# RNA Bioinformatics and Combinatorial Dynamic Programming

## ...through enumerative combinatorics

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LIX, CNRS/Ecole Polytechnique, France

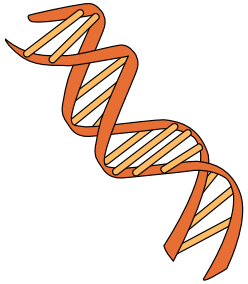
AMIB Team-Project, Inria, Saclay, France

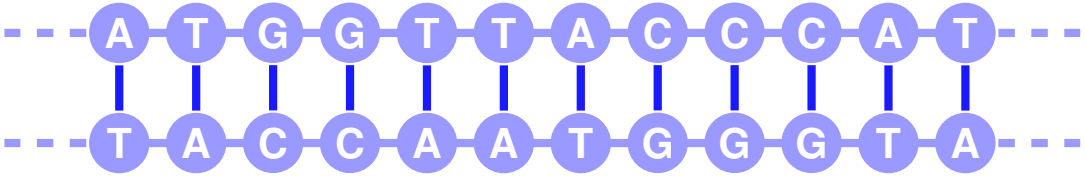
PIMS-Simon Fraser University, Burnaby, Canada

# Fundamental *dogma* of molecular biology

**DNA**

$\{A, C, G, T\}^\star$





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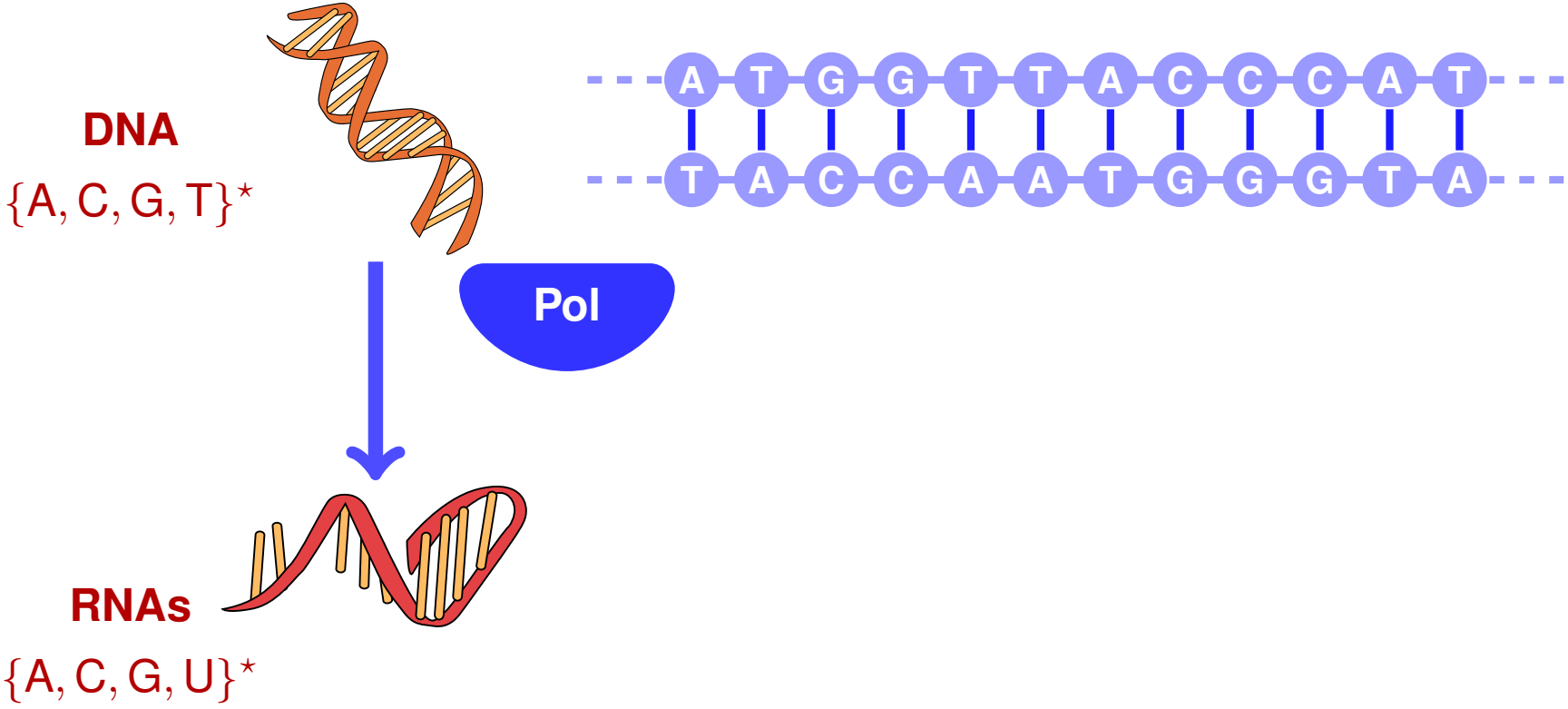

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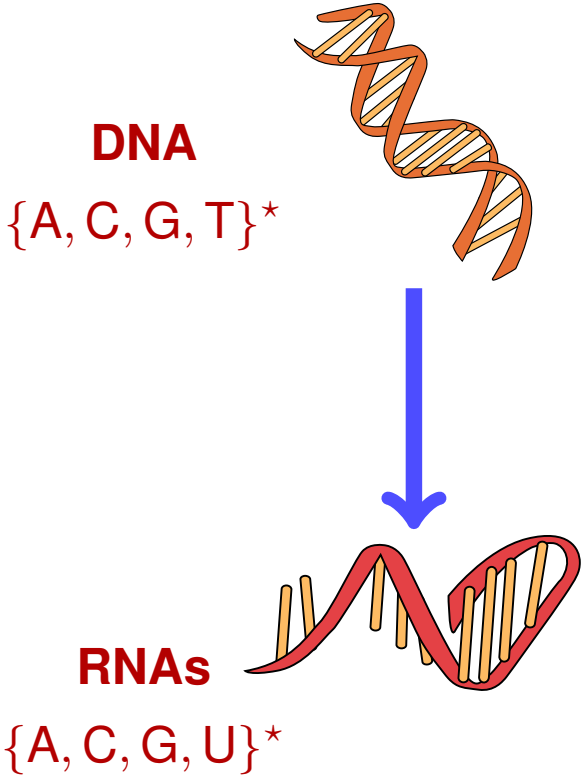


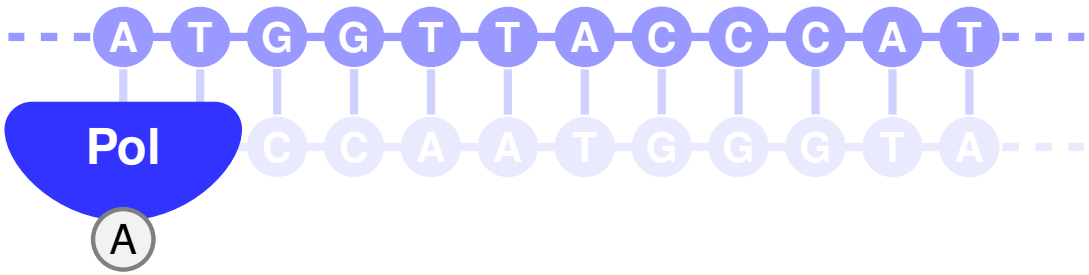

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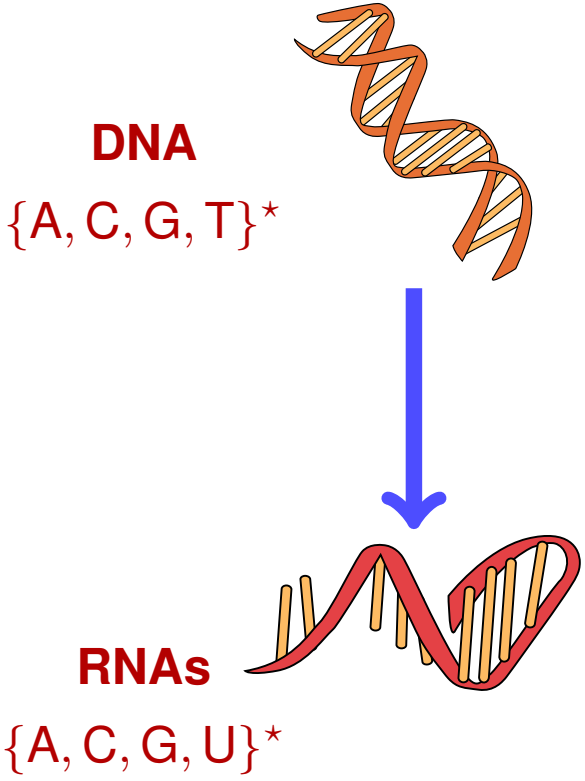


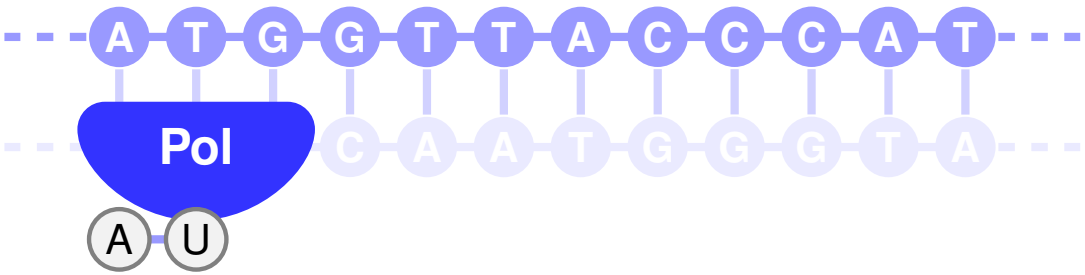

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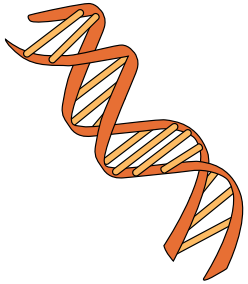

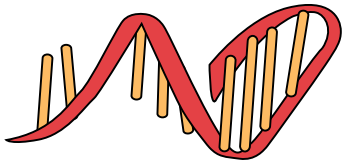

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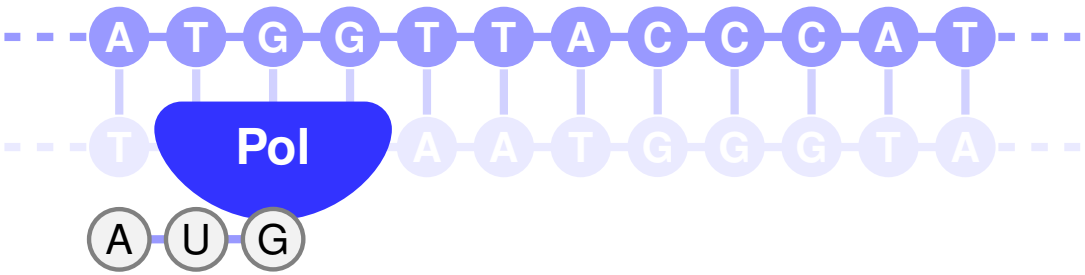

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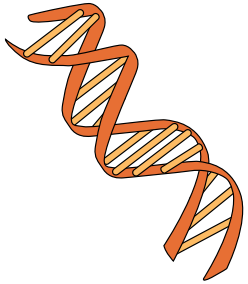

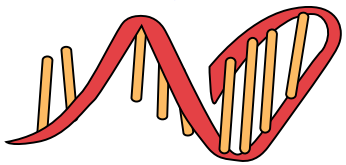

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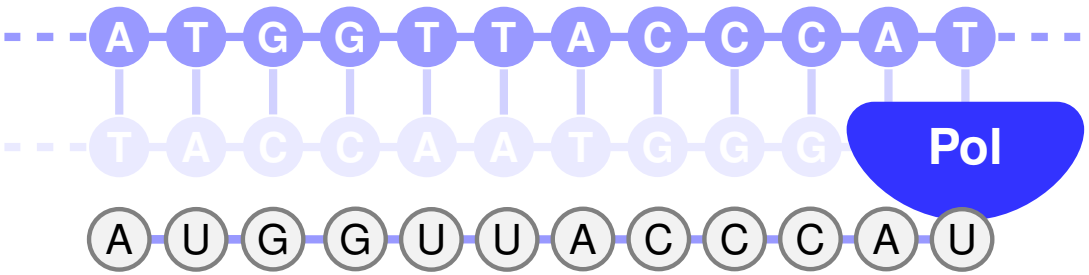

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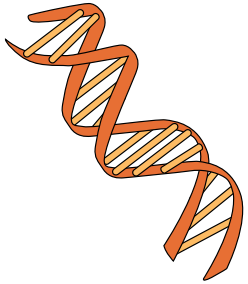

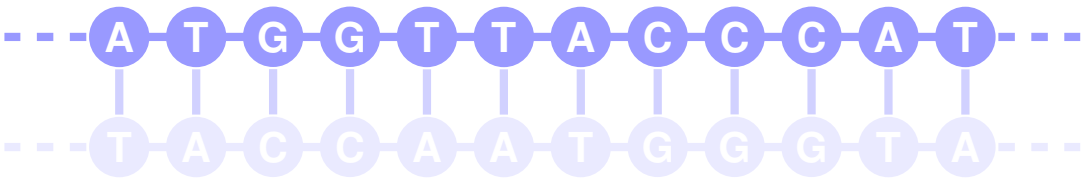


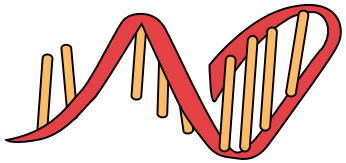

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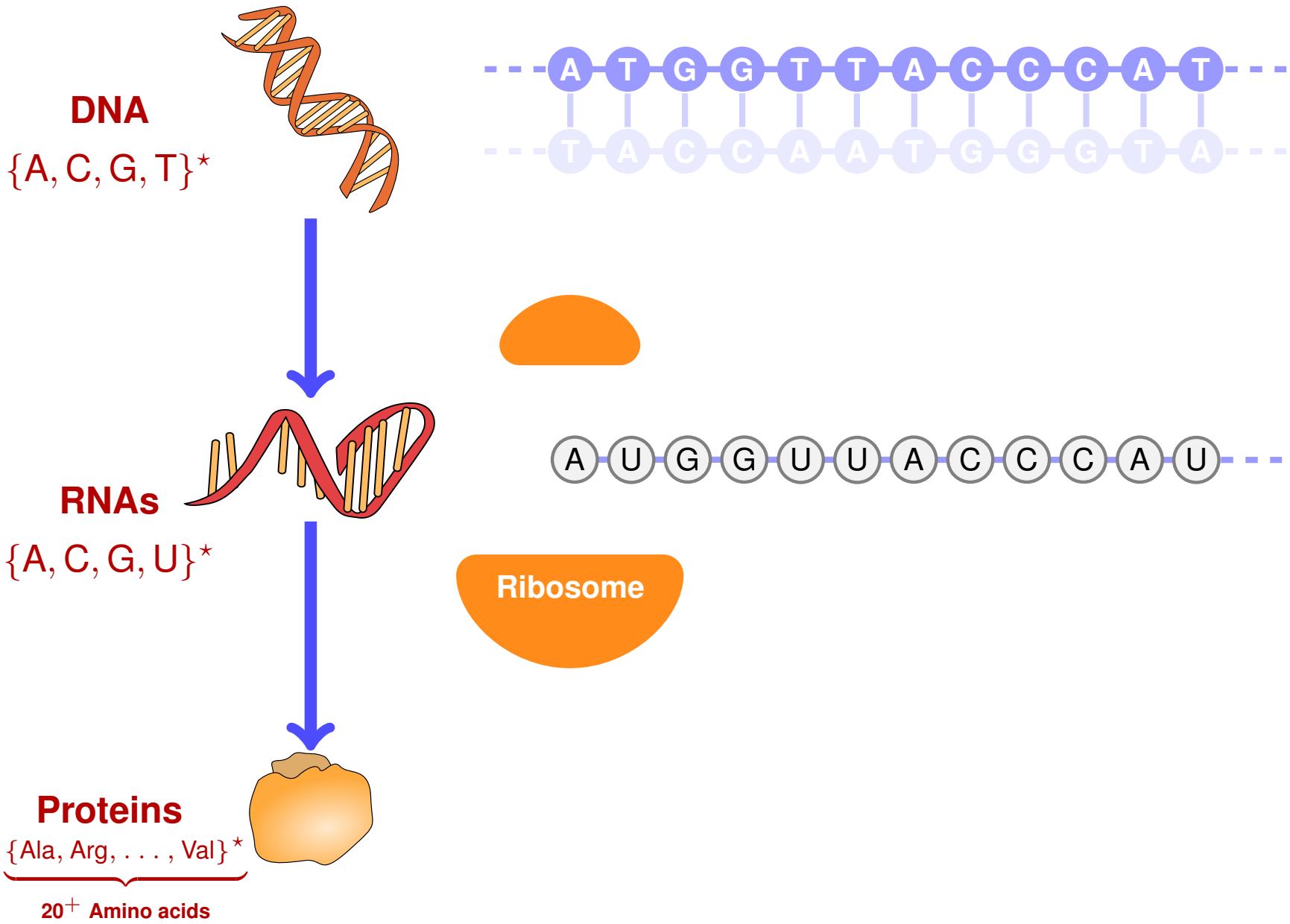

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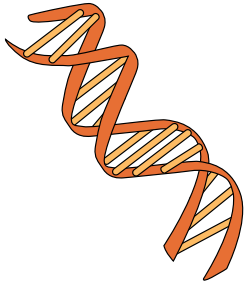

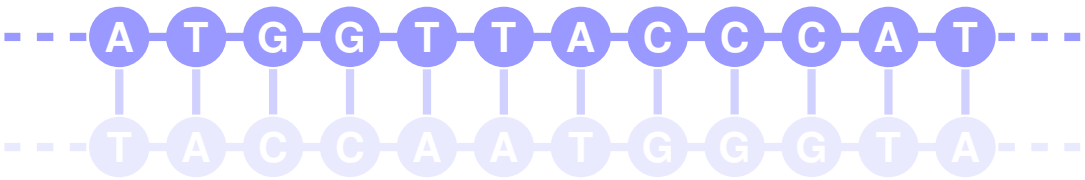


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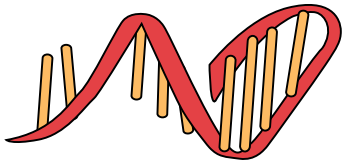

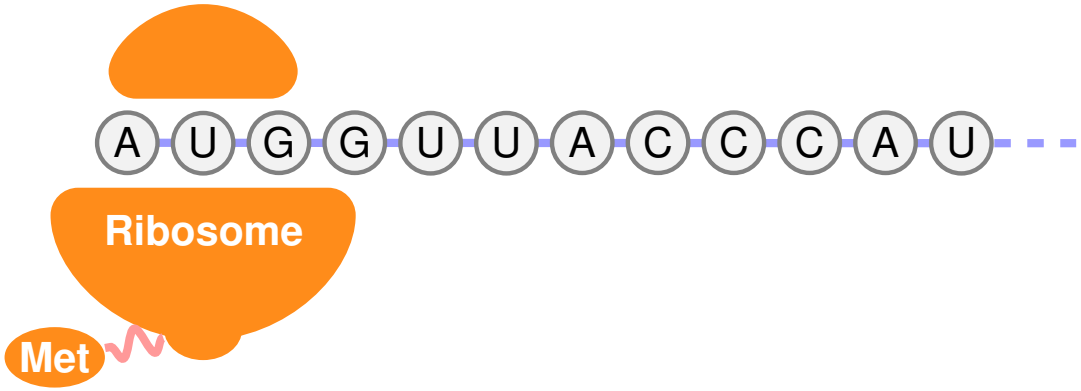


**Proteins**

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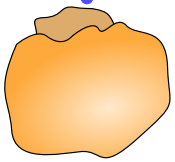

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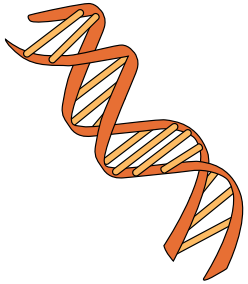

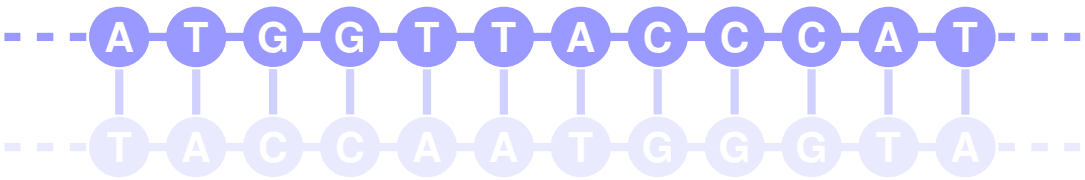


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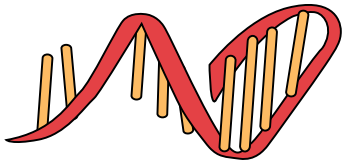

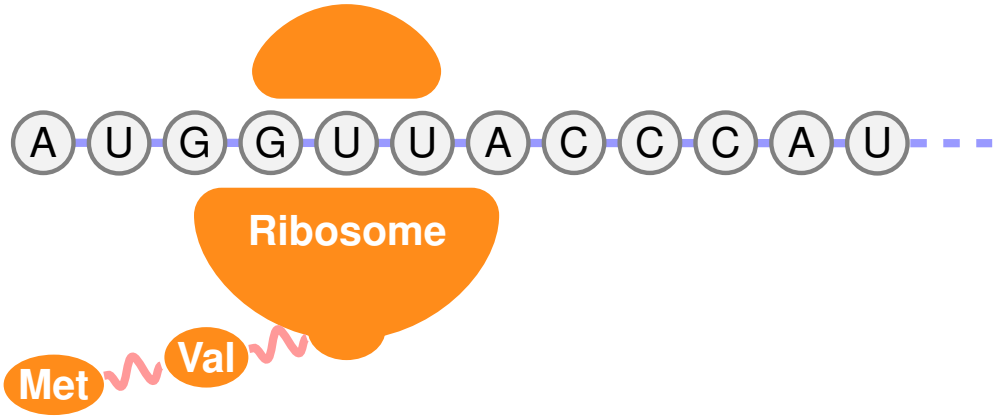


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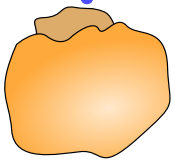

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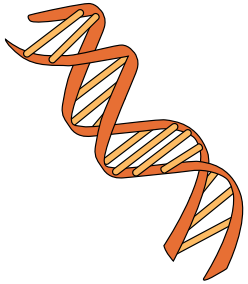

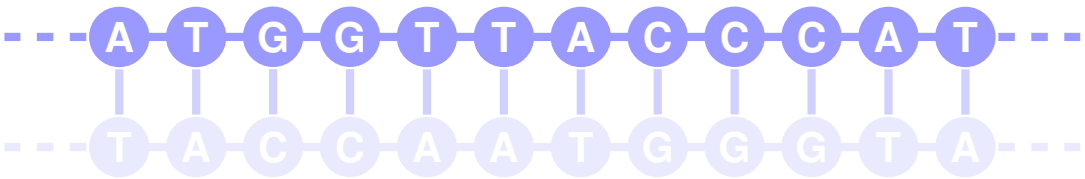


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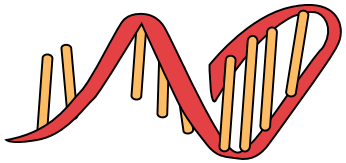

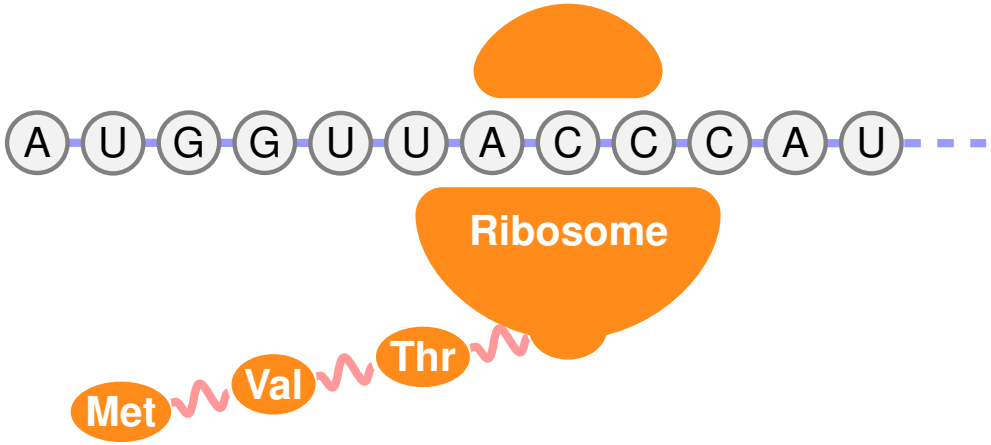


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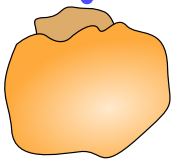

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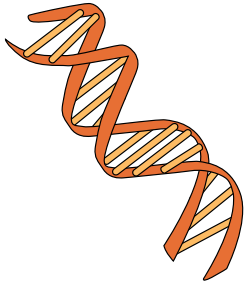

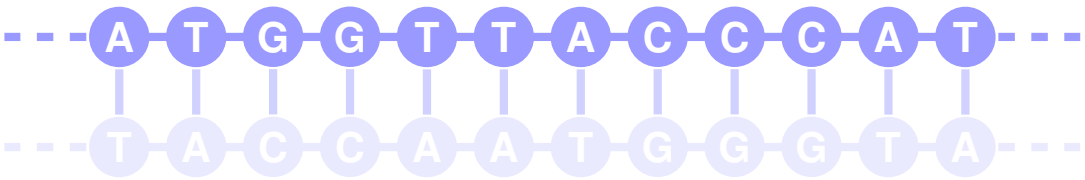


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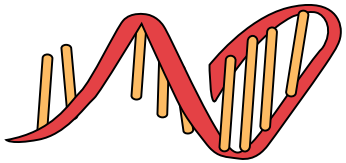

