From Fisher to Feynman: nonequilibrium statistics of molecular evolution

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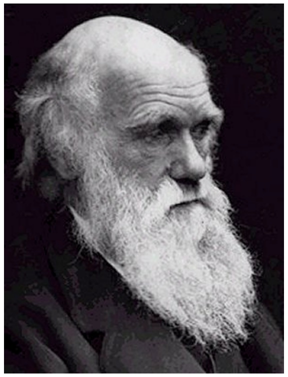
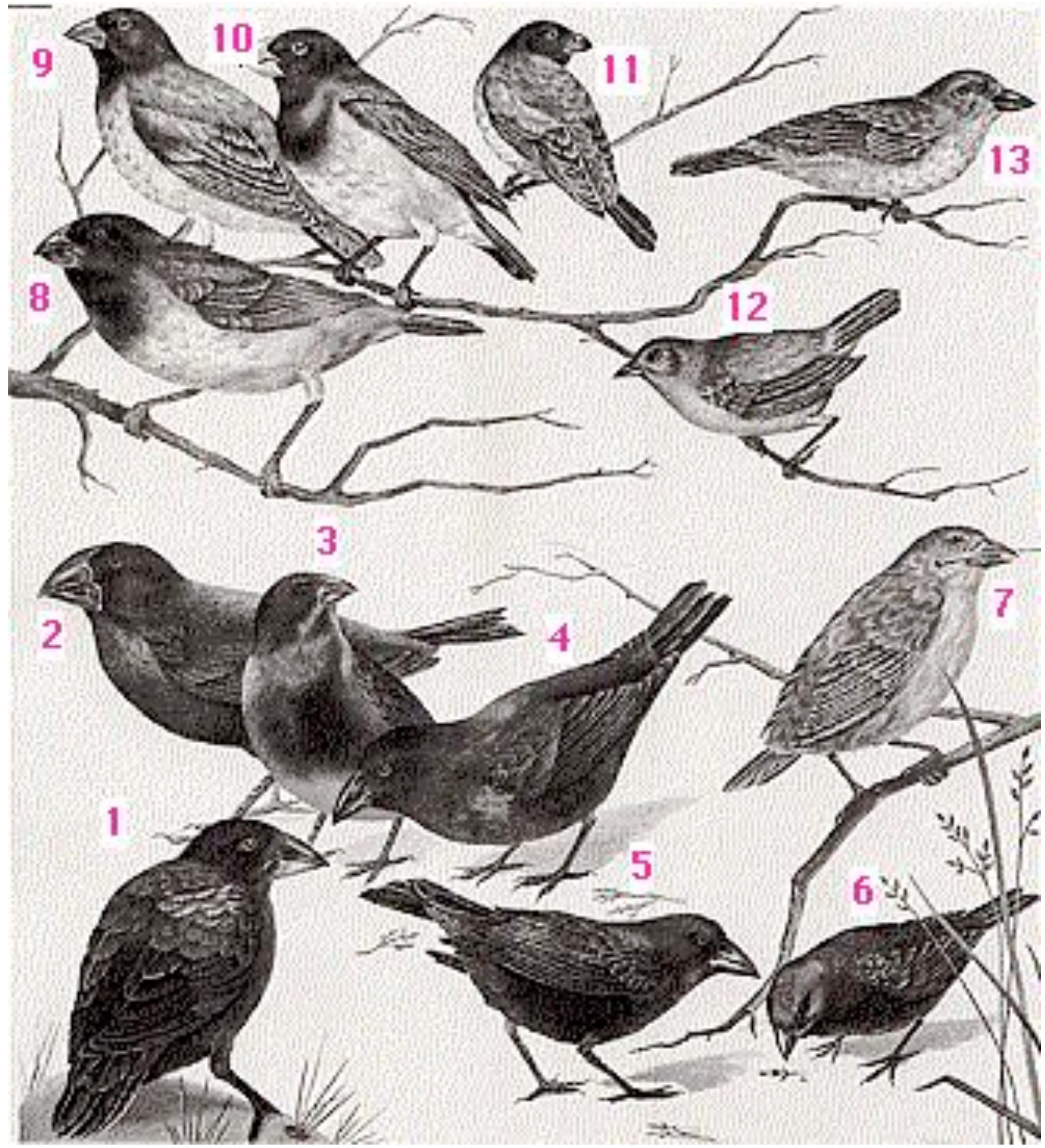
Darwinian evolution and adaptation



