BME 42-620 Engineering Molecular Cell Biology

Lecture 03:

Basics of Evolution Theory;

Overview of Model Organisms

Basics of MATLAB

Outline

- A brief review of the previous lecture
- Basics of evolution theory
- Overview of model organisms
- Basics of MATLAB

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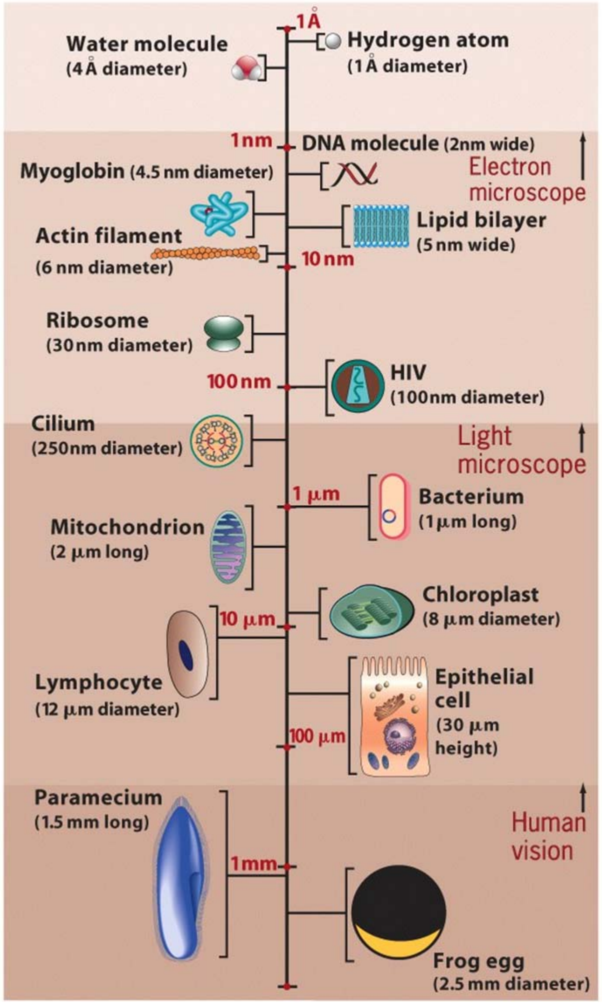
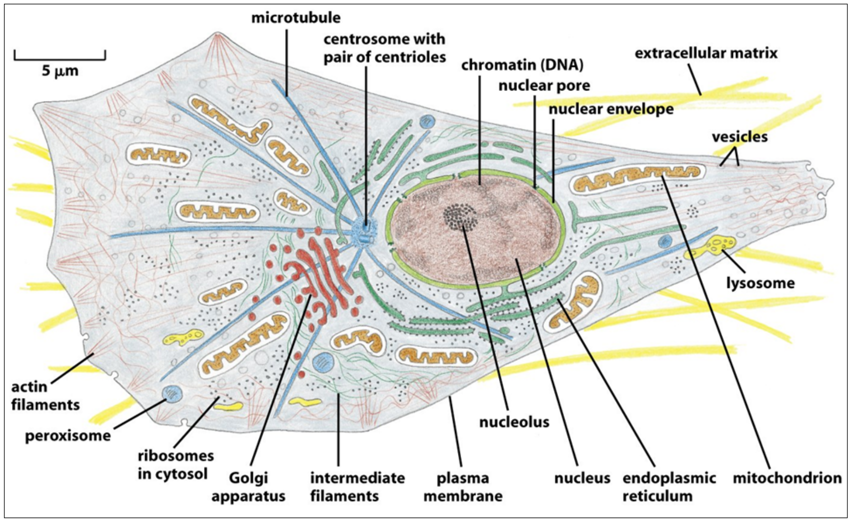
Scales of Cells and Cellular Organelles

