

# BIOE 498 / BIOE 599: Computational Systems Biology for Medical Applications

CSE 599V: Advancing Biomedical Models

Lecture 1: Introduction and Biochemistry Basics

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\*eScience Institute, Computer Science & Engineering

\*\*BioEngineering



# Agenda

- Course Introductions & Overview
  - BIOE 498/599
  - CSE 599V
- Biochemistry basics

## Lecture Notes

<https://github.com/ModelEngineering/advancing-biomedical-models/tree/master/Lectures>

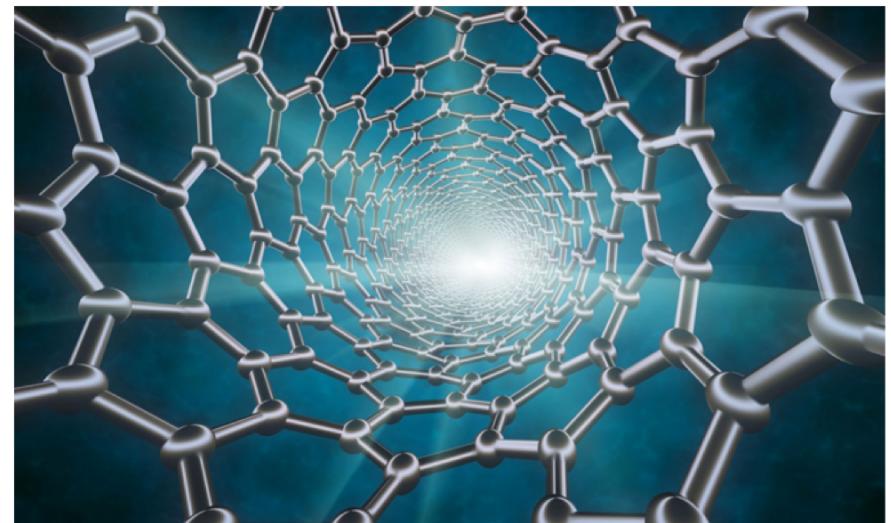


# Why Biomedical Engineering?

## Precision Medicine



## Novel Materials

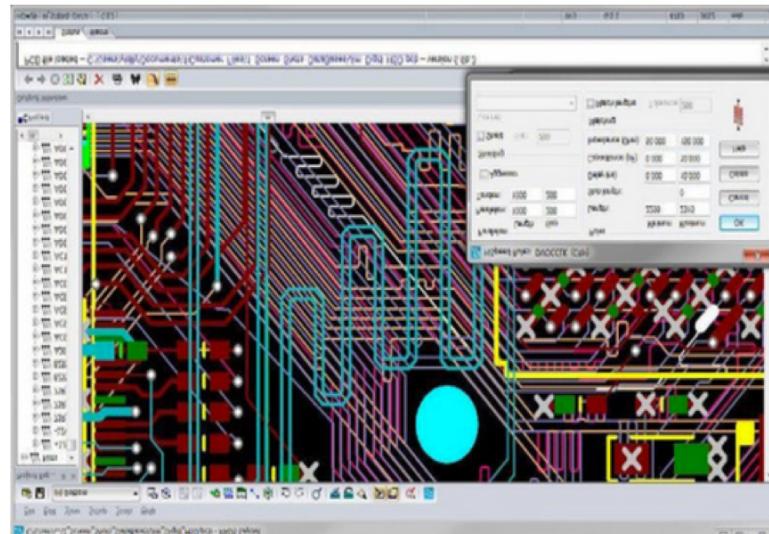


# Why Models?

**Disasters should occur in silico,  
not in vivo.**



**Emulate experience with  
hardware design.**



**(Not knowing about  
eigenvalues can be disastrous.)**



# Scientific Goals of Modeling in Biology++

- To explain biological processes that result in observed phenomena
- To predict previously unobserved phenomena
- To identify key generic mechanisms
- To guide experiments:
  - Suggest new experiments
  - Help interpret experiments
  - Experiments are limited in number and control, computer simulations can test many more perturbations to explore their consequences



# Course Goals

- BIOE & CSE: Develop skills with building quantitative models of biological systems.
- CSE: Develop a research agenda for tools for modeling biomedical systems.



# Instructors

- Herbert M Sauro, Associate Professor BIOE
  - PhD in Systems Biology
  - Current Research
    - Dynamics and operation of cellular processes
    - Clinically reliable approaches to modeling complex systems
- Joseph Hellerstein, Senior Fellow eScience Institute, Affiliate Professor CSE
  - PhD in Computer Science
  - Industry (30+ years): IBM Research, Microsoft, Google
    - Mathematical models of distributed computing systems
  - Research
    - Modeling evolution of microbial communities
    - Model Engineering (tools for building biomedical models)



# BIOE 599/498 Objectives & Grading

- Learning Objectives:
  - Explain the purpose and need for modeling in biomedicine.
  - Explain the basic conceptual approach used by a number of different modeling approaches.
  - Explain the modeling workflow and how modeling is an iterative process.
  - Implement basic modeling techniques such as model fitting, model selection and sensitivity analysis
  - Use the concept of uncertainty quantification and the limits of current modeling approaches.
  - Compare and contrast with other fields that model complex systems.
  - (For 599 only) Learn to critique published modeling papers.



# BIOE 599/498 Objectives & Grading

- Grading
  - 30% One assignment every two weeks
  - 20% Weekly short quiz
  - 20% Midterm stress testing
  - 30% Final stress testing of models



# CSE 599V Objectives & Grading

- Learning objectives
  - Explain the need for biomedical models
  - Construct kinetics models of simple biological systems
  - Describe tooling requirements for building biomedical models.
- Grading
  - Homework (2): 20%
  - Paper review: 30%
  - Course project (Define/prototype tool): 50%
- See <https://modelengineering.github.io/advancing-biomedical-models/> for course details.
  - Lecture notes will be linked from the syllabus page.



# Meeting Times

## BIOE

- Lab: M, 12:30-2:20, OUG 136
- Lecture: WF, 1:30-2:50, Benson 203

## CSE

- Optional Lab: M, 12:30-2:20, OUG 136
- Lecture: WF, 1:30-2:50
  - 09/26-11/05: Benson 203
  - 11/12-12/03: Mary Gates 058



# Resources

## Text Book

### Systems Biology: Introduction to Pathway Modeling

First Python Edition

*Herbert M. Sauro  
University of Washington  
Seattle, WA*

**BIOE** : <https://canvas.uw.edu/courses/1218899/pages/498a-slash-599-computational-systems-biology-for-medical-applications>

**CSE**: <https://modelengineering.github.io/advancing-biomedical-models/>



# Software

- The class will feature in-class exercises, so please bring a laptop to class
- Software: Tellurium (<http://tellurium.analogmachine.org/>)
- For detailed installation instructions see <https://github.com/sys-bio/tellurium#installation-instructions>
- For a huge database of curated models see:
- <https://www.ebi.ac.uk/biomodels/>



# Syllabus By Week

Joint

**1**  
**Basics of Biochemistry & Modeling**

**2**  
**Systems Biology Modeling**

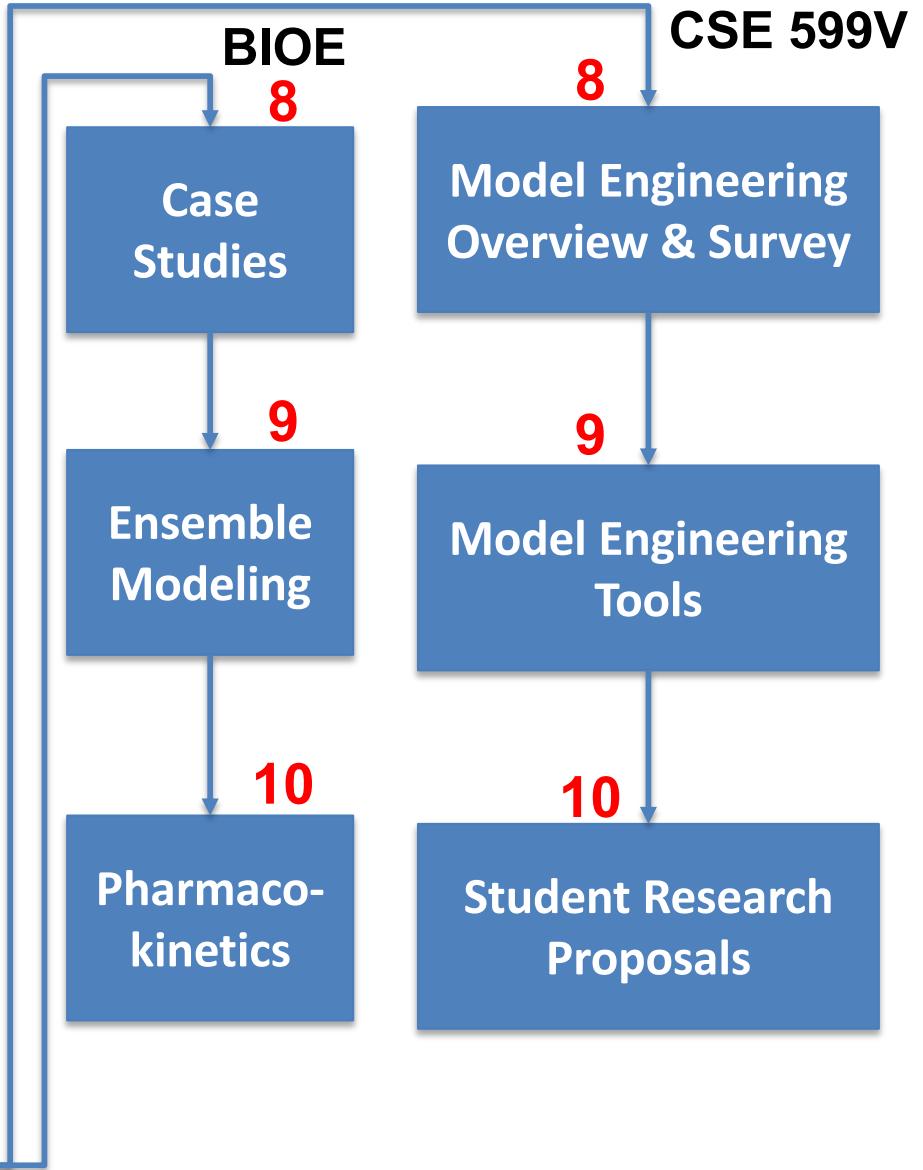
**3**  
**Build a Model**

**4**  
**Fitting Parameters & Debugging Models**

**5**  
**Uncertainty in Models & Parameters**

**6**  
**Modeling Workflows & Standards**

**7**  
**Student Reviews of Modeling Papers**



# Technical Statement of Course Objectives

- BIOE & CSE: Develop skills with building kinetics models that quantify cellular processes operating through biological networks that create and destroy biomolecules and biomolecular complexes.

