Neutrality, Epistasis & Evolvability: Can the Topology of Genome Space Affect Evolution?

Todd L. Parsons

Department of Biology
University of Pennsylvania
tparsons@sas.upenn.edu

University of Waterloo
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In Collaboration With

Jeremy Draghi
University of Pennsylvania

Günter Wagner
Yale University

Joshua Plotkin
University of Pennsylvania
Outline

1. The Genotype-Phenotype Map

2. Genotypes, Phenotypes & Neutral Networks

3. Some Mathematical Questions
   - One: Expected Time to Arrival of an Advantageous Phenotype
   - Two: Neutrality, Hitchhiking, and Epistasis
   - Three: Expected Phenotypic Diversity per Generation

4. Conclusions
The genotype-phenotype map:

- Fitness is determined by phenotype, not genotype.
- Many-to-one: many genotypes give rise to the same phenotype, making the latter robust to mutation.
- E.g. RNA as string of nucleotides (genotype) vs. secondary structure (phenotype)

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Generalities & Specifics: RNA Folding

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Neutrality and Epistasis

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An RNA genome is a string from the alphabet of nucleotides \{U, C, A, G\}. All genomes of length \(L\) form a lattice:

- \(4^L\) vertices, one for each possible genome.
- Each vertex is adjacent to \(3L \ll 4^L\) neighbours that differ at one site.
- \(\sim \frac{1}{3}\) neighbours are silent.
- Any two neighbours share exactly two common neighbours.
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The genotype-phenotype map can be visualised as a colouring of the vertices, same colour $\iff$ same phenotype.

Each phenotype determines a *neutral network* - the subgraph consisting of genotypes that correspond to the same phenotype.
Rethinking Fitness Landscapes

Barton et al. Evolution

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The Robustness/Evolvability Debate

How do neutral networks affect evolvability? Two arguments:

- Neutral mutations leave the phenotype unchanged, so increasing robustness decreases the rate at which new phenotypes are found. Therefore robustness slows evolutionary change (Ancel & Fontana 2000, Carter et al. 2005, Cowperthwaite et al. 2008, Parter et al. 2008, Draghi & Wagner 2009.)

- Many neutral genotypes will coexist, occupying more of genotype space. Thus the population is more likely to be adjacent to novel phenotypes. Thus robustness accelerates evolution (Bloom et al. 2006, Aldana et al. 2007, Elena & Sanjuan 2008, McBride et al. 2008.)
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A Mathematician Wades In...

We may thus cast some of the robustness/evolvability debate as three mathematical questions. Assume that two neighbouring genotypes are in the same neutral network with probability $q$ (robustness):

1. How does the expected time to find a new advantageous phenotype vary with $q$?
2. How does this affect the long-term rate of substitution?
3. How does the expected phenotypic diversity of the population change with increasing $q$?
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A Model Genotype-Phenotype Map

We will assume that the space of phenotypes shares a similar topology to genotype space and can be described by a few parameters:

- There are $P \gg 1$ phenotypes.
- Each genotype is adjacent to $K \ll P$ phenotypes.
- Two adjacent phenotypes have, on average, $(1 - f)K$ common phenotypic neighbours; all others are independently drawn.
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Empirically Parameterising the Model Map

We used the Vienna RNA package to calculate the minimum free-energy secondary structures of RNA nucleotide sequences. The resulting genotype-phenotype map was analysed to estimate $P$, $K$, and $f$ for a range of sequence lengths, $L$:

![Graphs showing $P$, $K$, and mean $f$ vs. sequence length $L$.]
Question One

To elaborate on our first question, suppose that we have a population that has evolved to equilibrium on the neutral network of the most fit phenotype. Assume all other phenotypes are substantially less fit, and thus absent.

Suppose that the environment changes, and now one of the adjacent phenotypes is now more fit.

What can we say about $\tau$, the expected waiting time before the first individual with a genotype encoding the more fit phenotype arises?
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The Moran Model

To have a complete model, we need to specify the population dynamics. We do this via a discrete time Moran model:

- The population is of fixed size $N$.
- At each time step, a randomly-chosen individual produces one offspring that replaces any individual, including the parent, with equal probability.
- At birth, individuals mutate to a new genotype with probability $\mu = \frac{\beta}{N}$.

