BE/APh 161: Physical Biology of the Cell, Winter 2018
Homework #10
Due 5PM, March 14, 2018.

Please submit this homework as a PDF (no Word documents or text emails).

This is a special homework in that the questions are very open ended. I find that thinking about how you would teach a class really helps codify the central principles and help you to see the forest through the trees. While different from the other homeworks this term, this homework will certainly be very valuable to both you and me.

Problem 10.1 (Spindle dynamics in the *C. elegans* zygote)**.**
Over the course of about five years, Stephan Grill and coworkers performed a series of studies on the *C. elegans* embryo. We will look at two aspects of their studies. First, we will interpret experimental results of the velocities of fragments of a severed centrosome by modeling how dynein motors that are attached to the cortex pull on microtubules. Then, we will come up with a theoretical model to explain the observed oscillations of the spindle prior to cytokinesis.

a) *Part (a) is worth 30 points.* Grill ablated the centrosome at either the posterior or anterior end of the spindle and then observed the velocity of the fragments as they moved radially away from the ablation site, as shown in Fig. 1.

   i) Come up with a model describing the speeds of the fragments. Using that model, derive a probability distribution describing fragment speeds. This question is intentionally open-ended, and there is not enough of a roadmap to give you a "right" answer (not that there is one). It is meant to allow you to discuss and come up with models working with your classmates with guidance from the course staff.

   ii) Ideally, we would like to have the entire data set of velocities from each ablation experiment, but those are unavailable. Instead, we have the mean and variance of the fragment velocities for each experiment. Using your result in part (i), derive an expression relating the variance in the velocities of a given ablation to the mean of the velocities of a given ablation.

   iii) Perform a regression on the variance versus velocity data, which you can download here, to make a rough assessment of your model's validity (does it capture the key features of the curve?) and to get estimates for model parameters.[1]

[1]Note that this is not a great way to analyze these data, but more sophisticate statistical inference is outside the scope of this course.

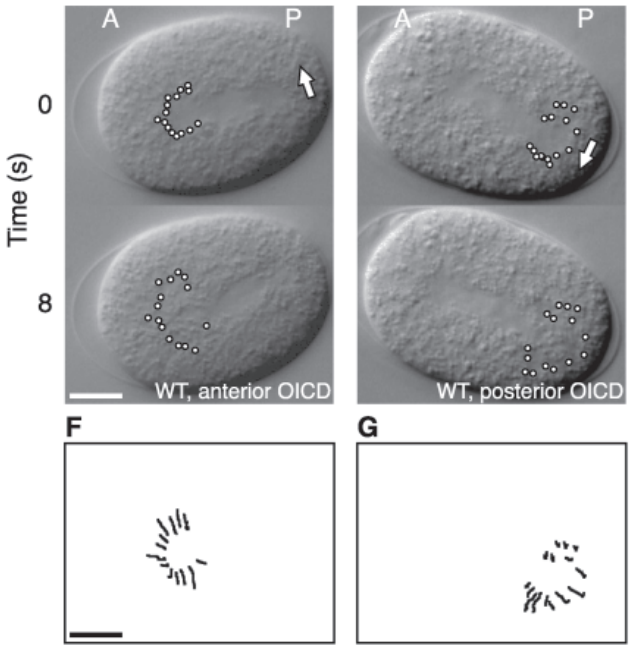

Figure 1: Schematic of centrosome ablation, or, as Grill and coworkers call it, optically induced centrosome disintegration, OICD. Upon alblation, fragments moved radially, and their velocities were determined.

b) *Part (b) is worth 20 points extra credit.* We will now study spindle oscillation. I will give a bit more guidance here for now, but you will still rely on in-class discussion for this. The centriole of the spindle is attached to the cortex via microtubules that are themselves acted upon by dynein force generators, as shown in Fig. 2. These motors pull the centriole toward the cortex.

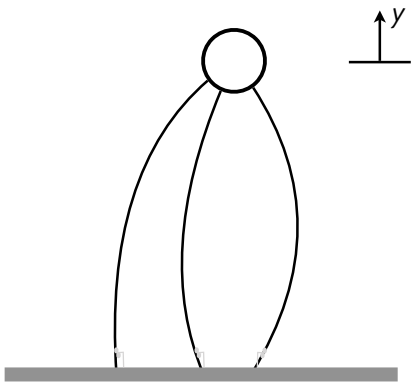

Figure 2: The centriole (circle) is connected to to the cortex (dark gray) via micortubules (black lines), which are themselves acted upon by force generators (light gray). Note the definition of the coordinate system, with y denoting the position of the centriole relative to the cortex.