*The remainder of today's lecture will explain each of the underlined terms.*

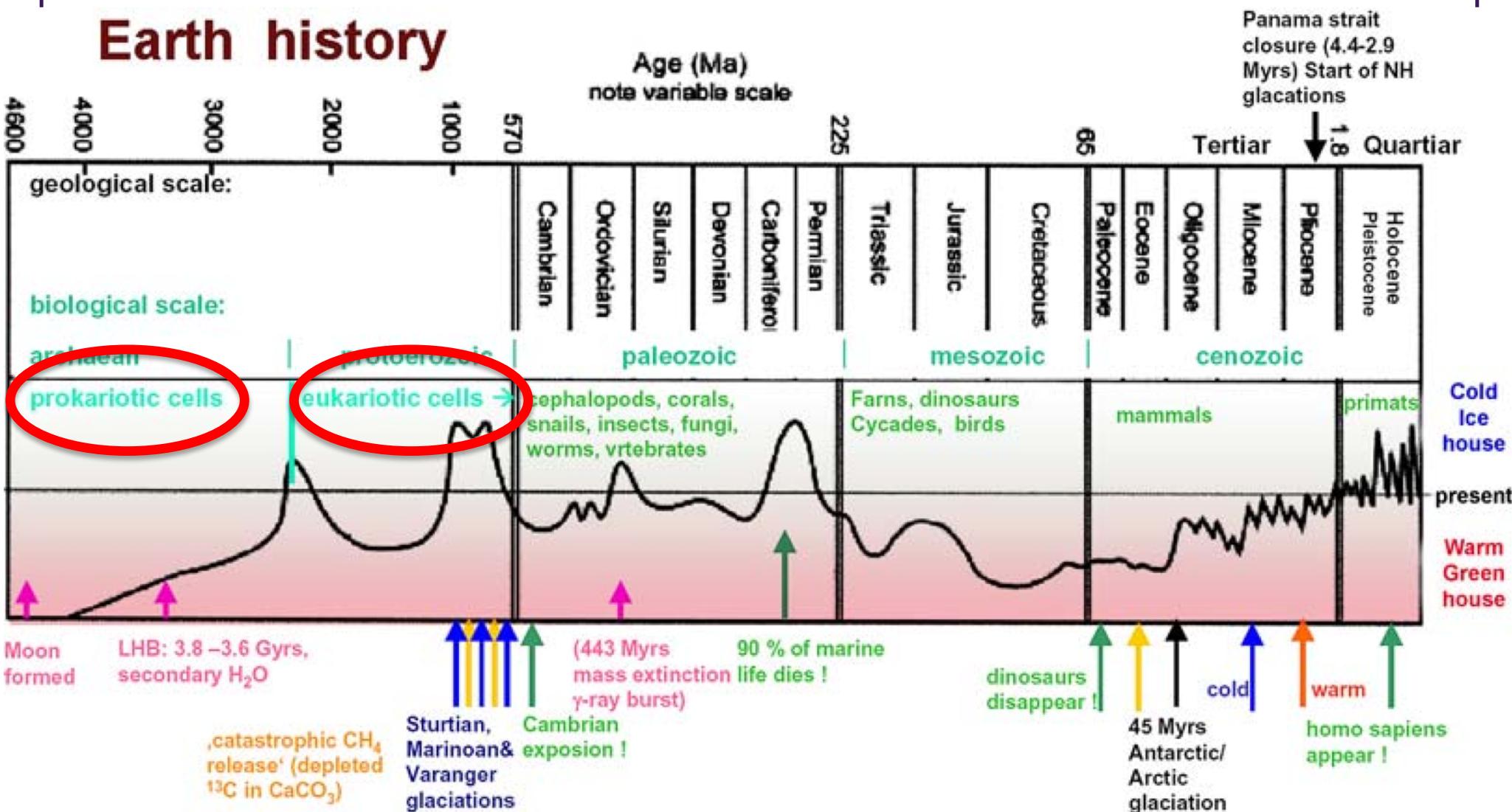


# Biochemistry Basics

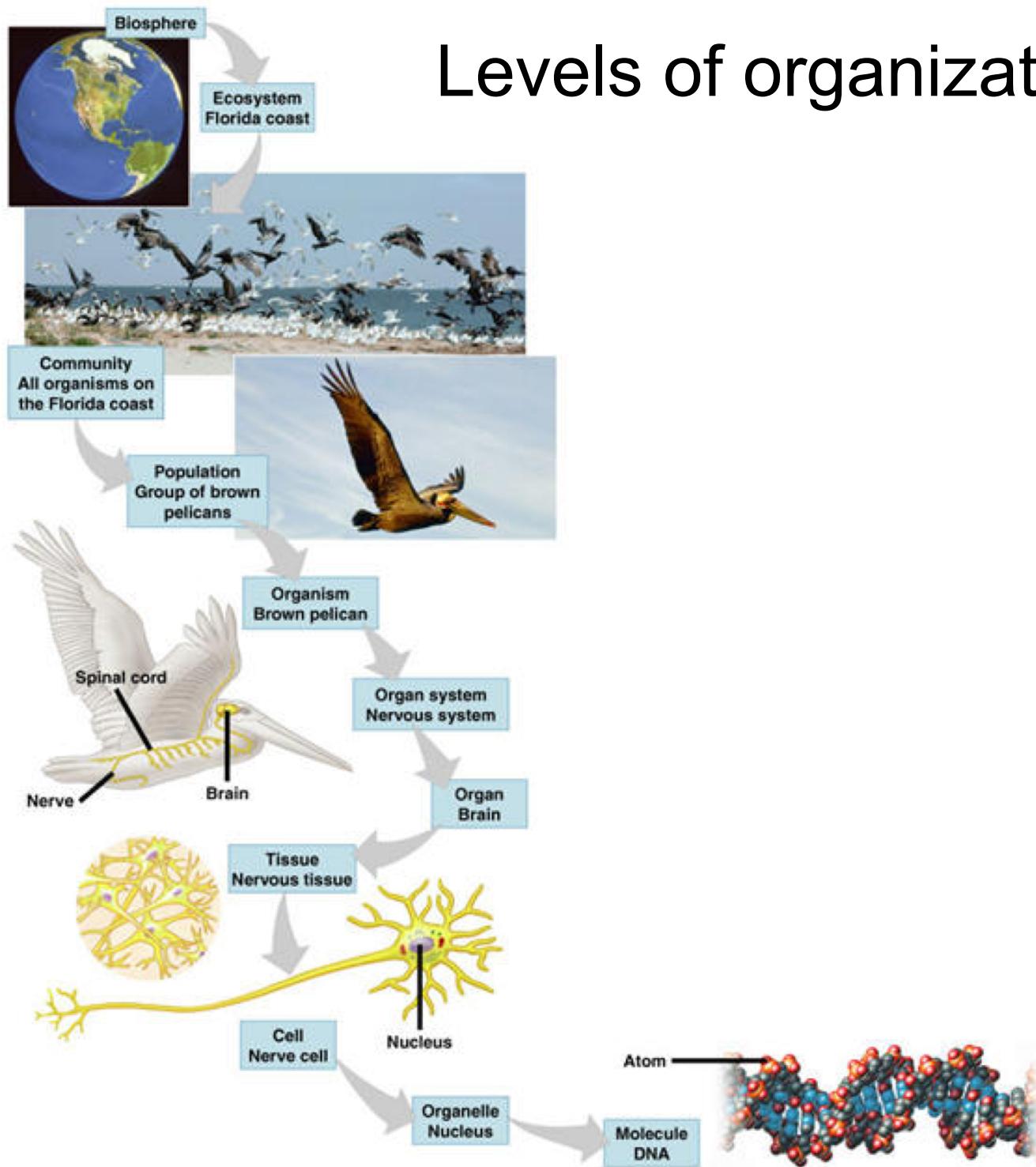
- A brief history of life, its organization, and processes.
- Structure of a cell
- Biomolecules, biomolecular complexes, enzymes
- Kinetics models
- Biological networks



