Gene regulation: From biophysics to evolutionary genetics

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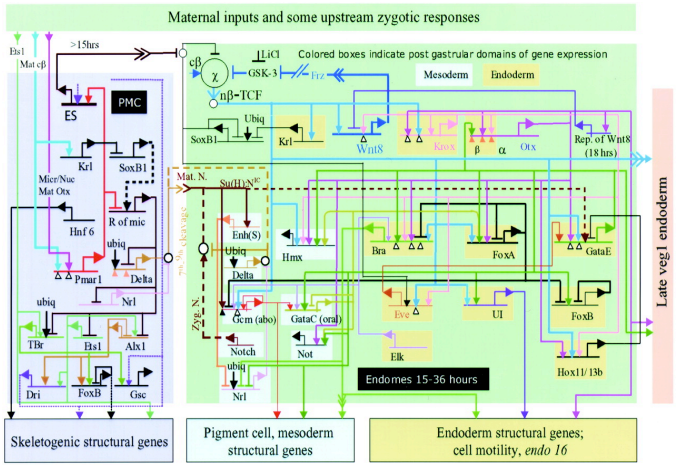
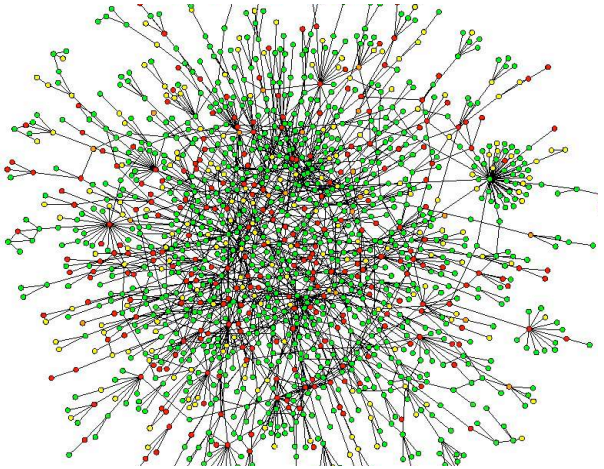
Structure and dynamics of molecular networks





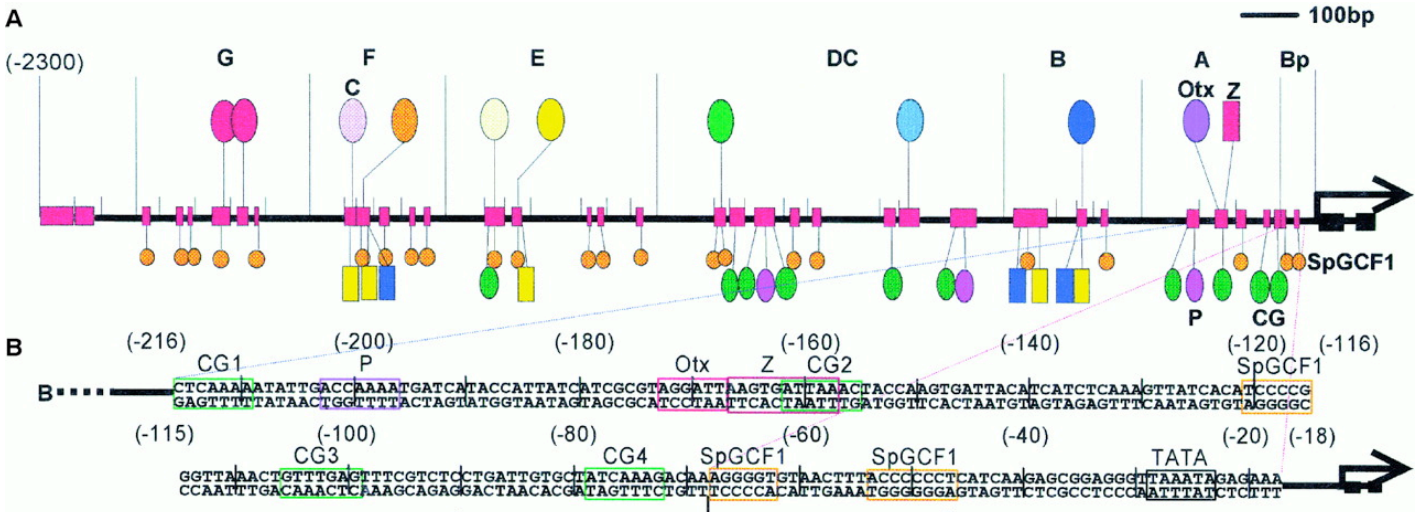
- Structure: Random parts?
  Functional design?

- Evolution: Pathways?
  Tempo?

1. Evolution of regulatory DNA

Genomic encoding of network interactions

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



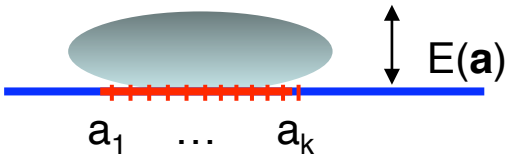
[Bolouri and Davidson, 2002]

- Input-output relation?

  Evolutionary dynamics?