- **Adaptative evolution** of phenotypes in a population occurs due to **natural variation** and **natural selection.**

- Adaptive evolution is an ongoing process, because **selection pressures keep changing.**



Determinants of molecular evolution

- **Equation of motion** for the **population fractions** (frequencies) $x = (x_1, \ldots x_n)$ of phenotypes or genotypes in a population:

$$\frac{dx}{dt} = s(x)g(x) + mx + \eta(x,t)$$

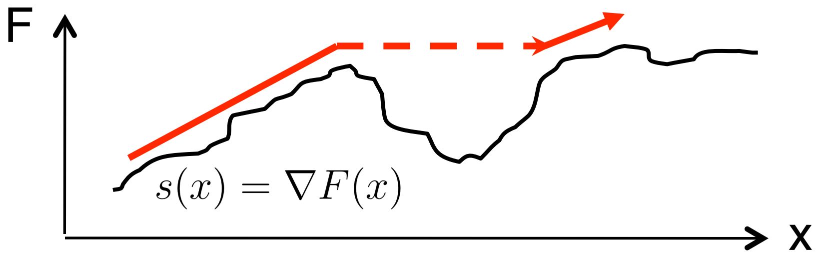
- $s(x)g(x)$: **selection**
- mx: **mutations**
- $\eta(x,t)$: **reproductive fluctuations** (genetic drift), with $\langle \eta(x,t)\eta(x,t') \rangle = \frac{g(x)}{N}\,\delta(t-t')$

- **Equation of motion** for the **frequency distribution**:

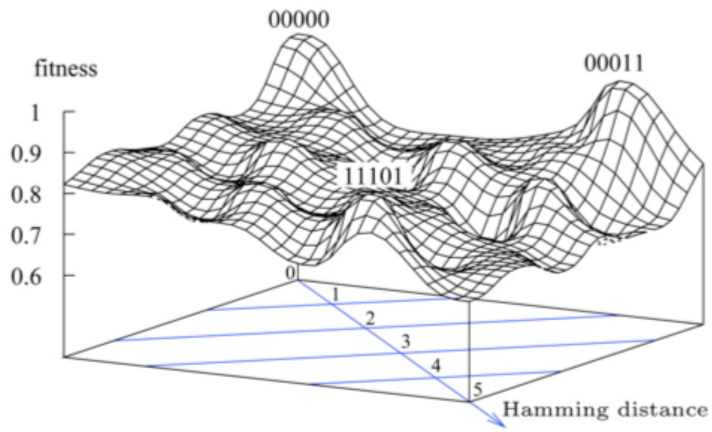
$$\frac{\partial}{\partial t}P(x,t) = \nabla \left[\frac{1}{N}\nabla g(x) - s(x)g(x) - mx \right] P(x,t)$$

Adaptative evolution

- Evolution in a **fitness landscape** (S. Wright 1932) **:**
  - *interplay of selection and genetic drift*
  - *longer time intervals: mutations*



