CSCI x490 Algorithms for Computational Biology

Lecture Note 4 (by Liming Cai)

April 21, 2016

Part IV Probabilistic Models and Learning

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Probabilistic models

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Probabilistic models

- Characterization of data observable from a system

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- Expression of uncertainty of data with probability theory

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- Expression of uncertainty of data with probability theory
- Automatic learning of the system from data
- Computational inference/prediction of unknown

Part IV Probabilistic Models and Learning

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1. Parameter Re-estimation for HMMs

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2. SCFG for Co-evolution

Part IV Probabilistic Models and Learning

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Part IV Probabilistic Models and Learning

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  $P(D|\theta)$ is maximized when θ is the frequencies obtained from D.

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- How to compute $P(D, e|\theta_{old})$ and $P(D|\theta_{old})$?

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The algorithm to compute $\sum_{\pi} P(x, \pi|\theta_{old})$ is **Forward Algorithm**.

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where position j partitions the sequence x into two segments $x_{[1..j]}$ and $x_{[j+1..n]}$.

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Part IV Probabilistic Models and Learning

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  Backward Algorithm computes for suffixes instead of prefixes.

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- etc..

Part IV Probabilistic Models and Learning

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- iterate the above steps until $\frac{|P(D|\theta_{new}) - P(D|\theta_{old})|}{P(D|\theta_{old})} < \Delta$. for a given constant Δ.

Called Forward-backward algorithm.

Part IV Probabilistic Models and Learning

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Part IV Probabilistic Models and Learning

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Part IV Probabilistic Models and Learning

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- correlation patterns are limited.

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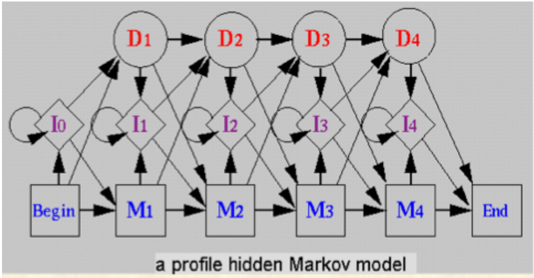

We can use a different notation for the HMM.

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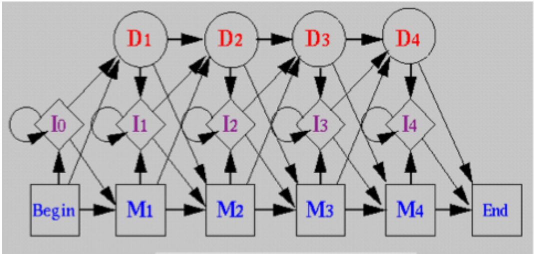

a profile hidden Markov model

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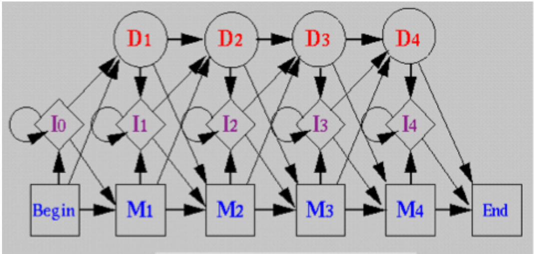

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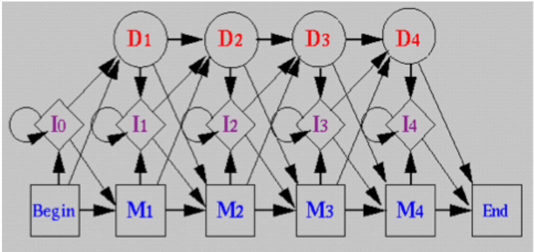

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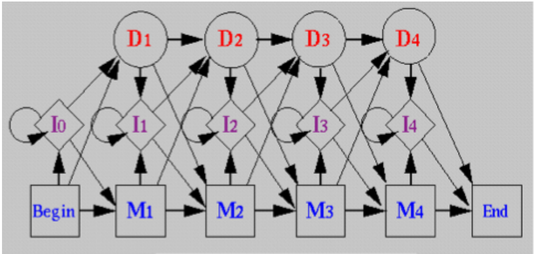

