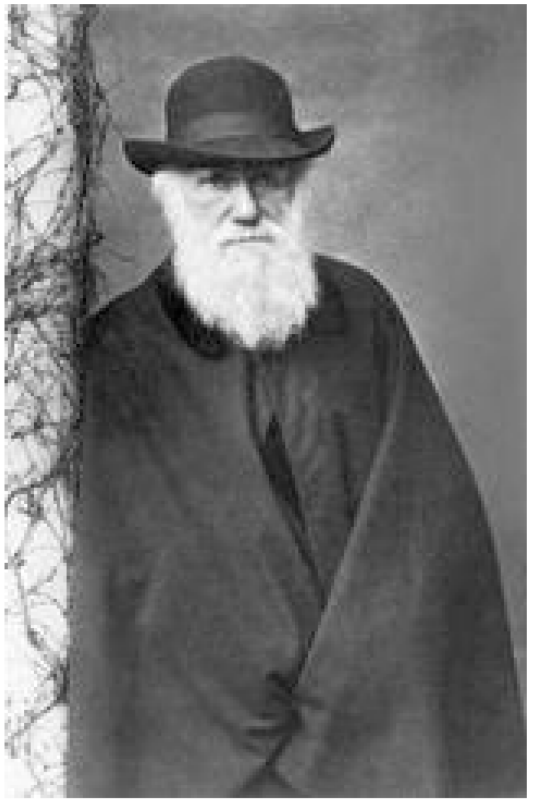
On Cultivating the sixth sense

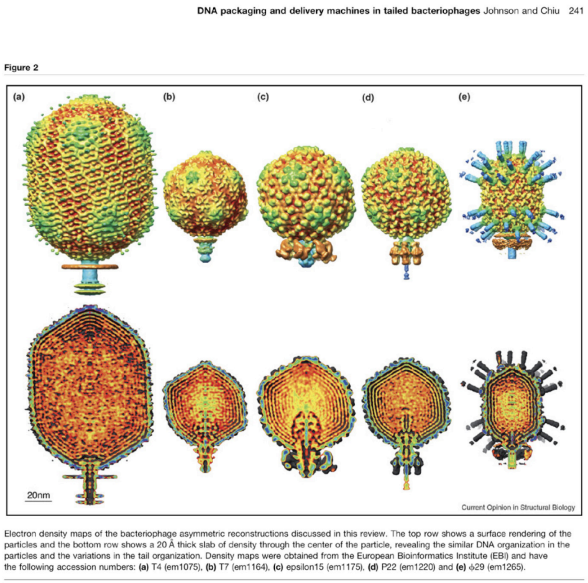
- ***"…in after years I have deeply regretted that I did not proceed far enough at least to understand something of the great leading principles of mathematics, for men thus endowed seem to have an extra sense."***

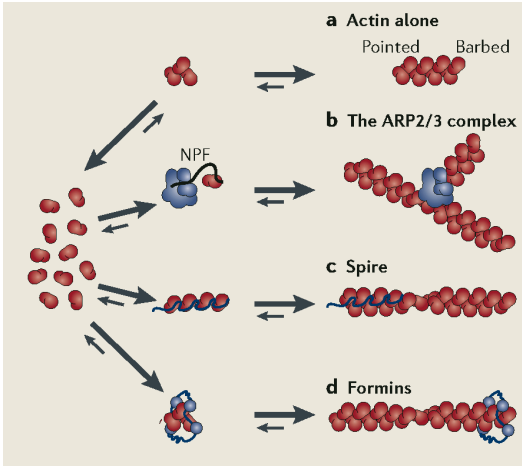


Talk Outline

The Argument

- *An analogy – astronomy to biology.*
- *Surprises, sanity checks and mechanisms.*
- *Some examples from genome science.*





Managing Genomes

- *An experiment to change your life for.*
- *The physics of genome packing.*

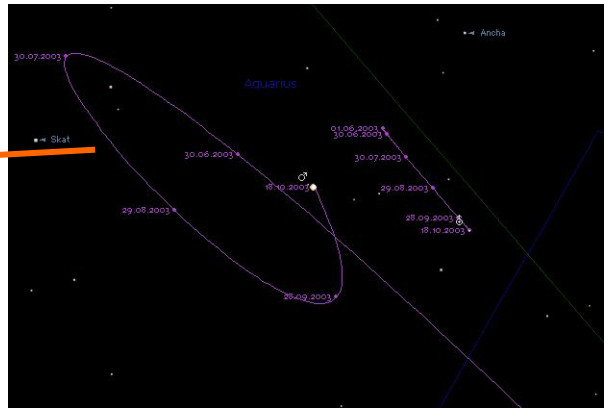
Where to Go

- *How cells decide.*
- *Constructing the cytoskeleton.*
- *Other random walks*

Idea: Link between compelling biological (information management) and physical (random walks) themes.

"Measure what is measurable, and make measurable what is not so" - Galileo (supposedly)

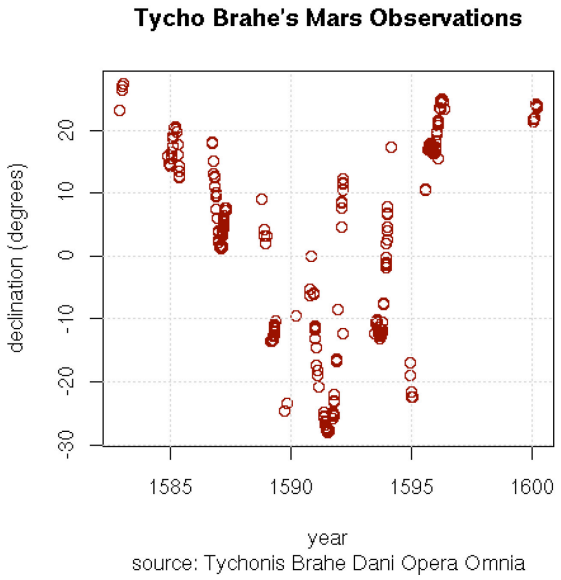
- ***Science has always been propelled by new ways of observing and measuring the world around us.***
- ***A classic and important example: Tycho Brahe (1546-1601) and the emergence of modern astronomy and physics.***
- ***Proposition: Biology is enjoying a halcyon moment like that seen in astronomy over the 150 year period between 1543 and 1687.***



"By the study of the orbit of Mars, we must either arrive at the secrets of astronomy or forever remain in ignorance of them." -Johannes Kepler

New instruments = new science

- ***Tycho Brahe was intensely dissatisfied with the experimental state of the art in astronomy and consecrated his life to making instruments that were up to the challenge.***
- ***In parallel, he used those instruments diligently to measure the positions of heavenly bodies.***



Beyond the telescope: new instruments and new science

- ***The spectroscope was an addition to the telescope that made it possible to measure the composition and velocities of stars.***

A Correction.

IN my letter *re* "Birds attacking Butterflies and Moths," in NATURE for March 6 (p. 415), there occur the words, "I conclude, therefore, that they were last year's birds, which knew and disliked *D. limniace*." There is some slip here, for what I meant to say was, "I conclude, therefore, that last year's bird knew and disliked *D. limniace*." This, it will be seen, agrees with the context; I only used one Babbler last year, and offered *D. limniace* to this only. F. FINN.

Indian Museum, Calcutta, March 27.

SOME SCIENTIFIC CENTRES.

IV.—THE HEIDELBERG PHYSICAL LABORATORY.

MOST travelled Englishmen are doubtless acquainted with the ancient town of Heidelberg, so famous for the beauty of its situation and the grandeur of its ruined castle. But far fewer know the charms of the long and romantic valley of the Neckar, at the almost sensational exit of which, from the Odenwald into the level plain of the Upper Rhine, Heidelberg stands. So also it is true that while most educated people connect Heidelberg with the great names of Kirchhoff and Bunsen and their epoch-making discoveries in spectrum analysis, it is only the special students who know how large in extent and [illegible] has steadily gone on for many years in the physical laboratory in the Friedrichsbau.

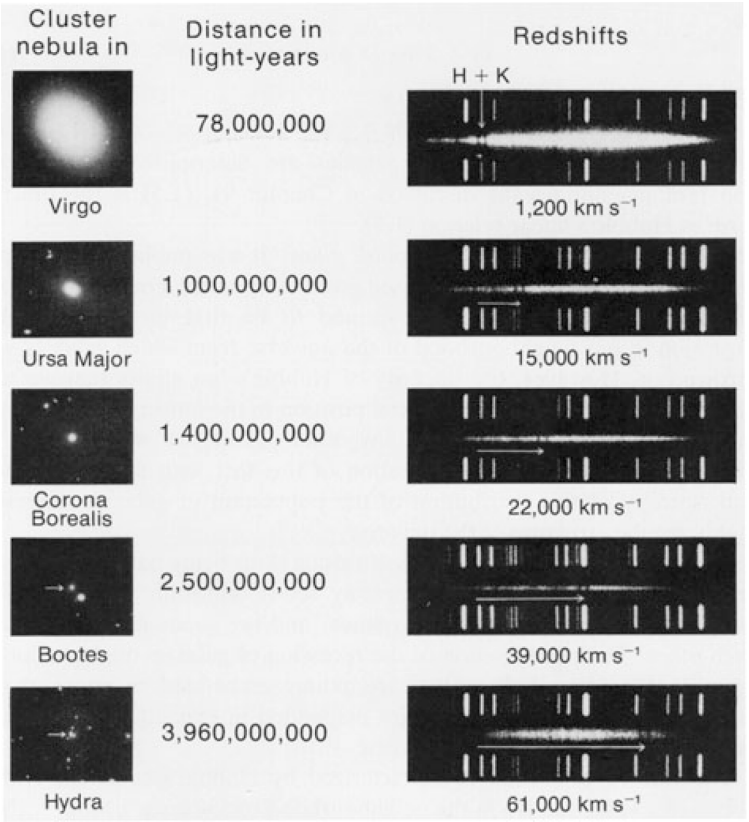
Its small beginnings in the middle of the last century are marked by the name of Kirchhoff scratched on the window of what is now the private room of the senior assistant. From this window one may look out over the Rhine plain towards busy Mannheim, as Bunsen and Kirchhoff did one night when a fire was raging there, and they were able by spectroscopic examination of the flames to ascertain that barium and strontium were present in the burning mass. But the same window also looks across the Neckar to the Heiligenberg, along the slopes of which runs the "Philosophers' Walk," the chief of the many paths among the wooded hills around the town, which the two friends were wont to traverse in their daily "constitutionals." Bunsen is known to have said that it was during such walks that his best ideas came to him. One day the thought occurred, "If we could determine the nature of the substances burning at Mannheim, why should we not do the same with regard to the sun? But people would say we must have gone mad to dream of such a thing." All the world knows now what the result was, but it must have been a great moment when Kirchhoff could say, "Bunsen, I *have* gone mad," and Bunsen, grasping what it all meant, replied, "So have I, Kirchhoff!"

[illegible] other apparatus of his, is preserved in the collections of the Laboratory, and well deserves the almost reverential awe with which it was examined by a certain foreign professor, who protested that objects of such historic interest should be kept in a fire-proof safe.

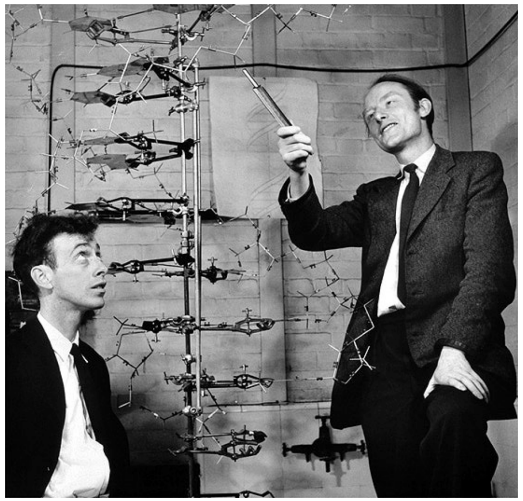
Kirchhoff, who in his later years suffered much from ill health, left Heidelberg in 1875 on his appointment as professor of theoretical physics at Berlin, where, by the way, he had no official laboratory, and carried on his experimental work (*e.g.* the research on the conductivities of the metals for heat and electricity) in the laboratory of his friend von Hansemann. His successor at Heidelberg was his former pupil, Quincke, who has been professor there ever since, and is now the "doyen" of German physicists, both by length of service—for though only sixty-seven he has been a professor for more than forty years—and by the amount and variety of his scientific work. It is true that this work has not been of the kind that gets into the newspapers, but the real students will certainly value it none the less on that account, and even the beginner in science has heard of "Quincke's Interference Tube" and his standard measurements of capillary constants. English students may well take some special interest in Quincke, for his personal relations with English men of science (*e.g.* Lord Kelvin and Sir Henry Roscoe) have been particularly close; he is never tired of dwelling with admiration on the achievements of Young, Faraday and Kelvin—and in the case of Young in particular of vindicating his priority in respect of many of the ideas in light and sound often regarded as original to Fresnel and Helmholtz—and nowhere have his own researches been more highly valued than in this country, as is shown by the long list of Universities (Cambridge, Oxford, Glasgow) and learned societies (from the Royal Society downwards) which have conferred their honours upon him.

