CSC 334: Topics in Computational Biology

Midterm: Fall 2015

Due: Tuesday, November 3 at 1pm

- This is a take-home exam with unlimited time from when it is out to when it is due.
- It is open-notes, so you may use any course materials. If you use any online resources that haven't been part of this class, please cite them.
- No communication about the exam with anyone in the class (or outside the class). However, you can email me if you need clarification.
- If there is a clarification I think should be made to the entire class, I'll post it on Piazza.
- I will still have office hours on Monday 4-6pm and Wednesday 5:30-7pm, but I might not say much!
- Turn in your exam to me in person or put it under the door of my office if I am not there (not in the bin outside).
- If you are unable to make it to my office to turn in the exam before the deadline, email me to make other arrangements such as scanning your exam.
- If you are unable to make progress on any part of the exam, tell me what you tried; describe your thought process.

Name	

Part 1	/10
Part 2	/25
Part 3	/10
Part 4	/20
Part 5	/10
Part 6	/25
Total	/100

Part 1: Genome Assembly

For this part, you are given two reads and tasked with assembling them into a genome (10pts):

read 1: GTCACA
read 2: ACACTT

(a) Draw the traditional read overlap graph for these two reads. For the overlap length, what are the two options and which one would you choose?

(b) Draw the de Brujin graph for these two reads, using $k = 3$. Velvet has a slightly more compact way of drawing the graph, but here use k-mers as nodes and directed edges for overlaps of $k - 1$ that occur in the read. (You don't need to do the reverse compliment.)

(c) Trace out the path through the de Brujin graph and write out the corresponding "genome".

Part 2: String Alignment

In class we learned an algorithm for *global* string alignment (Needleman-Wunsch), which returns the optimal alignment between two strings over their entire lengths. There are many variations of Needleman-Wunsch for different tasks. One variation is used for *local* alignment (Smith-Waterman), which returns substrings of the original strings that are very similar. For example, if we wanted to find very similar (highly conserved) gene sequences shared between two very different (highly diverged) species, we might use local alignment. (25pts)

Let our two strings be S and T, with length$(S) = n$ and length$(T) = m$. Let match(a, b) be the match score between characters a and b, and let g be the gap penalty. The modifications below turn a global recursion into a local one:

Initialization:

$$\begin{aligned} \text{score}(i, 0) &= 0, \quad \text{for} \quad i = 0, 1, \cdots, n \\ \text{score}(0, j) &= 0, \quad \text{for} \quad j = 0, 1, \cdots, m \end{aligned}$$

Recursion:

$$\text{score}(i, j) = \max \begin{cases} 0 \\ \text{score}(i-1, j-1) + \text{match}(S[i], T[j]) \\ \text{score}(i-1, j) + g \\ \text{score}(i, j-1) + g \end{cases}$$

Termination:

The highest score(s) in the DP table represent the end points of the best local alignment(s). Backtrace from these cells as before until a zero is reached to find the local alignments.

(a) Explain the relationship between these modifications and and the goal of *local* alignment.

(b) For the overlap graph in Part 1, it might be helpful to use string alignment to compute the overlaps. To start off this idea, fill in the DP table below for the two reads from Part 1, using the *local* alignment algorithm above. For the cell $(i, j) = (4, 4)$, show your work clearly using the recursion above.

	-	A	C	A	C	T	T
-							
G							
T							
C							
A							
C							
A							

(c) What is the best local alignment score? Traceback to find the best local alignment(s) that this score corresponds to. Was this procedure useful for finding read overlaps?

(d) Make a modification to the termination procedure that would ensure that only read overlap alignments are returned.

Part 3: Burrows Wheeler Transform

Implement the BWT in python (your own original code), using the skeleton `midterm.py` online. Submit your code on Moodle. (10pts)

(a) Implement the helper function `cyclic_perms(S)`, which should return a list of all cyclic permutations of S, i.e. $\pi(S)$.

(b) Sort the cyclic permutations to obtain π^{sorted} (you can use the built-in python function `sorted(lst)`).

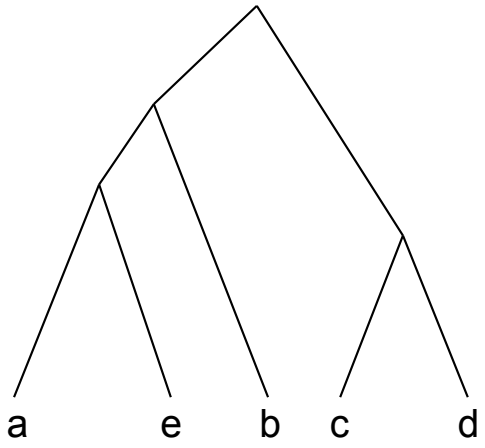
(c) Return the BWT (last column). Use it to obtain the BWT for read 1: GTCACA.

