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Homework 5
Due May 15th at the beginning of lecture

Instructions:
You are welcome to discuss concepts with your classmates but must compose your own answers. If you are unsure of the honor code for this course, please ask or look at the course website. http://www.its.caltech.edu/~bi1/Bi1__Micro-_to_Macro-Biology/Policies.html
The goal of this assignment is to help you understand a dense research paper and the molecular basis of cellular information processing. Many of the questions do not have a single correct answer. You will be given full credit as long as your answer is reasonable.
The answers must be legible and should not extend past the allotted space. Keep in mind that a few well-written sentences can give a higher score than a whole page of text.
Remember to write your full name and section number on each page.

Part A – Thinking critically about the Meselson & Stahl paper
Meselson, Matthew & Stahl, Franklin W (1958) "The replication of DNA in Escherichia coli." *PNAS*.44:671-682.
Prior to Meselson & Stahl's work (performed at Caltech in 1958!), there had been numerous hypotheses for the mechanism of DNA replication. In *The replication of DNA in Escherichia coli*, we learn that most of these hypotheses differed in their predictions concerning the distribution of atoms among the progeny molecules produced from parental molecules during replication.

1) In no more than 3 sentences and <u>using your own words</u>: What were the key observations in Meselson & Stahl's paper? (6 points)

2) One alternative hypothesis for DNA replication was that the parental double helix (*i.e.* two strands) remains associated after cell division. What distribution of DNA molecules would be expected in the centrifugation experiments after the first and second generations if this 'conservative' mechanism were indeed the case? (3 points)

3) What do you think was the most clever part of Meselson & Stahl's approach? (2 points)

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4.) What central biological principle(s) does this paper illustrate (i.e., how does it fit in within the themes you are learning about in lecture)? (4 points)

Part B – Practicing applying the central dogma

1) Thinking back to the GASP phenotype and applying your understanding of the central dogma, how do you think an error-prone mutant strain (*e.g.* one with lower-fidelity DNA-repair polymerases) would perform in a GASP experiment compared to the wild-type? (4 points)

2) a. Using this DNA sequence transcribe, it into mRNA. Be sure to label the directionality of the strands. (2 points)
5' – CCTGCCTCTGCGGATGAAAATGCG – 3'

b. Translate your mRNA sequence from the previous question into a peptide sequence (use the codon chart in Fig.1 and the single letter abbreviation). Be sure to label the directionality of the peptide. (2 points)
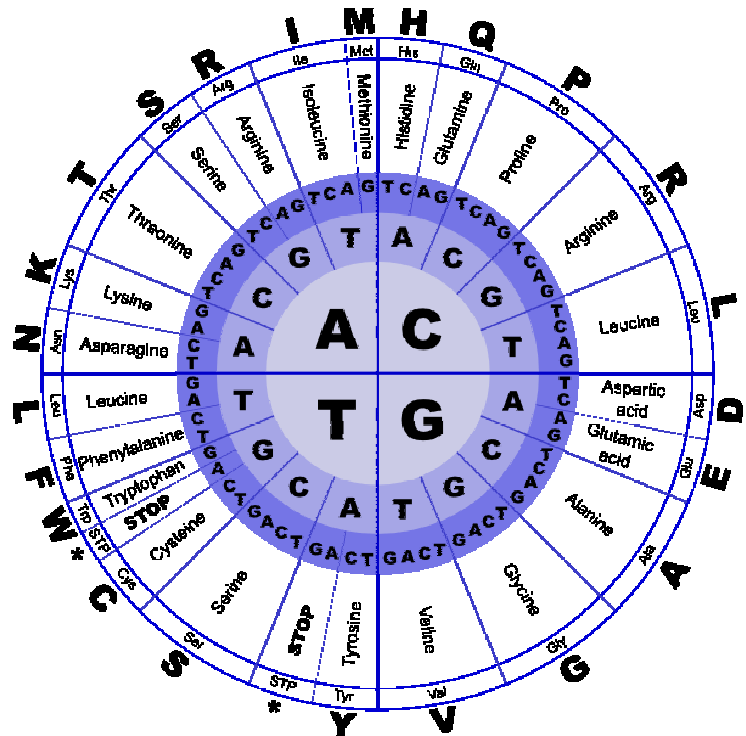

Fig.1 Codon chart. Example: ATG encodes the amino acid methionine (abbreviated as Met or M).

