APh161: Physical Biology of the Cell

Winter 2007

When: TTh, 8:30-10:00 AM. We will have an aggressive set of makeup lectures right from the start of the term since I will miss class several times during the term.

Who: You and me (Rob Phillips, x 3374, *phillips@pboc.caltech.edu*, 159 Broad). The TAs for the course are Eric Peterson, x5876, *eric@caltech.edu* 155 Broad and David Van Valen, x 5876, *vanvalen@caltech.edu* 155 Broad. I am always happy to see you, but with certainty, the best way to contact me is by email. After that, the best approach is to schedule a time to see me through my assistant, Katie Miller (x6337, *kmiller@caltech.edu*, 138 Broad).

Where: 104 Watson

What: See below!

How: Lecture twice a week and weekly homework. No exams. Your grades will be based upon your homework grades. I will NOT accept ANY late homeworks (late means anytime after class starts the day the homework is due) unless you have a mindblowingly good excuse - this means a note from someone like a doctor or a Dean. (Please do not even ask me for an extension - the answer is NO). As for collaboration, you may discuss the homework with others, but your explanations and derivations must be your own and your logic should be carefully explained and the *significance* of your results should also be explained. If you hand us a sloppy (either sloppy thinking or writing) homework the grader will likely be unable to penetrate your logic and you will lose points.

Reading: The course webpage will have a repository of required reading from the original literature. However, the two most important texts for the course are a) **Essential Cell Biology** by Alberts *et al.*, and b) **Physical Biology of the Cell**, an incomplete draft of a book that I am writing with J. Kondev at Brandeis University and Julie Theriot of Stanford University. The book will be made available online as we go along.

1 Course Overview and Philosophy

It is a wonderful time to be thinking about the workings of the living world. Historic advances in molecular biology, structural biology and the use of physical techniques such as optical traps have provided an unprecedented window on the mechanics of the cell. The aim of this course is to study the cell and its components using whatever tools we need in order to make quantitative and predictive statements about cellular life. The main intellectual thread of the course will be the idea that the type of quantitative data which is becoming routine in biology calls for a corresponding quantitative modelling framework. The plan of the course is to elucidate general principles with exciting case studies. In 2007, in preparation for teaching Bi1 with Pamela Bjorkman, many of my case studies will be related to viruses and the response of the immune system. Note that science is driven by experiment. Nowhere is this more evident than in the life sciences. As a result, for those that are most serious I encourage simultaneous enrollment in the laboratory course, APh162 - Physical Biology Laboratory, which will be built around a series of experiments which are designed to correspond with material covered in the lecture course APh161.

2 Tentative Course Outline

The course outline given below is intended to provide an overall sense of the topics we will cover and the general flow of the course. Certain individual topics might be added or deleted as I see fit.

1. **Cells and the Viruses that Infect Them**
   - *Anatomy of a Blood Test.* The blood test. Red blood cells and hemoglobin. Macrophage. T-cells and B-cells.
   - *Cells: A Rogue's Gallery.* Cell theory. Pasteur: Fermentation and Pathogens. Cells and the Human Body. Prokaryotes, Eukaryotes and Archaea.
   - *Viruses.* Viruses and the origins of molecular biology. Tobacco mosaic virus, cowpea chlorotic mottle virus and the *in vitro* "reconstitution of life". Bacteriophage. Influenza. HIV.
2. **Statistical Mechanics for the Life Sciences**
   - *Analytical Engine of Statistical Mechanics.* Microstates. State variables and energies. The Boltzmann distribution. States and Weights.
   - *Applications.* Binding reactions (especially hemoglobin). Ion channels. Viruses binding to receptors. Immune presentation. Polymerase. Viral assembly.
3. **The Cell Cycle and Viral Life Cycles**
   - *The Biology and Physics of Growth Curves.* Cell growth curves. Viral growth curves. Other kinds of growth curves (often fluorescence).
   - *The Eukaryotic Cell Cycle.* The Inventory of a Cell. Growth. Cell Division.
   - *Bacterial Viruses.* Genome management. Viral assembly.
   - *Life cycle of retroviruses.* Viral entry. Genome management. Viral assembly. Viral exit and maturation. Immune response.

