Motif finding with Gibbs sampling

CS 466

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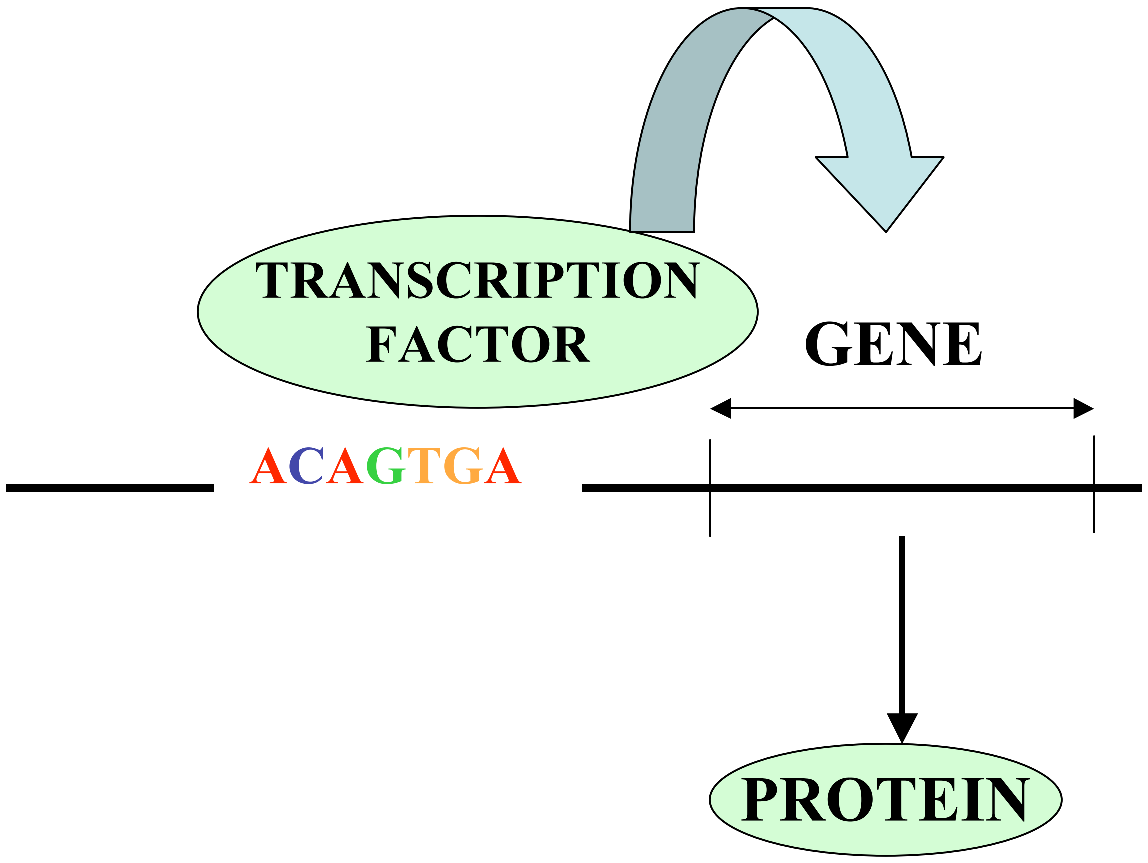
Regulatory networks

- Genes are switches, transcription factors are (one type of) input signals, proteins are outputs
- Proteins (outputs) may be transcription factors and hence become signals for other genes (switches)
- This may be the reason why humans have so few genes (the circuit, not the number of switches, carries the complexity)

