RNA Secondary Structure Prediction

BMI/CS 776

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Goals for Lecture

the key concepts to understand are the following

- RNA secondary structure
- secondary structure features: stems, loops, bulges
- Pseudoknots
- the Nussinov algorithm
- adapting Nussinov to take free energy into account

Why RNA Is Interesting

- in addition to messenger RNA (mRNA), there are other RNA molecules that play key roles in biology
  - ribosomal RNA (rRNA)
    - ribosomes are complexes that incorporate several RNA subunits in addition to numerous protein units
  - transfer RNA (tRNA)
    - transport amino acids to the ribosome during translation
  - the spliceosome, which performs intron splicing, is a complex with several RNA units
  - microRNAs and others that play regulatory roles
  - the genomes for many viruses (e.g. HIV) are encoded in RNA
  - etc.

- the folding of an mRNA can be involved in regulating the gene's expression

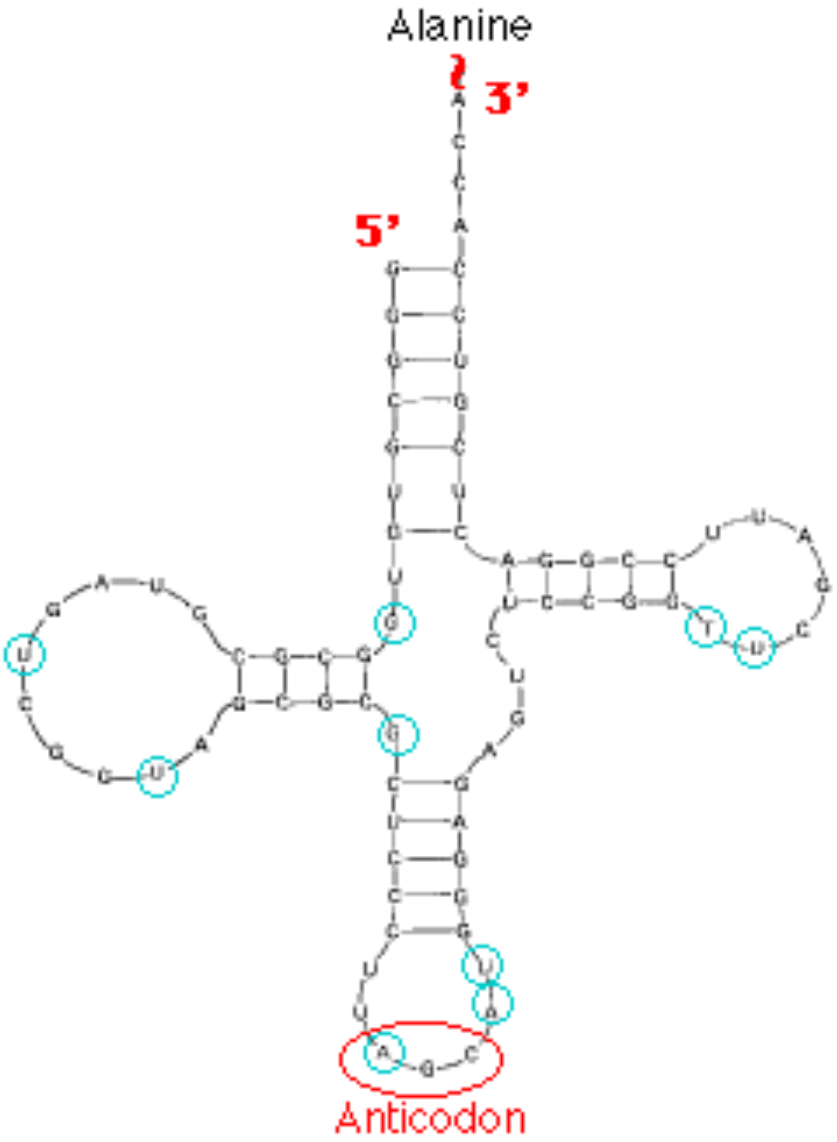
RNA Secondary Structure

- RNA is typically single stranded
- folding, in large part is determined by base-pairing

