Uncovering the phenotypic fitness landscape of microbes adapting to novel environments

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@GrantKinsler
Evolution Experiment in Glucose Limitation

Levy and Blundell et al. (2015)
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Thousands of independent adaptive events!

Venkataram and Dunn et al. (2016)
Evolution Experiment in Glucose Limitation

Thousands of independent adaptive events!

237/335 (71%) — Self-Diploidization
82/335 (24%) — Nutrient-Response pathways
14/335 (5%) — Something else

Venkataram and Dunn et al. (2016)
How many fitness-relevant phenotypes are impacted by adaptive mutations?
Genotype-to-Phenotype-to-...-to-Phenotype-to-Fitness Map

- Genotype
- mRNA levels
- Protein abundances
- Cell death
- Cell division rate
- Cell morphology
- Fitness
Subtle environmental perturbations can reveal fitness-relevant phenotypes.

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Genotype  mRNA levels  Protein abundances

Cell death  Cell division rate  Cell morphology

Fitness

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Genotype → mRNA levels → Protein abundances → Cell morphology → Cell division rate → Cell death → Fitness

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Remeasure Fitness of Adaptive Mutants

Venkataram and Dunn et al. (2016)
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Venkataram and Dunn et al. (2016)
Remeasure fitness of adaptive mutants

Venkataram and Dunn et al. (2016)
Remeasure fitness of adaptive mutants

Venkataram and Dunn et al. (2016)
A framework for using subtle perturbations
A framework for using subtle perturbations

Phenotype 1

Phenotype 2

Optimal combination of phenotypes
A framework for using subtle perturbations

Optimal combination of phenotypes

Ancestor
A framework for using subtle perturbations
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Predicting fitness in new environments using batch conditions

Good Prediction

Bad Prediction

Condition

DMSO
No Anc
GdA
1.8\% Gluc
Ferm_50hr
24hr
1.6\% Gluc
Ferm_44hr
1.4\% Gluc
Ferm_54hr
1.7\% Gluc
Rad_5uM
5 Day
2.5\% Gluc
Ben_2ug/mL
Flu_2ug/mL
7 Day
Predicting fitness in new environments using batch conditions

![Graph showing predictability of fitness conditions](#)
Predicting fitness in new environments using batch conditions

1 Trait Model

Good Prediction vs. Bad Prediction

Predictability vs. Condition

Subtle vs. Not-so-subtle
Predicting fitness in new environments using batch conditions

Good Prediction

Bad Prediction

Predictability

1 Trait Model

2 Trait Model

Subtle

Not-so-subtle

Condition

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GdA
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Subtle

Not-so-subtle
Predicting fitness in new environments using batch conditions

Subtle

Not-so-subtle
Predicting fitness in new environments using batch conditions

Predictability

Good Prediction

Bad Prediction

Subtle

Not-so-subtle

Condition

DMSO, No Anc, GdA, 1.8% Gluc, Ferm_50hr, 24hr, 1.6% Gluc, Ferm_44hr, Ferm_40hr, 1.4% Gluc, Ferm_54hr, 1.7% Gluc, Rad_5uM, 5 Day, 2.5% Gluc, Ben_2ug/mL, Flu_2ug/mL, 7 Day
Predicting fitness in new environments using batch conditions

![Graph showing predictability of fitness under various conditions.]

- **Good Prediction**
- **Bad Prediction**

Conditions:
- DMSO
- No Anc
- GdA
- 1.8% Gluc
- Ferm_50hr
- 24hr
- 1.6% Gluc
- Ferm_44hr
- Ferm_40hr
- 1.4% Gluc
- Ferm_54hr
- 1.7% Gluc
- Rad_5uM
- 5 Day
- 2.5% Gluc
- Ben_2ug/mL
- Flu_2ug/mL
- 7 Day

**Predictability**

**Subtle**

**Not-so-subtle**
Few (~2) fitness-relevant traits explain behavior across subtle perturbations.
Subtle

Not-so-subtle
Another phenotype matters here?
1 Big Batch Experiment

#1BigBatch
@GrantKinsler
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First #1BigBatch data is back! We sequenced 8 samples on 1 lane of HiSeq X, each with unique set of primers. For each primer, ~10% of reads were in pairs not included, showing high rates of index switching, which could impact frequency estimates. 

@GrantKinsler @PetrovADmitri

Evidence for Index Switching in #1BigBatch Sequencing

Update on #1BigBatch: we tested how different sources of technical variation influence our ability to estimate the relative frequencies of 500 barcoded yeast lineages. Want to bet which source contributes most noise? 

#1BigBet @GrantKinsler @PetrovADmitri

26% Inefficient cell lysis
18% Index switching
41% Stochasticity of PCR
15% Variation btw Hiseq runs

100 votes • Final results

7:37 PM - 6 Jun 2018
1. Subtle perturbations + precise fitness estimates give insight about phenotypic evolution

Preliminary conclusions about phenotypes involved in adaptation to glucose-limitation
Preliminary conclusions about phenotypes involved in adaptation to glucose-limitation

1. Subtle perturbations + precise fitness estimates give insight about phenotypic evolution

2. First step of adaptation (in this case) seems to involve few fitness-relevant phenotypes
Thanks!

Kerry Geiler-Samerotte

Dmitri Petrov

Petrov Lab

Yuping Li + Sherlock Lab

#1BigBatch

@GrantKinsler

SSE