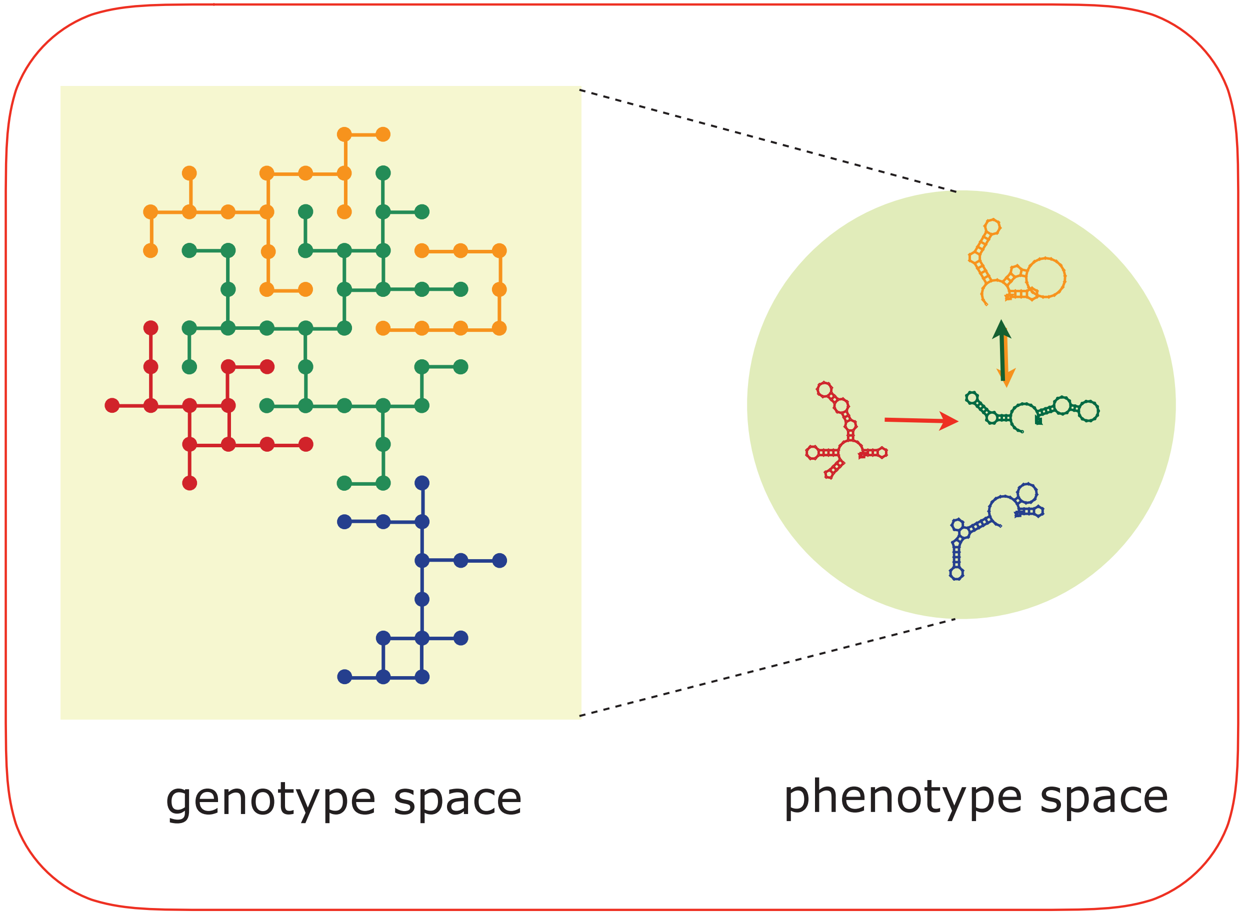
# Previous Lectures

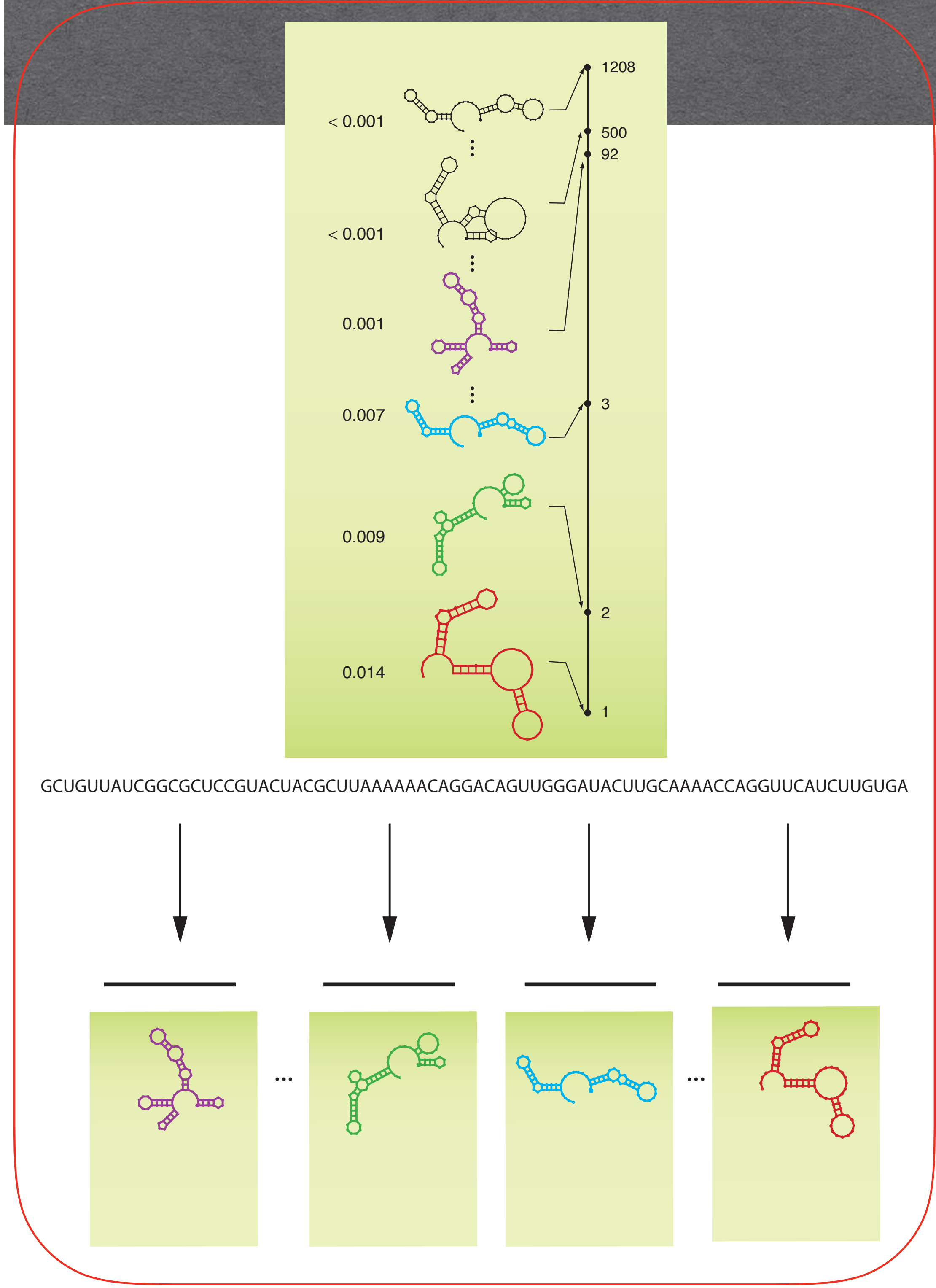
1. The Topology of the Possible
   (La représentation de l’information biologique)

# Take Home



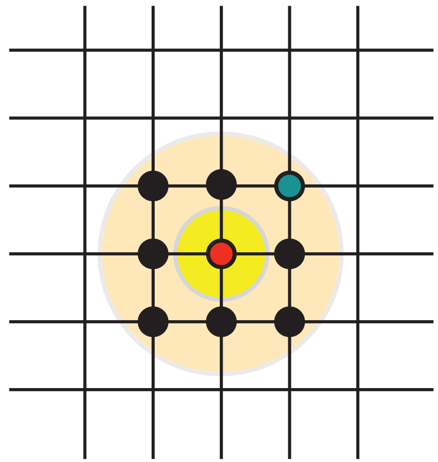

- “typical shapes”
- shape space covering
- neutral networks
- accessibility

- **evolvability**: robustness enables change
- **continuity in evolution**: nearness via accessibility

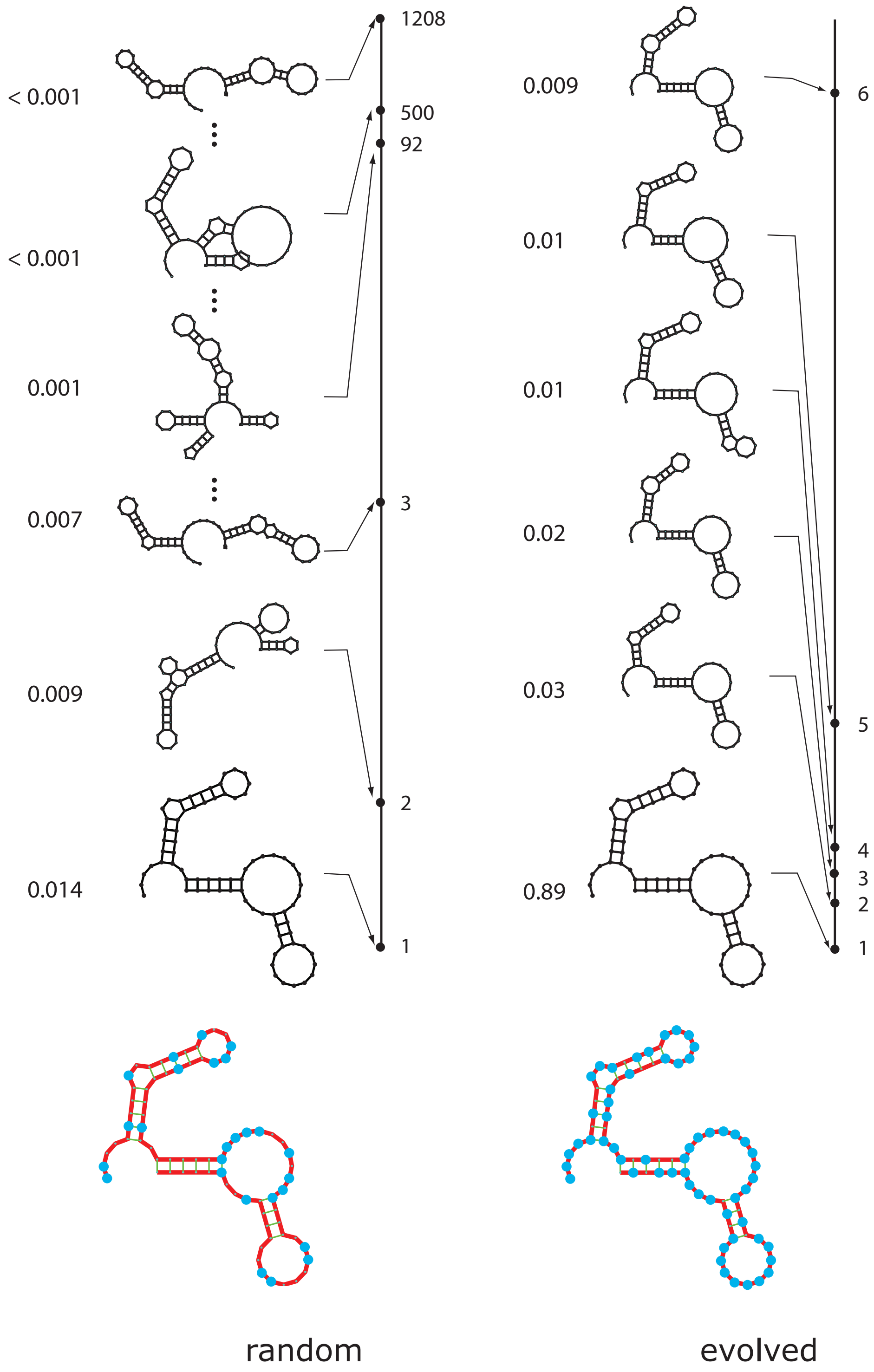



$$\left.\frac{\partial \text{ pheno}}{\partial \text{ env}}\right|_{\text{geno}} \qquad \left.\frac{\partial \text{ pheno}}{\partial \text{ geno}}\right|_{\text{env}}$$

- **plasticity mirrors variability**
- potential speed-up of evolution (Baldwin effect)

