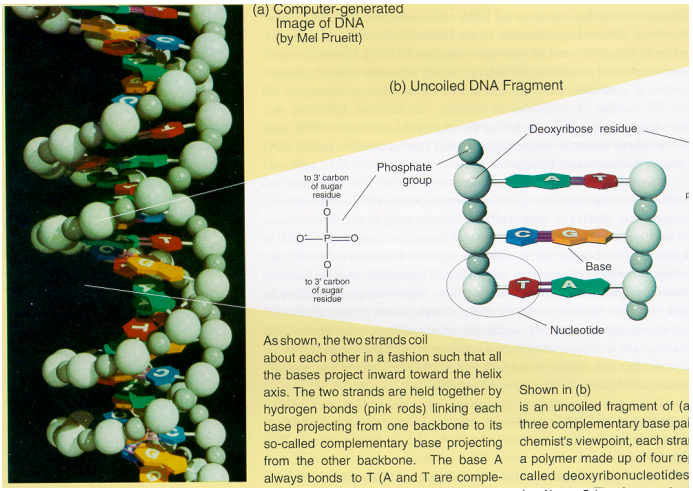
CSE 417: Algorithms and Computational Complexity

Winter 2009

W. L. Ruzzo

Dynamic Programming, II
RNA Folding

The Double Helix



http://www.rcsb.org/pdb/explore.do?structureId=1GAT

NATURE VOL. 227 AUGUST 8 1970

Central Dogma of Molecular Biology

by
FRANCIS CRICK
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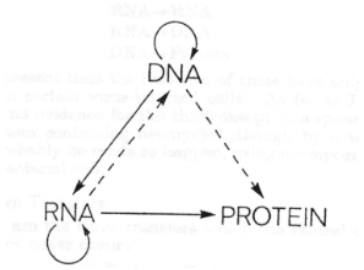
Hills Road,
Cambridge CB2 2QH

The central dogma of molecular biology deals with the detailed residue-by-residue transfer of sequential information. It states that such information cannot be transferred from protein to either protein or nucleic acid.

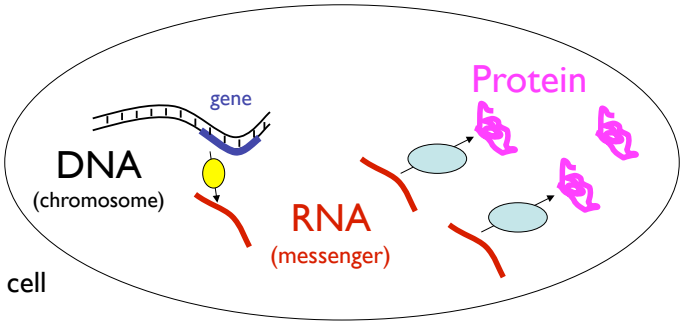
"The central dogma, enunciated by Crick in 1958 and the keystone of molecular biology ever since, is likely to prove a considerable over-simplification."

Fig. 2. The arrows show the situation as it seemed in 1958. Solid arrows represent probable transfers, dotted arrows possible transfers. The absent arrows (compare Fig. 1) represent the impossible transfers postulated by the central dogma. They are the three possible arrows starting from protein.



The "Central Dogma" of Molecular Biology

DNA → RNA → Protein



Non-coding RNA

Messenger RNA - codes for proteins

Non-coding RNA - all the rest

- Before, say, mid 1990's, 1-2 dozen known (critically important, but narrow roles)

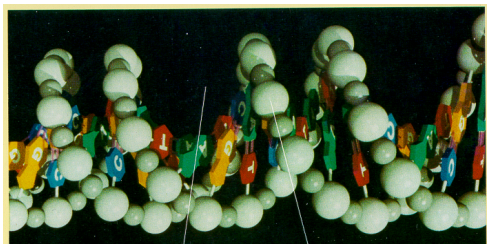
Since mid 90's dramatic discoveries

- Regulation, transport, stability/degradation
- E.g. "microRNA": 100s in humans => 50% of genes
- E.g. "riboswitches": 1000s in bacteria

DNA structure: dull

5'…ACCGCTAGATG…3'

3'…TGGCGATCTAC…5'

