

CS 466

Introduction to Bioinformatics

Lecture 13

Mohammed El-Kebir

November 3, 2021



Outline

- RNA secondary structure

Reading:

- Topics are not in Jones and Pevzner book but in lecture notes and slides
[Based on Chapter 10 in “Biological sequence analysis” by Durbin et al.]

Central Dogma of Molecular Biology

Three fundamental molecules:

1. DNA

Information storage.

2. RNA

Old view: Mostly a “messenger”.

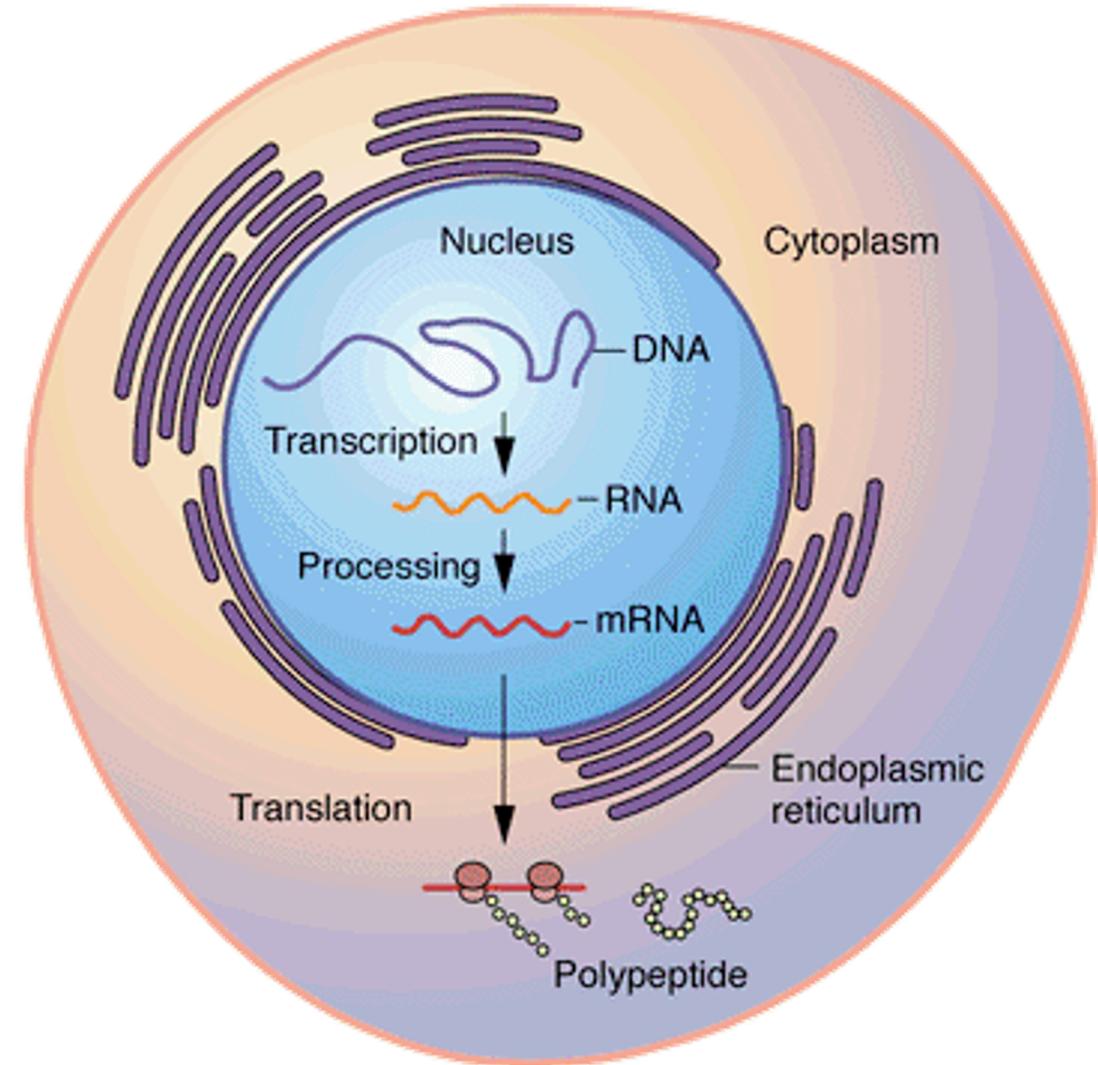
New view: Performs many important functions, through **3-D structure!**

3. Protein

Perform most cellular functions (biochemistry, signaling, control, etc.)

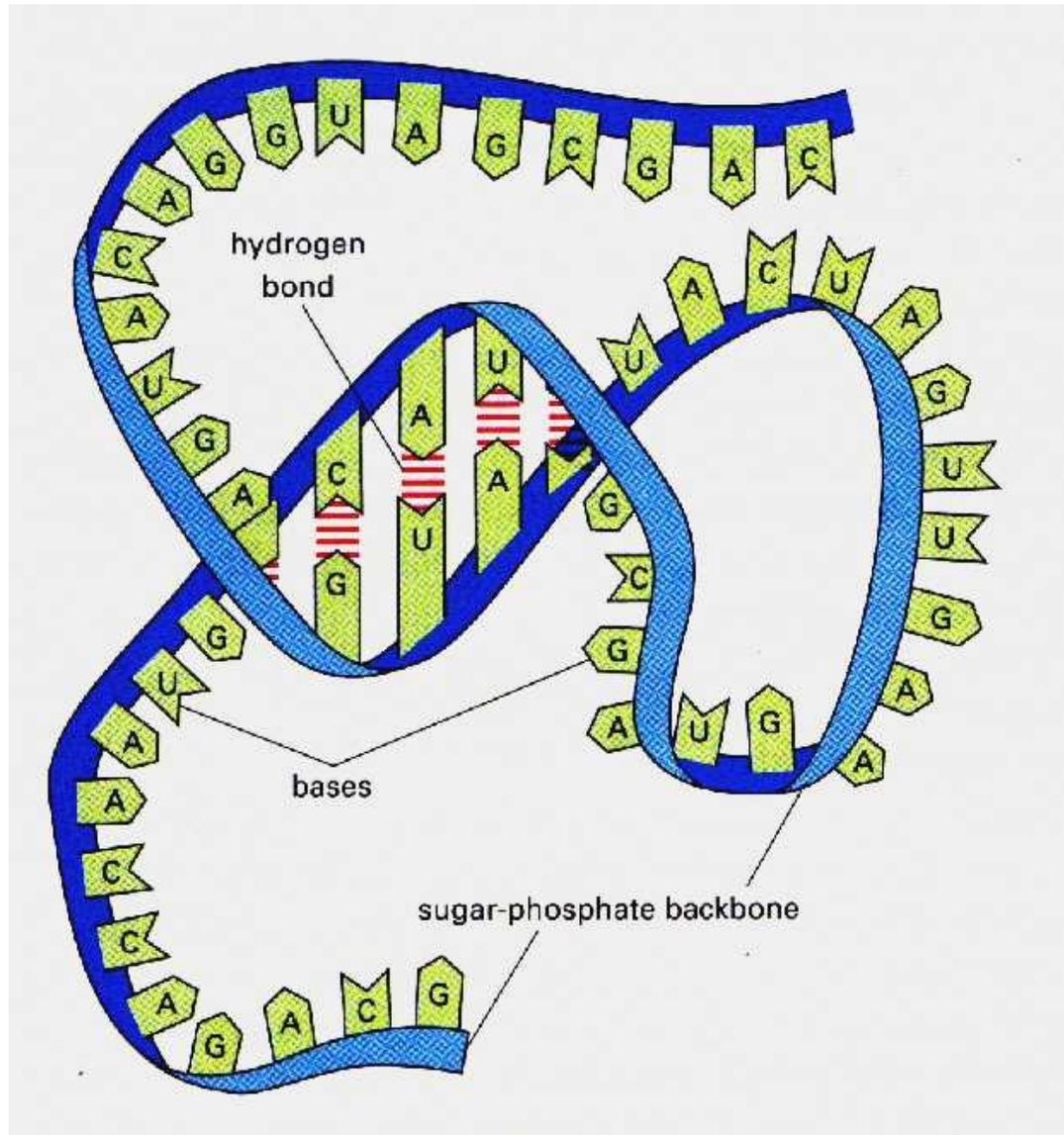
DNA → RNA → Protein

First proposed by Francis Crick in 1956.



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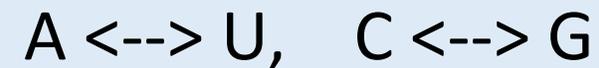
RNA



- **Single-stranded**

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

- Can fold into **structures** due to nucleotide complementarity.



- Comes in many flavors:

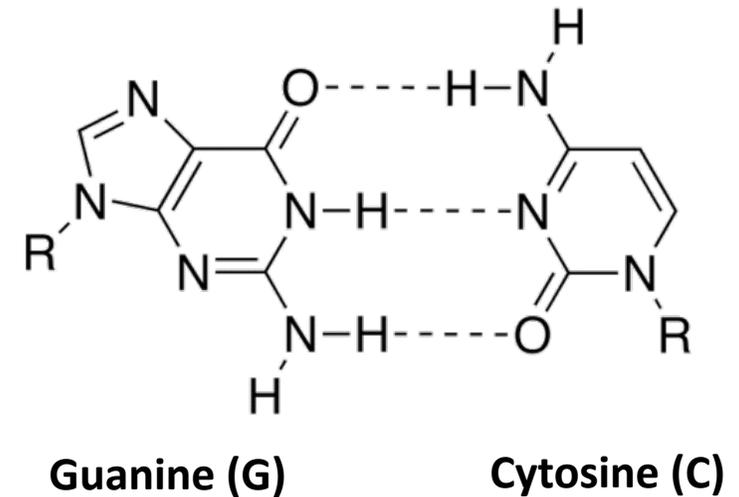
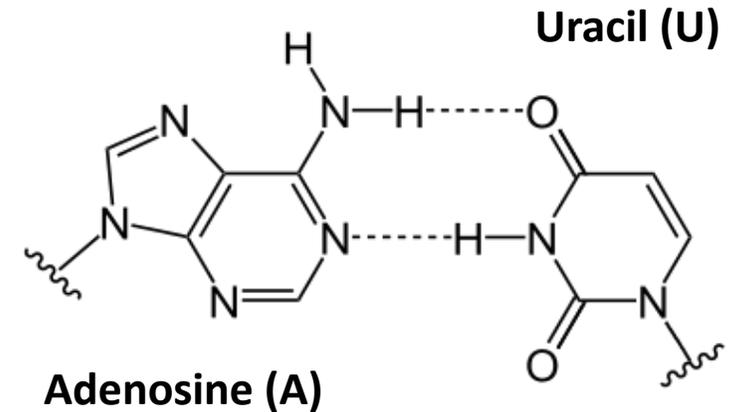
mRNA, rRNA, tRNA, tmRNA, snRNA,
snoRNA, scaRNA, aRNA, asRNA,
piwiRNA, etc.

