

# BE/APH161 – PHYSICAL BIOLOGY OF THE CELL

**Rob Phillips**

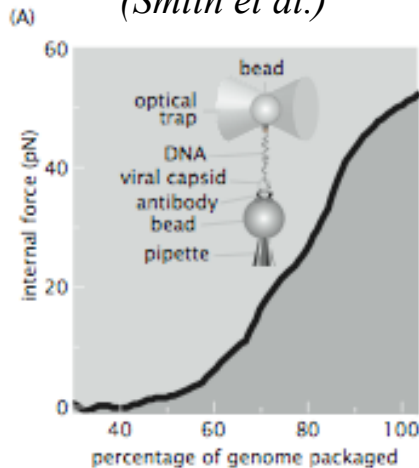
Applied Physics and Bioengineering  
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# A CALL TO ARMS: THE BIOLOGICAL FRONTIERS OF PHYSICS

- ◆ Often, biological data reports on functional relationships like those that are the lifeblood of physics.
- ◆ Data of this variety imposes much stricter demands on biological **theory**. No amount of words or cartoons suffice to describe such data.

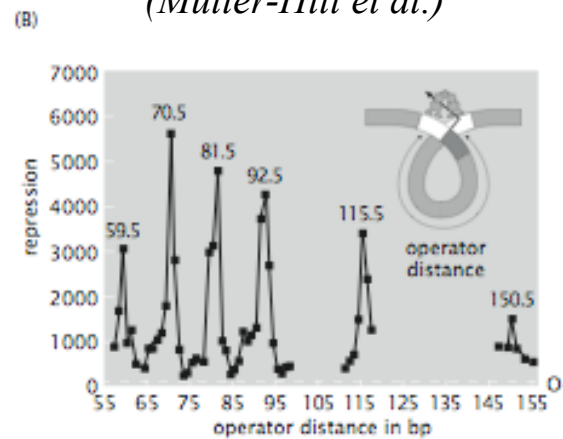
## Genome Management

(Smith et al.)



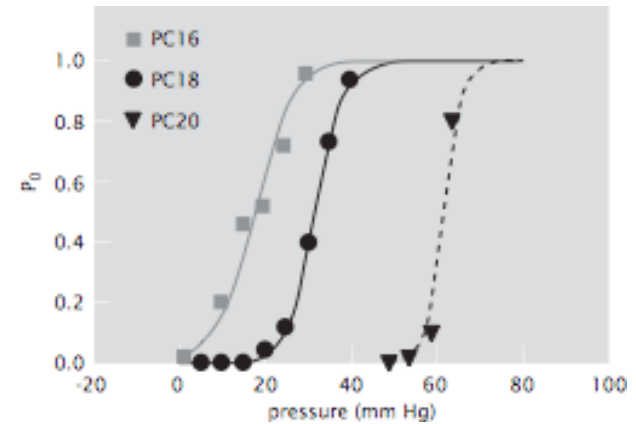
## Gene regulation

(Müller-Hill et al.)



## Mechanosensors

(Perozo et al.)



**Mathematics Is Biology's Next Microscope,  
Only Better; Biology Is Mathematics' Next  
Physics, Only Better**

Joel E. Cohen

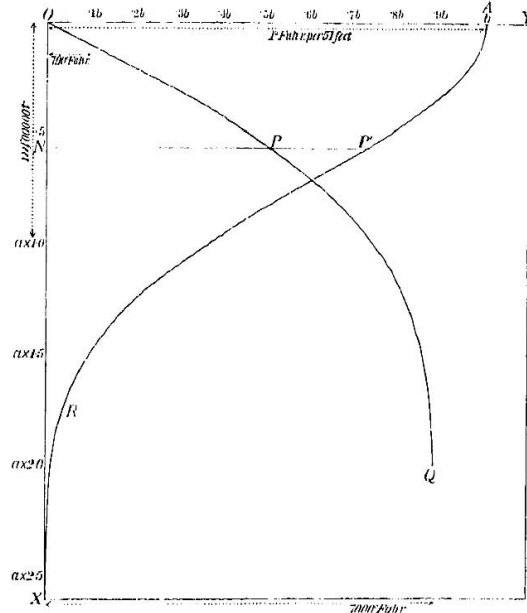
# “THE JOB OF THEORISTS IN BIOLOGY IS TO BE WRONG” – ANALOGIES THAT MIGHT MAKE THE POINT

XCIV.] ON THE SECULAR COOLING OF THE EARTH. 303

INCREASE OF TEMPERATURE DOWNWARDS IN THE EARTH.

$$\begin{aligned}
 ON &= x, & a &= 2\sqrt{xt}. \\
 NP &= bc^{-2/a^2} = y', & \frac{dy}{dx} &= \frac{V}{a} \cdot \frac{NP}{b \frac{1}{2} \sqrt{\pi}} \\
 NP &= \text{area } ONP'A + a = \frac{1}{a} \int_a^x y' dx^2, & v - v_0 &= V \cdot \frac{NP}{b \cdot \frac{1}{2} \sqrt{\pi}}
 \end{aligned}$$

The curve *OPQ* shows excess of temperature above that of the surface.  
The curve *APR* shows rate of augmentation of temperature downwards.

