A course on "Physical Models of Biological Systems"

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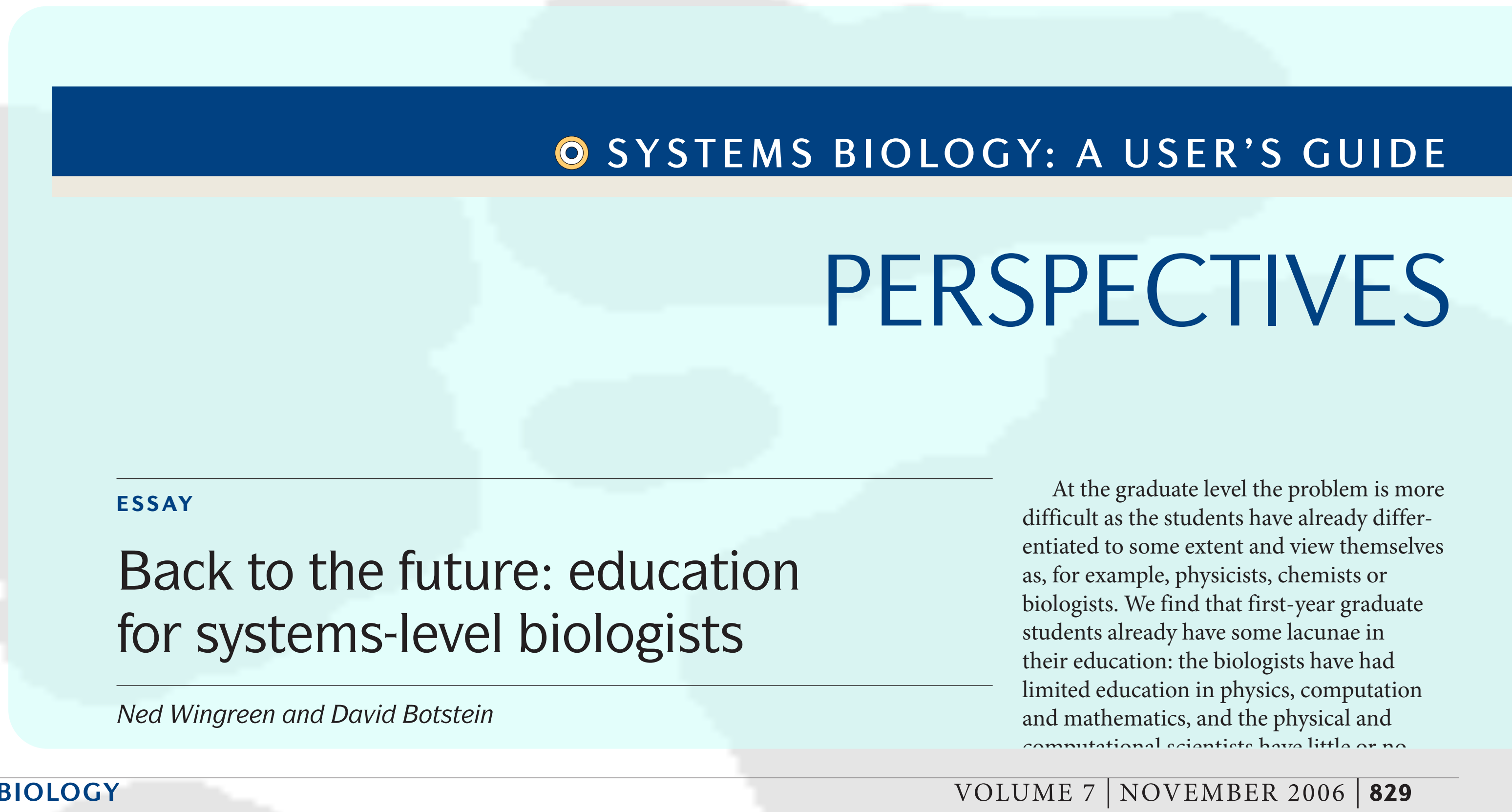

SYSTEMS BIOLOGY: A USER'S GUIDE

PERSPECTIVES

ESSAY

Back to the future: education for systems-level biologists

Ned Wingreen and David Botstein

At the graduate level the problem is more difficult as the students have already differentiated to some extent and view themselves as, for example, physicists, chemists or biologists. We find that first-year graduate students already have some lacunae in their education: the biologists have had limited education in physics, computation and mathematics, and the physical and

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BIO2010 report

RECOMMENDATION #1

Given the profound changes in the nature of biology and how biological research is performed and communicated, each institution of higher education should reexamine its current courses and teaching approaches (as described in this report) to see if they meet the needs of today's undergraduate biology students. Those selecting the new approaches should consider the importance of building a strong foundation in mathematics, physical, and information sciences to prepare students for research that is increasingly interdisciplinary

http://books.nap.edu/

Things one hears…

… explicitly or not.

- “Life science students need to study physical science so that they can learn to model their data.”
- “And physical science students will need a job some day, so they need to study life science.”
- “Students don’t need extensive discussion of historical examples of discovery. After all, they’re really not likely to go breaking any big paradigms. They’re more likely to become grunts.”
- “As such they need training in how to be good grunts who work effectively in teams … know the ins and outs of grant writing… ethics… animal treatment…”

Some goals

So much for what I *don't* think are the right goals.

- I do think an interdisciplinary lecture course can be useful if a practitioner of one discipline shows students pursuing a different discipline how his methods have been *useful in solving problems of independent interest in the other field.*
- There are some good reasons to make this an intermediate-level (sophomore+) course, not a tweak of freshman physics-for-premeds.
- It's good to frame topics around "how could anything like that possibly happen" puzzles.
- Here are some details.

What do we really want our undergrads to get, as early as possible?

Science needs imagination:

"Nature uses only the longest threads to weave her patterns, so each small piece of her fabric reveals the organization of the entire tapestry." --- Richard Feynman

Imagination must be coupled to discipline:

"Seek simplicity, and distrust it." --- Alfred North Whitehead

Science involves modeling:

"We all know that Art is not truth. Art is a lie that makes us realize the truth." --- Pablo Picasso

Quantitative models are the most falsifiable:

"A single number has more genuine and permanent value than an expansive library full of hypotheses." --- Robert Mayer, 1814--1878

BIO2010 report

" Many science and mathematics courses are taught as sets of facts, rather than by explaining how the material was discovered or developed over time. Covering the history of the field, demonstrating the process of discovery, or presenting other stories as examples of how scientists work—while clearly illustrating why the knowledge that has been gained is relevant to the lives and surroundings of the students—is an excellent way to engage undergraduates.