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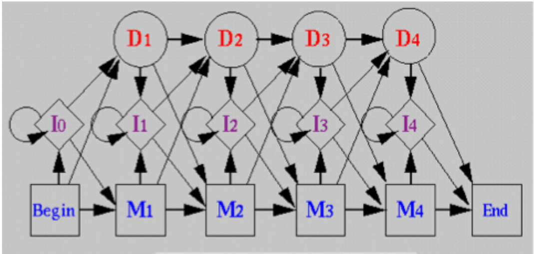

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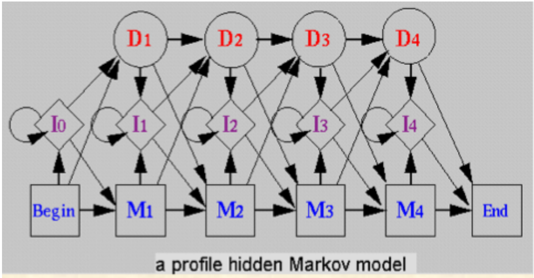

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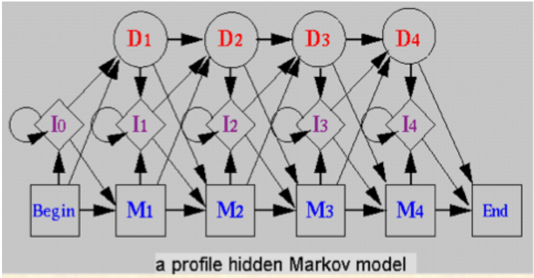

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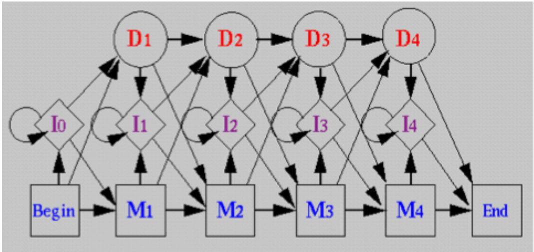

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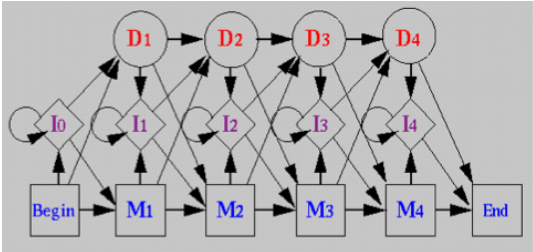

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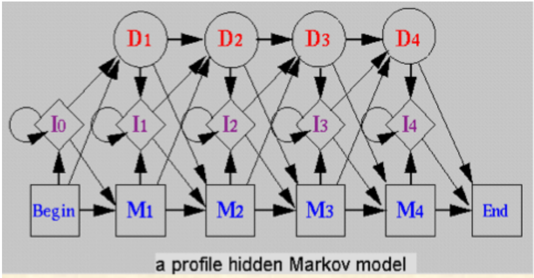

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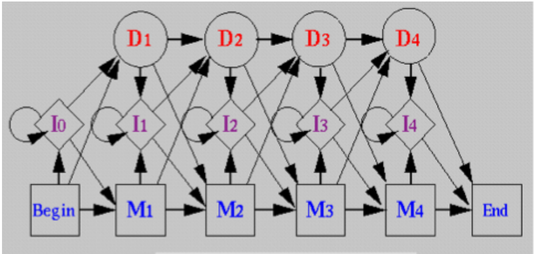

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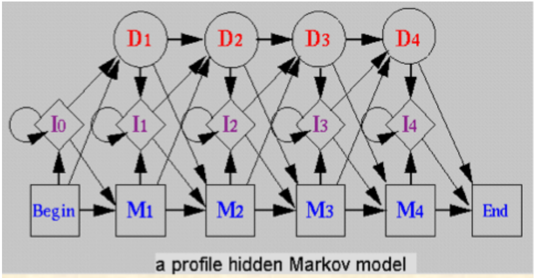
Part IV Probabilistic Models and Learning



We can use a different notation for the HMM.

