RNA Comparative Structure Modeling...

three steps ahead

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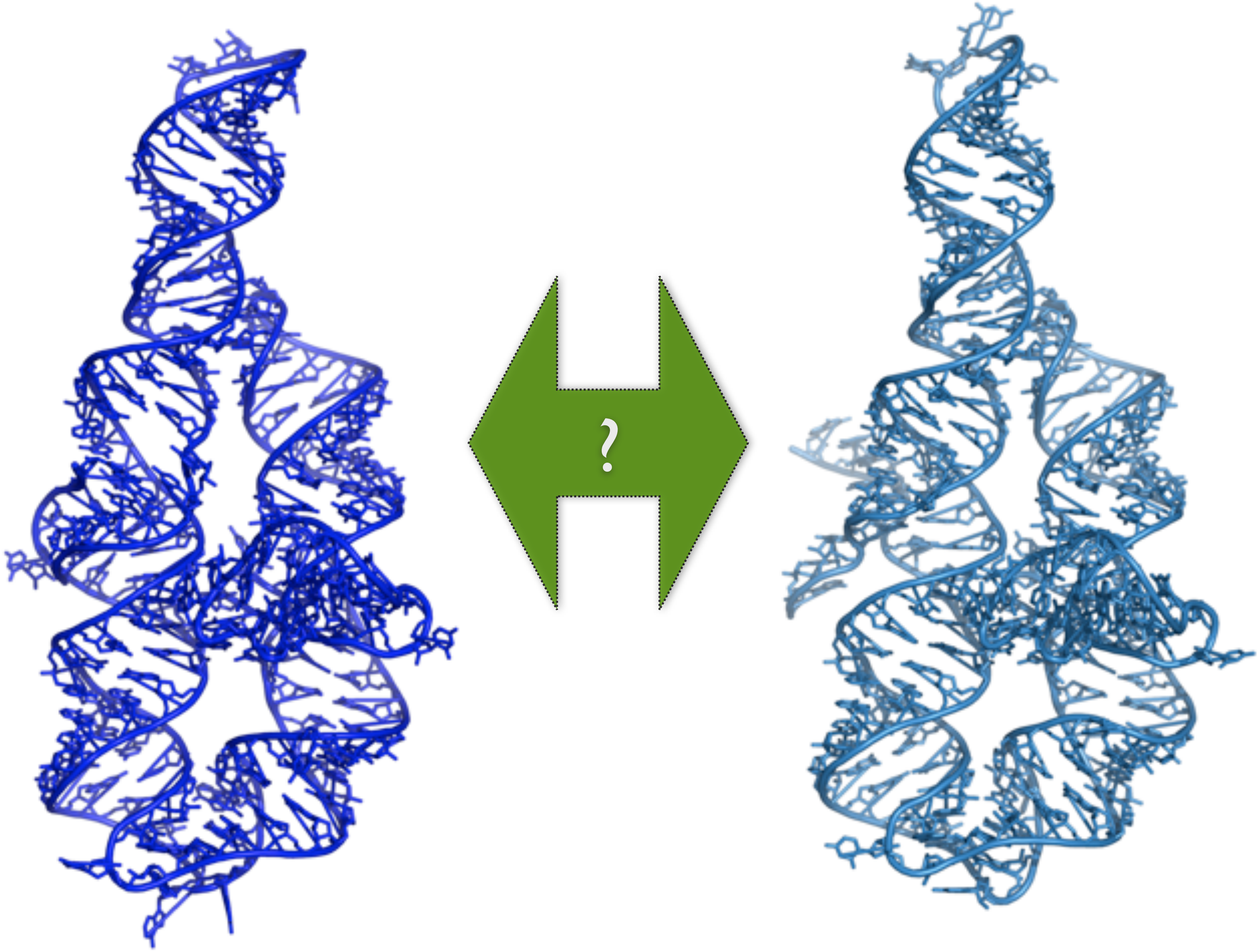
First step

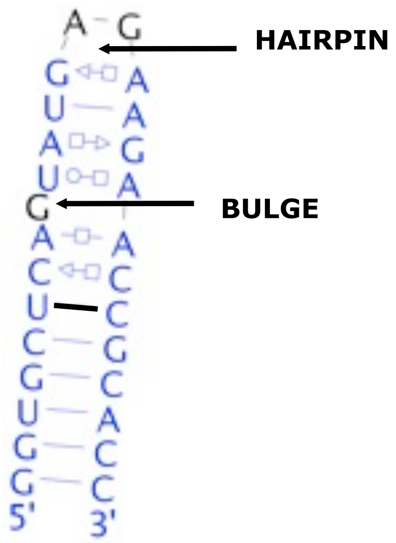
Can we reliably compare RNA structures?



RNA structure

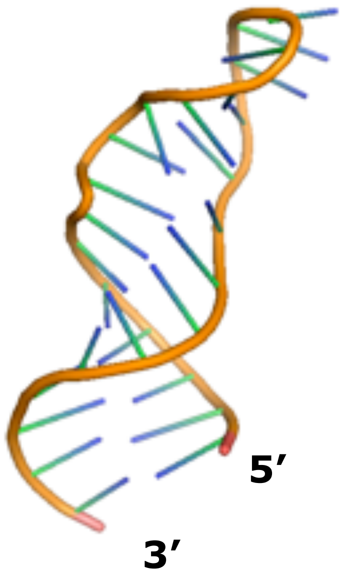
Primary Structure

>Mutant Rat 28S rRNA sarcin/ricin domain
GGUGCUCAGUAUGAGAAGAACCGCACC



Secondary Structure

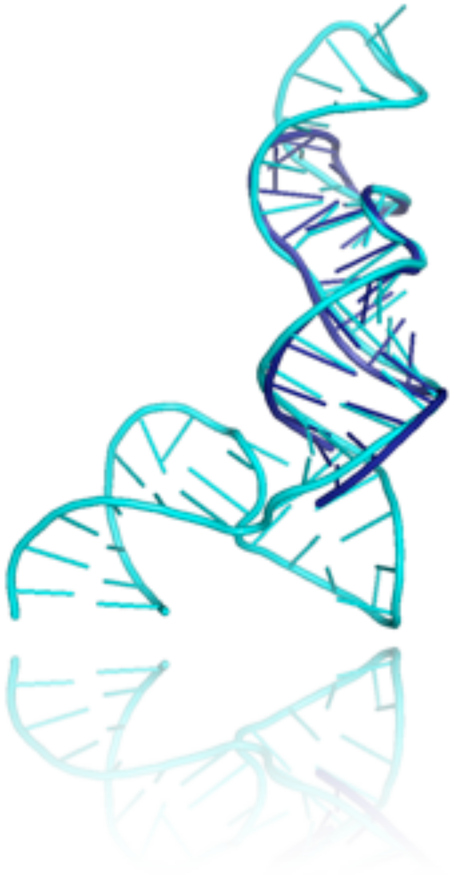
>Mutant Rat 28S rRNA sarcin/ricin domain
GGUGCUCAGUAUGAGAAGAACCGCACC
((((((((.((((..))))))))))))



Tertiary Structure

Secondary Structure interactions and other interactions like pseudoknots, hairpin-hairpin interactions etc.

Structural alignment



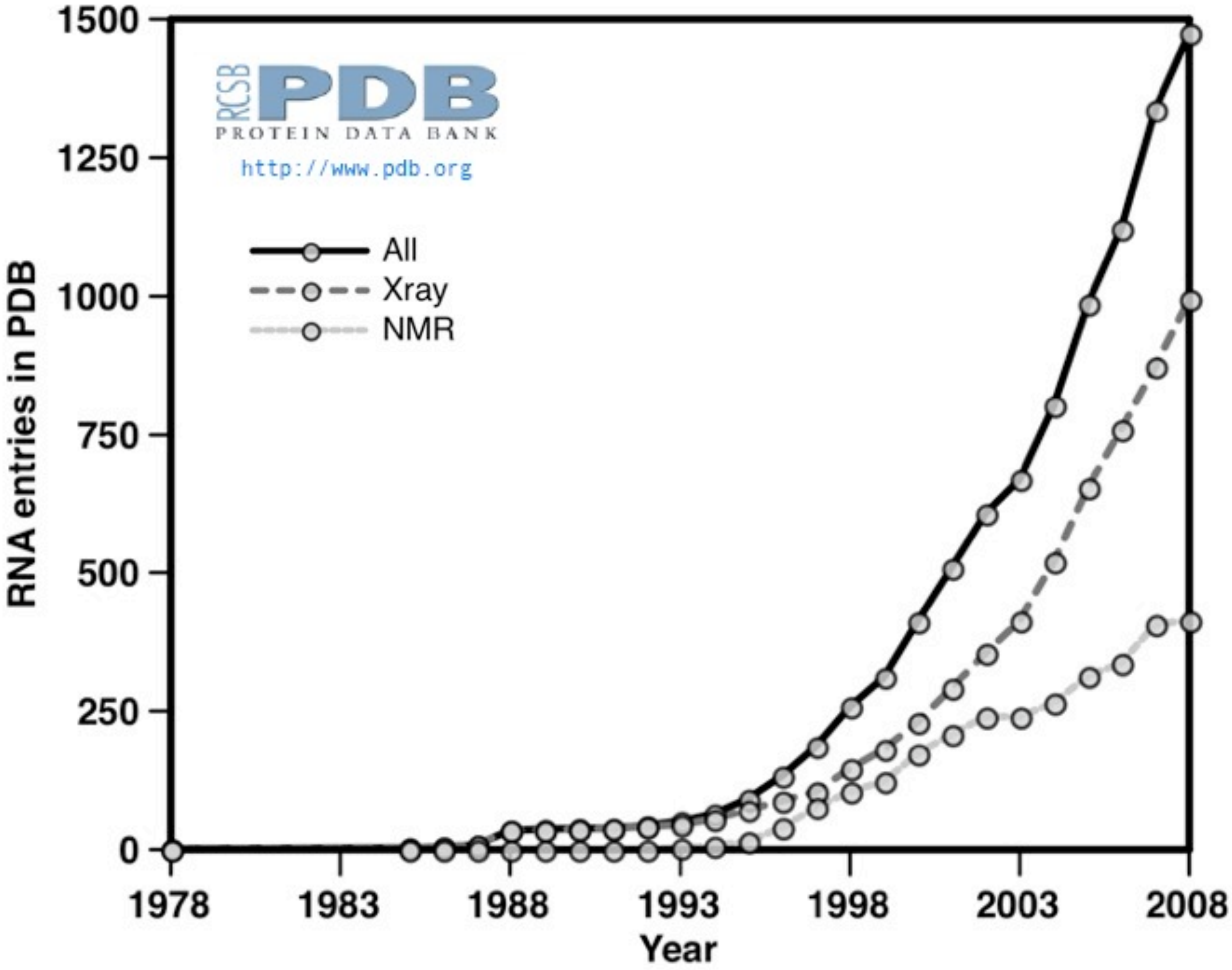
Structural alignment attempts to establish equivalences between two or more polymer structures based on their shape and three-dimensional conformation.

In contrast to simple structural superposition, where at least some equivalent residues of the two structures are known, structural alignment does not require prior knowledge of the equivalent positions.

Structural alignment has been used as a valuable tool for the comparison of proteins, including the inference of evolutionary relationships between proteins of remote sequence similarity.