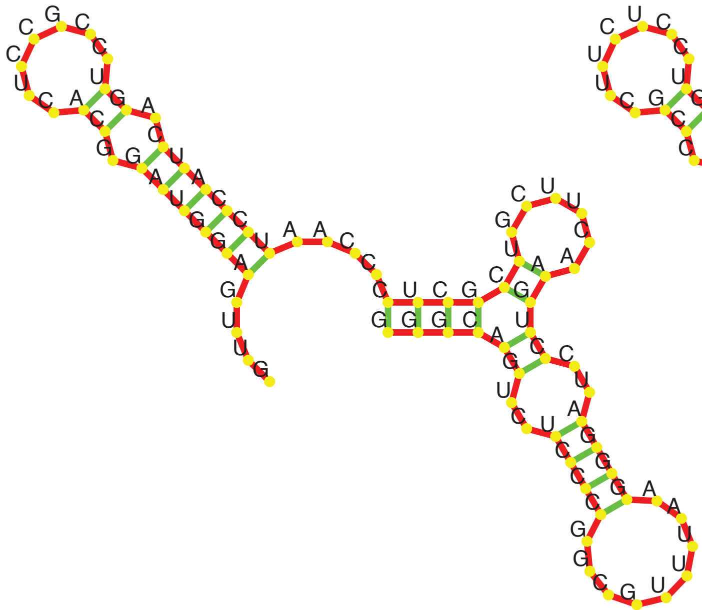


# Canalization

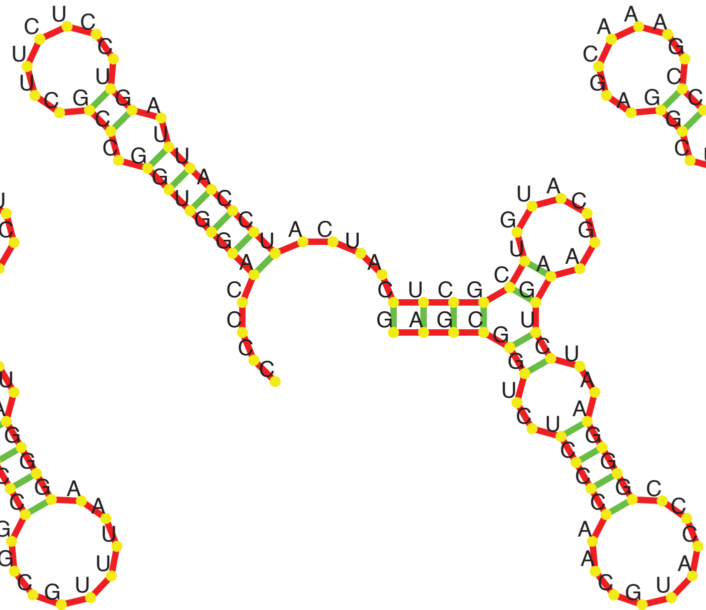



evolutionary reduction of plasticity
in a constant environment

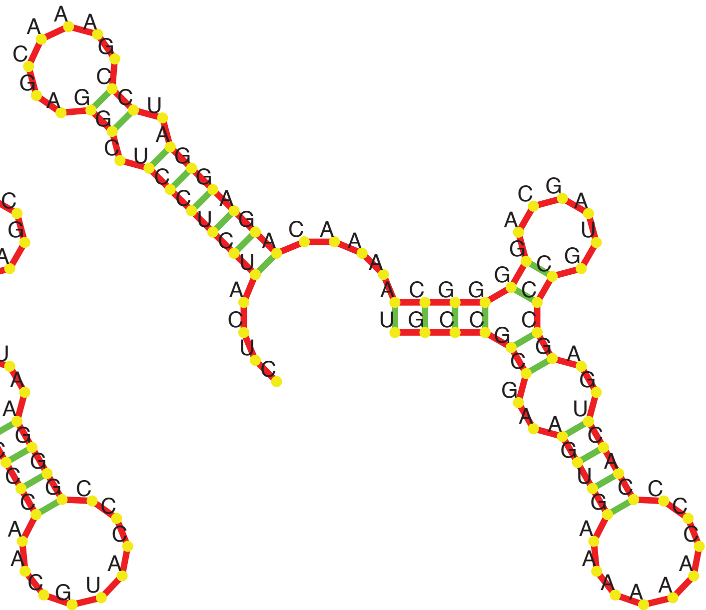
# Which structure is modular?



