Spring 2017 **CMSC 423: MidTerm 1** H. Corrada Bravo

Time: 1 Hour, 15 Minutes

WAIT FOR INSTRUCTIONS BEFORE BEGINNING

HONOR PLEDGE: "I pledge on my honor that I have not given or received any unauthorized assistance on this examination."

Signature and UID: _____

Print name: _____

- ***Write your answers with enough detail about your approach and concepts used, so that the grader will be able to understand it easily.***
- ***The sum of the grades is 105, but your grades would be out of 100 (thus you get 5 bonus points by solving all the problems).***
- ***Select the best choice for the first 6 problems and mark it by X in the table below.***

Problem	1	2	3	4	5	6
A						
B						
C						
D						
E						

DO NOT WRITE BELOW THIS LINE

Questions 1-6	/ 30	Question 9	/ 15	Question 12	/ 20
Question 7	/ 10	Question 10	/ 12	Total	/ 105
Question 8	/ 5	Question 11	/ 13		

Multiple-choice Problems (Answer THE BEST CHOICE in the Table of the First Page and NOT HERE):

1. **(3 points**) Which of these best represents the relationship between genotype and phenotype?

   a) there is **no** relationship between genotype and phenotype

   b) an individual's phenotype **completely** determines their genotype

   c) an individual's genotype **completely** determines their phenotype

   d) an individual's phenotype **partially** determines their genotype

   e) none of the above

2. **(6 points**) Consider the following DNA motif profile shown below. Which is the profile-most probable 3-mer in string `ATTCAGGA`? (Show your work.)

	Pos 1	Pos 2	Pos 3
A	.8	.6	.4
C	.2	.3	.5
G	0	.3	.1
T	0	0	0

a) ATT b) TTC c) CAG d) AGG e) GGA

3. **(2 points**) Which of the following resources *does **not*** contain high-throughput sequencing data from population experiments:

a) 1000 genomes project b) Pubmed

c) Short Read Archive d) (a) and (b) e) (a), (b) and (c)

4. **(10 points**) I used k-means clustering with k=2 and obtained the two cluster centers in Table 1. What are the cluster assignments for the three genes in Table 2? Show your work (drawing the genes and center helps, keep an eye out for uninformative time points).

	Time 0	Time 1	Time 2
Center 1	1	0	1
Center 2	-1	0	-1

Table 1. Centers

	Time 0	Time 1	Time 2
Gene A	2	0	2
Gene B	-1	0	0
Gene C	2	0	-1

Table 2. Genes

a) A: 1, B: 1, C: 2

b) A: 2, B: 2, C: 1

c) A: 1, B: 2, C: 2

d) A: 1, B: 2, C: 1

e) A: 2, B: 1, C: 2

5. **(6 points**) Consider cyclic peptide N-I-C-E. I claim that its cyclospectrum is the following:

{0, 103, 113, 114, 129, 216, 227, 232, 330, 345, 459}

I am wrong. Select **the best** explanation why. You can find the integer mass table below.

a) This is not a spectrum

b) It is missing the mass of peptide C-E-I

c) It is missing the mass of peptide C-E

d) This is its linear (not cyclic) spectrum

e) None of the above

G	A	S	P	V	T	C	I	L	N	D	K	Q	E	M	H	F	R	Y	W
57	71	87	97	99	101	103	113	113	114	115	128	128	129	131	137	147	156	163	186

6. **(3 points**) Which of the following are examples of sequence mutations?

a) Single Nucleotide Polymorphism (SNP) b) insertion c) complementation

d) (a) and (b) e) None of the above

Questions (show all derivations as appropriate for full credit):

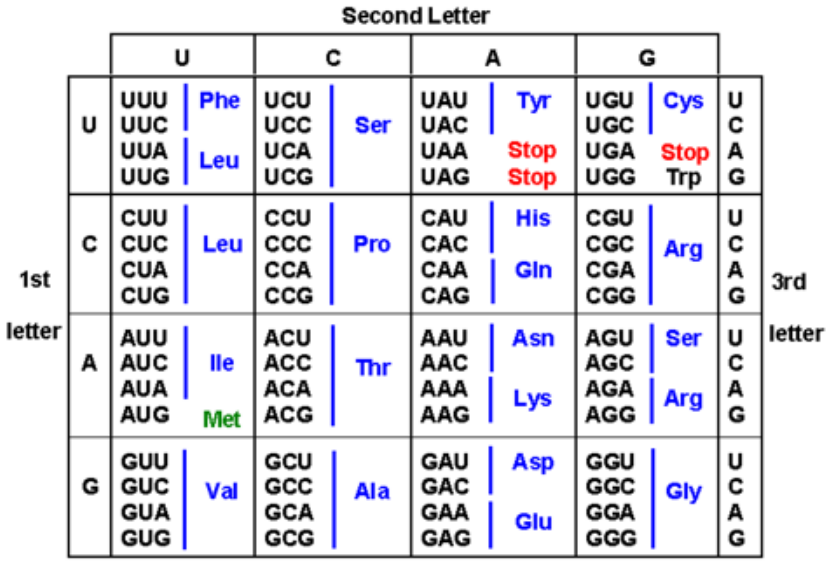
Problem 7. (10 points) (You can refer to the genetic code figure below). Consider RNA sequence S=… `CGCAUAUGAACAAGAC...`