RNA – Nucleotide Complementarity

RNA can fold into structures due to nucleotide complementarity:
 $A \leftrightarrow U$ and $G \leftrightarrow C$

$A \leftrightarrow U$ (2 hydrogen bonds)
is slightly weaker than
 $G \leftrightarrow C$ (3 hydrogen bonds)

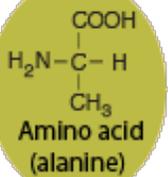
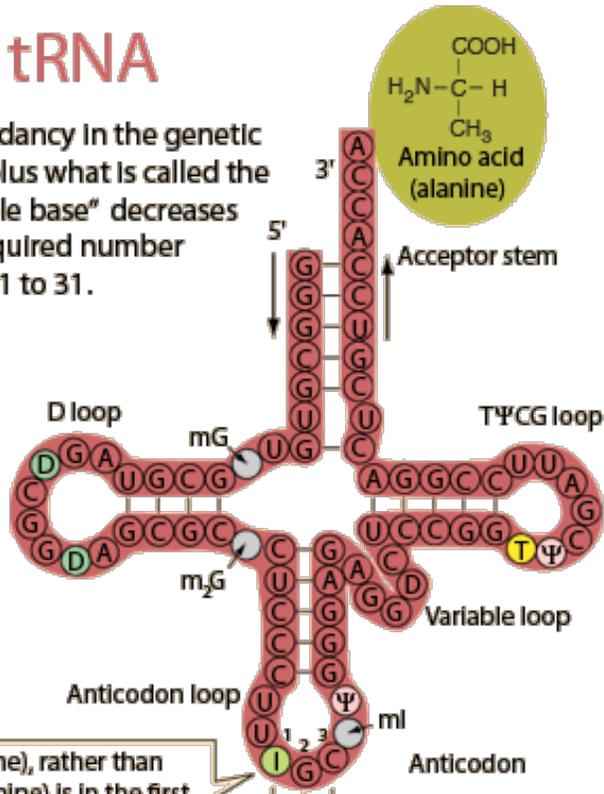
$G \leftrightarrow U$ also observed but not as stable



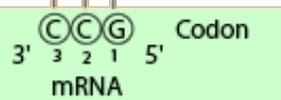
transfer RNA (tRNA) Secondary Structure

tRNA

Redundancy in the genetic code plus what is called the "wobble base" decreases the required number from 61 to 31.



I (Inosine), rather than G (guanine) is in the first position of the anticodon. It can bind to any of the four bases in the third position of the codon.



The code for alanine is redundant, with four codons coding for the same amino acid.

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

There are 64 codons in the genetic code, 61 of which code for an amino acid.

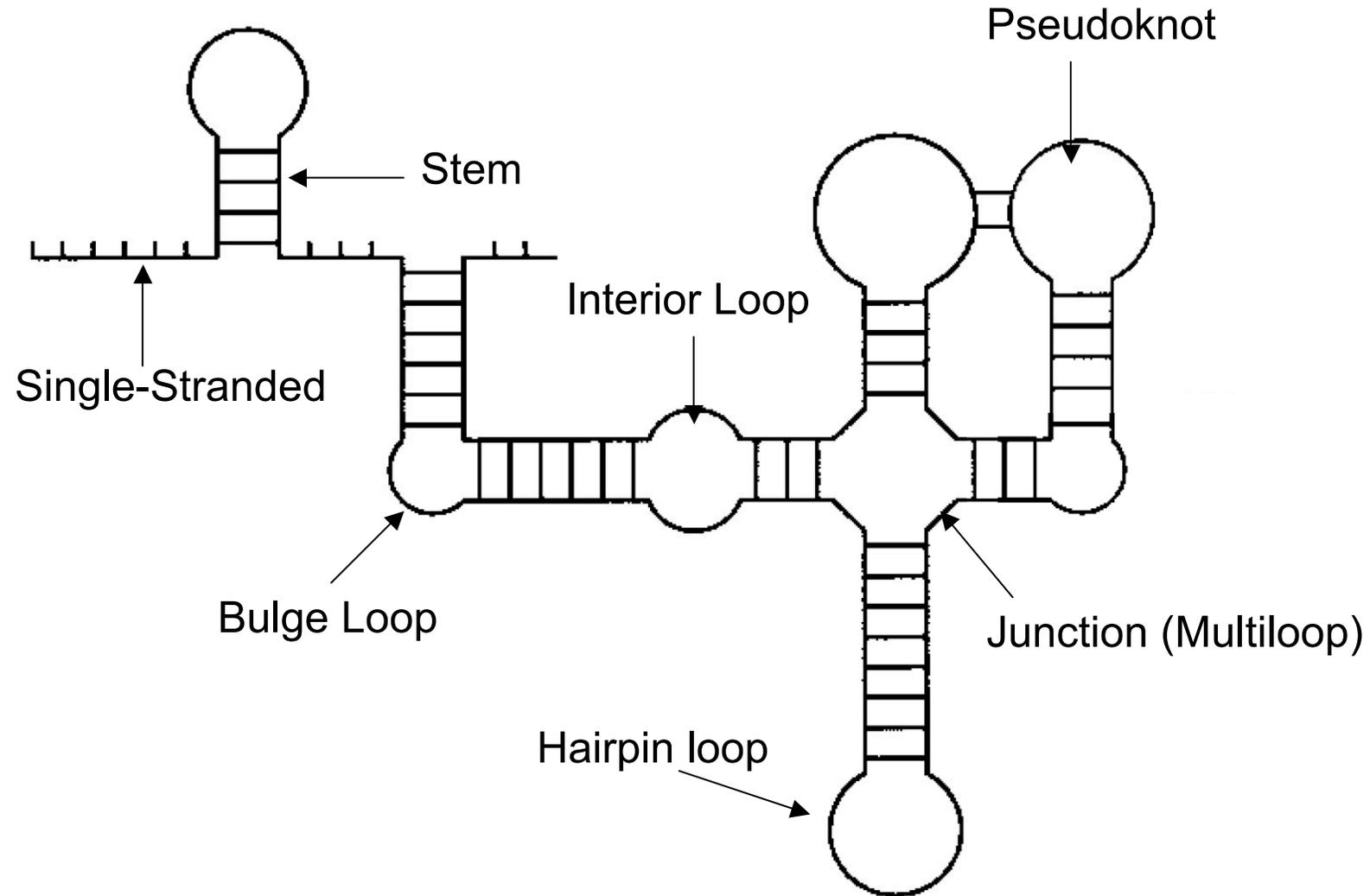
		Second base				
		U	C	A	G	
First base	U	UUU } Phenyl-alanine F UUC } UUA } Leucine L UUG }	UCU } Serine S UCC } UCA } UCG }	UAU } Tyrosine Y UAC } UAA } Stop codon UAG } Stop codon	UGU } Cysteine C UGC } UGA } Stop codon UGG } Tryptophan W	U C A G
	C	CUU } Leucine L CUC } CUA } CUG }	CCU } Proline P CCC } CCA } CCG }	CAU } Histidine H CAC } CAA } Glutamine Q CAG }	CGU } Arginine R CGC } CGA } CGG }	U C A G
	A	AUU } Isoleucine I AUC } AUA } AUG } Methionine start codon M	ACU } Threonine T ACC } ACA } ACG }	AAU } Asparagine N AAC } AAA } Lysine K AAG }	AGU } Serine S AGC } AGA } Arginine R AGG }	U C A G
	G	GUU } Valine V GUC } GUA } GUG }	GCU } Alanine A GCC } GCA } GCG }	GAU } Aspartic acid D GAC } GAA } Glutamic acid E GAG }	GGU } Glycine G GGC } GGA } GGG }	U C A G

<http://bioinfo.bisr.res.in/project/crat/pictures/codon.jpg>

RNA Secondary Structure Elements

Each base/nucleotide participates in at most one pairing

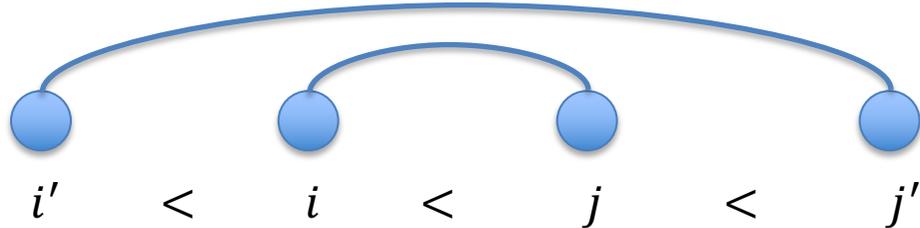
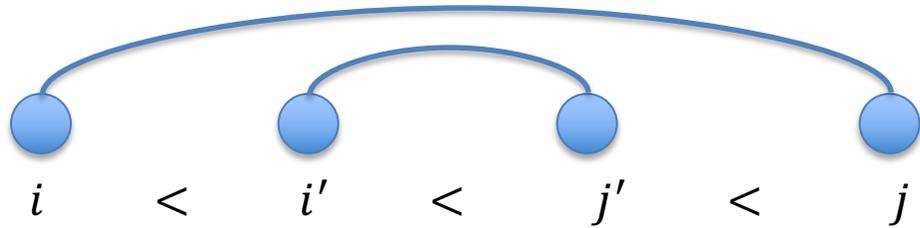
Secondary structure is determined by a set of non-overlapping base/nucleotide pairs



