I529: Machine Learning in Bioinformatics (Spring 2013)

MCMC: Markov Chain Monte Carlo

Yuzhen Ye
School of Informatics and Computing
Indiana University, Bloomington
Spring 2013

Contents

Review: 1st order Markov chain

*An **integer time stochastic process**, consisting of a set of **m>1** states $\{s_1,...,s_m\}$ and*

1. *An **m** dimensional **initial distribution vector** ($p(s_1),..,p(s_m)$)*
2. *An **m×m transition probabilities matrix M=** ($a_{s_i s_j}$)*

For example, for DNA sequence:
the states are {A, C, T, G} (m=4)
p(A) the probability of A to be the 1st letter
a_{AG} the probability that G follows A in a sequence.

Motivating problems for MCMC

- The integration operation that plays a fundamental role in Bayesian statistics
  - For calculating the normalizing constant
  - Marginal distribution
  - Expectation
- MCMC, first introduced by Metropolis (1953), provides an alternative whereby we sample from the posterior directly, and obtain sample estimates of the quantities of interest

Sampling and optimization

- 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 a maximum of f(x), then it is also maximum of p(x), thus we have a high probability of sampling x_{max}

Monte Carlo simulation

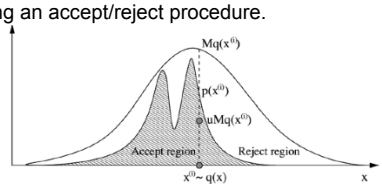
- The idea of Monte Carlo simulation is to draw an i.i.d set of N samples from a target density p(x) defined on a high-dimensional space X.

$$I_N(f) = \frac{1}{N}\sum_{i=1}^{N} f(x^{(i)}) \overrightarrow{N \to \infty} I(f) = \int_X f(x)p(x)dx$$

- The N samples can also be used to obtain a maximum of the objective function p(x)

Rejection sampling

- Sample from a distribution p(x), which is known up to a proportionality constant, by sampling from another easy-to-sample proposal distribution q(x) that satisfies p(x) <= Mq(x), using an accept/reject procedure.

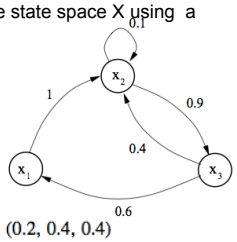


Ref: An introduction to MCMC for Machine Learning, 2003

MCMC algorithms

When samples cannot be drawn from p(x) directly but p(x) can be evaluated up to a normalizing constant, MCMC can be used, which is a strategy for generating samples x while exploring the state space X using a Markov chain mechanism.

$$T = \begin{bmatrix} 0 & 1 & 0 \\ 0 & 0.1 & 0.9 \\ 0.6 & 0.4 & 0 \end{bmatrix}$$



$\mu(x^{(1)}) = (0.5, 0.2, 0.3)$

$\mu(x^{(1)})T = (0.2, 0.6, 0.2)$

$\mu(x^{(1)})T^t$ converges to $p(x) = (0.2, 0.4, 0.4)$

MCMC: basics

- Any Markov chain which is irreducible and aperiodic will have a unique stationary distribution.
  - Irreducibility: from any state of the Markov chain, there is a positive probability of visiting all other states (i.e., the transition matrix cannot be reduced to separate smaller matrices).
  - Aperiodicity: the chain should not get trapped in cycles
- From any starting point, the chain will converge to the invariant distribution p(x), as long as T is a stochastic transition matrix that have the two properties: irreducibility & aperiodicity.
- MCMC samplers are irreducible and aperiodic Markov chains that have the target distribution a the invariant distribution

MCMC approaches

- The Metropolis-Hastings (MH) algorithm
  - The MH algorithm is the most popular MCMC method
  - Most practical MCMC algorithms can be interpreted as special cases or extensions of this algorithm
- Simulated annealing for global optimization
- Mixtures and cycles of MCMC kernels
  - It is possible to combine several samplers into mixtures and cycles of the individual samplers
- **The Gibbs sampler**

