

Quasispecies Dynamics on Correlated Fitness Landscapes

please see posters by

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Exact Phase Diagram of a Quasispecies Model
with a Mutation Rate Modifier

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Quasispecies Model (Eigen, 1971)

We consider an infinitely large microbial population: neglect fluctuations

Each individual's genotype is a binary string $\sigma \equiv \{\sigma_1, \dots, \sigma_L\}$, $\sigma_i = 0, 1$

Two basic reactions occur:

i. **Replication:** a genome σ produces $w(\sigma)$ copies of itself on an average

$w(\sigma)$: measure of fitness of genome σ

ii. **Mutation:** due to copying errors in genome σ , genome σ' is produced

If $0 \leftrightarrow 1$ with probability μ , the mutation probability

$$m(\sigma, \sigma') = \mu^{d(\sigma, \sigma')} (1 - \mu)^{L - d(\sigma, \sigma')}$$

where $d(\sigma, \sigma')$ is the Hamming distance between σ and σ'

Then the average fraction $p(\sigma, t)$ of genome σ obeys rate equation:

$$\frac{\partial p(\sigma, t)}{\partial t} = \sum_{\sigma'} \underbrace{m(\sigma, \sigma')}_{\text{Mutation}} \underbrace{w(\sigma') p(\sigma', t)}_{\text{Replication}} - \underbrace{p(\sigma, t) \sum_{\sigma'} w(\sigma') p(\sigma', t)}_{\text{Death term}}$$

The death term ensures that $\sum_{\sigma} p(\sigma, t) = 1$.

Steady State of Quasispecies Model

In the steady state, $p(\sigma)$ obeys a nonlinear equation

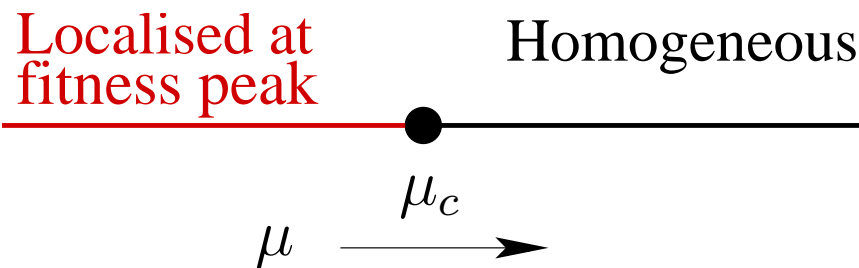
$$p(\sigma) = \frac{\sum_{\sigma'} m(\sigma, \sigma') w(\sigma') p(\sigma')}{\sum_{\sigma'} w(\sigma') p(\sigma')}$$

Phase transition occurs due to competition between replication and mutation

Example: $w(\sigma) = w_0 \delta_{\sigma, \mathbf{0}} + (1 - \delta_{\sigma, \mathbf{0}})$, $w_0 > 1$ (Nowak+ Schuster, 1989)

In the scaling limit $\mu \rightarrow 0$, $L \rightarrow \infty$, it can be shown that

