CISC 436/636 Computational Biology & Bioinformatics (Fall 2016)

RNA secondary structure

Facts about RNAs

- Mainly as “information carrier” in protein synthesis
  - mRNA
  - tRNA
- Also as catalysts
  - Ribozymes
- Also as regulator
  - RNAi
- Single strand
  - Intra-molecular pairing
  - Secondary structure
  - Essential for sequence stability and function

- Similarity in secondary structure plays a more important role than primary sequence in determining homology for RNAs

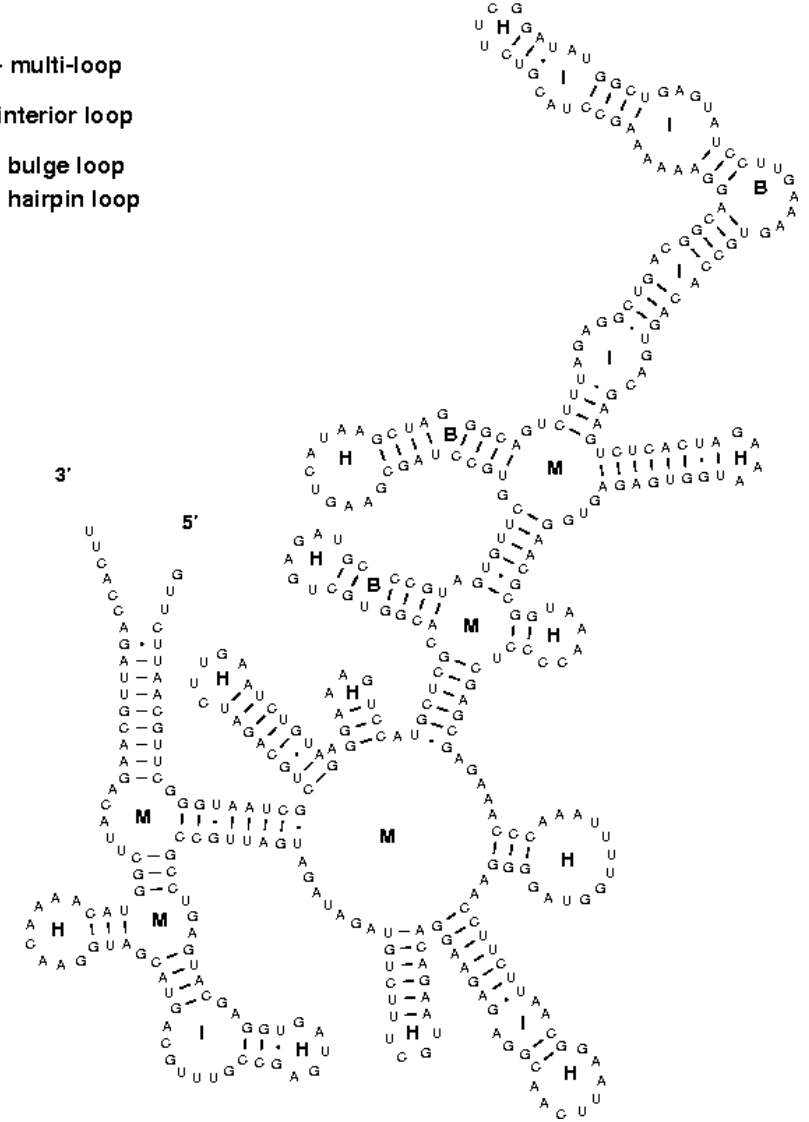
Bacillus subtilis RNase P RNA

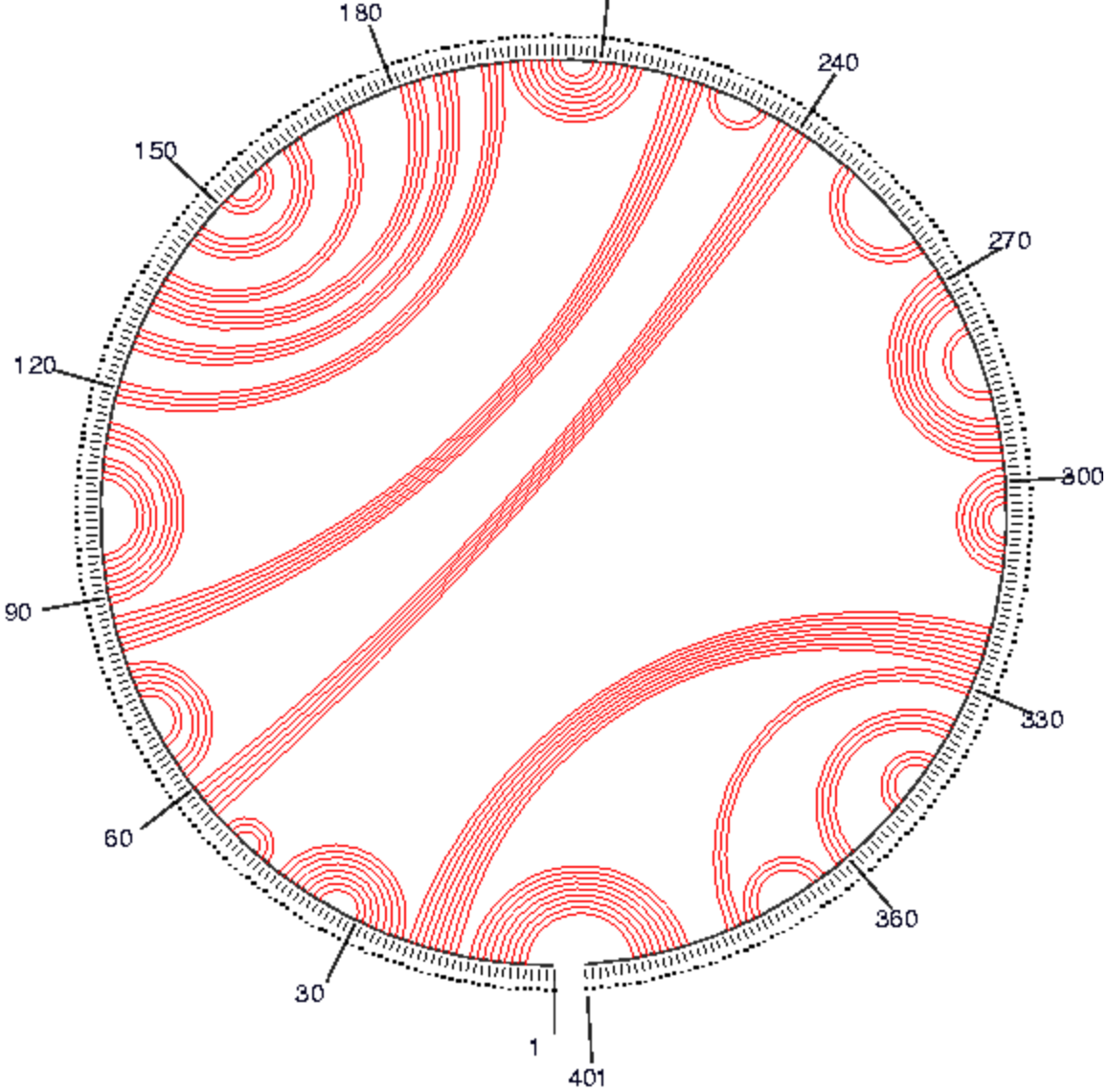
M - multi-loop

I - interior loop

B - bulge loop

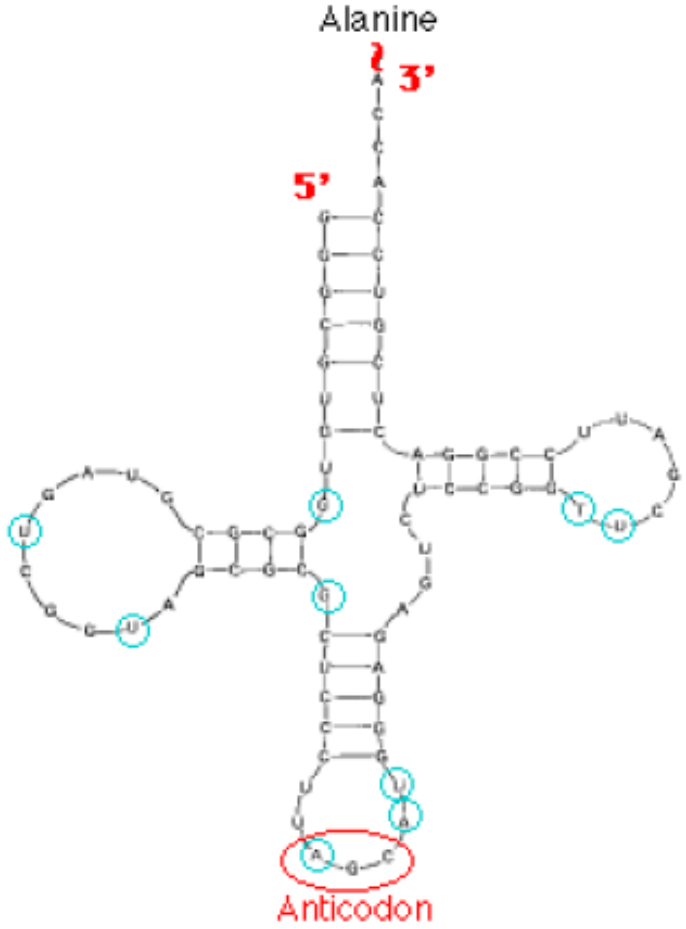
H - hairpin loop



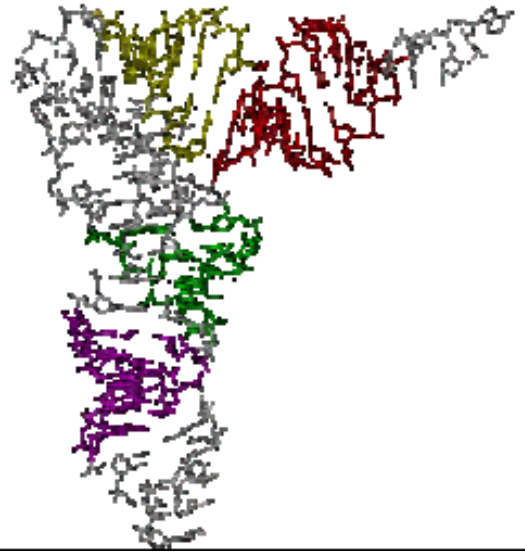


ENERGY = -85.7 Bacillus subtilis RNase P RNA

tRNA Secondary Structure

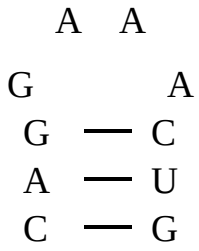


tertiary structure

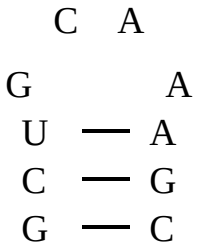


RNA stem loop

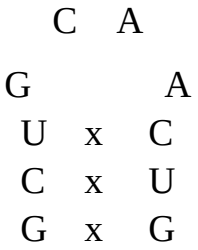
hybridization pairing: A-U, and C-G



seq1



seq2



