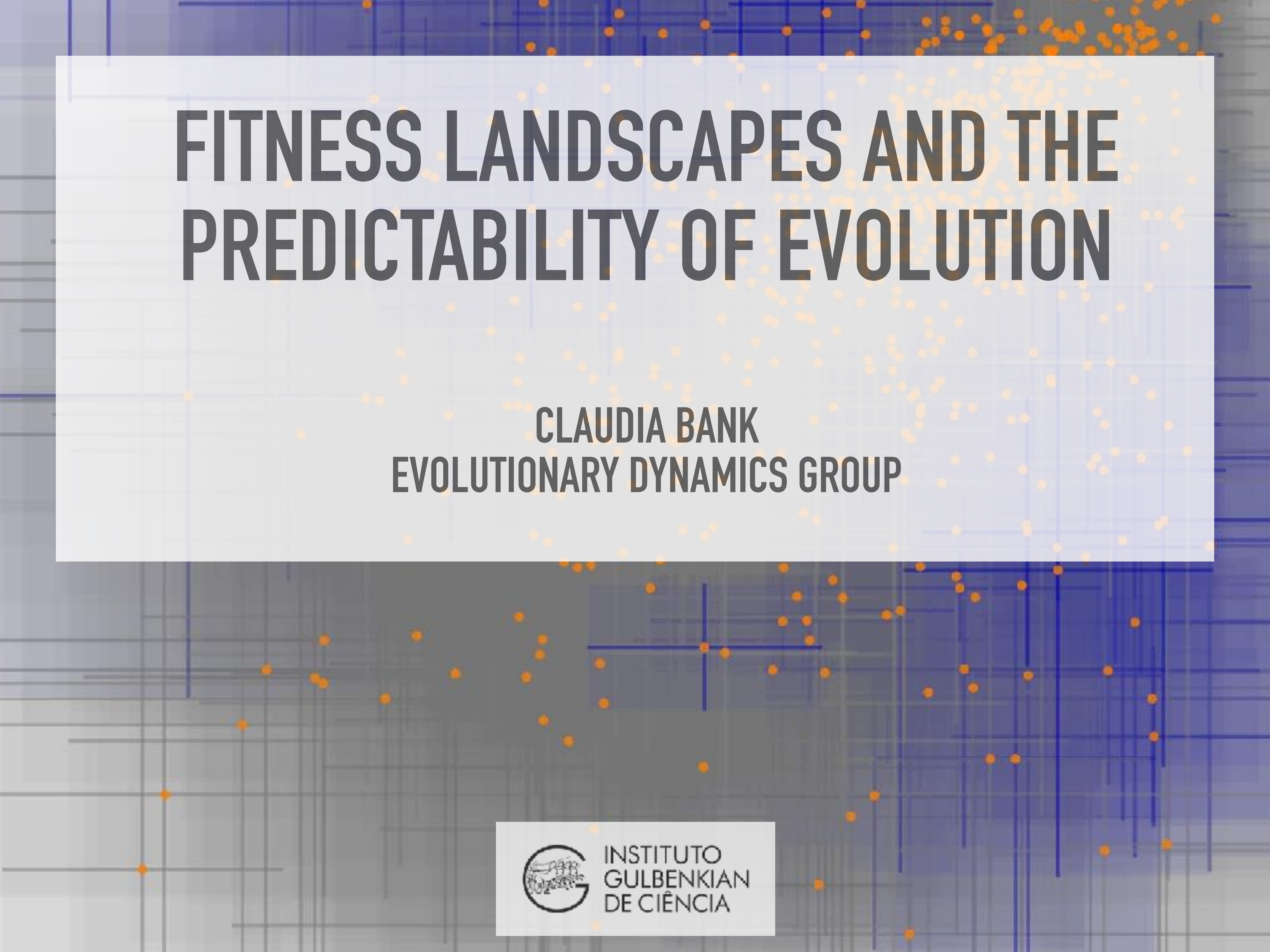
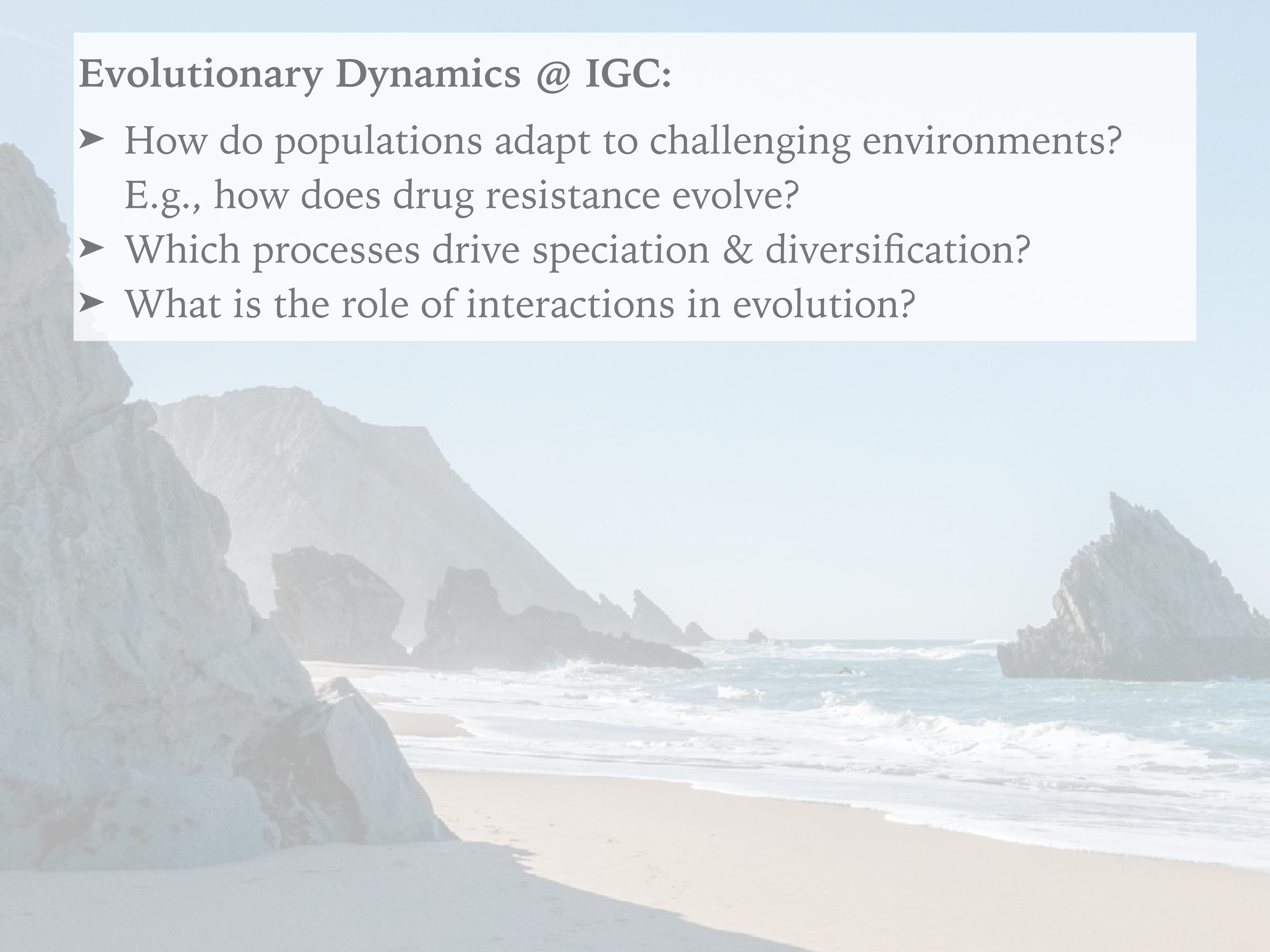


FITNESS LANDSCAPES AND THE PREDICTABILITY OF EVOLUTION

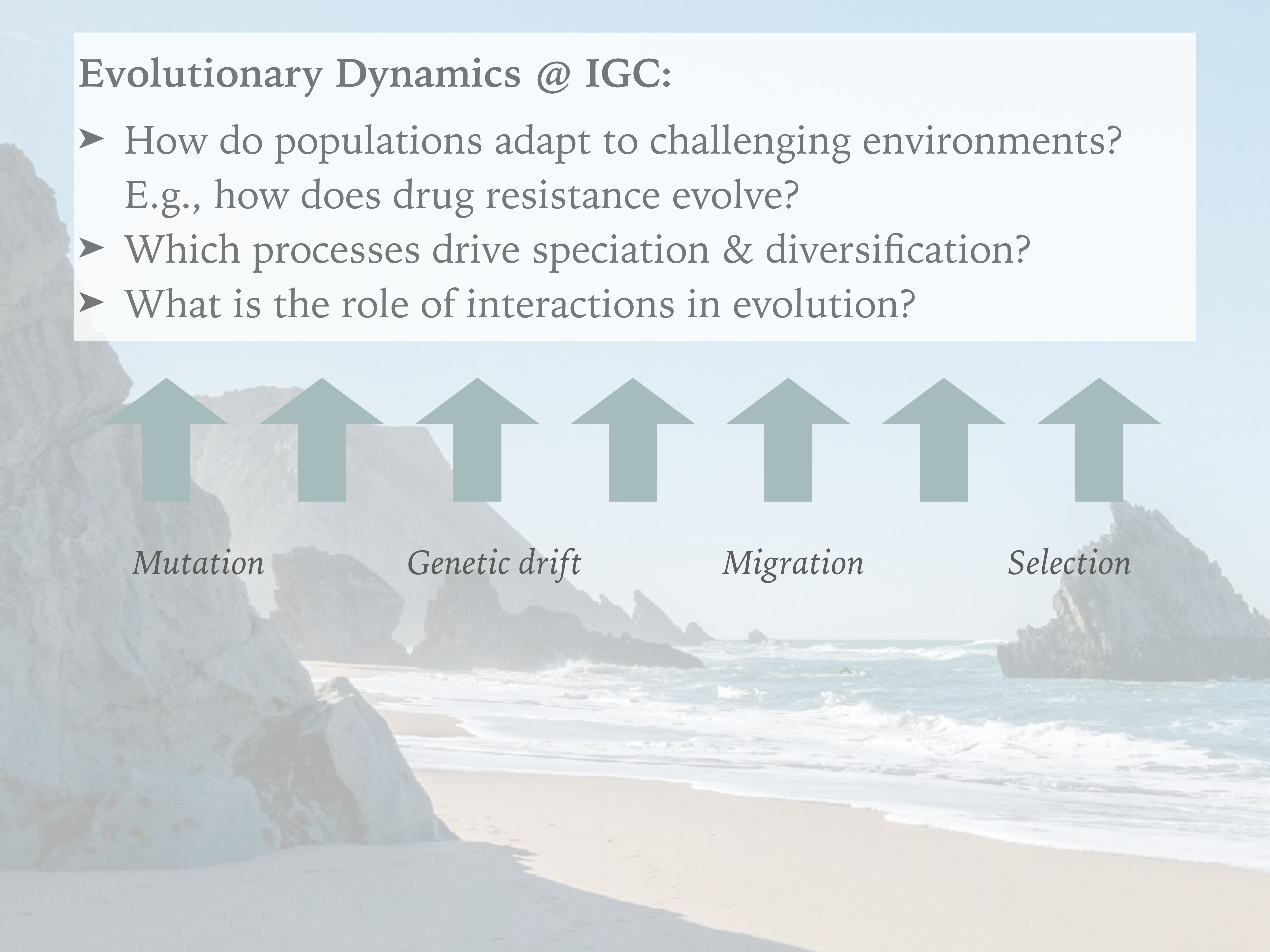
CLAUDIA BANK
EVOLUTIONARY DYNAMICS GROUP

INSTITUTO
GULBENKIAN
DE CIÊNCIA



Evolutionary Dynamics @ IGC:

- How do populations adapt to challenging environments?
  E.g., how does drug resistance evolve?
- Which processes drive speciation & diversification?
- What is the role of interactions in evolution?



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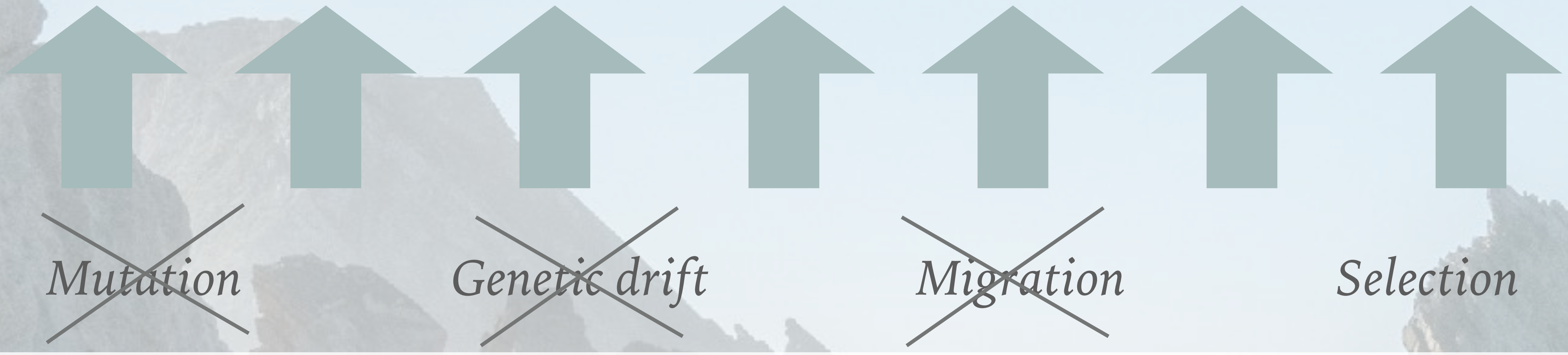

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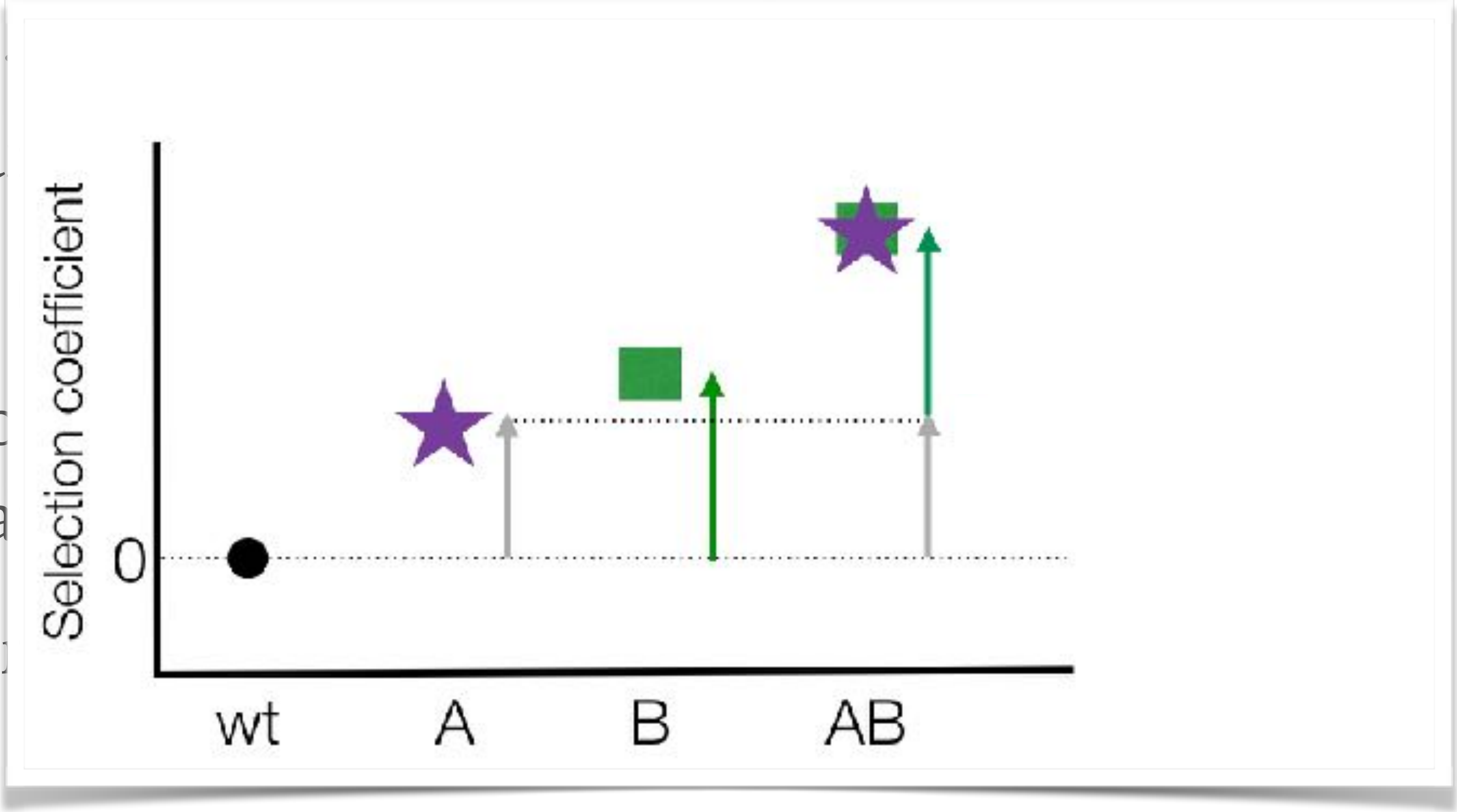

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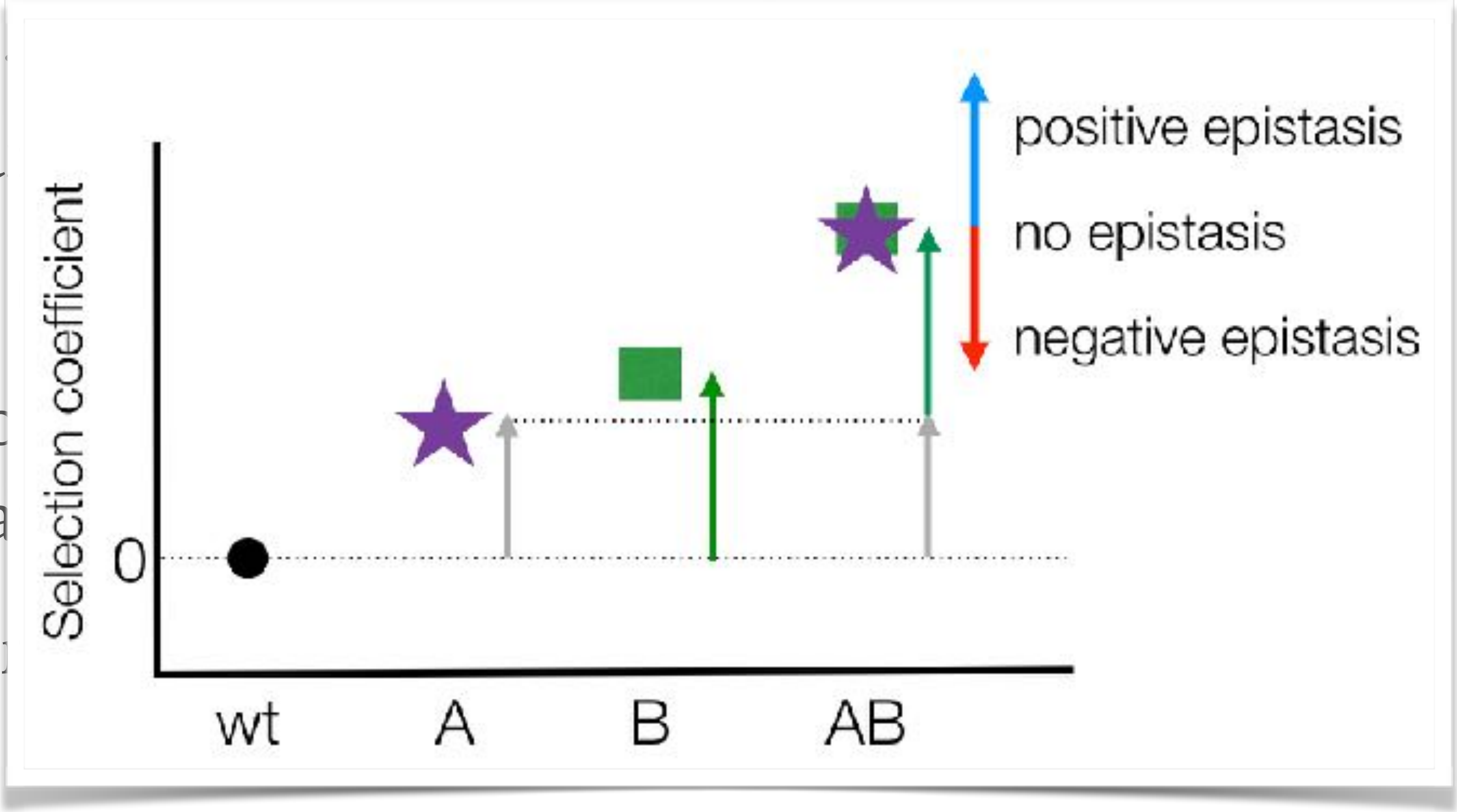

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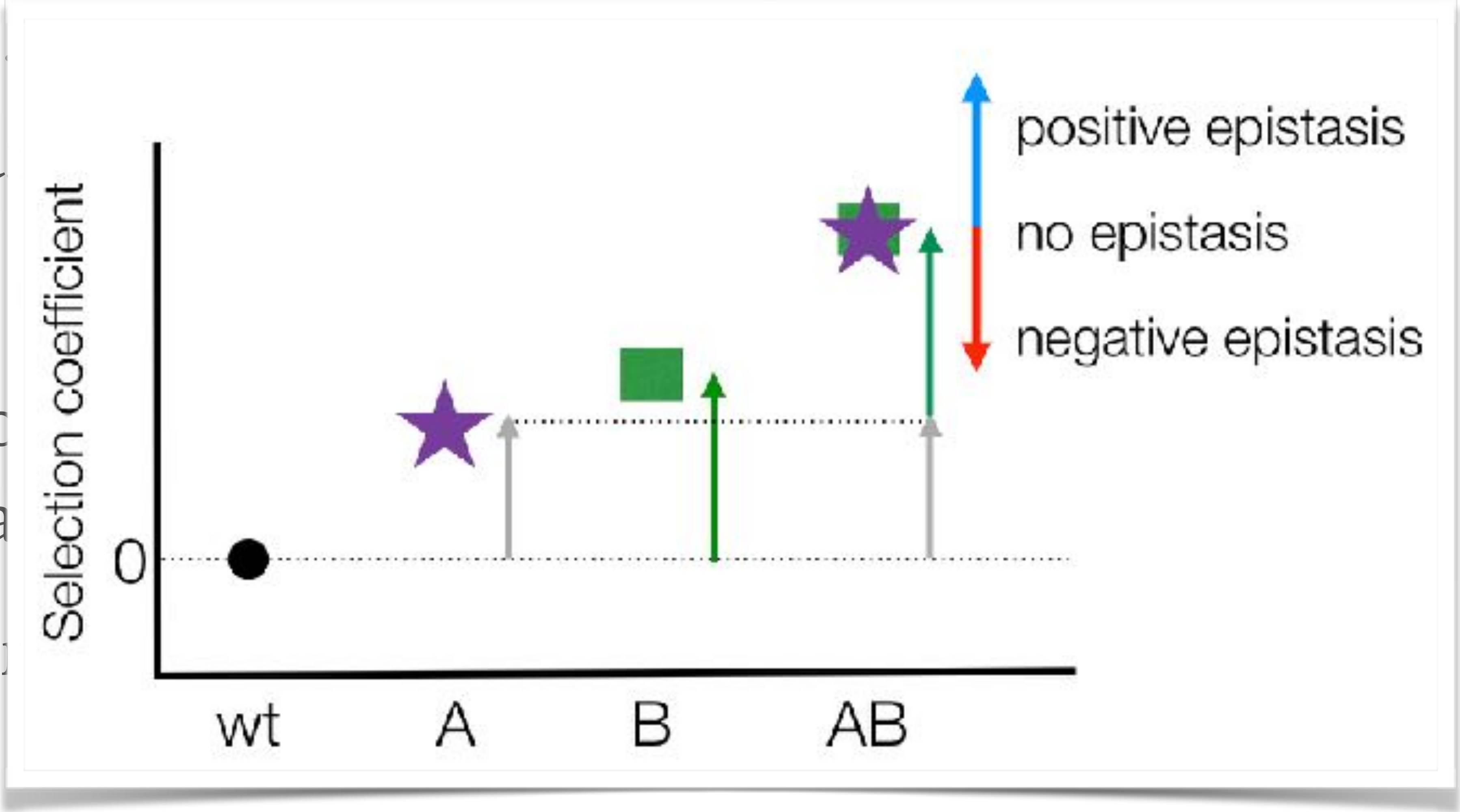

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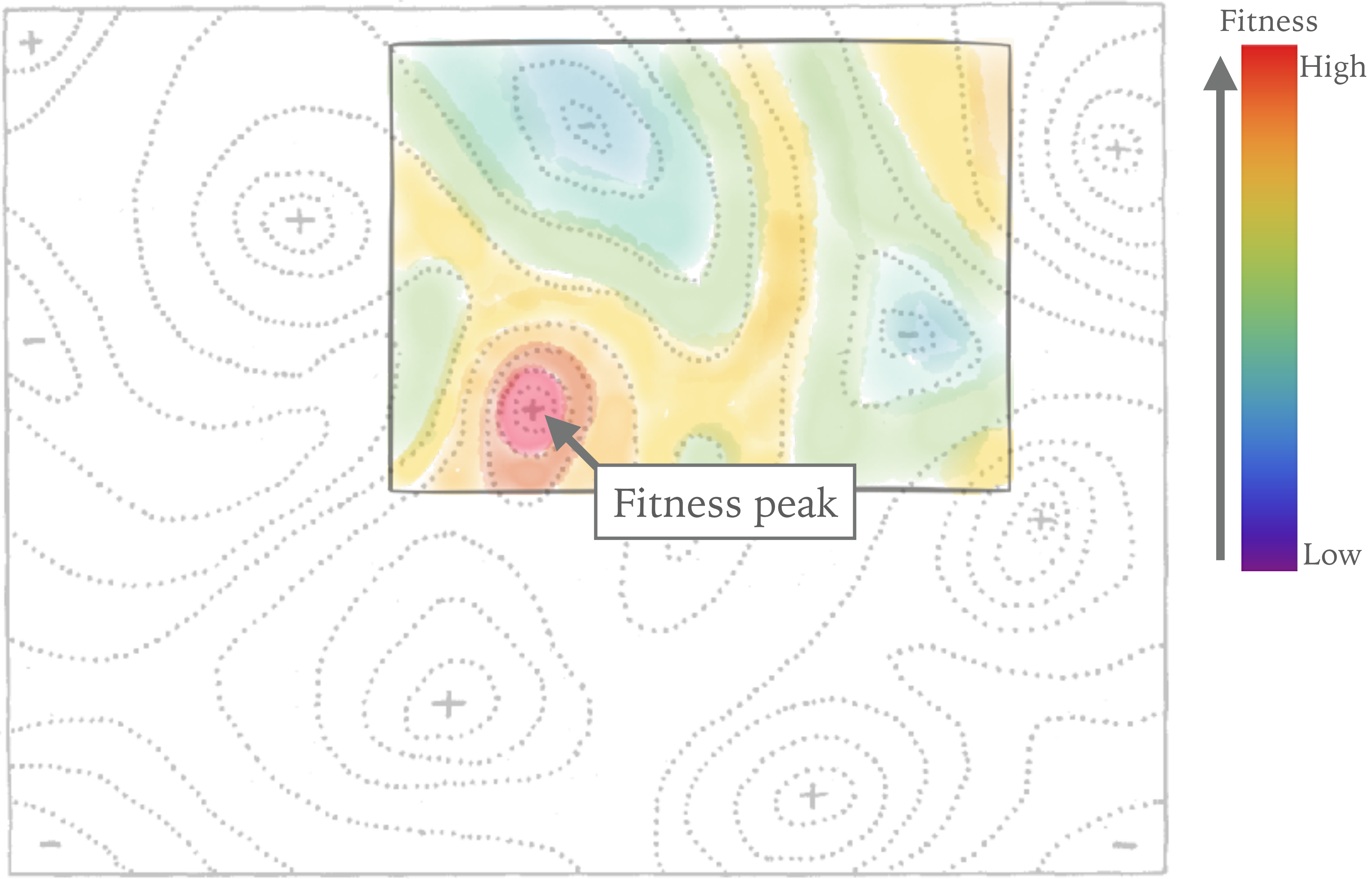
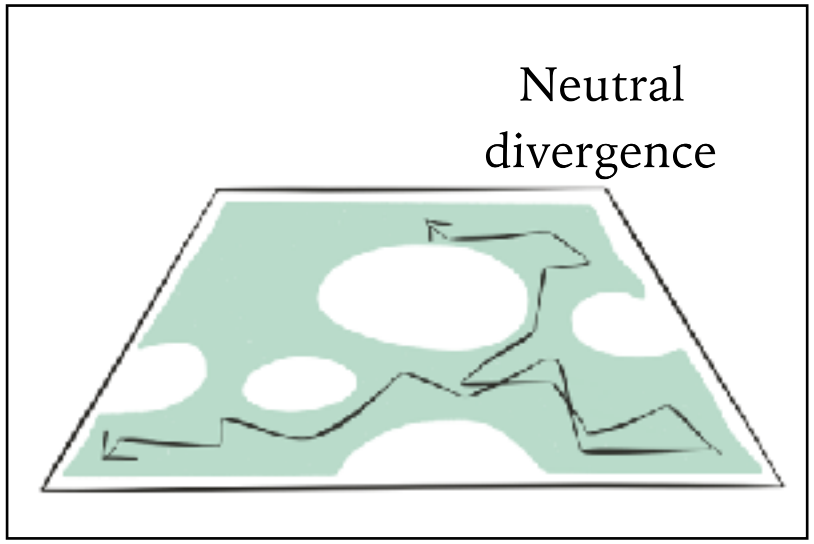
- What is the shape of the fitness landscape?

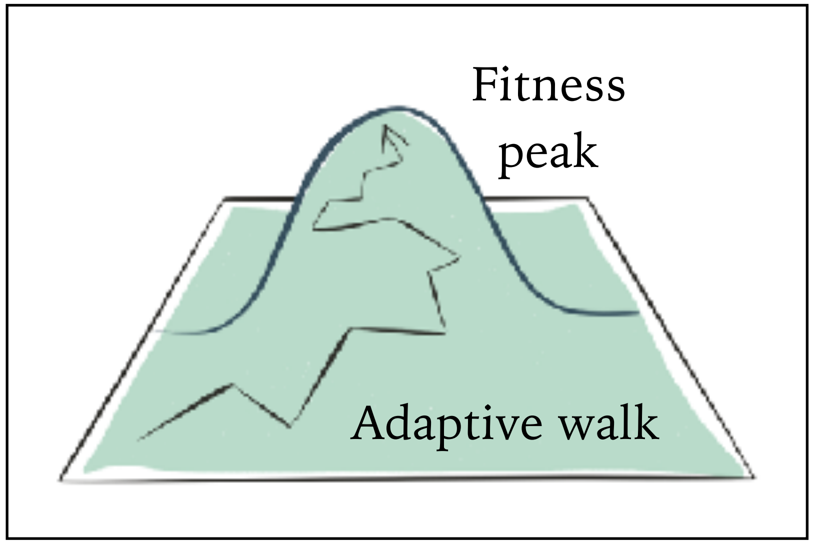
UNDERSTANDING EVOLUTION THROUGH FITNESS LANDSCAPES

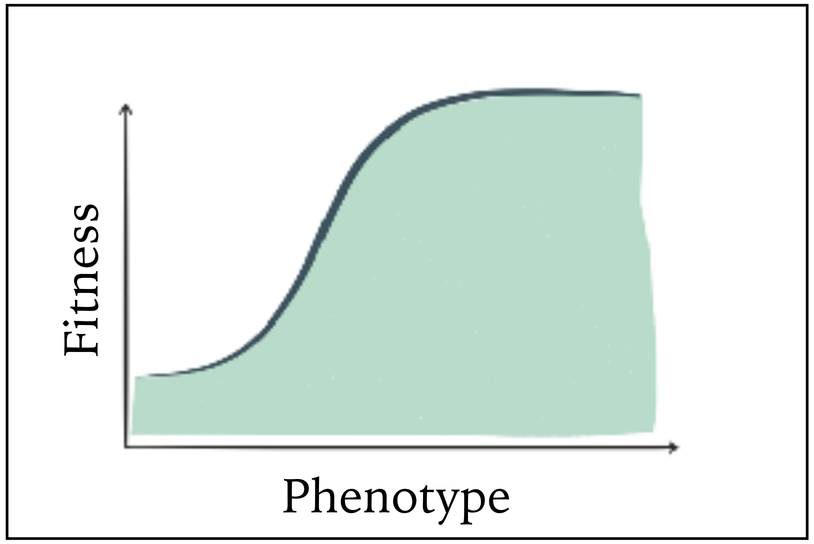


Wright, 1932

WHY FITNESS LANDSCAPES ARE APPEALING







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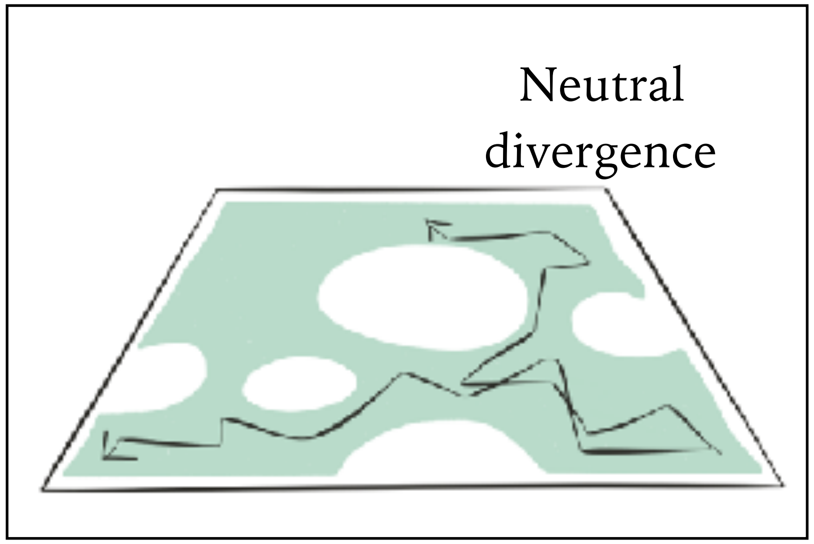

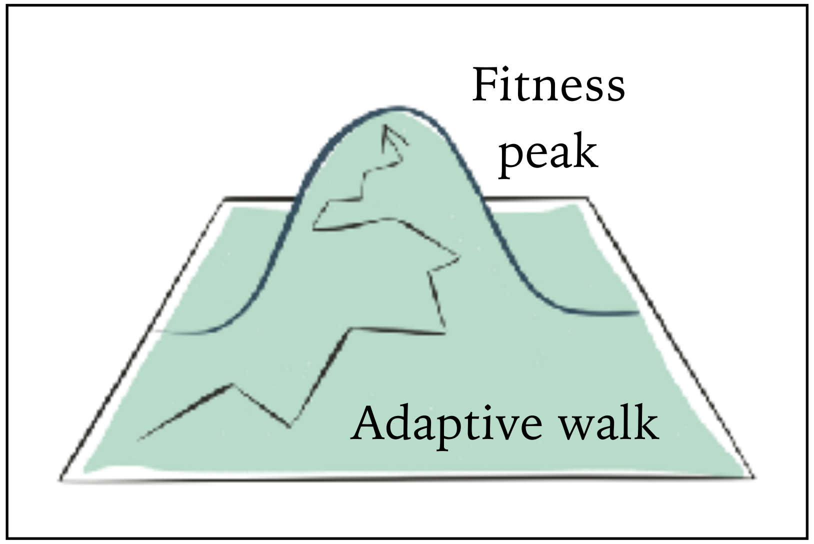

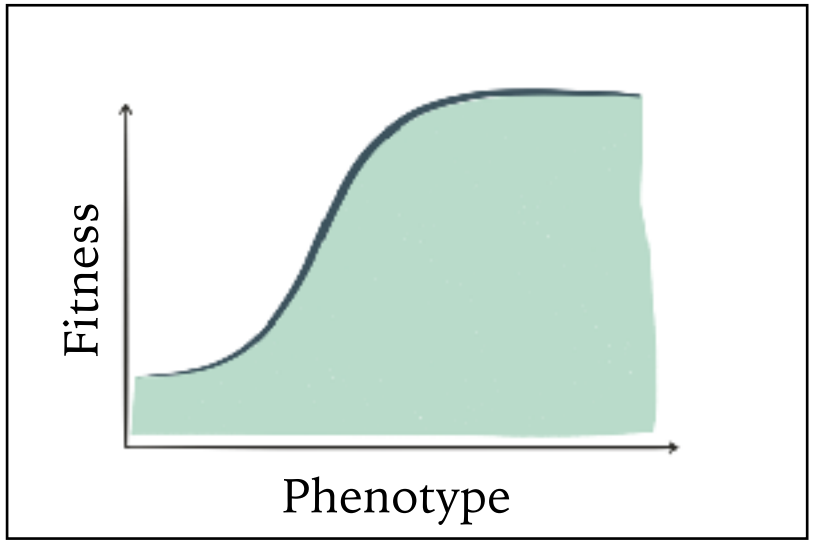

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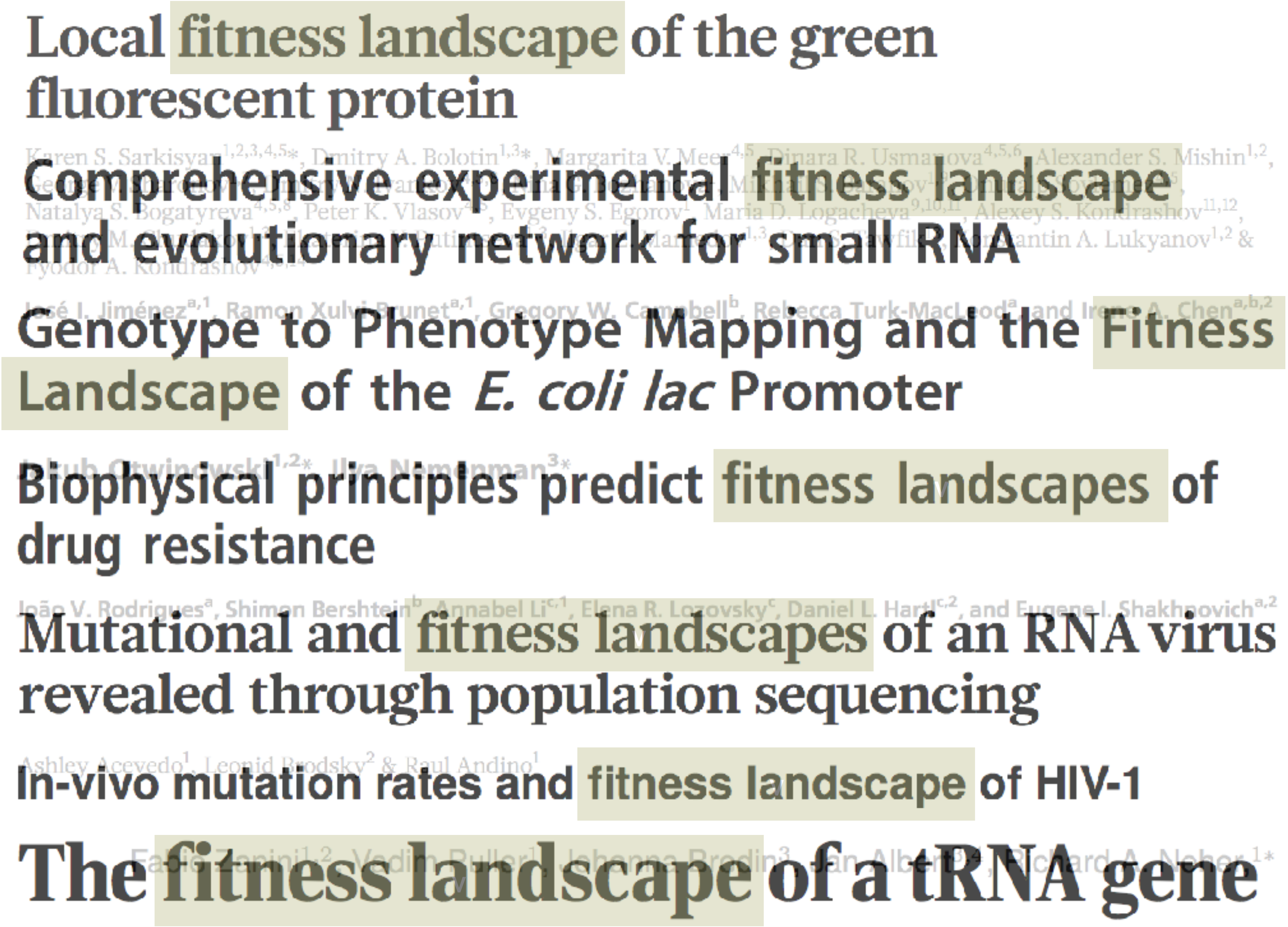


Local fitness landscape of the green fluorescent protein

Karen S. Sarkisyan[1,2,3,4,5*], Dmitry A. Bolotin[1,3*], Margarita V. Meer[4,5], Dinara R. Usmanova[4,5,6], Alexander S. Mishin[1,2],
[illegible]
Natalya S. Bogatyreva[4,5,8], Peter K. Vlasov[4,5], Evgeny S. Egorov[1], Maria D. Logacheva[9,10,11], Alexey S. Kondrashov[11,12],
[illegible] Konstantin A. Lukyanov[1,2] &
Fyodor A. Kondrashov

