Building College-University Partnerships for Nanotechnology Workforce Development

Biocompatibility and Cellular overview

Part 1

Introduction

- Nanomanufacturing supplies many unique materials and processes for biological applications. These may range from nanoparticles for drug delivery to prosthetic devices.
- So it is necessary to understand how biological entities like cells interact with products crafted on the nanoscale.
- This packet will review basic biology with emphasis on scale and interface with materials. Then we will look at common nanomanufactured biomaterials with associated applications.

Outline

- Biocompatibility
- Quick overview of cellular interaction
  - Scale, size, generic animal cell
- Nanoscale materials for biological interaction
  - Liposomes
  - Metal Nanoparticles
  - Nanoshells
  - Examples of bionano applications

Biocompatibility

- Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application.
- To engineer biocompatibility, the nanotechnologist must amalgamate an understanding of materials and biological response.
- The first part of this packet focuses on cellular function. This allows us to appreciate biological scale, and cellular activity.
- The second part of this packet examines the biological response to engineered materials at the nanoscale.

Biocompatibility

- The biological response to engineered material should consider both the short term response, and the long term response.
- Acute response is the near term reaction of the body to the biomaterial.
- Long term response can be chemical release, chemical degradation, shedding particles, etc.

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Cell Size

- The logistics of carrying out metabolism sets limits on the size range of cells
- As an object of a particular shape increases in size, its volume grows proportionally more rapidly than its surface area
- Eukaryotic cells
  - Have a nucleus
  - ~5 to 100 μm in diameter, depending upon function

Why Are Cells Microscopic?

- **For objects of the same shape, the smaller the object, the greater its surface area to volume ratio. (Also the nanoparticle definition)**
- If cells were larger, rates of chemical exchange with the extracellular environment might be inadequate to maintain the cell due to the great distance between the cell membrane and the nucleus

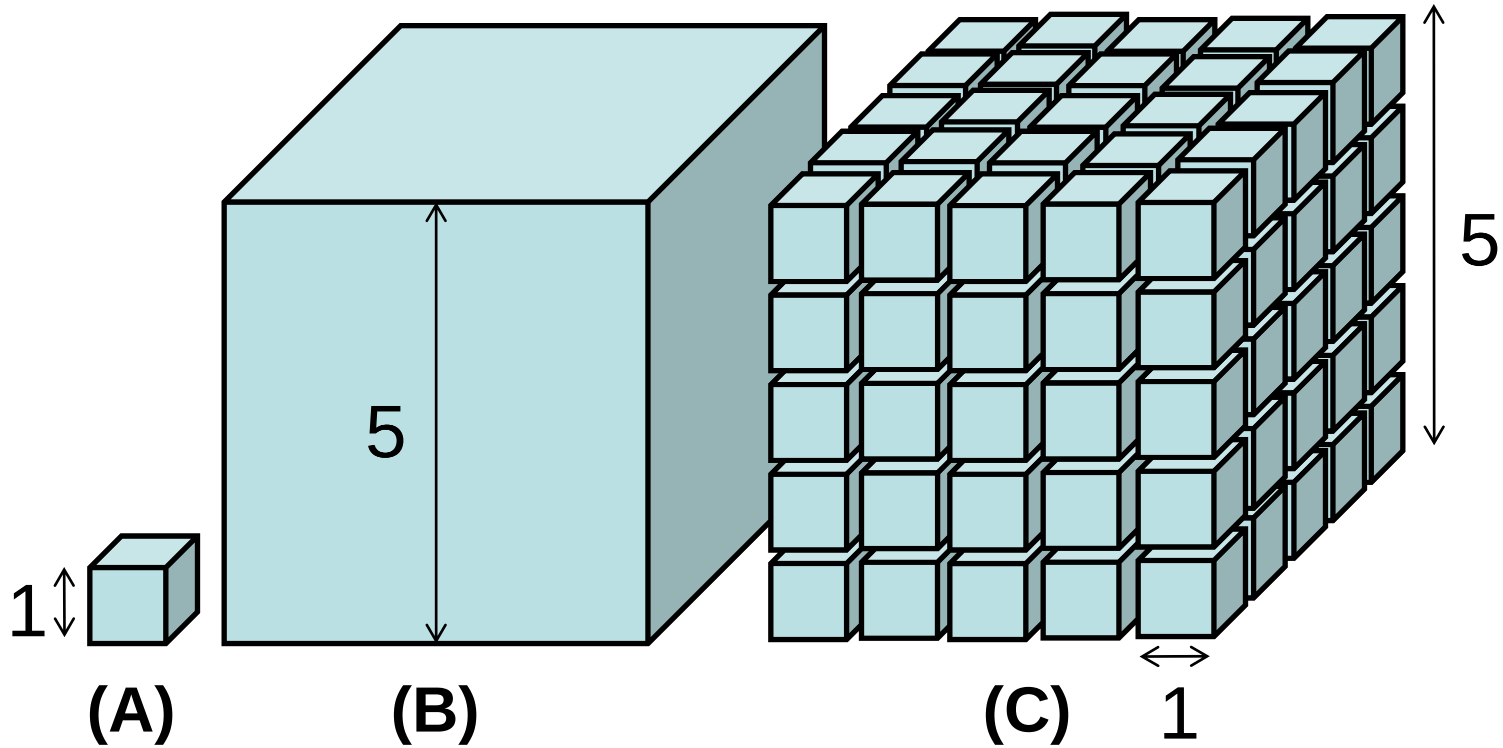
Why Are Cells Microscopic?

