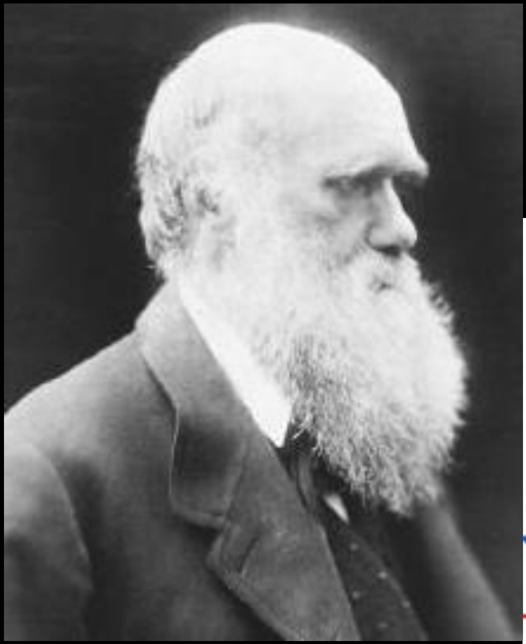
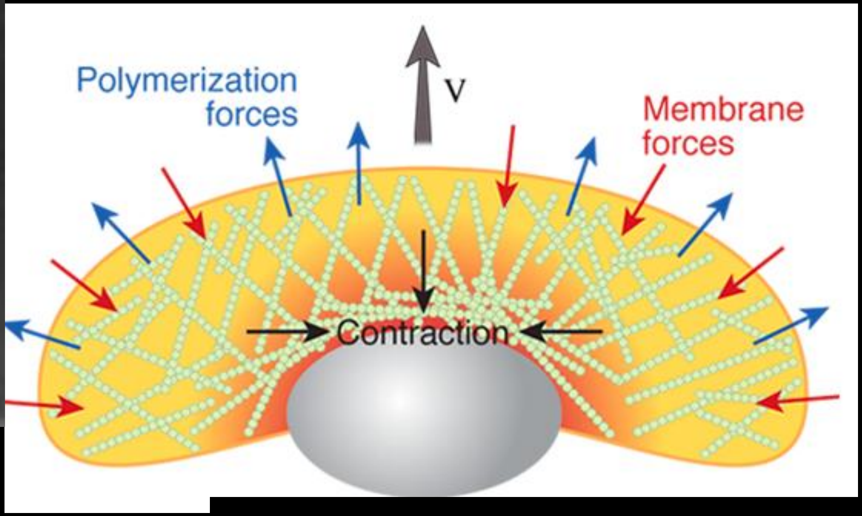
Physics and Biology: Evolution of Life and Evolution of Science

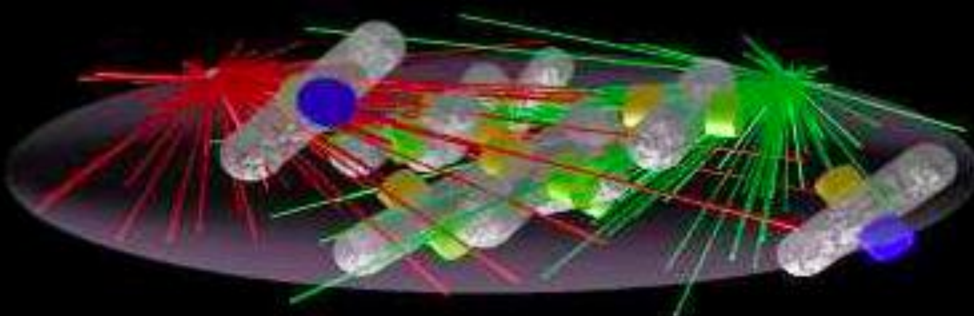


by
Nick Nicastro



BIOLOGY
MEETS
PHYSICS

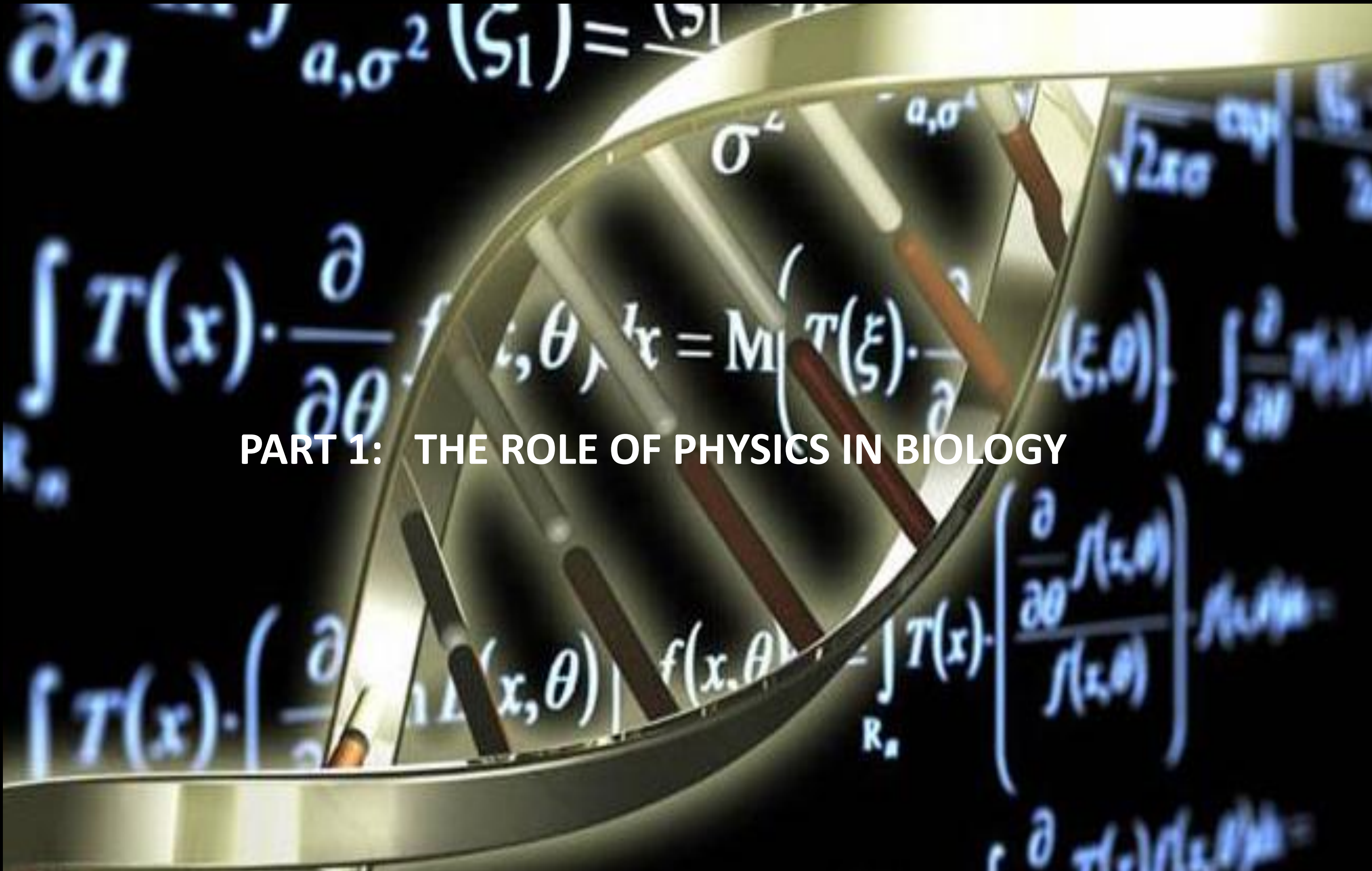
A presentation based on the 2011 Teachers' Conference at the Kavli Institute for Theoretical Physics, UCSB



PART 1: THE ROLE OF PHYSICS IN BIOLOGY

PART 2: THE EVOLUTION OF LIVING SYSTEMS

PART 3: PHYSICS , THE CELL, AND THE FUTURE



PART 1: THE ROLE OF PHYSICS IN BIOLOGY

All physical processes are driven by the principles of physics.

$$\vec{F} = m\vec{a} \quad \vec{p} = m\vec{v} \quad KE = \frac{1}{2}mv^2 = \frac{p^2}{2m} \quad W_{tot} = \Delta(KE) = KE_f - KE_i \quad A_{sphere\text{-}surface} = 4\pi r^2$$

$$\frac{mv^2}{R}$$

$$k = 8.99\,(10)^9\left[\frac{Nm^2}{C^2}\right] \quad k = \frac{1}{4\pi\varepsilon_o} \quad A_{circle} = \pi r^2$$

$$F = k\frac{q_1 q_2}{r^2} = \frac{1}{4\pi\varepsilon_o}\frac{q_1 q_2}{r^2} \quad \varepsilon_o = 8.85\,(10)^{-12}\left[\frac{C^2}{N m^2}\right] \quad \varepsilon_o = 8.85\,(10)^{-12}\left[\frac{C^2}{N m^2}\right] \quad V_{sphere} = \frac{4}{3}\pi r^3$$

$$E = \frac{F}{q} \quad E = k\frac{q}{r^2} = \frac{1}{4\pi\varepsilon_o}\frac{q}{r^2} \quad V = k\frac{q}{r} = \frac{1}{4\pi\varepsilon_o}\frac{q}{r} \quad V = \frac{U}{q} \quad \sim e^{-t/RC}$$

$$\sum_{surf} E_\perp \Delta A = \frac{q}{\varepsilon_o} \quad Q = VC \quad C = \frac{A\varepsilon_o}{d} \quad \sigma = \frac{Q}{A} \quad V = Ed \quad E = \frac{\sigma}{\varepsilon_o} \quad U = \frac{QV}{2} = \frac{CV^2}{2} = \frac{Q^2}{2C}$$

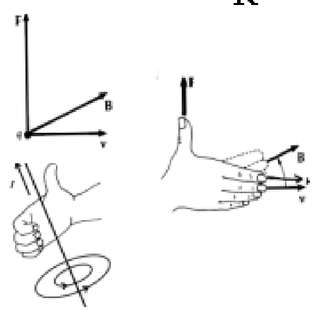
$$\sum_{junc} I_j = 0 \quad \sum_{loop} V_j = 0 \quad V = IR \quad P = IV = I^2 R = \frac{V^2}{R} \quad R_{eff} = R_1 + R_2 \quad \frac{1}{C_{eff}} = \frac{1}{C_1} + \frac{1}{C_2}$$

$$\frac{1}{R_{eff}} = \frac{1}{R_1} + \frac{1}{R_2} \quad C_{eff} = C_1 + C_2$$

$$F = qvB_\perp = qv_\perp B = qvB\sin(\theta)$$

$$F = ILB_\perp = I_\perp LB = ILB\sin(\theta)$$

$$\sum_{curv} B_\parallel \Delta l = \mu_o I_\perp$$

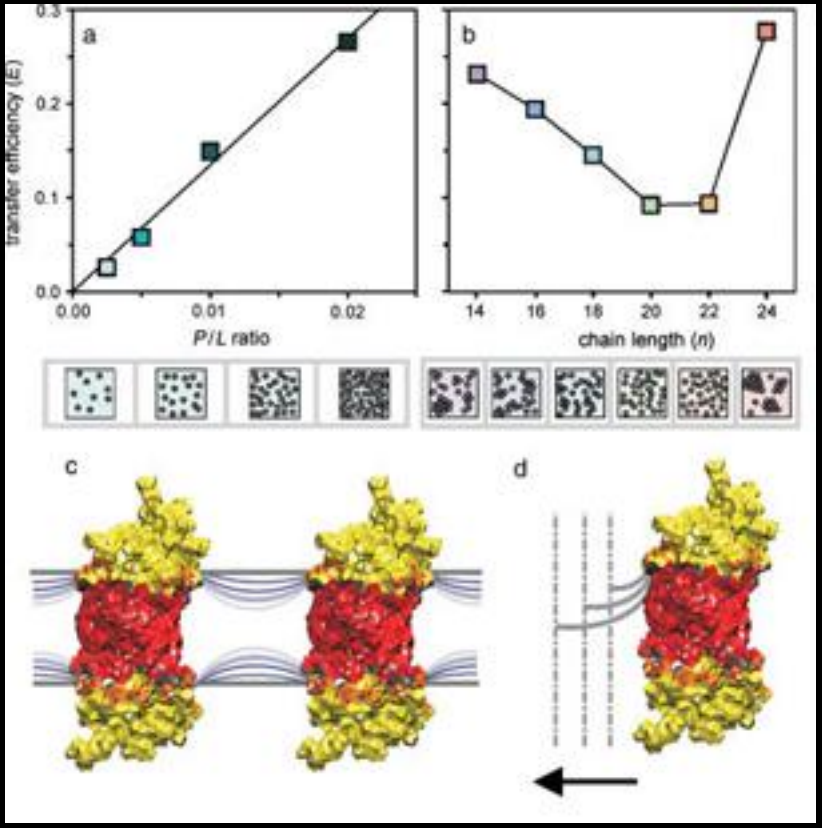


$$B = \frac{\mu_o I}{2\pi r}$$

$$\mu_o = 4\pi(10)^{-7}\ \text{Tm/A}$$

All physical processes are driven by the principles of physics.

When these processes are applied to living systems, the realms of physics and biology merge to define how organisms function, from the simplest forms of life to the most complex.



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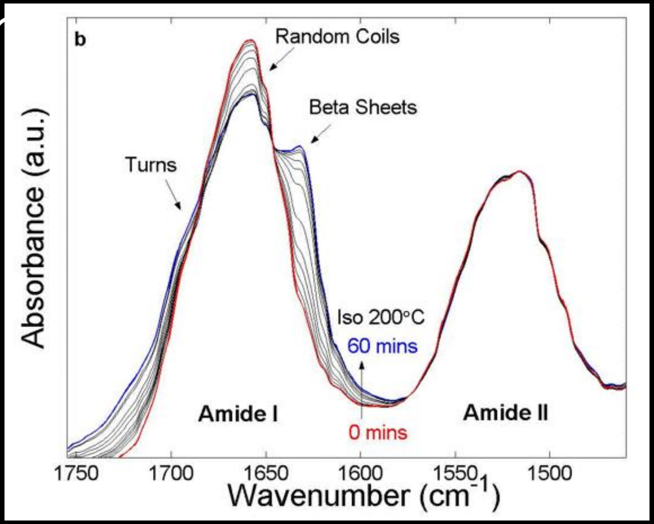

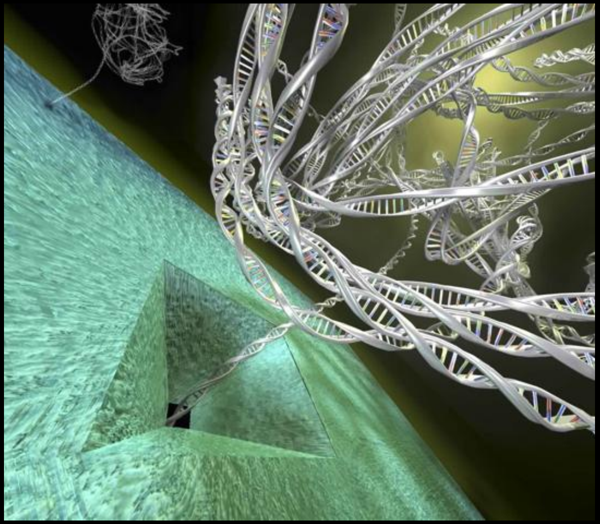

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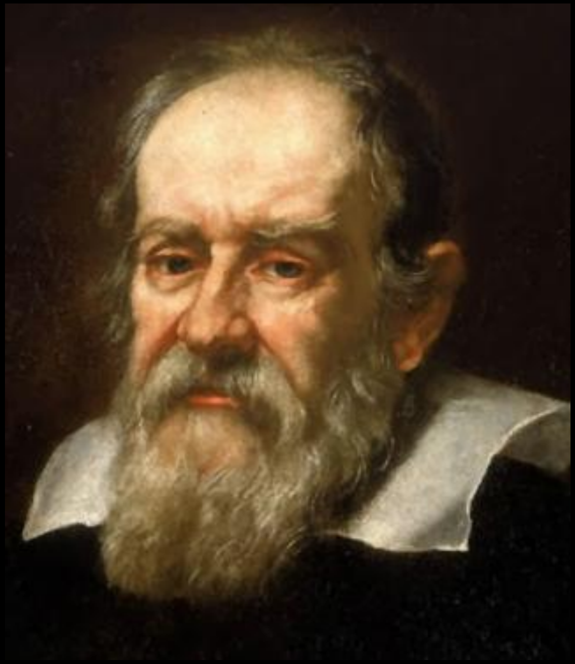
When these processes are applied to living systems, the realms of physics and biology merge to define how organisms function, from the simplest forms of life to the most complex.

The internal mechanisms involve and invoke the widest possible spectrum of disciplines of science and mathematics.

This presentation is designed to introduce you to some of the ways that physics helps us to understand how living systems evolve and function, and how we might someday apply these principles for the betterment of mankind.

“Measure what is measurable, and make measurable what is not.”

Galileo



"Science has been changed by new ways of observing and measuring the world"

R. Phillips

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Throughout human history, man has engaged science by careful observation of the world around him.

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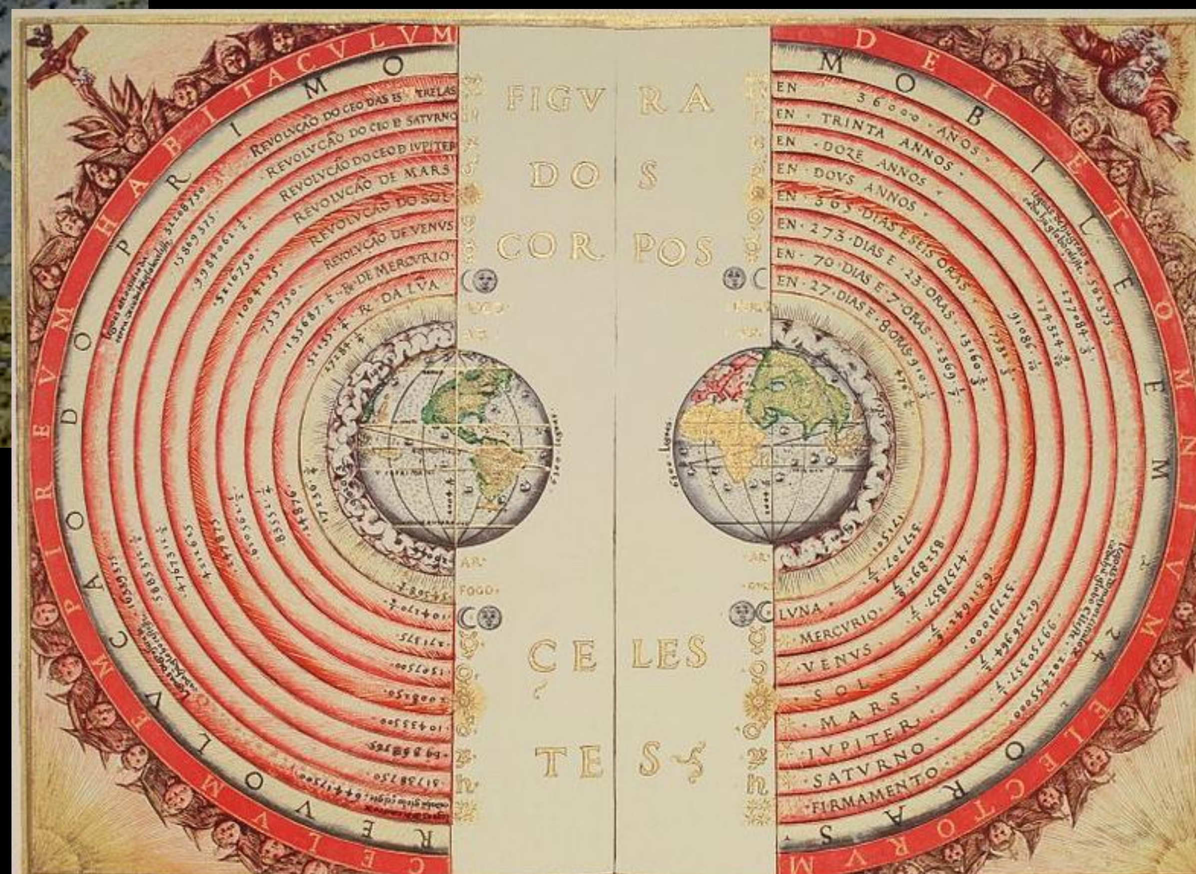

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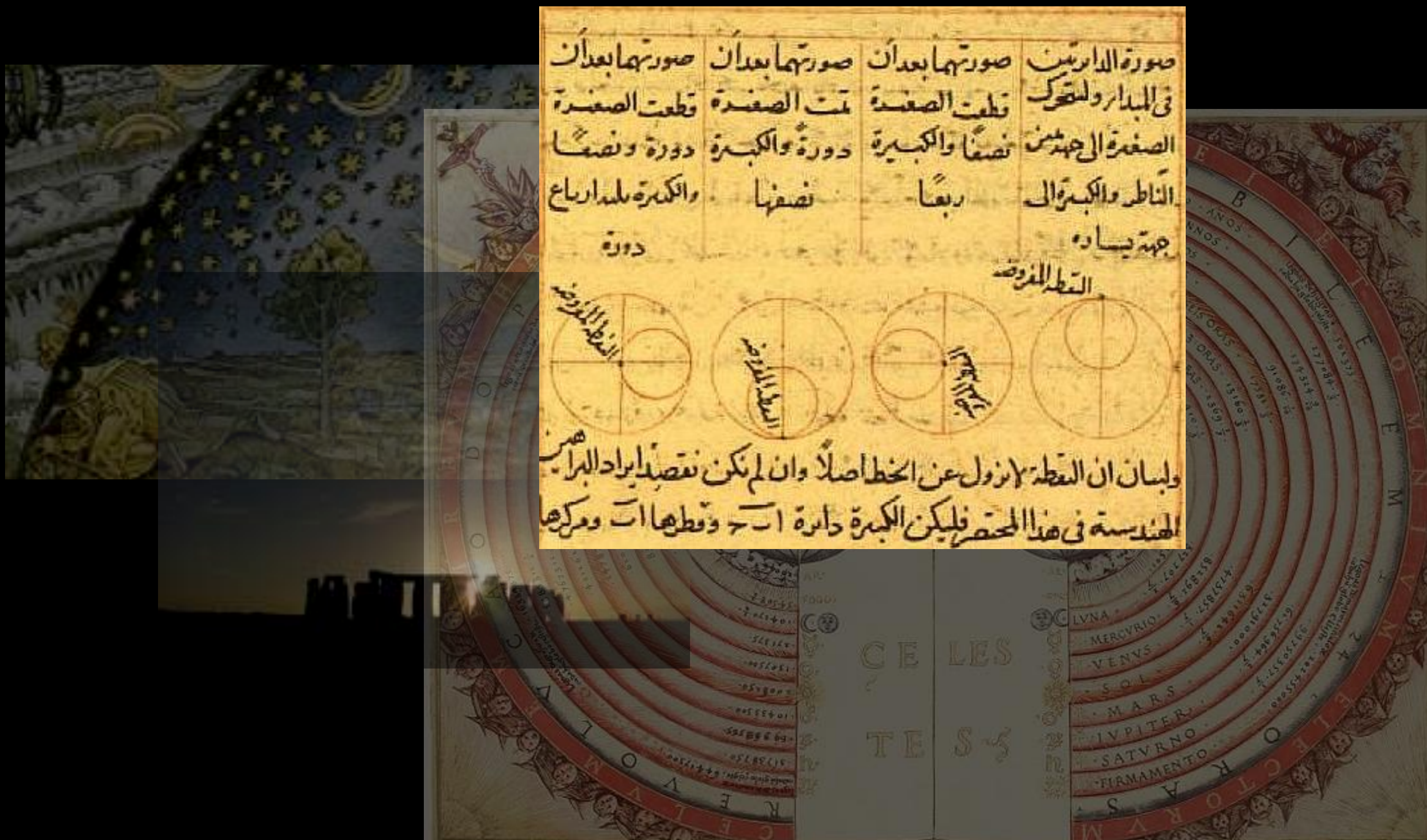

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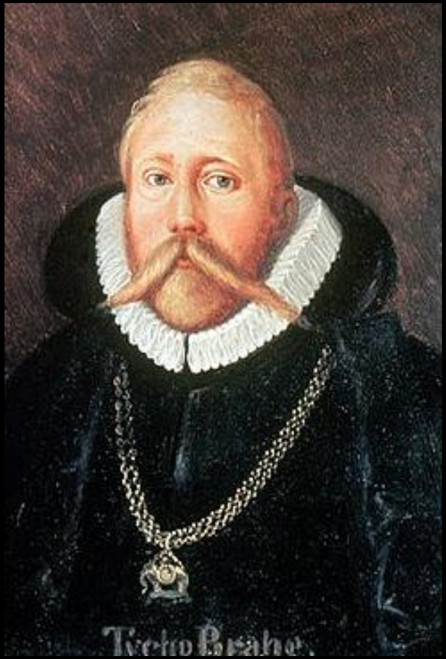

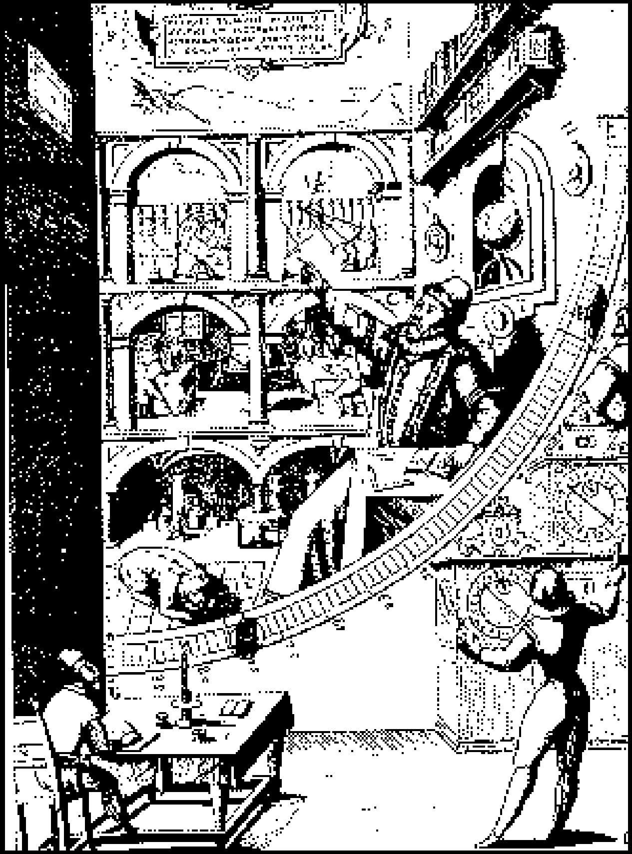

Although his measurements were precise, his scientific and religious prejudices about the universe kept him from understanding the motions.

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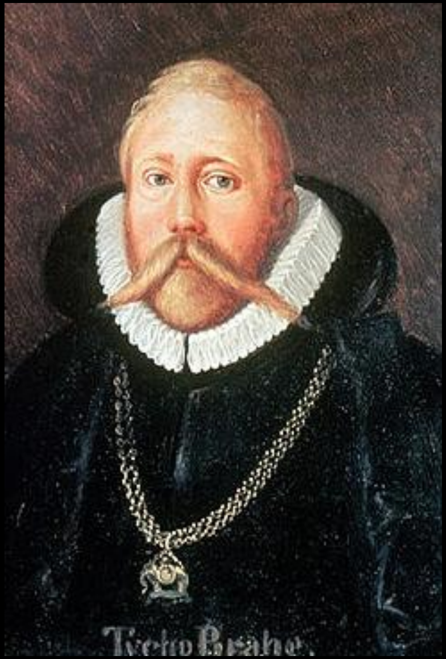

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When his contemporary, Johannes Kepler analyzed these measurements, unteathered by prejudice, his persistence and open-mindedness led him to explain the actual motion of the planets.

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Throughout human history, man has engaged science by careful observation of the world around him. In the 16th century, astronomer Tycho Brahe made careful measurements of the motion of Mars.

By using the Copernican model of the sun-centered universe, developed in 1543, Kepler would go on to define his Laws of Planetary Motion.

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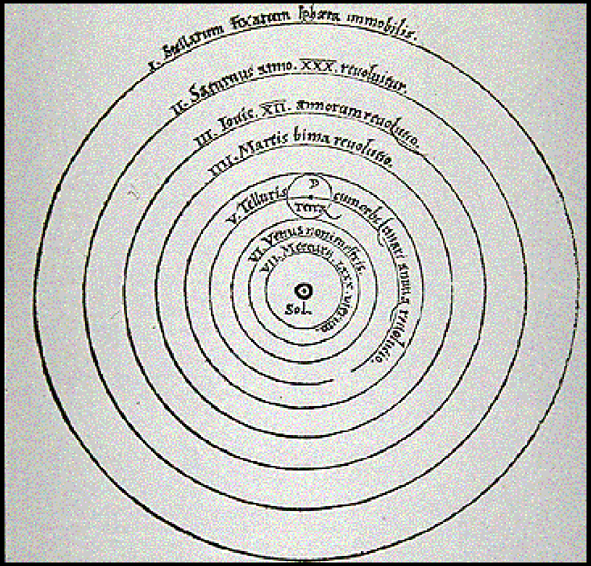

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In just under 60 years, biology has been completely rewritten.

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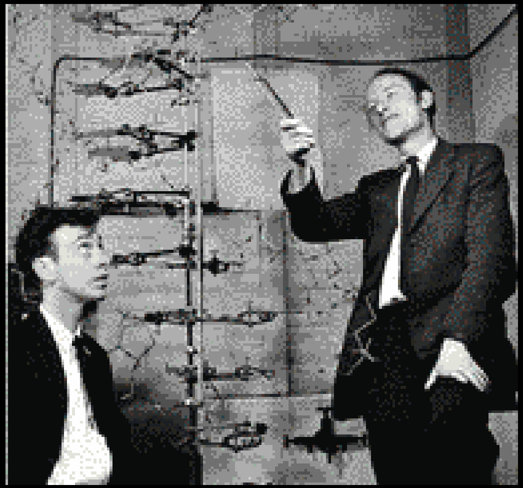

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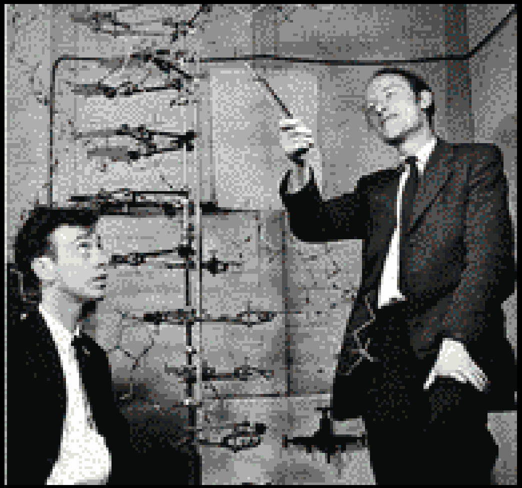

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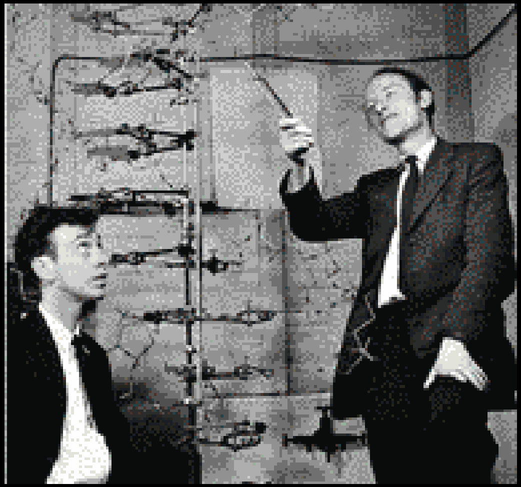
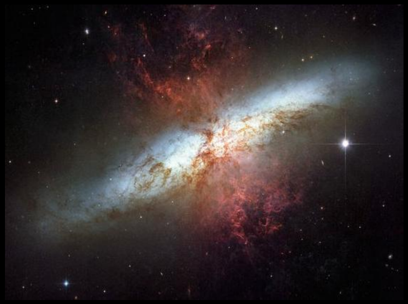
The science of physics has become an integral part in our understanding of this new domain.



The science of physics deals with the interrelationships between space, time, matter and energy.



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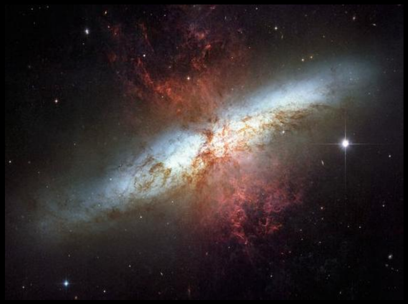

Biology of the 20th and 21st centuries deals with these same concepts on the molecular and cellular scale.

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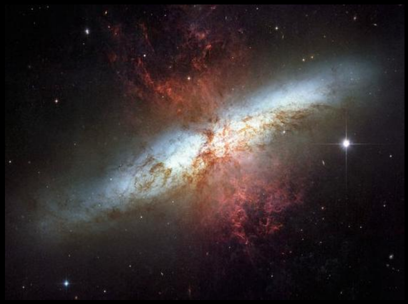

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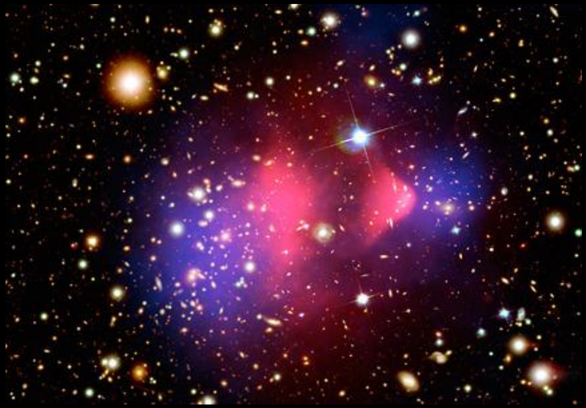
In the same way that Bunsen and Kirchhoff connected barium and strontium to fire, and linked these to the stars. . .



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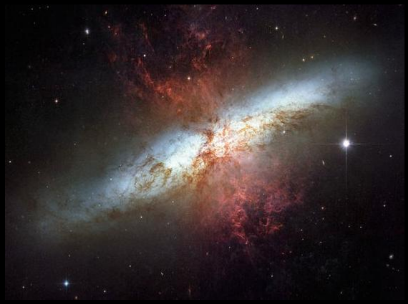

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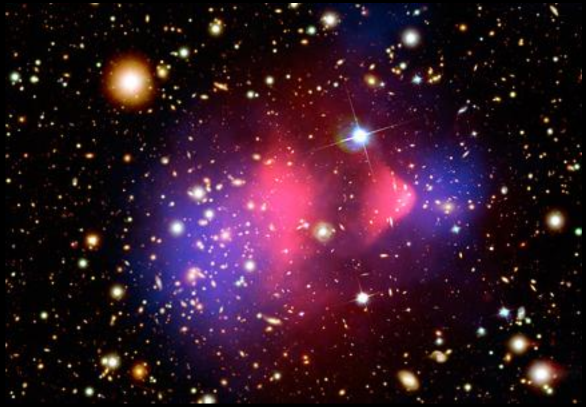
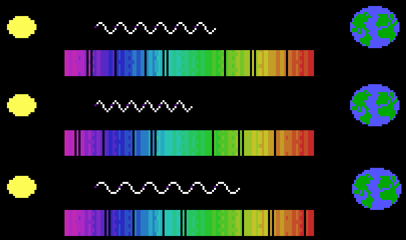
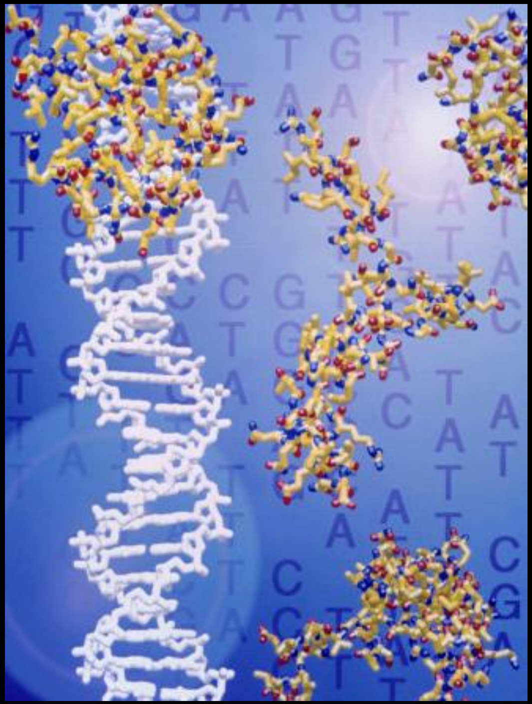
and the tools of spectroscopy made it possible to determine the



red shifts of galaxies. . .



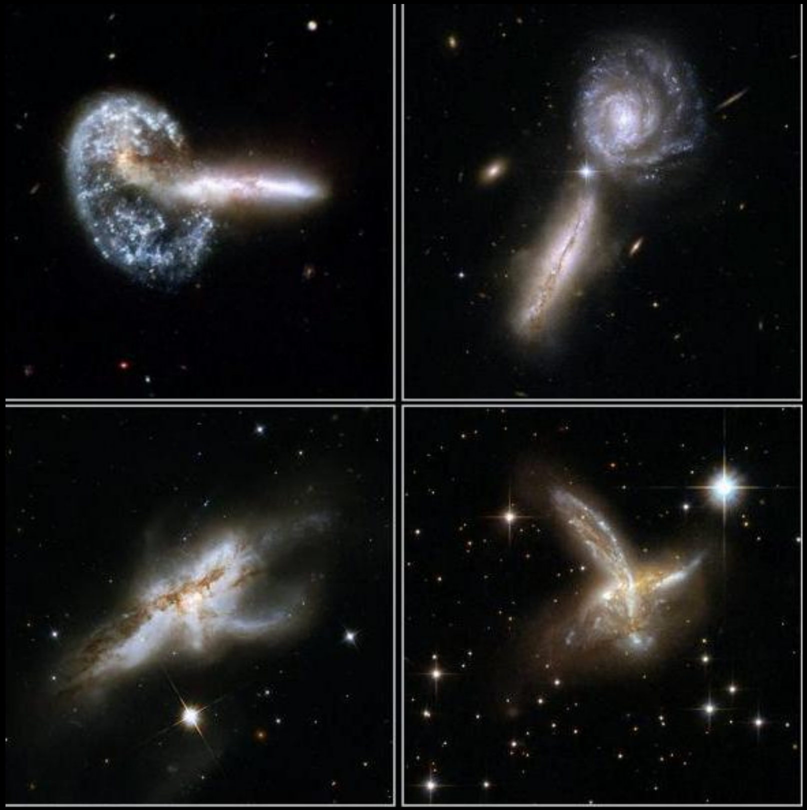
THE TOOLS OF MODERN DAY PHYSICS ARE BEING UTILIZED AND ADAPTED FOR THE LEAP INTO 21^{ST} CENTURY BIOLOGY



"Molecular and cellular biology have become more amenable to a research paradigm that melds experimental and theoretical investigations, and, more specifically, research that is geared toward an accurate description of how things move in space and time. It is, therefore, not surprising that physicists would be attracted to cell biological research."

C. Wolgemuth

Like astrophysicists investigating the interactions between galaxies. . .



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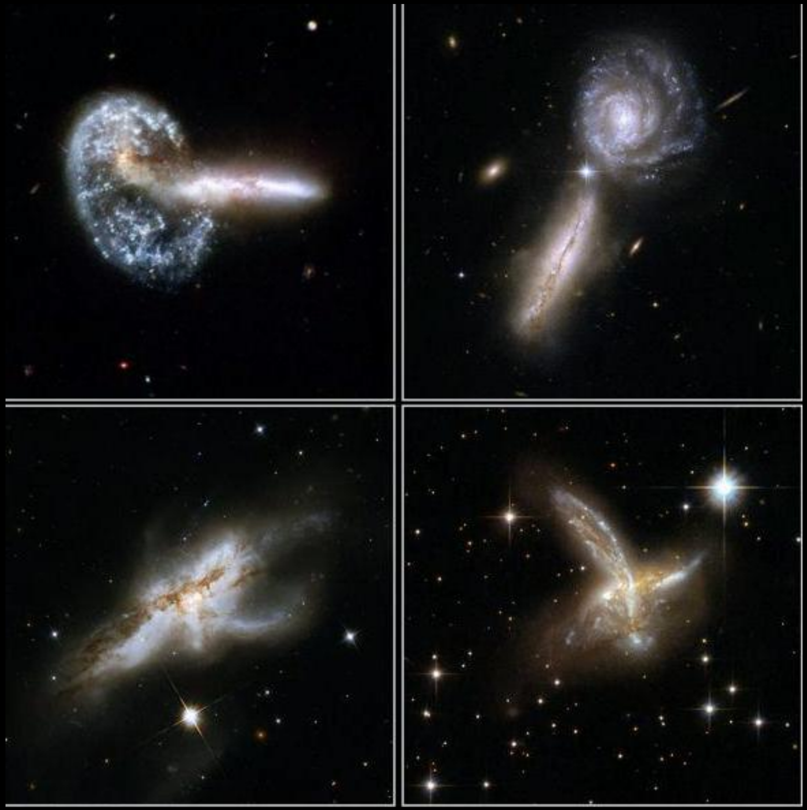
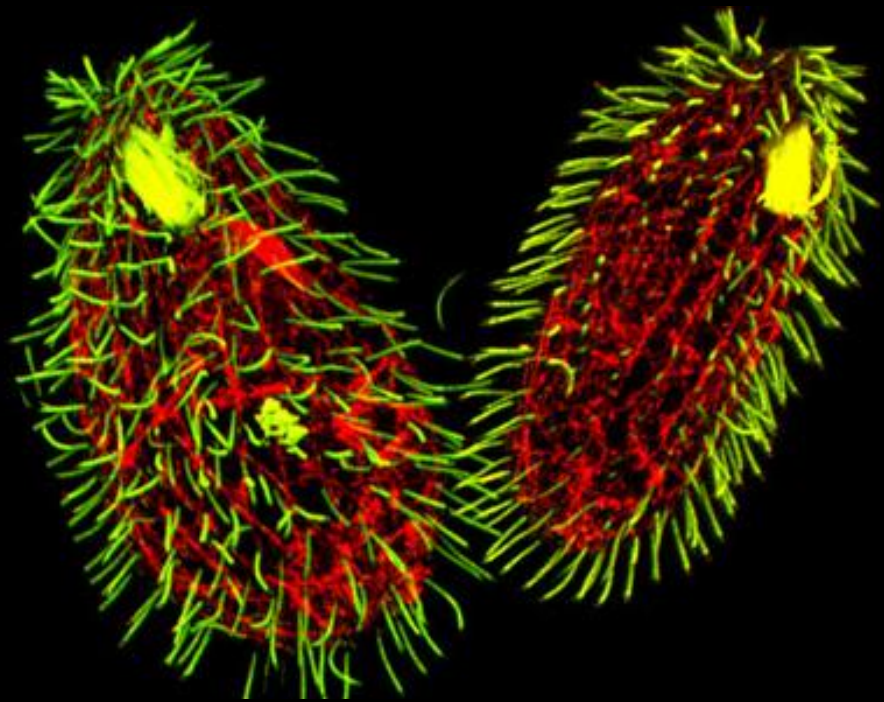


Cellular and molecular biologists investigate interactions within and between cells.



PRINCIPLES OF PHYSICS RELATE TO BIOLOGY

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a few examples. . .

