

Cours M2 BIBS - Séance 1

Repliement *in silico* de l'ARN

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. . . ou comment gagner 1 million de dollars en rendant la monnaie !!

Problème : Vous disposez de pièces de **1**, **20** et **50** centimes. Le client souhaite minimiser la monnaie reçue (en nombre de pièces).

Comment rendre **N** en monnaie sans perdre un client ?

Stratégie 1 : Commencer par les *grosses* pièces puis compléter avec les *petites*.

$$21 = ??$$

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$$55 = \text{€50} + \text{€5} + \text{€5} + \text{€5} + \text{€5} + \text{€5}$$

60??

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$$60 = \text{€}50 + \text{€}1 + \text{€}1 + \text{€}1 + \text{€}1 + \text{€}1 + \text{€}1 + \text{€}1 + \text{€}1 + \text{€}1 + \text{€}1 ??$$

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$$= \text{€20} + \text{€20} + \text{€20} !$$

Problème *a priori* (?!) non-résolvable en général par une approche *gloutonne* car problème plus simple NP-complet (Existe t il même une façon efficace de rendre la monnaie ? \Rightarrow 1M\$).

Stratégie 2 : Il existe une récurrence donnant le nombre minimal de pièce :

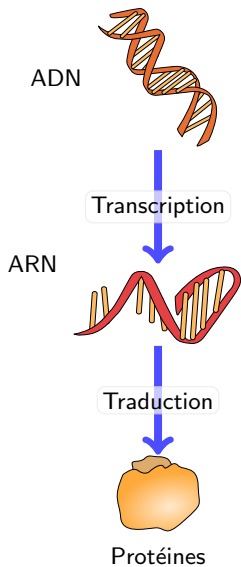
$$NbPieces(N) = \text{Min} \begin{cases} \text{1€} & \rightarrow 1 + NbPieces(N - 1) \\ \text{2€} & \rightarrow 1 + NbPieces(N - 20) \\ \text{5€} & \rightarrow 1 + NbPieces(N - 50) \end{cases}$$

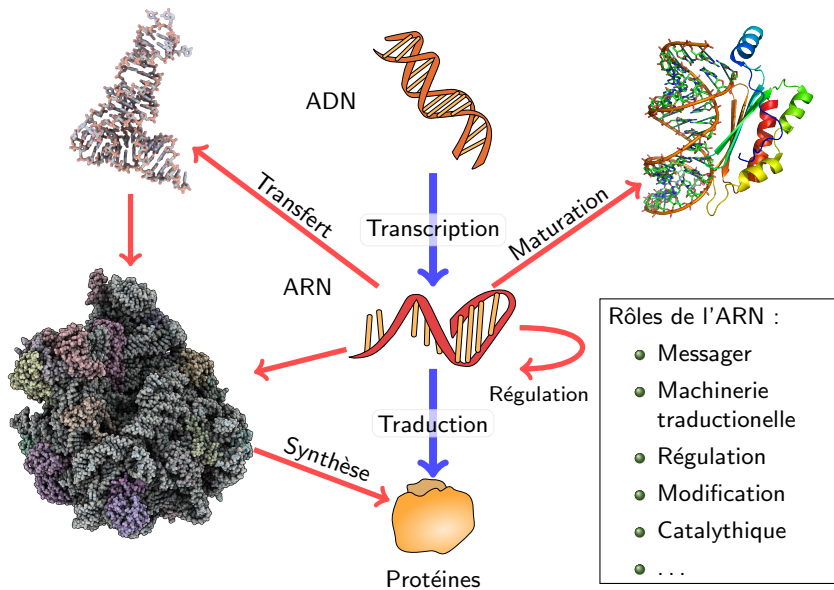
Avec un peu de mémoire (N résultats intermédiaires/cas à retenir), on peut alors répondre après $N \times \#Pièces$ calculs.

Remarque : On n'a pas gagné le million, car N a une valeur **exponentielle sur son codage**. Cet algorithme est donc en temps **exponentiel** au regard de la théorie de la complexité.

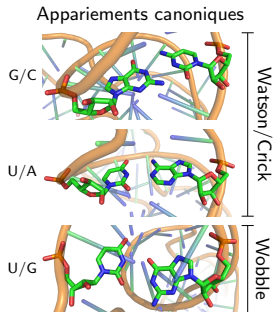
Mais on a **optimisé, en évitant un parcours exhaustif** de l'arbre des possibles :
 \Rightarrow Programmation dynamique.

- 1 Introduction
 - Fonction(s) de l'ARN
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ARN = Biopolymère composé de nucléotides A,C,G et U
A : Adénosine, C : Cytosine, G : Guanine et U : Uracile



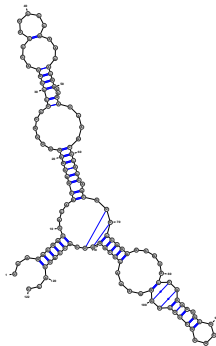
Repliement de l'ARN = Processus stochastique continu dirigé par (résultant en) un appariement des nucléotides.

Comprendre le repliement des ARN aide à comprendre et prédire leur fonction.

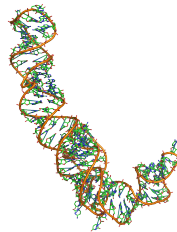
Trois¹ niveaux de représentation :

```
UUAGCGGCCACAGC
GGUGGGGUUGCCUCC
CGUACCCAUCCGAA
CACGGAAGAUAGCC
CACCAGCGUCCGGG
GAGUACUGGAGUGCG
CGAGCCUCUGGAAA
CCCGGUUCGCCCA
CC
```

Structure primaire



Structure secondaire



Structure tertiaire

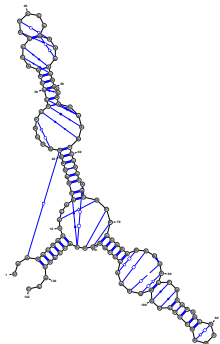
Source : 5s rRNA (PDB 1K73 :B)