RNA Structure

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



RNA structure datasets

RNA STRUCTURE*	**1,101**
RNA CHAINS	**2,179**
Non-Redundant RNA CHAINS**	**744**
RNA CHAINS (20≤ Length ≤310)	**313**
HIGH RESOLUTION RNA SET***	**54**

NR95

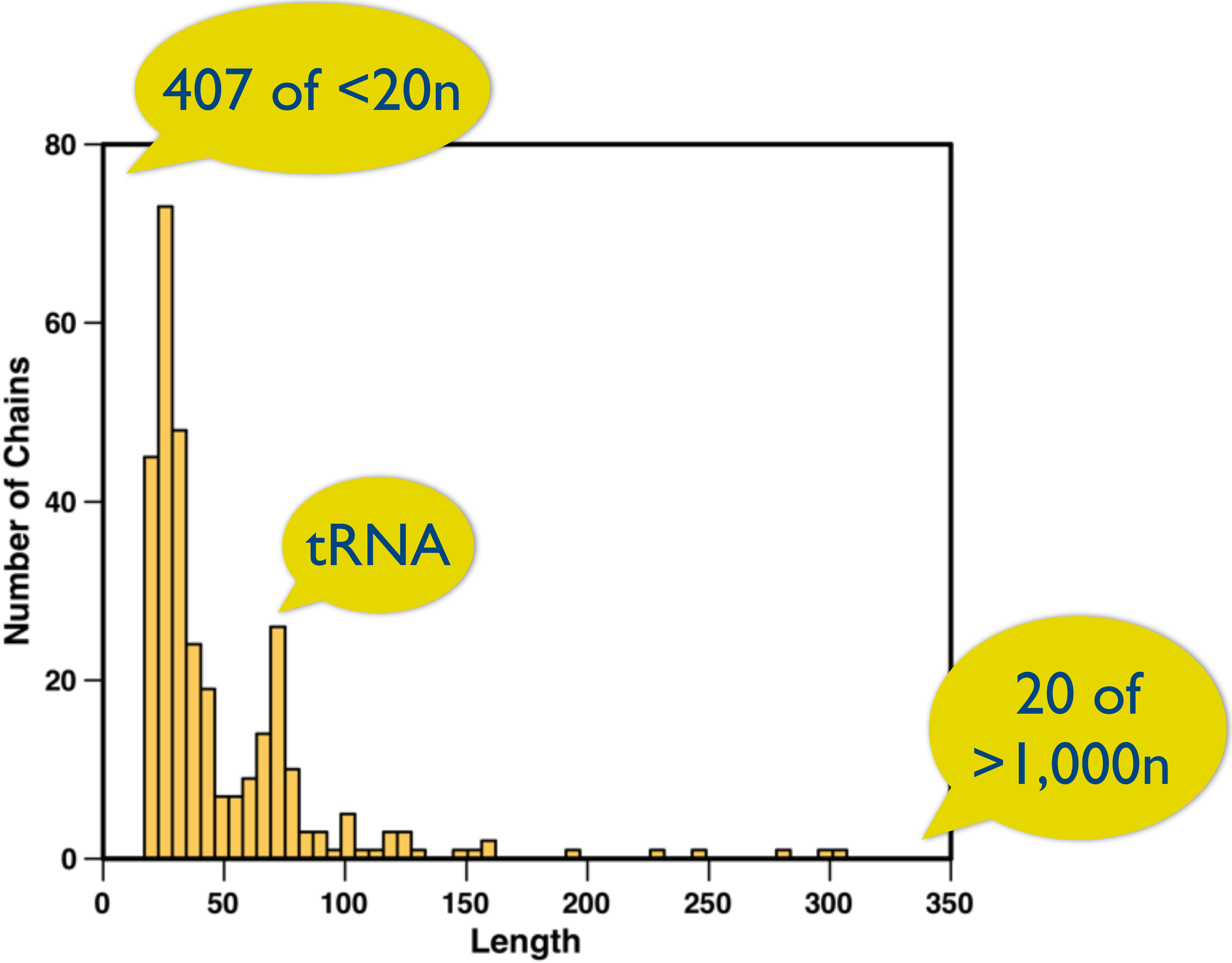
HR

** from PDB November 06.*

*** non-redundant 95% sequence identity*

**** Resolution below 4.0 Å and with no missing backbone atoms.*

Dataset distribution



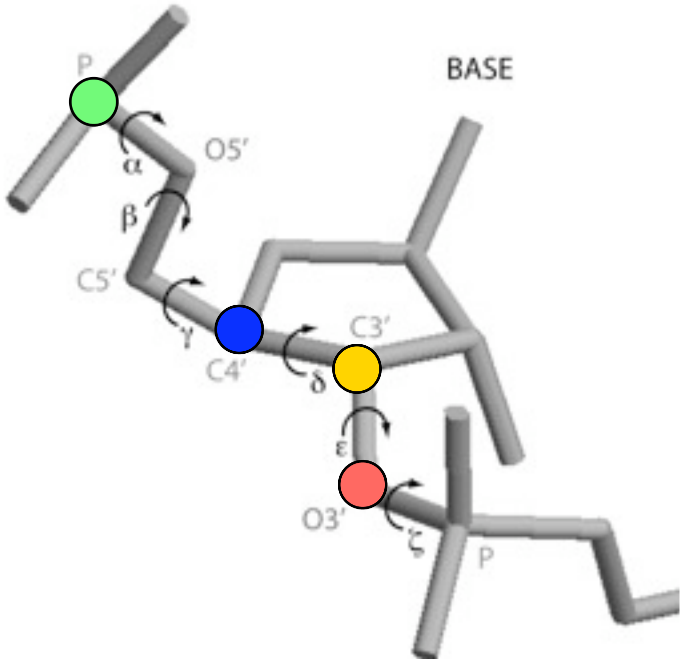
407 of <20n

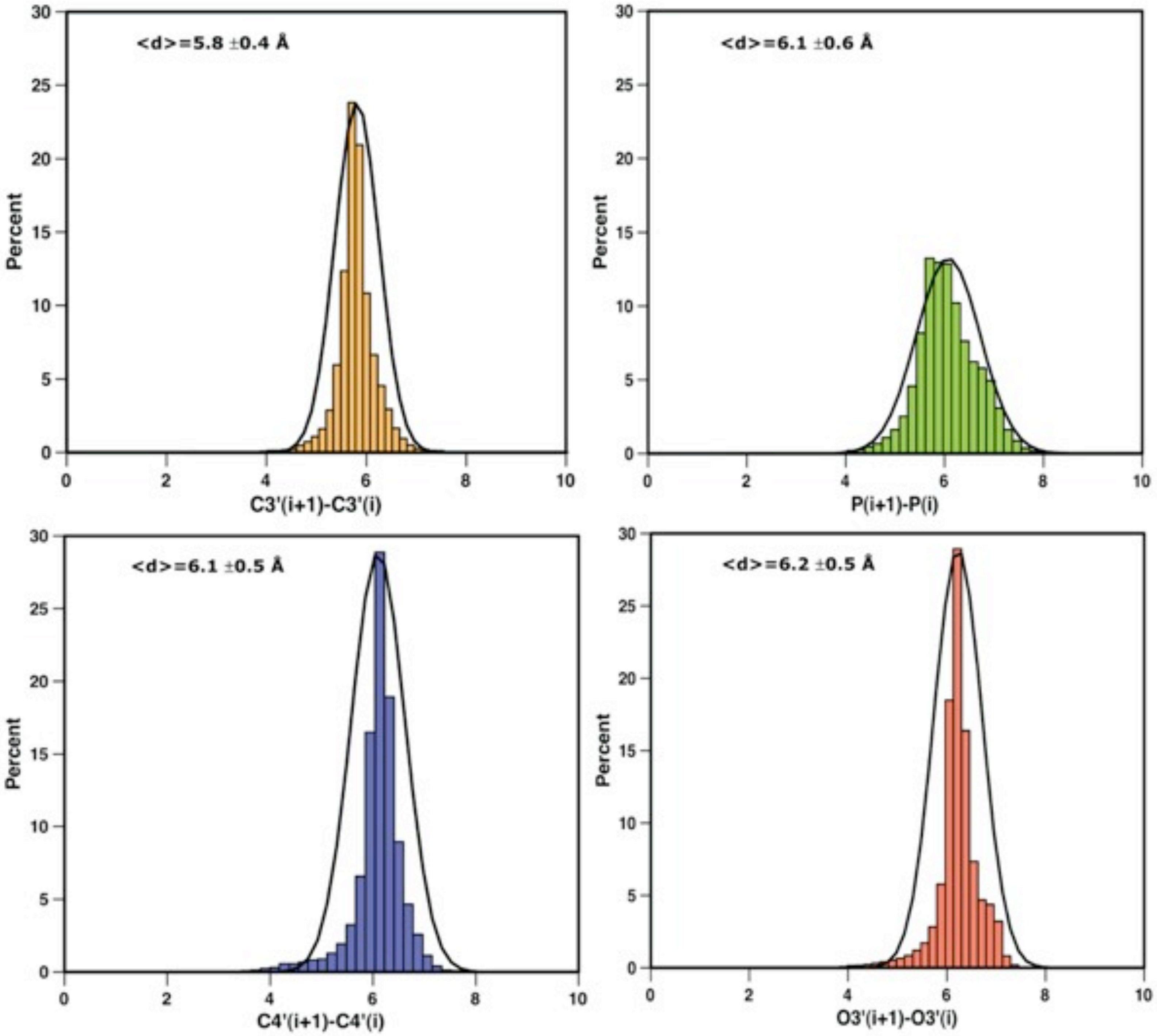
tRNA

20 of >1,000n

Atom selection

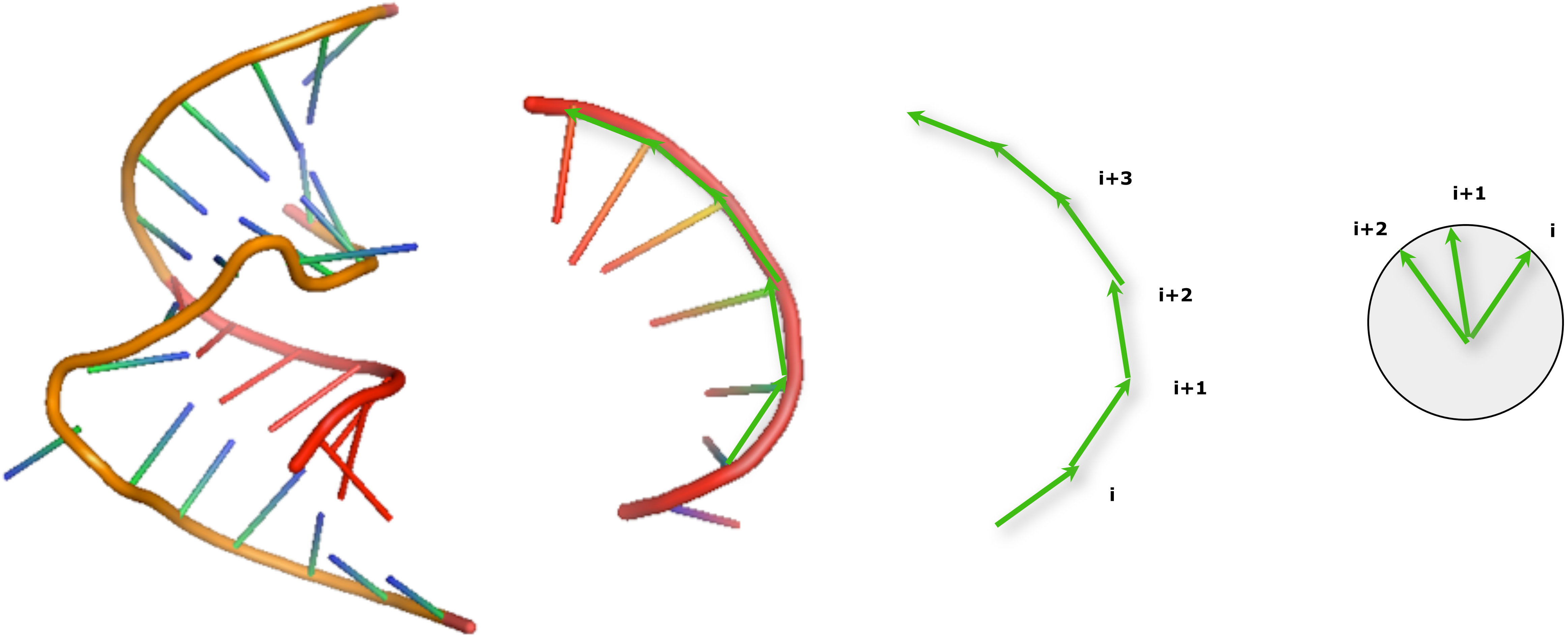
The best backbone atom that represents the RNA structure has been selected by evaluating the distribution of the distances between consecutive atoms in structures from the NR95 set.





