Complexity and enumerative aspects of multiple RNA design

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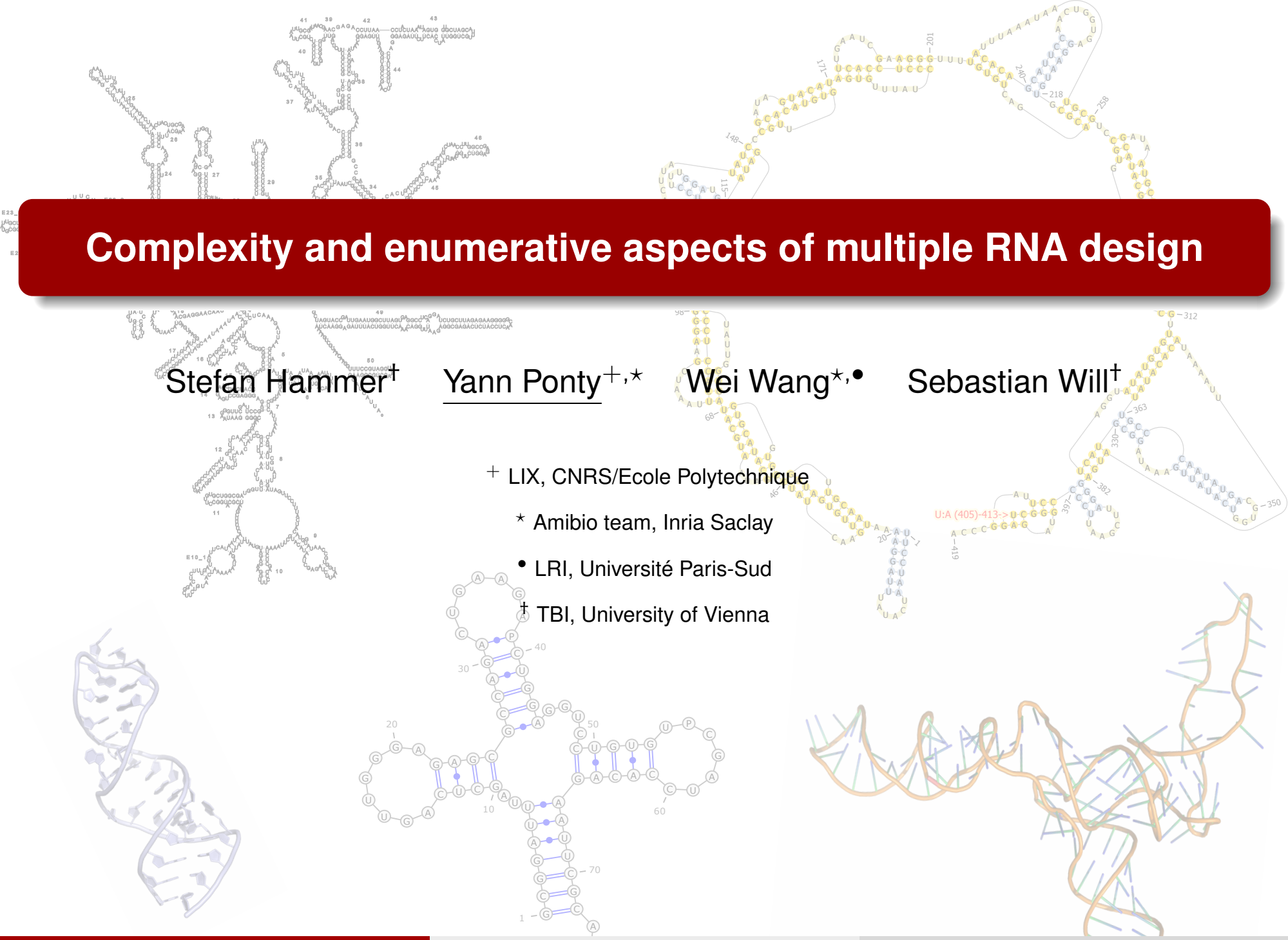
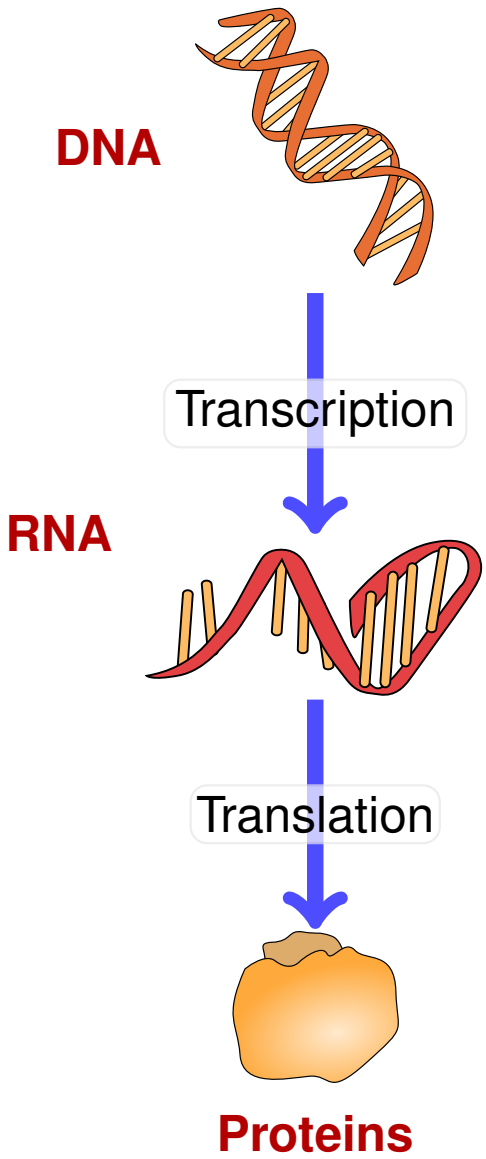
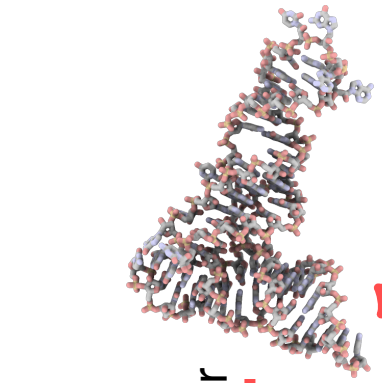
[†] TBI, University of Vienna

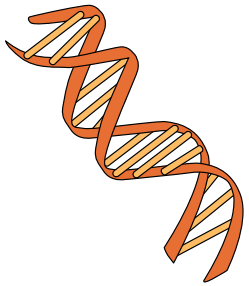


Fundamental *dogma* of molecular biology



Fundamental *dogma* of molecular biology (v2.0)





DNA

Carrier

Transfer

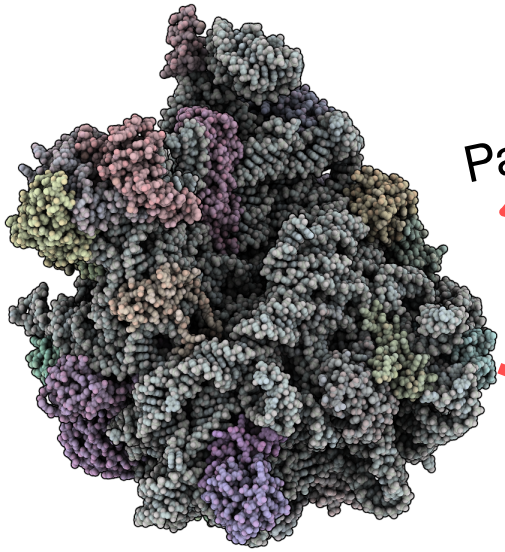
Transcription

Maturation

RNA

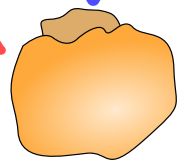
Participates

Regulation



Translation

Synthesis



Proteins

RNA functions

- Messenger
- Translation
- Regulation
- Enzyme
- Catalytic
- . . .

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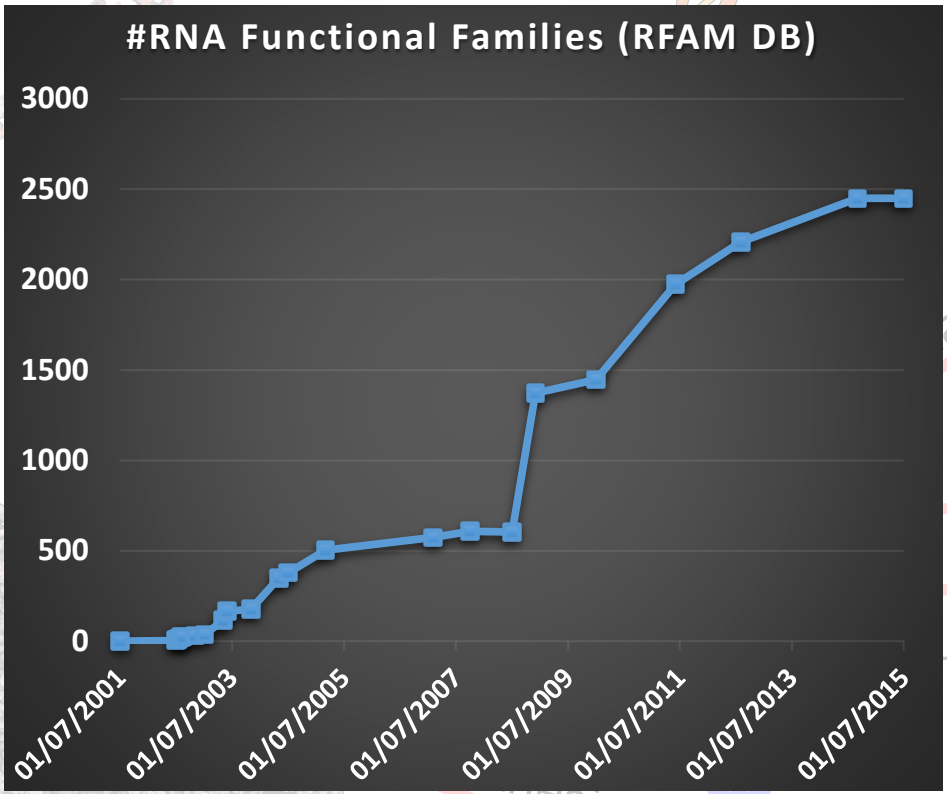

aturation

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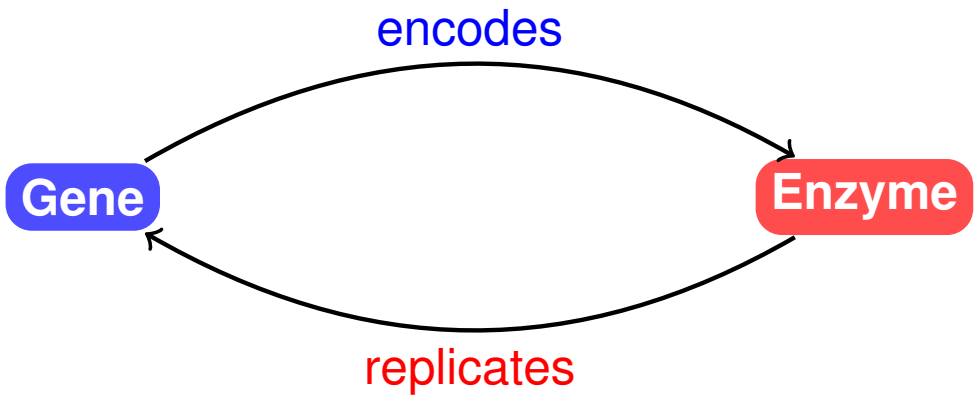
Proteins

RNA world: Resolving the *chicken vs egg* paradox at the origin of life...



A gene big enough to specify an enzyme would be too big to replicate accurately without the aid of an enzyme of the very kind that it is trying to specify. So the system *apparently cannot get started*.

[...] This is the RNA World. To see how plausible it is, we need to look at why proteins are good at being enzymes but bad at being replicators; at why DNA is good at replicating but bad at being an enzyme; and finally why *RNA might just be good enough at both roles to break out of the Catch-22.*

R. Dawkins. *The Ancestor's Tale: A Pilgrimage to the Dawn of Evolution*

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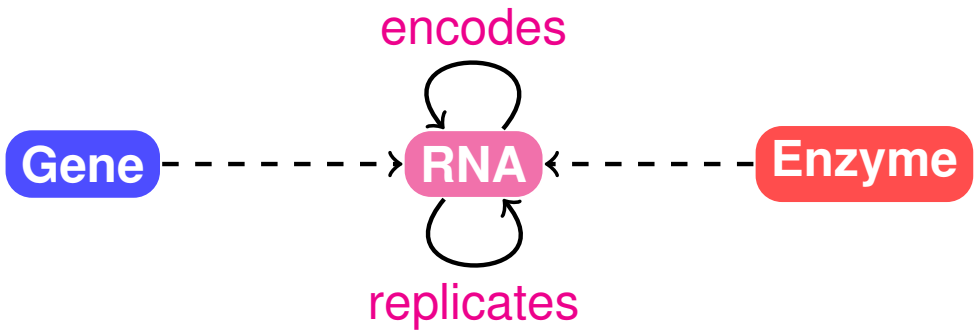

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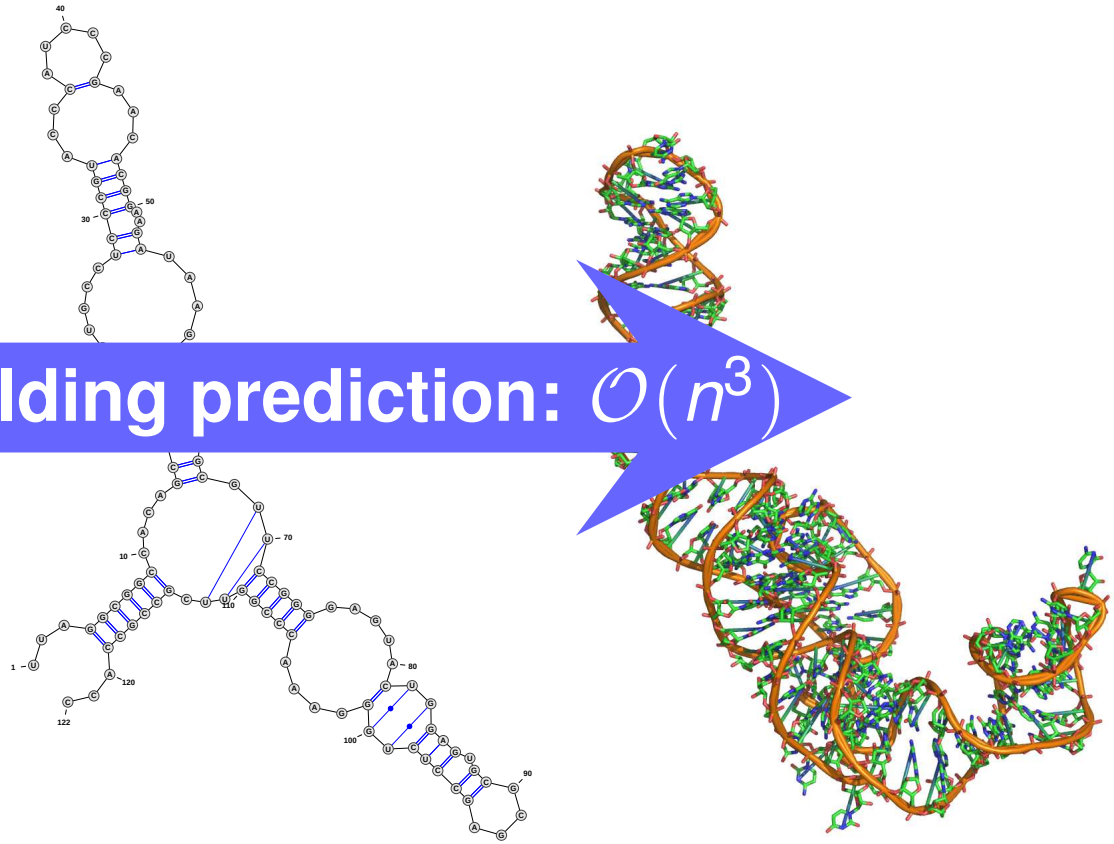
RNA sequence and structure(s)

