Extraction et classification automatiques de motifs dans les structures tertiaires

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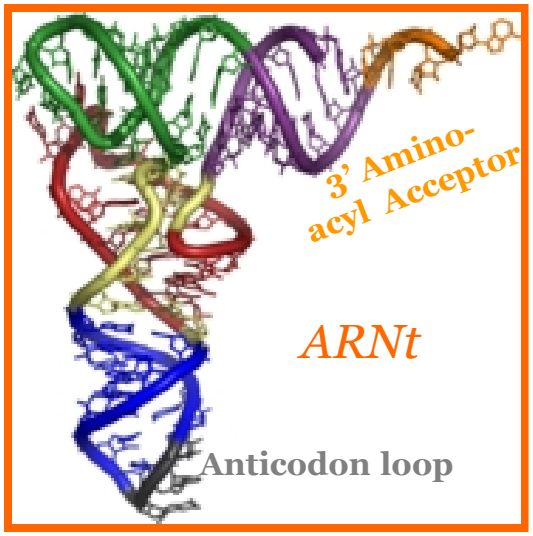
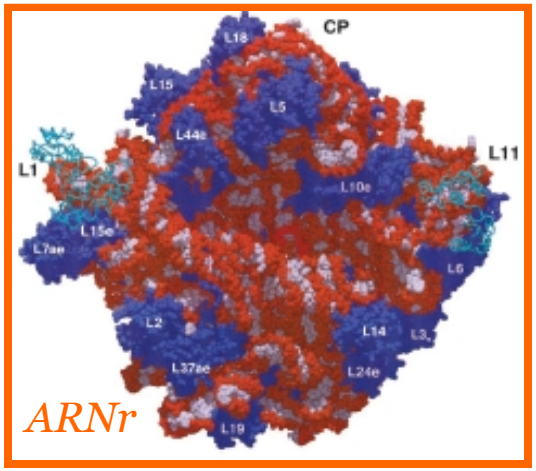
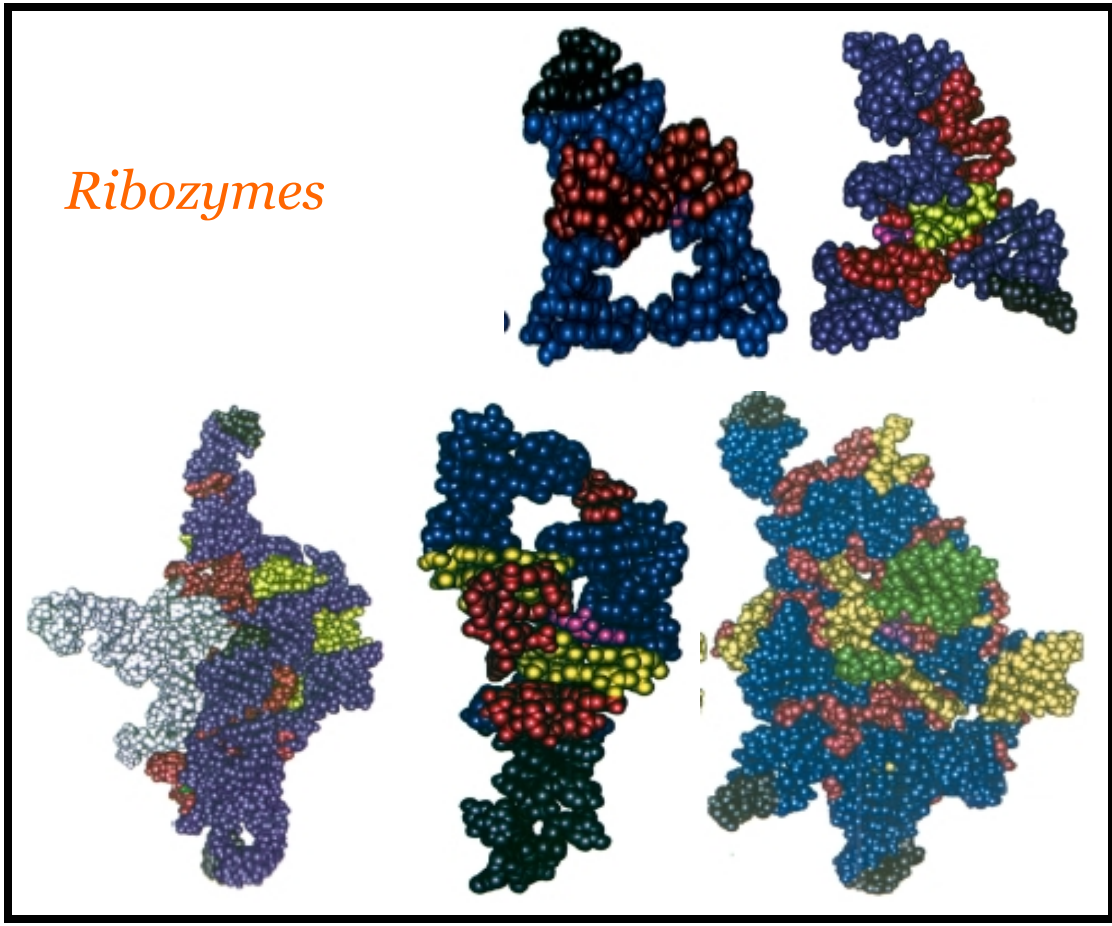
Structure de l'ARN





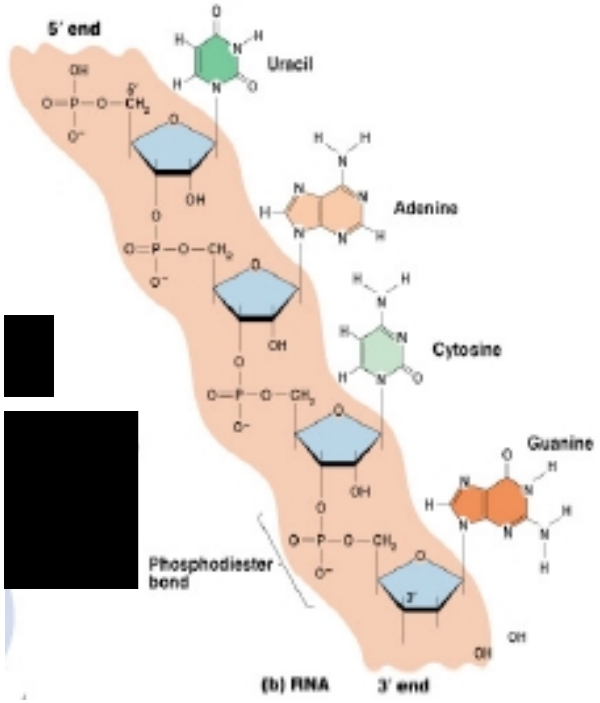


[Catalytic RNA, F. Walter & E. Westhof, els, 2002]

Structure de l'ARN

ARN = une chaîne de nucléotides qui

5' end



3' end

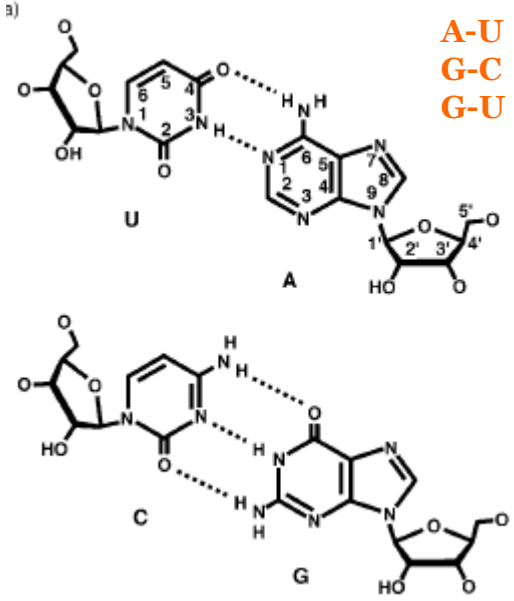
[© 2003 Pearson Education, Inc., Publishing as Benjamin Cummings]

5'....UACGUCGAU...3'

Structure de l'ARN

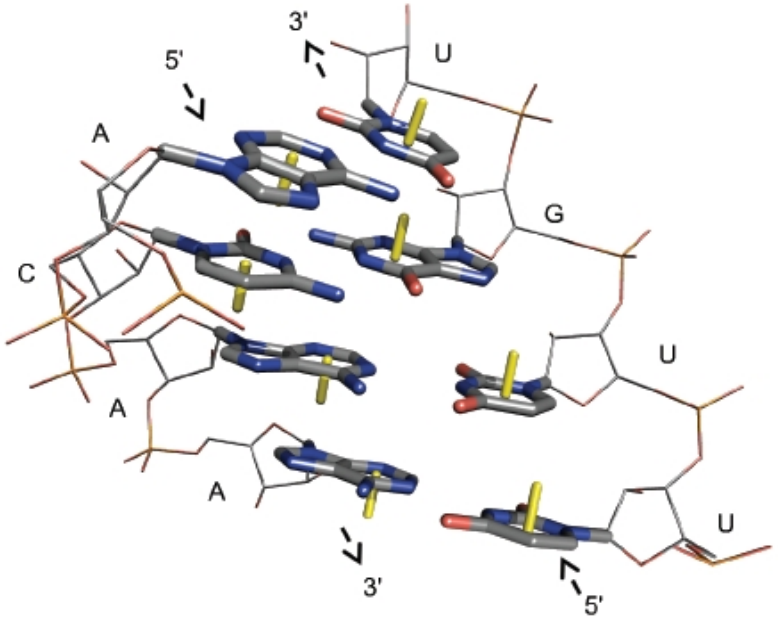
qui se replie en hélices de type A

Appariements WC
canoniques



ET

Stacking



[Tertiary motifs in RNA structure and folding,
J. Doudna et al., Angew Chem Int Ed Engl. 1999]

[Base stacking annotation, F. Major & P. Thibault, presented at the RNA ontology consortium workshop, RNA society meeting, Seattle WA, June 19-20 2006]

Structure de l'ARN

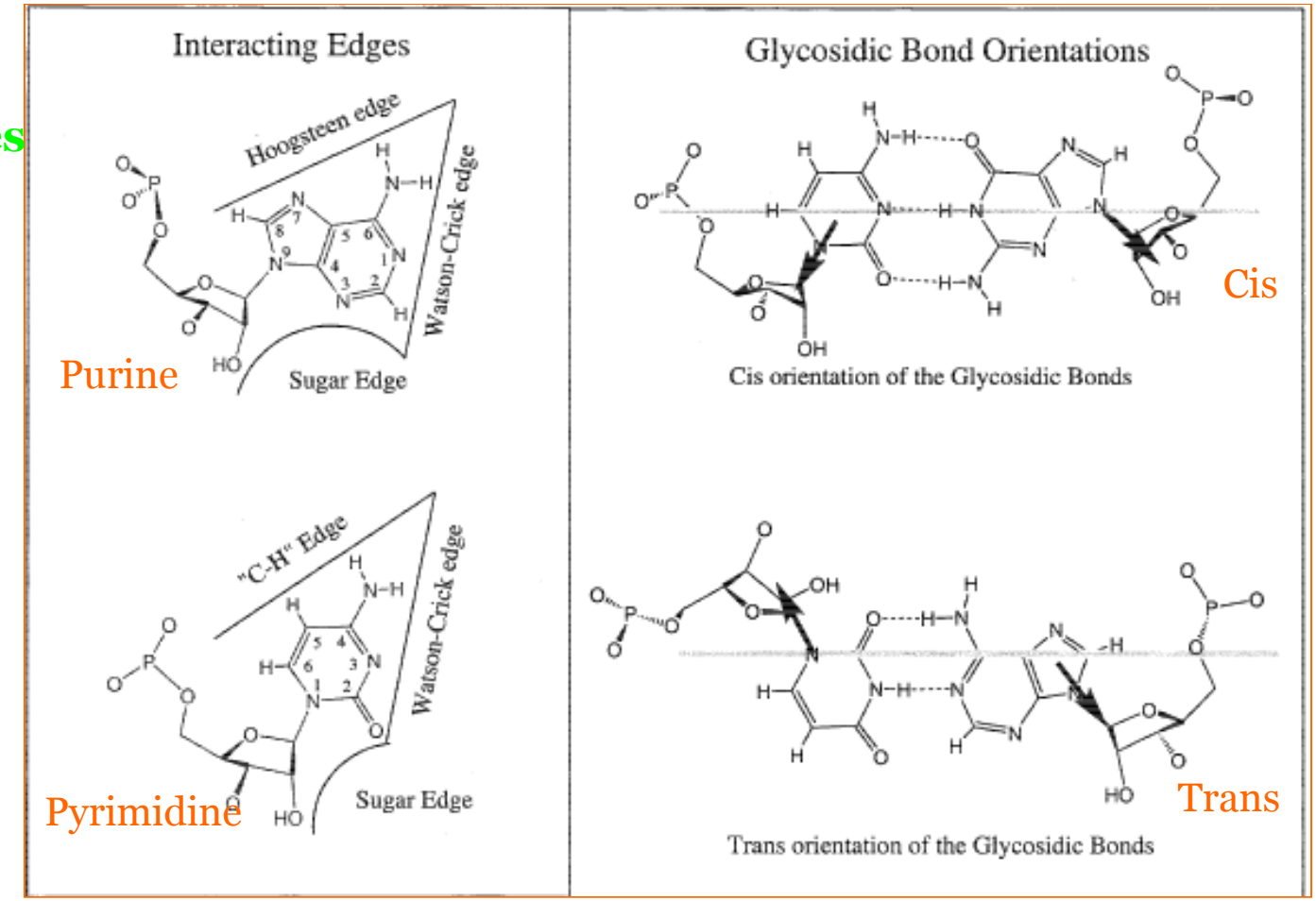
Nomenclature Leontis-Westhof (LW)

3 Interacting Edges

- Hoogsteen (H)
- Watson-Crick (W)
- Sugar (S)

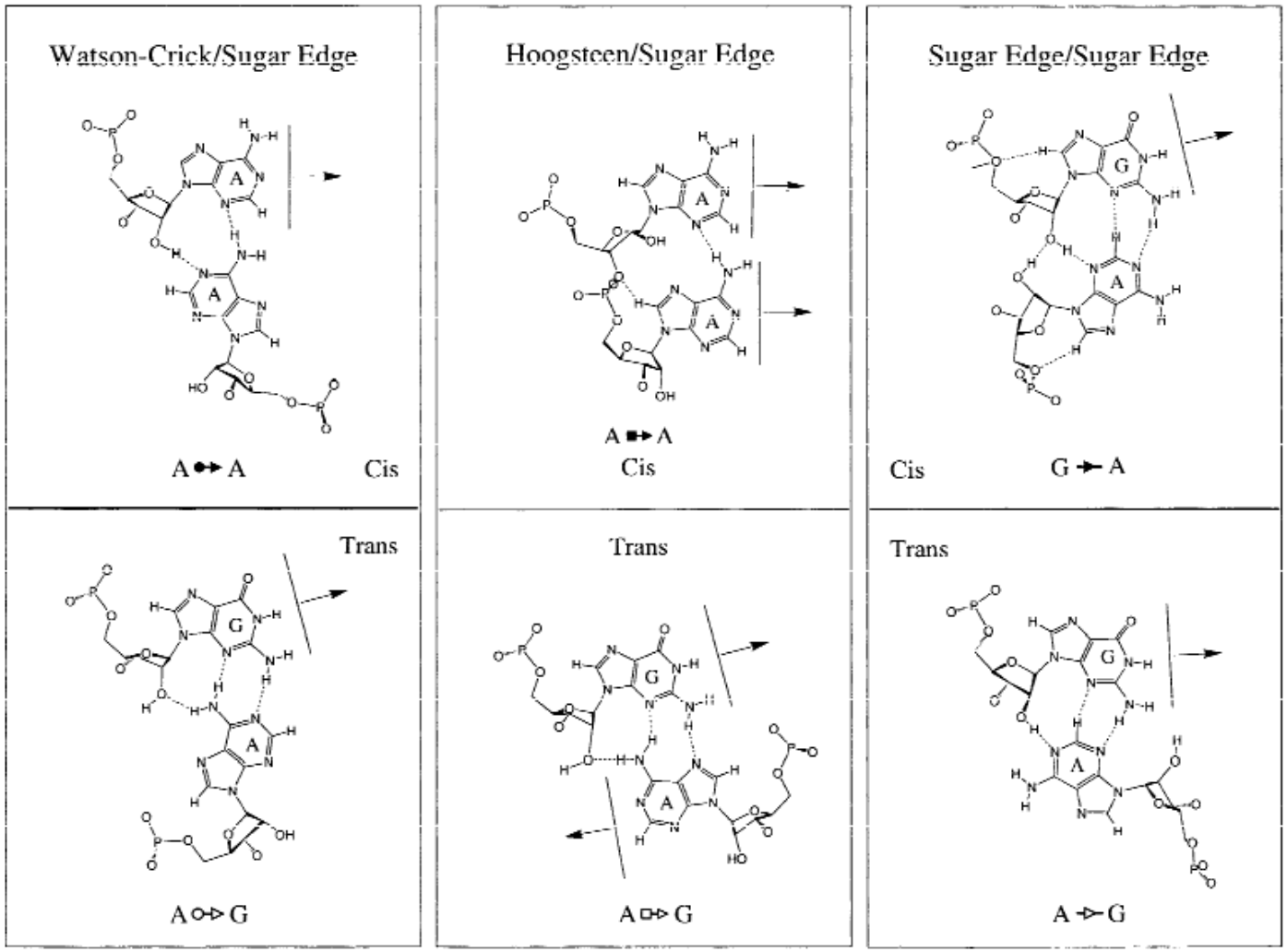
2 Orientations

- Cis
- Trans



[The Non-WC base pairs and their isostericity matrices, Leontis et al., NAR 2002]

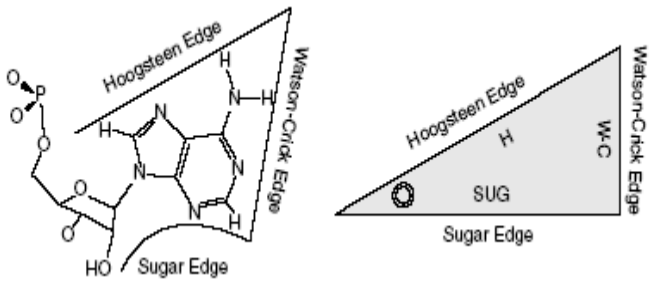
Liaisons non canoniques

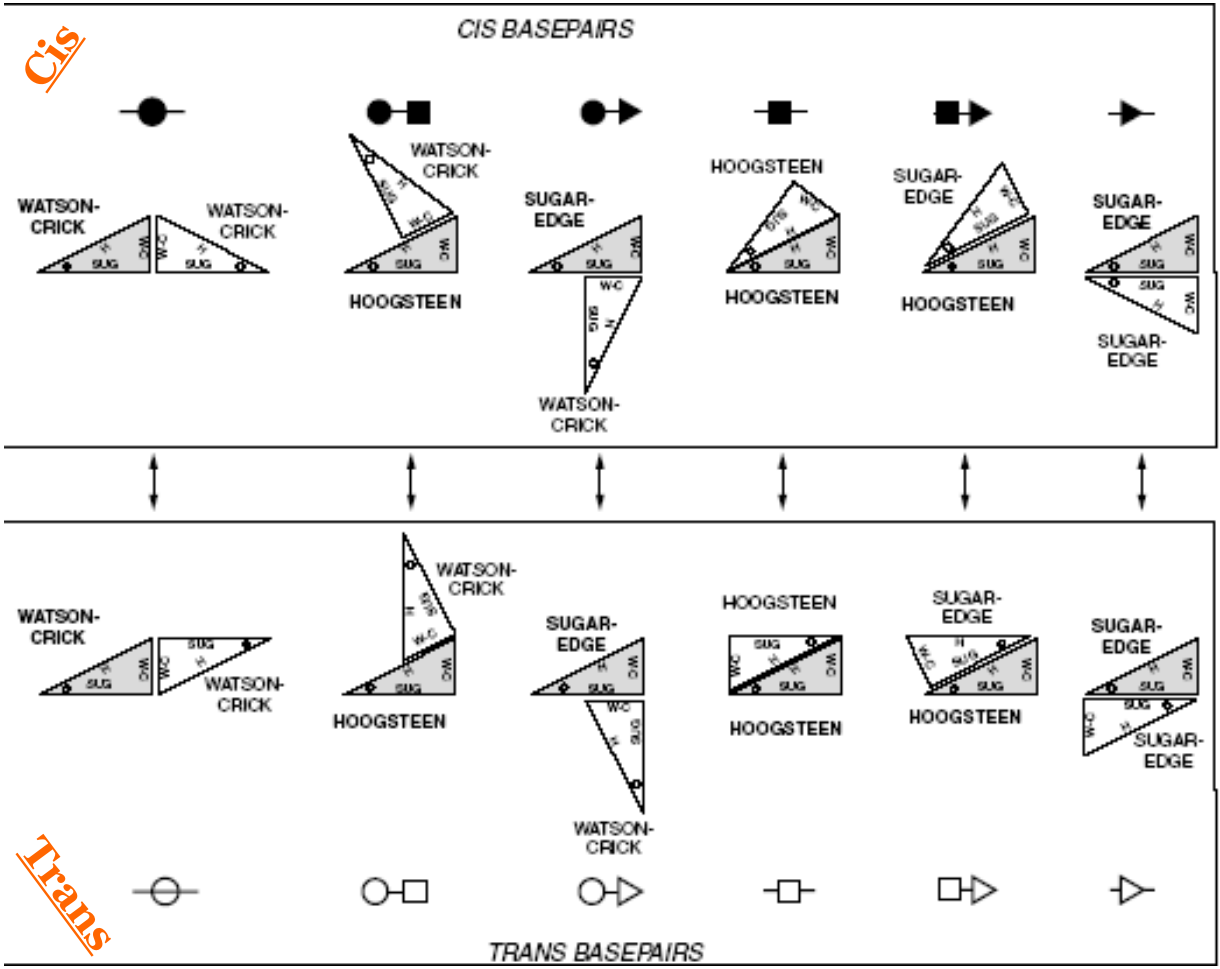


[Leontis & Westhof, RNA 2001]