PHYSICS	**BIOLOGY**

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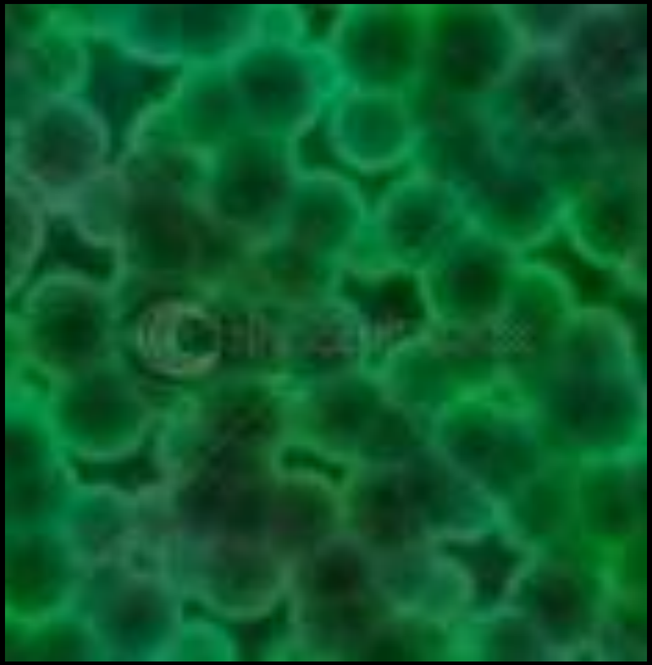
a few examples. . .

PHYSICS		**BIOLOGY**
"lattice"		**of nuclei**

PRINCIPLES OF PHYSICS RELATE TO BIOLOGY

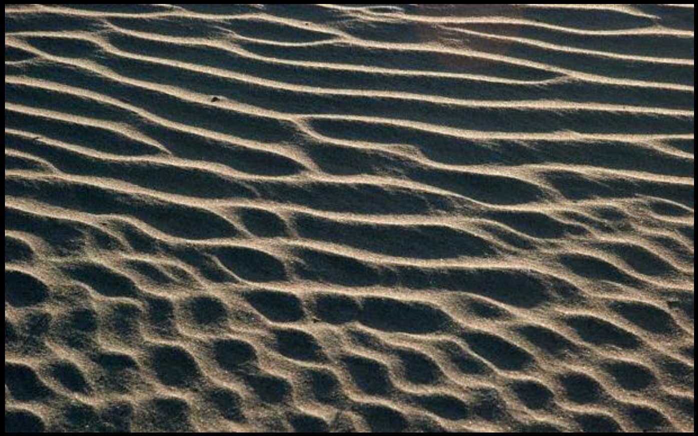
a few examples. . .

PHYSICS | **BIOLOGY**

"pattern formation "

morphogenesis

sand + wind =



sand ripples

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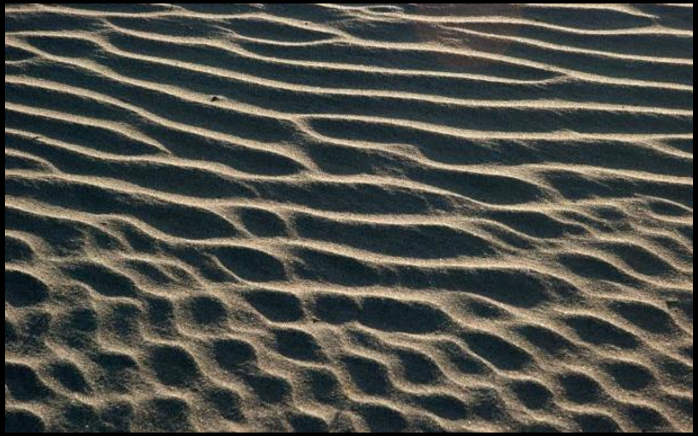

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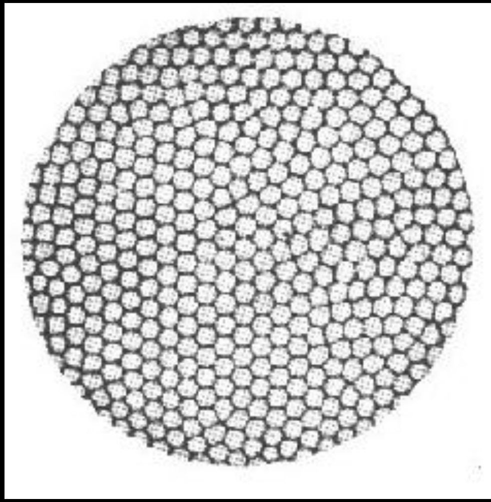
Water + Heat + Buoyancy =



Rayleigh-Benard Convection

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Rayleigh-Benard Cells

PRINCIPLES OF PHYSICS RELATE TO BIOLOGY

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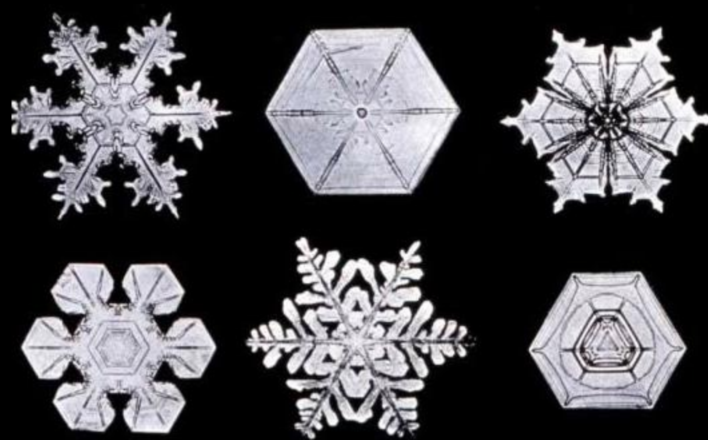
Water + Winter =



Snowflakes

PRINCIPLES OF PHYSICS RELATE TO BIOLOGY

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PHYSICS

BIOLOGY

“pattern formation”

morphogenesis

“waves of division”

The science of pattern formation deals with statistically-ordered outcomes of self-organization.

PRINCIPLES OF PHYSICS RELATE TO BIOLOGY

a few examples. . .

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In 1952, Alan Turing formulated a type of “mathematical biology”

PRINCIPLES OF PHYSICS RELATE TO BIOLOGY

a few examples. . .

PHYSICS	**BIOLOGY**
"pattern formation "	**morphogenesis**

"waves of division"

He published one paper on the subject called "The Chemical Basis of Morphogenesis," putting forth the Turing hypothesis of pattern formation.

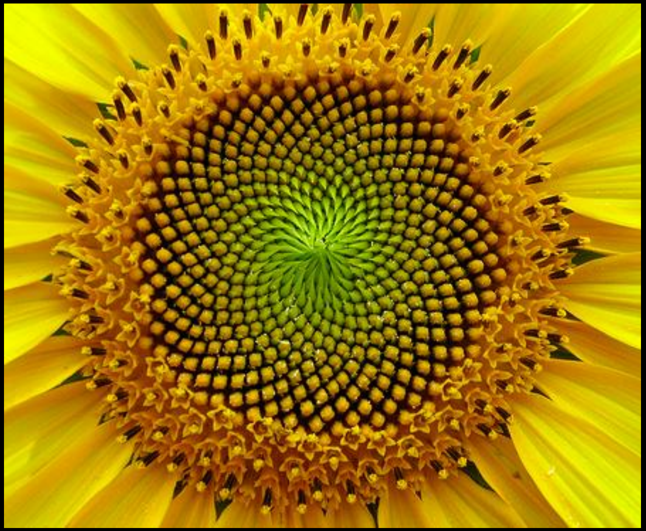
PRINCIPLES OF PHYSICS RELATE TO BIOLOGY

a few examples. . .

PHYSICS	**BIOLOGY**
“pattern formation ”	**morphogenesis**

“waves of division”

His central interest in the field was understanding Fibonacci phyllotaxis, the existence of Fibonacci numbers in plant structures. He used reaction–diffusion equations which are central to the field of pattern formation.



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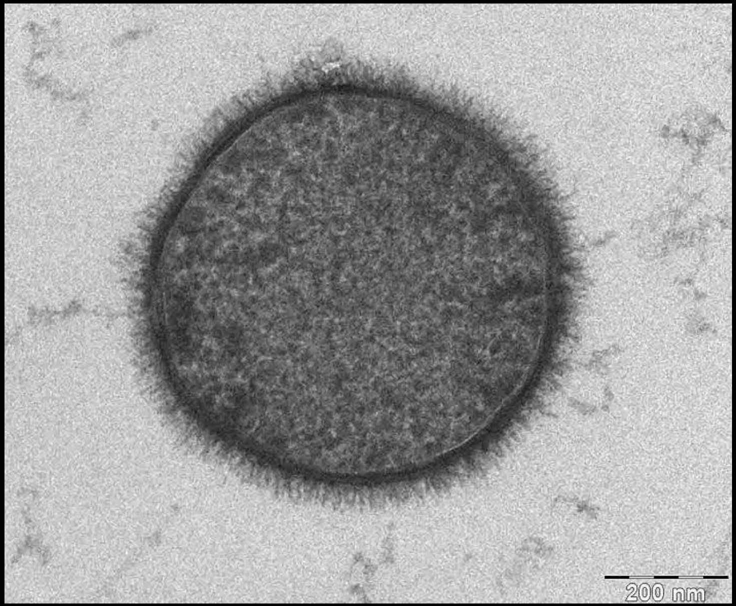
PHYSICS	**BIOLOGY**
"pattern formation"	**morphogenesis**

"waves of division"

The formation of patterns in the growth of bacterial colonies has extensively been studied experimentally.

Colonies of Bacillus subtilis on a Petri dish



PRINCIPLES OF PHYSICS RELATE TO BIOLOGY

a few examples. . .

PHYSICS	**BIOLOGY**
"flow"	**Flow of cells; Cell proliferation and spatial patterning of gene expression.**

PRINCIPLES OF PHYSICS RELATE TO BIOLOGY

a few examples. . .

PHYSICS

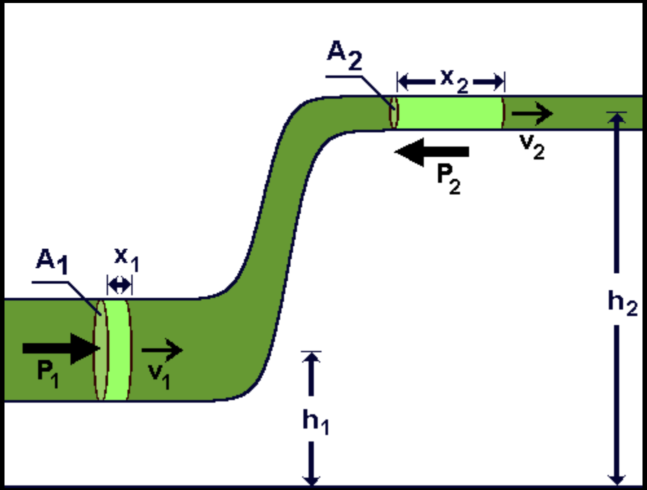
“flow”

In physics, flow relates to a dynamic fluid motion of atoms or molecules. In 1738 Daniel Bernoulli (1700-1782) formulated the famous equation for fluid flow that bears his name. The Bernoulli Equation is a statement derived from conservation of energy and work-energy ideas that come from Newton's Laws of Motion.

$$P + \rho g h + \rho v^2/2 = \text{Constant.}$$

BIOLOGY

Flow of cells;
Cell proliferation and spatial patterning of gene expression.



Water flowing through a smooth pipe.

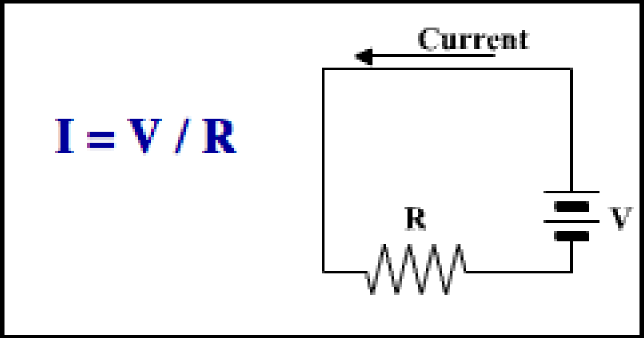
PRINCIPLES OF PHYSICS RELATE TO BIOLOGY

a few examples. . .

PHYSICS	**BIOLOGY**
"flow"	**Flow of cells; Cell proliferation and spatial patterning of gene expression.**

It can also relate to a flow of electrons, known as an electrical current.

The amount of charge moving past a specified point in a given amount of time is measured in Amps.



PRINCIPLES OF PHYSICS RELATE TO BIOLOGY

a few examples. . .

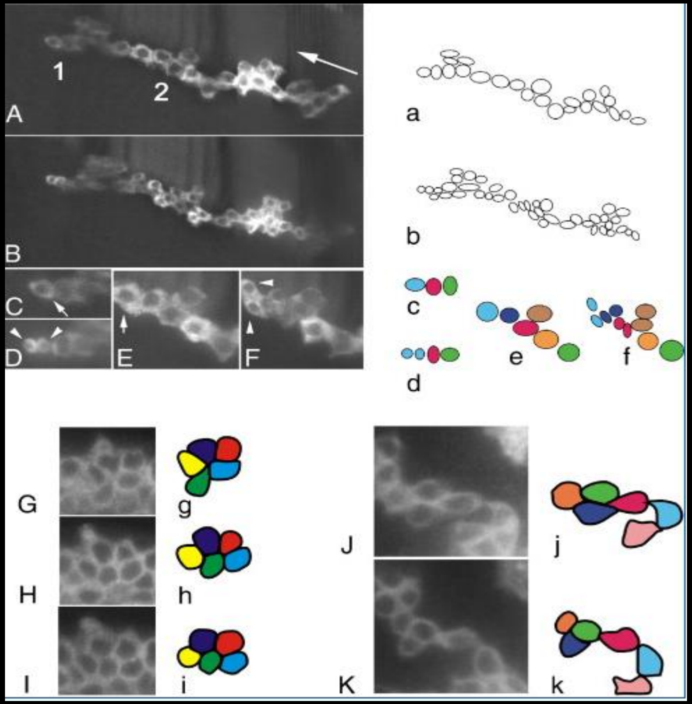
PHYSICS

"flow"

In biology, morphogenesis is attained by intercellular interactions (direct and indirect manifestations of physics). This creates a movement of cells influenced by many factors occurring on the molecular and cellular level.

BIOLOGY

Flow of cells;
Cell proliferation and spatial patterning of gene expression.



PRINCIPLES OF PHYSICS RELATE TO BIOLOGY

a few examples. . .

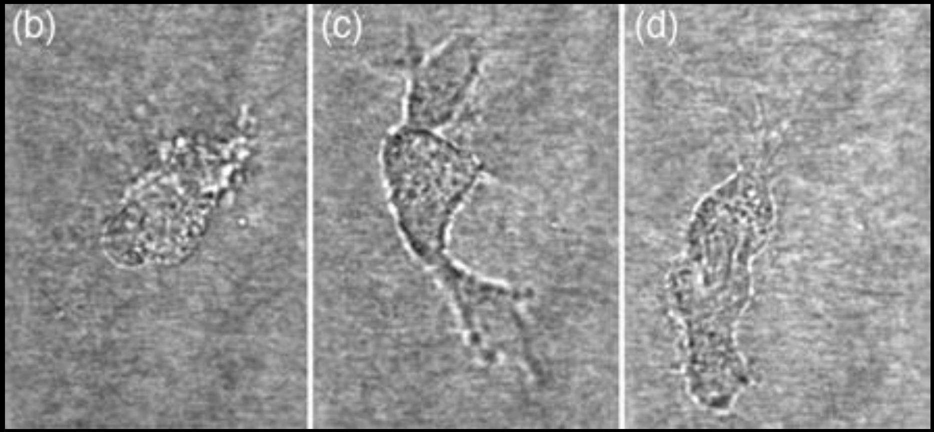
PHYSICS

BIOLOGY

"flow"

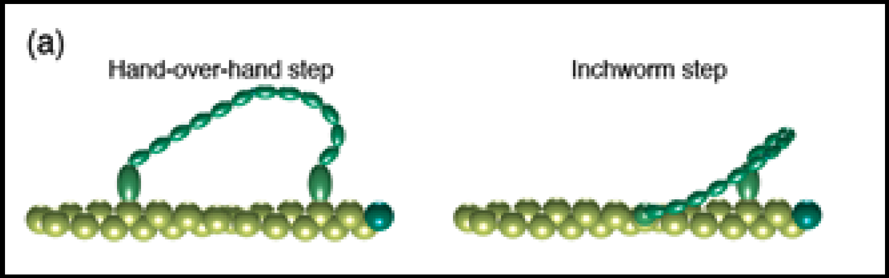
Flow of cells;
Cell proliferation and spatial patterning of gene expression.

The complexity of cellular biology. (a) A subset of the chemical reactions that drive eukaryotic cell crawling. In brief, cells sense the environment through membrane bound proteins. Activation of these receptors leads to activation of a number of other proteins that promote the polymerization of actin. The biochemical reactions that govern the dynamics of actin are included. These chemical reactions produce cell motility. (b)–(d) Time series of a cancer cell (HT1080 fibrosarcoma cell) moving through a collagen I matrix. There are two hour intervals between each frame. (Images courtesy of D. Wirtz, Johns Hopkins University.)



Some more examples where physics has shed light on biology.

a) Physics-based simulations of the walking of myosin VI predicted that the molecule would produce both hand-over-hand and inchworm type movements, which was later confirmed with single molecule experiments. (Image courtesy of S. X. Sun, Johns Hopkins University.)



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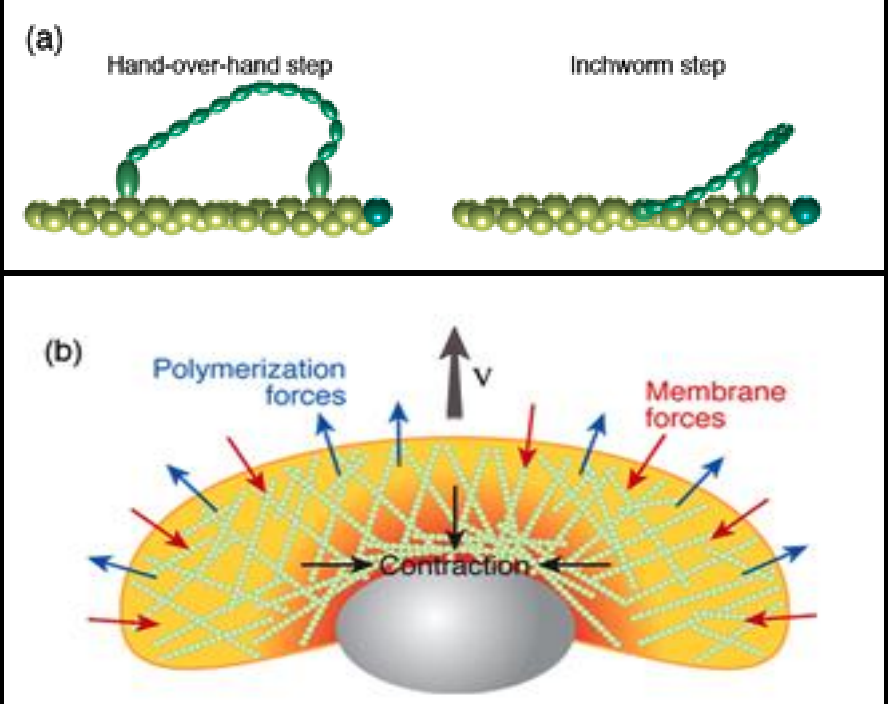
a) Physics-based simulations of the walking of myosin VI predicted that the molecule would produce both hand-over-hand and inchworm type movements, which was later confirmed with single molecule experiments. (Image courtesy of S. X. Sun, Johns Hopkins University.)

b) A crawling cell is driven primarily by the dynamics of its actin cytoskeleton, a network of filaments that polymerize at the leading edge of the cell. Force balance on the crawling cell comes from membrane forces (tension and bending), a polymerization forces, and contractile forces generated inside the cell by myosin motors and other unknown mechanisms. Here we depict a fish keratocyte, which crawls at a roughly constant speed V, while maintaining a steady cell shape. The cell body is shown in gray.



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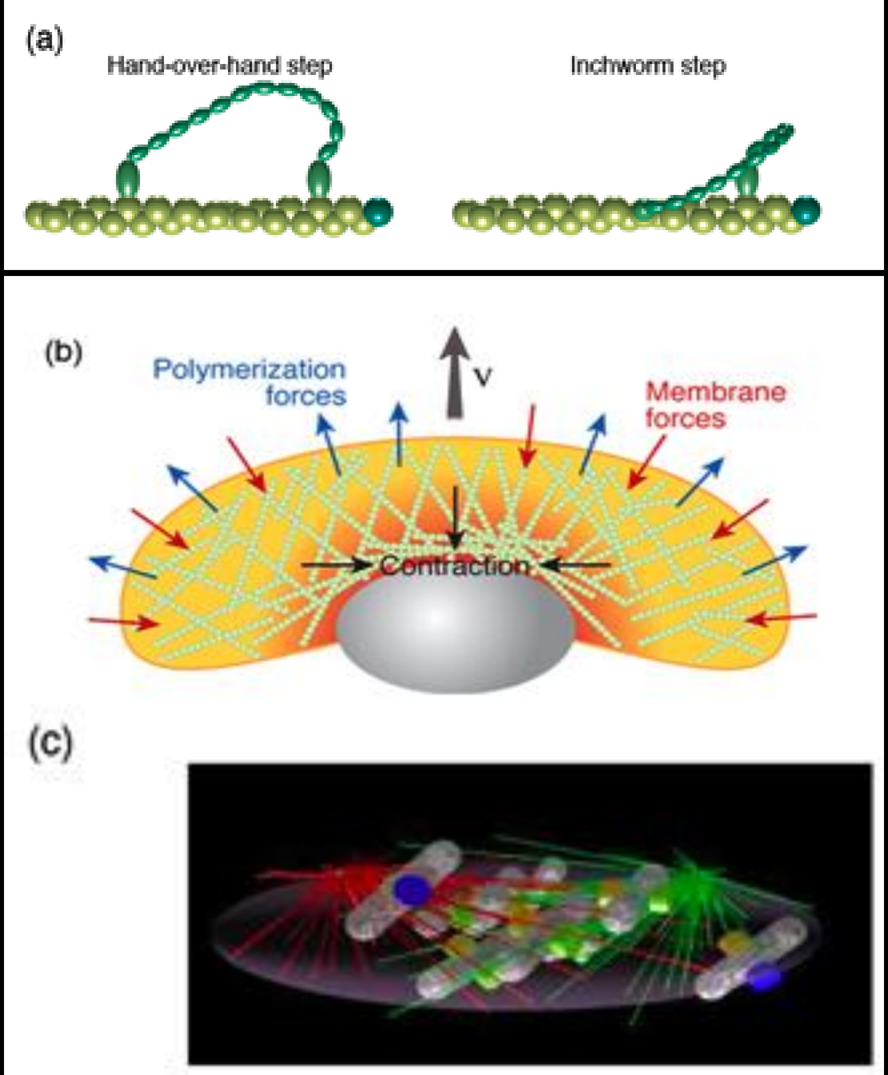
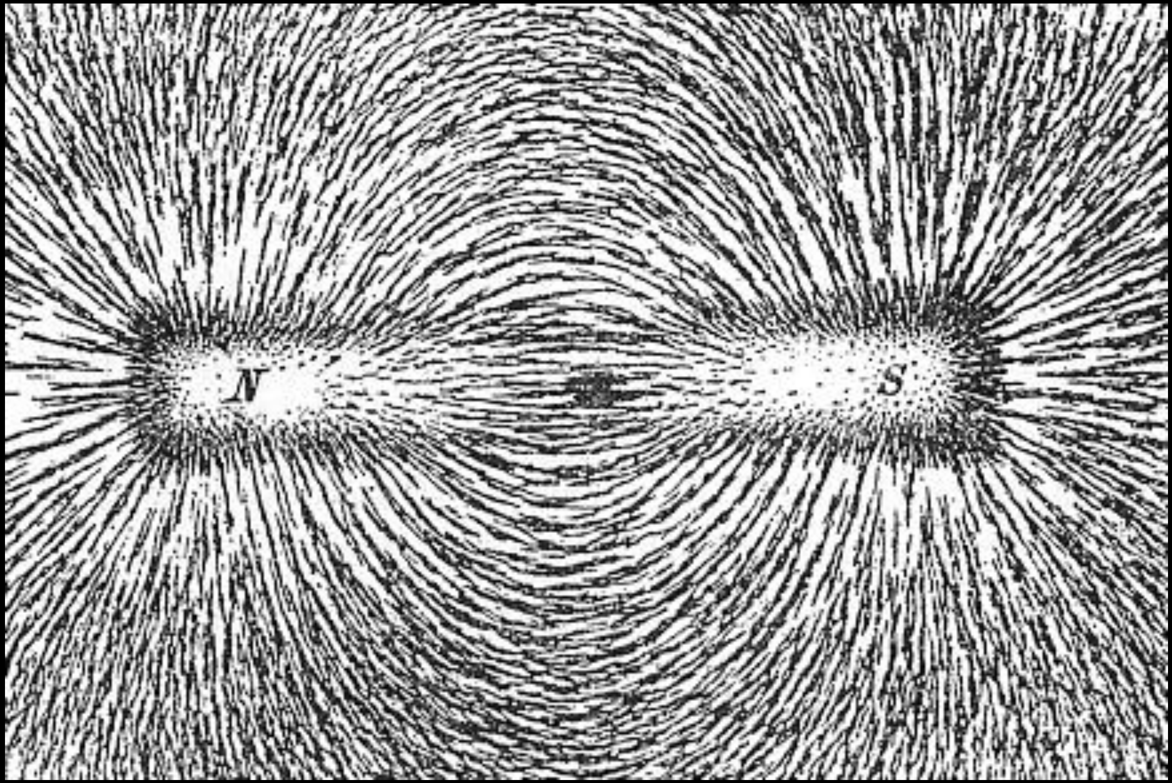
c) Stochastic simulations of microtubules determined some of the constraints for the accurate and efficient capturing of chromosomes during the formation of the mitotic spindle. (Image courtesy of A. Mogilner, University of California, Davis.)



Some more examples where physics has shed light on biology.

Magnetic Field Theory:



A magnetic field is a region of space where a magnetic detector will experience a force.
A magnet has a North and South Pole. If a bar magnet is split into two pieces, each piece will have a North and South Pole. This will continue to happen as you break the magnet into smaller and smaller pieces. A compass aligns with the poles of the earth, which itself is like a giant magnet.

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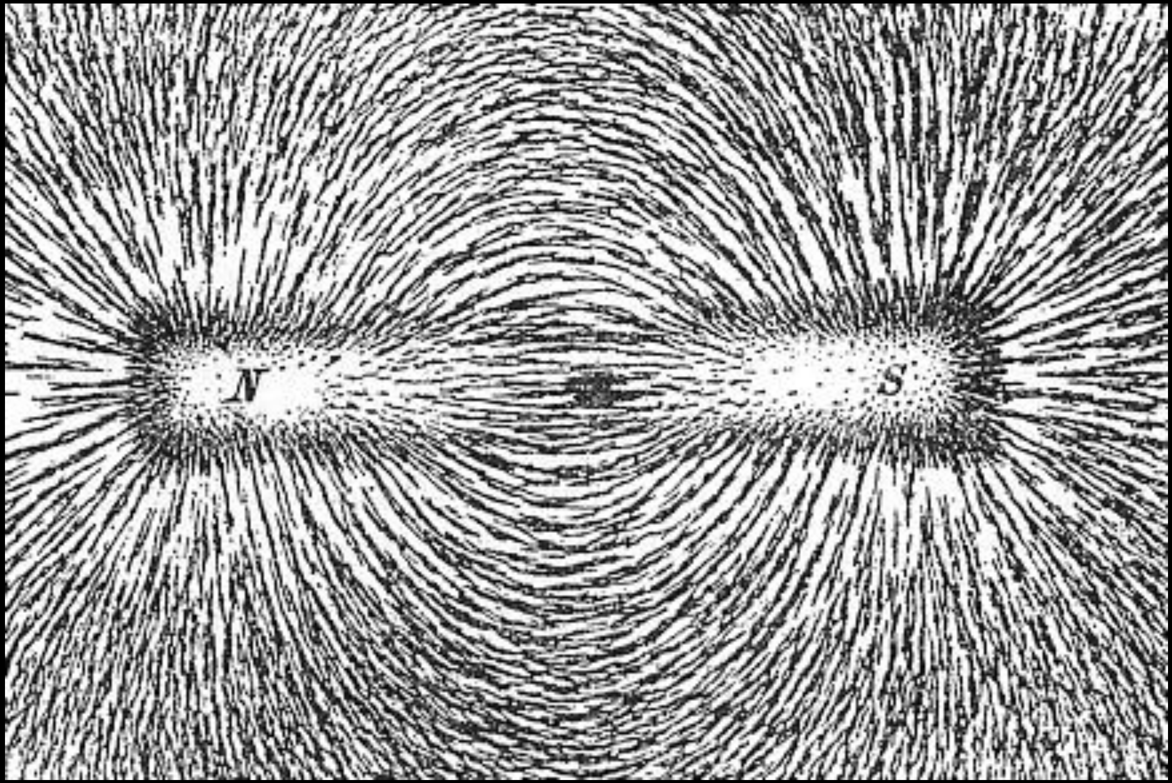
Magnetic Field Theory:



Pieces of iron filings placed over a magnet will line up with the magnetic field surrounding it. The individual filings are said to be "magnetically polarized."

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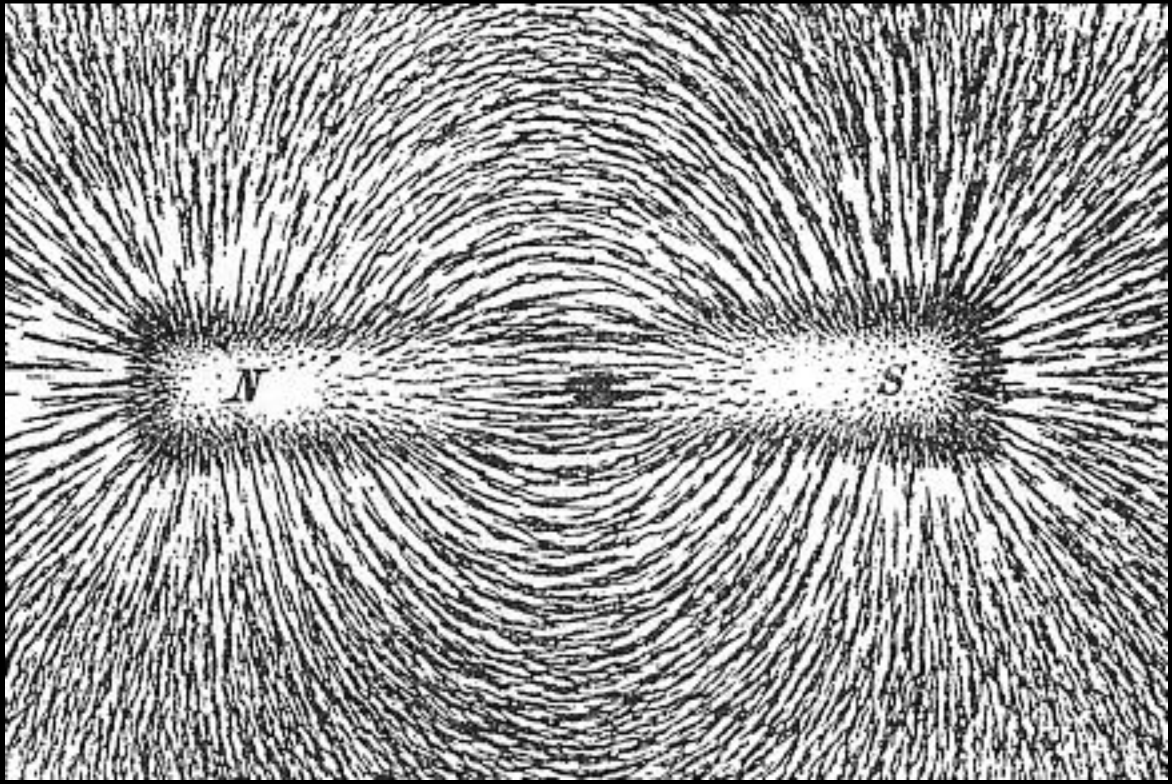

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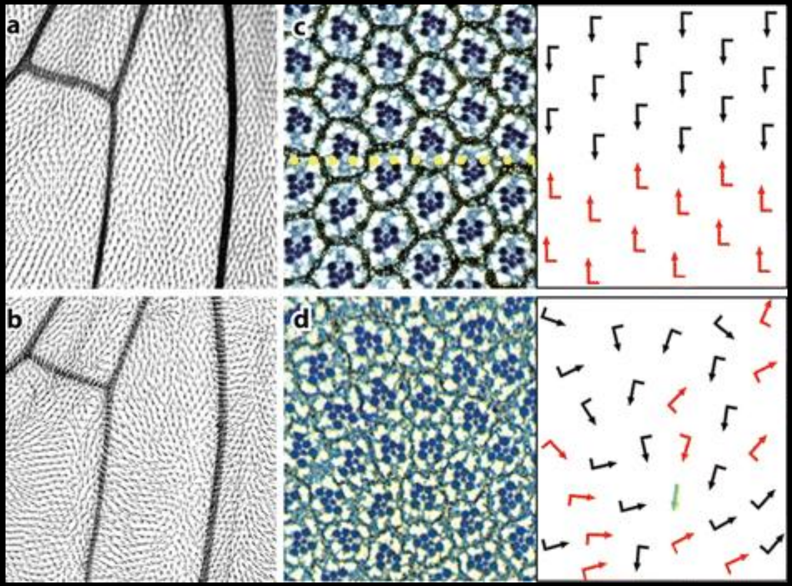
BUT DID YOU KNOW THAT CELLS CAN BECOME POLARIZED TOO?

Some more examples where physics has shed light on biology.

This is generally referred to as planar cell polarity (PCP; or historically, tissue polarity). Genetic screens in Drosophila pioneered the discovery of core PCP factors, and subsequent work in vertebrates has established that the respective pathways are evolutionarily conserved.



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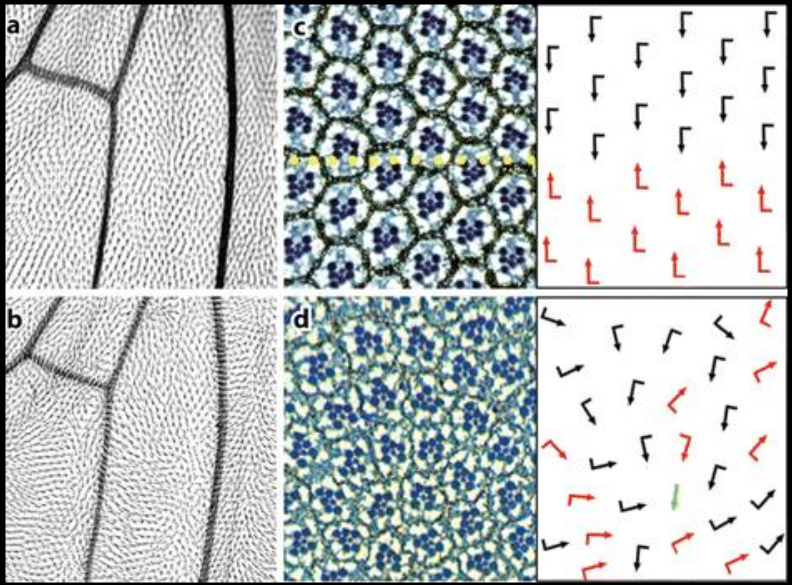
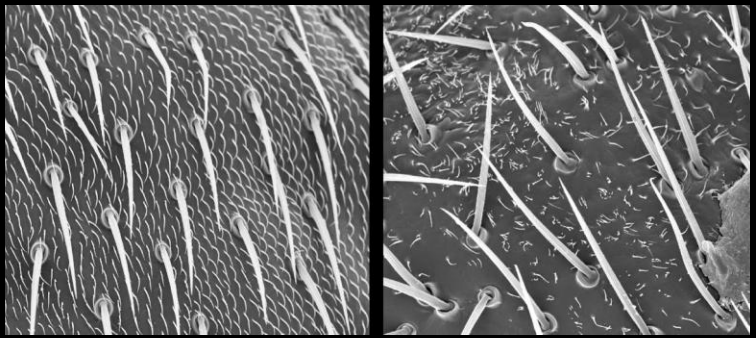


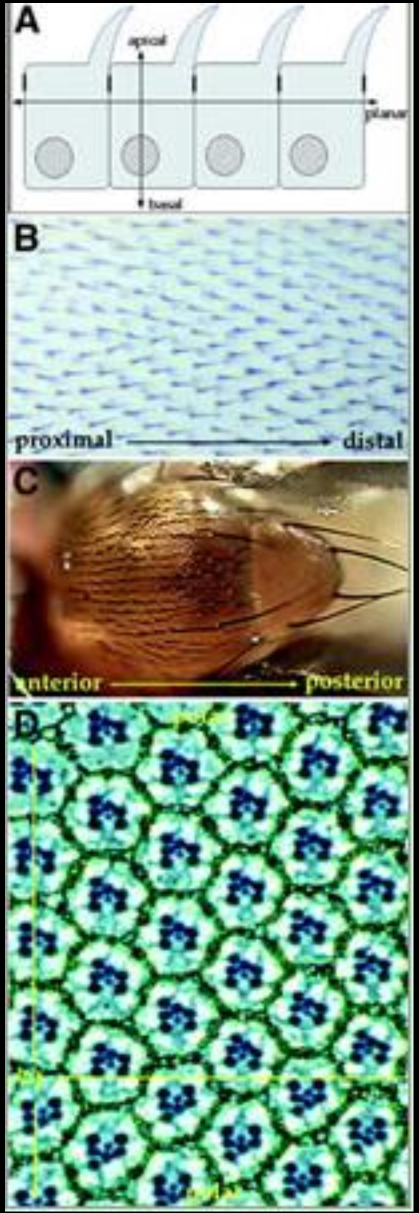
The planar cell polarity (PCP) pathway functions to orient cells within the plane of an epithelial tissue. The fruit fly is a great model system for studying the PCP pathway—the bristles on the fly's back and wing hairs grow in a certain direction as a result of the orientation of the cells, making it easy for researchers to see problems in the pathway. A recent paper has found a role for a transmembrane proton pump protein called VhaPRR in PCP signaling. Images are electron micrographs of bristles with (left) or without (right) normal levels of VhaPRR. Without VhaRRR, the bristles are disoriented, as well as the small epithelial hairs underneath.



Reference: Tobias Hermle, Deniz Saltukoglu, Julian Grünewald, Gerd Walz and Matias Simons. Current Biology 20(14): 253-258. ©2010 Elsevier Ltd. All rights reserved.

Some more examples where physics has shed light on biology.

Planar polarity in Drosophila. A schematic drawing of planar polarity in an epithelial sheet is shown in (A). Planar polarity is perpendicular to apical–basal polarity. Examples of polarized tissues are shown for the wing (B), dorsal thorax (C) and eye (D). Note that the axis of polarity is different in the three examples, and that each tissue displays different aspects of polarity, e.g. single cells are polarized in the wing as shown by the ordered appearance of the hairs, whereas groups of cells are reflecting polarization in other tissues.



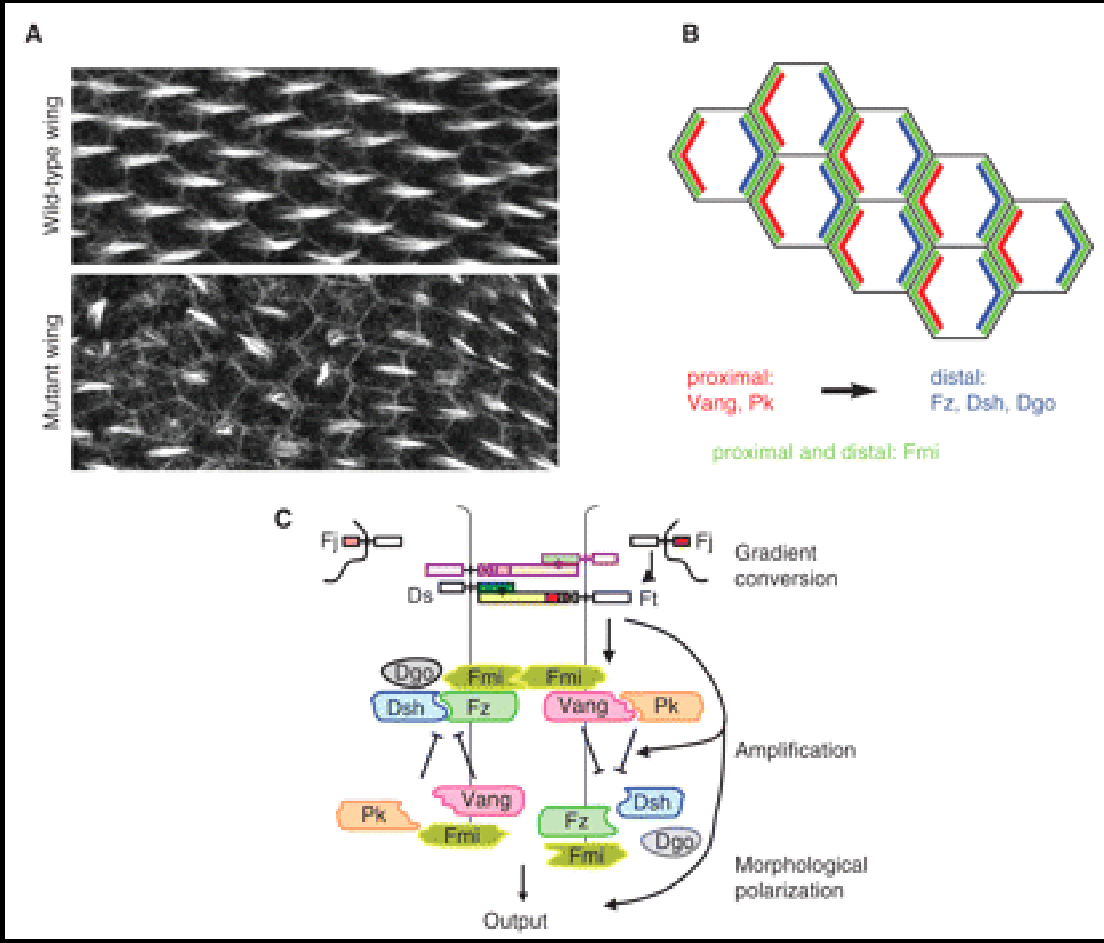
Some more examples where physics has shed light on biology.

Planar cell polarity in Drosophila.

(A) Image of wild type (top panel) and PCP mutant Drosophila pupal wing epithelium, labeled with phalloidin to stain actin.

(B) Schematic of PCP protein asymmetric cortical distribution in the fly wing epithelium showing Pk and Vang enriched on the proximal, Fz, Dsh, and Dgo on the distal and Fmi on both proximal and distal sides of each cell.

(C) A model for organization of the PCP pathway in Drosophila. Heterodimers of Ft and Ds show biased orientation at each cell boundary, resulting from graded expression of Fj and Ds. Asymmetrically oriented Ft-Ds heterodimers bias the function of a feedback loop consisting of the core PCP proteins, Fmi, Fz, Dsh, Dgo, Vang, and Pk.



A SERIOUS ROLE FOR THEORY IN BIOLOGY

In the same way that physics branches into both the experimental and the theoretical in its methods, new technologies are enabling biological researchers to acquire large amounts of data in diverse studies leading to better understanding of functional relationships.