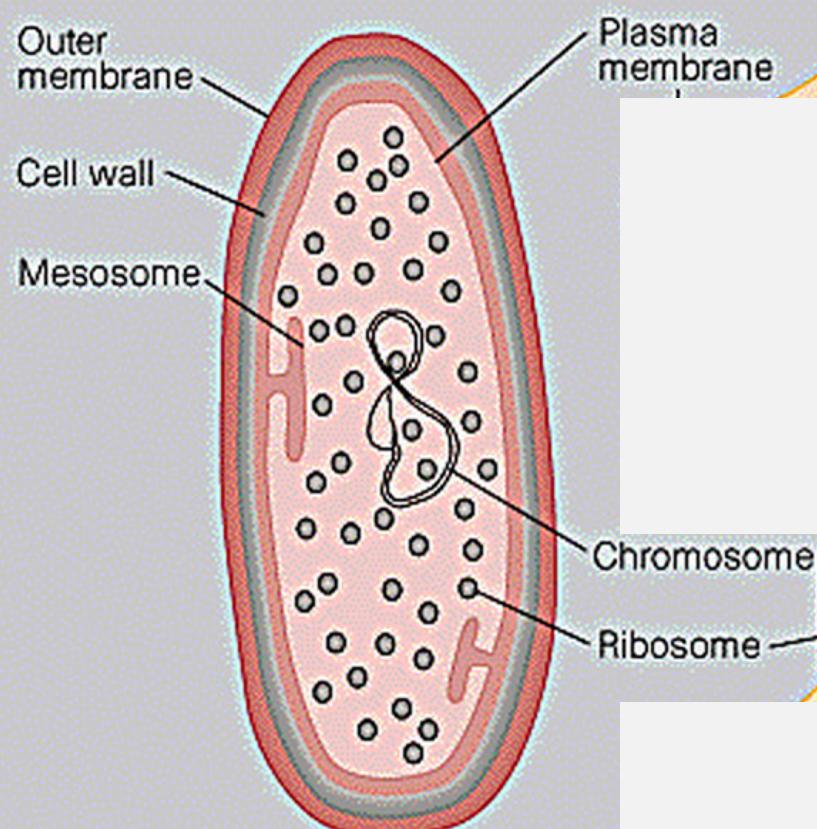
# Earth history

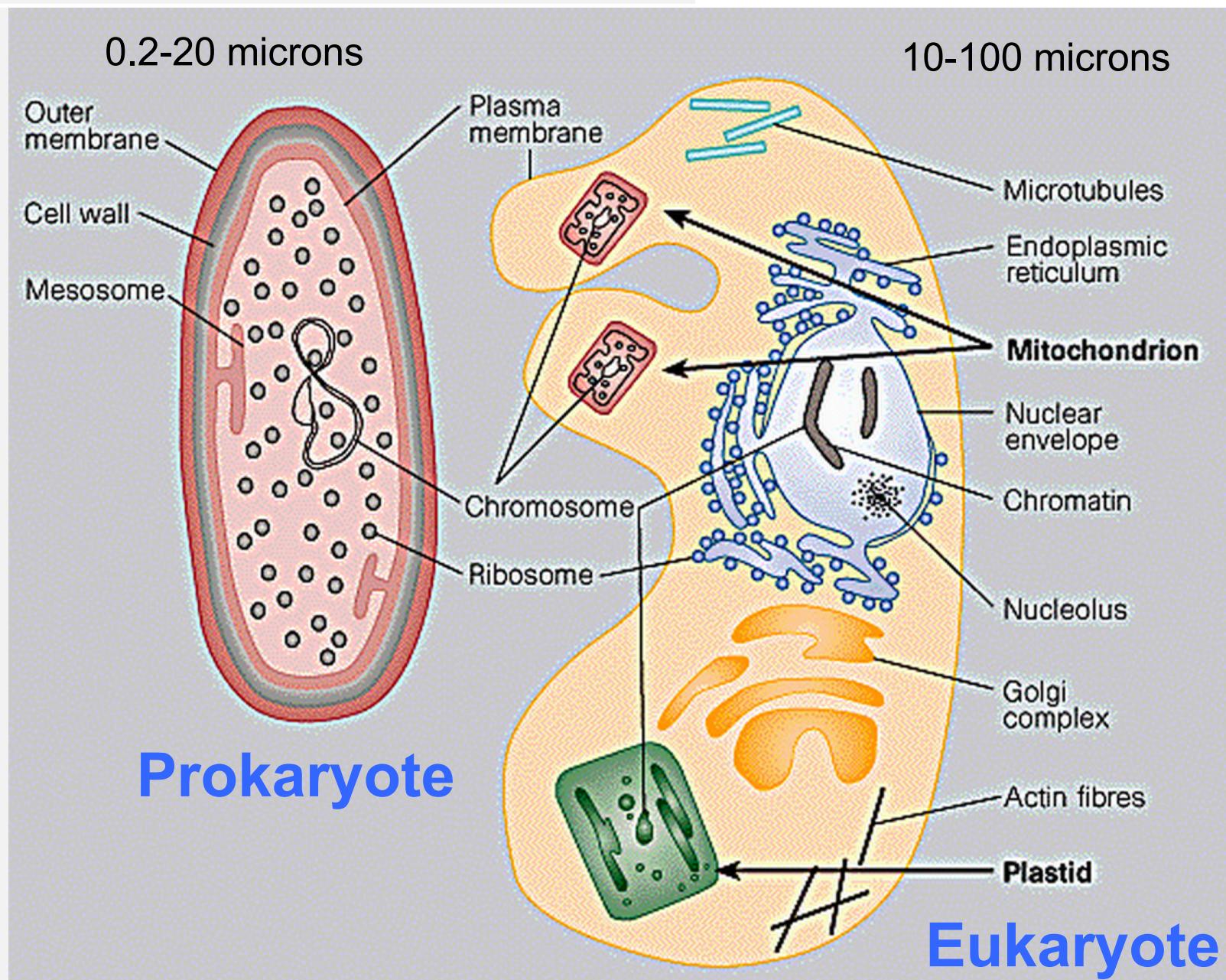


# Levels of organization of life



0.2-20 microns

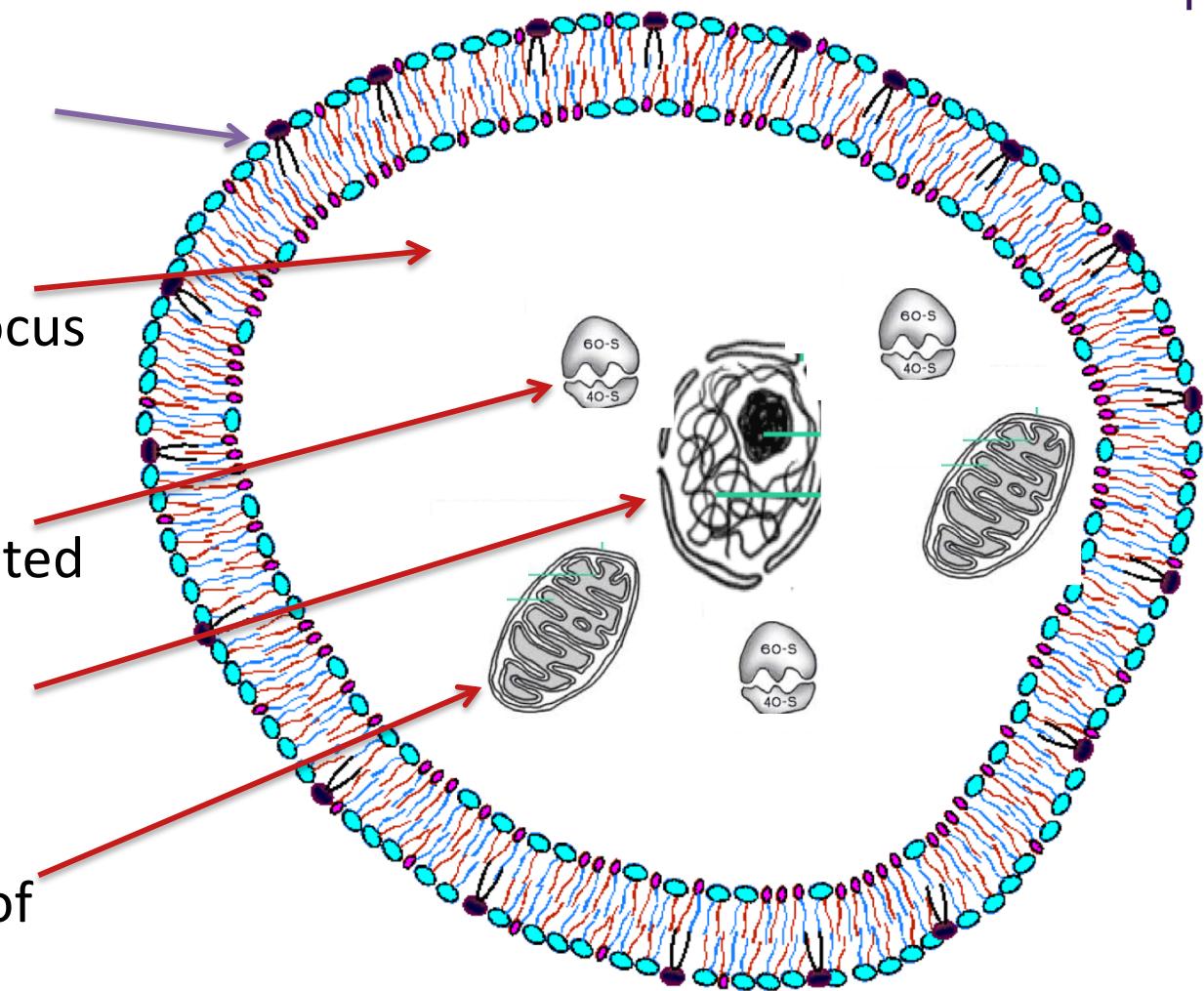




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# Simplified Cell Structure

- Plasma membrane – controls entry and exit of molecules
- Cytosol – interior of cell minus the organelles & locus of many pathways
- Ribosome – constructs proteins from mRNA created in nucleus
- Nucleus – exports mRNA and other molecules
- Mictochondrion – Locus of key energy pathways



# Some Cellular Processes

- Build and degrade structures
- Replicate (mitosis)
- Metabolize
  - Take in food; transform it into cell energy
- Expel molecules (e.g., waste)
- Locomotion

Done by a sequence of chemical reactions (pathways) on biomolecules.

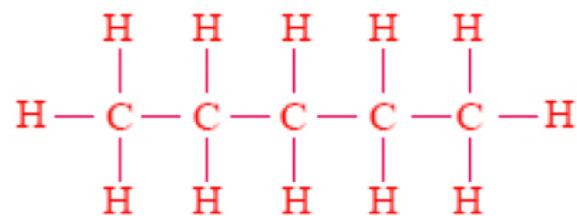
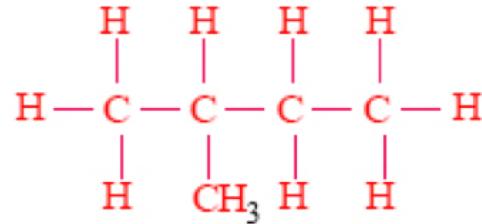
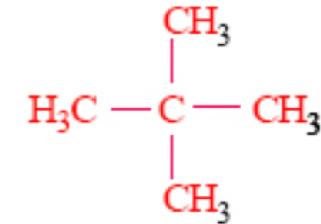


# Key Biomolecules

- Hydrocarbons (Aliphatic molecules)
- Carbohydrate
- Lipid
- Protein
- Nucleic Acid Polymers (RNA, DNA)



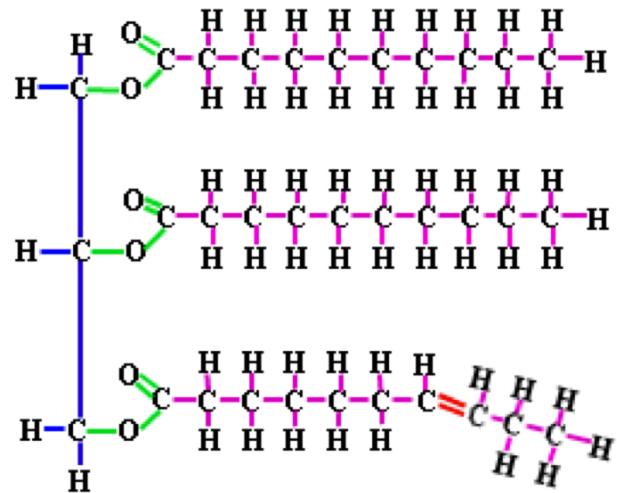
# Hydrocarbons

Pentane  $\text{C}_5\text{H}_{12}$ 2-Methylbutane (isopentane)  
 $\text{C}_5\text{H}_{12}$ 2,2-Dimethylpropane  $\text{C}_5\text{H}_{12}$ 

- Only carbon and hydrogen
- Starting point for building biomolecules
- Uses
  - High energy



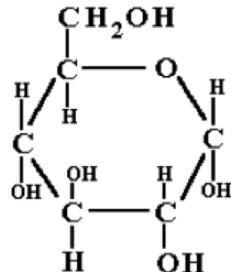
# Lipids



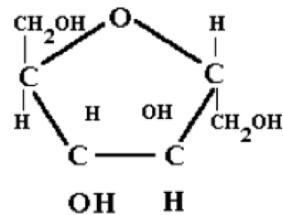
- Polar head group plus chains of hydrocarbons
- Uses
  - Energy storage
  - Membranes