1. Enfin, presque ...

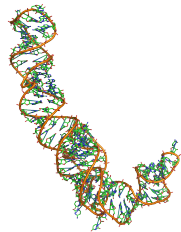
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UUAGCGGCCACAGC
GGUGGGGUUGCCUCC
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GAGUACUGGAGUGCG
CGAGCCUCUGGAAA
CCCGGUUCGCCCA
CC
```

Structure primaire



Structure secondaire⁺



Structure tertiaire

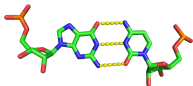
Source : 5s rRNA (PDB 1K73 :B)

1. Enfin, presque ...

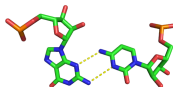
- Appariements non-canoniques

Toute paire de base **autre que** $\{(A-U), (C-G), (G-U)\}$

Ou interagissant sur un bord non-standard (WC/WC-Cis) [LW01].



Paire CG canonique (WC/WC-Cis)



Paire CG non canonique (Sucre/WC-Trans)

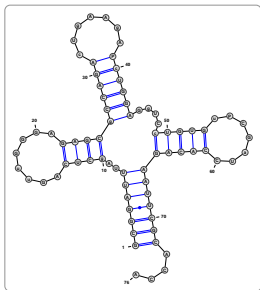
- Pseudonoeuds



Structure pseudonoeud d'un Ribozyme du Groupe I (PDBID : 1Y0Q :A)

Plus expressif, mais repliement général *in silico* avec pseudonoeud :

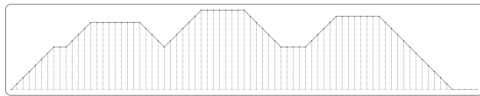
⇒ NP-Complexe [LP00] ... polynomial pour certaines classes [CDR⁺04].



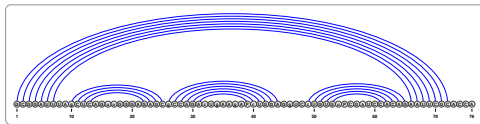
Graphe planaire (outer planar)

((((((...(((.....))))))(((.....))))))...(((.....))))))....

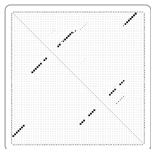
Expression bien parenthésée



Mountain view



Linéaire



Dot plot

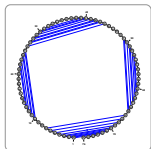
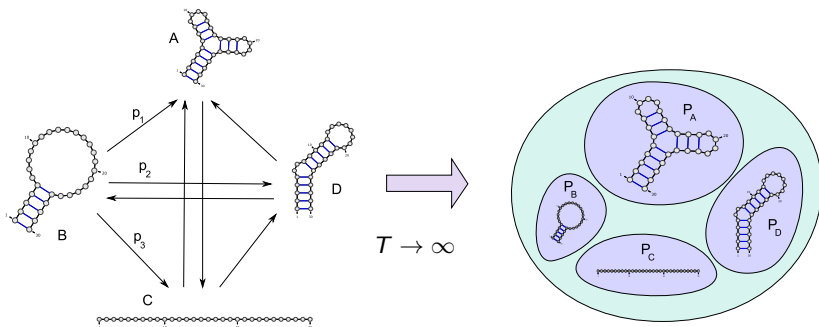


Diagramme de Feynman

Représentation différentes et équivalentes
⇒ Aide l'intuition algorithmique
+ Propriétés algébriques sympathiques
⇒ Algorithmique efficace !

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A l'échelle nanoscopique, la structure de l'ARN *fluctue*.



Convergence vers une **distribution stationnaire** de probabilité, l'**équilibre de Boltzmann**, où la probabilité est exponentiellement faible sur l'**énergie libre**.

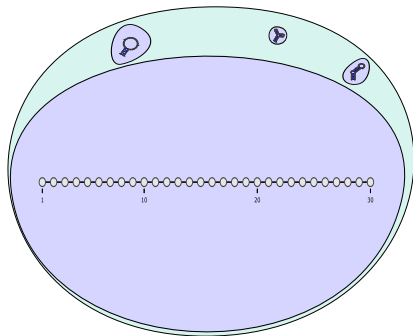
Corollaire : La conformation initiale est sans d'importance.

Problèmes soulevés :

Étant donnés des modèles pour l'**ensemble des conformations** et l'**énergie libre**.

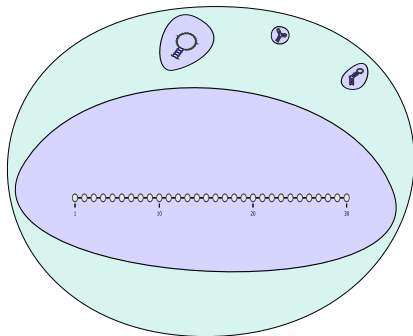
- Déterminer la structure la plus probable (= Énergie libre minimale) à l'équilibre
- Déterminer des propriétés moyennes de l'ensemble de Boltzmann

Transcription : ARN synthétisé sans appariement (Sauf exception)



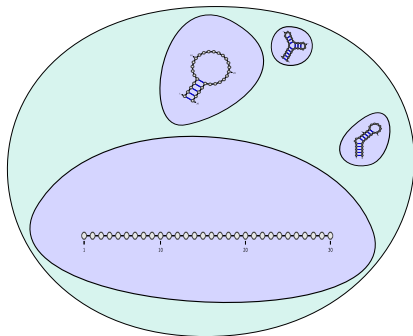
$T = 0$

Transcription : ARN synthétisé sans appariement (Sauf exception)



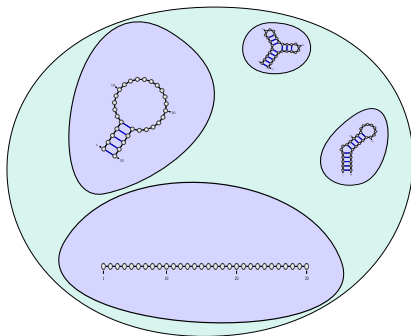
$T = 1h$

Transcription : ARN synthétisé sans appariement (Sauf exception)



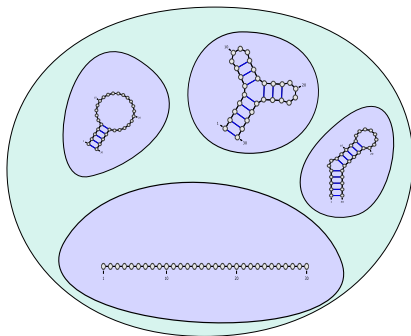
$$T = 2h$$

Transcription : ARN synthétisé sans appariement (Sauf exception)



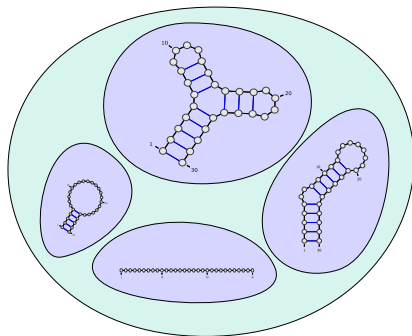
$T = 5h$

Transcription : ARN synthétisé sans appariement (Sauf exception)



$$T = 10h$$

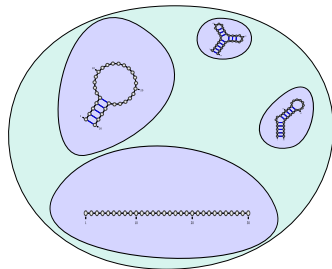
Transcription : ARN synthétisé sans appariement (Sauf exception)



$$T \rightarrow \infty$$

Mais majorité des ARNm dégradés avant 7h (Org. : Souris [SSN⁺09]).

Transcription : ARN synthétisé sans appariement (Sauf exception)



$T = 10h$

Mais majorité des ARNm dégradés avant 7h (Org. : Souris [SSN⁺09]).

- A. Déterminer la structure la plus probable (= Energie libre min.) à l'équilibre
- B. Déterminer des propriétés moyennes de l'ensemble de Boltzmann
- C. Déterminer la structure la plus probable à temps T .
(c.f. H. Isambert par simulation, NP-complet en déterministe [MTSC09])

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Programmation dynamique = Technique générale pour l'optimisation.

Condition : Solution optimale pour P peut être reconstruite à partir de solutions pour des sous-problèmes strictes de P .

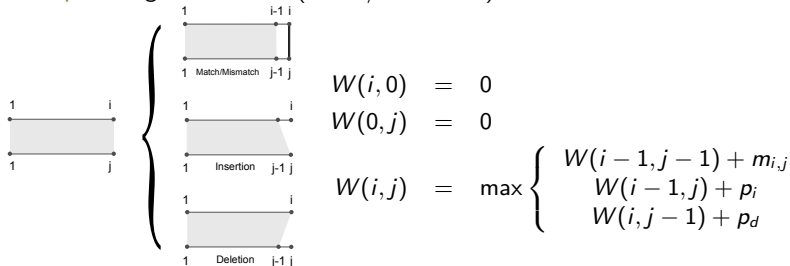
Bioinformatique :

Espace de solutions *discret* (alignements, repliements)

+ Fonction objectif *additive* (score, énergie)

⇒ Schéma de programmation dynamique efficace.

Exemple : Alignement local (Smith/Waterman)



Un schéma fait intervenir des *classes* de sous-problèmes dont on sait calculer le score du *champion*.

Étant donné un schéma, deux étapes :

- **Calcul matrices** : Sauvegarde des meilleurs scores sur classes de sous-problèmes (Ordre inverse de celui induit par les dépendances).
- **Remontée** : Reconstitue le parcours ayant mené au meilleur score. (Parcours = Instance)

Complexité du calcul dépend alors :

- **Taille** de l'espace des sous-problèmes
- **Nombres** de sous-problèmes considérés (#Termes décomposition)

Exemple S/W :

$$i : 1 \rightarrow n + 1 \Rightarrow \Theta(n)$$

$$j : 1 \rightarrow m + 1 \Rightarrow \Theta(m)$$

Trois opération pour chaque sous-calcul

$\Rightarrow \Theta(m.n)$ temps/mémoire



Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 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 | | | | | | | | |

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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 | | | | | | | | |

Exemple : Alignement local de séquences AGCACACA et 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 | 1 | | | | | | |
| G | 0 | | | | | | | | |
| C | 0 | | | | | | | | |
| A | 0 | | | | | | | | |
| C | 0 | | | | | | | | |
| A | 0 | | | | | | | | |
| C | 0 | | | | | | | | |
| A | 0 | | | | | | | | |

Diagram illustrating the dynamic programming table for local sequence alignment. The table shows the alignment of AGCACACA (row) and ACACACTA (column). The value 2 is highlighted in the cell (A, C), indicating a match. Red arrows point from the 2 to the 1 in the cell (A, A) and from the 1 to the 0 in the cell (A, T). A black arrow points from the 0 in the cell (A, C) to the 2 in the cell (A, C).

Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