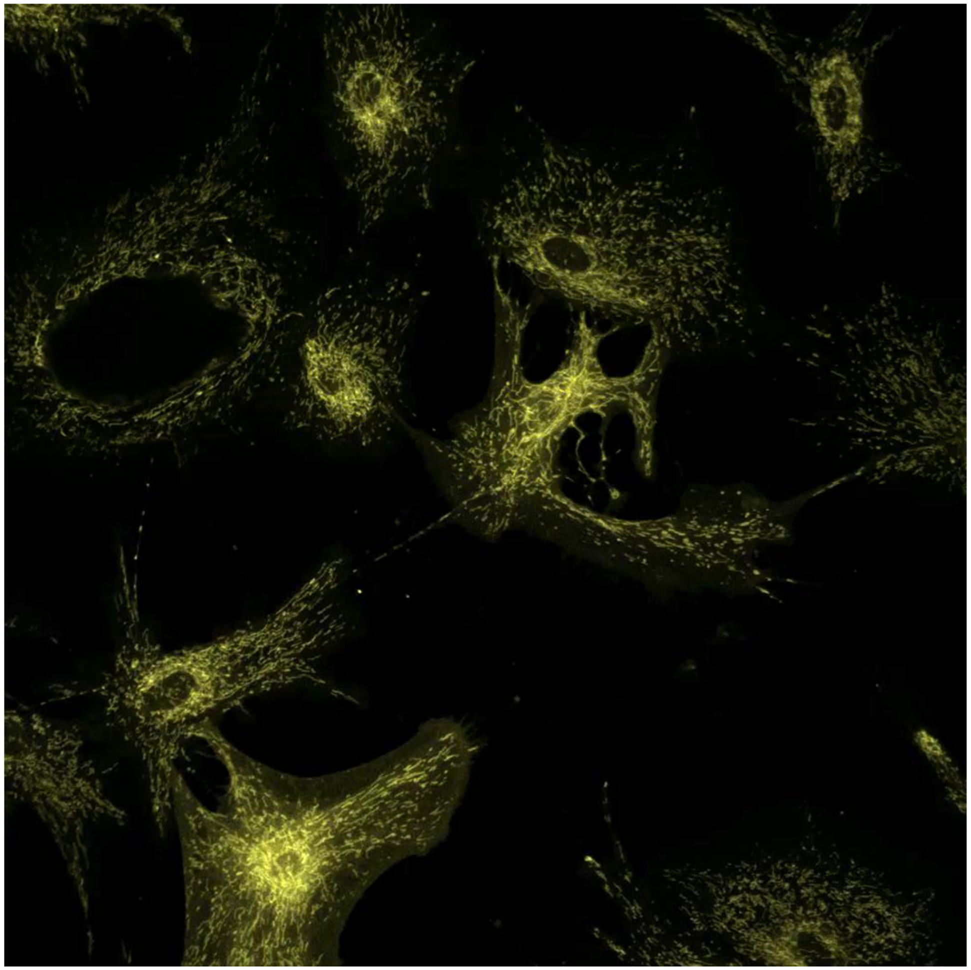


- Live imaging: light microscopy
- Below 100nm, electron microscopy
- Below 1 nm: crystallography, NMR, spectroscopy

