Modelling Biochemical Operations on RNA Secondary Structures*

Mercè Llabrés and Francesc Rosselló

Dept. of Mathematics and Computer Science,
Research Institute of Health Science (IUNICS),
University of the Balearic Islands,
07122 Palma de Mallorca (Spain)
{merce.llabres,cesc.rossello}@uib.es

Abstract. In this paper we model several simple biochemical operations on RNA molecules that modify their secondary structure by means of a suitable variation of Große-Rhode’s Algebra Transformation Systems.

1 Introduction

Biochemical processes are responsible for most of the information processing that takes place inside the cell. In the recent years, several representations and simulations of specific biochemical processes have been proposed using well known rewriting formalisms borrowed from Theoretical Computer Science. Let us mention, for instance, Fontana’s lambda calculus chemistry [3,4], recently revised by Müller [9] (for a recent survey on artificial chemistry, see [14]), the stochastic Petri net approach [5], the $\pi$-calculus representation of biochemical processes carried out by networks of proteins [10], and the graph replacement approach to DNA operations [8]. In the latter, an ad hoc graph replacement formalism is developed to formalize DNA biochemical operations like annealing or denaturing, by considering DNA double strands to be special graphs.

There is another popular line of research in theoretical biochemistry that aims to represent the three-dimensional structure of biopolymers, and specially of DNA and RNA, by means of different kinds of formal grammars; see, for instance, [7,13] for two surveys on this topic. The ultimate goal of such a representation is to understand how the three-dimensional structure of a biopolymer is determined from its sequence of monomers (for instance, how the sequence of ribonucleotides of an RNA molecule determines its secondary structure; see below for the relevant details of RNA’s biochemistry), and how this structure evolves when the biopolymer is modified through biochemical processes.

Sooner or later, this two lines of research should intersect, and the main goal of this paper is to move these two lines of research a step closer. We formalize some simple biochemical processes on RNA molecules, like for instance

* This work has been partially supported by the Spanish DGES, grant BFM2000-1113-C02-01.
ribonucleotide removals or mutations, and their effect on their three-dimensional structures by means of a variant of Große Rhode’s Algebra Transformation Systems (ATS) \cite{AT} on partial algebras \cite{partial} representing RNA biomolecules.

Before entering into more details, it is time to introduce a little biochemistry. As probably everybody knows, RNA molecules, together with DNA molecules and proteins, form the molecular basis of life. An RNA molecule can be viewed as a chain of ribonucleotides, and each ribonucleotide is characterized by the base attached to it, which can be either adenine (A), cytosine (C), guanine (G) or uracil (U). An RNA molecule is uniquely determined by the sequence of bases along its chain, and it has a definite orientation. Such an oriented chain of ribonucleotides is called the primary structure of the RNA molecule.

In the cell and in vitro, each RNA molecule folds into a specific three-dimensional structure that determines its biochemical activity. To determine this structure from the primary structure of the molecule is one of the main open problems in computational biology, and partial solutions have been proposed using Stochastic Context Free Grammars and Dynamic Programming, among other tools; see, for instance, \cite[Chaps. 9, 10]{Stochastic}.

This three-dimensional structure is held together by weak interactions called hydrogen bonds between pairs of non-consecutive bases.\footnote{Actually, for a hydrogen bond to be stable, the bases involved in it must be several nucleotides apart, but for simplicity we shall only consider the restriction that they must be non-consecutive.} Almost all these bonds form between complementary bases, i.e., between A and U and between C and G, but other pairings do also occur sporadically. For simplicity, in this paper we shall only consider pairings between complementary bases.

In most representations of RNA molecules, the detailed description of their three-dimensional structure is overlooked and the attention is focused on its secondary structure: the set of its base pairs, or contacts. Secondary structures are actually a simplified representation of RNA molecules’ three-dimensional structure, but that is enough in some applications, as different levels of “graining” are suitable for different problems. Two restrictions are usually added to the definition of secondary structure:

- If two bases $b_i$ and $b_j$ are paired, then neither $b_i$ or $b_j$ can bond with any other base; this restriction is called the unique bonds condition.
- If contacts exist between bases $b_i$ and $b_j$ and between bases $b_k$ and $b_l$, and if $b_k$ lies between $b_i$ and $b_j$, then $b_l$ also lies between $b_i$ and $b_j$; this restriction is called the no-pseudoknots condition.