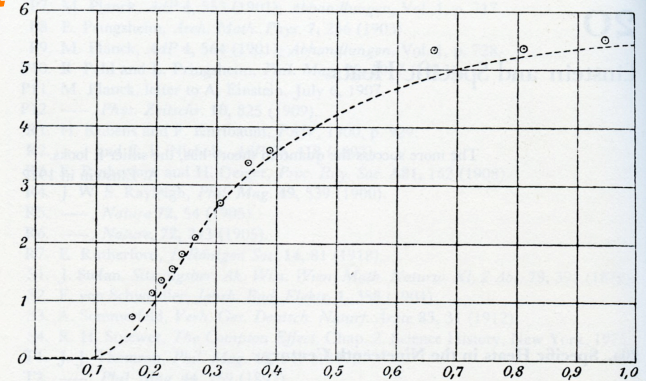


\* A table of the values of this integral, sometimes now called the "Error Function," is to be found in Table III. of De Morgan's article on "The Theory of Probabilities," *Encyclopaedia Metropolitana*, Edition 1845, Vol. II. W. T. March 27, 1889.

## Data of Dulong and Petit

CHALEURS SPÉCIFIQUES (1).	POIDS RELATIFS des atomes (2).	PRODUITS du poids de chaque atome par la capacité correspondante.	
Bismuth,	0,0288	13,30	0,3830
Plomb,	0,0293	12,95	0,3794
Or,	0,0298	12,43	0,3704
Platine,	0,0314	12,16	0,3740
Etain,	0,0514	7,35	0,3779
Argent,	0,0557	6,75	0,3759
Zinc,	0,0927	4,03	0,3736
Tellure,	0,0912	4,03	0,3675
Cuivre,	0,0949	3,957	0,3755
Nickel,	0,1035	3,69	0,3819
Fer,	0,1100	3,392	0,3731
Cobalt,	0,1498	2,46	0,3685
Soufre,	0,1880	2,011	0,3780

## Data of Weber



The first published graph dealing with the quantum theory of the solid state: Einstein's expression for the specific heat of solids [given in Eq. 20.4] plotted versus  $h\nu/kT$ . The little circles are Weber's experimental data for diamond. Einstein's best fit to Weber's measurements corresponds to  $h\nu/k \cong 1300K$ .

- ◆ **“In order to recognize an anomaly, one needs a theory or a rule or at least a prejudice.” – Pais on Einstein’s work on specific heats.**
- ◆ **Lord Rayleigh: “What would appear to be wanted is some escape from the destructive simplicity of the general conclusion [derived from equipartition].” – quoted in Pais, “Subtle is the Lord”**

*On the Secular Cooling of the Earth*

By Lord Kelvin (William Thomson)

Excerpt. *Transactions of the Royal Society of Edinburgh*, Vol. XXIII, pp. 167-169, 1864.

# OUR STARTING POINT: STICK IN THE SAND ESTIMATES

- ◆ **Inspiring tradition from Archimedes to Newton to Fermi to Weiskopf to our own Caltech Physics Department (i.e my talk title is not an accident!**
- ◆ **Concept: mathematicize the cartoons – that is, take the mechanisms suggested by biological cartoons seriously and see if they lead us to paradoxes when recast as precise mathematical arguments.**

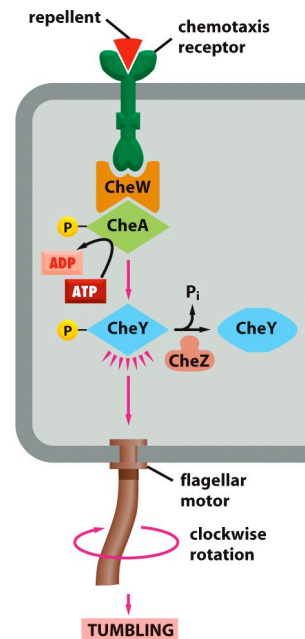


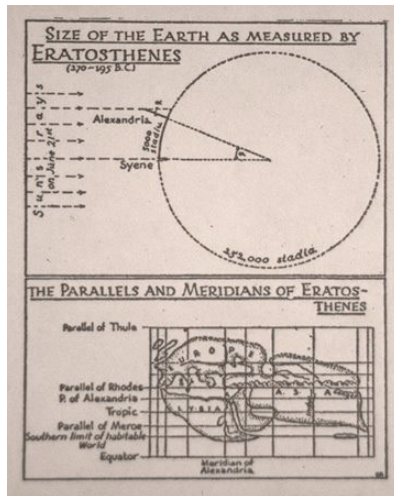
Figure 15-73 Molecular Biology of the Cell 5/e (© Garland Science 2008)



