Exposition on Phenotype Spaces: A Topological Model of Evolutionary Proximity

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January 17, 2017

The construction of a topological space for the secondary structure of RNA molecules.

Outline

Genotype-Phenotype Relationship

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Example

The collection of genes responsible for eye color for a particular individual is the genotype and the observable eye coloration is the phenotype.

RNA: genotype sequence, primary structure

Definition

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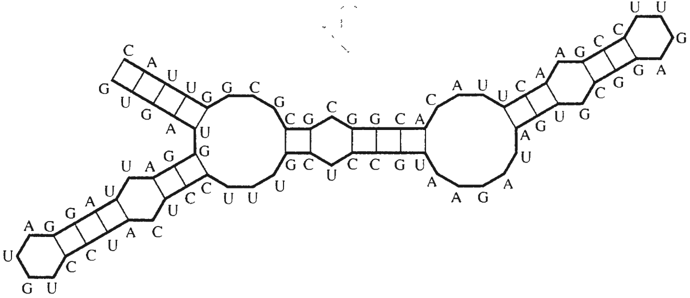

Figure 1 : RNA molecule folded and bonded chain of nucleotides.

RNA Shape Bonding Diagram

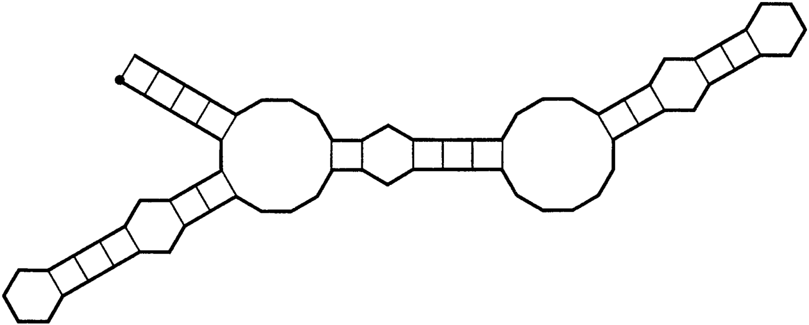

Figure 2 : RNA molecule bonding diagram (**secondary structure** or **shape**).

Different nucleotide sequences may generate the same secondary structure or shape.

RNA genotype and phenotype relationship

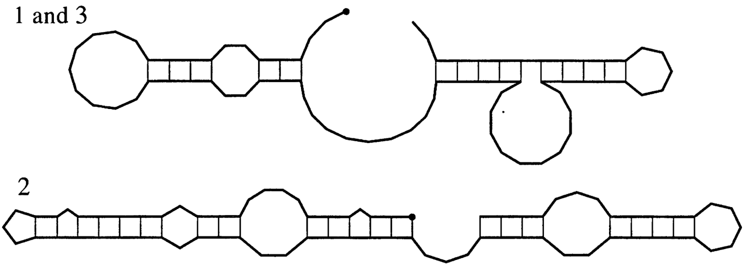

Figure 3 : Different bonding diagrams for different nucleotide sequences.

1. GGGCAGUCUC CCGGCGUUUA AGGGAUCCUG AACUUCGUCG CUCCCAUCCA AUCAGUCCGC CUCACGGAUG GAGUUG
2. GGGCAGUCUC CCGGCGUUUA AGGAAUCCUG AACUUCGUCG CUCCCAUCCA AUCAGUCCGC CUCACGGAUG GAGUUG
3. GGGCAGUCUC CCGGCCUUUA AGGGAUCCUG AACUUCGUCG CUCCCAUCCA AUCAGUCCGC CUCACGGAUG GAGUUG

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Example

GCCGCGCC
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Consider all the 10 nucleotide sequences consisting of only guanine and cytosine

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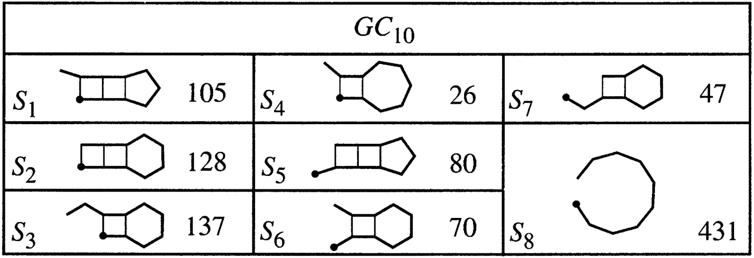

Figure 4 : The eight RNA shapes $\{\sigma_1, \ldots, \sigma_8\}$ that result from $2^{10} = 1024$ possible 10 nucleotide sequences consisting of only guanine (G) and cytosine (C).

