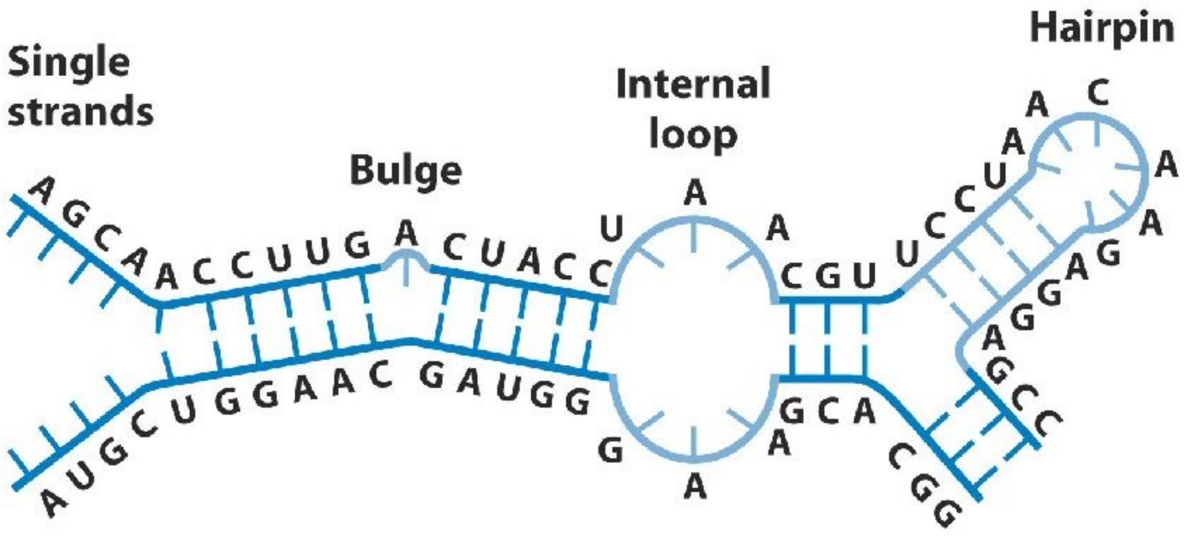
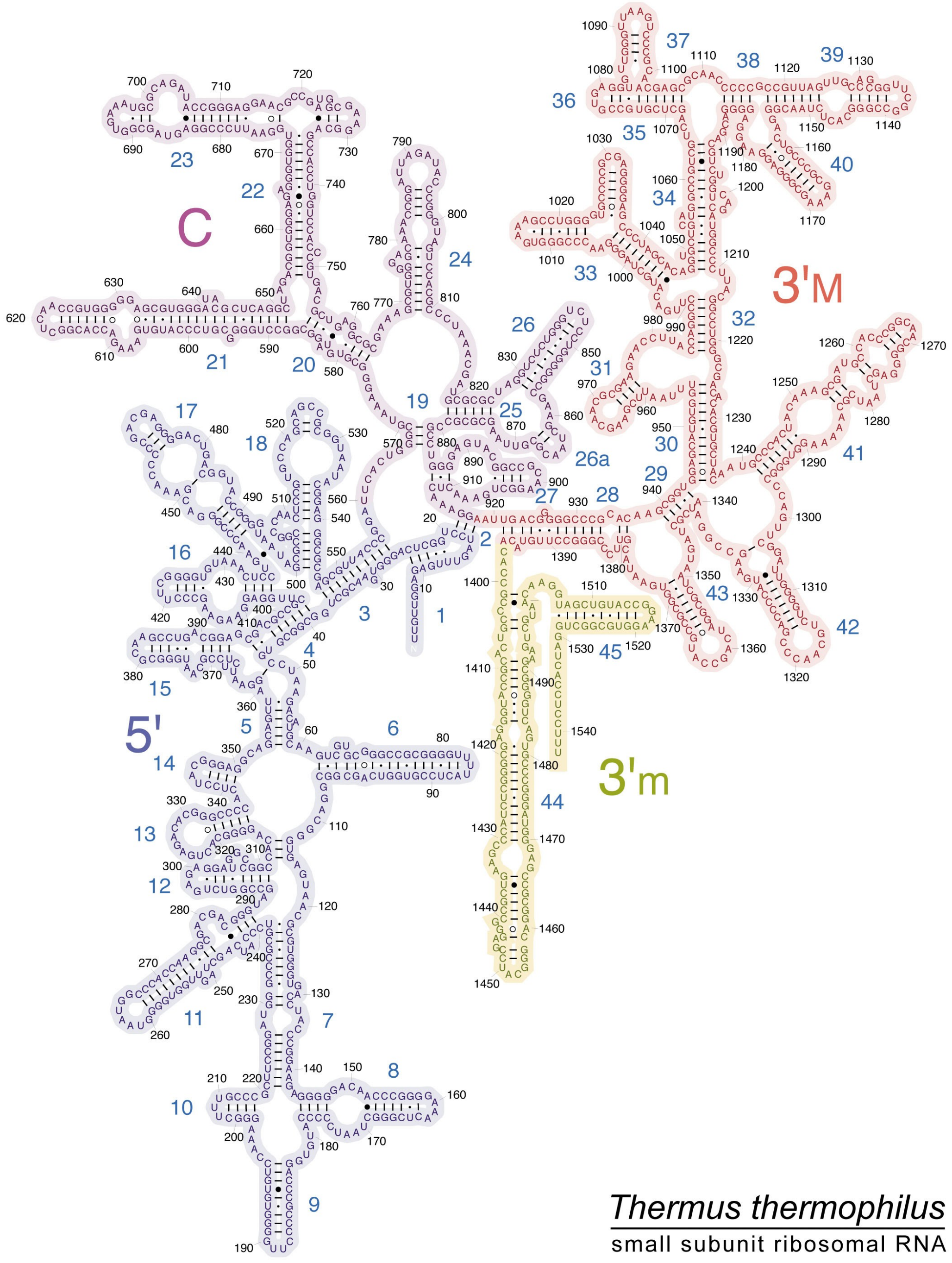
CMSC423: Bioinformatic Algorithms, Databases and Tools Lecture 20