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For example, the DIFFUSION EQUATION can not only describe the distribution of carbon in steel, but can also be applied to conformations of DNA or polyethylene!

$$\frac{\partial u}{\partial t} = \gamma \frac{\partial^2 u}{\partial x^2} + p(x,t),$$

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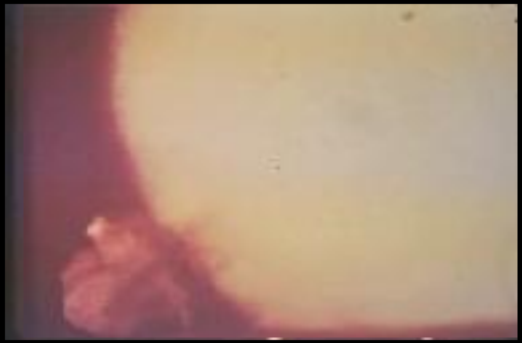

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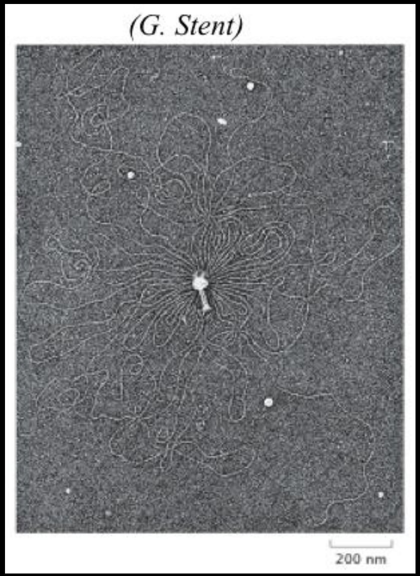
In biology, this would be analogous to estimating genome length of exploding genomes.



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FUNDAMENTAL PROBLEMS

+

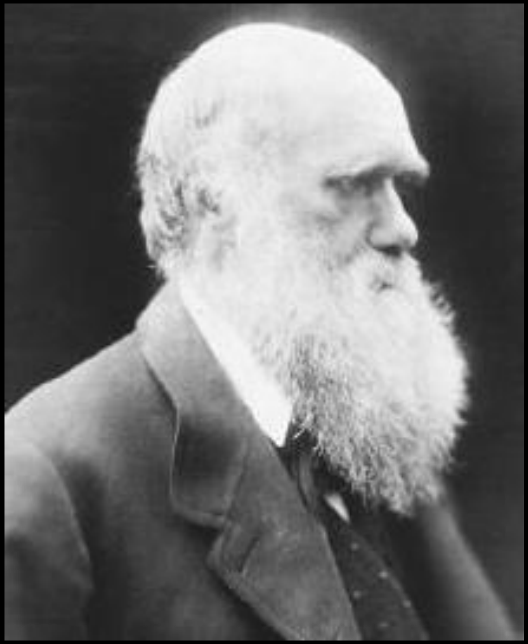
QUANTITATIVE DATA

=

NEED FOR PREDICTIVE MODELS TO DIRECT EXPERIMENTAL STUDY

PART 2: THE EVOLUTION OF LIVING SYSTEMS

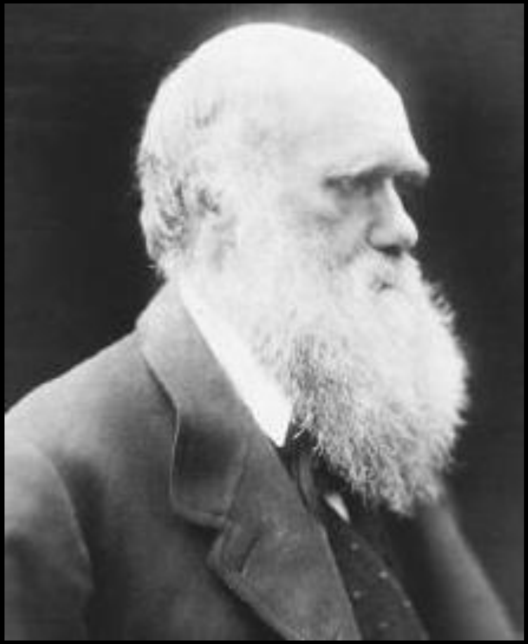
A SERIOUS ROLE FOR THEORY IN BIOLOGY



The renowned biologist, Charles Darwin (1809-1882), was said to posses a “6^{th} sense” (figuratively speaking).

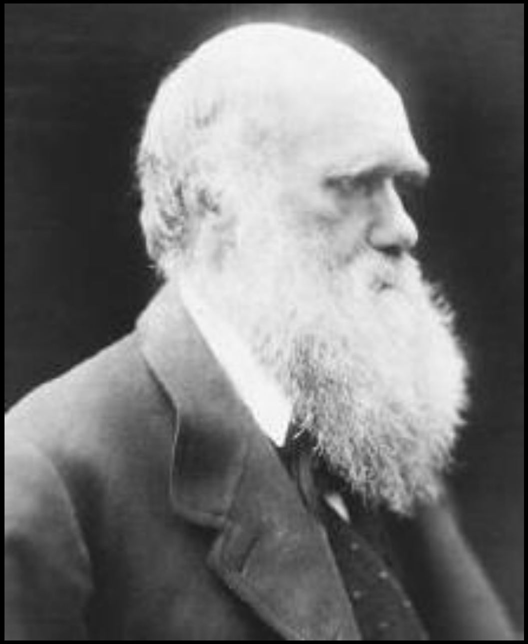
Darwin had an almost uncanny ability to see “outside the box.” His unwavering patience and ability to study cause and effect without bias or prejudice proved significant to the development of natural science.

A SERIOUS ROLE FOR THEORY IN BIOLOGY



His Theories of Evolution and Natural Selection transformed how we perceive the development of life on Earth.

A SERIOUS ROLE FOR THEORY IN BIOLOGY

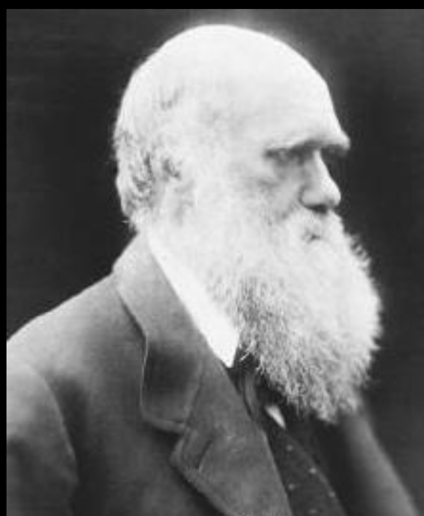
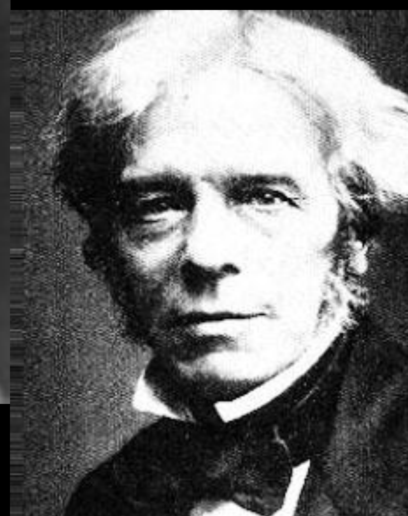
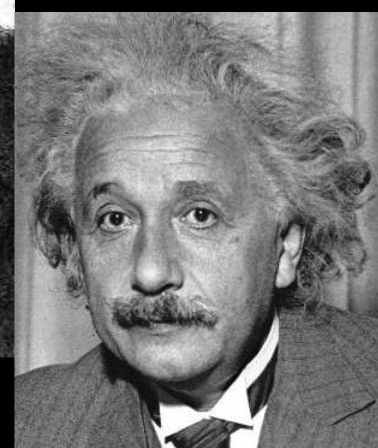


"Nothing in biology makes sense, except in the light of evolution."

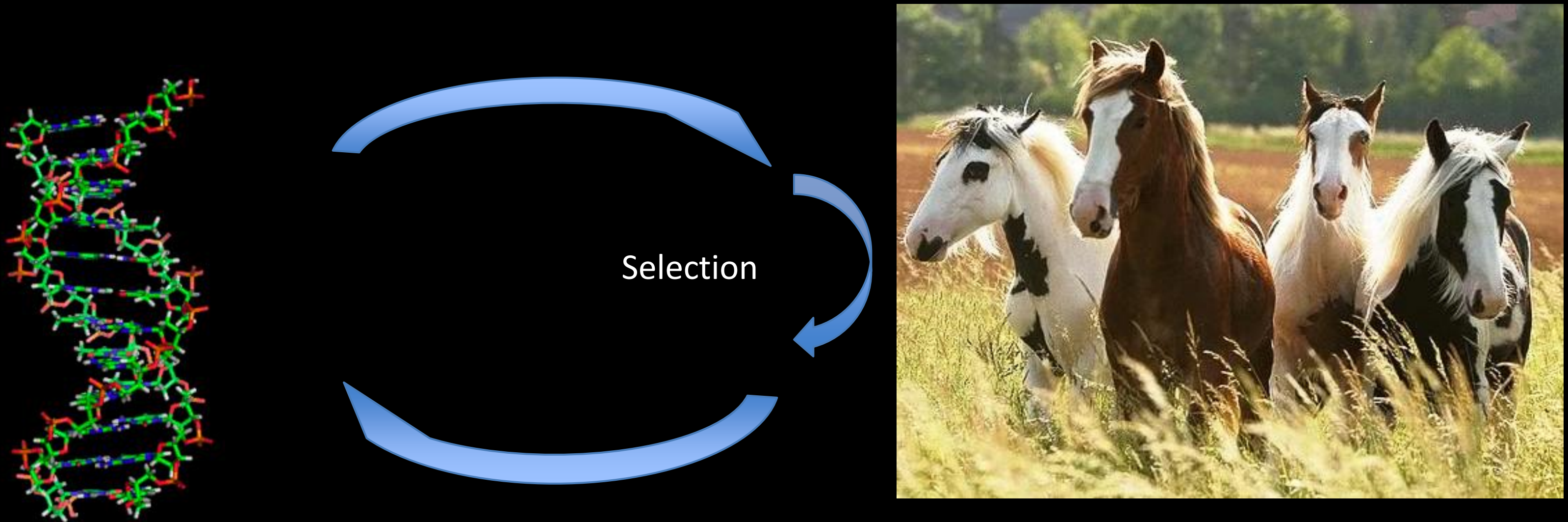
T. Dobzhansky

A SERIOUS ROLE FOR THEORY IN BIOLOGY

Like Darwin in biology, Faraday and Einstein in physics, or Davy in chemistry, it will take this type of “6^{th} sense” thinking to move natural science ahead in the 21^{st} century.

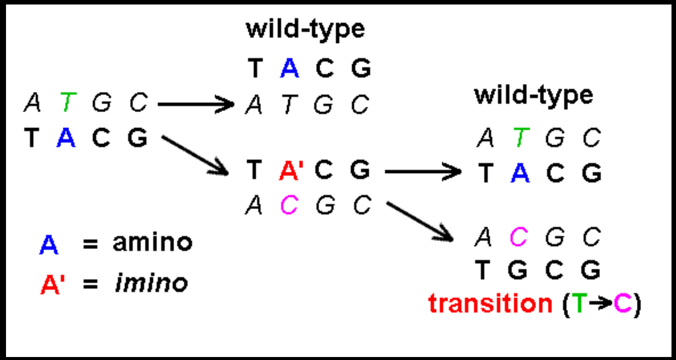





EVOLUTION IN THE 21ST CENTURY: BIOLOGY MEETS PHYSICS



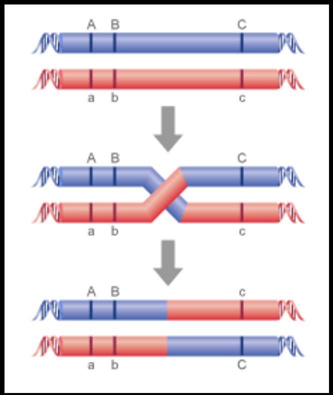
Mutation & Recombination

Genotypes



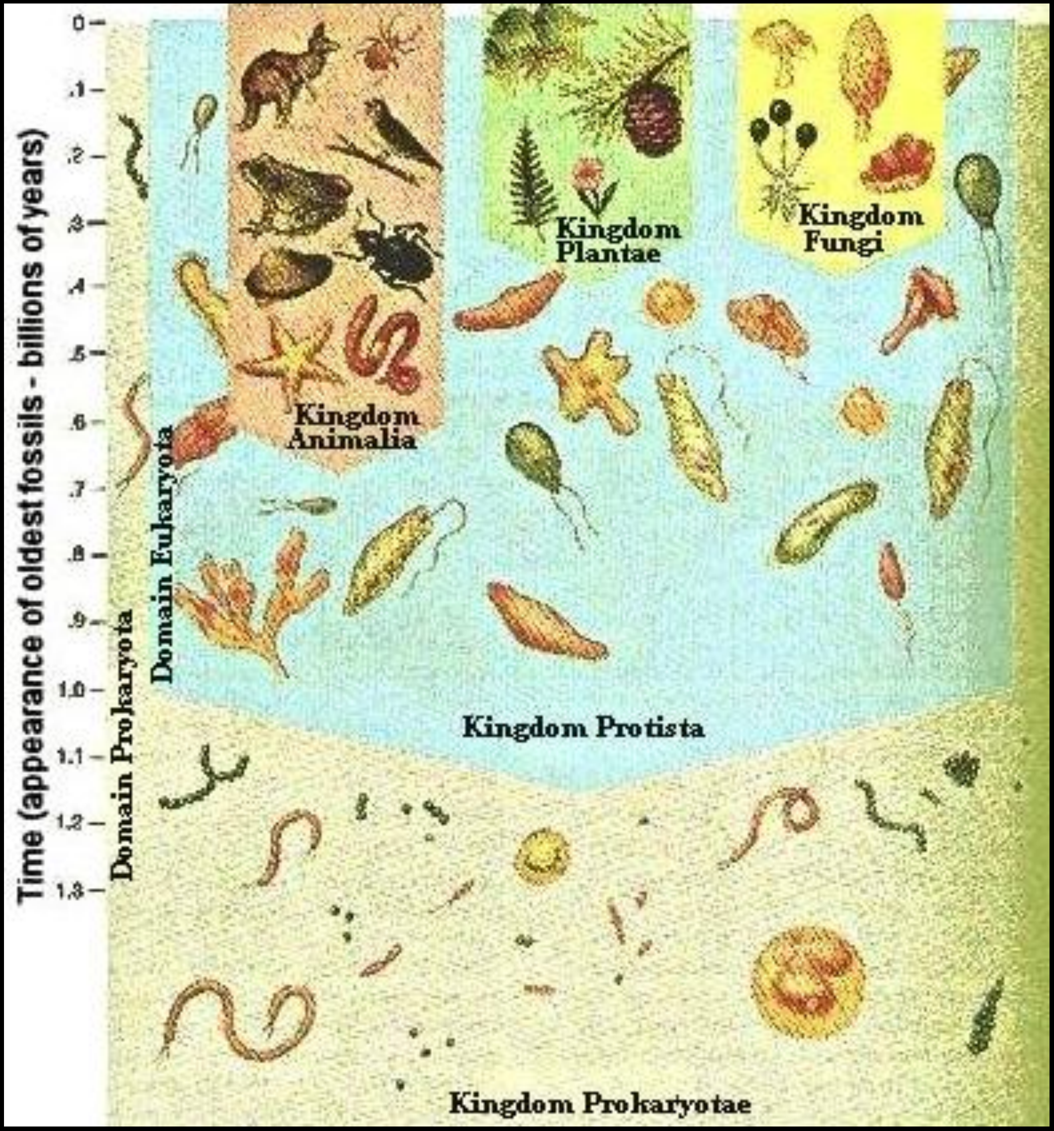
Mutation

Sex & Recombination



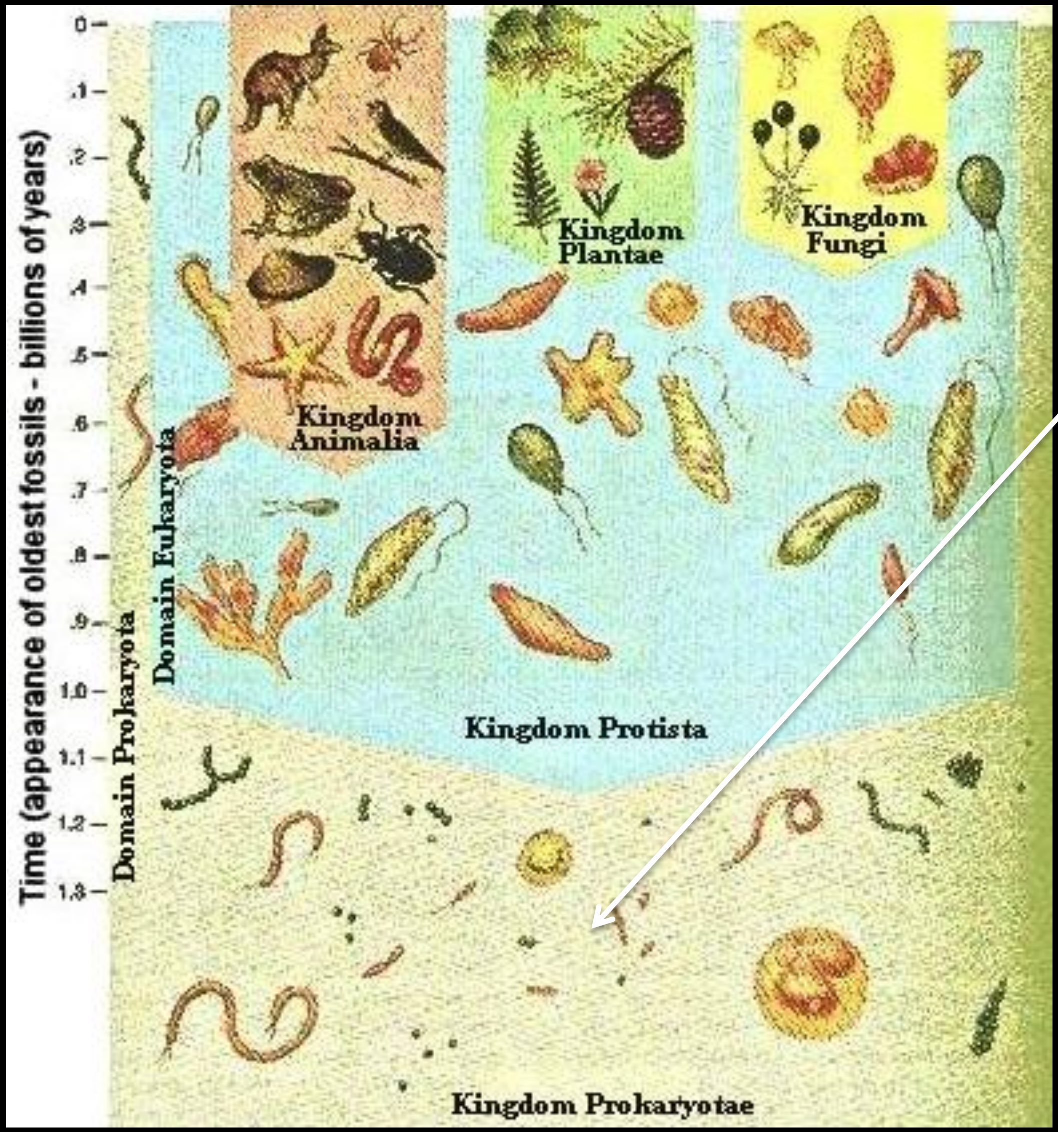
Selection

EVOLUTION IN THE 21ST CENTURY: BIOLOGY MEETS PHYSICS



Biology used to classify living organisms into five "kingdoms."

EVOLUTION IN THE 21ST CENTURY: BIOLOGY MEETS PHYSICS



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PROKARYOTES
(no nucleus, no organelles)

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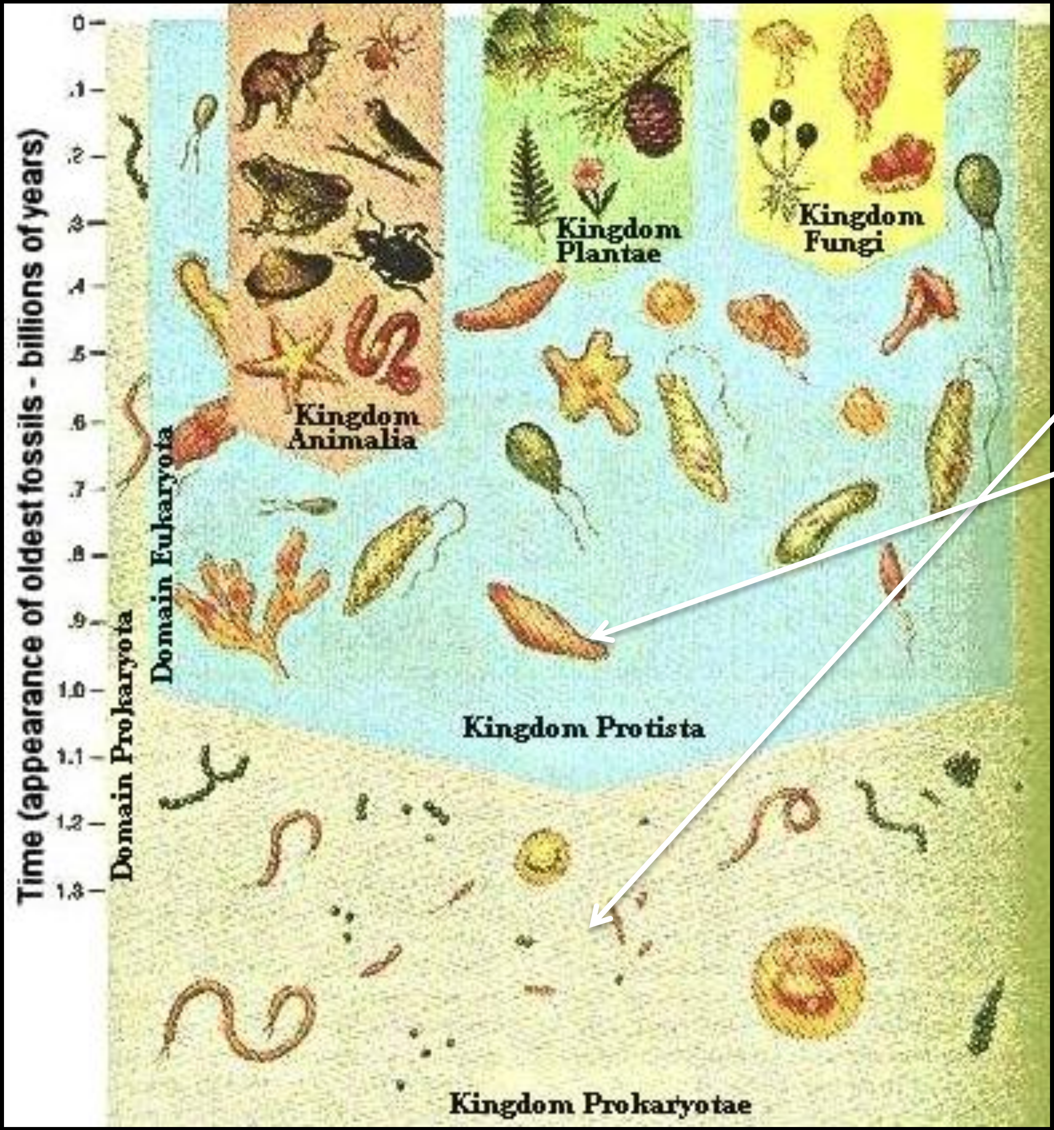

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PROTISTA
(possess nucleus and organelles)

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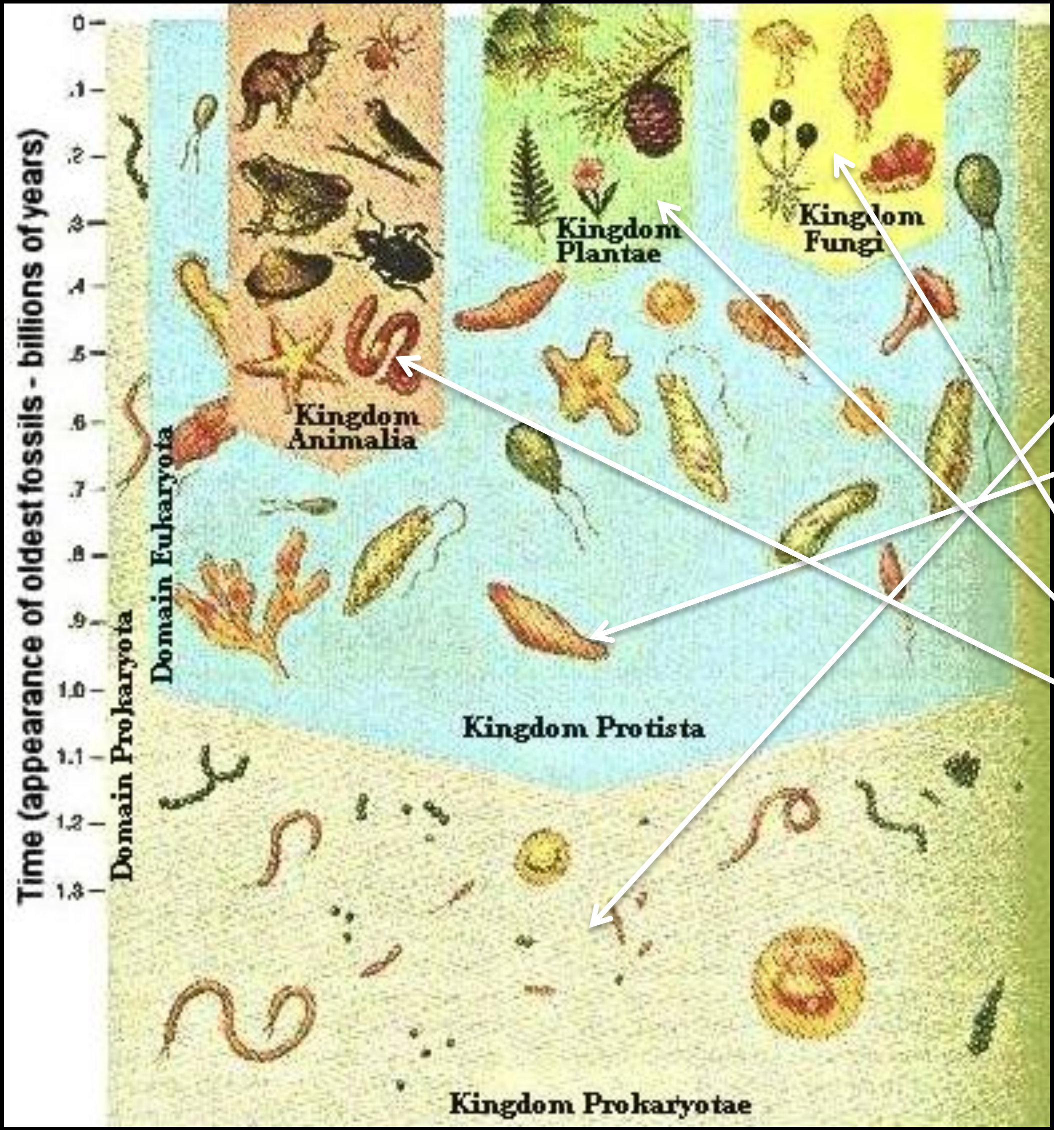

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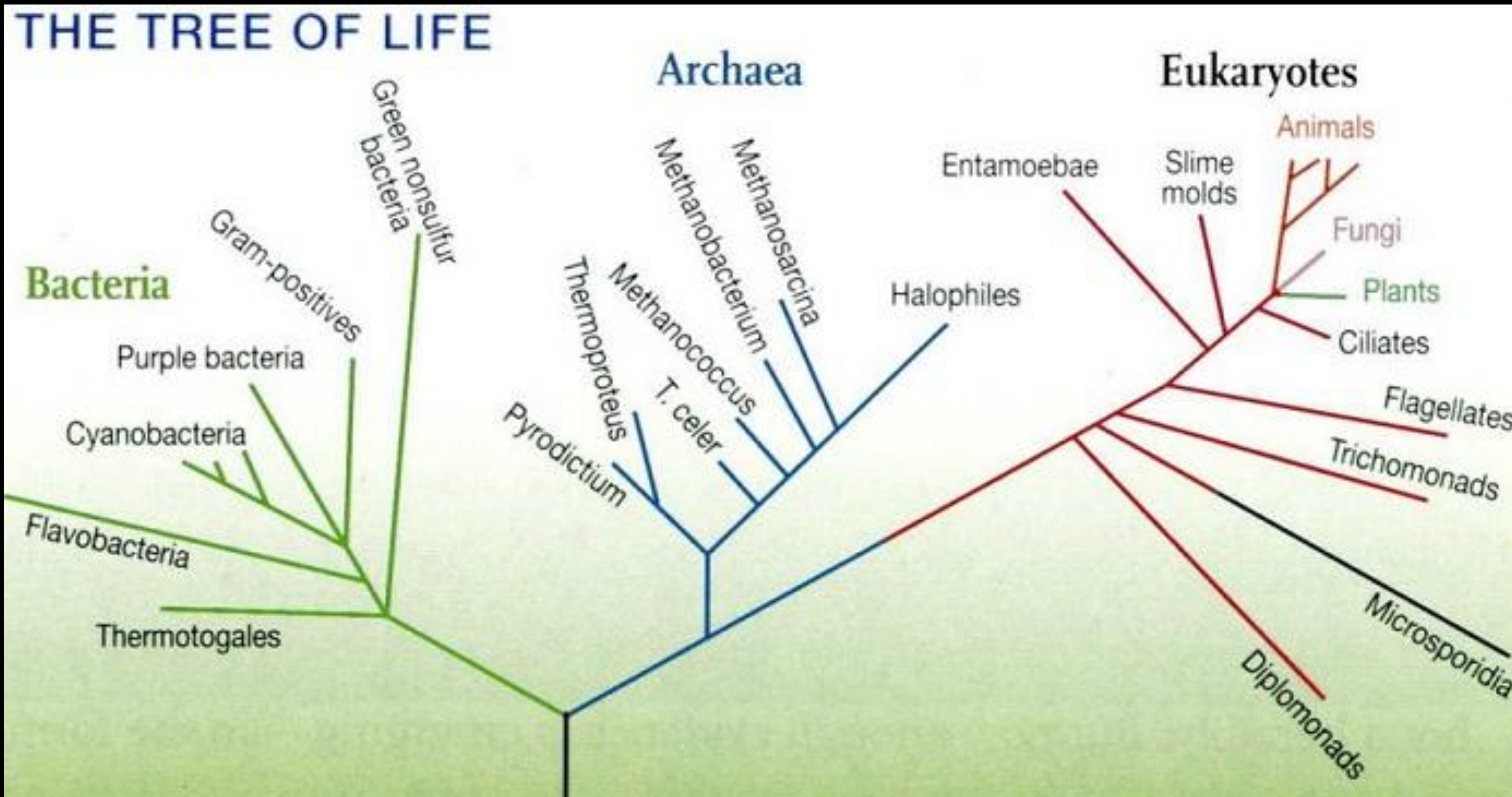
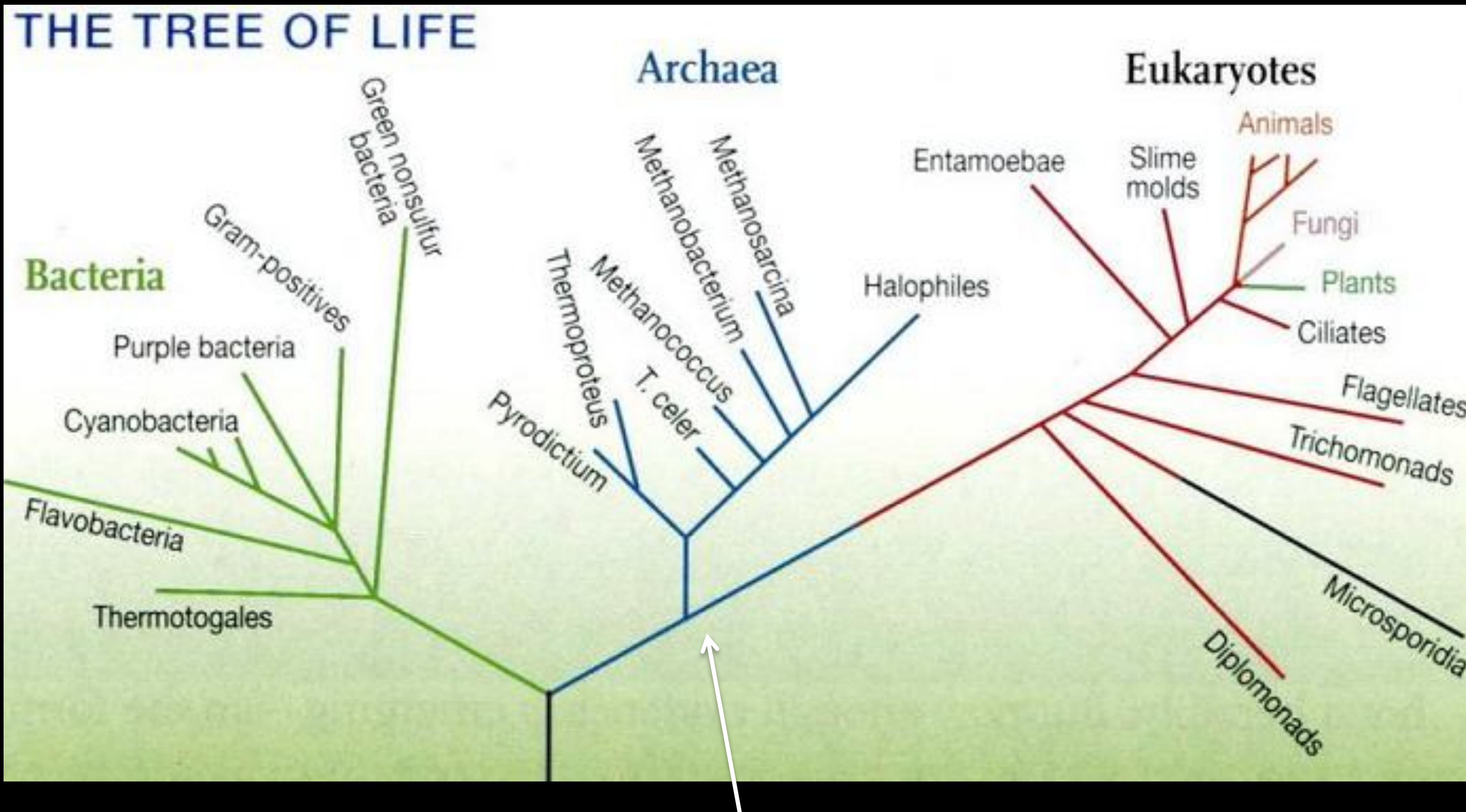
FUNGI
PLANTS
ANIMALS

EVOLUTION IN THE 21ST CENTURY: BIOLOGY MEETS PHYSICS



This view was later refined to 3 branches:

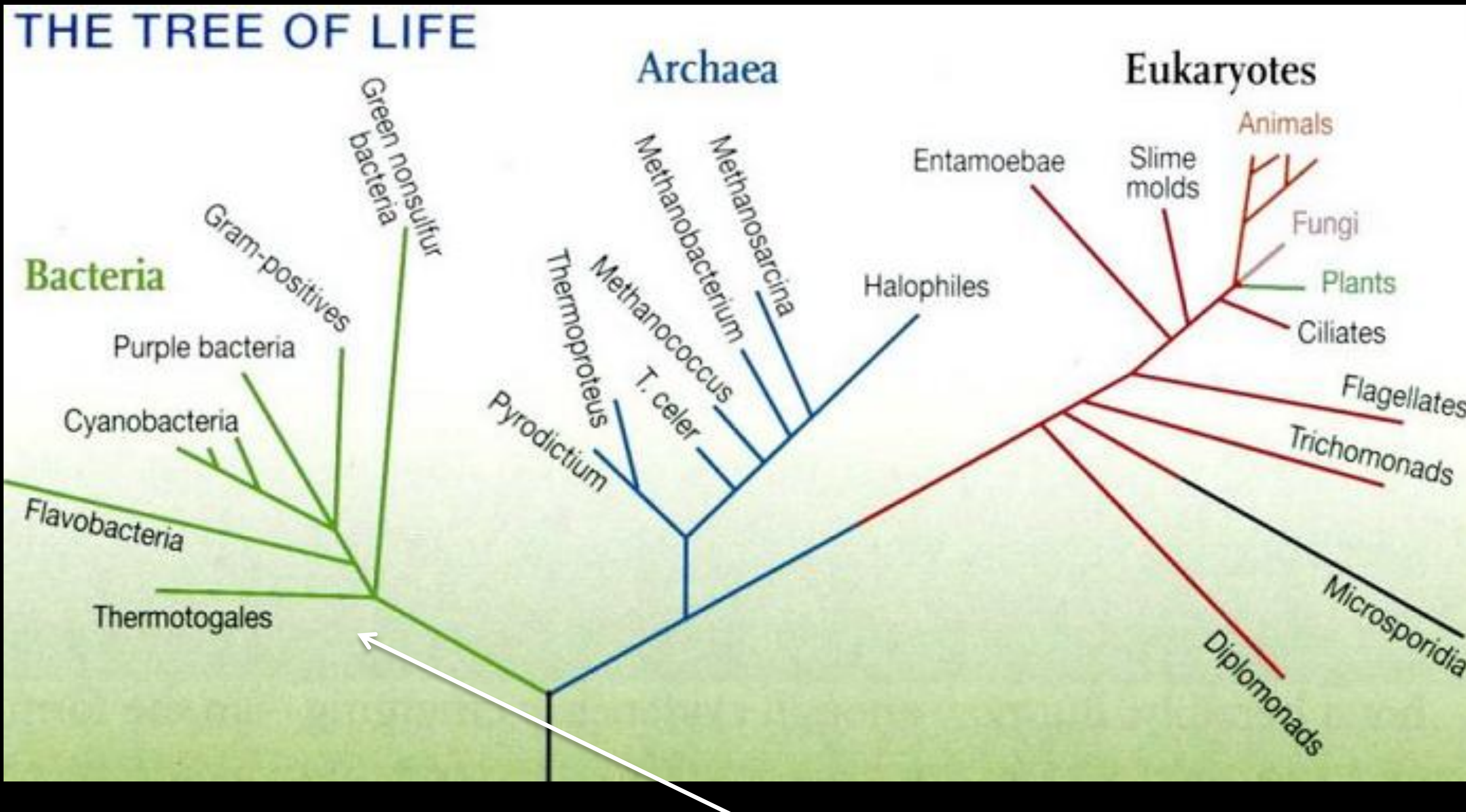
EVOLUTION IN THE 21ST CENTURY: BIOLOGY MEETS PHYSICS



This view was later refined to 3 branches: **Archaea**

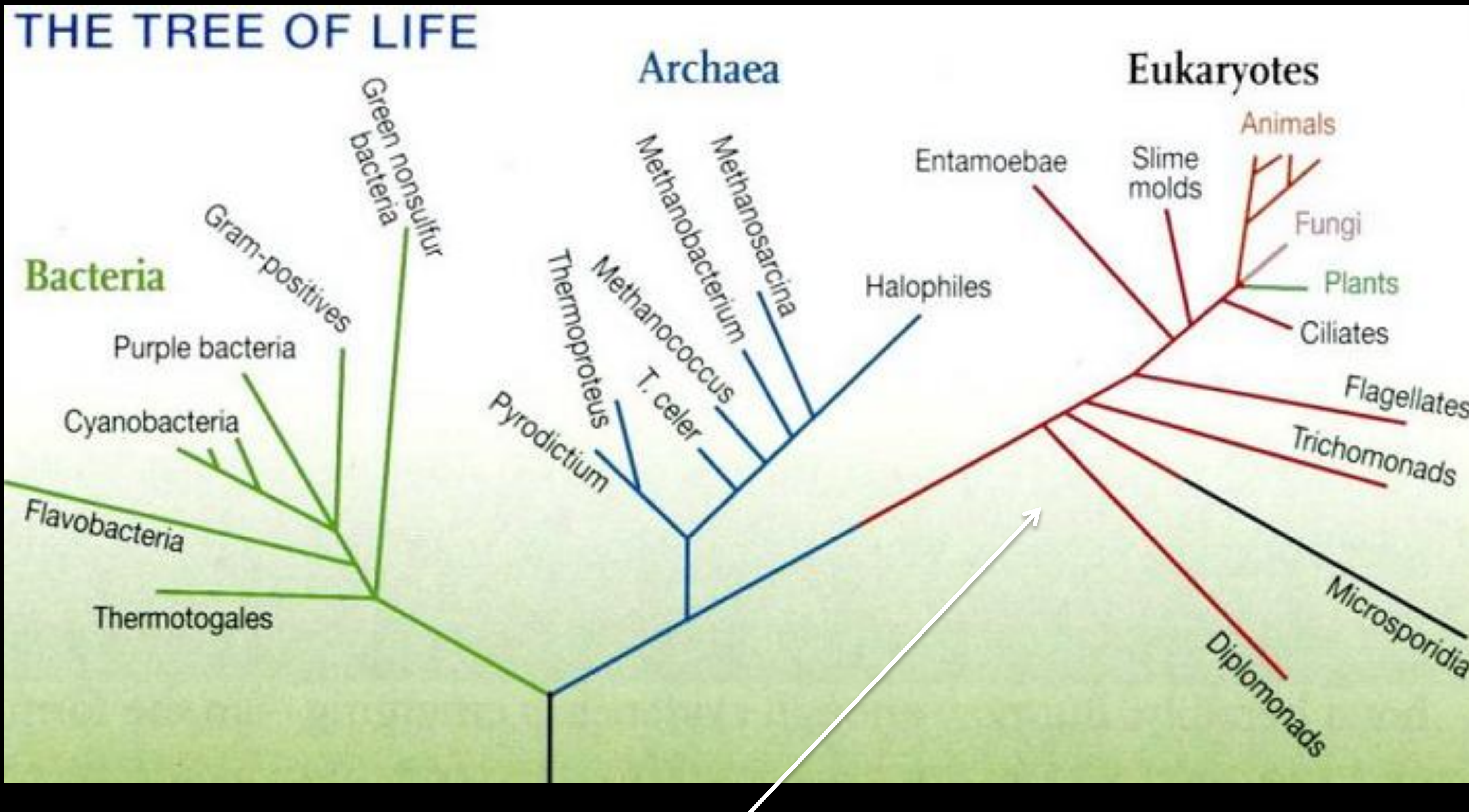
(primitive unicellular organisms that live in most extreme environments)

EVOLUTION IN THE 21ST CENTURY: BIOLOGY MEETS PHYSICS



This view was later refined to 3 branches: **Bacteria:**
(unicellular organisms without nucleus or cell structure)

EVOLUTION IN THE 21ST CENTURY: BIOLOGY MEETS PHYSICS

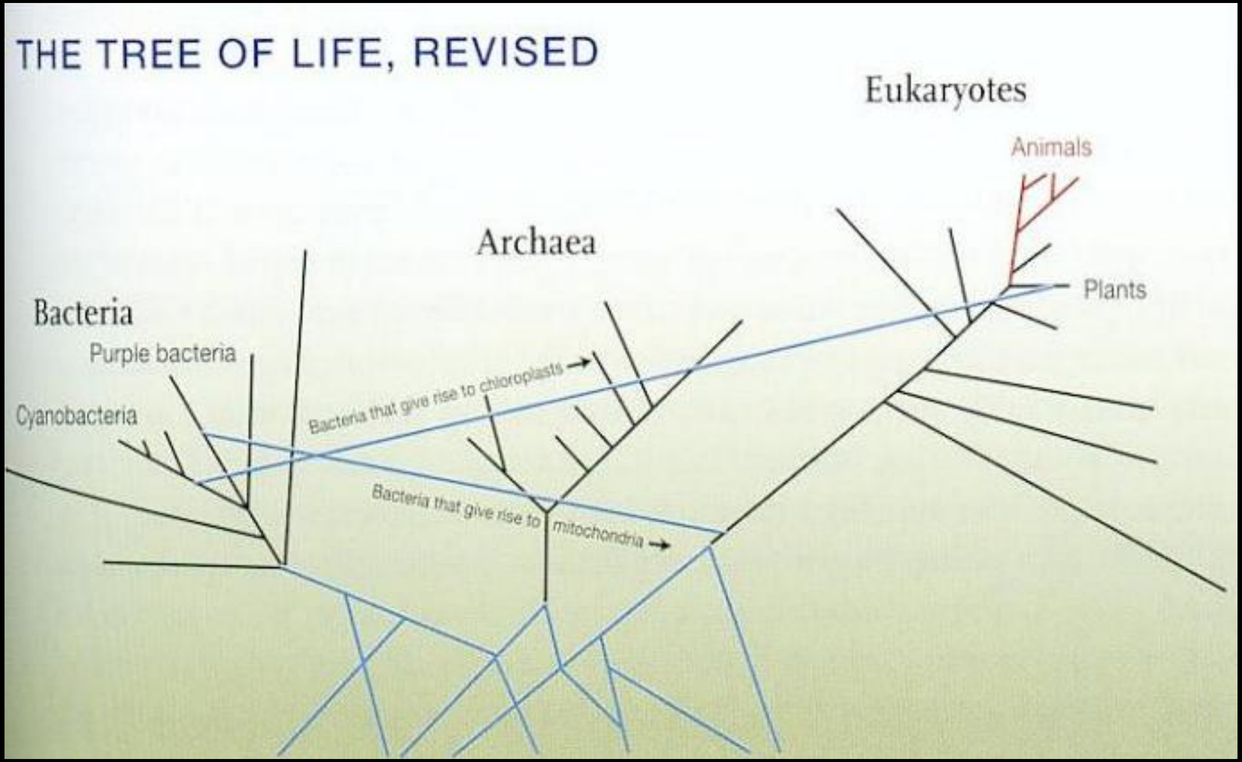


This view was later refined to 3 branches: **Eukaryotes:**

(any organism with one or more cells that have visible nucleus and organelles)

EVOLUTION IN THE 21ST CENTURY: BIOLOGY MEETS PHYSICS

New evidence suggests that the Tree of Life may be more complicated.



