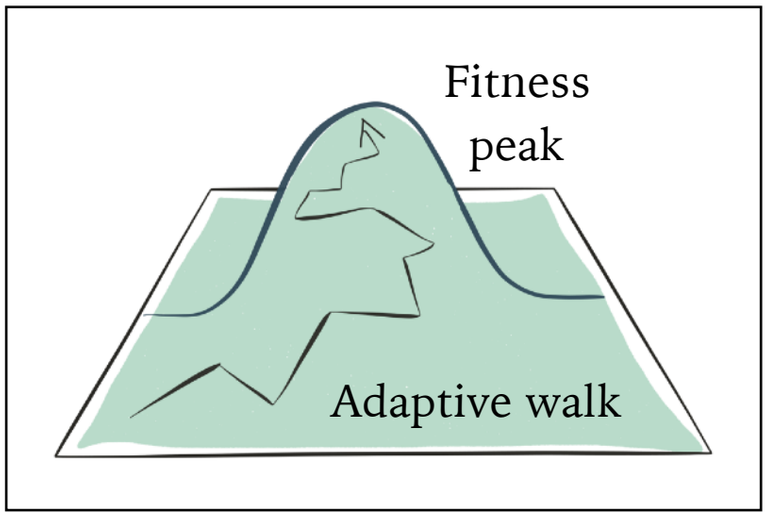
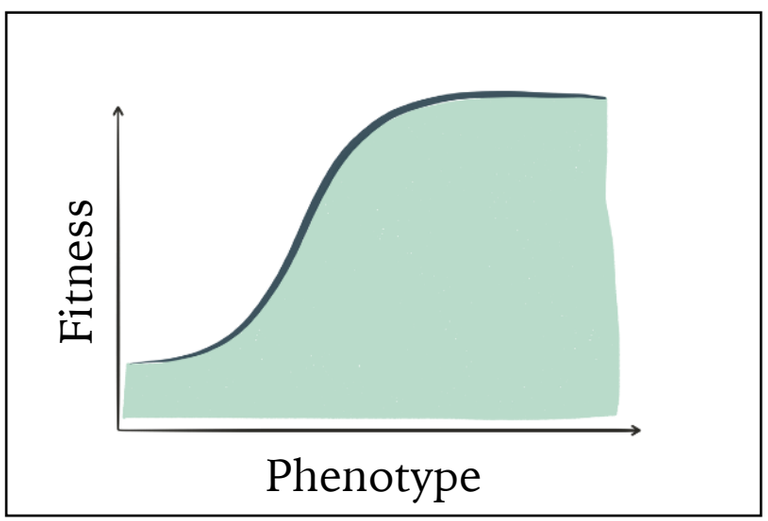






- fitness landscapes yield information on the predictability and repeatability of evolution
- it becomes increasingly simple to measure empirical fitness landscapes
- accumulating data on gene networks and pathways

Local fitness landscape of the green fluorescent protein

Comprehensive experimental fitness landscape and evolutionary network for small RNA

Genotype to Phenotype Mapping and the Fitness Landscape of the *E. coli lac* Promoter

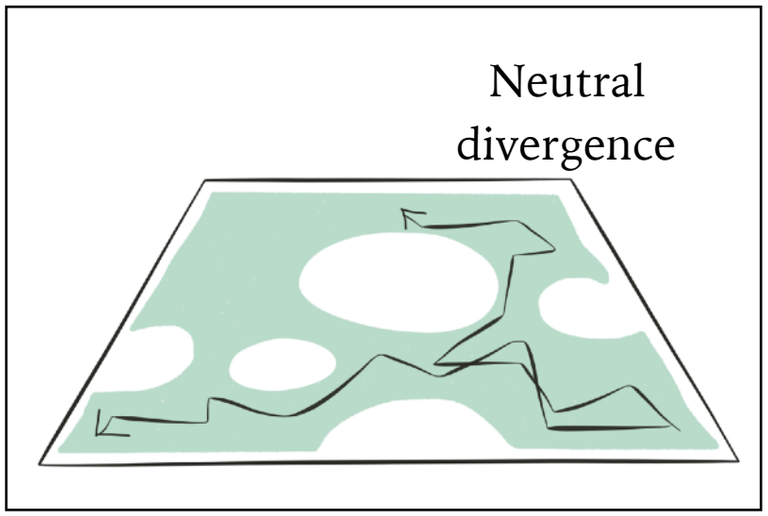
Biophysical principles predict fitness landscapes of drug resistance

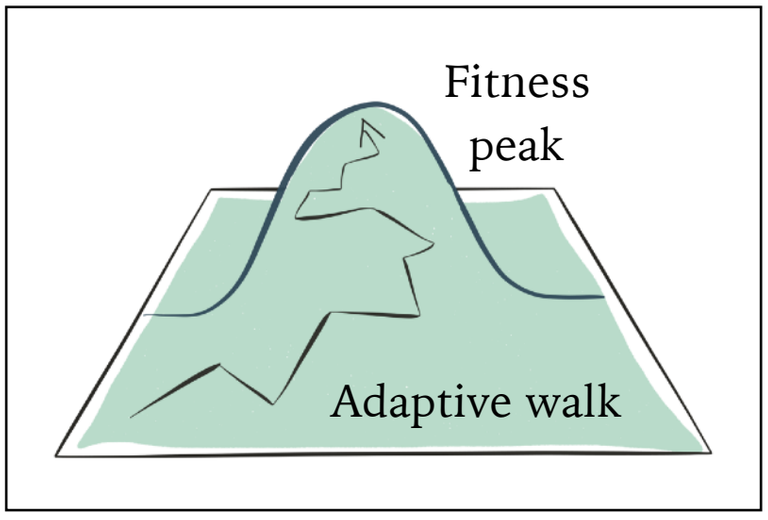
Mutational and fitness landscapes of an RNA virus revealed through population sequencing

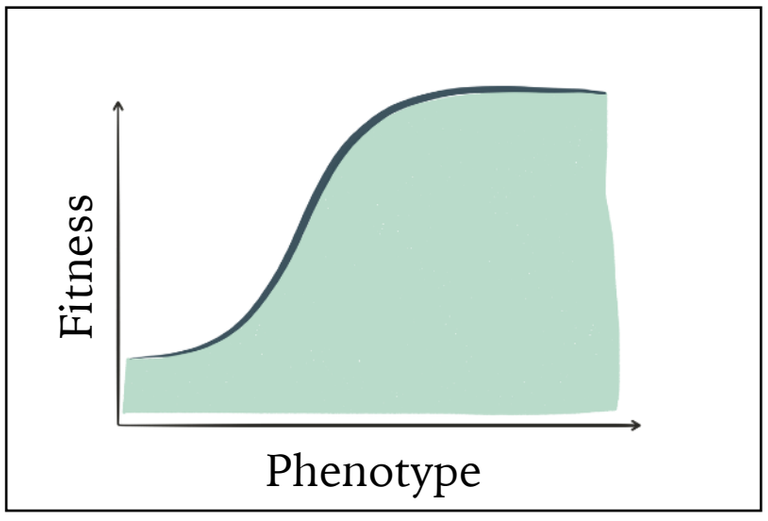
In-vivo mutation rates and fitness landscape of HIV-1

The fitness landscape of a tRNA gene

WHY FITNESS LANDSCAPES ARE DIFFICULT







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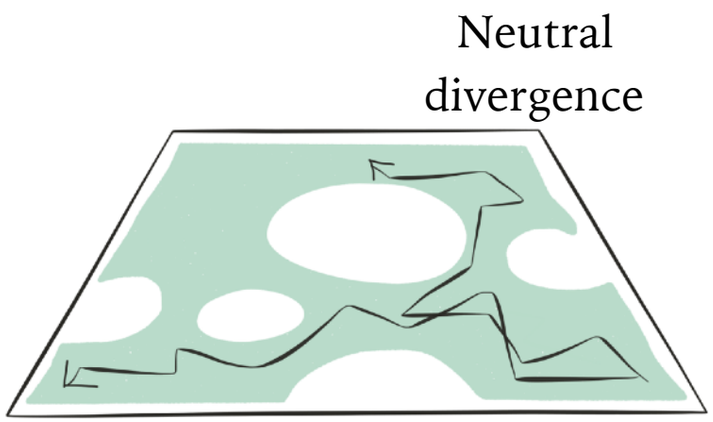

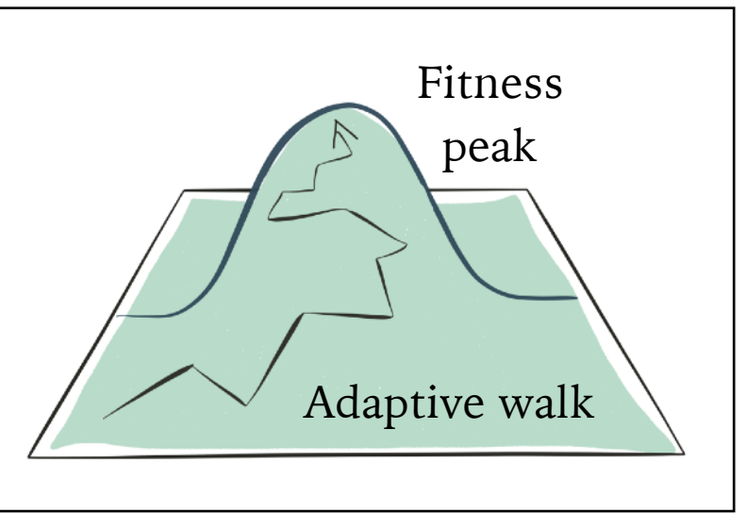

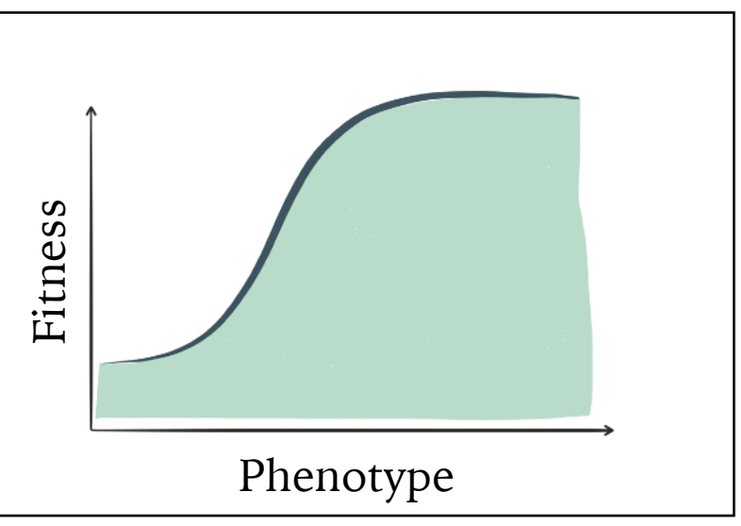

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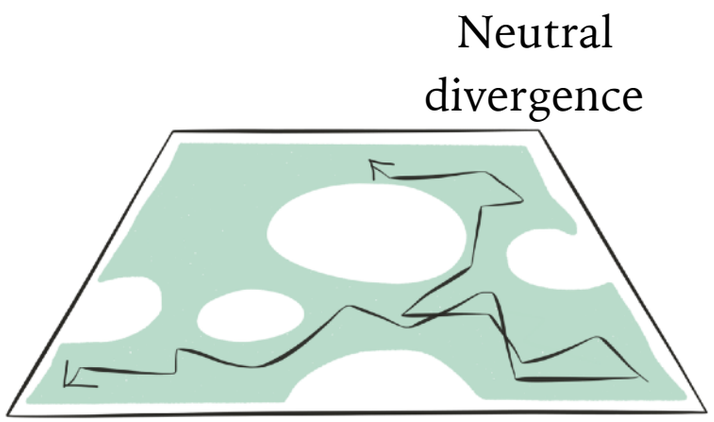

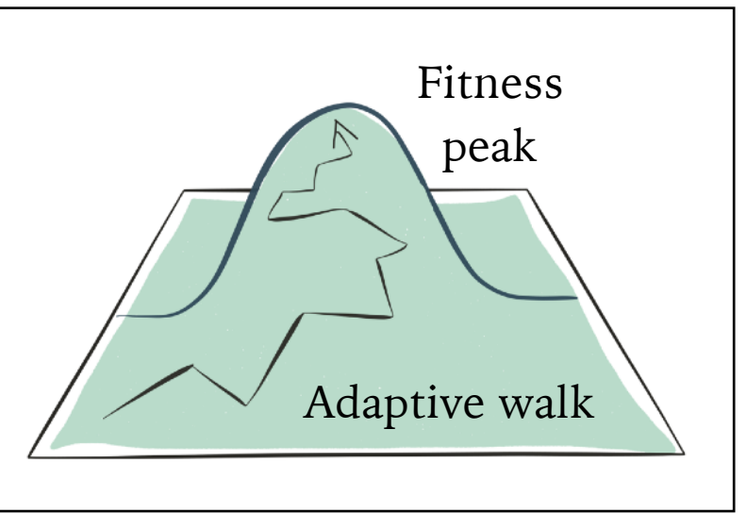

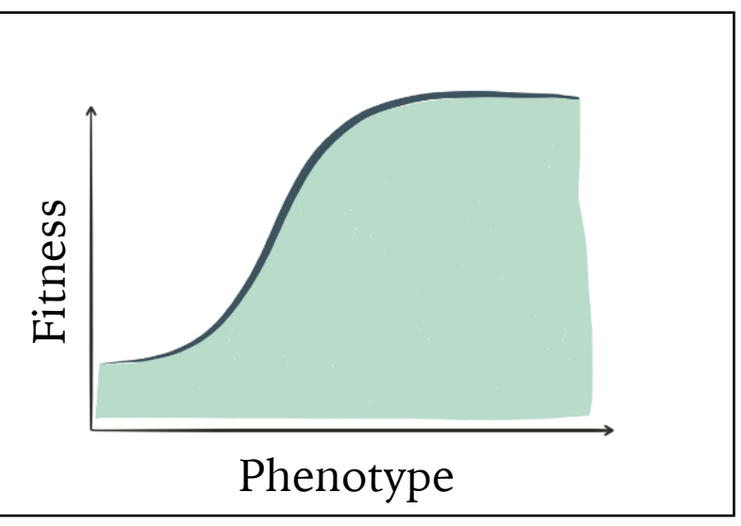

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But:

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E.g.: Can we predict costs of anti-microbial resistance across environments?

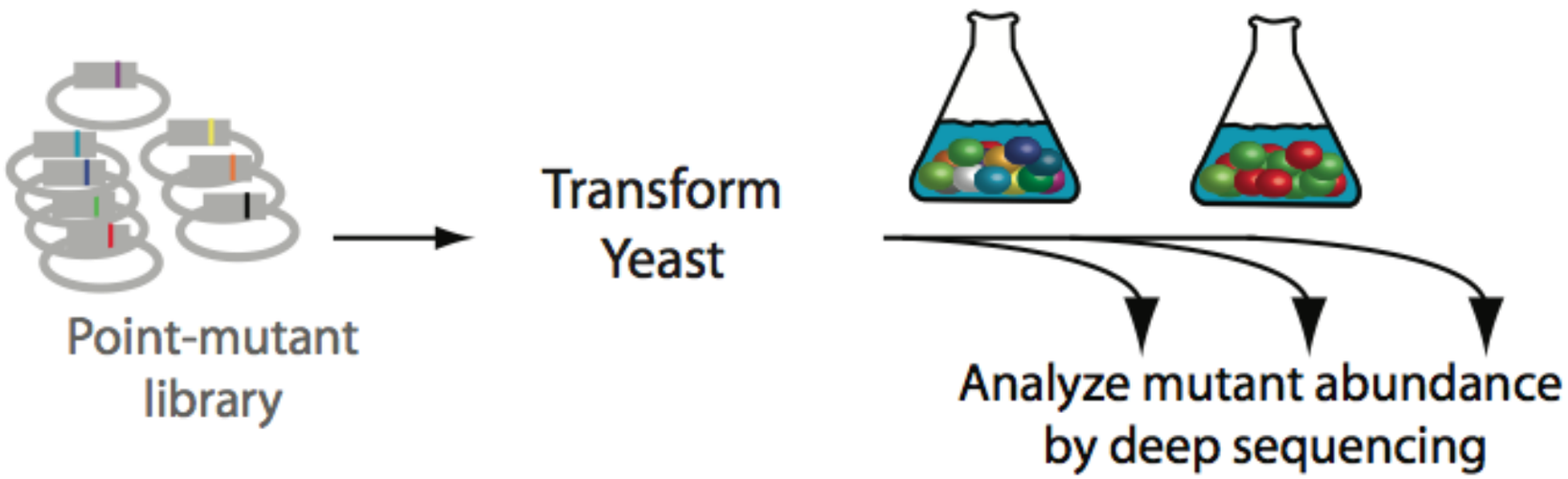
THE EXPERIMENTAL APPROACH: DEEP MUTATIONAL SCANNING

- Systematic high-throughout sampling of hundreds of chosen mutations (including those that are strongly deleterious)
- Bulk competitions ensure identical conditions for all mutants
- Genetic background is precisely controlled (minimized potential for secondary mutations)

Dan Bolon

Ryan Hietpas

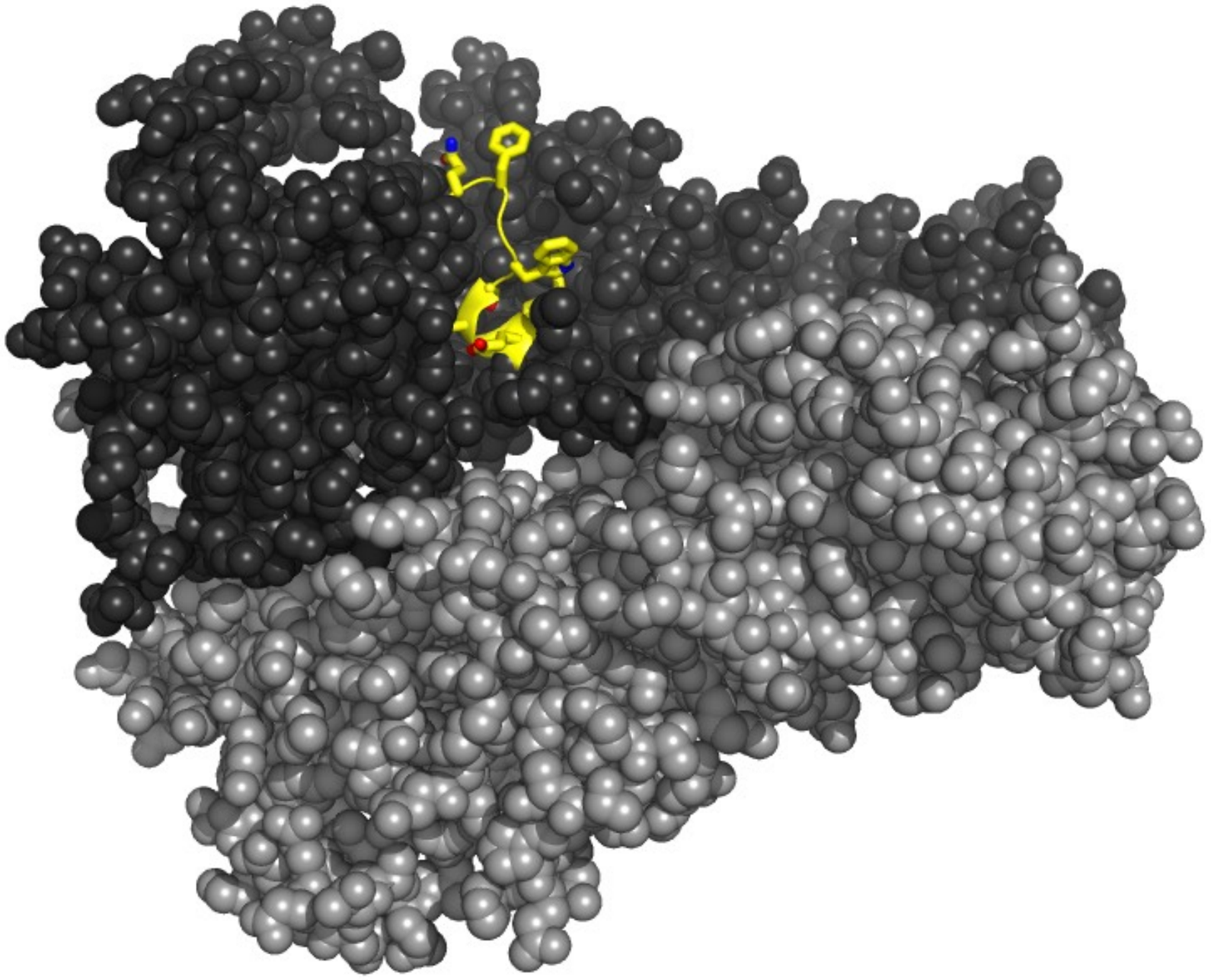
Jeff Jensen



Hietpas, Jensen & Bolon, PNAS, 2011

WHAT WE DID SO FAR

Engineered mutations from a 9 aa region from Hsp90 (aa positions 582-590) in *Saccharomyces cerevisiae*



