Latent phenotypic complexity of adaptation in a single environment

Grant Kinsler

Stanford University

@GrantKinsler

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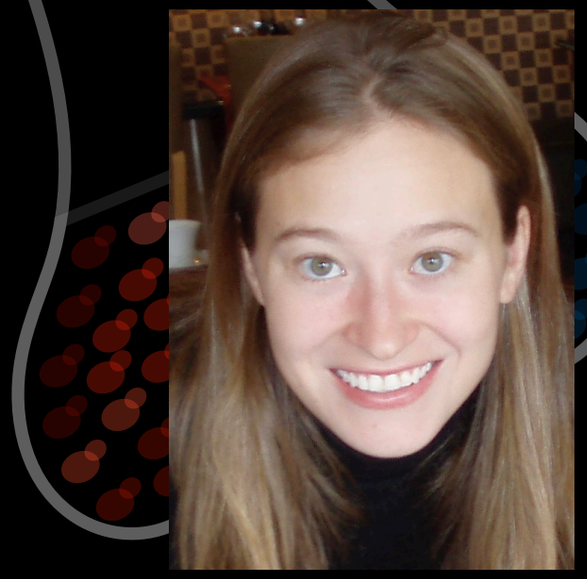
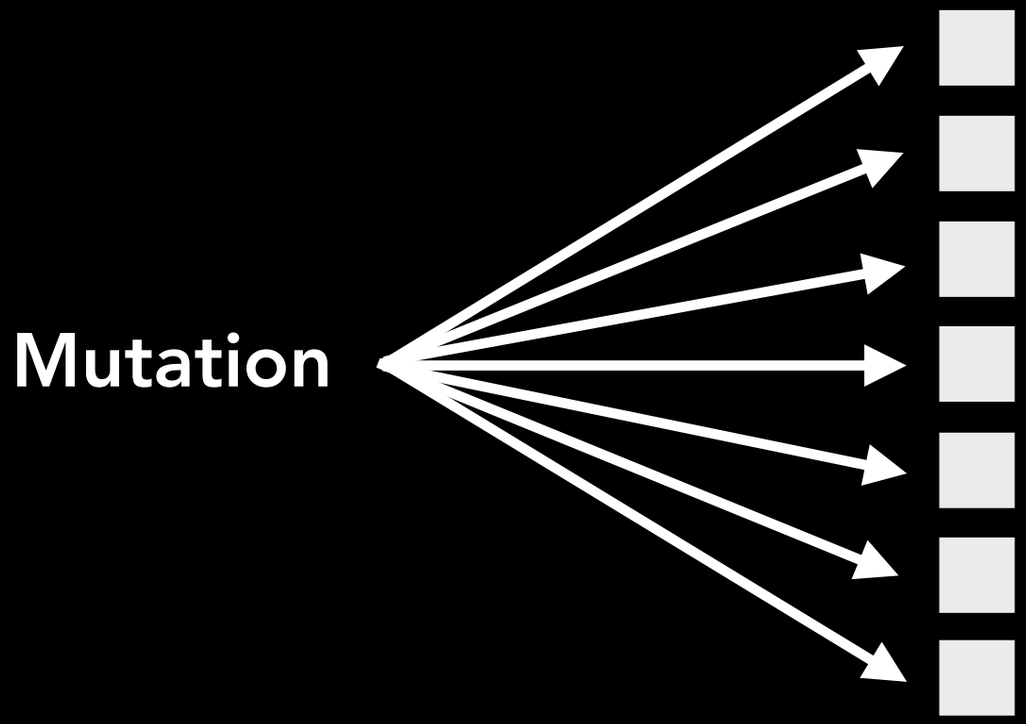


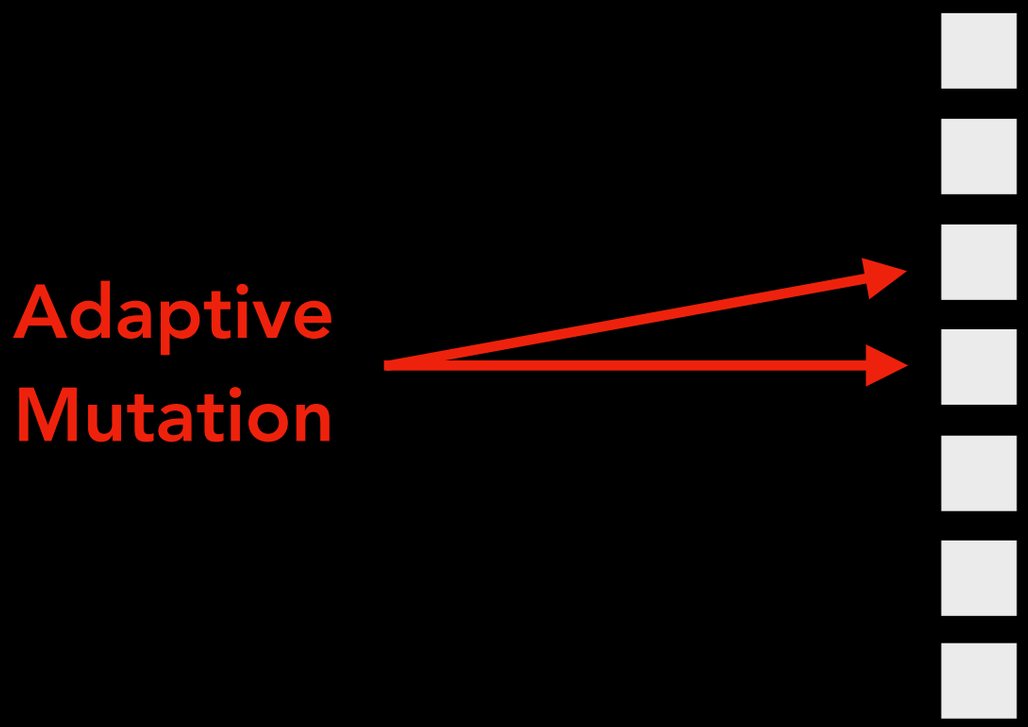
Kerry Geiler-Samerotte

ASU BIODESIGN INSTITUTE
ARIZONA STATE UNIVERSITY

Organisms are integrated, so mutations should affect many traits



Adaptive mutations affect few phenotypes



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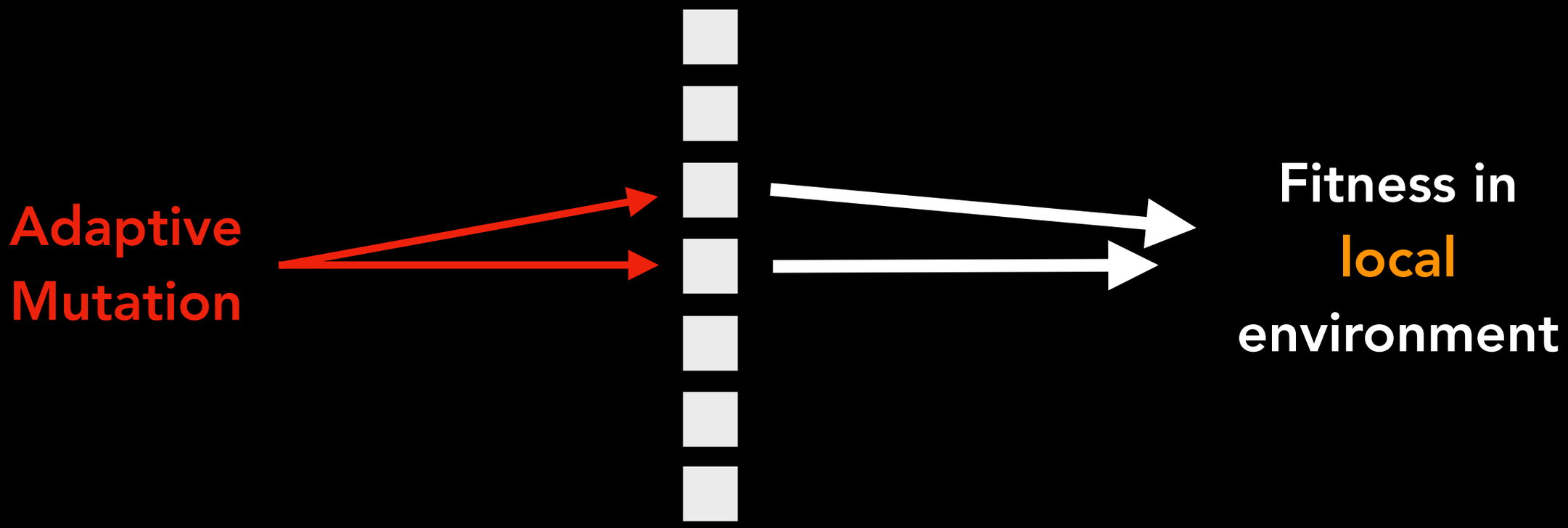

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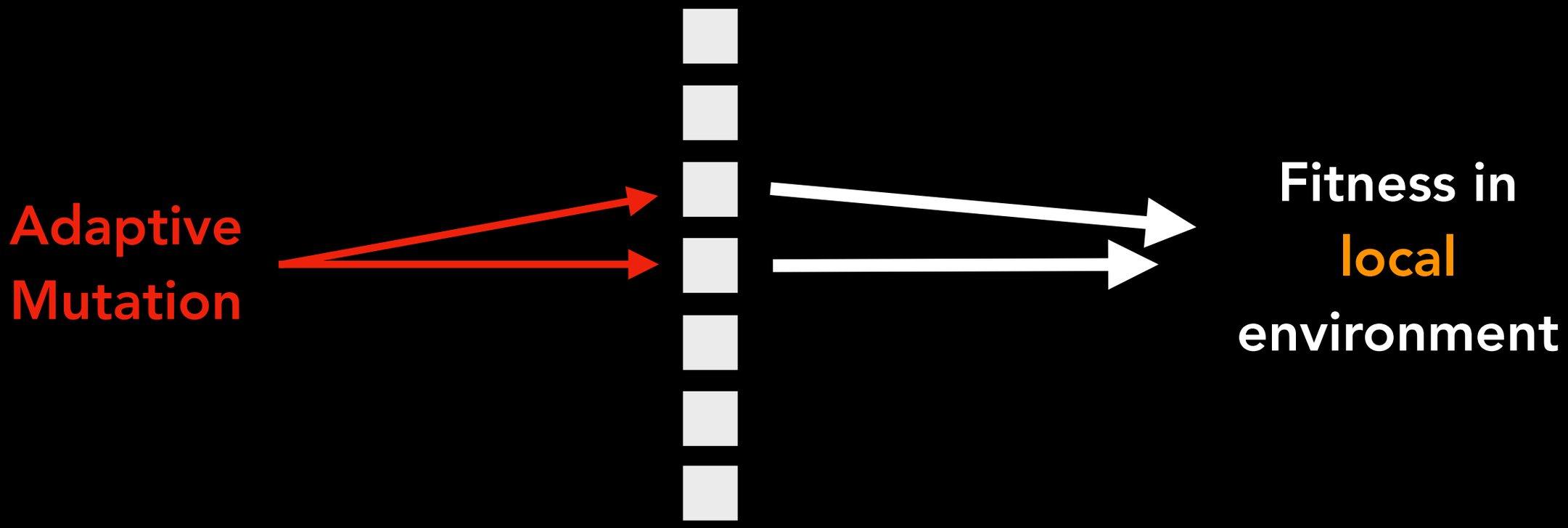

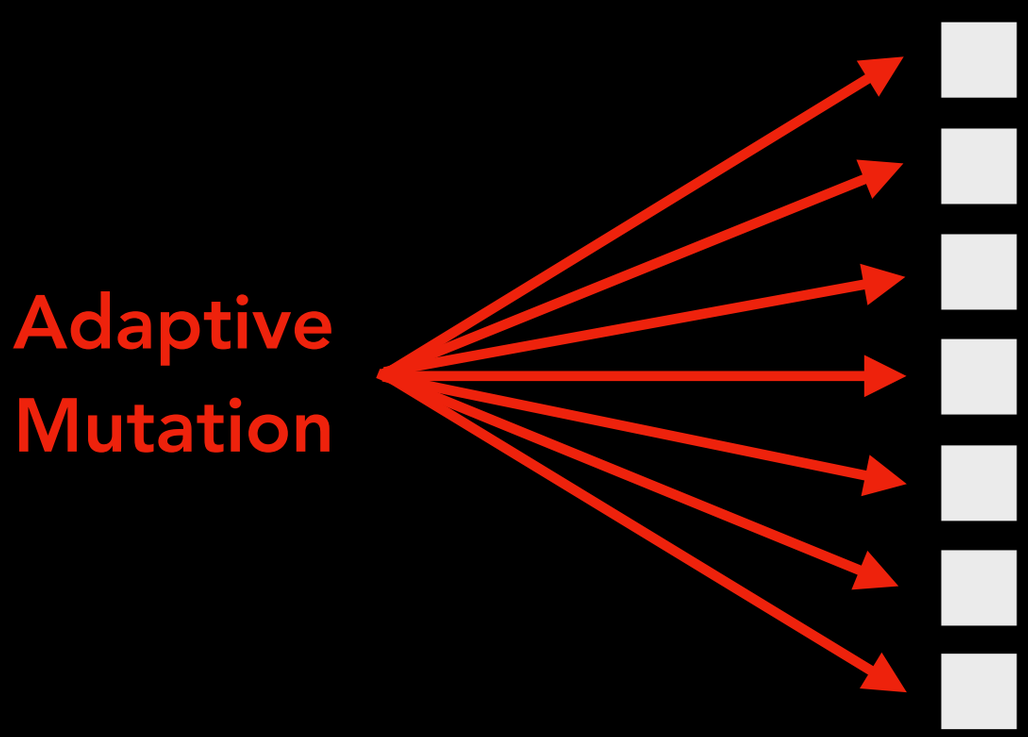

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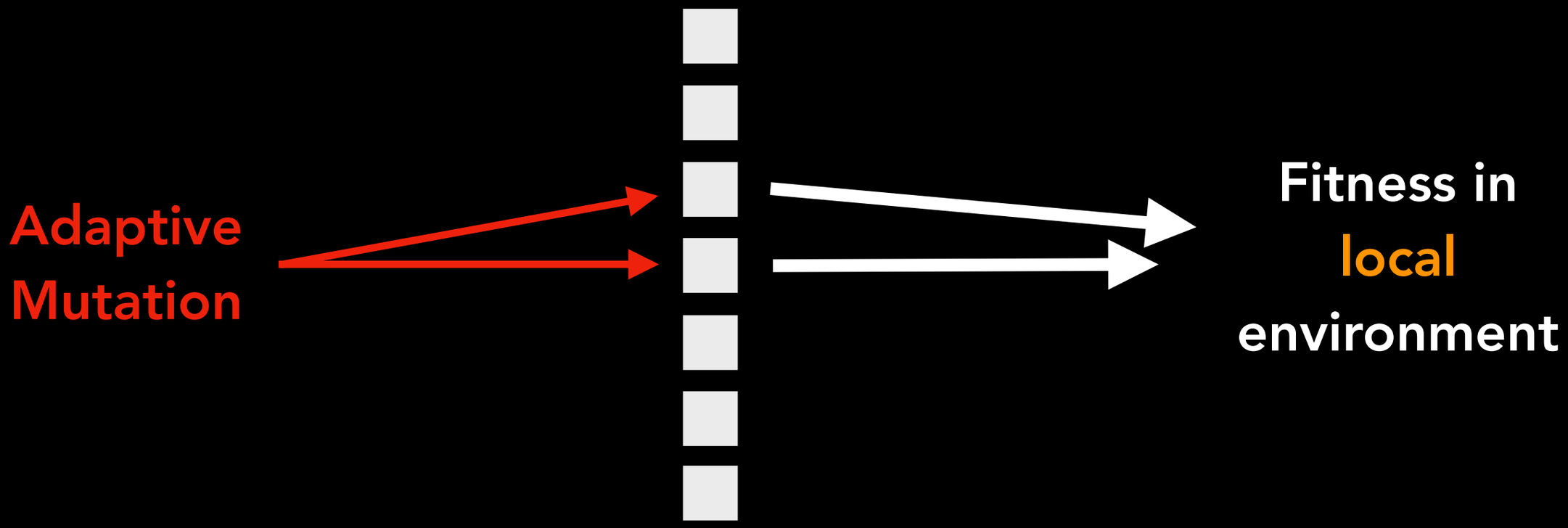

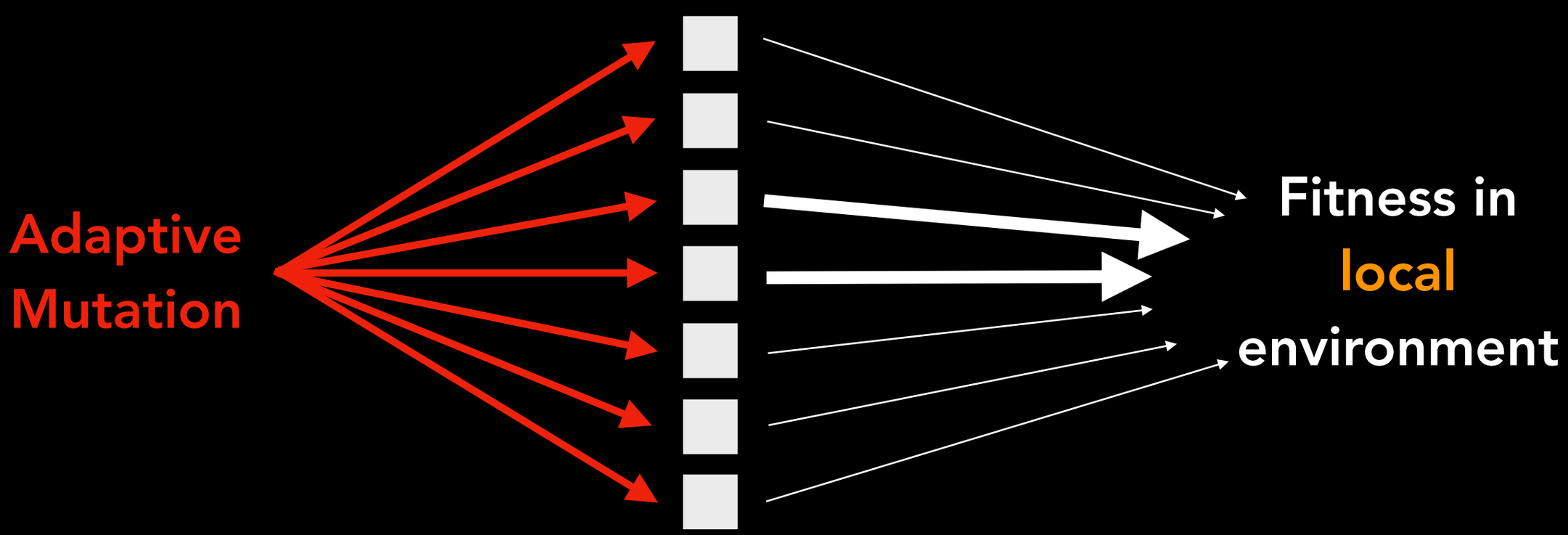

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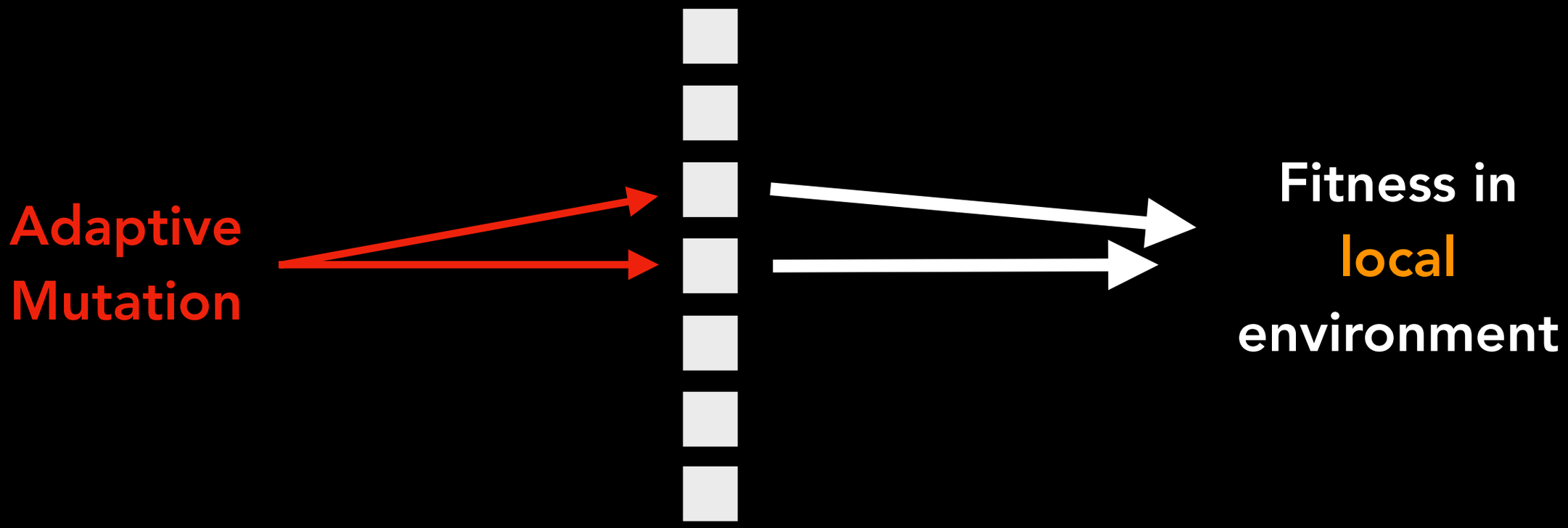
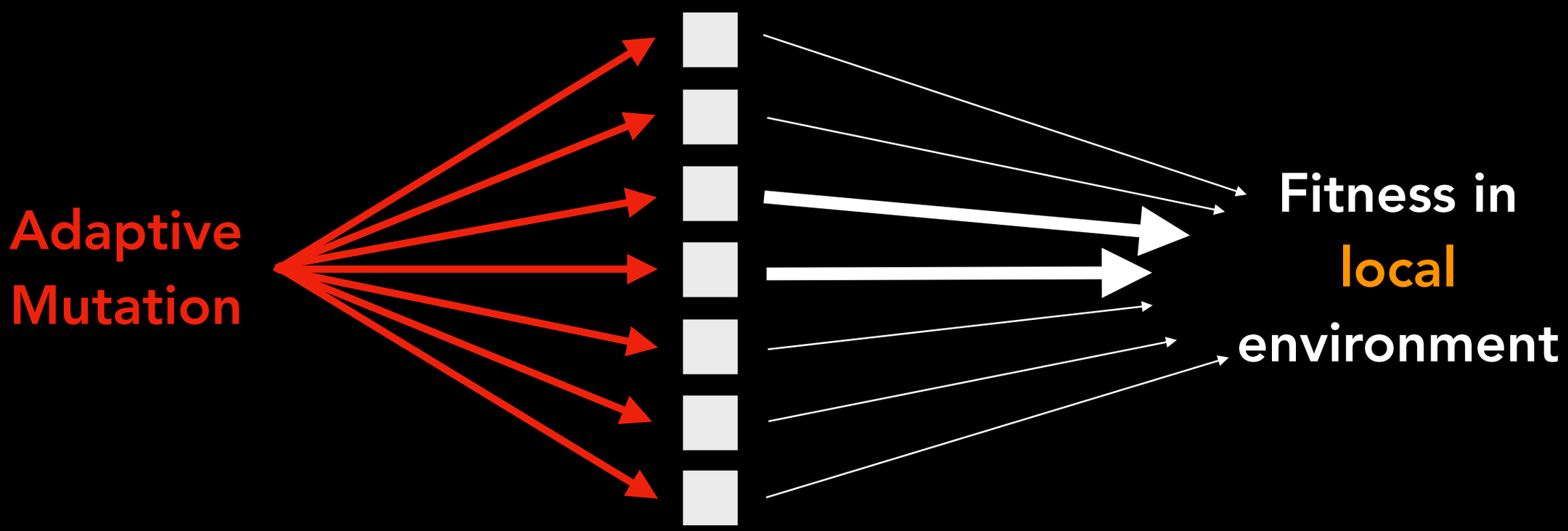