- *Evolution.* Sequences and alignments. Antibiotic resistance. Viral evolution.

4. **Genome Management in Cells and Viruses.**

   - *Genome sequences of viruses.* Genome sizes. Viral parts list revisited.
   - *Processes of the central dogma.* Copying genomes. Gene expression using "thermodynamic models". Gene expression - dynamics (kinetic proofreading). Genetic switches. Cell cycle oscillator.
   - *Chromosome geography and stochastic decision making.* How are genomes arranged in viruses and cells. Stochastic decision making and recombination - recombination in viruses and elsewhere. V(D)J recombination and DNA mechanics.
   - *Evolution and cis-regulatory rearrangement.* Generating novelty without changing coding regions. Case studies: flies to fishes.

5. **Signaling**

   - *Chemotaxis.* Phenomenology of chemotaxis. Simple models.
   - *Post-Translational Protein Modification.* Phenomenology of phosphorylation. Case studies and simple models.
   - *Physical limits of signaling.* Generating sharp features in embryos.
   - *Electrical Signaling in Cells.* How cells talk. Biological electricity. The action potential.

6. **Viruses at Membranes**

   - *Membrane Phenomenology.* lipids, membrane area, membrane composition, ions and ion transport.
   - *Viral entry.* Energetics of membrane bending.
   - *Viruses and organelle rearrangement.*

3 Bibliography

My logic in providing the following list of references is to give you a wide view of some of the important books (both pedagogically and as scholarly works) that have been written to describe this important field. In addition to the works listed here, you should count on a steady supply of readings from the current literature. Indeed, this course is going to be reading intensive since most of the audience will lack either the biological or physical background and will have to make up for such holes in part through extracurricular reading. One of my main hopes with this list is to avoid flying the flag of any particular discipline, whether it be biology, physics or chemistry. We should worry less about the names of disciplines and be more open to taking tools from whatever quarter they may be needed. NOTE: you will get much more out of the course if you make a point of doing the reading.

B. Alberts, D. Bray, A. Johnson, J. Lewis, M. Raff, K. Roberts and P. Walter, *Essential Cell Biology*, Garland Publishing, 2003. This book has become one of my prized possessions and is usually the first place I look each time I am trying to understand the current thinking on biological phenomena.

D. Boal, *Mechanics of the Cell*, Cambridge University Press, 2001. This book will serve as one of the main texts for the quarter. Boal has assembled a very nice collection of insights into the ways in which mechanics can be applied to the living world.

K. Sneppen and G. Zocchi, *Physics in Molecular Biology*, Cambridge University Press, 2005. This book is one of a growing number of attempts on the part of physicists to make a case for the role of quantitative analysis and physical reasoning in attacking real biological problems. There are many interesting topics scattered throughout the book.

S. Carroll, *Endless Forms Most Beautiful*, W. W. Norton and Company, 2005. This book is certainly one of the highlights of 2005 for me. I read it three times and think it is provocative and calls attention to some of the most interesting questions in biology. In particular, it addresses the connection between evolution and development.

M. Kirschner and J. Gerhart, *The Plausibility of Life*, Yale University Press, 2005. This book is similar in spirit to that of Carroll and discusses the insights that modern molecular and developmental biology have provided into evolution. These same authors have written a second amazing book *Cells, Embryos and Evolution*. It is a very serious undertaking, but full of interesting ideas.

A. Murray and T. Hunt, *The Cell Cycle*, Oxford University Press, 1993. This book is by two of the leaders in this field and though it is probably dated, it is full of interesting facts and ideas. Here too, I am keen on the idea of unleashing tools like those described in this class to think about real cell biology issues such as the cell cycle.

J. Howard, *Mechanics of Motor Proteins and the Cytoskeleton*, Sinauer Associates, 2001. Howard's book is full of interesting insights and will serve as our second central source of reading.