RNA = Linear Polymer = Sequence in $\{A, C, G, U\}^\star$



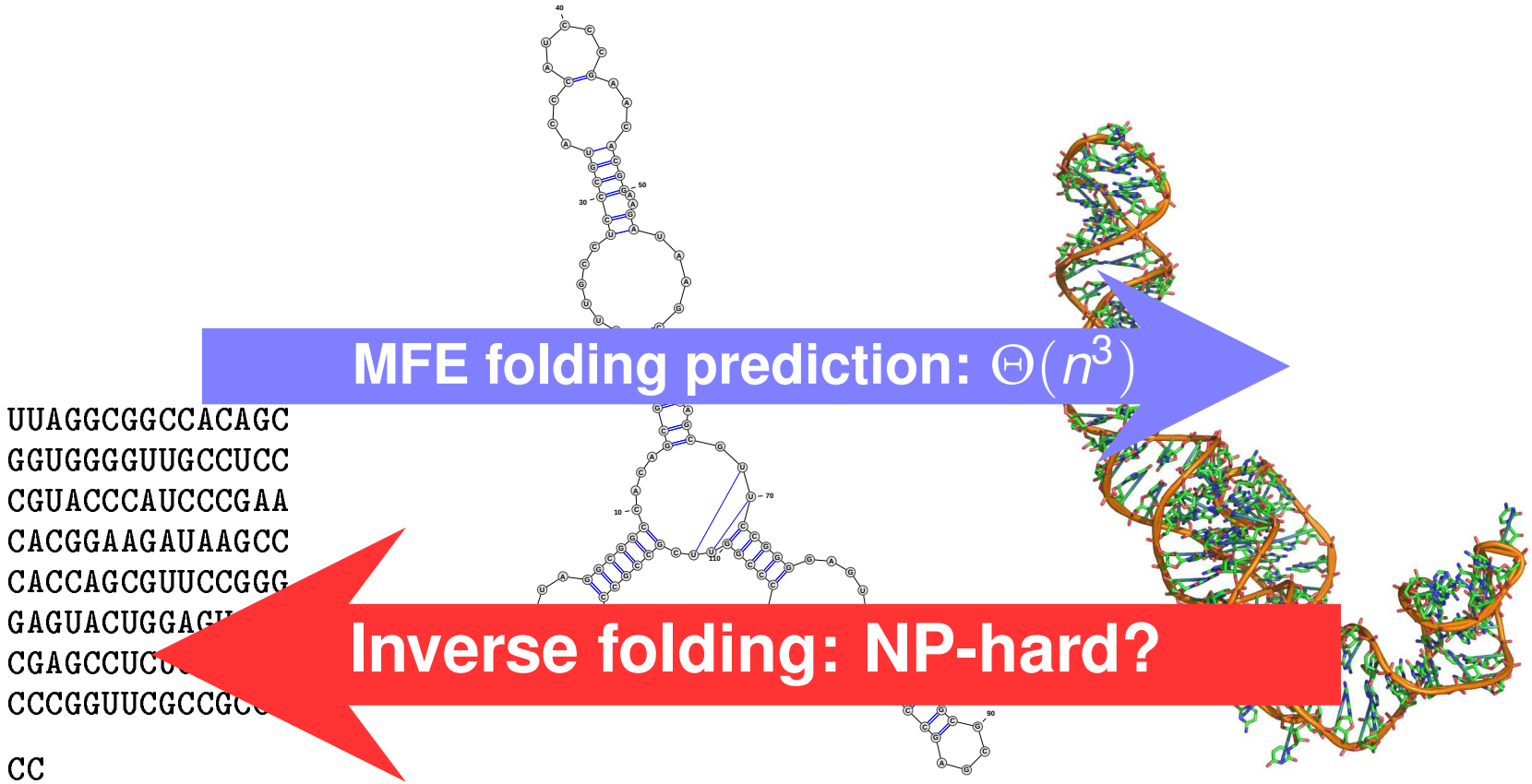

```
UUAGGCGGCCACAGC
GGUGGGGUUGCCUCC
CGUACCCAUCCCGAA
CACGGAAGAUAAGCC
CACCAGCGUUCCGGG
GAGUACUGGAGUGCG
CGAGCCUCUGGGAAA
CCCGGUUCGCCGCCA

CC
```

Primary Structure | Secondary Structure | Tertiary Structure

5s rRNA (PDBID: 1K73:B)

RNA inverse folding

RNA = Linear Polymer = Sequence in $\{A, C, G, U\}^\star$



Primary Structure Secondary Structure Structure Tertiaire

5s rRNA (PDBID: 1K73:B)

Design objectives

Positive structural design

Optimize **affinity** of designed sequences towards target structure
Or simply ensure their compatibility with **one or several** structures

Examples: Most stable sequence for given fold...

Negative structural design

Limit affinity of designed sequences towards **alternative structures**

Examples: Lowest free-energy, High Boltzmann probability/Low entropy...

Additional constraints:

- **Forbid** motif list to appear **anywhere** in design
- **Force** motif list to appear **each at least once**
- **Limit** available alternatives at certain positions
- **Control** overall composition (GC-content)

Existing approaches for negative design

Based on local search...

- RNAInverse - TBI Vienna
- Info-RNA - Backofen@Freiburg
- RNA-SSD - Condon@UBC
- NUPack - Pierce@Caltech
- RNAFBinv - Barash@Ben Gurion

...bio-inspired algorithms...

- ERB - Gantjabesh@Tehran
- FRNAKenstein - Hein@Oxford
- AntaRNA - Backofen@Freiburg

...exact approaches...

- RNAIFold - Clote@Boston College
- CO4 - Will@Vienna

RNA negative design remains a very active area of research ...

...whose computational complexity remains largely unknown!

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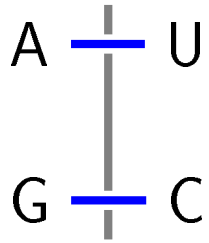
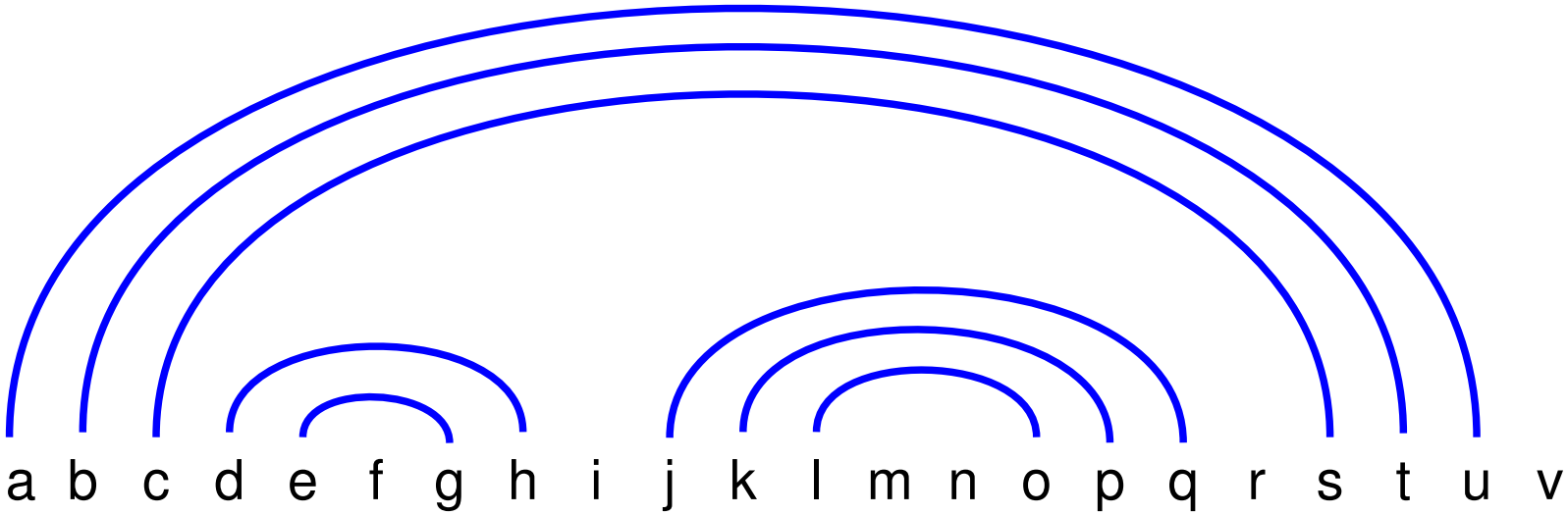
Counting compatible sequences: Watson-Crick + Single structure



Compatible Base Pairs = Only **Watson-Crick** base pairs



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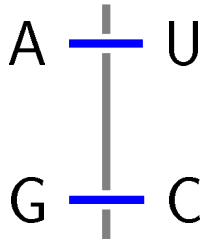

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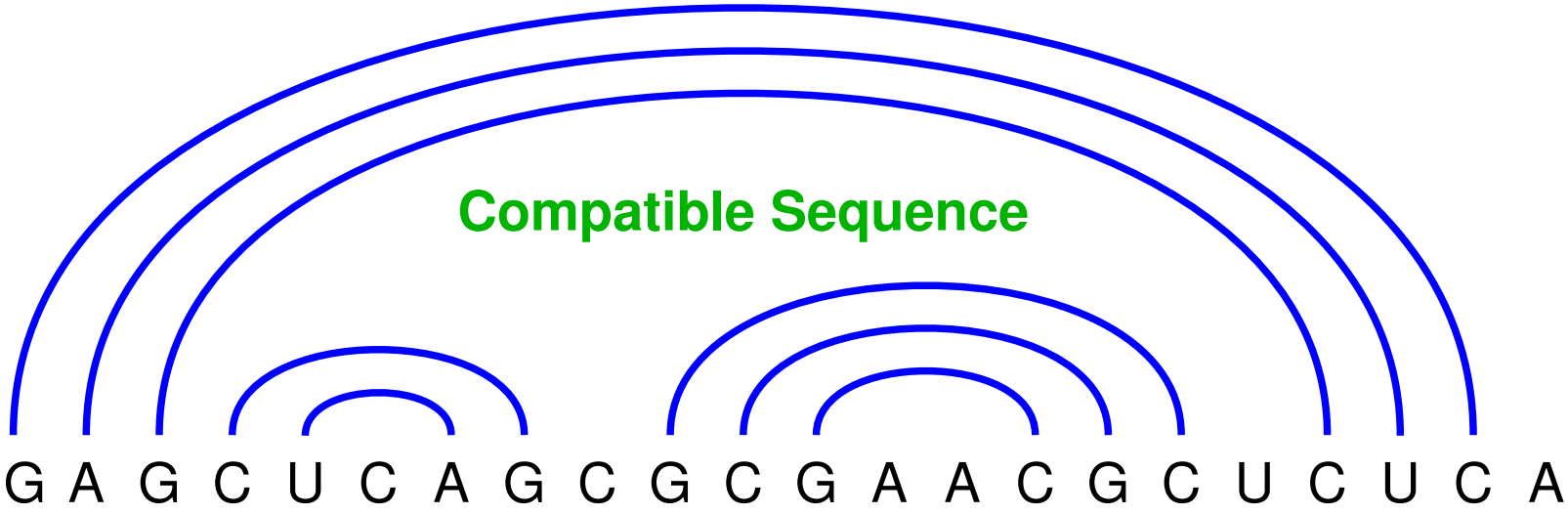

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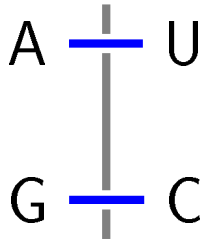

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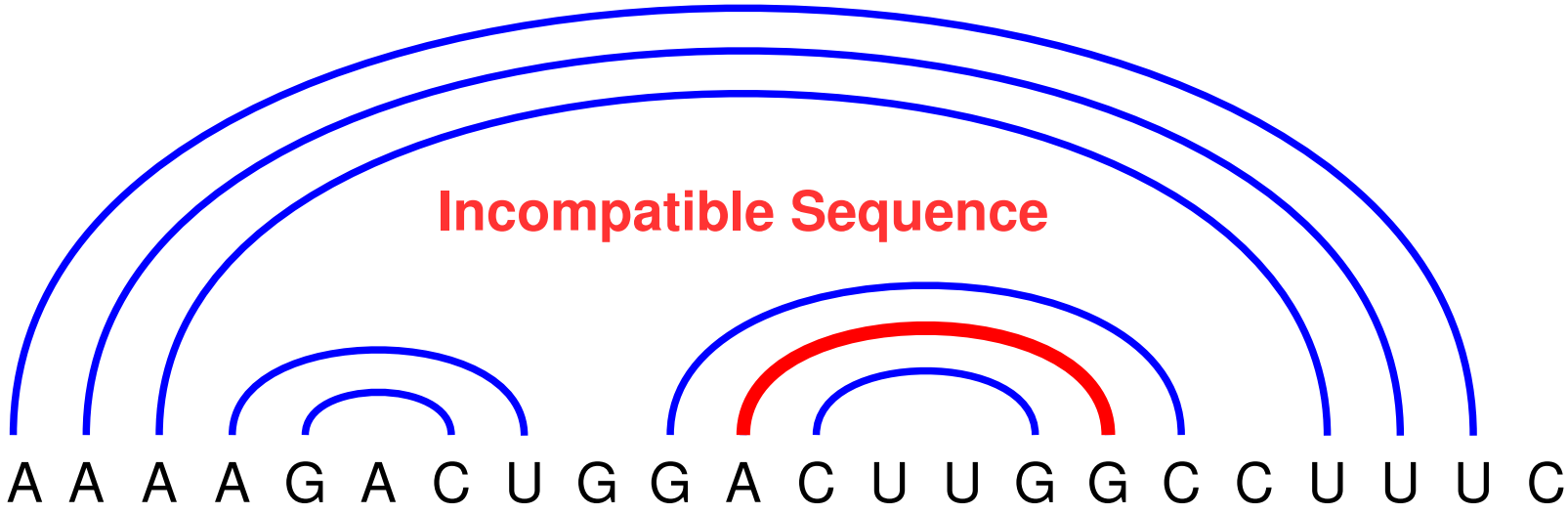

Question: How many **Compatible** sequences?

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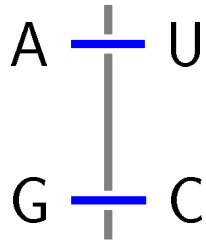

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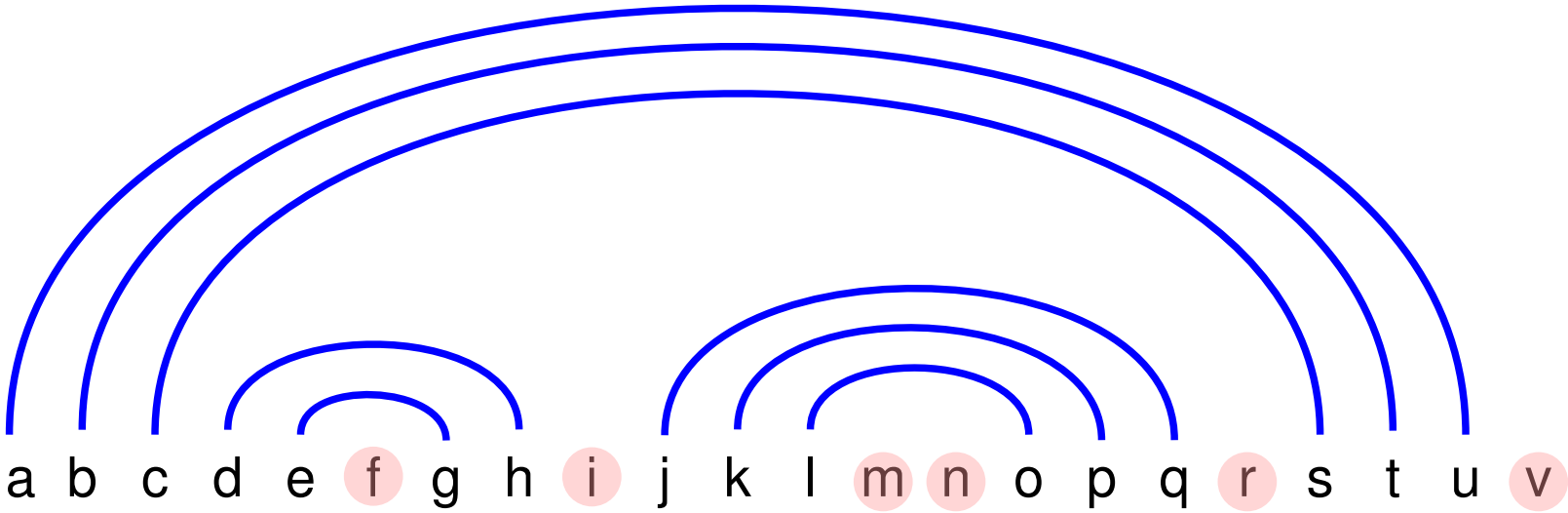

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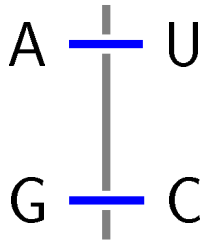

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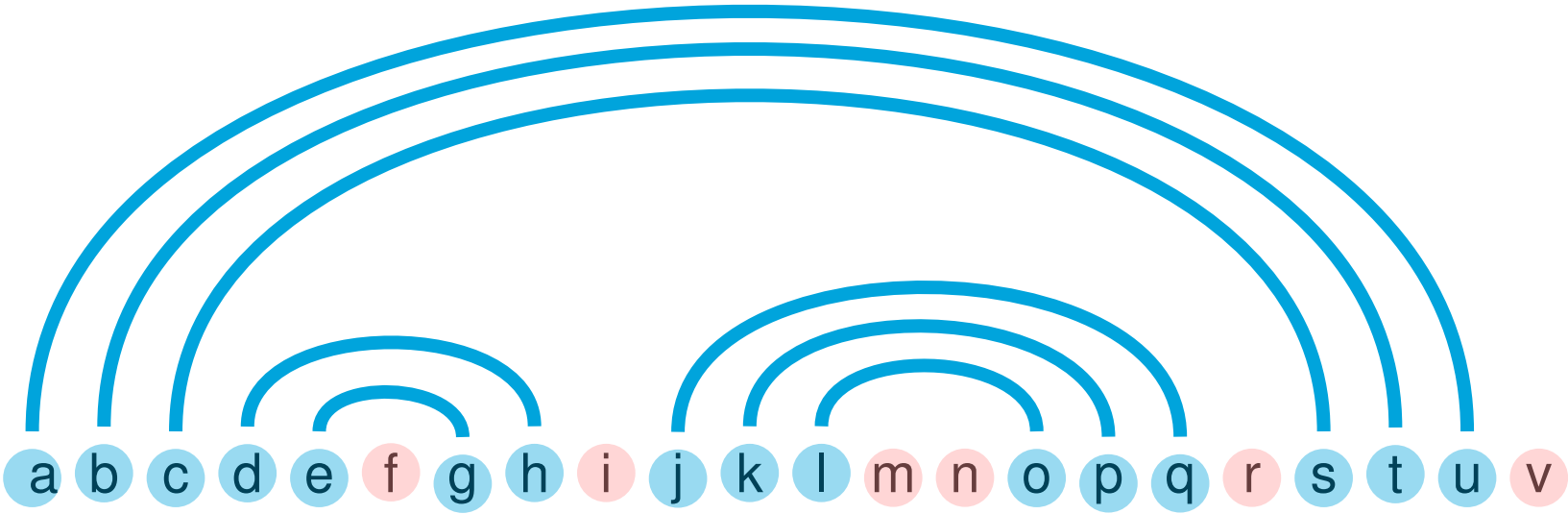