Adaptive mutations affect few fitness-relevant phenotypes



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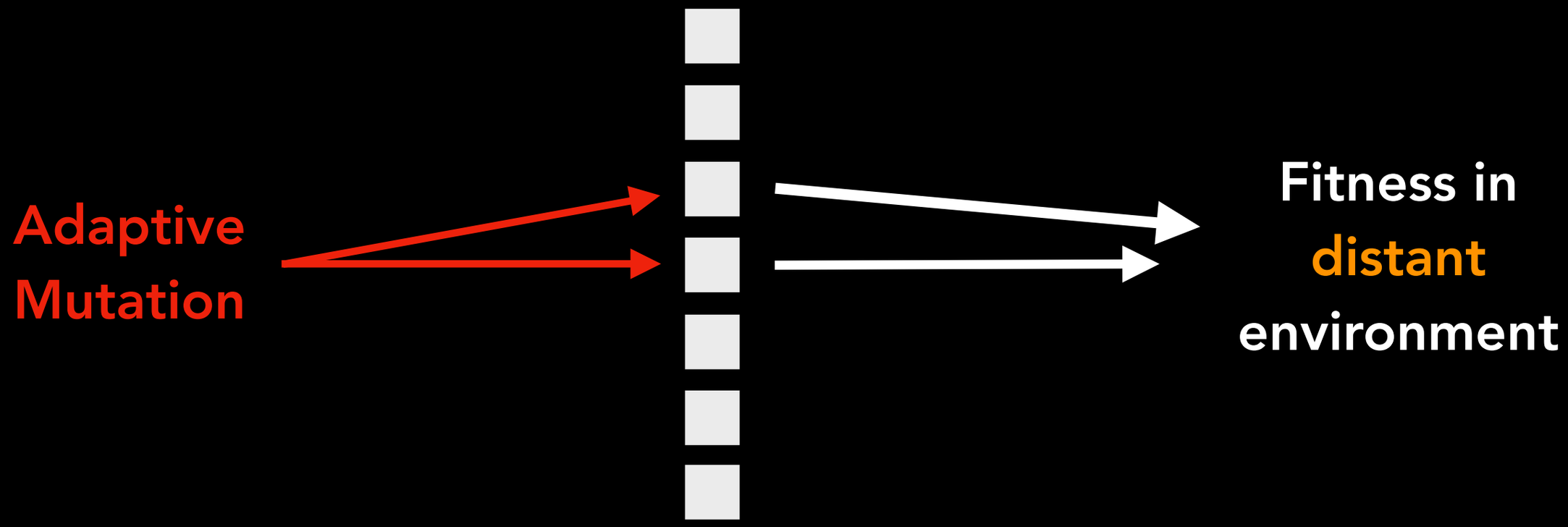
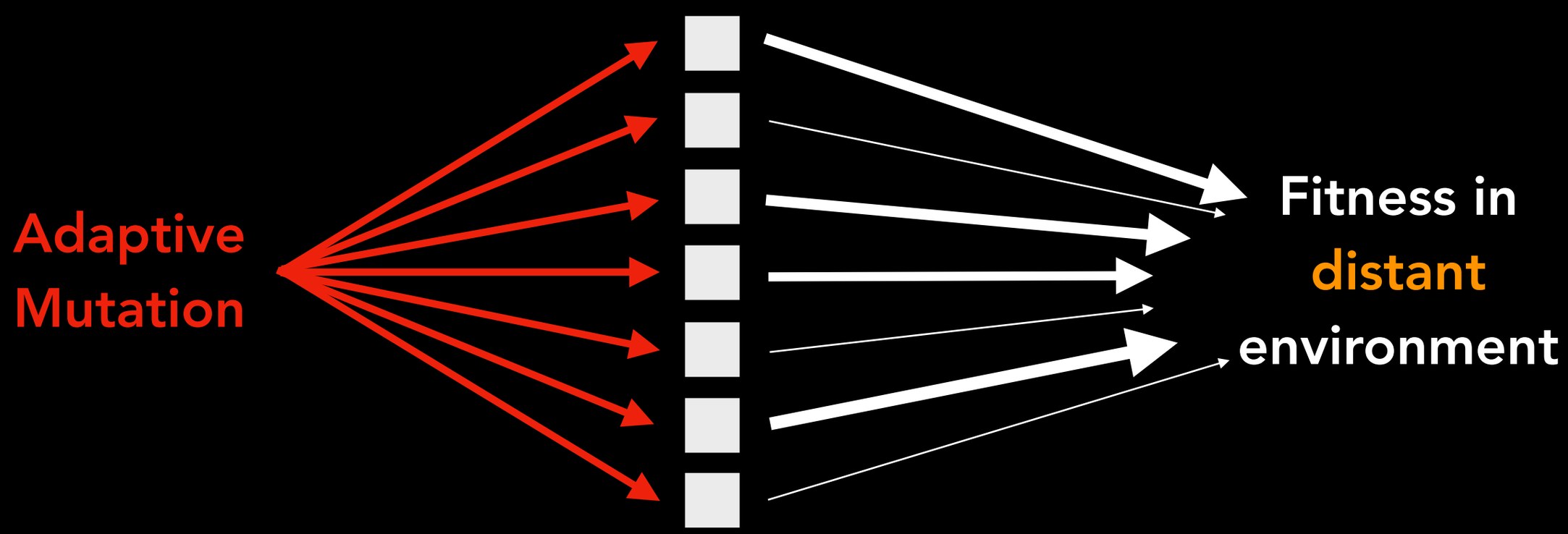
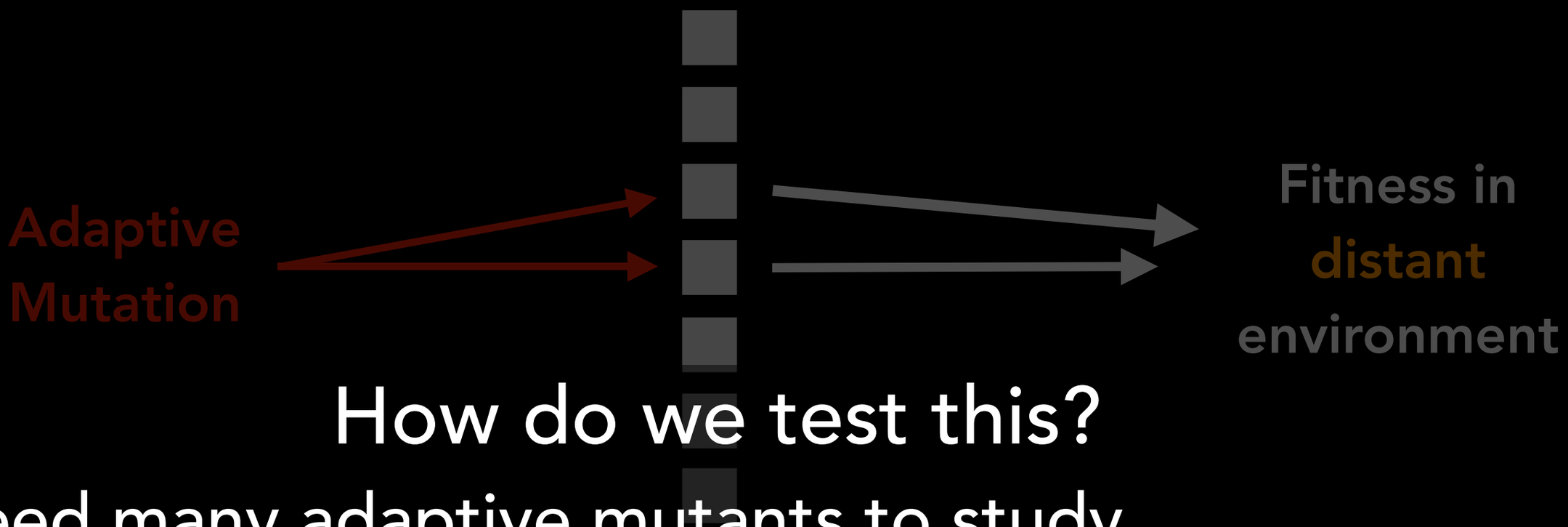


Adaptive mutations affect few fitness-relevant phenotypes

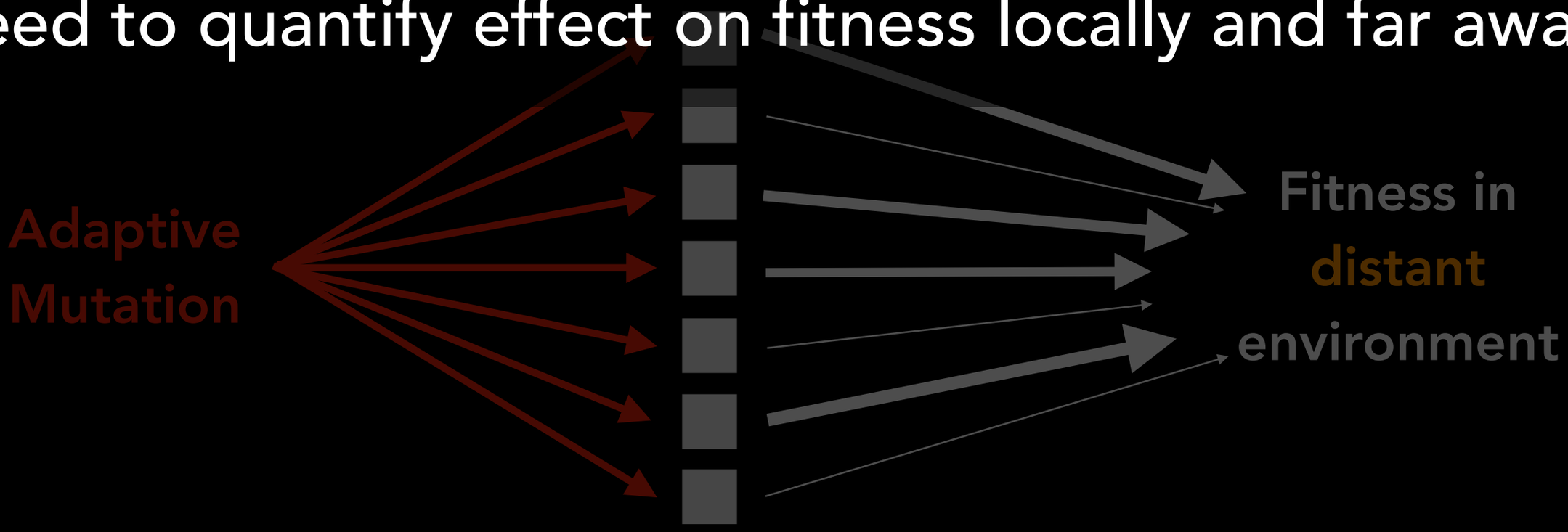


Adaptive mutations affect few phenotypes

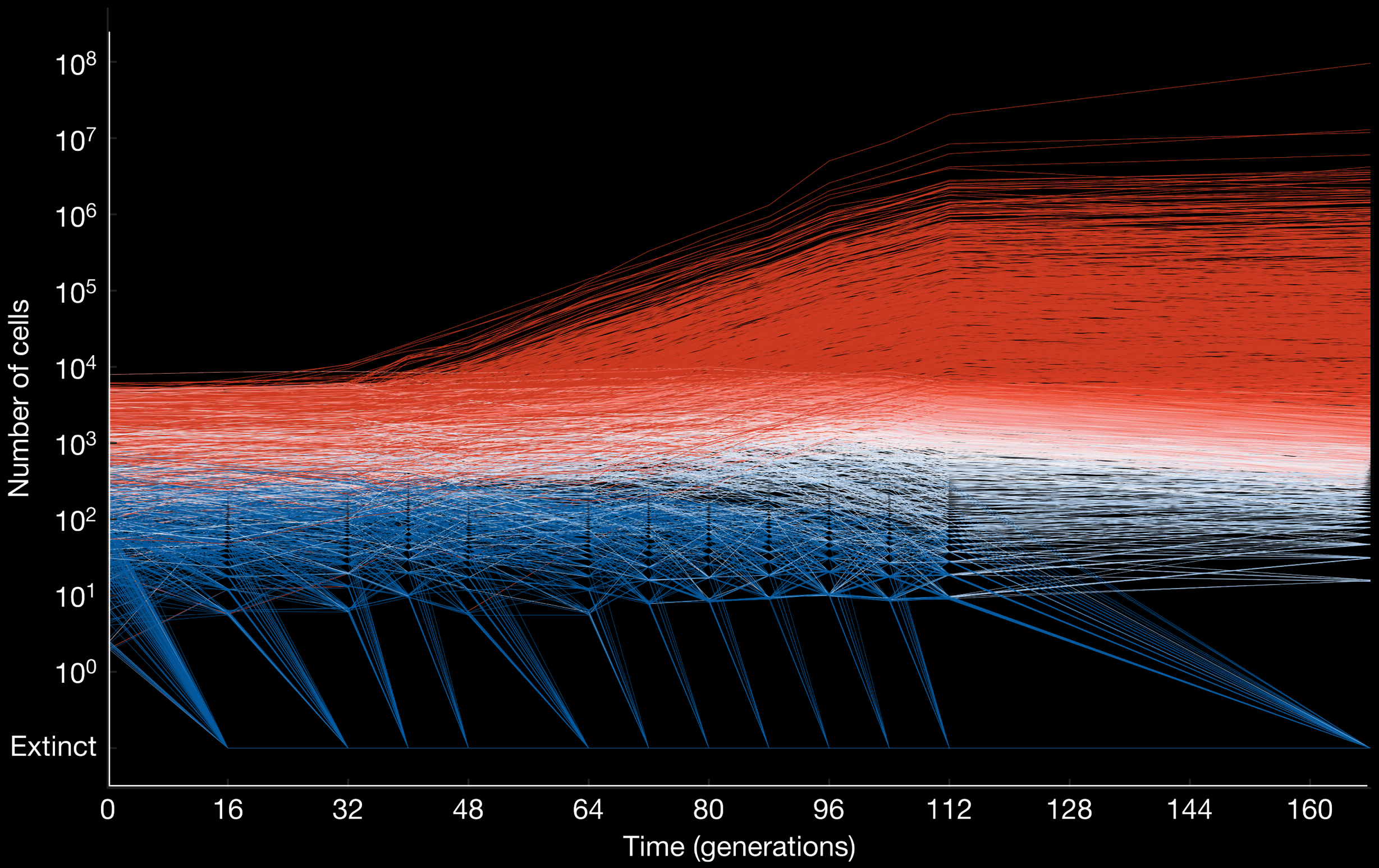


How do we test this?

1. Need many adaptive mutants to study
2. Need to identify fitness-relevant phenotypes
3. Need to quantify effect on fitness locally and far away

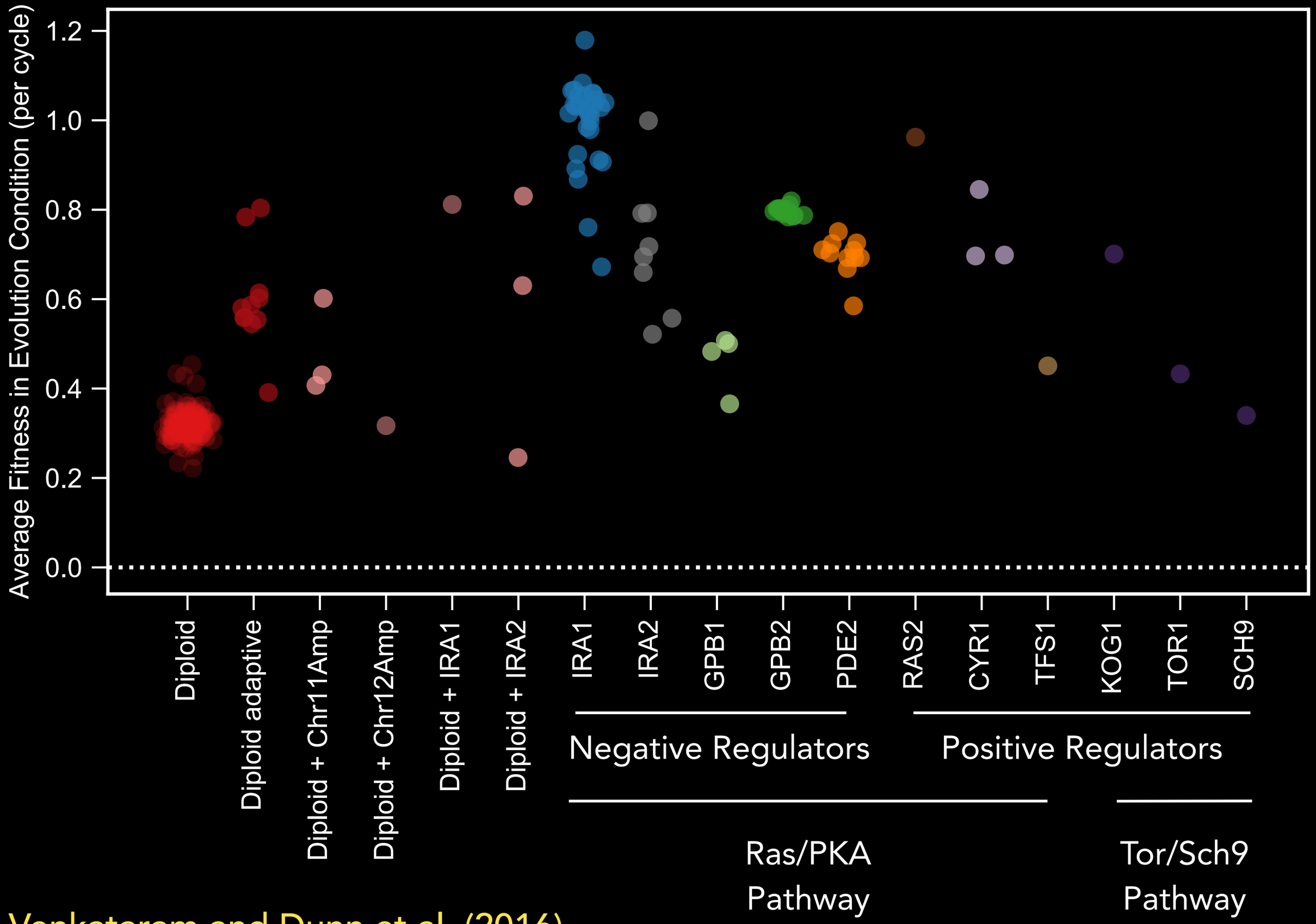


DNA barcoding allows us to track and isolate thousands of adaptive mutants



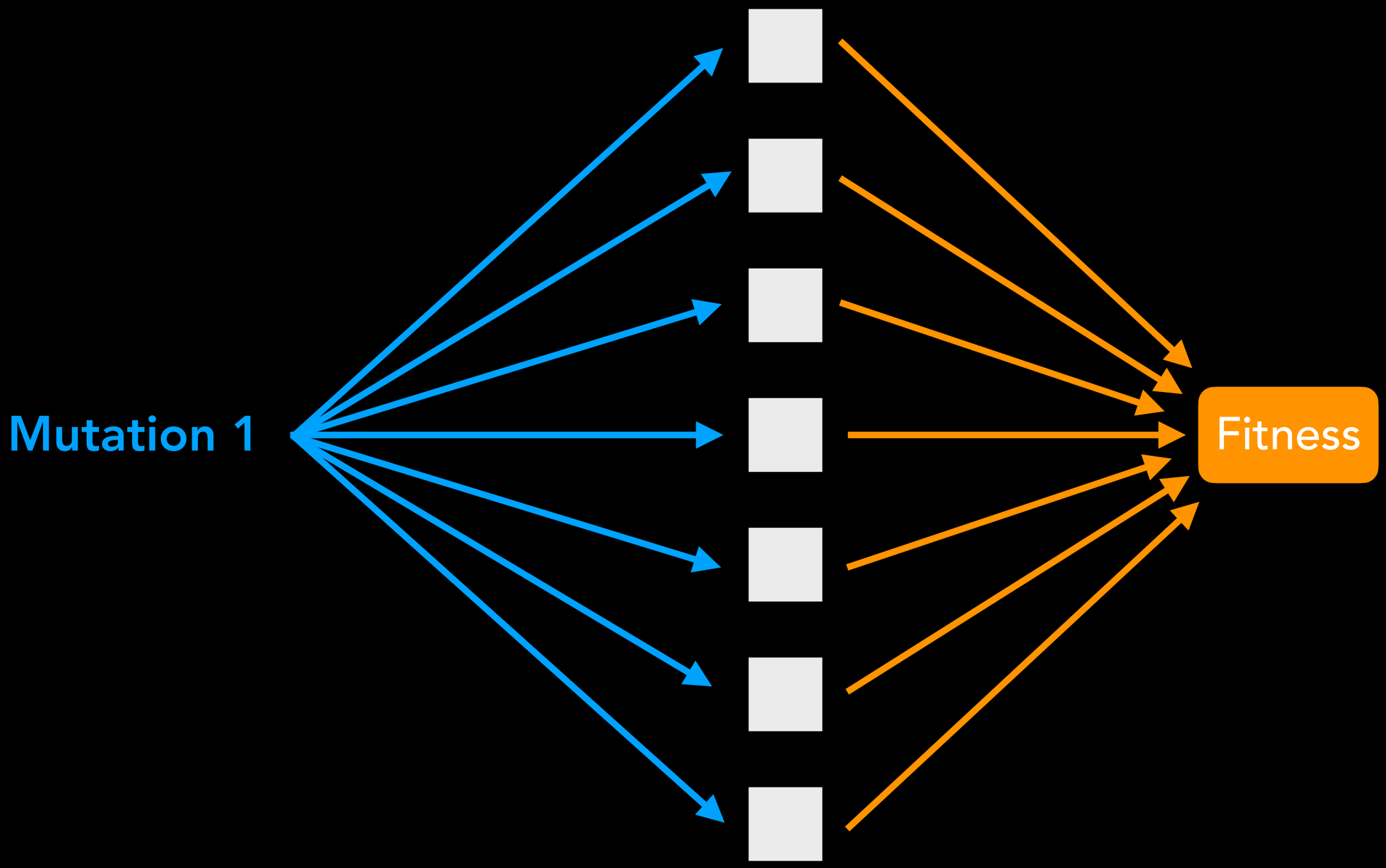
Levy and Blundell et al. (2015)

Many strongly adaptive mutants

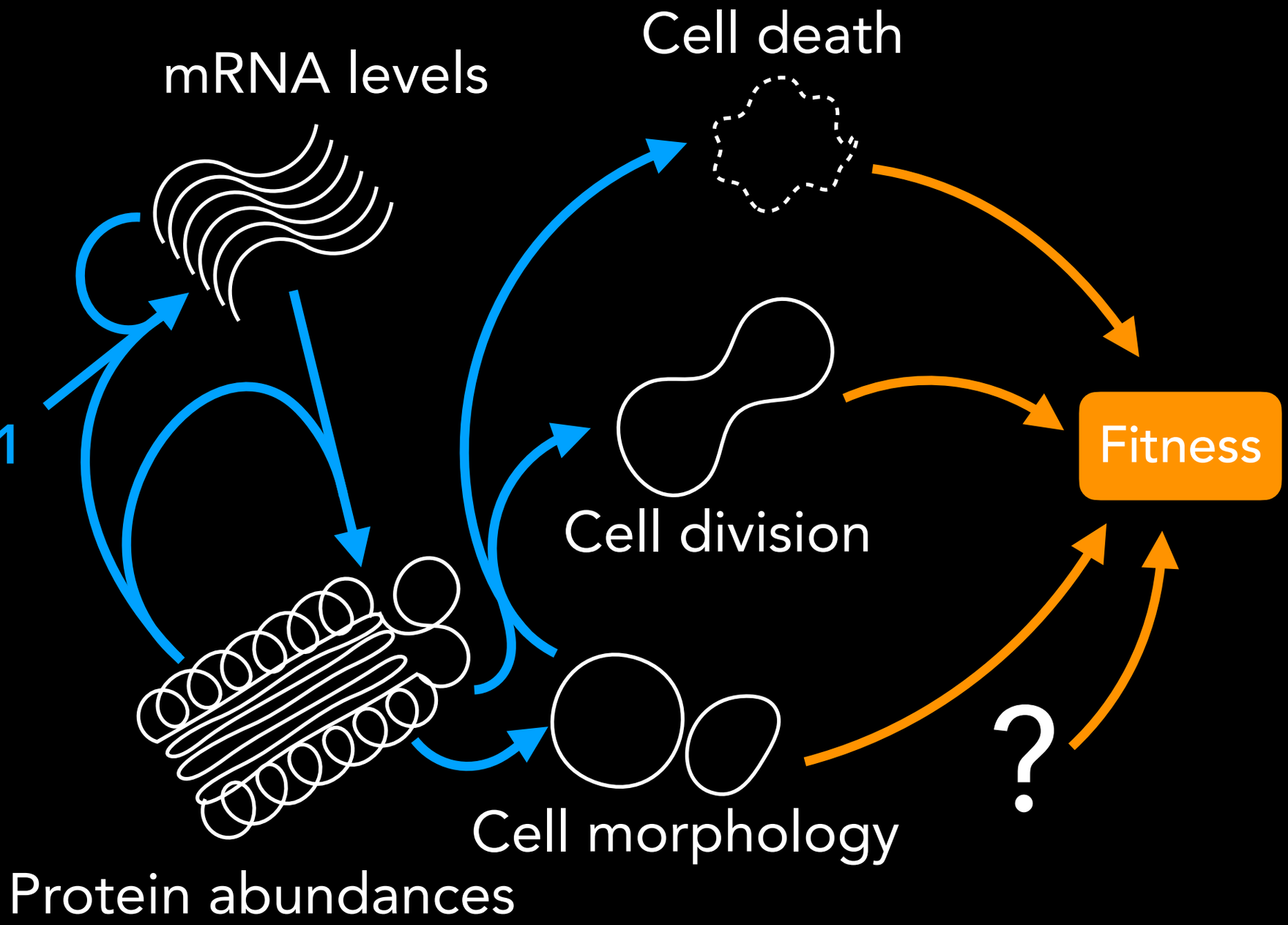


Venkataram and Dunn et al. (2016)

