Stochastic Context Free Grammars for RNA Structure Modeling

BMI/CS 776
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Spring 2011

Goals for Lecture

the key concepts to understand are the following

- transformational grammars
- the Chomsky hierarchy
- context free grammars
- stochastic context free grammars
- parsing ambiguity
- the Inside and Outside algorithms
- parameter learning via the Inside-Outside algorithm

Modeling RNA with Stochastic Context Free Grammars

- consider tRNA genes
  - 274 in yeast genome, ~1500 in human genome
  - get transcribed, like protein-coding genes
  - don’t get translated, therefore base statistics much different than protein-coding genes
  - but secondary structure is conserved
- to recognize new tRNA genes, model known ones using stochastic context free grammars [Eddy & Durbin, 1994; Sakakibara et al. 1994]
- but what is a grammar?

Transformational Grammars

- a transformational grammar characterizes a set of legal strings
- the grammar consists of
  - a set of abstract *nonterminal* symbols

    $$\{s,\ c_1,\ c_2,\ c_3,\ c_4\}$$

  - a set of *terminal* symbols (those that actually appear in strings)

    $$\{\mathrm{A},\ \mathrm{C},\ \mathrm{G},\ \mathrm{U}\}$$

  - a set of *productions*

$$
\begin{array}{lll}
c_1 \rightarrow \mathrm{U}c_2 & c_2 \rightarrow \mathrm{A}c_3 & c_3 \rightarrow \mathrm{A} \\
 & c_2 \rightarrow \mathrm{G}c_4 & c_3 \rightarrow \mathrm{G} \\
 & & c_4 \rightarrow \mathrm{A}
\end{array}
$$

A Grammar for Stop Codons

$$s \rightarrow c_1 \quad c_1 \rightarrow \mathrm{U}c_2 \quad c_2 \rightarrow \mathrm{A}c_3 \quad c_3 \rightarrow \mathrm{A} \quad c_4 \rightarrow \mathrm{A}$$

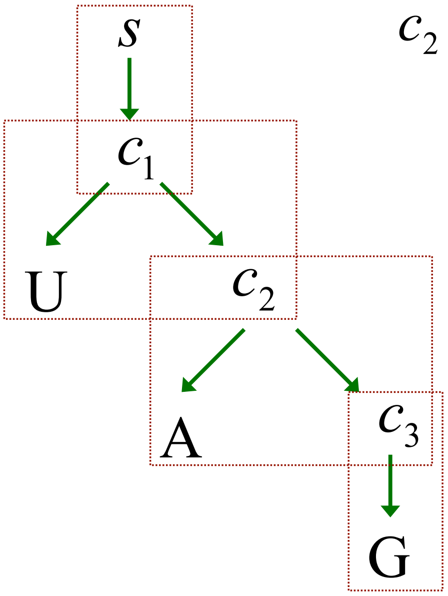
$$c_2 \rightarrow \mathrm{G}c_4 \quad c_3 \rightarrow \mathrm{G}$$

- this grammar can generate the 3 stop codons: UAA, UAG, UGA
- with a grammar we can ask questions like
  - what strings are derivable from the grammar?
  - can a particular string be derived from the grammar?

The Parse Tree for UAG

$$s \rightarrow c_1 \quad c_1 \rightarrow \mathrm{U}c_2 \quad c_2 \rightarrow \mathrm{A}c_3 \quad c_3 \rightarrow \mathrm{A} \quad c_4 \rightarrow \mathrm{A}$$

$$c_2 \rightarrow \mathrm{G}c_4 \quad c_3 \rightarrow \mathrm{G}$$



The Derivation for UAG

$$s \rightarrow c_1 \qquad c_1 \rightarrow \mathrm{U}c_2 \qquad c_2 \rightarrow \mathrm{A}c_3 \qquad c_3 \rightarrow \mathrm{A} \qquad c_4 \rightarrow \mathrm{A}$$

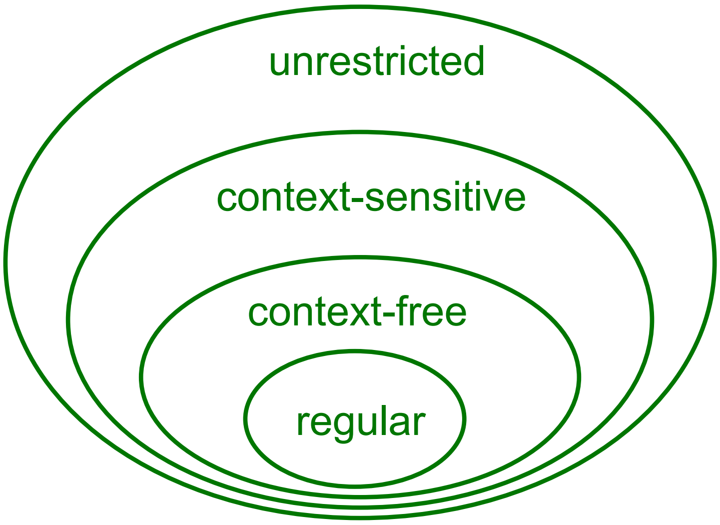
$$c_2 \rightarrow \mathrm{G}c_4 \qquad c_3 \rightarrow \mathrm{G}$$

$$s \Rightarrow c_1 \Rightarrow \mathrm{U}c_2 \Rightarrow \mathrm{UA}c_3 \Rightarrow \mathrm{UAG}$$

