

Chapter 1 Molecular logic of life

General principals that can see and may use

Read these notes on your own. I will probably not cover this material in lecture

Problems 1, 4, 6, 7, 10, 11

1.0 Introduction

- a. What is difference between living & nonliving matter? Can I get the class to bring these up?
 - i. Complexity
Nonliving - mixtures of relatively simple chemicals
Living thousands of chemicals in various hierarchical organization and unique 3D structure
 - ii. Use of energy
Nonliving - does not use - decays toward disordered state
Living - E used & transformed to do work, to keep & maintain organization
 - iii. Replication
Nonliving little growth- except maybe crystal
Living - can self replicate
 - iv. Mechanisms for sensing and responding to environment.
 - v. Defined function for each component and regulated interactions between components.
 - vi. A history of evolutionary change
(Opps - defining life by evolution? Not very creationist)

1.1 Cellular Foundations

A. Cells are Structural and Functional Units of all living organisms

Share certain structural features

- i. Plasma membrane (PM)-
Defines periphery of cell
Composed of lipids and proteins
Tough, pliable, hydrophobic
Most polar or charged molecules cannot pass
Need transport proteins
Use hydrophobic interaction to hold together so flexible
- ii. Cytoplasm
What's inside the PM
Cytosol - highly concentrated aqueous solution
Proteins metabolites, RNA & whatnot
Lots of different suspended particles
Ribosomes, mitochondria, etc
- iii. Nucleus or nucleoid
Holds genetic material

Eukaryotes permanent membrane bound structure
 Prokaryotes not separate from cytoplasm but depending on part of
 cell cycle bits and pieces are membrane associated

B. Cellular dimensions limited by O₂ diffusion

On the small side

bacteria 1-2 um long

Smallest bacteria - mycoplasmas

Diameter .1 uM volu 10⁻¹⁴ ml

Ribosome about .02 um diamter

So only a few ribosomes

Probably sets the lower size limit

On the large size

Plant & animal cells 5-100 um

Size probably set by how fast O₂ can diffuse from membrane

C. Three Distinct domains of life

Domains or kingdoms **Figure 1-4**

archaebacteria

Prokaryotes

Recently discovered

Not well characterized

Extreme environments - salt lakes, hot springs, ocean vents, acid
 bogs

Probably diverged from eubacteria long ago

eubacteria

Also prokaryotes

All over, soil, surface water, in other organisms, living and dead

Eukarya

Eukaryotes - have a nucleus and other organelles

Archea and Bacteria divided into subgroups based on metabolism

Aerobic - habitats with lots of O₂ main energy source oxidation

Anaerobic - habitat devoid of O₂ other reaction not using O₂

Obligate anaerobes - Die in O₂

Also classify according to how get E and C **Figure 1-5**

Phototropes - use sunlight for E

Autotrophes - Get all C needed from CO₂

Heterotrophes - require organic nutrients

Chemotrophs - use oxidation chemical reaction for E

(Only heterotrophes here)

Lithotrophs - oxidize inorganic compounds for E

Organotrophs - oxidized organic compounds for E

D. *Escherichia coli* is most studied prokaryote

Will see lots of data on this bugger so better talk a bit about him in this general intro

Figure 1-6

usually harmless, lives in intestinal tract

2 micrometers long <1 micrometer wide

has protective outer membrane outside plasma membrane

Between inner and outer has a peptidoglycan layer

Outer layer will not bind Gram's stain - hence gram negative

Gram positive lack outer membrane and have thicker peptidoglycan together referred to as cell envelope, relatively rigid, hold cellular shape plasma membrane has protein for transport of ions