Georg Hermann Quincke was born at Frankfort a. O. in 1834 of partly Huguenot extraction. One who has seen the diagrams, with circles worthy of Giotto, which he draws on the blackboard, or had experience of his apparently intuitive knowledge of the possibilities of the most various materials and mechanical processes, might well be inclined to regard this kind of power, so valuable to the physicist, as an inheritance from some skilful Huguenot ancestor. From 1852 onwards he studied at Berlin, and then for a time at Königsberg, attracted thither (with others, such as Kirchhoff and Clebsch) by the fact that F. E. Neumann was delivering the only course of lectures on mathematical physics then to be heard in Germany. Neumann's mathematical and experimental genius had considerable influence on Quincke, and it was here that the profound interest in molecular physics which has dominated his life-work was aroused [illegible] connection with the theory of capillarity. But Neumann allowed his pupils too little scope for originality, and Quincke removed to Heidelberg, where (in 1854) Kirchhoff had just been appointed professor of physics. Under him Quincke carried out (in 1856) his first physical research, an investigation of the lines of flow of an electric current from one point to another of a metal plate. With a plate made of adjoining semicircles of copper and lead, Kirchhoff's law of the refraction of currents was confirmed, viz. that the *tangents* of the angles of incidence and refraction are in a constant ratio, though, curiously enough, this ratio was not found equal to that of the conductivities of the two metals, as the theory requires, but only about half as great. During this time—in which Matthiessen and Roscoe were among his fellow students—Quincke also worked much with Bunsen, especially in gas and mineral analysis, and, indeed, his first published paper was on the red and grey gneiss of the Erzgebirg (1856). Doubtless the association with Bunsen did something to cultivate Quincke's native faculty for the ingenious adaptation of the simplest materials, of which more hereafter.

From Heidelberg Quincke returned to Berlin, "promovierte" in 1858, became "Privat docent" in 1859, in 1860 was appointed professor at the Royal Prussian "Gewerbe Akademie" and in 1865 "ausserordentlicher" professor at the University of Berlin, posts which he held till 1872. His courses of lectures included the only one in mathematical physics then given in Berlin. But as regards original work the young professor was much hampered by the fact that he had neither stores of apparatus nor even a decent library of scientific literature at his disposal. In both respects he was much aided by his friend Wilhelmy (of invert sugar fame), who possessed a good deal of apparatus brought from Paris, and by Mitscherlich. Before this Mitscherlich had introduced him to G. Wiedemann, and a beautifully kept juvenile note-book had led to his drawing the figures for some of Wiedemann's publications. How well he was capable of such work will be clear to all who have seen his lithographed sheets of instructions for practical work in use in his present laboratory, with their admirable diagrams.

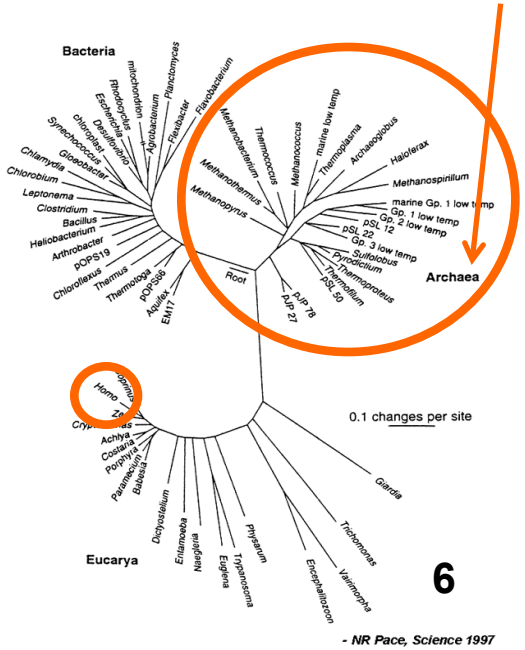


The biological moment: New ways of seeing the unseen have transformed our view of the living world



- ***At the time my parents were born, most people thought proteins were the molecules of heredity. In just under 60 years, biology has been completely rewritten.***
- ***The ability to read and write DNA has completely changed the face of biology.***
- ***Example: an entirely new domain of life.***

unknown before 1970s



- ***Proposition: Biology is enjoying a halcyon moment like that seen in astronomy over the 150 year period between 1543 and 1687.***

- NR Pace, Science 1997

Don’t Forget to see the unseen

- ***The “great plate count anomaly”. Hard to know what is out there, hard to study and really hard to find out how they depend upon and hurt each other.***

Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 6578–6583, June 1998

Perspective

Prokaryotes: The unseen majority

William B. Whitman†, David C. Coleman‡, and William J. Wiebe§*

*Departments of *Microbiology, ‡Ecology, and §Marine Sciences, University of Georgia, Athens GA 30602*

ABSTRACT **The number of prokaryotes and the total amount of their cellular carbon on earth are estimated to be $4–6 \times 10^{30}$ cells and 350–550 Pg of C (1 Pg = 10^{15} g), respectively. Thus, the total amount of prokaryotic carbon is 60–100% of the estimated total carbon in plants, and inclusion of prokaryotic carbon in global models will almost double estimates of the amount of carbon stored in living organisms. In addition, the earth’s prokaryotes contain 85–130 Pg of N and 9–14 Pg of P, or about 10-fold more of these nutrients than do plants, and represent the largest pool of these nutrients in living organisms. Most of the earth’s prokaryotes occur in the open ocean, in soil, and in oceanic and terrestrial subsurfaces, where the numbers of cells are 1.2×10^{29}, 2.6×10^{29}, 3.5×10^{30}, and $0.25–2.5 \times 10^{30}$, respectively. The numbers of heterotrophic prokaryotes in the upper 200 m of the open ocean, the ocean below 200 m, and soil are consistent with average turnover times of 6–25 days, 0.8 yr, and 2.5 yr, respectively. Although subject to a great deal of uncertainty, the estimate for the average turnover time of prokaryotes in the subsurface is on the order of $1–2 \times 10^3$ yr. The cellular production rate for all prokaryotes on earth is estimated at 1.7×10^{30} cells/yr and is highest in the open ocean. The large population size and rapid growth of prokaryotes provides an enormous capacity for genetic diversity.**

portion of these cells are the autotrophic marine cyanobacteria and *Prochlorococcus* spp., which have an average cellular density of 4×10^4 cells/ml (6). The deep (>200 m) oceanic water contains 5×10^4 cells/ml on average. From global estimates of volume, the upper 200 m of the ocean contains a total of 3.6×10^{28} cells, of which 2.9×10^{27} cells are autotrophs, whereas ocean water below 200 m contains 6.5×10^{28} cells (Table 1).

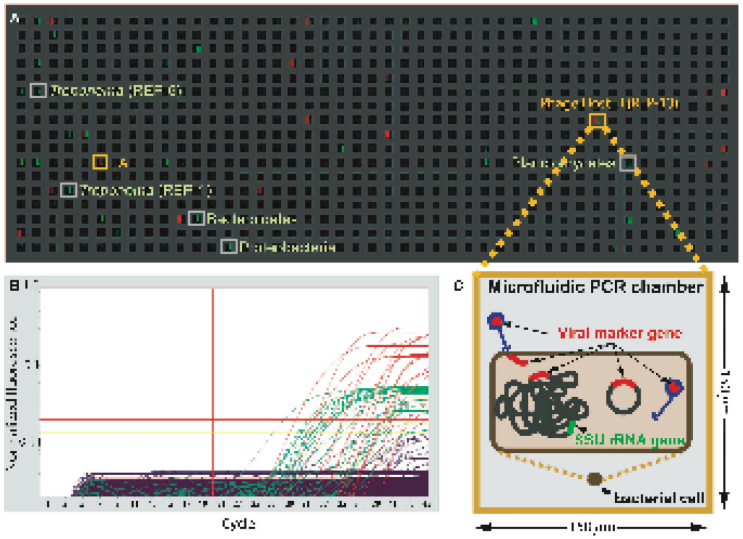
The upper 10 cm of sediment in the open ocean is included in the oceanic habitat because, as a result of animal mixing and precipitation, it is essentially contiguous with the overlying water column. Most of the marine sediment is found in the continental rise and abyssal plain, so the numbers of prokaryotes were calculated from an arithmetic average of the cellular densities in the studies cited by Deming and Baross (ref. 9; Table 1). The Nova Scotian continental rise was excluded from this calculation because of its unusual hydrology (10).

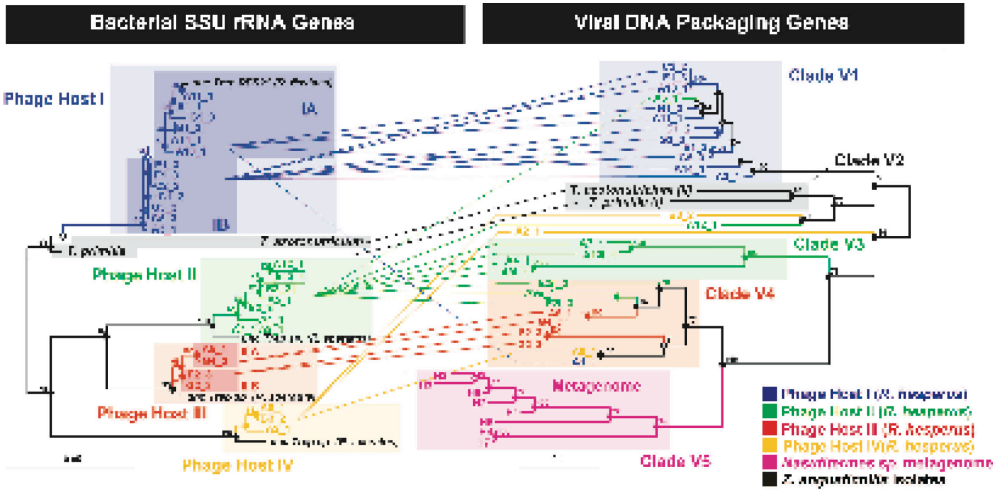
There are fewer estimates of the number of prokaryotes in freshwaters and saline lakes (5). Given an average density of 10^6 cells/ml, the total number of cells in freshwaters and saline lakes is 2.3×10^{26}. This value is three orders of magnitude below the numbers of prokaryotes in seawater.

In the polar regions, a relatively dense community of algae and prokaryotes forms at the water–ice interface in annual sea

Viruses and their hosts

- ***The question: how do we find what viruses are in a natural environments? More importantly yet, who are their hosts?***

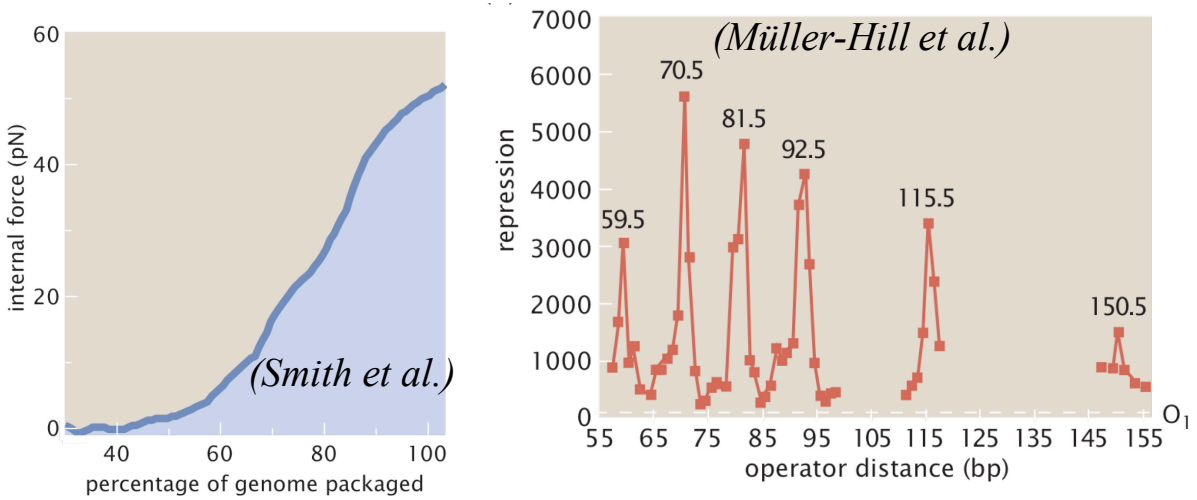




Experiments to change your life for: A serious role for theory in biology

- ***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.***
- ***This approach allows us to see things that we can't see with words and cartoons alone (i.e. Darwin's sixth sense).***

Genome Management ***Gene regulation***



- ***How can we even know if these results are surprising?***

"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.

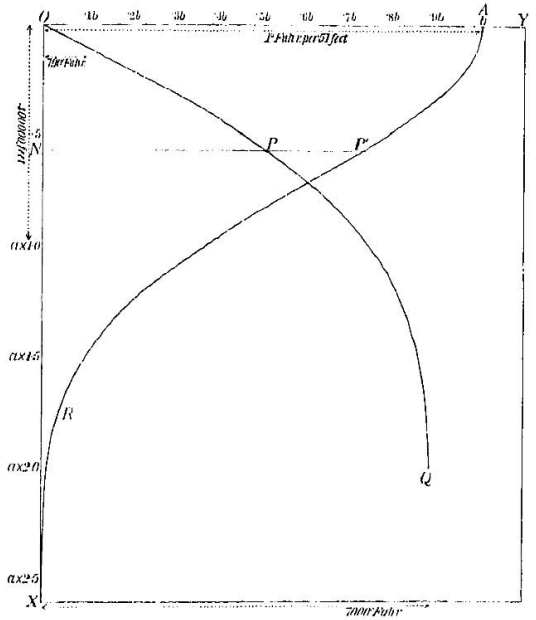
$ON = x.$ $\quad a = 2\sqrt{\kappa t}.$

$NP = be^{-x^2/a^2} = y'.$ $\quad \frac{dv}{dx} = \frac{V}{a} \cdot \frac{NP}{b\frac{1}{2}\sqrt{\pi}}.$

$NP = \text{area } ONP'A \div a = \frac{1}{a}\int_0^x y'dx'.$ $\quad v - v_0 = V \cdot \frac{NP}{b \cdot \frac{1}{2}\sqrt{\pi}}.$

The curve OPQ shows excess of temperature above that of the surface.

The curve $AP'R$ 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.