Some Shorthand

$$\begin{array}{l} c_2 \rightarrow \mathrm{A}c_3 \\ c_2 \rightarrow \mathrm{G}c_4 \end{array} \quad \Longleftrightarrow \quad c_2 \rightarrow \mathrm{A}c_3 \mid \mathrm{G}c_4$$

The Chomsky Hierarchy



unrestricted

context-sensitive

context-free

regular

- a hierarchy of grammars defined by restrictions on productions

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The Chomsky Hierarchy

- regular grammars $u \rightarrow \mathrm{X}v \qquad u \rightarrow \mathrm{X}$
- context-free grammars $u \rightarrow \beta$
- context-sensitive grammars $\alpha_1 u \alpha_2 \rightarrow \alpha_1 \beta \alpha_2$
- unrestricted grammars $\alpha_1 u \alpha_2 \rightarrow \gamma$

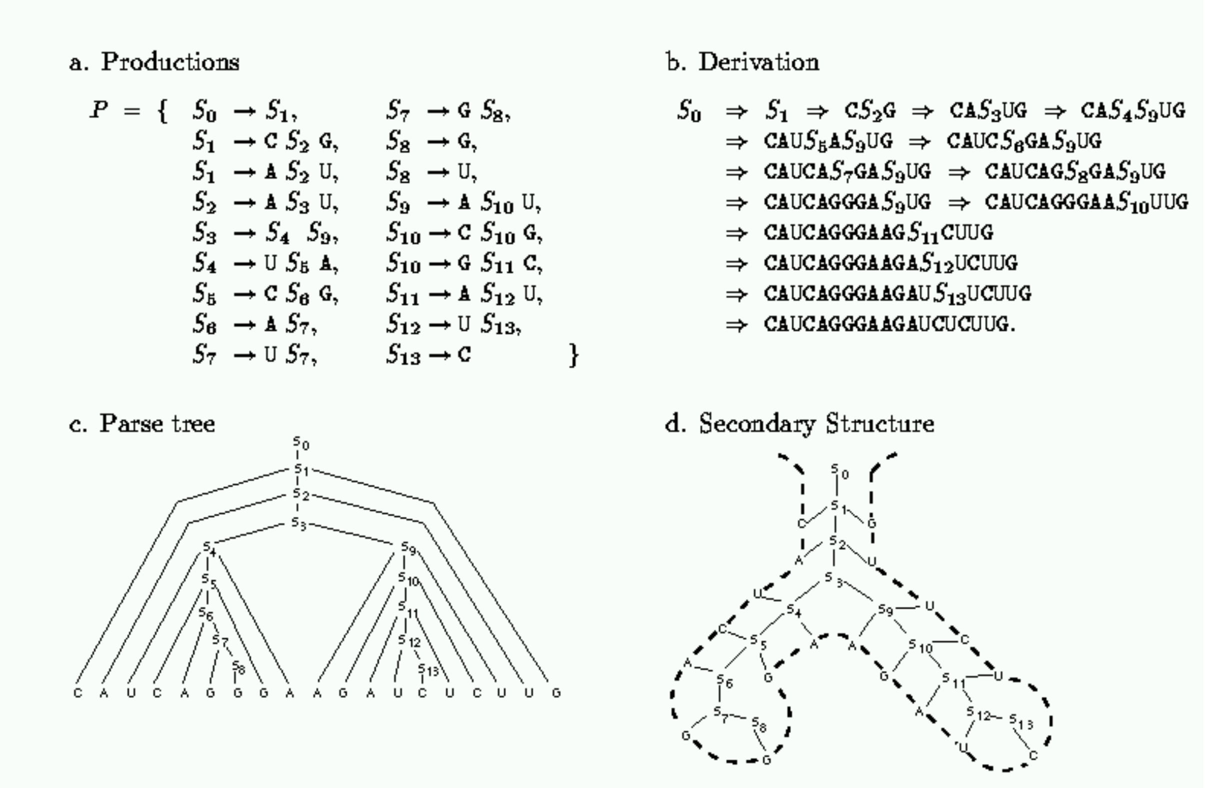
u, v are nonterminals
X is a terminal
α, γ are any sequence of terminals/nonterminals
β is any non-null sequence of terminals/nonterminals