Nesting and Pseudoknot

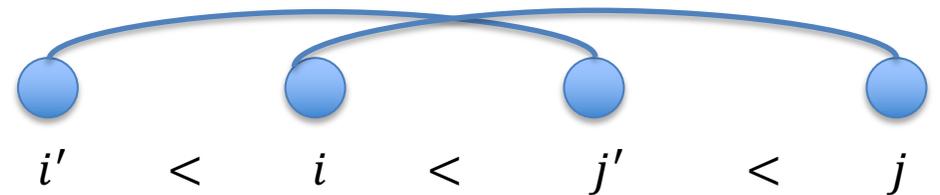
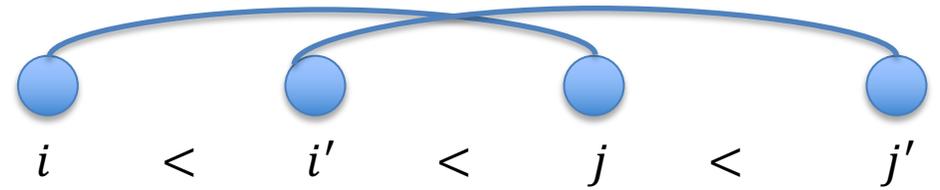
Base pairs (i, j) and (i', j') are **nested**
provided

$$i < i' < j' < j \quad \text{or} \quad i' < i < j < j'$$



Base pairs (i, j) and (i', j') form a
pseudoknot provided

$$i < i' < j < j' \quad \text{or} \quad i' < i < j' < j$$

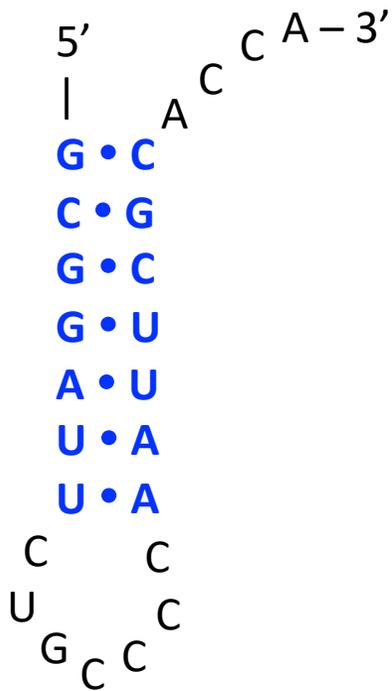


Most RNA molecules consist of nested base pairs

Nesting and Pseudoknot – Examples

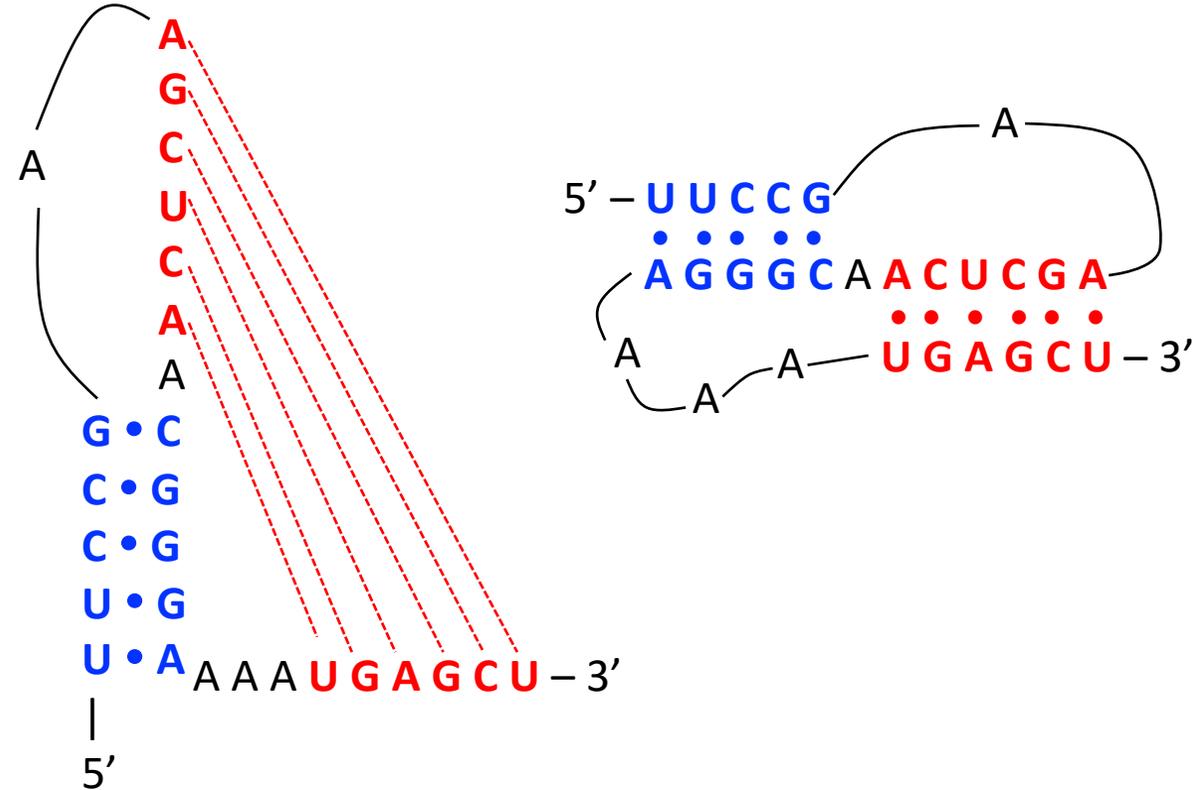
Nesting

5' – GCGGAUUCUGCCCCAA UUCGCACCA – 3'



Pseudoknot

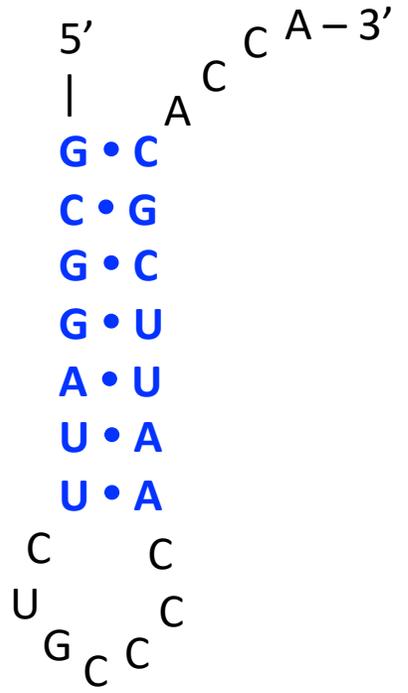
5' – UUCCGAAGCUC AACGGGAAAUGAGCU – 3'



Nesting and Pseudoknot – Examples

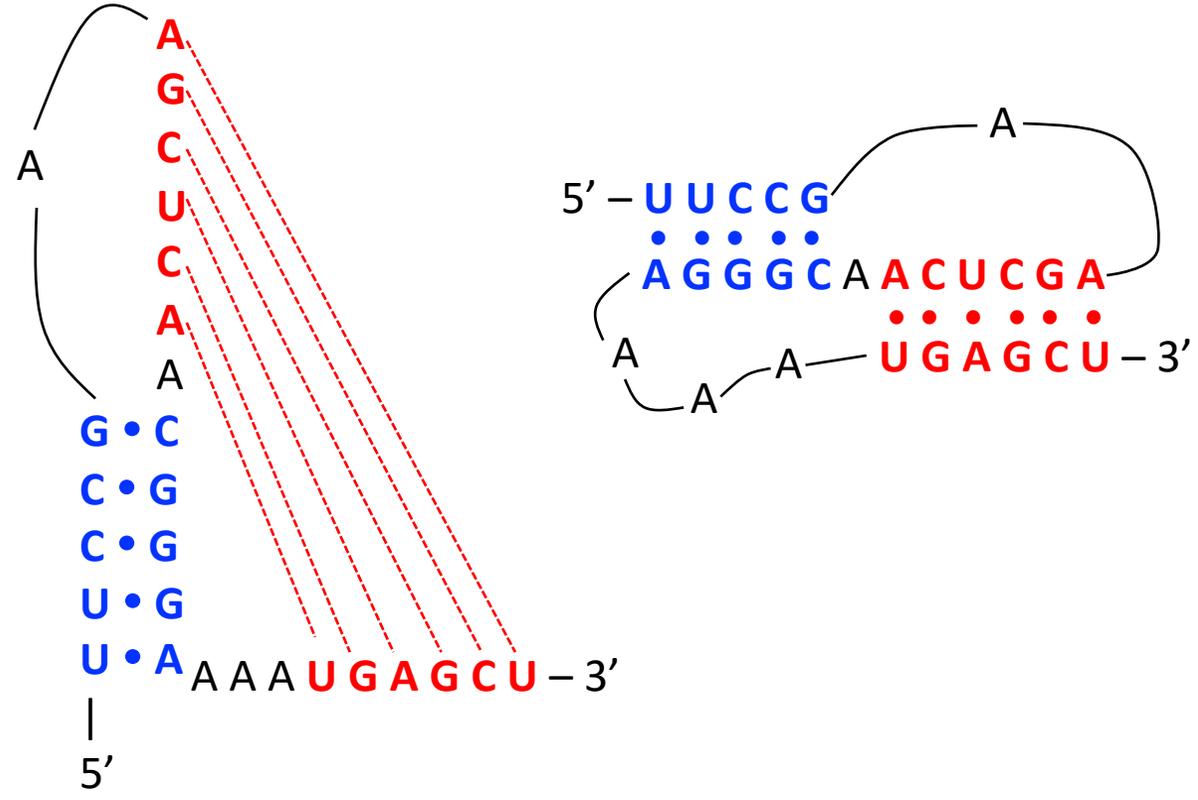
Nesting

5' – GCGGAUUCUGCCCCAAUUCGCACCA – 3'
 (((((((- - - - -)))))) - - - -



Pseudoknot

5' – UUCCGAAGCUCAACGGGAAAUGAGCU – 3'
 (((((- (((((-))))) - - -)))))



Nussinov Algorithm

RNA can fold into structures due to nucleotide complementarity:



Secondary structure is determined by a set of non-overlapping complimentary base pairs

Nussinov Algorithm

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$A \leftrightarrow U$ and $G \leftrightarrow C$

Secondary structure is determined by a set of non-overlapping complementary base pairs

Question: How to find maximum number of such pairs?

5' – G C G G A U U C U G C C C C A A U U C G C A C C A – 3'

Nussinov Algorithm

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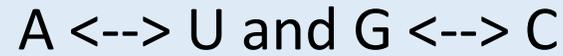
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Question: How to find maximum number of such pairs?