On the Secular Cooling of the Earth

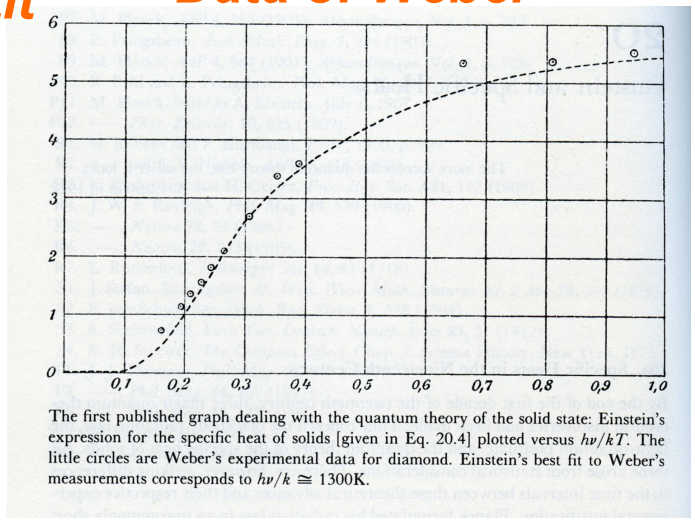
By Lord Kelvin (William Thomson)

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

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



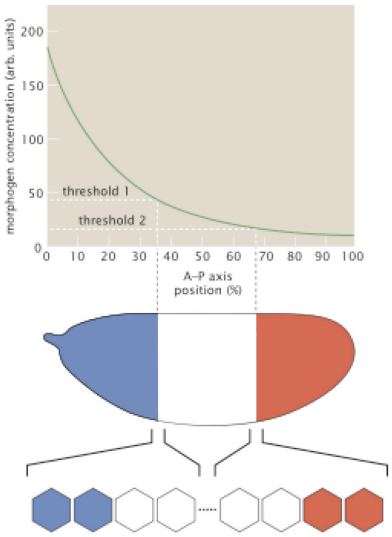
The first published graph dealing with the quantum theory of the solid state: Einstein's expression for the specific heat of solids [given in Eq. 20.4] plotted versus $h\nu/kT$. The little circles are Weber's experimental data for diamond. Einstein's best fit to Weber's measurements corresponds to $h\nu/k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

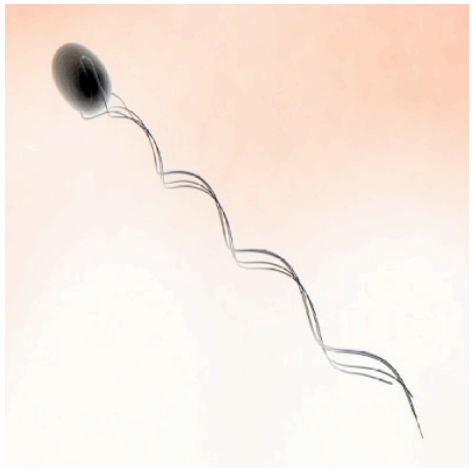
- ***"In order to recognize an anomaly, one needs a theory or a rule or at least a prejudice." – Pais on Einstein's work on specific heats.***
- ***Goal of my teaching: Building Prejudiced Students!***

A question of proximity

http://www.igh.cnrs.fr/equip/mechali/images/embryon.jpg

- ***Proximity of topics in physical biology is completely different than in cell biology. The same ideas on molecular detection and counting operate in embryonic development as in bacterial chemotaxis.***
- ***In fat Alberts, bacterial chemotaxis is on pg. 941 and Drosophila development 400 pages later on pg. 1328. From the kind of physical perspective I will advocate today, they can be on the same few pages.***





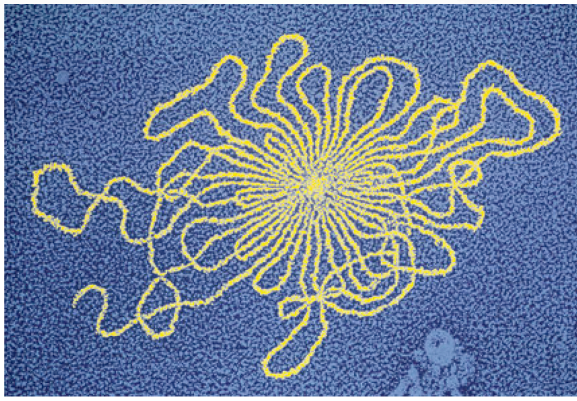
Biological proximity

Physical proximity

“The unreasonable effectiveness of mathematics in the natural sciences”

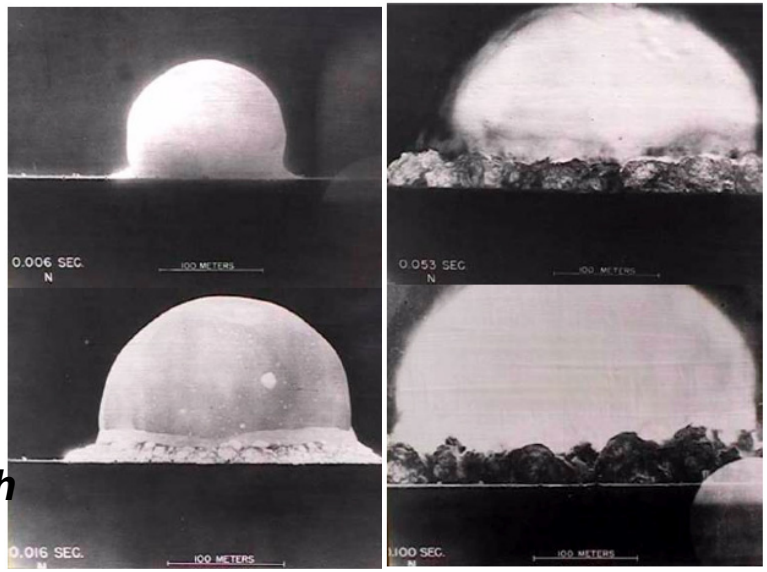
- ***Isn’t it wonderful that the same underlying equations describe the distribution of carbon in steel and the conformations of DNA or polyethylene?***
- ***“Theories of the known, which are described by different physical ideas may be equivalent in all their predictions and are hence scientifically indistinguishable. However, they are not psychologically identical when trying to move from that base into the unknown. For different views suggest different kinds of modifications which might be made and hence are not equivalent in the hypotheses one generates from them in ones attempt to understand what is not yet understood.” - Feynman Nobel Lecture***
- ***The physical world view: a psychologically inequivalent way of generating hypotheses about living matter.***

$$\frac{\partial p}{\partial t} = D\frac{\partial^2 p}{\partial x^2}$$

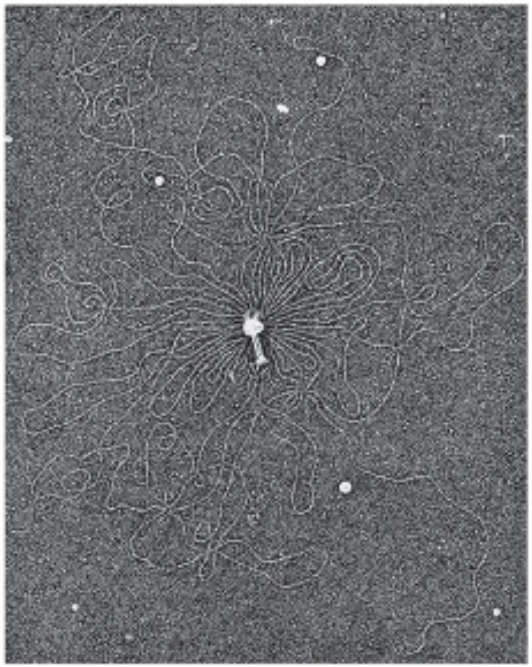


Bombs and Exploding Genomes: An analogy

- ***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!***



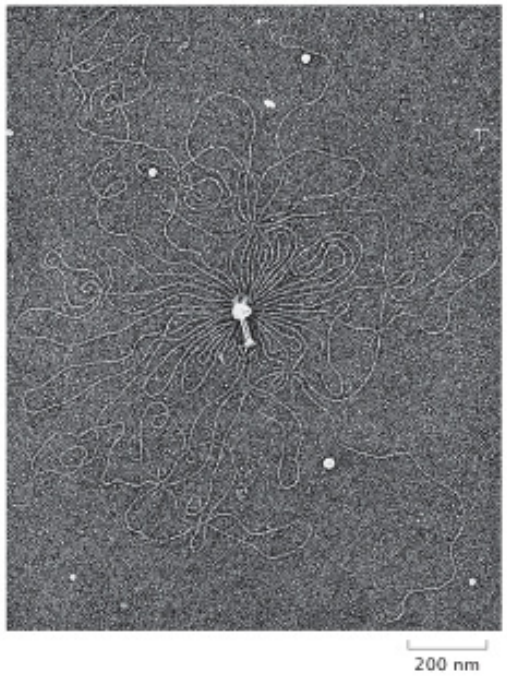
(G. Stent)



Random Walks: 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.***

(G. Stent)



(R. Kavenoff)

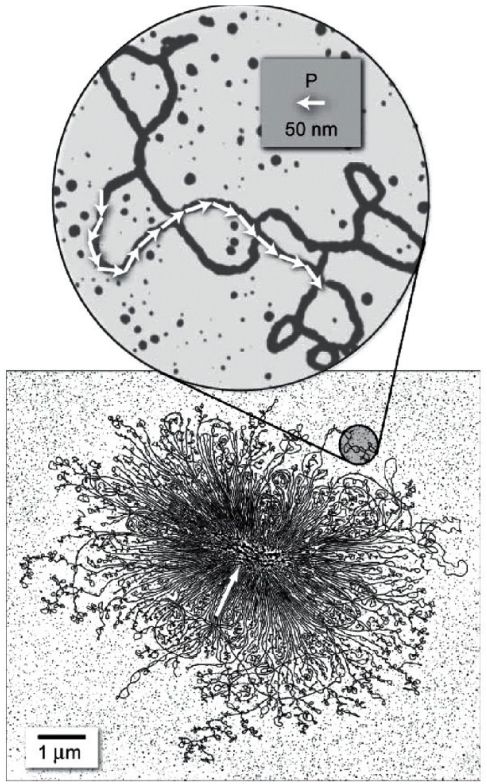


Figure 8.6 Physical Biology of the Cell (© Garland Science 2009)

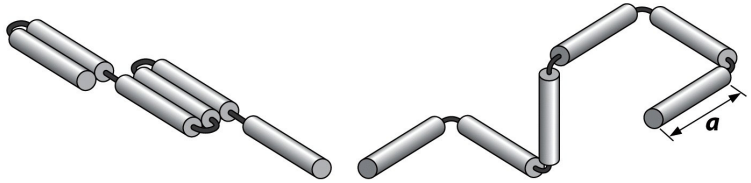
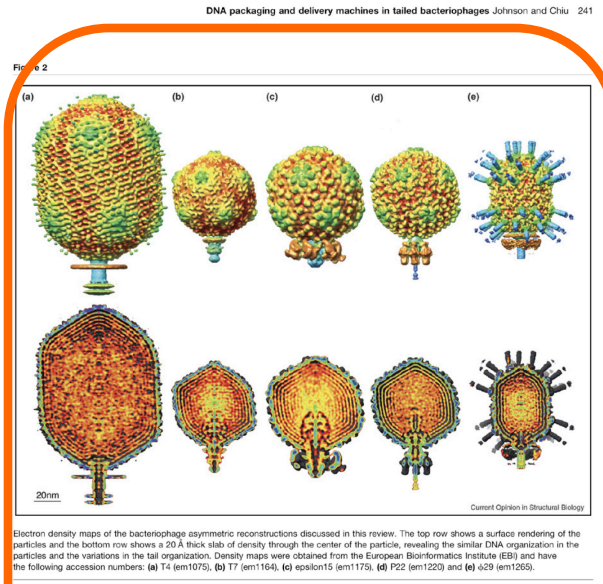


Figure 8.1 Physical Biology of the Cell (© Garland Science 2009)

Talk Outline

The Argument

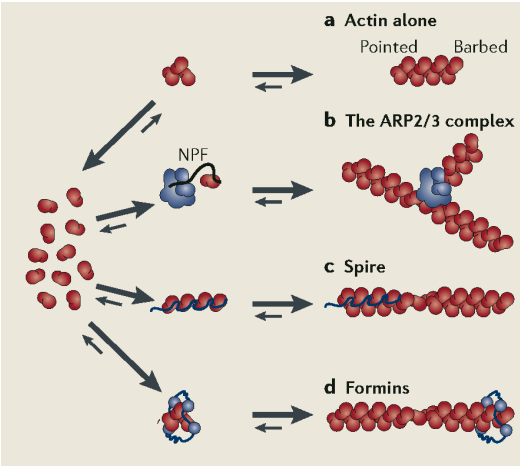
- *An analogy – astronomy to biology.*
- *Surprises, sanity checks and mechanisms.*
- *Some examples from genome science.*



Electron density maps of the bacteriophage asymmetric reconstructions discussed in this review. The top row shows a surface rendering of the particles and the bottom row shows a 20 Å thick slab of density through the center of the particle, revealing the similar DNA organization in the particles and the variations in the tail organization. Density maps were obtained from the European Bioinformatics Institute (EBI) and have the following accession numbers: **(a)** T4 (em1075), **(b)** T7 (em1164), **(c)** epsilon15 (em1175), **(d)** P22 (em1220) and **(e)** ϕ29 (em1265).

Managing Genomes

- *An experiment to change your life for.*
- *The physics of genome packing.*

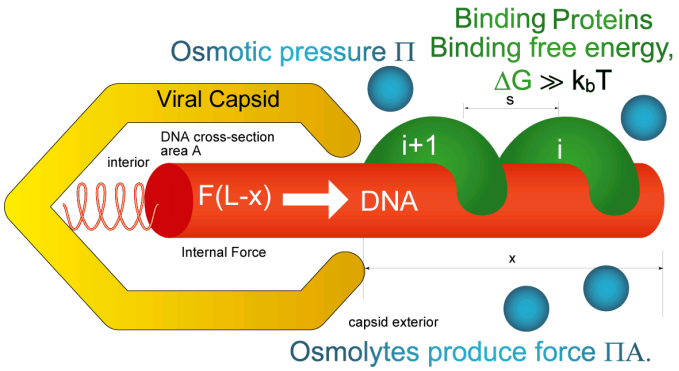


Where to Go

- *How cells decide.*
- *Constructing the cytoskeleton.*
- *Other random walks*

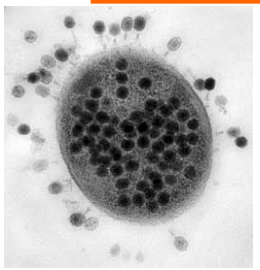
Idea: Link between compelling biological (information management) and physical (random walks) themes.

