CSI5126. Algorithms in bioinformatics

RNA Secondary Structure **Search Problem**

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Summary

We learnt that **RNA** evolves so as to preserve **bair pairs** patterns more than sequence. We discussed the impact on traditional bioinformatics approaches. Finally, we derived a dynamic programming algorithm to solve the **inference problem**. In this lecture, we will consider the **search problem**.

General objective

- **Implement** a pattern matching algorithm using context free grammars specifically to detect sequences who could fold into a specific structure.

Reading

- Richard Durbin, Sean R. Eddy, Anders Krogh, and Graeme Mitchinson (1998). Biological sequence analysis. Probabilistic models of proteins and nucleic acids. Cambridge University Press. Pages 277-297.

Project

- **Presentations**: 20 minutes
  - Tuesday, November 27, 2018
  - Thursday, November 29, 2018
  - Tuesday, December 4, 2018

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https://docs.google.com/document/d/1gfcGDWWF4iLxpxLEAaBHDi-aY6Ome_p9D5RE2evLJE0

Summary

- RNA molecules play **important cellular roles**
- **Secondary structure** is more preserved than sequence
- **Nussinov-Jacobson** is an $\mathcal{O}(n^3)$ algorithm that maximizes the total number of base pairs
- MFOLD (by **Zuker**) is an $\mathcal{O}(n^3)$ algorithm that minimizes the free energy
- The **accessible pairs, cycles and order notation** are key to understand the recurrence equations of MFE methods
- **Consensus methods***, based on Sankoff 1985 algorithm, perform more consistently, but have a high time/space complexity

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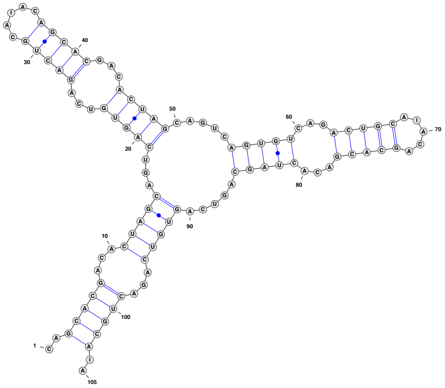
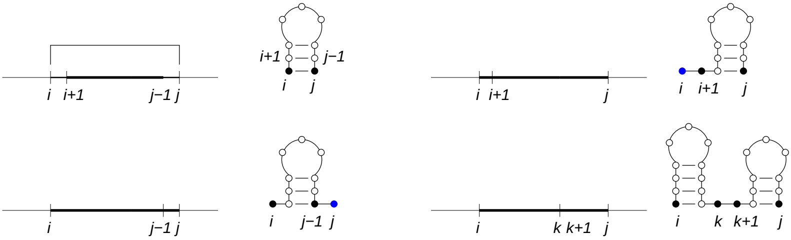
RNA **secondary structure**




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

Inference problem: Nussinov-Jacobson



Nussinov-Jacobson algorithm

Initialisation:

$$\gamma(i, i+k) \quad = \quad 0 \quad \text{for k} = 0 \text{ to } 1 \text{ and for i} = 1 \text{ to n} - \text{k}.$$

Recurrence:

$$\gamma(i,j) = \max \begin{cases} \gamma(i+1, j-1) + \delta(i,j); \\ \gamma(i+1, j); \\ \gamma(i, j-1); \\ \max_{i<k<(j-1)}[\gamma(i,k) + \gamma(k+1, j)]. \end{cases}$$

Matching score:

$$\delta(i,j) = \begin{cases} 1, \text{if } a_i : a_j \in \{A:U, U:A, G:C, C:G\} \bigcup \{G:U, U:G\}; \\ 0, \text{otherwise}. \end{cases}$$

	G	G	G	A	A	A	U	C	C
G	0	0	0	0	0	0	1	2	3
G	0	0	0	0	0	0	1	2	3
G		0	0	0	0	0	1	2	2
A			0	0	0	0	1	1	1
A				0	0	0	1	1	1
A					0	0	1	1	1
U						0	0	0	0
C							0	0	0
C								0	0

Other **paradigms**

- Reporting **sub-optimal structures** (MFOLD, SFOLD)
- **Partition function** and the McCaskill's calculation of P_{ij}'s
- **Folding kinetics**, identifying ribo-switches
- **MFE** for secondary structure for **interacting RNA molecules**
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Now **what**?

A secondary structure was inferred!

- It can be analyzed in order to **propose new experiments**, to **propose a mechanism of action**, or to **develop novel therapeutic approaches** (a new drug for instance)
- It can be used for finding new members of its family (**homologues**) and this requires adapted database searching techniques
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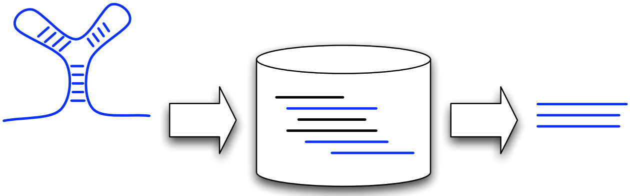
Database **search problem**

Find all sequences matching a user specified **secondary structure motif** or all the **sequences that can be folded into a user specified structure**



