Objectives

Dynamic Programming: Computational Biology Applications

- RNA Secondary Structure
- Sequence Alignment

Review: Dynamic Programming

What is the key idea?

What is our approach to solve a problem using dynamic programming?

Review: Dynamic Programming

What is the key idea?

- Memoization: remember the answer for subproblems
  - Improves running time
  - Tradeoff in space

What is our approach to solve a problem using dynamic programming?

- Figure out what we're optimizing
- Figure out how to break the problem into subproblems
- Figure out how to compute solution from subproblems
- Define the recurrence relation between the problems

What was the Key to Solving each of these Problems?

Weighted interval scheduling

Segmented least squares

Knapsack

What was the Key to Solving each of these Problems?

Weighted interval scheduling

- Binary decision: job was in or wasn't
- Know conflicts→ reduce problem

Segmented least squares

- Knew last point was definitely in one segment
  - Could reduce
- Multiway decision→ many possibilities for segment starting point

Knapsack

- If select an item, reduce available size by item's size
  - Find opt solution for smaller weight, remaining items

Applications of Dynamic Programming to Computational Biology

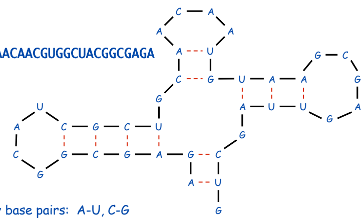
RNA SECONDARY STRUCTURE

RNA Secondary Structure

RNA. String $B = b_1b_2\ldots b_n$ over alphabet { A, C, G, U }

Secondary structure. RNA is single-stranded so it 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: Which Pairs Can We Combine?

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

- [Watson-Crick] S is a *matching* and each pair in S is a Watson-Crick complement: 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 $i < k < j < l$

RNA Secondary Structure

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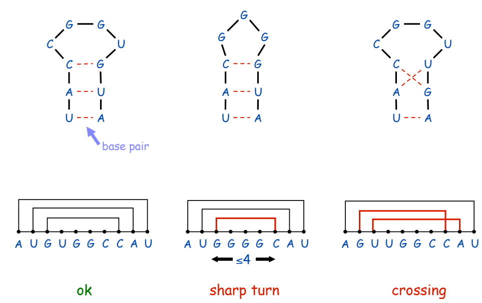
Free energy. Usual hypothesis is that an RNA molecule will form the secondary structure with the *optimum total free energy*. approximate by number of base pairs

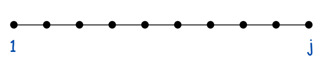
Goal. Given an RNA molecule $B = b_1b_2\ldots b_n$, find a secondary structure S that maximizes the number of base pairs

Examples of RNA Secondary Structure



Toward a Solution

First attempt. OPT(j) = maximum number of base pairs in a secondary structure of the substring $b_1b_2\ldots b_j$



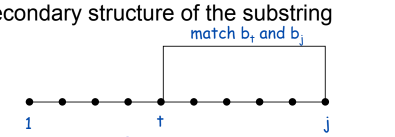
Towards a recurrence relation…

- What are the possibilities?
  - What does b_j match with?
- What are the subproblems?

Toward a Solution

First attempt. OPT(j) = maximum number of base pairs in a secondary structure of the substring $b_1b_2\ldots b_j$

Relation:



- If j isn't involved in a pair: Opt(j-1)
- If j is involved, results in two sub-problems
  - Finding secondary structure in: $b_1b_2\ldots b_{t-1}$ ← OPT(t-1)
  - Finding secondary structure in: $b_{t+1}b_{t+2}\ldots b_{j-1}$ ← need more subproblems

Doesn't match our subproblem (doesn't start at 1)
Need to start anywhere

Dynamic Programming Over Intervals

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

- What are the different cases?
- How does it affect the recurrence relation?
  - For example, when will we know that there isn't a pair?

Dynamic Programming Over Intervals

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

Recurrence Relation

Putting it all together…

j not in a base pair in optimal solution

```
▪ Opt(i,j) = max( Opt(i,j-1),
       max_t( 1+Opt(i,t-1)+Opt(t+1,j-1) ) )
```

j in a base pair in optimal solution
Adds 1 pair
Look at remaining letters

RNA Algorithm

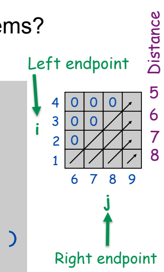
Q. What order to solve the sub-problems?

