Towards a quantitative genetics of complex cellular traits

Michael Lässig

Institute for Theoretical Physics, University of Cologne

Thanks

Theory of quantitative traits:

Torsten Held (Cologne)
Daniel Klemmer (Cologne)
Armita Nourmohammad (Princeton)
Stephan Schiffels (Sanger)

Drosophila gene expression:

Armita Nourmohammad (Princeton)
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Johannes Berg (Cologne)

DFG Deutsche Forschungsgemeinschaft

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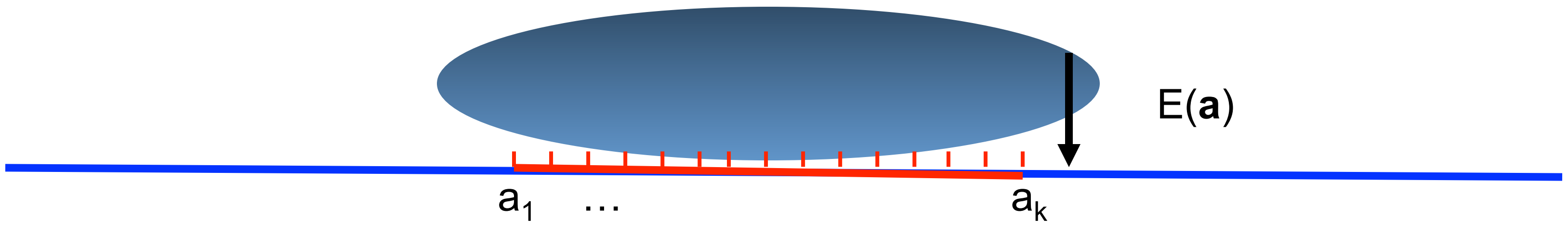
CORDIS
The European Commission
Community Research
Improving Human Research Potential & the Socio-economic Knowledge Base

Examples of phenotypes

- **Molecular traits:**

  Molecular binding interations, e.g., between transcription factors and regulatory DNA



- **Cellular traits:**

  metabolic, regulatory, and signaling pathways

- **Organismic traits:**

  body weight and size, shapes, metabolic rates
  fitness, longevity

➔ **Quantitative traits occur in coarse-grained descriptions of increasing level.**

Evolutionary theories

- Sequence level: population genetics
- Cellular level: systems biology
- Organismic level: quantitative genetics

→ **Evolutionary systems biology**

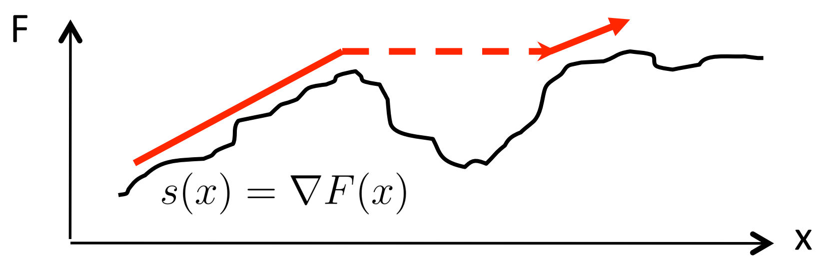
- **We need to rethink the quantitative genetics of molecular traits.**