| | | A | C | A | C | A | C | T | A |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 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 | | | | | | | | |
| A | 0 | | | | | | | | |

Diagram illustrating the dynamic programming table for local sequence alignment. The table shows the maximum score $W(i, j)$ for aligning the prefix of length i of the first sequence (AGCACACA) with the prefix of length j of the second sequence (ACACACTA). The table is filled with 0s, indicating that the maximum score is 0 for all prefixes. Red arrows highlight the path from $(0,0)$ to $(1,2)$ (score 2), then to $(1,3)$ (score 1), and finally to $(1,4)$ (score 2).

Exemple : Alignement local de séquences AGCACACA et ACACA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

$$W(i, 0) = 0$$

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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 | | | | |
| G | 0 | | | | | | | | |
| C | 0 | | | | | | | | |
| A | 0 | | | | | | | | |
| C | 0 | | | | | | | | |
| A | 0 | | | | | | | | |
| C | 0 | | | | | | | | |
| A | 0 | | | | | | | | |

Diagram illustrating the dynamic programming table for local sequence alignment. The table shows the alignment of the sequence AGCACACA (rows) against the sequence ACACA (columns). The values in the table represent the maximum score for the alignment up to that point. Red arrows indicate the path of the optimal alignment: (0,0) to (1,1) to (2,2) to (3,3) to (4,4). A grey arrow points from (1,4) to (1,5), and a black arrow points from (1,5) to (2,5).

Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

| | | 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 | | | | | | | | |
| A | 0 | | | | | | | | |
| C | 0 | | | | | | | | |
| A | 0 | | | | | | | | |
| C | 0 | | | | | | | | |
| A | 0 | | | | | | | | |

Diagram illustrating the dynamic programming table for local sequence alignment. The table shows the alignment of AGCACACA (row 1) and ACACACTA (row 2). Red arrows indicate the path of the optimal alignment: (0,0) to (1,1), (1,1) to (1,2), (1,2) to (1,3), (1,3) to (1,4), (1,4) to (1,5), (1,5) to (1,6), (1,6) to (1,7), (1,7) to (1,8), and (1,8) to (1,9). The values in the table represent the maximum score for each subproblem.

Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

| | | 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 | | | | | | | | |
| A | 0 | | | | | | | | |
| C | 0 | | | | | | | | |
| A | 0 | | | | | | | | |
| C | 0 | | | | | | | | |
| A | 0 | | | | | | | | |

Diagram illustrating the dynamic programming table for local sequence alignment. The table shows the alignment of the sequences AGCACACA (top row) and ACACACTA (left column). The values in the cells represent the maximum score for the alignment up to that point. Red arrows indicate the path of the optimal alignment: (0,0) to (1,1), (1,1) to (2,2), (2,2) to (3,3), (3,3) to (4,4), (4,4) to (5,5), (5,5) to (6,6), (6,6) to (7,7), (7,7) to (8,8), and (8,8) to (9,9).

Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

| | | 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 | | | | | | | | |
| C | 0 | | | | | | | | |
| A | 0 | | | | | | | | |
| C | 0 | | | | | | | | |
| A | 0 | | | | | | | | |

Diagram illustrating the dynamic programming table for local sequence alignment. The table shows the maximum score $W(i, j)$ for aligning the prefix of length i of the first sequence (AGCACACA) with the prefix of length j of the second sequence (ACACACTA). Red arrows indicate the optimal path from the top-left cell (0,0) to the bottom-right cell (3,3), showing matches (A-C, C-A, A-C) and insertions/deletions (G, T, A).

Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

| | | 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 | | | | | | | | |
| A | 0 | | | | | | | | |
| C | 0 | | | | | | | | |
| A | 0 | | | | | | | | |

Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

| | | 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 |

Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

| | | A | C | A | C | A | C | T | A |
|---|---|---|---|---|---|----|----|----|----|
| 0 | 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 |

Exemple : Alignement local de séquences AGCACACA et ACACACTA

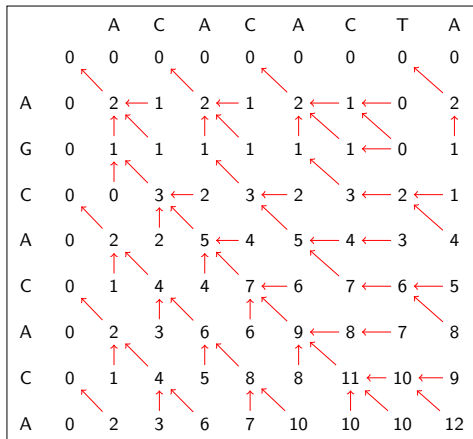
Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

Meilleur alignement



Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

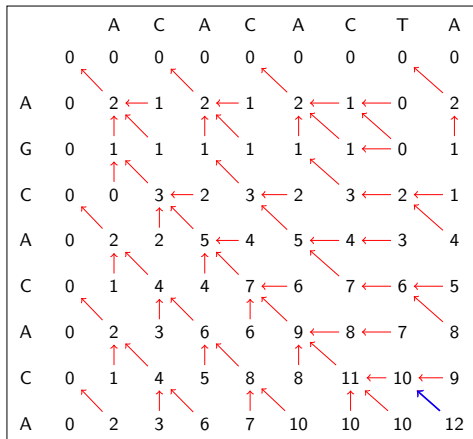
$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

Meilleur alignement

A
A



Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

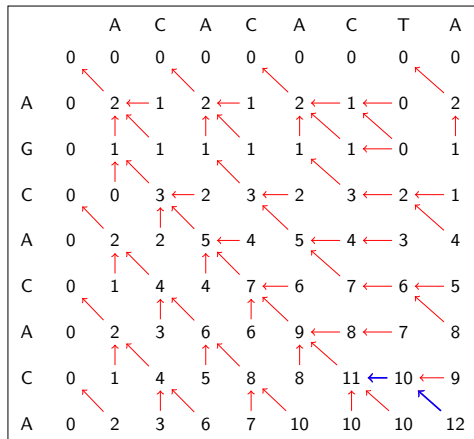
$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

Meilleur alignement

- A
T A



Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

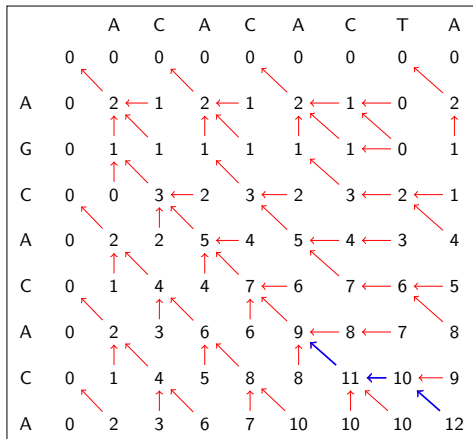
$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

Meilleur alignement

C - A
C T A



Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

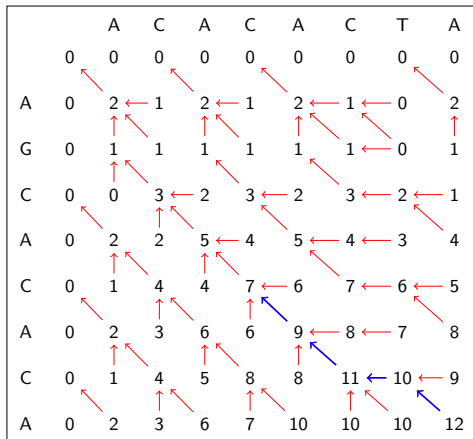
$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

Meilleur alignement

A C - A
A C T A



Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

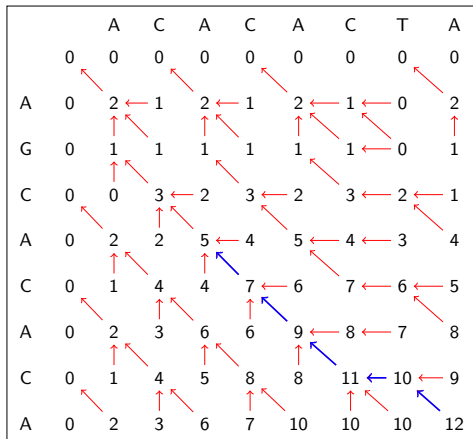
$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

Meilleur alignement

C A C - A
C A C T A



Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

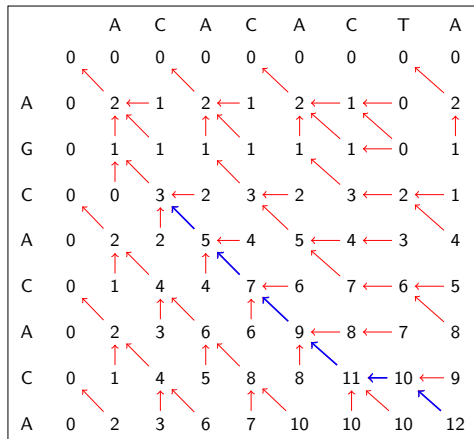
$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

Meilleur alignement

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



Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

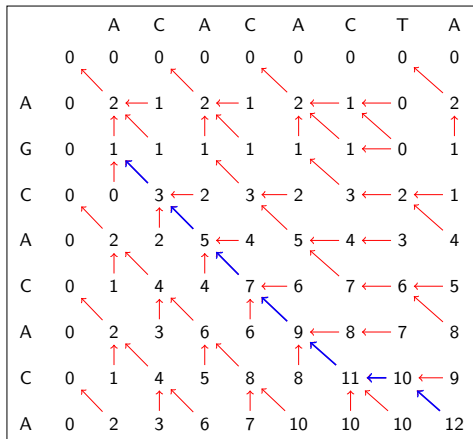
