

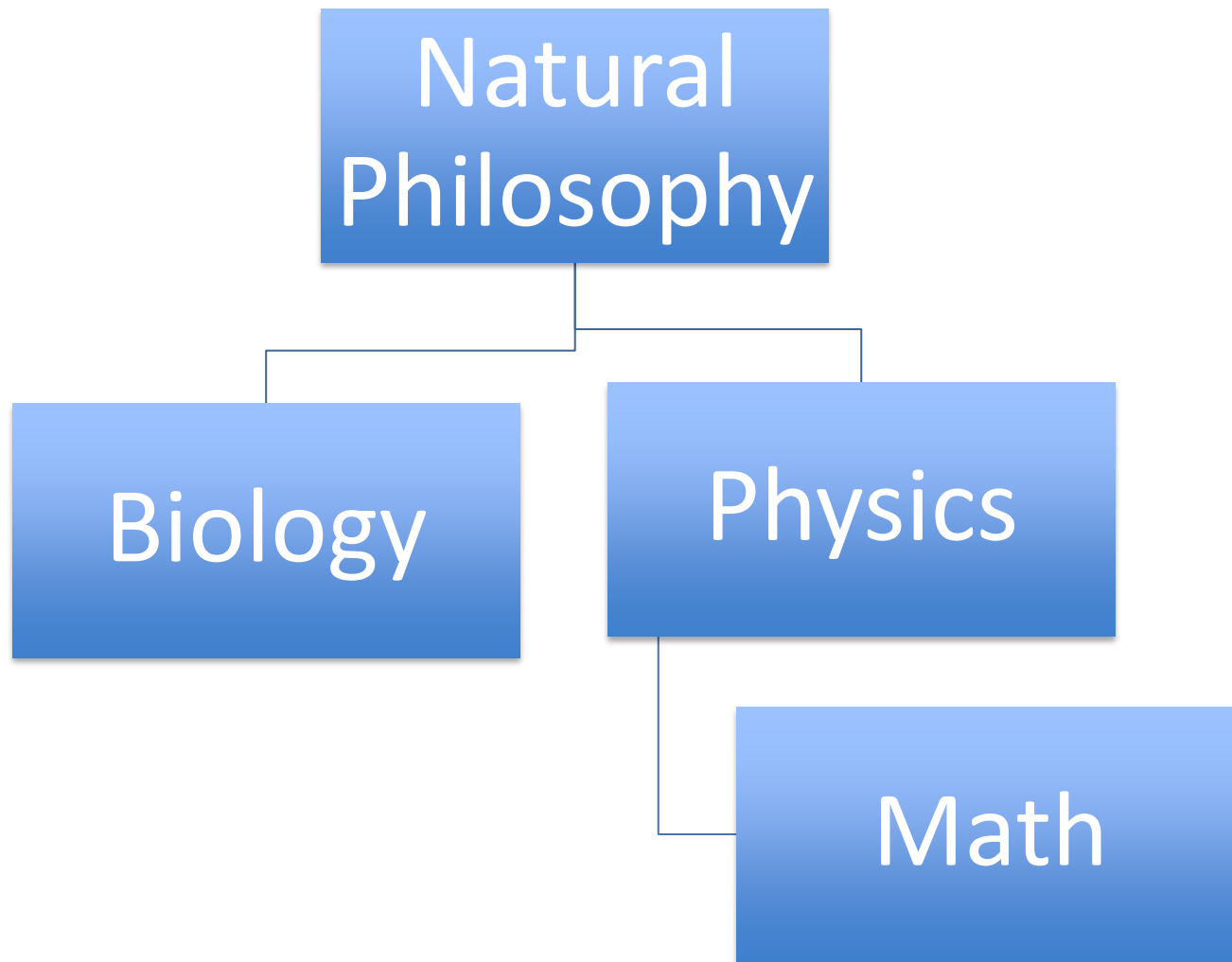
# **Biology & Physics at KITP**

**By**

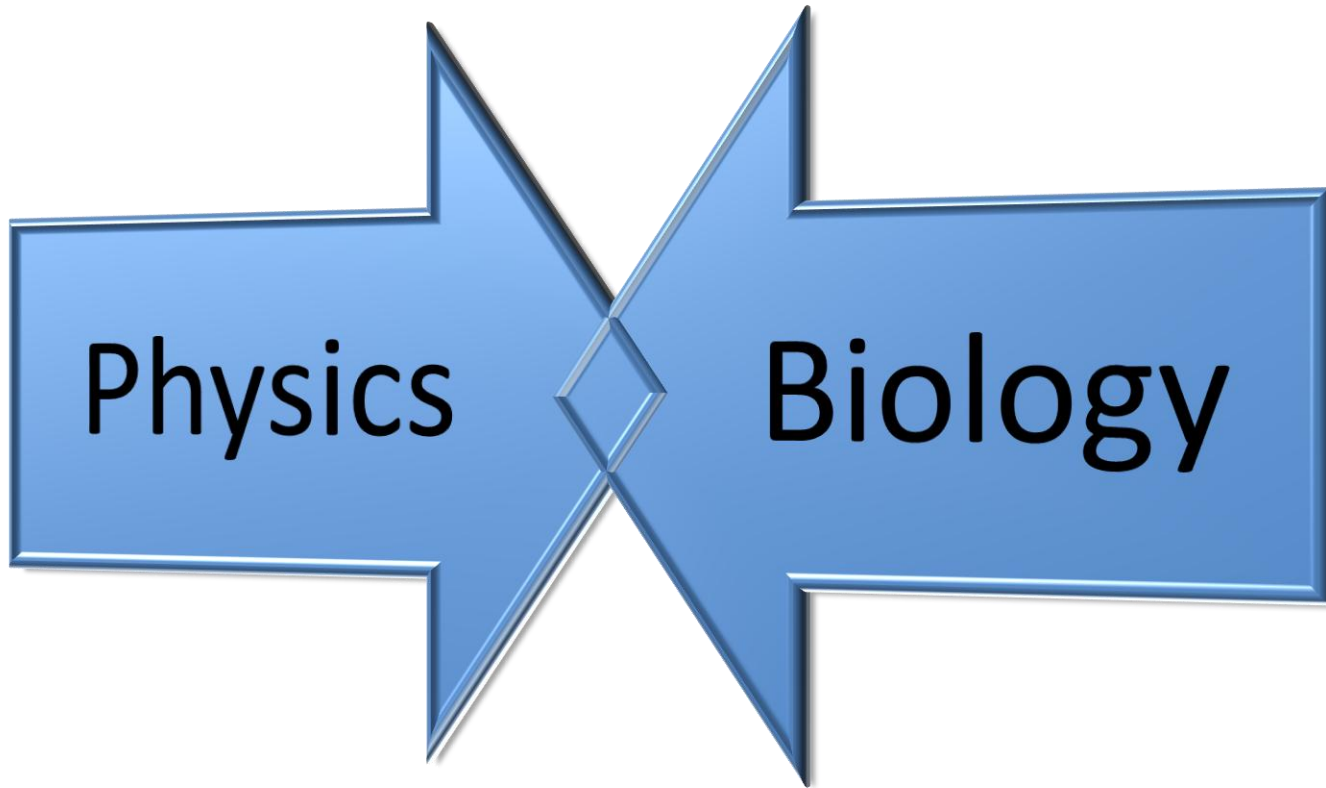
**Terry Hipsher**

# Unexpected Physics in Biology

Boris Shraiman (UCSB, KITP)

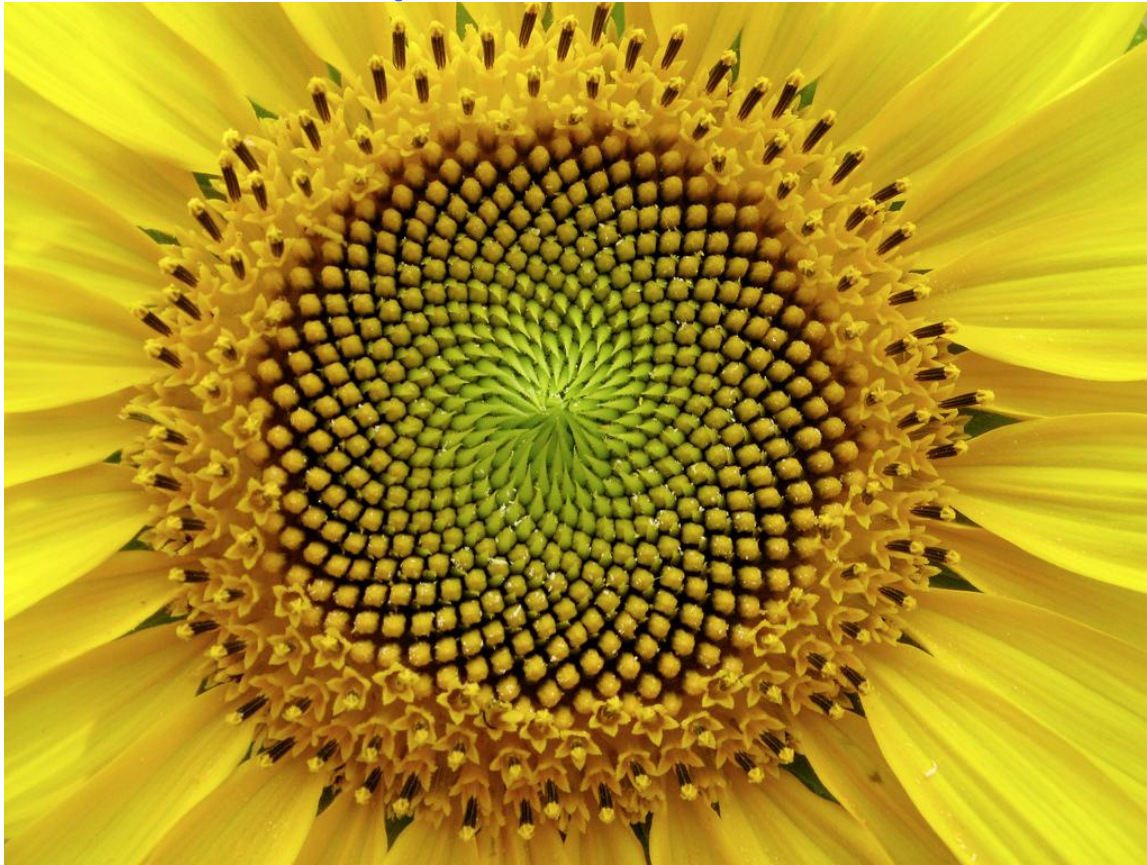


# Today

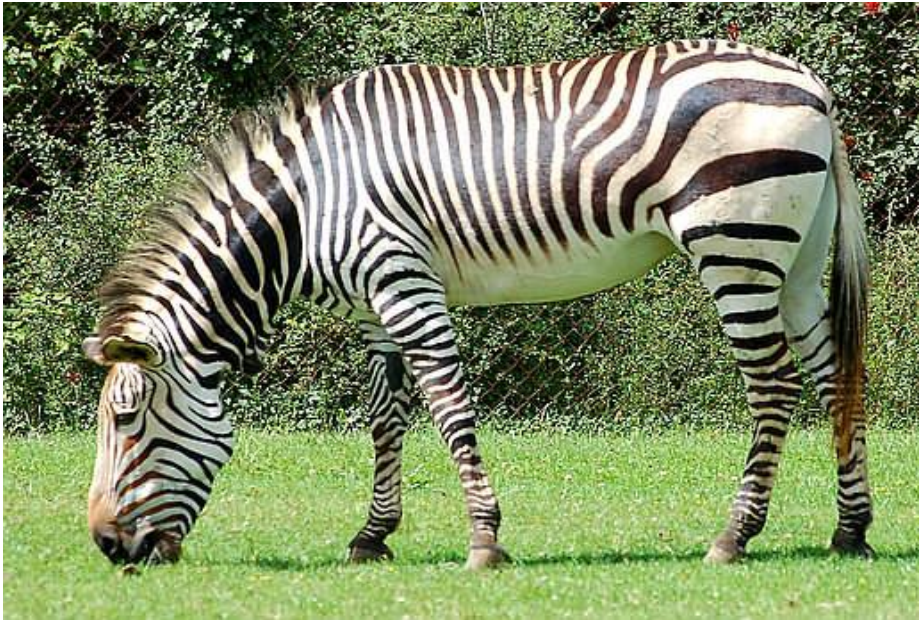


# Morphogenesis: generation of form

- D'Arcy Thompson (1917)
- Wrote book: [On Growth and Form](#)
- Fibonacci sequence in sunflowers



- Alan Turing (1952)
- Chemical basis of morphogenesis-morphogen
- diffusion of activators and inhibitors
- example: zebra stripes

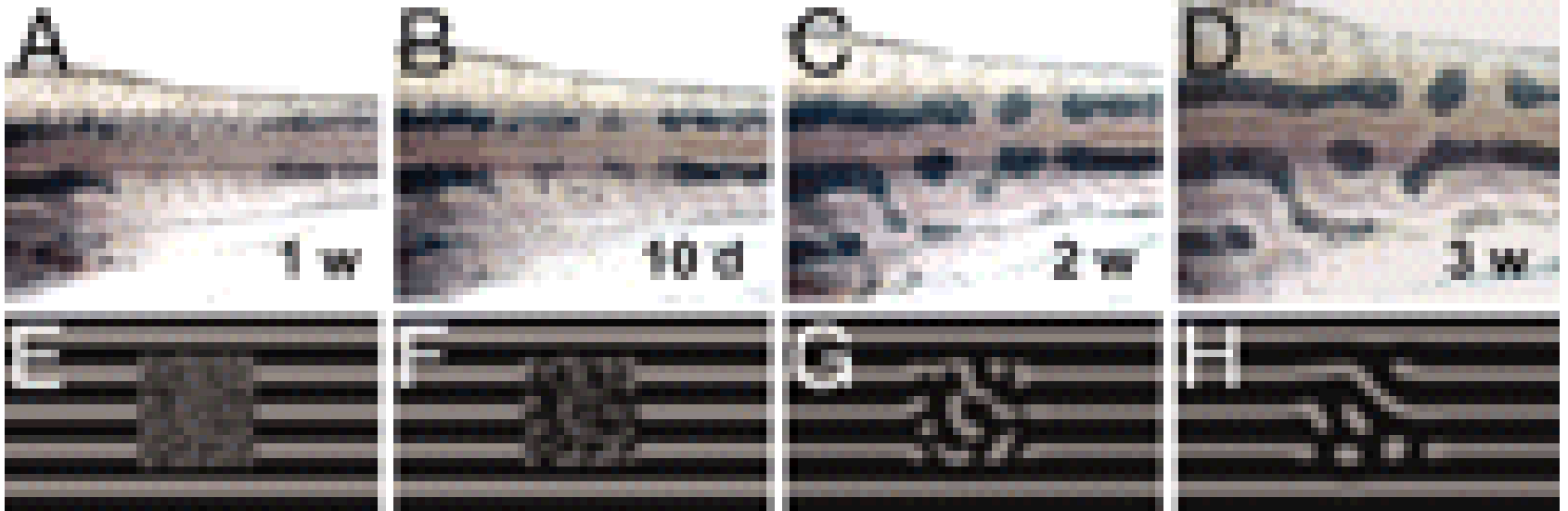


[Morphogenesis Applet](#)