A. Do shortest intervals first

```
Initialize M[i,j] = 0 for i >= j-4

RNA(b1,…,bn):
   for k = 5, 6, …, n-1     (distances)
      for i = 1, 2, …, n-k  (start)
         j = i + k   (end)
         M[i, j] = max(M[i,j-1],
              max_t(1+M[i,t-1]+M[t+1,j-1]) )

   return M[1, n]
```



Costs?

RNA Algorithm

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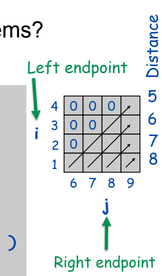


Running time: $O(n^3)$

Dynamic Programming Summary

Recipe

- Characterize structure of problem
- Recursively define value of optimal solution
- Compute value of optimal solution
- Construct optimal solution from computed information

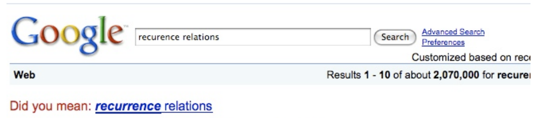
Dynamic programming techniques

- Binary choice: weighted interval scheduling
- Multi-way choice: segmented least squares
- Adding a new variable: knapsack
- Dynamic programming over intervals: RNA secondary structure

Top-down vs. bottom-up: different people have different intuitions

SEQUENCE ALIGNMENT

Problem



How does Google know what I really meant?

String Similarity

How similar are two strings?

- ocurrance
- occurrence

We intuitively can tell that these two are similar

- Systematic measurement?

String Similarity

How similar are two strings?

- ocurrance
- occurrence

Measurements

- Gap (-): add a letter
- Mismatch

o c u r r a n c e -
o c c u r r e n c e

6 mismatches, 1 gap

o c - u r r a n c e
o c c u r r e n c e

1 mismatch, 1 gap

o c - u r r - a n c e
o c c u r r e - n c e

0 mismatches, 3 gaps

Which is the best measurement?

Applications of String Similarity

Basis for Unix `diff` ← Covered in CS297 this spring

- Longest common subsequence

Spam filters

- Similarity to known spam message

Computational biology

- Ex: Figuring out how similar two genomes (sequences of A, C, G, T) are

Alignment with **non** English/natural language strings are less obvious how to align

Edit Distance

[Levenshtein 1966, Needleman-Wunsch 1970]

- Gap penalty: δ
- Mismatch penalty: α_{pq}
  - If p and q are the same, then mismatch penalty is 0
- **Cost** = sum of gap and mismatch penalties

Parameters allow us to tweak cost

C T G A C C T A C C T
C C T G A C T A C A T

$\alpha_{TC} + \alpha_{GT} + \alpha_{AG} + 2\alpha_{CA}$

- C T G A C C T A C C T
C C T G A C - T A C A T

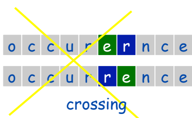
$2\delta + \alpha_{CA}$

Sequence Alignment

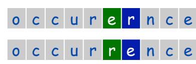
Goal: Given two strings $X = x_1\ x_2 \ldots x_m$ and $Y = y_1\ y_2 \ldots y_n$ find alignment of minimum cost

An *alignment* M is a set of ordered pairs x_i-y_j such that each item occurs in at most one pair and **no** crossings

The pair x_i-y_j and $x_{i'}$-$y_{j'}$ *cross* if $i < i'$, but $j > j'$.



crossing



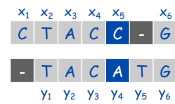
2 mismatches

Sequence Alignment Example

X = CTACCG

Y = TACTG

Solution: $M = x_2$-y_1 , x_3-y_2, x_4-y_3, x_5-y_4 , x_6-y_6



What is the cost of M?

$$\text{cost}(M) = \underbrace{\sum_{(x_i, y_j) \in M} \alpha_{x_i y_j}}_{\text{mismatch}} + \underbrace{\sum_{i\,:\,x_i \text{ unmatched}} \delta + \sum_{j\,:\,y_j \text{ unmatched}} \delta}_{\text{gap}}$$

Recall: mismatch penalty is 0 if x_i and y_j are the same

Sequence Alignment Case Analysis

Consider the last character of the strings X and Y: x_M and y_N

What are the possibilities for x_M and y_N in terms of the alignment?

Sequence Alignment Case Analysis

Consider last character of strings X and Y: x_M and y_N

- Case 1: x_M and y_N are aligned
- Case 2: x_M is not matched
- Case 3: y_N is not matched

Sequence Alignment Case Analysis

Consider last character of strings X and Y: x_M and y_N

- Case 1: x_M and y_N are aligned
- Case 2: x_M is not matched
- Case 3: y_N is not matched

OPT(i, j) = min cost of aligning strings $x_1\ x_2 \ldots x_i$ and $y_1\ y_2 \ldots y_j$

What are the costs for these cases?