Nomenclature Leontis Westhof (LW)

12 Familles





[The annotation of RNA Motifs, N.B. Leontis & E. Westhof, Conference Review 2000]

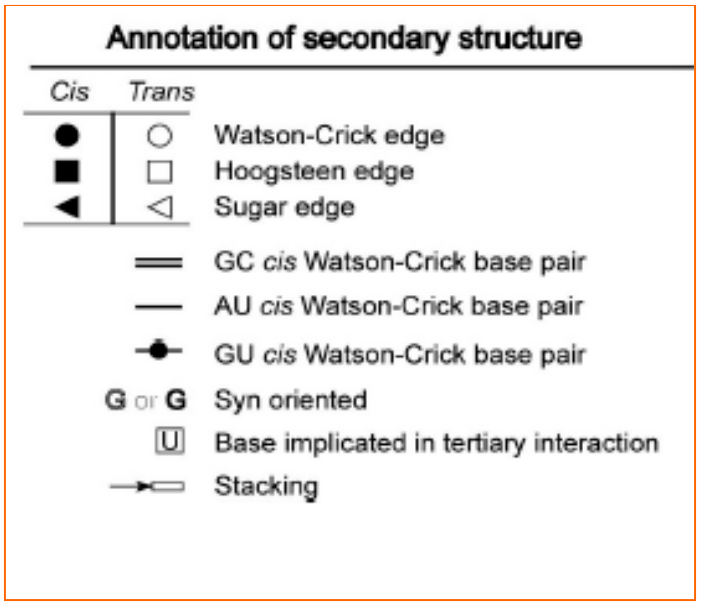
Nomenclature Leontis Westhof (LW)

Annotation

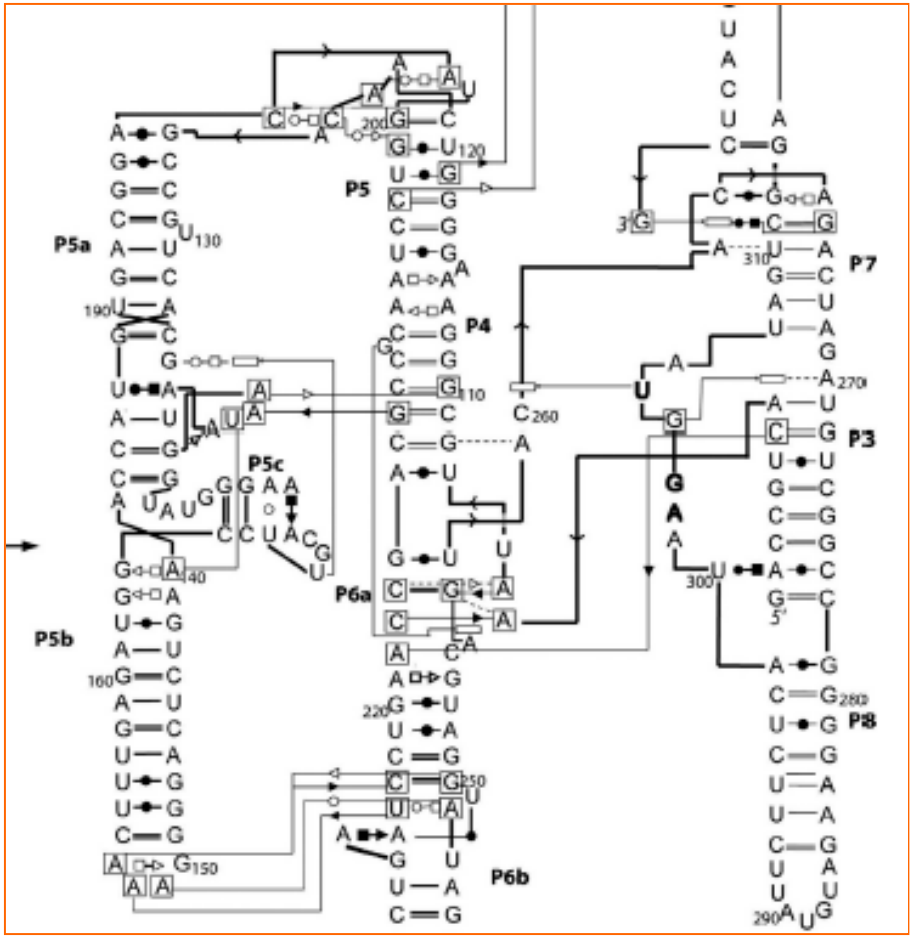
No.	Glycosidic bond orientation	Interacting edges	Symbol	Default local strand orientation
1	*cis*	Watson–Crick/Watson–Crick		Anti-parallel
2	*trans*	Watson–Crick/Watson–Crick		Parallel
3	*cis*	Watson–Crick/Hoogsteen		Parallel
4	*trans*	Watson–Crick/Hoogsteen		Anti-parallel
5	*cis*	Watson–Crick/Sugar edge		Anti-parallel
6	*trans*	Watson–Crick/Sugar edge		Parallel
7	*cis*	Hoogsteen/Hoogsteen		Anti-parallel
8	*trans*	Hoogsteen/Hoogsteen		Parallel
9	*cis*	Hoogsteen/Sugar edge		Parallel
10	*trans*	Hoogsteen/Sugar edge		Anti-parallel
11	*cis*	Sugar edge/Sugar edge		Anti-parallel
12	*trans*	Sugar edge/Sugar edge		Parallel

[The annotation of RNA Motifs, NB. Leontis & E. Westhof, Comparative and functional genomics, 2002]

Nomenclature Leontis Westhof (LW)

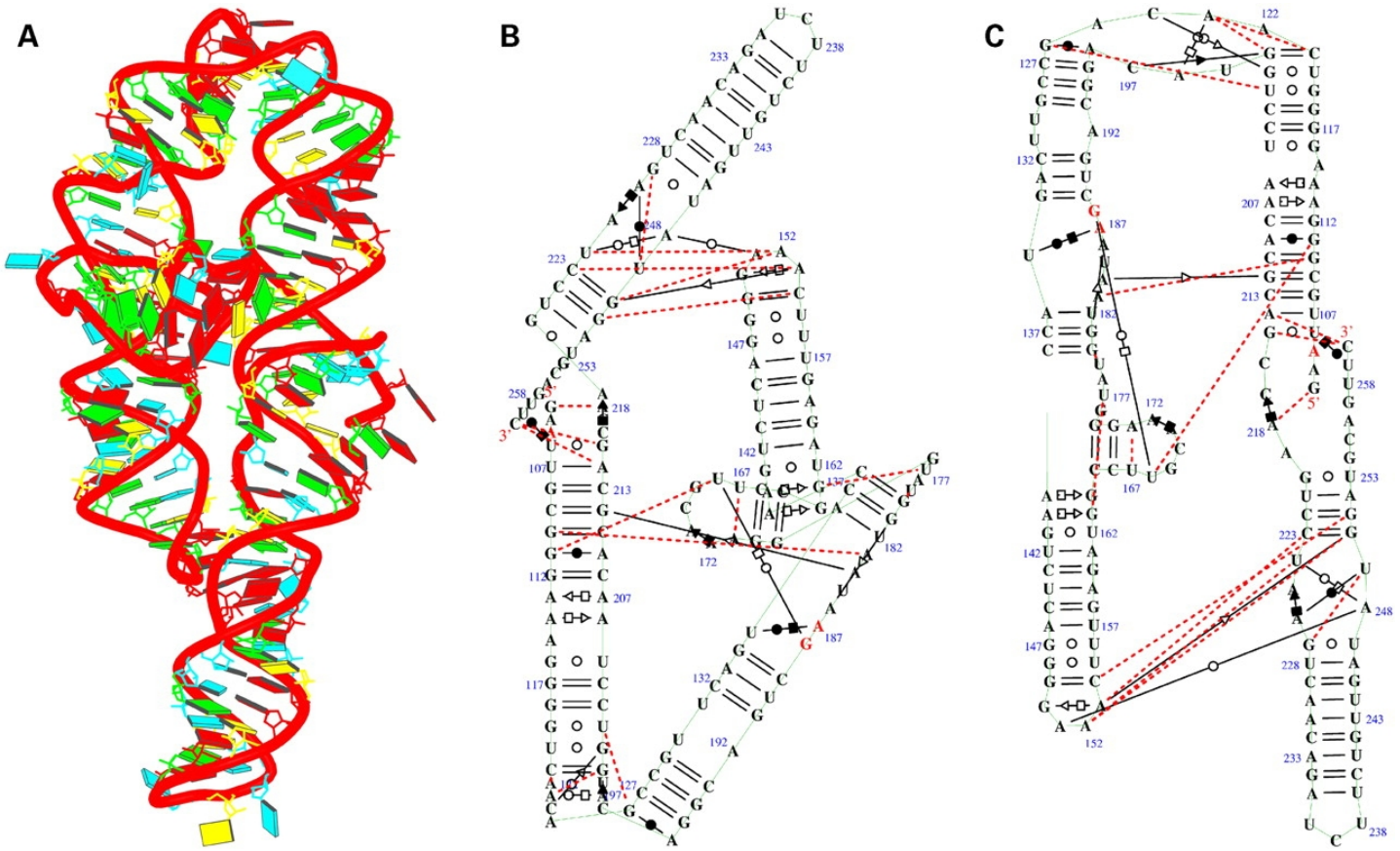


Graphe d'ARN = graphe de degré borné, étiqueté sur les sommets et sur les arêtes, contenant un chemin hamiltonien (connu).



Group I intron (detail). [The interaction Networks of structured RNAs, A. Lescoute & E. Westhof, NAR 2006]

De la 3D au graphe d'ARN



RNAView [H. Yang et al., NAR 2003]

(aussi: MC-annotate [P. Gendron et al., J Mol Biol 2001])

Comment l'ARN se replie-t-il ?

- Vers une conformation d'énergie libre minimale
- De façon hiérarchique :

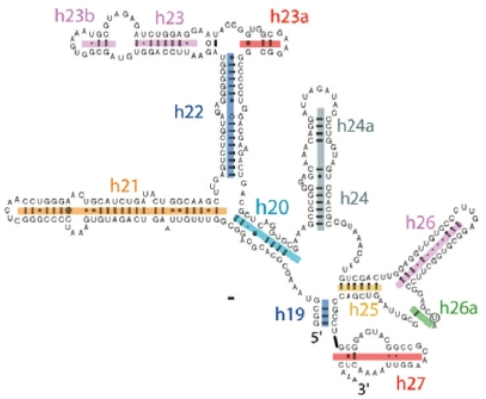
1. les interactions fortes et « locales »

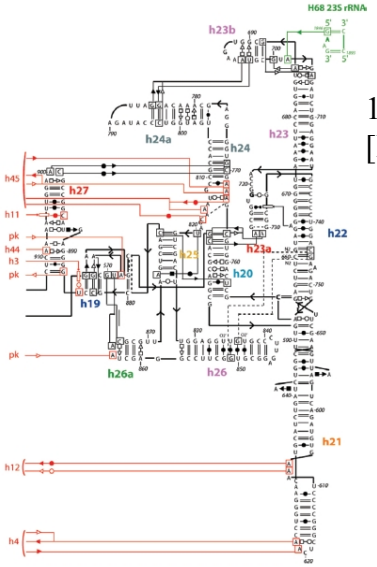
   = structure secondaire
   (sans pseudo-noeud)

2. les interactions faibles
   les interactions à longue portée

   = structure 3D

[Tinoco et al. J. Mol. Biol. 1999]

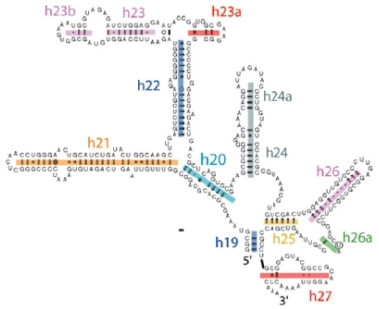




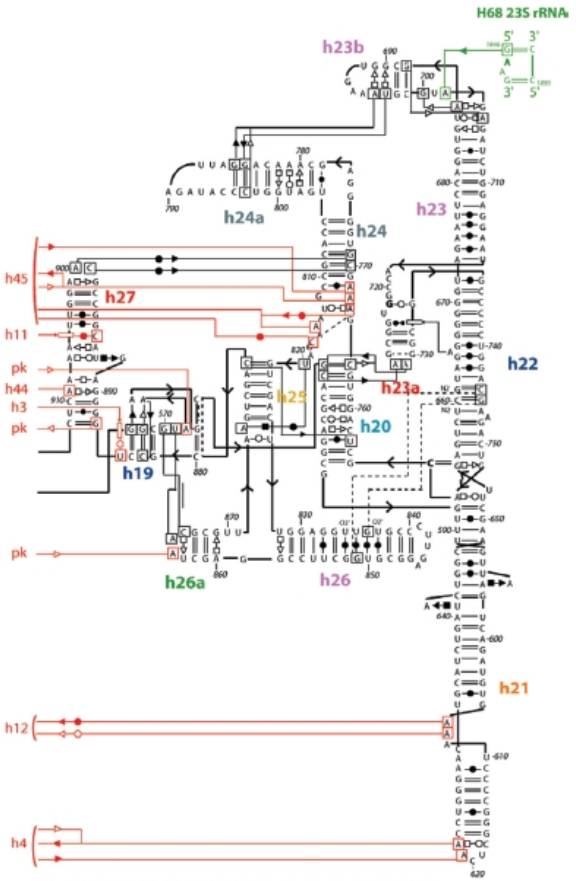
16S central domain
[Lescoute & Westhof 2006]

Interactions canoniques et non canoniques

• Les interactions canoniques forment les hélices et déterminent la structure secondaire.



• Les interactions non canoniques
  • forment les **motifs structuraux,**
  • sont responsables de la plupart des interactions entre les éléments de la structure secondaire.

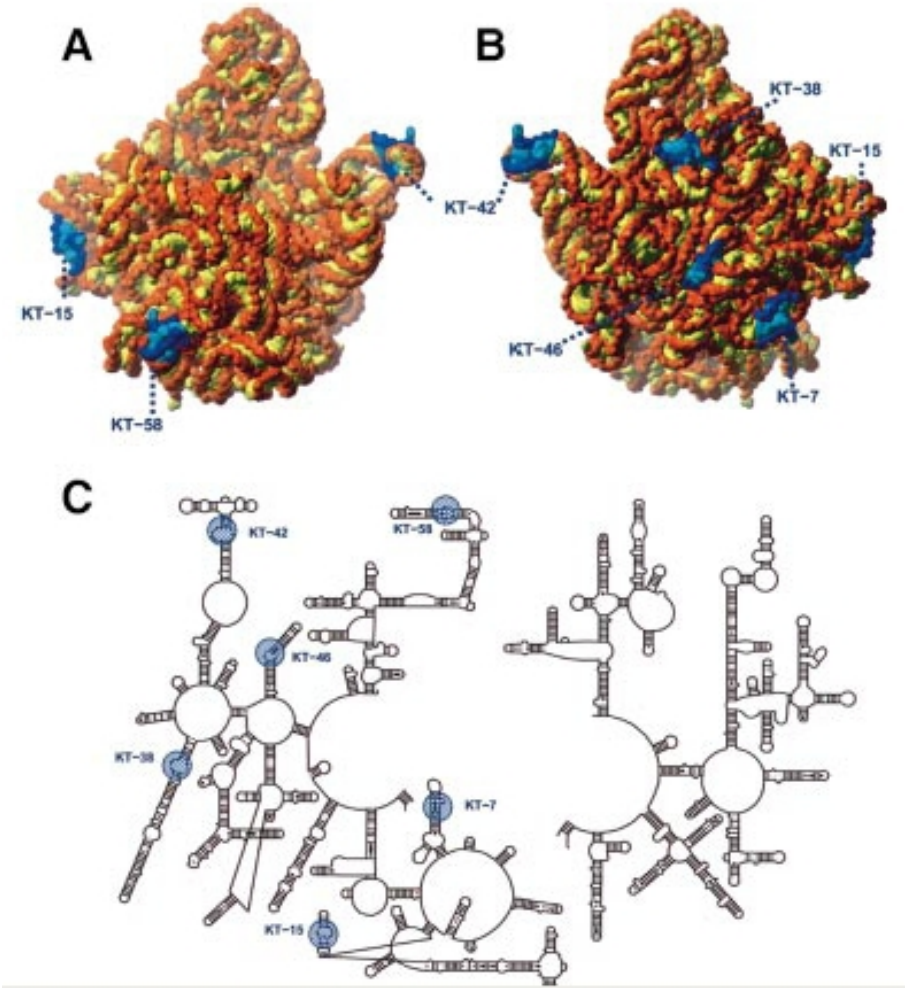


16S central domain
[Lescoute & Westhof 2006]

Motifs structuraux

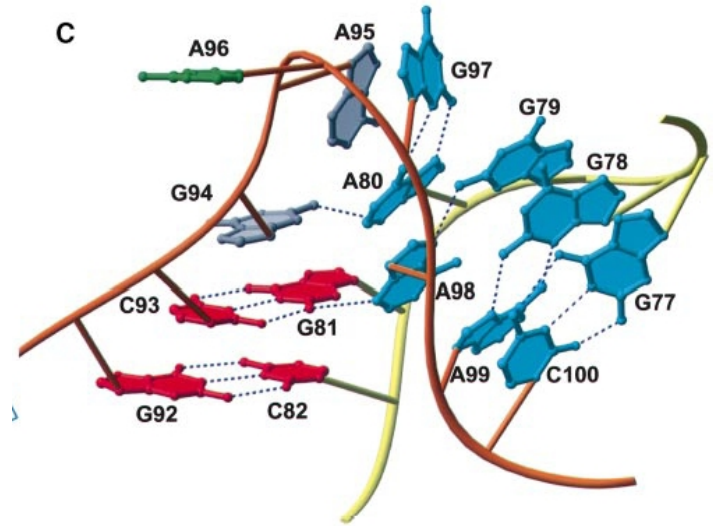
« Small, recurrent, stacked arrays of isosteric basepairs that intersperse the 2D structural elements (internal, junction, terminal loops) and fold into essentially identical 3D structures »

[Leontis & Westhof 2001]