1. Evolutionary equilibrium of regulatory DNA

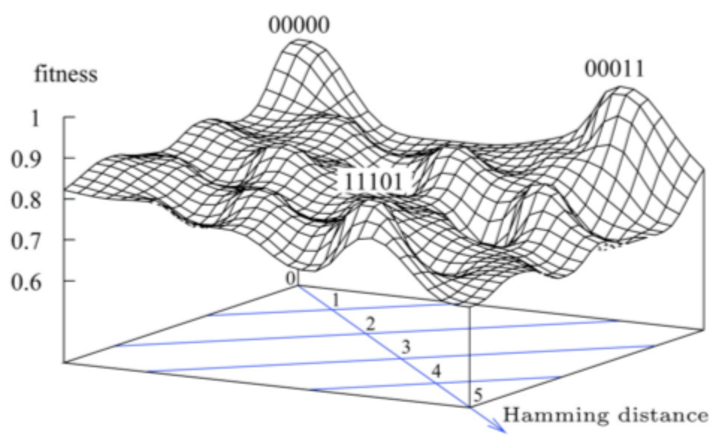
Fitness landscapes

- Evolution in a **fitness landscape** (S. Wright 1932) **:**

  - *interplay of selection and genetic drift*
  - *longer time intervals: mutations*



- Experimental fitness landscape in the fungus *Aspergillus niger*



[A. de Visser, SC. Park, J. Krug 09]

Statistical mechanics of evolutionary equilibrium

- If the **neutral** process under mutations and genetic drift has an **equilibrium frequency distribution** $P_0(x)$, the process in an **arbitrary fitness landscape** also has an equilibrium

$$P_{\rm eq}(x) = P_0(x)\, \exp[2NF(x)] \,.$$

- **Average fitness** measures the **information of population states**:

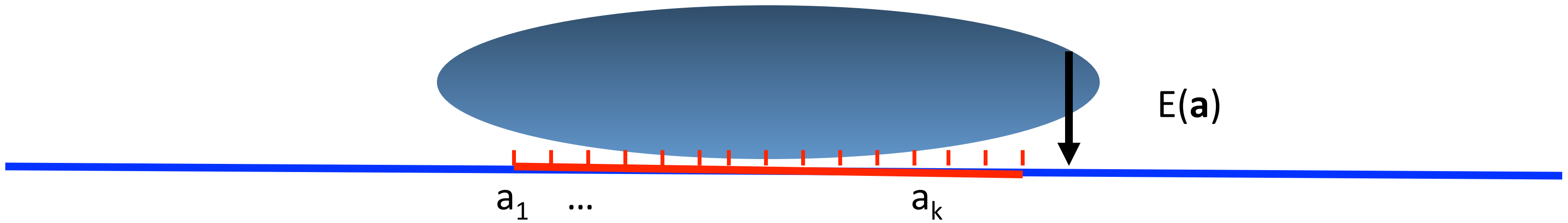
$$\langle 2NF \rangle = \int P_{\rm eq}(x)\, \log \frac{P_{\rm eq}(x)}{P_0(x)}\, dx = H(P_{\rm eq}|P_0) \;.$$

KL entropy

[J.Berg, S.Willmann, M.L., BMC Evol. Biol. 2004, V. Mustonen, M.L., PNAS 2010]

Cis-regulatory elements: from sequence to phenotype

- Transcription factor proteins bind to **DNA target sites,** catalyzing transcription.