The genotype-phenotype relationship is a many-to-one relationship.

Mathematical Model

Folding of the RNA Sequence to its Corresponding Shape

The folding process is modeled as a surjective function

$$\phi : S \to \Sigma$$

from the set S of all sequences of fixed length onto the set Σ of all minimum free energy secondary structures corresponding to that length.

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Let $\alpha, \beta \in \Sigma$, then we say that β is **accessible** from α, $\alpha \mapsto \beta$ if there exists a pair $a, b \in S$ such that a and b differ by a point mutation, and $\phi(a) = \alpha$ and $\phi(b) = \beta$.

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Let $\alpha, \beta \in \Sigma$, then we say that β is **accessible** from α, $\alpha \mapsto \beta$ if there exists a pair $a, b \in S$ such that a and b differ by a point mutation, and $\phi(a) = \alpha$ and $\phi(b) = \beta$.

Definition

The set of all genotype sequences in S that result in a particular RNA shape $\sigma \in \Sigma$ is called the **neutral network** or neutral set of σ and is denoted $N(\sigma) = \{s | \sigma = \phi(s)\}$.

Construction of Point Mutation Probabilities

Model

Let $\alpha, \beta \in \Sigma$

- $m_{\alpha,\beta}$ is the number of point mutations that change a sequence from $N(\alpha)$ to $N(\beta)$

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- Note that $m_{\alpha,\beta} = m_{\beta,\alpha}$
- $m_{\alpha,\star}$ is the number of point mutations that change a sequence to a sequence in any other neutral network.

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Definition

The **mutation probability**, $p_{\alpha,\beta}$ is defined by

$$\boxed{p_{\alpha,\beta} = \frac{m_{\alpha,\beta}}{m_{\alpha,\star}}}$$

Notice that $p_{\alpha,\beta}$ may not necessarily be equal to $p_{\beta,\alpha}$ since $m_{\alpha,\star}$ may not equal $m_{\beta,\star}$. Hence, the mutation probability is asymmetric and does not serve as a metric for mutation probabilities.

Definition Metric (Distance Function)

Definition

Let X be a non-empty set. A real-valued function d defined on $X \times X$, i.e. ordered pairs of elements in X, is called a **metric** or **distance function** on X iff it satisfies, for every $a, b, c \in X$ the following axioms:

(M1) $d(a, b) \geq 0$ and $d(a, a) = 0$

(M2) (Symmetry) $d(a, b) = d(b, a)$

(M3) (Triangle Inequality) $d(a, c) \leq d(a, b) + d(b, c)$

(M4) If $a \neq b$, then $d(a, b) > 0$

Table 1 : Mutation probabilities for the RNA shapes $\sigma_1, \ldots, \sigma_8$.

	σ_1	σ_2	σ_3	σ_4	σ_5	σ_6	σ_7	σ_8
σ_1		0.13	0.15	0.08	0.07	0.09	0.04	0.44
σ_2	0.11		0.15	0	0.11	0.18	0.05	0.40
σ_3	0.12	0.15		0.03	0.09	0.06	0.05	0.50
σ_4	0.29	0	0.14		0.07	0.09	0.06	0.35
σ_5	0.08	0.15	0.12	0.02		0.08	0.08	0.47
σ_6	0.12	0.29	0.09	0.03	0.09		0.03	0.35
σ_7	0.08	0.12	0.13	0.03	0.13	0.05		0.46
σ_8	0.18	0.19	0.24	0.04	0.15	0.11	0.09	

Construction RNA Shape Space

Algorithm 1 Construction RNA Shape Space

for $i = 1, \ldots, 8$ **do**
  Let $R_i = \{\sigma_i \cup \{\sigma_j | p_{i,j} > 1/7\}\}$
end for

Mutation Probabilities

Table 2 : Construction of $\mathscr{R}_{1/7}$ from Table 1 Mutation probabilities.

