BMI/CS 776
Lecture 3

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2007.01.30

Outline

- Evolution on trees
- Markov chains
- Poisson processes
- Substitution matrices

Modeling evolution on trees - goals

- Given sequence data, we would like to:
  - Compare different tree topologies
  - Predict evolutionary scenarios
    - Reconstruct ancestral sequences
    - Identify mutation events
    - Estimate mutation rates

Modeling evolution on trees - methods

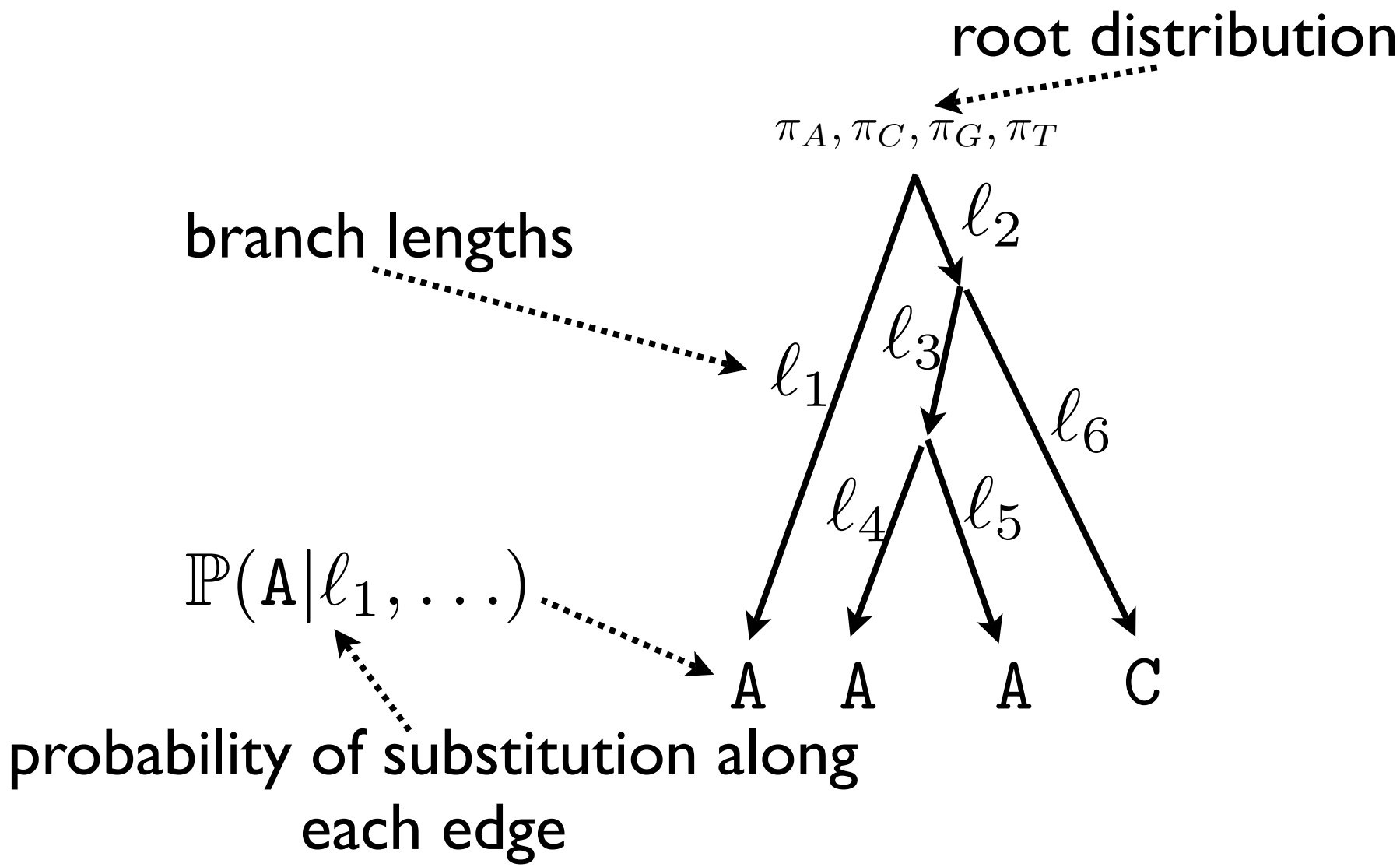
- Statistical methods
  - Continuous time Markov model
  - Poisson processes
  - Maximum likelihood
  - Tree graphical models