Much of today's biomedical research is at the interface between biology and the physical, mathematical, or information sciences. Most colleges and universities already require their biology majors to enroll in courses in mathematics and physical science. However, faculty often do not integrate these subjects into the biology courses they teach. This can result in students with a shortsighted view of the connections between all the scientific disciplines involved in the study of the biological world, and produce students who do not see the relevance of their other science courses to their chosen field of study. "

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BIO2010 report

RECOMMENDATION #1.3

The principles of physics are central to the understanding of biological processes, and are increasingly important in sophisticated measurements in biology. The committee recommends that life science majors master the key physics concepts listed below. Experience with these principles provides a simple context in which to learn the relationship between observations and mathematical description and modeling.

The typical calculus-based introductory physics course taught today was designed to serve the needs of physics, mathematics, and engineering students. It allocates a major block of time to electromagnetic theory and to many details of classical mechanics. In so doing, it does not provide the time needed for in-depth descriptions of the equally basic physics on which students can build an understanding of biology. By emphasizing exactly solvable problems, the course rarely illustrates the ways that physics can be applied to more recalcitrant problems. Illustrations involving modern biology are rarely given, and computer simulations are usually absent. Collective behaviors and systems far from equilibrium are not a traditional part of introductory physics.

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Specific goals

- In the course we study some classic case studies of successful reductionistic models of complex phenomena, emphasizing the key steps of (1) **making estimates,** often based on dimensional analysis, (2) using them to figure out which physical variables and phenomena will be **most relevant** to a given system, and which may be disregarded, and (3) **finding analogies** to purely physical systems whose behavior is already known. By the way, *these are the skills most valued in students who go on to careers outside pure science*.

- A **model** is a distillation of the known relevant behavior of a system into just a few rules. A good model can help us see the forest for the trees; in Picasso's phrase, it is ``the lie that makes us realize the truth." But as scientists, we want to take our existing models and poke them, looking for soft spots. We want to look for biologically relevant, incompletely tested aspects of the model. We want to find its falsifiable predictions, then devise uncluttered experiments that bear as directly as possible on those predictions. *Quantitative predictions are often the sharpest tool for poking a model.*

- The course develops many ideas from **probability** theory. But it's not a course on descriptive statistics, the design of clinical trials, and so on. Rather we'll look at case studies where *important insights into biological systems emerged from an appreciation of the intrinsically random nature of the interactions in complex systems.* Along the way we introduce some of the key ideas of biological physics, for example the concept of random walks.

- Long ago, in a course like this we'd have to be content with me telling students what faraway people had done; they couldn't roll up your sleeves and do the actual science themselves, because it was too difficult to make computers do anything. *Luckily all that has changed.* We learned and used ***Matlab***. Whatever students may do in science after this course, the skills they get with *Matlab* will be useful to them.