Biophysics of transcriptional regulation

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



- **Binding energy** E(**a**) can be obtained from
  - low-throughput measurements [Fields et al. 97]
  - position weight matrix of functional sites [Berg and v.Hippel 86]
  - ChIP-chip data [Float et al. 05, Kinney et al. 06]
  - *high-throughput measurements* [Maerkl and Quake 07].

- E(**a**) depends on the site sequence **a** = (a_1,…,a_k):

$$E = \sum_{i=1}^{k} \epsilon_i(a_i) \quad + \text{ nonlinear terms?}$$

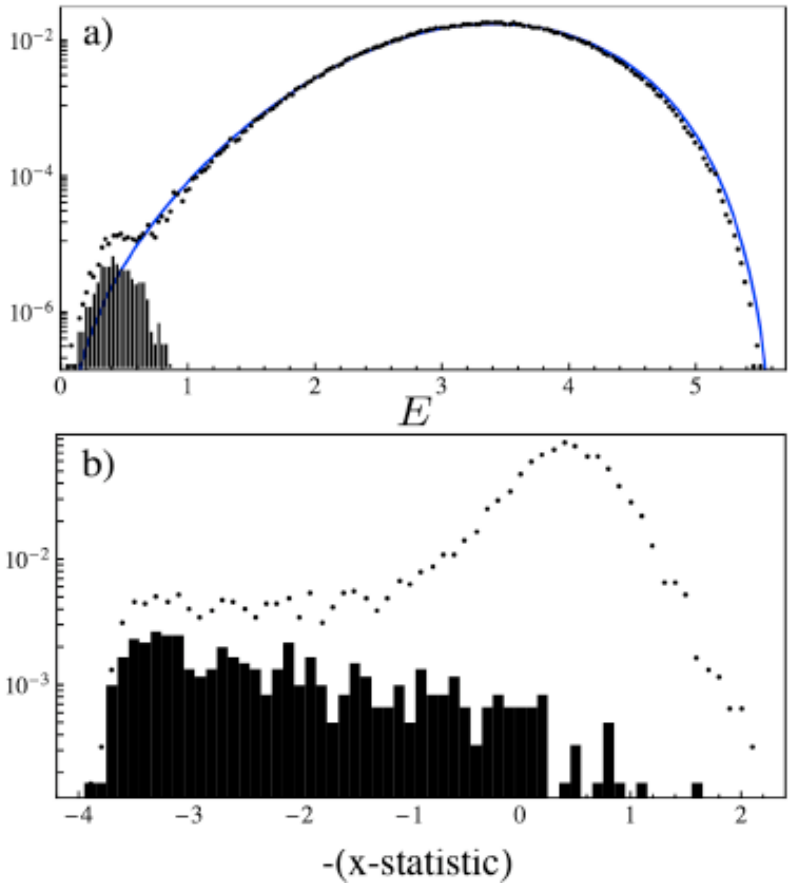
- E(**a**) is the **molecular phenotype** of a site, which **quantifies its functionality**.

Cis-regulatory elements: from sequence to phenotype

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

- This phenotype predicts **binding intensity** to promoters in yeast:

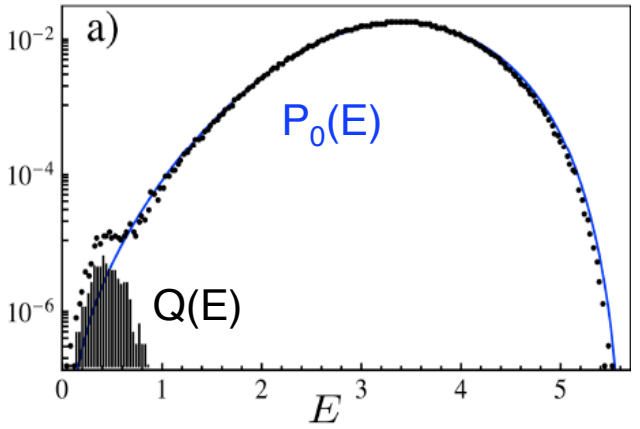
[Mustonen, Kinney, Callen, M.L., PNAS 2008]



ChIP-chip data for Abf1 binding in yeast
[Lee et al., Science 2002]

Cis-regulatory elements: from phenotype to fitness

- For broad-acting transcription factors, **high-affinity sites** ($E < E_b$) are statistically **overrepresented**.

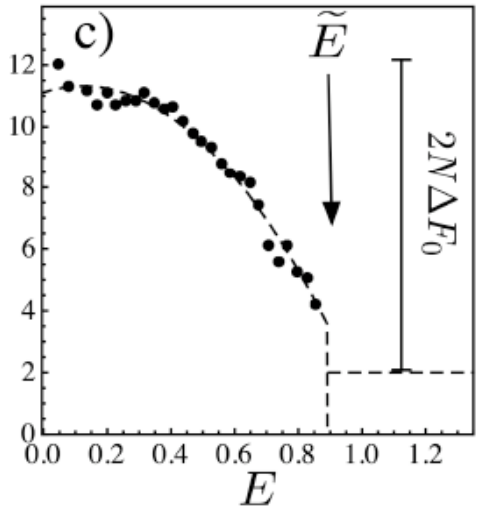


- At stationarity, the ensembles of functional and background sites determine the **average fitness landscape** F(E) of a site:

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

- This predicts a **moderate fitness effect per functional site:**

$$2NF_0 \approx 10$$



Abf1 binding sites in S. cerevisiae

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

Population genetics

- **Selection**: sequence state **a** has fitness

$$F(\mathbf{a}) = \frac{d}{dt}\langle \log N(\mathbf{a})\rangle_{\mu=0} - \text{const.}$$

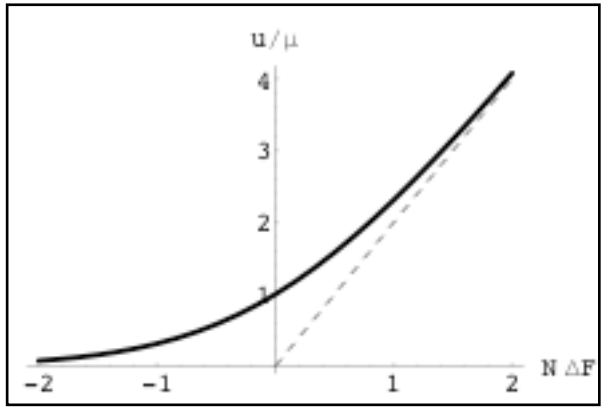
- **Point mutations:**

$$\mathbf{a} = (\ldots, a, \ldots) \rightarrow \mathbf{b} = (\ldots, b, \ldots)$$

Population genetics

- **Genetic drift:**

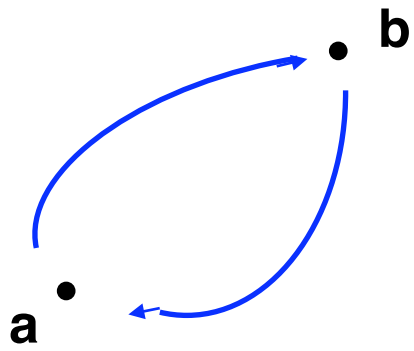
  Kimura-Ohta substitution rates



$$u_{\mathrm{a}\to\mathrm{b}} = \mu_{\mathrm{a}\to\mathrm{b}} \frac{1-\exp[-2(F(\mathrm{a})-F(\mathrm{b}))]}{1-\exp[-2N(F(\mathrm{a})-F(\mathrm{b}))]}$$

Ratio of forward and backward rates:

$$\frac{u_{\mathrm{a}\to\mathrm{b}}}{u_{\mathrm{b}\to\mathrm{a}}} = \frac{\mu_{\mathrm{a}\to\mathrm{b}}}{\mu_{\mathrm{b}\to\mathrm{a}}} \exp[2N(F(\mathrm{b}) - F(\mathrm{a}))]$$



Population genetics

- **Evolutionary equilibria in sequence space:**

  Given two families of loci,
  - **background loci** with stationary sequence distribution $P_0(\mathbf{a})$ under neutral evolution
  - **functional loci** with stationary sequence distribution $Q(\mathbf{a})$ under selection

    the fitness landscape $F(\mathbf{a})$ for the functional loci is given by

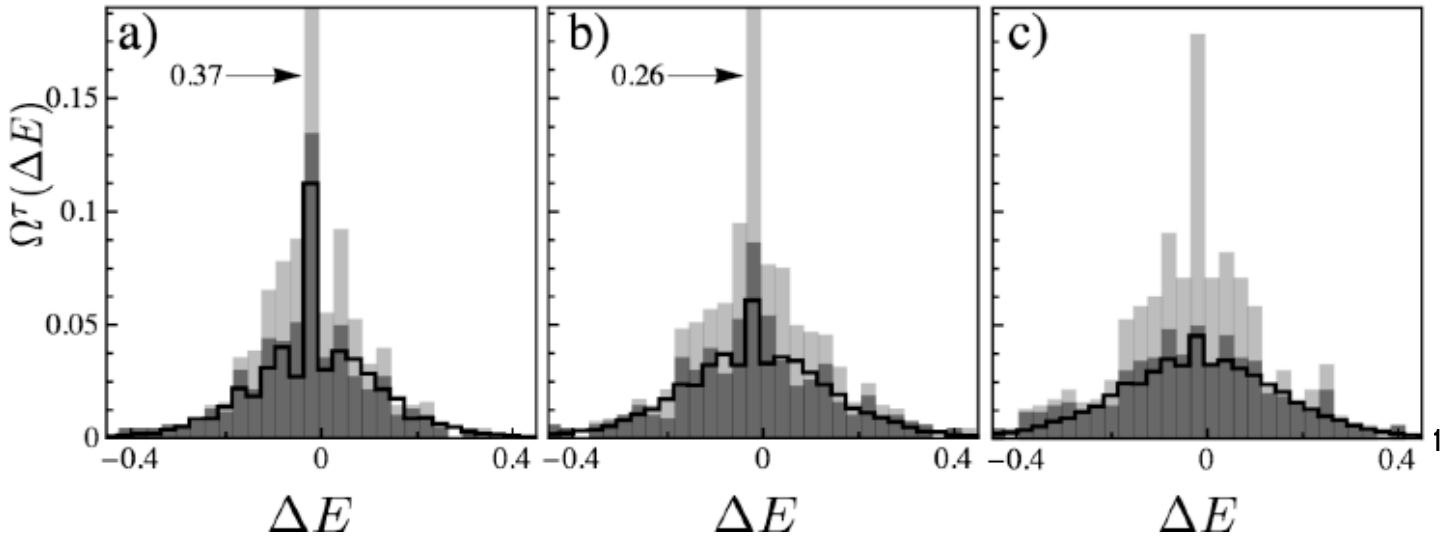
$$Q(\mathbf{a}) = P_0(\mathbf{a}) \exp[2NF(\mathbf{a}) + \text{const.}]$$

  N: effective population size.