Need to constrain space of feasible solutions!

Nussinov Algorithm

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ALGORITHMS FOR LOOP MATCHINGS*

RUTH NUSSINOV,[†] GEORGE PIECZENIK,[‡] JERROLD R. GRIGGS[¶]
AND DANIEL J. KLEITMAN[§]

Problem: Given RNA sequence $\mathbf{v} \in \{A, U, C, G\}^n$, find a *pseudoknot-free secondary structure* with the maximum number of complementary base pairings

Nussinov Algorithm – Dynamic Programming

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5' – G C G G A U U C U G C C C C A A U U C G C A C C A – 3'

Nussinov Algorithm – Dynamic Programming

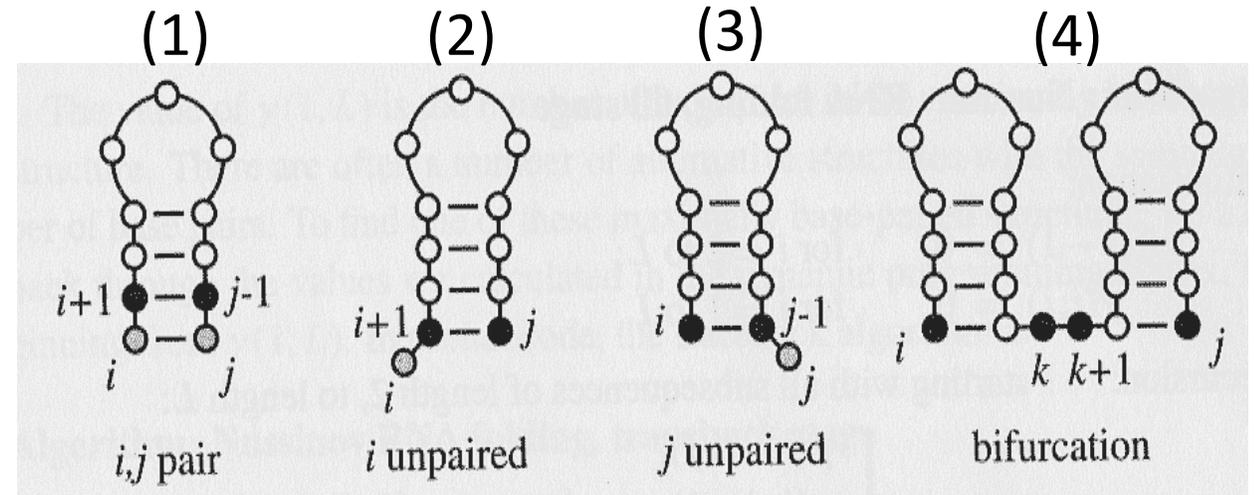
Problem: Given RNA sequence $\mathbf{v} \in \{A, U, C, G\}^n$, find a *pseudoknot-free secondary structure* with the maximum number of complementary base pairings

Let $s[i, j]$ denote the maximum number of pseudoknot-free complementary base pairings in subsequence v_i, \dots, v_j

Nussinov Algorithm – Dynamic Programming

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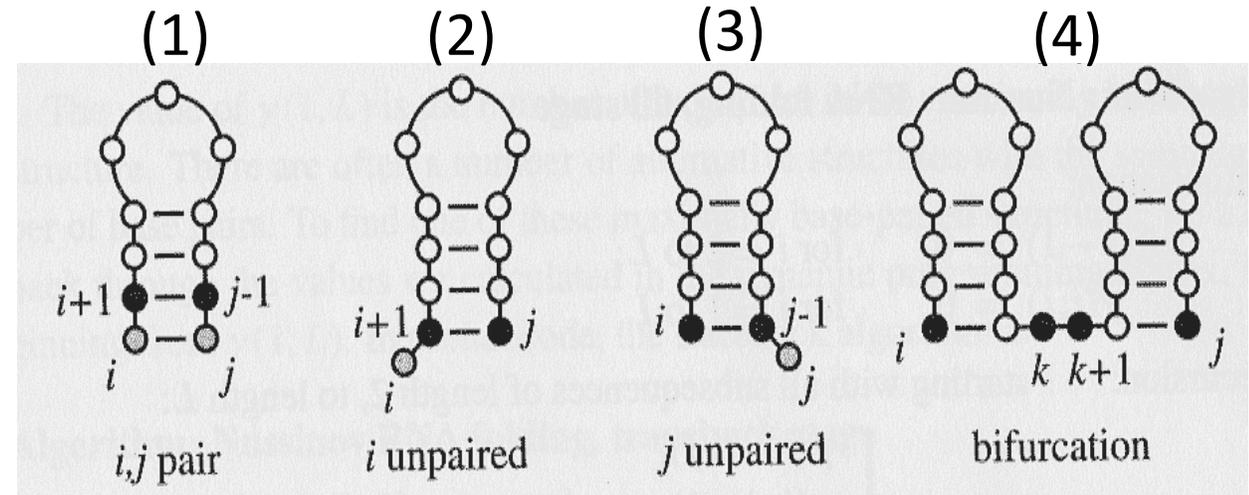
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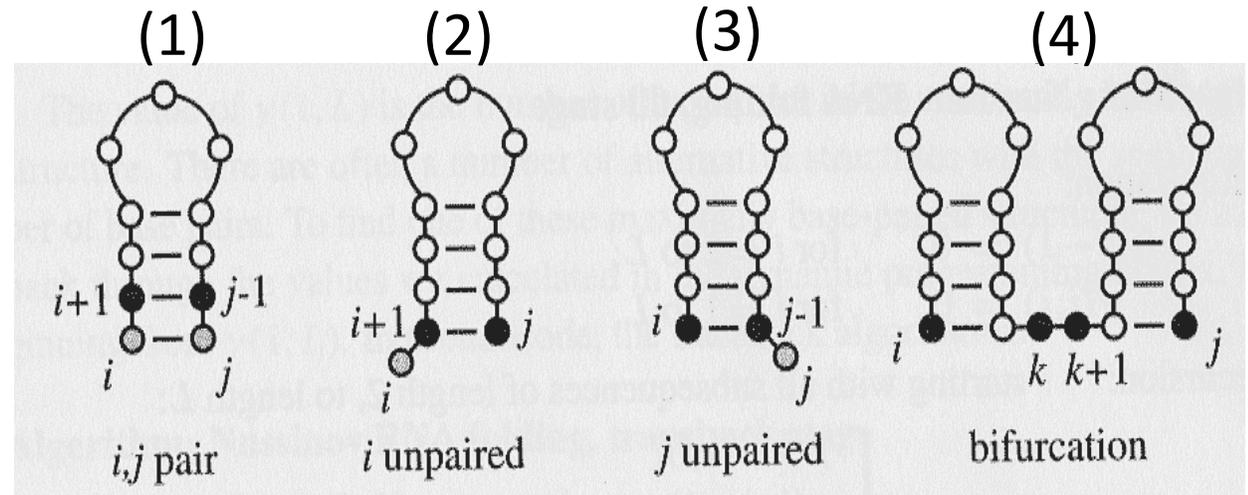


$$s[i, j] = \max \begin{cases} 0, & \text{if } i \geq j, \\ s[i + 1, j - 1] + 1, & \text{if } i < j \text{ and } (v_i, v_j) \in \Gamma, \text{ (1)} \\ s[i + 1, j - 1], & \text{if } i < j \text{ and } (v_i, v_j) \notin \Gamma, \text{ (1*)} \\ s[i + 1, j], & \text{if } i < j, \text{ (2)} \\ s[i, j - 1], & \text{if } i < j, \text{ (3)} \\ \max_{i < k < j} \{s[i, k] + s[k + 1, j]\}, & \text{if } i < j, \text{ (4)} \end{cases}$$

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Question:
Which case is redundant?

Develop Intuition

$$s[i, j] = \max \begin{cases} 0, & \text{if } i \geq j, \\ s[i + 1, j - 1] + 1, & \text{if } i < j \text{ and } (v_i, v_j) \in \Gamma, \\ s[i + 1, j - 1], & \text{if } i < j \text{ and } (v_i, v_j) \notin \Gamma, \\ s[i + 1, j], & \text{if } i < j, \\ s[i, j - 1], & \text{if } i < j, \\ \max_{i < k < j} \{s[i, k] + s[k + 1, j]\}, & \text{if } i < j, \end{cases}$$

	(((((-	-	-	-	-	-	-	-	-	-)	-	-))))				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23			
	G	C	U	C	G	G	G	U	U	C	C	C	U	A	U	U	C	A	A	G	A	G	C			
0																								G	1	
0	0																								C	2
0	0	0																							U	3
0	0	0	0																						C	4
0	0	0	0	0																					G	5
0	0	0	0	0	0																				G	6
0	0	0	0	0	0	0																			G	7
0	0	0	0	0	0	0	0																		U	8
0	0	0	0	0	0	0	0	0																	U	9
0	0	0	0	0	0	0	0	0	0																C	10
0	0	0	0	0	0	0	0	0	0	0															C	11
0	0	0	0	0	0	0	0	0	0	0	0														C	12
0	0	0	0	0	0	0	0	0	0	0	0	0													U	13
0	0	0	0	0	0	0	0	0	0	0	0	0	0												A	14
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0											U	15
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0										U	16
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0								C	17
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0							A	18
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0						A	19
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0					G	20
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				A	21
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			G	22
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		C	23

Develop Intuition

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	((((((-	-	-))	-	(-)	-	-)))					
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23		
	G	C	U	C	G	G	G	U	U	C	C	C	U	A	U	U	C	A	A	G	A	G	C		
0																							G	1	
0	0																							C	2
0	0	0																						U	3
0	0	0	0																					C	4
0	0	0	0	0																				G	5
0	0	0	0	0	0																			G	6
0	0	0	0	0	0	0																		G	7
0	0	0	0	0	0	0	0																	U	8
0	0	0	0	0	0	0	0	0																U	9
0	0	0	0	0	0	0	0	0	0															C	10
0	0	0	0	0	0	0	0	0	0	0														C	11
0	0	0	0	0	0	0	0	0	0	0	0													C	12
0	0	0	0	0	0	0	0	0	0	0	0	0												U	13
0	0	0	0	0	0	0	0	0	0	0	0	0	0											A	14
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0										U	15
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0									U	16
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0								C	17
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0							A	18
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0						A	19
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0					G	20
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				A	21
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			G	22
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		C	23

Nussinov Algorithm – Traceback Step

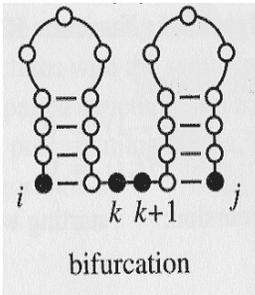
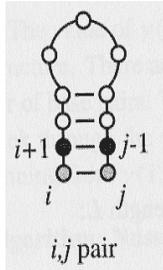
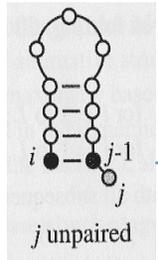
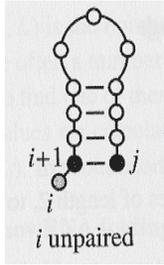
Push $(1, n)$ onto stack
 Repeat until stack is empty:

pop (i, j)
 if $i \geq j$ continue
 else if $s[i+1, j] = s[i, j]$
 push $(i+1, j)$
 else if $s[i, j-1] = S[i, j]$
 push $(i, j-1)$
 else if $s[i+1, j-1] + 1 = s[i, j]$
 record (i, j) base pair
 push $(i+1, j-1)$
 else for $k = i+1$ to $j-1$
 if $s[i, k] + s[k+1, j] = s[i, j]$
 push $(k+1, j)$
 push (i, k)
 break (for loop)

Question: Will this return one alignment? Or all alignments?