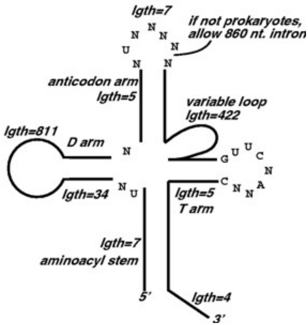
Non-probabilistic approaches

- The first practical approaches were **non-probabilistic**
- A **description language** allows the users to represent structural motifs, and search databases
- **RNAMOT**, **RNABOB**, **PatScan**, and **RNAMOTIF**

```
parms
    wc += gu;

descr
    h5(minlen=6,maxlen=7)
        ss(len=2)
        h5(minlen=3,maxlen=4)
            ss(minlen=4,maxlen=
        h3
        ss(len=1)
        h5(minlen=4,maxlen=5)
            ss(len=7)
        h3
        ss(minlen=4,maxlen=21)
        h5(minlen=4,maxlen=5)
            ss(len=7)
        h3
     h3
     ss(len=4)
```

A.



RNAMOT

- Gautheret D., Major F. & Cedergren R. (1990) Pattern searching/alignment with RNA primary and secondary structures: an effective descriptor for tRNA. *Comp. Appl. Biosc.* **6**, 325-331.
- Laferriere A., Gautheret D. & Cedergren R. (1994) An RNA pattern matching program with enhanced performances and portability. *Comp. Appl. Biosci.* **10**, 209-210.
- rna.igmors.u-psud.fr/gautheret/download

RNABOB

*RNABOB is an implementation of D. Gautheret's RNAMOT, but with a different underlying algorithm **using a non-deterministic finite state machine with node rewriting rules**. (Computer scientists would probably cringe in horror. It works, and it's fast, but is it street legal in a computer science department? Who knows.) If you're looking for an RNA motif that fits a hard consensus pattern — a la PROSITE patterns, but with base-pairing — you might check out RNABOB.*

- `http://eddylab.org/software.html`

RNAMOTIF

- Macke et al. (2001) *Nuc. Acids. Res.* **29**(22):4724-4735.
- **Sophisticated scripting language**
- Matches can be **ranked** using a user-defined scoring function
- **Minimum free energy** can be used in the definition of the scoring function
- casegroup.rutgers.edu/casegr-sh-2.5.html

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- These computer programs are practical and can be applied to large data-sets
- **Hard consensus pattern means hit-or-miss**
  - The major difficulties arises from the subjectivity in deriving the best descriptor for a family of sequences
  - It can be quite difficult to design a pattern with both high sensitivity and high specificity

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  - N. El-Mabrouk, M. Raffinot, J.E. Duchesne, M. Lajoie and N. Luc. Approximate Matching of Secondary Structures. *Journal of Bioinformatics and Computational Biology*, Vol. **3**, No. 2, pp. 317-342, 2005.
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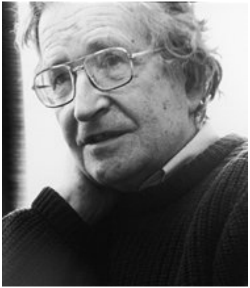
- **Probabilistic**, a principled approach

Transformational **grammars**

- Pioneered by **Noam Chomsky** in the ’50s to model natural languages
- **Formal grammars allow to determine what novel sentences are grammatical or not**
- Transformational grammars are sometimes called **generative grammars**
- **We look at non-probabilistic grammars first!**



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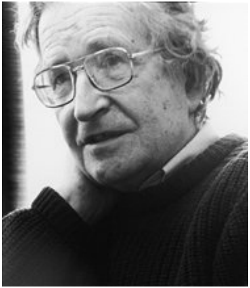

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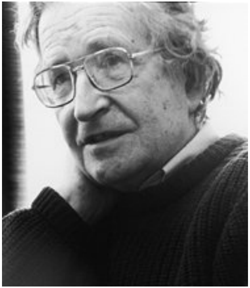

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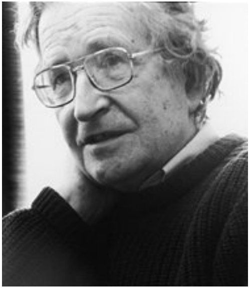
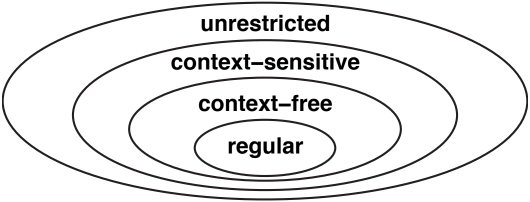


Chomsky hierarchy of transformational grammars



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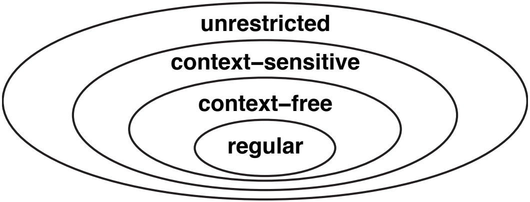

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Transformational grammars: **definitions**

- Constituted of **symbols** and **rewriting rules** (also called **production rules**) having the following form,

$$\alpha \rightarrow \beta$$

- 2 types of symbols: **terminal** symbols and **non-terminal** symbols
- The **left-hand side** of a rule contains **at least one non-terminal symbol**, which is rewritten into the right hand-side of the rule
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\end{array}
$$

- A **derivation** is the successive application of the rules starting with S (the start nonterminal).