random

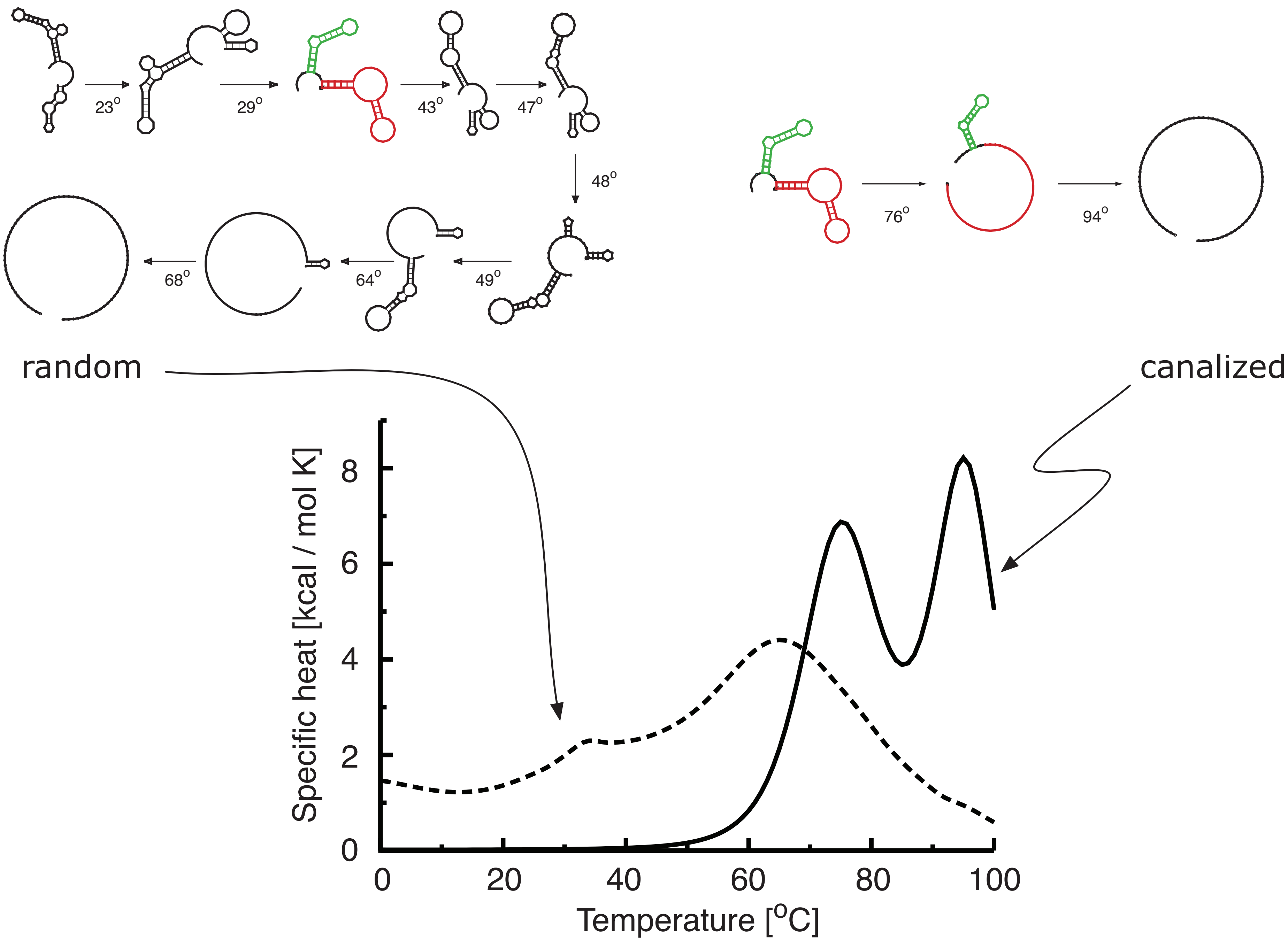


neutral evolution

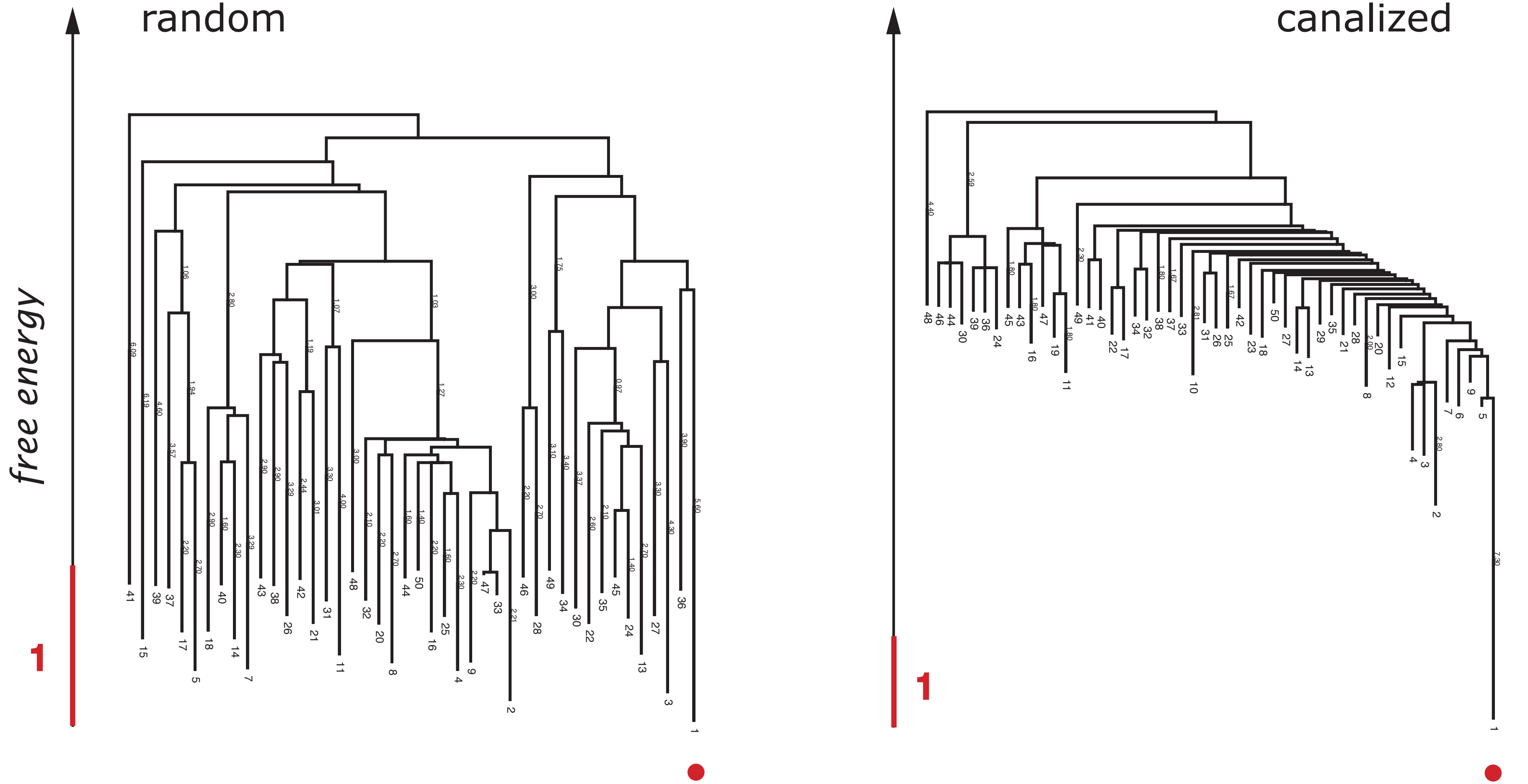


canalized

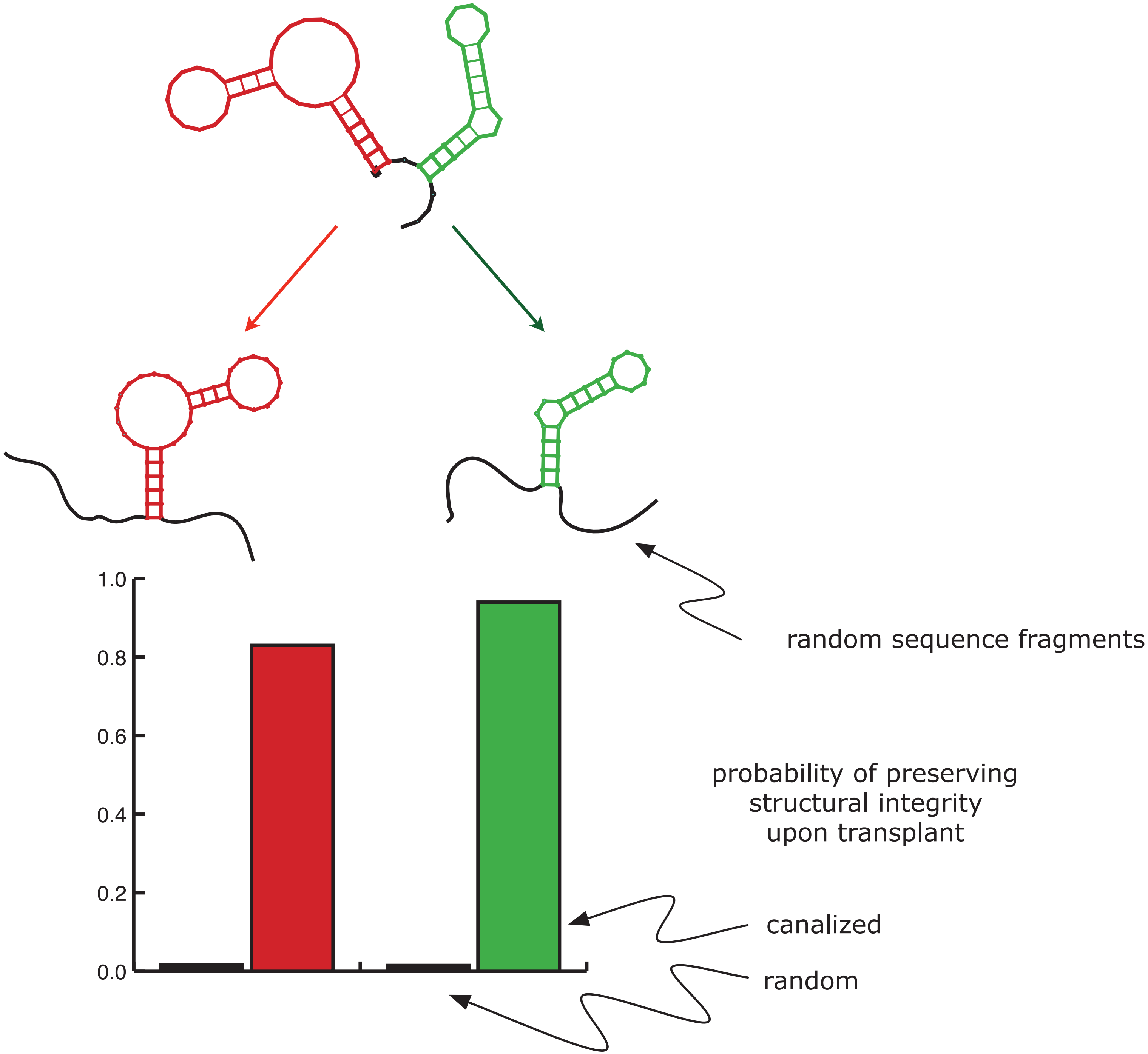
# Thermo-physical Modularity



# Kinetic Modularity



# Context Independence (Autonomy)



# Neutral Evolution of The Predecessor Function...

$$\mathbf{pred} \equiv \lambda x_1.((x_1)\underbrace{\lambda x_2.((x_2)\lambda x_3.x_3)\lambda x_4.\lambda x_5.((x_2)x_4)(x_4)x_5)}_{S}\underbrace{\lambda x_6.(x_1)\lambda x_7.\lambda x_8.\lambda x_9.x_9}_{A}$$

$$(\mathbf{pred})\mathbf{n} = (S)^n A_n$$

$\mathbf{n} \equiv 0$ $\quad A_0 \equiv \mathbf{0}$

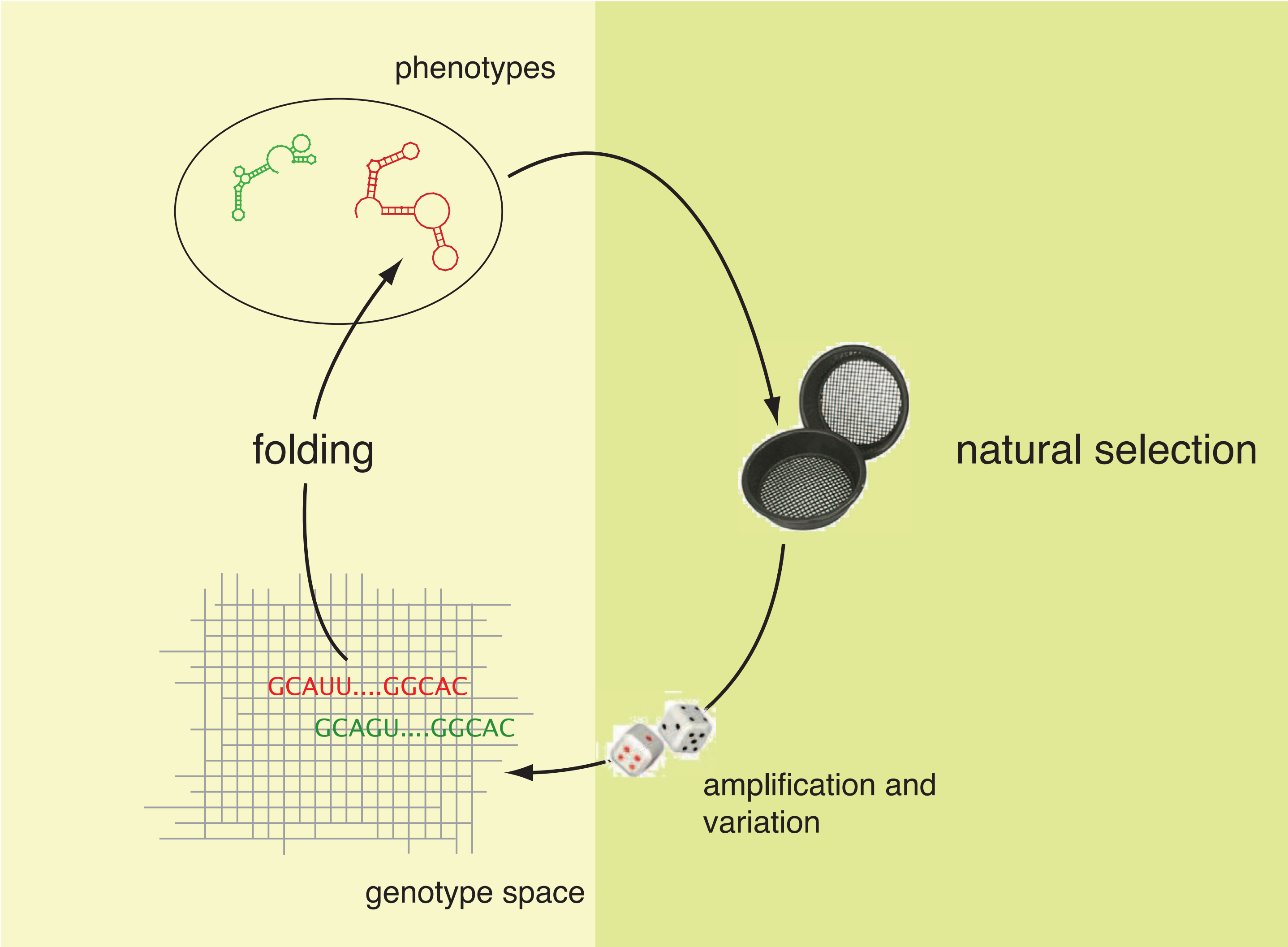
$\mathbf{n} > 0$ $\quad A_{n>o} \equiv A'$

