RNA as a combinatorial object

Asymptotics of RNA Shapes

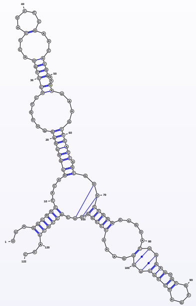
Yann Ponty

Bioinformatics Team
École Polytechnique/CNRS/INRIA AMIB – France

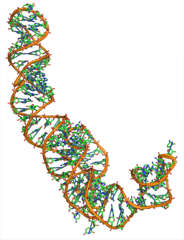
November 27, 2009

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

Primary structure



Secondary structure



Tertiary structure

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

Definition

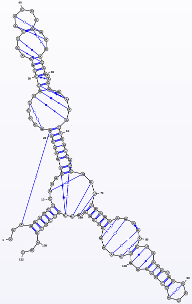
Secondary structures of RNA =

Maximal non-crossing subset of canonical base-pairs.

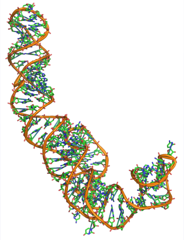
RNA structure

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

Primary structure



Secondary^{+} structure



Tertiary structure

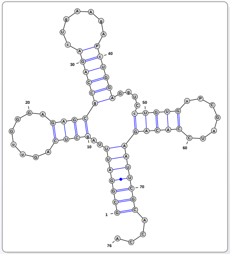
Source: 5s rRNA (PDBID: 1K73:B)

Definition

Secondary structures of RNA =
Maximal non-crossing subset of canonical base-pairs.

Outline

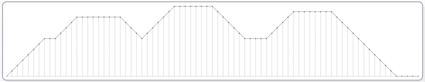
Various representations for a versatile molecule



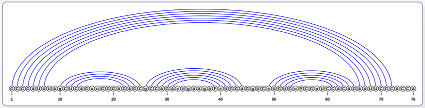
Outer planar graph

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

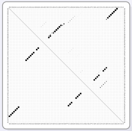
Well-parenthesized expression



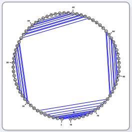
Mountain view



Non intersecting arcs



Dot plot

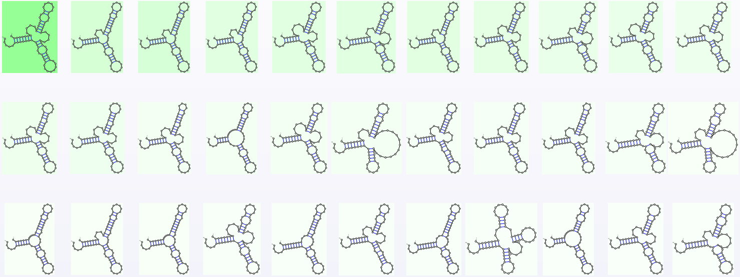


Feynman's diagram

Different objects
yet
Common combinatorial structure

Why use combinatorics?

Boltzmann ensemble is a (weighted) combinatorial class.



Studying it as such *cleans out the details* and helps:

- Assess asymptotic properties of sec. str.
- Investigate worst and average-case complexities
- Obtain better algorithms for RNA

Generating functions

Let $|.|$ be a size function over objects (Sequences, trees, ...). Combinatorial classes are (infinite) sets $\mathcal{C}$ of objects whose restrictions $\mathcal{C}_n$ to objects of size n are of finite cardinality.

Definition (Generating functions)

Let $\mathcal{C}$ be a combinatorial class and $c_n = |\mathcal{C}_n|$ the number of objects of size n in $\mathcal{C}$, then the generating function of $\mathcal{C}$ is $C(z)$ s. t.

$$C(z) = \sum_{s \in C} z^{|s|} = \sum_{n \geq 0} c_n z^n$$

Closed forms for $C(z)$ are often easy to find ...

DNA example: $\mathcal{D} := \{a, c, g, t\}^* \Rightarrow d_n = 4^n$
and $C(z) = 1 + 4z + 16z^2 + 64z^3 + \ldots = \sum_{n \geq 0} 4^n z^n = \frac{1}{1-4z}$

...and very often much simpler than for c_n!!!

DSV/symbolic method

From a class specification, one can directly establish the gen. fun.

Historically on languages, from Schützenberger's observation that

Gen. fun. are commutative images of languages

Grammar	Generating function	Coefficients
$C \to \varepsilon$	$C(z) = z^0 = 1$	$c_n = \mathbb{1}_{\{0\}}(n)$
$C \to t$	$C(z) = z^1 = z$	$c_n = \mathbb{1}_{\{1\}}(n)$
$C \to A \mid B$	$C(z) = A(z) + B(z)$	$c_n = a_n + b_n$
$C \to A.B$	$C(z) = A(z) \cdot B(z)$	$c_n = \sum_{k=0}^{n} a_k b_{n-k}$

Remark: One needs to ensure that unions are disjoint and concatenations unambiguous.

DNA example : $\{a, c, g, t\}^* \Leftrightarrow D \to a.D \mid c.D \mid g.D \mid t.D \mid \varepsilon$

$$\Rightarrow D(z) = z \cdot D(z) + z \cdot D(z) + z \cdot D(z) + z \cdot D(z) + 1$$

DSV/symbolic method

From a class specification, one can directly establish the gen. fun.

