M2 AMI2B - Lecture 1
Algorithmic foundations

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Outline

Foreword . . .

. . . or how to make a million bucks by giving change parsimoniously!!

Problem: You have access to unlimited amount of **1**, **20** and **50** cents coins.
A client prefers to travel light, i.e. to **minimize the #coins**.
How to give **N** cents back in change without losing a customer?

Strategy #1: Start with *heaviest* coins, and then complete/fill-up with coins of *decreasing* value.

$21 = ??$

55

60

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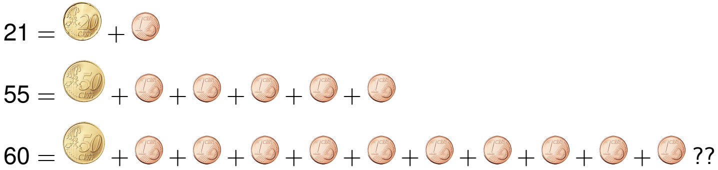

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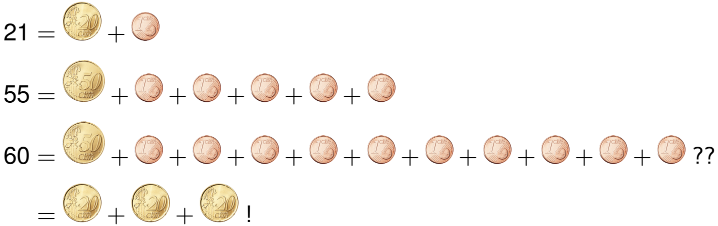

Problem *a priori (?!)* non-solvable using such a *greedy* approach, as a (simpler) problem is already NP-complete (thus Efficient solution $\Rightarrow$ 1M$).

Strategy #2: Brute force enumeration → $\#\text{Coins}^N$ (Ouch!)

Strategy #3: The following recurrence gives the minimal number of coins:

$Min\#Coins(N) = \text{Min}$ of:

-  → $1 + Min\#Coins(N-1)$
-  → $1 + Min\#Coins(N-20)$
-  → $1 + Min\#Coins(N-50)$

With some memory (N intermediate computations), the minimum number of coins can be obtained after $N\times\#\text{Coins}$ operations. An optimal set of coins can be obtained by **tracing back** the choices performed at each stage, leading to the minimum.

Remark: We still haven't won the million, as N has **exponential value compared to the length of its encoding**, so the algorithm does not qualify as *efficient* (i.e. polynomial).

Still, this approach is much more efficient than a brute-force enumeration:
⇒ Dynamic programming.

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Still, this approach is much more efficient than a brute-force enumeration:

$\Rightarrow$ Dynamic programming.

Dynamic programming = General optimization technique.
Prerequisite: Optimal solution for problem P can be derived from solutions to strict sub-problems of P.

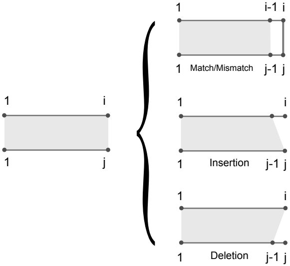
Bioinformatics :

Discete solution space (alignments, structures...)

+ Additively-inherited objective function (cost, log-odd score, energy...)

$\Rightarrow$ Efficient dynamic programming scheme

Example: Local Alignment (Smith/Waterman)



$$
\begin{aligned}
W(i,0) &= 0\\
W(0,j) &= 0\\
W(i,j) &= \max\begin{cases} W(i-1,j-1)+m_{i,j}\\ W(i-1,j)+p_i\\ W(i,j-1)+p_d\end{cases}
\end{aligned}
$$

Algorithmic details

Dynamic programming scheme defines a space of (sub)problems and a recurrence that relates the score of a problem to that of smaller problems.

Given a scheme, two steps :

- **Matrix filling:** Computation and tabulation of best scores (Computed from smaller problems to larger ones).
- **Traceback:** Reconstruct best solution from contributing subproblems.

