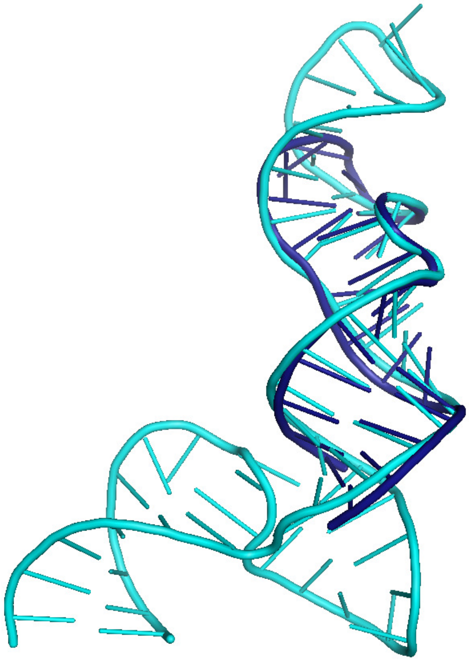
SARA: a method for RNA structural alignment and function annotation



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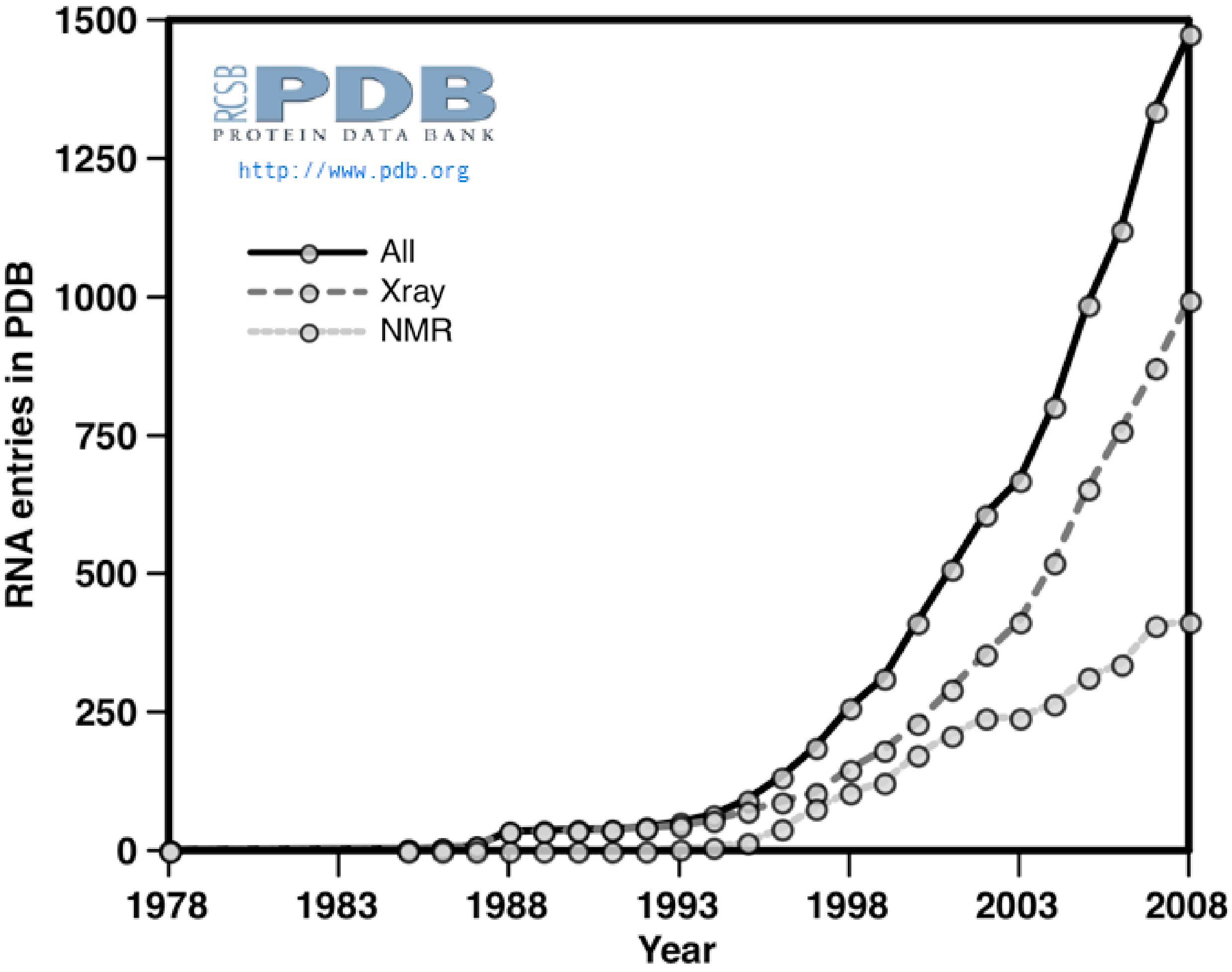
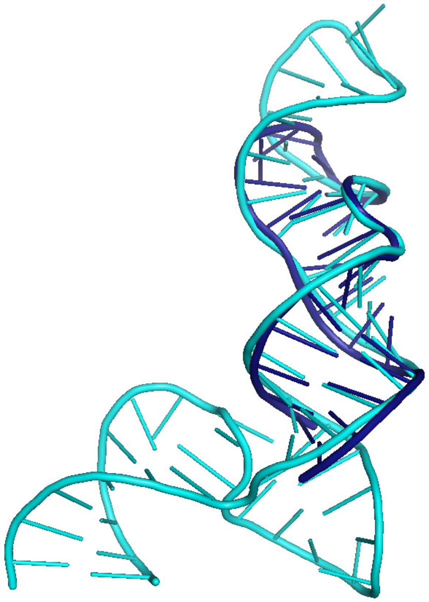
RNA Structure

