International Journal of Advanced Computer and Mathematical Sciences ISSN 2230-9624.
Vol 2, Issue 3, 2011, pp 117-125 http://bipublication.com

FUZZY PROXIMITY IN PHENOTYPE SPACE

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ABSTRACT:
Evolutionary change in biology is the change in genetic material of a population of organism, through successive generation. The course of biological evolution cannot be understood without the dichotomy of genotype-phenotype. The mapping φ from genotype to phenotype hence lies at the heart of any meaningful theory of evolution. Different types of generalized topologies (pretopology, peritopology etc); are being used to model the genotype and phenotype spaces. In this paper we have attempted to study the model using fuzzy topology. We have also discussed the continuity of evolutionary map in this setting.

Keywords: Genotype, Phenotype, Evolutionary map, Fuzzy topology. 2010, Mathematical subject classification, Primary 92C40, 92D15, 92D20; Secondary 54A40. 54A05,

1. INTRODUCTION:

Evolutionary biology concerns the extent to which the history of life has proceeded gradually or has been punctuated by discontinuous transition at the level of phenotypes. To distinguish continuous from discontinuous evolutionary changes, a relation of nearness between the phenotypes is needed. Genotype and phenotype are two aspects of same molecule, genotype is internally coded, inheritable information possessed by all living organisms, while the phenotype is the physical realization of that information. For example, the collection of genes responsible for eye color in a particular individual is a genotype. The observable eye coloration in the individual is the corresponding phenotype. The idea of phenotype demonstrated on the ribonucleic acid (RNA) is ideally suited to explore the concepts of evolution in a wide context and it is also simple in computational matter. The nucleotide chain that is unfolded is called the genotype (primary structure) for the molecule, composed of letters A, G, C and U namely adenine ,guanine, cytosine and uracil respectively, and the associated bonding diagram of it is called phenotype. It is also referred to as the RNA shape or secondary structure. All the secondary structures used in the discussion is of minimum free energy with fixed length. There is a unique RNA shape which is associated to each genotype sequence; as a result of this we get the canonical map from the set of genotype to phenotype. This canonical map in not one-to-one since, multiple genotype sequences can result in the same RNA shape.

Fontana, Stadler, Stadler, and Wagner argue that “continuous” changes in the RNA sequences can lead to apparent jumps at the phenotypic level, so that evolution is not solely influenced by natural selection and genetic drift, but is also directed by internal dynamics[12].If

the phenotypes are organized according to the genetic accessibility, the resulting space lacks a metric and is formalized by an unfamiliar structure, known as a pertopology. Fontana and Schuster [4, 5] and Cupal et al.[2, 8] equipped then phenotypes with topology based on probability of mutation. Stadler et al.[9] suggested that the set of phenotypes P with a pretopology defined in terms of the GP-map $\boldsymbol{f : G \rightarrow P}$ can describe the evolutionary mechanism. . In order to analyze the "jumps" in the shapes of RNA sequences, the authors equip the genotype set with a *pretopology* [11]. A probabilistic version of pretopology was also suggested by Stadler and Stadler (2006). Fredric et al [8] improved the model by considering probabilistic atopology. They also proposed an alternative model which is intrinsically non-topological.

The problem with this structure is the need of selection of a cut-off value. It was pointed out in Stadler et al.[12] that the need for an ad-hoc choice of a cut-off point is not satisfying and calls for the introduction of a probabilistic or fuzzy version of topology. Such a probabilistic version was briefly discussed in Stadler and Stadler [13] and further pursued by Mynard et al.[6].

The motivation behind introducing proximity notion in phenotype set is to discuss continuity of evolutionary trajectory. However to discuss continuity using the above models we need to select some threshold value and it is very difficult to decide upon some biologically meaningful threshold value. We consider this as a major disadvantage of the existing models. So to overcome the problem of selecting a threshold value we propose a generalized model which will encompass the existing model. Our model will involve notion of fuzzy set theory. We discuss some preliminary notions of fuzzy set and fuzzy topology in the next section.