Statistical goal

- Given X, a set of homologous nucleotide characters, we wish to model the generation of these characters on a tree

$$\mathbb{P}(X|T)$$

Form of the models



Simple case

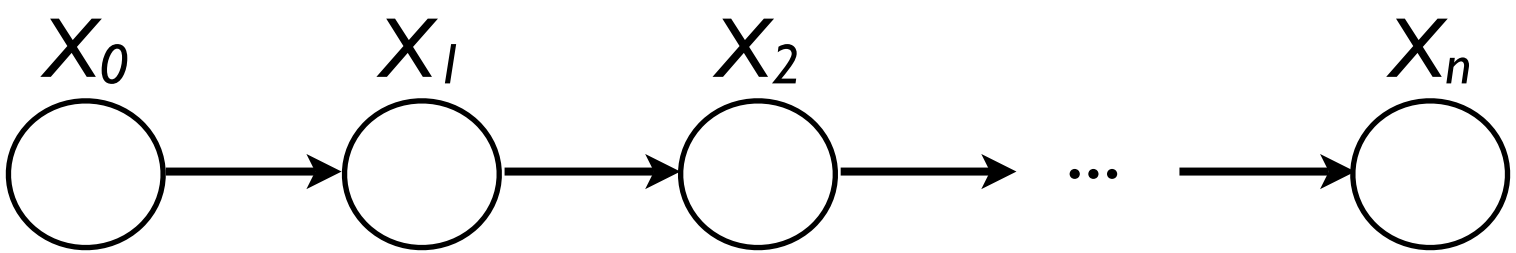
X_r: character state at root

X_l: character state at leaf

$$\begin{aligned}\mathbb{P}[X_r = x_r, X_l = x_l] &= \mathbb{P}[X_r = x_r]\mathbb{P}[X_l = x_l | X_r = x_r] \\ &= \pi_{x_r}\mathbf{P}_{x_r,x_l}\end{aligned}$$

$$\mathbb{P}[X_r, X_l] = \mathbf{\Pi P}$$

Markov chains



$$\mathbb{P}[X_n = x | X_{n-1} = x_{n-1}, X_{n-2} = x_{n-2}, \ldots, X_0 = x_0] = \mathbb{P}[X_n = x | X_{n-1} = x_{n-1}]$$

$$x \in \Sigma: \text{ the state space}$$

$$\mathbf{P}_{x,y} := \mathbb{P}[X_{i+1} = y | X_i = x]$$

$$\mathbf{P}^{(n)}_{x,y} = \mathbb{P}[X_{i+n} = y | X_i = x]$$

Continuous time Markov process

Definition 3.13 A continuous time Markov process is a sequence of Σ-valued random variable $\{Y_t, t \geq 0\}$ satisfying:

$$\mathbb{P}[Y_{t+s} = j | Y_t = i, Y_u = x_u, u \in [0, t)] = \mathbb{P}[Y_{t+s} = j | Y_t = i] \tag{3.9}$$

for all $i, j \in \Sigma$ and $s, t > 0$.

Counting process

Definition 3.1 (Counting process) A counting process is a sequence of random variables $\{X_t, t \in \mathbb{R}^+ \cup \{0\}\}$ which satisfies:

1. X_t takes on values in $\mathbb{Z}^+ \cup \{0\}$ for all t,
2. $X(s) \leq X(t)$ for $s < t$,
3. $\mathbb{E}[X_t] < \infty$,
4. $X(t) - lim_{h \to 0^+} X(t-h)$ is either 0 or 1.

Poisson process (Def I)

Definition 3.2 (Definition 1) A Poisson process with rate $\lambda \in \mathbb{R}^+$ is a counting process $\{X_t, t \geq 0\}$ satisfying:

1. For all $t_0 = 0 < t_1 < \cdots < t_n$, the differences $X_{t_1} - X_{t_0}, \ldots, X_{t_n} - X_{t_{n-1}}$ are independent random variables.

2. For all $s, t, u \geq 0$, $X_{s+t} - X_s \sim X_{u+t} - X_u$.

3. $\mathbb{P}[X_h = 1] = \lambda h + o(h)$, $\mathbb{P}[X_h \geq 2] = o(h)$.

4. $\mathbb{P}[X_0 = 0] = 1$.

Poisson distribution

$$\mathbb{P}[X = k] = \frac{e^{-\lambda}\lambda^k}{k!}$$

$$\lambda > 0$$

$$k = 0, 1, 2, \ldots$$

Limiting version of binomial distribution with n large, p small, and $np = \lambda$

Taylor series for e

$$e^x = 1 + x + \frac{x^2}{2} + \frac{x^3}{6} + \ldots = \sum_{k=0}^{\infty} \frac{x^k}{k!}$$

converges for all x

Poisson process (Def II)

Definition 3.5 (Definition 2) A Poisson process with rate $\lambda \in \mathbb{R}^+$ is a counting process $\{X_t, t \geq 0\}$ satisfying:

1. For all $t_0 = 0 < t_1 < \cdots < t_n$, the differences $X_{t_1} - X_{t_0}, \ldots, X_{t_n} - X_{t_{n-1}}$ are independent random variables.

2. For all $s, t \geq 0$, $X_{s+t} - X_s \sim Poisson(\lambda t)$.

3. $\mathbb{P}[X_0 = 0] = 1$.