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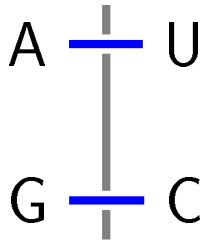

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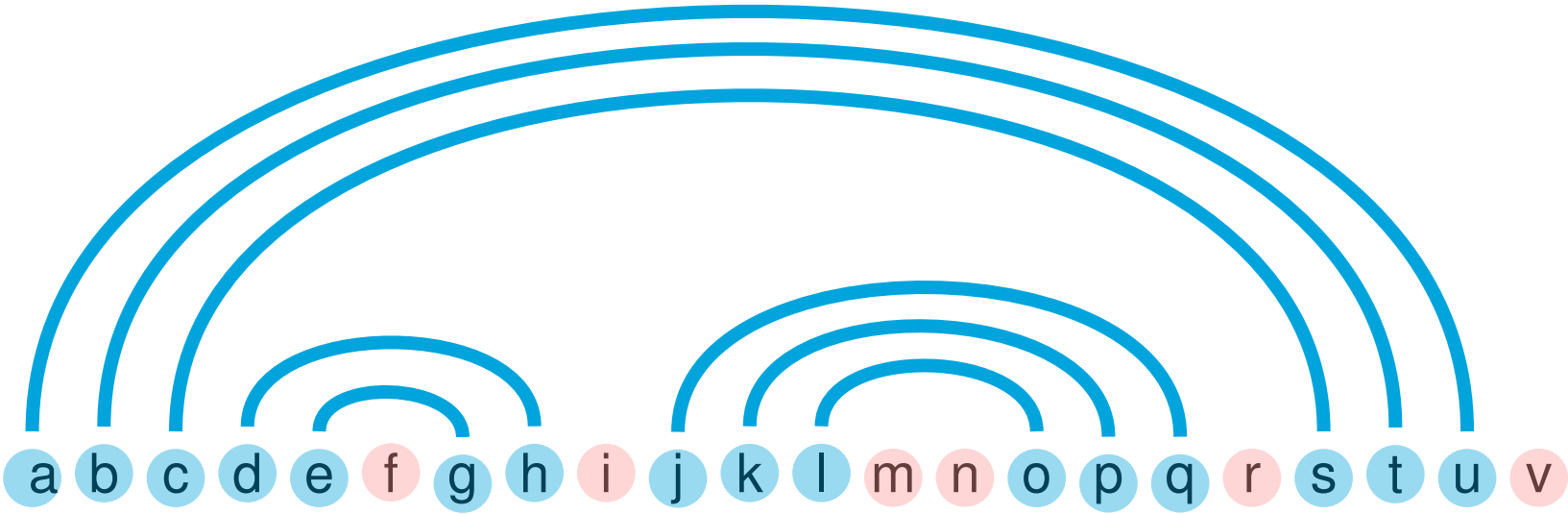
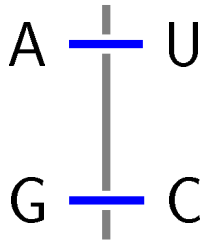


Question: How many **Compatible** sequences?

Answer: $4^{\#\text{BPs}} \times 4^{\#\text{Unpaired}} \rightarrow 268\,435\,456$

Counting compatible sequences: Watson-Crick + Two structures



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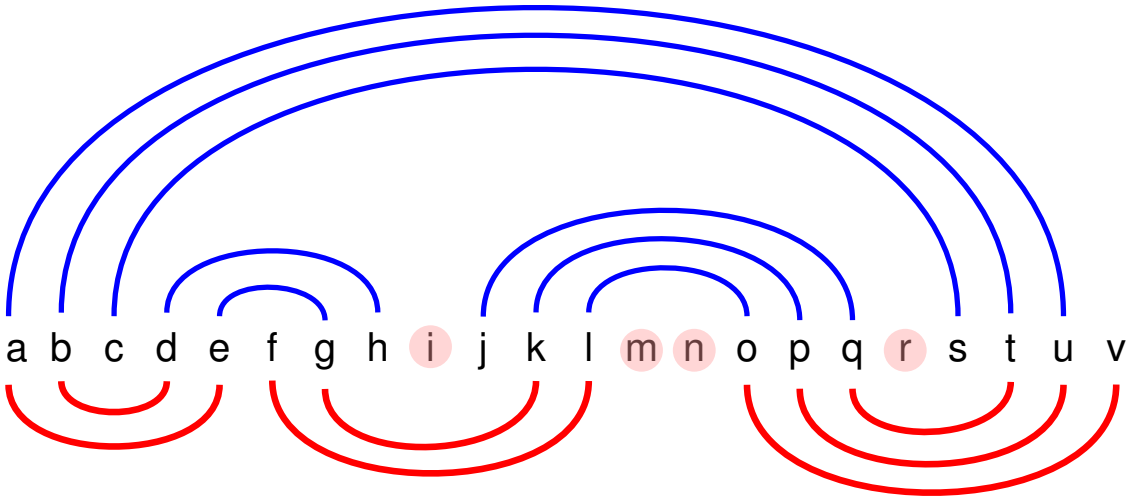
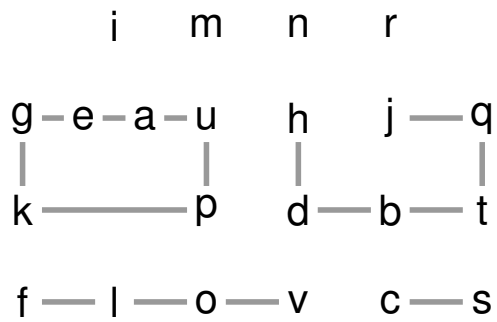


Dependency graph:
Cycles + Paths



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Answer: $\neq \varnothing!$ (both base-pairs and dependency graphs **bipartite**)

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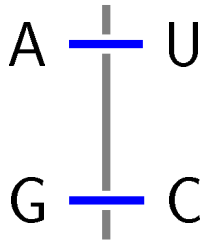

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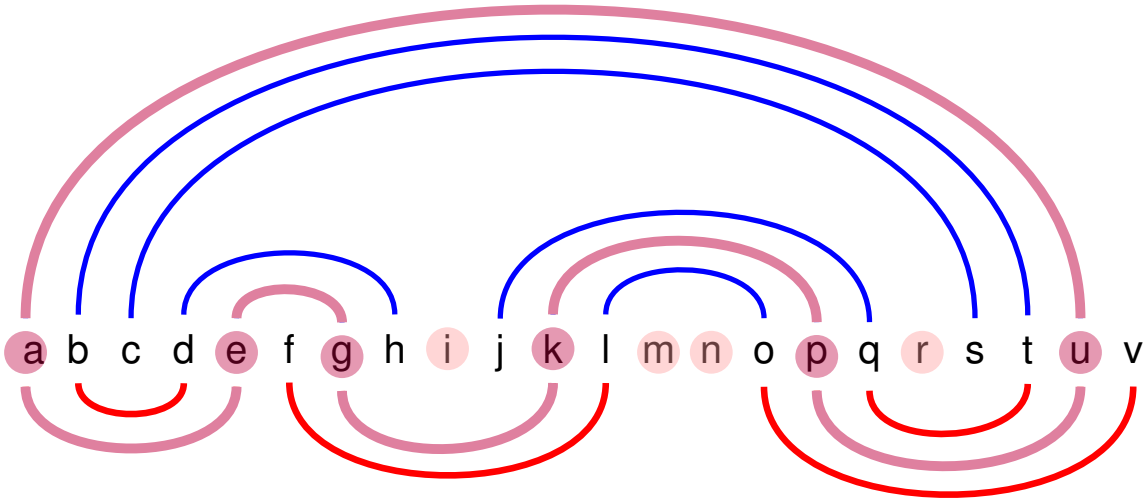

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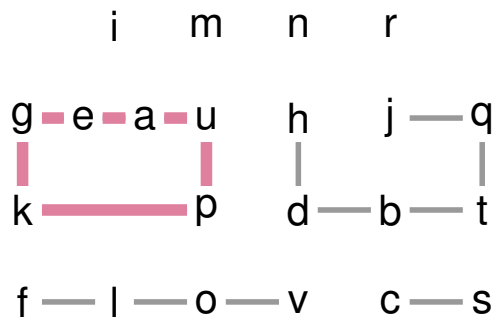

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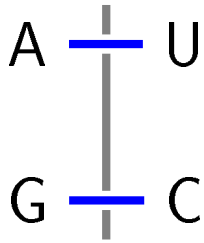

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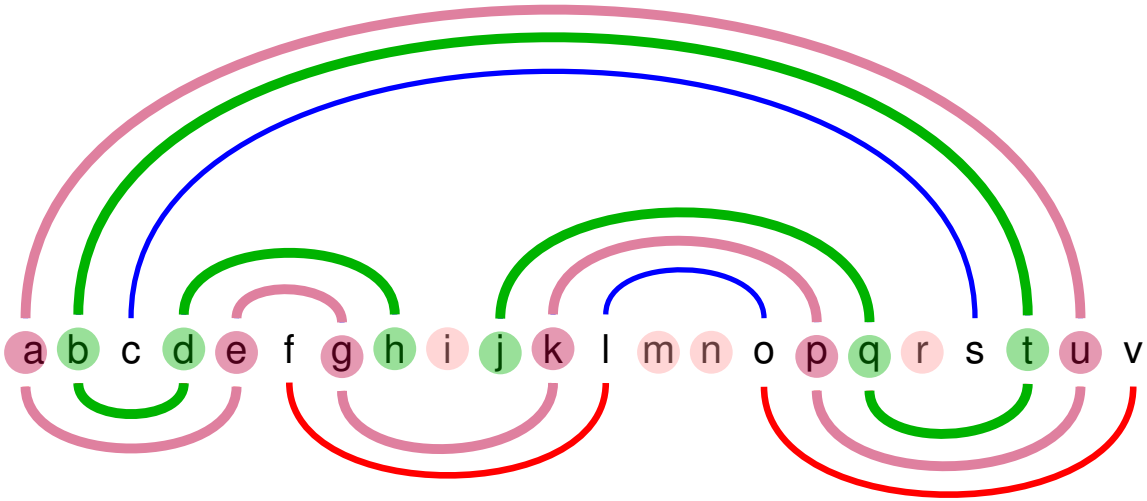

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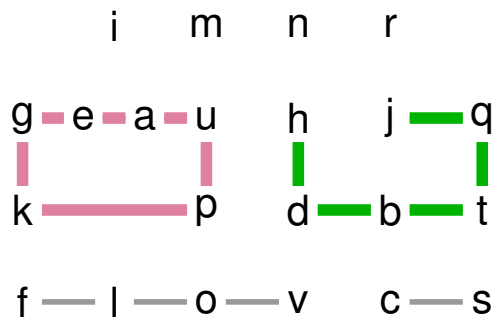

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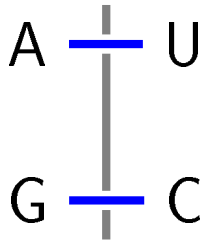

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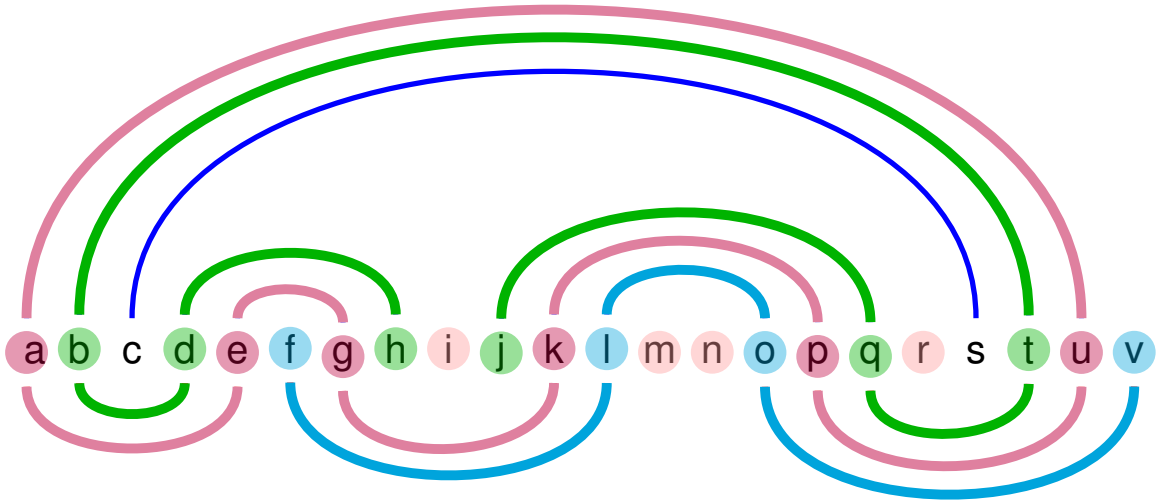

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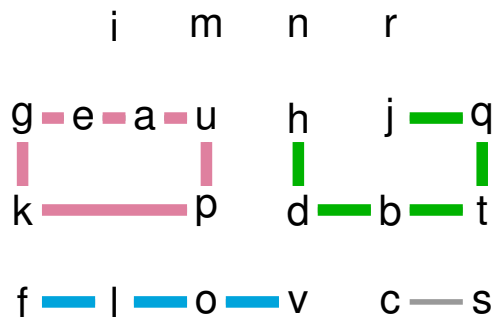

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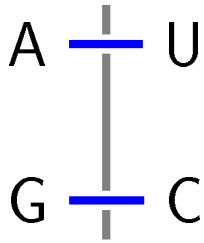

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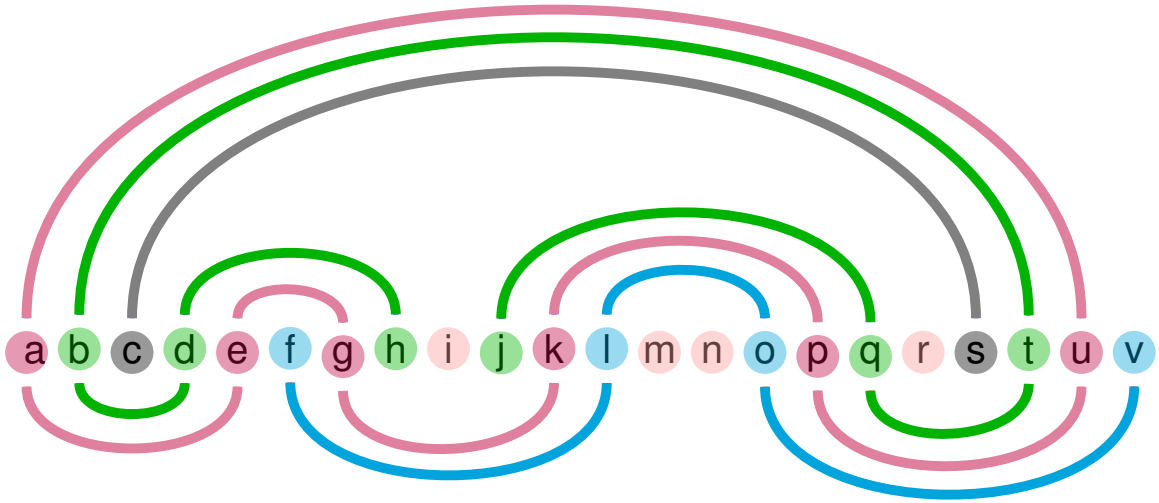

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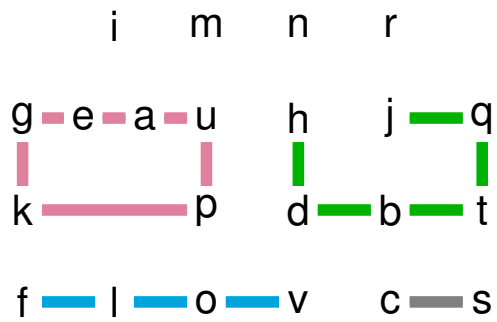

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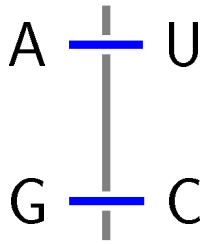
$4^{\#\text{CCs}} \rightarrow 65\,536$

Counting compatible sequences: Watson-Crick + > 2 structures



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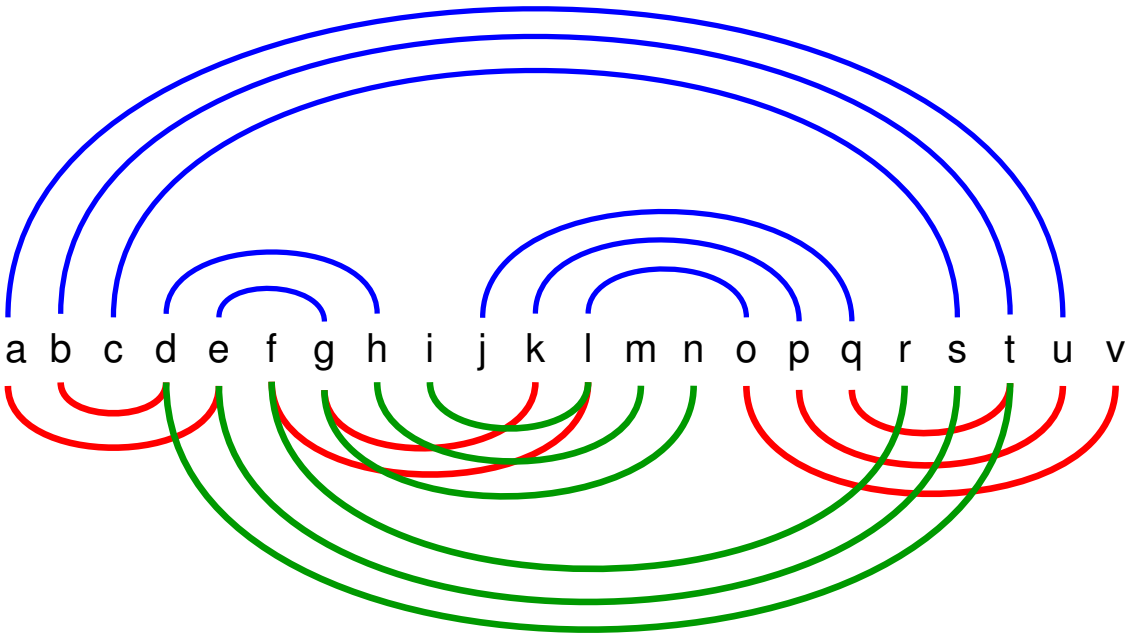
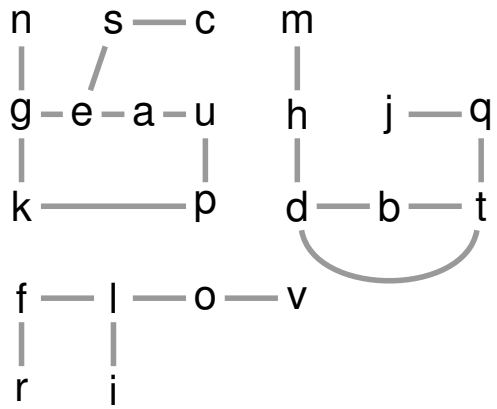


Dependency graph:

Cycles, Paths, Trees...



