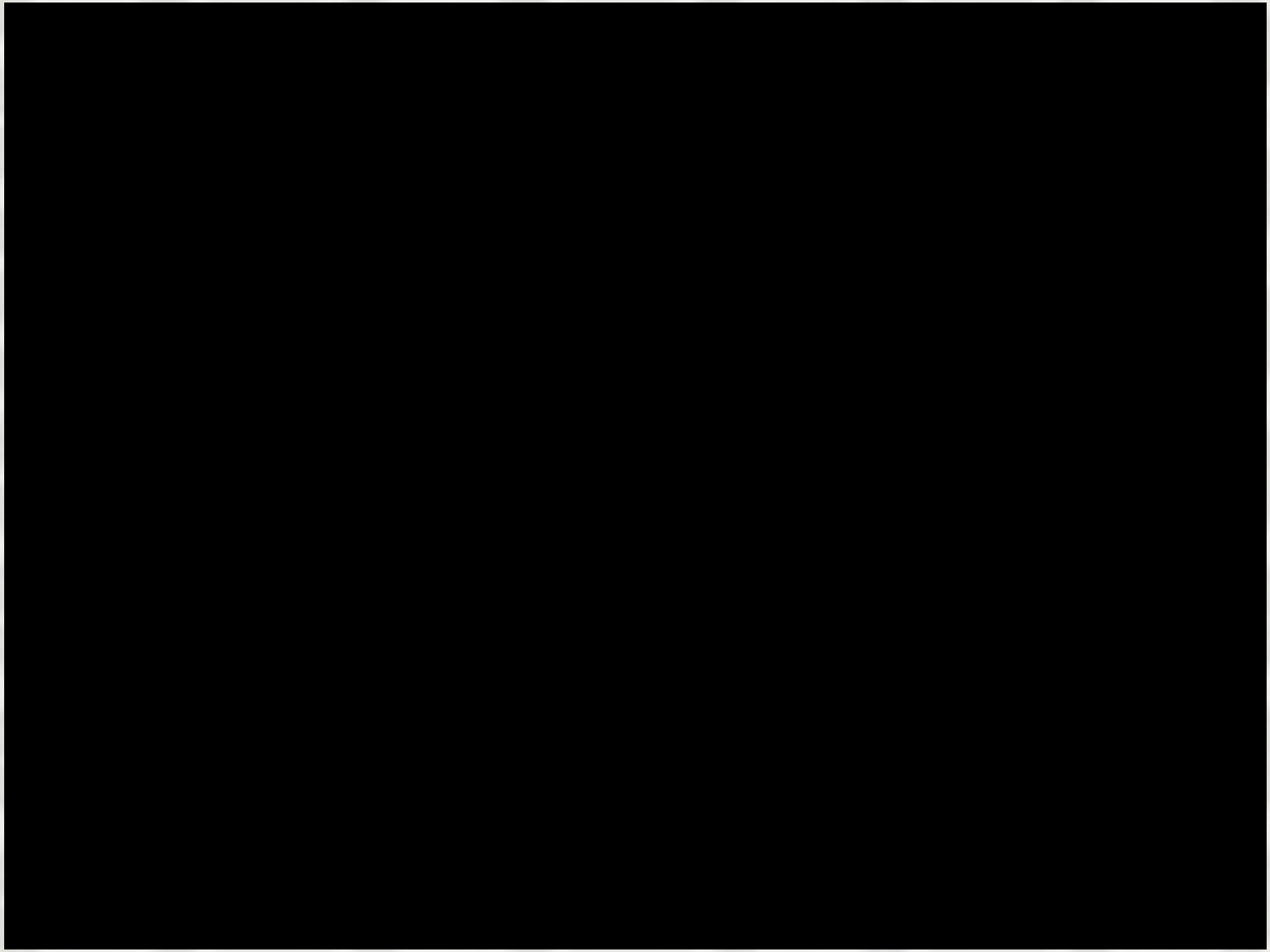

noise
motility
morphogen
receptor
tether
evolution
actin
polymerization
activator
fluorescent
model
protein
ligand
interaction
behavior
quantitative
deterministic
environment
circuit
adhesion
stochastic
gene
filament
repressor
cell

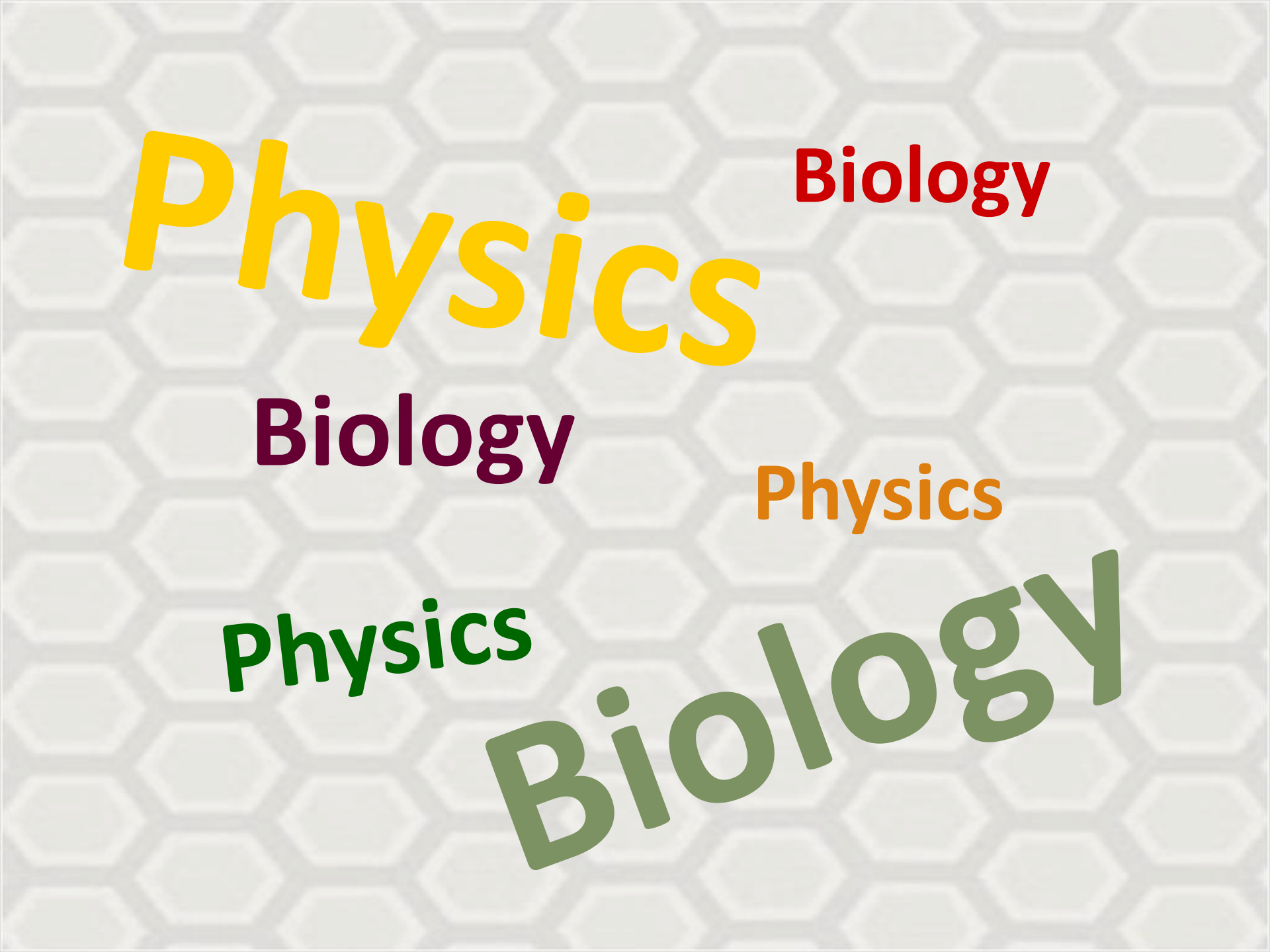
Physics and Biology:

Evolution of Life
and
Evolution of Science

The Inner Life of a Cell

Biovisions at Harvard University




Physics
Biology
Biology
Physics
Physics
Biology

Why physics AND biology?

- Technological advancements have provided the means to look at biological systems in more detail.
- There is a vast amount of quantitative data which provides insight to complex physical systems under the influence of their fluctuating environments.
- Analysis of this data lies at the boundary between physics and biology.

“Biology today is where physics was at the beginning of the twentieth century. It is faced with a lot of facts that need an explanation.”

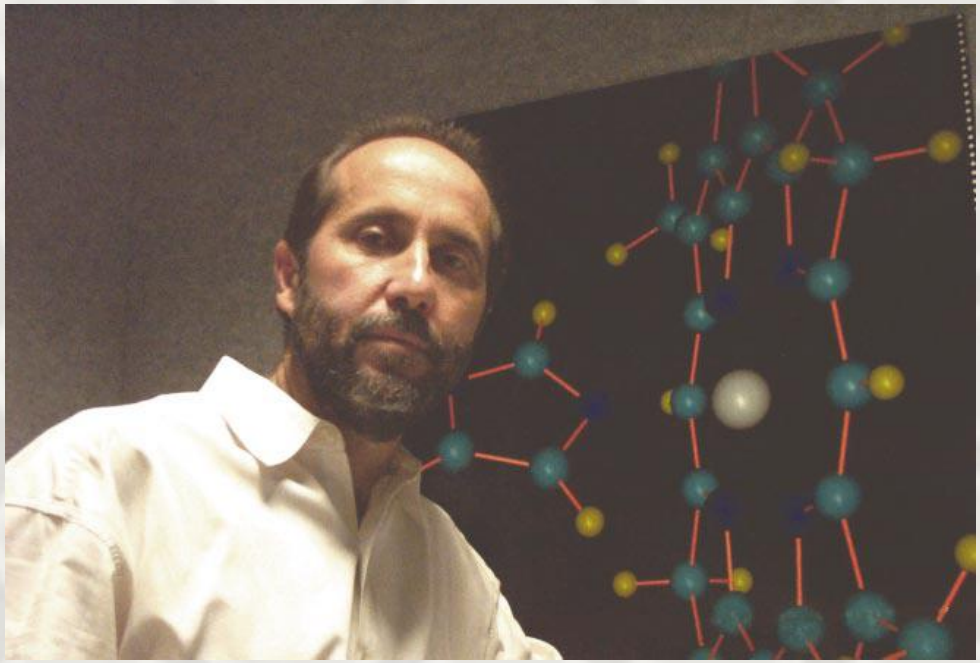
José Onuchicco

director of the Center for Theoretical Biological Physics

(CTBP) at the

University of

California, San Diego



There is a need for **predictive models** to direct new **experimentation** and **answer questions**.