CFGs and RNA

- context free grammars are well suited to modeling RNA secondary structure because they can represent base pairing preferences
- a grammar for a 3-base stem with and a loop of either GAAA or GCAA

$$
\begin{aligned}
s &\rightarrow \mathrm{A}w_1\mathrm{U} \mid \mathrm{C}w_1\mathrm{G} \mid \mathrm{G}w_1\mathrm{C} \mid \mathrm{U}w_1\mathrm{A} \\
w_1 &\rightarrow \mathrm{A}w_2\mathrm{U} \mid \mathrm{C}w_2\mathrm{G} \mid \mathrm{G}w_2\mathrm{C} \mid \mathrm{U}w_2\mathrm{A} \\
w_2 &\rightarrow \mathrm{A}w_3\mathrm{U} \mid \mathrm{C}w_3\mathrm{G} \mid \mathrm{G}w_3\mathrm{C} \mid \mathrm{U}w_3\mathrm{A} \\
w_3 &\rightarrow \mathrm{GAAA} \mid \mathrm{GCAA}
\end{aligned}
$$

CFGs and RNA



a. Productions

$$
P = \{\ \begin{array}{ll}
S_0 \rightarrow S_1, & S_7 \rightarrow \mathrm{G}\ S_8, \\
S_1 \rightarrow \mathrm{C}\ S_2\ \mathrm{G}, & S_8 \rightarrow \mathrm{G}, \\
S_1 \rightarrow \mathrm{A}\ S_2\ \mathrm{U}, & S_8 \rightarrow \mathrm{U}, \\
S_2 \rightarrow \mathrm{A}\ S_3\ \mathrm{U}, & S_9 \rightarrow \mathrm{A}\ S_{10}\ \mathrm{U}, \\
S_3 \rightarrow S_4\ S_9, & S_{10} \rightarrow \mathrm{C}\ S_{10}\ \mathrm{G}, \\
S_4 \rightarrow \mathrm{U}\ S_5\ \mathrm{A}, & S_{10} \rightarrow \mathrm{G}\ S_{11}\ \mathrm{C}, \\
S_5 \rightarrow \mathrm{C}\ S_6\ \mathrm{G}, & S_{11} \rightarrow \mathrm{A}\ S_{12}\ \mathrm{U}, \\
S_6 \rightarrow \mathrm{A}\ S_7, & S_{12} \rightarrow \mathrm{U}\ S_{13}, \\
S_7 \rightarrow \mathrm{U}\ S_7, & S_{13} \rightarrow \mathrm{C}
\end{array}\ \}
$$

b. Derivation

$$
\begin{aligned}
S_0 &\Rightarrow S_1 \Rightarrow \mathrm{C}S_2\mathrm{G} \Rightarrow \mathrm{CA}S_3\mathrm{UG} \Rightarrow \mathrm{CA}S_4S_9\mathrm{UG} \\
&\Rightarrow \mathrm{CAU}S_5\mathrm{A}S_9\mathrm{UG} \Rightarrow \mathrm{CAUC}S_6\mathrm{GA}S_9\mathrm{UG} \\
&\Rightarrow \mathrm{CAUCA}S_7\mathrm{GA}S_9\mathrm{UG} \Rightarrow \mathrm{CAUCAG}S_8\mathrm{GA}S_9\mathrm{UG} \\
&\Rightarrow \mathrm{CAUCAGGGA}S_9\mathrm{UG} \Rightarrow \mathrm{CAUCAGGGAA}S_{10}\mathrm{UUG} \\
&\Rightarrow \mathrm{CAUCAGGGAAG}S_{11}\mathrm{CUUG} \\
&\Rightarrow \mathrm{CAUCAGGGAAGA}S_{12}\mathrm{UCUUG} \\
&\Rightarrow \mathrm{CAUCAGGGAAGAU}S_{13}\mathrm{UCUUG} \\
&\Rightarrow \mathrm{CAUCAGGGAAGAUCUCUUG}.
\end{aligned}
$$

