Biological Physics (Physics 444/544)
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Final Project

Goals

- Learn more about biophysical topics.
- Learn about experimental design and methods.

Timeline, and Guidelines

- **Topic:** Your topic should **not** be closely related to your research. Please **talk to me** if you'd like to discuss possibilities, if you'd like suggestions, or if you'd like to chat about what "closely" means!
- **Papers:** Whatever topic you choose, your presentation and writeup should discuss at least three research papers. These should be three "primary" papers, not review papers. It's of course good to read review papers to get a sense of the topic. There will not be time or space to discuss all three in detail; focus on key points of one (or part of one) study and briefly discuss the others, or pick pieces (e.g. one important figure) from various studies.
- By Tuesday of Week 6 (**Oct. 31**): Comment on two papers you've looked at, about two different topics. Note the key points, and whether the topic would (in your opinion) be a good choice for the final project. This is noted in HW5.
- By Tuesday of Week 7 (**Nov. 7**): Select a topic and be ready to give a 1-2 minute summary of the general idea in class. There will be a Canvas-based sign-up sheet for projects, and each topic can be chosen by at most one 544 (graduate) student and one 444 (undergraduate) student. Note that the in-class summary is just to share topics; you don't need to have finished your readings.
- By Tuesday of Week 8 (**Nov. 14**): Select the three "primary" papers that your project will cover. It's fine to change your mind after this, but I want to make sure that you have a possible set of papers at this point.
- **Presentation (544 Graduate Students):** In class, 15 minutes + 5 min. questions. This will either be on the last day of class, in Week 10, or during Finals Week. (We'll discuss this in class.) *Comment:* Giving a 15 minute talk that is both clear and informative is difficult! It requires mastery of the material as well as practice for clarity and timing.
- **Written part:** Due Tuesday, Dec. 5, 2023 5pm. (Through Canvas; PDF.)

Presentation Components

- **[16/100] Background.** Give a general background to the topic, and explain key concepts.
- **[4/100] Questions / Aims.** What was unknown in the studies you read, and *why should we care*?
- **[24/100] Experimental Design / Methods.** How does the technique work? Possibly useful questions: what instruments are needed? What is the sensitivity or resolution? How is "raw" data analyzed?
- **[13/100] Important findings or results.** Focus on things that struck you as particularly interesting or important.
- **[10/100] Future Directions.** How would you extend this work? What's an interesting or important experiment to be done, and how (roughly) could you do it? Be brief – you'll expand on this in the written part.
- **[17/100] Overall clarity of presentation.**

Paper Components

- **[444 Undergraduate students]** This should cover all the "presentation components" above, *except* Future Directions. Aim for about 3-5 single-spaced pages, and definitely include figures. You'll probably want to describe Methods in more detail than the papers do.
- **[544 Graduate students; 16/100]** In the written part, propose a future experiment and discuss why it is interesting and how you would structure it in terms of both data collection and analysis. Write 2-3 single-spaced pages (including figures). Figures are very helpful. Note that you do not need to include any of the "presentation components" in the written part; assume we've seen the presentation.

Suggested Topics

Super-resolution microscopy

Comments:

- There are several sub-categories of this: localization-based methods (PALM, STORM); Stimulated Emission Depletion; Structure Illumination. I suggest focusing on just one.

Possible starting points:

- (Very basic intro) https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2014/press.html
- (Wikipedia) https://en.wikipedia.org/wiki/Super-resolution_microscopy
- (Video) https://www.ibiology.org/ibioseminars/cell-biology/jennifer-lippincott-schwartz-part-3.html (The previous parts deal with basics of fluorescence imaging.)

- (On analysis techniques for localization-based methods) A. R. Small, R. Parthasarathy, Superresolution Localization Methods. *Annual Review of Physical Chemistry*. **65**, 107–125 (2014). (See also references therein.)

Be sure to discuss:

- Science that super-resolution microscopy has made possible – not just the technique itself.

Single-molecule biophysics

Comments: You may want to focus on manipulating single DNA or RNA molecules.

Possible starting points:

- Papers from Carlos Bustamante's group (UC Berkeley), Steve Block's group (Stanford)
- (video) https://www.ibiology.org/ibioseminars/biophysics-chemical-biology/carlos-bustamante-part-1.html
- C. Bustamante, J. C. Macosko, G. J. Wuite, Grabbing the cat by the tail: manipulating molecules one by one. *Nat. Rev. Mol. Cell. Biol.* **1**, 130–136 (2000).
- K. C. Neuman, S. M. Block, Optical Trapping. *Rev. Sci. Instr.* **75**, 2787–2809 (2004).
- C. Bustamante, J. Liphardt, F. Ritort, The Nonequilibrium Thermodynamics of Small Systems. *Phys. Today*. **58**, 43–48 (2005). [This is more about using biomolecules to learn about new physics, rather than the opposite; that would also make a fine topic!]