Bacterial genetics

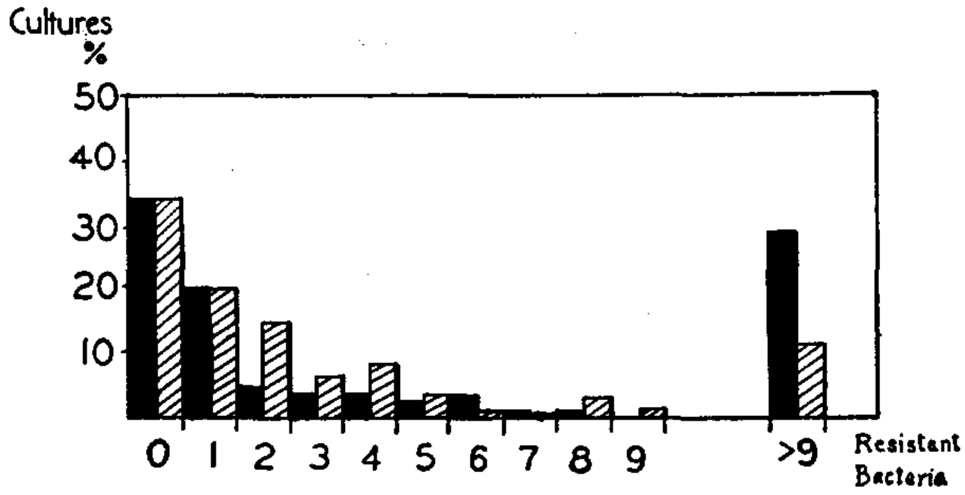


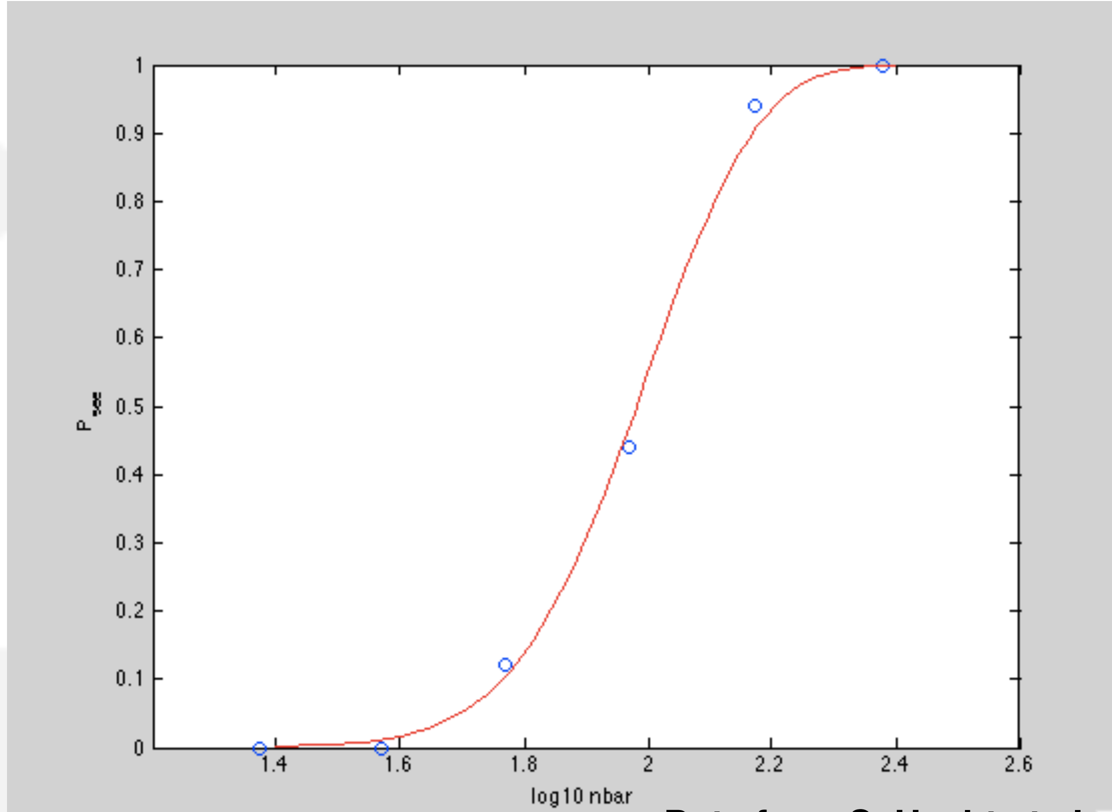
FIGURE 2.—Experimental (Experiment No. 23) and calculated distributions of the numbers of resistant bacteria in a series of similar cultures. Solid columns: experimental. Cross-hatched columns: calculated.

Luria & Delbruck, 1947

- Luria and Delbruck noticed a statistical peculiarity in their data -- a huge tail. They came up with a "Mendel, not Lamarck" model for resistance, and detailed quantitative predictions for such distributions that distinguished their model from the alternative.
- They had to work very, very hard. But now it's trivial for students to simulate in *Matlab*.

Vision

A complex system, impossibly difficult to understand.



Data from S. Hecht et al

- Hecht et al measured the probability of seeing a flash vs intensity. They were led from this information to the conclusion that single photons can excite rod cells, and that a quorum of >*N* simultaneous rod-cell firings is registered consciously.
- Students can fit their data in *Matlab* and find *N.*

Genetic switching

Monod found something funny in the growth of bacteria in mixed medium.
He ended up with the operon model.

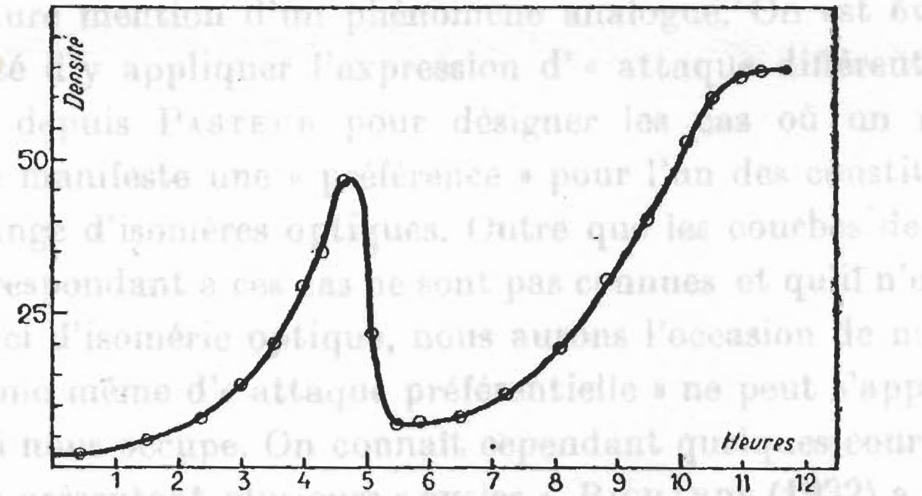
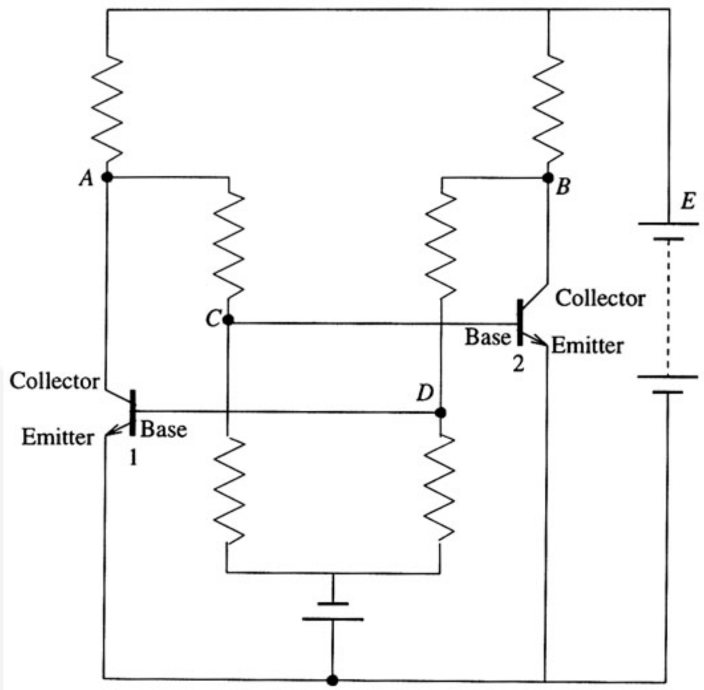


FIG. 33. — Croissance d'une culture de *B. subtilis* en milieu synthétique, en présence d'un mélange de saccharose et de dextrine, le milieu contenant 0,15 p. 1.000 de chaque sucre.