2. Brief review of accessibility notion on genotype:

The structure of genotype space is uniquely determined by the genetic operators at work: mutation, recombination, genome rearrangements, etc. In the case of point mutations and constant length genomes the situation is straight forward. Naturally, sequences that differ by a single mutation are neighbors in "sequence space". Each sequence of the genotype set is a word of length l, which can "mutate" into any of its $3l$ *one-error mutants*, that is, into any of the sequences that differ in exactly one coordinate from it. The genotype set becomes the set of vertices of a Hamming graph (in which two sequences are adjacent if and only if they differ in one coordinate), with a loop added at each vertex, so that a sequence is allowed to avoid mutation. In the model proposed in Stadler et al. (2001), the loop at each vertex is not added and non-mutation is not considered. However Mynard(2010) chose to endow each edge (including the loop at each vertex) with a probability $1/3l+1$, so a random walk on this graph therefore represents a series of mutations occurring—or not—at regular time intervals. For simplicity, we denote the resulting weighted digraph by G again. The phenotype set is then the vertex set of the quotient graph P induced by f . To describe this graph, let us denote the probability that a sequence $x \in G$ mutates into a sequence $y \in G$ by

$$\text{Prb}(y \cap x) = \begin{cases} \frac{1}{3l+1} & \text{if } d(x,y) \leq 1 \\ 0 & \text{else} \end{cases}$$

where $dG : G \times G \rightarrow N$ denotes the Hamming distance in G between two sequences (so that $dG(x, y) \leq 1$ iff $x = y$ or y is a one-error mutant of x). In above probability of transition, we make an explicit choice of a probability of transition, but only to illustrate how such probabilities lead to the neighborhood structure. Indeed, while it might reflect the process by which mutants are produced, the actual probability of transition to a specific genotype at the individual and population levels is clearly much more complex.

However, another way to define the probability of transition is

$$\text{Prb}(y \cap x) = \begin{cases} 1 - m & \text{if } x = y \\ \frac{m}{3l} & \text{if } d(x,y) = 1 \\ 0 & \text{else} \end{cases}$$

Where $m : N \rightarrow [0, 1]$ is the relatively small probability of mutation then the earlier. Of course, other possibilities for Prb($y \cap x$) could be explored.

The probabilities of transition defined above deals with only for one and less than one point mutation only but it can be improved further for more than one point mutation. It may be much more complex and influenced by various biological factors. All the specific probabilities appear in the discussion are just to understand the mathematical aspects, rather than to provide meaningful quantitative information. Although we can treat these to be possibility of transition by relaxing the restriction of sum of total probability is one. We like to mention that for a particular mutation also the possibility of transition may possess different values, suppose for one point mutation it will takes different values and similarly for more point mutation also it holds the same.

The possibility of transitions in the sequence space G leads us to a meaningful notion of fuzzy set assign to each sequence on *G*. A sequence in *G* possesses different possibilities to attain any other sequence in *G* through several mutations; we can assign those possibilities of transition to each of the sequence as some grades for their attainability. Keeping all these aspects in mind, we obtain each sequence of *G* to be a fuzzy subset of *G* with membership functions define like,

$\mu^{si} : G \rightarrow [0,1]$, i= 1, 2, 3,… ,L

where L(=4^l) in the number of sequences and l is the length of a sequence in *G*. which may be one of the possibility of transitions of the sequences. Taking all these fuzzy set to be a fuzzy neighborhood of an element of G, we get a system fuzzy neighborhood by collection all the fuzzy neighborhoods of the elements of G. Each of these fuzzy neighborhoods contains all the elements of G with different grade.

If the collection of all the fuzzy neighborhoods on *G* is considered to be a fuzzy sub-base, we get the required fuzzy topology on the set *G* of genotype by taking finite intersection and arbitrary union of the fuzzy neighborhoods on *G*.