RNA folding

RNA folding

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



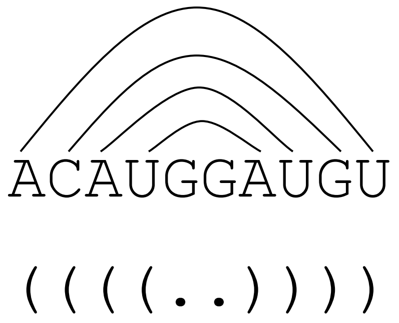


Thermus thermophilus

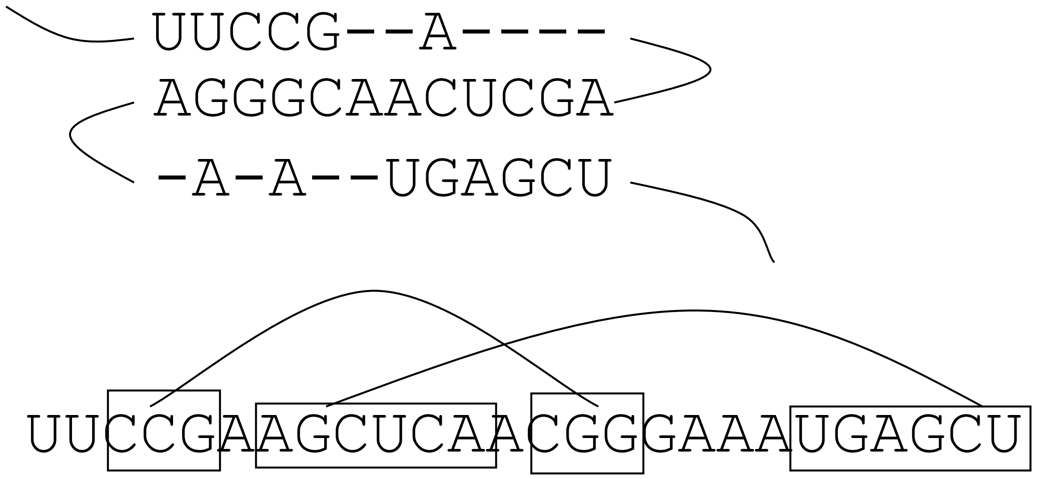
small subunit ribosomal RNA

Types of structures

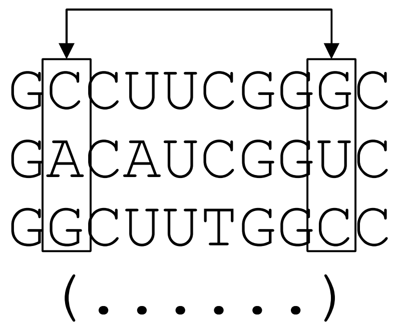
- Nested (hairpin)



- Pseudo-knots



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)

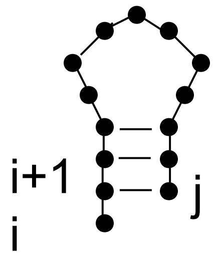
Nussinov's algorithm

- 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

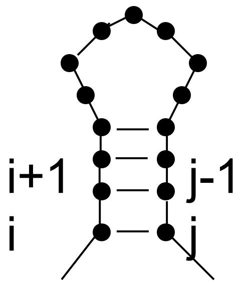
Nussinov's algorithm

F[i,j] is the maximum of:



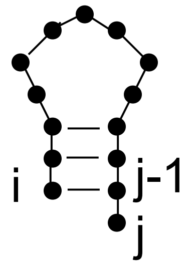
I. F[i+1,j]

S[i] unpaired



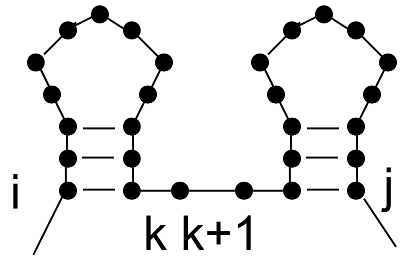
III. F[i+1,j-1] + 1
if S[i+1] complementary
to S[j-1]

S[i] paired with S[j]