Comprehensive experimental fitness landscape and evolutionary network for small RNA

José I. Jiménez[a,1], Ramon Xulvi-Brunet[a,1], Gregory W. Campbell[b], Rebecca Turk-MacLeod[a], and Irene A. Chen[a,b,2]

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

Jakub Otwinowski[1,2*], Ilya Nemenman[3*]

Biophysical principles predict fitness landscapes of drug resistance

João V. Rodrigues[a], Shimon Bershtein[b], Annabel Li[c,1], Elena R. Lozovsky[c], Daniel L. Hartl[c,2], and Eugene I. Shakhnovich[a,2]

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

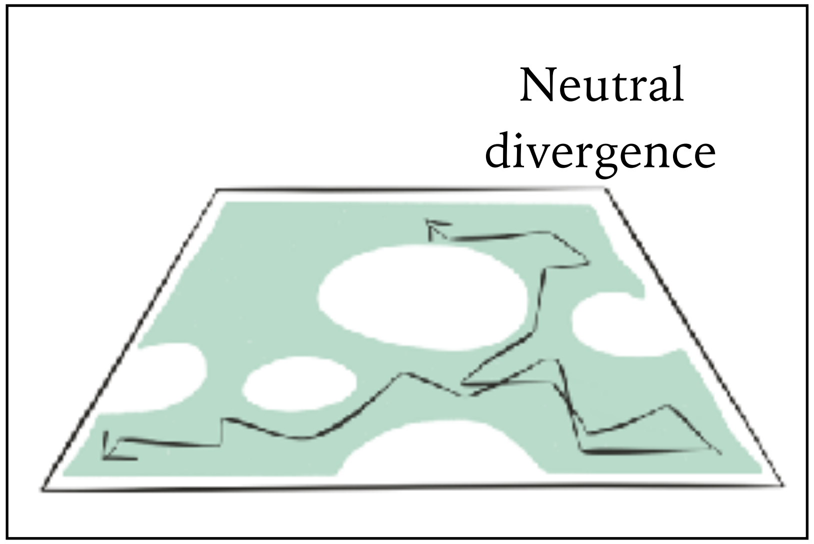
Ashley Acevedo[1], Leonid Brodsky[2] & Raul Andino[1]

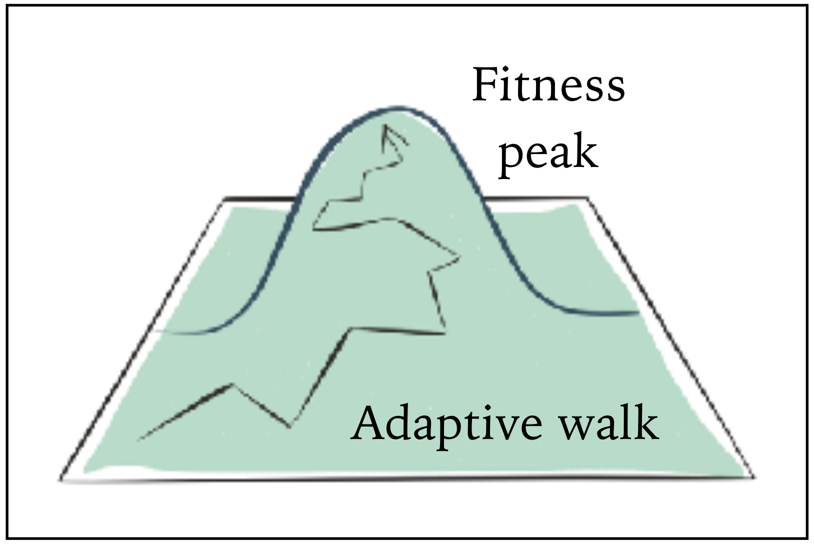
In-vivo mutation rates and fitness landscape of HIV-1

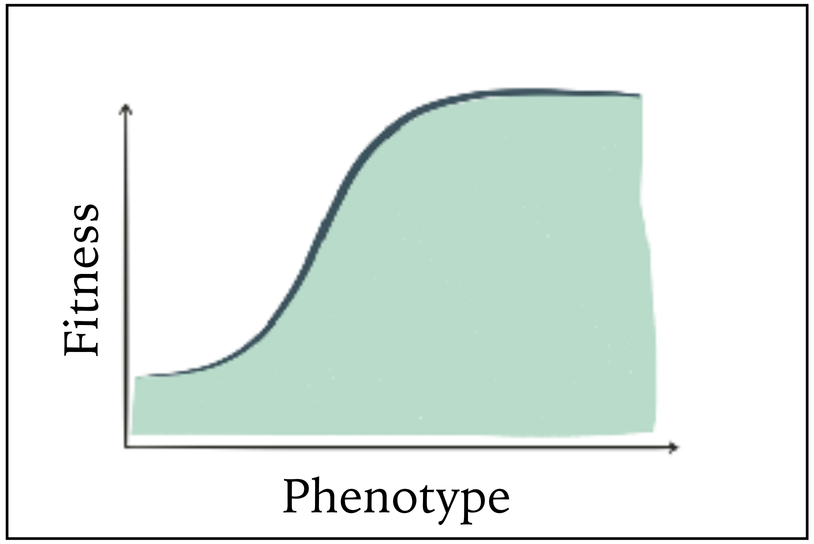
Fabio Zanini[1,2], Vadim Puller[1], Johanna Brodin[3], Jan Albert[3,4], Richard A. Neher[1*]

The fitness landscape of a tRNA gene

WHY FITNESS LANDSCAPES ARE DIFFICULT







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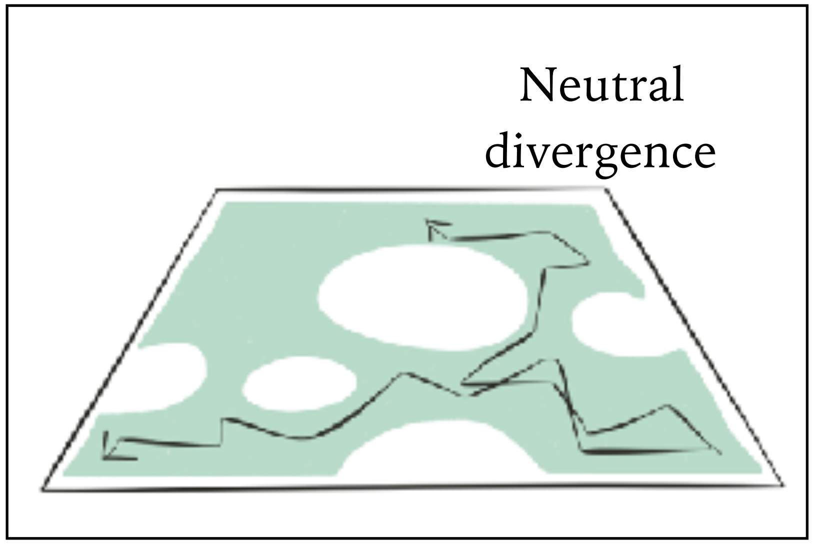

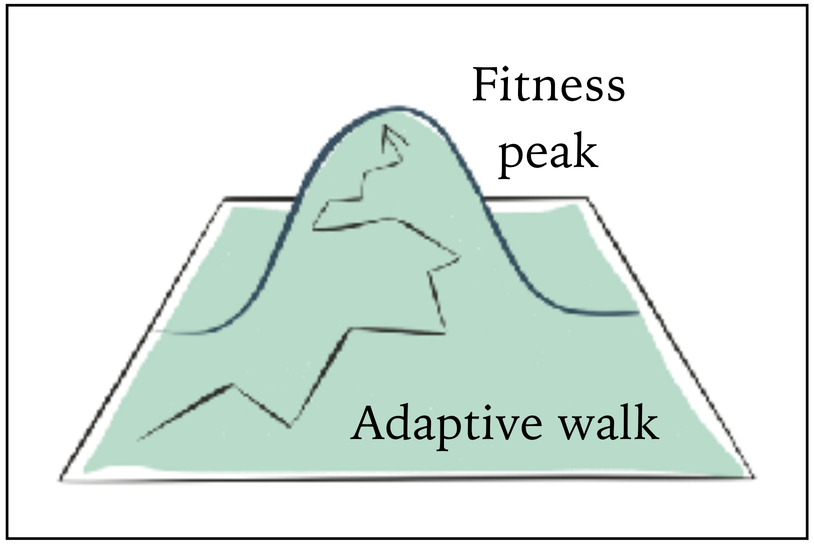

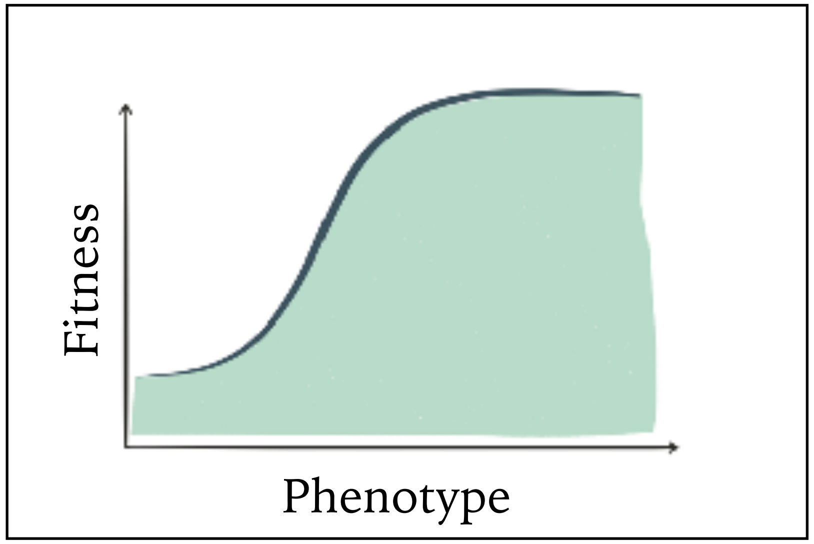

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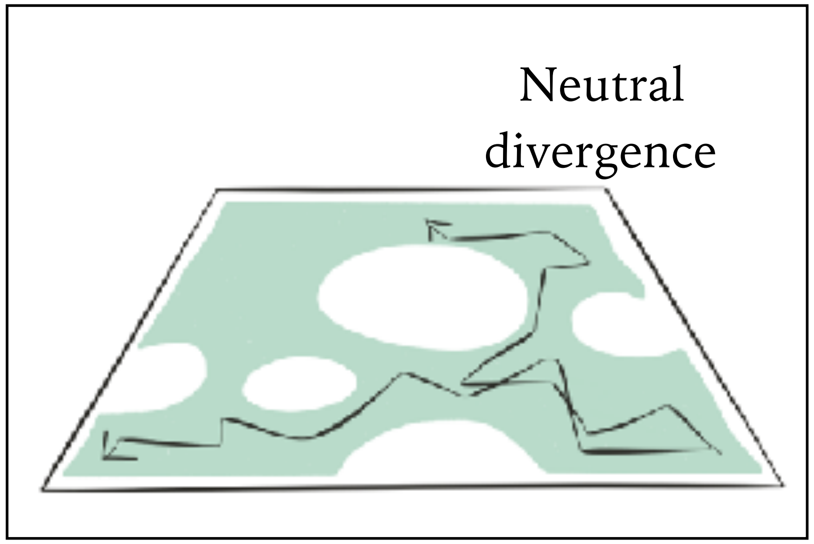

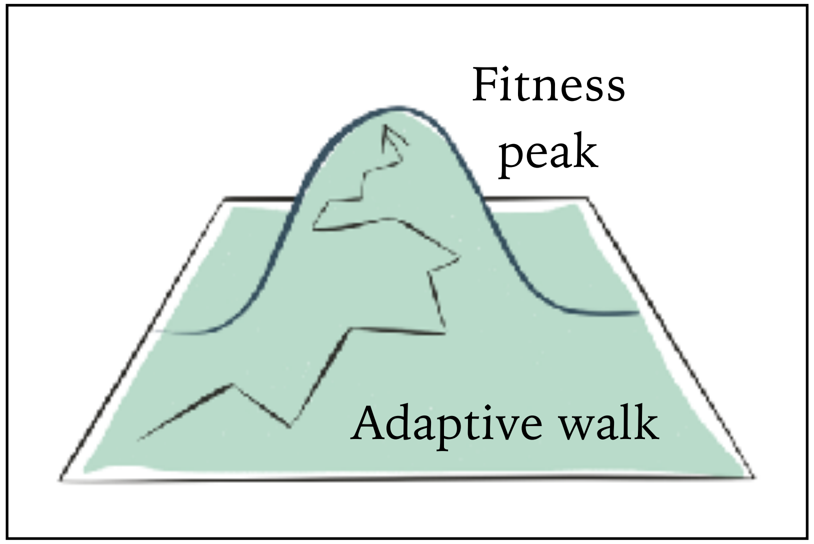

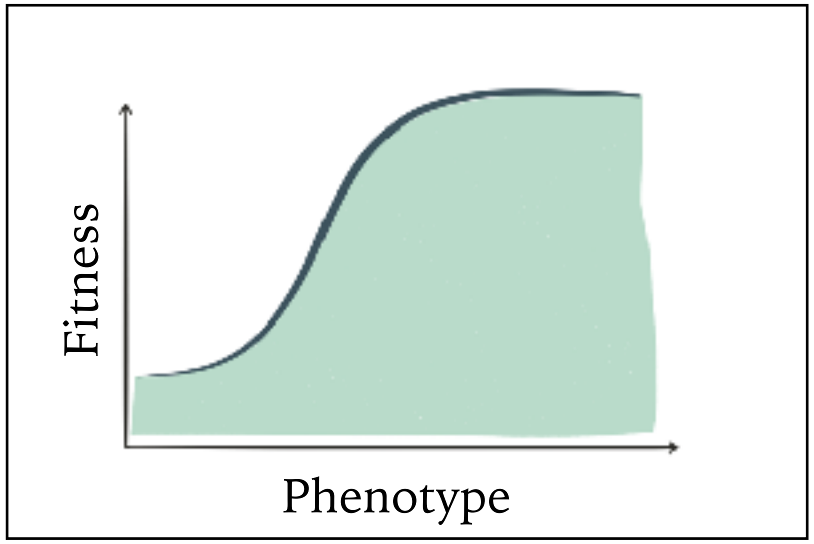

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E.g.: Can we predict costs of anti-microbial resistance across environments?

PROJECTS IN THE LAB

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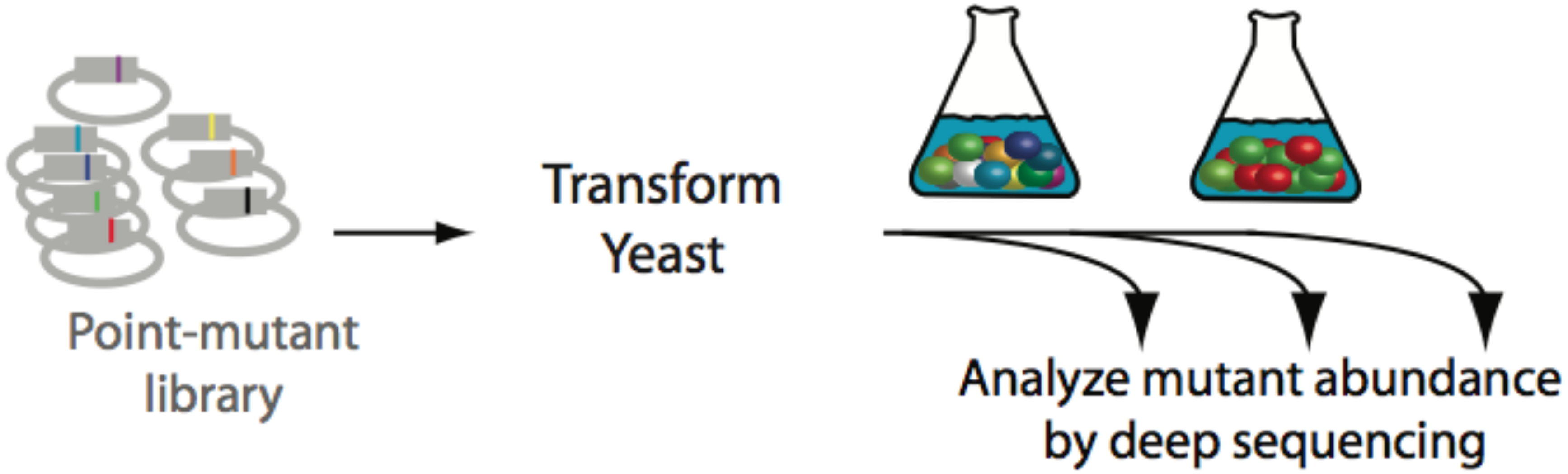
THE EXPERIMENTAL APPROACH: DEEP MUTATIONAL SCANNING

- 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



Point-mutant library

Transform Yeast

Analyze mutant abundance by deep sequencing

Hietpas, Jensen & Bolon, PNAS, 2011

THE EXPERIMENTAL APPROACH: DEEP MUTATIONAL SCANNING

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

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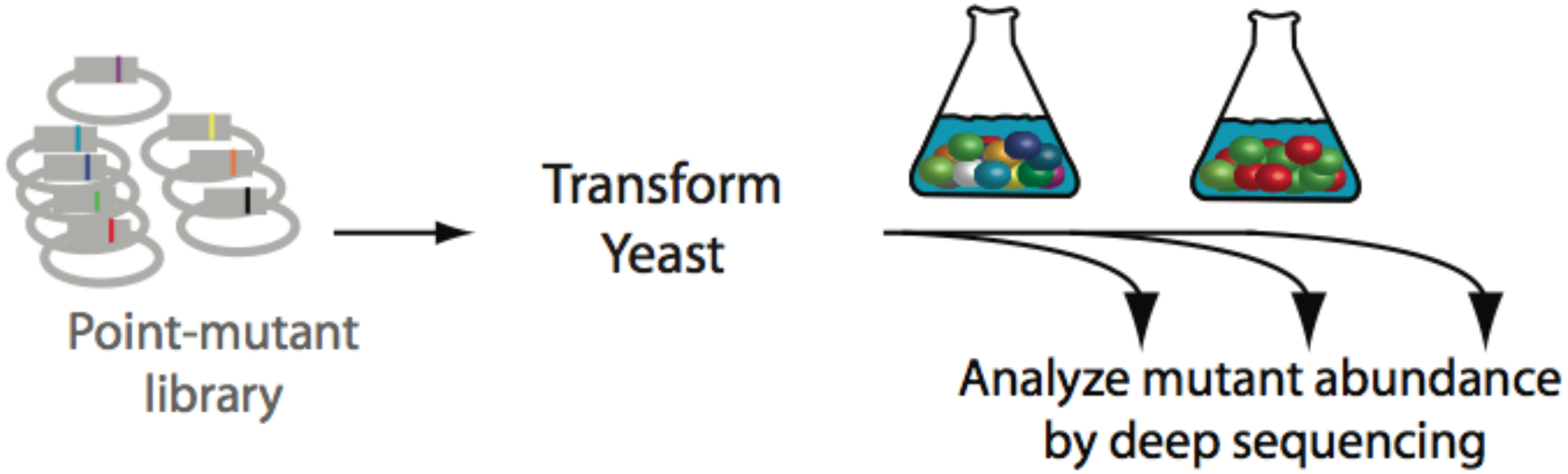
Ryan Hietpas

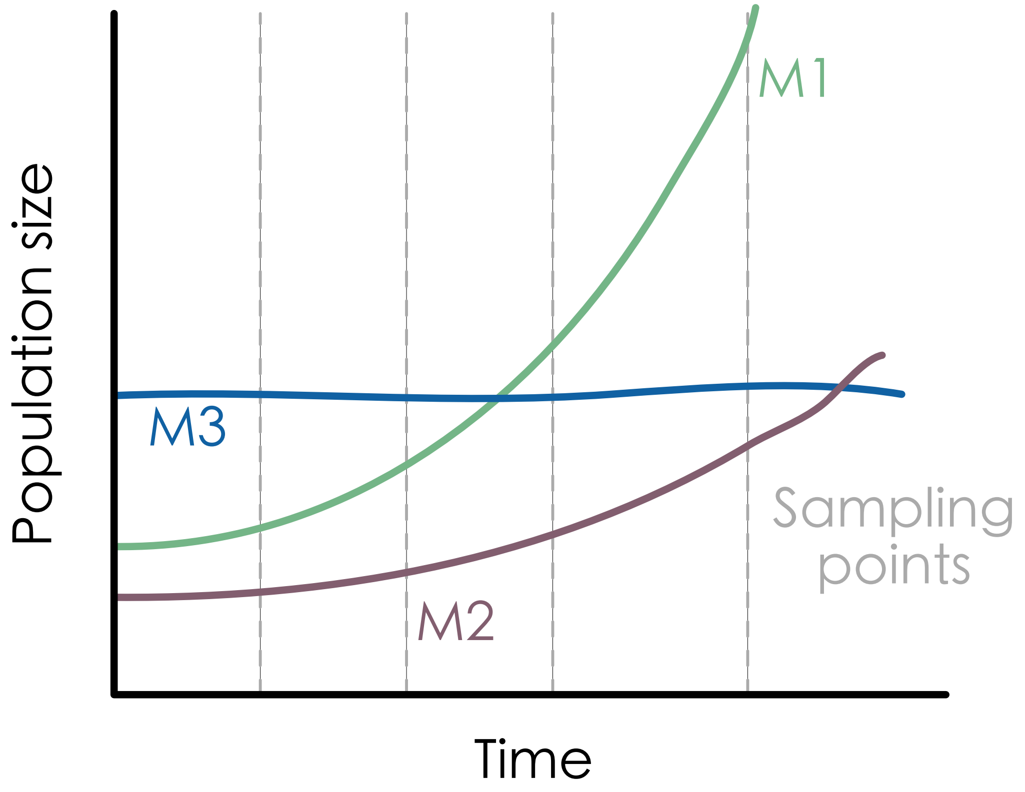


Jeff Jensen

Hietpas, Jensen & Bolon, PNAS, 2011

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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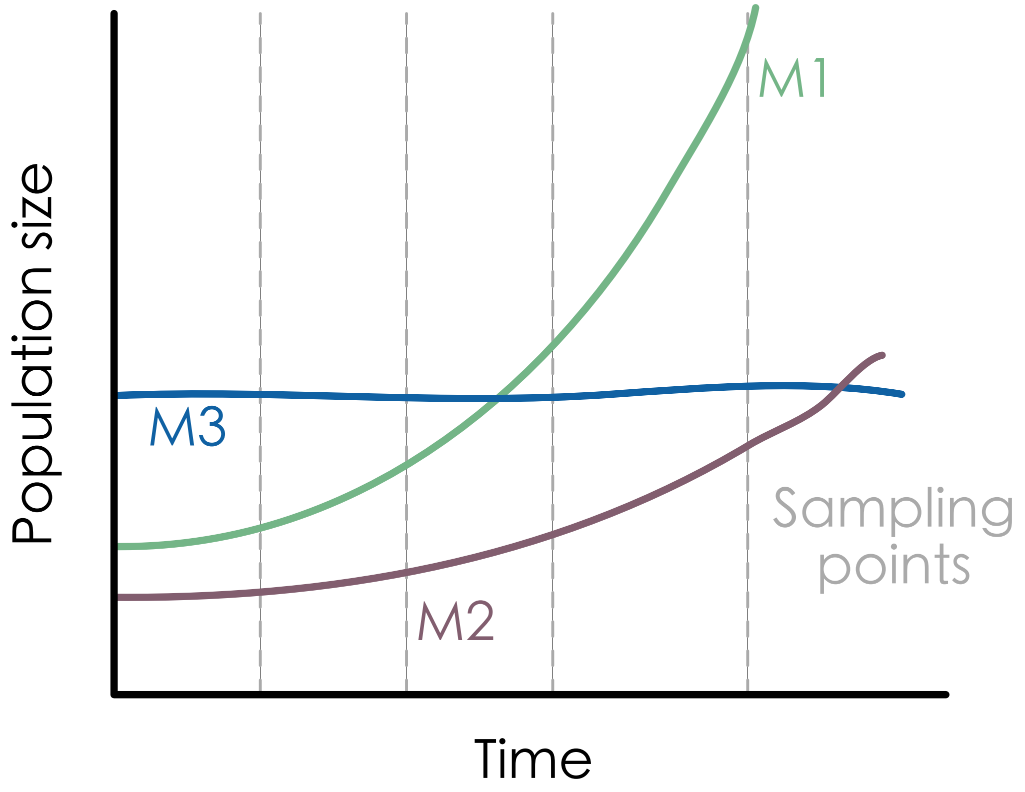


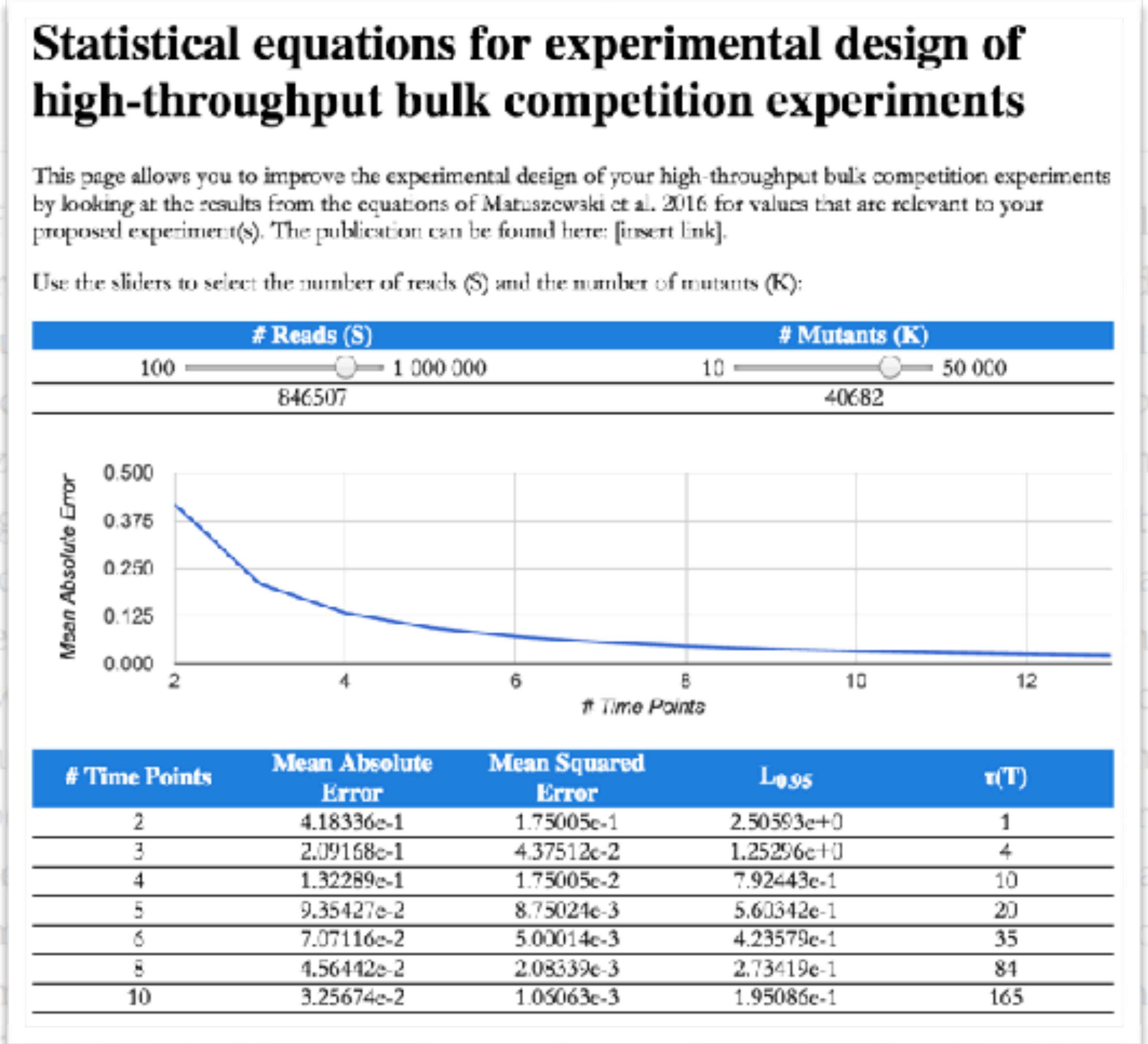
- What is the attainable experimental accuracy?
- How do experimental details (number and timing of samples, sequencing coverage, number of mutants, etc.) affect the outcome?

A statistical guide to the design of deep mutational scanning experiments

Sebastian Matuszewski*,†,§,§§, Marcel E. Hildebrandt*,§, Ana-Hermina Ghenu‡, Jeffrey D. Jensen*,† and Claudia Bank^{*,†,‡,§§,1}

*School of Life Sciences, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland, †Swiss Institute of Bioinformatics (SIB), Lausanne, Switzerland, ‡Instituto Gulbenkian de Ciência, Oeiras, Portugal, §equal contribution, §§co-corresponding author

- optimize experimental setup for deep mutational scanning approaches
- statistical predictions applicable via interactive web tool: www.evoldynamics.org/tools



Statistical equations for experimental design of high-throughput bulk competition experiments

This page allows you to improve the experimental design of your high-throughput bulk competition experiments by looking at the results from the equations of Matuszewski et al. 2016 for values that are relevant to your proposed experiment(s). The publication can be found here: [insert link].

Use the sliders to select the number of reads (S) and the number of mutants (K):

# Reads (S)	# Mutants (K)
100 — 1 000 000	10 — 50 000
846507	40682

# Time Points	Mean Absolute Error	Mean Squared Error	$L_{0.95}$	$\tau(T)$
2	4.18336e-1	1.75005e-1	2.50593e+0	1
3	2.09168e-1	4.37512e-2	1.25296e+0	4
4	1.32289e-1	1.75005e-2	7.92443e-1	10
5	9.35427e-2	8.75024e-3	5.60342e-1	20
6	7.07116e-2	5.00014e-3	4.23579e-1	35
8	4.56442e-2	2.08339e-3	2.73419e-1	84
10	3.25674e-2	1.05063e-3	1.95086e-1	165

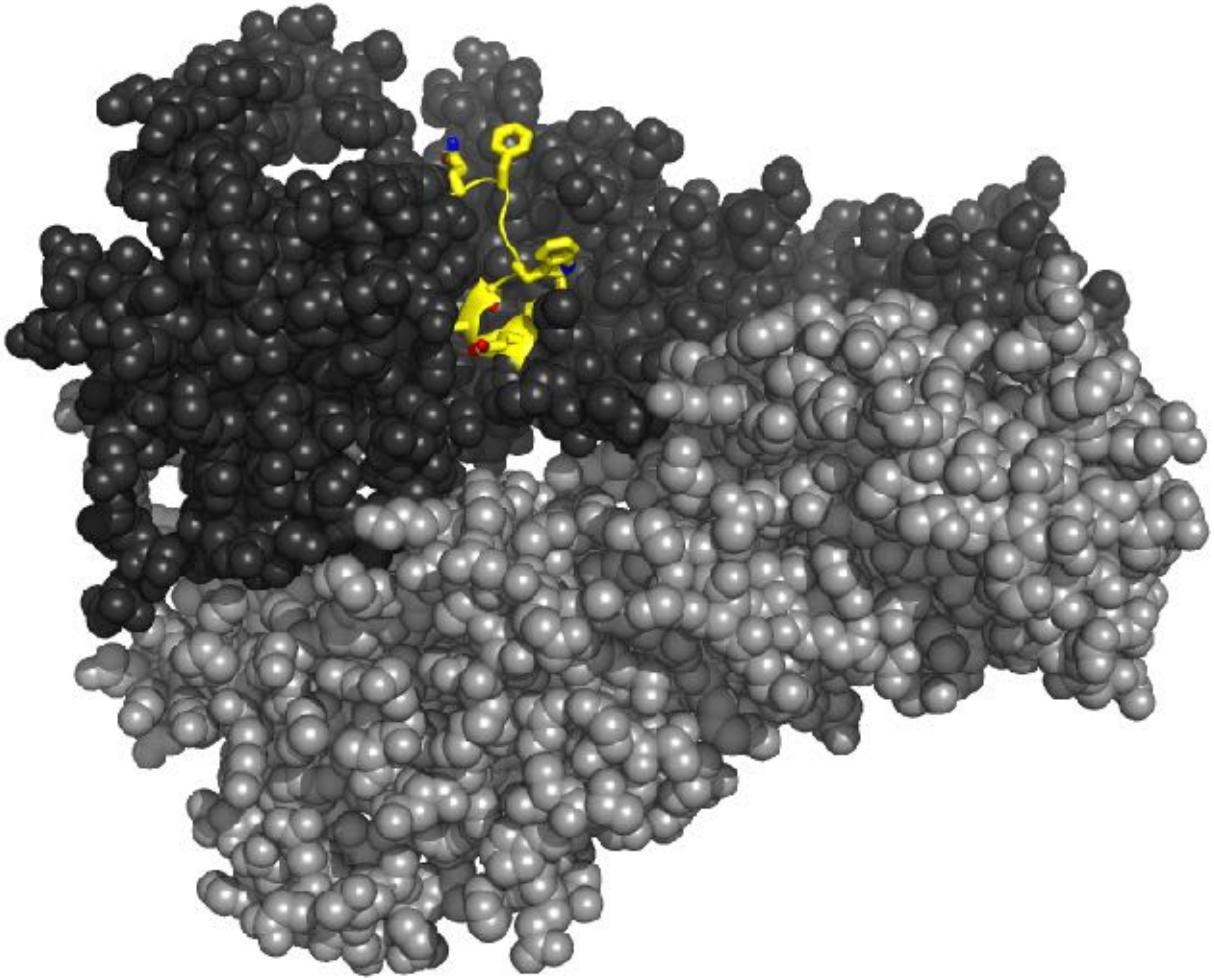
Hermina Ghenu

KEYWORDS Experimental Design; Experimental Evolution; Distribution of Fitness Effects; Mutation; Population Genetics

Genetics, 2016

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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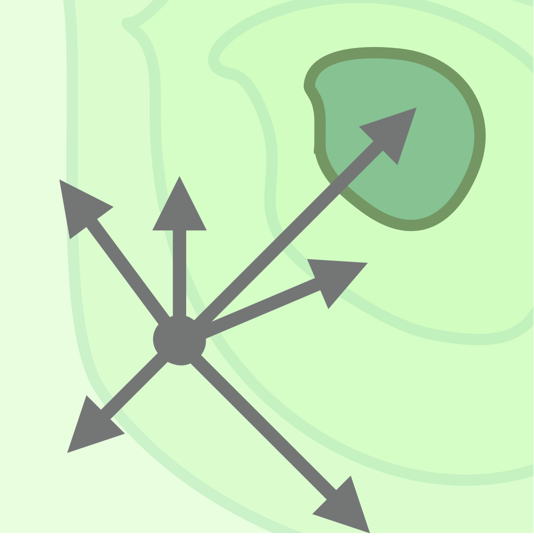

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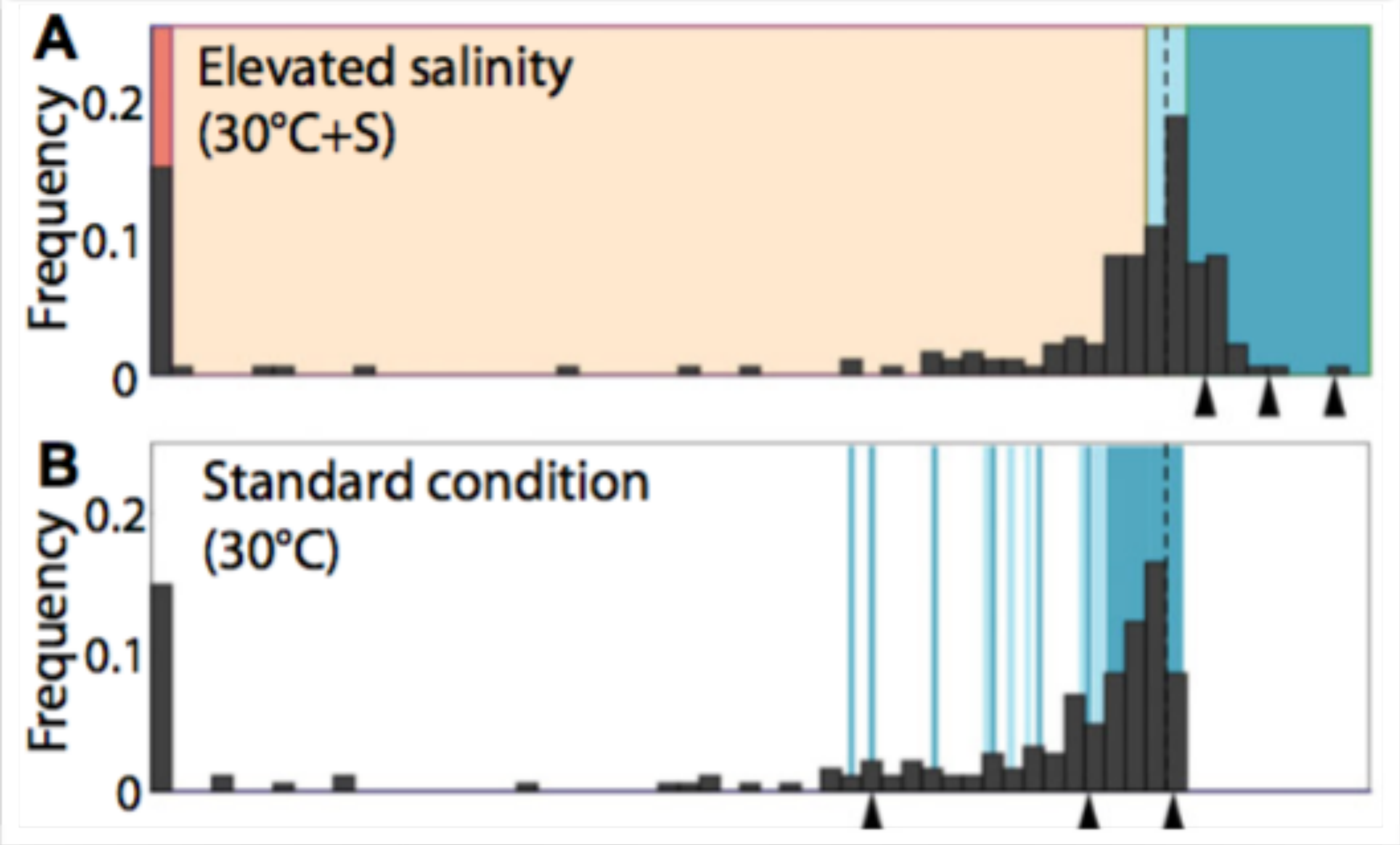
Compare DFEs across 4 environments - high costs of adaptation **Hietpas*, Bank* et al., 2013, Evolution**

Distribution of Fitness Effects (DFE) across environments



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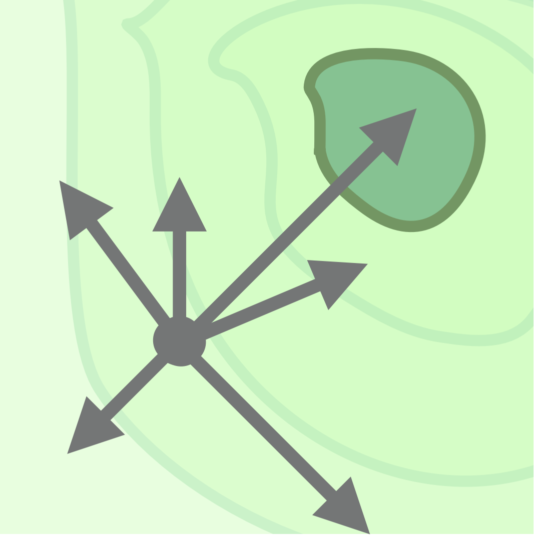