$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

Meilleur alignement

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



Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

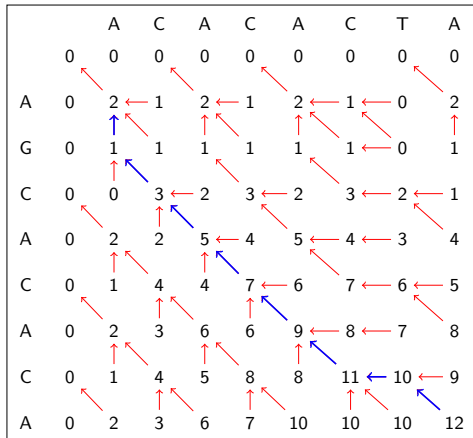
$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

Meilleur alignement

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



Exemple : Alignement local de séquences AGCACACA et ACACACTA

Coûts : Match $m_{i,j} = +2$, Insertion/Déletion $p_i = p_j = -1$

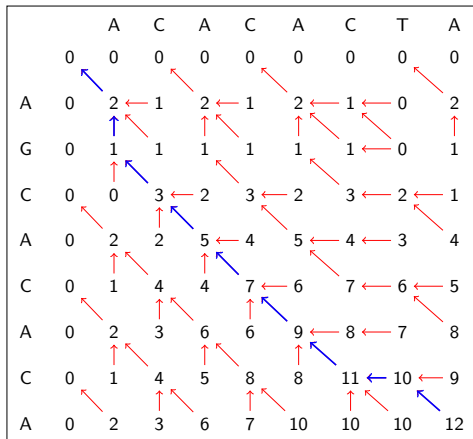
$$W(i, 0) = 0$$

$$W(0, j) = 0$$

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

Meilleur alignement

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



Propriétés requise d'un schéma :

- **Validité** : \forall sous-problème, la valeur obtenue doit être celle de la fonction objectif.

Preuve souvent assez technique.

Propriétés souhaitables d'un schéma :

- **Complétude** : Espace des solutions engendré par la décomposition.
Des astuces algorithmiques peuvent *couper des branches* . . .
- **Non-ambiguïté** : Chaque solution est *engendrée* au plus une fois.

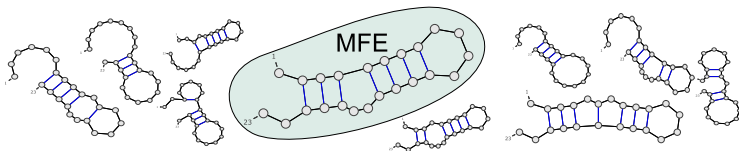
\Rightarrow Possibilité d'**énumérer** l'espace des solutions.

- 1 Introduction
 - Fonction(s) de l'ARN
 - Repliement et structure
 - Représentations de la structure secondaire
- 2 Formalisation du repliement et outils disponibles
 - Aparté thermodynamique
 - Programmation dynamique : Rappels
- 3 Minimisation de l'énergie libre
 - Modèle de Nussinov
 - Modèle de Turner
 - MFold/Unafold
 - Performances et approches comparatives
 - Vers une prédiction ab-initio 3D

Problème A : Déterminer la structure d'énergie minimale.

Repliement *ab initio* =

Trouver structure d'un ARN ω uniquement à partir de sa séquence.



- **Conformations** : Ensemble S_ω des structures secondaires compatibles avec la structure primaire ω (contrainte d'appariements).
- **Fonction d'énergie** Énergie libre associant une valeur numérique $E_{\omega,S}$ (KCal.mol^{-1}) à tout couple séquence/conformation (ω, S) .
- **Structure native** : Conformation *fonctionnelle* de la molécule.

Remarques :

- Pas nécessairement unique (Cinétique ou structures bi-stables)
- Présence de pseudo-noeuds : Ambiguïté, quelle est la structure native ?

Modèle de Nussinov/Jacobson (NJ)

Plus proche voisins simple :

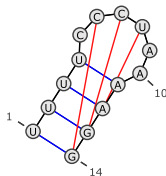
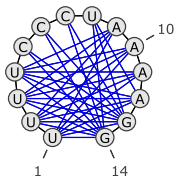
- Seuls les appariements contribuent à l'énergie
- Uniquement liaisons Watson/Crick (A/U,C/G) et Wobble (G/U)

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

Repliement dans NJ \Leftrightarrow Maximisation du nombre de paires de bases.

Exemple :

UUUJCCCUAAAAGG

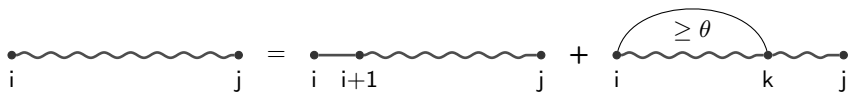


Variante : Pondérer les paires selon leur nombre de liaisons hydrogène

$$\Delta G(G \equiv C) = -3$$

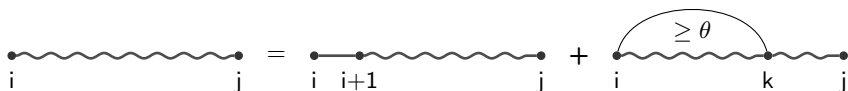
$$\Delta G(A = U) = -2$$

$$\Delta G(G - U) = -1$$



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

$$N_{i,j} = \min \begin{cases} N_{i+1,j} & i \text{ non apparié} \\ \min_{k=i+\theta+1}^j E_{i,k} + N_{i+1,k-1} + N_{k+1,j} & i \text{ apparié à } k \end{cases}$$



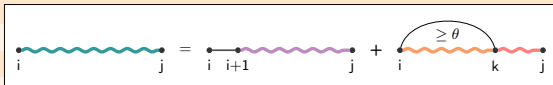
$$N_{i,t} = 0, \quad \forall t \in [i, i + \theta]$$

$$N_{i,j} = \min \begin{cases} N_{i+1,j} & i \text{ non apparié} \\ \min_{k=i+\theta+1}^j E_{i,k} + N_{i+1,k-1} + N_{k+1,j} & i \text{ apparié à } k \end{cases}$$

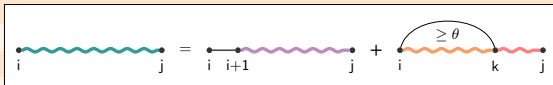
Correction : On cherche à montrer que l'énergie de la structure d'énergie la plus faible ($MFE_{1,n}$) est bien calculée dans $N_{1,n}$. Dans toute structure secondaire restreinte à $[i, j]$ la première position i est :

- **Soit non-appariée :** $MFE_{i,j}$ est constituée des appariements de $MFE_{i+1,j}$.
- **Soit appariée à k :** $MFE_{i,j}$ contient l'appariement (i, k) et l'union des appariements de $MFE_{i+1,k-1}$ et de $MFE_{k+1,j}$. En effet, tout appariement entre les régions $[i + 1, k - 1]$ et $[k + 1, j]$ **croiserait** (i, k) (Pseudonoed).

| | 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 | |

$$\text{Sequence } i \dots j = \text{Sequence } i \dots i+1 \dots j + \max_{i < k < j} \{ \text{Sequence } i \dots k-1, \text{Sequence } k \dots j \}$$

| | 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 | 2 | 2 | 4 | 5 | 7 | 7 | 8 | 8 | 10 | |
| A | | | | | | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 5 | 5 | 5 | 8 | 8 | 8 | |
| C | | | | | | | 0 | 0 | 0 | 0 | 0 | 2 | 5 | 5 | 5 | 8 | 8 | 8 | |
| U | | | | | | | | 0 | 0 | 0 | 0 | 2 | 3 | 5 | 5 | 6 | 7 | 7 | |
| U | | | | | | | | | 0 | 0 | 0 | 2 | 3 | 5 | 5 | 5 | 7 | 7 | |
| C | | | | | | | | | | 0 | 0 | 0 | 3 | 3 | 3 | 5 | 5 | 5 | |
| U | | | | | | | | | | | 0 | 0 | 0 | 2 | 2 | 2 | 3 | 3 | |
| U | | | | | | | | | | | | 0 | 0 | 0 | 0 | 1 | 2 | 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 | |

$i \text{---} j = i \text{---} i+1 \text{---} j + i \text{---} k \text{---} j$

$\geq \theta$

| | 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 | |

$i \text{---} j = i \text{---} i+1 \text{---} j + i \text{---} k \text{---} j$

$\geq \theta$

| | 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 |

$i \text{---} j = i \text{---} i+1 \text{---} j + i \text{---} k \text{---} j$

$\geq \theta$

| | 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 | 2 | 2 | 4 | 5 | 7 | 7 | 8 | 10 | | |
| A | | | | | | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 5 | 5 | 5 | 8 | 8 | | |
| C | | | | | | | 0 | 0 | 0 | 0 | 0 | 2 | 5 | 5 | 5 | 8 | 8 | | |
| U | | | | | | | | 0 | 0 | 0 | 0 | 2 | 3 | 5 | 5 | 6 | 7 | | |
| U | | | | | | | | | 0 | 0 | 0 | 2 | 3 | 5 | 5 | 5 | 7 | | |