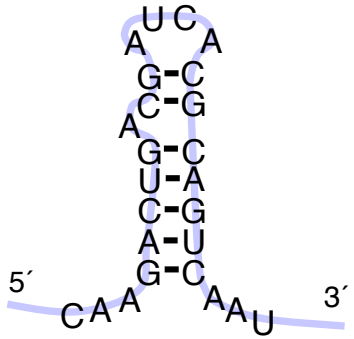


RNA Secondary Structure:
RNA makes helices too

Base pairs

A-U

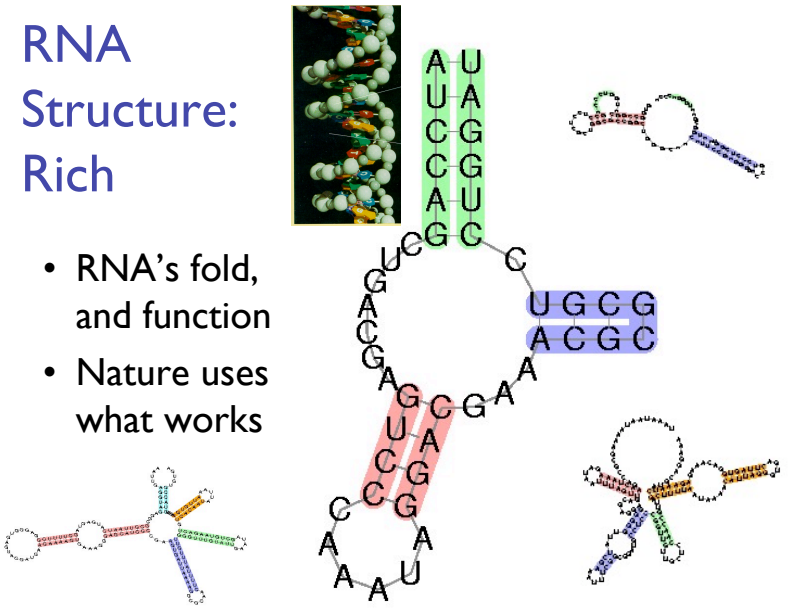
C-G



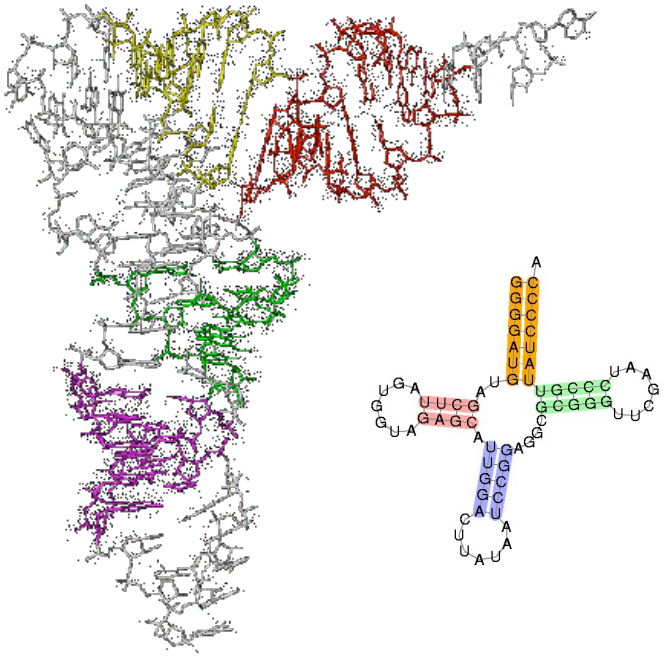
Usually *single* stranded

RNA Structure: Rich

- RNA's fold, and function
- Nature uses what works

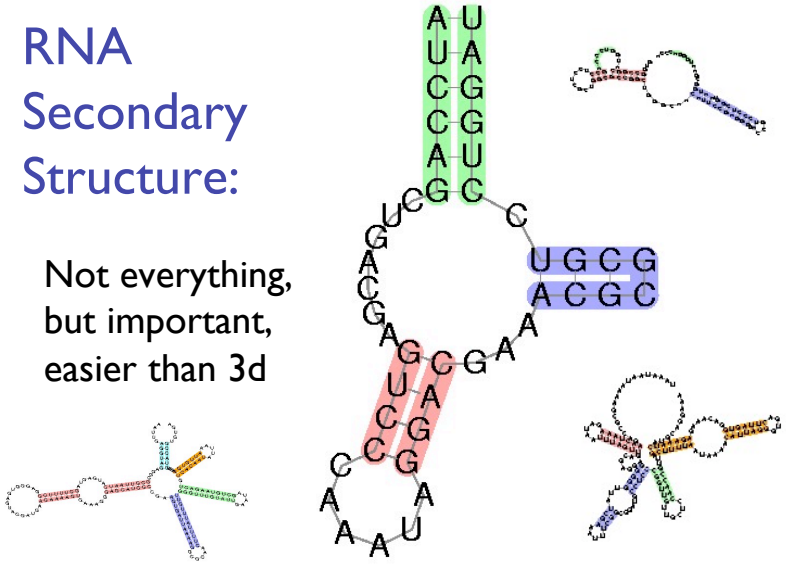


http://www.rcsb.org/pdb/explore.do?structureId=1EVV



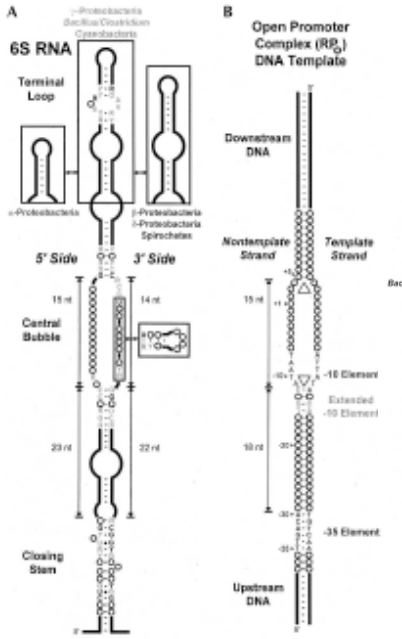
RNA Secondary Structure:

Not everything, but important, easier than 3d

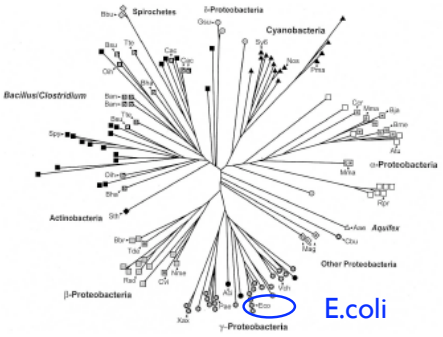


Why is structure important?

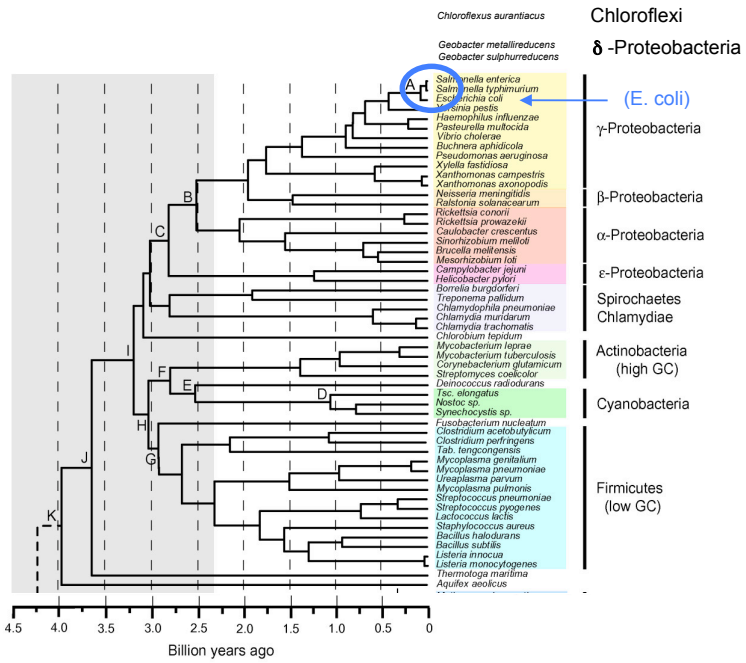
- For protein-coding, similarity in sequence is a powerful tool for finding related sequences
  - e.g. "hemoglobin" is easily recognized in all vertebrates
- For non-coding RNA, many different sequences have the same structure, and structure is most important for function.
  - So, using structure plus sequence, can find related sequences at much greater evolutionary distances