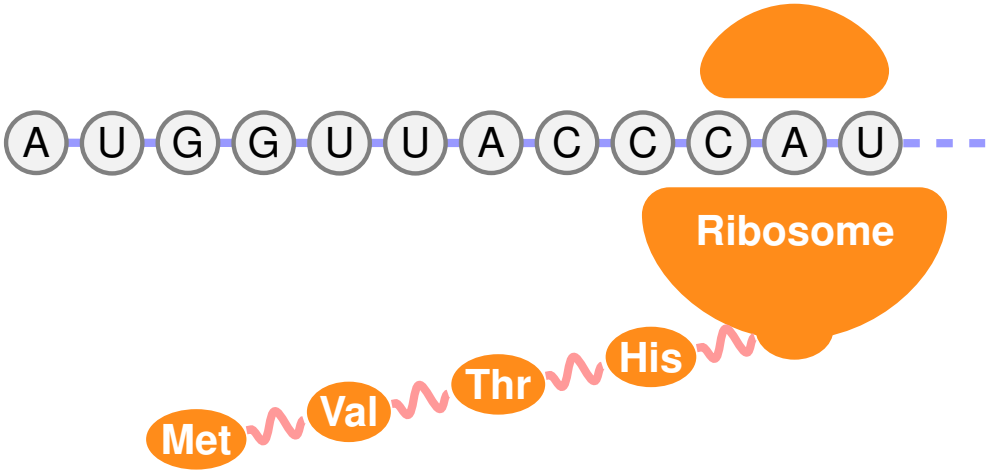


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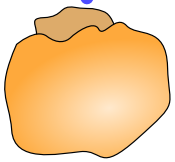

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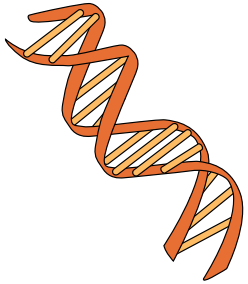

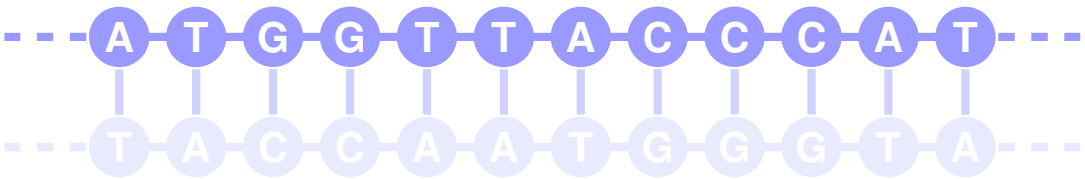


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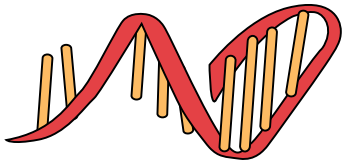


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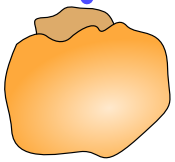

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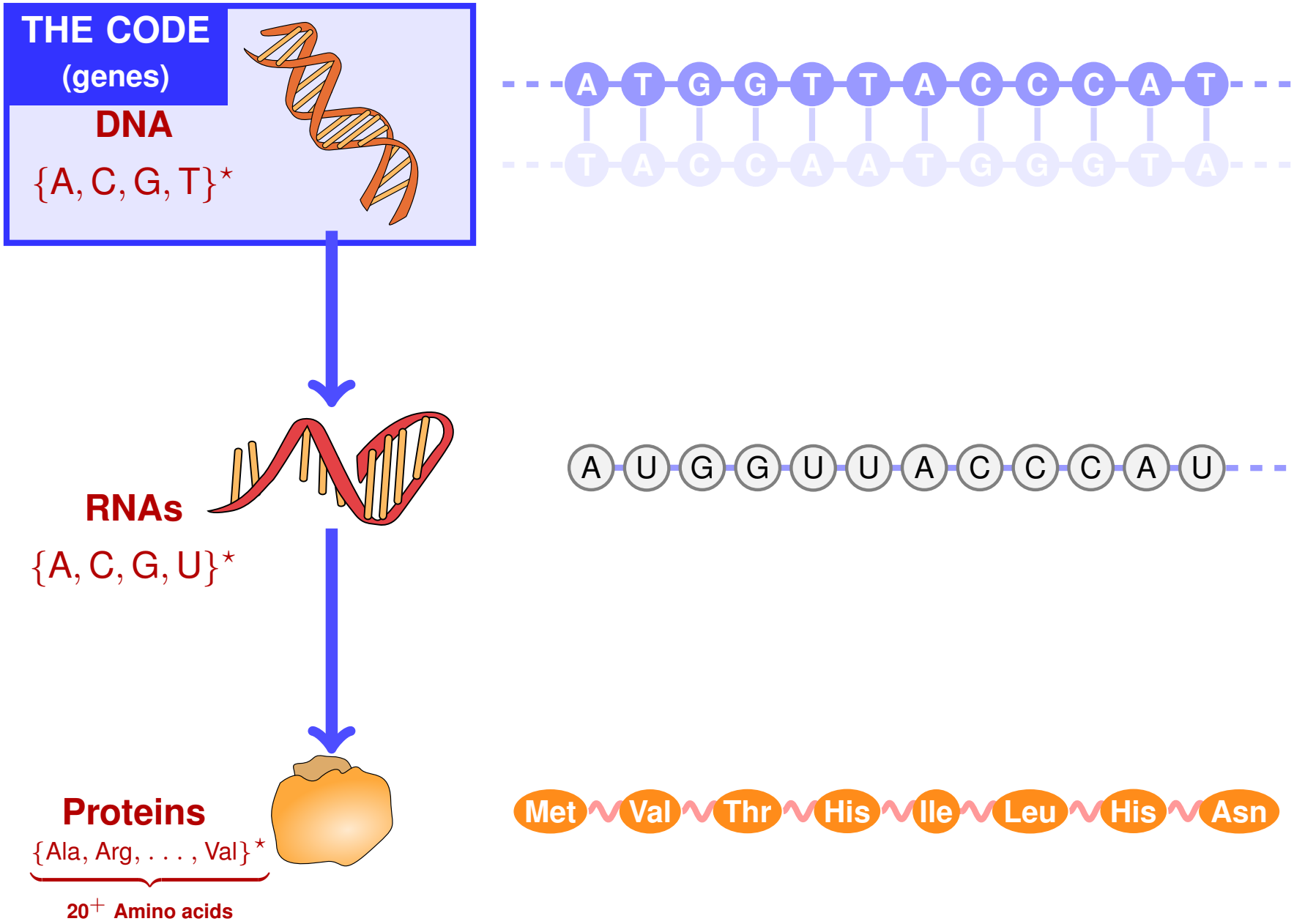

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**THE CODE**
**(genes)**

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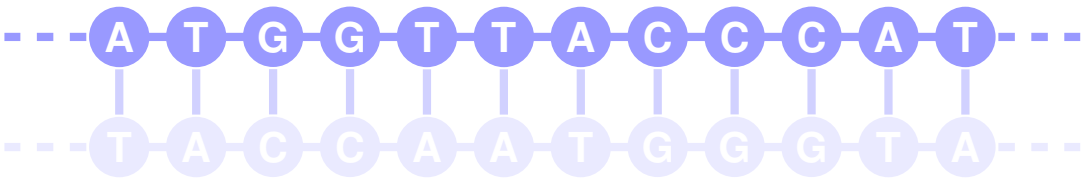


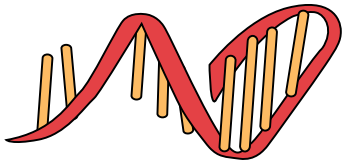

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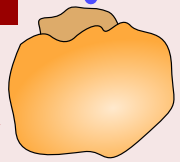
**THE MACHINE**
**(enzymes)**



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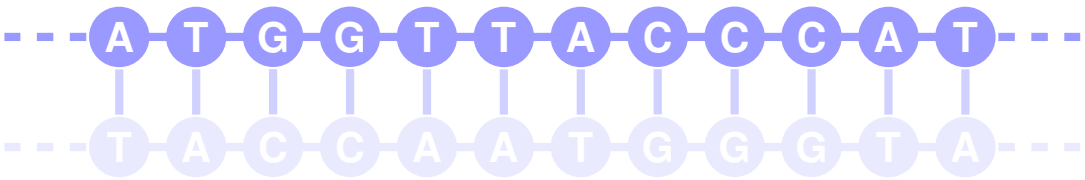


**MEH...**

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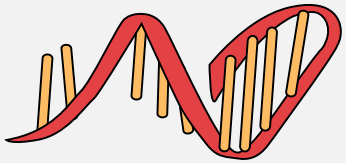


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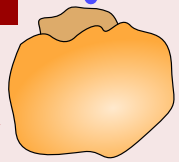

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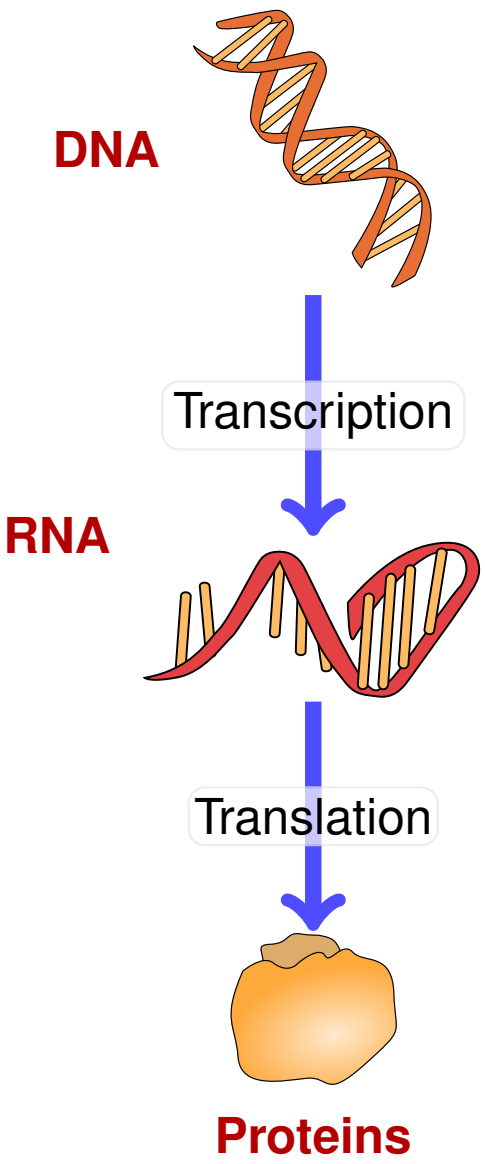

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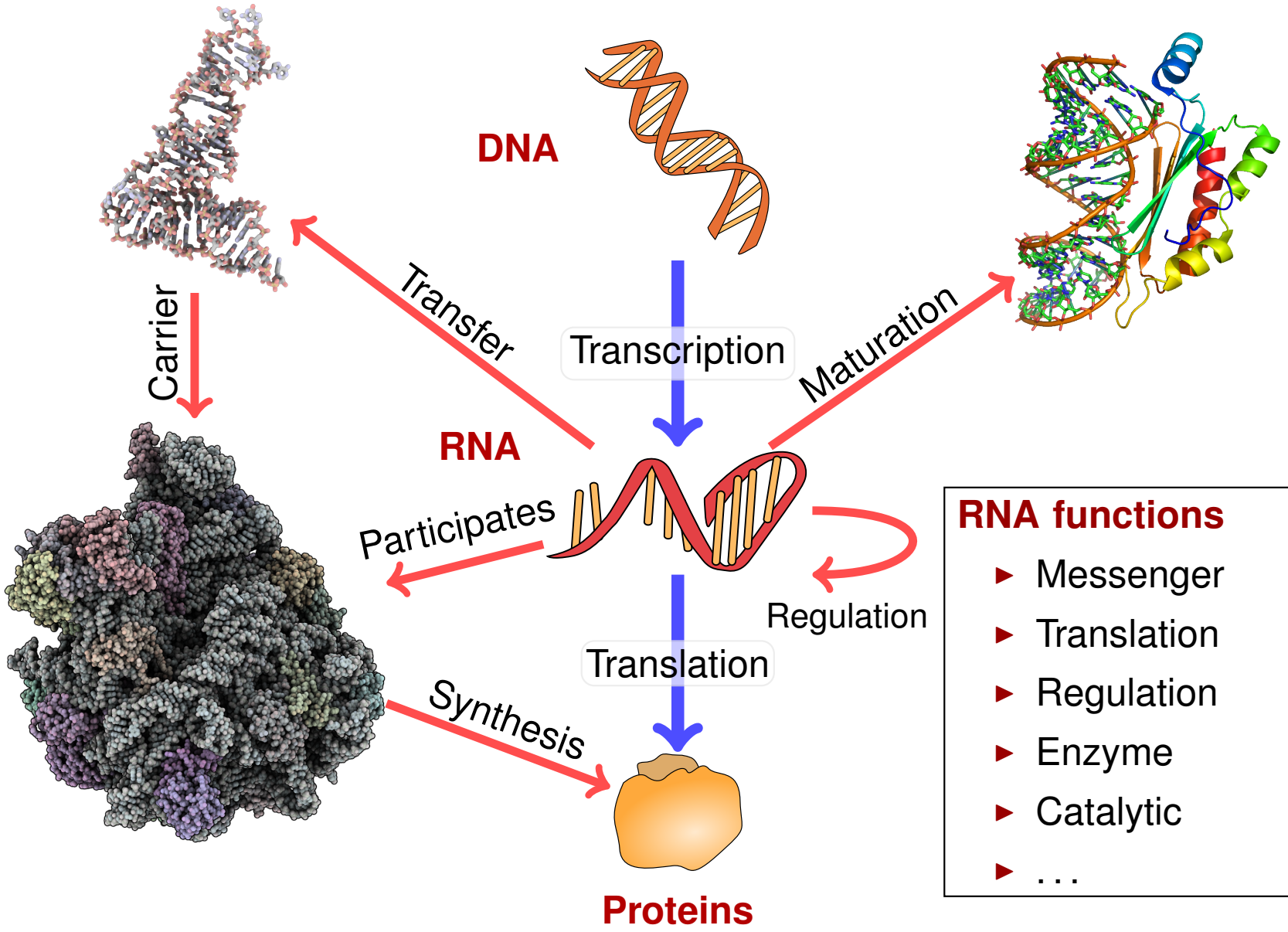


**RNA functions**

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

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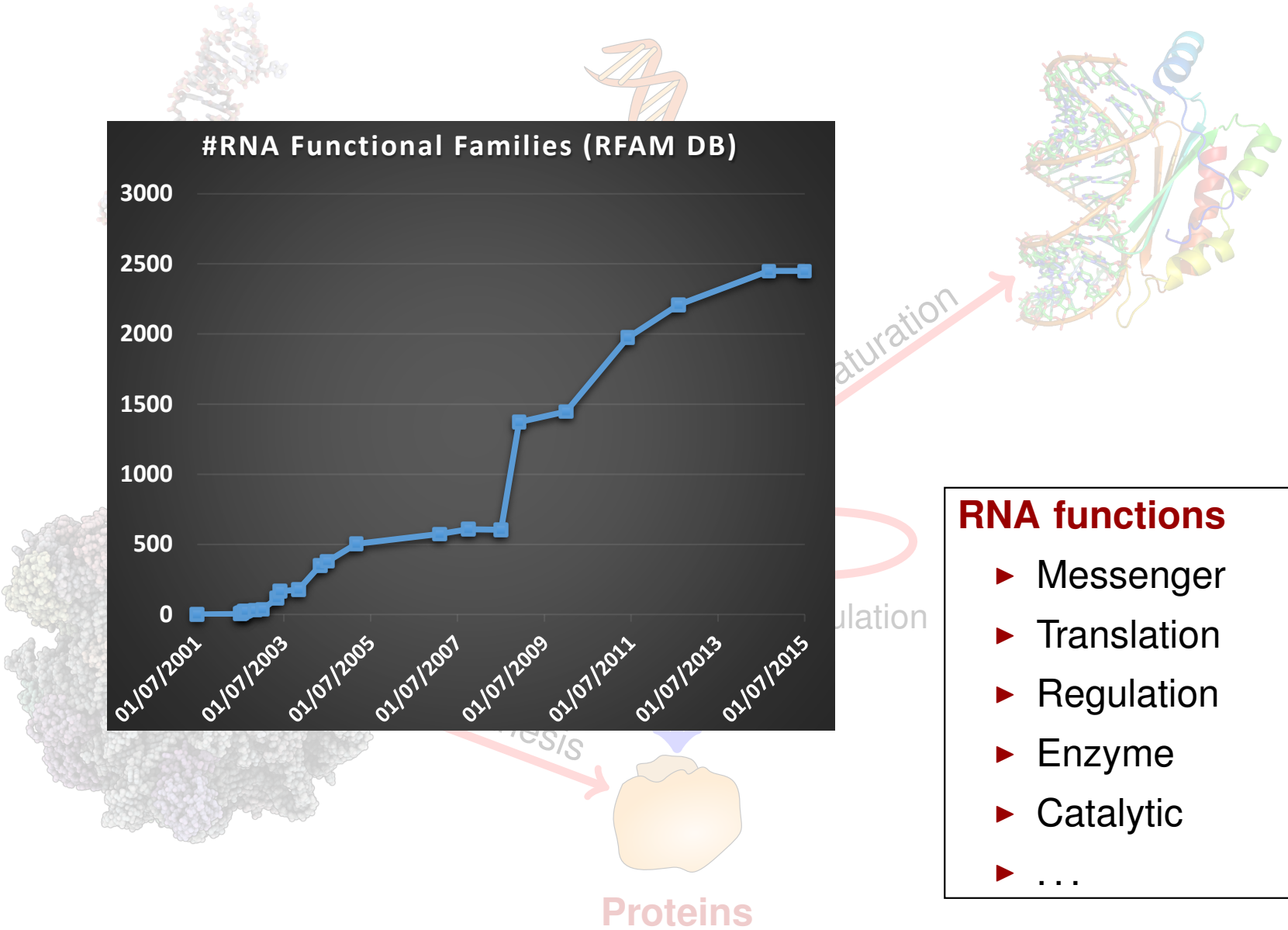


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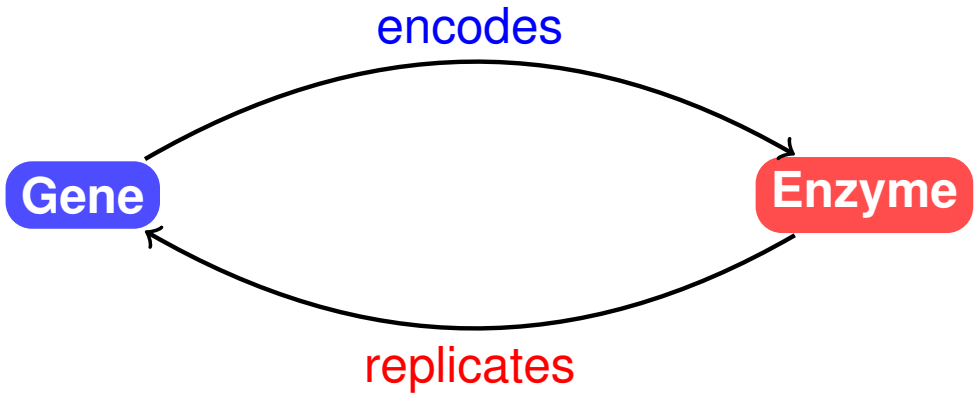
# RNA world: Resolving the *chicken vs egg* paradox at the origin of life...





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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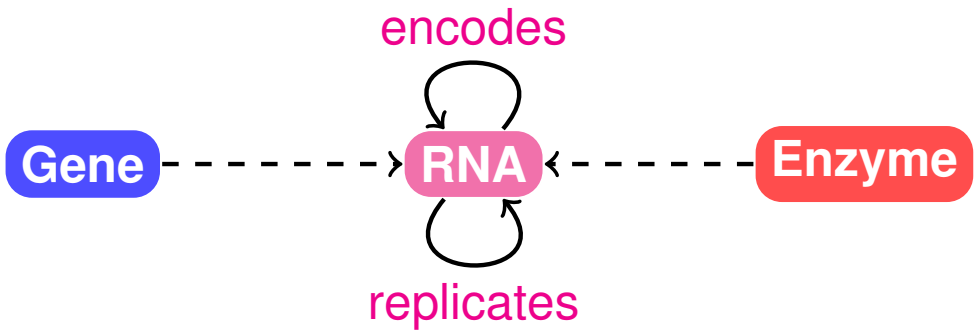




A gene big enough to specify an enzyme would be too big to replicate accurately without the aid of an enzyme of the very kind that it is trying to specify. So the system *apparently cannot get started*.

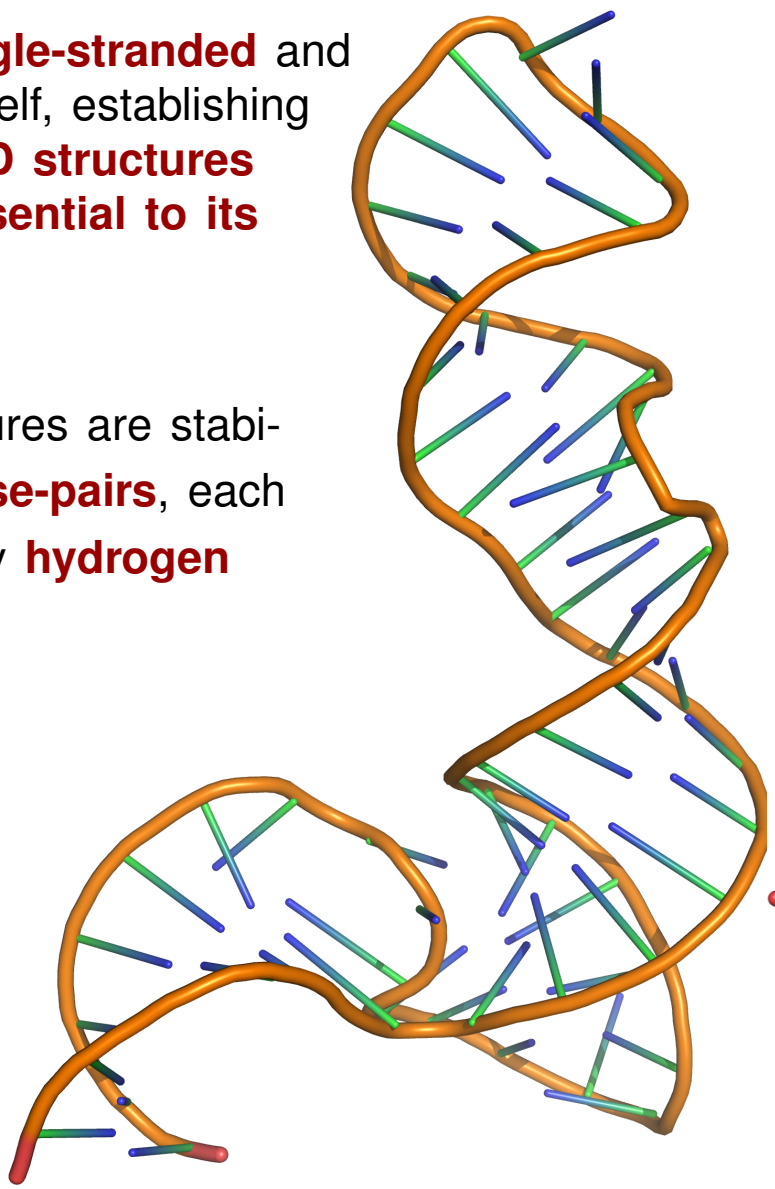
[...] This is the RNA World. To see how plausible it is, we need to look at why proteins are good at being enzymes but bad at being replicators; at why DNA is good at replicating but bad at being an enzyme; and finally why *RNA might just be good enough at both roles to break out of the Catch-22.*

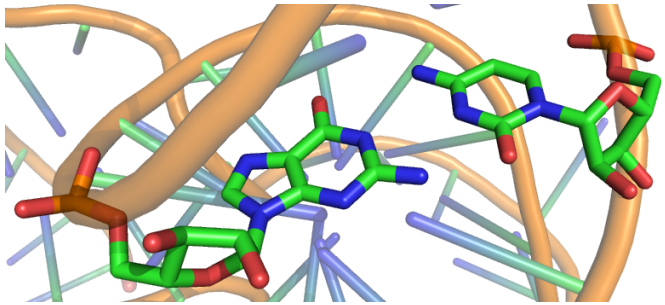
**R. Dawkins**. *The Ancestor's Tale: A Pilgrimage to the Dawn of Evolution*

# RNA folding

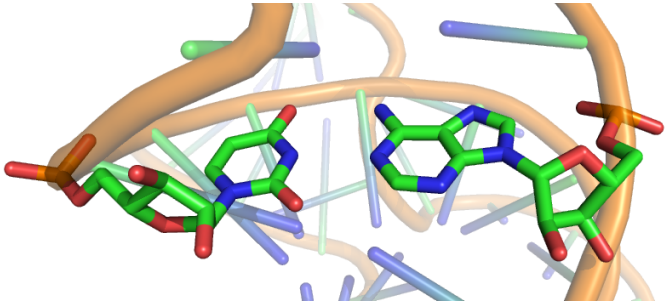
RNA is **single-stranded** and **folds** on itself, establishing **complex 3D structures** that are **essential to its function(s)**.

RNA structures are stabilized by **base-pairs**, each mediated by **hydrogen bonds**.



