MCMC: Markov Chain Monte Carlo

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Review: 1^{st} order Markov chain

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

1. *An* ***m*** *dimensional* ***initial distribution vector*** $(p(s_1), \ldots, p(s_m))$
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 1^{st} *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

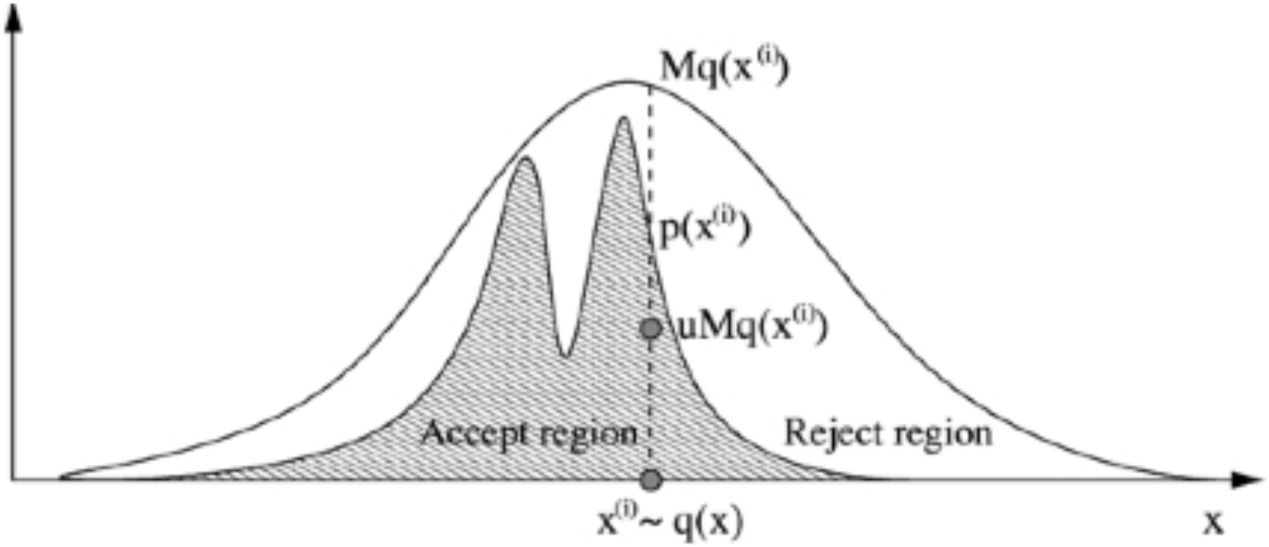
- The idea of Monte Carlo simulation is to draw an i.i.d set of N samples from a target density p(x) defined on a high-dimensional space X.

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

- 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

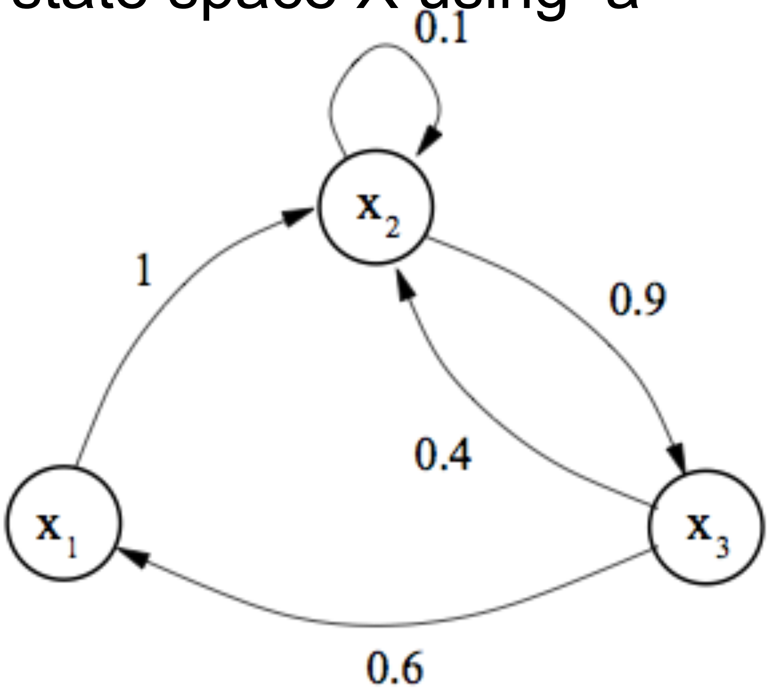
When samples cannot be drawn from p(x) directly but p(x) can be evaluated up to a normalizing constant, MCMC can be used, which is a strategy for generating samples x while exploring the state space X using a Markov chain mechanism.