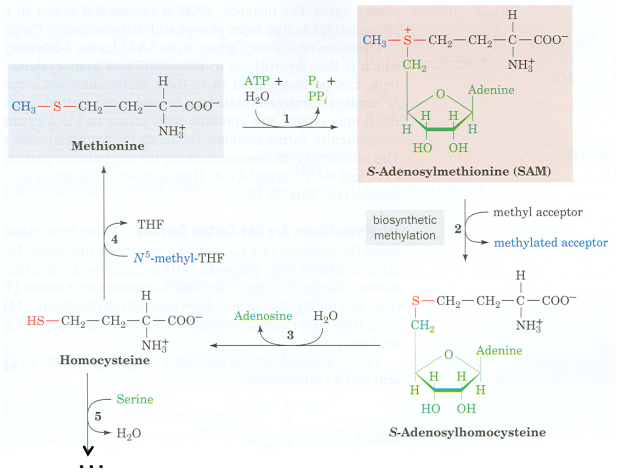
6S mimics an open promoter



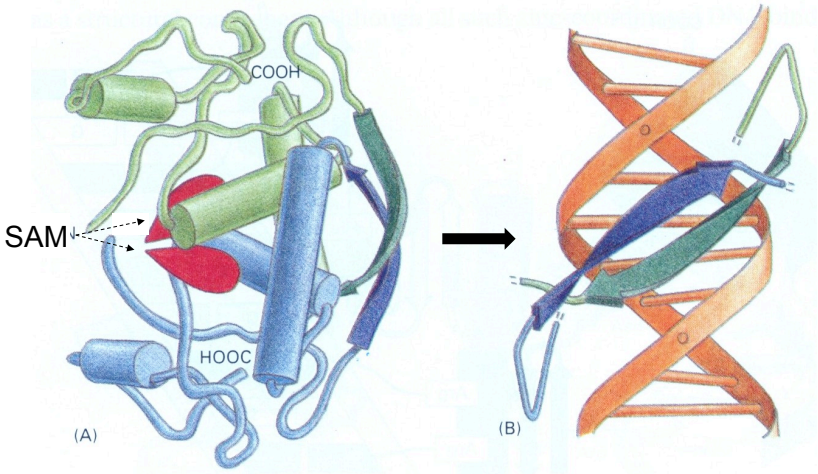
Barrick et al. *RNA* 2005
Trotochaud et al. *NSMB* 2005
Willkomm et al. NAR 2005



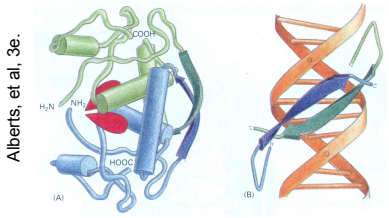
In Bacteria: A typical biosynthetic cycle around a critical metabolite ("SAM")



Gene Regulation: The MET Repressor

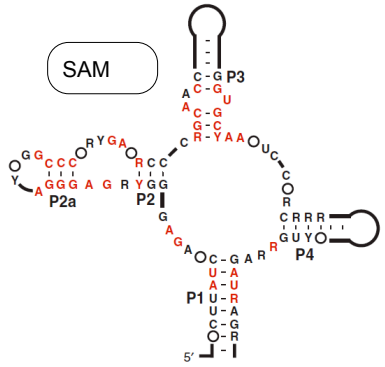


Protein Alberts, et al, 3e. DNA

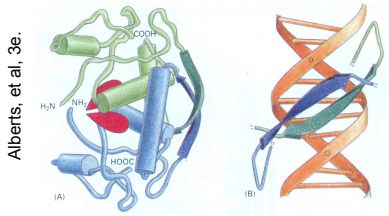


The protein way

Riboswitch alternative

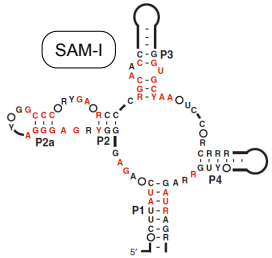


Grundy & Henkin, Mol. Microbiol 1998
Epshtein, et al., PNAS 2003
Winkler et al., Nat. Struct. Biol. 2003



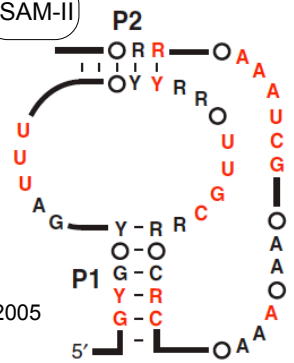
The protein way

Riboswitch alternatives



Grundy, Epshtein, Winkler et al., 1998, 2003

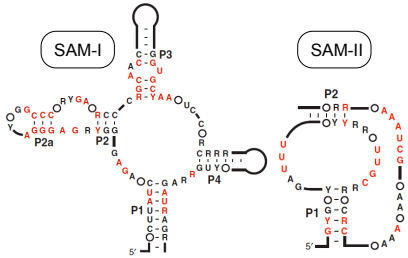
SAM-II



Corbino et al., Genome Biol. 2005

The protein way

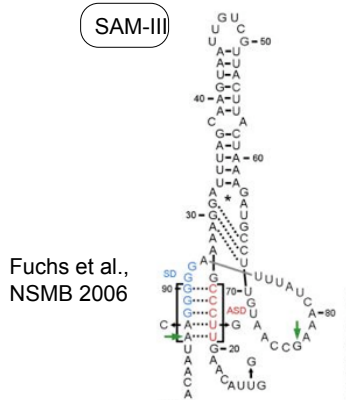
Riboswitch alternatives



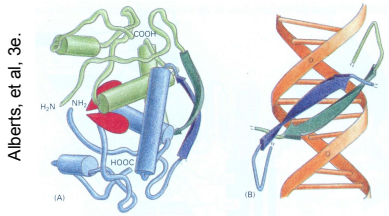
Grundy, Epshtein, Winkler et al., 1998, 2003