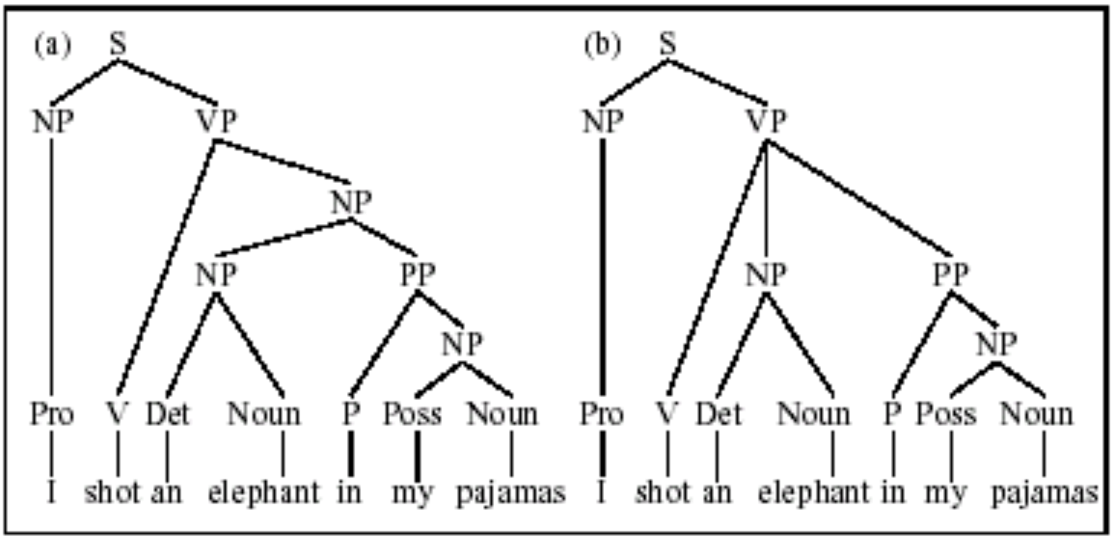
c. Parse tree

d. Secondary Structure

Figure from: Sakakibara et al. *Nucleic Acids Research*, 1994

Ambiguity in Parsing

"I shot an elephant in my pajamas. How he got in my pajamas, I'll never know." – Groucho Marx



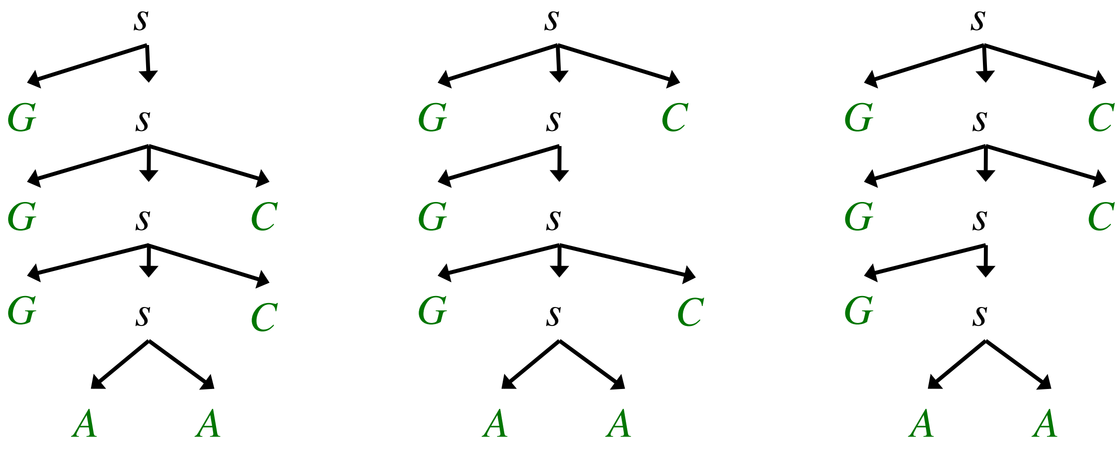
An Ambiguous RNA Grammar

$s \rightarrow G\ s\ C$

$s \rightarrow G\ s$

$s \rightarrow A\ A$

- with this grammar, there are 3 parses for the string *GGGAACC*



A Probabilistic Version of the Stop Codon Grammar

$$s \xrightarrow{1.0} c_1 \qquad c_1 \xrightarrow{1.0} \mathrm{U}c_2 \qquad c_2 \xrightarrow{0.7} \mathrm{A}c_3 \qquad c_3 \xrightarrow{0.2} \mathrm{A} \qquad c_4 \xrightarrow{1.0} \mathrm{A}$$

$$c_2 \xrightarrow{0.3} \mathrm{G}c_4 \qquad c_3 \xrightarrow{0.8} \mathrm{G}$$

- each production has an associated probability
- the probabilities for productions with the same left-hand side sum to 1
- *this* grammar has a corresponding Markov chain model

Stochastic Context Free Grammars

(a.k.a. Probabilistic Context Free Grammars)

$$s \rightarrow \overset{0.25}{\mathrm{A}w_1\mathrm{U}} \mid \overset{0.25}{\mathrm{C}w_1\mathrm{G}} \mid \overset{0.25}{\mathrm{G}w_1\mathrm{C}} \mid \overset{0.25}{\mathrm{U}w_1\mathrm{A}}$$

$$w_1 \rightarrow \overset{0.1}{\mathrm{A}w_2\mathrm{U}} \mid \overset{0.4}{\mathrm{C}w_2\mathrm{G}} \mid \overset{0.4}{\mathrm{G}w_2\mathrm{C}} \mid \overset{0.1}{\mathrm{U}w_2\mathrm{A}}$$

$$w_2 \rightarrow \overset{0.25}{\mathrm{A}w_3\mathrm{U}} \mid \overset{0.25}{\mathrm{C}w_3\mathrm{G}} \mid \overset{0.25}{\mathrm{G}w_3\mathrm{C}} \mid \overset{0.25}{\mathrm{U}w_3\mathrm{A}}$$

$$w_3 \rightarrow \overset{0.8}{\mathrm{GAAA}} \mid \overset{0.2}{\mathrm{GCAA}}$$

Stochastic Grammars?