Historically on languages, from Schützenberger's observation that

Gen. fun. are commutative images of languages

Grammar	Generating function	Coefficients
$C \to \varepsilon$	$C(z) = z^0 = 1$	$c_n = \mathbb{1}_{\{0\}}(n)$
$C \to t$	$C(z) = z^1 = z$	$c_n = \mathbb{1}_{\{1\}}(n)$
$C \to A \mid B$	$C(z) = A(z) + B(z)$	$c_n = a_n + b_n$
$C \to A.B$	$C(z) = A(z) \cdot B(z)$	$c_n = \sum_{k=0}^{n} a_k b_{n-k}$

Remark: One needs to ensure that unions are disjoint and concatenations unambiguous.

DNA example : $\{a, c, g, t\}^* \Leftrightarrow D \to a.D \mid c.D \mid g.D \mid t.D \mid \varepsilon$

$$\Rightarrow D(z) = 4z \cdot D(z) + 1$$

DSV/symbolic method

From a class specification, one can directly establish the gen. fun.

Historically on languages, from Schützenberger's observation that

Gen. fun. are commutative images of languages

Grammar	Generating function	Coefficients
$C \to \varepsilon$	$C(z) = z^0 = 1$	$c_n = \mathbb{1}_{\{0\}}(n)$
$C \to t$	$C(z) = z^1 = z$	$c_n = \mathbb{1}_{\{1\}}(n)$
$C \to A \mid B$	$C(z) = A(z) + B(z)$	$c_n = a_n + b_n$
$C \to A.B$	$C(z) = A(z) \cdot B(z)$	$c_n = \sum_{k=0}^{n} a_k b_{n-k}$

Remark: One needs to ensure that unions are disjoint and concatenations unambiguous.

DNA example : $\{a, c, g, t\}^* \Leftrightarrow D \to a.D \mid c.D \mid g.D \mid t.D \mid \varepsilon$

$$\Rightarrow D(z) = \frac{1}{1 - 4z}$$

Main principles

Disclaimer

What follows, although true in this context, is embarassingly simplistic.
A rigorous presentation can (and must) be found in Flaj./Sedg. 08.

A singularity is a point $z = \rho$ where $C(z)$ is no longer analytic.
Asymptotics of coeff c_n are driven by the singularities of $C(z)$.

1^{st} principle

Location of the dominant (smallest) singularity ρ dictates the exponential growth $\Rightarrow \frac{c_n}{\rho^{-n}} = o(\alpha^n),\ \forall \alpha > 1$.

DNA example: $D(z) = 1/(1-4z) \Rightarrow \rho = 1/4 \Rightarrow d_n \sim 4^n P(n)$.

Basic scale

2^{nd} principle

Nature of ρ dictates subexponential part $P(n)$ s.t. $c_n \sim \rho^{-n} P(n)$.

Basic scale: If one can rewrite $C(z)$ as

$$C(z) = f(z) + g(z)(1 - z/\rho)^{\alpha}$$

where f and g are analytic $\forall |z| < |\rho|$ and non-null at ρ, then

$$c_n \equiv [z^n]C(z) \sim \frac{g(\rho)\rho^{-n}}{\Gamma(-\alpha)n^{\alpha+1}}$$

Example: $D(z) = \frac{1}{1-4z} \Rightarrow c_n \sim 4^n$
$(\rho = 1/4, \alpha = -1, f(z) = 0,$ and $g(z) = 1)$

General methodology

Asymptotic estimates are obtained using a 4 steps meta-algorithm:

1. Find the right model
2. Translate into grammar
3. Translate into system and solve g. f.
4. Singularity analysis yields asymptotics

General methodology

Asymptotic estimates are obtained using a 4 steps meta-algorithm:

1. Find the right model
2. Translate into grammar
3. Translate into system and solve g. f.
4. Singularity analysis yields asymptotics

General methodology

Asymptotic estimates are obtained using a 4 steps meta-algorithm:

1. Find the right model
2. Translate into grammar
3. Translate into system and solve g. f.
4. Singularity analysis yields asymptotics

General methodology

Asymptotic estimates are obtained using a 4 steps meta-algorithm:

1. Find the right model
2. Translate into grammar
3. Translate into system and solve g. f.
4. Singularity analysis yields asymptotics

Let us count dot-bracket notations (Motzkin words)

1

Appetizer: Motzkin words

Let us count dot-bracket notations (Motzkin words)

1 

2 $M \rightarrow \bullet M \mid (M)M \mid \varepsilon$

Appetizer: Motzkin words

Let us count dot-bracket notations (Motzkin words)

1 

2 $$M \rightarrow \bullet\, M \;\mid\; (\, M\,)\, M \;\mid\; \varepsilon$$

3 $$M(z) = z \cdot M(z) + z \cdot M(z) \cdot z \cdot M(z) + 1$$
$$= \frac{1-z\pm\sqrt{1-2z-3z^2}}{2z^2}$$

Let us count dot-bracket notations (Motzkin words)

1 

2 $$M \rightarrow \bullet\, M \quad | \quad (\, M\,)\, M \quad | \quad \varepsilon$$

3 $$M(z) = z \cdot M(z) + z \cdot M(z) \cdot z \cdot M(z) + 1$$

$$= \begin{cases} \frac{1-z+\sqrt{1-2z-3z^2}}{2z^2} = \frac{1}{z^2} - \frac{1}{z} - 1 - z - 2z^2 + \mathcal{O}(z^3) \\ \frac{1-z-\sqrt{1-2z-3z^2}}{2z^2} = \mathbf{1+z+2z^2+4z^3+9z^4} + \mathcal{O}(\mathbf{z}^5) \end{cases}$$

