Generalized Topological Spaces in Evolutionary Theory and Combinatorial Chemistry

Bärbel M. R. Stadler* and Peter F. Stadler
Institut für Theoretische Chemie und Molekulare Strukturbiologie Universität Wien
*Corresponding author: Tel: ++43 1 4277 52745, Fax: ++43 1 4277 52793, Email: baer@tbi.univie.ac.at
www.tbi.univie.ac.at~{baer,studla}

June 21 2001

The search spaces in combinatorial chemistry as well as the sequence spaces underlying (molecular) evolution are conventionally thought of as graphs. Recombination, however, implies a non-graphical structure of the combinatorial search spaces. These structures, and their implications for search process itself, are heretofore not well understood in general. In this contribution we review a very general formalism from point set topology and discuss its application to combinatorial search spaces, fitness landscapes, evolutionary trajectories, and artificial chemistries.

1 INTRODUCTION

Fitness and energy landscapes have become a unifying theme in fields as diverse as drug design, spin glass physics, molecular structure, protein folding, combinatorial optimization, and evolutionary theory since they were first introduced as models of biological adaptation in the 1930s [1]. In each case, there is a function f, e.g., a molecular index, a Hamiltonian, a cost-function, or a fitness, that evaluates each member $x \in X$ of a (usually very large) configuration set X. These configurations can be (organic) molecules, spin configurations, conformations of polypeptide chain, tours of a TSP, or genotypes of viruses or living organisms. Implicitly, we are also given an additional structure on X that describes a notion of nearness, reachability, distance, separatedness, or similarity. In QSAR [2, 3], for example we have a measure of similarity or distance between the molecular graphs, maybe in terms of the number of synthesis steps in which they differ; spin configurations may be related by the number of spin flips that inter-convert them. In the case of a peptide chain we might be interested whether one conformation can be converted into the other with a small number of rotations around backbone bonds without steric obstructions, and biological genotypes are related by the genetic operators mutation, recombination, duplication, deletion, and (gene)-rearrangement.

Most of these examples have an inherently discrete configuration space X, in the following sense: (i) X is finite (but typically very large), or (ii) there is no meaningful notion of two configurations being "arbitrarily close" together. Two configurations of an Ising spin glass, for instance, are either identical or they differ by inverting the orientation of at least one spin. The potential energy surface of a molecule, on the other hand, is a manifold and hence smooth. The underlying configuration space is the high-dimensional Euclidean vector space of atomic coordinates.

Molecular potential energy surfaces, which constitute one of the most important issues of theoretical chemistry, are therefore usually dealt with in the language of differential geometry [11, 12]. On the other hand in the context of combinatorial optimization and molecular biology an essentially graph-theoretical formalism has been developed [13, 14, 15, 16, 17]. The physics of disordered systems is commonly described in the language of statistical mechanics [18]. The few examples mentioned in the previous paragraphs emphasize the fact that landscapes have the real valued function $f : X \to \mathbb{R}$ in common, while the *structure* of the underlying *configuration space* can be vastly different. It is highly desirable, therefore, to have a formalism that, at least at the conceptual level, can deal with all the examples above and that, in particular, bridges the gap between combinatorial models on the one hand and the

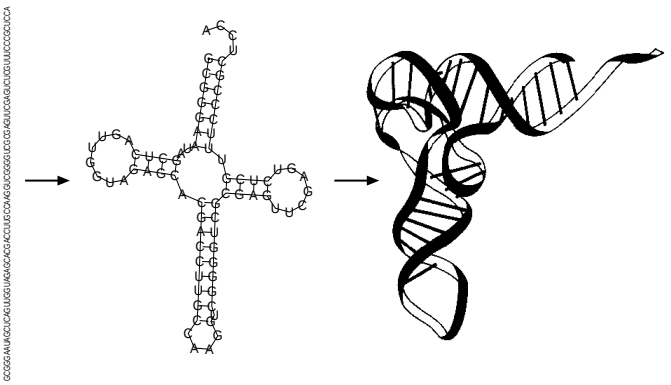

Figure 1: An RNA molecule folds by first establishing the secondary structure (pattern of base pairs) which in a second step forms the three-dimensional structure of the molecule. Secondary structures are not only good approximations to the actual 3D structure but they can also be computed efficiently given only the sequence information by means of a dynamic programming algorithm [4, 5]. An RNA molecule is both genotype (its sequence is genetic information) and phenotype (its 3D shape can bind specifically to other molecules or even perform catalytic functions), which can then be "evaluated" by the environment e.g. in a replication [6] or a SELEX [7] experiment. RNA models thus serve as a paradigm of biologically realistic fitness landscapes. These are also based on the concatenation of the genotype-phenotype map (RNA folding in this case) and subsequent evaluation of the phenotype (here: structure). For details we refer to the literature, e.g. [8, 9, 10].

differentiable surfaces on the other hand.

Much of the work reported here is the out-flow of the realization that there is a significant discrepancy between the current implementation of the Neo-Darwinian model of evolution and computational case studies [19]. The theory typically assumes that the set of possible phenotypes is organized into a highly symmetric and regular space equipped with a notion of distance; most conveniently, a Euclidean vector space [20]. Recent computational work on a biophysical genotype-phenotype model based on the folding of RNA sequences into their secondary structures, Fig 1, however, suggests a rather different picture [21, 22, 23]: If phenotypes are organized according to genetic accessibility, the resulting space lacks a metric and is formalized by an unfamiliar structure, in the simplest case a *pretopology* [19]. A related study on the structure of the genotype spaces that are induced by so-called unequal cross-over (or non-homologous recombination) [24] shows, furthermore, that pretopologies are adequate for mutation spaces but behave somewhat "unnatural" for certain recombination spaces.

This contribution is organized as follows: In section 2 we review some basic results from generalized point set topology. Then we apply these concepts to the description of search spaces of various kinds. In section 4 we consider a series of topological concepts related to point and set separation and their translations to graphs. Continuity, one of the key concepts in topology, is the topic of section 5. Then we apply the topological language to local optima and saddle points in fitness landscapes. A short review of some further applications and open questions conclude this contribution.

2 GENERALIZED TOPOLOGIES

Textbooks on topology, e.g. [25, 26] usually start by defining a topology on a set X by means of a collection $\mathcal{O}$ of open sets or a collection $\mathcal{C}$ of closed sets that satisfy four axioms:

(I0) $\emptyset \in \mathcal{C}$.
(I1) $X \in \mathcal{C}$.
(I2) If $A_i \in \mathcal{C}$ for all $i \in I$, then $\bigcap\{A_i | i \in I\} \in \mathcal{C}$.
(I3) If $A, B \in \mathcal{C}$ then $A \cup B \in \mathcal{C}$.

Here I is an arbitrary, possibly infinite, index set. The corresponding axioms for open sets are obtained by exchanging unions and intersections. In the following we write $\mathcal{P}(X)$ for the set of all subsets (the power-set) of X.

In lattice theory more general so-called *intersection structures* are considered that fulfil only (I2), see e.g., [27, 28]. From $(X, \mathcal{C})$ one derives a *closure function* $\mathsf{cl} : \mathcal{P}(X) \to \mathcal{P}(X)$ that associates with each set $A \subseteq X$ its closure:

$$\mathsf{cl}(A) = \bigcap\{B \in \mathcal{C} | A \subseteq B\} \tag{1}$$

The function cl has two important properties: (i) it is *isotone*, i.e., $A' \subseteq A$ implies $\mathsf{cl}(A') \subseteq \mathsf{cl}(A)$ and (ii) it is *idempotent*, i.e., $\mathsf{cl}(\mathsf{cl}(A)) = \mathsf{cl}(A)$. Given an isotone and idempotent closure function cl, one obtains the associated intersection structure by setting $\mathcal{C} = \{C | C = \mathsf{cl}(A)\}$. Taking additional axioms into account leads to specialized intersection structures including topological spaces. For example, in the case of topped intersection structures, which satisfy also (I1), the closure function is *expanding*, i.e., $A \subseteq \mathsf{cl}(A)$.