…the notion "probability of a sentence" is an entirely useless one, under any known interpretation of this term.

— Noam Chomsky
(famed linguist)

Every time I fire a linguist, the performance of the recognizer improves.

— Fred Jelinek
(former head of IBM speech recognition group)

Credit for pairing these quotes goes to Dan Jurafsky and James Martin, *Speech and Language Processing*

Three Key Questions

- How likely is a given sequence?
  the Inside algorithm
- What is the most probable parse for a given sequence?
  the Cocke-Younger-Kasami (CYK) algorithm
- How can we learn the SCFG parameters given a grammar and a set of sequences?
  the Inside-Outside algorithm

Chomsky Normal Form

- it is convenient to assume that our grammar is in *Chomsky Normal Form*; i.e all productions are of the form:

$v \rightarrow yz$	right hand side consists of two nonterminals
$v \rightarrow A$	right hand side consists of a single terminal

- any CFG can be put into Chomsky Normal Form

Converting a Grammar to CNF

$$\begin{aligned} s &\rightarrow G\ s\ C \\ s &\rightarrow G\ s \\ s &\rightarrow A\ A \end{aligned} \quad \Longrightarrow \quad \begin{aligned} s &\rightarrow b_G\ p \\ p &\rightarrow s\ b_C \\ s &\rightarrow b_G\ s \\ s &\rightarrow b_A\ b_A \\ b_G &\rightarrow G \\ b_C &\rightarrow C \\ b_A &\rightarrow A \end{aligned}$$

Parameter Notation

- for productions of the form $v \rightarrow yz$, we'll denote the associated probability parameters

$t_v(y, z)$ transition

- for productions of the form $v \rightarrow A$, we'll denote the associated probability parameters

$e_v(A)$ emission

Determining the Likelihood of a Sequence: The Inside Algorithm

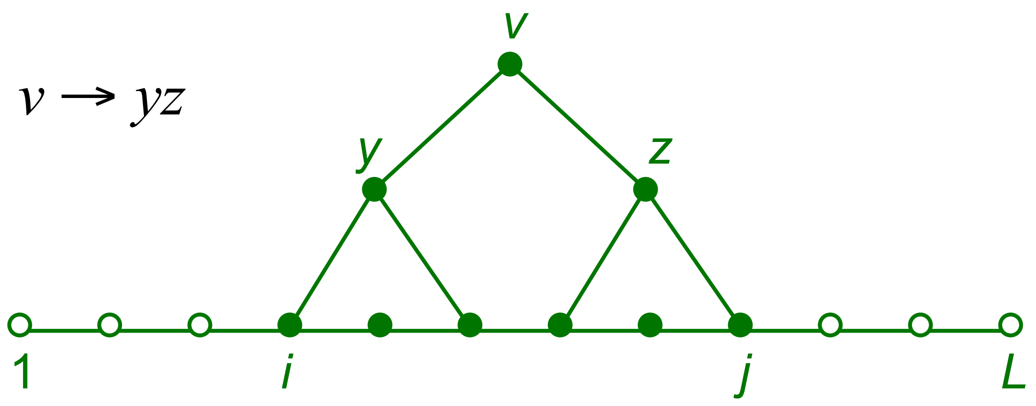
- a dynamic programming method, analogous to the Forward algorithm
- involves filling in a 3D matrix

$$\alpha(i, j, v)$$

representing the probability of all parse subtrees rooted at nonterminal v for the subsequence from i to j

Determining the Likelihood of a Sequence: The Inside Algorithm

$v \rightarrow yz$



- $\alpha(i, j, v)$: the probability of all parse subtrees rooted at nonterminal v for the subsequence from i to j