Complexity of algorithm depends on:

- **Cardinality** of sub-problem space
- **Number of alternatives** considers at each step (#Terms in recurrence)

Smith&Waterman example:

- i: $1 \to n+1 \Rightarrow \Theta(n)$
- j: $1 \to m+1 \Rightarrow \Theta(m)$
- 3 operations at each step

$\Rightarrow \Theta(m.n)$ time/memory

$$
\begin{aligned}
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W(i,j) &= \max \begin{cases} W(i-1,j-1) + m_{i,j} \\ W(i-1,j) + p_i \\ W(i,j-1) + p_d \end{cases}
\end{aligned}
$$

Complete example

Example: Local alignment of AGCACACA and ACACACTA
Costs: Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

$$\begin{aligned} W(i,0) &= 0 \\ W(0,j) &= 0 \\ W(i,j) &= \max \begin{cases} W(i-1,j-1) + m_{i,j} \\ W(i-1,j) + p_i \\ W(i,j-1) + p_d \end{cases} \end{aligned}$$

		A	C	A	C	A	C	T	A
	0	0	0	0	0	0	0	0	0
A	0								
G	0								
C	0								
A	0								
C	0								
A	0								
C	0								
A	0								

Complete example

Example: Local alignment of `AGCACACA` and `ACACACTA`

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		A	C	A	C	A	C	T	A
	0	0	0	0	0	0	0	0	0
A	0	2							
G	0								
C	0								
A	0								
C	0								
A	0								
C	0								
A	0								

Complete example

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		A	C	A	C	A	C	T	A
	0	0	0	0	0	0	0	0	0
A	0	2	1						
G	0								
C	0								
A	0								
C	0								
A	0								
C	0								
A	0								

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		A	C	A	C	A	C	T	A
	0	0	0	0	0	0	0	0	0
A	0	↘ 2 →	1 →	↘↓ 2					
G	0								
C	0								
A	0								
C	0								
A	0								
C	0								
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		A	C	A	C	A	C	T	A
	0	0	0	0	0	0	0	0	0
A	0	2	1	2	1				
G	0								
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		A	C	A	C	A	C	T	A
	0	0	0	0	0	0	0	0	0
A	0	↘ 2	→ 1	↘ 2	→ 1	↘ ↓ → 2	↘ ↓ → 1	↘ ↓ → 0	↘ ↓ → 2
G	0								
C	0								
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	0	0	0	0	0	0	0	0	0
A	0	2	1	2	1	2	1	0	2
G	0	1	1	1	1	1	1	0	1
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A	0	2	1	2	1	2	1	0	2
G	0	1	1	1	1	1	1	0	1
C	0	0	3	2	3	2	3	2	1
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A	0	2	1	2	1	2	1	0	2
G	0	1	1	1	1	1	1	0	1
C	0	0	3	2	3	2	3	2	1
A	0	2	2	5	4	5	4	3	4
C	0								
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C	0	0	3	2	3	2	3	2	1
A	0	2	2	5	4	5	4	3	4
C	0	1	4	4	7	6	7	6	5
A	0	2	3	6	6	9	8	7	8
C	0	1	4	5	8	8	11	10	9
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C	0	0	3	2	3	2	3	2	1
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C	0	0	3	2	3	2	3	2	1
A	0	2	2	5	4	5	4	3	4
C	0	1	4	4	7	6	7	6	5
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	0	0	0	0	0	0	0	0	0
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A	0	2	2	5	4	5	4	3	4
C	0	1	4	4	7	6	7	6	5
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Best alignment

A
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Best alignment

```
-  A
T  A
```

Complete example

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C	0	0	3	2	3	2	3	2	1
A	0	2	2	5	4	5	4	3	4
C	0	1	4	4	7	6	7	6	5
A	0	2	3	6	6	9	8	7	8
C	0	1	4	5	8	8	11	10	9
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Best alignment

```
C - A
C T A
```

Complete example

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		A	C	A	C	A	C	T	A
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A	0	2	1	2	1	2	1	0	2
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Best alignment

A	C	-	A
A	C	T	A

Complete example

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		A	C	A	C	A	C	T	A
	0	0	0	0	0	0	0	0	0
A	0	2	1	2	1	2	1	0	2
G	0	1	1	1	1	1	1	0	1
C	0	0	3	2	3	2	3	2	1
A	0	2	2	5	4	5	4	3	4
C	0	1	4	4	7	6	7	6	5
A	0	2	3	6	6	9	8	7	8
C	0	1	4	5	8	8	11	10	9
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Best alignment

C	A	C	-	A
C	A	C	T	A

Complete example

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		A	C	A	C	A	C	T	A
	0	0	0	0	0	0	0	0	0
A	0	2	1	2	1	2	1	0	2
G	0	1	1	1	1	1	1	0	1
C	0	0	3	2	3	2	3	2	1
A	0	2	2	5	4	5	4	3	4
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Best alignment