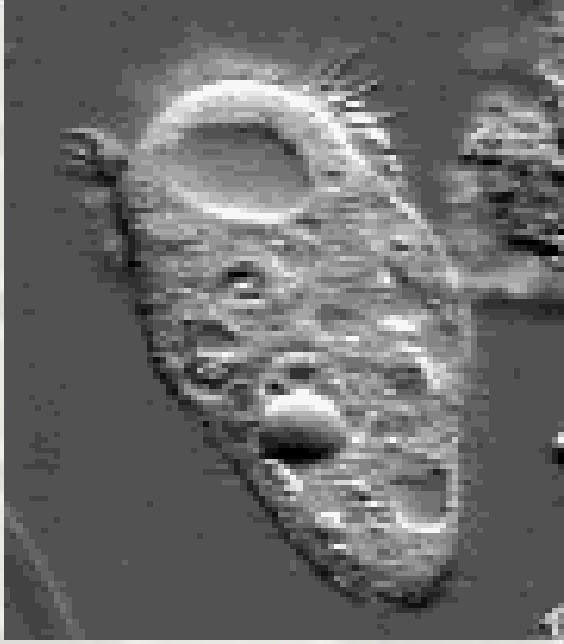
Examples of the questions…

- *How do cells decide where to go?*
- *How do cells act like circuits?*
- *How can we explain morphogenesis?*
- *How can we fight evolving viruses?*

Physics enters the world of cell motility and polymerization.

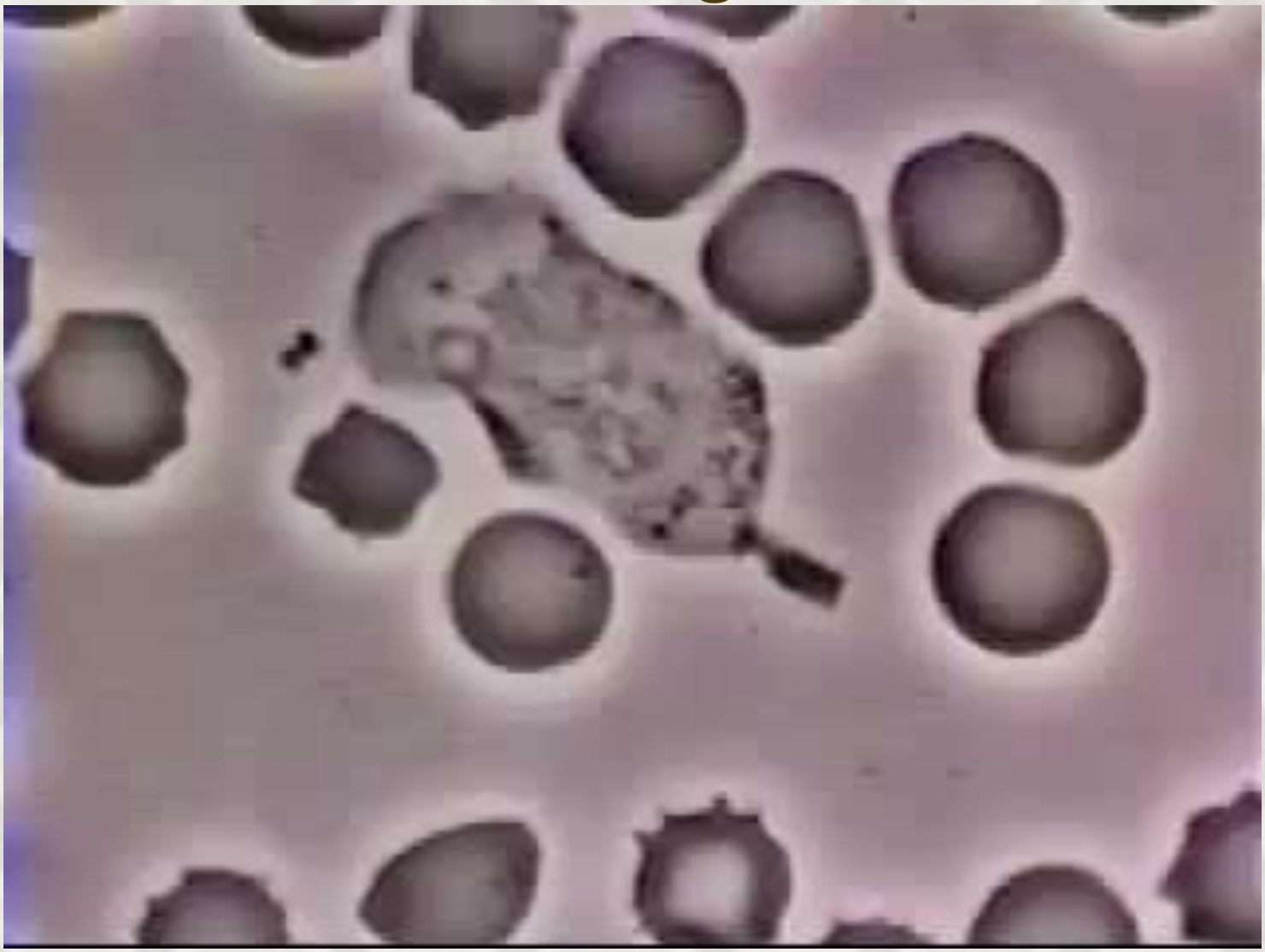
How do cells decide where to go?

Susan Lee, *Firtel lab,*
cell moving toward chemoattractant

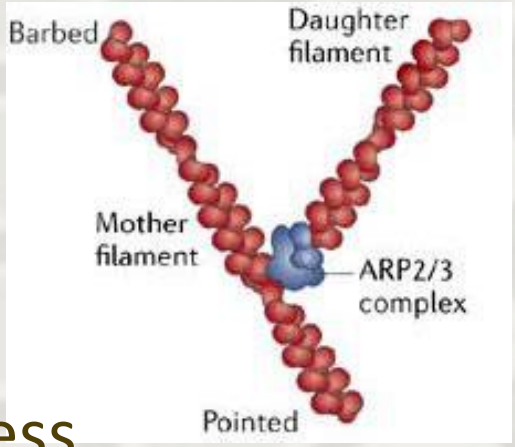


- All living things are made up of cells.
- Molecular and cellular biology are mainly about proteins and their interactions.
- Current technology has provided a vast amount of data dealing with many areas of cell dynamics.

White blood cell hunting a bacterium
David Rogers



•Cell motility arises with actin protein.



•Actin assembles into filaments.

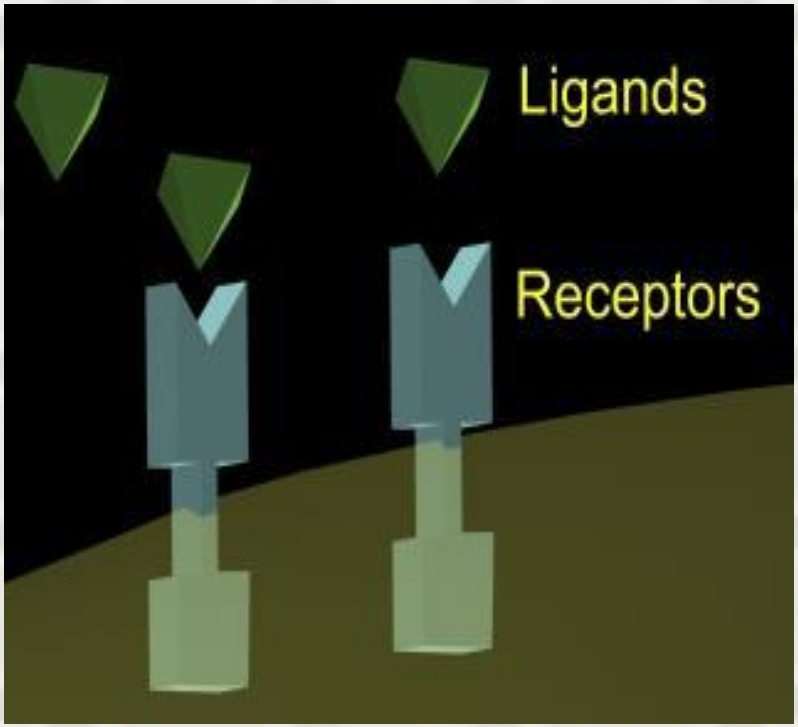
•ATP hydrolizes in a polymerization process causing the filaments to do work, for example pushing on membranes.

•But how do cells know when and where to put the new filaments?

•A protein, ARP (actin related protein), binds to the cell, and where it does, it stimulates the formation of new actin filaments.

•To bind in a particular location, the ARP must get activated by a signal.

•This signal is transmitted by receptors and ligands.

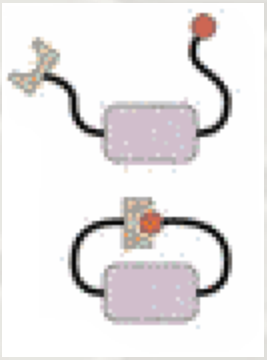


•Receptors and ligands are critical in all biological systems, allowing cells to communicate with other cells.

