Problem/Question	Points
Question 1	/ 6
Question 2	/ 10
Question 3	/ 10
Question 4	/ 10
Question 5	/ 12
Problem 1	/ 15
Problem 2	/ 15
Problem 3	/ 12
Problem 4	/ 10
Total	/ 100

Take-home Exam
Issued: Tuesday March 10 at 2:00pm on bcourses
Due: Tuesday March 10 at 4:00pm on bcourses

Instructions:

- **You are free to consult the course Reader, handouts, your class notes and suggested readings.**
- **Honor Code: I have neither *given* nor *received* aid in this examination. I have taken an active part in seeing to it that others as well as myself uphold the spirit and letter of this Honor Code.**

Name: **Signature:**

QUESTION 1 (6 points) (Protein Background)

a. Name and describe the two most common types of secondary structure that exist in proteins.
b. Do all domains of proteins have a fixed secondary structure? Explain.

QUESTION 2 (10 points) (Cell Migration)

A common experiment is to measure cell migration speed under various influences. Two parameters are known to have strong effects on cell migration speed: ligand density and substrate stiffness.

Suppose that a substrate with variable stiffness and ligand densities is developed. At the start of an experiment, scientists pick a stiffness of 5 kPa and then tune ligand density to maximize migration speed. They then maintain this ligand density and set substrate stiffness to 50 kPa. Shortly explain how migration speed will change.

QUESTION 3 (10 points) (Extracellular Matrix)

a. List two uses of the extracellular matrix to surrounding cells.

b. Which of the following proteins or protein classes are components of the extracellular matrix?

- ☐ Glycoproteins
- ☐ Vinculin
- ☐ Talin
- ☐ Integrin
- ☐ Fibronectin
- ☐ Collagen

c. Several varieties of ligands are important to the formation of cell - ECM adhesions.
   i. Give an example of one of the ligands involved in cellular adhesions.
   ii. Give an example of a cellular protein that ligands interact with.

QUESTION 4 (10 points) (Integrins)

An important step in cellular adhesion is integrin entering the open-extended conformation. Integrin can be encouraged to enter or remain in this conformation by factors on the inside and outside of the cell.

a. What is an internal factor that could push integrin to open?
b. How does mechanical force influence the behavior of integrin?

QUESTION 5 (12 points) (Focal Adhesions)

Cells are normally plated on substrates with constant stiffness, but it's also possible for substrates to have a stiffness gradient, in which one end of the substrate has a low stiffness which gradually transitions to a high stiffness at the opposite end.

a. If ligand densities are held constant, which direction would cells normally migrate in on this type of substrate?
b. Shortly explain why cells would migrate like this. Reference the properties of cellular adhesion and the role of mechanotransduction.

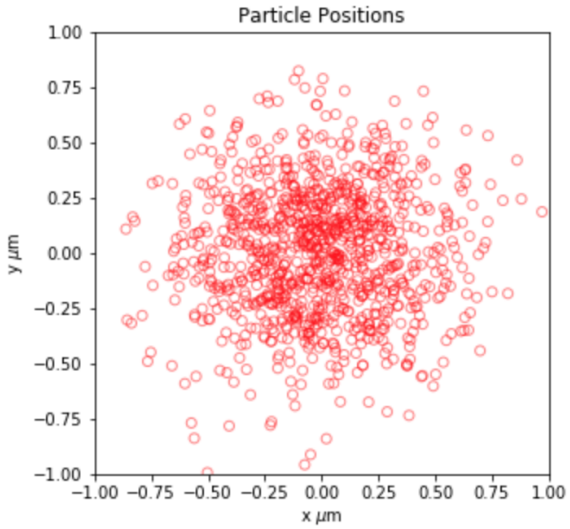
PROBLEM 1 (15 points) (Diffusion)

A globular (spherical) protein with radius 5 nm diffuses in water with a viscosity of 8.90×10^{-4} Pa·s and temperature of 300 K.

a. Estimate how long it will take for the protein to diffuse an average distance of 25 µm.

b. Suppose the protein now needs to diffuse 75 µm instead of 25 µm, from the nucleus of its cell to the cell membrane. By what factor will the diffusion time change?

c. Under the right conditions, researchers can use the properties of diffusion to make experimental observations. In one such experiment, the image below was produced by releasing thousands of fluorescent versions of the protein from part a into a cell. They were then allowed to diffuse from the starting position at (0, 0) for 10 seconds, before the scatterplot below was generated by plotting the x and y positions of each particle.



After averaging over all points in the plot above, $\langle r^2 \rangle = (0.5\ \mu m)^2 = 2.5 \cdot 10^{-13}\ m^2$. Knowing this, what is the viscosity of cytoplasm in the cell? You may assume that the particles are diffusing in two dimensions.

d. **(Grad Students Only)** Consider the protein diffusing in three dimensions. In our normal formula for diffusion, we calculate the expected value of r^2, where r is the total distance from the starting point. However, it's also possible to derive the expected value of r_x^2, where r_x is the distance from the starting point along the x-axis only. What is the formula for $\langle r_x^2 \rangle$ over long timescales? Show your work. [Hint: It may help to start with the normal formula for $\langle r^2 \rangle$.]

PROBLEM 2 (15 points) (Protein Dynamics).
Consider an extremely larger globular protein with radius 2μm, also in water with a viscosity of 8.90×10^{-4} Pa·s. We will model it as a sphere with density 10^{-5} kg/cm^3, giving it a mass of $8 \cdot 10^{-16}$ kg and a drag coefficient of $6\pi \cdot 8.90 \times 10^{-4} \cdot 2 \times 10^{-6} = 3.36 \times 10^{-8}$ N · s/m. The protein is attached to a tether with a spring stiffness of 4 pN/nm.

a. The protein is pulled 1μm from its natural resting point and held still before being released. Write out the differential equation describing its motion. What are the boundary conditions for the equation?
b. Qualitatively describe the protein's motion after being released. Is it underdamped, overdamped, or critically damped?
c. What is the protein's time constant?
d. The protein's radius expands by a factor of 10 but its density remains the same. How does the protein's motion change qualitatively?

PROBLEM 3 (12 points) (Entropy)

In the classic hairpin polymer model, a series of n segments are connected by joints with angles of either 0 or 180 degrees. So, a microstate for the hairpin model can be represented by a list of joint angles for the n-1 joints between the n segments.

a. Consider a hairpin model with 11 segments. Calculate the number of microstates in the model and the total entropy of the model.
b. Consider a hairpin model with n segments. How much will the entropy of the hairpin model increase when a single additional segment and its corresponding joint are added?
c. A common macroscopic measurement for the hairpin model is the number of hairpins. How many microstates correspond to a macroscopic measurement of 5 hairpins for the original model with 11 segments?

PROBLEM 4 (10 points). (Boltzmann Distribution)
A four-residue protein can take on four different conformations pictured below. Three conformations are unfolded (partially or fully open) and have energy E, and one conformation is folded (compact) and has energy zero. (Assume that the multiplicity of each of these conformations is one.)

a. At temperature T, what is the probability of finding the molecule in an unfolded conformation, P_U? What is the probability that it is compact, P_F?
b. What happens to the probability P_F, calculated in a, in the limit of very large and very low temperatures?
c. What is the probability ratio of the unfolded vs. folded conformations?