- Example: fitness landscape in the fungus *Aspergillus niger*



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

Adaptative evolution

- **Fundamental Theorem of Natural Selection**
  (R.A. Fisher 1930)**:**

  - *deterministic evolution under time-independent selection alone*

$$\frac{d}{dt} F(t) = s^2(x(t))$$

  - *evolution under time-dependent selection: nonequilibrium*

$$\frac{d}{dt} \Phi(t) = s^2(x(t), t)$$

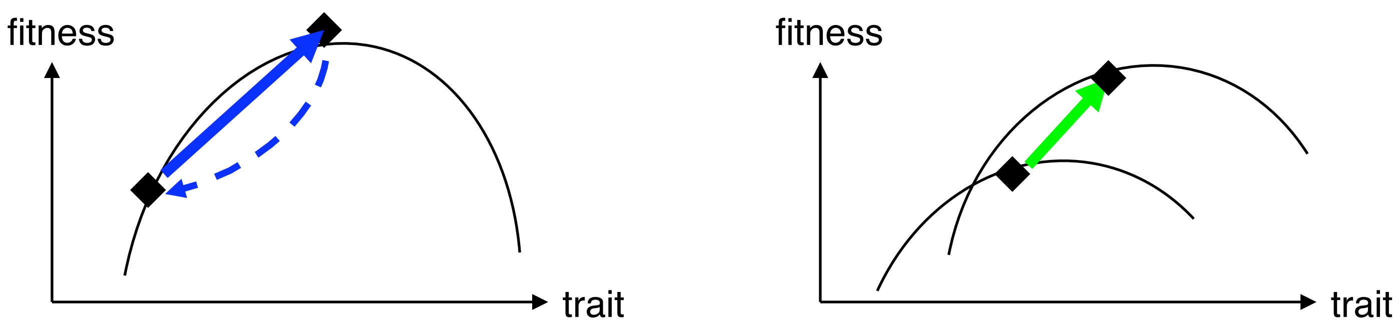
fitness flux

- **Is there an entropy principle of biological evolution?**
  (Schrödinger, *What Is Life* 1943)

Adaptive evolution

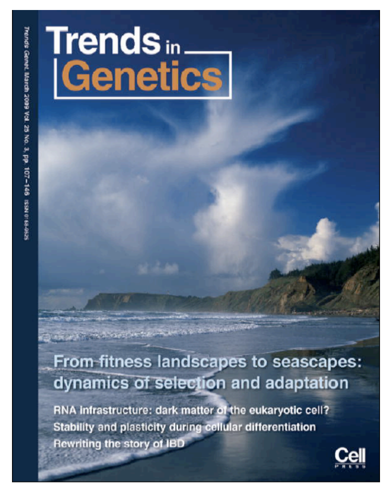
- A comprehensive **theory of molecular evolution** must include:

1. **stochastic forces** (mutations and genetic drift)
2. **evolutionary histories, correlations between genomic changes**:
   distinguish *compensatory evolution* from *adaptation:*



3. time-dependent selection:
   nonequilibrium **fitness seascapes**

V. Mustonen, M.L., March 2009



1. Fitness flux theorem

Population histories and fitness flux

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

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

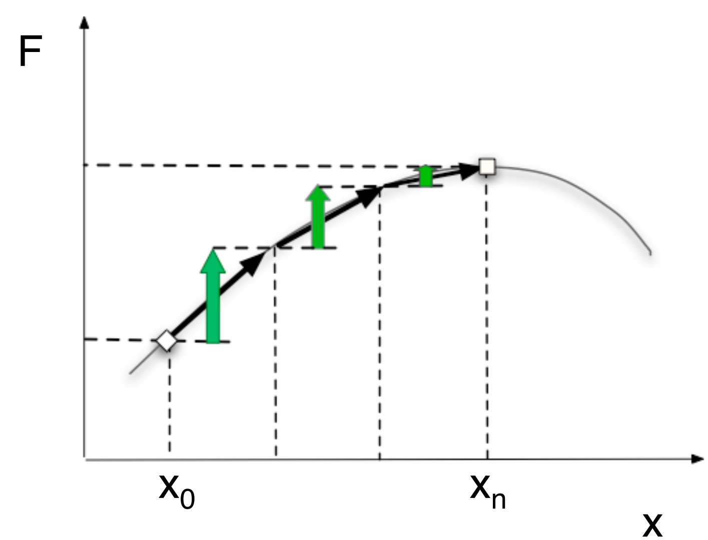
- The **fitness flux** of a population history is the cumulative **selective effect of frequency changes:**