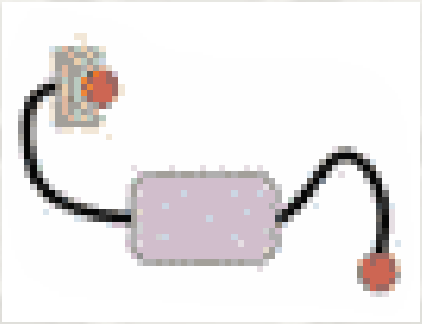
•Ligands promote cell adhesion. They are sometimes attached to flexible tethers that can bind to receptors on nearby cells.

•Consider a tethered ligand and receptor.

•When the ligand and receptor are together, they are inactive and can't tell actin to be formed.



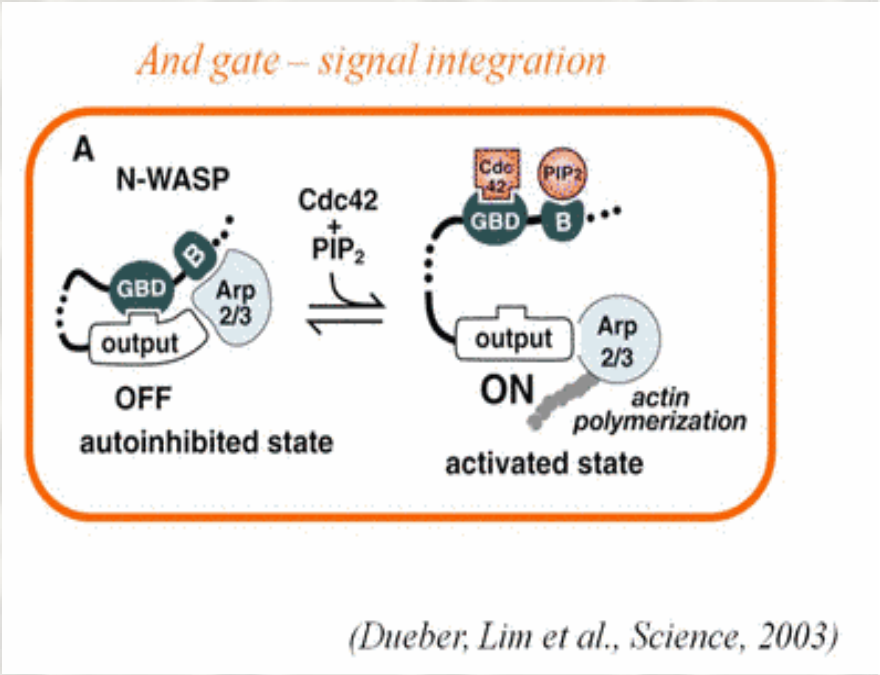
•Add a soluble competitor of the ligand (an external ligand) without a tether.



•At some point of concentration, the external ligand will win.

•Actin can be formed.

•As the concentration of external ligand is increased, more ligand receptor interactions will occur.



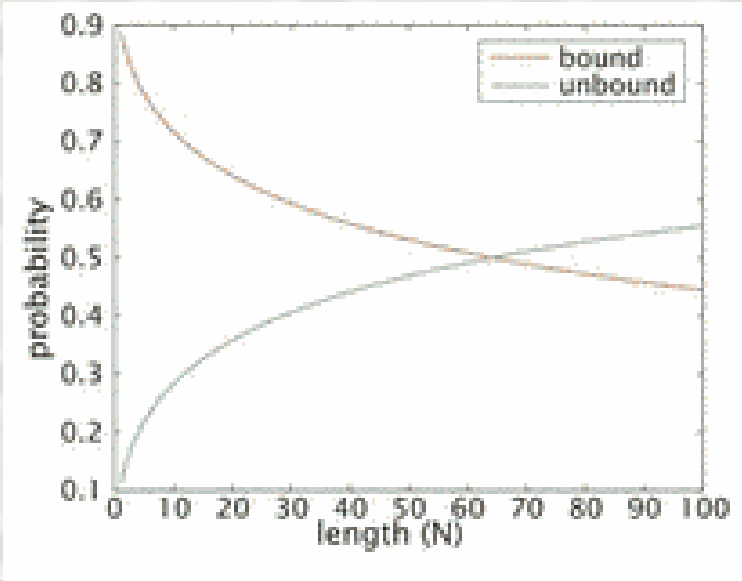
•The probability of binding depends on the length of the tether.

•When the separation is close to the tether's fully extended length, the ligands lock quickly onto the binding site and the ligand and receptor pull together.

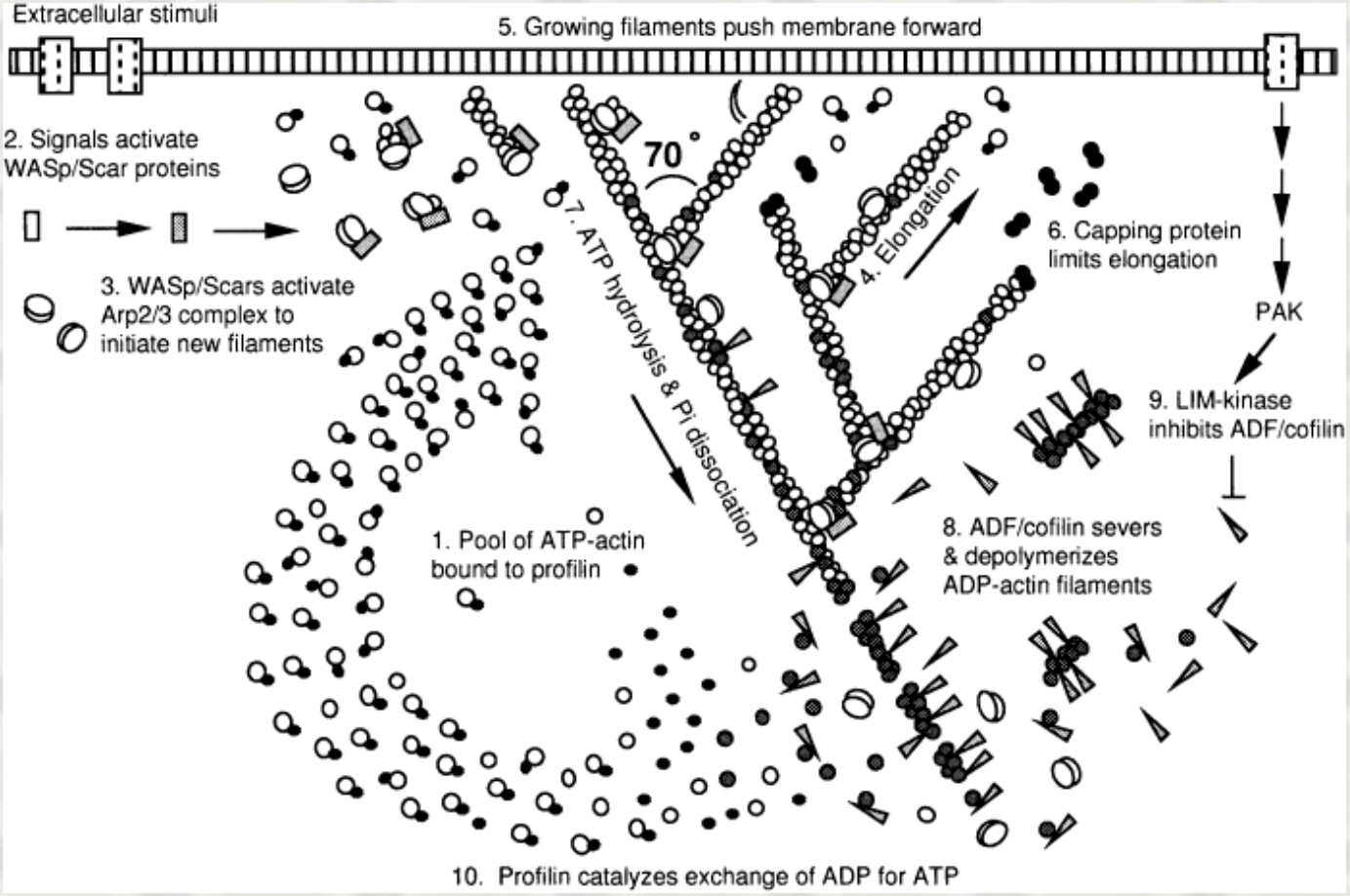
•Surface force measurements and the probability of the interactions (involving a binomial distribution related to statistical mechanics) can be studied.