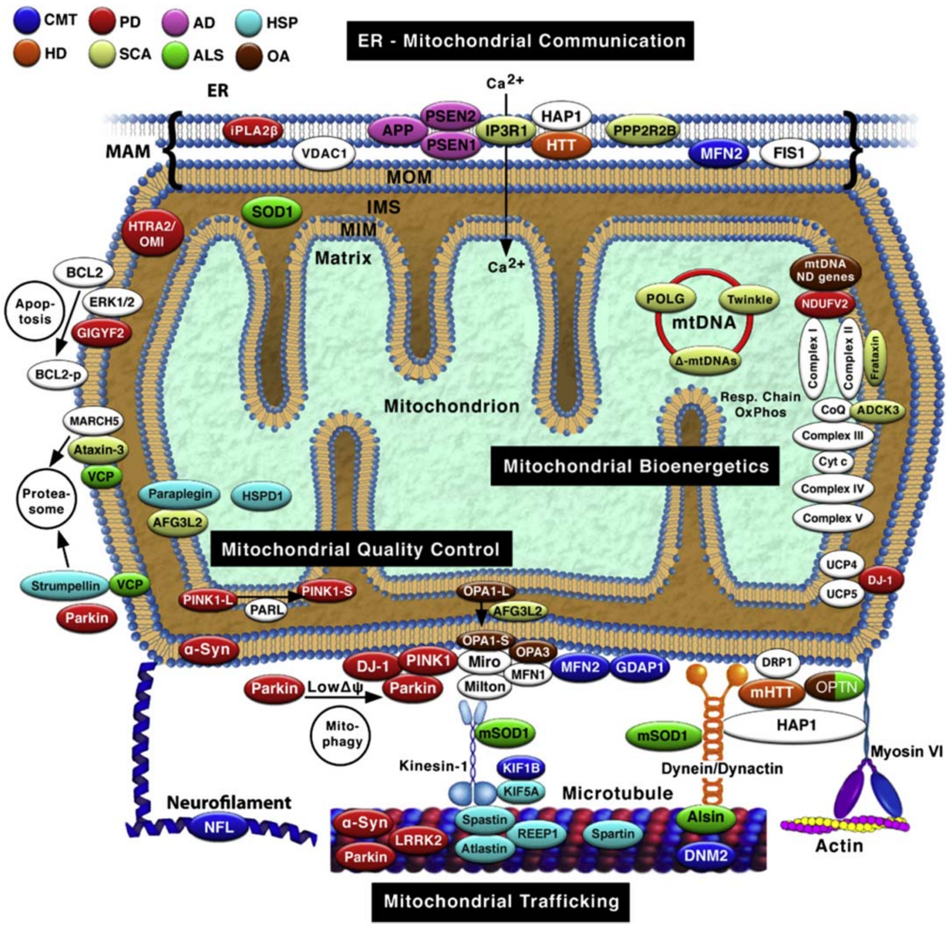
Energy Generation/Distribution: Mitochondria

- Generation and distribution of ATP.
- Regulation of many other metabolic processes, including aging.





A More Detailed View of Mitochondria



Schon & Prezedborski,
Neuron, 70:1033, 2011

System Level Analysis of Cells

- Discussion: how to study a cell at a system level?
  - To understand the functions of individual units
  - To understand the interactions between different units
  - To understand such interactions in space and time
  - To use simplified model systems
  - …

- Some examples of related projects:
  - Virtual cell program: http://vcp.med.harvard.edu/
  - Cell modeling: http://www.ccam.uchc.edu/index.html

Reading Assignment 1

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Remarkable Diversity and Specificity at Cellular and Organismal Levels