Sequence Alignment Cost Analysis

Consider last character of strings X and Y: x_M and y_N

- Case 1: x_M and y_N are aligned
  - Pay mismatch for x_M-y_N + min cost of aligning rest of strings
  - $OPT(M, N) = \alpha_{X_m Y_n} + OPT(M-1, N-1)$
- Case 2: x_M is not matched
  - Pay gap for x_M + min cost of aligning rest of strings
  - $OPT(M, N) = \delta + OPT(M-1, N)$
- Case 3: y_N is not matched
  - Pay gap for y_N + min cost of aligning rest of strings
  - $OPT(M, N) = \delta + OPT(M, N-1)$

Sequence Alignment Cost Analysis

Base costs? → i or j is 0

- What happens when we run out of letters in one string before the other?

X = CTACCG
Y = TACTG

Sequence Alignment: Problem Structure

Gaps for remainder of Y

$$OPT(i,j) = \begin{cases} j\delta & \text{if } i=0 \\ \min \begin{cases} \alpha_{x_i y_j} + OPT(i-1,j-1) \\ \delta + OPT(i-1,j) \\ \delta + OPT(i,j-1) \end{cases} & \text{otherwise} \\ i\delta & \text{if } j=0 \end{cases}$$

Gaps for remainder of X

Sequence Alignment: Algorithm

Cost parameters

```
Sequence-Alignment(m, n, x1x2...xm, y1y2...yn, δ, α)
   for i = 0 to m
      M[0, i] = iδ
   for j = 0 to n
      M[j, 0] = jδ

   for i = 1 to m
      for j = 1 to n
         M[i, j] = min(α[xi, yj] + M[i-1, j-1],
                        δ + M[i-1, j],
                        δ + M[i, j-1])
   return M[m, n]
```

Costs?

Sequence Alignment: Analysis

```
Sequence-Alignment(m, n, x1x2...xm, y1y2...yn, δ, α)
   for i = 0 to m
      M[0, i] = iδ
   for j = 0 to n
      M[j, 0] = jδ

   for i = 1 to m
      for j = 1 to n
         M[i, j] = min(α[xi, yj] + M[i-1, j-1],
                        δ + M[i-1, j],
                        δ + M[i, j-1])
   return M[m, n]
```

O(mn)

Example

X = bait Y = boot

α = 1, for vowel mismatch
α = 2, for other mismatches
δ = 2

j →

i ↓

		b	a	i	t
	0	2	4	6	8
b	2				
o	4				
o	6				
t	8				

Example

X = bait Y = boot

α = 1, for vowel mismatch
α = 2, for other mismatches
δ = 2

j →

i=1 ↓

		b	a	i	t
	0	2	4	6	8
b	2	0	2	4	6
o	4				
o	6				
t	8				

Example

X = bait Y = boot

α = 1, for vowel mismatch
α = 2, for other mismatches
δ = 2

j →

i=2 ↓

		b	a	i	t
	0	2	4	6	8
b	2	0	2	4	6
o	4	2	1	3	5
o	6				
t	8				

Example

X = bait Y = boot

α = 1, for vowel mismatch
α = 2, for other mismatches
δ = 2

j →

i=3 ↓

		b	a	i	t
	0	2	4	6	8
b	2	0	2	4	6
o	4	2	1	3	5
o	6	4	3	2	4
t	8				

Example

X = bait Y = boot

α = 1, for vowel mismatch
α = 2, for other mismatches
δ = 2

j →

i=4 ↓

		b	a	i	t
	0	2	4	6	8
b	2	0	2	4	6
o	4	2	1	3	5
o	6	4	3	2	4
t	8	6	5	4	2

Example

X = bait Y = boot

α = 1, for vowel mismatch
α = 2, for other mismatches
δ = 2

j →

i=4 ↓

		b	a	i	t
	0	2	4	6	8
b	2	0	2	4	6
o	4	2	1	3	5
o	6	4	3	2	4
t	8	6	5	4	2

Sequence Alignment: Algorithm

```
Sequence-Alignment(m, n, x1x2...xm, y1y2...yn, δ, α)
   for i = 0 to m
      M[0, i] = iδ
   for j = 0 to n
      M[j, 0] = jδ

   for i = 1 to m
      for j = 1 to n
         M[i, j] = min(α[xi, yj] + M[i-1, j-1],
                       δ + M[i-1, j],
                       δ + M[i, j-1])
   return M[m, n]
```

What are the space costs?

When computing M[i,j], which entries in M are used?

This Week

Problem Set 5 due Friday

Keep reading Chapter 6