Table 1: The basic axioms for extended topological spaces.

	closure	neighborhood
K0	$\mathsf{cl}(\emptyset) = \emptyset$	$X \in \mathcal{N}(x)$
K1	$A \subseteq B \implies \mathsf{cl}(A) \subseteq \mathsf{cl}(B)$ $\mathsf{cl}(A \cap B) \subseteq \mathsf{cl}(A) \cap \mathsf{cl}(B)$ $\mathsf{cl}(A) \cup \mathsf{cl}(B) \subseteq \mathsf{cl}(A \cup B)$	$N \in \mathcal{N}(x)$, $N \subseteq N'$ $\implies$ $N' \in \mathcal{N}(x)$
K2	$A \subseteq \mathsf{cl}(A)$	$N \in \mathcal{N}(x) \Rightarrow x \in N$
K3	$\mathsf{cl}(A \cup B) \subseteq \mathsf{cl}(A) \cup \mathsf{cl}(B)$	$N', N'' \in \mathcal{N}(x) \implies$ $N' \cap N'' \in \mathcal{N}(x)$
K4	$\mathsf{cl}(\mathsf{cl}(A)) = \mathsf{cl}(A)$	$N \in \mathcal{N}(x) \iff$ $\mathsf{int}(N) \in \mathcal{N}(x)$
K5	$\bigcup_{i \in I} \mathsf{cl}(A_i) = \mathsf{cl}\left(\bigcup_{i \in I} A_i\right)$	$\mathcal{N}(x) = \emptyset$ or $\exists N(x) : N(x) \subseteq N$ iff $N \in \mathcal{N}(x)$

There is, however, no *a priori* reason to assume that a closure function must be idempotent. Following the ideas of Day [29], Hammer [30, 31] and Gniłka [32] we explore here the surprising fact that meaningful topological concepts can already be defined on a set X endowed with an arbitrary set-valued set-function cl, which we will interpret as a generalized closure operator. Hence we call $\mathsf{cl}(A)$ is the *closure* of the set A.

The "conjugate" or "dual" of the closure function is the *interior* defined by

$$\begin{aligned} \mathsf{int}(A) &= X - \mathsf{cl}(X - A)\,, \\ \mathsf{cl}(A) &= X - \mathsf{int}(X - A)\,. \end{aligned} \tag{2}$$

A set *open* if $\mathsf{int}(A) = A$, and *closed* if $\mathsf{cl}(A) = A$, respectively. In topological space the closure of any set is closed and the interior of any set is open, i.e., $\mathsf{cl}(\mathsf{cl}(A)) = \mathsf{cl}(A)$ and $\mathsf{int}(\mathsf{int}(A)) = \mathsf{int}(A)$. A topological space in the usual sense satisfies the closure axioms (K0), (K1), (K2), (K3), and (K4) in Tab. 1. Omitting (K4) leads to the so-called pretopological spaces [33] while the intersection structures mentioned above satisfy only (K1) and (K4).

A set N is a *neighborhood* of a point $x \in X$ if x is contained in the interior of N. We write $\mathcal{N}(x)$ for the collection of all neighborhoods of x. The *neighborhood function* $\mathcal{N} : X \to \mathcal{P}(\mathcal{P}(X))$, which assign to each $x \in X$ the collection of its neighbors is therefore given by

$$\mathcal{N}(x) = \left\{N \in \mathcal{P}(X) \middle| x \in \mathsf{int}(N)\right\} \tag{3}$$

Given the neighborhoods of each point $x \in X$ is is possible to obtain the associated closure and interior functions [29]:

$$\begin{aligned} x \in \mathsf{cl}(A) &\iff (X - A) \notin \mathcal{N}(x) \\ x \in \mathsf{int}(A) &\iff A \in \mathcal{N}(x) \end{aligned} \tag{4}$$

In other words, closures, interiors, and neighborhoods are equivalent constructions on a set X. It is therefore possible to translate properties of the closure function cl into

Table 2: Generalized topological spaces.
Defining axioms are indicated by •, axioms that are implied by a smaller set of defining axioms are shown as ∘.

Axiom	K0	K1 isotonic	K2 expanding	K3 sub-additive	K4 idempotent	K5 additive
Extended Topology	•	•				
Brissaud	•		•			
Smyth space	•	•		•		
Intersection space		•			•	
Neighborhood space	•	•	•			
Convex closure space	(•)	•	•		•	
Pretopology	•	•	•	•		
Topology	•	∘	•	•	•	
Alexandroff space	•	∘	•	∘		•
Alexandroff topology	•	∘	•	∘	•	•

properties of the neighborhood function, and *vice versa*. Table 1 summarizes the basic axioms in both languages. Axiom (K4), for example, can then be rephrased in the more familiar form *Each neighborhood* $N \in \mathcal{N}(x)$ *contains an* open *neighborhood*, namely $\mathsf{int}(N) = \mathsf{int}(\mathsf{int}(N))$.

Almost all approaches to extending the framework of topology at least assume isotony (K1), *cf.* [34, 30, 29, 35, 32] and many others. The importance of isotony is emphasized by numerous equivalent conditions, some of which are listed in Tab. 1. Čech's book [33] shows that most of the fundamental results of point set topology can be obtained assuming only (K0), (K1), (K2), and (K3). Such spaces are usually called *pretopologies*. The best-studied combinations of the basic axioms are summarized in Tab. 2.

In a finite space isotony and sub-additivity (K1+K3) are equivalent to additivity. In infinite spaces this not true: recall that only the intersection of finitely many open sets is open again, axiom (K5) however establishes this property for arbitrary index sets I. It turns out that Alexandroff spaces in many respects behave like finite spaces [36, 37, 38]. They have applications for instance in digital image processing and the semantics of modal logic, see e.g. [39, 40, 41]. This is not surprising since Alexandroff spaces are essentially the directed graphs as we shall see below.

3 SEARCH SPACES

3.1 From Vectors to Metrics and Neighborhoods

In the introduction we have already encountered potential energy surfaces. Their underlying configuration space is a (high-dimensional) Euclidean vector space $\mathbb{R}^d$, where the dimension is determined by the number N of atoms, $d = 3N$. The canonical distance on $\mathbb{R}^d$ is

$$d(x,y) = \sqrt{(x-y)\cdot(x-y)} \tag{5}$$

A distance measure $d : X \times X \to \mathbb{R}_0^+$ is a *metric* if it satisfies the conditions:
(M0) $d(x,y) = 0$ implies $x = y$,
(M1) $d(x,x) = 0$,
(M2) $d(x,y) = d(y,x)$,
(M3) $d(x,y) + d(y,z) \geq d(x,z)$
for all $x, y, z \in X$. Of course Eq.(5) defines a metric.

A topological neighborhood of a point x in a metric space is a set N that contains an ε-ball

$$B_\varepsilon(x) = \{y \in X | d(x,y) < \varepsilon\} \tag{6}$$

for some $\varepsilon > 0$. Thus the neighborhood system of x is

$$\mathcal{N}(x) = \{N \subseteq X | \exists \varepsilon > 0 : B_\varepsilon(x) \subseteq N\} \tag{7}$$

It is straightforward to verify that $\mathcal{N}(x)$ satisfies (K0), (K1), (K2), (K3) and (K4) whenever d is a metric.