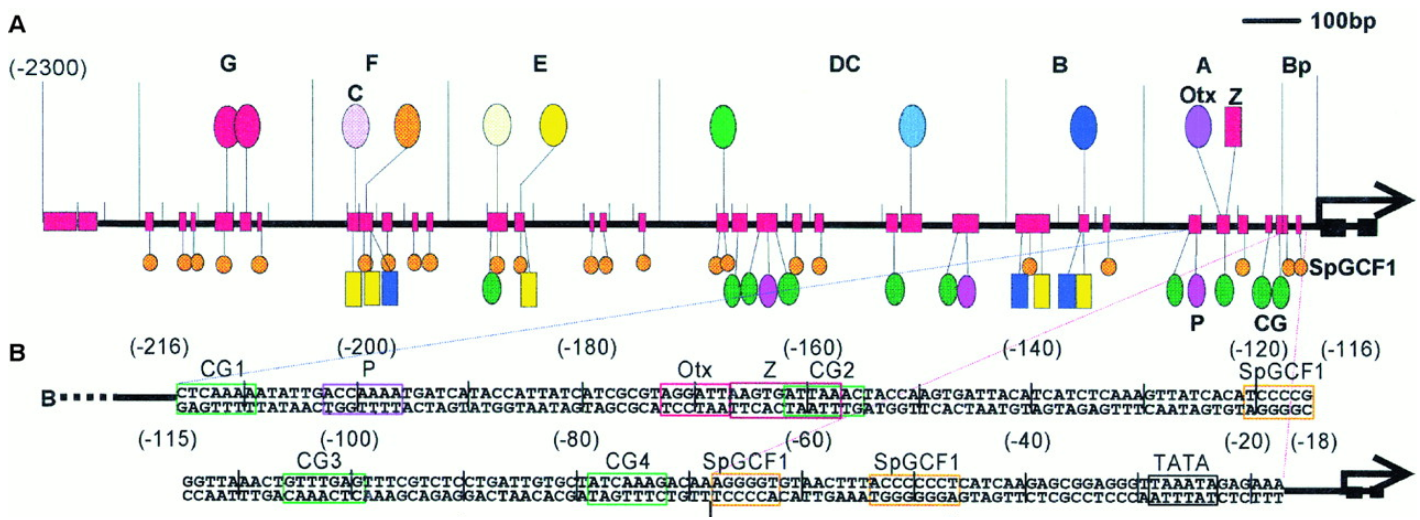


- **Binding energy** E(**a**) of a site **a** = (a_1,…,a_k) can be obtained from genomics and biophysical measurements.

- The binding energy E(**a**) is the **molecular phenotype** of a site, which **quantifies its functionality**.

Complexity of regulatory interactions

- Multiple binding sites allow for complex regulation of individual genes in higher organisms:



[Bolouri and Davidson, 2002]

- Input-output relation?

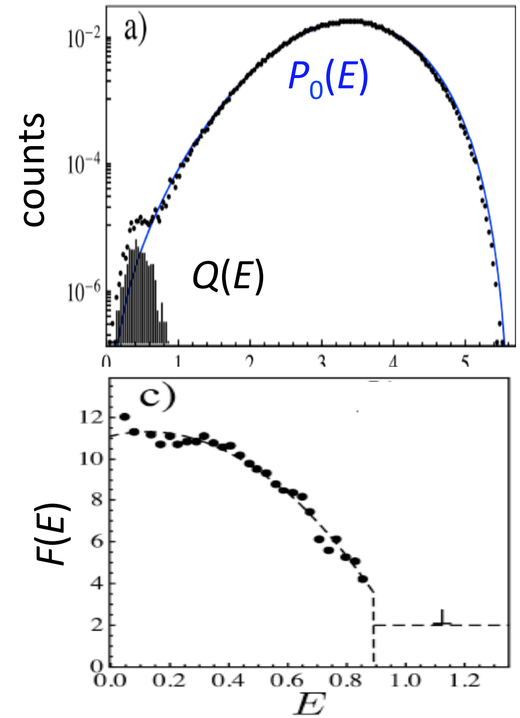
  Evolutionary dynamics?

Cis-regulatory elements: from phenotype to fitness

- Genomic analysis determines the distributions $P_0(E)$ and $Q(E)$.

- **Mesa fitness landscape** inferred at equilibrium

$$2NF(E) = \log \frac{Q(E)}{P_0(E)} + \text{const.}$$



Abf1 binding sites in S. cerevisiae

- This landscape successfully predicts binding site divergence across yeast species.