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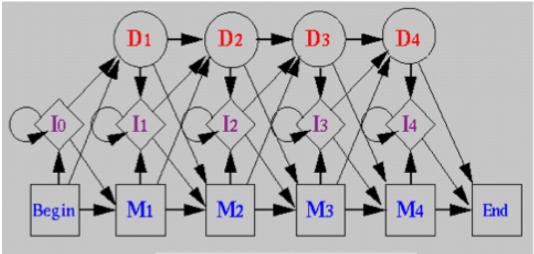
Part IV Probabilistic Models and Learning



a profile hidden Markov model

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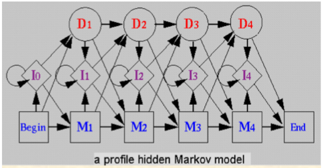
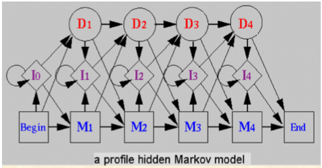
  $Begin \to D_1$
- $M_i \to eM_{i+1}$
  $M_i \to eI_i$
  $M_i \to D_{i+1}$

Part IV Probabilistic Models and Learning



sequence $acggt$

Part IV Probabilistic Models and Learning



a profile hidden Markov model

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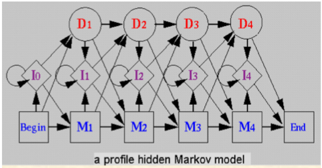
Part IV Probabilistic Models and Learning



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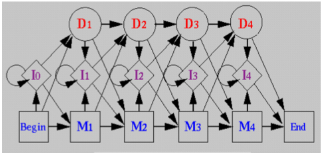
Part IV Probabilistic Models and Learning



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  $M_i \rightarrow tM_{i+1}, \quad M_i \rightarrow tI_i, \quad I_i \rightarrow tM_{i+1},$ for $i = 1, 2, 3.$
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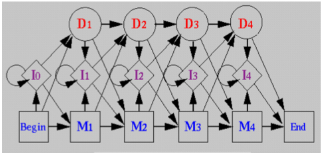
we use rules to produce $acggt$:

Part IV Probabilistic Models and Learning



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$$Begin$$

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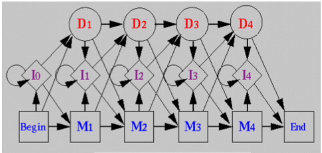

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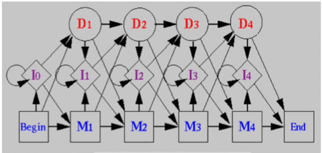
$$Begin \Rightarrow aM_1$$

Part IV Probabilistic Models and Learning



a profile hidden Markov model

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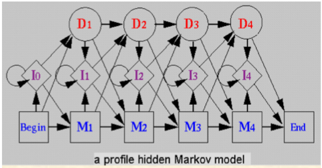
Part IV Probabilistic Models and Learning



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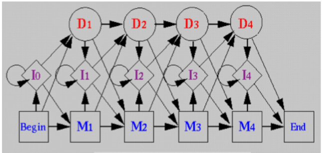

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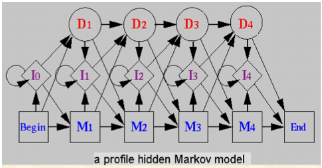
Part IV Probabilistic Models and Learning



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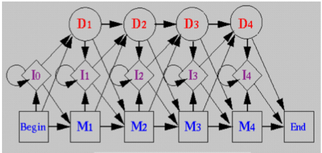
Part IV Probabilistic Models and Learning



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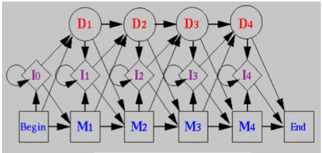

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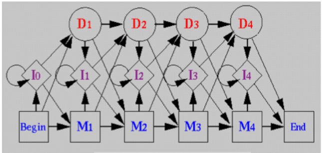
Called a **derivation**

Part IV Probabilistic Models and Learning



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Called a **derivation** $\Longleftrightarrow$ a **path** in HMM.

Part IV Probabilistic Models and Learning

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- Can rules be designed to model complex relationships among letters?