also cytochrome used to make ATP from ADP

Outer membrane may short hairlike have pili to help adhere to other cells

some strains have 1 or more flagella for motion

inside the usual cytoplasm and nucleoid

Cytoplasm

15,000 ribosomes

Thousand of copies of About 1,000 different enzymes

Metabolites, cofactors, inorganic ions

One or more Plasmids small circular pieces of DNA, independent of nucleoid

Usually genetic code for a small number of useful proteins

Antibiotic resistance

Toxin resistance

Not necessary so useful for experiments

Nucleoid

Single circular piece of DNA

If single strand 1,000 time length of cell

Packaged in proteins to less than 1 micrometer in longest dimension

E. Eukaryotic Cells - Membrane bound organelles

Figure 1-7

5-100 um diameter

Volume 1,000 - 1,000,000 x prokaryotes

Nucleus and a variety of membrane bound organelles

Mitochondria

Endoplasmic Reticulum

Golgi complexes

Lysosomes

Plants have chloroplasts

If open up cell gently can separate organelles based on density

That is how we figure out what proteins are in each organelle

F. Cytoplasm is organized by cytoskeleton

Not just a thick liquid, but a 3D meshwork of filaments- the Cytoskeleton

Actin filaments

Microtubules

Intermediate filaments

Not permanent structures

Constantly forming and un-forming

Hold overall cellular structure

Used to move things around in cell

Used for budding, exocytosis and endocytosis

G. Cells build Supramolecular Structures

From Gen Chem you should remember that many interesting biological chemicals are 'Biopolymers' - A polymer built from various biological monomers **Figure 1-10 for instance**

But there is a tremendous gap between a biopolymer and the macromolecular structures you can see in a microscope

Figure 1-11?

These macromolecular structures are complexes of lipids, proteins, nucleic acids and saccharides that are held together largely by non-covalent interactions

You should review

Ionic (Charge/Charge) interactions

Polar interactions

Hydrogen bonding

Van der Waals interactions

And we will add a new one - the hydrophobic interaction

(More on this later)

Bottom line - all of these large complex structures are held together by 100's or 1000's of very weak interactions.

H. In Vitro studies may overlook important interactions

Early Biochemistry - Take it out and isolate it to understand it. Accepted proof that you understood something was that you had to be able to synthesize it via organic chemistry and have it function the same way

Very successful, but miss important interactions between things

Central Challenge in Biochemistry is to understand all interaction up and down the organizational hierarchy to understand how the cell and the

organism function as a whole.

1.2 Chemical Foundations

99% of all atoms in cell H,C,N,O

Only 30 elements really needed

Most of these are in first 3 rows (Figure 1-12)

A. Biomolecules are C compounds with a variety of functional groups

Keeping in mind H,C,N and O what functional groups can you remember from O chem?

Amine, Carboxylic acid, alcohol, ketone, aldehyde, ether, ester.

Go through figure 1-15 for others

B. Cells contain a Universal set of small molecules

Cytosol of all cells contain the same 100-200 small molecules (Mw 100-500)

Memorize them (that's a joke)

Small molecules unique to an organism are called the *Secondary Metabolites*

Sum total of all small molecules metabolome

(why does everybody have to have a genome knock-off phrase)

C. Macromolecules are the major cell constituents

Proteins - polymers of amino acids

nucleic acids - polymers of nucleotides

polysaccharides - polymers of sugars

lipids - not so much a polymer, but a collection of oily hydrocarbons

Nucleic acids and proteins, exact sequence can be extremely important

polysaccharides and lipids exact sequence less important

D. 3-D structure is described by *Configuration & Conformation*

As in O Chem, Covalent bond and functional groups are important

But in Biochem will see that arrangement of these atoms in 3-D space is even more important.

Configuration - Different spatial arrangement that can only be resolved by breaking bonds

Comes from either double bonds with no freedom of rotation

Or C centers with C compounds with 4 different constituents - stereoisomers

Double bonds

Geometric or Cis Trans isomers
Remember these, if not review!

Asymmetric C's

Chiral centers

C with 4 different substituents

A structure and its mirror image

Called *enantiomer*

So 2 stereoisomers for each center

What is a diastereomer?

Pairs of stereoisomers that are not mirror images

In O Chem you learned proper nomenclature, and book reviews at this point. In Biochem we use some older, less accurate nomenclatures, will review when we get to it.

Have wrong configuration you die!

Will reintroduce concepts of stereo chem as needed

Also configuration around double bonds (cis-trans)

Conformation-

Different spatial arrangements obtained by rotating bonds

Many different conformation will be possible

Certain one will be favored energetically

E. Interactions between biomolecules are stereospecific

When two biomolecules interact they have to have the correct 3-D fit

Hence interactions are stereospecific

-Becomes especially important in making drugs

- wrong stereoisomer can have negligible biological activity

In some cases event has negative effects

- so you organic chemists need to pay attention

1.3 Physical Foundations

Cells must perform work to stay alive

How cells obtain and use chemical E is another aspect of Biochemistry

A. Living Organisms never at equilibrium, but rather a dynamic steady state

i. From Gen Chem - How do you tell if at equilibrium?

Concentrations do not change

But that wasn't the whole story talked about kinetics

Some reactions are slow, so take very long to reach equilibrium

Given the above, how do you tell if at equilibrium?

