Exam 1 Study Guide

September 30, 2024

This study guide is intended to help you to review for the first in-class exam. This is not an exhaustive list of the topics covered in the class and there is no guarantee that these questions are representative of the questions on the exam. You should also review the notes you took in class, the notes and readings on the syllabus, and your homework assignments.

This exam is closed book. You may bring two pages (or one page, front and back) of your own notes. No electronic devices may be used during the exam. There is a clock in the class room. You will not need a calculator to answer the questions.

Pairwise sequence alignment

- Terminology: Alphabet, sequence, string, subsequence, substring.
- Dynamic programming algorithms for *local*, *global* and *semi-global* alignment.
    - Be familiar with the basic components of these algorithms: initialization, recursion, optimal score, traceback.
    - What is the computational complexity of alignment with dynamic programing?
    - How do the basic algorithmic components differ for *local*, *global* and *semi-global* alignment?
        - What types of scoring functions are (un)suitable for each of these?
        - Do any of the three types of alignment impose more restrictive criteria on the scoring function used? If so, what is the rationale for these criteria?
- Scoring functions
    - Similarity scoring. What are the required properties of simple similarity functions for sequence alignment? Which alignment problems can be solved with similarity scoring and which cannot? Why or why not?
    - What is edit distance? How does distance scoring differ from similarity scoring? Which alignment problems can be solved with edit distance and which cannot? Why or why not?

  - You should be able to explain how changing a scoring function will influence the nature of optimal alignments obtained with respect to that scoring function.
  - What is meant by the expected per site alignment score under a model of chance alignment? What is meant by residue background frequencies?

- Applications: Given a particular sequence analysis scenario (e.g., sequence assembly, identifying introns, etc.), you should be able to state which type of alignment is most appropriate and why.

Markov chains

- Definitions and terminology
  - States
  - The state probability distribution at time t
  - The initial state probability distribution.
  - The transition probability matrix. What requirements must a matrix satisfy to be a valid transition probability matrix?
  - What is the Markov property?
  - Absorbing states, reflecting states, periodic states.
- We discussed finite-state, discrete-time, time-homogeneous Markov chains. You should understand each of these terms.
- What is a periodic Markov chain? What is an irreducible Markov chain?
- n-step transitions in Markov chains: Given a transition matrix for 1 time step, you should understand how to construct a transition matrix for n time steps.
- Stationary state distributions.
  - What is the formal definition of a stationary distribution?
  - What is a limiting distribution?
  - Given the transmission matrix of Markov chain, how is the stationary distribution calculated?
  - How can you verify that a given distribution is the stationary distribution?
  - What properties may prevent a Markov chain from having a stationary distribution?
  - Under what conditions, is the stationary distribution the limiting distribution?
  - What properties are required for a Markov chain to have a unique stationary distribution?

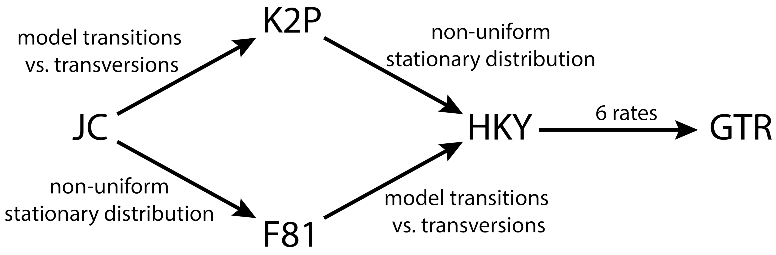
Markov models of nucleotide substitution

- What kinds of questions can be answered with sequence evolution models?
- In this section of the course, we focused on ungapped alignments of sequences of the same length. Why?
- What is the basic structure of a Markov model of DNA substitution?
  - What do the states of represent?
  - What is the meaning of transitions between states?
  - What are the underlying assumptions of such models?
- The Jukes Cantor (JC) model
  - What are the underlying assumptions?
  - How are transitions modeled?
  - What is the stationary distribution?
  - How is the rate parameter of the JC model related to the overall substitution rate?
  - The Jukes Cantor transition matrix gives the probability of a substitution occurring in a single time step. From this, we derived
    - the probability of observing nucleotide x at a given site and observing a different nucleotide y after elapsed time, t,
    - the probability of observing nucleotide x at a given site and observing the same nucleotide after elapsed time, t;
    - the probability of observing x aligned with y in an ungapped alignment of two sequence that have been diverging independently from a common ancestor for elapsed time t;
    - the probability of a mismatch at a given site in sequences that have been diverging independently from a common ancestor for time t;
    - the expected number of substitutions that occurred since the divergence of a pair of present-day sequences, given the number of mismatches observed in their alignment.