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

- Flux in a **fitness landscape:**

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

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



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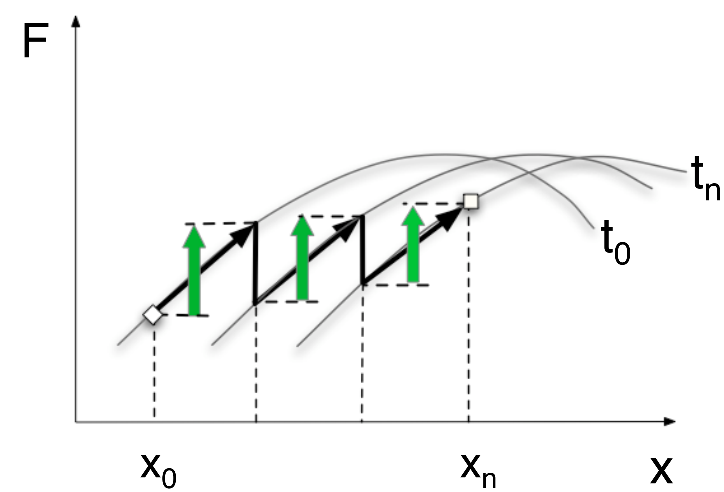
- Flux in a **fitness seascape:**
  $s(x,t) = \nabla F(x,t)$

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



Evolutionary equilibrium and fitness

- 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

$$P_{\rm eq}(x) = P_0(x)\, {\rm e}^{NF(x)} \;.$$

- Hence, **fitness** measures the **information of population states**:

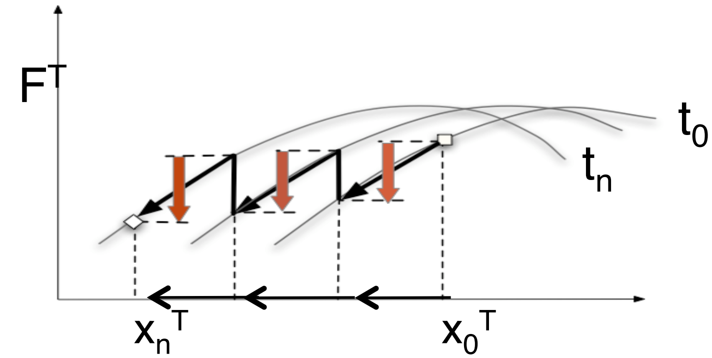
$$N\langle F\rangle_{\rm eq} = \int dx\, P_{\rm eq}(x) \log \frac{P_{\rm eq}(x)}{P_0(x)} \equiv H(P_{\rm eq}|P_0)\,.$$

KL entropy

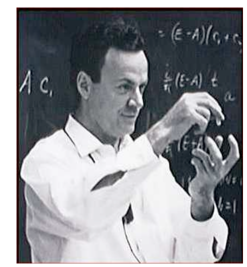
[J.Berg, S.Willmann, M.L., BMC Evol. Biol. 2004,
V. Mustonen, M.L., PNAS 2010, in press]

Fitness flux and time reversal

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



- The probabilities of forward and reverse history are related:



$$\mathcal{P}(\mathbf{x}^T) = \mathcal{P}(\mathbf{x})\, \mathrm{e}^{-N\Phi(\mathbf{x}) \quad + \quad \Delta\mathcal{H}(\mathbf{x})}$$

fitness flux

entropy difference of initial conditions

$$\mathcal{H}(x,t) \equiv \log[P(x,t)/P_0(x)]$$

$$\Delta\mathcal{H}(\mathbf{x}) = \mathcal{H}(x_n,t_n) - \mathcal{H}(x_0,t_0)$$

- Hence, fitness flux measures the **information of the evolution process:**

$$N\langle\Phi\rangle = H(\mathcal{P}|\mathcal{P}^T) \; - \; H(P(t_n)|P_0) + H(P(t_0)|P_0)$$

Fitness flux theorem

- **Theorem:** For an evolutionary process with mutations, genetic drift and selection given by an arbitrary fitness seascape,

$$\left\langle e^{-N\Phi+\Delta\mathcal{H}}\right\rangle = 1 \; .$$

$\langle\ldots\rangle$: average over population histories,
$\Delta\mathcal{H}(\mathbf{x}) = \mathcal{H}(x_n, t_n) - \mathcal{H}(x_0, t_0)$

.