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

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

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

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



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
```

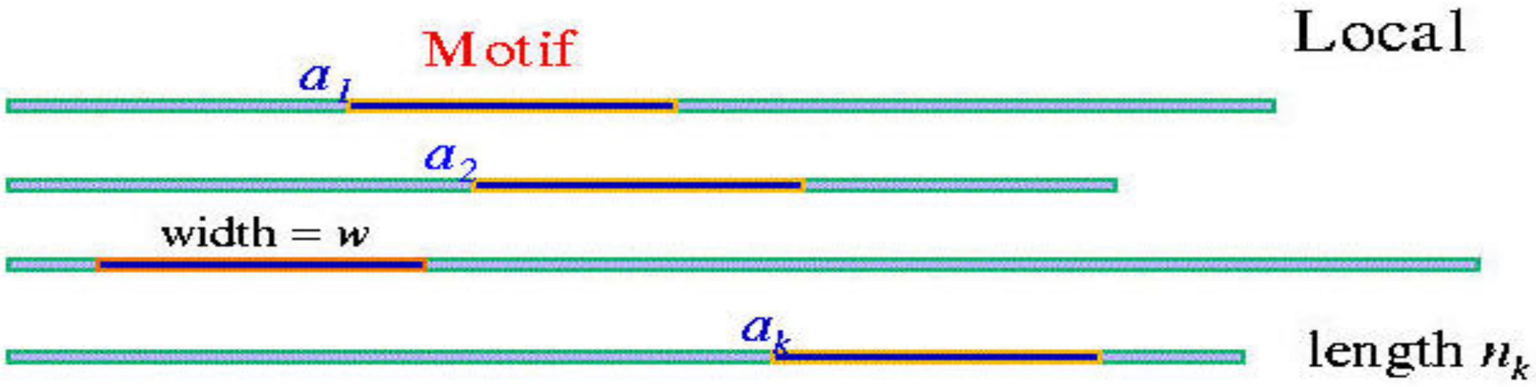
- Find the motif in each of the individual sequences

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: $S = \{S_1, S_2, \ldots, S_N\}$
- Starting positions of motifs: $A = \{a_1, a_2, \ldots, a_N\}$
- 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:

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

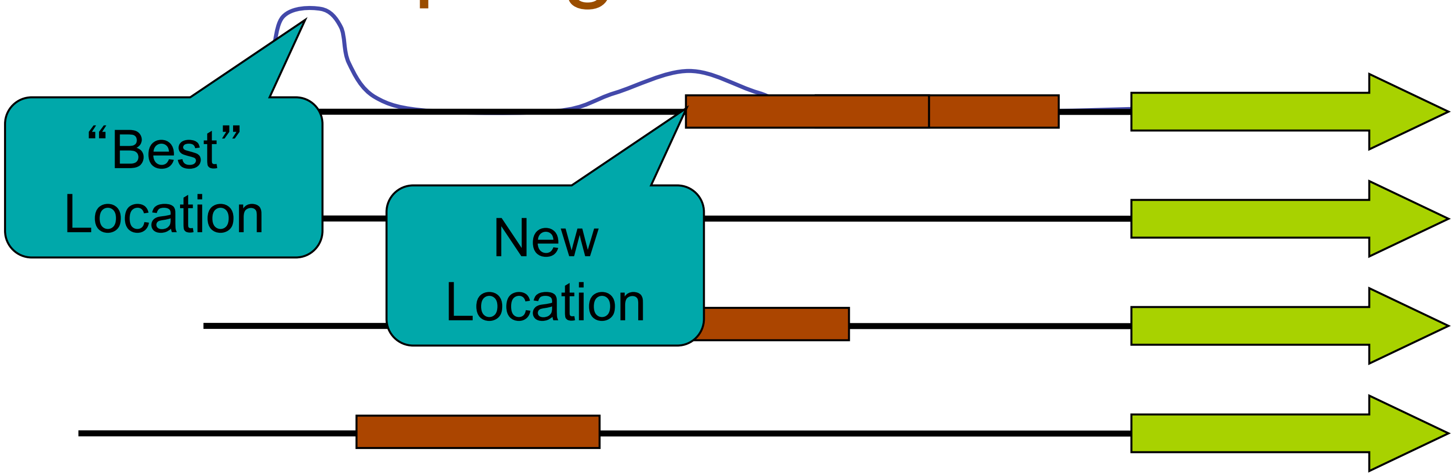
Motif model (θ) : q_{ij} = P(symbol at the i-th position = j)
Background model (θ_0): p_j = P(symbol = j)
c_{ij}: #(symbol j at position i)

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

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 $p(x_1, x_2, \ldots x_n)$, let each state of the Markov chain represent $(x_1, x_2, \ldots x_n)$, the probability of moving to a state $(x_1, x_2, \ldots x_n)$ is: $p(x_i \mid x_1, \ldots x_{i-1}, x_{i+1}, \ldots x_n)$. It is a algorithm in a class of sampling techniques called *Markov Chain Monte Carlo (MCMC)* method.

