Combinatorial approaches to RNA folding
Part III: Stocastic algorithms via language theory

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2. Formal language theory. Use a formal grammar to algorithmically generate secondary structures: production rules convert symbols into strings according to the langauge's syntax.

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In this lecture, we will study the formal language theory approach.

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Also in the 1950s, the structure of DNA, the newly discovered fundamental building block of life, was finally understood.

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Assiging probabilities to the production rules defines stochastic context-free grammars (SCFG).

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A grammar is a collection of production rules that dictate how to change temporary nonterminal symbols into strings.

One begins with a (nonterminal) start symbol S, and nonterminal symbols are repeatedly turned into strings until there are no nonterminals remaining.

The language L generated by such a grammar is the set of all strings over Γ that can be generated in a finite number of steps from the start symbol S.

Notational convention

We will use

1. capital letters to denote nonterminal (temporary) symbols;
2. lower-case letters to denote terminal symbols;
3. greek-letters to denote strings of symbols.

What is a grammar?

An example

Consider the alphabet of terminal symbols $\Sigma = \{a, b\}$ and nonterminal symbols $N = \{S, A\}$ with production rules:

$$\begin{array}{rcl} S & \longrightarrow & aAa \\ A & \longrightarrow & bbA \mid bb \end{array}$$

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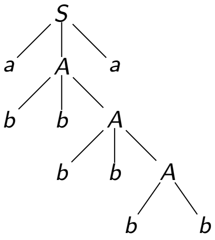
The following sequence of rules below is a derivation of the string $\alpha = abbbbbba$:

$$S \longrightarrow aAa \longrightarrow abbAa \longrightarrow abbbbAa \longrightarrow abbbbbba.$$

This grammar generates the langauge precisely the set $L = \{ab^{2n}a \mid n \geq 0\}$.

The derivation shown above of the string $\alpha = abbbbbba$ can be described by the following parse tree.



Notice that α can be read off from the tree by starting at S and "walking around" the tree in a counter-clockwise order.

This grammar is context free: no terminal symbols appear on the left-hand-side of the rules.

Regular grammars

There is a hierarchy of types of grammars (The "Chomsky heirarchy"):

grammar	language	automaton	production rules
type 3	regular	finite state automata (FSA)	$A \to a,\ A \to aB$
type 2	context-free	non-deterministic pushdown automaton	$A \to \gamma$
type 1	context-sensitive	linear bounded non-deterministic Turing machine	$\alpha A \beta \to \alpha \gamma \beta$
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- from type 3 arises hidden Markov models

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Knudsen-Hein grammar

- nonterminal symbols: $\{S, L, F\}$
- terminal symbols: $\{d, d', s\}$.

The s denotes an isolated base and (d, d') denotes a base pair.

Production rules:

$$\begin{array}{llcll}
S \longrightarrow LS & \text{with probability } p_1 & \text{or} & L & \text{with probability } q_1 \\
L \longrightarrow dFd' & \text{with probability } p_2 & \text{or} & s & \text{with probability } q_2 \\
F \longrightarrow dFd' & \text{with probability } p_3 & \text{or} & LS & \text{with probability } q_3.
\end{array}$$

An ambiguous grammar

Consider the grammar $S \longrightarrow SS|a$.

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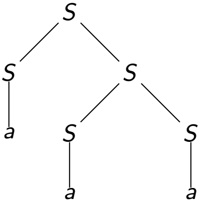
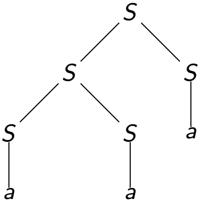
There are multiple leftmost derivations of the string aaa. Here are two possible left parse trees:





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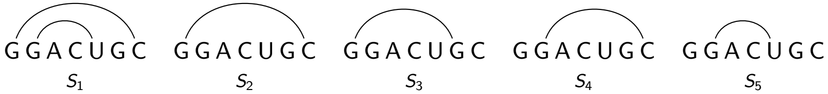
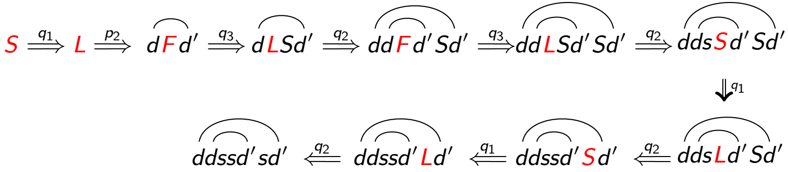
- This grammar is unambiguous.