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

Complete example

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		A	C	A	C	A	C	T	A
	0	0	0	0	0	0	0	0	0
A	0	2	1	2	1	2	1	0	2
G	0	1	1	1	1	1	1	0	1
C	0	0	3	2	3	2	3	2	1
A	0	2	2	5	4	5	4	3	4
C	0	1	4	4	7	6	7	6	5
A	0	2	3	6	6	9	8	7	8
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Best alignment

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

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$$W(i,j) = \max \begin{cases} W(i-1,j-1) + m_{i,j} \\ W(i-1,j) + p_i \\ W(i,j-1) + p_d \end{cases}$$

		A	C	A	C	A	C	T	A
	0	0	0	0	0	0	0	0	0
A	0	2	1	2	1	2	1	0	2
G	0	1	1	1	1	1	1	0	1
C	0	0	3	2	3	2	3	2	1
A	0	2	2	5	4	5	4	3	4
C	0	1	4	4	7	6	7	6	5
A	0	2	3	6	6	9	8	7	8
C	0	1	4	5	8	8	11	10	9
A	0	2	3	6	7	10	10	10	12

Best alignment

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

Example: Local alignment of `AGCACACA` and `ACACACTA`
Costs: Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

$$
\begin{aligned}
W(i,0) &= 0 \\
W(0,j) &= 0 \\
W(i,j) &= \max \begin{cases} W(i-1,j-1) + m_{i,j} \\ W(i-1,j) + p_i \\ W(i,j-1) + p_d \end{cases}
\end{aligned}
$$

		A	C	A	C	A	C	T	A
	0	0	0	0	0	0	0	0	0
A	0	2	1	2	1	2	1	0	2
G	0	1	1	1	1	1	1	0	1
C	0	0	3	2	3	2	3	2	1
A	0	2	2	5	4	5	4	3	4
C	0	1	4	4	7	6	7	6	5
A	0	2	3	6	6	9	8	7	8
C	0	1	4	5	8	8	11	10	9
A	0	2	3	6	7	10	10	10	12

Best alignment

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

Outline

1. Introduction
   - Dynamic programming 101
   - Dynamic programming: Reminder

2. **Minimal free-energy folding prediction**
   - Nussinov-style RNA folding
   - Turner energy model
   - MFold/Unafold

Nussinov/Jacobson energy model (NJ)

Base-pair maximization (with a twist):

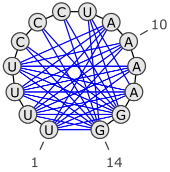
- Additive model on independently contributing base-pairs;
- Canonical base-pairs only: Watson/Crick (A/U,C/G) and Wobble (G/U)

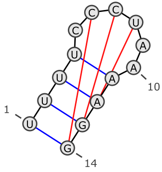
$$\Rightarrow E_{\omega,S} = -\#Paires(S)$$

Folding in NJ model ⇔ Base-pair (weight) maximization

Example:

UUUUCCCUAAAAGG





Variant: Weight each pair with −#Hydrogen bonds

ΔG(G≡C) = -3 ΔG(A=U) = -2 ΔG(G−U) = -1

Nussinov/Jacobson model

Nussinov/Jacobson energy model (NJ)

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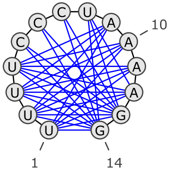

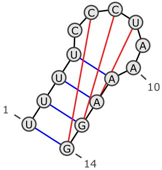

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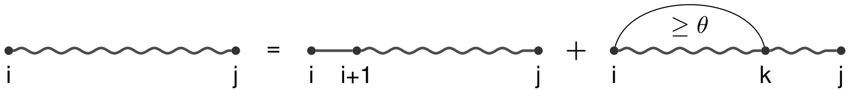
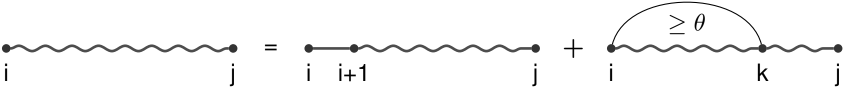
Nussinov/Jacobson DP scheme



$$
\begin{aligned}
N_{i,t} &= 0, \quad \forall t \in [i, i+\theta] \\
N_{i,j} &= \min \begin{cases} N_{i+1,j} & i \text{ unpaired} \\ \min\limits_{k=i+\theta+1}^{j} \Delta G_{i,k} + N_{i+1,k-1} + N_{k+1,j} & i \text{ paired with } k \end{cases}
\end{aligned}
$$