seq3

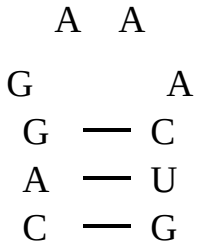
where "-" stands for a pairing, and "x" for no pairing.

In the above example, seq1 and seq2 fold into a similar structure, whereas seq3 does not.

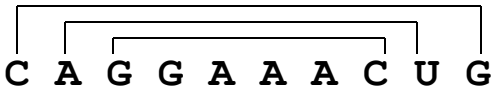
Pairwise alignments disregarding such structural restrictions may be misleading; seq2 and seq3 have 70% sequence identity, seq1 and seq3 have 60%, whereas seq1 and seq2 have only 30%.

Representations for palindromic structures

1)



2)



3)

```
C A G G A A A C U G
( ( ( . . . . ) ) )
```

There is a 1-1 correspondence between RNA secondary structures and well-balanced parenthesis expressions, where the balancing parentheses correspond to base pairings via hydrogen bonds.

Secondary structure prediction

Base pair maximization algorithm [Nussinov]

$m_{i,j}$: maximal # of base pairs that can be formed for sequence $s_i \ldots s_j$.

$d_{i,j}$ = 1, if s_i and s_j are paired

= 0, otherwise

Initialization

$m_{i,i-1} = 0$ for i= [2, L]

$m_{i,i} = 0$ for i = [1,L]

Recursion