Corbino et al., Genome Biol. 2005

SAM-III

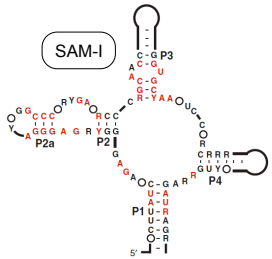


Fuchs et al., NSMB 2006

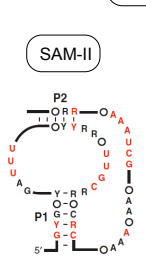


The protein way

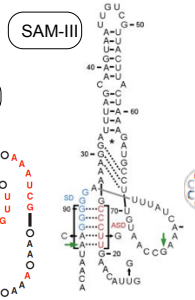
Riboswitch alternatives



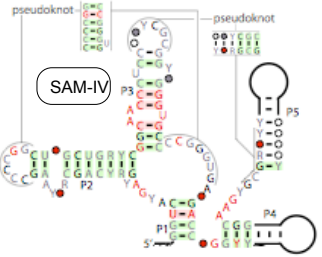
Grundy, Epshtein, Winkler et al., 1998, 2003



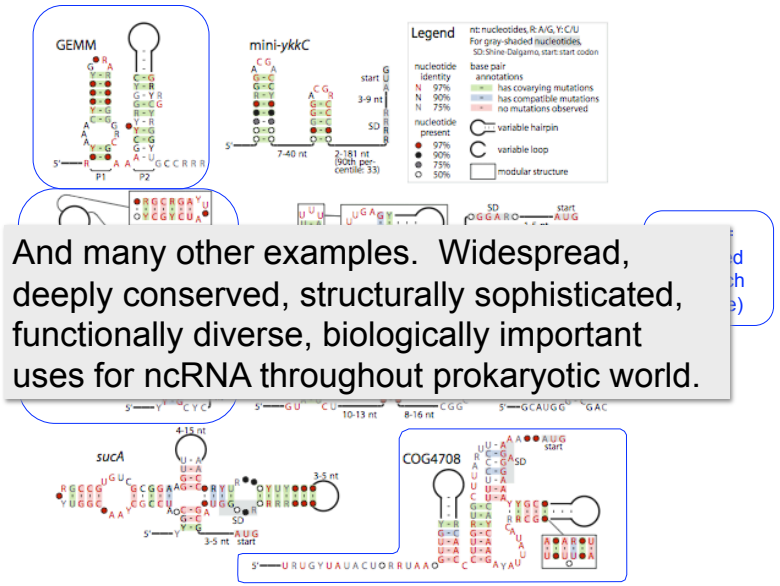
Corbino et al., Genome Biol. 2005



Fuchs et al., NSMB 2006



Weinberg et al., RNA 2008



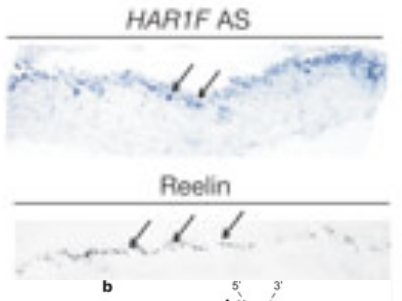
And many other examples. Widespread, deeply conserved, structurally sophisticated, functionally diverse, biologically important uses for ncRNA throughout prokaryotic world.

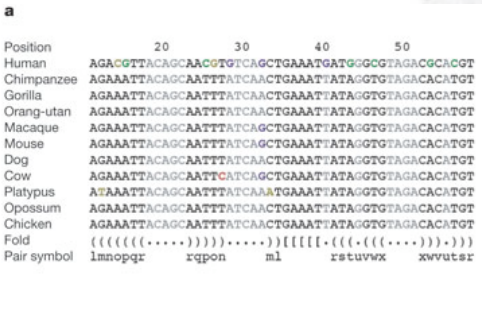
Weinberg, et al. Nucl. Acids Res., July 2007 35: 4809-4819.

Vertebrates

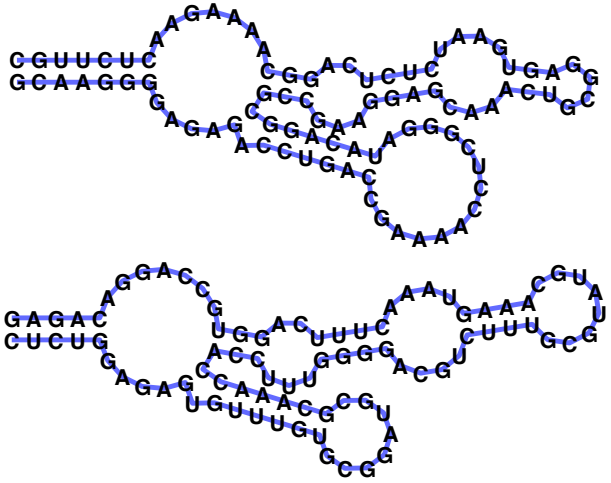
- Bigger, more complex genomes
- <2% coding
- But >5% conserved in sequence?
- And 50-90% transcribed?
- And *structural* conservation, if any, invisible (without proper alignments, etc.)
  - What's going on?

Fastest Human Gene?



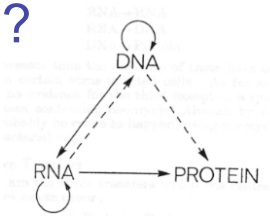


Q: What's so hard?



A: Structure often more important than sequence

Origin of Life?



Life needs
- information carrier: DNA
- molecular machines, like enzymes: Protein
- making proteins needs DNA + RNA + proteins
- making (duplicating) DNA needs proteins

Horrible circularities! How could it have arisen in an abiotic environment?

Origin of Life?

RNA can carry information, too

RNA double helix; RNA-directed RNA polymerase

RNA can form complex structures

RNA enzymes exist (ribozymes)

RNA can control, do logic (riboswitches)

The "RNA world" hypothesis:
1st life was RNA-based

6.5 RNA Secondary Structure

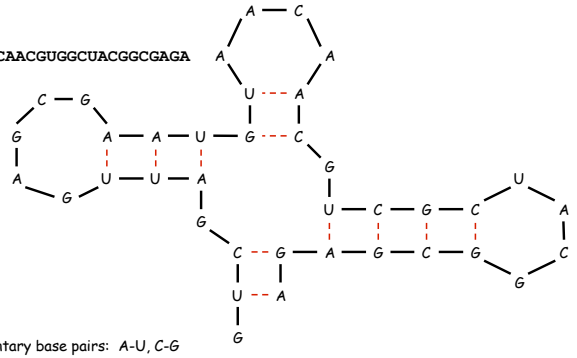
Nussinov's Algorithm – core technology
for RNA structure prediction

RNA Secondary Structure

RNA. String $B = b_1 b_2 \ldots b_n$ over alphabet { A, C, G, U }.