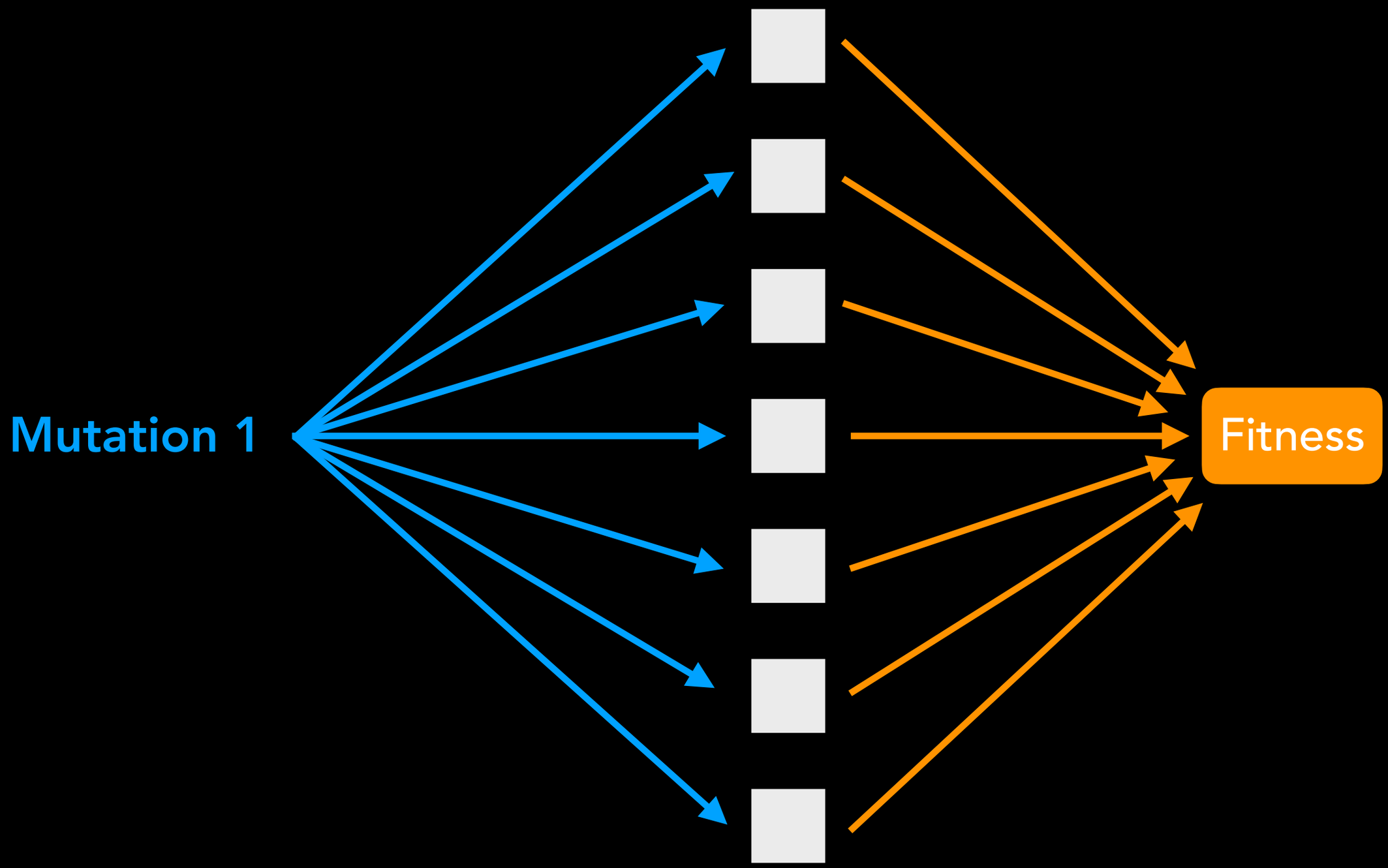
Genotype-to-Phenotype-to-Fitness Map



Genotype-to-Phenotype-to-…-to-Phenotype-to-Fitness Map



Revealing Fitness-Relevant Phenotypes with Environmental Perturbations



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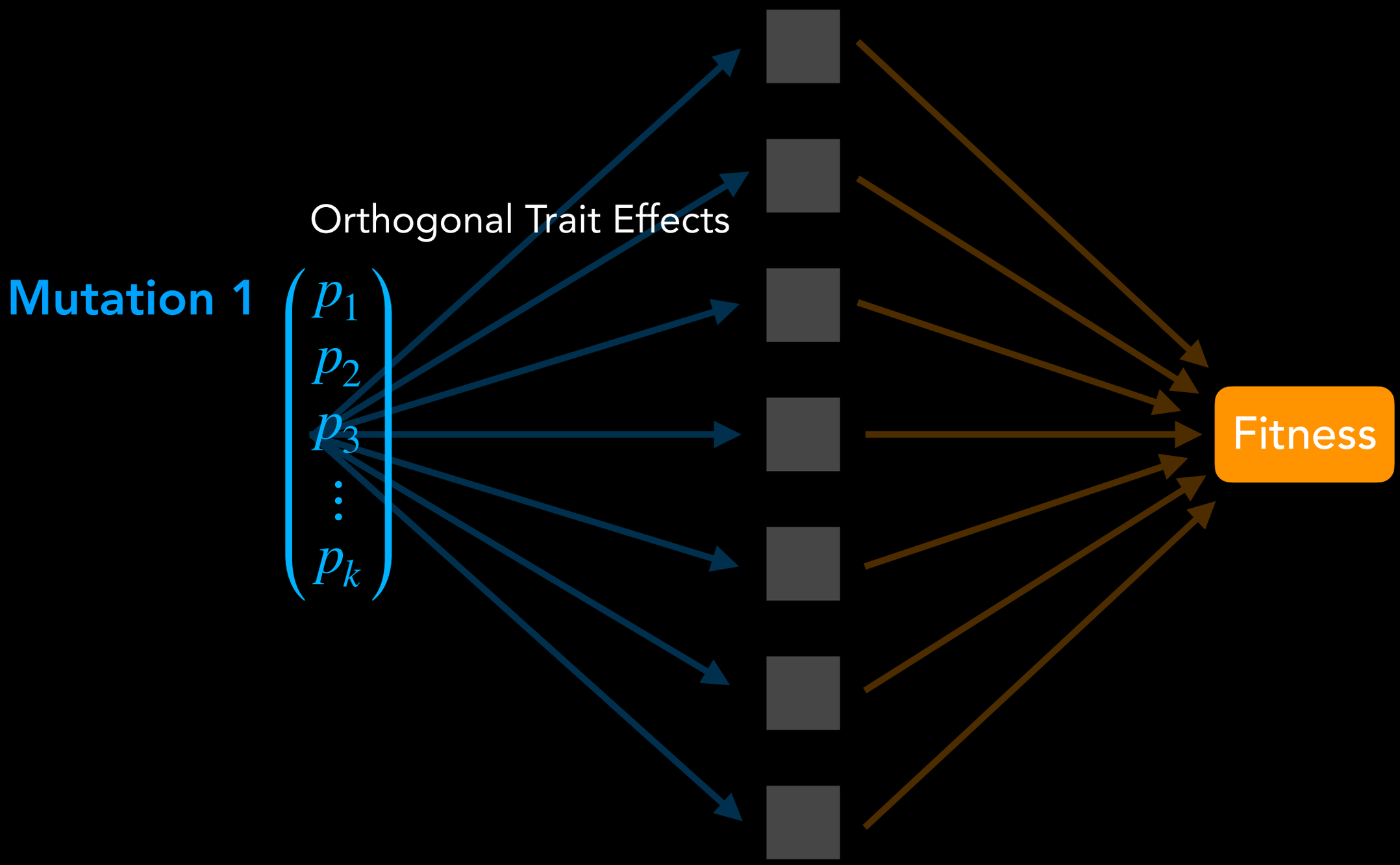

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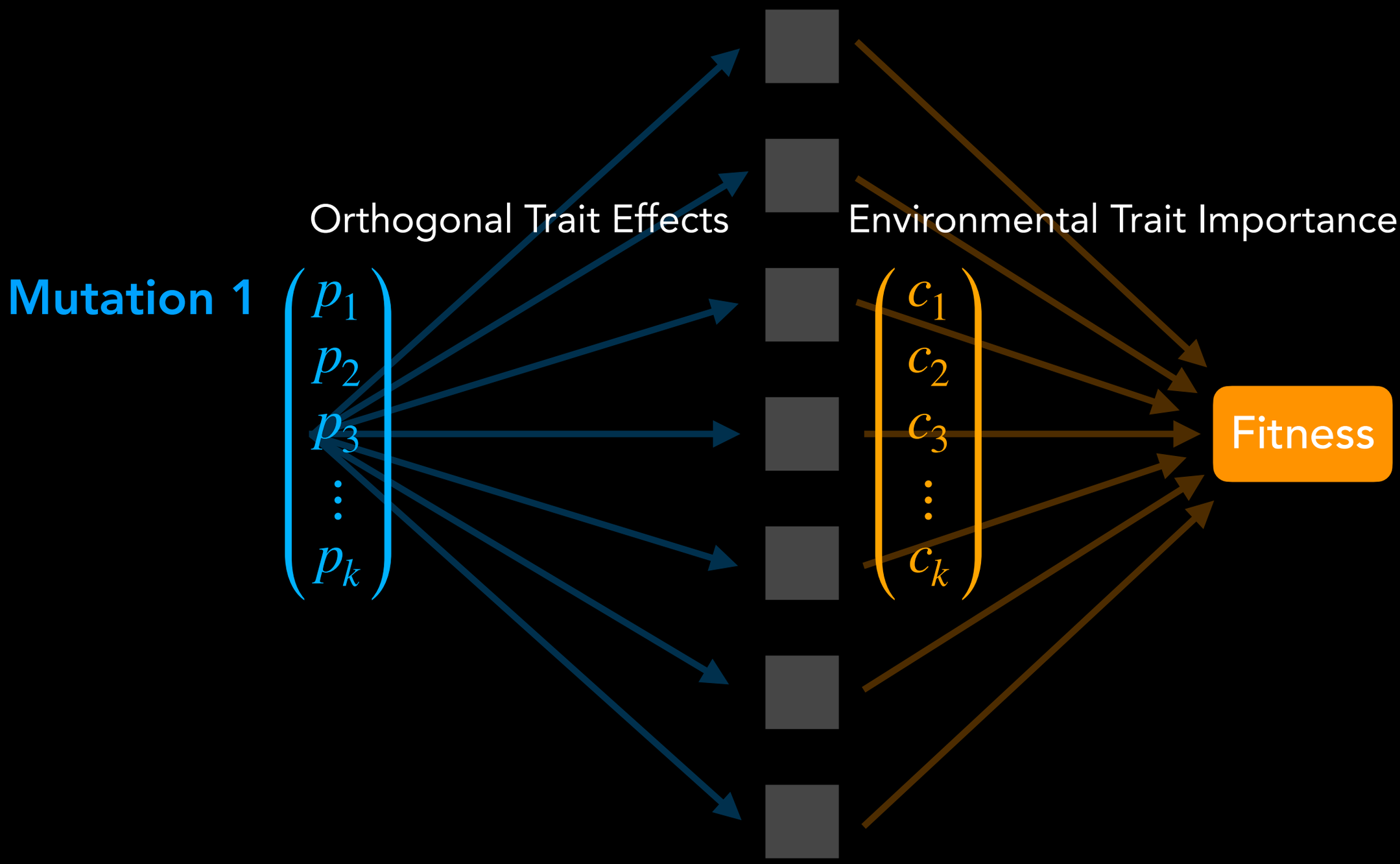

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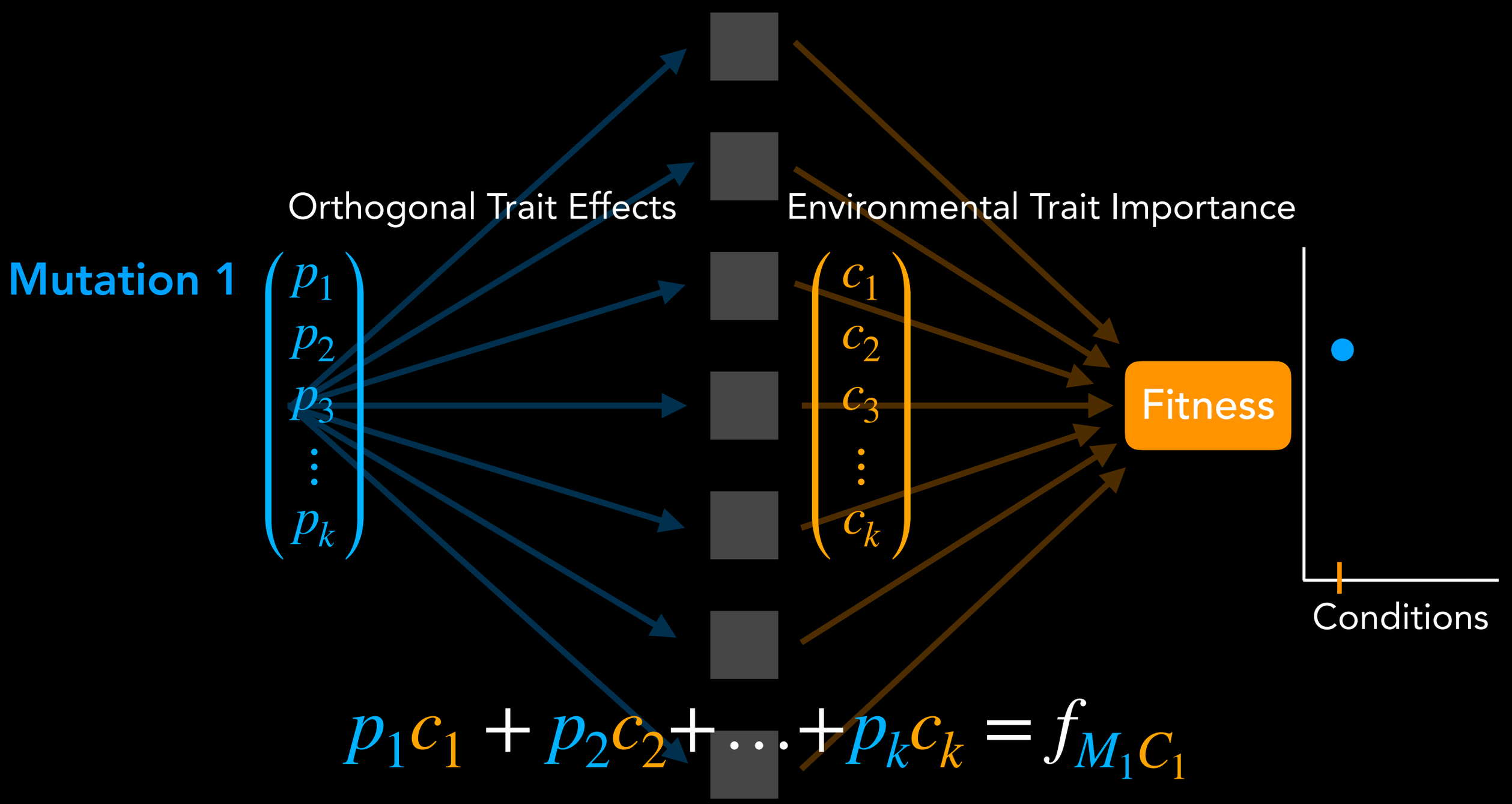
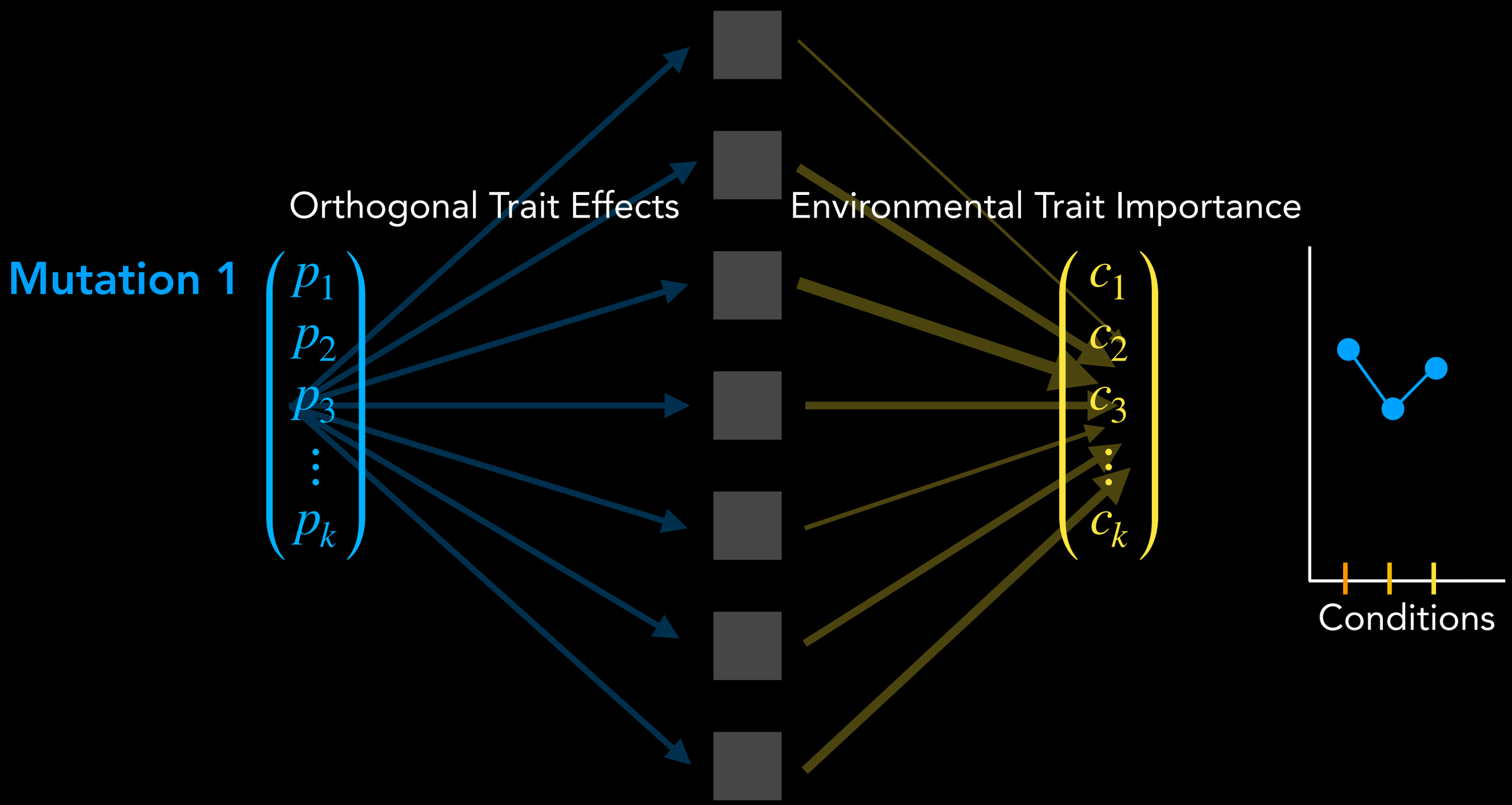


$$p_1c_1 + p_2c_2 + \ldots + p_kc_k = f_{M_1C_1}$$

Revealing Fitness-Relevant Phenotypes with Environmental Perturbations

Revealing Fitness-Relevant Phenotypes with Environmental Perturbations



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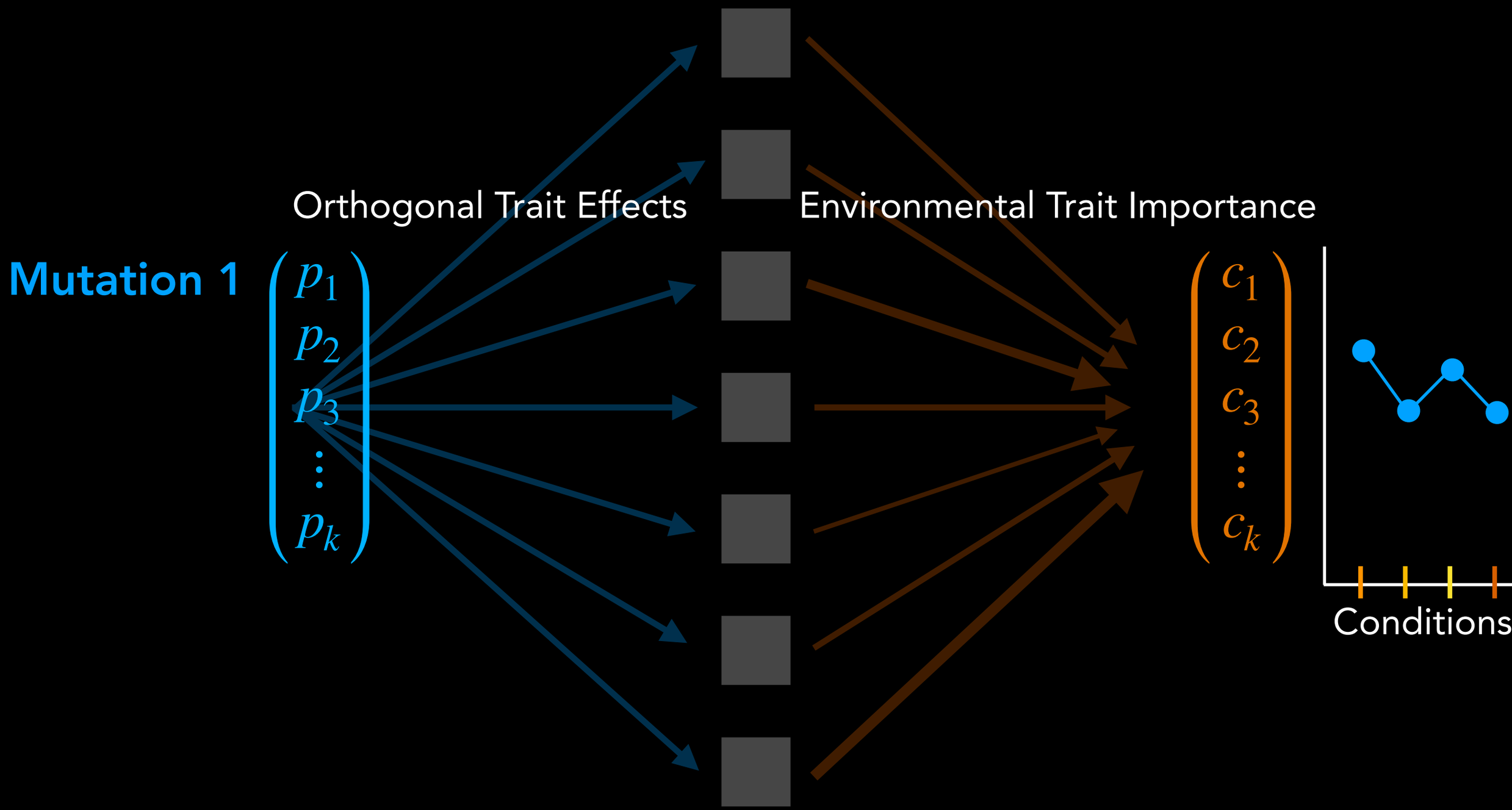

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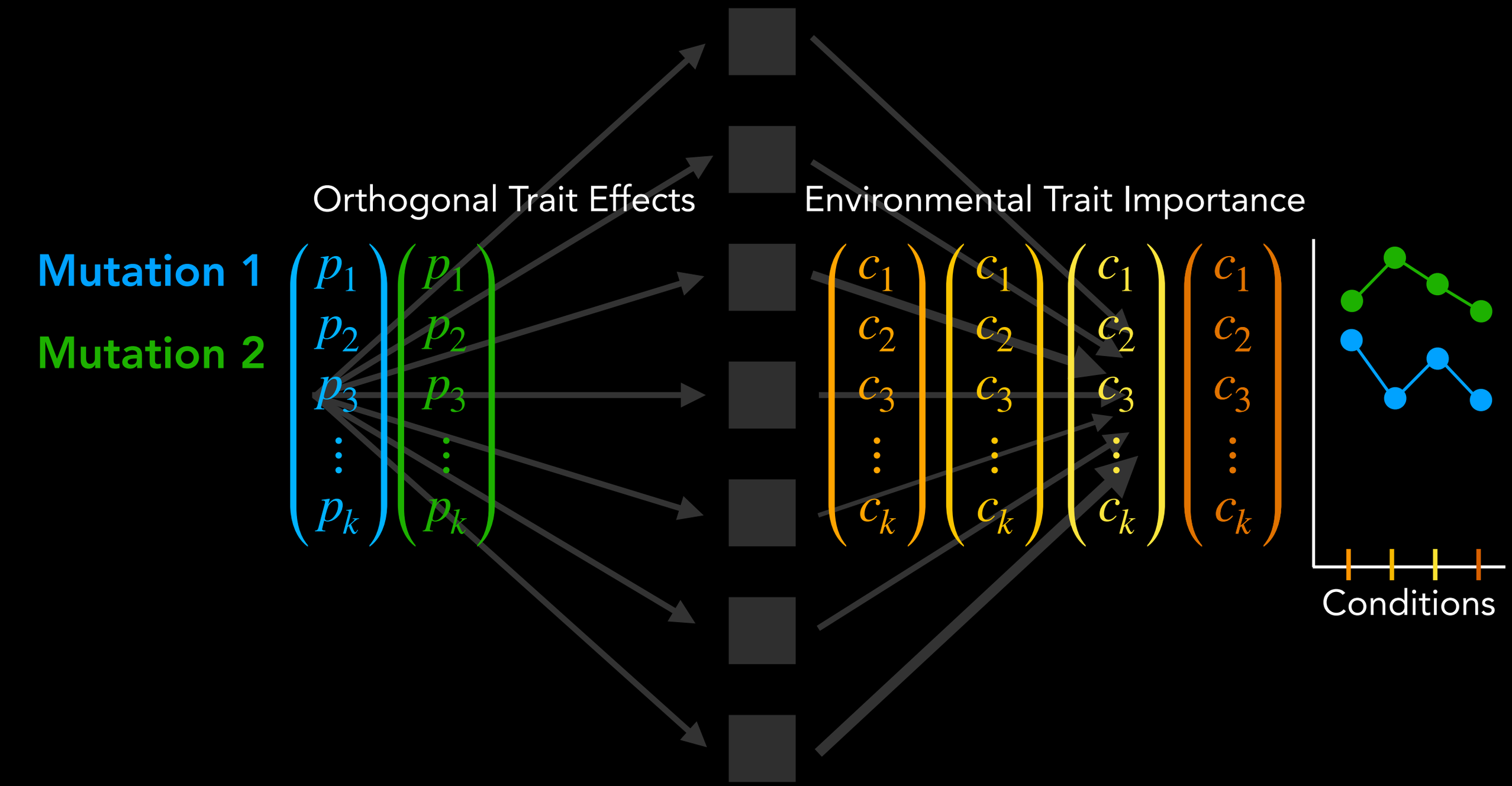

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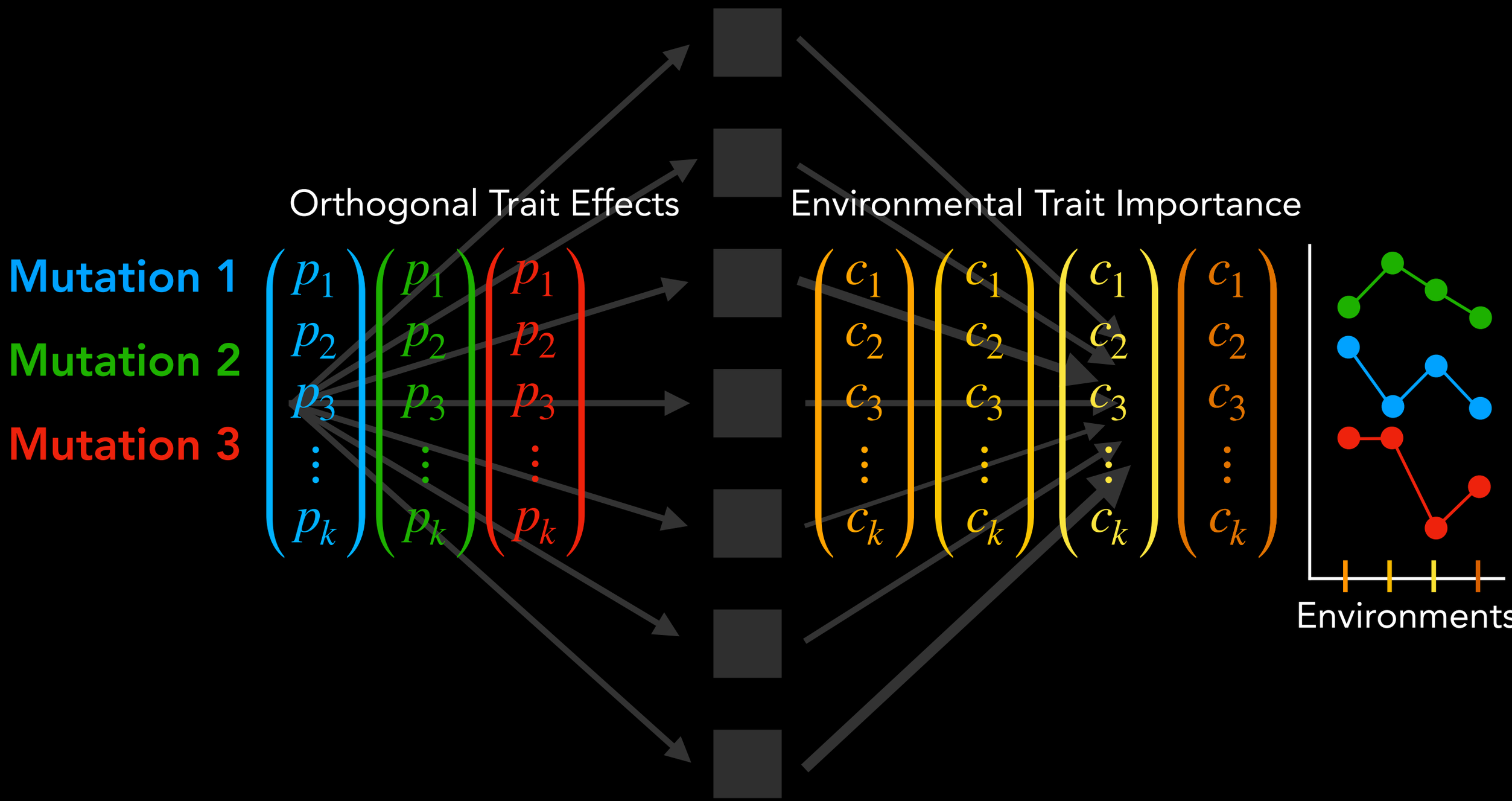