$$S \Rightarrow cS_2 \Rightarrow cgS_1 \Rightarrow cgcS_2 \Rightarrow cgcgS_1 \Rightarrow cgcg$$

- The **language** generated by G, denoted $\mathcal{L}(G)$, is all the strings that can be **derived** from S, $\{w|S \stackrel{*}{\Rightarrow} w\}$.
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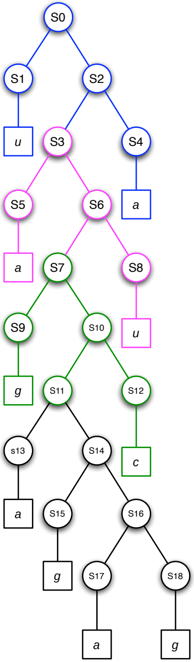
- Terminals are **leaves** and non-terminals are **internal nodes**
- What was the **input string**?
- Can you **enumerate some of the productions** of the grammar?



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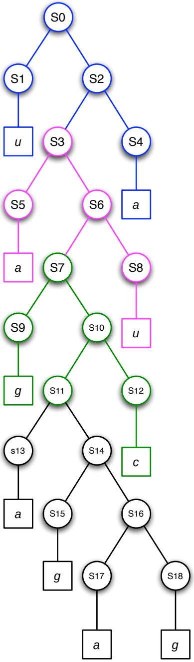

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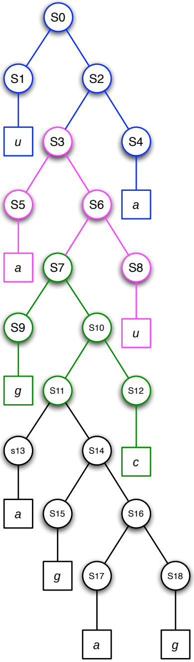

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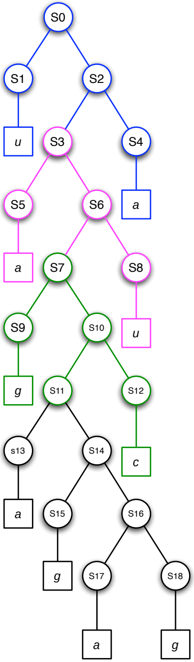
- Can you **enumerate some of the productions** of the grammar?



Transformational **grammars**

- A small example

$$
\begin{array}{lclcl}
S & \rightarrow & gS_1 & | & cS_2 \\
S_1 & \rightarrow & cS_2 & | & \epsilon \\
S_2 & \rightarrow & gS_1 & | & \epsilon
\end{array}
$$

- Give examples of sentences accepted (generated) by the grammar.
- Which class of grammar is this?

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Chomsky hierarchy of transformational grammars

Grammar type	Decidability	Productions
Regular		
Context-free		
Context-sensitive		
Unrestricted		

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Grammar type	Decidability	Productions
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Prosite

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- www.expasy.ch/prosite

RNA **secondary structure**

- Write a grammar whose language consists of **all** the sequences folding into either of the following two stem-loop structures.

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  G A           A G
 A   G         G   A
  N-N'          N-N'
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-

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- CYK is a widely used algorithm for the parsing of **context-free grammars** (CFG)

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```

$$
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S_1 &\rightarrow u & S_6 &\rightarrow S_7 S_8 \\
S_2 &\rightarrow S_3 S_4 & S_8 &\rightarrow u \\
S_4 &\rightarrow a & S_7 &\rightarrow S_9 S_{10} \\
S_3 &\rightarrow S_5 S_6 & S_9 &\rightarrow g
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\begin{array}{lll lll lll lll}
S & \rightarrow & S_1 S_2 & S_5 & \rightarrow & a & S_{10} & \rightarrow & S_{11} S_{12} & S_{15} & \rightarrow & g \\
S_1 & \rightarrow & u & S_6 & \rightarrow & S_7 S_8 & S_{12} & \rightarrow & c & S_{16} & \rightarrow & S_{17} S_{18} \\
S_2 & \rightarrow & S_3 S_4 & S_8 & \rightarrow & u & S_{11} & \rightarrow & S_{13} S_{14} & S_{17} & \rightarrow & a \\
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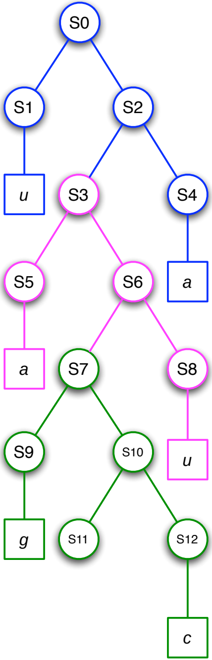
S0
S1
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u
S3
S4
S5
S6
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a
S7
S8
S9
S10
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S11
S12
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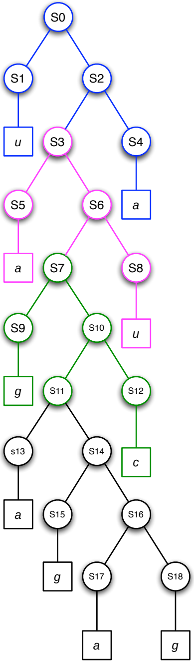
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Cocke-Younger-Kasami (CYK) algorithm: **example**