We will refer to $N$ time steps as one generation.
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For our purposes, it suffices to gather the genotypes into three classes:

A. Genotypes in the neutral network, not adjacent to genotypes in the advantageous phenotype.

B. *Adaptable* genotypes in the neutral network, adjacent to genotypes in the advantageous phenotype.

C. *Target* genotypes that encode the advantageous phenotype.
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Further Reducing the Problem

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C. *Target* genotypes that encode the advantageous phenotype.
A genotypes may mutate to \( B \) genotypes & \( B \)'s to \( A \)'s. After the environment changes, \( B \)'s may also mutate to \( C \)'s:

\[
\begin{align*}
\mu(1 - \frac{fK}{P})q & \quad \mu\left(\frac{fK}{P}\right)q \\
\mu(1 - \frac{fK}{P})q & \quad - \quad - \quad - \quad \frac{\mu}{K}(1 - q) \\
\mu\left(\frac{fK}{P}\right)q & \quad \mu\left(\frac{fK}{P}\right)q
\end{align*}
\]

All other mutations are lethal and no replacement occurs.
A Markov Chain with Killing

Since the population is held fixed at $N$, and we are only interested in $\tau$, the first arrival time of any genotype in $C$, all the dynamics of interest can be captured by a Markov chain on $\{0, \ldots, N\} \cup \{\Delta\}$:

$$X_N(n) = \begin{cases} 
\text{the number of individuals with } B \text{ genotypes} & \text{if } n < \tau \\
\Delta & \text{if } n \geq \tau.
\end{cases}$$

i.e. $\tau = \inf_{n>0} X_N(n) = \Delta$, and $\Delta$ is an absorbing state for $X_N$. 

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Markov Generator

\( X_N(n) \) has transition probabilities

\[
Q_{i,j}^N = \mathbb{P} \{ X_N(n + 1) = j \, | \, X_N(n) = i \} ,
\]
given by

\[
Q_{i,i+1}^N = (1 - \mu) \left( \frac{i}{N} \right) \left( \frac{N - i}{N} \right) + \mu \left( \frac{fK}{P} \right) q \left( \left( \frac{N - i}{N} \right)^2 + \left( \frac{i}{N} \right) \left( \frac{N - i}{N} \right) \right),
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\[
Q_{i,i-1}^N = (1 - \mu) \left( \frac{i}{N} \right) \left( \frac{N - i}{N} \right) + \mu \left( 1 - \frac{fK}{P} \right) q \left( \left( \frac{i}{N} \right)^2 + \left( \frac{i}{N} \right) \left( \frac{N - i}{N} \right) \right),
\]
\[
Q_{i,\Delta}^N = \frac{\mu}{K} (1 - q) \left( \frac{i}{N} \right),
\]
\[
Q_{i,i}^N = 1 - Q_{i,i+1}^N - Q_{i,i-1}^N - Q_{i,\Delta}^N,
\]
\[
Q_{\Delta,\Delta}^N = 1,
\]
\[
Q_{i,j}^N = 0 \quad \text{otherwise.}
\]
Two Limiting Processes

We consider two limiting processes,

$$\frac{1}{N} X_N(\lfloor N^2 t \rfloor) \overset{\mathcal{L}}{\rightarrow} Y(t)$$

to investigate the behaviour when $X_N(0) \propto N$, and

$$\frac{1}{\sqrt{N}} X_N(\lfloor N^{3/2} t \rfloor) \overset{\mathcal{L}}{\rightarrow} Z(t)$$

to focus in on the behaviour for small initial numbers of $B$ genotypes, $X_N(0) \propto \sqrt{N}$. 
One: Expected Time to Arrival of an Advantageous Phenotype

\[ Y(t) \]

\[ Y(t) \] is a continuous time jump process, which jumps to \( \Delta \) after a random time, exponentially distributed with rate \( -\frac{\beta(1-q)}{K} Y(0) \).