- **Corollary: Φ increases almost universally,**

$$\langle\Phi\rangle \geq \Delta H \, .$$

$\Delta H = \langle\Delta\mathcal{H}\rangle = H(P(t_n)|P_0) - H(P(t_0)|P_0)$
entropy difference between initial and final state.

[V. Mustonen, M.L., PNAS 2010, in press]

Modes of fitness evolution

- **Equilibrium:**

$$\langle \Phi \rangle = 0$$

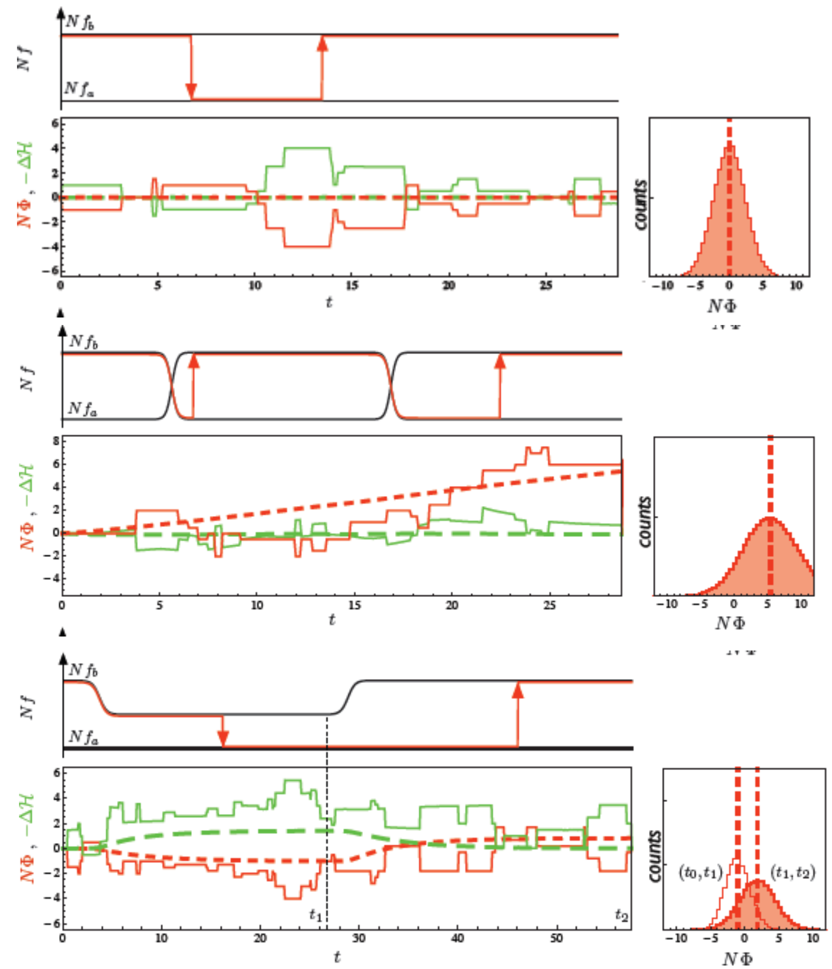
- **Stationary nonequilibrium:**

$$\langle \Phi \rangle > 0$$

- **Demographic nonequilibrium:**

$\langle \Phi \rangle < 0$ declining pop. size

$\langle \Phi \rangle > 0$ recovery



- **Strong-selection limit:** Fundamental theorem of natural selection

$$\frac{d}{dt}\Phi(t) = s^2(x(t), t)$$

2. Evolution and entropy

Thermodynamics | Biological evolution

- **(-) energy**