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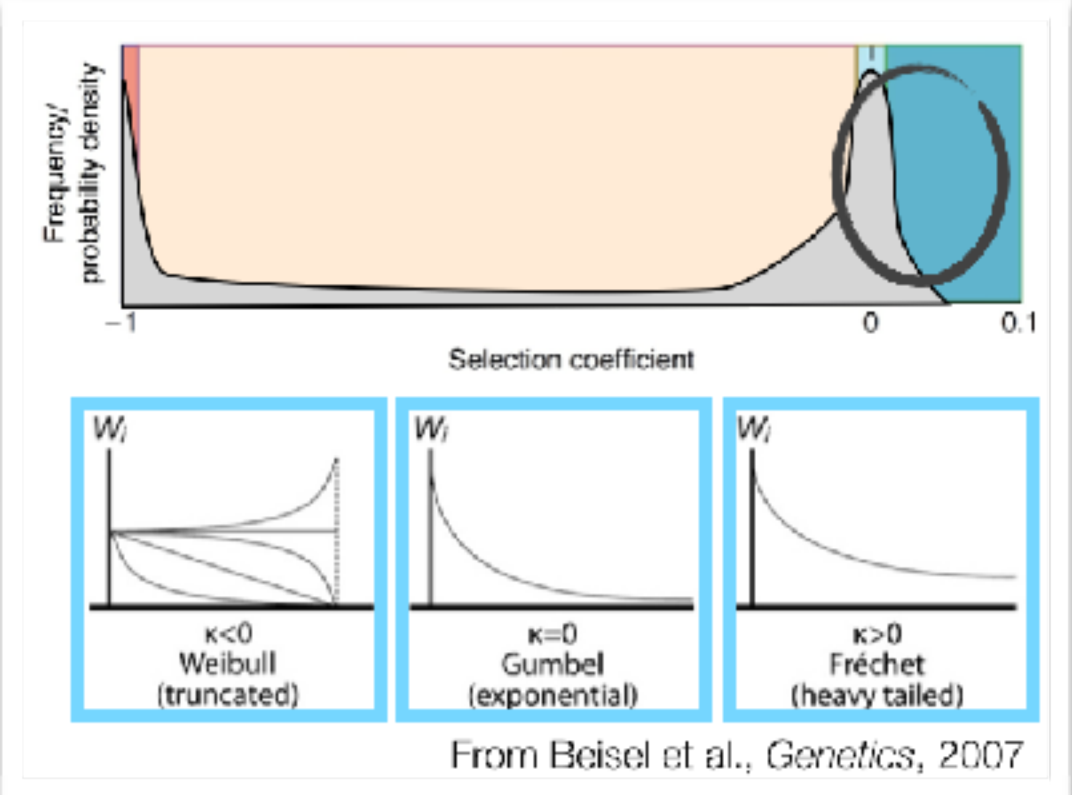
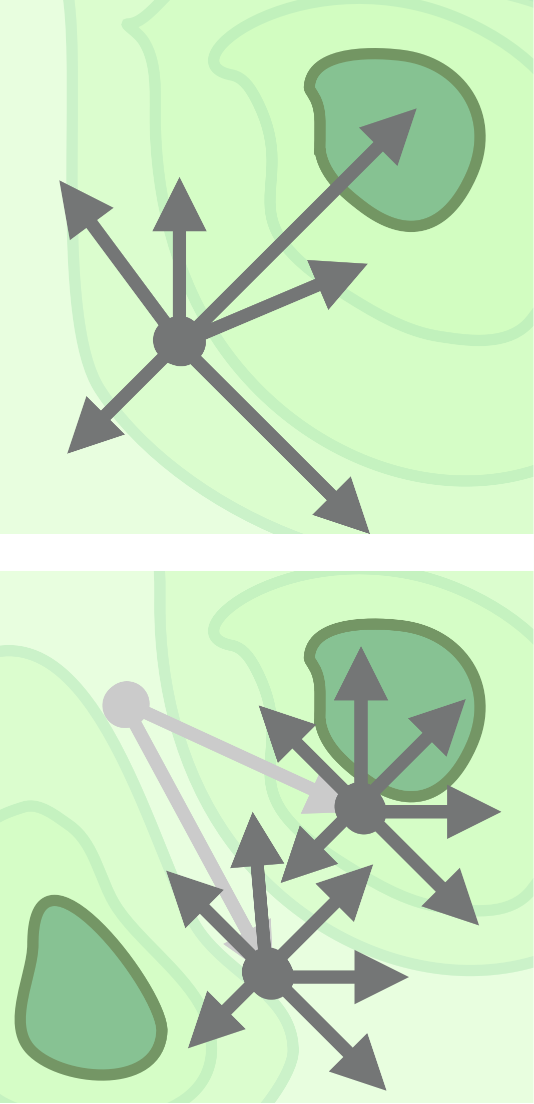
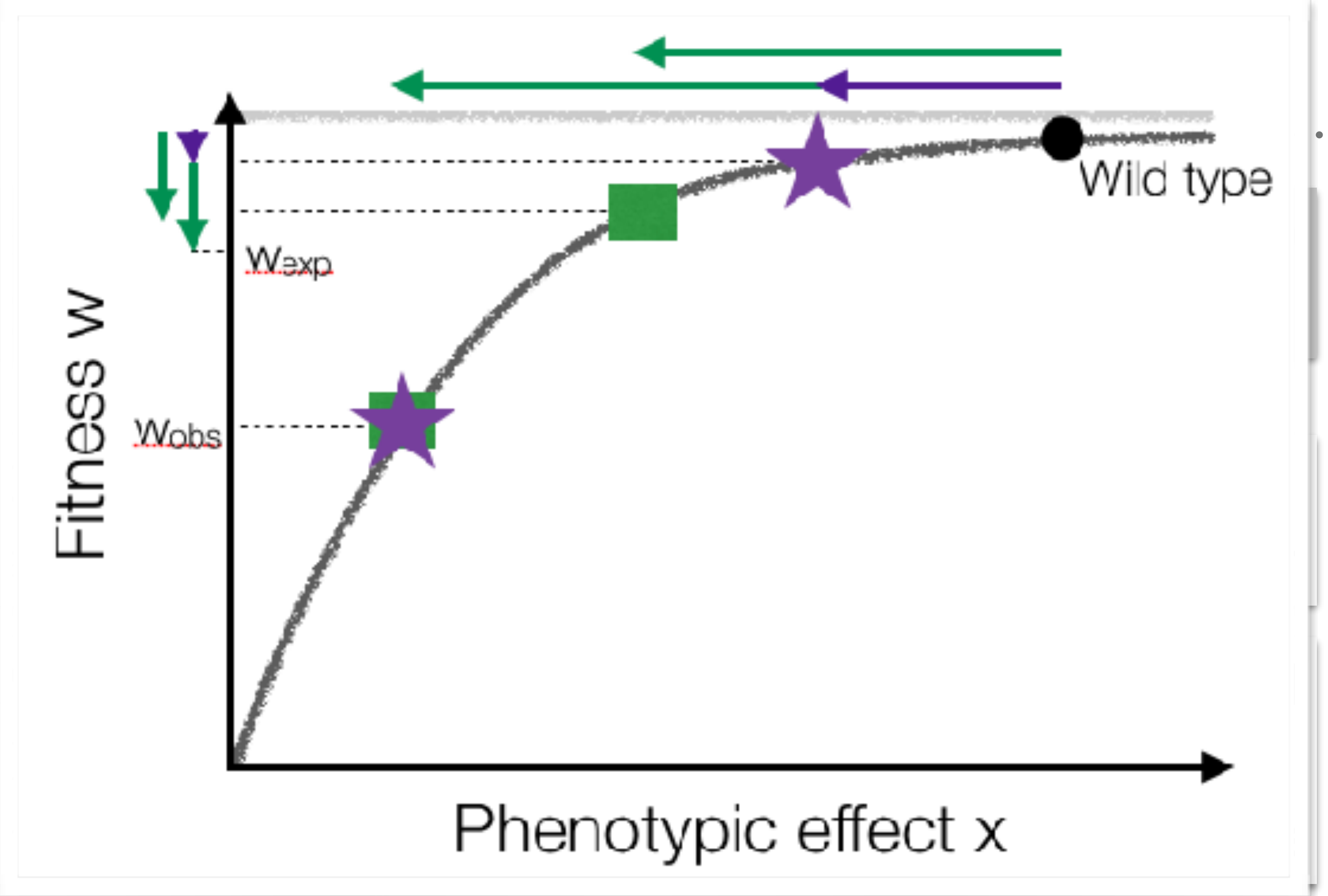
MCMC method to estimate selection coefficients, and DFEs across 6 environments - heavy-tailed DFE for most challenging environment **Bank et al., 2014, Genetics**



From Beisel et al., *Genetics*, 2007

WHAT WE DID SO FAR





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

Bank et al., 2015, MBE

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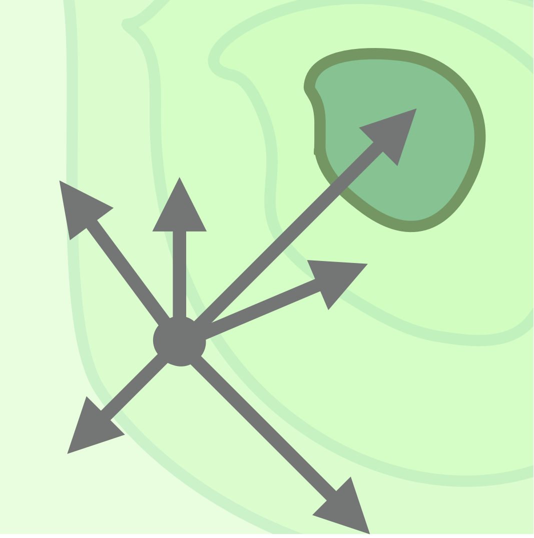

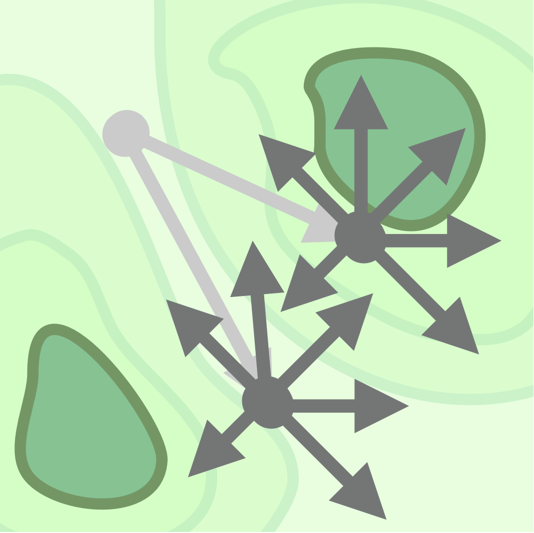

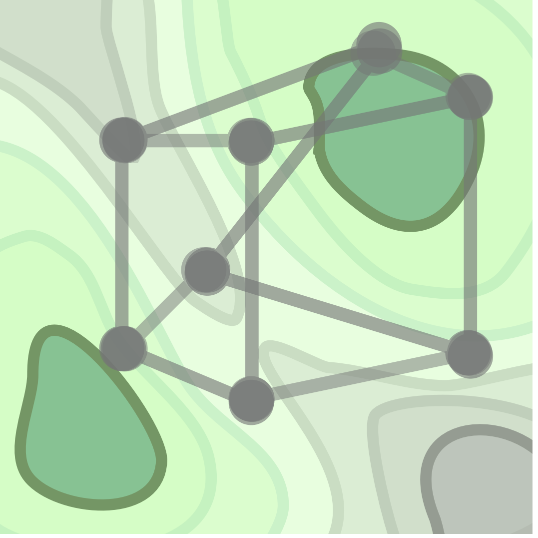

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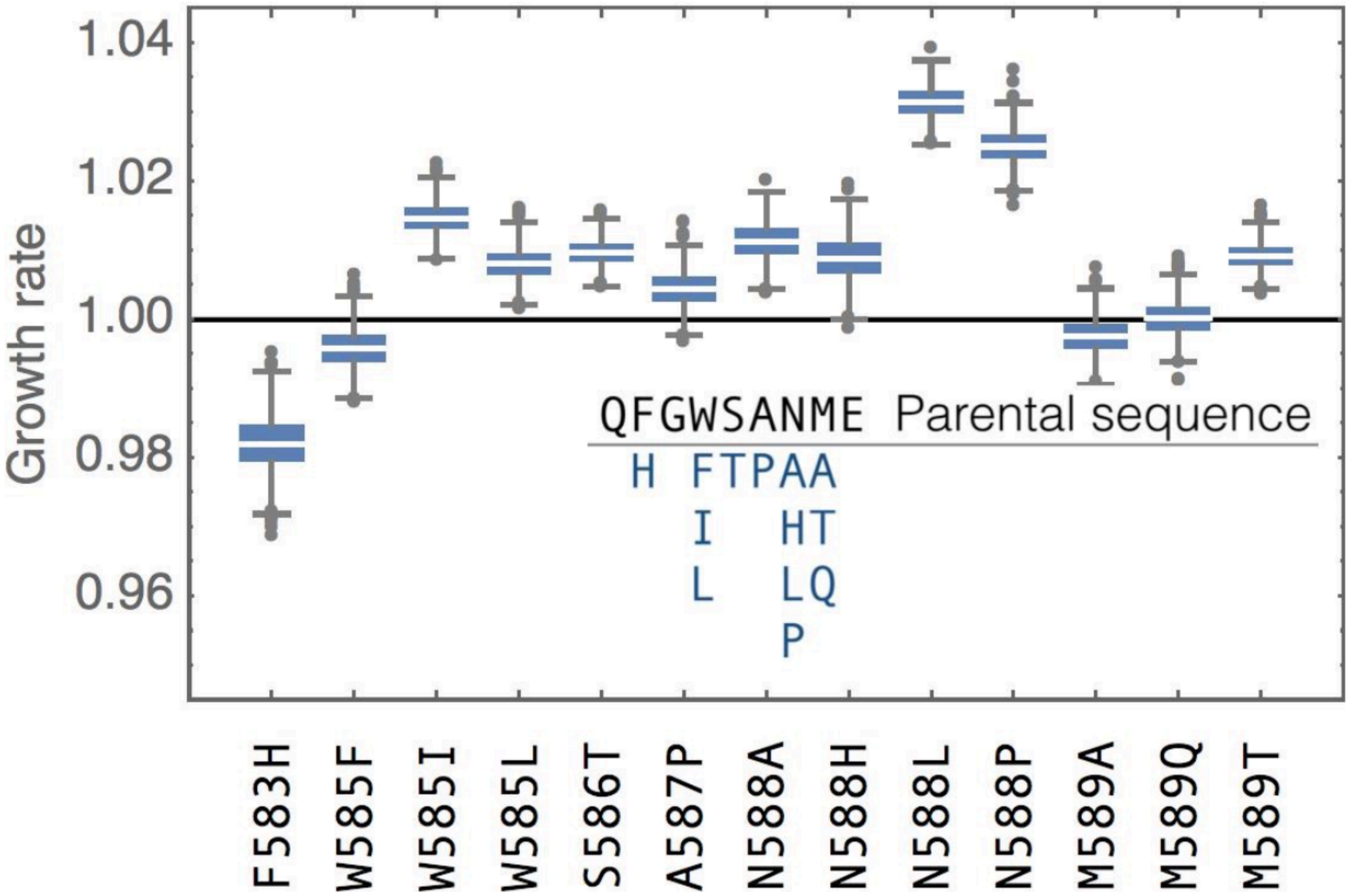
Guide to experimental design of deep mutational scanning studies **Matuszewski*, Hildebrandt* et al., 2016, Genetics**

Complete fitness landscape of 640 combinations of mutations **Bank*, Matuszewski* et al., 2016, PNAS**

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



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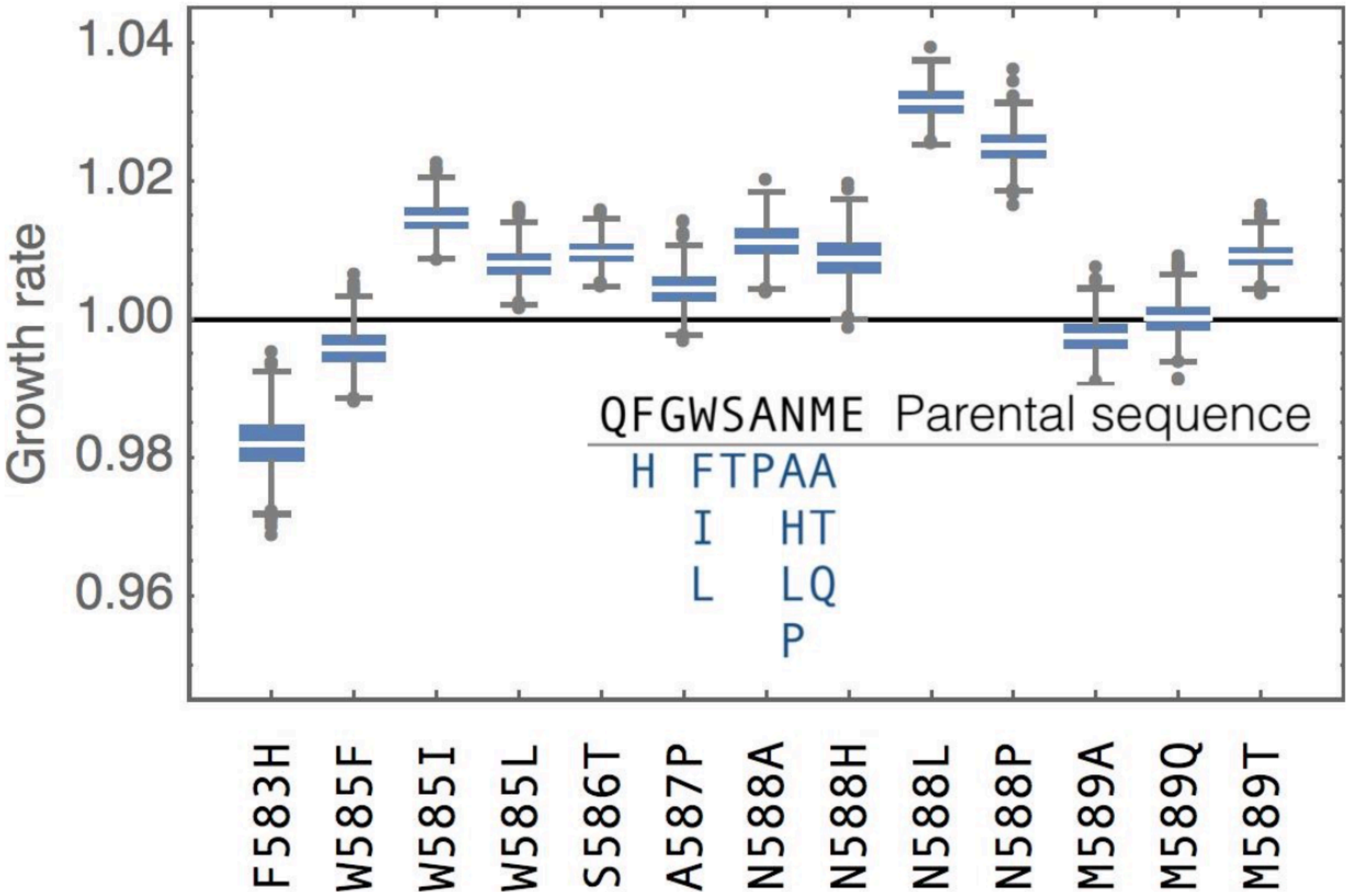
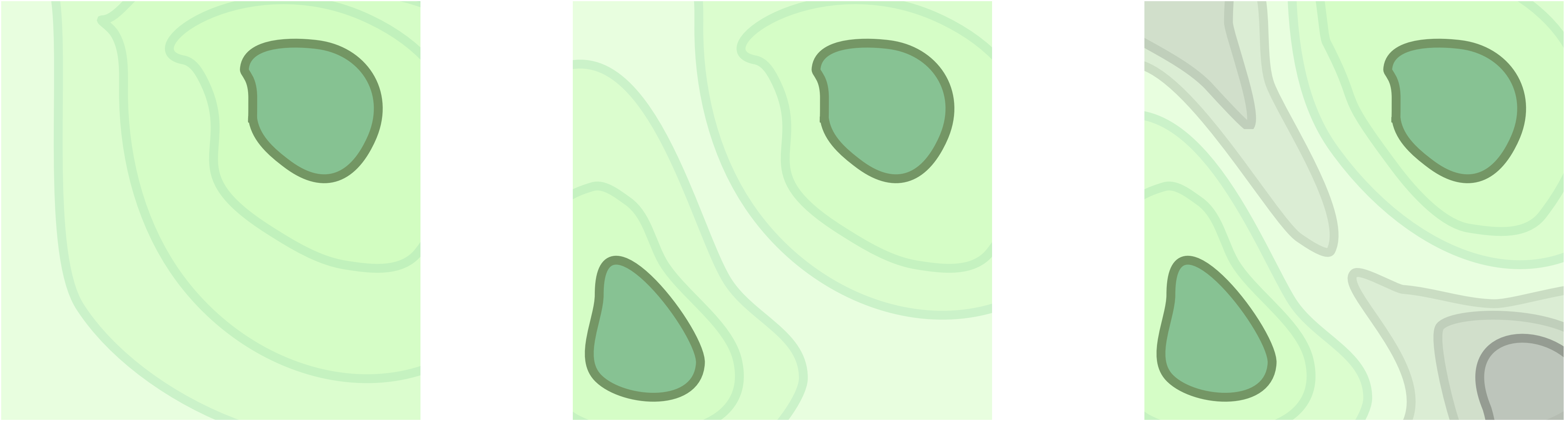


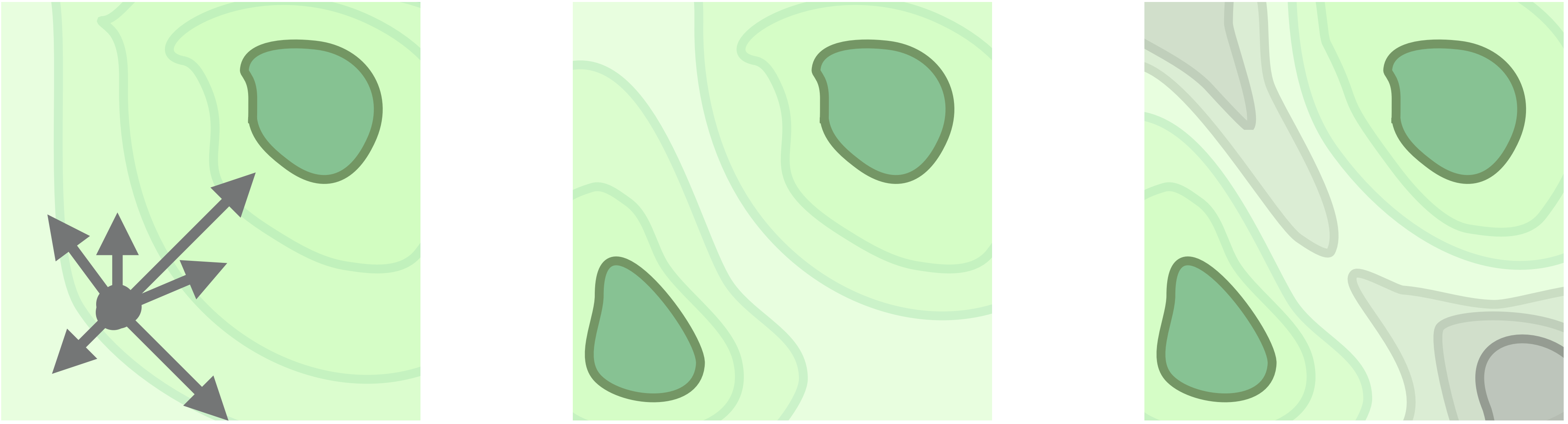
- ➤ relatively “unbiased" selection of mutations
- ➤ multi-allelic fitness landscape

3 QUESTIONS



3 QUESTIONS

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



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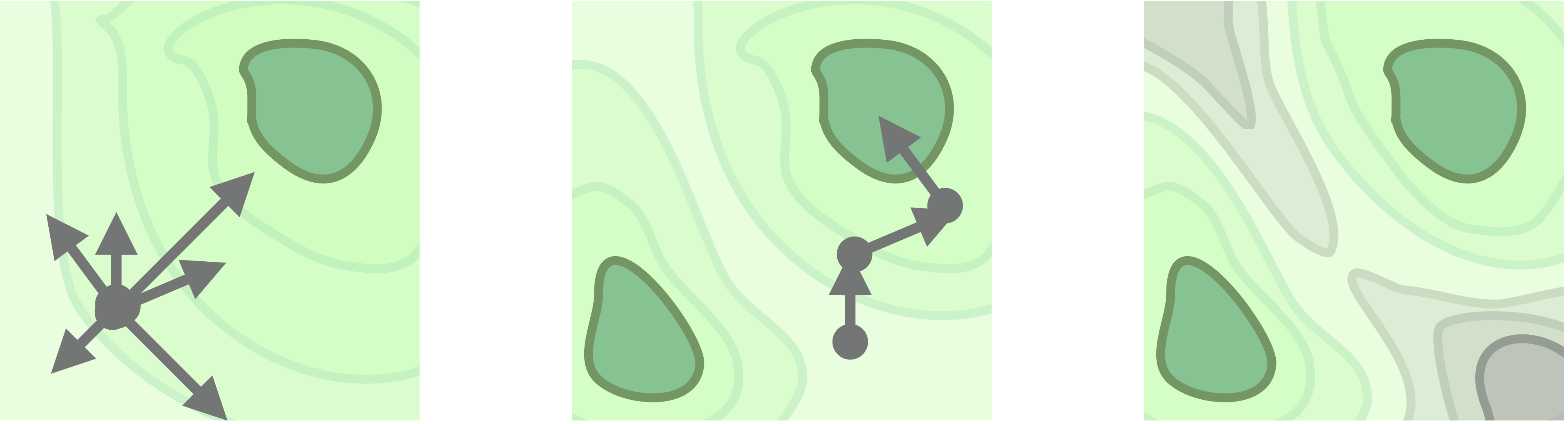

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- Do single step mutations predict the way to the global optimum?
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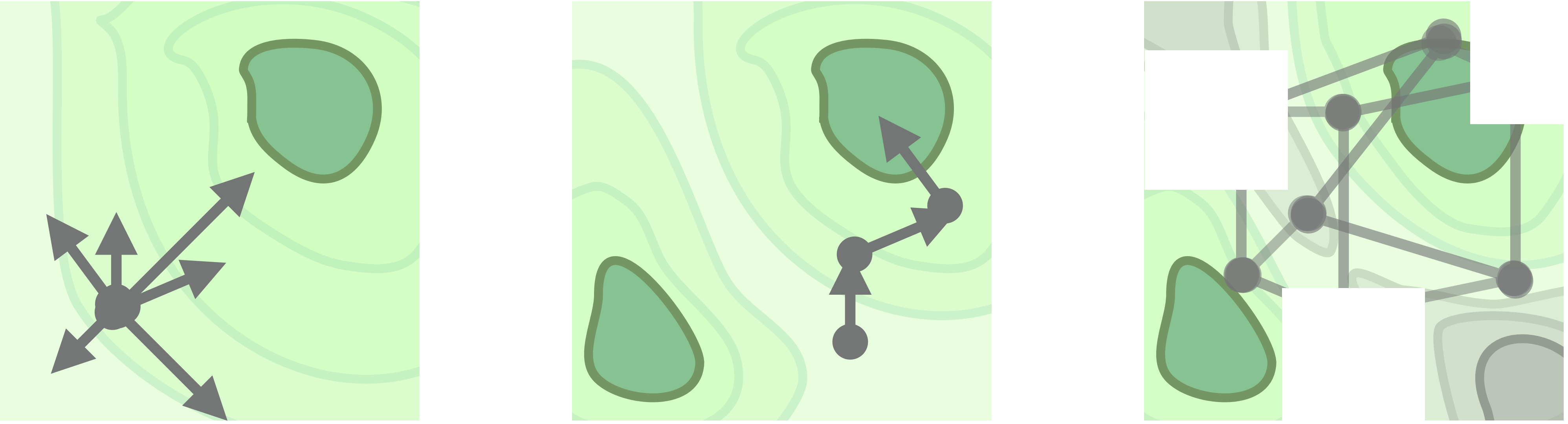
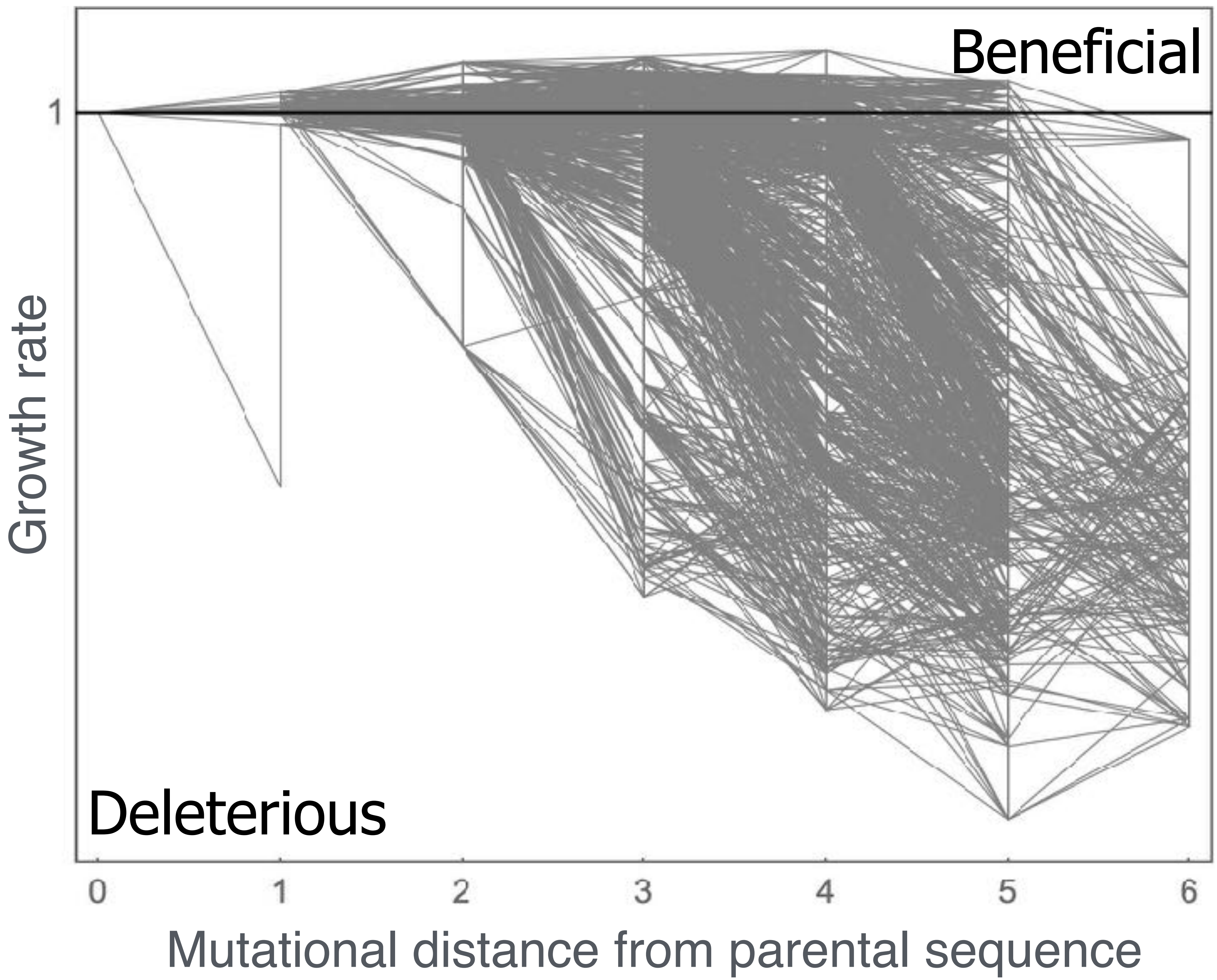


A PICTURE OF THE WHOLE LANDSCAPE



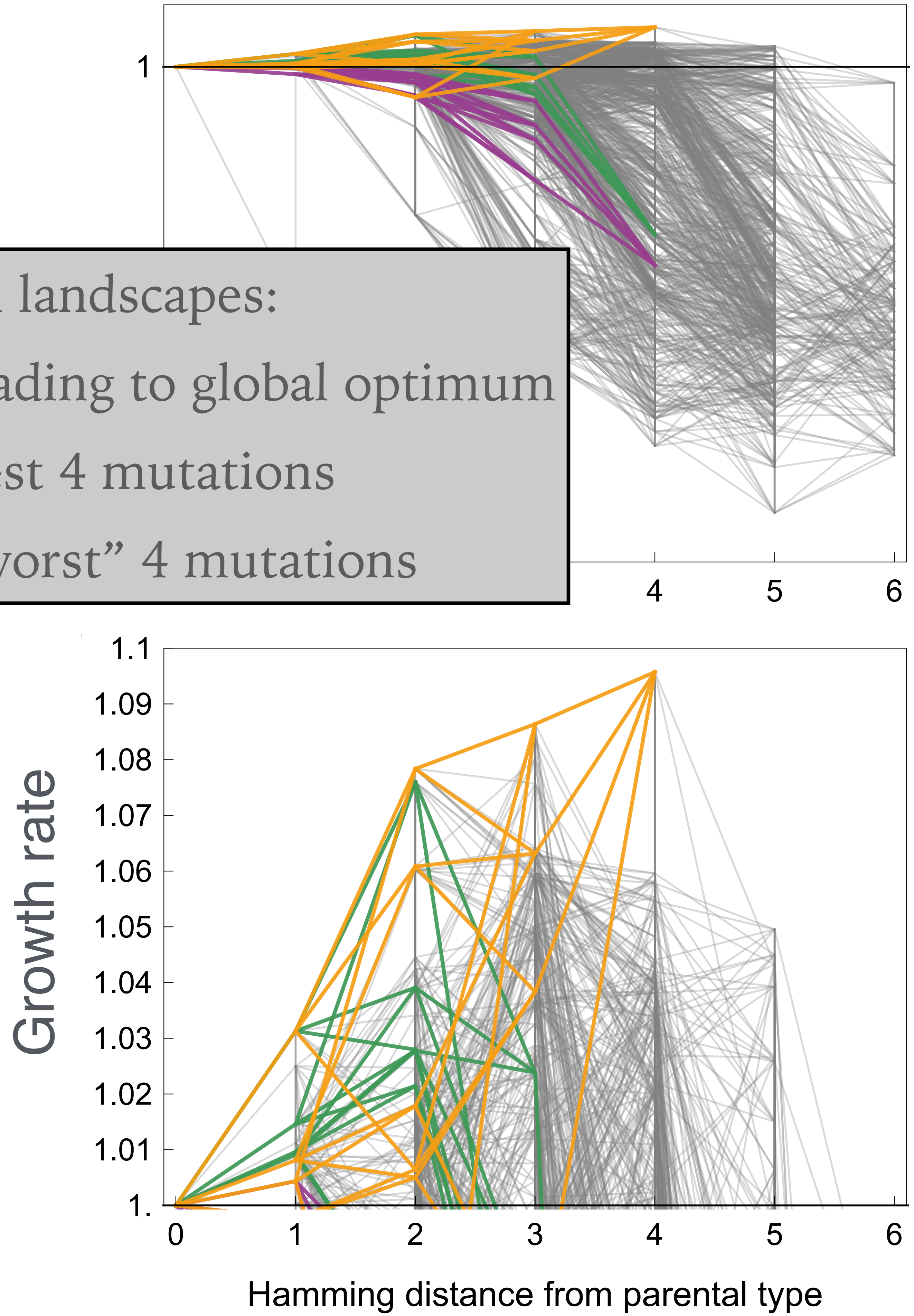
1 – DO SINGLE STEP MUTATIONS PREDICT THE WAY TO THE GLOBAL OPTIMUM?

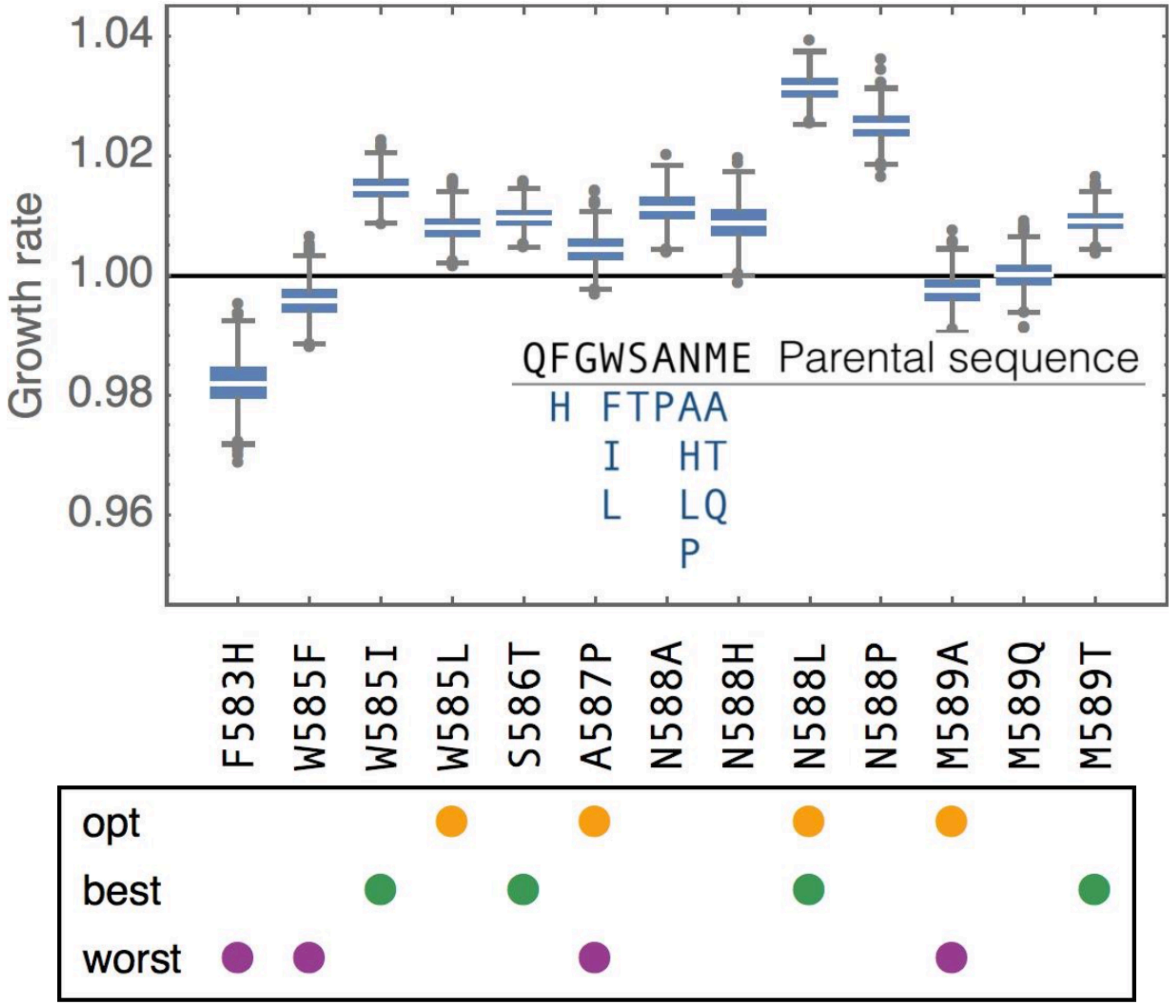
Focal landscapes:

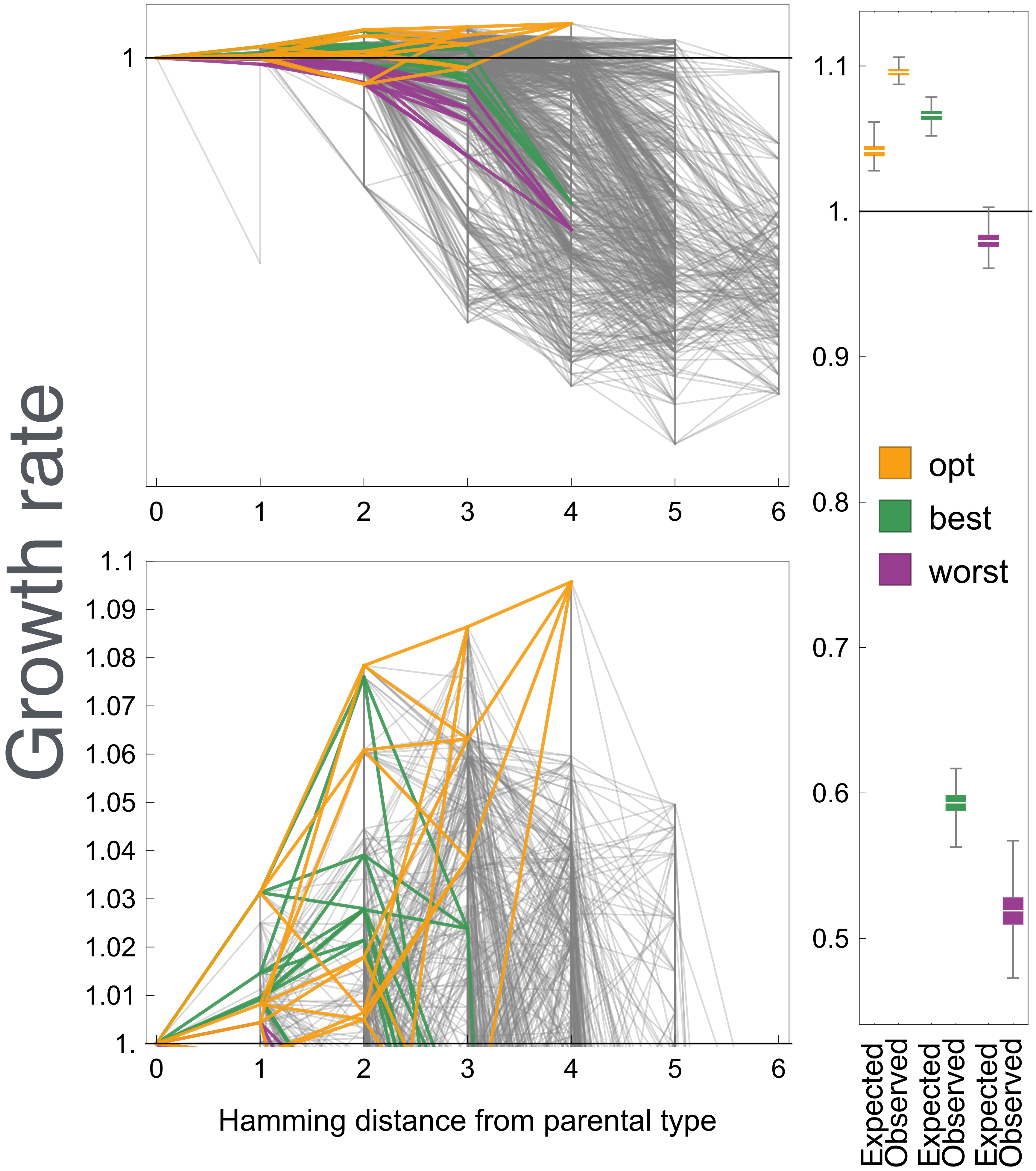
1) leading to global optimum

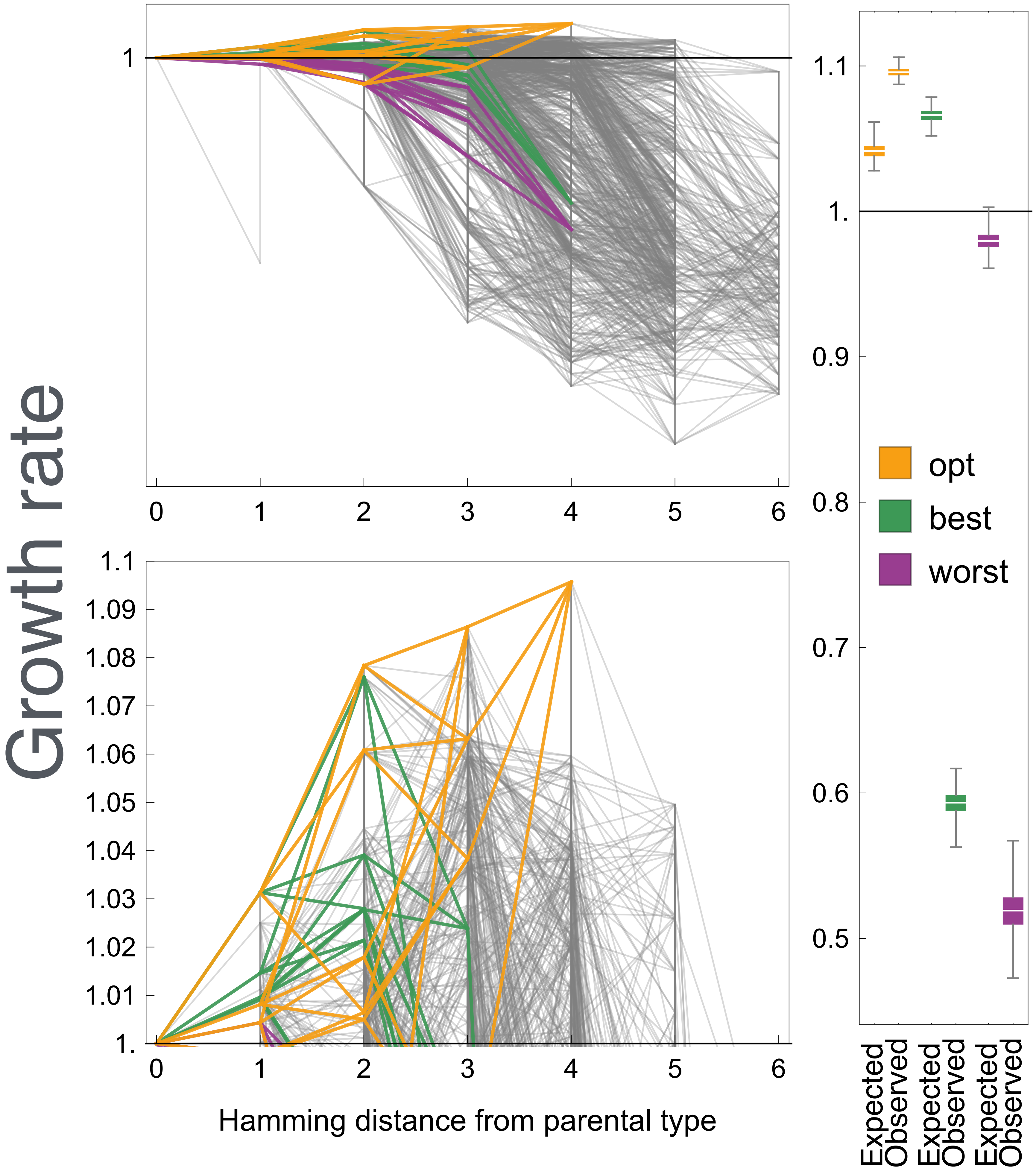
2) best 4 mutations

3) “worst” 4 mutations



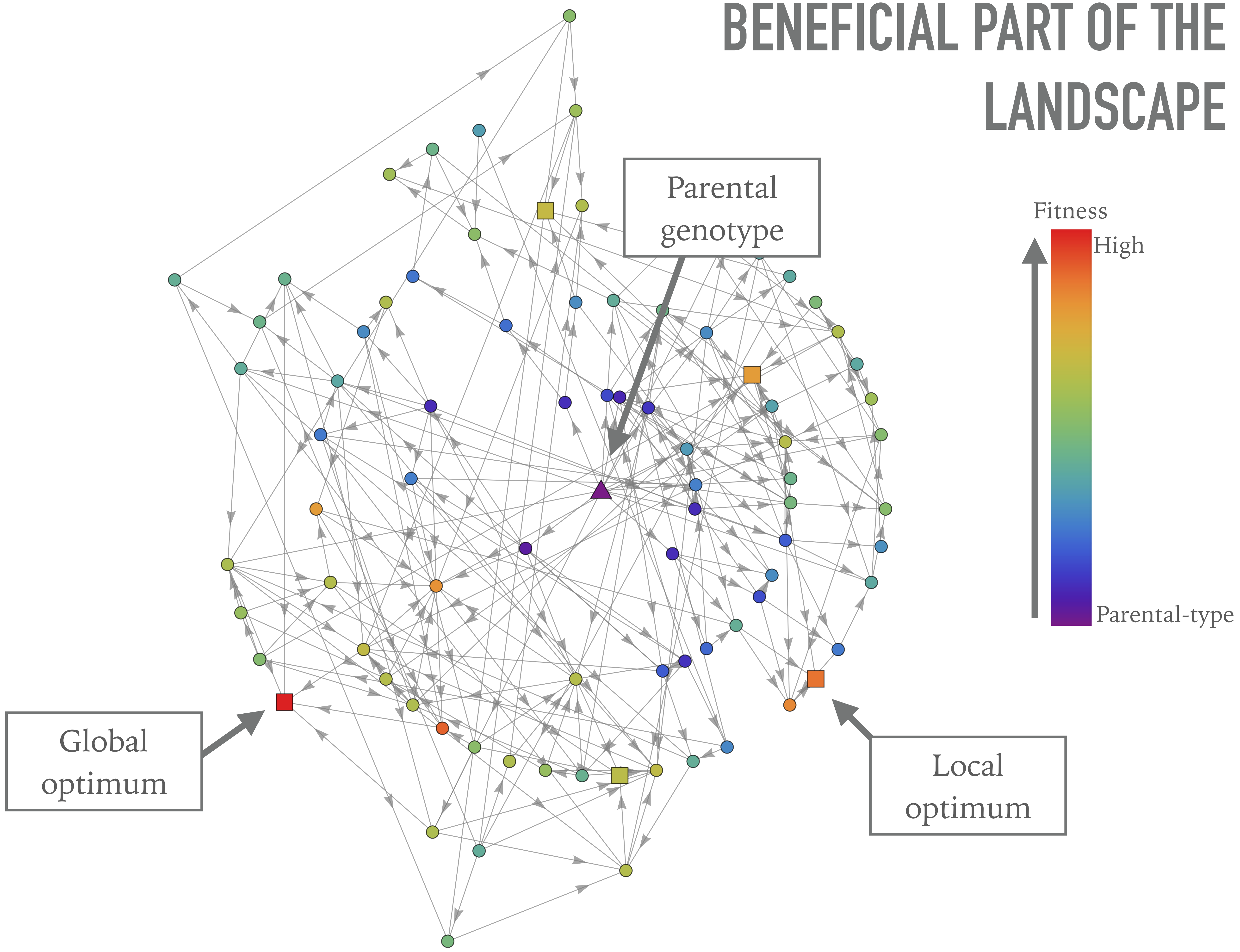



Growth rate
1
0
1
2
3
4
5
6
1.1
1.09
1.08
1.07
1.06
1.05
1.04
1.03
1.02
1.01
1.
0
1
2
3
4
5
6
Hamming distance from parental type
1.1
1.
0.9
0.8
0.7
0.6
0.5
opt
best
worst
Expected
Observed
Expected
Observed
Expected
Observed



Strong positive and negative epistasis in the landscape.

BENEFICIAL PART OF THE LANDSCAPE



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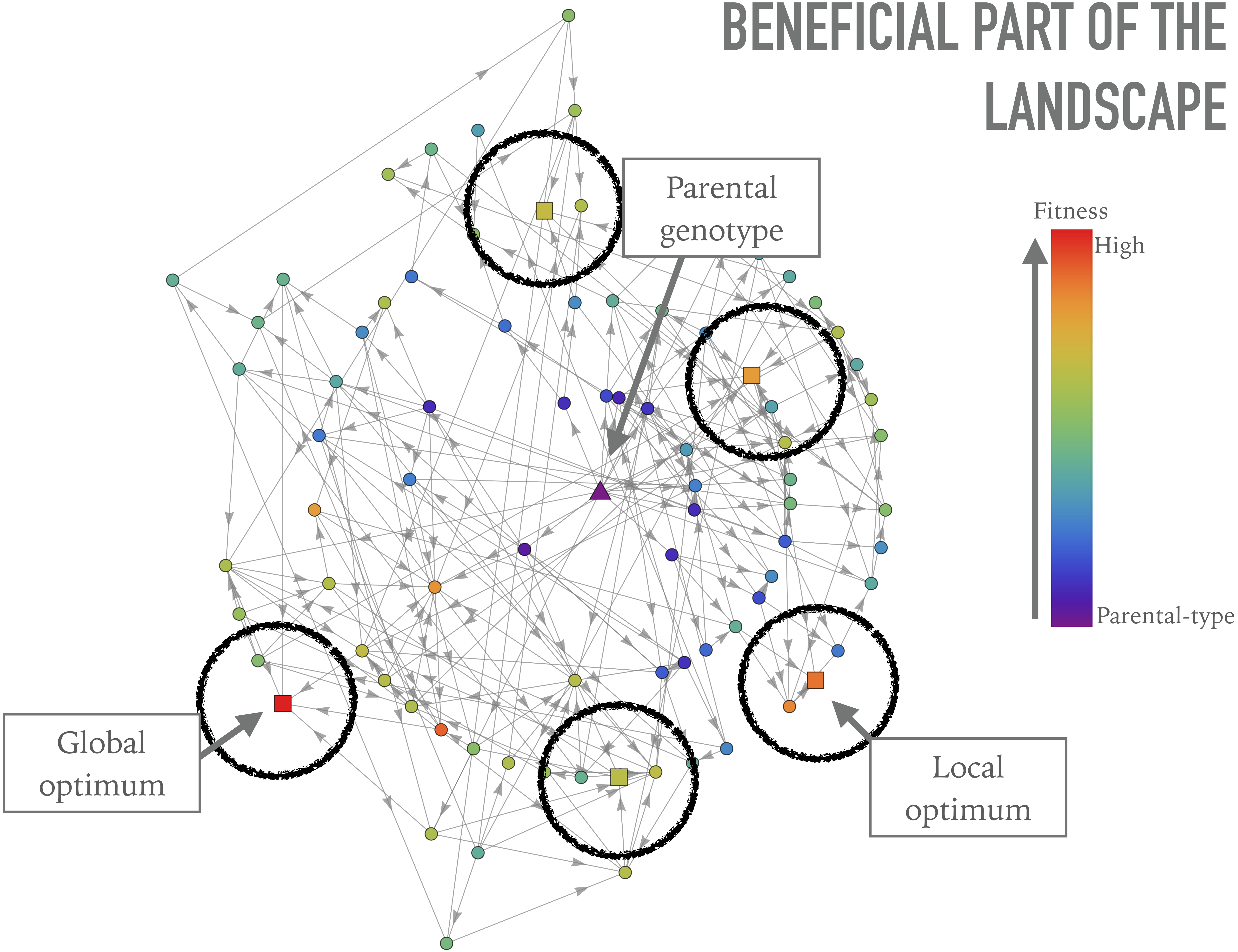
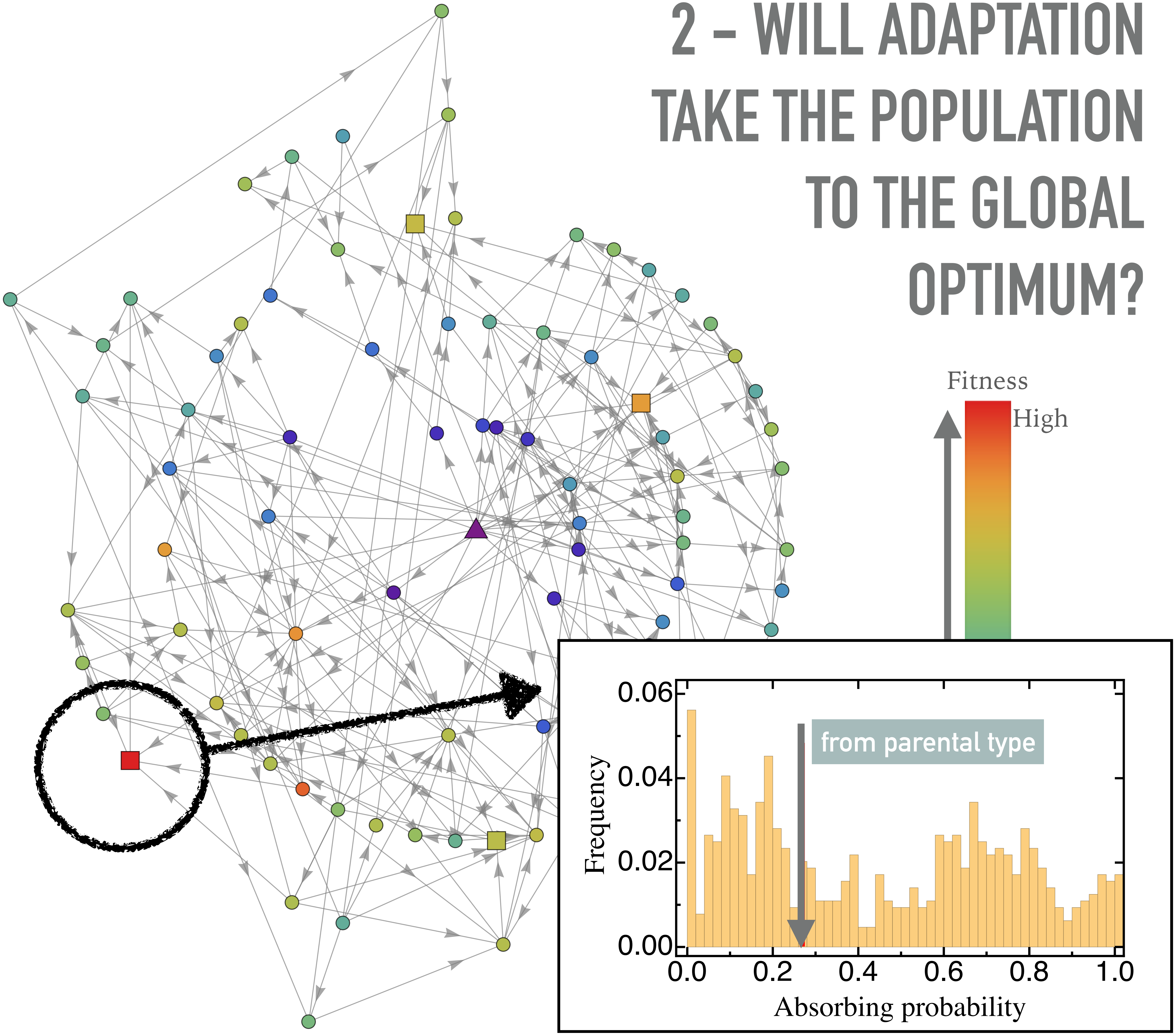


2 – WILL ADAPTATION TAKE THE POPULATION TO THE GLOBAL OPTIMUM?



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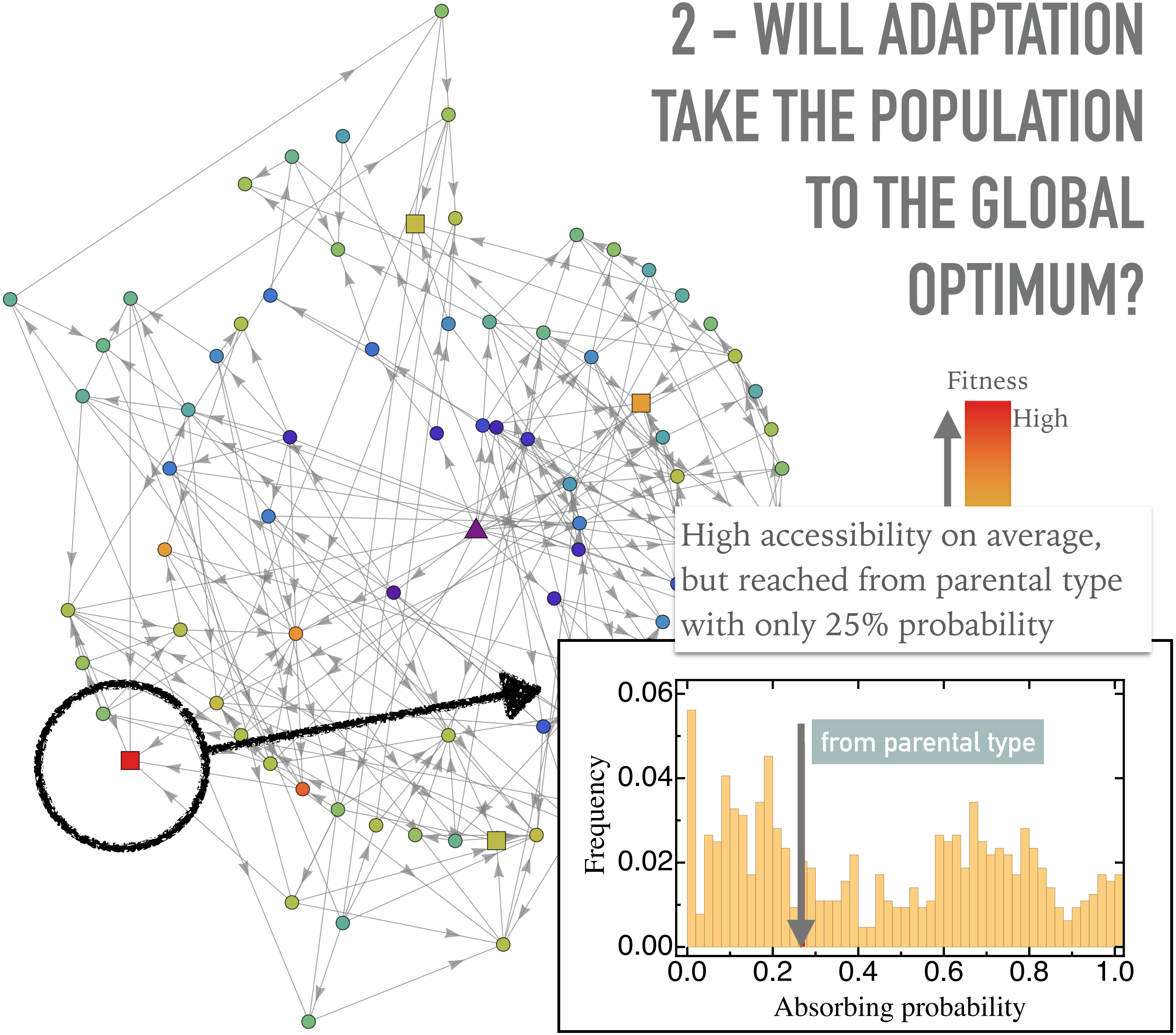

High accessibility on average, but reached from parental type with only 25% probability

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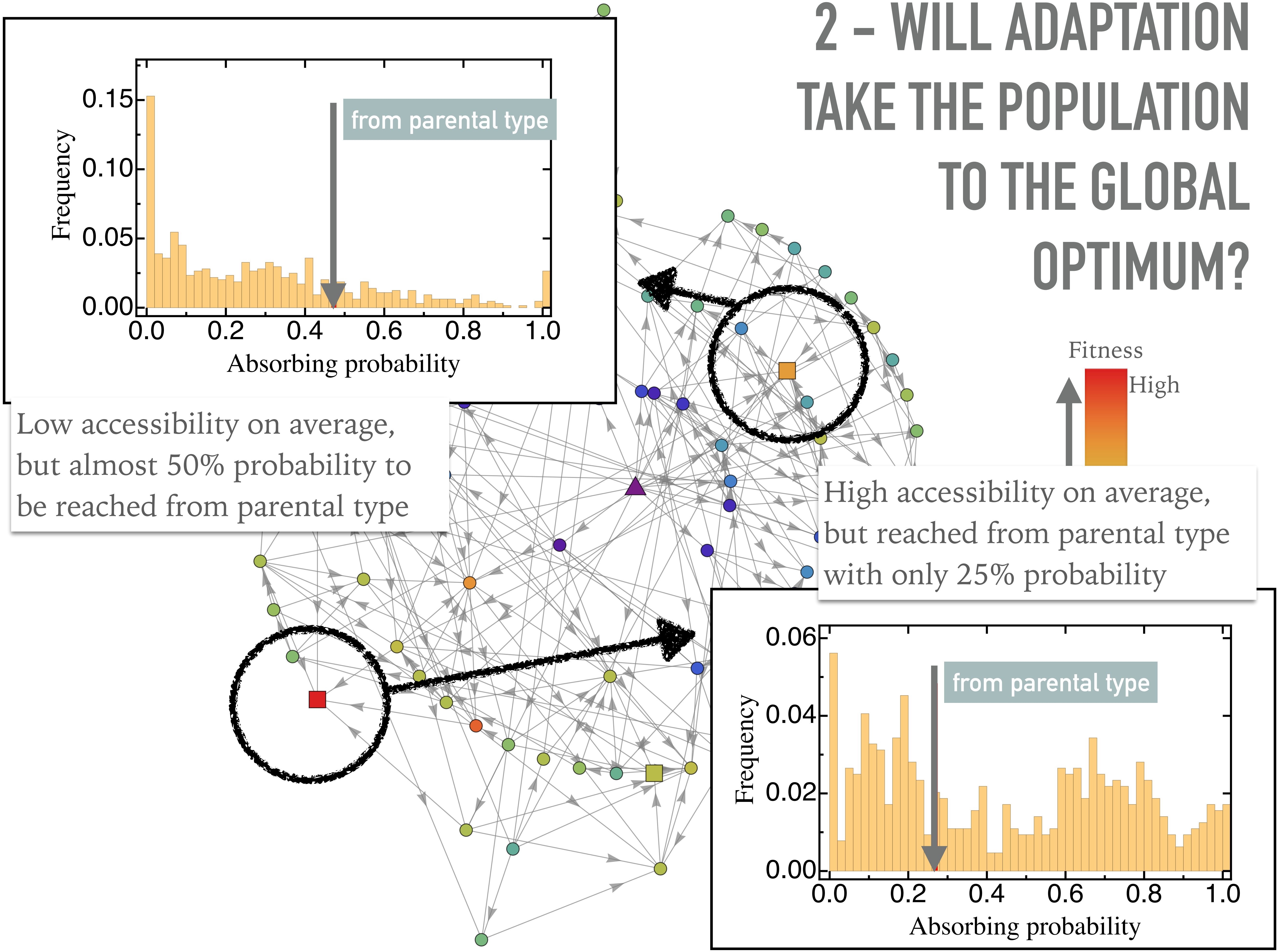

Low accessibility on average, but almost 50% probability to be reached from parental type

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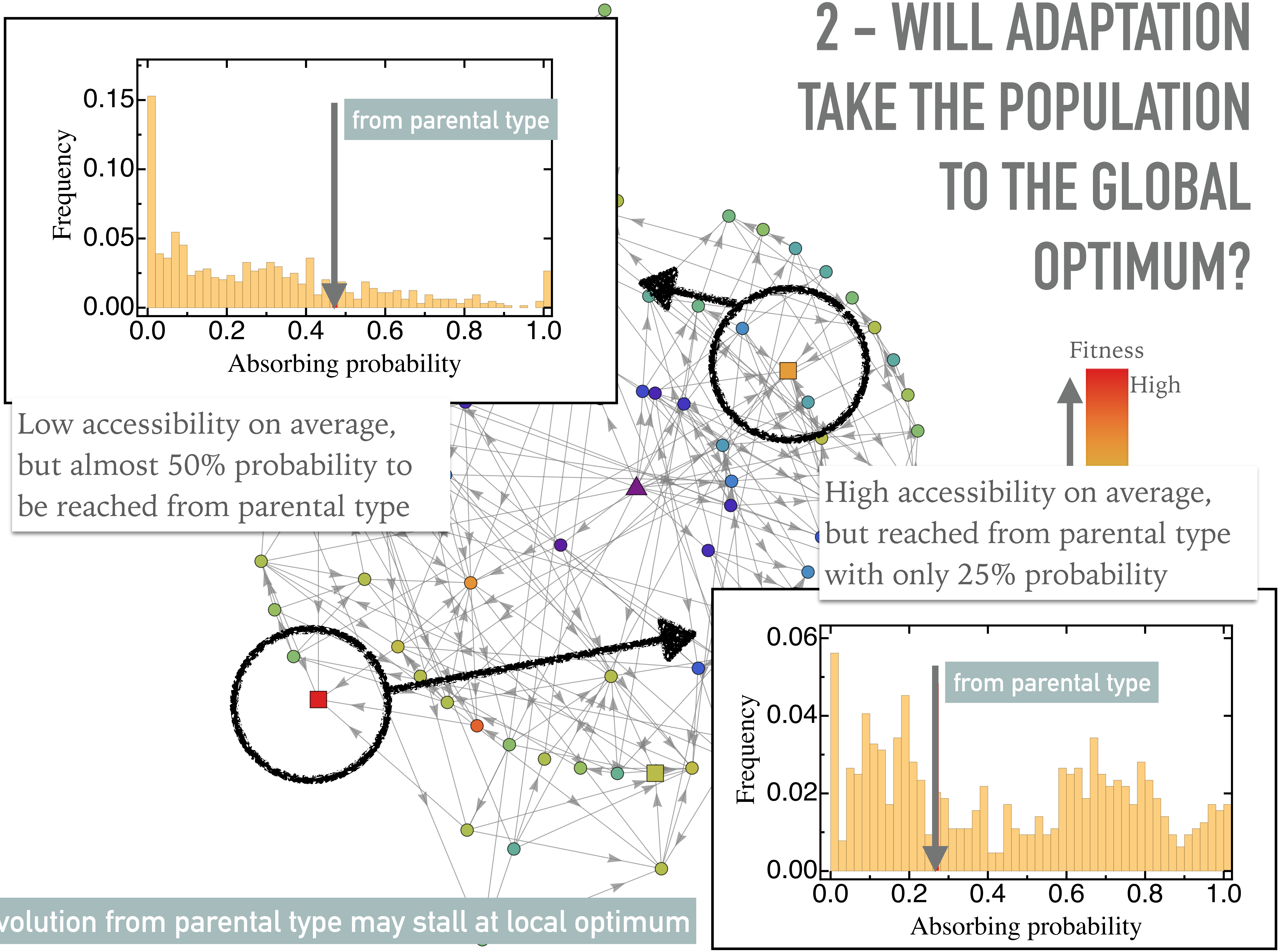

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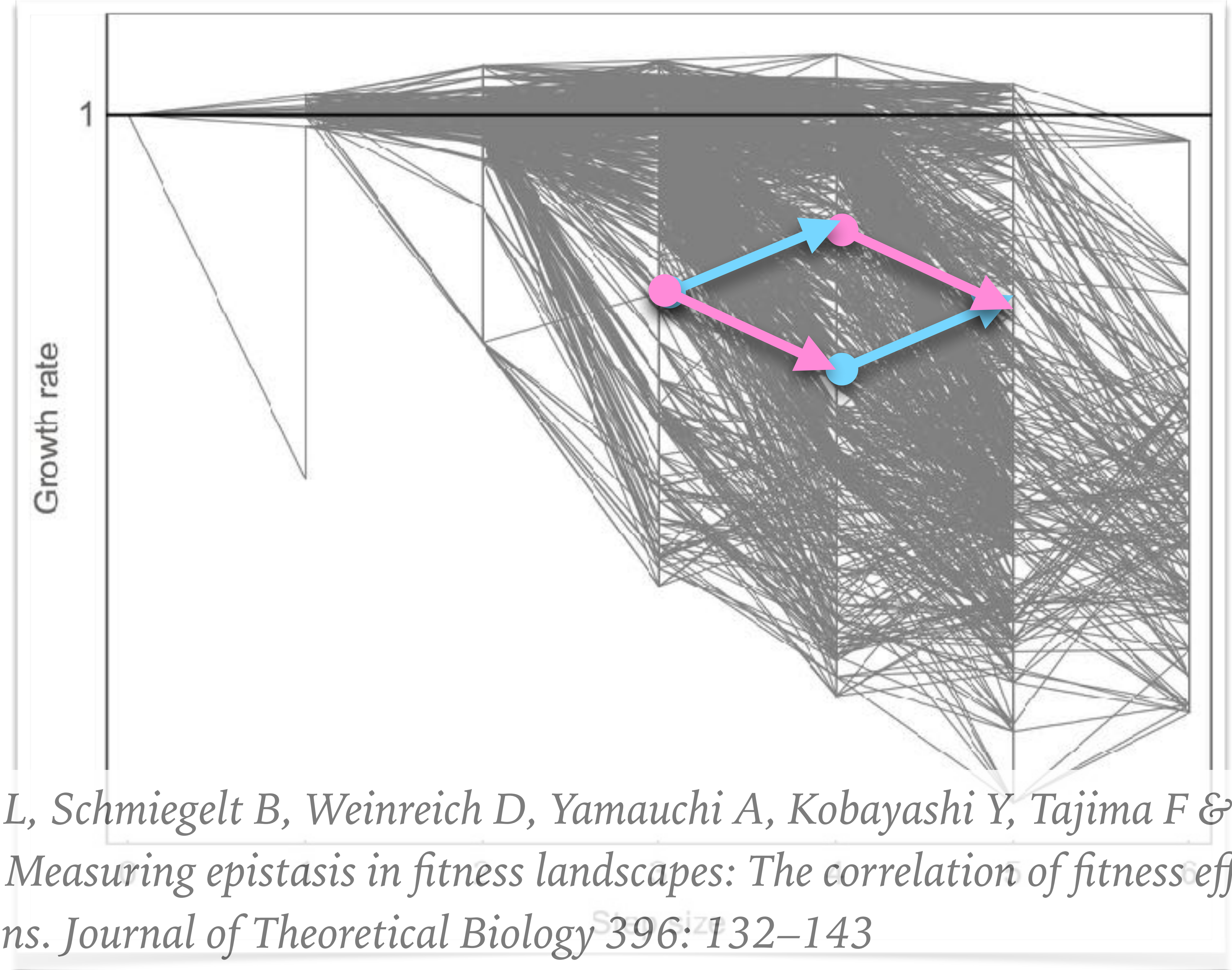
High accessibility on average, but reached from parental type with only 25% probability

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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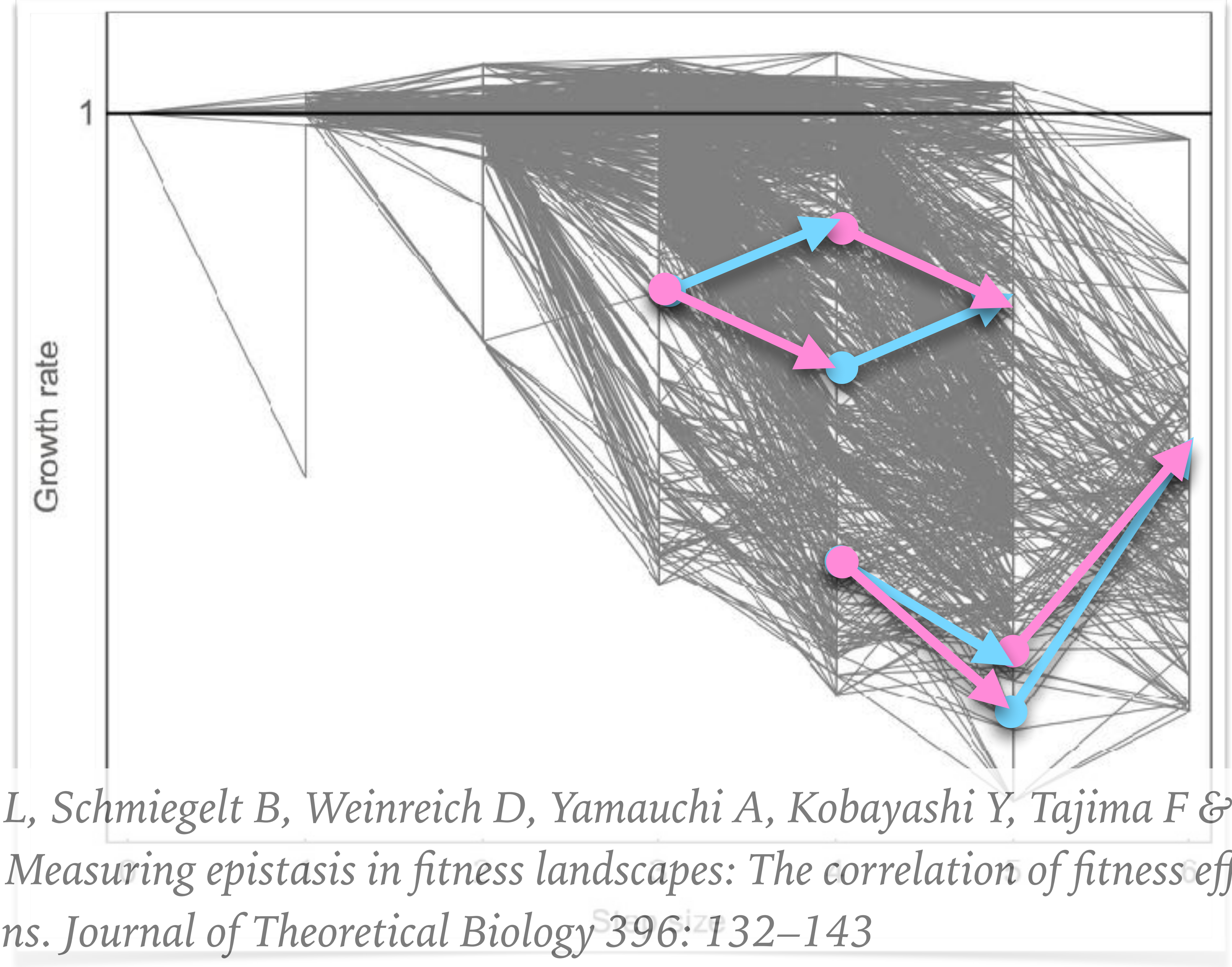

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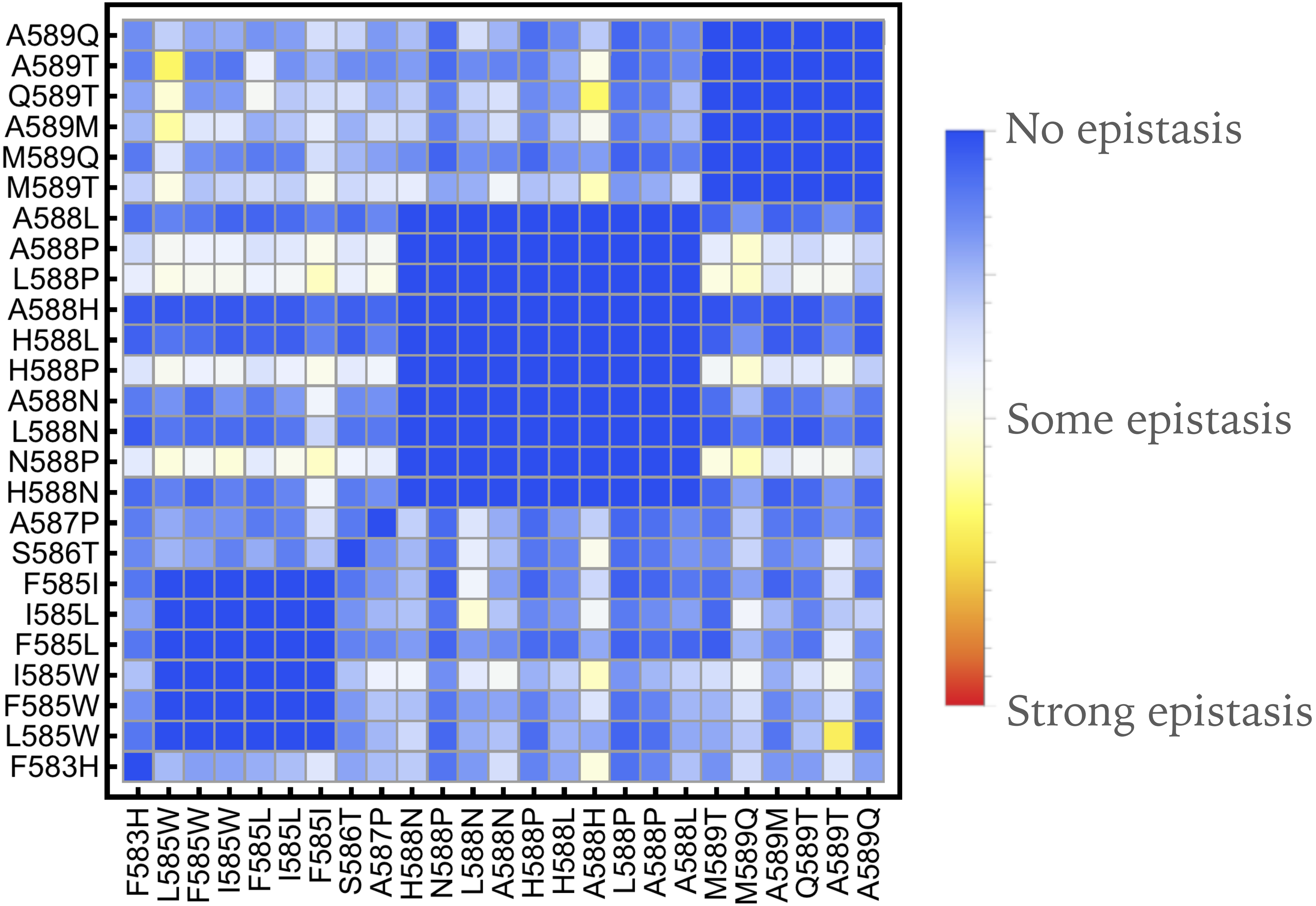
HOW CAN WE MEASURE FITNESS LANDSCAPES AND WHAT CAN WE LEARN FROM THIS EXERCISE?