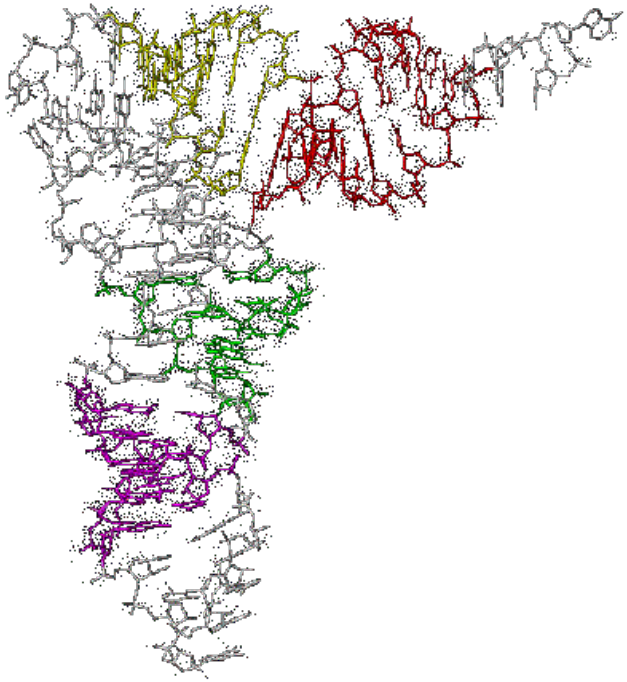
  A–U and **C–G** are the canonical base pairs

  other bases will sometimes pair, especially **G–U**
- the base-paired structure is referred to as the *secondary structure* of RNA
- related RNAs often have homologous secondary structure without significant sequence similarity

