Sequence-Structure Relations of Single RNA Molecules and Cofolded RNA Complexes

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Outline

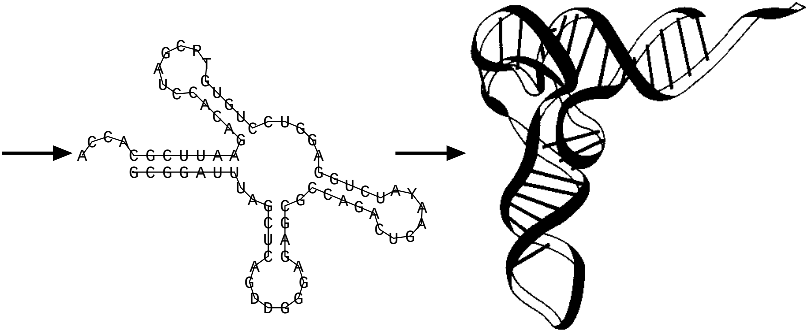
Motivation
- Folding RNA
- Overview

Results
- RNA sequence to structure mapping
- Co-folding two RNA molecules

Discussion

RNA primary, secondary and tertiary structure

GCGGGAAUAGCUCAGUUGGUAGAGCACGACCUUGCCAAGGUCGGGGUCGCGAGUUCGAGUCUCGUUUCCCGCUCCA



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Relation between RNA sequences and their secondary structures

- RNA sequence to structure mapping
- Evolutionary dynamics of an RNA population in a flow reactor
- RNA-RNA interaction by co-folding two RNA molecules

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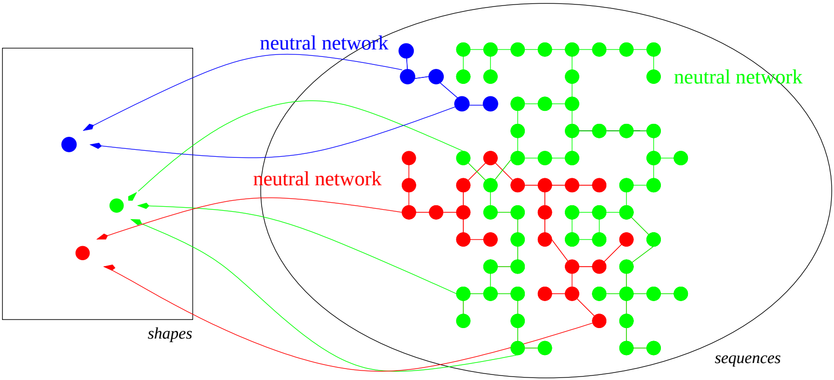
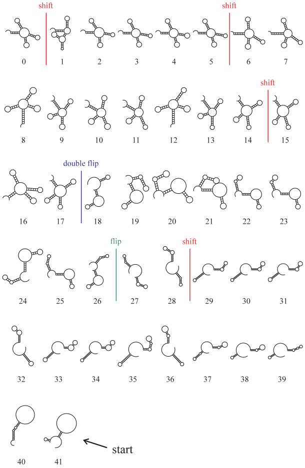
RNA sequence to structure mapping



Evolutionary dynamics in a flow reactor



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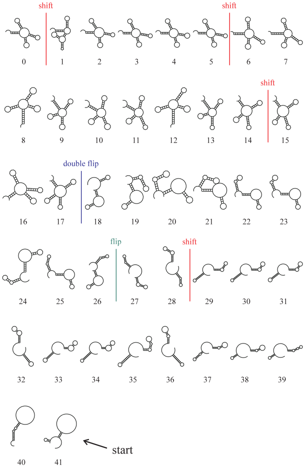

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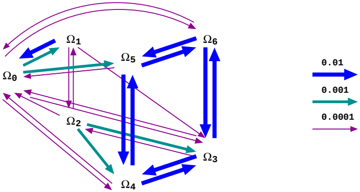
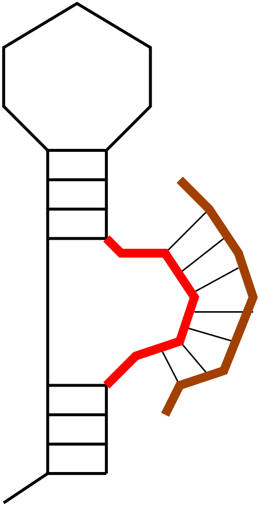
`(((((((..((((........)))).(((((.......))))).....(((((.......))))).)))))))...`	Ω_5	2
`.((((((..((((........)))).(((((.......))))).....(((((.......))))).))))))....`	Ω_6	2