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

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

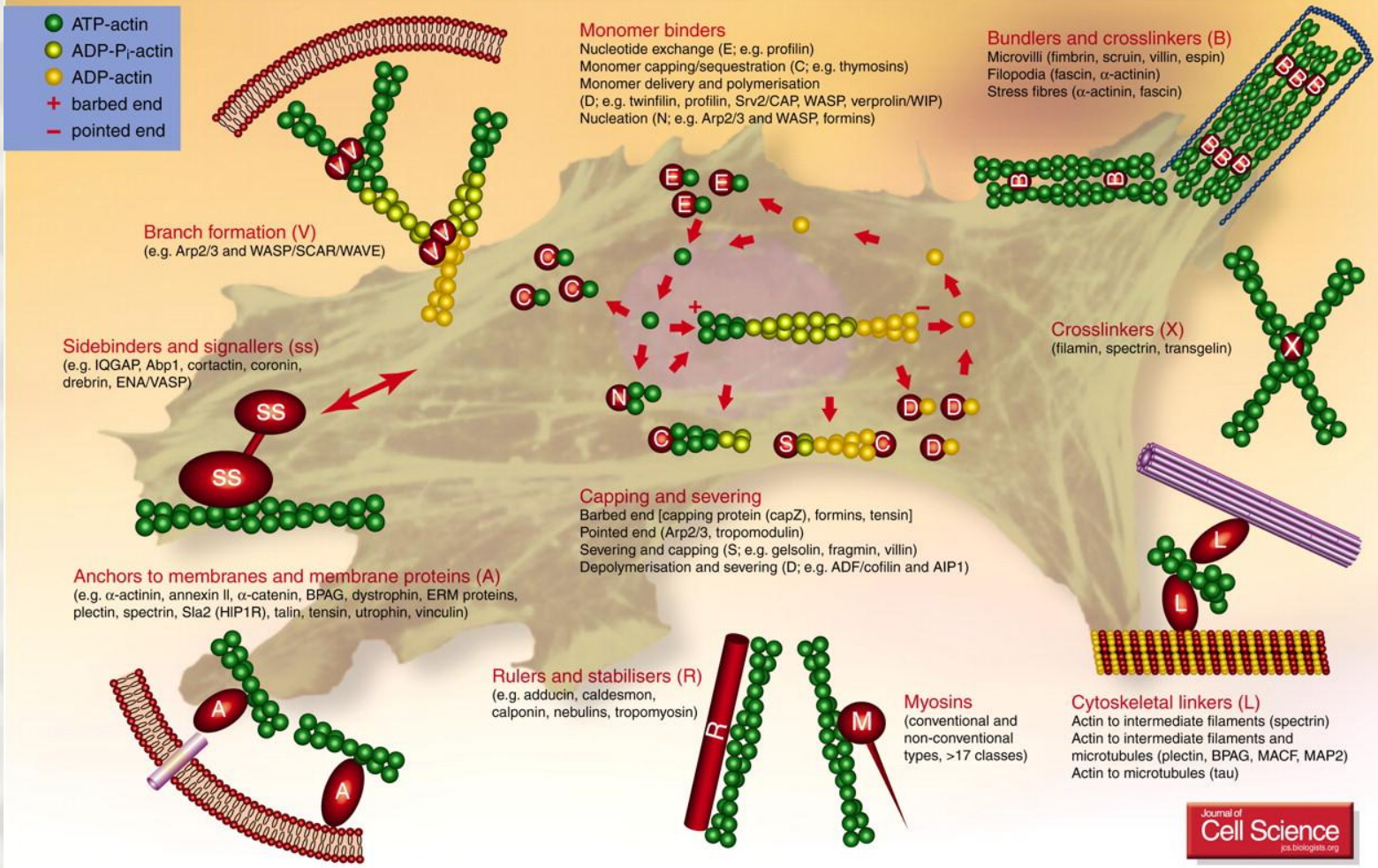


model for mechanisms controlling actin filament dynamics in cells



Actin-binding Proteins

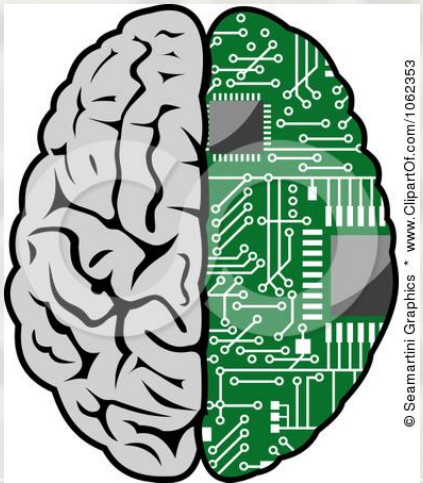
Steven J. Winder and Kathryn R. Ayscough



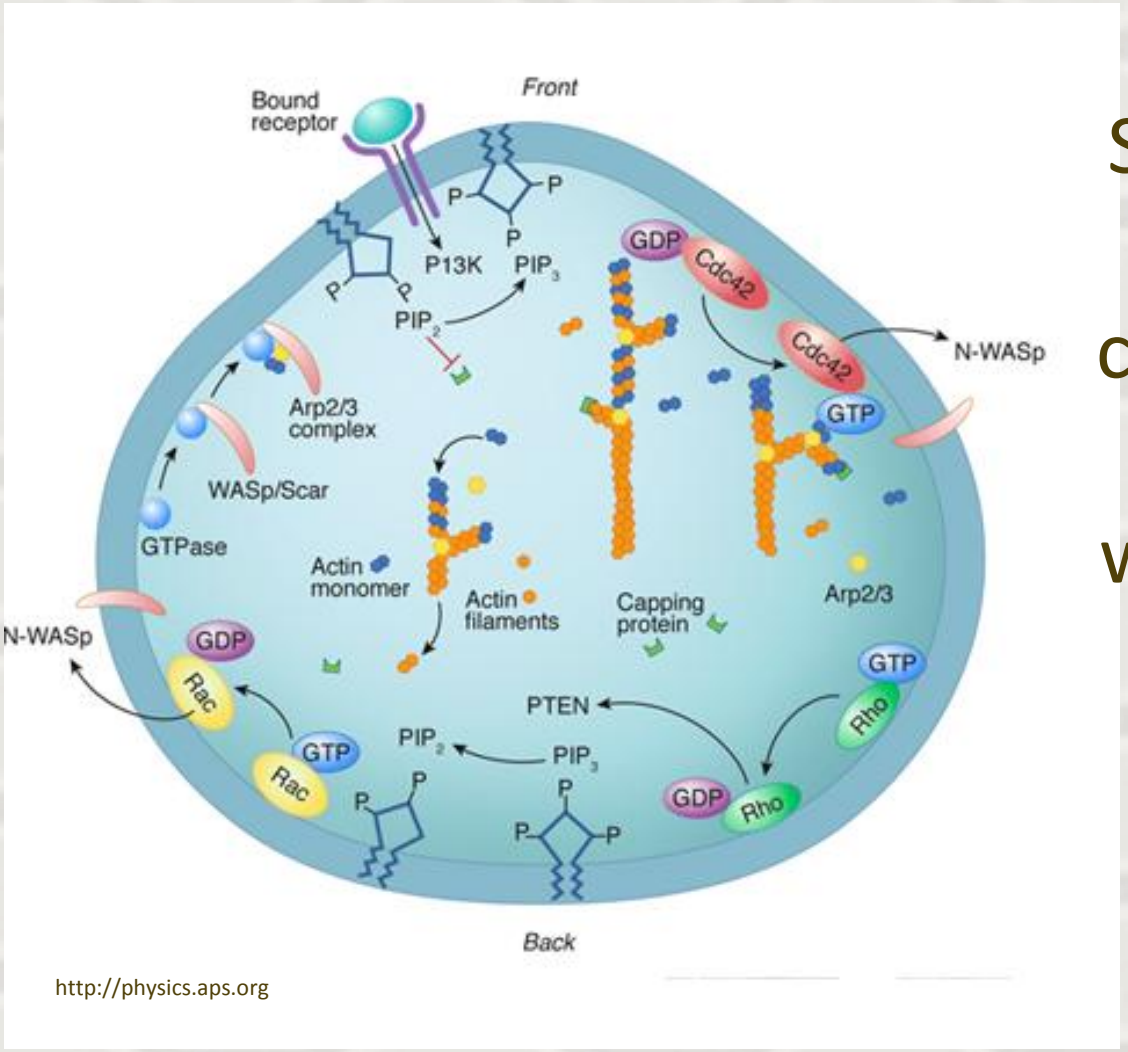
Winder S J , Ayscough K R J Cell Sci 2005;118:651-654

Physics enters the world of molecular and cellular biology.

How do cells act like circuits?



“Simple” chemical reaction network for a single cellular reaction

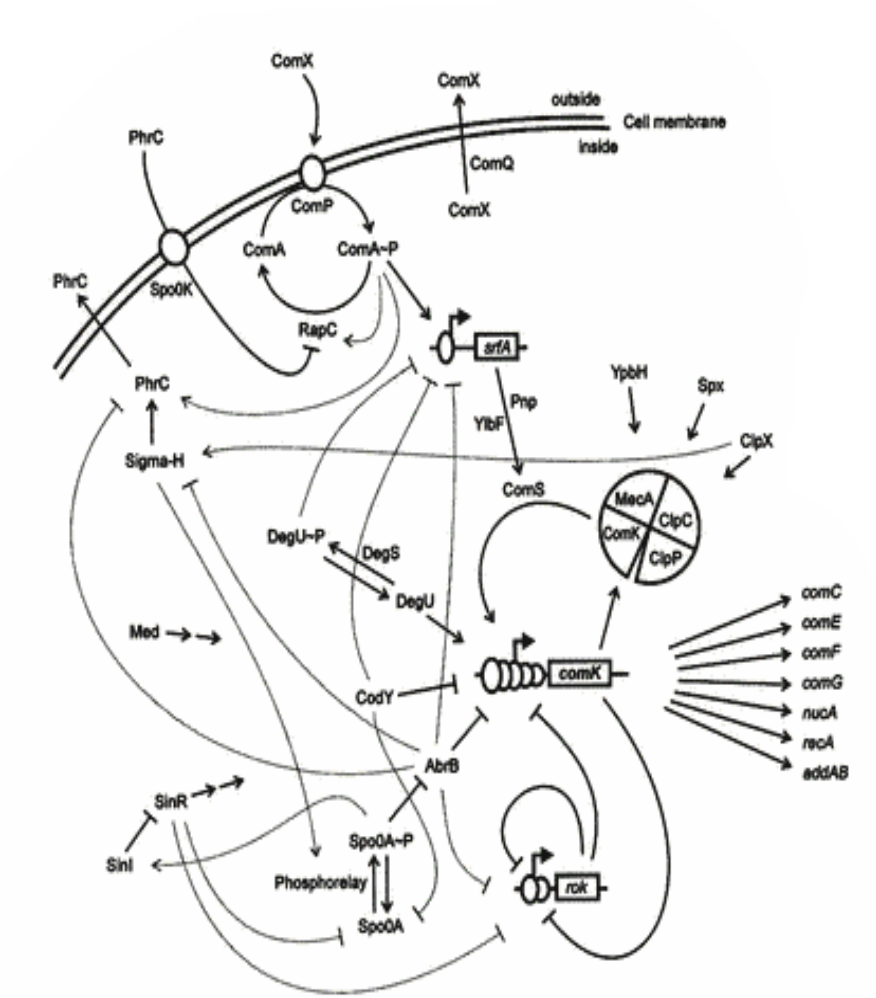


http://physics.aps.org

Scientists want to analyze these complex networks and determine ways to assemble models of biological reactions.

