RNA structures
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Find Structure of RNA's
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Comparison of RNA Structure
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Bioinformatics
(RNA structures)

Marc Hellmuth

What is RNA (Ribonucleic acid)?

- single-stranded polymer

- polymer made of nucleotides+backbone

- guanine (G), adenine (A), uracil (U), cytosine (C)

- alternating sugar (ribose) and phospat groups (related to phosphoric acid) nucleotides are attached to sugar

- the nucleotides of polymer can bind (A-U, C-G, G-U), i.e., unlike DNA it is more often found in nature as a single-strand folded unto itself, rather than a paired double-strand.
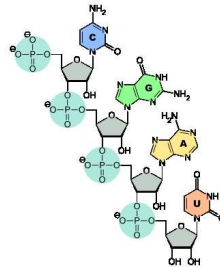
primary structure

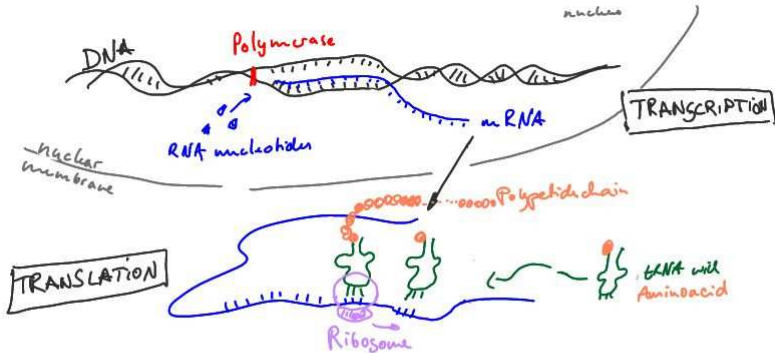5'-end GCGGAUUUAGCUCAGUUGGGAGAGCGCCAGACUGAAGAUCUGGAGGUCCUGUGUUCGAUCCACAGAAUUCGCACCA 3'-end

secondary structure
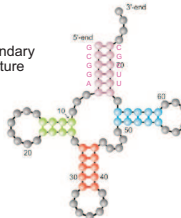
tertiary structure

Protein Synthesis - well-known mRNA

RNA function

coding RNA

- mRNA: convey genetic information from DNA to the ribosome

many RNAs do not code for protein
(about 97% are non-protein- coding in eukaryotes)

non-coding RNA

- tRNA: linking codons to aminoacids
- rRNA (ribosomalRNA): part of of the ribosome, essential for protein synthesis
- snRNA (Small nuclear RNA, $\sim$ 150 nt) : splicing and other functions
- miRNA (microRNA, 21-22 nt): regulation of gene expression
- . . .

RNA can even act as genome (virus)

RNA - WORLD - HYPOTHESIS: self-replicating RNA molecules are precursors to all current life on Earth.

RNA Structure

Function is determined by structure.

primary structure

5'-end GCGGAUUUAGCUCAGUUGGGAGAGCGCCAGACUGAAGAUCUGGAGGUCCUGUGUUCGAUCCACAGAAUUCGCACCA 3'-end

secondary structure

tertiary structure

RNA structures
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Find Structure of RNA's
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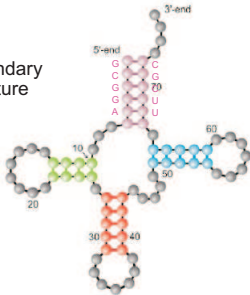
Comparison of RNA Structure
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Base Pairing Rules $\mathbb{B}$

- Watson-Crick base pairings
    - Adenin (A) - Uracil (U)
    - Cytosin (C) - Guanin (G)
- wobble base pairings
    - Guanin (G) - Uracil (U)

RNA Structure

In what follows: $\mathbb{A} = \{A, C, G, U\}$

A **primary structure** (of length n) is a sequence $s = s_1 \ldots s_n \in \mathbb{A}^n$.