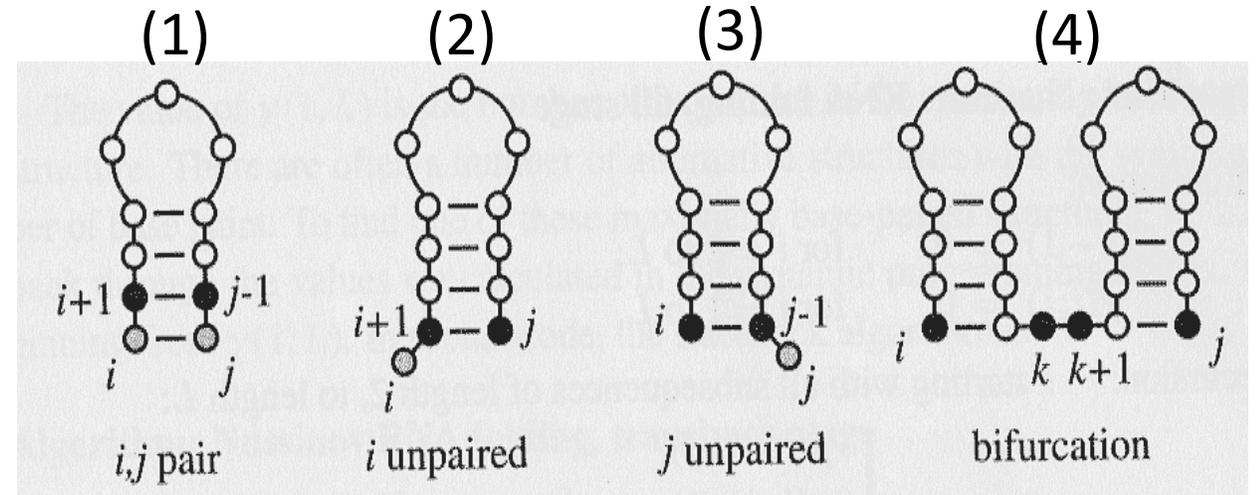
Question: Can we do this recursively?

We only need to know matches.



Nussinov Algorithm – Example

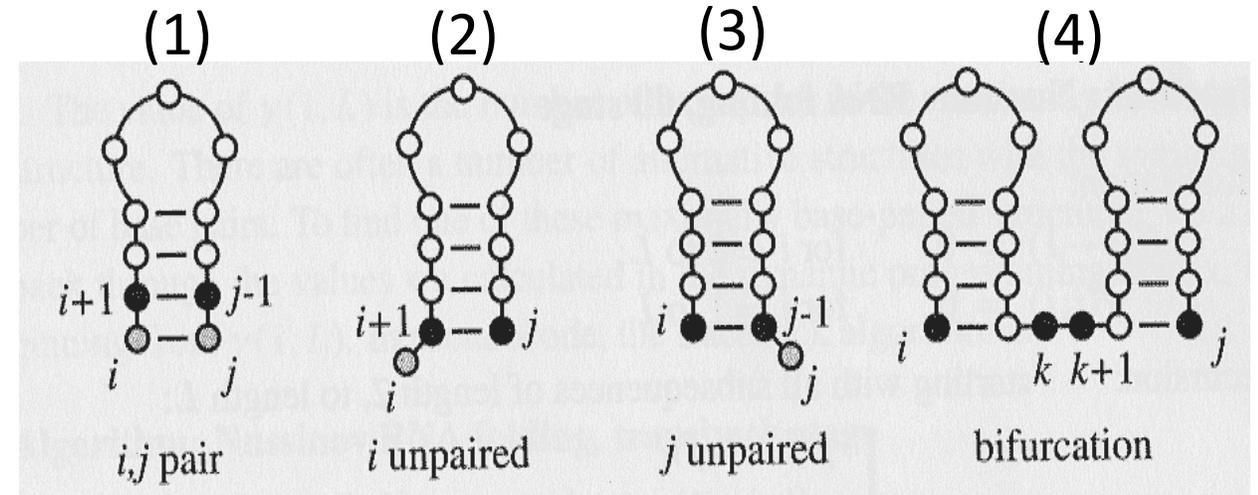
	G	G	G	A	A	A	U	C	C
G	0								
G	0	0							
G	0	0	0						
A	0	0	0	0					
A	0	0	0	0	0				
A	0	0	0	0	0	0			
U	0	0	0	0	0	0	0		
C	0	0	0	0	0	0	0	0	
C	0	0	0	0	0	0	0	0	0



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Nussinov Algorithm – Example

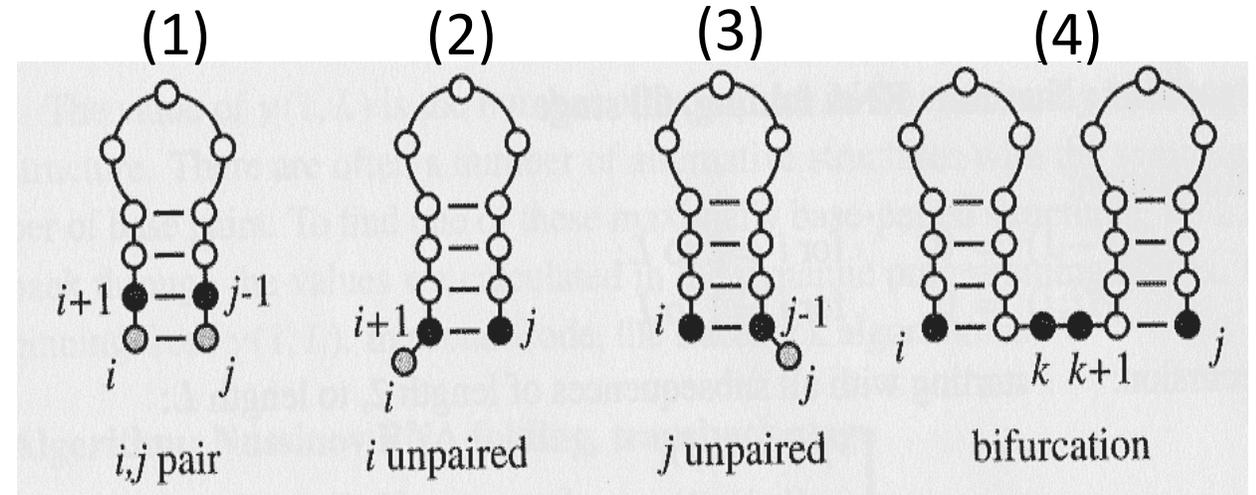
	G	G	G	A	A	A	U	C	C
G	0	0							
G	0	0	0						
G	0	0	0	0					
A	0	0	0	0	0				
A	0	0	0	0	0	0			
A	0	0	0	0	0	0	1		
U	0	0	0	0	0	0	0	0	
C	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0



$$s[i, j] = \max \begin{cases} 0, & \text{if } i \geq j, \\ s[i + 1, j - 1] + 1, & \text{if } i < j \text{ and } (v_i, v_j) \in \Gamma, \text{ (1)} \\ s[i + 1, j - 1], & \text{if } i < j \text{ and } (v_i, v_j) \notin \Gamma, \text{ (1*)} \\ s[i + 1, j], & \text{if } i < j, \text{ (2)} \\ s[i, j - 1], & \text{if } i < j, \text{ (3)} \\ \max_{i < k < j} \{s[i, k] + s[k + 1, j]\}, & \text{if } i < j, \text{ (4)} \end{cases}$$