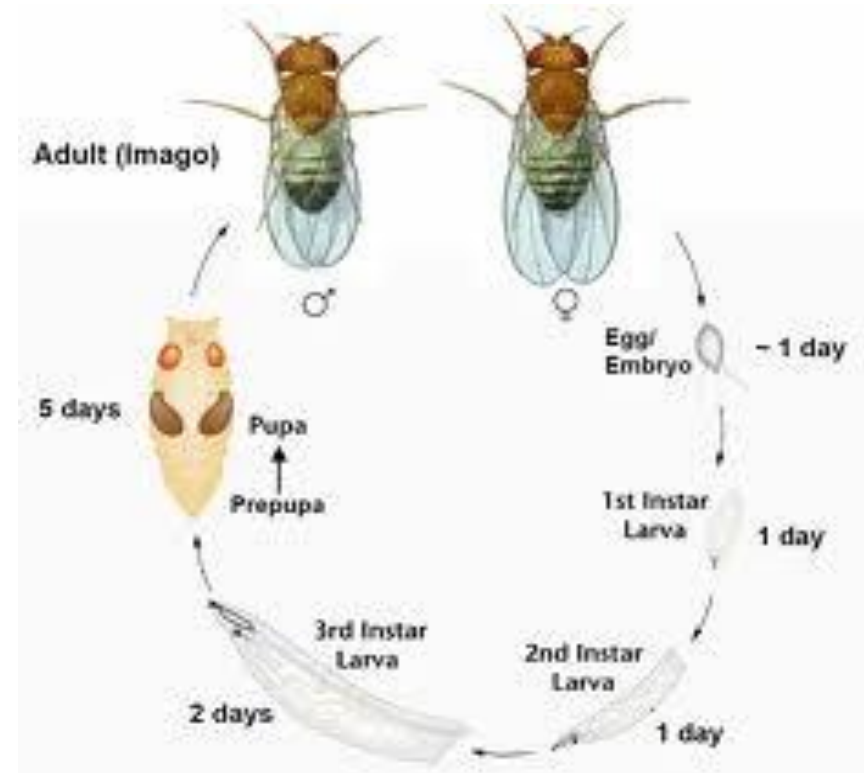
# Leopard gene of zebrafish



- rate of production of activator results in different stripe patterns

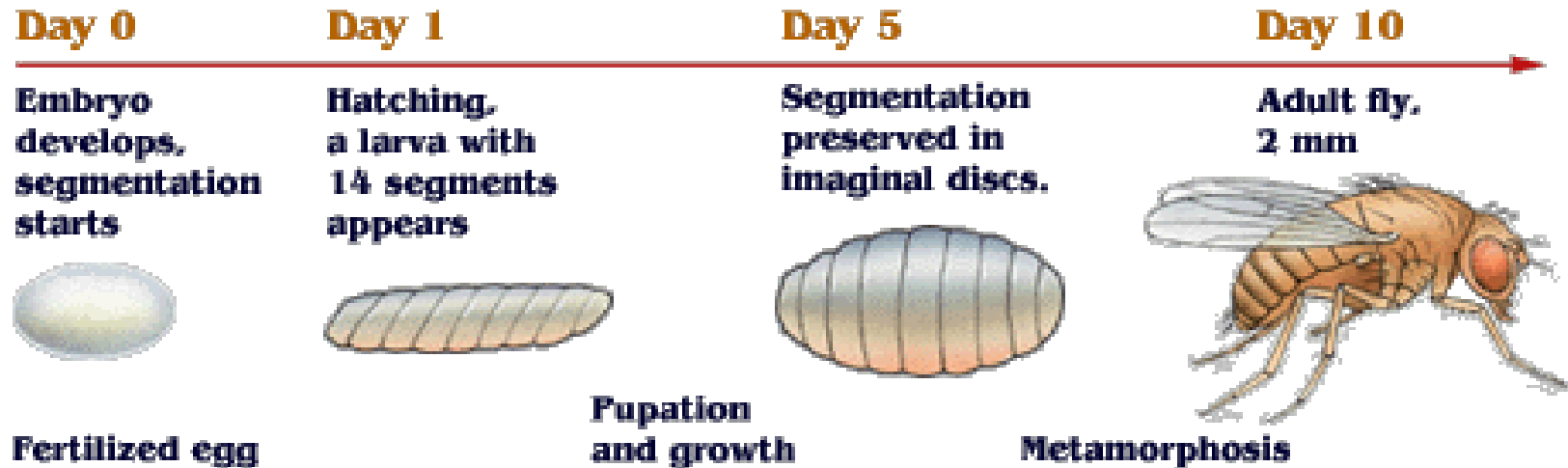


# Drosophila Life Cycle



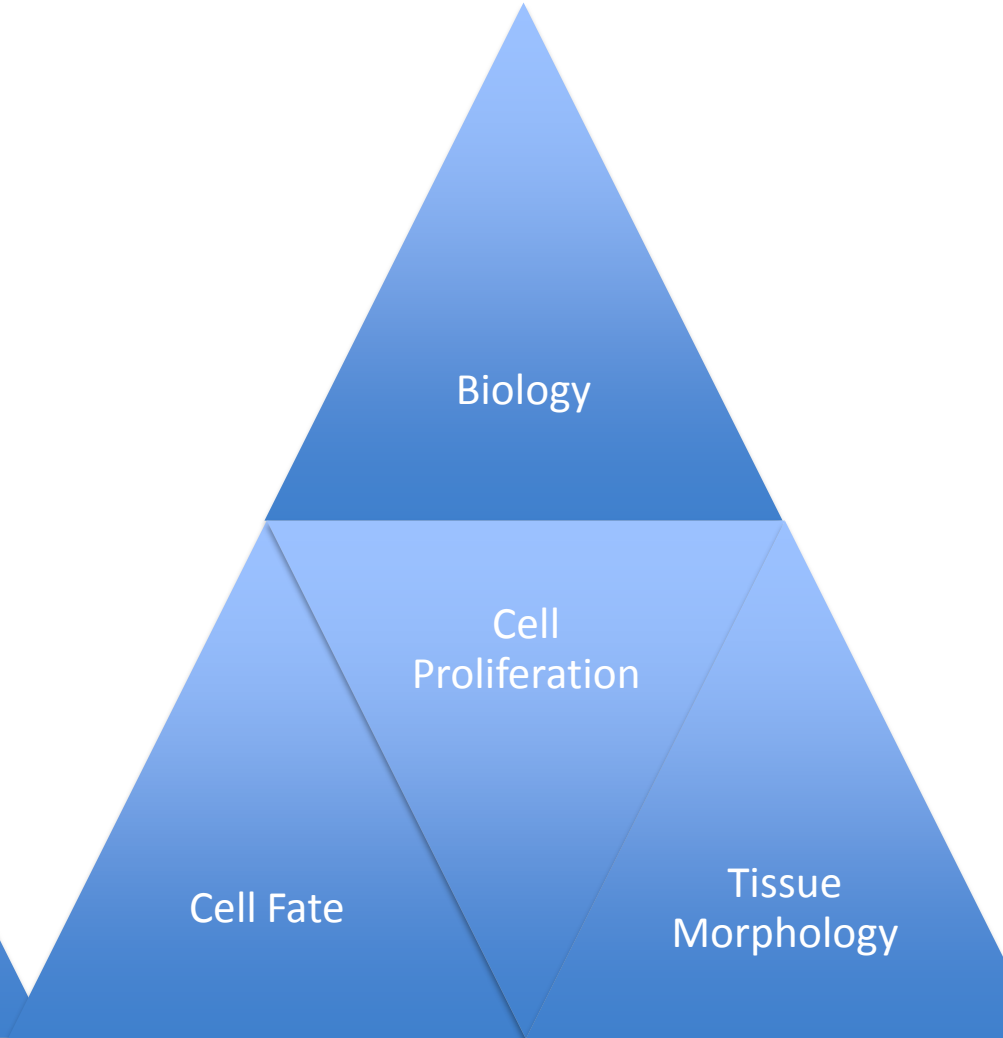
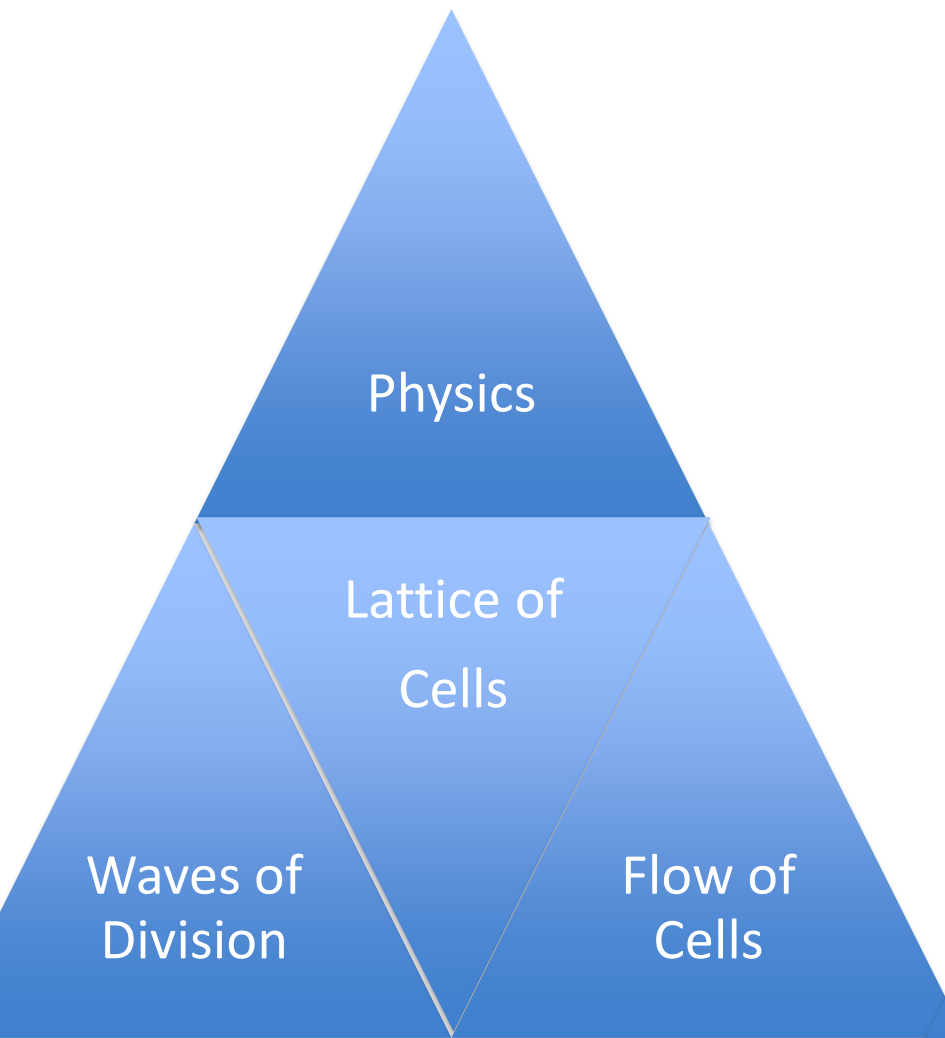
# Fruit Fly Development

## Eric Wieschaus





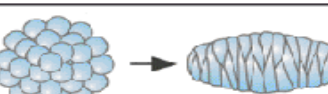

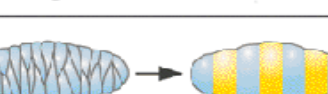
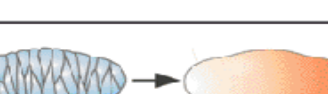
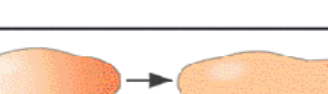


[Drosophila Embryogenesis Movie](#)

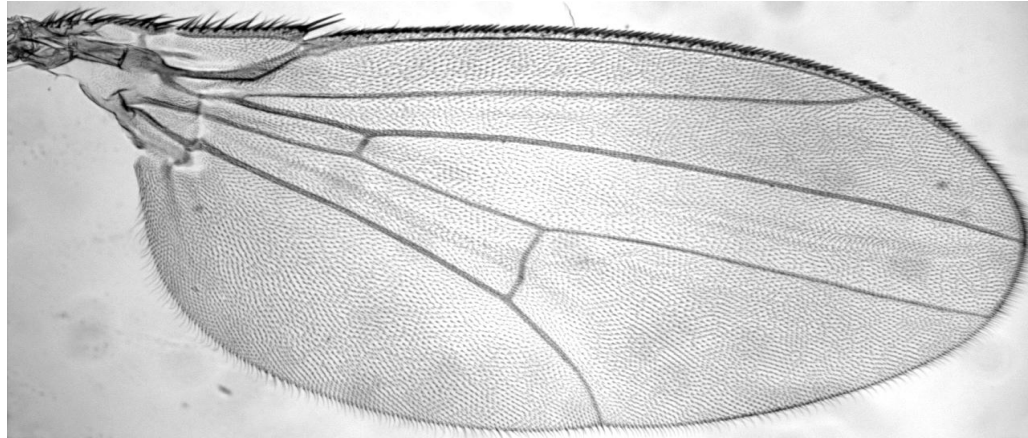




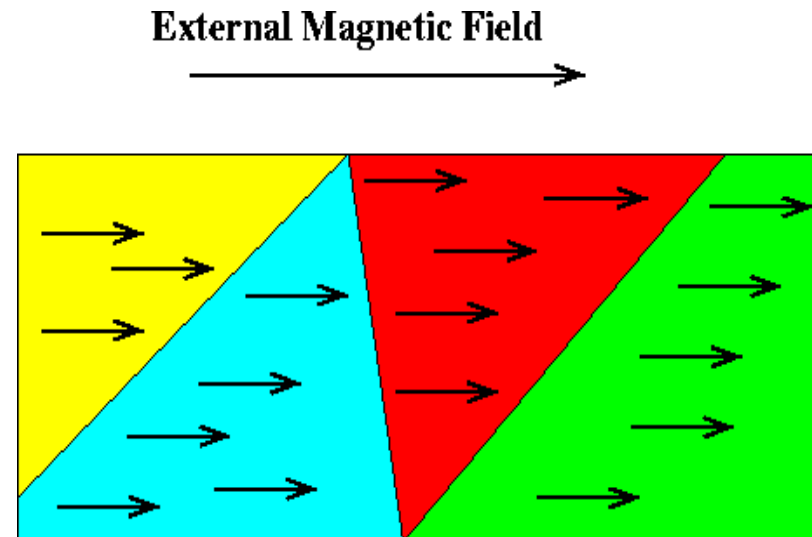
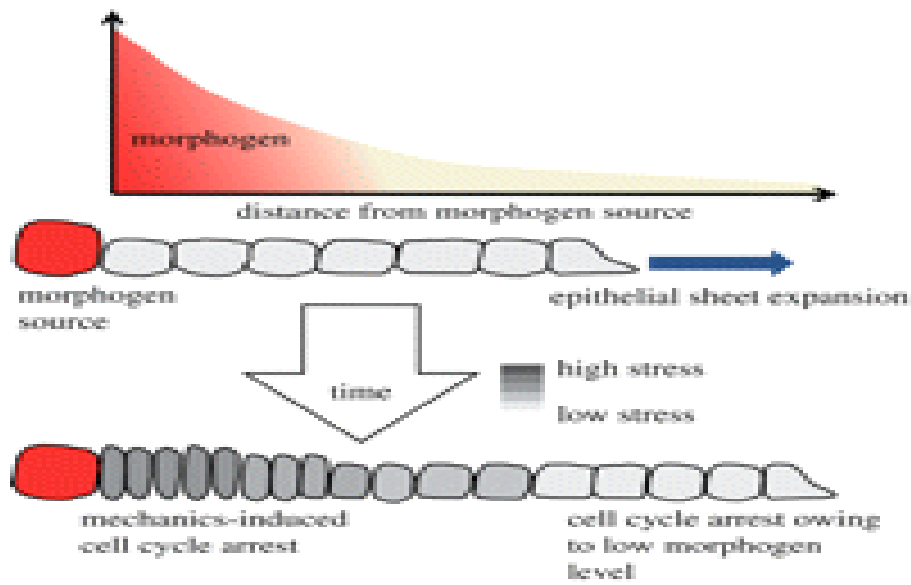
# Genes, Physics & Morphogenesis

DPM	molecules	physics	evo-devo role	effect
ADH	cadherins	adhesion	multicellularity	
LAT	Notch	lateral inhibition	coexistence of alternative cell states	
DAD	cadherins	differential adhesion	phase separation; tissue multilayering	
POL <sub>a</sub>	Wnt	cell surface anisotropy	topological change; interior cavities	
POL <sub>p</sub>	Wnt	cell shape anisotropy	tissue elongation	
ECM	chitin; collagen	stiffness; dispersal	tissue solidification; elasticity; EMT	
OSC	Wnt + Notch	chemical oscillation	segmentation; periodic patterning	
MOR	TGF-β/BMP; FGF; Hh	diffusion	pattern formation	
TUR	MOR + Wnt + Notch	dissipative structure	segmentation; periodic patterning	