- When the number of \( B \) genotypes is initially large, a \( C \) genotype arises well before the number of \( B \)'s appreciably change.
- \[ \mathbb{E}_{Y(0)}[\tau] = \frac{1}{\frac{\beta(1-q)}{K} Y(0)} \] is monotonically increasing in \( q \).
- This supports the “robustness reduces evolvability” view.
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This supports the “robustness reduces evolvability” view.
$Z(t)$ is a diffusion with killing, with probability density function satisfying

$$
\partial_t p(z, t) = \partial_z^2 [zp(t, z)] - \frac{\beta f K q}{P} \partial_z p(t, z) - \frac{\beta (1 - q)}{K} z p(t, z).
$$

- Only the rate of leaving $Z(t) = 0$ and arriving at $C$ really matter.
- Can get an analytic expression for $E_{Z(0)}[\tau]$, but it’s rather ugly;

$$
E[\tau | Z(0) = 0] = \frac{2 \frac{\beta f K q}{P} - 2}{\sqrt{\frac{\beta (1 - q)}{K}}} \frac{\Gamma \left( \frac{1}{2} \frac{\beta f K q}{P} \right)^2}{\Gamma \left( \frac{\beta f K q}{P} \right)}.
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One: Expected Time to Arrival of an Advantageous Phenotype

$$\mathbb{E}_N X_N(0) = 0 \begin{bmatrix} \tau \end{bmatrix}$$

This is non-monotonic (concave up) in $q$:

$$\mu = 0.001, N = 10000, P = 100, K = 20, f = 1$$
In fact, the two expressions for $\mathbb{E}_{X_N(0)}[\tau]$ coincide for large $X_N(0)$:

\[
X_N(0) = 100 \quad X_N(0) = 500 \quad X_N(0) = 1000
\]

$\mu = 0.001$, $N = 10000$, $P = 100$, $K = 20$, $f = 1$
One: Expected Time to Arrival of an Advantageous Phenotype

Initial Distribution

If we assume that prior to the change in environment, the $A$ and $B$ genotypes are in equilibrium, then the initial frequency distribution of $B$ genotypes, $\nu \sim \text{Beta} \left( N\mu \left( 1 - \frac{fK}{P} \right) q, N\mu \left( \frac{fK}{P} \right) q \right)$:

$$\mu = 0.001, \ N = 10000, \ P = 100, \ K = 20, \ f = 1, \ q = 0.05$$
Expected First Arrival Time

Integrating over this distribution gives the expected time to the arrival of $C'$:

$$\mu = 0.001, \ N = 10000, \ K = 20, \ P = 100$$

Thus, both sides of the debate are correct - at intermediate $q$, the time to adaptation is minimised.
Simple Maths vs. Complex Biology

Expected arrival time for a more fit genotype, for simulated populations of RNA using the Vienna algorithm, $N = 500$, $\mu = 0.0002$. $K$, $P$, and $f$ as determined previously.
One of the cornerstones of modern phylogenetics is Kimura’s *Molecular Clock*:

- in a population of $N$ individuals,
- that acquire neutral mutations in a Poisson process with rate $\mu_n$,
- which will eventually fix with probability $\frac{1}{N}$,

The rate of *neutral substitution* is

$$\mu_n N\frac{1}{N} = \mu_n,$$

which is *independent* of the population size.
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Genetic Hitchhiking

Kimura derived the Molecular Clock under the assumption that beneficial mutations were exceedingly rare.


A beneficial mutation could subsequently arise in an individual carrying a neutral mutation, which then “hitchhikes” to fixation with the favourable mutation.

Genetic Hitchhiking and the Molecular Clock

- It was originally suggested that hitchhiking could explain discrepancies between the fossil record and dates of species divergence estimated via the Molecular Clock.
- Some argued that neutral alleles could have increased fixation probabilities by hitchhiking with a beneficial allele.
- However, Birky & Walsh (1988) showed that hitchhiking left the fixation probability of a neutral allele unchanged.
- Their result assumes that phenotypically identical individuals, independent of their genotype, are equally likely to obtain a subsequent beneficial mutation.
- However, as we’ve seen, when one considers neutral networks, this is not necessarily the case.
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To obtain a crude estimate of the rate of neutral substitution in our model, we’ll adapt the pseudo-hitchhiking model of Gillespie (2000):