The unique bonds condition simply captures the fact that the “bond” between two consecutive bases is of different nature, as a part of the molecule’s backbone. The no-pseudoknots condition is usually added in order to enable the use of dynamic programming methods to predict RNA secondary structures and, although real three-dimensional RNA structures have (pseudo)knots, we impose it here to show the scope of our approach: if pseudoknots are allowed, one simply has to allow them in the algebraic representation of RNA secondary structures.
and to remove the corresponding production rules from the rewriting system. Thus,

This allows traditionally to represent an RNA molecule as a labelled graph, with nodes representing the ribonucleotides, and their labels denoting the bases attached to them, and arcs of two different kinds: ones representing the order of the bases in the primary structure (the backbone) and the rest representing the bonds that form the secondary structure (the contacts) \[11,12\]. Our representation is slightly different: the backbone is represented by a partial algebra corresponding, essentially, to a labelled finite chain, and then the contacts are specified as arcs of a graph on the nodes of the backbone.

There are some biochemical operations that can be carried out on an RNA molecule. For instance, a ribonucleotide can be added or removed somewhere in the primary structure, a contact can form between two complementary bases, or it can be removed, and a base can mutate into another base. These operations may have collateral effects: for instance, if a base mutates into another one and it was involved in a contact, then this contact will disappear, as the corresponding bases will no longer be complementary, and if a nucleotide is removed and as a consequence two nucleotides forming a contact become consecutive, then this contact will also break.

It is precisely when we tried to specify these side effects that we were not able to use simple graph transformation systems in an easy way, and we decided to use the ATS approach. ATS is a very powerful algebra rewriting formalism, introduced by M. Große-Rhode in 1999 in order to specify the behavior of complex states software systems. It is operationally described, but not categorically formalized, and it takes care of side effects of the application of rules, similar to those found in our work. Unfortunately, even the ATS formalism as defined in \[6\], which was designed with software engineering specification applications in mind, was not suitable, as it stands, for our purposes. Thus we have slightly modified a simplified version of it, and we have dubbed the resulting formalism Withdrawal-based Algebra Transformation Systems (WATS). The reason is that, in our approach, the inconsistencies are eliminated by retreating, i.e., by removing, in a controlled way, the elements and operations that produce them, while in the original ATS approach the inconsistencies were eliminated by adding operations and identifying points.

The rest of this paper is organized as follows. In Section 2 we represent RNA molecules as suitable partial algebras, in Section 3 we briefly introduce the WATS formalism, and then in Section 4 we show how to represent the aforementioned biochemical operations on RNA molecules by means of WATS production rules. A final section on Conclusions closes the paper.

2 RNA Molecules as Partial Algebras

Roughly speaking, we represent the primary structure of an RNA molecule as a chain \( \underline{n} \) of length \( n \in \mathbb{N} \) with a label in \( \{A, C, G, U\} \) attached to each element of
the chain, representing the base attached to the corresponding ribonucleotide, and its secondary structure by means of ordered pairs in $\mathbb{N} \times \mathbb{N}$.

Let $\Sigma_{ps}$ be the following many-sorted signature:

\[
\begin{align*}
\text{Sorts} & : \text{Nat, Bases} \\
\text{Ops} & : \text{succ} : \text{Nat} \to \text{Nat} \\
& \quad \text{First, Last} : \rightarrow \text{Nat} \\
& \quad A, C, G, U : \rightarrow \text{Bases} \\
& \quad \text{minor} : \text{Nat, Nat} \to \text{Nat} \\
& \quad \text{label} : \text{Nat} \to \text{Bases} \\
& \quad \kappa : \text{Bases} \rightarrow \text{Bases}
\end{align*}
\]

An RNA primary structure is a finite partial $\Sigma_{ps}$-algebra

\[
P = (P_{\text{Nat}}, P_{\text{Bases}}; \\
\quad \text{First}^P, \text{Last}^P, A^P, C^P, G^P, U^P, \text{succ}^P, \text{minor}^P, \text{label}^P, \kappa^P)
\]

such that:

i) $(P_{\text{Nat}}, \text{First}^P, \text{Last}^P, \text{succ}^P)$ is a chain with successor operation $\text{succ}^P$, first element $\text{First}^P$ and last element $\text{Last}^P$.