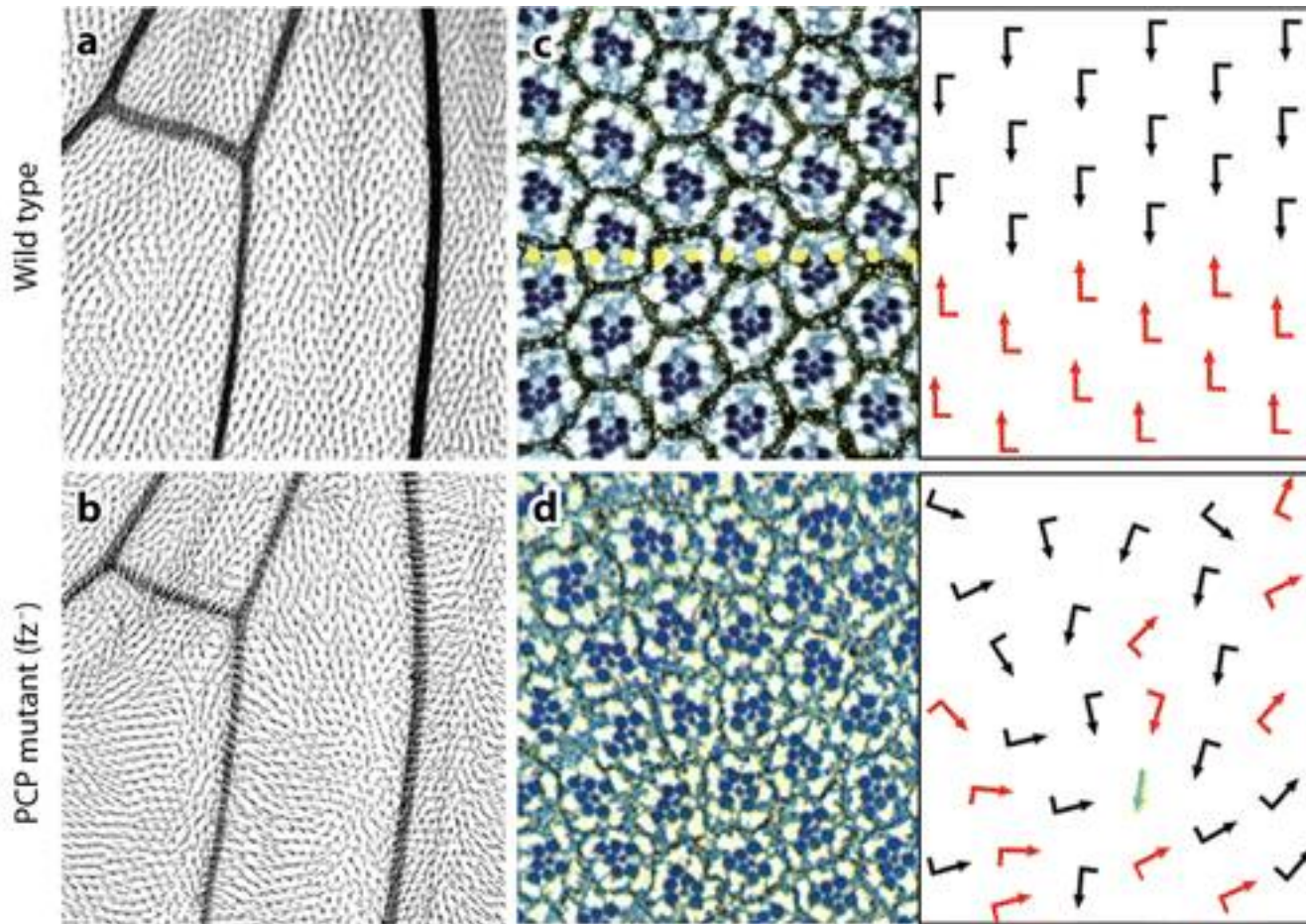
# Global Polarization in Fly Wing



- Morphogen gradient vs Ferromagnetism



# Molecular nature of Planar Cell Polarization (PCP)



# Physical Biology of the Cell

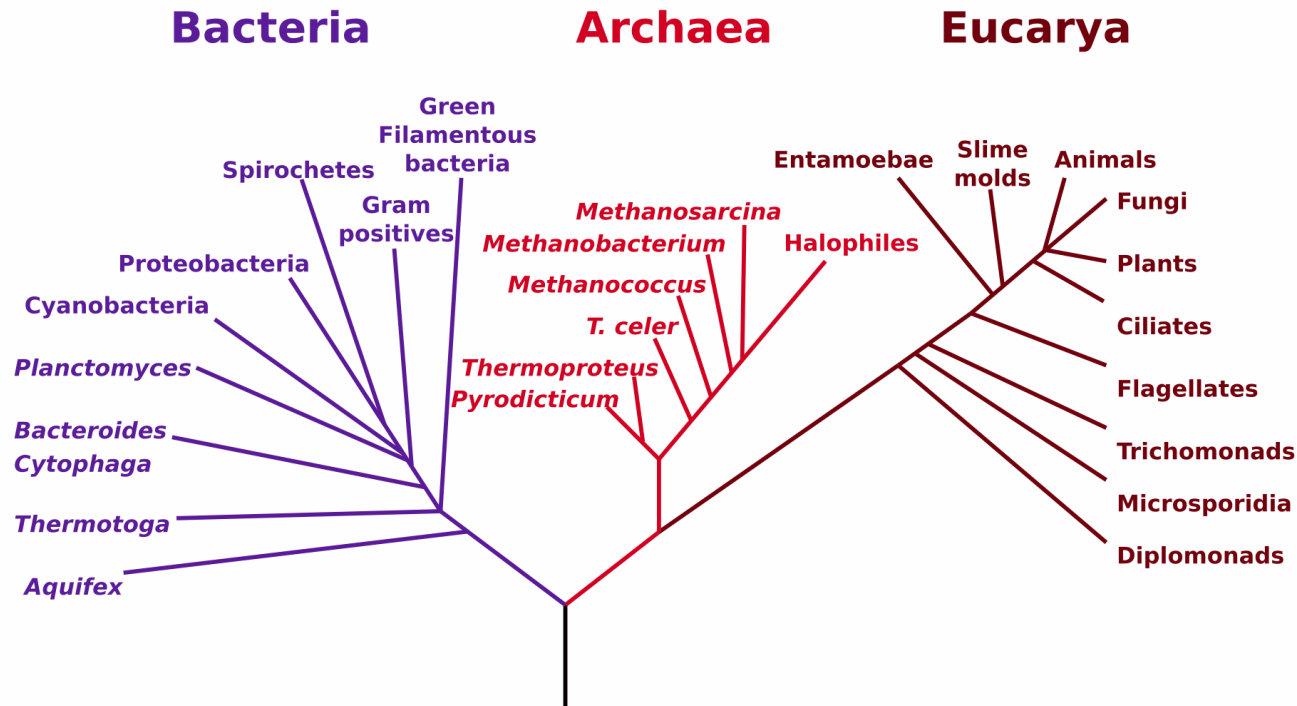
Rob Phillips (Caltech)

- Science has always been propelled by new ways of observing and measuring the world
- Example: Tycho Brahe built new instruments which led to a better understanding of the solar system
- Example: Kepler used Tycho's data to discover the elliptical, not circular, orbit of Mars around the Sun

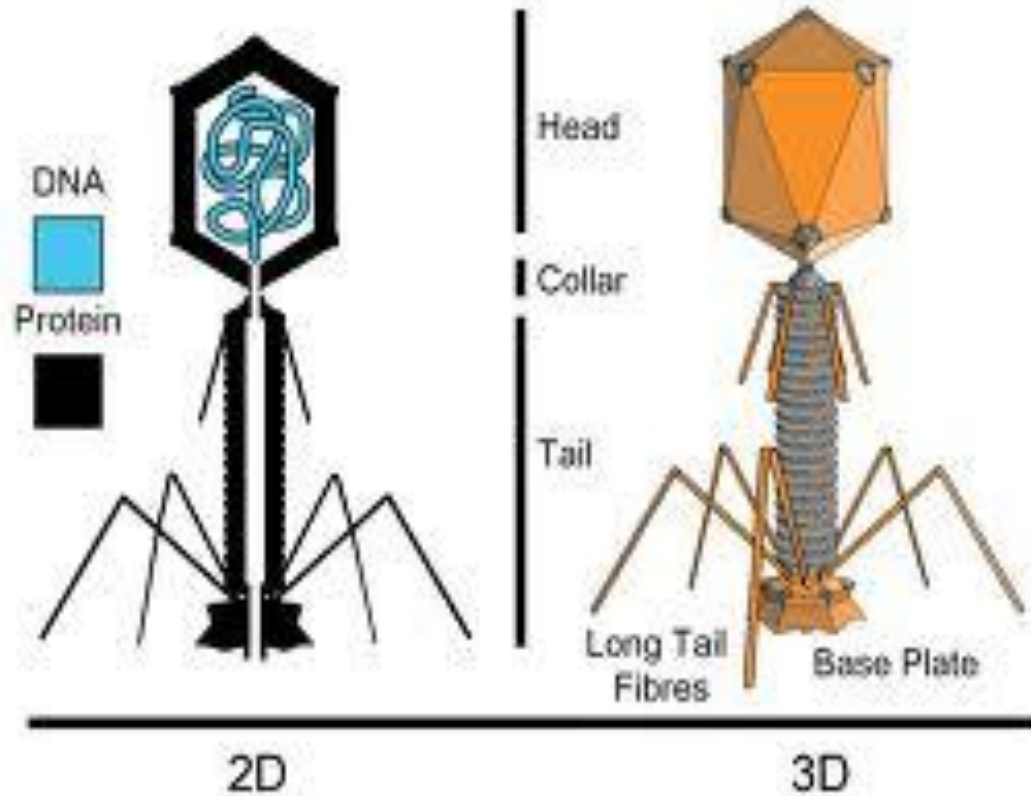
# Biology

- Carl Woese discovered Archaea-a new Domain of life by studying ribosomal RNA

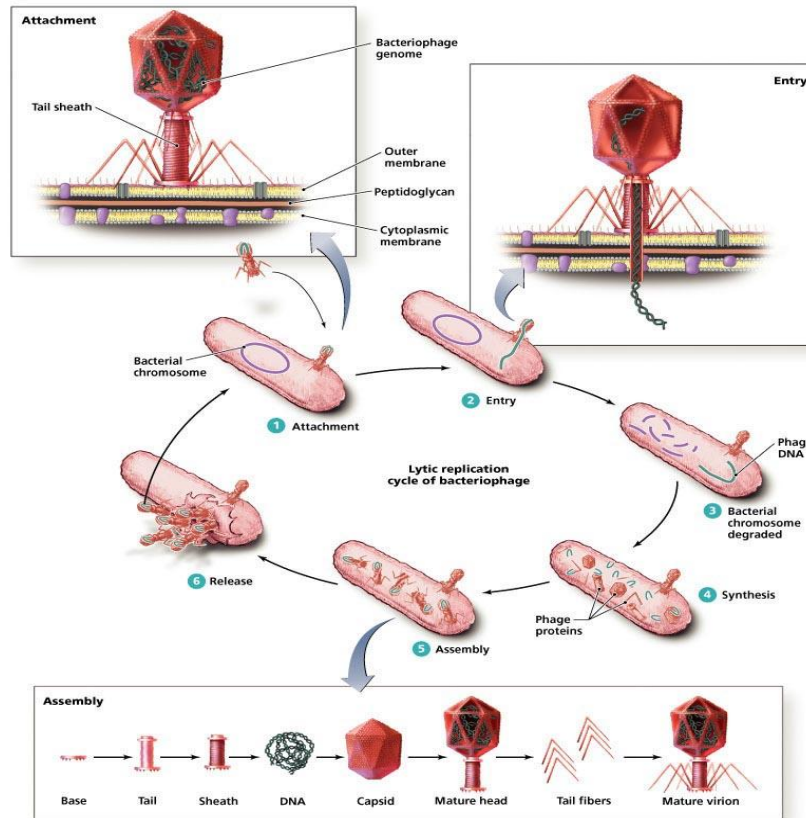
## Phylogenetic Tree of Life



# Bacteriophage



# Bacteriophage Lytic Cycle



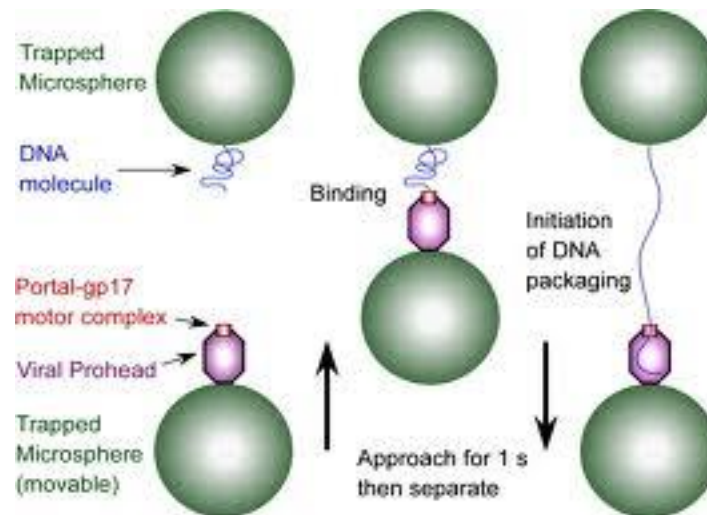
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## [Bacteriophage Lytic Cycle Movie](#)

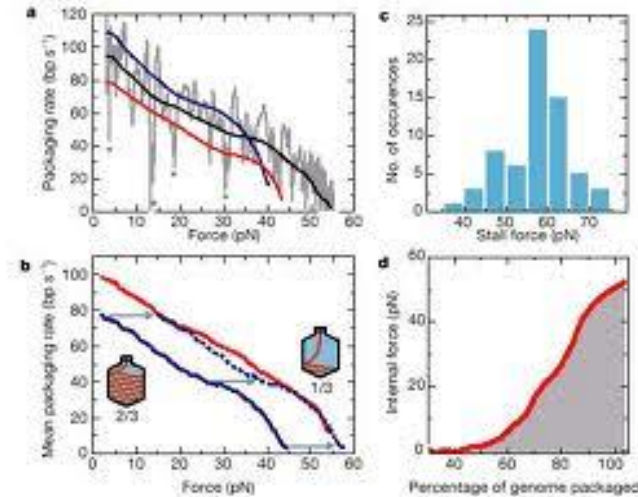
## [Lytic Cycle Step by Step](#)



# Optical Tweezers Measure Forces



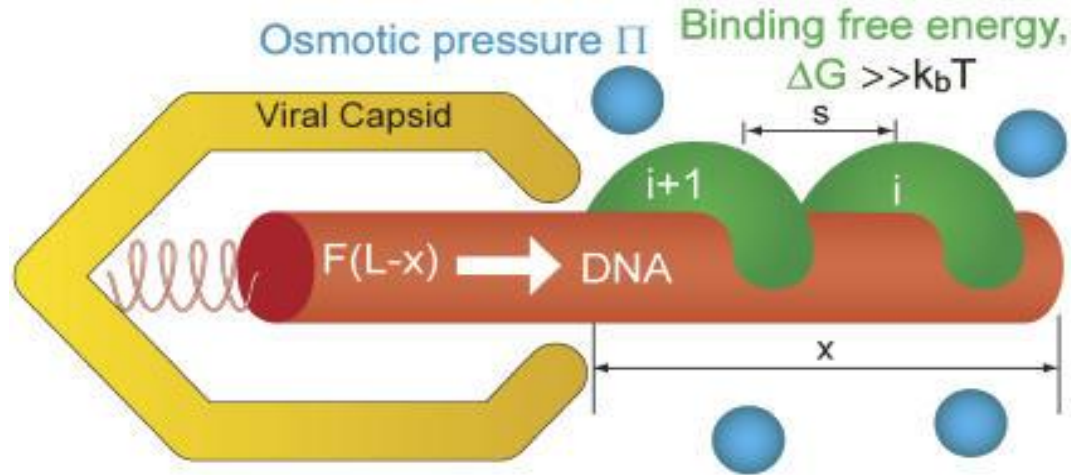
# DNA Packaging in Bacteriophages



Area under curve in bottom right graph is a measure of the energy required to pack DNA inside the head of the phage.

Notice the energy increases greatly as more DNA is packed. High energy is due to DNA **stiffness** and **negative charge**.