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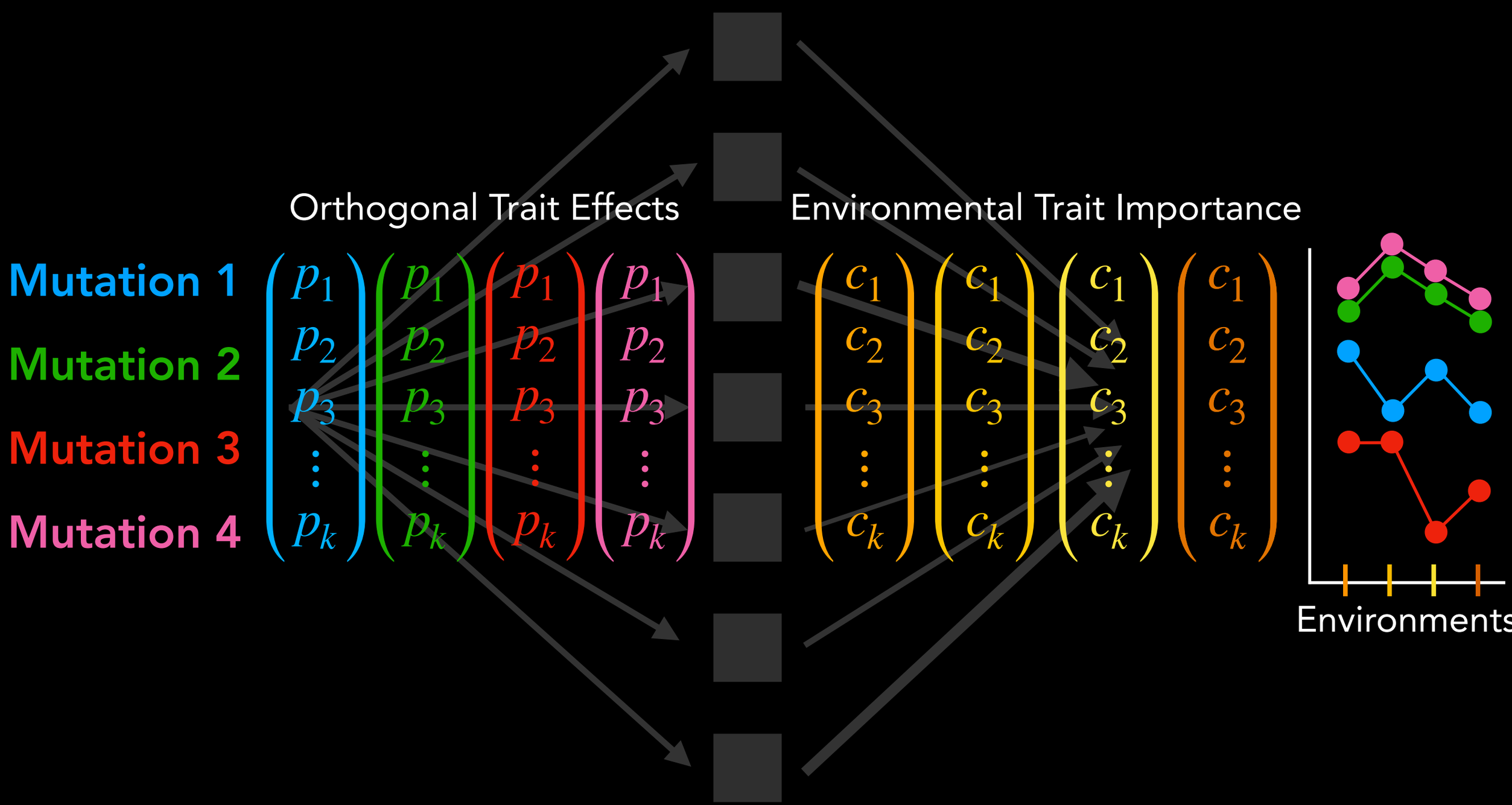

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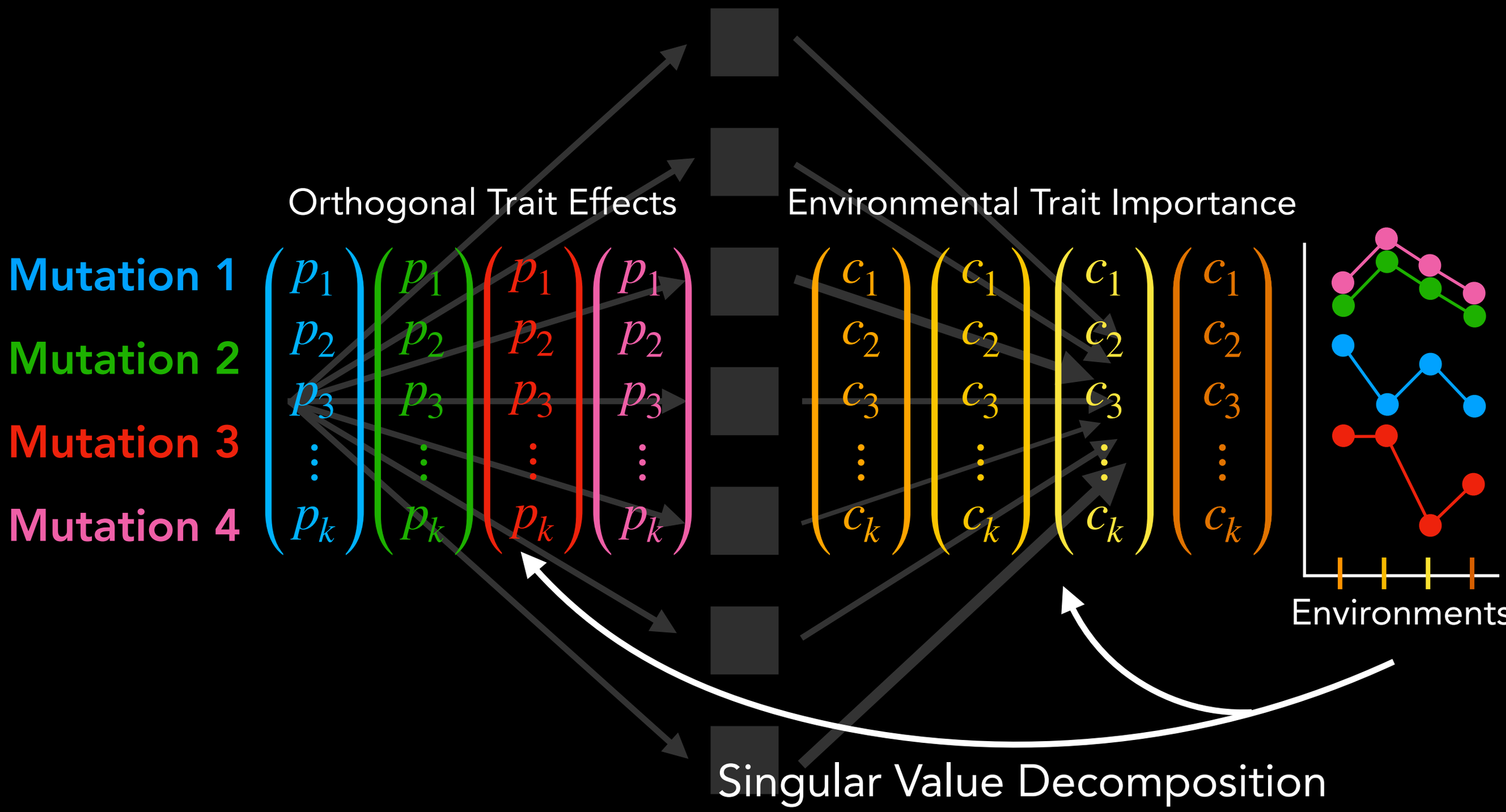

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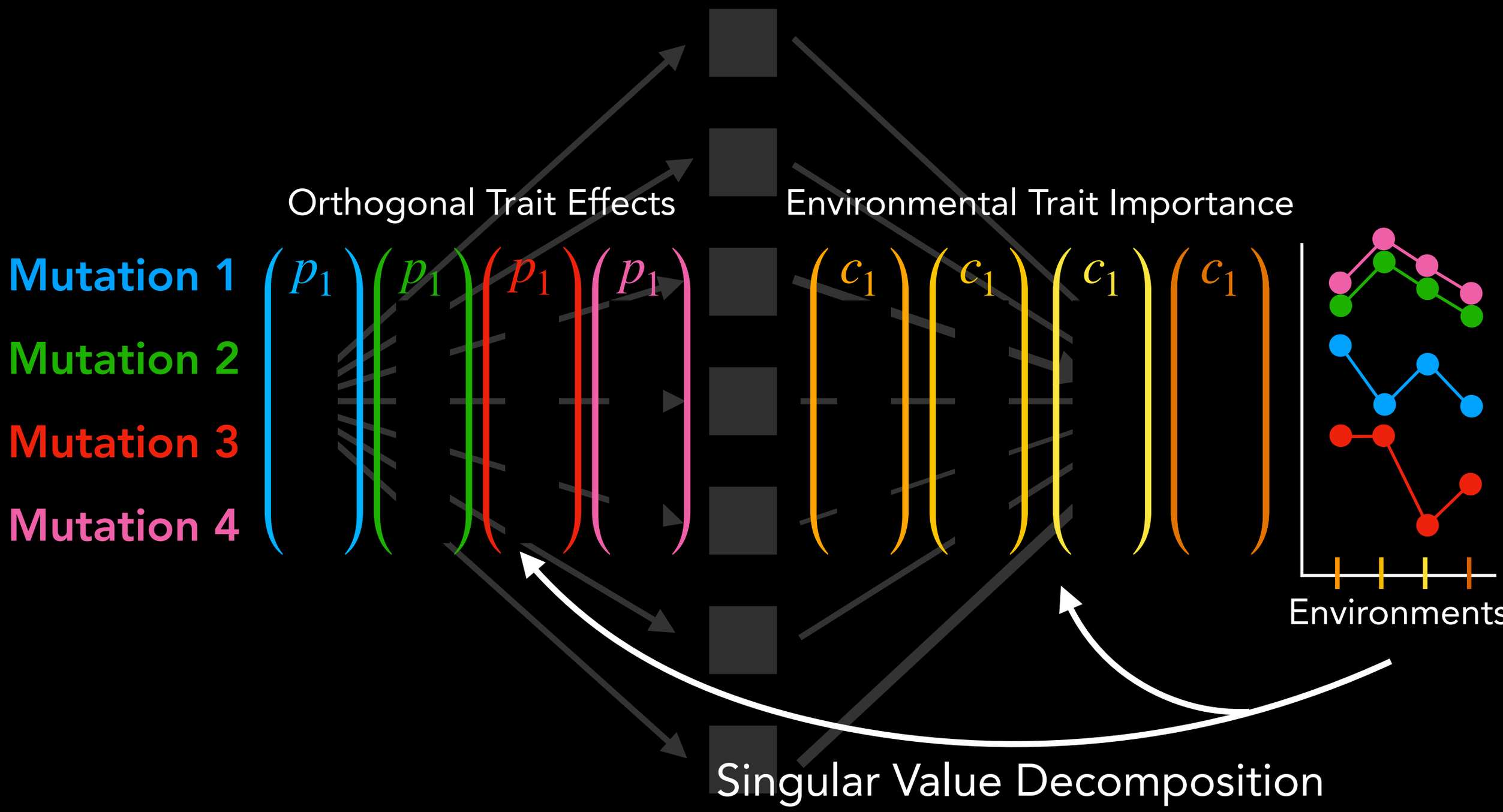

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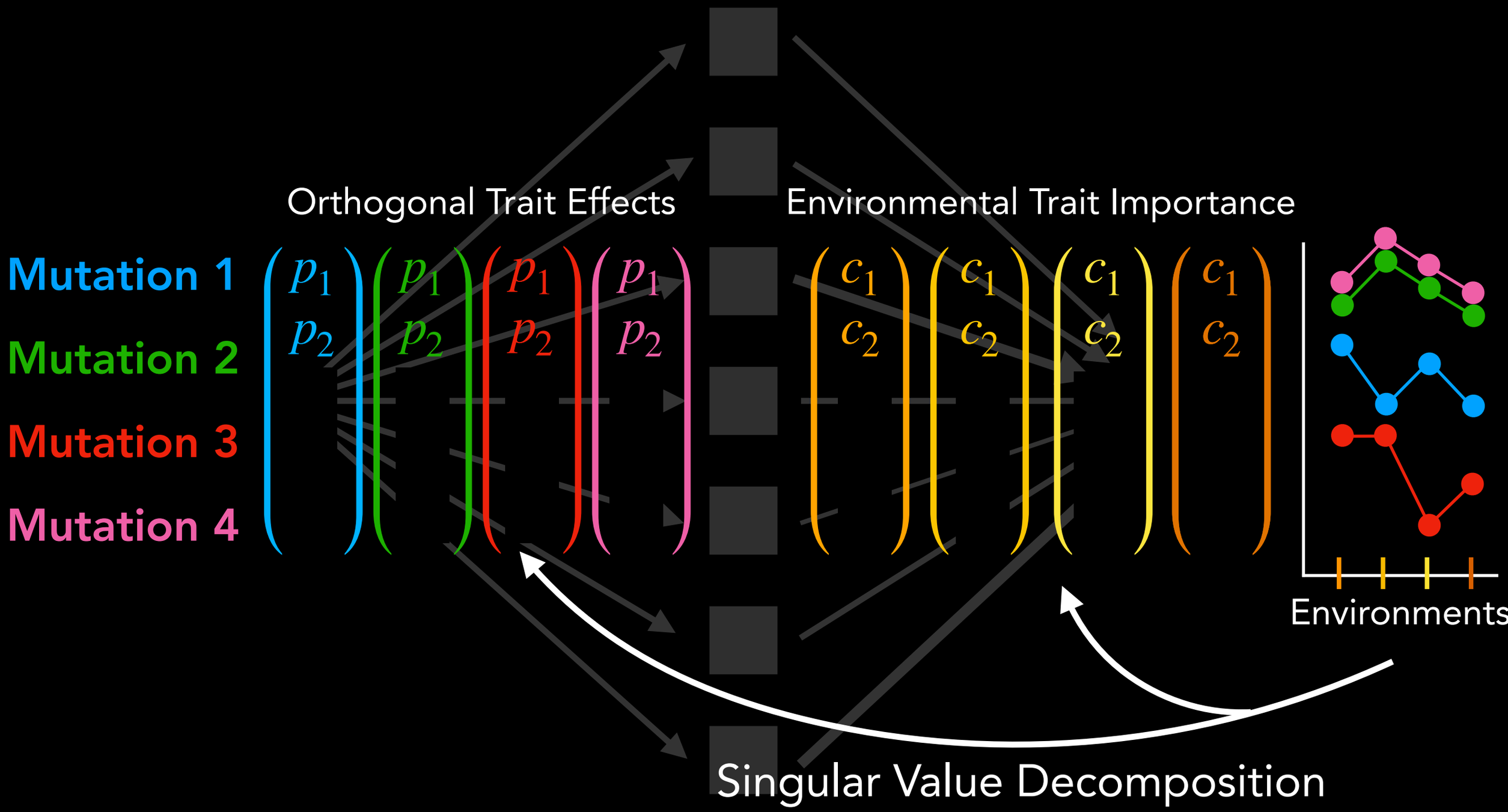

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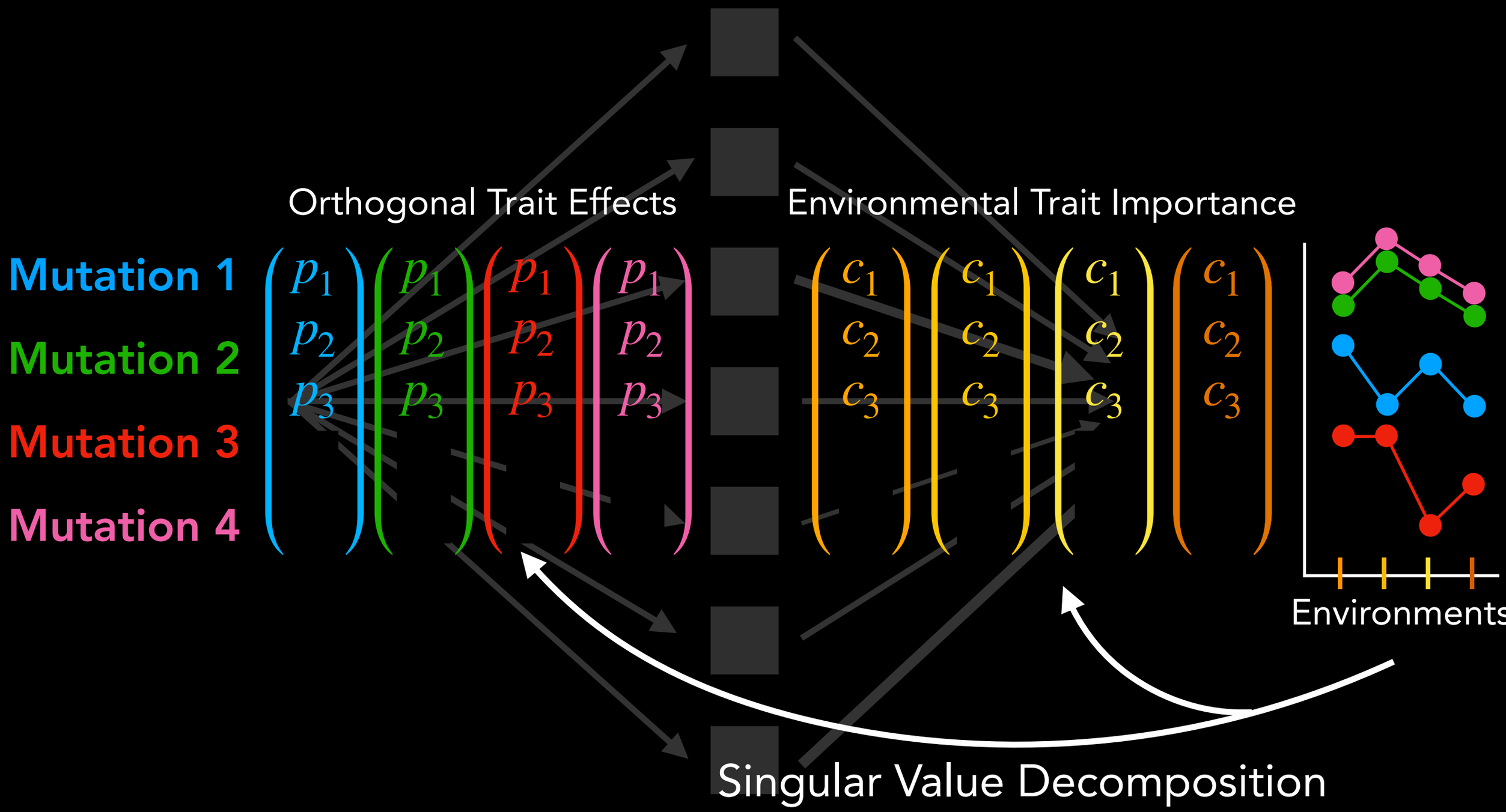

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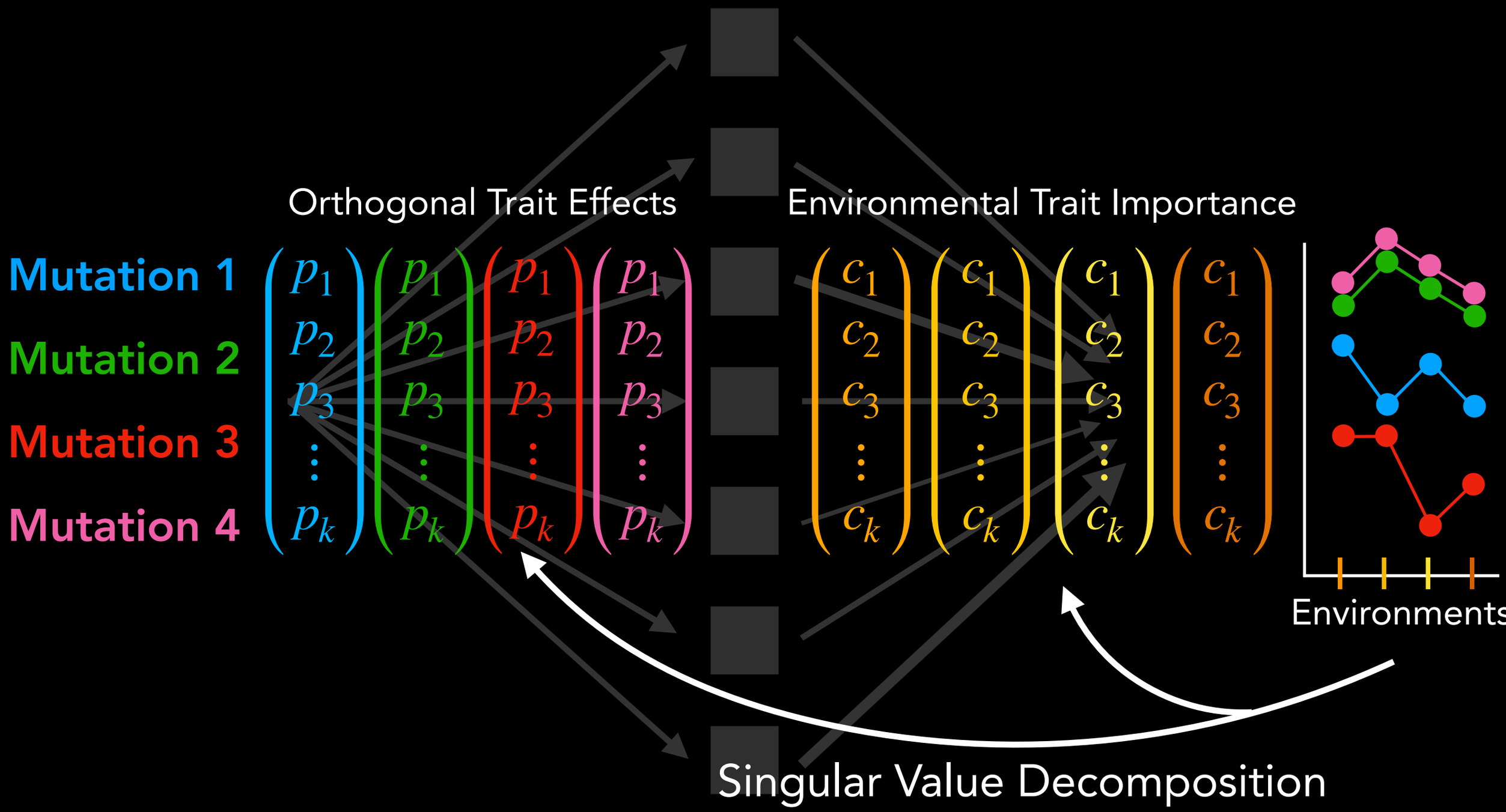


We Measured Fitness In Many Environments Using Barcoding

9 batches of Evolution Condition

Fermentation Series

8 hour fermentation 4 lag 28 resp
12 hour fermentation 4 lag 28 resp
18 hour fermentation 4 lag 28 resp
22 hour fermentation 4 lag 28 resp

Respiration/Stationary Series

1 Day Transfer 3 Day Transfer
4 Day Transfer 5 Day Transfer
6 Day Transfer 7 Day Transfer

Glucose/Oxygenation

w/ 1.4% glucose w/ 1.8% glucose
1.5% in Baffled flask x2

1.4% 1.6% 1.7% 1.8% 2.5% glucose
in Baffled

Drugs

+ 8.5uM GdA x2 + 17uM GdA
+ 0.5ug FCZ + 2ug FCZ
+ 0.4ug Benomyl + 2ug Benomyl
+ DMSO

Carbon Sources

+ 0.5% Raf + 1% Raf
+ 1% Glycerol + 1% EtOH
+ 1% Suc 1% Raf

Salts

+ 0.2M NaCl + 0.5M NaCl
+ 0.2M KCl + 0.5M KCl

We Measured Fitness In Many Environments Using Barcoding

9 batches of Evolution Condition

Fermentation Series

8 hour ferme[illegible] 4 lag 28 resp

12 hour ferme

18 hour ferme

22 hour ferme

Respiration

1 Day Transf

4 Day Transf

6 Day Transf

Glucos

w/ 1.4% glucose w/ 1.8% glucose

1.5% in Baffled flask x2

1.4% 1.6% 1.7% 1.8% 2.5% glucose

in Baffled

~400 mutants in 45 conditions

for a total of

~18,000 fitness measurements

Drugs

+ 8.5uM GdA x2 + 17uM GdA

+ 0.5ug FCZ + 2ug FCZ

2ug Benomyl

rces

+ 1% Raf

1% EtOH

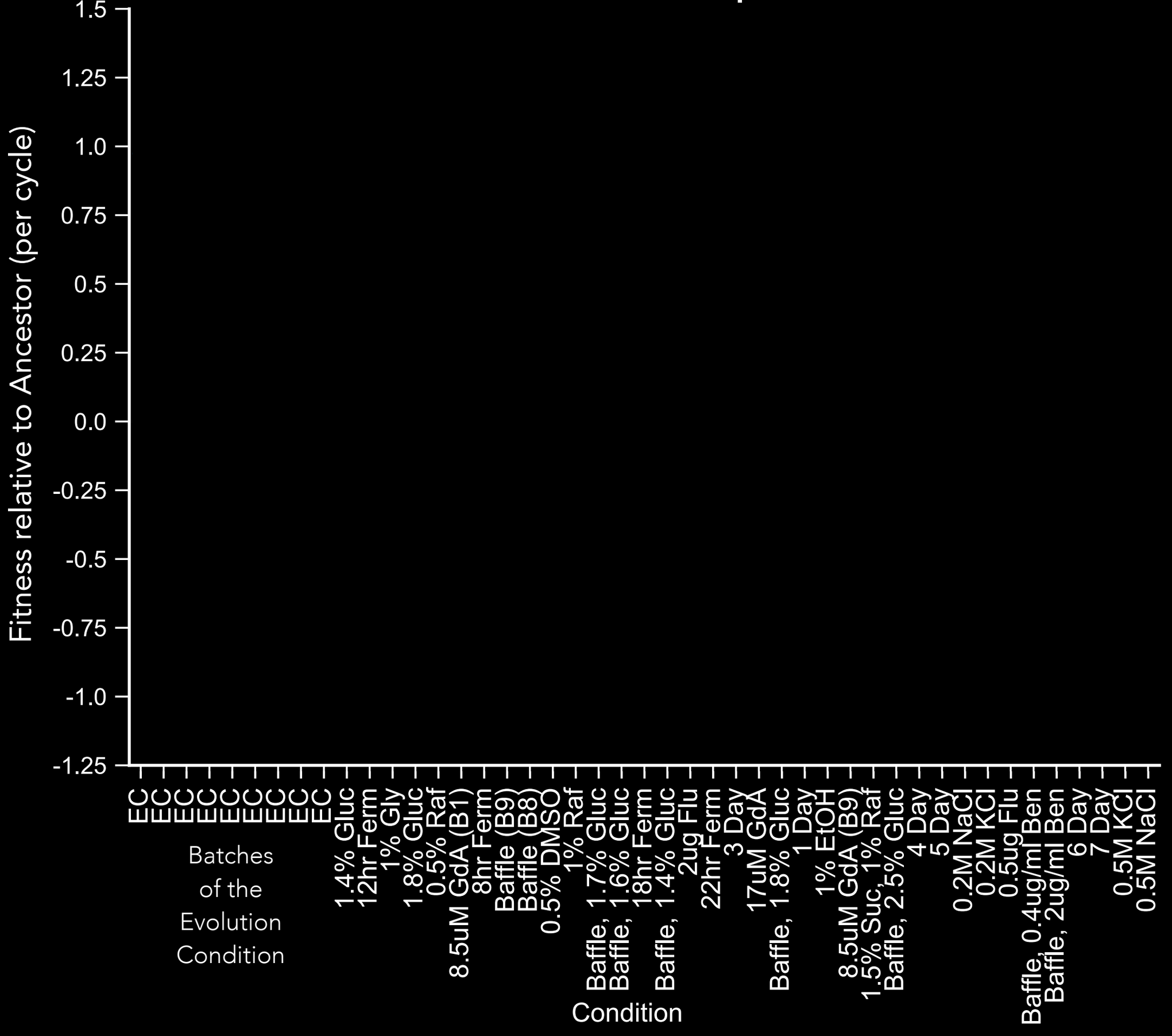
Raf

[illegible]