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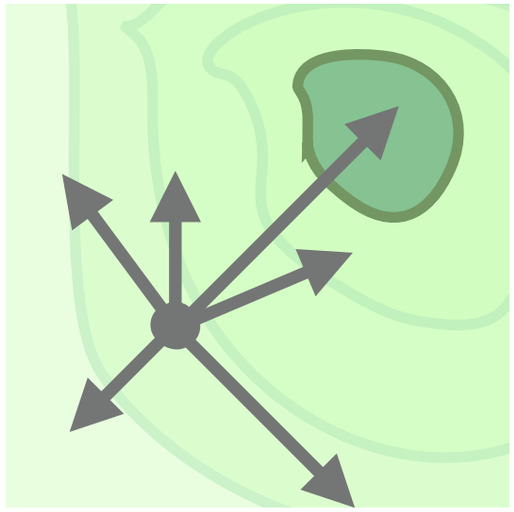

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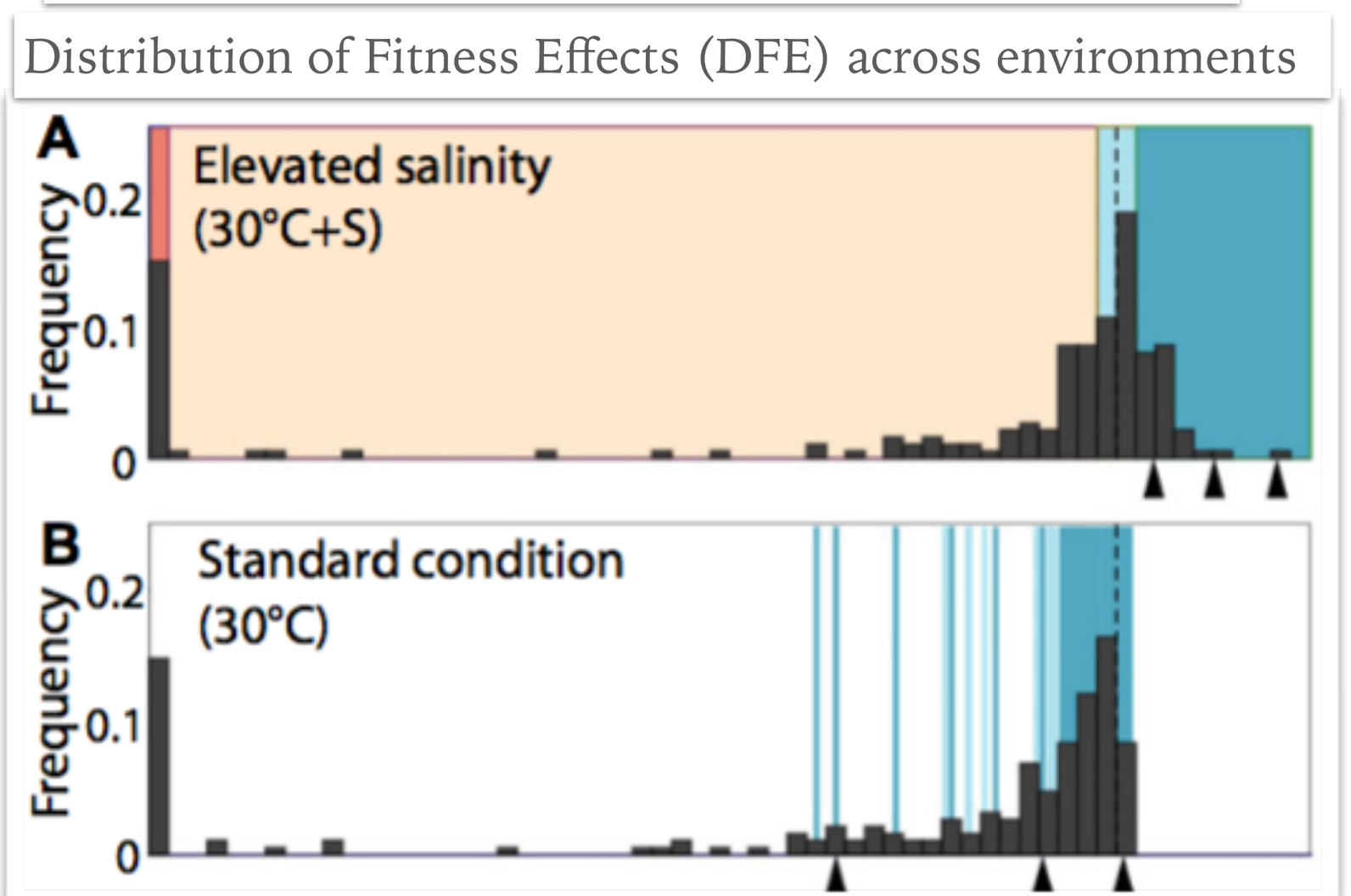
Compare DFEs across 4 environments - high costs of adaptation

Distribution of Fitness Effects (DFE) across environments



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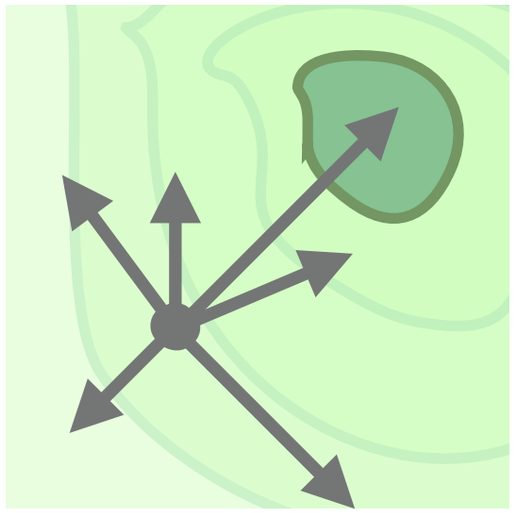

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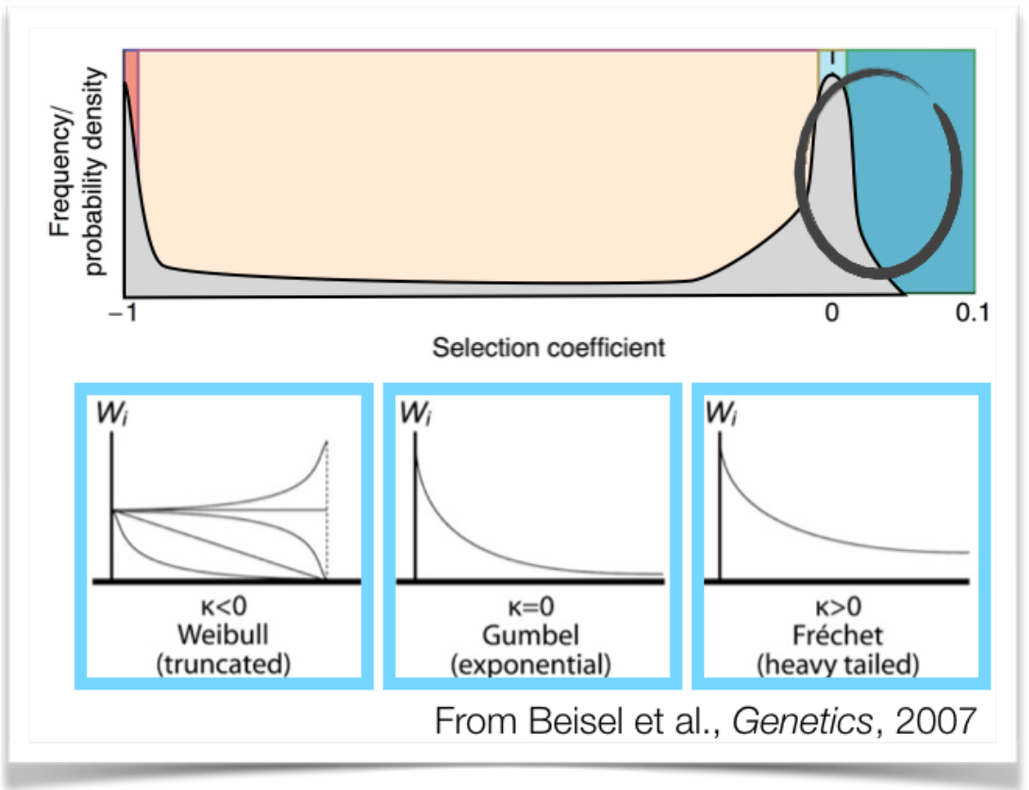
MCMC method to estimate selection coefficients, and DFEs across 6 environments - heavy-tailed DFE for most challenging environment



From Beisel et al., *Genetics*, 2007

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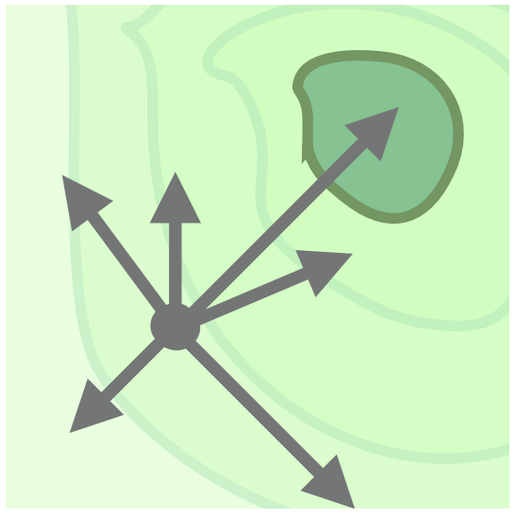

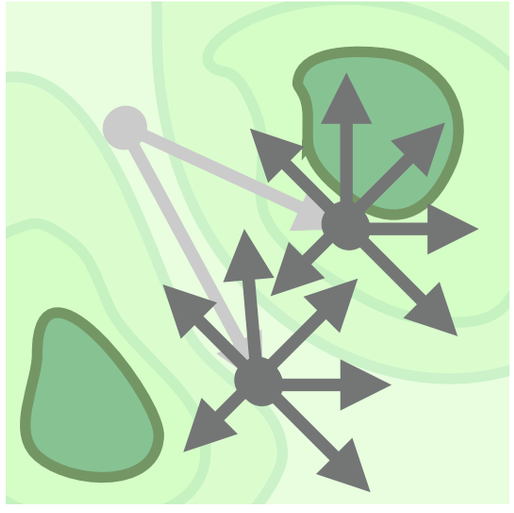

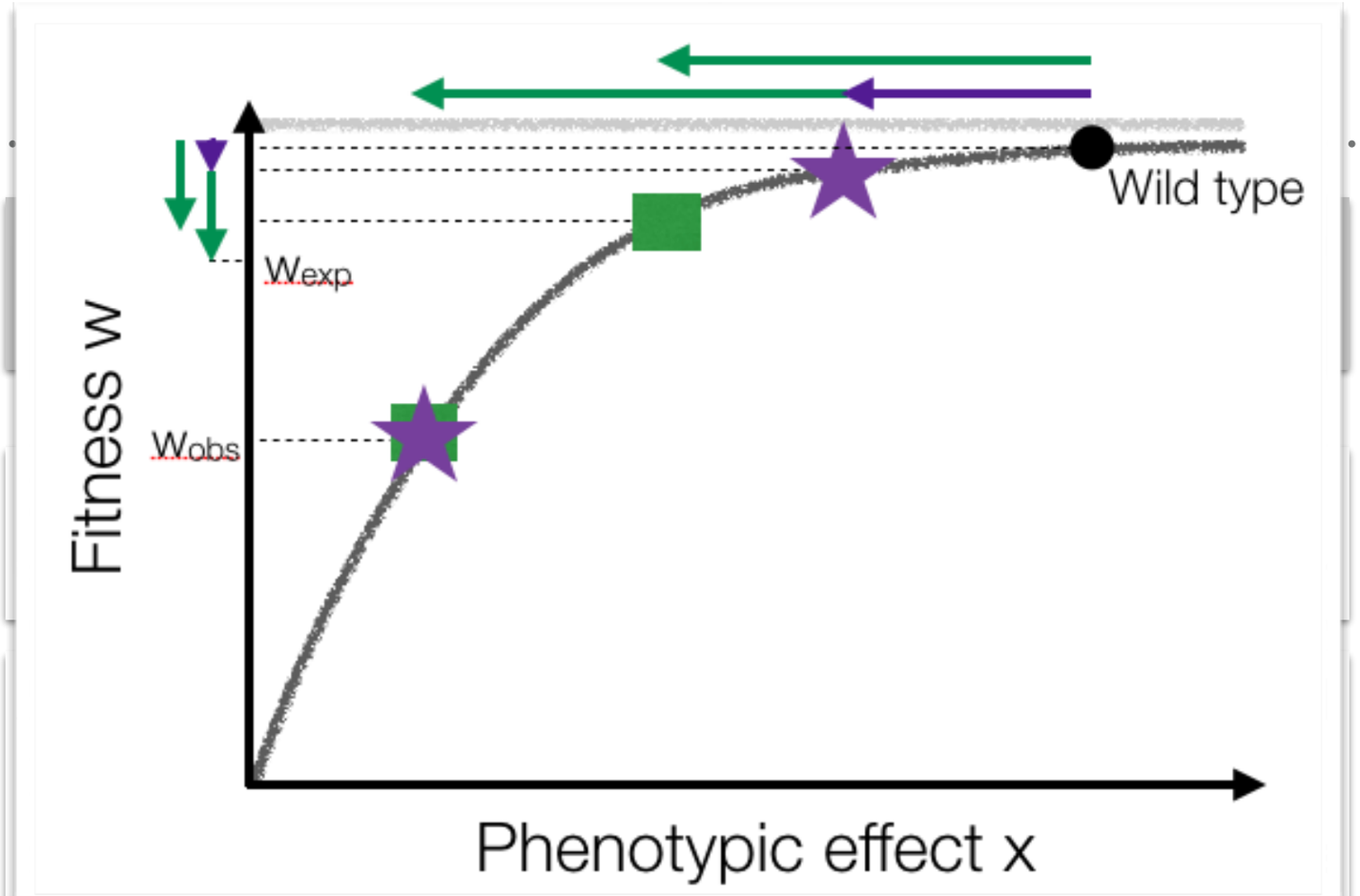

DFEs on 7 genetic backgrounds - ubiquitous negative epistasis indicating an underlying concave fitness landscape

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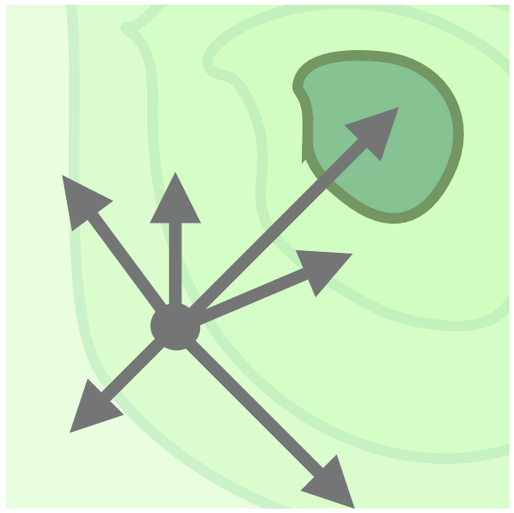

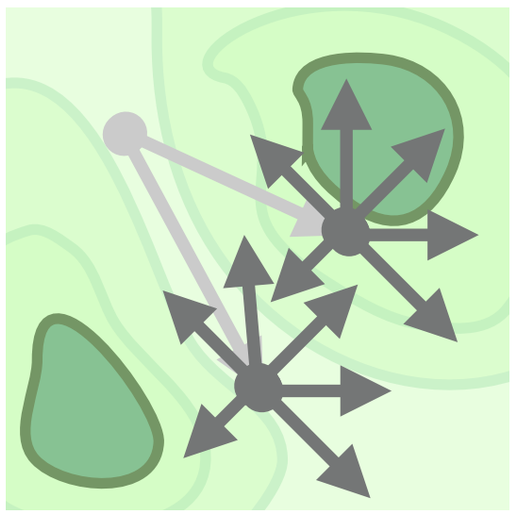

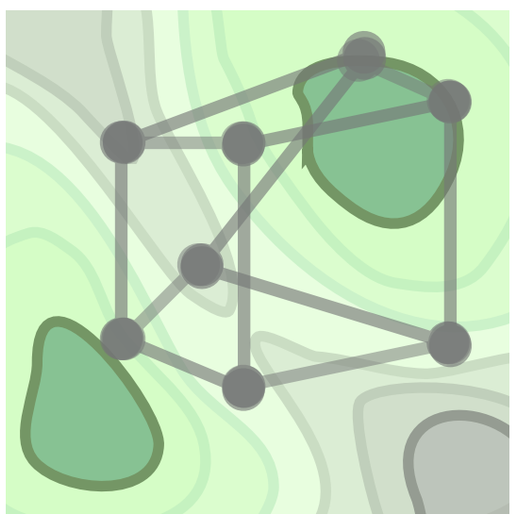

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Compare DFEs across 4 environments - high costs of adaptation **Hietpas*, Bank* et al., 2013, Evolution**

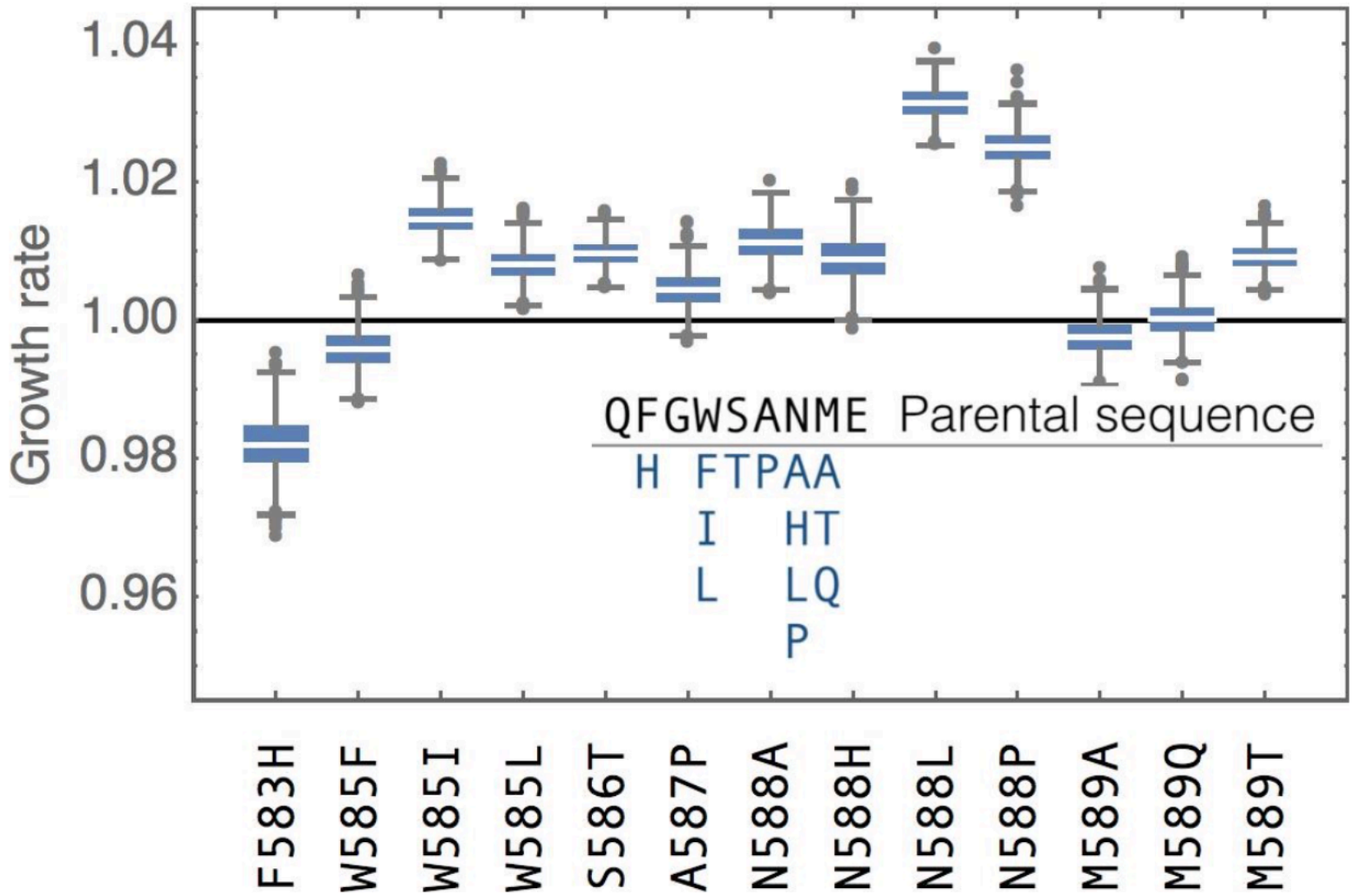
MCMC method to estimate selection coefficients, and DFEs across 6 environments - heavy-tailed DFE for most challenging environment **Bank et al., 2014, Genetics**