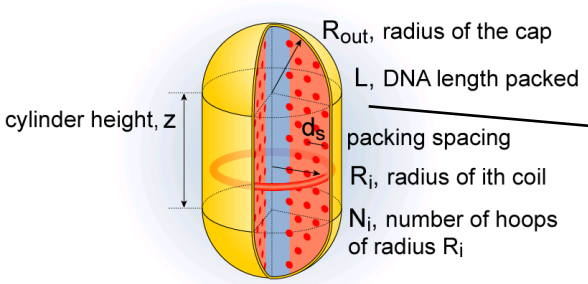
Physical Consequences of the Tight Squeeze in the Life Cycle of a Bacteriophage



Forceful ejection

Rate of ejection: ≈ 100 - 10000bp/sec





Construct a physical model of these processes.

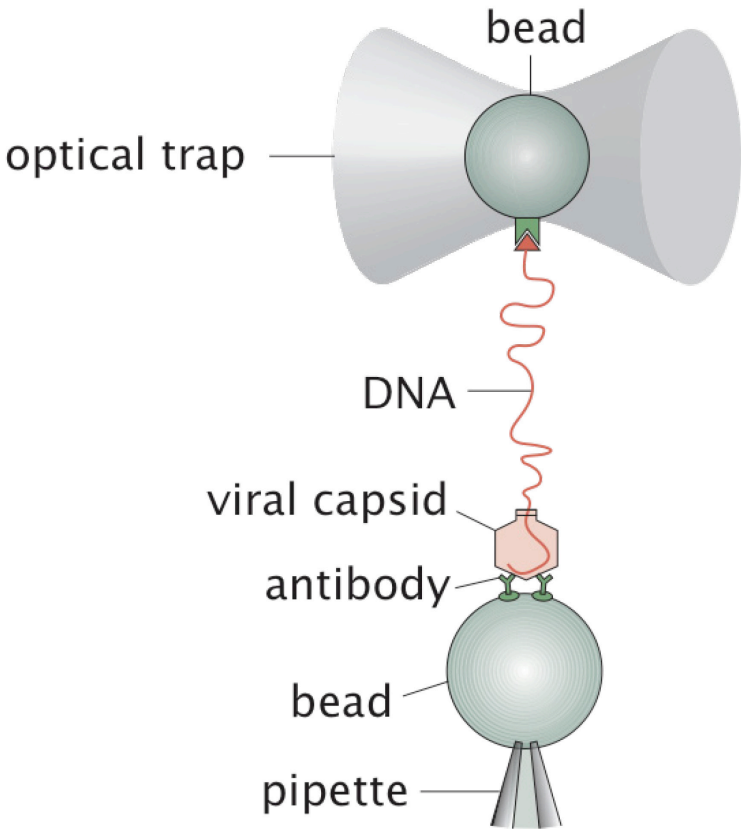
Rate of packing: 100bp/sec

"Some assembly required"

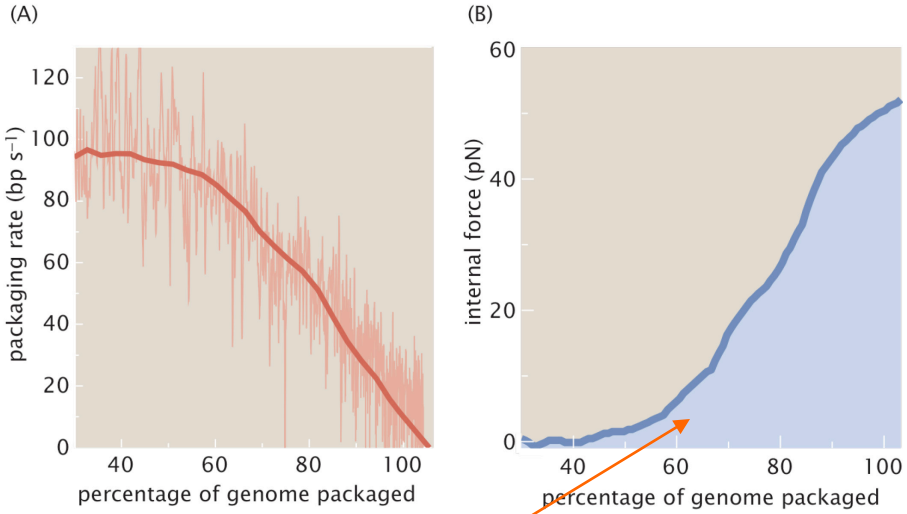
Self-assembly

From Hershey-Chase to Optical Tweezers: Phage are Stressed Out!

An experiment to change your life for



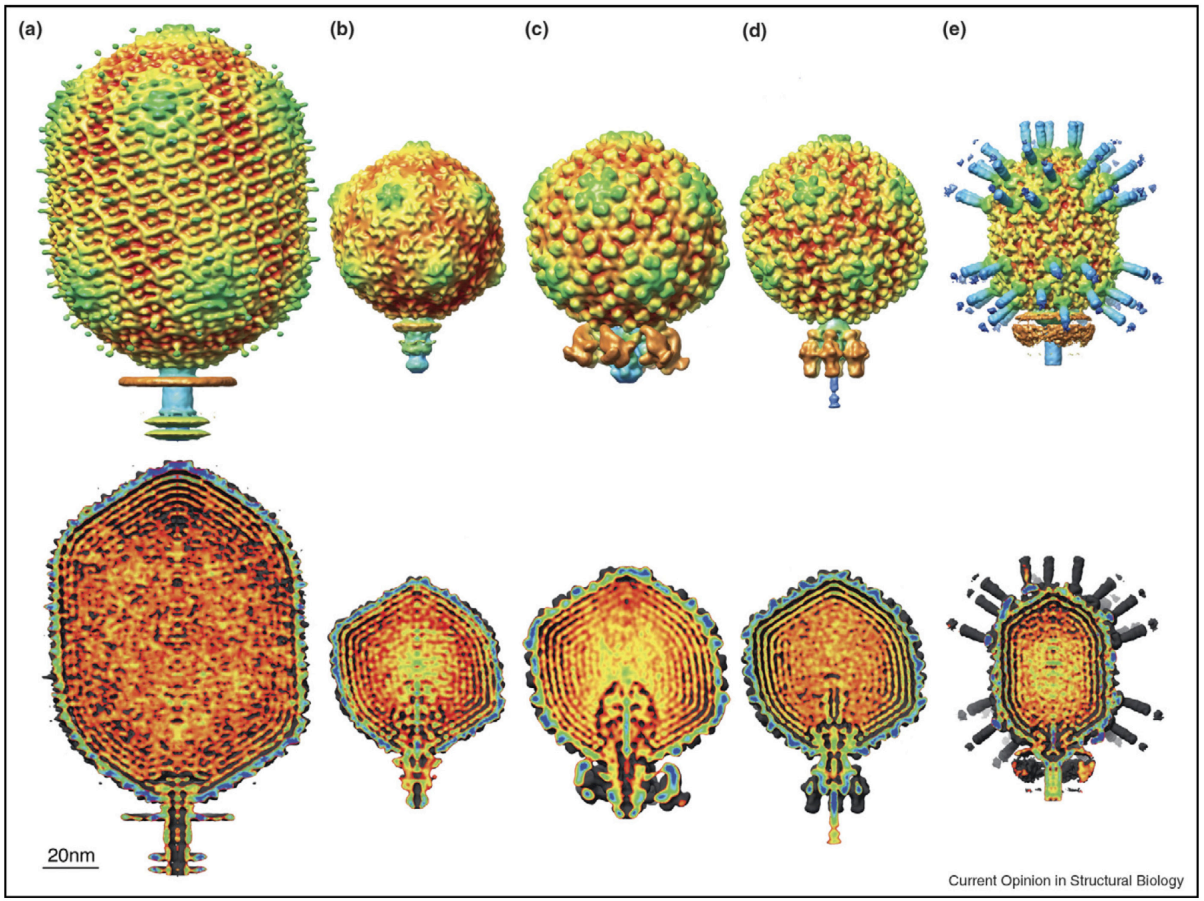
(Smith, Bustamante et al.)



Force resisting further packaging

Capsids and their genomes

Figure 2



Electron density maps of the bacteriophage asymmetric reconstructions discussed in this review. The top row shows a surface rendering of the particles and the bottom row shows a 20 Å thick slab of density through the center of the particle, revealing the similar DNA organization in the particles and the variations in the tail organization. Density maps were obtained from the European Bioinformatics Institute (EBI) and have the following accession numbers: **(a)** T4 (em1075), **(b)** T7 (em1164), **(c)** epsilon15 (em1175), **(d)** P22 (em1220) and **(e)** ϕ29 (em1265).

Relevant Scales in the Squeeze

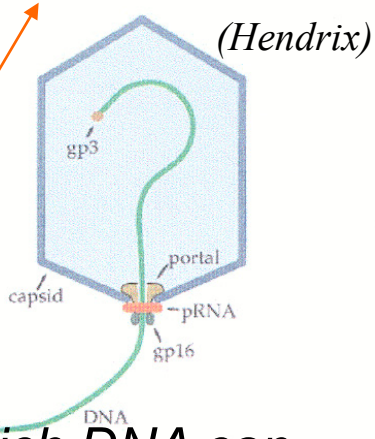
Governing dimensionless parameter

(check it out for sperm, other viruses, etc.)

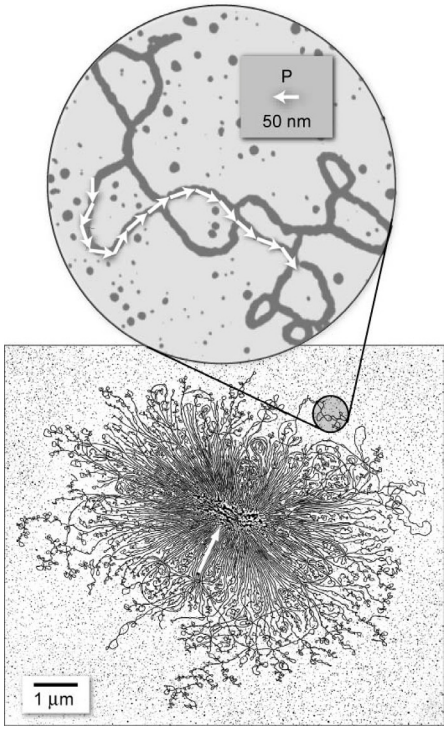
$$\frac{\Omega_{genome}}{\Omega_{capsid}} = \frac{N_{bp}\Omega_{bp}}{\Omega_{capsid}} \approx \frac{1}{2}$$

$$\Omega_{bp} \approx 1000\mathring{A}^3$$

Capsid size = 40nm



(Hendrix)



Persistence length of DNA, length over which DNA can be thought of as being stiff.

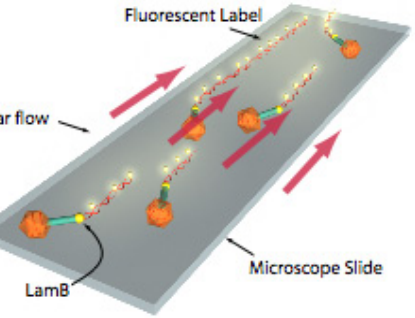
$$\xi_p = \frac{EI}{k_B T} \approx 50nm$$

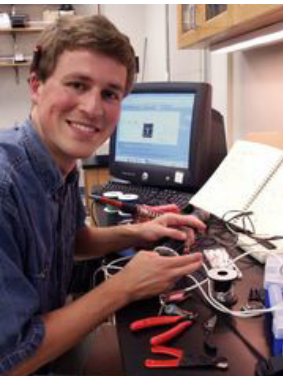
There is a negative charge every .17nm of length along DNA – electrostatic energy crucial also.

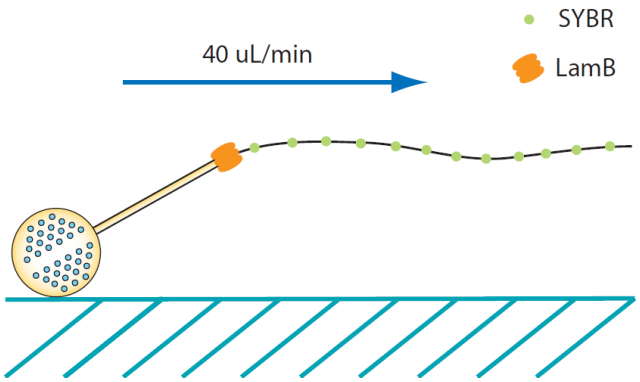
The idea: assemble these two energies to reckon the packing forces (Riemer & Bloomfield, Odijk, Gelbart et al., Grosberg et al.)