Part IV Probabilistic Models and Learning

Consider rules for RNA sequences

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- $H_i \rightarrow aH_{i+1}u$

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- a derivation an RNA sequence that folds into a stem-loop

$$H_0$$

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$$H_0 \Rightarrow aH_1u \Rightarrow agH_2cu$$

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$$\Rightarrow agaaL_4ucu$$

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  $H_i \to cH_{i+1}g$
  $H_i \to gH_{i+1}c$
  $H_i \to L_i$

  $L_i \to aL_{i+1}$
  $L_i \to cL_{i+1}$
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  $L_i \to \epsilon$ (empty)

- a derivation an RNA sequence that folds into a stem-loop

$$H_0 \Rightarrow aH_1u \Rightarrow agH_2cu \Rightarrow agaH_3ucu \Rightarrow agaL_3ucu$$

$$\Rightarrow agaaL_4ucu \Rightarrow agaaaL_5ucu$$

Part IV Probabilistic Models and Learning

Consider rules for RNA sequences

- $H_i \to aH_{i+1}u$
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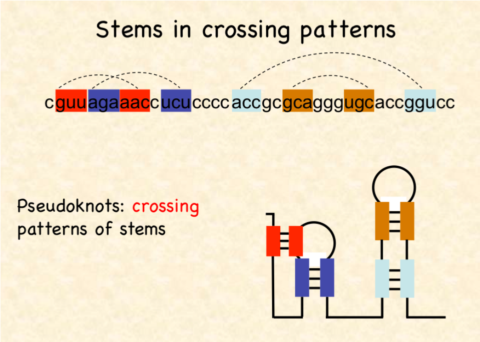
Part IV Probabilistic Models and Learning

RNA secondary structure examples:



Part IV Probabilistic Models and Learning

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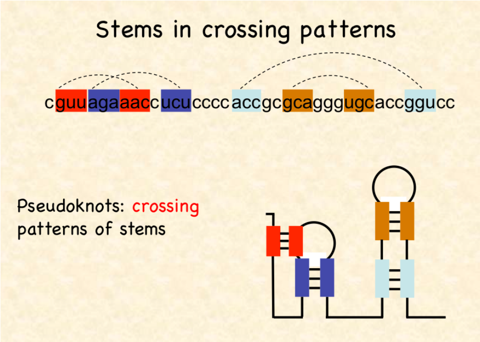

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Part IV Probabilistic Models and Learning

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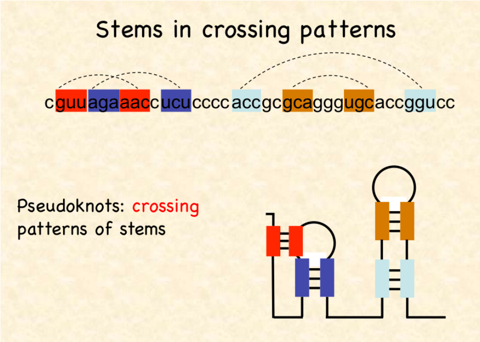
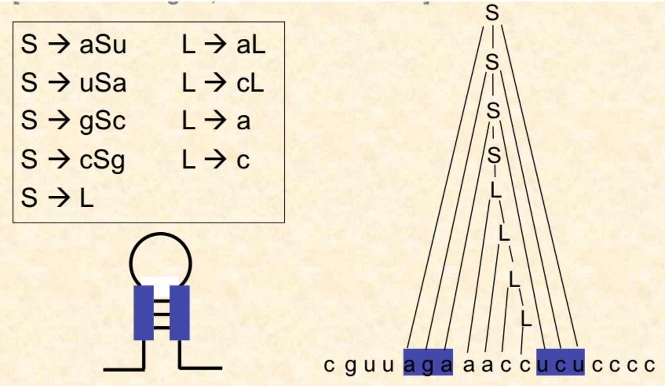


- nesting, parallel patterns are context-free, while
- crossing patterns are not!

Part IV Probabilistic Models and Learning

Illustration of context-free grammar derivation:



Part IV Probabilistic Models and Learning

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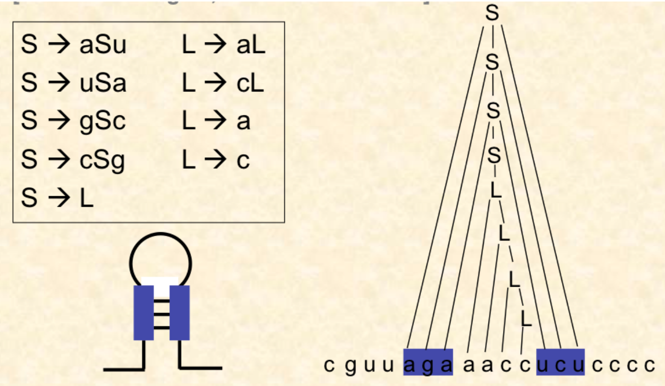