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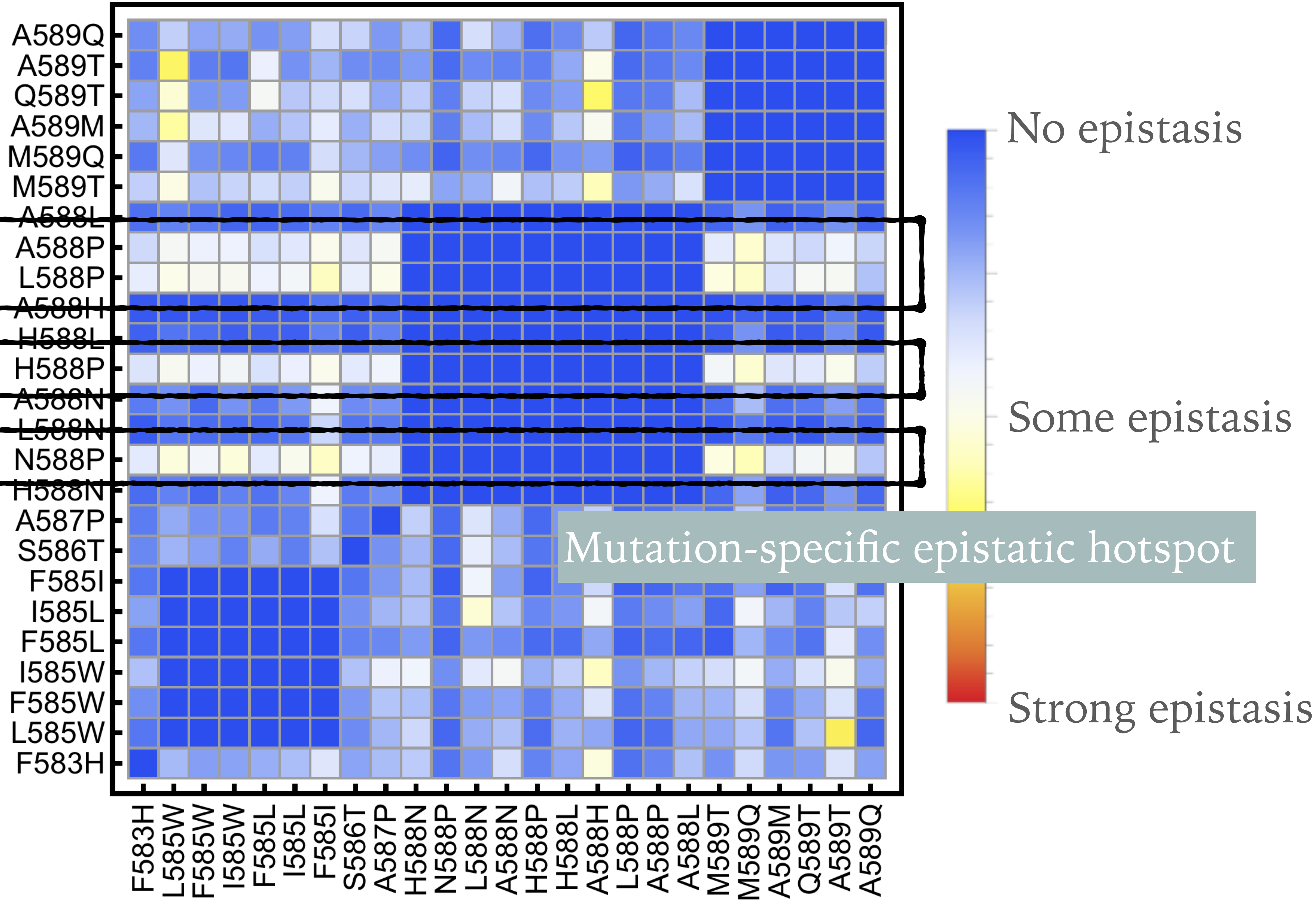
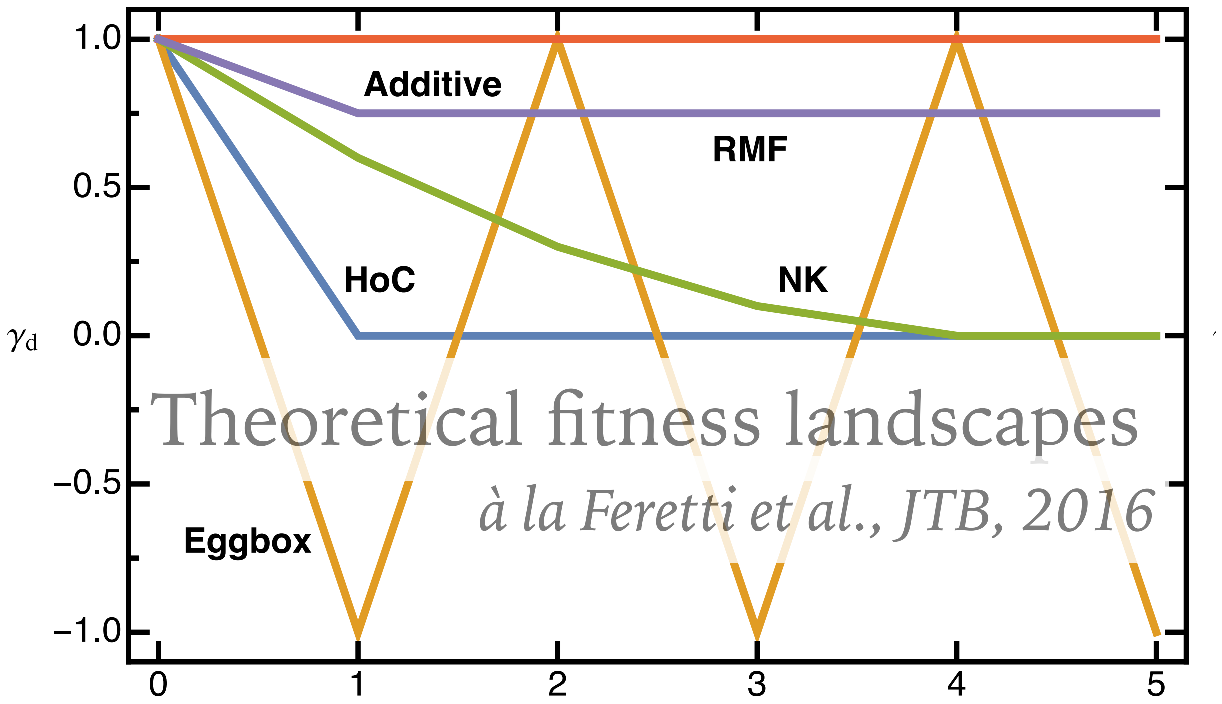


Mutation-specific epistatic hotspot

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



Theoretical fitness landscapes

à la Feretti et al., JTB, 2016

Epistasis measure gamma$_d$ with increasing Hamming distance d

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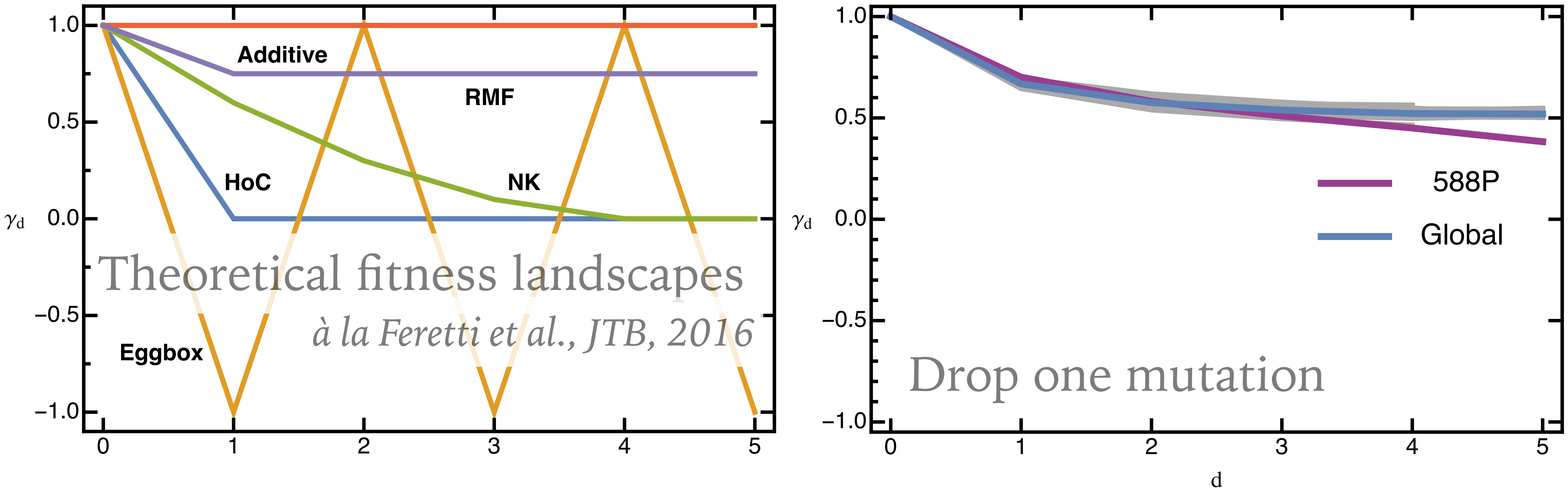
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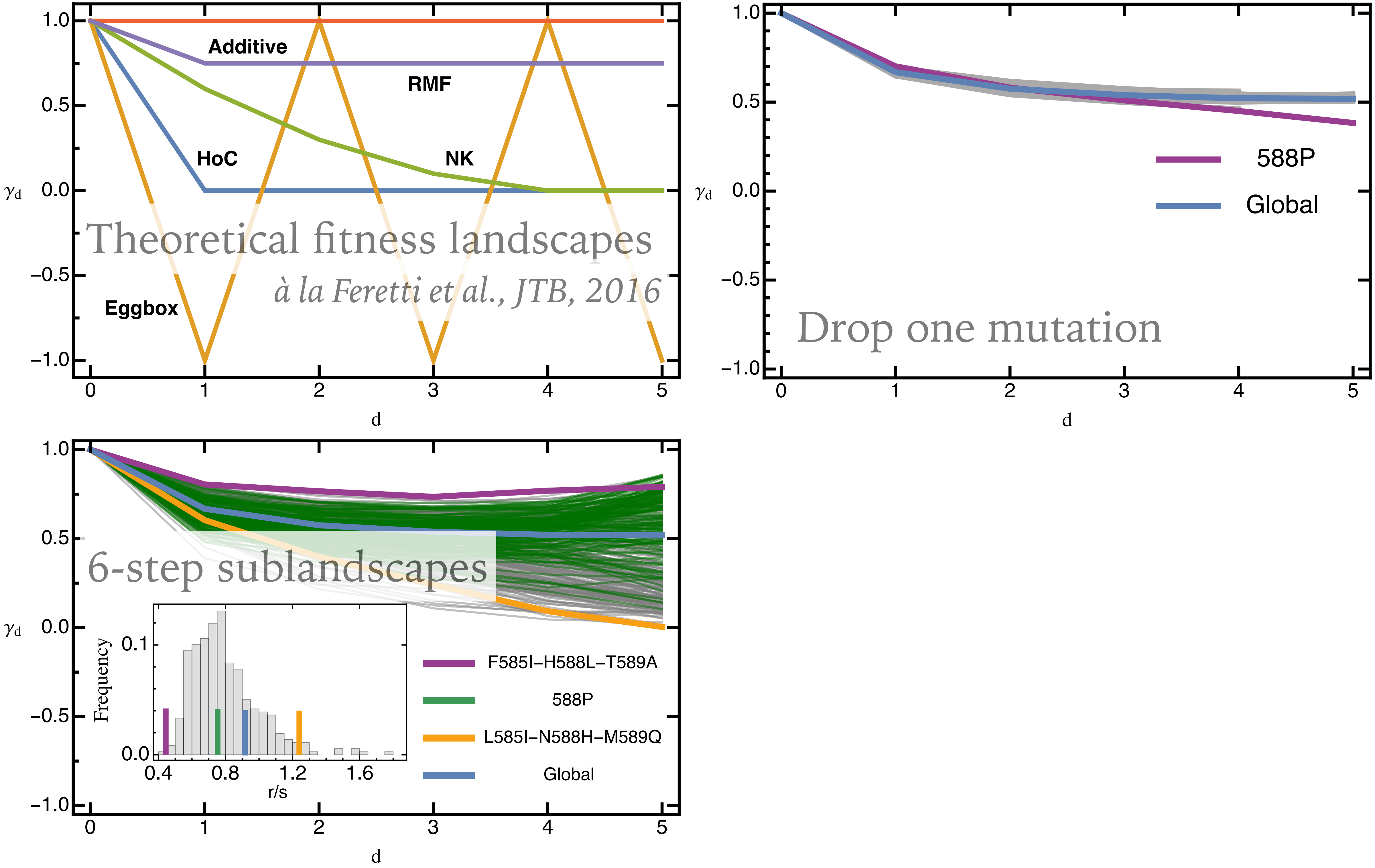

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Drop one mutation

6-step sublandscapes

Epistasis measure gamma$_d$ with increasing Hamming distance d

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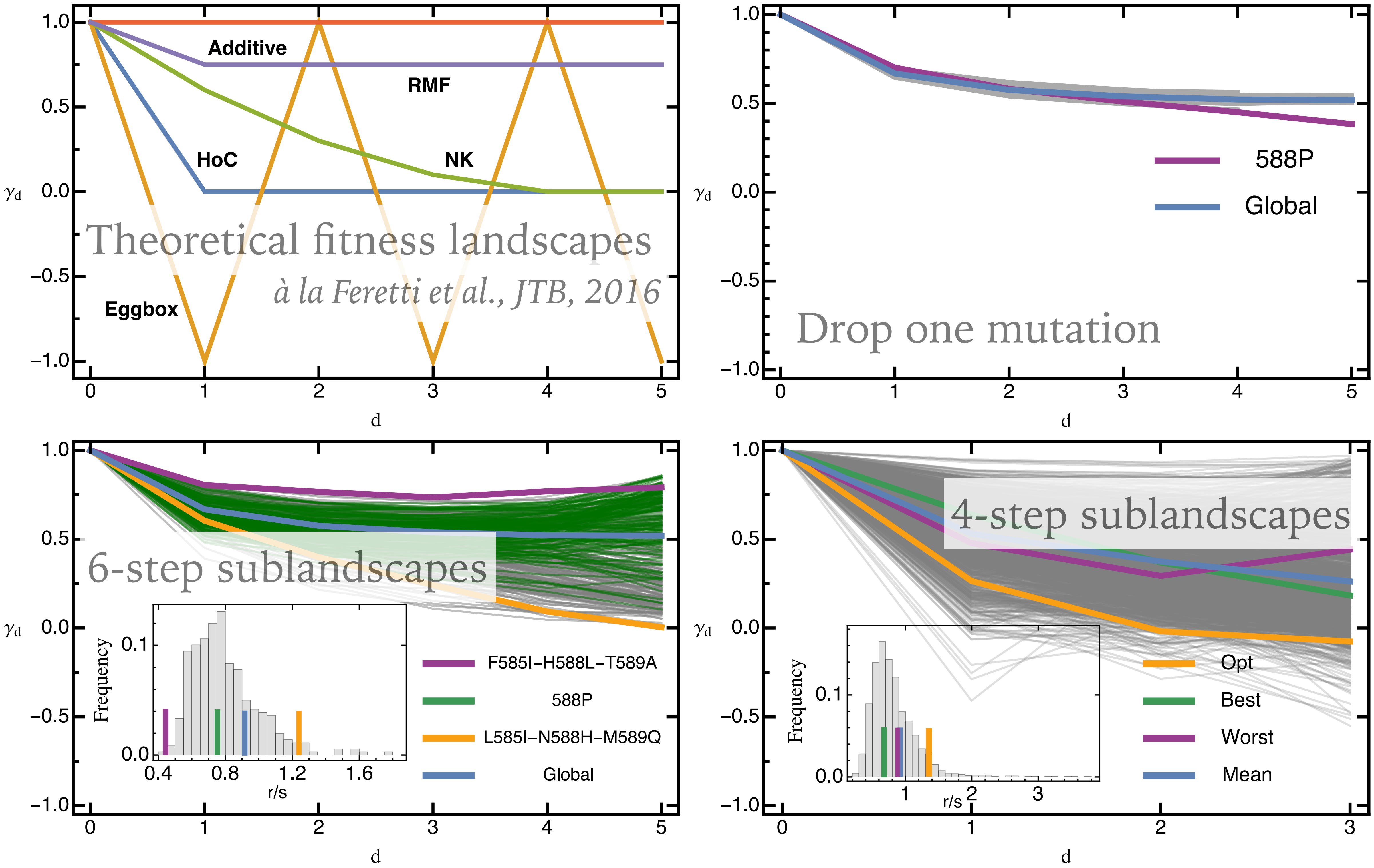


Theoretical fitness landscapes

à la Feretti et al., JTB, 2016

Drop one mutation

6-step sublandscapes

4-step sublandscapes

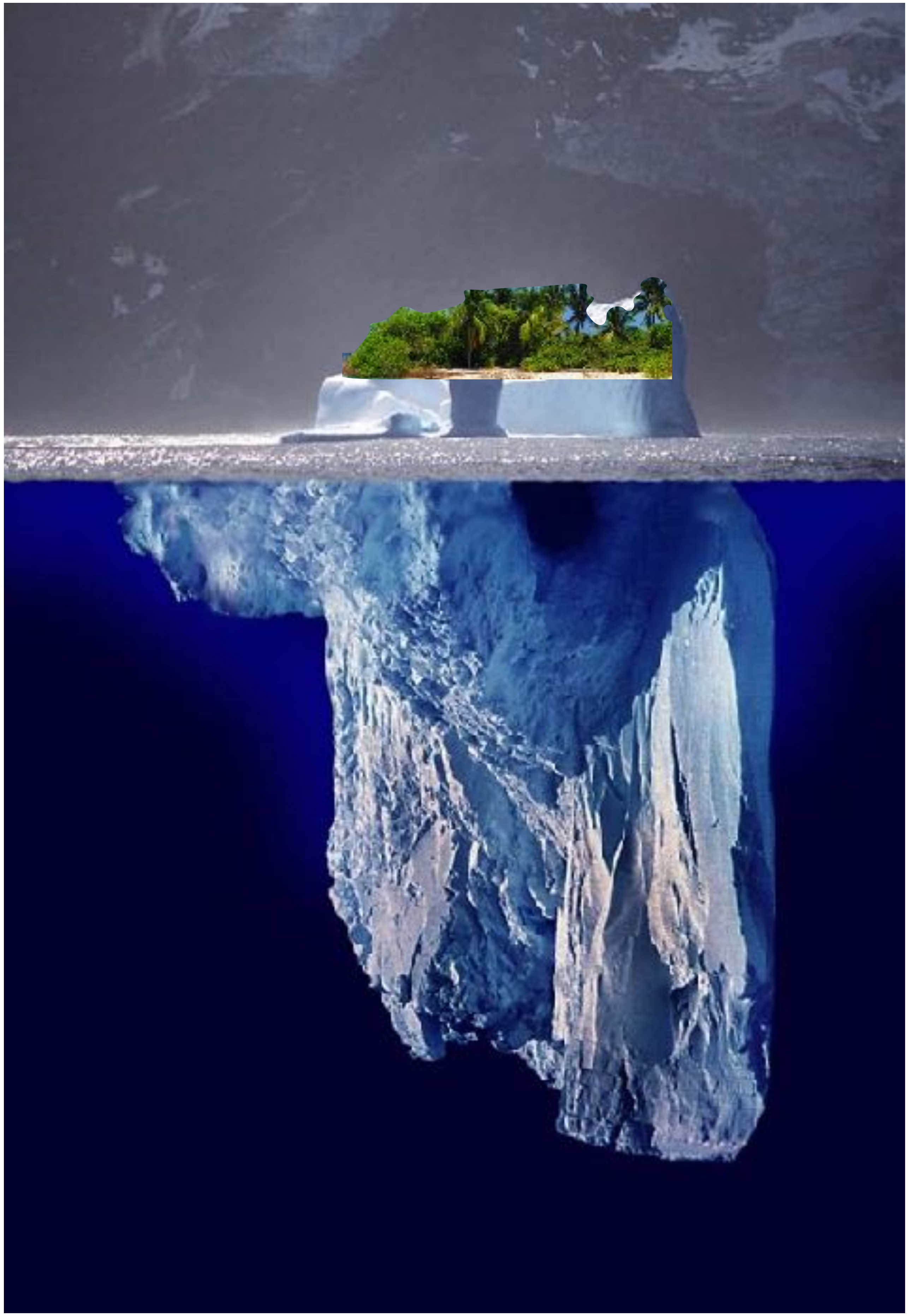
Epistasis measure gamma$_d$ with increasing Hamming distance d

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.



SUMMARY/CONCLUSION

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

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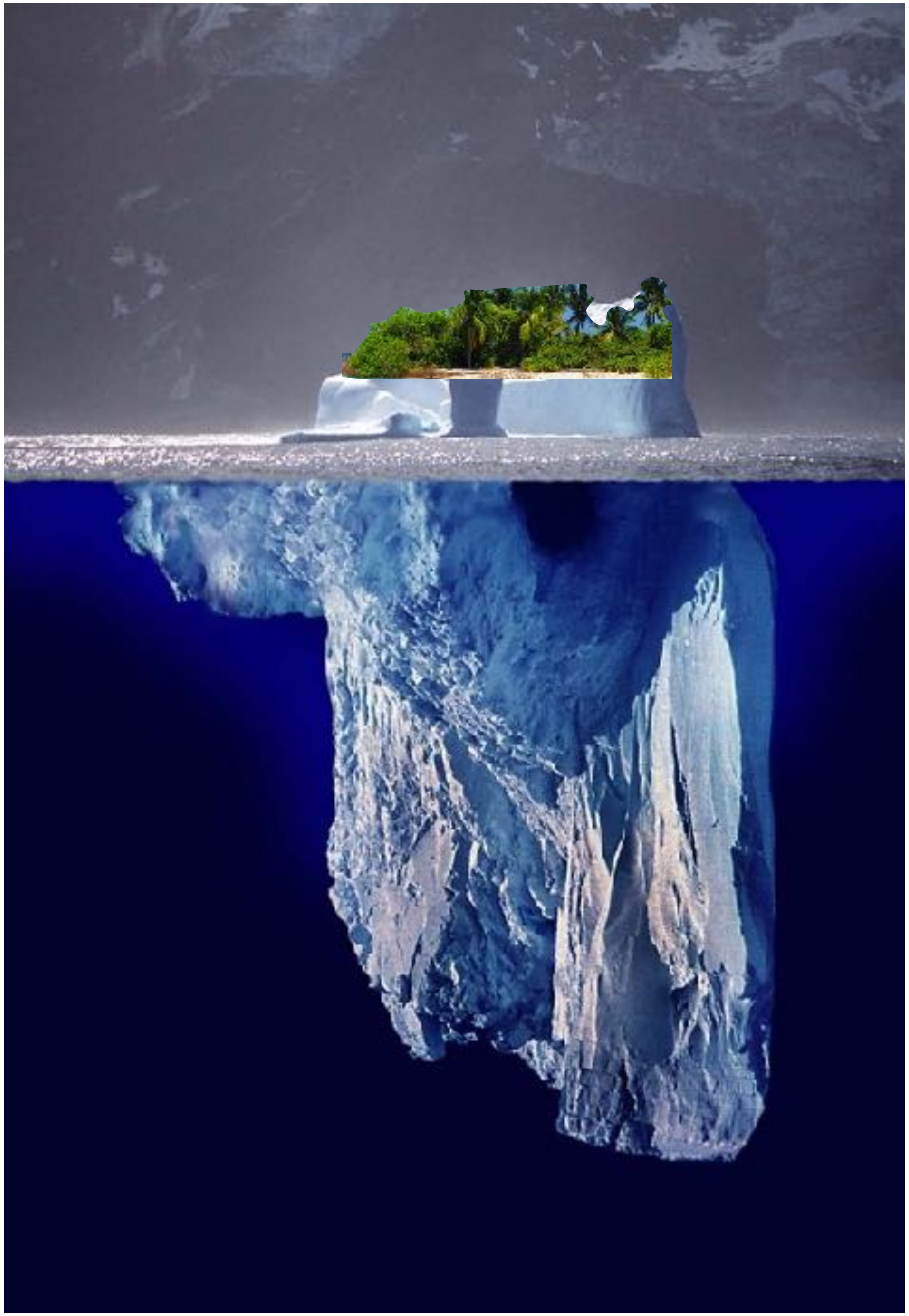
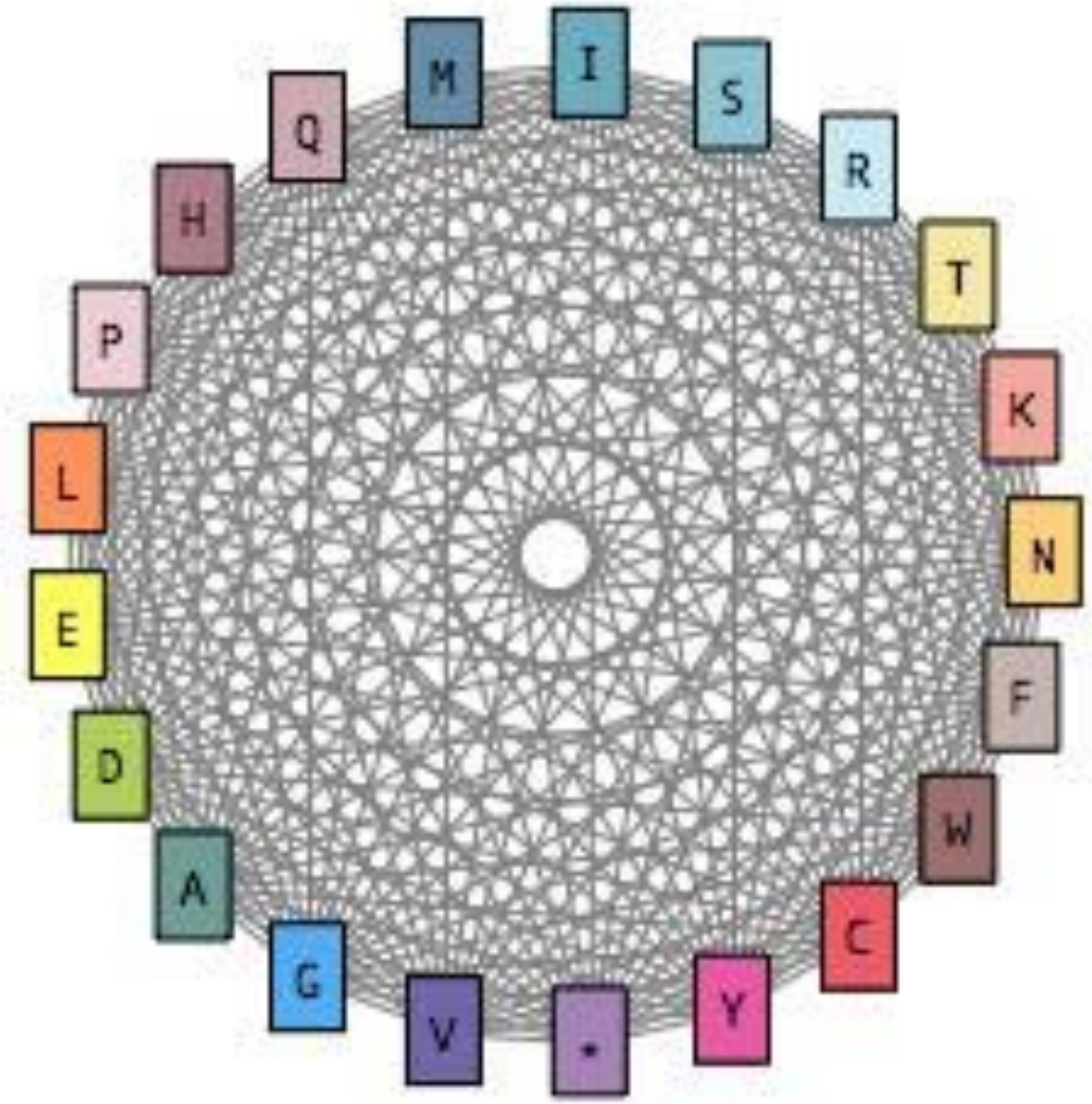
So far, limited predictive potential, but lots of ideas for the future…



FUTURE ENDEAVORS

- identify/develop informative measures and (mechanistic) models to characterize empirical fitness landscapes
- understand how fitness landscapes change across environments and genetic backgrounds
- study the role of epistasis and fitness landscapes across levels of organization and time scales

THE FITNESS LANDSCAPE OF SYNONYMOUS MUTATIONS



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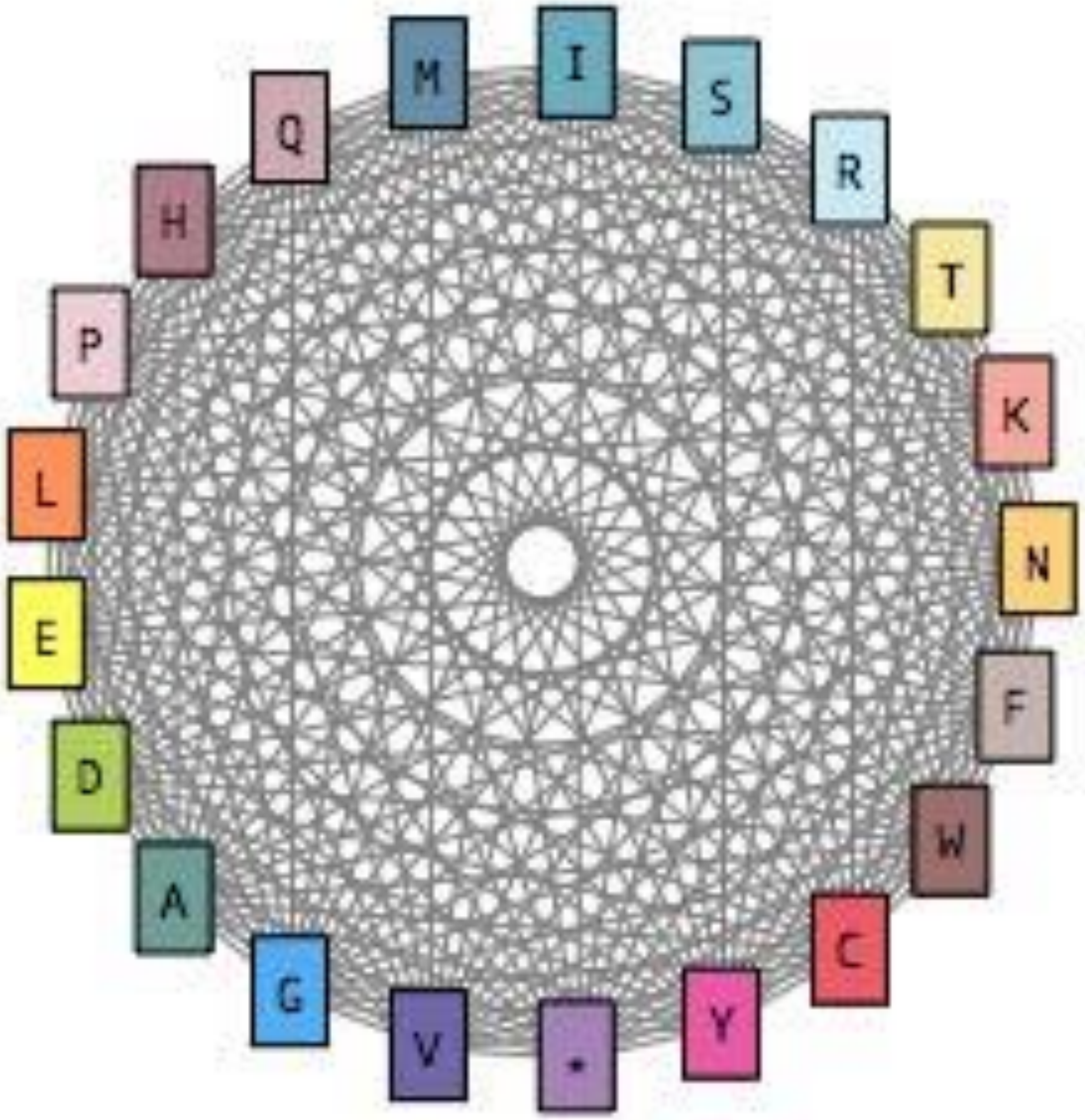

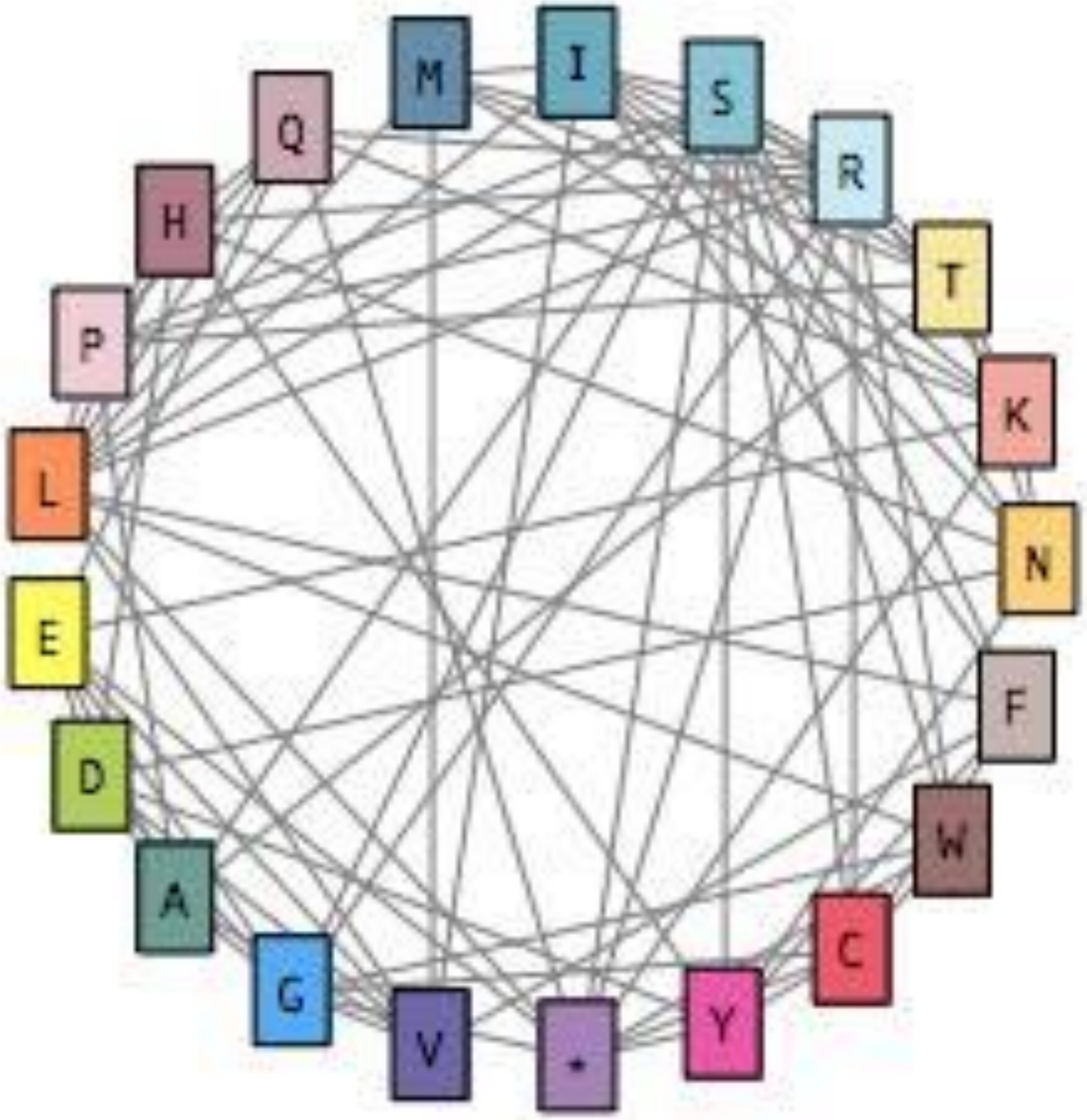

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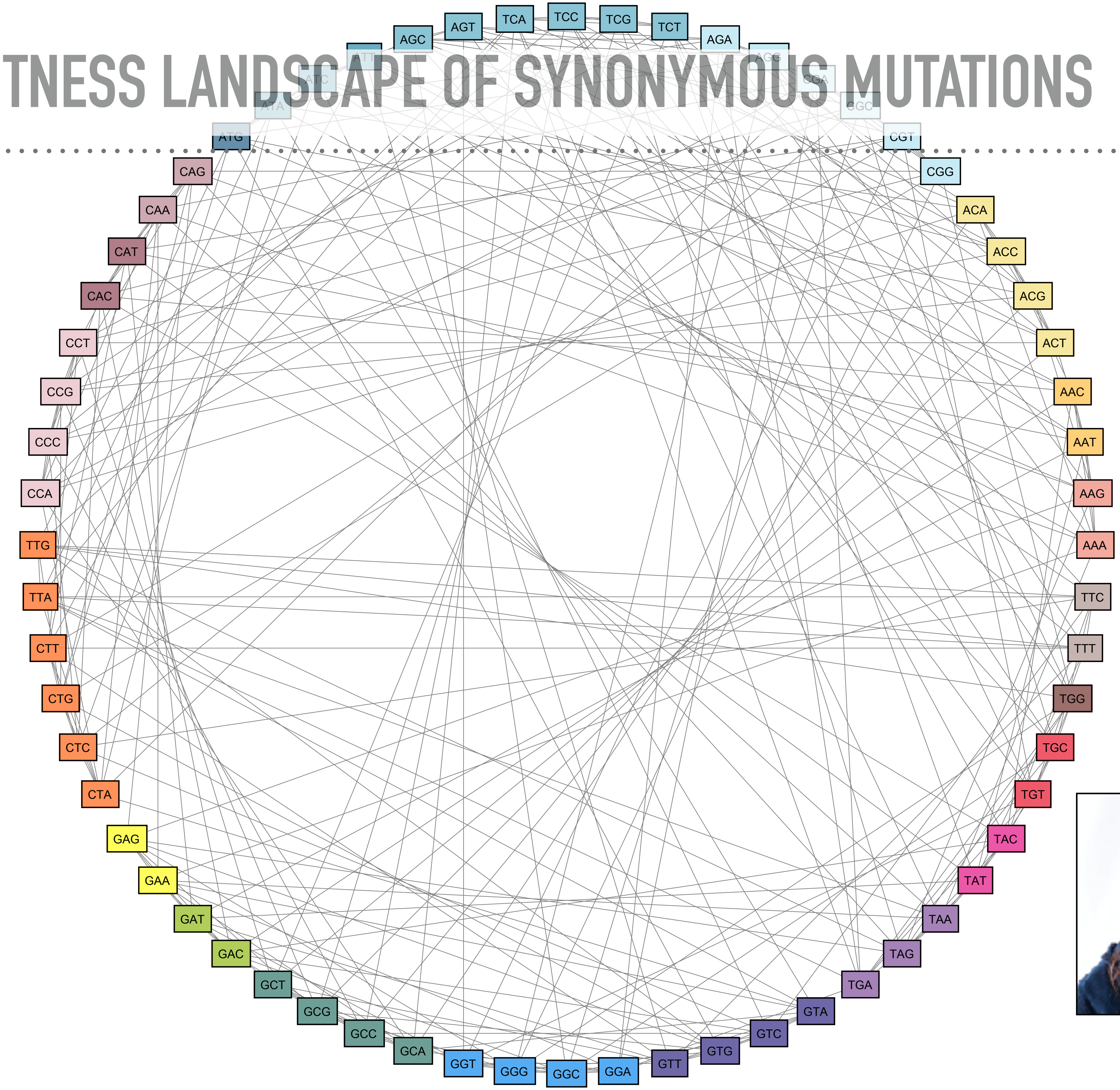
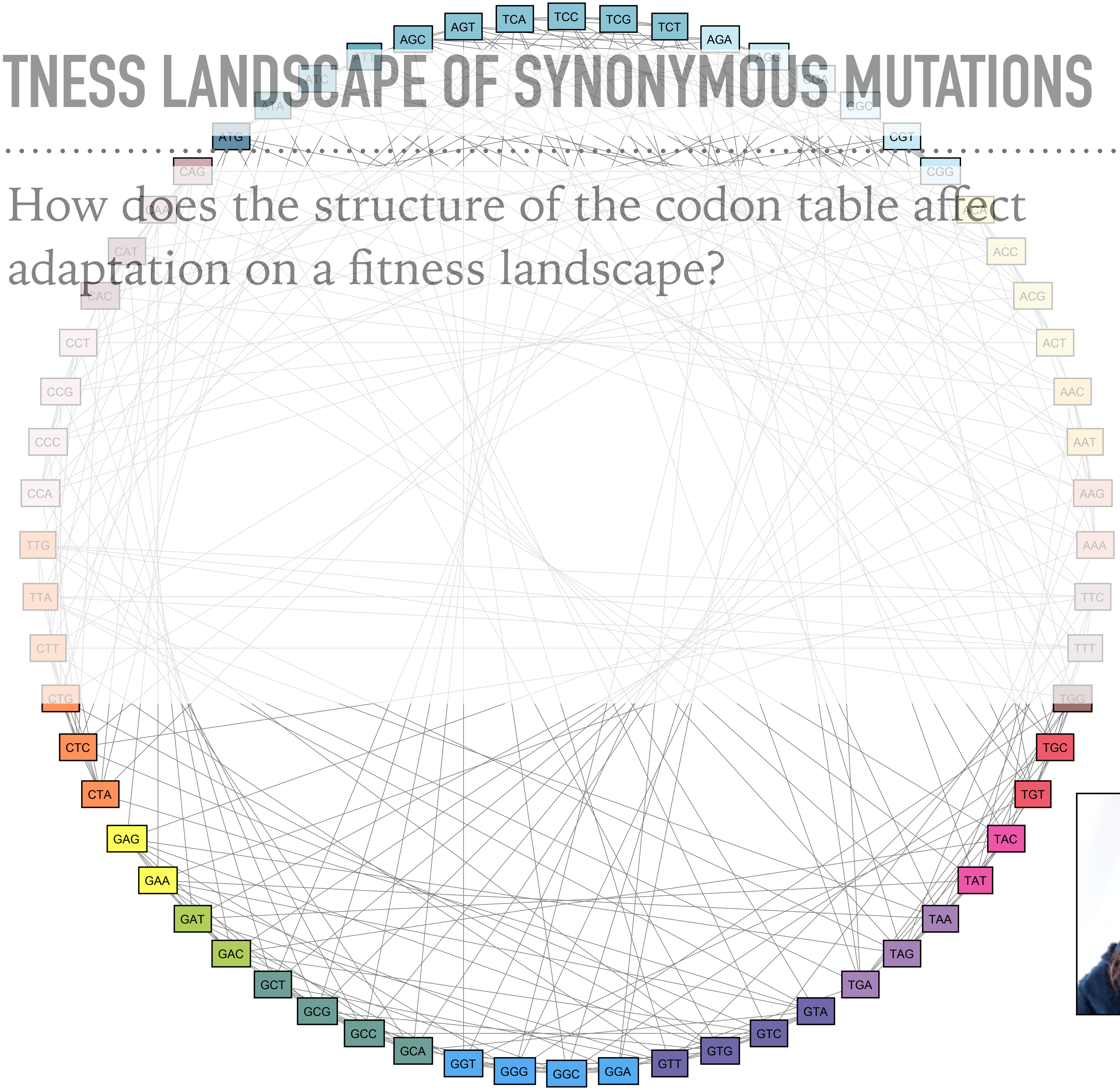


Inês Fragata

THE FITNESS LANDSCAPE OF SYNONYMOUS MUTATIONS

- How does the structure of the codon table affect adaptation on a fitness landscape?