$$
\begin{array}{rcl}
S & \rightarrow & AB \mid BC \\
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\end{array}
$$

$$V(i, l) = \{W | W \stackrel{\star}{\Rightarrow} \mathbf{s}[i, i + l - 1]\}$$

s	b	a	a	b	a
i	1	2	3	4	5
$l = 1$	B	A, C	A, C	B	A, C
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$$B \rightarrow CC \mid b$$
$$C \rightarrow AB \mid a$$

$$V(i,l) = \{W | W \stackrel{\star}{\Rightarrow} \mathbf{s}[i, i+l-1]\}$$

s	b	a	a	b	a
i	1	2	3	4	5
$l=1$	B	A, C	A, C	B	A, C
$l=2$	S, A	B	S, C	S, A	
$l=3$	$\emptyset$	B	B		
$l=4$	$\emptyset$	S, A, C			
$l=5$	S, A, C				

Cocke-Younger-Kasami (CYK) algorithm: **example**

$$
\begin{array}{rcl|l}
S & \rightarrow & AB & BC \\
A & \rightarrow & BA & a \\
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\end{array}
$$

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Cocke-Younger-Kasami (CYK) algorithm: **example**

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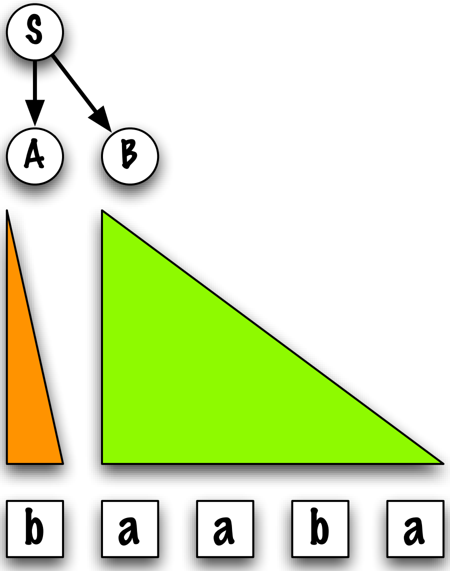
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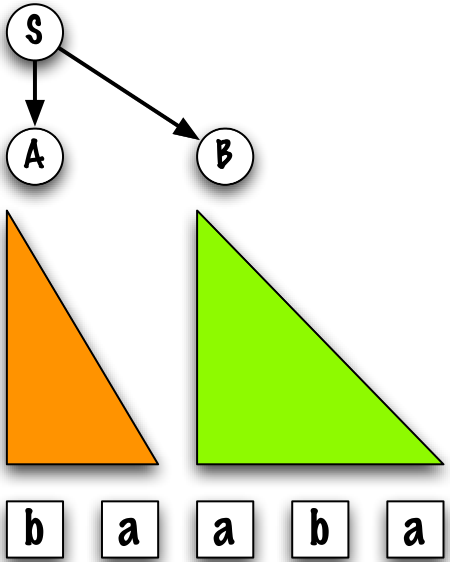
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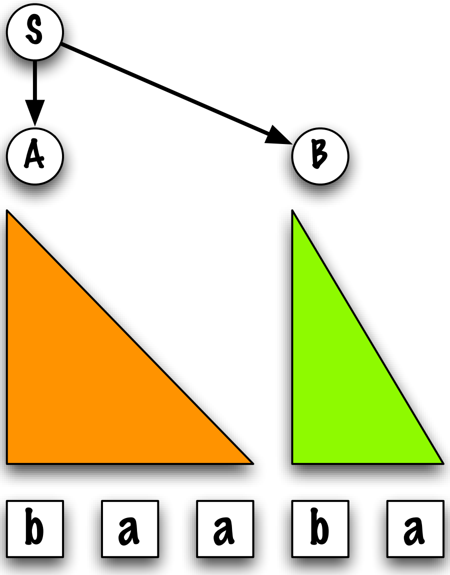
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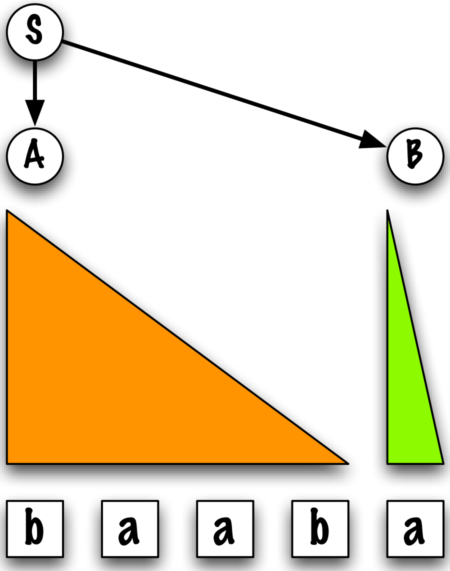
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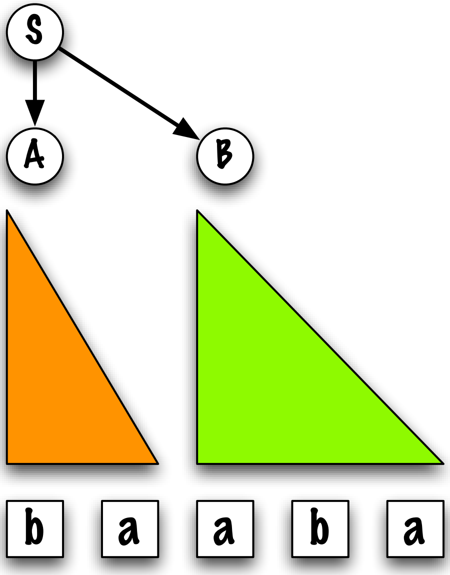
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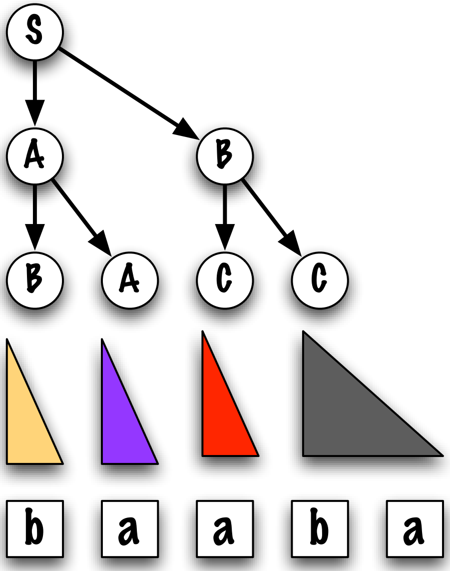
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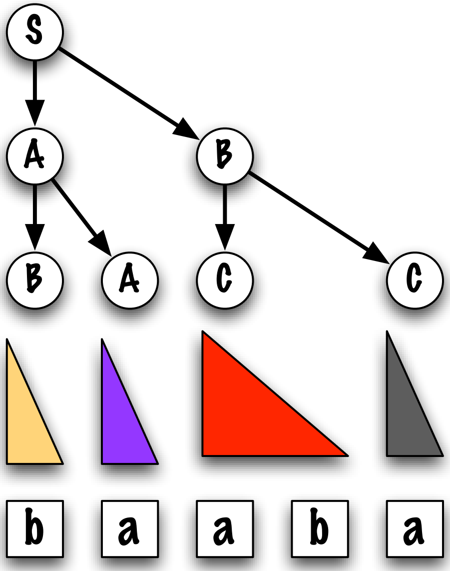
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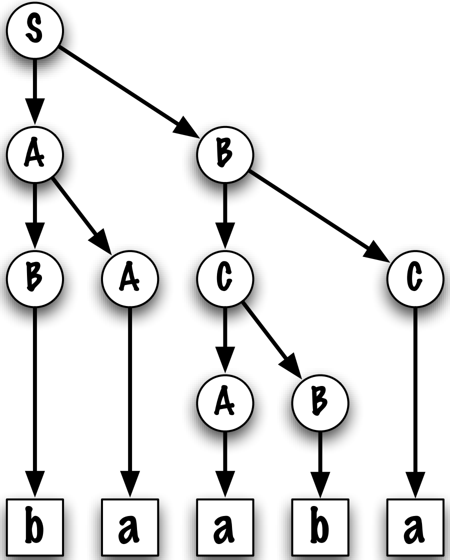
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Cocke-Younger-Kasami (CYK) algorithm: **algorithm**

```
{ Initialization }

for i = 1 to n do
    V(i,1) = {A | A → a is a production and s[i] = a}

{ Iteration }

for l = 2 to n do
  for i = 1 to n - l + 1 do
    V(i,l) = ∅
    for k = 1 to l - 1 do
        V(i,l) = V(i,l)  ∪
                 {A | A → BC,
                      B ∈ V(i,k) and
                      C ∈ V(i+k,l-k)}
```