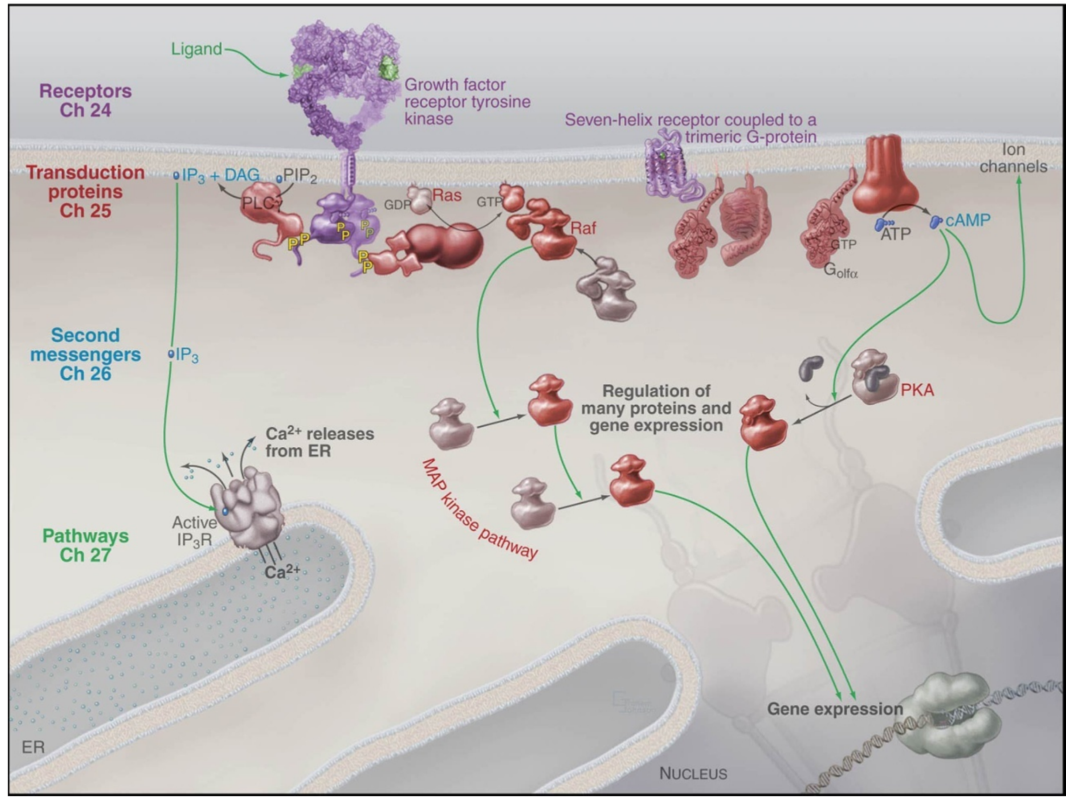
- Example: receptors

  > 800 G protein coupled receptors in human

  > 1000 G protein coupled receptors in mice just for sensing of smell

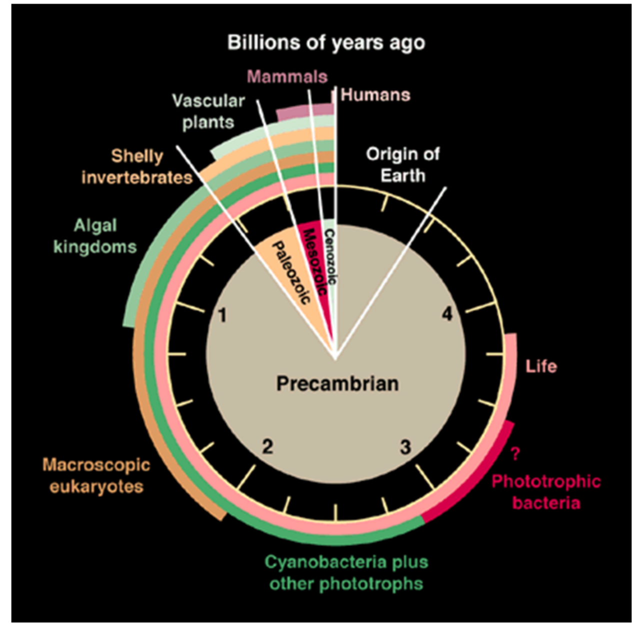
- Remarkable diversity and specificity at the organismal level as well.

- Where does this come from?

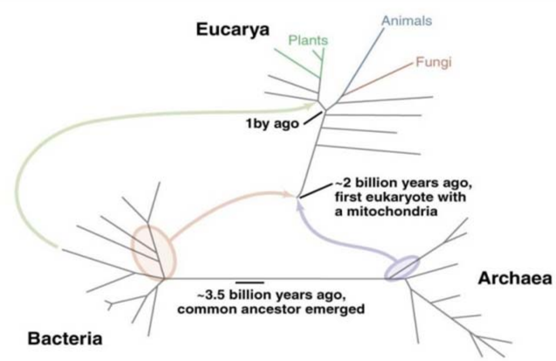


Cells Come from a Common Ancestor

- Earth forms ~4.5 billion years ago.
- The common ancestor, a primitive microscopic cell, lived over 3.5 billion years ago.
- Prokaryotes start ~2.7 billion years ago.
- The first eukaryote with a mitochondrion lived ~2 billion years ago.