Co-folding two RNA molecules



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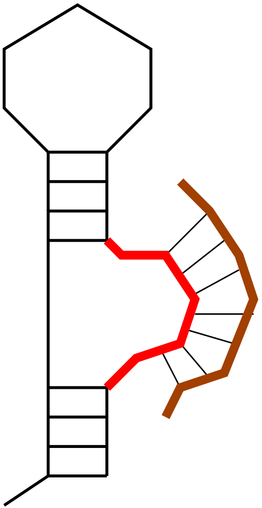

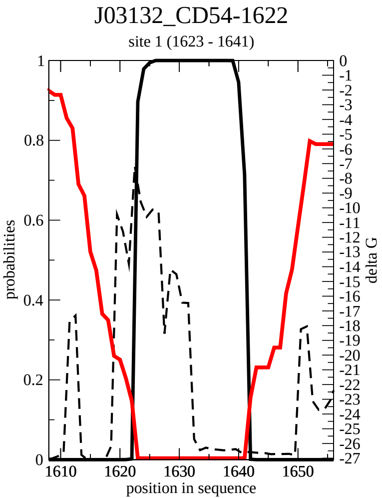

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RNAup

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Generic properties of RNA folding

- More sequences than structures
- Few common and many rare structures
- Common structures form extended neutral networks
- Shape space covering

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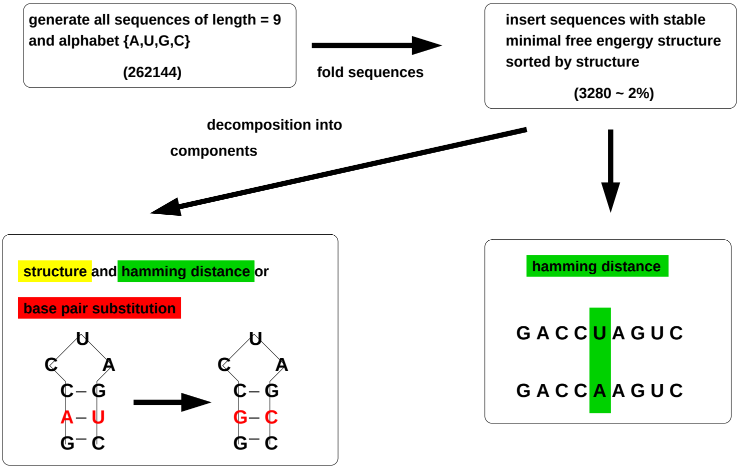
Exhaustive folding and enumeration of the sequence spaces $\mathcal{I}_{AUGC}^{(\ell=9)}$ and $\mathcal{I}_{AUGC}^{(\ell=10)}$

PostgreSQL Database



generate all sequences of length = 9 and alphabet {A,U,G,C}

(262144)

fold sequences

insert sequences with stable minimal free engergy structure sorted by structure

(3280 ~ 2%)

decomposition into components

structure and hamming distance or

base pair substitution

hamming distance

GACCUAGUC

GACCAAGUC

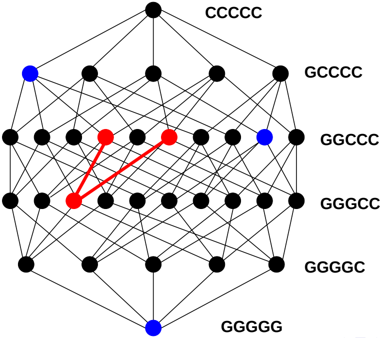
Stored Procedures **Vigl Graph Library** **Vienna RNA package**

More sequences than structures

$$3^\ell \text{ structures} < 4^\ell \text{ sequences}$$

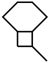
`(((...)))`   `GCGAUGCGC`

- $\mathcal{I}^{(\ell=9)}_{AUGC}$
  - stable mfe structure $3239 \sim 2.3\%$
  - 4 different structures
- $\mathcal{I}^{(\ell=10)}_{AUGC}$
  - stable mfe structure $40345 \sim 3.8\%$
  - 9 different structures