$$(S)A' \equiv \mathbf{0}$$

$$(S)^{n-1}\mathbf{0} \equiv \mathbf{n-1}$$

# 2.
# The Propagation of Genetic, Phenotypic, and Molecular information

# A Small Scale Model of (A Cartoon Of) Evolution




variation

selection

# Flow Reactor @ "constant flow"

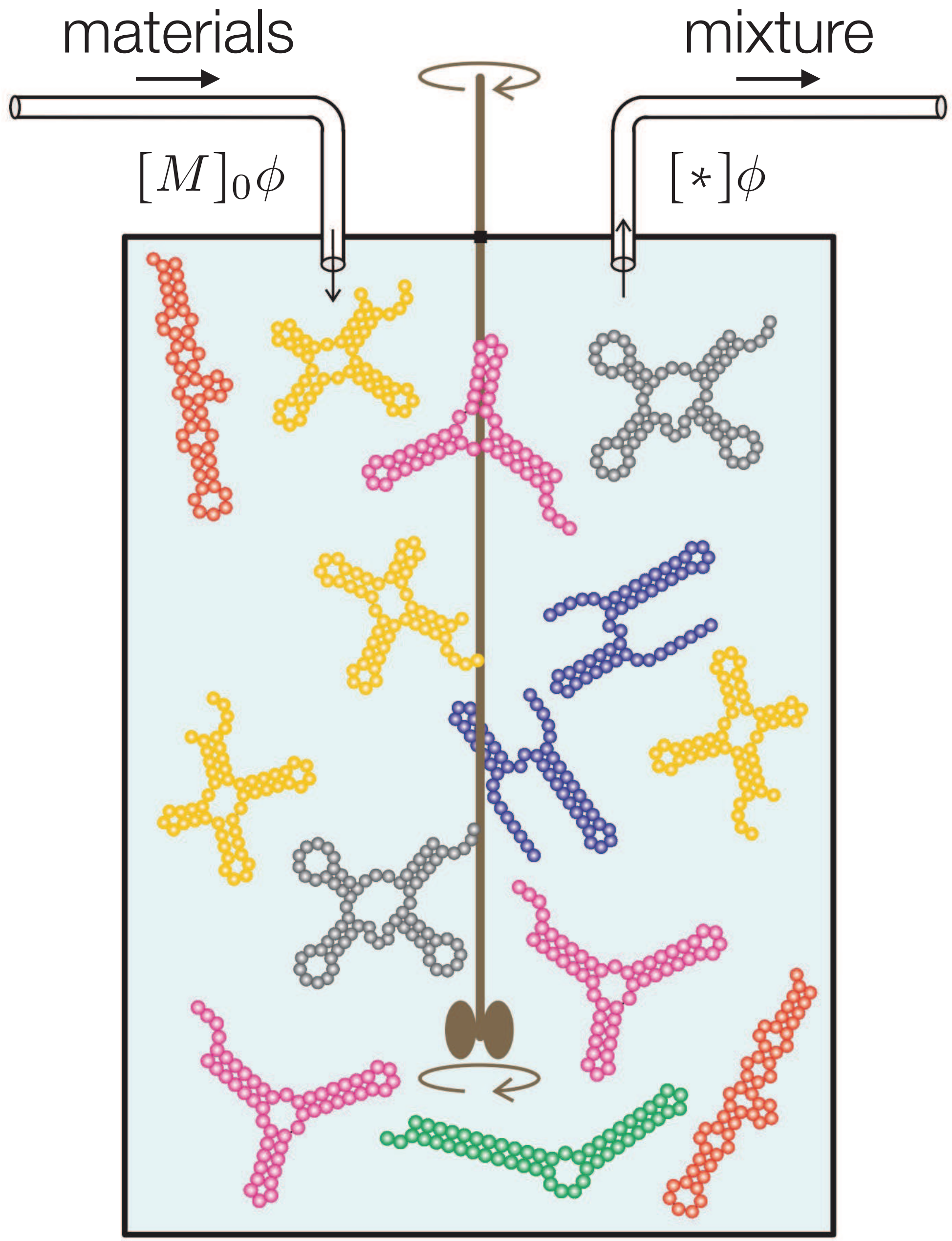
$$I_i + M \xrightarrow{f_i} I_i + I_i$$

$$I_i \xrightarrow{\phi} \varnothing$$

$$i = 1, \ldots, n$$

$$M \xrightarrow{\phi} \varnothing$$

$$\frac{d}{dt}[I_i] = f_i[M][I_i] - \phi[I_i]$$



# Flow Reactor @ "constant organization"

$$I_i \xrightarrow{f_i} I_i + I_i$$

$$I_i \xrightarrow{\phi(t)} \varnothing \qquad i = 1, \ldots, n$$

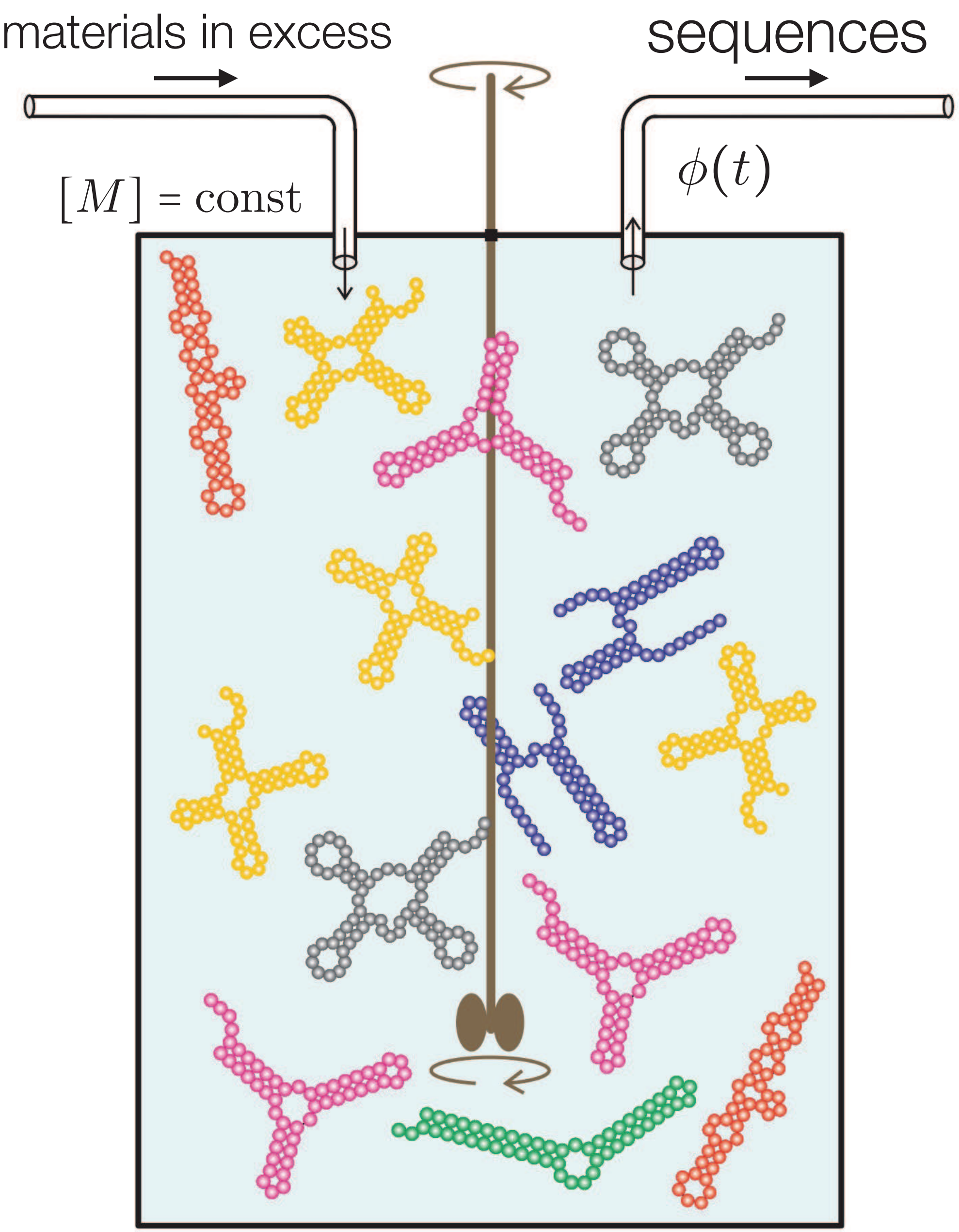
$$\frac{d}{dt}[I_i] = f_i[I_i] - \phi(t)[I_i]$$

$$\sum_i [I_i] = \text{const}$$

$$c_i(t) = [I_i]$$

$$\frac{d}{dt} c_i(t) = f_i c_i(t) - \phi(t) c_i(t)$$

$$\dot{c}_i = f_i c_i - \phi c_i$$



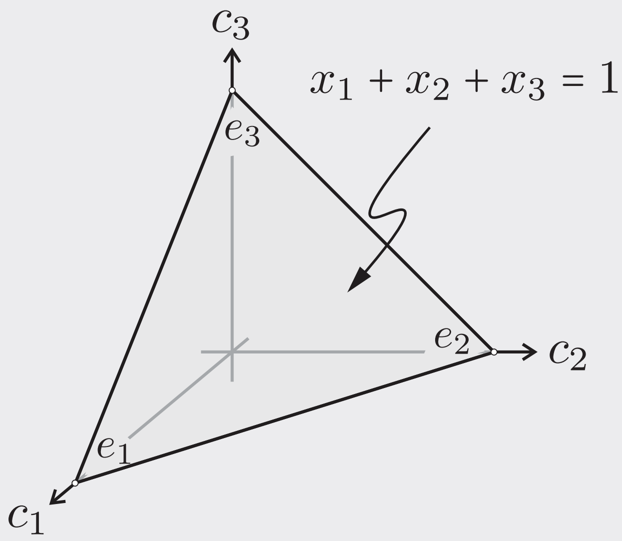
# Darwinian Selection

$$\dot{c}_i = f_i c_i - \phi c_i$$

$\phi(t)$ s.t. $\sum_i \dot{c}_i = 0$

$$x_i = \frac{c_i}{\sum_{j=1}^{n} c_j} \quad \text{with} \quad \sum_{j=1}^{n} x_j = 1$$

change to
relative concentrations




$$\dot{x}_i = f_i x_i - \phi x_i$$

$$\phi = \sum_{j=1}^{n} f_j x_j = \overline{f(t)}$$

$$\dot{x}_i = f_i x_i - \overline{f(t)} x_i = x_i \left( f_i - \overline{f(t)} \right)$$

"Darwinian selection"

# Darwinian Selection

$$\dot{x}_i = f_i x_i - \overline{f(t)} x_i = x_i \left( f_i - \overline{f(t)} \right)$$

"Darwinian selection"

$$f_m = \max\{f_i; i = 1, \ldots, n\}$$

assume a maximal $f_i$

$$\lim_{t\to\infty} x_m(t) = 1$$

$$\lim_{t\to\infty} x_i(t) = 0, \qquad \forall\, i \neq m$$

asymptotic behavior

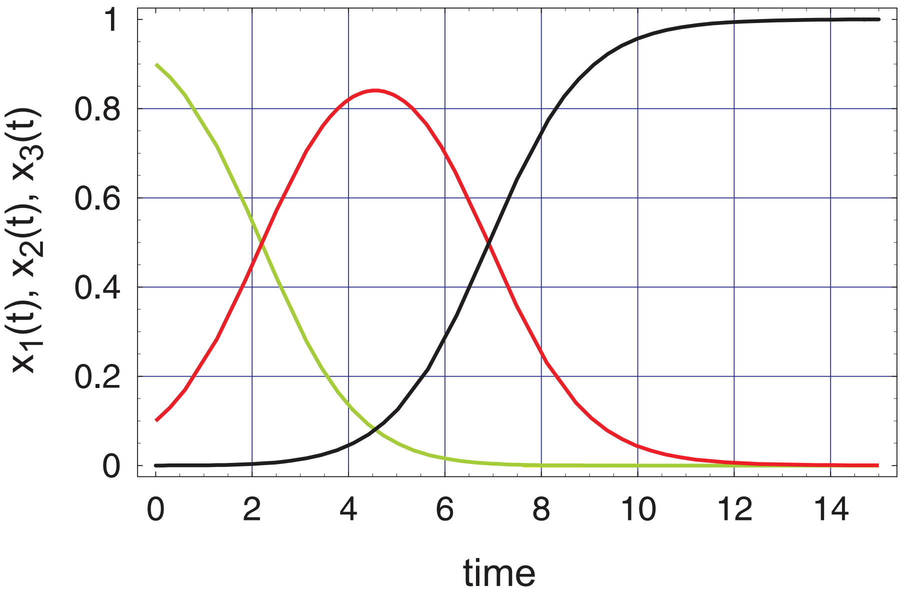
Note:

$$\frac{d}{dt}\phi = \sum_j f_j \dot{x}_j = \sum_j f_j \left( f_j x_j - x_j \sum_k f_k x_k \right)$$

$$= \overline{f^2} - \overline{f}^2 = \mathrm{var}(f)$$

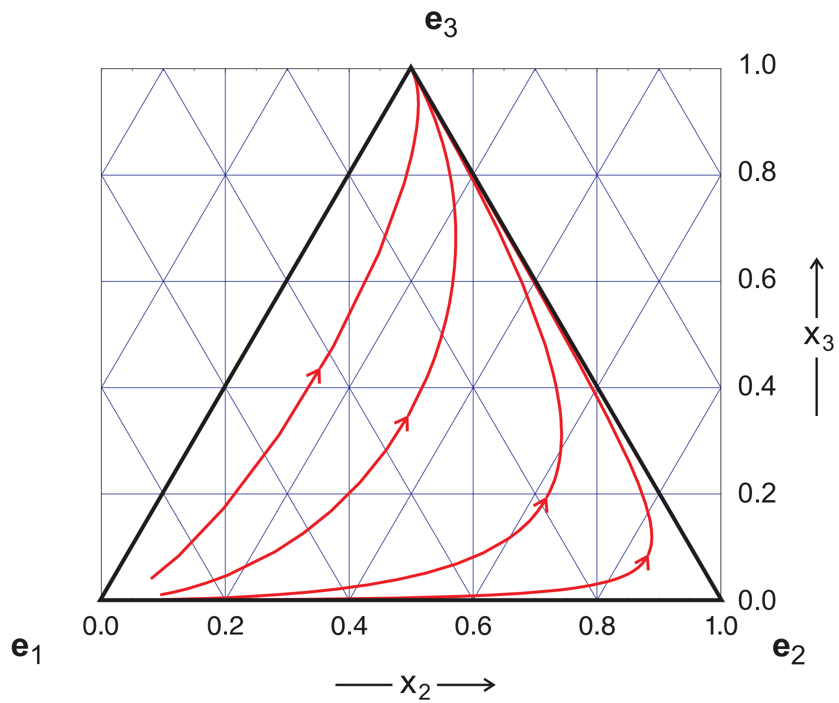
cf. Fisher's fundamental theorem

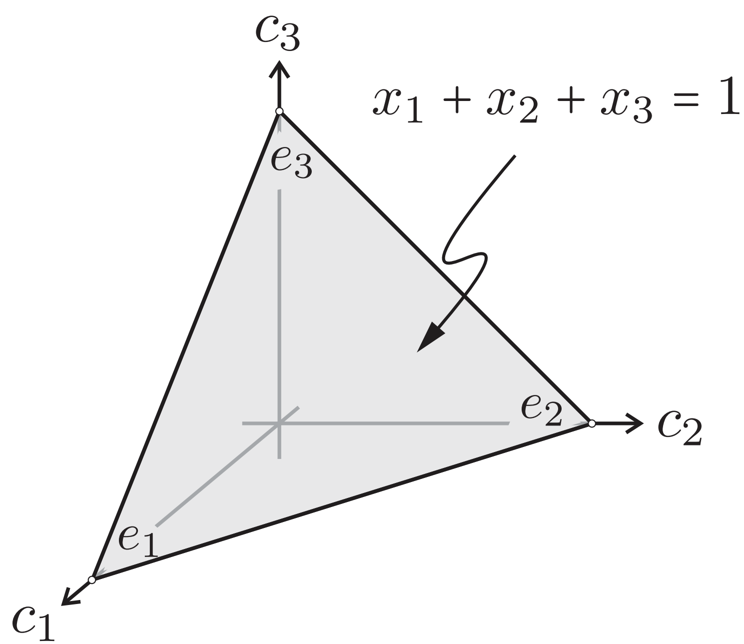
# Darwinian Selection




$$f_1 = 1, \quad f_2 = 2, \quad f_3 = 3$$

$$(x_1(0), x_2(0), x_3(0)) = (0.9000, 0.0999, 0.0001)$$




courtesy of Peter Schuster, Vienna

# Darwinian Selection with Mutation

$$\dot{x}_i = f_i x_i - \phi x_i \qquad \phi = \sum_{j=1}^{n} f_j x_j = \overline{f(t)}$$

no mutation

include mutation

$$I_i \xrightarrow{Q_{ii} f_i} I_i + I_i$$

$$I_i \xrightarrow{Q_{ji} f_i} I_i + I_j \qquad j \neq i$$

$Q_{ij}$ is the rate of production of i from j

with $\sum_{i=1}^{n} Q_{ij} = 1$

$$\dot{x}_i = \sum_{j=1}^{n} Q_{ij} f_j x_j - \phi x_i \qquad \phi = \sum_{j=1}^{n} f_j x_j = \overline{f(t)}$$

$$Q = \begin{pmatrix} Q_{11} & Q_{12} & \cdots & Q_{1n} \\ Q_{21} & Q_{22} & \cdots & Q_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ Q_{n1} & Q_{n2} & \cdots & Q_{nn} \end{pmatrix}$$

$$z_i(t) = x_i(t) \exp\left( \int_0^t \phi(\tau) d\tau \right)$$

nonlinear transform (integrating factor)

$$\dot{z}_i = \sum_{j=1}^{n} Q_{ij} f_j z_j$$

coupled *linear* system

# Darwinian Selection with Mutation

$$\dot{z}_i = \sum_{j=1}^{n} Q_{ij} f_j z_j$$

$$\dot{\boldsymbol{z}} = \boldsymbol{W}\boldsymbol{z}$$

$$\boldsymbol{W} = \boldsymbol{Q}\boldsymbol{F}$$

diagonal

positive off-diagonal elements

$$\boldsymbol{L}^{-1}\boldsymbol{W}\boldsymbol{L} = \boldsymbol{\Lambda}$$

$$\zeta(t) = \boldsymbol{L}^{-1}\boldsymbol{z}(t) \qquad \boldsymbol{z}(t) = \boldsymbol{L}\zeta(t)$$