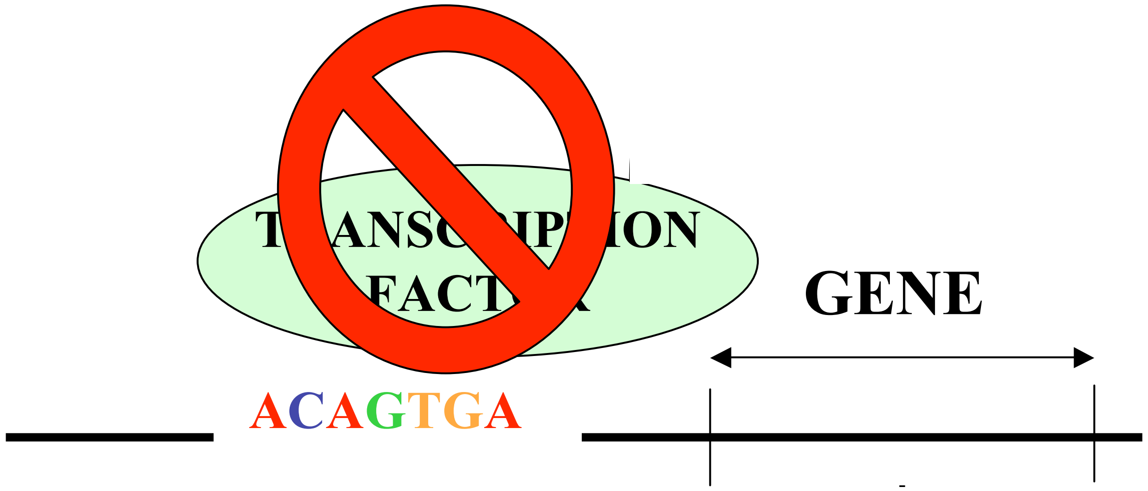
Decoding the regulatory network

- Find patterns (“motifs”) in DNA sequence that occur more often than expected by chance
  - These are likely to be binding sites for transcription factors
  - Knowing these can tell us if a gene is regulated by a transcription factor (i.e., the “switch”)

Transcriptional regulation

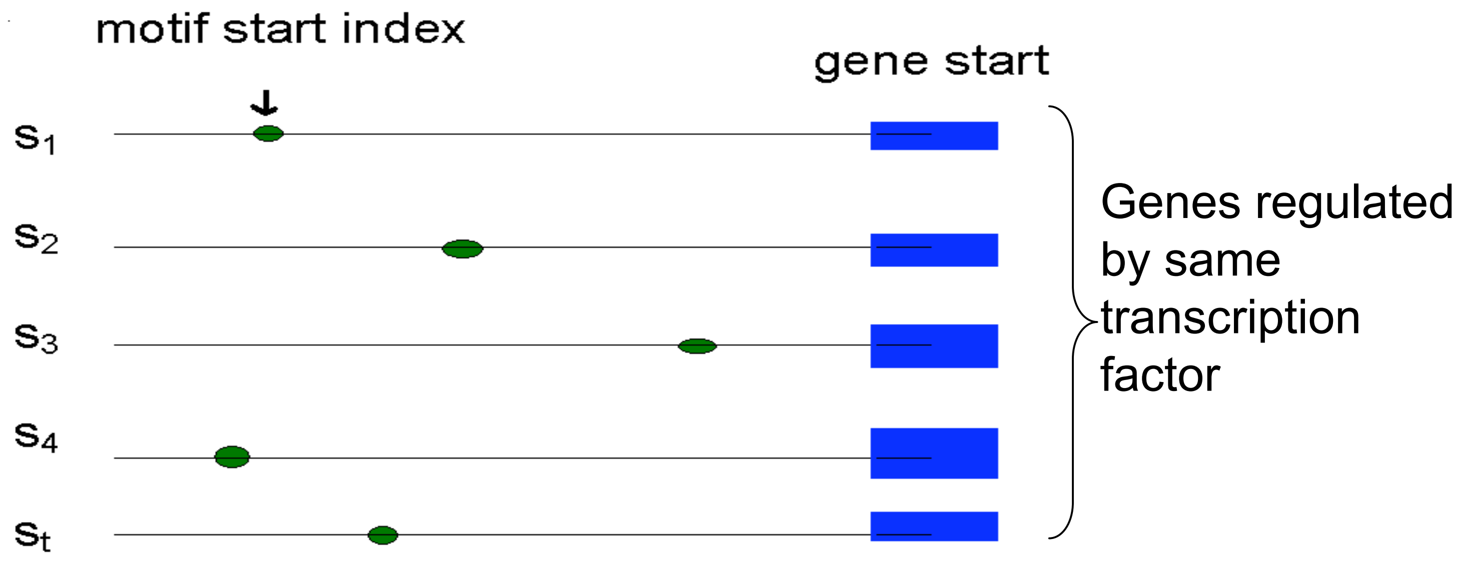


Transcriptional regulation



A motif model

- To define a motif, lets say we know where the motif starts in the sequence
- The motif start positions in their sequences can be represented as $\boldsymbol{s} = (s_1, s_2, s_3, \ldots, s_t)$



Motifs: Matrices and Consensus

```
Alignment      a G g t a c T t
               C c A t a c g t
               a c g t T A g t
               a c g t C c A t
               C c g t a c g G
              _________________
```

Matrix

A	3	0	1	0	3	1	1	0
C	2	4	0	0	1	4	0	0
G	0	1	4	0	0	0	3	1
T	0	0	0	5	1	0	1	4

```
              _________________
Consensus      A C G T A C G T
```