A **secondary structure** *Sec* is a collection of ordered pairs (i, j), where $1 \leq i < j \leq n$, s.t. the following properties hold:

1. If $(i, j), (k, l) \in Sec$, then it is not the case that $i < k < j < l$.

2. If $(i, j), (k, l) \in Sec$ and $i \in (k, l)$ implies that $i = k$ and $j = l$.

3. If $(i, j) \in Sec$, then $j > i + \theta$, where θ is a fixed integer and usually taken to be 3.

A secondary structure *Sec* for a given sequence $s = s_1 \ldots s_n \in \mathbb{A}^n$ is a secondary structure fullfilling in addition

4. If $(i, j) \in Sec$, then $s_i s_j \in \mathbb{B} = \{AU, UA, GC, CG, GU, UG\}$.

If item 4. is fullfilled, then we say that the sequence $s \in \mathbb{A}^n$ realizes *Sec*.

A **tertiary structure** is basically the 3D structure, i.e., refers to locations of the atoms in three-dimensional space.

RNA structures
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Find Structure of RNA's
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Comparison of RNA Structure
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RNA Structure

$$s = s_1 \ldots s_n \in C_n = \{A, C, G, U\}^n$$

primary structure

5'-end GCGGAUUUAGCUCAGUUGGGAGAGCGCCAGACUGAAGAUCUGGAGGUCCUGUGUUCGAUCCACAGAAUUCGCACCA 3'-end

secondary structure
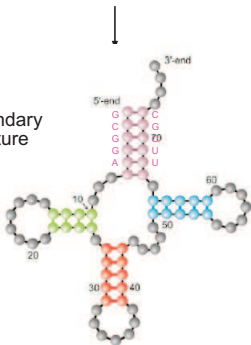
tertiary structure

RNA Secondary Structure Representation
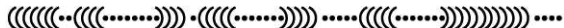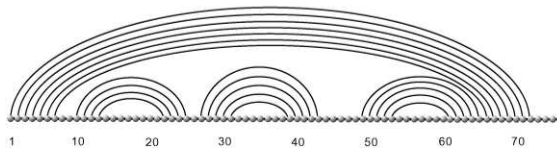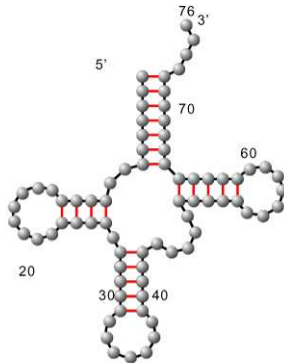
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RNA Secondary Structure Representation

- A Circular Plot
- B "Squiggle" Plot
- C Mountain Plot
- D Dot Plot
- E Bracket Notation

RNA Secondary Structure Prediction

RNA folding: hierarchical process in which secondary structure is broadly considered as sufficient approximation assessing the most relevant characteristics of an RNA molecule

Prediction w.r.t. what? We need some optimization criterion. e.g.

- Number of Basepairs
- Min. Free Energy
- Mutual Information Content

Set of all feasible second.structures $\mathbb{S}(x)$ of an RNA sequence x is called *folding space*. Structure prediction means to select the "most-likely" structure from elements of $\mathbb{S}(x)$.

RNA structures
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Find Structure of RNA's
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Counting Secondary Structures

Theorem
Let $S(n)$ denote the number of secondary structures of size n and $\theta = 1$. Then $S(0) = 0$, $S(1) = 1$ and for $n \geq 1$,

$$S(n+1) = S(n) + S(n-1) + \sum_{k=2}^{n-1} S(k-1)S(n-k)$$

and

$$S(n) \geq 2^{n-2}.$$

Theorem
Let $S(n,k)$ denote the number of secondary structures of size n that contain exactly k basepairs ($\theta = 1$). Set $S(n,0) = 1$ for all n and $S(n,k) = 0$ for $k \geq \frac{n}{2}$. Then for $n \geq 2$,

$$S(n+1,k+1) = S(n,k+1) + \sum_{j=1}^{n-1} \left[\sum_{i=0}^{k} S(j-1,i)S(n-j,k-i) \right].$$

Corollary

$$S(n) = \sum_{k=0}^{\lfloor n/2 \rfloor} S(n,k).$$

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Realizability

A sequence $s \in \mathbb{A}^n$ *realizes* or *is compatible with* a secondary structure S of length n if for any $(i, j) \in S$ it holds that $s_i, s_j \in \mathbb{B}$.