Gibbs sampling



“Best” Location

New Location

- 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

A	~~.1~~	~~.2~~	~~.1~~	~~.4~~	~~.1~~	~~.3~~
C	~~.2~~	~~.2~~	~~.2~~	~~.2~~	~~.5~~	~~.4~~
G	~~.4~~	~~.5~~	~~.4~~	~~.2~~	~~.2~~	~~.2~~
T	~~.3~~	~~.1~~	~~.2~~	~~.2~~	~~.2~~	~~.1~~

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

ETC…

Gibbs sampling

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

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

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

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

$$\ldots,\ldots$$

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

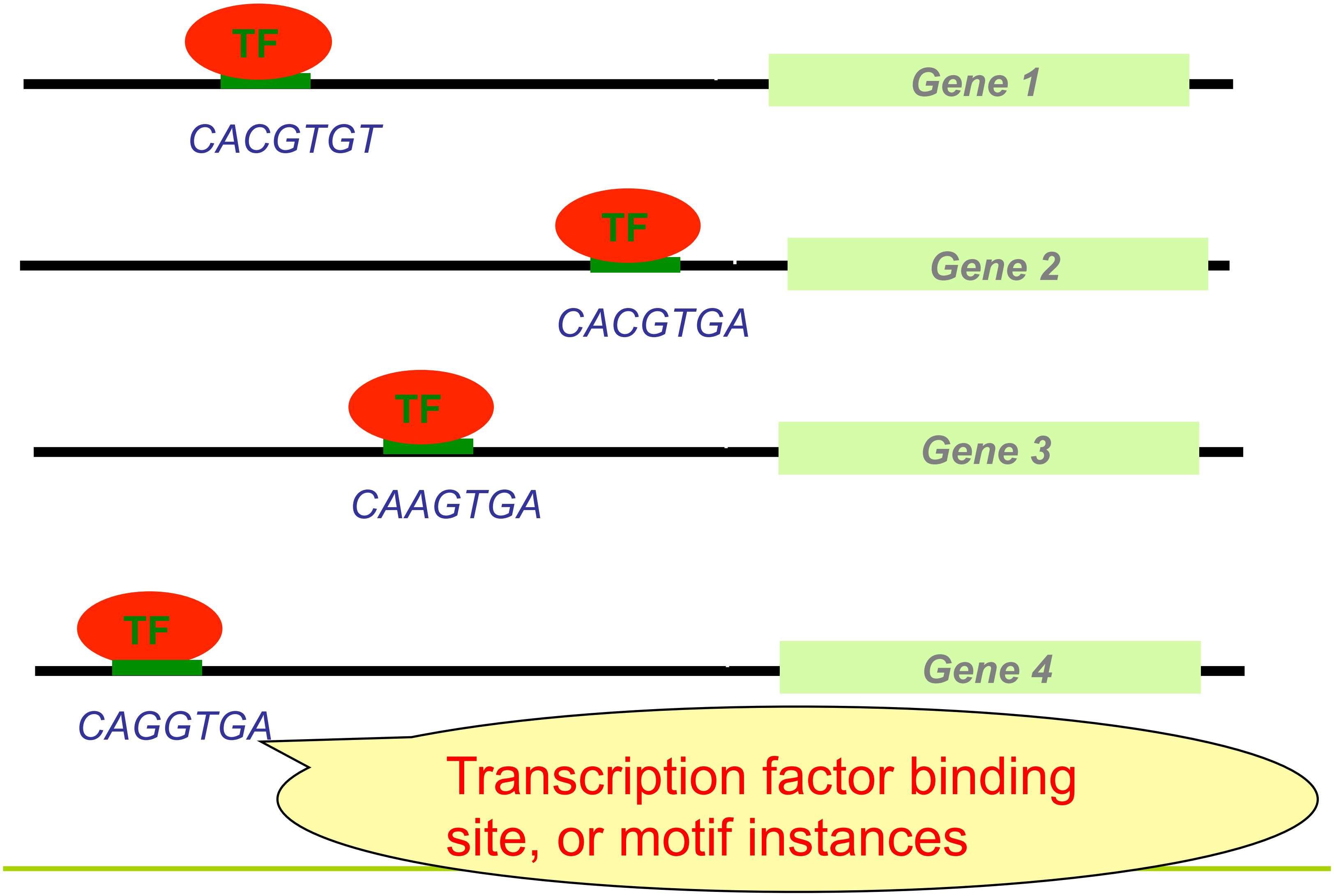
Estimator of θ

- 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 $B=\Sigma_j b_j$

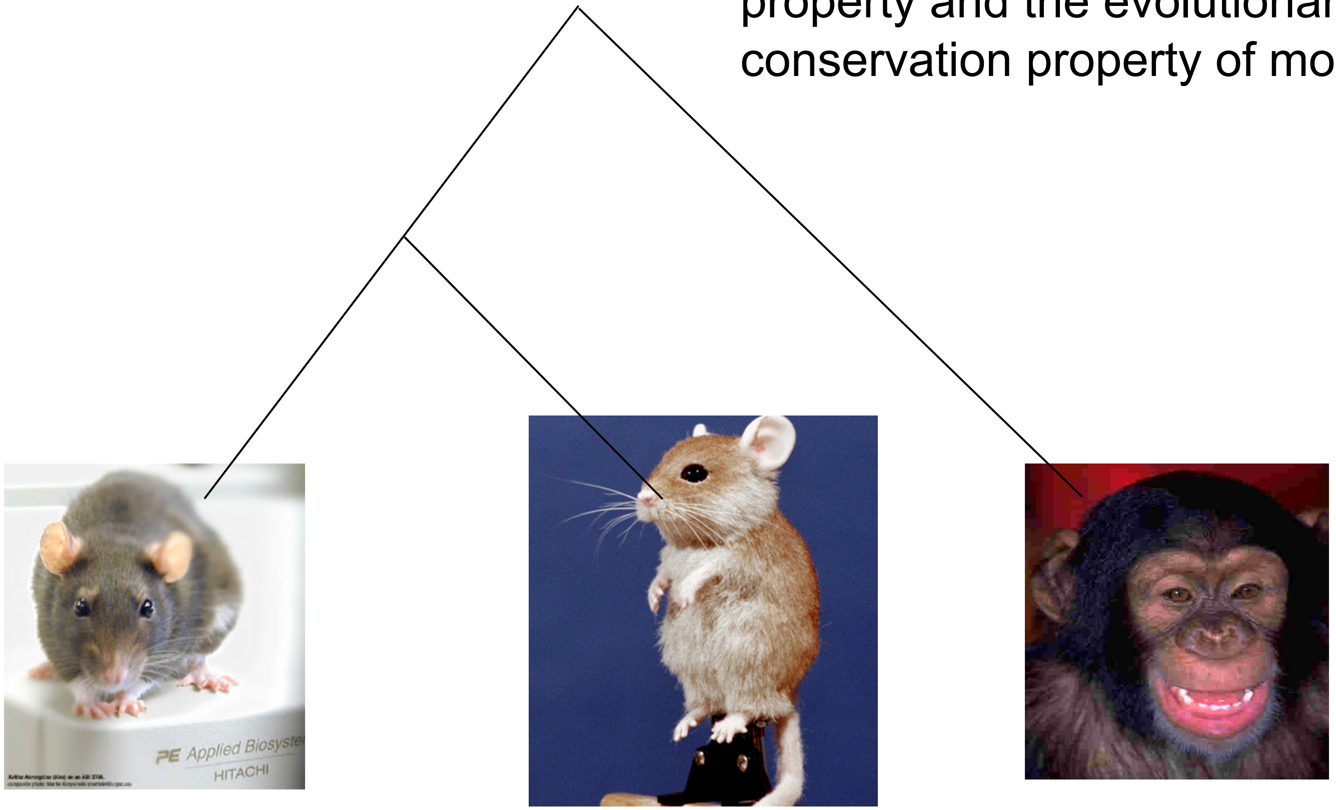
Finding TF binding sites



Transcription factor binding site, or motif instances

Sampling motifs on trees

Using both the overpresentation property and the evolutionary conservation property of motifs



CACGTGACC

CACGTGAAC

CACGTGAAC

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

Implementation: Initialization