- Line up the patterns by their start indexes

$$\mathbf{s} = (s_1, s_2, \ldots, s_t)$$

- Construct “position weight matrix” with frequencies of each nucleotide in columns
- Consensus nucleotide in each position has the highest frequency in column

Position weight matrices

- Suppose there were t sequences to begin with
- Consider a column of a position weight matrix
- The column may be (t, 0, 0, 0)
  - A perfectly conserved column
- The column may be (t/4, t/4, t/4, t/4)
  - A completely uniform column
- “Good” profile matrices should have more conserved columns

Information Content

- In a PWM, convert frequencies to probabilities
- PWM W: $W_{\beta k}$ = frequency of base β at position k
- q_β = frequency of base β by chance
- Information content of W:

$$\sum_{k} \sum_{\beta \in \{A,C,G,T\}} W_{\beta k} \log \frac{W_{\beta k}}{q_\beta}$$

Information Content

- If $W_{\beta k}$ is always equal to q_β, i.e., if W is similar to random sequence, information content of W is 0.
- If W is different from q, information content is high.

Detecting Subtle Sequence Signals: a Gibbs Sampling Strategy for Multiple Alignment

Lawrence et al. 1993

Motif Finding Problem

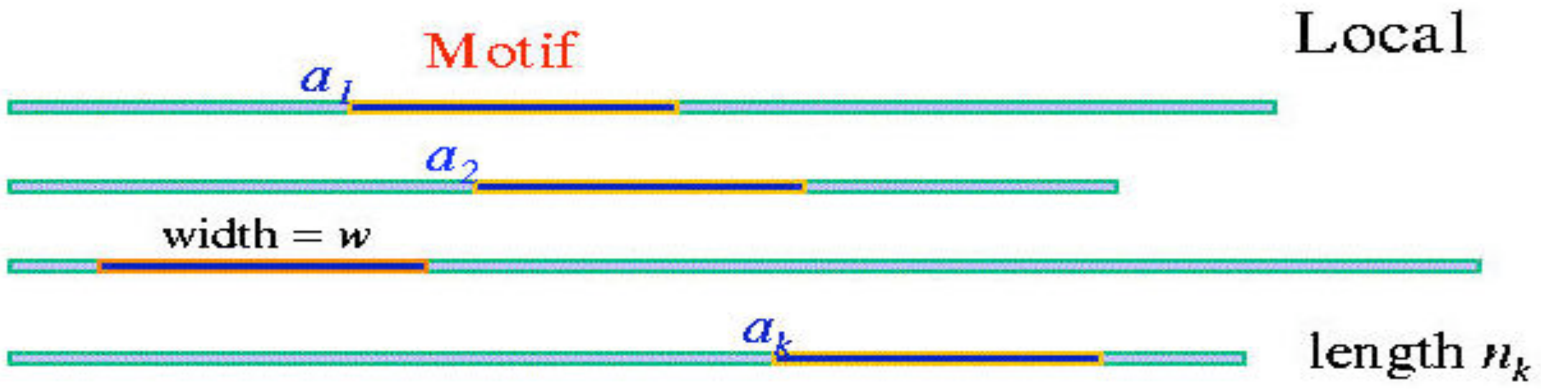
- Given a set of sequences, find the motif shared by all or most sequences, while its starting position in each sequence is unknown
- Assumption:
  - Each motif appears exactly once in one sequence
  - The motif has fixed length

Generative Model

- Suppose the sequences are aligned, the aligned regions are generated from a motif model
- Motif model is a PWM. A PWM is a position-specific multinomial distribution.
  - For each position i, a multinomial distribution on (A,C,G,T): q_{iA},q_{iC},q_{iG},q_{iT}
- The unaligned regions are generated from a background model: p_A,p_C,p_G,p_T

Notations

- Set of symbols: Σ
- Sequences: S = {S_1, S_2, …, S_N}
- Starting positions of motifs: A = {a_1, a_2, …, a_N}
- Motif model (θ) : q_{ij} = P(symbol at the i-th position = j)
- Background model: p_j = P(symbol = j)
- Count of symbols in each column: c_{ij}= count of symbol, j, in the i-th column in the aligned region



Probability of data given model

$$P(S \mid A, \theta) = \prod_{i=1}^{W} \prod_{j=1}^{|\Sigma|} q_{ij}^{c_{ij}} \qquad P(S \mid A, \theta_0) = \prod_{i=1}^{W} \prod_{j=1}^{|\Sigma|} p_{j}^{c_{ij}}$$