• *dependency graph or shape graph $G(S_1, \ldots, S_k)$*

QUESTION:

On what conditions is it possible to find *one* sequence, which is realizing *all* sec.str. $S_1, \ldots, S_k$ of the same size?

equivalent to:

What properties have to be fulfilled in $G(S_1, \ldots, S_k)$, s.t. there exists a single sequence, which is realizing all $S_1, \ldots, S_k$?

Intersection Theorem

$C(S)$ denotes the set of all sequences that realize Secondary Structure S.

Intersection Theorem [Reidys et al. 1995]
For any two secondary structures S_1 and S_2 of same size holds: $C(S_1) \cap C(S_2) \neq \emptyset$.

Generalized Intersection Theorem [Flamm et al. 2001]
$\bigcap_{i=1}^{k} C(S_i) \neq \emptyset \Leftrightarrow G(S_1, \ldots, S_k)$ is bipartite.

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RNA folding

Aim: For given sequence $s \in \mathbb{A}^n$ find "most-likely" or "optimal" structure. "optimal" := e.g. max. number of basepairs, min free energy, mutual information content (for more than one sequence) ...

Inferring Structure by Comparative Sequence Analysis

RNA sequence evolution is constrained by structure ($\rightarrow$ function)

"homologous" RNA's = RNA's that share a "common" structure

There are exampled of different RNA's that have a common structure, but almost no sequence similarity (conserved structure)
(e.g. tRNA structure conserved across species)

Drastic changes in sequences can often be tolerated as long compensatory mutations maintain base pairings.

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Inferring Structure by Comparative Sequence Analysis

The key idea is to identify the interactions (i.e., the Watson-Crick correlated positions that result from compensatory mutations) in a multiple alignment, e.g.:

seq1	G	C	C	U	U	C	G	G	G	C
seq2	G	A	C	U	U	C	G	G	U	C
seq3	G	G	C	U	U	C	G	G	C	C

The amount of correlation of two columns of a multiple alignment can be computed as the mutual information content measure:

"if you tell me the identity of position i, how much do I learn about the identity of position j ?"

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Inferring Structure by Comparative Sequence Analysis

A method used to locate covariant positions in a multiple sequence alignment is the mutual information content of two columns (=measure of the variables' mutual dependence).

$f_i(X)$ is rel. frequency of base $X \in \{A, C, G, U\}$ in i-th column of $\mathscr{A}$.

$f_{ij}(XY)$ is rel. frequency of simultaneously finding $X \in \{A, C, G, U\}$ in i-th column of $\mathscr{A}$ and $Y \in \{A, C, G, U\}$ in j-th column of $\mathscr{A}$

If the base frequencies of any two columns i and j are independent of each other then,

$$\frac{f_{ij}(XY)}{f_i(X)f_j(Y)} \approx 1$$

If these frequencies are correlated, then this ratio will be greater than 1.

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Inferring Structure by Comparative Sequence Analysis

Given alignment $\mathscr{A}$ of RNA sequences.
Mutual Information Score[1] is defined as

$$M_{i,j} = \sum_{XY} f_{ij}(XY) \log_2 \frac{f_{ij}(XY)}{f_i(X)f_j(Y)},$$

with: $f_i(X)$ is rel. frequency of base $X \in \{A, C, G, U\}$ in i-th column of $\mathscr{A}$
and $f_{ij}(XY)$ is rel. frequency of simultaneously finding $X \in \{A, C, G, U\}$ in i-th column of $\mathscr{A}$
and $Y \in \{A, C, G, U\}$ in j-th column of $\mathscr{A}$

$$M_{i,j} \in [0, 2]$$

Intuitively, $M_{A,B}$ measures the information that A and B share: For example, if variables A and B are independent ($f(AB) = f(A)f(B) \Rightarrow \log(1) = 0$), then knowing A does not give any information about B and vice versa, so $M_{A,B} = 0$. At the other extreme, if A is a deterministic function of B (and vice versa) then all information conveyed by A is shared with B: knowing A determines the value of B and vice versa.