$$-E(x,t)$$

- **thermodynamic equilibrium**

$$P_{\mathrm{eq}}(x) = C\,\mathrm{e}^{-\beta E(x)}$$

- **heat flux**

$$Q(\mathbf{x}) = \sum_{i=1}^{n} \Delta x_i\,(-\nabla E)(x_i,t_i)$$

- **local entropy**

$$\mathcal{S}(x,t) = -\log P(x,t)$$

- **fluctuation theorem**

$$\left\langle \mathrm{e}^{-\beta Q - \Delta\mathcal{S}} \right\rangle = 1$$

$$\beta\langle Q\rangle + \Delta S = \Delta S_{\mathrm{tot}} \geq 0$$

[Seifert 05, cf. Jarzynski 97, Crook 99].

- **fitness**

$$F(x,t)$$

- **evolutionary equilibrium**

$$P_{\mathrm{eq}}(x) = P_0(x)\mathrm{e}^{NF(x)}$$

- **fitness flux**

$$\Phi(\mathbf{x}) = \sum_{i=1}^{n} \Delta x_i\,\nabla F(x_i,t_i)$$

- **local entropy**

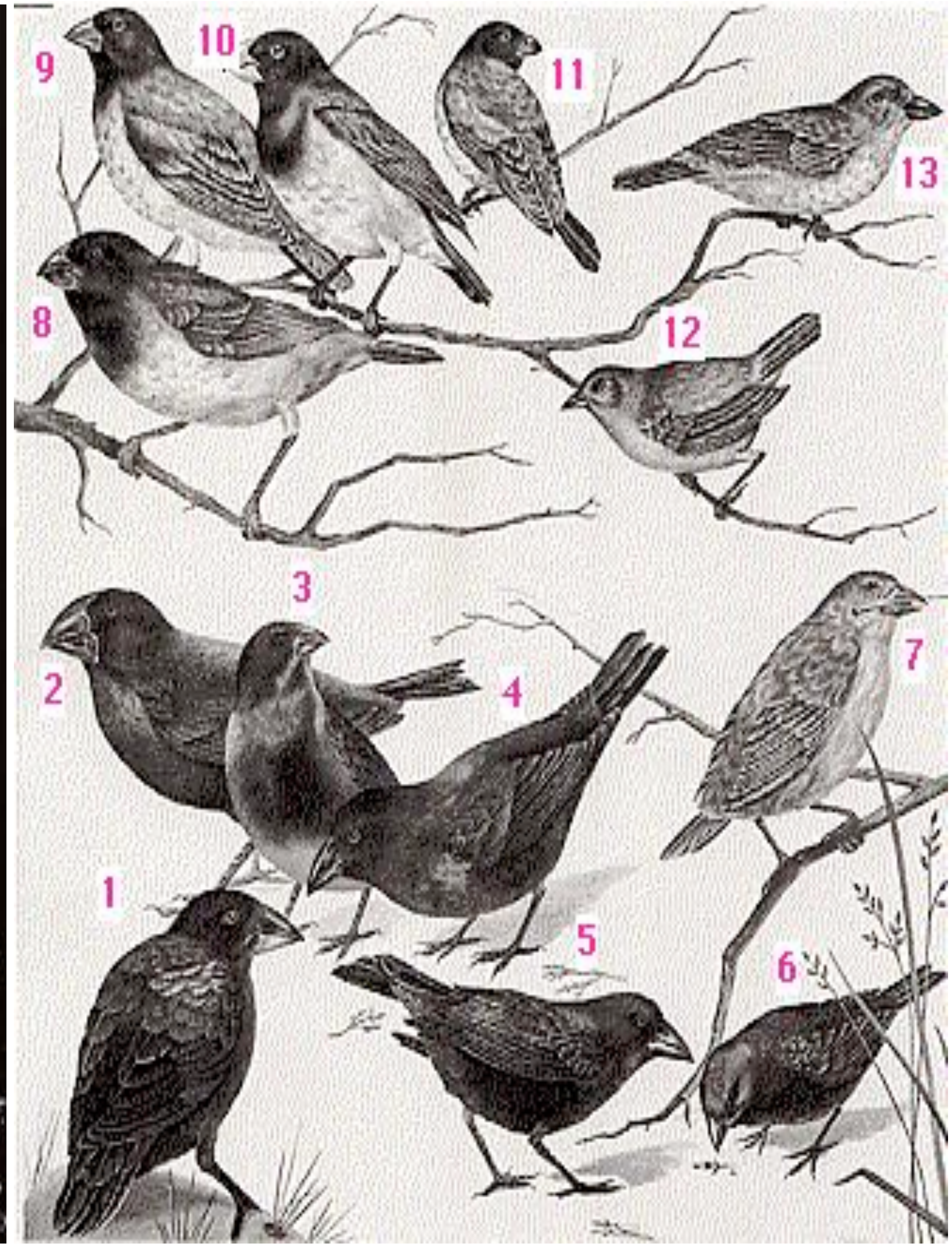
$$\mathcal{H}(x,t) = \log \frac{P(x,t)}{P_0(x)}$$