Given an input of size n and grammar having m nonterminal symbols, CYK runs in $\mathcal{O}(mn^2)$ space and $\mathcal{O}(m^2n^3)$ time.

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- An **RNA secondary structure** (motif) can be represented as a CFG (in CNF)
- CYK can be used for **finding all** its occurrences in a database
- CYK finds an **exact match**
- **Still hit-or-miss algorithm**
- **Gene Myers adapted the algorithm for finding approximate matches**

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Discussion

A	C	C	U
A	C	U	U
A	C	C	U
G	C	C	C
(	.	.	)
A	U	U	U
A	C	C	U
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- *AUUU* is not accepted
- *ACCU* and *GCUC* are both accepted, but one is the **consensus** and the other the **exception**

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Stochastic (Context-Free) grammars

- Because of their discrete nature, it's difficult to design patterns that **1)** are **specific enough 2)** and yet will be **general enough** to match unseen cases
- Any grammar in the Chomsky hierarchy can be transformed into a **probabilistic model**
- In practice, because the cost of parsing a string (sequence or database) using context-sensitive and unrestricted grammars is prohibitive, applications are restricted to **regular** and **context-free** grammars

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Stochastic grammars

A **stochastic context-free grammar** (SCFG) for an RNA will have production rules of the following forms:

$$S_0 \rightarrow (.25) : g\, S_1\, c \mid (.25) : c\, S_1\, g \mid (.25) : a\, S_1\, u \mid (.25) : u\, S_1\, a$$

to represent base-pairs, and

$$S_i \rightarrow (.50) : u\, S_j \mid (.50) : g\, S_j$$

to represent single stranded regions.