[Berg, Willmann, M.L., BMC Evol. Biol. 2004,
Mustonen, M.L., PNAS 2005, Mustonen, Kinney, Callen, M.L., PNAS 2008]

Conclusions (1)

- **Biophysical observables provide molecular phenotypes for evolutionary analysis.**

- **These can be used to infer phenotypic fitness landscapes.**

- **The mesa fitness landscape is shaped by thermodynamics of intra-cellular processes.**

Generalization to

- *higher genomic complexity?*
- *non-equilibrium adaptive processes?*

2. Evolutionary statistics of quantitative traits

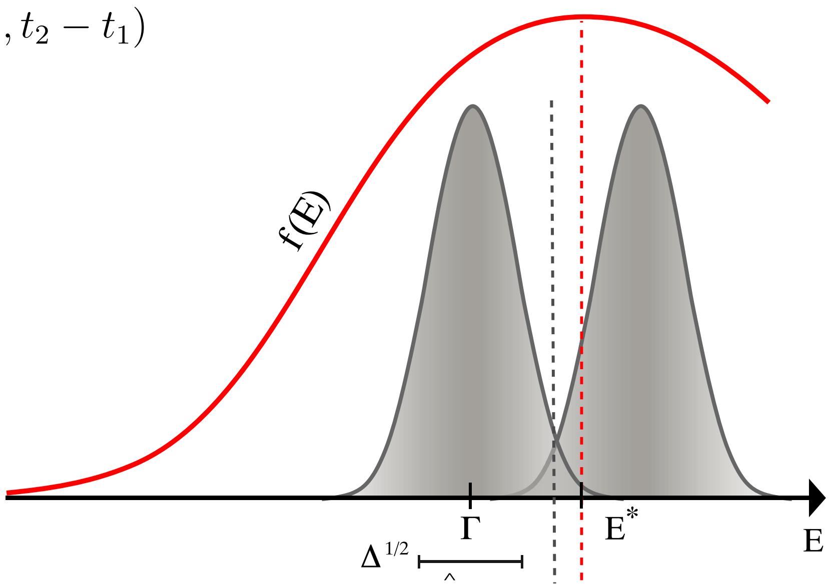
Evolutionary statistics of phenotypes

- **Trait mean and diversity** within one population:

$$\Gamma \equiv \overline{E} = \int E\,\mathcal{W}(E)\,dE, \qquad \Delta \equiv \overline{(E-\Gamma)^2} = \int (E-\Gamma)^2\,\mathcal{W}(E)\,dE,$$

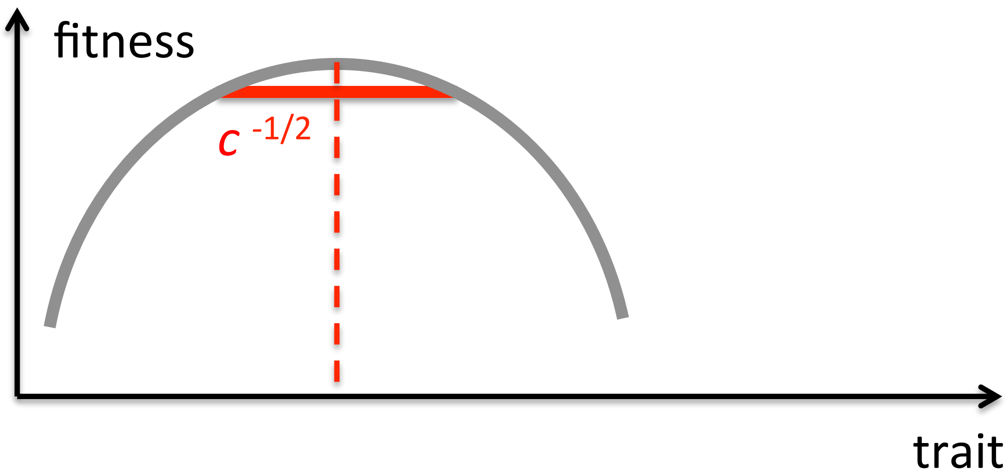
- **Trait divergence** between populations:

$$\left\langle (\Gamma(t_1) - \Gamma(t_2))^2 \right\rangle = \int d\Gamma_1 d\Gamma_2\; Q(\Gamma_2; \Gamma_1, t_2 - t_1)$$



