On Reidys and Stadler’s metrics for RNA secondary structures

F. Rosselló
Departament de Matemàtiques i Informàtica,
Institut Universitari d’Investigació en Ciències de la Salut (IUNICS),
Universitat de les Illes Balears,
07122 Palma de Mallorca (Spain)
E-mail: cesc.rossello@uib.es

Abstract
We compute explicitly several abstract metrics for RNA secondary structures defined by Reidys and Stadler.

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1 Introduction
As it is well known, an RNA molecule can be viewed as a chain of (ribo)nucleotides with a definite orientation. Each of these nucleotides is characterized by (and in practice identified with) the base attached to it, which can be adenine (A), cytosine (C), guanine (G), or uracil (U). Thus, an RNA molecule with \( N \) nucleotides can be mathematically described as a word of length \( N \) over the alphabet \( \{A, C, G, U\} \), called the primary structure of the molecule.

In the cell and in vitro each RNA molecule folds into a three-dimensional structure, which determines its biochemical function. This structure is held together by weak interactions called hydrogen bonds between pairs of non-consecutive bases: actually, a hydrogen bond can only form between bases that are several positions apart in the chain, but we shall not take this restriction into account here. Most of these bonds form between Watson-Crick complementary bases, i.e., between \( A \) and \( U \) and between \( C \) and \( G \), but a significant amount of bonds also form between other pairs of bases \[9\]. The secondary structure of an RNA molecule is a simplified model of this three-dimensional structure, consisting of an undirected graph with nodes its bases and arcs its base pairs or contacts; the length of a secondary structure is the number of its nodes. A restriction is added to the definition of secondary structure: a base can only pair with at most one base. This restriction is called the unique bonds condition.

An important problem in molecular biology is the comparison of these RNA secondary structures, because it is assumed that a preserved three-dimensional structure corresponds to a preserved function. Moreover, the comparison of RNA secondary structures of a fixed

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length is used in the prediction of RNA secondary structures to reduce the output of alternate structures when suboptimal solutions, and not only optimal, are considered [10, § IX]. In a seminal paper on the algebraic representation of biomolecular structures [7], C. Reidys and P. F. Stadler introduced three abstract metrics on the set of RNA secondary structures of a fixed length based on their algebraic models and independent of any notion of graph edition, and they discussed their biophysical relevance. They ended that paper by asking, among other questions, whether there exists any relation between the metrics for RNA secondary structures they had defined. In this paper we answer this question by explicitly computing these metrics. In a subsequent paper [4] we plan to generalize these metrics to contact structures without unique bonds, as for instance protein structures.

2 Main results

From now on, let $[n]$ denote the set $\{1, \ldots, n\}$, for every positive integer $n$.

**Definition 1** An RNA secondary structure of length $n$ is an undirected graph without multiple edges or self-loops $\Gamma = ([n], Q)$, for some $n \geq 1$, whose arcs $\{j, k\} \in Q$, called contacts, satisfy the following two conditions:

i) For every $j \in [n]$, $\{j, j+1\} \notin Q$.

ii) For every $j \in [n]$, if $\{j, k\}, \{j, l\} \in Q$, then $k = l$.

Condition (i) translates the impossibility of a contact between two consecutive bases, while condition (ii) translates the unique bonds condition. We should point out that this definition of RNA secondary structure is not the usual one, as the latter forbids the existence of (pseudo)knots: pairs of contacts $\{i, j\}$ and $\{k, l\}$ such that $i < k < j < l$. This rather unnatural condition is usually required in order to enable the use of dynamic programming methods to predict RNA secondary structures [10], but real secondary structures can contain knots and thus we shall not impose this restriction here. Therefore, our RNA secondary structures correspond to what in the literature on secondary structure modelling has been called contact structures with unique bonds [7, 8] or 1-diagrams [2].

We shall denote from now on a contact $\{j, k\}$ by $j \cdot k$ or $k \cdot j$, without distinction. A node is said to be isolated in an RNA secondary structure when it is not involved in any contact.

Let $S_n$ stand for the set of all RNA secondary structures of length $n$ and let $S_n$ be the symmetric group of permutations of $[n]$.