Let us count dot-bracket notations (Motzkin words)

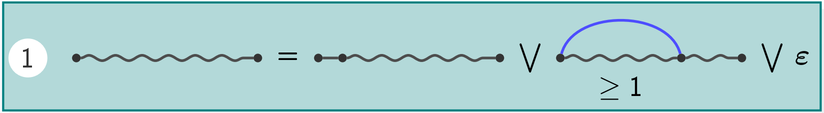
1 

2 $M \rightarrow \bullet\, M \mid (\, M\,)\, M \mid \varepsilon$

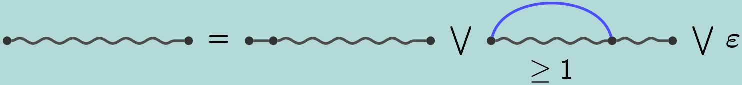
3
$$M(z) = z \cdot M(z) + z \cdot M(z) \cdot z \cdot M(z) + 1$$
$$= \frac{1-z-\sqrt{1-2z-3z^2}}{2z^2}$$

4
$$\rho = 1/3,\ M(z) = \frac{1-z}{2z^2} - g(z)\cdot\sqrt{1-z/\rho}, \text{ and } g(z) := \frac{\sqrt{1+z}}{2z^2}$$
$$\Rightarrow s_n \equiv [z^n]M(z) \sim \frac{g(\rho)\rho^{-n}}{\Gamma(-\alpha)n^{\alpha+1}} = \frac{3\sqrt{3}}{2\sqrt{\pi}} \cdot \frac{3^n}{n\sqrt{n}}(1+\mathcal{O}(1/n))$$

Consider RNA secondary structures (Waterman 78)



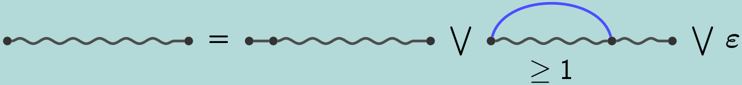
Consider RNA secondary structures (Waterman 78)

1 

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

Consider RNA secondary structures (Waterman 78)

1

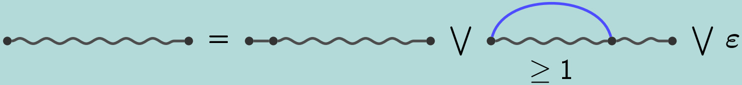


2

$$\begin{array}{lcl} S & \rightarrow & \bullet\, S \mid (\ \mathbf{T}\ )\ S \mid \varepsilon \\ \mathbf{T} & \rightarrow & \bullet\, S \mid (\ \mathbf{T}\ )\ S \end{array}$$

RNA secondary structures

Consider RNA secondary structures (Waterman 78)

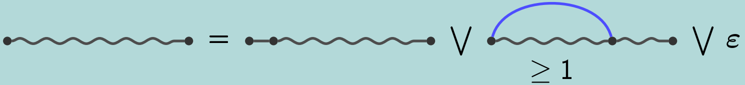
1 

2
$$
\begin{aligned}
S &\rightarrow \bullet\, S \mid (\, \mathbf{T}\,)\, S \mid \varepsilon \\
\mathbf{T} &\rightarrow \bullet\, S \mid (\, \mathbf{T}\,)\, S
\end{aligned}
$$

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

Consider RNA secondary structures (Waterman 78)

1



2

$$
\begin{aligned}
S &\rightarrow \bullet\, S \mid (\ \mathbf{T}\ )\ S \mid \varepsilon \\
\mathbf{T} &\rightarrow \bullet\, S \mid (\ \mathbf{T}\ )\ S
\end{aligned}
$$

3

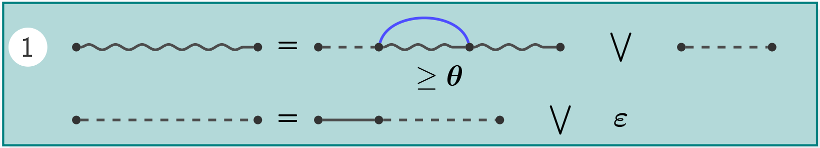
$$S(z) = \frac{1-z+z^2-\sqrt{1-2z-z^2-2z^3+z^4}}{2z^2}$$

4

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

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

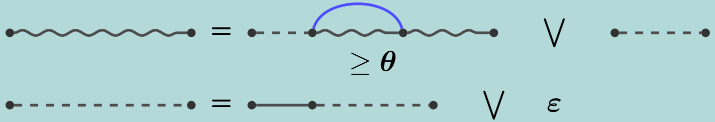
Let us generalize the θ constraint



RNA secondary structures

Let us generalize the θ constraint

1



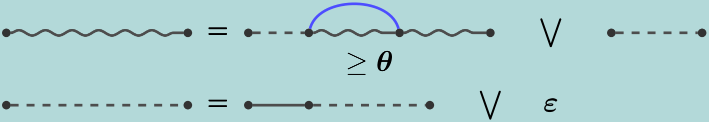
2

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

RNA secondary structures

Let us generalize the θ constraint

1



2

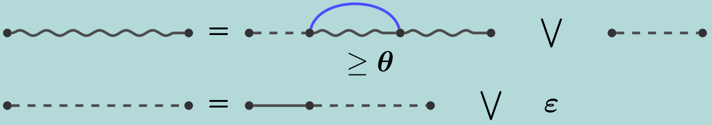
$$S \rightarrow U\,(\,\mathbf{T}\,)\,S \mid U \qquad U \rightarrow \bullet\, U \mid \varepsilon$$