EVOLUTION IN THE 21ST CENTURY: BIOLOGY MEETS PHYSICS

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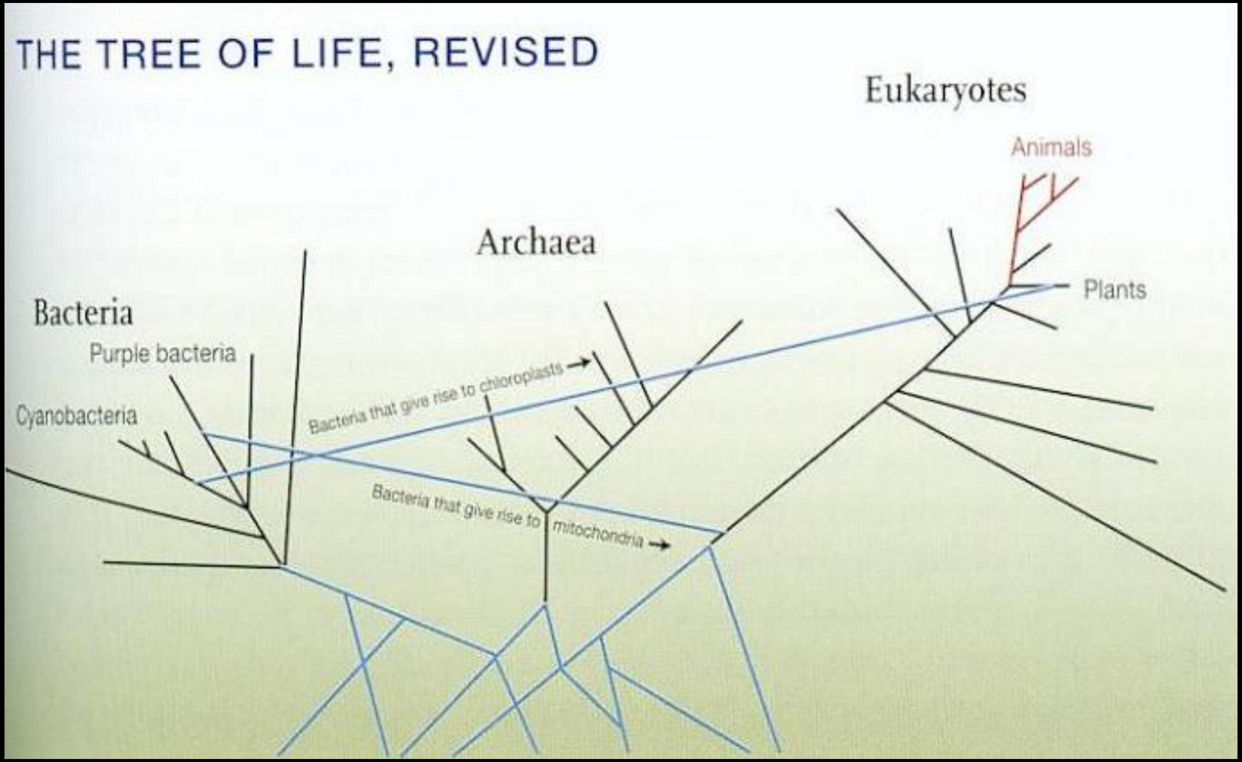
Early life may not have existed as distinct species; instead they may have traded their genes promiscuously.



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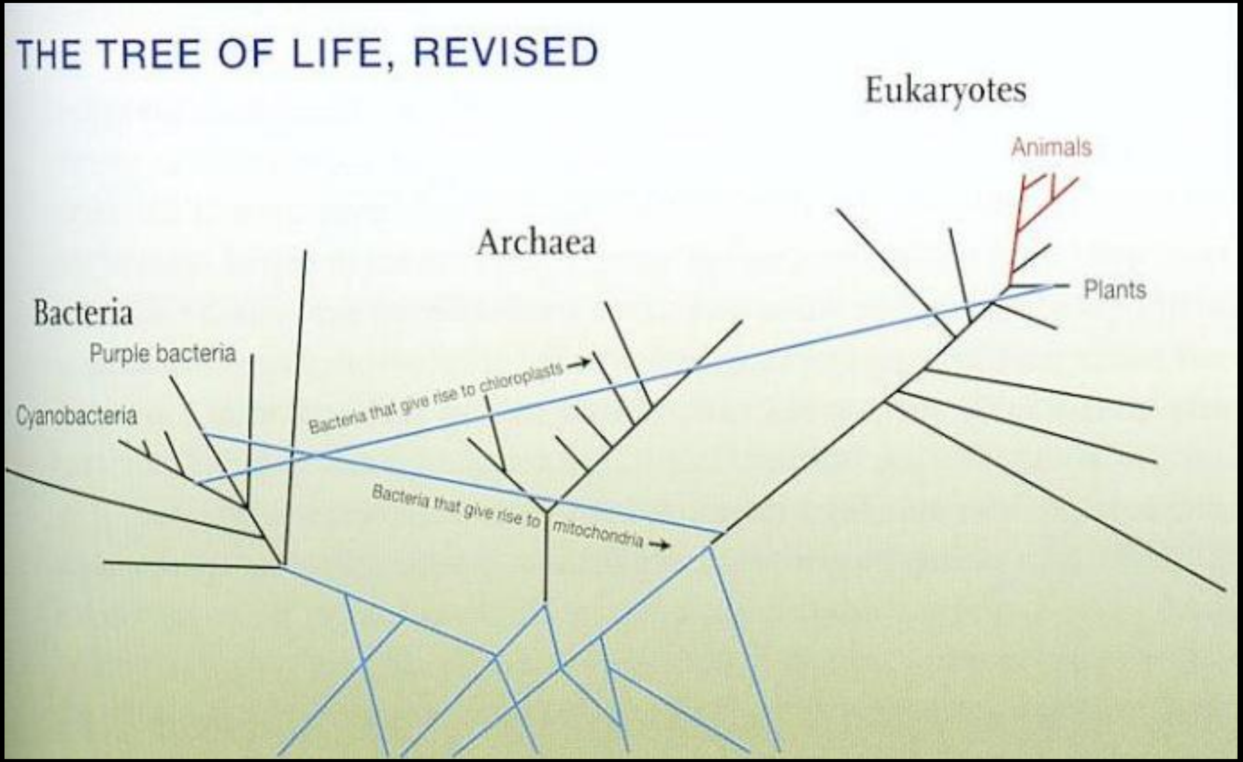
Life may descend from a huge primordial menagerie rather than from a single common ancestor.



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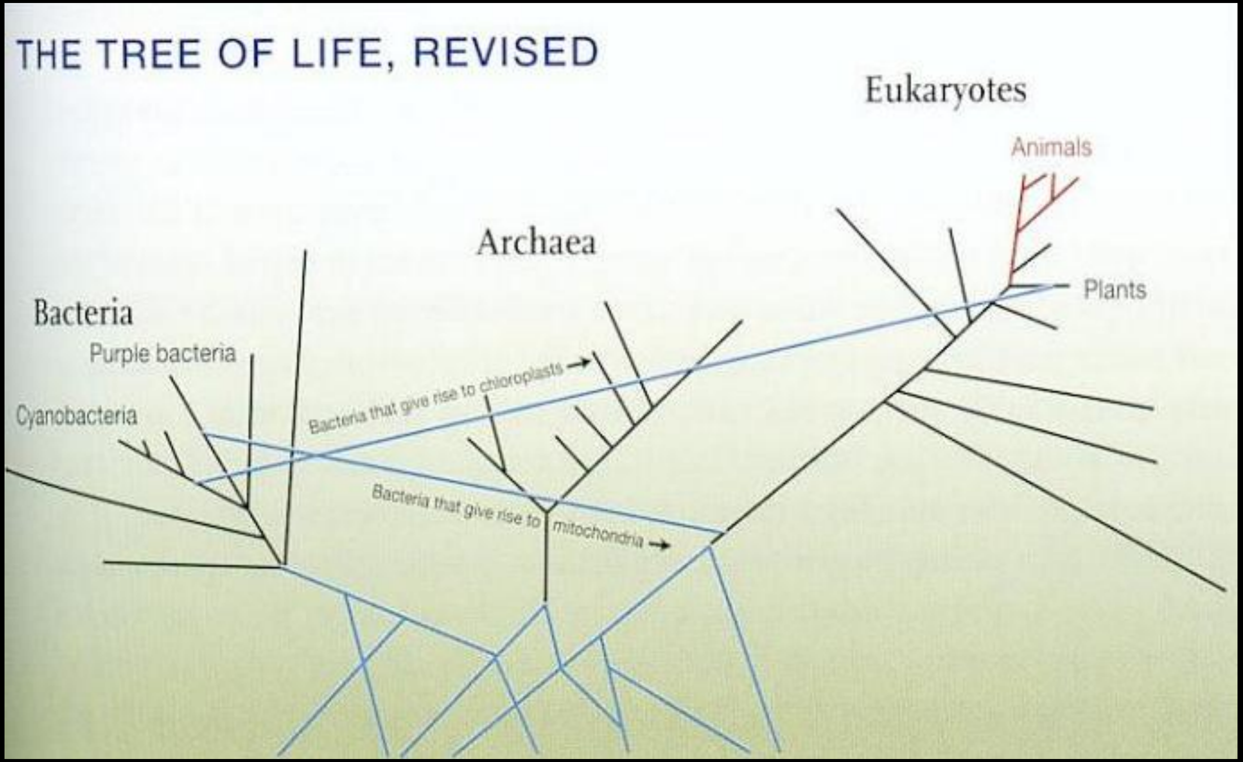
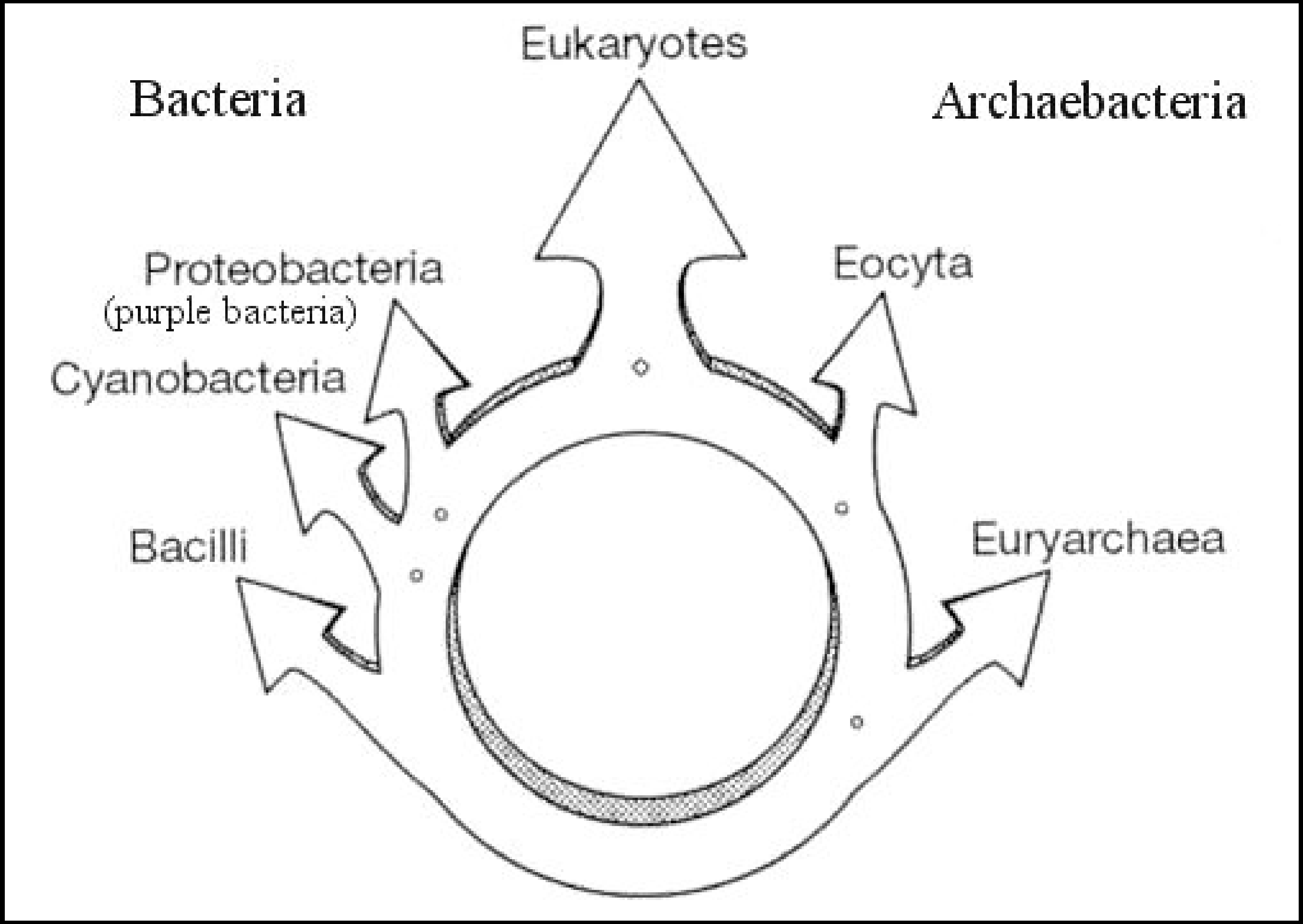


In 2004, this view replaced the "Tree of Life," and replaced it with . . .

EVOLUTION IN THE 21ST CENTURY: BIOLOGY MEETS PHYSICS



A *"RING OF LIFE"* (eukaryotes are the product of the fusion of genomes between some type of archaea with some type of bacteria)

But, how do we know the ***time scale*** of this evolutionary tract?

EVOLUTION IN THE 21ST CENTURY: BIOLOGY MEETS PHYSICS

But, how do we know the ***time scale*** of this evolutionary tract?

ANOTHER APPLICATION OF PHYSICS:

The use of ***radioactive carbon dating***!

WHAT IS RADIOACTIVE CARBON, AND HOW IS IT USED FOR DATING FOSSILS?

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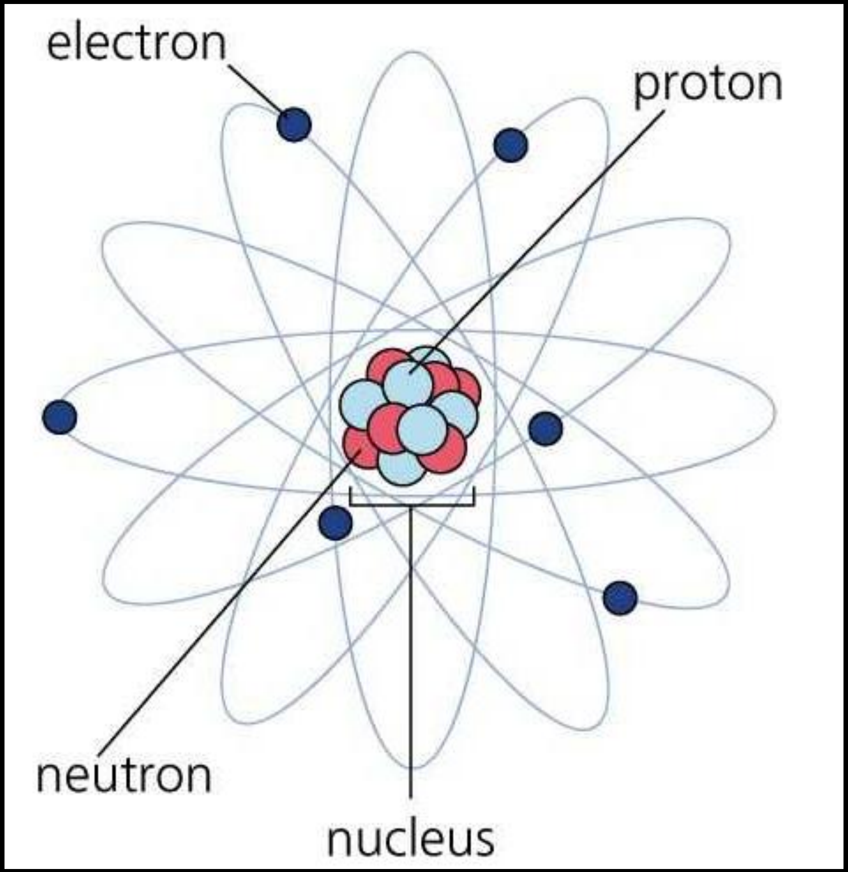
Carbon is an element that has 6 protons and usually 6 neutrons. The atomic number of carbon is 6 while the atomic mass of carbon is approximately 12. If carbon has 6 or 7 neutrons, it is considered to be stable but if it happens to have 8, then it is radioactive.



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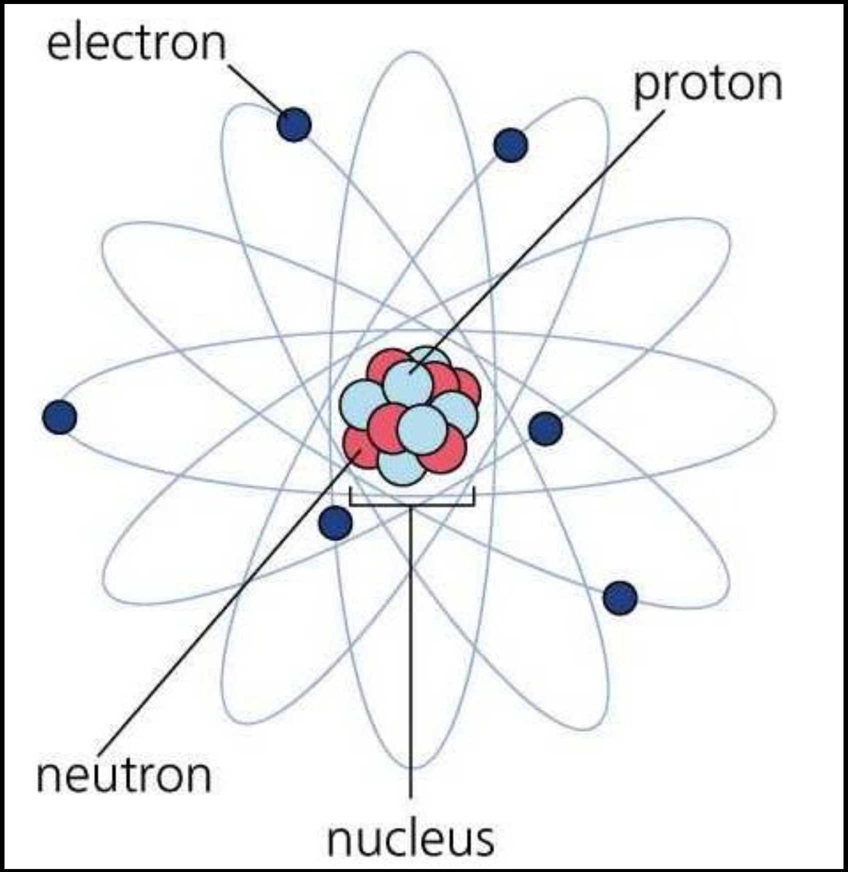
How is Carbon-14 produced, and how is it used in determining the age of fossils?



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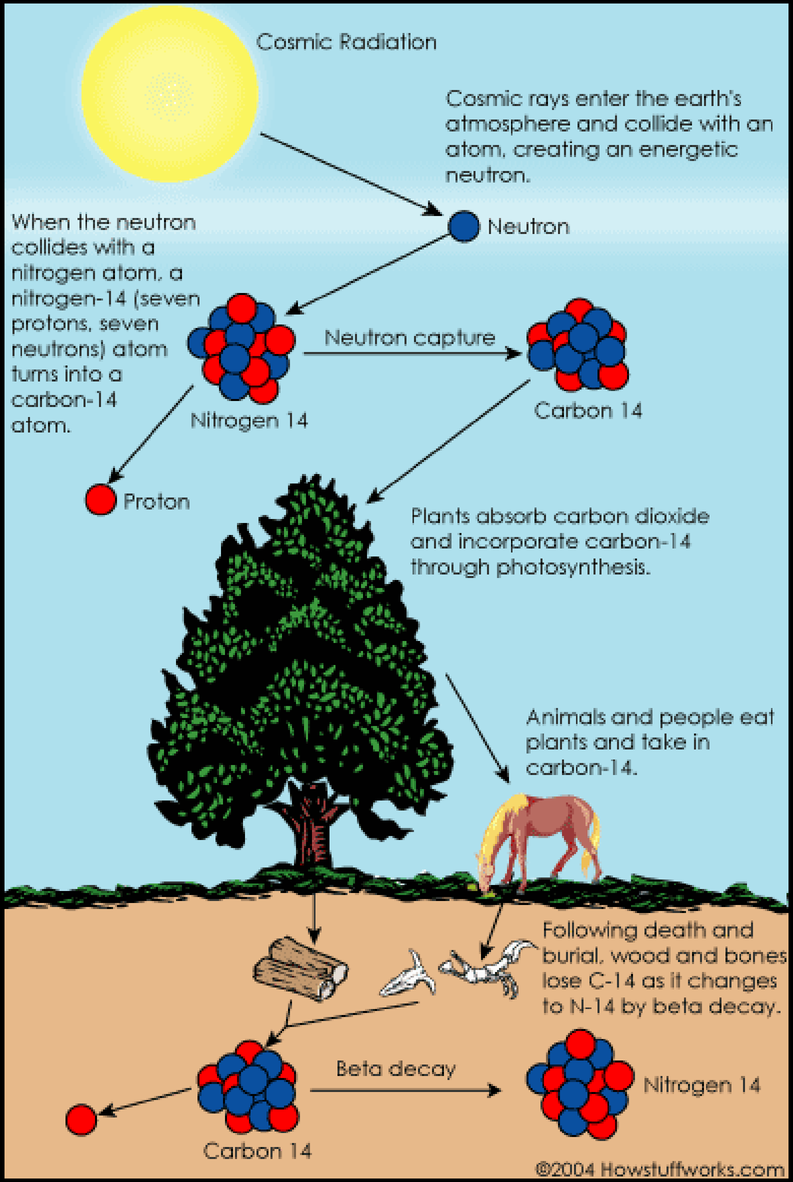

When carbon is radioactive, it decays into nitrogen; its half-life is 5,730 years. Which means if there are 12,000 atoms of radioactive carbon, after 5,730 years, there will only be 6,000 radioactive carbon atoms, and 6,000 nitrogen atoms.

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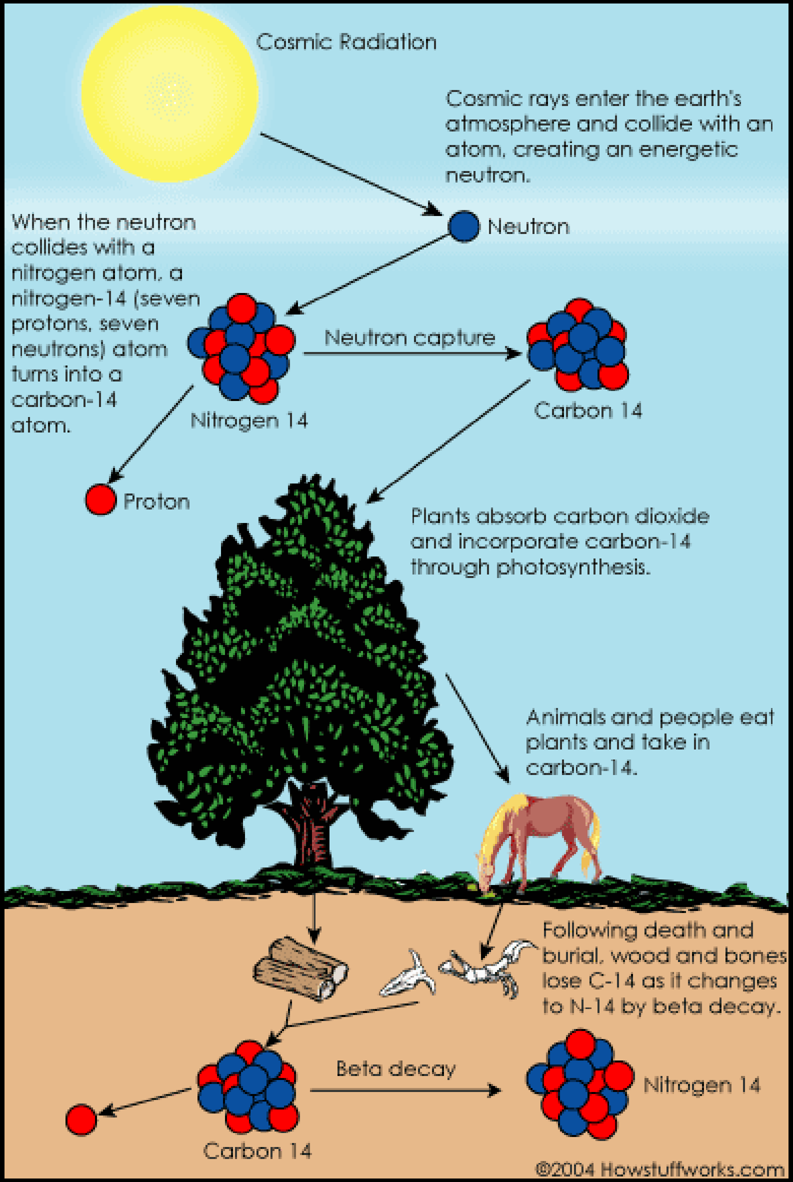

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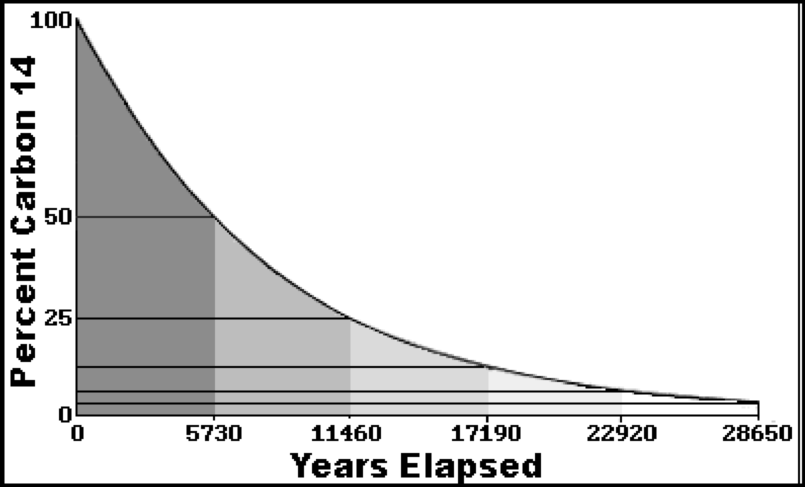

Graph depicting the decay rate of Carbon-14.

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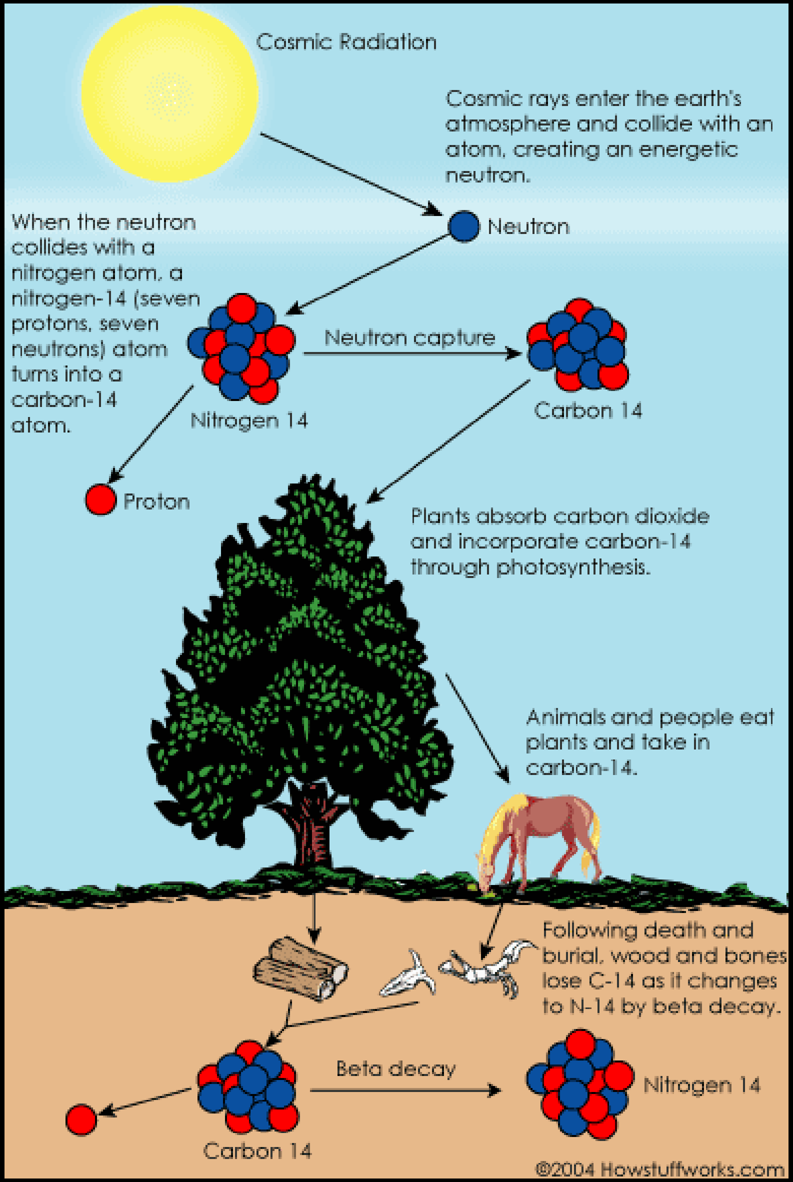

All living things are made out of carbon because it is one of the most plentiful elements on this Earth. If an organism is living, then the amount of radioactive carbon stays at a constant. The moment that organism dies however, the carbon starts to decay.

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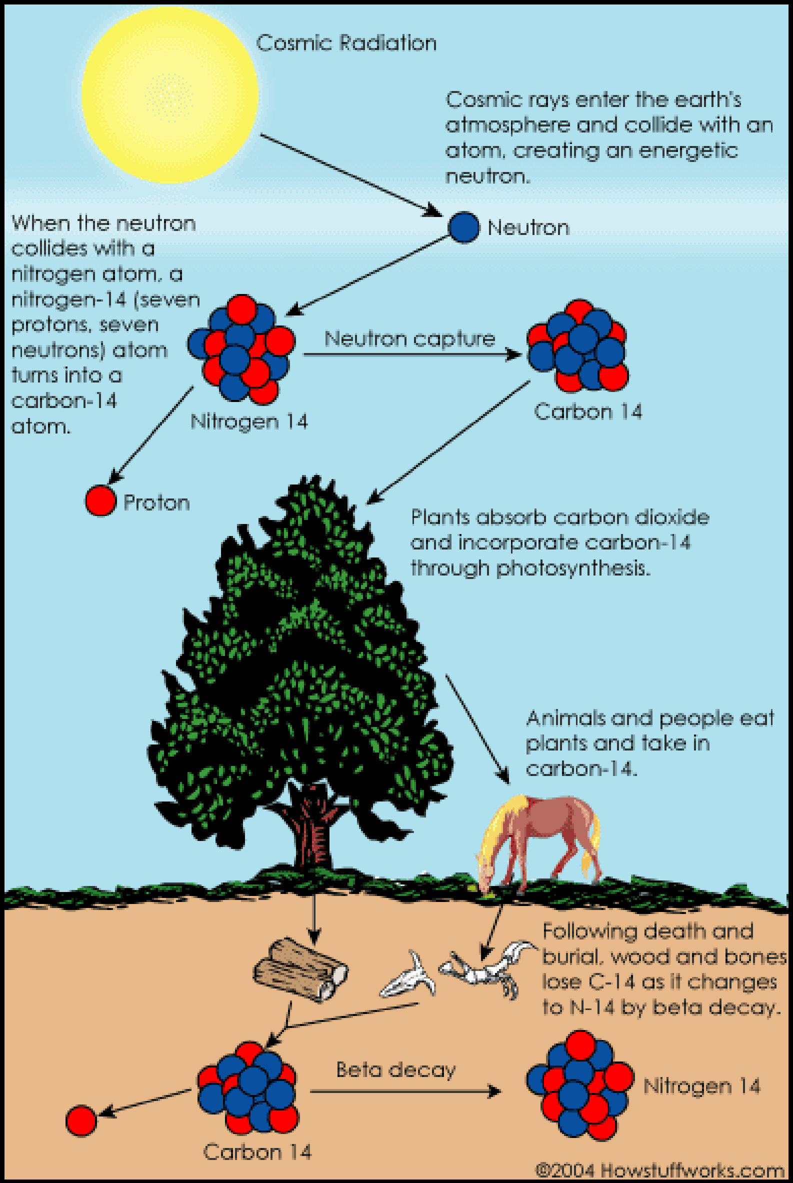

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The fact that the ratio of C14 to C12 is fairly constant (~ 10-12) in living organisms and that C14 is radioactive would yield the age of the organism since its death (no more accumulation of C14) if we measure the leftover amount of C14 in the sample.

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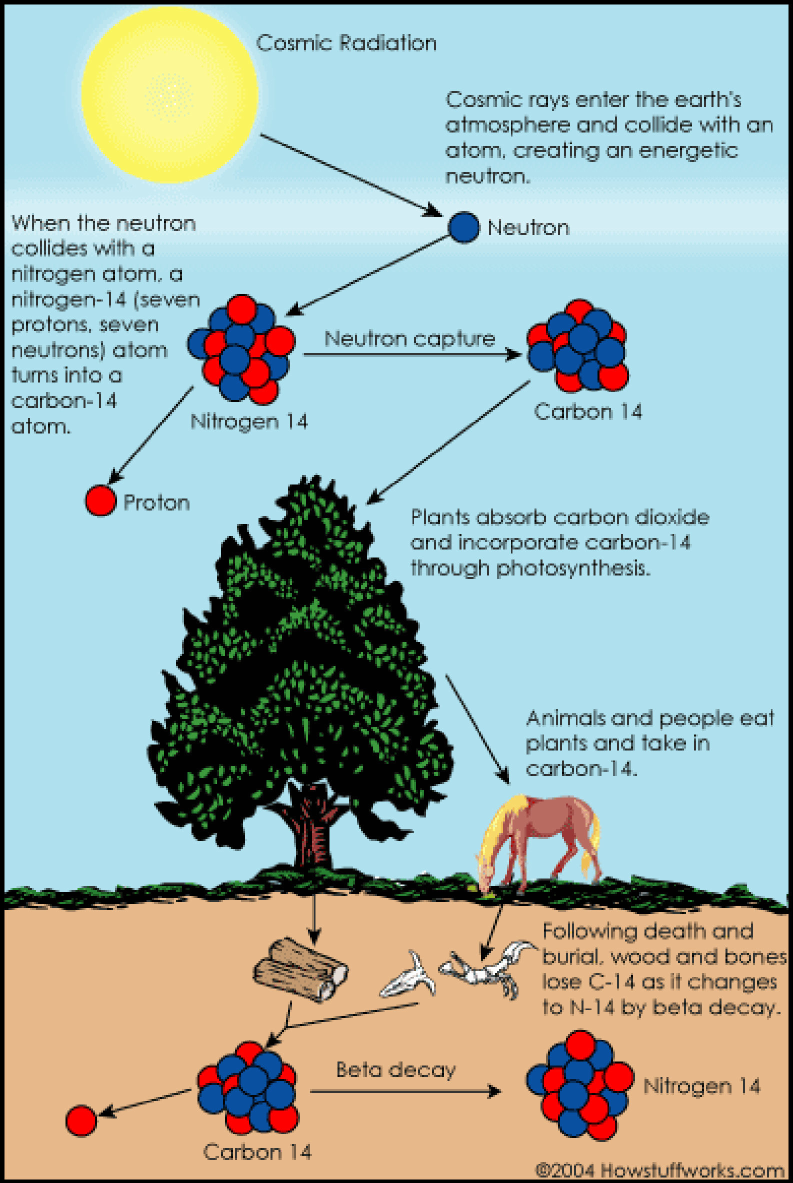

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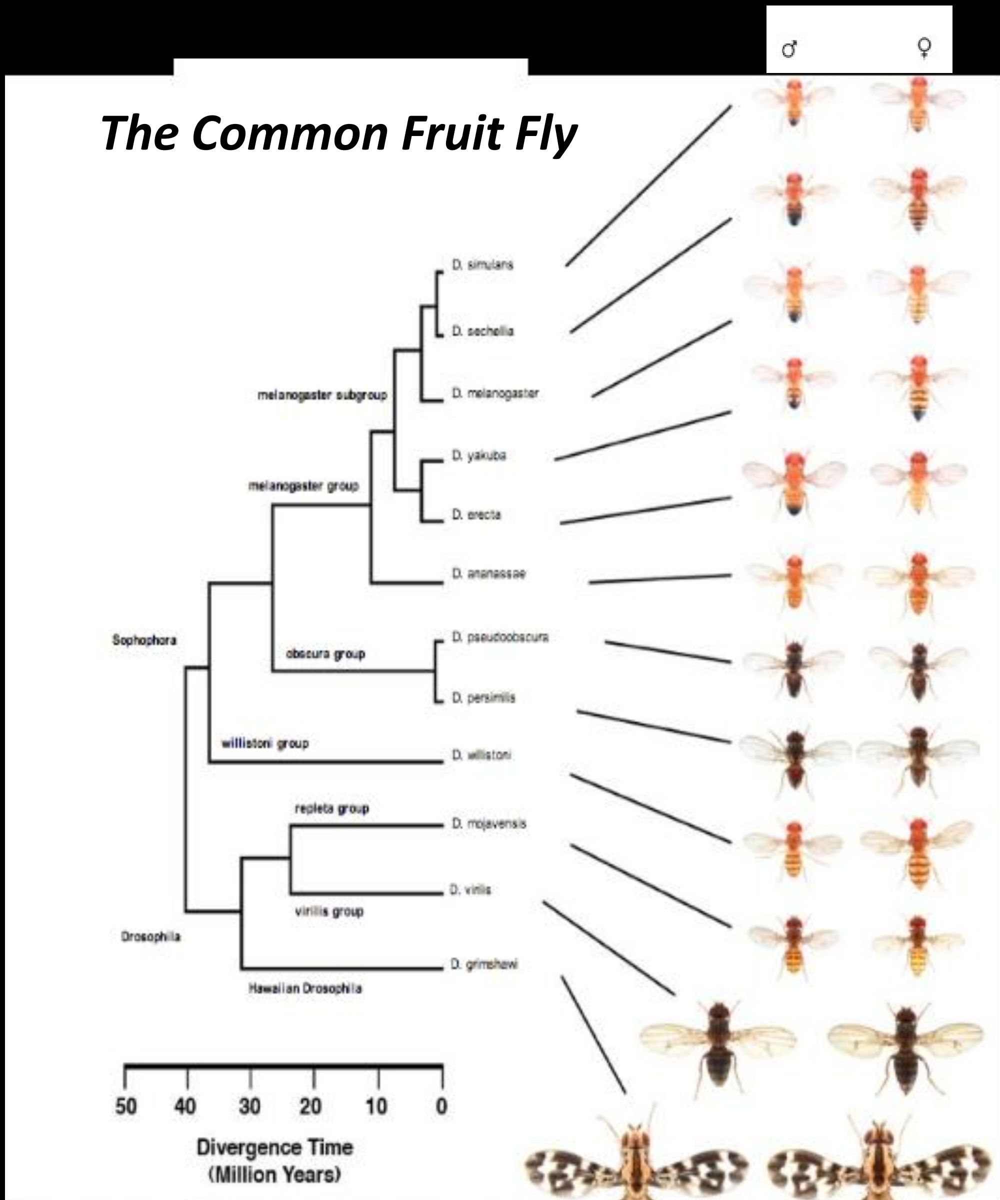
Carbon Dating only works on organic material like wood, animal skin, animal bones, and actual animals themselves but it will not work on substances like rocks, water, or metal.

We also observe and analyze the evolution of. . .