DFEs on 7 genetic backgrounds - ubiquitous negative epistasis indicating an underlying concave fitness landscape

Guide to experimental design of deep mutational scanning studies

Complete fitness landscape of 640 combinations of mutations

high salinity environment
13 single-aa mutations
2 replicates
all possible combinations of aa's
≈1600 nt mutations



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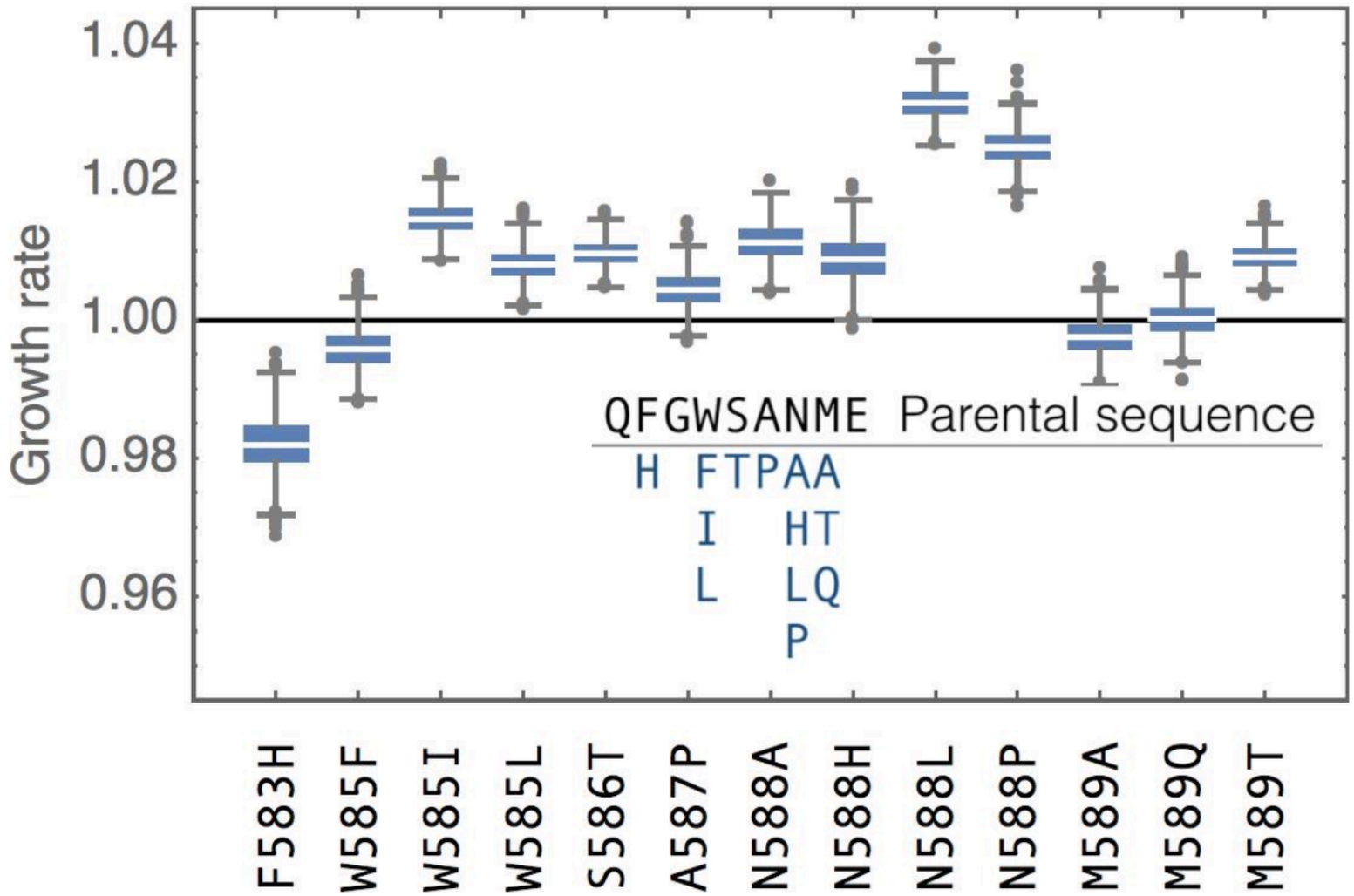
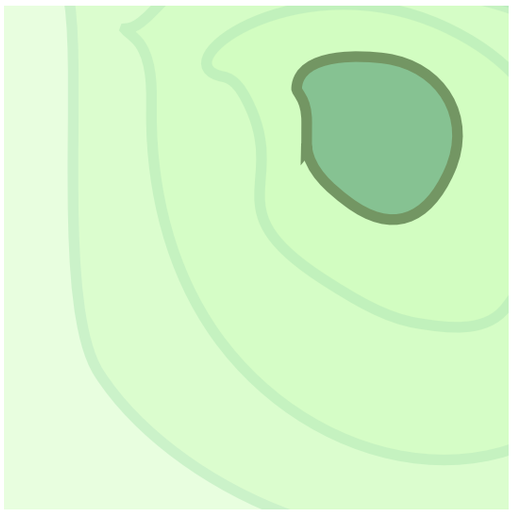
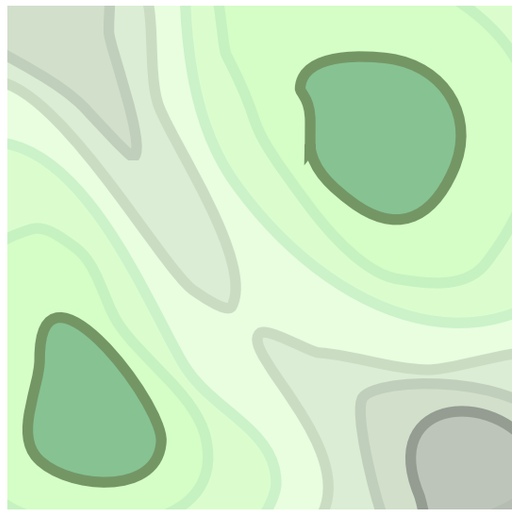


- relatively “unbiased" selection of mutations
- multi-allelic fitness landscape

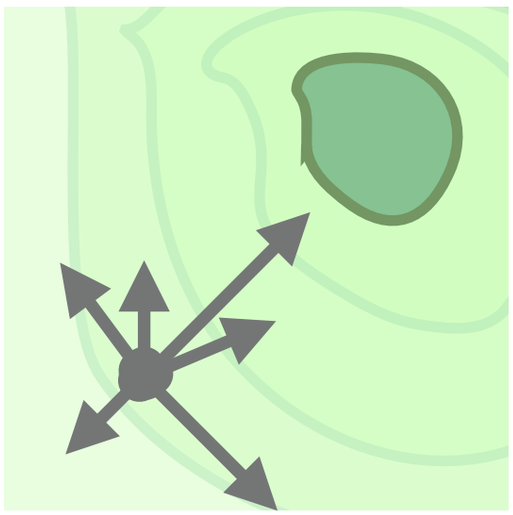
3 QUESTIONS

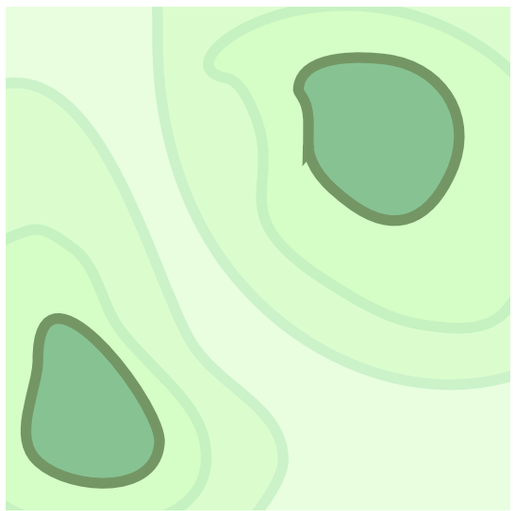


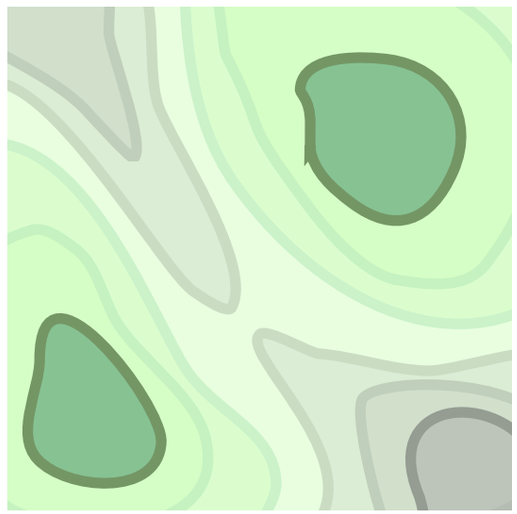


3 QUESTIONS

- Do single step mutations predict the way to the global optimum?







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- Do single step mutations predict the way to the global optimum?
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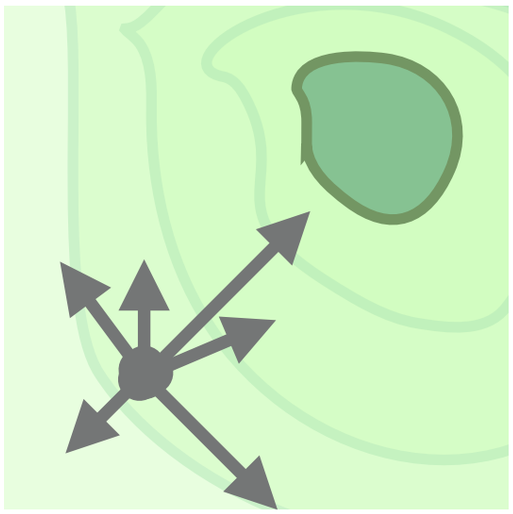
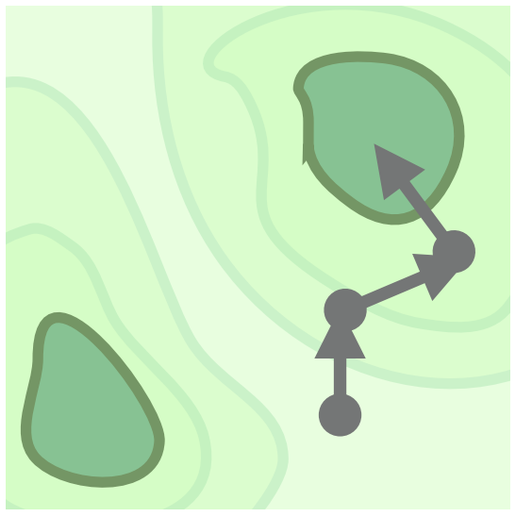
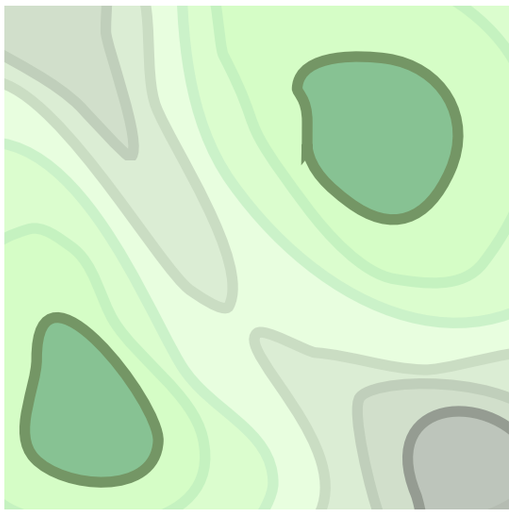
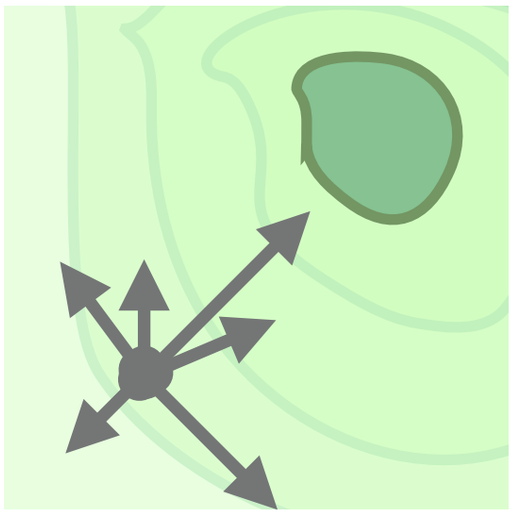


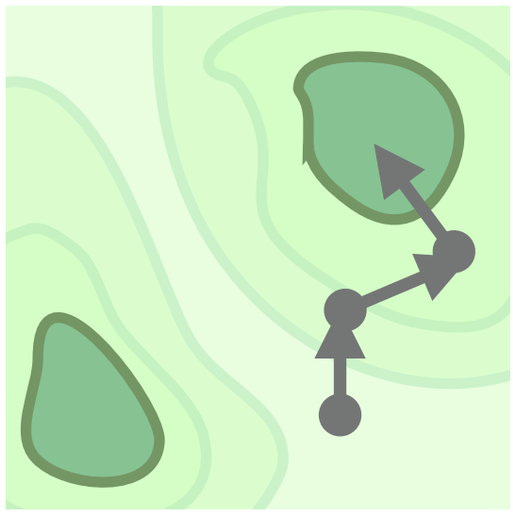


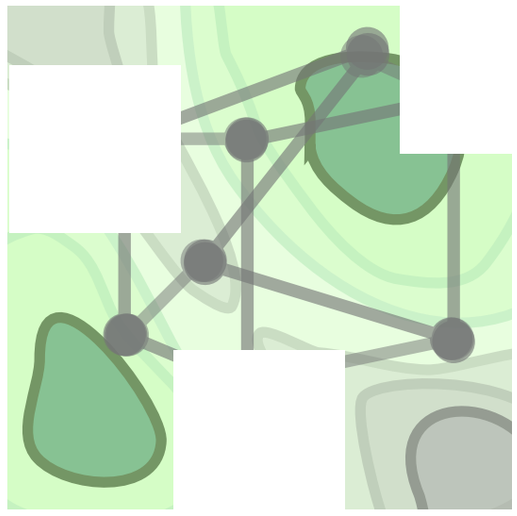


3 QUESTIONS

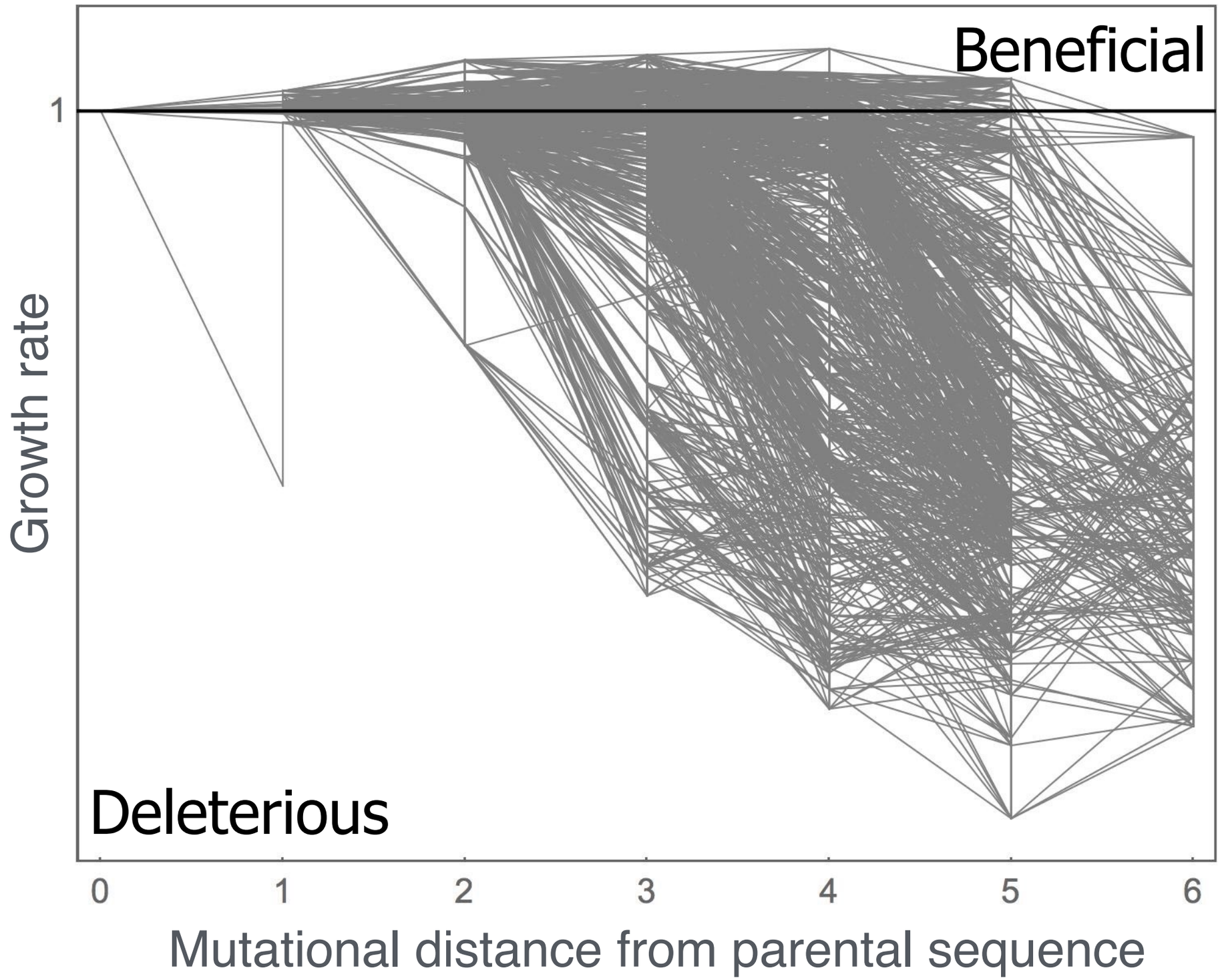
- Do single step mutations predict the way to the global optimum?
- Will adaptation take the population to the global optimum?
- Can we infer an unknown part of the fitness landscape?