II. F[i,j-1]

S[j] unpaired



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

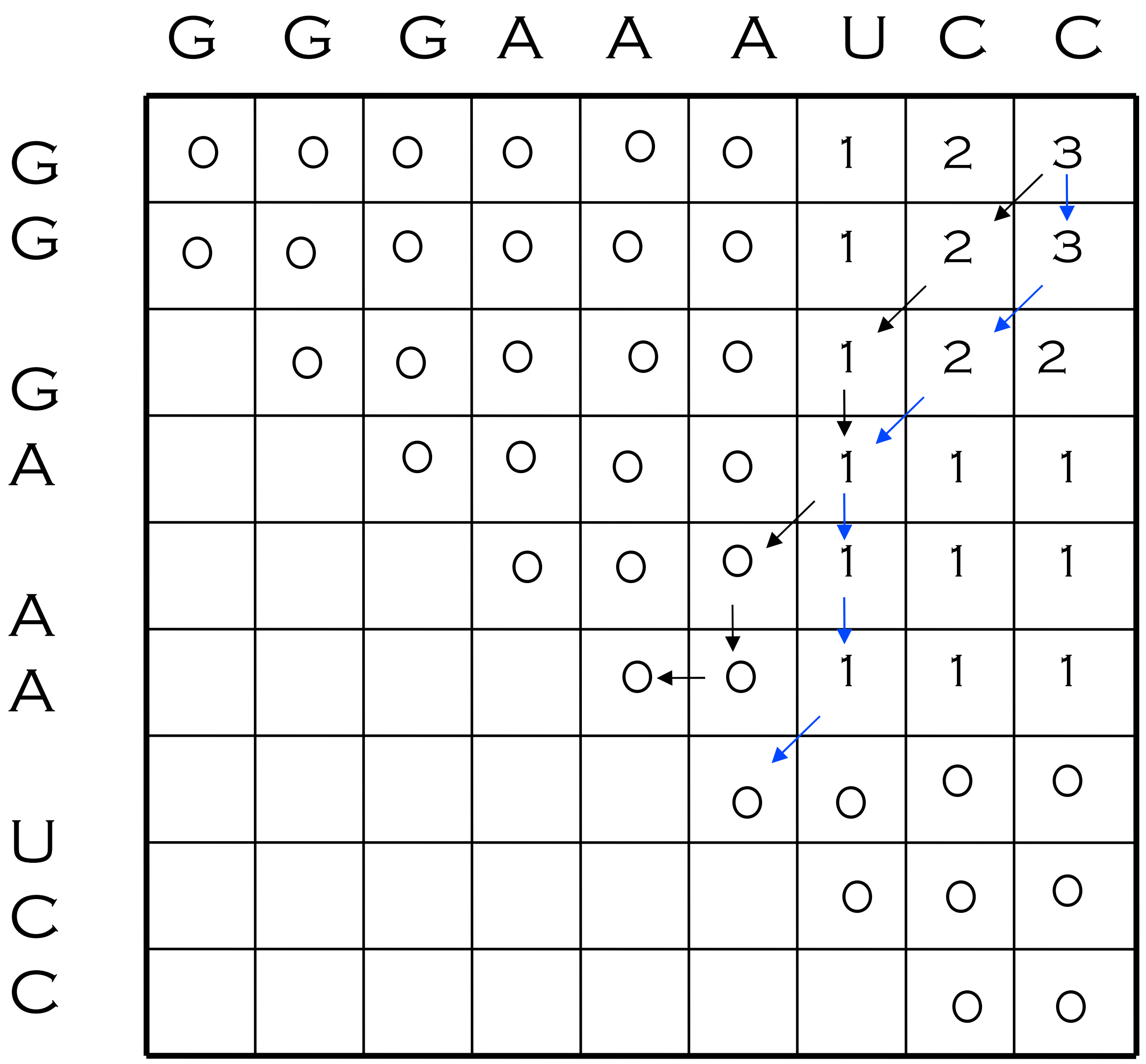
Branch

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									

$$\begin{cases} F[i+1, j] \\ F[i, j-1] \\ F[i+1, j-1] + 1 \text{ (if paired)} \\ \max_k F[i,k] + F[k+1,j] \end{cases}$$



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

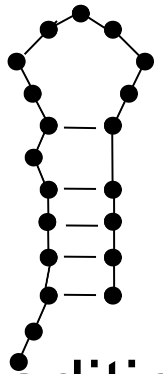
GGGAAAUCC

((.(..)))

.((..()))

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
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Question

How do you change Nussinov's algorithm to allow the computation of the stacking energy?

Hint: think affine gap penalties.

Protein folding

- Protein shape determines protein function
- Protein sequence determines protein shape (Anfinsen’s experiment)
- Levinthal’s paradox – space of possible protein conformations is exponentially large, yet proteins fold fast (µsec – minutes).
- Corollary: proteins must “know” how to fold (i.e. they don’t search the entire space of conformations)

- Note: much easier to find a protein's sequence than its structure

Protein folding

- Note: mis-folded proteins may cause disease (e.g. Creutzfeld-Jakob a.k.a. mad cow)
- Drugs (e.g. antibiotics) often inhibit protein function – knowing structure can help design drugs

- Folding@home – lend your computer’s unused cycles to help fold proteins (like SETI@home) (do you believe in evolution or aliens ?)