Monod 1949

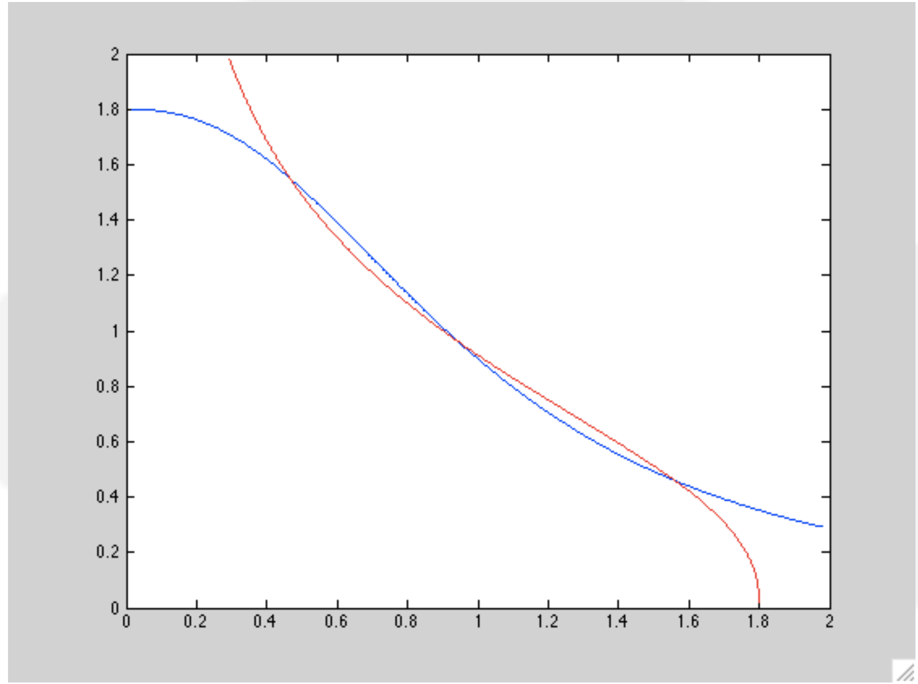


ure 12.10. The flip-flop circuit.

Could bacteria somehow be implementing a two-state switch like the ones that changed human civilization in the 20th century?

Switching, II

Students can write a model of two mutually repressing genes, make the phase-plane analysis, and find the region of bistability in *Matlab.*



It's not speculation -- now the transfer functions of each element have been measured. The era of synthetic biology has arrived.

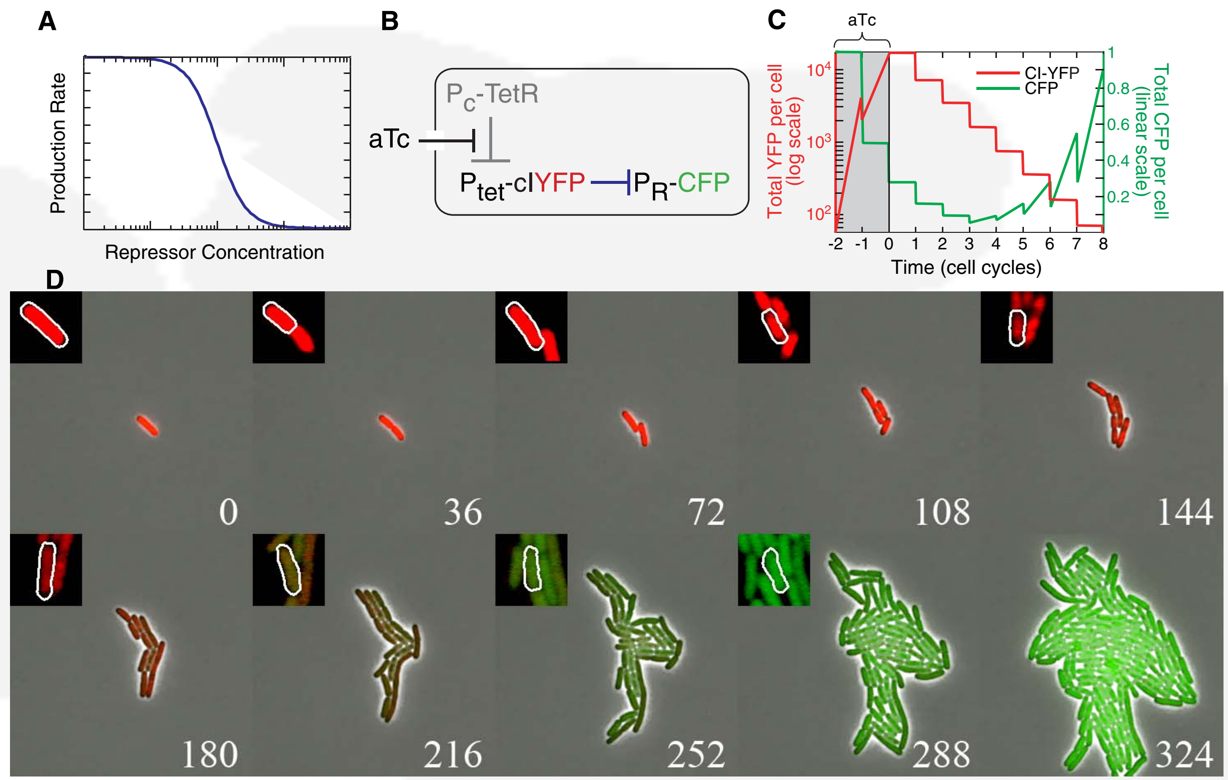
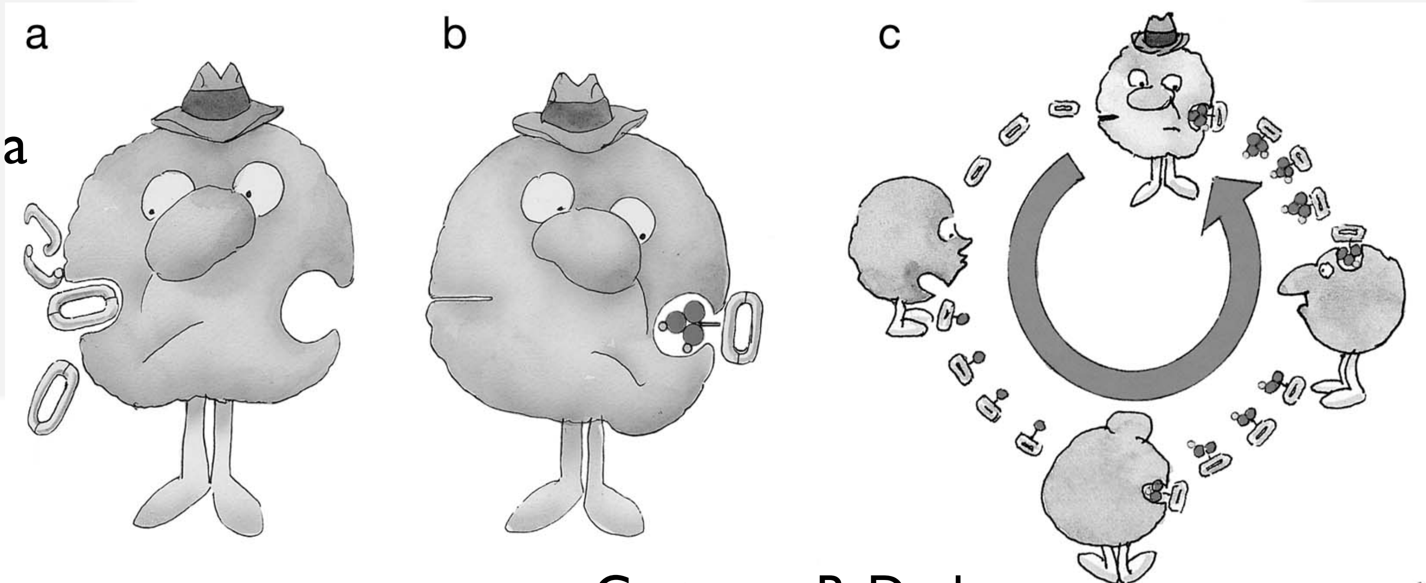