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

RNA secondary structures

Let us generalize the θ constraint

1



2

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

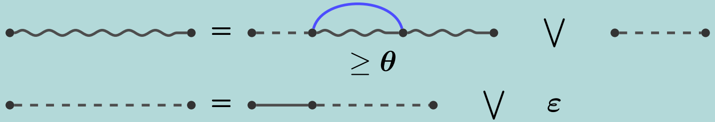
3

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

RNA secondary structures

Let us generalize the θ constraint

1



2

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

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

3

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

4

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

θ	0	1	3	10
β	3.	2.62	2.29	2.02

Half-time report

Message #1

Finding the right decomposition (DP) is a combinatorial task.

Message #2

Applying automatic theorems gives precise asymptotic equivalents.

Message #3

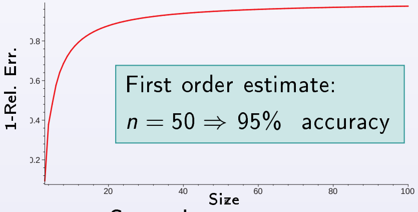
There is a large exponential number of structures of size n:
Homopolymer model: $\Omega(2^n)$ Stickiness model: $\mathcal{O}(1.8^n/n^{3/2})$

Message #1

Finding the right decomposition (DP) is a combinatorial task.

Message #2

Applying automatic theorems gives precise asymptotic equivalents.



Secondary structures

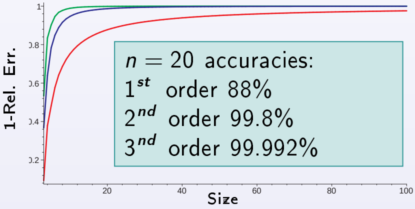
Half-time report

Message #1

Finding the right decomposition (DP) is a combinatorial task.

Message #2

Applying automatic theorems gives precise asymptotic equivalents.



Secondary structures

Half-time report

Message #1

Finding the right decomposition (DP) is a combinatorial task.

Message #2

Applying automatic theorems gives precise asymptotic equivalents.

Message #3

There is a large exponential number of structures of size n:
Homopolymer model: $\Omega(2^n)$ Stickiness model: $\mathcal{O}(1.8^n/n^{3/2})$

Outline

Presentation

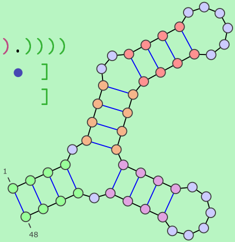
Definition (RNA shapes [Giegerich *et al*])

Coarse-grain representation hierarchy for RNA sec. struct.

Based on the *underlying backbone* structure.

Example

Sec. str.	((((.((((..((((......))))))))((((......)))).))))
π'-shape	[• [• [•]] [•] •]
π-shape	[[- -] [ ]]



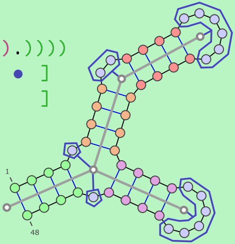
Definition (RNA shapes [Giegerich *et al*])

Coarse-grain representation hierarchy for RNA sec. struct.

Based on the *underlying backbone* structure.

Example

Sec. str.	((((.((((..((((......))))))))((((......)))).))))
π'-shape	[• [• [•]] [•] •]
π-shape	[[_ _] [ ]]



Contract identical consecutive characters

Presentation

Definition (RNA shapes [Giegerich *et al*])

Coarse-grain representation hierarchy for RNA sec. struct.

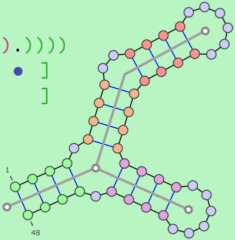
Based on the *underlying backbone* structure.

Example

Sec. str. ((((.((((..((((......))))))))((((......)))).))))

π'-shape [• [• [•]] [•] •]

π-shape [[_ _] [ ]]

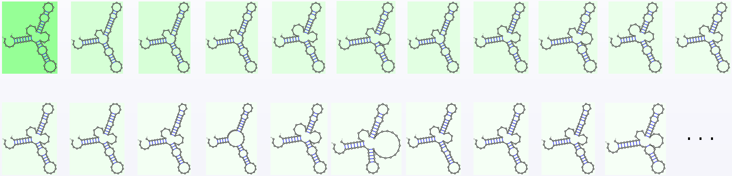


Remove unpaired regions

Contract nested helices

Motivation

RNA shapes allow a hierarchical search in the Boltzmann ensemble

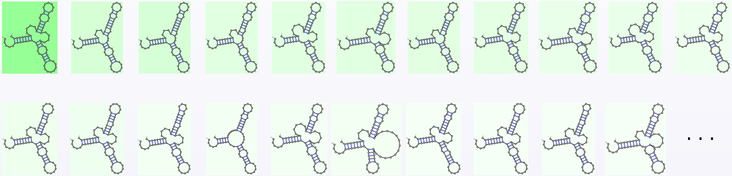


. . .