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Inside Calculation Example

$s \rightarrow b_G\ p$

$p \rightarrow s\ b_C$

$s \rightarrow b_G\ s$

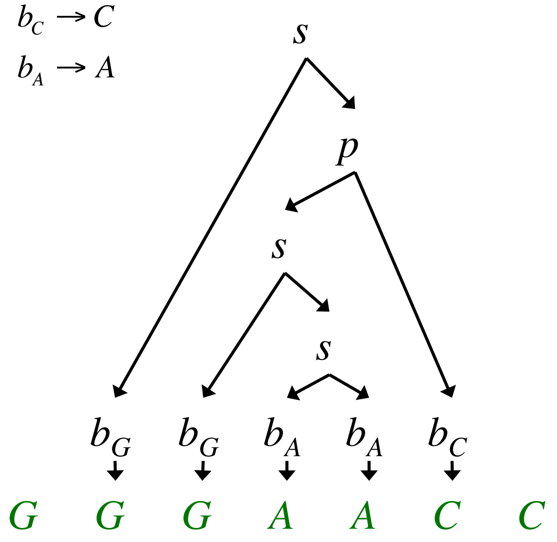
$s \rightarrow b_A\ b_A$

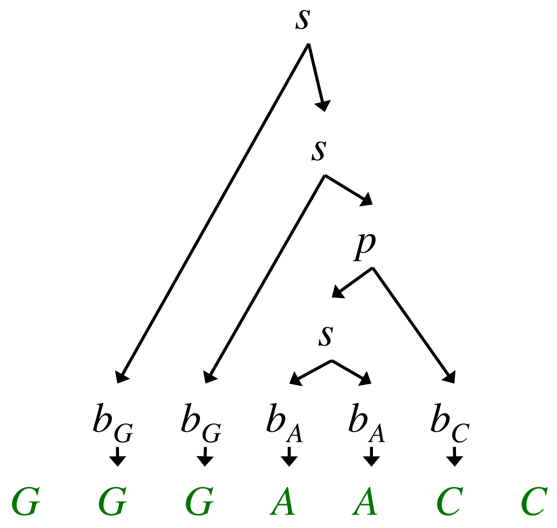
$b_G \rightarrow G$

$b_C \rightarrow C$

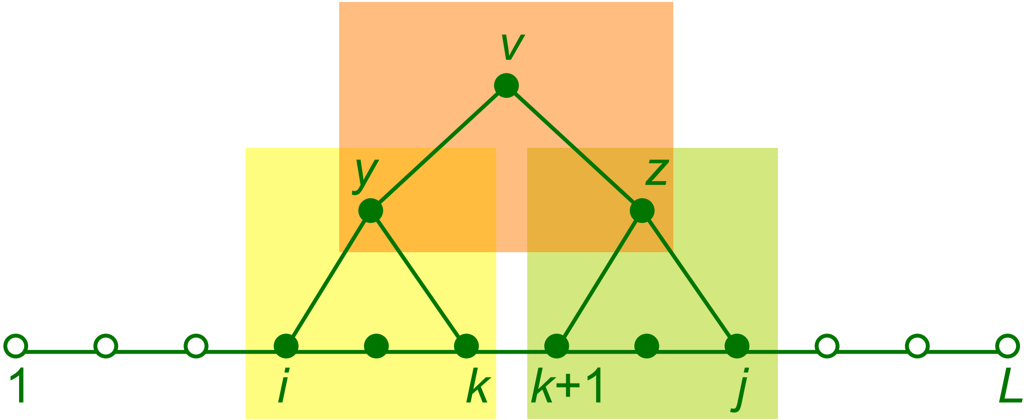
$b_A \rightarrow A$

$$\alpha(2,6,s) = t_s(b_G, p)\ \alpha(2,2,b_G)\ \alpha(3,6,p) + t_s(b_G, s)\ \alpha(2,2,b_G)\ \alpha(3,6,s)$$





Determining the Likelihood of a Sequence: The Inside Algorithm



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

M is the number of nonterminals in the grammar

The Inside Algorithm

- initialization (for $i = 1$ to L, $v = 1$ to M)

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

- iteration (for $i = 1$ to $L - 1$, $j = i+1$ to L, $v = 1$ to M)

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

- termination

$$\Pr(x) = \alpha(1, L, \underset{\substack{\uparrow\\ \text{start nonterminal}}}{1})$$

Learning SCFG Parameters

- if we know the parse tree for each training sequence, learning the SCFG parameters is simple
  - no hidden part of the problem during training
  - count how often each parameter (i.e. production) is used
  - normalize/smooth to get probabilities

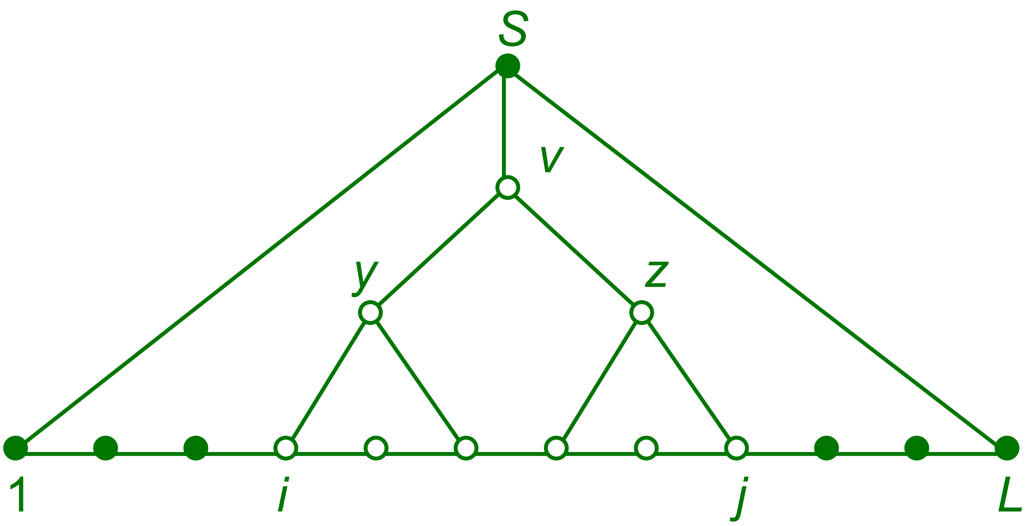
- more commonly, there are many possible parse trees per sequence – we don't know which one is correct
  - thus, use an EM approach (Inside-Outside)
  - iteratively
    - determine expected # times each production is used
      - consider all parses
      - weight each by it's probability
    - set parameters to maximize these counts