3.2 Simple Move Sets

Let us now turn to the simplest discrete spaces. Search in a discrete setting is usually based on a collection of rules that inter-convert configurations. As an example consider the famous *Traveling Salesman Problem* [42]: Given a list of n cities our salesman has to visit each city exactly once and then to return to the starting point thereby minimizing the total travel costs. A configuration of this optimization problem is therefore a permutation of the cities. Sensible *move sets* consist for instance of transpositions of cities. Drawing an arc from tour x to tour y whenever y can be obtained from x in a single move arranges the configuration space as a directed graph Γ. (For transpositions of course, we can omit the direction of the arcs since applying the same transposition again returns y to x, hence tours are either connected by arcs in both directions or not at all. In general, however, there is no reason why the move set must be symmetric.

Mutation organizes the possible sequences (genotypes) in much the same way. Again, the simplest model of point mutations leads to a symmetric graph, but realistic models of deletion and reduplication break this symmetry. A combinatorial chemistry approach using a fixed collection of reagents is another instance of the same abstract situation.

Let us write $\vec{\Gamma}(x)$ for the forward neighbors of x, i.e., our graph has arcs (x,y) iff $y \in \vec{\Gamma}(x)$ for all $x \in X$. Define the closure function on (the vertex set of) a directed graph as

$$\mathsf{cl}(A) = \bigcup_{x \in A} (\vec{\Gamma}[x] \cup \{x\}) \,. \tag{8}$$

In particular, the closure of a point x consists of the forward neighbors of x and x itself. Similarly, $\mathsf{cl}(A)$ contains exactly those vertices that can be reached from somewhere in A in at most one step. In this sense $\mathsf{cl}(A)$ is A together with its *boundary*

$$\partial A = \mathsf{cl}(A) - \mathsf{int}(A) = \mathsf{cl}(A) \cap \mathsf{cl}(X - A) \tag{9}$$

Note that we could base our entire discussion just as well on "boundary" as the elementary notion, *cf.* [43].

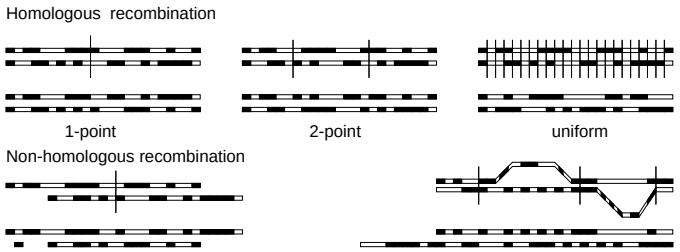

Figure 2: Recombination mechanisms. Homologous recombination works on aligned sequences of equal length. The number of cross-over points may vary. In the extreme case of uniform recombination each locus is transmitted independently to the offspring genes. In contrast, non-homologous recombination works on imperfectly aligned sequences.

Let us now analyze the closure function cl defined in Eq.(8). By definition $\mathsf{cl}(\emptyset) = \emptyset$ and $x \in \mathsf{cl}(x)$. Furthermore cl is additive, hence directed graphs give rise to Alexandroff spaces. Conversely, every finite pretopological space can be associated with a unique directed graph by virtue of $\vec{\Gamma}[x] = \mathsf{cl}(x) \setminus \{x\}$. It is not surprising therefore that Alexandroff spaces have proved useful in digital topology: after all they are isomorphic to (possibly infinite) directed graphs.

The important point about the spaces considered here is that moves only depend on a single "parent". Thus Eq.8 properly represents what we see if we use a population A of searchers instead of a single one, namely independent parallel searches. Each searcher moves independent of the rest of the population, hence the accessible boundary is the union of what is accessible to the individual searchers. This is reflected by the additivity of the closure function.

3.3 Recombination Spaces

Genetic algorithms, however, are based on the idea of advantageous building blocks spreading through the population. This is achieved by recombination of two parental genotypes. In Fig. 2 we sketch the most prominent mechanism of recombination. The abstract description of recombination spaces is pioneered in [44, 45, 46]. It is based on the notion of the *recombination function* $\mathcal{R} : X \times X \to \mathcal{P}(X)$. The *recombination set* $\mathcal{R}(x, y)$ consists of all potential offsprings that can be obtained from the two parents x and y. Recombination in general satisfies two basis axioms:
(X1) $\{x, y\} \in \mathcal{R}(x, y)$,
(X2) $\mathcal{R}(x, y) = \mathcal{R}(y, x)$.
Condition (X1) states that replication may occur without recombination, and (X2) means that the role of the parents is exchangeable.

The closure operator associated with a recombination function was introduced by Gitchoff and Wagner [44] as

$$\mathsf{cl}(A) = \bigcup_{x,y \in A} \mathcal{R}(x, y)\,; \tag{10}$$

Theorem. The closure space (X, cl) arising from any recombination function $\mathcal{R}$ satisfies (K0), (K1), and (K2).
Proof. (K1) is implicit in the definition. (K2) follows directly for (X1):

$$A = \bigcup_{x,y \in A} \{x, y\} \subseteq \bigcup_{x,y \in A} \mathcal{R}(x, y) = \mathsf{cl}(A)\ .$$

(K1) follows analogously:

$$\begin{aligned}\mathsf{cl}(A) \cup \mathsf{cl}(B) &= \bigcup_{x,y \in A} \mathcal{R}(x, y) \cup \bigcup_{x,y \in B} \mathcal{R}(x, y) \\ &\subseteq \bigcup_{x,y \in A \cup B} \mathcal{R}(x, y) = \mathsf{cl}(A \cup B)\end{aligned}$$

The inclusion above is strict in general, hence recombination closure is not sub-additive in general. □

3.4 Chemistry

Artificial chemistries, such as W. Fontana's `AlChemy` [47], are based on a *reaction algebra* of the form

$$\mathsf{A} + \mathsf{B} \to \mathsf{A} * \mathsf{B} \tag{11}$$

with a reaction product $\mathsf{A} * \mathsf{B}$ uniquely determined by the educts A and B. Including also the possibility that A and B not to react, or as in Fontana's papers, regarding replication-like reactions of the form $\mathsf{A}+\mathsf{B} \to \mathsf{A}+\mathsf{B}+\mathsf{A}*\mathsf{B}$ yields "recombination sets" of the form $\mathcal{R}(x, y) = \{x, y, x * y\}$.

It is not hard to see that this theorem can be generalized to arbitrary off-spring generating functions $\mathcal{X} : X^m \to \mathcal{P}(X)$ satisfying
(X1') $\{x_1, x_2, \ldots, x_m\} \in \mathcal{X}(x_1, x_2, \ldots, x_m)$.
This allows for more general reaction mechansims

$$\mathsf{A}_1 + \mathsf{A}_2 + \cdots + \mathsf{A}_\mathsf{m} \to \mathsf{B}_1 + \mathsf{B}_2 + \cdots + \mathsf{B}_\mathsf{n} \tag{12}$$

with sets E of educts and sets $P = \mathcal{R}(E)$ products with arbitrary sizes. The associated closure is then given by

$$\mathsf{cl}(A) = \bigcup \{\mathcal{R}(E) \big| E \subseteq A\}\,. \tag{13}$$

Given a set A of molecular species, $\mathsf{cl}(A)$ is the set of all reaction products that can be formed from (subsets of) the educt set A by means of a chemical reaction. This generalized topological space thus may serve as a conceptual framework for the study of chemical reaction networks.

We use the term *neighborhood space* for closure spaces that satisfy (K0), (K1), and (K2), because the neighborhood systems $\mathcal{N}(x)$ satisfy at least the intuitively obvious properties of neighborhoods: Each point is contained in all its neighborhoods (K2), larger neighborhoods enclose smaller ones (K1), and hence the entire space is the largest neighborhood of each of its points (K0).