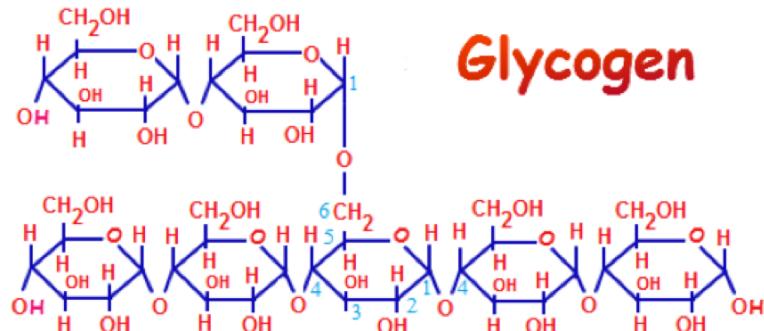
# Carbohydrates



Glucose



Fructose



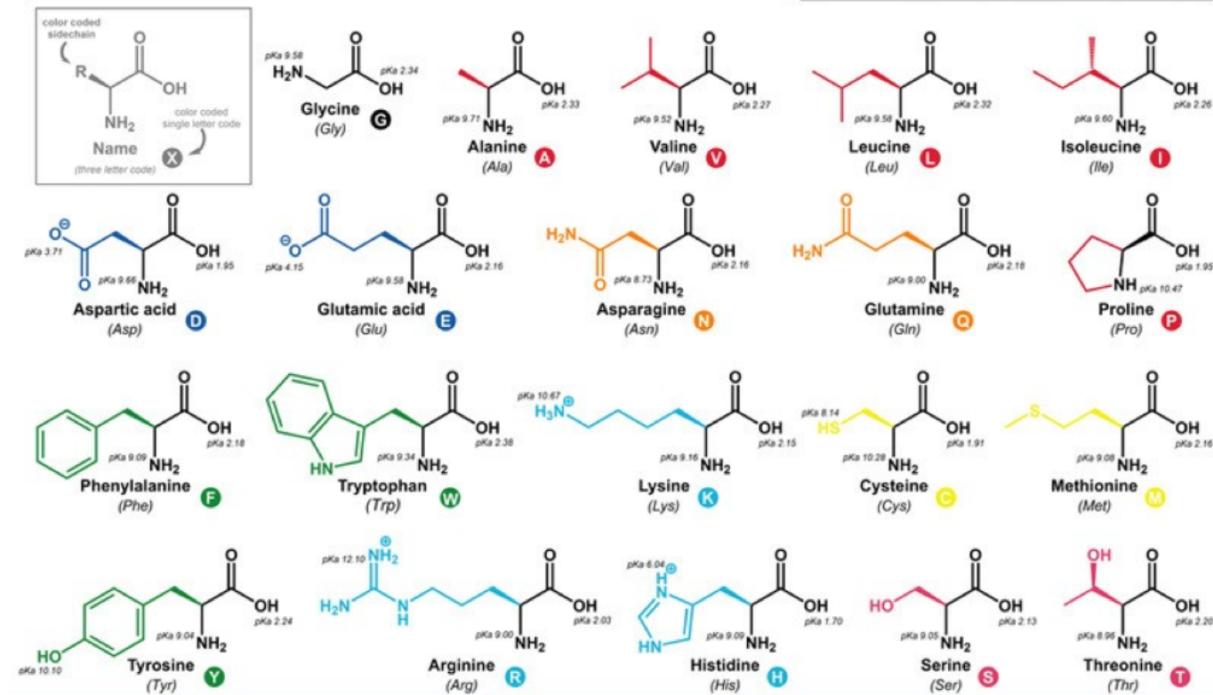
Glycogen

- Carbohydrate formula:  $C_nH_{2n}O_n$
- Uses
  - Signaling
  - Identification
  - Energy
  - Carbon source



# Protein

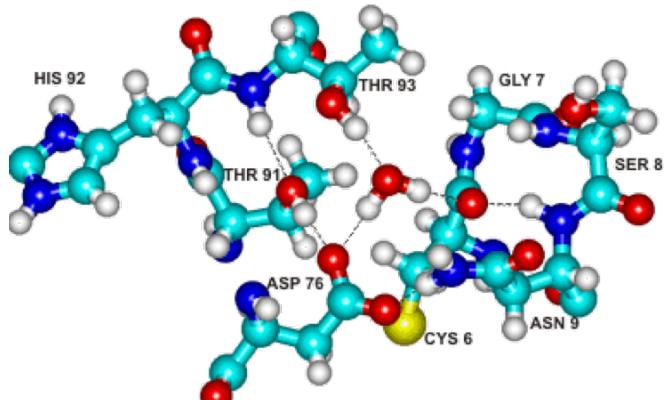
## Amino Acids



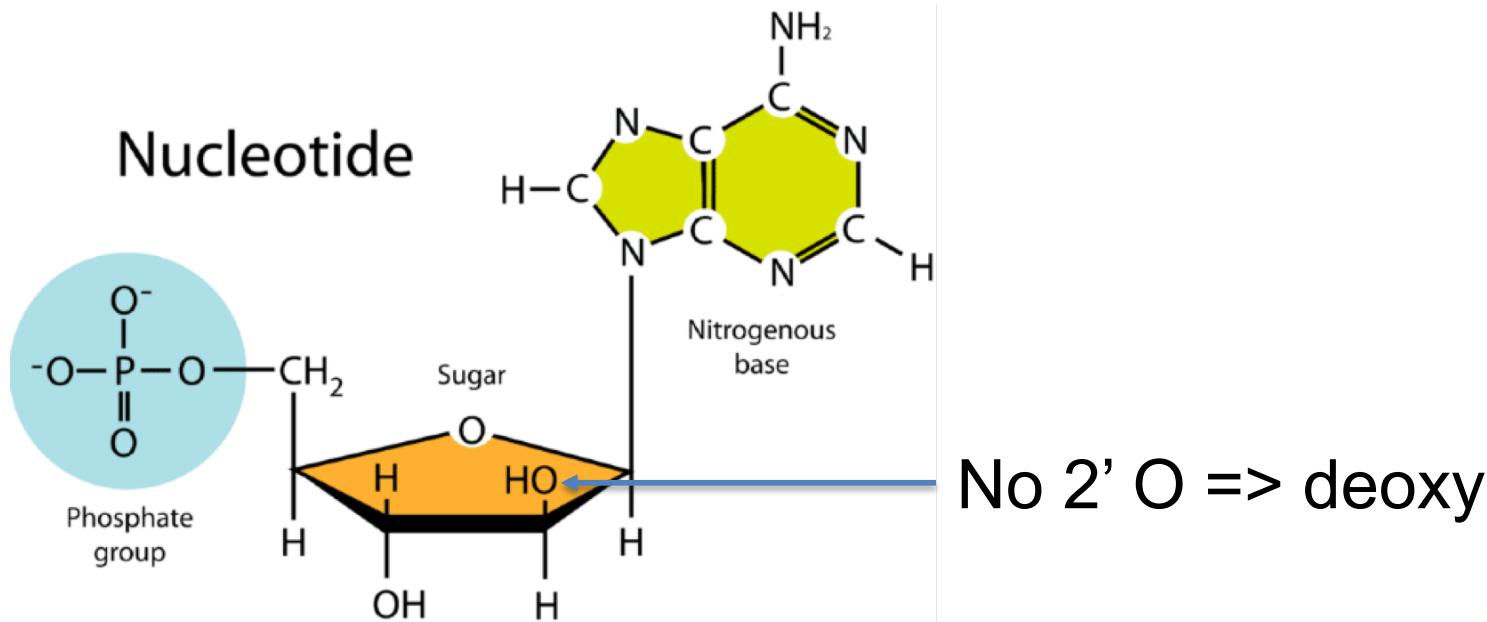
- Protein building blocks
- Determines protein structure
- Determines protein activity

## Protein

- Enzymes – help transform biomolecules
- Transcription Factors (TF) – modify gene activity
- Signaling
- Cellular structures