| C | | | | | | | | | | 0 | 0 | 0 | 3 | 3 | 3 | 5 | 5 | | |
| U | | | | | | | | | | | 0 | 0 | 0 | 2 | 2 | 2 | 3 | | |
| U | | | | | | | | | | | | 0 | 0 | 0 | 0 | 1 | 2 | | |
| A | | | | | | | | | | | | | 0 | 0 | 0 | 0 | 0 | | |
| G | | | | | | | | | | | | | | 0 | 0 | 0 | 0 | | |
| A | | | | | | | | | | | | | | | 0 | 0 | 0 | | |
| C | | | | | | | | | | | | | | | | 0 | 0 | | |
| G | | | | | | | | | | | | | | | | | 0 | | |
| A | | | | | | | | | | | | | | | | | | 0 | |

$i \text{---} j = i \text{---} i+1 \text{---} j + i \text{---} k \text{---} j$

The diagram shows a sequence of nucleotides from index i to j . This is decomposed into:

- A sequence from i to $i+1$ (represented by a purple wavy line).
- A sequence from $i+1$ to j (represented by a blue wavy line).
- A sequence from i to k (represented by an orange wavy line) with a loop back to j (represented by a red wavy line). The loop length is indicated as $\geq \theta$.

| | 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 | 2 | 2 | 4 | 5 | 7 | 7 | 8 | 10 | | |
| A | | | | | | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 5 | 5 | 5 | 8 | 8 | | |
| C | | | | | | | 0 | 0 | 0 | 0 | 0 | 2 | 5 | 5 | 5 | 8 | 8 | | |
| U | | | | | | | | 0 | 0 | 0 | 0 | 2 | 3 | 5 | 5 | 6 | 7 | | |
| U | | | | | | | | | 0 | 0 | 0 | 2 | 3 | 5 | 5 | 5 | 7 | | |
| C | | | | | | | | | | 0 | 0 | 0 | 3 | 3 | 3 | 5 | 5 | | |
| U | | | | | | | | | | | 0 | 0 | 0 | 2 | 2 | 2 | 3 | | |
| U | | | | | | | | | | | | 0 | 0 | 0 | 0 | 1 | 2 | | |
| A | | | | | | | | | | | | | 0 | 0 | 0 | 0 | 0 | | |
| G | | | | | | | | | | | | | | 0 | 0 | 0 | 0 | | |
| A | | | | | | | | | | | | | | | 0 | 0 | 0 | | |
| C | | | | | | | | | | | | | | | | 0 | 0 | | |
| G | | | | | | | | | | | | | | | | | 0 | | |
| A | | | | | | | | | | | | | | | | | | 0 | |

$i \text{---} j = i \text{---} i+1 \text{---} j + i \text{---} k \text{---} j$

$\geq \theta$

| | 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 |

Diagram illustrating the Nussinov/Jacobson algorithm for RNA secondary structure prediction. It shows a sequence from index i to j . The sequence is partitioned into two parts: a subsequence from i to $i+1$ and a subsequence from $i+1$ to j . The second part is further partitioned into a subsequence from $i+1$ to k and a subsequence from k to j . A curved arrow above the subsequence from $i+1$ to k is labeled with the inequality $\geq \theta$, representing a minimum energy gap constraint.

| | 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 | |

$$i \text{---} j = i \text{---} i+1 \text{---} j + i \text{---} k \text{---} j \quad (\text{with } i \text{---} k \text{ having } \geq \theta)$$

| | 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 | |

$i \text{---} \dots \text{---} j = i \text{---} i+1 \text{---} \dots \text{---} j + i \text{---} \overset{\geq \theta}{\text{loop}} \text{---} k \text{---} \dots \text{---} j$

| | 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 | |

Diagram illustrating the decomposition of a sequence from i to j into a sequence from i to $i+1$ and a sequence from i to k to j , with a loop of size $\geq \theta$ between i and k .

| | 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 | 2 | 2 | 4 | 5 | 7 | 7 | 8 | 10 | 10 | |
| A | | | | | | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 5 | 5 | 5 | 8 | 8 | 8 | |
| C | | | | | | | 0 | 0 | 0 | 0 | 0 | 2 | 5 | 5 | 5 | 8 | 8 | 8 | |
| U | | | | | | | | 0 | 0 | 0 | 0 | 2 | 3 | 5 | 5 | 6 | 7 | 7 | |
| U | | | | | | | | | 0 | 0 | 0 | 2 | 3 | 5 | 5 | 5 | 7 | 7 | |
| C | | | | | | | | | | 0 | 0 | 0 | 3 | 3 | 3 | 5 | 5 | 5 | |
| U | | | | | | | | | | | 0 | 0 | 0 | 2 | 2 | 2 | 3 | 3 | |
| U | | | | | | | | | | | | 0 | 0 | 0 | 0 | 1 | 2 | 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 | |

$i \text{---} j = i \text{---} i+1 \text{---} j + i \text{---} k \text{---} j$

$\geq \theta$

| | 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 | |

Diagram illustrating the Nussinov-Jacobson dynamic programming recurrence. It shows a sequence of nucleotides from index i to j . The sequence is partitioned into two parts: a subsequence from i to $i+1$ and a subsequence from $i+1$ to j . The second part is further partitioned into a subsequence from $i+1$ to k and a subsequence from k to j . A curved arrow above the subsequence from $i+1$ to k is labeled with the inequality $\geq \theta$, indicating a minimum energy threshold for a loop structure.

| | 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 | |

$i \text{---} j = i \text{---} i+1 \text{---} j + i \text{---} k \text{---} j$

The loop from k to j is labeled $\geq \theta$.

| | 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 | 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 | |

Diagram illustrating the decomposition of a sequence from index i to j into two parts: a sequence from i to $i+1$ and a sequence from $i+1$ to j , plus a sequence from i to k with a loop of size $\geq \theta$.

| | 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 | 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 | |

$i \text{---} j = i \text{---} i+1 \text{---} j + i \text{---} k \text{---} j$

$\text{---} i \text{---} i+1 \text{---} j + i \text{---} k \text{---} j$

$\text{---} i \text{---} k \text{---} j$

| | 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 | 2 | 2 | 4 | 5 | 7 | 7 | 8 | 10 | | |
| A | | | | | | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 5 | 5 | 5 | 8 | 8 | | |
| C | | | | | | | 0 | 0 | 0 | 0 | 0 | 2 | 5 | 5 | 8 | 8 | | | |
| U | | | | | | | | 0 | 0 | 0 | 0 | 2 | 3 | 5 | 5 | 6 | 7 | | |
| U | | | | | | | | | 0 | 0 | 0 | 2 | 3 | 5 | 5 | 5 | 7 | | |