standard linear algebra

$$\boldsymbol{L}^{-1}\dot{\boldsymbol{z}} = \boldsymbol{L}^{-1}\boldsymbol{W}\boldsymbol{z} = \boldsymbol{L}^{-1}\boldsymbol{W}\boldsymbol{L}\zeta$$

$$\dot{\zeta} = \boldsymbol{\Lambda}\zeta$$

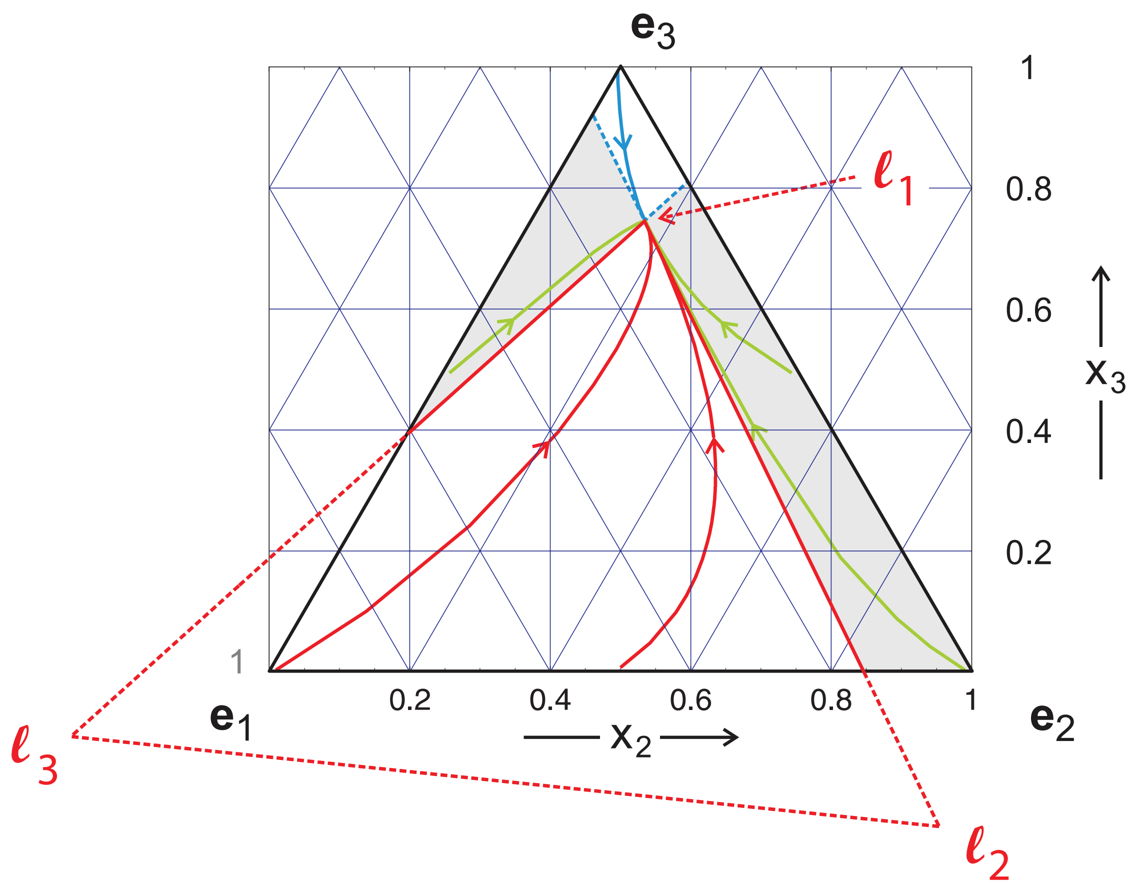
Perron-Frobenius applies

$$\zeta_k t = \zeta_k(0)\exp(\lambda_k t)$$

# The Quasispecies

$$\boldsymbol{x}(t) = \sum_{i=1}^{n} x_i(t)\boldsymbol{e_i} = \sum_{k=1}^{n} \xi_k(t)\boldsymbol{l_k}$$

$$\dot{\xi}_k = \xi_k\left(\lambda_k - \phi\right) \qquad \phi = \sum_k \lambda_k \xi_k = \overline{\lambda}$$




$f_1 = 1.9,\ f_2 = 2.0,\ f_3 = 2.1 \qquad Q_{ii} = 0.98,\ Q_{ij} = 0.01$

change of coordinates

eigenvectors of $\boldsymbol{W}$

same form as before

and also $\frac{d}{dt}\phi = \overline{\lambda^2} - \overline{\lambda}^2$

$\boldsymbol{l_1}$ —the "quasi-species"

white/red—increasing $\overline{f}$

white/blue—non-increasing $\overline{f}$

grey/green—possibly non-monotonic $\overline{f}$

# Error Threshold

$$\dot{x}_i = \sum_{j=1}^{n} Q_{ij} f_j x_j - \phi x_i \qquad \phi = \sum_{j=1}^{n} f_j x_j = \overline{f(t)}$$

neglect "backflow"

$$\sum_{i \neq m} Q_{mi} f_i x_i \overset{!}{=} 0$$

"single-peak" landscape

$$f_m > f_i = f \;\; \forall i \neq m$$

$$\dot{x}_m = Q_{mm} f_m x_m - \phi x_m = (Q_{mm} f_m - \phi) x_m$$

$$\dot{x}_{j \neq m} = Q_{jj} f_j x_j + Q_{jm} f_m x_m - \phi x_j$$

$$\phi = f_m x_m + f \sum_{j \neq m} x_i = f_m x_m + f(1 - x_m)$$

$$\dot{x}_m = 0 \;\Rightarrow\; \phi = Q_{mm} f_m$$

solve

$$\overline{x}_m = \frac{Q_{mm}\sigma_m - 1}{\sigma_m - 1} \quad \text{with} \quad \sigma_m = \frac{f_m}{f}$$

$\sigma_m$ superiority of master

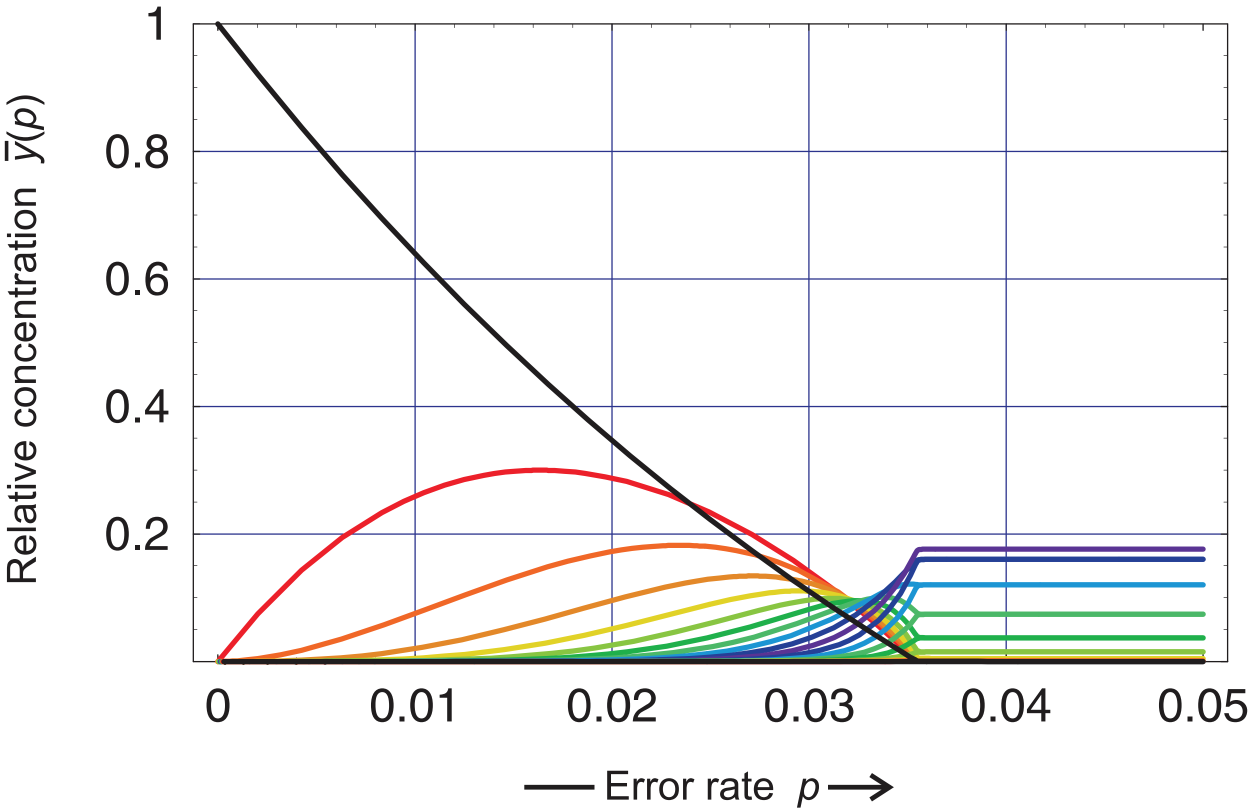
$$\overline{x}_m > 0 \;\Rightarrow\; Q_{mm}\sigma_m > 1$$

"error threshold"

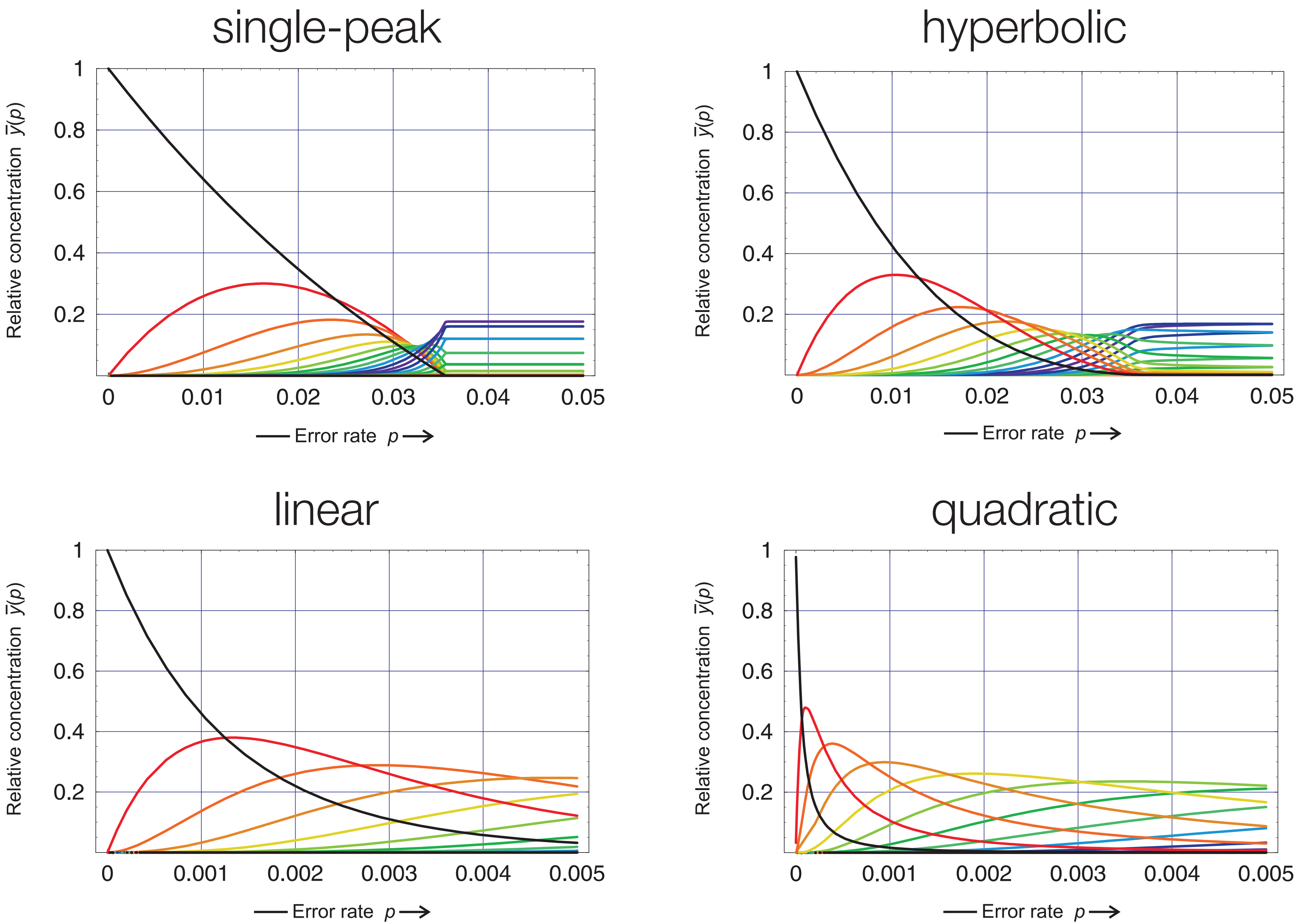
# Error Threshold

$\overline{x}_m > 0 \;\Rightarrow\; Q_{mm}\sigma_m > 1$ uniform error model: $Q_{mm} = (1-p)^l$

