A Universal Temperature Dependence of Mutational Fitness Effects

David Berger
Department of Ecology and Genetics, Uppsala University
Can organisms adapt?

- Response to Selection
- Historical Contingency
- Balanced Polymorphism
- Deleterious Polymorphism

Genotype / Phenotype space
Is evolution repeatable?

Response to Selection

Historical Contingency

Balanced Polymorphism

Deleterious Polymorphism
Is evolution repeatable?

- Response to Selection
- Historical Contingency
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Genotype / Phenotype space

\[ \sim S \]
Is evolution repeatable?

Response to Selection

- Historical Contingency
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Genotype / Phenotype space

\(~ S ~\)
Is evolution repeatable?

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Genotype / Phenotype space

$\sim S$
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Genotype / Phenotype space

\[ \sim S \]
Is evolution repeatable?

- Response to Selection
- Historical Contingency
- Balanced Polymorphism
- Deleterious Polymorphism

Do some environments impose stronger selection than others?
- Selection varies across environments
- Limited understanding of patterns
- "Selection increases under stress"
- Selection varies across environments
- Limited understanding of patterns
- "Selection increases under stress"

- Theory does not predict a general increase in selection under stress
- "Outcome dependent on local curvature of the fitness landscape"
PREDICTING THE STRENGTH OF SELECTION ON NEW MUTATIONS USING PROTEIN BIOPHYSICS

Richard Walters
**Protein Folding**

\[ W \approx P_{\text{folded}} = \frac{1}{1 + e^{\Delta G / RT}} \]

Mean stability:

\[ \Delta G \sim -7 \text{ kcal/mol} \]

*De Pristo et al. 2005 Nature*  
*Echave & Wilks 2017 Ann Rev Biophysics*
Protein Folding

Temperature and mutation decrease protein stability, resulting in misfolded protein

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W \approx P_{\text{folded}} = \frac{1}{1 + e^{\Delta G / RT}}
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\[
W^* \approx P^*_{\text{folded}} = \frac{1}{1 + e^{(\Delta G + \Delta \Delta G) / RT}}
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mean stability:

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\Delta G \sim -7 \text{ kcal/mol}
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mean mutational effect:

\[
\Delta \Delta G \sim +0.9
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\[ \omega = \text{wildtype fitness} \]
\[ \omega^* = \text{mutant fitness} \]
\[ s = 1 - \omega^*/\omega \]
\[ W \approx P_{\text{folded}} = \frac{1}{1 + e^{\Delta G / RT}} \]

\[ W^* \approx P^*_{\text{folded}} = \frac{1}{1 + e^{(\Delta G + \Delta \Delta G) / RT}} \]

Mean stability:
\[ \bar{\Delta G} \sim -7 \text{ kcal/mol} \]

Mean mutational effect:
\[ \bar{\Delta \Delta G} \sim +0.9 \]

Strength of selection should increase with temperature:
\[ s = 1 - \frac{\omega^*/\omega}{\omega} \]
META ANALYSIS

\[ \log_e \left( \frac{\Delta \omega_s}{\Delta \omega_b} \right) \]

11 Species
27 Studies
98 Estimates

ABIOTIC STRESS

Berger et al. In review.
META ANALYSIS

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\log_e \left( \frac{\Delta \omega_s}{\Delta \omega_b} \right)
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11 Species
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ABIOTIC STRESS

Berger et al. *In review.*
META ANALYSIS

$\log_e (\Delta \omega_s / \Delta \omega_b)$

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Total</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Low Temp</td>
<td>18</td>
<td>P = 0.008</td>
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<tr>
<td>High Temp</td>
<td>20</td>
<td>P &lt; 0.001</td>
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</table>

Berger et al. *In review.*
META ANALYSIS

\[
\log_e \left( \frac{\Delta \omega_s}{\Delta \omega_b} \right)
\]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sample Size</th>
<th>P-value</th>
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<tbody>
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<td>High = 0</td>
<td>n = 98</td>
<td>P &lt; 0.001</td>
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<tr>
<td>High = Low</td>
<td>n = 60</td>
<td>P = 0.012</td>
</tr>
<tr>
<td>High = Other</td>
<td>n = 18</td>
<td>P = 0.008</td>
</tr>
</tbody>
</table>

ABIOTIC STRESS

Berger et al. *In review.*
A UNIVERSAL TEMPERATURE DEPENDENCE OF MUTATIONAL FITNESS EFFECTS

\[
\log_e \left( \frac{\Delta \omega_s}{\Delta \omega_b} \right)
\]

\[\Delta T = (T_{stress} - T_{benign})\]

\[R^2 = 0.42\]

Stress: \[P > 0.3\]

Temp: \[P = 0.002\]

Temp²: \[P = 0.03\]

organism
- C. briggsae
- C. elegans
- C. maculatus
- C. neoformans
- D. melanogaster
- E. coli
- S. cerevisiae
A UNIVERSAL TEMPERATURE DEPENDENCE OF MUTATIONAL FITNESS EFFECTS

\[ \log(e^{(\Delta s / \Delta s_b)}) \]

\[ \text{Stress: } P > 0.3 \]
\[ \text{Temp: } P = 0.002 \]
\[ \text{Temp}^2: P = 0.03 \]

\[ R^2 = 0.42 \]

- **organism**
  - C. briggsae
  - C. elegans
  - C. maculatus
  - C. neoformans
  - D. melanogaste
  - E. coli
  - S. cerevisae

\[ \Delta T (T_{stress} - T_{benign}) \]

\[ \log(e^{(s / s_b)}) \]

\[ \Delta T (T - T_{ref}) \]

\[ -15 \quad -10 \quad -5 \quad 0 \quad 5 \quad 10 \quad 15 \]

\[ 0 \quad 1 \quad 2 \quad 3 \quad 4 \]

\[ -1 \quad 0 \quad 1 \quad 2 \]

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- Environmental stress does not increase purifying selection
- Universal increase in selection at high temperature
- Mechanistic basis attributed to biophysics of protein function
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- Genomic signatures of selection and future evolvability
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P-0577 in Symposia 54:
DIRECT AND INDIRECT GENETIC EFFECTS OF SEXUAL SELECTION ON MUTATION RATE

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