$m_{i,j} = \max \{ m_{i+1,j},$

$m_{i,j-1},$

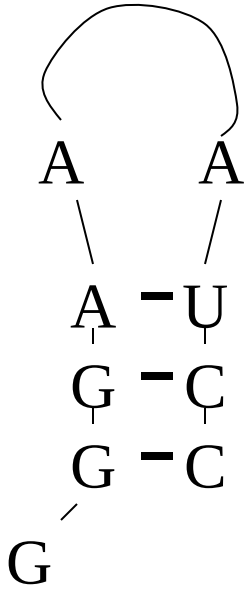
$m_{i+1,j-1} + d_{i,j},$

$\max_{i<k<j} \{ m_{i,k} + m_{k+1,j} \}$ // bifurcation

$\}$

Dynamic programming table

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



Time Complexity: $O(L^3)$, where L is sequence length

Space complexity: $O(L^2)$

Secondary structure prediction

Minimum energry algorithm [Zuker]

$E_{i,j}$: minimum energy for an optimal fold formed by sequence $s_i \ldots s_j$.
$e_{i,j}$ = -5, if s_i , s_j is CG or GC
= -4, if s_i , s_j is AU or UA
= -1, if s_i , s_j is GU or UG

Initialization
$E_{i,i-1} = 0$ for i= [2, L]
$E_{i,i} = 0$ for i = [1,L]

Recursion

$E_{i,j}$= min {$E_{i+1,j}$,
$E_{i,j-1}$,
$E_{i+1,j-1}$+ $e_{i,j}$,
$\min_{i<k<j} \{E_{i,k} + E_{k+1,j}\}$ // bifurcation
}

Resources

Lecture notes:

http://www.bioinfo.rpi.edu/~zukerm/lectures/RNAfold-html/

RNA informatics:

http://www-lbit.iro.umontreal.ca/RNA_Links/RNA.shtml

Software:

-Vienna RNA fold

- Mfold (http://www.bioinfo.rpi.edu/zukerm/export/)