Unit Vector I

Representation



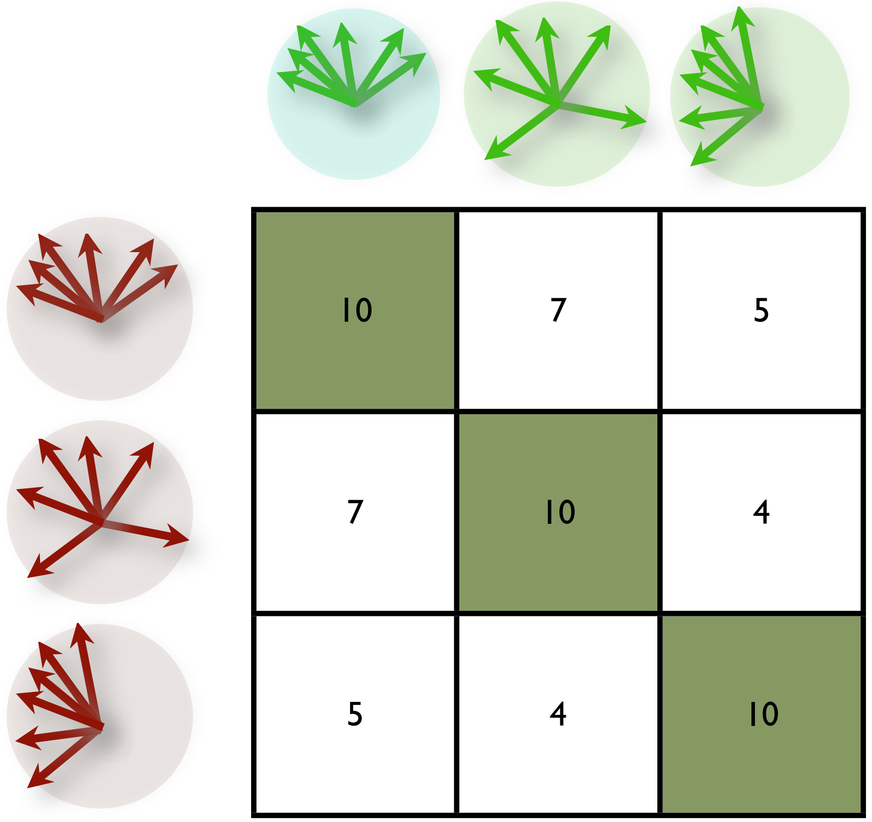
A Unit Vector is the normalized vector between two successive C3’ atoms.

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

Ortiz et al. *Proteins* 2002

Unit Vector II

Scoring



10	7	5
7	10	4
5	4	10

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

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

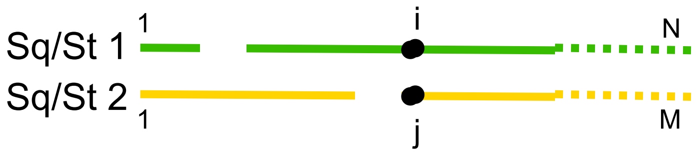
$$\Delta(URMS^R, URMS^{ij}) = 10 \Rightarrow URMS^R > URMS^{ij}$$
$$\Delta(URMS^R, URMS^{ij}) = 0 \Rightarrow URMS^R \leq URMS^{ij}$$

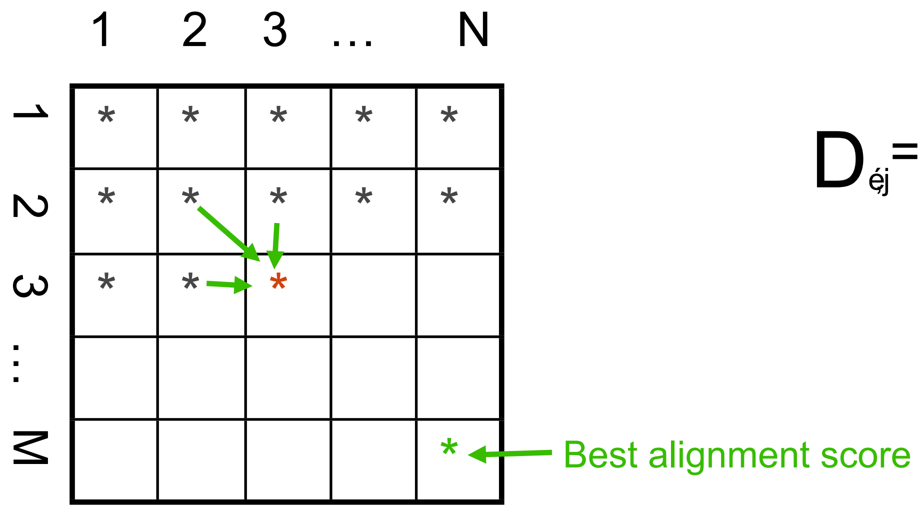
For each position i, the k consecutive unit vectors are grouped and aligned to the j set of unit vectors. Each pair of aligned unit vectors will be evaluated by calculating Unit Root Mean Square distance ($URMS^{ij}$).

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 than calculated normalizing $URMS^{ij}$ to the $URMS^R$ value.

Alignment





$$D_{éj}=\min\begin{cases}D_{i,j-1}+\text{Score}_{(\text{Ä},rj)}\\ D_{i-1,j-1}+\text{Score}_{(ri,rj)}\\ D_{i-1,j}+\text{Score}_{(ri,\text{Ä})}\end{cases}$$

Backtracking to get the best alignment

A Dynamic Programming procedure is then 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 corresponding C3’ within 3.5 Å in the space are evaluated. The number of close atoms is used to evaluate the percentage of structural identity (PSI) using a variant of the MaxSub algorithm.

Needleman and Wunsch J. Mol.Biol 1970
Siew et al. Bioinformatics 2000

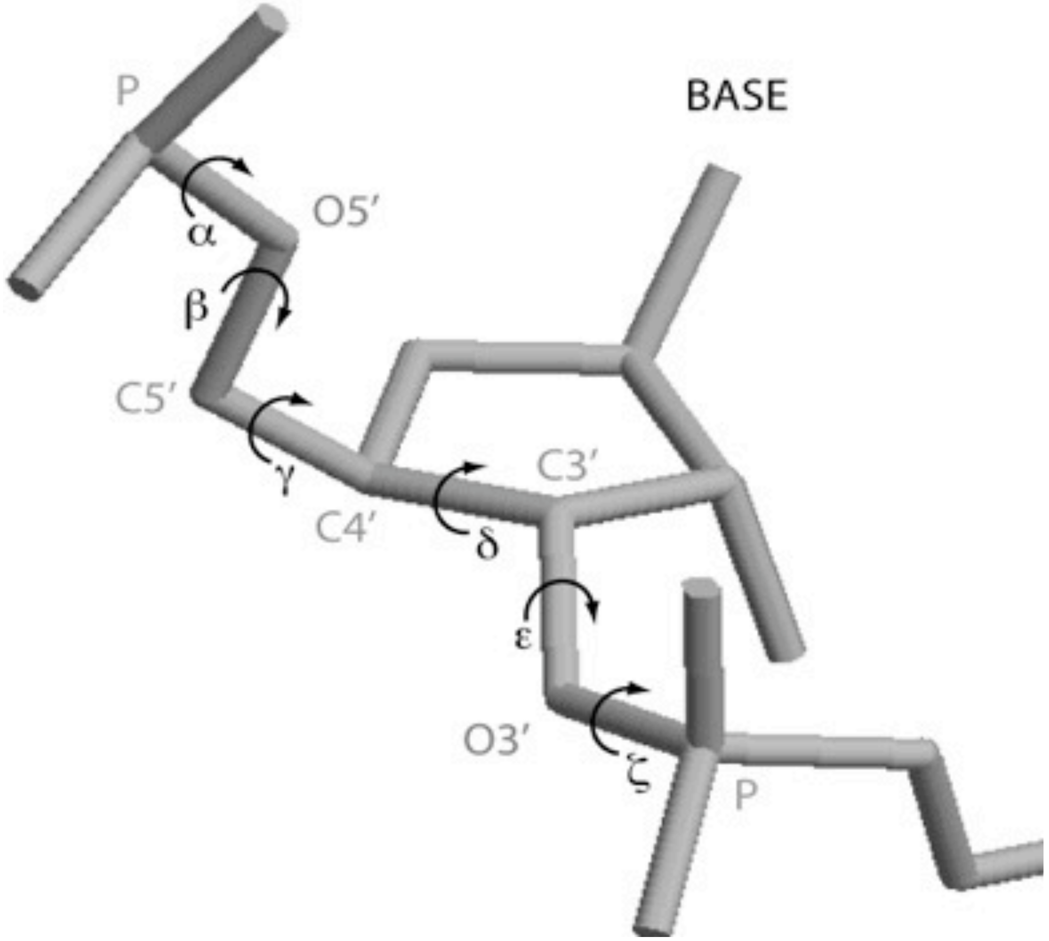
Random RNA

In order to build a background distribution that reproduce the scores given by the structural alignments of unrelated RNA sequences, we generated a set 300 random RNA sequences and structures with sequence length uniformly distributed between 20 and 320 nucleotides.

The RNA backbone can be described given the 6 torsion angle (α,β,γ,δ,ε,ζ) for each nucleotide.

The RNA backbone is rotameric and only 42 conformation have been described from a set o high resolution structures .

According to this observation we generated the 300 structures, randomly selecting the backbone angles among the 42 possible conformations.

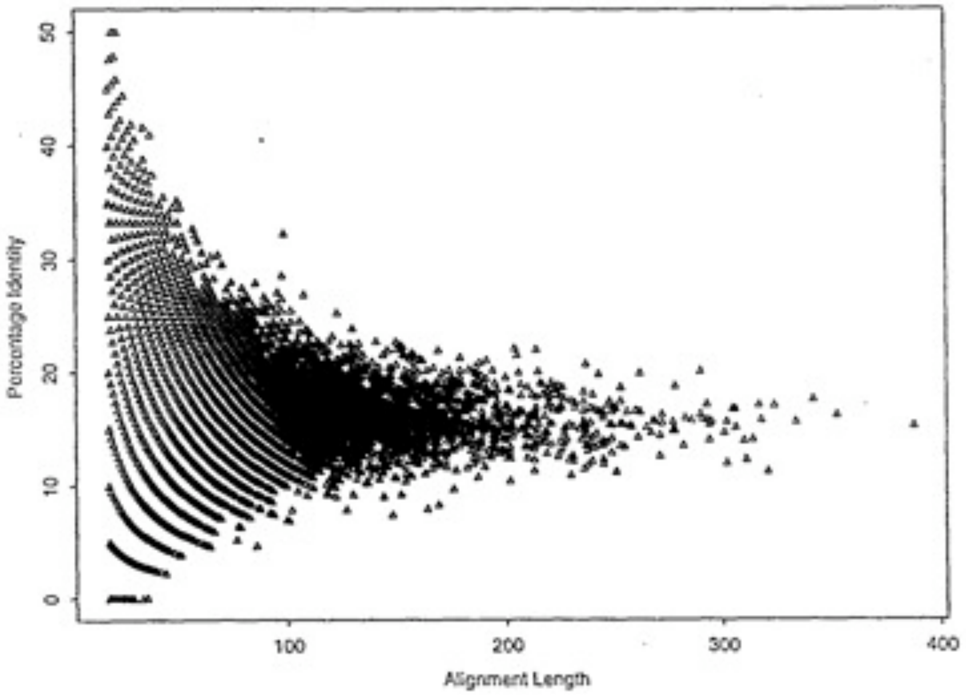


Murray et al PNAS 2003

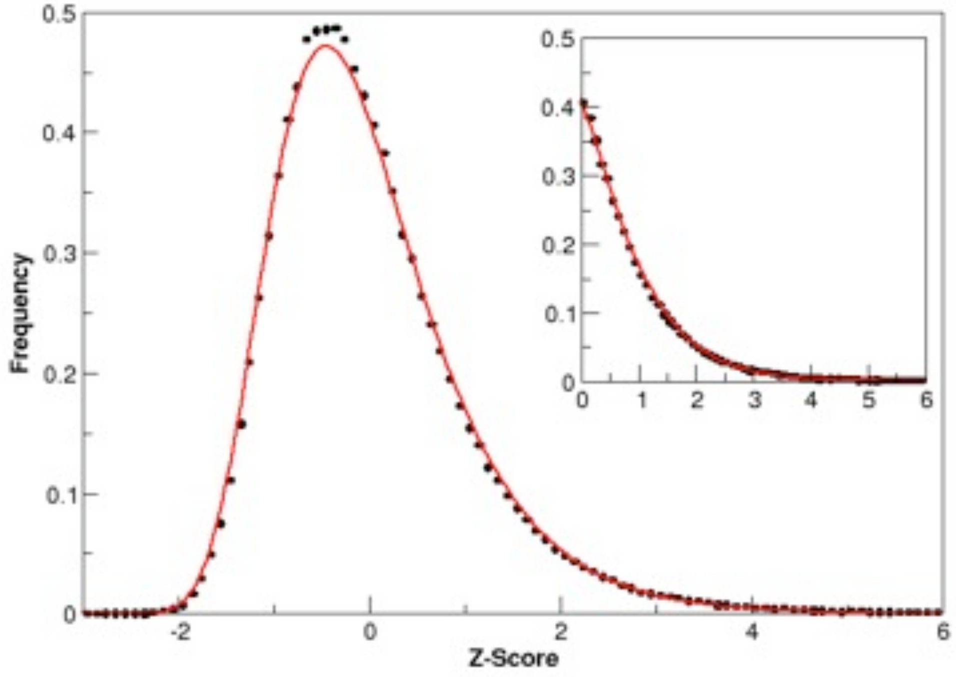
Background distribution

Considering a dataset of 300 random RNA structures, we have produced ~45,000 pairwise alignments that resulted in a empirical distribution. From such distribution we can then evaluate μ and σ needed to calculated the p-value for P(s>=x).