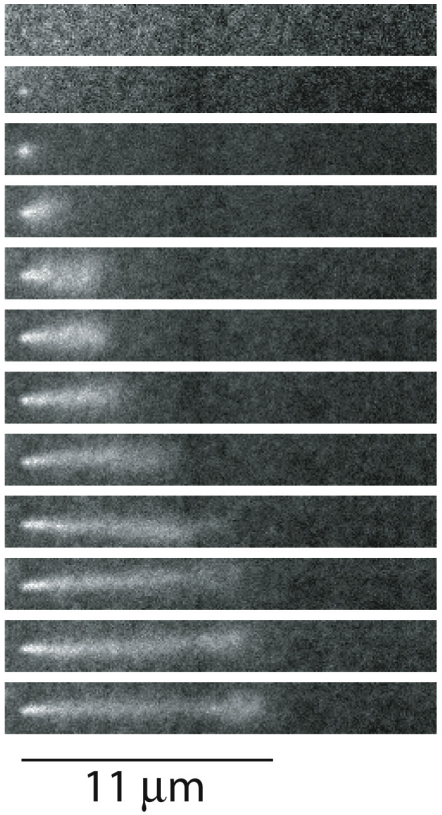
Concept of Single Molecule Ejection Experiment

- ***Viruses attached to cover slip in a weak flow (performed on T5 by Mangenot et al and taught to Paul Grayson).***
- ***Solution contains LamB and fluorescent label.***
- ***Monitor the extent of ejection as a function of time***





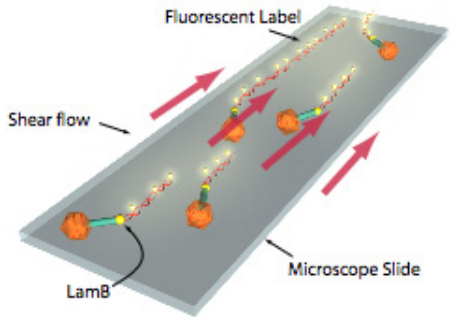




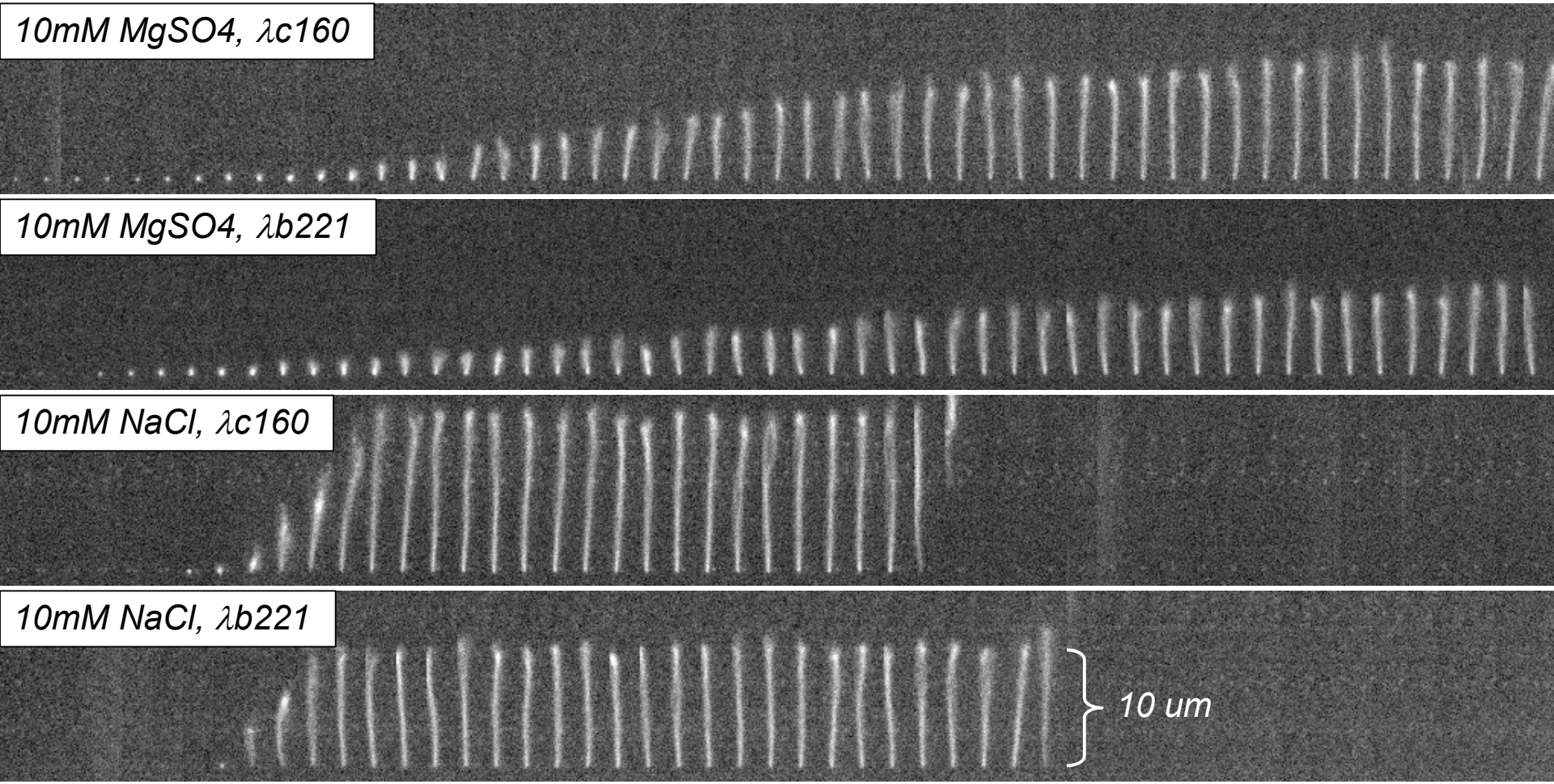
lambda ejection (1s frames)

Results of Single Molecule Ejection Experiment

- ***Key outcome: we can explicitly measure the velocity of ejection.***
- ***Single virus analysis reveals features of the ejection process that are masked by bulk experiments.***

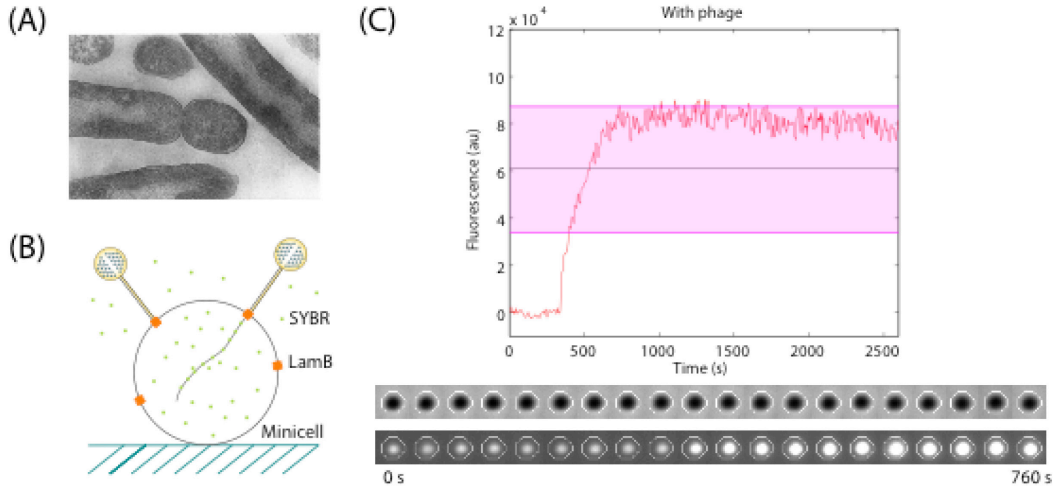


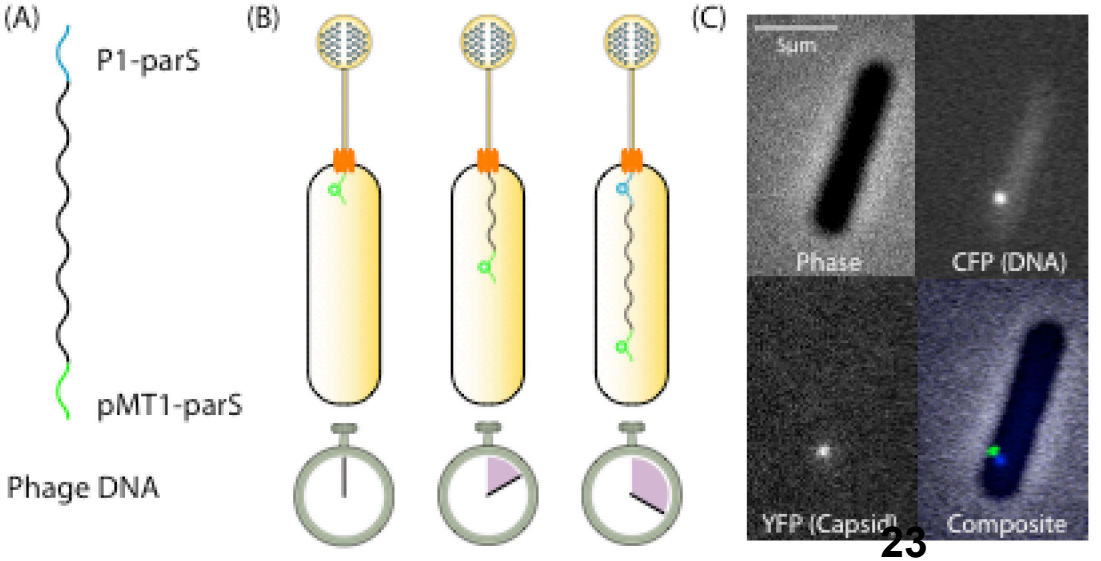
Single Molecule Ejection Trajectories



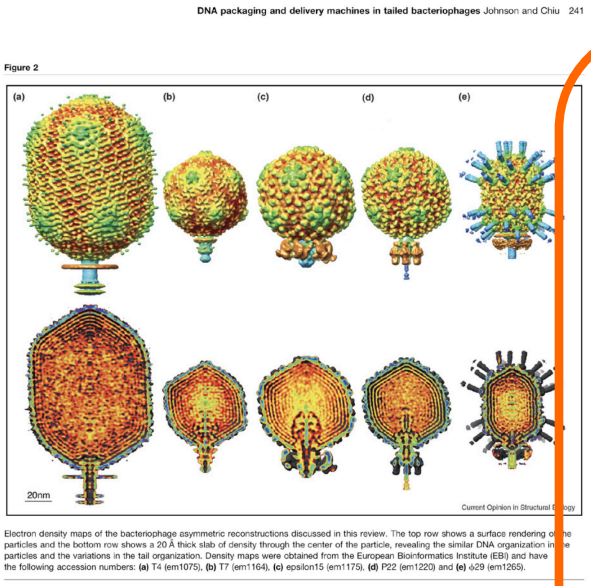
Ejection in living cells

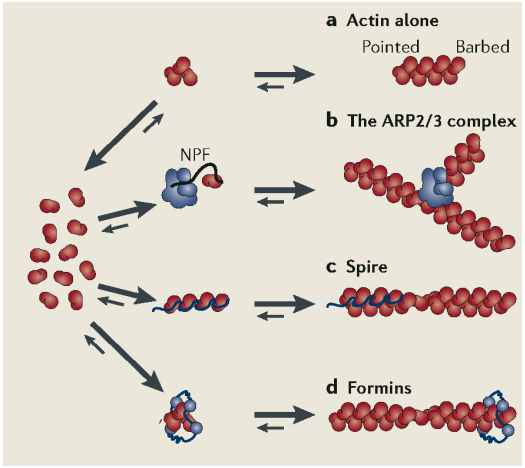
- ***We have seen that we can watch ejections into solution. But what about the problem we really care about which is how genomes get into living cells?***





Talk Outline





The Argument

- *An analogy – astronomy to biology.*
- *Surprises, sanity checks and mechanisms.*
- *Some examples from genome science.*

Managing Genomes

- *An experiment to change your life for.*
- *The physics of genome packing.*

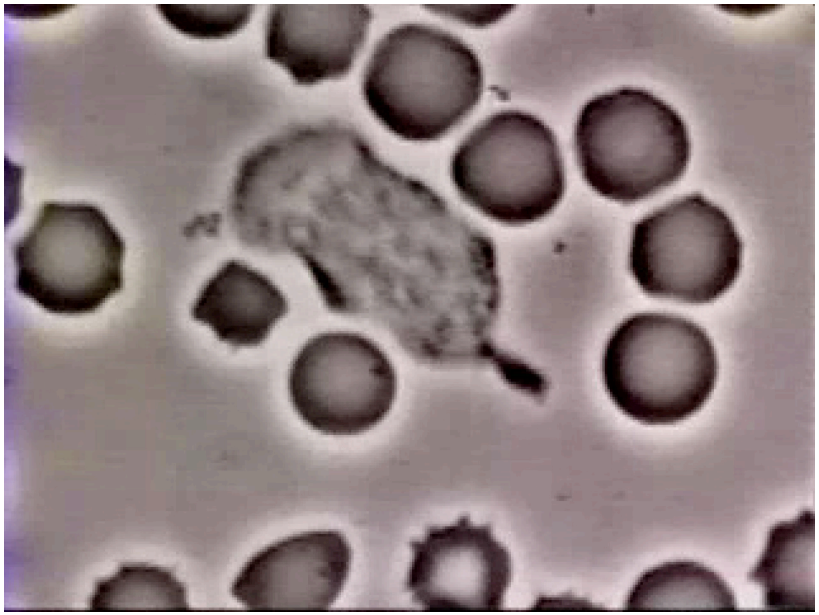
Where to Go

- *How cells decide.*
- *Constructing the cytoskeleton.*
- *Other random walks*

Idea: Link between compelling biological (information management) and physical (random walks) themes.

Why is the rogers video so beloved?