Stochastic grammars: **problems**

- Given a sequence finding the most likely parse (**alignment**)
- Probability that this SCFG produces that sequence (**scoring**)
- Estimating the probabilities of the model (**training**)

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- Given a sequence finding the most likely parse (**alignment**)
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Notation

- Given an SCFG in Chomsky normal form with M nonterminal symbols, $W = W_1, .., W_m$ and W_1 the start symbol
- Let v, w and z denote the indices for the nonterminal symbols, W_v, W_y and W_z
- Production rules are of the form:

$$W_v \rightarrow W_y W_z \text{ and } W_v \rightarrow a$$

- Let the probability parameters be called,

$$t_v(y, z)$$

  for *transitions* and

$$e_v(a)$$

  for *emissions*
- Finally, let i, j and k be the indices for the symbols x_i, x_j and x_k in the sequence x of length n

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CYK algorithm (**alignment**)

```
{ Initialization }
```

for $i = 1$ to n, $v = 1$ to M

$$\gamma(i, 1, v) = e_v(x_i)$$

```
{ Iteration }
```

for $l = 2$ to n, $i = 1$ to $n - l + 1$, $v = 1$ to M

$$\gamma(i, l, v) = \max_{y,z} \max_{k=1,\ldots,l-1} \{\gamma(i, k, y)\gamma(i + k, l - k, z)t_v(y, z)\}$$

```
{ Termination }
```

$$\log P(x, \hat{\pi}|\theta) = \gamma(1, n, 1).$$

Cocke-Younger-Kasami (CYK) algorithm: **non-probabilistic**

```
{ Initialization }

for i = 1 to n do
    V(i,1) = {A | A → a is a production and s[i] = a}

{ Iteration }

for l = 2 to n do
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        V(i,l) = ∅
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            V(i,l) = V(i,l)  ∪
                      {A | A → BC, B ∈ V(i,k) and C ∈ V(i+k
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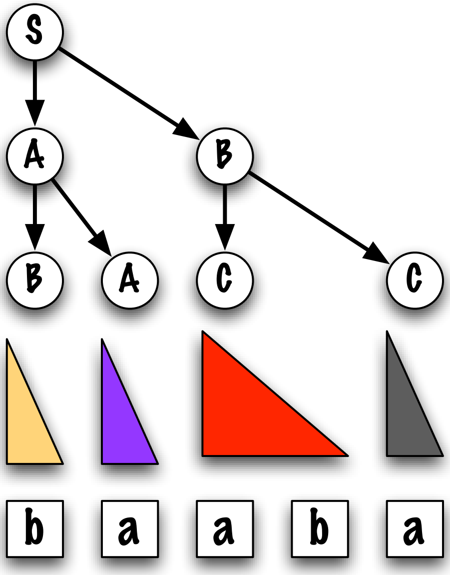
S
A
B
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C
C
b
a
a
b
a

CYK algorithm: **probabilistic**

```
{ Initialization }
```

for $i = 1$ to n, $v = 1$ to M

$$\gamma(i, 1, v) \quad = \quad log \;\; e_v(x_i)$$

```
{ Iteration }
```

for $l = 2$ to n, $i = 1$ to $n - l + 1$, $v = 1$ to M

$$\gamma(i, j, v) \quad = \quad \max_{y,z} \;\; \max_{k=1,\ldots,l-1} \;\; \{\gamma(i, k, y) + \gamma(i+k, l-k, z) + \log \;\; t_v(y, z)\}$$

```
{ Termination }
```

$$\log \;\; P(x, \hat{\pi} | \theta) \quad = \quad \gamma(1, n, 1).$$

Complexity

Memory $O(L^2M)$
Time $O(L^3M^3)$

CYK algorithm: inside (scoring)

{ Initialization }

for $i = 1$ to n, $v = 1$ to M

$$\alpha(i, 1, v) = e_v(x_i)$$

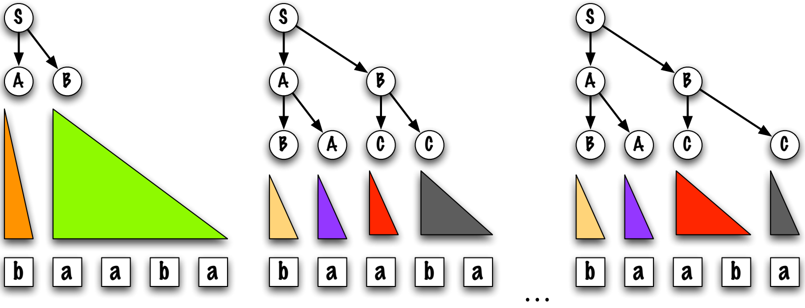
{ Iteration }

for $l = 2$ to n, $i = 1$ to $n - l + 1$, $v = 1$ to M

$$\alpha(i, l, v) = \sum_{y=1}^{M} \sum_{z=1}^{M} \sum_{k=1,\ldots,l-1} \{\alpha(i, k, y)\alpha(i+k, l-k, z)t_v(y, z)\}$$

{ Termination }

$$\log P(x|\theta) = \alpha(1, n, 1).$$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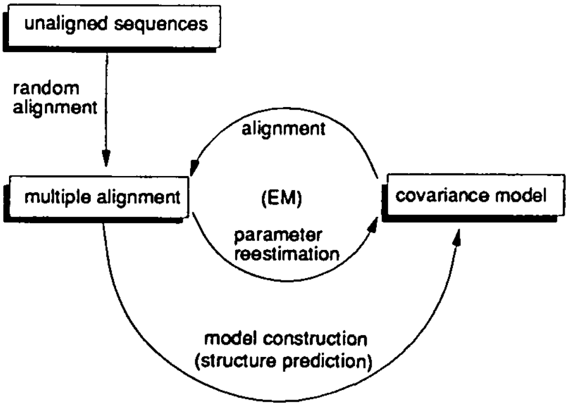
Estimating the probabilities

The transition and emission probabilities are estimated from the user input data (alignment and structure).

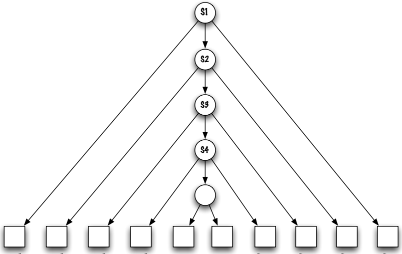
- **In theory:**
  - The **inside-outside**, an iterative **expectation-maximization** (EM), algorithm can be used for parameter re-estimation
- **In practice:**
  - Parameters are extracted from a user input alignment

Expectation-Maximization (EM)

Iterative algorithm for finding the **maximum-likelihood** estimates of the parameters.



Estimating the parameters