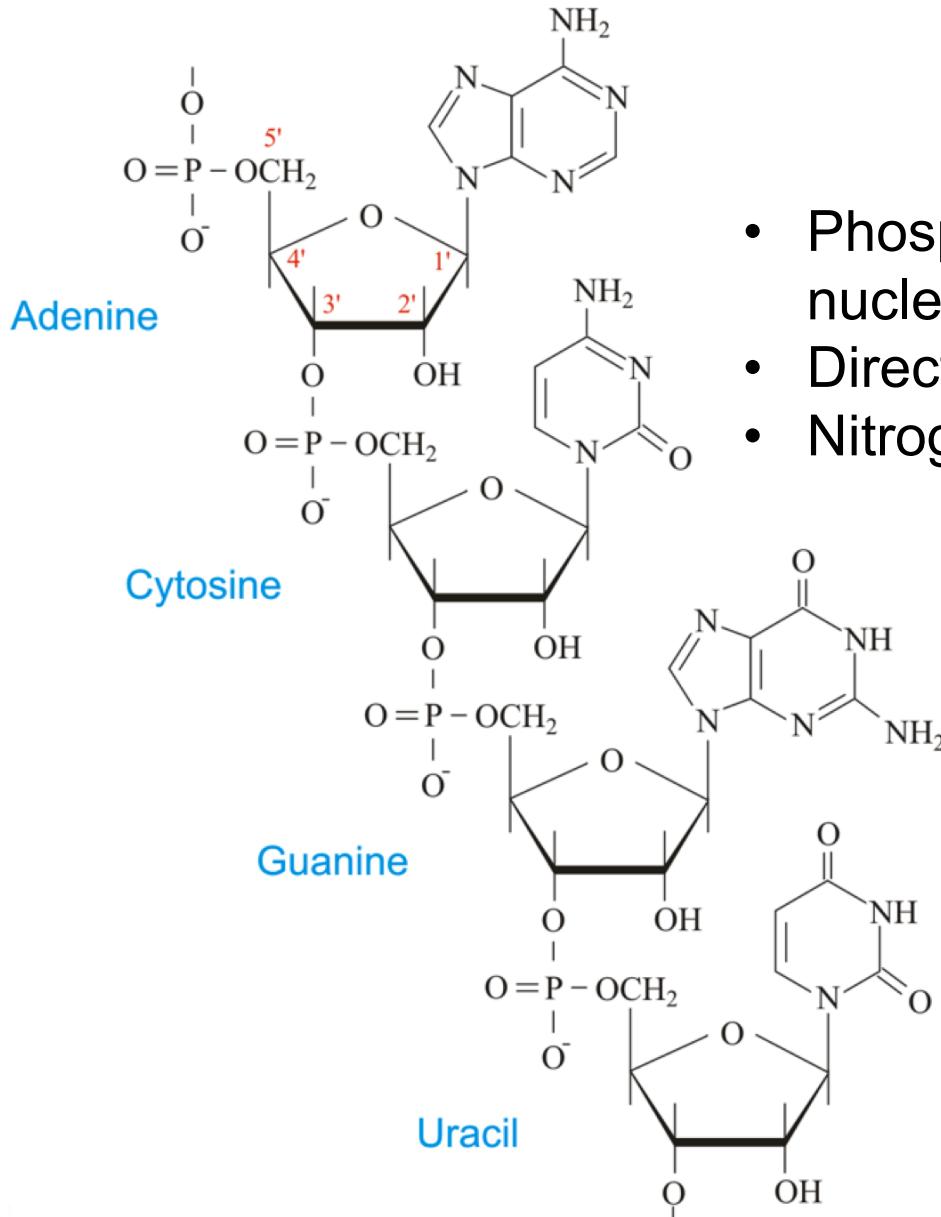


# Nucleotides



- Has 3 parts: nitrogenous base, ribose (sugar), Phosphate

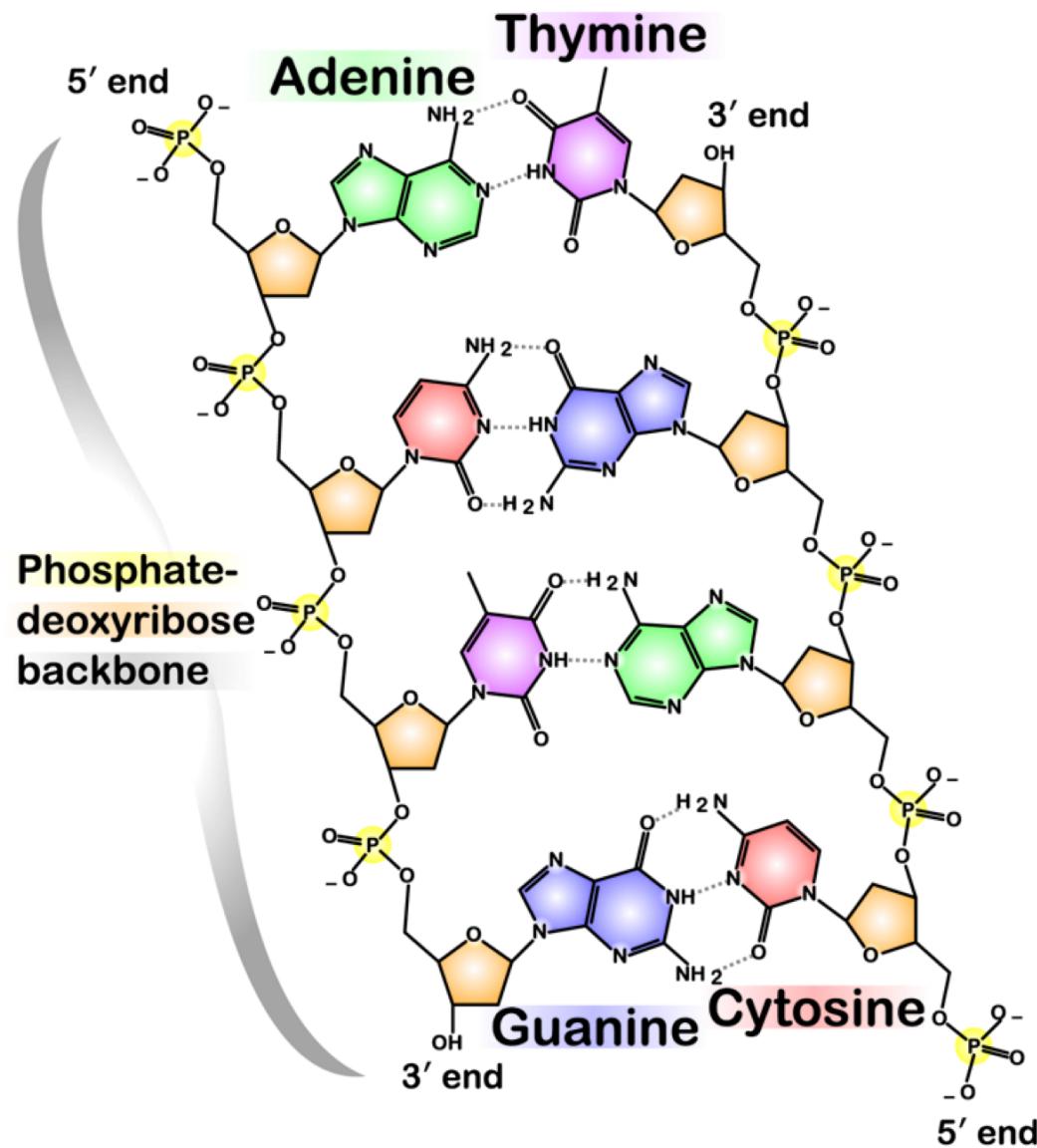
# Ribonucleic Acid (RNA)



- Phosphate group connects the nucleotides
- Directional: 5' & 3' ends
- Nitrogenous bases are A, C, G, U

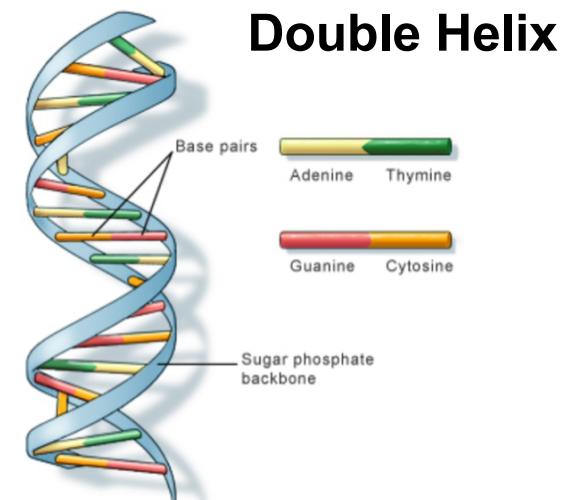


# Deoxyribonucleic Acid (DNA)

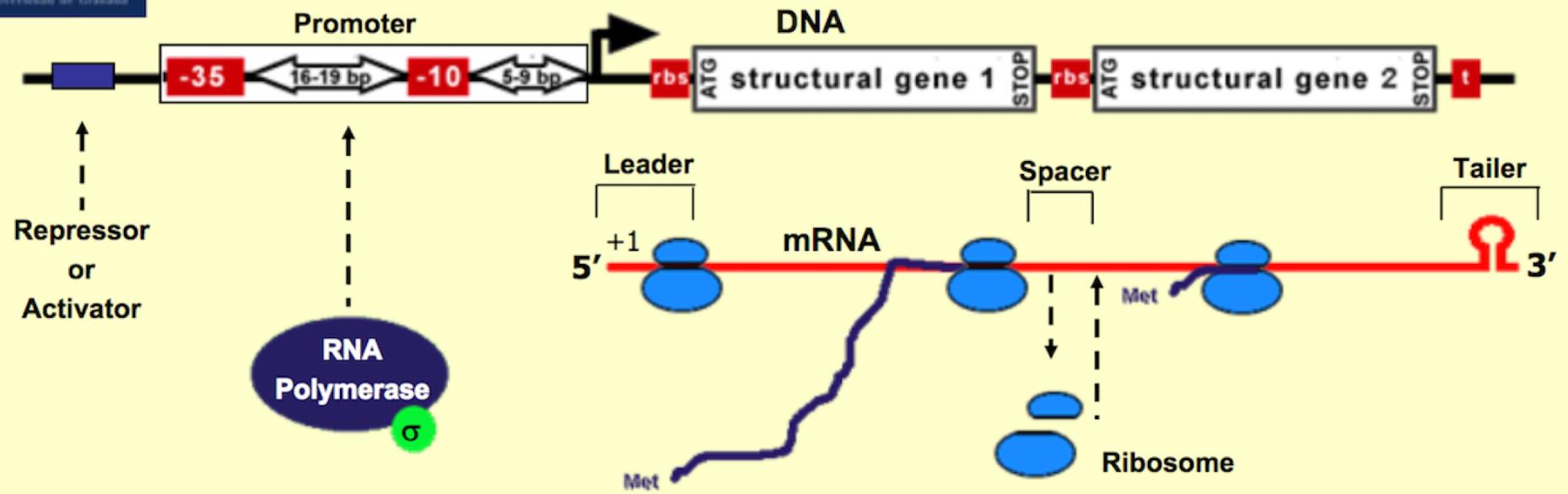


Directional: 5' & 3' ends  
 Nitrogenous bases are G, C, A, T (not U)  
 Double stranded.

- Hydrogen bonding between nitrogenous bases
- Anti-parallel



## Prokaryotic Gene Organisation



**Transcription:** 2 consensus sequences and the startpoint

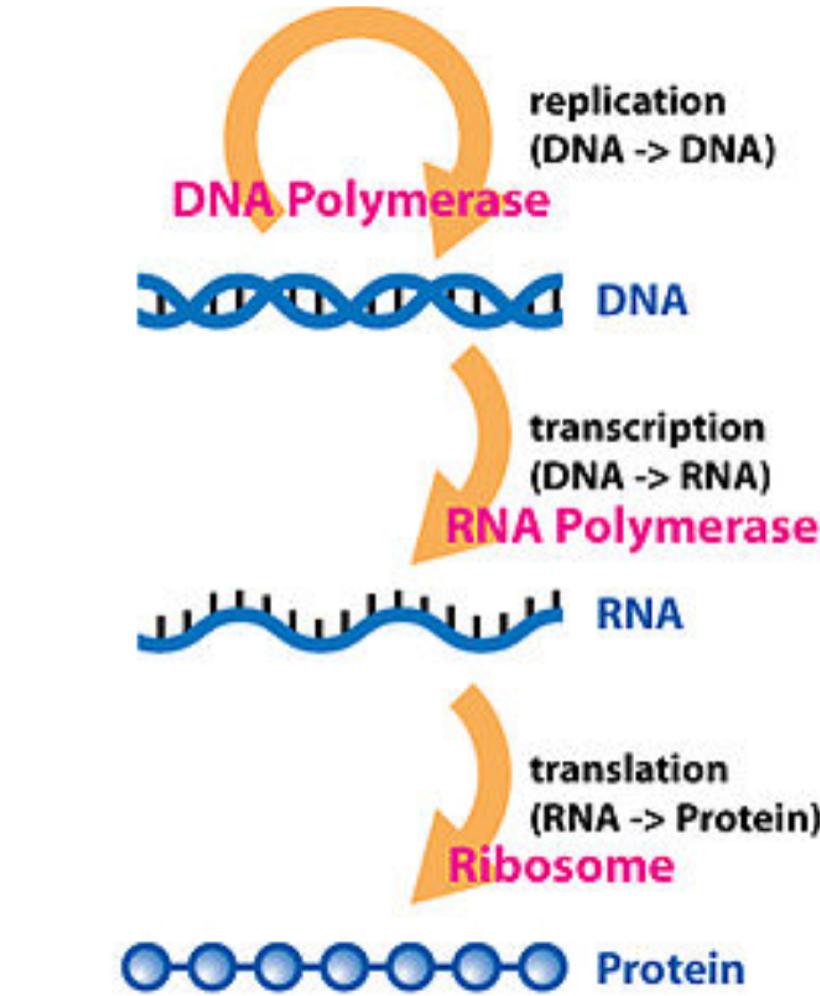
- 10: TAATA       $T_{80}A_{95}t_{45}A_{60}a_{50}T_{96}$