Calculate Q $Q \neq K$ not at equilibrium

Calculate ΔG , if $\Delta G \neq 0$ not at equilibrium

ii. Chemical composition of a mature individual may not appear to change

But population of molecules is under constant revision

All molecules from small to macro are constantly being torn down and rebuilt.

Even though conc of Hemoglobin and glucose in blood is relatively constant

Glucose from breakfast will not last the day. Either oxidized to CO_2 or transformed to fat or glycogen

Hemoglobin carrying O_2 in blood will not last the month, will be degraded and replaced

iii. Referred to as **dynamic steady state**

Rate of breakdown is balanced by rate of creation

Still sounds like could be equilibrium, because equilibrium is achieved when rate of forward reaction = rate of backward reaction

So let's check ΔG of reaction:

Chemicals in organism - Chemical in environment

ΔG of almost every compound will be big and positive

That means unfavorable

That means want to break down

IF Energy says we should be breaking down, why don't we?

Maintenance of dynamic steady state requires E

Run out of E you die, then start to achieve true equilibrium with surroundings

So life is a scramble to intake enough E that you maintain your

overall E above that of the environment

B. Organisms transform E and matter from surroundings

Back to Thermodynamic terms

i. The **System** - reactants, products, and any needed solvent

ii. The **Surroundings** - everything else in universe

iii. New terms

Isolated system - system exchanges neither E nor matter with surroundings

Closed system - system exchanges E but not matter with surroundings

Open system - system exchanges E and matter with surroundings

iv. Organisms are open systems - exchange E and matter with surroundings

Derive E either by chemical transformations of matter

Or direct absorption of sunlight

C. Flow of electrons provides E for organisms

Nearly all organisms get their E directly or indirectly from the sun

Plants:



Non plants



Both oxidation reduction reaction

most reaction in between are oxidation reduction reaction

Can understand much of E flow by looking at potentials of redox reactions

Will review when we get there

D. Creating and maintaining order requires Work and E

Remember the second law of thermodynamics?

Entropy (disorder) of universe is constantly increasing?

What is wrong with living organisms from this point of view?

Big theme so far is that organisms are highly organized

So the Universe is greatly displeased with us.

i. A reminder of terminology

Entropy (S) a measure of randomness

Is defined at + when randomness increases

Enthalpy (H) a measure of E stored chemical bonds

Free Energy (G) - for a closed system

Energy available to do work

$$\Delta G = \Delta H - T\Delta S$$

Spontaneous only if negative

Endergonic energy requiring reaction

Exergonic energy releasing reaction

To make a E rich compound like ATP you will have to mix a strongly exergonic reaction with an second endergonic reaction so the net reaction is favorable. This leads us to:

E. Energy Coupling links reaction in Biology

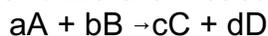
Bioenergetics - Study of energy transformations in living systems

In general link an unfavorable reaction with a + ΔG

with a second favorable reaction with a more - ΔG

So the NET of adding the two reaction together has a net - ΔG and is favorable

F. K_{eq} and ΔG are measures of a reaction's tendency toward spontaneity



$$K_{eq} = \frac{[C]^c[D]^d}{[A]^a[B]^b}$$

$K > 1$ spontaneous (reaction go to right)

$K < 1$ non spontaneous (reaction goes toward left)

$\Delta G < 0$ Spontaneous

$\Delta G > 0$ non-spontaneous

$\Delta G = 0$ at equilibrium

Can transform one into the other

$$\Delta G^\circ = -RT \ln K_{eq}$$

But don't forget kinetics: Just because favorable, still may not occur if kinetics is slow

G. Enzymes promote sequences of chemical reactions

Just mentioned that a reaction may be kinetically slow

can speed it up with a catalyst

Enzymes are biological catalysts

How do catalysts work?

Figure 1-27

Most reaction have a activation energy

Energy required to get to a transition state

Enzyme lower activation E

(Will discuss how in a later chapter)

Most enzymes highly specific

1 reaction 1 or more enzymes

So 100's of enzymes
 Most enzymes are proteins
 But there are a few that use RNA!