	σ_1	σ_2	σ_3	σ_4	σ_5	σ_6	σ_7	σ_8
σ_1	✓		✓					✓
σ_2		✓	✓			✓		✓
σ_3		✓	✓					✓
σ_4	✓			✓				✓
σ_5		✓			✓			✓
σ_6		✓				✓		✓
σ_7							✓	✓
σ_8	✓	✓	✓		✓			✓

$$\mathscr{R}_{1/7} = \{\{\sigma_1, \sigma_3, \sigma_8\}, \{\sigma_2, \sigma_3, \sigma_6, \sigma_8\}, \{\sigma_2, \sigma_3, \sigma_8\}, \{\sigma_1, \sigma_4, \sigma_8\}, \{s_2, s_5, s_8\}, \{\sigma_2, \sigma_6, \sigma_8\}, \{\sigma_7, \sigma_8\}, \{\sigma_1, \sigma_2, \sigma_3, \sigma_5, \sigma_8\}\}$$

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σ_6		✓				✓		✓
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σ_8	✓	✓	✓		✓			✓

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(Note:$\mathscr{R}_{1/7} = \{R_i\}_1^8$ is not a topology.)

Definition Topological Space

Definition

Let X be a nonempty set. A collection $\mathcal{T}$ of subsets of X is a **topology** on X if and only if $\mathcal{T}$ satisfies the following axioms:

O1: $\emptyset$ (empty set) and X are in $\mathcal{T}$.

O2: The union of the elements of any subcollection of $\mathcal{T}$ is in $\mathcal{T}$.

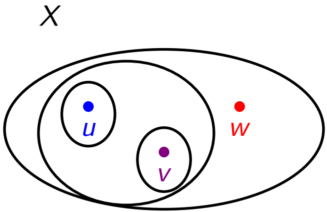
O3: The intersection of the elements of any finite subcollection of $\mathcal{T}$ is in $\mathcal{T}$.

The members of $\mathcal{T}$ are then called $\mathcal{T}$-**open sets**, or simply **open sets**. The pair $(X, \mathcal{T})$ is called a **topological space**.

Example Topological Space

Example

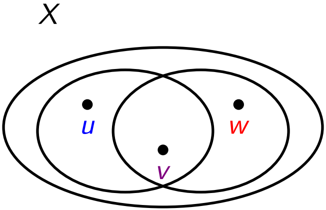
$X = \{u, v, w\}$, $\mathcal{T} = \{X, \emptyset, \{u\}, \{v\}, \{u, v\}\}$



Non-Example Topological Space

Example

$X = \{u, v, w\}$, $\mathcal{T} = \{X, \emptyset, \{u, v\}, \{v, w\}\}$ is **NOT** a topology on X. Why?



Construction of the minimal basis for the phenotype space of RNA shapes.

Algorithm 2

Extend $\mathscr{R}_{1/7}$
Let $\mathscr{T}_{1/7}$ be the **minimal topology** on GC_{10} containing $\mathscr{R}_{1/7}$.
for σ_i **do**
  take all of the sets R_j that contain σ_i
  let B_i be their intersection.
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$\mathscr{B}_{1/7} = \{B_i\}_{i=1}^{8}$ is the minimal basis for $\mathscr{T}_{1/7}$

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This resulting topological space is referred to as a **phenotype space**.

Definition Basis

Definition

Let X be a set and $\mathscr{B}$ be a colection of subsets of X. We say $\mathscr{B}$ is a **basis** (for a topology on X) if the folowing statements hold:

(i) For each $x \in X$, there is a $B \in \mathscr{B}$ such that $x \in B$.

(ii) If B_1 and B_2 are in $\mathscr{B}$ and $x \in B_1 \cap B_2$, then there exists B_3 in $\mathscr{B}$ such that $x \in B_3 \subset B_1 \cap B_2$.

