Latent phenotypic complexity of adaptation in a single environment

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Kerry Geiler-Samerotte
Organisms are integrated, so mutations should affect many traits.
Adaptive mutations affect few phenotypes
Adaptive mutations affect few phenotypes

Fitness in local environment
Adaptive mutations affect few phenotypes

Fitness in local environment
Adaptive mutations affect few phenotypes

Fitness in local environment

Adaptive Mutation

Fitness in local environment
Adaptive mutations affect few phenotypes

Adaptive mutations affect few fitness-relevant phenotypes

Fitness in local environment
Adaptive mutations affect few phenotypes

Adaptive mutations affect few fitness-relevant phenotypes

Fitness in distant environment

Fitness in distant environment
Adaptive mutations affect few phenotypes

Fitness in distant environment

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.
Many strongly adaptive mutants

Venkataram and Dunn et al. (2016)
Genotype-to-Phenotype-to-Fitness Map

Mutation 1

Fitness
Genotype-to-Phenotype-to-...-to-Phenotype-to-Fitness Map

- mRNA levels
- Cell death
- Cell division
- Cell morphology
- Protein abundances
- Fitness

Mutation 1
Revealing Fitness-Relevant Phenotypes with Environmental Perturbations

Mutation 1 → Fitness
Revealing Fitness-Relevant Phenotypes with Environmental Perturbations

Orthogonal Trait Effects

Mutation 1

\[
\begin{pmatrix}
  p_1 \\
  p_2 \\
  p_3 \\
  \vdots \\
  p_k
\end{pmatrix}
\]
Revealing Fitness-Relevant Phenotypes with Environmental Perturbations

Mutation 1

\[
\begin{pmatrix}
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\]

Orthogonal Trait Effects

Environmental Trait Importance

\[
\begin{pmatrix}
  c_1 \\
  c_2 \\
  c_3 \\
  \vdots \\
  c_k
\end{pmatrix}
\]

Fitness
Revealing Fitness-Relevant Phenotypes with Environmental Perturbations

\[ p_1c_1 + p_2c_2 + \ldots + p_kc_k = f_{M1C1} \]
Revealing Fitness-Relevant Phenotypes with Environmental Perturbations

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Orthogonal Trait Effects

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Environmental Trait Importance

Fitness

Mutation 1
Revealing Fitness-Relevant Phenotypes with Environmental Perturbations

Orthogonal Trait Effects

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Conditions
Revealing Fitness-Relevant Phenotypes with Environmental Perturbations

Orthogonal Trait Effects

Environmental Trait Importance

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Mutation 3

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Environments
Revealing Fitness-Relevant Phenotypes with Environmental Perturbations

Orthogonal Trait Effects

Environments

Mutation 1

Mutation 2

Mutation 3

Mutation 4

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Singular Value Decomposition

Environments
Revealing Fitness-Relevant Phenotypes with Environmental Perturbations

Orthogonal Trait Effects

Environmental Trait Importance

Mutation 1

Mutation 2

Mutation 3

Mutation 4

Singular Value Decomposition

Environments
Revealing Fitness-Relevant Phenotypes with Environmental Perturbations

Orthogonal Trait Effects

Environmental Trait Importance

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Mutation 1

Mutations 2

Mutation 3

Mutation 4

Environments

Singular Value Decomposition
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Singular Value Decomposition
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
- 4 Day Transfer
- 6 Day Transfer
- 3 Day Transfer
- 5 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
- + 0.5ug FCZ
- + 0.4ug Benomyl
- + 17uM GdA
- + 2ug FCZ
- + 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**
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- 12 hour fermentation
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- + 0.5M NaCl
- + 0.2M KCl
- + 0.5M KCl

**Drugs**
- + 8.5uM GdA x2
- + 17uM GdA
- + 0.5ug FCZ
- + 2ug FCZ
- + 0.5ug Benomyol
- + 2ug Benomyol

~400 mutants in 45 conditions for a total of
~18,000 fitness measurements
Fitness Profiles Across Multiple Environments

Fitness relative to Ancestor (per cycle)
Fitness Profiles Across Multiple Environments