Nussinov Algorithm – Example

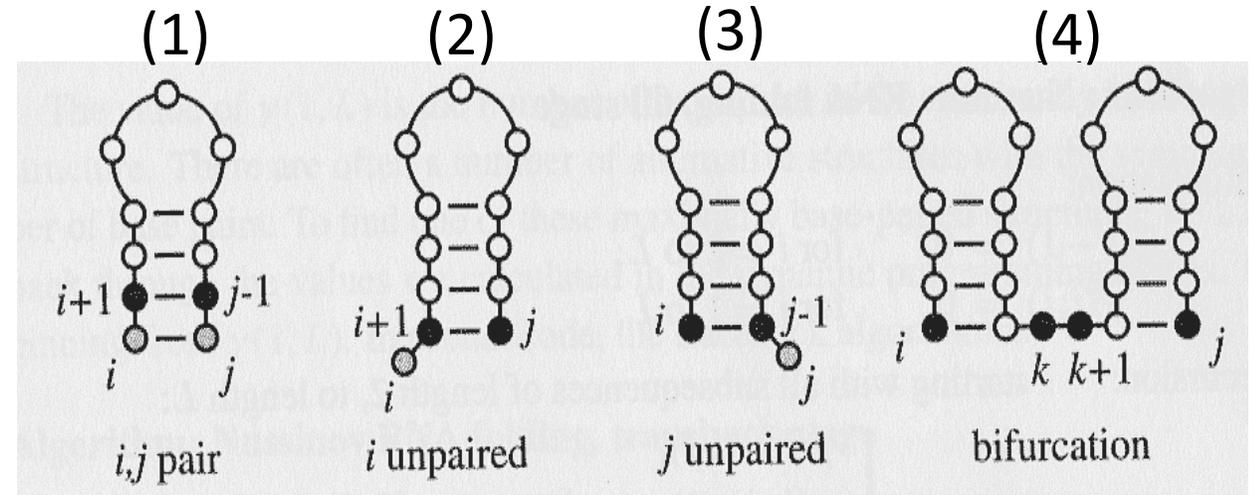
	G	G	G	A	A	A	U	C	C
G	0	0	0						
G	0	0	0	0					
G	0	0	0	0	0				
A	0	0	0	0	0	0			
A	0	0	0	0	0	0	1		
A	0	0	0	0	0	0	1	1	
U	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0



$$s[i, j] = \max \begin{cases} 0, & \text{if } i \geq j, \\ s[i + 1, j - 1] + 1, & \text{if } i < j \text{ and } (v_i, v_j) \in \Gamma, \text{ (1)} \\ s[i + 1, j - 1], & \text{if } i < j \text{ and } (v_i, v_j) \notin \Gamma, \text{ (1*)} \\ s[i + 1, j], & \text{if } i < j, \text{ (2)} \\ s[i, j - 1], & \text{if } i < j, \text{ (3)} \\ \max_{i < k < j} \{s[i, k] + s[k + 1, j]\}, & \text{if } i < j, \text{ (4)} \end{cases}$$

Nussinov Algorithm – Example

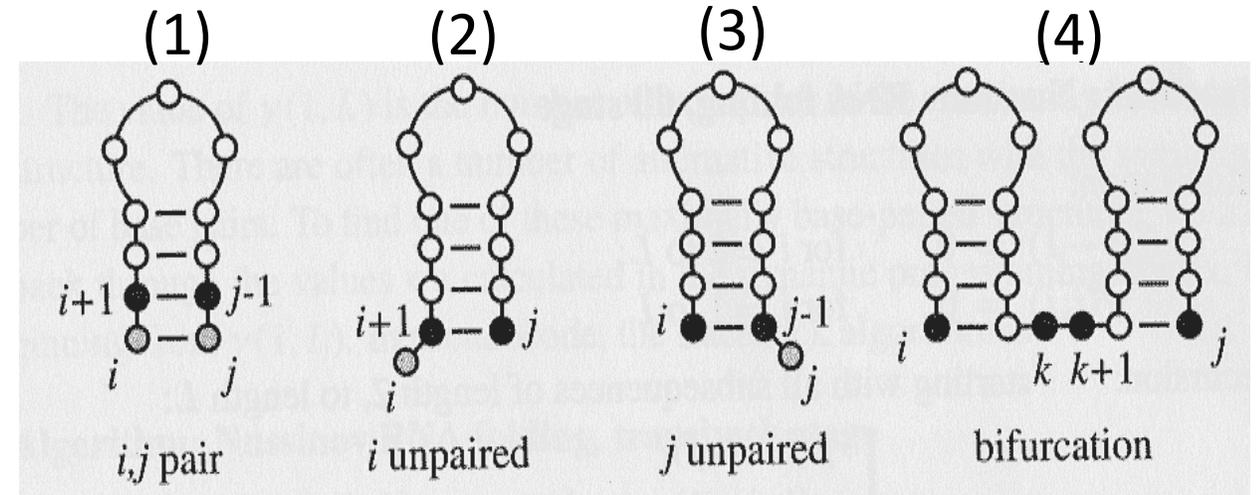
	G	G	G	A	A	A	U	C	C
G	0	0	0	0					
G	0	0	0	0	0				
G	0	0	0	0	0	0			
A	0	0	0	0	0	0	1		
A	0	0	0	0	0	0	1	1	
A	0	0	0	0	0	0	1	1	1
U	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0



$$s[i, j] = \max \begin{cases} 0, & \text{if } i \geq j, \\ s[i + 1, j - 1] + 1, & \text{if } i < j \text{ and } (v_i, v_j) \in \Gamma, \text{ (1)} \\ s[i + 1, j - 1], & \text{if } i < j \text{ and } (v_i, v_j) \notin \Gamma, \text{ (1*)} \\ s[i + 1, j], & \text{if } i < j, \text{ (2)} \\ s[i, j - 1], & \text{if } i < j, \text{ (3)} \\ \max_{i < k < j} \{s[i, k] + s[k + 1, j]\}, & \text{if } i < j, \text{ (4)} \end{cases}$$

Nussinov Algorithm – Example

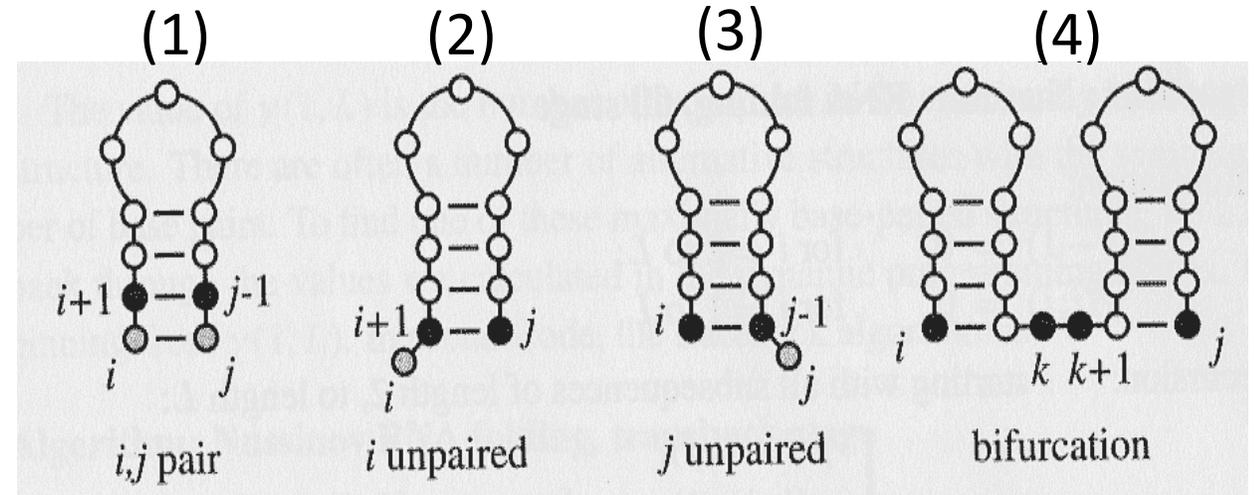
	G	G	G	A	A	A	U	C	C
G	0	0	0	0	0	0	1	2	3
G	0	0	0	0	0	0	1	2	3
G	0	0	0	0	0	0	1	2	2
A	0	0	0	0	0	0	1	1	1
A	0	0	0	0	0	0	1	1	1
A	0	0	0	0	0	0	1	1	1
U	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0



$$s[i, j] = \max \begin{cases} 0, & \text{if } i \geq j, \\ s[i + 1, j - 1] + 1, & \text{if } i < j \text{ and } (v_i, v_j) \in \Gamma, \text{ (1)} \\ s[i + 1, j - 1], & \text{if } i < j \text{ and } (v_i, v_j) \notin \Gamma, \text{ (1*)} \\ s[i + 1, j], & \text{if } i < j, \text{ (2)} \\ s[i, j - 1], & \text{if } i < j, \text{ (3)} \\ \max_{i < k < j} \{s[i, k] + s[k + 1, j]\}, & \text{if } i < j, \text{ (4)} \end{cases}$$

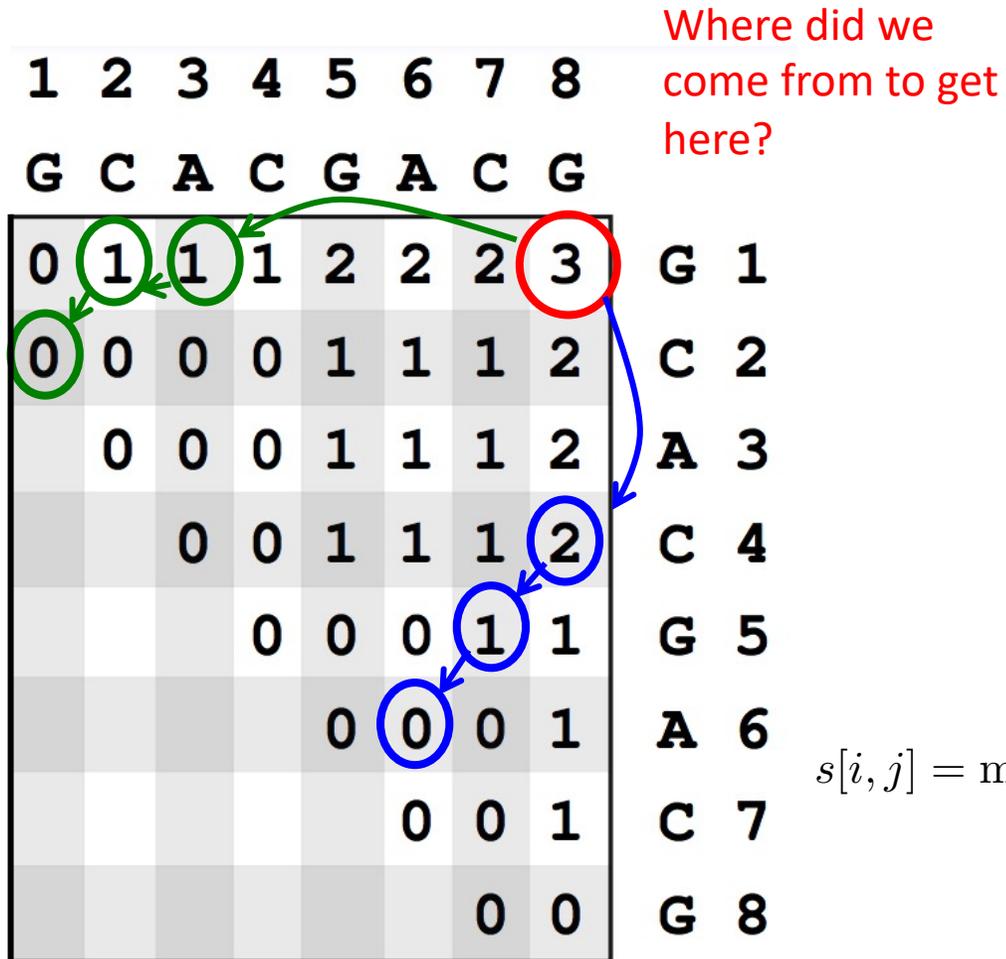
Nussinov Algorithm – Example

	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	0	1	2	2
A	0	0	0	0	0	0	1	1	1
A	0	0	0	0	0	0	1	1	1
A	0	0	0	0	0	0	1	1	1
U	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0