Figure S1: Snapshots of a typical regulator dilution experiment using the O_R2^*-λ-cascade strain. *Panels show the same microcolony as Fig. 1D, with greater time-resolution. CI-YFP protein is shown in red and CFP is shown in green. Times, in minutes, are indicated on*

Rosenfeld et al 2005

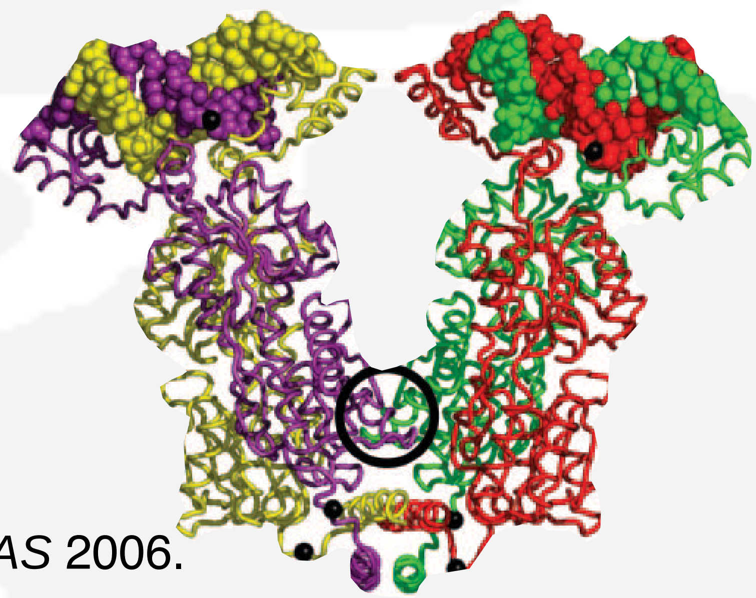
Macromolecules are physical objects

Allostery can implement a control strategy.



Cartoon: B. Dodson

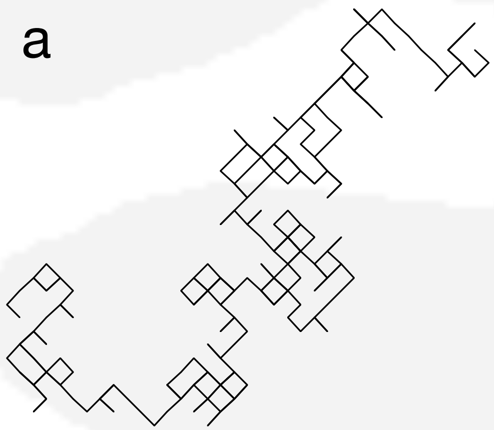
Students can use molecular visualization software to look at structure and see clues to function for themselves.



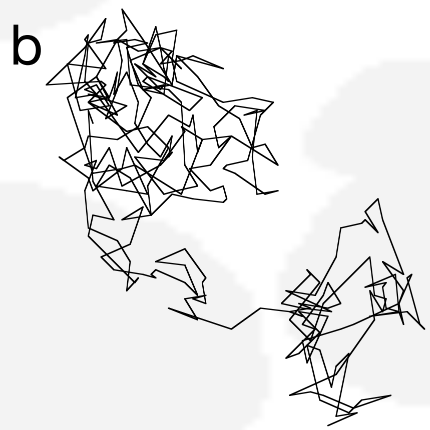
PDB picture from D Swigon et al. *PNAS* 2006.

Random walks

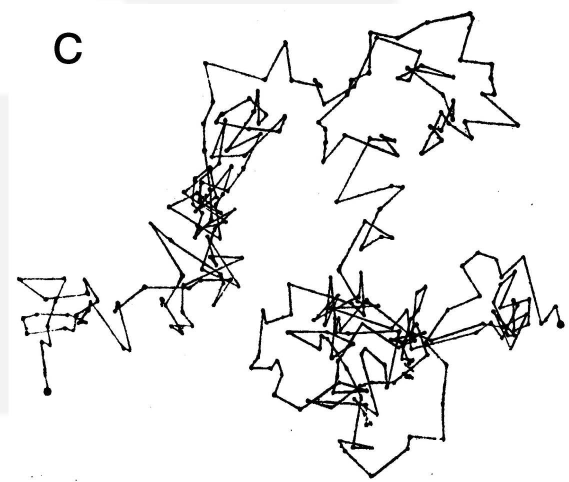
Simple walk:



Sampled walk:



Real Brownian motion:

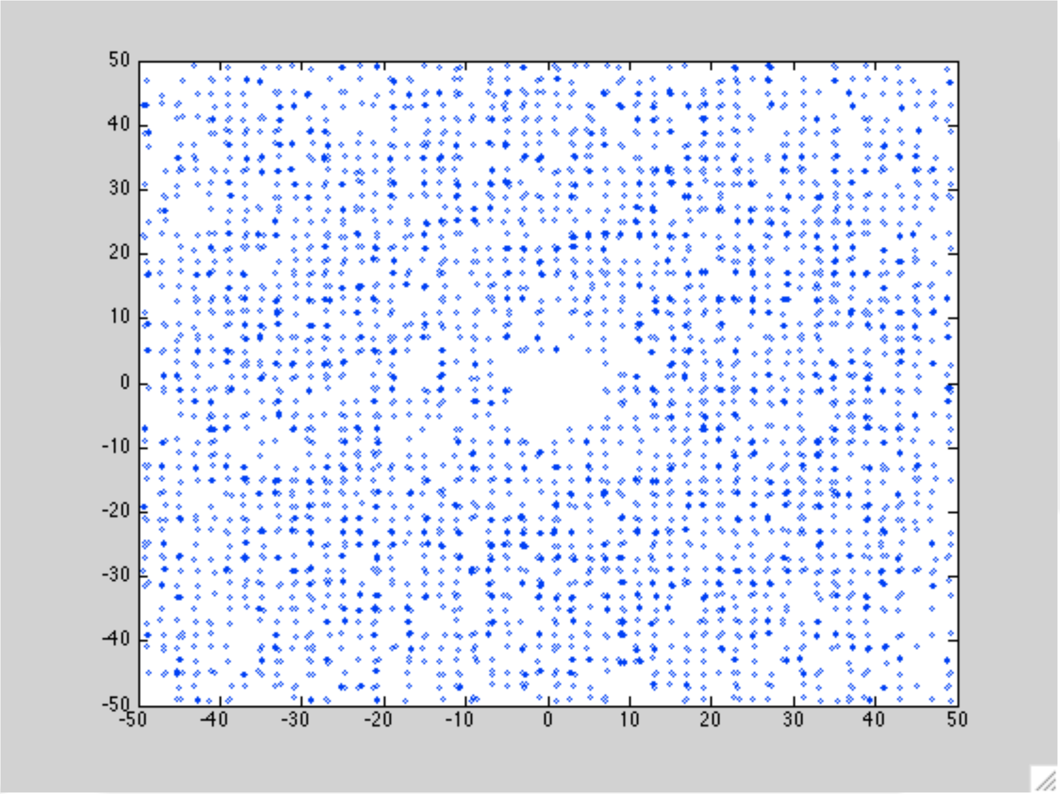


Students can simulate a random walk, then run it again and again to grasp the generic similarity of these figures despite the fact that they're always different in detail.
Then they can find the mean-square displacement to confirm the diffusive law.

P Nelson, *Biological Physics*, updated ed 2008.

Diffusion

We can show that the diffusive flux of oxygen to a bacterium is limited by its size. But that derivation is a bit abstract. We don't see the oxygen molecules.

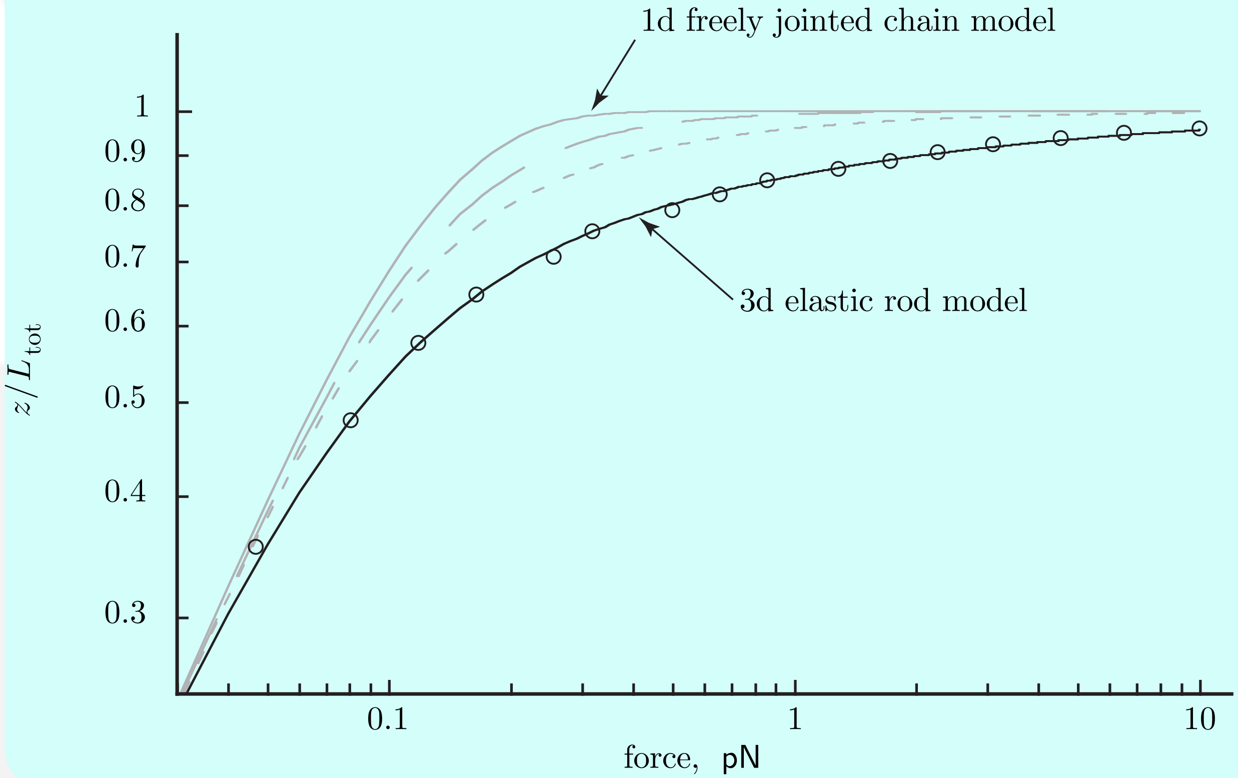


Students can simulate random walks in *Matlab* and find the diffusive flux to an absorbing sphere. They can then find the flux to a reflecting sphere with absorbing patches -- a calculation they *cannot* do analytically, and one with big implications (Berg and Purcell).