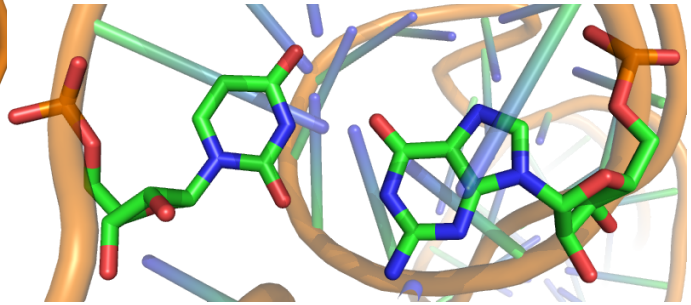


G/C



U/A

Watson/Crick base-pairs



U/G

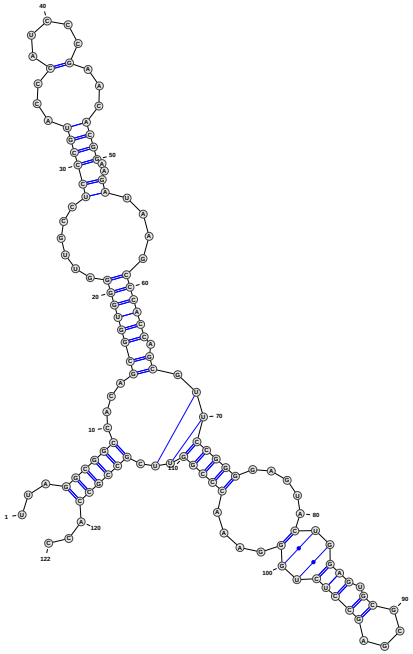
Wobble base-pair

**Canonical base-pairs**

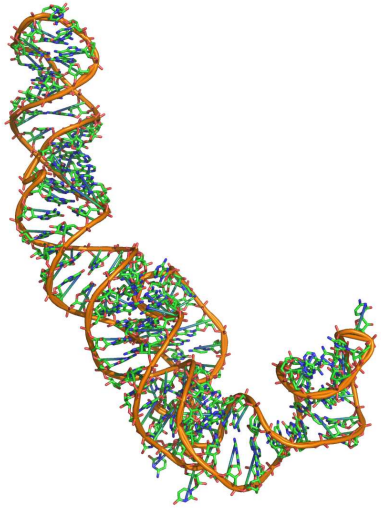
# RNA structure(s)

```
UUAGGCGGCCACAGC
GGUGGGGUUGCCUCC
CGUACCCAUCCCGAA
CACGGAAGAUAAGCC
CACCAGCGUUCCGGG
GAGUACUGGAGUGCG
CGAGCCUCUGGGAAA
CCCGGUUCGCCGCCA
CC
```

Primary structure



Secondary structure



Tertiary structure

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

**Definition (Secondary Structure)**

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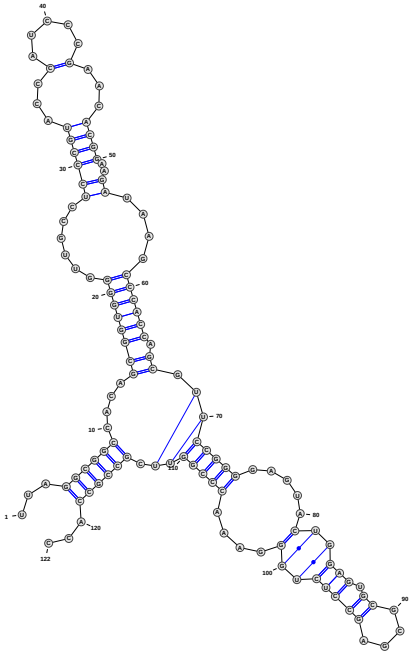

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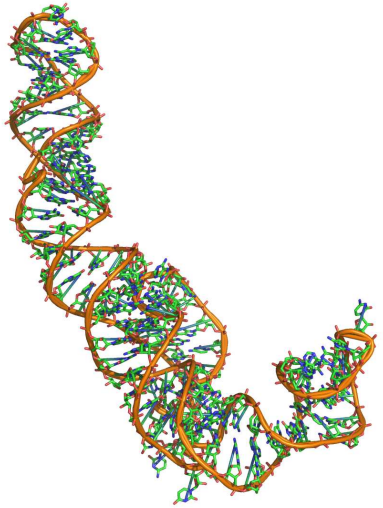

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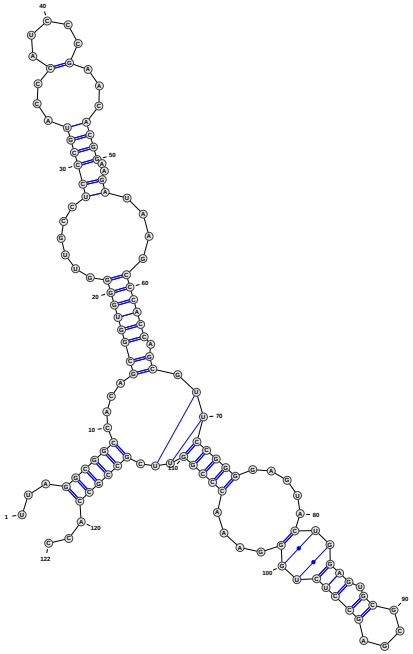

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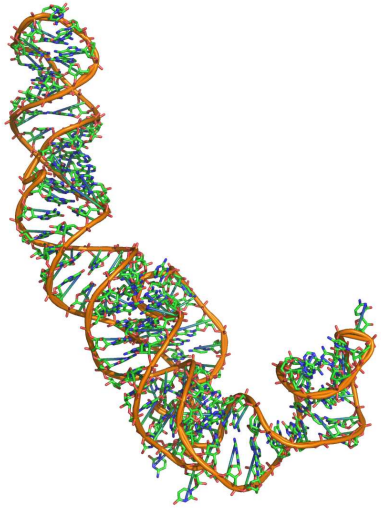

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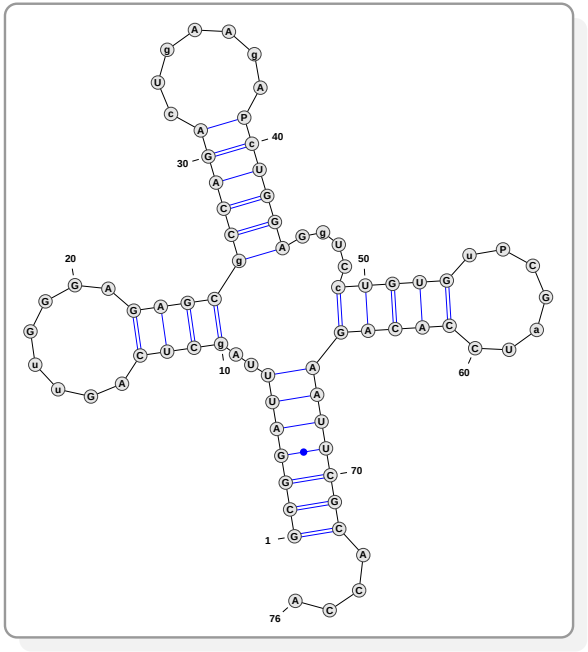
# Various representations for a versatile biomolecule



Outer-planar graphs

Hamiltonian-path, $\Delta(G) \leq 3$, 2-connected*

**Supporting intuitions**

Different representations

Common combinatorial structure

* Additional steric constraints

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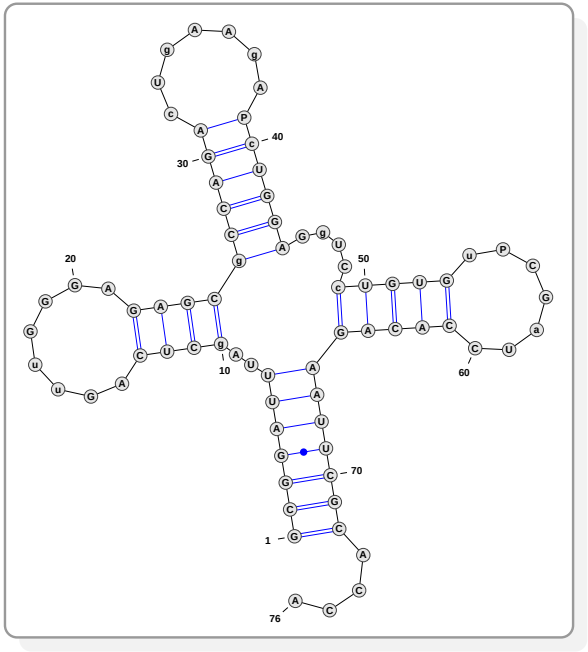

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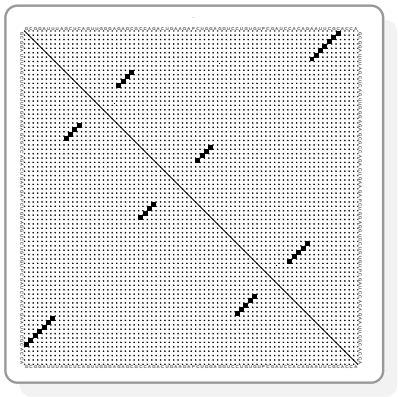

Dot plots

Adjacency matrices$^\star$

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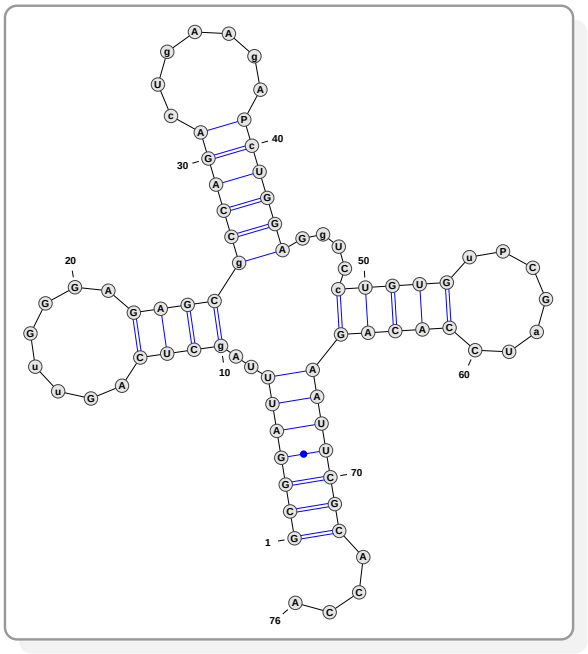

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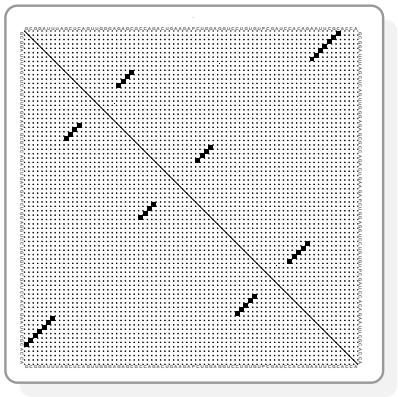

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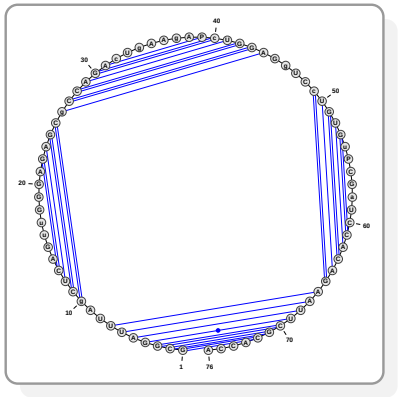

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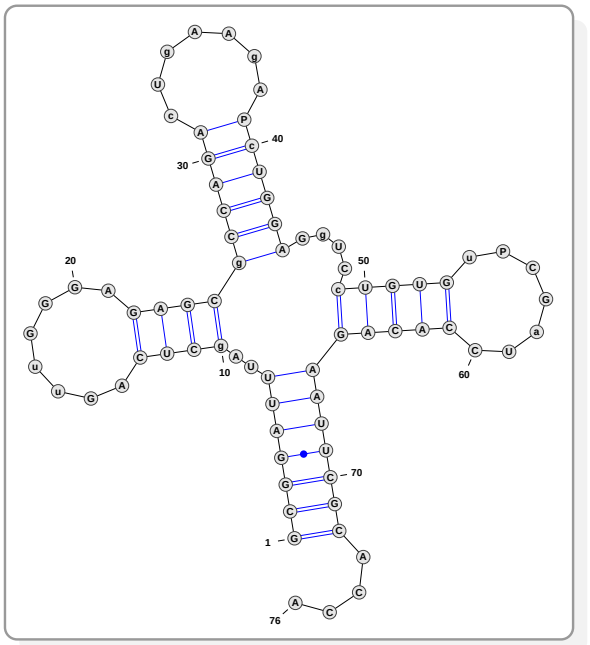

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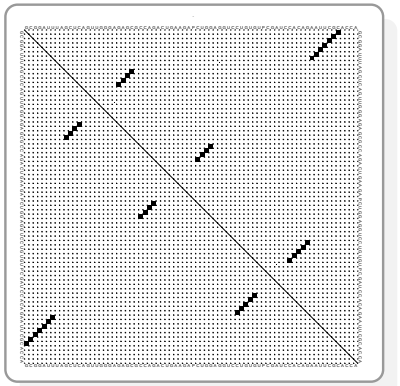
```
(((((((..((((........))))((((((.......))))))....(((((.......)))))))))))).....
```

Motzkin words$^\star$



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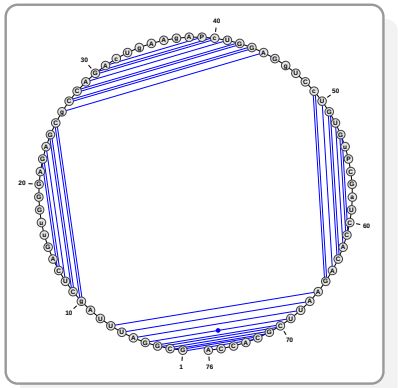

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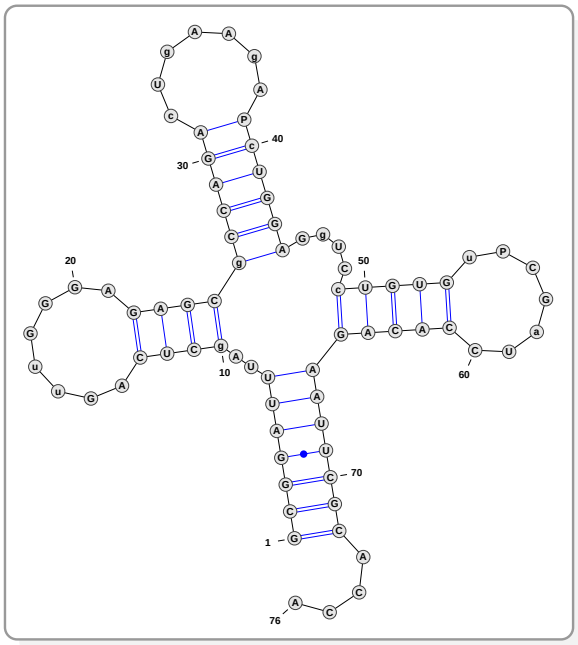

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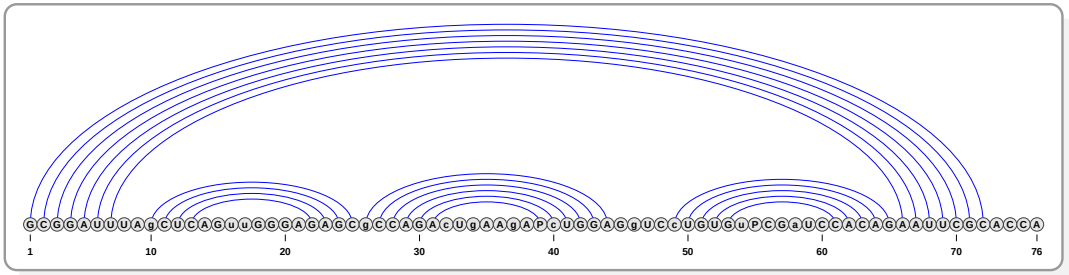
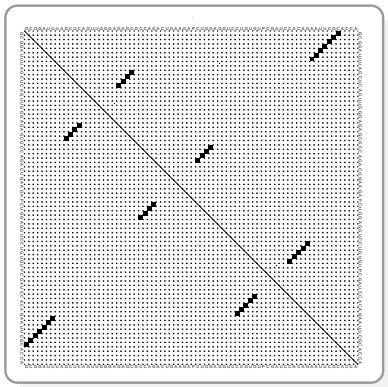


Non-crossing arc-annotated sequences$^\star$



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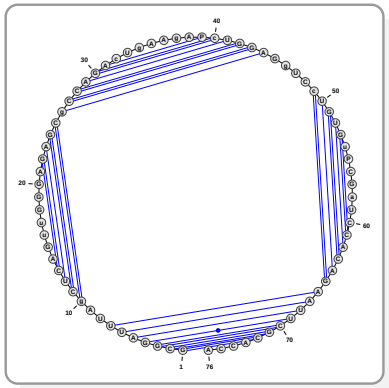

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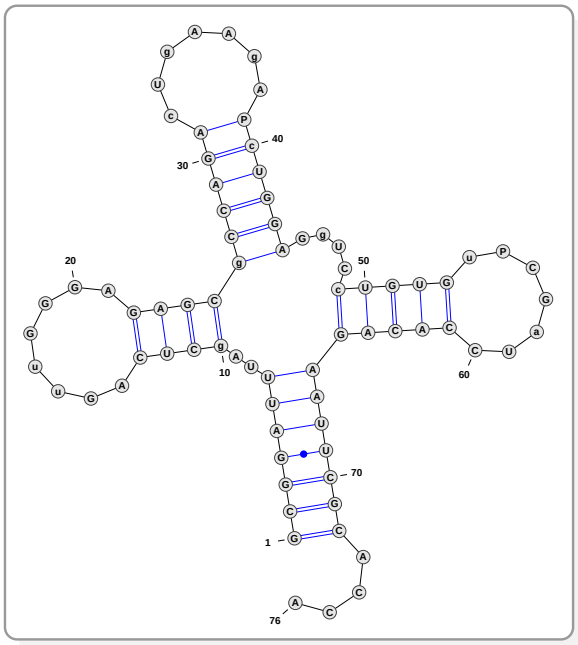

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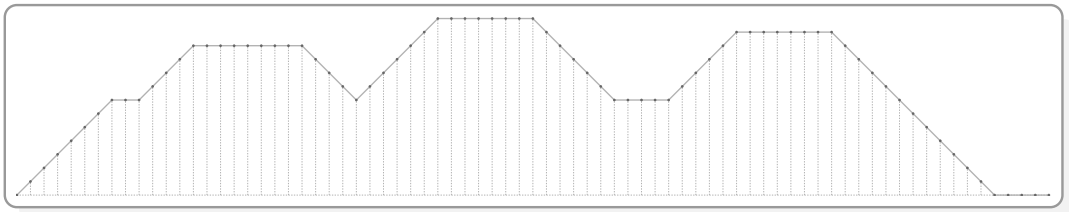
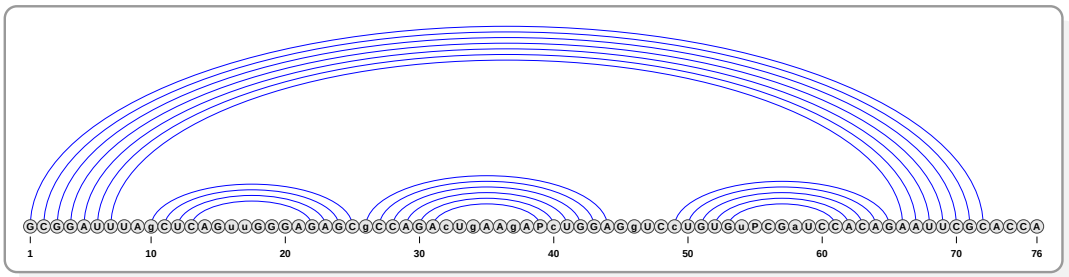


Positive 1D meanders$^\star$ over $\mathcal{S} = \{+1, -1, 0\}$



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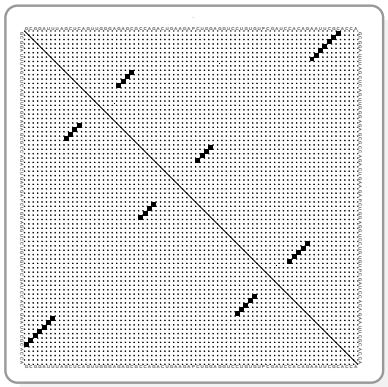

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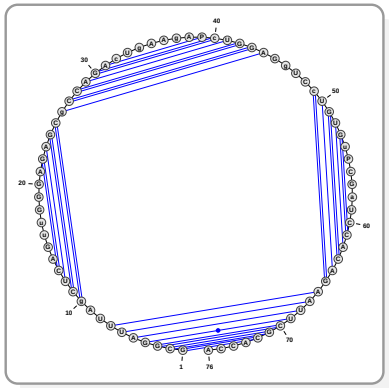

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# Part 1. Enumerative aspects

# Life through the lens of enumerative combinatorics

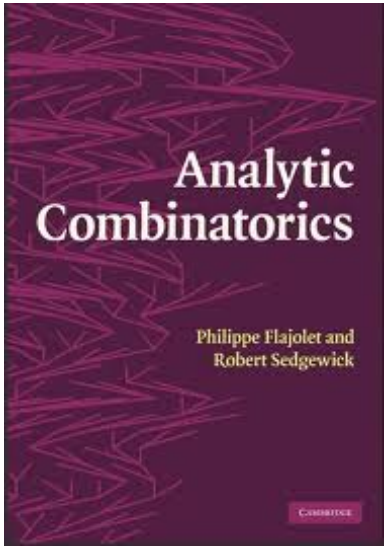
**Enumerative combinatorics** can be used to characterize the **precise (asymptotic) behavior** of **abstract models** for RNA sequence/structure.

**Typical problems**

- How many secondary structures on $n$ nucleotides? [Waterman, 1978]
- Expected #structures compatible with random RNA? [Zuker and Sankoff, 1984]
- Average distance between extremities? [Clote, Ponty, and Steyaert, 2012b]

The **symbolic method**, a **generic framework** for enumeration:

1. Find a suitable decomposition
2. Rephrase into grammar/specification
3. Translate equations & solve for generating function(s)
4. Singularity analysis yields asymptotics



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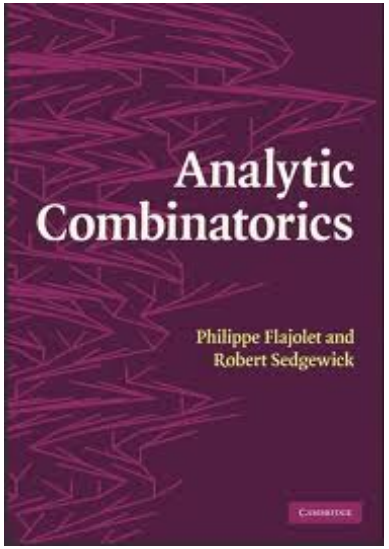

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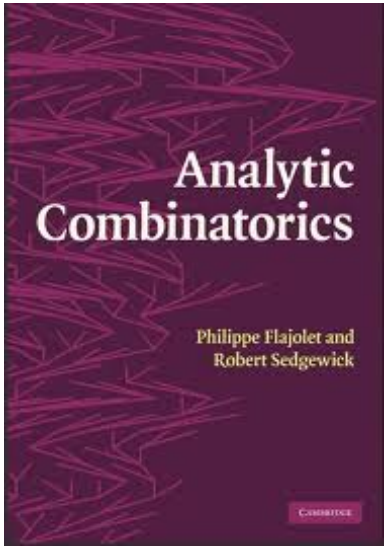

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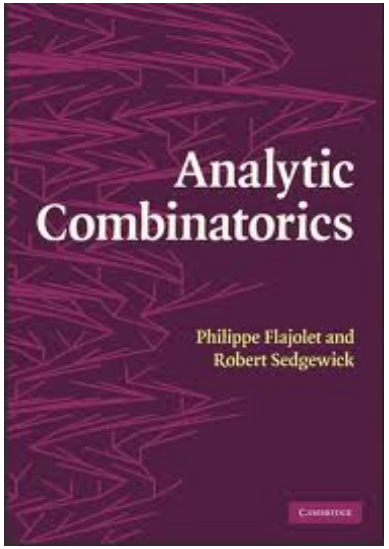

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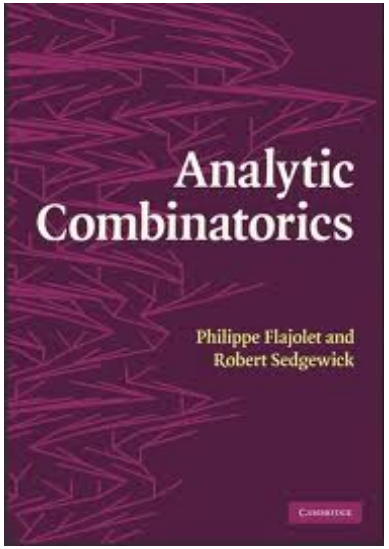

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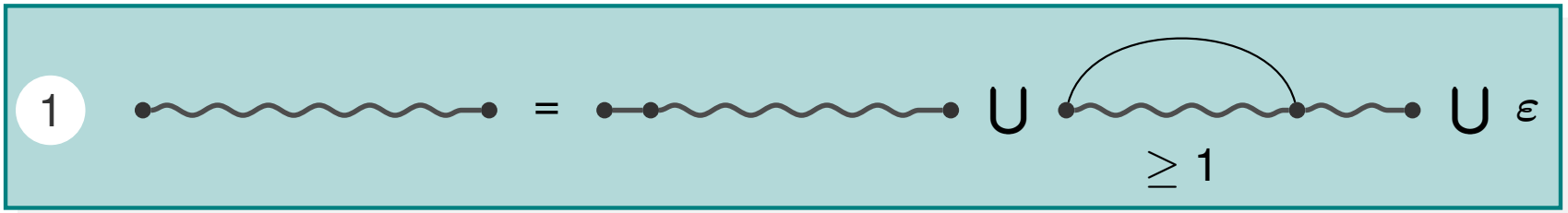
# RNA secondary structures

**Goal: Generating function $S(z) = \sum_{n \geq 0} s_n z^n$**

where $s_n$ = #Secondary structures of length $n$

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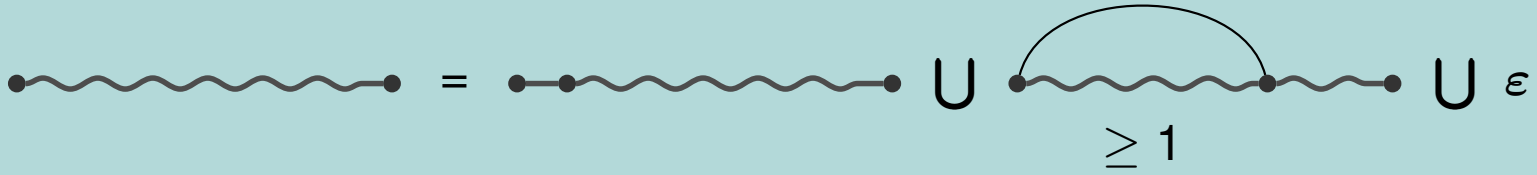