- By dividing a large cell into smaller cells, the surface-area to-volume ratio is maximized
  - This serves the cell's need for acquiring nutrients and expelling waste products
- This relationship explains why larger organisms do not have larger cells, but more of them

Cell Size

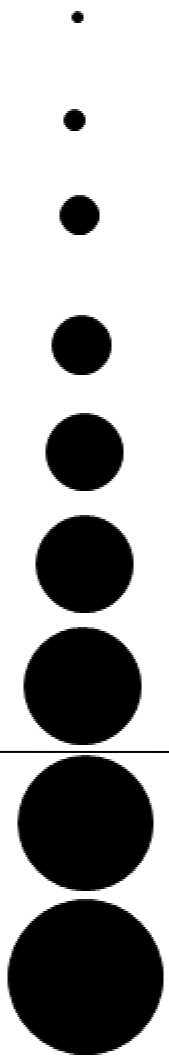
- How does this “standardization” of cell size impact nanotechnology?
- Universal size for cells means universal scaling and this dictates the manufacturing tool set.
- Same design algorithms and tools for mice cells as elephant cells.
- Techniques and applications can be shared across the nano-biomaterial market.

Cell Size vs. Surface Area



	A	B	C
Surface Area	6	150	750
Volume	1	125	125
Surface Area to Volume Ratio	6	1.2	6