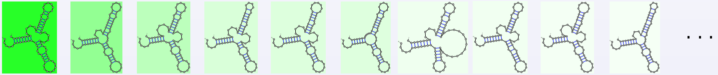
10000 samples ⇒ 1727 Secondary structures. . .

Motivation

RNA shapes allow a hierarchical search in the Boltzmann ensemble



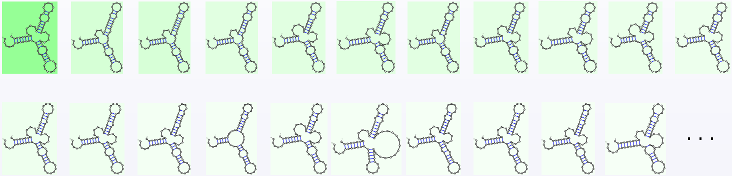
10000 samples $\Rightarrow$ 1727 Secondary structures...



...406 π'-shapes...

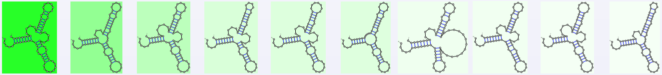
Motivation

RNA shapes allow a hierarchical search in the Boltzmann ensemble



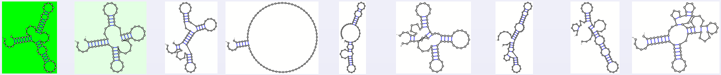
. . .

10000 samples $\Rightarrow$ 1727 Secondary structures. . .



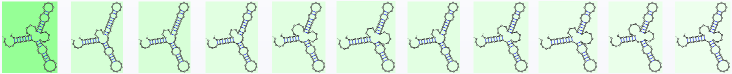
. . .

. . . 406 π'-shapes. . .



. . . but only 9 π-shapes!

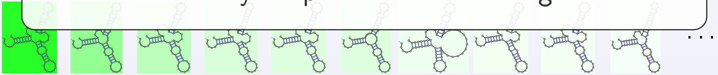
RNA shapes allow a hierarchical search in the Boltzmann ensemble



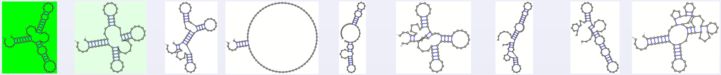
Is it reasonable to perform an exhaustive search of all possible shapes compatible with input structure?

10000 samples ⇒ 1727 Secondary structures. . .

How many shapes must we investigate?



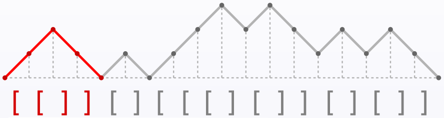
. . . 406 π'-shapes. . .



. . . but only 9 π-shapes!

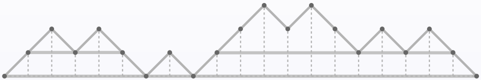
π-shapes

Objective: Count π-shapes with $2n$ parentheses.



1 π-shapes are bracket words avoiding the `[[...]]` motif.

Objective: Count π-shapes with $2n$ parentheses.

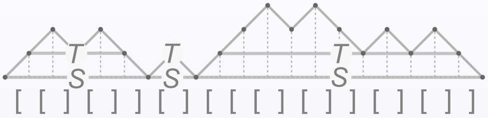


[[ ] [ ]] [ ] [[[ ] [ ]] [ ] [ ]]

1. π-shapes are bracket words avoiding the [[...]] motif.

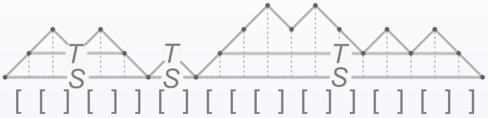
2. $$S \;\rightarrow\; [\, S_{/\{[..]\}} \,]\, S \;\mid\; [\, S_{/\{[..]\}} \,]$$

Objective: Count π-shapes with $2n$ parentheses.



1. π-shapes are bracket words avoiding the `[[...]]` motif.
2. $S \rightarrow [\,\mathbf{T}\,]\,S \mid [\,\mathbf{T}\,] \qquad \mathbf{T} \rightarrow [\,\mathbf{T}\,]\,S \mid \varepsilon$

Objective: Count π-shapes with $2n$ parentheses.

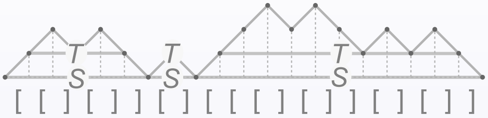


1. π-shapes are bracket words avoiding the [[...]] motif.

2. $S \to [\,\mathbf{T}\,]\,S \mid [\,\mathbf{T}\,] \qquad \mathbf{T} \to [\,\mathbf{T}\,]\,S \mid \varepsilon$

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

Objective: Count π-shapes with $2n$ parentheses.



1. π-shapes are bracket words avoiding the `[[...]]` motif.

2. $S \rightarrow [\,\mathbf{T}\,]\,S \mid [\,\mathbf{T}\,] \qquad \mathbf{T} \rightarrow [\,\mathbf{T}\,]\,S \mid \varepsilon$

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

4. $$s_{2n} \sim \frac{\sqrt{3}}{2\sqrt{\pi}} \cdot \frac{3^n}{n\sqrt{\pi}}(1 + \mathcal{O}(1/n)) \quad \text{and} \quad s_{2n+1} = 0$$

Remark: Doesn't this look familiar???