Initialization

Parameters are sampled using prior distributions;

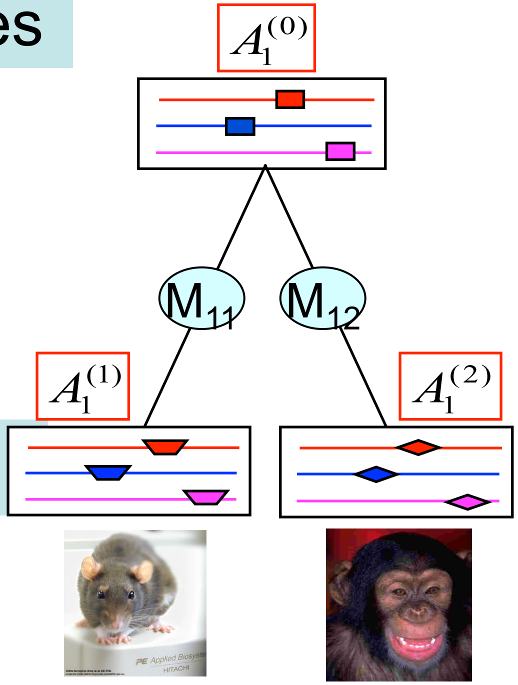
Motif instances in current species are sampled from sequences directly for each current species;

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

$$\Pr(A_1^{(0)} \mid A_{[-1]}^{(0)}, A_1^{(1)}, A_1^{(2)}, \Theta_0, p_1, p_2, w, M_{11}, M_{12})$$

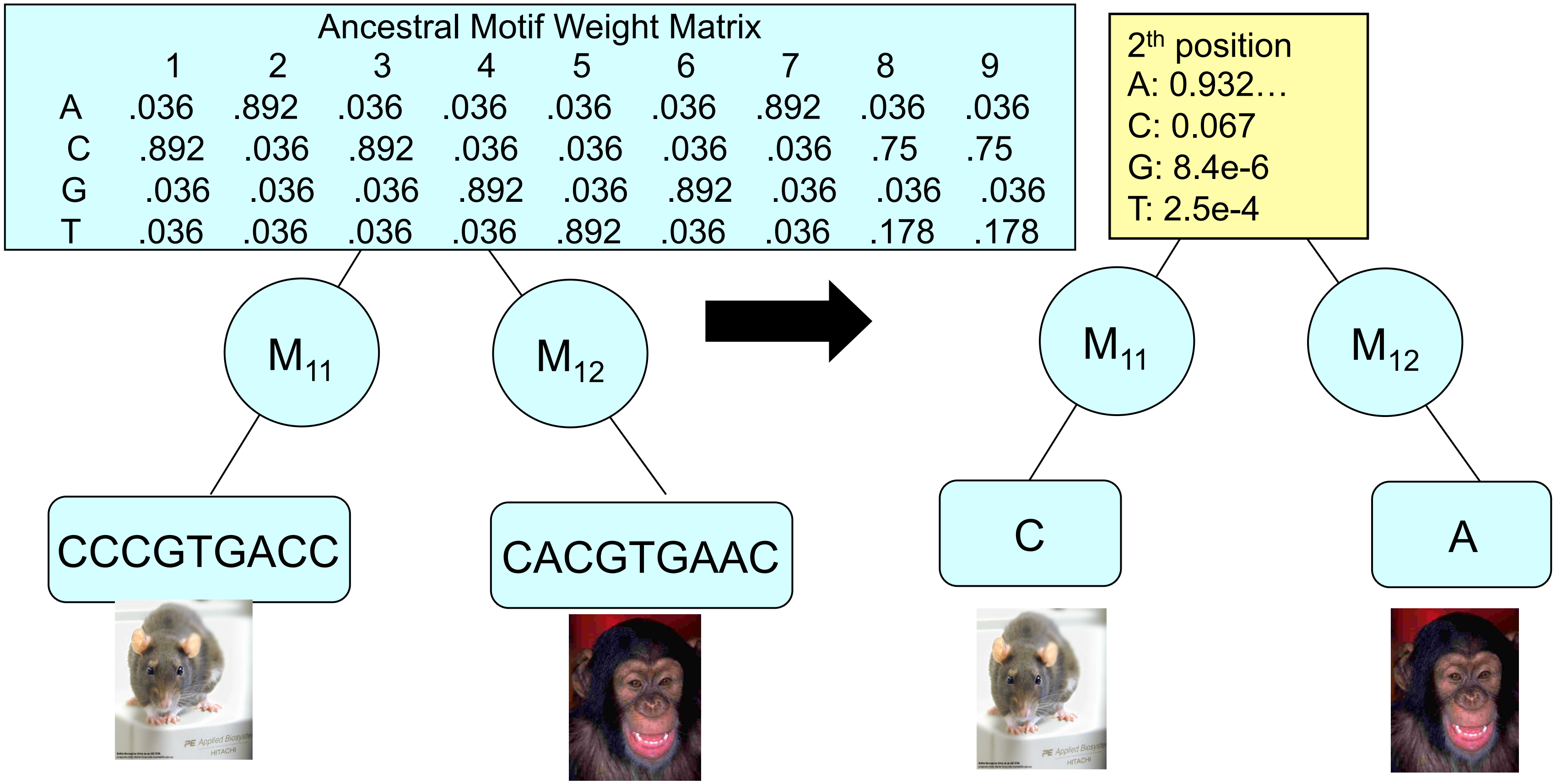


Updating motif instances in current species

$$\Pr(A_1^{(1)} \mid A_1^{(0)}, S, \Theta_0, p_1, w, M_{11})$$

Motif instance updating

Updating motif instance in ancestral species



Ancestral Motif Weight Matrix