Fitness relative to Ancestor (per cycle)

IRA1 nonsense

Batches of the Evolution Condition

Condition
Fitness Profiles Across Multiple Environments

Fitness relative to Ancestor (per cycle)

Diploid

Batches of the Evolution Condition

Condition
Fitness Profiles Across Multiple Environments

Fitness relative to Ancestor (per cycle)

Batches of the Evolution Condition

GPB2
Fitness Profiles Across Multiple Environments

Fitness relative to Ancestor (per cycle)
Fitness Profiles Across Multiple Environments

Fitness relative to Ancestor (per cycle)

IRA1 nonsense
GPB2
PDE2
Diploid

Batches of the Evolution Condition
Fitness Profiles Across Multiple Environments

Subtle perturbations

Strong perturbations

Fitness relative to Ancestor (per cycle)

IRA1 nonsense
GPB2
PDE2
Diploid

Condition

0.4ug/ml Ben
Baffle, 2ug/ml Ben
Baffle, 0.4ug/ml Ben
Baffle, 0.2M NaCl
0.2M NaCl
0.5M KCl
Baffle, 0.5M KCl
0.5M NaCl
0.2M KCl
1% EtOH
1% DMSO
2ug/ml Flu
22hr Fem
3 Day
17uM GdA
Baffle, 1.4% Gluc
Baffle, 1.8% Gluc
Baffle, 1.6% Gluc
8 hr Fem
1% Raf
1% Raf
1% Raf
1% Raf
Diploid

Batches of the Evolution Condition
Subtle perturbations reveal 8 fitness-relevant phenotypes
Limit of Detection

Subtle perturbations reveal 8 fitness-relevant phenotypes

Variance explained by component

Number of Components

Components detected from noise

Limit of Detection
Subtle perturbations reveal 8 fitness-relevant phenotypes
Subtle perturbations reveal 8 fitness-relevant phenotypes

![Graph showing variance explained by component against number of components. The graph indicates that the limit of detection is at 10^-3, and 95.2% and 3.3% of the variance is explained by the first few components. Components detected from noise are shown below the limit of detection.]
Subtle perturbations reveal 8 fitness-relevant phenotypes

Limit of Detection

Components detected from noise

95.2%
3.3%
0.40%
Subtle perturbations reveal 8 fitness-relevant phenotypes

Components detected from noise

Limit of Detection

Variances explained by component

Number of Components
Subtle perturbations reveal 8 fitness-relevant phenotypes.
The phenotype space from subtle perturbations clusters mutations by gene.

- GPB2
- PDE2
- IRA1
- High-Fitness Diploids
- Diploid
- IRA1
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

- Construct model w/ subtle perturbations
- Test model in subtle perturbations
- Test model in strong perturbations
5 largest phenotypes explain most variation in subtle perturbations.
5 largest phenotypes explain most variation in subtle perturbations.
5 largest phenotypes explain most variation in subtle perturbations
5 largest phenotypes explain most variation in subtle perturbations

- 1-component model
- 5-component model
- 8-component model
Phenotype space can predict fitness in strong perturbations!

- 1-component model
- 5-component model
- 8-component model

Subtle Perturbations

Strong Perturbations
Phenotype space can predict fitness in strong perturbations!
Smallest 3 components add predictive power in strong perturbations

Subtle Perturbations

1-component model

5-component model

8-component model

Strong Perturbations

Weighted Coefficient of Determination ($R^2$)
Smallest 3 components add predictive power in strong perturbations
Smallest 3 components add predictive power in strong perturbations.
Genotype: GPB2, PDE2, IRA1, Diploid
Phenotypes: fitness in evolution condition
Fitness:

Fitness in Evolution Condition
Thanks!

Kerry Geiler-Samerotte

Dmitri Petrov

Yuping Li
Sandeep Venkataram
Atish Agarwala

Monica Sanchez
Tuya Yokoyama

Petrov Lab
Adaptive mutations affect few **fitness-relevant** phenotypes

Latent phenotypic effects represent global phenotypic diversity generated by local adaptation
8th component drives significant improvement in 6 Day condition
Specific mutant effects in 8th component drive improvement

6 Day condition