Empirical



Analytic



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

Karlin and Altschul, 1990 *PNAS* **87**, pp2264

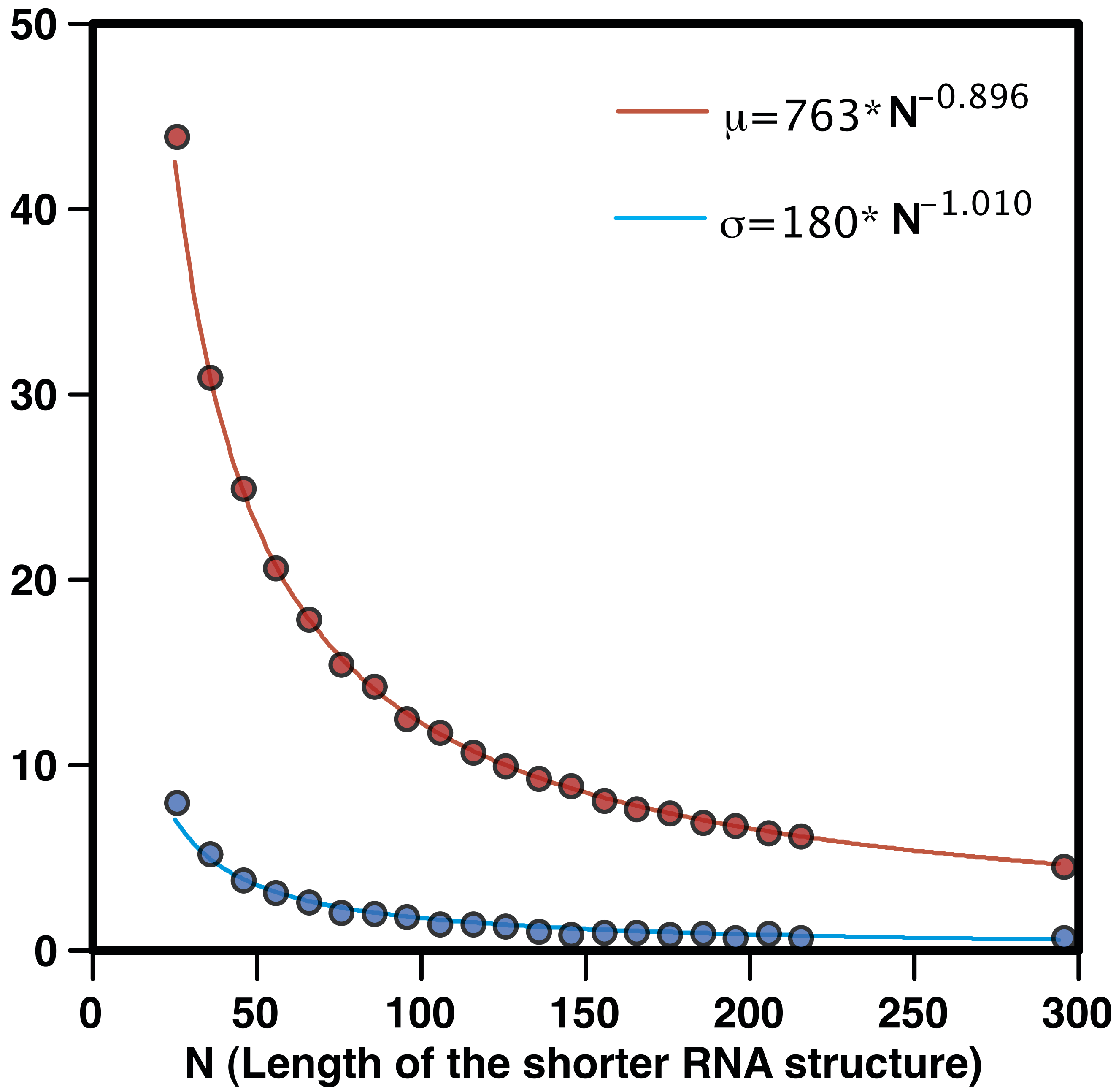
Mean and sigma

The score distribution depends on the length of the molecule.

We divided the resulting structural alignments (~45,000) in 30 bins according to the shorter sequence length of the two random structures (N).

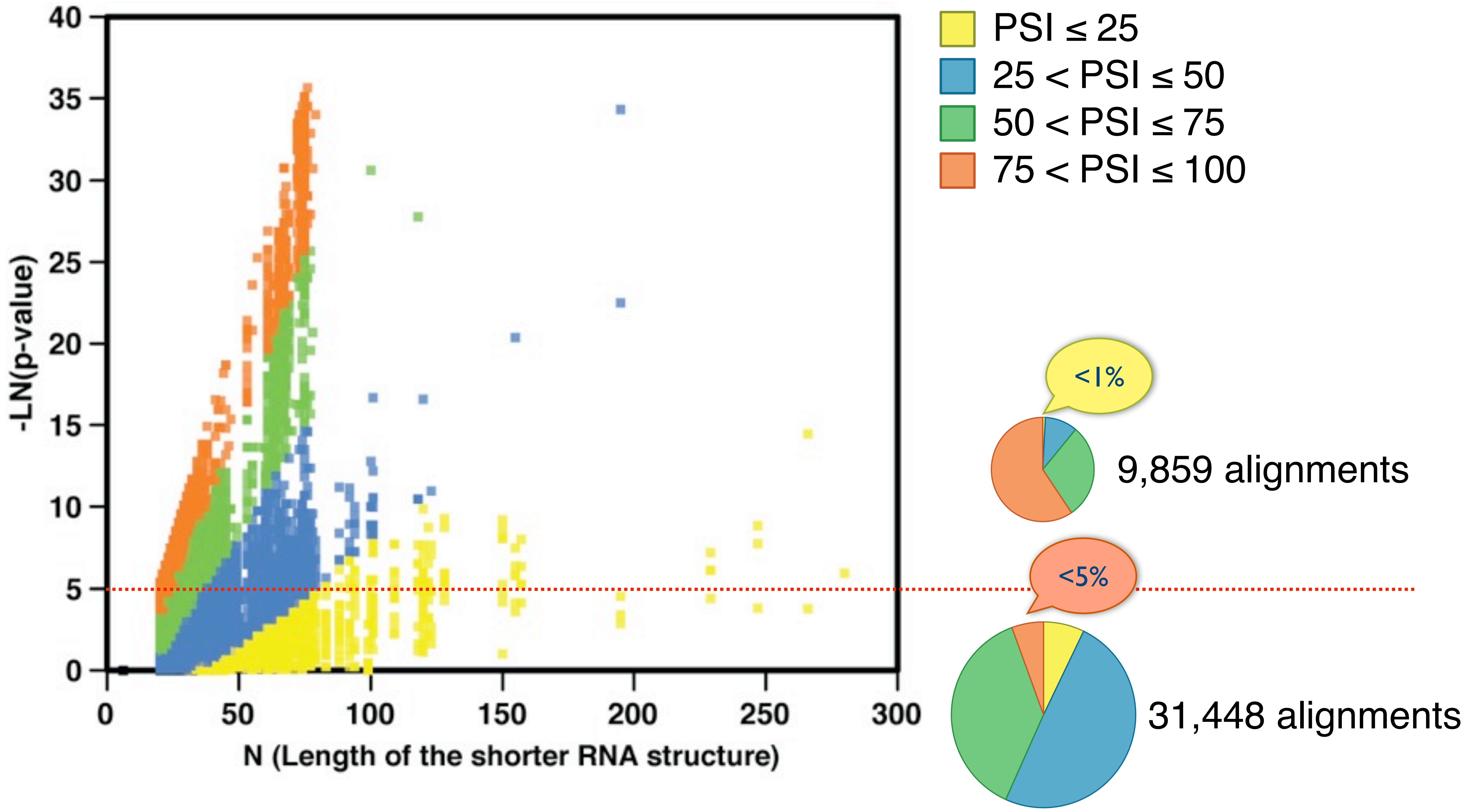
For each bin the µ and σ values are evaluated fitting the data to an EVD.

The relations between N and µ, σ values are extrapolate fitting them to a power low function (r≈0.99).

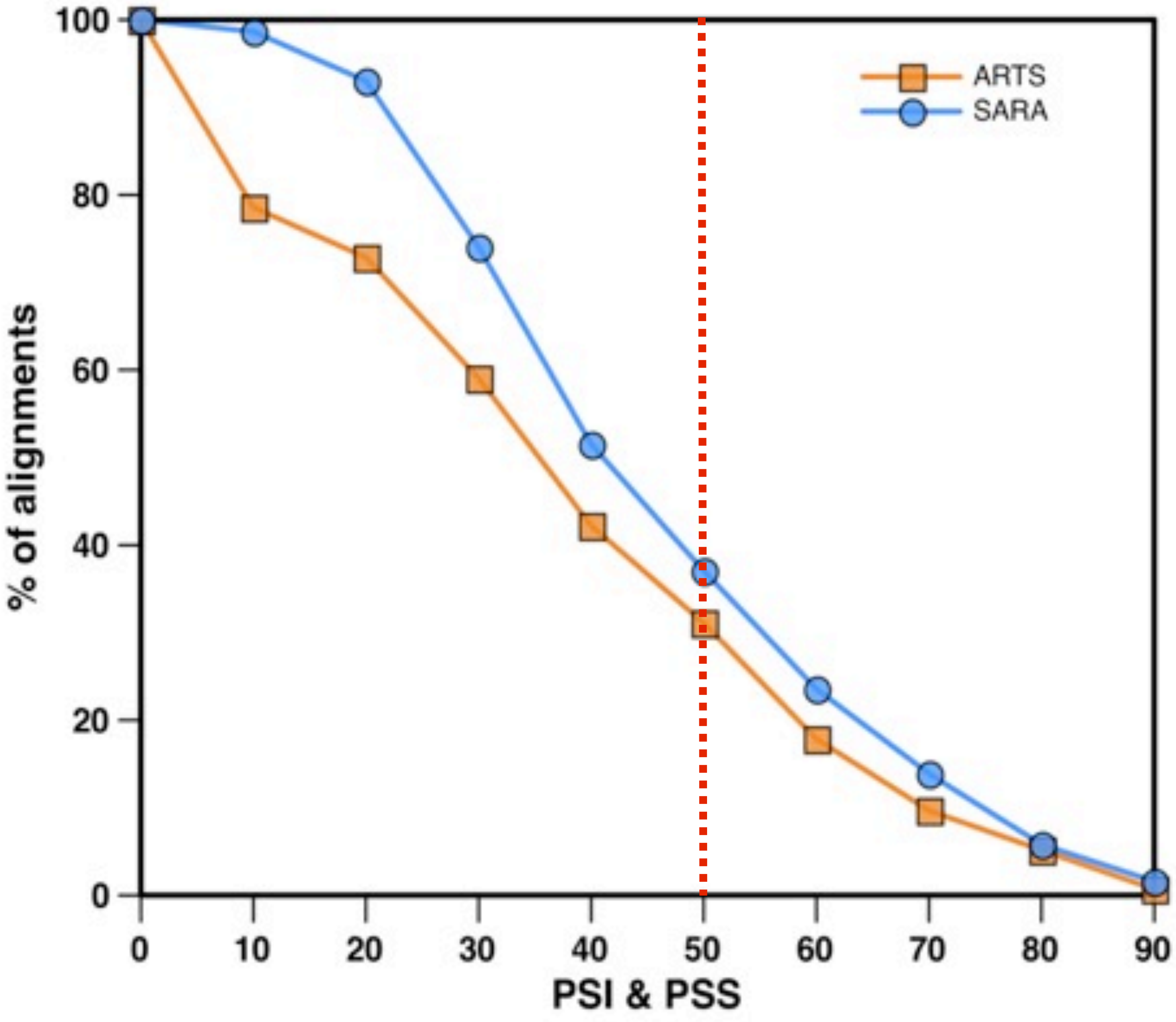


Statistical significance

all-against-all comparison of structures in the NR95 set



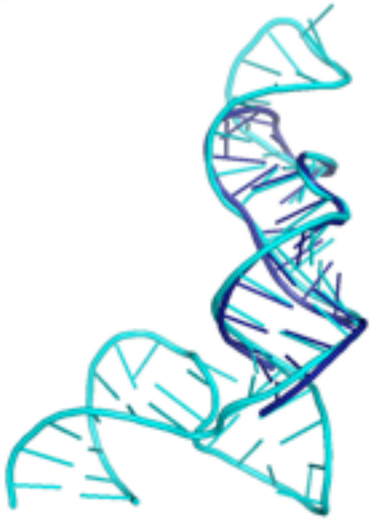
SARA .vs. ARTS



PSI: % of structure identity

PSS: % of secondary structure identity

Cut-off distance: 4.0 Å



SARA

Percentage of structure identity (PSI) 92.6%
Percentage of sequence identity 48.0%
Percentage of SSE identity 100.0%
RMSD 1.78 Å