In order to avoid unnecessary technical complications we will therefore assume from here on that (K0+K1+K2) holds.

4 MORE TOPOLOGICAL PROPERTIES

4.1 Separation Axioms

It is impossible to give a comprehensive overview of all the various topological properties that can be studied in neighborhood spaces. In Tab. 3 we collect the specifications of

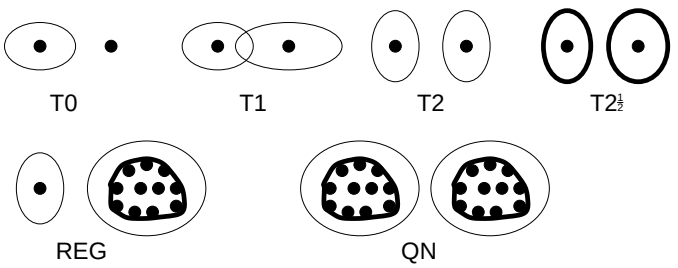

Figure 3: Separation Axioms. Individual points are shown as •, neighborhoods are shown as thin ovals, and closures are indicated by thick boundaries. (T0) means that for any two distinct points there is a neighborhood of one of them that does not contain the other point. (T1) means that for any two points there are neighborhoods that do not contain the other point. (T2) requires the existence of disjoint neighborhoods for any two points, and (T2$\frac{1}{2}$) requires that there are neighborhoods such that their closures are disjoint for any two points. Regularity (REG) and quasi-normality (QN) deals in the same way with separation of a point from the closure of set and with the separation of the closures of two sets, respectively. The axioms are defined more formally in Tab. 3.

a number of important symmetry, regularity, and point-separation properties. A particular search space may or may not have these properties. The listing of axioms in Tab. 3 is admittedly a bit terse. Nevertheless, we can give here only a few hints about their importance and pointers to the literature.

The (R0) axiom was introduced by Šanin [48], it is related to the compatibility of the neighborhood space with so-called uniform spaces [33, 49]. Reciprocal spaces [50] are also related to uniformities. Axiom (S) corresponds to symmetry when specialized to finite graphs: there is one-to-one correspondence between finite pretopological spaces satisfying (S) and finite undirected graphs. The hierarchy of separation axioms is of utmost importance in topology. Many of the most important results require that the Hausdorff axiom (T2) is satisfied. The regularity axiom (REG) comes in two different flavors: the first version looks like a separation axiom, assuring the existence of a pair of neighborhoods that separate individual points from the closures of arbitrary sets. The other version is a natural condition in (filter) convergence theory [51]. A pictorial version of some of the separation and symmetry properties is given in Fig. 3.

The proofs of the implications summarized in Tab. 3 are not all trivial. They are, however, very similar to the proofs of the analogous statements for pretopological spaces in [33], see also the appendix in [24]. Supplemental material containing most of the proof is available in electronic form at `www.tbi.univie.ac.at`.

For the important case of graphs we see that (R0) and (T0) have opposite meanings: A graph satisfies (R0) provided $y \in \vec{\Gamma}(x)$ iff $x \in \vec{\Gamma}(y)$, i.e., between two vertices there is either an arc in both directions or no arc. The class of symmetric digraphs is isomorphic to the undirected graphs, i.e., finite (R0)-pretopologies can be identified with the undirected graphs. (T0) on the other hand means that between two points there is an arc in at most one direction. The finite (T0) pretopologies are therefore the anti-symmetric digraphs. It follows that (T1) graphs have no arcs at all. The translation of regularity and normality to graph theoretical properties is considered in [23] for the case of finite topological spaces.

Table 3: Important axioms for neighborhood spaces. For most of the axioms we list both the neighborhood and the equivalent closure version.

Symmetry Axioms	
R0	$x \in \bigcup\{\mathcal{N}(y)\} \implies y \in \bigcup\{\mathcal{N}(x)\}$ $x \in \mathsf{cl}(\{y\}) \implies y \in \mathsf{cl}(\{x\})$
S	$x \in \bigcup\{\mathcal{N}(y)\} \implies \mathcal{N}(x) = \mathcal{N}(y)$ $\mathsf{cl}(A) \cap \mathsf{cl}(\{x\}) \neq \emptyset \implies x \in \mathsf{cl}(A)$
RE	If $N_x \cap N_y \neq \emptyset$ for all $N_x \in \mathcal{N}(x)$, $N_y \in \mathcal{N}(y)$ then $\mathcal{N}(x) = \mathcal{N}(y)$
(RE) $\implies$ (S) $\implies$ (R0)	
Regularity Axioms	
REG	$\forall N \in \mathcal{N}(x) : \exists U \in \mathcal{N}(x)$ s.t. $\mathsf{cl}(U) \subseteq N$. If $A \neq \emptyset$, $x \notin \mathsf{cl}(A)$: $\exists U \in \mathcal{N}(x)$, $V \in \mathcal{N}(A)$ s.t. $U \cap V = \emptyset$
QN	$A, B \neq \emptyset$, $\mathsf{cl}(A) \cap \mathsf{cl}(B) = \emptyset \implies$ $\exists U \in \mathcal{N}(A)$, $V \in \mathcal{N}(B)$: $U \cap V = \emptyset$
(REG) $\implies$ (R0)	
Separation Axioms (assume $x \neq y$)	
T0	$\exists N_x \in \mathcal{N}(x)$: $y \notin N_x$ or $\exists N_y \in \mathcal{N}(y)$: $x \notin N_y$ $y \notin \mathsf{cl}(\{x\})$ or $x \notin \mathsf{cl}(\{y\})$
T1	$\exists N_x \in \mathcal{N}(x)$, $N_y \in \mathcal{N}(y)$ s.t. $x \notin N_y$, $y \notin N_x$ $\mathsf{cl}(x) \subseteq \{x\}$ (T1) = (T0+R0)
T2	$\exists N_x \in \mathcal{N}(x)$ and $N_y \in \mathcal{N}(y)$ s.t. $N_x \cap N_y = \emptyset$ Proper prefilters converge to at most one point (T2) = (T0+R0)
T2$\frac{1}{2}$	$\exists N_x \in \mathcal{N}(x)$, $N_y \in \mathcal{N}(y)$: $\mathsf{cl}(N_x) \cap \mathsf{cl}(N_y) = \emptyset$
T3	(T3) = (T0+REG)
T4	(T4) = (T0+R0+QN)
(T4) $\implies$ (T3) $\implies$ (T2$\frac{1}{2}$) $\implies$ (T2) $\implies$ (T1) $\implies$ (T0)	

The neighborhood function can be extended from points in X to subsets in X by defining $\mathcal{N}(A) = \bigcap_{x \in A} \mathcal{N}(x)$. In other words, N is a neighborhood of a set A iff it is a neighborhood of each of the points in A.

The closure spaces derived even from homologous recombination lack additivity, hence they cannot be identified with graphs with vertex set X. They may serve however, as examples of non-trivial finite (T1) spaces, since we have $\mathsf{cl}(\{x\}) = \mathcal{R}(x, x) = \{x\}$.