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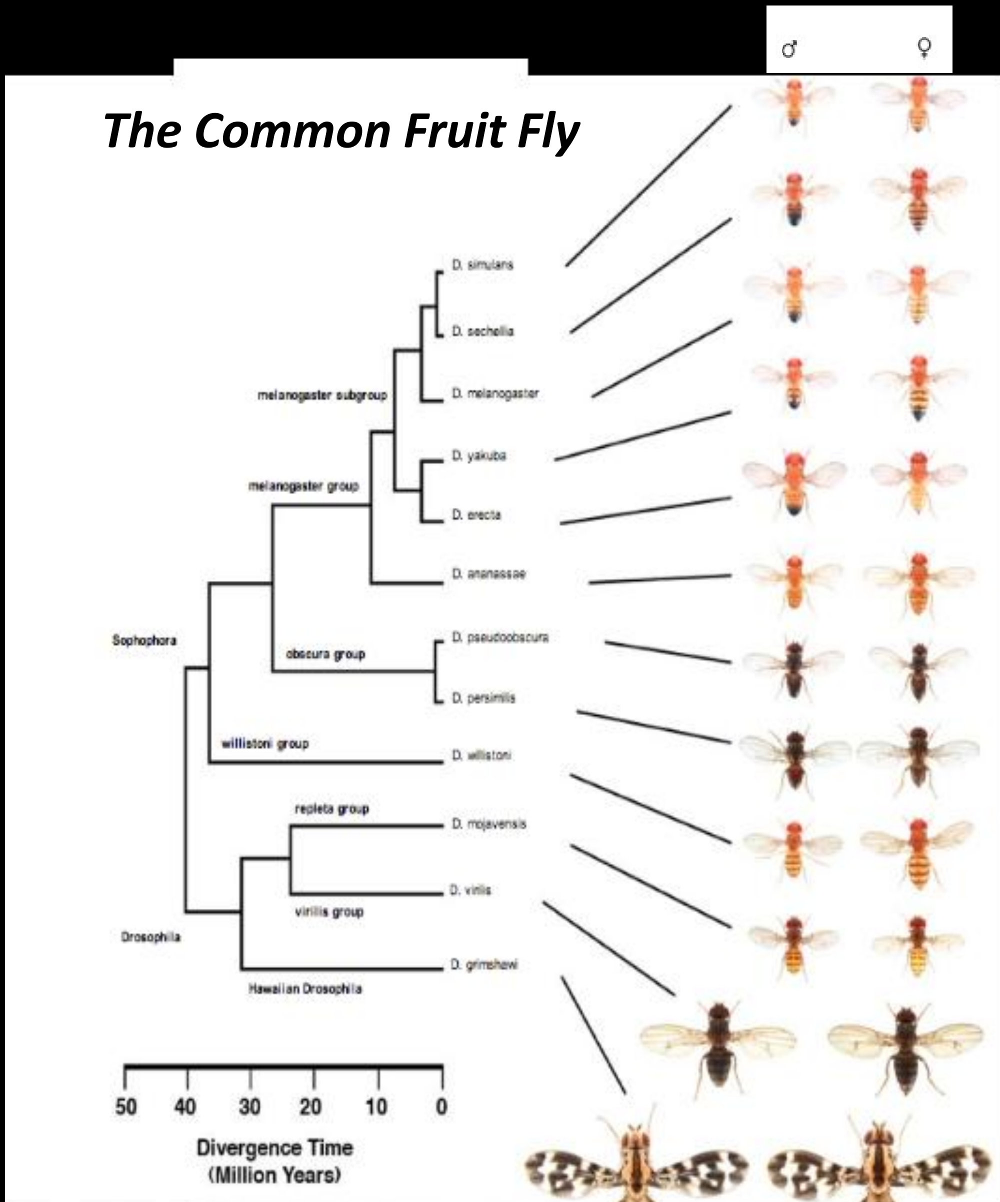

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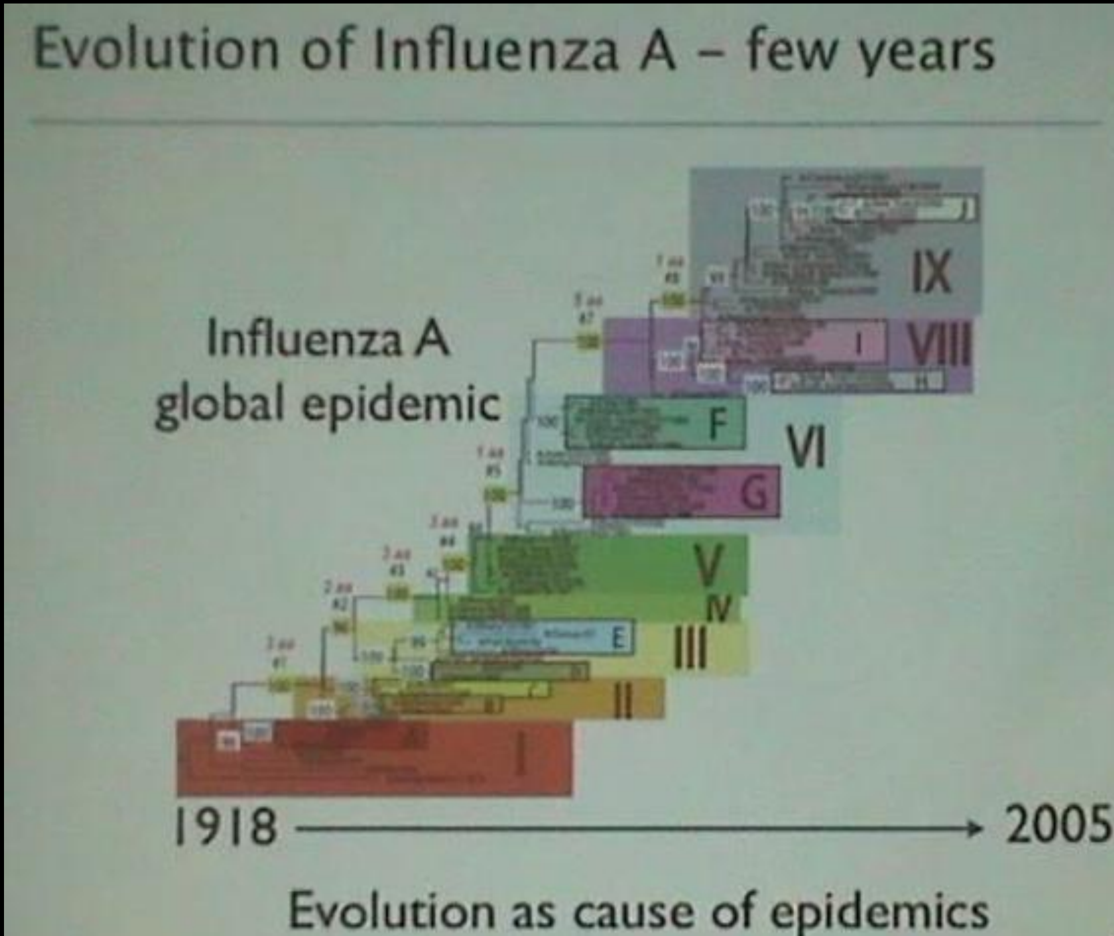

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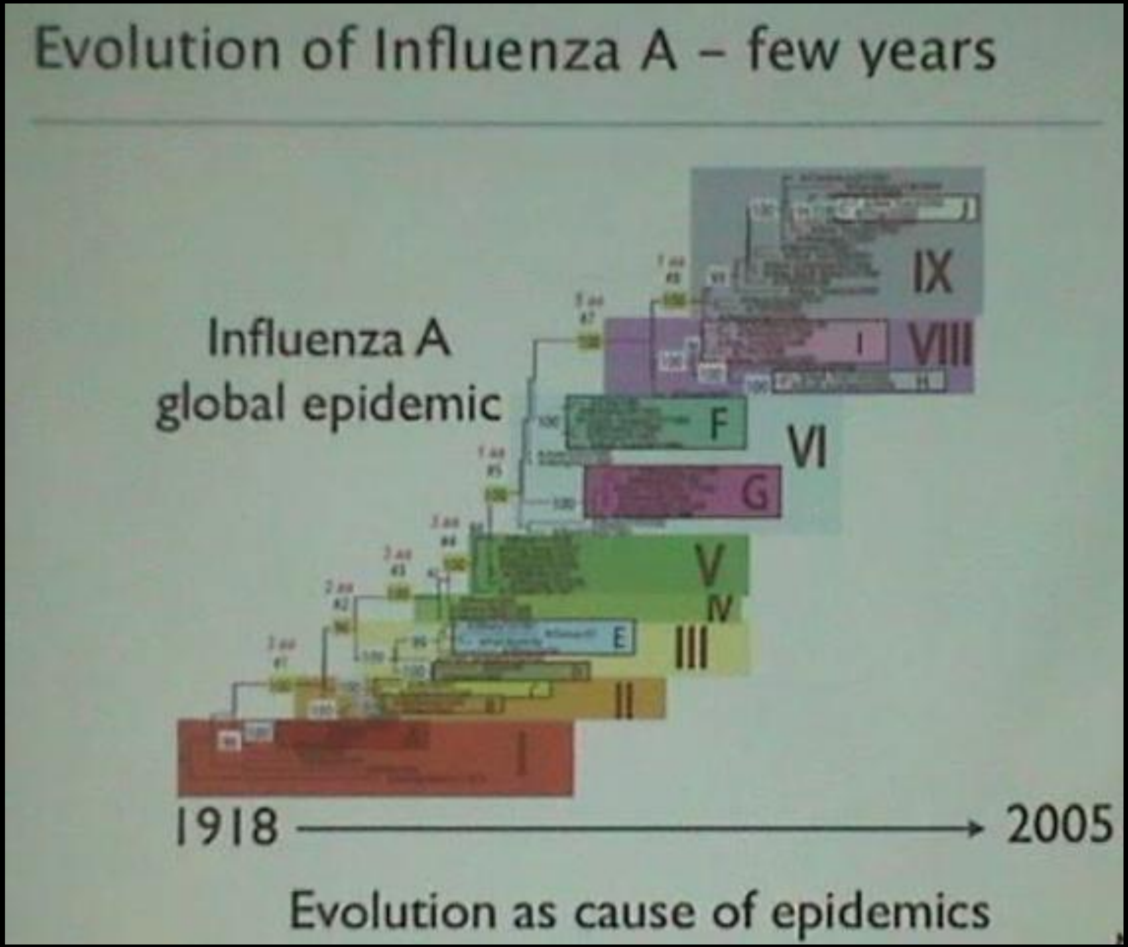

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VIRUSES

(LIKE INFLUENZA A)

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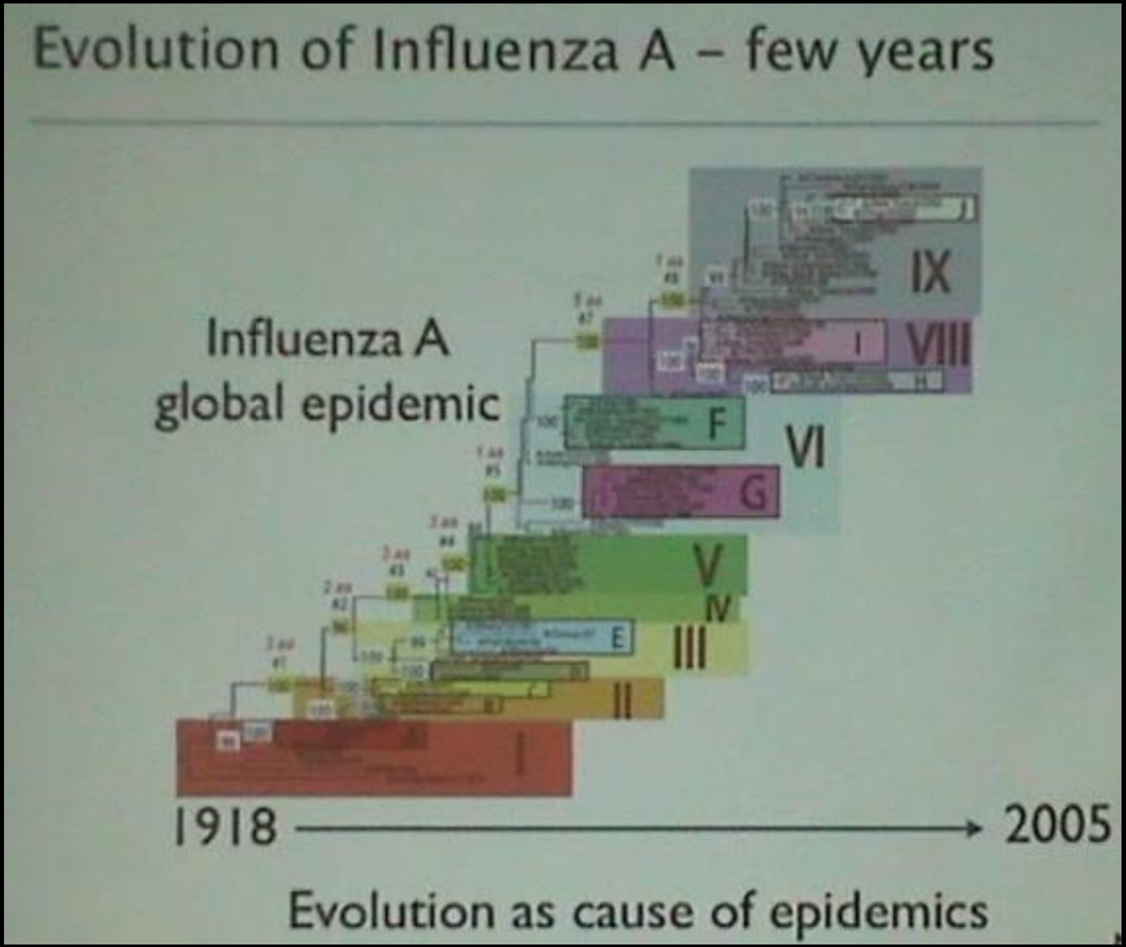

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As opposed to tracing through millions of years of the evolutionary history of complex organisms (like fruit flies), the evolution of a particular virus can be observed in a matter of decades, since it mutates and evolves so rapidly.

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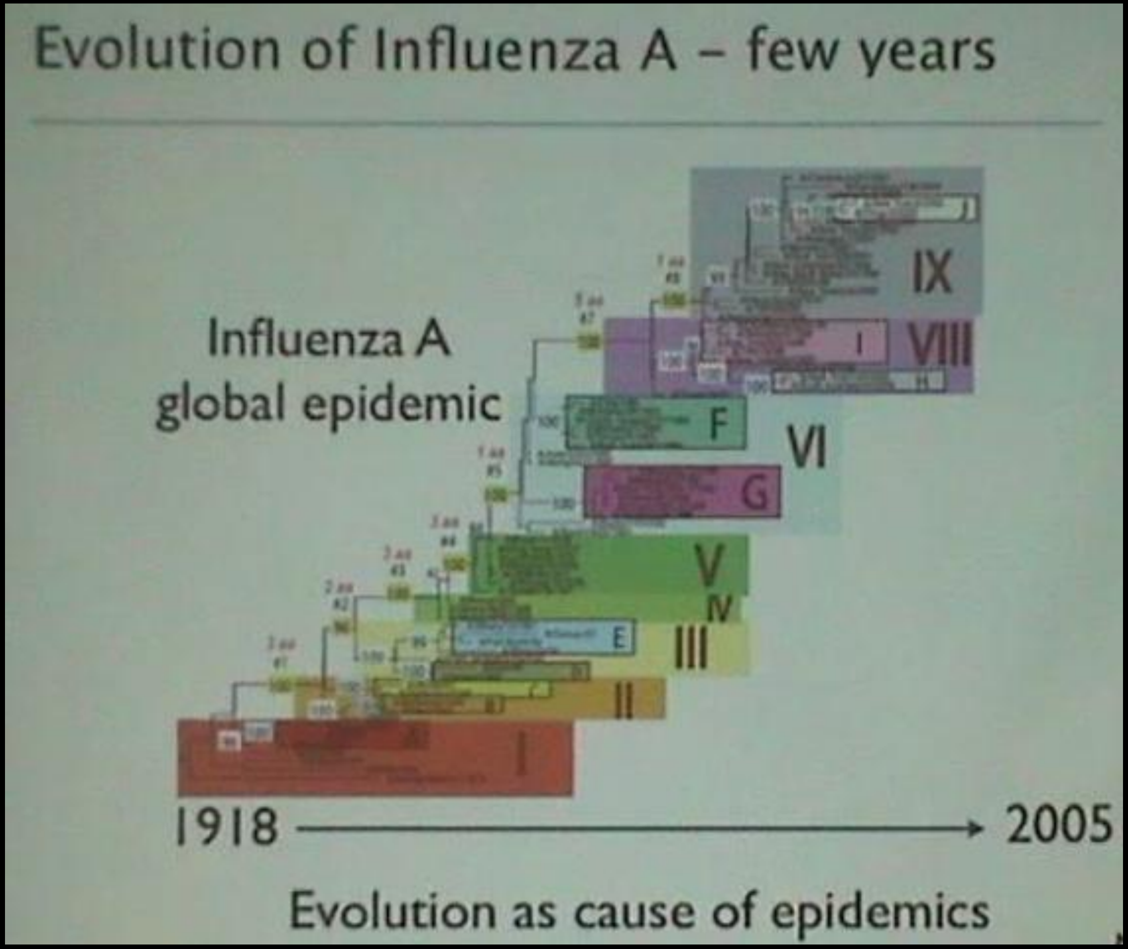

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VIRUSES

(LIKE INFLUENZA A)

An understanding of the evolutionary dynamics of the influenza virus determines scientists' ability to survey and control the virus.

We also observe and analyze the evolution of. . .
an even more recent and deadly virus. . .

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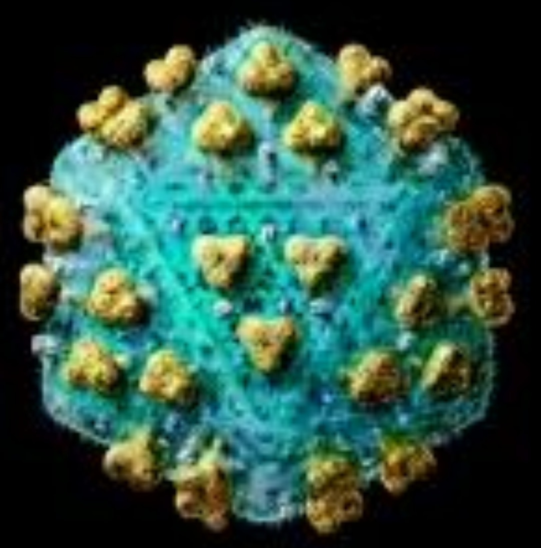
The Human Immunodeficiency Virus (HIV)



←-------------100 nm --------------------→

Over the past few decades, we have seen the development and evolution of one of the world's most dangerous viruses.

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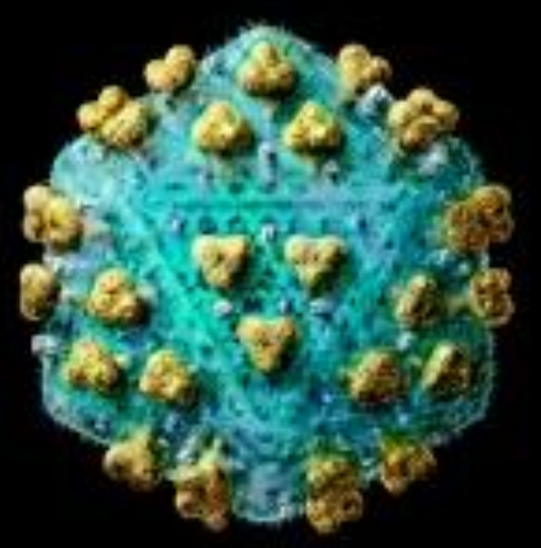

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Over the past few decades, we have seen the development and evolution of one of the world's most dangerous viruses.

The HIV virus has affected millions of people and has rapidly evolved mechanisms to fight off chemical vaccines.

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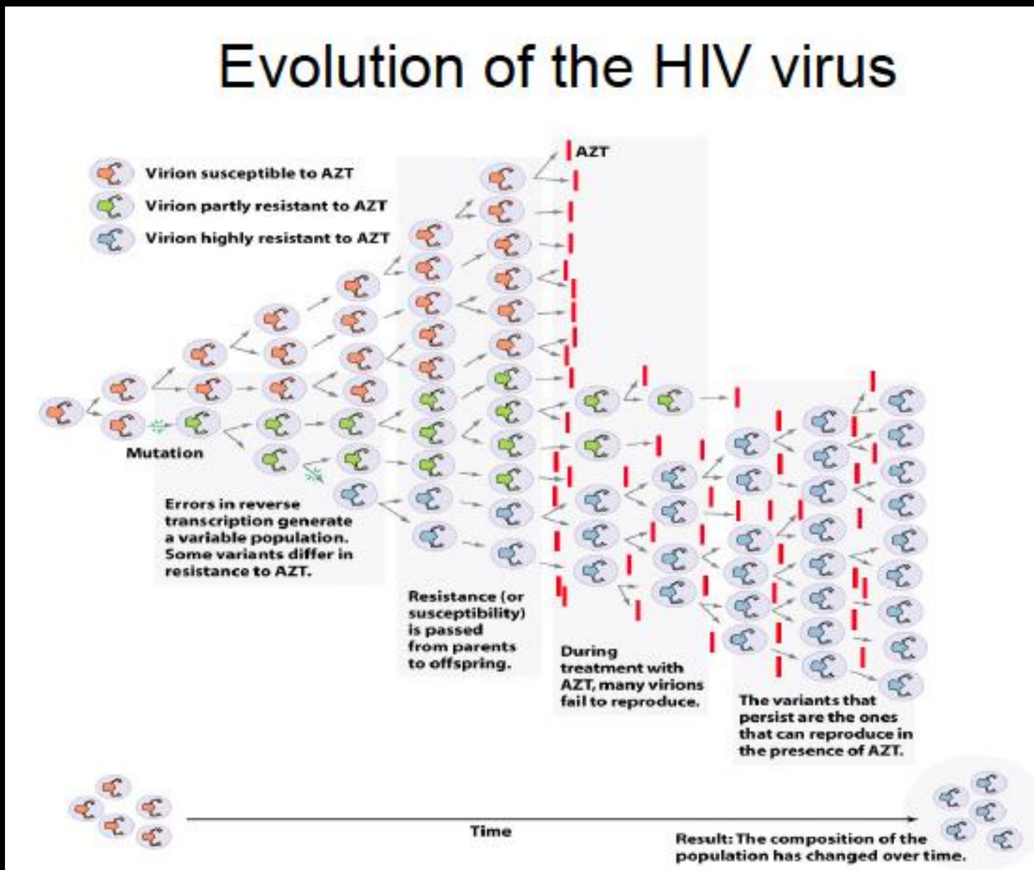

Figure 1-14 Evolutionary Analysis, 4/e

Why does HIV evolve so rapidly?

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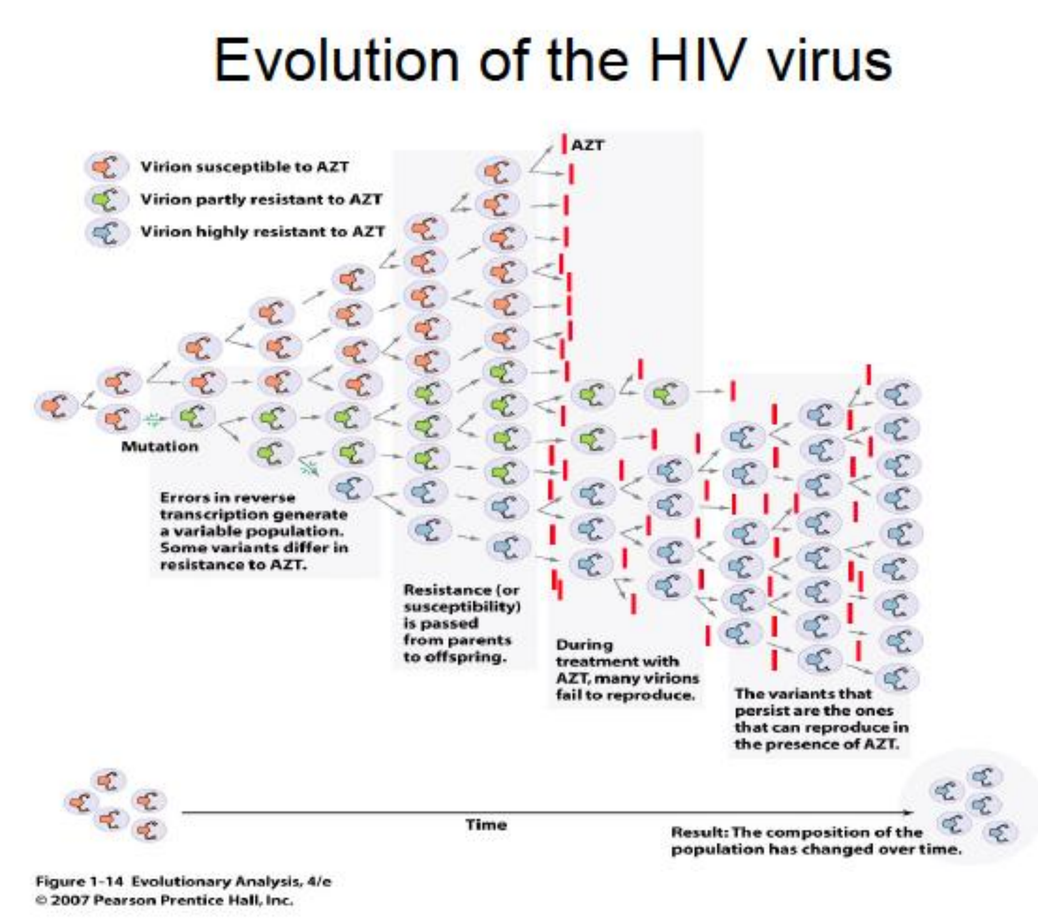

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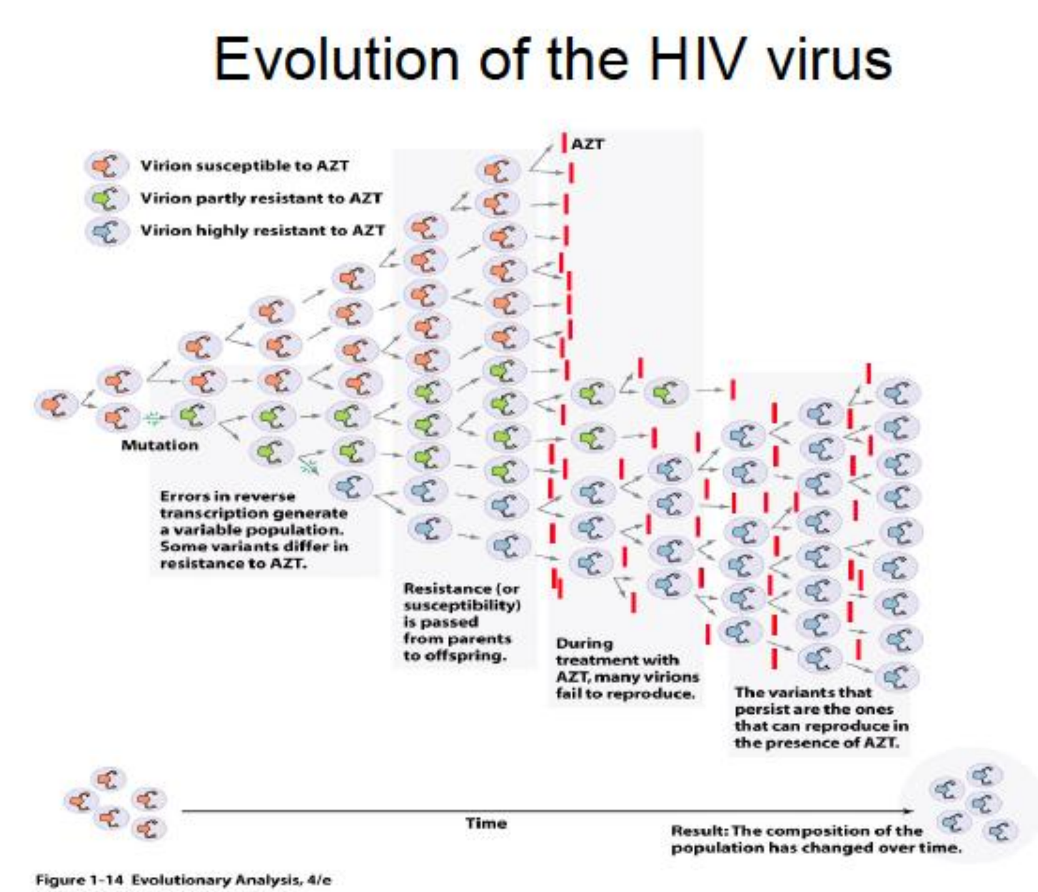

Figure 1-14 Evolutionary Analysis, 4/e
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Why does HIV evolve so rapidly?

***Its high mutation rate**
1,000,000 times higher than ours!

***Its short generation time**
1 year = 300 viral generations
This means that
10 years of viral evolution =
2 to 3 MILLION YEARS of human evolution!

SO, HOW CAN PHYSICS HELP IN UNDERSTANDING THE MECHANISMS BY WHICH CELLS GROW AND EVOLVE?

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WILL WE ACTUALLY BE ABLE TO *CONTROL* CELLULAR MECHANISMS?


PART 3: PHYSICS , THE CELL, AND THE FUTURE

ALL LIVING THINGS ARE MADE OF CELLS

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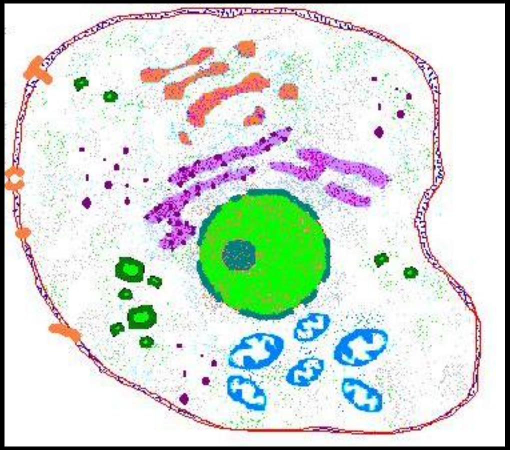

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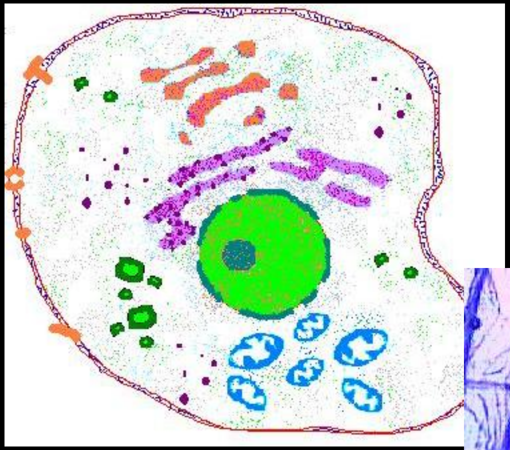

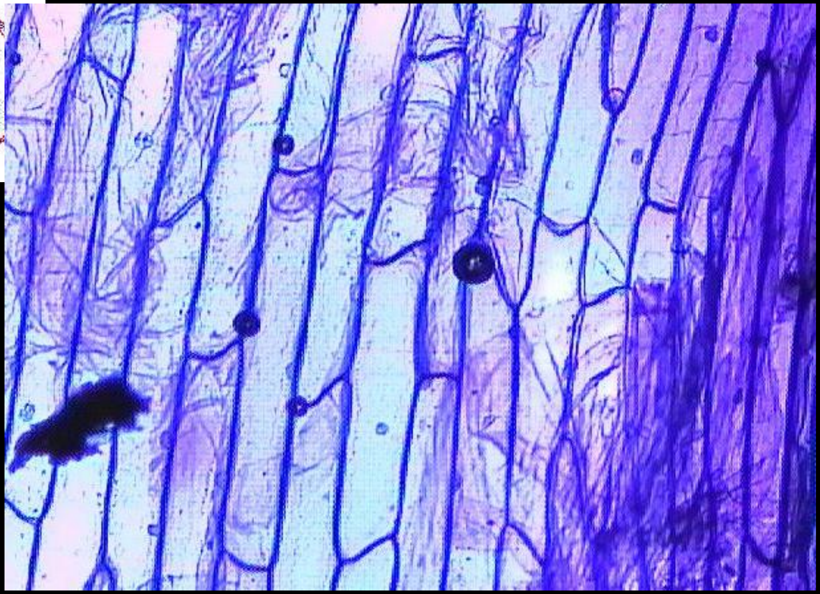

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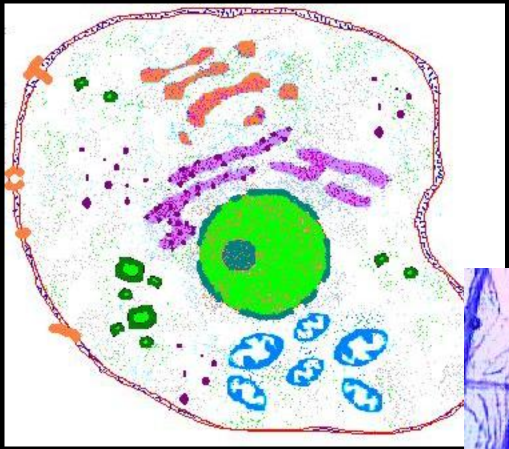

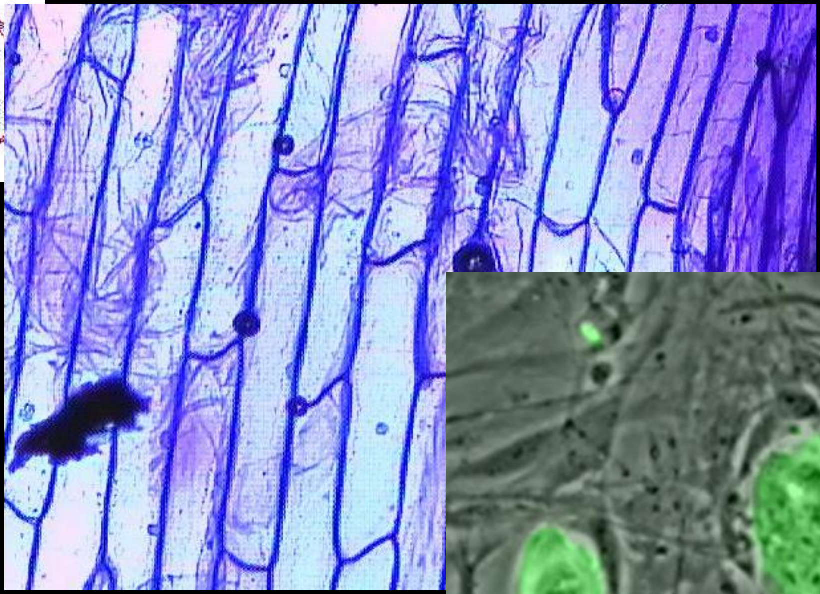

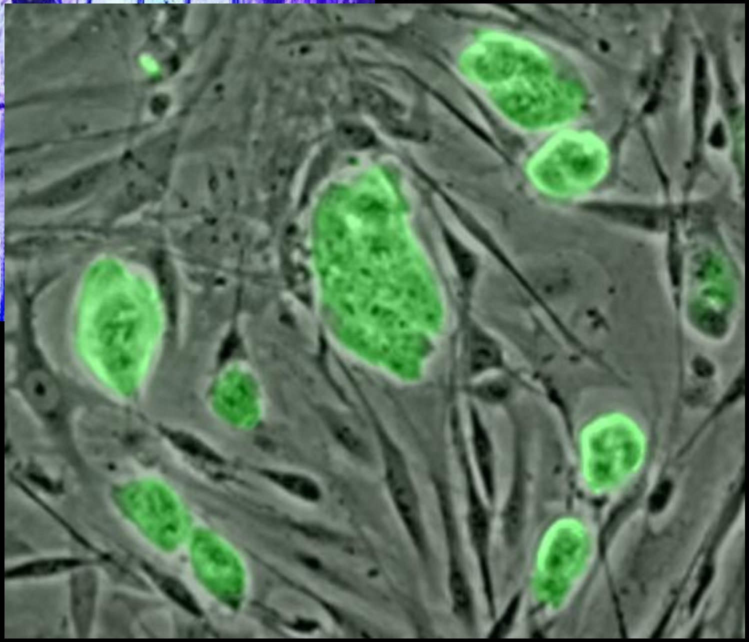

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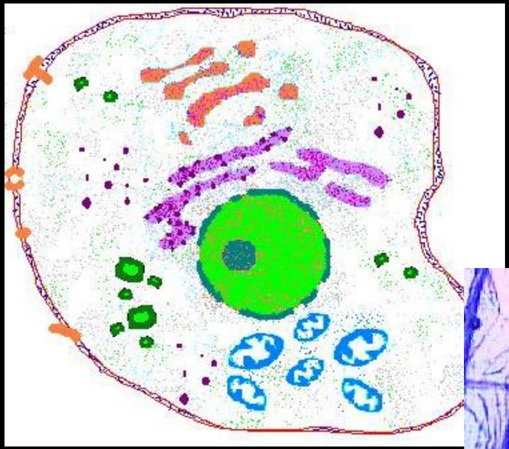
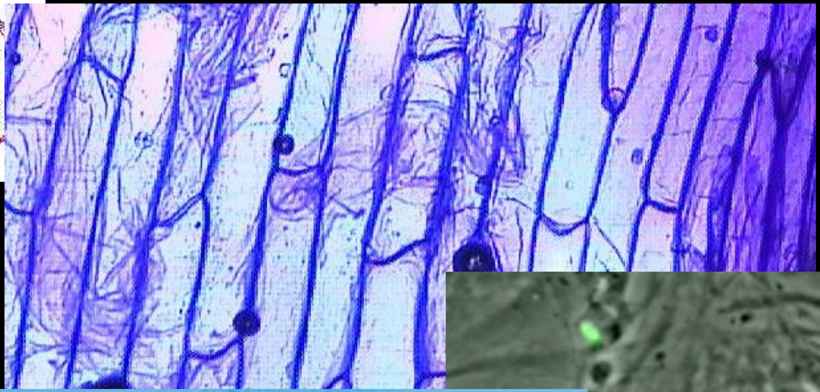
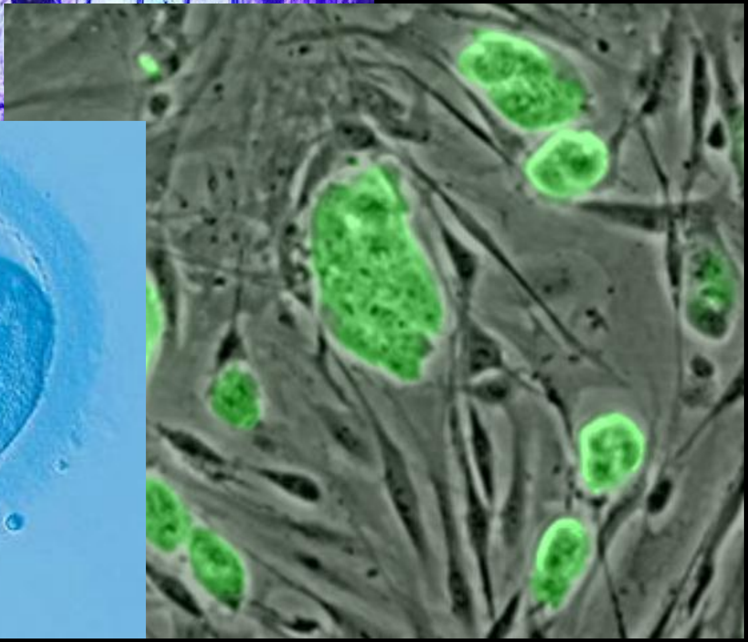


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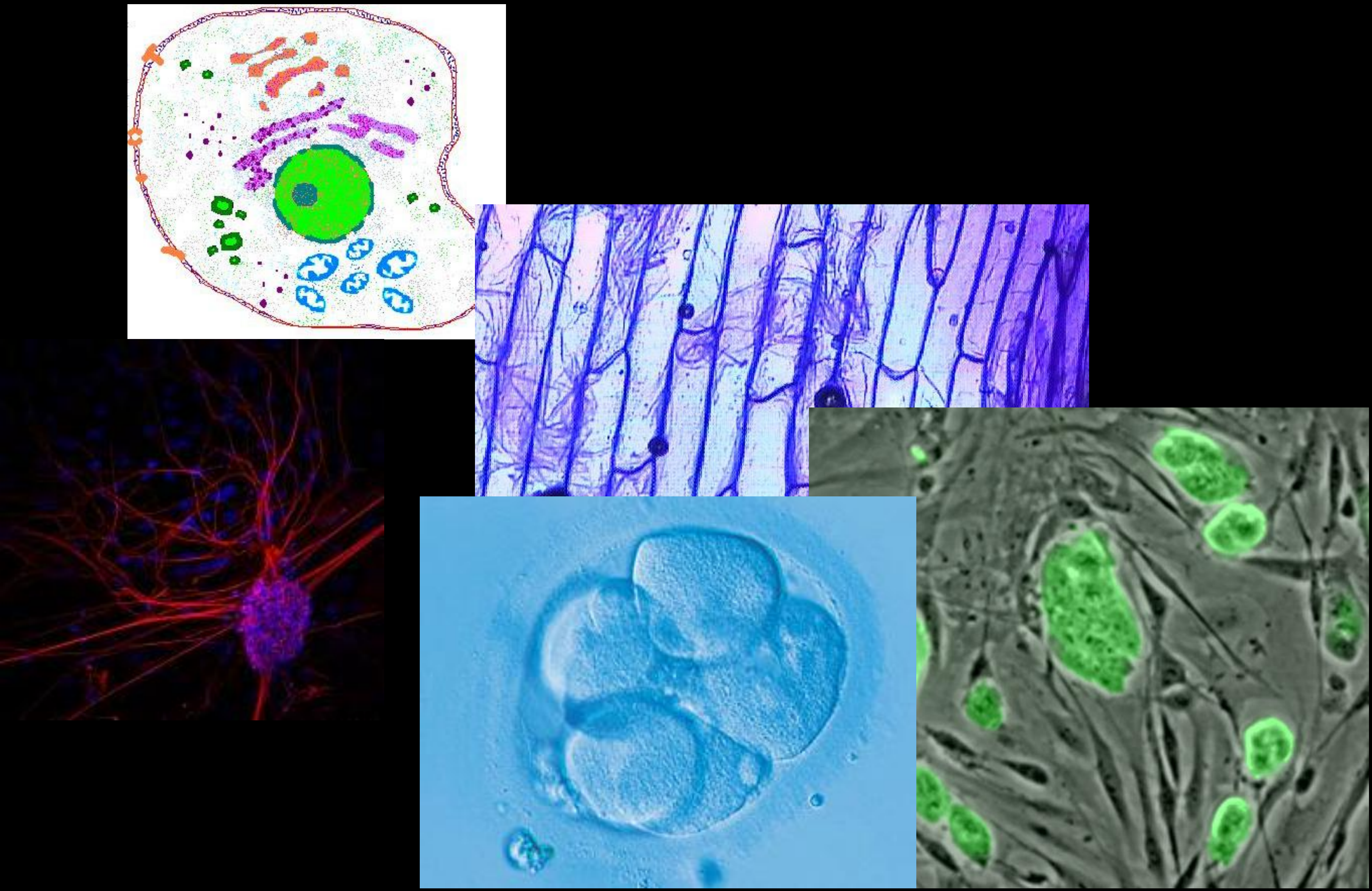

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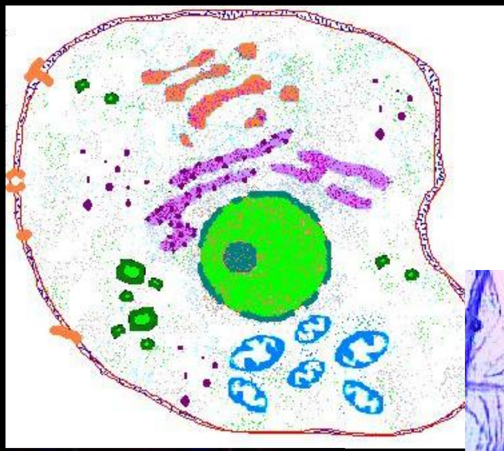