3. BRIEF REVIEW OF ACCESSIBILITY RELATION AND ACCESSIBILITY TOPOLOGY:

One obvious approach would be to simply define a distance measure between shapes based on morphological comparison and then derive a notion of neighborhood. This would yield a metric space of shapes. The problem with this procedure is that it does not reect evolutionary accessibility among shapes; because the variational operators

underlying the definition of shape distance do not correspond to physical events or processes that occur naturally. In evolution, a shape is modified through mutations in the underlying sequence, rather than by direct modification of the shape, and the phenotypic effect of a mutation is determined by the folding map. An evolutionary meaningful relation of nearness between shapes must be mediated by the folding map and not be independent of it. A structure β which is highly dissimilar from a structure α on syntactic ground might nonetheless be near to α on the count of being accessible from α by a small mutation in α's sequence. Alternatively, among two syntactically highly similar structures, one might nonetheless fail to be evolutionarily accessible from the other. Notice that such a relation of accessibility does not quantify distance, but expresses a weaker notion of neighborhood. Pursuing this line we are led to a topology rather than a metric on the set of phenotypes. **T**he set of possible sequences (of fixed length) is naturally organized into a shape because point mutations induce a canonical neighborhood. The neighborhood of a sequence consists of all one –error mutants. The problem is how to organize the set of possible shapes into a space.

Accessibility means that a sequence whose shapes is β arises by mutation from a sequences whose shapes is α. Shape β near to a shape α if β is very likely to be accessible from α. The easy accessibility of phenotypes estimate a statistical frequency with which a mutation in α's sequences yields the mutant shape β. When a shape α is realized by a large class of sequences, "nearness" of β to α comes to mean that β must arise from α with a high probability when averaged over all sequences folding into α[4].

Similar types of accessibility in [5] is defined like this β is accessible from α, or $\beta \leftarrow \alpha$, if there exists a pair $x.y \in G$ with $d(x,y)=1$ and $f(x)=\alpha$ and $f(y)=\beta$, where $f : G \rightarrow P$, GP-map and d represents the hamming distance. In this notation the set of structures accessible from α is written as a $\{\beta \mid \beta \leftarrow \alpha\}$. Here the authors have described two frequency ratios based on the multiplicity of accessibility of phenotypes regarding how often they occur. One is the *neighborhood frequency* $\nu(\beta, \alpha) = N(\beta, \alpha) / N_\alpha$ and the other is the *occurrence frequency* $\upsilon(\beta, \alpha) = N(\beta, \alpha) / 3lN_\alpha$, l is the length of a sequence in the sequence space. Then the authors construct the required topology on the set of RNA-shapes with neighborhood defined like

$$\psi_\in(\alpha) = \{\beta \in P \mid \rho(\beta, \alpha) \geq \in\},$$

Where $0 < \in \leq 1$ and $0 \leq \rho(\beta, \alpha) \leq 1$ denotes a measure for the frequency of β in the boundary of S_α, such as $\nu(\beta, \alpha)$ or $\upsilon(\beta, \alpha)$. Note that in general $\rho(\beta, \alpha)$ is not symmetric. Technically a neighborhood of α is any set $\psi_\in(.)$ containing α.

Cupal, J., Kopp, S., Stadler, P.F. (2000) a topology that is derived from the probabilities with which of one phenotype is accessible from another through changes at the genotypic level. Since sequence space is so large that not all possible sequence are ever realized in the course of simulation run (or during the history of evolution), Fontana & Schuster [4] argue that one should consider more restrictive condition for accessibility. The authors have said that β is accessible fromα, only if the probability is high enough that a population located on the neutral network S(α) will find a sequence

folding into β. Let us write $\partial S(\alpha)$ for the set of all sequences that are obtained as point mutations of elements from the neutral set $S(\alpha)$ and that are not themselves members of $S(\alpha)$. The set $\partial S(\alpha)$ is known as the boundary of $S(\alpha)$ in sequence space. We may now consider the distribution of structures that are formed by the sequences in $\partial S(\alpha)$. For any two structures α; $\beta \in P$ define $D(\beta \leftarrow \alpha) = S(\beta) \cap \partial S(x)$ as the set of all neighbors of α that fold into β. Accessibility may now be based on the size of $D(\beta \leftarrow \alpha)$ relative to $S(\alpha)$, $S(\beta)$, or their boundaries. Probably the most natural quantity is the ratio probability $|D(\beta \leftarrow \alpha)| = |\partial S(\alpha)|$ that a non-neutral mutant of an α-sequence folds into the shape β. In [4] two related measures are used: The neighborhood frequency $\nu(\beta; \alpha)$ is the fraction of sequences folding into α that have at least one neighbor folding into β. Conversely, the frequency of occurrence $\nu(\beta; \alpha)$ is the fraction of mutants of α- sequences that fold into β. In symbols :