**Definition 2** For every $\Gamma = ([n], Q) \in S_n$, say with $Q = \{i_1 \cdot j_1, \ldots, i_k \cdot j_k\}$, let

$$\pi(\Gamma) = \prod_{t=1}^{k} (i_t, j_t) \in S_n,$$

where $(i, j)$ denotes the transposition in $S_n$ defined by $i \leftrightarrow j$.

Reidys and Stadler proved in [7] that the mapping $\pi : S_n \rightarrow S_n$ is injective and that $\pi(\Gamma)$ is an involution for every $\Gamma \in S_n$. This representation of RNA secondary structures as involutions is then used by these authors to define the following metric, called the involution metric.
Proposition 1 The mapping $d_{\text{inv}} : S_n \times S_n \to \mathbb{R}$ sending every $(\Gamma_1, \Gamma_2) \in S_n^2$ to the least number $d_{\text{inv}}(\Gamma_1, \Gamma_2)$ of transpositions necessary to represent the permutation $\pi(\Gamma_1)\pi(\Gamma_2)$, is a metric.

The following proposition computes explicitly this metric. In it, and henceforth, $A \Delta B$ denotes the symmetric difference $(A \cup B) - (A \cap B)$ of the sets $A$ and $B$, and $|A|$ stands for the cardinal of the finite set $A$.

Proposition 2 For every $\Gamma_1 = ([n], Q_1), \Gamma_2 = ([n], Q_2) \in S_n$,

$$d_{\text{inv}}(\Gamma_1, \Gamma_2) = |Q_1 \Delta Q_2| - 2\Omega,$$

where $\Omega$ is the number of cyclic orbits of length greater than 2 induced by the action on $[n]$ of the subgroup $\langle \pi(\Gamma_1), \pi(\Gamma_2) \rangle$ of $S_n$.

Proof. Let $\Gamma_1 = ([n], Q_1)$ and $\Gamma_2 = ([n], Q_2)$ be two RNA secondary structures of length $n$. To simplify the language, we shall refer to the orbits induced by the action of $\langle \pi(\Gamma_1), \pi(\Gamma_2) \rangle$ on $[n]$ simply by orbits. Notice that we can understand such an orbit as a subset $\{i_1, i_2, \ldots, i_m\}$ of $[n]$, $m \geq 1$, such that

$$i_1 \cdot i_2, i_2 \cdot i_3, \ldots, i_{m-1} \cdot i_m \in Q_1 \cup Q_2$$

and maximal with this property, i.e., such that any other contact in $Q_1 \cup Q_2$ involving $i_1$ or $i_m$ can only be $i_1 \cdot i_m$. The unique bonds condition (or, in group-theoretical terms, the fact that the transpositions defining each $\pi(\Gamma_i)$ are pairwise disjoint) implies that if $\{i_1, i_2, \ldots, i_m\}$ is an orbit, then either

$$i_1 \cdot i_2, i_3 \cdot i_4, \ldots, \in Q_1 \text{ and } i_2 \cdot i_3, i_4 \cdot i_5, \ldots \in Q_2$$

or

$$i_1 \cdot i_2, i_3 \cdot i_4, \ldots, \in Q_2 \text{ and } i_2 \cdot i_3, i_4 \cdot i_5, \ldots, \in Q_1.$$

Such an orbit is cyclic if $m = 2$ and $i_1 \cdot i_2 \in Q_1 \cap Q_2$, or $m \geq 3$ and $i_1 \cdot i_m \in Q_1 \cup Q_2$, and an orbit is linear in all other cases. The fact that $\pi(\Gamma_1), \pi(\Gamma_2)$ are both involutions implies that the cardinal of cyclic orbits is always even: roughly speaking, if $i_1 \cdot i_2 \in Q_1$ in a cyclic orbit, then $i_1 \cdot i_m \in Q_2$ and hence $i_{m-1} \cdot i_m \in Q_1$.