ii) The operation $\text{minor}^P$ models the strict minority relation on this chain: $\text{minor}^P(x, y) = x$ if and only if there exists some $n \geq 1$ such that $y = (\text{succ}^P)^n(x)$.

iii) The values of the nullary operations $A^P, C^P, G^P, U^P$ are pairwise different, $P_{\text{Bases}} = \{A^P, C^P, G^P, U^P\}$, and on this set the operation $\kappa^P$ is given by the involution

\[
\kappa^P(A^P) = U^P, \quad \kappa^P(U^P) = A^P, \quad \kappa^P(C^P) = G^P, \quad \kappa^P(G^P) = C^P.
\]

iv) The operation $\text{label}^P$ is total.

Notice that all these conditions except the last one cannot be specified through quasi-equations, since they are not satisfied by a trivial (with only one element of each sort) total $\Sigma_{ps}$-algebra.

Let $\Sigma_{ss}$ be now the signature containing $\Sigma_{ps}$ and, in addition, the following sorts and operation symbols:

\[
\begin{align*}
\text{Sorts} & : \text{Contacts} \\
\text{Ops} & : p_1 : \text{Contacts} \to \text{Nat} \\
& \quad p_2 : \text{Contacts} \to \text{Nat}
\end{align*}
\]

An RNA secondary structure is a partial $\Sigma_{ss}$-algebra

\[
B = (B_{\text{Nat}}, B_{\text{Bases}}, B_{\text{Contacts}}; \\
\quad \text{First}^B, \text{Last}^B, A^B, C^B, G^B, U^B, \text{succ}^B, \text{minor}^B, \text{label}^B, \kappa^B, p_1^B, p_2^B)
\]
whose $\Sigma_{ps}$-reduct is an RNA primary structure and it satisfies moreover the following quasi-equations:

1. $p^B_1$ and $p^B_2$ are total
2. $p^B_1(x) = p^B_1(y) \Rightarrow x = y$
3. $p^B_2(x) = p^B_2(y) \Rightarrow x = y$
4. $p^B_1(x) = p^B_2(y) \Rightarrow x = y$
5. $\text{minor}(\text{succ}^B(p^B_1(x)), p^B_2(x)) = \text{succ}^B(p^B_1(x))$
6. $\text{minor}(p^B_1(x), p^B_1(y)) = p^B_1(x) \land \text{minor}(p^B_1(y), p^B_2(x)) = p^B_1(y) \Rightarrow \text{minor}(p^B_2(y), p^B_2(x)) = p^B_2(y)$
7. $\kappa^B(\text{label}^B(p^B_1(x))) = \text{label}^B(p^B_2(x))$

In such an RNA secondary structure, each element $c$ of sort \textit{Contacts} represents, of course, a contact between nucleotides $p^B_1(c)$ and $p^B_2(c)$. Equations (2), (3) and (4) represent the unique bonds condition, equation (5) represents the fact that there cannot exist a contact between a nucleotide and itself or its successor in the primary structure, equation (6) represents the no-ps eudoknots condition, and equation (7) represents the fact that a contact can only pair complementary bases. Notice that, if we simply omit equation (6) then, pseudoknots are allowed in the representation of RNA molecules.

Let $\Gamma_{ss} = (\Sigma_{ss}, CE)$ be the specification whose set of consistence equations $CE$ are the quasi-equations (1) to (7) above. Let $\text{Alg}_{\Gamma_{ss}}$ the category whose objects are all partial $\Sigma_{ss}$-algebras, i.e., those partial $\Sigma_{ss}$-algebras satisfying equation (1) to (7), and the morphisms between them are the plain homomorphisms, and let $\text{Alg}_{RNA}$ be the full subcategory of $\text{Alg}_{\Gamma_{ss}}$ supported on the RNA secondary structures.

3 Withdrawal-based $\Sigma_{ss}$-Algebra Transformation Systems

Our Withdrawal-based Algebra Transformation Systems (WATS) are a modification of a simplified version of the Algebra Transformation Systems (ATS) introduced in [6]. This modification only affects the last step in the definition of the application of a rewriting rule through a matching, and therefore all definitions previous to that one are the same as in the original ATS formalism. Since we are only interested in rewriting RNA secondary structures, we shall only give the main definitions for the signature $\Sigma_{ss}$ introduced in the previous section.