4.2 Connectedness

The notion of connectedness is closely related to the separation properties. Two sets A and B are semi-separated if there are neighborhoods $N' \in \mathcal{N}(A)$ and $N'' \in \mathcal{N}(B)$ such that $A \cap N'' = N' \cap B = \emptyset$. This condition can also be expressed as

$$\mathsf{cl}(A) \cap B = A \cap \mathsf{cl}(B) = \emptyset\,. \tag{14}$$

A subset Z of X is *connected* if it is not the disjoint union of two semi-separated sets. This definition translates into the *Hausdorff-Lennes condition*: A set Z is connected in an isotone closure space (X, cl) if and only if for every

proper subset $A \subset Z$, $A \neq \emptyset$, $A \neq Z$, holds

$$[\mathsf{cl}(A) \cap (Z - A)] \cup [A \cap \mathsf{cl}(Z - A)] \neq \emptyset\,. \qquad (15)$$

The collection $\mathcal{Q}(X, \mathsf{cl})$ of connected sets has the following properties:
(c1) $\{z\} \in \mathcal{Q}(X, \mathsf{cl})$ for all $z \in X$.
(c2) $Y, Z \in \mathcal{Q}(X, \mathsf{cl})$, $Y \cap Z \neq \emptyset \implies Y \cup Z \in \mathcal{Q}(X, \mathsf{cl})$.
(c3) $Z \in \mathcal{Q}(X, \mathsf{cl})$ implies $\mathsf{cl}(Z) \in \mathcal{Q}(X, \mathsf{cl})$.
In this context it is interesting to point at attempts to use connectedness as the primitive concept of topology [52, 53].

In the graph case (c3) means that $\mathsf{cl}(\{x\})$ is connected. Using (c2) repeatedly one sees that two points x and y lie in a common connected set if there is a sequence $x = x_1, x_2, \ldots, x_l = y$ of vertices such that $x_{k+1} \in \mathsf{cl}(\{x_k\})$ or $x_k \in \mathsf{cl}(\{x_k\})$. Using this observation one can show that the graph-theoretical notion of connectedness (by means of an un-oriented path between x and y) and the topological concept expressed by Eq.(15) coincide.

4.3 Convergence

The notion of convergence, probably familiar to the reader in terms of sequences and their limit points, must be formulated in a more abstract language to be useful in the realm of neighborhood spaces. At the heart of this theory is Cartan's [54, 55] notion of a *filter*. Consider a set system $\mathcal{F} \subseteq \mathcal{P}(X)$ and the following properties:
(ISO) $F \in \mathcal{F}, F \subset F' \implies F' \in \mathcal{F}$
(F0) $\emptyset \notin \mathcal{F}$
(F1) $F', F'' \in \mathcal{F} \implies F' \cap F'' \neq \emptyset$;
equivalently: $F \in \mathcal{F} \implies -F \notin \mathcal{F}$
(F2) $F', F'' \in \mathcal{F} \implies F' \cap F'' \in \mathcal{F}$
(F3) $F \in \mathcal{F} \iff X - F \notin \mathcal{F}$
A set system satisfying the isotony condition (ISO) is a *stack*, if (F0) holds in addition we say the stack is proper. A stack satisfying the "pair-wise intersection property" (F1) is a *prefilter*. A proper stack satisfying (F2) is a *filter*. A filter is always a proper prefilter. A stack with property (F3) is *universal*. A universal filter is an *ultrafilter*. Obviously (F3) implies (F1) but not (F2).

We have already encountered such set systems: The neighborhood systems $\mathcal{N}(x)$ are proper stacks in isotone spaces, proper prefilters in neighborhood spaces, and filters in pretopological spaces. What does that have to do with convergence? Well, the "ends" $E_n = \{a_k | k \geq n\}$ of a sequence a_n define a particular filter $\mathcal{F}$ that consists of the sets E_n and all their super-sets. Recall the usual definition of convergence: (a_n) converges to $\hat{x}$ if for each neighborhood $N \in \mathcal{N}(x)$ there is an integer n_0 such that $a_k \in N$ for all $k \geq n_0$. This can be rephrased as $E_n \subseteq N$. Using the fact that both $\mathcal{N}(x)$ and $\mathcal{F}$ are isotonic, this means that each neighborhood is a super-set of a set E_n in $\mathcal{F}$, i.e., $\mathcal{N}(x) \subseteq \mathcal{F}$. What works for sequences can be turned into a definition for all proper prefilters $\mathcal{F}$ [56, 57, 58]:

$$\mathcal{F} \to x \quad \iff \quad \mathcal{N}(x) \subseteq \mathcal{F} \qquad (16)$$

Instead of neighborhoods or closure one can in fact make convergence the primitive notion of a generalized topology [59]. (This approach is usually based on filters but can easily be extended to proper prefilters.) One starts with a set X, the set $\mathfrak{J}(X)$ of all proper prefilters on X and a relation $\to$ on $\mathfrak{J}(X) \times S$ that specifies which prefilter converges to which points. The neighborhood systems are then defined as

$$\mathcal{N}(x) = \bigcap \{\mathcal{F} \in \mathfrak{J}(X) | \mathcal{F} \to x\} \qquad (17)$$

This very general notion of convergence has applications for the so-called *statisficing* process in the theory of decision making [60].

5 CONTINUOUS FUNCTIONS

The notion of continuity lies at the heart of topological theories. Its importance is emphasized by a large number of equivalent definitions, see e.g. [61, 62]. Let (X, cl) and (Y, cl) be two isotone spaces. Then $f : X \to Y$ is continuous if one (and hence all) of the following equivalent conditions holds:

(i) $\mathsf{cl}\big(f^{-1}(B)\big) \subseteq f^{-1}(\mathsf{cl}(B))$ for all $B \in \mathcal{P}(Y)$.
(ii) $f^{-1}(\mathsf{int}(B)) \subseteq \mathsf{int}\big(f^{-1}(B)\big)$ for all $B \in \mathcal{P}(Y)$.
(iii) $B \in \mathcal{N}(f(x))$ implies $f^{-1}(B) \in \mathcal{N}(x)$ for all $x \in X$.
(iv) $f(\mathsf{cl}(A)) \subseteq \mathsf{cl}(f(A))$ for all $A \in \mathcal{P}(X)$.
(v) $\mathcal{F} \to x$ implies $f(\mathcal{F}) \to f(x)$ for all $x \in X$.

We say that $f : X \to Y$ is *continuous in* x if $B \in \mathcal{N}(f(x))$ implies $f^{-1}(B) \in \mathcal{N}(x)$. Obviously, $f : X \to Y$ is continuous if it is continuous in each $x \in X$.

Instead of the familiar examples of continuous functions $f : \mathbb{R} \to \mathbb{R}$, let us consider a function $f : (X, E) \to (X', E')$ from one directed graph into another one. From condition (iv) and additivity we conclude that f is continuous iff
$f(\mathsf{cl}(\{x\})) \subseteq \mathsf{cl}(\{f(x)\})$, i.e., if the forward neighbors of x are mapped into the forward neighbors of $f(x)$. An important example of such a mapping is the *genotype-phenotype map* that assigns to each genotype g a phenotype $\psi = f(g)$.

The central question in this context is how to organize the set of phenotypes, that is, which neighborhood system is *natural* for phenotypes? The corresponding question for genotypes poses no difficulty as we have seen above, since physical processes exist which directly change genotypes and hence provide a natural closure function for sets of possible genotypes. Phenotypes, however, are not modified directly. Phenotypic innovation is the result of genetic modification mediated by development (the genotype-phenotype map). This reasoning motivated [21] to consider a notion of phenotypic neighborhood induced by the genotype-phenotype map which differs fundamentally from a notion of nearness among phenotypes based solely on the comparison of their morphological features.