| C | | | | | | | | | | 0 | 0 | 0 | 3 | 3 | 3 | 5 | 5 | | |
| U | | | | | | | | | | | 0 | 0 | 0 | 2 | 2 | 2 | 3 | | |
| U | | | | | | | | | | | | 0 | 0 | 0 | 0 | 1 | 2 | | |
| A | | | | | | | | | | | | | 0 | 0 | 0 | 0 | 0 | | |
| G | | | | | | | | | | | | | | 0 | 0 | 0 | 0 | | |
| A | | | | | | | | | | | | | | | 0 | 0 | 0 | | |
| C | | | | | | | | | | | | | | | | 0 | 0 | | |
| G | | | | | | | | | | | | | | | | | 0 | | |
| A | | | | | | | | | | | | | | | | | | 0 | |

The diagram shows the equation: $\text{Path}(i, j) = \text{Path}(i, i+1) + \text{Path}(i+1, j)$. The path from $i+1$ to j is shown with a loop of length $\geq \theta$.

| | 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 | |

$i \text{---} j = i \text{---} i+1 \text{---} j + i \text{---} k \text{---} j$

$\geq \theta$

| | 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 | 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 | |

$i \text{---} j = i \text{---} i+1 \text{---} j + i \text{---} k \text{---} j + \overset{\geq \theta}{\text{arc}}(i, k)$

| | 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 | 2 | 2 | 4 | 5 | 7 | 7 | 8 | 10 | |
| A | | | | | | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 5 | 5 | 5 | 8 | 8 | |
| C | | | | | | | 0 | 0 | 0 | 0 | 0 | 2 | 5 | 5 | 8 | 8 | | |
| U | | | | | | | | 0 | 0 | 0 | 0 | 2 | 3 | 5 | 5 | 6 | 7 | |
| U | | | | | | | | | 0 | 0 | 0 | 2 | 3 | 5 | 5 | 7 | | |
| C | | | | | | | | | | 0 | 0 | 0 | 3 | 3 | 3 | 5 | 5 | |
| U | | | | | | | | | | | 0 | 0 | 2 | 2 | 2 | 3 | | |
| U | | | | | | | | | | | | 0 | 0 | 0 | 0 | 1 | 2 | |
| A | | | | | | | | | | | | | 0 | 0 | 0 | 0 | 0 | |
| G | | | | | | | | | | | | | | 0 | 0 | 0 | 0 | |
| A | | | | | | | | | | | | | | | 0 | 0 | 0 | |
| C | | | | | | | | | | | | | | | | 0 | 0 | |
| G | | | | | | | | | | | | | | | | | 0 | |
| A | | | | | | | | | | | | | | | | | | 0 |

Diagram illustrating the Nussinov/Jacobson algorithm for RNA secondary structure prediction. It shows a sequence from index i to j . The sequence is partitioned into two parts: a subsequence from i to $i+1$ and a subsequence from $i+1$ to j . The second part is further partitioned into a subsequence from $i+1$ to k and a subsequence from k to j . A curved arrow above the subsequence from $i+1$ to k is labeled with the inequality $\geq \theta$, representing a minimum loop size constraint.

| | 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 | 2 | 2 | 4 | 5 | 7 | 7 | 8 | 10 | |
| A | | | | | | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 5 | 5 | 5 | 8 | 8 | |
| C | | | | | | | 0 | 0 | 0 | 0 | 0 | 2 | 5 | 5 | 5 | 8 | 8 | |
| U | | | | | | | | 0 | 0 | 0 | 0 | 2 | 3 | 5 | 5 | 6 | 7 | |
| U | | | | | | | | | 0 | 0 | 0 | 2 | 3 | 5 | 5 | 5 | 7 | |
| C | | | | | | | | | | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 5 | 5 |
| U | | | | | | | | | | | 0 | 0 | 0 | 2 | 2 | 2 | 3 | |
| U | | | | | | | | | | | | 0 | 0 | 0 | 0 | 1 | 2 | |
| A | | | | | | | | | | | | | 0 | 0 | 0 | 0 | 0 | |
| G | | | | | | | | | | | | | | 0 | 0 | 0 | 0 | |
| A | | | | | | | | | | | | | | | 0 | 0 | 0 | |
| C | | | | | | | | | | | | | | | | 0 | 0 | |
| G | | | | | | | | | | | | | | | | | 0 | |
| A | | | | | | | | | | | | | | | | | | 0 |

$$\text{Sequence } i \dots j = \text{Sequence } i \dots i+1 \dots j + \max_{k \geq i+2} \left(\text{Sequence } i \dots k \dots j \right) \text{ if } \Delta G_{i,k} \geq \theta$$

| | 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 | 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 |

$i \dots j = i \dots i+1 \dots j + i \dots k \dots j$

$\geq \theta$

| | 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 | |

Diagram illustrating the decomposition of an RNA segment from index i to j . The segment is shown as a wavy line with a green-to-purple gradient. It is equal to the sum of two segments: a straight line from i to $i+1$ and a wavy line from $i+1$ to j with a purple-to-orange gradient. The second segment is further decomposed into a wavy line from i to k and a straight line from k to j , with a curved arrow labeled $\geq \theta$ above the wavy part.

| | 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 | 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 | |

$i \text{---} j = i \text{---} i+1 \text{---} j + i \text{---} k \text{---} j$

$\geq \theta$

| | 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 | 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 | |

$$\text{Sequence } i \dots j = \max \left(\text{Sequence } i \dots i+1 + \text{Sequence } i+1 \dots j, \text{ Sequence } i \dots k + \text{Sequence } k \dots j \right)$$
 where $k \geq i+2$ and the pair (i, k) has a score $\geq \theta$.

| | 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 | |

$i \dots j = i \dots i+1 \dots j + i \dots k \dots j$

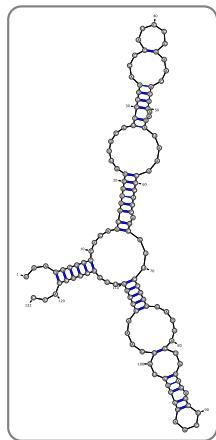
$\geq \theta$

| | 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 | |

$i \text{---} j = i \text{---} i+1 \text{---} j + i \text{---} k \text{---} j$

$\geq \theta$

Basée sur décomposition **non-ambiguë** en **boucles** de la structure 2^{aire} :



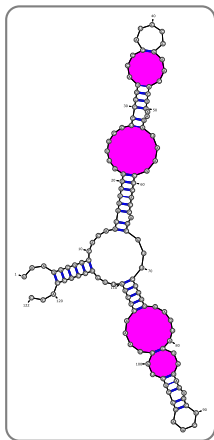
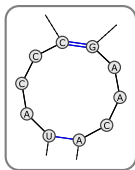
Énergies libres ΔG des boucles dépendent des bases, asymétrie, bases *libres* (dangle) ...

Déterminées expérimentalement
+ Interpolation pour grandes boucles.

Meilleure résultats grâce à la prise en compte de l'empilement.

Basée sur décomposition **non-ambiguë** en **boucles** de la structure 2^{aire} :

- Boucles internes



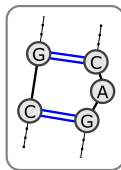
Énergies libres ΔG des boucles dépendent des bases, asymétrie, bases *libres* (dangle) ...