+ 0.2M NaCl + 0.5M NaCl

+ 0.2M KCl + 0.5M KCl

Fitness Profiles Across Multiple Environments



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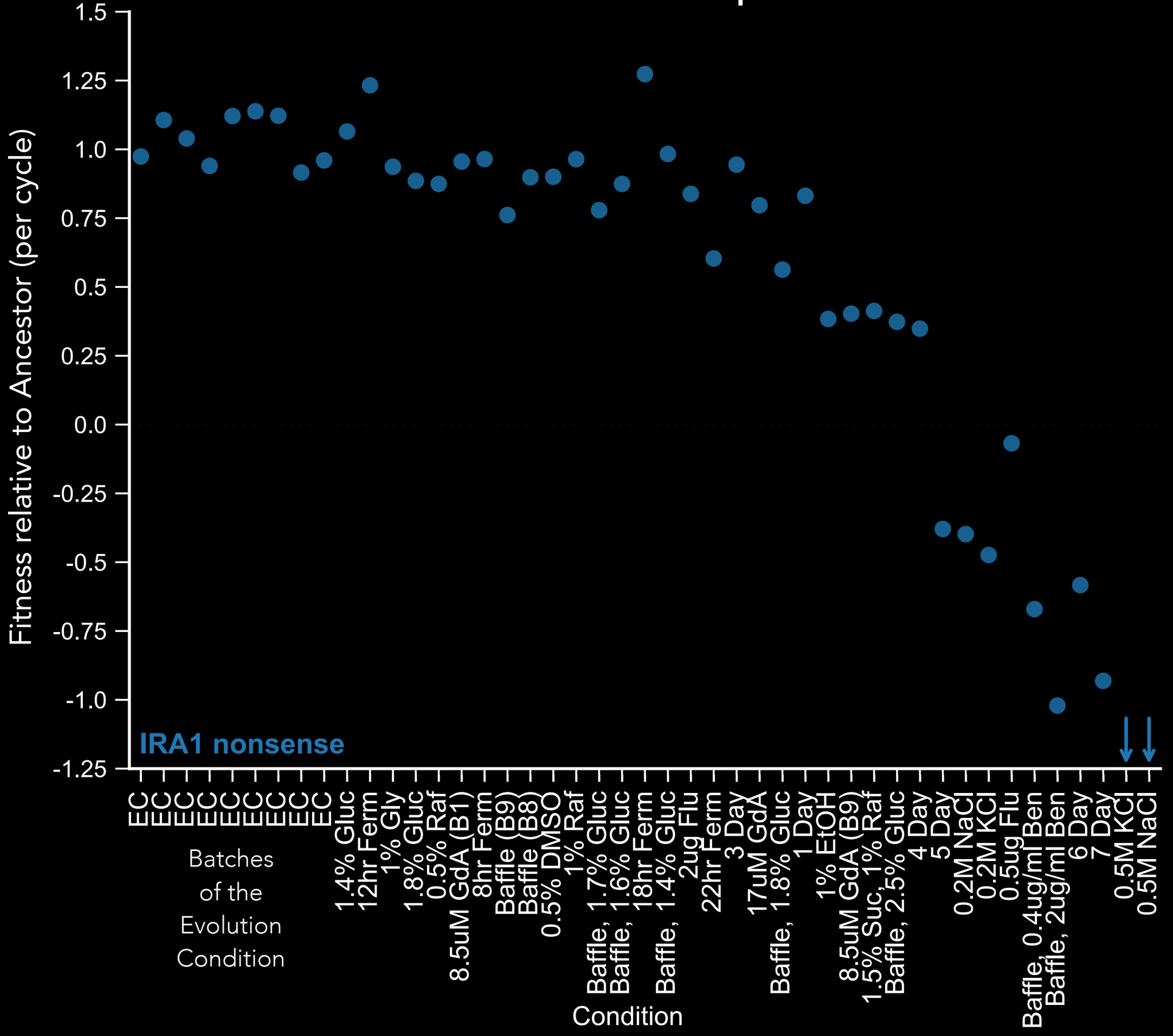

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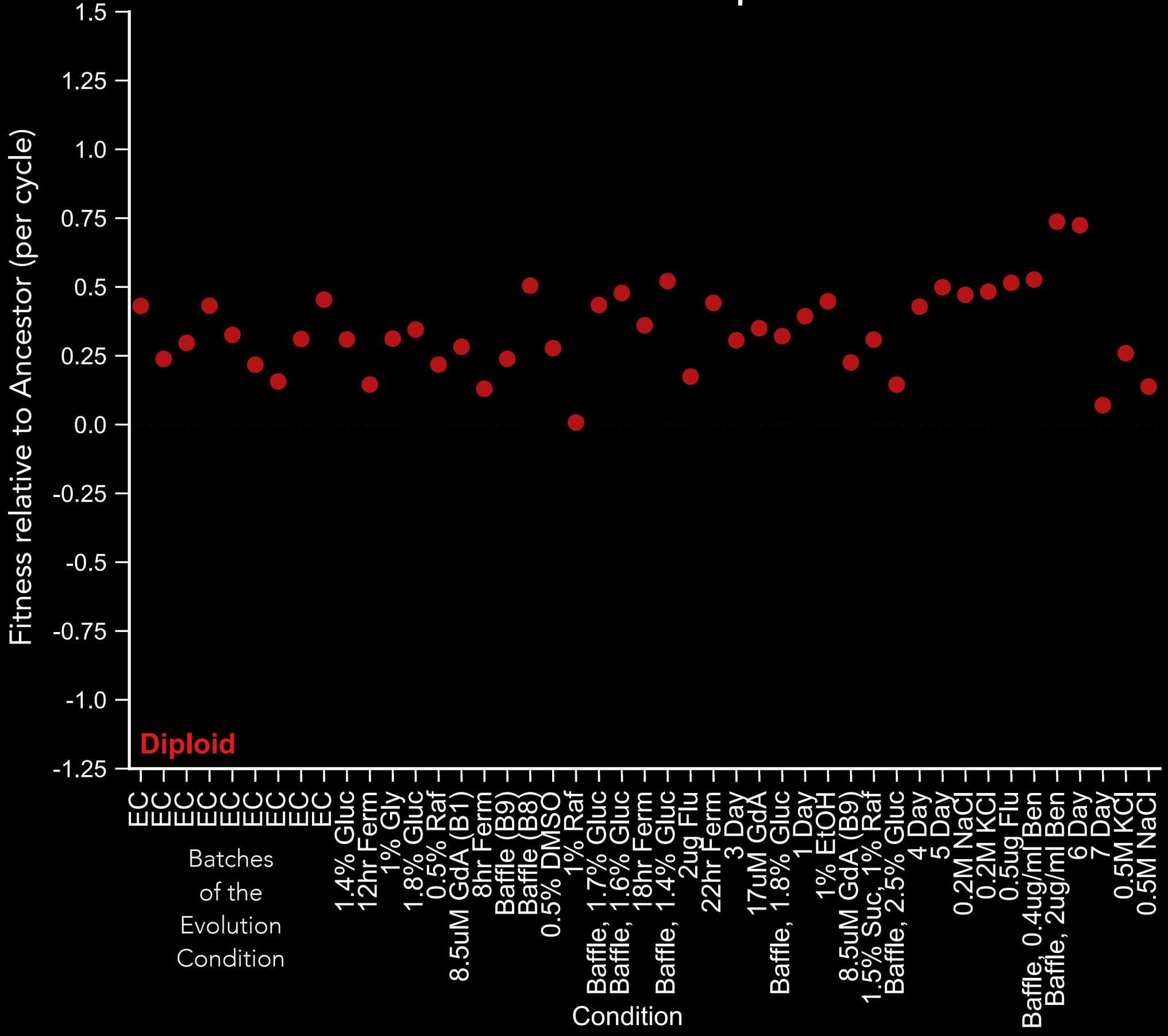

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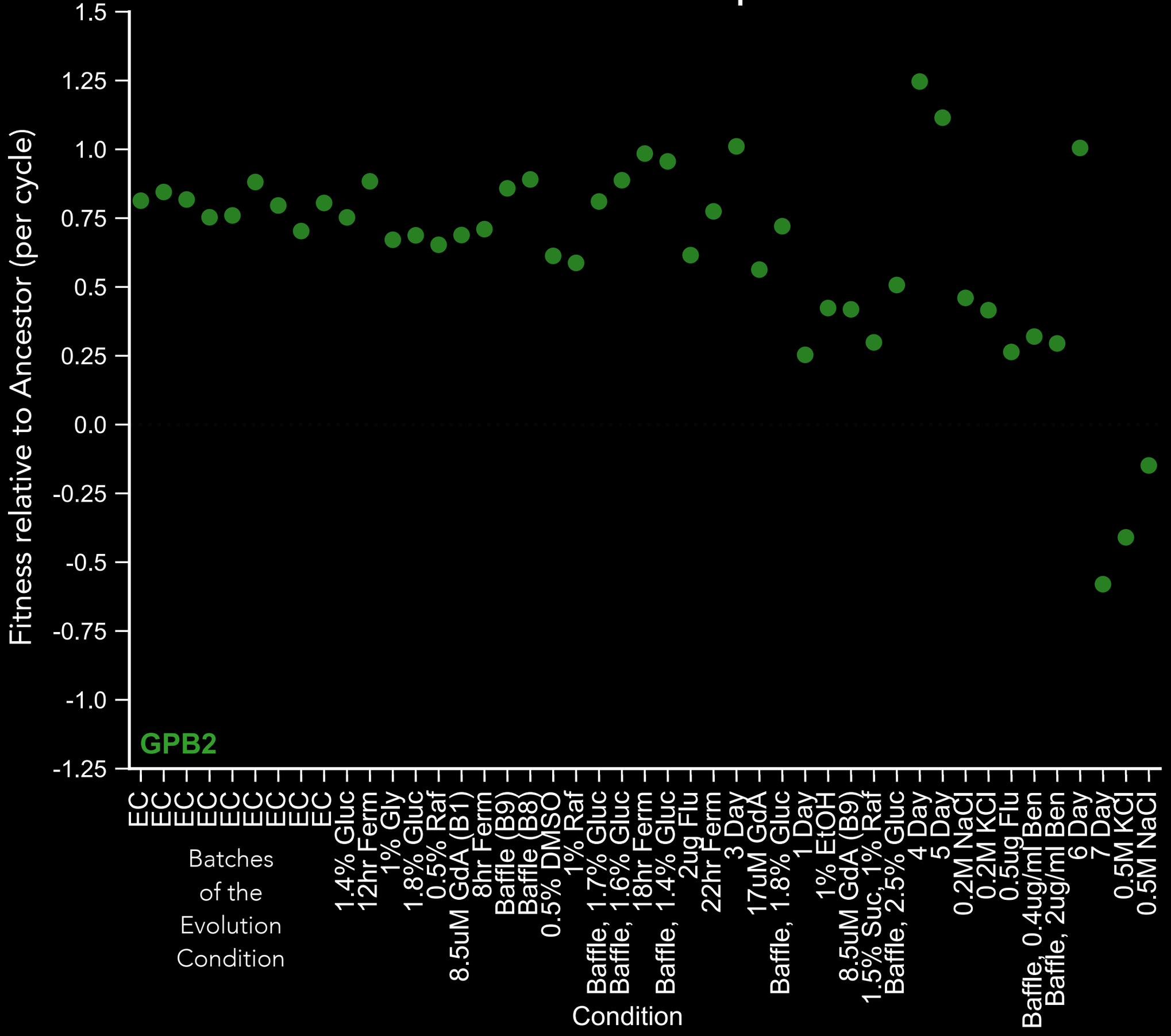

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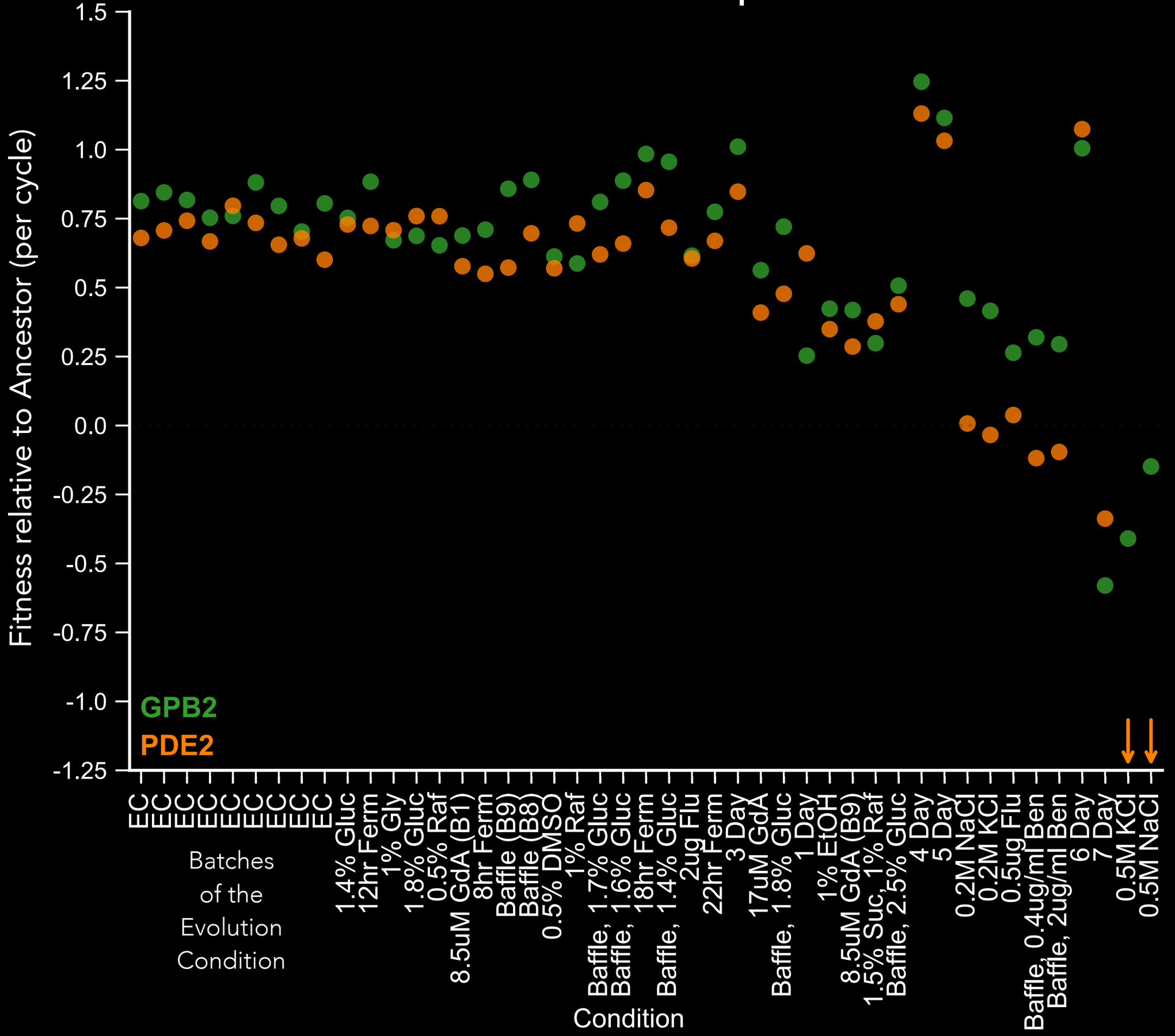

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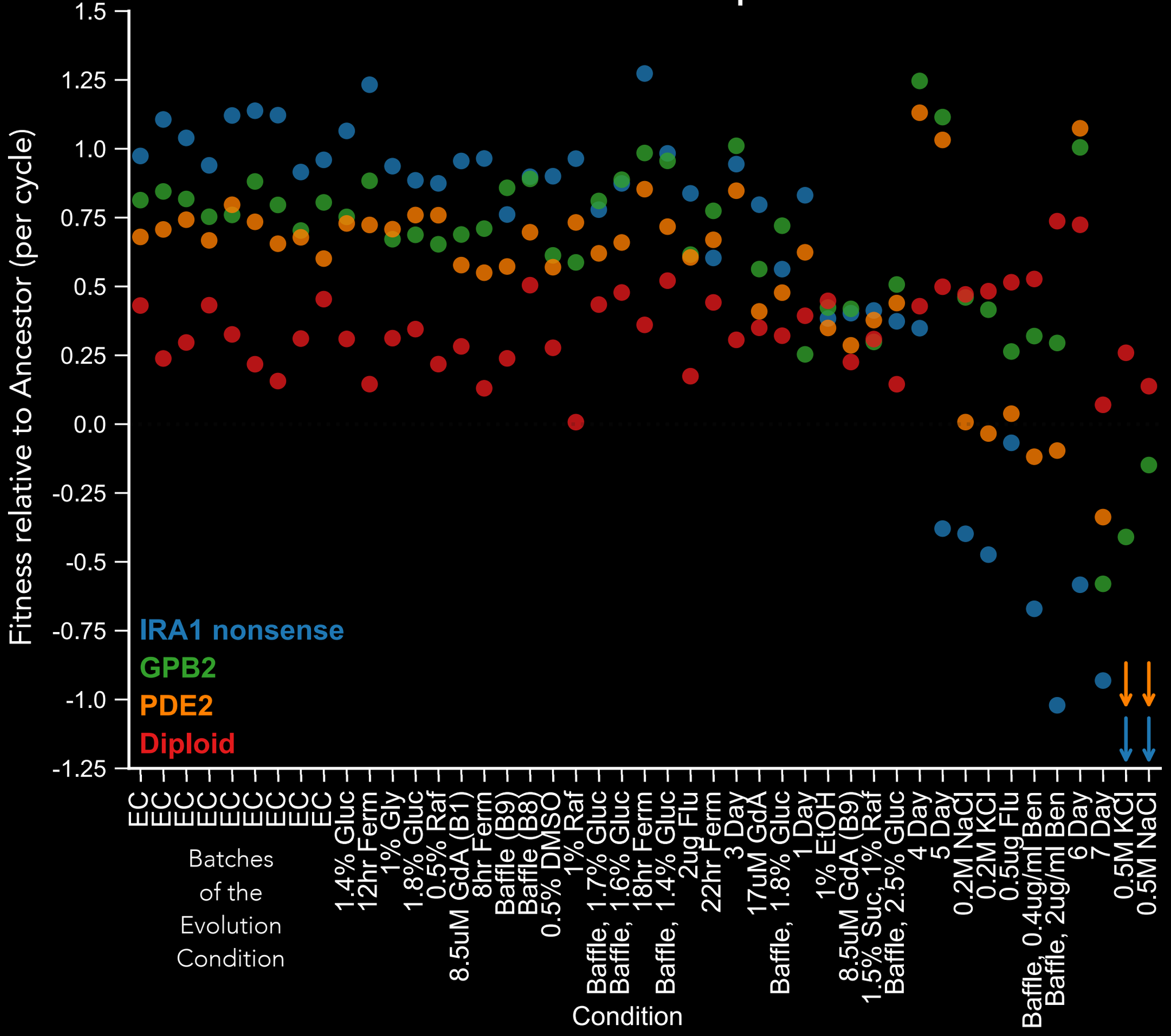

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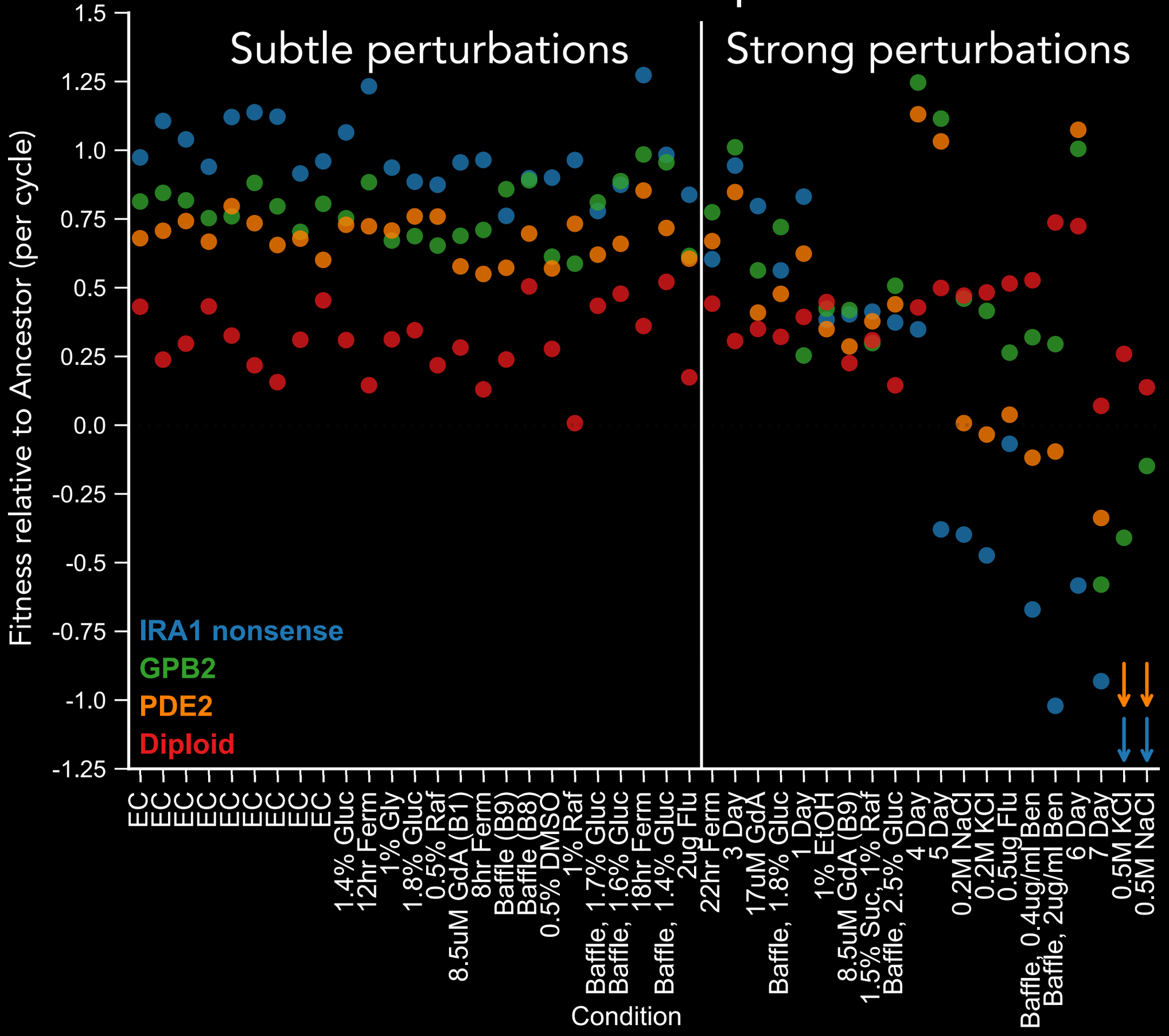
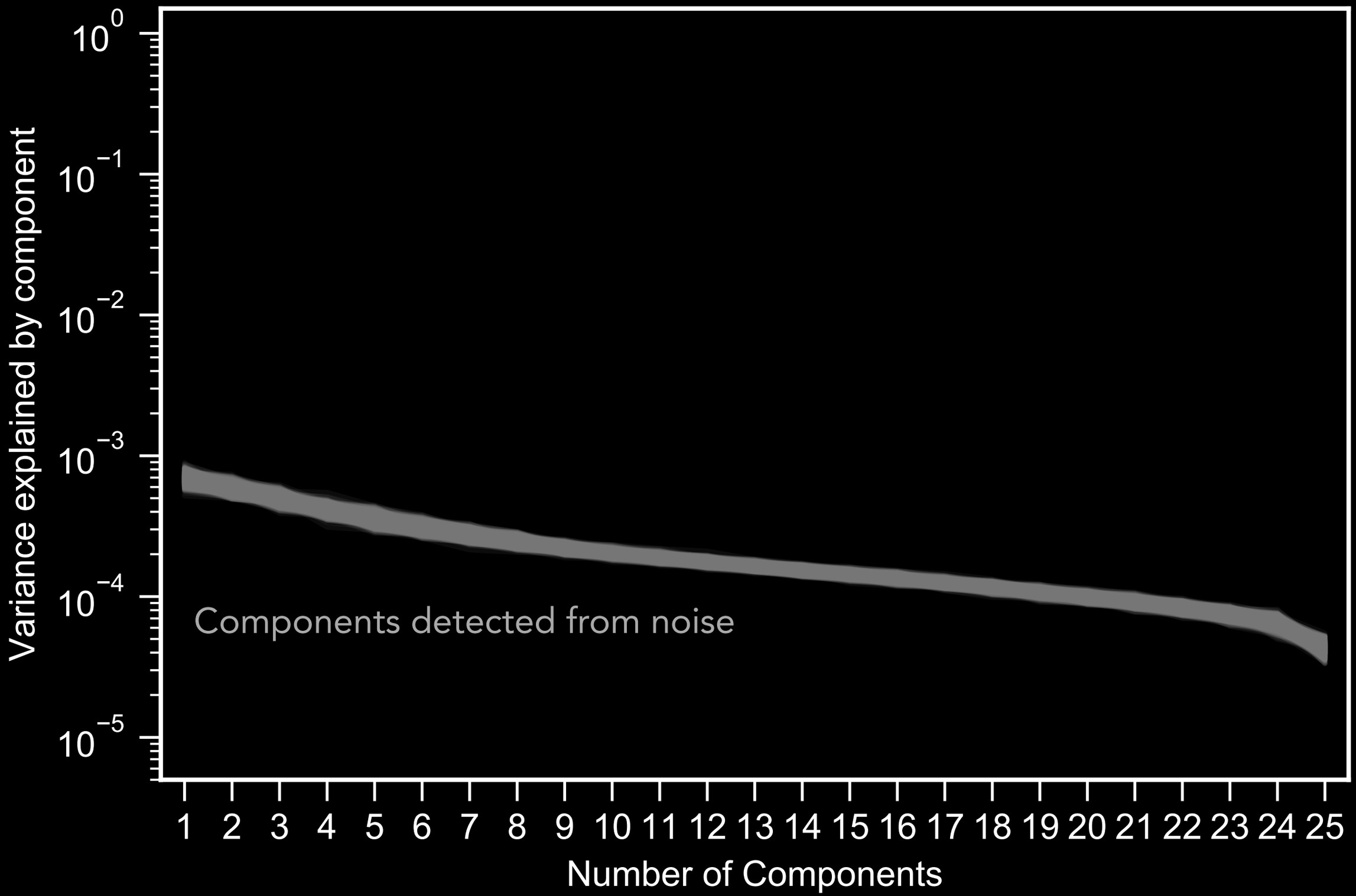