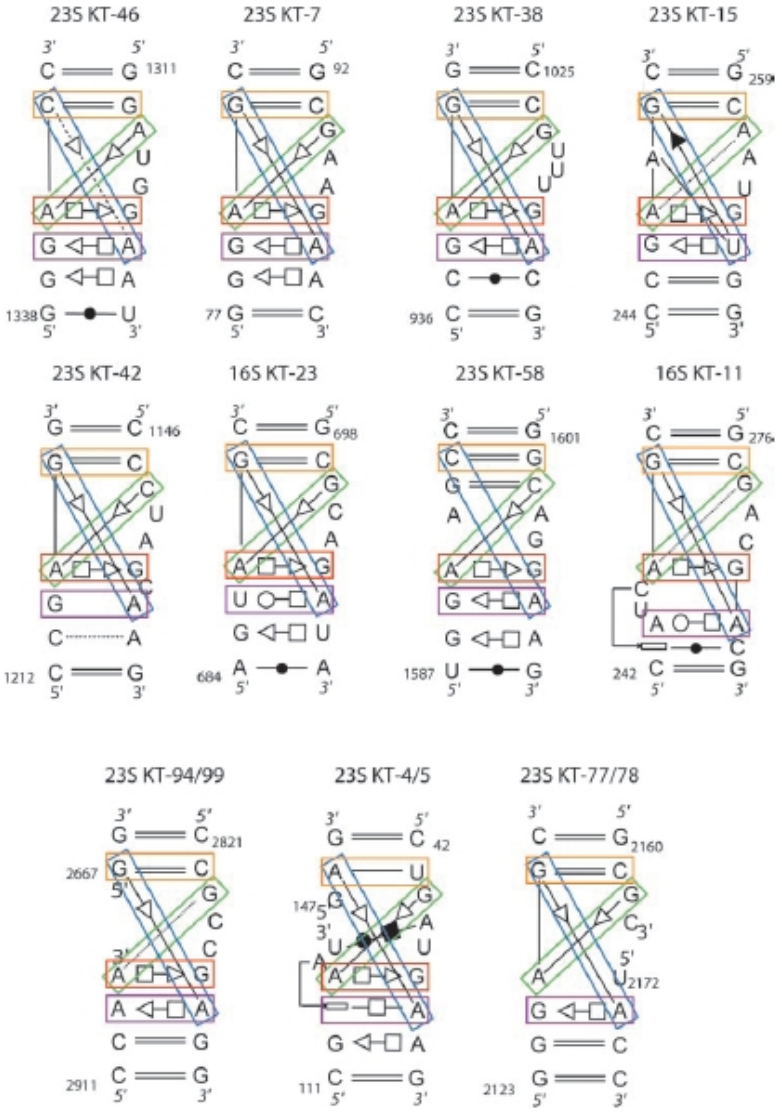


[The kink-turn: a new RNA secondary structure motif, D.J. Klein et al., The EMBO journal, 2001]

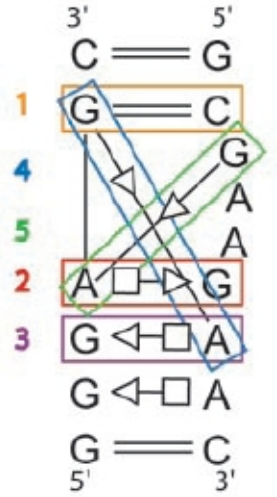
Exemple : le Kink-turn



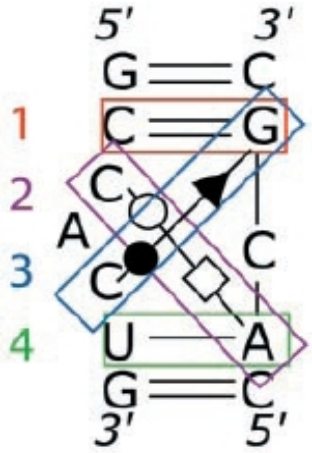
rmsd=1.7 Å



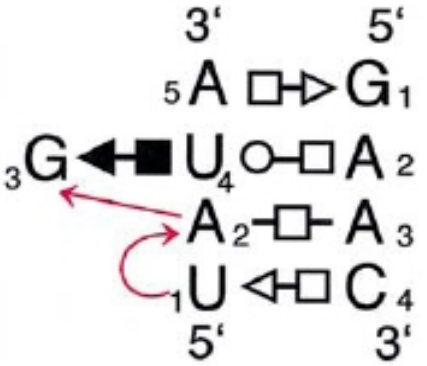
Quelques motifs structuraux



Kink-turn



C-loop



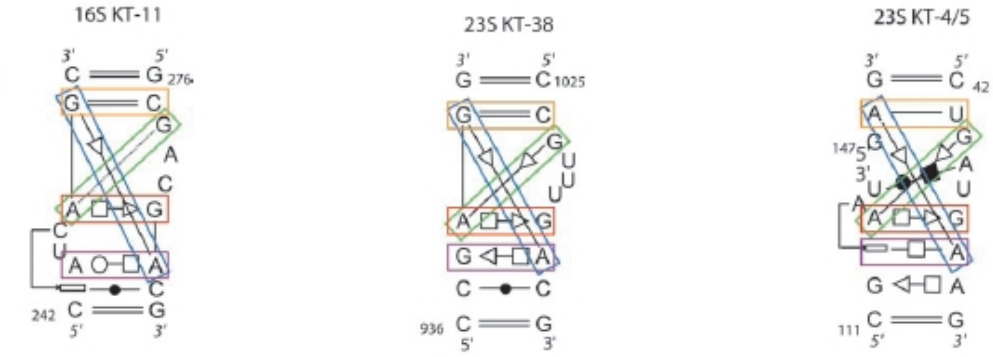
Sarcin-ricin

Découvrir de nouveaux motifs ?

Les motifs connus ont été découverts dans les structures PDB

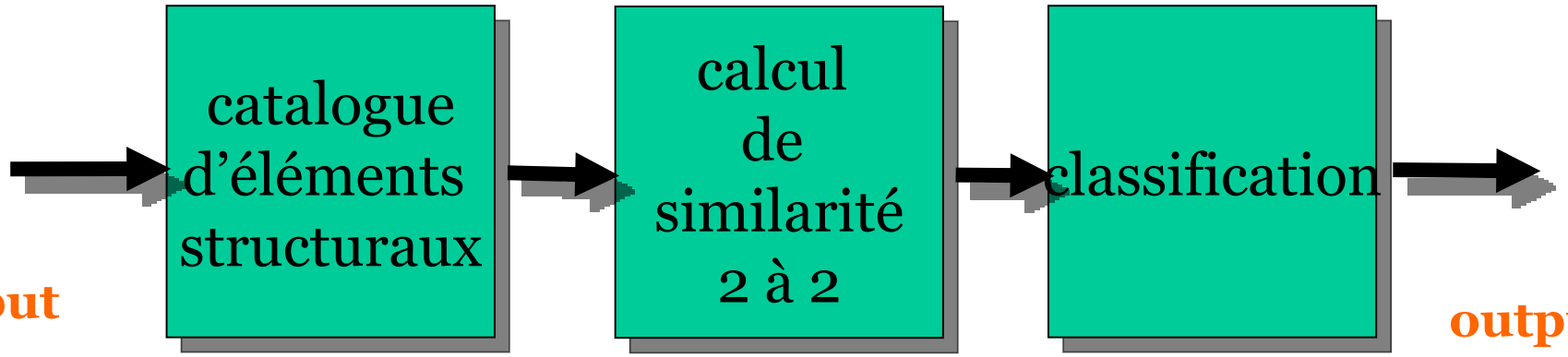
- soit à l'oeil,

- soit automatiquement par comparaison des formes géométriques. Approche très sensible aux différences de structure primaire/secondaire (insertions/suppressions)



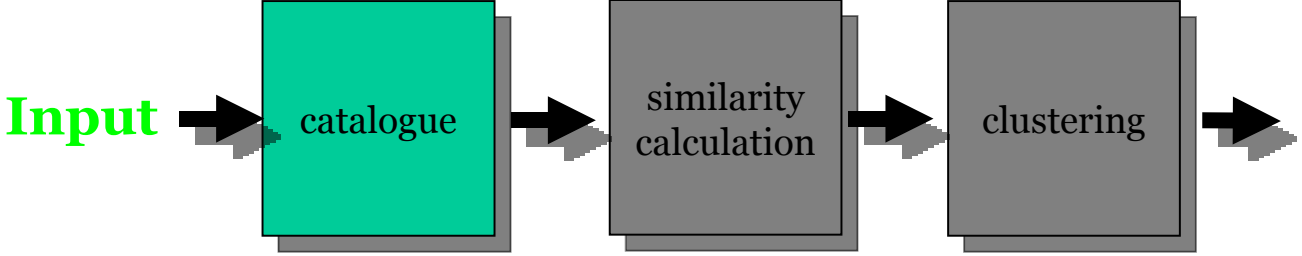
⇨ Une nouvelle approche basée sur le graphe de la structure.

Principe général

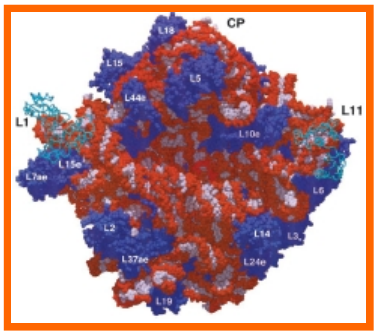


RNA graph
(from PDB file)

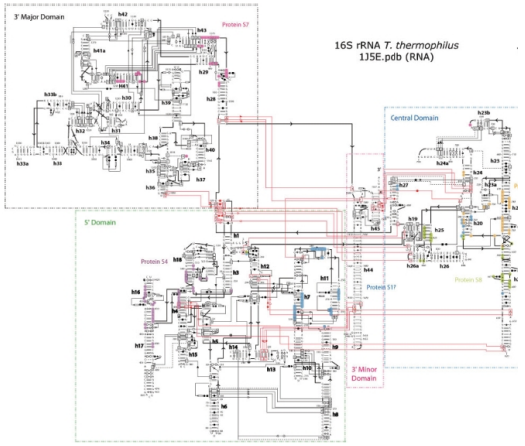
Potential RNA motifs



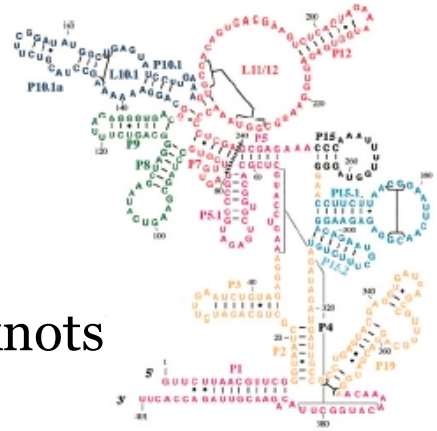
3D structure (PDB file)



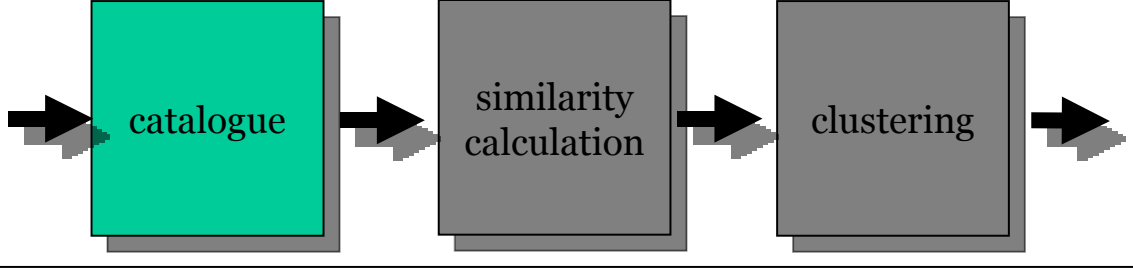
RNA graph



1. Remove pseudoknots + non-WC basepairs



2D structure without pseudoknots

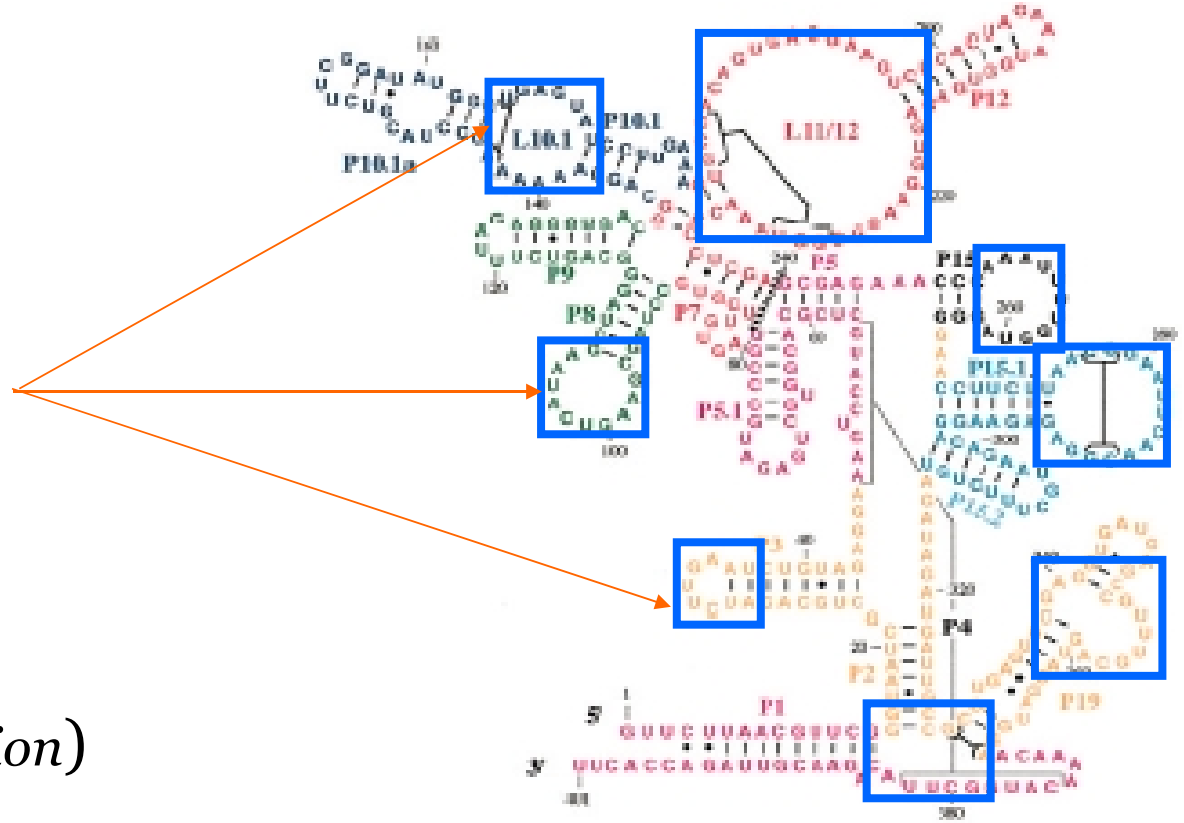


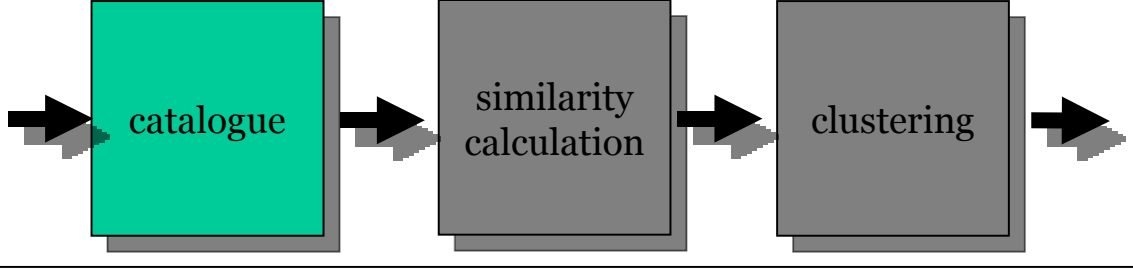
2. Identify 2D structural elements

- Bulges
- Internal
- Junction
- Terminal

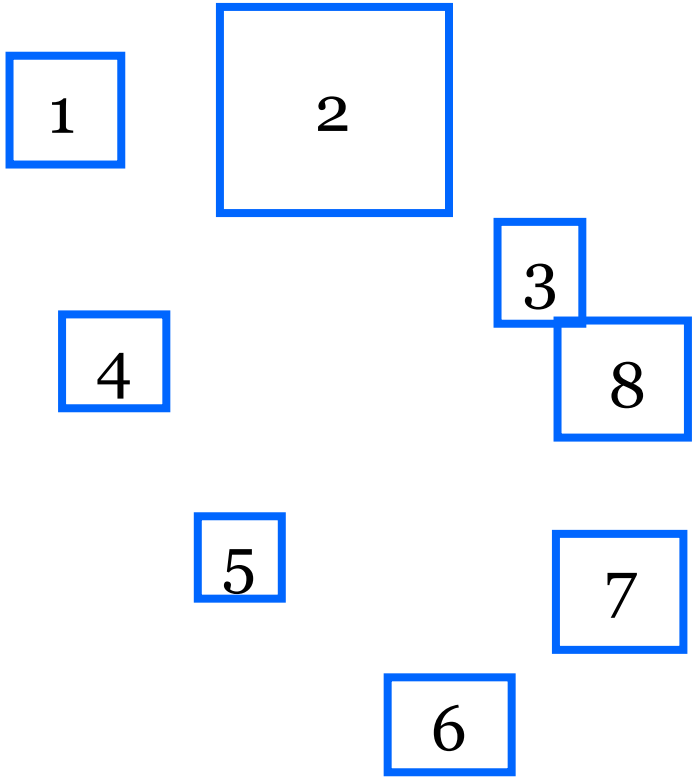
} loops

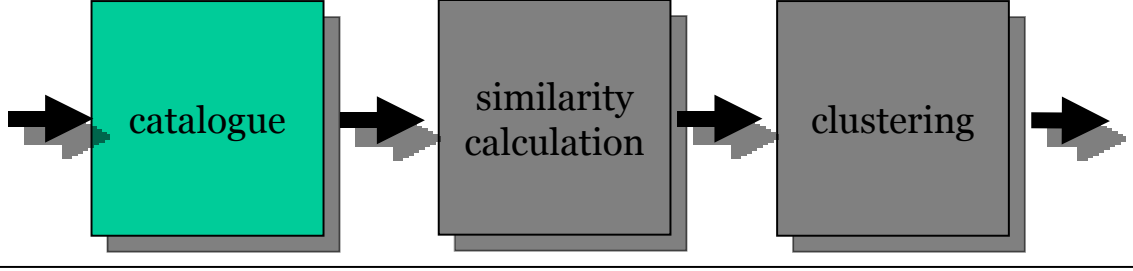
(*use tree representation*)