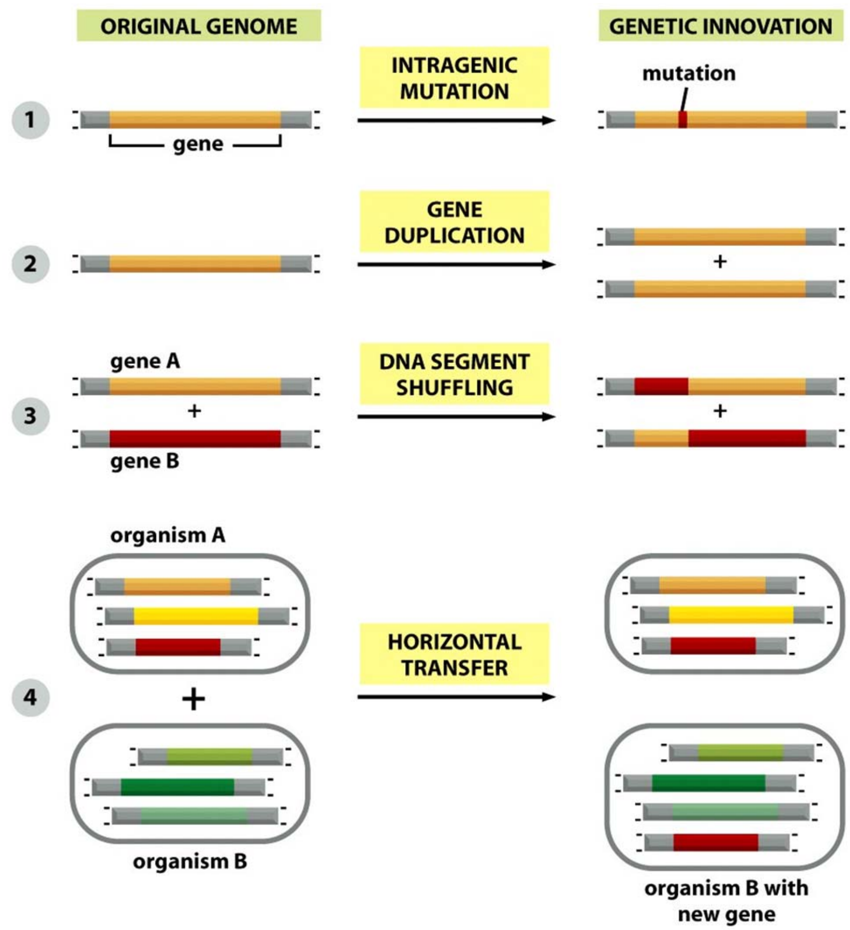


D. J. Des Marais, *Science*, 289:1703, 2000



Genetic Basis of Evolution

- Evolution is the great unifying principle in biology.
- Generation of new genes
  - Mutation
  - Duplication
  - Segment shuffling
  - Transfer



Elements of Natural Selection Theory (I)

- Proliferation: organisms produce more offspring than can survive.
- Genetics: Organisms pass genetic traits from generation to generation.
- Variation: there is variation in every population.
- Competition: organisms compete for limited resources.
- Natural selection: those organisms with the most beneficial traits are more likely to survive and produce.

Elements of Natural Selection Theory (II)

- Genetic changes of natural selection survivors are preserved.

- Regarding detailed evolution mechanisms, multiple models have been proposed but no conclusive consensus reached so far.

- Significant progress has been made towards understanding the molecular genetic basis of evolution.