[J.Berg, S. Willmann, M.L., **BMC Evol. Biol.** (2004)]
[V. Mustonen, M.L., **Proc. Natl. Acad. Sci.** (2005)]

Phenotypic evolution of binding sites

- The inferred fitness landscape quantitatively **predicts the evolution of the phenotype E**:

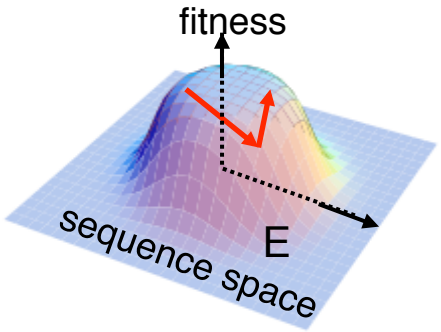


Abf1 binding energy differences of sites in S. cerevisiae, S.paradoxus, S. mikatae, S. bayanus

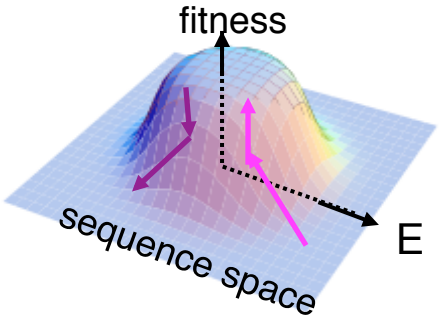
[Mustonen, Kinney, Callen, M.L., PNAS 2008]

Pathways of promoter evolution

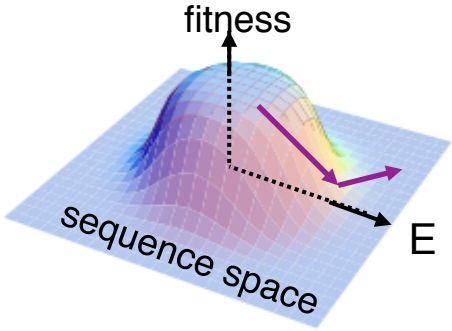
- **Conservation of site** and **function**



- **Site turnover**



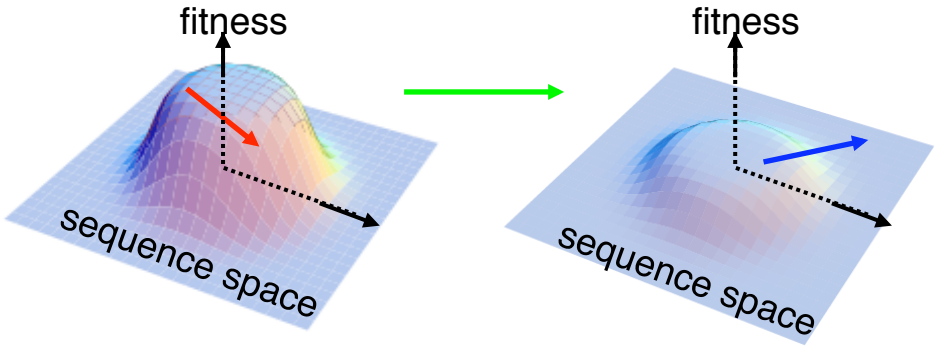
+ conservation of function



+ turnover of function

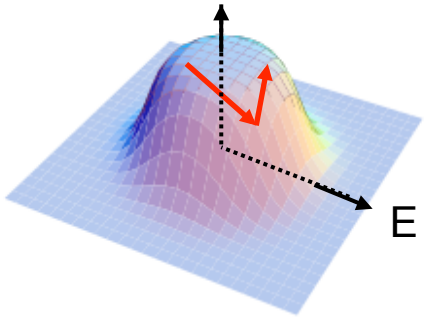
- **Time-dependent selection**

+ adaptation



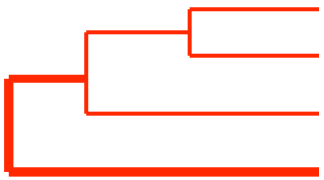
Conservation of binding sites

- Sequences of conserved sites evolve by **compensatory mutations**:



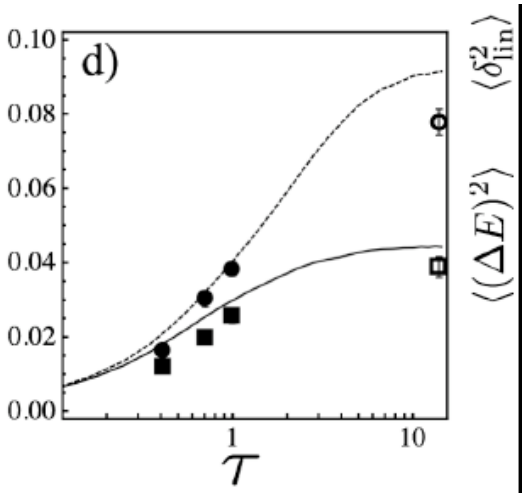
$$\Delta E = \sum_i \Delta\epsilon_i \qquad \text{but} \qquad \mathrm{var}(\Delta E) < \sum_i \mathrm{var}(\Delta\epsilon_i)$$

- Hence, the **energy phenotype is more constrained than the site sequence**:



[cf. Kellis et al., Nature 2003]

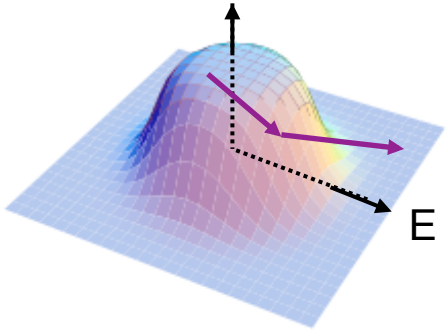
[Mustonen, Kinney, Callen, M.L., PNAS 2008]



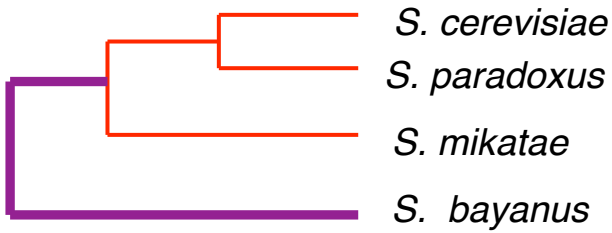
divergence time from *cer*

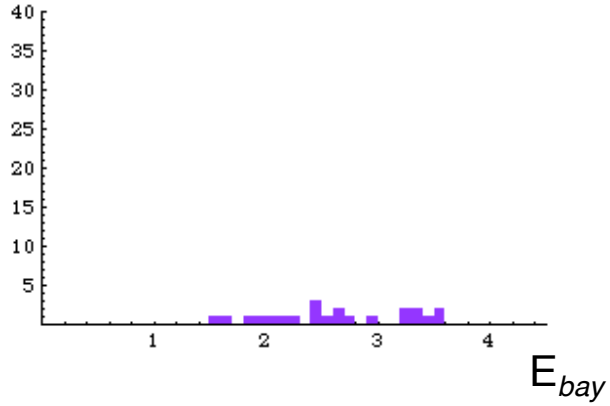
Loss and gain of function

- **Turnover** of **promoter function** determines loss and gain of regulatory interactions:



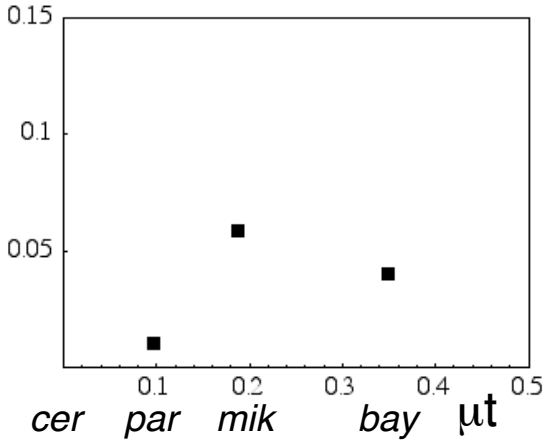
- **Species-specific loss of sites**:





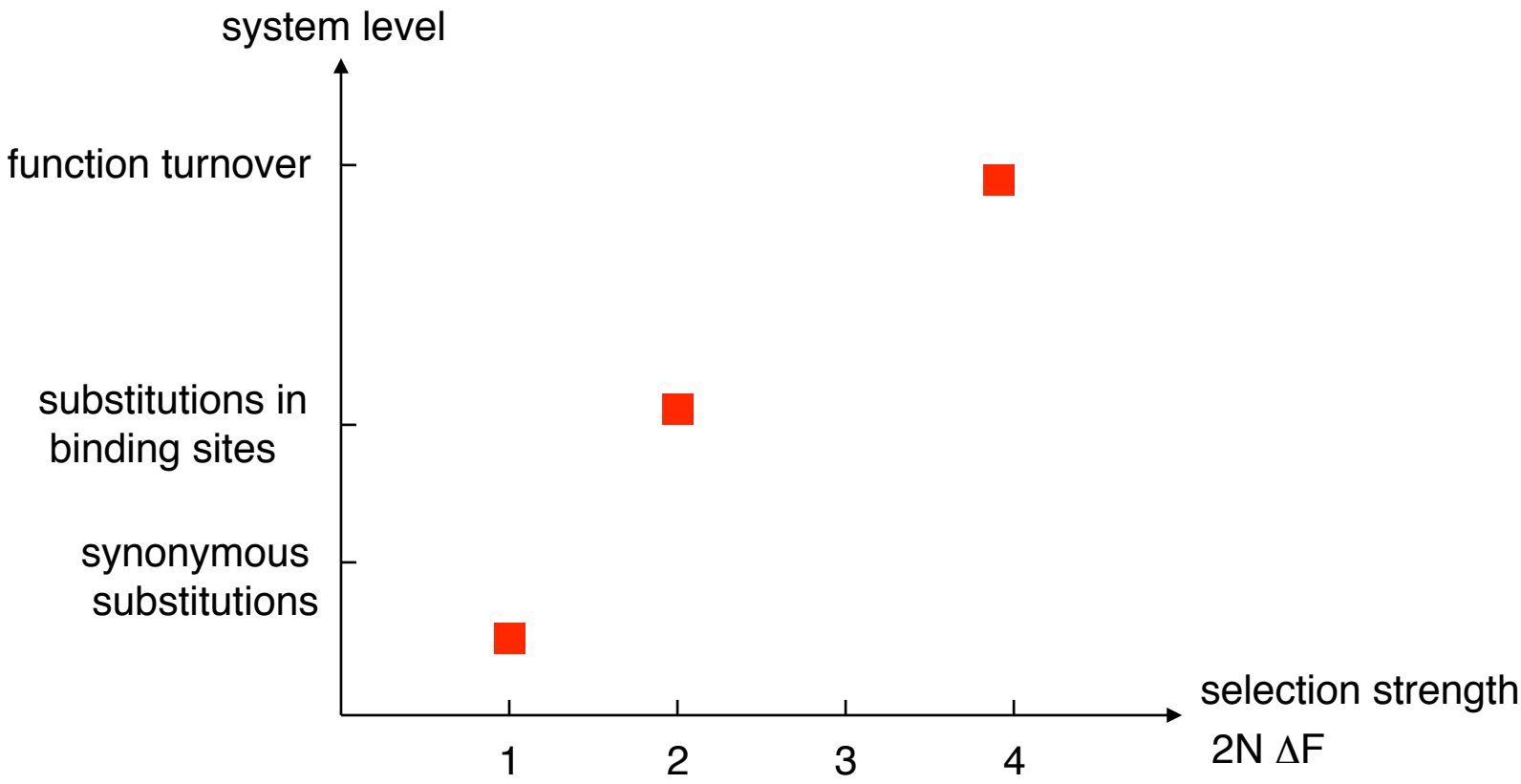
- **Functional turnover rate**

$$\gamma_f \sim 0.1\ \mu$$



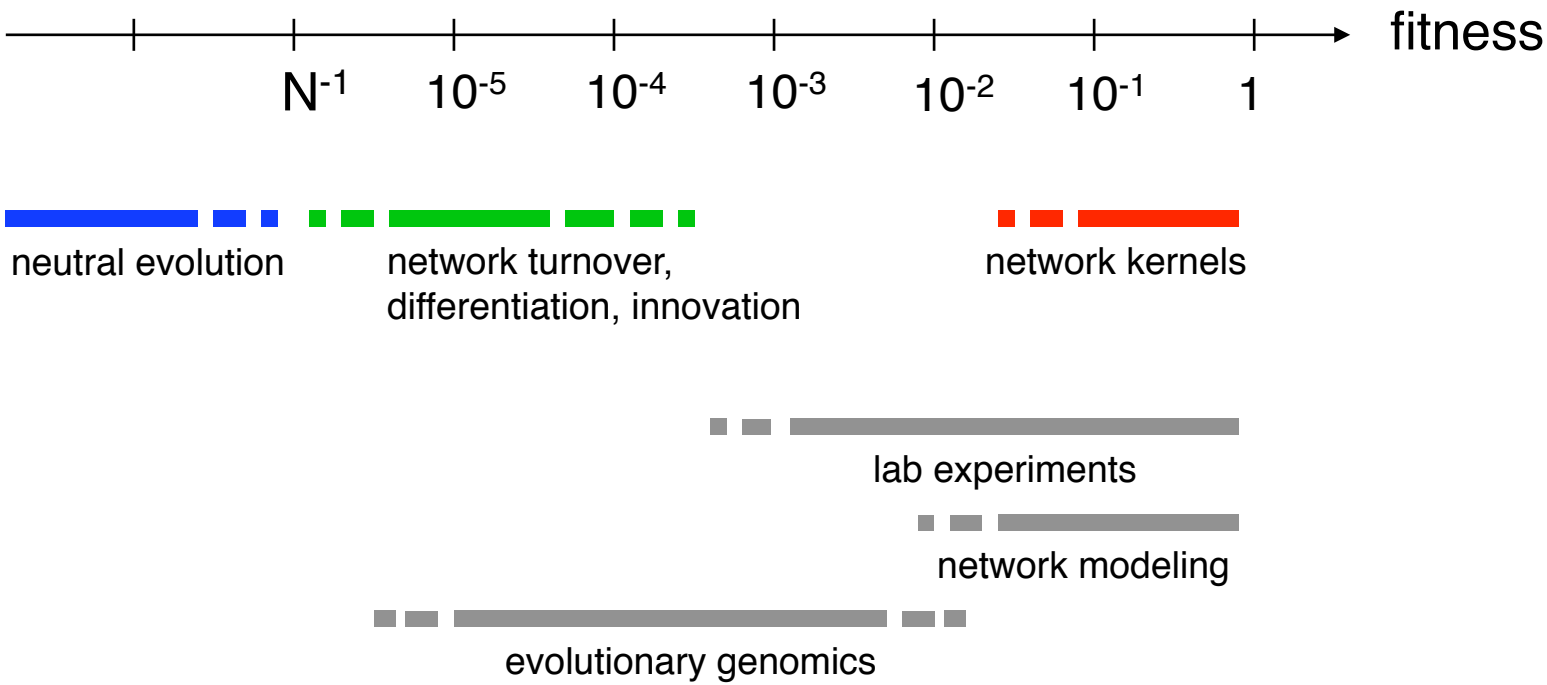
[J. Kinney, V. Mustonen, C. Callan, M.L., PNAS 2008]