3. For each 2D structural element, restore local non-WC basepairs

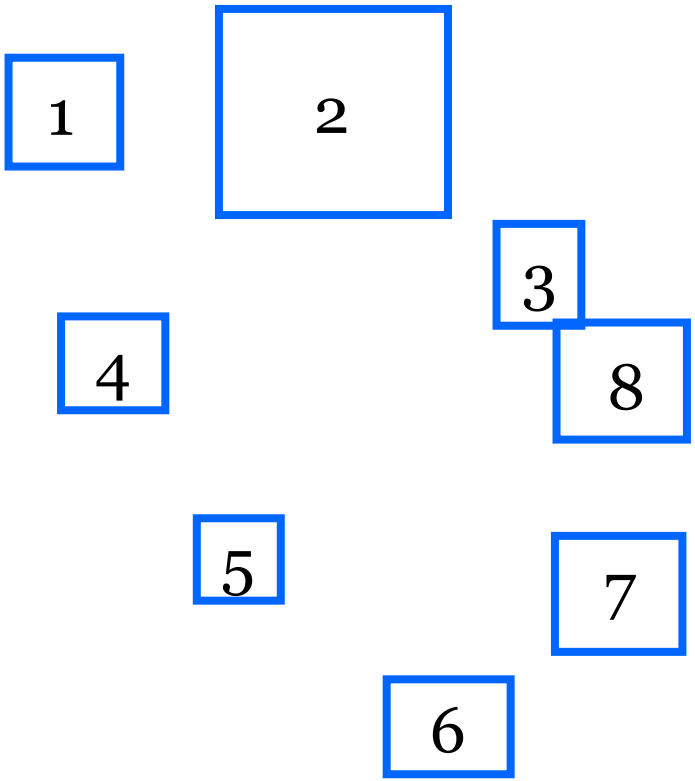


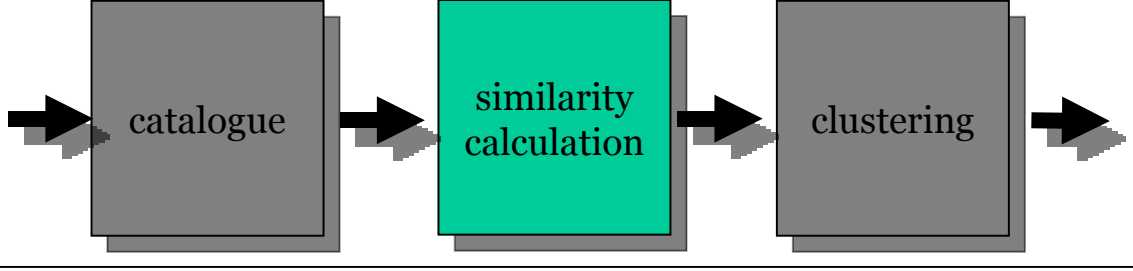


Output

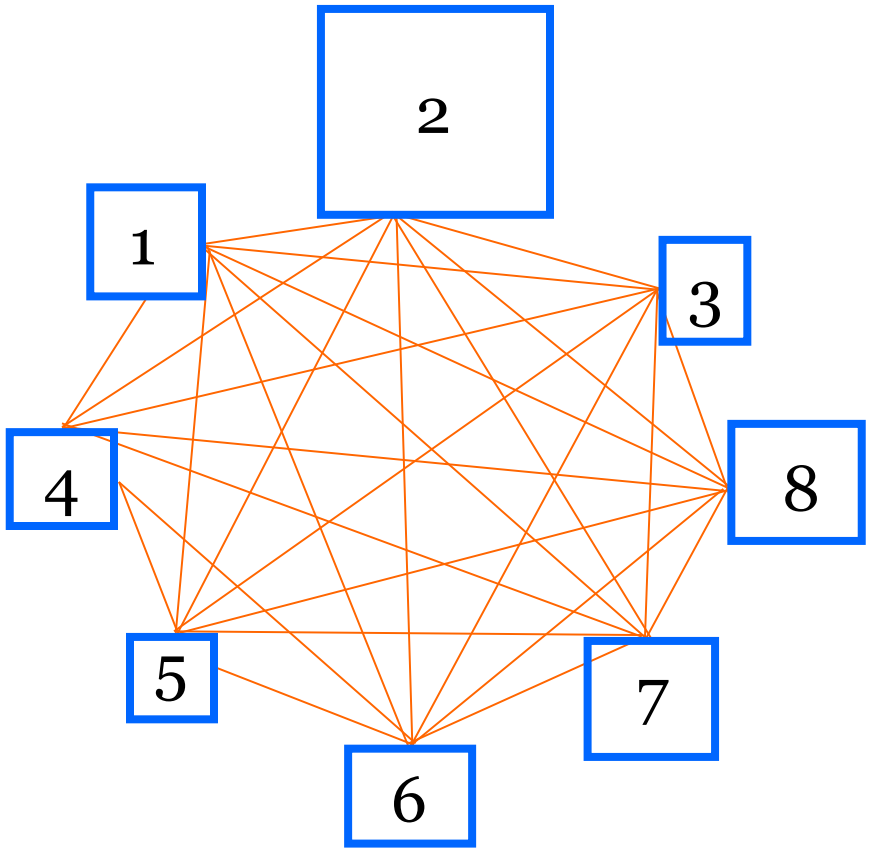
catalogue
List of RNA subgraphs

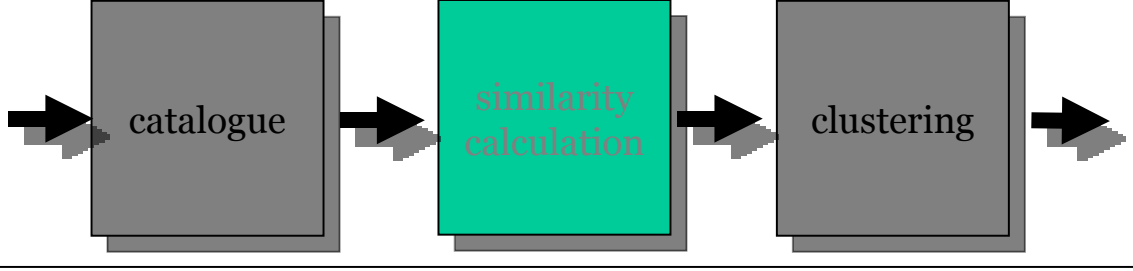
3. For each 2D structural element, restore local non-WC basepairs





4. Calculate a pairwise similarity measure between subgraphs i and j

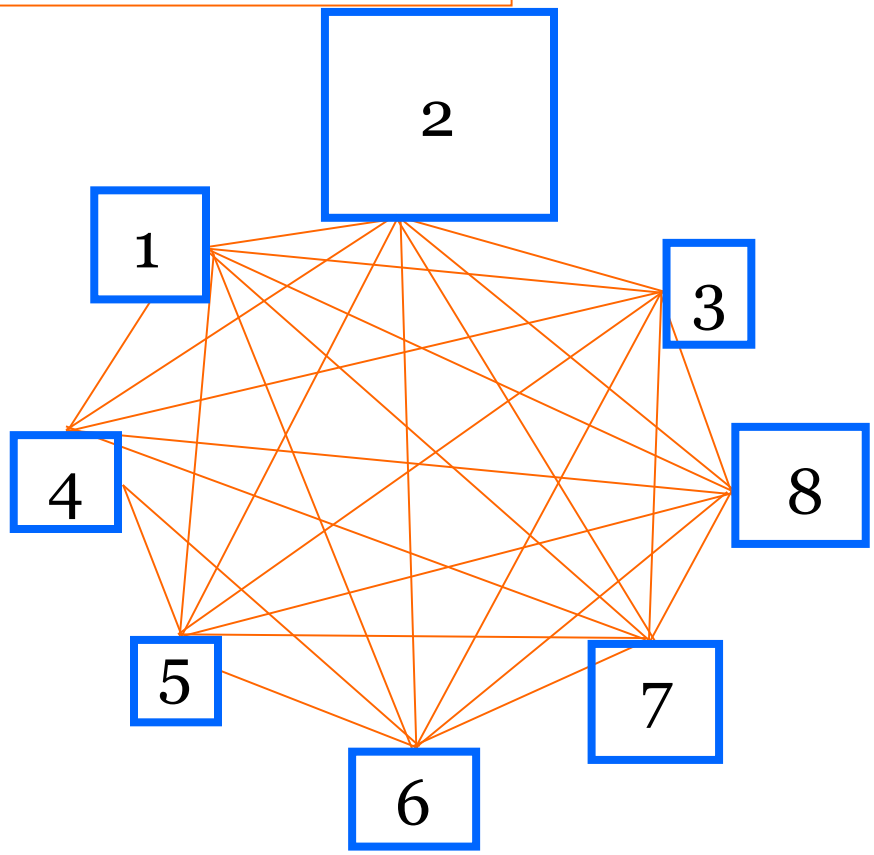


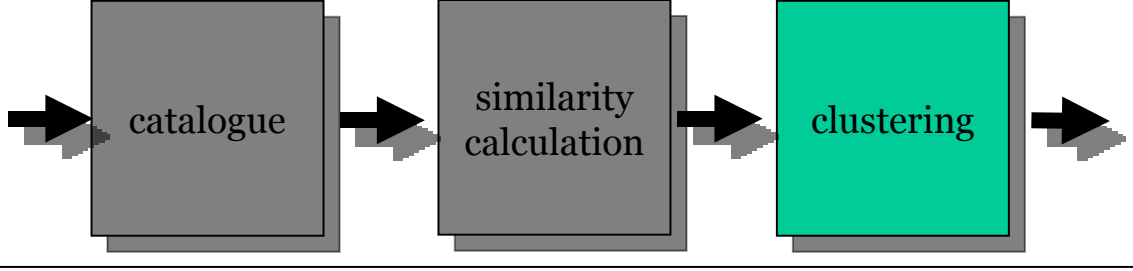


Output

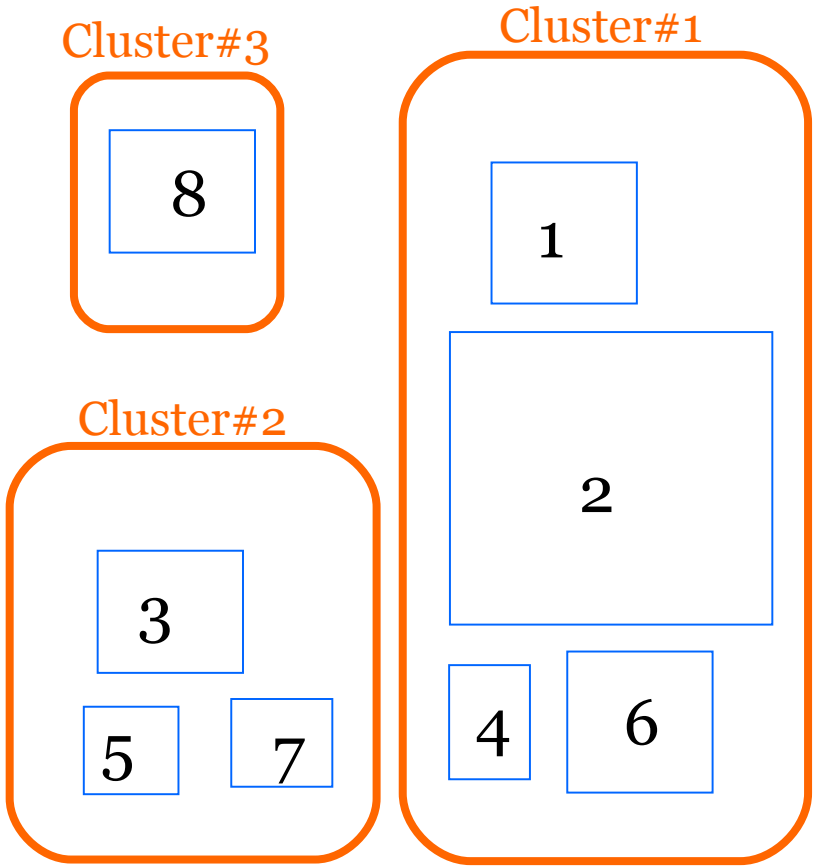
Similarity matrix

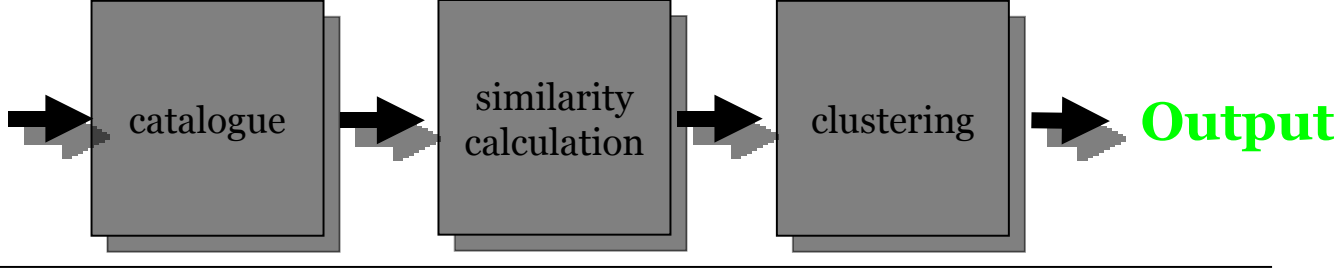
4. Calculate a pairwise similarity measure between subgraphs i and j





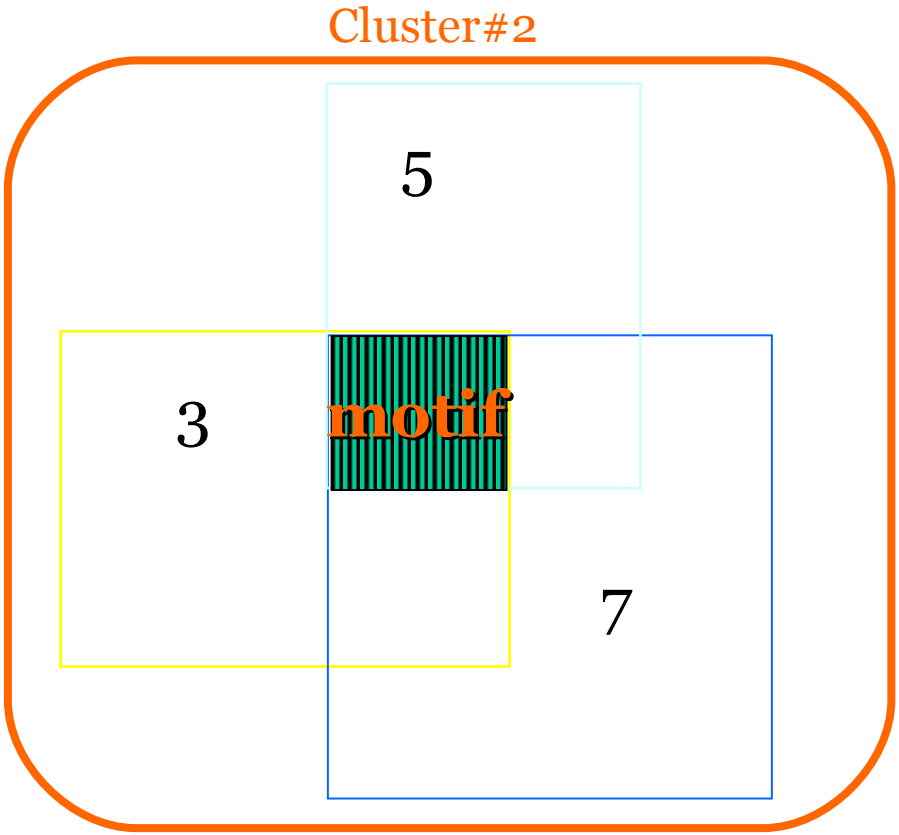
5. Cluster subgraphs with **high** similarity value



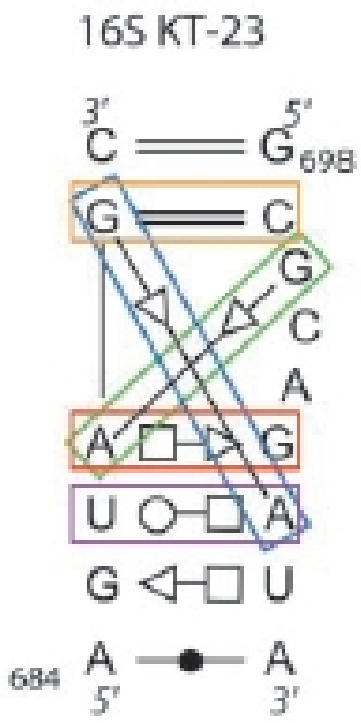


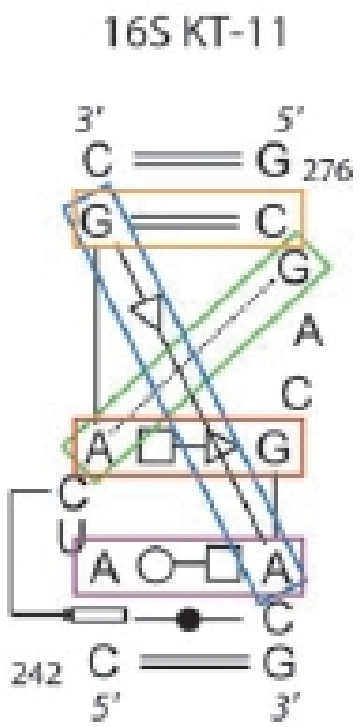
motif :

subgraph common to members of the cluster



Example

Similarity (

, 

) **= ?**

➔ *some definitions …*

Definitions

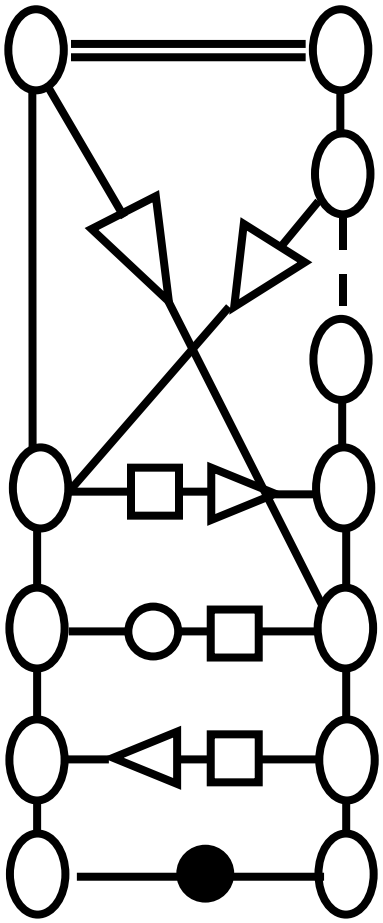
Non-canonical size of G :

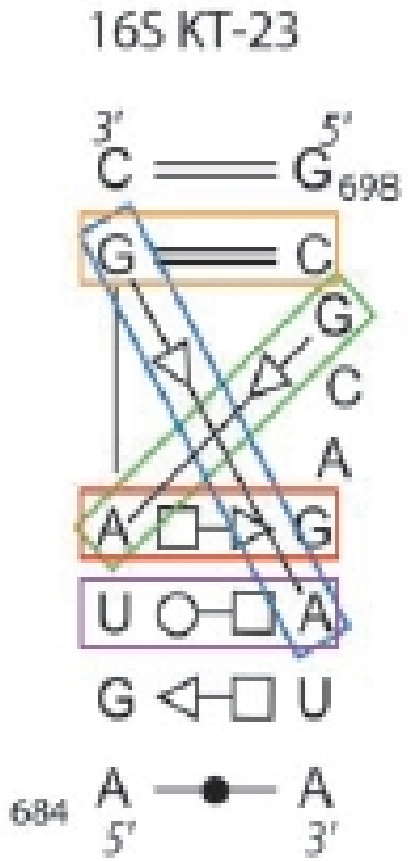
|| G || = Number of its non-canonical edges

Example:

|| 16S KT-23 || = 6

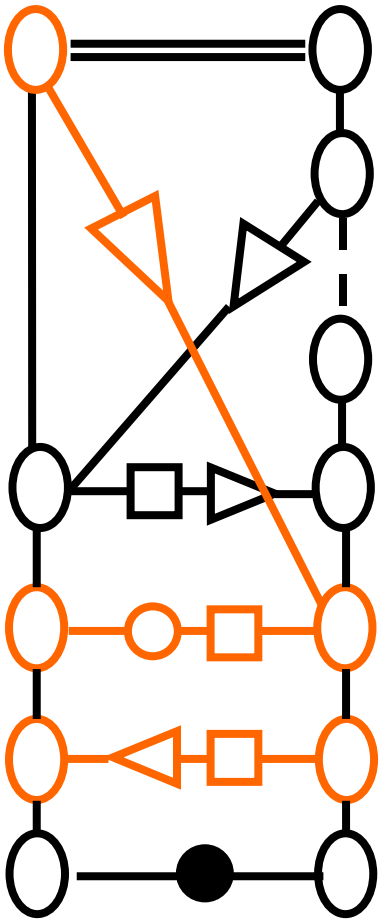
16S KT-23





Definitions

16S KT-23

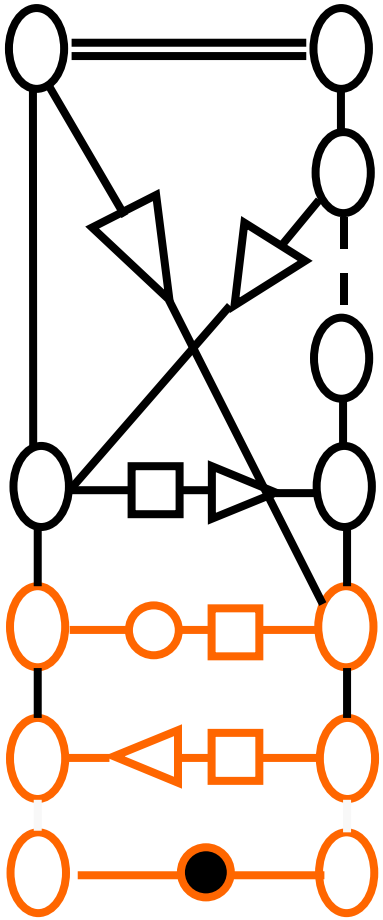


A **Non-canonical subgraph**
=
Subgraph whose all edges are non-canonical

Example 1

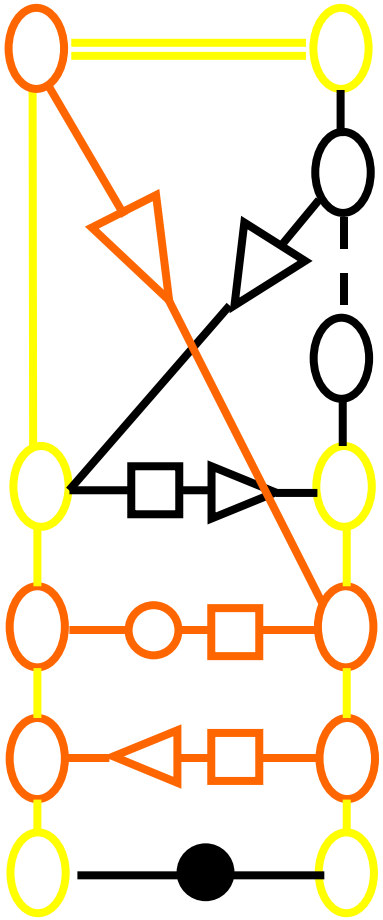
Example 2

16S KT-23



Definitions

16S KT-23



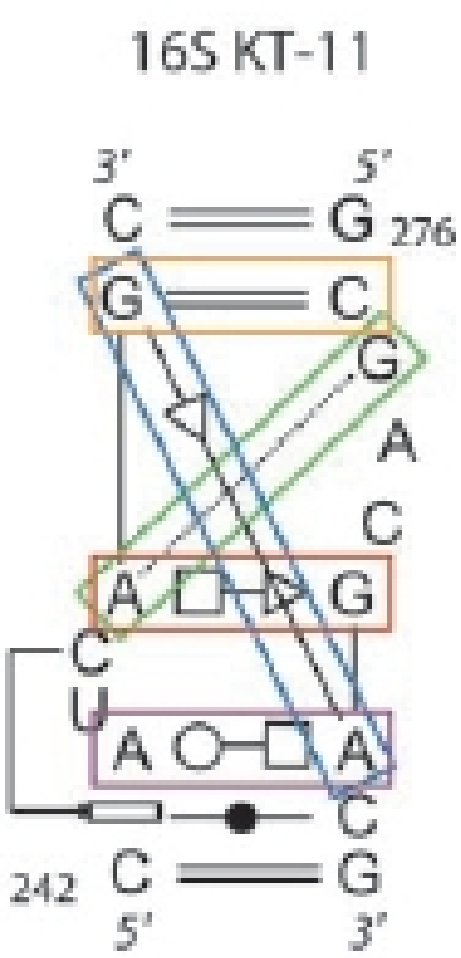
A **completion** of a non-canonical subgraph H of G