- References

  - S. B. Carroll, *Endless forms most beautiful*, W.W. Norton, 2006
  - S. B. Carroll et al, *From DNA to diversity*, Wiley-Blackwell, 2004

Darwin: "Origin of Species"

"It is interesting to contemplate a tangled bank, clothed with many plants of many kinds, with birds singing on the bushes, with various insects flitting about, and with worms crawling through the damp earth, and to reflect that these elaborately constructed forms, so different from each other, and dependent upon each other in so complex a manner, have all been produced by laws acting around us. These laws, taken in the largest sense, being Growth with reproduction; Inheritance which is almost implied by reproduction; Variability from the indirect and direct action of the conditions of life, and from use and disuse; a Ratio of Increase so high as to lead to a Struggle for Life, and as a consequence to Natural Selection, entailing Divergence of Character and the Extinction of less improved forms. Thus, from the war of nature, from famine and death, the most exalted object which we are capable of conceiving, namely, the production of the higher animals, directly follows. There is grandeur in this view of life, with its several powers, having been originally breathed by the Creator into a few forms or into one; and that, whilst this planet has gone circling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being evolved."

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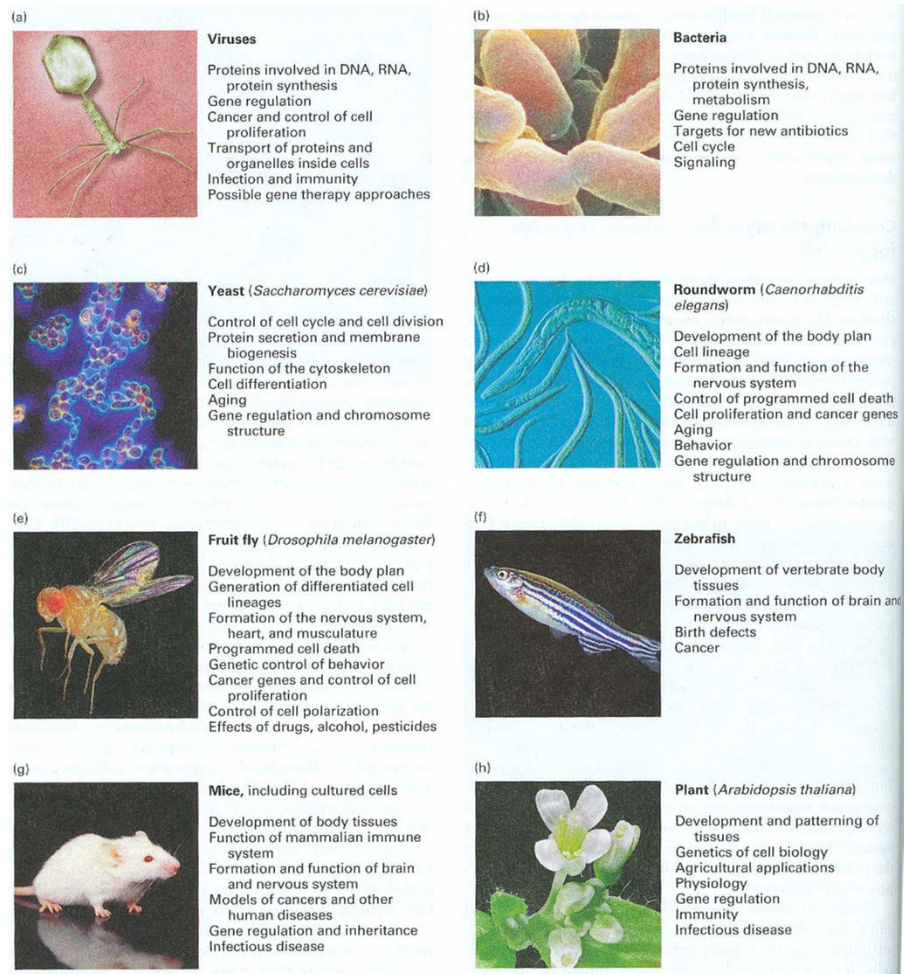
Model Organisms