Using Circuit Diagrams

- Diagrams can also be drawn to represent these interactions, these genetic chemical circuits.
- What are the principles of circuit design for these types of circuits?
  - They are different because…
    - They are dynamic
      - Concentrations of the proteins changes
    - They are noisy
      - Subject to “stochastic” fluctuations, non-deterministic
    - Circuits are very complex
      - There is a “web of interactions” that needs to be simplified

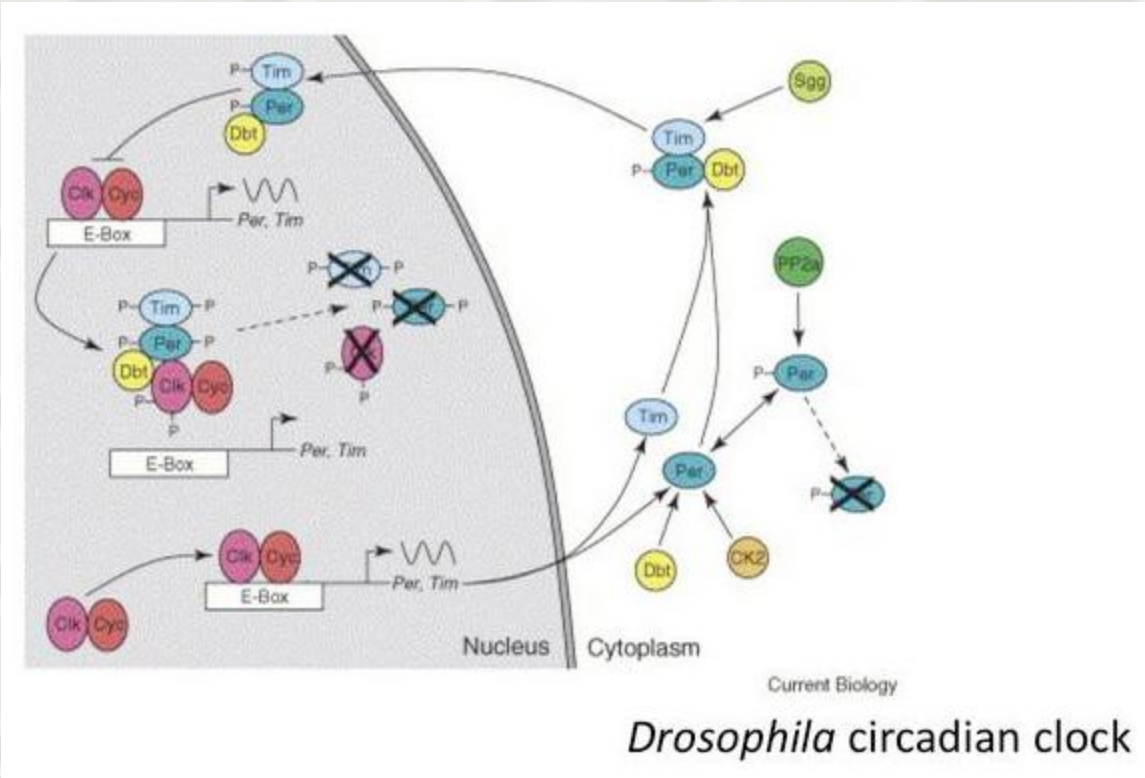


Competence circuit diagram from Hamoen et al. *Microbiology*. 2003

How can we get a quantitative understanding of these circuits?

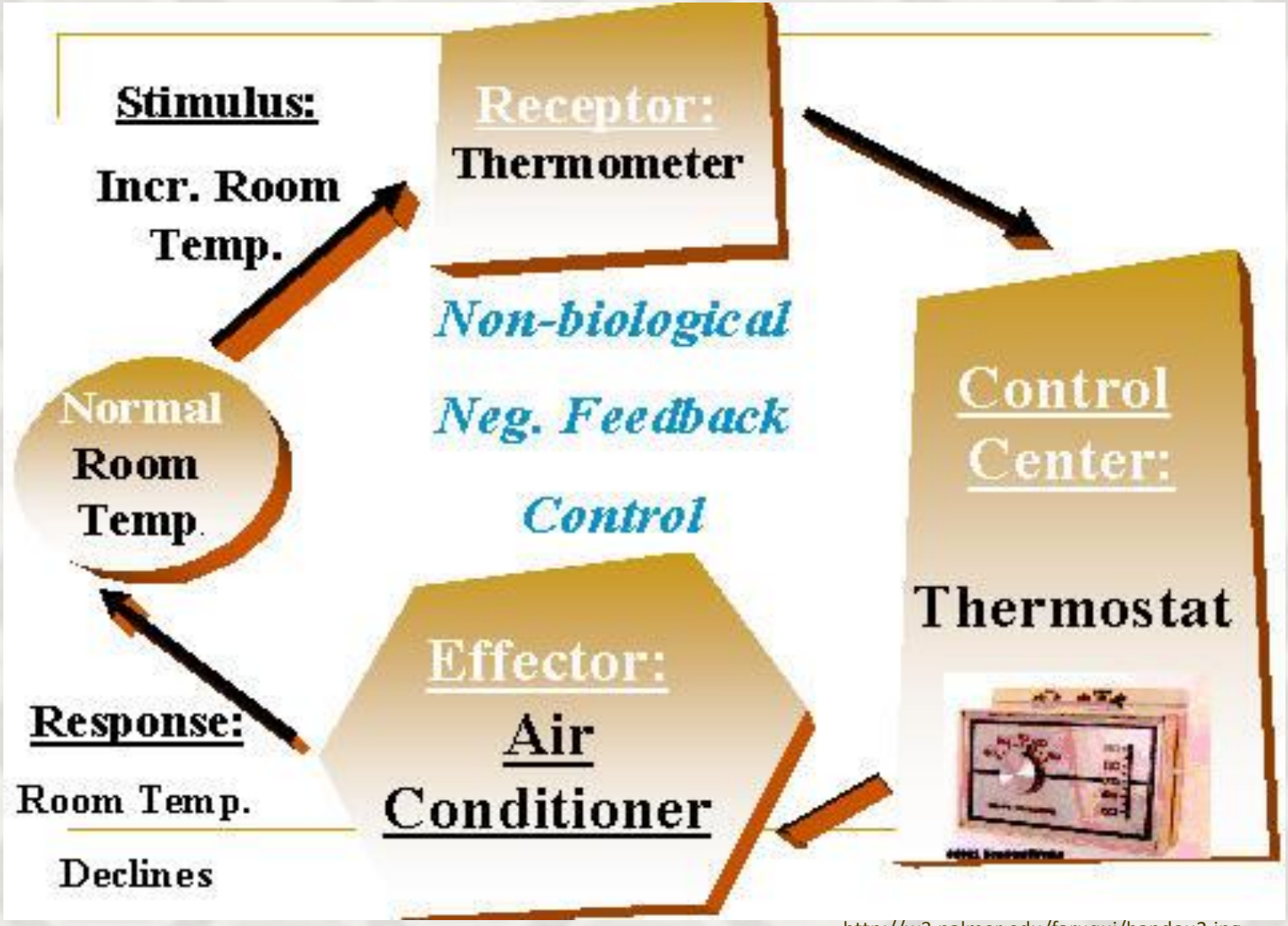
1. Construct (using synthetic biology) simple gene circuits, place them in cells, and see what they do.

2. Isolate a single cell and use movies to analyze the circuits.



Drosophila circadian clock

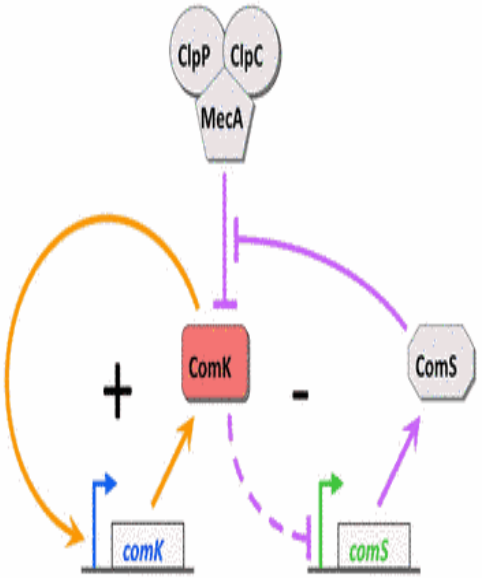
One type of circuit used by cells is a negative feedback loop…



http://w3.palmer.edu/faruqui/handou2.jpg

Cells can keep track of time using a type of "negative feedback loop".