Evolution under stablizing selection

- **Fitness landscape model:** Minimal dynamics under stabilizing selection



$$\frac{d\Gamma}{dt} = -\langle\Delta\rangle \frac{2c}{E_0^2}(\Gamma - E^*) - 2\mu(\Gamma - \Gamma_0) + \eta_\Gamma(t)$$

with noise generated by genetic drift: $\langle \eta_\Gamma(t)\eta_\Gamma(t')\rangle = \frac{\langle\Delta\rangle}{2N}\delta(t-t')$

+ similar equation for Δ

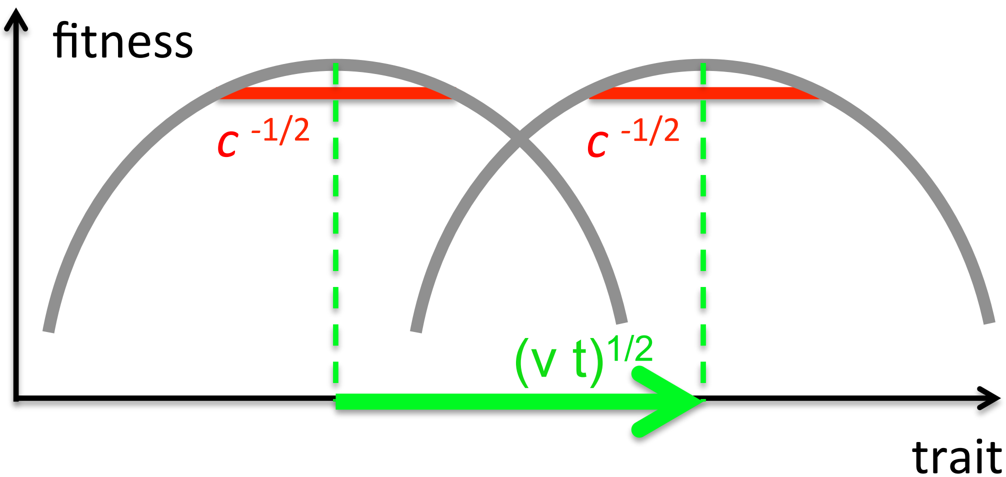
- **The landscape model generates equilibria of trait mean and variance:**

$$Q_{\rm eq}(\Gamma) = \frac{1}{Z}\tilde{Q}_0(\Gamma)\exp\left[2N\tilde{F}(\Gamma)\right], \qquad Q_{\rm eq}(\Delta) = \frac{1}{Z}Q_0(\Delta)\exp[2N\tilde{F}(\Delta)],$$

[Nourmohammad. Schiffels, ML, JSTAT 2013]

Adaptive evolution

- **Fitness seascape model:**
  Minimal adaptive dynamics



$$\frac{d\Gamma}{dt} = -\langle\Delta\rangle \frac{2c}{E_0^2}(\Gamma - E^*(t)) - 2\mu(\Gamma - \Gamma_0) + \eta_\Gamma(t)$$

$$\frac{dE^*}{dt} = \frac{\upsilon}{r^2}(E^* - \mathcal{E}) + \eta_{E^*}$$

with noise generated by genetic drift and fitness peak displacements:

$$\langle\eta_\Gamma(t)\eta_\Gamma(t')\rangle = \frac{\langle\Delta\rangle}{2N}\,\delta(t-t') \qquad \langle\eta_{E^*}(t)\eta_{E^*}(t')\rangle = \upsilon E_0^2\,\delta(t-t')$$

+ similar equation for Δ.