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THE FITNESS LANDSCAPE OF SYNONYMOUS MUTATIONS

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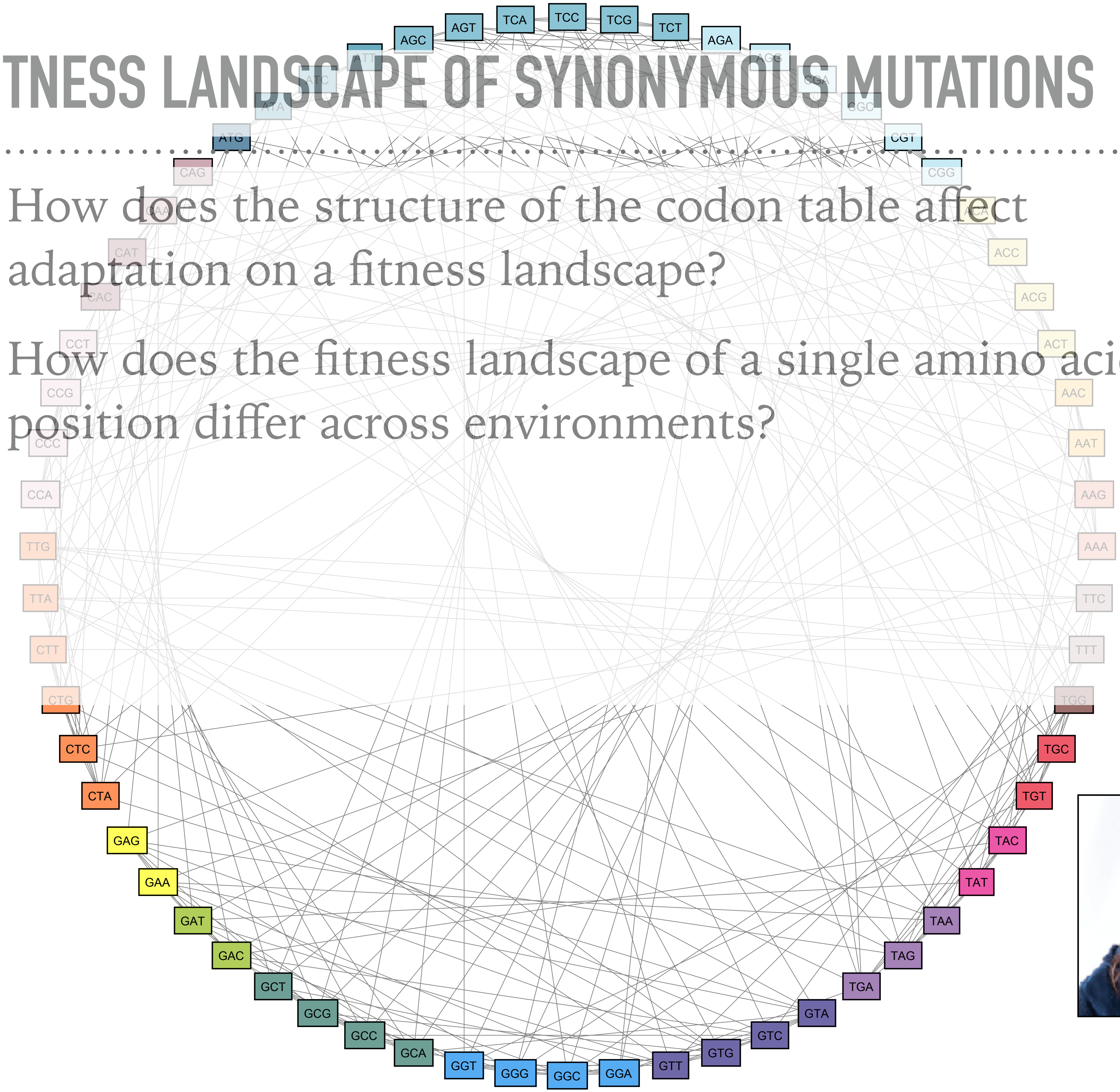
- How does the fitness landscape of a single amino acid position differ across environments?



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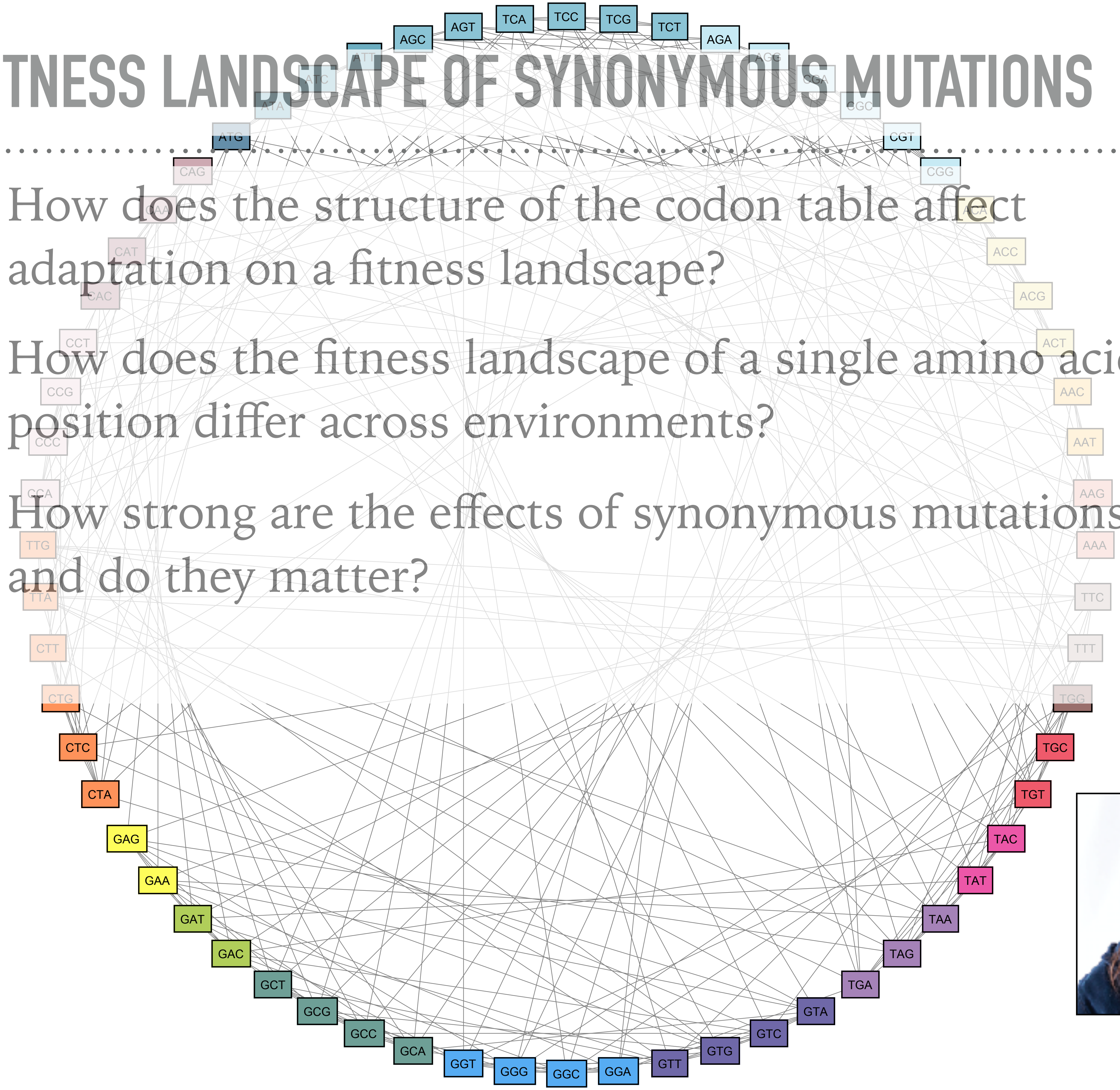

- How does the structure of the codon table affect adaptation on a fitness landscape?
- How does the fitness landscape of a single amino acid position differ across environments?
- How strong are the effects of synonymous mutations, and do they matter?

Inês Fragata

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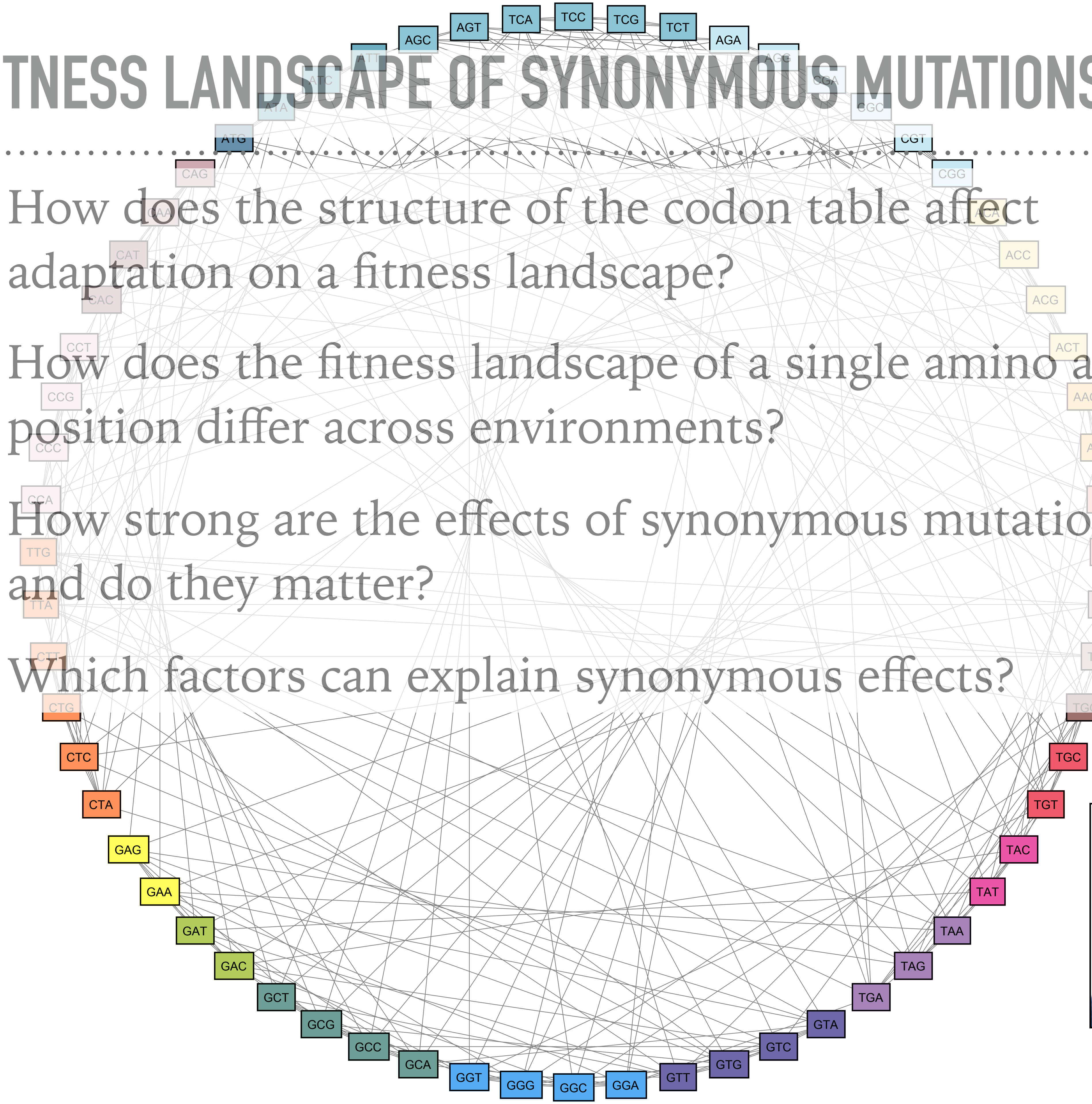

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- Which factors can explain synonymous effects?

Inês Fragata

THE FITNESS LANDSCAPE OF SYNONYMOUS MUTATIONS

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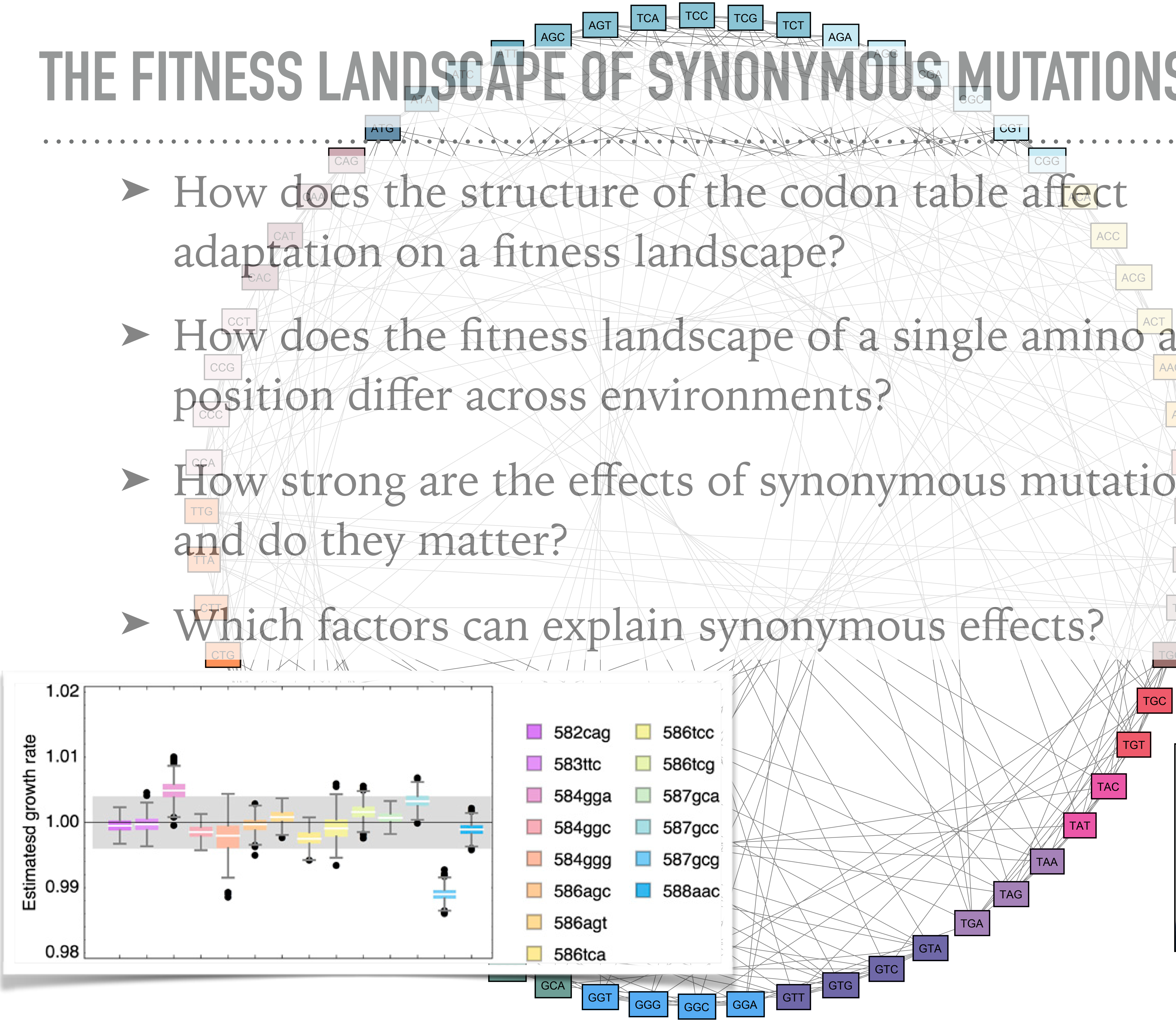

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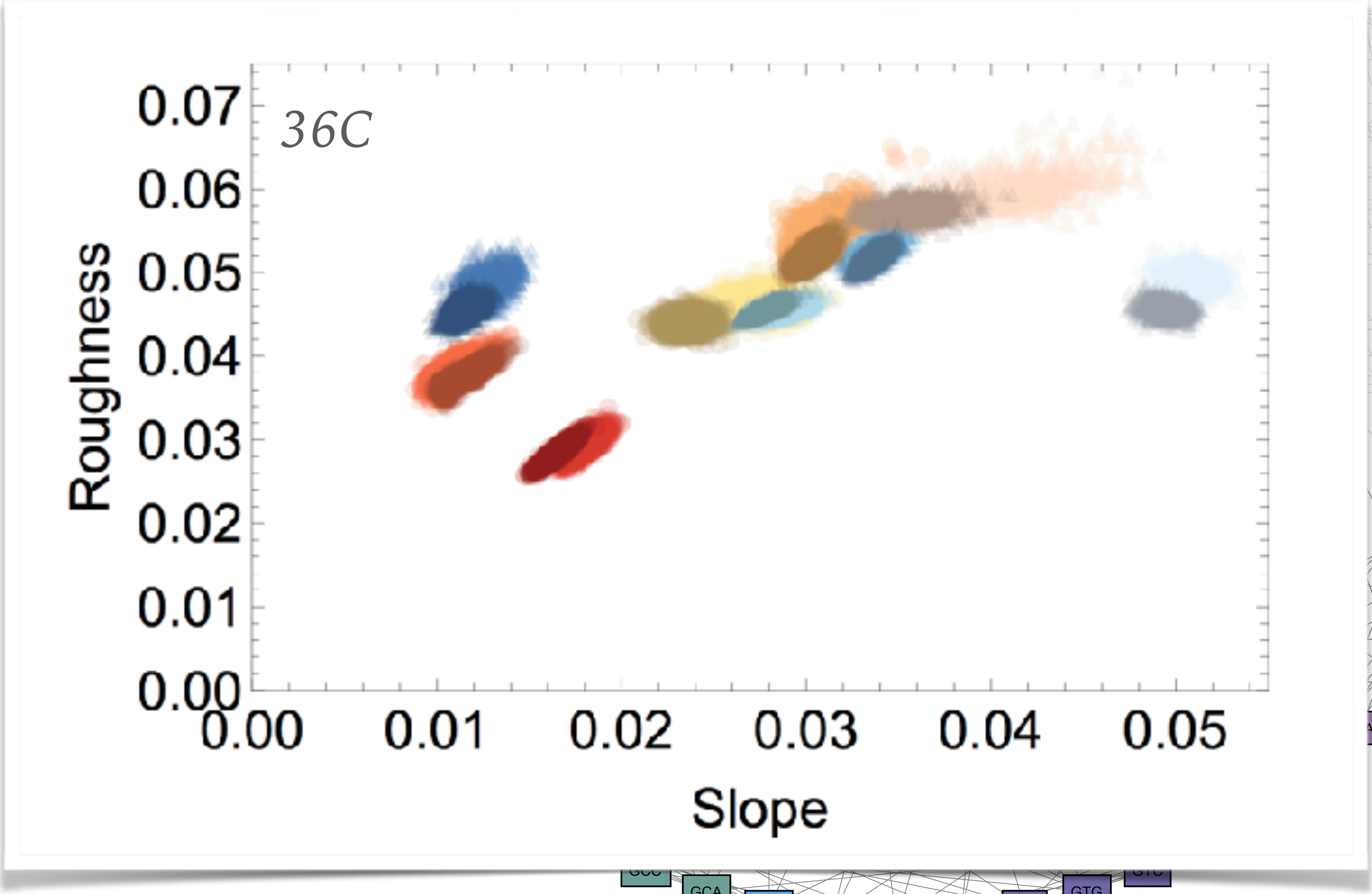
THE FITNESS LANDSCAPE OF SYNONYMOUS MUTATIONS

- Compare landscape without synonymous effects with a landscape that has synonymous effects



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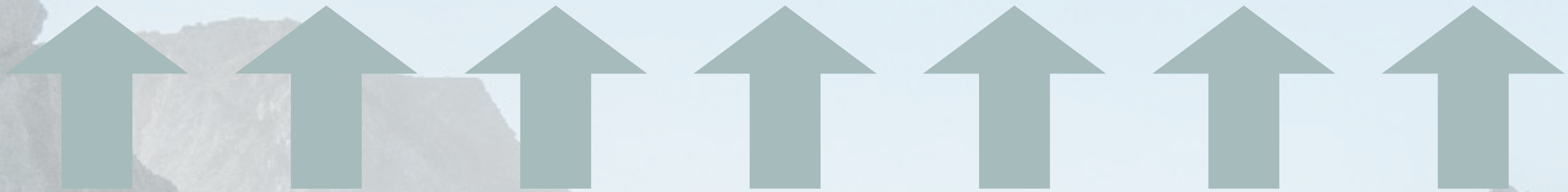
Evolutionary Dynamics @ IGC:

- How do populations adapt to challenging environments? E.g., how does drug resistance evolve?
- Which processes drive speciation & diversification?
- What is the role of interactions in evolution?

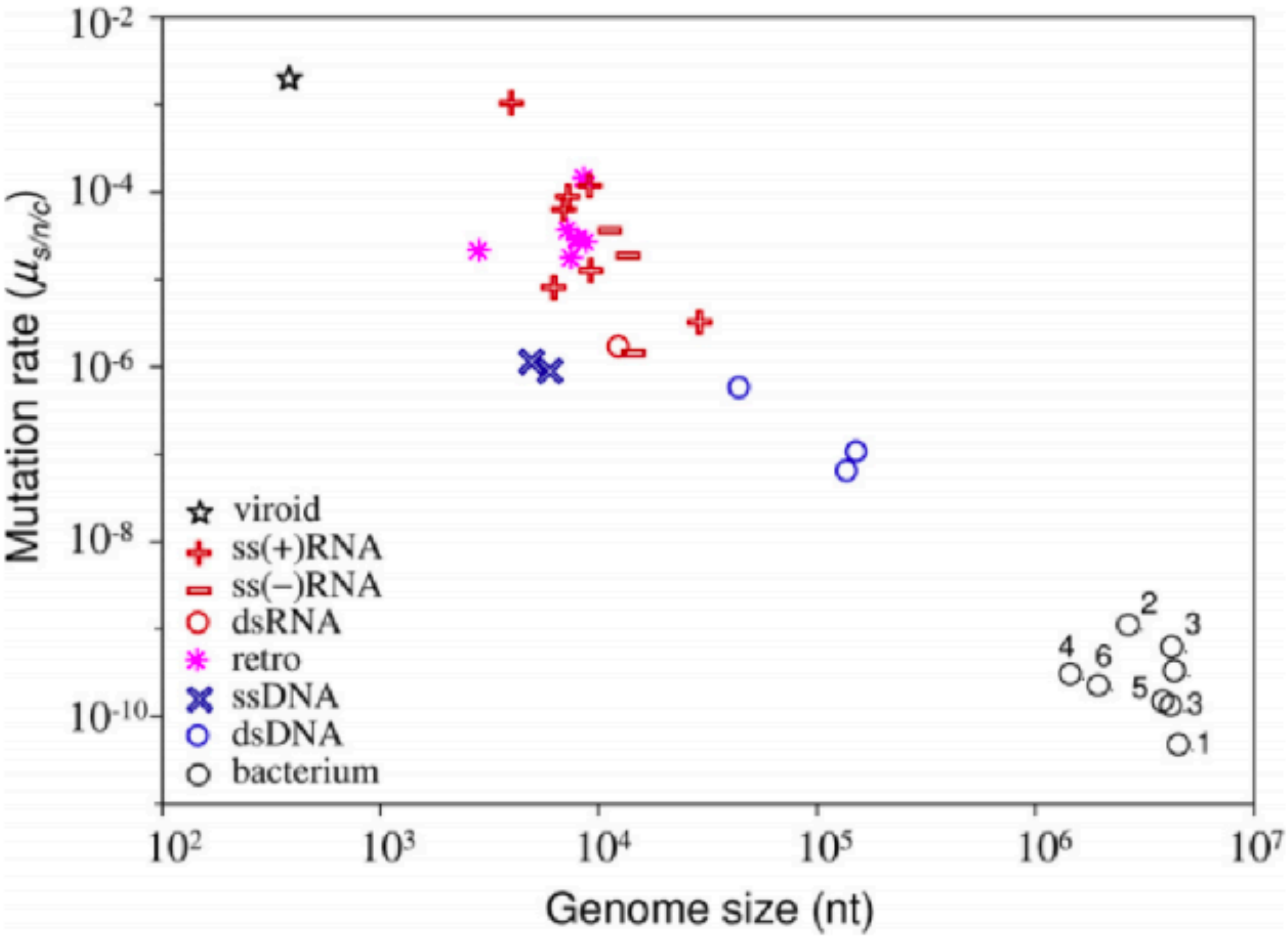


Mutation *Genetic drift* ~~*Migration*~~ *Selection*

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*

MUTAGENIC DRUGS AGAINST RNA VIRUS INFECTIONS

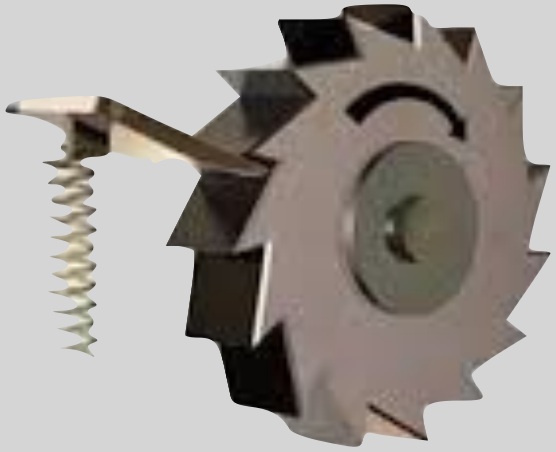


- RNA viruses have exceptionally large mutation rates.

From Sanjuán et al., 2010, JVI

MUTATIONAL MELTDOWN/LETHAL MUTAGENESIS

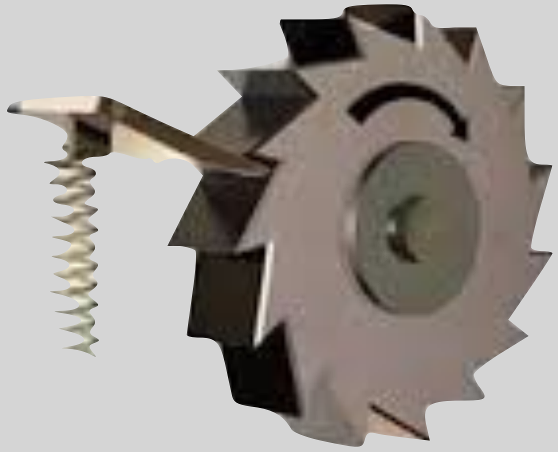
Muller's ratchet: the step-wise loss of the fittest genotype due to accumulation of deleterious mutations in asexual populations



MUTATIONAL MELTDOWN/LETHAL MUTAGENESIS

- a population goes extinct because it accumulates too many deleterious mutations (such that the absolute growth rate becomes <1) - this can be caused by mutation pressure or random genetic drift (or both)

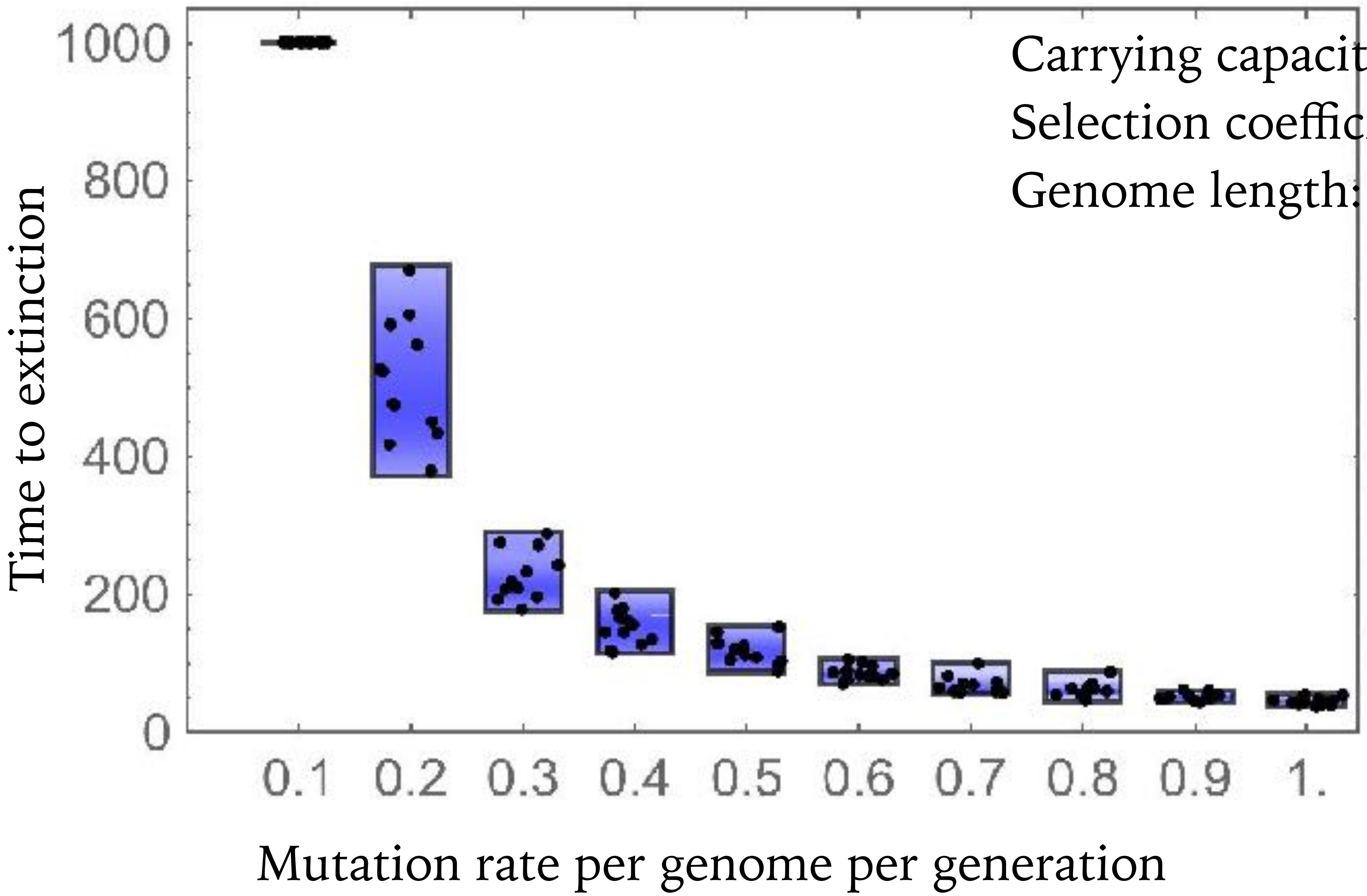
Muller's ratchet: the step-wise loss of the fittest genotype due to accumulation of deleterious mutations in asexual populations



E.g., Lynch et al., 1990, Evolution

MUTAGENIC DRUGS AGAINST RNA VIRUS INFECTIONS

Simulated example



Carrying capacity: 250
Selection coefficient: -0.05
Genome length: 1000

MUTAGENIC DRUGS AGAINST RNA VIRUS INFECTIONS

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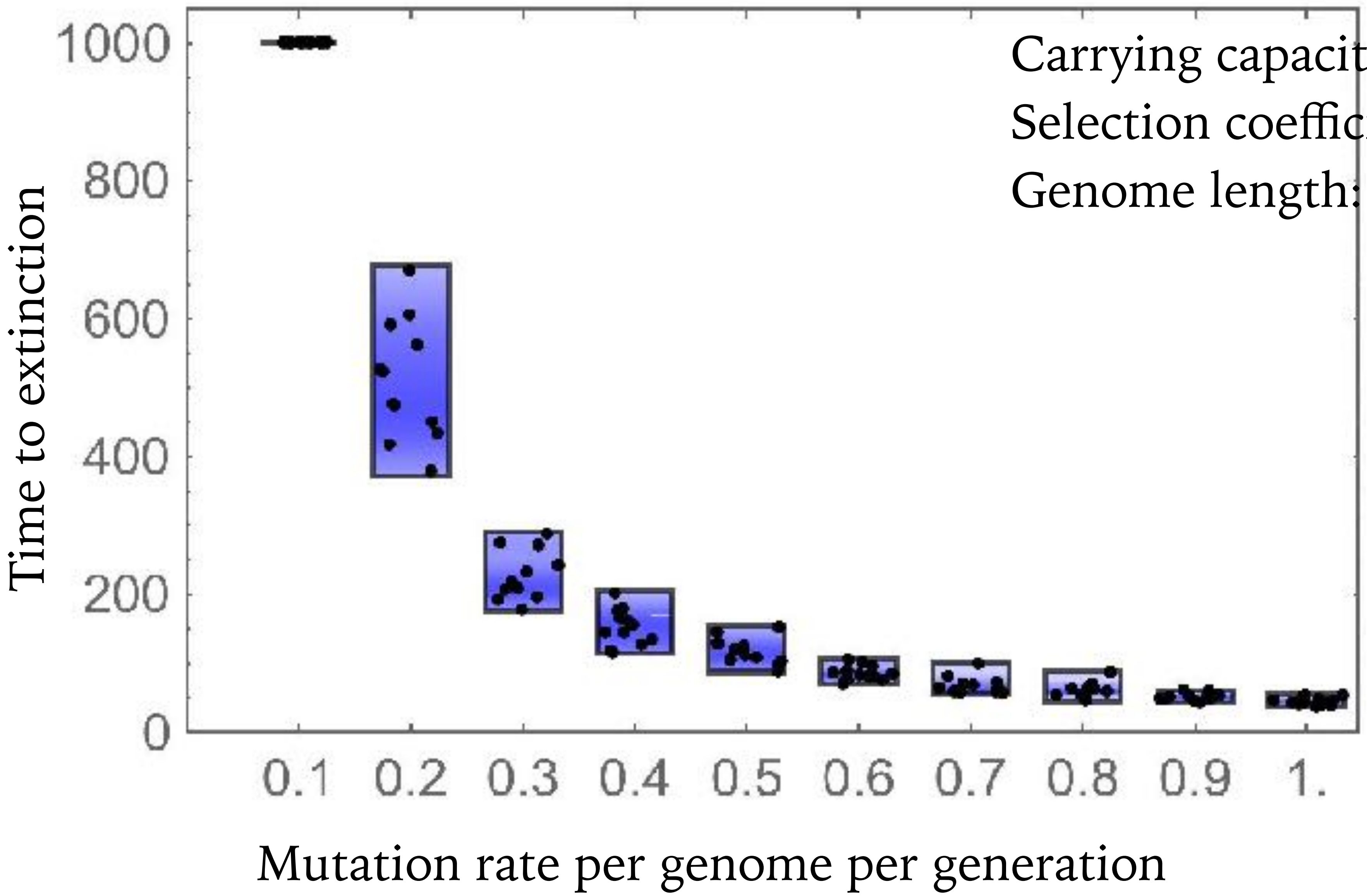

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- Mutagenic drug favipiravir approved for use against influenza in Japan and discussed as promising candidate drug against various RNA viruses.

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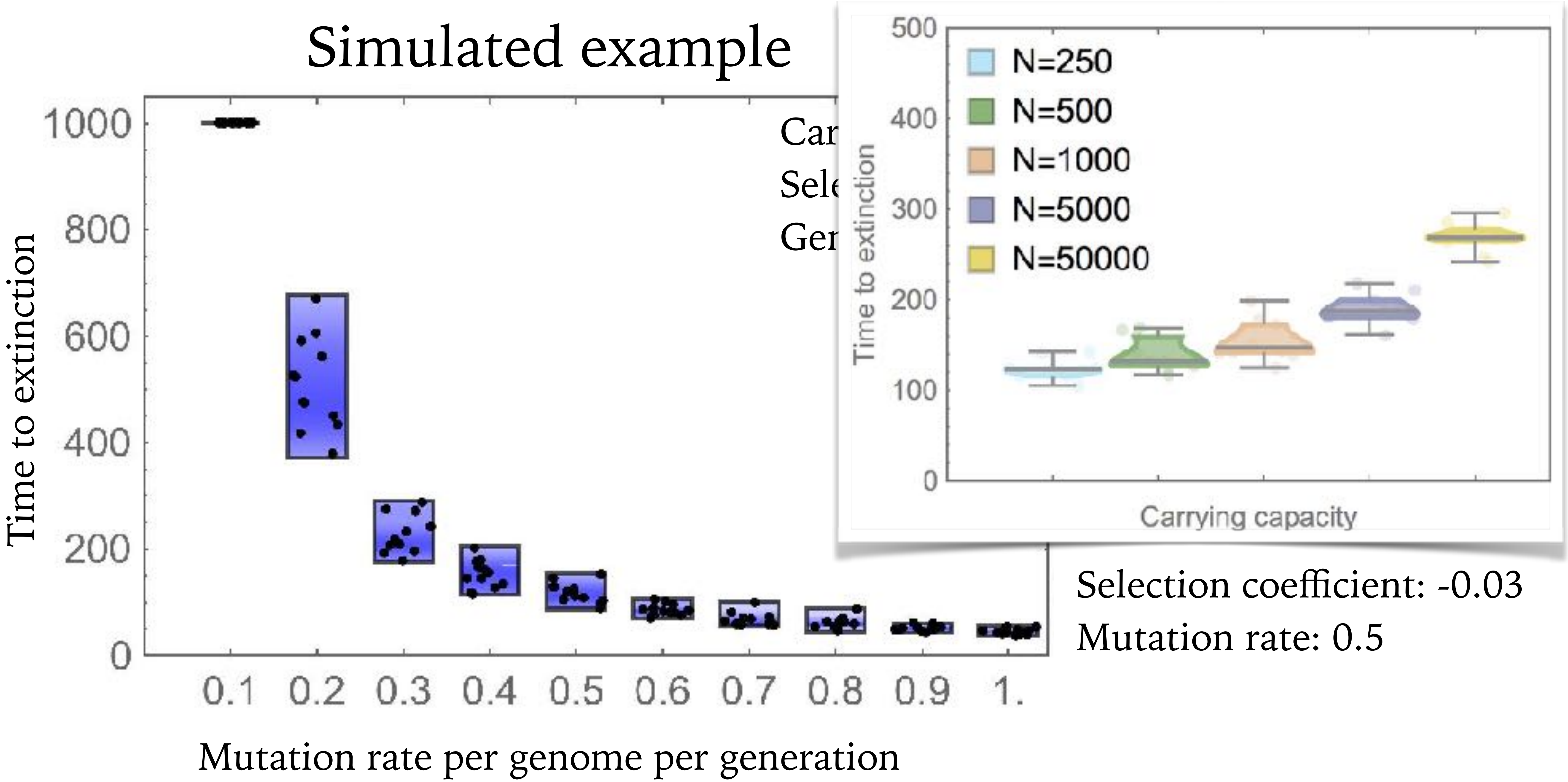

Car
Sele
Ger

Selection coefficient: -0.03
Mutation rate: 0.5

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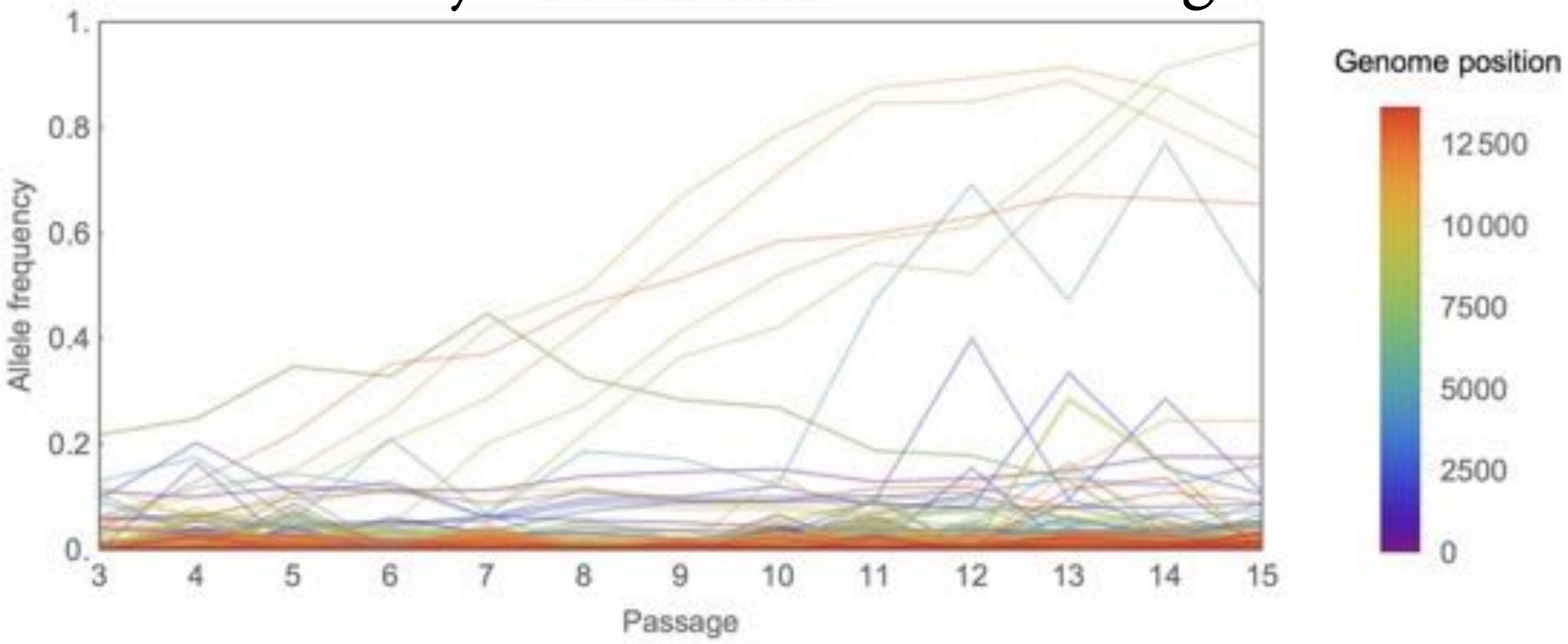
INFLUENZA A LABORATORY EVOLUTION UNDER MUTAGENIC DRUG TREATMENT

Laboratory evolution without drug



Bank et al., 2016, Evolution

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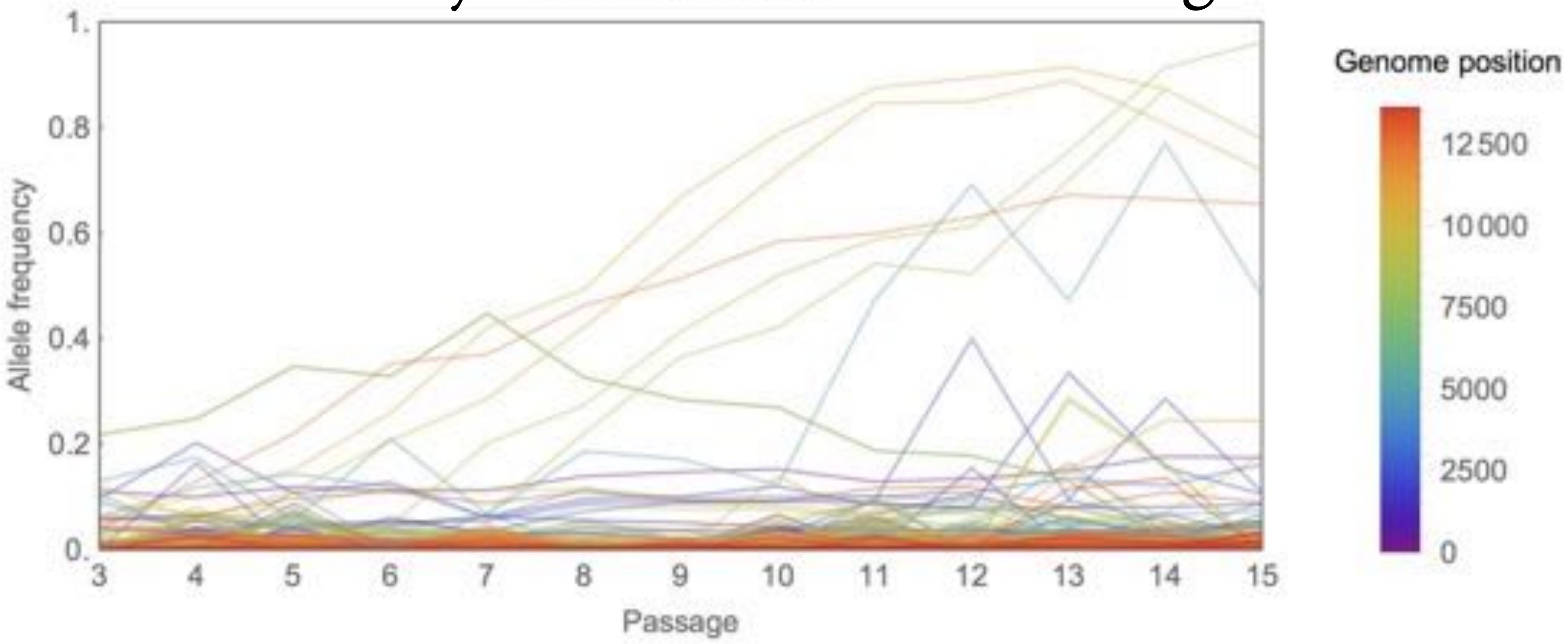

- Using laboratory evolution combined with time-serial genome-wide sequencing we can quantify the evolutionary dynamics of influenza virus.