Subtle perturbations reveal 8 fitness-relevant phenotypes



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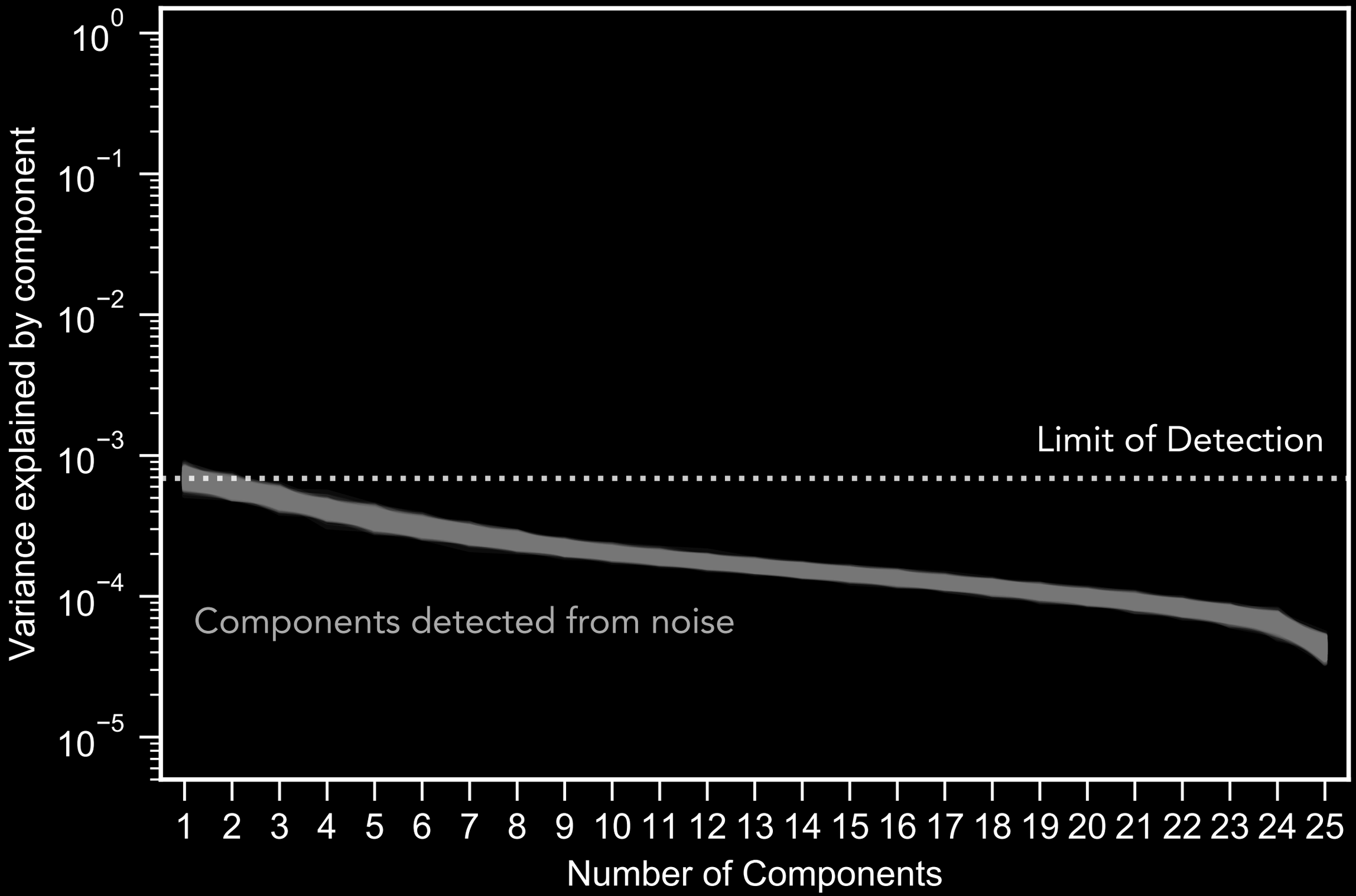

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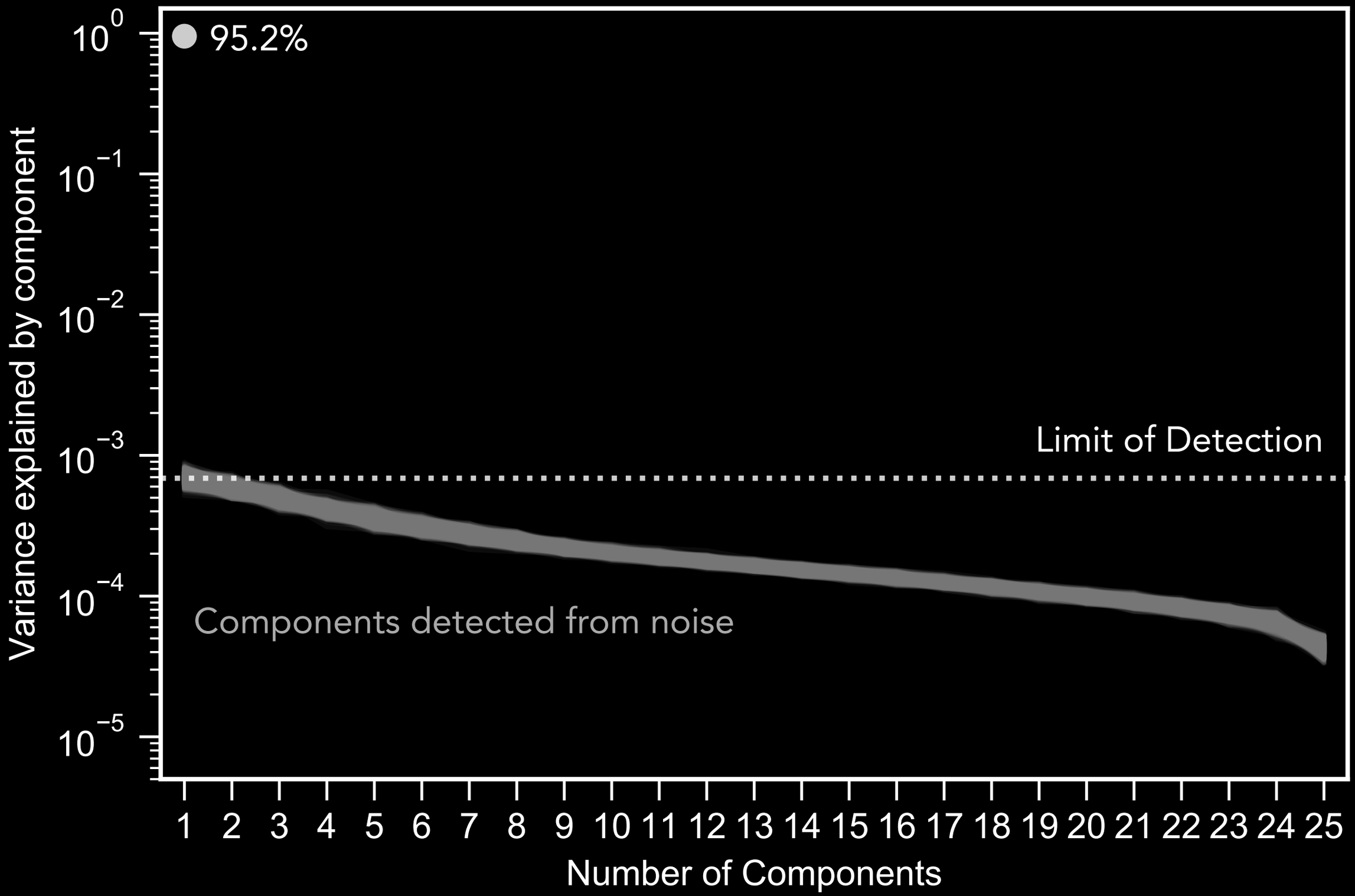

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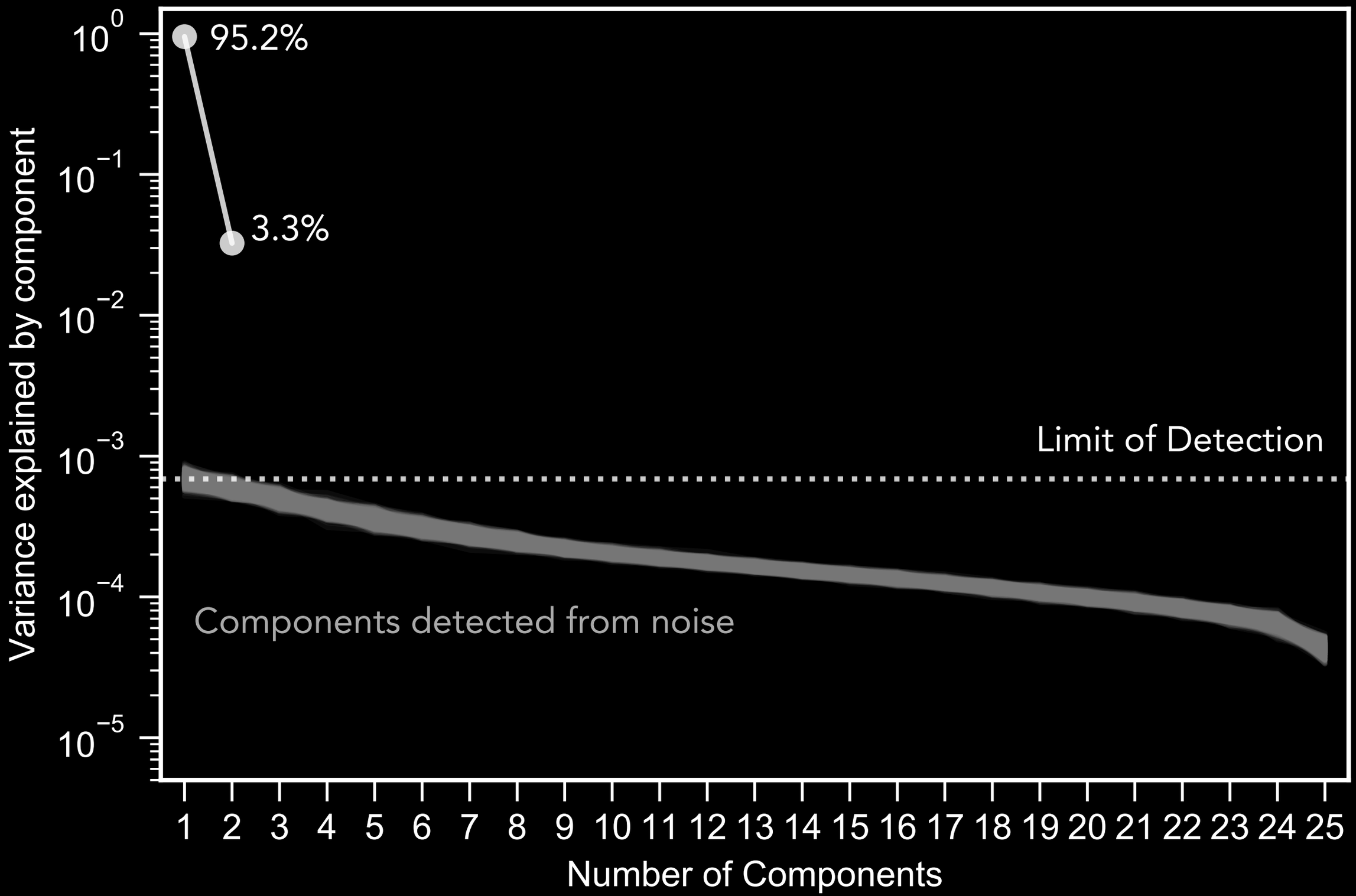

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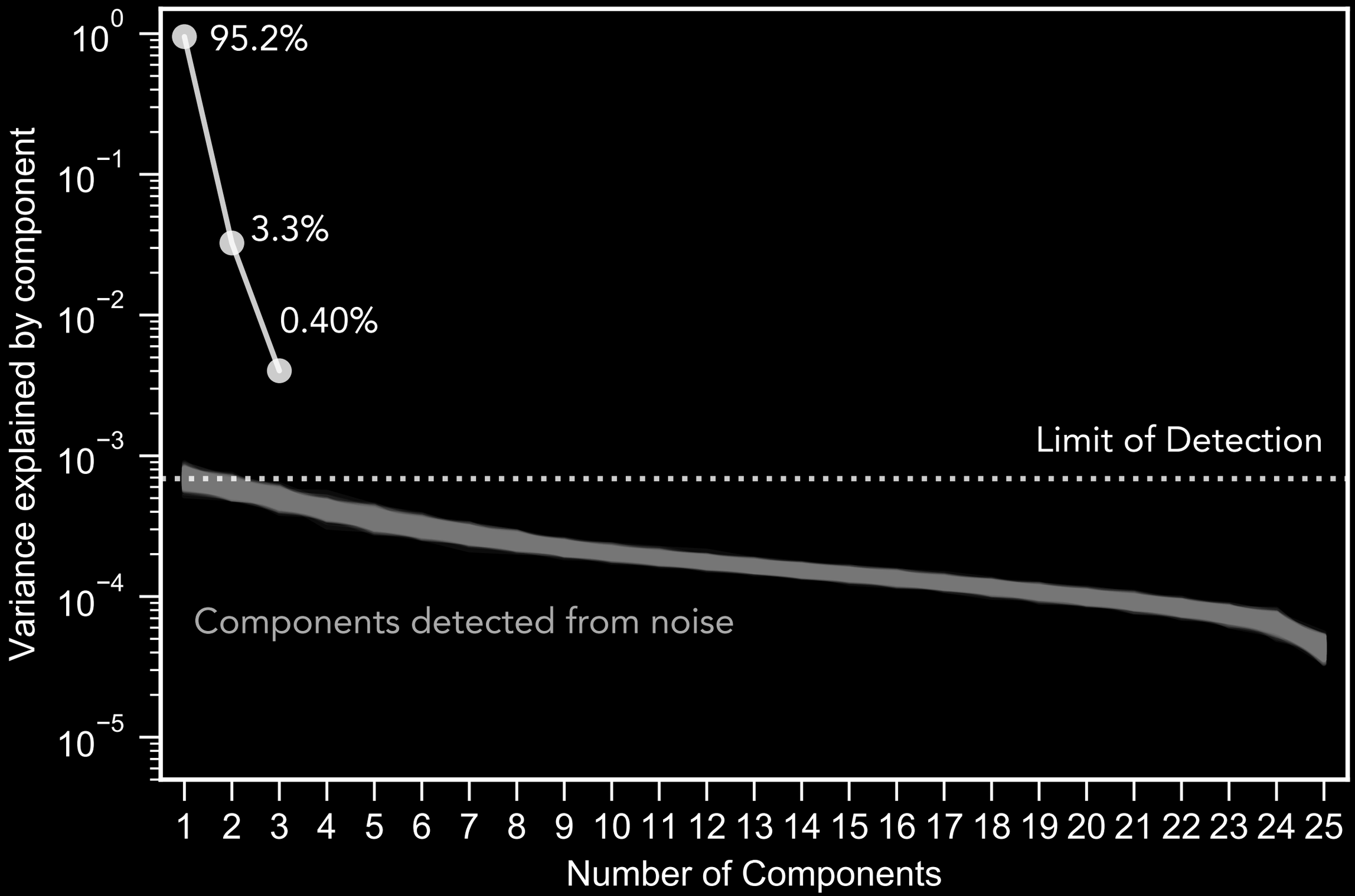

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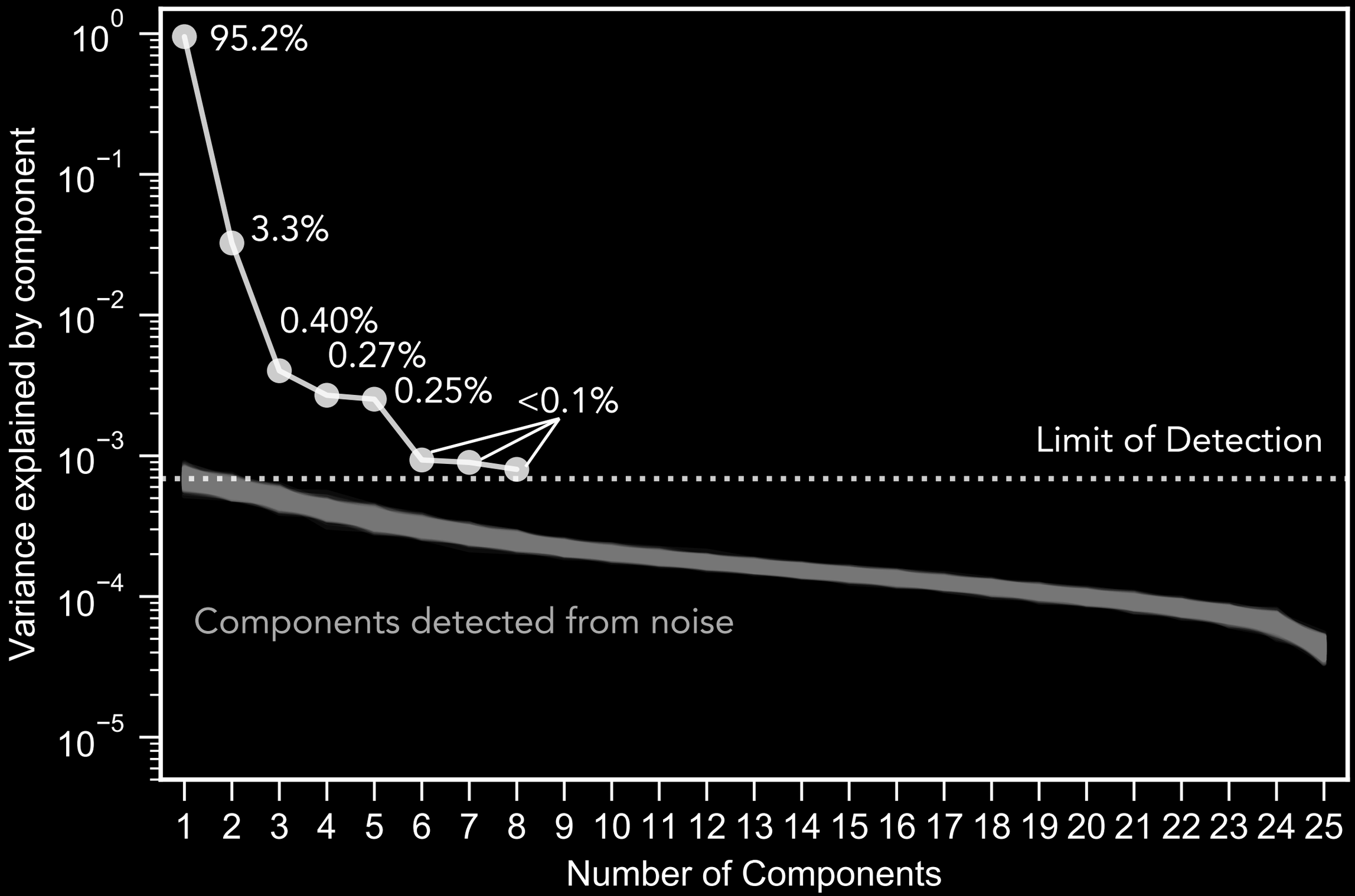

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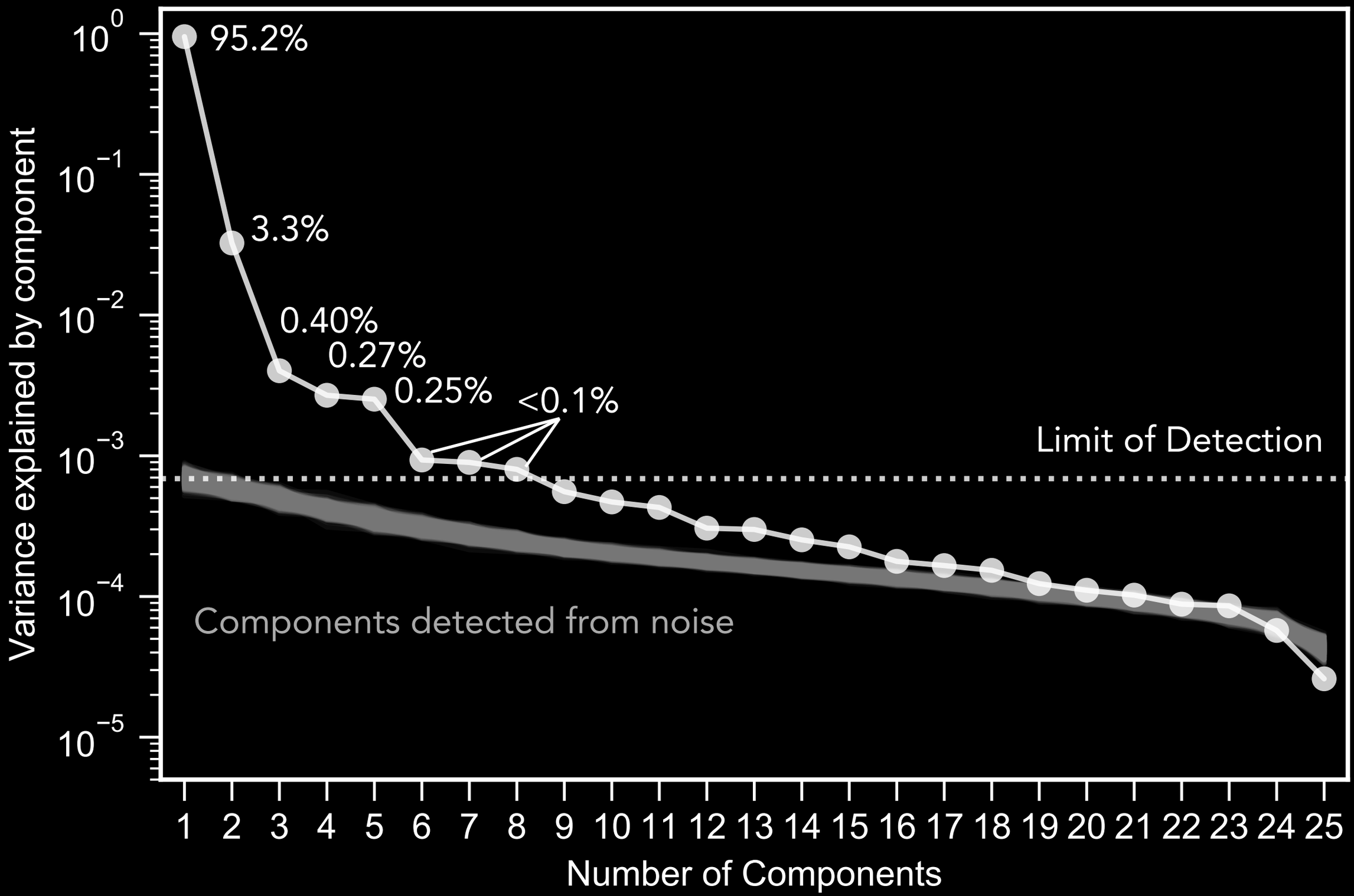
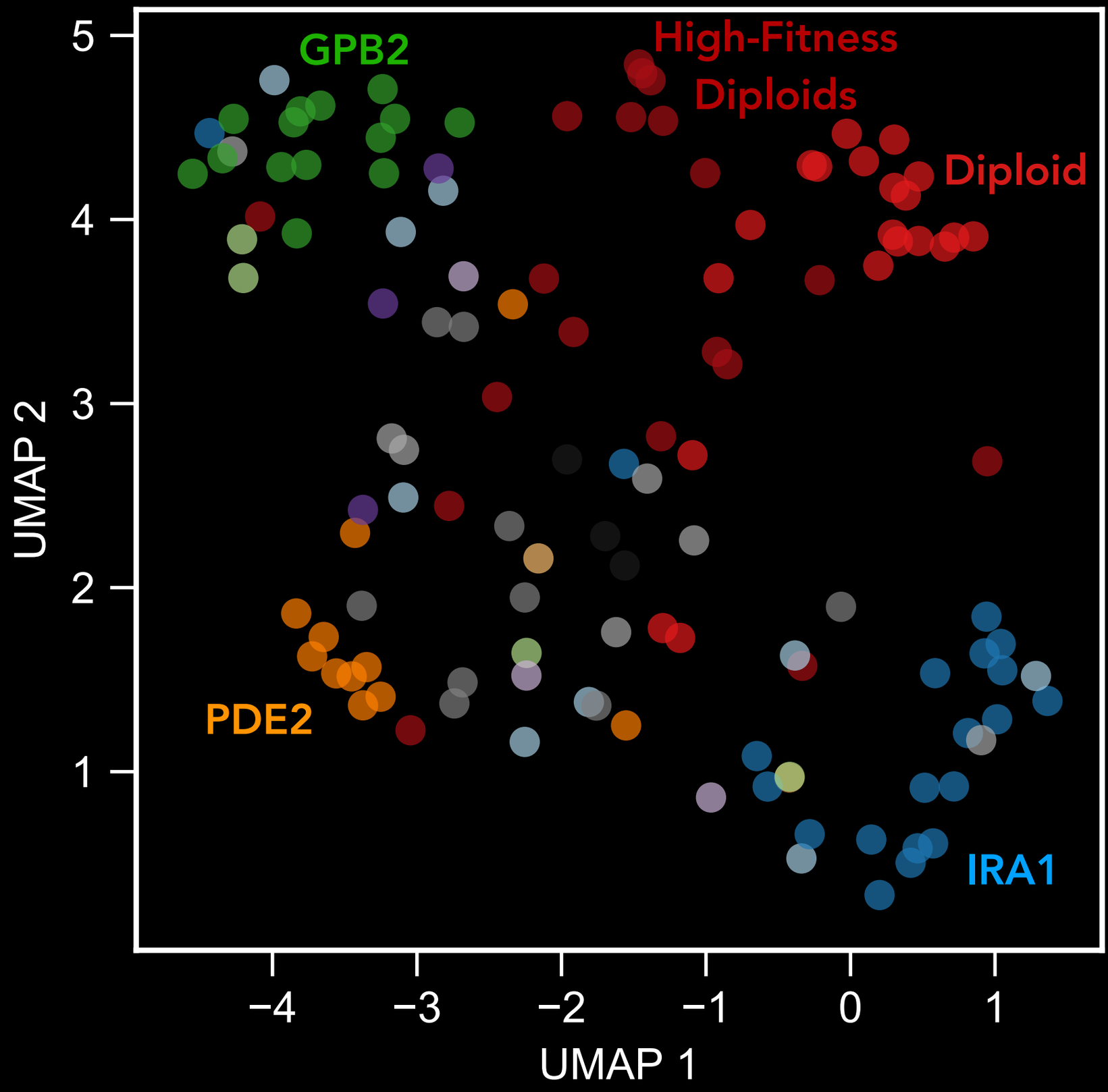