O. Mouritsen, *Life - As a Matter of Fat*, Springer, 2005. This book gives a number of insights into the role of lipids. My view is that lipids are short changed in the discussion of biological systems. Another book that I like a lot more is R. Robertson, *The Lively Membranes*, Cambridge University Press, 1983. Yes, the book is probably dated, but I like the tone and the figures.

G. Forgacs and S. Newman, *Biological Physics of the Developing Embryo*, Cambridge University Press, 2005. I am not sure yet whether I like this book or not, but at any rate, it is yet another example of the physics types trying to take stock of biological phenomena. Developmental biology is one of my favorite topics and clearly it will admit of an increasing participation on the part of quantitative scientists.

R. Burton, *Physiology by Numbers*, Cambridge University Press, 2000. This book is on my list because it attempts to take stock of many of the processes of physiology from the perspective of "a feeling for the numbers" as we have done in the class.

R. Schleif, *Genetics and Molecular Biology*, Johns Hopkins University Press,

1993. This is another one of my favorite books on molecular biology. Schleif has many interesting things to say about a variety of topics that we cover in the class.

Nelson, P., *Biological Physics: Energy, Information, Life*, W. H. Freeman and Company, 2004. Phil Nelson's book represents a view of parts of biology from a fully quantitative perspective and makes for enlightening reading.

Ptashne, M.,*A Genetic Switch*, Blackwell Science, 1992 and Ptashne, M.and Gann, A., *Genes and Signals*, Cold Spring Harbor Laboratory Press, 2002. I am a huge reader and always have been and as a result collect lists of great books given to me by any and everyone. Ptashne's two books make it onto my all time classics list. The clarity of the thinking and the farreaching vision which attempts to tame the complexity of biological specificity is truly inspiring. I also encourage you to listen to Ptashne's lectures at Rockefeller University which you can find online.

Dill, K. and Bromberg, S., *Molecular Driving Forces*, Garland Publishing, 2002. This fantastic book gives a proper description of the power and versatility of statistical mechanics as opposed to the schoolboy exercises that make for the main substance of most books on statistical mechanics. The applications to real world problems in biology and chemistry are as refreshing as they are enlightening.

Carroll S. B., Grenier J. K. and Weatherbee, S. D., *From DNA to Diversity*, Blackwell Science, 2001. This book is of the same high quality as those by Ptashne (and indeed, was inspired by Ptashne's *A Genetic Switch*). From my unsophisticated perspective, the way I view this book is as an attempt to bring together modern thinking on gene regulatory networks, developmental biology and the theory of evolution. Like Ptashne, these authors try to follow one key idea to its extreme, namely, the idea that animals share the same "genetic toolkit" that dictate body pattern.

G. Fain, *Sensory Transduction*, Sinauer Associates, 2003. Fain's book covers one of my favorite topics, namely, how organisms take external stimuli and do something with it. Two related books that will touch on the processing of information are G. Matthews, *Cellular Physiology of Nerve and Muscle* and M. Blaustein, J. Kao and D. Matteson, *Cellular Physiology.*

A. Lesk, *Introduction to Bioinformatics*, Oxford University Press, 2002. I find this to be the most amusing and thoughtful book on bioinformatics that I know of. I enjoy his exercises which lead us to consider differences between wooly mammoths and elephants, etc.

A. Y. Grosberg and A. R. Khokhlov, *Statistical Physics of Macromolecules*, AIP Press, 1994. I find this to be a fantastic book, full of interesting insights into the ways in which polymer physics can be used to explore problems of biological interest.

S. Vogel, *Life in Moving Fluids*, Princeton University Press, 1994. I love this book and although it is not centrally related to the present course, I couldn't resist recommending it. In addition, Vogel has recently made a synthesis of his thinking on the mechanics of life in his *Comparative Biomechanics*, Princeton University Press, 2003. I have yet to spend enough time with this book, but my general impression is that Vogel has the Midas touch so it is likely destined to become a classic.