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Answer: Non-bipartite $\rightarrow \varnothing$; Bipartite $\rightarrow 4^{\#CCs} = 64$

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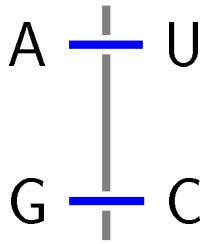

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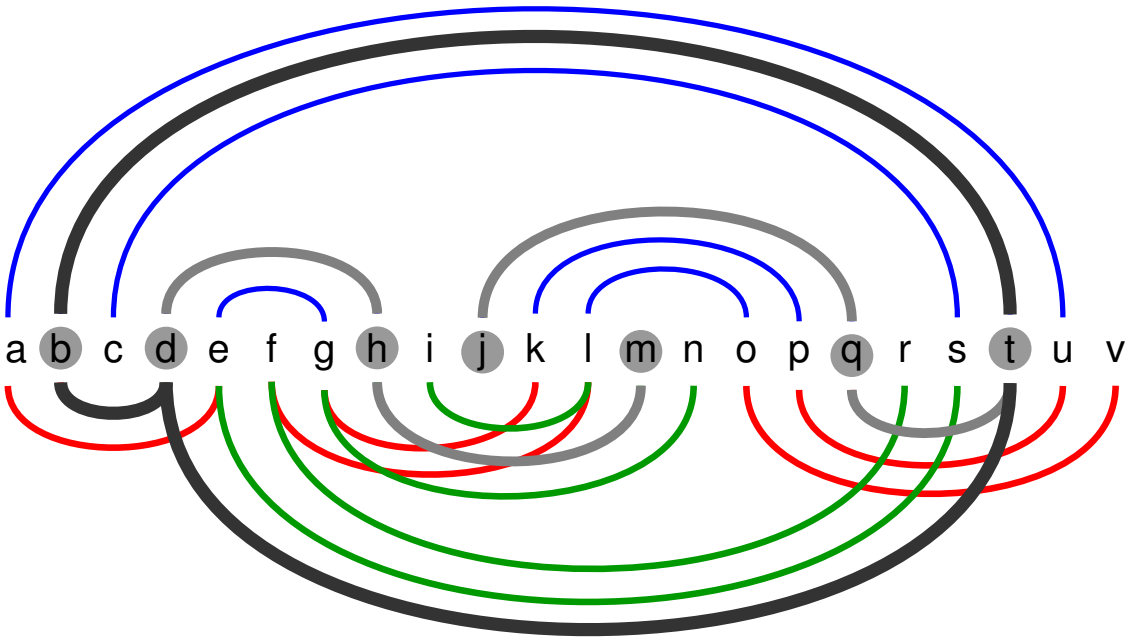

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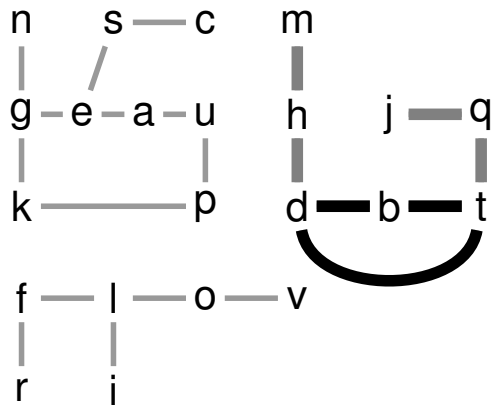

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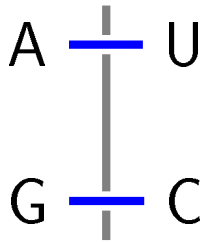

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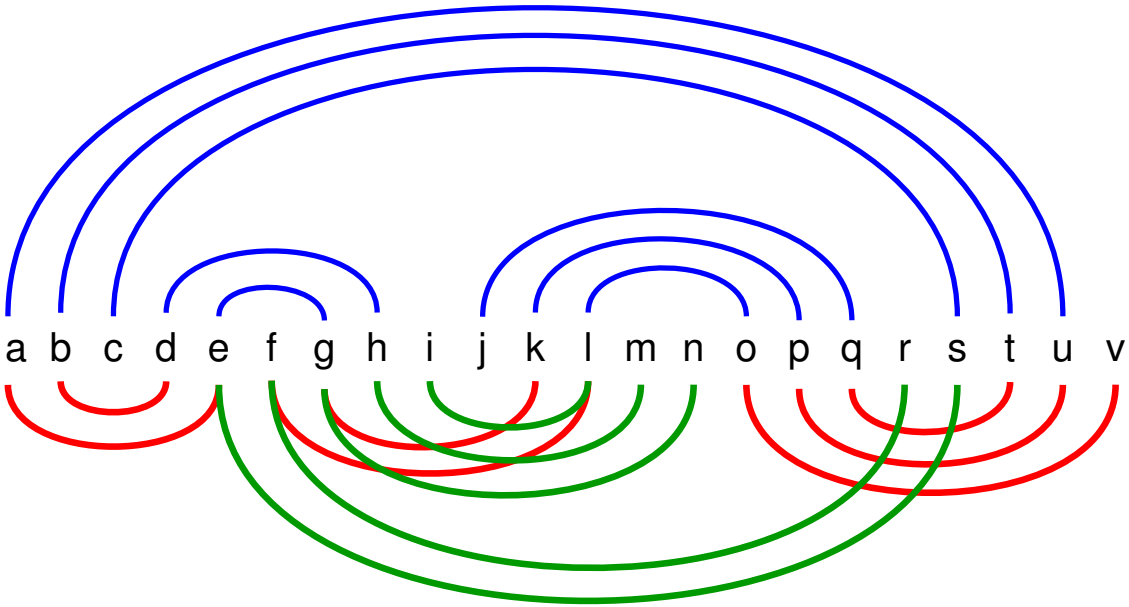
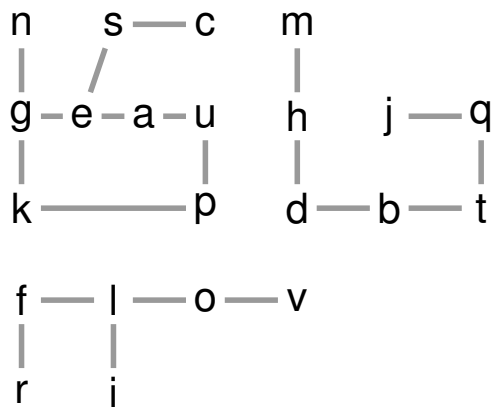


Dependency graph:

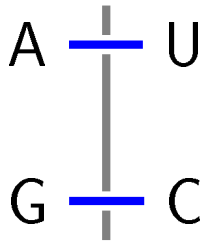
Cycles, Paths, Trees...



Question: How many **Compatible** sequences?

Answer: Non-bipartite $\rightarrow \varnothing$; Bipartite $\rightarrow 4^{\#CCs} = 64$

Counting compatible sequences: Watson-Crick + > 2 structures



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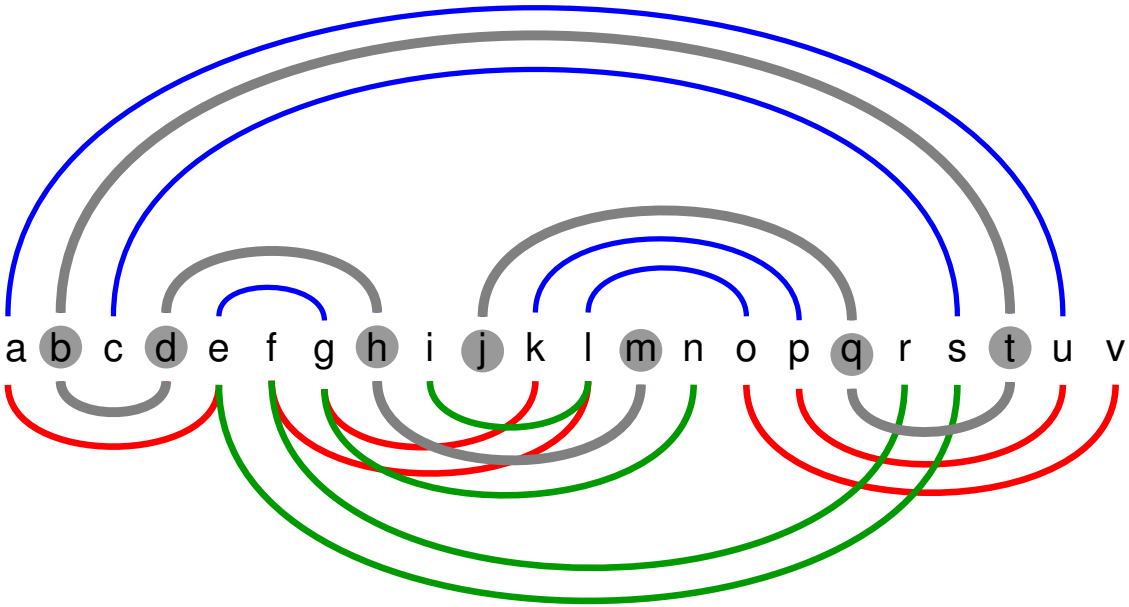

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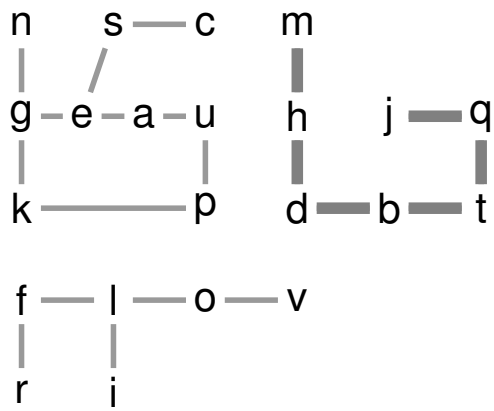

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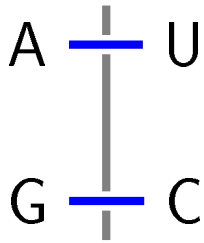

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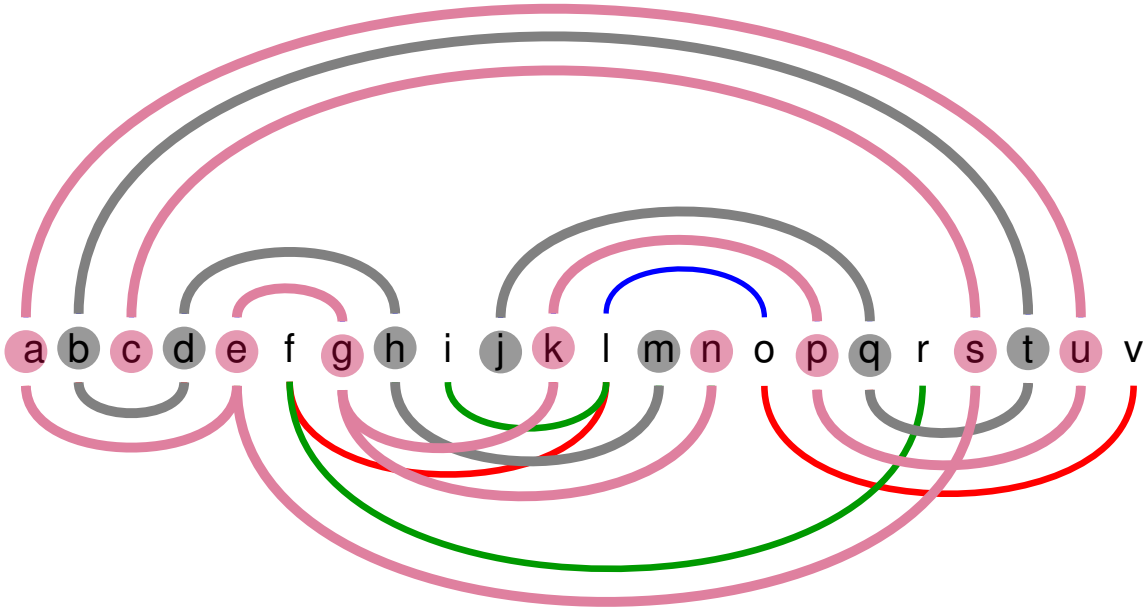

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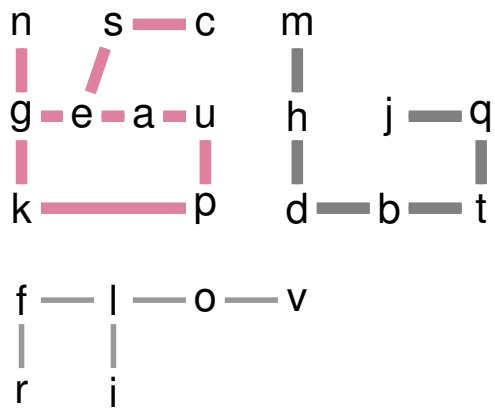

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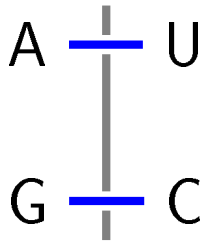

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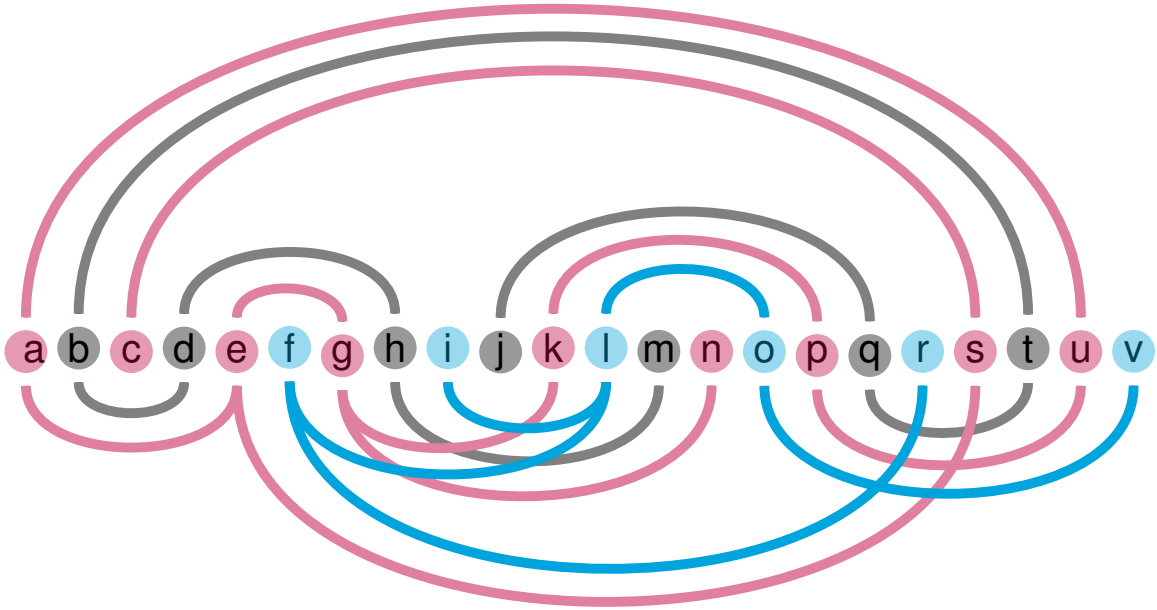

Dependency graph:

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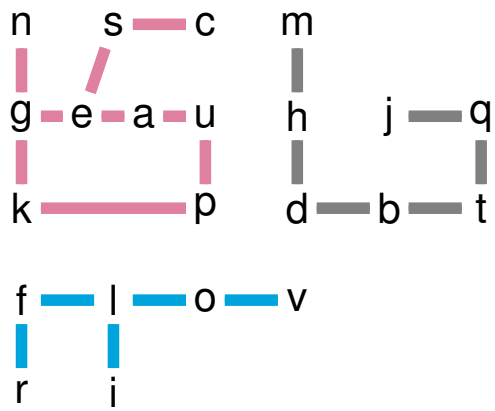

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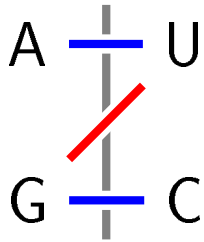
Counting compatible sequences: WC/Wobble + Single structure



