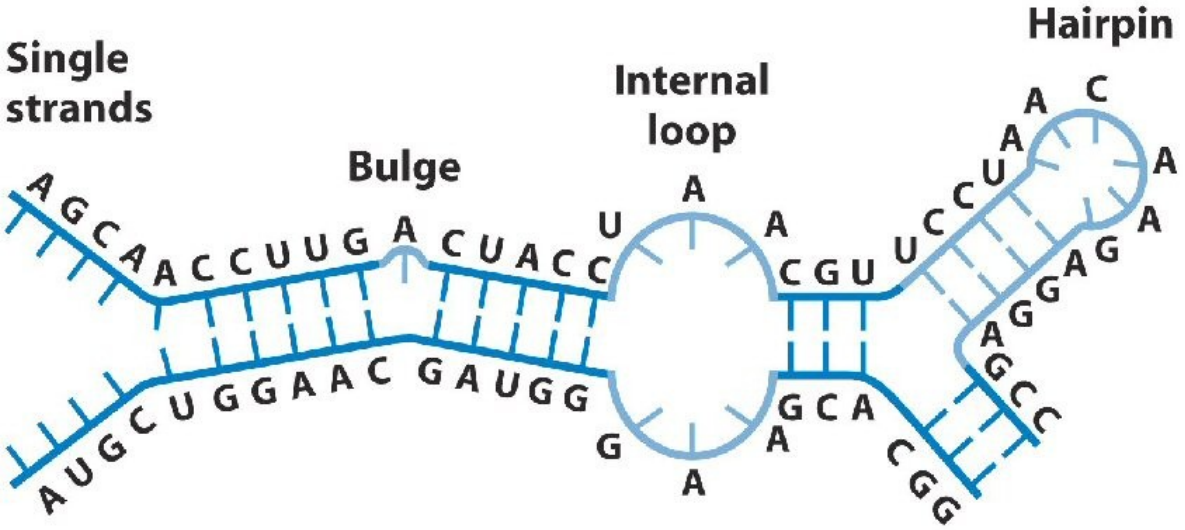
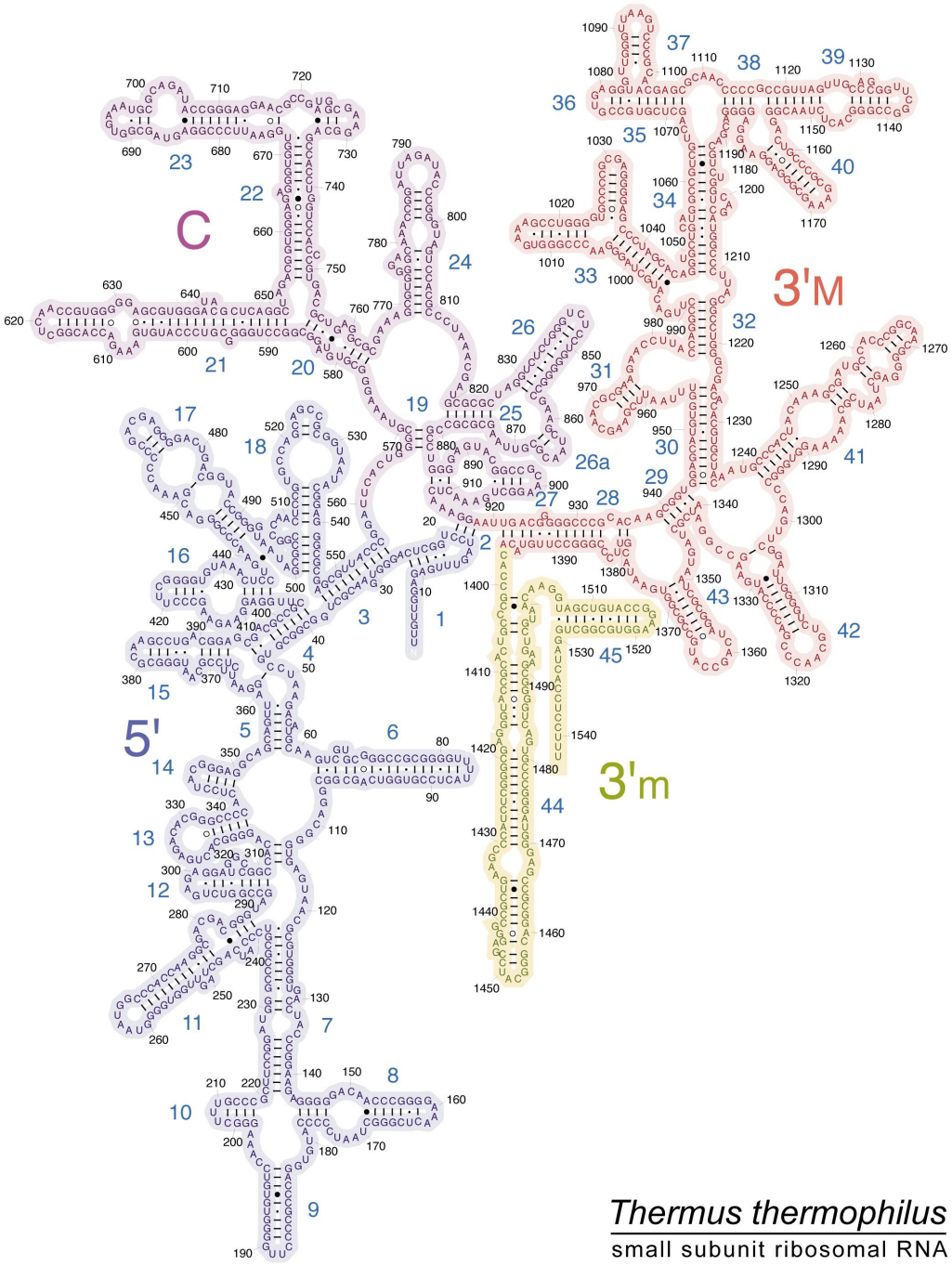
CMSC423: Bioinformatic Algorithms, Databases and Tools