Limitations

Number of π-shapes of size n

$$\neq$$

Number of π-shapes compatible with RNA of size n

Reasons:

1. Shapes of size $\leq n$ should be considered
2. Forming a hairpin loop [ ] *takes* at least $\theta + 2$ bases

2 $S \rightarrow [\, T \,]\, S \mid [\, T \,] \qquad T \rightarrow [\, T \,]\, S \mid \varepsilon$

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

4 For n even: $s_{2n} \sim \frac{3\sqrt{3}}{4\sqrt{\pi}} \cdot \frac{3^n}{n\sqrt{\pi}}(1 + \mathcal{O}(1/n)) \approx 0.48 \cdot \frac{3^n}{n\sqrt{n}}$

Limitations

Number of π-shapes of size n

$\neq$

Number of π-shapes compatible with RNA of size n

Reasons:

1. Shapes of size $\leq n$ should be considered
2. Forming a hairpin loop [ ] *takes* at least $\theta + 2$ bases

2 $$S \rightarrow [\,T\,]\,S \mid [\,T\,] \qquad T \rightarrow [\,T\,]\,S \mid \bullet^{\theta}$$
$$R \rightarrow \square\, \mathrm{S} \mid \varepsilon$$

3 $$R(z) = \frac{1 - z^2 - \sqrt{1 - 2z^2 - 3z^4}}{2z^2(\mathbf{1} - \mathrm{z})}$$

4 $$r_{2n} \sim \frac{3\sqrt{3}}{4\sqrt{\pi}} \cdot \frac{3^n}{n\sqrt{n}}(1 + \mathcal{O}(1/n)) \Rightarrow r_n \approx 2.07 \cdot \frac{1.73^n}{n\sqrt{n}}$$

Limitations

Number of π-shapes of size n

$\neq$

Number of π-shapes compatible with RNA of size n

Reasons:

1. Shapes of size $\leq n$ should be considered
2. Forming a hairpin loop [ ] *takes* at least $\theta + 2$ bases

2

$$S \rightarrow [\ T\ ]\ S \mid [\ T\ ] \qquad T \rightarrow [\ T\ ]\ S \mid \bullet^{\theta}$$

$$R \rightarrow \square\ \mathrm{S} \mid \varepsilon$$

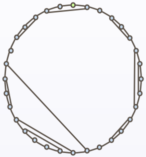
3

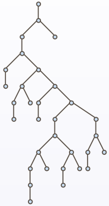
$$R(z) = \frac{1 - z^{\theta+2} - \sqrt{1 - 2z^{\theta+2} - 4z^{\theta+4} + z^{2\theta+4}}}{2z^2(1-z)}$$

4

$$\theta = 3 \Rightarrow r_n \approx 2.44 \frac{1.32^n}{n\sqrt{n}}$$

A surprising bijection





Theorem

$\#\pi$ *shapes of size* n = $\#$*Motzkin words of length* $2n+2$

Proof.

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

$$S(z) = 1 + z^2 M(z^2) \quad \Rightarrow \quad s_n = m_{2n+2}$$

$\square$

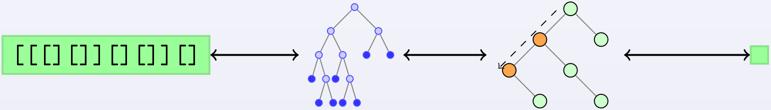
These two classes are in bijection.
How to state it? Can we exploit it?

Explicit bijection

Let $\psi, \phi : \{\,[\,,\,]\,\}^* \to \{\,(\,,\,)\,,\bullet\}$ such that

$$
\begin{aligned}
\psi((\ A\ )\ B) &= \begin{cases} \phi(A) & \text{If } B = \varepsilon \\ \phi(A) \bullet \psi(B) & \text{Otherwise} \end{cases} \\
\phi((\ A\ )\ B) &= \phi(A)[\psi(B)] \\
\phi(\varepsilon) &= \varepsilon.
\end{aligned}
$$

Then ψ is a **bijection** between s_{2n+2} and m_n.



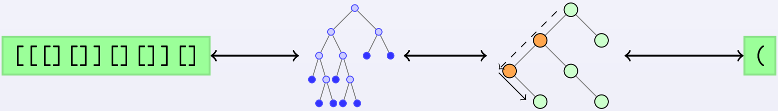
$2n+2$ letters | $2n+2$ edges | n edges

Explicit bijection

Let $\psi, \phi : \{\, [\, ,\,]\, \}^* \to \{\, (\, ,\,)\, , \bullet\}$ such that

$$\begin{aligned}
\psi((\ A\ )\ B) &= \begin{cases} \phi(A) & \text{If } B = \varepsilon \\ \phi(A) \bullet \psi(B) & \text{Otherwise} \end{cases} \\
\phi((\ A\ )\ B) &= \phi(A)[\psi(B)] \\
\phi(\varepsilon) &= \varepsilon.
\end{aligned}$$

Then ψ is a **bijection** between s_{2n+2} and m_n.



