Fall 2015 **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	/ 20	Total
Question 7	/ 10	Question 10	/ 15	
Question 8	/ 10	Question 11	/ 20	

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

1. **(3 points**) Which of the following is a *non-synonymous* mutation? *You can find the RNA translation code in Problem 7.*

   a) AGA->AGC b) GGT->GGA c) CGG->AGG

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

2. **(10 points**) Consider the following DNA motif profile shown below. In which position of string ATTCAGGA is the highest probability 3-mer found? (Note: assume 1-indexing so the first kmer (ATT) is in position 1. 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) 1 b) 2 c) 4 d) 5 e) 6

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 given below (Table 1). What would be the cluster assignments for the three genes given below (Table 2)? Show your work (a drawing is sufficient).

Table 1. Centers

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

Table 2. Genes

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

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. **(2 points**) What is an *open reading frame* (ORF)?

a) any translatable sequence of nucleotides

b) any sequence of codons

c) a long enough sequence of aminoacids

d) a long enough sequence of codons without an intervening stop codon

e) None of the above

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):

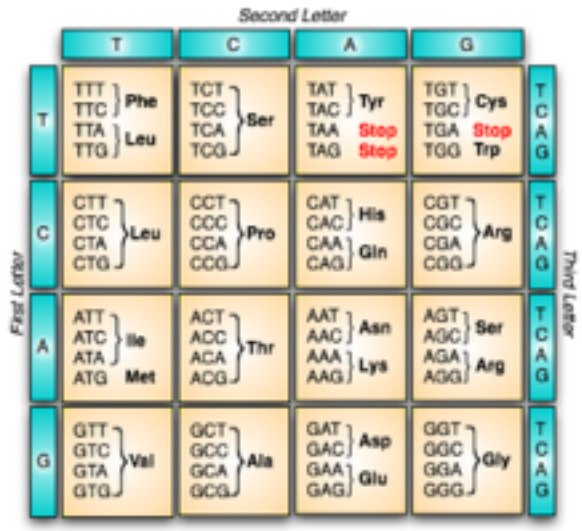
Problem 7. (10 points) (You can refer to the genetic code figure below). Consider nucleotide sequence S=…CGCATATGAACAAGA**...**

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

(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. (10 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. (20 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 below 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=1/6.

Problem 10. (15 points). Write down an expression for the probability that the length *k* prefix of a randomly generated DNA string of length *n* is equal to the reverse complement of its length *k* suffix. E.g., ACGTATTAACGT is one such string for n=12 and k=4.

(a) Solve assuming $2k \leq n$

(b) Solve assuming $k \leq n < 2\mathrm{k}$

Problem 11 (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.

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 does $HiddenMatrix_{ij}$ correspond to in soft k-means?

3. How is each entry $HiddenMatrix_{ij}$ 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 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. Write the mathematical expression to calculate the *jth* cluster center. 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 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.