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[1] goes back to Shannon information theory and entropy
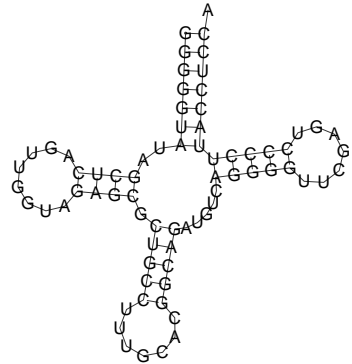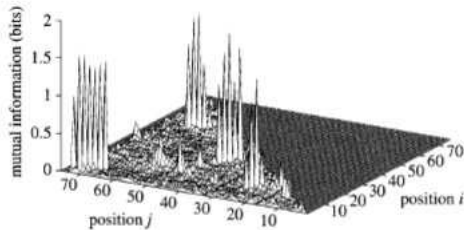
RNA structures
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Find Structure of RNA's
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Comparison of RNA Structure
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Inferring Structure by Comparative Sequence Analysis[2]

RNA structures
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Comparison of RNA Structure
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Inferring Structure by Comparative Sequence Analysis

Exmpl.

	1	2	3	4	5	6
seq1	C	G	C	G	A	U
seq2	C	G	G	C	C	G
seq3	C	G	C	G	G	C
seq4	C	G	G	C	U	A

$M_{3,4} = 1$
$M_{5,6} = 2$
$M_{1,2} = 0$ although in all cases there can be bp

Problems:
One need large datasets of highly diverse and homologous (how do I know this?)
sequences.

RNA folding - Maximize Number of Basepairs - Nussinov Algorithms

RNA folding: hierarchical process in which secondary structure is broadly considered as sufficient approximation assessing the most relevant characteristics of an RNA molecule.

Directly compute structure for a given sequence.

Observation: Best substructure $[i, j]$ can be obtained from substructures of $[i, j]$ - 4 cases:

i, j pair i unpaired j unpaired   bifurcation

RNA structures
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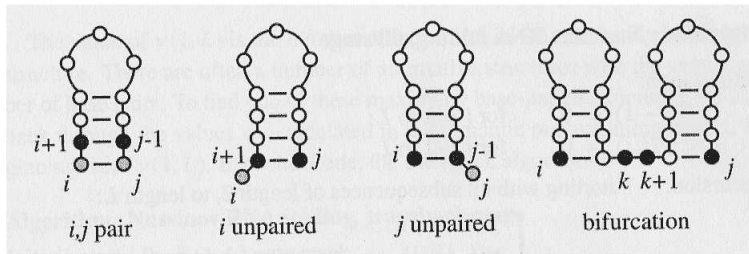
Nussinov Algorithm - Basepair Maximization

1: **INPUT:** $s = s_1 \ldots s_n \in \{A, C, G, U\}^n$
2: **for** $i, j = 1, \ldots, n$ **do**
3:      $E_{i,i-1} = E_{i,i} = 0, \delta_{ij} = \left\{ \begin{array}{ll} 1 & \text{, if } s_i s_j \in \mathbb{B} \\ 0 & \text{, else} \end{array} \right.$
4: **end for**
5: **for** $L = 1, \ldots, n-1$ **do**
6:      **for** $i = 1, \ldots, n-L$ **do**
7:          $j = i + L$
8:          $E_{i,j} = \max \left\{ \begin{array}{l} E_{i+1,j} \\ E_{i,j-1} \\ E_{i+1,j-1} + \delta_{ij} \\ \max_{i<k<j}\{E_{i,k} + E_{k+1,j}\} \end{array} \right.$
9:      **end for**
10: **end for**
11: print "Max Nr Basepairs:" $E_{1,n}$

RNA structures
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Find Structure of RNA's
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Comparison of RNA Structure
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Nussinov Algorithm - Basepair Maximization