$$p(\mathbf{0}) = 1 - \frac{\mu}{\mu_c}, \quad \mu < \mu_c = L^{-1} \ln w_0$$

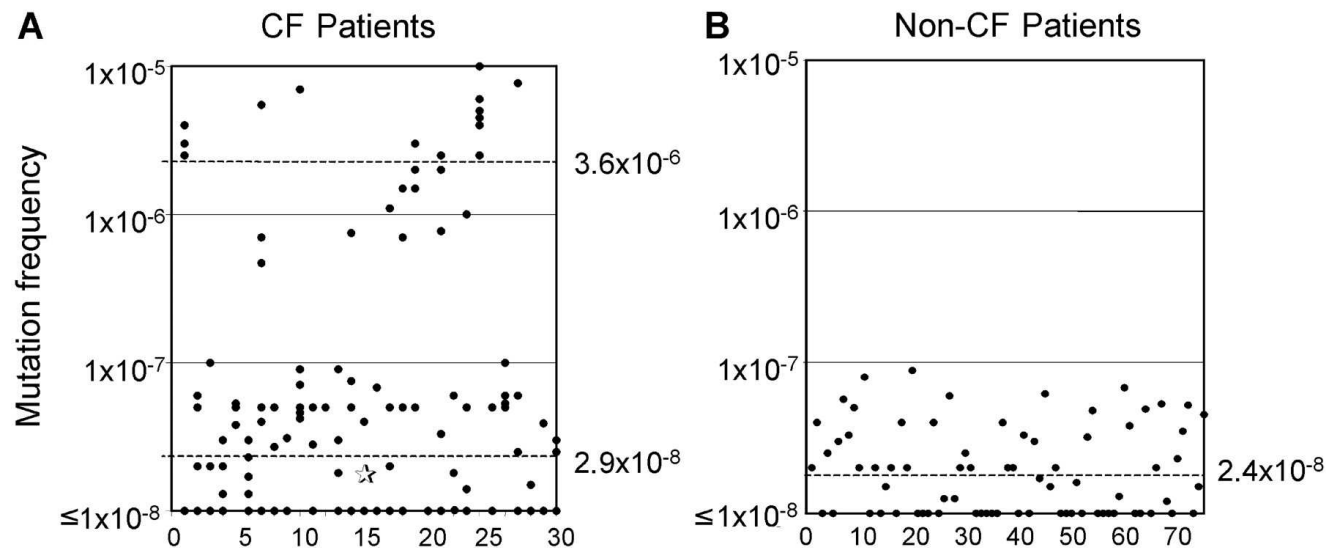


Populations with High Mutation Rates

At large times, population should have low mutation rate

But subpopulations with high mutation rates have been observed

Lung infection: 20% of bacterial population with $\times 100\mu$ (Oliver et al., 2000)



Chemostat: 0.1% – 0.5% with $\times 10 - 100\mu$ (1980s; Mao et al., 1997)

Can we predict the mutator fraction?

Coupled Quasispecies Model

Mutators arise due to failure of error repair system in normal strains

iii. Mutator generation: Mutation rate controlling bit $\rightarrow \sigma \equiv \{\sigma_1, \dots, \sigma_L; \nu\}$

$$\{\sigma_1, \dots, \sigma_L; \mu\} \xrightarrow{f} \{\sigma_1, \dots, \sigma_L; \lambda\mu\}, \lambda > 1$$

Steady state is described by a set of coupled nonlinear equations:

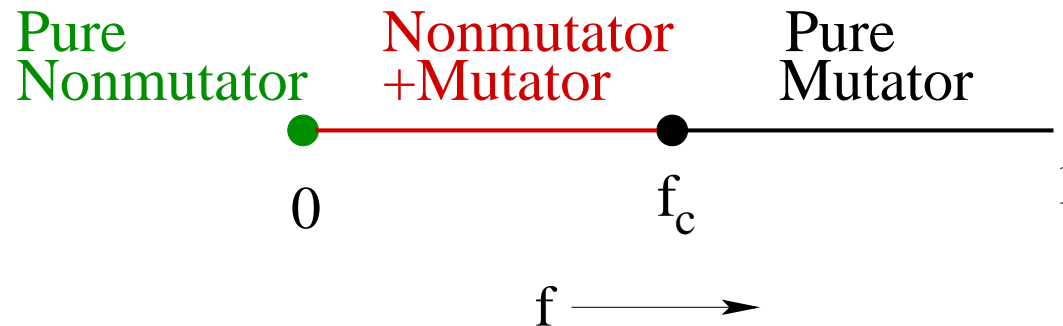
$$p(\sigma) = \frac{(1 - f) \sum_{\sigma'} m(\sigma, \sigma') w(\sigma') p(\sigma')}{\sum_{\sigma'} w(\sigma') [p(\sigma') + P(\sigma')]}$$

$$P(\sigma) = \frac{\sum_{\sigma'} M(\sigma, \sigma') w(\sigma') P(\sigma') + f \sum_{\sigma'} m(\sigma, \sigma') w(\sigma') p(\sigma')}{\sum_{\sigma'} w(\sigma') [p(\sigma') + P(\sigma')]}$$

Nonequilibrium Phase Transition

- + Nonmutators favored since low mutation rate (quasispecies theory)
- Nonmutators lost due to irreversible mutator generation reaction

$$\{\sigma_1, \dots, \sigma_L; \mu\} \xrightarrow{f} \{\sigma_1, \dots, \sigma_L; \lambda\mu\}, \lambda > 1$$



Previous works (Taddei, 1997; Kessler+Levine, 1998; Johnson, 1999) did not consider the possibility of a phase transition

Reduction to Uncoupled Problem

The average fitness $\bar{w} = \sum_{\sigma} w(\sigma) [p(\sigma) + P(\sigma)]$ can be calculated