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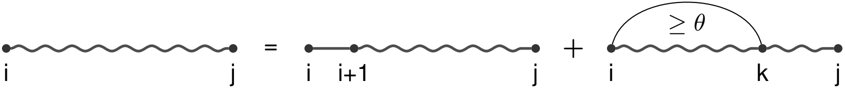
Correctness. Goal = Show that MFE over interval $[i, j]$ is indeed found in $N_{i,j}$ after completing the computation. Proceed by induction:

- Assume that property holds for any $[i', j']$ such that $j' - i' < n$.
- Consider $[i, j]$, $j - i = n$. Let $\text{MFE}_{i,j}$:= Base-pairs of best struct. on $[i, j]$. Then first position i in $\text{MFE}_{i,j}$ = is either:
  - **Unpaired:** $\text{MFE}_{i,j} = \text{MFE}_{i+1,j}$ $\rightarrow$ free-energy $= N_{i+1,j}$
  - **Paired to k:** $\text{MFE}_{i,j} = \{(i,k)\} \cup \text{MFE}_{i+1,k-1} \cup \text{MFE}_{k+1,j}$.
    (Indeed, any BP between $[i+1, k-1]$ and $[k+1, j]$ would cross (i,k))
    $\rightarrow$ free-energy $= \Delta G_{i,k} + N_{i+1,k-1} + N_{k+1,j}$

Nussinov/Jacobson DP scheme



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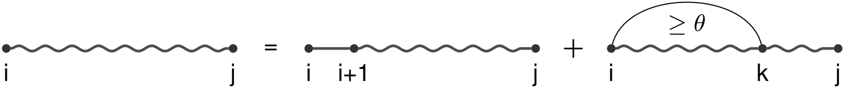
Nussinov/Jacobson DP scheme



$$N_{i,t} = 0, \quad \forall t \in [i, i+\theta]$$

$$N_{i,j} = \min \begin{cases} N_{i+1,j} & i \text{ unpaired} \\ \min\limits_{k=i+\theta+1}^{j} \Delta G_{i,k} + N_{i+1,k-1} + N_{k+1,j} & i \text{ paired with } k \end{cases}$$

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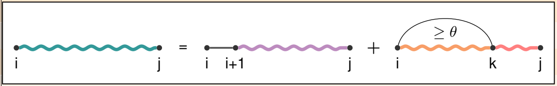
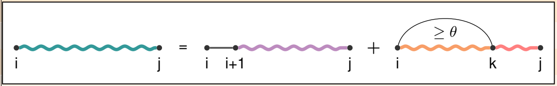
    $\rightarrow$ free-energy $= \Delta G_{i,k} + N_{i+1,k-1} + N_{k+1,j}$

$\Rightarrow$ $N_{i,j}$ indeed contains MFE over $[i, j]$.

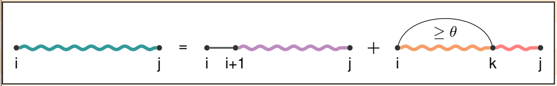
	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
G														0	0	0	0	0
A															0	0	0	0
C																0	0	0
G																	0	0
A																		0



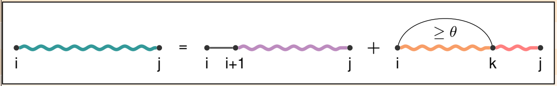
	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
G														0	0	0	0	0
A															0	0	0	0
C																0	0	0
G																	0	0
A																		0



	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
G														0	0	0	0	0
A															0	0	0	0
C																0	0	0
G																	0	0
A																		0

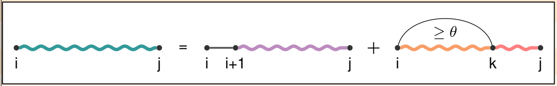


	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
G														0	0	0	0	0
A															0	0	0	0
C																0	0	0
G																	0	0
A																		0



Nussinov/Jacobson

	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	(	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
G														0	0	0	0	0
A															0	0	0	0
C																0	0	0
G																	0	0
A																		0