The motif finding problem

- Given a set of DNA sequences:

```
cctgatagacgctatctggctatccacgtacgtaggtcctctgtgcgaatctatgcgtttccaaccat
agtactggtgtacatttgatacgtacgtacaccggcaacctgaaacaaacgctcagaaccagaagtgc
aaacgtacgtgcaccctctttcttcgtggctctggccaacgagggctgatgtataagacgaaaatttt
agcctccgatgtaagtcatagctgtaactattacctgccacccctattacatcttacgtacgtataca
ctgttatacaacgcgtcatggcggggtatgcgttttggtcgtcgtacgctcgatcgttaacgtacgtc
```

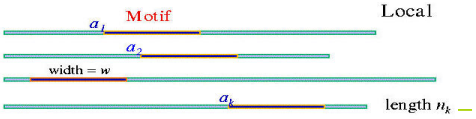
- Find the motif in each of the individual sequences

The motif finding problem

- If starting positions **s**=(s_1, s_2,… s_t) are given, finding consensus is easy because we can simply construct (and evaluate) the profile to find the motif.
- But… the starting positions **s** are usually not given. How can we find the "best" profile matrix?
  - Gibbs sampling
  - Expectation-Maximization algorithm

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 (θ_0): 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 motif instances



Motif finding problem

- Problem: find starting positions and model parameters simultaneously to maximize the posterior probability:

$$\max_{\theta,A} P(\theta, A \mid S)$$

- This is equivalent to maximizing the likelihood by Bayes' Theorem, assuming a uniform prior distribution over different models:

$$\max_{\theta,A} P(S \mid A, \theta)$$

Equivalent scoring function

- Maximize the log-odds ratio:

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

Motif model (θ) : q_{ij} = P(symbol at the i-th position = j)
Background model (θ_0): p_j = P(symbol = j)
c_{ij}: #(symbol j at position i)

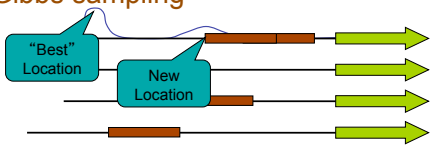
$$F = \log\frac{P(S \mid A,\theta)}{P(S \mid A,\theta_0)} = \sum_{i=1}^{W}\sum_{j=1}^{|\Sigma|} c_{ij}\log\frac{q_{ij}}{p_j}$$

Log of the ratio

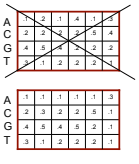
Gibbs sampling

- Idea: a joint distribution in a high dimension may be hard to sample from, but it may be easy to sample from the conditional distributions where all variables are fixed except one
- To sample from p(x_1, x_2, …x_n), let each state of the Markov chain represent (x_1, x_2, …x_n), the probability of moving to a state (x_1, x_2, … x_n) is: p(x_i |x_1, …x_{i-1},x_{i+1},…x_n). It is a algorithm in a class of sampling techniques called *Markov Chain Monte Carlo (MCMC)* method.

Gibbs sampling



- Start with random motif locations and calculate a motif model
- Randomly select a sequence, remove its motif and recalculate temporary model
- With temporary model, calculate probability of motif at each position on sequence
- **Select new position based on this distribution**
- Update model and Iterate



ETC…

Gibbs sampling

Initialization, t=0, sample $\left(x_1^{(0)}, x_2^{(0)}, x_3^{(0)}, \ldots, x_n^{(0)}\right)$

$$x_1^{(t+1)} \sim P\left(x_1 \mid x_2^{(t)}, x_3^{(t)}, \ldots, x_n^{(t)}\right)$$

$$x_2^{(t+1)} \sim P\left(x_2 \mid x_1^{(t+1)}, x_3^{(t)}, \ldots, x_n^{(t)}\right)$$

$$x_3^{(t+1)} \sim P\left(x_2 \mid x_1^{(t+1)}, x_2^{(t+1)}, x_4^{(t)}, \ldots, x_n^{(t)}\right)$$