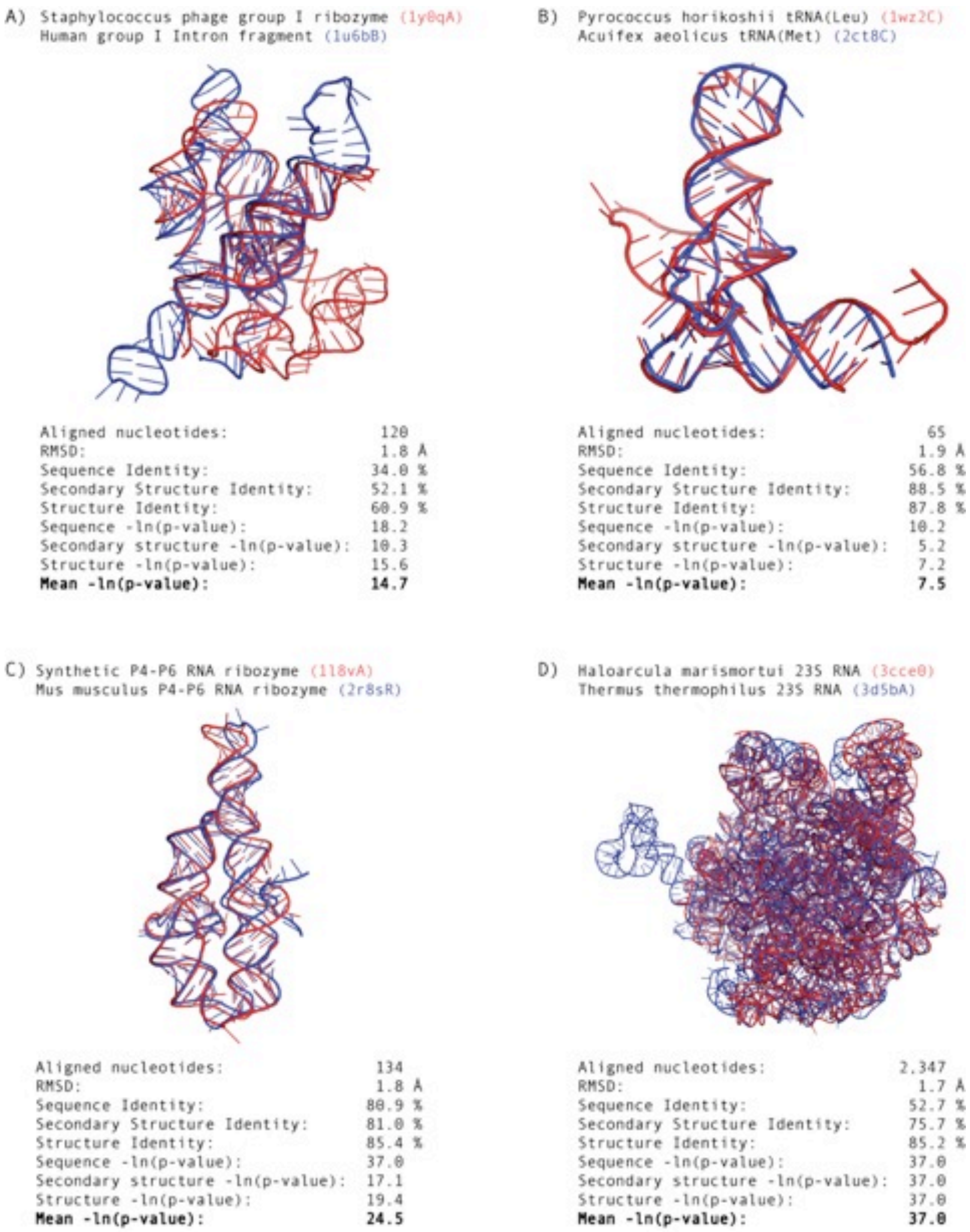
```
>1q96 Chain:A
-------------------ggugcucaguaugag--------aagaaccgcacc-------
>1un6 Chain:E
gccggccacaccuacggggccugguuaguaccugggaaaccugggaauaccaggugccggc
```

ARTS

Percentage of structure identity (PSI) 76.9%
Percentage of sequence identity 20.0%
Percentage of SSE identity 79.2%
RMSD 1.66Å

```
>1q96 Chain:A
--------------------gugcucaguaugaga-----aga-accgcacc--------
>1un6 Chain:E
ccggccacaccuacggggccugguuaguaccugggaaaccugggaauaccaggugccggc
```

SARA Alignments



A) Staphylococcus phage group I ribozyme (1y0qA)
Human group I Intron fragment (1u6bB)

Aligned nucleotides:	120
RMSD:	1.8 Å
Sequence Identity:	34.0 %
Secondary Structure Identity:	52.1 %
Structure Identity:	60.9 %
Sequence -ln(p-value):	18.2
Secondary structure -ln(p-value):	10.3
Structure -ln(p-value):	15.6
Mean -ln(p-value):	**14.7**

B) Pyrococcus horikoshii tRNA(Leu) (1wz2C)
Acuifex aeolicus tRNA(Met) (2ct8C)

Aligned nucleotides:	65
RMSD:	1.9 Å
Sequence Identity:	56.8 %
Secondary Structure Identity:	88.5 %
Structure Identity:	87.8 %
Sequence -ln(p-value):	10.2
Secondary structure -ln(p-value):	5.2
Structure -ln(p-value):	7.2
Mean -ln(p-value):	**7.5**

C) Synthetic P4-P6 RNA ribozyme (118vA)
Mus musculus P4-P6 RNA ribozyme (2r8sR)

Aligned nucleotides:	134
RMSD:	1.8 Å
Sequence Identity:	80.9 %
Secondary Structure Identity:	81.0 %
Structure Identity:	85.4 %
Sequence -ln(p-value):	37.0
Secondary structure -ln(p-value):	17.1
Structure -ln(p-value):	19.4
Mean -ln(p-value):	**24.5**

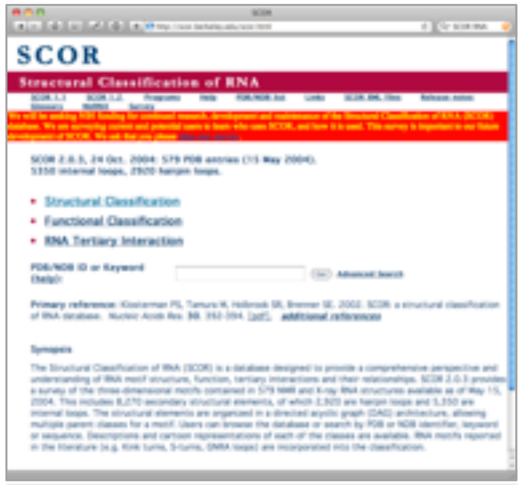
D) Haloarcula marismortui 23S RNA (3cce0)
Thermus thermophilus 23S RNA (3d5bA)

Aligned nucleotides:	2,347
RMSD:	1.7 Å
Sequence Identity:	52.7 %
Secondary Structure Identity:	75.7 %
Structure Identity:	85.2 %
Sequence -ln(p-value):	37.0
Secondary structure -ln(p-value):	37.0
Structure -ln(p-value):	37.0
Mean -ln(p-value):	**37.0**

Second step...

Can we reliably predict RNA function from structure?

RNA function annotation



SCOR

Structural Classification of RNA

SCOR 1.1 SCOR 1.2 Programs Help PDB/NDB list Links SCOR XML Files Release notes Glossary NURNA Survey

We will be seeking NIH funding for continued research, development and maintenance of the Structural Classification of RNA (SCOR) database. We are surveying current and potential users to learn who uses SCOR, and how it is used. This survey is important to our future development of SCOR. We ask that you please take our survey.

SCOR 2.0.3, 24 Oct. 2004: 579 PDB entries (15 May 2004).
5350 internal loops, 2920 hairpin loops.

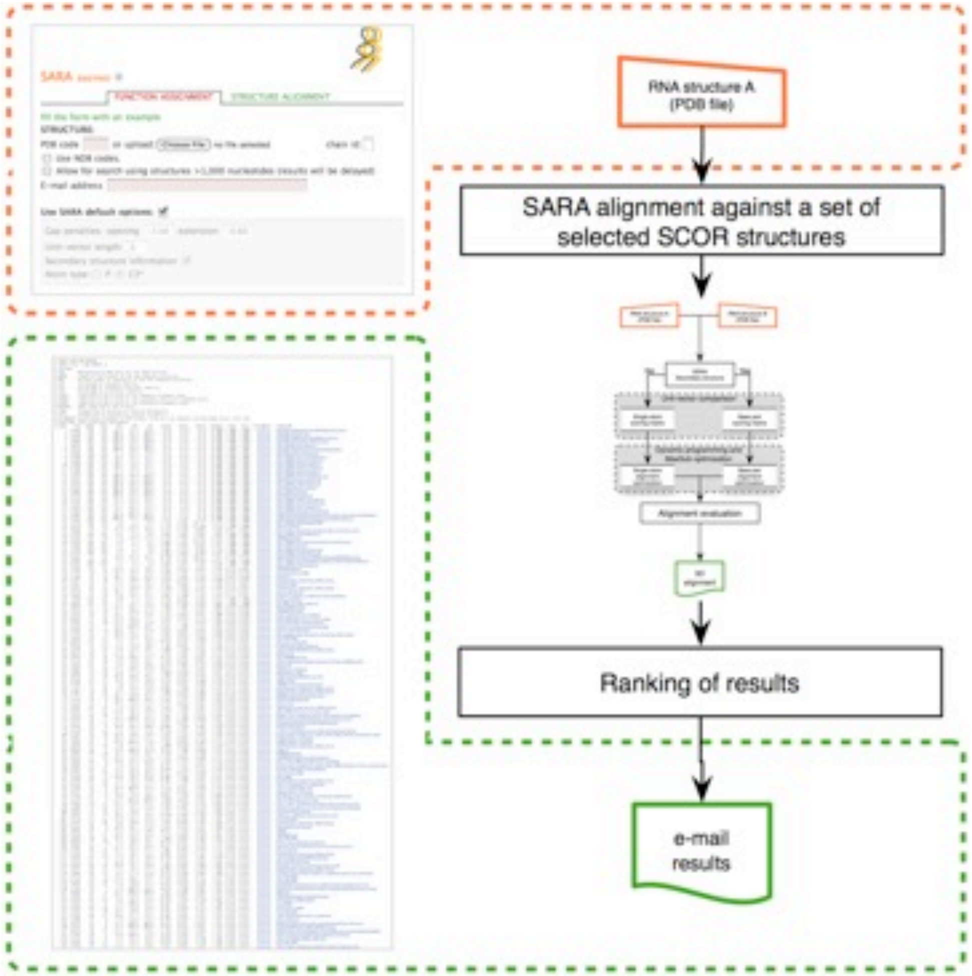
- Structural Classification
- Functional Classification
- RNA Tertiary Interaction

PDB/NDB ID or Keyword (help): Go Advanced Search

Primary reference: Klosterman PS, Tamura M, Holbrook SR, Brenner SE. 2002. SCOR: a structural classification of RNA database. Nucleic Acids Res. 30: 392-394. [pdf]. additional references

Synopsis

The Structural Classification of RNA (SCOR) is a database designed to provide a comprehensive perspective and understanding of RNA motif structure, function, tertiary interactions and their relationships. SCOR 2.0.3 provides a survey of the three-dimensional motifs contained in 579 NMR and X-ray RNA structures available as of May 15, 2004. This includes 8,270 secondary structural elements, of which 2,920 are hairpin loops and 5,350 are internal loops. The structural elements are organized in a directed acyclic graph (DAG) architecture, allowing multiple parent classes for a motif. Users can browse the database or search by PDB or NDB identifier, keyword or sequence. Descriptions and cartoon representations of each of the classes are available. RNA motifs reported in the literature (e.g. Kink turns, S-turns, tRNA loops) are incorporated into the classification.