	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	(	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
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U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
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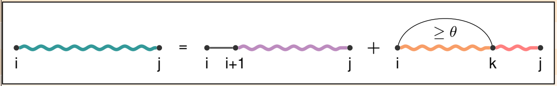
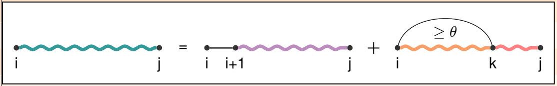
A															0	0	0	0
C																0	0	0
G																	0	0
A																		0



Nussinov/Jacobson

	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	(	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
G														0	0	0	0	0
A															0	0	0	0
C																0	0	0
G																	0	0
A																		0



	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	(	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
G														0	0	0	0	0
A															0	0	0	0
C																0	0	0
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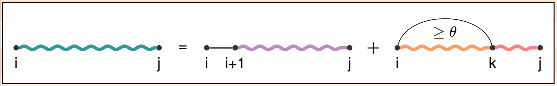
A																		0



	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	(	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
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A															0	0	0	0
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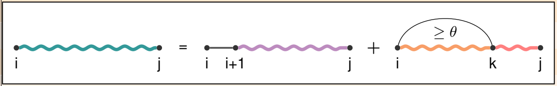

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C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
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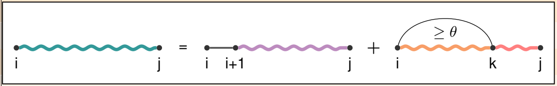

Nussinov/Jacobson

	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	(	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
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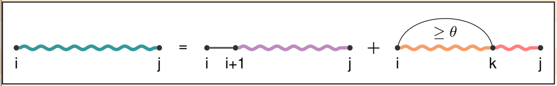

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C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
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A															0	0	0	0
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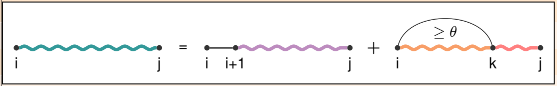

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	(	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
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U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
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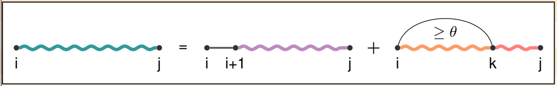

Nussinov/Jacobson

	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	(	(	.	.	.	.	.	.	.	.	.	.	.	.	.	)	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
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A															0	0	0	0
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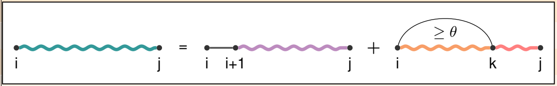

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	(	(	.	.	.	.	.	.	.	.	.	.	.	.	.	)	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
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A															0	0	0	0
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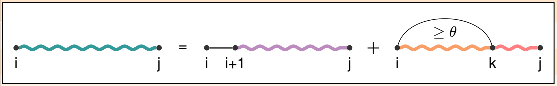

Nussinov/Jacobson

	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	(	(	.	.	.	.	.	.	.	.	.	.	.	.	.	)	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
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A															0	0	0	0
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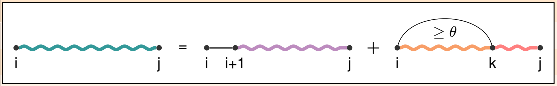

	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	(	(	(	.	.	.	)	.	.	.	.	.	.	.	.	)	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
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A															0	0	0	0
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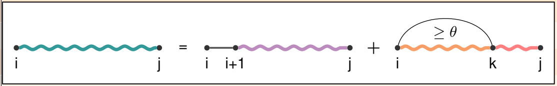

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	(	(	(	.	.	.	)	.	.	.	.	.	.	.	.	)	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
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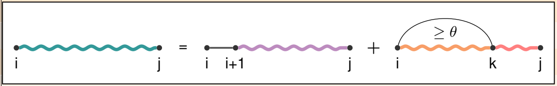

	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	(	(	(	.	.	.	)	.	.	.	.	.	.	.	.	)	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
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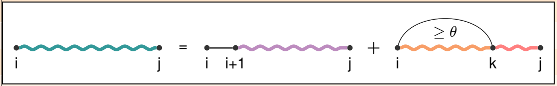

Nussinov/Jacobson

	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	(	(	(	.	.	.	)	.	.	.	.	.	.	.	.	)	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
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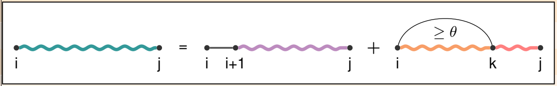