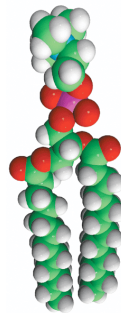
# THE ORDER OF MAGNITUDE TRADITION: A LIST OF FAVORITES



- ◆ **In high school, I found science uninspiring. On a Saturday night, at a friend's house, I learned of Eratosthenes estimate of the radius of the Earth and was hooked just like that. One Saturday night devoted to a simple estimate beat 3 years of school.**
- ◆ **Newton worked out the number of "Paris feet" that the moon falls in one minute and also noted that "a body in our regions" (i.e. on the surface of the Earth) will "describe 60 x 60 x 15 1/2 Paris feet" thus satisfying himself of the inverse square law.**

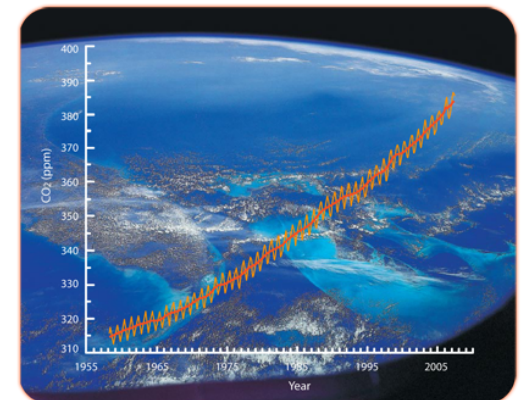


- ◆ **From Franklin to Rayleigh and the size of a lipid molecule. Rayleigh's oil estimate results in lipid size of 1.67 nm!**
- ◆ **Keeling's first great discovery can be used to estimate how many gigatons of carbon are fixed every year.**



<http://www.phys-astro.sonoma.edu/observatory/eratosthenes/>

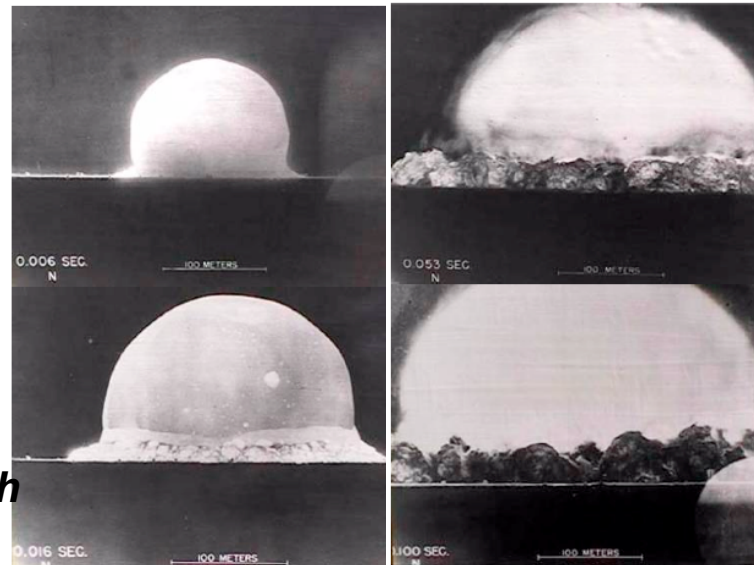
- ◆ **Estimates as a call to arms, as a producer of conundrums and surprises, as a tool to bring astronomically large numbers down to Earth and as a sanity check on purported mechanisms.**



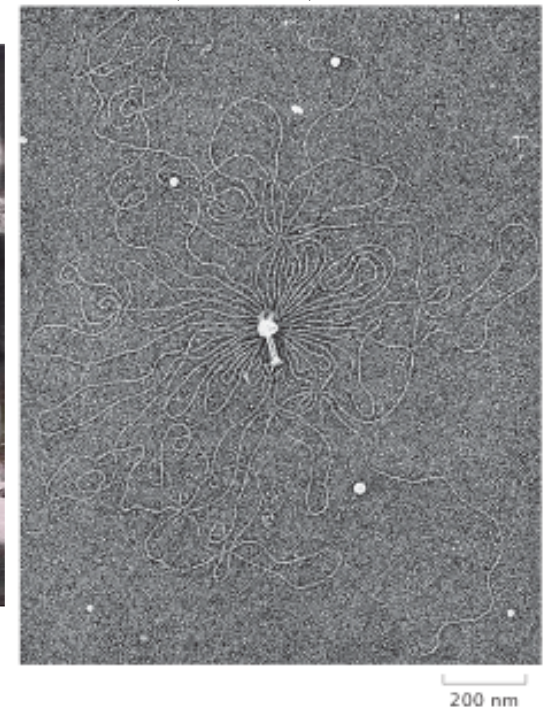


# BOMBS AND EXPLODING GENOMES: AN ANALOGY

- ♦ **Politicians and generals can make some information “classified” and it can be circumvented by cleverness.**
- ♦ **This is a segue into our main topic: genomes and their use. Estimates on genome management.**
- ♦ **Same idea could be used to estimate genome length by examining exploding genomes.**
- ♦ **The concept: figure out the length of the genome using a single picture and pure thought!**



(G. Stent)



# ESTIMATIONS ON GENOME MANAGEMENT: HOW BIG ARE GENOMES?

- Use the simplest nunchuk physics of random walks to estimate the genome size (i.e. size in terms of number of base pairs).
- What makes DNA different from some other polymer? The persistence length!
- The radius of gyration scales as  $N^{1/2}$ , which allows us to estimate the number of such Kuhn segments and hence back out the genome length.
- Note: This also tells us that work needs to be done to squish genomes into their hosts.