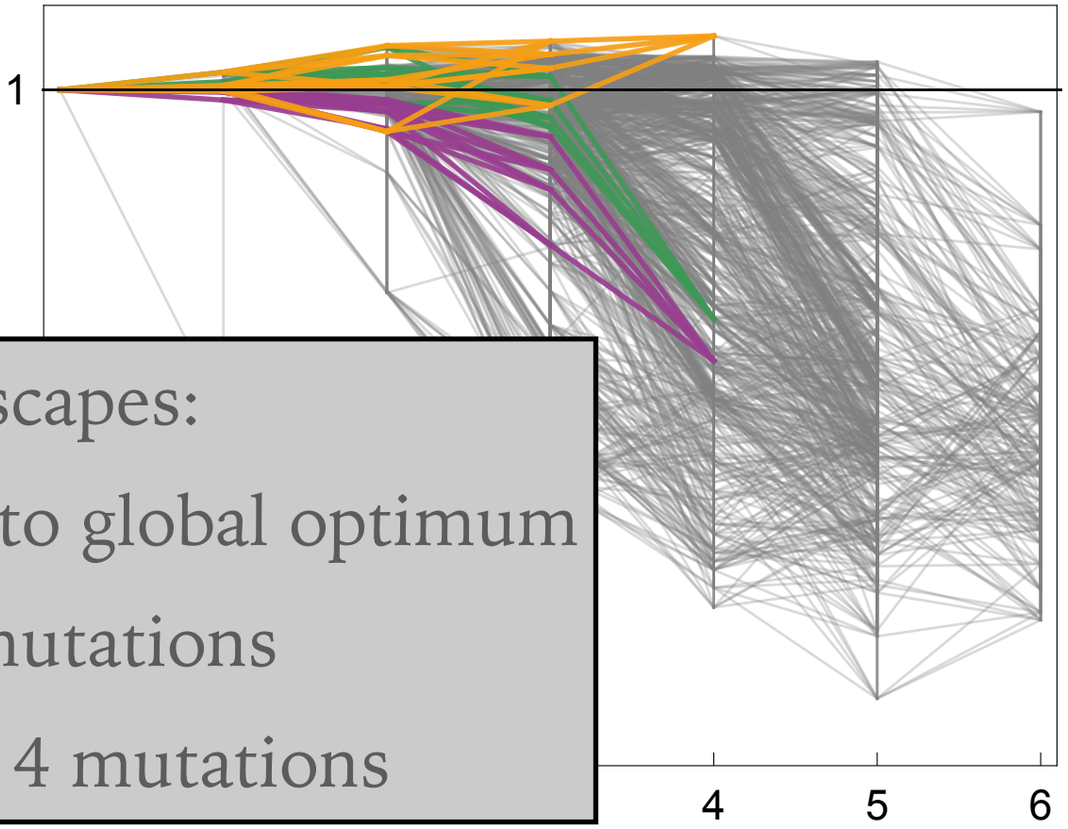




A PICTURE OF THE WHOLE LANDSCAPE



1 – DO SINGLE STEP MUTATIONS PREDICT THE WAY TO THE GLOBAL OPTIMUM?

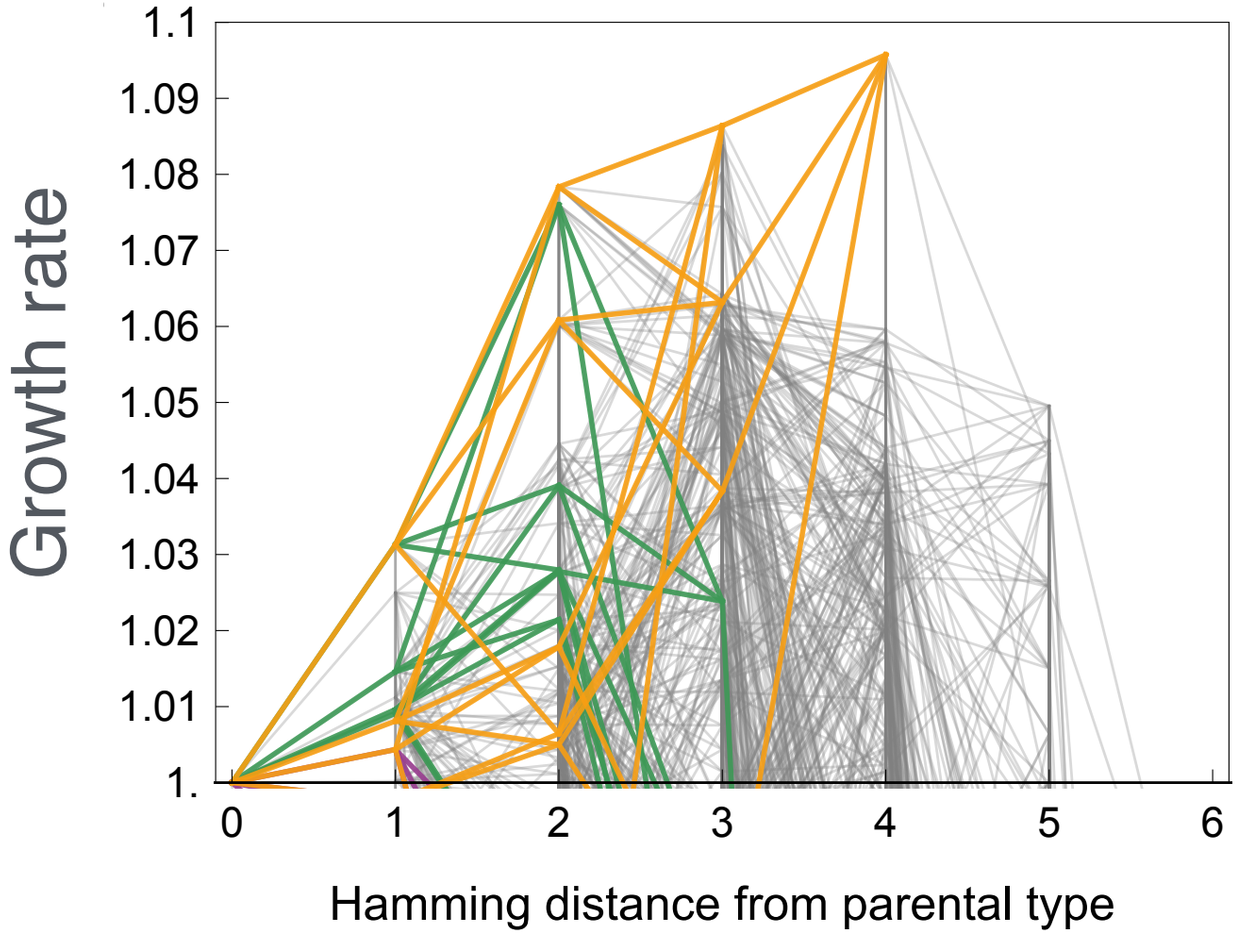


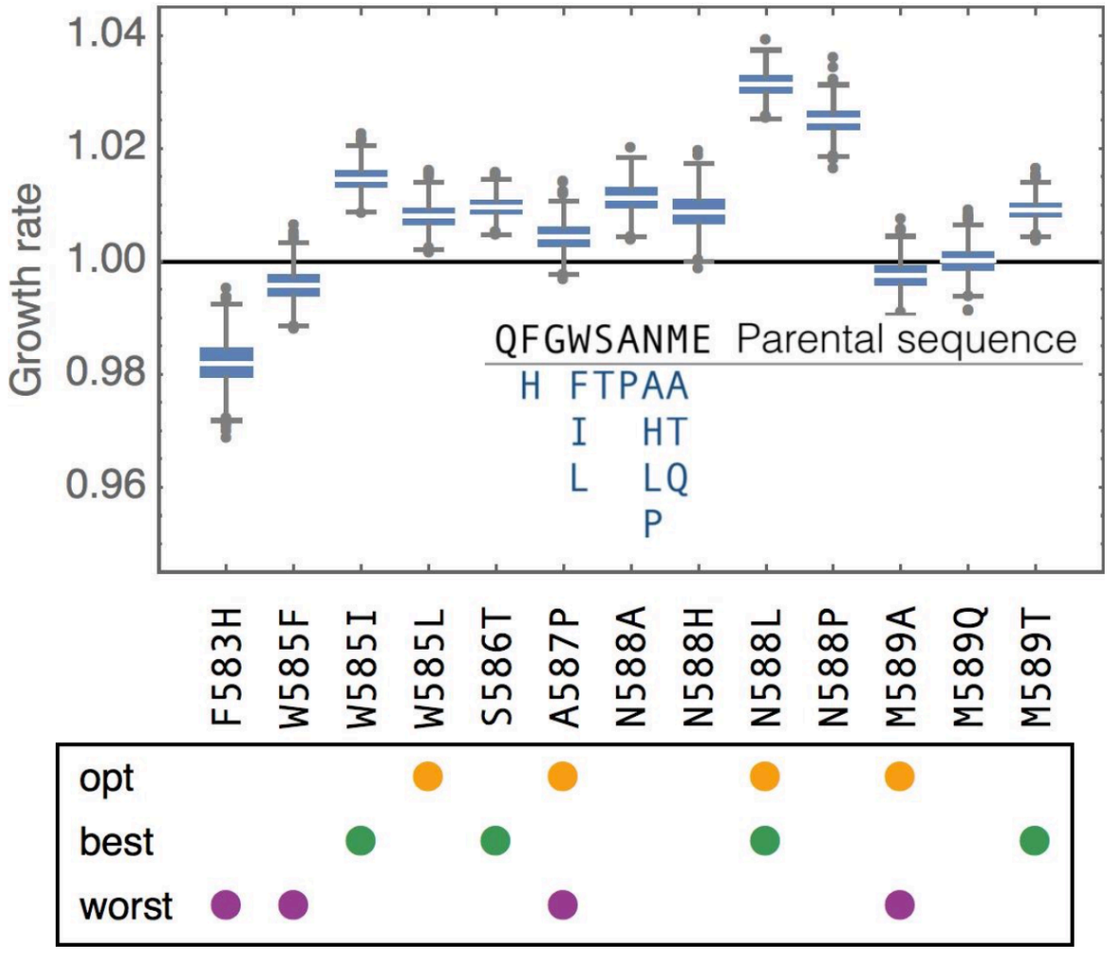
Focal landscapes:

1) leading to global optimum

2) best 4 mutations

3) "worst" 4 mutations





Growth rate

1
0 1 2 3 4 5 6

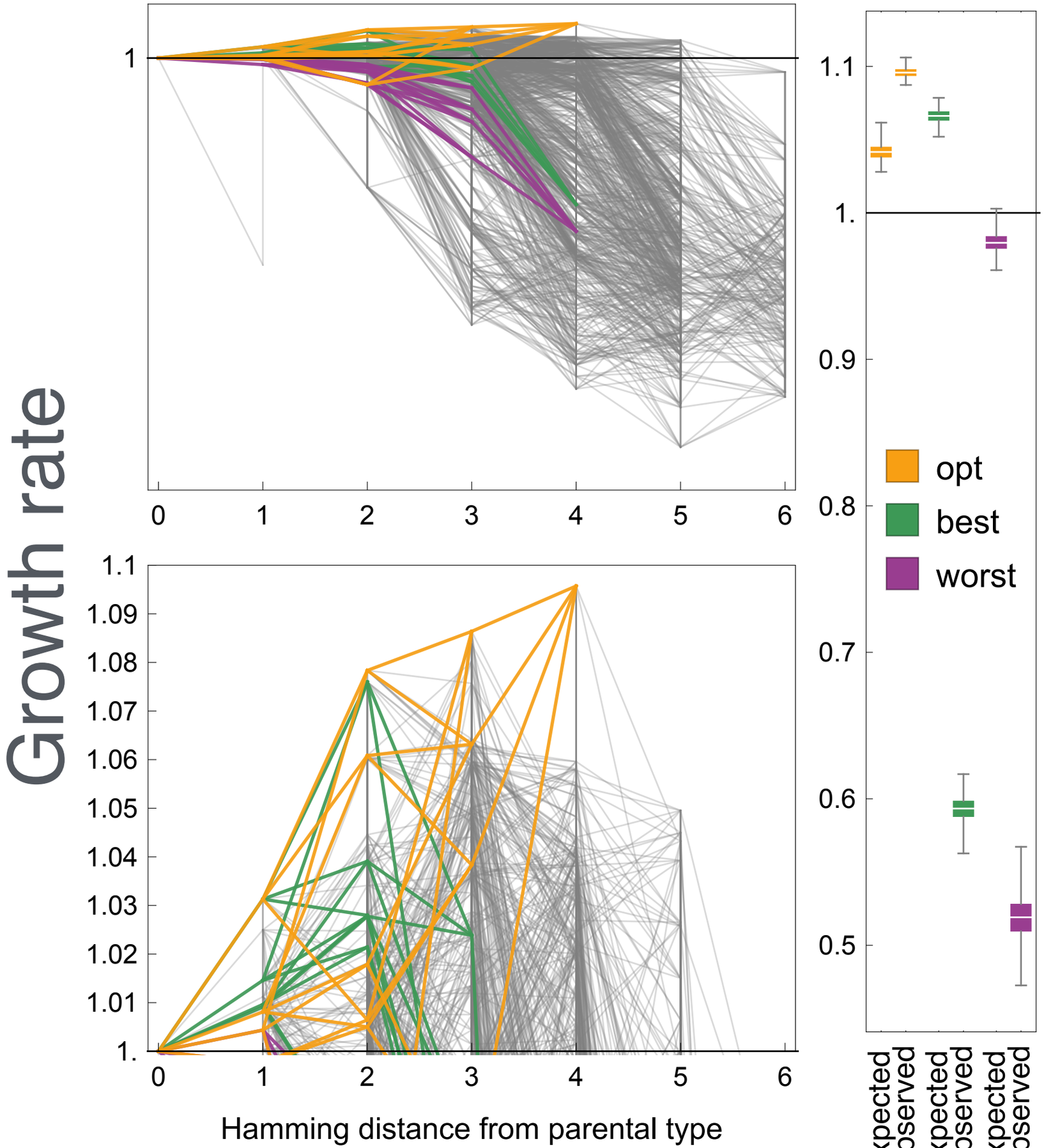
1.1
1.09
1.08
1.07
1.06
1.05
1.04
1.03
1.02
1.01
1.
0 1 2 3 4 5 6

Hamming distance from parental type

1.1
1.
0.9
0.8
0.7
0.6
0.5

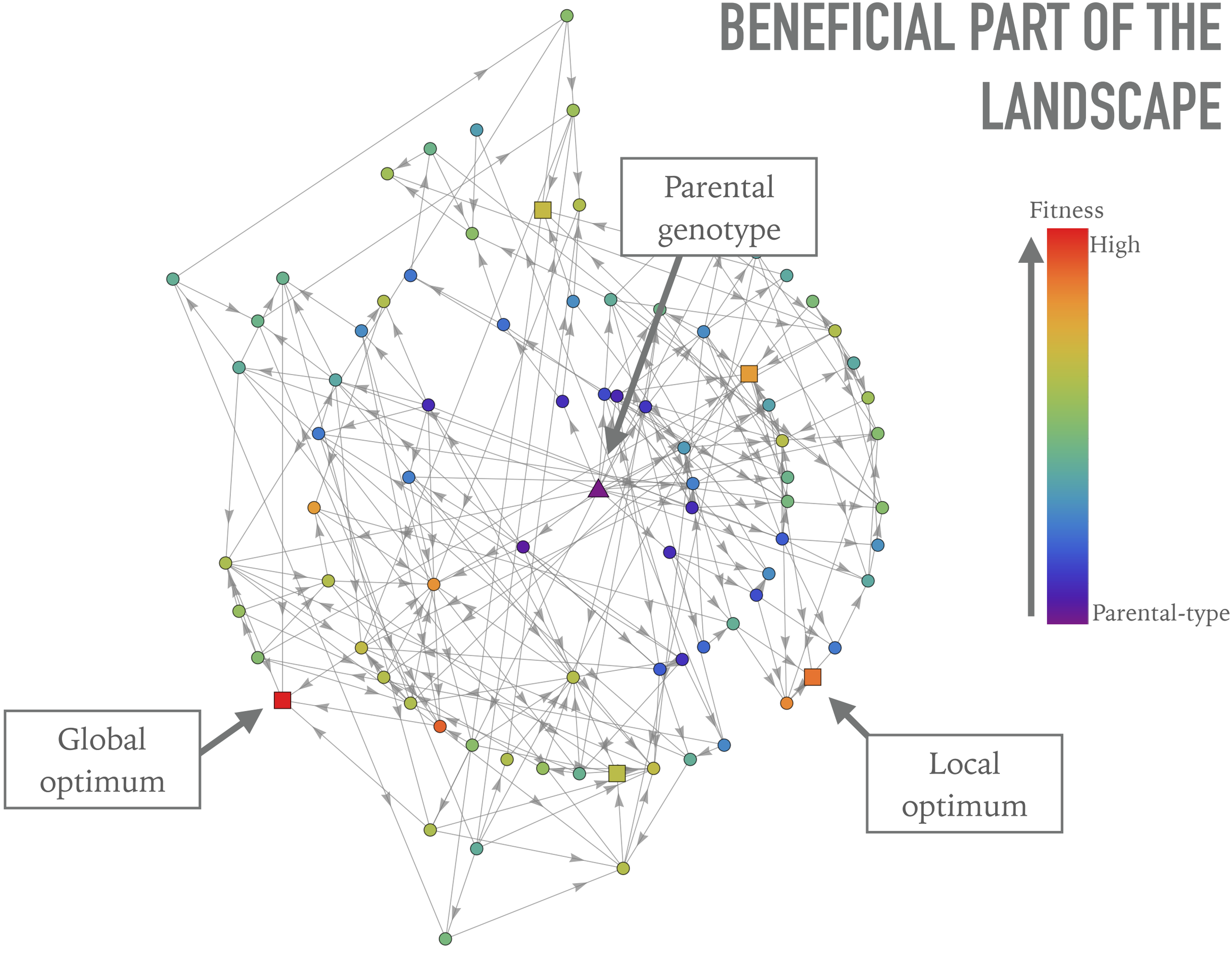
opt
best
worst

Expected
Observed
Expected
Observed
Expected
Observed



Strong positive and negative epistasis in the landscape.