- **fitness flux theorem**

$$\left\langle \mathrm{e}^{-N\Phi + \Delta\mathcal{H}} \right\rangle = 1$$

$$N\langle\Phi\rangle - \Delta H \geq 0$$

Thermodynamics | Biological evolution

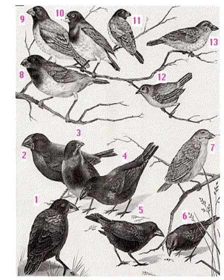


Thermodynamics

- **Second Law**

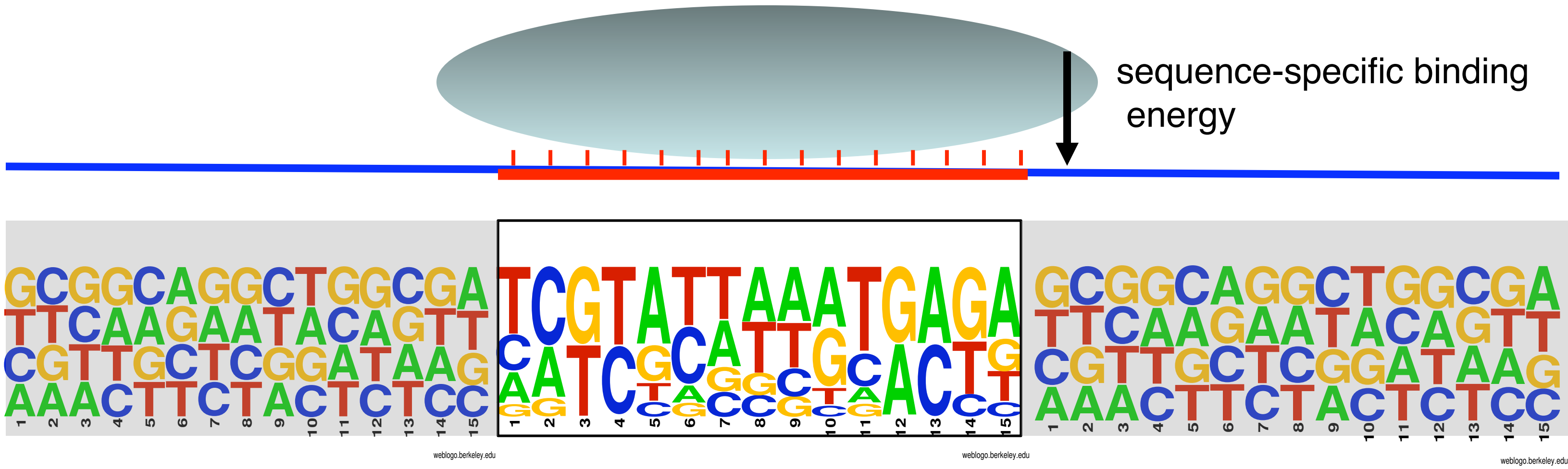
Biological evolution

- **Adaptation can decrease entropy!**



Genomic information

- Transcription factors bind to **DNA target sites**.