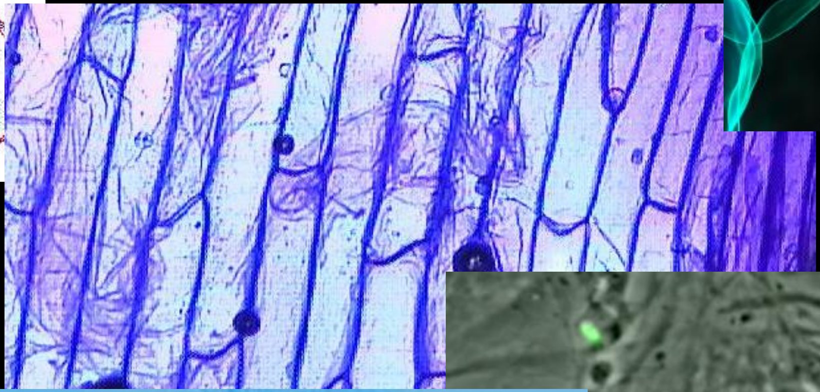

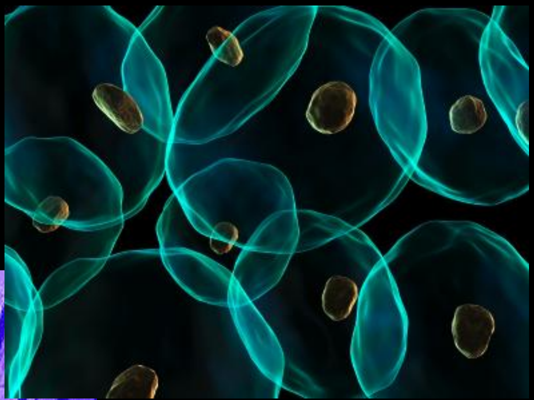

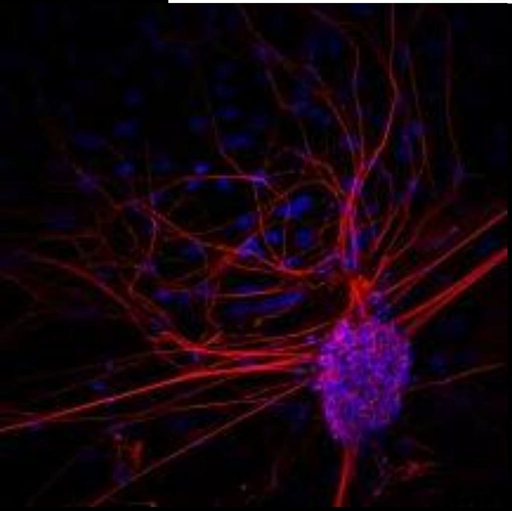

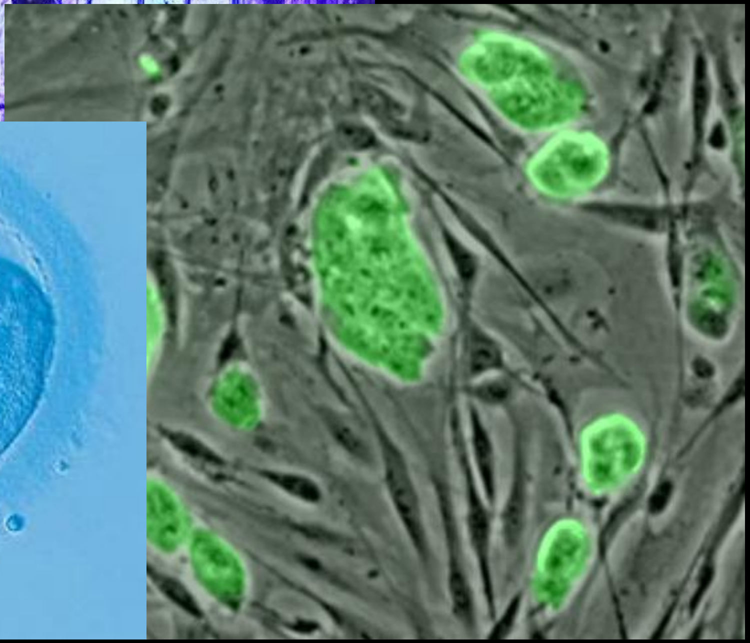

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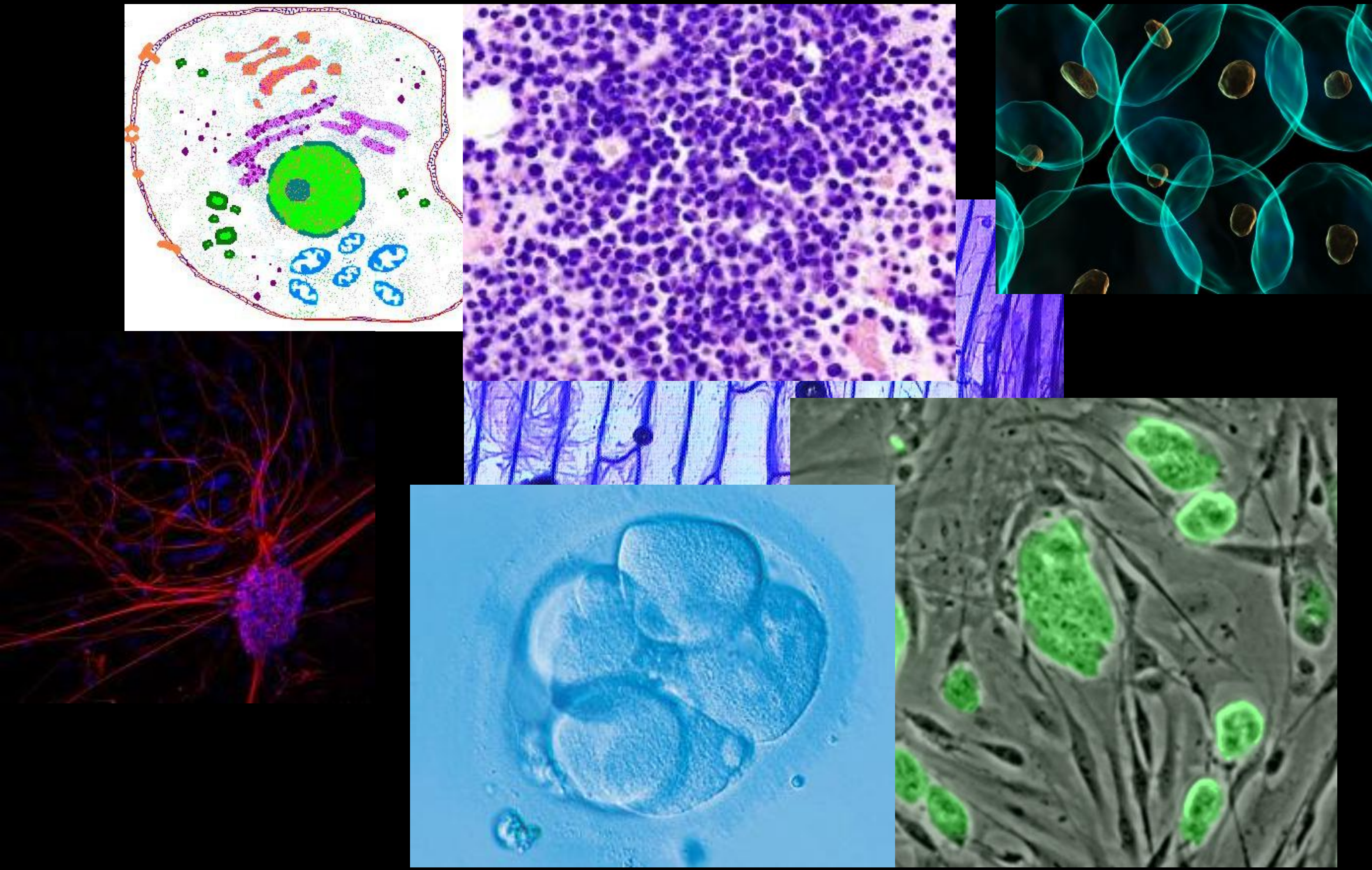

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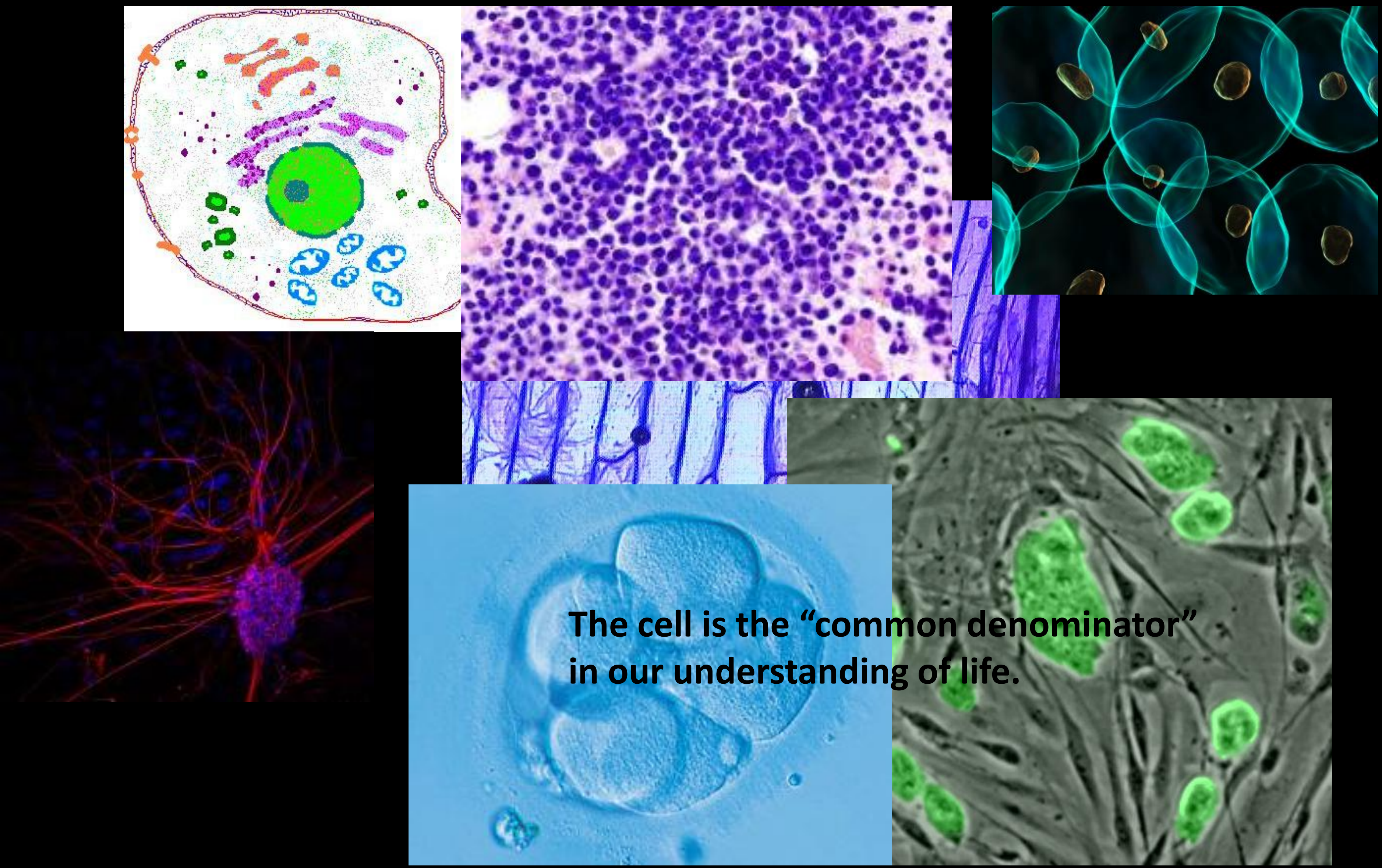

The cell is the "common denominator" in our understanding of life.

CELLS HAVE TO:

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1. Regulate their own growth and division.

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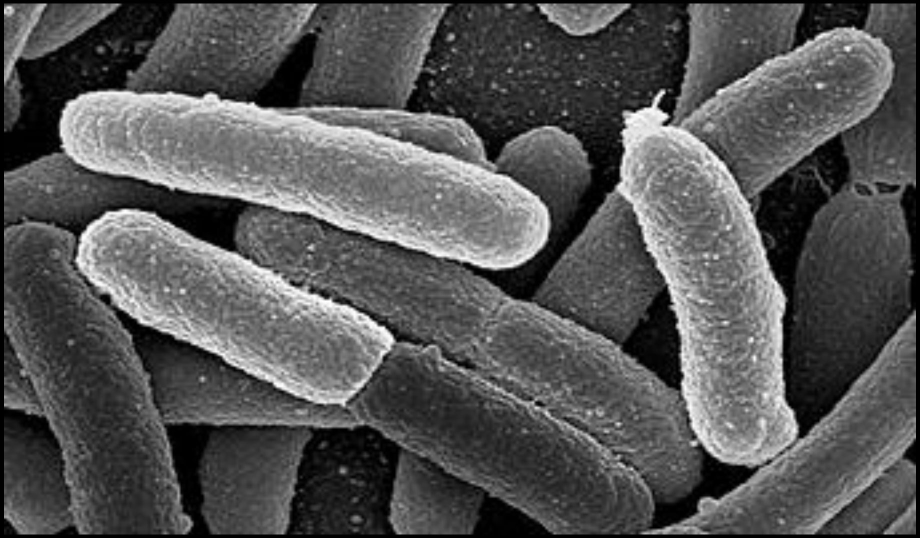
JUST HOW CAN THE CELL DO ALL THESE AMAZING THINGS?

Instead of looking at a large population of cells, like e-coli



A group of e-coli cells. Each cell is about 1 micron long.

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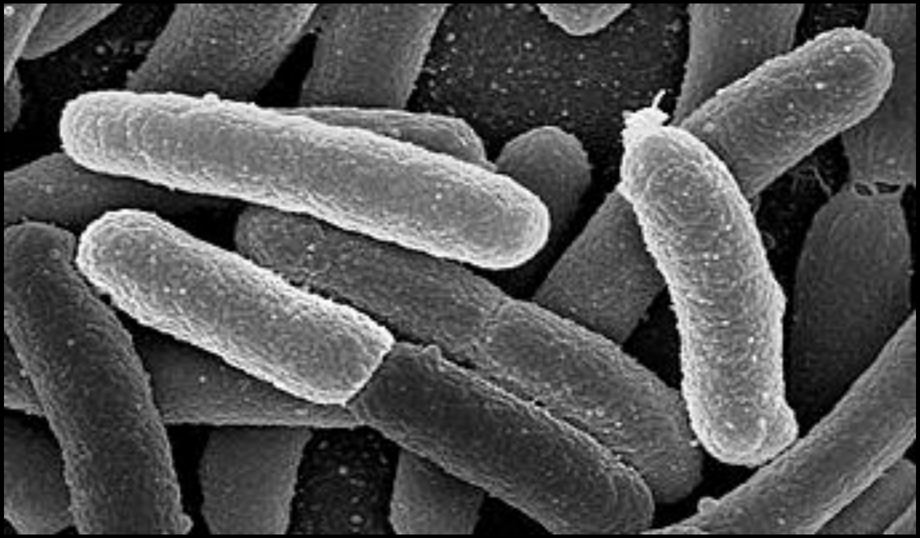
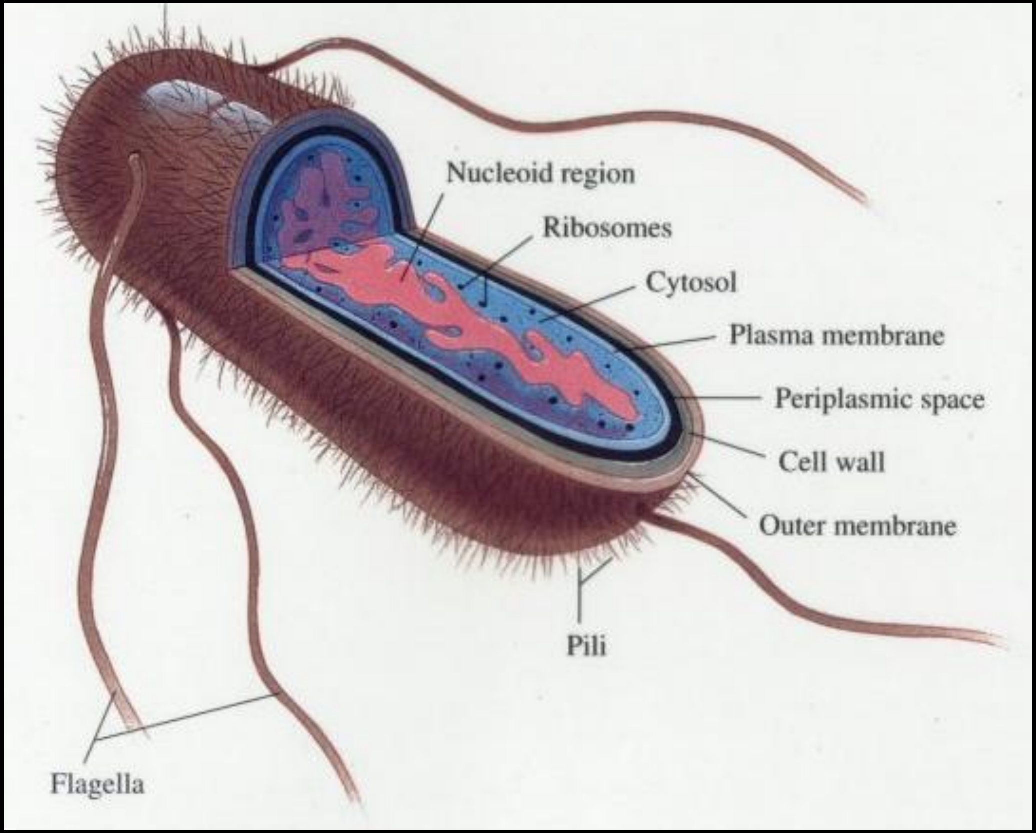


A group of e-coli cells. Each cell is about 1 micron long.

Let’s look at one cell and isolate its behavior and metabolism.

IF YOU COULD LOOK INSIDE ONE E-COLI CELL, YOU WOULD OBSERVE A HIGH-DENSITY COMPLEX ARRANGEMENT OF PROTEINS, NUCLEIC ACID (DNA/RNA), WHERE A SINGLE PROTEIN WOULD HAVE DIFFICULTY MOVING WITHIN THE CELL.



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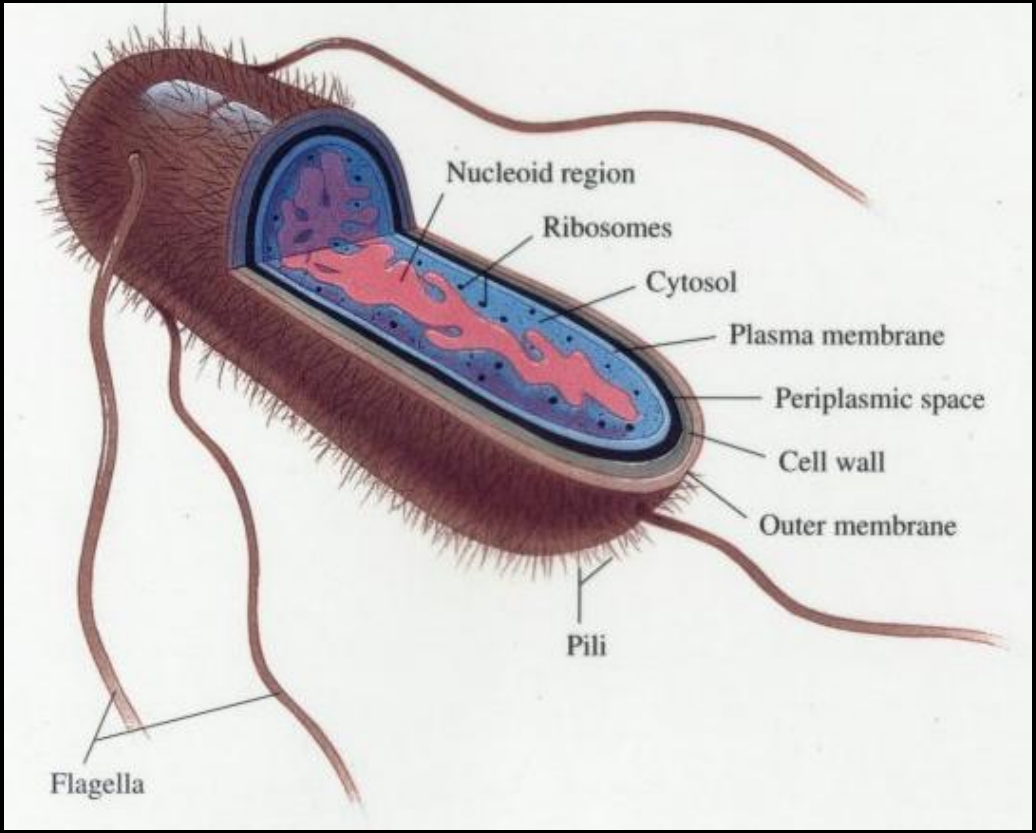
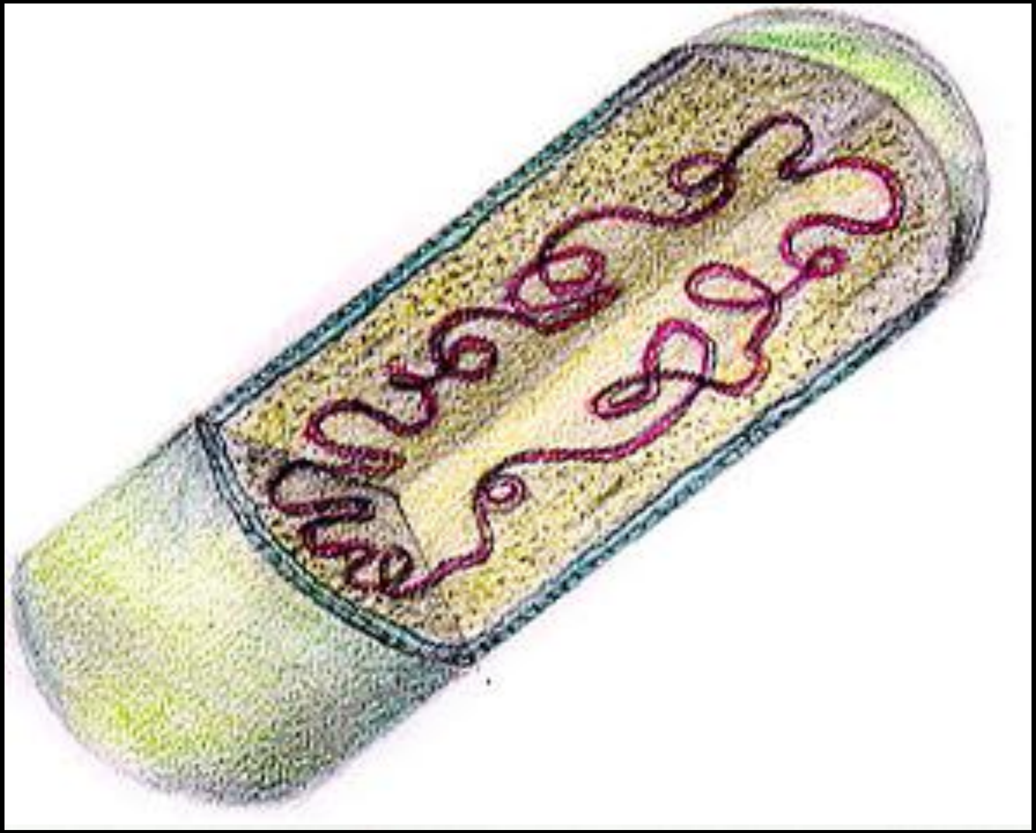


The physics related to the motion of a single protein in a cell is very different (and much slower) than that protein's motion in, for example, water.

EVEN MORE IMPORTANTLY, WHAT IS THE PHYSICS BEHIND THE THE MECHANISMS WITHIN THE CELL THAT ALLOW IT TO METABOLIZE?



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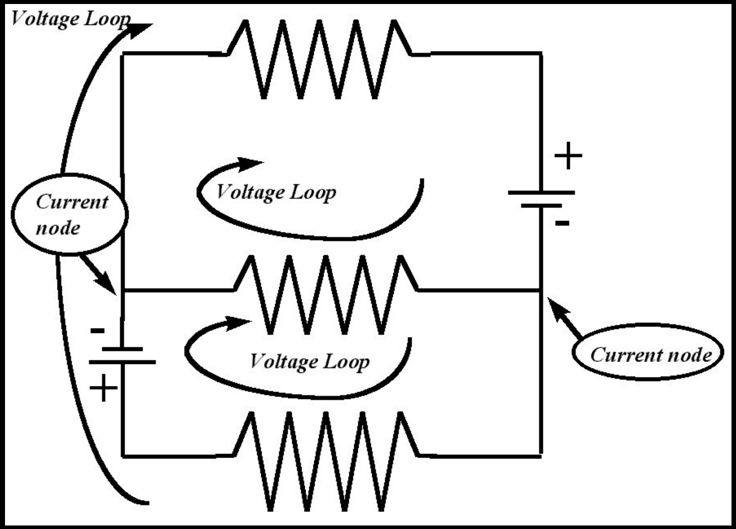
MUCH IN THE SAME WAY THAT ELECTRICAL CIRCUITS ARE DESIGNED TO PERFORM A SPECIFIC TASK,



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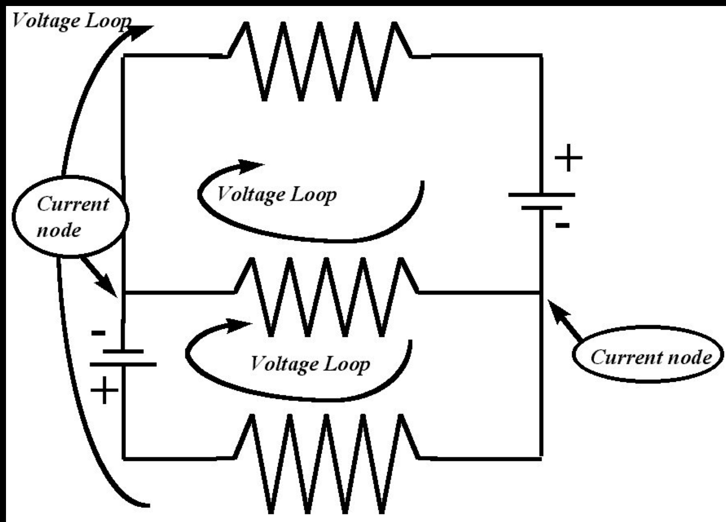

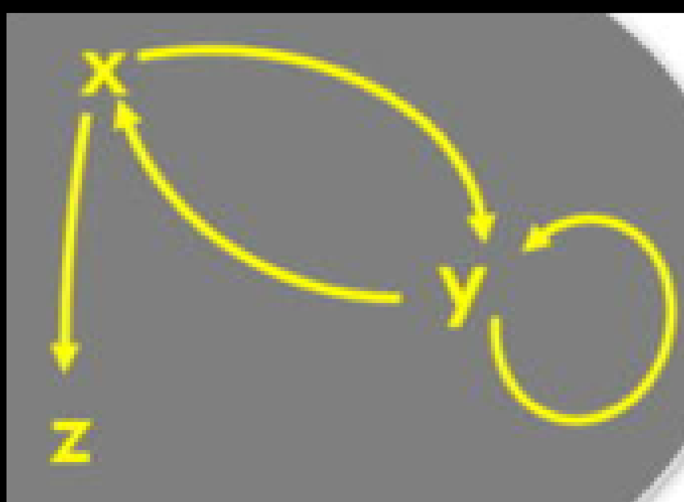

Many bacterial systems rely on dynamic "genetic circuits" to control critical processes.

A major goal of systems biology is to understand these behaviors in terms of individual genes and their interactions.

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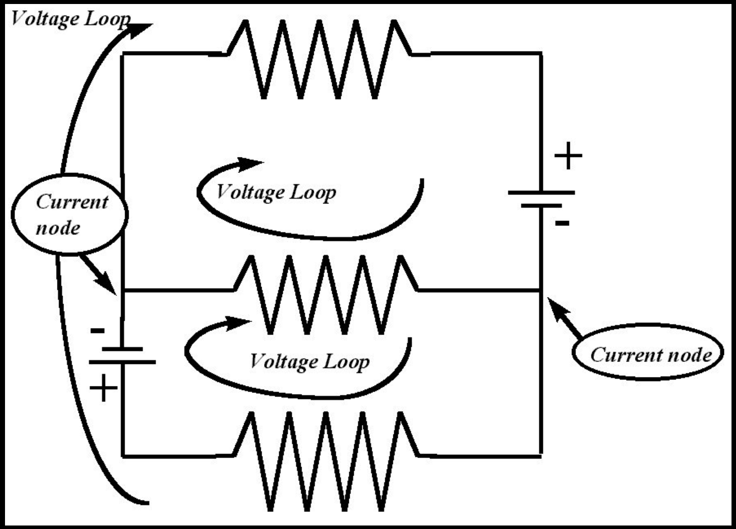

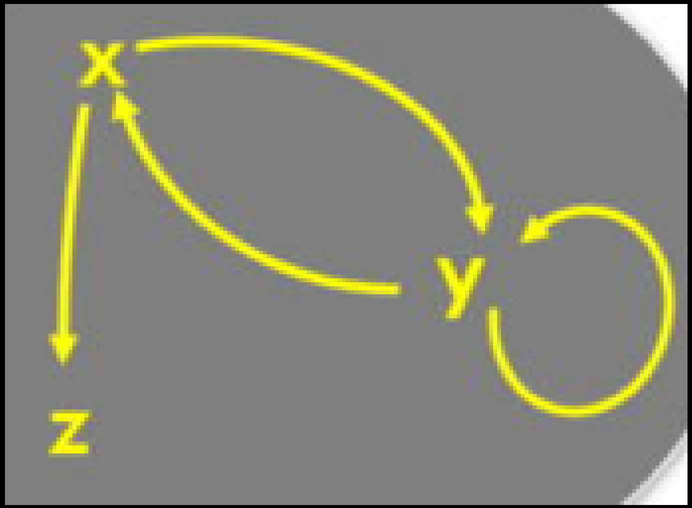

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"Gene circuits" involve specific interactions between genes and proteins.

Circuit level view: genes and gene products interact to generate an ordered behavioral program.

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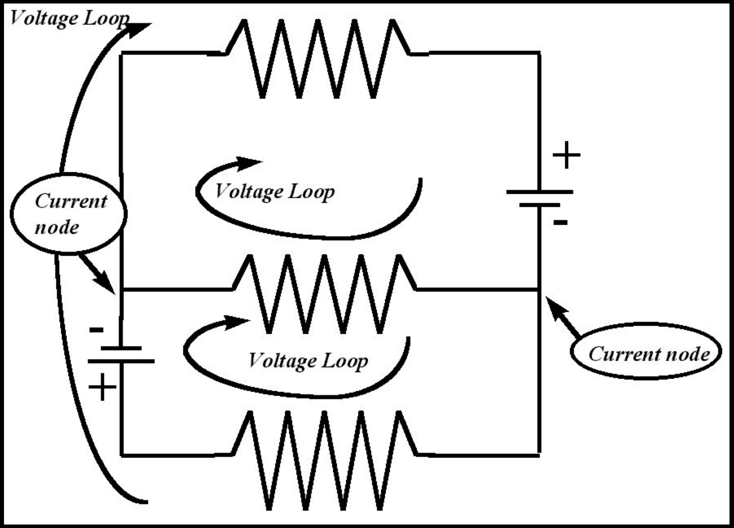

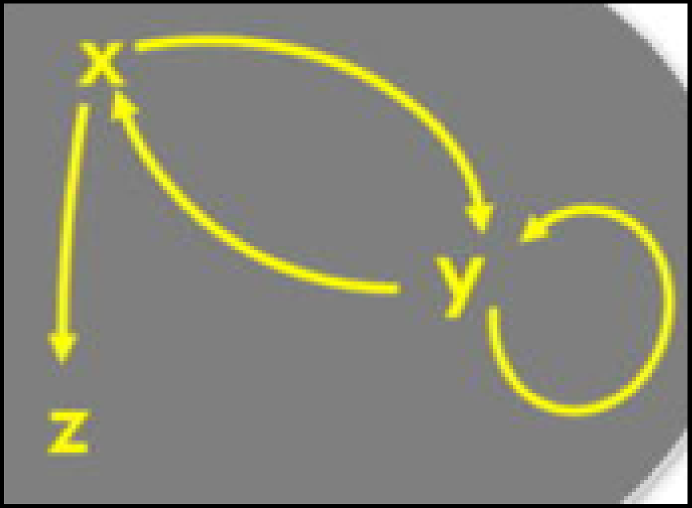

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“Gene circuits” involve specific interactions between genes and proteins.

Circuit level view: genes and gene products interact to generate an ordered behavioral program.

e.g.: protein “x” activates and regulates gene “y” which activates protein “y” which has a positive impact on “x” , which may then activate another gene, “z”.

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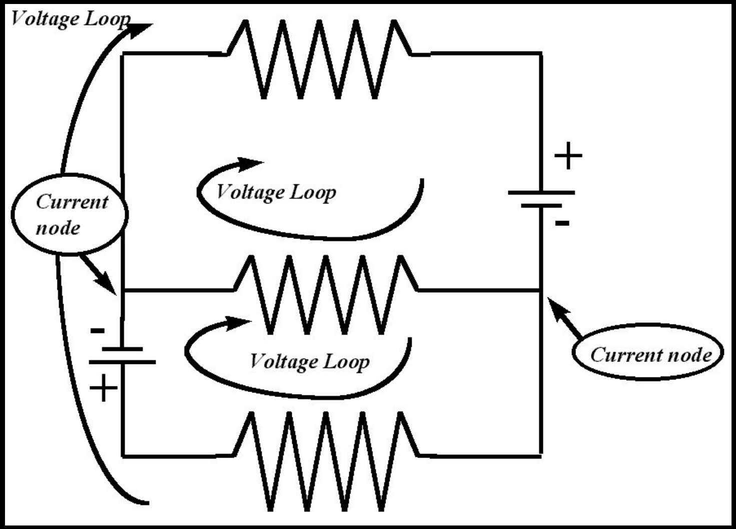

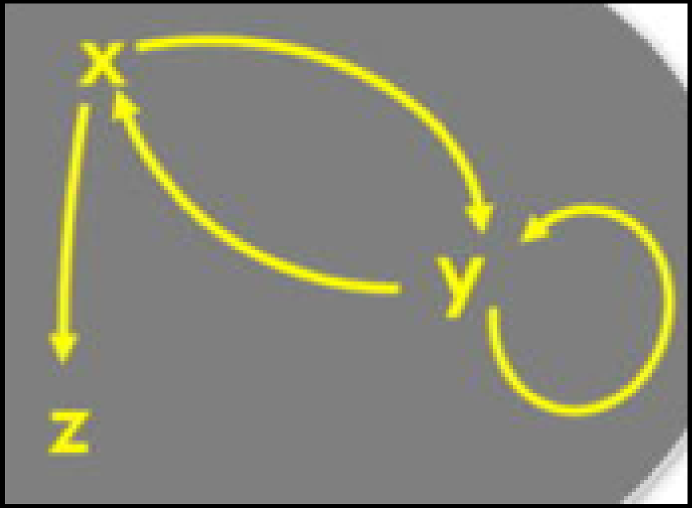

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A major goal of systems biology is to understand these behaviors in terms of individual genes and their interactions.

These circuits (diagrams) represent the *regulatory logic* of the cell.

They are like circuit diagrams, but for *chemical circuits*.

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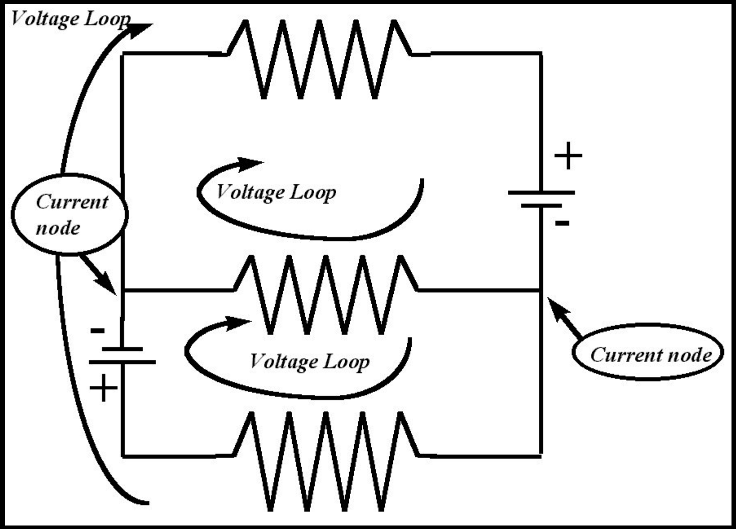

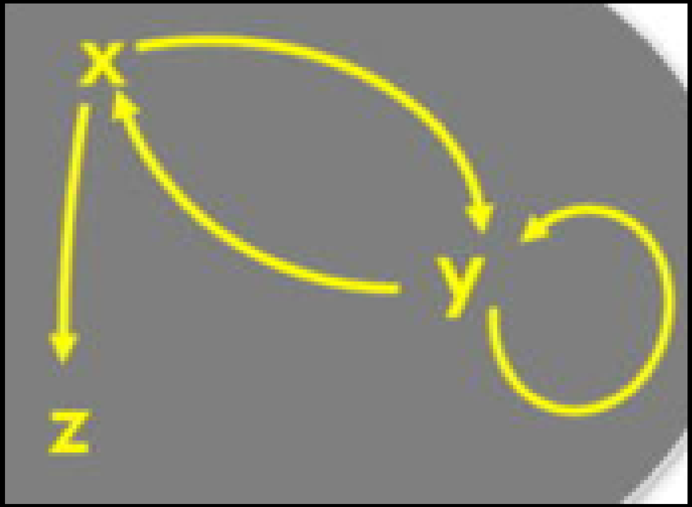

Many bacterial systems rely on dynamic “genetic circuits” to control critical processes.

A major goal of systems biology is to understand these behaviors in terms of individual genes and their interactions.

These circuits (diagrams) represent the *regulatory logic* of the cell.

They are like circuit diagrams, but for *chemical circuits*.

So the question is, “What are the principles of circuit design for *these* kinds of circuits?”

Ohm's Law and Kirchhoff's Laws are used in the analysis of electrical circuits.

What are the principles of these *genetic chemical circuits* that operate inside cells?

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What are the principles of these *genetic chemical circuits* that operate inside cells?

Electrical laws are able to analyze and predict the outcome in a particular circuit, but it is *very difficult* to predict the outcome of genetic chemical circuits!

WHY????

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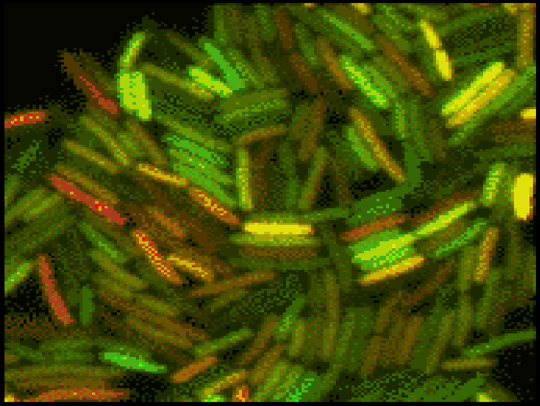

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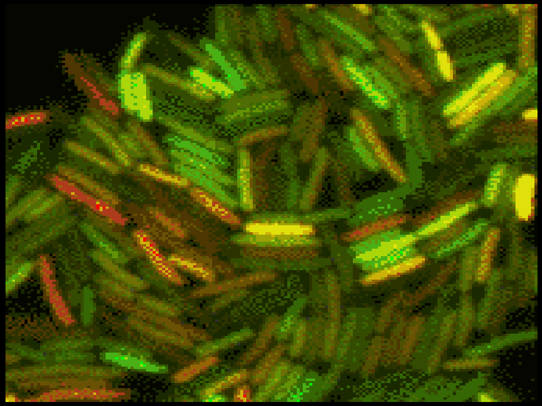
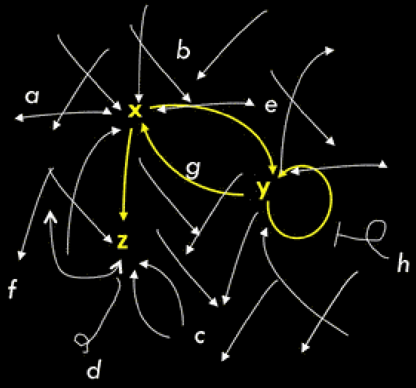
3. These circuits are very COMPLICATED. There are many interactions – some may not be relevant.





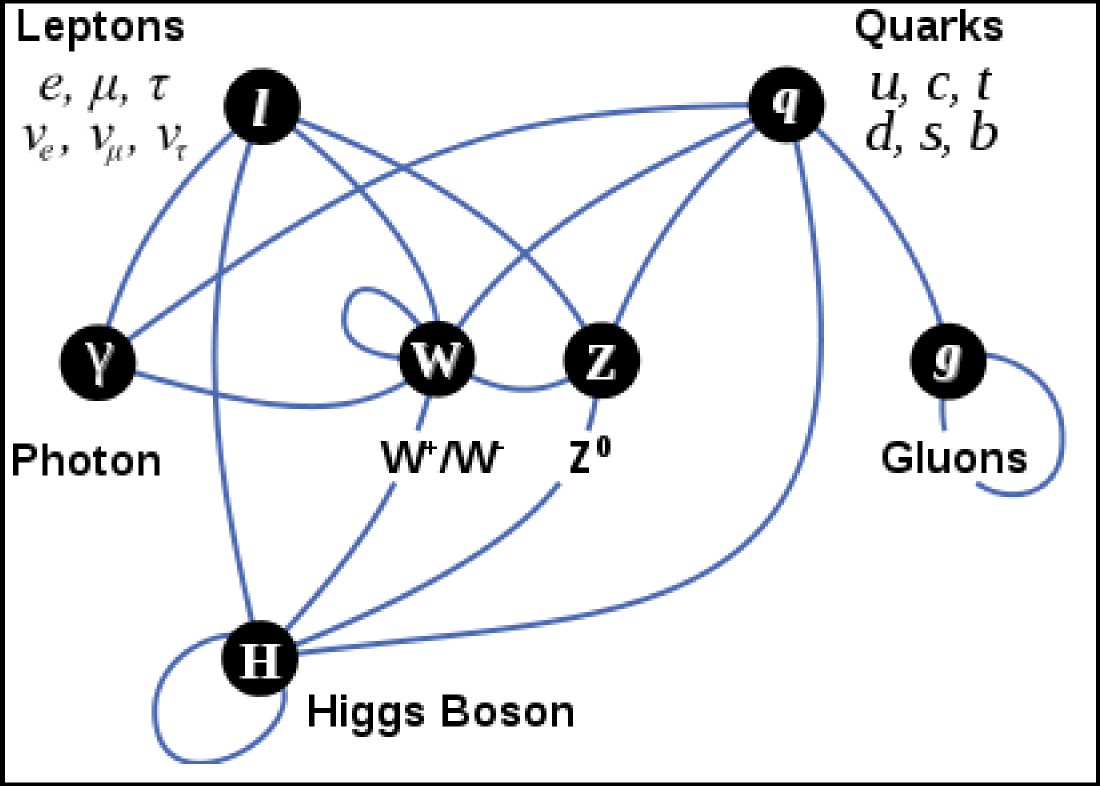
So then, how is it possible to understand cellular behavior, given its "non-deterministic" nature?

So then, how is it possible to understand cellular behavior, given its “non-deterministic” nature?

Is there some “CORE CIRCUIT” that we *can* understand - some basic, simple “module lurking inside of this *really complicated* web of interaction?

ONE FINAL EXAMPLE FROM PHYSICS.

Particle physicists search for the most basic types of high energy particles and how they interact to help us better understand the fundamental forces and particles in nature.