$$\nu(\beta,\alpha) = \left| S(\alpha) \cap \partial S(\beta) \right| / \left| S(\alpha) \right| = \left| D(\alpha \rightarrow \beta) \right| / \left| (S(\alpha) \right|$$

$$\upsilon(\beta, \alpha) = \left| S(\beta) \cap \partial S(\alpha) \right| / \left| (\eta - 1)^{l} S(\alpha) \right| = \left| D(\beta \rightarrow \alpha) \right| / \left| (\eta - 1)^{l} S(\alpha) \right|$$

where η=4 for natural RNA sequences and *l* is a length of a sequence in the sequence space.

A simple possibility for defining accessibility is to set a threshold value $\in > 0$. Hence $\beta \leftarrow \alpha$ iff $\left| D(\beta \leftarrow \alpha) \right| \geq \in \left| \partial S(\alpha) \right|$. A related class of accessibility relations arises by ranking the neighbors of α with respect to $\left| D(\beta \leftarrow \alpha) \right|$ and accepting only a fixed number highest –ranking structures as accessible. A threshold could be also introduced individually for each x depending on the form of the size distribution of the sets $\left| D(\beta \leftarrow \alpha) \right|$ or $\left| D(\alpha \leftarrow \beta) \right|$. Given a shape α, a shape β may be accessible from α with respect to some $\in > 0$ and may not be so with respect to another. So we see that this notion of accessibility is not a crisp concept but a graded one.

Let $N(\alpha) = \{\beta \in P : \beta \leftarrow \alpha\}$ be the set of the structures that are accessible from α (including α itself). Any particular definition of accessibility hence translates into a finite collection

$N = \{ N(\alpha) : \alpha \in P\}$ of subsets of the shape space P, such that $\alpha \in N(\alpha)$ for all $\alpha \in P$.

N considered as a sub-basis generates a topology in P. This is a finite topology and so there exists a unique non-redundant basis, $B = \{ B(\alpha) = \cap N(\beta) : \alpha \in N(\beta) , \alpha \in P\}$.

In [12] Stadler et al, presents different neighborhood structures like accessibility pretopology ξ_a , shadow pretopology ξ_s. The accessibility pretopology is in fact the quotient pretopology on P given by the GP map *f* and the pretopology on G induced by the adherence operator adh_ξ, where $adh_\xi A = \{ x \in G : \exists\, y \in A, d_G(x, y) \leq 1\}$, $A \subseteq G$ and $d_G : G \times G \rightarrow \mathbf{N}$ is the hamming distance. In accessibility pretopology a phenotype α is in the ξ_a -neighborhood of β when $\alpha = f(x)$, for a one-error mutant x of a sequence y such that $f(y) = \beta$, where *f* is the folding map. In other words $N\xi_a(\beta)$ is the set of all phenotypes that are accessible from β by a single mutation. In shadow pretopology, α is in the ξ_s -neighborhood of β if every sequence y folding into β admits a one-error mutant x folding into α. These are two extreme requirements. The former is too weak a condition to be a neighborhood

whereas the later is too strong a requirement. A more meaningful structure is also proposed where the neighborhood structure is given by

$N\xi_\delta(\alpha) = \{\beta \in P : Prb(\alpha \leftarrow \beta) \geq \delta\}$- - - - (i)

where $Prb(\alpha \leftarrow \beta)$ gives the like hood (probability) of phenotype α changing to β. Mynard et al.[13] showed that ξ_δ defined by (i) satisfies the following :

(1) $\xi_\delta \geq \xi_a$ for every $\delta > 0$;

(2) $\xi_\delta = \xi_a$ for every $\delta \in (0, \min\{ [1/(3l+1)|f^{-1}(\alpha)|] : \alpha \in P\}$;

(3) ξ_δ may not be comparable with ξ_s.