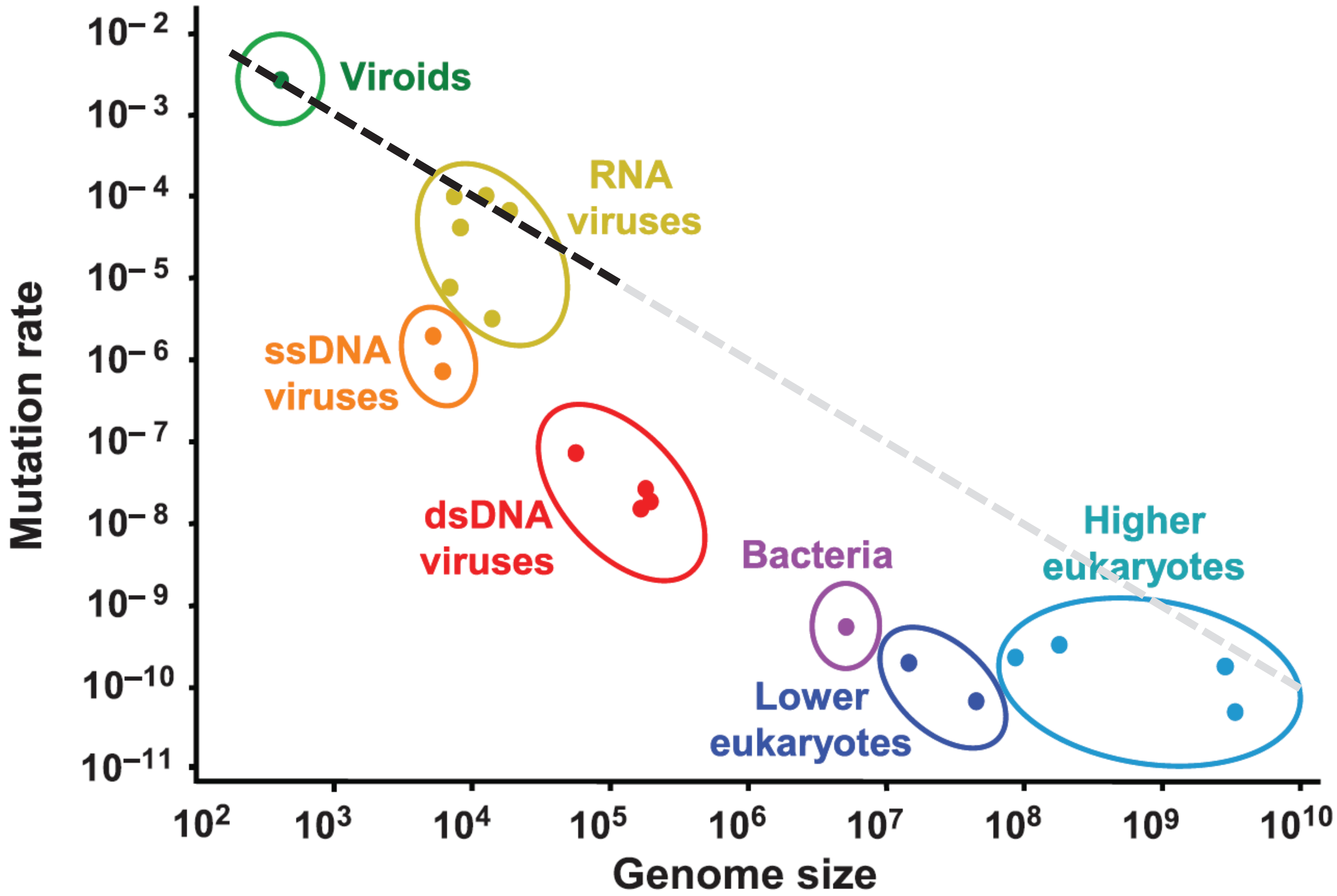
$$p_c = 1 - \sigma_m^{-\frac{1}{l}} \approx \frac{\ln \sigma_m}{l} \quad \text{or} \quad l_{\max} = \frac{\ln \sigma_m}{p}$$



# Error Thresholds on Landscapes



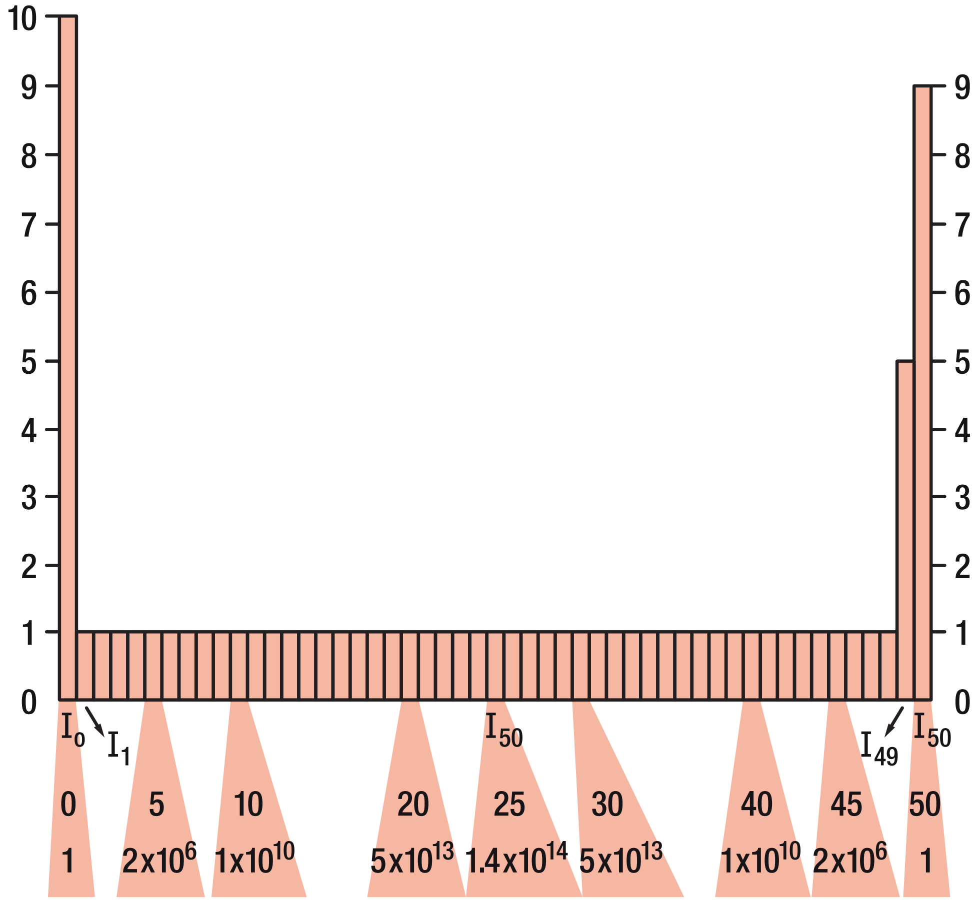
# Mutation Rates and Genome Size




Selma Gago, Santiago F. Elena, Ricardo Flores, Rafael Sanjuán. 2009, Extremely high mutation rate of a hammerhead viroid. *Science* **323**:1308

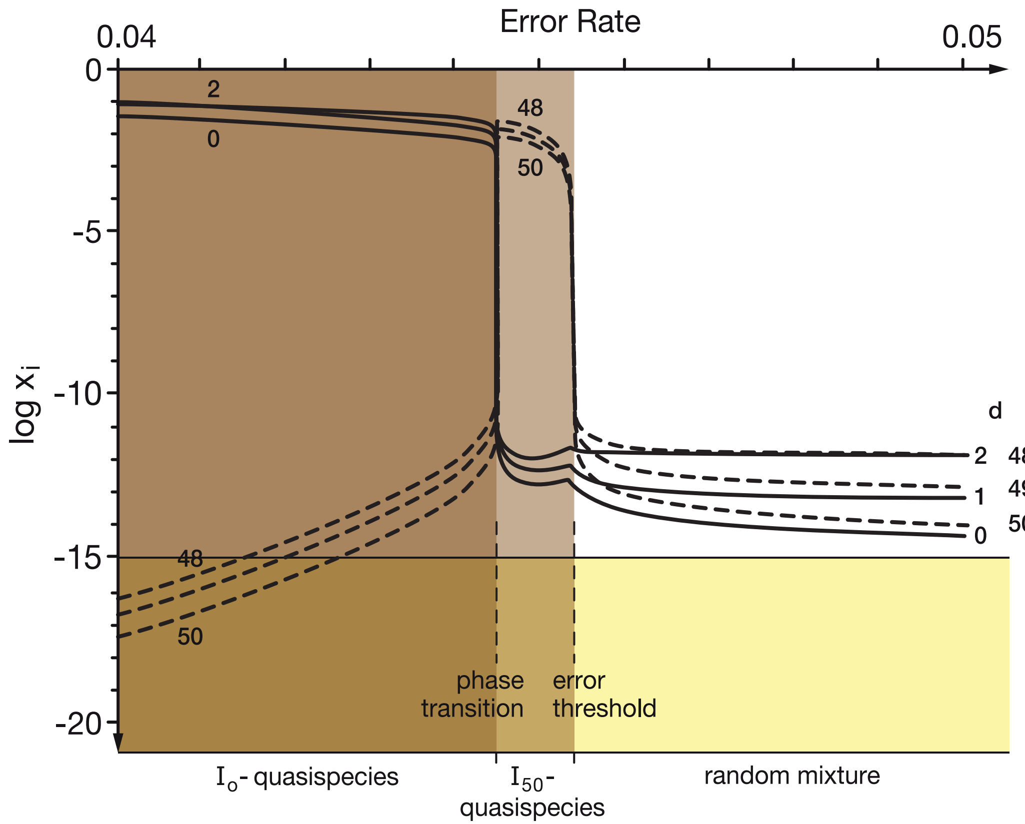
# The Quasispecies is The Unit of Selection

two-peak landscape




error class

stationary distributions




Manfred Eigen "From Strange Simplicity to Complex Familiarity: A Treatise on Matter, Information, Life and Thought", OUP, 2013. p539 quasispecies

$$\dot{x}_i = \sum_{j=1}^{n} Q_{ij} f_j x_j - \overline{f(t)} x_i$$

$$\boldsymbol{W} = \boldsymbol{QF}$$

$$\dot{\boldsymbol{x}} = (\boldsymbol{W} - \overline{f(t)})\boldsymbol{x}$$

$$\dot{x}_i = (f_i - \overline{f(t)}) x_i + \sum_{j=1}^{n} \mu_{ij} x_j$$

$$\boldsymbol{W} = \boldsymbol{\mu} + \boldsymbol{F}$$

selection-mutation model

# Phenotypic Error Threshold

$$\dot{x}_i = \sum_{j=1}^{n} Q_{ij} f_j x_j - \phi x_i \qquad \phi = \sum_{j=1}^{n} f_j x_j = \overline{f(t)}$$

neglect “backflow”

$$\sum_{i \neq m} Q_{mi} f_i x_i \overset{!}{=} 0$$

$$\dot{x}_m = Q_{mm} f_m x_m - \phi x_m = (Q_{mm} f_m - \phi) x_m$$

“single-peak” landscape

$$f_m > f_i = f \;\; \forall i \neq m$$

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$$\eta_m = \sum_{i=1}^{k} x_i \qquad i = 1, \ldots, k$$

equivalence classes

$$\dot{\eta}_m = \sum_{i=1}^{k} \dot{x}_i = \left( (Q_{kk} + \lambda_m (1 - Q_{kk})) f_m - \phi \right) \eta_m$$

include mutational flow within neutral network

fraction of neutral mutants (all equally accessible)

$$p_c = 1 - \left( \frac{1 - \lambda_m \sigma_m}{(1 - \lambda_m) \sigma_m} \right)^{1/l}$$

“phenotypic error threshold”