- **The seascape model generates non-equilibrium adaptive evolution.**

[Held, Nourmohammad, ML, JSTAT 2014]

Interlude: Quantifying adaptation

- A **population history** is a sequence of frequency measurements

$$\mathbf{x} = (x_0, \ldots, x_n) \quad \text{at times} \quad (t_0, \ldots, t_n).$$

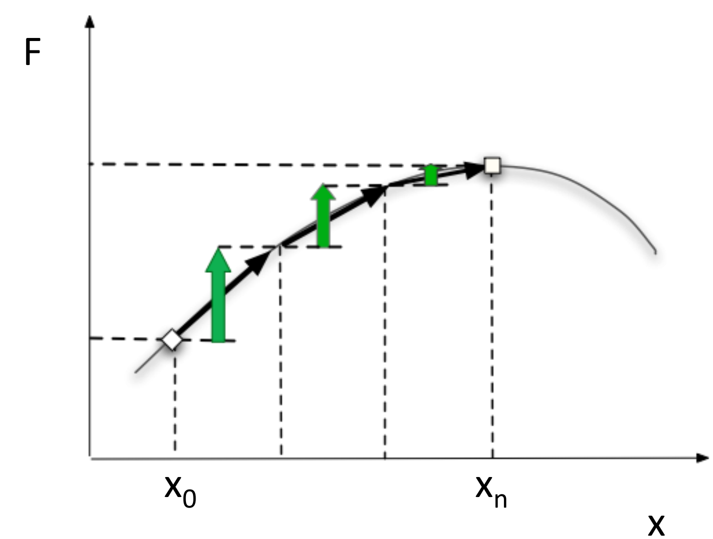
- The **fitness flux** of a population history is the cumulative **selective effect of frequency changes:**

$$\Phi(\mathbf{x}) \equiv \sum_{i=1}^{n} \Delta x_i \, s(x_i, t_i).$$

- Flux in a **fitness landscape:**

$$s(x) = \nabla F(x)$$

$$\begin{aligned}\Phi(\mathbf{x}) &= \sum_{i=1}^{n} \Delta x_i \, \nabla F(x_i) \\ &= F(x_n) - F(x_0).\end{aligned}$$



Interlude: Quantifying adaptation

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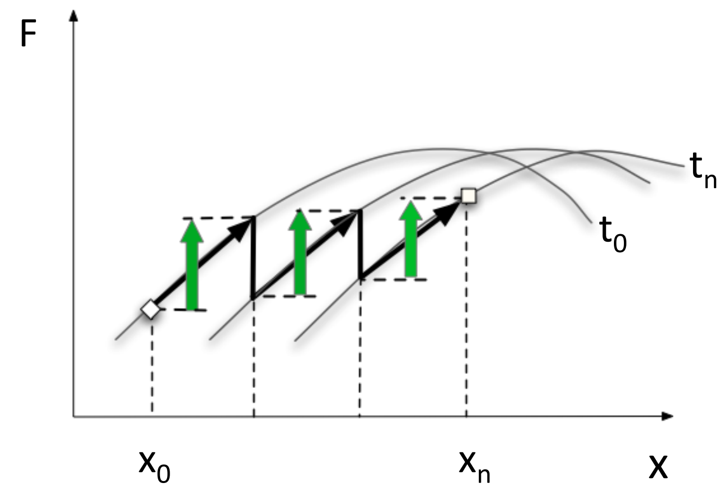
- Flux in a **fitness seascape:**

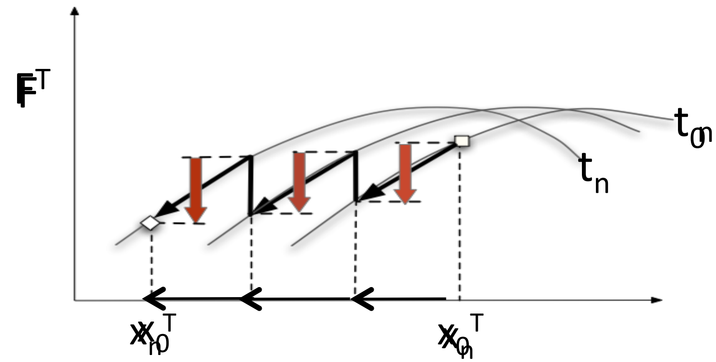
$$s(x,t) = \nabla F(x,t)$$

$$\begin{aligned}\Phi(\mathbf{x}) &= \sum_{i=1}^{n} \Delta x_i \, \nabla F(x_i, t_i) \\ &\neq F(x_n, t_n) - F(x_0, t_0).\end{aligned}$$