The Knudsen-Hein grammar: an example

Consider the sequence $\mathbf{b} =$ G G A C U G C, which can fold into seven secondary structures, if one allows loop sizes of minimum length 3. In addition to the unfolded structure S_0, here are five of the six others:



Here is the derivation of the first secondary structure shown above:



$$S \xRightarrow{q_1} L \xRightarrow{p_2} dFd' \xRightarrow{q_3} dLSd' \xRightarrow{q_2} ddFd'Sd' \xRightarrow{q_3} ddLSd'Sd' \xRightarrow{q_2} ddsSd'Sd'$$

$$\Downarrow^{q_1}$$

$$ddssd'sd' \xLeftarrow{q_2} ddssd'Ld' \xLeftarrow{q_1} ddssd'Sd' \xLeftarrow{q_2} ddsLd'Sd'$$

The probability of generating this secondary structure S_1 with the Knudsen-Hein grammar is

$$P(S_1) = q_1 p_2 q_3 q_2 q_3 q_2 q_1 q_2 q_1 q_2 = p_2^2 q_1^3 q_2^3 q_3^2 \,.$$

The Knudsen-Hein grammar: another example

The following is a derivation of the structure S_2 from the previous example:

$$S \xrightarrow{q_1} L \xrightarrow{p_2} \overparen{dFd'} \xrightarrow{q_3} \overparen{dLSd'} \xrightarrow{p_1^3} \overparen{dLLLSd'} \xrightarrow{q_1} \overparen{dLLLLd'} \xrightarrow{q_2^5} \overparen{dsssssd'}$$

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Assuming that our sequence is $\mathbf{b}$ (this is a "conditional probability"), the probability of it folding into S_i is simply a weighted average:

$$P(S_i \mid \mathbf{b}) = \frac{P(S_i)}{P(S_0) + P(S_1) + P(S_2) + P(S_3) + P(S_4) + P(S_5)}.$$

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Unfortunately, *a priori*, we know neither.

The prediction problem

For example, here are the probabilties of each secondary structure conditioned on the the fixed sequence $\mathbf{b} = GGACUGC$. (Since $P(S_2|\mathbf{b}) = P(S_3|\mathbf{b}) = P(S_4|\mathbf{b})$, only one of these is listed.)

(p_1, q_1)	(p_2, q_2)	(p_3, q_3)	$P(S_0|\mathbf{b})$	$P(S_1|\mathbf{b})$	$P(S_2|\mathbf{b})$	$P(S_5|\mathbf{b})$
(.45, .55)	(.5, .5)	(.5, .5)	.01142	.45772	.07583	.30335
(.5, .5)	(.5, .5)	(.5, .5)	.02222	.35556	.08889	.35556
(.25, .75)	(.75, .25)	(.25, .75)	.00000	.98017	.00227	.01211
(.75, .25)	(.25, .75)	(.75, .25)	.64390	.00279	.04240	.22612
(.75, .25)	(.75, .25)	(.75, .25)	.07511	.07913	.04451	.7122
(.869, .131)	(.788, .212)	(.895, .105)	.25314	.00568	.01547	.69477

The prediction problem

For example, here are the probabilties of each secondary structure conditioned on the the fixed sequence $\mathbf{b} = GGACUGC$. (Since $P(S_2|\mathbf{b}) = P(S_3|\mathbf{b}) = P(S_4|\mathbf{b})$, only one of these is listed.)

(p_1, q_1)	(p_2, q_2)	(p_3, q_3)	$P(S_0\|\mathbf{b})$	$P(S_1\|\mathbf{b})$	$P(S_2\|\mathbf{b})$	$P(S_5\|\mathbf{b})$
(.45, .55)	(.5, .5)	(.5, .5)	.01142	.45772	.07583	.30335
(.5, .5)	(.5, .5)	(.5, .5)	.02222	.35556	.08889	.35556
(.25, .75)	(.75, .25)	(.25, .75)	.00000	.98017	.00227	.01211
(.75, .25)	(.25, .75)	(.75, .25)	.64390	.00279	.04240	.22612
(.75, .25)	(.75, .25)	(.75, .25)	.07511	.07913	.04451	.7122
(.869, .131)	(.788, .212)	(.895, .105)	.25314	.00568	.01547	.69477

What remains to be done:

1. Find the probability parameters. Can be done by either:
   - the Cocke-Younger-Kasami (CYK) algorithm; [HMM analogue: Vitebri algorithm]
   - the inside-outside algorithm; [HMM analgoue: forward-backward algorithm]
2. Find the most likely derivation. Done by dynamic programming.