Mutator phase: For $f > f_c$, $p(\sigma) = 0$ for all σ

$$\bar{w}_{>} = \sum_{\sigma} w(\sigma) P(\sigma)$$

Mixed phase: For $f < f_c$, reduce coupled equation for $p(\sigma)$ to uncoupled

$$\bar{w}_{<} = (1 - f) \sum_{\sigma} w(\sigma) \tilde{p}(\sigma)$$

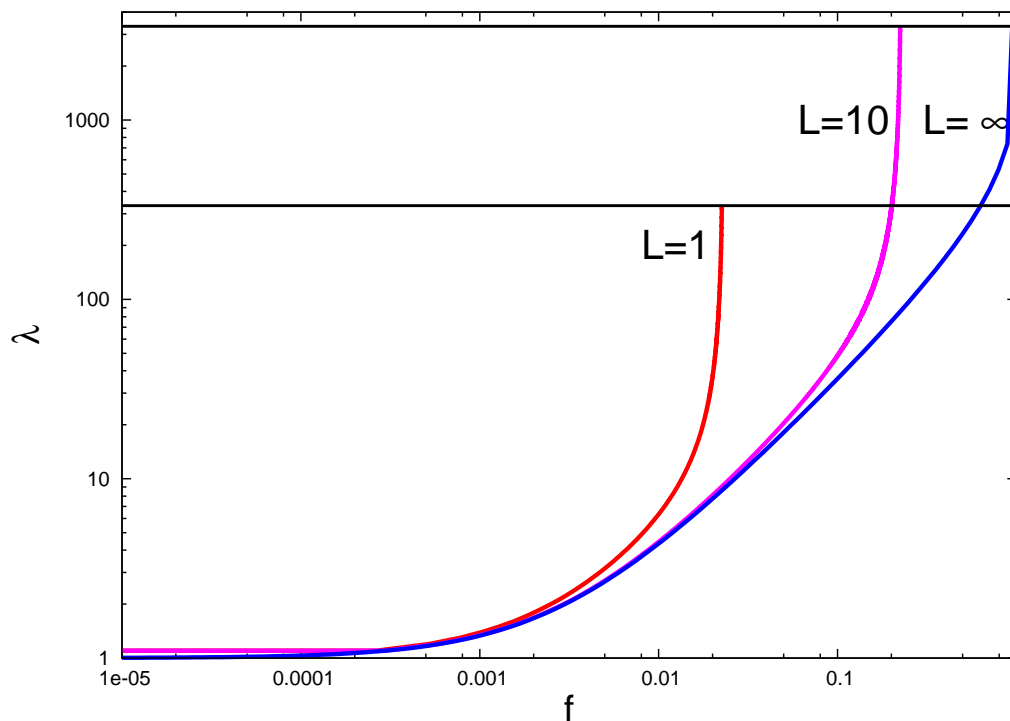
where $\tilde{p}(\sigma)$ obeys single population equation

For $w(\sigma) = \prod_{i=1}^L (1 - s)^{\sigma_i}$, single population problem is solvable

Exact Phase Diagram

Matching $\bar{w}_<$ and $\bar{w}_>$ gives the phase boundary:

$$(1 - f_c)^{1/L} = \frac{(2 - s)(1 - \lambda\mu) + \sqrt{4\lambda^2\mu^2(1 - s) + s^2(1 - \lambda\mu)^2}}{(2 - s)(1 - \mu) + \sqrt{4\mu^2(1 - s) + s^2(1 - \mu)^2}}$$



Mutator Fraction in Mixed Phase

In scaling limit $\mu \rightarrow 0$, $L \rightarrow \infty$, total mutator fraction P can be computed

$$P = \frac{f(1-P)}{1-f} \sum_{m=0}^{\infty} \left(\frac{1-f_c}{1-f} \right)^m e^{\frac{(\lambda-1)\mu L(1-(1-s)^m)}{s}}$$