SARA

FUNCTION ASSIGNMENT | STRUCTURE ALIGNMENT

Fill the form with an example

STRUCTURE:

PDB code ☐ or upload (Choose File) no file selected chain id: ☐

☐ Use NDB codes

☐ Allow for search using structures >1,000 nucleotides (results will be delayed)

E-mail address

Use SARA default options: ☑

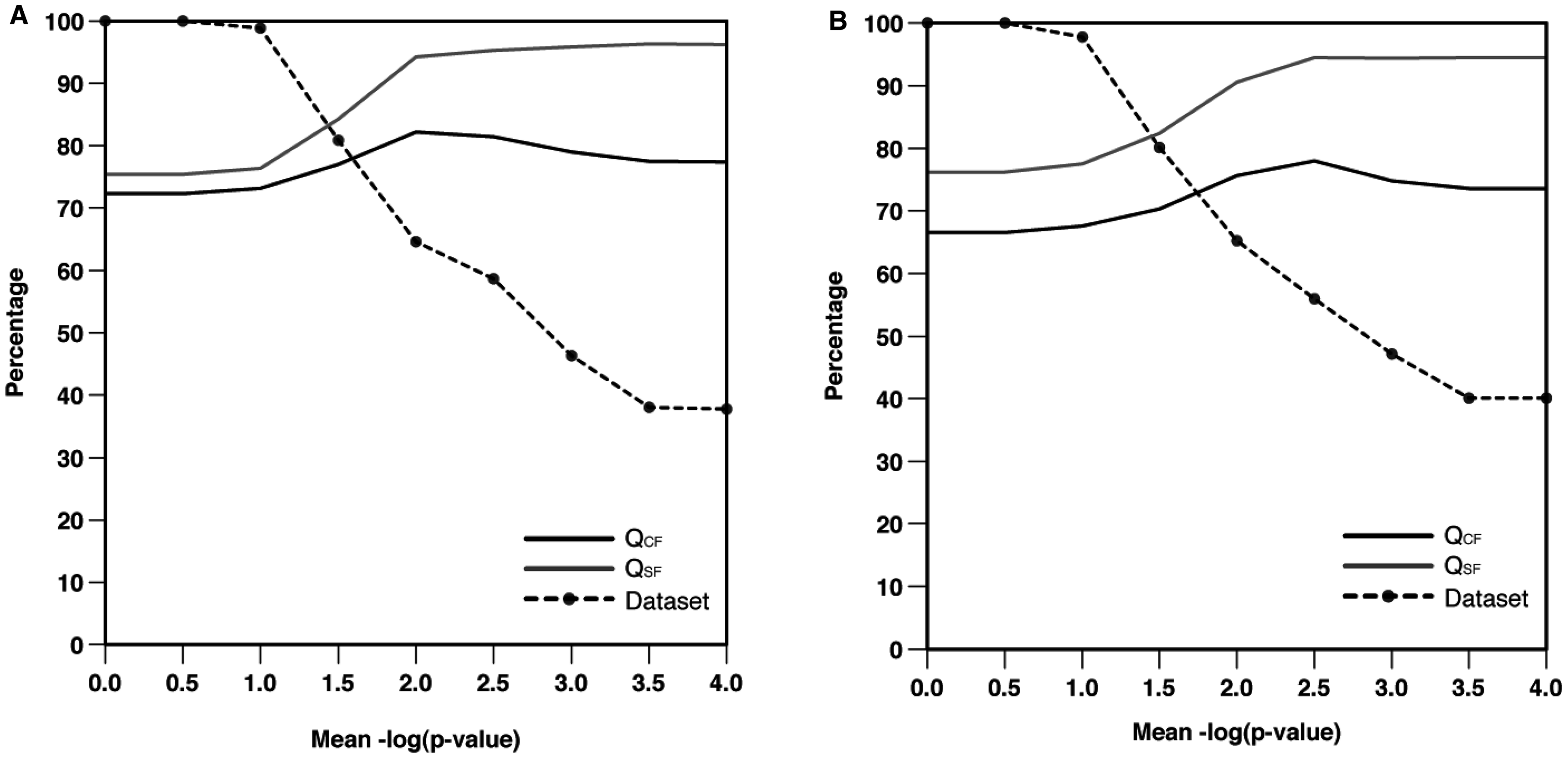
Capriotti and Marti-Renom Bioinformatics 2008
Tamura et al. NAR 2004

Results

Datasets	Number of chains	Number of alignments	Number of different SCOR functions
RNA09	451	101 475	
BgALI	451	50 995	
FSCOR	419		168
R-FSCOR	192		168
T-FSCOR	227		88

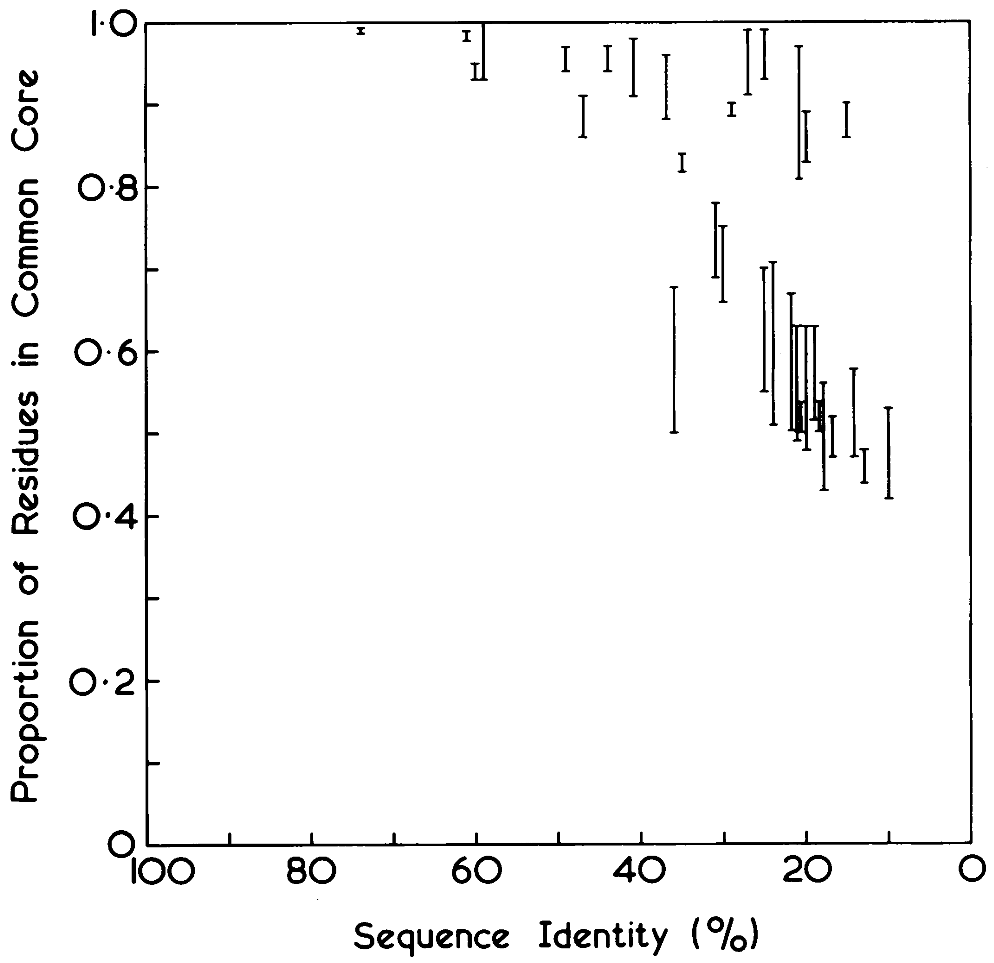
leave one out on FSCOR

performances on T-FSCOR

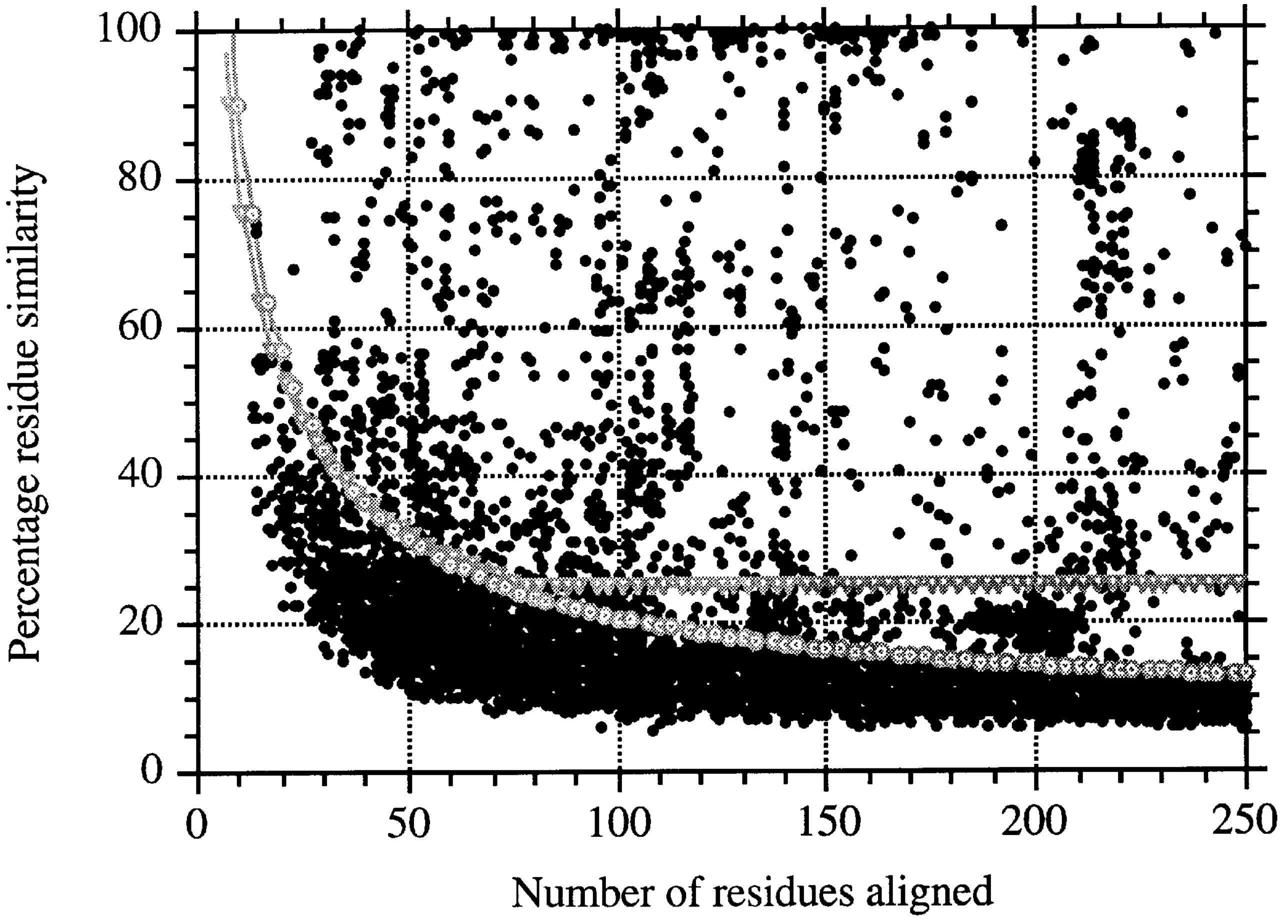


Third step...

To what extend can we do comparative RNA structure prediction?