- Commonly used animal models
  - fruit fly
  - C. elegan
  - mice/rat



Lodish et al, *Mol. Cell. Biol.*, 6e, W. H. Freeman, 2008

Model Organisms

Organism	Genome Size (Mb)	Genes	Homologous Recombination	Meiotic Recombination	Biochemistry
E. coli	4.6	4,288	Yes	No	Excellent
S. cerevisiae	12.1	6,144	Yes	Yes	Good
S. pombe	14	4,900	Yes	Yes	Good
C. elegans	97	18,266	Difficult	Yes	Poor
Drosophila	180	13,338	Difficult	Yes	Fair
Arabidopsis	100	25,706	No	Yes	Poor
Mouse	2500	22,011	Yes	Yes	Good
Human*	2900	22,808	Yes*	Yes	Good

*cultured cells

Why Use Model Organisms

- Made possible by evolution

  - Remarkable similarities between genes/proteins in different organisms

  - Often possible to insert genes/proteins from one organism into the genome of the other to rescue functions.

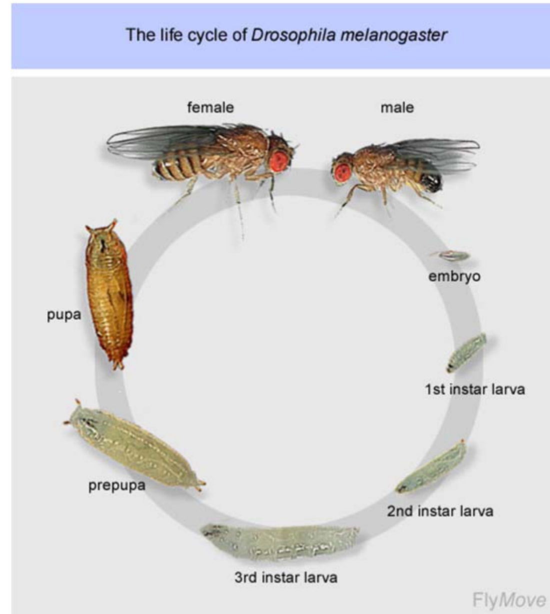
- Model organisms provide a way to tackle diversity.

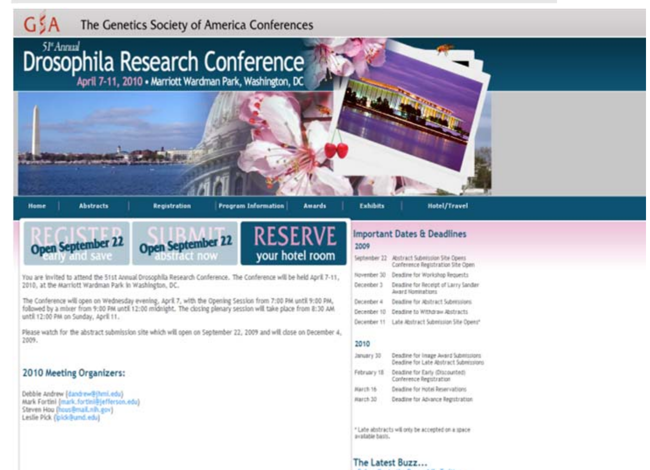
- Model organisms are chosen for the ease of studying them.

- Often there is substantial shared resources for cost effectiveness in studying model organisms.