- Target sites have a more **specific sequence** than background DNA.

- **Information gain (entropy loss)**
in the adaptive formation of a new site (in bacteria or yeast):

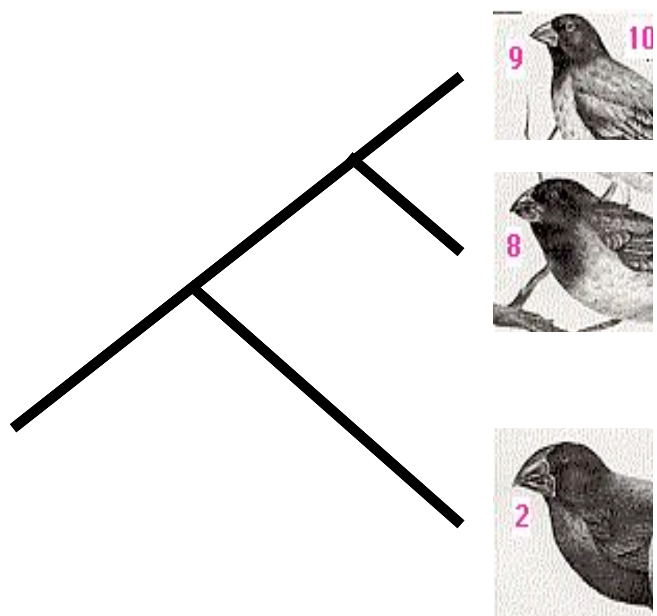
$$\Delta H \approx 15 \text{ bytes.}$$

[Mustonen, M.L., PNAS 2005, Mustonen, Kinney, Callen, M.L., PNAS 2008]

- **Information content of the entire genome?**

3. Irreversibility of evolution

(The length of time's arrow)



Adaptation and fitness flux in flies

AAGTCAGTCGATCAGTTCTCGAATAAGTCAGTCCTTCAGTTCTCGAAT
AAGTCAGTCGATCAGTTCTCGAATAAGTCAGTCCTTCAGTTCTCGAAT
AAGTCAGTCGATCAGTTCTCGAATAAGTCAGTCCATCAGTTCTCGAAT
AAGTCAGTCGATCAGTTCTCGAATAAGTCAGTCCATCAGTTCTCGAAT
AAGTCAGTCCATCAGTTCTCGAATAAGTCAGTCCATCAGTTCTCGAAT *Drosophila melanogaster*

AAGTCAGTCCATCACTTCTCGAATAAGTCAGTCCATCAGATCTCGAAT *Drosophila simulans*

[Glinka et al 2003, Ometto et al 2005]

- Cross-species data and polymorphisms within species are used to infer **rate** and **average selection coefficient** of **substitutions.**

- Adaptation is quantified by a **positive fitness flux:**

  Φ **=** (*rate*) x (*average selection coefficient of substitutions*).

- This indicates a **stationary nonequilibrium process:**
  - **Selection coefficients at individual sites fluctuate** at nearly the rate of neutral substitutions.
  - There is a **surplus of beneficial over deleterious substitutions.**

[Mustonen and M.L, PNAS 2007]

- **Amount of genome-wide adaptation?**

Conclusions

- Adaptive evolution is a **stochastic nonequilibrium process** quantified by **fitness flux** Φ.

- *Drosophila* genomes:
  evidence for adaptive evolution driven by **fitness seascapes.**

- Fitness flux theorem:
  Increase of Φ is a nearly universal evolutionary principle.