Poisson process (Def III)

Definition 3.6 (Definition 3) A Poisson process with rate $\lambda \in \mathbb{R}^+$ is a counting process $\{X_t, t \geq 0\}$ satisfying:

1. For all $t_0 = 0 < t_1 < \cdots < t_n$, the differences $X_{t_1} - X_{t_0}, \ldots, X_{t_n} - X_{t_{n-1}}$ are independent random variables.

2. For all $s, t \geq 0$, $\mathbb{P}[X_{s+t} - X_s = 0] = e^{-\lambda t}$.

3. $\mathbb{P}[X_0 = 0] = 1$.

Poisson→Continuous time Markov process

- State transition at each Poisson event
- Transition according to an event substitution probability matrix, *R*

X_t: number of events by time t

$$\mathbb{P}[X_t = k] = \frac{e^{-\lambda t}(\lambda t)^k}{k!}$$

$$\mathbf{R} = \begin{pmatrix} r_{AA} & r_{AC} & r_{AG} & r_{AT} \\ r_{CA} & r_{CC} & r_{CG} & r_{CT} \\ r_{GA} & r_{GC} & r_{GG} & r_{GT} \\ r_{TA} & r_{TC} & r_{TG} & r_{TT} \end{pmatrix}$$

$$\sum_j r_{ij} = 1$$

Matrix exponentiation

For a square matrix, A

$$e^A \quad := \quad \sum_{k=0}^{\infty} \frac{A^k}{k!}$$

Exercise 3.10 Show that

1. $e^{c\mathbf{I}} = e^c\mathbf{I}$ for any $c \in \mathbb{R}$.
2. $e^{A+B} = e^A e^B$ if A and B commute.
3. $det(e^A) = e^{trace(A)}$.
4. If A is invertible then $e^{ABA^{-1}} = Ae^B A^{-1}$.

Substitution matrix derivation

$$
\begin{aligned}
\mathbf{P}(t) &= \sum_{k=0}^{\infty} \mathbf{R}^k \mathbb{P}[X_t = k] \\
&= \sum_{k=0}^{\infty} \mathbf{R}^k \frac{(\lambda t)^k e^{-\lambda t}}{k!} \\
&= e^{-\lambda t} \mathbf{I} \sum_{k=0}^{\infty} \mathbf{R}^k \frac{(\lambda t)^k}{k!} \\
&= e^{(-\mathbf{I})\lambda t} \sum_{k=0}^{\infty} \frac{(\mathbf{R}\lambda t)^k}{k!} \\
&= e^{(-\mathbf{I})\lambda t} e^{\mathbf{R}\lambda t} = e^{\mathbf{Q}\lambda t}
\end{aligned}
$$

$\mathbf{Q} = \mathbf{R} - \mathbf{I},$

Rate matrix: Q

The matrix $\mathbf{Q} = \mathbf{R} - \mathbf{I}$ *satisfies*

$$q_{ij} \geq 0 \quad \textit{for} \quad i \neq j,$$

$$\sum_{j \in \Sigma} q_{ij} = 0 \quad \textit{for all} \quad i \in \Sigma,$$

$$q_{ii} < 0 \quad \textit{for all} \quad i \in \Sigma.$$

Substitution matrix: P

Exercise 3.12 Let $\mathbf{Q}$ be any matrix satisfying the conditions of Lemma 3.11 and let $\mathbf{P}(t) = e^{\mathbf{Q}\lambda t}$. Show that

1. $\mathbf{P}(s+t) \;=\; \mathbf{P}(s) \cdot \mathbf{P}(t)$ (Chapman–Kolmogorov equations),
2. $\mathbf{P}(t)$ is the unique solution to the forward differential equation $\mathbf{P}'(t) = \lambda \mathbf{P}(t) \cdot \mathbf{Q}$, $\mathbf{P}(0) = \mathbf{I}$ for $t \geq 0$
3. $\mathbf{P}(t)$ is the unique solution to the backward differential equation $\mathbf{P}'(t) = \lambda \mathbf{Q} \cdot \mathbf{P}(t)$, $\mathbf{P}(0) = \mathbf{I}$ for $t \geq 0$,
4. $\mathbf{P}^{(k)}(0) = \mathbf{Q}^k$.
5. A matrix $\mathbf{Q}$ is a rate matrix if and only if the matrix $\mathbf{P}(t) = e^{\lambda \mathbf{Q} t}$ is a stochastic matrix (non-negative with row sums equal to one) for every $t \geq 0$.

Substitution matrix → Continuous time Markov process

$$\mathbf{P}_{ij}(t) = \mathbb{P}[Y_t = j | Y_0 = i]$$

Probability that nucleotide has changed from character i to character j in time t.

- Hides "silent" events of two types:
  - self transitions (e.g., A→A)
  - back mutation (e.g., A→C→A)