They have argued that a biologically realistic cut-off δ consistent with the approach in Stadler et al. must satisfy $\min\{ [1/_{(3l+1)|f^{-1}(\alpha)|}] : \alpha \in P\} < \delta < \min\{Prb(\alpha \leftarrow \alpha) : \alpha \in P\}$. The problem with this structure is the need of selection of a cut-off value. It was pointed out in Stadler et al.[12] that the need for an ad-hoc choice of a cut-off point is not satisfying and calls for the introduction of a probabilistic or fuzzy version of topology. Such a probabilistic version was briefly discussed in Stadler and Stadler [11] and further pursued by Mynard et al.[6].

Again in [13] a *accessibility closure* on the phenotype defined for a set Φ of phenotypes consists of all mutants arising from $f^1(\Phi)$ by

$$C_\infty(\Phi) = f(Cl(f^1(\Phi))$$

Also defined a more restrictive closure for a small population on the phenotype space

$$C_E(\Phi) = f(Cl(f^1(\Phi) \cap E)$$

Note that $C_E(\Phi) \subseteq C_\Phi(\Phi)$ whenever $E \subseteq \Phi$, i.e., smaller population produce an effectively finer closure function on phenotype, and say that ϕ is easy accessible from ξ if $n^*(\phi,\xi)$ exceeds some threshold value.

4. FUZZY TOPOLOGY

In this section we discuss some preliminaries on fuzzy sets and fuzzy topology that will be required in the sequel.

Fuzzy (sub)sets are generalization of classical (sub)sets. In a classical subset an element of the universal set either belongs to the subset or not which can be identified by the corresponding characteristic function $\chi_A : X \rightarrow \{0, 1\}$ such that $\chi_A(x) = 1$, if $x \in A$ and $\chi_A(x) = 0$, if $x \notin A$. Here the boundary of a fuzzy subset is not precisely defined and so an element of the universal set belongs to the fuzzy subset with some level of membership which can be identified by the membership function μ_A. In short fuzzy set expresses the concept of graded membership.

Mathematically a fuzzy set A of a universal set X is a function

$\mu_A : X \rightarrow [0,1]$

For each $x \in X$, $\mu_A(x)$ is called the membership grade of x in A. For convenience the fuzzy subset as well as the corresponding membership function is represented by μ.

The family of all fuzzy sets of X consisting of all the mapping from X to I = [0,1] is denoted by I^X.

Given a fuzzy set A defined on X and any number $\alpha \in [0, 1]$, the α-cut, ${}^\alpha A$ and the strong α-cut, ${}^{\alpha+}A$ are the crisp sets

$${}^\alpha\mu_A = \{x \mid \mu_A(x) \geq \alpha\}$$
$${}^{\alpha+}\mu_A = \{x \mid \mu_A(x) > \alpha\}.$$

Thus α-cut of A is a classical subset of X consisting of all elements whose grade of membership in the fuzzy subset A is greater than or equal to α. Similarly the strong α-cut of A is a classical subset of X consisting of all elements whose grade of membership in the fuzzy subset A is strictly greater than α.

Given two fuzzy sets, A and B, their standard intersection, $A \cap B$, and standard union $A \cup B$, are defined for all $x \in X$ by the equations

$\mu_{A \cap B}(x) = \min [\mu_A(x), \mu_B(x)]$

$\mu_{A \cup B}(x) = \max [\mu_A(x), \mu_B(x)]$.

For infinite collection of fuzzy subsets, min and max are respectively replaced by infimum and supremum.

Let X be a non- empty set and *T* be a class of subsets of X. *T* will be called a (classical) topology on X, if

T1. $\Phi, X \in T$

T2. Arbitrary union of sets of *T* is in *T*.

T3. Finite intersection of sets of *T* is in *T*

Each member of T is called an open subset of X and complement of an open subset is called a closed subset.

(X, T) is called a topological space.