Déterminées expérimentalement
+ Interpolation pour grandes boucles.

Meilleure résultats grâce à la prise en compte de l'empilement.

Basée sur décomposition **non-ambiguë** en **boucles** de la structure 2^{aire} :

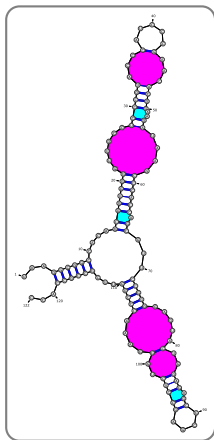
- Boucles internes
- Renflements



Énergies libres ΔG des boucles dépendent des bases, asymétrie, bases *libres* (dangle) ...

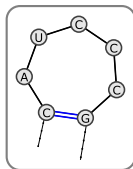
Déterminées expérimentalement
+ Interpolation pour grandes boucles.

Meilleure résultats grâce à la prise en compte de l'empilement.



Basée sur décomposition **non-ambiguë** en **boucles** de la structure 2^{aire} :

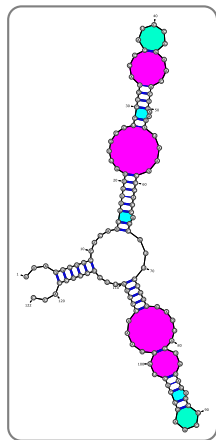
- Boucles internes
- Renflements
- Boucles terminales



Énergies libres ΔG des boucles dépendent des bases, asymétrie, bases *libres* (dangle) ...

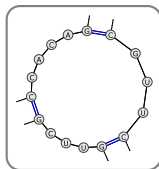
Déterminées expérimentalement
+ Interpolation pour grandes boucles.

Meilleure résultats grâce à la prise en compte de l'empilement.



Basée sur décomposition **non-ambiguë** en **boucles** de la structure 2^{aire} :

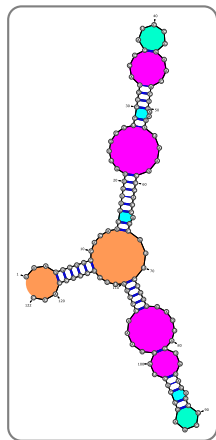
- Boucles internes
- Renflements
- Boucles terminales
- Boucles multiples



Énergies libres ΔG des boucles dépendent des bases, asymétrie, bases *libres* (dangle) ...

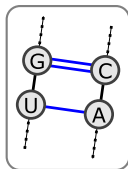
Déterminées expérimentalement
+ Interpolation pour grandes boucles.

Meilleure résultats grâce à la prise en compte de l'empilement.



Basée sur décomposition **non-ambiguë** en **boucles** de la structure 2^{aire} :

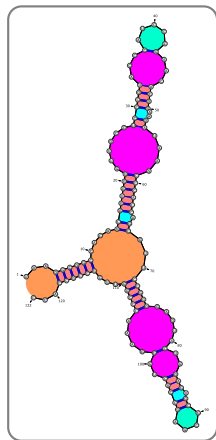
- Boucles internes
- Renflements
- Boucles terminales
- Boucles multiples
- Empilements

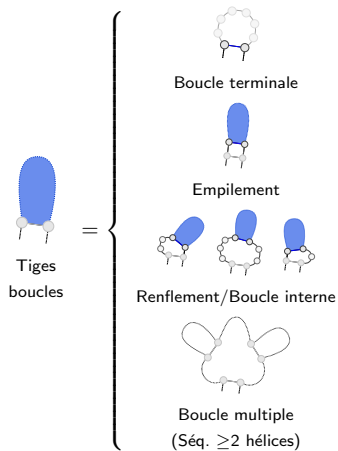


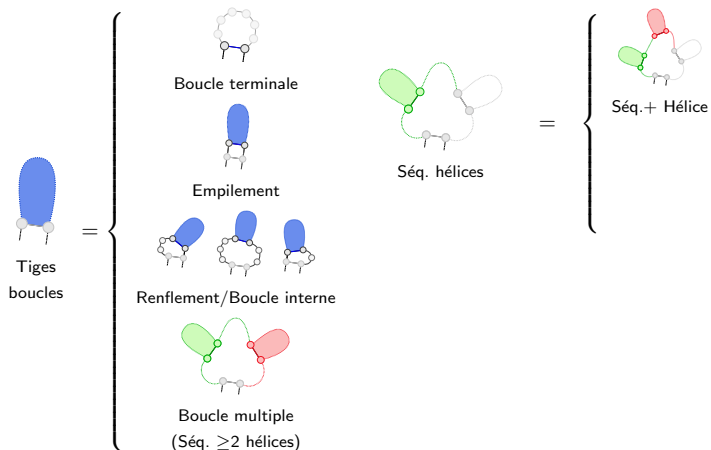
Énergies libres ΔG des boucles dépendent des bases, asymétrie, bases *libres* (dangle) ...

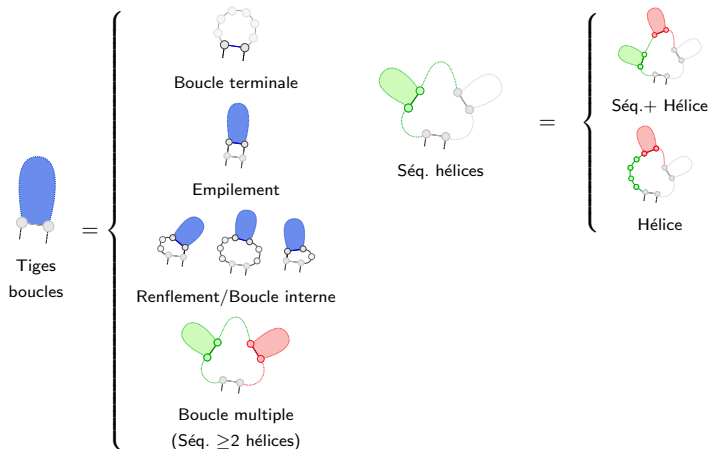
Déterminées expérimentalement
+ Interpolation pour grandes boucles.

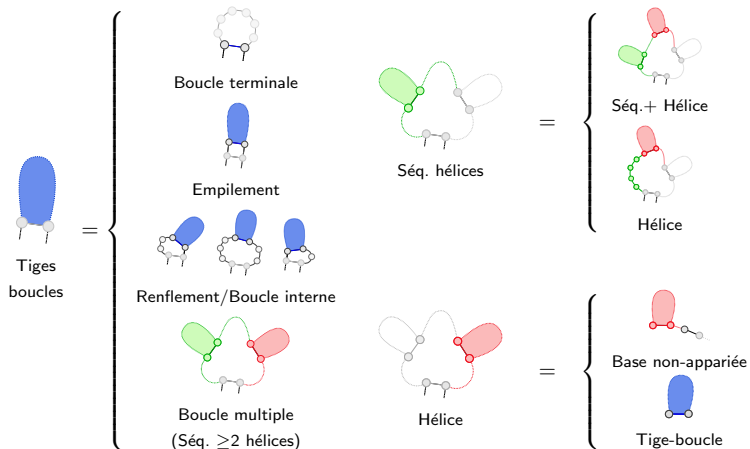
Meilleure résultats grâce à la prise en compte de l'empilement.



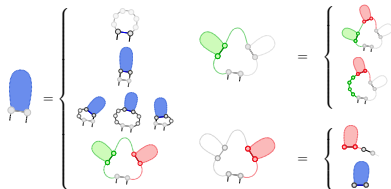








- $E_H(i, j)$: Energie de boucle terminale *fermée* par une paire (i, j)
- $E_{Bl}(i, j)$: Energie de renflement ou boucle interne *fermée* par une paire (i, j)
- $E_S(i, j)$: Energie d'empilement $(i, j)/(i + 1, j - 1)$
- a, c, b : Pénalité de boucle multiple, hélice et non-appariées dans multiboucle.



Calcul des matrices

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

Reconstruction de la structure d'énergie minimale :

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

 2. Avec une astuce pour les bulges/boucles internes ...

Reconstruction de la structure d'énergie minimale :

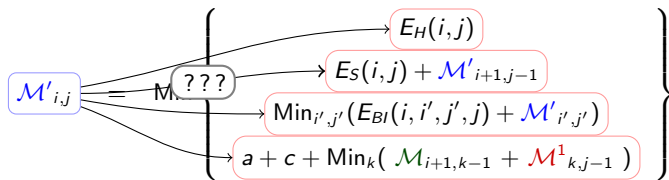
$$\mathcal{M}'_{i,j} = \text{Min} \left\{ \begin{array}{l} E_H(i,j) \\ E_S(i,j) + \mathcal{M}'_{i+1,j-1} \\ \text{Min}_{i',j'} (E_{BI}(i,i',j',j) + \mathcal{M}'_{i',j'}) \\ a + c + \text{Min}_k (\mathcal{M}_{i+1,k-1} + \mathcal{M}^1_{k,j-1}) \end{array} \right\}$$

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

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

2. Avec une astuce pour les bulges/boucles internes ...

Reconstruction de la structure d'énergie minimale :



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

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

$\mathcal{O}(n)$ contributeurs potentiels au Min :

⇒ Complexité au pire en $\mathcal{O}(n^2)$ pour un backtrack naïf.

Reconstruction de la structure d'énergie minimale :

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

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

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

$\mathcal{O}(n)$ contributeurs potentiels au Min :

⇒ Complexité **au pire en $\mathcal{O}(n^2)$** pour un **backtrack naïf**.

Garder les meilleures contributions aux Min ⇒ **Backtrack en $\mathcal{O}(n)$**

Complexités temps/mémoire en $\mathcal{O}(n^3)/\mathcal{O}(n^2)$ pour le précalcul²

2. Avec une astuce pour les bulges/boucles internes ...

Reconstruction de la structure d'énergie minimale :

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

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

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

$\mathcal{O}(n)$ contributeurs potentiels au Min :

⇒ Complexité **au pire en $\mathcal{O}(n^2)$** pour un **backtrack naïf**.

Garder les meilleures contributions aux Min ⇒ **Backtrack en $\mathcal{O}(n)$**

Complexités temps/mémoire en $\mathcal{O}(n^3)/\mathcal{O}(n^2)$ pour le précalcul²

⇒ **UnaFold [MZ08]** calcule la structure secondaire d'énergie minimale.

2. Avec une astuce pour les bulges/boucles internes ...

Definition (Repliement ab initio)

Partant de la séquence, trouver la conformation minimisant une fonction d'énergie.

Avantages :

- Explication mécanique
- Complexité raisonnable
 $\mathcal{O}(n^3)/\mathcal{O}(n^2)$ temps/mémoire
- Exploration exhaustive

Limites :

- Pas de cinétique
- Pas d'info évolutive
- Performances limitées

Definition (Approche comparative)

Partant de plusieurs séquences homologues ou d'un alignement, trouver une conformation de score (énergie+alignement) élevé.

Avantages :

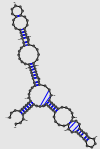
- Meilleures performances
- Affinement permanent

Limites :

- Complexité élevée
- Exploration non-exhaustive

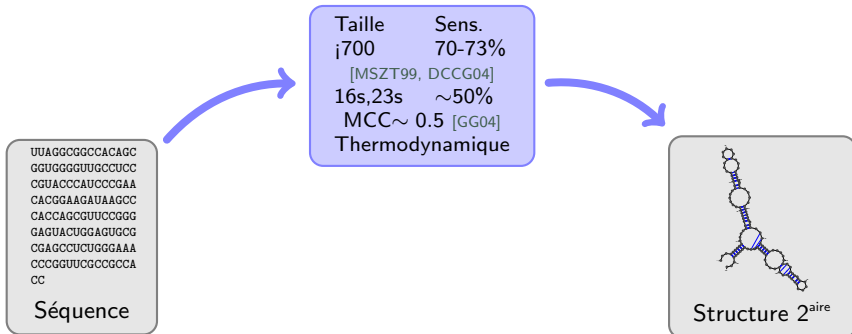
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CGUACCCAUCCCGAA  
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GAGUACUGGAGUGCG  
CGAGCCUCUGGGAAA  
CCCAGUUCGCCCA  
CC
```