where $f_c = 1 - e^{-(\lambda-1)\mu L}$

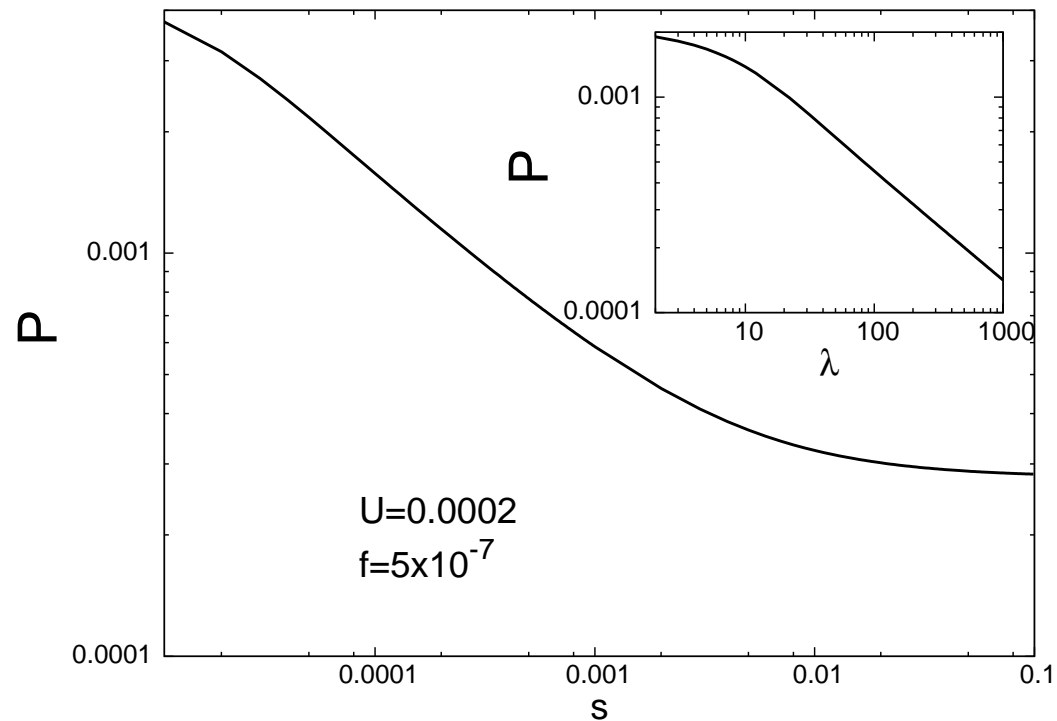
For biologically realistic situations, $f \ll s \ll (\lambda-1)\mu L$:

$$P \approx \frac{f\sqrt{2\pi}}{f\sqrt{2\pi} + (1-f)\sqrt{(\lambda-1)\mu Ls}}$$

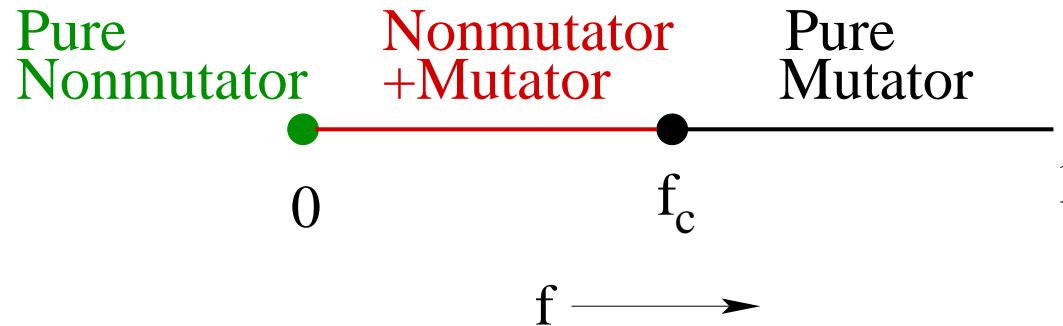
Mutator Fraction in Experiments on *E. Coli*

Genome mutation rate $U = \mu L = 2 \times 10^{-4}$ (Drake et al., 1998)

Probability $f = 5 \times 10^{-7}$ (Ninio, 1991)