Given: $s = GGGAAAUCC$
Init: $E_{i,i-1} = 0$ and $E_{i,i} = 0$

		1	2	3	4	5	6	7	8	9
		G	**G**	**G**	**A**	**A**	**A**	**U**	**C**	**C**
1	**G**	**0**								
2	**G**	**0**	**0**							
3	**G**		**0**	**0**						
4	**A**			**0**	**0**					
5	**A**				**0**	**0**				
6	**A**					**0**	**0**			
7	**U**						**0**	**0**		
8	**C**							**0**	**0**	
9	**C**								**0**	**0**

RNA structures
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Find Structure of RNA's
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Comparison of RNA Structure
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Nussinov Algorithm - Basepair Maximization

$$E_{i,j} = \max \begin{cases} E_{i+1,j} \\ E_{i,j-1} \\ E_{i+1,j-1} + \delta_{ij} \\ \max_{i<k<j}\{E_{i,k} + E_{k+1,j}\} \end{cases}$$

		1	2	3	4	5	6	7	8	9
		G	**G**	**G**	**A**	**A**	**A**	**U**	**C**	**C**
1	**G**	0	0							
2	**G**	0	0	0						
3	**G**		0	0	0					
4	**A**			0	0	0				
5	**A**				0	0	0			
6	**A**					0	0	**1**		
7	**U**						0	0	0	
8	**C**							0	0	0
9	**C**								0	0

RNA structures
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Comparison of RNA Structure
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Nussinov Algorithm - Basepair Maximization

$$E_{i,j} = \max \begin{cases} E_{i+1,j} \\ E_{i,j-1} \\ E_{i+1,j-1} + \delta_{ij} \\ \max_{i<k<j}\{E_{i,k} + E_{k+1,j}\} \end{cases}$$

		1	2	3	4	5	6	7	8	9
		G	**G**	**G**	**A**	**A**	**A**	**U**	**C**	**C**
1	**G**	0	0	0						
2	**G**	0	0	0	0					
3	**G**		0	0	0	0				
4	**A**			0	0	0	0			
5	**A**				0	0	0	**1**		
6	**A**					0	0	**1**	**1**	
7	**U**						0	0	0	0
8	**C**							0	0	0
9	**C**								0	0

Nussinov Algorithm - Basepair Maximization

$$E_{4,7} = \max \begin{cases} E_{5,7} \\ E_{4,6} \\ E_{5,6} + \delta_{4,7} \\ \max_{4<k<7}\{E_{4,k} + E_{k+1,7}\} \end{cases}$$

		1	2	3	4	5	6	7	8	9
		G	**G**	**G**	**A**	**A**	**A**	**U**	**C**	**C**
1	**G**	0	0	0	0					
2	**G**	0	0	0	0	0				
3	**G**		0	0	0	0	0			
4	**A**			0	0	0	0	🟥		
5	**A**				0	0	0	1		
6	**A**					0	0	1	1	
7	**U**						0	0	0	0
8	**C**							0	0	0
9	**C**								0	0

Nussinov Algorithm - Basepair Maximization

$$E_{4,7} = \max \begin{cases} E_{5,7} = 1 \\ E_{4,6} = 0 \\ E_{5,6} + \delta_{4,7} = 1 \\ \max_{4<k<7}\{E_{4,k} + E_{k+1,7}\} = 1 \end{cases}$$

		1	2	3	4	5	6	7	8	9
		G	**G**	**G**	**A**	**A**	**A**	**U**	**C**	**C**
1	**G**	0	0	0	0					
2	**G**	0	0	0	0	0				
3	**G**		0	0	0	0	0			
4	**A**			0	0	0	0	**1**		
5	**A**				0	0	0	1		
6	**A**					0	0	1	1	
7	**U**						0	0	0	0
8	**C**							0	0	0
9	**C**								0	0

Nussinov Algorithm - Basepair Maximization

$$E_{i,j} = \max \begin{cases} E_{i+1,j} \\ E_{i,j-1} \\ E_{i+1,j-1} + \delta_{ij} \\ \max_{i<k<j-1}\{E_{i,k} + E_{k+1,j}\} \end{cases}$$