Séquence

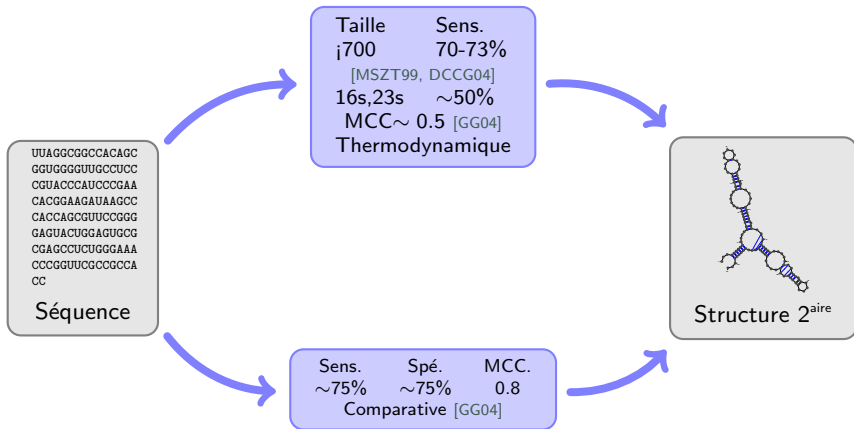


Structure 2^{aire}

$$\text{Rappel : } MCC = \frac{t^+ t^- - f^+ f^-}{\sqrt{(t^+ + f^+)(t^+ + f^-)(t^- + f^+)(t^- + f^-)}}$$



$$\text{Rappel : } MCC = \frac{t^+ t^- - f^+ f^-}{\sqrt{(t^+ + f^+)(t^+ + f^-)(t^- + f^+)(t^- + f^-)}}$$



Rappel :
$$MCC = \frac{t^+t^- - f^+f^-}{\sqrt{(t^++f^+)(t^++f^-)(t^-+f^+)(t^-+f^-)}}$$

But : De la séquence à des modèles tri-dimensionnels!!!

```
UUAGGCGGCCACAGC
GGUGGGGUUGCCUCC
CGUACCCAUCCCGAA
CACGGAAGAUAGCC
CACCAGCGUCCGGG
GAGUACUGGAGUGCG
CGAGCCUCUGGGAAA
CCCGGUUCGCCCA
CC
```

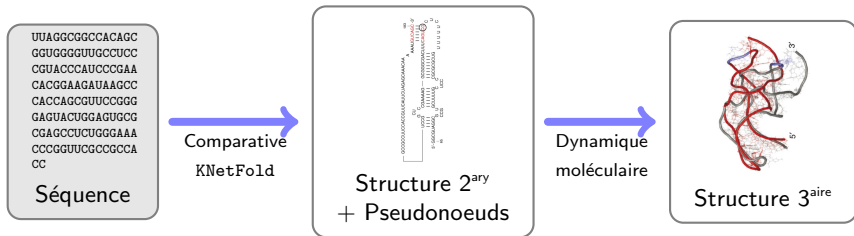
Séquence



Structure 3^{aire}

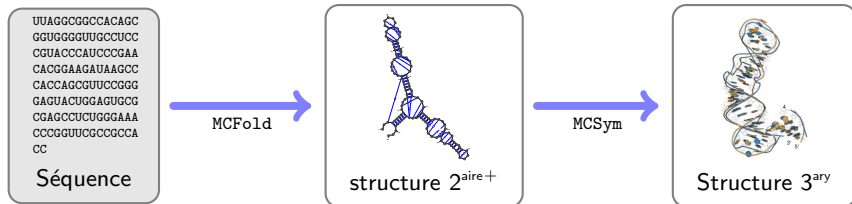
But : De la séquence à des modèles tri-dimensionnels !!!

- Modèles comparatifs + Dynamique moléculaires : RNA2D3D [SYKB07]



But : De la séquence à des modèles tri-dimensionnels !!!

- Pipeline MC-Fold/MC-sym [PM08]





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Exercice : Parsing/repliement des structures secondaires (Python)

[http://www.lix.polytechnique.fr/~ponty/enseignement/
2013-01-BIBS-TP1-RappelsPython.pdf](http://www.lix.polytechnique.fr/~ponty/enseignement/2013-01-BIBS-TP1-RappelsPython.pdf)