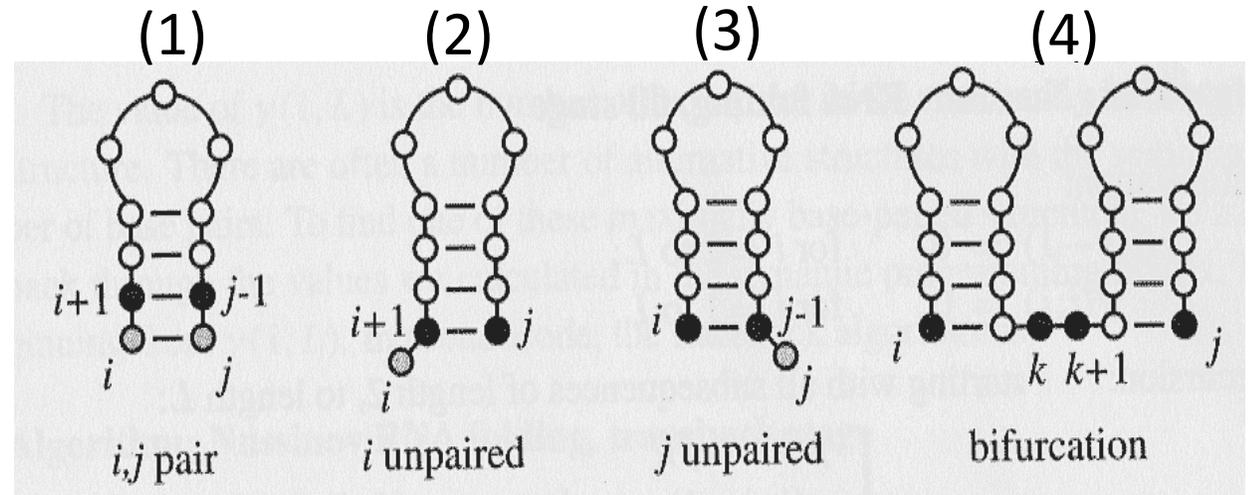


$$s[i, j] = \max \begin{cases} 0, & \text{if } i \geq j, \\ s[i + 1, j - 1] + 1, & \text{if } i < j \text{ and } (v_i, v_j) \in \Gamma, \text{ (1)} \\ s[i + 1, j - 1], & \text{if } i < j \text{ and } (v_i, v_j) \notin \Gamma, \text{ (1*)} \\ s[i + 1, j], & \text{if } i < j, \text{ (2)} \\ s[i, j - 1], & \text{if } i < j, \text{ (3)} \\ \max_{i < k < j} \{s[i, k] + s[k + 1, j]\}, & \text{if } i < j, \text{ (4)} \end{cases}$$

Nussinov Algorithm – Example With Bifurcation



GCACGACG
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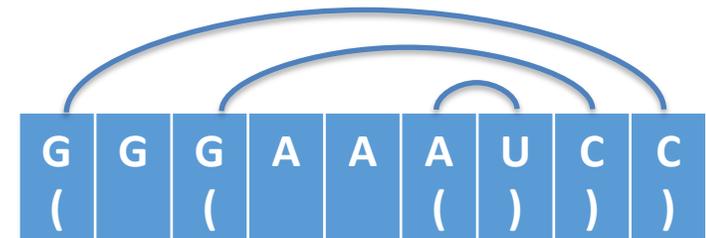
$$s[i, j] = \max \begin{cases} 0, & \text{if } i \geq j, \\ s[i + 1, j - 1] + 1, & \text{if } i < j \text{ and } (v_i, v_j) \in \Gamma, \text{ (1)} \\ s[i + 1, j - 1], & \text{if } i < j \text{ and } (v_i, v_j) \notin \Gamma, \text{ (1*)} \\ s[i + 1, j], & \text{if } i < j, \text{ (2)} \\ s[i, j - 1], & \text{if } i < j, \text{ (3)} \\ \max_{i < k < j} \{s[i, k] + s[k + 1, j]\}, & \text{if } i < j, \text{ (4)} \end{cases}$$

Nussinov Algorithm – Alternative Solutions

	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	0	1	2	2
A	0	0	0	0	0	0	1	1	1
A	0	0	0	0	0	0	1	1	1
A	0	0	0	0	0	0	1	1	1
U	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0

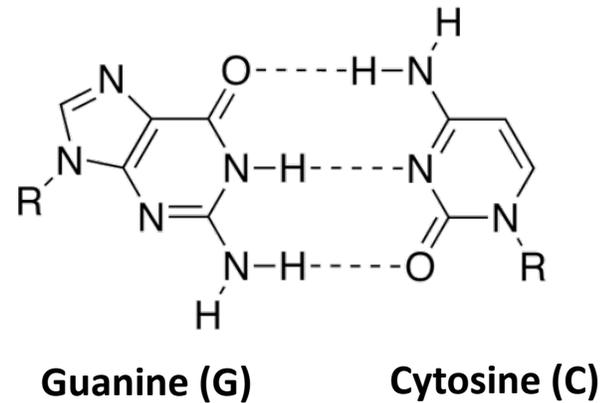
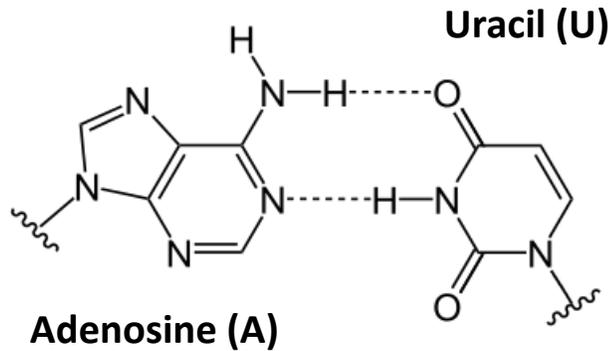
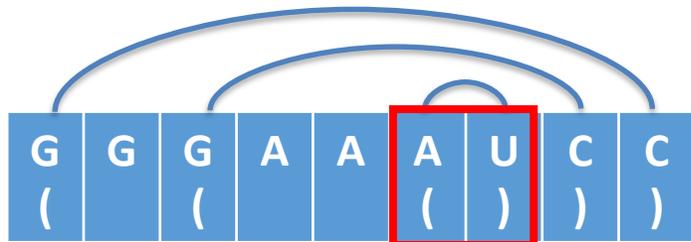
	G	G	G	A	A	A	U	C	C
G	0	0	0	0	0	0	1	2	3
G	0	0	0	0	0	0	1	2	3
G	0	0	0	0	0	0	1	2	2
A	0	0	0	0	0	0	1	1	1
A	0	0	0	0	0	0	1	1	1
A	0	0	0	0	0	0	1	1	1
U	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0

	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	0	1	2	2
A	0	0	0	0	0	0	1	1	1
A	0	0	0	0	0	0	1	1	1
A	0	0	0	0	0	0	1	1	1
U	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0



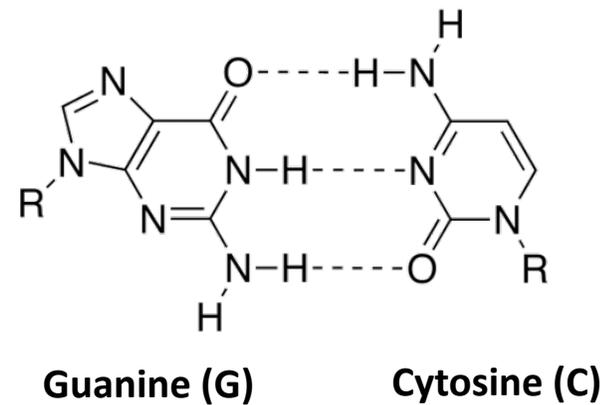
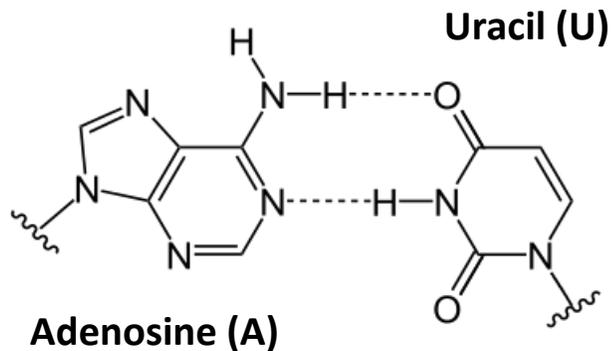
Does this make sense?

	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	0	1	2	2
A	0	0	0	0	0	0	1	1	1
A	0	0	0	0	0	0	1	1	1
A	0	0	0	0	0	0	1	1	1
U	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0

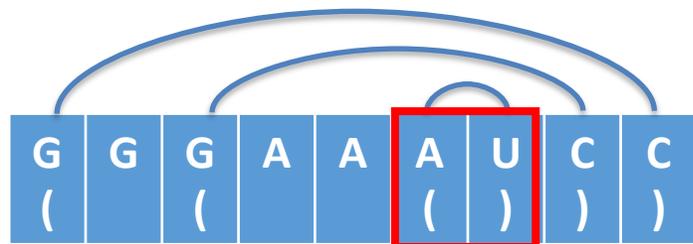


Does this make sense?