2 $S \rightarrow \bullet\, S \mid (\, S_{>0} \,)\, S \mid \varepsilon$

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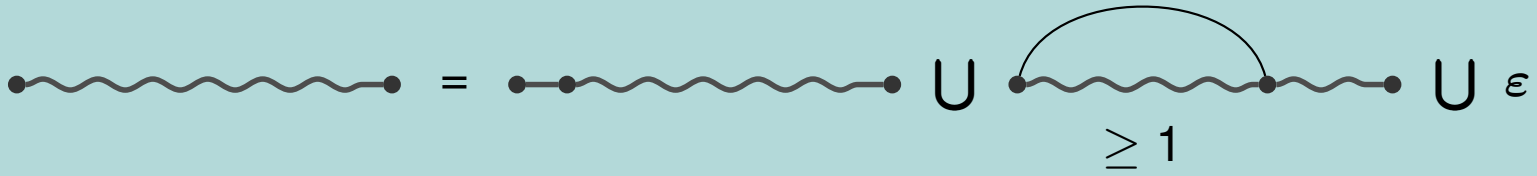


2

$$S \rightarrow \bullet S \mid (\mathbf{T}) S \mid \varepsilon$$

$$\mathbf{T} \rightarrow \bullet S \mid (\mathbf{T}) S$$

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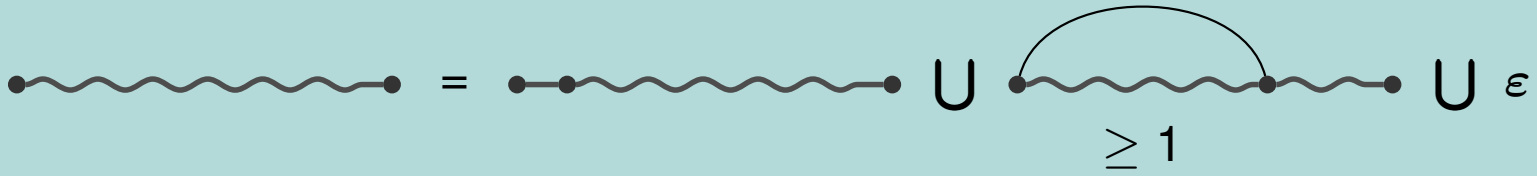



2

$$S \rightarrow \bullet\, S \mid (\,\mathbf{T}\,)\, S \mid \varepsilon$$

$$\mathbf{T} \rightarrow \bullet\, S \mid (\,\mathbf{T}\,)\, S$$

3

$$S(z) = \frac{1 - z + z^2 - \sqrt{1 - 2z - z^2 - 2z^3 + z^4}}{2z^2}$$

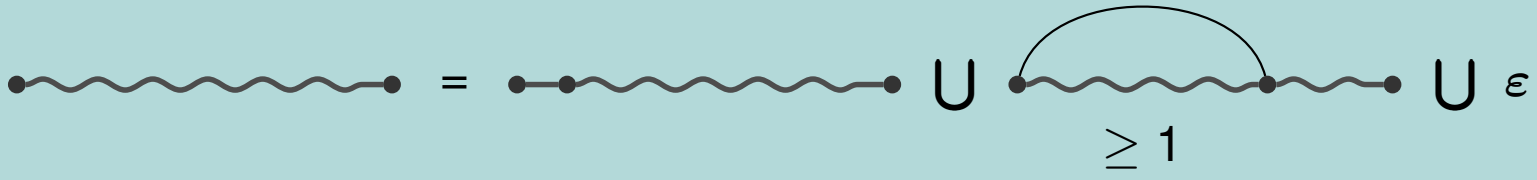
[Waterman, 1978] & [Vauchaussade de Chaumont and Viennot, 1985]

# RNA secondary structures

**Goal: Generating function $S(z) = \sum_{n \geq 0} s_n z^n$**

where $s_n$ = #Secondary structures of length $n$

1




2

$$S \rightarrow \bullet\, S \mid (\, \mathbf{T}\, )\, S \mid \varepsilon$$

$$\mathbf{T} \rightarrow \bullet\, S \mid (\, \mathbf{T}\, )\, S$$

3

$$S(z) = \frac{1 - z + z^2 - \sqrt{1 - 2z - z^2 - 2z^3 + z^4}}{2z^2}$$

4

$$\rho = \frac{3 - \sqrt{5}}{2} = 1 - \phi$$

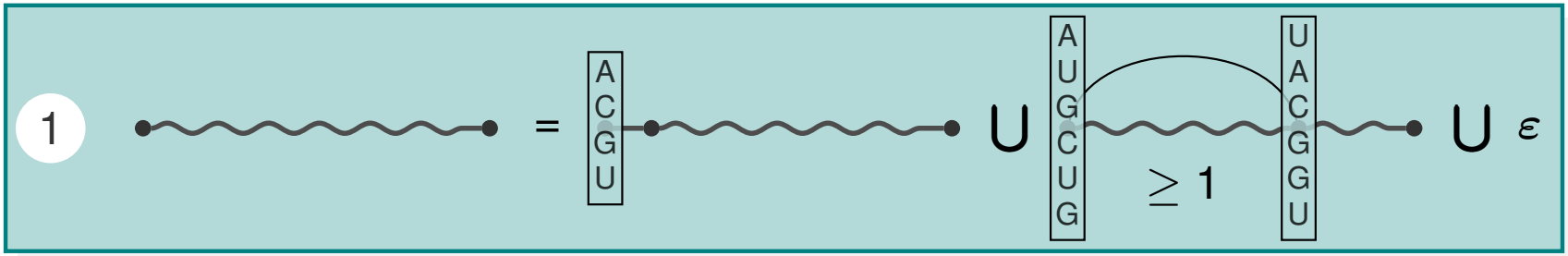
$$s_n = \sqrt{\frac{15 + 7\sqrt{5}}{8\pi}} \cdot \frac{\left(\frac{3+\sqrt{5}}{2}\right)^n}{n\sqrt{n}} (1 + \mathcal{O}(1/n)) \sim 1.1 \cdot \frac{2.6^n}{n\sqrt{n}}$$

[Waterman, 1978] & [Vauchaussade de Chaumont and Viennot, 1985]

# Expected #secondary structures compatible with RNA

**Goal: Generating function $S(z) = \sum_{n \geq 0} s_n z^n$**

where $s_n$ = #Compatible (Sequence/Sec. struct.) pairs of length $n$




[Zuker and Sankoff, 1984]

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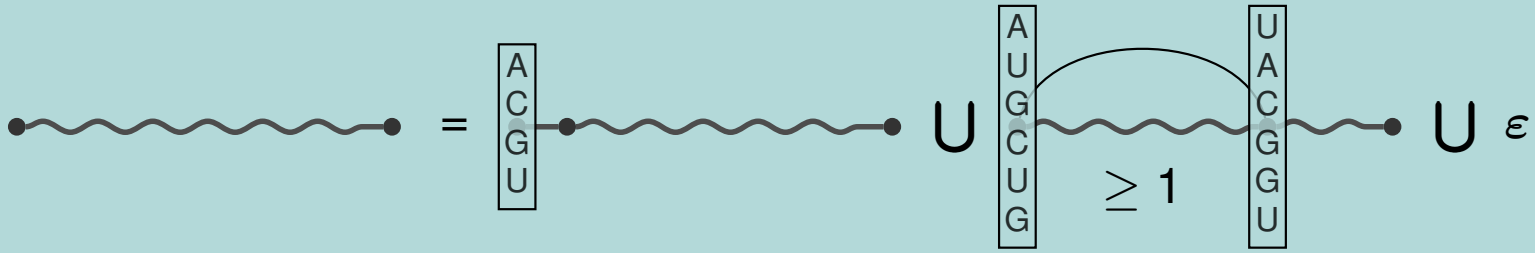


2

$$S \to \begin{array}{l} ({}_{\mathrm{A}}\, T\,)_{\mathrm{U}}\, S \\ ({}_{\mathrm{U}}\, T\,)_{\mathrm{A}}\, S \\ ({}_{\mathrm{G}}\, T\,)_{\mathrm{C}}\, S \\ ({}_{\mathrm{C}}\, T\,)_{\mathrm{G}}\, S \\ ({}_{\mathrm{U}}\, T\,)_{\mathrm{G}}\, S \\ ({}_{\mathrm{G}}\, T\,)_{\mathrm{U}}\, S \end{array} \Bigg| \begin{array}{l} \bullet_{\mathrm{A}}\, S \\ \bullet_{\mathrm{U}}\, S \\ \bullet_{\mathrm{G}}\, S \\ \bullet_{\mathrm{C}}\, S \end{array} \Bigg| \, \varepsilon \qquad T \to \begin{array}{l} ({}_{\mathrm{A}}\, T\,)_{\mathrm{U}}\, S \\ ({}_{\mathrm{U}}\, T\,)_{\mathrm{A}}\, S \\ ({}_{\mathrm{G}}\, T\,)_{\mathrm{C}}\, S \\ ({}_{\mathrm{C}}\, T\,)_{\mathrm{G}}\, S \\ ({}_{\mathrm{U}}\, T\,)_{\mathrm{G}}\, S \\ ({}_{\mathrm{G}}\, T\,)_{\mathrm{U}}\, S \end{array} \Bigg| \begin{array}{l} \bullet_{\mathrm{A}}\, S \\ \bullet_{\mathrm{U}}\, S \\ \bullet_{\mathrm{G}}\, S \\ \bullet_{\mathrm{C}}\, S \end{array} .$$

[Zuker and Sankoff, 1984]

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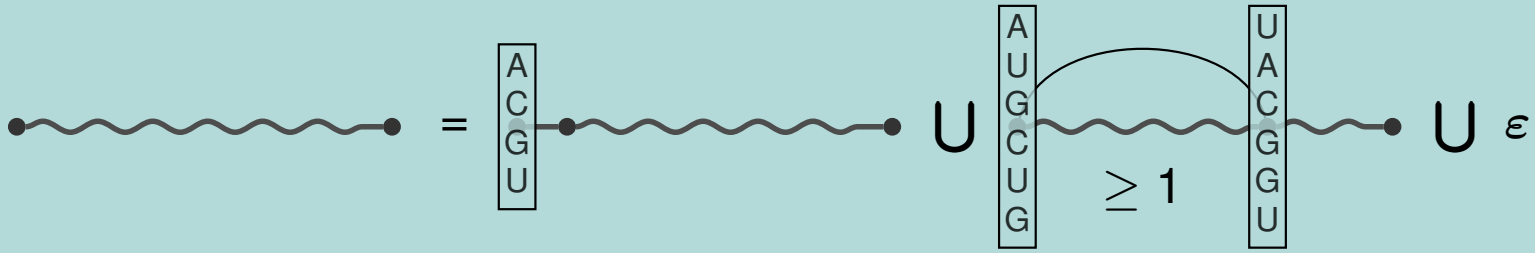


2

$$S \to {}_{A}T_{U}\,S \;\; {}_{U}T_{A}\,S \;\; {}_{G}T_{C}\,S \;\; {}_{C}T_{G}\,S \;\; {}_{U}T_{G}\,S \;\; {}_{G}T_{U}\,S \;\Big|\; \bullet_{A}S \;\; \bullet_{U}S \;\; \bullet_{G}S \;\; \bullet_{C}S \;\Big|\; \varepsilon$$

$$T \to {}_{A}T_{U}\,S \;\; {}_{U}T_{A}\,S \;\; {}_{G}T_{C}\,S \;\; {}_{C}T_{G}\,S \;\; {}_{U}T_{G}\,S \;\; {}_{G}T_{U}\,S \;\Big|\; \bullet_{A}S \;\; \bullet_{U}S \;\; \bullet_{G}S \;\; \bullet_{C}S.$$

3

$$S(z) = \frac{1-4z+6z^2-\sqrt{1-8z-4z^2-48z^3+36z^4}}{12z^2}$$

[Zuker and Sankoff, 1984]

# Expected #secondary structures compatible with RNA

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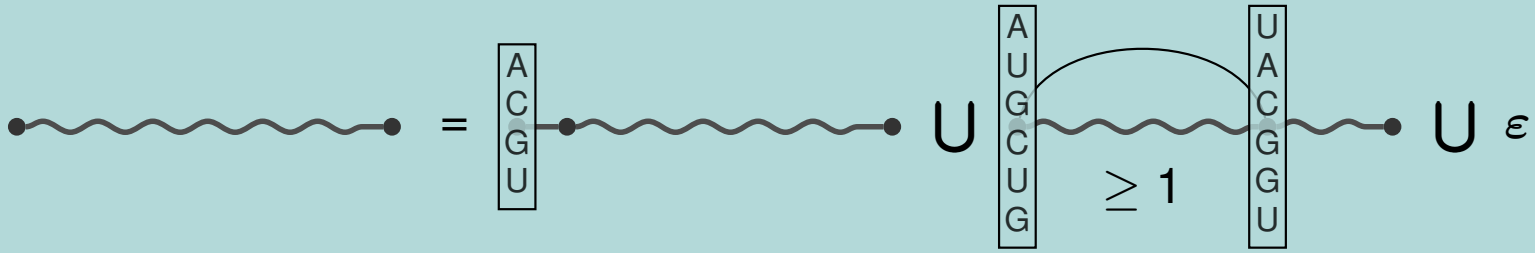


2

$$S \to {}_{(A}\,T\,{}_{)U}\,S \;\; {}_{(U}\,T\,{}_{)A}\,S \;\; {}_{(G}\,T\,{}_{)C}\,S \;\; {}_{(C}\,T\,{}_{)G}\,S \;\; {}_{(U}\,T\,{}_{)G}\,S \;\; {}_{(G}\,T\,{}_{)U}\,S \;\Big|\; \bullet_A S \;\; \bullet_U S \;\; \bullet_G S \;\; \bullet_C S \;\Big|\; \varepsilon$$

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$$S(z) = \frac{1-4z+6z^2-\sqrt{1-8z-4z^2-48z^3+36z^4}}{12z^2}$$

4

$$\rho = \text{InfSing}(1-8z-4z^2-48z^3+36z^4) \quad 1/\rho \approx 8.164$$

$$s_n \in \Theta\left(\frac{\rho^{-n}}{n\sqrt{n}}\right) \quad \to \quad \text{Expected\#Sec.Str.}=s_n/4^n \in \Theta(2.04^n/n\sqrt{n})$$

[Zuker and Sankoff, 1984]

# RNA secondary structures ($\theta$ constraint)

**Goal: Generating function $S_\theta(z) = \sum_{n\geq 0} s_{\theta,n}\, z^n$**

where $s_{\theta,n}$ = #Secondary structures of length $n$
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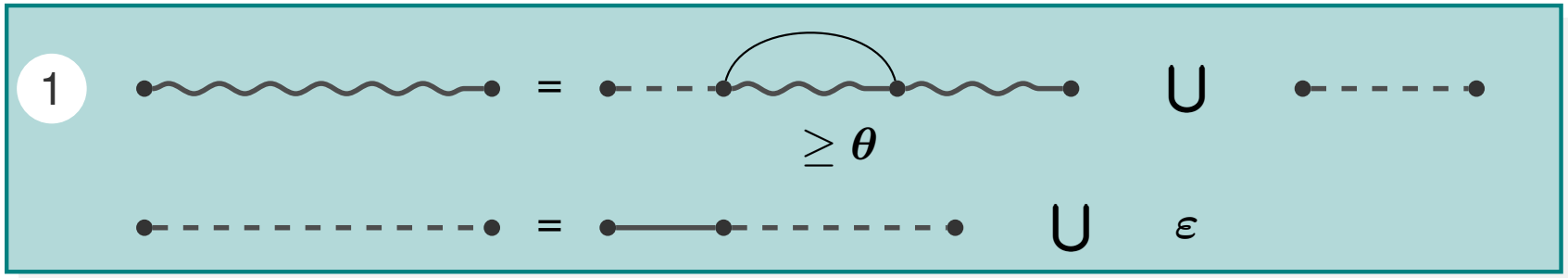

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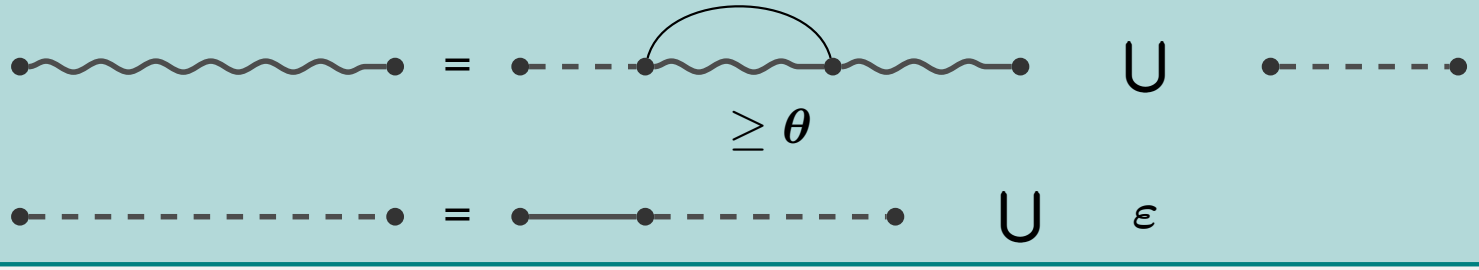


2 $\quad S \rightarrow U\,(\,S_{\geq\theta}\,)\,S \mid U \qquad U \rightarrow \bullet\, U \mid \varepsilon$

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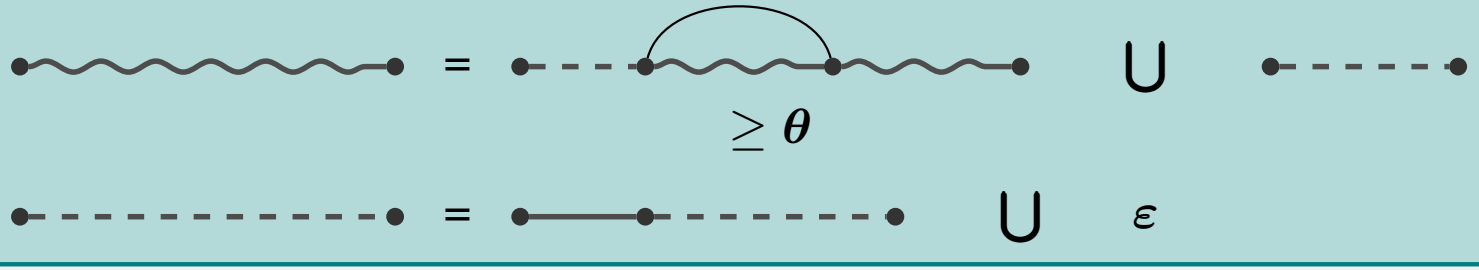


2

$$S \rightarrow U\,(\,\mathbf{T}\,)\,S \mid U \qquad U \rightarrow \bullet\, U \mid \varepsilon$$

$$\mathbf{T} \rightarrow U\,(\,\mathbf{T}\,)\,S \mid \bullet^{\theta}\, U$$

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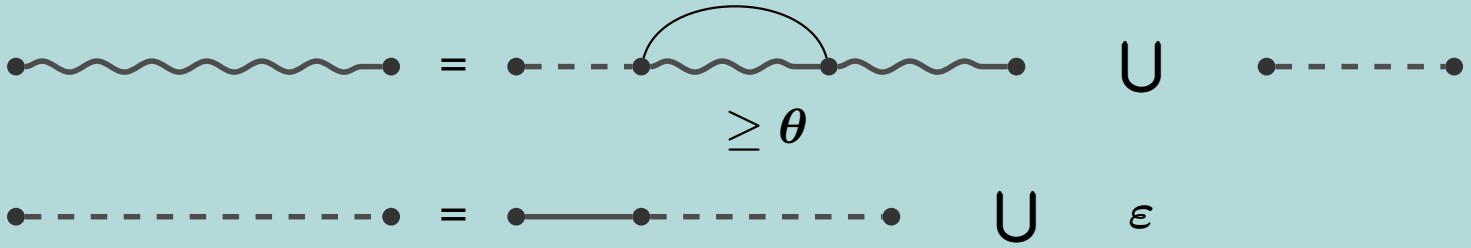


2

$$S \rightarrow U\,(\,\mathbf{T}\,)\,S \mid U \qquad U \rightarrow \bullet\, U \mid \varepsilon$$

$$\mathbf{T} \rightarrow U\,(\,\mathbf{T}\,)\,S \mid \bullet^{\theta}\, U$$

3

$$S_\theta(z) = \frac{1-2z+2z^2-z^{\theta+2}-\sqrt{1-4z+4z^2-2z^{\theta+2}+4z^{\theta+3}-4z^{\theta+4}+z^{2\theta+4}}}{(1-z)2z^2}$$

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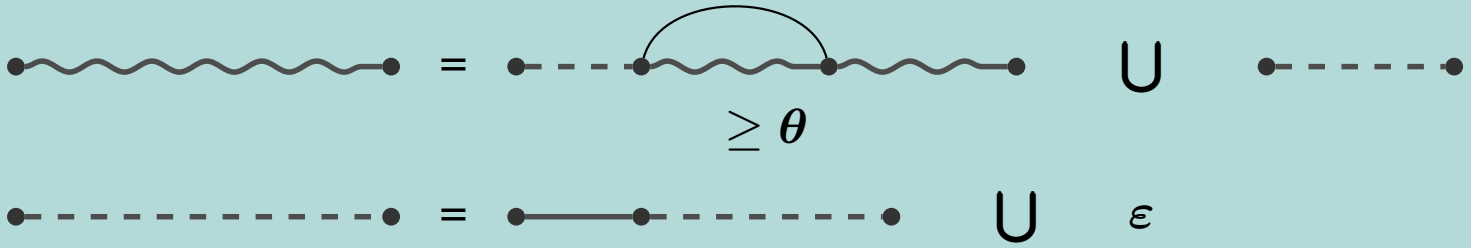


2

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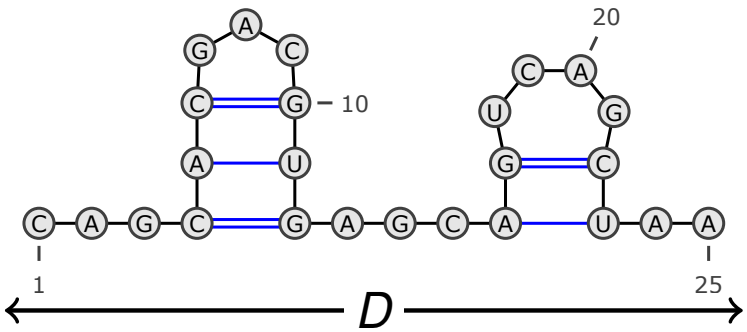
4

$$s_n \sim K.\frac{\beta^n}{n\sqrt{n}}(1+\mathcal{O}(1/n))$$

| $\theta$ | 0 | 1 | 3 | 10 |
|---|---|---|---|---|
| $\beta$ | 3. | 2.62 | 2.29 | 2.02 |

# 5'–3' Distance: Expectation through derivation




**Goal:** $S(z,u) = \sum_{n\geq 0} \sum_{d\geq 0} s_{\theta,n,d}\, z^n\, u^d$

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and 5'-3' distance $= d$

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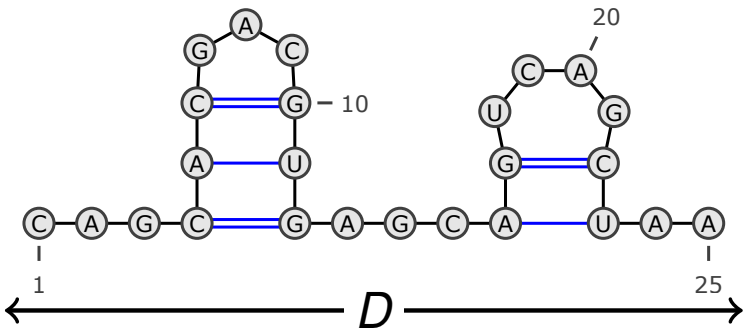


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2

$$T \to [S_{\geq\theta}]T| \bullet T|\varepsilon \qquad S \to (S_{\geq\theta})S| \circ S|\varepsilon$$
$$S_{\geq\theta} \to (S_{\geq\theta})S| \circ S_{\geq\theta}|\circ^{\theta}$$

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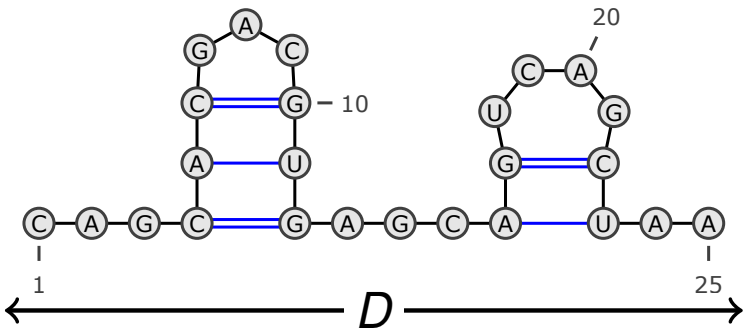


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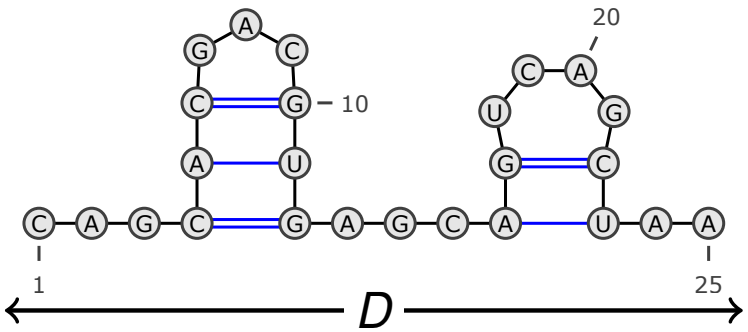
3

$$E_\theta(z) = \left.\frac{\partial T(z,u)}{\partial u}\right|_{u=1} = \frac{\begin{pmatrix} 2-9z+14z^2-8z^3+2z^5 \\ +z^{\theta+2}(-4+10z-10z^2+2z^3)+z^{2\theta+4}(2-z) \\ -(2-5z+4z^2-2z^{\theta+2}+z^{\theta+3})\sqrt{\Delta_\theta} \end{pmatrix}}{2(1-z)^2 z^4}$$

$$\Delta_\theta := 1-4z+4z^2-2z^{\theta+2}+4z^{\theta+3}-4z^{\theta+4}+z^{2\theta+4}$$

[Clote, Ponty, and Steyaert, 2012b]

# 5'–3' Distance: Expectation through derivation

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$$\Delta_\theta := 1-4z+4z^2-2z^{\theta+2}+4z^{\theta+3}-4z^{\theta+4}+z^{2\theta+4}$$

4

$$D_n \sim \frac{2-5\rho+4\rho^2-2\rho^{\theta+2}+\rho^{\theta+3}}{(1-\rho)\rho^2} - 1,\ \rho \text{ smallest root of } \Delta_\theta = 0$$