```
( ( ( ( . . ) ) ) )
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G G G G A - C C C C
U G G G A A C C C A
G G G G A U C C C U
G G G G A A C C C C
```
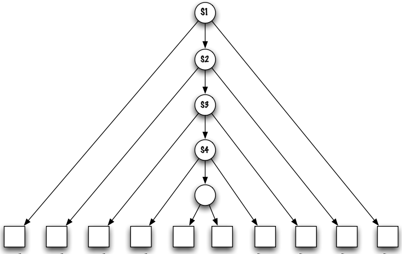

$$S \xrightarrow{0.8} g\, S_1\, c$$
$$S \xrightarrow{0.2} u\, S_1\, a$$
$$S_1 \xrightarrow{1.0} g\, S_2\, c$$
$$S_2 \xrightarrow{0.8} g\, S_3\, c$$
$$S_2 \xrightarrow{0.2} a\, S_3\, u$$
$$S_3 \xrightarrow{1.0} g\, S_4\, c$$
$$S_4 \xrightarrow{1.0} S_5 S_6$$
$$S_5 \xrightarrow{1.0} a$$
$$S_6 \xrightarrow{0.4} a$$
$$S_6 \xrightarrow{0.4} u$$
$$S_6 \xrightarrow{0.2} \epsilon$$

Estimating the parameters




```
( ( ( ( . . ) ) ) )
G G A G A U C U C C
G G G G A - C C C C
U G G G A A C C C A
G G G G A U C C C U
G G G G A A C C C C
```

$$S \xrightarrow{0.8} g\, S_1\, c$$
$$S \xrightarrow{0.2} u\, S_1\, a$$
$$S_1 \xrightarrow{1.0} g\, S_2\, c$$
$$S_2 \xrightarrow{0.8} g\, S_3\, c$$
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$$S_4 \xrightarrow{1.0} S_5 S_6$$
$$S_5 \xrightarrow{1.0} a$$
$$S_6 \xrightarrow{0.4} a\, S_6$$
$$S_6 \xrightarrow{0.4} u\, S_6$$
$$S_6 \xrightarrow{0.2} \epsilon$$

tRNA: a more **realistic input**