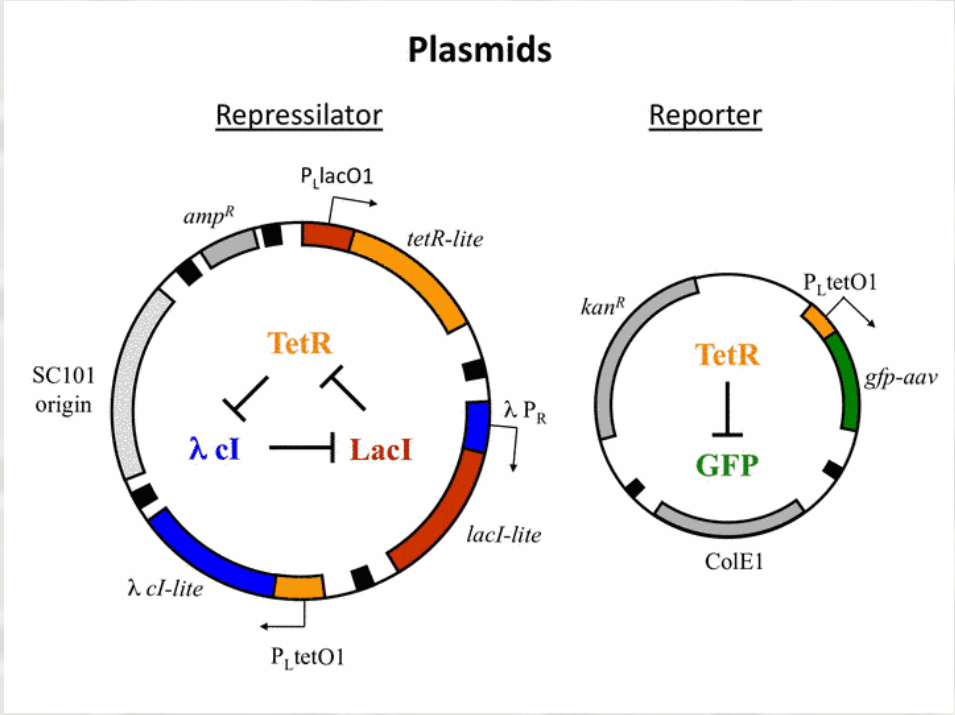
- Proteins are produced and leave the nucleus of the cell.
- Take time to come back into the nucleus.
- When they return, they turn off their own expression.
- This causes the concentration of those proteins to lessen.
- Eventually the concentration is low enough that they no longer turn off their own expression and begin to be produced again.
- This is called a "time delayed negative feedback loop".



Combination of fast positive and slow negative feedback loops

An oscillating system using 3 repressor genes…

- A repressor turns off the expression of another gene.
- TetR can turn off the expression of λcI (ecoli uses it to keep itself dormant). λcI can turn off the expression of LacI. LacI can turn off the expression of TetR in one continuous loop.
- When one increases, it decreases the next, which increases the third, and decreases the original again.

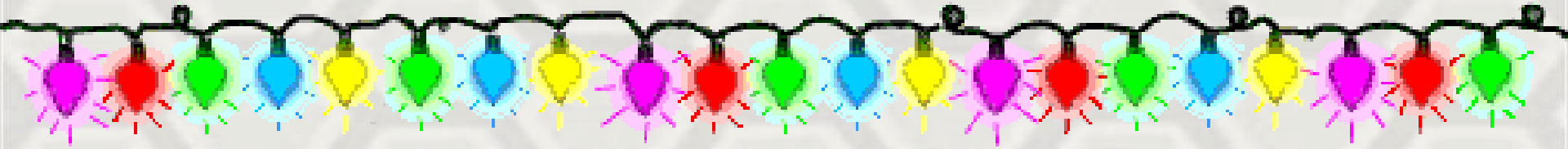


A different sort of example…

- Another time delayed negative feedback loop occurs in most fission nuclear power facilities.
- As heat rises, the moderator (water) is less effective at slowing the neutrons to the correct speed to cause a reaction.
- So…as heat rises, the fission slows, causing the heat to lessen.
- When it does, the fission process picks up again.

And another…

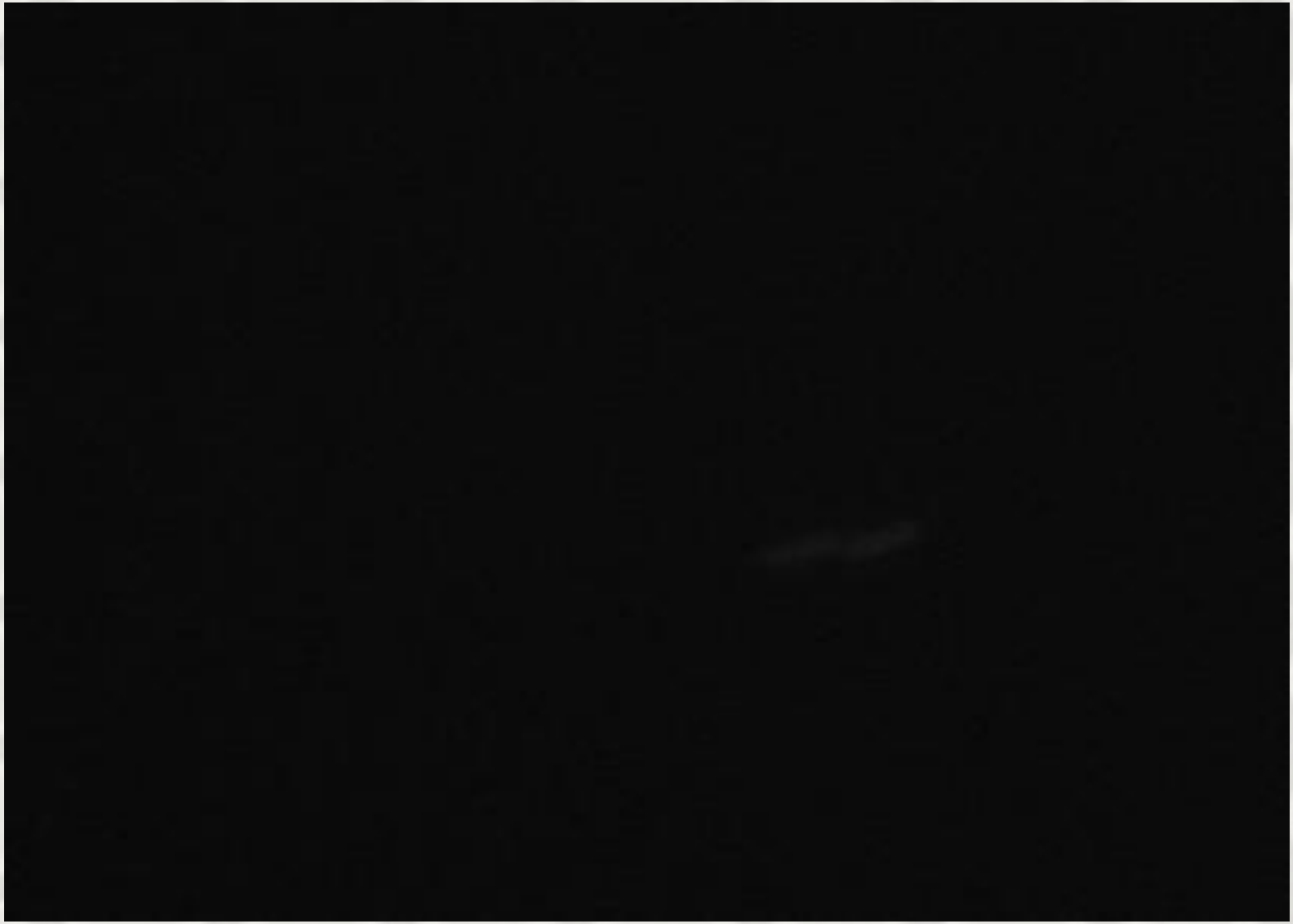
- Flashing lights
- A metal is used that straightens (expands) when hot and bends (contracts) when cool.
- When cool, the metal makes a connection in the circuit, causing the light to go on.
- As current flows through the metal, it heats up and then straightens, breaking the connection, and the light goes off.



In order to see what's going on…

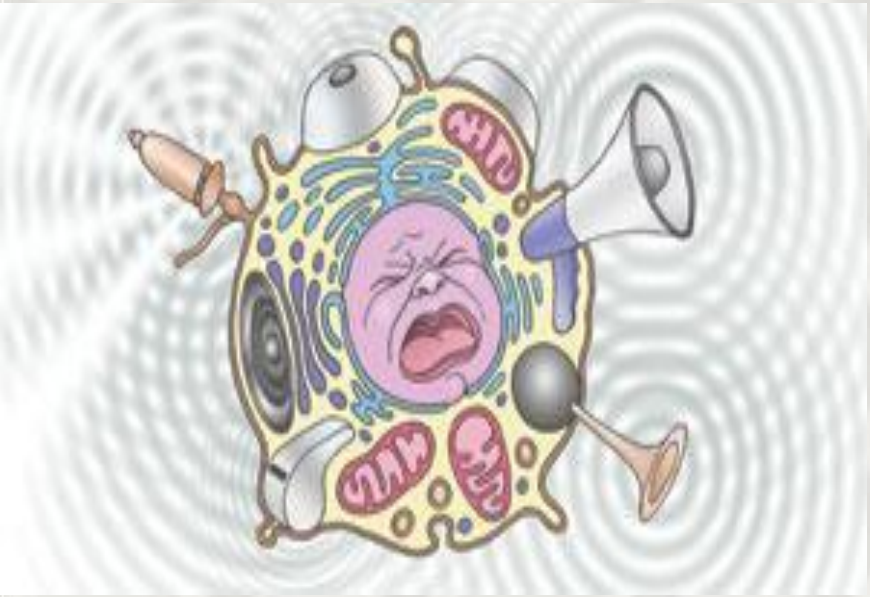
- In 1994, the green fluorescent protein in jellyfish was cloned and was able to be used in other organisms.
- The GFP (green fluorescent protein) is added to the circuit and controlled by the TetR.
- As TetR increases, the GFP decreases – lights go off.
- As TetR decreases, the GFP increases – lights go on.

Due to the expression of a fluorescent protein gene, the E. coli cells oscillate on and off.



Behaviors can be programmed into cells but the cells aren't usually all in sync.