Secondary structure. RNA is usually single-stranded, and tends to loop back and form base pairs with itself. This structure is essential for understanding behavior of molecule.

Ex: GUCGAUUGAGCGAAUGUAACAACGUGGCUACGGCGAGA



complementary base pairs: A-U, C-G

RNA Secondary Structure (somewhat oversimplified)

Secondary structure. A set of pairs $S = \{ (b_i, b_j) \}$ that satisfy:

- [Watson-Crick.]
  - S is a *matching* , i.e. each base pairs with at most one other, and
  - each pair in S is a Watson-Crick pair: A-U, U-A, C-G, or G-C.
- [No sharp turns.] The ends of each pair are separated by at least 4 intervening bases. If $(b_i, b_j) \in S$, then $i < j - 4$.
- [Non-crossing.] If (b_i, b_j) and (b_k, b_l) are two pairs in S, then we cannot have $i < k < j < l$. (Violation of this is called a *pseudoknot*.)

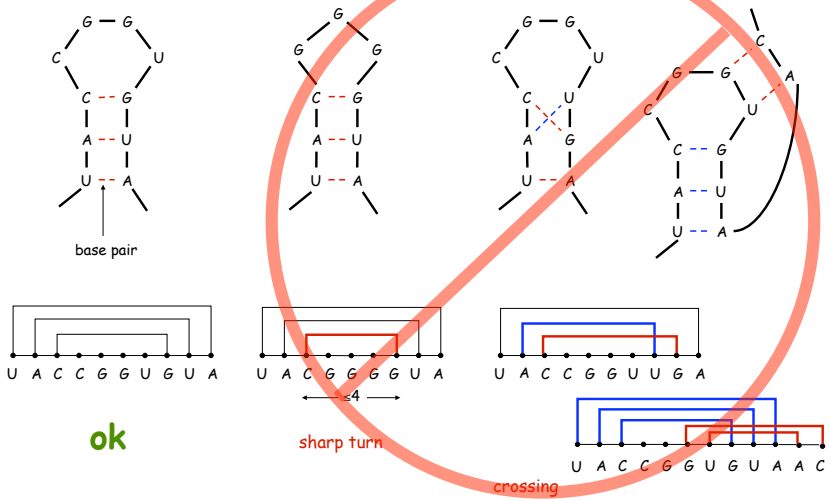
Free energy. Usual hypothesis is that an RNA molecule will form the secondary structure with the optimum total free energy.

approximate by number of base pairs

Goal. Given an RNA molecule $B = b_1 b_2 \ldots b_n$, find a secondary structure S that maximizes the number of base pairs.

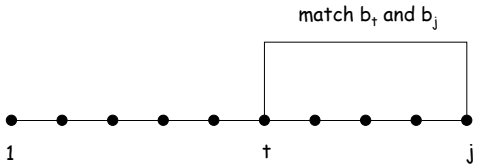
RNA Secondary Structure: Examples

Examples.



RNA Secondary Structure: Subproblems

First attempt. OPT[j] = maximum number of base pairs in a secondary structure of the substring $b_1 b_2 \ldots b_j$.



Difficulty. Results in two sub-problems.

- Finding secondary structure in: $b_1 b_2 \ldots b_{t-1}$. ← OPT(t-1)
- Finding secondary structure in: $b_{t+1} b_{t+2} \ldots b_{j-1}$. ← not OPT of anything; need more sub-problems

Dynamic Programming Over Intervals: (R. Nussinov's algorithm)

Notation. OPT[i, j] = maximum number of base pairs in a secondary structure of the substring $b_i b_{i+1} \ldots b_j$.

- Case 1. If $i \geq j - 4$.
  - OPT[i, j] = 0 by no-sharp turns condition.
- Case 2. Base b_j is not involved in a pair.
  - OPT[i, j] = OPT[i, j-1]
- Case 3. Base b_j pairs with b_t for some $i \leq t < j - 4$.
  - non-crossing constraint decouples resulting sub-problems
  - $OPT[i, j] = 1 + \max_t \{ OPT[i, t-1] + OPT[t+1, j-1] \}$

take max over t such that $i \leq t < j-4$ and b_t and b_j are Watson-Crick complements

Key point: Either last base is unpaired (case 1,2) or paired (case 3)

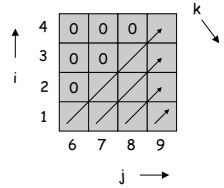
Remark. Same core idea in CKY algorithm to parse context-free grammars.

Bottom Up Dynamic Programming Over Intervals

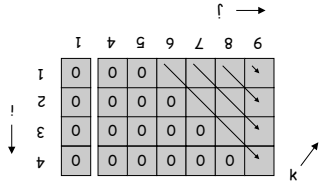
Q. What order to solve the sub-problems?
A. Do shortest intervals first.