The Inside-Outside Algorithm

- we can learn the parameters of an SCFG from training sequences using an EM approach called Inside-Outside
- in the E-step, we determine
  - the expected number of times each *nonterminal* is used in parses $c(v)$
  - the expected number of times each *production* is used in parses $c(v \rightarrow yz)$

    $c(v \rightarrow A)$
- in the M-step, we update our production probabilities

The Outside Algorithm



- $\beta(i, j, v)$: the probability of parse trees rooted at the start nonterminal, excluding the probability of all subtrees rooted at nonterminal v covering the subsequence from i to j

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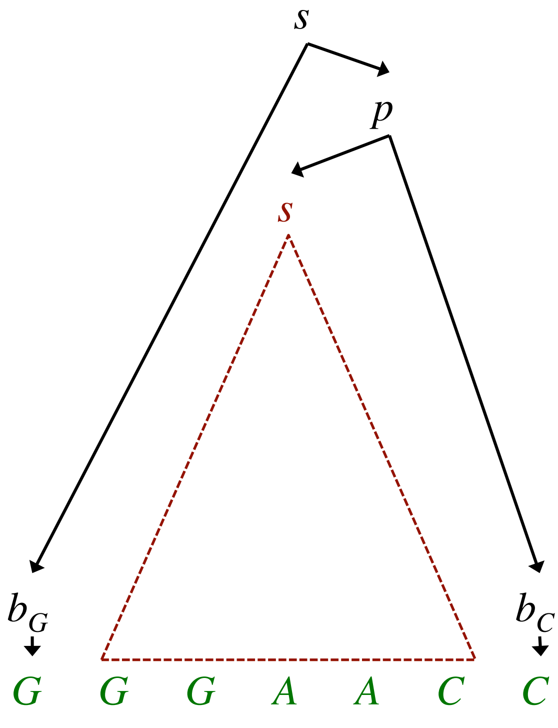
Outside Calculation Example

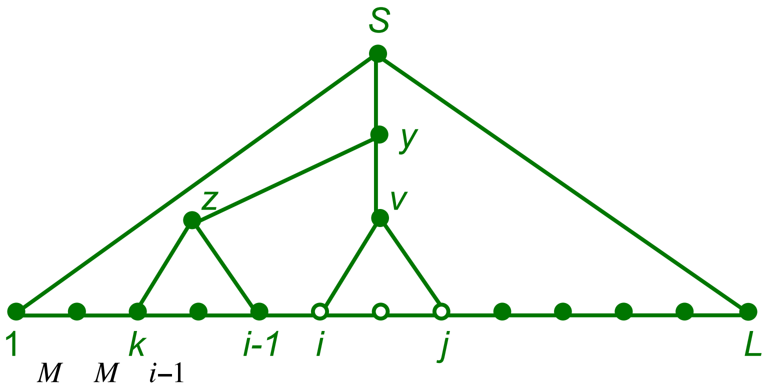
$s \rightarrow b_G\ p$
$p \rightarrow s\ b_C$
$s \rightarrow b_G\ s$
$s \rightarrow b_A\ b_A$
$b_G \rightarrow G$
$b_C \rightarrow C$
$b_A \rightarrow A$

$$\beta(2,\ 6,\ s) = t_p(s,\ b_C)\alpha(7,\ 7,\ b_C)\beta(2,\ 7,\ p)$$



The Outside Algorithm

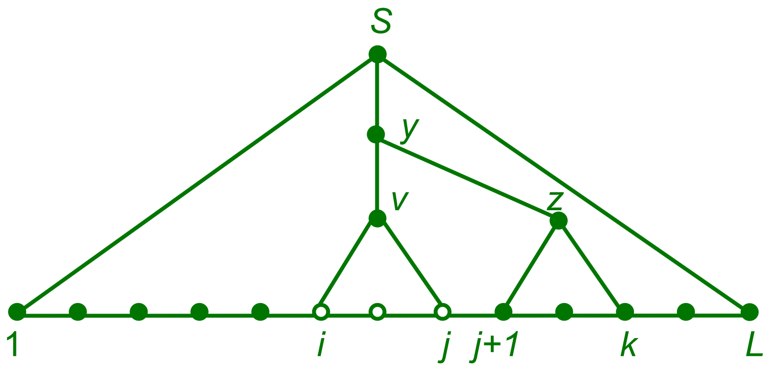
- we can recursively calculate $\beta(i, j, v)$ from β values we've calculated for y
- the first case we consider is where v is used in productions of the form: $y \rightarrow zv$



$$\sum_{y=1}^{M} \sum_{z=1}^{M} \sum_{k=1}^{i-1} t_y(z,v)\ \alpha(k,i-1,z)\ \beta(k,j,y)$$