    You should understand each of these quantities and know how to apply them in simple scenarios. For the exam, you do not need to know how to derive these quantities.
- The Kimura 2 parameter (K2P) model
  - Kimura's model of DNA substitution distinguishes between transitions and transversions. What are transitions and transversions? Note that the word "transition" has two different meanings in this context. It is used to describe the progression from one state to another state in a Markov chain. It is also used to describe a class of nucleic acid substitutions. You should understand both of these meanings.

  - What are the underlying assumptions of K2P?
  - What are the parameters of the model?
  - What is the stationary distribution of this model?
  - The Jukes-Cantor model can be use to estimate various properties of alignments (e.g., the probability of a mismatch, corrections for multiple substitutions). These are listed above. The Kimura 2 parameter model can also be used to estimate these properties of alignments. You are not expected to know the equations for the Kimura 2 parameter model, but if you were given the equations, you should be able to interpret them and understand how to apply them.

- The DNA substitution model hierarchy: We discussed a hierarchy of increasingly complex models of DNA sequence evolution. In addition to the JC and K2P models, which we discussed in detail, we considered the Felsenstein (F81) model, the Hasegawa, Kishino, Yano (HKY) model, and the General Time Reversible (GTR) model.


K2P
model transitions vs. transversions
non-uniform stationary distribution
JC
HKY
6 rates
GTR
non-uniform stationary distribution
F81
model transitions vs. transversions

- For each of the five models you should understand
  - What are the underlying assumptions of the model?
  - How many parameters does the model have? What do those parameters represent?
  - What is the meaning of transitions between states in the model?
  - What is the relationship between the transition matrix and the stationary distribution of the model? How does one constrain the other?

- How are the different models related?
  - Non-uniform *transition probabilities*
    - The K2P, HKY, and GTR models all allow for different rates for different nucleic acid pairs. The K2P and HKY models distinguish between transitions and transversions. The GTR model allows for a different substitution rate for each of the six possible pairs of nucleotides. For each pair, the rates are the same in both directions, i.e., transitions from A to G and from G to A proceed at the same rate.
    - The JC model assumes all substitutions proceed at the same rate.
  - Non-uniform *stationary distributions*

    - ∗ Both the JC and the K2P models have uniform stationary distributions. This distribution is an implicit consequence of the symmetric structure of the transition matrices of these models.
    - ∗ The F81, HKY, and GTR models allow for different underlying base frequencies.
  - How do models compare in terms of complexity?
  - How can you decide which model to use?
  - Given the transition matrix for a nucleic acid substitution model, can you determine which of the five models the matrix represents?

- Limitations:
  - Properties of sequence evolution that are not captured by the models we learned in class include
    - ∗ interactions between different sites in the same sequence,
    - ∗ insertions and deletions,
    - ∗ site-dependent rate variation (different rates at different sites), and
    - ∗ time-dependent rate variation (changes in rate over time).
  - What are the trade-offs associated with using a more complex models versus a less complex model?

Log-odds formulation

- A likelihood ratio compares the probability that an observation is the outcome of a process described by an alternate hypothesis, H_A, and the probability that the observation is due to chance, described by the null hypothesis, H_0. You should understand the interpretation of a likelihood ratio in the context of a pairwise alignment. What are the alternate and null hypotheses, H_A and H_0, in this context?

- Why are the advantages of using the log likelihood ratio, instead of simply the likelihood ratio?

- How can the log likelihood ratio be used to constructing a scoring function for an alignment?

- What does it mean if the likelihood ratio is less than one? Greater than one?

- What does it mean if the log-likelihood ratio is less than zero? Greater than zero?