	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	(	(	(	.	.	.	)	.	.	.	.	.	.	.	.	)	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
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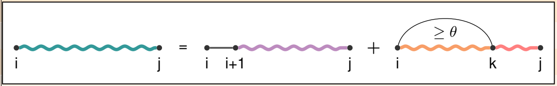

Nussinov/Jacobson

	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	(	(	(	.	.	.	)	.	.	.	.	.	.	.	.	)	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
A						0	0	0	0	0	2	2	2	5	5	5	8	8
C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
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C										0	0	0	0	3	3	3	5	5
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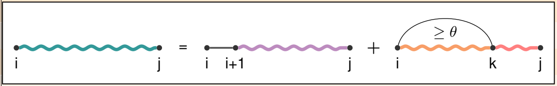

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	(	(	(	.	.	.	)	.	.	.	.	.	.	.	.	)	)	.
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G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
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U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
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C							0	0	0	0	0	0	2	5	5	5	8	8
U								0	0	0	0	0	2	3	5	5	6	7
U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
U											0	0	0	0	2	2	2	3
U												0	0	0	0	0	1	2
A													0	0	0	0	0	0
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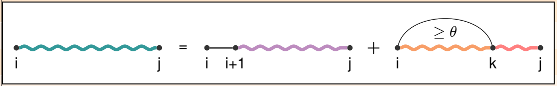

	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	(	(	(	.	.	.	)	.	(	.	.	.	.	.	)	)	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
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U									0	0	0	0	2	3	5	5	5	7
C										0	0	0	0	3	3	3	5	5
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U												0	0	0	0	0	1	2
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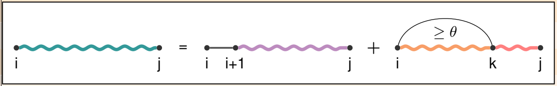

	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	(	(	(	.	.	.	)	.	(	.	.	.	.	.	)	)	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
U					0	0	0	0	0	0	2	2	4	5	7	7	8	10
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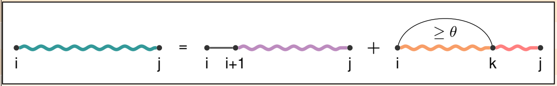

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C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
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A				0	0	0	0	2	2	2	2	4	4	5	7	7	8	10
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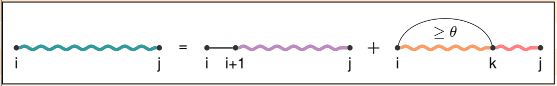

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G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
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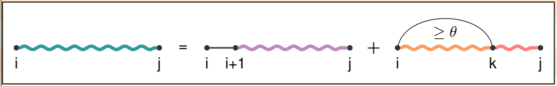

	C	G	G	A	U	A	C	U	U	C	U	U	A	G	A	C	G	A
	(	(	(	.	.	.	)	.	(	(	.	.	.	)	)	)	)	.
C	0	0	0	0	0	0	3	4	4	6	6	6	6	9	9	11	14	14
G		0	0	0	0	0	3	4	4	6	6	6	6	7	9	11	11	11
G			0	0	0	0	3	3	3	5	5	5	5	6	8	10	10	10
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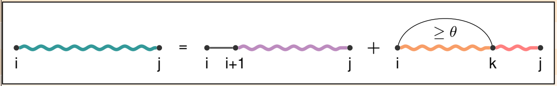
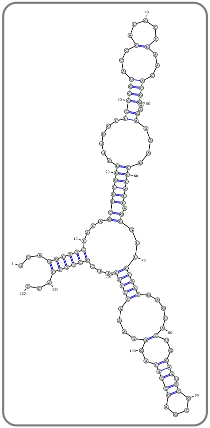


Based on unambiguous decomposition of 2^{ary} structure into loops:

- Internal loops
- Bulges
- Terminal loops
- Multi loops
- Stackings



Free-energy Δ G of a loop depend on bases, assymmetry, dangles . . .

Experimentally determined
+ Interpolated for larger loops.

Improved results by taking stacking into account.