		1	2	3	4	5	6	7	8	9
		G	**G**	**G**	**A**	**A**	**A**	**U**	**C**	**C**
1	**G**	0	0	0	0	0	0	1	2	3
2	**G**	0	0	0	0	0	0	1	2	3
3	**G**		0	0	0	0	0	1	2	2
4	**A**			0	0	0	0	1	1	1
5	**A**				0	0	0	1	1	1
6	**A**					0	0	1	1	1
7	**U**						0	0	0	0
8	**C**							0	0	0
9	**C**								0	0

RNA structures
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Find Structure of RNA's
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Comparison of RNA Structure
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Traceback Nussinov Algorithm - Basepair Maximization

Traceback(matrix E, $i = 1$, $j = n$)
if $i < j$ **then**
    if $E_{i,j} = E_{i+1,j}$ **then**   *// i unpaired*
        Traceback(E, i+1, j)
    else if $E_{i,j} = E_{i,j-1}$ **then**   *// j unpaired*
        Traceback(E, i, j-1)
    else if $E_{i,j} = E_{i+1,j-1} + \delta_{i,j}$ **then**   *// i, j pair*
        print "basepair (i, j)"
        Traceback(E, i+1, j-1)
    else for $k = i+1, \ldots, j-1$ **do**
        if $E_{i,j} = E_{i,k} + E_{k+1,j}$ **then**   *// combined structures*
            Traceback(E, i, k)
            Traceback(E, k+1, j)
            break

Nussinov Algorithm - Basepair Maximization

Traceback (similar as in Needleman-Wunsch Algorithm):

		1 **G**	2 **G**	3 **G**	4 **A**	5 **A**	6 **A**	7 **U**	8 **C**	9 **C**
1	**G**	0	0	0	0	0	0	1	2	**3**
2	**G**	0	0	0	0	0	0	1	2	**3**
3	**G**		0	0	0	0	0	1	**2**	2
4	**A**			0	0	0	0	**1**	1	1
5	**A**				0	0	0	**1**	1	1
6	**A**					0	0	**1**	1	1
7	**U**						**0**	0	0	0
8	**C**							0	0	0
9	**C**								0	0