RNA folding

RNA folding

- Function of RNA molecules depends on how they fold, based on nucleotide base-pairing

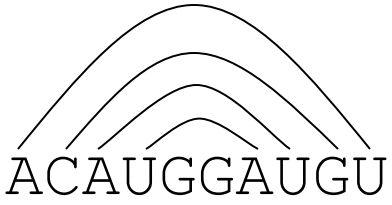




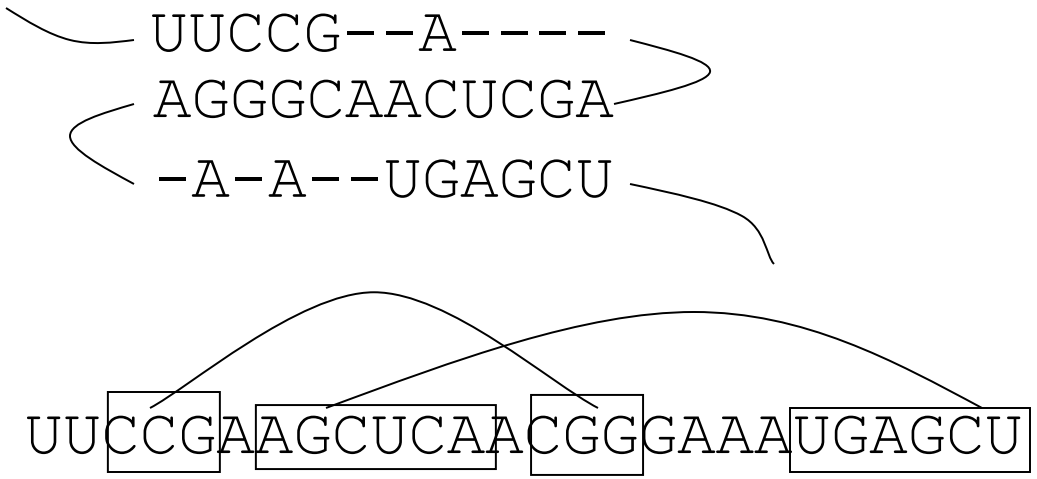
Thermus thermophilus
small subunit ribosomal RNA

Types of structures

- Nested (hairpin)



- Pseudo-knots



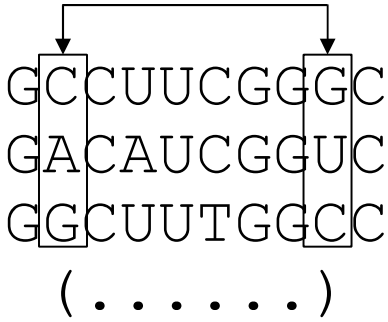
RNA folding... not just for RNA

- RNA – given the sequence figure out how it folds
- Parsing
  - Given a grammar
  - Parse a string of letters (text, program) according to grammar

$$A \rightarrow BC$$
$$A \rightarrow \alpha$$
$$S \rightarrow \lambda$$

- ... example
  - Given a C program
  - Find whether parentheses, braces, and brackets are matched up correctly
  - if not, where are the likely errors (find the smallest number of corrections that would make the progam balanced)
- Both can be solved by the same algorithm