[Clote, Ponty, and Steyaert, 2012b]

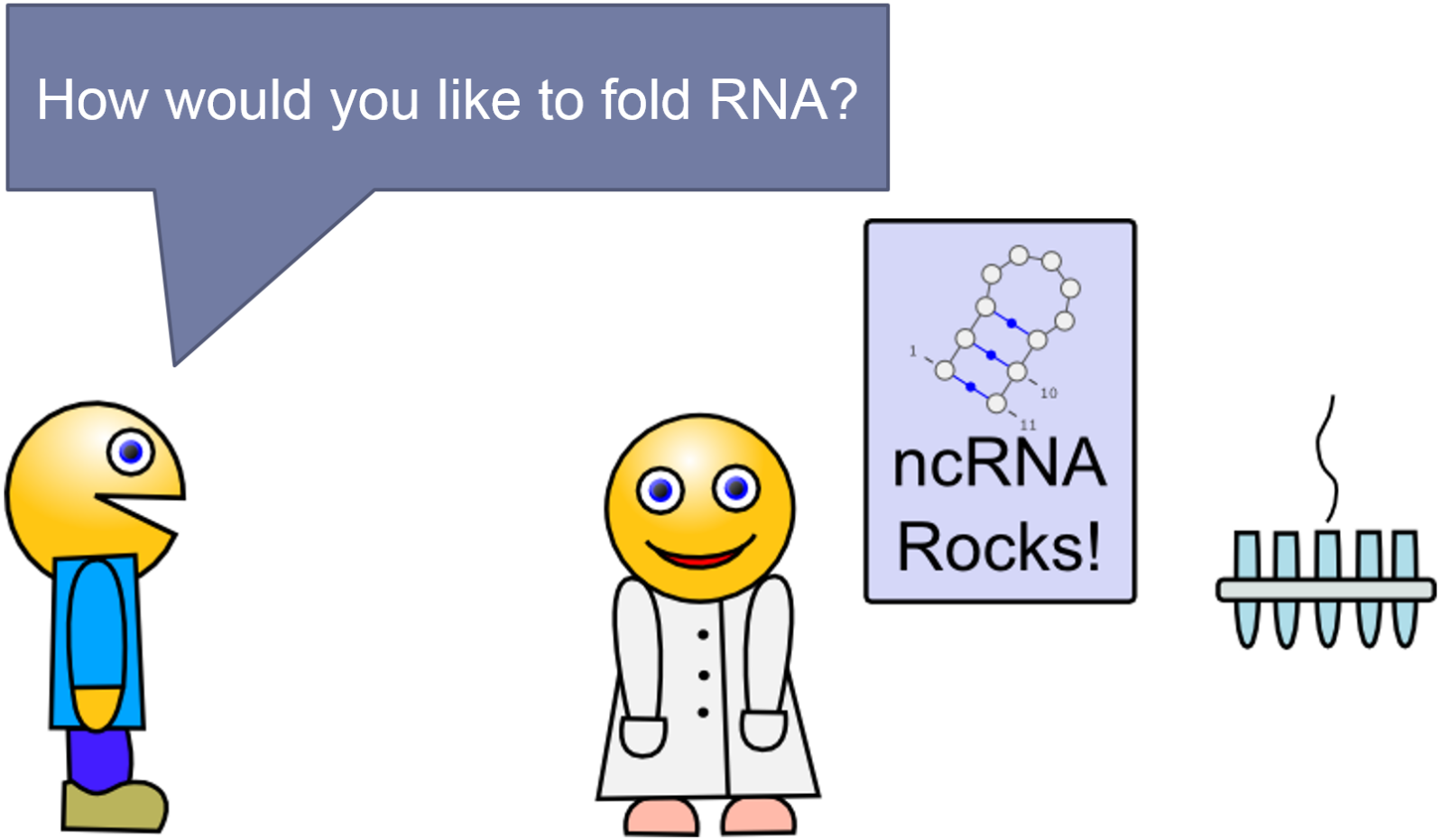
# Intermezzo

“*Traduttore tradittore*”

I can solve graph problems, why not predict RNA $2^{ary}$ structures?

...


CS
rulez!


How would you like to fold RNA?
1
10
11
ncRNA
Rocks!

... ...


CS
rulez!


## Common sense rules:

- Crossing interactions should be allowed
- But restricted to topologically valid structures
- Energy model should be realistic
- Robustness of prediction should be testable

Satisfying these rules makes the problem NP-Hard, but we can still decently approximate it, assuming that …
… APX … greedy … dynamic programming … P=NP(?)…

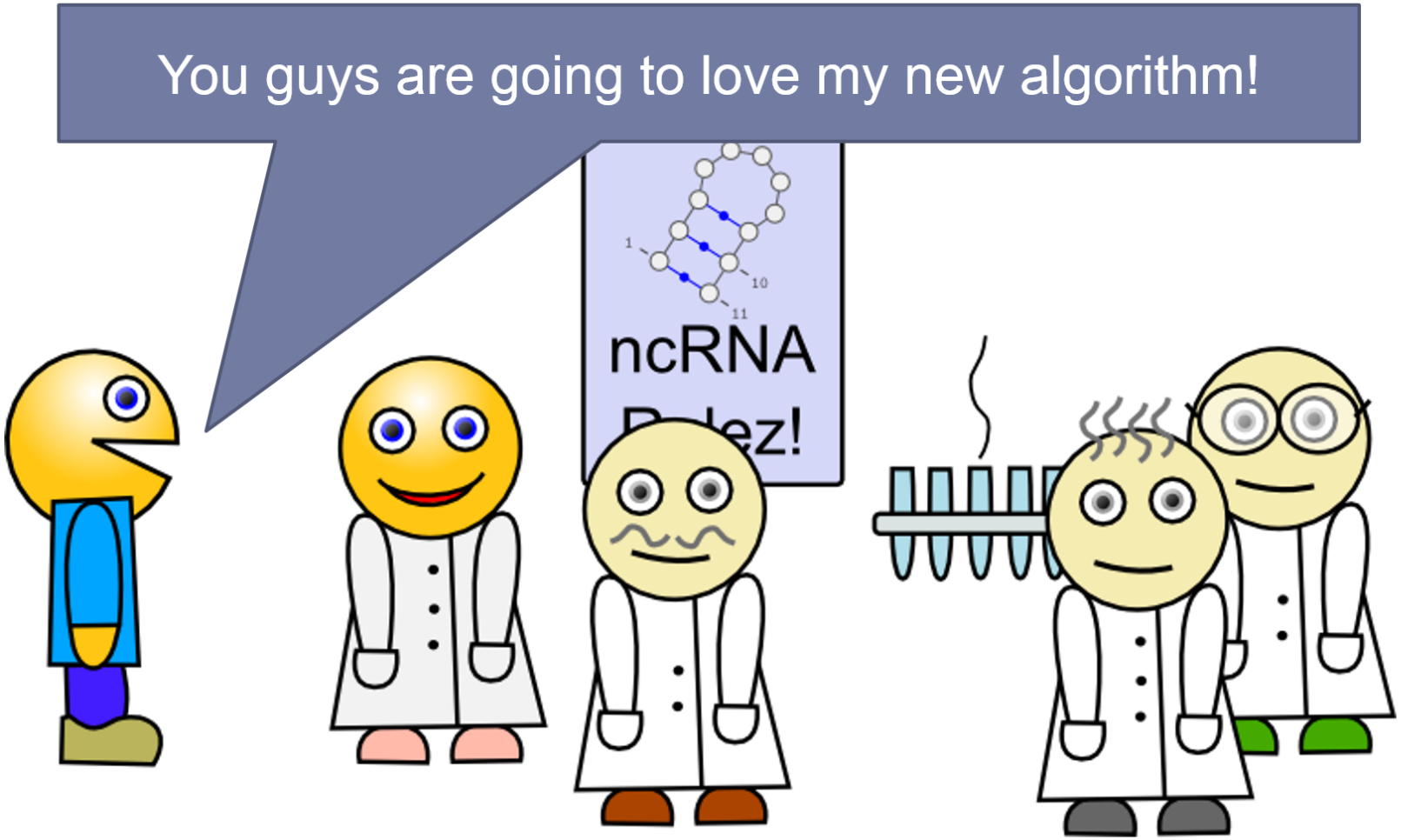
... ... ...

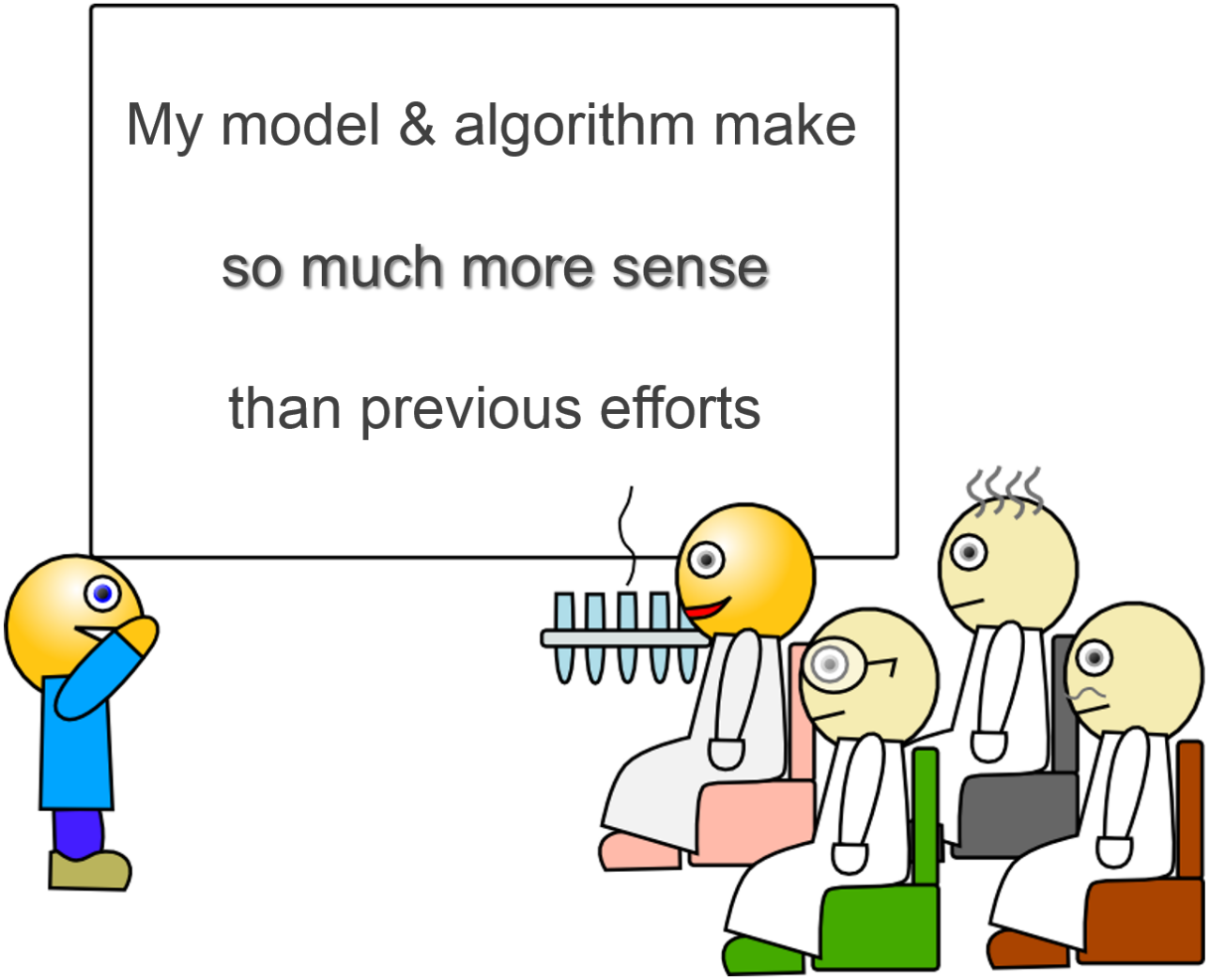

CS
rulez!


Common sense rules:

- Crossing interactions should be allowed
- But restricted to topologically valid structures
- Energy model should be realistic
- Robustness of prediction should be testable

+ Ninja algorithmic skills
+ Hard work
= Pretty decent algorithm

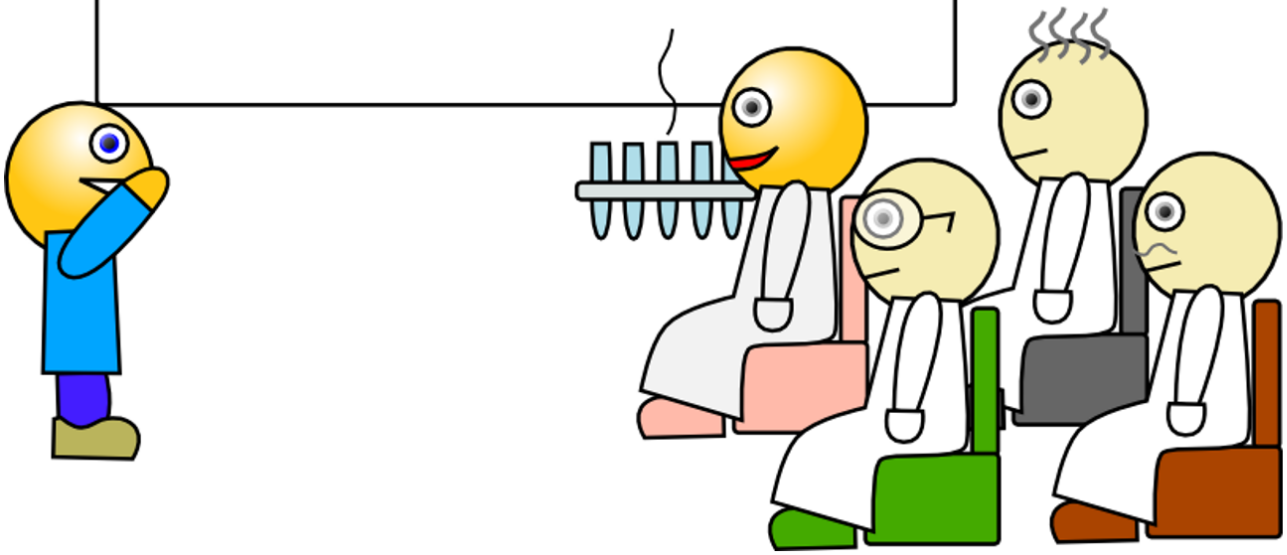

You guys are going to love my new algorithm!
ncRNA


My model & algorithm make
so much more sense
than previous efforts

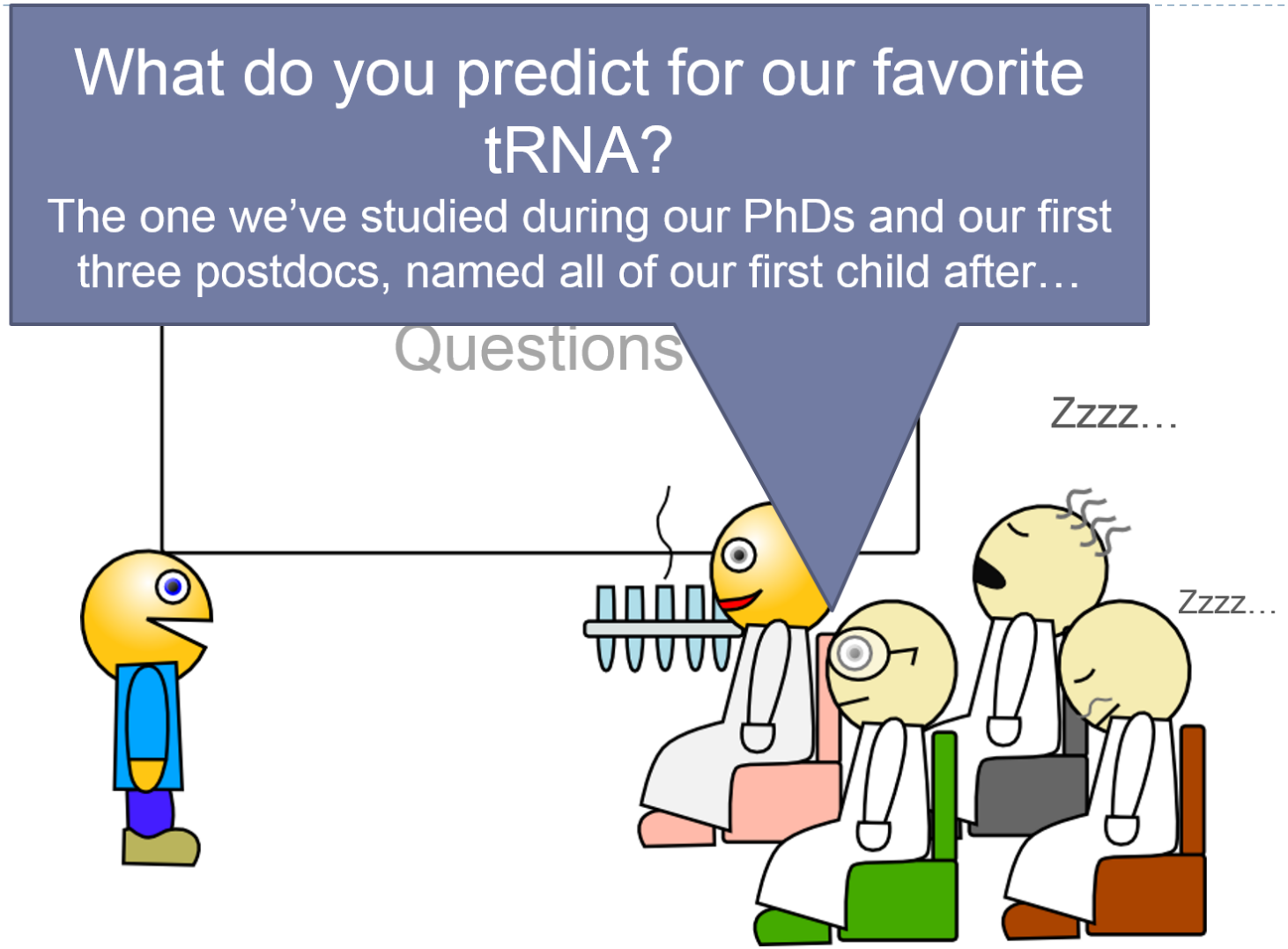
Theorem 35. The easy part

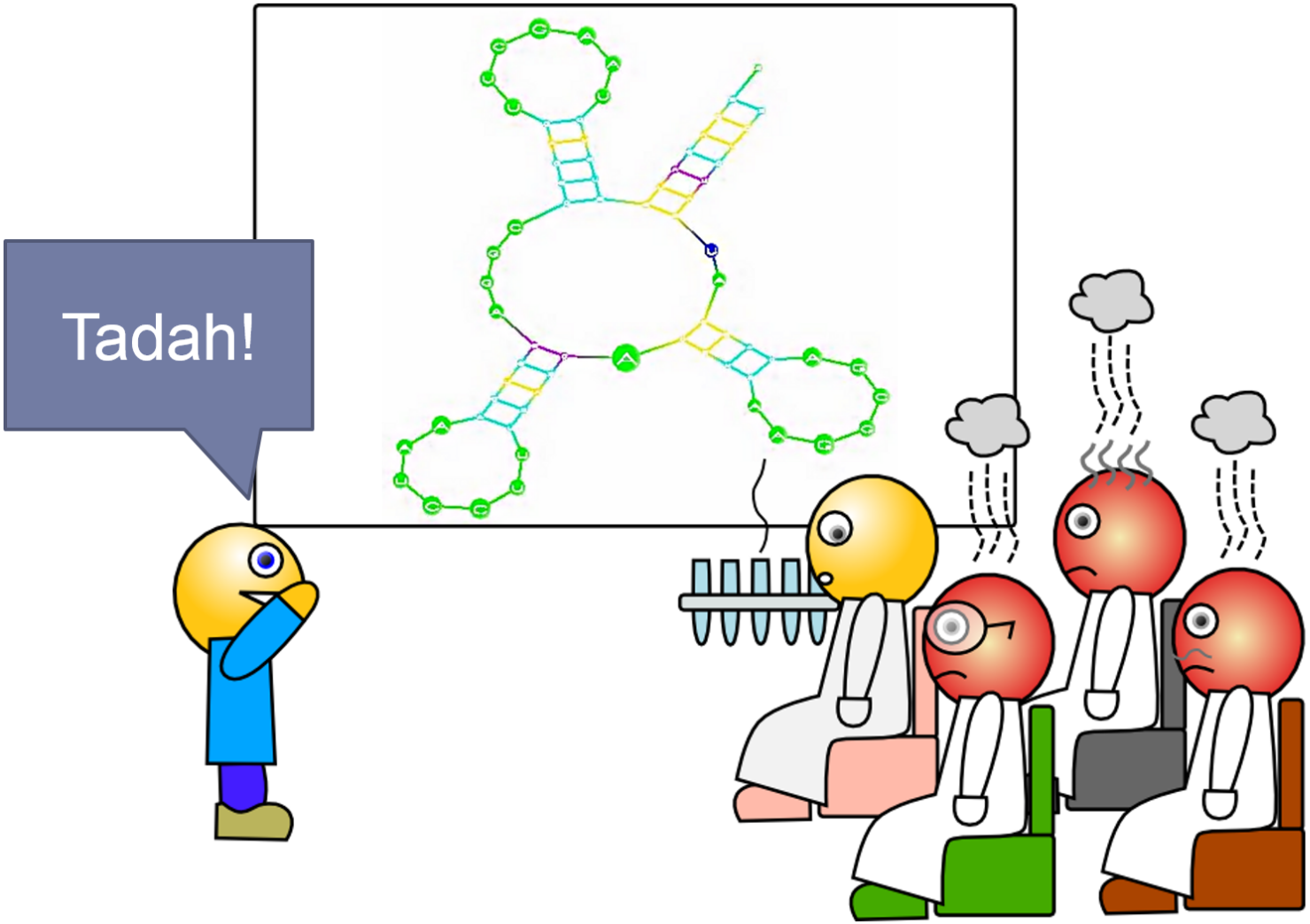
$$(x+a)^n = \sum_{k=0}^{n} \binom{n}{k} x^k a^{n-k}$$