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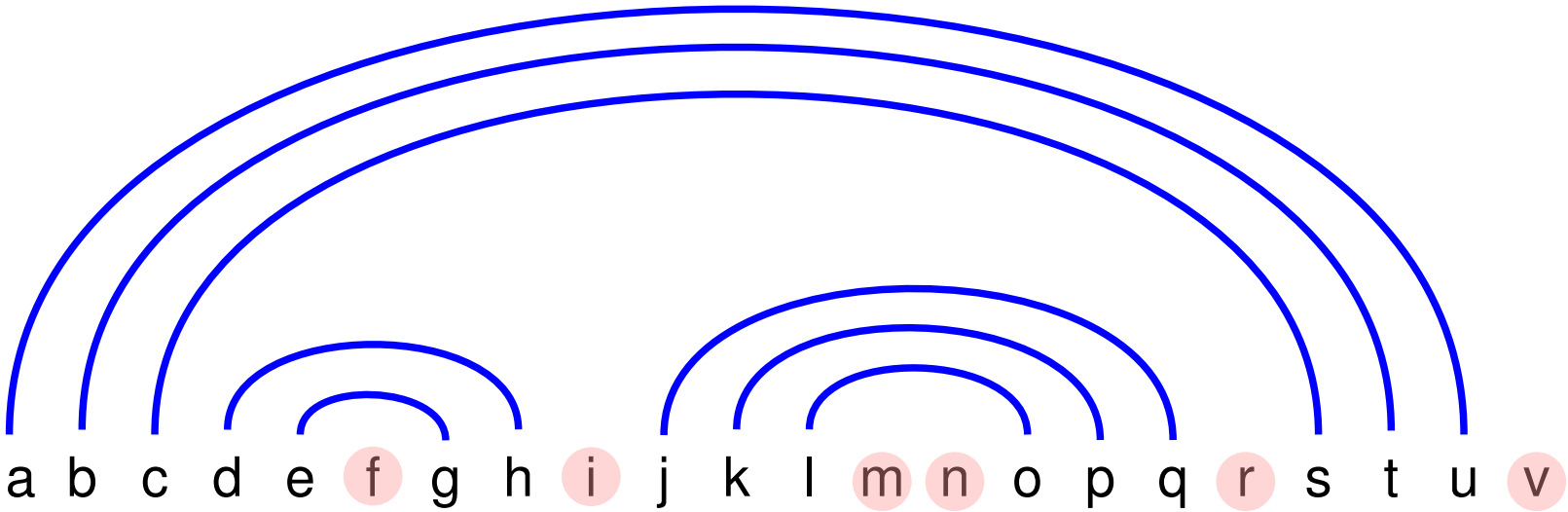

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Answer: $4^{\#\text{Unpaired}} \times 6^{\#\text{BPs}} \rightarrow 6\,879\,707\,136$

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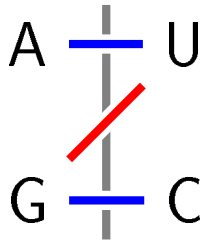

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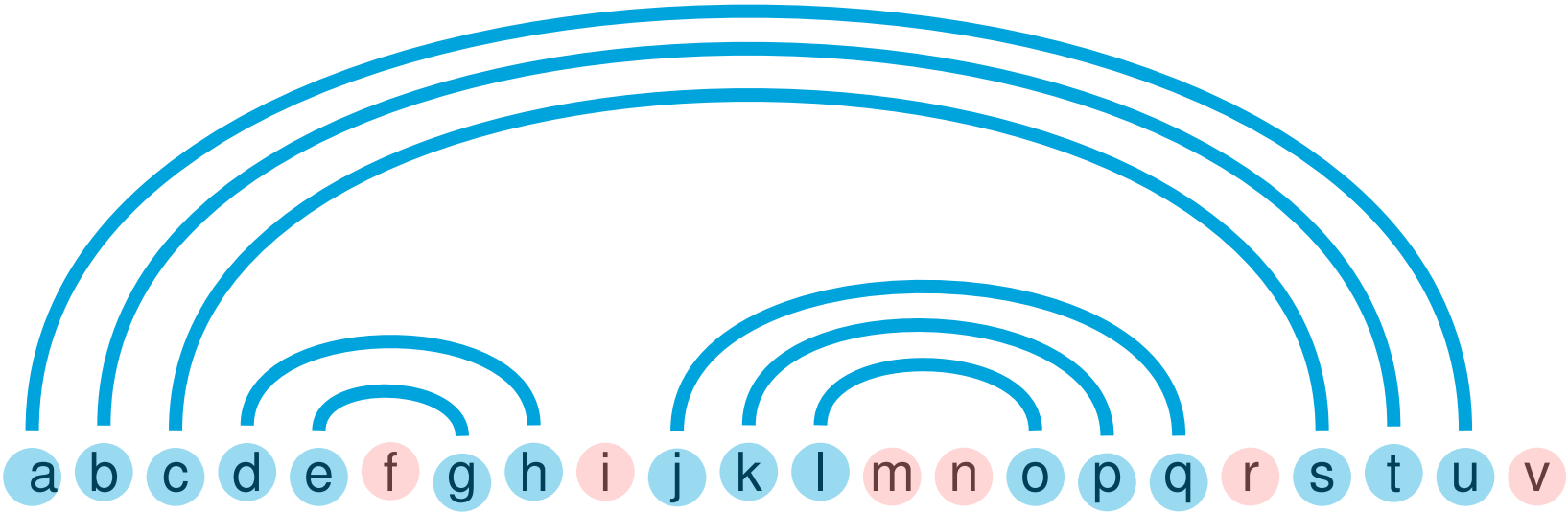

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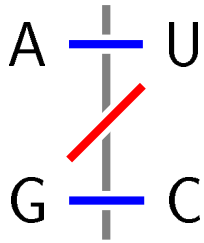

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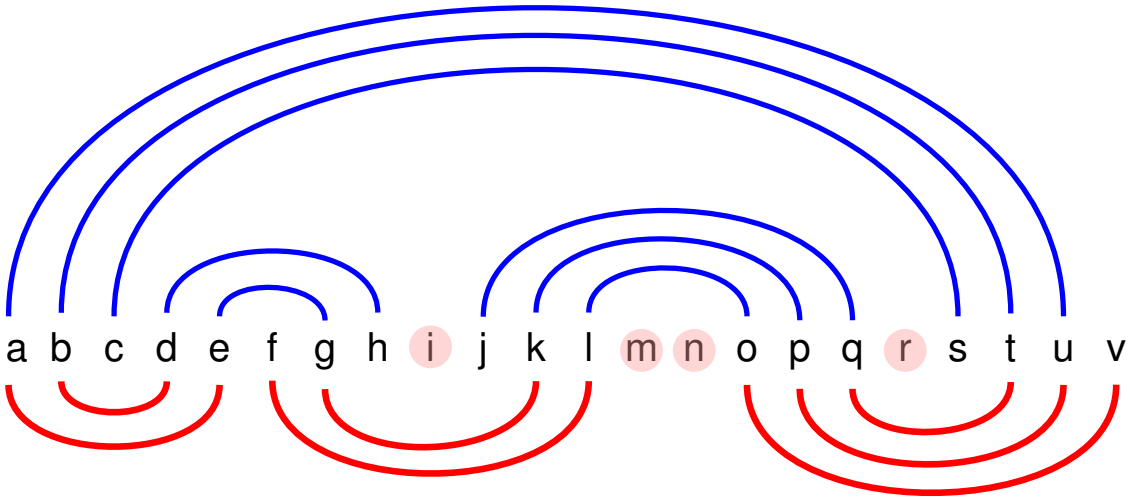
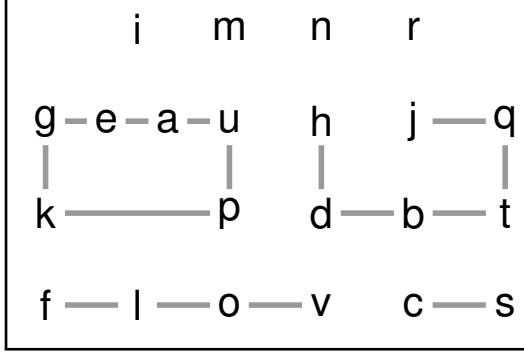


Dependency graph:
Cycles + Paths



Question: How many **Compatible** sequences?

Answer: $\neq \varnothing$! (base-pairs and dependency graphs **always bipartite**)

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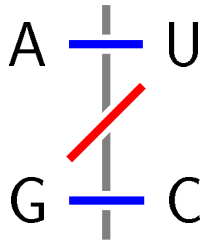

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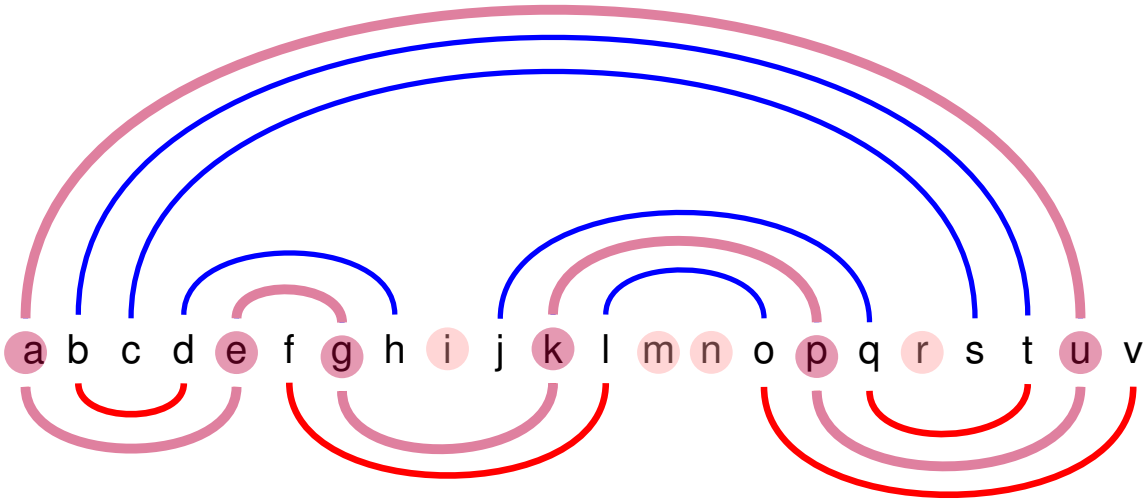

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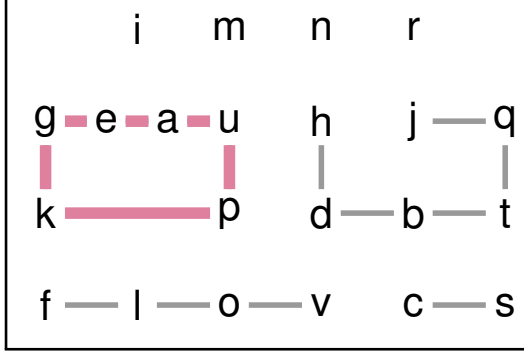

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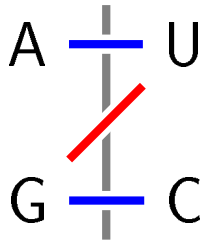

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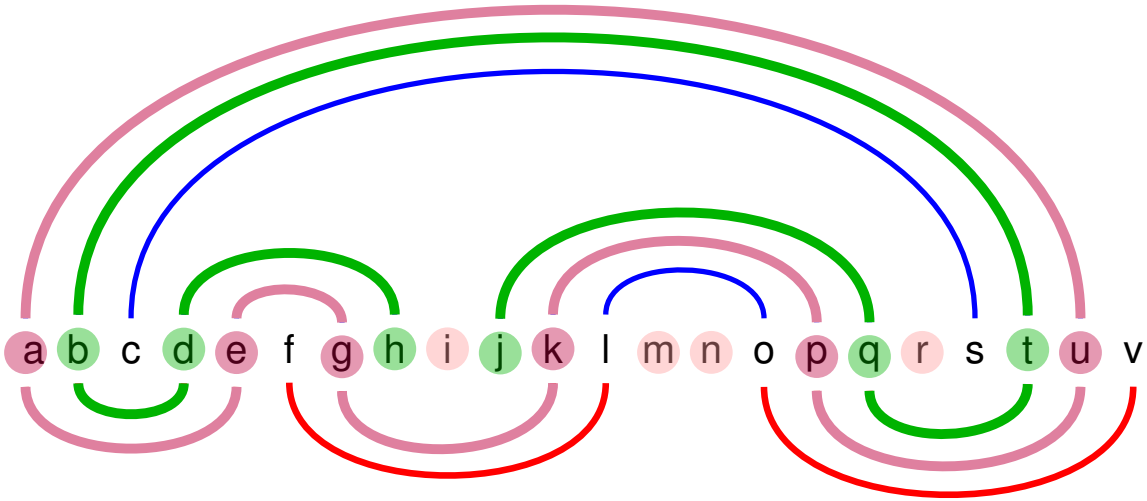

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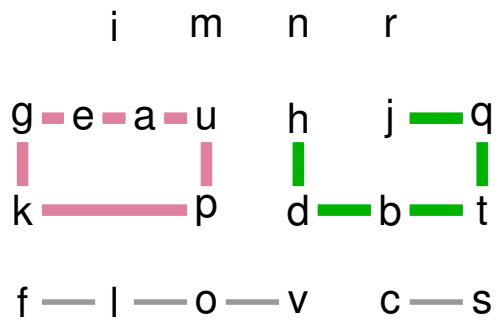

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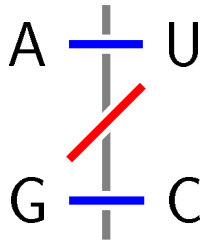

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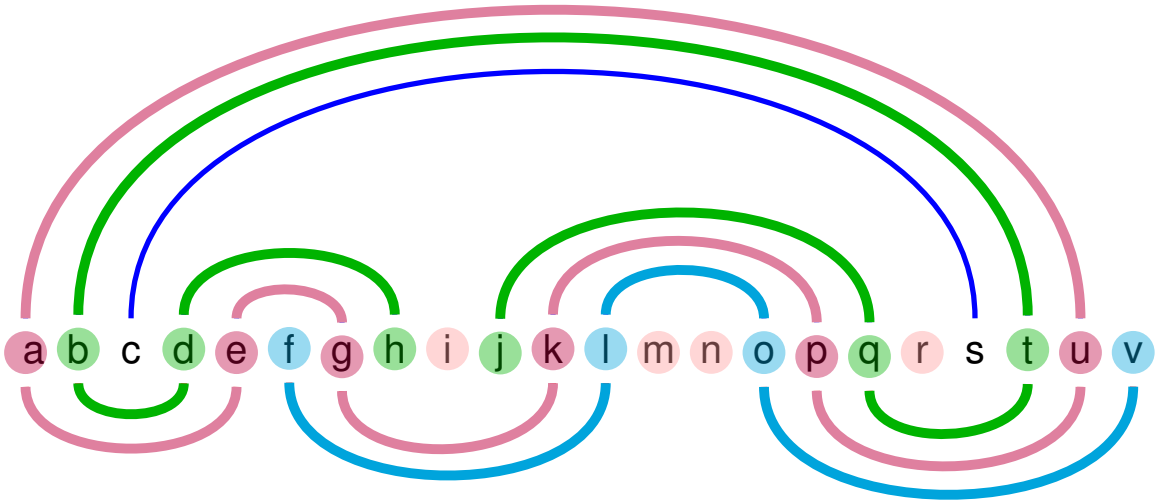

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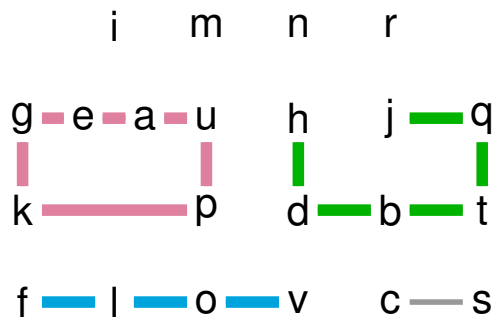
Cycles + Paths



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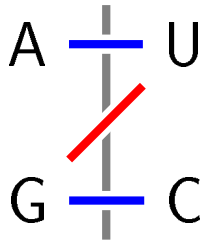

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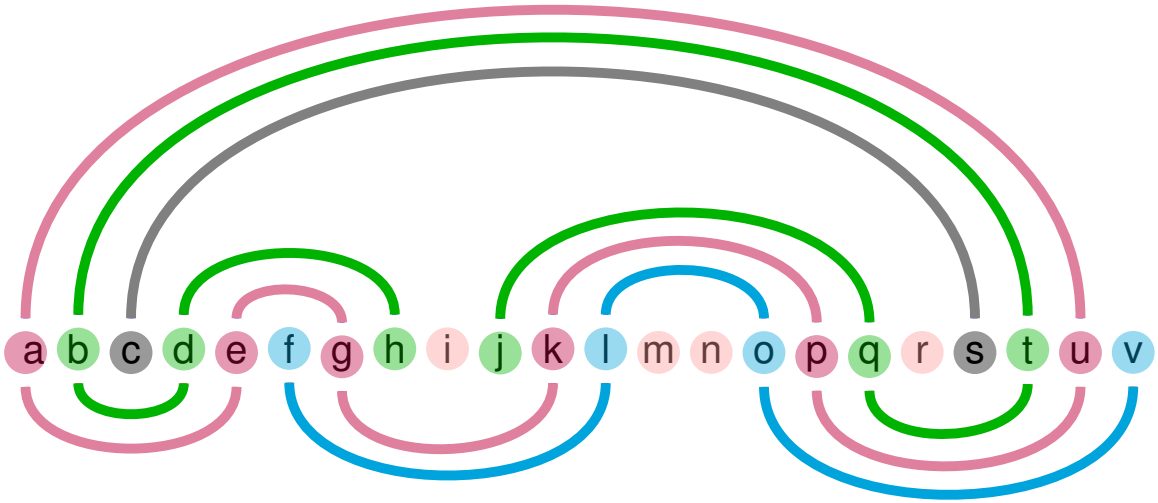