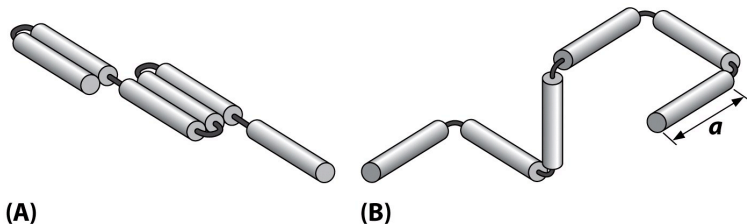


Figure 8.1 Physical Biology of the Cell (© Garland Science 2009)

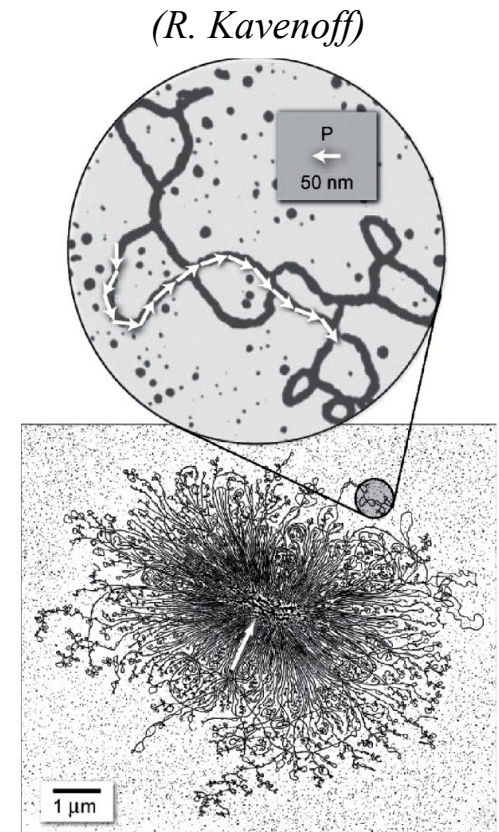
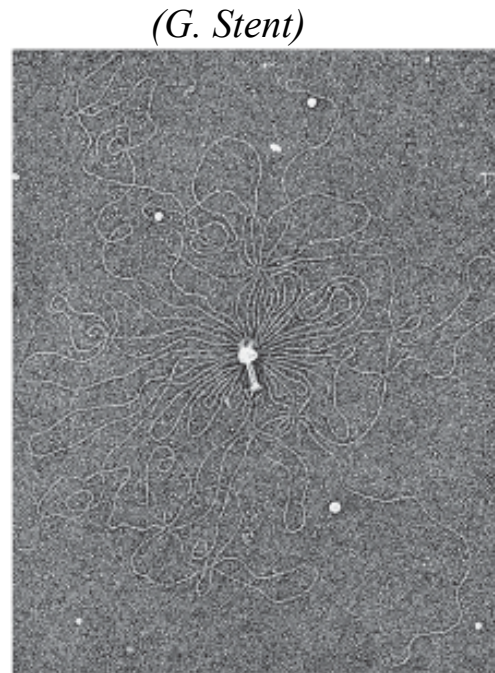
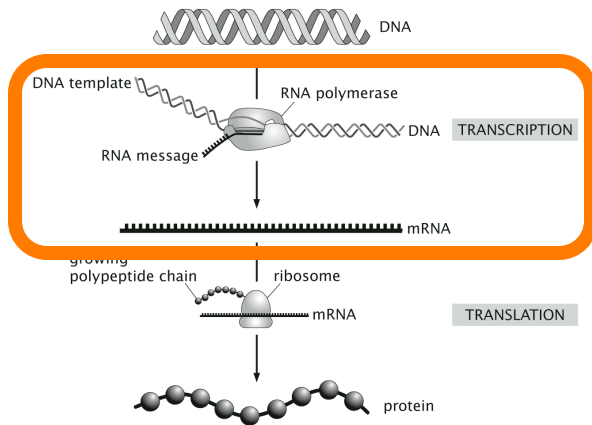