Bank et al., 2016, Evolution

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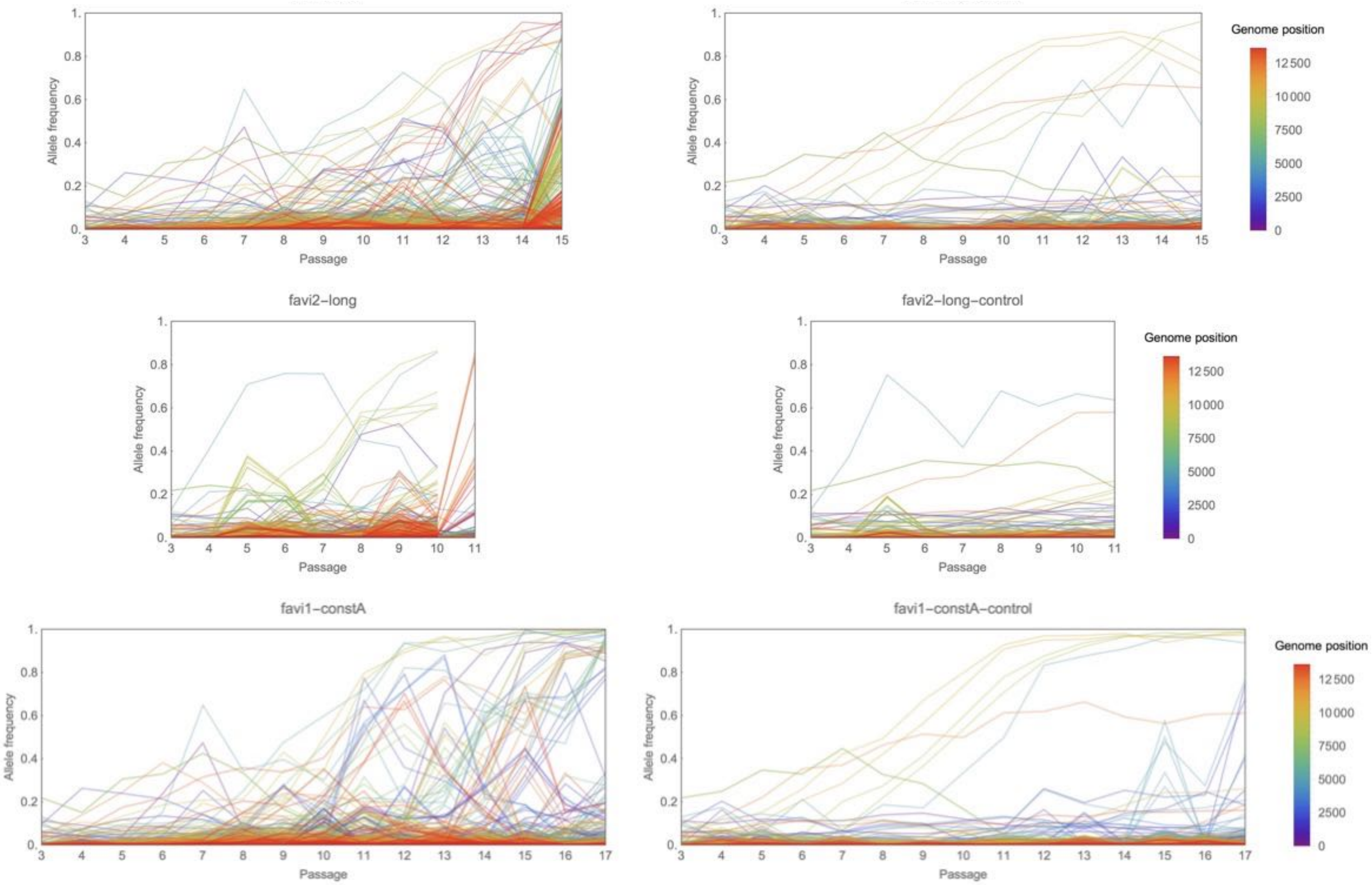

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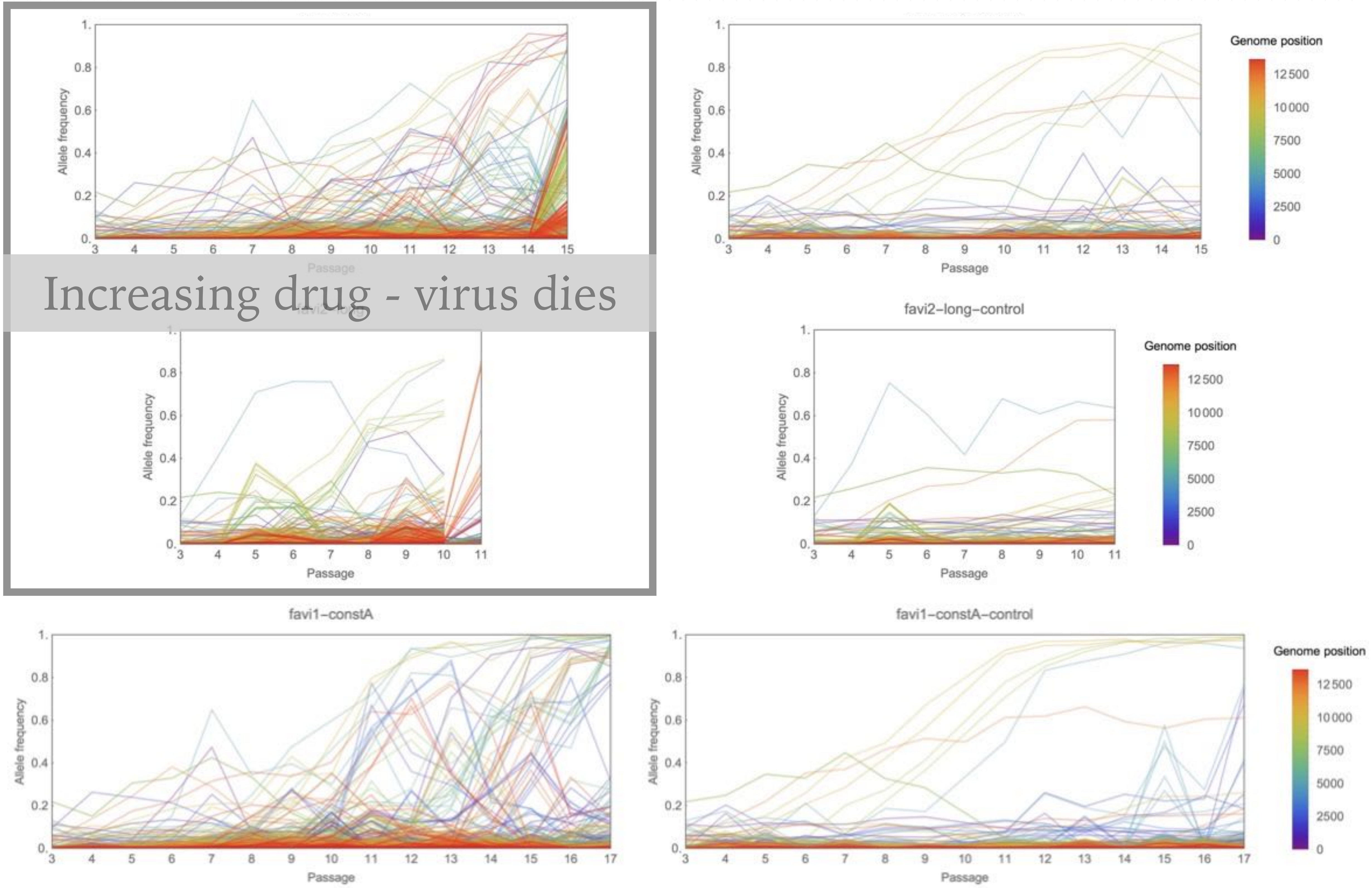

Increasing drug - virus dies

Bank et al., 2016, Evolution

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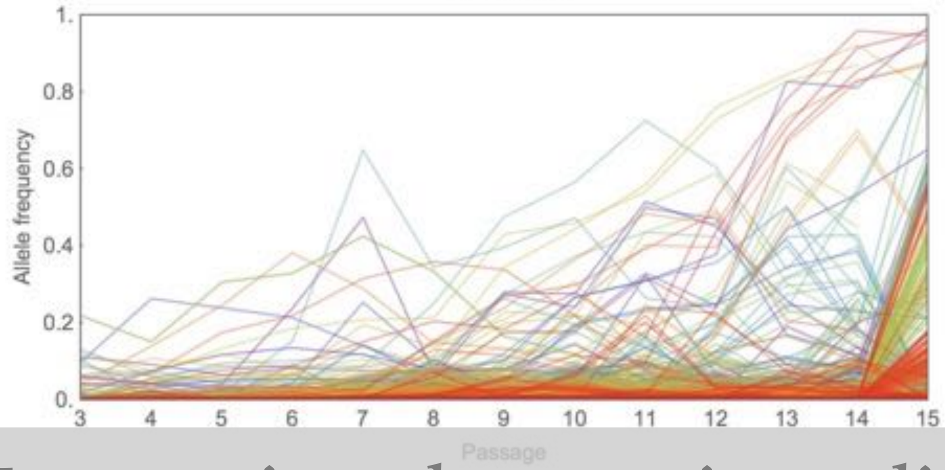

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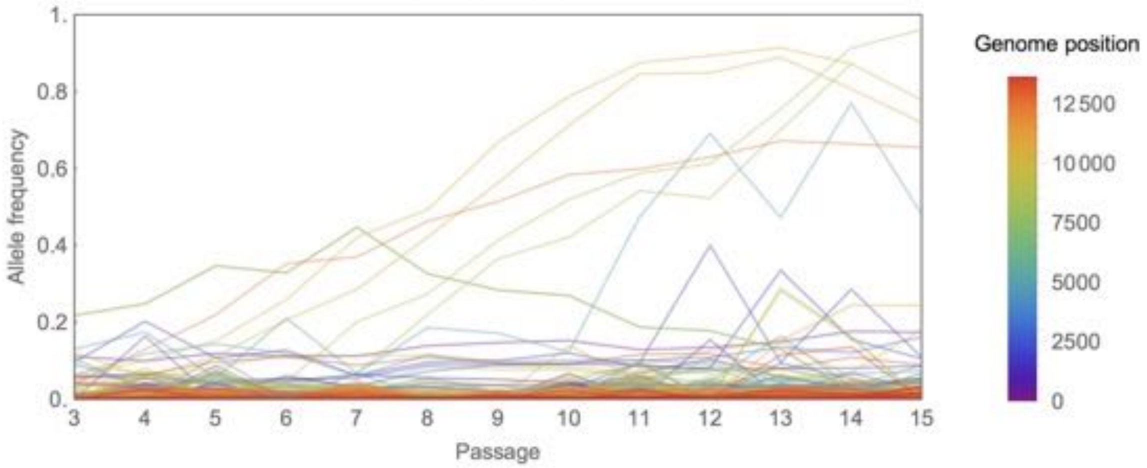
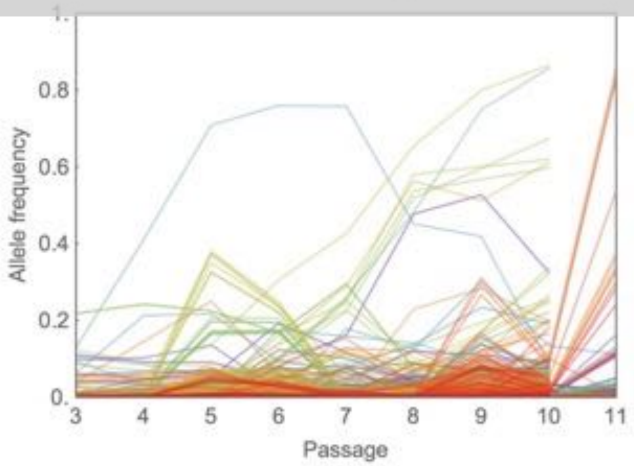
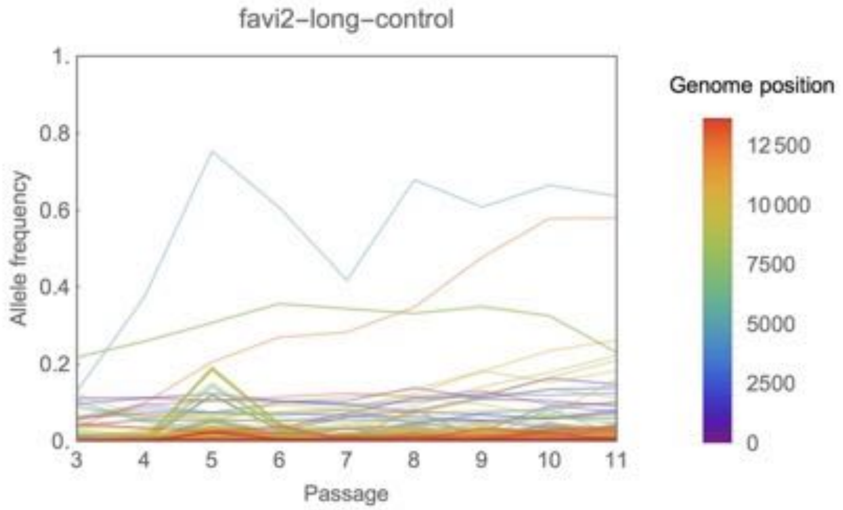
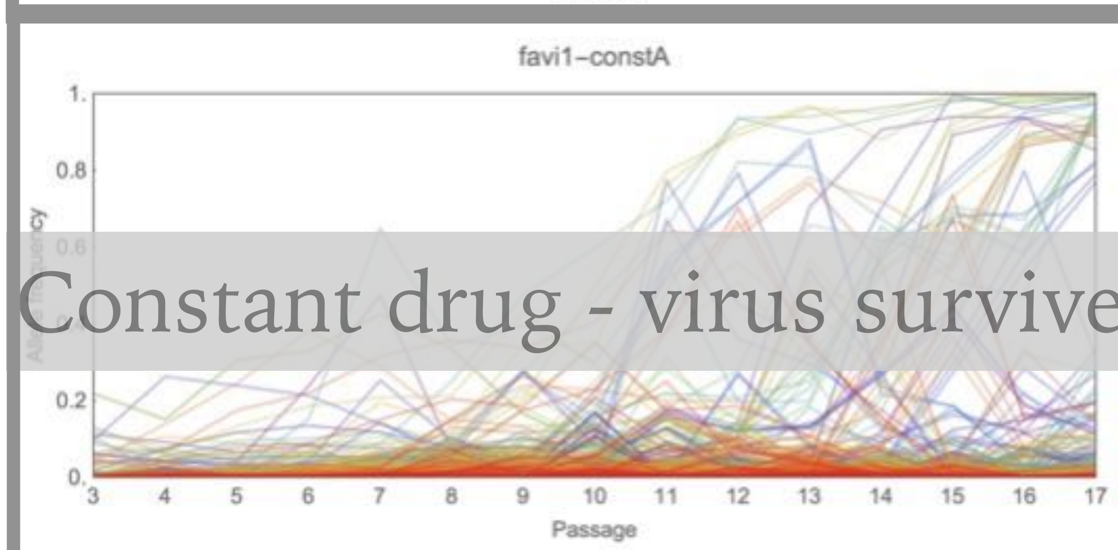
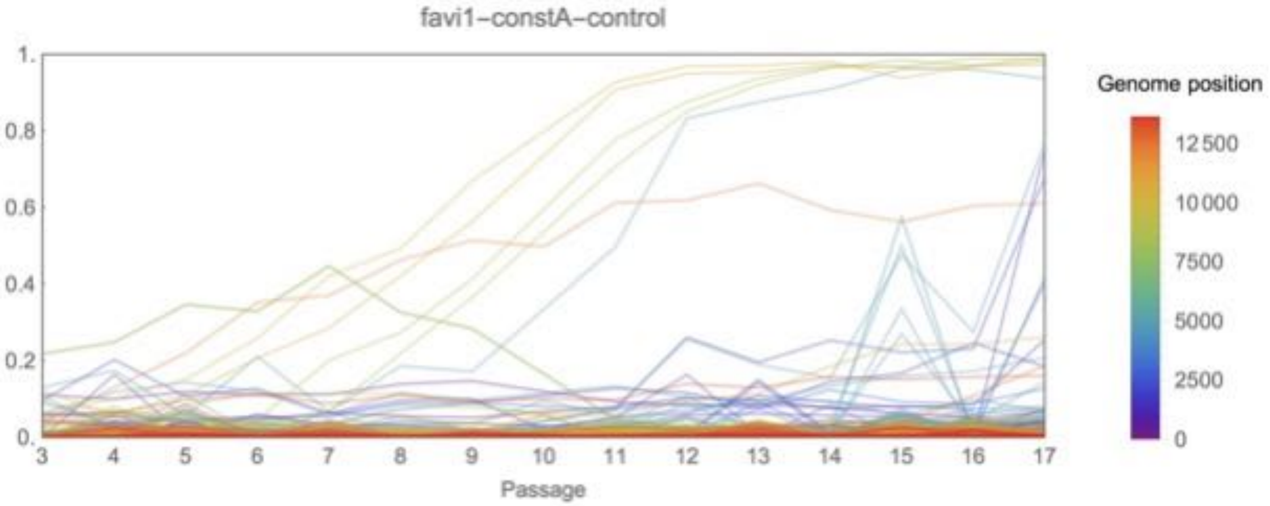








Constant drug - virus survives



Bank et al., 2016, Evolution

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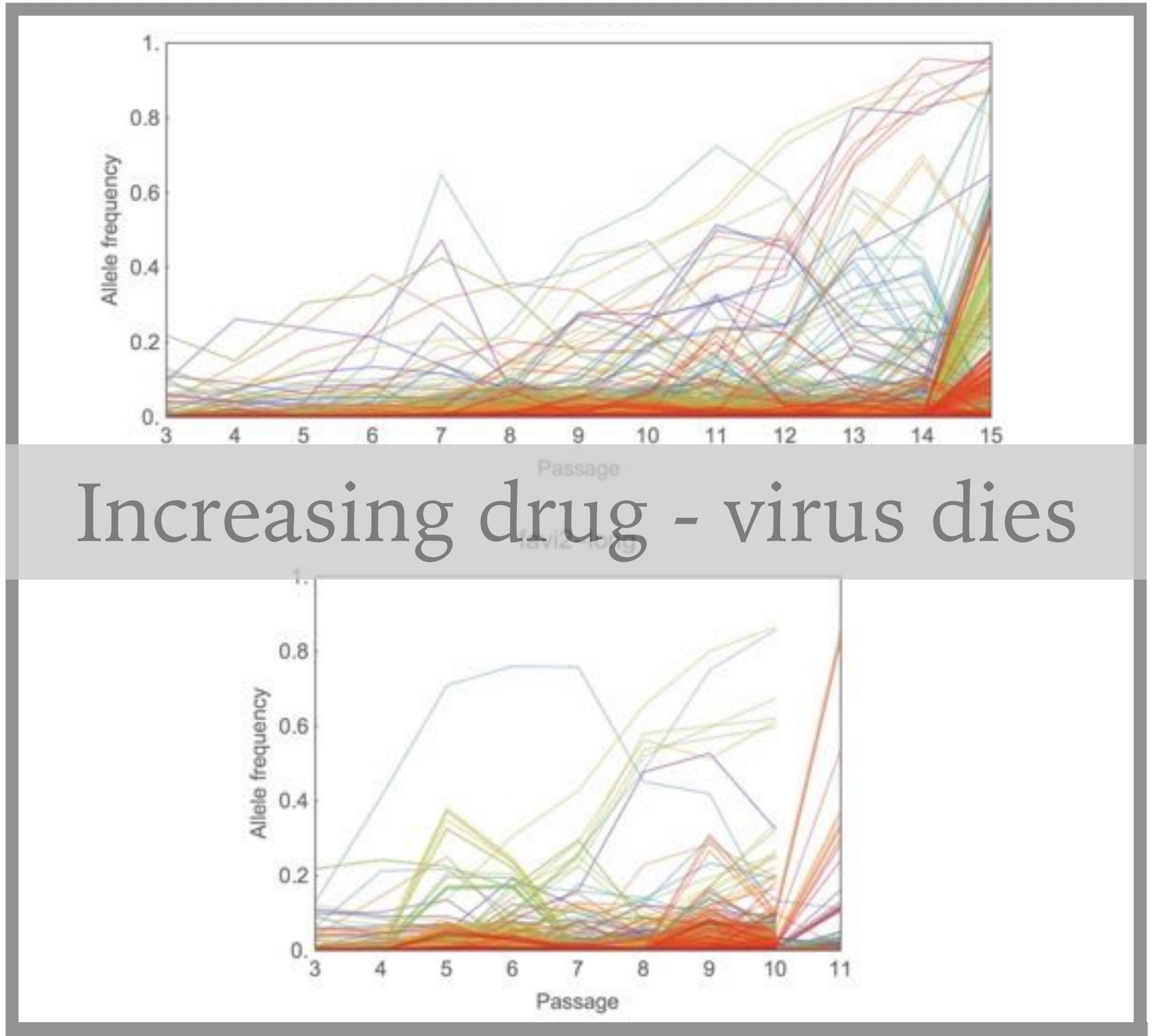

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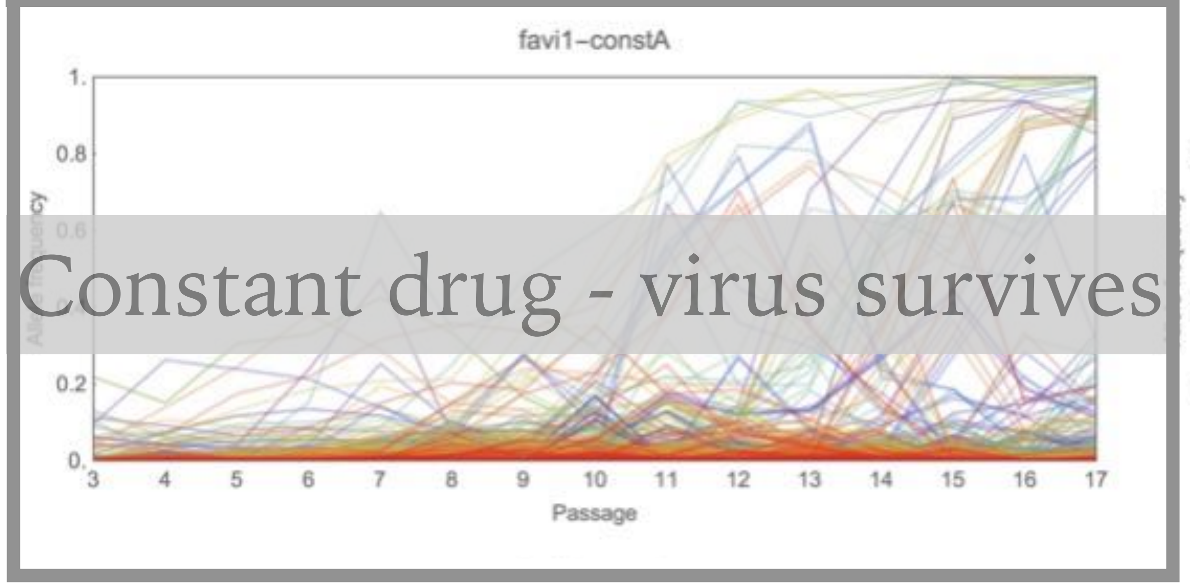
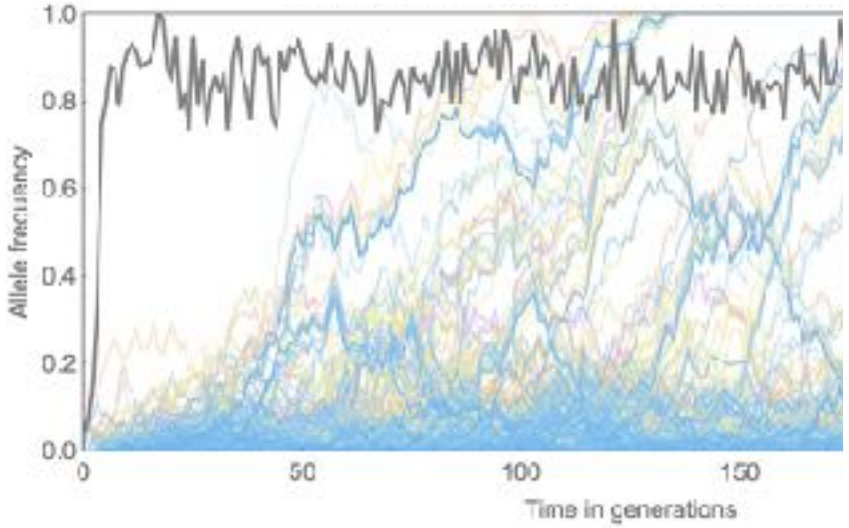
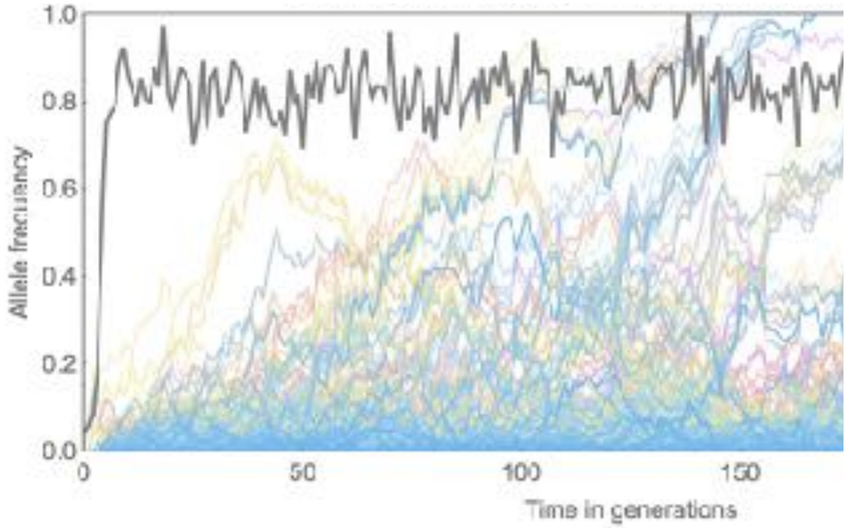


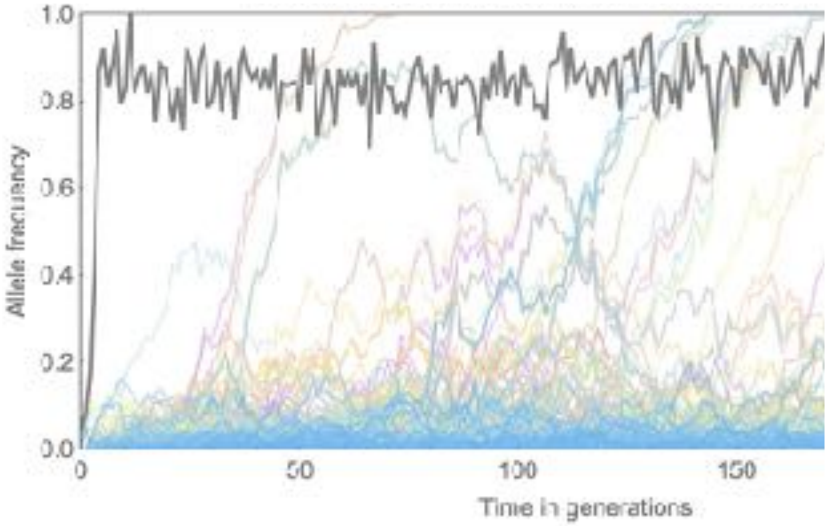
Constant drug - virus survives

- ➤ Favipiravir effective at high/increasing concentration, but indication of population recovery (i.e., adaptation to drug treatment) at constant (intermediate) concentrations.
- ➤ What is the signature of different adaptation mechanisms? How good are our methods for detection of candidate loci? How informative are allele frequencies?

SIMULATE EVOLUTION OF A CLONAL POPULATION WITH HIGH MUTATION RATES







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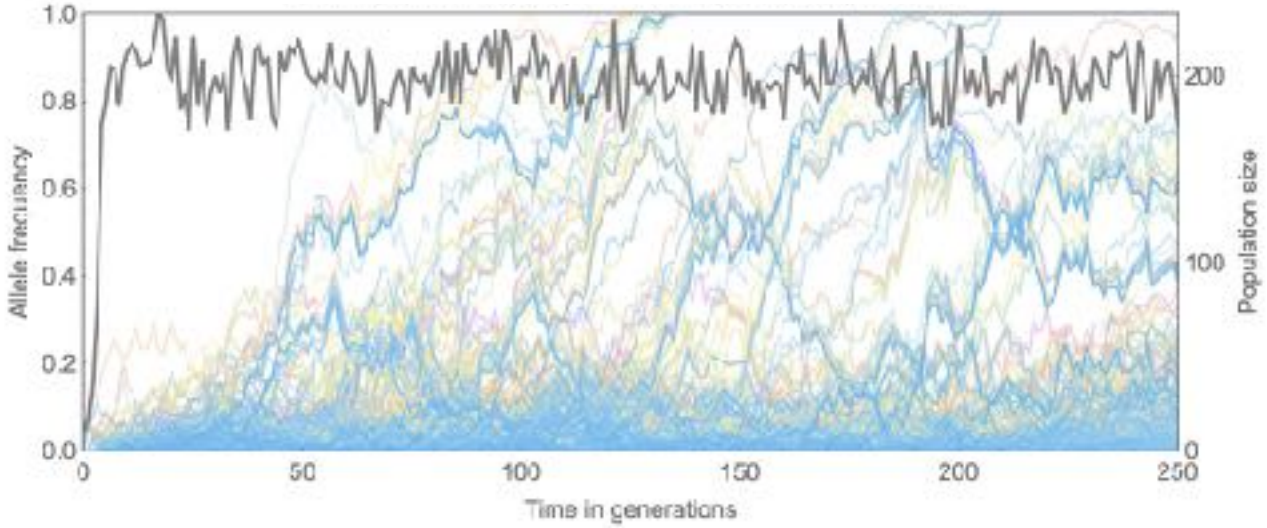
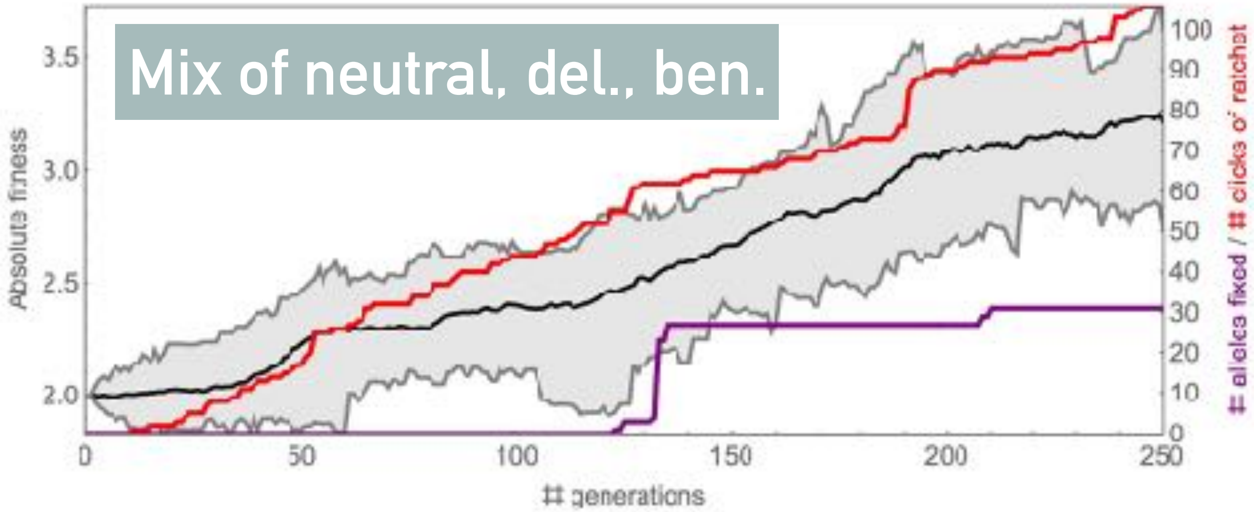
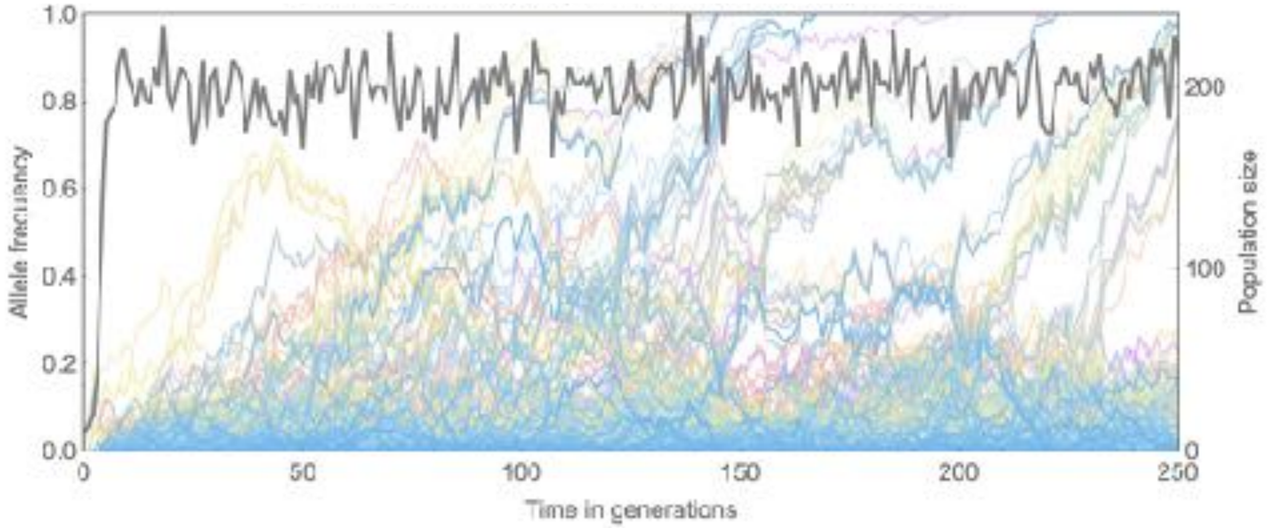
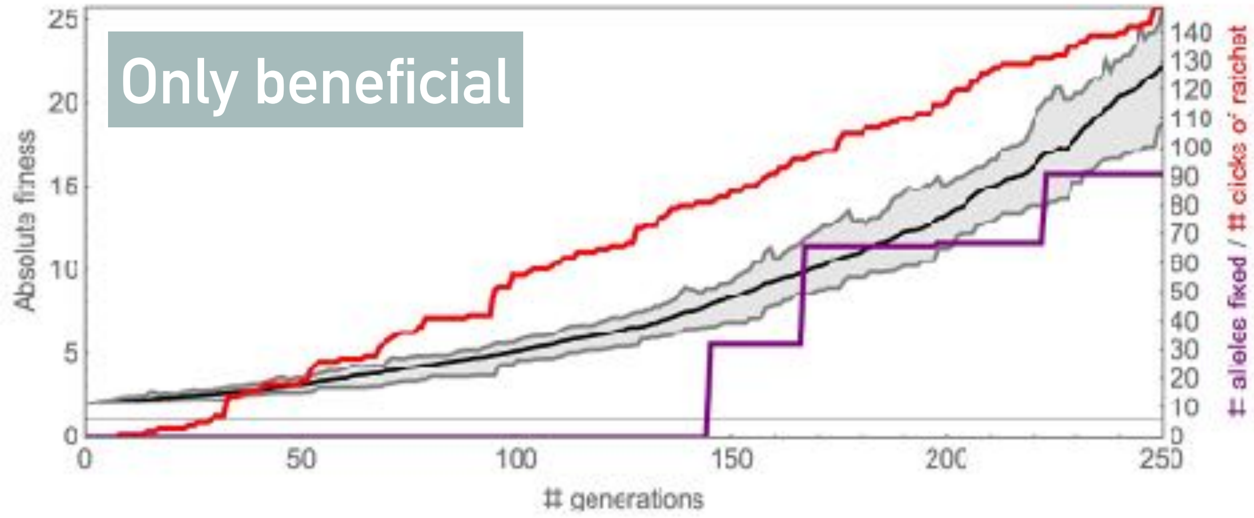
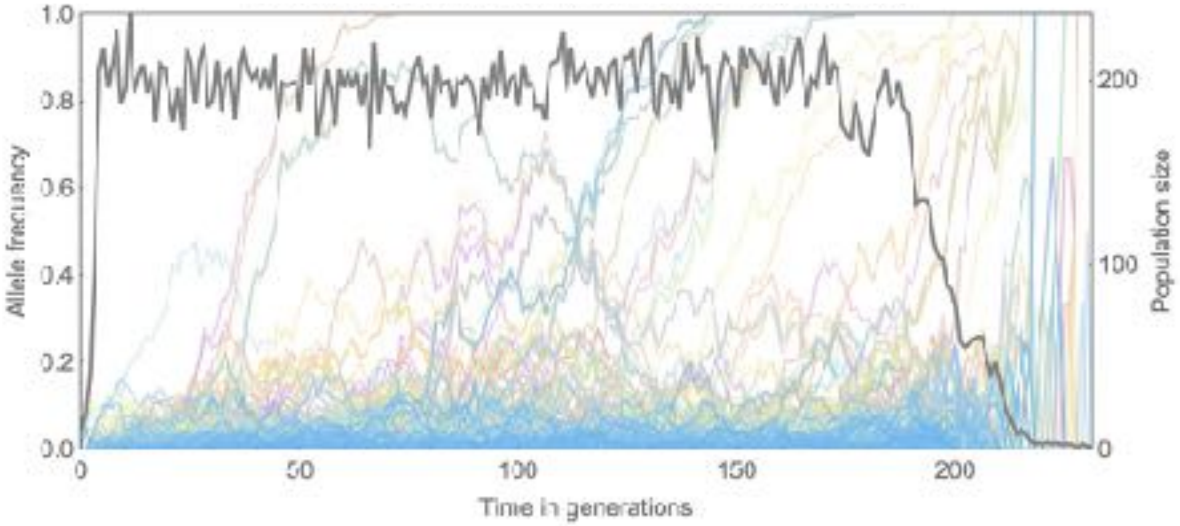
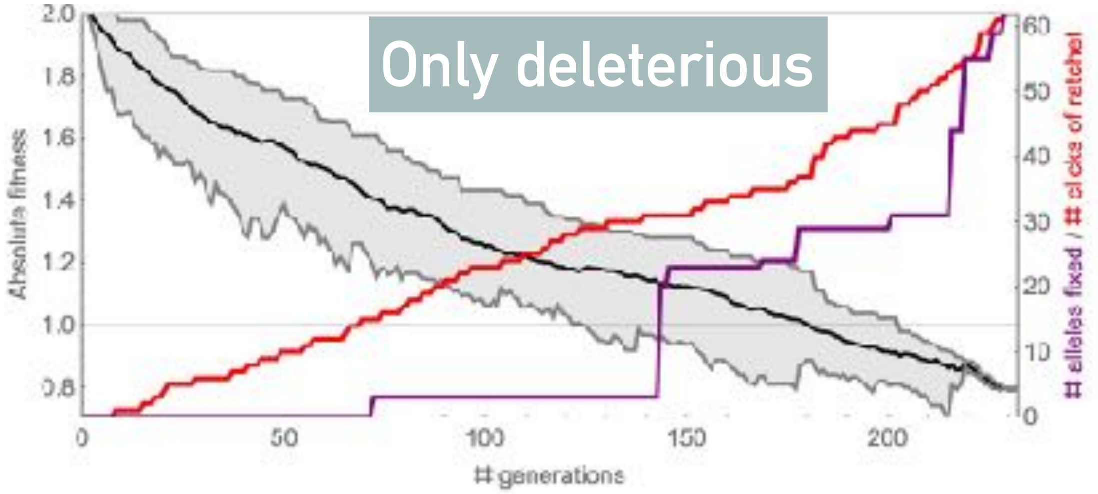



Mix of neutral, del., ben.