Single molecule protein experiments would also be a good focus – see papers by Michael Woodside, for example.

Material properties of the cytoskeleton

Possible starting points:

- (Videos) https://www.ibiology.org/ibioseminars/cell-biology/julie-theriot-part-1.html, https://www.ibiology.org/ibioseminars/cell-biology/julie-theriot-part-2.html
- Papers on actin rheology by David Weitz' group, e.g. M. L. Gardel *et al.*, Microrheology of entangled F-actin solutions. *Phys. Rev. Lett.* **91**, 158302 (2003); J. H. Shin *et al.*, Relating microstructure to rheology of a bundled and cross-linked F-actin network in vitro. *Proc. Natl. Acad. Sci. USA*. **101**, 9636–9641 (2004).
- Recent work on the remarkable activity-induced properties of protein networks, e.g. David A. Gagnon, Claudia Dessi, John P. Berezney, Remi Boros, Daniel T.-N. Chen, Zvonimir Dogic, and Daniel L. Blair, Shear-Induced Gelation of Self-Yielding Active Networks, *Phys. Rev. Lett.* **125,** 178003 (2020).
- Papers on the *bacterial* cytoskeleton, only recently discovered! This paper describes an amazing relationship between bacterial filaments and cellular curvature: S. Hussain, et al., MreB filaments align along greatest principal membrane curvature to orient cell wall synthesis. *eLife*. **7**, e32471 (2018).

- "The cell as a material," K. E. Kasza, A. C. Rowat, J. Liu, T. E. Angelini, C. P. Brangwynne, G. H. Koenderink, and D. A. Weitz, Current Opinion in Cell Biology 19, 101-107 (2007). A short review article on the complex mechanical properties of cellular cytoskeletal networks, especially as probed in cell-free, in vitro experiments. (I)

Molecular motors

Comments: You may want to focus on one type of motor protein, for example the "linear" motors that walk along cytoskeletal filaments, or rotary motors like ATP synthase, and you may also want to focus one technique such as optical trapping for studying them.

Possible starting points:

- (Videos) https://www.ibiology.org/cell-biology/motor-proteins/#part-1 (and subsequent parts)
- See the "single molecule biophysics" list, including C. Bustamante, J. C. Macosko, G. J. Wuite, Grabbing the cat by the tail: manipulating molecules one by one. *Nat. Rev. Mol. Cell. Biol.* **1**, 130–136 (2000).
- On the torque of the flagellar motor: W. S. Ryu, R. M. Berry, H. C. Berg, Torque-generating units of the flagellar motor of Escherichia coli have a high duty ratio. *Nature.* **403**, 444–447 (2000).

The biophysicist's guide to the bacterial flagellar motor – 2017 review.
https://www.tandfonline.com/doi/full/10.1080/23746149.2017.1289120
"The biophysicist's guide to the bacterial flagellar motor," J. A. Nirody, Y.-R. Sun, and C.-J. Lo, Advances in Physics: X **2,** 324–343 (2017).

Immune signaling at cell surfaces

Possible starting points:

- Grakoui, S. K. Bromley, C. Sumen, M. M. Davis, A. S. Shaw, P. M. Allen, M. L. Dustin, The immunological synapse: a molecular machine controlling T cell activation. *Science.* **285**, 221–227 (1999).
- S. Y. Qi, J. T. Groves, A. K. Chakraborty, Synaptic pattern formation during cellular recognition. *Proc. Natl. Acad. Sci. USA.* **98**, 6548–6553 (2001). Theory – is it correct?
- K. D. Mossman, G. Campi, J. T. Groves, M. L. Dustin, Altered TCR signaling from geometrically repatterned immunological synapses. *Science.* **310**, 1191–1193 (2005).
- R. S. Ganti, W.-L. Lo, D. B. McAffee, J. T. Groves, A. Weiss, A. K. Chakraborty, How the T cell signaling network processes information to discriminate between self and agonist ligands. *PNAS.* **117**, 26020–26030 (2020).

Embryonic development

Comments: Developmental biology is a huge field, with a long history. Recently, there has been great work on biophysical aspects of development, a bit of which we've seen in the course.