BENEFICIAL PART OF THE LANDSCAPE



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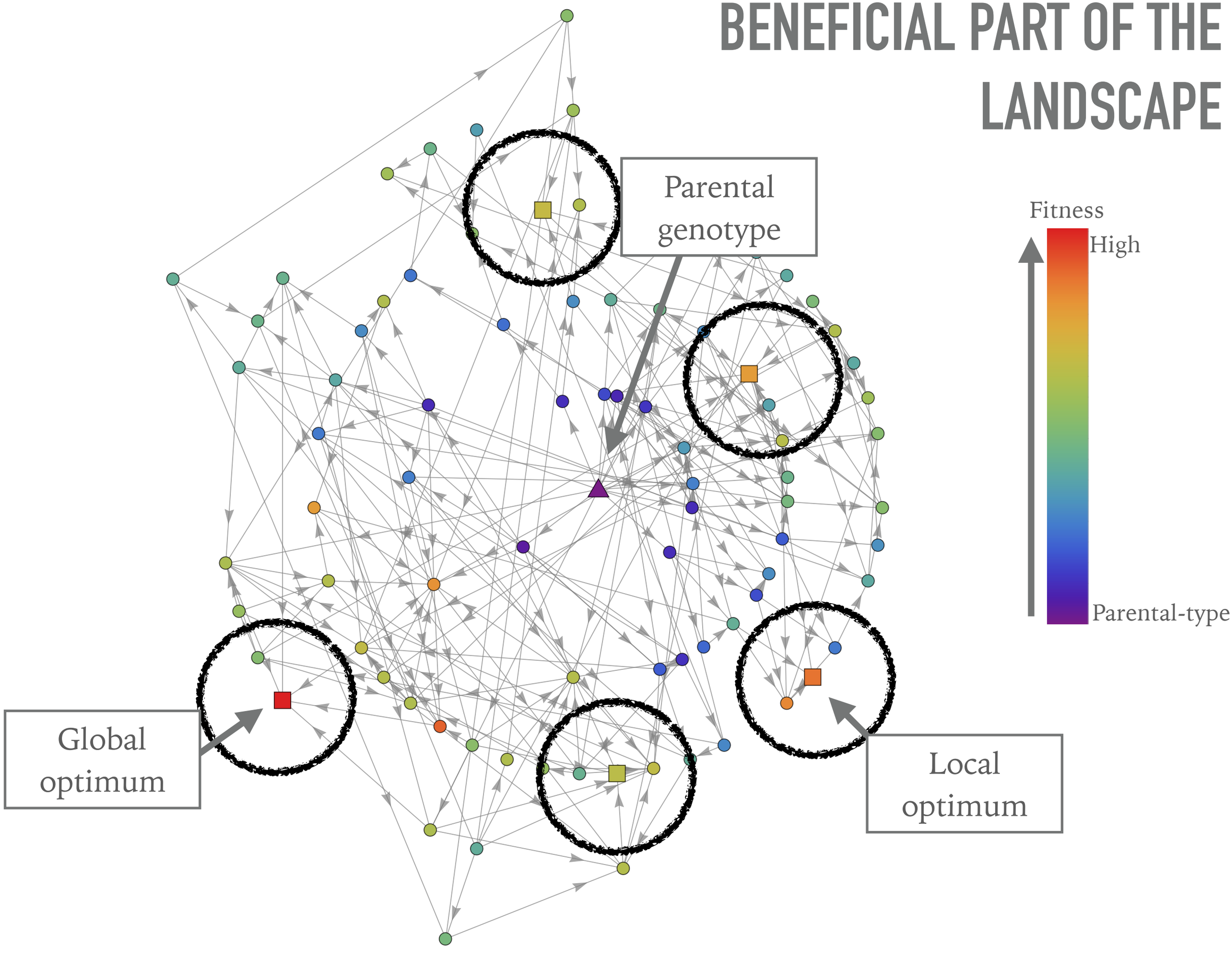
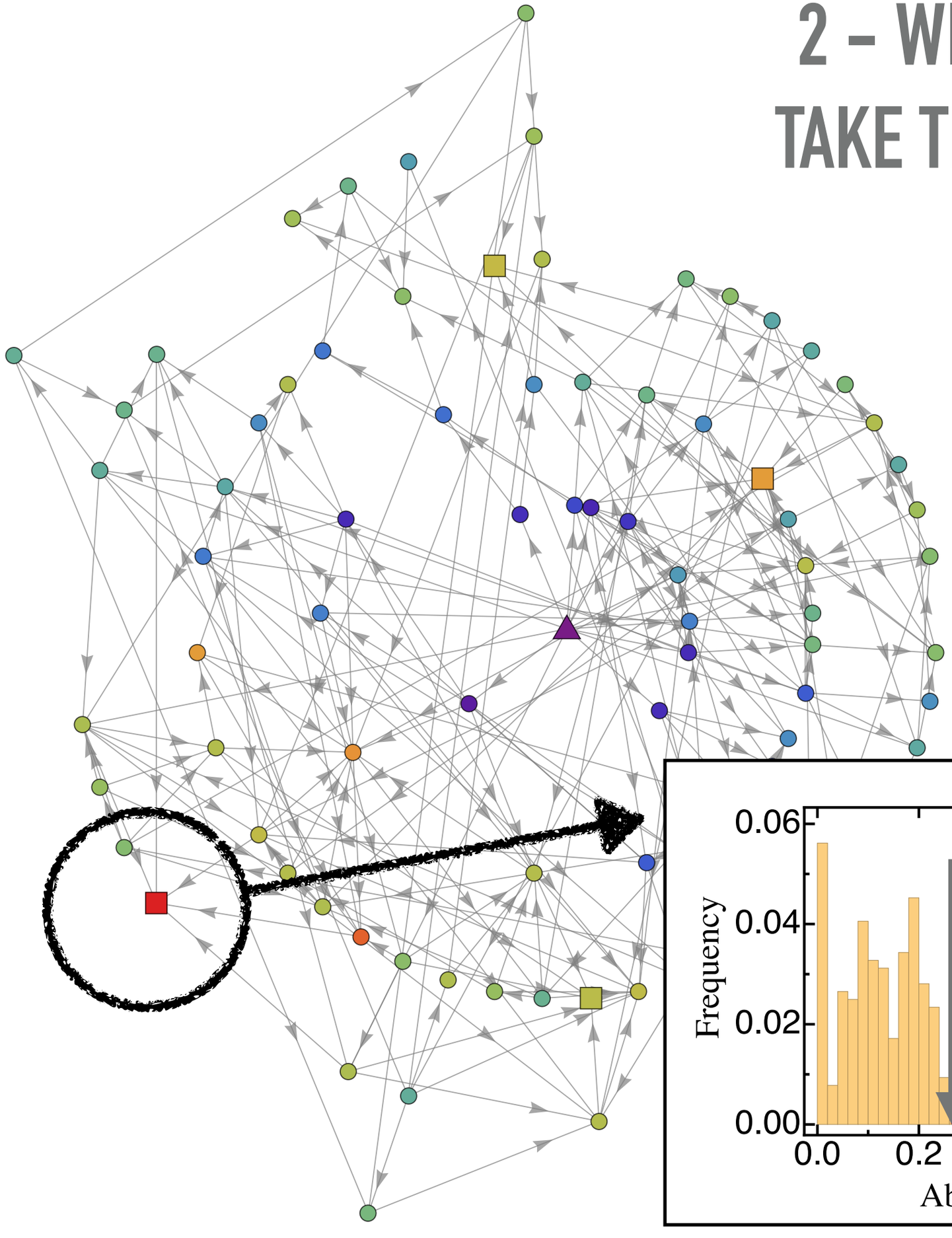
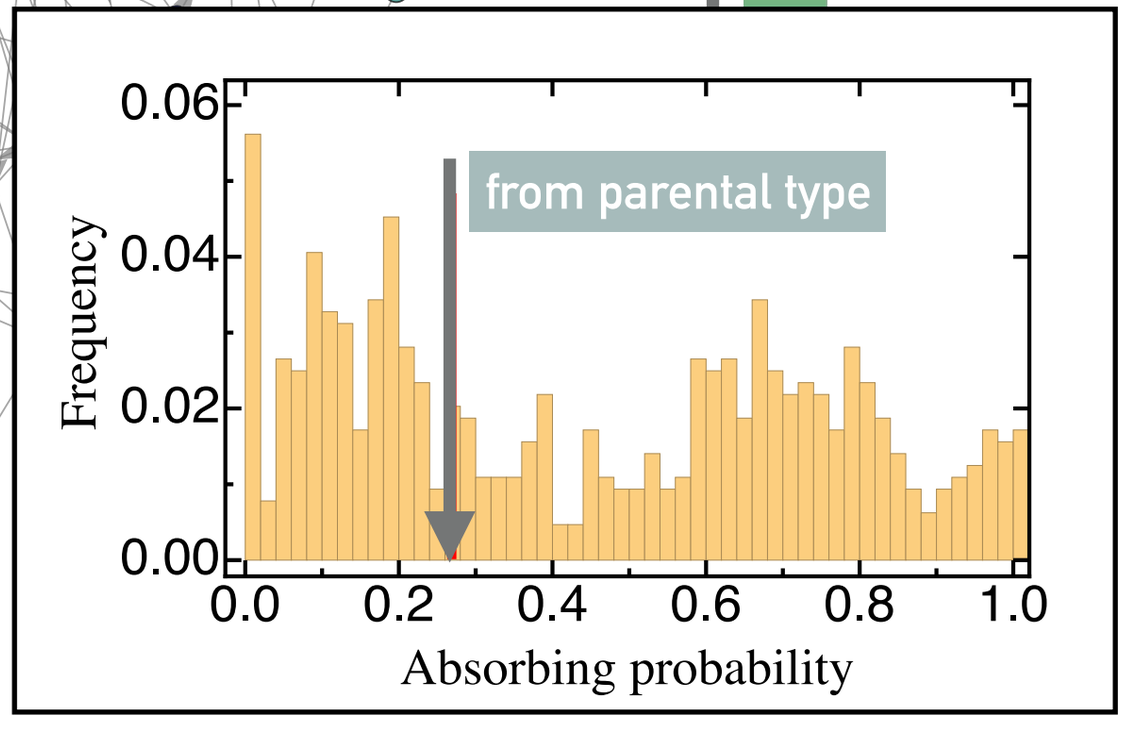


2 – WILL ADAPTATION TAKE THE POPULATION TO THE GLOBAL OPTIMUM?





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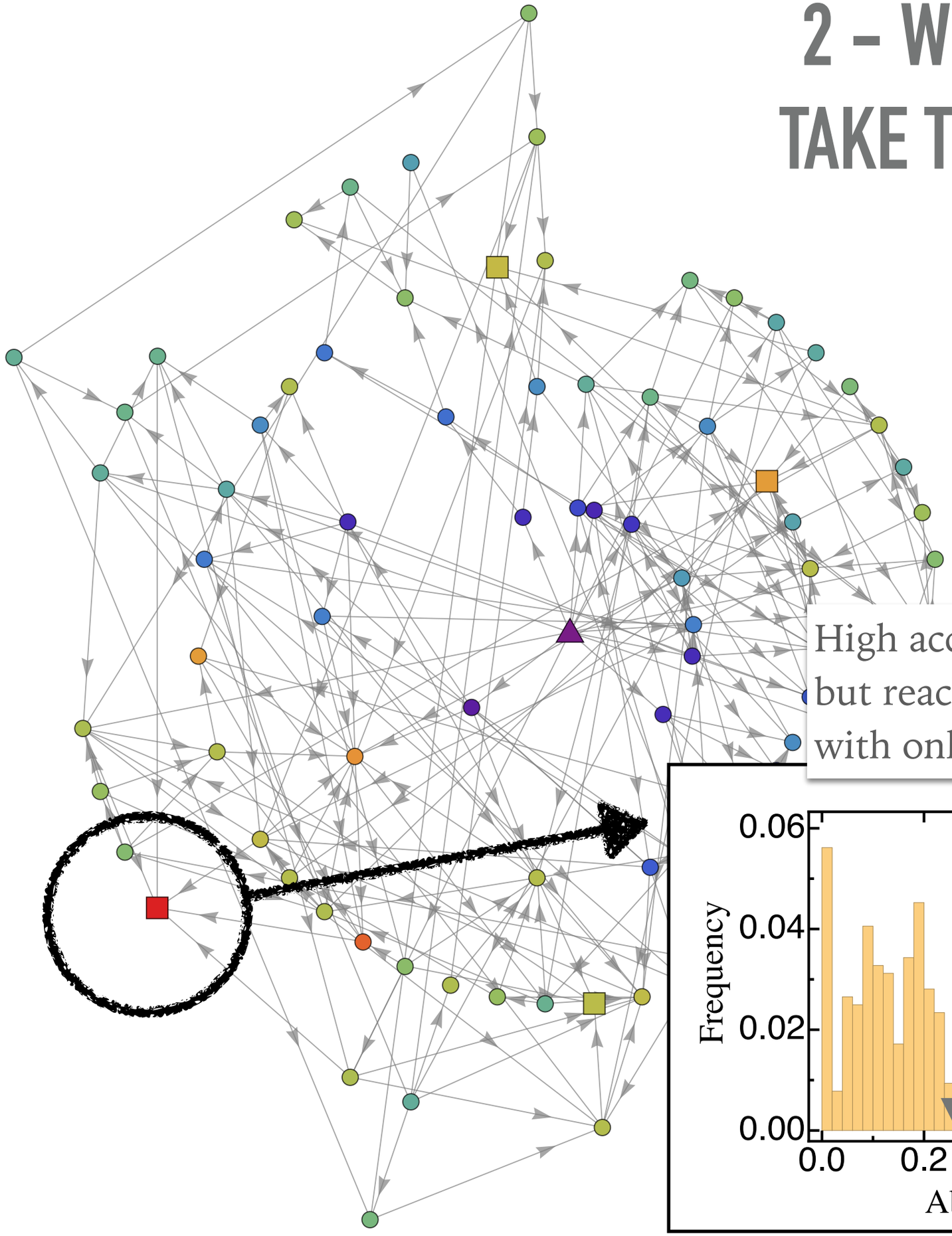
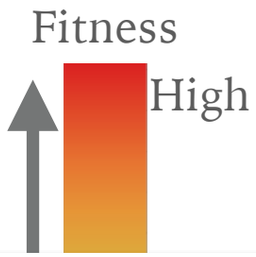
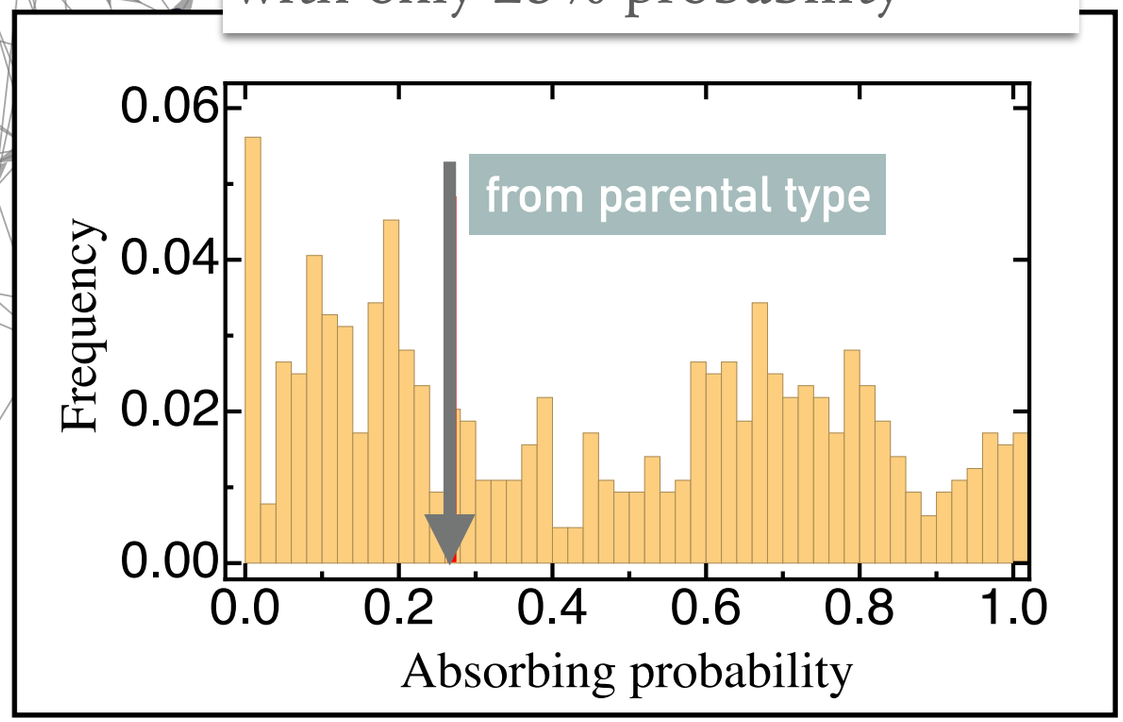




High accessibility on average, but reached from parental type with only 25% probability



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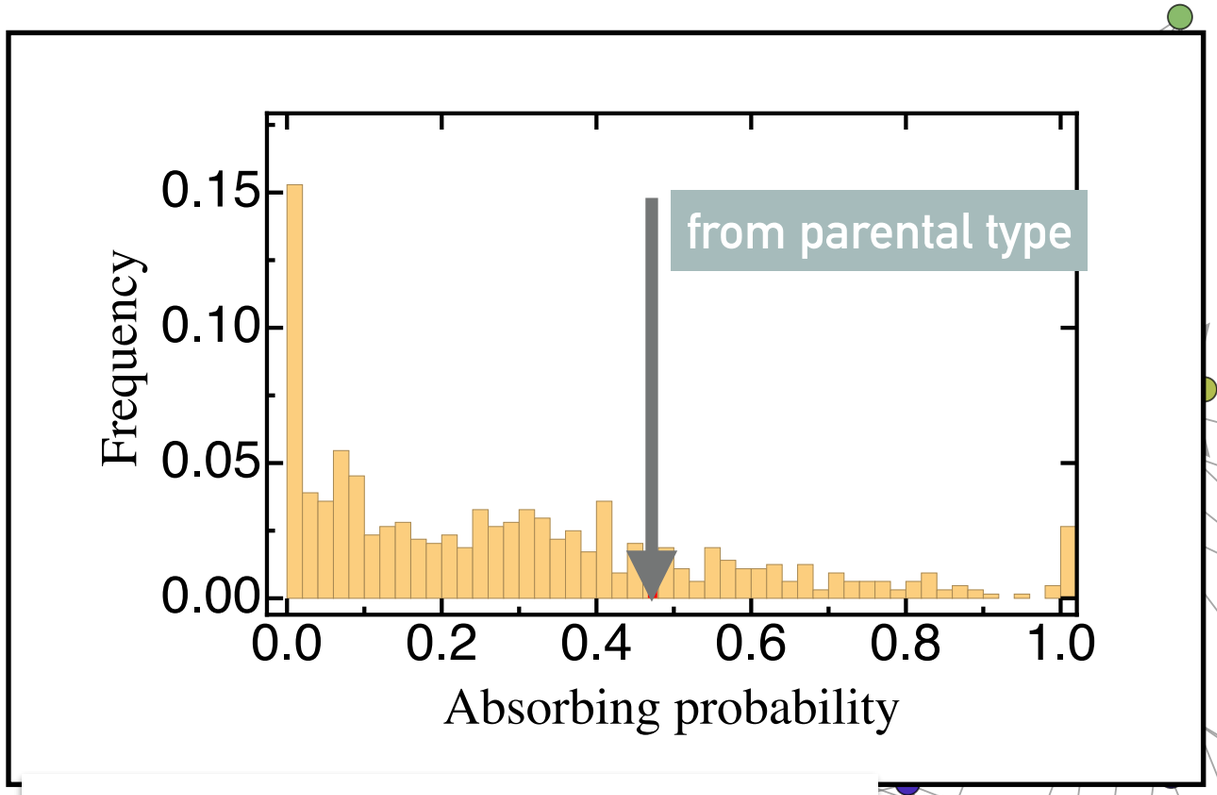
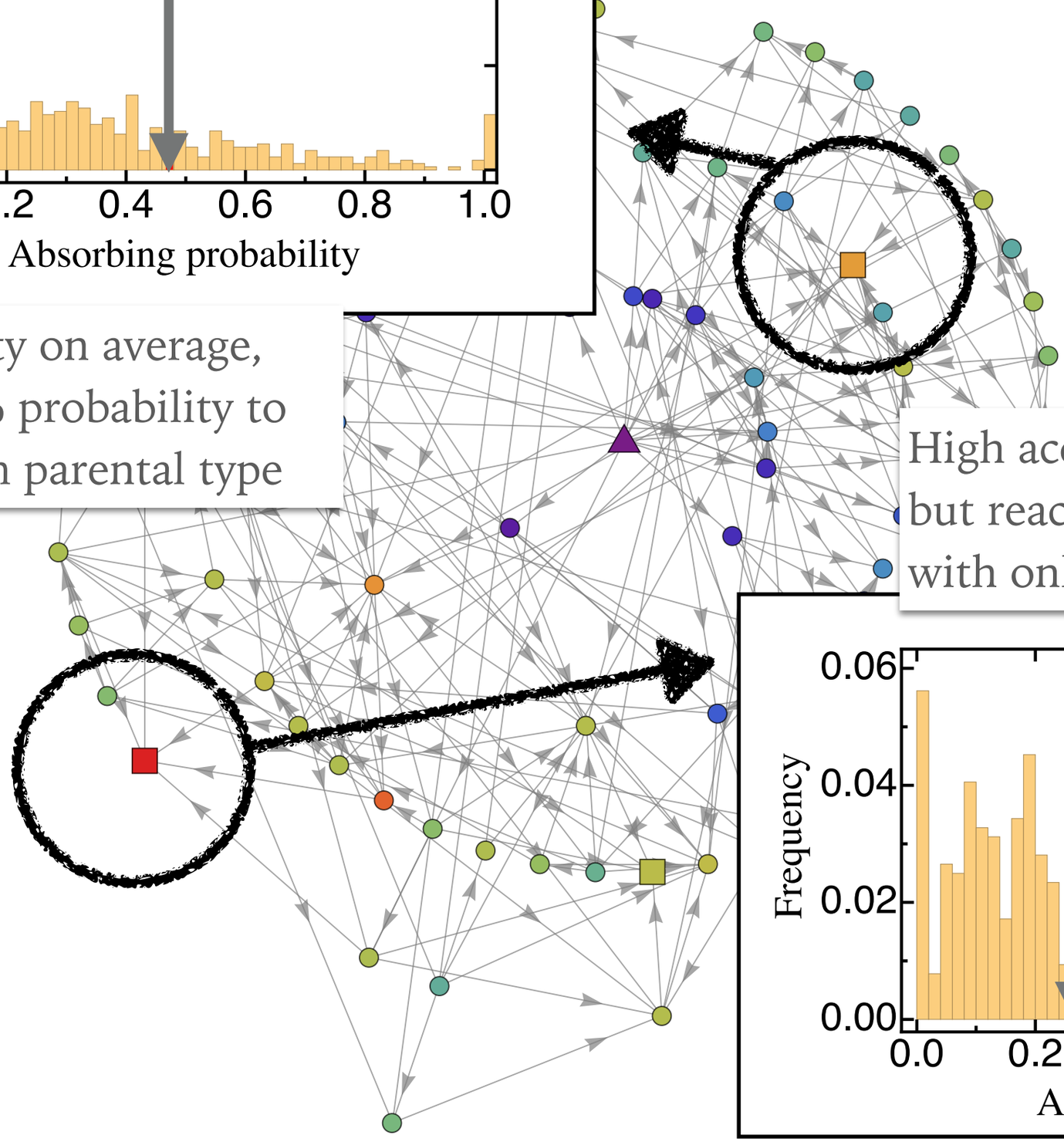
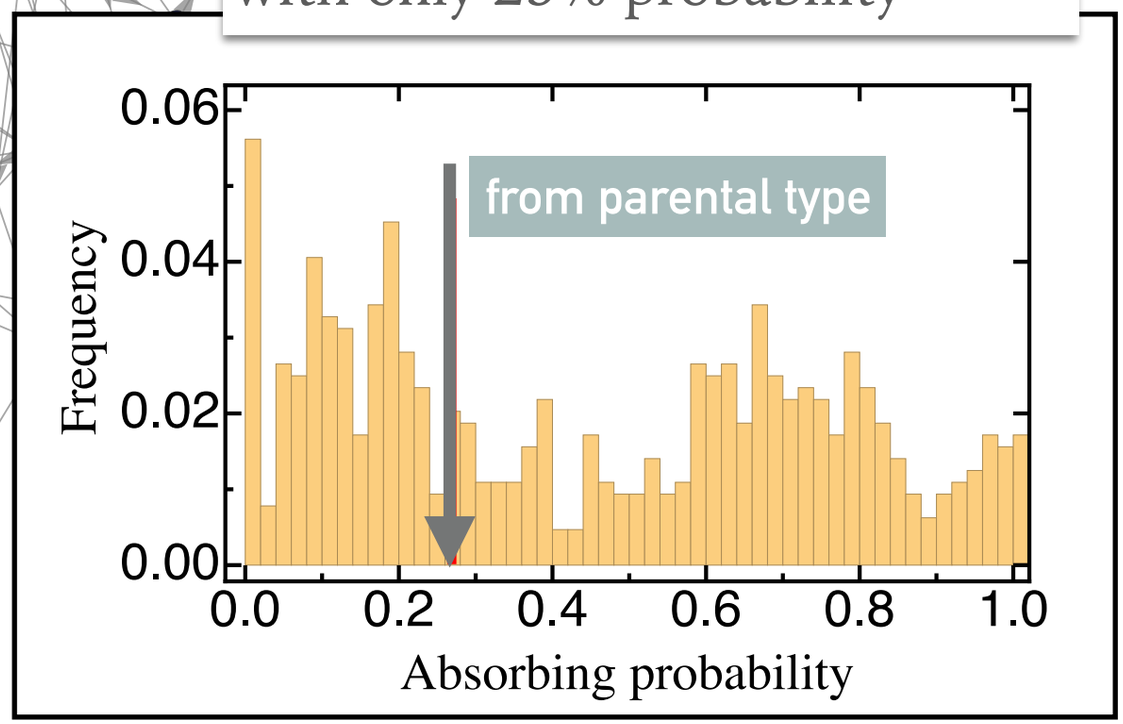