The phenotype space from subtle perturbations clusters mutations by gene



Use Cross-Validation to Test Predictive Power

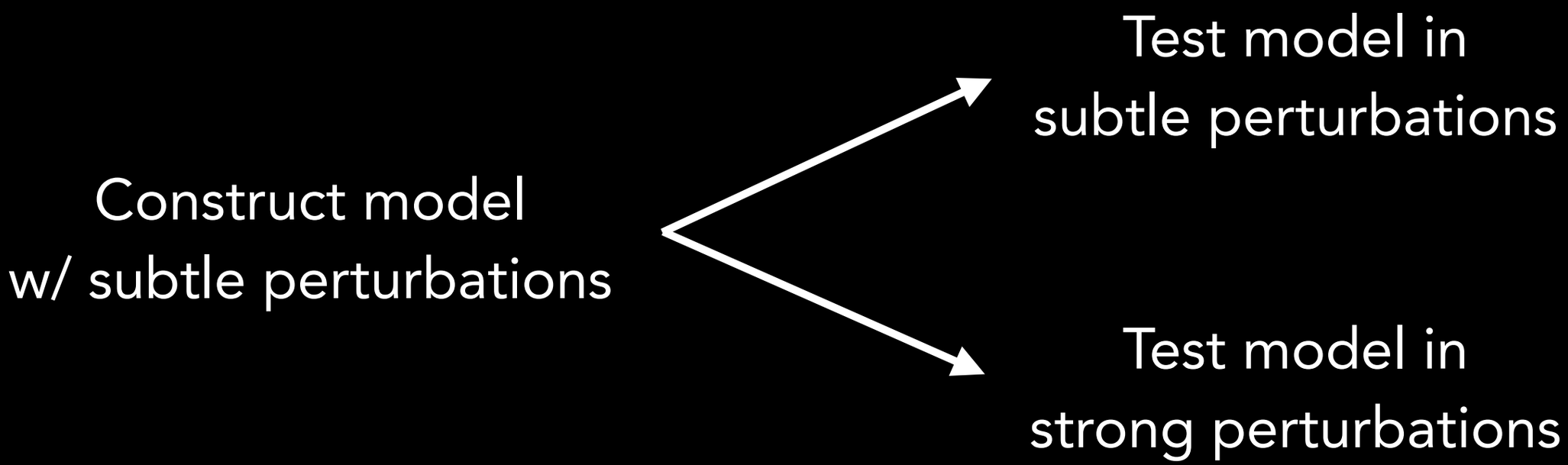
Construct model
w/ subtle perturbations

Use Cross-Validation to Test Predictive Power

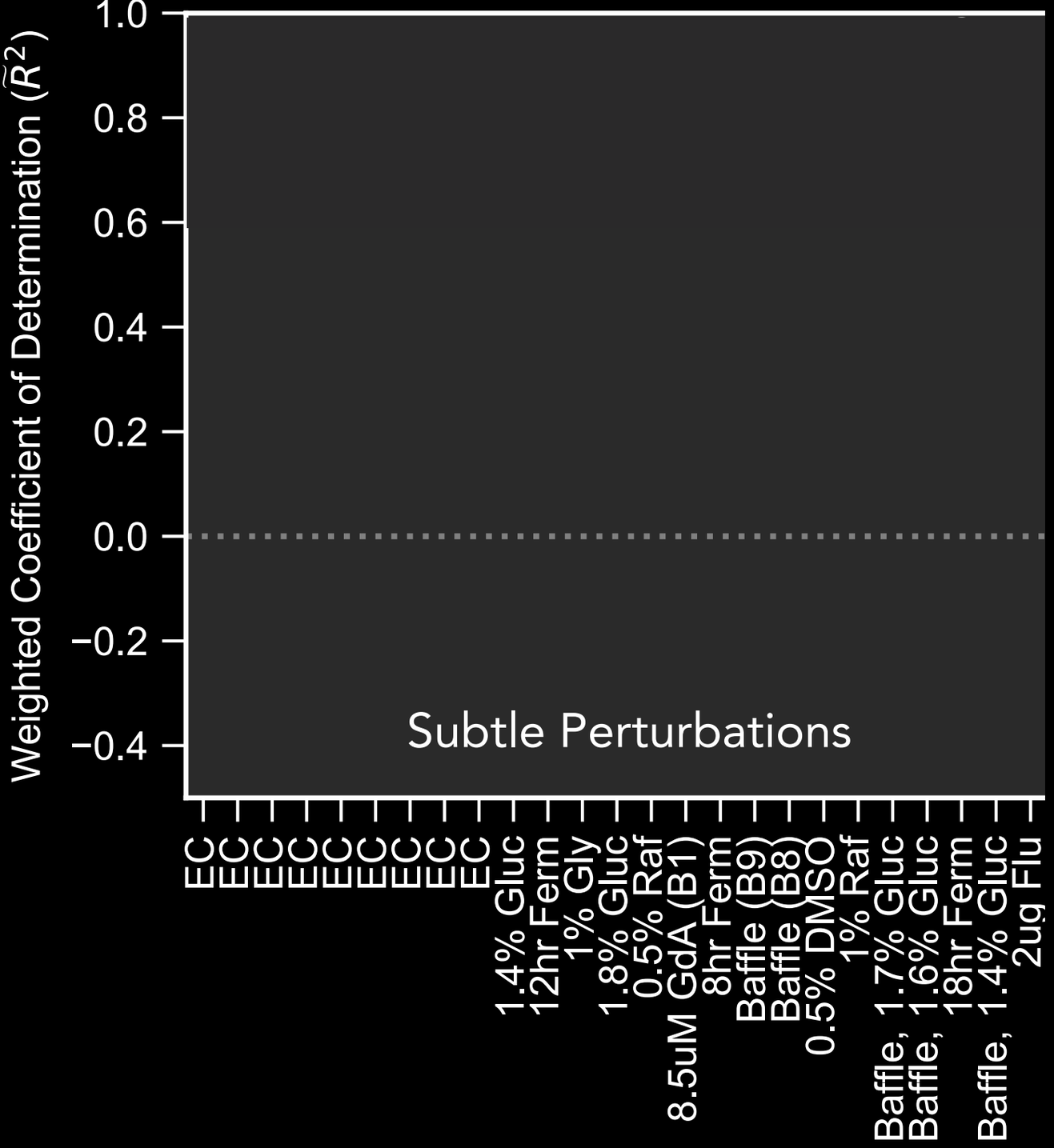
Construct model
w/ subtle perturbations

Test model in
subtle perturbations

Use Cross-Validation to Test Predictive Power



5 largest phenotypes explain most variation in subtle perturbations



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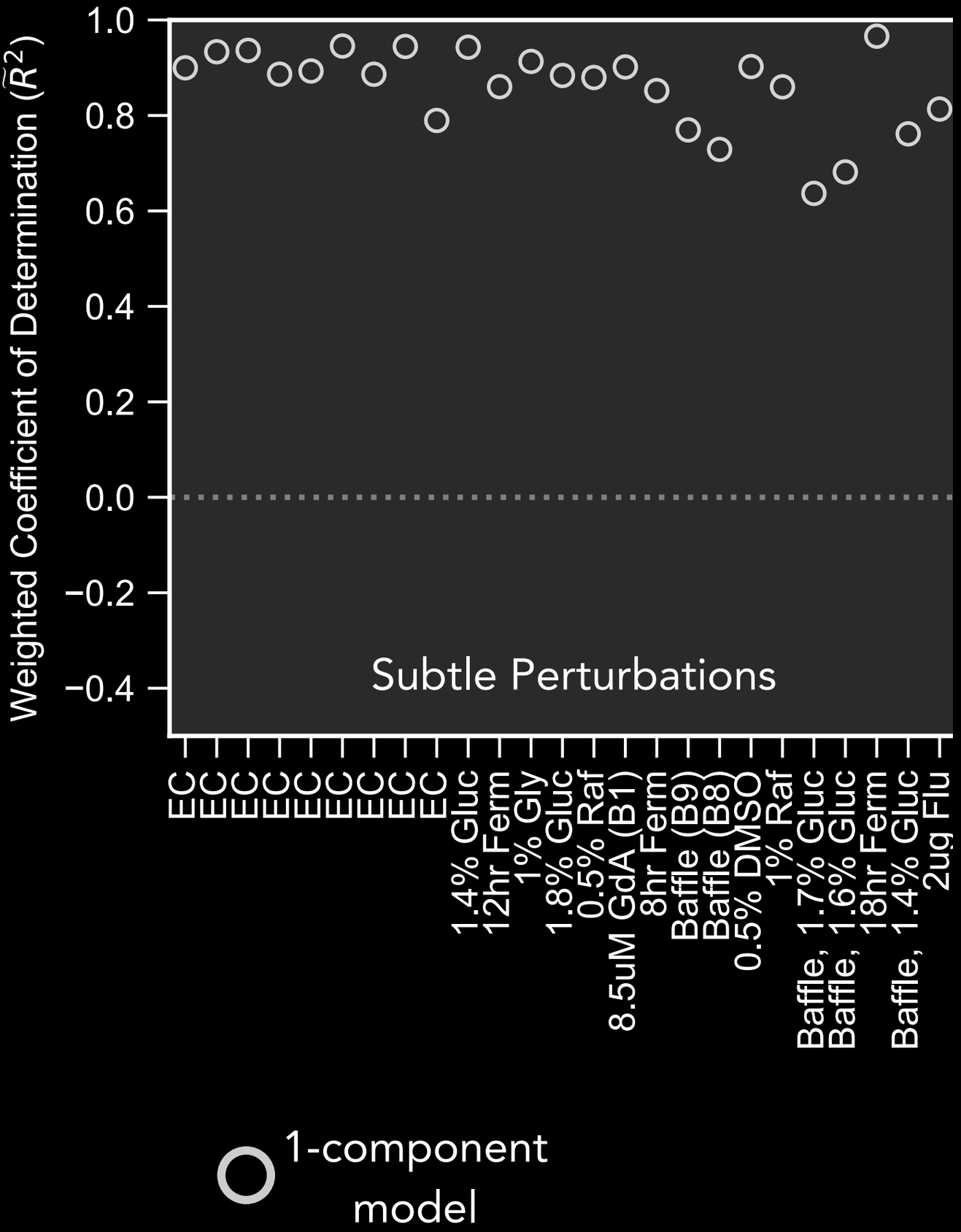
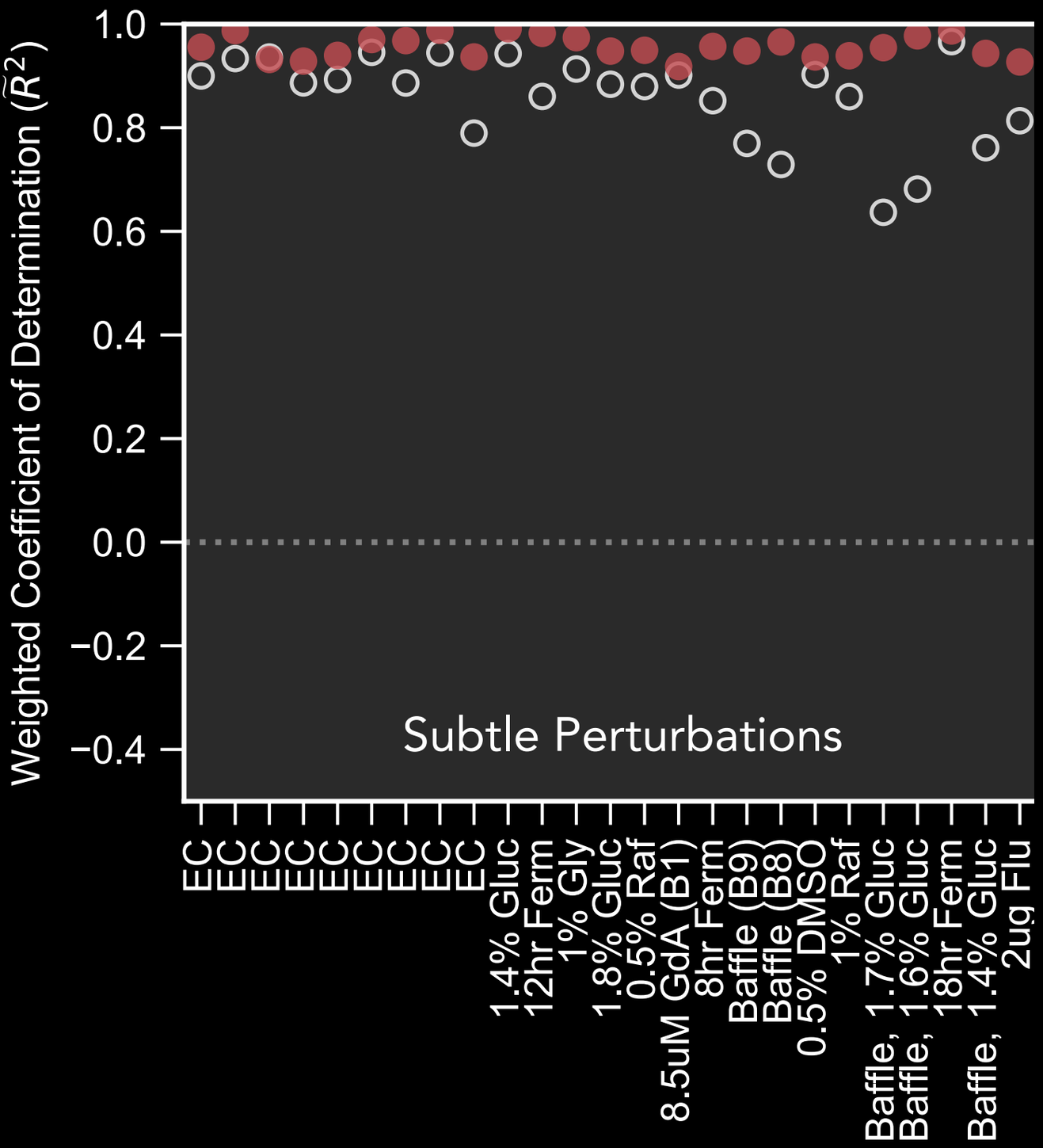


1-component model

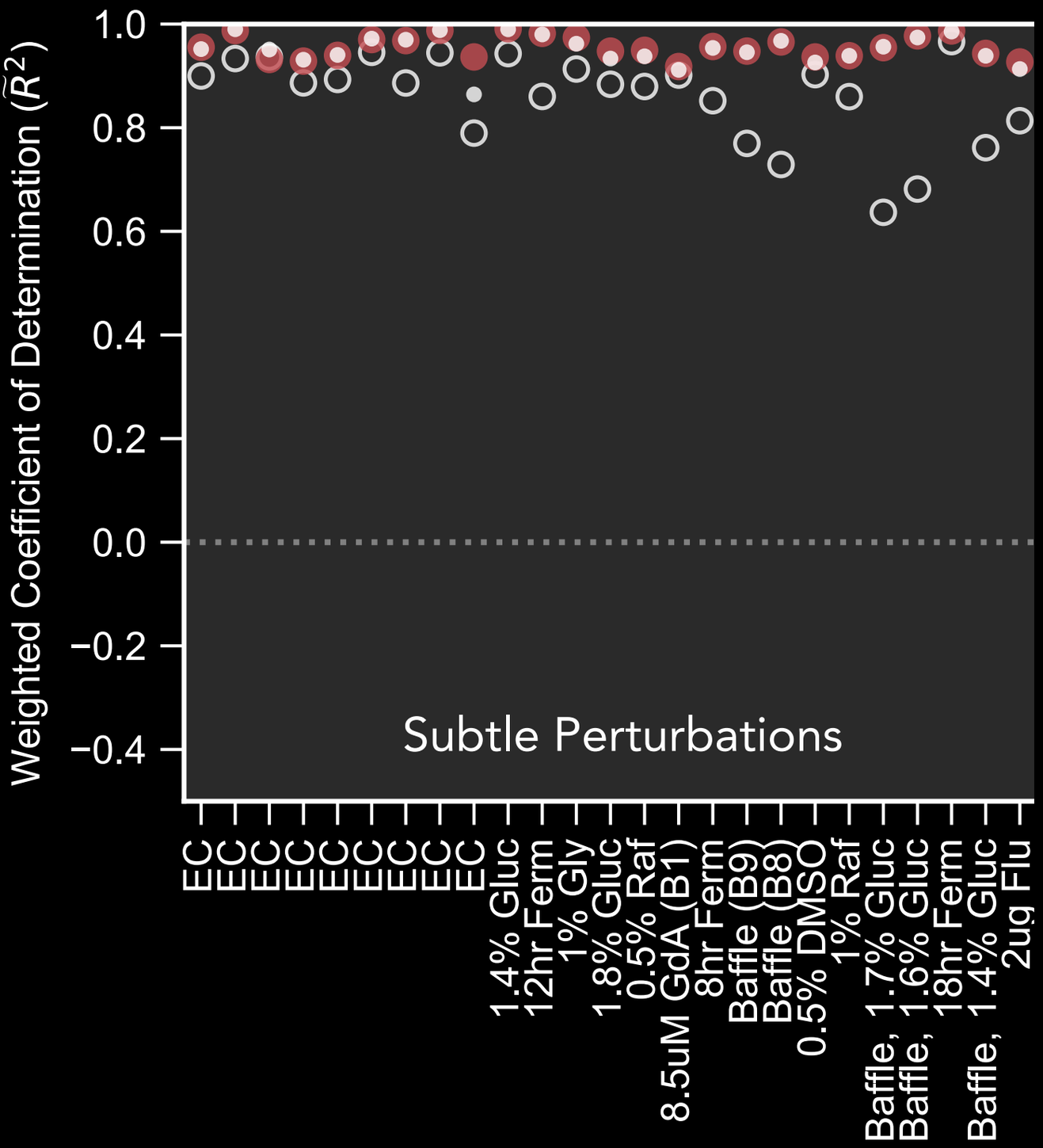
5 largest phenotypes explain most variation in subtle perturbations



1-component model

8-component model

5 largest phenotypes explain most variation in subtle perturbations

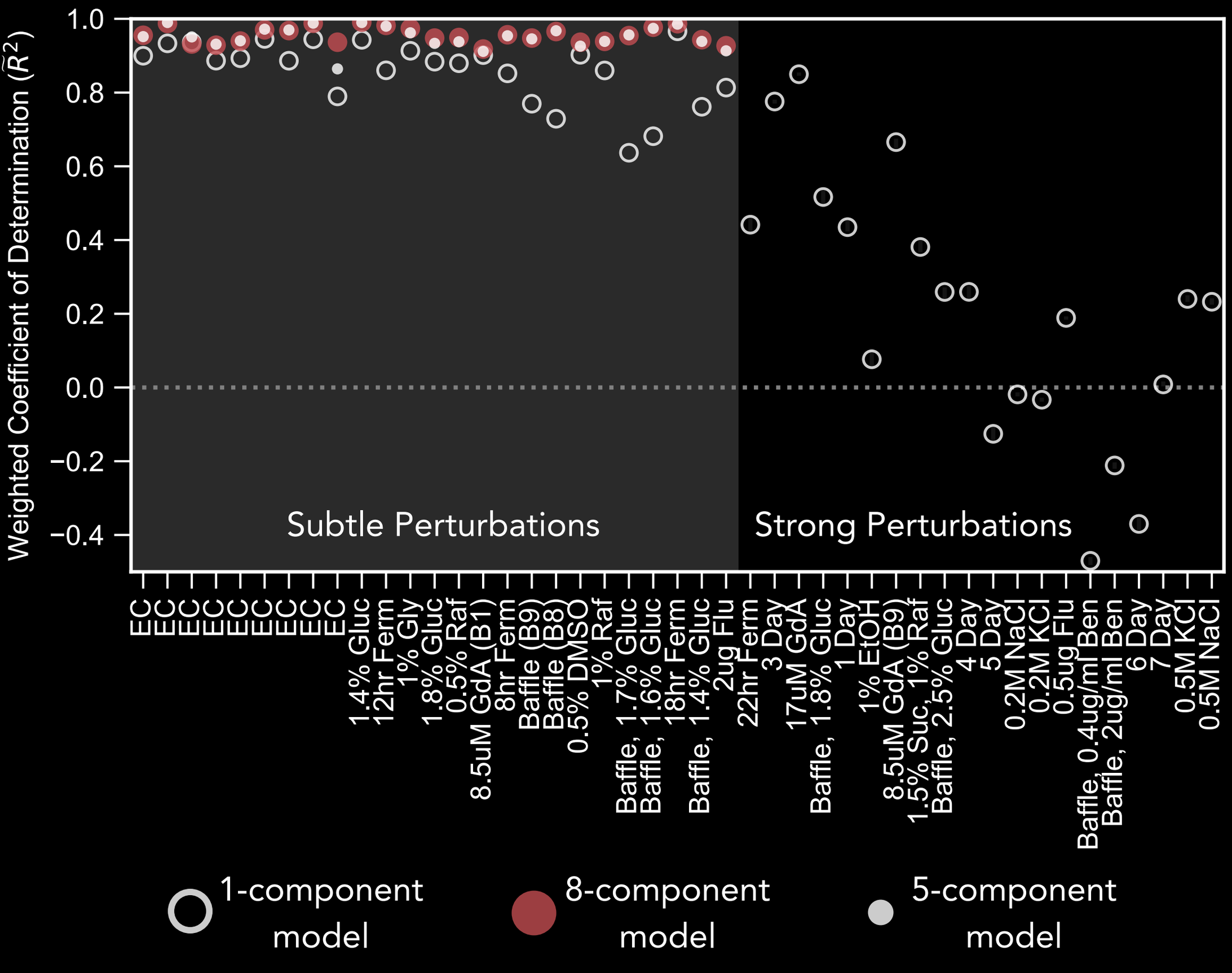


1-component model

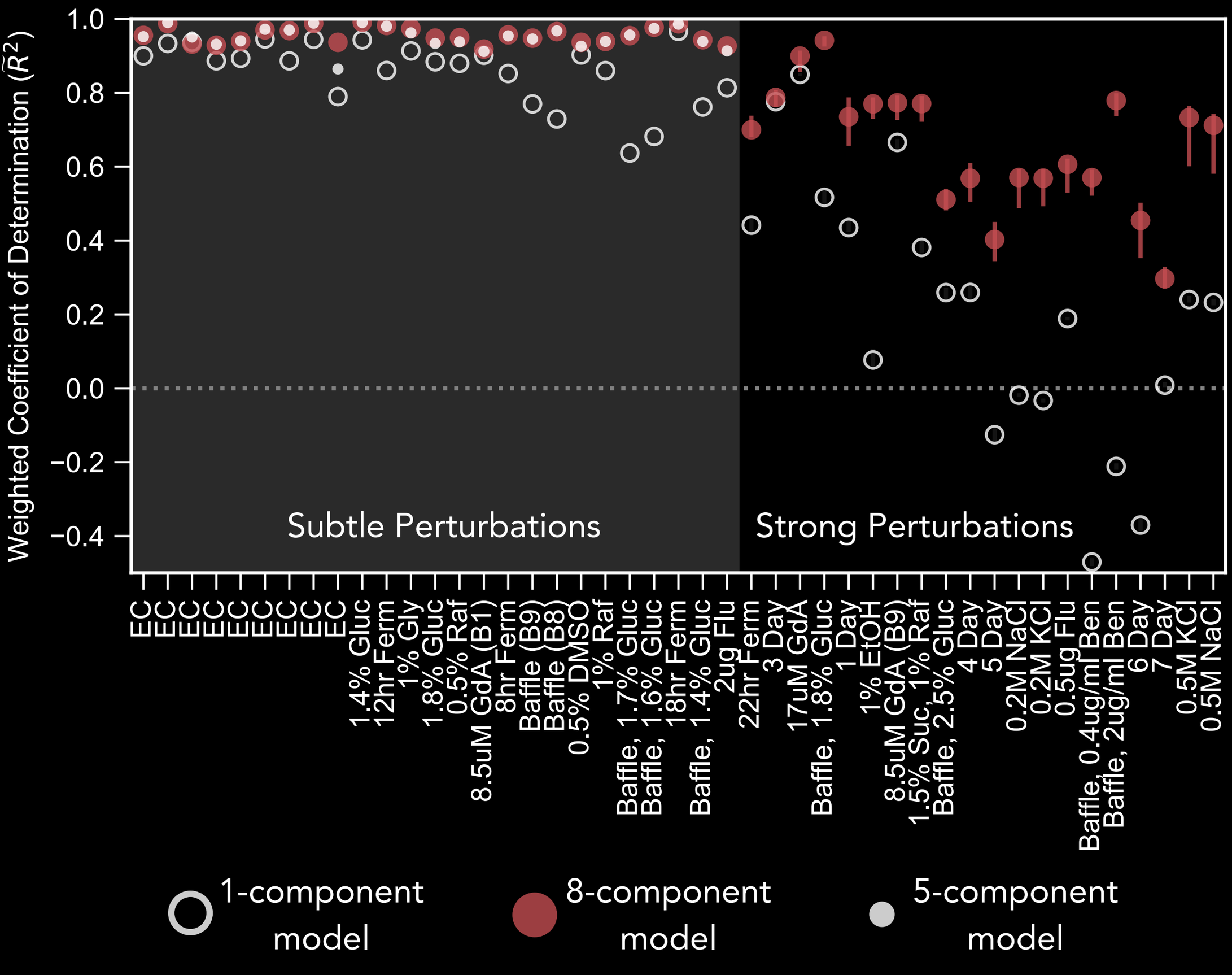
8-component model

5-component model

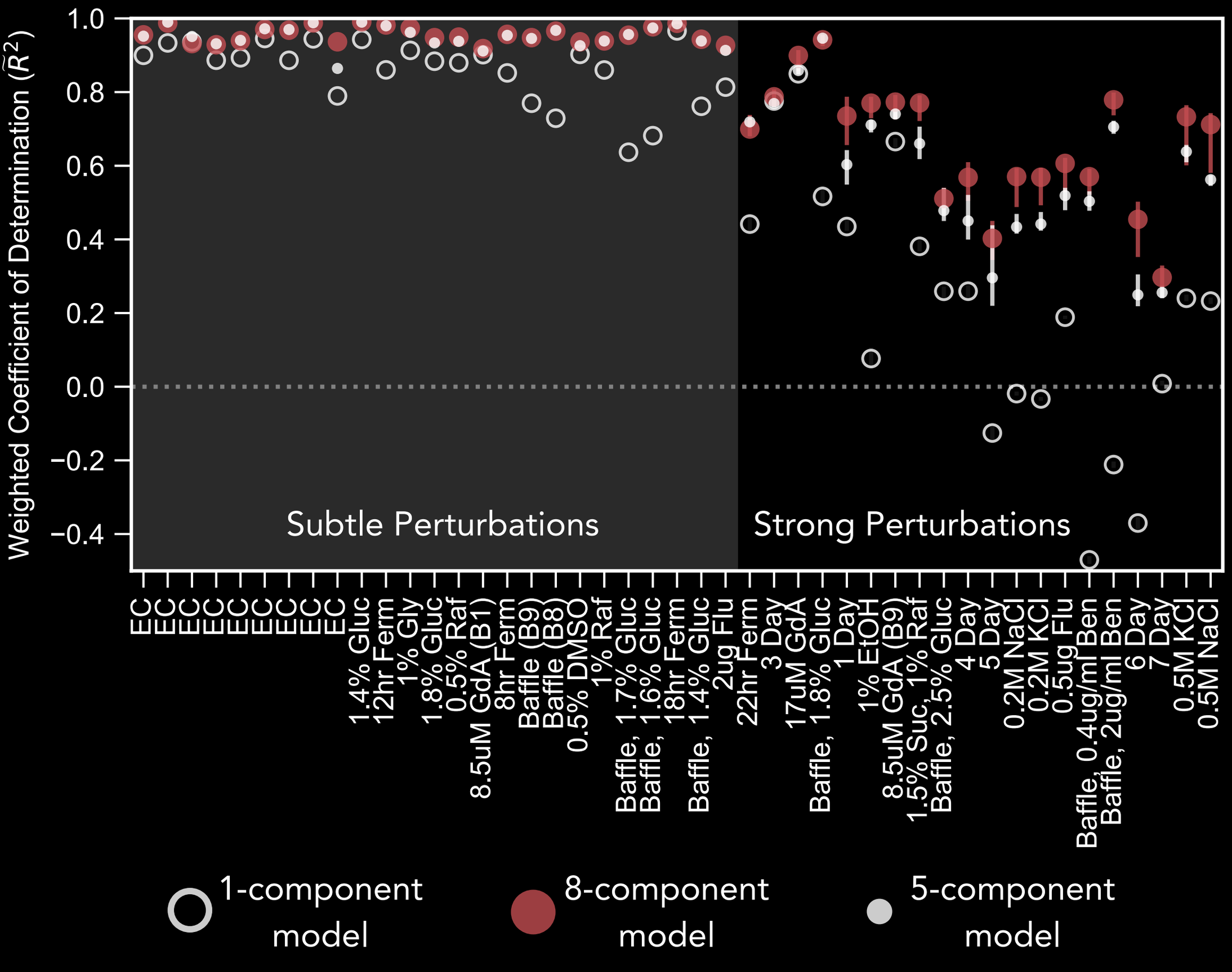
Phenotype space can predict fitness in strong perturbations!