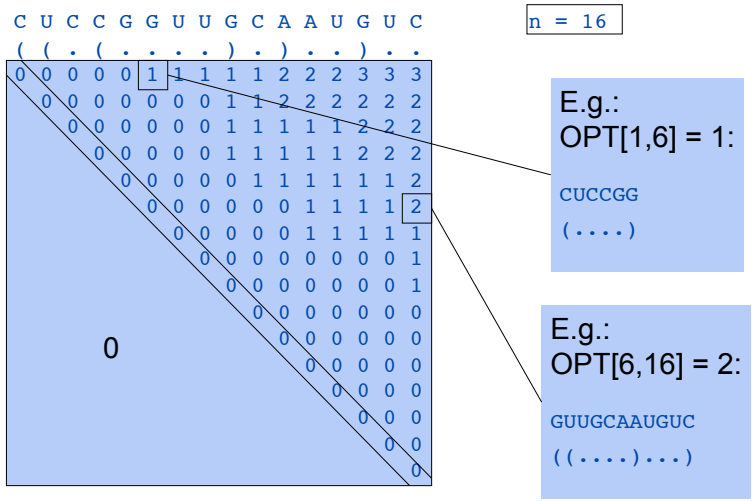
```
RNA(b1,…,bn) {
   for k = 5, 6, …, n-1
      for i = 1, 2, …, n-k
         j = i + k
         Compute OPT[i, j]

   return OPT[1, n]
}
```

using recurrence

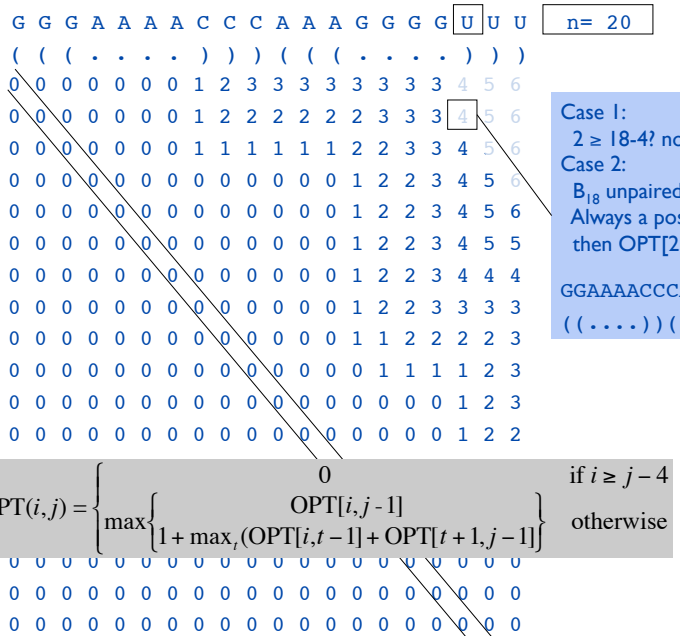


Running time. $O(n^3)$.





Computing one cell: OPT[2,18] = ?



$$OPT(i,j) = \begin{cases} 0 & \text{if } i \geq j-4 \\ \max\left\{ \begin{array}{c} OPT[i,j-1] \\ 1+\max_t(OPT[i,t-1]+OPT[t+1,j-1]) \end{array} \right\} & \text{otherwise} \end{cases}$$

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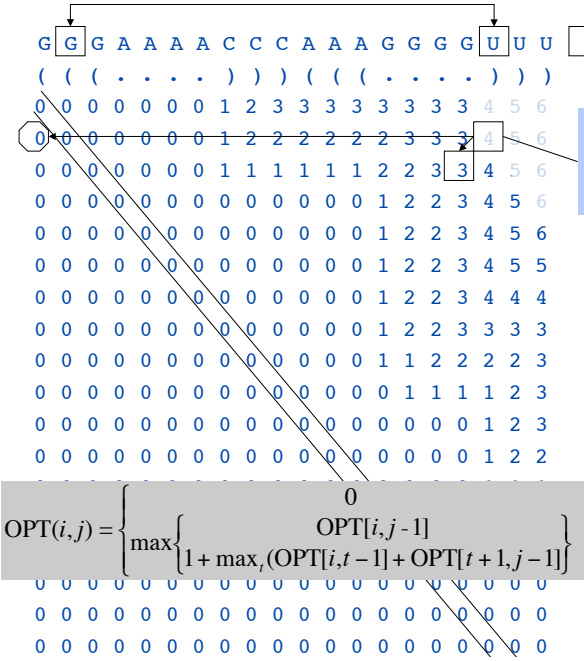

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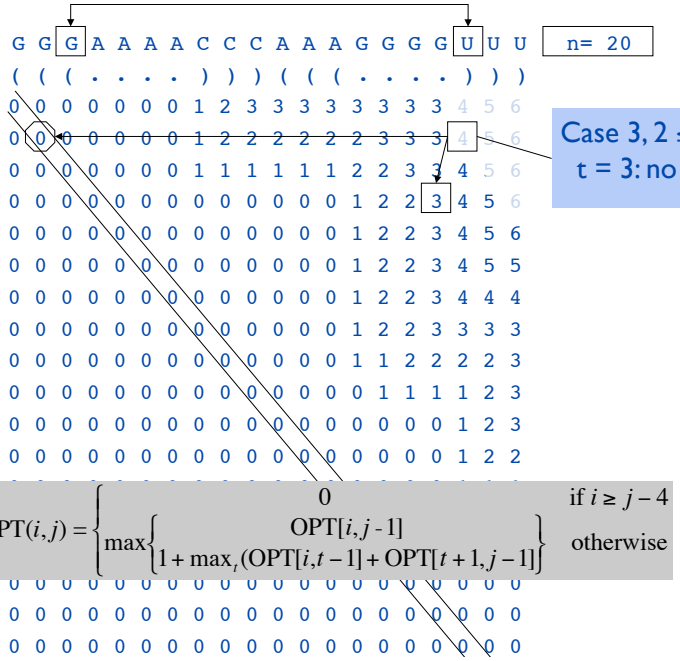