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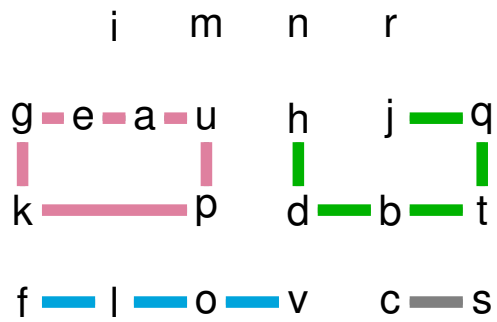

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$$\#\text{Designs}(G) = \prod_{c \in CC(G)} \#\text{Designs}(cc)$$

Counting compatible designs for paths and cycles

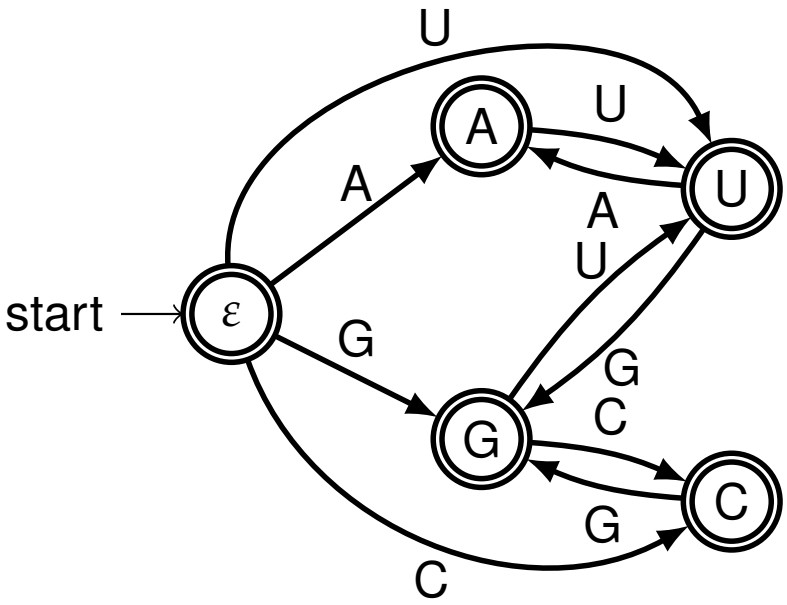
Theorem (#Compatible designs for paths and cycles)

The numbers $p(n)$ and $c(n)$ of compatible designs for paths and cycles of length n are:

$$p(n) = 2\,\mathcal{F}_{n+2} \qquad \text{and} \qquad c(n) = 2\,\mathcal{F}_n + 4\,\mathcal{F}_{n-1}$$

where $\mathcal{F}_n$ is the n-th Fibonacci number, s.t. $\mathcal{F}_0 = 0$, $\mathcal{F}_1 = 1$ and $\mathcal{F}_n = \mathcal{F}_{n-1} + \mathcal{F}_{n-2}$.

For paths: A simple DFA generates compatible sequences



Remark: A $\leftrightarrow$ C/G $\leftrightarrow$ U symmetry

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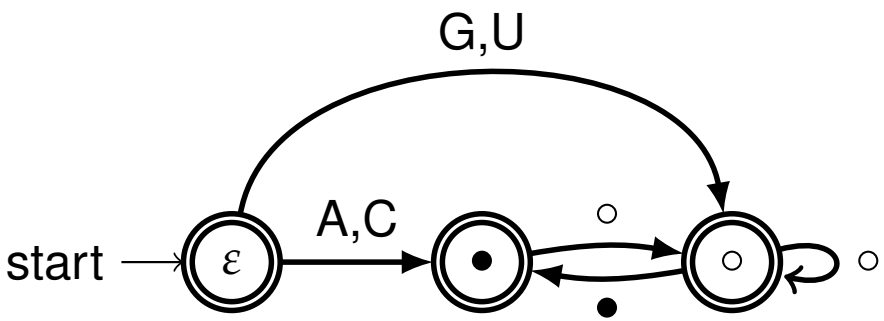

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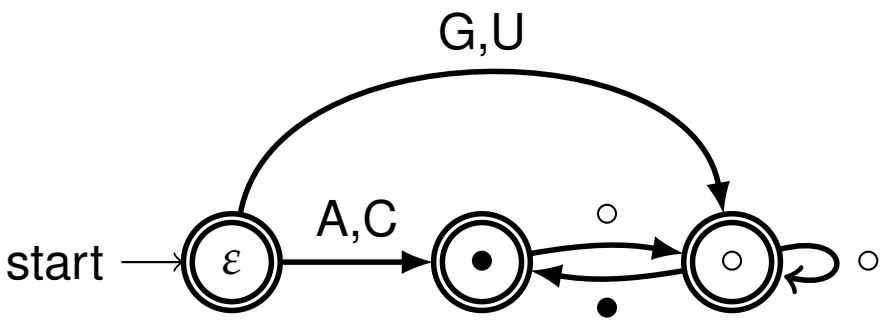

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$$m_\bullet(n) = m_\circ(n-1)$$

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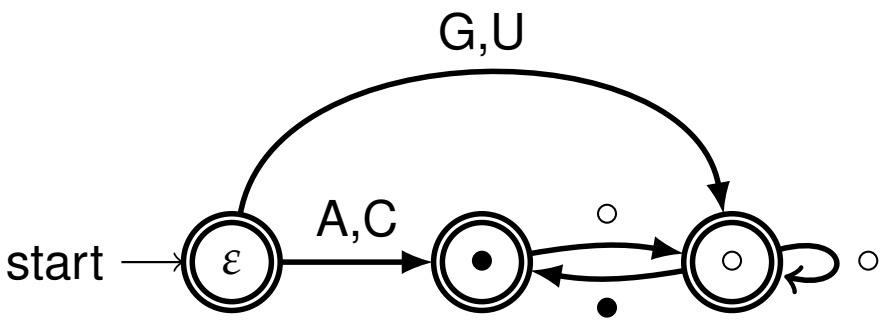

Remark: A $\leftrightarrow$ C/G $\leftrightarrow$ U symmetry

$$\begin{aligned} m_\bullet(n) &= m_\circ(n-1) \\ m_\circ(n) &= m_\circ(n-1) + m_\bullet(n-1) \\ &= m_\circ(n-1) + m_\circ(n-2) \\ &= \mathcal{F}(n+2) \end{aligned}$$

Counting compatible designs for paths and cycles

Theorem (#Compatible designs for paths and cycles)

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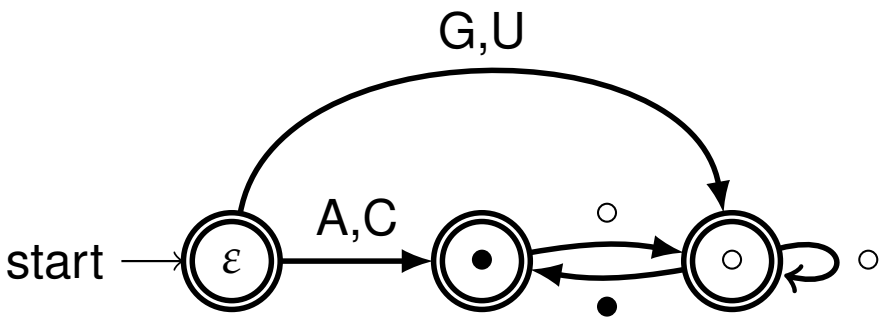

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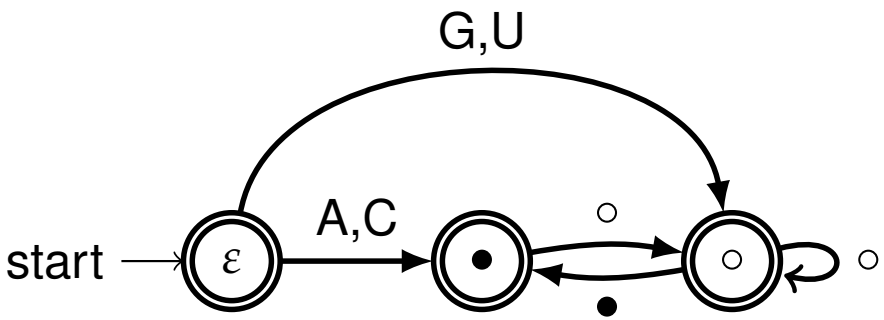

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(Since $m_\circ(0) = 1$ and $m_\circ(1) = 2$)

$$p(n) := m_\varepsilon(n) = 2\,m_\bullet(n-1) + 2\,m_\circ(n-1) = 2(\mathcal{F}(n) + \mathcal{F}(n+1)) =, \mathcal{F}(n+2)$$

Counting compatible designs for paths and cycles

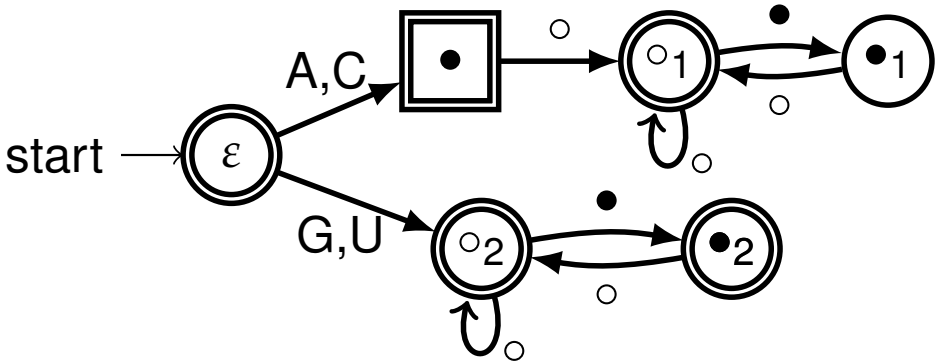
Theorem (#Valid designs for paths and cycles)

The numbers $p(n)$ and $c(n)$ of compatible designs for paths and cycles of length n are:

$$p(n) = 2\,\mathcal{F}_{n+2} \qquad \text{and} \qquad c(n) = 2\,\mathcal{F}_n + 4\,\mathcal{F}_{n-1}$$

where $\mathcal{F}_n$ is the n-th Fibonacci number, s.t. $\mathcal{F}_0 = 0$, $\mathcal{F}_1 = 1$ and $\mathcal{F}_n = \mathcal{F}_{n-1} + \mathcal{F}_{n-2}$.

For cycle: A *barely more involved* DFA generates compatible sequences



Remark: A $\leftrightarrow$ C/G $\leftrightarrow$ U symmetry

$$m_{\circ_2}(n) = \mathcal{F}(n+2)$$
$$m_{\circ_1}(n) = \mathcal{F}(n+1)$$

(Since $m_{\circ_1}(0) = 1$ and $m_{\circ_1}(1) = 1$)

$$c(n) := m_\varepsilon(n) = 2\,m_{\circ_1}(n-2) + 2\,m_{\circ_2}(n-1)$$
$$= 2(\mathcal{F}(n-1) + \mathcal{F}(n+1)) = 2\,\mathcal{F}(n) + 4\,\mathcal{F}(n-1)$$

Counting compatible designs for paths and cycles

Theorem (#Valid designs for paths and cycles)

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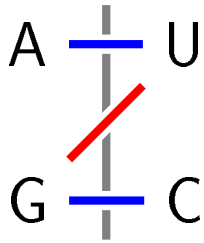
Theorem (#Compatible designs for general 2-structures graphs)

Let G be the dependency graph associated with 2 RNA structures (max degree=2). The number $\#\text{Designs}(G)$ of compatible designs for G is given by

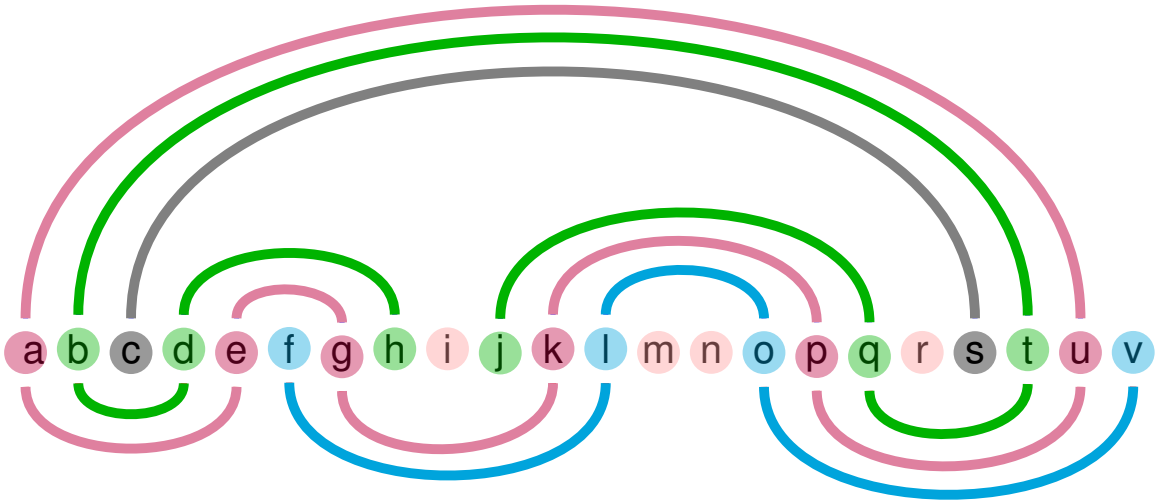
$$\#\text{Designs}(G) = \prod_{p \in \mathcal{P}(G)} 2\,\mathcal{F}_{|p|+2} \times \prod_{c \in \mathcal{C}(G)} \left(2\,\mathcal{F}_{|c|} + 4\,\mathcal{F}_{|c|-1}\right)$$

where G decomposes into paths $\mathcal{P}(G)$ and cycles $\mathcal{C}(G)$.

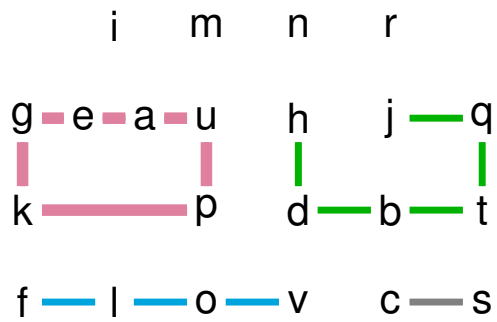
Counting compatible sequences: WC/Wobble + Two structures



Compatible Base Pairs = Include **Wobble** base pairs



Dependency graph:
Cycles + Paths

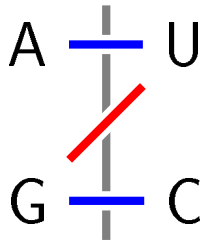


Question: How many **Compatible** sequences?

Answer: $\neq \varnothing$! (base-pairs and dependency graphs **always bipartite**)

$$\#\text{Designs}(G) = \prod_{c \in CC(G)} \#\text{Designs}(cc) = 2\,322\,432$$

Counting compatible sequences: Watson-Crick + > 2 structures



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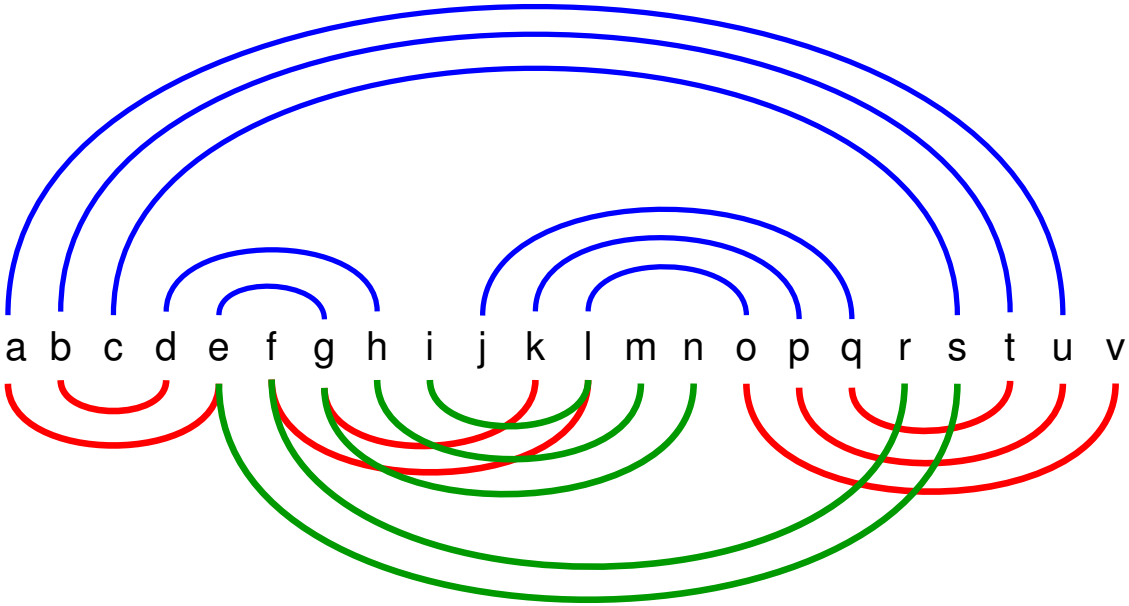
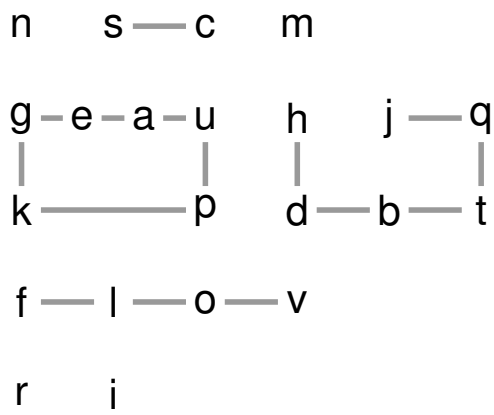


Dependency graph:

Cycles, Paths, Trees...