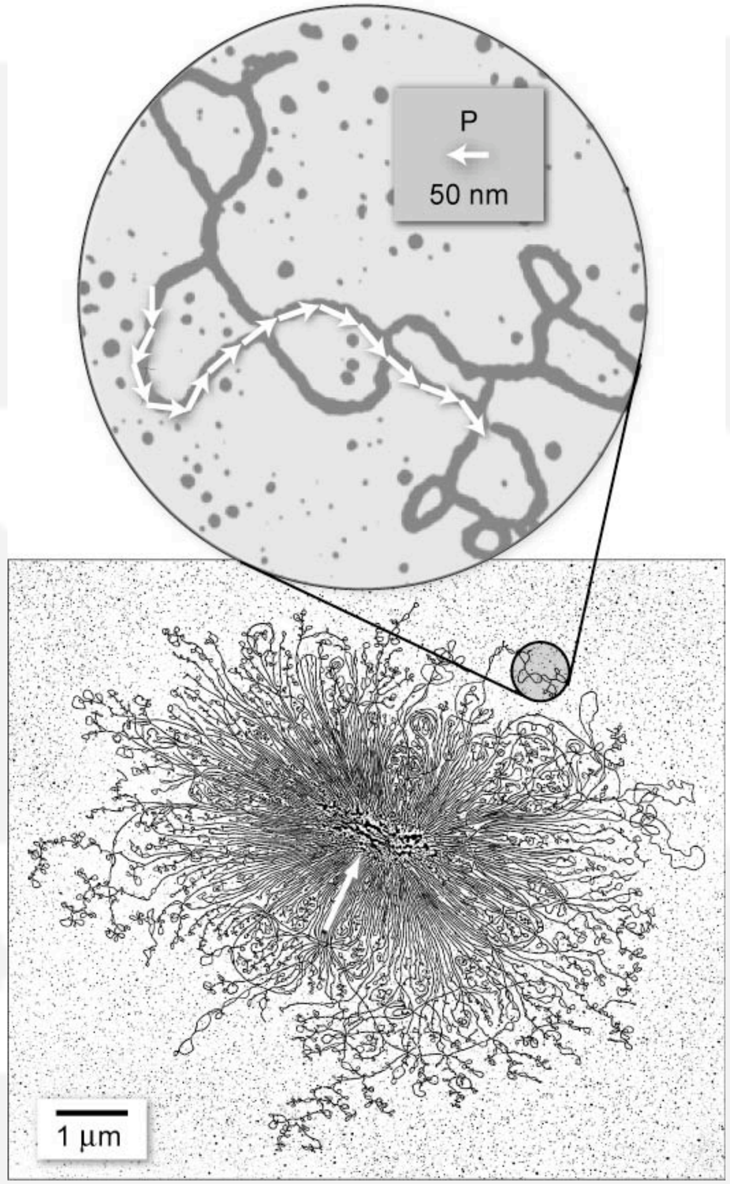
Polymer statistics

Random walks are ubiquitous in biological physics. Once you learn something interesting about diffusion, suddenly you've got something about elastic energy storage in insect wings.

Students can take simple models motivated by macroscopic mechanics, add thermal motion, and get connection to recent experimental data on single molecules.



P Nelson *Biological Physics* (updated ed. 2008).

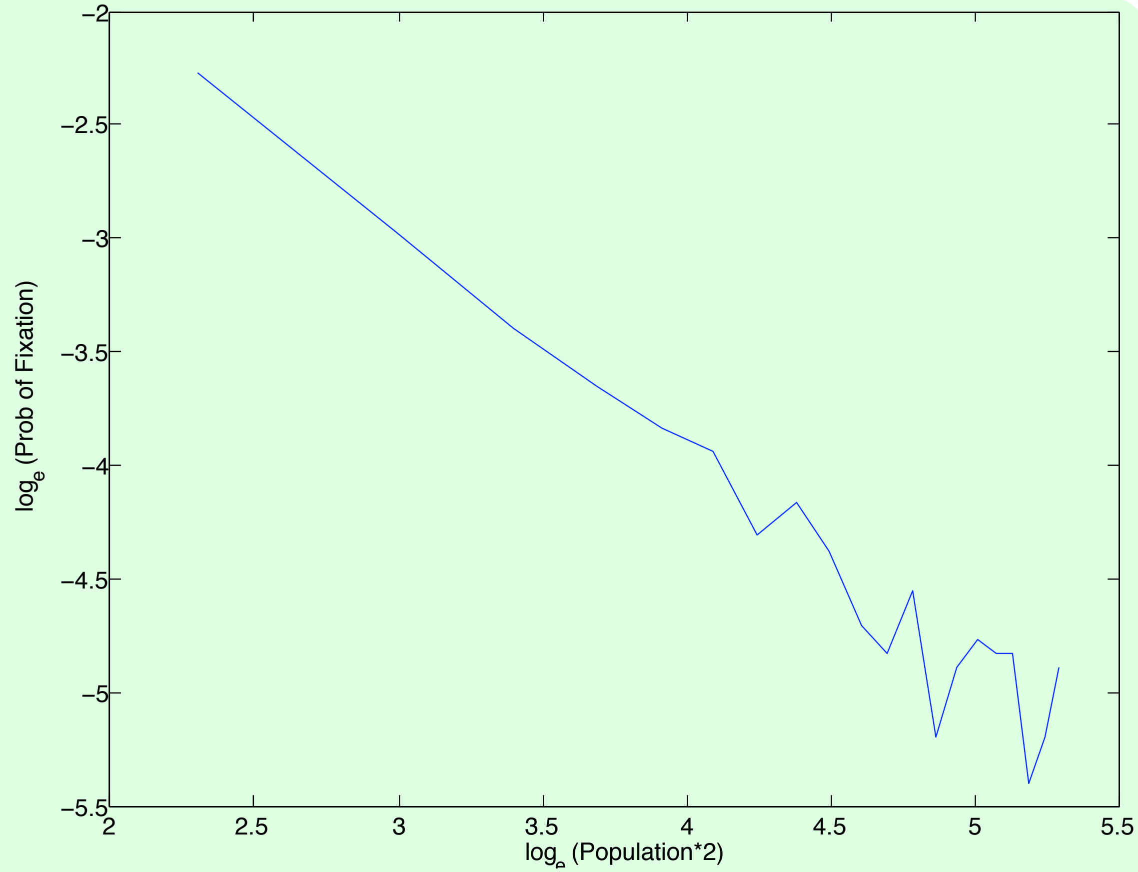


Ruth Kavenoff, reprinted in Phillips, Kondev, and Theriot, *Physical Biology of the Cell (2009).*

Genetic drift

Genetic drift is also a random walk -- with non-constant "diffusion constant." Kimura had to work very, very hard to solve this model, but it led to the very important result that probability of fixation is proportional to 1/(population).