Low accessibility on average, but almost 50% probability to be reached from parental type



Fitness
High

High accessibility on average, but reached from parental type with only 25% probability



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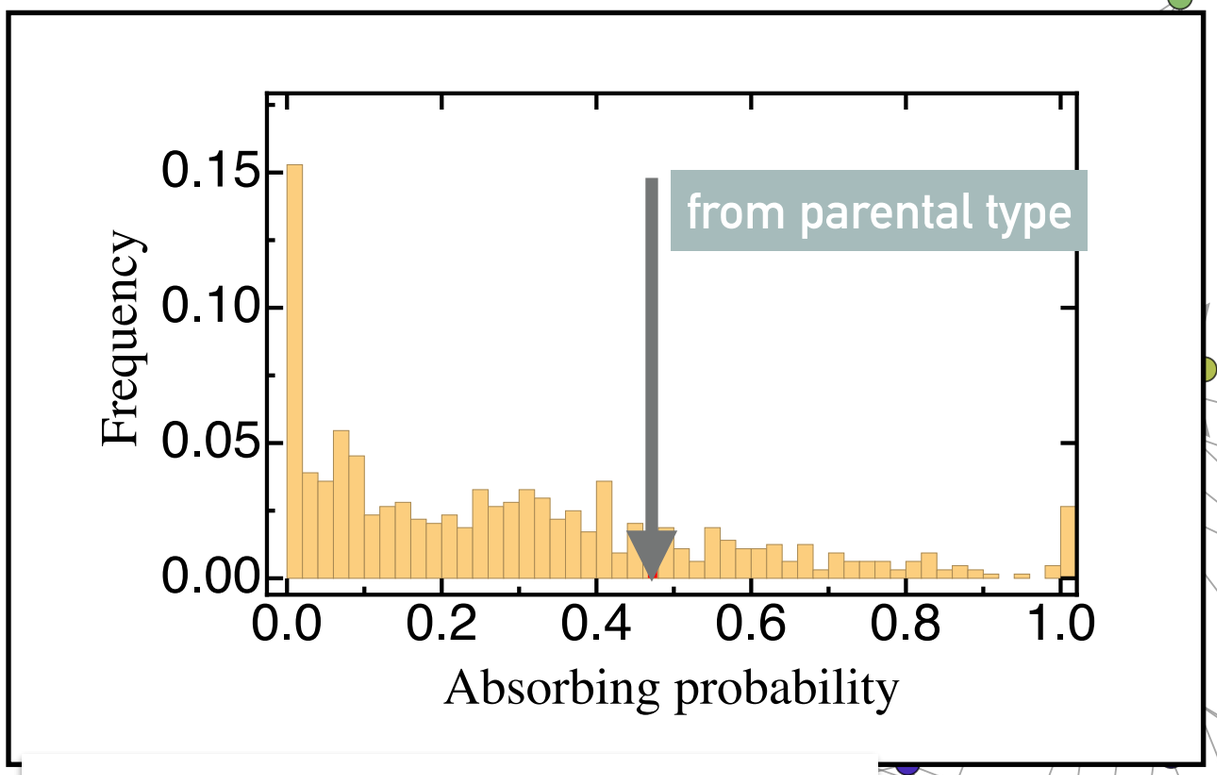

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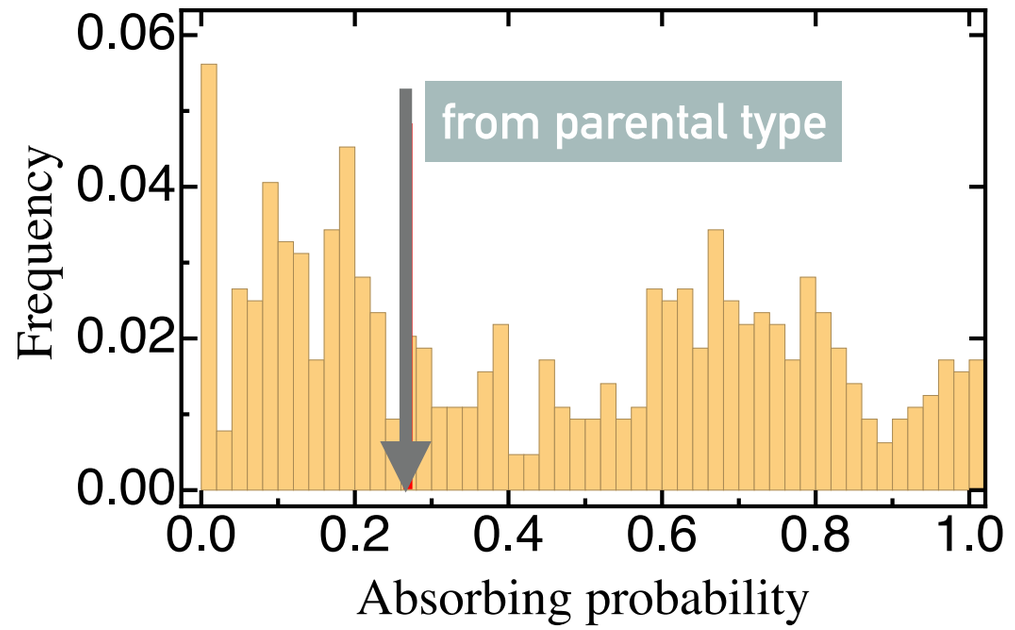
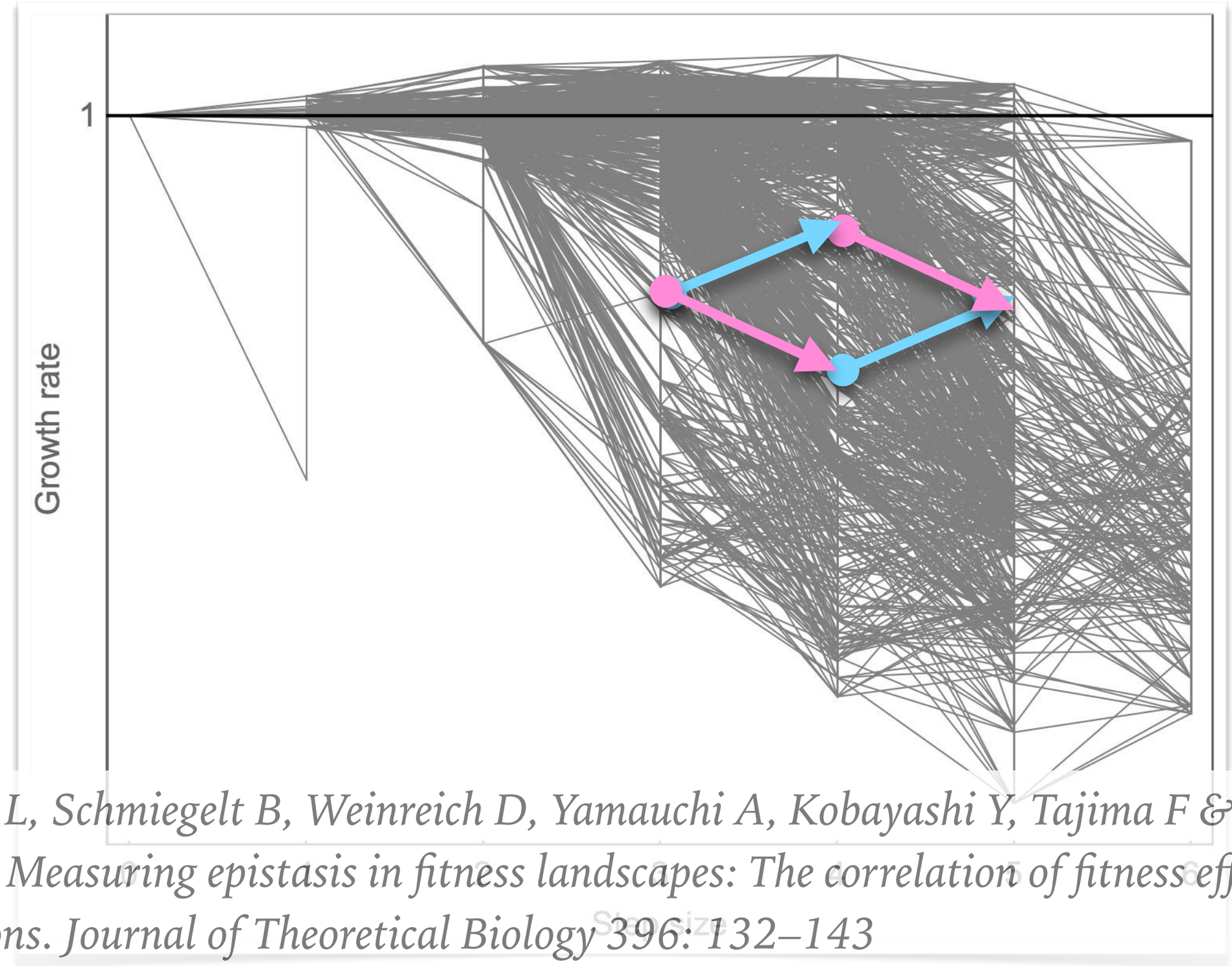


Evolution from parental type may stall at local optimum

LANDSCAPE STATISTICS INDEPENDENT OF REFERENCE



Ferretti L, Schmiegelt B, Weinreich D, Yamauchi A, Kobayashi Y, Tajima F & Achaz G (2016) Measuring epistasis in fitness landscapes: The correlation of fitness effects of mutations. Journal of Theoretical Biology 396: 132–143

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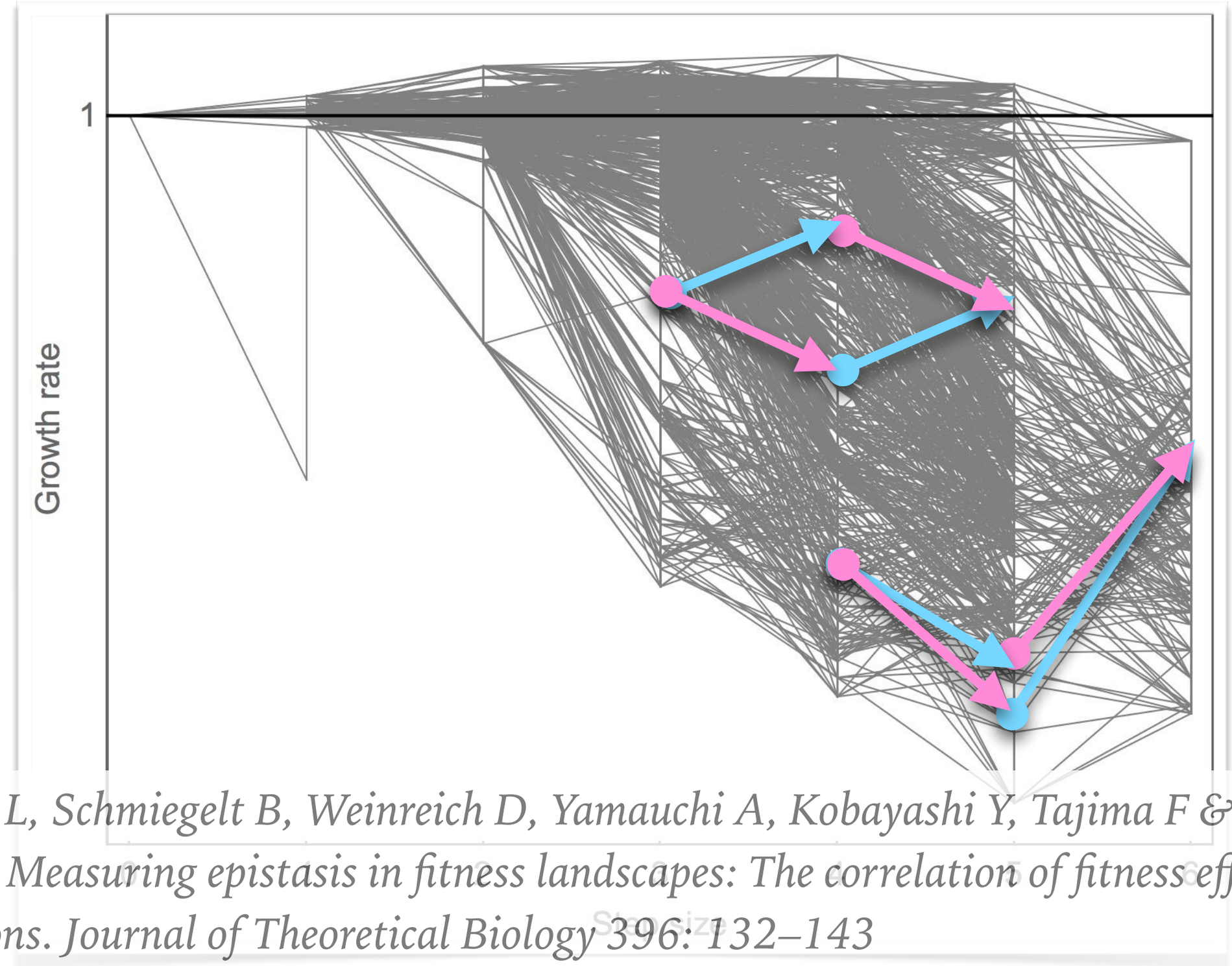

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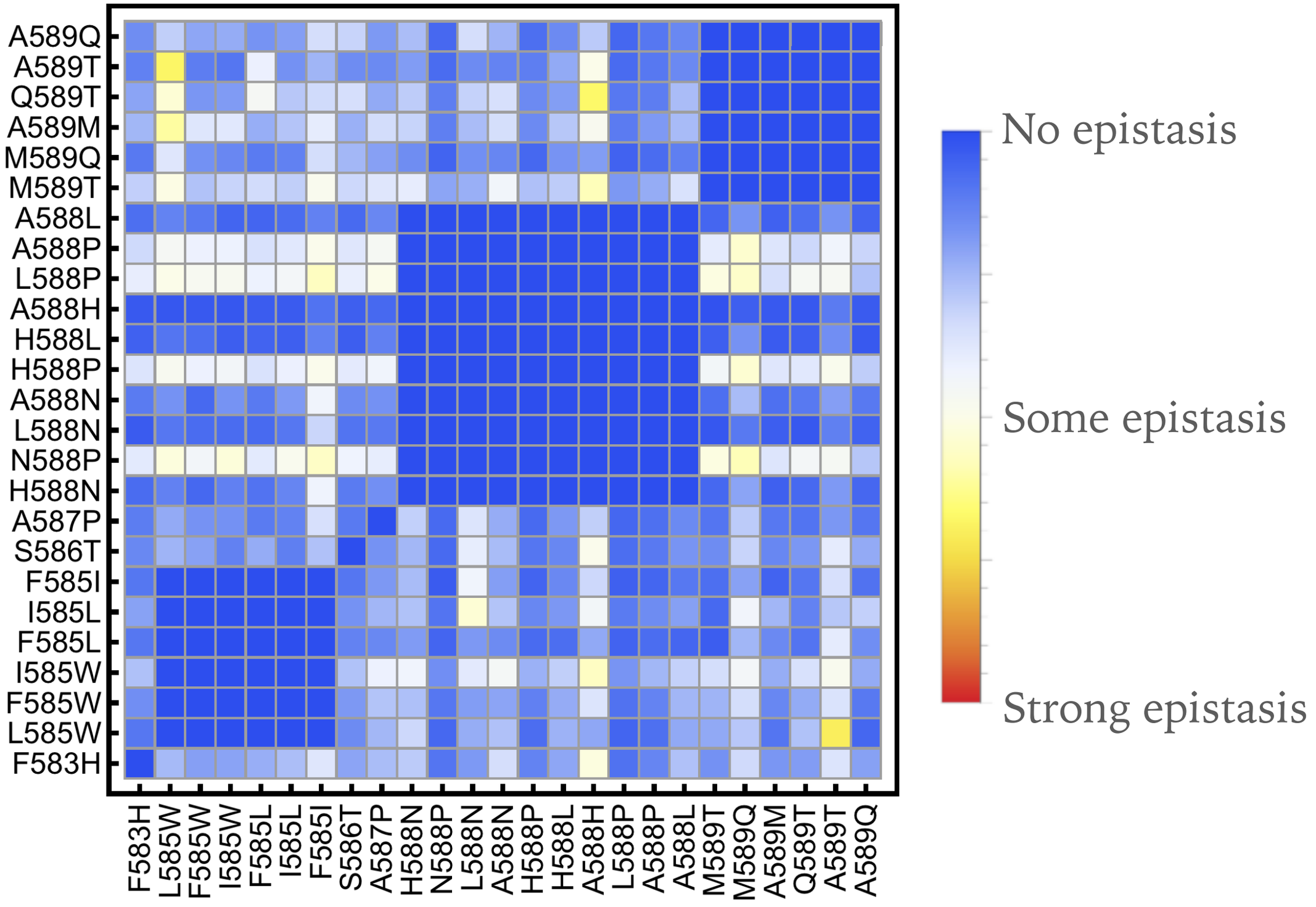
HOW CAN WE MEASURE FITNESS LANDSCAPES AND WHAT CAN WE LEARN FROM THIS EXERCISE?