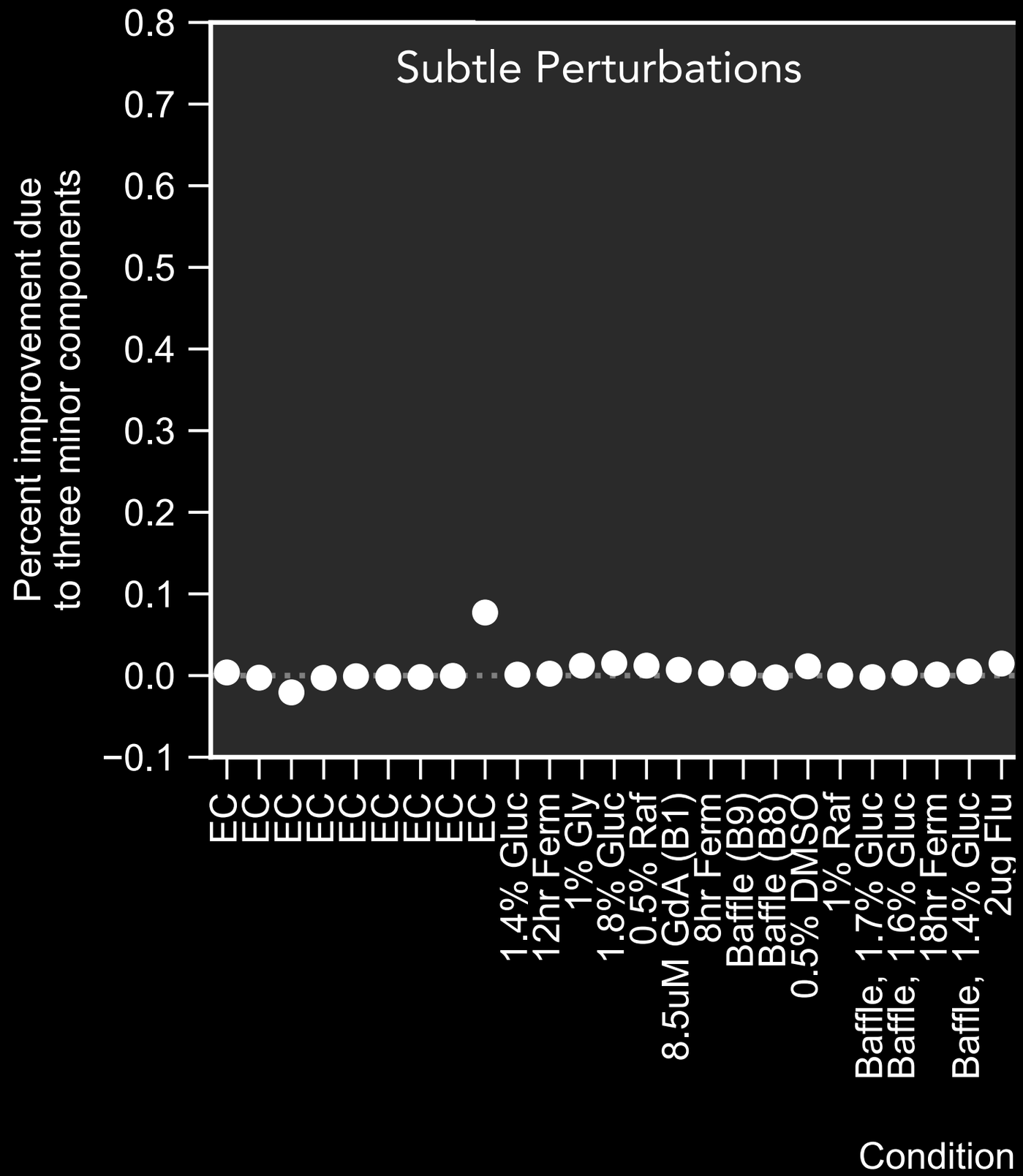
Phenotype space can predict fitness in strong perturbations!



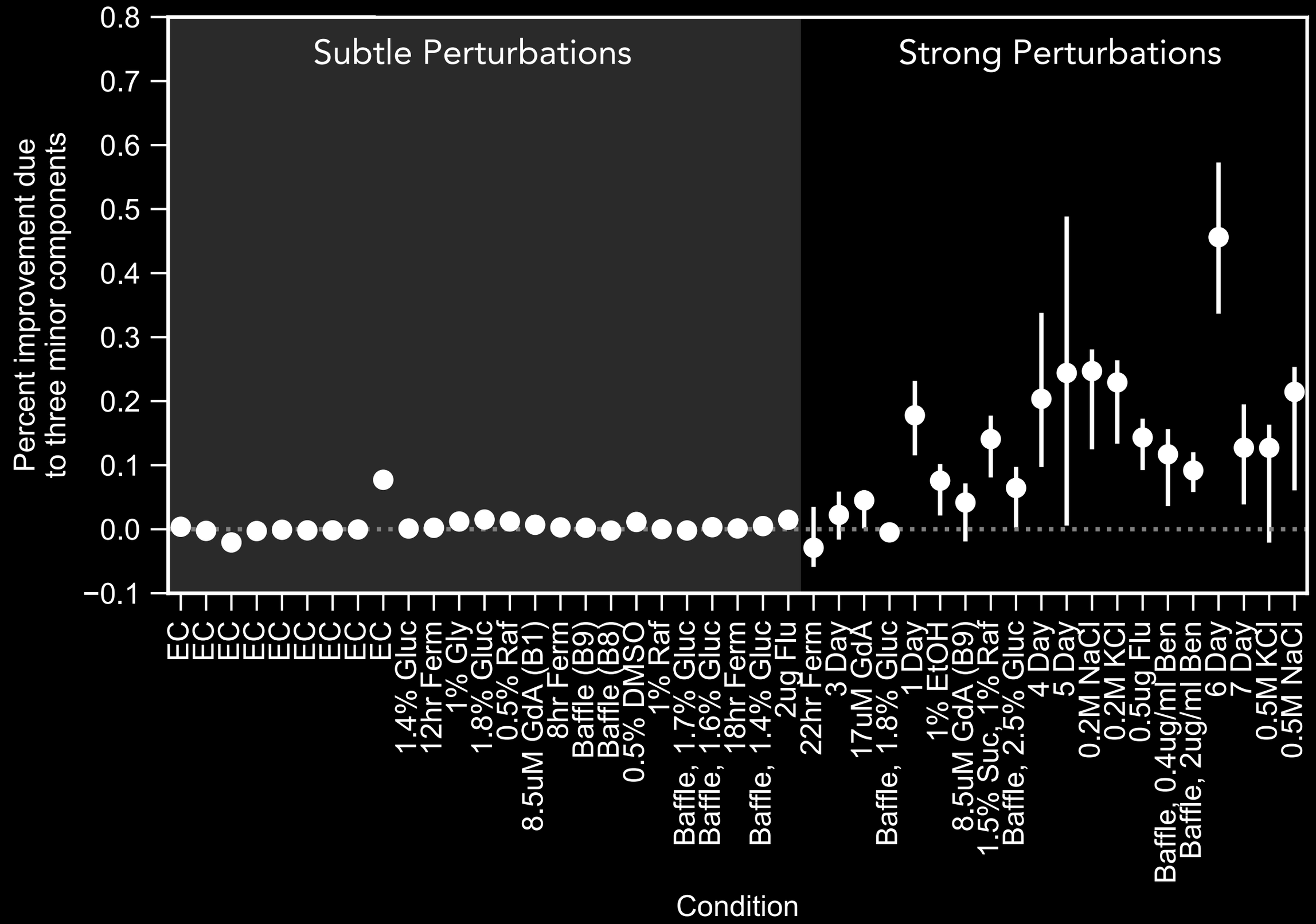
Smallest 3 components add predictive power in strong perturbations



Smallest 3 components add predictive power in strong perturbations



Smallest 3 components add predictive power in strong perturbations



Genotype

Phenotypes

Fitness

GPB2

PDE2

IRA1

Diploid

Fitness in Evolution Condition

Genotype

Phenotypes

Fitness

GPB2

PDE2

IRA1

Diploid

Fitness in Evolution Condition

Genotype

Phenotypes

Fitness

GPB2

PDE2

IRA1

Diploid

Fitness in
6 Day

Thanks!

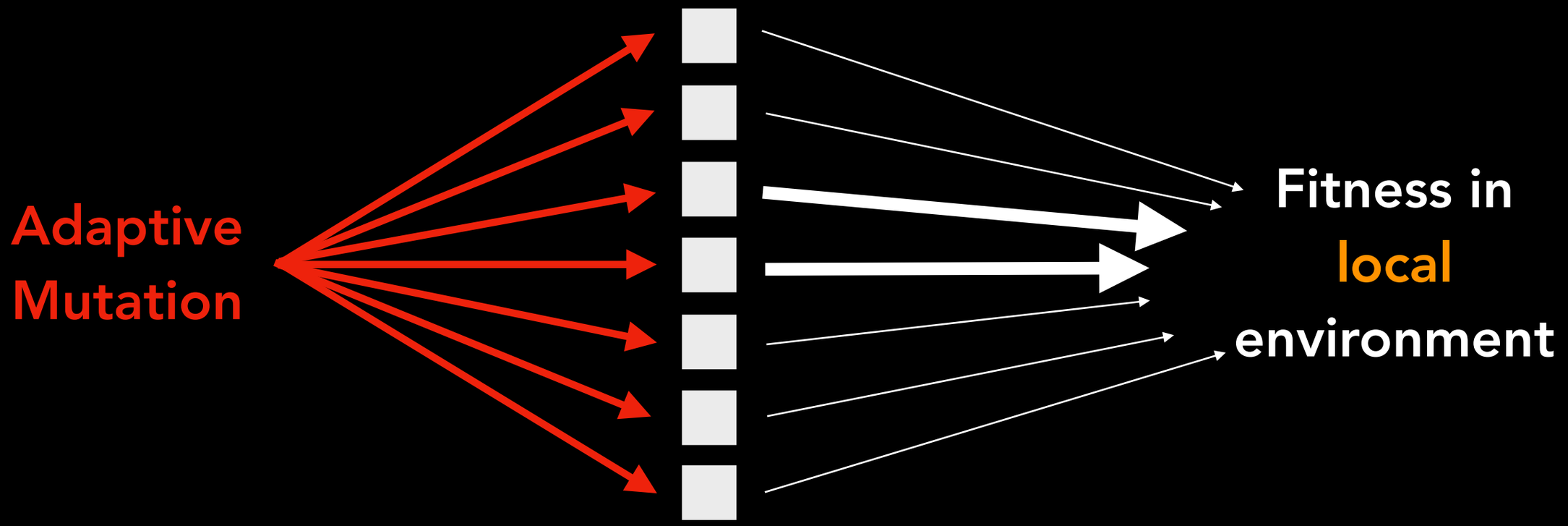
Kerry Geiler-Samerotte

Dmitri Petrov

Yuping Li
Sandeep Venkataram
Atish Agarwala

Monica Sanchez
Tuya Yokoyama

Adaptive mutations affect few fitness-relevant phenotypes



Latent phenotypic effects represent
global phenotypic diversity
generated by local adaptation

@GrantKinsler

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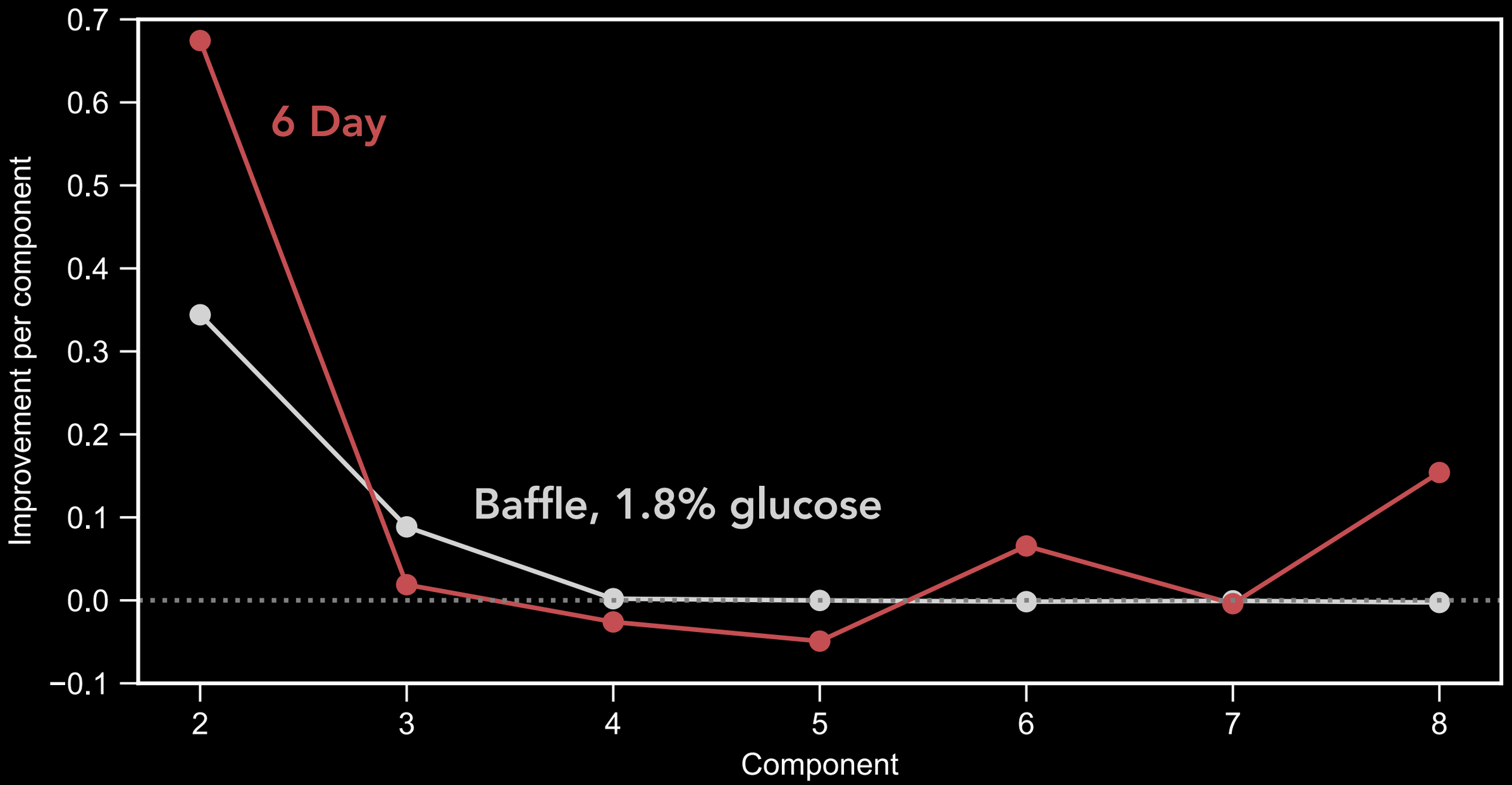
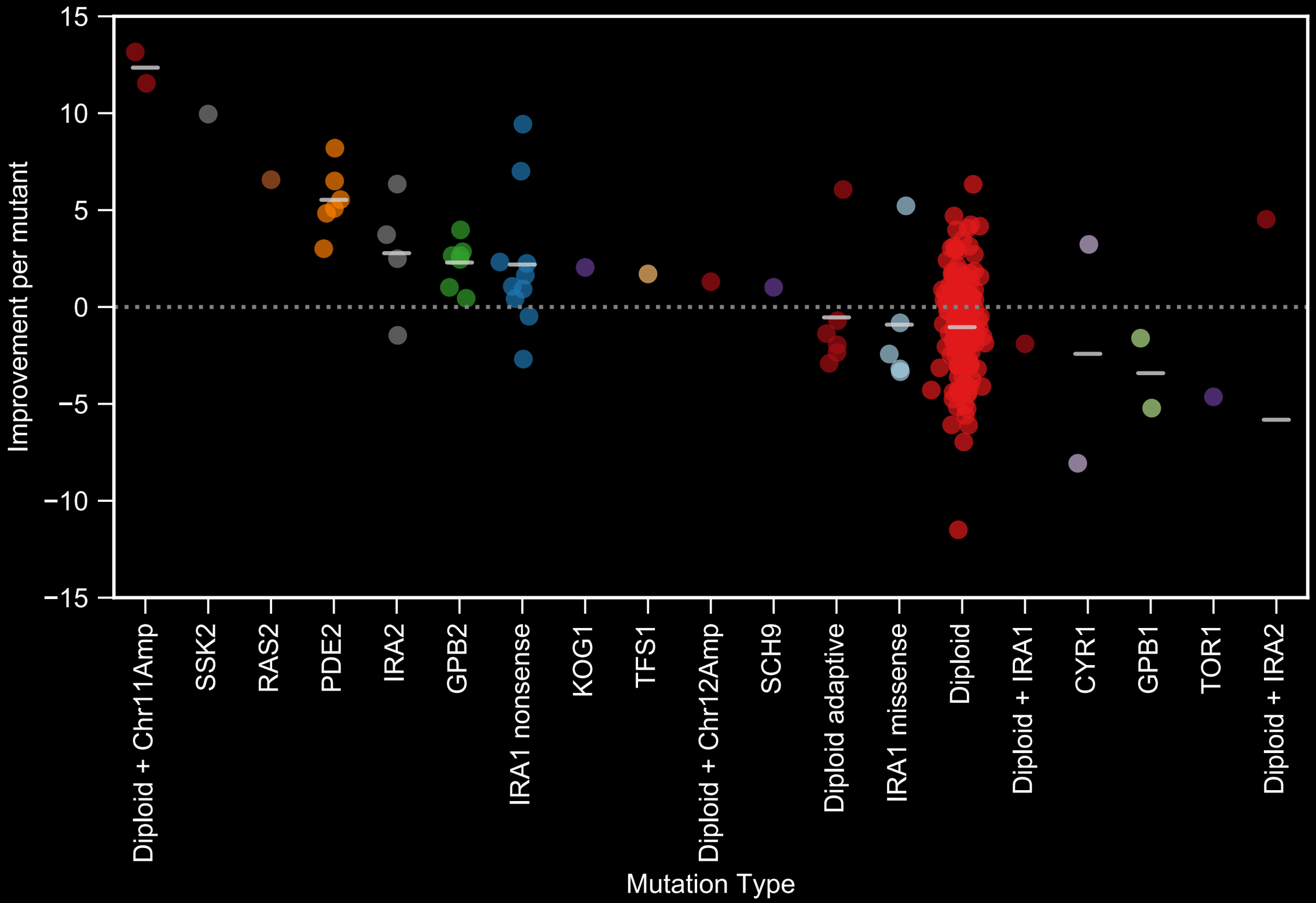
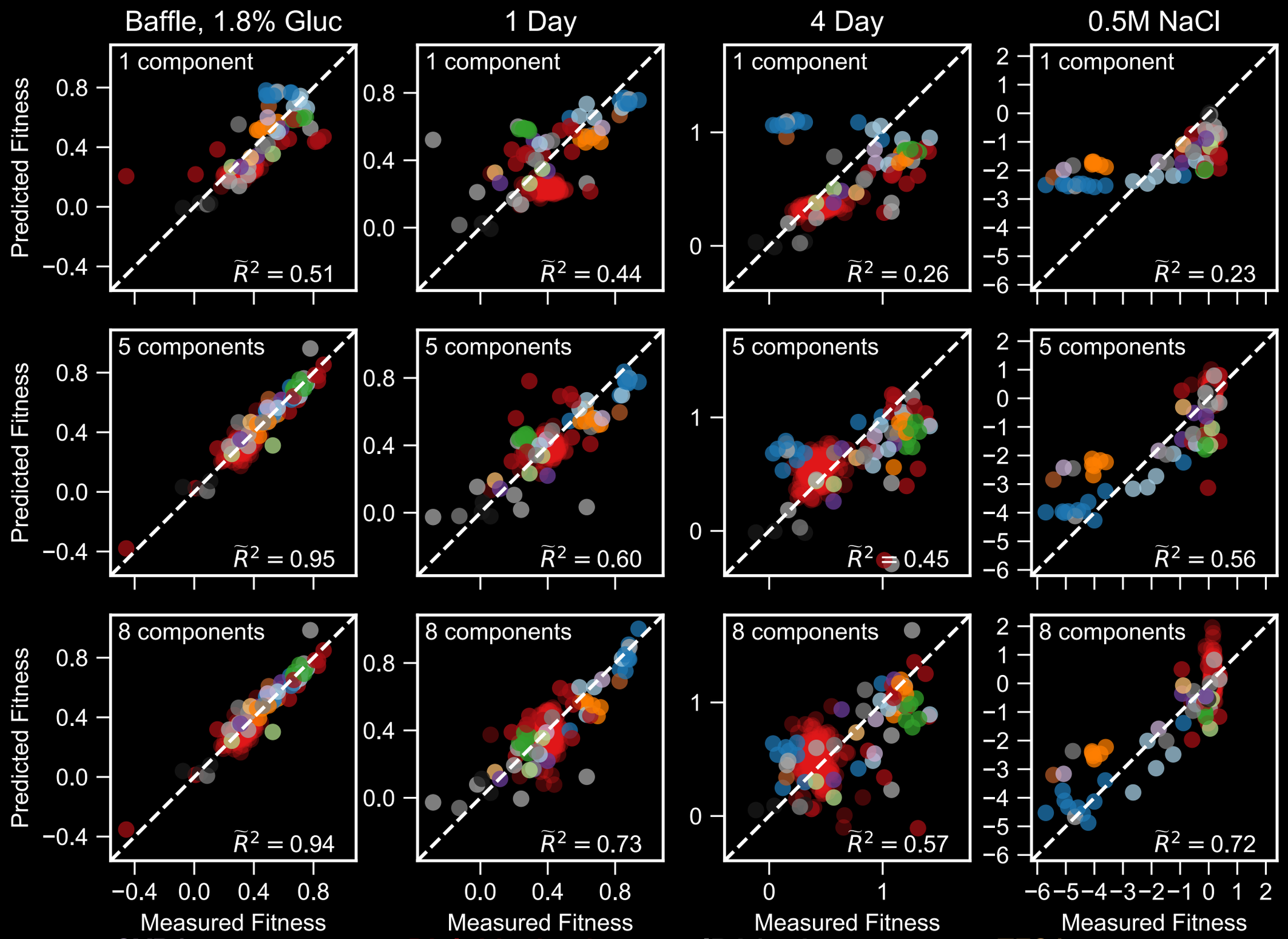
8th component drives significant improvement in 6 Day condition



Specific mutant effects in 8th component drive improvement

6 Day condition




Baffle, 1.8% Gluc
1 Day
4 Day
0.5M NaCl
1 component
5 components
8 components
Predicted Fitness
Measured Fitness
$\widetilde{R}^2 = 0.51$
$\widetilde{R}^2 = 0.44$
$\widetilde{R}^2 = 0.26$
$\widetilde{R}^2 = 0.23$
$\widetilde{R}^2 = 0.95$
$\widetilde{R}^2 = 0.60$
$\widetilde{R}^2 = 0.45$
$\widetilde{R}^2 = 0.56$
$\widetilde{R}^2 = 0.94$
$\widetilde{R}^2 = 0.73$
$\widetilde{R}^2 = 0.57$
$\widetilde{R}^2 = 0.72$
CYR1
Diploid
Diploid + Chr11Amp
Diploid + Chr12Amp
Diploid + IRA1
Diploid + IRA2
Diploid adaptive
ExpNeutral
GPB1
GPB2
IRA1 missense
IRA1 nonsense
IRA1 other
IRA2
KOG1
PDE2
RAS2
SCH9
TFS1
TOR1
other adaptive