```
# STOCKHOLM 1.0
#=GF AU    Koala

DA0260           GGGCGAAUAGUGUCAGC.GGGAGCACACCAGACUUGCAUCUGGUAG.GGAGGGUUCGAGUCCCUCUUUGUCCAC
#=GR DA0260 SS   (((((((..((((.........)))).(((((......))))).....(((((.......))))))))))))..
DA0261           GGGCGAAUAGUGUCAGC.GGGAGCACACCAGACUUGCAUCUGGUAG.GGAGGGUUCGAGUCCCUCUUUGUCCAC
#=GR DA0261 SS   (((((((..((((.........)))).(((((......))))).....(((((.......))))))))))))..
DA0340           GGGCUCGUAGCUCAGC..GGGAGAGCGCCGCCUUUGCAGGCGGAGGCCGCGGGUUCAAAUCCCGCCGAGUCCA.
#=GR DA0340 SS   (((((((..((((.........)))).(((((......))))).....(((((.......))))))))))))..
DA0380           GGGCCCAUAGCUCAGU..GGUAGAGUGCCUCCUUUGCAGGAGGAUGCCCUGGGUUCGAAUCCCAGUGGGUCCA.
#=GR DA0380 SS   (((((((..((((.........)))).(((((......))))).....(((((.......))))))))))))..
DA0420           GGGCCCAUAGCUCAGU..GGUAGAGUGCCUCCUUUGCAGGAGGAUGCCCUGGGUUGGAAUCCCAGUGGGUCCA.
#=GR DA0420 SS   (((((((..((((.........)))).(((((......))))).....(((((.......))))))))))))..
DA0580           GGGCCCGUAGCUCAGACUGGGAGAGCGCCGCCCUUGCAGGCGGAGGCCCCGGGUUCAAAUCCCGGUGGGUCCA.
#=GR DA0580 SS   (((((((..((((.........)))).(((((......))))).....(((((.......))))))))))))..
DA0620           GGGCCCGUAGCUCAGACUGGGAGAGCGCCGCCCUUGCAGGCGGAGGCCCCGGGUUCAAAUCCCGGUGGGUCCA.
#=GR DA0620 SS   (((((((..((((.........)))).(((((......))))).....(((((.......))))))))))))..
```

Stochastic Context-Free Grammars (**SCFG**)

Sean Eddy, one of the pioneers of the use of **SCFG**s in bioinformatics, has developed several tools: `http://eddylab.org/software.html`

- **RSEARCH** aligns an RNA query to target sequences, using SCFG algorithms to score both secondary structure and primary sequence alignment simultaneously;
- **Infernal**. RNA structure analysis using covariance models (new);
- **COVE**. RNA structure analysis using covariance models (old).

RSearch

- **Input**: an RNA sequence and its secondary structure
- **Output**: similar RNAs on the basis of both primary sequence and secondary structure
- R.J. Klein and S.R. Eddy (2003) RSEARCH: Finding homologs of single structured RNA sequences. *BMC Bioinformatics*, **4**:44, 2003 (doi:10.1186/1471-2105-4-44)

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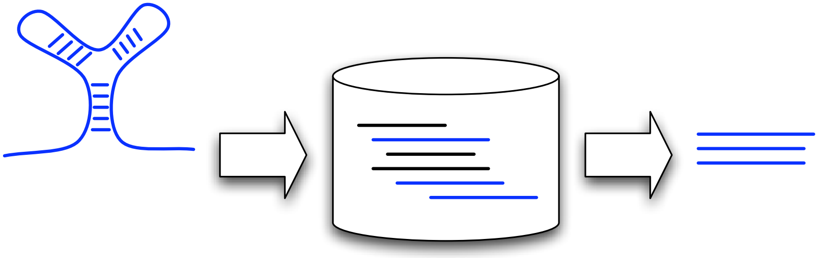
RSearch



```
# STOCKHOLM 1.0
#=GS Holley DE tRNA-Ala that Holley sequenced from Yeast genome
Holley
   GGGCGTGTGGCGTAGTCGGTAGCGCGCTCCCTTAGCATGGGAGAGGtCTCCGGTTCGATTCCGGACTCGTCCA
#=GR Holley SS
   (((((.(..((((........)))).(((((.......))))).....(((((.......)))))).))))).
//
```

Remarks

- **RIBOSUM** substitution matrices (analogous to residue substitution scores such as PAM and BLOSUM but for base pairs)
- Reports the statistical significance of all the matches
- Execution time is $\mathcal{O}(NM^3)$ where N is the size of the database and M is the length of the input sequence
- "(…) a typical single search of a metazoan genome may take a few thousand CPU hours."

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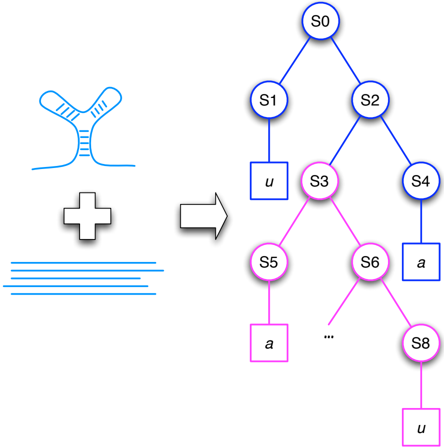
INFERNAL

- **INFERNAL 1.1**
  Nawrocki, E. P. & Eddy, S. R. Infernal 1.1: 100-fold faster RNA homology searches. *Bioinformatics* **29**, 2933–2935 (2013).
- **Rfam 14** (August 2018, 2791 families, hand curated)
- Kalvari, I. et al. Rfam 13.0: shifting to a genome-centric resource for non-coding RNA families. *Nucleic Acids Res* **46**, D335–D342 (2018).

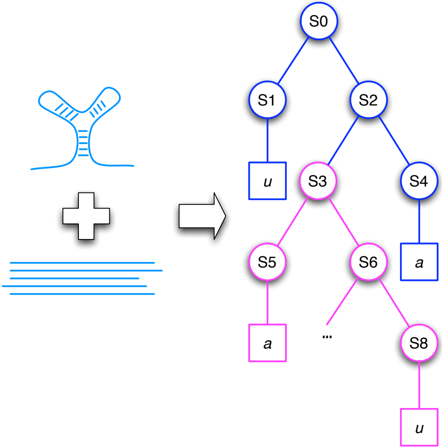
INFERNAL/Rfam covariance models



INFERNAL/Rfam covariance models

```
# STOCKHOLM 1.0

#=GC SS_cons   <<<<..>>>>
seq1           GGAGAUCUCC
seq2           GGGGAUCCCC
seq3           UGGGAACCCA
seq4           GGGGAUCCCU
seq5           GGGGAACCCC
//
```



Summary

- Hard consensus patterns are difficult to design
- SCFGs are powerful but slow
(thousands of hours for scanning a bacterial genome)
- Specialised programs have been developed, each recognising a specific structure; these programs are generally sensitive, specific and (relatively) fast:
  - tRNAscan-SE (by Sean Eddy)
  - detects 99% of the known tRNAs
  - with an error rate of 1 false positive per 15 billion nucleotides

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Pensez-y!

L'impression de ces notes n'est probablement pas nécessaire!