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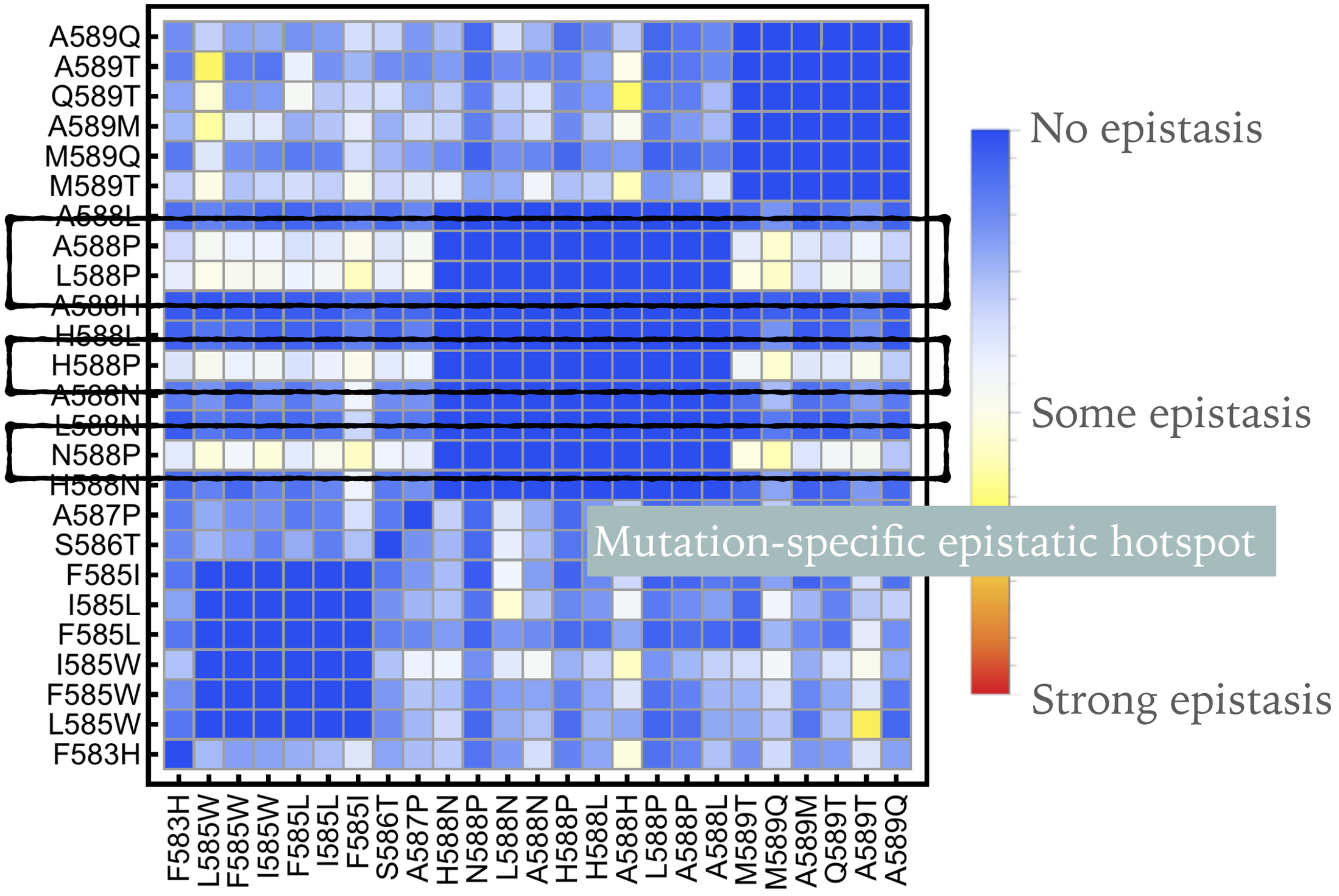
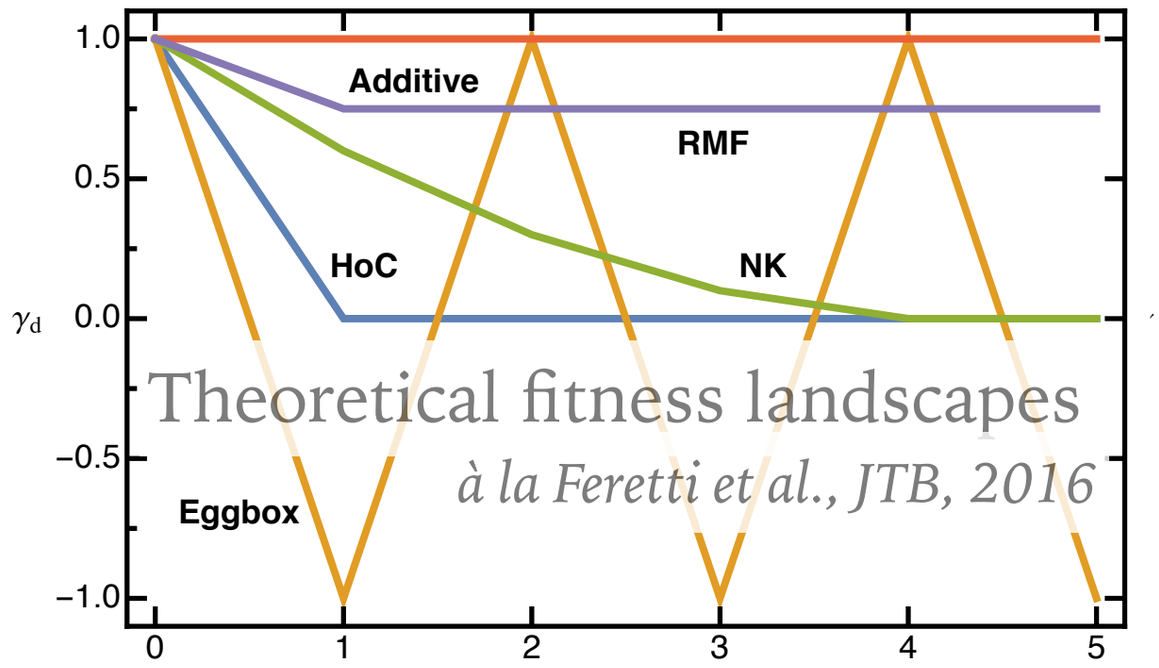


3 – CAN WE INFER AN UNKNOWN PART OF THE LANDSCAPE?



Epistasis measure $gamma_d$ with increasing Hamming distance d

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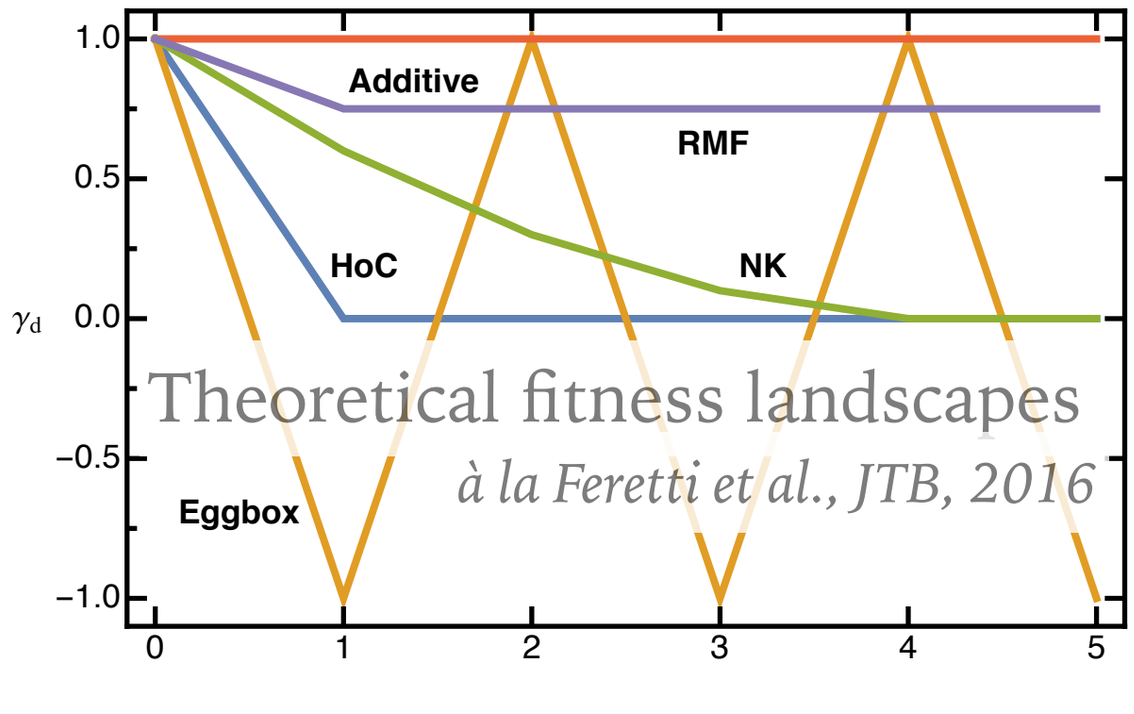

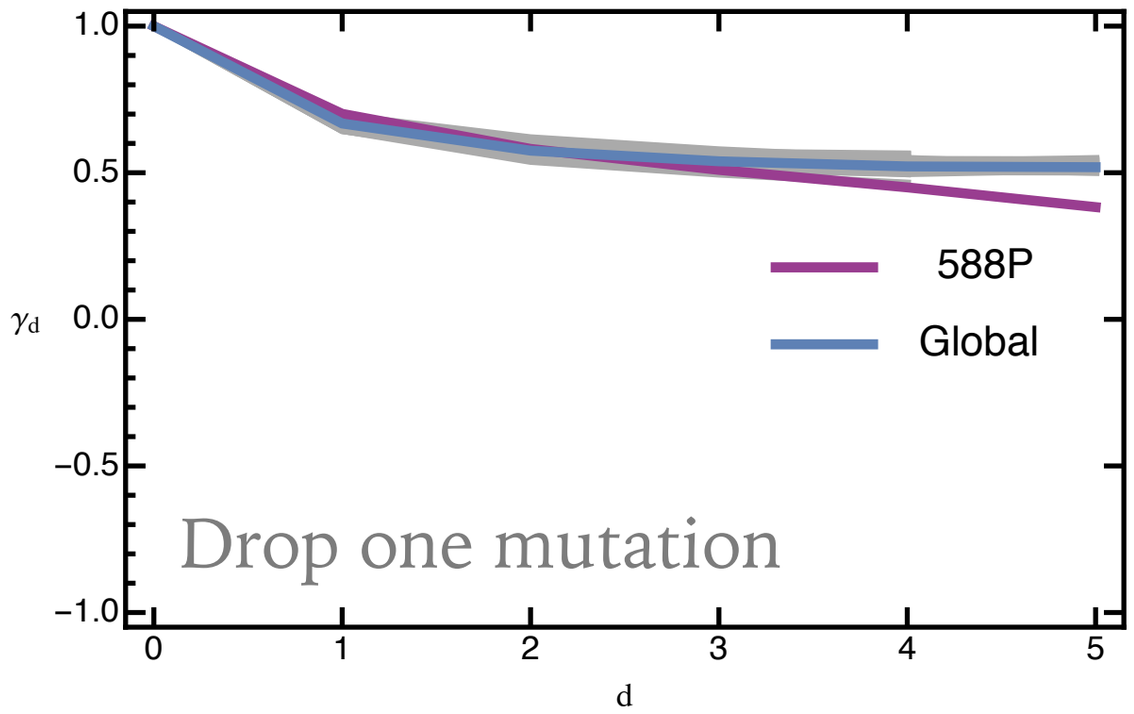

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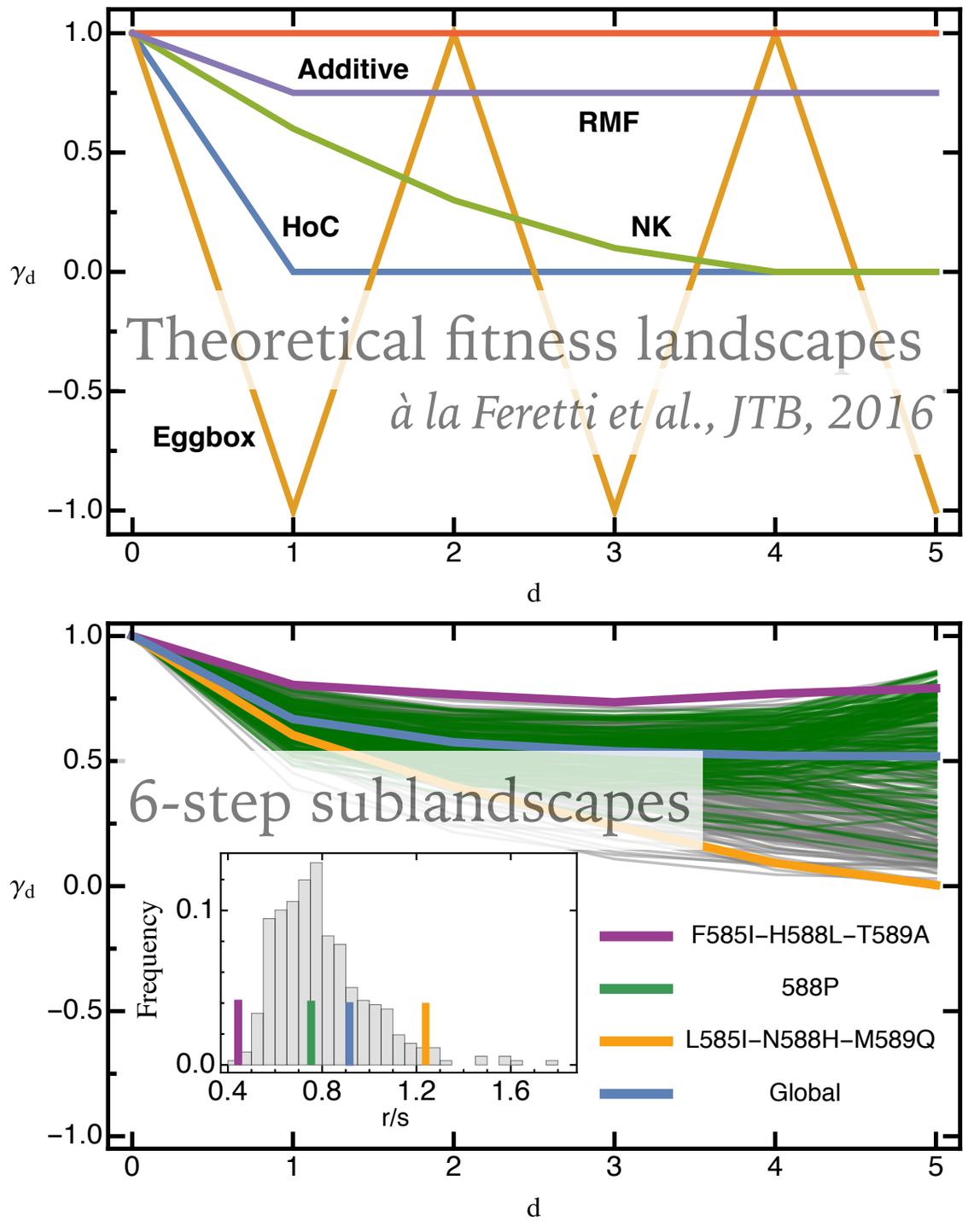