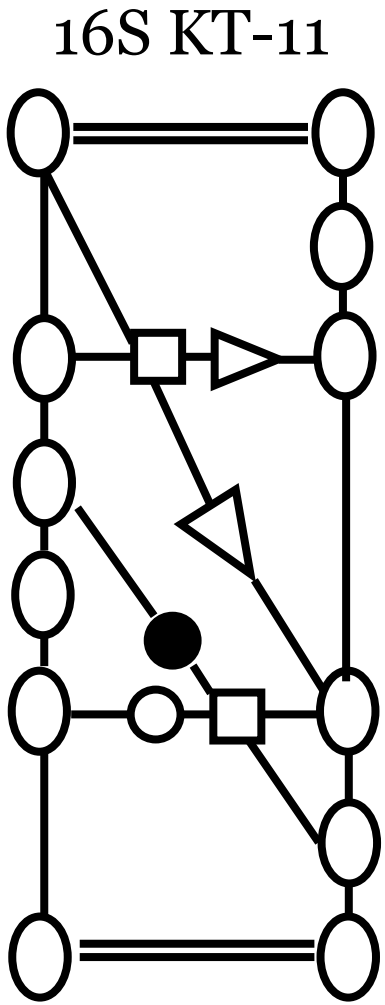
=

H + {all canonical + backbone edges of G having at least one end in H}

Definitions

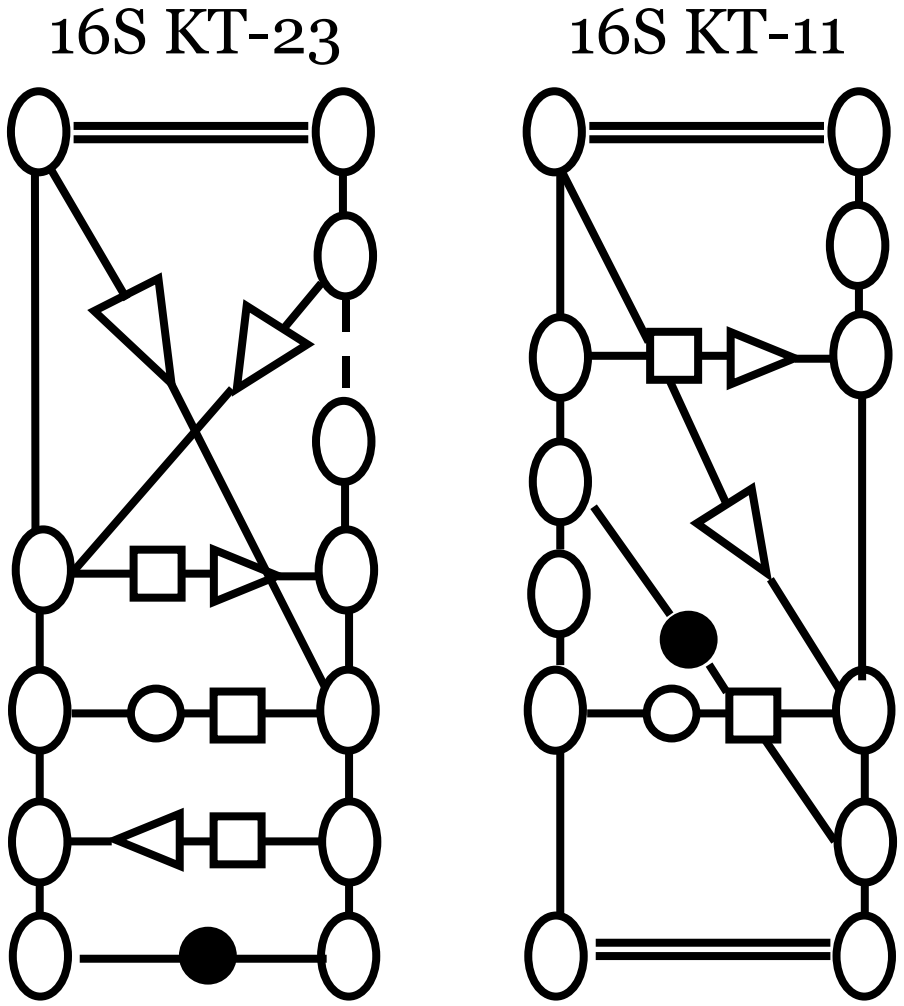
Another graph…





Definitions

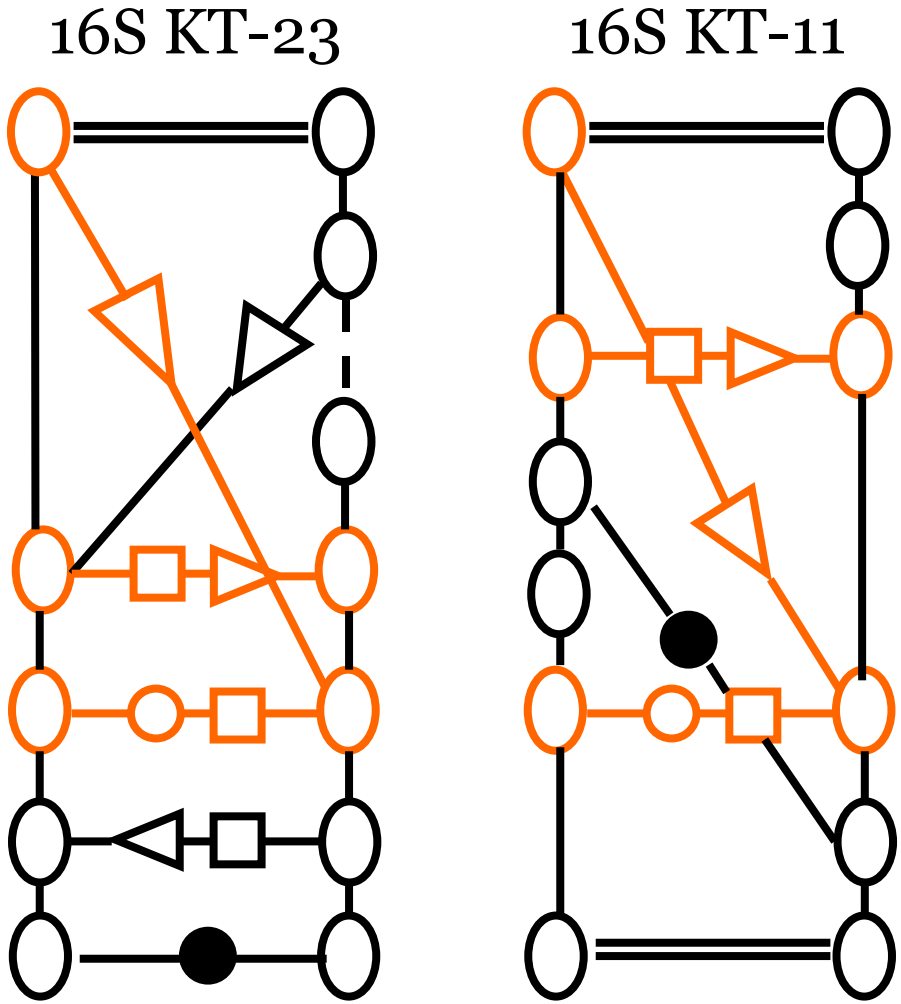
A **common non-canonical** subgraph H to G1 and G2 ....



Definitions

A **common non-canonical** subgraph H to G1 and G2

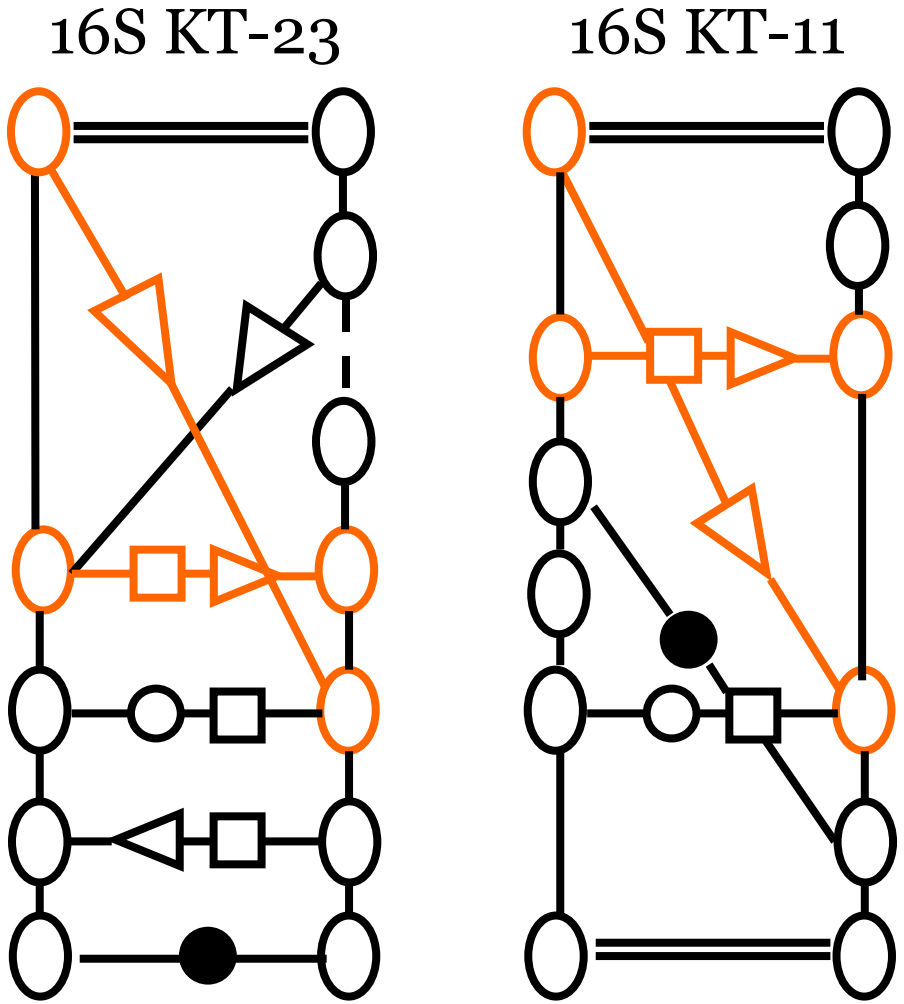
Example 1



Definitions

A **common non-canonical** subgraph H to G1 and G2

Example 2



Definitions

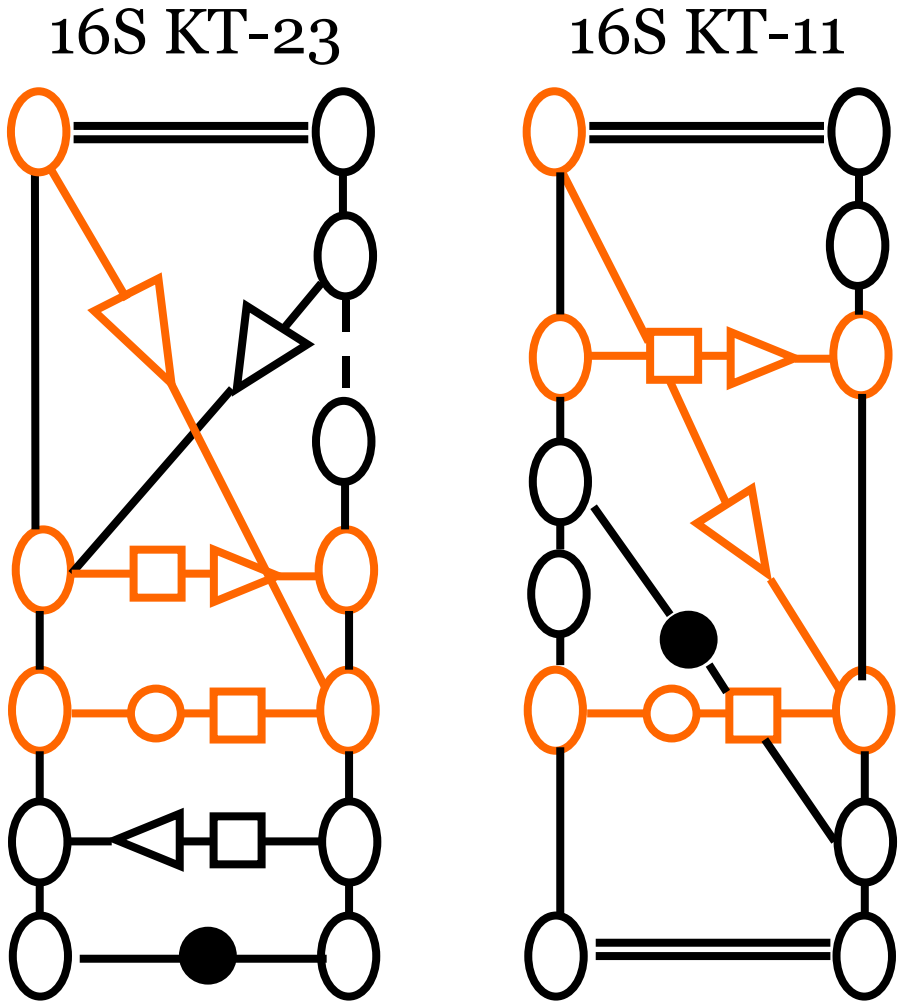
An **extensible common non-canonical** subgraph to G1 and G2

=

A **non-canonical** subgraph **common** to G1 and G2 whose **completions** in G1 and G2 are **isomorphic**

Example 1:

- common non-canonical subgraph

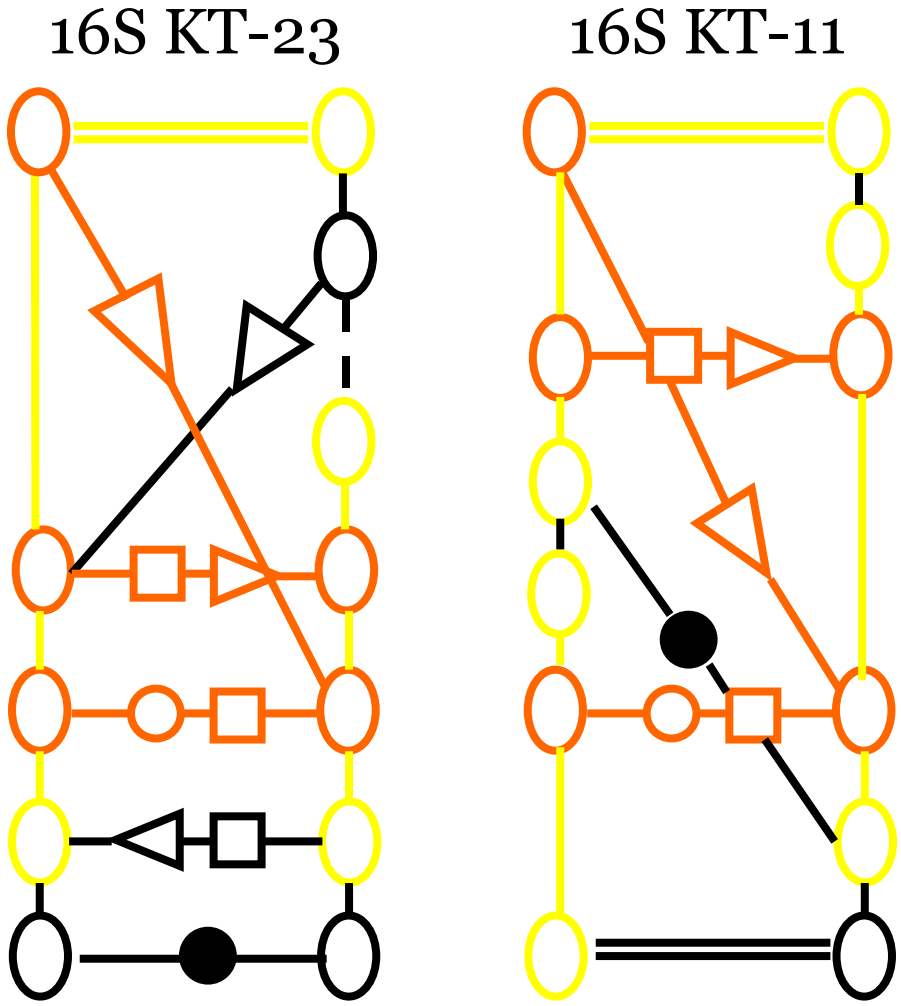


Definitions

An **extensible common non-canonical** subgraph to G1 and G2

=

A **non-canonical** subgraph **common** to G1 and G2 whose **completions** in G1 and G2 are **isomorphic**



Example 1:

- common non-canonical subgraph
- completions

Definitions

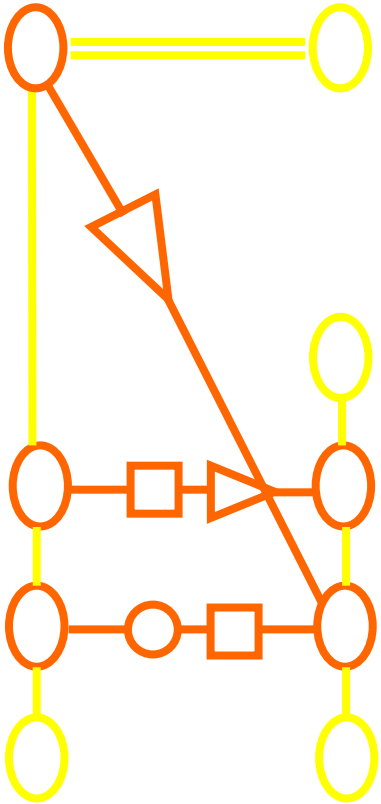
An **extensible common non-canonical** subgraph to G1 and G2

=

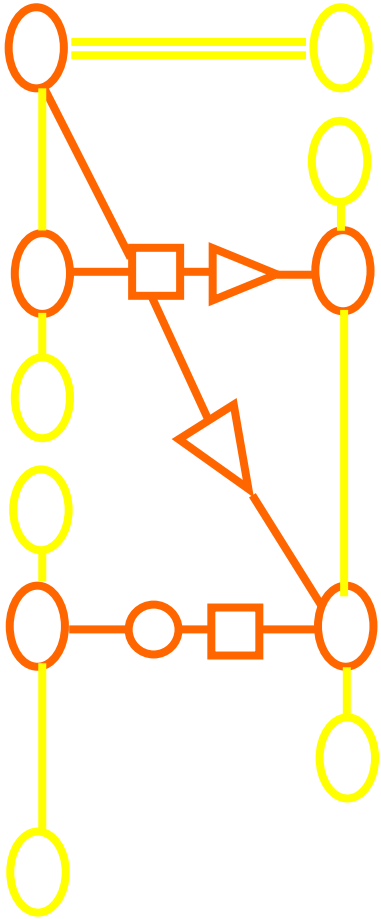
A **non-canonical** subgraph **common** to G1 and G2 whose **completions** in G1 and G2 are **isomorphic**

Example 1:

16S KT-23



16S KT-11

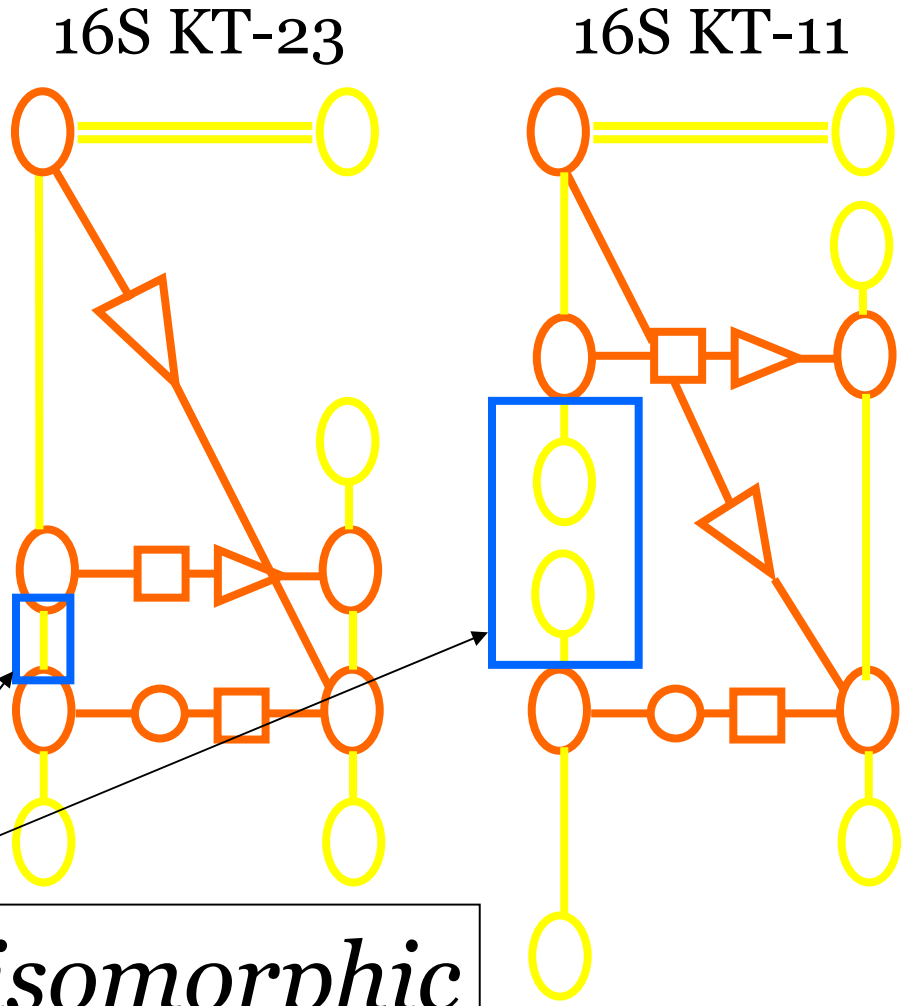


Definitions

An **extensible common non-canonical** subgraph to G1 and G2

=

A **non-canonical** subgraph **common** to G1 and G2 whose **completions** in G1 and G2 are **isomorphic**

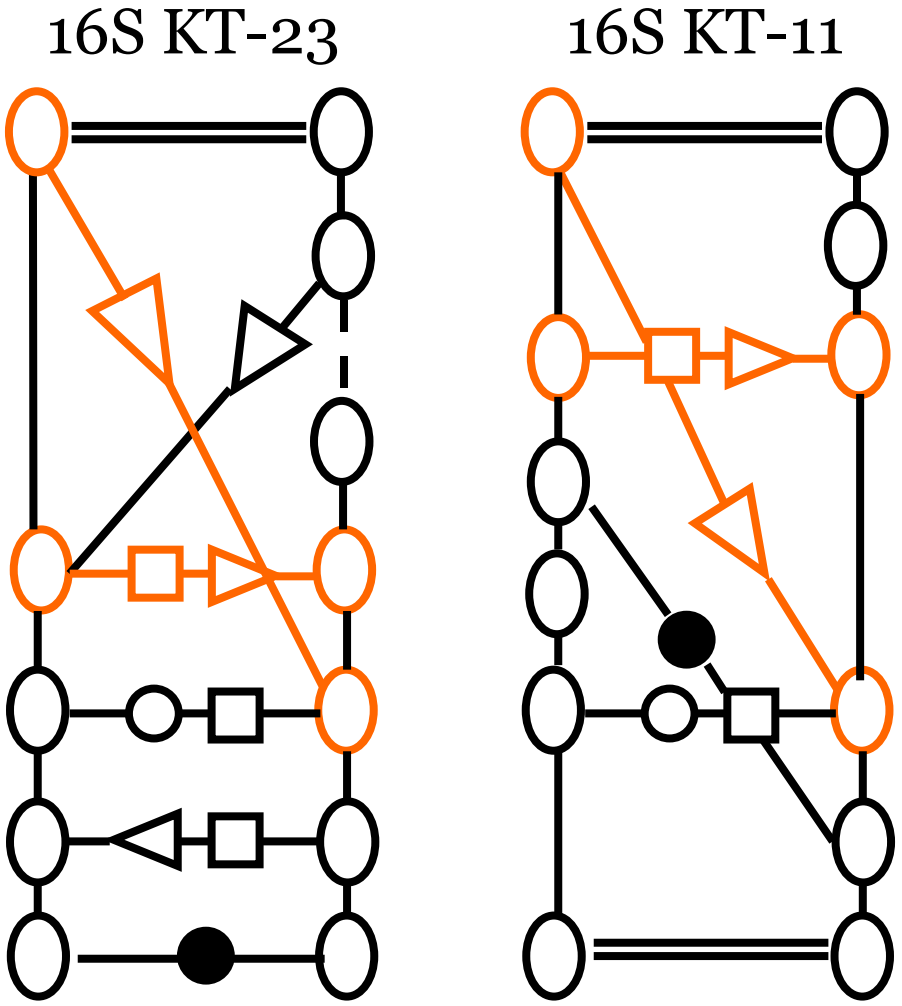


Example 1:

Completions NOT isomorphic

Definitions

An **extensible common non-canonical** subgraph to G1 and G2

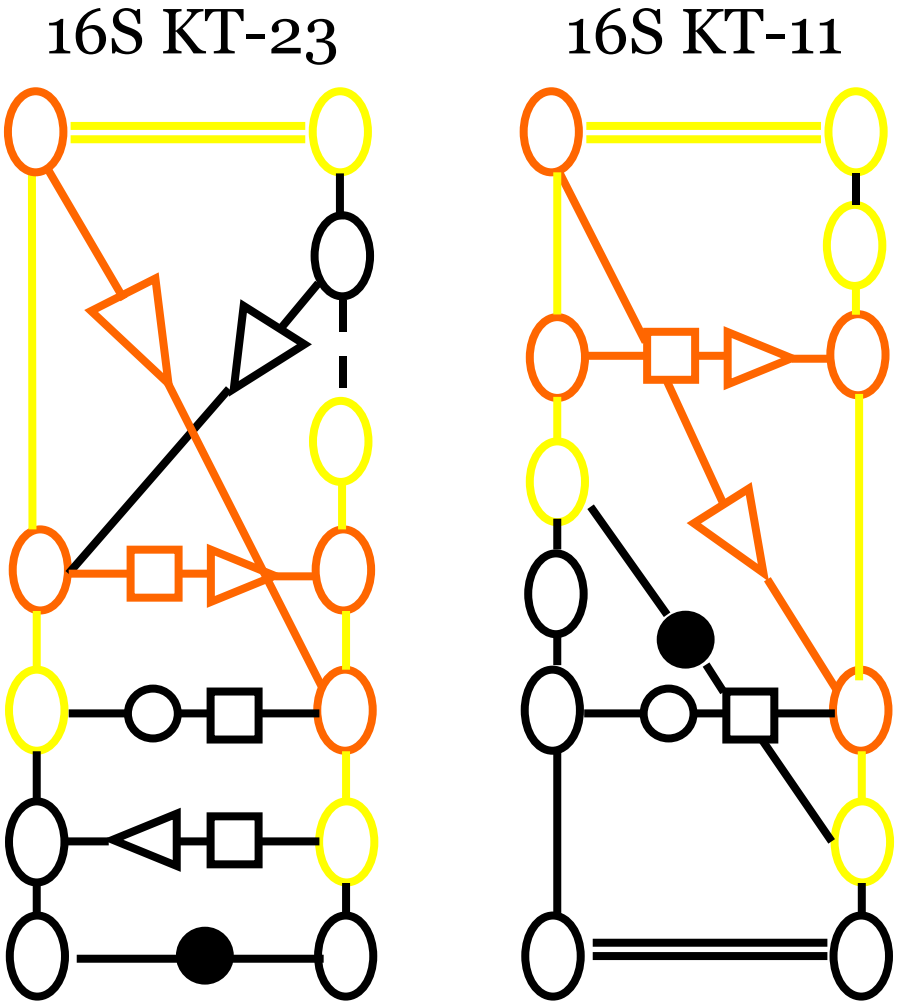


Example 2:

- common non-canonical subgraph

Definitions

An **extensible common non-canonical** subgraph to G1 and G2

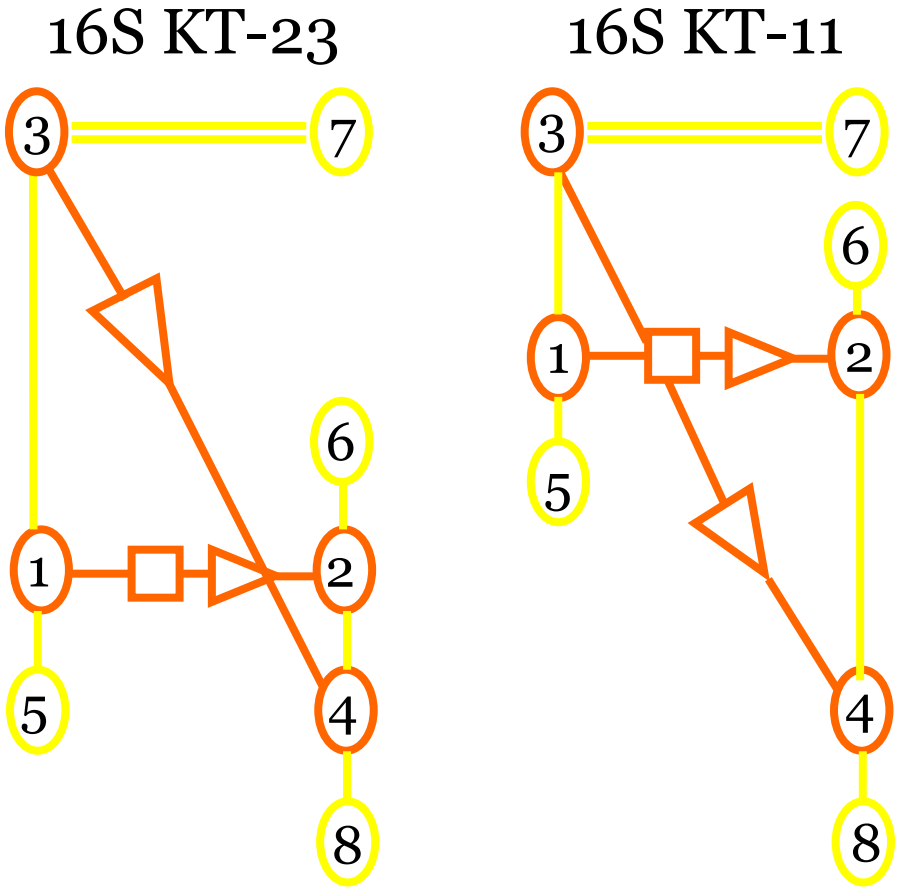


Example 2:

- common non-canonical subgraph
- completions

Definitions

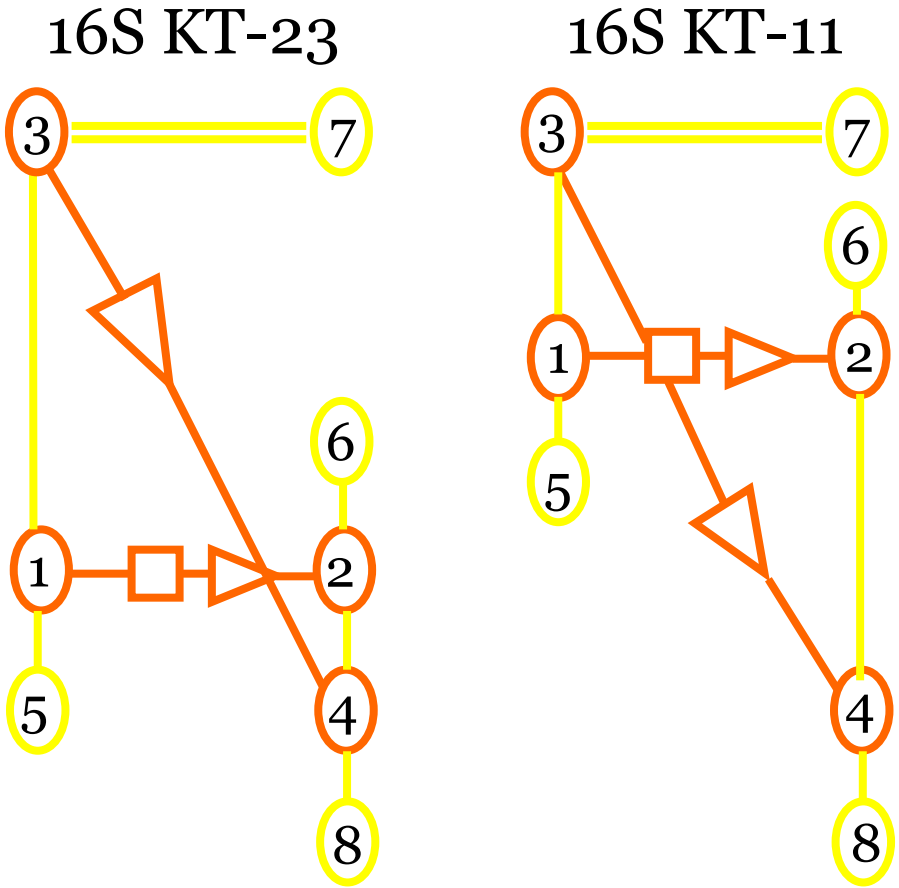
An **extensible common non-canonical** subgraph to G1 and G2



Example 2:

Definitions

An **extensible common non-canonical** subgraph to G1 and G2



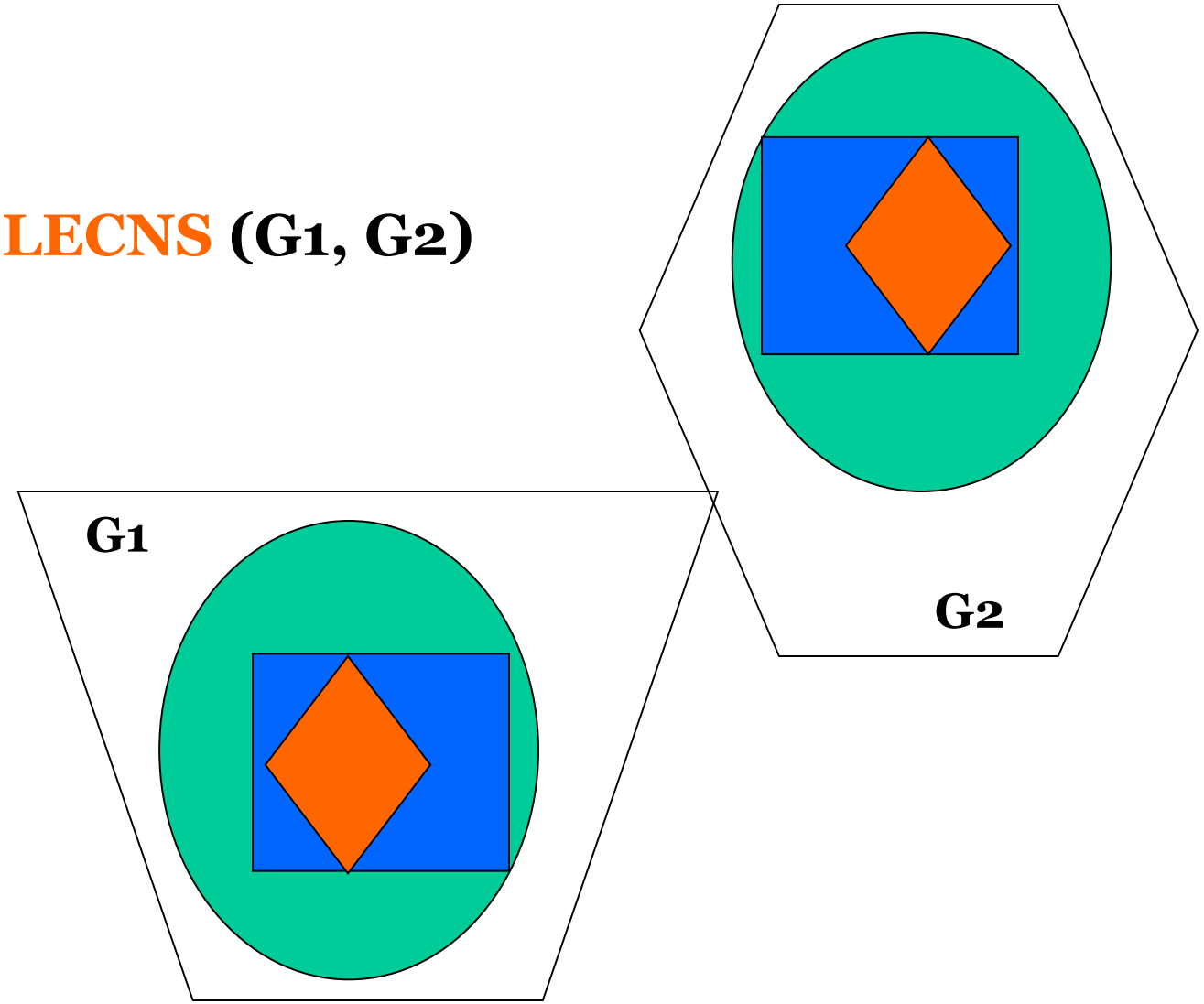
Example 2:

Completions ARE isomorphic

Definitions

Largest
Extensible
Common
Non-canonical
Subgraph

LECNS (G1, G2)

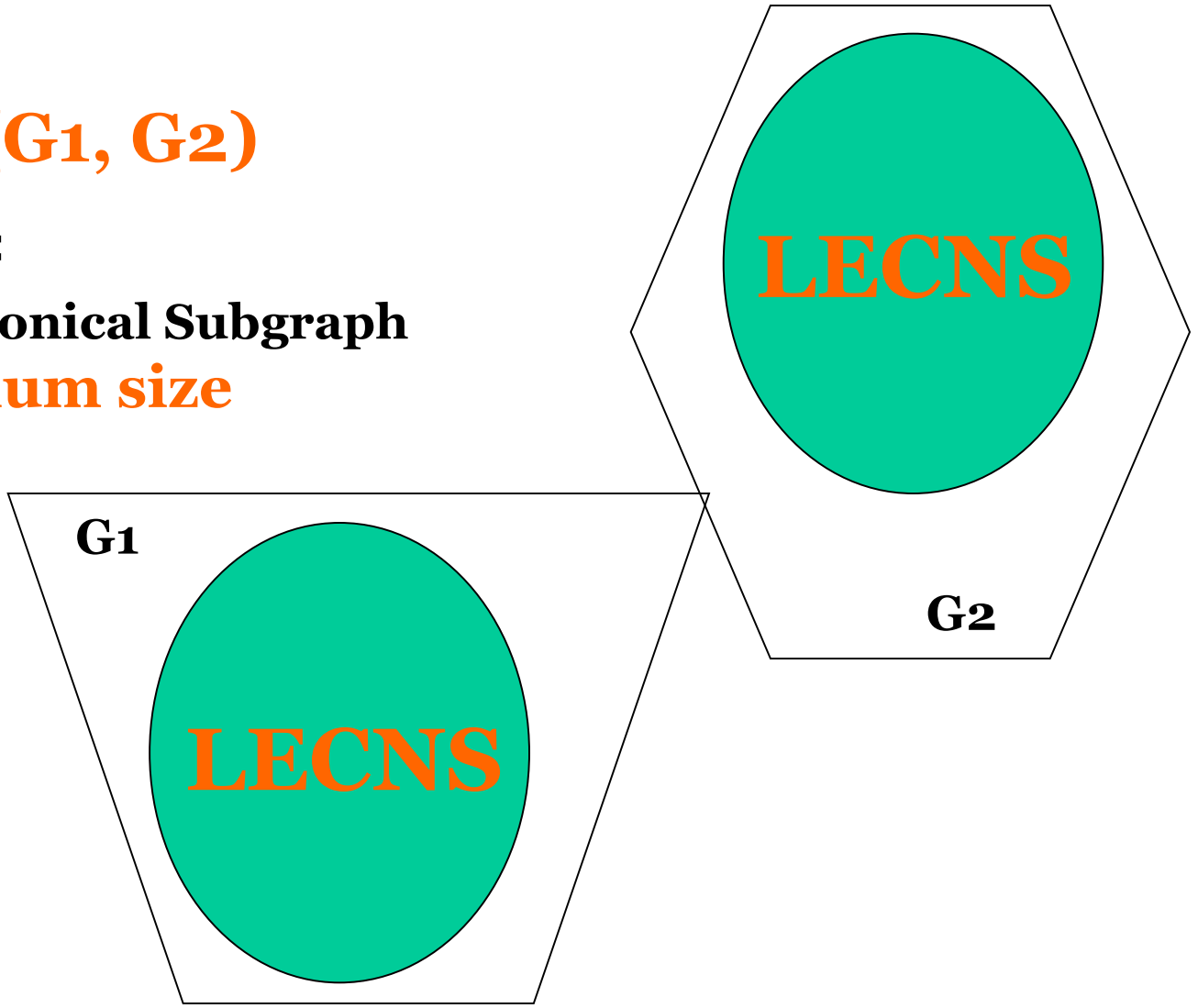


Definitions

LECNS (G1, G2)