Example: *Drosophila melanogaster*

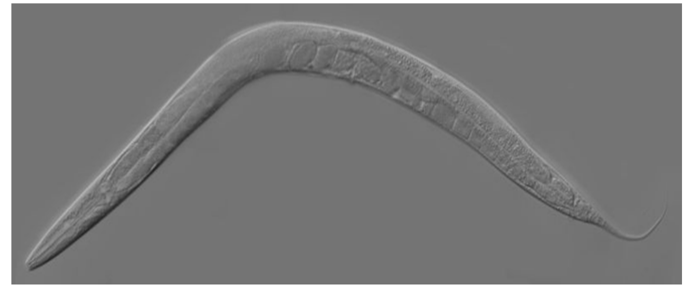
- Genetic model system
- Often used to study development
- Many human disease models
- Generation time: ~10-15 days
- Resources:
  http://flybase.bio.indiana.edu/
- ~75% of known human disease genes have matches in the fruit fly genome





Example: *Caenorhabditis elegans*

- Research started in 1974 by Sydney Brenner.
- Often used to study development, nervous system, aging.
- Generation time: ~4 days
- One of the simplest organisms with a nervous system. Connectivity of its 302 neurons have been fully mapped.
- Resources: http://www.wormbase.org/



Limitation of Model Systems

- Our ultimate goal is to control human disease.
- None of the models can fully reproduce human physiology.
- Cultured human cell lines are also limited in many way.

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MATLAB Overview

- MATLAB stands for "matrix laboratory“, a product of MathWorks Inc. (Natick, Massachusetts).

- It is both a language and a development and application environment.

- History of MATLAB
  - First developed in 1970's by Cleve Moler, coauthor of LINPACK & EISPACK

  - First written in FORTRAN; Later rewritten in C

  - Commercial development initiated by Jack Little
    - MathWorks was founded in 1984.

  - In 2000, rewritten based on LAPACK.

Sources:
http://www.mathworks.com/company/aboutus/founders/clevemoler.html
http://www.mathworks.com/company/aboutus/founders/jacklittle.html
http://www.mathworks.com/company/newsletters/news_notes/clevescorner/dec04.html

Advantages of MATLAB (I)

- MATLAB provides reliable and efficient numerical computation with friendly user interfaces.
    - Maple, Mathematica strong in symbolic computation

- Examples of numerical computation issues
    - Precision; numerical stability
    - Underflow and overflow
    - Code quality (debugging, exception handling)
    - Code efficiency (optimization)

- Visit www.netlib.org for more information about different numerical packages.

Advantages of MATLAB (II)

- Fast prototyping: MATLAB is an interpreted language
- Extensive toolboxes
- Versatile graphics
- Cross-platform: Windows, Unix, Linux, Mac OS
- Support parallel computing
- Support object oriented programming
- Large groups of users

  MATLAB file exchange **(use with caution)**

  http://www.mathworks.com/matlabcentral/

MATLAB Toolboxes (I)

- A large collection of basic math functions are provided in the MATLAB base package.

- Function extensions are packaged as toolboxes.

- Math and optimization
  - Optimization toolbox
  - PDE toolbox
  - Genetic algorithm and direct search algorithm

- Statistics & data analysis
  - Statistics toolbox
  - Curve fitting toolbox
  - Spline toolbox
  - Neural network toolbox

MATLAB Toolboxes (II)

- Signal & image processing
  - Signal processing toolbox
  - Image processing toolbox
  - Wavelet toolbox

- Third party toolboxes
  - Pattern recognition toolbox: www.prtools.org
  - Wavelet toolbox: http://www-stat.stanford.edu/~wavelab/

Limitations of MATLAB

- Operation details are hidden.

- Limited efficiency: MATLAB is an interpreted language.
  - Compiler also available
  - Can use MEX (MATLAB executable) to call DLL implemented in C

- Lack of properties to support large scale software development
  - E.g. Implicit & dynamic data type

- MATLAB is the required implementation language for this class.

MATLAB Practice

- How to write a MATLAB function
  - Video

- Reminder: MATLAB computation results can be saved in .mat files and loaded back.

- Reminder: MAT files are exchangeable on different platforms.

Getting Help with MATLAB

- First, read related references and practice.
- For a specific function, it is often helpful to look in MATLAB online help.
- For a general question, it is often helpful to check related toolbox manuals.
- If none of these works, direct your questions to the instructor.

Required Reading

- MBoC 5/e chapter 1

Questions?