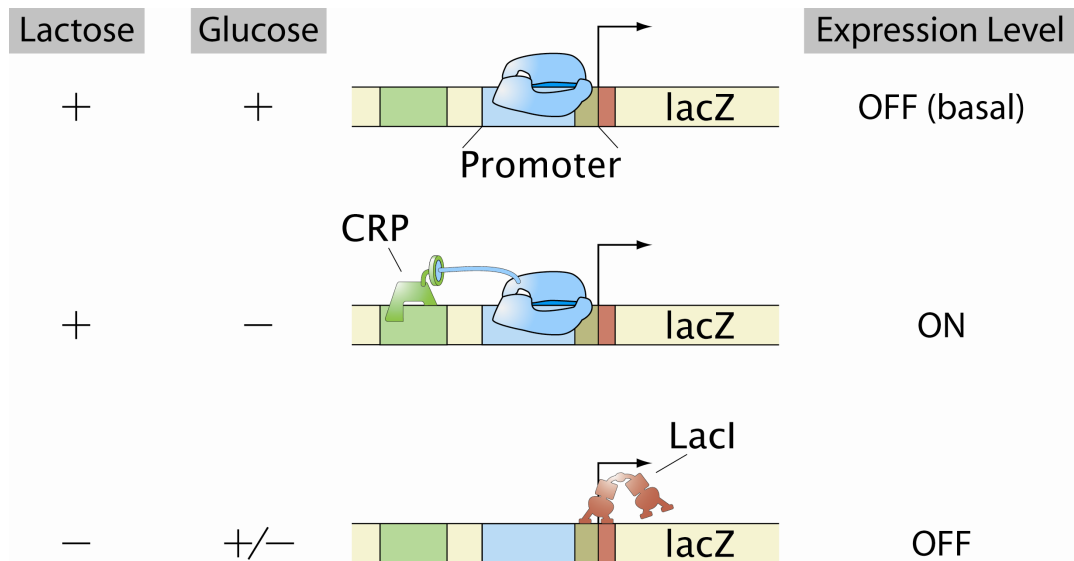
Figure 8.6 Physical Biology of the Cell (© Garland Science 2009)



# HOW GENES ARE CONTROLLED: THE JOURNEY FROM DNA TO ACTIVE PROTEINS

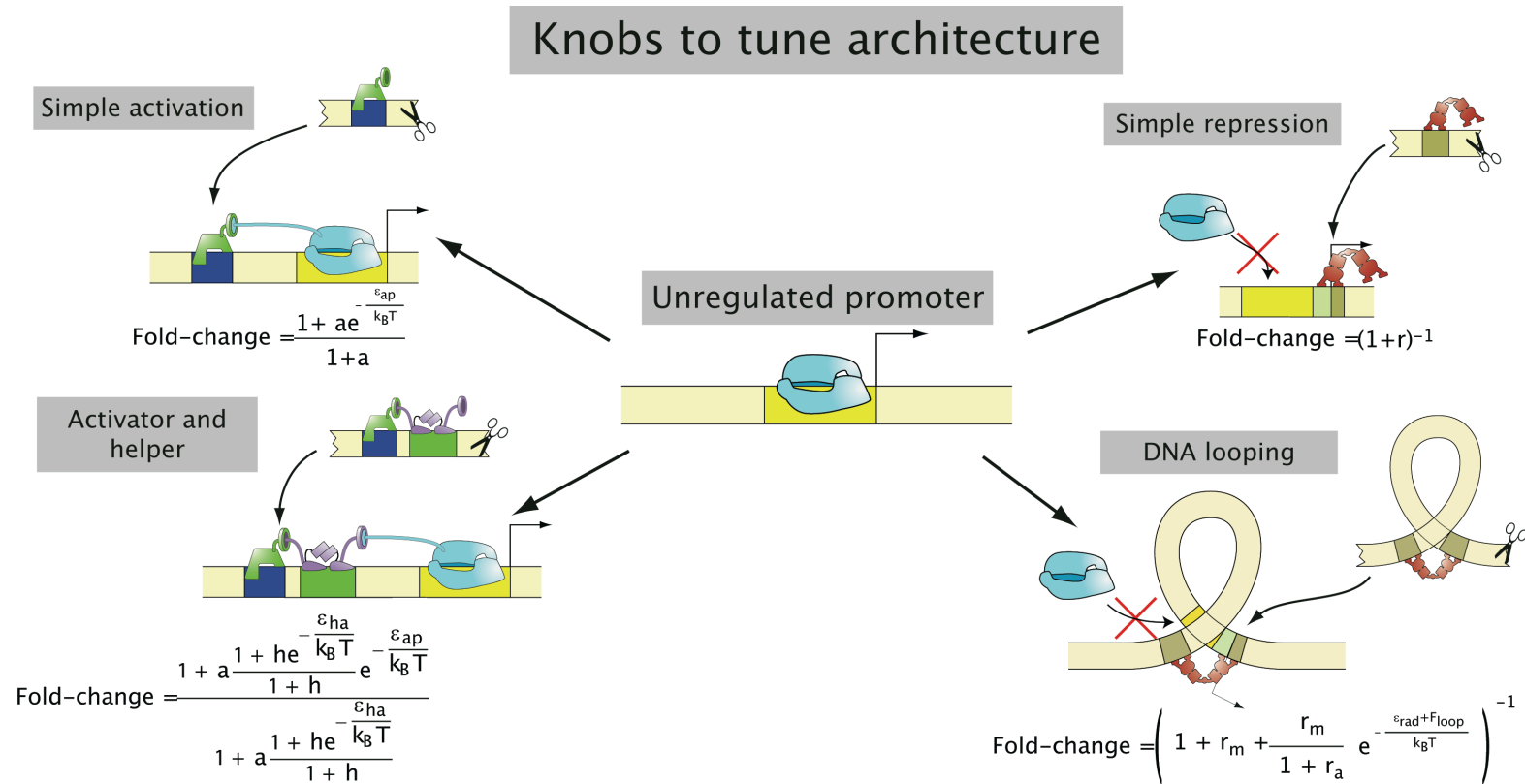


- As noted above, Francis Crick referred to nucleic acids and proteins as **“the two great polymer languages”**. The insight of Jacob and Monod was that there are genes that control other genes, permitting the flow of information from DNA to proteins only when certain conditions are met.
- Metabolic genes for lactose usage in *E. coli* - the **hydrogen atom** of gene regulation.