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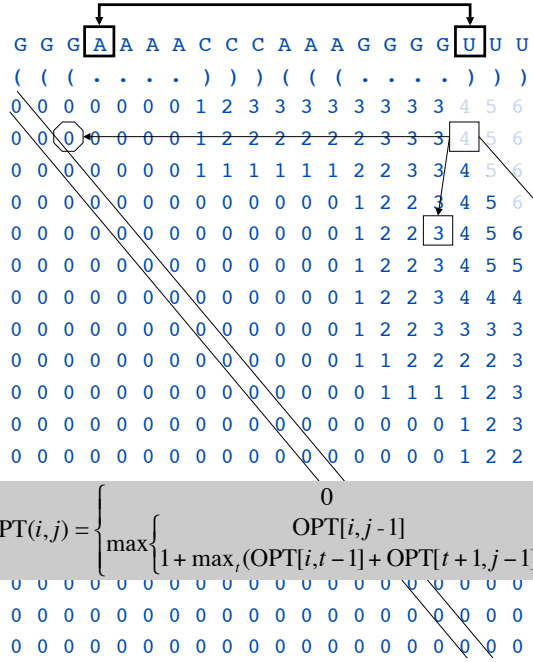
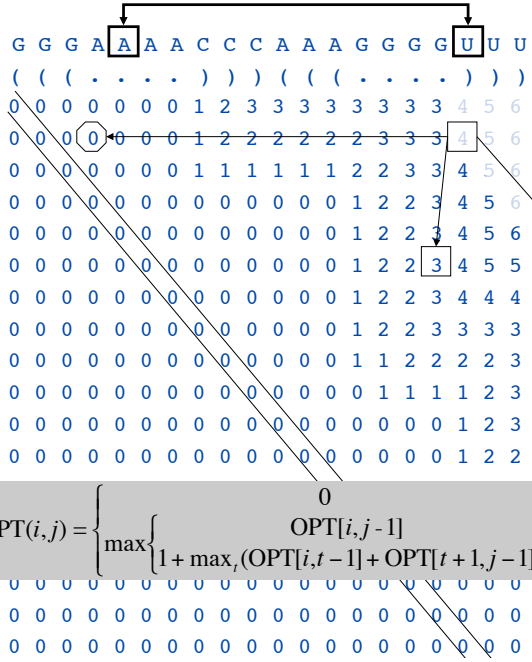


Case 3, 2 ≤ t <18-4:
t = 4: yes pair
OPT[2,18]≥1+0+3

GG**A**AAACCCAAAGGGG**U**
..(...(((....)))).

$$OPT(i,j) = \begin{cases} 0 & \text{if } i \geq j-4 \\ \max\left\{ \begin{array}{c} OPT[i,j-1] \\ 1+\max_t(OPT[i,t-1]+OPT[t+1,j-1]) \end{array} \right\} & \text{otherwise} \end{cases}$$

Computing one cell: OPT[2,18] = ?

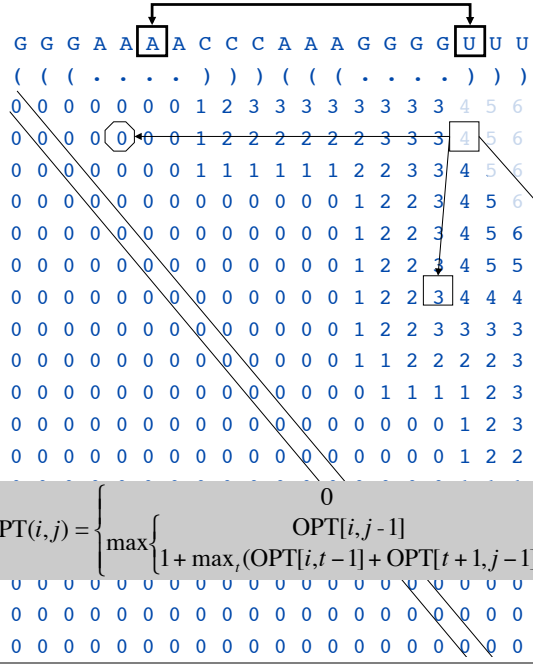


Case 3, 2 ≤ t <18-4:
t = 5: yes pair
OPT[2,18]≥1+0+3

GGA**A**AACCCAAAGGGG**U**
...(..(((....)))).

$$OPT(i,j) = \begin{cases} 0 & \text{if } i \geq j-4 \\ \max\left\{ \begin{array}{c} OPT[i,j-1] \\ 1+\max_t(OPT[i,t-1]+OPT[t+1,j-1]) \end{array} \right\} & \text{otherwise} \end{cases}$$

Computing one cell: OPT[2,18] = ?

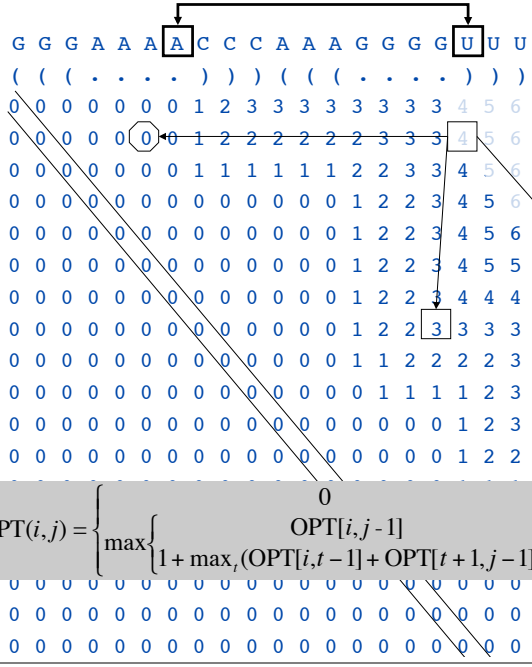


Case 3, 2 ≤ t <18-4:
t = 6: yes pair
OPT[2,18]≥1+0+3

GGAA**A**ACCCAAAGGGG**U**
....(.(((....)))).

$$OPT(i,j) = \begin{cases} 0 & \text{if } i \geq j-4 \\ \max\left\{ \begin{array}{c} OPT[i,j-1] \\ 1+\max_t(OPT[i,t-1]+OPT[t+1,j-1]) \end{array} \right\} & \text{otherwise} \end{cases}$$

Computing one cell: OPT[2,18] = ?

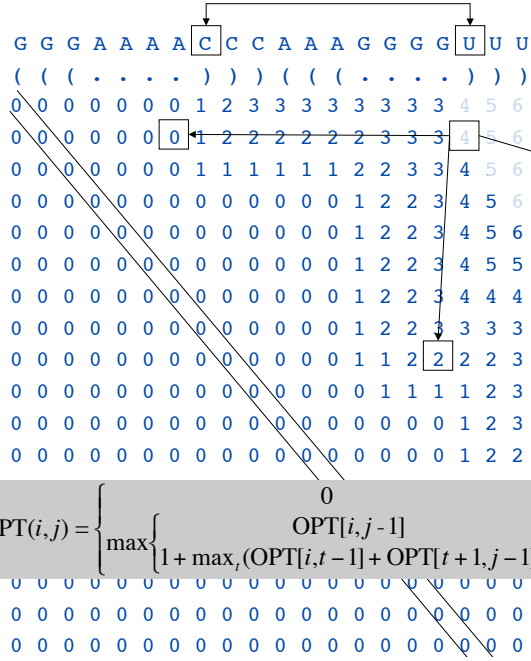


Case 3, 2 ≤ t <18-4:
t = 7: yes pair
OPT[2,18]≥1+0+3

GGAAA**A**CCCAAAGGGG**U**
.....((((....)))).