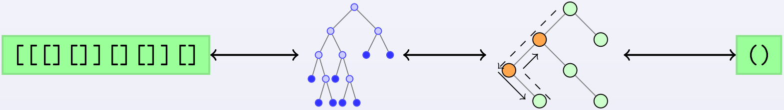
$2n+2$ letters $\quad$ $2n+2$ edges $\quad$ n edges

Explicit bijection

Let $\psi, \phi : \{\,[\,,\,]\,\}^* \to \{\,(\,,\,)\,,\bullet\}$ such that

$$
\begin{aligned}
\psi((\ A\ )\ B) &= \begin{cases} \phi(A) & \text{If } B = \varepsilon \\ \phi(A) \bullet \psi(B) & \text{Otherwise} \end{cases} \\
\phi((\ A\ )\ B) &= \phi(A)[\psi(B)] \\
\phi(\varepsilon) &= \varepsilon.
\end{aligned}
$$

Then ψ is a **bijection** between s_{2n+2} and m_n.



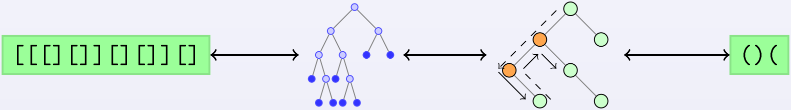
$2n+2$ letters $\qquad$ $2n+2$ edges $\qquad$ n edges

Explicit bijection

Let $\psi, \phi : \{ [\,, \,] \}^* \rightarrow \{ (\,, \,) \,, \bullet \}$ such that

$$
\begin{aligned}
\psi((\ A\ )\ B) &= \begin{cases} \phi(A) & \text{If } B = \varepsilon \\ \phi(A) \bullet \psi(B) & \text{Otherwise} \end{cases} \\
\phi((\ A\ )\ B) &= \phi(A)[\psi(B)] \\
\phi(\varepsilon) &= \varepsilon.
\end{aligned}
$$

Then ψ is a **bijection** between s_{2n+2} and m_n.



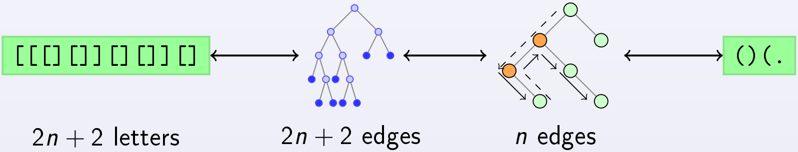
$2n+2$ letters $\quad$ $2n+2$ edges $\quad$ n edges

Explicit bijection

Let $\psi, \phi : \{\, [\, ,\,]\, \}^* \rightarrow \{\, (\, ,\,)\, , \bullet\}$ such that

$$\begin{aligned}
\psi((\ A\ )\ B) &= \begin{cases} \phi(A) & \text{If } B = \varepsilon \\ \phi(A) \bullet \psi(B) & \text{Otherwise} \end{cases} \\
\phi((\ A\ )\ B) &= \phi(A)[\psi(B)] \\
\phi(\varepsilon) &= \varepsilon.
\end{aligned}$$

Then ψ is a **bijection** between s_{2n+2} and m_n.

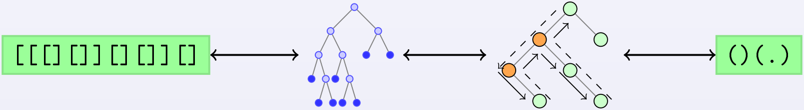


Explicit bijection

Let $\psi, \phi : \{\,[\,,\,]\,\}^* \rightarrow \{\,(\,,\,)\,,\bullet\}$ such that

$$
\begin{aligned}
\psi((\ A\ )\ B) &= \begin{cases} \phi(A) & \text{If } B = \varepsilon \\ \phi(A) \bullet \psi(B) & \text{Otherwise} \end{cases} \\
\phi((\ A\ )\ B) &= \phi(A)[\psi(B)] \\
\phi(\varepsilon) &= \varepsilon.
\end{aligned}
$$

Then ψ is a **bijection** between s_{2n+2} and m_n.



$2n+2$ letters

$2n+2$ edges

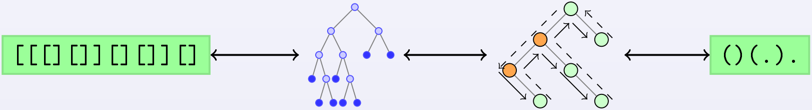
n edges

Explicit bijection

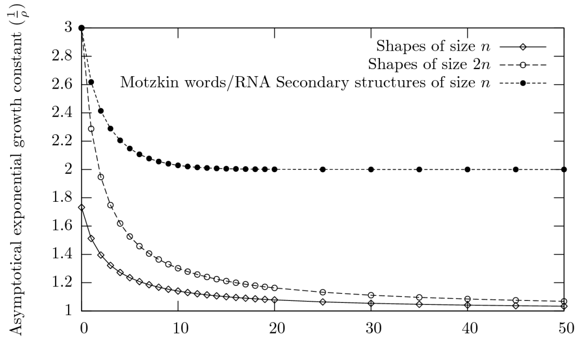
Let $\psi, \phi : \{\, [\, ,\,]\, \}^* \rightarrow \{\, (\, ,\,)\, , \bullet \}$ such that

$$
\begin{aligned}
\psi((\ A\ )\ B) &= \begin{cases} \phi(A) & \text{If } B = \varepsilon \\ \phi(A) \bullet \psi(B) & \text{Otherwise} \end{cases} \\
\phi((\ A\ )\ B) &= \phi(A)[\psi(B)] \\
\phi(\varepsilon) &= \varepsilon.
\end{aligned}
$$

Then ψ is a **bijection** between s_{2n+2} and m_n.