So, to simplify the notations, let us denote by $S$, $\Omega$ and $\eta$ the set of sorts, the set of operation symbols and the arity function of the signature $\Sigma_{ss}$. For every $\varphi \in \Omega$, set $\eta(\varphi) = (\omega(\varphi), \sigma(\varphi)) \in S^* \times S$.

A $\Sigma_{ss}$-presentation is a pair $P = (P_S, P_E)$ where $P_S = (P_s)_{s \in S}$ is an $S$-set, whose elements will be called \textit{generators}, and $P_E$ is a set of \textit{equations} with variables in $P_S$

$$t = t', \quad t, t' \in T_{\Sigma_{ss}}(P_S)_s, \quad s \in S.$$
A special type of equations are the function entries, of the form

$$\varphi(\underline{a}) = b, \quad \varphi \in \Omega, \ \underline{a} \in P^e_\varphi S, \ b \in P_{\varphi} E.$$

A presentation is functional when all its equations are function entries, and a functional presentation is consistently functional when for every $$\varphi \in \Omega$$ and $$\underline{a} \in P^e_\varphi S$$, there is at most one function entry of the form $$\varphi(\underline{a}) = b$$ in $$P_{\varphi} E$$.

Let $$p : P_S \rightarrow P'_S$$ be a mapping of $$S$$-sets. If $$e$$ is an equation $$t = t'$$ with $$t, t' \in T_{\Sigma_s}(P_S)$$, then we shall denote by $$e[p]$$ the equation $$t(p) = t'(p)$$ where $$t(p), t'(p) \in T_{\Sigma_s}(P'_S)$$ are the terms obtained from $$t$$ and $$t'$$, respectively, by replacing all variables in them by their corresponding images under $$p$$. In particular, if $$e$$ is the function entry $$\varphi(\underline{a}) = b$$, then $$e[p]$$ stands for the function entry $$\varphi(p(\underline{a})) = p_\sigma(\varphi)(b)$$. Given a mapping of $$S$$-sets $$p : P_S \rightarrow P'_S$$ and any set $$E$$ of equations with variables in $$P_S$$, let

$$E[p] = \{e[p] \mid e \in E\}.$$

A morphism of $$\Sigma_s$$-presentations $$p : (P_S, P_E) \rightarrow (P'_S, P'_E)$$ is then a mapping of $$S$$-sets $$p : P_S \rightarrow P'_S$$ such that $$P'_{E[p]} \subseteq P'_E$$.

A $$\Sigma_s$$-rewriting rule is a pair of $$\Sigma_s$$-presentations, written $$r = (P_l \leftarrow \rightarrow P_r)$$, where $$P_l = (X_l, E_l)$$ and $$P_r = (X_r, E_r)$$ are functional presentations. Informally, the left-hand side presentation in such a rule specifies the elements and operations that must be removed from the algebra which the rule is applied to, while its right-hand side presentation specifies the elements and operations to be added. The generators that occur in a rule play the role of variables (and therefore we shall usually call them variables): those appearing in the left-hand side presentation must be matched into the algebra to rewrite, and those appearing in the right-hand side presentation must be matched into the resulting algebra, in such a way that if a variable occurs in both parts of a rule, its image must be preserved. In the sequel, we shall assume that all variables that occur in rewriting rules are taken from a universal $$S$$-set $$X$$ that is globally fixed and disjoint from all sets of operation symbols in the signatures we use. We shall also assume that $$X$$ is large enough to contain equipotent copies of the carrier sets of all algebras we are interested in.

For every $$\Sigma_s$$-rewriting rule $$r = (P_l \leftarrow \rightarrow P_r)$$, with $$P_l = (X_l, E_l)$$ and $$P_r = (X_r, E_r)$$, let:

$$X^0_l = X_l - X_r, \quad X^0_r = X_r - X_l,$$

$$E^0_l = E_l - E_r, \quad E^0_r = E_r - E_l.$$

For every $$\Gamma_s$$-algebra $$A = (A, (\varphi^A)_{\varphi \in \Omega_s})$$, let $$A_S = A$$ and

$$A_e = \{\varphi(\underline{a}) = b \mid \varphi \in \Omega_s, \ \underline{a} \in \text{dom} \varphi^A, \ \varphi^A(\underline{a}) = b\}.$$