- Context-free grammar derivation is a tree (because of simultaneous emissions)

Part IV Probabilistic Models and Learning

Illustration of CFG derivation again:

1. A CFG	2. A derivation of "accuggacccuuagaggu"
S → aSu	S → aSu
S → cSg	→ acSgu
S → gSc	→ accSggu
S → uSa	→ accuSaggu
S → a	→ accuSSaggu
S → c	→ accugScSaggu
S → g	→ accuggSccSaggu
S → u	→ accuggaccSaggu
S → SS	→ accuggacccSgaggu
	→ accuggaccuSagaggu
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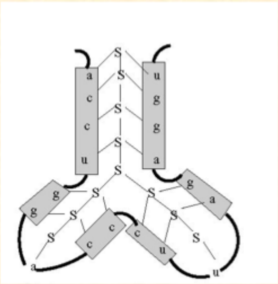

1. A CFG   2. A derivation of "accuggacccuuagaggu"   3. Corresponding structure

Part IV Probabilistic Models and Learning

S → aSu
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S → SS
→ SSS
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→ accuggaccSggu
→ ......
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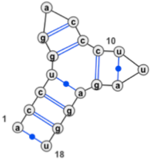
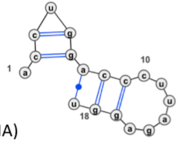


(Drawn with VARNA)



(A CFG applied on the same sequence with two alternative syntactic structures)

Part IV Probabilistic Models and Learning

Stochastic context-free grammar (SCFG):

- Probability distributions are associated with grammar rules

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π_B: $\underline{S} \Rightarrow_6 \underline{S}S \Rightarrow_1 a\underline{S}bS \Rightarrow_4 aab\underline{S} \Rightarrow_1 aaba\underline{S}b \Rightarrow_5 aababb = x$

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$$Prob(\pi_A, x) = 0.4 \times 0.4 \times 0.1 \times 0.1 = 0.016$$
$$Prob(\pi_B, x) = 0.2 \times 0.4 \times 0.1 \times 0.4 \times 0.1 = 0.0032$$

Part IV Probabilistic Models and Learning

RNA secondary structure modeling with SCFG:

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[Sakakibara et al, 1994, Eddy and Durbin 1994,
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Rivas et al, 2012]

Part IV Probabilistic Models and Learning

Stochastic grammars for (RNA) tertiary structure modeling?

Part IV Probabilistic Models and Learning

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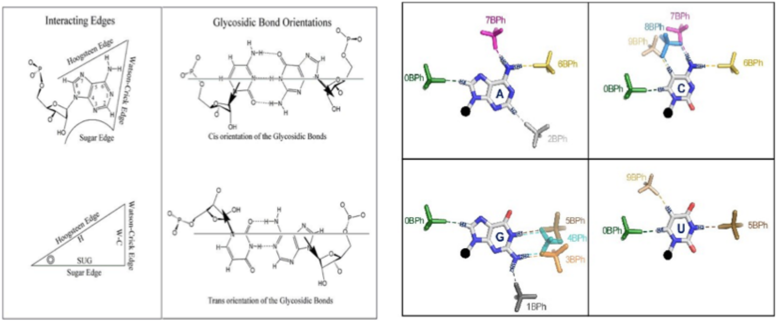
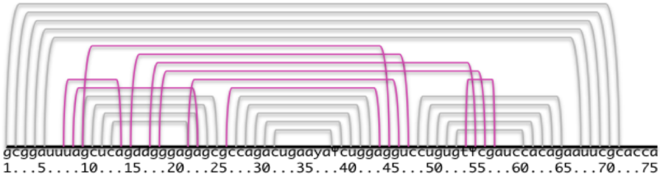


(Leontis et al, 2003; Zirbel et al, 2009. 12 base-base, 10 base-phosphate, and 10 base-ribose families)

All nucleotide interactions of a tRNA (excluding stacking)



Part IV Probabilistic Models and Learning

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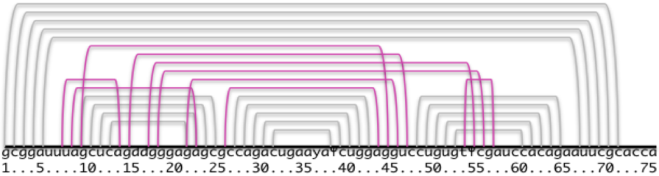