For pretopological spaces a rather complete answer to this question is given in [19] in terms of the neighborhood systems: A natural definition of neighborhoods must lie somewhere "between" the accessibility pretopology $\mathcal{A}$ and

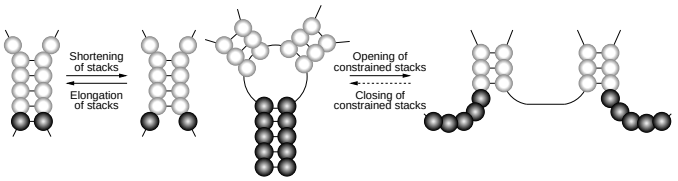

Figure 4: Structural modifications of RNA Secondary Structures that correspond to continuous transitions. Shorting and elongation of stacks as well as opening of constrained stacks in general leads to easily accessible structures. Closing a constrained stack, on the other hand, leads to inaccessible structures for realistic definitions of neighborhoods in phenotype space and hence corresponds to discontinuous transitions.

the shadow pretopology $\mathcal{C}$:

$$\begin{aligned} \mathcal{A}(\psi) &= \bigcap_{g \in f^{-1}(\psi)} f(\mathcal{N}(g)) \\ \mathcal{C}(\psi) &= \bigvee_{g \in f^{-1}(\psi)} f(\mathcal{N}(g)) \end{aligned} \tag{18}$$

Both neighborhood systems describe when a phenotype θ is close to a phenotype ψ in phenotype space. The accessibility pretopology requires that there is a genotype folding into θ "close" to a genotype folding into ψ *somewhere* in sequence space, the shadow is more restrictive, requiring that such a genotype exists close to *every* genotype with phenotype ψ. It appears natural to use an intermediate definition, where one requires that there is typically a sequence folding into θ near to a sequence folding into θ. This notion of nearness encapsulates that in reality one deals with populations. For example, "near" could be defined to mean "within $\mathsf{cl}(P)$ where P is a population of genotypes that predominantly folds into ψ".

The concept of a path in X is also based on continuity. A *path* from x to y is a continuous function $\varphi : [t', t''] \to X$ with $x = \varphi(t')$ and $y = \varphi(t'')$, where $[t', t'']$ is a closed interval on the real line. An *arc* is a path that is one-to-one, i.e., if $\varphi(t_1) \neq \varphi(t_2)$ whenever $t_1 \neq t_2$. A subset $A \subseteq X$ is *path-connected* (arc-connected) if for all $x, y \in A$ there is a path (arc) ϕ^{xy} with $\phi(t_x) = x$, $\phi(t_y) = y$, and $\phi([t_x, t_y]) \subseteq A$. Obviously, arc-connectedness implies path-connectedness, which in turn implies connectedness. Naturally, one could replace $\mathbb{R}$ by another totally ordered connected space $\mathbb{X}^>$ in the definition of path connectedness.

In the case of finite graphs it seems unnatural to use the real line $\mathbb{R}$ as time axis. Rather one would like to deal with a discrete sequence of events. This can for instance be achieved by using the infinite directed path $\mathbb{Z}^>$ as time axis. The points of $\mathbb{N}^>$ are the integers (which correspond to the measured time points) and $\mathsf{cl}(\{k\}) = \{k, k+1\}$. The digraph representation of this space looks like:

$$\cdots \to \bullet \to \bullet \to \bullet \to \bullet \to \bullet \to \ldots$$

It is easy to verify that "$\mathbb{N}^>$-path-connectedness", i.e., the existence of a continuous map $\delta : \mathbb{N}^> \to (X, \mathsf{cl})$ coincides with the familiar definition of strong connectedness on finite graphs [19].

An "evolutionary trajectory" is then a map $\phi : \mathbb{N}^> \to (X, \mathsf{cl})$. If (X, cl) is an Alexandroff space, i.e., a graph, we conclude from the discussion above that ϕ is continuous in k if and only if $\phi(k+1) \in \mathsf{cl}(\phi(k))$, i.e., iff there is an arc from $\phi(k)$ to $\phi(k+1)$ in the graph representation of (X, cl). The usefulness of this concept is demonstrated in [22] by establishing an (approximate) correspondence between a pretopology on RNA phenotype space and structural modification of RNA secondary structures that correspond to such continuous transitions between adjacent time-points, see Fig. 4. A most important observation here is that the opening of a constrained stack is a continuous transition, while closing the same stack is not continuous; thus phenotype spaces are typically not symmetric.

6 VALLEYS OF LANDSCAPES

Descriptions of fitness landscapes usually contains terms such as "local minimum", "saddle point", "valley", or "ruggedness" [13, 17]. Many of these concepts have natural topological counterparts. Adaptive walks, for instance, correspond to monotonic continuous functions of the form $\mathbb{X}^> \to (X, \mathsf{cl})$. Below we discuss just two topics in some more detail: local minima and saddle points. We assume throughout this section that (X, cl) is a connected neighborhood space, since we can treat each component of a non-connected space separately. We make no restrictions on the function $f : X \to \mathbb{R}$, and we note that the real line $\mathbb{R}$ can be replaced by any connected totally ordered space.

A *local minimum* $\hat{x} \in X$ is a point for which a neighborhood $N \in \mathcal{N}(x)$ exists such that $f(x) \leq f(y)$ for all $y \in N$. A seemingly stronger condition is the following: For each neighborhood $U \in \mathcal{N}(x)$ there is a neighborhood $N \subseteq U$ such that $f(x) \leq f(y)$ for all $y \in N$. Of course, in pretopological spaces both versions are equivalent. In general neighborhood spaces, however, the second condition is strictly stronger since the intersection of two neighborhoods need not be a neighborhood in this case.

Local minima and saddle points together define the valley structure of a landscape. Closely related are the level sets (cycles), i.e., the connected components of $X_c = \{x \in X | f(x) \leq c\}$, where connectedness of course is defined by the closure function cl. We write $B_c(x)$ for the connected component of X_c that contains the point x. These sets are called cycles in the theory of simulated annealing. They form a hierarchical (tree-like) structure that has recently received considerable attention in biopolymer folding and spin glass physics [63, 64, 65, 66, 67], see Fig. 5 for an example.

The meaning of "saddle point" on a PES is clear: A point $x \in \mathcal{R}^d$ is a (non-degenerate) saddle point if the gradient of the energy function $-f$ vanishes, $(\nabla f)(x) = 0$, and if the Hessian $(\nabla\nabla^+ f)(x)$ has $d-1$ negative and 1 positive eigenvalues. A suitable topological way of expressing this is based on the geometric intuition of saddle points. For a path $\phi : \mathbb{R} \to (X, \mathsf{cl})$ and a landscape $f : X \to \mathbb{R}$ we define its height as

$$H(\phi) = \sup\{f(z) | z \in \phi([0,1])\} \tag{19}$$

Let x and y be two points in X and let $\mathbf{P}_{xy}(A)$ be the set of all paths connecting x and y that are contained in A.

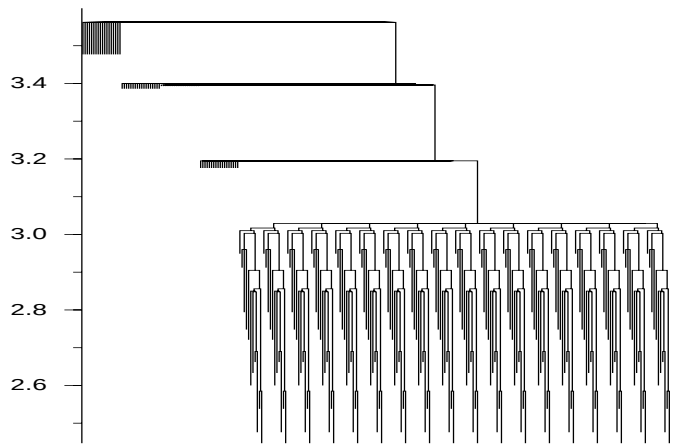

Figure 5: Barrier Tree of a random Traveling Salesman Problem on 9 cities. The move set are transpositions on (the permutation representations of) the tours. The "rotational" and "reversion" symmetries of the tours are reflected by the ninefold and two-fold degeneracies at the branching points.