A match $$m$$ for a $$\Sigma_s$$-rewriting rule $$r = (P_l \leftarrow \rightarrow P_r)$$ in $$A$$ is simply a presentation morphism $$m : P_l \rightarrow (A_S, A_E)$$. The extension

$$m^* : X_l \cup X_r \rightarrow A_S \sqcup X^0_r$$
of $m$ is defined by\footnote{As always, we identify any set with its image into its disjoint union with any other set.}

$$m^*(x) = \begin{cases} m(x) \in A_S & \text{if } x \in X_l \\ x \in X_r^0 & \text{if } x \in X_r^0 = X_r - X_l \end{cases}$$

The application of $r$ to $A$ through $m$ rewrites then $A$ into the partial $\Gamma_{ss}$-algebra $B$ defined, step by step, as follows:

1) Set $B_S = (A_S - m(X_l^0)) \sqcup X_r^0$. This step removes from $A$ the elements that are images of elements in $X_l$ that do no longer belong to $X_r$, and adds to it the elements in $X_r$ that did not belong to $X_l$.

2) Set $B_E = (A_E - E_l^0[m]) \sqcup E_r^0[m^*]$. This step removes from $A$ the operations that are images of function entries in $E_l$ that do no longer belong to $E_r$, and adds to it the equations in $E_r$ that did not belong to $E_l$, with variables in $B_S$.

3) Since the presentation $(B_S, B_E)$ is functional, it defines a partial $\Sigma_{ss}$-algebra with carrier set $B = B_S$ by simply translating the function entries in $B_E$ into operations; if this presentation is not consistently functional, then we must identify elements in $B$ in order to remove inconsistencies. This step can be formally described by means of a functor left adjoint to a functor that sends every $\Sigma_{ss}$-algebra to its presentation $(A_S, A_E)$.

4) If the $\Sigma_{ss}$-algebra defined in this way satisfies equations (1) to (7), we are done. Otherwise, there are two possibilities:

- Every contact $x \in B_{Contacts}$ that violates equations (1), (5) or (7) is removed.
- After performing all removals in the previous step, if there are still pairs of contacts $x, y \in B_{Contacts}$ that violate equations (2), (3), (4) or (6), then, if one of them comes from $X_l^0$ and the other comes from $A_S$, the one from $X_l^0$ is removed and the other one preserved, and otherwise both are removed.

It is in step (4) where the main difference between Große-Rhode’s original ATS formalism and our WATS formalism lies. In ATS, the $\Sigma_{ss}$-algebra obtained in (3) would be forced to satisfy equations (1) to (7) by taking its universal solution in $\text{Alg}_\Gamma_{ss}$, and thus adding operations and identifying elements. In our formalism, violations of equations (1) to (7) are obviated by simply removing in a controlled way the contacts that yield them.

4 Biochemical operations modelled by means of WATS

The biochemical operations considered in this paper are the addition, deletion and mutation of a ribonucleotide and the addition and deletion of a contact. Each of these biochemical operations can be modelled as a rewriting step of a
WATS by the applications of a $\Sigma_{ss}$-rewriting rule to a RNA secondary structure. The rewriting rules that model these biochemical operations are the following ones.

**Adding a nucleotide:** We have to consider three different cases, corresponding to adding the new nucleotide at the beginning of the chain, at the end, or in the middle of it. In this case, each rule must be understood as having a parameter $x$ which corresponds to the base attached to the new nucleotide. So, there are four different values of this parameter, the nullary operation symbols $A$, $U$, $C$ and $G$.

- **Rule $P_{add\text{-}base\text{-}first}(x)$** has:
  - as $P_l$ the set of variables $X_l = \{k_1\}$ of sort $Nat$ and the set of equations $E_l = \{\text{First} = k_1\}$;
  - as $P_r$ the set of variables $X_r = \{t, k_1, k_0\}$, of sorts $t \in \text{Bases}$ and $k_1, k_0 \in Nat$, and the set of equations $E_r = \{\text{First} = k_0, \text{suc}(k_0) = k_1, \text{label}(k_0) = t, x = t\}$.