Secondary Structure

```
 .   (   (   .   .   (   )   )   )
 G   G   G   A   A   A   U   C   C
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RNA structures
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Find Structure of RNA's
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Comparison of RNA Structure
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Nussinov drawbacks

Maximizing the nr of bp does not lead to biological meaningful structures:

Stacking of bp not considered:

   (((.   )   )   )   stable

   (   )   (   )   .   (   )   instable

Size of intern loop not considered:

instable   stable   instable

Nevertheless, although Nussinov-Alg is too simple to be accurate, it is stepping-stone for later algorithms

RNA structures
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Find Structure of RNA's
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Comparison of RNA Structure
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RNA MinFreeEnergy (MFE) Folding

Define energy model for RNA that takes into account local energy contributions
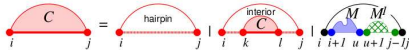from loop and stacking regions.
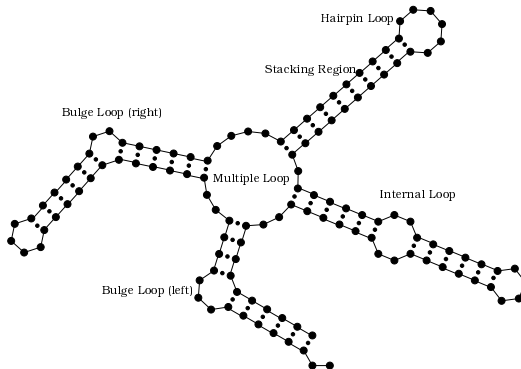
- More realistic: thermodynamics and statistical mechanics.
- Stability of an RNA sec.str. coincides with thermodynamic stability
- Quantified as the amount of free energy released/used by forming bp.

RNA structures
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Find Structure of RNA's
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Comparison of RNA Structure
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RNA MinFreeEnergy (MFE) Folding

Define energy model for RNA that takes into account local energy contributions
contributions from loop and stacking regions.
The Turner rules are a set of experimentally determined parameters which allow
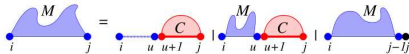us to predict the stability of RNA secondary structures.

overall ΔG = -4.6 kcal/mol
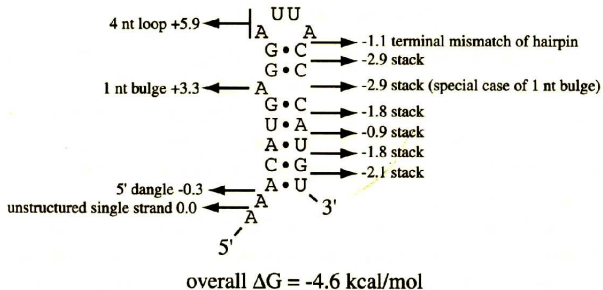
MFE-folding via Loop Decomposition

$$F_{i,j} = \min \left\{ \begin{array}{l} F_{i+1,j}, \\ \min\limits_{i<k\leq j} C_{i,k} + F_{k+1,j} \end{array} \right\}$$
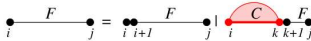
$$C_{i,j} = \min \left\{ \begin{array}{l} \mathcal{H}(i,j), \\ \min\limits_{i<k<l<j} C_{k,l} + \mathcal{I}(i,j;k,l), \\ \min\limits_{i<u<j} M_{i+1,u} + M^1_{u+1,j-1} + a \end{array} \right\}$$

$$M_{i,j} = \min \left\{ \begin{array}{l} \min\limits_{i<u<j} (u-i+1)c + C_{u+1,j} + b, \\ \min\limits_{i<u<j} M_{i,u} + C_{u+1,j} + b, \\ M_{i,j-1} + c \end{array} \right\}$$

$$M^1_{i,j} = \min \left\{ \begin{array}{l} M^1_{i,j-1} + c, \\ C_{i,j} + b, \end{array} \right\}$$

First proposed by Zuker et al.

init: $F_{i,j} = 0$, $C_{i,j} = M_{i,j} = M^1_{i,j} = \infty$.

- $F_{1,n}$ stores the energy value of the thermodynamically most stable structure, its Minimum Free Energy (MFE).
- traceback structure
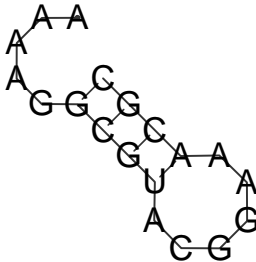
MFE-folding via loop decomposition: remarks

- $F_{i,j}$: free energy of the opt. sub-struct. on the sub-seq. $s_i \ldots s_j$.
- $C_{i,j}$: free energy of the opt. sub-struct. on the sub-seq. $s_i \ldots s_j$ given that i and j form a base pair.
- $M_{i,j}$: free energy of the opt. sub-struct. on the sub-seq. $s_i \ldots s_j$ given that $s_i \ldots s_j$ is part of a multi-loop and has at least one "component".
- $M^1_{i,j}$: free energy of the opt. sub-struct. on the sub-seq. $s_i \ldots s_j$ given that $s_i \ldots s_j$ is part of a multi-loop and has exactly one component which has the closing pair (i, h) for some h satisfying $i < h \leq j$.
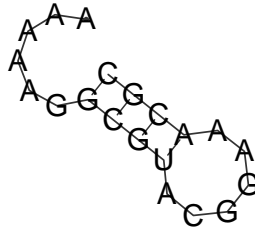
RNA structures
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Find Structure of RNA's
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Comparison of RNA Structure
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RNA Fold