	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	0	1	2	2
A	0	0	0	0	0	0	1	1	1
A	0	0	0	0	0	0	1	1	1
A	0	0	0	0	0	0	1	1	1
U	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0

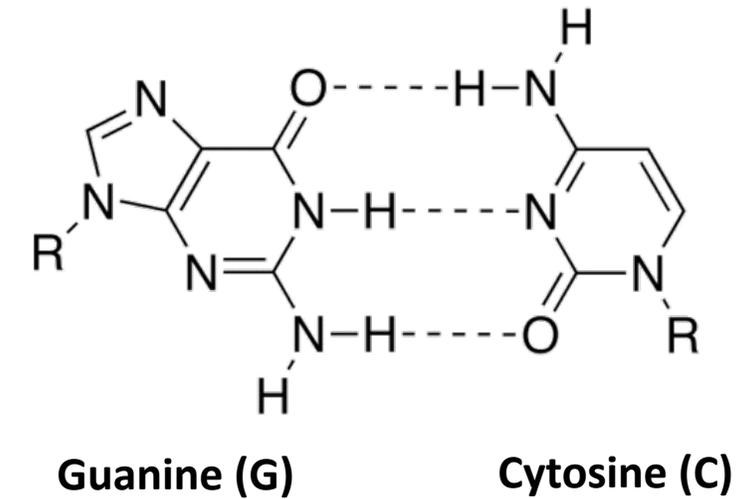
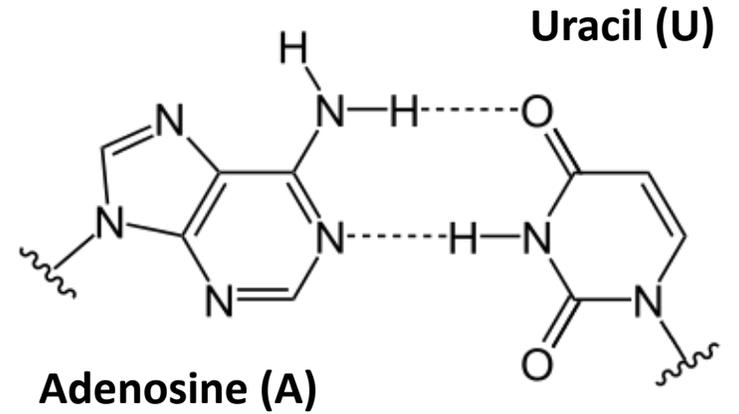
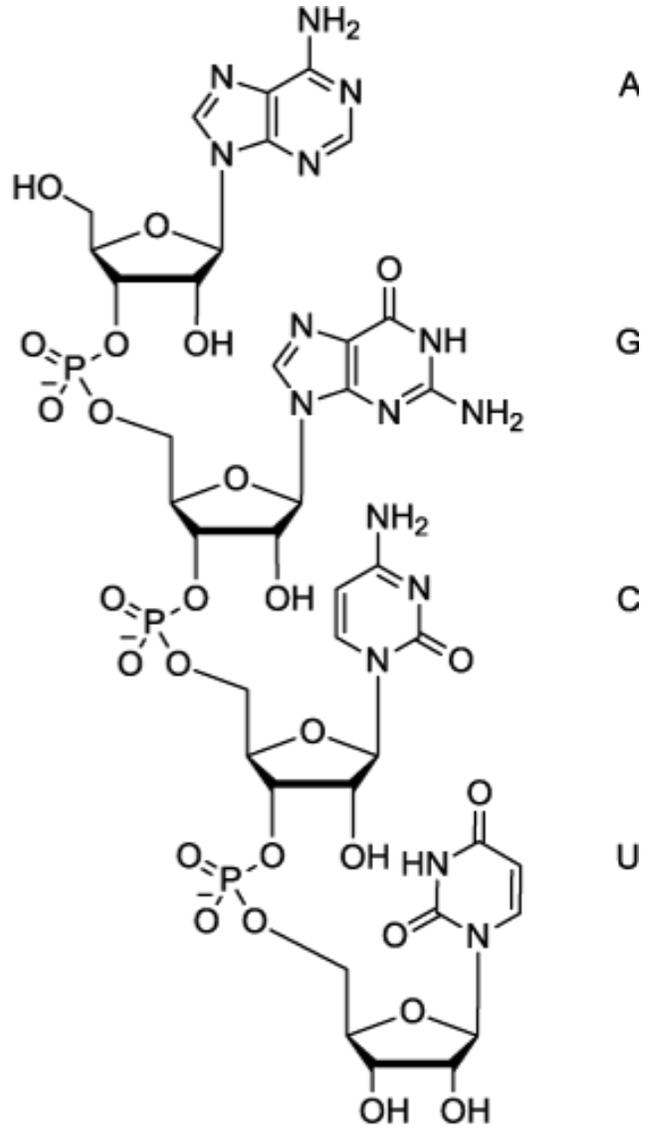


	1	2	3	4	5	6	7	8	
G	0	1	1	1	2	2	2	3	G 1
C	0	0	0	0	1	1	1	2	C 2
A		0	0	0	1	1	1	2	A 3
C			0	0	1	1	1	2	C 4
G				0	0	0	1	1	G 5
A					0	0	0	1	A 6
C						0	0	1	C 7
G							0	0	G 8

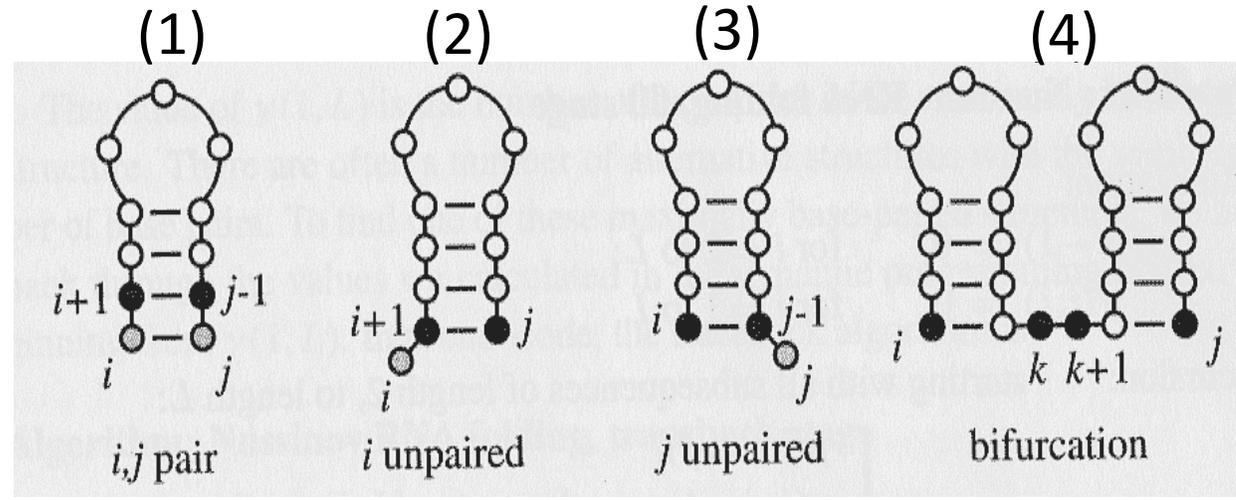


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Extension: Hairpin Loops with Minimum Length ℓ



Extension: Hairpin Loops with Minimum Length ℓ



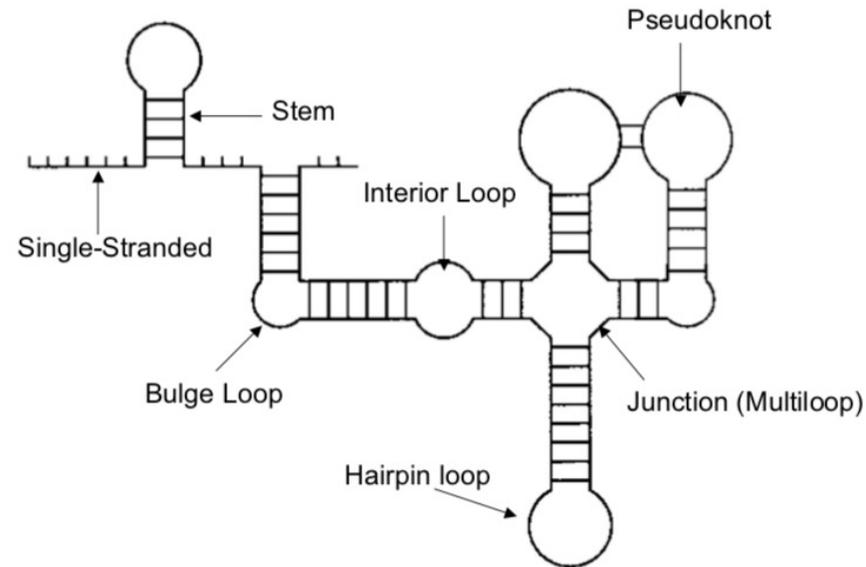
$$s[i, j] = \max \begin{cases} 0, & \text{if } i + \ell \geq j, \\ s[i + 1, j - 1] + 1, & \text{if } i + \ell < j \text{ and } (v_i, v_j) \in \Gamma, \\ s[i + 1, j - 1], & \text{if } i + \ell < j \text{ and } (v_i, v_j) \notin \Gamma, \\ s[i + 1, j], & \text{if } i + \ell < j, \\ s[i, j - 1], & \text{if } i + \ell < j, \\ \max_{i+\ell < k < j} \{s[i, k] + s[k + 1, j]\}, & \text{if } i + \ell < j, \end{cases} \begin{matrix} (1) \\ (1^*) \\ (2) \\ (3) \\ (4) \end{matrix}$$

RNA Secondary Structure Prediction in Practice

Rather than maximize number of compl. base pairs, minimize free energy (FE)

Zuker's algorithm: Dynamic programming w/ three matrices similar to affine gap penalties

- $V(i,j)$: FE of optimal structure of $s[i..j]$ assuming i,j form a base pair
- $VBI(i,j)$: FE of optimal structure of $s[i..j]$ assuming i,j closes a bulge or internal loop
- $VM(i,j)$: FE of optimal structure of $s[i..j]$ assuming i,j closes a multibranch loop



FE minimization with pseudoknots is NP-hard
[Lyngso and Pedersen, RECOMB 2000]

Summary

- RNA is a sequence of four bases/nucleotides {A, U, C, G}
- RNA folds into structures due to base/nucleotide complementarity
 - A \leftrightarrow U and C \leftrightarrow G
- RNA secondary structure is defined by a set of non-overlapping complementary nucleotide pairs
- Pseudoknot-free structures have no “crossing” pairs
- Nussinov Algorithm: Dynamic programming to find pseudoknot-free structure with maximum number of complementary nucleotide pairs

Reading:

- Topics are not in Jones and Pevzner book but in lecture notes and slides [Based on Chapter 10 in “Biological sequence analysis” by Durbin et al.]