- **Natural selection acts on complex systems in a scale-dependent way:**



Evolutionary systems biology

- **Laboratory experiments, modeling**, and **evolutionary genomics** address **complementary aspects** of biological systems:



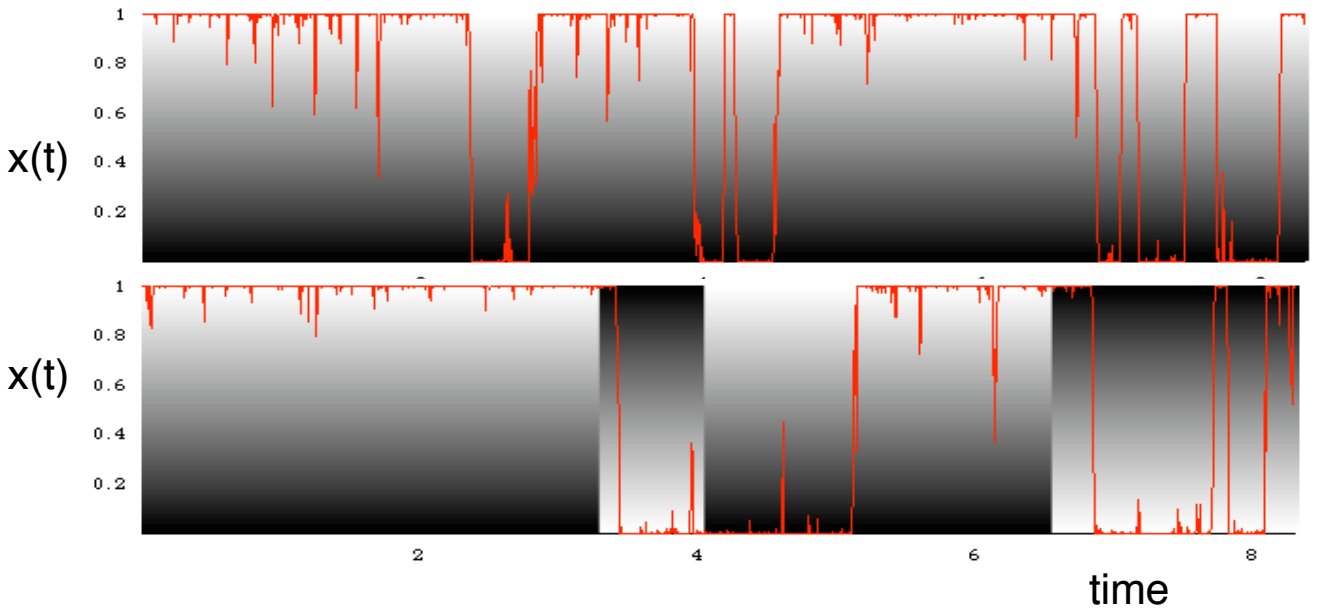
2. Evolution of the Drosophila genome

From fitness landscapes to seascapes

- Phenotypic concept of Darwinian selection:
  newly arising selection and response by **adaptation**.

- Can we trace the **time-dependence** of selection
  in genomic data?

Genome evolution under constant and fluctuating selection



- Allele frequency x(t) evolves under
  selection, mutations, stochastic fluctuations (genetic drift).

- **Constant selection** leads to **evolutionary equilibrium,** p_{eq} (x).

- **Fluctuating selection**

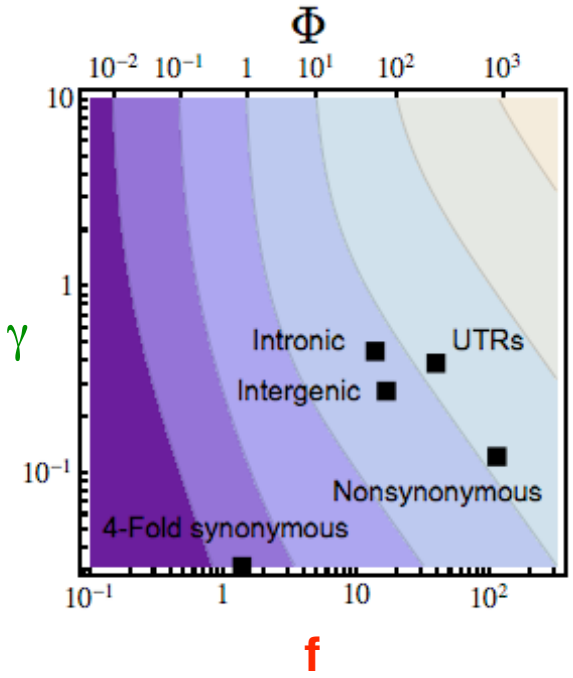
  $\Delta F(t) = f\,\chi(t)$ with **switching rate** γ,

  leads to **adaptation:** excess number of uphill mutations w/r to equilibrium.