Scoring Function

- Maximize the log-odds ratio:

$$P(S \mid A, \theta) = \prod_{i=1}^{W} \prod_{j=1}^{|\Sigma|} q_{ij}^{c_{ij}} \qquad P(S \mid A, \theta_0) = \prod_{i=1}^{W} \prod_{j=1}^{|\Sigma|} p_{j}^{c_{ij}}$$

$$F = \log \frac{P(S \mid A, \theta)}{P(S \mid A, \theta_0)} = \sum_{i=1}^{W} \sum_{j=1}^{|\Sigma|} c_{ij} \log \frac{q_{ij}}{p_j}$$

- Is greater than zero if the data is a better match to the motif model than to the background model

Optimization and Sampling

- To maximize a function, f(x):
  - Brute force method: try all possible x
  - Sample method: sample x from probability distribution: p(x) ~ f(x)
  - Idea: suppose x_{max} is argmax of f(x), then it is also argmax of p(x), thus we have a high probability of selecting x_{max}

Markov Chain sampling

- To sample from a probability distribution p(x), we set up a Markov chain s.t. each state represents a value of x and for any two states, x and y, the transitional probabilities satisfy:

$$p(x)\Pr(x \to y) = p(y)\Pr(y \to x)$$

- This would then imply that if the Markov chain is "run" for "long enough", the probability thereafter of being in state x will be p(x)

$$\lim_{N\to\infty} \frac{1}{N} C(x) = p(x)$$

Gibbs sampling to maximize F

- Gibbs sampling is a special type of Markov chain sampling algorithm
- Our goal is to find the optimal $A = (a_1,\ldots a_N)$
- The Markov chain we construct will only have transitions from A to alignments A' that differ from A in only one of the a_i
- In round-robin order, pick one of the a_i to replace
- Consider all A' formed by replacing a_i with some other starting position a_i' in sequence S_i
- Move to one of these A' probabilistically
- Iterate the last three steps

Algorithm

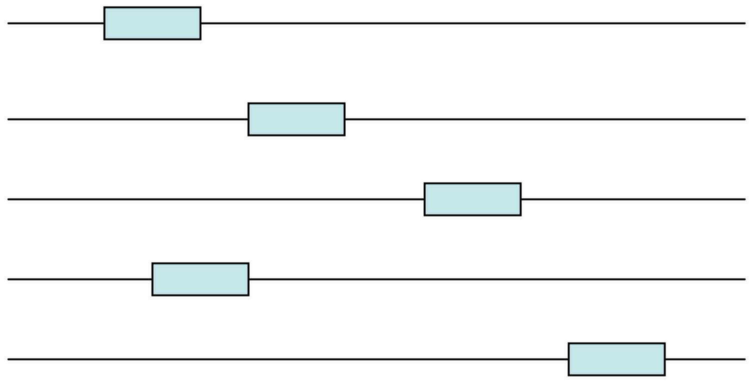
```
Randomly initialize $A^0$;
Repeat:
   (1) randomly choose a sequence z from S;
       $A^* = A^t \setminus a_z$; compute $\theta^t$ from $A^*$;   $q_{ij} = \frac{c_{ij}}{\sum_k c_{ik}}$
   (2) sample $a_z$ according to $P(a_z = x)$, which is
       proportional to $Q_x/P_x$; update $A^{t+1} = A^* \cup x$;

Select $A^t$ that maximizes F;
```

Q_x: the probability of generating x according to θ^t;

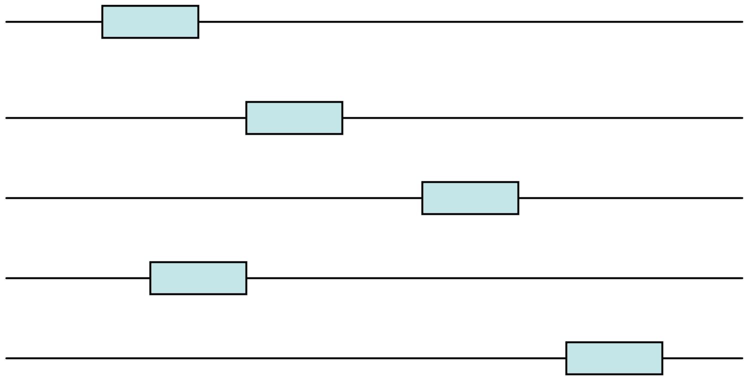
P_x: the probability of generating x according to the background model