- Neutral mutations are assumed to occur at rate $\mu q$.
- A fraction $\frac{fK}{P}$ of neutral mutations are to adaptable genomes.
- Beneficial mutations occur at rate $\frac{\mu(1-q)}{K}$.
- The selective advantage of a beneficial mutation is $s \gg \frac{1}{N}$.
- Beneficial mutations fix with probability $\pi(s) = \frac{1-e^{-s}}{1-e^{-Ns}}$.
- The length of a selective sweep is $\sim \frac{\ln N}{s}$, which we will take as negligible.
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- Neutral mutations are assumed to occur at rate $\mu q$.
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Substitution Rate in the Pseudo-Hitchhiking Model

\[ N = 5000, \mu = 0.004, s = 0., N \mu q \left( \frac{fK}{P} \right) = 0.01, \frac{N \mu (1-q)}{K} = 0.001 \]
A Pseudo-Hitchhiking Estimate

Suppose a selective sweep has just occurred and the population is monomorphic:

- With probability $1 - \frac{fK}{P}$, no individual is adaptable; with probability $\frac{fK}{P}$ all individuals are adaptable.
- If no individual is adaptable, we’ve already estimated the waiting time to the arrival of a new beneficial type;

\[
\mathbb{E} [\tau_{\text{non}}] = \sqrt{N} \frac{2 \frac{\beta fKq}{P} - 2}{\sqrt{\frac{\beta(1-q)}{K} \pi(s)}} \frac{\Gamma \left( \frac{1}{2} \frac{\beta fKq}{P} \right)^2}{\Gamma \left( \frac{\beta fKq}{P} \right)}.
\]

- If all individuals are adaptable, the waiting time until the next mutation to sweep is $\tau_{\text{adapt}} \sim \text{Exponential} \left( \frac{\mu(1-q)}{K} \right)$. The probability of a neutral mutation fixing in this time is negligible.
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- If all individuals are adaptable, the waiting time until the next mutation to sweep is $\tau_{adapt} \sim \text{Exponential} \left( \frac{\mu(1-q)}{K} \right)$. The probability of a neutral mutation fixing in this time is negligible.
Thus, if $\tau_{\text{neutral}}$ is the waiting time until the arrival of the next beneficial mutation to fix, we have

$$\mathbb{E}[\tau_{\text{neutral}}] \sim \left(1 - \frac{fK}{P}\right) \mathbb{E}[\tau_{\text{non}}] + \left(\frac{fK}{P}\right) (\mathbb{E}[\tau_{\text{adapt}}] + \mathbb{E}[\tau_{\text{neutral}}])$$

i.e.

$$\mathbb{E}[\tau_{\text{neutral}}] \sim \frac{1 - \frac{fK}{P}}{\left(1 - \frac{fK}{P}\right) \mathbb{E}[\tau_{\text{non}}] + \left(\frac{fK}{P}\right) \mathbb{E}[\tau_{\text{adapt}}]}$$

which depends on population size to $O(N^{-\frac{1}{2}})$. 

Two: Neutrality, Hitchhiking, and Epistasis

A Pseudo-Hitchhiking Estimate
Two: Neutrality, Hitchhiking, and Epistasis

Theoretical Neutral Substitution Rates

\[ N = 1000, \mu = 0.01, \theta_{NE} = N\mu q, \theta_B = \frac{N\mu (1-q)}{K} \]
RNA Neutral Substitution Rates

$N = 5000$ (solid black), $N = 800$ (hollow red) $\mu = 0.004$, $s = 0.1$

Rates for RNA decrease, as the availability of beneficial mutations decrease, but remain elevated above the classical theory.
On to our third problem. Does increasing the robustness, $q$, increase or decrease the phenotypic diversity in a population?

- We will investigate $\Phi(q)$, the expected number of phenotypes that arise each generation.
- If $K = P$, increasing robustness can only reduce phenotypic diversity.
- If $q$ is large, few mutations lead to new phenotypes, so $\Phi(q)$ is eventually decreasing.
- What about a small amount of robustness? Look at $\frac{d\Phi}{dq} \bigg|_{q=0}$. 

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To begin, we need to have a sense of how many neutral genotypes are present at equilibrium.

- If $L \gg 0$, the probability that any single site in the genome receives more than one mutation is negligible.
- Every mutation gives rise to a new genotype.
- If $\theta_n = N \mu q \frac{1 - \mu^N}{1 - \mu q}$ is the normalised rate of neutral mutations and if $a_i$ is the number of alleles present $i$ times, the probability of any configuration $a = (a_1, \ldots, a_N)$ satisfies the Ewens’ distribution:

$$P(a) = \frac{N!}{(\theta_n)_N} \prod_{j=1}^{N} \frac{(\theta_n/j)^{a_j}}{a_j!}.$$
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The Moran Infinite Alleles Model

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$$P(a) = \frac{N!}{(\theta_n)_N} \prod_{j=1}^{N} (\frac{\theta_n}{j})^{a_j} \frac{a_j!}{a_j!}.$$
Mutations to new phenotypes occur at rate $\theta_q = N \mu (1 - q)$.