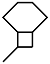
Few common and many rare structures

$\mathcal{I}^{(\ell=9)}_{AUGC}$



`((....)).`

73.2%



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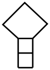
15.5%



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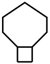
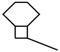
9.9%



`((.....))`

1.4%

$\mathcal{I}^{(\ell=10)}_{AUGC}$



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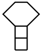
22.8%



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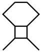
20.6%



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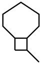
19.7%



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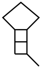
16.7%



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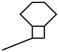

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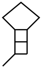
4.7%



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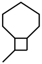
4.1%



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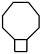
2.0%

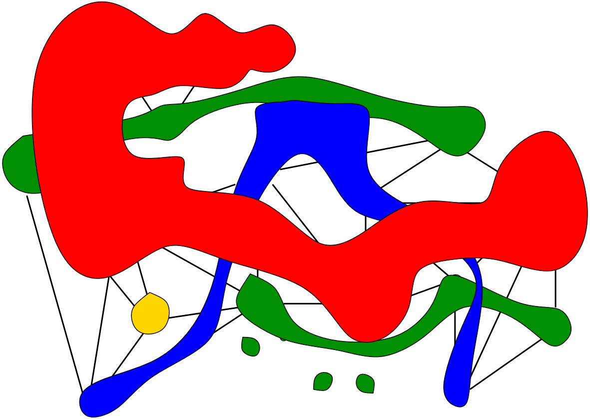


`((......))`

1.9%

Common structures form extended neutral networks

((....)).	**73.2%**
.((....))	**15.5%**
(((...)))	**9.9%**
((.....))	**1.4%**



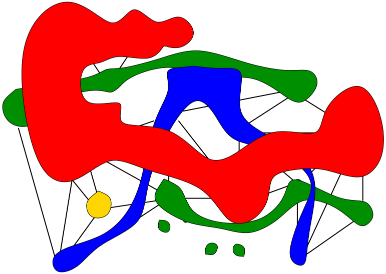
Shape space covering

((....)).

.((....))

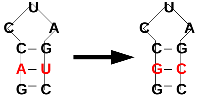
(((...)))

((.....))



structure and hamming distance or

base pair substitution



hamming distance

G A C C U A G U C

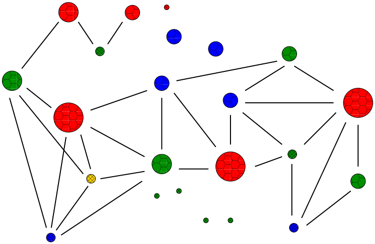
G A C C A A G U C

((....)).

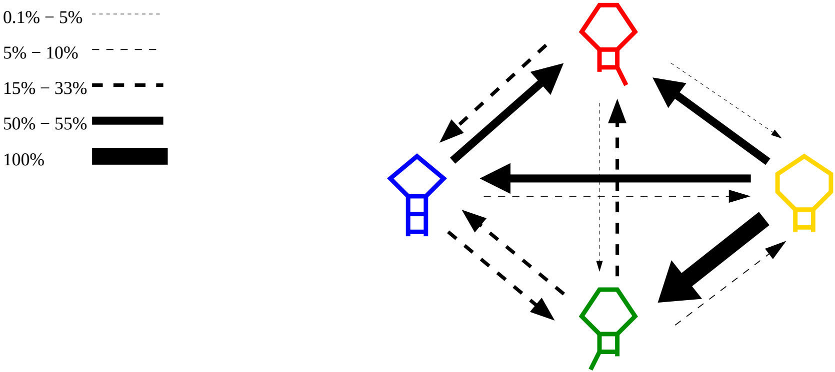
.((....))

(((...)))

((.....))