Algorithm



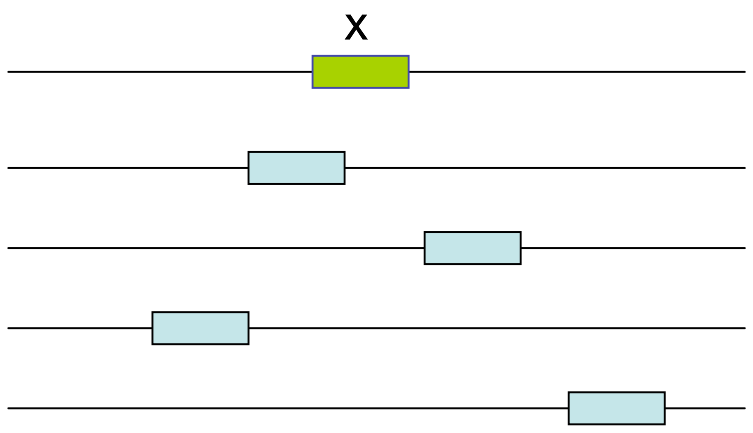
Current solution A^t

Algorithm



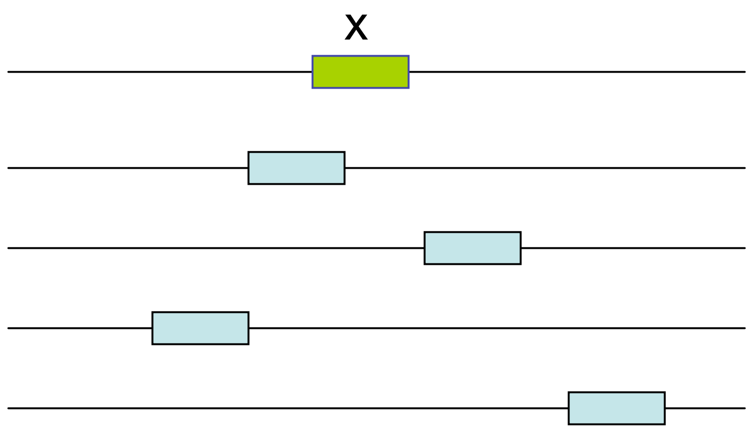
Choose one a_z to replace

Algorithm



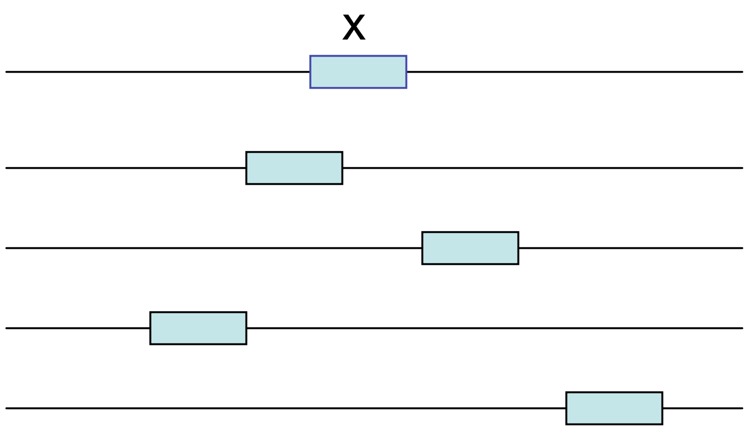
For each candidate site x in sequence z, calculate Q_x and P_x: Probabilities of sampling x from motif model and background model resp.

Algorithm



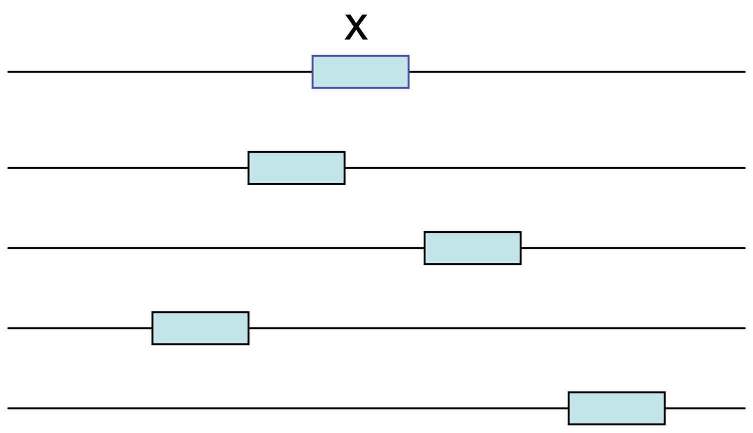
Among all possible candidates, choose one (say x) with probability proportional to Q_x/P_x

Algorithm



Set $A^{t+1} = A^* \cup x$

Algorithm



Repeat

Local optima

- The algorithm may not find the “global” or true maximum of the scoring function

- Once “A^t” contains many similar substrings, others matching these will be chosen with higher probability

- Algorithm will “get locked” into a “local optimum”
  - all neighbors have poorer scores, hence low chance of moving out of this solution