Interlude: Quantifying adaptation

- Each population history **x** has a **reverse history x^T,** in which all frequency transitions have opposite fitness effects:



- **Fitness flux measures adaptation as deviation from evolutionary equilibrium**

$$\mathcal{P}^T(\mathbf{x}^T) = \mathcal{P}(\mathbf{x}) \, \exp[-2N\Phi(\mathbf{x}) + \Delta\mathcal{H}(\mathbf{x})]$$

fitness flux

entropy difference of initial conditions

- **Average fitness flux** measures the **information of the adaptive process**:

$$\langle 2N\Phi \rangle = H(\mathcal{P}|\mathcal{P}^T) + \text{boundary terms}$$

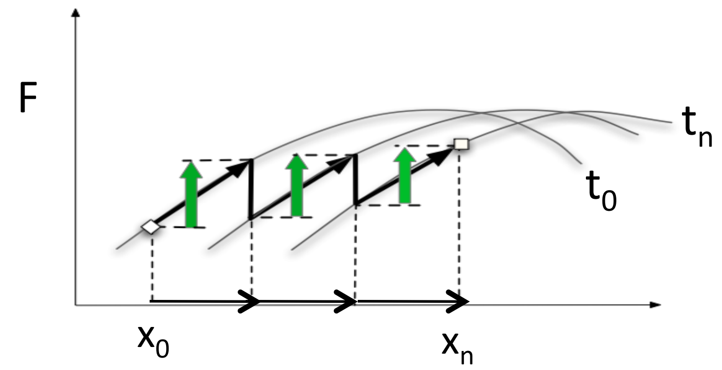
KL entropy

[Mustonen, M.L., PNAS 2010]

Interlude: Quantifying adaptation

- **Phenotypic fitness flux**

$$\Phi(\tau) = \int_0^\tau \frac{\partial F(\Gamma,t)}{\partial \Gamma}\,\frac{d\Gamma}{dt}\,dt$$



- **Average fitness flux in the seascape model:**

$$\langle 2N\Phi(\tau)\rangle = c\,\upsilon\,\tau$$

.

Inferring adaptation of quantitative traits

- **Scaled divergence-diversity ratio:**

$$\Omega(\tau) = 2\mu N \frac{\langle D(\tau) \rangle}{\langle \Delta \rangle}$$

- **Ω test:** The time-dependence of Ω measures evolution in a seascape:

- stabilizing strength

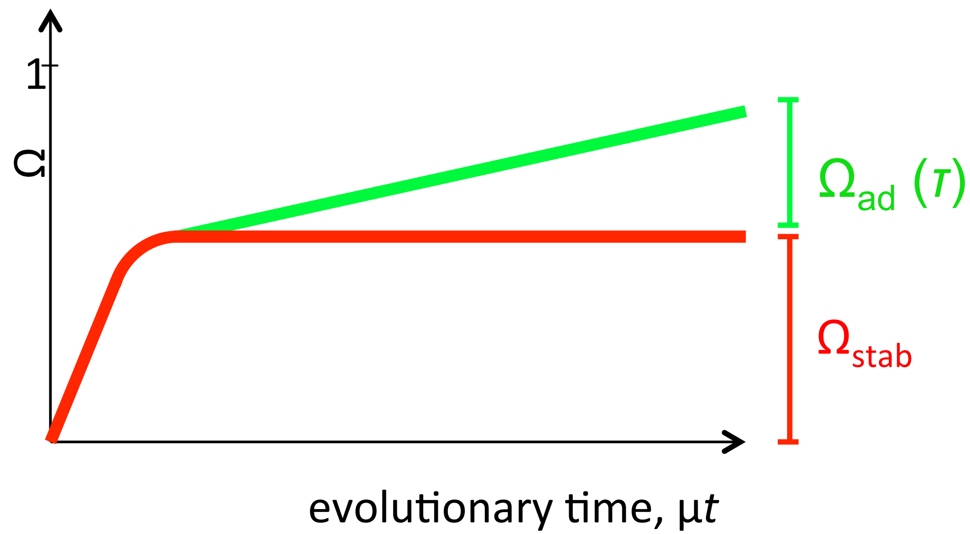
$$c \approx \frac{1}{\Omega_{\mathrm{stab}}}$$