If two transpositions appearing in the product $\pi(\Gamma_1)\pi(\Gamma_2)$ are not disjoint, then the indexes involved in them belong to the same orbit. Moreover, two disjoint transpositions always commute. This allows us to reorganize the transpositions in the product $\pi(\Gamma_1)\pi(\Gamma_2)$, assembling them into subproducts corresponding to orbits. More specifically, if for every orbit $O$ and for every $i = 1, 2$ we let

$$\pi(O, \Gamma_i) = \prod_{k,l \in O} (k,l),$$

then

$$\pi(\Gamma_1)\pi(\Gamma_2) = \prod_{O \in \{\text{orbits}\}} \pi(O, \Gamma_1)\pi(O, \Gamma_2).$$

Since the orbits are pairwise disjoint, this finally shows that the least number of transpositions which $\pi(\Gamma_1)\pi(\Gamma_2)$ decomposes into is equal to the sum of the least numbers of transpositions
which $\pi(O, \Gamma_1)\pi(O, \Gamma_2)$ decompose into, for every orbit $O$. It remains to compute this last number for each type of orbit $O$.

If $O$ is a linear orbit of length $m = 1$, then $\pi(O, \Gamma_1)\pi(O, \Gamma_2) = \text{Id}$, and it corresponds to a node that is isolated both in $\Gamma_1$ and in $\Gamma_2$.

Let now $O = \{i_1, \ldots, i_m\}$ be a linear orbit of length $m \geq 2$. Consider first the case when $i_1, i_2, i_3, i_4, \ldots, i_{m-1}, i_m \in Q_1$ and $i_2, i_3, i_4, \ldots, i_m \in Q_2$; in particular, $m$ is even. Then

$$\pi(O, \Gamma_1)\pi(O, \Gamma_2) = (i_1, i_2)(i_3, i_4)\cdots(i_{m-1}, i_m)(i_2, i_3)\cdots(i_{m-2}, i_{m-1})$$

$$= (i_2, i_4, \ldots, i_m, i_{m-1}, i_{m-3}, \ldots, i_3, i_1),$$

a cycle of length $m$ that decomposes into the product of $m-1$ transpositions (and it is the least number of transpositions required to represent it), which is exactly the number of contacts of $Q_1 \cup Q_2$ involved in this orbit.

A similar argument shows that in all other cases for a linear orbit $O$, the permutation $\pi(O, \Gamma_1)\pi(O, \Gamma_2)$ is equal to a cycle of length the number of elements of the orbit, and thus the least number of transpositions this product decomposes into is equal to the number of contacts of $Q_1 \cup Q_2$ involved in this orbit $O$, all of them belonging again to $Q_1 \Delta Q_2$.

If $O$ is a cyclic orbit of length $m = 2$, say $O = \{i_1, i_2\}$, then $\pi(O, \Gamma_1)\pi(O, \Gamma_2) = (i_1, i_2)(i_1, i_2) = \text{Id}$. Notice that cyclic orbits of length 2 correspond to contacts in $Q_1 \cap Q_2$.

Finally, assume that $O$ is a cyclic orbit of length $m \geq 3$, say $O = \{i_1, \ldots, i_m\}$ with $i_1, i_2, i_3, i_4, \ldots, i_{m-1}, i_m \in Q_1$ and $i_2, i_3, i_4, \ldots, i_{m-2}, i_{m-1}, i_m, i_1 \in Q_2$; remember that $m$ is in this case even. Then

$$\pi(O, \Gamma_1)\pi(O, \Gamma_2) = (i_1, i_2)(i_3, i_4)\cdots(i_{m-1}, i_m)(i_2, i_3)\cdots(i_{m-2}, i_{m-1})(i_m, i_1)$$

$$= (i_2, i_4, \ldots, i_m)(i_{m-1}, i_{m-3}, \ldots, i_3, i_1),$$

the product of two disjoint cycles of length $m/2$. Since each cycle requires $m/2 - 1$ transpositions, the least number of transpositions the permutation $\pi(O, \Gamma_1)\pi(O, \Gamma_2)$ decomposes into is equal to $m - 2$, the number of contacts of $Q_1 \cup Q_2$ involved in this orbit $O$ (all of them belonging again to $Q_1 \Delta Q_2$) minus 2.

To sum up, and if we call $\Omega$ the number of cyclic orbits of length greater than 2,

$$d_{inv}(\Gamma_1, \Gamma_2) = |\{\text{contacts involved in linear orbits}\}|$$

$$+ |\{\text{contacts involved in cyclic orbits of length greater than 2}\}| - 2\Omega$$

$$= |Q_1 \Delta Q_2| - 2\Omega,$$

as we claimed.