# Phenotypic Error Threshold

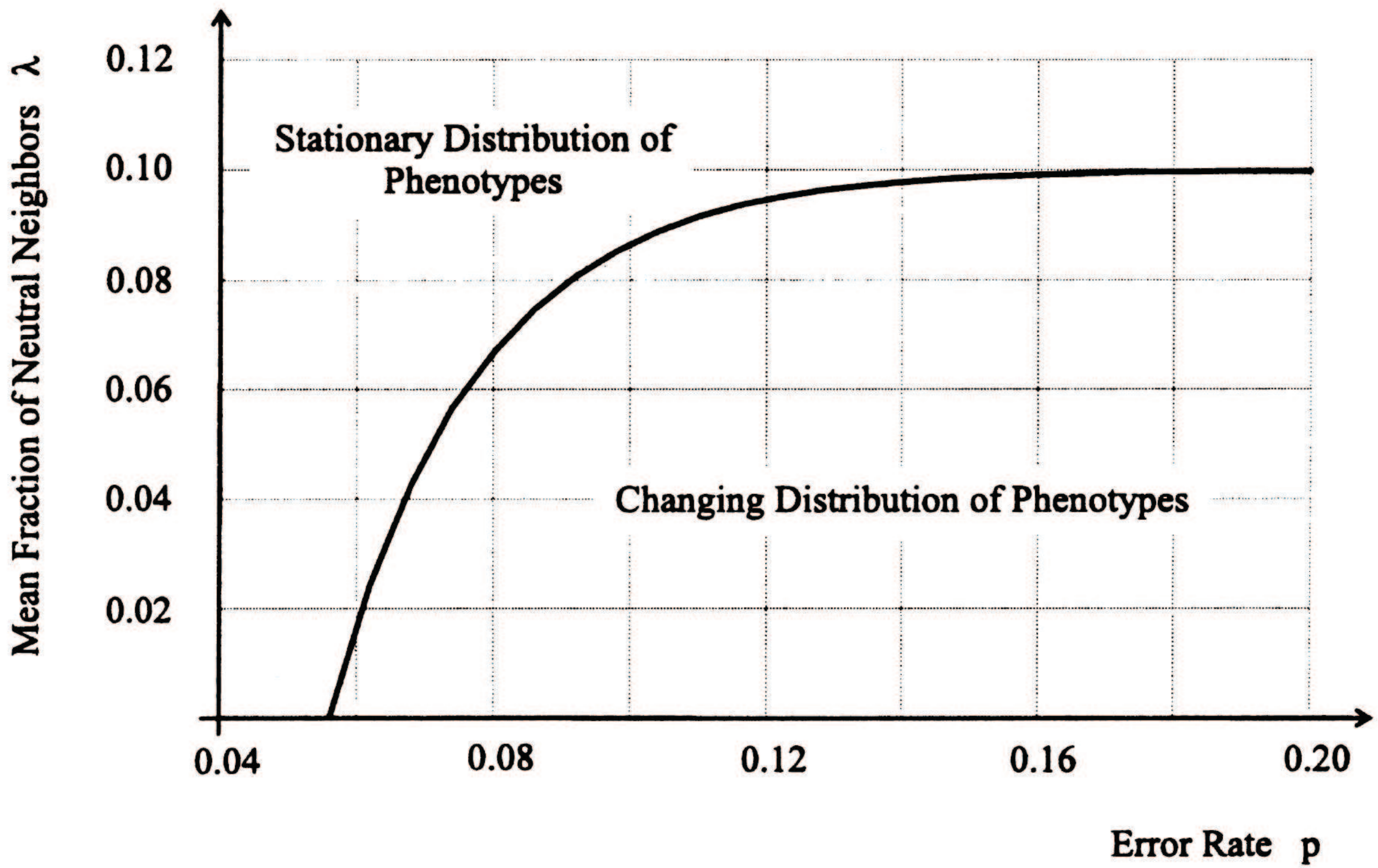
$$p_c = 1 - \left( \frac{1 - \lambda_m \sigma_m}{(1 - \lambda_m) \sigma_m} \right)^{1/l}$$

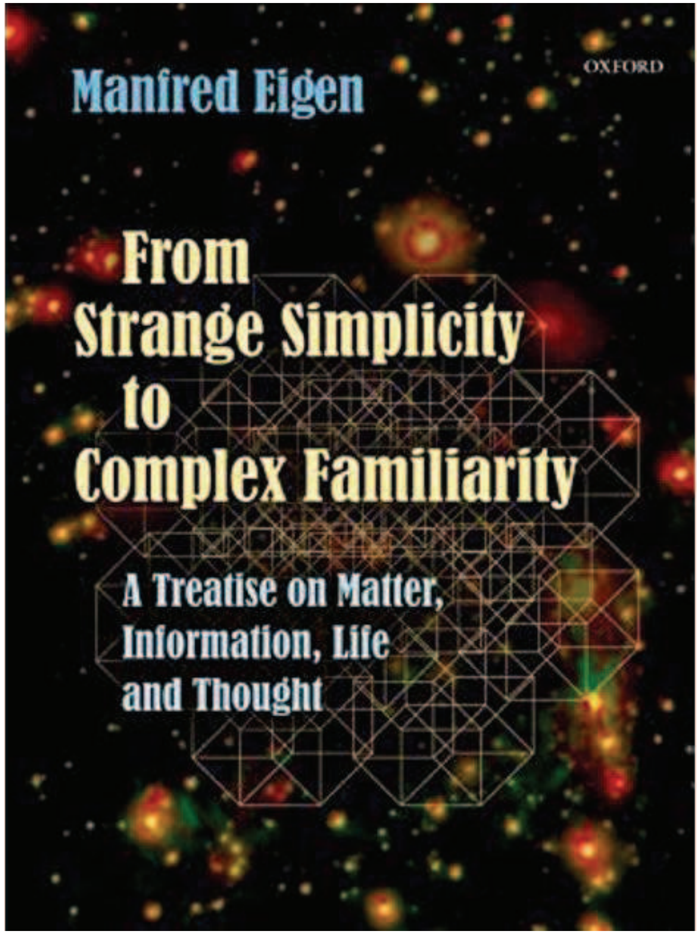
sequence length

superiority of master network

fraction of neutral mutants

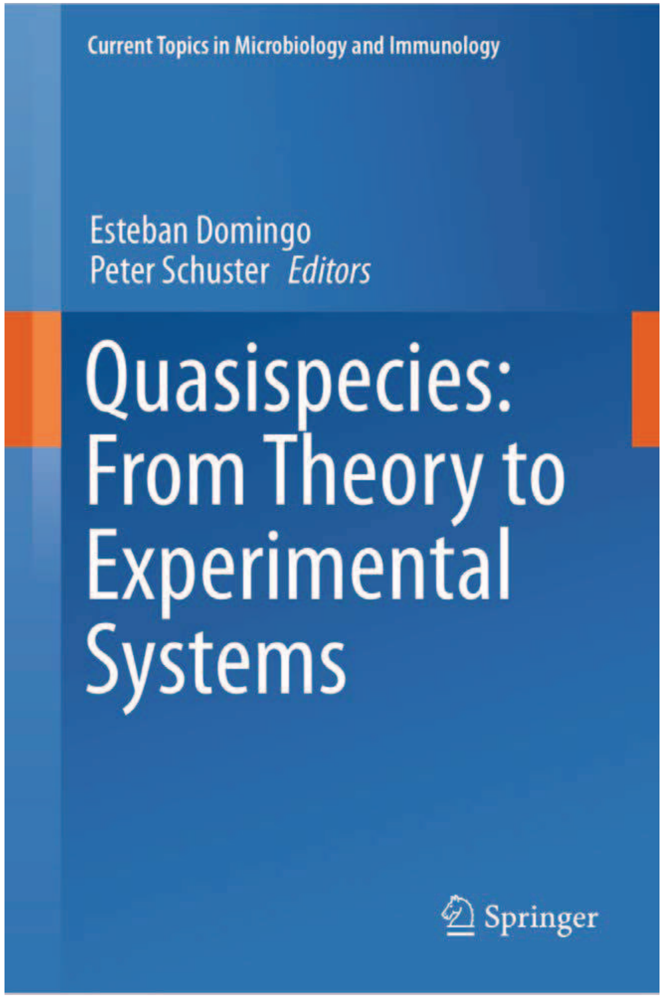
*P. Schuster, W. Fontana / Physica D 133 (1999) 427–452*





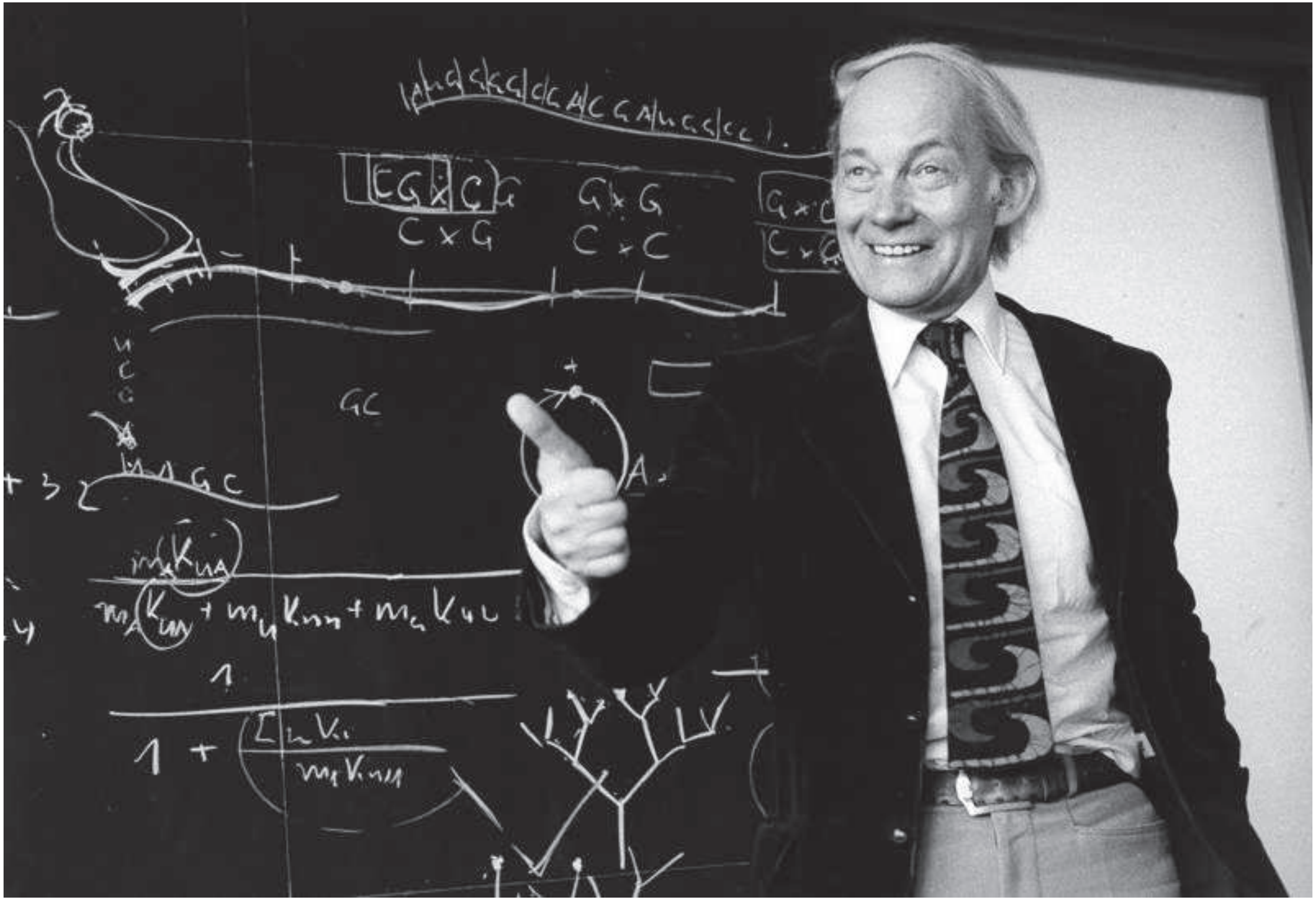

**Peter Schuster**, *"The Mathematics of Darwinian Systems"*, Appendix in

**Manfred Eigen** *"From Strange Simplicity to Complex Familiarity: A Treatise on Matter, Information, Life and Thought"*, OUP, 2013