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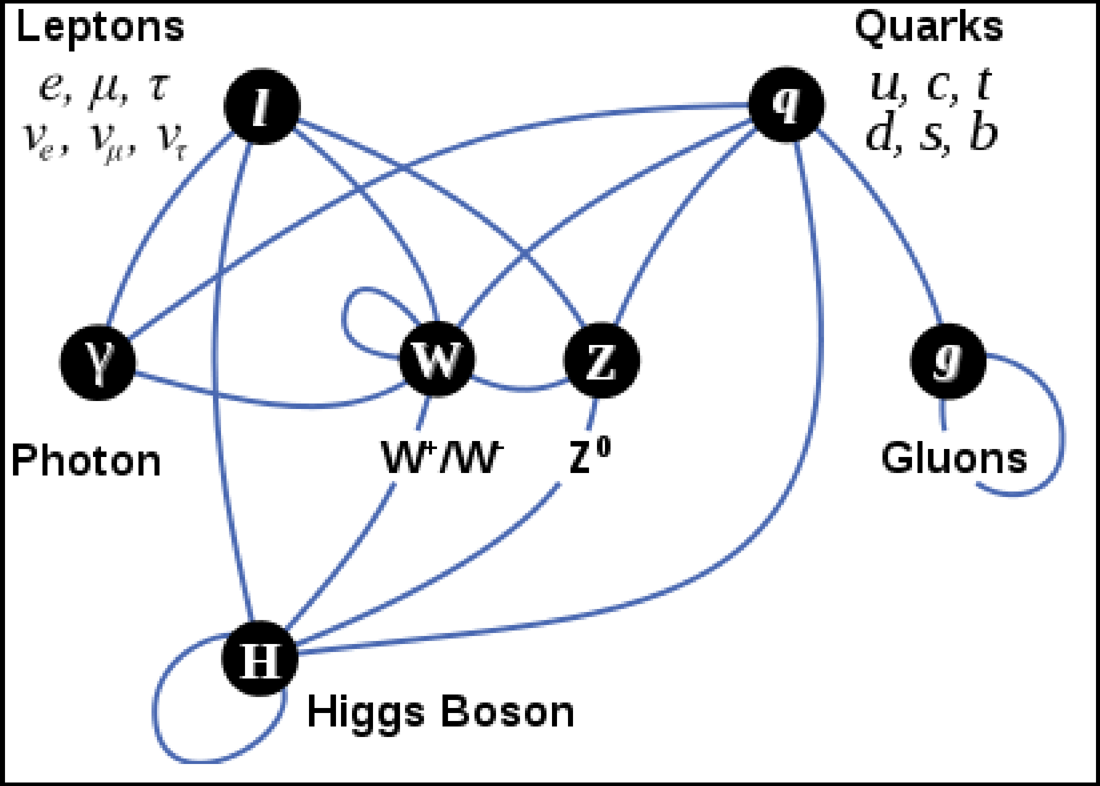
This method of reducing nature's scale to smaller and smaller pieces is known as "atomism."

Molecular and cellular biologists of the 21st century are taking a different approach.



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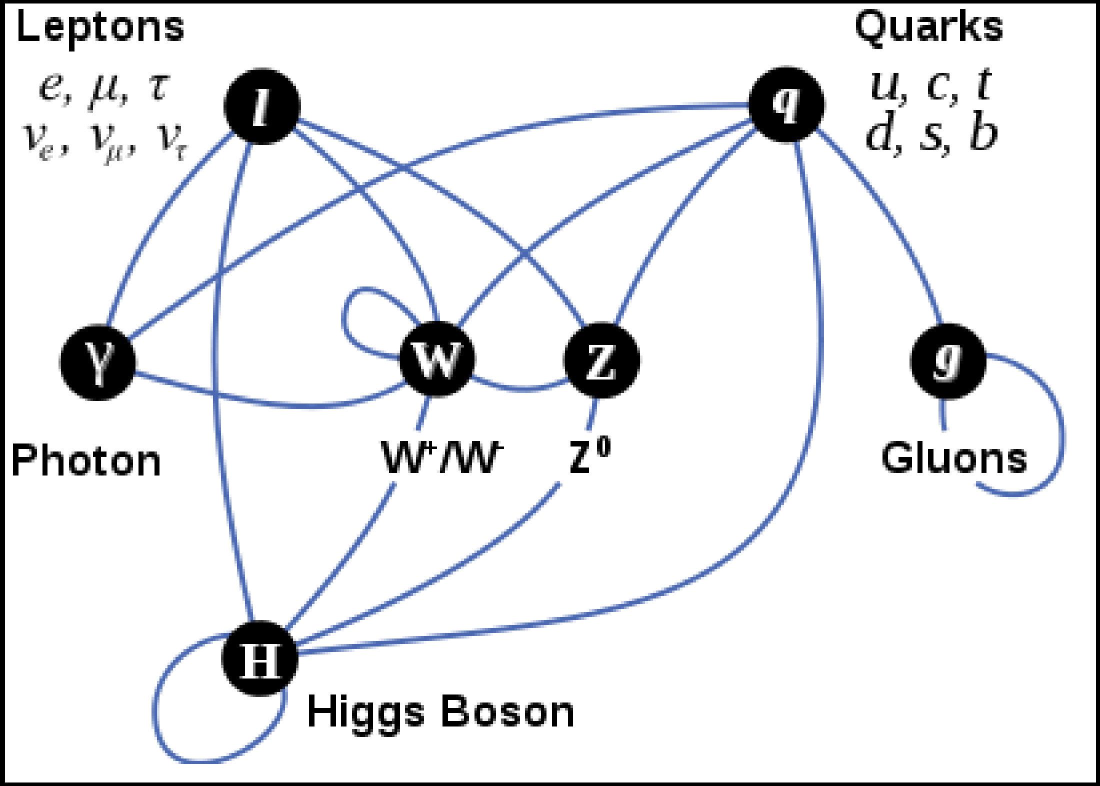
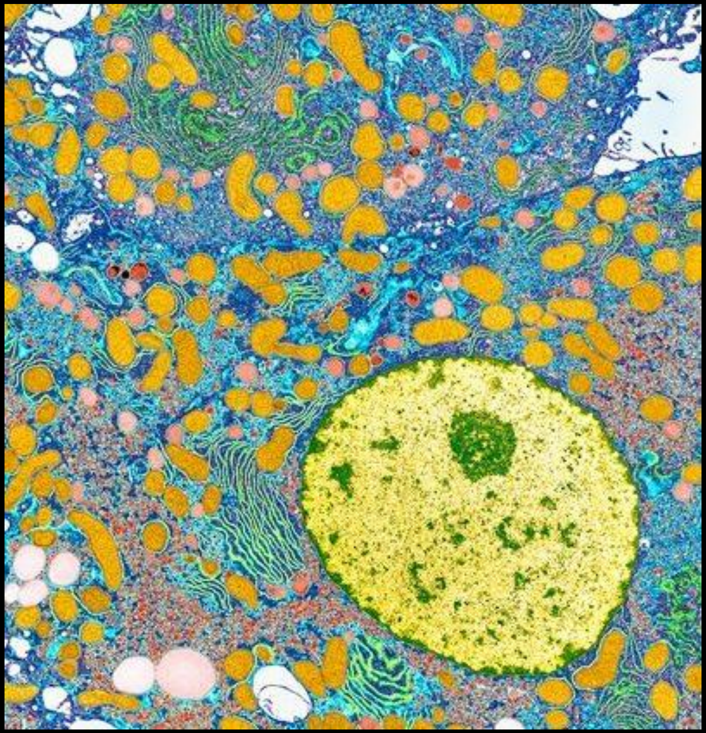


Rather than trying to "deconstruct" complex systems, scientists today are instead looking at a model for a *simple gene circuit* – a "bottom-up" approach to get a quantitative understanding of the principles of gene circuit design - known as SYNTHETIC BIOLOGY.

As was mentioned earlier, one of the functions of a cell is its ability to keep track of time.



Keeping track of time is not only an important human characteristic, but can be applied to all life at the cellular level. It is a very primitive and fundamental property whether the cell is a human cell, a fly cell, or even a bacteria.

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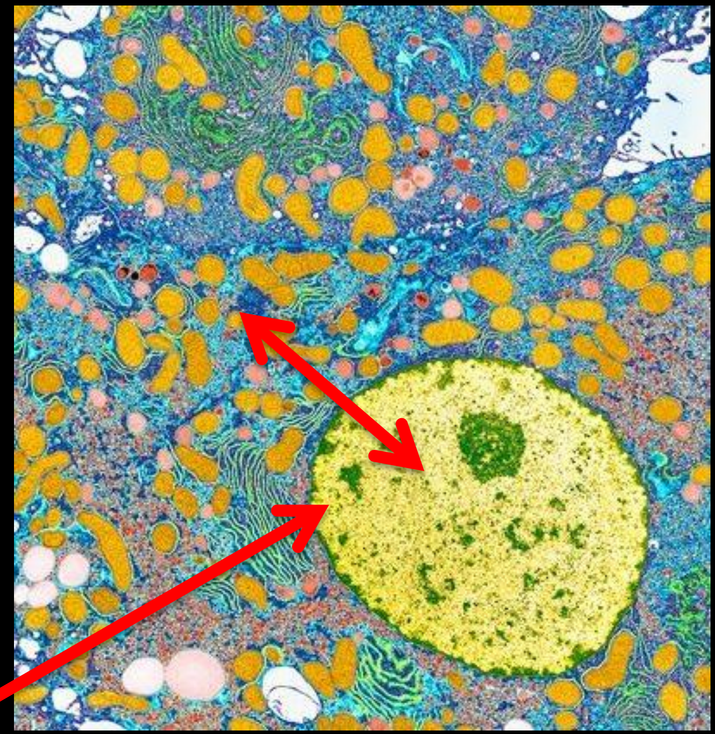

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Cellular clocks work as “feedback loops” where proteins are produced and then go out of the nucleus into the cell. It takes them time to reenter the nucleus, where they are able to regulate (turn off) their own expression, causing the concentration of those proteins to gradually decline until they can no longer turn themselves off; then they begin a new cycle.

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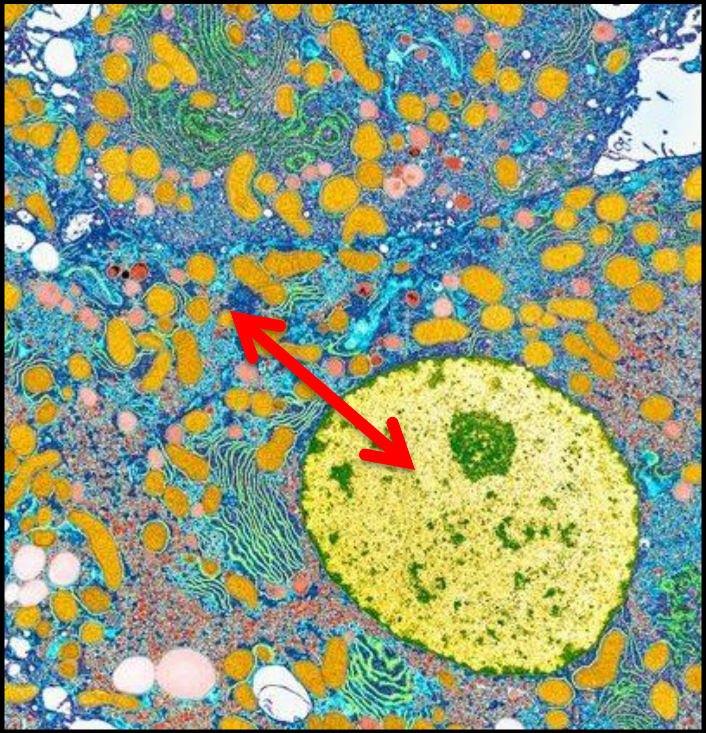

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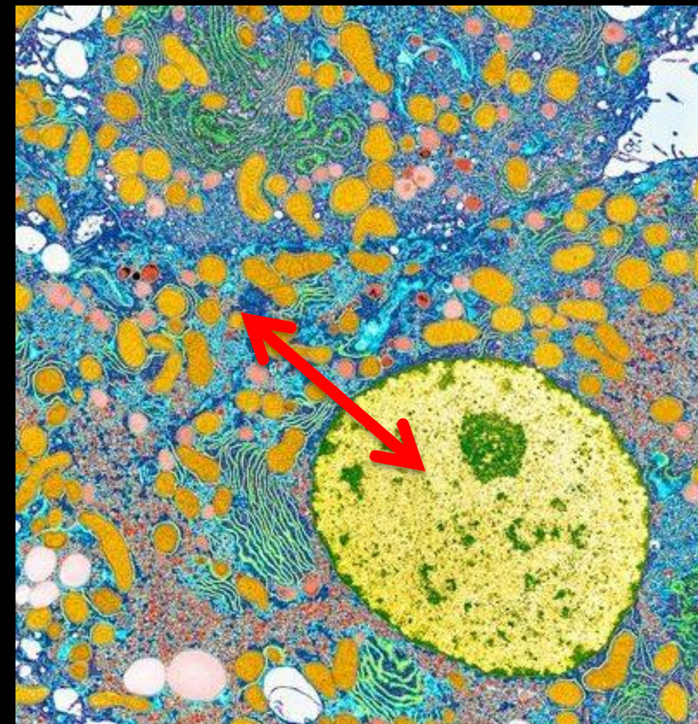

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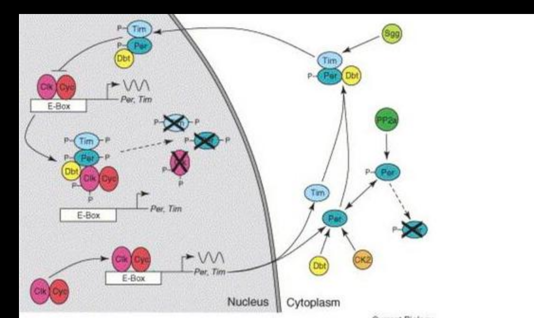
In this manner, cells have evolved accurate clock circuits!



Drosophila circadian clock

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HERE'S AN ANALOGY TO HELP YOU UNDERSTAND HOW NEGATIVE FEEDBACK LOOPS WORK.

NEGATIVE FEEDBACK LOOPS

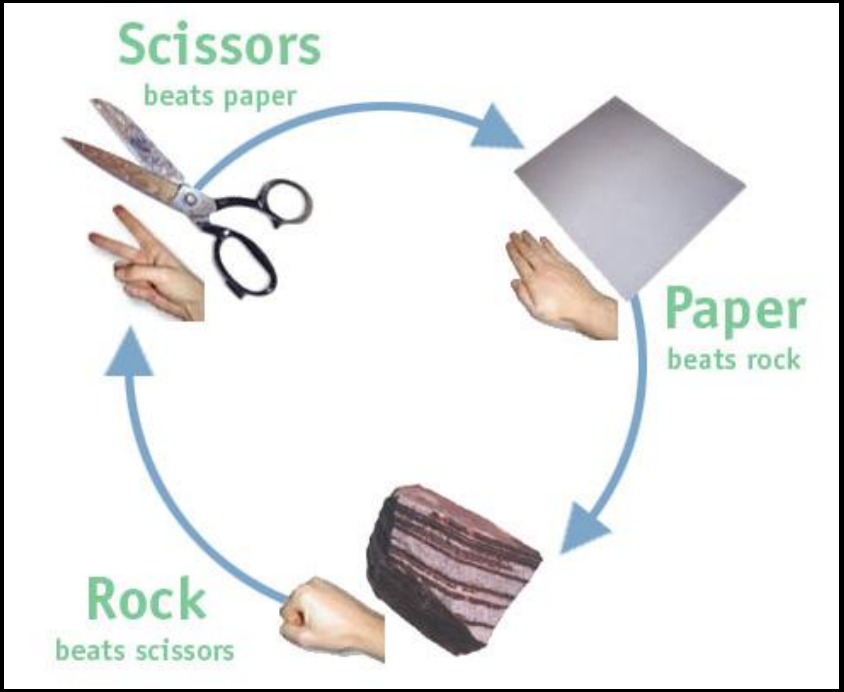
In the game "ROCK, PAPER, SCISSORS," the objective is to select a gesture which defeats that of the opponent. Gestures are resolved as follows:

Rock blunts or breaks scissors: that is, rock defeats scissors.

Scissors cut paper: scissors defeats paper.

Paper covers, sands or captures rock: paper defeats rock.

If both players choose the same gesture, the game is tied and the players throw again.



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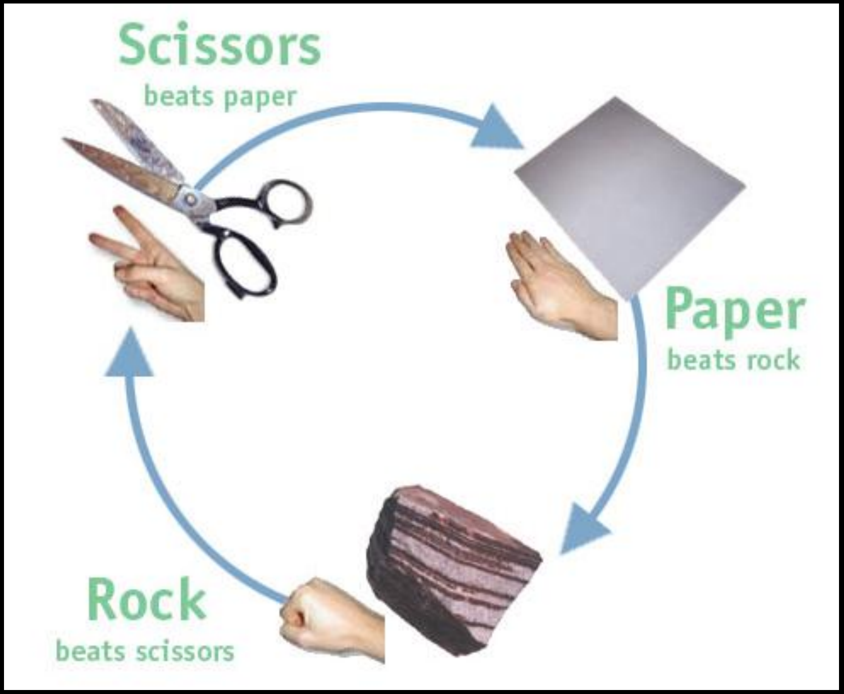

A lot of rocks would "kill" a lot of scissors, which, in turn lead to in increase in paper. The increase in paper would "kill" the rocks, and then the rocks would go away, allowing for the scissors to start building up again, etc.

The cycle (time to take for this to happen) can be thought of as an "oscillation."

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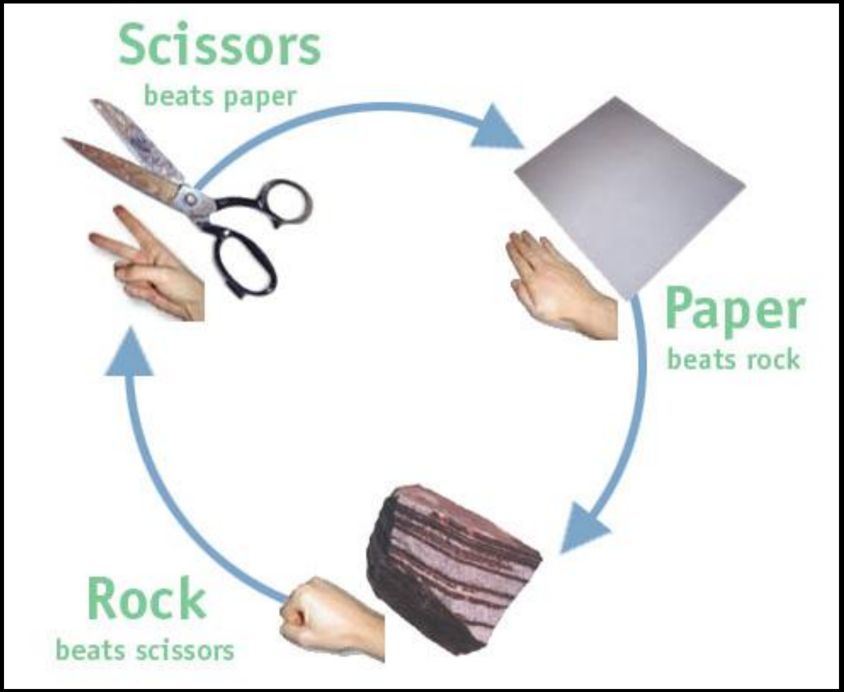

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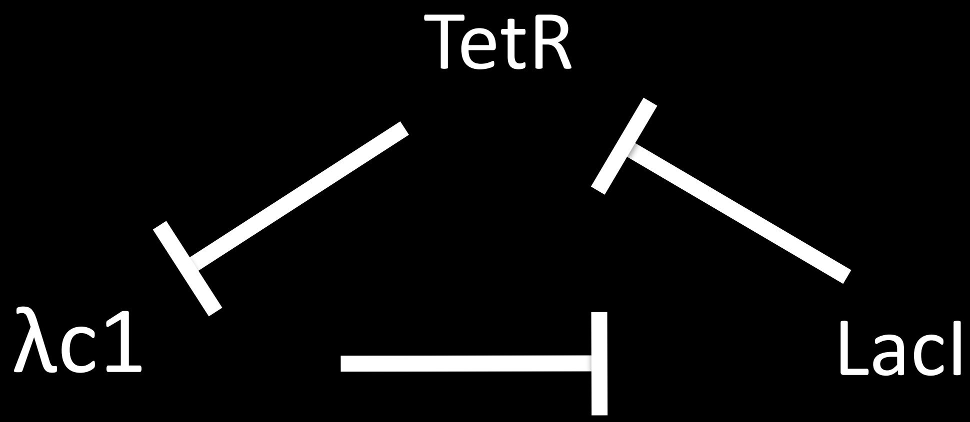
THIS TYPE OF SYSTEM CAN BE MADE OF GENES!

USING 3 WELL-UNDERSTOOD GENES:

"TetR" (this gene makes some bacteria resistant to the antibiotic tetracyclene)

"λc1" (this gene comes from the virus that infects e-coli)

"LacI" (this gene allows e-coli cells to metabolize lactose [milk sugar])



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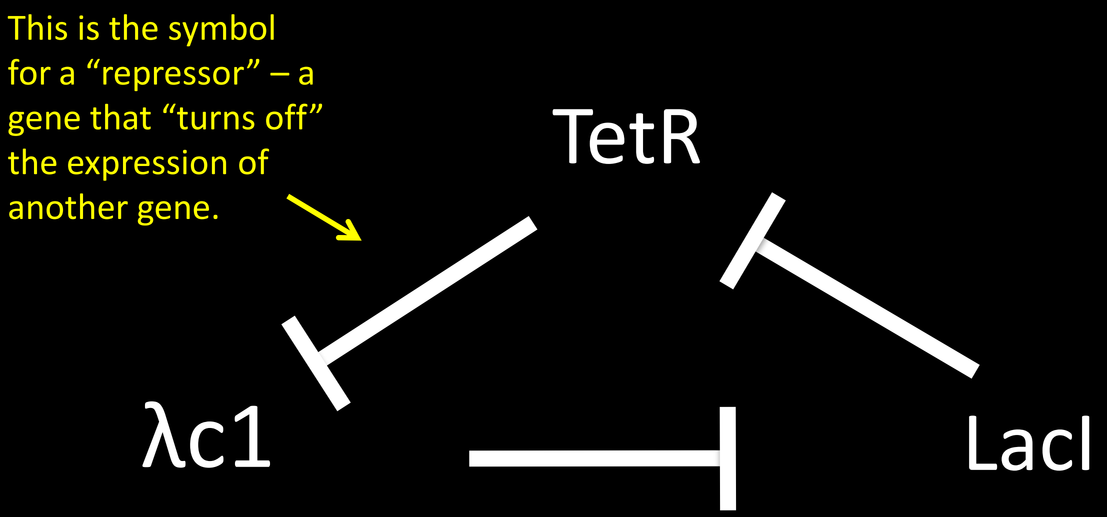

Using a green fluorescent protein in this plasmid allows visual distinction between this and other proteins in the organism – which means that the oscillation rate of these green plasmid proteins can be monitored microscopically.

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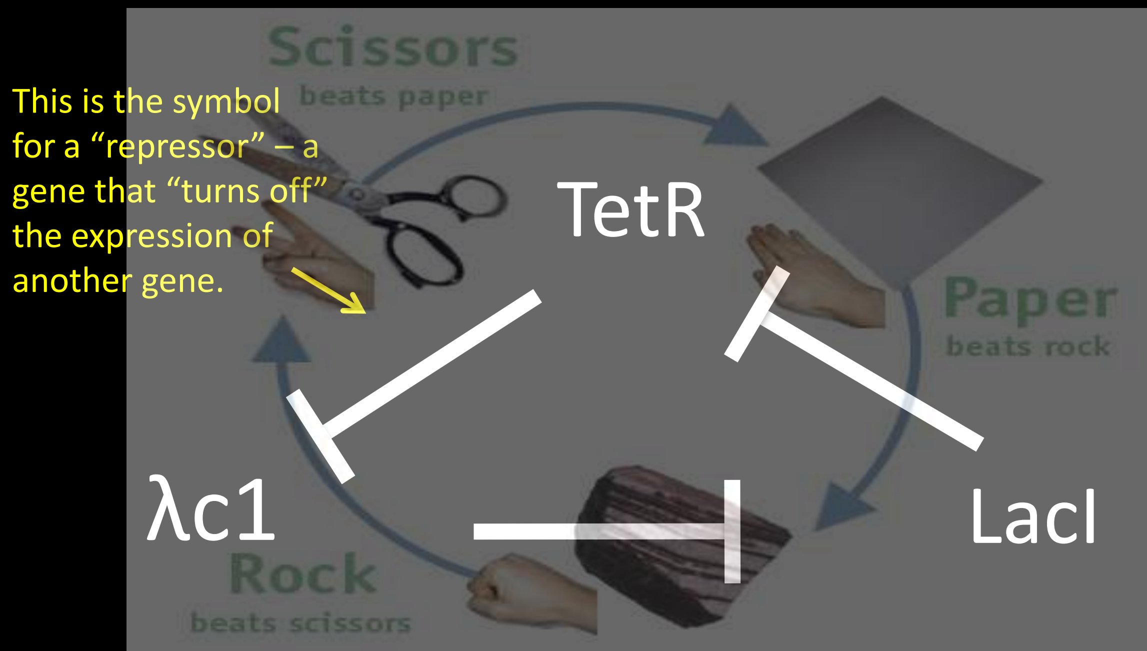

This combination of proteins, known as a “plasmid” is what builds a “circular” DNA molecule known as a “repressilator” - A synthetic genetic circuit designed to produce clock-like oscillations in the levels of is components. The circuit consists of a ‘rock-scissors-paper’ feedback loop of three repressors, in which the first represses the expression of the second, the second the third, and the third the first.

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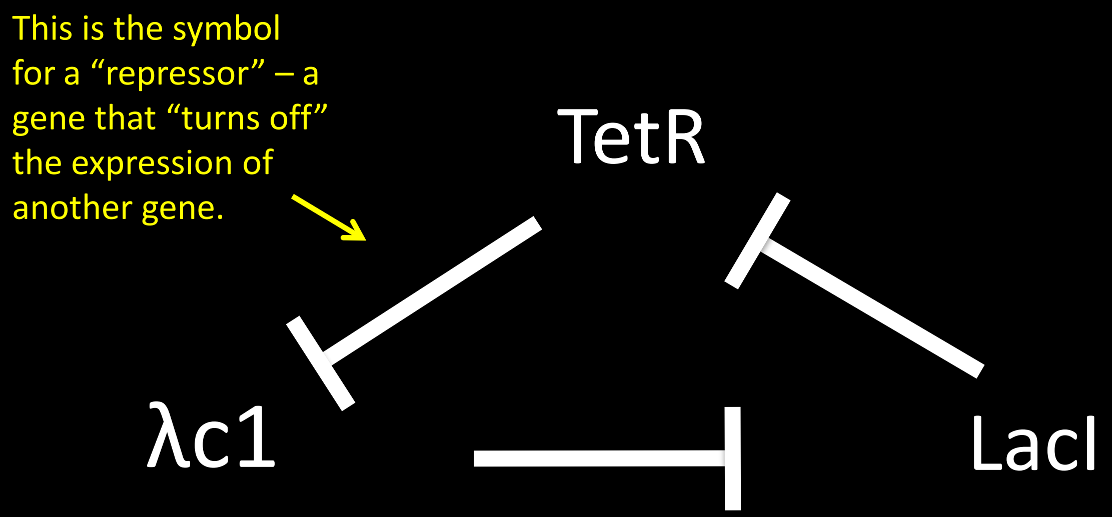
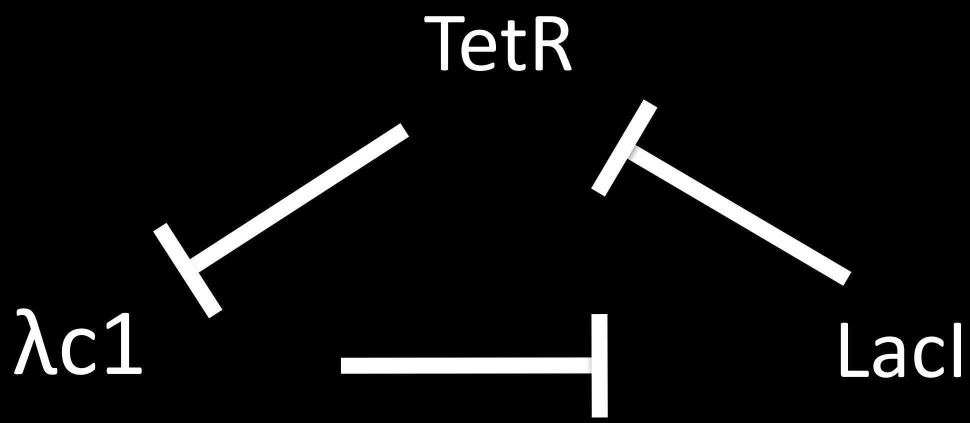
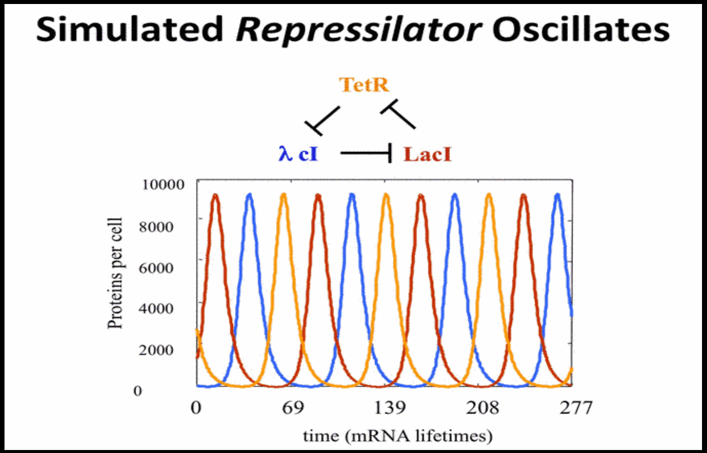
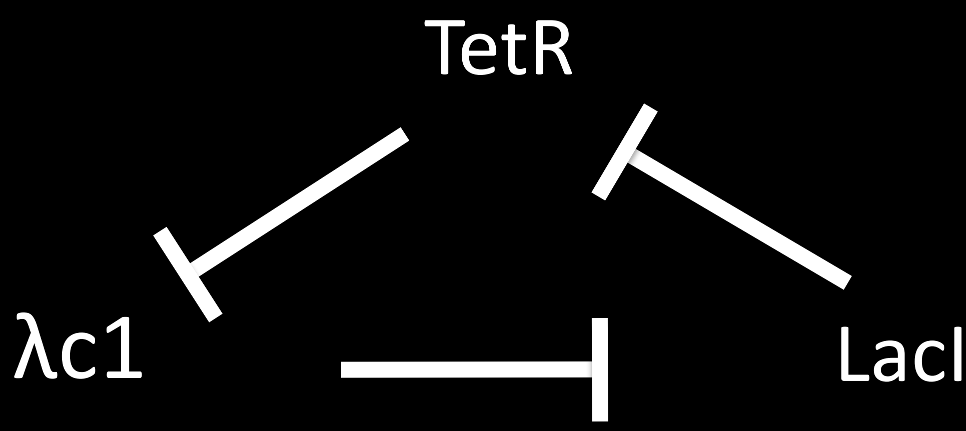


SO WHAT DOES THIS MEAN???



It is possible to program behavior in cells!!





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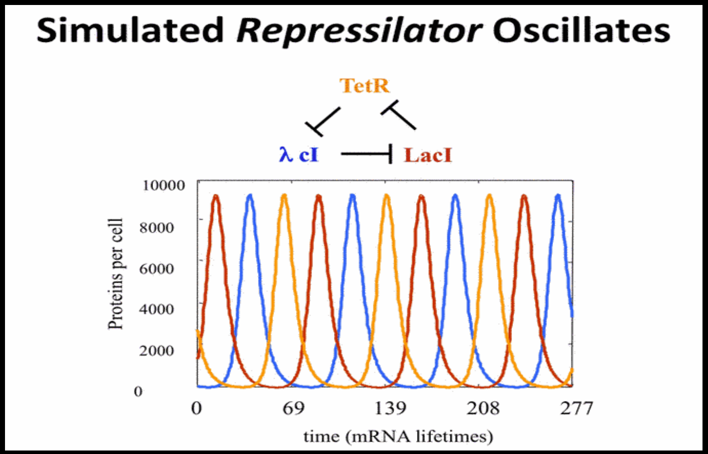
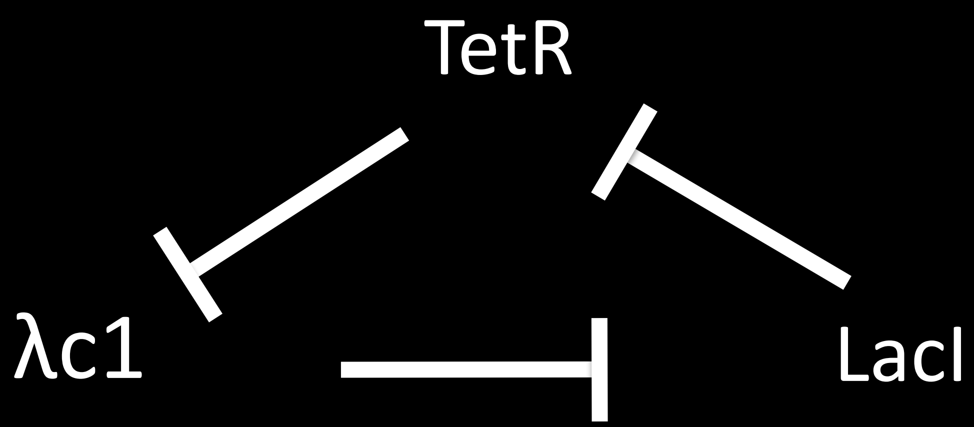
Genetic “circuits” can be designed to create a specific oscillation inside of a cell.





It is possible to program behavior in cells!!

The cyclic nature of this feedback loop can be measured in movies (time-lapse microscopy) of the event using green fluorescent protein.

However, there may be much variability in the frequency, leading to the possibility that components of cells are subject to STOCHASTIC FLUCTUATIONS (inherently random) and therefore, NON-DETERMINISTIC.

THE CELLS MAY BE DIFFERENT FROM EACH OTHER (ON A MICROSCOPIC LEVEL) – SO, TWO SIMILAR CELLS MAY REACT DIFFERENTLY TO THE SAME STIMULUS.

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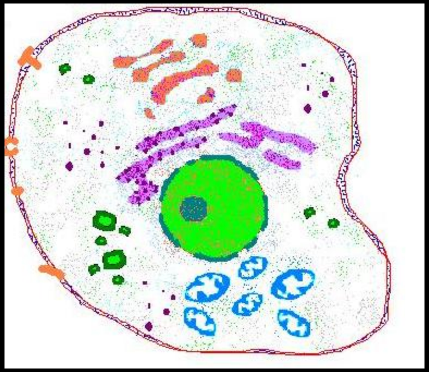
But they never really do!

In the same manner, two "identical" cells (even sister cells) would be impossible at the molecular level!

So it would be impossible to determine if the same stimulus would produce the same effect!

How can we tell then if cellular functions given the same stimulus, are stochastic or deterministic?



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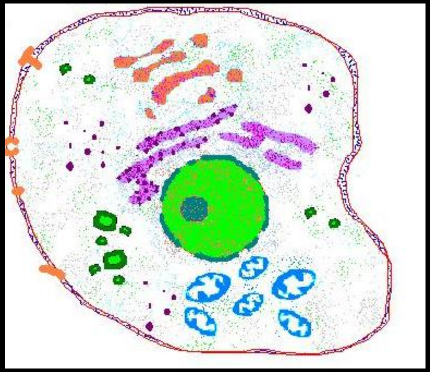

Stochastic
(random)

Deterministic
(predictable)

Researchers today ***can*** take *two identical genes* and put them in the same cell.

One of these genes is slightly altered (change one letter of one gene and change its color from green to red).

Since the cell can’t tell the difference, after some regulatory process takes place, compare the colors of the gene expressions.

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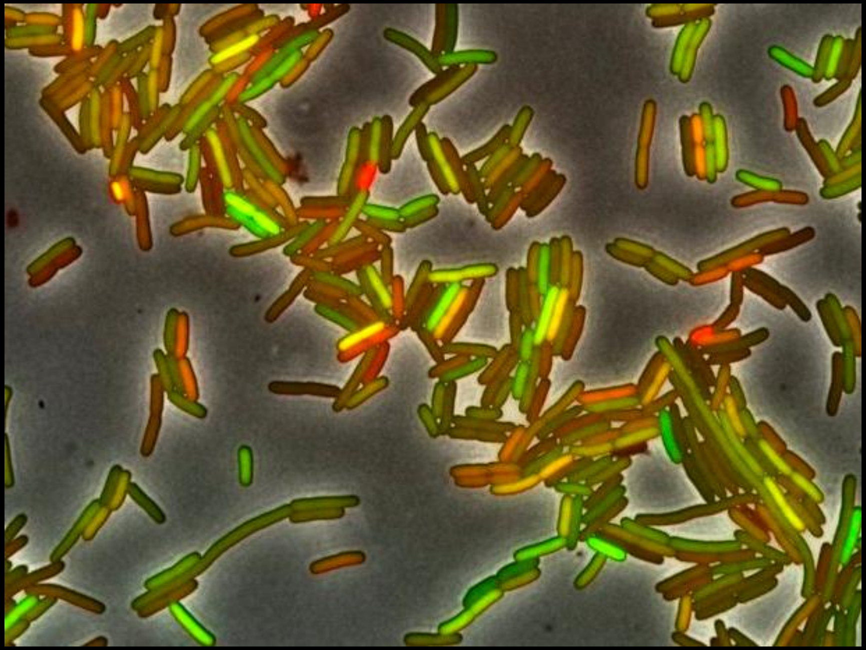
In a stochastic system, some cells would appear very green and others very red.

When this was done in the laboratory using e-coli cells, the end result looked like this:



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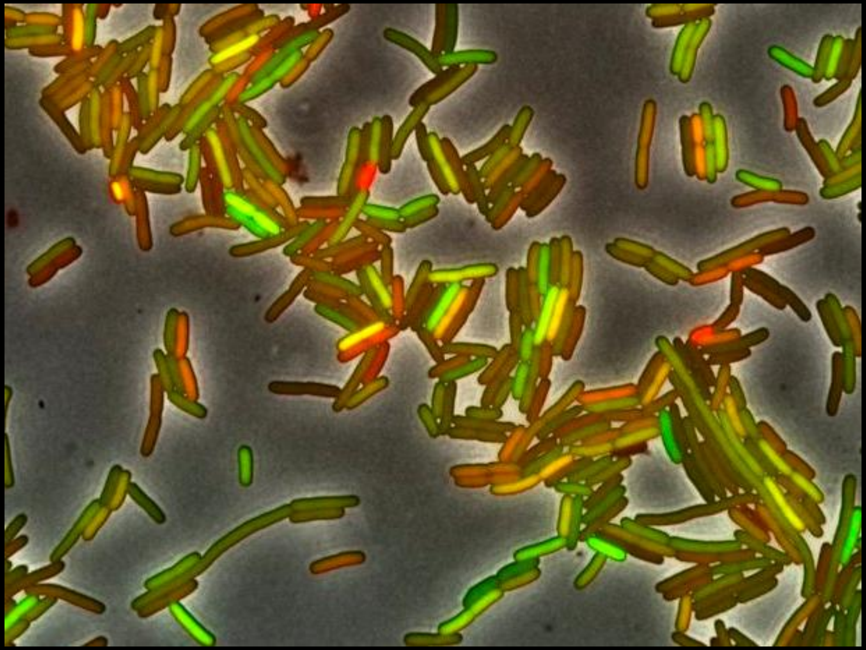

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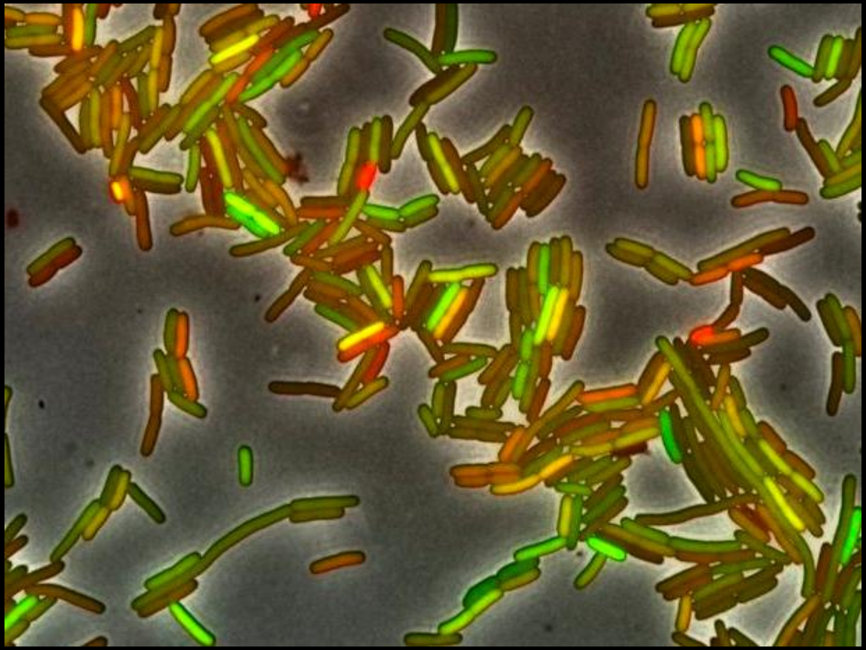

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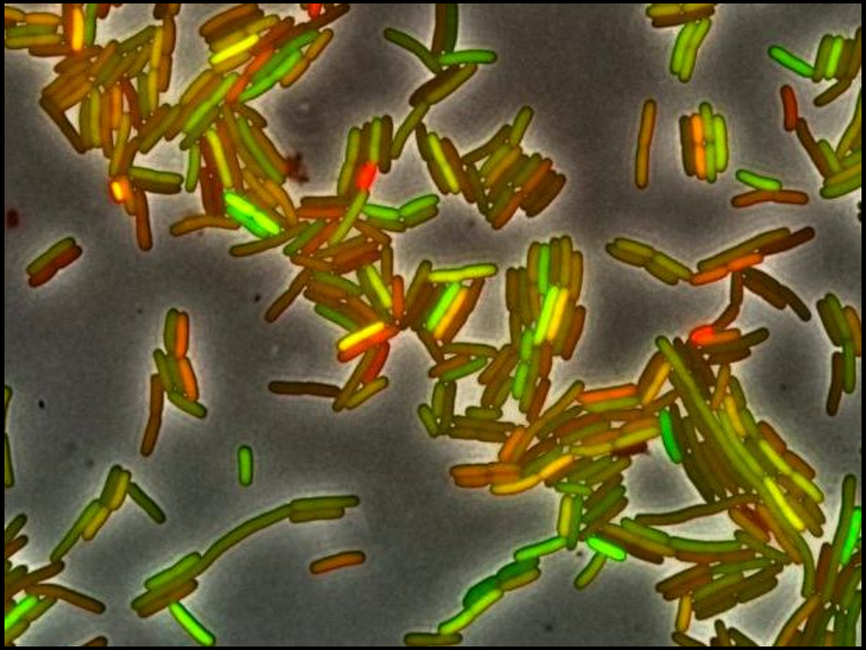
These cells can be analyzed quantitatively by measuring the amount of red and green in each cell, therefore establishing correlations.



A surprising recent discovery has shown that under some conditions, the cell can also be *very deterministic*!

HOW IS THIS POSSIBLE?