Currently **more than 1500 RNA structures** are deposited in the PDB (Mar 09)



Structural alignment

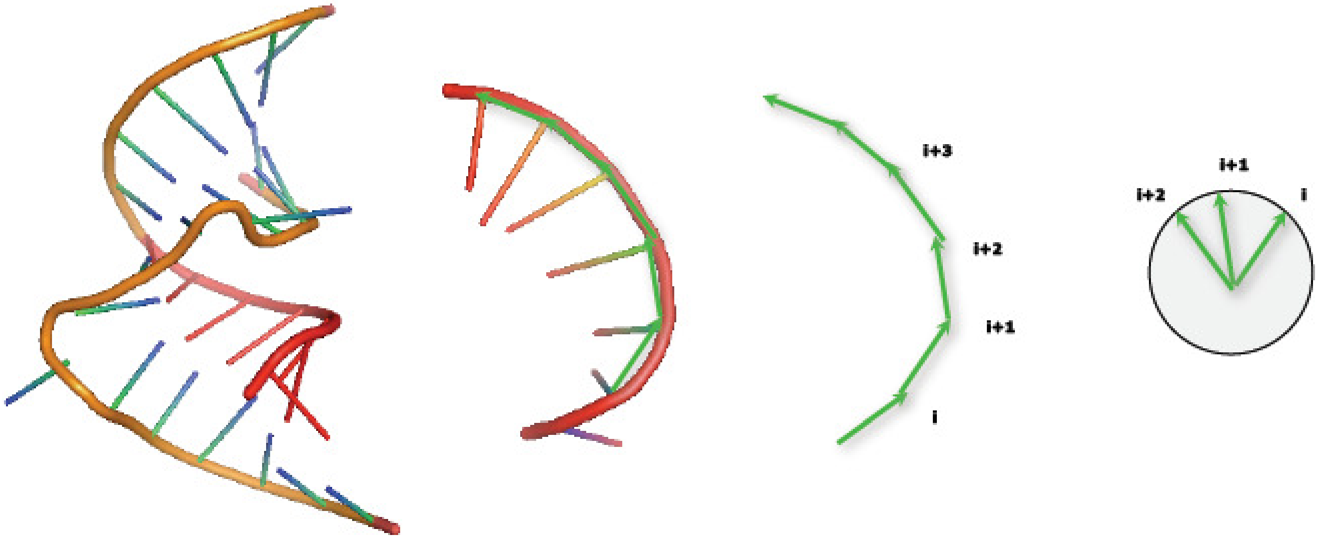


Structural alignment attempts to estabish equivalences between two or more polymer structures based on their shape and their **three-dimensional conformations.**

In contrast to the structural superimposition, where at least some equivalences are known, structural alignments **does not require any a priori knowledge of the equivalents positions**.