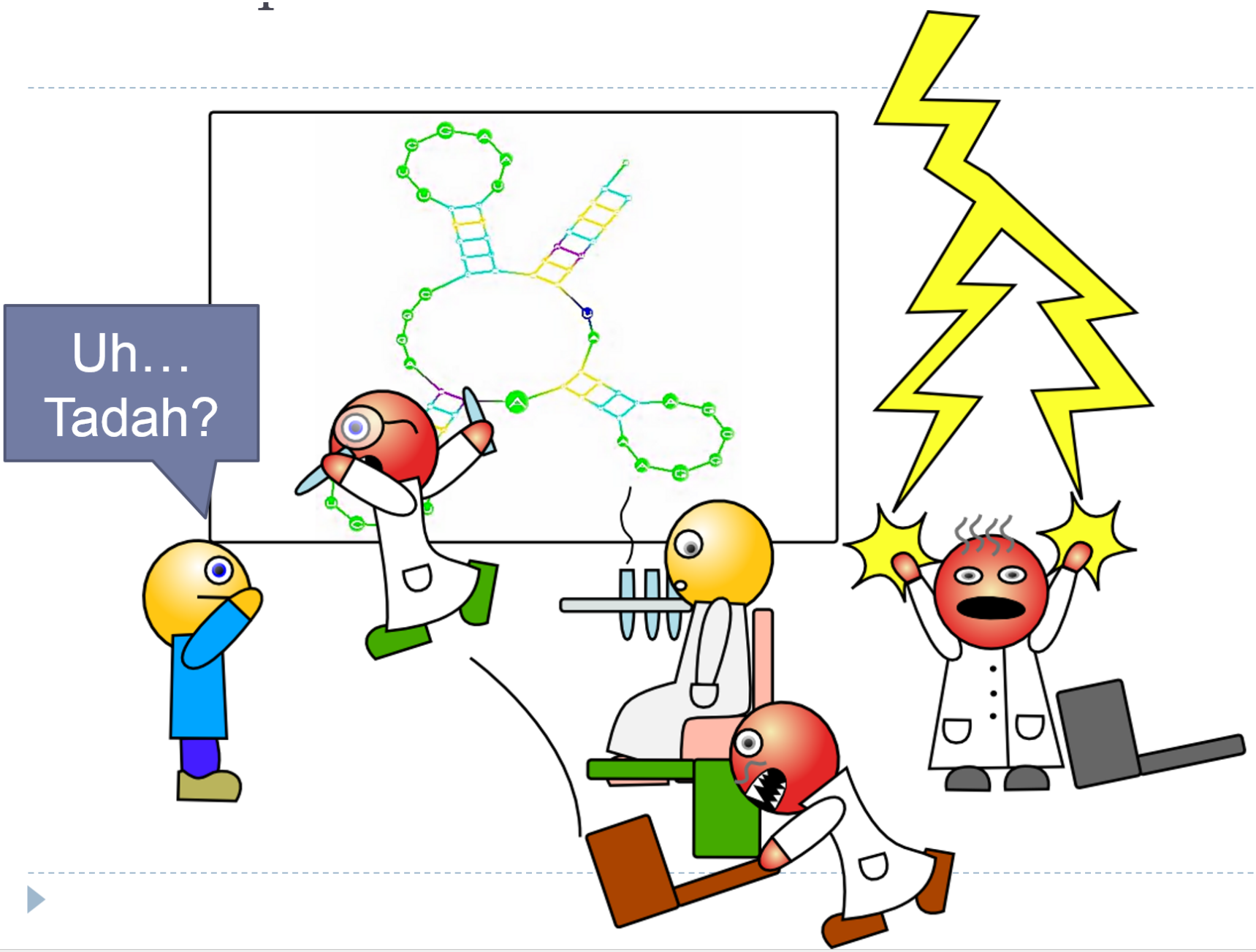
And the rest follows trivially

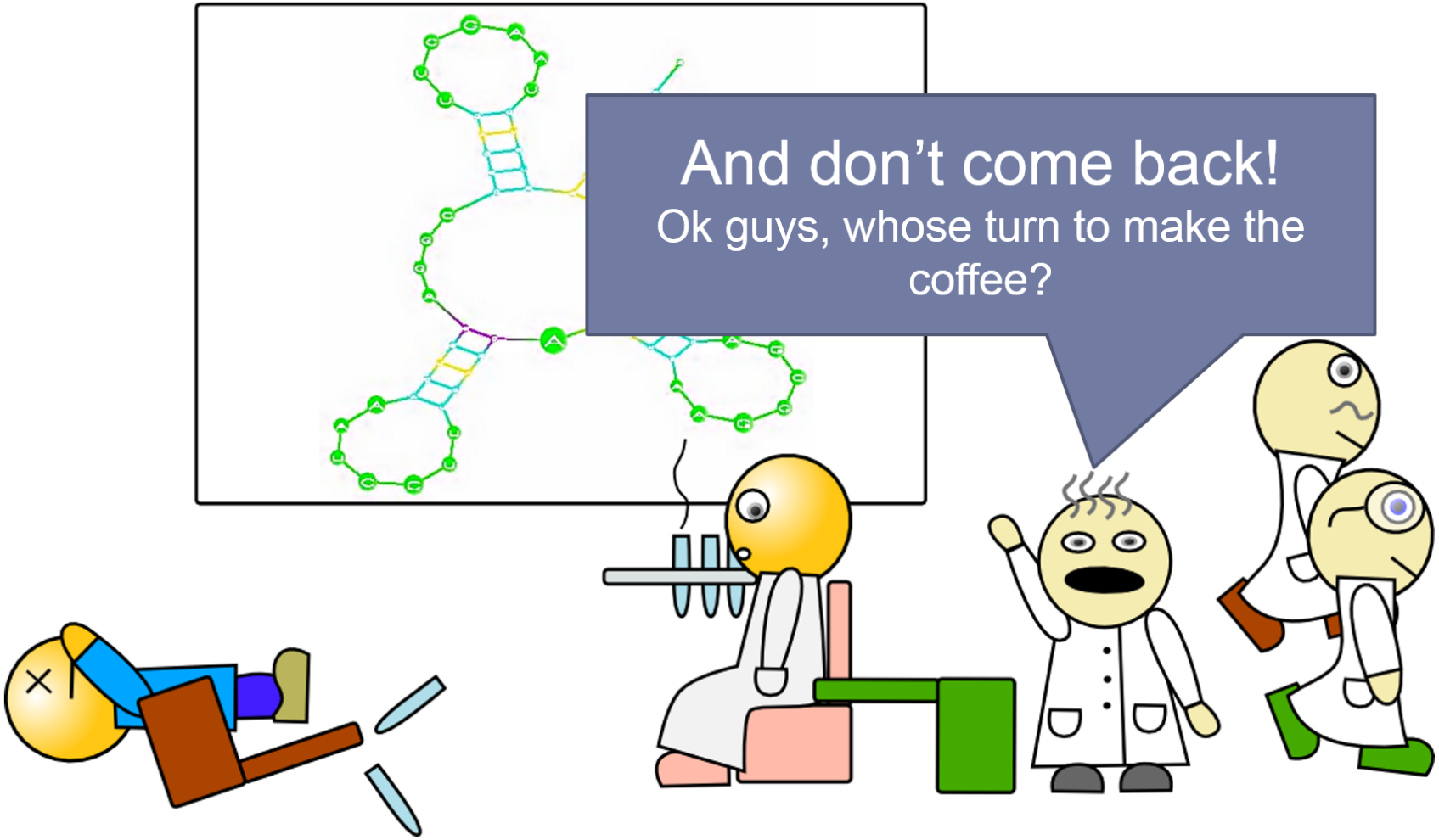


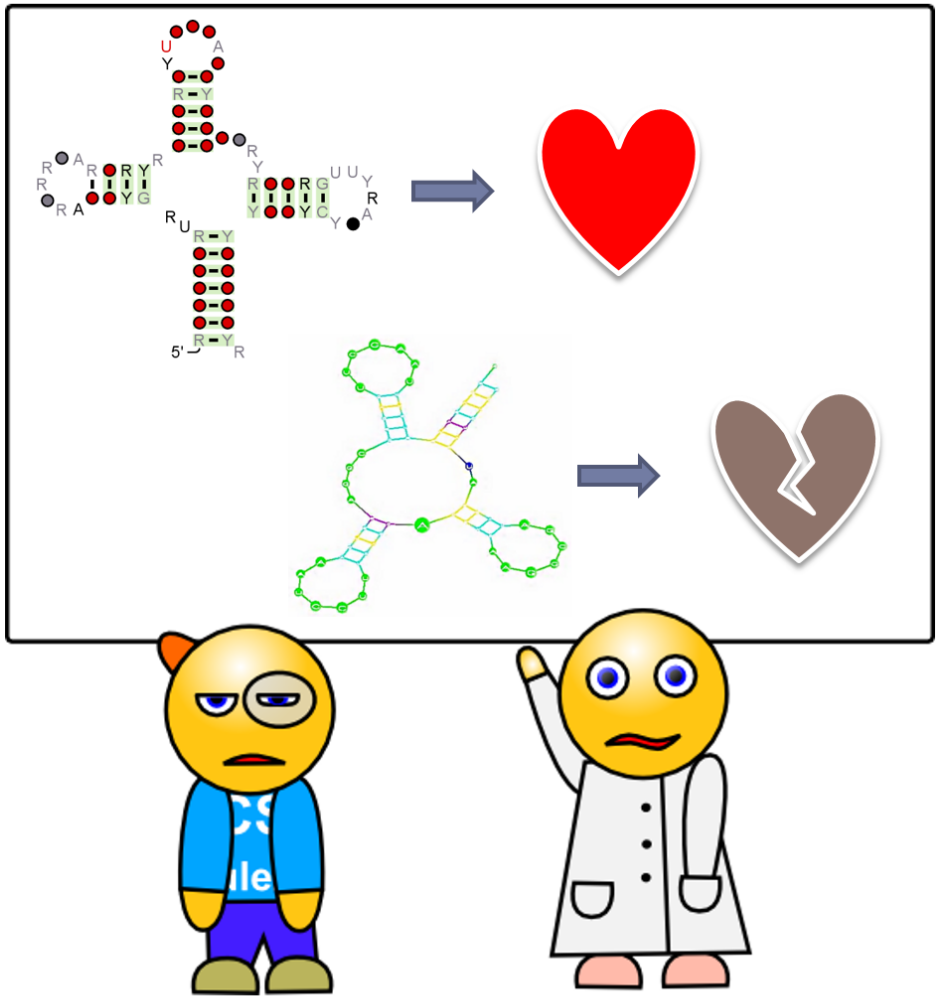

Thanks for listening.
Questions?
Zzzz…
Zzzz…

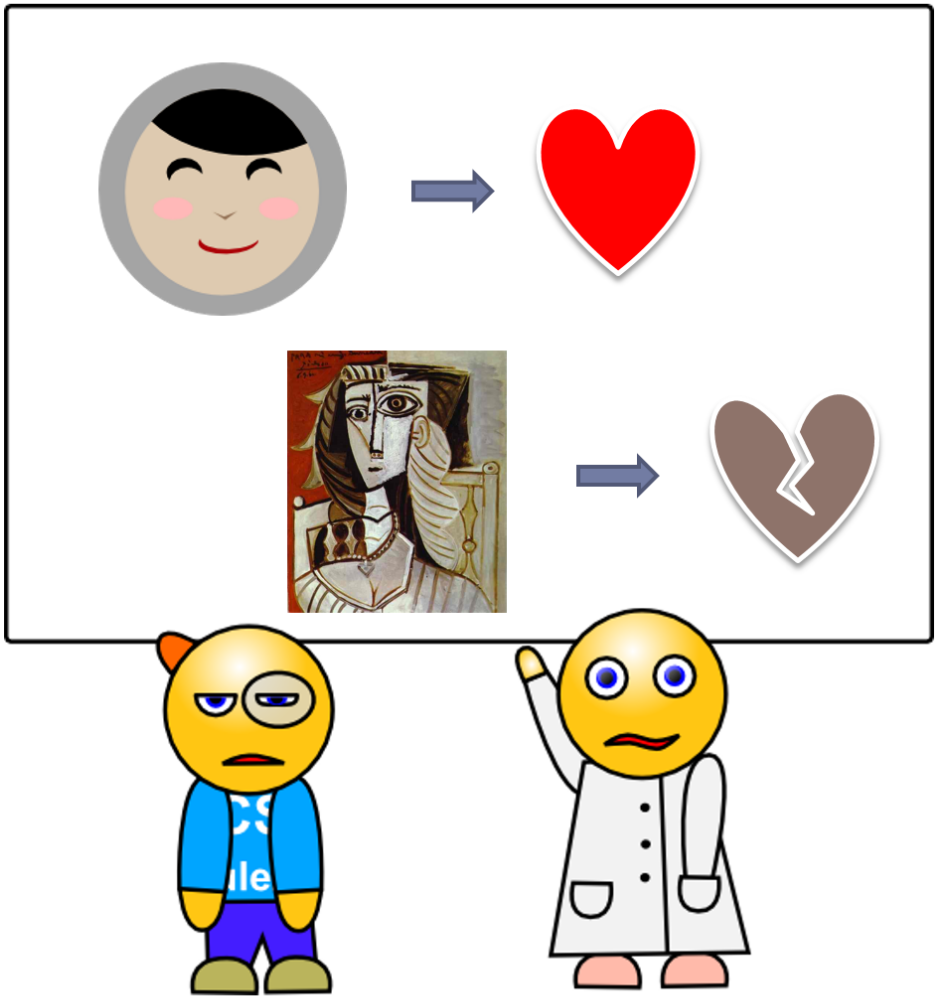

What do you predict for our favorite tRNA?
The one we've studied during our PhDs and our first three postdocs, named all of our first child after…
Questions
Zzzz…
Zzzz…


Tadah!


Uh…
Tadah?


And don’t come back!
Ok guys, whose turn to make the coffee?

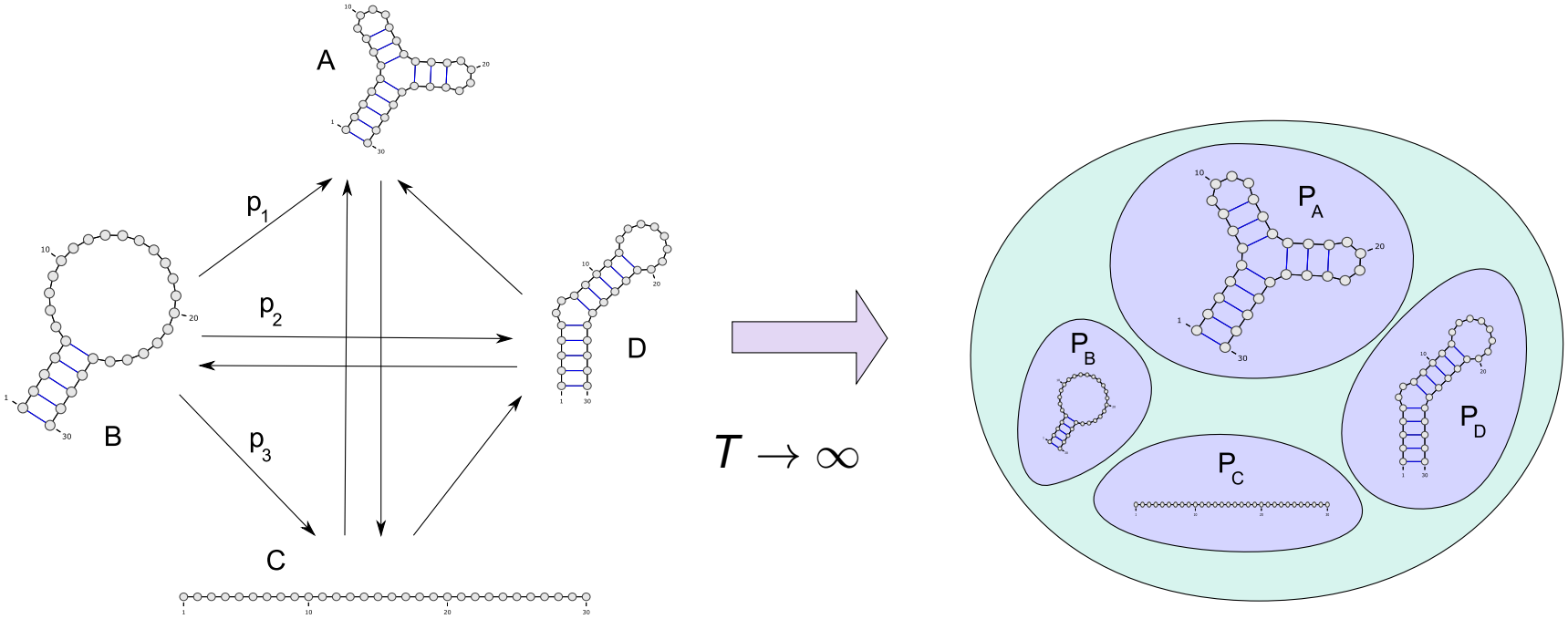




# Part. 2: Predicting how RNA folds

# Thermodynamics view

At the **nanoscale**, **RNA folding** can be adequately viewed as a **Markov process**, whose **stationary distribution** is the **Boltzmann distribution**.




## Definition (Thermodynamic equilibrium)

Each structure $S$ *compatible* with an RNA $w$ observed with probability:

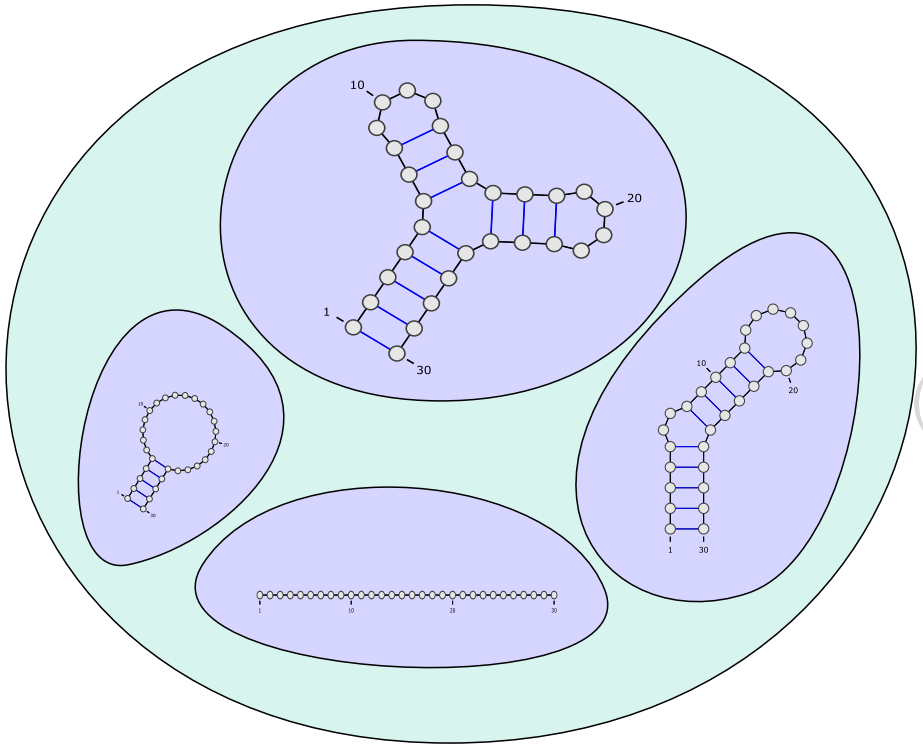
$$\mathbb{P}(S \mid w) = \frac{e^{\frac{-E_w(S)}{kT}}}{\mathcal{Z}_w} \qquad \text{and} \qquad \mathcal{Z}_w \equiv \sum_{S'} e^{\frac{-E_w(S')}{RT}} \quad \{\text{Partition function}\}$$

$E_w(S)$: **free-energy** of $S$ over $w$; $R$: Boltzmann constant; and $T$: temperature.

# Thermodynamics vs Kinetics

## Paradigms for RNA structure prediction

- **1978–1990s** Most probable structure = Minimal Free-Energy (MFE)
- **1990s–2010s** Functional structure(s) = Boltzmann ensemble (partition function)
- **2010s–????** Embracing the kinetics view




$T \to \infty$

mRNA half-life: $\sim$7h
(Mouse [Sharova et al., 2009])

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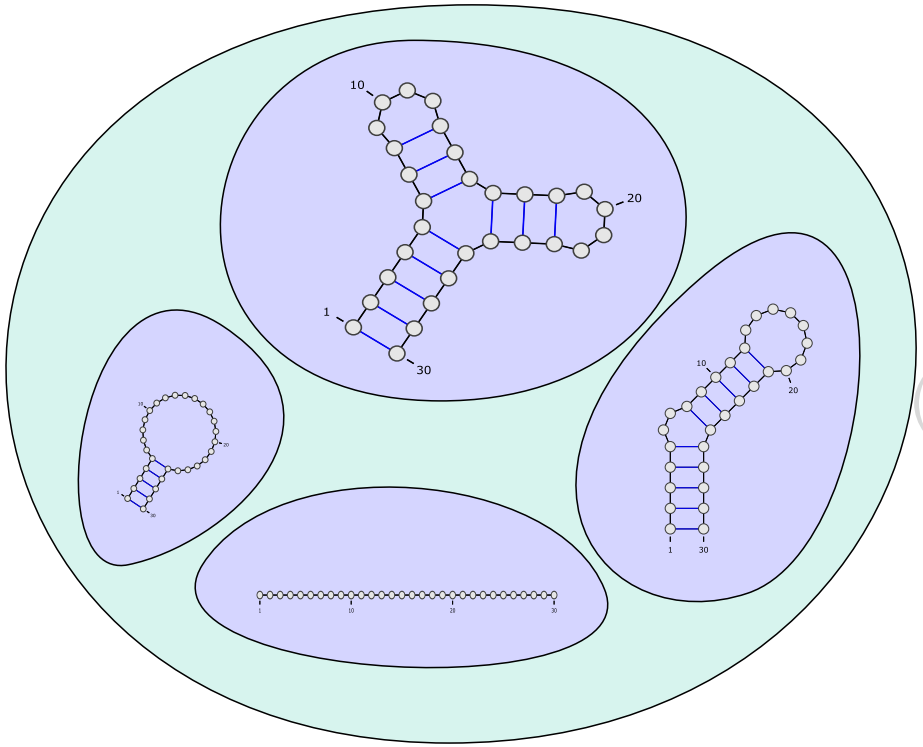


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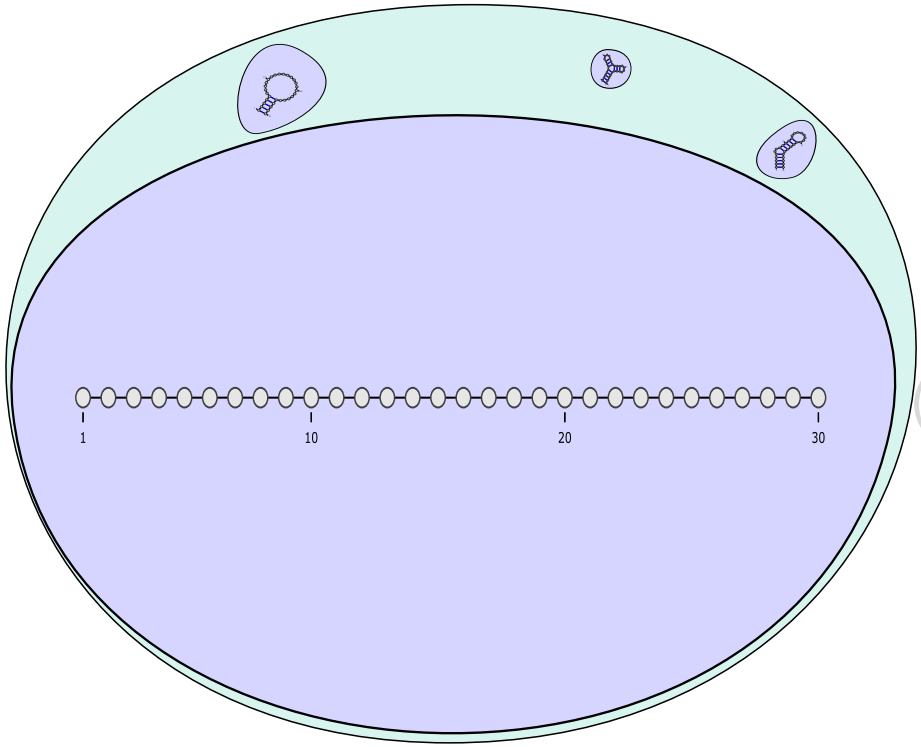


$T = 0$h

mRNA half-life: $\sim$7h
(Mouse [Sharova et al., 2009])

# Thermodynamics vs Kinetics

## Paradigms for RNA structure prediction

- **1978–1990s** Most probable structure = Minimal Free-Energy (MFE)
- **1990s–2010s** Functional structure(s) = Boltzmann ensemble (partition function)
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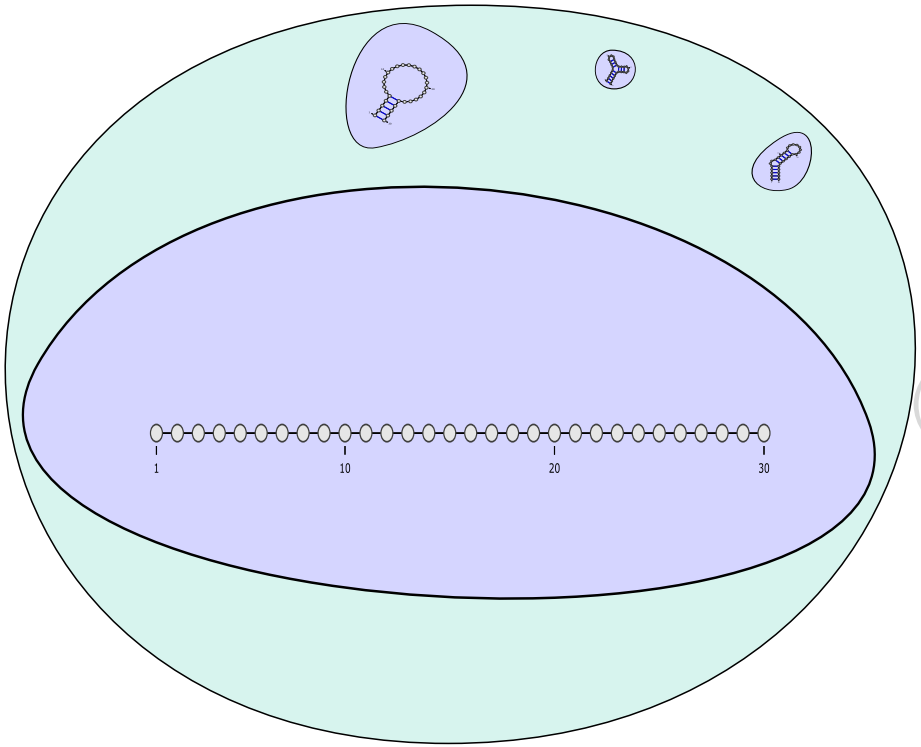


$T = 1\text{h}$

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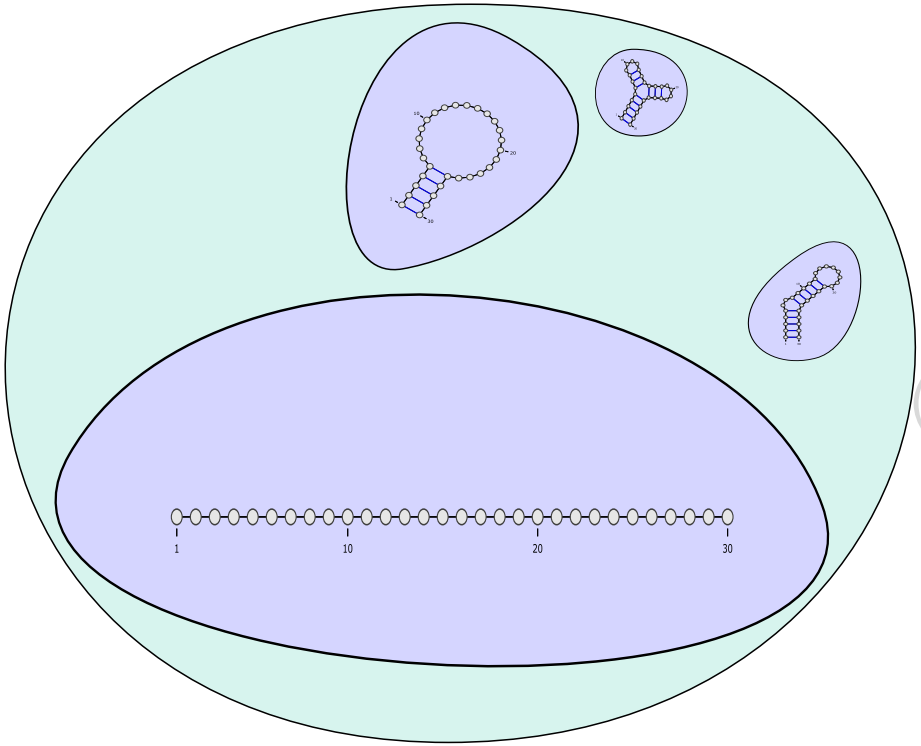


$T = 2\text{h}$

mRNA half-life: $\sim$7h
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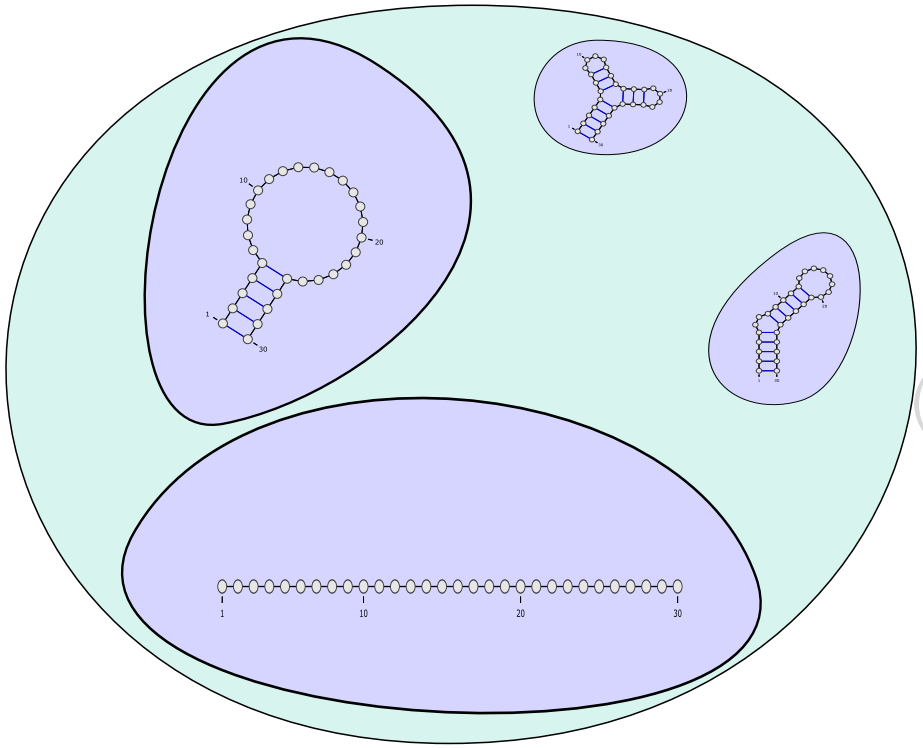