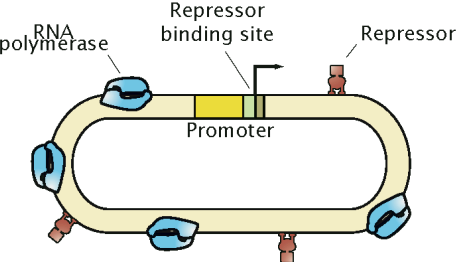
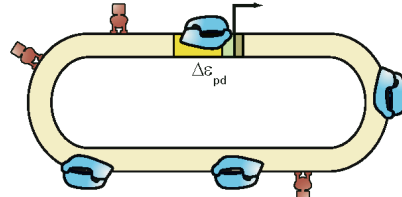
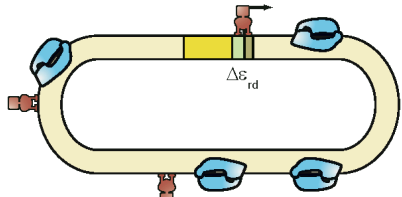
# CAN WE COMPUTE HOW CELLS DECIDE?



- ◆ **The level of gene expression is described by a function that depends upon parameters such as the number of repressors and activators.**
- ◆ **Key point: Systematic variation of parameters and examine the biological outcome. We are interested in the “fold-change” when parameters are tuned.**
- ◆ **The equations are falsifiable predictions for a wide variety of regulatory architectures.**

# STATISTICAL MECHANICS TO ESTIMATE THE LEVEL OF GENE EXPRESSION

- ◆ **The real estate in the vicinity of the promoter is under the control of molecular bouncers: activators and repressors.**
- ◆ **“Thermodynamic models” (Ackers & Shea, Buchler, Gerland & Hwa, Vilar & Leibler, etc.) permit us to compute the probability of promoter occupancy as a function of the many parameters that can be controlled quantitatively. *Do such models make sense?***

STATE	ENERGY	MULTIPLICITY	WEIGHT (MULTIPLICITY x BOLTZMANN WEIGHT)
 <p>RNA polymerase, Repressor binding site, Repressor, Promoter</p>	$R\epsilon_{rd}^{NS} + P\epsilon_{pd}^{NS}$	$\frac{N_{NS}!}{P! R! (N_{NS}-P-R)!} \approx \frac{(N_{NS})^{P+R}}{P! R!}$	$\frac{(N_{NS})^{P+R}}{P! R!} e^{-\beta R\epsilon_{rd}^{NS}} e^{-\beta P\epsilon_{pd}^{NS}}$
 <p><math>\Delta\epsilon_{pd}</math></p>	$R\epsilon_{rd}^{NS} + (P-1)\epsilon_{pd}^{NS} + \epsilon_{pd}^S$	$\frac{N_{NS}!}{(P-1)! R! [N_{NS}-(P-1)-R]!} \approx \frac{(N_{NS})^{(P-1)+R}}{(P-1)! R!}$	$\frac{(N_{NS})^{(P-1)+R}}{(P-1)! R!} e^{-\beta R\epsilon_{rd}^{NS}} e^{-\beta(P-1)\epsilon_{pd}^{NS}} e^{-\beta\epsilon_{pd}^S}$
 <p><math>\Delta\epsilon_{rd}</math></p>	$(R-1)\epsilon_{rd}^{NS} + P\epsilon_{pd}^{NS} + \epsilon_{rd}^S$	$\frac{N_{NS}!}{P! (R-1)! [N_{NS}-P-(R-1)]!} \approx \frac{(N_{NS})^{P+(R-1)}}{P! (R-1)!}$	$\frac{(N_{NS})^{P+(R-1)}}{P! (R-1)!} e^{-\beta(R-1)\epsilon_{rd}^{NS}} e^{-\beta P\epsilon_{pd}^{NS}} e^{-\beta\epsilon_{rd}^S}$