# Physics of DNA Ejections



- [Bacteriophage Lambda DNA Ejection Movie](#)
- Kinematic equations (L vs T) can be determined from this video
- Try to find relationship between velocity and driving force

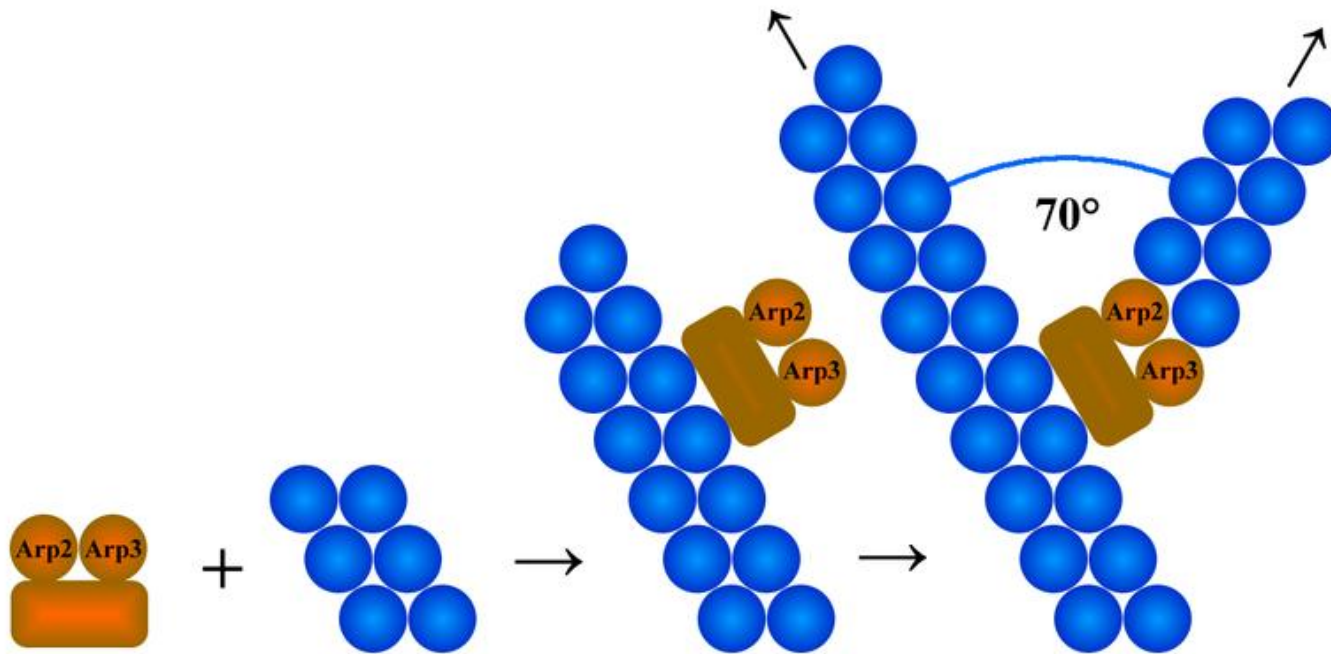
# David Roger's Classic Video

- Neutrophil Eating Staph aureus bacteria (surrounded by red blood cells)

# Cell Motility & Actin Polymerization

- How do cells decide where to move?
- [Cell Motility Video](#)- 2nd video down
- Lysteria bacteria hijack host actin polymerization machinery in order to move around-they look like comets

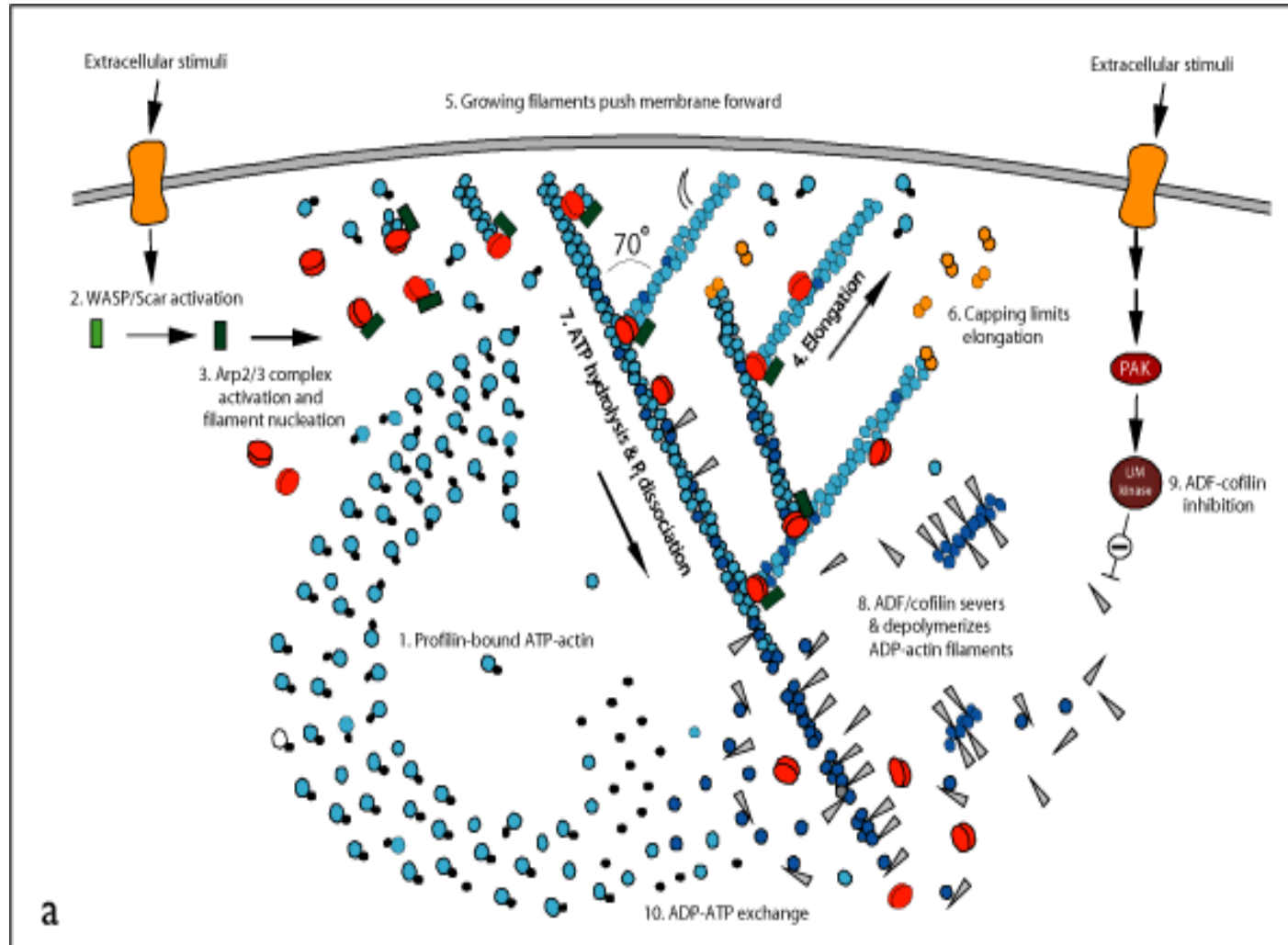
# Polymerization of Actin



Side branching model of the Arp2/3 complex. Activated Arp2/3 complex binds to the side of a "mother" actin filament. Both Arp2 and Arp3 form the first two subunits in the new "daughter" filament.

# Cell Motility & Actin Polymerization

## Leading Edge of Cell



# Life at the Single Cell Level

## Michael Elowitz (Caltech)

- Cells contain a high density of molecules
- Gene circuits involve specific interactions between genes and proteins
- Similar to electrical circuits, but different
  - **not stable, dynamic**
  - **noisy, or nondeterministic**
  - **complex**



# Synthetic Biology

- Construct simple gene circuits
- Use movies to analyze gene circuits at the single-cell level
- Goal: quantitative understanding of gene circuit design principles

# Clock Circuits-Circadian Rhythms

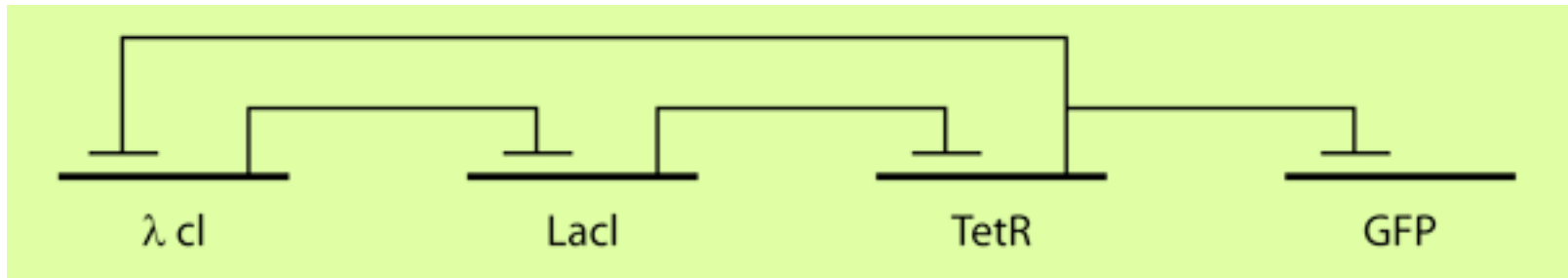
- found in *Drosophila*, humans, and single celled bacteria
- *Drosophila* have a time-delayed negative feedback loop for producing proteins

# Repressilator

- a synthetic genetic clock
- similar to rock, paper, scissors game



# Repressilator



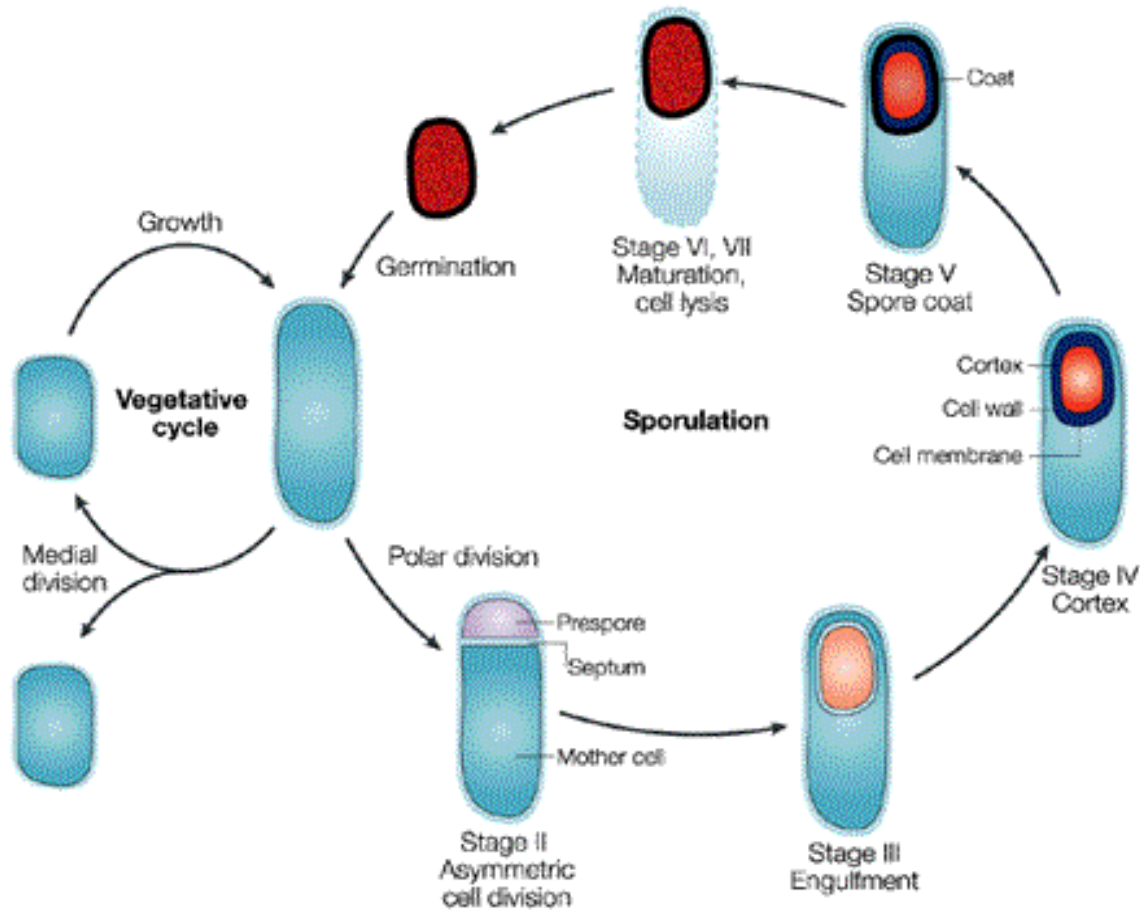
- The repressilator consists of three genes connected in a feedback loop, such that each gene represses the next gene in the loop, and is repressed by the previous gene
- Green fluorescent protein(GFP) is used as a reporter so that the behavior of the network can be observed using fluorescence microscopy.



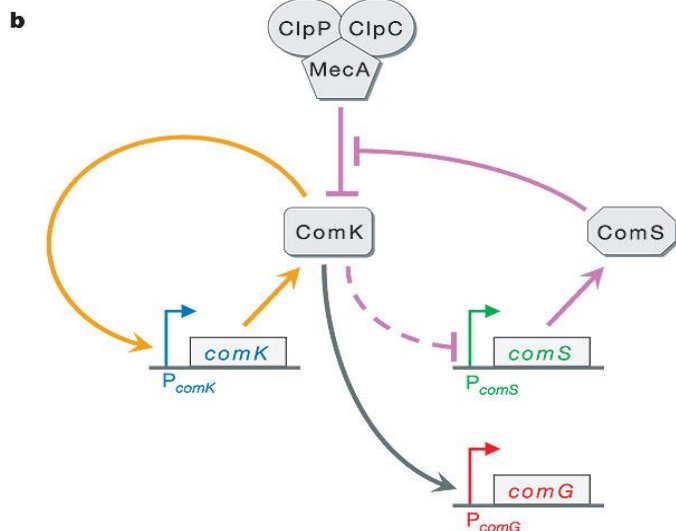
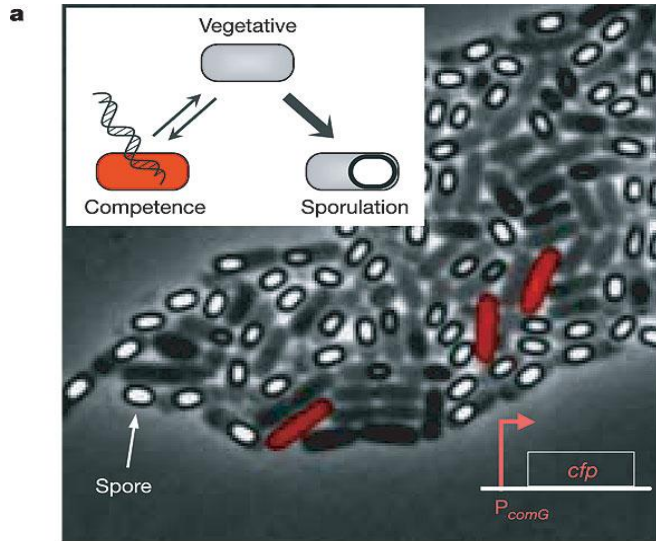
# Repressilator Movies

- [Repressilator Turning on and off movie](#) –click last movie
- [Hasty Lab Movie](#)
- [Elowitz Lab Movies](#)

# Bacillus subtilis Life Cycle



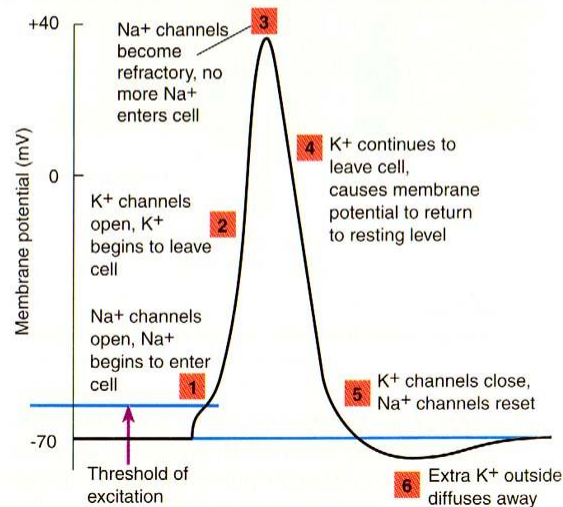
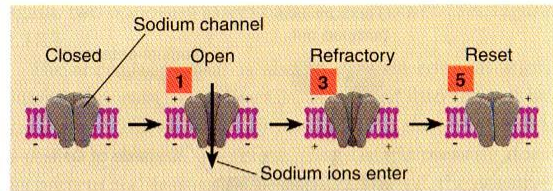
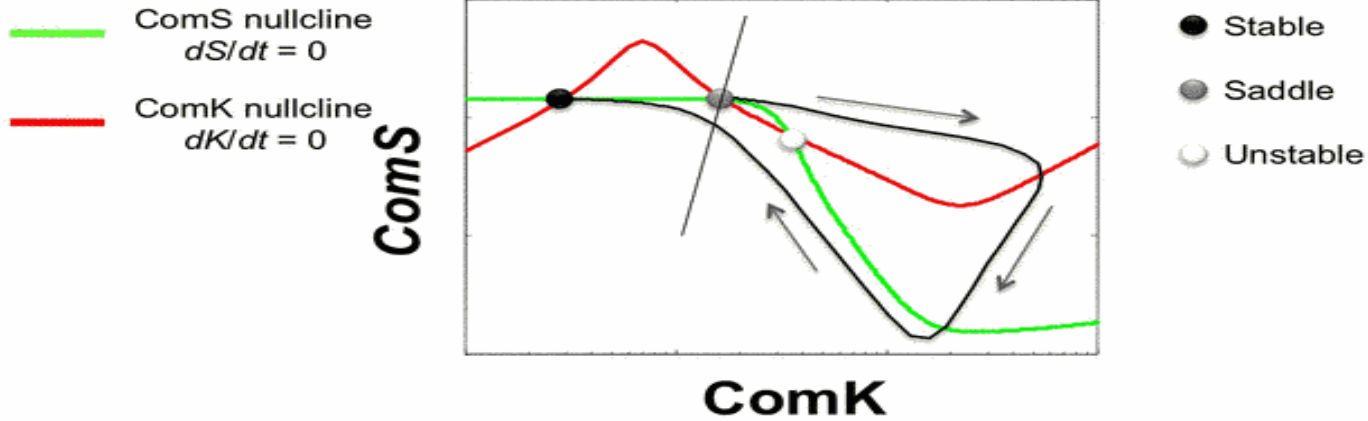
# Feedback Circuits in *Bacillus subtilis*



Map of interactions within the core competence circuit (MeKS). The transcriptional autoregulatory positive feedback loop of ComK and the ComS-mediated indirect negative feedback loop are depicted in orange and purple, respectively. ComS competes with ComK for degradation by the MecA–ClpP–ClpC complex, effectively interfering with degradation of ComK (curved purple inhibitory arrow). The dashed purple line from ComK to  $P_{comS}$  denotes indirect repression. The activities of the promoters labelled in red, blue and green were measured in this study