In what follows, we will again use a linear force-velocity curve.

$$f = f_0 - f_1 v, \tag{10.1}$$

where v is the velocity of the motor, f_1 is the slope of the force velocity curve, and f_0 is the stall force.

i) There are several forces acting on the cortex. What are they? Why must they all sum to zero?

ii) We will write down a differential equation for the probability p that a given force generator is engaged. Specifically,

$$\frac{\mathrm{d}p}{\mathrm{d}t} = k_{\mathrm{on}}(1-p) - k_{\mathrm{off}}p. \tag{10.2}$$

Explain why this is a reasonable form for the dynamics of p.

iii) The rate constant for motor disengagement is load dependent. That is, the higher the load, the less likely the motor is to disengage. This is commonly found with motor proteins. Explain why

$$k_{\mathrm{off}} = k_{\mathrm{off}}^0 \left(1 - \frac{f_1}{f_c}\dot{y}\right), \tag{10.3}$$

where the over-dot denotes differentiation with respect to time and f_c is a force scale for the load dependence.

iv) Derive an updated differential equation for $p(t)$. You should write it in terms of a time scale $\tau = 1/(k_{\mathrm{on}} + k_{\mathrm{off}}^0)$ and the mean engagement probability $p_0 = \tau k_{\mathrm{on}}$.

v) If the speed changes slowly over the response time of the motors, i.e., $|\ddot{y}| \ll |\dot{y}/\tau|$, we can approximate p as a Taylor series to first order in the velocity and its derivative.

$$p \approx a + b\dot{y} + c\ddot{y}. \tag{10.4}$$

Insert this expression into the differential equation you derived in part (iv) and compare terms to get the constants a, b, and c.

vi) The above equation applys for the bottom side of the cortex. Use symmetry arguments to write an expression that applies for the top side of the cortex. I.e., you should have

$$\text{bottom: } p_- \approx a + b\dot{y} + c\ddot{y}, \tag{10.5}$$

$$\text{top: } p_+ \approx a' + b'\dot{y} + c'\ddot{y}. \tag{10.6}$$

Work out what a', b', and c' are.

vii) Use these expressions in your force balance to write down the complete equation of motion. Show that the result is a damped harmonic oscillators, possibly with negative damping.

viii) Work out for what parameter values oscillations that grow in amplitude are possible. Comment on the results.

Problem 10.2 (Problems for this class, 50 points)**.**
Write a substantial problem with a complete solution that you think would be enlightening to assign to next year's students. If you like, you may instead write two shorter problems (like problems 1.4 or 7.1), naturally also with complete solutions. The topic of the problem may be anything covered in lecture or in any of the readings (including chapters of books we did not explicitly go over this term). Explain why you think the problem you came up with will be enlightening for the students who do it.

Problem 10.3 (Your turn, 50 points)**.**
This problem statement is modified from a problem Rob Phillips assigned in this course when he taught it. He basically asked exactly what I would like to ask you.

a) Some have argued that only by quantitation will we really be able to come to terms with the complexity of living organisms. The quantitative approach advocated in this class is meant to give you a feel for how such quantitative dissection of biological problems might work. Others have argued that the approach we have taken is a mopping up operation which amounts to dotting the i's and crossing the t's already worked out by biologists. Write one paragraph defending each of these two points of view. One document you might find interesting to look at is Bio2010 from the National Academies of Sciences.

b) For this part of this problem, I would like you to develop a syllabus for a course (like this one) to train quantitative cell biologists. Make a syllabus for the course. Start with one brief paragraph on the mission of your course. Issues that you might want to consider include:

i) Is it important to do hard calculations, or is that the province of other physics courses and our goal here is to illustrate the style of thinking?

ii) Are street-fighting estimates a part of the way you will present the material (if yes, why; if no, why not?).

iii) How will you organize the material? Note that in typical biology books DNA and actin would never be in the same chapter, but for *PBoC2* they are both in Chapter 10 as examples of "beam theory."

iv) The course is only 10 weeks long. What will you cover, what will you skip, and why? How will you balance the desire to cover more topics

with the resulting superficiality?

This is not a look up something in Wikipedia question, nor is it a request to regurgitate what I did in the course. There is substantial overlap between what I do in the course and what Rob does when he teaches it, but there are clear differences as well. In many senses, physical biology of the cell is a new and unfinished topic. I am asking you how to organize this topic and to present it to advanced Caltech undergrads and to grad students at the beginning of their grad careers. What are the important points?

c) Finally, I would like a little feedback on this edition of the course. What subject did you find most interesting from the course? What subject did you find least interesting? Please answer with several sentences only, but justify your outlook and tastes (to the extent possible).