With this notation we define the *barrier* separating x and y as

$$E[x,y] = \inf\{H(\phi)|\phi \in \mathbf{P}_{xy}(X)\} \tag{20}$$

Now we are in the position to give a topological definition of a saddle point: $s \in X$ is a saddle point if there is a neighborhood $N \in \mathcal{N}(s)$, two points $x_1, x_2 \in N - \{s\}$, and a path $\phi \in \mathbf{P}_{x_1x_2}(N)$ such that $f(s) = E[x_1, x_2] = H(\phi)$. Just as in the case of local minima, the alternative definition requiring that each neighborhood N' contains a neighborhood N with the above properties is equivalent in pretopological spaces and stronger in general. We suggest here a definition based on paths because the computational studies on combinatorial landscapes, Fig. 5 are based on eqns.(19) and (20).

An alternative definition uses the concept of "merging basins" [66]. We say that m is a *merging point* between the basins of the two points x and y if
(i) $B_c(x) \cap B_c(y) = \emptyset$ for all $c < f(m)$, and
(ii) $m \in B_{f(m)}(x) = B_{f(m)}(y)$.
For a *local merging point* we require that there is a neighborhood $N \in \mathcal{N}(s)$ such that (i) and (ii) are satisfied with the connected components of $N \cap X_c$ instead of those of X_c. Local merging points need not be merging points since two components of $N \cap X_c$ might belong to the same component of X_c. Note that our definition makes a local minimum a merging point between x and x, since $B_c(x) = \emptyset$ iff $c < f(x)$. On undirected graphs and on $\mathbb{R}^d$ with sufficiently smooth f it is easily seen that x is a merging point if and only if it is a saddle point or a local minimum. In general, however, we suspect that saddles and minima are always merging points, but the converse will not necessarily be true.

7 DISCUSSION

We have described here a mathematical formalism that encompasses both combinatorial landscapes on graphs and smooth potential functions defined on vector spaces. This allows us to define concepts such as minima, saddle points, trajectories, or continuity independent of the details of the state space. This general approach also leads to new topological concepts such as the merging points discussed above.

In this contribution we have focused on the exhibition of the formalism itself rather than on real or potential applications. The notion of product spaces and the factorization of pretopological spaces, which is discussed in detail in [19], for examples, leads to a formalization of the concept of a *character* in organismic biology. A character in the language corresponds to a factor of phenotype space. A character complex [68] then consists of characters that are linked by correlations in the fitness function. In [24] we explore the connection of pretopological spaces with metric distance measures. It can be shown that the genotype spaces arising from unequal crossover are inconsistent with metric distances. Even if the genotype spaces are symmetric, we have to assume that accessibilities at the phenotypic level are non-symmetric and hence incompatible with metric structures, as the example of RNA folding shows [21]. Experimentally testable predictions about certain aspects of developmental biology can be derived from this picture, see [24].

More importantly, however, the topological approach poses a set of novel questions that are at the heart of our understanding of evolutionary processes and possibly play an important role in a phenomenological theory of (synthetic) chemistry. How do we model changes in the genotype-phenotype map and/or the underlying closure function in genotype space. Such variations are for example the inevitable result of changes in the environment. In organic synthesis, for examples, reaction products, and hence the sets $\mathcal{R}(E)$ vary with the reaction conditions. In biology, mutations in the developmental genes may cause changes in the genotype-phenotype mapping. It appears natural to approach such questions, which "live" on spaces of (generalized) topologies or spaces of functions between (generalized) topological spaces again in topological terms.

Acknowledgments

This work is supported in part by the Austrian *Fonds zur Förderung der Wissenschaftlichen Forschung*, Project Nos. P-13887-MOB (B.M.R.S.) and P-13565 (P.F.S.).

REFERENCES

(1) Wright, S., The roles of mutation, inbreeding, crossbreeeding and selection in evolution. In: Jones, D. F., ed., *Int. Proceedings of the Sixth International Congress on Genetics*, vol. 1, **1932** 356–366.

(2) Kubinyi, H., *QSAR: Hansch Analysis and Related Approaches*, vol. 1 of *Methods and Principles in Medicinal Chemistry*. Weinheim: VCH, **1995**.

(3) Hansch, C.; Leo, A.; Hoeckman, D., *Exploring QSAR*. Washington: American Chemical Society, **1995**.

(4) Zuker, M.; Sankoff, D., RNA secondary structures and their prediction. *Bull. Math. Biol.* **1984**, *46*, 591–621.

(5) Hofacker, I. L.; Fontana, W.; Stadler, P. F.; Bonhoeffer, S.; Tacker, M.; Schuster, P., Fast Folding and Comparison of RNA Secondary Structures. *Monatsh. Chem.* **1994**, *125*, 167–188.

(6) Mills, D.; Peterson, R.; Spiegelman, S., An Extracellular Darwinian Experiment with a Self-Duplicating Nucleic Acid Molecule. *Proc. Nat. Acad. Sci. USA* **1967**, *58*, 217.

(7) Klug, S.; Famulok, M., All you wanted to know about SELEX. *Mol. Biol. Reports* **1994**, *20*, 97–107.

(8) Schuster, P.; Fontana, W.; Stadler, P. F.; Hofacker, I. L., From Sequences to Shapes and Back: A case study in RNA secondary structures. *Proc. Roy. Soc. Lond. B* **1994**, *255*, 279–284.

(9) Schuster, P.; Stadler, P. F.; Renner, A., RNA Structures and Folding: From conventional to new issues in structure predictions. *Curr. Opinions Structural Biol.* **1997**, *7*, 229–235.

(10) Flamm, C.; Hofacker, I. L.; Stadler, P. F., RNA *in silico*: The Computational Biology of RNA Secondary Structures. *Adv. Complex Syst.* **1999**, *2*, 65–90.

(11) Mezey, P. G., *Potential Energy Hypersurfaces*. Amsterdam: Elsevier, **1987**.

(12) Heidrich, D.; Kliesch, W.; Quapp, W., *Properties of Chemically Interesting Potential Energy Surfaces*, vol. 56 of *Lecture Notes in Chemistry*. Berlin: Springer-Verlag, **1991**.

(13) Kauffman, S., *The Origin of Order*. New York, Oxford: Oxford University Press, **1993**.

(14) Stadler, P. F., Landscapes and Their Correlation Functions. *J. Math. Chem.* **1996**, *20*, 1–45.

(15) Stadler, P. F., Fitness Landscapes Arising from the Sequence-Structure Maps of Biopolymers. *J. Mol. Struct. (THEOCHEM)* **1999**, *463*, 7–19.

(16) Stadler, P. F.; Tinhofer, G., Equitable Partitions, Coherent Algebras and Random Walks: Applications to the Correlation Structure of Landscapes. *MATCH* **1999**, *40*, 215–261.

(17) Reidys, C. M.; Stadler, P. F., Combinatorial Landscapes. *SIAM Review* **2001**, submitted, SFI preprint 01-03-14.

(18) Mézard, M.; Parisi, G.; Virasoro, M., *Spin Glass Theory and Beyond*. Singapore: World Scientific, **1987**.

(19) Stadler, B. M. R.; Stadler, P. F.; Fontana, W.; Wagner, G. P., The Topology of the Possible: Formal spaces underlying patterns of evolutionary change. *J. Theor. Biol.* **2000**, submitted, Santa Fe Institute Preprint #00-12-070.

(20) Futuyma, D. J., *Evolutionary Biology*. Sunderalnd, Massachusetts: Sinauer Associates, **1998**.

(21) Fontana, W.; Schuster, P., Continuity in Evolution: On the Nature of Transitions. *Science* **1998**, *280*, 1451–1455.