Turner energy model

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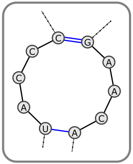

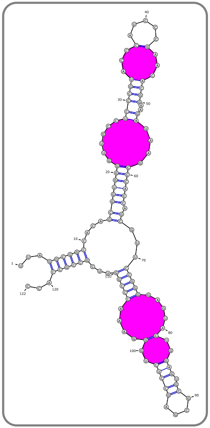

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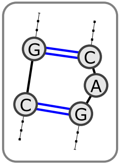

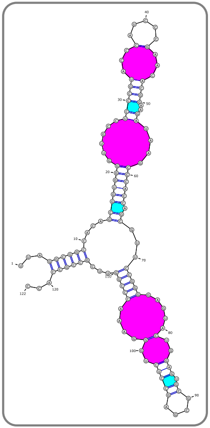

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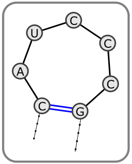

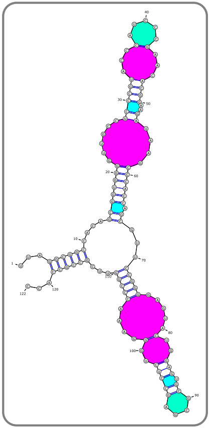

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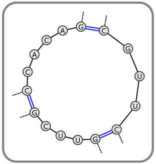

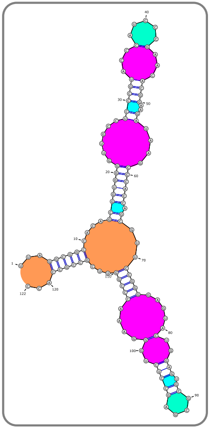

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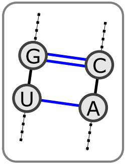

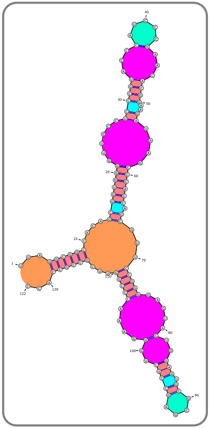

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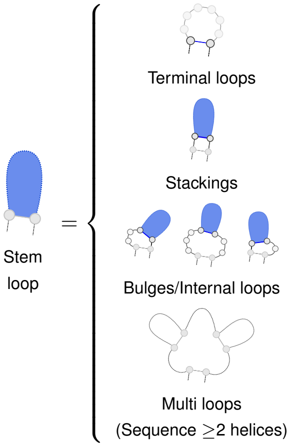
MFE DP equations



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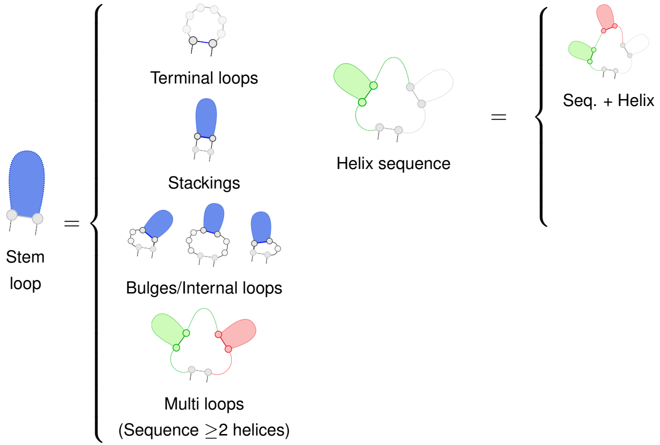

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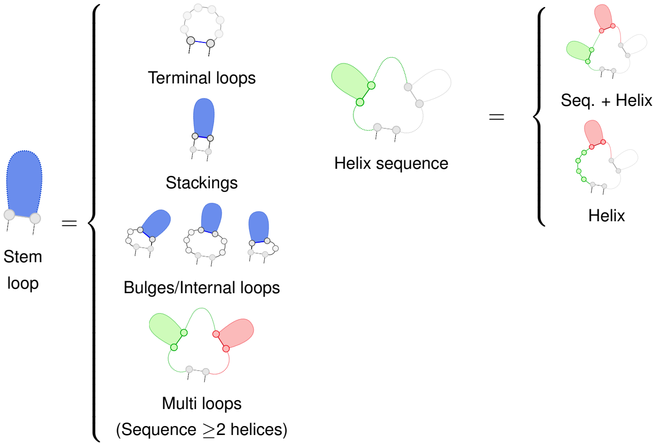