Adaptation and fitness flux

- Substitutions and polymorphism spectra [Glinka et al 2003, Ometto et al 2005] are used to infer a **surplus of beneficial over deleterious substitutions.**

- Adaptation is quantified by a positive
  fitness flux = (substititution rate) x
  (average selection coefficient of substitutions).



[Mustonen and M.L, PNAS 2007]

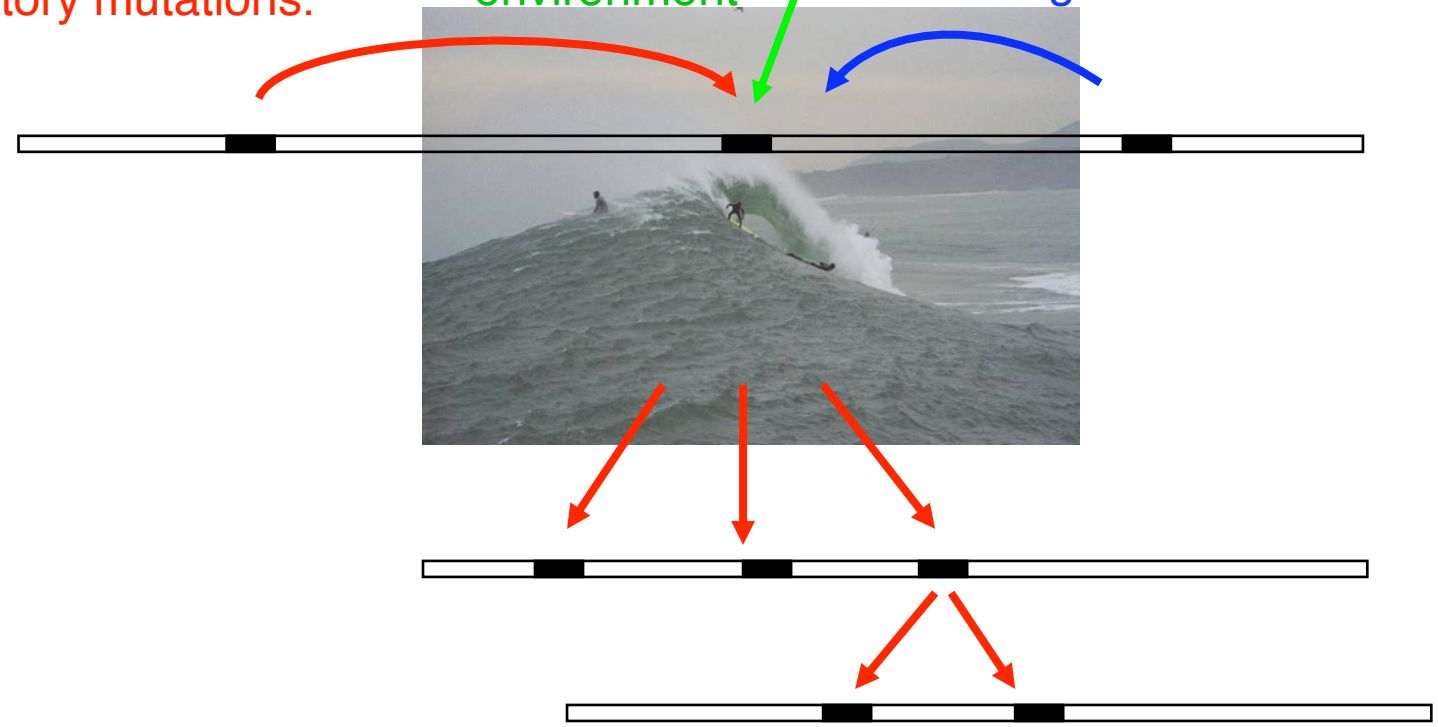
Fitness seascapes

- **What drives the waves**?

systems component:
correlations (epistasis) cause compensatory mutations.

external component:
time-dependent environment

genomic component:
linkage to other loci



- **Nonequilibrium + correlations:**
  one external change can trigger an avalanche of responses.

Conclusions

- Adaptive evolution should be viewed as a **nonequilibrium phenomenon.**
- Adaptation can be quantified by the **fitness flux** in a population over a given time interval.
- The biophysical **binding energy** is a **quantitative molecular phenotype** for regulatory sequences in yeast.
- Genomic **sequence analysis** can be used to infer **fitness landscapes** for this phenotype.
- In *Drosophila*, **fitness seascapes** drive **adaptive evolution**.
- Review articles:
  From Biophysics to evolutionary genetics, M.L., BMC Bioinformatics 2007
  From fitness landscapes to seascapes: The dynamics of selection and adaptation, V. Mustonen and M.L., Trends in Genetics 2009