The number and structure of the orbits induced by the action of $(\pi(\Gamma_1), \pi(\Gamma_2))$ on $[n]$ are related to the probability of transition from the neutral network of $\Gamma_1$ (the set of sequences that fold into it) to that of $\Gamma_2$: see [7, §3] and the references cited therein.

Let now $\text{Sub}(S_n)$ be the set of subgroups of $S_n$.

**Definition 3** For every $\Gamma = ([n], Q)$ in $S_n$, say with $Q = \{i_1, j_1, \ldots, i_k, j_k\}$, let

$$T(\Gamma) = \{(i_1, j_1), \ldots, (i_k, j_k)\}$$

be the set of the transpositions corresponding to the contacts in $Q$ and let $G(\Gamma) = (T(\Gamma))$ be the subgroup of $S_n$ generated by this set of transpositions.
Reidys and Stadler also proved in [7] that the mapping $G : \mathcal{S}_n \rightarrow \text{Sub}(\mathcal{S}_n)$ is injective, and then they used this representation of RNA secondary structures as permutation subgroups to define the following subgroup metric.

**Proposition 3** The mapping $d_{sgr} : \mathcal{S}_n \times \mathcal{S}_n \rightarrow \mathbb{R}$ defined by

$$d_{sgr}(\Gamma_1, \Gamma_2) = \ln \left( \frac{|G(\Gamma_1) \cdot G(\Gamma_2)|}{|G(\Gamma_1) \cap G(\Gamma_2)|} \right)$$

is a metric.

Next proposition shows that this metric simply measures, up to a constant factor, the cardinal of the symmetric difference of the sets of contacts.

**Proposition 4** For every $\Gamma_1 = ([n], Q_1), \Gamma_2 = ([n], Q_2) \in \mathcal{S}_n$,

$$d_{sgr}(\Gamma_1, \Gamma_2) = (\ln 2)|Q_1 \Delta Q_2|.$$  

**Proof.** Since the transpositions generating a group $G(\Gamma)$, with $\Gamma \in \mathcal{S}_n$, are pairwise disjoint, there is a bijection between $G(\Gamma)$ and the powerset $P(T(\Gamma))$: each element of $G(\Gamma)$ is the product of a subset of $T(\Gamma)$ in a unique way. Hence, $|G(\Gamma_1)| = 2^{|Q_1|}$ and $|G(\Gamma_2)| = 2^{|Q_2|}$.

On the other hand, by the uniqueness of the decomposition of a permutation into a product of disjoint cycles, a permutation belongs to $G(\Gamma_1) \cap G(\Gamma_2)$ if and only if it is a product of transpositions belonging to both $G(\Gamma_1)$ and $G(\Gamma_2)$. Therefore,

$$G(\Gamma_1) \cap G(\Gamma_2) = \langle T(\Gamma_1) \cap T(\Gamma_2) \rangle = \langle (i, j) \mid i \cdot j \in Q_1 \cap Q_2 \rangle,$$

and then, arguing as in the previous paragraph, we see that $|G(\Gamma_1) \cap G(\Gamma_2)| = 2^{|Q_1 \cap Q_2|}$.

Now, it is well known that

$$|G(\Gamma_1) \cdot G(\Gamma_2)| = \frac{|G(\Gamma_1)| \cdot |G(\Gamma_2)|}{|G(\Gamma_1) \cap G(\Gamma_2)|},$$

and hence

$$d_{sgr}(\Gamma_1, \Gamma_2) = \ln \left( \frac{|G(\Gamma_1) \cdot G(\Gamma_2)|}{|G(\Gamma_1) \cap G(\Gamma_2)|^2} \right) = \ln 2^{|Q_1| + |Q_2| - 2|Q_1 \cap Q_2|} = \ln 2^{|Q_1 \Delta Q_2|},$$

as we claimed. 

Notice in particular that, should Reidys and Stadler had defined their subgroup metric as $\log_2(|G(\Gamma_1) \cdot G(\Gamma_2)|/|G(\Gamma_1) \cap G(\Gamma_2)|)$, it would coincide with $|Q_1 \Delta Q_2|$.