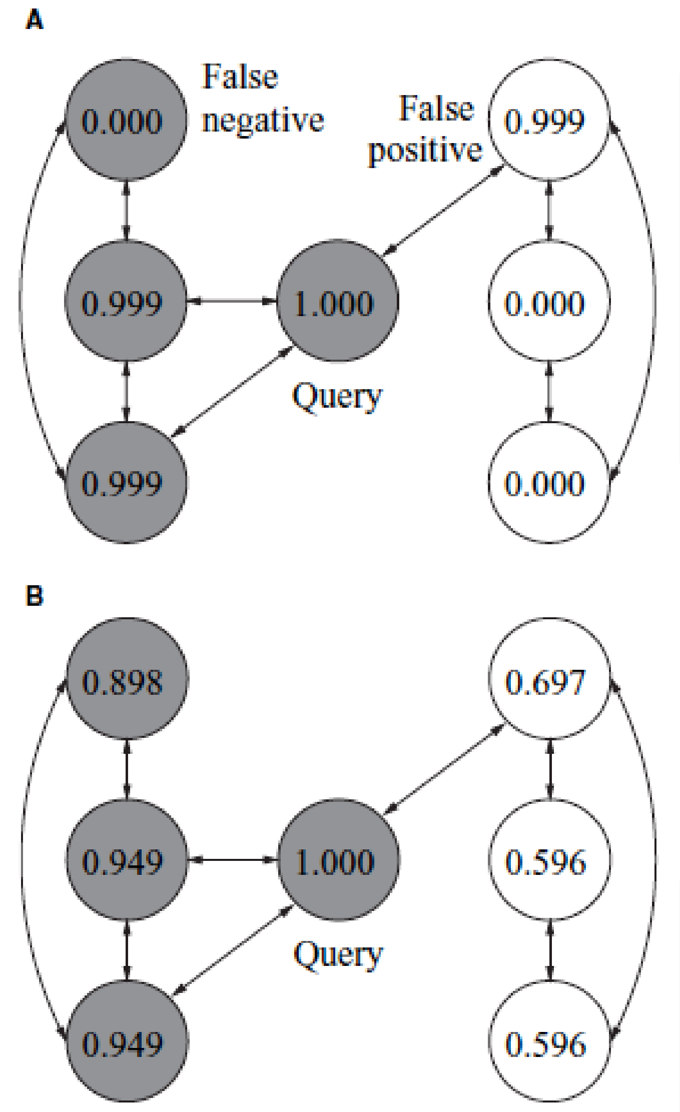
Students can trivially simulate this system and obtain this result in *Matlab.*



Proteomics

If you're looking at an unknown gene, and it resembles a lot of kinase genes, then maybe it's a kinase.
But resemblance can be hard to spot.
Nonlocal sequence homologies can be important.
Diffusive processes *on graphs* can tease out those nonlocal aspects.

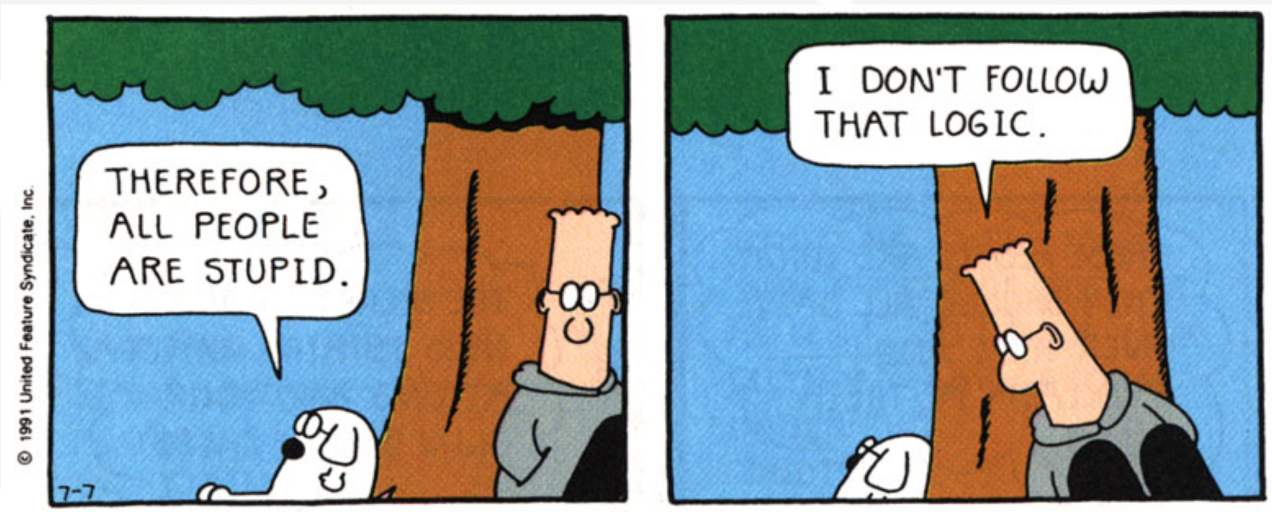
Well, that's yet another random-walk problem. It's also the basis of the Google PageRank algorithm.



Noble et al FEBS 2005

First clean up our own act

- Often we just stop after merely showing that physics "works." We must keep the intrinsic interest of the results and tools front and center.
- Usually our textbooks are devoid of real experimental data. Students need to see real data because it's not as nice as fake data, and yet nevertheless sometimes strong conclusions can be drawn from it.
- In our urgent desire to get the basics down, we often forget to put in current discoveries, with appropriate links to the basics.
- We theorists sometimes overdo the theory:



Last word

Remember to have fun yourself. Students feel it.

Thanks

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