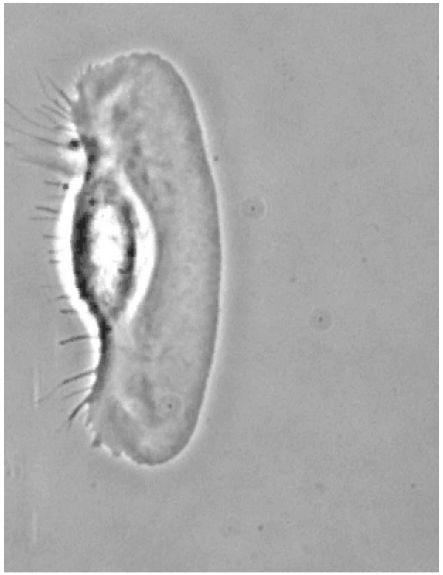
- ***It is often said that a picture is worth a thousand words. This tantalizingly "simple" video reveals a thousand research programs with deep roots back to early studies of immunity by Metchnikoff and reaching to the present day and the quantitative study of the physical limits on biological action.***
- ***We will consider a little vignette that centers on the question of how the cell knows where to install new actin filaments.***

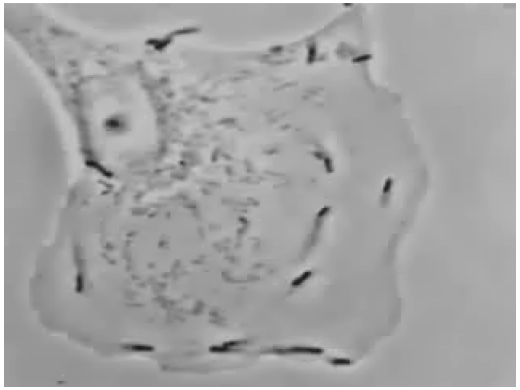


Cell Motility and Actin Polymerization

- ***Motility is driven by the protein actin. Actin assembles into long filaments.***
- ***Through hydrolysis of ATP, these filaments can actually do work as a result of this polymerization process by pushing on membranes, for example.***

(Theriot et al.)





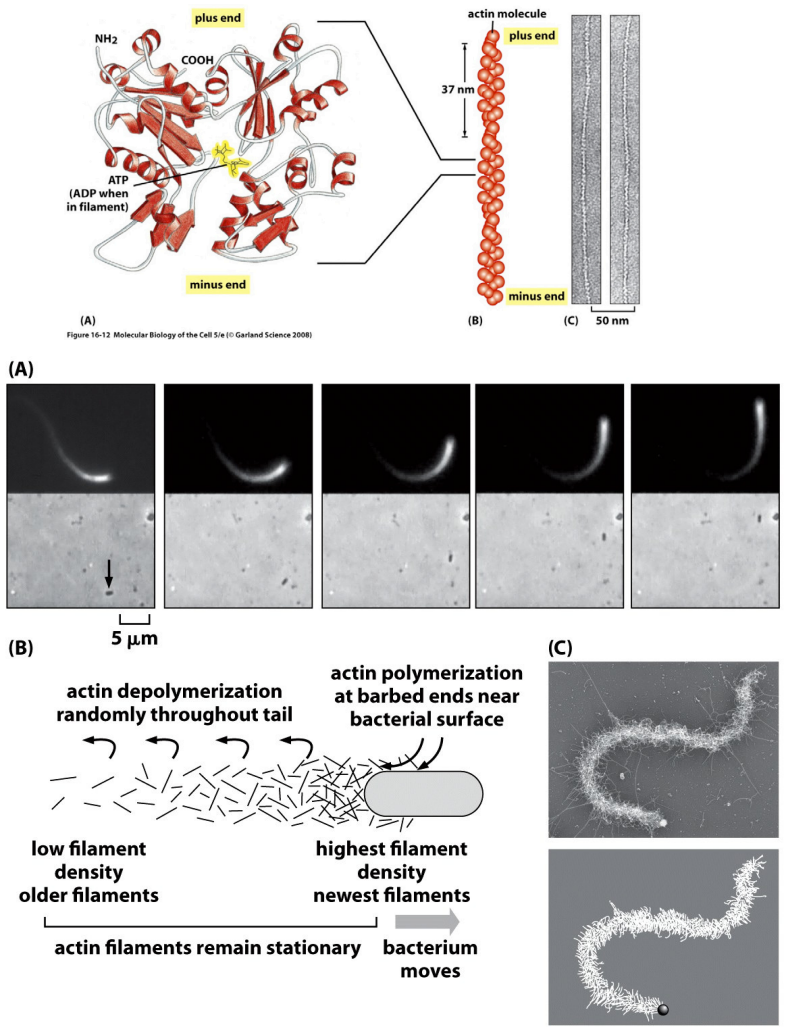
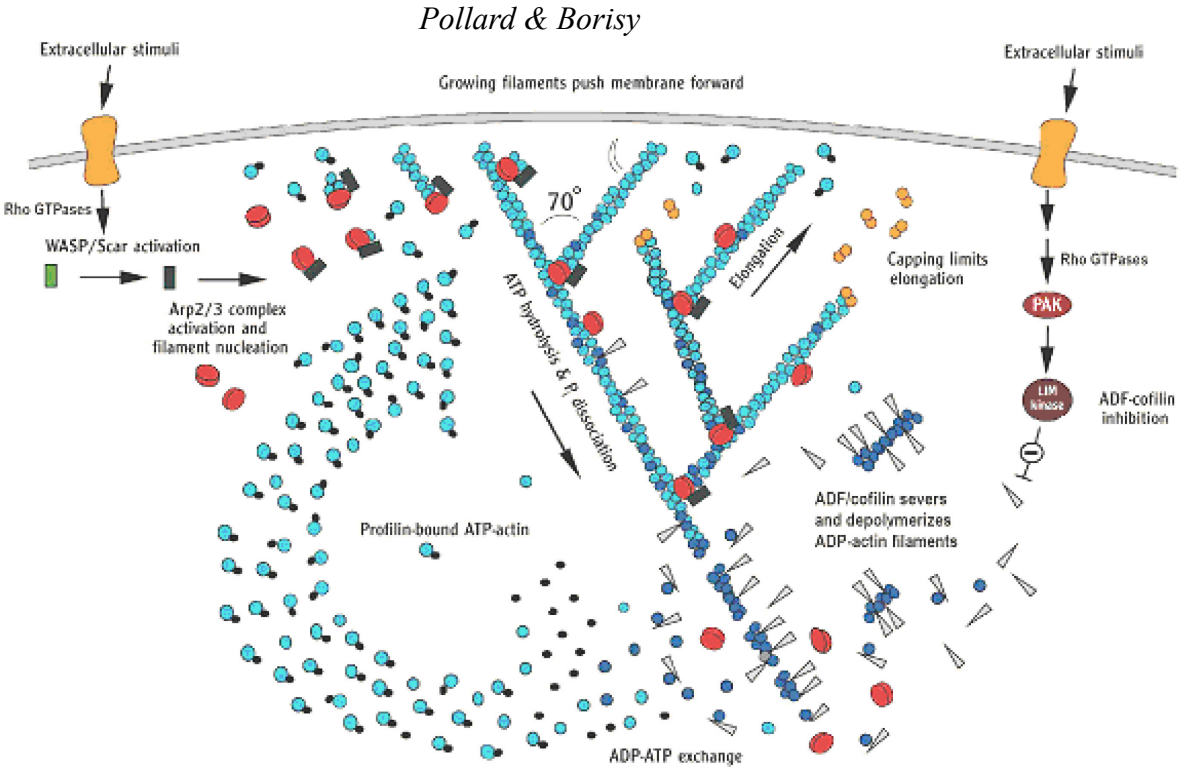


Figure 15.3 Physical Biology of the Cell (© Garland Science 2009)

Space-time Control of Actin Polymerization at the Leading Edge

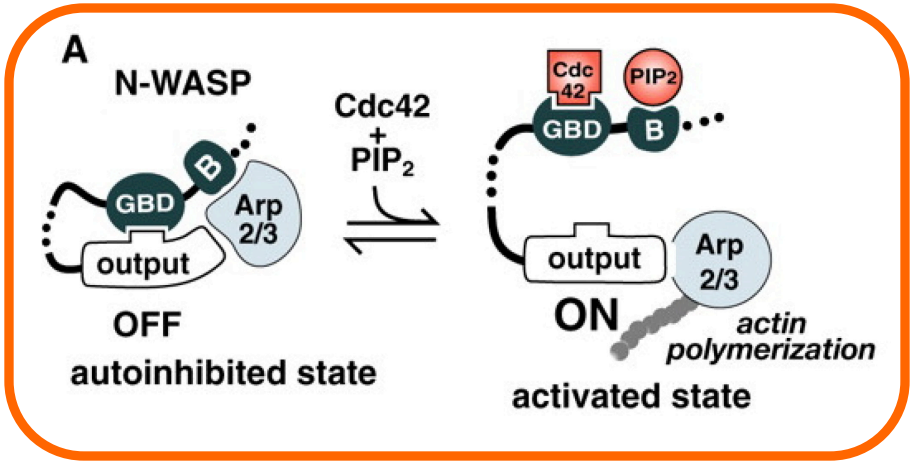
- ***Spacetime control of polymerization is mediated by a host of different proteins that do stuff such as: cap, nucleate, branch, sequester, etc. the actin itself.***
- ***Our story will focus on one little piece of this complex system, namely, the way in which Arp2/3 leads to the synthesis of new filaments.***
- ***Key point: signal integration – how do cells know when and where to put in new actin filaments?***



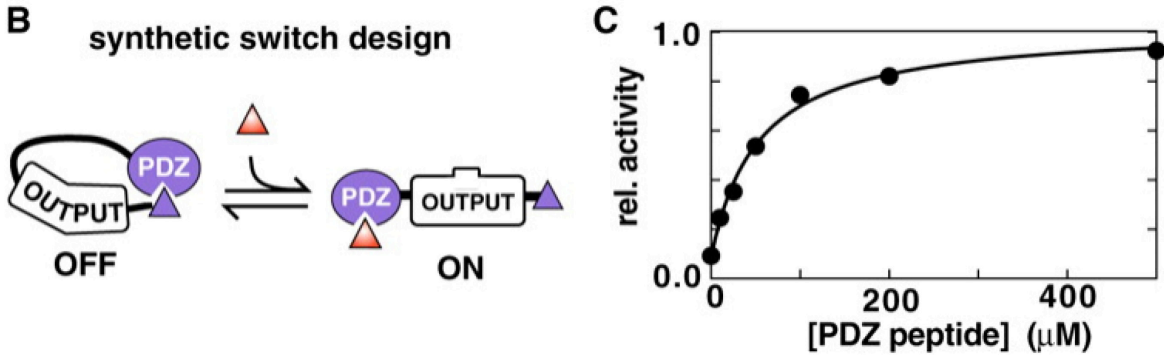
Signaling and Polymerization

- ***External signals activate Arp2/3 which in turn nucleates actin polymerization.***
- ***Group of Wendell Lim has used a Lego approach to mix and match components so that signals normally reserved for other circuits can induce polymerization.***
- ***Do we really "understand" how these molecules work? Let theory and predictions be the judge of that!***

And gate – signal integration

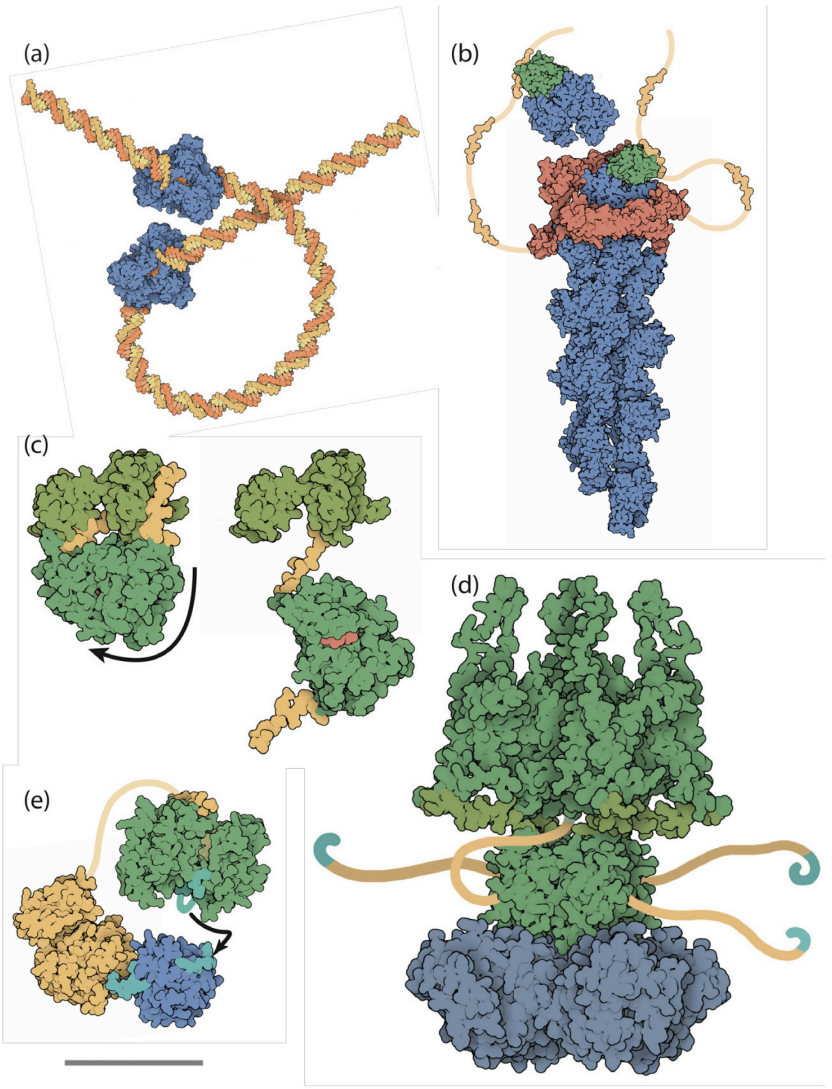


(Dueber, Lim et al., Science, 2003)



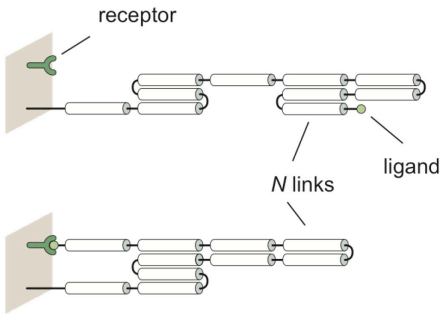
Tethering motifs in biology

- ***Motifs like those described on the previous slide are specific examples of the much more general phenomenon of "tethering".***
- ***Hidden within the tethering concept is the notion that often, proteins should be thought of as two-state systems.***