# CELLS DECIDE: WHERE TO GO

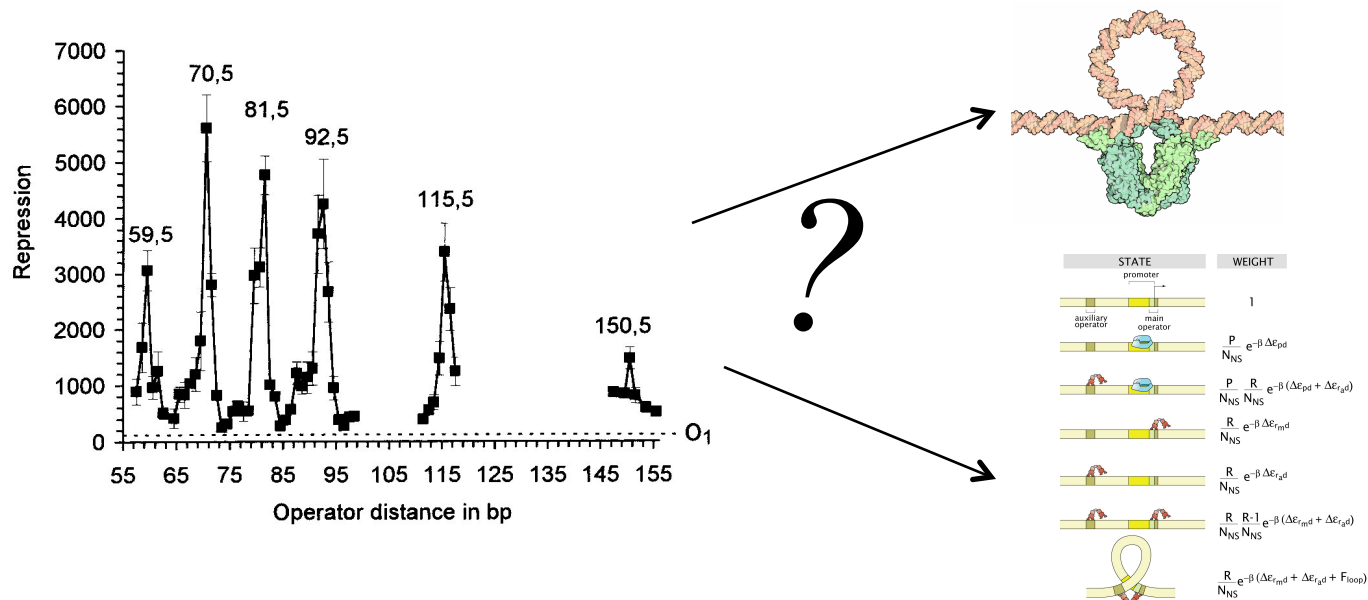
## *The Hunters of the Immune Response*



- ♦ ***There is another kind of rapid response to environmental cues that is much faster than gene regulation.***
- ♦ ***The “decision” about where to go next is highly regulated and results in the synthesis of new cytoskeletal filaments at the leading edge of the cell.***
- ♦ ***Once again, there is an interesting random walk story behind the scenes.***

# CONCLUSIONS

- ◆ **Strongly held opinion: quantitative data demands quantitative models. *The traditional verbal and cartoon approach is incommensurate with the data.***
- ◆ **We are in the stage when often stick in the sand estimates or simple back of the envelope calculations suffice to provide the kinds of polarizing predictions referred to in the quote from Rayleigh.**
- ◆ **A Caltech qualifier story: “If you don’t know what to ask them, ask them about diffusion (i.e. random walks).” – John Hopfield – Random walks have great biological reach. This talk: use of random walks in thinking about cellular decision making.**
- ◆ **Einstein on his ETH experience: “The most fascinating subject at the time that I was a student was Maxwell’s theory”, “we waited in vain for a presentation of Maxwell’s theory”.**
- ◆ **The study of living matter is one of most fascinating subjects of the day (don’t care if it is called biology or physics or bioengineering or tomato soup).**



# WARNING: CRITICISMS OF THE APPROACH

- ♦ ***What is a biophysicist? Scott Fraser had an answer for me. “You can’t be interdisciplinary without the disciplines”.***
- ♦ ***Many of the most important recent discoveries in biology such as the role of small RNAs have not required any physical input.***
- ♦ ***Biologists want “new biology” and physicists want “new physics”. For now, perhaps both groups view “physical biology” as dotting “i”s and crossing “t”s. The only way I know how to progress is by making thorough attack on specific, detailed case studies and seeing if the approach pays off.***



# ACKNOWLEDGEMENTS

*Julie Theriot*

*Jane Kondev*

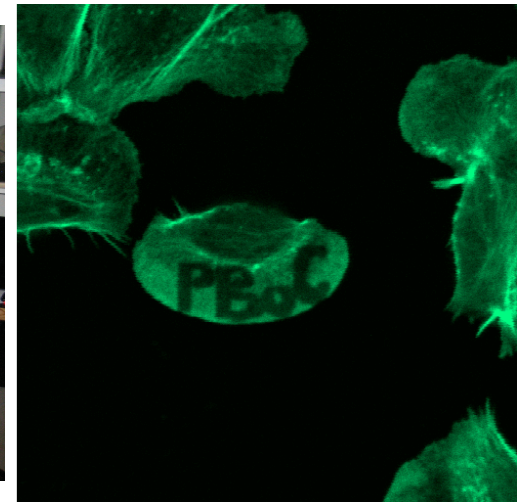
*Nigel Orme*

*Lin Han, Hernan Garcia, Stephanie Johnson*

*Ron Milo*

*David Van Valen and Mikko Haatja*

*RP group – thanks for the fun and education!*



# EXTRA SLIDES FOR QUESTIONS

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# APPLICATION OF FORCE BY POLYMERIZING ACTIN FILAMENTS

- ◆ *In this beautiful experiment, the force applied by cytoskeletal filaments is measured using an AFM.*
- ◆ *Our focus here though is on the decision making aspects rather than the force generation characteristics.*