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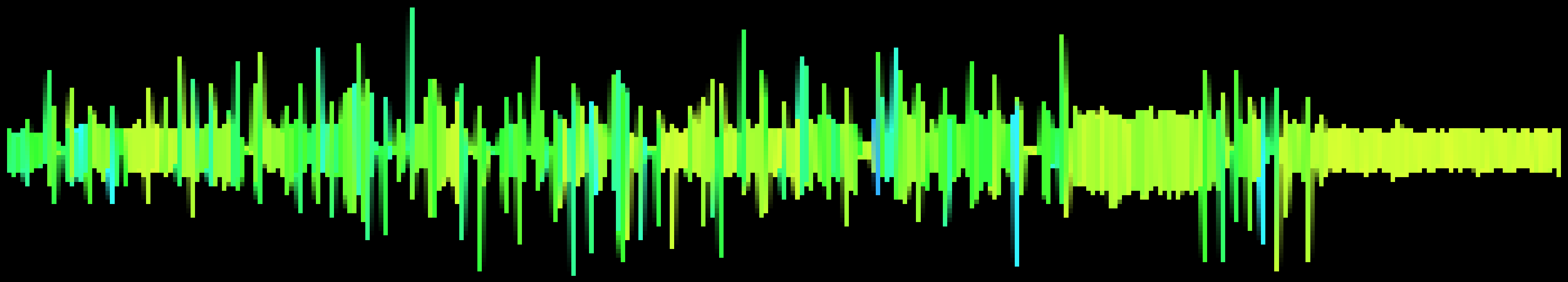
In physics, "noise" is a random fluctuation in an electrical signal – a characteristic of all electronic circuits.



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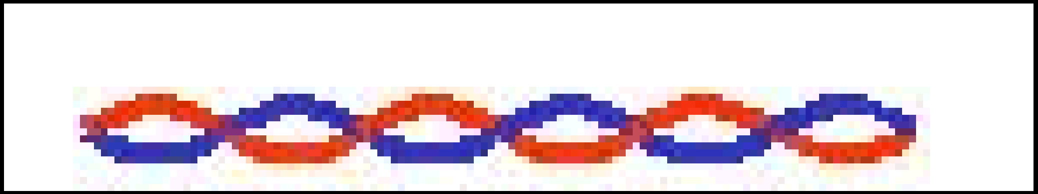
NOTE: Although electrical noise is common in physics applications, noise may also pertain to unwanted background interference, either acoustic or visual, analog or digital. Thermal noise may also be generated due to heat within a conductor.



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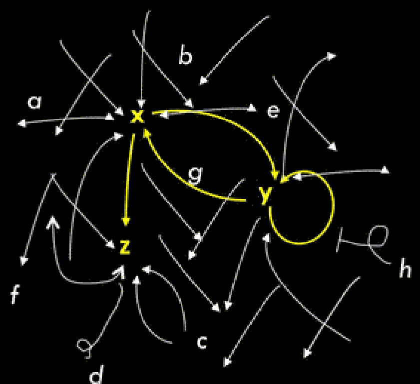
Similarly, within each living cell there are myriad "genetic circuits," each composed of a distinct set of biochemical reactions that contribute to some biological process. Randomness in those reactions contributes to biological noise, technically referred to as stochastic fluctuations.



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Essentially, noise in biological systems is directly related to the stochastic fluctuations, not unlike the quantum fluctuations in a QM field.

Noise in one particular genetic circuit might be *beneficial*, linked to a process that controls cell fate.

In a series of theoretical calculations and actual experiments, researchers found that the particular circuit they investigated appears to have evolved in this bacterium to amplify cellular noise.

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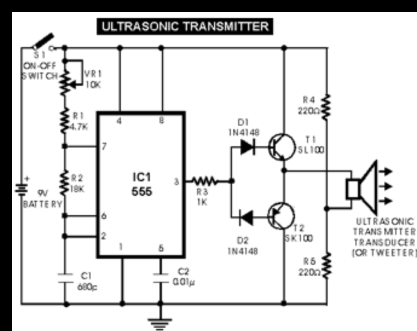
This is like examining each capacitor or switch in an electrical circuit in an attempt to understand the function of the electrical device in which the circuit is housed.



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They determined that by “dampening” the noise level within the bacterial cells, they could prevent the cells' transformation between states, essentially "tuning" cellular behavior.

Someday, controlling specific cellular functions could be as easy as

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Tuning in a radio station!

It has also been found that noise can play an important role in the way cells communicate with each other!

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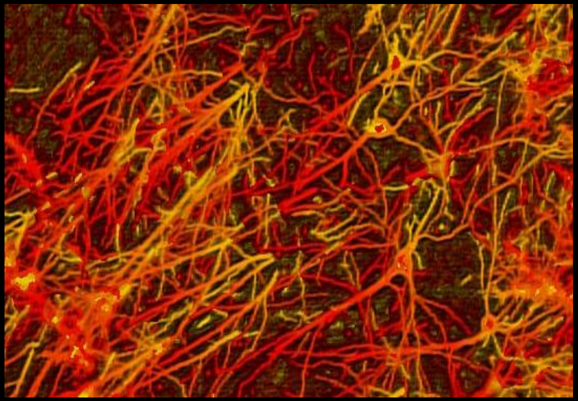

NEURONS in the brain

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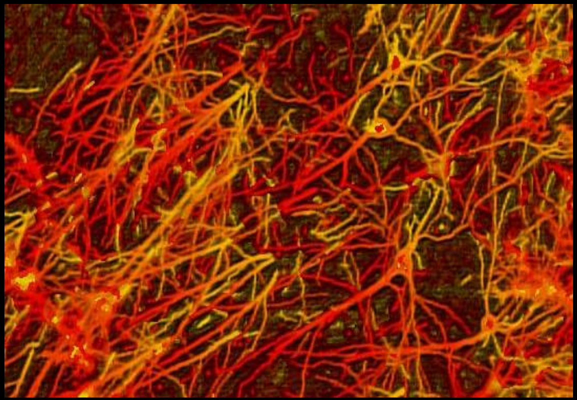
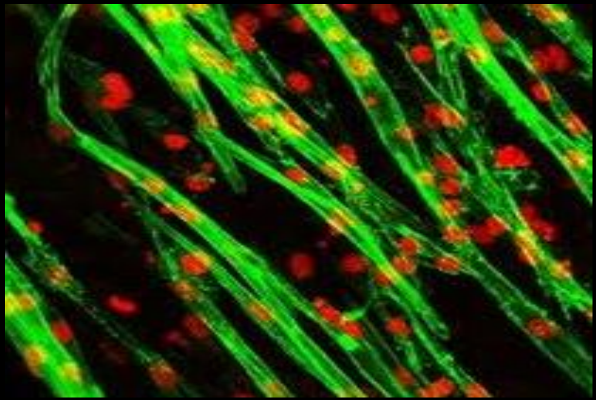


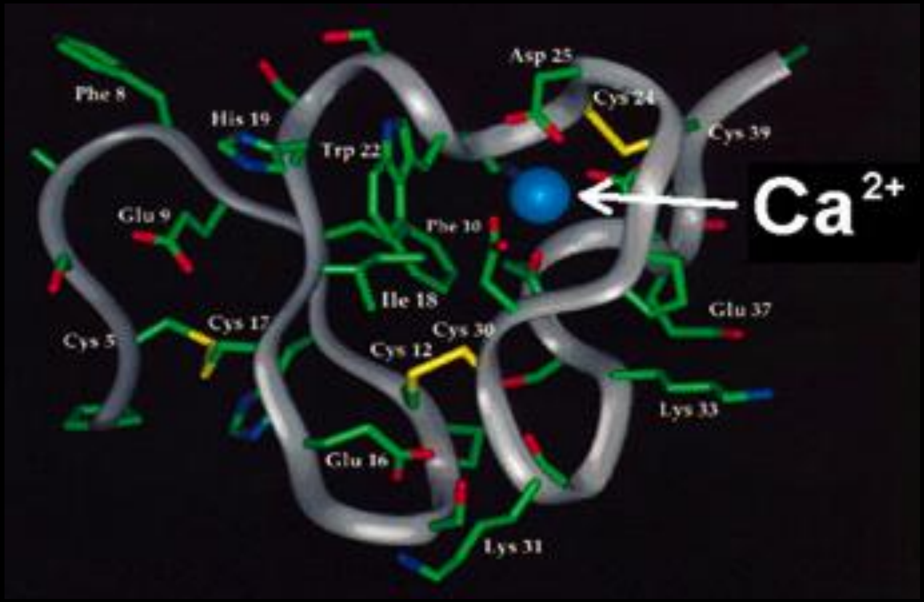
NEURONS in the brain



HEART Cells

It has also been found that noise can play an important role in the way cells communicate with each other!

Cells use SIGNALING CIRCUITS (pathways) to do this. Some examples:



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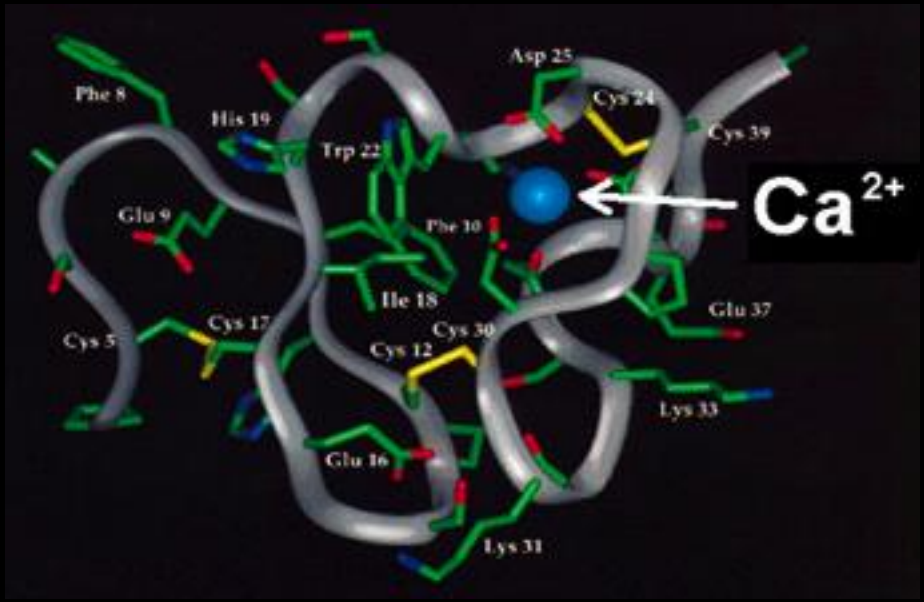

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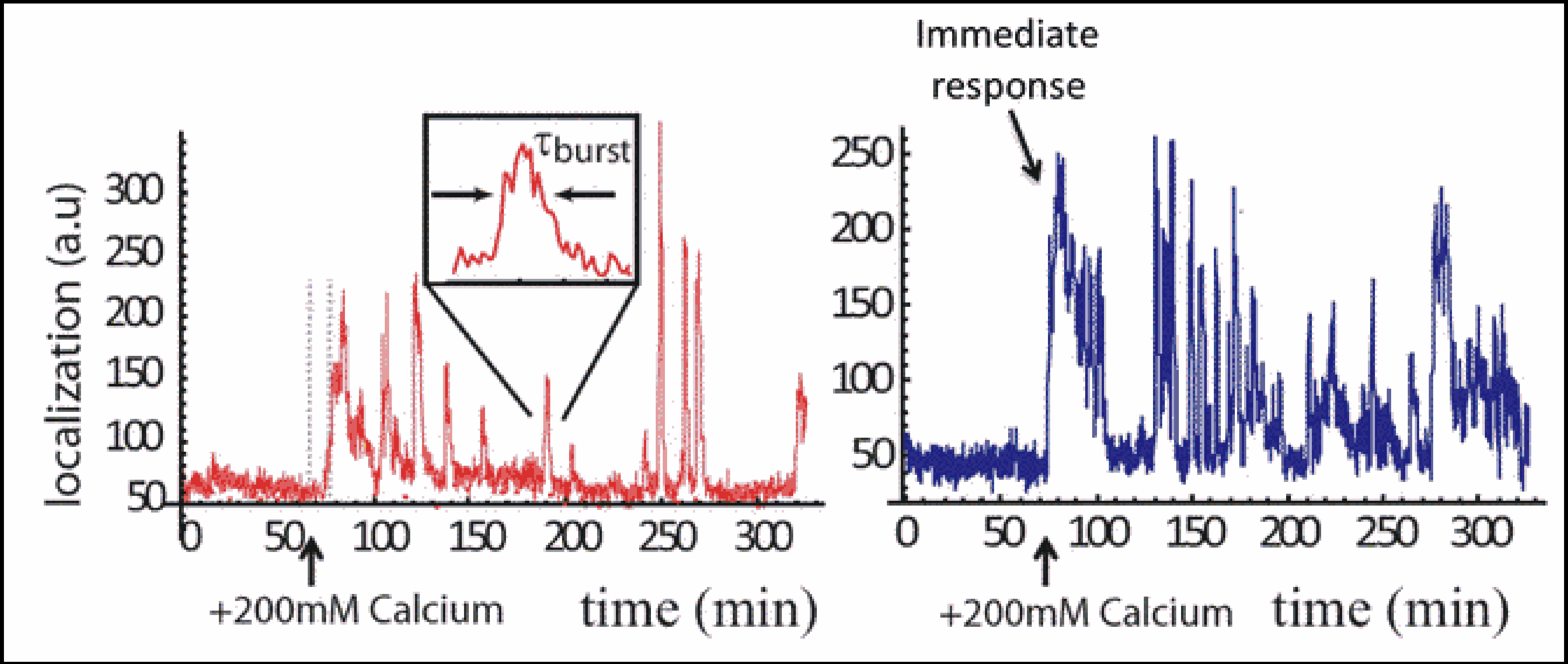
NEW GENES PRODUCED AS A RESULT CAN BE OBSERVED AND MEASURED. (e.g. Crz1)

AS THE NUMBER OF CALCIUM IONS CHANGE, THE NEW GENES PRODUCED ARE LOCALIZED IN "STOCHASTIC BURSTS."



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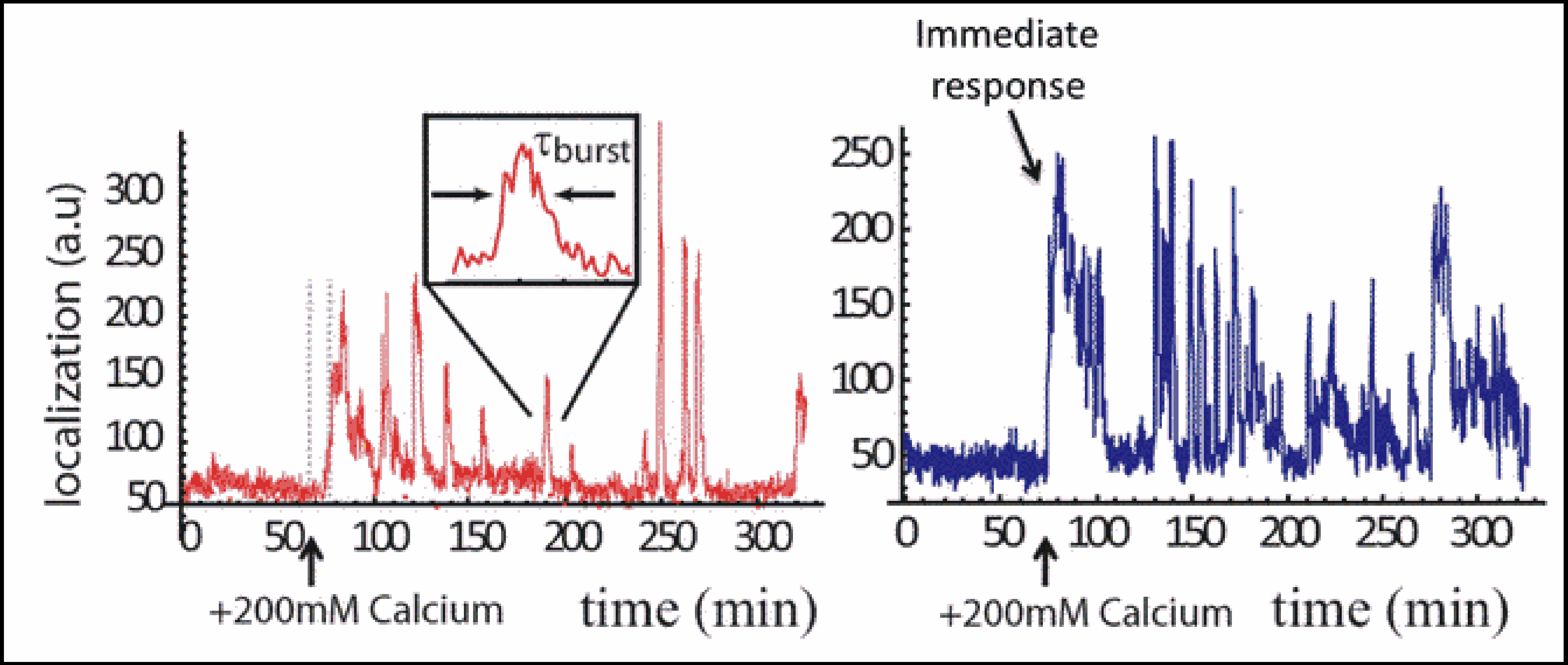

As Ca ions increase, the frequency of the bursts also increase (not the duration). This higher input -> higher frequency implies that this is a *frequency modulated (FM)* signaling system!

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(As opposed to Amplitude Modulation.)

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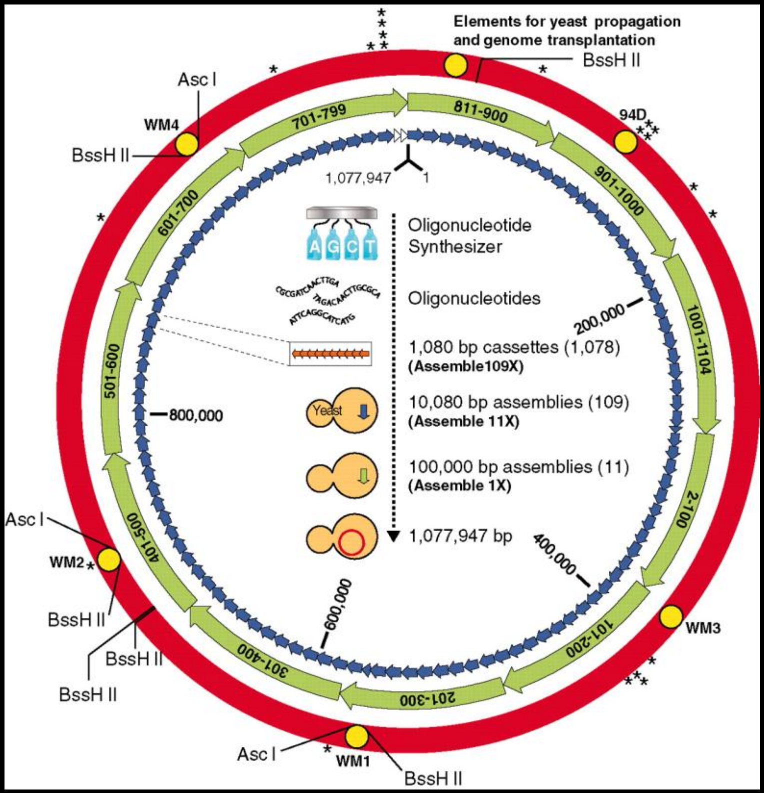
The assembly of a synthetic M. mycoides genome in yeast.



D G Gibson et al. Science 2010;329:52-56

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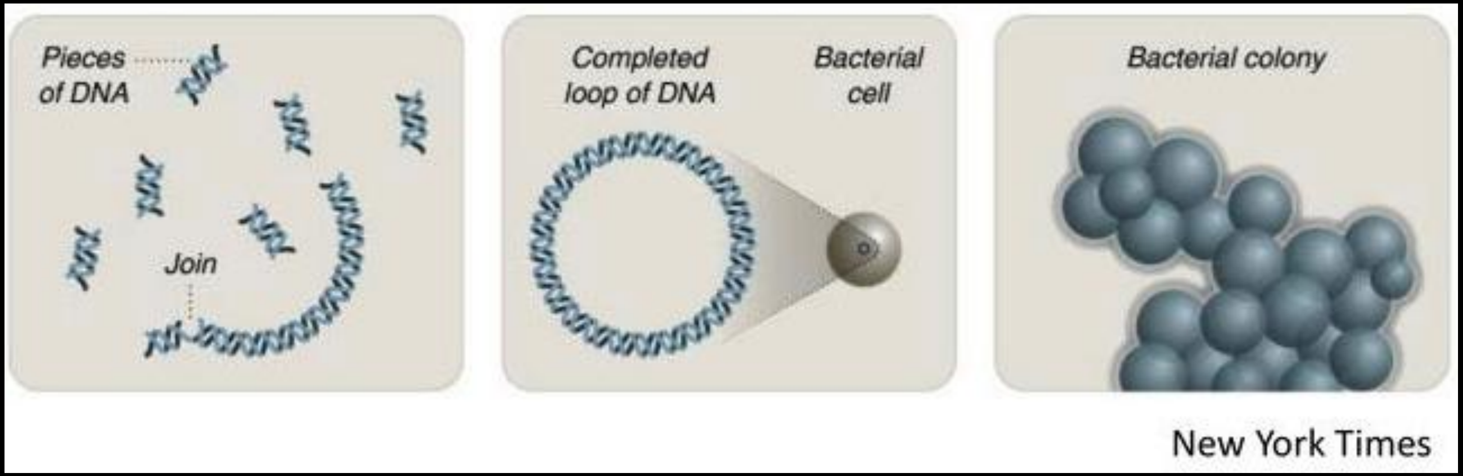

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HOW WAS THIS DONE?

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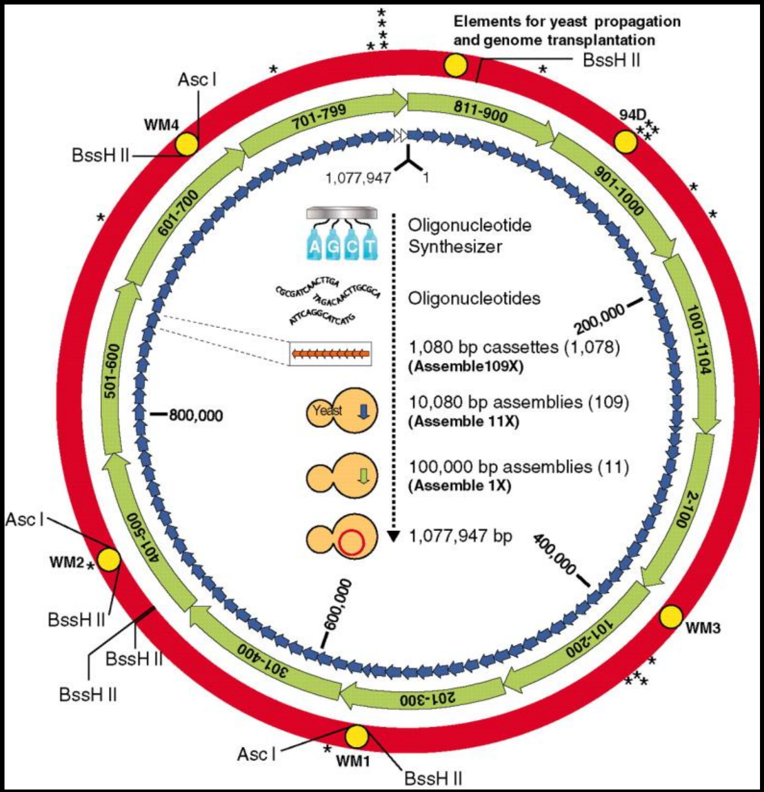

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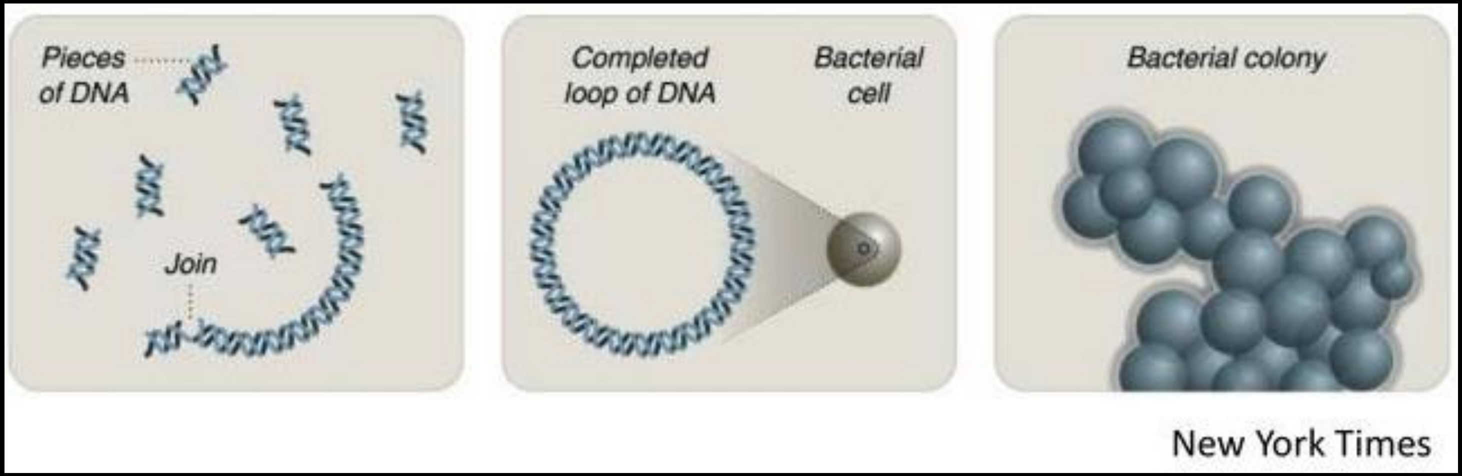
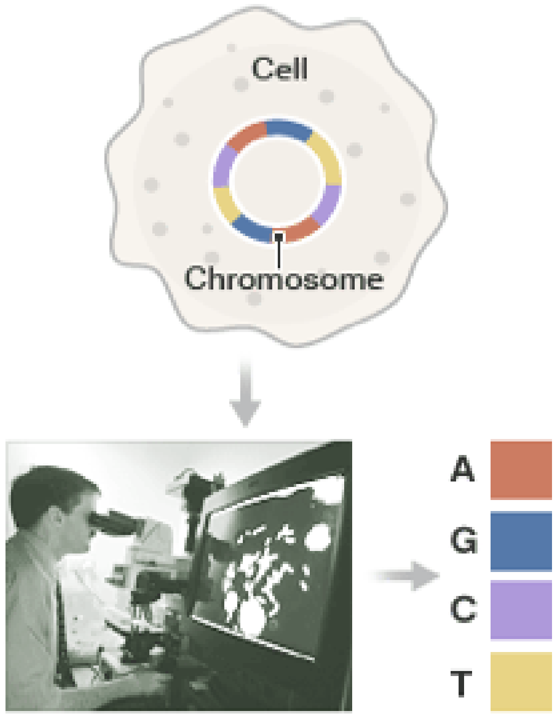


THE DESIGN AND CONSTRUCTION OF A GENOME:

How a synthetic cell was created



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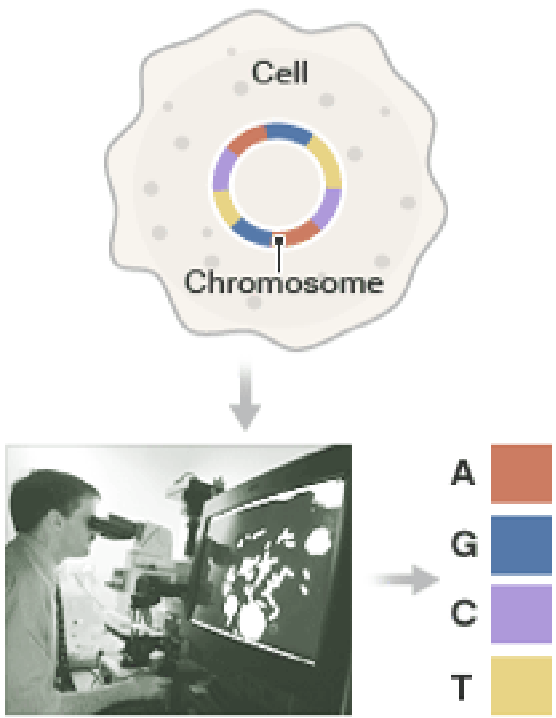

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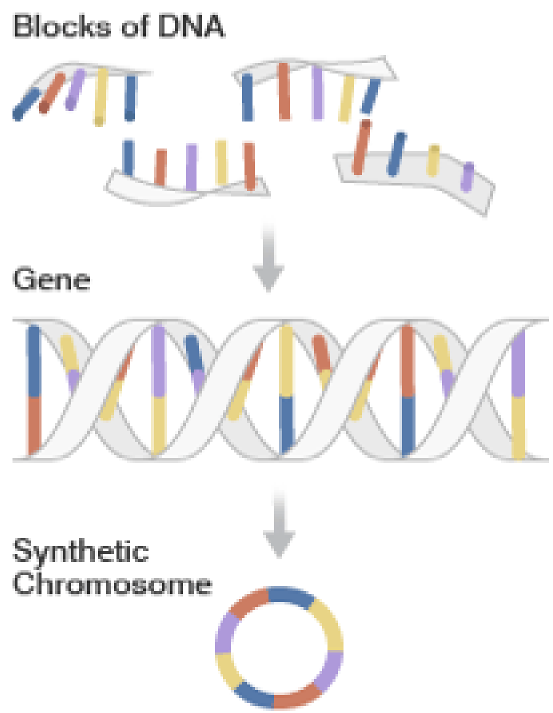

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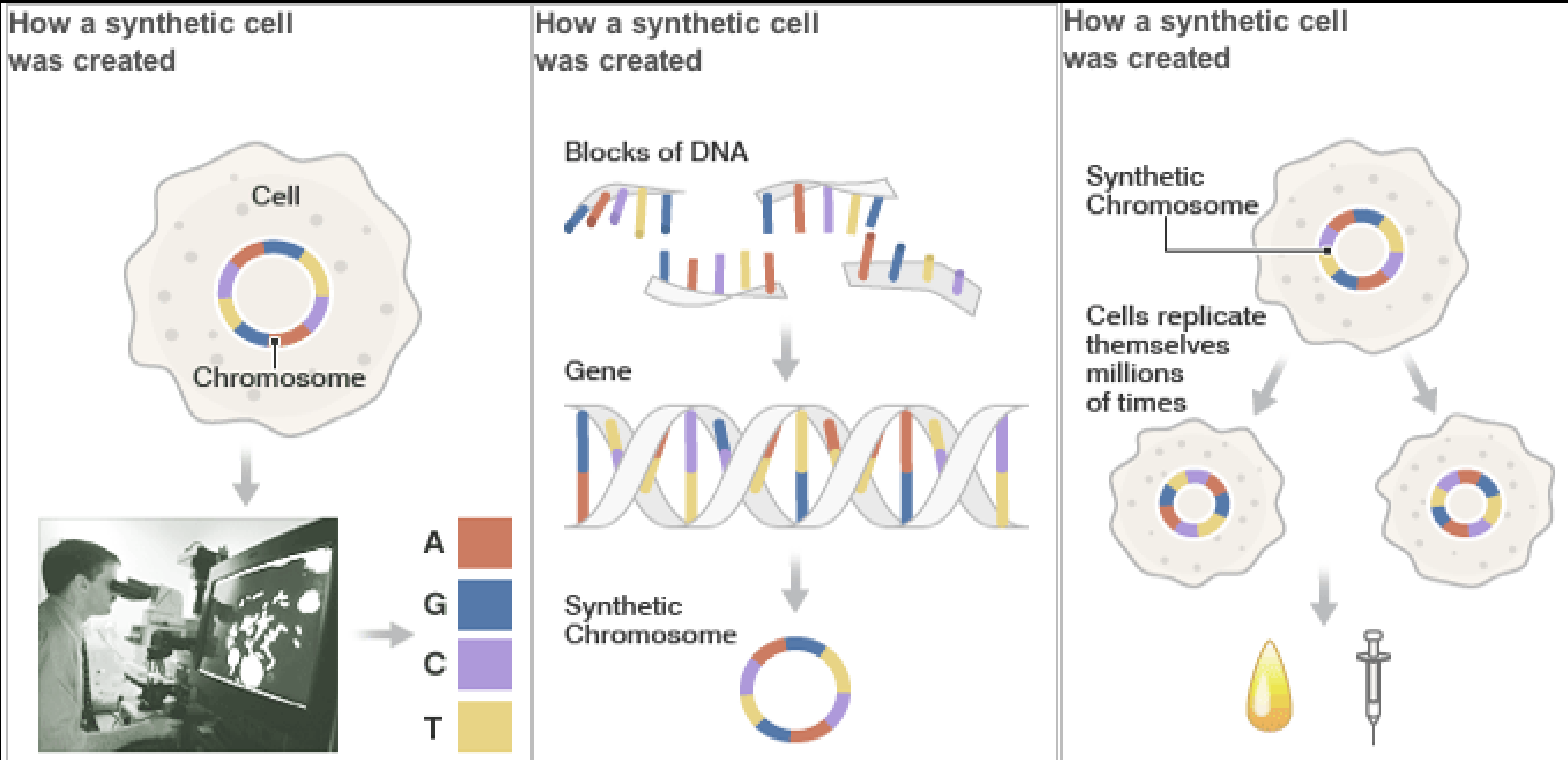

The scientists "decoded" the chromosome of an existing bacterial cell - using a computer to read each of the letters of genetic code.

They copied this code and chemically constructed a new synthetic chromosome, piecing together blocks of DNA.

The team inserted this chromosome into a bacterial cell which replicated itself. Synthetic bacteria might be used to make new fuels and drugs.

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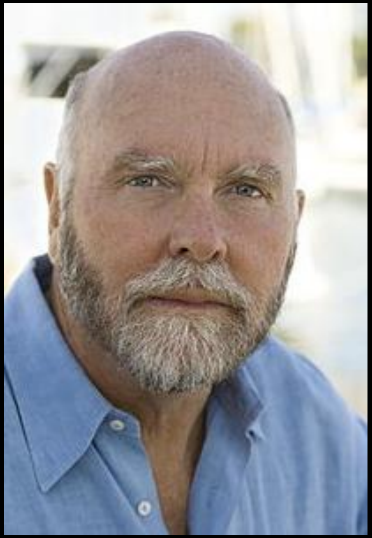

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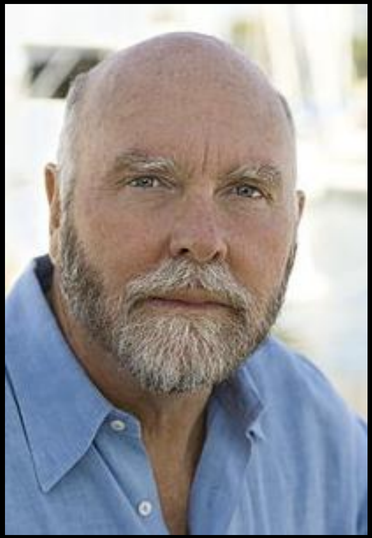

SO WHAT DOES THIS MEAN?

IN SUMMARY. . .

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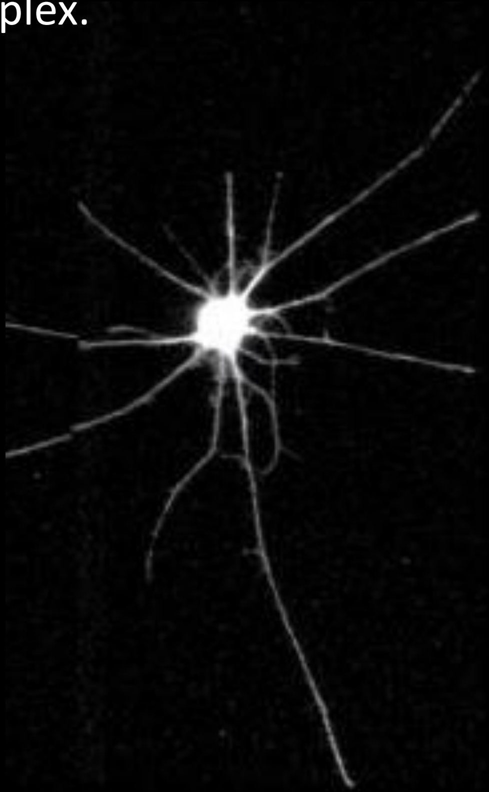
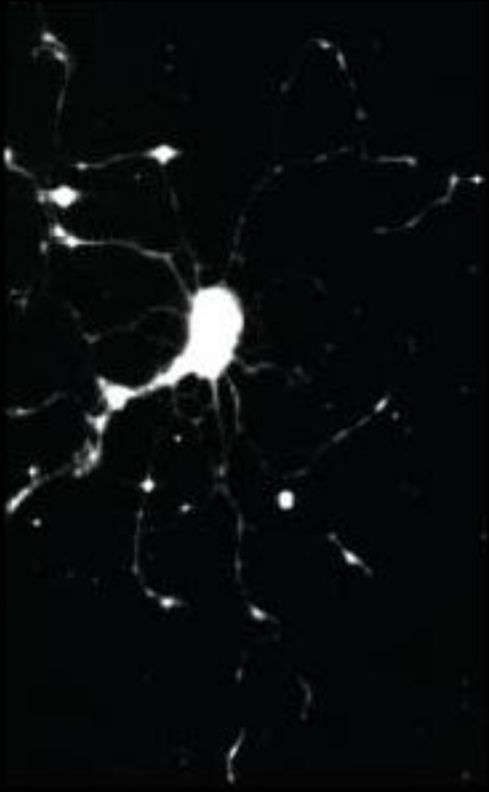
By understanding the underlying molecular and cellular mechanisms that create and influence the development of cells, we can gain a better insight into the evolutionary pathways of all organisms, from the simplest to the most complex.





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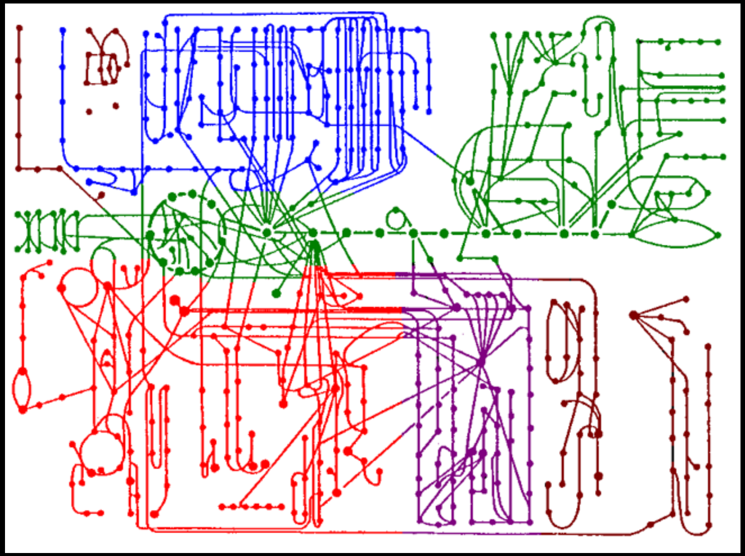
By being able to intervene and alter specific metabolic pathways, we will be in position to deal with diseased or mutant cells. This will be a key factor in curing diseases of all types.



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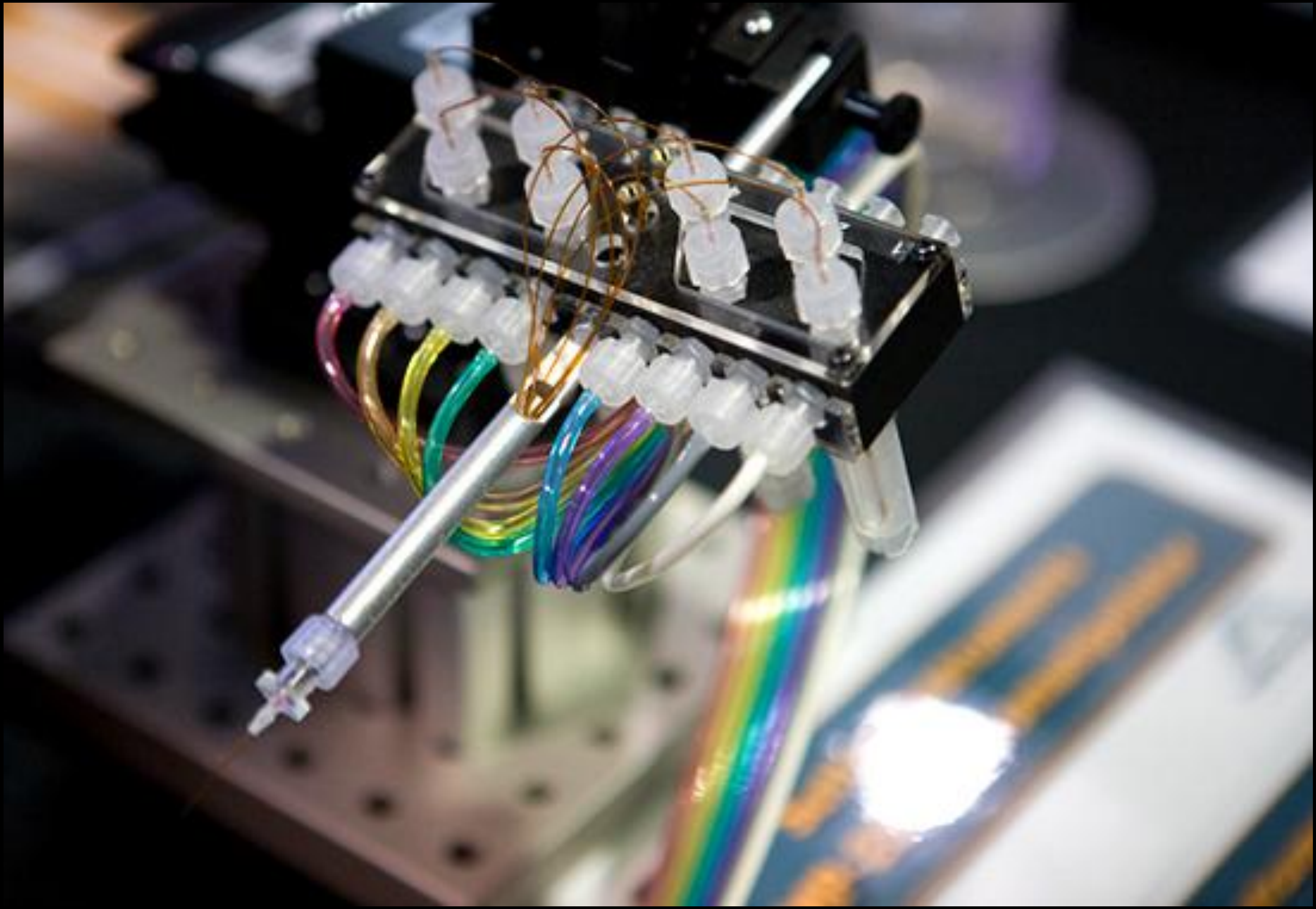
By the reality that the diversity of life on Earth is only a *subset* of the *potential* diversity, using the same molecules, the same principles, working differently.

AND THAT THE TOOLS OF PHYSICS ARE BEING ADAPTED AND APPLIED TO BRING US INTO THIS NEW REALM



CREDITS

THE PRESENTERS:

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Conference Coordinator
"Unexpected Physics in Biology"

ROB PHILLIPS (California Institute of Technology)
"Physical Biology of the Cell"

RICHARD NEHER (Max Planck Institute, Germany)
"Watching Evolution Happen"

MICHAEL ELOWITZ (California Institute of Technology)
"Life at the Single Cell Level"

The Rockefeller University Laboratory of Molecular Biology & Biochemistry

Charles W. Wolgemuth