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c. Is the translated sequence part of a known protein? Use the search tool Protein BLAST to figure this out: http://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE=Proteins
Make sure the coverage is 100%, and that the protein is known. What is the name of a protein that contains the sequence and what's known about the function of this protein? (3 points)

d. One constraint for protein size is the error rate of transcription and translation. Given that, in bacteria, transcription typically makes one error every 10,000 nucleotides, what length of RNA can be made error free with a chance greater than 50%? (2 point)

e. *In addition* to transcriptional errors, the ribosome has an estimated error rate of about one mistake every 10,000 amino acids. Use this information to estimate how long a protein can be made that is free of either transcriptional or translational errors more than 50% of the time? Discuss the result in context of the size of the biggest proteins in *E. coli* (~2,300 amino acids) and *H. sapiens* (about 35,000 amino acids). (4 points)

Part C – Understanding the structure of proteins
1) After its synthesis by the ribosome, most proteins adopt a specific three-dimensional structure.
a. Draw a peptide bond. Which bonds are free to rotate? (2 points)

b. How many different conformations can a protein with a length of 200 amino acids theoretically adopt, assuming that two conformations are allowed per peptide bond? It can be estimated that it takes 10^{-13} seconds for a peptide bond to adopt a new conformation. How many years would it take to sequentially sample the entire "conformation space" of a 200 amino acid long protein? (2 points)

c. Speculate which mechanisms in the cell may exist to ensure that most proteins adopt their functional conformations within a few seconds after production (2-3 sentences). (2 points)

d. Misfolded proteins are often toxic to cells and can cause disease. Research which of the following diseases is strongly associated with misfolded proteins: Alzheimer's, Parkinson's and Huntington's disease, Malaria, Sickle cell anemia, Prion based diseases, Tuberculosis, Cystic fibrosis. Which proteins are misfolded in each case? (4 points)

2) The enzyme carbonic anhydrase acts in the erythrocytes (red blood cells) of humans, where it allows CO_2 to be dissolved as HCO_3^- in the blood and then exhaled as CO_2 in the lungs.

a. In which other context, discussed in lecture, is this type of enzyme important in nature? (2 points)

b. Over the last five decades research groups all over the world have been working to determine these structures experimentally. Why is this data so important for biology (max. 3 sentences)? (2 points)

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c. A cartoon representation of the tertiary structure of cadmium carbonic anhydrase is pictured below. Describe the information this image contains and use it as an example to illustrate the concepts of the secondary and tertiary structure of proteins (maximum 8 sentences). (4 points)
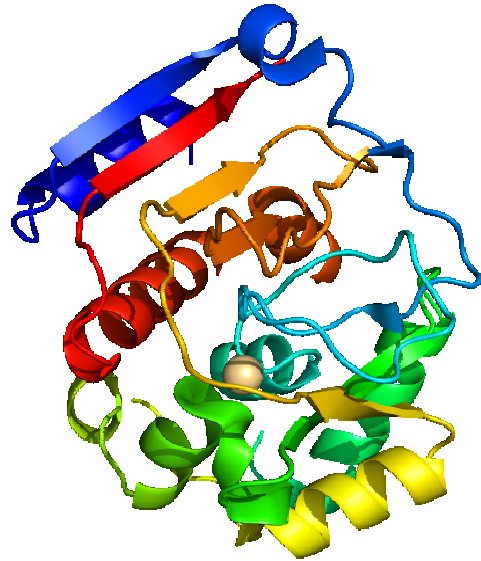

Fig.2 Cartoon representation of a cadmium carbonic anhydrase (PDB entry 3BOB).