J. M. Berg, J. L. Tymoczko and L. Stryer, *Biochemistry*, W. H. Freeman and Company, 2002. There are a host of interesting books on biochemistry (I also very much like this books main competitor - Lehninger) and my hope is that you will overcome any distaste you might have for the mindless memorization that seems to dictate the pedagogy that many of us have been exposed to and be open to the many beautiful problems in this area.

I. M. Klotz, *Ligand-Receptor Energetics*, John Wiley and Sons, 1997 and *Introduction to Biomolecular Energetics*, Academic Press, 1986. Like Ptashne, Klotz brings personality, originality and clarity to his books and I admire that enormously. I have spent much time with the first of these two books since Klotz works very hard to teach us how to think about molecules in interaction, and as he points out in the preface, it is only when viewed through the prism of their interactions that molecules are of interest to life.

J. D. Watson, T. A. Baker, S. P. Bell, A. Gann, M. Levine and R. Losick, *Molecular Biology of the Gene*, Cold Spring Harbor Laboratory Press, 2004. I find this book to be both brilliantly and beautifully executed. Chap. 16 on gene regulation in prokaryotes is a pleasure to behold and I also enjoyed reading chap.12 on the apparatus of transcription.

B. Lewin, *Genes VII*, Oxford University Press, 2000. I have enjoyed dipping into this book now and again for insights into genes and their action.

E. Bier, *The Coiled Spring: How Life Begins*, Cold Spring Harbor Laboratory Press, 2000. I really enjoyed reading this book on developmental biology - this is a fascinating area full of beautiful problems. The idea being explored is that all animals have more or less the same genes and yet they turn out very differently. We turn out so differently because different decisions are made about when and where to turn these genes on. I should note that before I got to the end I was overwhelmed by nomenclature that I have not yet mastered. I will definitely try this one again soon.

J. Israelachvili, *Intermolecular and Surface Forces*, Academic Press, 1992. The subject of this book is much larger than is implied by the title. We will make reference to Israelachvili's discussion both when discussing forces in the material world and also in the context of self-assembly.

C. R. Calladine and H. R. Drew, *Understanding DNA*, Academic Press, 1999. This book provides a window on DNA which makes a good deal of contact with the perspective that will be brought to this important molecule in the course.

M. Doi, *Introduction to Polymer Physics*, Oxford University Press, 1996. this book is short and sweet and provides a readable introduction to many of the ideas from polymer physics that we will borrow in our attempt to understand the mechanics of biological macromolecules.

P.-G. de Gennes, *Scaling Concepts in Polymer Physics*, Cornell University Press, 1979. de Gennes classic epitomizes the appeal of "universal" insights, especially as practiced by a master.

A. Y. Grosberg and A. R. Khokhlov, *Giant Molecules*, Academic Press, 1997. A very nice introduction to the physics of macromolecules. Describes many of the arguments that will be made in our course.

U. Seifert, *Configurations of fluid membranes and vesicles*, Adv. Phys., **46**, 13 (1997). Seifert provides a detailed description of the elasticity of membranes as well as insights into the current understanding of equilibrium shapes.

H. C. Berg, *Random Walks in Biology*, Princeton University Press, 1993. A must read. Berg has all sorts of fun and interesting things to say. I would hold this book up as another example of a book of the highest quality built around simple ideas applied in a thoughtful manner to important problems (like Ptashne, Klotz, de Gennes and some of the others on this list).

M. Doi and S. F. Edwards, *The Theory of Polymer Dynamics*, Clarendon Press, 1986. Doi and Edwards have some important discussions of the motion of polymers in crowded environments.

H. Echols, *Operators and Promoters* and H. F. Judson, *The Eighth Day of Creation*. I round out the list with these two very interesting books on the history of molecular biology. Judson's book is one of my three all time favorite scientific biographies and is instructive both on the science and on the types of personalities that did that science. Echols was a molecular biologist himself and tells the story of the development of molecular biology in very compelling terms - if you read this book you will learn much biology.