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Part IV Probabilistic Models and Learning

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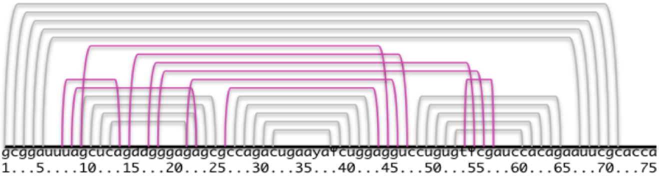

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Part IV Probabilistic Models and Learning

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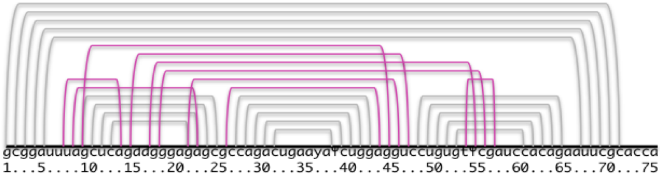

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- purple relation is context-sensitive.
- We need a higher-order model for such complex relations!

Part IV Probabilistic Models and Learning

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3. Markov networks and learning

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- Compute joint probability distribution $P(X)$ from observed random variables $X = \langle X_1, \ldots, X_n \rangle$

  Example 1: molecule residues forming structure

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  Example 2: gene networks from expression data

Part IV Probabilistic Models and Learning

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  e.g., molecule residues are random variables

    molecular structure is defined over their joint distribution, involving multi-body interactions.

    Markov network model approximates multi-body interactions with pairwise interactions.

Part IV Probabilistic Models and Learning

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Questions to answer:

Part IV Probabilistic Models and Learning

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Part IV Probabilistic Models and Learning

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Part IV Probabilistic Models and Learning

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- Can we compute G and $P_G(X)$ efficiently?

Part IV Probabilistic Models and Learning

The framework of Chow and Liu 1968:

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Part IV Probabilistic Models and Learning

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Part IV Probabilistic Models and Learning

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  1. the problem becomes computationally intractable;
  2. relying on heuristics.

Part IV Probabilistic Models and Learning

Assume we have a Markov tree T for variable $X = \{X_1, \ldots, X_n\}$ with with a root X_1

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Part IV Probabilistic Models and Learning

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- $P_T(X) = P(X_1) \prod_{i=2}^{n} P(X_i | X_{\pi(i)})$
- Minimizing $D_{KL}(P(X), P_T(X))$ would tell us what T should be.

Part IV Probabilistic Models and Learning

Kullback-Leilber divergence:

$$D_{KL}((P(X), P_T(X)) = \sum_x P(x) \log_2 \frac{P(x)}{P_T(x)}$$

Part IV Probabilistic Models and Learning

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Part IV Probabilistic Models and Learning

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Part IV Probabilistic Models and Learning

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Part IV Probabilistic Models and Learning

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continued from the previous page

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Part IV Probabilistic Models and Learning

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$$D_{KL}((P(X), P_T(X)) = -H(X) + \sum_{i=1}^{n} H(X_i) - \sum_{i=2}^{n} I(X_i, X_{\pi(i)})$$

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Part IV Probabilistic Models and Learning

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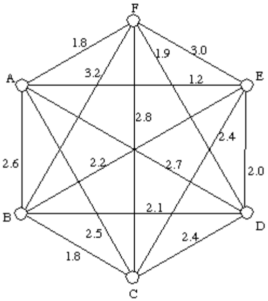
- find a maximum spanning tree T of G_X;
  (max spanning tree has the same algorithm as min spanning tree)

Part IV Probabilistic Models and Learning

Formulated complete graph:



Part IV Probabilistic Models and Learning

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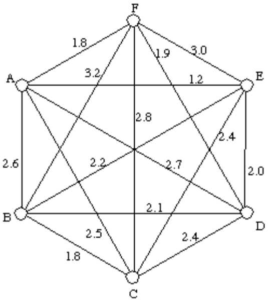
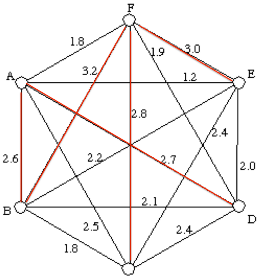


A maximum spanning tree:



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