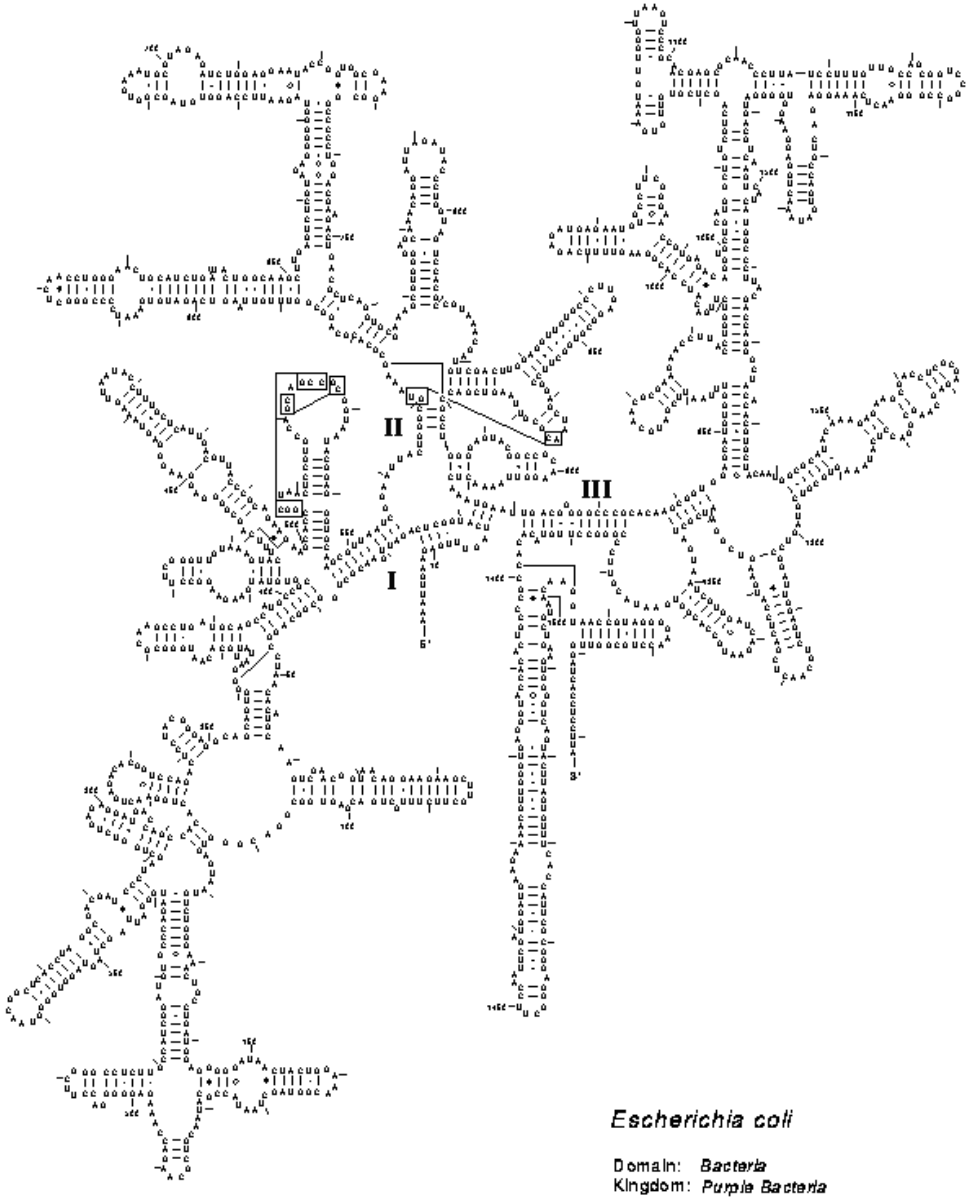
tRNA Secondary Structure



tertiary structure



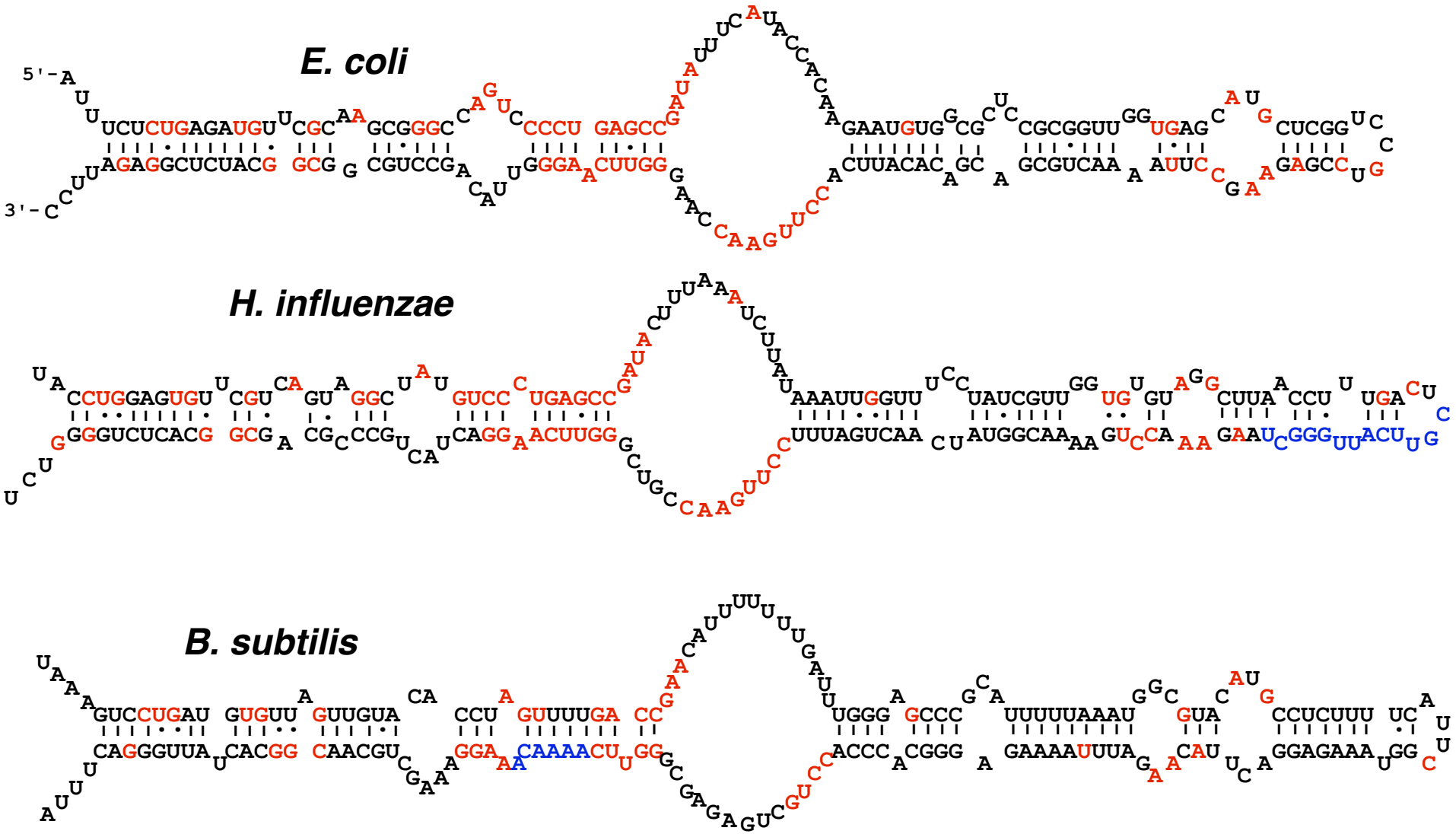
Small Subunit Ribosomal RNA



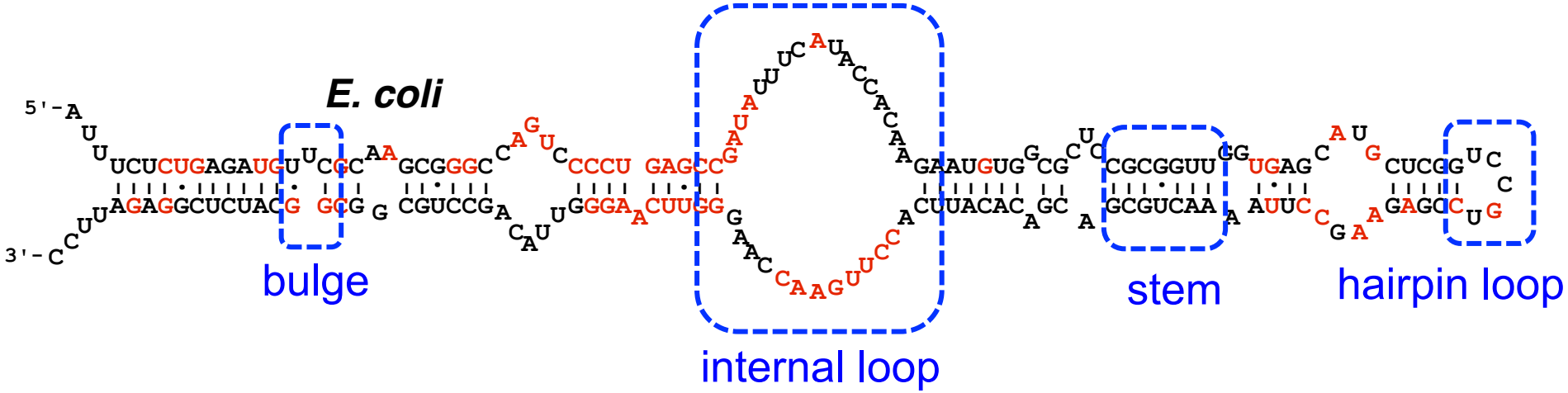
Escherichia coli

Domain: *Bacteria*
Kingdom: *Purple Bacteria*
Order: *gamma*

6S RNA Secondary Structure



Secondary Structure Features



Four Key Problems

- predicting RNA secondary structure
  Given: RNA sequence
  Do: predict secondary structure that sequence will fold into

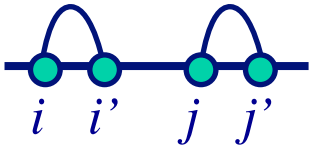
- searching for instances of a given structure
  Given: an RNA sequence or its secondary structure
  Do: find sequences that will fold into a similar structure

- modeling a family of RNAs
  Given: a set of RNA sequences with similar secondary structure
  Do: construct a model that captures the secondary structure regularities of the set