# Excitability: A Design Principle for Probabilistic, Transient Differentiation

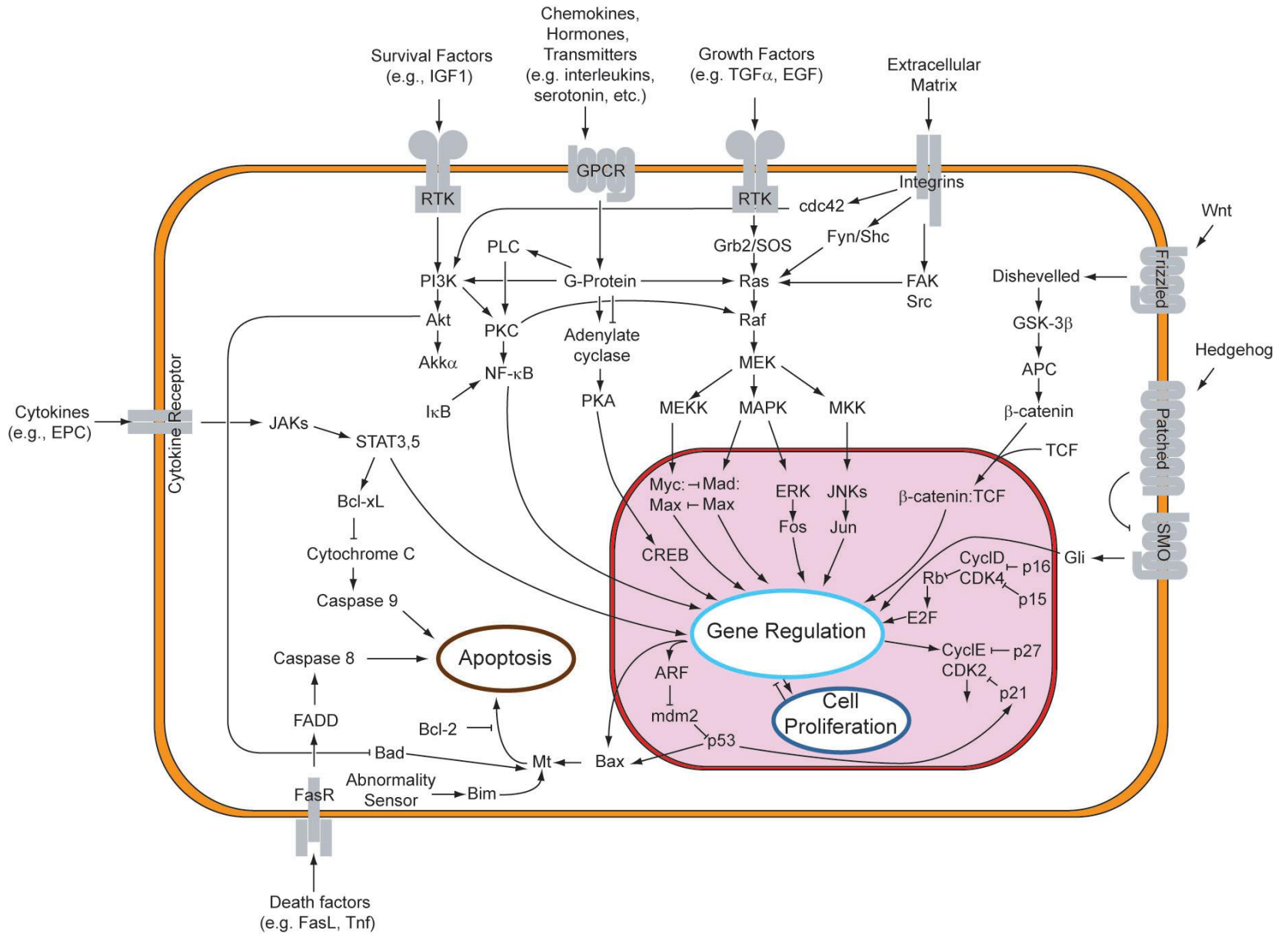


Action potential in neurons is another excitable system in biology

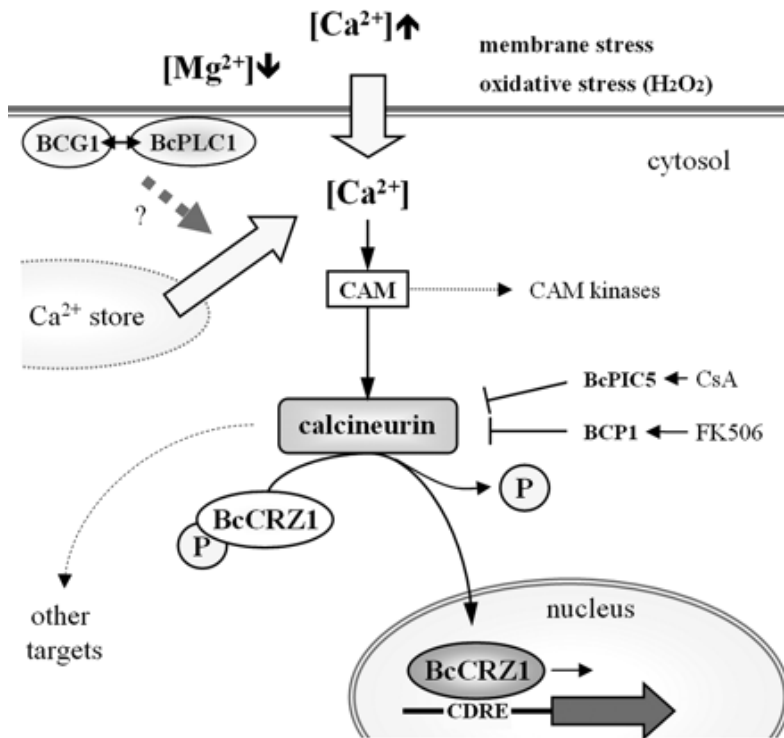
# Why are cells noisy?

- Expression of regulatory proteins in bacteria is variable, or "noisy"
- Noise is evolvable
- Why?
- Hypothesis: noise causes differentiation or **diversity**, ie. vegetative vs. competent cells
- Experiment: making cells large, by reducing cell division frequency, reduces the amount of differentiation in *B. subtilis*

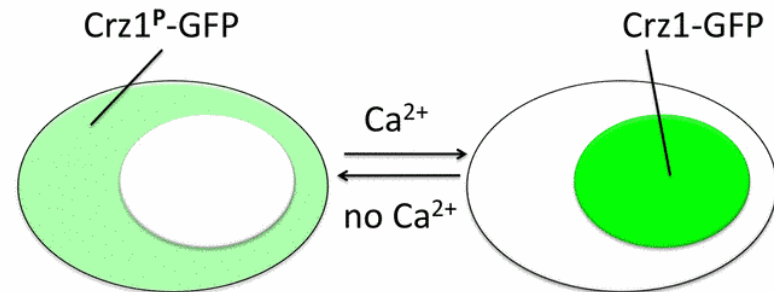
# Cell Signaling Pathways



# Calcium signaling using GFP-Crz1 hybrid protein (green fluorescent protein; crz1 is a transcription factor)

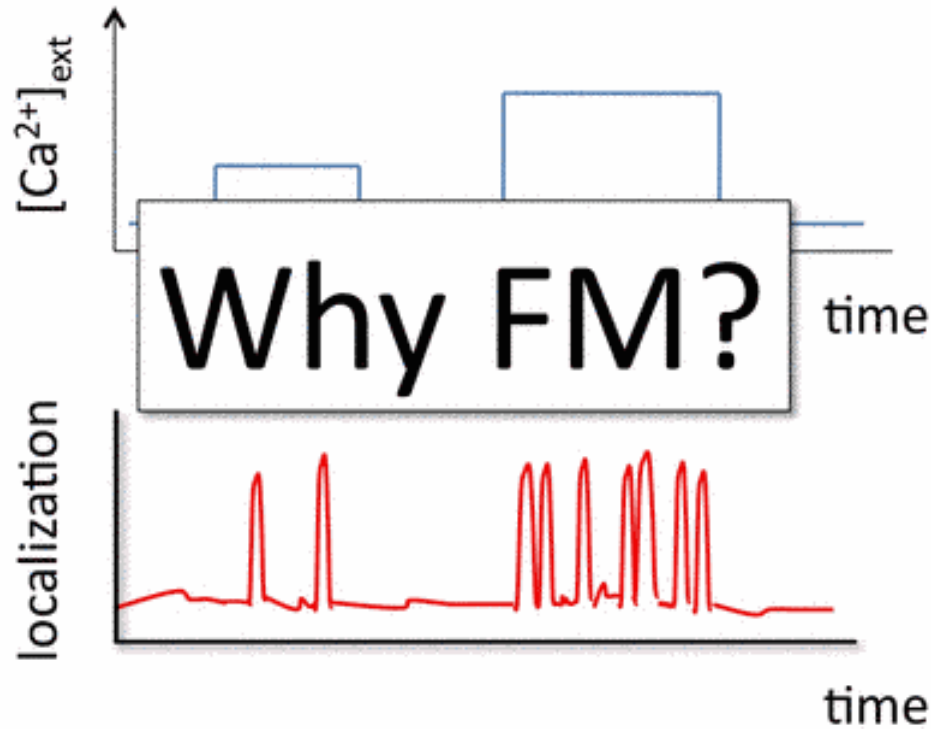


Crz1-GFP localization can be observed in individual cells

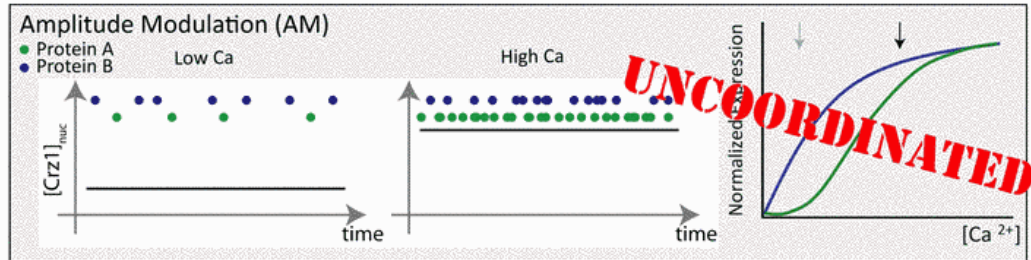
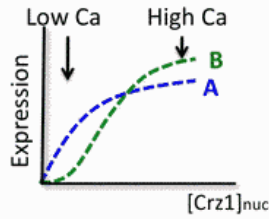


# Calcium Signaling uses FM

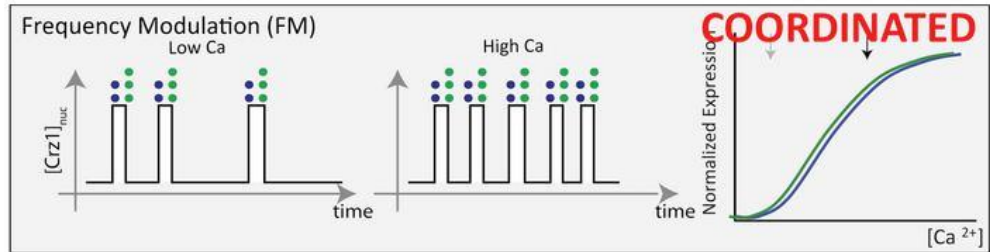
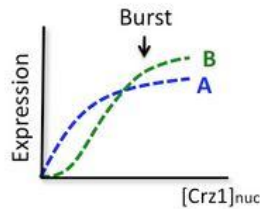
## Frequency Modulation (FM)



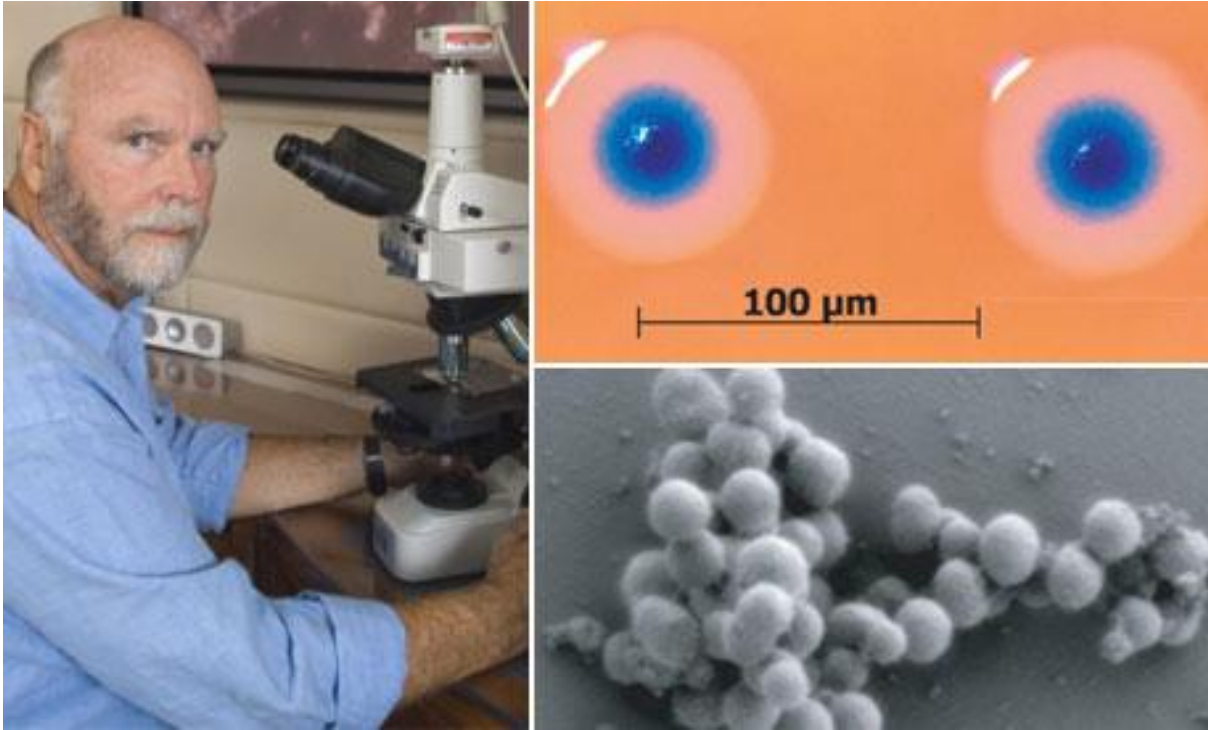
# AM Fails to Coordinate Expression



# FM Coordinates Expression



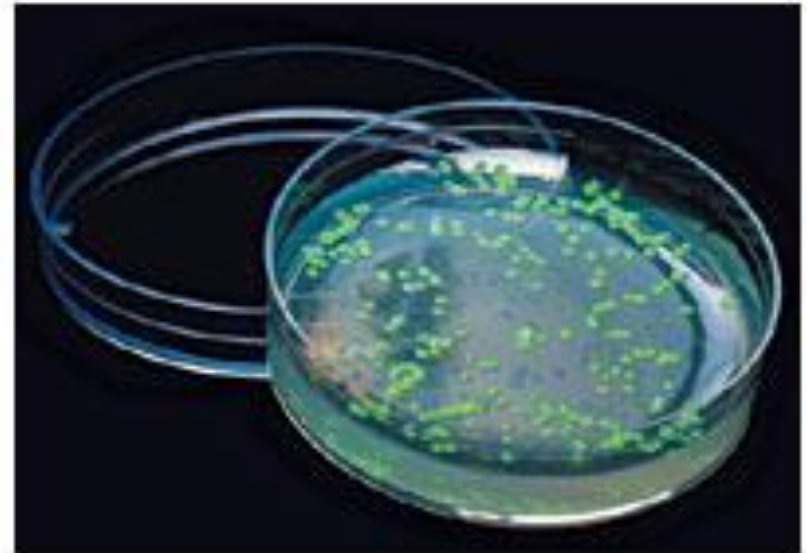
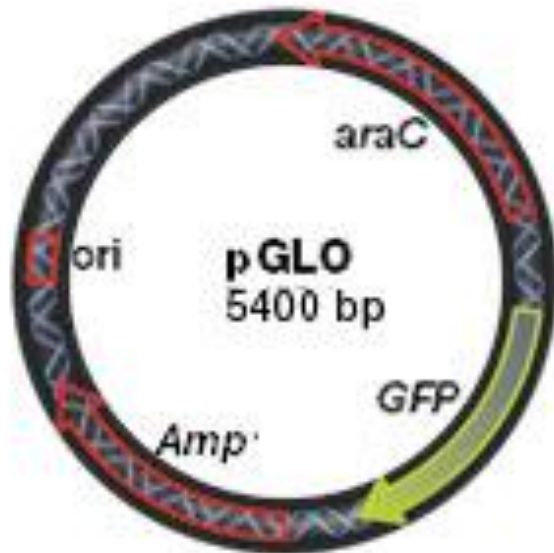
# Synthetic Life