- 35: TTGACA       $T_{82}T_{84}G_{78}A_{65}C_{54}a_{45}$

**Translation:** rbs (ribosomal binding site)

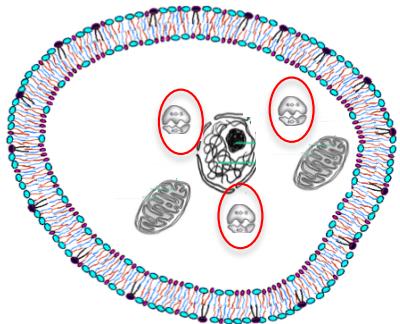
Shine Delgarno    AGGAGG

# The central dogma relates DNA, RNA, and protein\*.



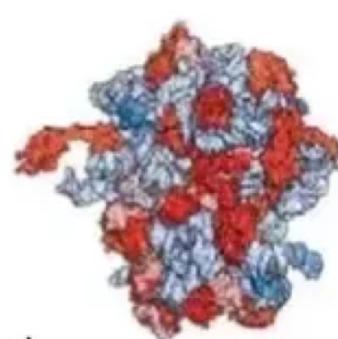
\*Wikipedia

# Cells Contain Complexes of Biomolecules

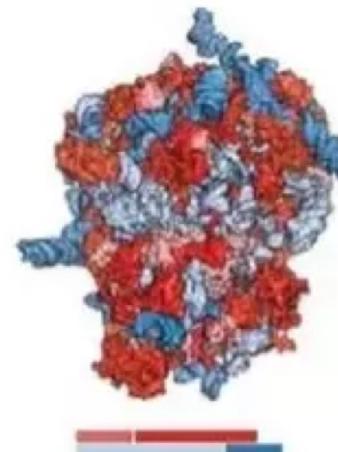


## Ribosome

Bacteria  
(*T. thermophilus* or *E. coli*)



Lower eukaryotes  
(*S. cerevisiae*)



Melnikov, S.  
et al. 2012.  
One core,  
two shells:  
bacterial and  
eukaryotic  
ribosomes.  
*Nature*  
Structural &  
Molecular  
Biology,  
19(6), 560-  
567.

Blue = rRNA  
Red = protein  
Light = conserved  
Dark = unique

2.3 MDa

54 proteins  
3 rRNA

3.3 MDa

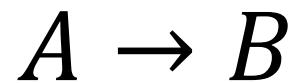
79 proteins  
4 rRNA



# Chemical Reactions Create And Destroy Biomolecules & Biomolecular Complexes

Reactants

Products



Reaction Types

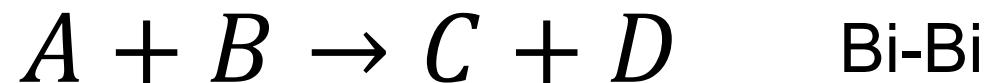
Mono-Mono



Bi-Mono



Mono-Bi



Bi-Bi



# Examples



- Type of reaction?
- Reactants?
- Products?



- Type of reaction?
- Reactants?
- Products?

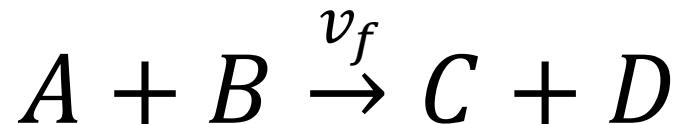


**Reversible reaction**



# Chemical Kinetics Basics

- How fast do reactions go:  $v_f$



- Mass action kinetics
  - Constant times the concentrations of the reactants

$$v_f = k * A * B$$



# Reversible Reactions & Steady State

- Reversible reaction ex:  $AB \xrightleftharpoons[v_r]{v_f} A + B$
- What are the concentrations of reactants and products when the reactions have run for a long time? This occurs when  $v_f = v_r$ .
- Mass action kinetics steady state

$$v_f = v_r \equiv k_f * AB - k_r * A * B = 0$$

**Disassociation Constant**

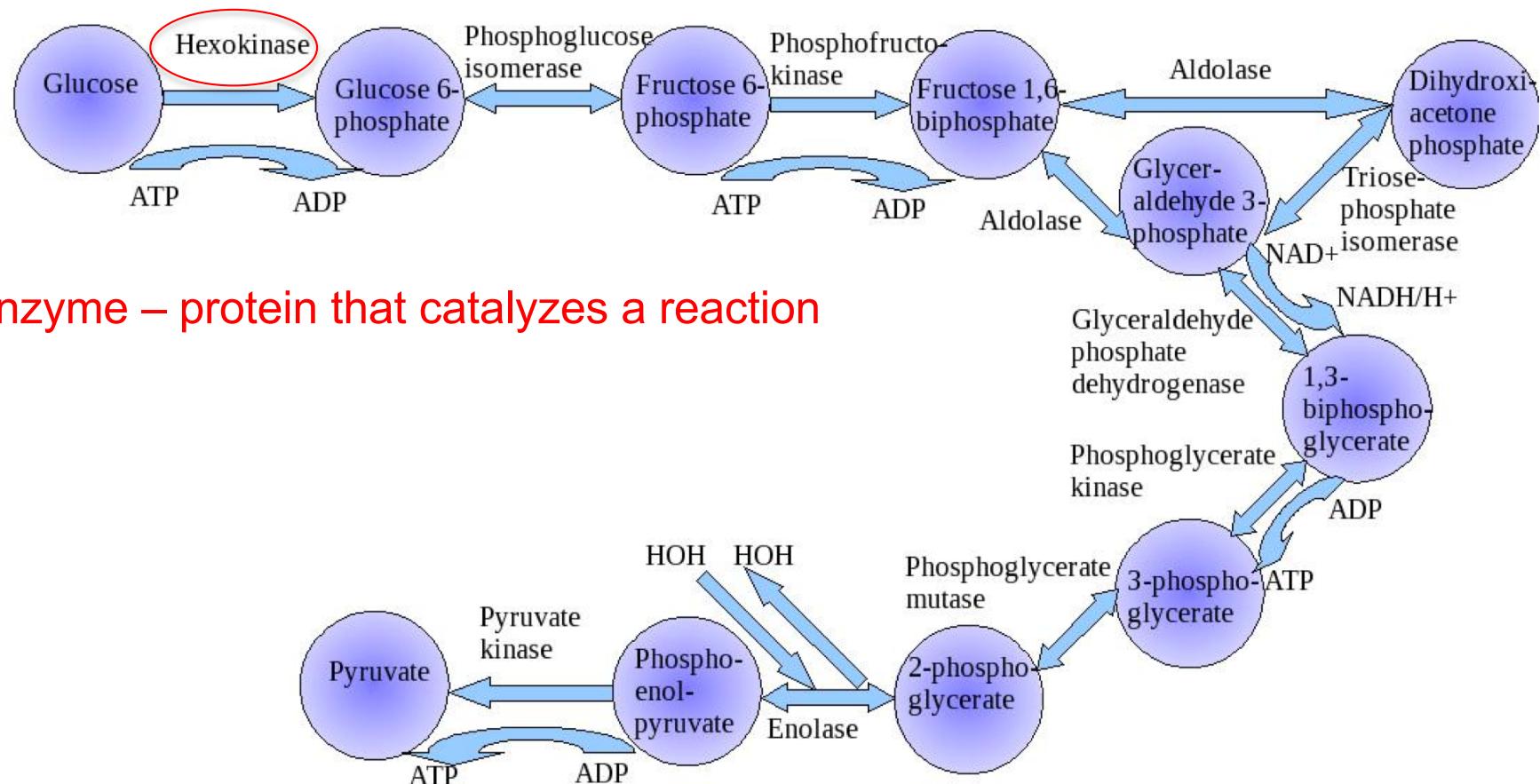
$$K_D = \frac{k_f}{k_r} = \frac{A * B}{AB}$$