Structural alignment has been used as valuable tool for the comparison of proteins including the **inference of evolutionary relationship** between proteins with low level of sequence similatity.

Unit Vector representation

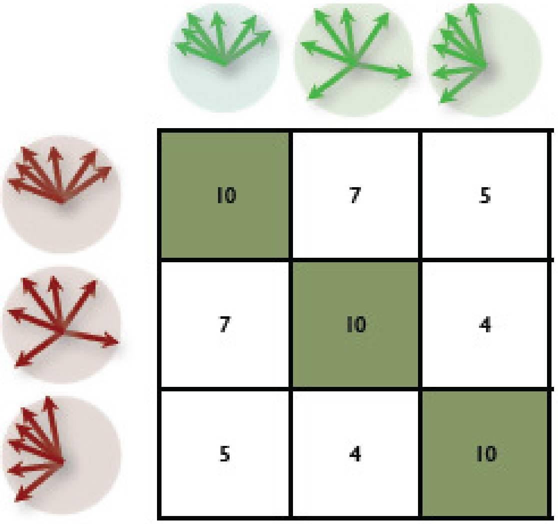


A **Unit Vector** is the **normalized vector between two successive atoms of the same type.**

For each position *i* consider the ***k*** **consecutive vectors, which will be mapped into a unit sphere** representing the local structure of *k* nucleotides.

Ortiz et al. Proteins 2002

Unit Vector scoring



10	7	5
7	10	4
5	4	10

$$URMS^R = \sqrt{2.0 - \frac{2.84}{\sqrt{k}}}$$

$$S_{ij} = \frac{(URMS^R - URMS^{ij})}{URMS^R} \Delta(URMS^R, URMS^{ij})$$

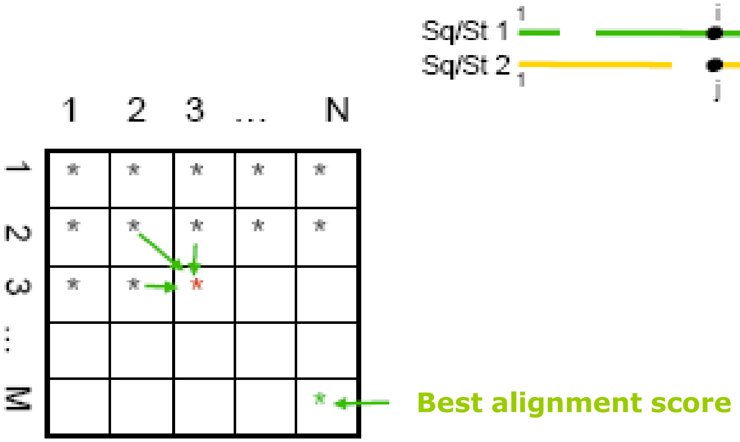
$$\Delta(URMS^R, URMS^{ij}) = 10 \Rightarrow URMS^R > URMS^{ij}$$
$$\Delta(URMS^R, URMS^{ij}) = 0 \Rightarrow URMS^R \le URMS^{ij}$$

For each position *i*, the ***k* consecutive unit vectors** are grouped and **aligned** to the *j* set of unit vectors. Each pair of aligned unit vectors will be **evaluated by calculating Unit Root Mean Square distance** ($URMS^{ij}$).

The obtained **URMS values** are **compared the minimum expected URMS** distance between two **random** set of *k* unit vectors ($URMS^R$).

The alignment score is then calculated normalizing $URMS^{ij}$ to the $URMS^R$ value.

Alignment



$$D_{ij}=\max\begin{cases} D_{i-1,j-1} & + s(x_i,y_j)\\ D_{i-1,j} & + g \\ D_{i,j-1} & + g\end{cases}$$

Backtracking to get the best alignment

A **Dynamic Programming** procedure is applied to search for the optimal structural alignment using a **global alignment with zero end gap penalties**.

The **maximum subset of local structures** that have their equivalent selected atoms **within 4.0 Å** in the space are calculated by a variant of the MaxSub algorithm.