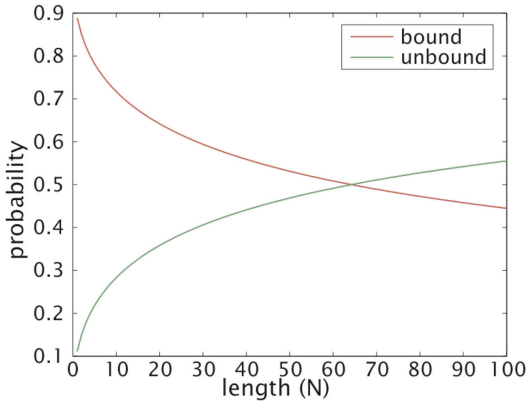


The physics of tethered ligands

(A)

STATE	MULTIPLICITY	BOLTZMANN FACTOR	STATISTICAL WEIGHT
	2^N	$e^{-\beta\varepsilon_{solution}}$	$2^N \times e^{-\beta\varepsilon_{solution}}$
	$\frac{N!}{\left(\left(\frac{N}{2}\right)!\right)^2}$	$e^{-\beta\varepsilon_b}$	$\frac{N!}{\left(\left(\frac{N}{2}\right)!\right)^2} \times e^{-\beta\varepsilon_b}$

(B)



- ***We begin with the toy problem of a receptor and a partner tethered ligand.***
- ***We ask how the probability of ligand-receptor binding depends upon the length of the tether (the key tuning variable for these problems).***

$$p_{bound} = \frac{p_{loop} e^{-\beta\Delta\epsilon}}{1 + p_{loop} e^{-\beta\Delta\epsilon}}$$

$$p_{loop} = \frac{\frac{N!}{((\frac{N}{2})!)^2}}{2^N}$$

$$p_{unbound} = \frac{1}{1 + p_{loop} e^{-\beta\Delta\epsilon}},$$

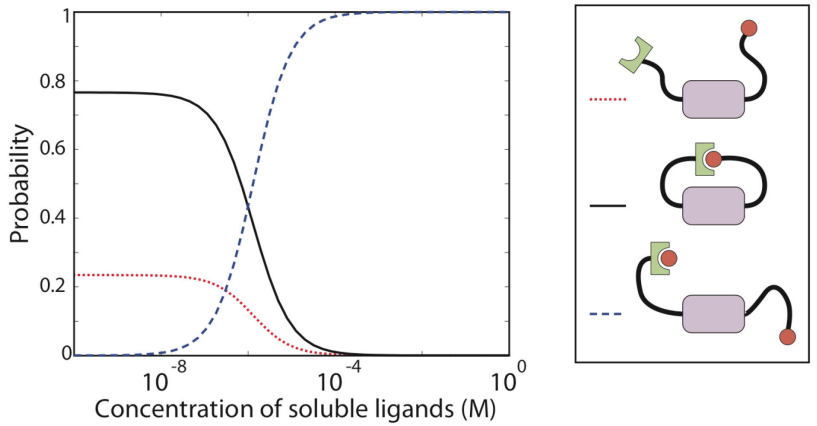
Concentration dependence of the Switch

- ***The switch changes state when p_loop and c/c_0 are comparable.***
- ***This calculation serves as the starting point for the much more interesting case of signal integration by tethered ligand-receptor pairs. Further, it leaves in its wake very specific prejudices about how such tethered pairs work (i.e. length dependence of the tether).***

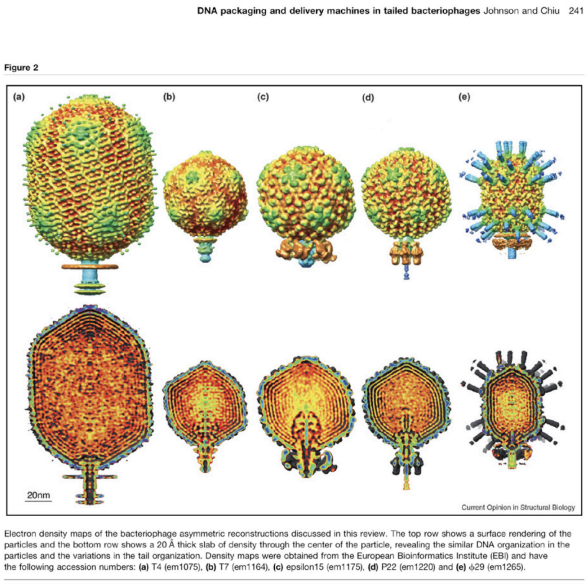
(a)

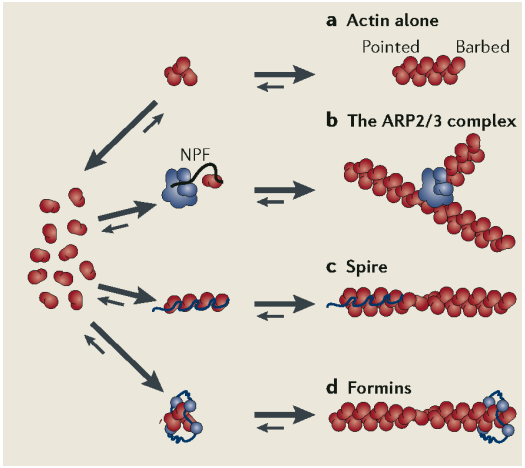
STATE	ENERGY	STATISTICAL WEIGHT: MULTIPLICITY	STATISTICAL WEIGHT: BOLTZMANN WEIGHT
N_R links, N_L links	$(L+1)\varepsilon_s$	$\frac{\Omega!}{L!(\Omega-L)!} \times 2^{N_R} 2^{N_L}$	$e^{-\beta(L+1)\varepsilon_s}$
	$\varepsilon_b + L\varepsilon_s$	$\frac{\Omega!}{L!(\Omega-L)!} \times \frac{(N_R+N_L)!}{\left(\left(\frac{N_R+N_L}{2}\right)!\right)^2}$	$e^{-\beta L\varepsilon_s} e^{-\beta\varepsilon_b}$
	$\varepsilon_b + L\varepsilon_s$	$\frac{\Omega!}{(L-1)!(\Omega-(L-1))!} \times 2^{N_R} 2^{N_L}$	$e^{-\beta L\varepsilon_s} e^{-\beta\varepsilon_b}$

(b)



Talk Outline





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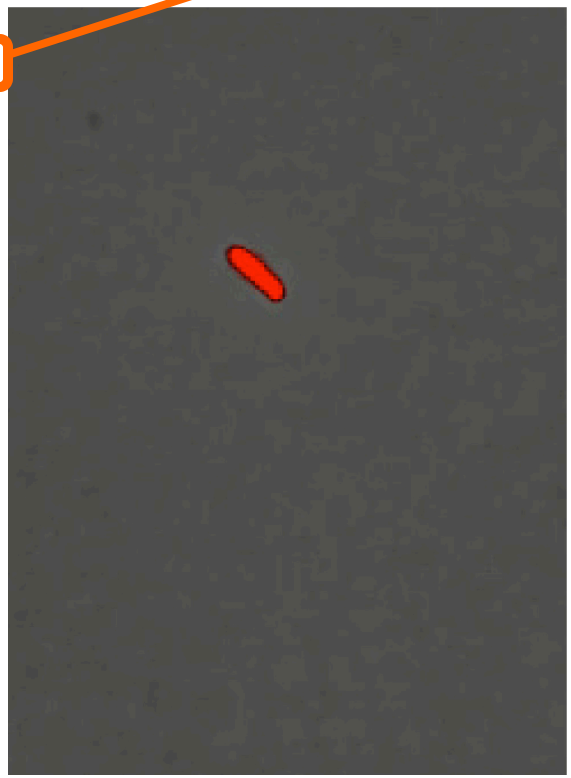
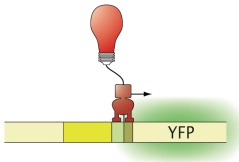
Idea: Link between compelling biological (information management) and physical (random walks) themes.

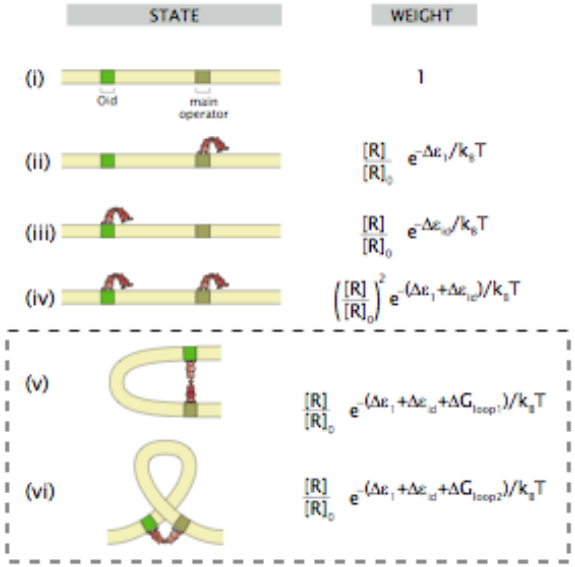
Random walks : Using Drunks to Count Proteins and Measure Expression

- ***Find new ways to count, new watches, new rulers.***
- ***Key point: in order to use the statistical mechanical theory, we must know the number of transcription factors. This suggested a cool new way to count and to measure the whole fold-change function.***
- ***KEY PROBLEM: no calibration factor between fluorescence and number of proteins.***

$$fold\ change = (1 + \frac{R}{N} e^{-\beta \Delta\varepsilon})^{-1}$$



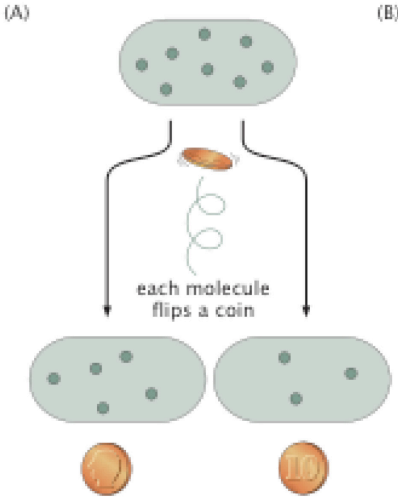


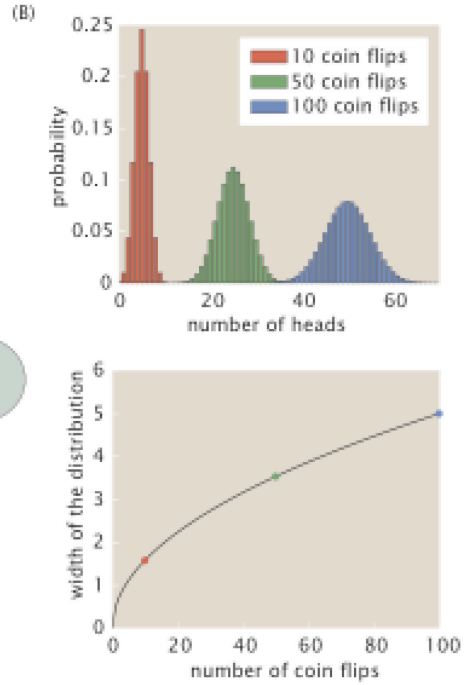


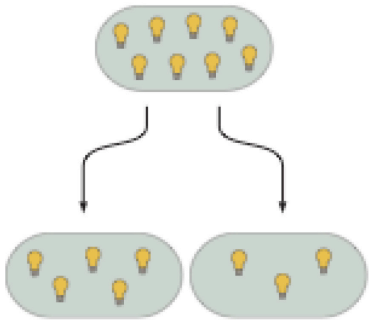
(Rosenfeld, Young, Alon, Swain, Elowitz, Science, 2005)

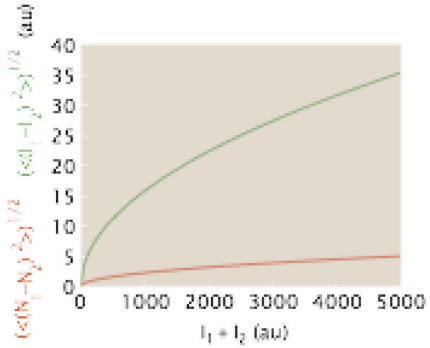
Cells do vegas

- ***If the partitioning is random, then the statistics will be like those resulting from coin flips.***
- ***Indeed, one of the main points of my whole talk is the way in which again and again there are secrets hidden in distributions.***
- ***Cleverly, the fluctuations can be used to establish the standard candle!***