The third metric on $\mathcal{S}_n$ proposed by Reidys and Stadler is actually a general way of defining metrics, rather than a single one, and it uses Magarshak and coworkers’ algebraic representation of RNA secondary structures [3, 5, 6], recently extended in [1] to cope with contacts other than Watson-Crick complementary base pairs. These authors represent an RNA secondary structure $\Gamma = ([n], Q)$ as an $n \times n$ complex symmetric matrix $S_\Gamma = (s_{i,j})_{i,j=1,...,n}$ where

$$s_{i,j} = \begin{cases} 
-1 & \text{if } i \neq j \text{ and } i \cdot j \in Q \\
1 & \text{if } i = j \text{ and } i \cdot l \notin Q \text{ for every } l \\
0 & \text{otherwise}
\end{cases}$$
Since $S_{\Gamma}^{-1} = S_{\Gamma}$ for every $\Gamma \in S_n$, one can define for any $\Gamma_1, \Gamma_2 \in S_n$ the transfer matrix $T_{\Gamma_1, \Gamma_2} = S_{\Gamma_2} \circ S_{\Gamma_1}$. Then, Reidys and Stadler propose to measure the difference between two RNA secondary structures by defining a metric through

$$(\Gamma_1, \Gamma_2) \mapsto \| T_{\Gamma_1, \Gamma_2} \|,$$

where $\| \cdot \|$ stands for some length function on the group $GL(n, \mathbb{C})$ of $n \times n$ invertible complex matrices [7, Def. 9, Lem. 6] (actually, Reidys and Stadler propose to use a matrix norm $\| \cdot \|$, but it is probably a misprint, as it would not yield a metric). A simple and well-known length function on $GL(n, \mathbb{C})$ is

$$\| A \| = \text{rank}(A - \text{Id}),$$

which allows to define a metric on $S_n$

$$d_{mag}(\Gamma_1, \Gamma_2) = \text{rank}(T_{\Gamma_1, \Gamma_2} - \text{Id}).$$

This metric turns out to be equal to the involution metric $d_{inv}$ defined above.

**Proposition 5** For every $\Gamma_1, \Gamma_2 \in S_n$, $d_{mag}(\Gamma_1, \Gamma_2) = d_{inv}(\Gamma_1, \Gamma_2)$.

The proof of this proposition is similar to (and simpler than) the proof of [1, Thm. 17], which establishes essentially this equality for the generalized algebraic representation of RNA secondary structures in the sense of Magarshak introduced in that paper, and therefore we omit it.

**References**

[1] J. Casasnovas, J. Miró, F. Rosselló, On the algebraic representation of RNA secondary structures with G.U pairs, to appear in *Journal of Mathematical Biology* (DOI: 10.1007/s00285-002-0188-0).

[2] C. Haslinger, P. F. Stadler, RNA structures with pseudo-knots: Graph-theoretical, combinatorial, and statistical properties, *Bulletin of Mathematical Biology* 61 (1999), 437–467.

[3] A. Kister, Y. Magarshak, J. Malinsky, The theoretical analysis of the process of RNA molecule self-assembly, *BioSystems* 30 (1993), 31–48.

[4] M. Llabrés, F. Rosselló, A new abstract metric for arbitrary contact structures, in preparation; a preliminary version will be presented at the *First Joint AMS-RSME Conference* (Sevilla 2003).

[5] Y. Magarshak, Quaternion representation of RNA sequences and tertiary structures, *BioSystems* 30 (1993) 21–29.

[6] Y. Magarshak, C. J. Benham, An algebraic representation of RNA secondary structures, *J. of Biomolecular Structures & Dynamics* 10 (1993) 465–488.

[7] C. Reidys, P. F. Stadler, Bio-molecular shapes and algebraic structures, *Computers & Chemistry* 20 (1996), 85–94.

[8] P. Schuster, P. F. Stadler, Discrete models of biopolymers, to appear in *Handbook of Computational Chemistry* (M.J.C. Crabbe, M. Drew and A. Konopka, eds.), Marcel Dekker (in press); see also Univ. Wien TBI Preprint No. pks-99-012 (1999).

[9] E. Westhof, V. Fritsch, RNA folding: Beyond Watson-Crick pairs, *Structure with Folding & Design* 8 (2000) R55–R65.

[10] M. Zuker, The use of dynamic programming algorithms in RNA secondary structure prediction, In *Mathematical methods for DNA sequences* (M. Waterman, ed.), CRC Press (1989), 159–184.