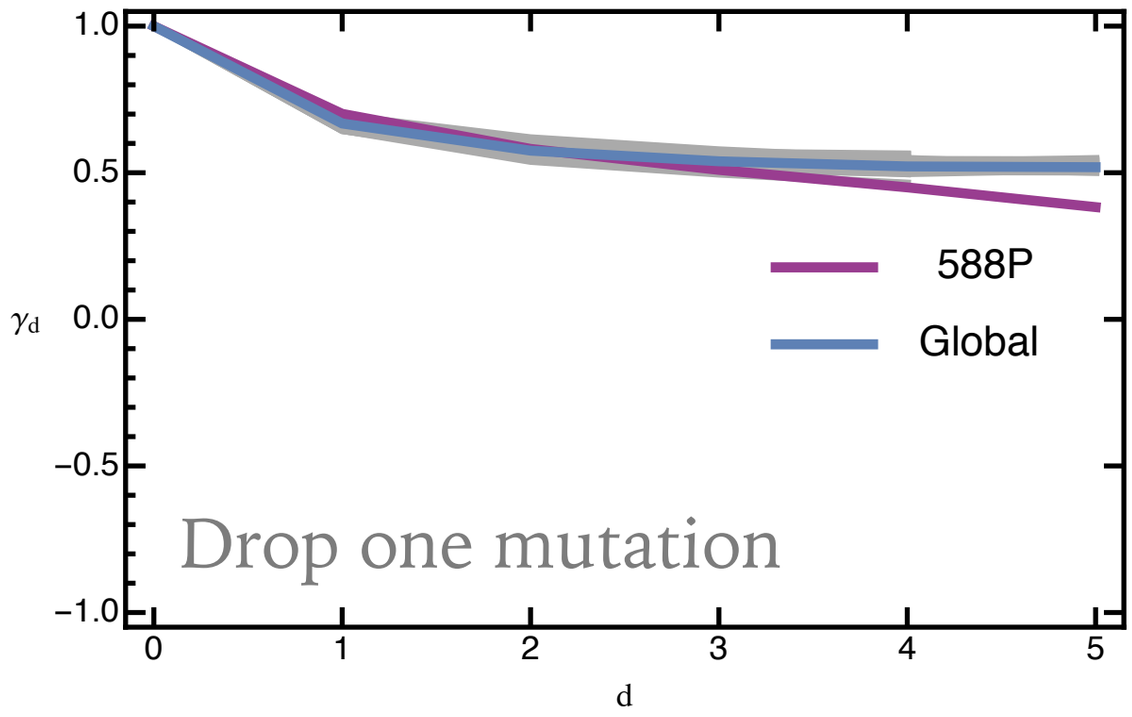

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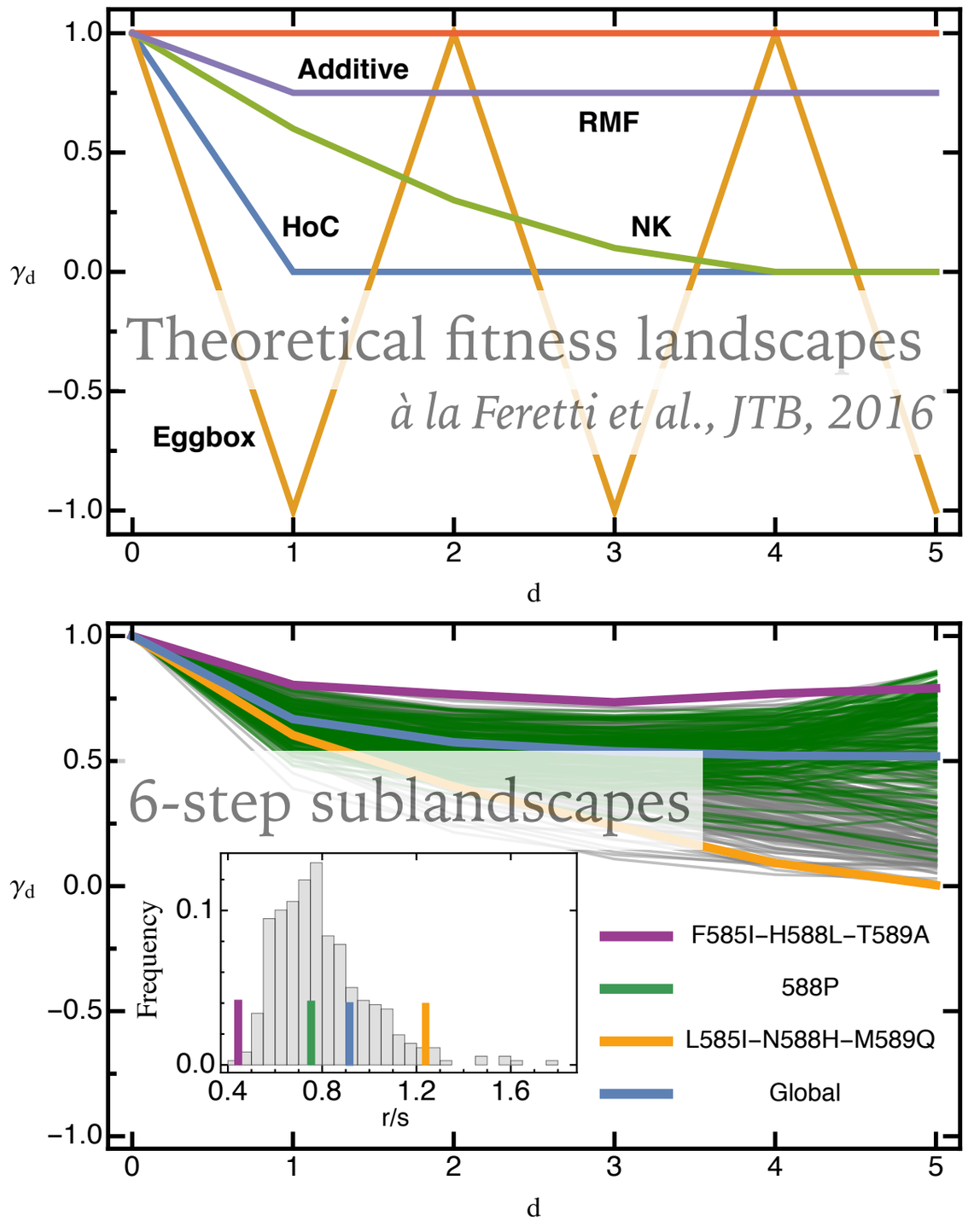
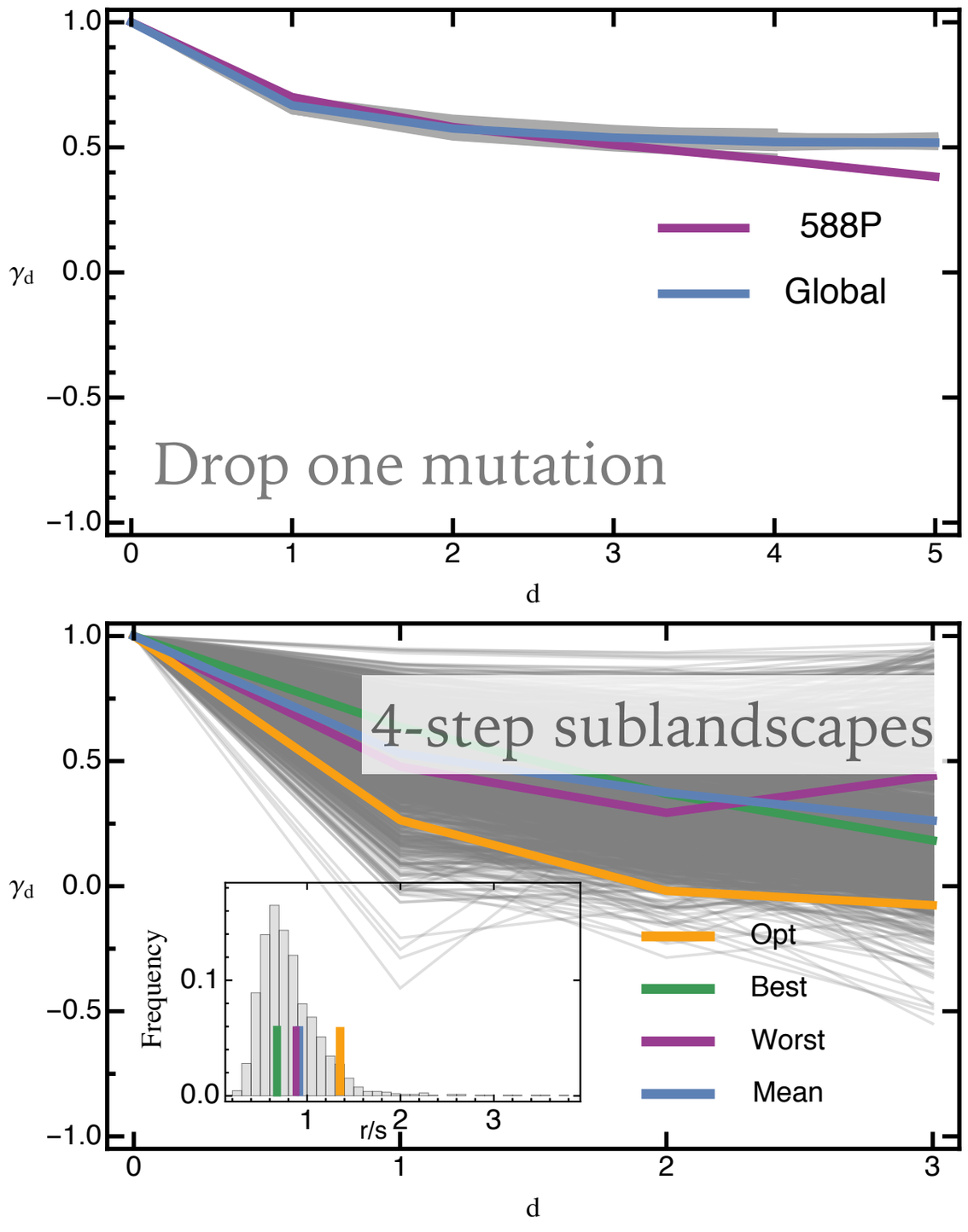




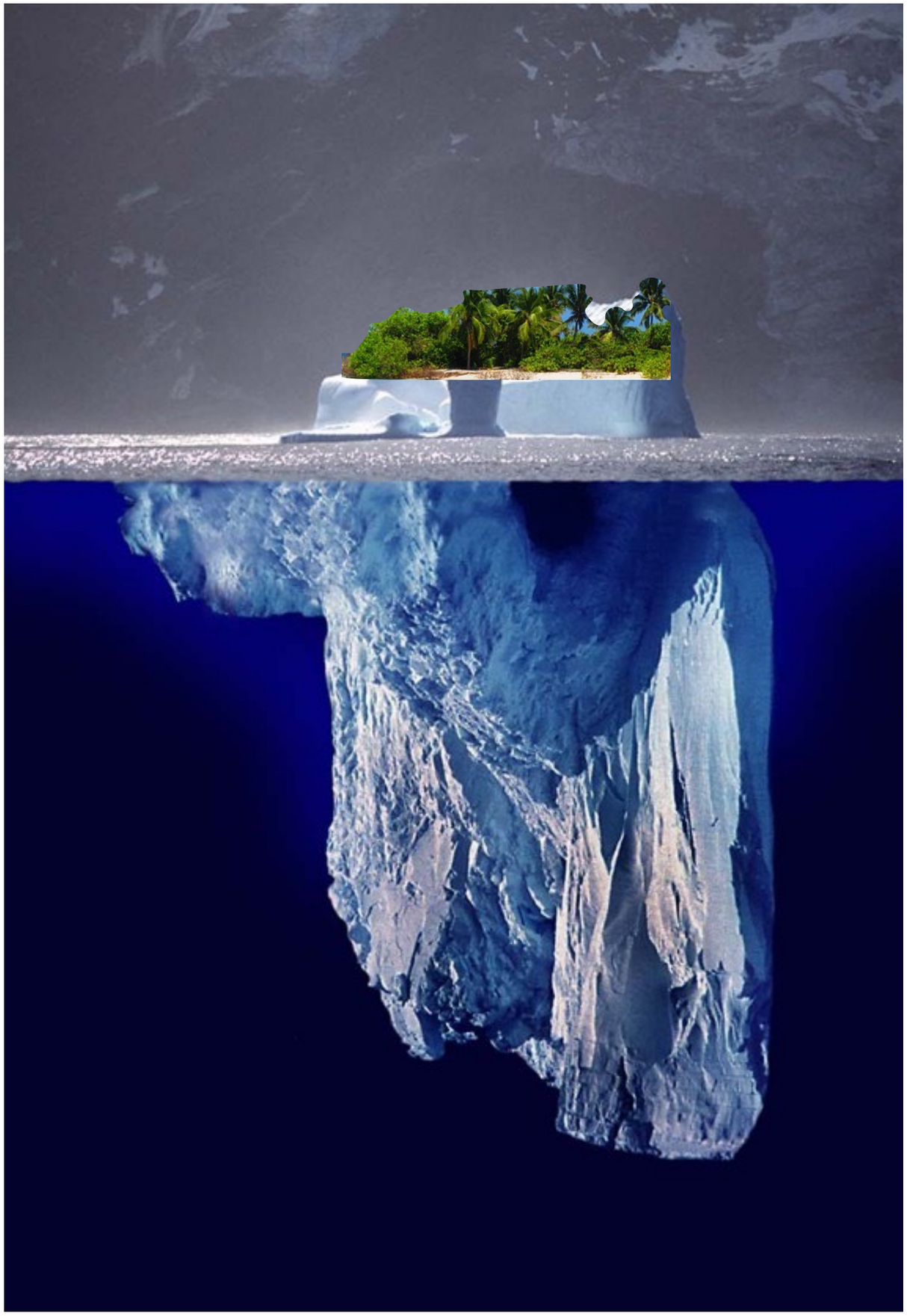
Epistasis measure gamma_d with increasing Hamming distance d

SUMMARY/CONCLUSION

On average, our intragenic fitness landscape looks rugged and negative epistasis is common.

The global peak is accessible and reached via a highly synergistic combination of four mutations.

However, when evolving from parental type, adaptation may stall at a local peak.



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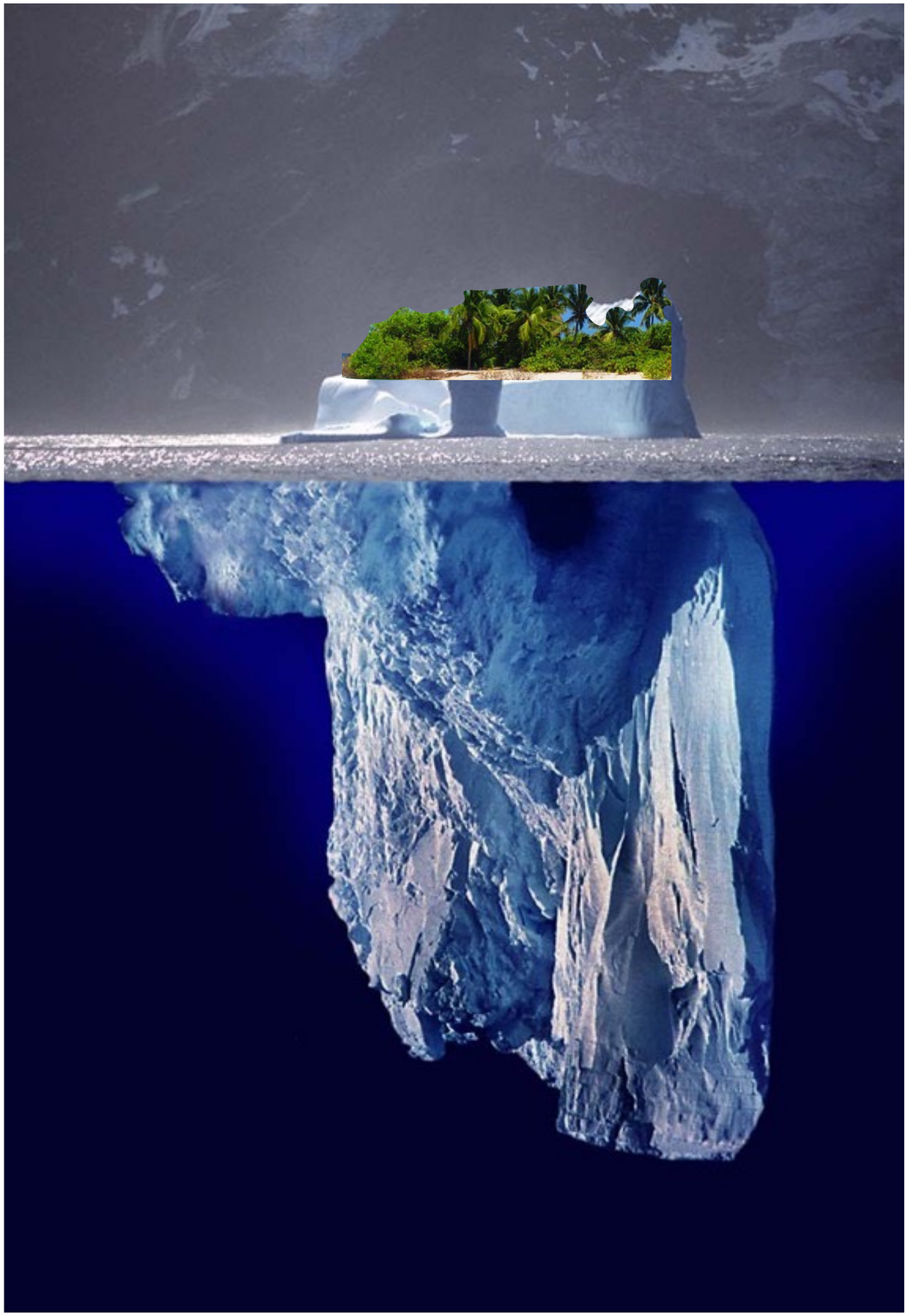
So far, limited predictive potential, but lots of ideas for the future…



FISHER OR WRIGHT OR…?

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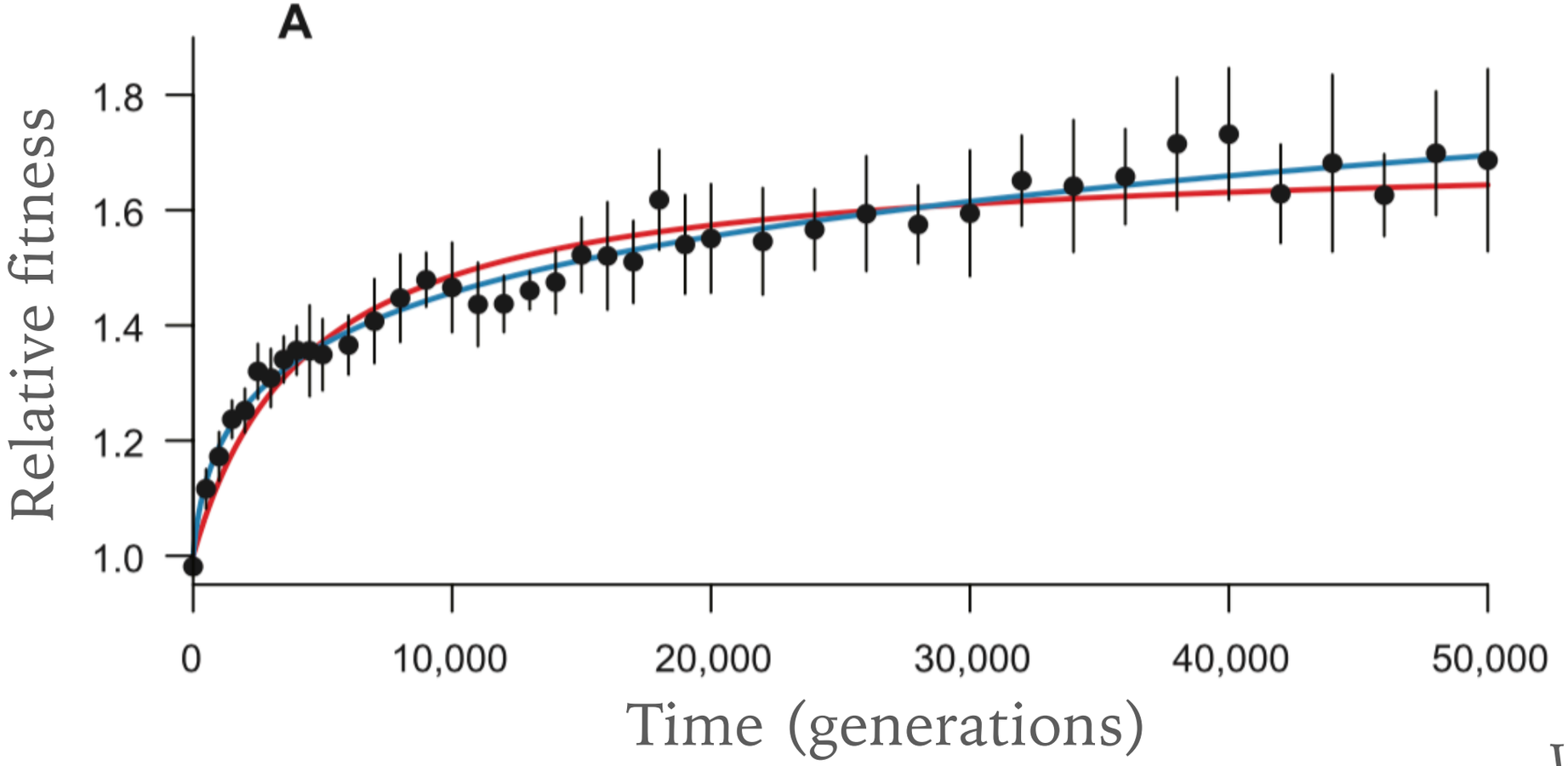
- But adaptation is also miraculous in constant environments with high population sizes - how is that possible?



Wiser et al. 2013

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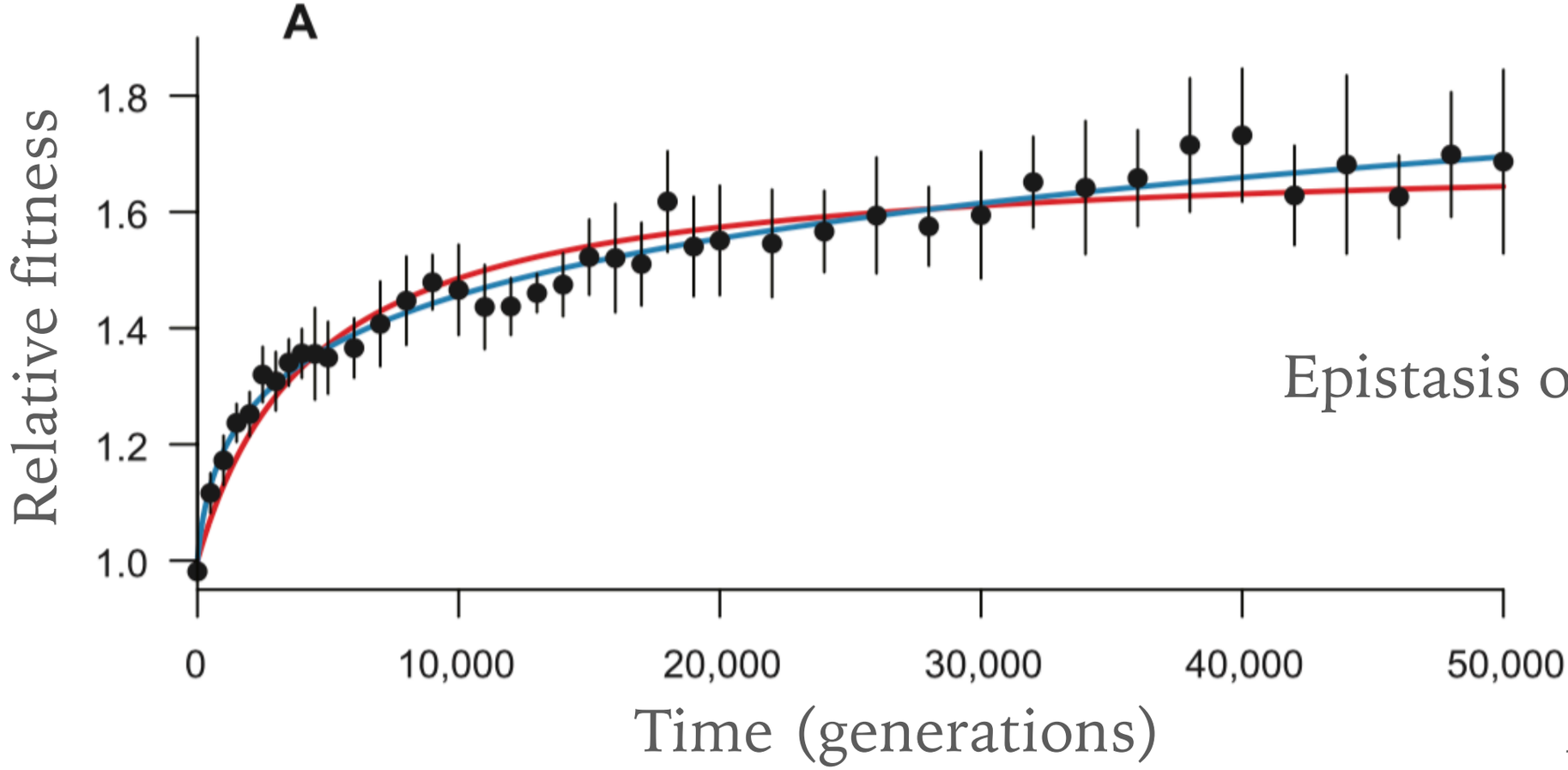

Epistasis or ecology?

Wiser et al. 2013

What would YOU like to know about fitness landscapes?

HTTPS://MICROBIAL.ECO-EVO.SCIENCE/

ACKNOWLEDGEMENTS

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