$T = 5$h

mRNA half-life: $\sim$7h
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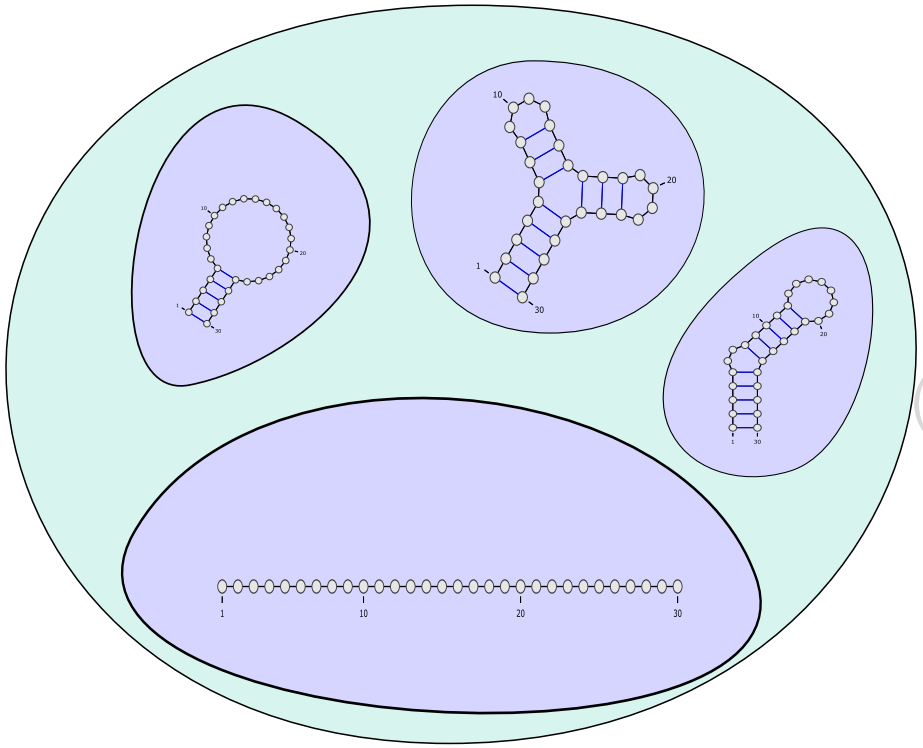

$T = 10$h

mRNA half-life: $\sim$7h
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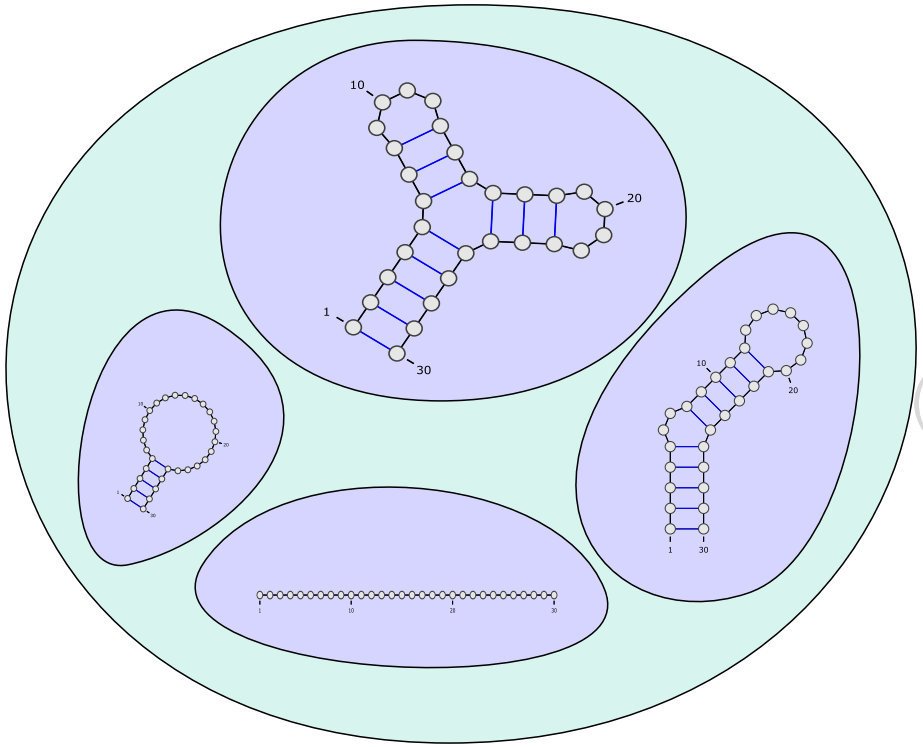


$T \to \infty$

mRNA half-life: $\sim$7h
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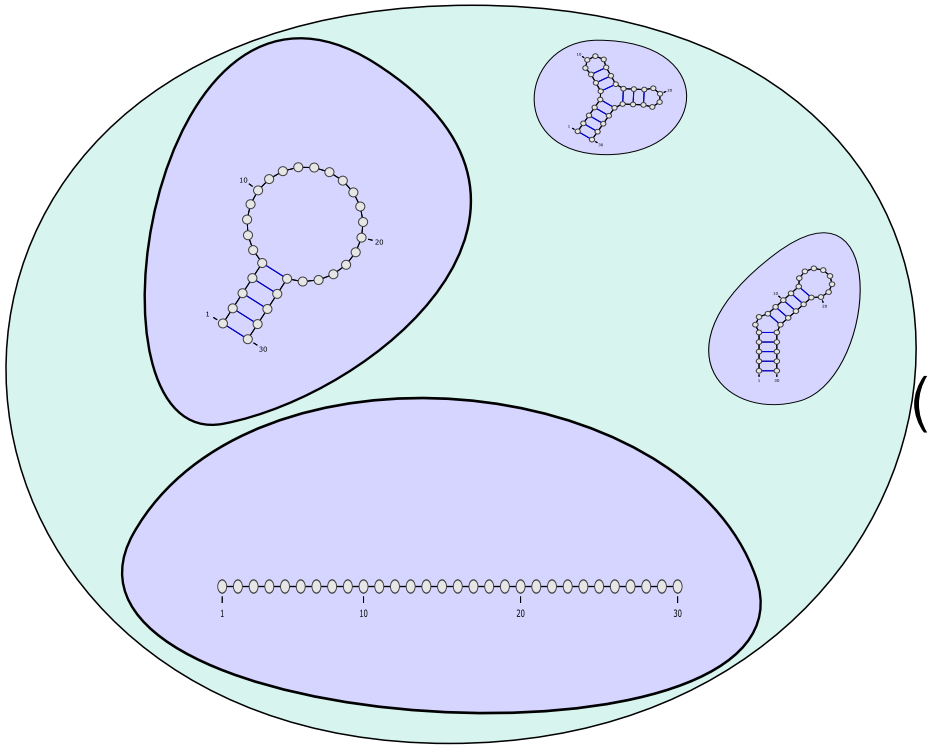

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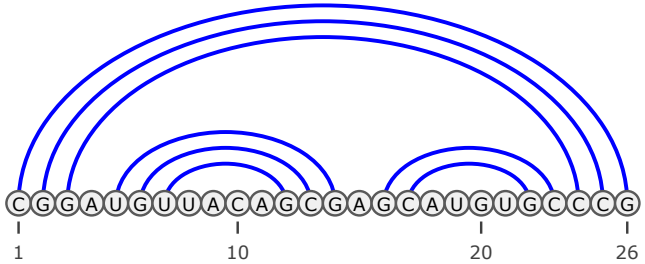
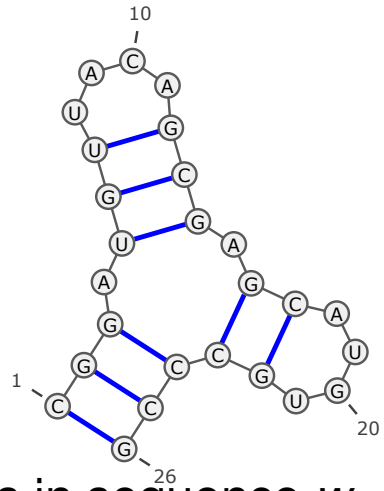
# Free-energy




- **RNA structure $S$:** (Partial) matching of positions in sequence $w$
- **Motifs:** Sequence/structure features (e.g. pairs, Stacking pairs, Nearest neighbor...)
- **Energy model.**

  **Motif** $\rightarrow$ Free-energy contribution $\Delta G(\cdot) \in \mathbb{R}^- \cup \{+\infty\}$

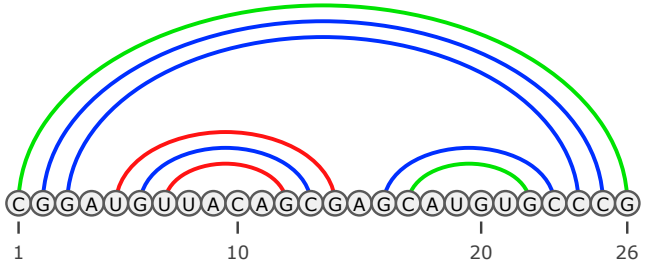
  **Free-Energy $E_w(S)$:** Sum over (independently contributing) motifs in $S$

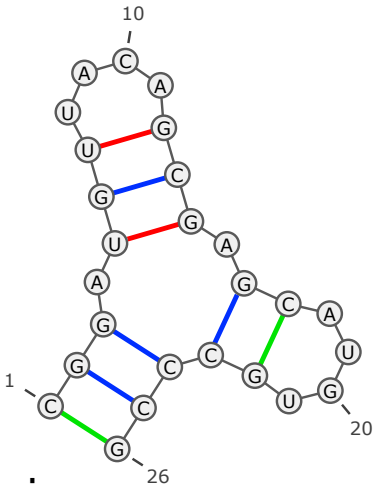
**Nussinov/Jacobson energy model** [Nussinov and Jacobson, 1980]

**Pairs:** $\Delta G(x, y) = \begin{cases} -1 \ (-3/-2/-1) & \text{if } (x, y) = (G \equiv C)/(A = U)/(G - U) \\ +\infty & \text{otherwise.} \end{cases}$

**Rem.:** Structure prediction $\approx$ Energy minimization $\Leftrightarrow$ Base-pair maximization
$\Leftrightarrow$ Max (weighted) independent set in circle graph

# Free-energy

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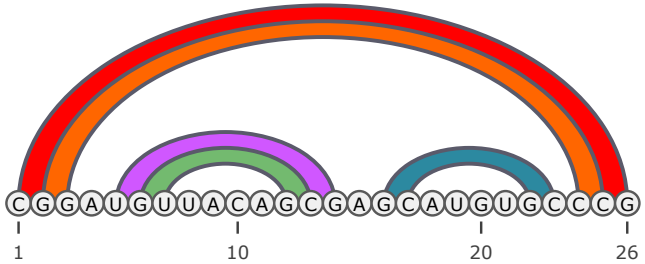


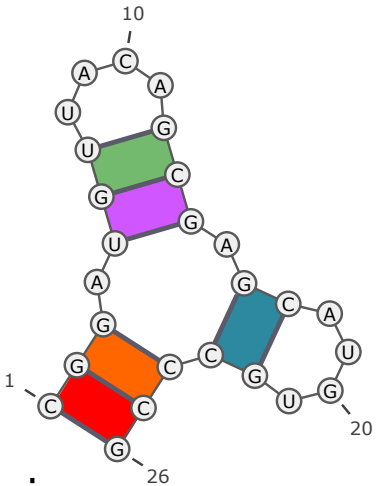


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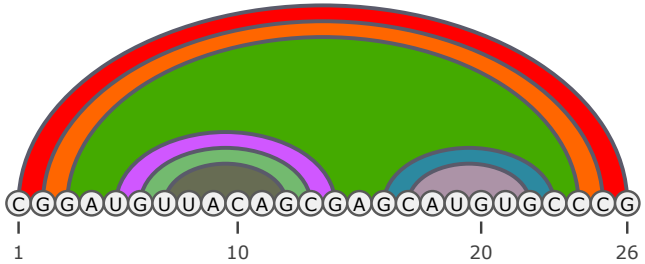


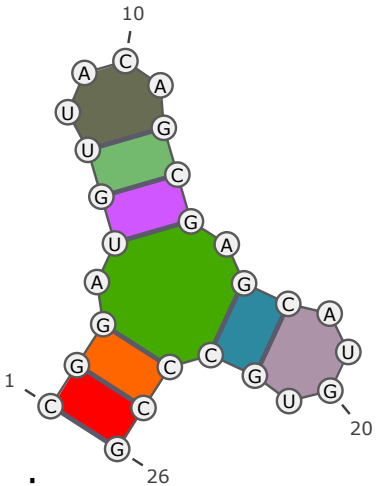


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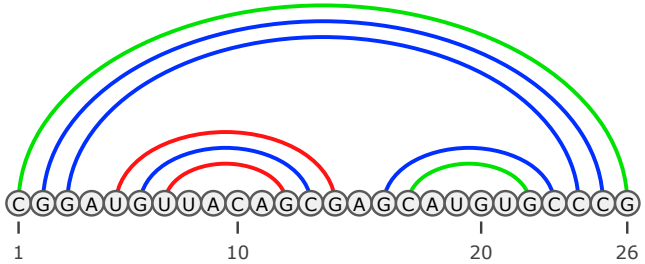


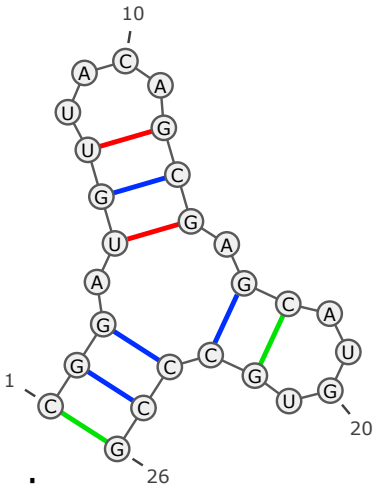


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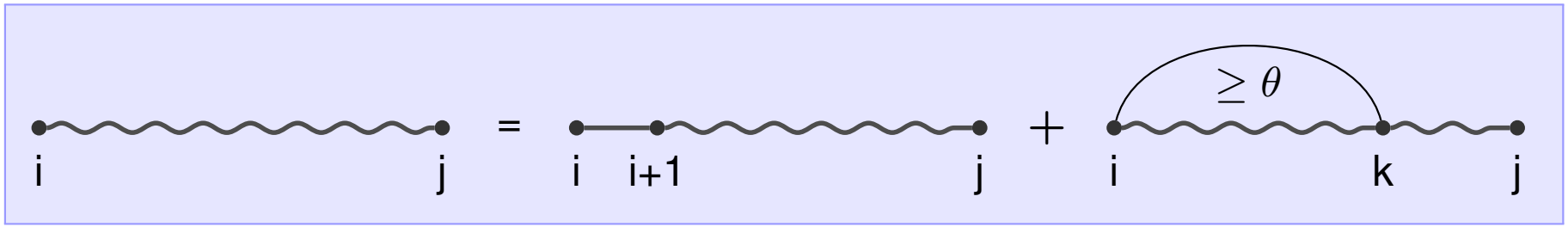
**Theorem (Nussinov and Jacobson [1980])**

*Max #base-pairs/min weight structure is computable in $\mathcal{O}(n^3)/\mathcal{O}(n^2)$ time/memory*




$E_{i,k}$: Free-energy contribution of base-pair $(i,k)$. $(-1/+\infty$ or $\Delta G(s_i \overset{?}{\equiv} s_k))$

$\boldsymbol{N}_{i,j}$ : Max #base-pairs over interval $[i,j]$

$$\begin{aligned}
\boldsymbol{N}_{i,t} &= 0, \quad \forall t \in [i, i+\theta] \\
\boldsymbol{N}_{i,j} &= \min \begin{cases} \boldsymbol{N}_{i+1,j} & \{i \text{ unpaired}\} \\ \min\limits_{k=i+\theta+1}^{j} E_{i,k} + \boldsymbol{N}_{i+1,k-1} + \boldsymbol{N}_{k+1,j} & \{i \text{ paired to } k\} \end{cases}
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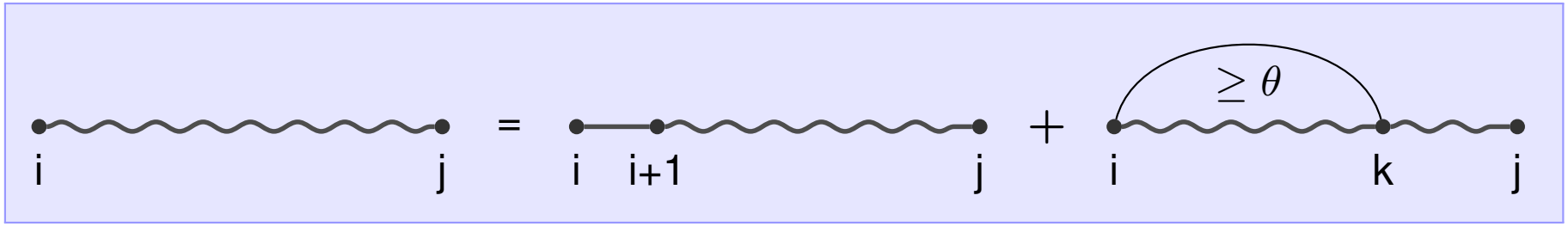


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$C_{i,j}$ : Number of secondary structures compatible with interval $[i,j]$

$$C_{i,t} = 1, \quad \forall t \in [i, i+\theta]$$

$$C_{i,j} = \sum \begin{cases} C_{i+1,j} & \{i \text{ unpaired}\} \\ \sum_{k=i+\theta+1}^{j} \mathbb{1}_{\text{comp.}(i,k)} \times C_{i+1,k-1} \times C_{k+1,j} & \{i \text{ paired to } k\} \end{cases}$$

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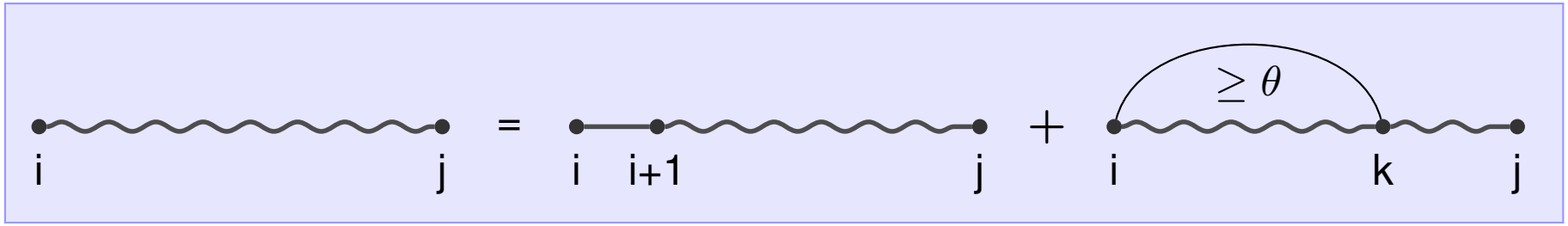


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$\mathcal{Z}_{i,j} = \sum_{\substack{S \text{ comp.} \\ \text{with } w_{[i,j]}}} e^{\frac{-E_W(S)}{RT}}$ = Partition function of structures compatible with interval $[i,j]$

$$\mathcal{Z}_{i,t} = \mathbf{1}, \quad \forall t \in [i, i+\theta]$$

$$\mathcal{Z}_{i,j} = \sum \begin{cases} \mathcal{Z}_{i+1,j} & \{i \text{ unpaired}\} \\ \sum_{k=i+\theta+1}^{j} e^{\frac{-E_{i,k}}{RT}} \times \mathcal{Z}_{i+1,k-1} \times \mathcal{Z}_{k+1,j} & \{i \text{ paired to } k\} \end{cases}$$

# Dynamic programming (DP) for RNA folding

**Many extensions:**

- Nearest-neighbor/Turner energy model [Zuker and Stiegler, 1981]
- Comparative folding [Sankoff, 1985]
- Equilibrium base-pairing probabilities [McCaskill, 1990]
- Moments of additive features [Miklós et al., 2005; Ponty and Saule, 2011]
- $\Delta$ kcal.mol$^{-1}$ suboptimal structures of MFE [Wuchty et al., 1999]
- Basic crossing structures [Rivas and Eddy, 1999]...
- Exact sampling in Boltzmann distr. [Ding and Lawrence, 2003; Ponty, 2008]
- Moments of additive features [Miklós et al., 2005; Ponty and Saule, 2011]
- Maximum expected accuracy structure [Do et al., 2006]
- Distance-classified partitioning of Boltzmann ens. [Freyhult et al., 2007]

**Made possible by:**

- **Completeness**/**Unambiguity** of decomposition
  $\exists$ energy-preserving bijection between **derivations of DP scheme** and **search space**
- Objective function **additive** with respect to DP scheme

$\Rightarrow$ **Combinatorial Dynamic Programming**

# Part. 3: Combinatorial Dynamic Programming

# Reasoning structurally about dynamic programming

- $I$ : Instance (aka problem)
- $Q$ : State space for dyn. prog. scheme (LHS terms, $I$ initial state)
- $\Delta_q$ : Search space for state $q$
- $\mathcal{D}_q$ : Derivations of DP scheme from state $q \in Q_i$
- **Semantics function** $\Phi : \mathcal{D}_q \to \Delta_I$

$$V_q = \bigoplus \begin{cases} E_{1,q} \otimes V_{q_{1,1}} \otimes V_{q_{1,2}} \otimes \cdots \\ E_{2,q} \otimes V_{q_{2,1}} \otimes V_{q_{2,2}} \otimes \cdots \\ \vdots \\ E_{k,q} \otimes V_{q_{k,1}} \otimes V_{q_{k,2}} \otimes \cdots \end{cases}$$

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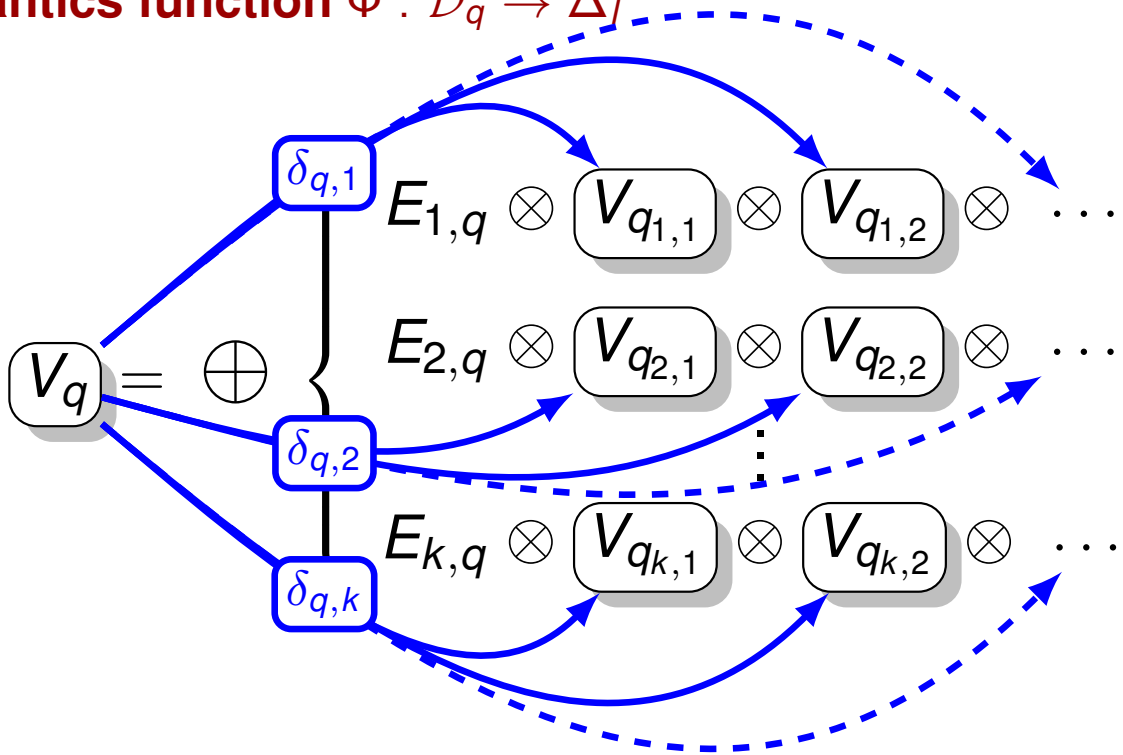