Question: How many **Compatible** sequences?

Answer: Non-bipartite $\rightarrow \varnothing$; Bipartite $\rightarrow$

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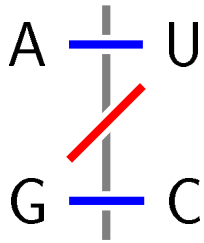

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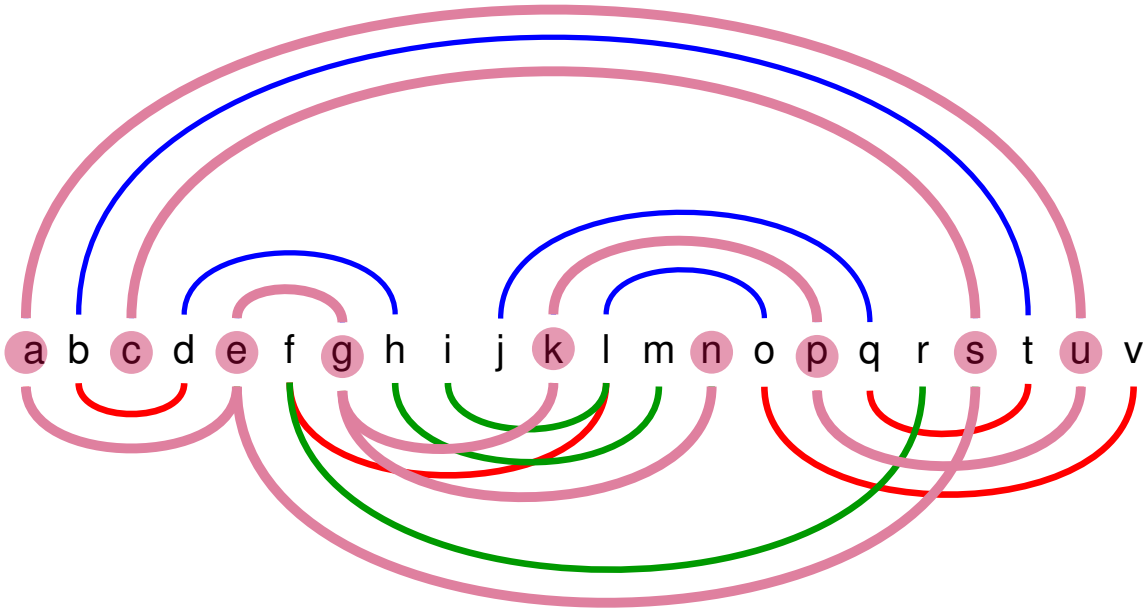

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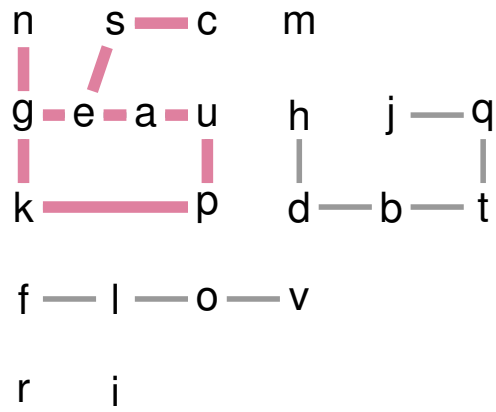
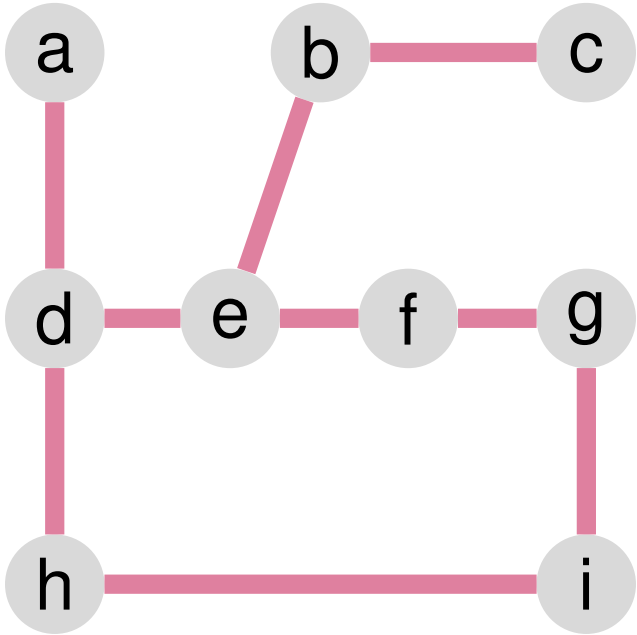
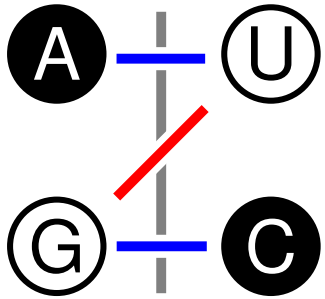


Question: How many **Compatible** sequences?

Answer: Non-bipartite $\rightarrow \varnothing$; Bipartite $\rightarrow \prod_{cc \in CC(G)} 2 \times \#IS(cc)$

Bijection between Independent Sets and Valid Designs





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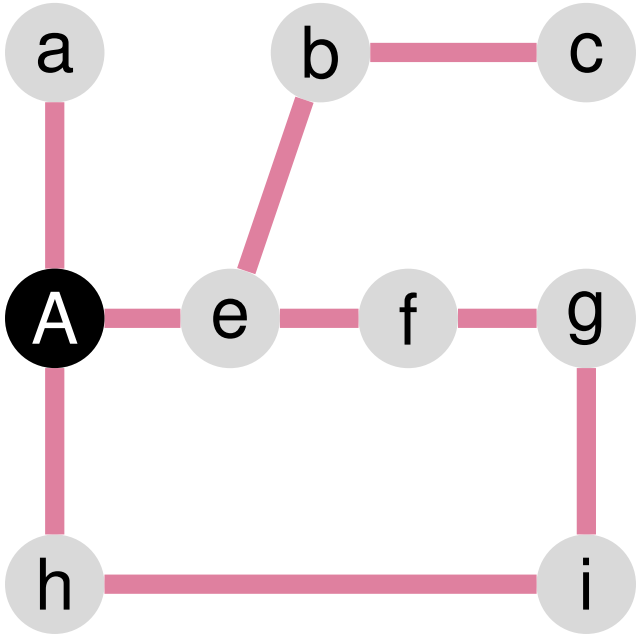

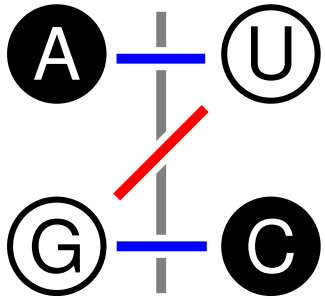

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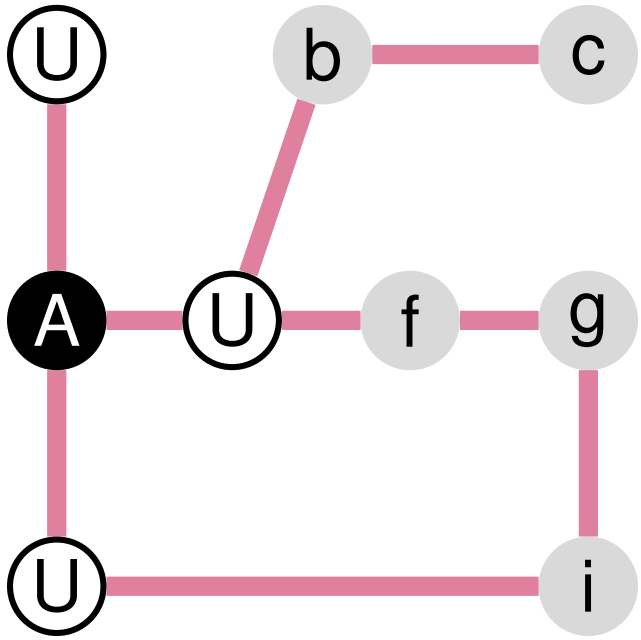

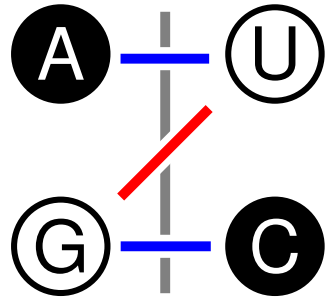

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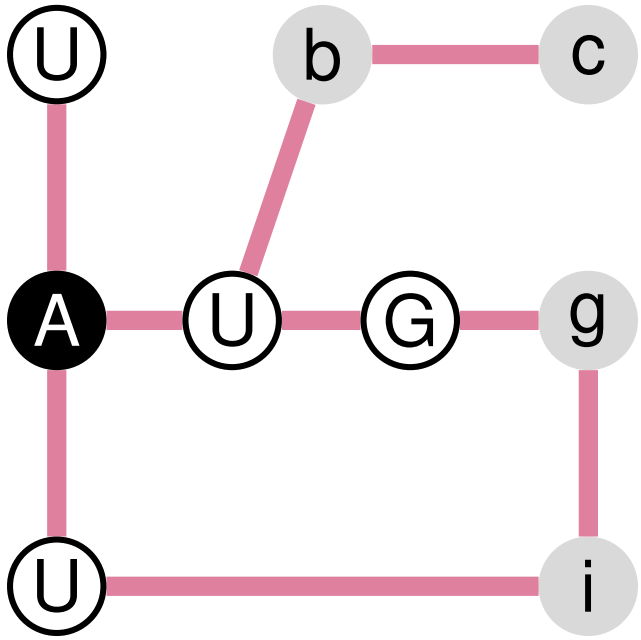

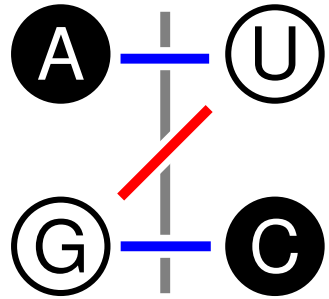

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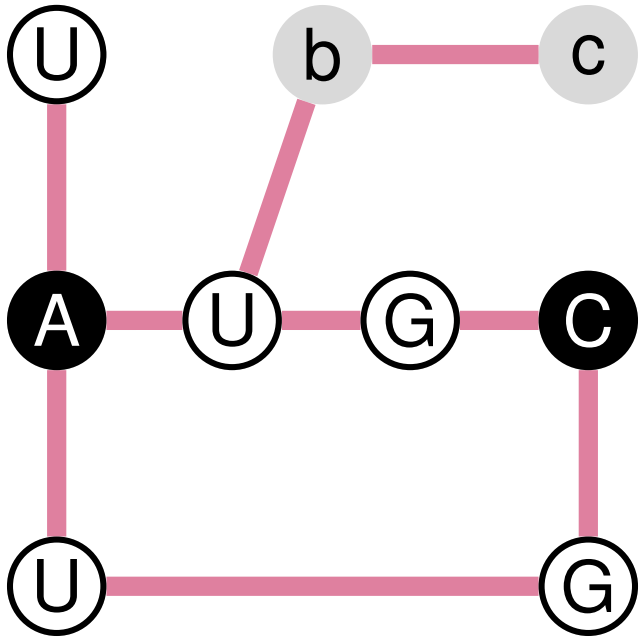

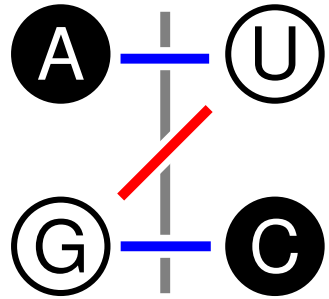

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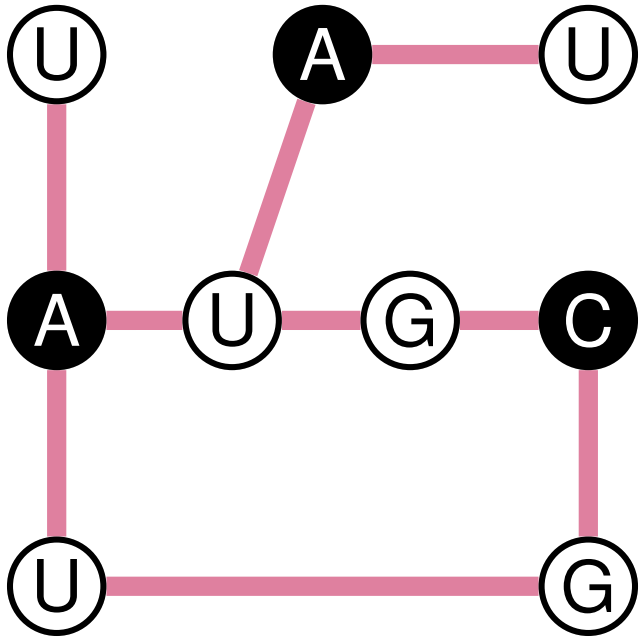

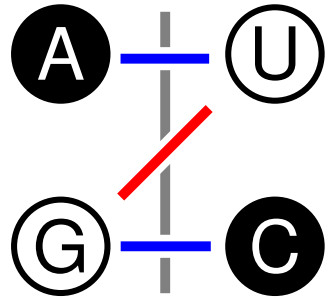

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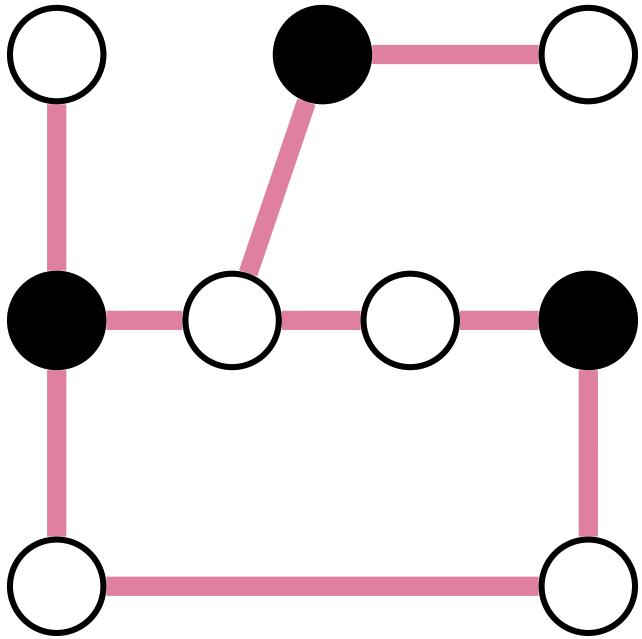

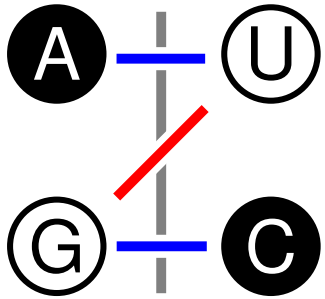

Remark: No adjacent **black letters** in compatible designs

Up to trivial symmetry* (*e.g.* top-left position $\in \{\mathsf{G}, \mathsf{A}\}$):

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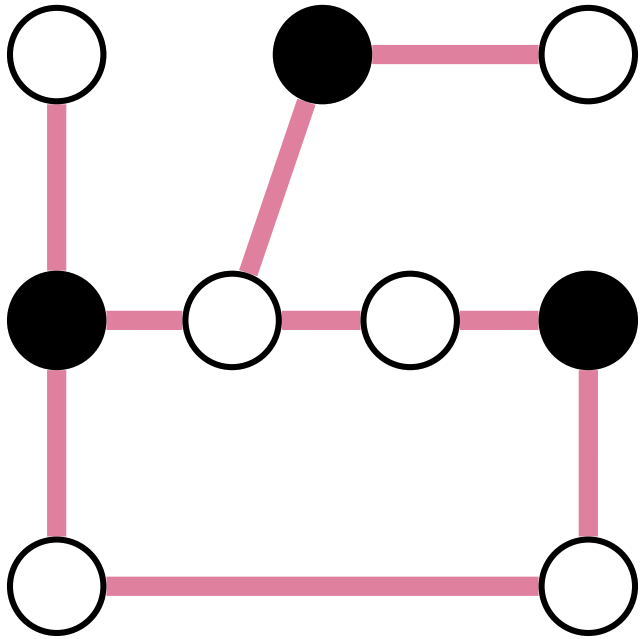

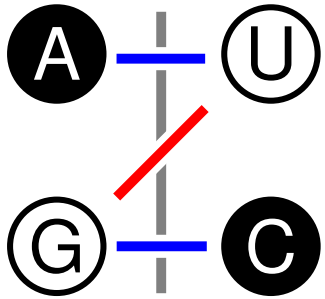

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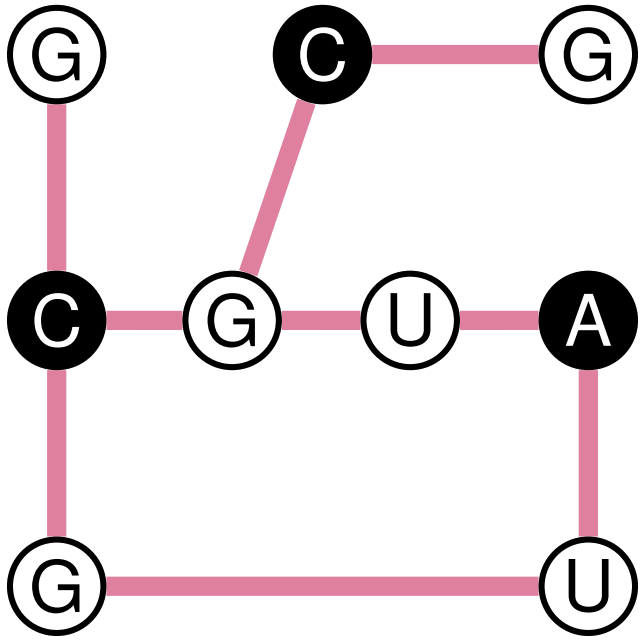

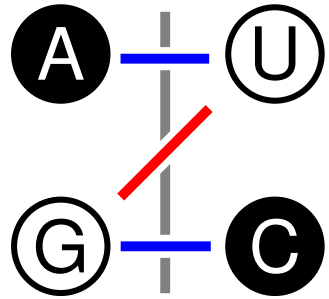

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$\Rightarrow$ Bijection between $\mathrm{Designs}^\star(\mathrm{cc})$ and $\mathrm{IndependentSets}(\mathrm{cc})$.