- Craig Venter's group has synthesized the entire genome of a bacterium
- [Craig Venter Video](#)

# Genetic Engineering in the Classroom

- [Bio-rad Transformation Kit URL](#)

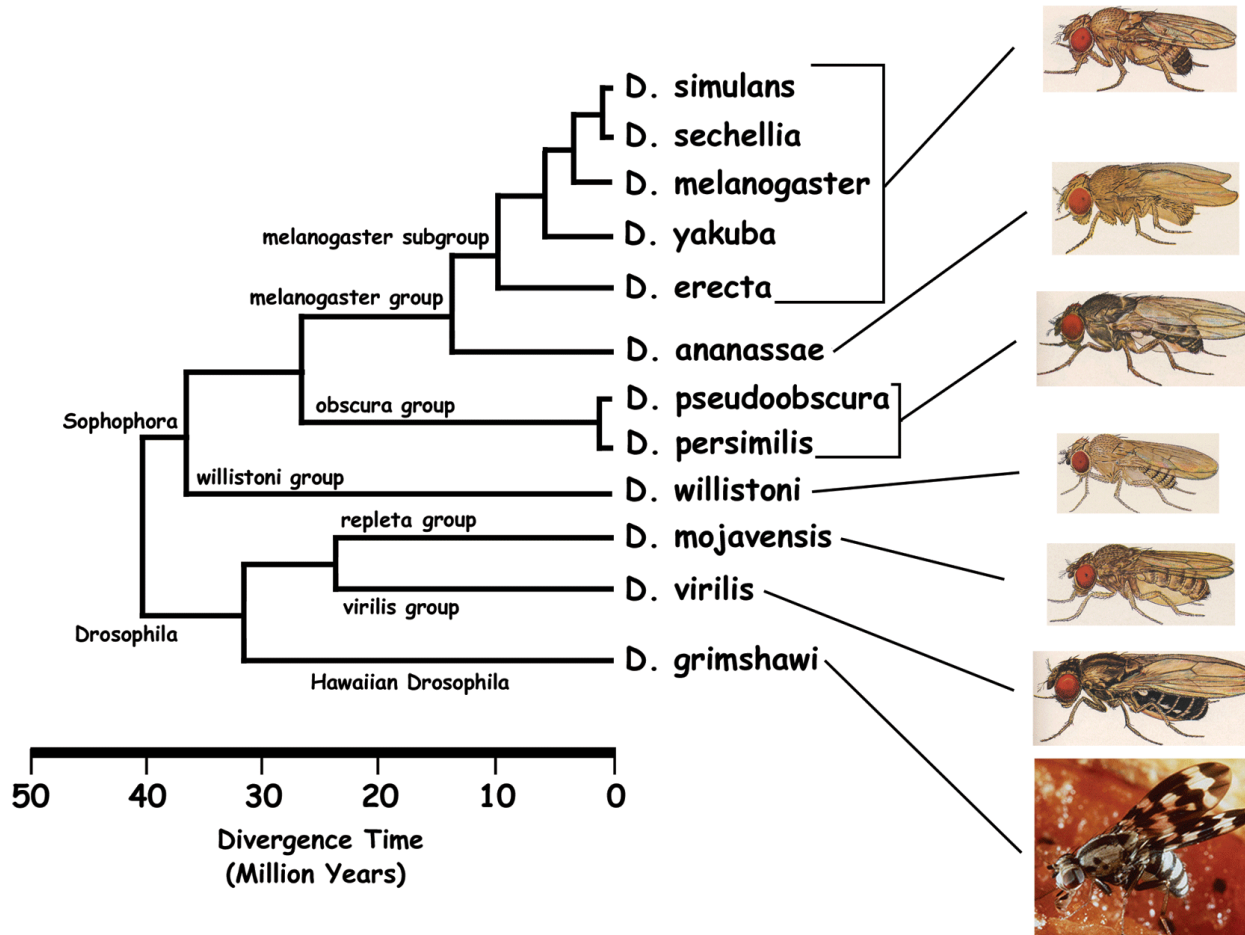




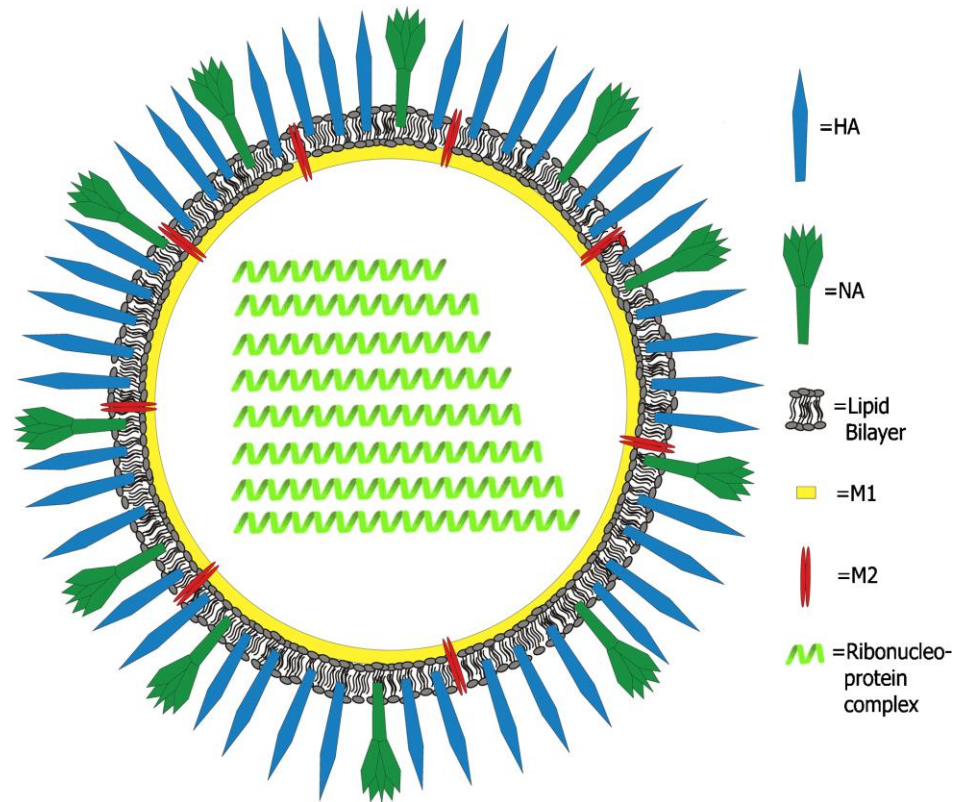
# Watching Evolution Happen

## Richard Neher (Max Planck Inst)

- Drosophila Fruit Flies



- Influenza Virus-has 8 RNA segments which can be packaged in different ways when they infect birds, pigs, or humans



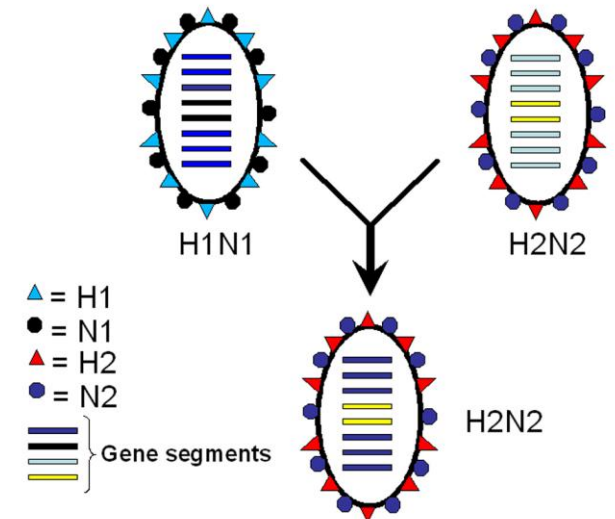
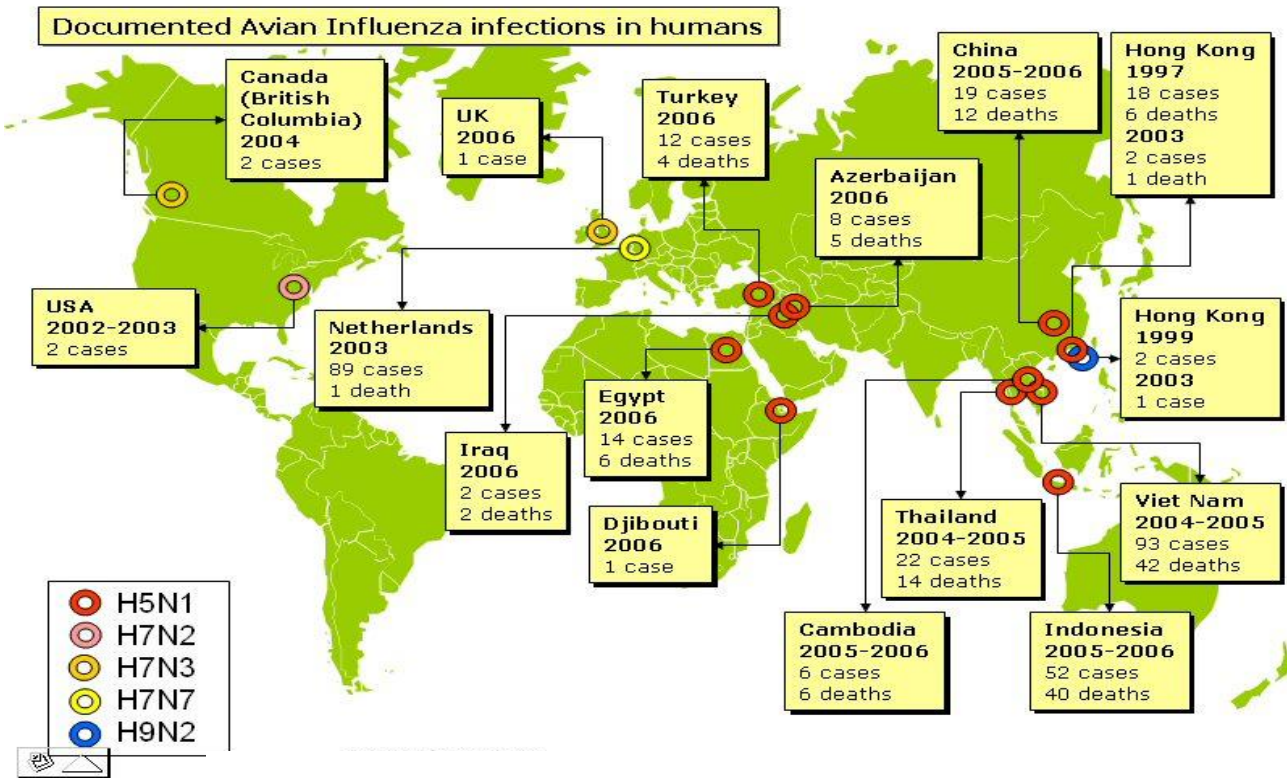
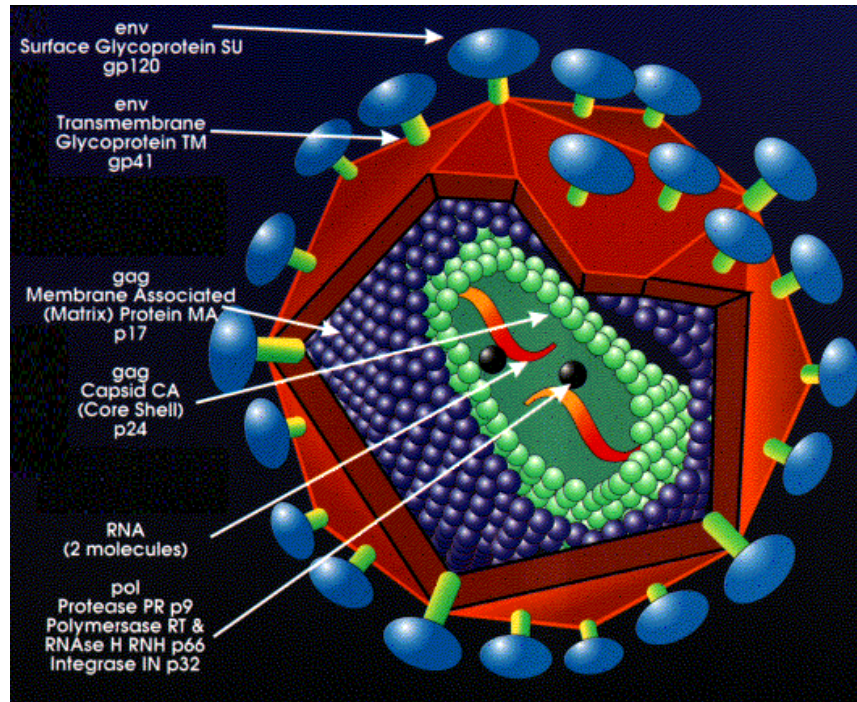


Figure 4. Mechanism of reassortment of RNA segments of influenza virus

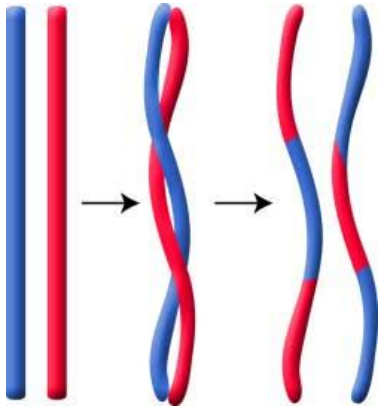
# HIV- human immunodeficiency virus



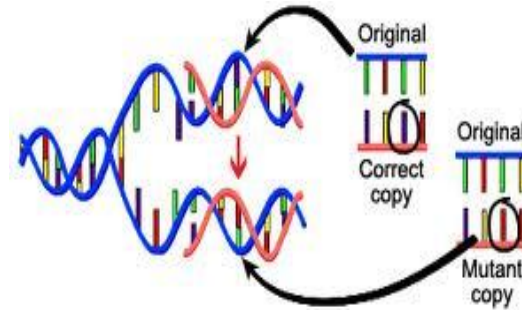
- HIV has rapid mutation rate which makes finding a vaccine difficult
- 8% divergence in DNA in 10 years in a single patient
- Evolves to avoid host immune system and antiviral drugs