Shape space topology induced by the sequence-structure map



Discussion

- study topology of RNA sequence to structure mapping by exhaustive folding and enumeration of sequence spaces
- extended neutral networks allow a population of RNA molecules to explore sequence space by neutral drift
- asymmetric accessibility relations support evolutionary innovation

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Outlook

- functional RNAs work by interacting with other RNAs
- Camille Stephan-Otto Attolini et al. studied the cofolding map of interacting RNA sequences:
  - the cofolding map admits large neutral networks and long neutral paths similar to the folding map of single RNA molecules
- tool to compute RNA-RNA interaction by co-folding two RNA molecules

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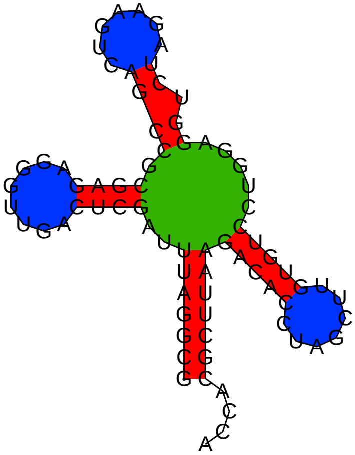
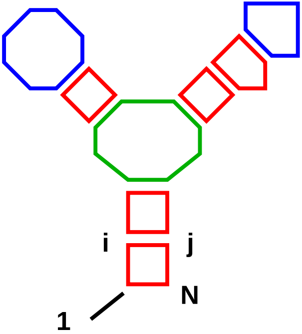
RNA Secondary Structure



- Hairpin Loops
- Interior Loops
- Multiloops
- Exterior Loop

Loop decomposition of RNA Secondary Structure

- $F(S) = \sum_{L \in S} F_L$.



Basic Algorithms

- McCaskill: Dynamic programming algorithm for calculation of the full equilibrium partition function Z for RNA secondary structure in $O(N^3)$

- Vienna RNA Package

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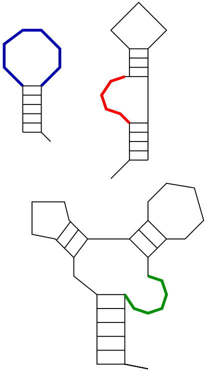
Complete ensemble of secondary structures

Probability of an unstructured region



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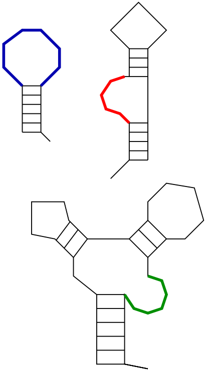
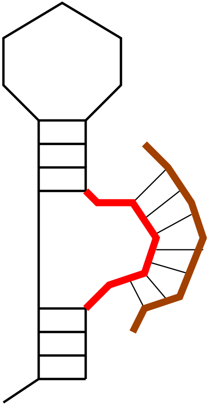


Probability of interaction in unstructured regions



Information provided by our algorithm

- structural context of a binding site
  - $P_u[i,j]$ region $[i,j]$ contains no secondary structure
- location of possible binding sites
  - $P^*[i,j]$ probability of a regional interaction
- energetics of RNA-RNA interaction
  - $\Delta G = \Delta G_u + \Delta G_h$

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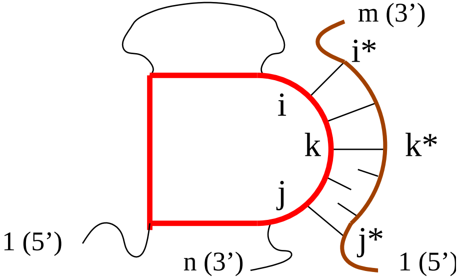
$P_u[i,j]$ region $[i,j]$ contains no secondary structure

$$P_u[i,j] = \underbrace{\frac{Z[1,i-1]\times 1\times Z[j+1,N]}{Z[1,N]}}_{\text{exterior}} + \underbrace{\sum_{p<i\le j<q} P_{pq}\frac{Z_{pq}[i,j]}{Z^b[p,q]}}_{\text{enclosed}}.$$

Z^I Interaction of region $[i, j]$ with region $[i^*, j^*]$



$$Z^I[i, j, i^*, j^*] = \sum_{\substack{i<k<j \\ i^*>k^*>j^*}} Z^I[i, k, i^*, k^*] e^{-\frac{1}{kT} I(k, k^*; j, j^*)}.$$

probability and optimal free energy of an interaction

- conditional probability given that two molecules bind at all

$$P^*[i,j] = \frac{Z^*[i,j]}{\sum_{k<l} Z^*[k,l]}. \qquad Z^*[i,j] = P_u[i,j] \sum_{i^*>j^*} Z^I[i,j,i^*,j^*].$$