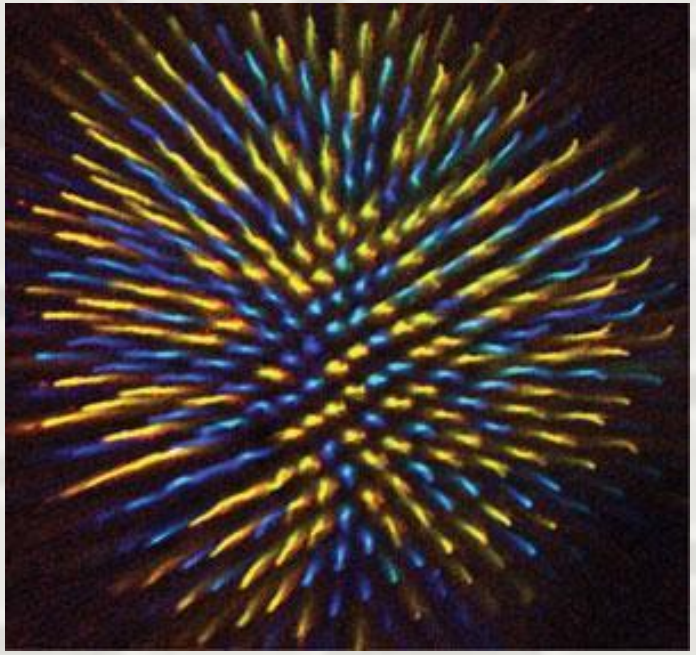
- Even with the genotype and environment of two cells being the same , they don't necessarily do the same thing.
- The components of cells are subject to random (stochastic, non-deterministic) fluctuations.
- Cells typically operate in highly variable and noisy manner, with big fluctuations from cell to cell.



Mutations can affect how much and how variably a gene is expressed.

Cellular Noise…

- may create diversity. A noisier, more diverse system has a greater chance of survival in unpredictable settings.
- could hinder signal and response mechanisms in cells.
- might be a cause of mutations.
- increases with age.



The pattern of photoreceptors in the eyes of the fruit fly depend on random activation of the spineless gene.

D. VASILIAUSKAS www.nature.com

Physics enters the world of biological form and structure.

How can we explain morphogenesis?

Illustration of lung cells; nsf.gov

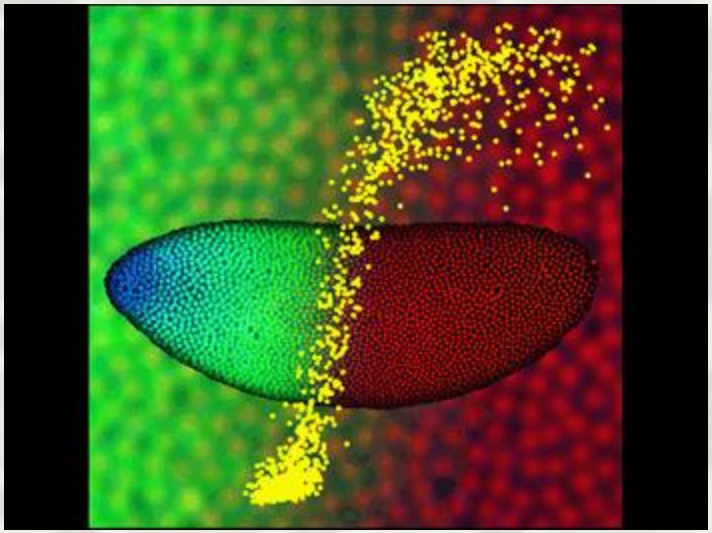
Morphogenesis is the biological process through which an organism develops its shape. Changes in morphogenetics may be triggered by:

- Hormones
- Chemicals
- Mechanical stresses

In 1952, Turing wrote a paper “The Chemical Basis of Morphogenesis”.

Alan Mathison Turing
1912-1954

He suggested that animal and plant development are governed by morphogens, chemicals which influence the movement and organization of cells.



A Drosophila embryo shortly after fertilization

- nuclei at the surface (blue)
- Hunchback protein (green)
- DNA (red)

Morphogen molecules communicate positional information to individual nuclei.

The activator which activates itself and spreads out (diffuses), also produces an inhibitor which slows down the activator.

- A low amount of activator means stability, uniform mix of activator and inhibitor.

- More activator means more instability. This results in more activator in some places than others. It is higher in spots or ridges and low in between. Patterns (stripes and spots) develop.

Physics enters the world of evolution.

How can we fight evolving viruses?

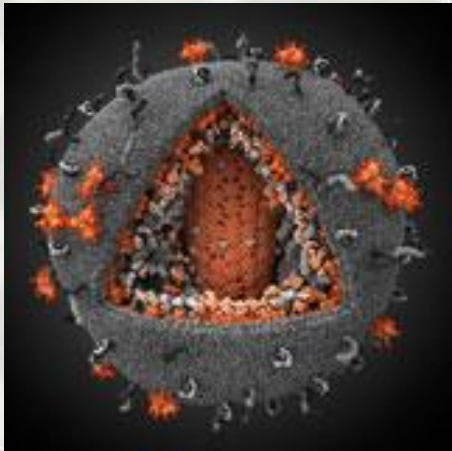


Illustration of HIV particle; nsf.gov

Viral evolution

- While plants and animals evolve over hundreds of millions of years, viruses can evolve over only a few years

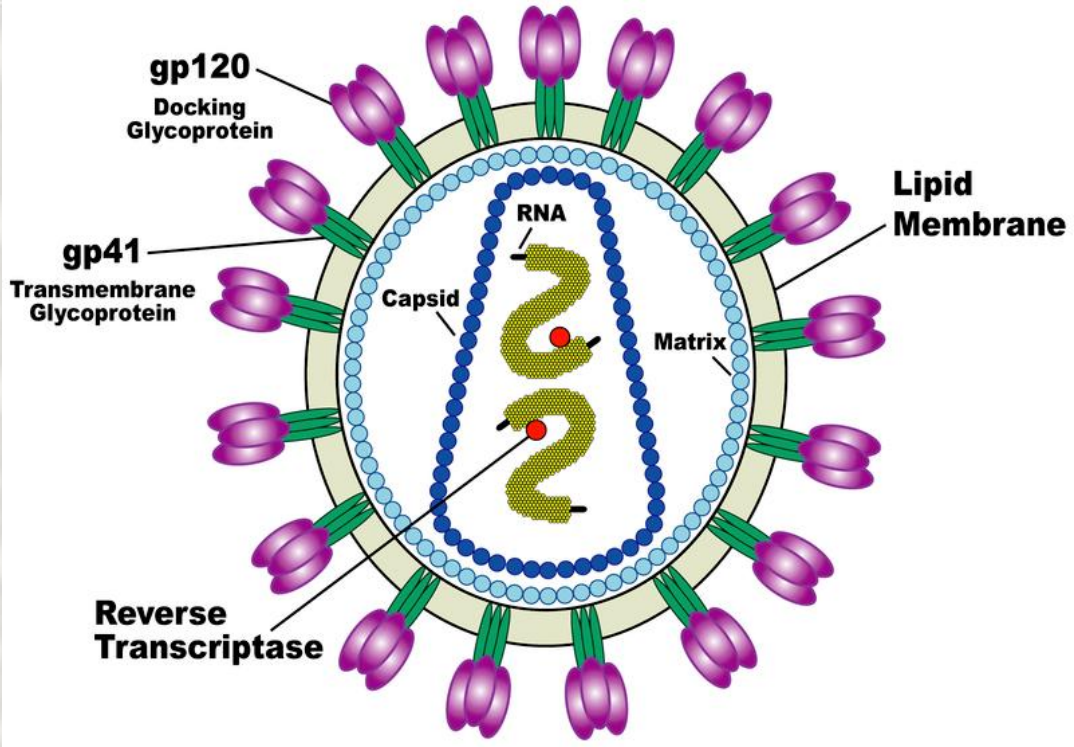
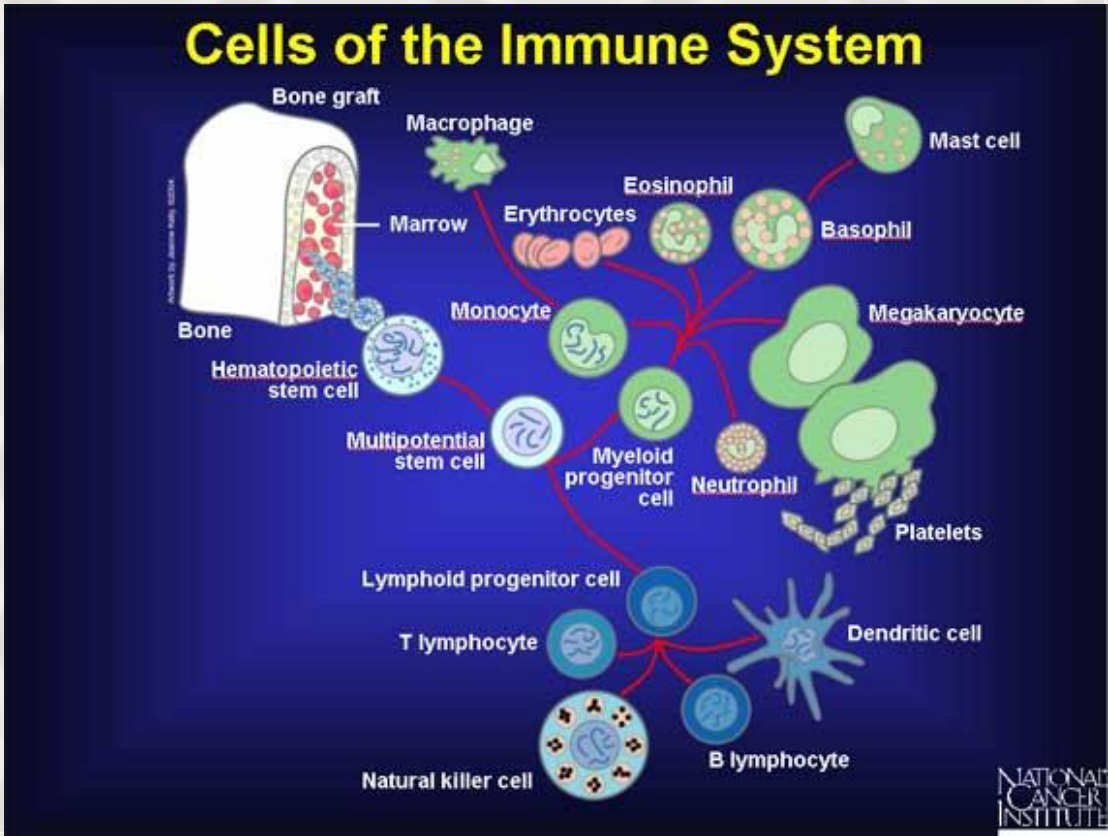


Diagram of HIV

- Because this poses a threat to humans, analyzing and modeling these viral genomes is of great significance.