$$OPT(i,j) = \begin{cases} 0 & \text{if } i \geq j-4 \\ \max\left\{ \begin{array}{c} OPT[i,j-1] \\ 1+\max_t(OPT[i,t-1]+OPT[t+1,j-1]) \end{array} \right\} & \text{otherwise} \end{cases}$$

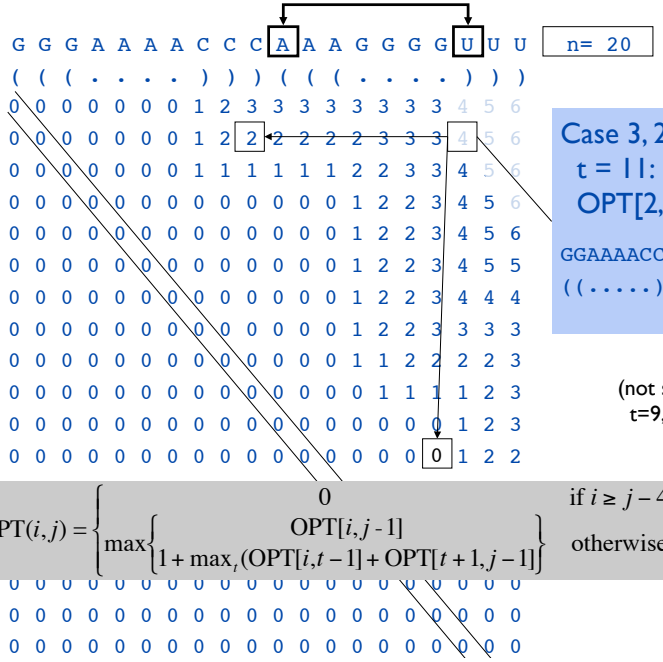
Computing one cell: OPT[2,18] = ?



Case 3, $2 \le t < 18-4$:
t = 8: no pair

$$OPT(i,j) = \begin{cases} 0 & \text{if } i \ge j-4 \\ \max\left\{ \begin{array}{c} OPT[i,j-1] \\ 1+\max_t(OPT[i,t-1]+OPT[t+1,j-1]) \end{array} \right\} & \text{otherwise} \end{cases}$$

Computing one cell: OPT[2,18] = ?

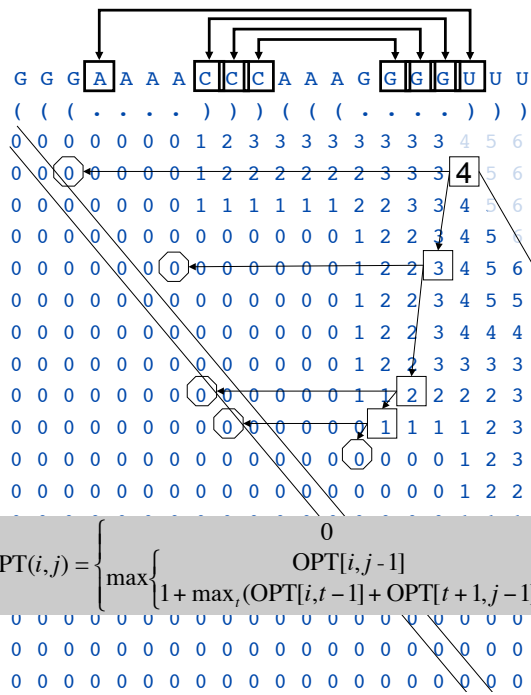


Case 3, $2 \le t < 18-4$:
t = 11: yes pair
OPT[2,18]≥1+2+0

GGAAAACCC**AAA**GGGG**U**
((.....))(.....)

(not shown:
t=9,10, 12,13)

$$OPT(i,j) = \begin{cases} 0 & \text{if } i \ge j-4 \\ \max\left\{ \begin{array}{c} OPT[i,j-1] \\ 1+\max_t(OPT[i,t-1]+OPT[t+1,j-1]) \end{array} \right\} & \text{otherwise} \end{cases}$$



Computing one cell: OPT[2,18] = 4

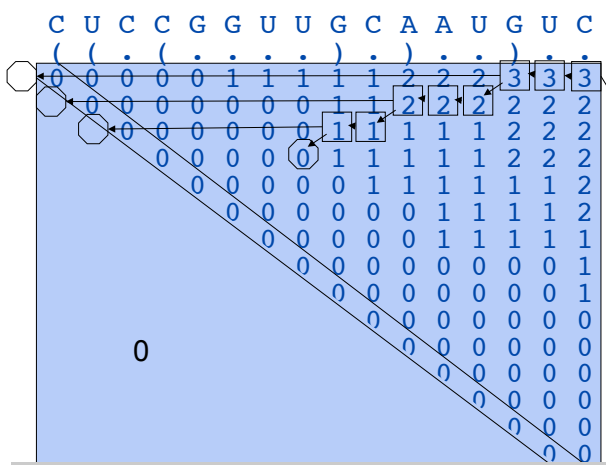
Overall, Max = 4
several ways, e.g.:

GGAAAACCCAAAGGGGU
..(...(((....)))).

tree shows trace back:
square = case 3
octagon = case 1

$$OPT(i,j) = \begin{cases} 0 & \text{if } i \ge j-4 \\ \max\left\{ \begin{array}{c} OPT[i,j-1] \\ 1+\max_t(OPT[i,t-1]+OPT[t+1,j-1]) \end{array} \right\} & \text{otherwise} \end{cases}$$

Another Trace Back Example



E.g.:
OPT[1,16] = 3:

CUCCGGUUGCAAUGUC
((.(....).)..)..

$$OPT(i,j) = \begin{cases} 0 & \text{if } i \ge j-4 \\ \max\left\{ \begin{array}{c} OPT[i,j-1] \\ 1+\max_t(OPT[i,t-1]+OPT[t+1,j-1]) \end{array} \right\} & \text{otherwise} \end{cases}$$