```
http://rna.tbi.univie.ac.at/cgi-bin/RNAfold.cgi
```

```
  RNAfold < trna.fa
>AF041468
GGGGGUAUAGCUCAGUUGGUAGAGCGCUGCCUUUGCACGGCAGAUGUC
AGGGGUUCGAGUCCCCUUACCUCCA
(((((((..((((........)))).(((((.......))))).....
(((((.......))))))))))))).
-31.10 kcal/mol
```

RNA structures
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Find Structure of RNA's
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Comparison of RNA Structure
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Symmetric Difference

AAAAGGCGUACGGAAACGC
. . . . . ((((. . . . . .))))

AAAAAGGCGUACGGAAACGC
. . . . . . ((((. . . . . .))))

$S_1 = \{(6,19),(7,18)(8,17)(9,16)\}$
$S_2 = \{(7,20),(8,19)(9,18)(10,17)\}$

$$|S_1 \Delta S_2| = 8$$

RNA structures
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Find Structure of RNA's
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Comparison of RNA Structure
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String Alignment

$S_1 = (((. . (((. . . .))))))$ $S_2 = (((. . . . . .)))$

>String Alignment:
>$(((. . (((. . . .))))))$
>$(((. . \star \star \star . . . .))) \star \star \star$

>"Structure" Alignment:
>$(((. . (((. . . .))))))$
>$(((. . \star \star \star . . . . \star \star \star)))$

RNA structures
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Find Structure of RNA's
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Comparison of RNA Structure
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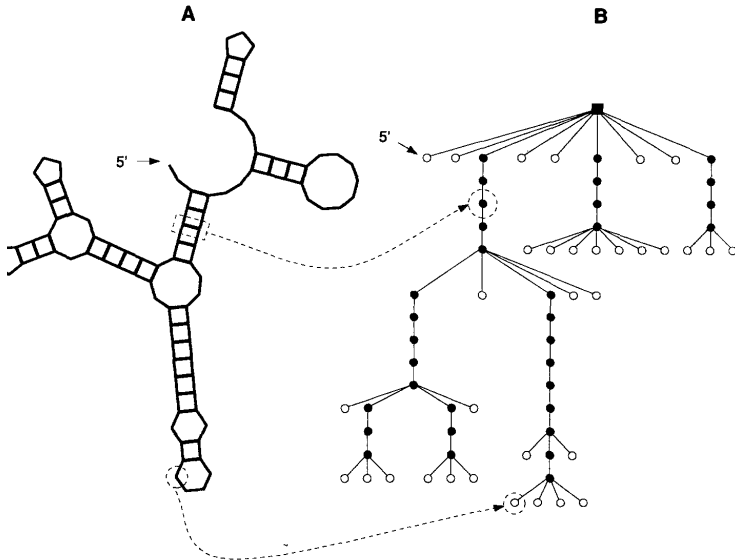
Tree Edit Distance

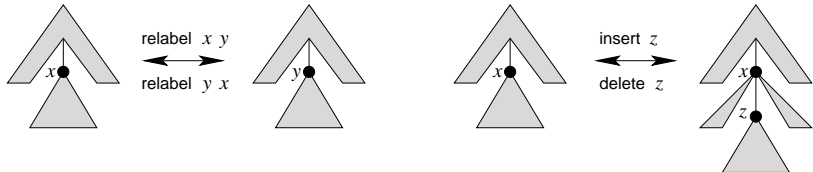# Tree Edit Distance

There are three basic edit operations with associated costs γ:

relabel $x \to y$ with $\gamma(x \to y)$

insert $\emptyset \to z$ with $\gamma(\emptyset \to z)$

delete $z \to \emptyset$ with $\gamma(z \to \emptyset)$

RNA structures
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Find Structure of RNA's
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Comparison of RNA Structure
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Tree Edit Distance

$\gamma(S)$, (ordered) edit map M , $\gamma(S) = \gamma(M)$

$$D(F_1, F_2) = \min \begin{cases} D(F_1 - v_1, F_2) + \gamma(v_1 \rightarrow \emptyset), \\ D(F_1, F_2 - v_2) + \gamma(\emptyset \rightarrow v_2), \\ D(T(v_1) - v_1, T(v_2) - v_2) + \\ D(F_1 \setminus T(v_1), F_2 \setminus T(v_2)) + \gamma(v_1 \rightarrow v_2) \end{cases}$$

where:

$$D(\emptyset, \emptyset) = 0$$
$$D(\emptyset, F_2) = D(\emptyset, F_2 - v_2) + \gamma(\emptyset \rightarrow v_2)$$
$$D(F_1, \emptyset) = D(F_1 - v_1, \emptyset) + \gamma(v_1 \rightarrow \emptyset)$$