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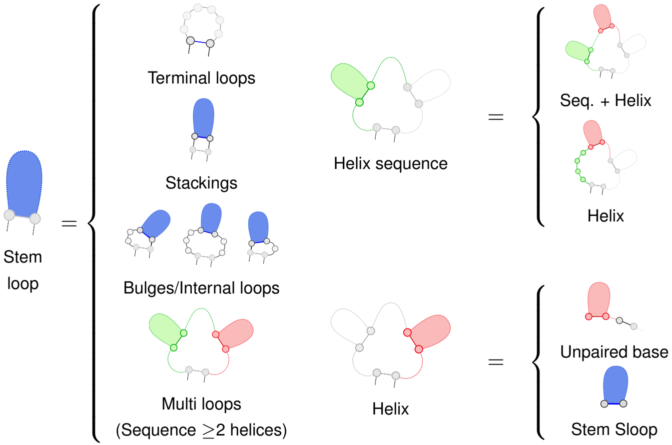
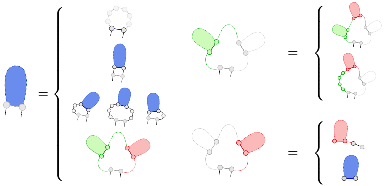


- $E_H(i,j)$: Energy of terminal loop *enclosed by* (i,j) pair
- $E_{BI}(i,j)$: Energy of bulge or internal loop *enclosed by* (i,j) pair
- $E_S(i,j)$: Energy of stacking $(i,j)/(i+1,j-1)$
- Penalty for multi loop (a), and occurrences of unpaired base (b) and helix (c) in multi loops.



DP recurrence

$$\mathcal{M}'_{i,j} = \min \begin{cases} E_H(i,j) \\ E_S(i,j) + \mathcal{M}'_{i+1,j-1} \\ \text{Min}_{i',j'}\left(E_{BI}(i,i',j',j) + \mathcal{M}'_{i',j'}\right) \\ a + c + \text{Min}_k\left(\mathcal{M}_{i+1,k-1} + \mathcal{M}^1_{k,j-1}\right) \end{cases}$$

$$\mathcal{M}_{i,j} = \text{Min}_k \left\{ \min\left(\mathcal{M}_{i,k-1}, b(k-1)\right) + \mathcal{M}^1_{k,j} \right\}$$

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Backtracking

Backtracking to reconstruct most stable structure from MFE:

$$\mathcal{M}'_{i,j} = \text{Min}\left\{\begin{array}{c} E_H(i,j) \\ E_S(i,j) + \mathcal{M}'_{i+1,j-1} \\ \text{Min}_{i',j'}(E_{BI}(i,i',j',j) + \mathcal{M}'_{i',j'}) \\ a + c + \text{Min}_k(\mathcal{M}_{i+1,k-1} + \mathcal{M}^1_{k,j-1}) \end{array}\right\}$$

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Complexity:

For each min, $\mathcal{O}(n)$ potential contributors
$\Rightarrow$ **Worst-case** complexity in $\mathcal{O}(n^2)$ for **naive backtrack**.
Keep best contributor for each Min $\Rightarrow$ **Backtracking in $\mathcal{O}(n)$**

$\Rightarrow$ UnaFold [MZ08]/RNAFold [HFS+94] compute the MFE for the Turner model in **overall**[1] time/space complexities in $\mathcal{O}(n^3)/\mathcal{O}(n^2)$

[1] Using a trick/restriction for internal loops...

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$$\mathcal{M}'_{i,j} = \text{Min}\left\{\begin{array}{c} E_H(i,j) \\ E_S(i,j) + \mathcal{M}'_{i+1,j-1} \\ \text{Min}_{i',j'}\left(E_{BI}(i,i',j',j) + \mathcal{M}'_{i',j'}\right) \\ a + c + \text{Min}_k\left(\mathcal{M}_{i+1,k-1} + \mathcal{M}^1_{k,j-1}\right) \end{array}\right\}$$

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$$\mathcal{M}^1_{i,j} = \text{Min}_k\left\{b + \mathcal{M}^1_{i,j-1}, c + \mathcal{M}'_{i,j}\right\}$$

Complexity:

For each min, $\mathcal{O}(n)$ potential contributors
$\Rightarrow$ **Worst-case** complexity in $\mathcal{O}(n^2)$ for **naive backtrack**.
Keep best contributor for each Min $\Rightarrow$ **Backtracking in $\mathcal{O}(n)$**

$\Rightarrow$ UnaFold [MZ08]/RNAFold [HFS+94] compute the MFE for the Turner model in **overall**[1] time/space complexities in $\mathcal{O}(n^3)/\mathcal{O}(n^2)$

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