=

Common Non-canonical Subgraph of maximum size



Measure

$$\text{Sim}(G1, G2) = \frac{|| \text{LECNS}(G1, G2) ||}{\max(|| G1 ||, || G2 ||)}$$

Measure

$$Sim(G1, G2) = \frac{|| LECNS(G1, G2) ||}{\max(|| G1 ||, || G2 ||)}$$

Properties:

- $0 \leq sim \leq 1$
- $sim(G1, G2) = sim(G2, G1)$

Learning set

catalogue of *H.marismortui.23S (reference structure)*

209 elements

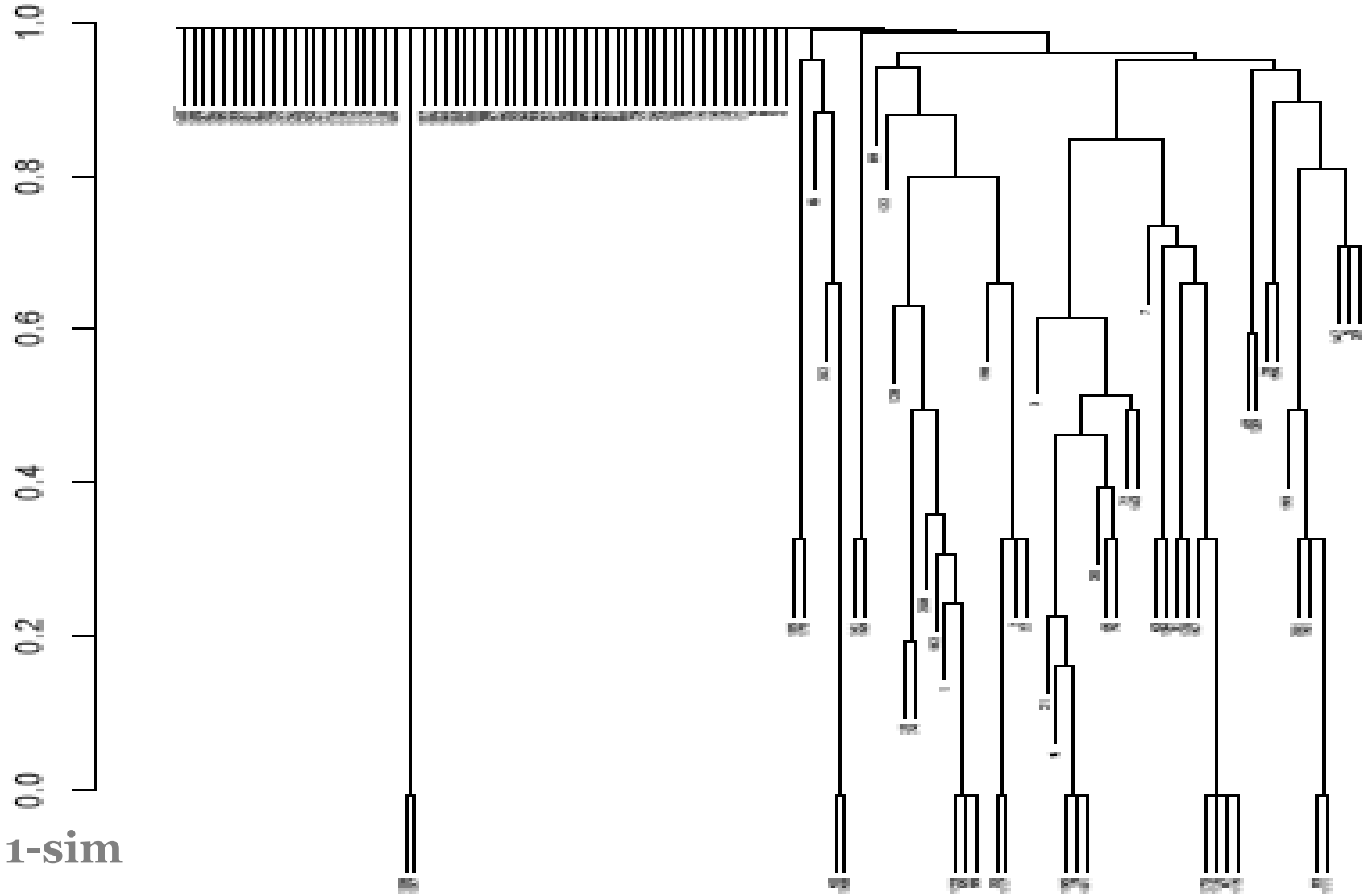
Method

Hierarchical clustering with average linkage (*UPGMA algorithm*)