# Steps of Evolution

## Crossing Over



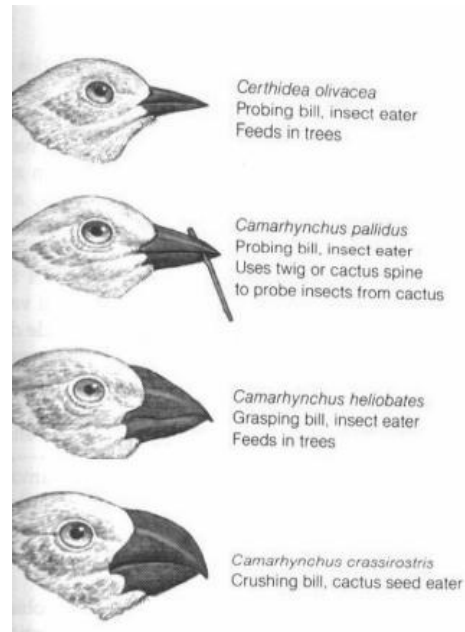
## Mutation



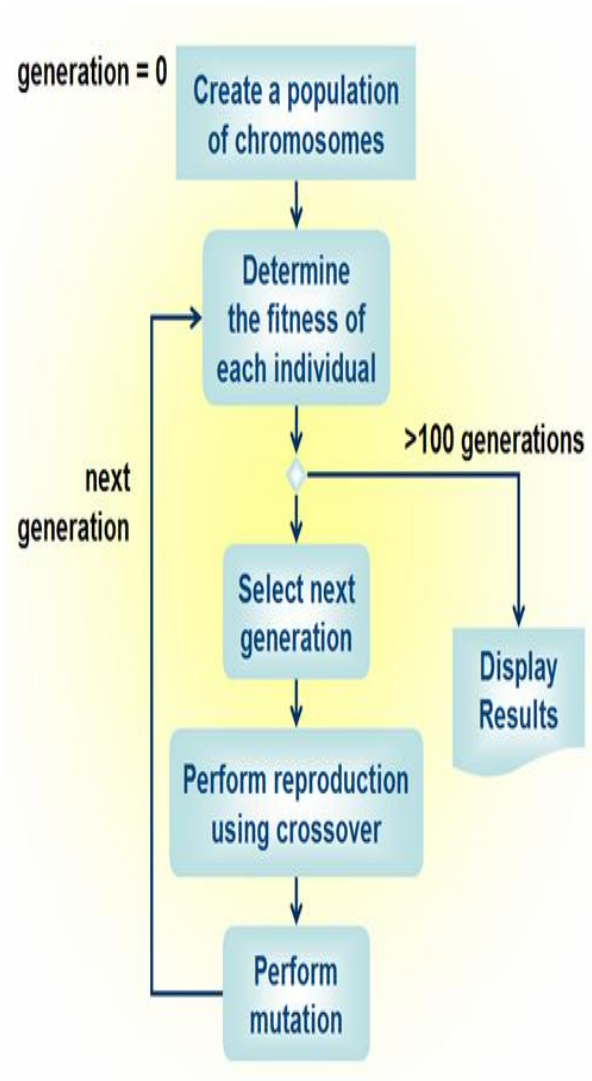
## Reproduction



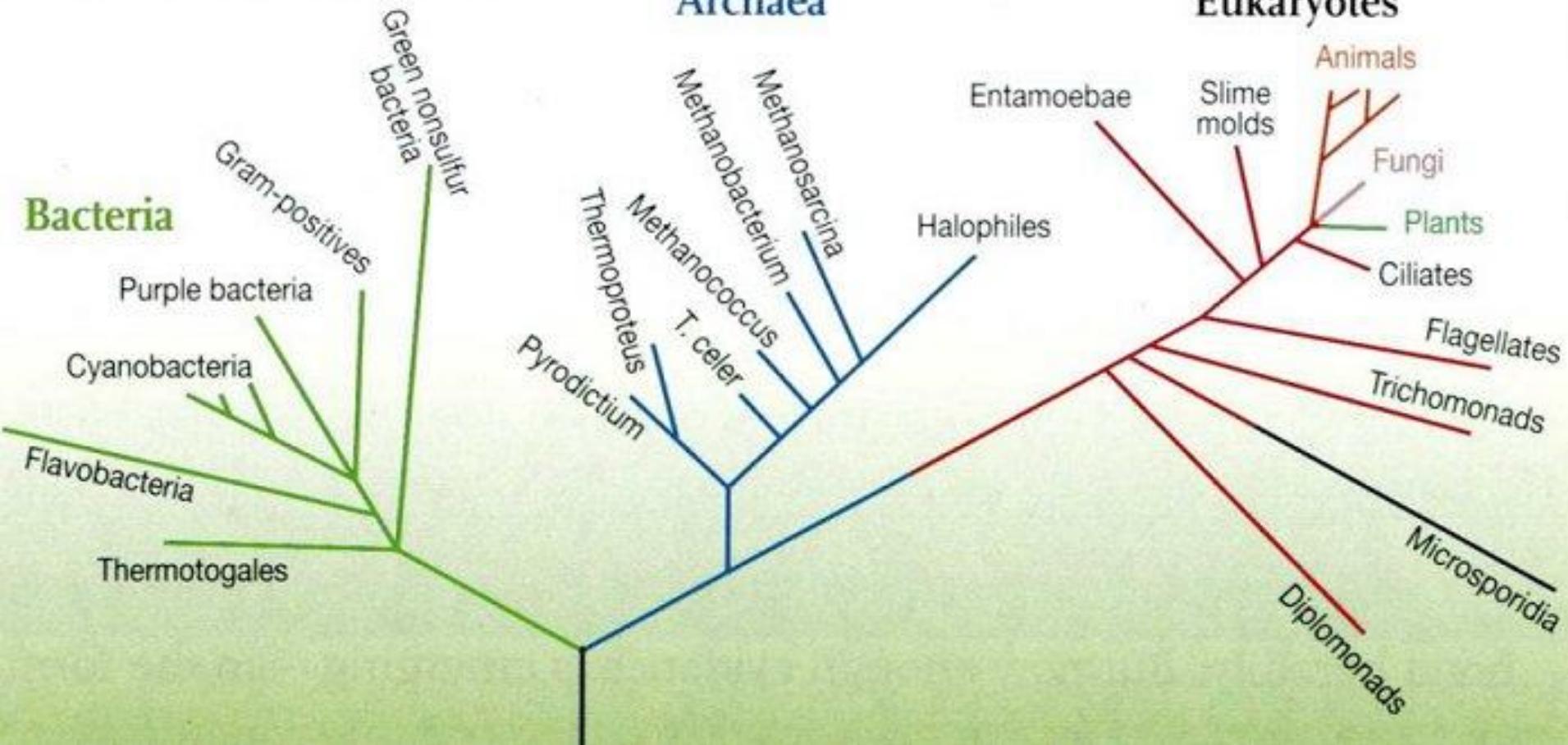
## Selection of Finch Beak Shape based on Diet



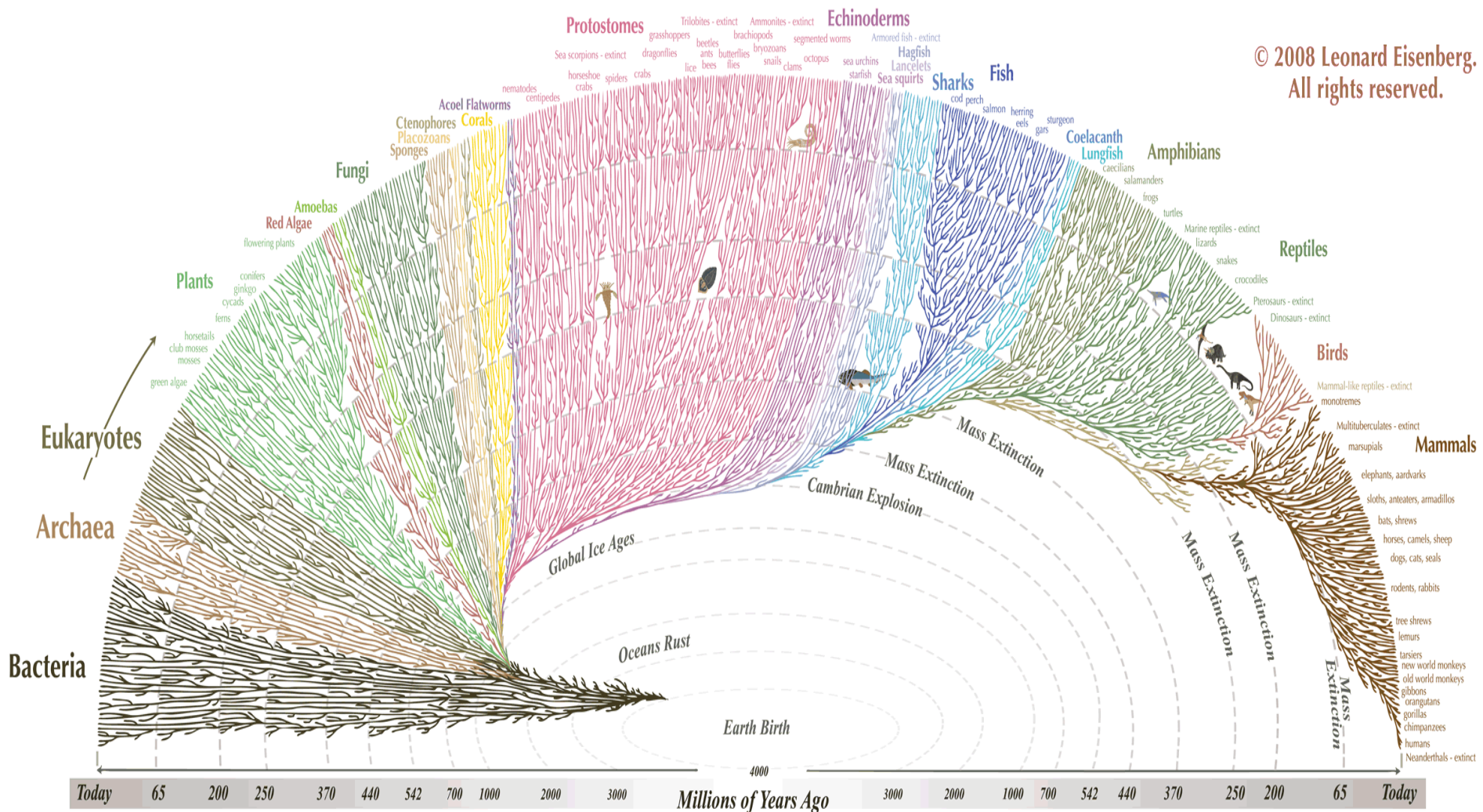
# Algorithm for Evolution



# THE TREE OF LIFE



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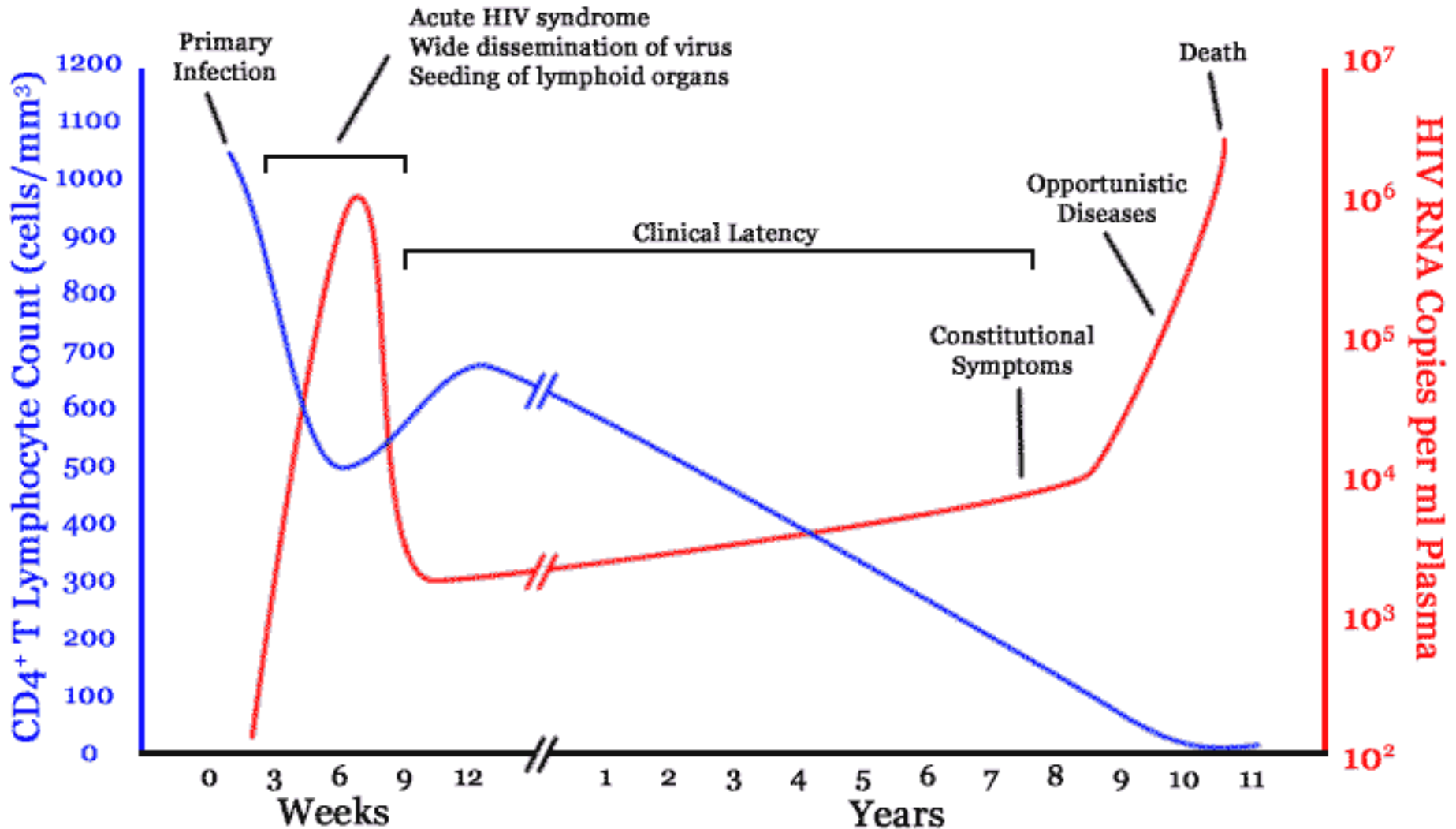
All the major and many of the minor living branches of life are shown on this diagram, but only a few of those that have gone extinct are shown. Example: Dinosaurs - extinct



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evogeneao.com

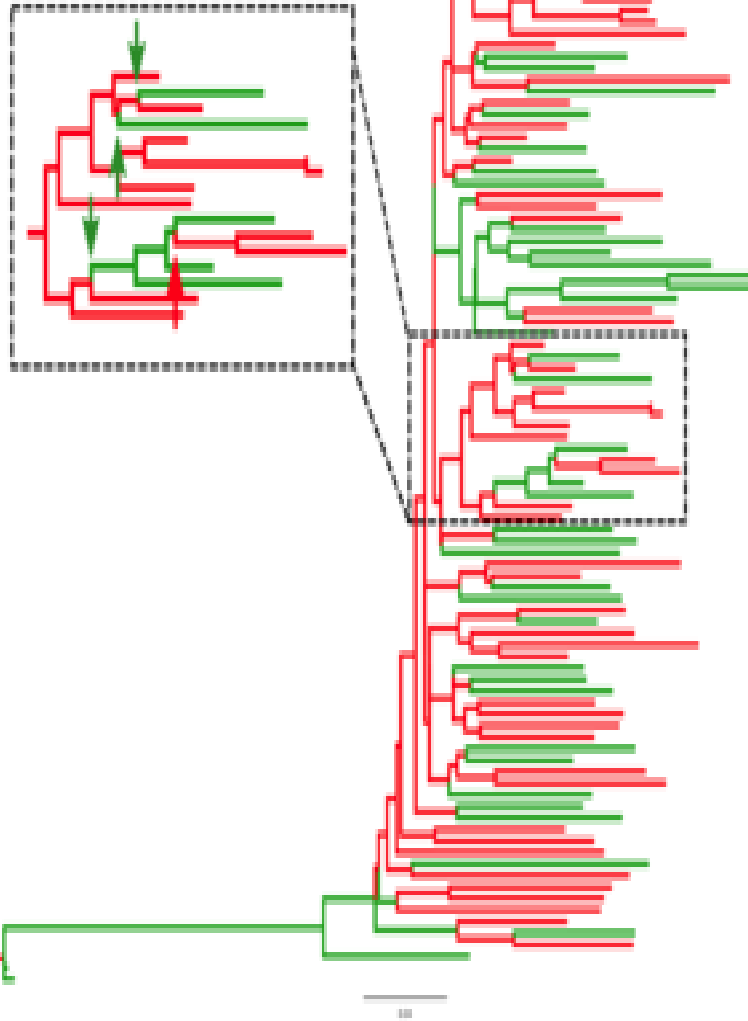


# HIV Disease Progression

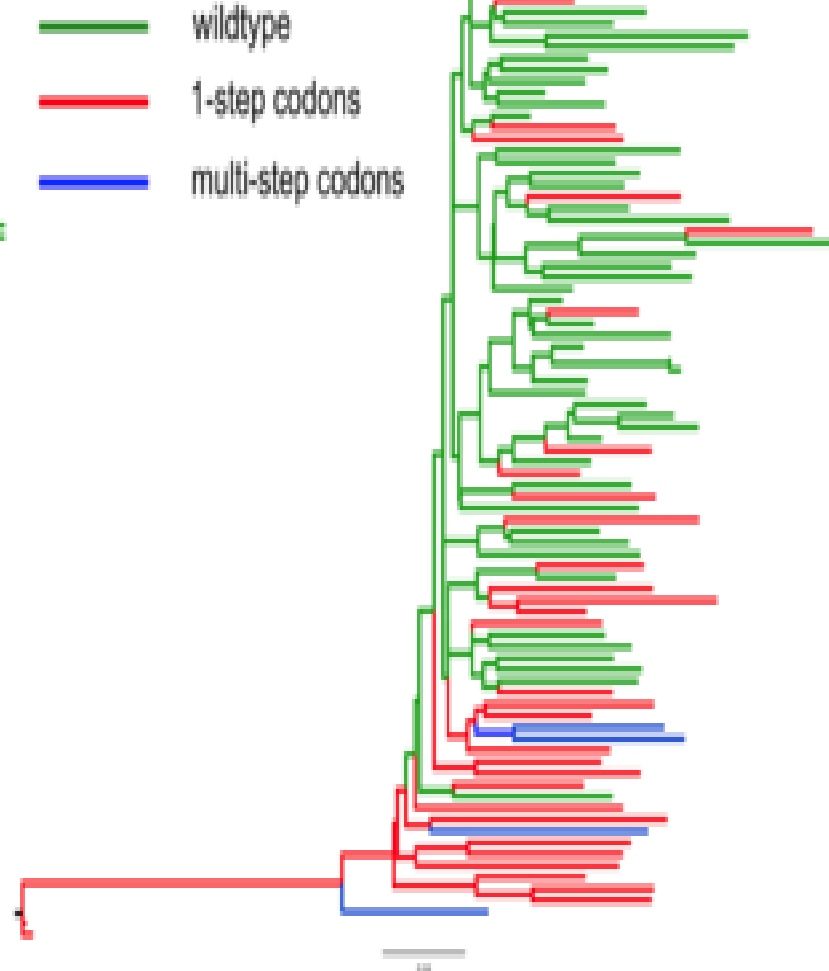


# HIV Evolution in a Single Patient

B

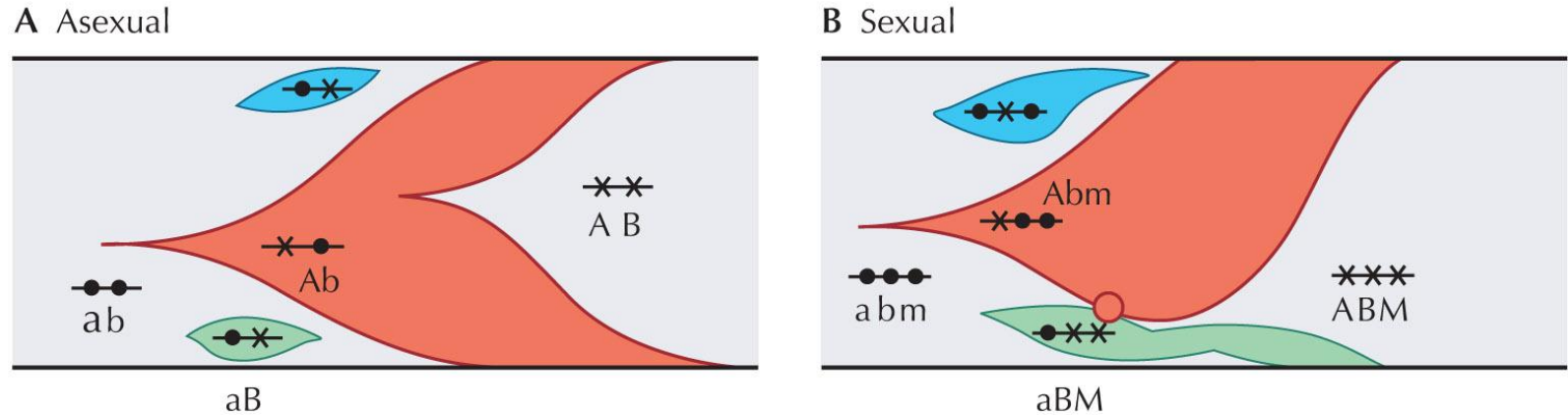


C



Analysis of HIV-1 evolution in acute infection and the influence of APOBEC (see publication in PLoS Pathogens, 2009)