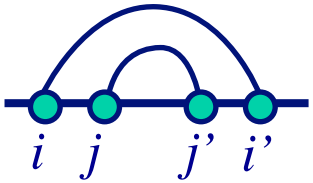
- identifying novel RNA genes
  Given: a pair of homologous DNA sequences
  Do: identify subsequences that appear to have highly conserved RNA secondary structure (putative RNA genes)

RNA Folding Assumption

- the algorithms we'll consider assume that base pairings do not cross
- for base-paired positions i, i' and j, j', with $i < i'$ and $j < j'$, we must have either

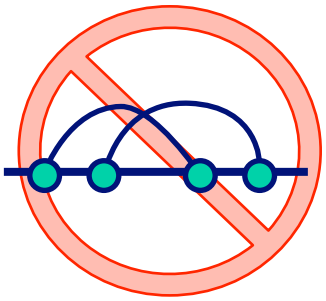


$i < i' < j < j'$ or $j < j' < i < i'$ (not nested)

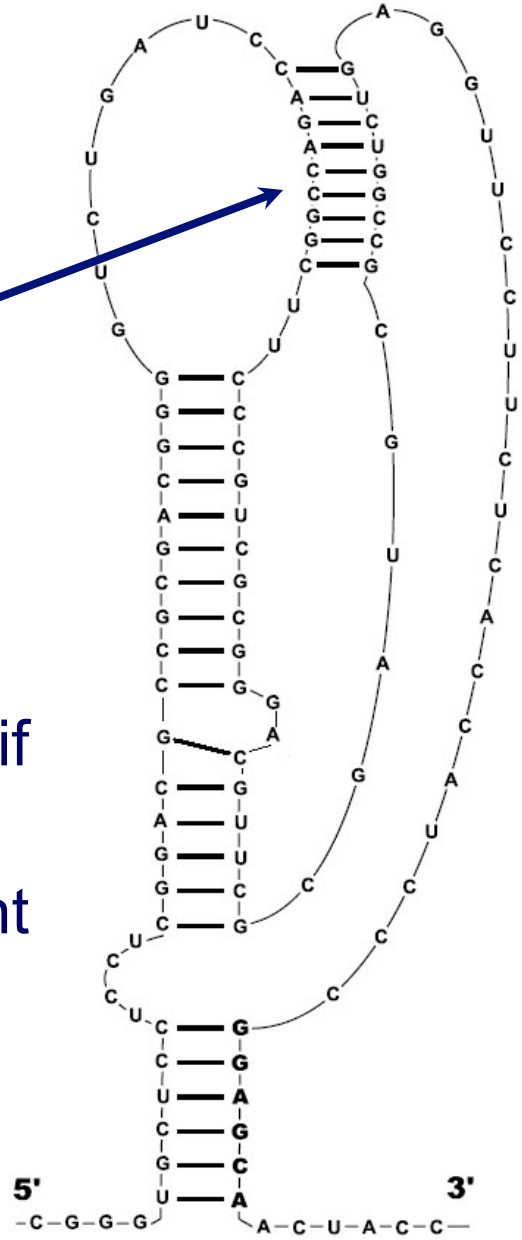


$i < j < j' < i'$ or $j < i < i' < j'$ (nested)

- can't have $i < j < i' < j'$ or $j < i < j' < i'$



Pseudoknots



- these crossings are called *pseudoknots*
- dynamic programming breaks down if pseudoknots are allowed
- fortunately, they are not very frequent

Figure from Seliverstov et al. *BMC Microbiology*, 2005

Simplest RNA Secondary Structure Task

Given:

- An RNA sequence
- The constraint that pseudoknots are not allowed

Do:

- Find a secondary structure for the RNA that maximizes the number of base pairing positions