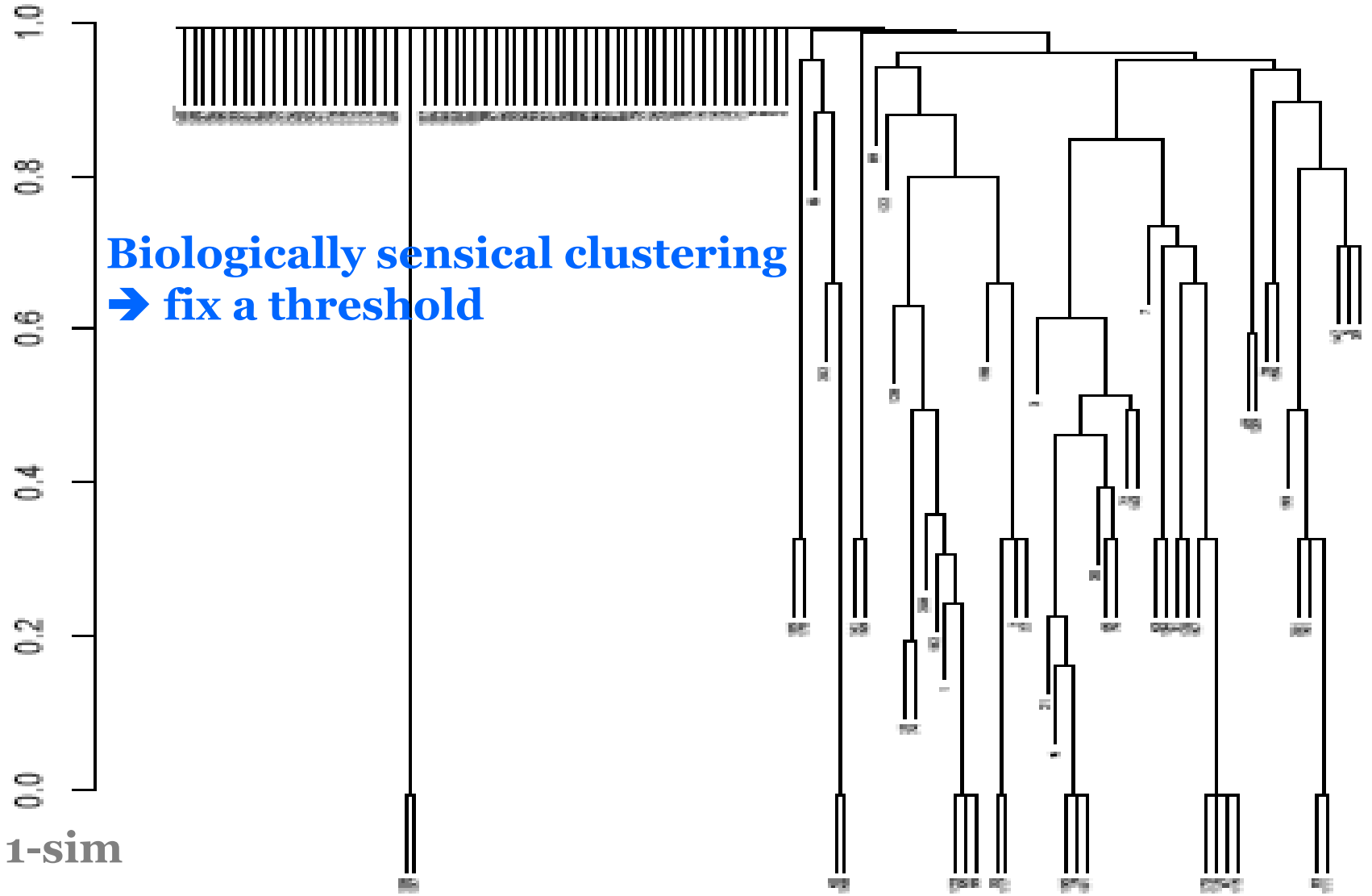
Output

Dendrogram of 2D structural elements

Hierarchical dendrogram *H.m 23S*

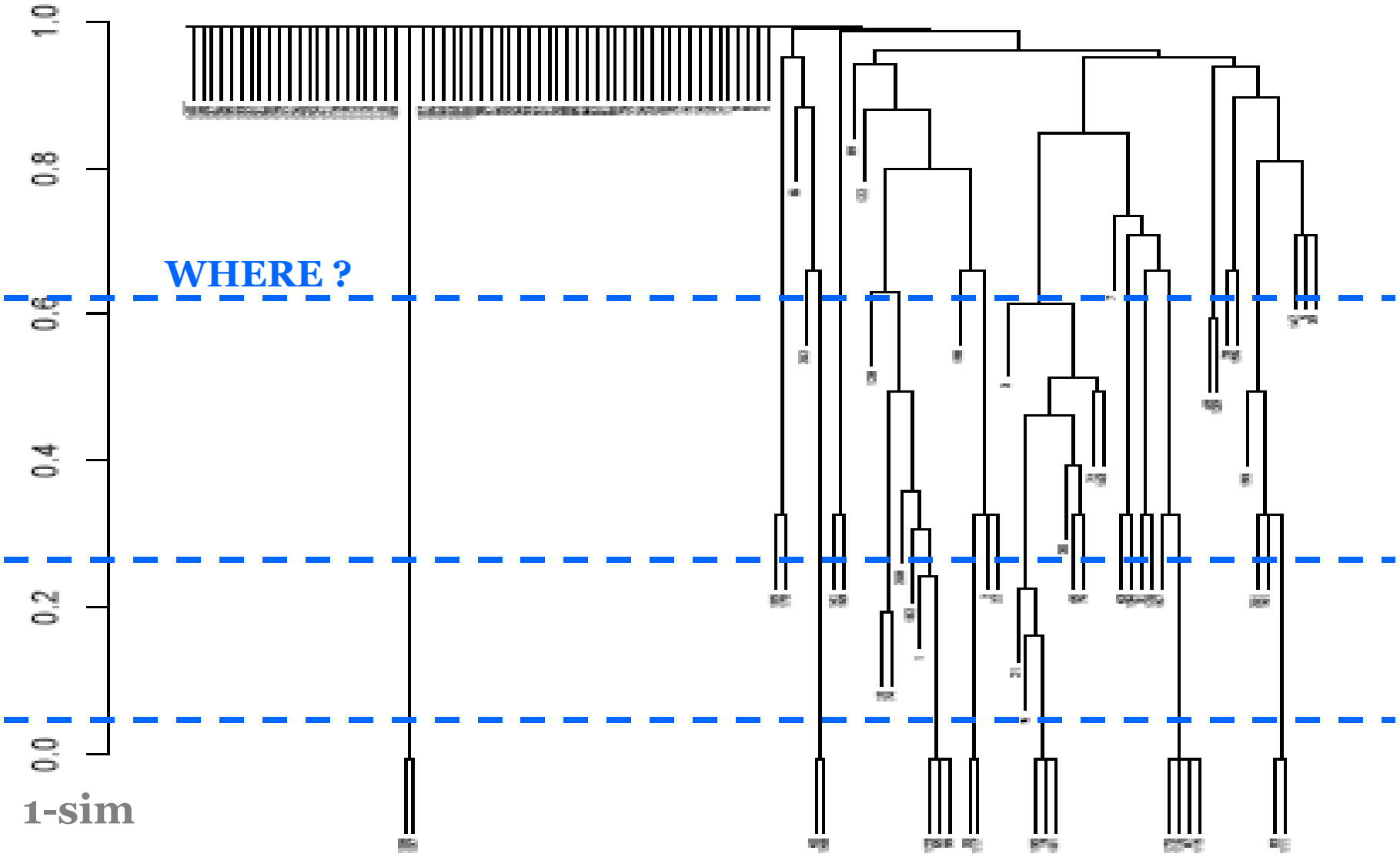


Hierarchical dendrogram *H.m 23S*

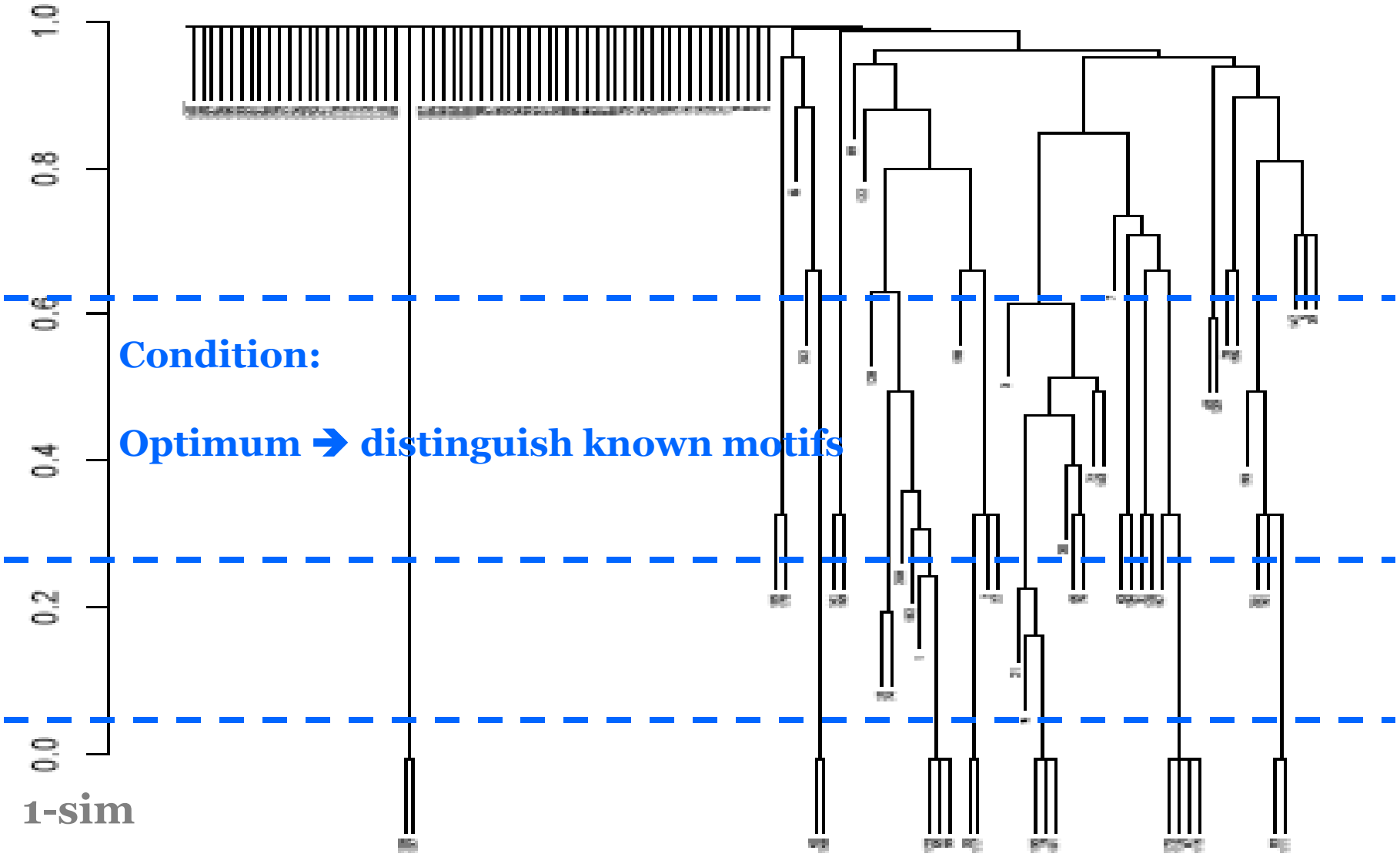


Biologically sensical clustering
➔ fix a threshold

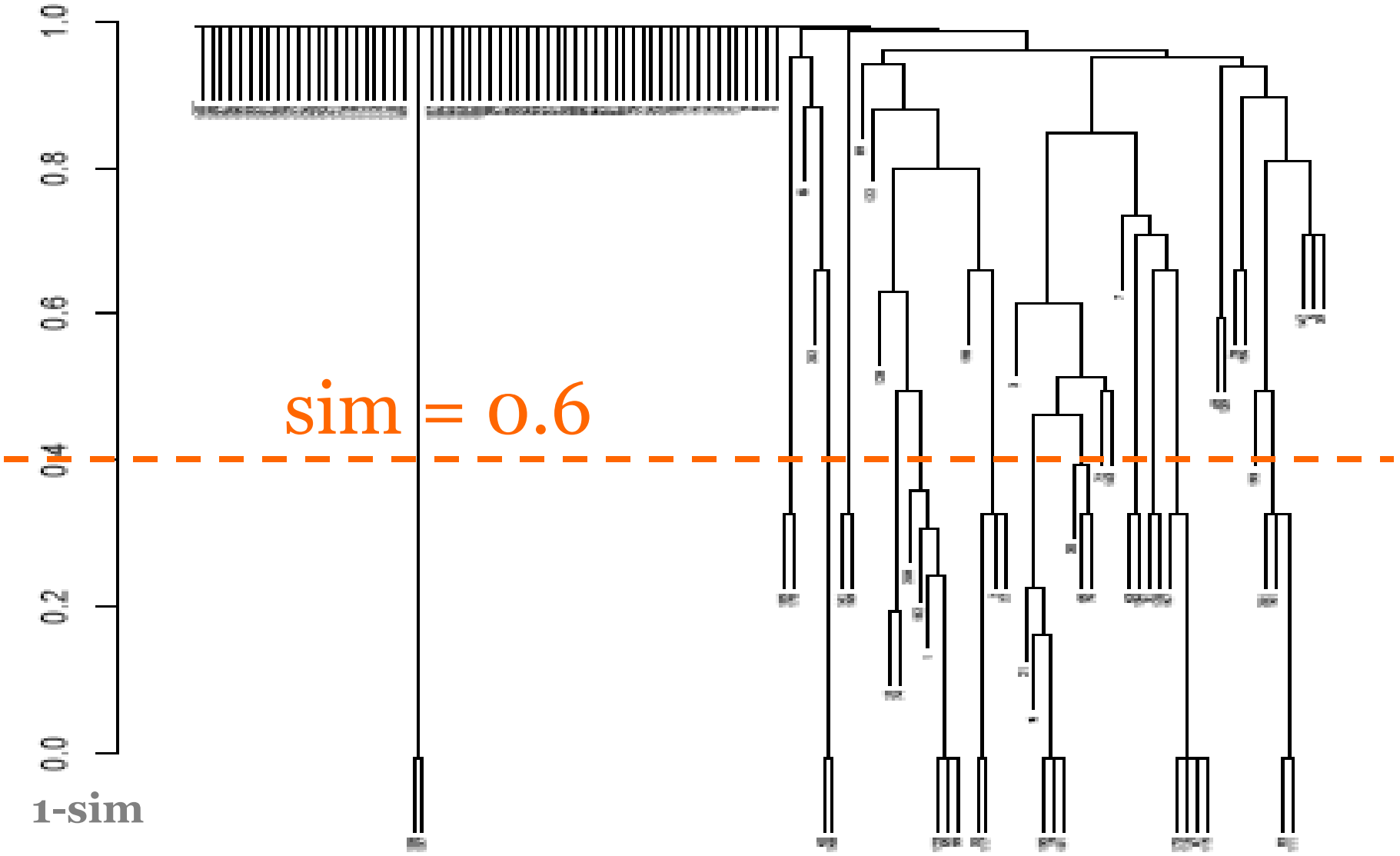
Hierarchical dendrogram H.m 23S



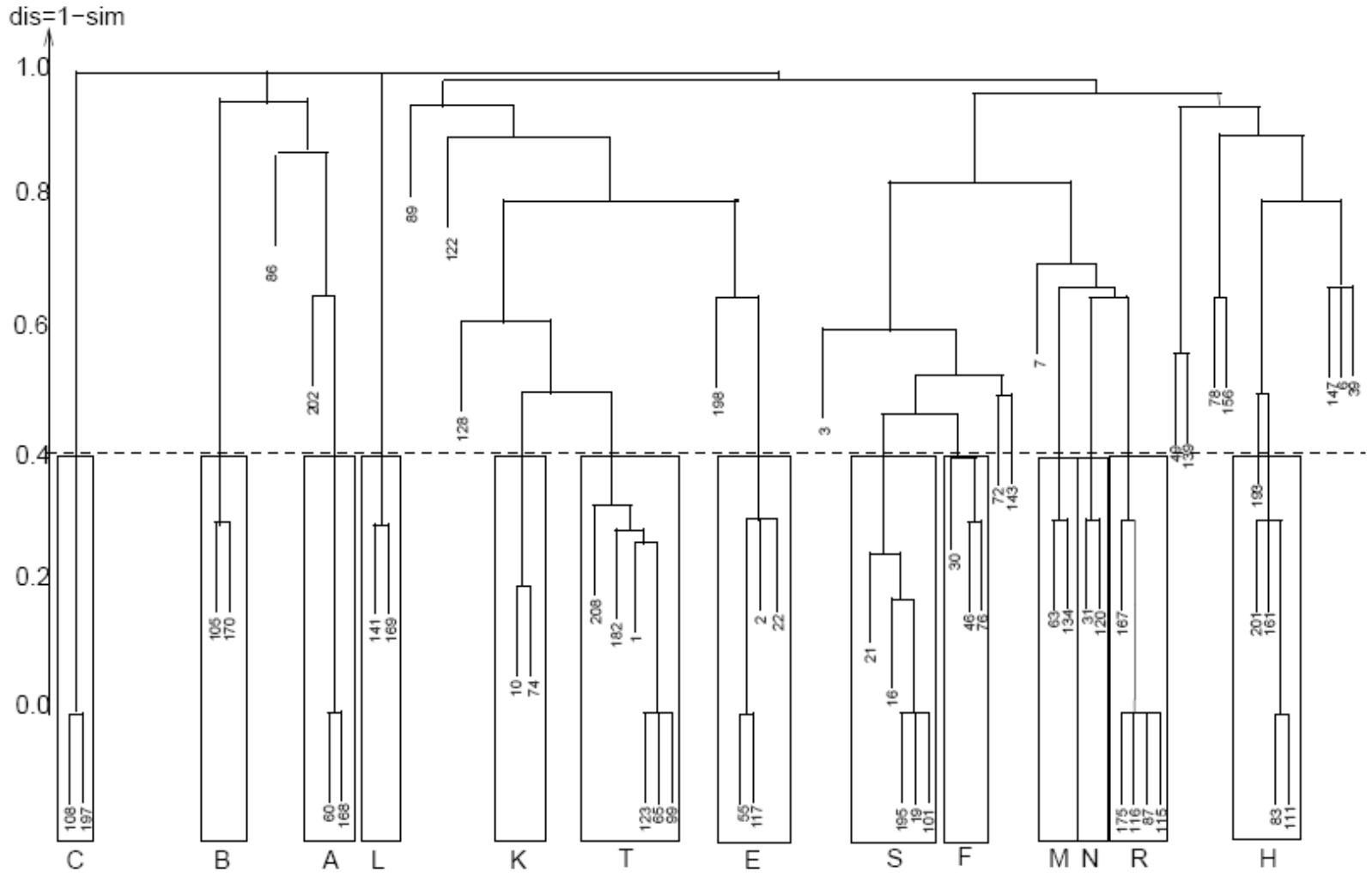
Hierarchical dendrogram *H.m 23S*



Hierarchical dendrogram *H.m 23S*



Hierarchical dendrogram *H.m 23S*

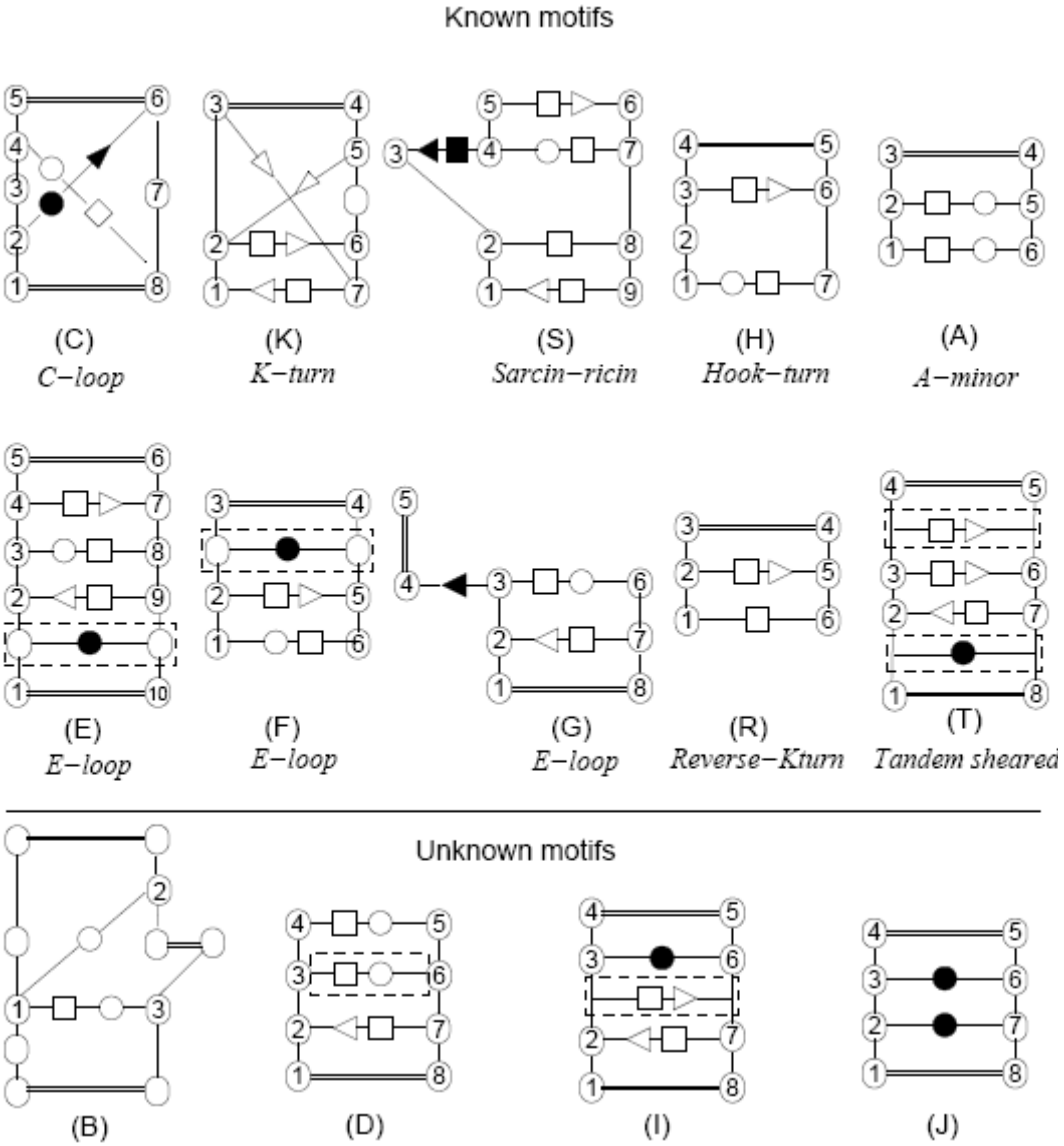


Results

3 organisms:

- 50S H.marismortui
- 50S E.coli
- 16S T.thermophilus

- 10 known motifs
- 4 putative new motifs



Results

3 organisms:

- 50S H.marismortui
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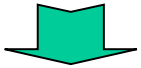


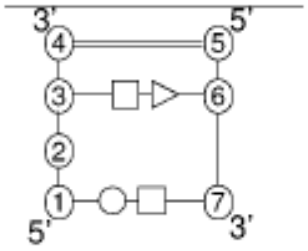
- 10 known motifs
- 4 putative new motifs

Motifs	Molecule	PDB file	Occur.	Known/Unknown
(C)	*H.m*23S	1s72	2	C-loop [22]
	*E.coli*23S	2aw4	2	C-loop [22]
(K)	*H.m*23S	1s72	2	Kturns KT-7, KT-38 [22]
(S)	*H.m*23S	1s72	6	Sarcin-ricin [18]
	*E.coli*23S	2aw4	5	Sarcin-ricin [18]
	*T.th*16S	1j5e	2	Sarcin-ricin [18]
(H)	*H.m*23S	1s72	5	Hook-turn [33]
	*E.coli*23S	2aw4	6	Hook-turn [33]
(A)	*H.m*23S	1s72	3	A-minor [23]
(E)	*H.m*23S	1s72	3	23S E-loop [18]
	*T.th*16S	1j5e	4	23S E-loop [18]
(F)	*E.coli*23S	2aw4	5	23S E-loop comprising sarcin G2664 [18]
	*H.m*23S	1s72	5	23S E-loop comprising composite sarcin G911 [18]
(G)	*E.coli*23S	2aw4	2	23S E-loop [18]
(R)	*H.m*23S	1s72	7	Reverse-Kturn [17]
	*E.coli*23S	2aw4	6	Reverse-Kturn [17]
(T)	*E.coli*23S	2aw4	8	Tandem sheared
	*H.m*23S	1s72	6	Tandem sheared comprising KT-46, KT-58 [22]
	*T.th*16S	1j5e	2	Tandem sheared
(B)	*H.m*23S	1s72	2	Unknown
(D)	*E.coli*23S	2aw4	2	Unknown
(I)	*T.th*16S	1j5e	2	Unknown
(J)	*T.th*16S	1j5e	2	Unknown

Table 1: List of the clusters formed in *H.m 23S*, *E.coli 23S* and *T.th 16S*.

An RNA motif

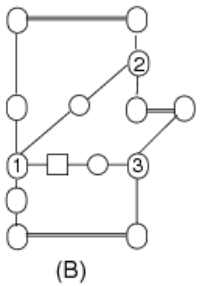
Hook turn

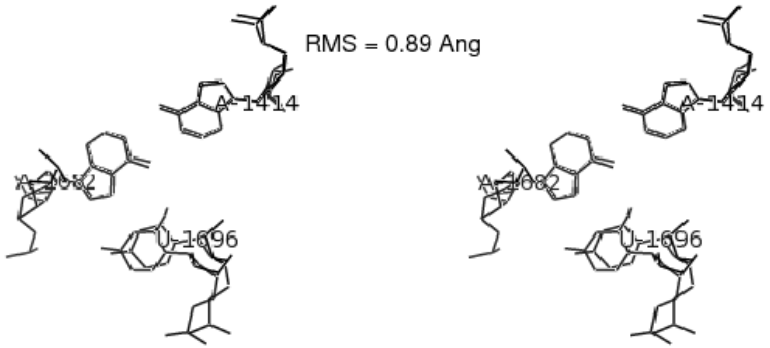


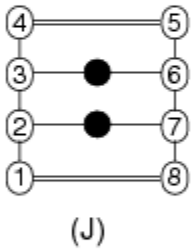
(H)

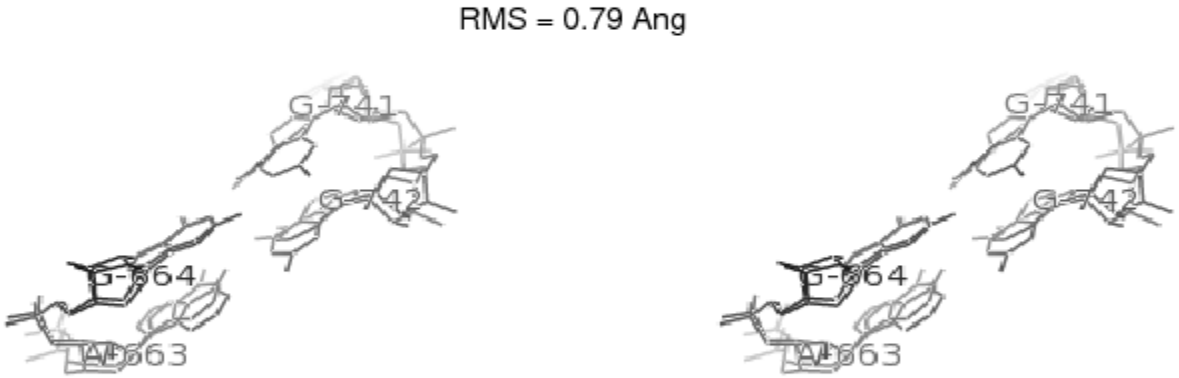
PDB	Inst.	(1)	(2)	(3)	(4)	(5)	(6)	(7)	Catalogue	RMSD (ref.H83)
1s72	H83	1096_U	1097_A	1098_A	1099_G	1257_C	1258_G	1259_A	Internal L.(83)	0.00
	H111	1457_U	1458_A	1459_A	1460_G	1483_C	1484_G	1485_A	Internal L.(111)	0.76
	H201	2774_U	2775_A	2776_A	2777_G	2797_C	2798_G	2799_A	Internal L.(201)	0.33
	H161	2242_U	2243_C	2244_A	2245_C	2256_G	2257_G	2258_A	Junction L.(161)	1.61
	H193	2673_U	2674_G	2675_A	2676_C	2809_G	2810_G	2811_A	Internal L.(193)	1.61
2aw4	H73	999_U	1000_A	1001_A	1002_G	1153_C	1154_G	1155_A	Internal L.(73)	0.42
	H101	1352_U	1353_A	1354_A	1355_G	1376_C	1377_G	1378_A	Internal L.(101)	0.69
	H106	1578_U	1579_A	1580_A	1581_G	1417_C	1418_G	1419_A	Internal L.(106)	0.31
	H205	2739_U	2740_A	2741_A	2742_G	2762_C	2763_G	2764_A	Internal L.(205)	0.52
	H161bis	2197_U	2198_A	2199_A	2200_C	2223_G	2224_G	2225_A	Junction L. (161)	1.60
	H196	2637_U	2638_G	2639_A	2640_G	2774_C	2775_G	2776_A	Internal L.(196)	1.66

Deux nouveaux motifs potentiels









Conclusions

- Une mesure de similarité sur les sous-graphes d'ARN qui capte bien la notion de motif structural : elle permet de retrouver les motifs connus, sans aucun a priori sur leur structure, forme, position.

- La suite : **motifs d'interaction**.

Merci à...

Dominique Barth

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Alexis Lamiable

Eric Westhof

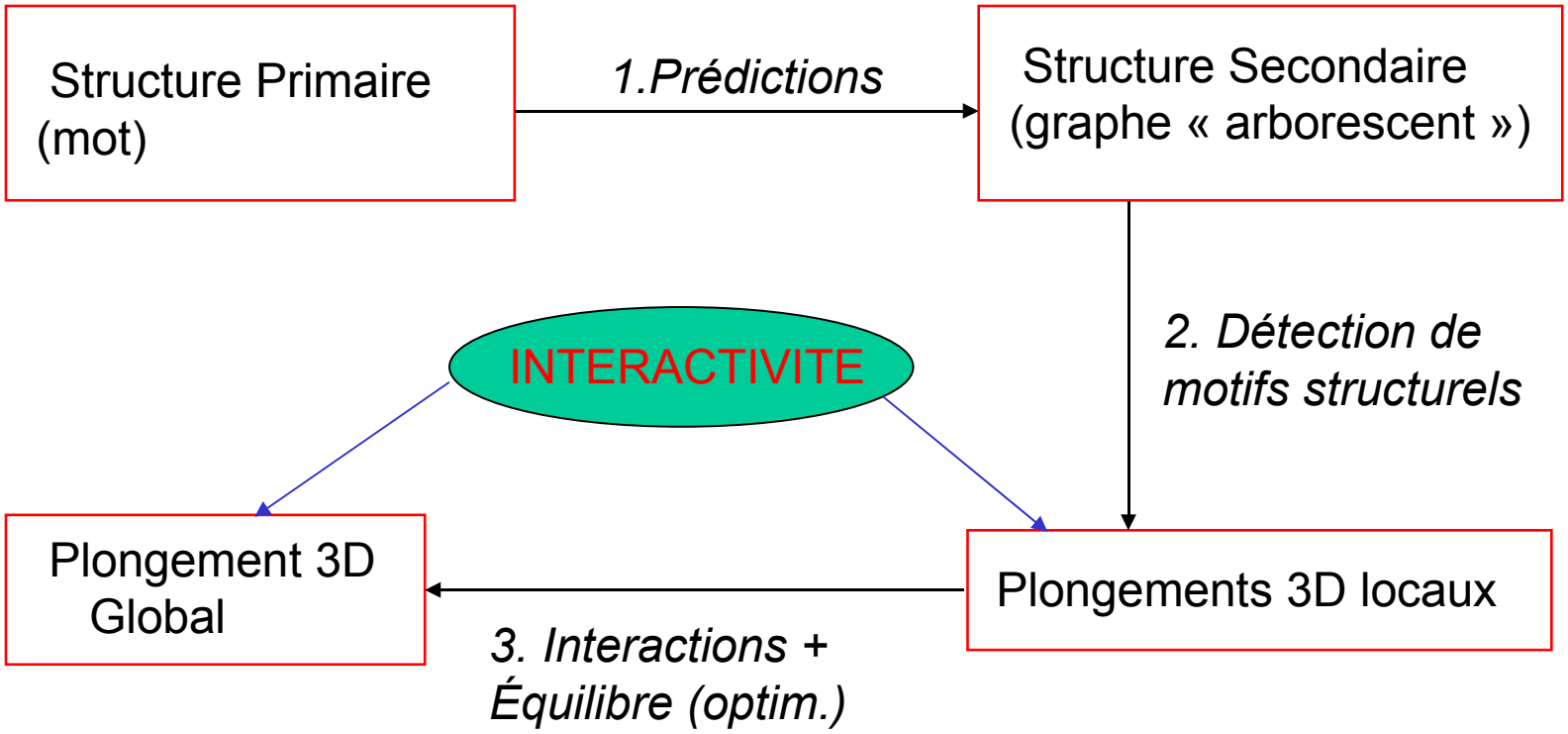
Franck Quessette

François Major

Fabrice Jossinet

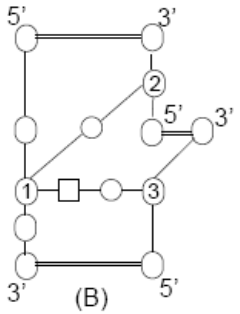
Sandrine Vial

Une approche pour la prédiction de l'architecture 3D de l'ARN

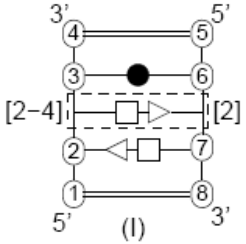


Projet PASAPAS (PRISM, LRI, IGM + IBMC)

Deux nouveaux motifs potentiels



PDB	Inst.	(1)	(2)	(3)	Catalogue	RMSD (ref.B105)
1s72	B170	2369_A	2356_A	2330_U	Junction L.(170)	0.89
	B105	1682_A	1414_A	1696_U	Junction L.(105)	0.00



PDB	Inst.	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	Catalogue	RMSD (ref. I47)
1j5e	I99	1303_C	1304_G	1307_U	1308_U	1329_A	1330_U	1333_A	1334_G	Internal L.(99)	1.85
	I47	605_U	606_G	611_A	612_C	628_G	629_G	632_A	633_G	Internal L.(47)	0.00