(22) Fontana, W.; Schuster, P., Shaping Space: The Possible and the Attainable in RNA Genotype-Phenotype Mapping. *J. Theor. Biol.* **1998**, *194*, 491–515.

(23) Cupal, J.; Kopp, S.; Stadler, P. F., RNA Shape Space Topology. *Artificial Life* **2000**, *6*, 3–23.

(24) Stadler, B. M. R.; Stadler, P. F.; Shpak, M.; Wagner, G. P., Recombination Spaces, Metrics, and Pretopologies. *Z. Phys. Chem.* **2001**, in press, SFI preprint 01-02-011.

(25) Gaal, S. A., *Point Set Topology*. New York: Academic Press, **1964**.

(26) Steen, L. A.; Seebach, Jr., J. A., *Counterexamples in Topology*. New York: Holt, Rinehart & Winston, **1970**.

(27) Soltan, W. P., *An Introduction in Axiomatic Theory of Convexity*. Kishinev: Shtiintsa, **1984**, russian.

(28) Davey, B. A.; Priestley, H. A., *Introduction to Lattice and Order*. Cambridge UK: Cambridge Univ. Press, **1990**.

(29) Day, M. M., Convergence, Closure, and Neighborhoods. *Duke Math. J.* **1944**, *11*, 181–199.

(30) Hammer, P. C., Extended Topology: Set-Valued Set Functions. *Nieuw Arch. Wisk. III* **1962**, *10*, 55–77.

(31) Gastl, G. C.; Hammer, P. C., Extended topology. Neighborhoods and convergents. In: N.N., ed., *Proceedings of the Colloquium on Convexity 1965*, Copenhagen, DK: Københavns Univ. Matematiske Inst., **1967** 104–116.

(32) Gniłka, S., On extended topologies. I: Closure operators. *Ann. Soc. Math. Pol., Ser. I, Commentat. Math.* **1994**, *34*, 81–94.

(33) Čech, E., *Topological Spaces*. London: Wiley, **1966**.

(34) Hammer, P. C., General Topoloy, Symmetry, and Convexity. *Trans. Wisconsin Acad. Sci., Arts, Letters* **1955**, *44*, 221–255.

(35) Brissaud, M. M., Les espaces prétopologiques. *C. R. Acad. Sc. Paris Ser. A* **1975**, *280*, 705–708.

(36) Alexandroff, P., Diskrete Räume. *Math. Sb. (N.S.)* **1937**, *2*, 501–518.

(37) Strong, R. E., Finite Topological Spaces. *Trans. Amer. Math. Soc.* **1966**, *123*, 325–340.

(38) Arenas, F. G., Alexandroff Spaces. *Acta Math. Univ. Comenianae* **1999**, *68*, 17–25.

(39) Eckhardt, U.; Latecki, L., Digital topology. Tech. Rep. 89, Hamburger Beitr. z. Angew. Math. A, **1994**.

(40) Smyth, M. B., Semi-metric, closure spaces and digital topology. *Theor. Computer Sci.* **1995**, *151*, 257–276.

(41) Galton, A., Continuous Motion in Discrete Space. In: Cohn, A. G.; Giunchiglia, F.; Selman, B., eds., *Principles of Knowledge Representation and Reasoning: Proceedings of the Seventh International Conference (KR2000)*, San Francisco, CA: Morgan Kaufmann Publishers, **2000** 26–37.

(42) Lawler, E. L.; Lenstra, J. K.; Kan, A. H. G. R.; Shmoys, D. B., *The Traveling Salesman Problem. A Guided Tour of Combinatorial Optimization*. London: John Wiley & Sons, **1985**.

(43) Albuquerque, J., La notion de "frontiere" en topologie. *Portug. Math.* **1941**, *2*, 280–289.

(44) Gitchoff, P.; Wagner, G. P., Recombination induced hypergraphs: a new approach to mutation-recombination isomorphism. *Complexity* **1996**, *2*, 37–43.

(45) Stadler, P. F.; Wagner, G. P., The Algebraic Theory of Recombination Spaces. *Evol. Comp.* **1998**, *5*, 241–275.

(46) Stadler, P. F.; Seitz, R.; Wagner, G. P., Evolvability of Complex Characters: Population Dependent Fourier Decomposition of Fitness Landscapes over Recombination Spaces. *Bull. Math. Biol.* **2000**, *62*, 399–428.

(47) Fontana, W.; Buss, L. W., What would be conserved if 'the tape were played twice'? *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 757–761.

(48) Šanin, N., On separation in topological space. *Dok. Akad. Nauk SSSR* **1943**, *38*, 110–113.

(49) Kent, D. C., On convergence groups and convergence uniformities. *Fund. Math.* **1967**, *60*, 213–222.

(50) Keller, H. H., Die Limes-Uniformisierbarkeit der Limesräume. *Math. Ann.* **1968**, *176*, 334–341.

(51) jr., H. J. B., Regular convergence spaces. *Indag. Math.* **1966**, *28*, 605–607.

(52) Wallace, A. D., Separation Spaces. *Ann. Math.* **1941**, 687–697.

(53) Hammer, P. C., Extended Topology: Connected Sets and Wallace Separations. *Portug. Math.* **1963**, *22*, 77–93.

(54) Cartan, H., Theorie des filtres. *C. R. Acad. Sci., Paris* **1937**, *205*, 595–598.

(55) Cartan, H., Filtres et ultrafiltres. *C. R. Acad. Sci., Paris* **1937**, *205*, 777–779.

(56) Thampuran, D. V., Extended Topology: filters and convergence I. *Math. Annalen* **1965**, *158*, 57–68.

(57) Thampuran, D. V., Neighborhood spaces and convergence. *Portug. Math.* **1974**, *33*, 43–49.

(58) Hamburg, P., Konvergenz in verallgemeinerten topologischen Räumen. *Portug. Math.* **1976**, *35*, 137–168.

(59) Kent, D. C., Convergence functions and their related topologies. *Fund. Math.* **1964**, *54*, 125–133.

(60) Erlandson, R. F., The Satisficing Process: A New Look. *IEEE Trans. Syst., Man, Cybern.* **1981**, *SMC-11*, 740–752.

(61) Hammer, P. C., Extended Topology: Continuity I. *Portug. Math.* **1964**, *25*, 77–93.

(62) Gniłka, S., On Continuity in Extended Topologies. *Ann. Soc. Math. Pol., Ser. I, Commentat. Math.* **1997**, *37*, 99–108.

(63) Vertechi, A. M.; Virasoro, M. A., Energy Barriers in SK spin glass models. *J. Phys. France* **1989**, *50*, 2325–2332.

(64) Klotz, T.; Kobe, S., "Valley Structures" in the phase space of a finite 3D Ising spin glass with $\pm I$ interactions. *J. Phys. A: Math. Gen.* **1994**, *27*, L95–L100.

(65) Garstecki, P.; Hoang, T. X.; Cieplak, M., Energy Landscapes, supergraphs, and "folding funnels" in spin systems. *Phys. Rev. E* **1999**, *60*, 3219–3226.

(66) Flamm, C.; Fontana, W.; Hofacker, I.; Schuster, P., RNA folding kinetics at elementary step resolution. *RNA* **2000**, *6*, 325–338.

(67) Ferreira, F. F.; Fontanari, J. F.; Stadler, P. F., Landscape statistics of the low autocorrelated binary string problem. *J. Phys. A: Math. Gen.* **2000**, *33*, 8635–8647.

(68) Wagner, G. P.; Schwenk, K., Evolutionary Stable Configurations: Functional Integration and the Evolution of Phenotypic Stability. In: ..., M. K. H., ed., *Evolutionary Biology*, vol. 31, New York: Kluwer Academic/Plenum Publishers, **2000** 155–217.