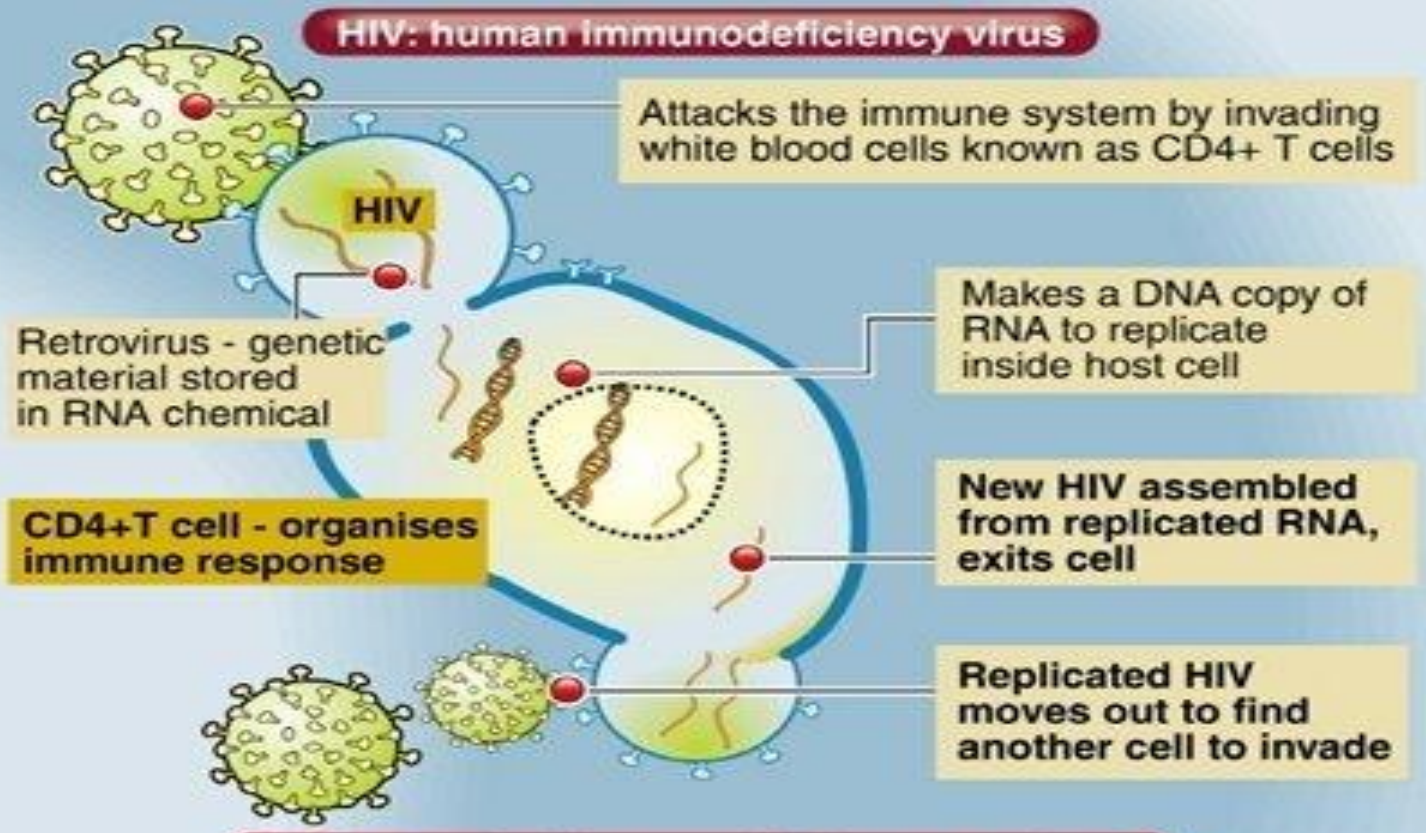
One reason viruses (like HIV) are hard to eradicate is because of their rapid evolution

- Difficult to develop vaccines
- Difficult for immune system to fight



What is HIV/AIDS?

33 million people are living with the virus



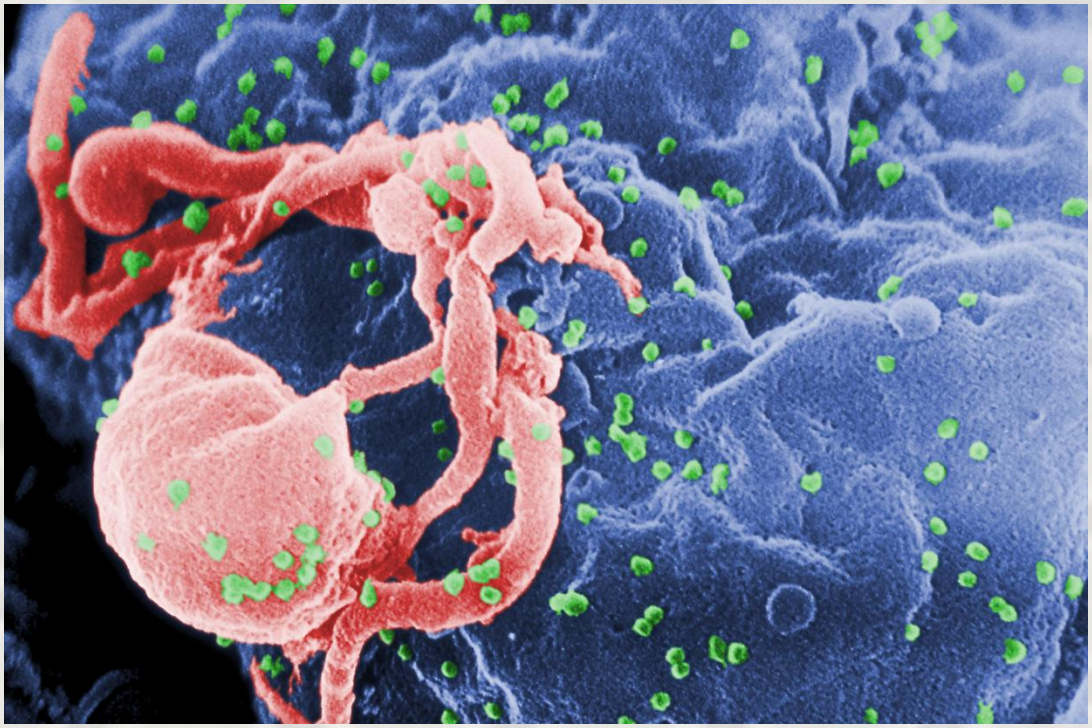
- Final stage of HIV infection
- Occurs when CD4+ T cell count below about 200/mm^3, normally 800-1200/mm^3, can take years to reach this stage
- Common infections of AIDS sufferers: lungs, intestines, brain, eyes, other organs; diarrhea, neurologic conditions, cancer

Sources: CDC/WHO/UNAIDS

230709 AFP

Evolution of HIV

- HIV does not develop in all people at the same rate
- The rate is related to genes controlling the production of immune system molecules called human leucocyte antigens (HLAs)
- Humans do not all have the same HLA genes



HIV budding from an immune cell

- HIV can adapt rapidly to the immune responses in human populations.

- This implies that effective vaccines would need to be changed frequently to keep up with the evolution of the virus (this is currently also done with the flu vaccine)

- Models of the evolutionary patterns need to be studied to get a step ahead of the virus.

Why physics AND biology?

These and other new frontiers of science require interdisciplinary research to continue to better humankind.

Explore Some More…

Visit the site http://physics.aps.org/articles/v4/4, read the article **Does cell biology need physicists?.** Using information in the article and from this presentation, answer the following questions.

1. Describe how a molecule can act as a motor.
2. Explain how polymerization, adhesion, and a contractile mechanism play a part in the movement of cells.
3. Choose and briefly describe at least three methods of cellular swimming.
4. Compare and contrast how bacteria and eukaryotic cells divide.
5. List and describe two ways that cells react to the stiffness of the surrounding environment.
6. How does the quote “It is easier to make a theory of everything than a theory of something” relate to the collaboration between physics and biology?
7. The author states that there are at least two ways that physics can “provide a simpler view of the astounding complexity” seen in biology. Describe one of these ways.

Using at least ten of the words from the box above, write a paragraph describing how physics and biology are working together to create predictive models. Your work is expected to exhibit detail and factually correct information.

The information presented in this lesson is based on the Kavli Institute for Theoretical Physics Teachers' Conference

Physics and Biology:
Evolution of Life and Evolution of Science

Thank you to all of the presenters, organizers, and sponsors:

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- Richard Neher (Max Planck Inst)
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- Rob Phillips (Caltech)
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- Rachel Ross (LCOGT)
- Boris Shraiman (UCSB, KITP)
- KITP
- NSF
- Simon and Diana Raab
- UCSB

And all of the other scientists and teachers that participated and made it a fascinating and productive day!