Valid designs and independent sets

Theorem (#Valid design for bipartite connected dependency graphs)

*Let G be a **bipartite connected** dependency graph, one has:*

$$\#\text{Designs}(G) = 2 \times \#\text{Designs}^{\star}(G) = 2 \times \#\text{IS}(G)$$

For a **bipartite** dependency graph G is then:

$$\#Designs(G) = \prod_{cc \in CC(G)} 2 \times \#IS(cc) = 2^{|CC(G)|} \times \#IS(G)$$

But $\#IS(G)$ is #P-hard on bipartite graphs **[Bubbley&Dyer'01]**
(+ Any G is a dependency graph)

Algorithm $\mathcal{A} \in P$ for $\#Designs(G) \rightarrow$ Algorithm $\mathcal{A}' \in P$ for $\#BIS \ldots$

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No polynomial algorithm for #Designs(G) unless $\#P = FP$ ($\Rightarrow P = NP$)

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Consequences

Corollary (#Approximability for ≤ 5 structures) [Weitz'06]

For any G built from ≤ 5 pseudoknotted structures, #Design(G) can be approximated within **any ratio** in **polynomial time** (PTAS)

Corollary (#BIS hardness for > 5 struct.) [Cai, Galanis, Goldberg, Jerrum, McQuillan'16]

Beyond 5 **pseudoknotted** structures, approximating #Design becomes **as hard as** approximating #BIS without any constraint.

Why pseudoknotted? Because any bipartite graph of max degree Δ can be **decomposed** into Δ matchings **in polynomial time** (Vizing's theorem).

Finally, strong connection between **counting** and **sampling** **[Jerrum, Valiant, Vazirani'86]**.

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Generating compatible sequences **(almost) uniformly** w.r.t. a set of structures is **#BIS-hard**.

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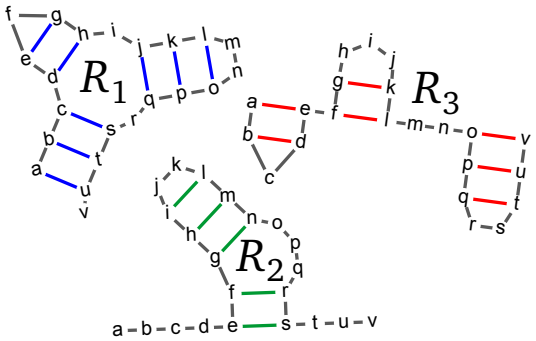
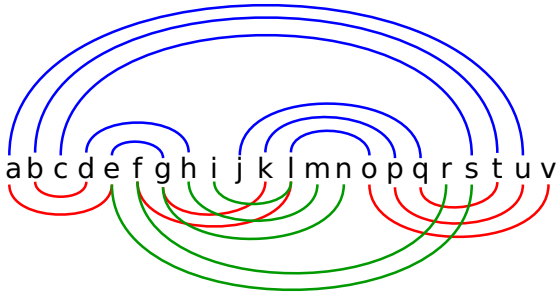
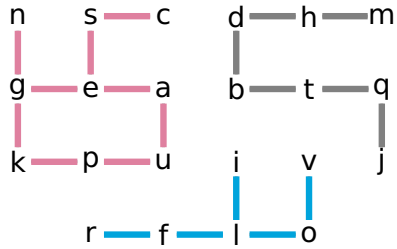
Perspectives: FPT and Boltzmann sampling algorithms



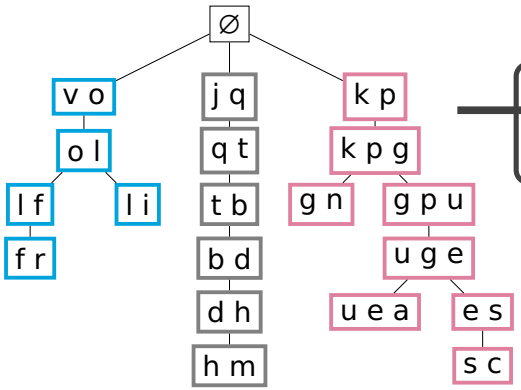
i) Input Structures

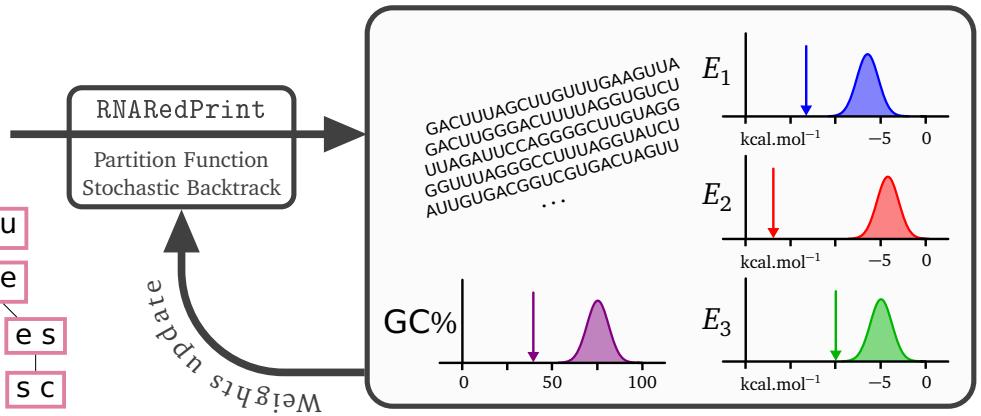


ii) Merged Base-Pairs



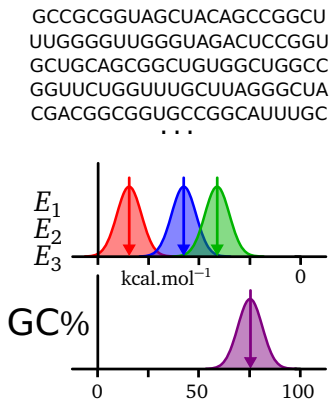
iii) Compatibility Graph





iv) Tree Decomposition

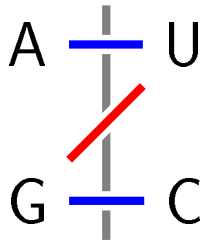
v) Weight Optimization (Adaptive Sampling)



vi) Final Designs

- **FPT algorithm** for counting based on **tree decomposition**
- Multidimensional Boltzmann sampling to control energies, GC...

Counting compatible sequences: Watson-Crick + > 2 structures



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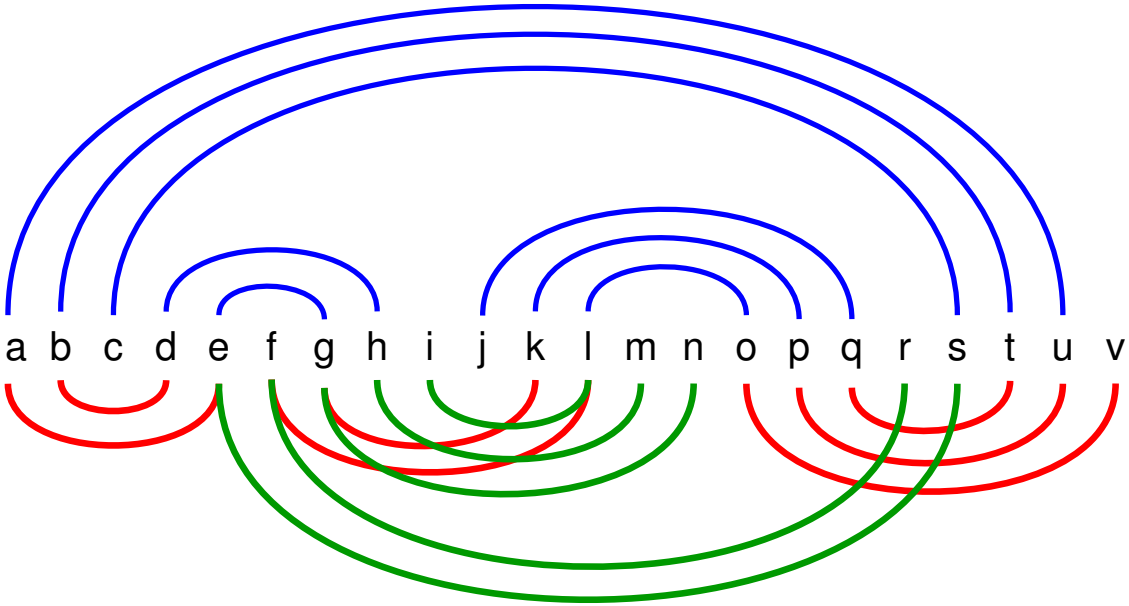

Dependency graph:

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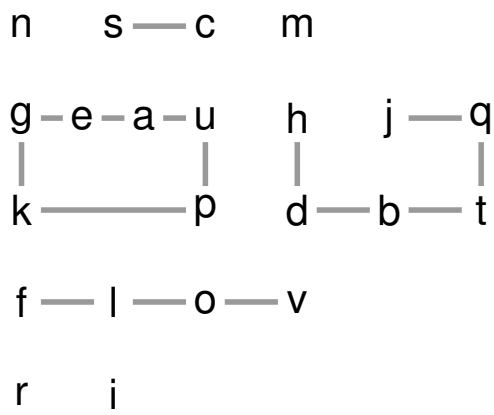

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Answer: Bipartite $\rightarrow$

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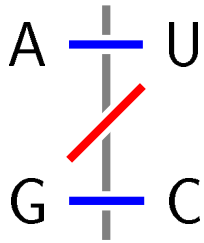

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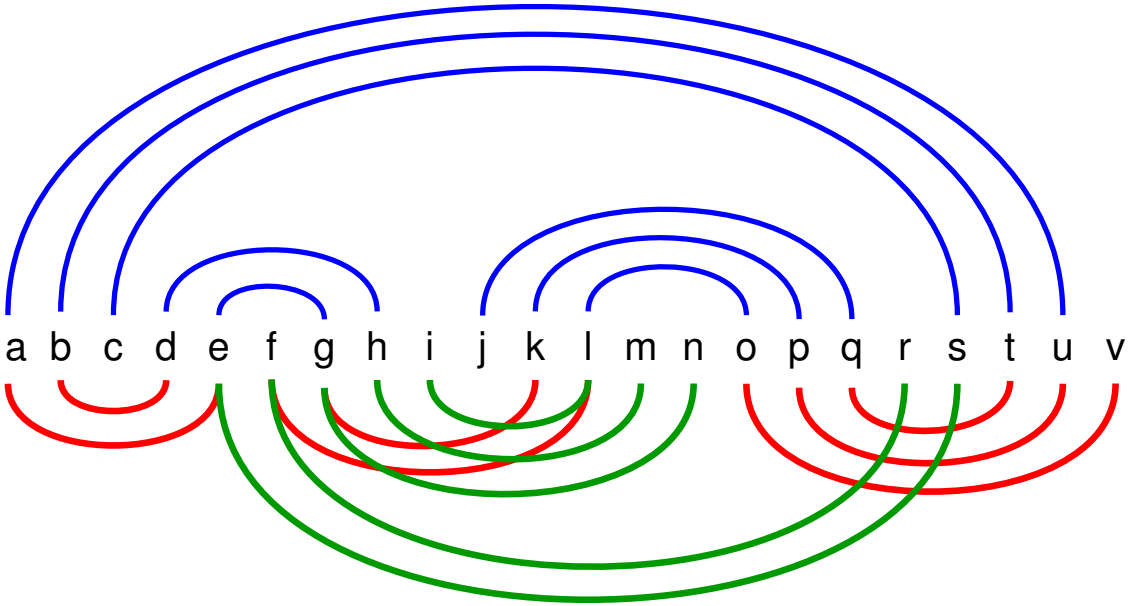

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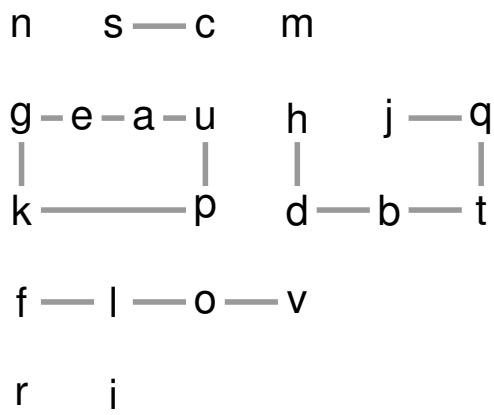

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Answer: Bipartite $\rightarrow$ $\prod_{cc \in CC(G)} 2 \times \#IS(cc) = 496\,672$

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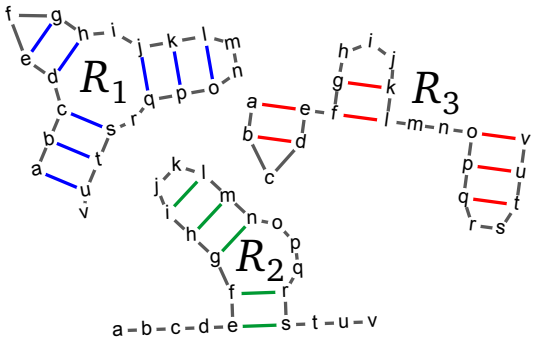

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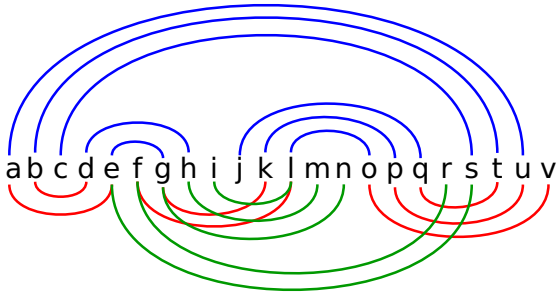
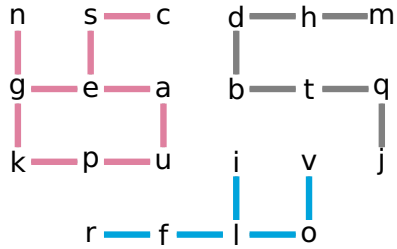
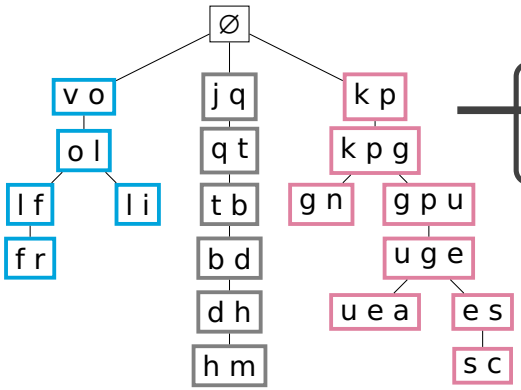
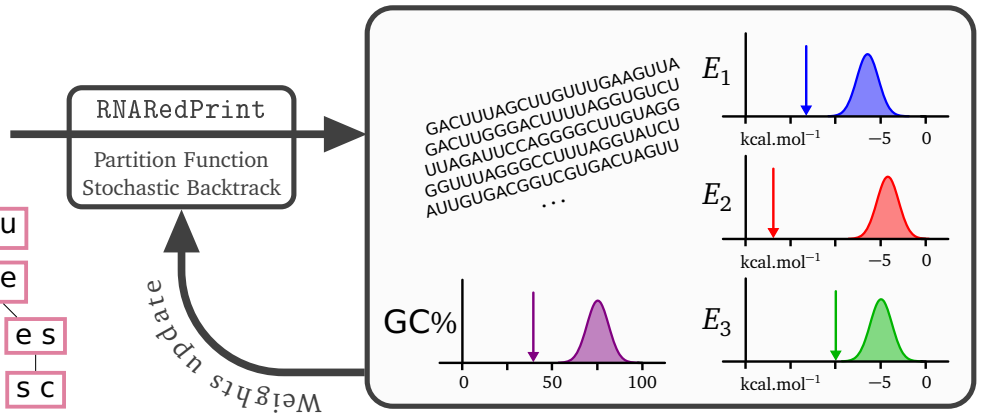


ii) Merged Base-Pairs



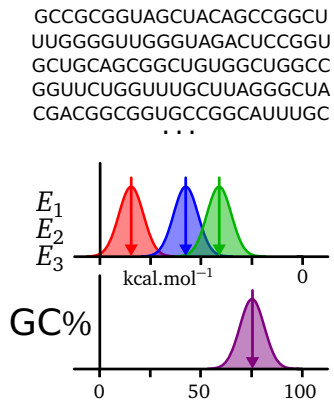
iii) Compatibility Graph





iv) Tree Decomposition

v) Weight Optimization (Adaptive Sampling)



vi) Final Designs

- **FPT algorithm** for counting based on **tree decomposition**
- **Multidimensional Boltzmann sampling** to control energies, GC...

Thanks!

Submission deadline **Nov 6th**

Registration open soon. . .