Possible starting points:

- There's a good overview, especially of transcriptional regulation, in **Physical Biology of the Cell**, by Rob Phillips, Jane Kondev, Julie Theriot and Hernan G. Garcia, Garland Science, New York, (2013).
- J. O. Dubuis, et al., "Positional information, in bits." *Proc. Natl. Acad. Sci.* **110**, 16301–16308 (2013).
- Papers from Thomas Gregor, William Bialek (theory)
- S. Toda, L. R. Blauch, S. K. Y. Tang, L. Morsut, W. A. Lim, Programming self-organizing multicellular structures with synthetic cell-cell signaling. *Science*. **361**, 156–162 (2018). [It's not embryonic development, but it borrows and uses ideas from development. Note the Foty and Steinberg papers cited here.]

Systems biology / Genetic circuits

Possible starting points:

- U. Alon, *Introduction to Systems Biology: And the Design Principles of Biological Networks* (CRC Press, 2007).
- J. Hasty, D. McMillen, J. J. Collins, Engineered gene circuits. *Nature*. **420**, 224–230 (2002).
- T. S. Gardner, C. R. Cantor, J. J. Collins, Construction of a genetic toggle switch in Escherichia coli. *Nature*. **403**, 339–342 (2000).
- M. B. Elowitz, S. Leibler, A synthetic oscillatory network of transcriptional regulators. *Nature*. **403**, 335–338 (2000). [We might discuss this in class; see recent papers that cite it.]
- A. Raj, A. van Oudenaarden, "Nature, Nurture, or Chance: Stochastic Gene Expression and Its Consequences." *Cell*. **135**, 216–226 (2008).

Organs-on-a-chip, and / or Organoids

Possible starting points:

- See especially work from Don Ingber (Harvard & Wyss Institute): https://wyss.harvard.edu/technology/human-organs-on-chips/, and papers like D. Huh et al., Reconstituting organ-level lung functions on a chip. *Science*. **328**, 1662–8 (2010).
- J. Cremer, I. Segota, C. Yang, M. Arnoldini, J. T. Sauls, Z. Zhang, E. Gutierrez, A. Groisman, T. Hwa, Effect of flow and peristaltic mixing on bacterial growth in a gut-like channel. *PNAS*. **113**, 11414–11419 (2016).
- E. Karzbrun, A. Kshirsagar, S. R. Cohen, J. H. Hanna, O. Reiner, Human brain organoids on a chip reveal the physics of folding. *Nat. Phys.* **14**, 515–522 (2018).
- There are at least a few companies commercializing organ-on-a-chip systems, e.g. Emulate (https://emulatebio.com/) and Mimetas (https://mimetas.com/page/gut-on-a-chip)

Be sure to discuss:

- Science that these devices has made possible – not just the technique itself.
- The relevant physics – see also papers on microfluidics and small-scale fluid flow (below)

Three-dimensional genome architecture

Comments: In the past few years, we've been able to probe the spatial organization of genomes, and have realized that rather than being random or disordered, there are structural principles that influence gene regulation.

Possible starting points:

- T. Misteli, The Self-Organizing Genome: Principles of Genome Architecture and Function. *Cell.* **183**, 28–45 (2020).
- M. J. Rowley, V. G. Corces, Organizational principles of 3D genome architecture. *Nature Reviews Genetics.* **19**, 789–800 (2018).
- H. D. Ou, S. Phan, T. J. Deerinck, A. Thor, M. H. Ellisman, C. C. O'Shea, ChromEMT: Visualizing 3D chromatin structure and compaction in interphase and mitotic cells. *Science.* **357**, eaag0025 (2017).

Active Matter

Comments: This is a fascinating topic that has exploded in recent years. There are more theory papers than experiments; be sure your project focuses on at least one experimental primary paper. I've listed two review papers here that may be useful (Bär et al., Alert et al.).

Possible starting points:

- S. Liu, S. Shankar, M. C. Marchetti, Y. Wu, Viscoelastic control of spatiotemporal order in bacterial active matter. *Nature.* **590,** 80–84 (2021).
- R. Alert, J. Casademunt, J.-F. Joanny, Active Turbulence. *Annual Review of Condensed Matter Physics.* **13,** 143–170 (2022).
- M. Bär, R. Großmann, S. Heidenreich, F. Peruani, Self-Propelled Rods: Insights and Perspectives for Active Matter. *Annual Review of Condensed Matter Physics.* **11,** 441–466 (2020).
- T. H. Tan, A. Mietke, J. Li, Y. Chen, H. Higinbotham, P. J. Foster, S. Gokhale, J. Dunkel, N. Fakhri, Odd dynamics of living chiral crystals. *Nature.* **607,** 287–293 (2022).
- O. J. Meacock, A. Doostmohammadi, K. R. Foster, J. M. Yeomans, W. M. Durham, Bacteria solve the problem of crowding by moving slowly. *Nat. Phys.* **17,** 205–210 (2021).