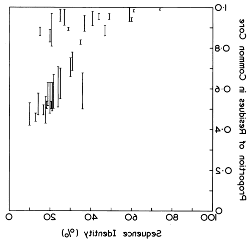


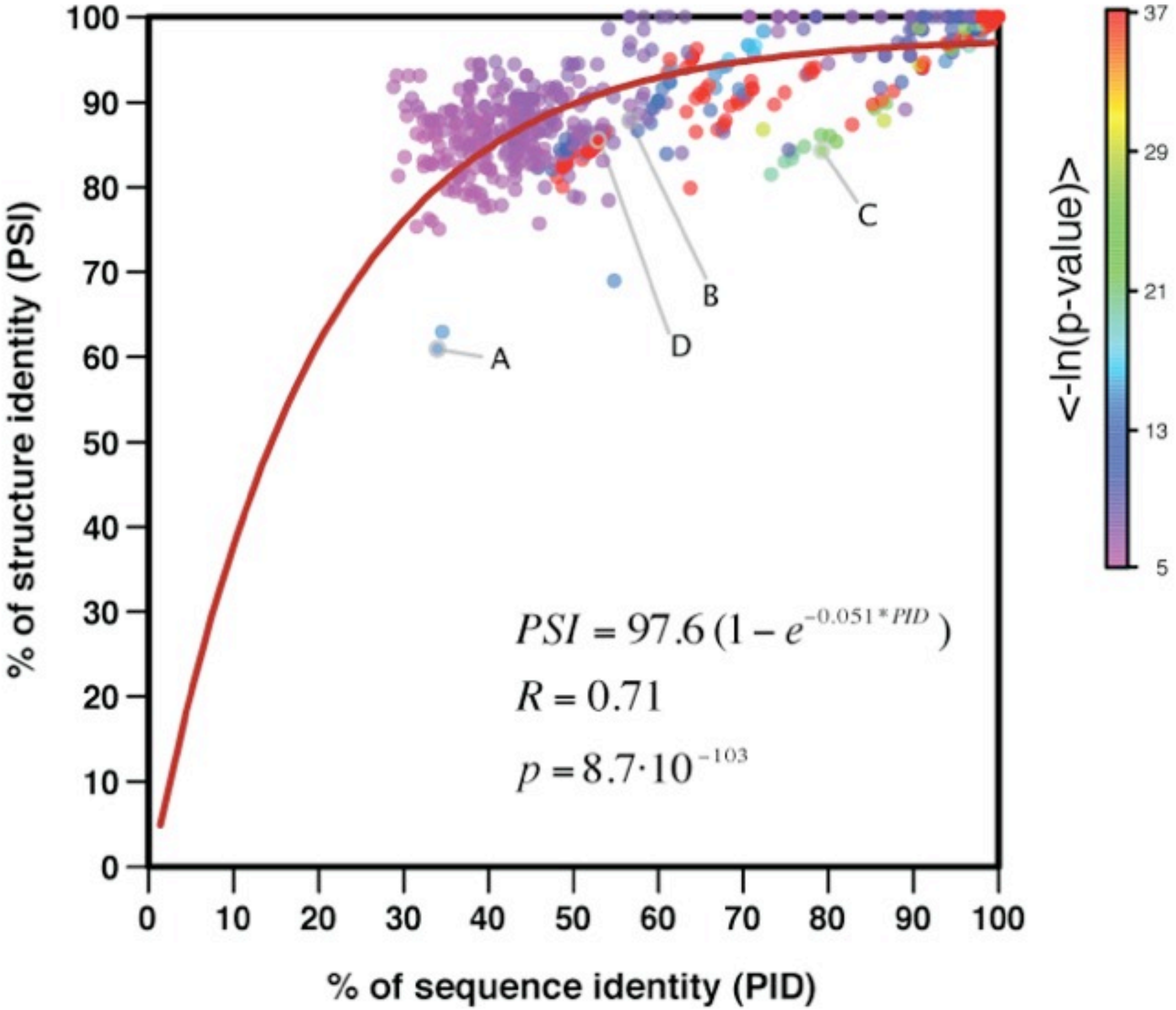
Chothia et al.. EMBO J (1986) vol. 5 (4) pp. 823-6



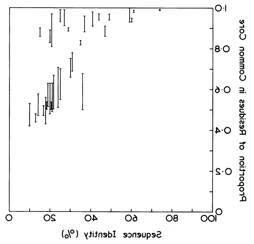
Rost. Protein Eng (1999) vol. 12 (2) pp. 85-94