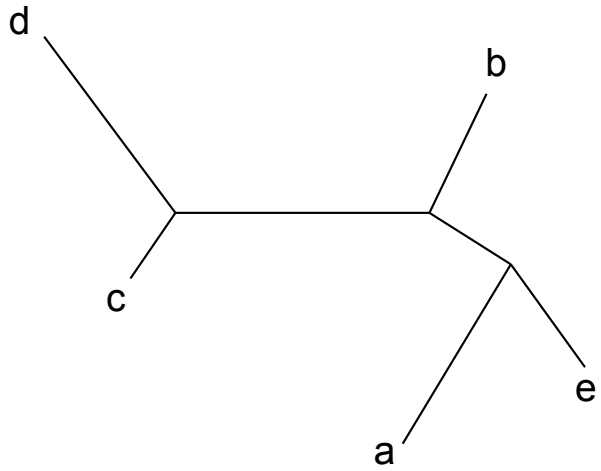
(d) Bonus (+2): Implement `reverse_bwt(L)` that takes the BWT as input and returns the original string S (it should not use π^{sorted}).

Part 4: Tree Building

Comparing the trees and distance matrices created by UPGMA and NJ. (20pts)

The following two trees and *induced* distance matrices were created by UPGMA and NJ. Use these distance matrix results and tree topologies to label *all* the branch lengths of both trees. Without knowing the original distance matrix, which induced distance matrix do you think is "closer" to the truth?





UPGMA	a	b	c	d	e
a	0	12	18	18	10
b		0	18	18	12
c			0	8	18
d				0	18
e					0

NJ	a	b	c	d	e
a	0	11	17	23	10
b		0	12	18	9
c			0	8	15
d				0	21
e					0

Part 5: Perfect Phylogeny

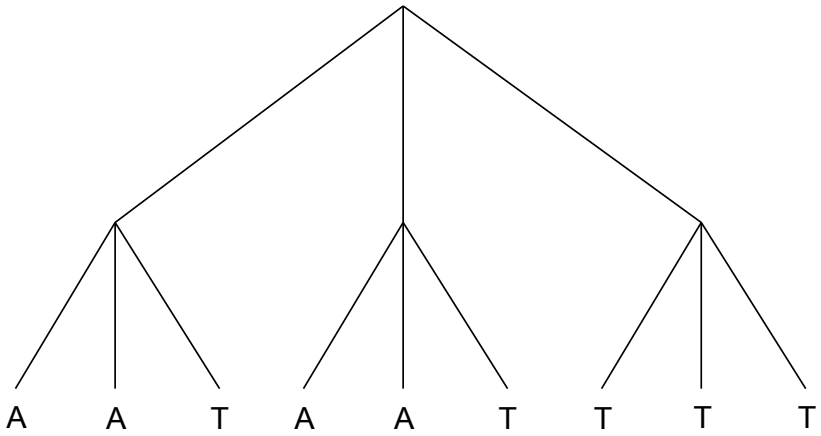
Use Gusfield's algorithm to reconstruct a phylogeny for the data below (6 sequences, 4 sites). Show your steps, but you don't need to use radix sort. Based on your results, does a perfect phylogeny exist for this dataset? Explain why or why not. (10pts)

sequence	site 1	site 2	site 3	site 4
a	0	1	1	1
b	0	0	0	0
c	1	0	1	0
d	0	1	0	0
e	1	0	1	0
f	0	0	1	1

Part 6: Ancestral Reconstruction

Fitch's algorithm for non-binary trees. (25pts)

(a) Run Fitch's algorithm on the ternary tree below to determine the base at every ancestral node. Given the result, how many mutations would be required to produce the data observed at the leaves? Is there a better solution? What is it and how many mutations does it involve?



(b) Create a new algorithm (with the same goal as Fitch's algorithm) that works for general non-binary trees. Explain the steps clearly, using a notation similar to Fitch in class (see notes for class meeting 15).

(c) Run your algorithm on the tree below to determine the base of every ancestral node (note that Fitch would be ambiguous in this case).