Can organize a series of sequential reactions into a pathway
Catabolic pathways - Catabolism - degrade compounds to release E
Anabolic pathways - Anabolism - use E to make compounds

ATP is link between the two

Overall sum referred to a **metabolism**

- H. Metabolism is regulated to achieve balance and economy
 Can break down metabolism into lot's of individual pathways
 Can study regulation of each pathway
 Cell strives to make just enough for its need and no more
 Will see lots of way to achieve this regulation
 But again cell is complex and can't look at one piece without seeing how it fits into the whole

1.4 Genetic Foundations

Major biological discovery of 20th century - first discovery that DNA is genetic material - then second, figuring out how it worked on the atomic scale

- A. Genetic Continuity is Vested in a Single DNA molecule
 E coli - thousand of genes incorporated into a single DNA
 Humans 23 single DNAs (chromosomes)
 Each had to be replicated EXACTLY for next generation
- B. Structure of DNA responsible for exact replication and repair
 2 complimentary strands
 use one as template to make other or for fix damage
- C. Linear sequence of DNA encodes protein 3D structure
 information in DNA is 1d (linear sequence)
 Have seen that protein have and need precise 3-D structure to operate
 DNA sequence make Protein sequence
 Protein sequence then fold into precise 3-D structure via mostly non-covalent interactions
 How this is encoded into sequence sometimes called the 'second genetic code'

1.5 Evolutionary Foundations

Note: Interesting theories, but nothing I would test on

A. Changes in DNA allow evolution

Replication of DNA is not perfect

Occasional mistakes called **mutations**

Some mutation harmful even lethal

Some silent

Some helpful

(Some both helpful and harmful)

If a mix of wild type and mutants find themselves in an environment when the mutant has an advantage,

Strong (mutant) survive

Weak (wild type) die off

Evolution

B. Biomolecules arose by chemical evolution

Oparin theory (1922)

Early earth rich in CH_4 NH_3 H_2O lacking O_2

E from various sources combined to give organic substances

Washed into sea and concentrated there

-Primordial soup-

Chemistry evolved into first cells

C. Chemical evolution can be simulated in the lab

1953 Miller in Urey's lab

Figure 1-33

Could make some needed organic compounds

more refined experiment have made polypeptide and RNA-like compounds

D. RNA or its precursors may have been first genes

Which came first DNA or protein?

Probably RNA

Has properties of both

Can replicate

Can catalyze reactions

E. Biological evolution began >3.5 billion years ago

earth formed 4.5 billion years ago

3.85 billion, Rock in Greenland with C in rock appears to have biological origin

F. First cell was probably a Chemotroph

primordial cell sitting in soup rich in organic chemicals, all it needed was to figure out how to use the E available

Next step probably use light to change H_2S to S or SO_4
 (The organisms still around as cyanobacteria)
 Then on to H_2O and release O_2 as a waste product

Atmosphere then slowly changed from O_2 deficient to O_2 rich
 A lot of obligate anaerobes probably died in a mass extinction

- G. Eukaryotes evolved from prokaryotes in several stages
 1.5 billion year ago probably first eukaryotic cells
 Can't do with fossil records
 Use morphology and DNA of cells to trace

Several things needed to be done

1. Evolve DNA higher level chromosome structure
2. Evolve membrane covered organelles including a membrane around the nucleus
3. Evolve endosymbiotic relationship
 - With light harvesting bacteria for photosynthesis
 - With good aerobic bacteria for mitochondria

- H. Molecular anatomy reveals the above evolution

Genome - Complete genetic endowment of an organism
 Have genome of several organisms from e coli to humans

By comparing sequences can begin to trace evolution
 Consistent with but more precise than looking at physical shape (phenotypes)

Homologs - two proteins that have a readily apparent genetic sequence

Paralogs - two homologous protein gene in the same species
 Presumably arise from gene duplication
 Similar in sequence and 3-D shape
 But may have acquired different function

Orthologs - homologous gene found in different species
 Usually have same function in both species
 Comparison of sequence changes helps trace evolution
 Sequence close, closely related
 Sequences different, not so closely related

Annotated Genome

Not only gene sequences but a guess of what each gene sequence actually does. Often based on Orthologs (above)

- I. Functional genomics shows allocation of gene to specific processes
Look at annotated genome and figure out how many protein are allocated to different specific functions

Right now ~40% in ecoli to human - function unknown

Cell transporters 10% e coli 8 % Arabidosis thaliana (plant) 4% Human

Gene for protein and RNA for protein synthesis ~ 4% Ecoli

H thaliana 2% synthesis 6% target to proper place in cell

More complex, more genome devoted to regulation

- J. Genomic comparisons important to Medicine
what can I say