7.36/7.91 recitation

2-19-2014

CB Lecture #4

Announcements / Reminders

Homework:

- PS#1 due Feb. 20th at noon.
- Late policy: ½ credit if received within 24 hrs of due date, otherwise no credit
- Answer key will be posted 24 hrs after due date

Project:

- Teams, Title, 1 paragraph summary due Tuesday Feb. 25
- Teams of 1-5 people unless approved by instructor

Basic Linear Algebra Review

- way to compactly represent and operate on sets of linear equations:

$$2x_1 + 4x_2 = 10$$
$$-5x_1 + x_2 = -3$$

can be written in row form (lecture): $\vec{x}A = \vec{b}$

or in column form: $A^T \vec{x}^T = \vec{b}^T$

where

$$\vec{x} = (x_1, \quad x_2) \qquad A = \begin{bmatrix} 2 & -5 \\ 4 & 1 \end{bmatrix} \qquad \vec{b} = (10, \quad -3)$$

Basic Linear Algebra Review

Simple operations:

- Dot product of two row vectors $\vec{x} = (x_1, \; x_2, \; x_3) \quad \vec{y} = (y_1, \; y_2, \; y_3)$

$$\vec{x} \cdot \vec{y} = (x_1, \; x_2, \; x_3) \cdot (y_1, \; y_2, \; y_3) = x_1 y_1 + x_2 y_2 + x_3 y_3$$

- Matrix multiplication:

$$A = \begin{bmatrix} — & \vec{a}_1 & — \\ — & \vec{a}_2 & — \\ & \vdots & \\ — & \vec{a}_m & — \end{bmatrix} \quad B = \begin{bmatrix} | & | & & | \\ \vec{b}_1^T & \vec{b}_2^T & \dots & \vec{b}_p^T \\ | & | & & | \end{bmatrix} \Longrightarrow A * B = \begin{bmatrix} \vec{a}_1 \cdot \vec{b}_1 & \vec{a}_1 \cdot \vec{b}_2 & \dots & \vec{a}_1 \cdot \vec{b}_p \\ \vec{a}_2 \cdot \vec{b}_1 & \vec{a}_2 \cdot \vec{b}_2 & \dots & \vec{a}_2 \cdot \vec{b}_p \\ \vdots & \vdots & \ddots & \vdots \\ \vec{a}_m \cdot \vec{b}_1 & \vec{a}_m \cdot \vec{b}_2 & \dots & \vec{a}_m \cdot \vec{b}_p \end{bmatrix}$$

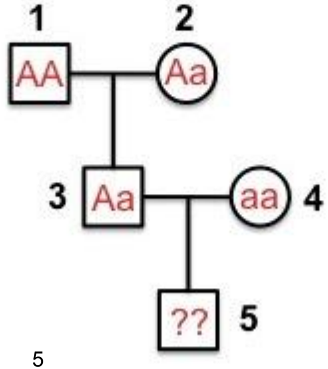
- Note that inner dimensions must agree:

If $A \in \mathbb{R}^{m \times n}$ and $B \in \mathbb{R}^{n \times p}$ then $A * B \in \mathbb{R}^{m \times p}$

Markov Models (Chains)

- Defined by a set of *n* possible states s_1, ..., s_n at each timepoint.
- **Markov property:** Transition from state *i* to *j* (with probability $P_{i,j}$) depends *only* on the previous state, not any states before that. In other words, the future is conditionally independent of the past given the present:

$$P(S_{t+1} = k | S_1 = s_1, ..., S_t = s_t) = P(S_{t+1} = k | S_t = s_t)$$



Example: if we know individual 3's genotype, there's no additional information that individuals 1 and 2 can give us about 5's genotype

- Probability of having a class having an exam that week
  - **not Markov**: prob. of having an exam during a week influenced by events further back than just 1 week (if there was an exam 2 weeks ago, likely not an exam this week)
- Board games whose moves are entirely determined by dice
  - **Markov**: prob. of future event depends only on the current board and outcome of dice roll

Markov Chains

- Instead of realizing a set of states (one particular state with probability 1 and all others with probability 0 at each timepoint), we can model more general processes by defining a probability *distribution* over states at each timepoint:

$$\vec{q}^{\,t} = (q_1, ..., q_n) \qquad 0 \leq q_i \leq 1, \sum_{i=1}^{n} q_i = 1$$

- Probability distribution changes over time according to transition matrix *P*

$$\vec{q}^{\,t+1} = \vec{q}^{\,t} P \qquad \qquad \vec{q}^{\,t+k} = \vec{q}^{\,t} P^k$$

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- Size and constraints on transition matrix P ?

Size: *n* x *n*

$$P = \begin{bmatrix} P_{1,1} & P_{1,2} & \cdots & P_{1,n} \\ P_{2,1} & P_{2,2} & \cdots & P_{2,n} \\ \vdots & \ddots & \ddots & \vdots \\ P_{n,1} & P_{n,2} & \cdots & P_{n,n} \end{bmatrix}$$

$$\sum_{j=1}^{n} P_{i,j} = 1 \quad \forall i$$

Interpretation: From current state *i*, you must end up in *some* state *j* after transition

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- If at time *t* the probability distribution over the *n* states is

$$\vec{q}^{\,t} = (q_1^t, q_2^t, ..., q_n^t)$$

what is the probability of being in state *i* at time *t*+1?