# Biochemical Pathway:

## *Collection of Reactions on Biomolecules*

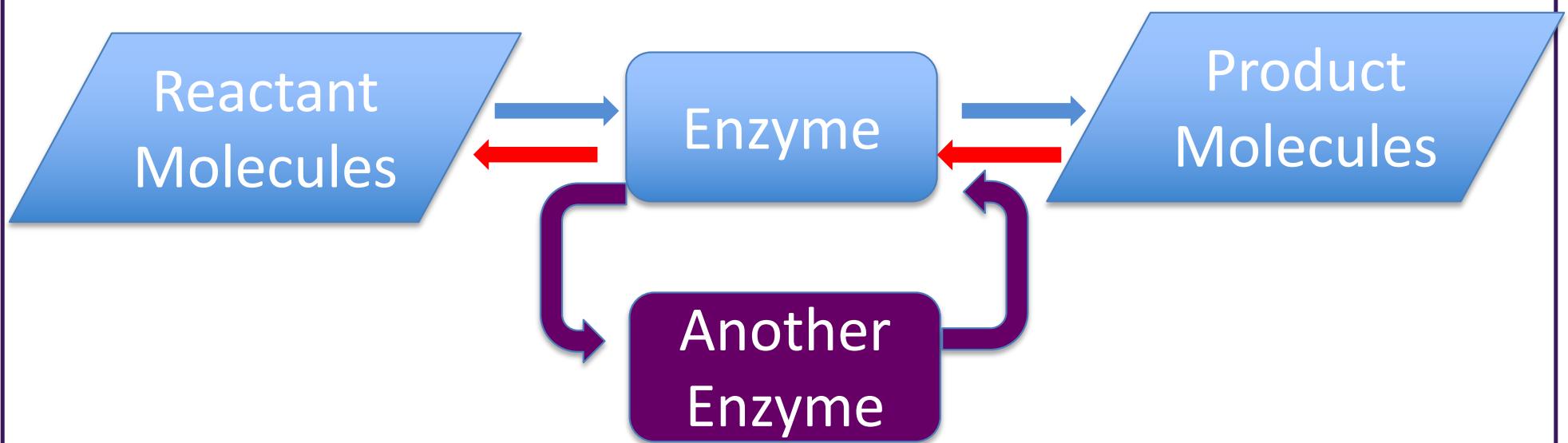
### Glycolysis



Enzyme – protein that catalyzes a reaction



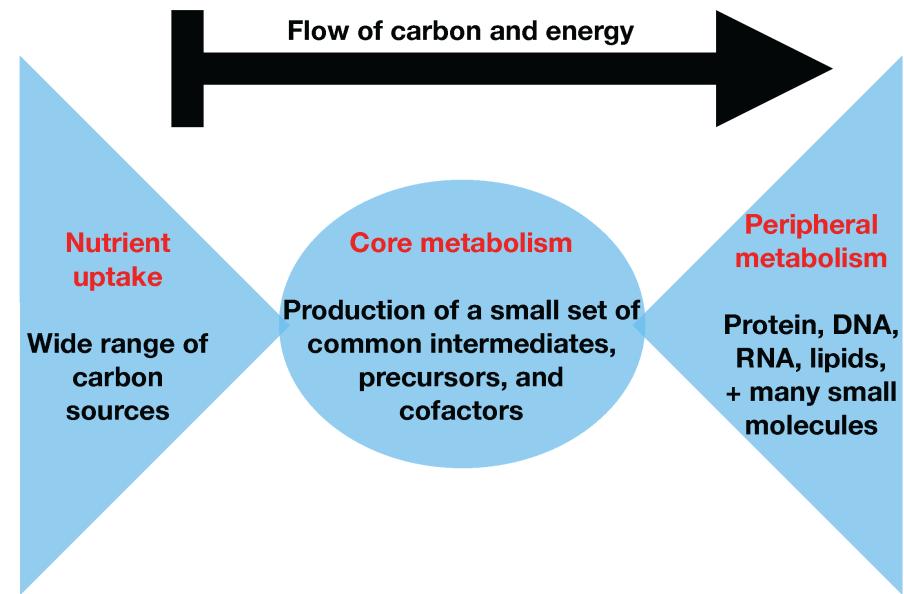
# Biochemical Reactions



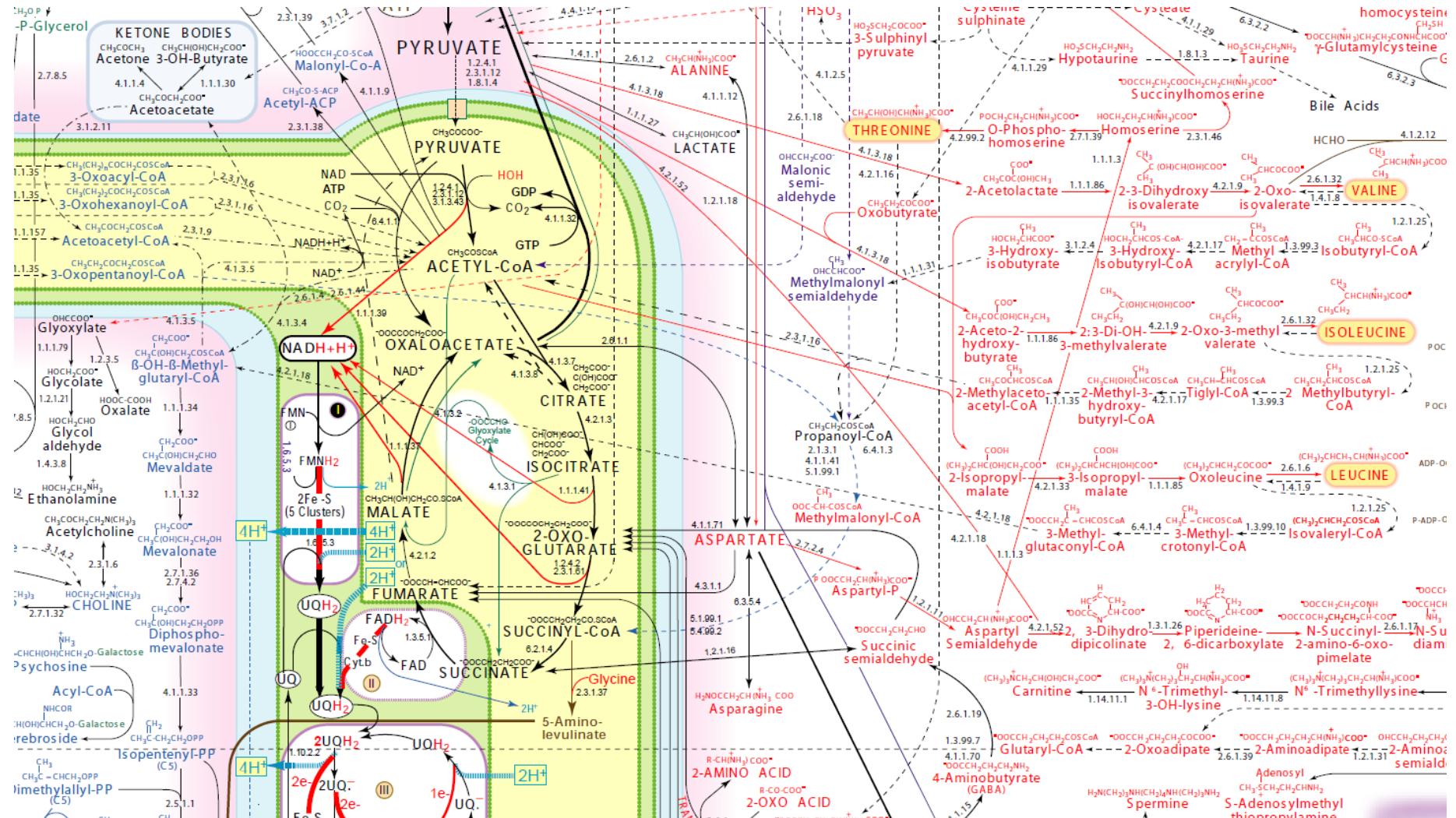
# Metabolic Network++

A **Metabolic network** is a network of chemical reactions in a cell that transforms biomolecules to create energy, create cellular structures, and perform cellular processes.

Digestion of glucose and other nutrients into cellular components and energy production (mostly ATP—adenosine triphosphate and NADH—nicotinamide adenine dinucleotide) are the classic functions of metabolism