…,…

$$x_n^{(t+1)} \sim P\left(x_n \mid x_1^{(t+1)}, x_3^{(t+1)}, \ldots, x_{n-1}^{(t+1)}\right)$$

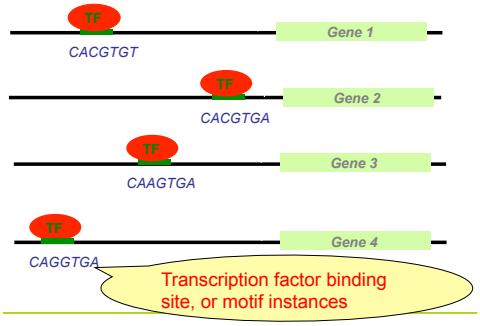
Estimator of θ

- Given an alignment A, i.e. the starting positions of motifs, θ can be estimated by its MLE with prior probabilities (e.g. Dirichlet prior with parameter b_j):

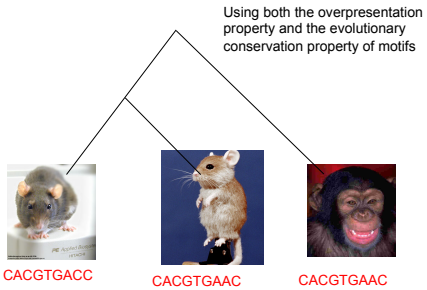
$$q_{ij} = \frac{c_{ij} + b_j}{N - 1 + B}$$

where $B=\Sigma_j b_j$

Finding TF binding sites



Sampling motifs on trees



Ref: Sampling motifs on phylogenetic trees, Li & Wong, PNAS, 2005

Implementation: Initialization

Initialization

Parameters are sampled using prior distributions;

Motif instances in current species are sampled from sequences directly for each current species;

Motif instances in ancestral species are randomly assigned with one of its immediate child motif instances.

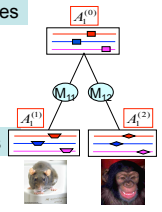
Motif instance updating

Updating motif instances in ancestral species

$$\Pr(A_i^{(0)} \mid A_{[-i]}^{(0)}, A_i^{(1)}, A_i^{(2)}, \Theta_0, p_1, p_2, w, M_{11}, M_{12})$$

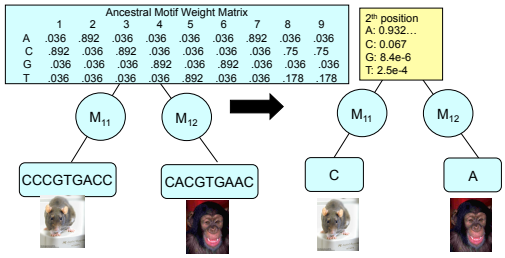
Updating motif instances in current species

$$\Pr(A_i^{(1)} \mid A_i^{(0)}, S, \Theta_0, p_1, w, M_{11})$$



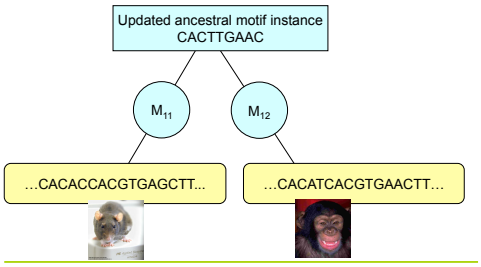
Motif instance updating

Updating motif instance in ancestral species



Motif instance updating

Updating motif instances for current species



Parameter sampling step

- Metropolis-Hasting algorithm is used to increase or decrease the width w of the motif by 1 from the left or right side

Other applications of Gibbs sampling

- Biclustering microarray data by Gibbs sampling
  - Microarray data is discretized
  - Bioinformatics, 2003
- Assignment of ambiguously mapped reads
  - Bioinformatics, 2010

Practical implementation issues

- How many iterations?
- One run or many?