	1	2	3	4	5	6	7	8	9
A	.036	.892	.036	.036	.036	.036	.892	.036	.036
C	.892	.036	.892	.036	.036	.036	.036	.75	.75
G	.036	.036	.036	.892	.036	.892	.036	.036	.036
T	.036	.036	.036	.036	.892	.036	.036	.178	.178

M_{11}

M_{12}

CCCGTGACC

CACGTGAAC

2th position
A: 0.932…
C: 0.067
G: 8.4e-6
T: 2.5e-4

M_{11}

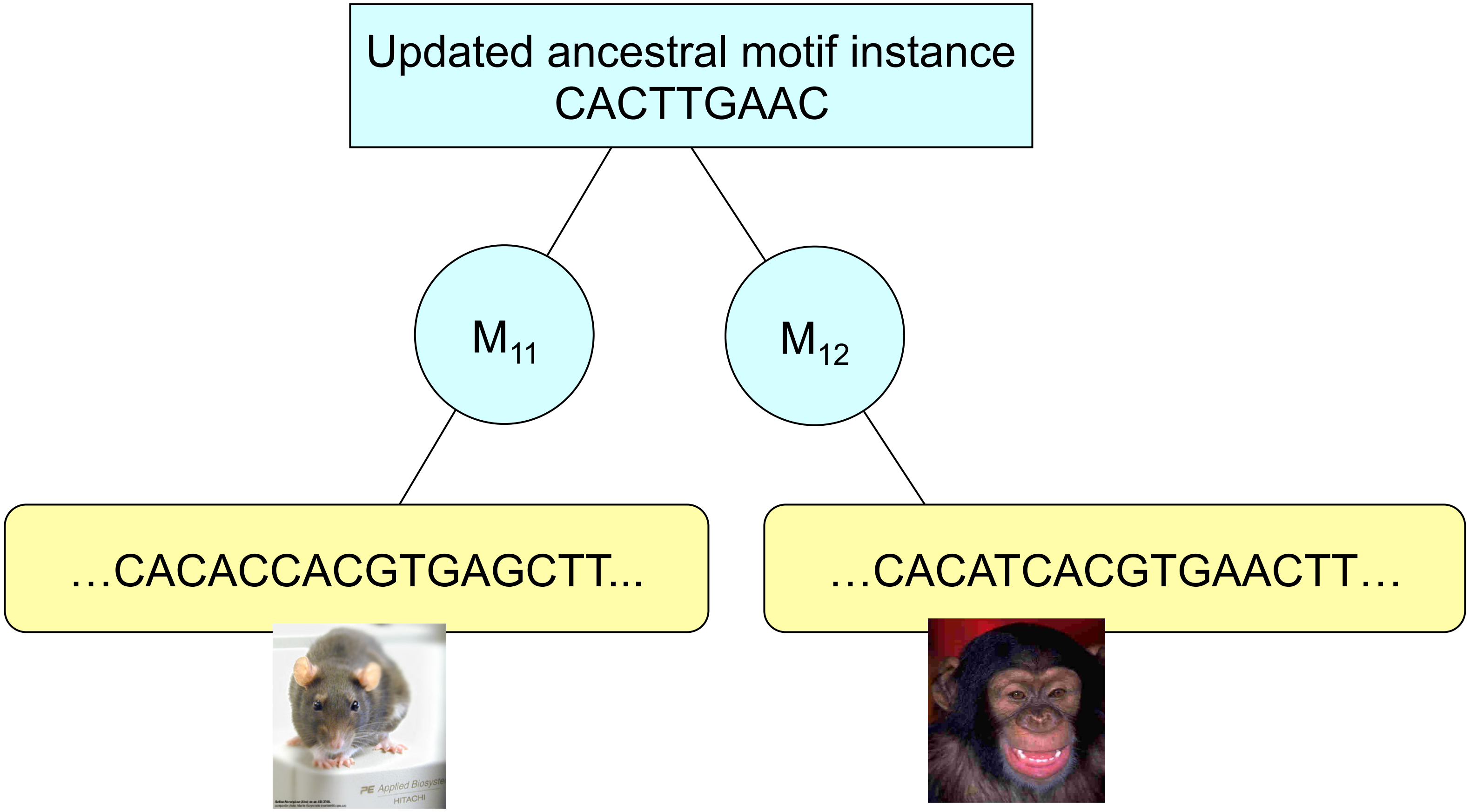
M_{12}

C

A

Motif instance updating

Updating motif instances for current species



Updated ancestral motif instance
CACTTGAAC

M_{11}

M_{12}

…CACACCACGTGAGCTT...

…CACATCACGTGAACTT…

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?