- optimal free energy of a regional interaction

$$\Delta G_i = min_{k \le i \le l}\{\Delta G[k,l]\}. \qquad \Delta G[i,j] = (-kT)\ln Z^*[i,j].$$

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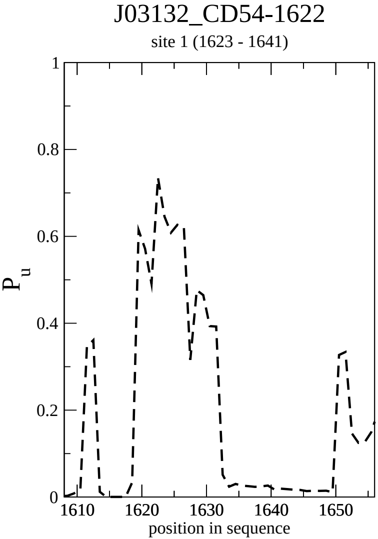
Interaction of CD54 mRNA with siRNA si1622



Vickers et. al. J.Biol.Chem., 278(9):7108-118,2003

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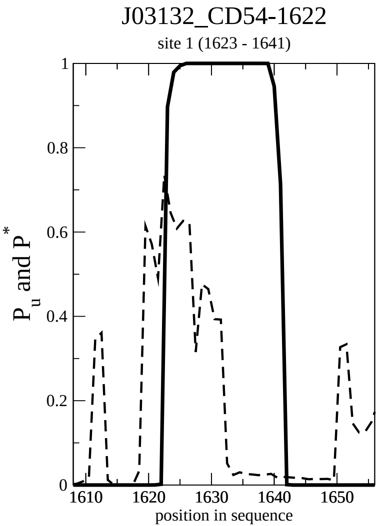

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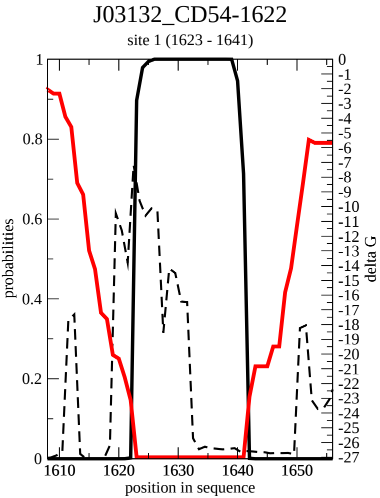

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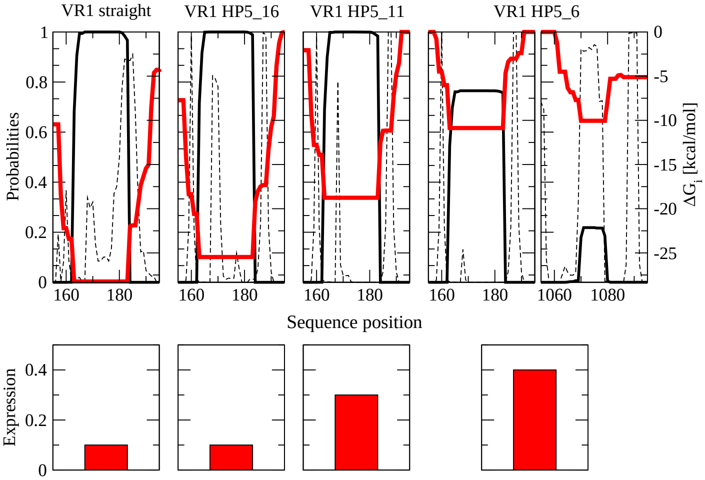
Local RNA target structure influences siRNA efficacy



Schubert et.al. J.Mol.Biol.,348(4):883-93,2005

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- Realistic description of interaction between small RNAs and their targets
- Structural context of a possible binding site
- Location of possible binding sites
- Energetics of RNA-RNA interaction
- Time complexity is $O(N^3)$, memory requirement $O(N^2)$

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Thanks to

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