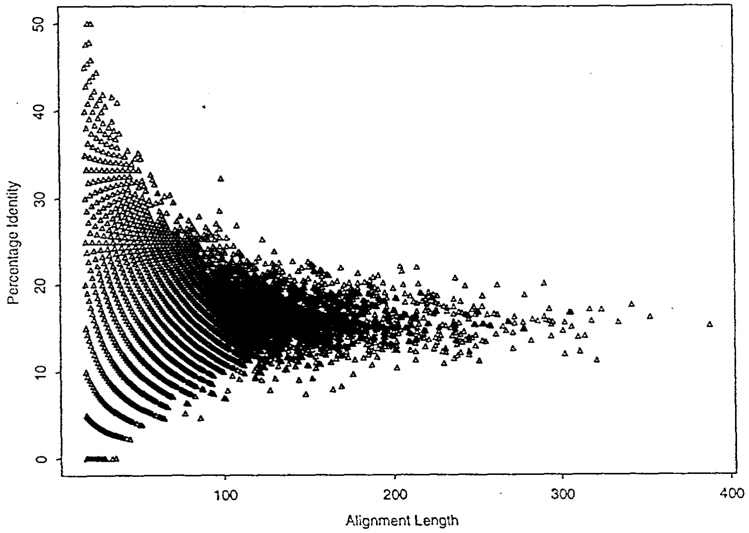
For each alignment the number of close atoms is used to **evaluate the percentage of sequence, secondary structure and tertiary structural identities.**

Needleman and Wunsch J.MB 1970
Siew et al. Bioinformatics 2000

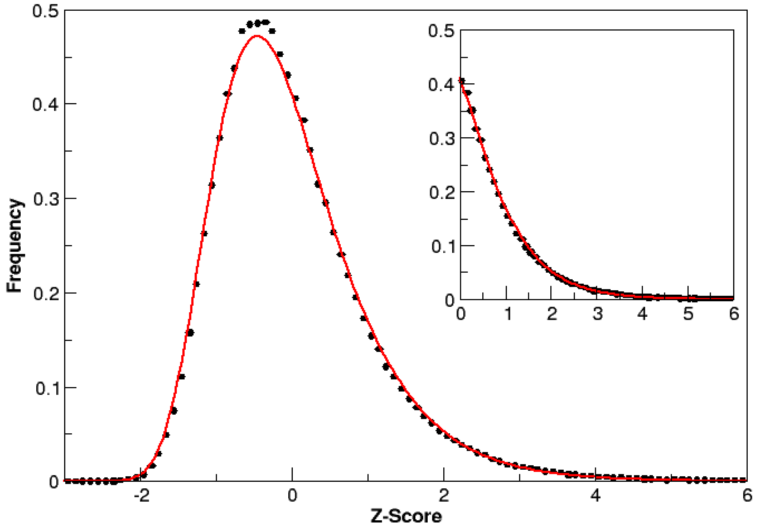
Background distribution

Considering **RNA sequences with identity below 25%** we have produced a **set of pairwise alignments** that has been used **to calculate the empirical background distribution.**
From such distribution we can then evaluate μ and σ needed to calculated the p-value for P(s≥x).

Empiric



Analytic



$$P(s \geq x) = 1\text{-}exp(-e^{-\lambda(\sigma-\mu)})$$

Karlin and Altschul PNAS 1990

RNA function annotation

The proposed algorithm to align RNA structures called **SARA** has been **applied** in the **development** of an automatic **method for RNA function annotation** based on structural alignment.

The adopted strategy consists in the **comparison of a query RNA** structure **with a set o representative RNA structures** with **function annotation reported in the SCOR** database.

For each comparison a score is returned and the **predicted fuction** will be assigned sorting the list pairwise alignments and **considering the fuction of the RNA with highest score.**

The **score** is the **mean logarithm of the negative P-values** obtaining comparing the **percentage of sequence, secondary structure and tertiary stucture identities** of the best alignment with their relative background distributions.

Capriotti and Marti-Renom Bioinformatics 2008
Tamura et al. NAR 2004

Datasets composition

We test our method selecting a set **no identical RNA structures with more than 20 nucleotides, 3 base pairs**.

A **set of RNA structure** has been collected considering only RNAs with **fuction annotation in SCOR** dataset.