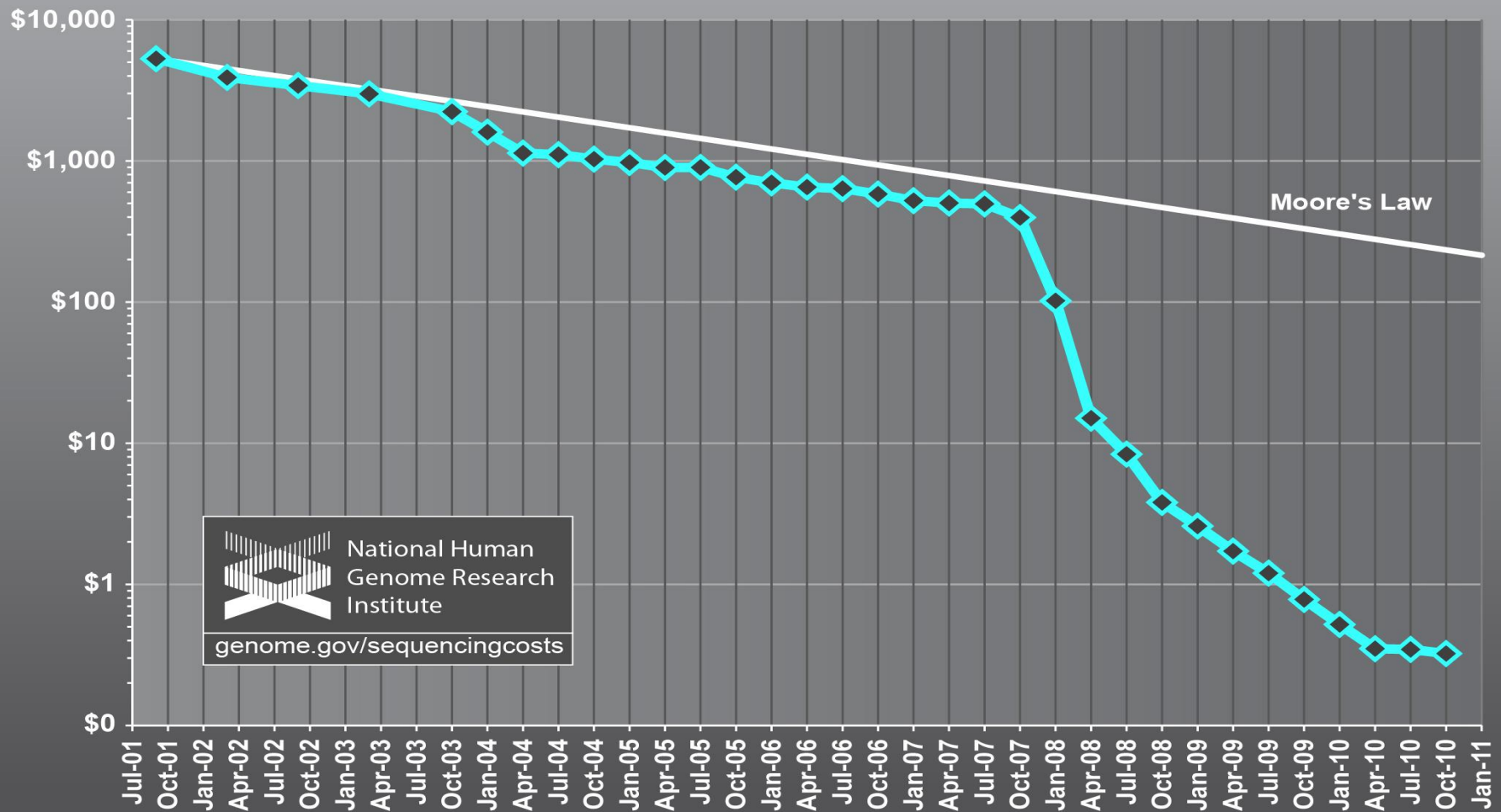
# Asexual vs Sexual Reproduction



**FIGURE 23.18.** The Fisher–Muller argument. (A) Favorable mutations must be established sequentially in an asexual population. For example, if allele A is destined to replace a, then any favorable alleles that occur at other loci (B, for instance) can only be fixed if they occur within a genome that carries A. (B) With sexual reproduction, favorable mutations at different loci can be combined; this leads to an advantage to modifiers that causes sex and recombination. A favorable allele B that occurs with the unfavorable allele a can be fixed if it can recombine into association with A (red circle); if this requires that a modifier allele M be present, then allele M will also tend to increase by hitchhiking.

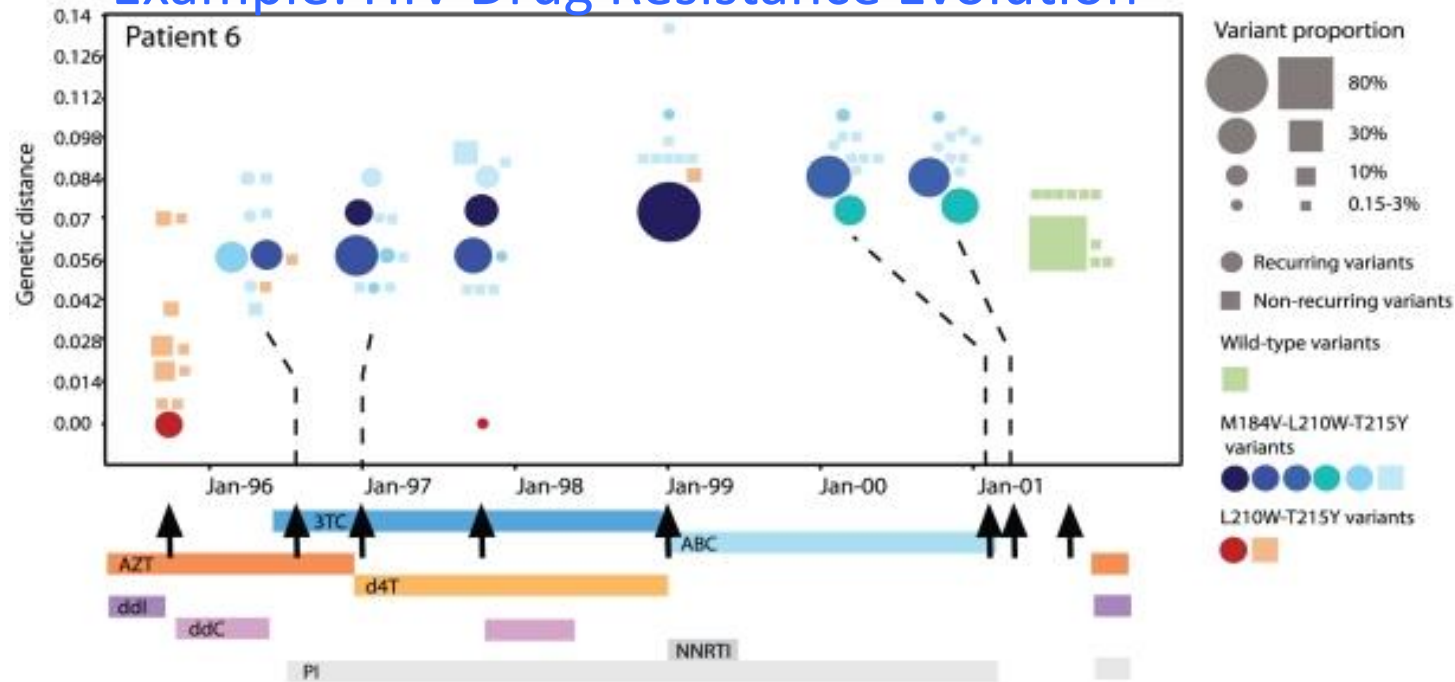
23.18, redrawn from Barton N. et al., *Science* **281**: 1986–1990, © 1998 American Association for the Advancement of Science

# Cost per Megabase of DNA Sequence



Decreased cost makes it possible to study the evolution of viruses, bacteria, and higher organisms at the DNA level

## Example: HIV Drug Resistance Evolution



For each patient the 10 most common variants in each time point are illustrated as circles (if recurring) or as cubes (if not recurring). The genetic distance of the variants in nucleotide changes/site (from the most frequent variant at the first time-point) is plotted over time. The frequency of the variants is proportional to the area of the circles and cubes. Treatment history is indicated by bars below each patient's graph; AZT; zidovudine, 3TC; lamivudine, d4T; stavudine, ddI; didanosine, ABC; abacavir, ddC; zalcitabine, TDF; tenofovir, NNRTI; non-nucleoside reverse transcriptase inhibitors, PI; protease inhibitors. Arrows indicate time for sampling. The genotype of the variants is color-coded, thus each combination of drug resistance mutations have a specific color (see guide to the right unique for each patient). There are at maximum six shades of each color enable means to follow specific variants over time. Thus, the most common variant receives the first shade and so on. The last shade is used for the remaining variants and for the non-recurring variants.

# Problems

- 1. How is the ratio of two successive Fibonacci numbers related to the **golden ratio**?
- 2. How is the golden ratio related to the **golden angle**? Why does this angle appear in a sunflower?
- 3. How much does it cost to sequence a person's genome consisting of approximately 3 billion bases? (\$0.30/Megabase as of Oct. 2010-slide 52)
- 4. How long does it take for an HIV infection to cause noticeable symptoms (slide 49)?
- 5. What is the generation time of *Drosophila* (slide 8)?
- 6. *Drosophila* embryos can make 6,000 cells in 2.5 hours. How many minutes are there per division?
- 7. Bacteriophage Lambda DNA contains 48,500 base pairs. Assuming the distance between base pairs is 0.34 nm, how long is it, and if it is ejected in 1.5 seconds, what is the DNA's average speed in m/sec?

# Answers

- 1. The ratio approaches the golden ratio: 1.618 for large fibonacci numbers:
- Calculations in **Mathematica**:

Find ratios of successive Fibonacci numbers:

```
In[1]:= Table[Fibonacci[n + 1]/Fibonacci[n], {n, 15}]
```

```
Out[1]= {1, 2, 3/2, 5/3, 8/5, 13/8, 21/13, 34/21, 55/34, 89/55, 144/89, 233/144, \
377/233, 610/377, 987/610}
```

Compare with continued fractions:

```
In[2]:= Table[FromContinuedFraction[Table[1, {n}]], {n, 15}]
```

```
Out[2]= {1, 2, 3/2, 5/3, 8/5, 13/8, 21/13, 34/21, 55/34, 89/55, 144/89, 233/144, \
377/233, 610/377, 987/610}
```

Convergence to the Golden Ratio:

```
In[3]:= N[%]
```

```
Out[3]= {1., 2., 1.5, 1.66667, 1.6, 1.625, 1.61538, 1.61905, 1.61765, 1.61818, \
1.61798, 1.61806, 1.61803, 1.61804, 1.61803}
```

- 2. In many cases, the head of a flower is made up of small seeds which are produced at the center, and then migrate towards the outside to fill eventually all the space (as for the sunflower but on a much smaller level). Each new seed appears at a certain angle in relation to the preceding one. For example, if the angle is 90 degrees, that is 1/4 of a turn, the result after several generations is that represented by figure 1.
- Of course, this is not the most efficient way of filling space. In fact, if the angle between the appearance of each seed is a portion of a turn which corresponds to a simple fraction, 1/3, 1/4, 3/4, 2/5, 3/7, etc (that is a simple rational number), one always obtains a series of straight lines. If one wants to avoid this rectilinear pattern, it is necessary to choose a portion of the circle which is an irrational number (or a nonsimple fraction). If this latter is well approximated by a simple fraction, one obtains a series of curved lines (spiral arms) which even then do not fill out the space perfectly (figure 2).
- In order to optimize the filling, it is necessary to choose the most irrational number there is, that is to say, the one the least well approximated by a fraction. This number is exactly the **golden mean**. The corresponding angle, the golden angle, is 137.5 degrees. (It is obtained by multiplying the non-whole part of the golden mean by 360 degrees and, since one obtains an angle greater than 180 degrees, by taking its complement). With this angle, one obtains the optimal filling, that is, the same spacing between all the seeds (figure 3).
- This angle has to be chosen very precisely: variations of 1/10 of a degree destroy completely the optimization. (In fig 2, the angle is 137.6 degrees!) When the angle is exactly the golden mean, and only this one, two families of spirals (one in each direction) are then visible: their numbers correspond to the numerator and denominator of one of the fractions which approximates the golden mean : 2/3, 3/5, 5/8, 8/13, 13/21, etc.
- These numbers are precisely those of the Fibonacci sequence (the bigger the numbers, the better the approximation) and the choice of the fraction depends on the time laps between the appearance of each of the seeds at the center of the flower.
- This is why the number of spirals in the centers of sunflowers, and in the centers of flowers in general, correspond to a Fibonacci number. Moreover, generally the petals of flowers are formed at the extremity of one of the families of spiral. This then is also why the number of petals corresponds on average to a Fibonacci number.

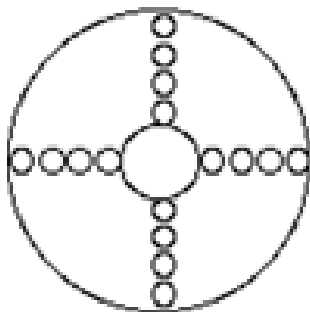


fig.1

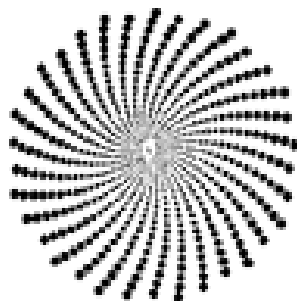


fig.2

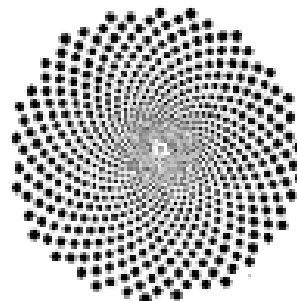


fig.3



- 3.  $3,000,000,000 \text{ bases} / 1,000,000 =$   
 $3000 \text{ Megabases}$   
 $3,000 \text{ Megabases} \times \$0.30 = \$900$
- 4. Approximately 8 years according to slide 49
- 5. About 10 days according to slide 8 (depends on temperature and population density)
- 6.  $2^n = 6000$ ;  $n \cdot \log_2(2) = \log_2(6000)$ ;  $n = 12.55$   
divisions;  $2.5 \text{ hr} \cdot 60 / 12.55 = 12 \text{ min/division}$
- 7.  $48,500 \cdot 0.34 \text{ E-9 m} = 1.65 \text{ E -5 m}$   
 $v=L/t= 1.65 \text{ E -5 m} / 1.5 = 1.1 \text{ E -5 m/s}$  or about  
11 micrometers/sec

**THE END**