Only beneficial




Only deleterious

CAN VIRUSES ADAPT TO MUTAGENIC DRUG TREATMENTS?

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- **By which mechanisms can viruses escape from mutagenic drug treatment? Can we detect the signatures of such adaptation? What are the dangers of mutagenic drugs?**
- An example of **evolutionary rescue**: an adaptation spreads in a population that is otherwise doomed to extinction due to a change in the environment

POTENTIAL MECHANISMS OF RESCUE FROM INCREASED MUTATION RATES

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Tolerance could be the most dangerous mechanism of adaptation to mutagenic drugs because it allows the virus to propagate at high mutation rates, which may allow rare/unseen/complex beneficial mutations to invade subsequently.

TODAY'S QUESTIONS

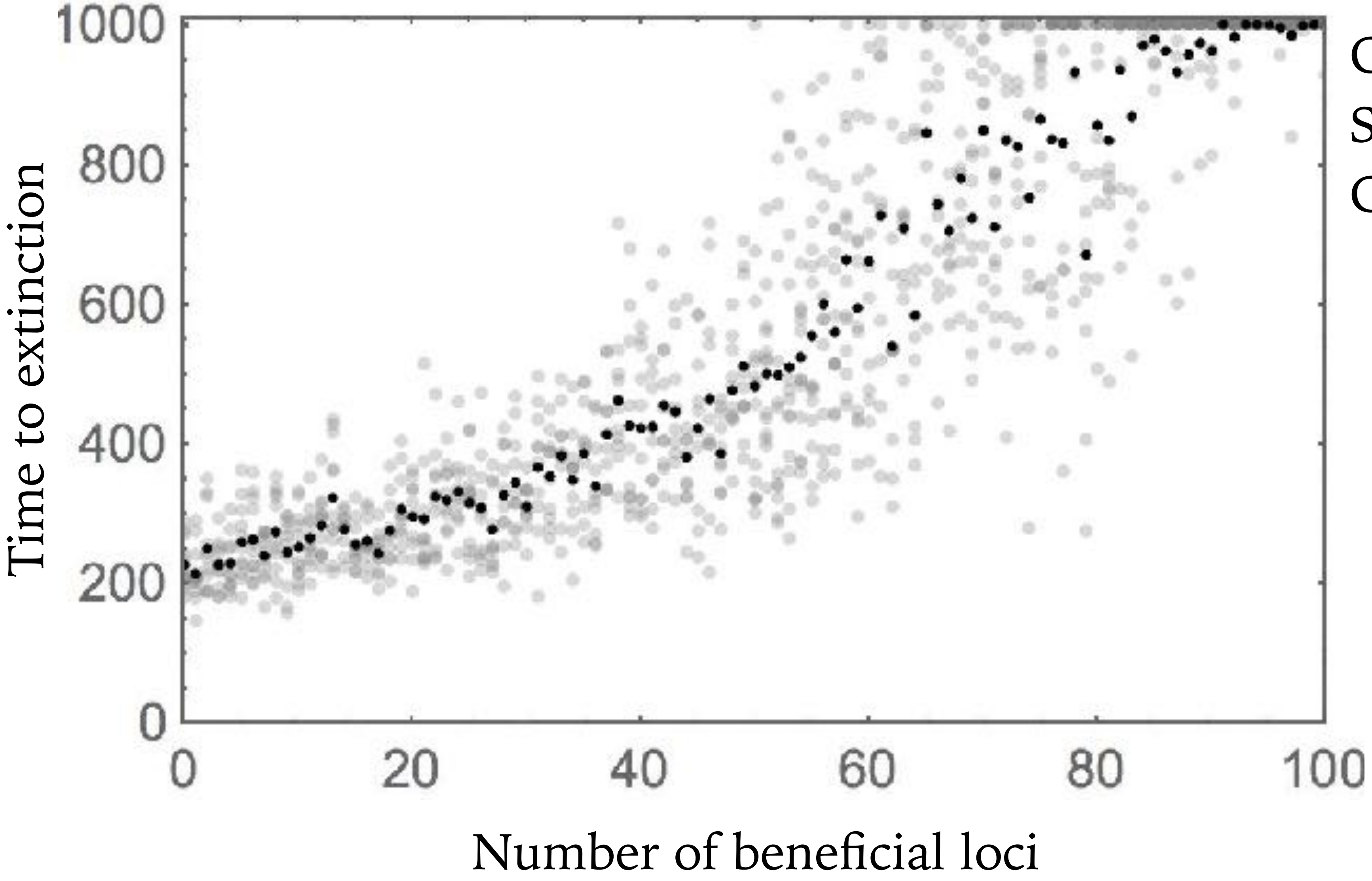
- How does the availability of “traditional" beneficials prolong extinction times?
- When does a mutation rate modifier invade?
- In which conditions does a modifier of the distribution of fitness effects (DFE) invade?

SIMULATION DETAILS

- Genome with L di-allelic loci [1000]
- Carrying capacity C of the clonal population [250], initial population size C_0 [invasion size: 10]
- Initial absolute growth rate R [2]
- Arbitrary distribution of fitness effects [-0.05; multiplicative]
- Mutation rate μ per genome per generation [0.3]
- Record haplotypes in each generation, stop if no extinction has occurred after 1000 generations (transmission/immune reaction)
- l loci with “adaptive" mutations; either beneficial, mutation rate modifier, or DFE modifier

Today: focus on extinction time & “rescue" probability

EXTINCTION TIMES WITH BENEFICIAL MUTATIONS



Carrying capacity: 250
Selection coefficient: +/-0.05
Genome length: 1000

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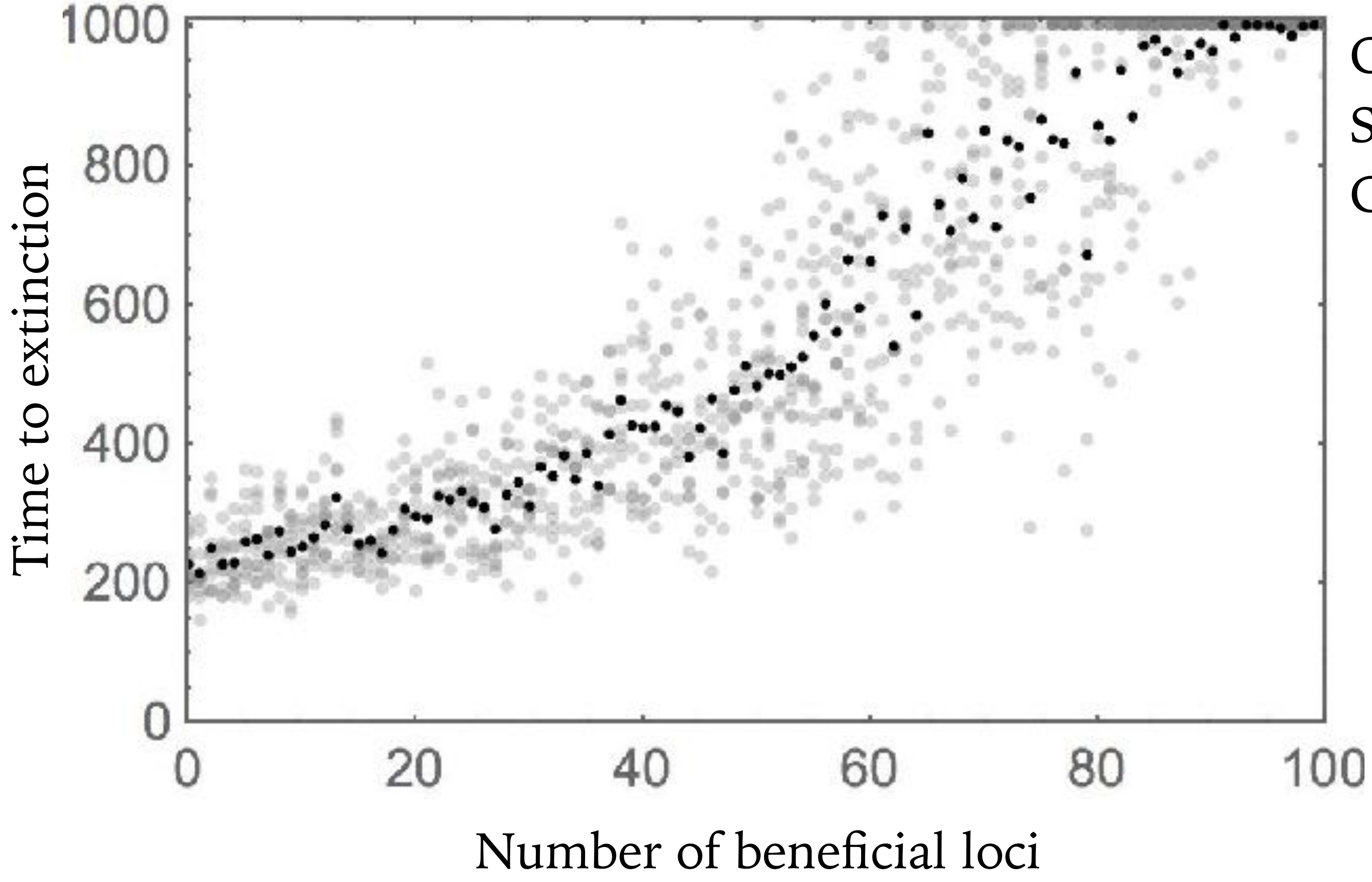

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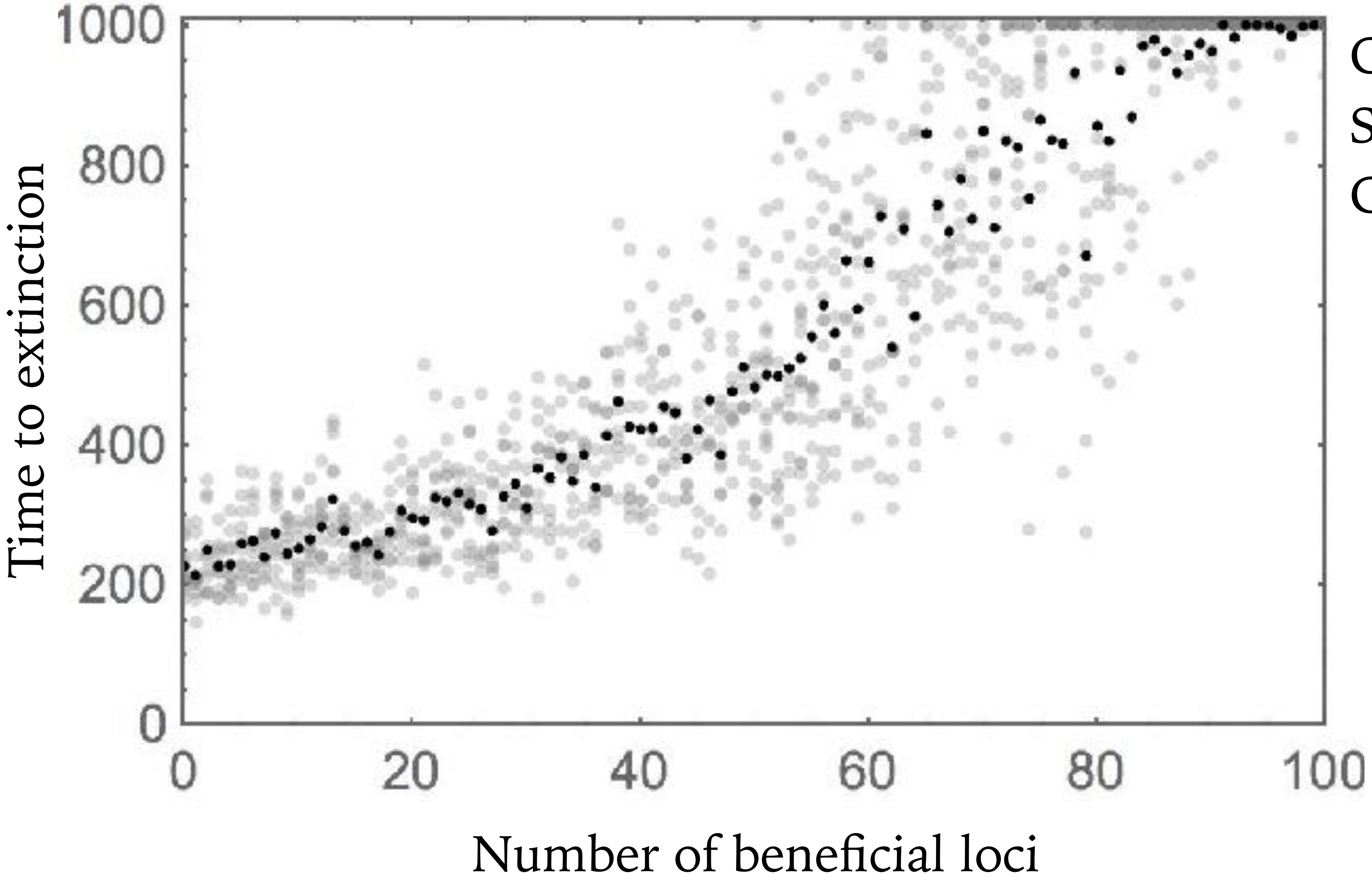

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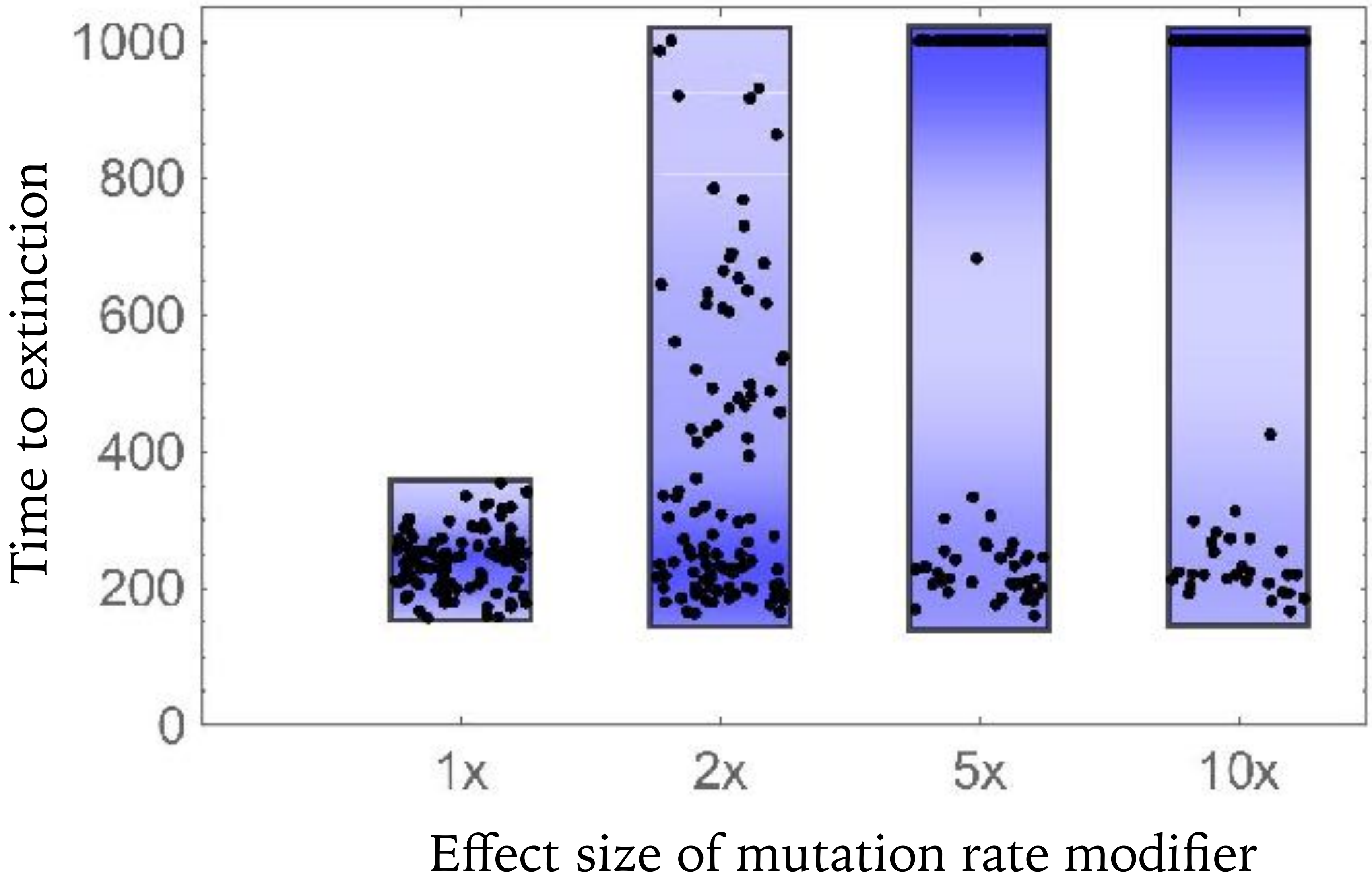
- Many beneficials necessary to allow for significantly prolonged time to extinction.
- Clonal interference impedes efficient spread of multiple beneficials and increases variance in extinction times.

INVASION OF A MUTATION RATE MODIFIER



Carrying capacity: 250
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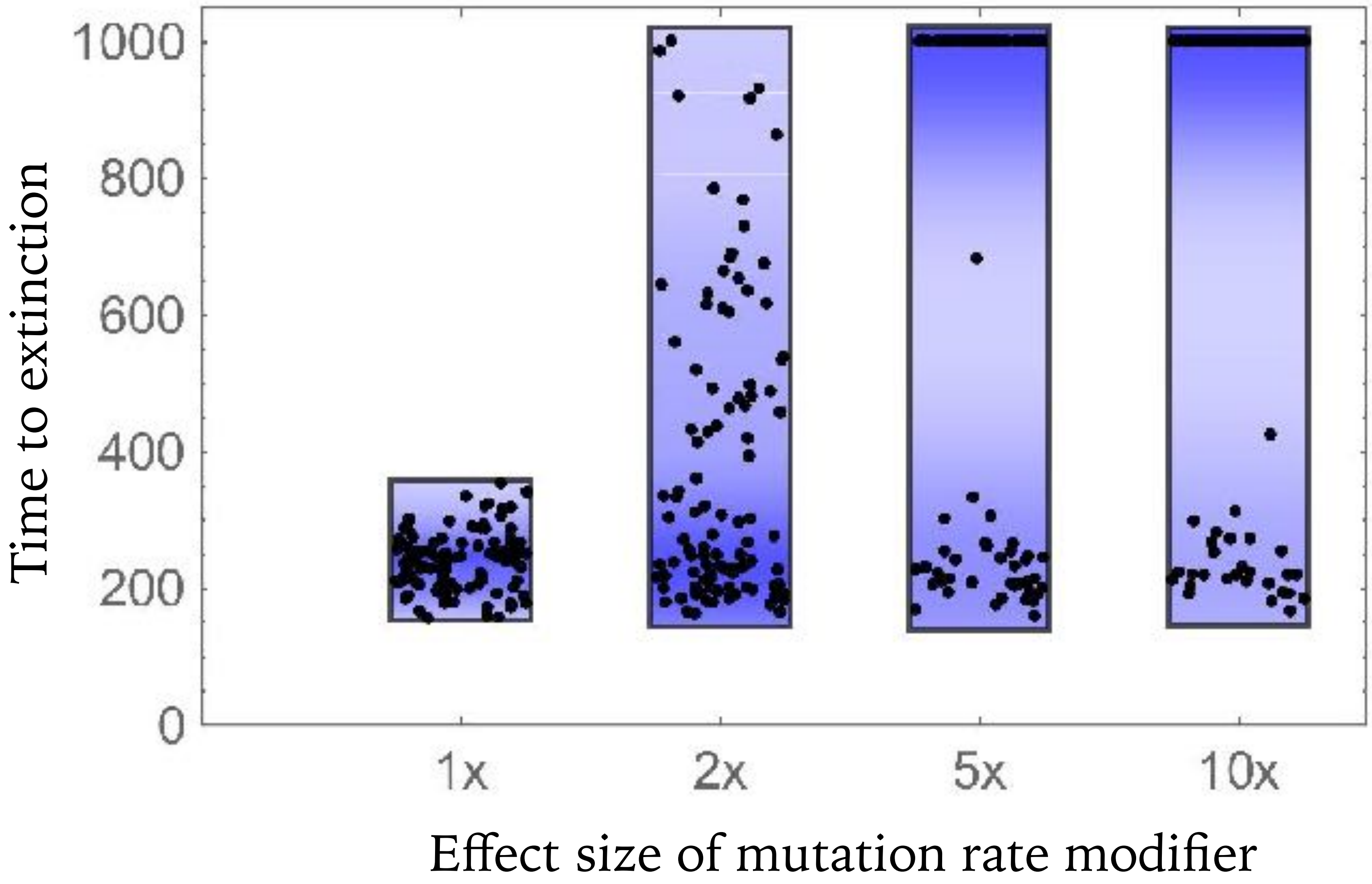
INVASION OF A MUTATION RATE MODIFIER

Max. expected: *18%* *100%* 100%

Rescued: *1%* *63%* 72%



Carrying capacity: 250
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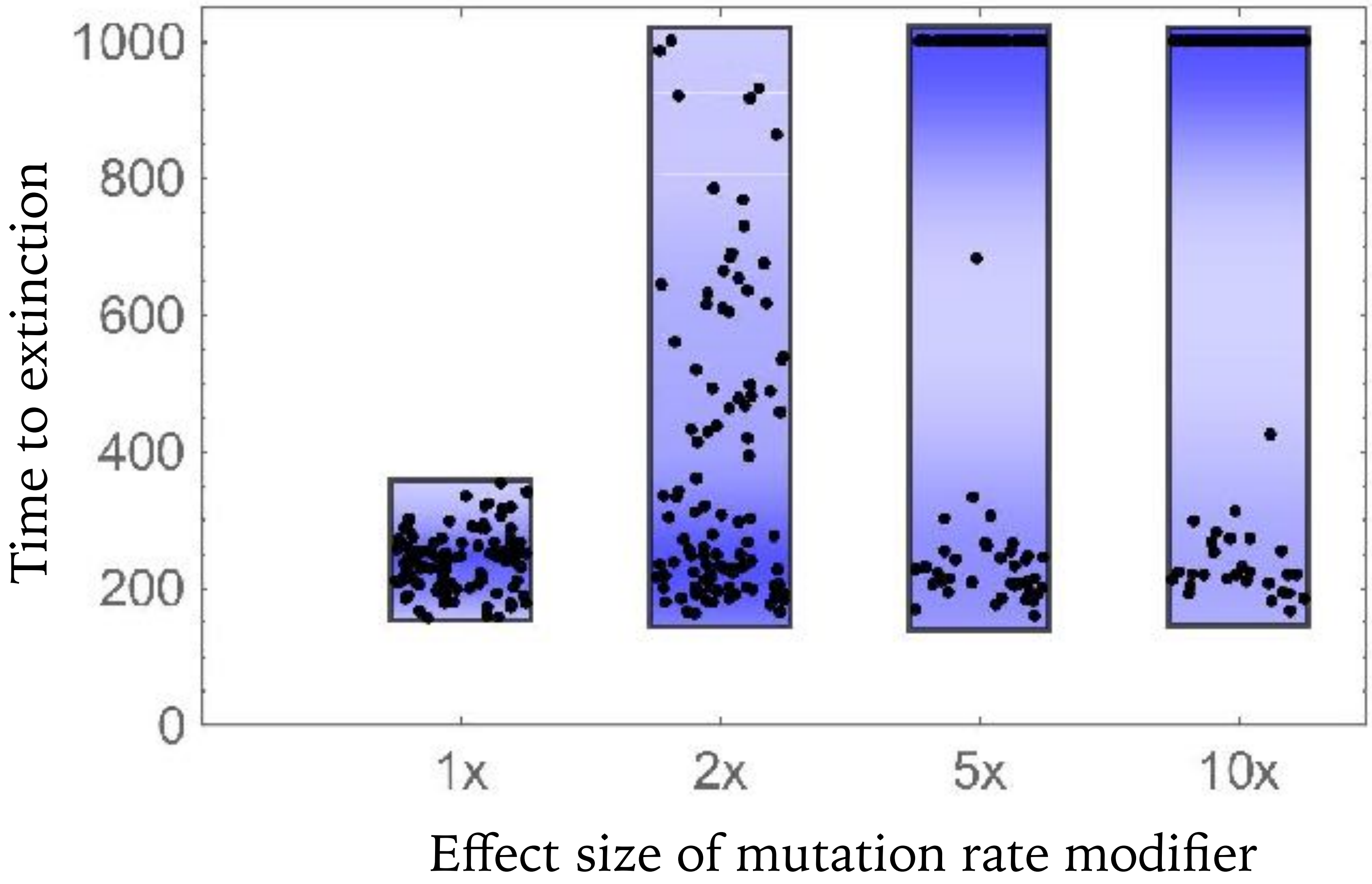
INVASION OF A MUTATION RATE MODIFIER

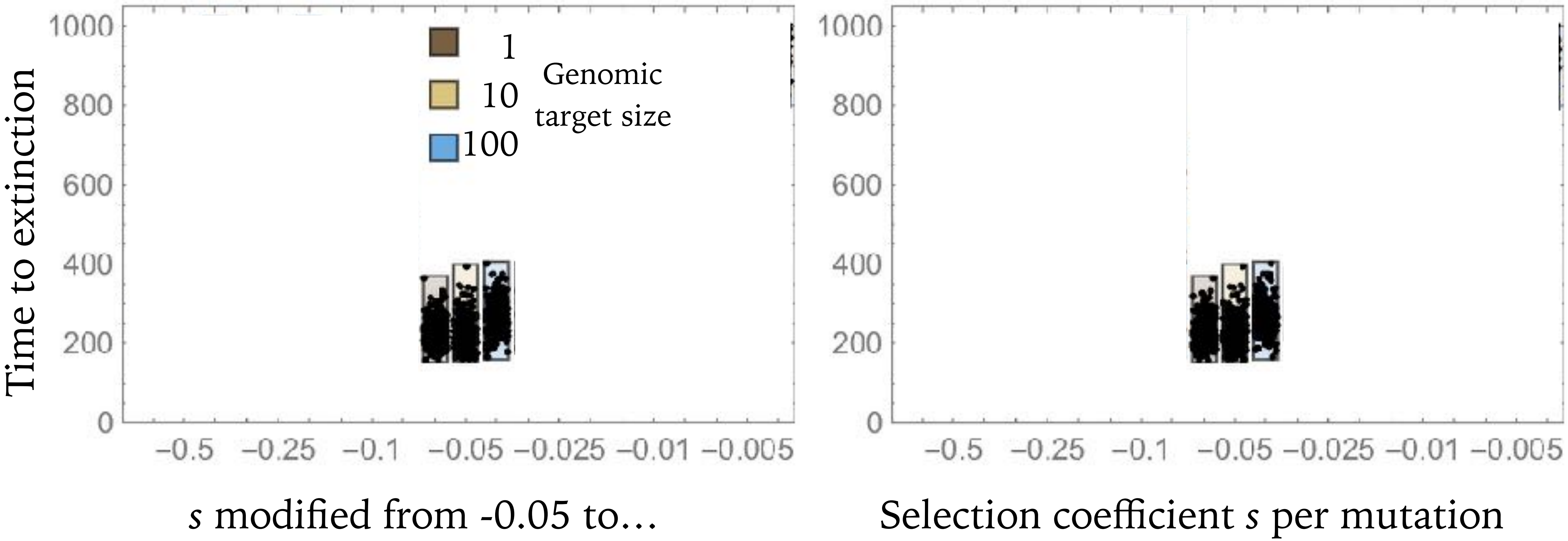
	1x	2x	5x	10x
Max. expected:	*18%*	*100%*	*100%*	100%
Rescued:	*1%*	*63%*	*72%*	



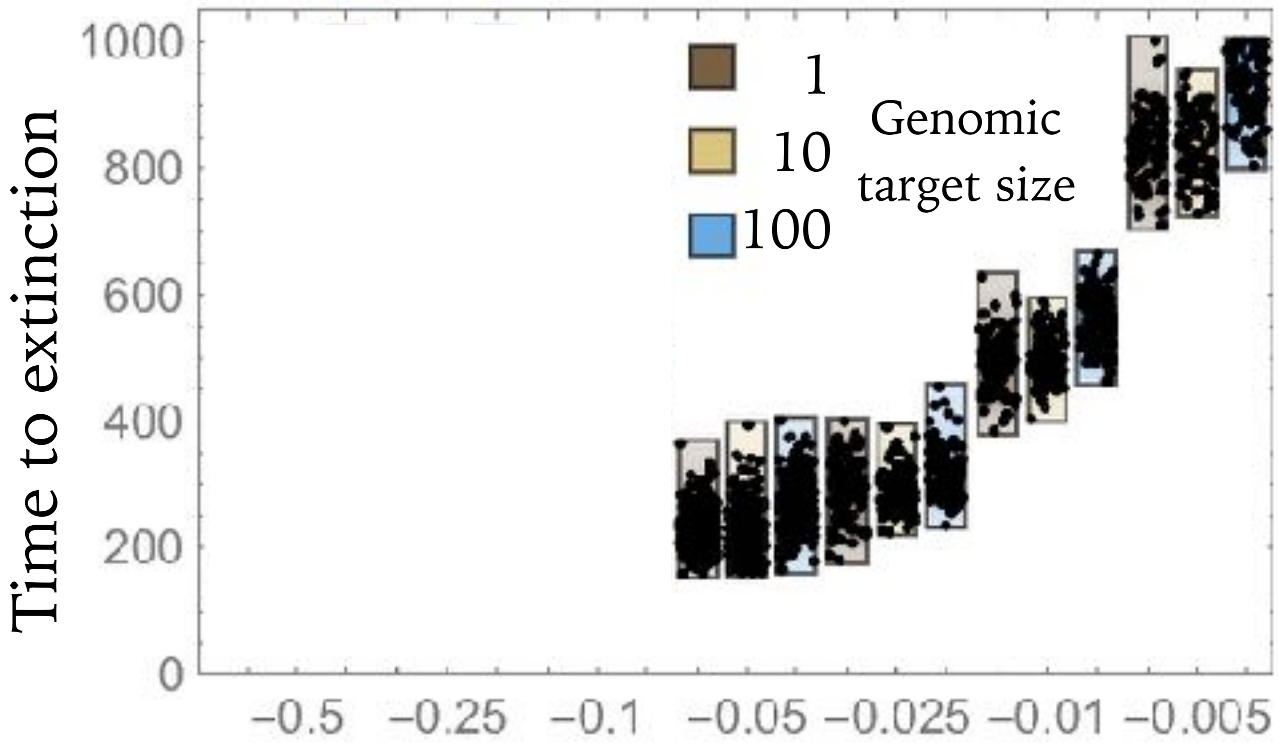
Carrying capacity: 250
Selection coefficient: +/-0.05
Genome length: 1000

- Mutation rate modifier of sufficient strength readily invades and rescues the population with high probability.

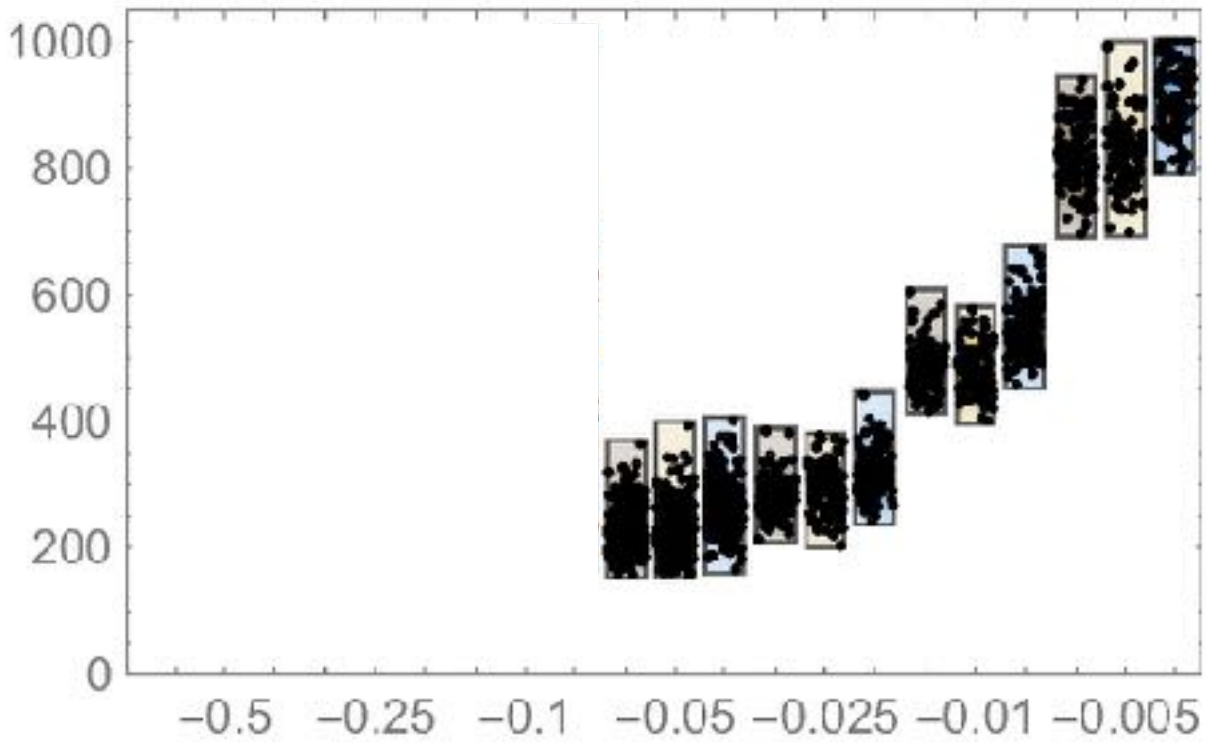
INVASION OF A DFE MODIFIER



INVASION OF A DFE MODIFIER



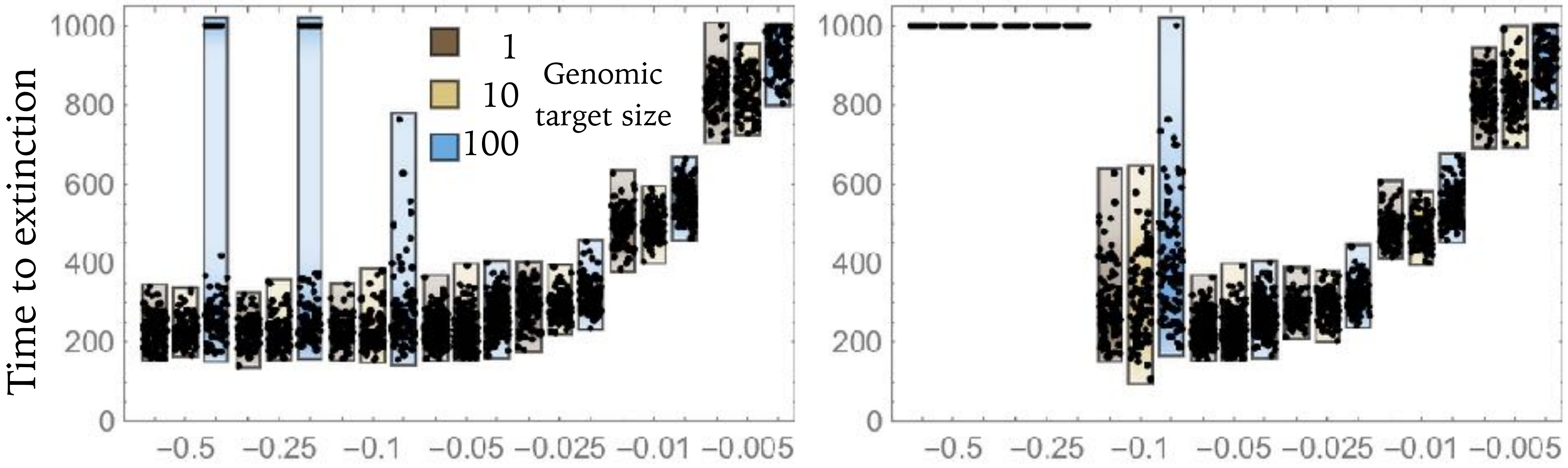
s modified from -0.05 to…



Selection coefficient *s* per mutation

INVASION OF A DFE MODIFIER

Rescued: *21% 22%* *1% 14%* *100%* *1%* *9%*



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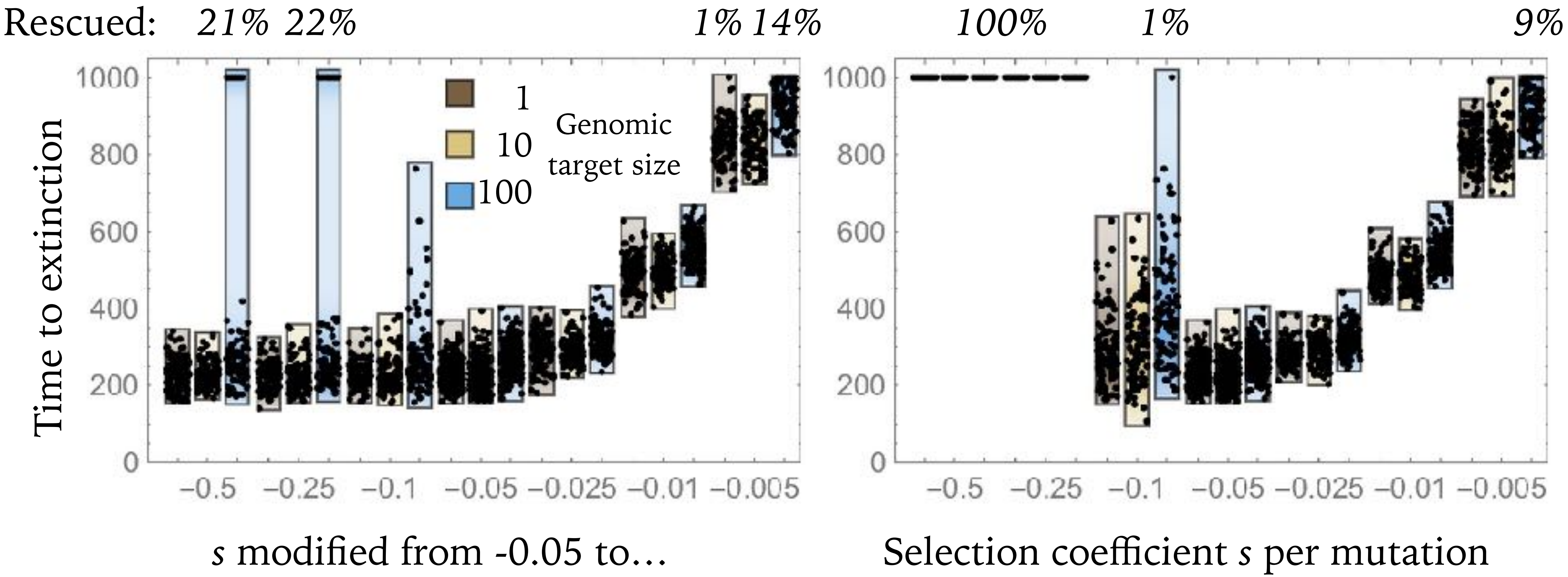
INVASION OF A DFE MODIFIER



- Both types of modifiers can invade; “chaperone” modifier invades easily but rarely rescues; “negative" modifier only invades under specific conditions but then rescues reliably.

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- Extinction process is rather deterministic over a large range of the parameter space.
- Many available beneficials are needed to prolong the extinction time (e.g., to successful transmission of the virus).
- If available, mutation rate modifiers readily invade and make the population resistant to mutagenic treatment.
- DFE modifiers in both directions can invade and make the virus tolerant to high mutation rates. This is possibly the most dangerous adaptation mechanism, because it could modify virus evolution also in absence of the drug.

ACKNOWLEDGEMENTS

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David Liberles, Temple University
Sebastian Matuszewski, EPFL
Vitor Sousa, University of Lisbon
Alex Wong, Carleton University

FUNDING

FUNDAÇÃO CALOUSTE GULBENKIAN

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