- **Rule $P_{add\text{-}base\text{-}last}(x)$** has:
  - as $P_l$ the set of variables $X_l = \{k_n\}$ of sort $Nat$ and the set of equations $E_l = \{\text{Last} = k_n\}$;
  - as $P_r$ the set of variables $X_r = \{t, k_n+1, k_n\}$, of sorts $t \in \text{Bases}$ and $k_n+1, k_n \in Nat$, and the set of equations $E_r = \{\text{Last} = k_{n+1}, \text{suc}(k_n) = k_{n+1}, \text{label}(k_{n+1}) = t, x = t\}$.

- **Rule $P_{add\text{-}base\text{-}middle}(x)$** has:
  - as $P_l$ the set of variables $X_l = \{k_i, k_j\}$ of sort $Nat$ and the set of equations $E_l = \{\text{suc}(k_i) = k_j\}$;
  - as $P_r$ the set of variables $X_r = \{t, k_i, k_j, k\}$, of sorts $t \in \text{Bases}$ and $k_i, k_j, k \in Nat$, and the set of equations $E_r = \{\text{suc}(k_i) = k, \text{suc}(k) = k_j, \text{label}(k) = t, x = t\}$.

**Remove a nucleotide:** We have to consider again three different cases, corresponding to removing the nucleotide at the beginning of the chain, at the end, or in the middle of it.

- **Rule $P_{del\text{-}base\text{-}first}$** has:
  - as $P_l$ the set of variables $X_l = \{k_1, k_0\}$, both of sort $Nat$, and the set of equations $E_l = \{\text{First} = k_0, \text{suc}(k_0) = k_1\}$;
  - as $P_r$ the set of variables $X_r = \{k_1\}$ of sort $Nat$ and the set of equations $E_r = \{\text{First} = k_1\}$.

- **Rule $P_{del\text{-}base\text{-}last}$** has:
  - as $P_l$ the set of variables $X_l = \{k_{n-1}, k_n\}$, both of sort $Nat$, and the set of equations $E_l = \{\text{Last} = k_n, \text{suc}(k_{n-1}) = k_n\}$;
  - as $P_r$ the set of variables $X_r = \{k_{n-1}\}$ of sort $Nat$ and the set of equations $E_r = \{\text{Last} = k_{n-1}\}$.

- **Rule $P_{del\text{-}base\text{-}middle}$** has:
  - as $P_l$ the set of variables $X_l = \{k_i, k_j, k_l\}$, all of them of sort $Nat$, and the set of equations $E_l = \{\text{suc}(k_i) = k_l, \text{suc}(k_j) = k_j\}$;
  - as $P_r$ the set of variables $X_r = \{k_i, k_j\}$ of sort $Nat$ and the set of equations $E_r = \{\text{suc}(k_i) = k_j\}$.
Mutating a base: The mutation of a base is specified by just redefining the operation label. Thus we consider the following rule:

- Rule $P_{mutation}$ has:
  - as $P_l$ the set of variables $X_l = \{x, y, k\}$, of sorts $x, y \in Bases$ and $k \in Nat$, and the set of equations $E_l = \{label(k) = x\}$;
  - as $P_r$ the set of variables $X_r = \{x, y, k\}$, of sorts $x, y \in Bases$ and $k \in Nat$ and the set of equations $E_r = \{label(k) = y\}$.

Adding a contact: To add a contact we simply add a new element of sort $Contact$ and the projections from it to the nucleotides it bonds.

- Rule $P_{add-contact}$ has:
  - as $P_l$ the set of variables $X_l = \{x, y, k, k_{i+1}, k_j\}$, of sorts $x, y \in Bases$ and $k_i, k_{i+1}, k_j \in Nat$, and the set of equations $E_l = \{suc(k_i) = k_{i+1}, \text{minor}(k_{i+1}, k_j) = k_{i+1}, \kappa(x) = y, \kappa(y) = x, \text{label}(k_i) = x, \text{label}(k_j) = y\}$;
  - as $P_r$ the set of variables $X_r = \{x, y, k, k_{i+1}, k_j\}$, of sorts $x, y \in Bases$, $k_i, k_{i+1}, k_j \in Nat$ and $c \in Contacts$, and the set of equations $E_r = \{\text{suc}(k_i) = k_{i+1}, \text{minor}(k_{i+1}, k_j) = k_{i+1}, \kappa(x) = y, \kappa(y) = x, p_1(c) = k_i, p_2(c) = k_j, \text{label}(k_i) = x, \text{label}(k_j) = y\}$.