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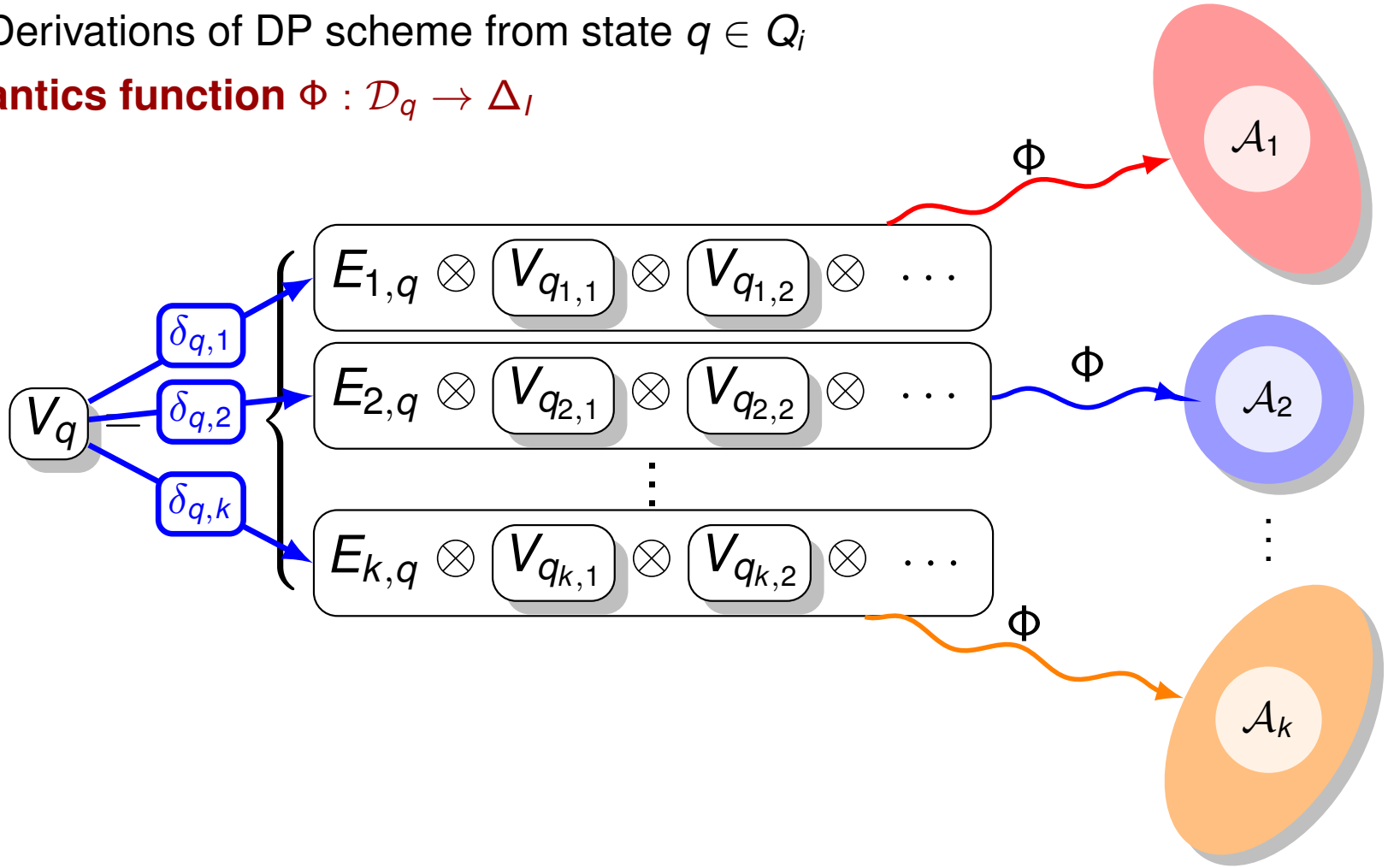

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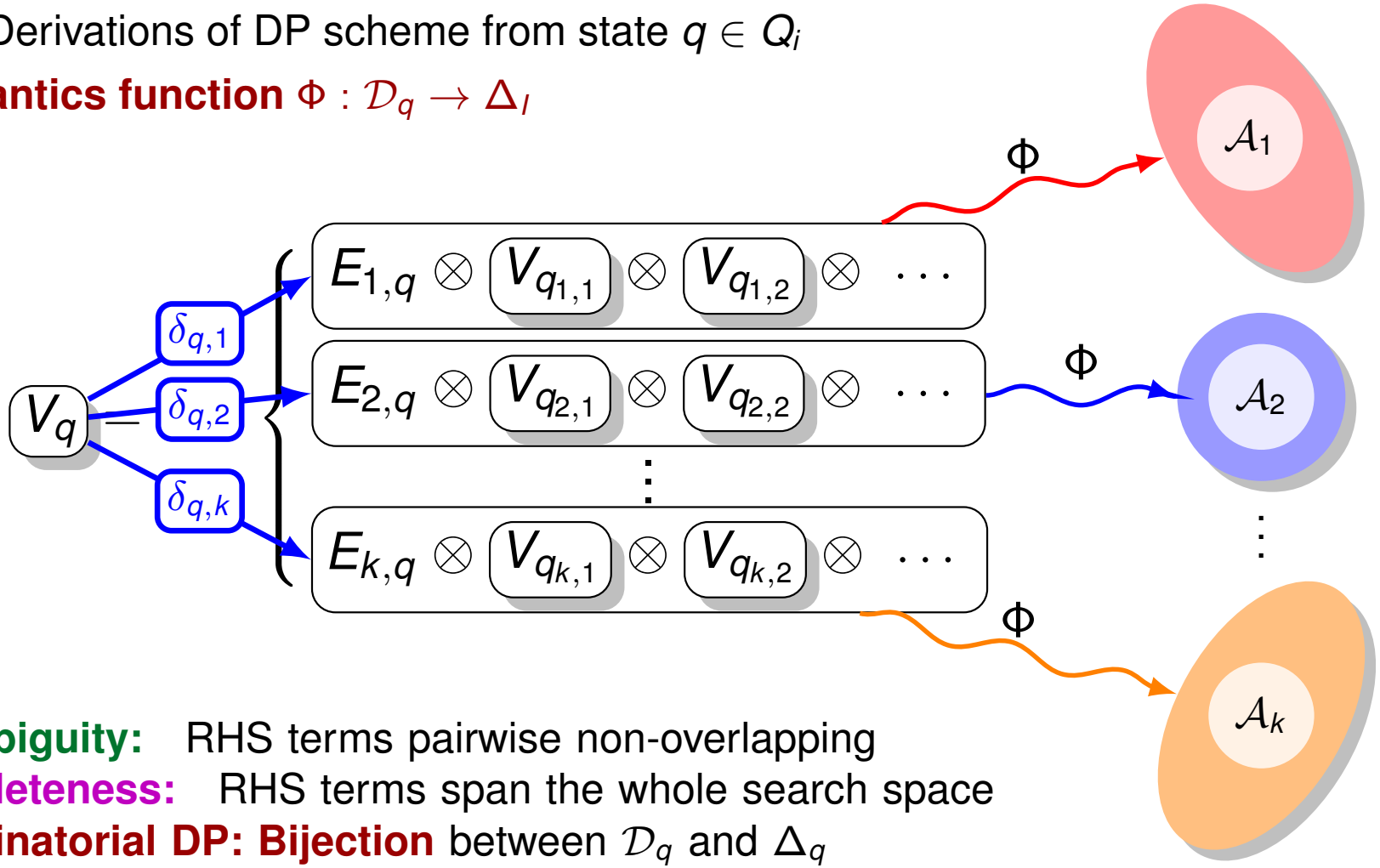
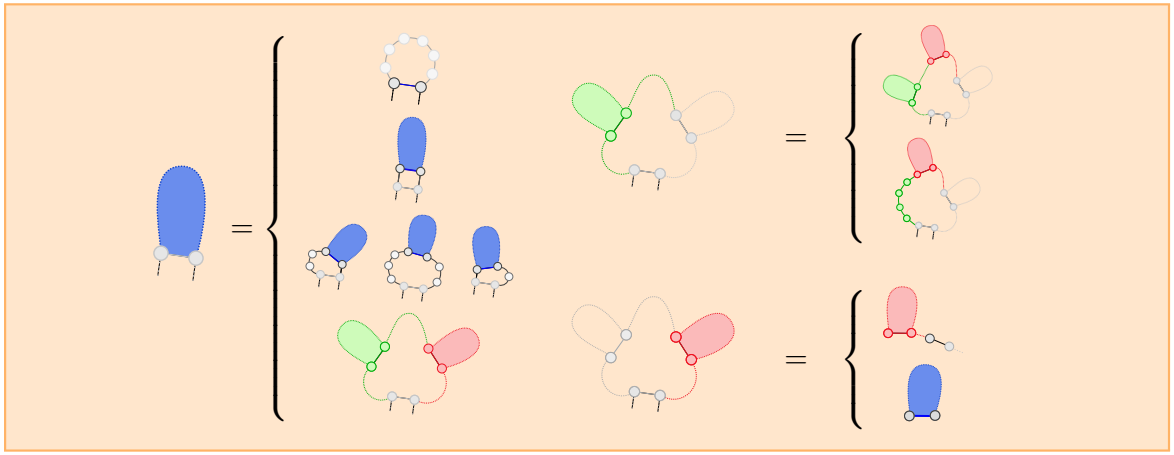


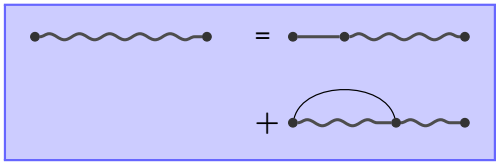

**Unambiguity:** RHS terms pairwise non-overlapping
**Completeness:** RHS terms span the whole search space
**Combinatorial DP: Bijection** between $\mathcal{D}_q$ and $\Delta_q$

# Combinatorics help in the design of DP schemes



MFold DP scheme [Zuker and Stiegler, 1981]

$\overset{??}{\Longleftrightarrow}$



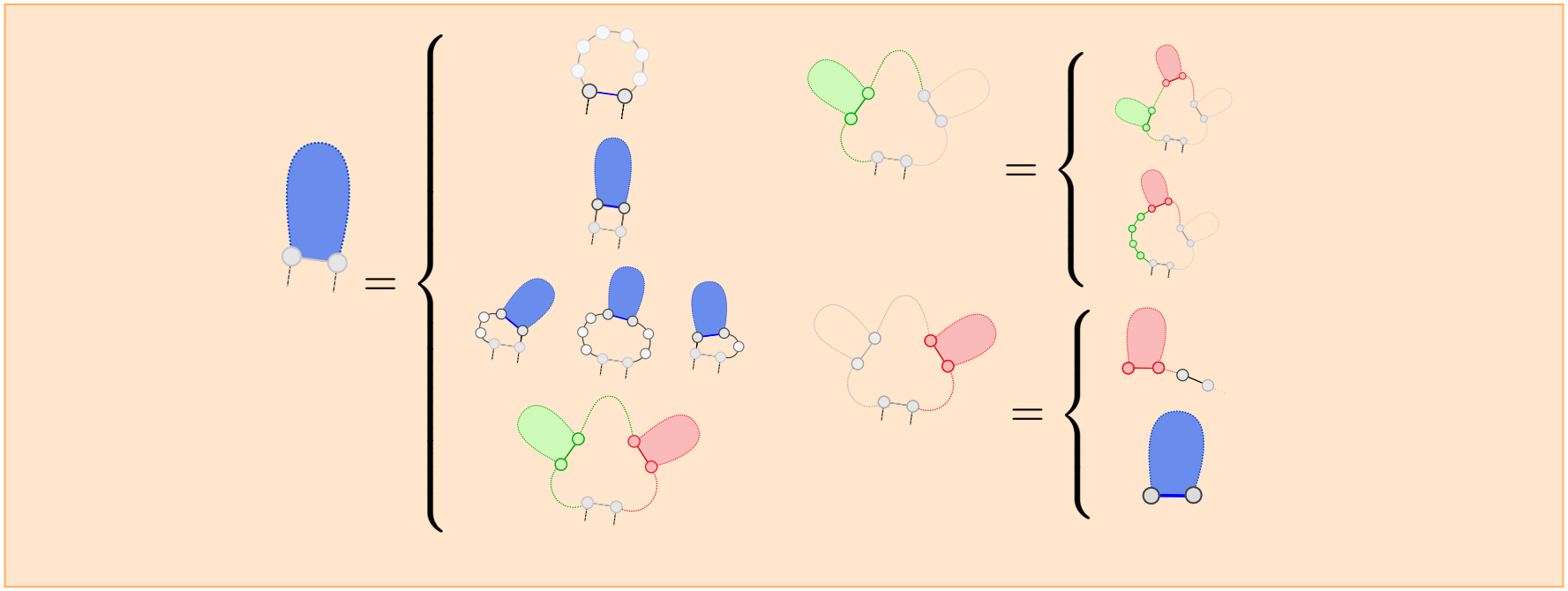
**Unambiguous** (pairwise non-overlapping generated search spaces)
**Completeness**? Use generating functions...

# Combinatorics help in the design of DP schemes

**Reminder:** Generating function of secondary structures [Waterman, 1978]

$$S(z) := \sum_{n \geq 0} s_n \, z^n = \frac{1 - z + z^2 - \sqrt{1 - 2z - z^2 - 2z^3 + z^4}}{2z^2}$$

- DP scheme **unambiguous** ($\Phi$ injective);
- **Completeness** can be established by cardinality argument ($|\Phi(\mathcal{D}_n)| = s_n$)



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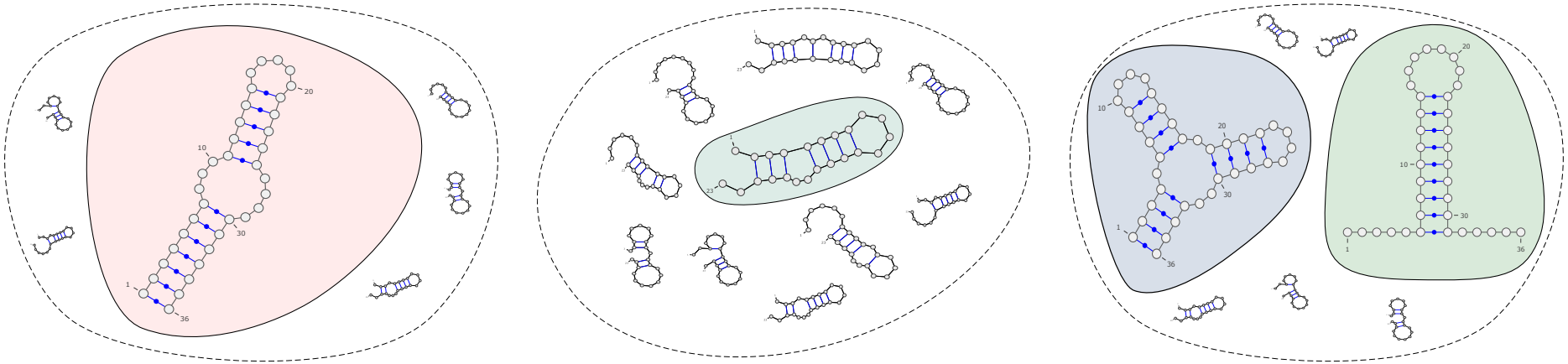
$$A(z) = \begin{cases} \mathrm{Seq}(z) \\ z^2 \, A(z) \\ z \, \mathrm{Seq}(z) \, z^2 \, A(z) + z^2 \, A(z) \, \mathrm{Seq}(z) \, z \\ \quad + z \, \mathrm{Seq}(z) \, z^2 \, A(z) \, \mathrm{Seq}(z) z \\ B(z) \, C(z) \end{cases} \qquad B(z) = \begin{cases} B(z) \, C(z) \\ \mathrm{Seq}(z) \, B(z) \end{cases} \qquad C(z) = \begin{cases} C(z) \, z \\ z^2 \, A(z) \end{cases}$$

$$\mathrm{Seq}(z) = 1 + z \, \mathrm{Seq}(z)$$

$$\begin{aligned} A(z) &= \frac{1 - z - z^2 - \sqrt{1 - 2z - z^2 - 2z^3 + z^4}}{2z^2} \\ &= W(z) - 1 \quad \text{(OMG! The } \textit{empty} \text{ secondary structure is missing...)} \end{aligned}$$

# Motivation



**Observation:** **Large diversity of pictures** for the Boltzmann ensemble, associated with specific **functions**.

How to extract **functional information** from the Boltzmann ensemble?

**Idea:** Observe the distribution of additive structural parameters.

(Examples: #BPs, Free-energy, #Multiloops. . . )

**However,** exact computation is costly + Mean, Variance. . . often sufficient.

. . . How to efficiently compute the **moments** of the distribution?

# Distribution of discrete additive features

**Discrete feature function** $\alpha : \mathcal{D}_I \to [0, M]$, additively associated with derivations.

**Random variable** $A \in \mathcal{D}_I$**:** Uniformly/Boltzmann-distributed random derivation.

**Problem:** Compute **explicit** distribution of $V$, defined as:

$$\forall m \in [0, M] : \mathbb{P}(\alpha(A) = m \mid I) \equiv \sum_{\substack{d \in \mathcal{D}_I \\ \alpha(d) = m}} \frac{1}{|\mathcal{D}_I|} = \frac{\overbrace{|\{d \in \mathcal{D}_I \mid \alpha(d) = m\}|}^{V_q^m}}{|\mathcal{D}_I|}$$

**Naive solution:** Explicit convolution products

$$\forall q \in Q, \quad V_q = \sum \begin{cases} V_{q_{1,1}} \times V_{q_{1,2}} \times \cdots \\ V_{q_{2,1}} \times V_{q_{2,2}} \times \cdots \\ \vdots \\ V_{q_{k,1}} \times V_{q_{k,2}} \times \cdots \end{cases}$$

# Distribution of discrete additive features

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**Interpolation** [Waldispühl and Ponty, 2011] **:**

- Consider polynomials $V_q(z) = \sum_{m=0}^{M} V_q^m \cdot z^m$;
- Evaluation of $V_q(z)$ possible in $\Theta(k\, |Q|)/\Theta(|Q|)$ for any given $z \in \mathbb{R}^+$;

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- Compute $V_{q_0}(z)$ on $M + 1$ distinct values $(z_1, z_2, \cdots, z_{M+1})$;
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**Discrete feature function** $\alpha : \mathcal{D}_I \to [0, M]$, additively associated with derivations.

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**Problem:** Given an instance $I$, compute $1^{\text{st}}, \ldots, p^{\text{th}}$ **moment** of $A$ :

$$\mathbb{E}(\alpha(A)^p \mid I) = \sum_{d \in \mathcal{D}_I} \mathbb{P}(d \mid I) \cdot \alpha(d) = \frac{\boxed{\sum_{d \in \mathcal{D}_I} \alpha(d)^p}}{|\mathcal{D}_I|} \longrightarrow \mathcal{X}_{i,j}$$

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**Why?**

- $1^{\text{st}}$ **moment:** Average free-energy, # base-pairs $\mu := \mathbb{E}(A)$
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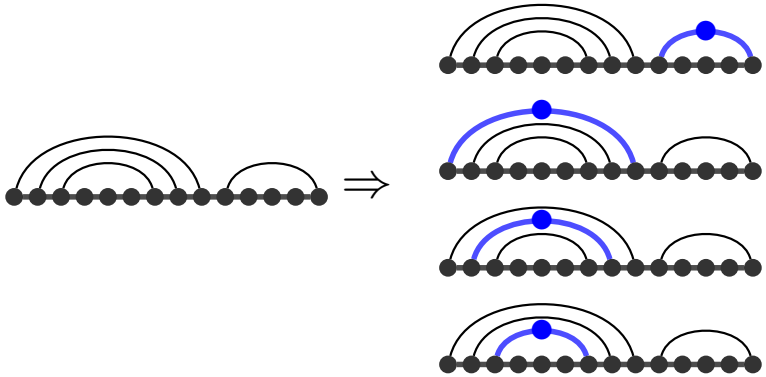
**Pointing derivations (formal derivative)** [Ponty and Saule, 2011]**:** $\to \Theta(2^p\, k\, |Q|)/\Theta(p\, |Q|)$

- **Transform equation** to generate derivations **pointed** on #RHS→LHS transitions.
- **Weight** each pointed transition with contribution to $\alpha$.



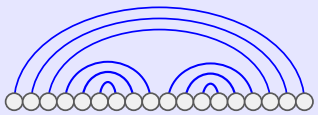
Counting in this decomposition
$\Leftrightarrow$ Compute $\mathcal{X}_{i,j}$

# Conclusion

# We need your help!


- **Crossing interactions (pseudoknots):** Finding the right parameter
- **Kinetics:** Markov process. . . computing energy barrier is hard! [Thachuk et al., 2010]
- **RNA Inverse folding/Design:** Complexity unknown, largely open!
- Constructing combinatorial DP scheme for classic problems

# Folding including crossing interactions

| | | Base-pairs | Stacking-Pairs | Nearest-Neighbor |
|---|---|---|---|---|
|  | Comp. | P [Nussinov and Jacobson, 1980] | P [Ieong et al., 2003] | P [Zuker and Stiegler, 1981] |
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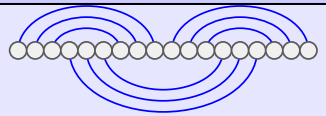
|  | Comp. | ??? | NP-Hard [Ieong et al., 2003] | NP-Hard [Ieong et al., 2003] |
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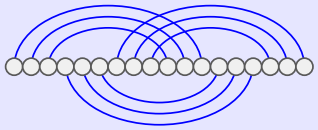
|  | Comp. | P [Tabaska et al., 1998] | NP-Hard [Lyngsø, 2004; Sheikh, Backofen, and Ponty, 2012] (any* Δ model) | NP-Hard [Lyngsø and Pedersen, 2000; Akutsu, 2000] |
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**Idea:** Parameterized complexity approach.

- **Bounded map genus** → Avoid **finite** set of substructures! [Vernizzi et al., 2006; Reidys et al., 2011]
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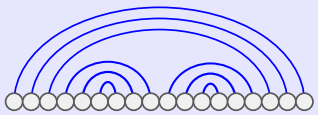
|  | Comp. | P [Nussinov and Jacobson, 1980] | P [Ieong et al., 2003] | P [Zuker and Stiegler, 1981] |
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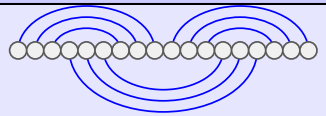
|  | Comp. | ??? | NP-Hard [Ieong et al., 2003] | NP-Hard [Ieong et al., 2003] |
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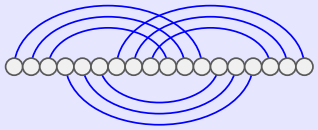
|  | Comp. | P [Tabaska et al., 1998] | NP-Hard [Lyngsø, 2004; Sheikh, Backofen, and Ponty, 2012] (any* Δ model) | NP-Hard [Lyngsø and Pedersen, 2000; Akutsu, 2000] |
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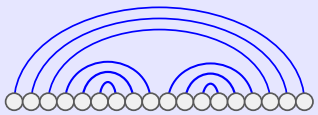
|  | Comp. | P [Nussinov and Jacobson, 1980] | P [Ieong et al., 2003] | P [Zuker and Stiegler, 1981] |
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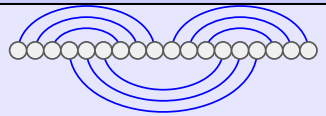
|  | Comp. | ??? | NP-Hard [Ieong et al., 2003] | NP-Hard [Ieong et al., 2003] |
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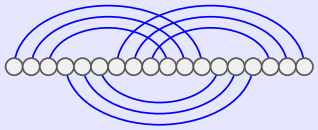
|  | Comp. | P [Tabaska et al., 1998] | NP-Hard [Lyngsø, 2004; Sheikh, Backofen, and Ponty, 2012] (any* Δ model) | NP-Hard [Lyngsø and Pedersen, 2000; Akutsu, 2000] |
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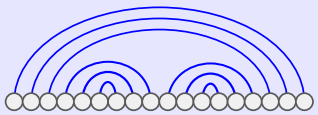
|  | Comp. | P [Nussinov and Jacobson, 1980] | P [Ieong et al., 2003] | P [Zuker and Stiegler, 1981] |
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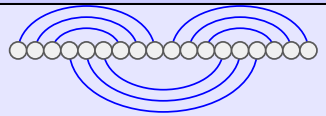
|  | Comp. | ??? | NP-Hard [Ieong et al., 2003] | NP-Hard [Ieong et al., 2003] |
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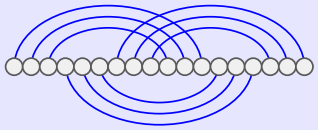
|  | Comp. | P [Tabaska et al., 1998] | NP-Hard [Lyngsø, 2004; Sheikh, Backofen, and Ponty, 2012] (any* Δ model) | NP-Hard [Lyngsø and Pedersen, 2000; Akutsu, 2000] |
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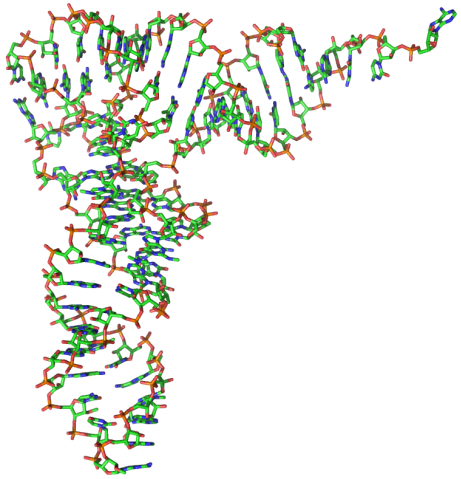

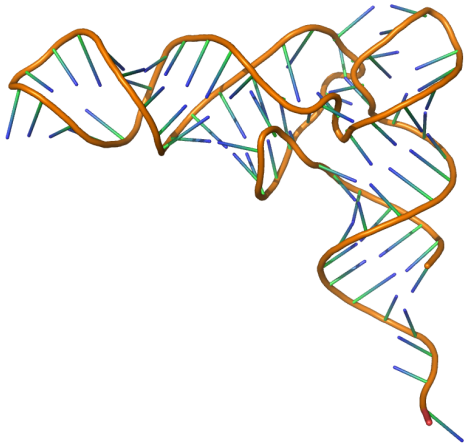

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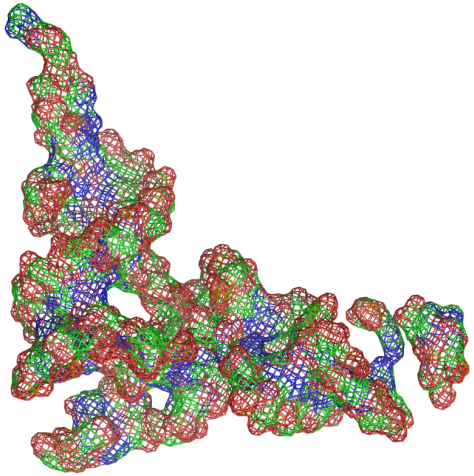

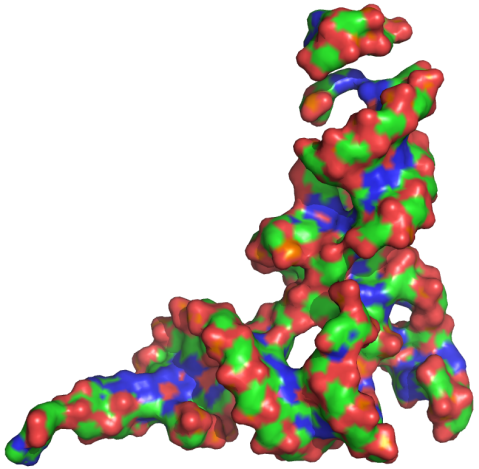

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