# Detailed Metabolic Network

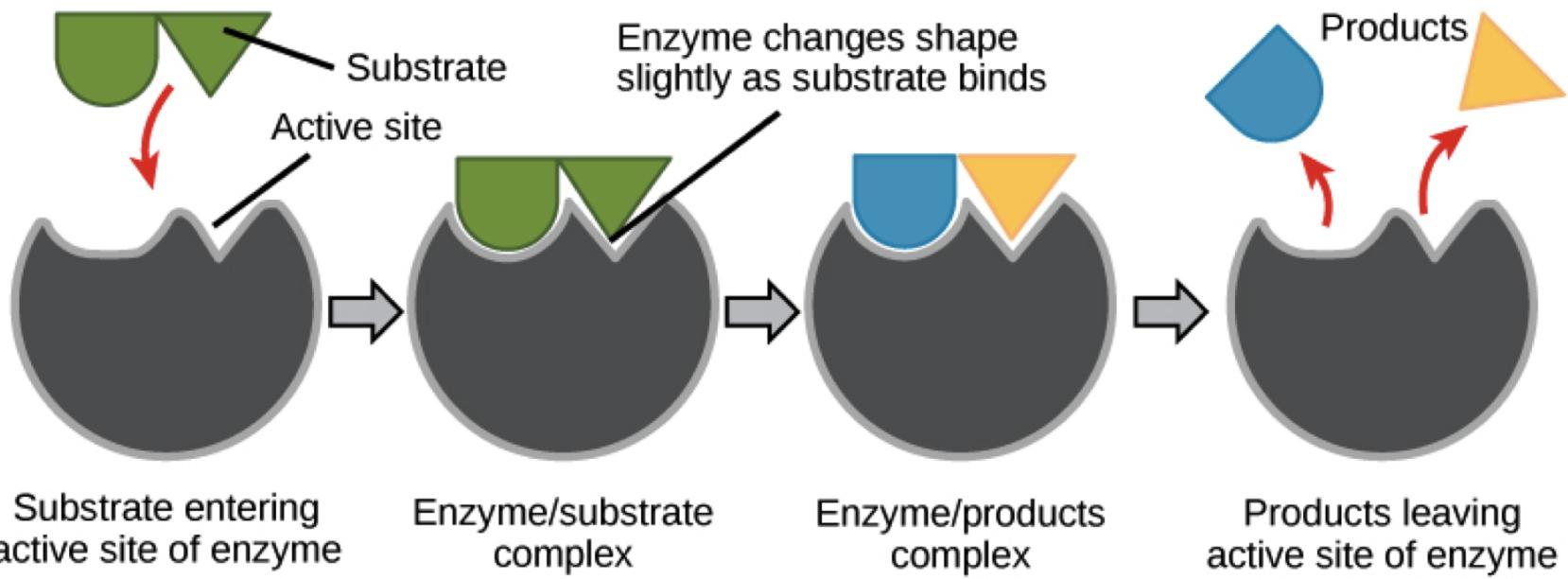


<http://www.iubmb-nicholson.org/chart.html>

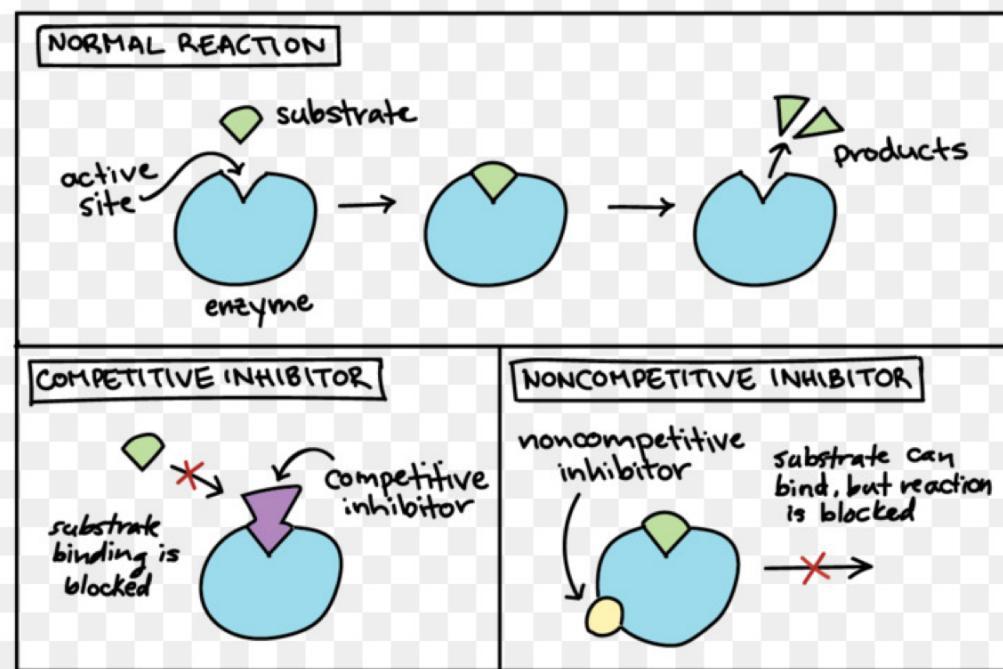
# Enzymes

- Proteins that accelerate biochemical reactions.
- Omni-present in biology

**Enzymes work by induced fit.**

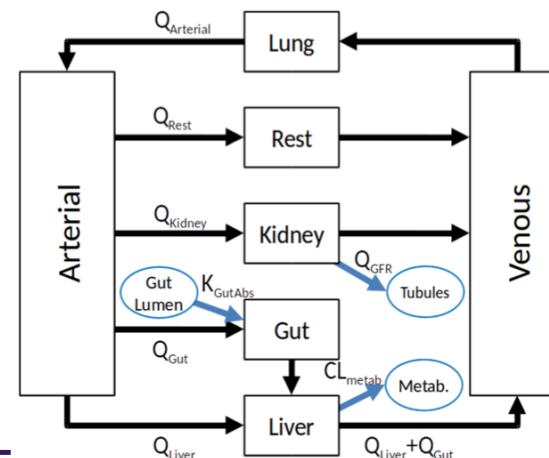
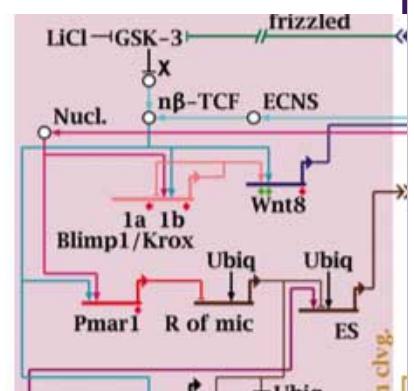
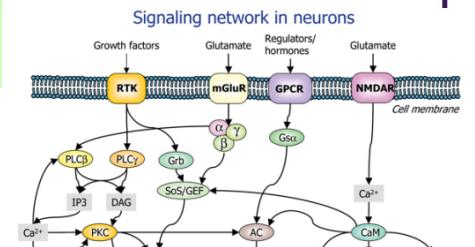
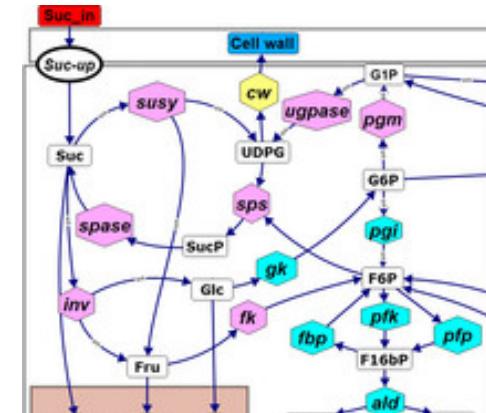


# Enzyme Inhibition



# Biological Networks++

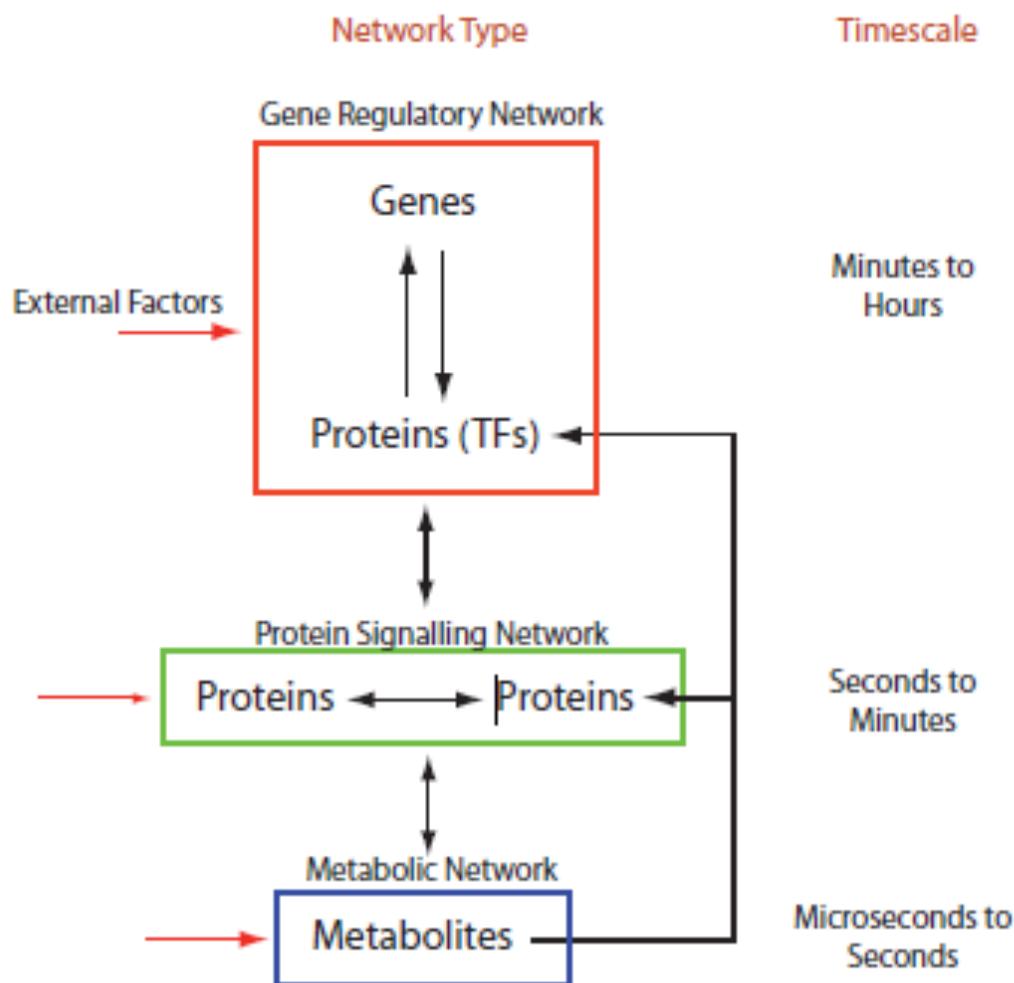
- Chemical Reaction and Metabolic Networks** that create and destroy chemical components of cells and tissues
- Signaling Networks** that transfer information between and within cells
- Regulatory Networks** that control the expression of genes and change cell types and behaviors
- Physiologically-Based Pharmacokinetic Networks** that describe the transport and processing of molecules throughout the body



++ James A. Glazier, Biocomplexity Institute Intelligent Systems Engineering, Indiana University, Bloomington, IN



# Relationships Between Types of Network++



How does the identity of the active networks in the cell change if we make a controlled change?

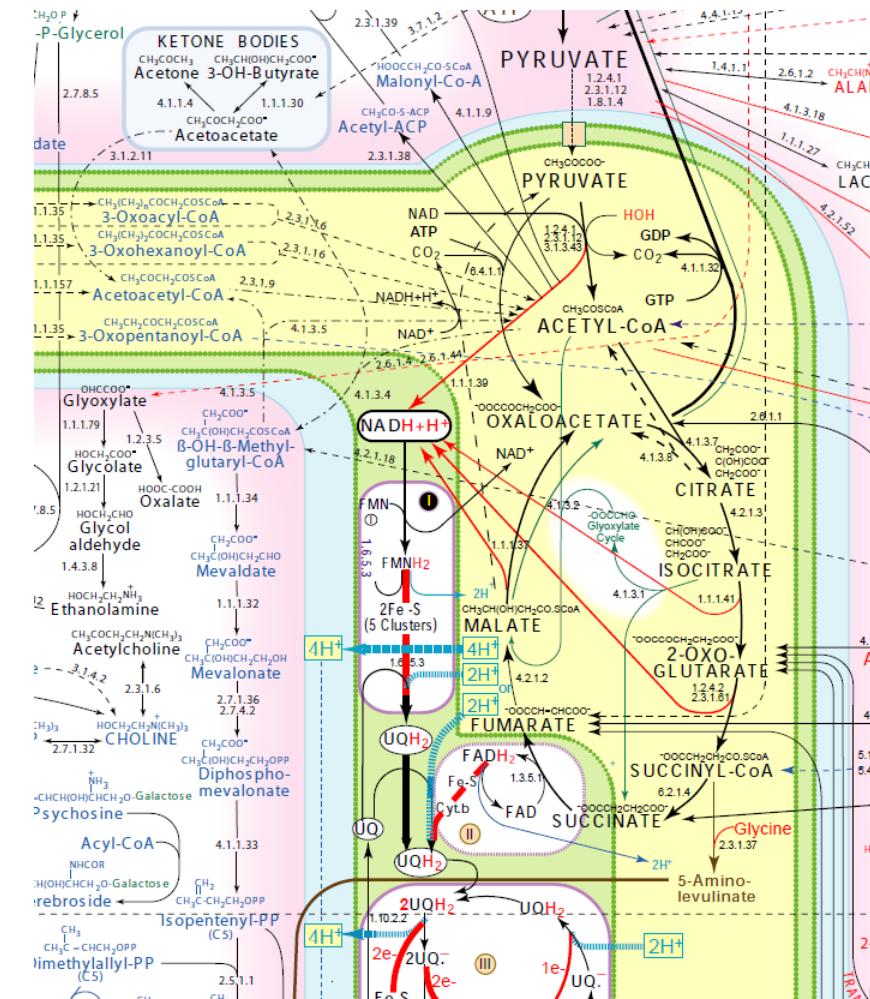
How does the states of the cell's active networks and cell behaviors change if we make a controlled change?

How does the production of cell components and energy change if we make a controlled change?



# Modeling Questions: How Do Concentrations/Fluxes Change?

- Environment:** e.g. temperature, illumination, pressure
- Substrate availability:** e.g. glucose, O<sub>2</sub> level
- Pathway structure,** by adding, removing or changing the nature of a component: e.g. with a genetic knock, out or knock in, or a drug



# Review

**Define and give examples of:**

- Cellular process
- Biomolecule
- Biomolecular complex
- Biological network
- Kinetics model