Predicting RNA Secondary Structure: the Nussinov Algorithm

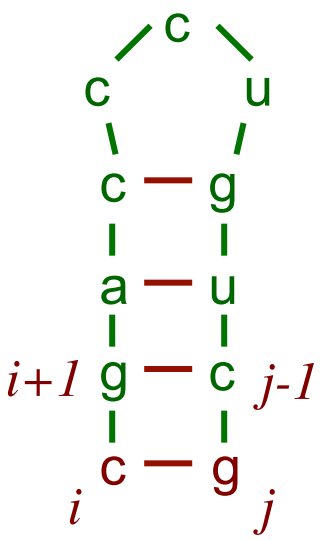
[Nussinov et al., *SIAM Journal of Applied Mathematics* 1978]

key idea:

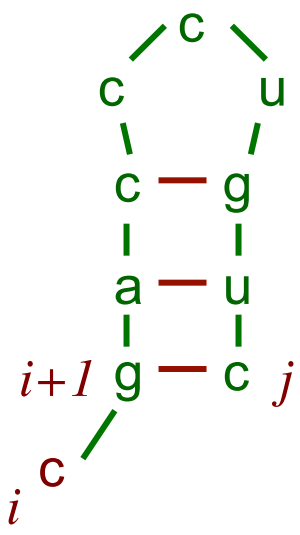
- do this using dynamic programming
  - start with small subsequences
  - progressively work to larger ones

DP in the Nussinov Algorithm

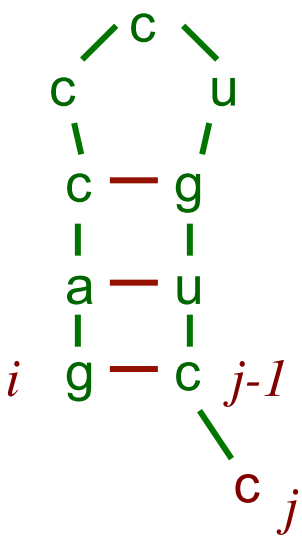
- incrementally find the best secondary structure for subsequences $[i, j]$
- consider four possibilities



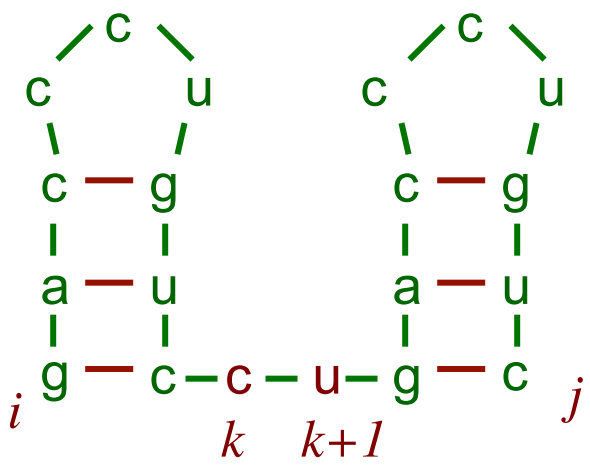
i, j paired



i unpaired



j unpaired



bifurcation: combine two substructures

DP in the Nussinov Algorithm

- let $\delta(i,j) = \begin{cases} 1 & \text{if } x_i \text{ and } x_j \text{ are complementary} \\ 0 & \text{otherwise} \end{cases}$
- initialization:

$$\gamma(i, i-1) = 0 \qquad \text{for } i = 2 \text{ to } L$$
$$\gamma(i, i) = 0 \qquad \text{for } i = 1 \text{ to } L$$

- recursion

$$\gamma(i,j) = \max \begin{cases} \gamma(i+1, j) \\ \gamma(i, j-1) \\ \gamma(i+1, j-1) + \delta(i,j) \\ \max\limits_{i<k<j} \left[\gamma(i,k) + \gamma(k+1, j) \right] \end{cases}$$

max # of paired bases in subsequence $[i,j]$

Nussinov Algorithm Traceback

push $(1, L)$ onto stack

repeat until stack is empty

pop (i, j)

if $i \geq j$ continue

else if $\gamma(i+1, j) = \gamma(i, j)$ push $(i+1, j)$

else if $\gamma(i, j-1) = \gamma(i, j)$ push $(i, j-1)$

else if $\gamma(i+1, j-1) + \delta(i, j) = \gamma(i, j)$

record i, j base pair

push $(i+1, j-1)$

else for $k = i+1$ to j-1 : if $\gamma(i, k) + \gamma(k+1, j) = \gamma(i, j)$

push $(k+1, j)$

push (i, k)

break

Predicting RNA Secondary Structure by Energy Minimization

- it's naïve to predict folding just by maximizing the number of base pairs
- however, we can generalize the key recurrence relation so that we're minimizing free energy instead

$$E(i,j) = \min \begin{cases} E(i+1,\, j) \\ E(i,\, j\text{-}1) \\ \min\limits_{i<k<j} \left[E(i,k) + E(k+1,\, j) \right] \\ P(i,j) \end{cases}$$