$$q_i^{t+1} = \sum_{s=1}^{n} q_s^t P_{s,i}$$

Markov Chains

- If all entries of P are strictly positive ($P_{i,j} > 0$), there is a “stationary” (or “limiting”) distribution in the limit of infinite time:

$$\lim_{t\to\infty} \vec{q}^{\,t} = \lim_{t\to\infty} \vec{q}P^t = \vec{r}$$

- The stationary distribution satisfies: $\vec{r} = \vec{r}P$

- Since all entries of distribution must sum to 1, can set up system of eqns to solve:

$$\vec{r} = (r_1, r_2, ..., 1 - \sum_{i=1}^{n-1} r_i)$$

- May also notice that $\vec{r}$ is an eigenvector of P with eigenvalue 1. Can use eigenvector approaches instead of systems of eqns to determine $\vec{r}$ if you’re familiar with those

Practice Problem

- You decided to make a model of purine (R) and pyrimidine (Y) evolution. Multiple sequence alignment of promoters (50% R, 50% Y) leads to:

$$PAM_1 = \begin{bmatrix} 0.995 & 0.005 \\ 0.015 & 0.985 \end{bmatrix}, P_{R,R} = 0.995, P_{R,Y} = 0.005, P_{Y,R} = 0.015, P_{Y,Y} = 0.985$$

- What is the composition of a sequence evolving under this model after a long time?

$$\text{Let } P_Y = 1 - P_R : \qquad (P_R, 1 - P_R) = (P_R, 1 - P_R) \begin{bmatrix} 0.995 & 0.005 \\ 0.015 & 0.985 \end{bmatrix}$$

$$\implies (P_R, P_Y) = (0.75, 0.25)$$

- What is PAM∞?

Since the (0.75, 0.25) outcome must be the same no matter where we start from (e.g. (1, 0) or (0, 1)):

$$\lim_{t \to \infty} PAM_t = \begin{bmatrix} 0.75 & 0.25 \\ 0.75 & 0.25 \end{bmatrix}$$

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- What would be the average % sequence identity between an initial sequence (composition 50% R, 50% Y) and the sequence evolved from this initial sequence under the PAM∞ matrix?

  - In PAM∞, $P_{R,R}$ = 0.75 and $P_{Y,Y}$ = 0.25. We start with 50% R and 50% Y. The fraction of R's remaining the same is (0.75)(0.50) = 0.375 and the fraction of Y's remaining the same is (0.25)(0.50) = 0.125. Therefore the total % sequence identity is 0.375+0.125 = 0.50 or 50%.

PAM vs. BLOSUM

- Evolutionary time measured in Percent Accepted Mutations (PAMs)
- One PAM: 1% of the residues have changed, averaged over all 20 amino acids.
- To get the relative frequency of each type of mutation, count the times it was observed in a database of multiple sequence *global* alignments
- The PAM1 is the matrix calculated from comparisons of sequences with no more than 1% divergence
- Mutation frequencies assume a Markov model of evolution. Other matrices derived from PAM1:

PAM250 ~ $(PAM1)^{250}$

- BLOSUM matrices are based on *local* alignments
- BLOSUM 62 is a matrix calculated from alignment of sequences with ~62% identity.
- BLOSUM matrices are based on observed alignments; unlike PAM, they are not extrapolated from comparisons of closely related proteins
- BLOSUM 62 is the default matrix in BLAST. It's tailored for comparisons of moderately distant proteins.
- Alignment of more distant proteins may be more accurate with a different matrix based on substitutions observed in more distantly evolved proteins

-See Nat. Biotech. 2 page primer for more in-depth discussion of BLOSUM62: http://selab.janelia.org/publications/Eddy-ATG2/Eddy-ATG2-reprint.pdf

Jukes-Cantor model

- the number of observed differences between two homologous sequences is smaller than the actual number of changes that have occurred, due to reversions (e.g. $A \rightarrow G \rightarrow A$)
  - can underestimate the genetic distance between the sequences
- How to compensate? need some model of how mutations occur

- Jukes-Cantor model assumes that all mutations are equally likely and occur with rate α ; if this is true, then you can apply the following correction:

$$K = -\frac{3}{4} \ln[1 - \frac{4}{3} P]$$

P = observed fraction sites that differ

K = actual number of substitutions

- This is very simple; other models are much more complex (e.g. Kimura, which has transitions $C \leftrightarrow T$ and $A \leftrightarrow G$ occurring more frequently than transversions $R \leftrightarrow Y$ and $Y \leftrightarrow R$).

Positive / Negative Selection

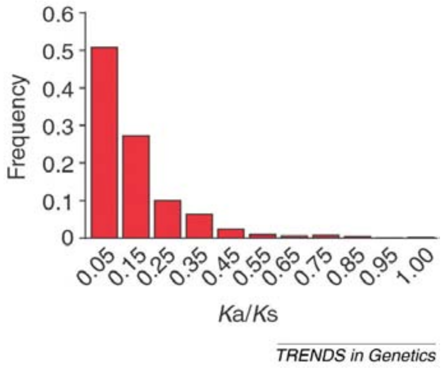
K_a/K_s (or dN/dS) test:

-K_a (or dN): # of nonsynonymous substitutions per nonsynonymous site

-K_s (or dS): # of synonymous substitutions per synonymous site

- What are typical K_a/K_s ratios you expect for protein-coding genes?

-Most proteins have evolved to a near-optimal sequence & structure, so most mutations will be deleterious (K_a/K_s<<1).



The frequency of different values of *Ka*/*K*s for 835 mouse–rat orthologous genes.

Hurst *Trends in Genetics* 18: 2002.

Source: Hurst, Laurence D. "The Ka/Ks Ratio: Diagnosing the Form of Sequence Evolution." *Trends in Genetics* 18, no. 9 (2002): 486-7.

K_a/K_s~1 generally means neutral evolution (averaged over calculated region) - e.g. pseudogenes

K_a/K_s > 1 generally means positive selection (e.g. immune system genes coevolving with parasites) - see first 3 pages of Sabeti review on Positive Selection in humans in “Resources” on course website