From multiple alignment to structure



- Find columns in the alignment where mutations are correlated
- Mutual information - how correlated are the columns?

$$M_{i,j} = \sum_{x_i, x_j} f_{x_i x_j} \log \left(\frac{f_{x_i x_j}}{f_{x_i} f_{x_j}} \right)$$

$M_{i,j}$ = mutual information between columns i and j
f_{xixj} = frequency of each of 16 pairs of nucleotides at columns i and j
f_{xi} = frequency of each of 4 nucleotides at column i
f_{xj} = frequency of each of 4 nucleotides at column j

Mutual information

- Ranges from 0 to 2 for a 4-letter alphabet
- Correlated columns - mutual information high
- Advantages:
  - Don't need to know how RNA folds - pseudo-knots should “pop” out of the alignment
- Disadvantages:
  - Need many sequences in an alignment (to compute frequencies)
  - The aligned sequences must be sufficiently divergent (conserved columns provide no information)

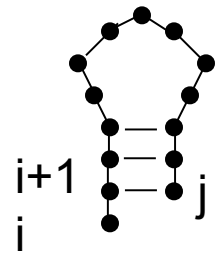
Nussinov's algorithm

- Assumes no pseudo-knots
- Dynamic programming approach – maximize # of pairings

- S – string of nucleotides representing the RNA molecule
- Sub-problem – F[i,j] – score of folding just S[i..j]
- Initial values: F[i-1,i] = F[i,i] = F[i, i+1] = 0

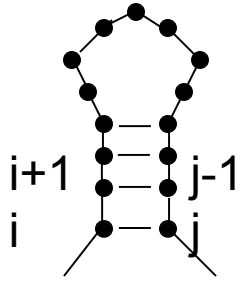
Nussinov's algorithm

F[i,j] is the maximum of:



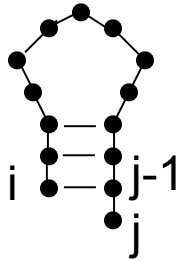
I. F[i+1,j]

S[i] unpaired



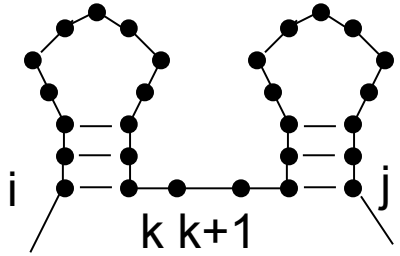
III. F[i+1,j-1] + 1
if S[i+1] complementary to S[j-1]

S[i] paired with S[j]