- driving rate

$$\upsilon \approx \frac{2\Omega_{\mathrm{ad}}(\tau)}{\tau}$$

- fitness flux

$$\langle 2N\Phi(\tau) \rangle \approx \frac{2\Omega_{\mathrm{ad}}(\tau)}{\Omega(\tau) - \Omega_{\mathrm{ad}}(\tau)}$$



[Held, Nourmohammad, ML, JSTAT 2014]

- **Comparison with other methods**

1. *Q_{st} / F_{st} analysis:*
   infers directional selection if it is the dominant part of selection on short time scales ($\Omega > \Omega_0$) .

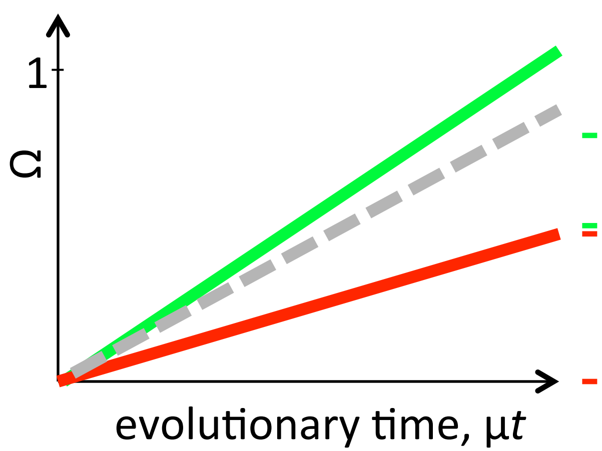
   Ω test:
   joint inference of directional and stabilizing selection (also for $\Omega > \Omega_0$) .

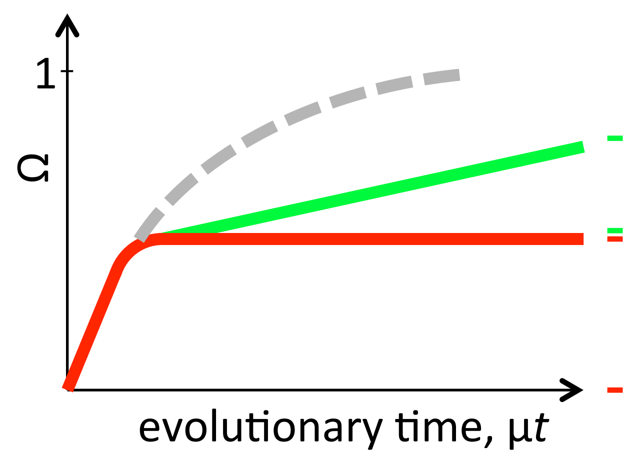
2. *Ornstein-Uhlenbeck model:*
   heuristics for equilibrium under stabilizing selection.

   Landscape model:
   determines Ornstein-Uhlenbeck parameters in terms of quantitative genestics

3. *McDonald-Kreitman test:*
   requires divergence data from query sequence vs. neutral sequence at one divergence time.

   Ω test:
   requires trait divergence data for at least two sufficiently large divergence times.





Conclusions (2)

- **The evolutionary statistics of complex quantitative traits shows *universal* characteristics.**

- **These can be used to infer phenotypic fitness** land- and **seascapes.**

- **The single-peak seascape - unifies stabilizing and directional selection.**
  - provides a minimal model for adaptive evolution.