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Let $\mathscr{B}$ be a basis on a set X. The **topology** $\mathscr{T}$ **generated by** $\mathscr{B}$ is obtained by defining the open sets to be the empty set and every set that is equal to a union of basis elements.

Basis $\mathscr{B}_{1/7}$ for topology $\mathscr{T}_{1/7}$

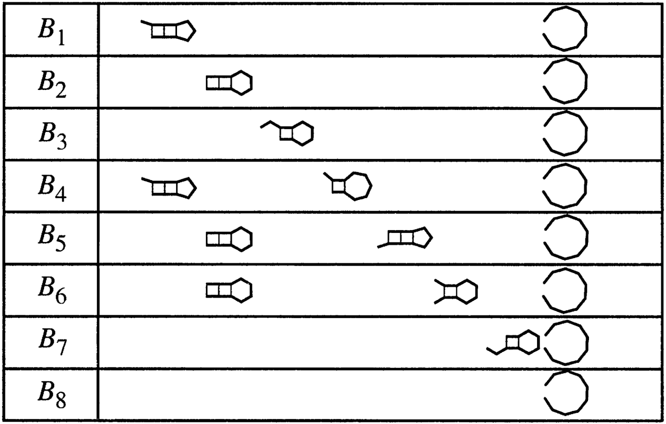

Figure 5 : Basis $\mathscr{B}_{1/7}$ for topology $\mathscr{T}_{1/7}$

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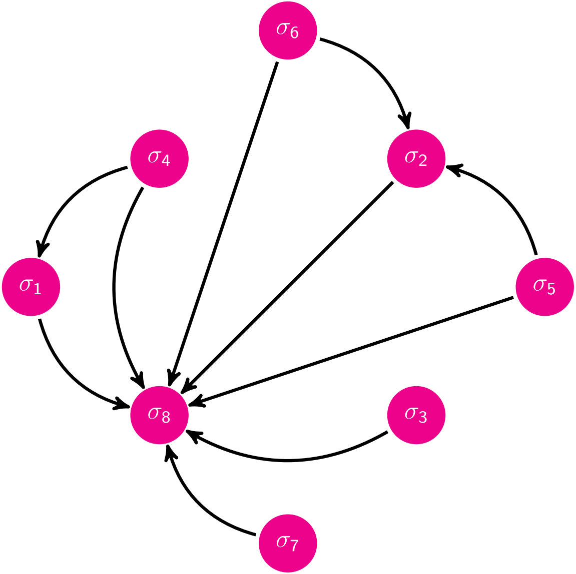

Figure 6 : Basis $\mathscr{B}_{1/7}$ represented by a directed graph.

This gives a formal way of defining continuous and discontinuous evolutionary changes.

Basis $\mathscr{B}_{1/10}$ for topology $\mathscr{T}_{1/10}$

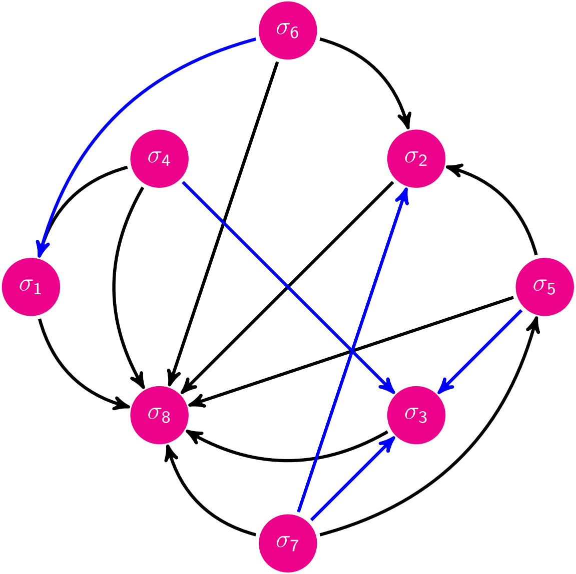

Figure 7 : Basis $\mathscr{B}_{1/10}$ represented by a directed graph.

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Thank you!

Questions?