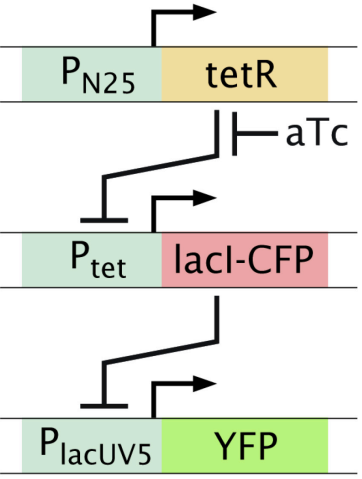


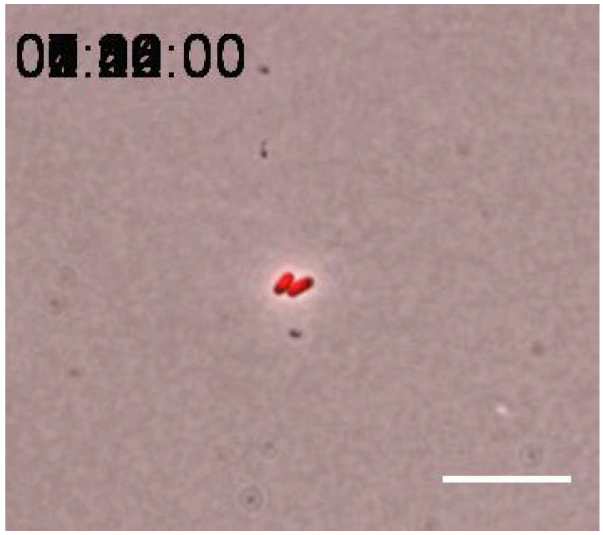


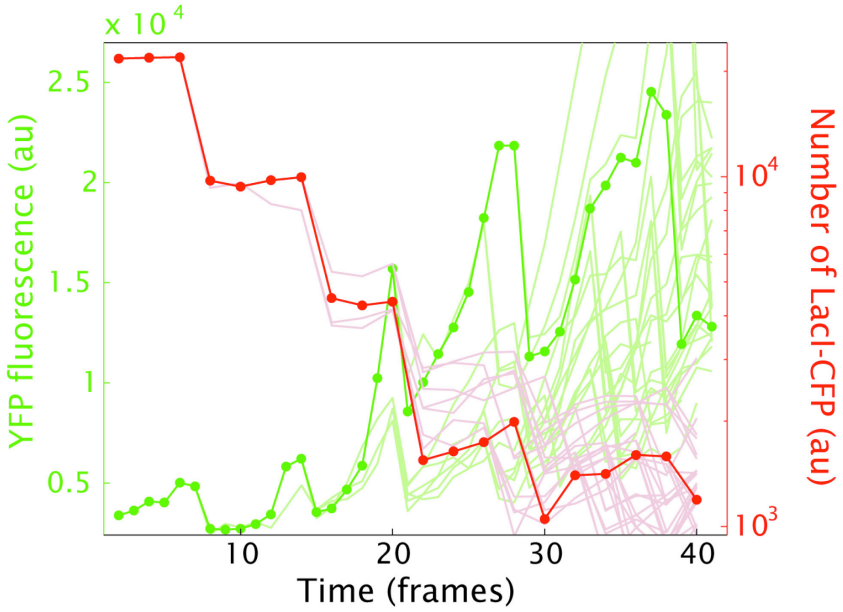


$$\sqrt{< (I_1 - I_2)^2 >} = \sqrt{\alpha I_{tot}}$$

The Dilution Circuit

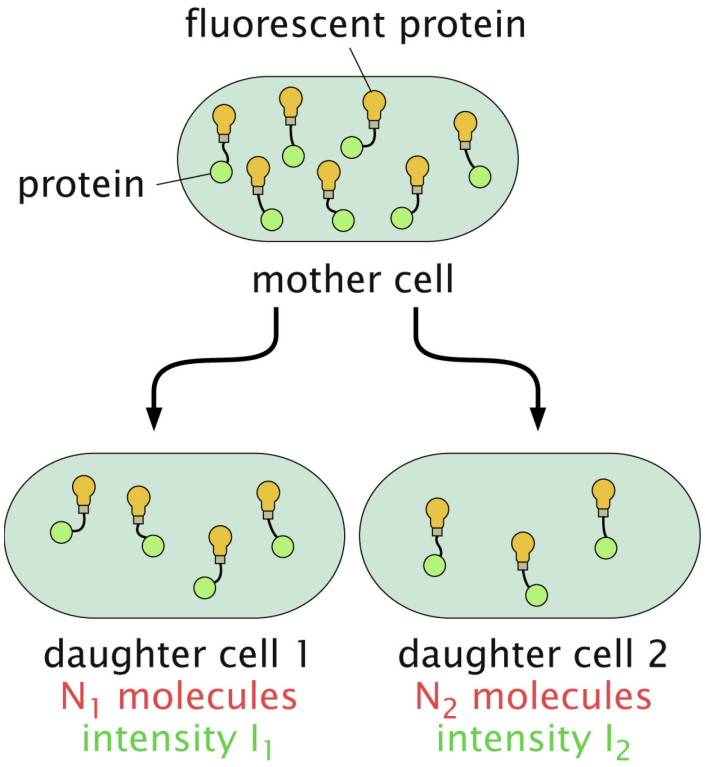


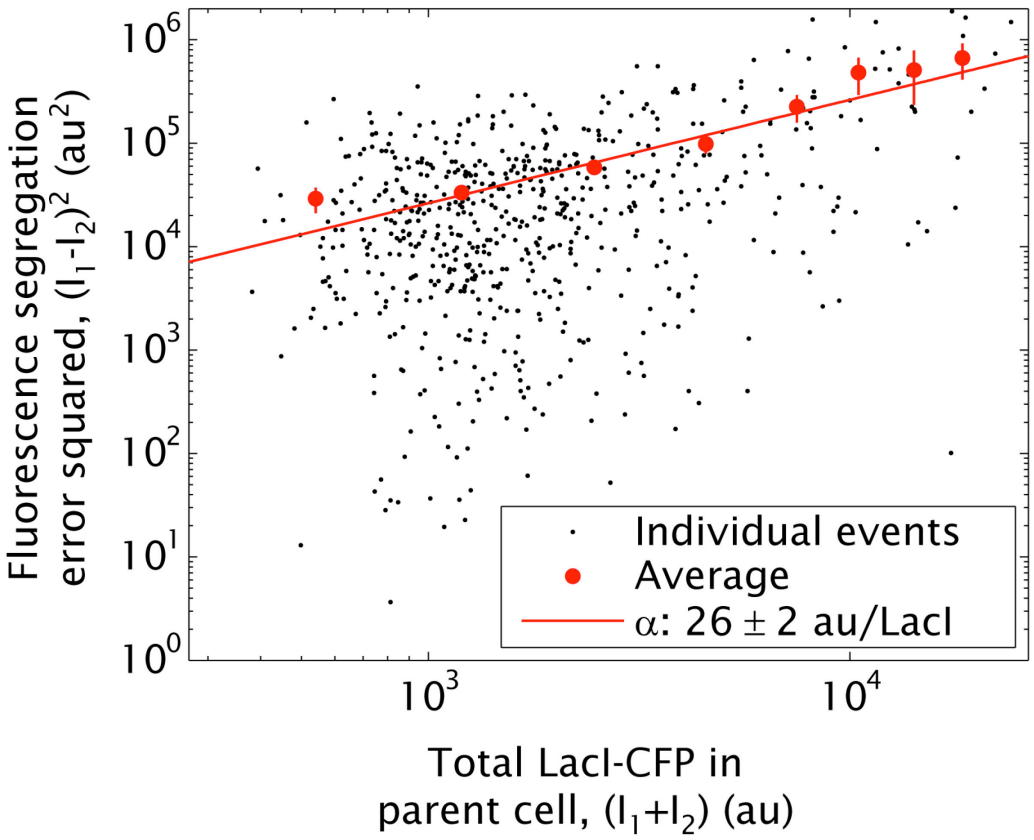




- ***We track the dilution of LacI-CFP and the production rate of YFP over time and over multiple generations.***

We Count Repressors Using Fluctuations

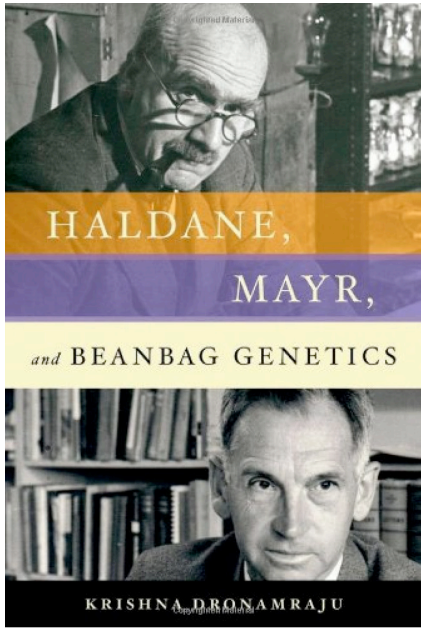




- ***Each point corresponds to a cell division event***
- ***Calibrate using $(I_1-I_2)^2 = a\,(I_1+I_2)$***

Beanbag genetics

- ***Two of the great evolutionary biologists of the last century had an ongoing debate about the uses and abuses of "beanbag genetics".***
- ***Opinion: the more ideological a field, the more that field is in need of data, the more clear it is that the subject is still not finished.***



- ***All just to say that lots of interesting things can be learned by coin flips, urn drawing, etc.***

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REPRINTS AND REFLECTIONS

A Defense of Beanbag Genetics*

JBS Haldane

My friend Professor Ernst Mayr, of Harvard University, in his recent book *Animal Species and Evolution*[1], which I find admirable, though I disagree with quite a lot of it, has the following sentences on page 263.

> The Mendelian was apt to compare the genetic contents of a population to a bag full of colored beans. Mutation was the exchange of one kind of bean for another. This conceptualization has been referred to as "beanbag genetics". Work in population and developmental genetics has shown, however, that the thinking of beanbag genetics is in many ways quite misleading. To consider genes as independent units is meaningless from the physiological as well as the evolutionary viewpoint.

Any kind of thinking whatever is misleading out of its context. Thus ethical thinking involves the concept of duty, or some equivalent, such as right-eousness or *dharma*. Without such a concept one is lost in the present world, and, according to the religions, in the next also. Joule, in his classical papers on the mechanical equivalent of heat, wrote of the duty of a steam engine. We now write of its horsepower. It is of course possible that ethical conceptions will in future be applied to electronic calculators, which may be given built-in consciences!

In another place[2] Mayr made a more specific challenge. He stated that Fisher, Wright, and I "have worked out an impressive mathematical theory of genetical variaion and evolutionary change. But what, precisely, has been the contribution of this mathematical school to evolutionary theory, if I may be permitted to ask such a provocative question?" "However," he continued in the next paragraph, "I should perhaps leave it to Fisher, Wright, and Haldane to point out what they consider their major contributions." While Mayr may certainly ask this question, I may not answer it at Cold Spring Harbor, as I have been officially informed that I am ineligible for a visa for entering the United States[†]. Fisher is dead, but when alive preferred attack to defense. Wright is one of the gentlest men I have ever met, and if he defends himself, will not counterattack. This leaves me to hold the fort, and that by writing rather than speech.

Now, in the first place I deny that the mathematical theory of population genetics is at all impressive, at least to a mathematician. On the contrary, Wright, Fisher, and I all made simplifying assumptions which allowed us to pose problems soluble by the elementary mathematics at our disposal, and even then did not always fully solve the simple problems we set ourselves. Our mathematics may impress zoologists but do not greatly impress mathematicians. Let me give a simple example. We want to know how the frequency of a gene in a population changes under natural selection. I made the following simplifying assumptions[3]:

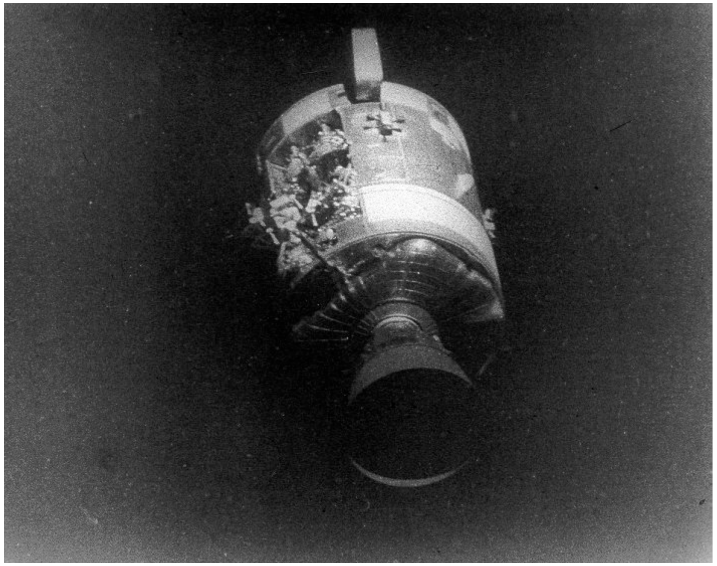
1. The population is infinite, so the frequency in each generation is exactly that calculated, not just somewhere near it.
2. Generations are separate. This is true for a minority only of animal and plant species. Thus even in so-called annual plants a few seeds can survive for several years.
3. Mating is at random. In fact, it was not hard to allow for inbreeding once Wright had given a quantitative measure of it.
4. The gene is completely recessive as regards fitness. Again it is not hard to allow for incomplete dominance. Only two alleles at one locus are considered.
5. Mendelian segregation is perfect. There is no mutation, non-disjunction, gametic selection, or similar complications.
6. Selection acts so that the fraction of recessives breeding per dominant is constant from one generation to another. This fraction is the same in the two sexes.

*Haldane, J.B.S. A Defense of Beanbag Genetics. Perspectives in Biology and Medicine 7:3 (1964), 343-359. © The Johns Hopkins University Press. Reproduced with permission of The Johns Hopkins University Press.

†In spite of this ineligibility I have, since writing this article, been granted an American visa, for which I must thank the federal government. However, I am not permitted to lecture in North Carolina, and perhaps in other states, without answering a question which I refuse to answer. Legislation to this effect does not, in my opinion, help American science.

Working problems with all tools at hand

- ***Gene Kranz – "Let's work the problem people". The concept embodied in his words is that we need to bring every possible tool at our disposal to bear on solving important problems with complete indifference to what these tools are called and what we are called (i.e. biologists, mechanicians, biochemists, mathematicians, engineers, physicists, etc.).***
- ***Biology will be (and already has been) transformed by invoking Darwin's "extra sense" and using it to "work the problem".***



Warning: Criticisms of the philosophy and implementation

- ***What is a biophysicist?. Superficiality is a many-headed, dangerous monster (wrong questions, ignorance of literature, "not even wrong", throwing out the meat of the problem, using models to "fit the data", etc.) "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. Not clear to me that Dulong and Petit, Weber, Brown and many others new they were engaged in getting "new physics" or " new biology" – they were just going down the rabbit hole.***
- ***Specificity is the soul of credibility.***

Acknowledgements

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RP group – thanks for the fun and education!