$2n+2$ letters $2n+2$ edges n edges



Impacts of θ on shapes and Motzkin are drastically different.

Theorem

Expectations of number of term. loops in Motzkin words and π-shapes scale like $m^t_n \sim \frac{n}{6} + \mathcal{O}(1)$ and $s^t_{2n+2} \sim \frac{2n}{3} + \mathcal{O}(1)$

Objective: Count π'-shapes compatible with RNA of length n.

1. π'-shapes = bracket words avoiding motifs `[[...]]` and ••

2. $R \rightarrow \square R \mid S \qquad S \rightarrow U [T] S \mid U \qquad U \rightarrow \diamond \mid \varepsilon$

   $T \rightarrow U [T] U [T] S \mid \diamond [T] \mid [T] \diamond \mid \diamond [T] \diamond \mid \bullet^{\theta}$

3. $\theta = 3,\ R(z) = \frac{1+2z^2+2z^3+z^4-z^5-z^6-\sqrt{1-4z^3-2z^4-2z^5+2z^6-7z^8-z^{10}+2z^{11}+z^{12}}}{2z^2(1-z^2)}$

4. $$r_n \sim 1.27\frac{1.81^n}{n\sqrt{n}}$$

π'-shapes

Objective: Count π'-shapes compatible with RNA of length n.

1 π'-shapes = bracket words avoiding motifs [[...]] and ●●

2 $R \rightarrow \square R \mid S \qquad S \rightarrow U\,[\,T\,]\,S \mid U \qquad U \rightarrow \diamond \mid \varepsilon$

$T \rightarrow U\,[\,T\,]\,U\,[\,T\,]\,S \mid \diamond[\,T\,] \mid [\,T\,]\diamond \mid \diamond[\,T\,]\diamond \mid \bullet^{\theta}$

3 $\theta = 3,\ R(z) = \frac{1+2z^2+2z^3+z^4-z^5-z^6-\sqrt{1-4z^3-2z^4-2z^5+2z^6-7z^8-z^{10}+2z^{11}+z^{12}}}{2z^2(1-z^2)}$

4 $r_n \sim 1.27\frac{1.81^n}{n\sqrt{n}}$

π'-shapes

Objective: Count π'-shapes compatible with RNA of length n.

1 π'-shapes = bracket words avoiding motifs [[...]] and ••

2 $R \to \square R \mid S \qquad S \to U\,[\,T\,]\,S \mid U \qquad U \to \diamond \mid \varepsilon$

$T \to U\,[\,T\,]\,U\,[\,T\,]\,S \mid \diamond[\,T\,] \mid [\,T\,]\diamond \mid \diamond[\,T\,]\diamond \mid \bullet^{\theta}$

3 $\theta = 3,\ R(z) = \frac{1+2z^2+2z^3+z^4-z^5-z^6-\sqrt{1-4z^3-2z^4-2z^5+2z^6-7z^8-z^{10}+2z^{11}+z^{12}}}{2z^2(1-z^2)}$

4 $r_n \sim 1.27\frac{1.81^n}{n\sqrt{n}}$

π'-shapes

Objective: Count π'-shapes compatible with RNA of length n.

1 π'-shapes = bracket words avoiding motifs [[. . .]] and ••

2 $R \rightarrow \Box\, R \mid S \qquad S \rightarrow U\,[\,T\,]\,S \mid U \qquad U \rightarrow \diamond \mid \varepsilon$

$T \rightarrow U\,[\,T\,]\,U\,[\,T\,]\,S \mid \diamond[\,T\,] \mid [\,T\,]\diamond \mid \diamond[\,T\,]\diamond \mid \bullet^{\theta}$

3 $\theta = 3,\ R(z) = \frac{1+2z^2+2z^3+z^4-z^5-z^6-\sqrt{1-4z^3-2z^4-2z^5+2z^6-7z^8-z^{10}+2z^{11}+z^{12}}}{2z^2(1-z^2)}$

4 $$r_n \sim 1.27\frac{1.81^n}{n\sqrt{n}}$$

Summary

Model	Asymptotic number
Sec. str. on n – Combinatorial	$1.1 \cdot \frac{\mathbf{2.6}^n}{n\sqrt{n}}$
Sec. str. on n – Empirical	$0.04 \cdot \frac{\mathbf{1.4}^n}{n\sqrt{n}}$
π-shapes of size n	$1.38 \cdot \frac{\mathbf{1.73}^n}{n\sqrt{n}}$
π-shapes compatible with sec. str. on n	$2.44 \cdot \frac{\mathbf{1.32}^n}{n\sqrt{n}}$
π-shapes – Empirical	$0.21 \cdot \frac{\mathbf{1.1}^n}{n\sqrt{n}}$
π'-shapes of size n	$0.99 \cdot \frac{\mathbf{2.41}^n}{n\sqrt{n}}$
π'-shapes compatible with sec. str. on n	$1.28 \cdot \frac{\mathbf{1.81}^n}{n\sqrt{n}}$

Conclusion

- For *context-free* objects, finding gen. fun. is easy…
  …and precise asymptotics estimates follow readily
- Bijection between Motkzin words and π-shapes
- Way less many shapes than sec. str.!
- Homopolymer model overestimates number of shapes
  Need for a probabilistic model for base-pairing
  But stickiness is not enough…

Collaborators: W. A. Lorenz and P. Clote (Boston College)