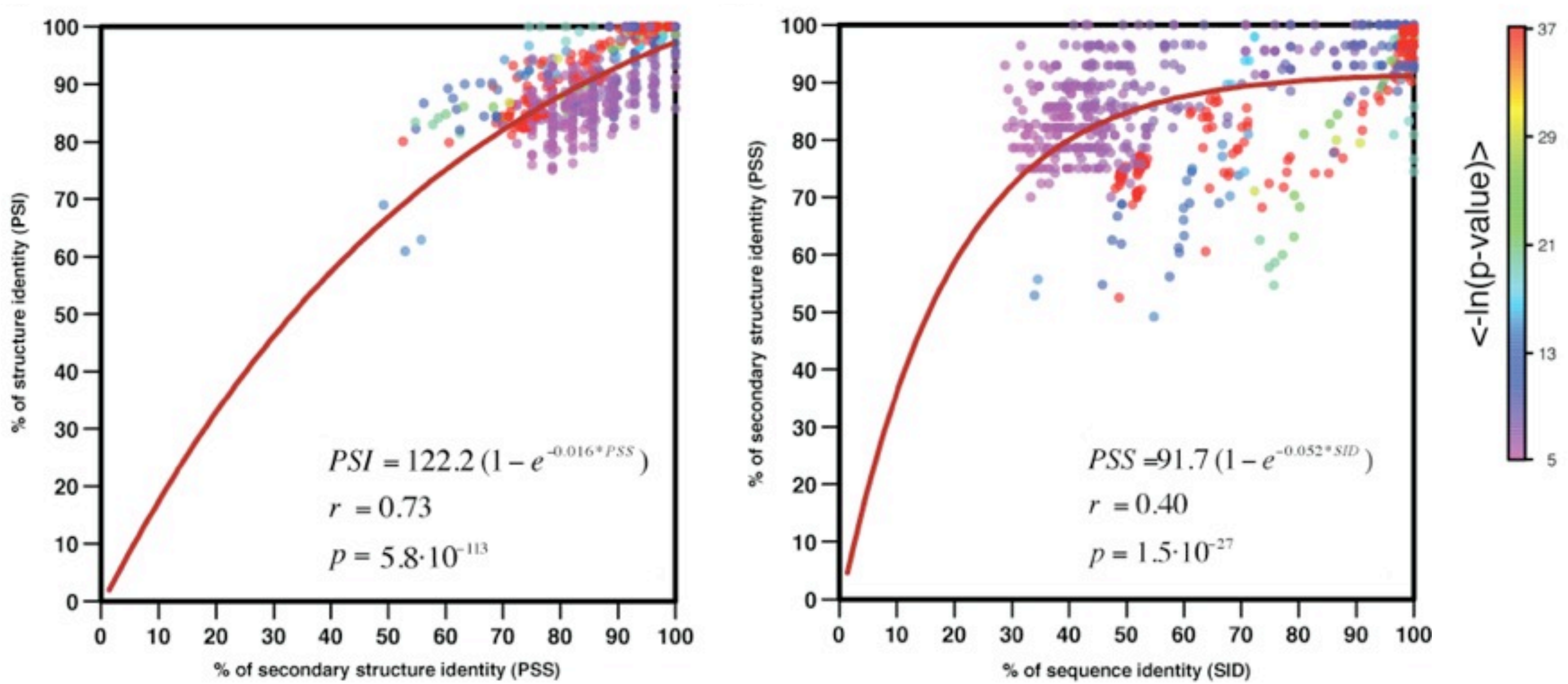
Stx/Seq relationship



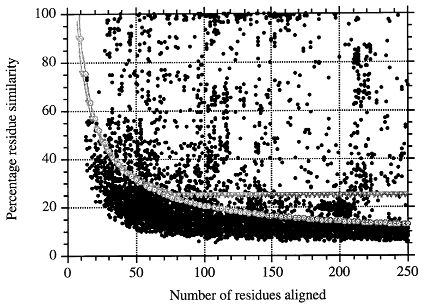


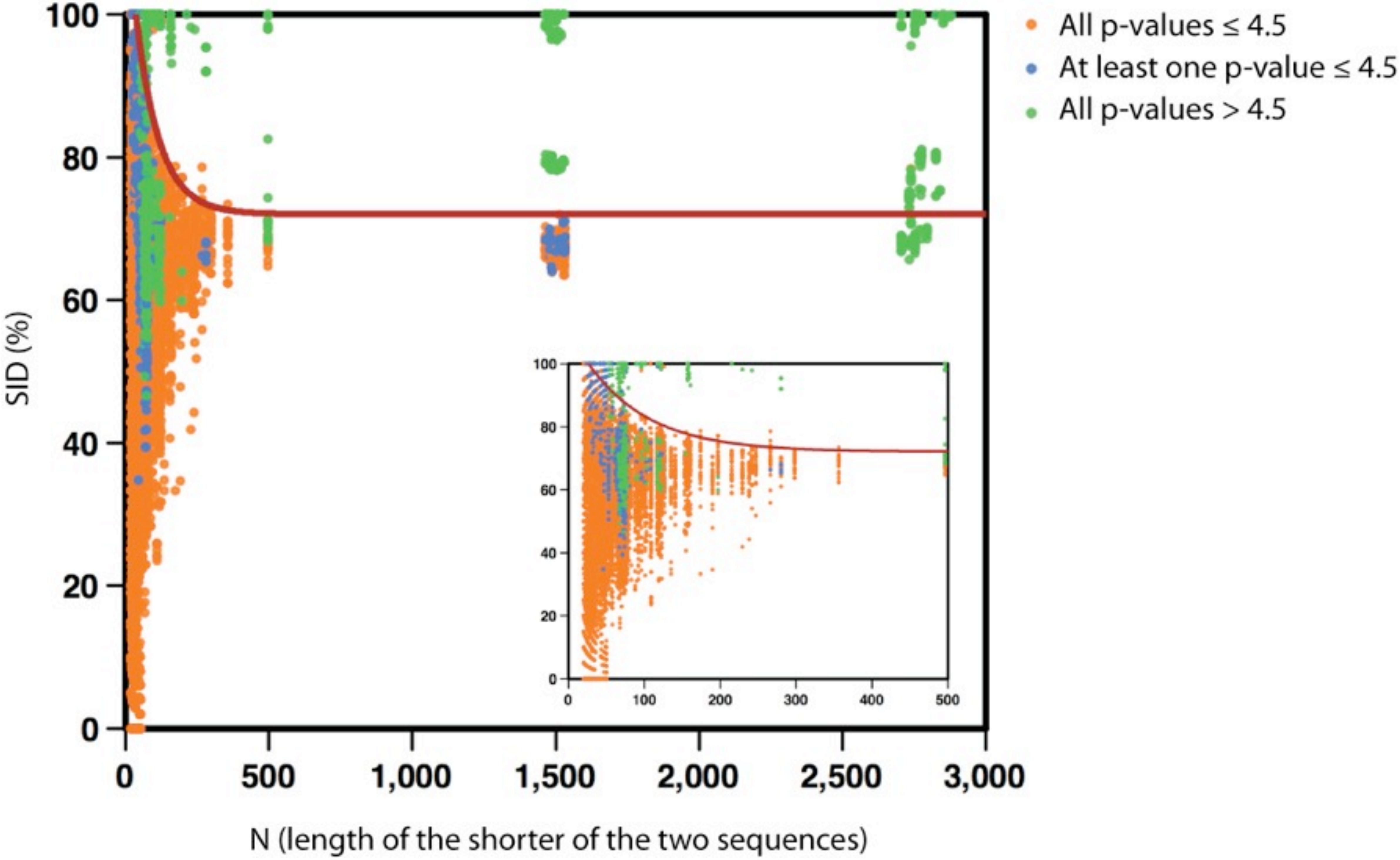
SSE/Stx/Seq relationship





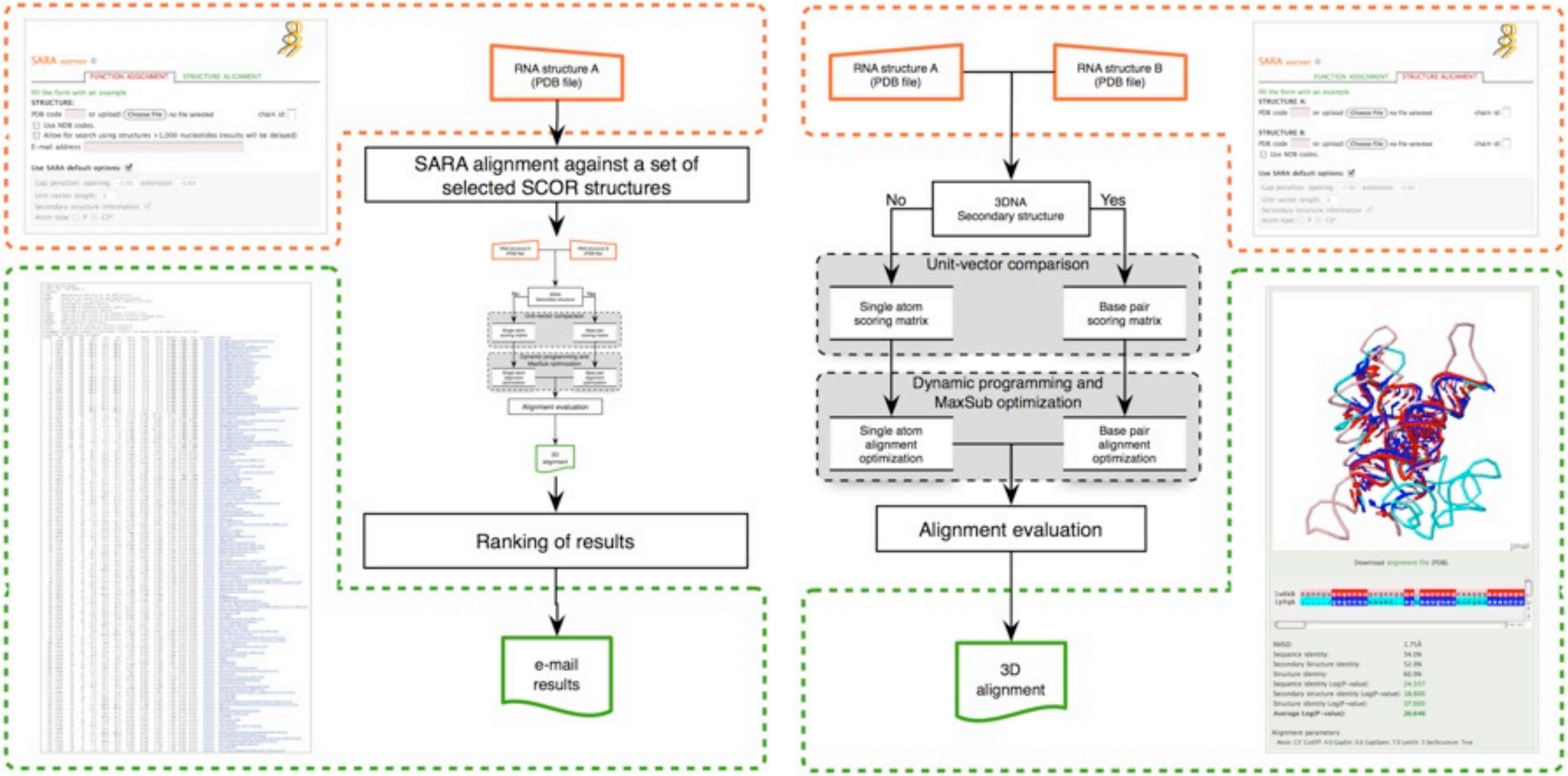
Twilight Zone





SARA server

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


RNA structure A
(PDB file)
SARA alignment against a set of selected SCOR structures
Ranking of results
e-mail results
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
Jmol
Download alignment file (PDB)

SARA server

FUNCTION ASSIGNMENT | STRUCTURE ALIGNMENT

Fill the form with an example

STRUCTURE:

PDB code ___ or upload: Choose File no file selected chain id: □

□ Use NDB codes.

□ Allow for search using structures >1,000 nucleotides (results will be delayed)

E-mail address ___

Use SARA default options: ☑

Gap penalties: opening -7.00 extension -0.60

Unit-vector length: 3

Secondary structure information ☑

Atom type: ○ P ● C3'

SARA server

FUNCTION ASSIGNMENT | STRUCTURE ALIGNMENT

Fill the form with an example

STRUCTURE A:

PDB code ___ or upload: Choose File no file selected chain id: □

STRUCTURE B:

PDB code ___ or upload: Choose File no file selected chain id: □

□ Use NDB codes.

Use SARA default options: ☑

Gap penalties: opening -7.00 extension -0.60

Unit-vector length: 3

Secondary structure information ☑

Atom type: ○ P ● C3'

RMSD:	1.71Å
Sequence identity:	34.0%
Secondary Structure identity:	52.0%
Structure identity:	60.0%
Sequence identity Log(P-value):	24.337
Secondary structure identity Log(P-value):	18.600
Structure identity Log(P-value):	37.000
Average Log(P-value):	26.646

Alignment parameters:
Atom: C3' CutOff: 4.0 GapExt: 0.6 GapOpen: 7.0 LenUV: 3 SecStructure: True

Capriotti et al. Bioinformatics (2008) vol. 24 (16) pp. i112-i118

SARA server

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

E. Capriotti, M. A. Marti-Renom (2008), *Bioinformatics* **24**:i112

BIOINFORMATICS

Vol. 24 ECCB 2008, pages i112–i118
doi:10.1093/bioinformatics/btn288

RNA structure alignment by a unit-vector approach

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ABSTRACT

Motivation: The recent discovery of tiny RNA molecules such as µRNAs and small interfering RNA are transforming the view of RNA as a simple information transfer molecule. Similar to proteins, the native three-dimensional structure of RNA determines its biological activity. Therefore, classifying the current structural space is paramount for functionally annotating RNA molecules. The increasing numbers of RNA structures deposited in the PDB requires more accurate, automatic and benchmarked methods for RNA structure comparison. In this article, we introduce a new algorithm for RNA structure alignment based on a unit-vector approach. The algorithm has been implemented in the SARA program, which results in RNA structure pairwise alignments and their statistical significance.

Results: The SARA program has been implemented to be of general applicability even when no secondary structure can be calculated from the RNA structures. A benchmark against the ARTS program using a set of 1275 non-redundant pairwise structure alignments results in ~6% extra alignments with at least 50% structurally superposed nucleotides and base pairs. A first attempt to perform RNA automatic functional annotation based on structure alignments indicates that SARA can correctly assign the deepest SCOR classification to >60% of the query structures.

Availability: The SARA program is freely available through a World Wide Web server http://sgu.bioinfo.cipf.es/services/SARA/

Contact: mmarti@cipf.es

Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 INTRODUCTION

Recent discoveries of new RNA functions are changing our view of RNA molecules and reinforcing the so-called 'RNA world' origin of life (Bartel, 2004; Dorsett and Tuschl, 2004; Doudna, 2000; Staple and Butcher, 2005). RNA is now known to play an important role in biological functions such as enzymatic activity (Staple and Butcher, 2005), gene transcriptional regulation (Bartel, 2004; Dorsett and Tuschl, 2004; Staple and Butcher, 2005) and protein biosynthesis regulation (Doudna, 2000). Therefore, much attention is lately being paid to the structural determination of RNA molecules. Such efforts have increased the pace of deposition of RNA structures in the Protein Data Bank (PDB) (Berman *et al.*, 2002). Currently (January 2008), the PDB database stores more than 1300 RNA structures. Such a wealth of data may allow, for first time, the analysis and characterization of the RNA structural space, which will help to characterize RNA function.

RNA folding is a hierarchical process by which base pairing formation affects the final three-dimensional (3D) conformation of the RNA molecule (Tinoco and Bustamante, 1999). Hence, algorithms for RNA secondary structure prediction have classically been used for characterizing RNA structure and function. Although more than two decades have past since the development of the first algorithms for RNA secondary structure prediction (Nussinov and Jacobson, 1980; Zuker and Sankoff, 1984; Zuker and Stiegler, 1981), there has been limited development in RNA tertiary structure analysis and, in particular, in RNA structure comparison. Only recently, the PRIMOS/AMIGOS (Duarte *et al.*, 2003; Wadley *et al.*, 2007), FR3D (Sarver *et al.*, 2008), ARTS (Dror *et al.*, 2005, 2006) and DIAL (Ferre *et al.*, 2007) programs have been developed for structurally comparing two RNA molecules. The PRIMOS/AMIGOS programs search for structural similarities of consecutive RNA fragments with five or more nucleotides by comparing specific η and θ pseudo angles as well as the sugar pucker phase. The FR3D program uses a base-centered approach for conducting a geometric search of local and composite RNA structures. The COMPADRES program, which implements the PRIMOS algorithm, has been applied for searching local structural motifs in known RNA structures (Wadley and Pyle, 2004). The ARTS program, which represents RNA structures by a set of contiguous four phosphate atoms or *quadrats*, detects similarities between *quadrats* after a rigid superimposition of two RNA structures followed by an optimization based on a bipartite graph strategy. Finally, the DIAL program, which implements a scoring function combining nucleotide, dihedral angles and base-paring similarities, compares the two RNA structures using a dynamic programming algorithm.

Although the PRIMOS/AMIGOS, ARTS and DIAL programs, result in accurate RNA structure alignments, they have some limitations: (i) the PRIMOS/AMIGOS program have limited applicability to searching only for local motifs regardless of global similarities between two structures, (ii) the DIAL method, in its default version, only calculates an alignment score and requires substantial computational time to return a statistical evaluation of its significance and (iii) ARTS requires the existence of secondary structure elements in both structures to compute the final alignment. To overcome such limitations, we have developed a new RNA 3D alignment method (SARA), which does not require the assignment of base pairs from structure and provides a statistical assessment of the significance of the resulting alignment. The SARA algorithm uses a unit-vector approach inspired by the MAMMOTH program for protein structure alignment (Ortiz *et al.*, 2002). The SARA program has been benchmarked for its alignment accuracy against the ARTS program as well as for its use in RNA function prediction. Its general applicability will allow an all-against-all comparison of known RNA structures, which will help in characterizing the relationship between sequence, structure and function of RNA molecules.

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SARA: a server for function annotation of RNA structures

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ABSTRACT

Recent interest in non-coding RNA transcripts has resulted in a rapid increase of deposited RNA structures in the Protein Data Bank. However, a characterization and functional classification of the RNA structure and function space have only been partially addressed. Here, we introduce the SARA program for pair-wise alignment of RNA structures as a web server for structure-based RNA function assignment. The SARA server relies on the SARA program, which aligns two RNA structures based on a unit-vector root-mean-square approach. The likely accuracy of the SARA alignments is assessed by three different *P*-values estimating the statistical significance of the sequence, secondary structure and tertiary structure identity scores, respectively. Our benchmarks, which relied on a set of 419 RNA structures with known SCOR structural class, indicate that at a negative logarithm of mean *P*-value higher or equal than 2.5, SARA can assign the correct or a similar SCOR class to 81.4% and 95.3% of the benchmark set, respectively. The SARA server is freely accessible *via* the World Wide Web at http://sgu.bioinfo.cipf.es/services/SARA/.

INTRODUCTION

It is now known that RNA molecules are essential for a wide range of biological processes (1–6), which is changing the view of RNA as a simple vector of genetic information and reinforcing the hypothesis on the original 'RNA world' (7,8). Biosynthesis and transcription regulation (1–3,5), enzymatic action (5) and chromosome replication (4) are some of the functions that RNA molecules are now known to perform. RNA structure determination, which is accelerating its pace of deposition in the Nucleic Acid Database (NDB) (9) and the Protein Data Bank (PDB) (10), is thus becoming an essential and necessary tool for RNA function annotation. Although there are not standard rules to infer function, at least for proteins (11–13), structure similarity is arguably one of the most reliable methods for comparative function annotation (14,15).

Several methods have already been developed for the alignment of two or more protein 3D structures (16). However, only few are available for RNA structure comparison (17–23). The PRIMOS and AMIGOS programs identify RNA structure motifs and compare RNA structures by describing them as a set of pseudo angles from the C4' and P atom trace (18,20). Both programs are limited to the comparison of RNA structures with the same number of nucleotides and only a newer version of AMIGOS can perform a comparison of a given structure against a set of RNA structures. The ARTS program was introduced as a general method for RNA structure alignment (17,24). ARTS describes RNA molecules with a set of 'quadrats' composed by four phosphate atoms of two consecutive base-pairs and uses a bipartite graph to find the maximum number of aligned 'quadrats' between two RNA structures. The DIAL program, developed to compare RNA structures using a dynamic programming algorithm (19), computes global, local and semi-global alignments by taking into account sequence similarity, dihedral angles and base-pair information from the two aligned structures. DIAL can also return the Boltzmann pair probabilities of the resulting alignments. However, such computation would double the runtime, hence the default in the DIAL server is not to calculate the pair probabilities. More recently, the SARSA server was developed to align two or more RNA structures using a structural alphabet of 23 nucleotide conformations (22). Both, the DIAL and SARSA servers were developed and benchmarked for their ability detecting short RNA motifs in a set of RNA structures. In contrast, the SARA program (21), which implementation for function assignment of RNA structures is here introduced, was recently developed to align two RNA structures based on a unit-vector alignment strategy (25). Given its implementation, an alignment by SARA shorter than 20 nt is likely to be indistinguishable from random structure alignments. The SARA program can be considered as an alternative

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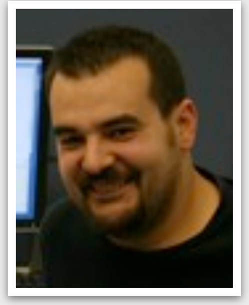

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