(a) Write down the aminoacid sequence resulting from translation of the open reading frame (ORF) starting in the second position of the string (i.e., first codon is `GCA`).

(b) Specify a *synonymous* nucleotide substitution in this ORF, i.e., does not change aminoacid sequence.

(c) Specify a *non-synonymous* nucleotide substitution in this ORF.

(d) Specify a substitution that closes this ORF; write down the resulting aminoacid sequence.



Problem 8. (5 points) Provide a definition of *reproducible data analysis.* Discuss its importance in experimental computational biology. Mention computational tools that can help ensure data analyses are reproducible.

Problem 9. (15 points) Consider the evolution game you worked on in Project 2. Remember that the binding rule in that case was `T[C|G]GTNNNNT[A|G]NT`, (i.e., in position 2 either `C` or `G` allows binding, in positions with `N` any base allows binding, and in position 10, either `A` or `G` allows binding).

(a) Write down a profile consistent with this binding rule, that is, a profile you would estimate from a population of 12-mers evolved according to the rules of our simulation in Project 2. Show and explain your work.

(b) Calculate the entropy of the profile you wrote down as answer for (a).

(c) Calculate the *relative* entropy of the profile for background frequencies b_A=1/3, b_C=1/6 b_G=1/6 b_T=1/3.

Problem 10. (12 points). Suppose we have a set of four amino acids with the following masses: A=10, B=30, C=50, and D=90. Consider the experimental cyclospectrum {0, 10, 10, 20, 50, 60, 60, 70}. Suppose we are running the branch-and-bound algorithm discussed in class to solve the cyclopeptide sequencing problem. Show all single amino acid expansions of peptide A-C, and indicate for each one, if they are consistent with the experimental cyclospectrum above. Show all your work. Explain for each expansion how you determined if it is consistent or not.

Problem 11. (13 points). How many DNA strings of length *n* are there where their prefix of length *k* is equal to its suffix of length *k*?. E.g., ACGTATTAACGT is one such string for n=12 and k=4.

Problem 12 (20 points) We've seen in class two algorithms that use probability estimates as part of an optimization problem: (a) in the Gibbs sampling algorithm for motif finding, we used the 'profile probability' of a k-mer to sample positions in DNA sequences containing a protein binding site, and (b) in the EM algorithm used in soft k-means, we used 'assignment probability' to calculate cluster centers using weighted averages. Design an EM algorithm to solve the motif finding problem, that is, estimate a profile.

1. In soft k-means, the parameters of interest were the k centers. What is the parameter of interest in motif finding?

2. In soft k-means, *HiddenMatrix* was a matrix with a row for each gene and a column for each cluster center. What probability does the value $HiddenMatrix_{ij}$ correspond to in soft k-means?

3. How is each entry $HiddenMatrix_{ij}$ calculated in soft k-means? Write the mathematical expression.

4. Now, let's define a similar *HiddenMatrix* for motif finding. It should have *t* rows (number of strings in Dna), how many columns should *HiddenMatrix* have in this case? What probability does $HiddenMatrix_{ij}$ correspond to in this case?

5. How would you compute $HiddenMatrix_{ij}$ for motif finding? Write a mathematical expression. Note: this is the *E-step* in your algorithm.

6. In soft k-means, *HiddenMatrix* was used to calculate weighted means as cluster centers. Write the mathematical expression to calculate the i-*th* cluster center as a weighted mean. Note: this is the *M-step* in fuzzy k-means.

7. Given *HiddenMatrix* for motif finding as you've defined above, how would you use it to calculate a motif profile? The key here is how to calculate *weighted nucleotide counts.* Write a mathematical expression for entry p_{cj} corresponding to nucleotide *c* and position *j* of the profile. Note: this is the *M-step* of your algorithm.