Removing a contact: To remove a contact we simply delete it.

- Rule $P_{del-contact}$ has:
  - as $P_l$ the set of variables $X_l = \{k_i, k_j\}$, of sorts $k_i, k_j \in Nat$ and $c \in Contacts$, and the set of equations $E_l = \{p_1(c) = k_i, p_2(c) = k_j\}$;
  - as $P_r$ the set of variables $X_r = \{k_i, k_j\}$, both of sort $Nat$, and the set of equations $E_r = \emptyset$.

It is not difficult to check that an RNA secondary structure is always rewritten by the application of any one of these rules through any matching into an RNA secondary structure, and that in each case their effect is the desired one. This must be done rule by rule and case by case.

5 Conclusion

We have modelled several simple biochemical operations on RNA molecules that modify their secondary structure by means of rewriting rules in a modified version of the Algebra Transformation Systems of Große-Rhode, which we have dubbed Withdrawal-based Algebra Transformation Systems. This modification has been made ad hoc for algebras representing RNA secondary structures, but we feel that the philosophy of removing inconsistencies by retreating should have applications in other contexts, and could probably be formalized for algebras over arbitrary specifications.

In this paper we have made some simplifications on the RNA secondary structure that could perfectly be avoided. For instance, if we want to allow contacts between pairs of basis other than the usual complementary pairs, like for instance between G and U (they are called wobble pairs, not so uncommon), then we only have to replace the involution $\kappa$ by a symmetric relation on the
carrier of sort *Bases*. And if we want to impose that two bases paired by a contact must be at least at a fixed distance, we only have to modify in a suitable way equation (5).

There are also other collateral effects that could, and probably should, be specified. For instance, isolated contacts tend to break, and pseudoknots should be allowed under certain circumstances.

References

1. Burmeister, P., *A Model Theoretic Oriented Approach to Partial Algebras*. Mathematical Research 32, Akademie-Verlag (1986).
2. Durbin, R., Eddy, S., Krogh, A., Mitchison, G., *Biological Sequence Analysis*. Cambridge Univ. Press (1998).
3. Fontana, W., “Algorithmic chemistry.” In *Artificial Life II* (Addison-Wesley, 1992), 159–210. Also Technical Report LA-UR 90-1959, Los Alamos National Lab. (1990).
4. Fontana, W., Buss, L. W. “The barrier of objects: from dynamical systems to bounded organization.” In *Boundaries and Barriers* (Addison-Wesley, 1996), 56–116.
5. Goss, P., Peccoud, J. “Quantitative modeling of stochastic systems in molecular biology by using stochastic Petri nets.” *Proc. Nat. Acad. Sciences USA* 95 (1998), 6750–6755.
6. Große-Rhode, M. “Specification of State Based Systems by Algebra Rewrite Systems and Refinements.” Technical Report 99-04, TU Berlin (March 1999).
7. Mayoh, B. “DNA Pattern multigrammars.” Technical Report (1994).
8. McCaskill, J., Niemann, U. “Graph replacement chemistry for DNA processing.” In *Proc. DNA6: 6th International Meeting on DNA based computers*, DIMACS Series in Discrete Mathematics and Theoretical Computer Science (AMS, to appear), 89–99.
9. Müller, S. *Functional Organization in Molecular Systems and the λ-calculus*. PhD Thesis, Univ. Wien (1999).
10. Regev, A., Silverman, W., Shapiro, E. “Representation and simulation of biochemical processes using the π-calculus process algebra.” In *Proc. Pacific Symposium on Biocomputing* 2001 (2001), 459–470.
11. C. Reidys, P. F. Stadler, Bio-molecular shapes and algebraic structures. *Computers & Chemistry* 20 (1996), 85–94.
12. P. Schuster, P. F. Stadler, Discrete models of biopolymers. Univ. Wien TBI Preprint No. pks-99-012 (1999).
13. Searls, D. B. “Formal Language and Biological Macromolecules”. In *Mathematical Support for Molecular Biology*, DIMACS Series in Discrete Mathematics and Theoretical Computer Science 47 (AMS, 1999), 117–140.
14. Speroni di Fenizio, P. “Artificial Chemistries.” *Bulletin EATCS* 76 (February 2002), 128–141.