Phase Transition in Experiments on *E. Coli*



Theoretical prediction (using experimental parameters): $f_c \approx 10^{-3}$

Typical spontaneous value : $f \sim 10^{-7}$

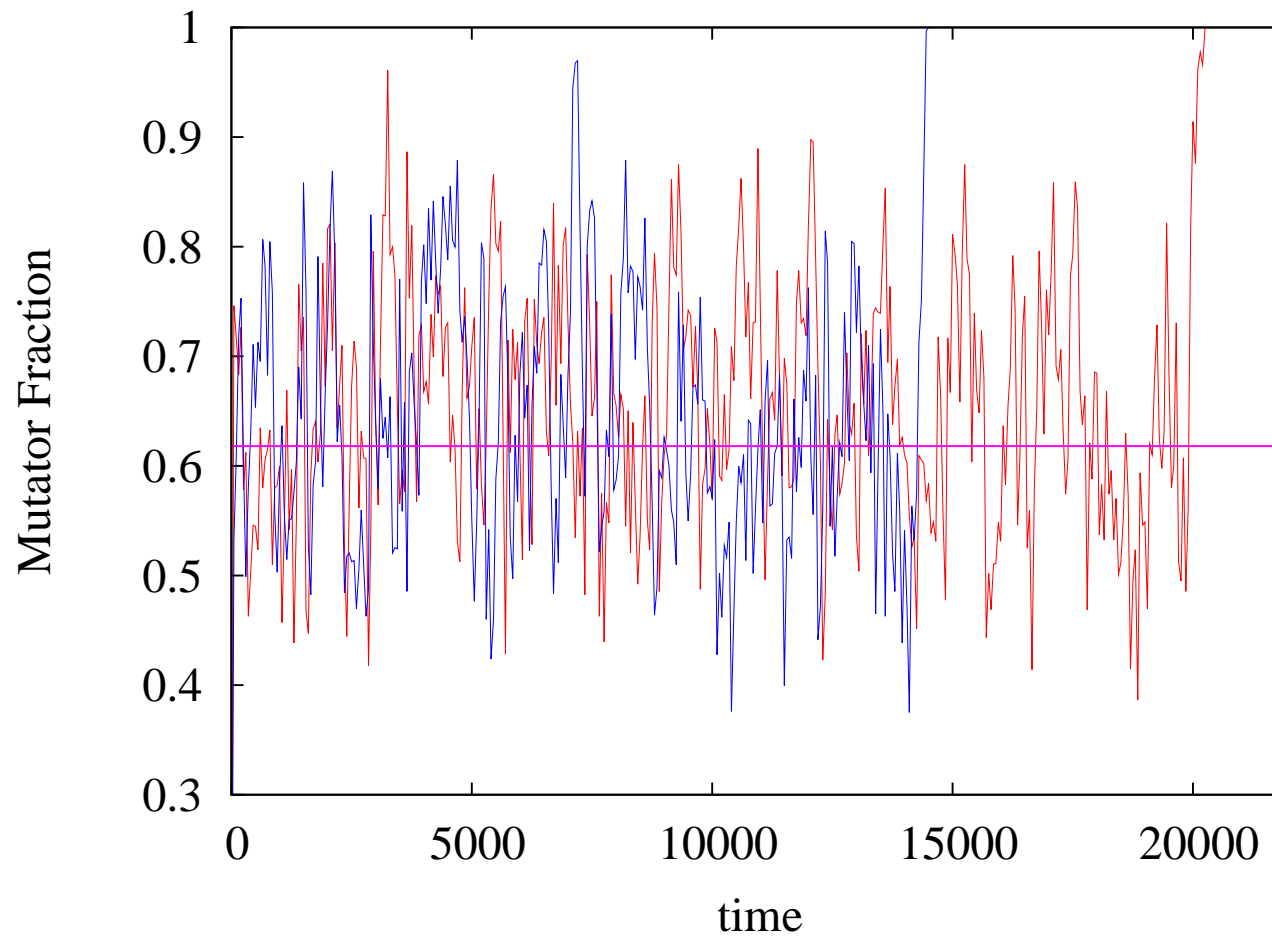
In experiments by Mao et al., 1997:

- without UV radiation, mutator fraction $< 0.5\%$ seen
- with UV radiation, mutator fraction $\sim 50\%$ seen

$$\text{UV dosage} \propto f$$

Stochastic Evolution

Real populations have finite size N and evolve stochastically



Stochastic Evolution

- For finite population and $f > 0$, we expect that:

the population always ends up in pure mutator phase in fixation time T_{fix}

Thus there is no phase transition in steady state of stochastic model

- Before fixation, the population fraction fluctuates about an equilibrium

Can be described by the steady state analysis of quasispecies model

- Experiments on *E. Coli* conducted at spontaneous forward rate:

Mao et al., 1997: $P < 0.5\%$, no. of generations $\sim 10^2$

Sniegowski et al., 1997: $P \approx 1$, no. of generations $\sim 10^4$

Fixation Time

How much time does it take to enter the pure mutator phase?

The dependence of fixation time on N , f needs to be worked out...