A collection of subsets of X is called a base if the arbitrary union of members of the collection is a topology on X and a collection of subsets of X is called a sub-base, if finite intersection of members of the collection gives a base for some topology on X. It is to be noted that any collection of subsets of X will be a sub-base for some topology on X provided the union of the collection is equal to X.

Let X be an arbitrary set, Y a topological space and *f* is a function from X into Y. The topology generated (induced) on X by the sub-base consisting of all inverse images of the open subsets of Y is called the initial topology on X. With respect to this initial topology the map from X to Y is continuous.

If in the definition of classical topology we replace the classical subsets by fuzzy subsets then what we get is called a fuzzy topology. In a similar manner we define fuzzy base, fuzzy sub-base and fuzzy initial topology.

A fuzzy subset μ is said to be a fuzzy neighbourhood of a point $x \in X$ if there exist an open fuzzy subset ν such that $\nu(x) > 0$ and $\nu \subseteq \mu$.

A map from a fuzzy topological space X to a fizzy topological space Y is said to be continuous if the inverse image of every open fuzzy set in Y is open in X.

The fuzzy topology on R (real numbers) consisting of all lower semi-continuous function from R to [0, 1] is called the usual fuzzy topology on R.

5. PHENOTYPIC NEARNESS WITH FUZZY TOPOLOGY:

Due to the difficulty of determining a realistic probability of transition between phenotypes that needs of an ad-hoc choice of a cut-off point, we base ourselves on the model that defines a induced fuzzy topological on the set P of phenotypes by the canonical map $f: G \to P$. We already have a fuzzy topological space on the set *G* of genotype and the phenotypes with the canonical map divides the set of genotypes into disjoint equivalent classes. So, it is natural to consider the quotient fuzzy topology on the set *P* of phenotype induced by the canonical map $\varphi: G \to P$. With this required fuzzy topology on the set of phenotypes, we are free from the difficulty to find the cut-off value for the accessibility of the phenotypes.

6. EVOLUTIONARY TRAJECTORY AND CONTINUITY

An evolutionary trajectory is a map ϕ from the time axis into phenotype space. The first question that arises is what neighbourhood structure should be considered in the phenotype space P. We have seen that the issue concerning the

(pre)topology in P is to find a consistent way to pick a suitable cut-off value of δ. To overcome this we have fuzzified the neighbourhood structure. The second question is regarding the neighbourhood structure in the time axis T. The time axis is usually described as well-known topological space, namely the real line with its standard (usual) topology. In the case of computer simulations and samples from the fossil record, which intrinsically represent time in the form of discrete steps, it is more natural to use the pretopology corresponding to the directed infinite path graph. In [9] Stadler et al, time axis T is taken to be discrete (the set of natural numbers) equipped with natural pretopology. The evolutionary map ϕ can be considered as composition of the genotype-phenotype map f and a map g from time axis to the genotype space, i.e., $\phi = gof$, where g describes the state of a sequence at time t. In Stadler et al.[9] the authors suggest possibility of multiple mutations between time t and t+1. But this does not seem consistence with the selection of discrete time [6].

Time flows continuous; however mutation/transformation takes place at discrete level. Suppose at instant t_0 the state of a sequence is x_0. The sequence mutates to x_1 at instant t_1, i.e., in the period $[t_0, t_1)$ the sequence x_0 does not change. Again at instant t_2 the sequence mutates to x_2. Thus mutation is taking place at discrete level while time is flowing continuously. So we prefer to take the time axis as positive real line $[0, \infty)$. Further as P equipped with the quotient fuzzy topology we feel it is natural to equip $[0, \infty)$ with the fuzzy usual topology. Also with the quotient fuzzy topology on P the folding map $f : G \to P$, is essentially continuous. Then discontinuity of the evolutionary map will depend upon the continuity of the map g. It may be noted that by replacing $[0, \infty)$ with the real line (with fuzzy usual topology) will not affect the continuity of the evolutionary map. So we can just consider the evolutionary trajectory as a map $\phi : R \to P$ where R and P have the relevant fuzzy topologies. However as all our practical studies will always involve finite time period we can simply restrict ourselves to some finite interval say, [a, b].

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