Let $A$ be the number of neutral genotypes present, and let $\alpha_{A,m}$ be the number of novel phenotypes that result from $m$ non-neutral mutations.

Then,

$$\Phi(q) = \sum_{m=0}^{\infty} \frac{\theta^m q^m e^{-\theta q}}{m!} \sum_{k=0}^{\infty} \mathbb{P}\{A = k\} \alpha_{k,m}.$$
From the Ewens’ distribution, we have

\[ P\{A = 1\} = 1 - \theta_0 q H_{N-1} + O(q^2), \]
\[ P\{A = 2\} = \theta_0 q H_{N-1} + O(q^2), \]

and

\[ P\{A = k\} = O(q^{k-1}) \quad k > 2, \]

where

\[ H_{N-1} = \sum_{i=1}^{N-1} \frac{1}{i}. \]
The probability that the $i^{th}$ mutation gives rise to a novel phenotype is

$$\left(1 - \frac{1}{K}\right)^{i-1},$$

so

$$\alpha_{1,m} = \sum_{i=1}^{m} \left(1 - \frac{1}{K}\right)^{i-1} = K \left(1 - \left(1 - \frac{1}{K}\right)^{m}\right).$$
Three: Expected Phenotypic Diversity per Generation

\[ \alpha_{2,m} \]

- Two genotypes: probability of \( N - i \) of the first and \( i \) of the second is (Joyce & Tavaré, 87)

\[
\left( \sum_{k=1}^{N-i} \frac{1}{\theta_n + k} \right)^{-1} \sum_{k=1}^{N-i} \frac{1}{\theta_n + k} \frac{(N-i-1)_{k-1}}{(N-1)_k}
\]

- Probability of \( j \) mutations to the first type and \( m - j \) to the second is Binomial \( (j, \frac{i}{N}) \).

- Expected number of new phenotypes resulting from \( j \) mutations to first type and \( m - j \) to second:

\[
\alpha_{1,j} + \alpha_{1,m-j} \left( \frac{fK}{P} \frac{K - \alpha_{1,j}}{K} + 1 - \frac{fK}{P} \right)
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Todd L. Parsons
Neutrality, Epistasis & Evolvability
Thus, up to $O(q^2)$,

$$\Phi(q) = \sum_{m=0}^{\infty} \frac{\theta_0^m e^{-\theta_0}}{m!} [(1 - \theta_0 q H_{N-1})\alpha_{1,m} + \theta_0 q H_{N-1} \alpha_{2,m}].$$

Lastly, if $q = 0$, there’s only one neutral genotype, so

$$\Phi(0) = \sum_{m=0}^{\infty} \frac{\theta_0^m e^{-\theta_0}}{m!} \alpha_{1,m}$$

Putting these together, we get

$$\frac{d\Phi(q)}{dq} \Big|_{q=0} = \sum_{m=0}^{\infty} \frac{\theta_0^m e^{-\theta_0}}{m!} [\theta_0 H_{N-1} (\alpha_{2,m} - \alpha_{1,m}) - (m - \theta_0) \alpha_{1,m}]$$
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For $K$ below an epistatic threshold, increasing robustness increases the phenotypic diversity.
Conclusions

- With a bit of math, we’ve been able to partially resolve debate regarding robustness and evolvability: increasing robustness can increase or decrease the rate of evolution, it all depends on how much.
- Our results show there is an optimal level of robustness $q$ that maximizes the rate of evolution.
- Can evolution lead to this optimum?
- We’ve also seen that this could substantially impact molecular estimates of divergence time.
- All of this raises questions about how we think about neutrality in evolution.
- However, this all relies on our hypotheses regarding phenotype space, which need further investigation, both mathematically and empirically.
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Thanks!

to you, for listening...

to Marek Stastna, for the opportunity to visit...

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and all the members of the Plotkin Lab, for many insightful conversations.