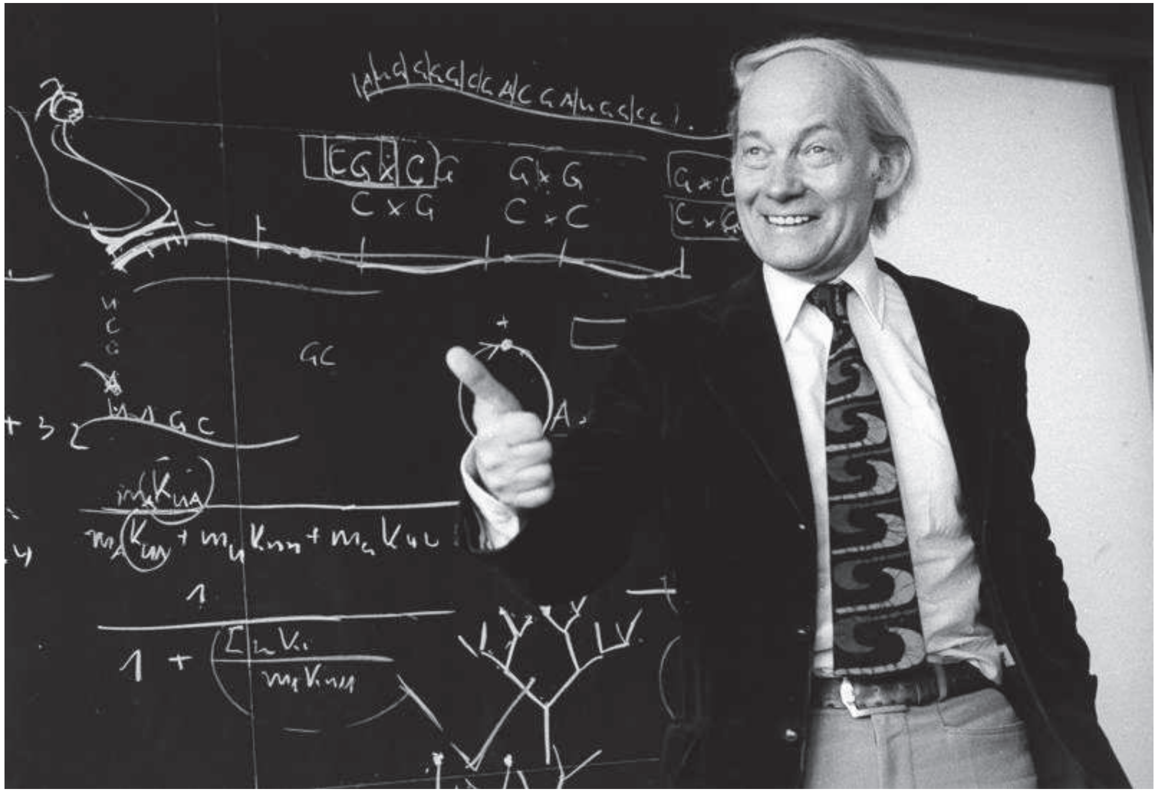



2016

especially chapters 1 and 4



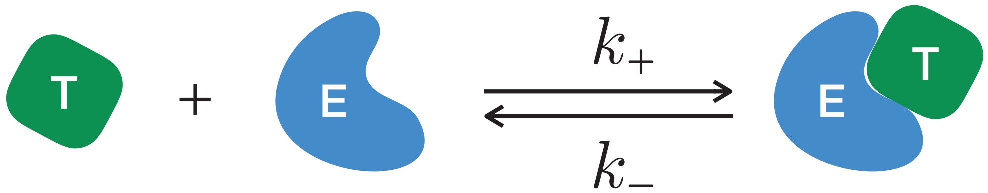
Manfred Eigen (1927-2019)



Manfred Eigen (1927-2019)


1971 German edition
preface by Manfred Eigen

# Basics




$$\mathrm{T} + \mathrm{E} \underset{k_-}{\overset{k_+}{\rightleftharpoons}} \mathrm{ET}$$

$$v_+ = v_-$$

kinetic equilibrium

thermodynamic equilibrium

$$\Delta G = 0$$

$$v_+ = k_+[E][T]$$

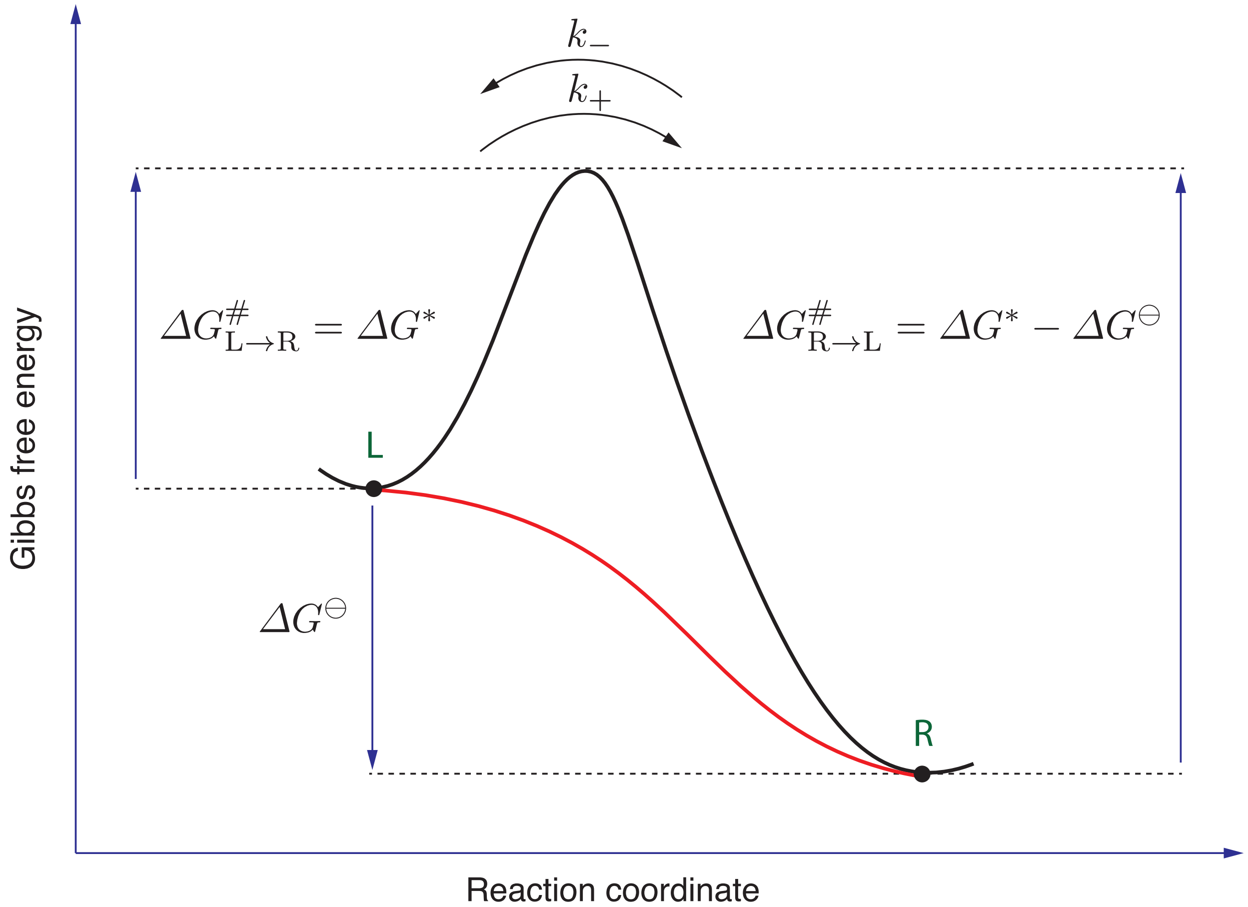
$$v_- = k_-[ET]$$

reaction velocity (flux)

$$\frac{k_+}{k_-} = \underbrace{\frac{[ET]_{eq}}{[E]_{eq}[T]_{eq}}}_{K} = \exp\left(-\frac{\Delta G^{\ominus}}{RT}\right)$$

equilibrium constant

connects energetics with kinetics

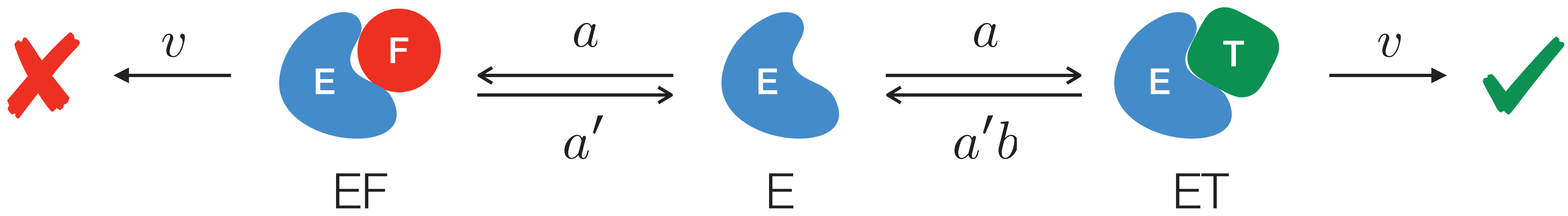



$$k = \omega \exp(-\Delta G^{\#}/RT)$$

$$k_+ = \omega \exp(-\Delta G^*/RT) = \omega'$$

$$k_- = \omega \exp(-\Delta G^*/RT) \exp(\Delta G^{\ominus}/RT) = \omega' \exp(\Delta G^{\ominus}/RT)$$

# Kinetic Proofreading Problem




**assume**

$$a \equiv k_+[F] = k_+[T]$$

**discriminating factor**

$$b = \exp\left(-(\Delta G_F^{\ominus} - \Delta G_T^{\ominus})\right) \stackrel{!}{=} \exp\left(-\Delta G_{FT}^{\ominus}\right)$$

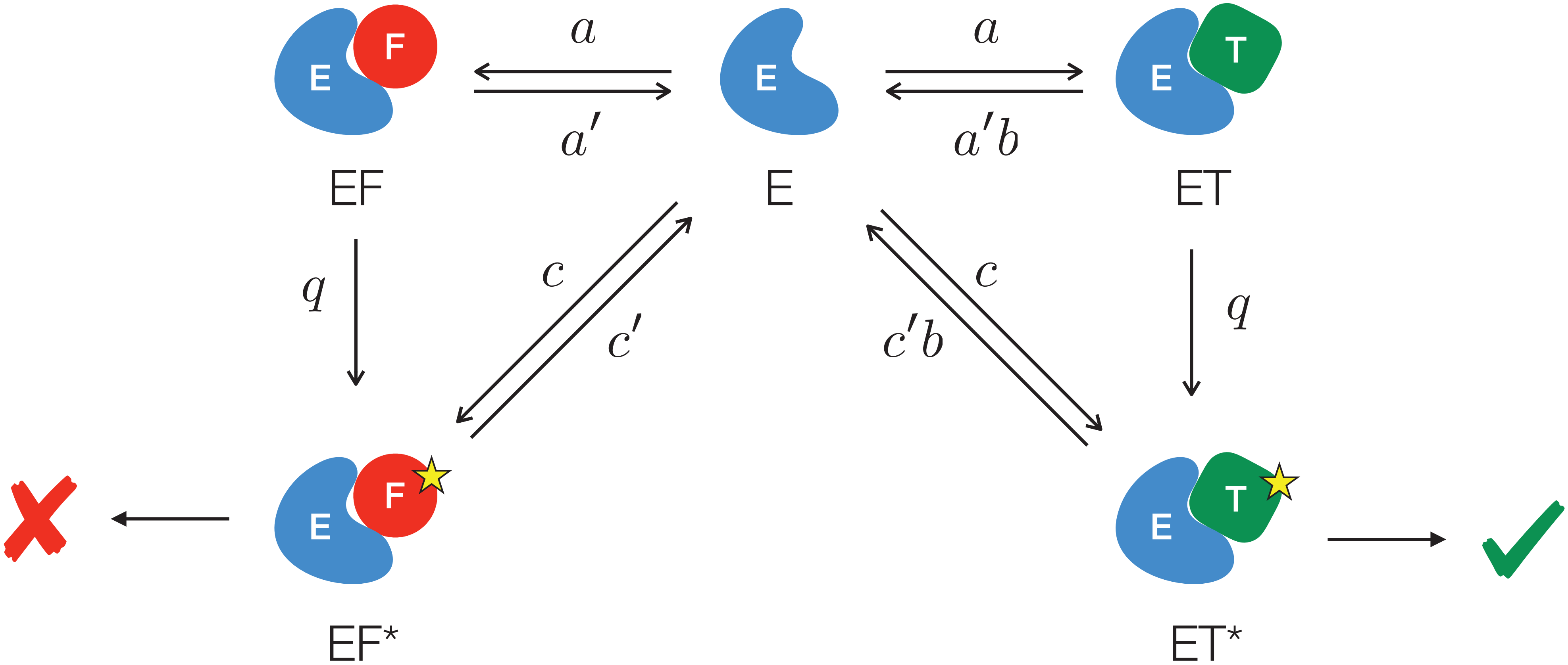
**at steady-state**

$$[ET] = \frac{a[E]}{a'b + v} \quad \text{and} \quad [EW] = \frac{a[E]}{a' + v}$$

**error rate**

$$\eta = \frac{v[EW]}{v[ET]} = \frac{[EW]}{[ET]} = \frac{a'b + v}{a' + v}$$

# Kinetic Proofreading Scheme




$$\eta = \frac{[EF^*]}{[ET^*]} = \frac{b(a'b+q)(a'c+(a+c)q)}{(a'+q)(a'bc+(a+c)q)}$$

drawing after J. Gunawardena and Jeremy Owen