R-FSCOR: **representative set of 192 RNA structures** with SCOR annotated functions. Cluster according **to deepest SCOR function and reclustered** considering a **percentage of structural identity threshold of 90%.**

Datasets	Number of chains	Number of alignments	Number of different SCOR functions
RNA08	451	101,475	-
BgALI	451	50,995	-
FSCOR	419	-	168
R-FSCOR	192	-	168
T-FSCOR	227	-	88

Method tests

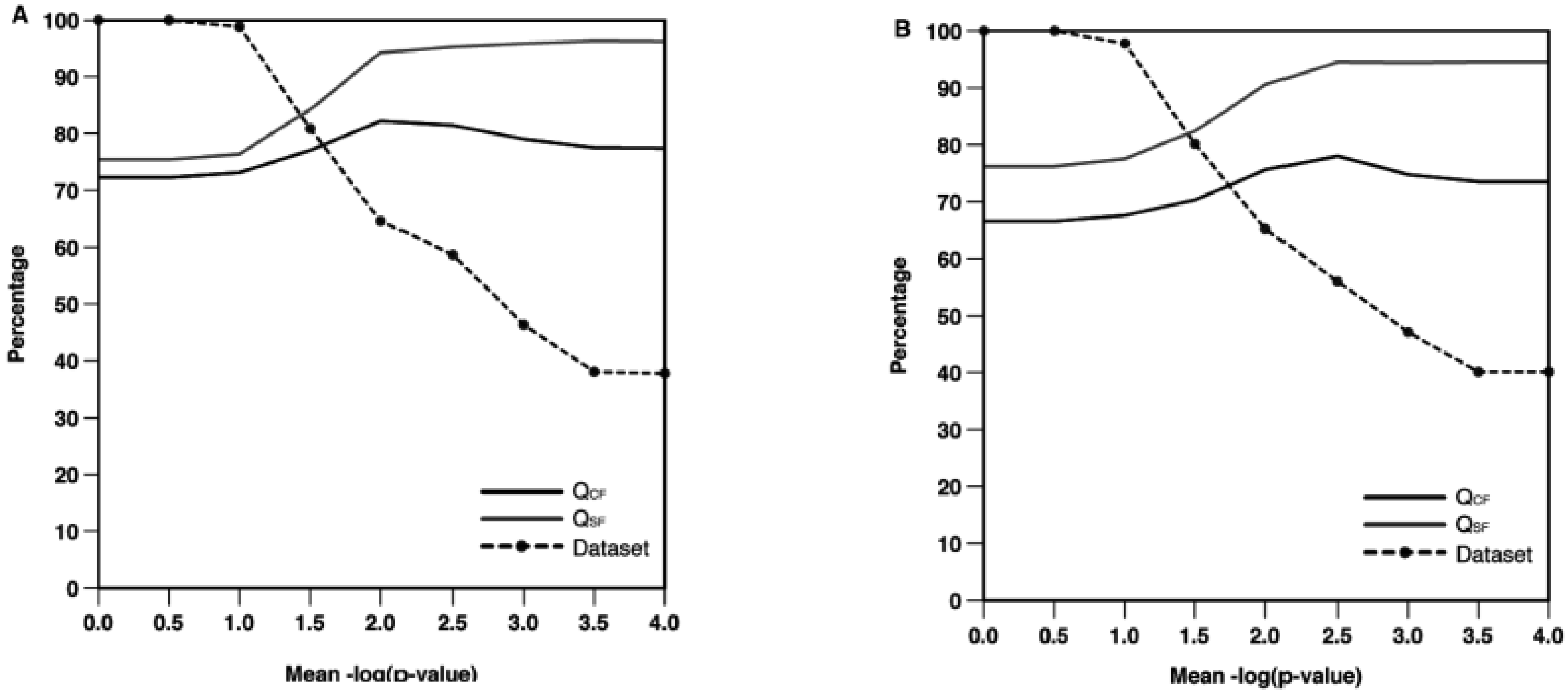
The **SARA method** for functional assignment has been **tested** calculating the **fraction of RNA for which a RNA with the same or similar function** is ranked **in the first position**. RNA with similar function differs only in the deepest SCOR classification term.

First test: Performance resulting from a **leave one out procedure over FSCOR** set.