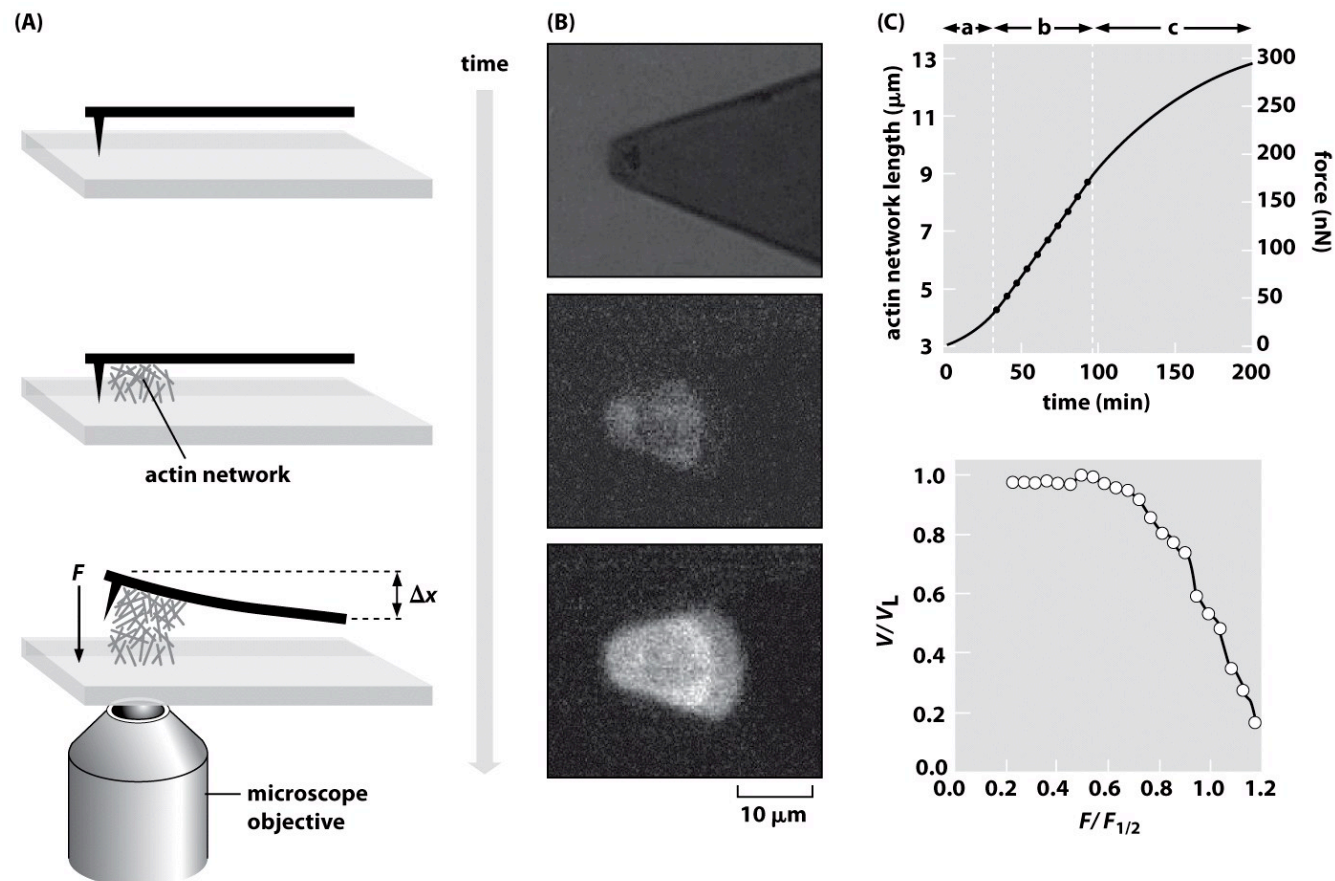
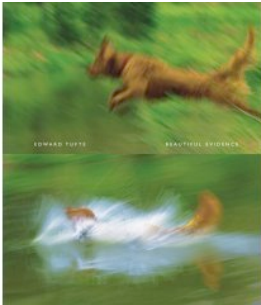


Figure 16.49 Physical Biology of the Cell (© Garland Science 2009)



# Beautiful Evidence, Envisioning Information



- ◆ I just finished Tufte's most recent, excellent book where he includes his biting assessment of "the cognitive style of powerpoint" so I am feeling guilty and self-conscious and tried to do a better job of constructing my presentation so you can better assess my message and the evidence supporting it.
- ◆ Tufte on "Envisioning Information" brings us to our topic: DNA as information and how is that related to the fact that DNA is a real world molecule (not just a set of letters)?