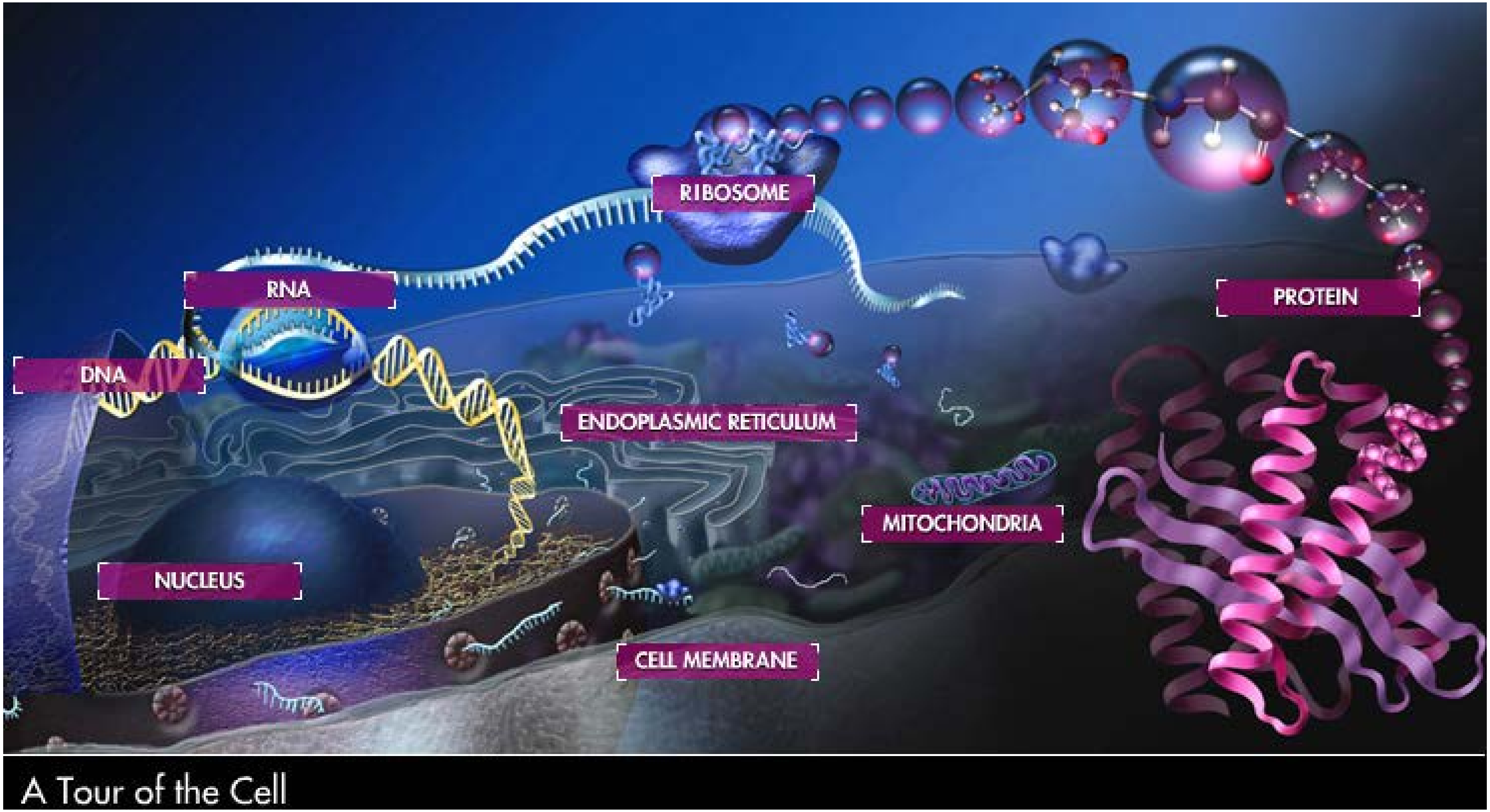
Relative Particle Sizes



Gas Molecules	**0.1 - 1 nm**
Virus	**2 – 100 nm**
Tobacco Smoke	**10 – 300 nm**
Bacteria	**0.2 – 10 µm**
Fog	**1 – 50 µm**
Adult Red Blood Cell	**7.5 µm**
Flour dust, pollens	**5 – 50 µm**
40 µm – Barely Visible to the Naked Eye	
Human Hair	**50 – 120 µm**
Beach Sand	**100 µm and up**

American Air filter Company

The Animal Cell



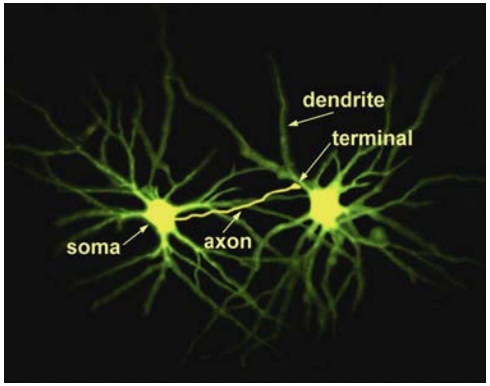
Source: http://www.nsf.gov/news/overviews/biology/interactive.jsp

Form Fits Function

- The previous slide of the animal cell is a generic representation of a cell, no one cell really looks like that.
- Cells are extremely diverse in appearance.
  - modified for specific purposes, express functionality.
- Different cells contain different amounts of organelles, depending on the role they play in the body.
- **Form Fits Function, and we select and modify materials to interact with cell function**
- Again, we will reference cell function, then relate this information with materials.