$P(i,j)$ ← case that i and j are base paired

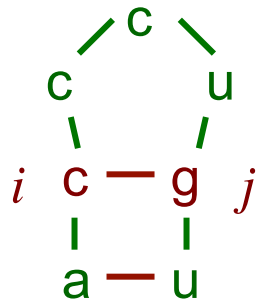
Predicting RNA Secondary Structure by Energy Minimization

- a sophisticated program, such as Mfold [Zuker et al.], can take into account free energy of the "local environment" of $[i, j]$

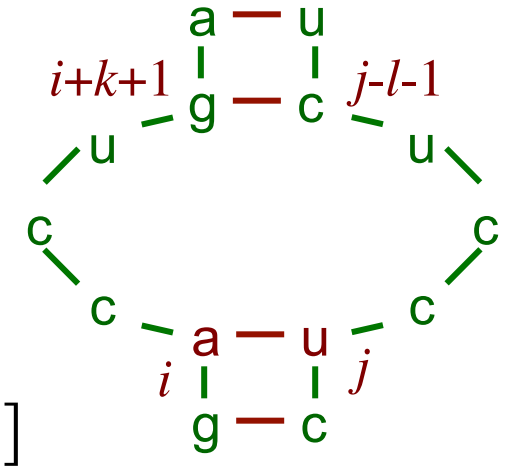
$$P(i,j) = \min \begin{cases} \alpha(i,j) + \text{LoopEnergy}(j-i-1) \\ \alpha(i,\ j) + \text{StackingEnergy}(i, j,\ i+1,\ j-1) + P(i+1,\ j-1) \\ \min\limits_{k \geq 1} \left[\alpha(i,\ j) + \text{BulgeEnergy}(k)\ +\ P(i+k+1,\ j-1) \right] \\ \min\limits_{k \geq 1} \left[\alpha(i,\ j) + \text{BulgeEnergy}(k)\ +\ P(i+1,\ j-k-1) \right] \\ \min\limits_{k,l\ \geq 1} \left[\alpha(i,\ j) + \text{LoopEnergy}(k+l)\ +\ P(i+k+1,\ j-l-1) \right] \\ \min\limits_{j>k>i} \left[\alpha(i,\ j) +\ E(i+1,\ k) + E(k+1, j-1) \right] \end{cases}$$

Predicting RNA Secondary Structure by Energy Minimization

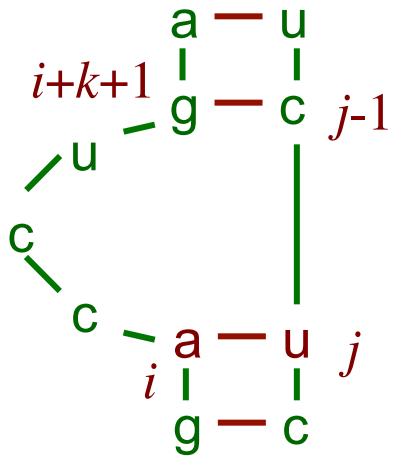
$$\alpha(i,j) + \text{LoopEnergy}(j-i-1)$$



$$\min_{k,l \geq 1}\left[\alpha(i,j) + \text{LoopEnergy}(k+l) \; + \; P(i+k+1,\, j-l-1)\right]$$



$$\min_{k \geq 1}\left[\alpha(i,j) + \text{BulgeEnergy}(k) \; + \; P(i+k+1,\, j-1)\right]$$



$$\alpha(i,j) + \text{StackingEnergy}(i,j,\, i+1,\, j-1) + P(i+1,\, j-1)$$