The Outside Algorithm

- the second case we consider is where v is used in productions of the form: $y \rightarrow vz$



$$\sum_{y=1}^{M} \sum_{z=1}^{M} \sum_{k=j+1}^{L} t_y(v,z)\ \alpha(j+1,k,z)\ \beta(i,k,y)$$

The Outside Algorithm

- initialization

$$\beta(1, L, 1) = 1 \qquad \text{(the } start \text{ nonterminal)}$$

$$\beta(1, L, v) = 0 \qquad \text{for } v = 2 \text{ to } M$$

- iteration (for $i = 1$ to L, $j = L$ to i, $v = 1$ to M)

$$\beta(i, j, v) = \sum_{y=1}^{M} \sum_{z=1}^{M} \sum_{k=1}^{i-1} t_y(z, v)\ \alpha(k, i-1, z)\ \beta(k, j, y)\ +$$

$$\sum_{y=1}^{M} \sum_{z=1}^{M} \sum_{k=j+1}^{L} t_y(v, z)\ \alpha(j+1, k, z)\ \beta(i, k, y)$$

The Inside-Outside Algorithm

- we can learn the parameters of an SCFG from training sequences using an EM approach called Inside-Outside
- in the E-step, we determine
  - the expected number of times each *nonterminal* is used in parses $c(v)$
  - the expected number of times each *production* is used in parses

$$c(v \to yz)$$

$$c(v \to A)$$

- in the M-step, we update our production probabilities

The Inside-Outside Algorithm

- the EM re-estimation equations (for 1 sequence) are:

$$\hat{e}_v(A) = \frac{c(v \rightarrow A)}{c(v)} = \frac{\sum_{i \mid x_i = A} \beta(i,i,v) e_v(A)}{\sum_{i=1}^{L} \sum_{j=i}^{L} \beta(i,j,v) \alpha(i,j,v)}$$

cases where v used to generate *A*

cases where v used to generate any subsequence

$$\hat{t}_v(y,z) = \frac{c(v \rightarrow yz)}{c(v)}$$

$$= \frac{\sum_{i=1}^{L-1} \sum_{j=i+1}^{L} \sum_{k=i}^{j-1} t_v(y,z)\ \beta(i,j,v)\ \alpha(i,k,y)\ \alpha(k+1,j,z)}{\sum_{i=1}^{L} \sum_{j=i}^{L} \beta(i,j,v)\ \alpha(i,j,v)}$$

Finding the Most Likely Parse: The CYK Algorithm

- involves filling in a 3D matrix

$$\gamma(i,j,v)$$

representing the most probable parse subtree rooted at nonterminal v for the subsequence from i to j

- and a matrix for the traceback

$$\tau(i,j,v)$$

storing information about the production at the top of this parse subtree

The CYK Algorithm

- initialization (for $i = 1$ to L, $v = 1$ to M)

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

$$\tau(i,i,v) = (0,0,0)$$

- iteration (for $i = 1$ to $L - 1$, $j = i+1$ to L, $v = 1$ to M)

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

$$\tau(i,j,v) = \arg\max_{\substack{y,z \\ k=i\ldots j-1}} \{\gamma(i,k,y) + \gamma(k+1,j,z) + \log t_v(y,z)\}$$

- termination

$$\log P(x,\hat{\pi} \mid \theta) = \gamma(1,L,\ \underset{\uparrow}{1})$$

start nonterminal

The CYK Algorithm Traceback

- initialization:

```
    push $(1, L, 1)$ on the stack
```

- iteration:

```
    pop $(i, j, v)$                  // pop subsequence/nonterminal pair
    $(y, z, k) = \tau(i, j, v)$      // get best production identified by CYK
    if $(y, z, k) == (0,0,0)$        // indicating a leaf
        attach $x_i$ as the child of $v$
    else
        attach $y, z$ to parse tree as children of $v$
        push$(i, k, y)$
        push$(k+1, j, z)$
```

Comparison of SCFG Algorithms to HMM Algorithms

	HMM algorithm	**SCFG algorithm**
optimal alignment	Viterbi	CYK
probability of sequence	forward	inside
EM parameter estimation	forward-backward	inside-outside
memory complexity	$O(LM)$	$O(L^2M)$
time complexity	$O(LM^2)$	$O(L^3M^3)$