Second test: Predicton accuracy on the **T-FSCOR** set composed by 227 **RNA structures in FSCOR and not in R-FSCOR.**

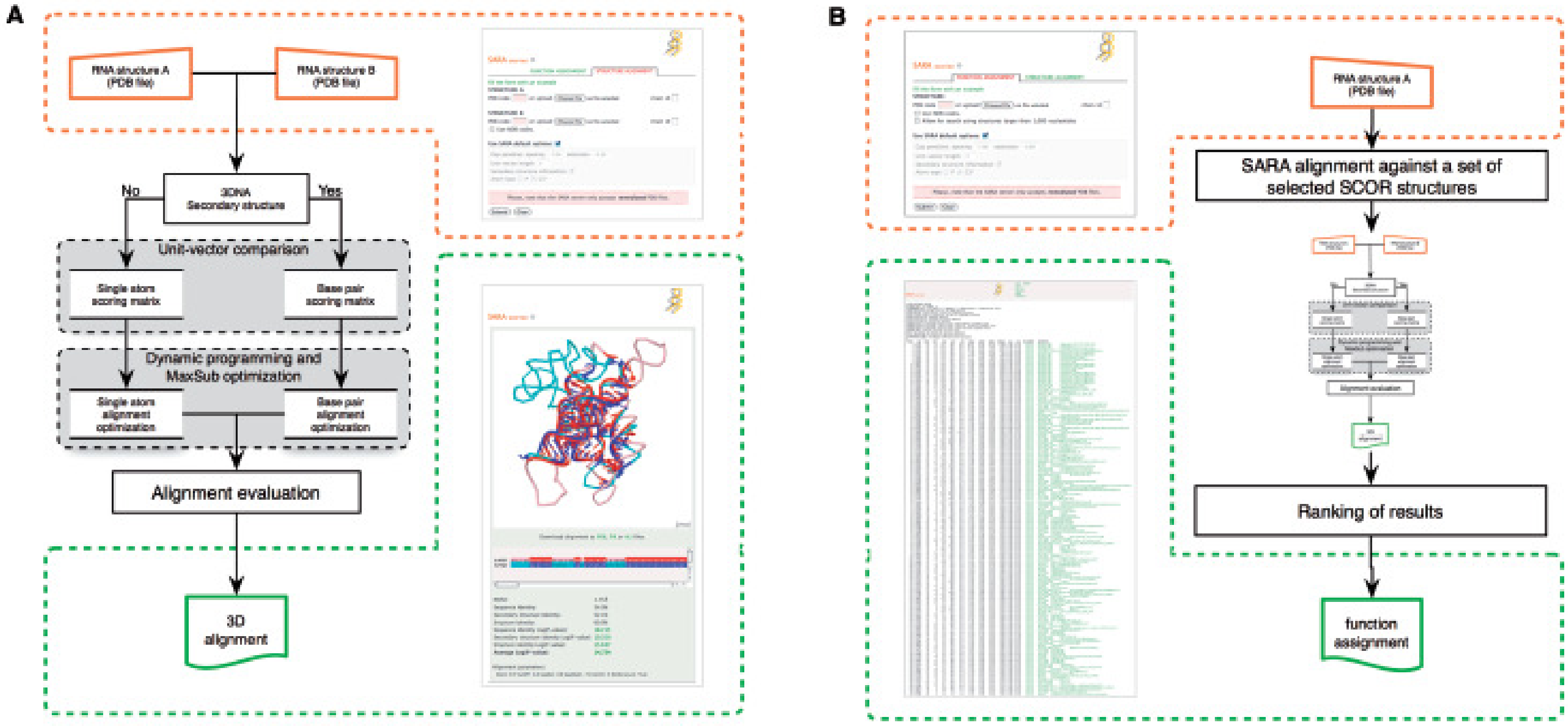
Results

The accuracy of **corrected function (Q_{CF})** and **similar function (Q_{SF})** assignment tasks has been plotted as a function of the mean negative logarithm of the P-values for the best alignment. In **(A)** the plot results from **leave one out on FSCOR** set and **(B) the performances on T-FSCOR** set



SARA server

http://sgu.bioinfo.cipf.es/services/SARA


A
RNA structure A (PDB file)
RNA structure B (PDB file)
No
3DNA Secondary structure
Yes
Unit-vector comparison
Single atom scoring matrix
Base pair scoring matrix
Dynamic programming and MaxSub optimization
Single atom alignment optimization
Base pair alignment optimization
Alignment evaluation
3D alignment
B
RNA structure A (PDB file)
SARA alignment against a set of selected SCOR structures
Ranking of results
function assignment

Capriotti and Marti-Renom NAR 2009

Acknowledgments

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