II. F[i,j-1]

S[j] unpaired



IV. $\max_k$ F[i,k]+F[k+1,j]

Branch

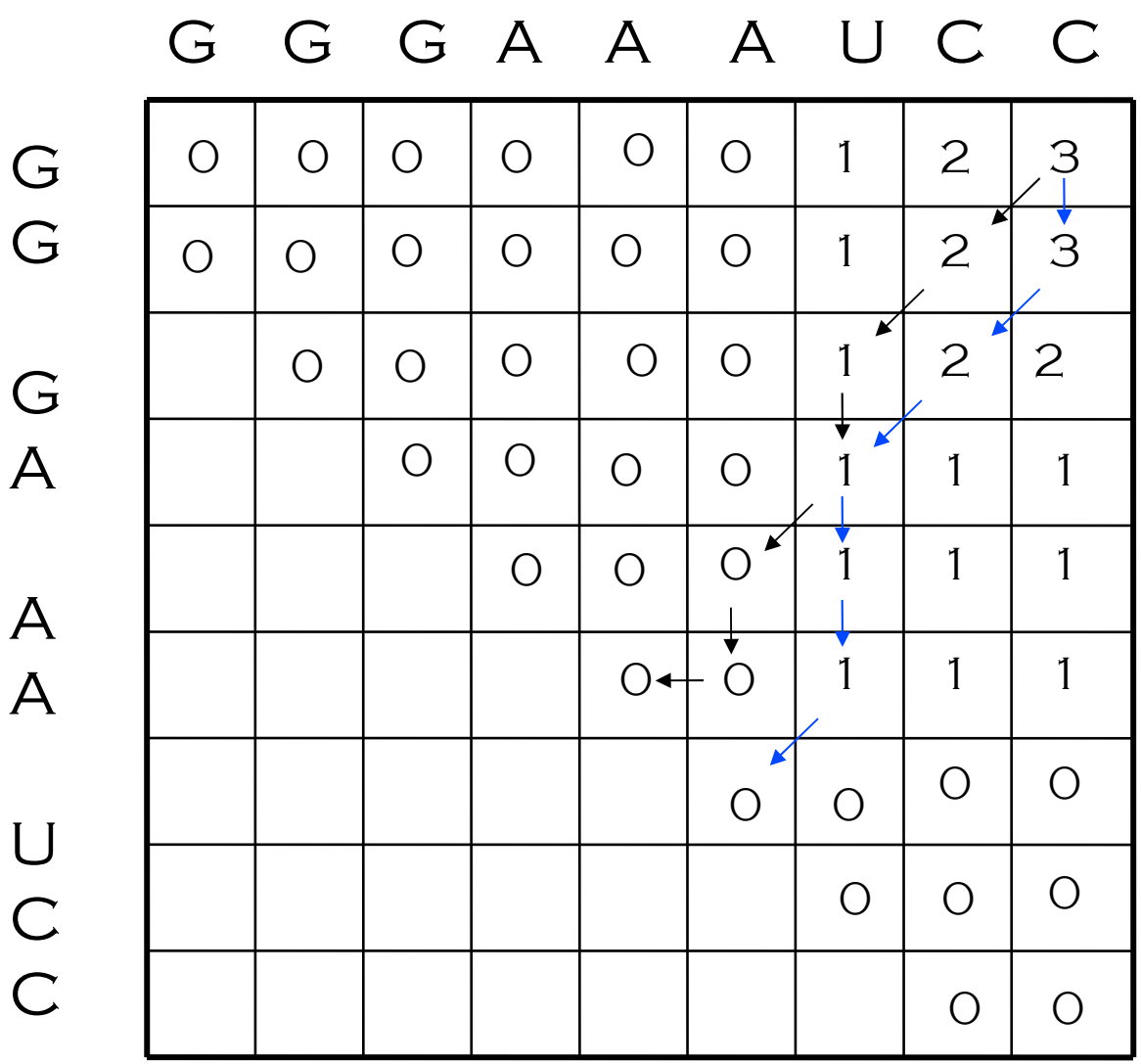
Questions

- In what order do we fill the dynamic programming table?
- How can we ensure that "loops" consist of at least k nucleotides?

- Note: related to CYK parsing algorithm for Chomsky Normal Form grammars

	G	G	G	A	A	A	U	C	C
G									
G									
G									
A									
A									
A									
U									
C									
C									

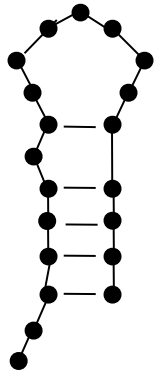
F[i+1, j]
F[i, j - 1]
F[i+1, j-1] + 1 (if paired)
$\max_k F[i,k] + F[k+1,j]$


G G G A A A U C C
G
G
G
A
A
A
U
C
C
0 0 0 0 0 0 1 2 3
0 0 0 0 0 0 1 2 3
0 0 0 0 0 1 2 2
0 0 0 0 0 1 1 1
0 0 0 0 0 1 1 1
0 0 0 0 1 1 1
0 0 0 0 0
0 0 0
0 0

GGGAAAUCC
((.(..)))
.((..()))

A better objective function

- Find the RNA fold that minimizes the Gibbs free energy
- Zucker's algorithm keeps track of:
  - Stacking energy - f(# of base-pairs in a stem)
  - Loop energy - f(length of loop)
  - Bulge energy - f(length of bulge)
  - Dangle energy - f(length of dangle)



- Computation is done with an extension of the traditional (Nussinov) dynamic programming approach
- One extension: compute sub-optimal folds
  - during backtracking, try multiple paths

Question

How do you change Nussinov's algorithm to allow the computation of the stacking energy (score depends on # of next-to-next pairings)?

Hint: think affine gap penalties.