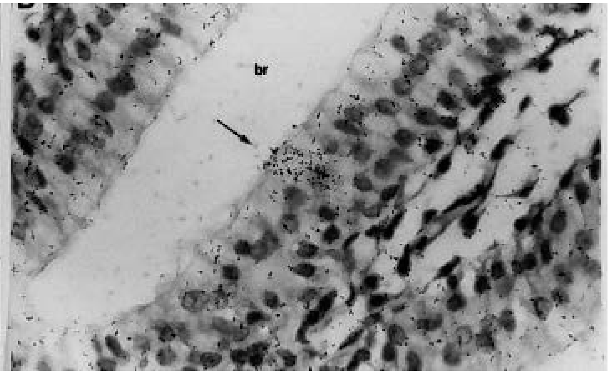
Cell Diversity

http://www.nida.nih.gov/pubs/Teaching/Teaching2/largegifs/slide5.gif



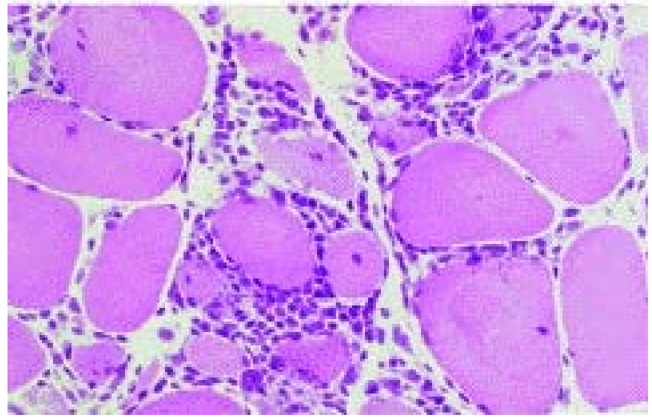
Neuron

http://wheat.pw.usda.gov/~lazo/methods/minn/chap-shoot2.fm.html



Epithelial cells- Line body cavities

http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=eurekah&part=A36863

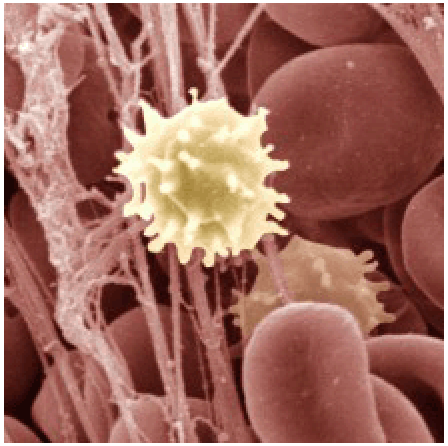


Connective Tissue cell

http://www.nlm.nih.gov/medlineplus/ency/images/ency/fullsize/19495.jpg

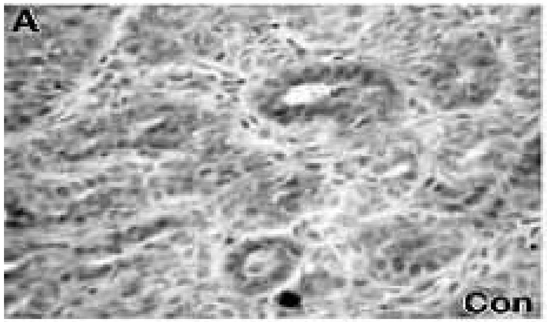
Skeletal Muscle cells

http://www.nih.gov/news/research_matters/june2009/06082009immune.htm



Erythrocytes-
Red and white blood cell

http://2002annualreport.nichd.nih.gov/deb/images/bondy_fig4.jpg

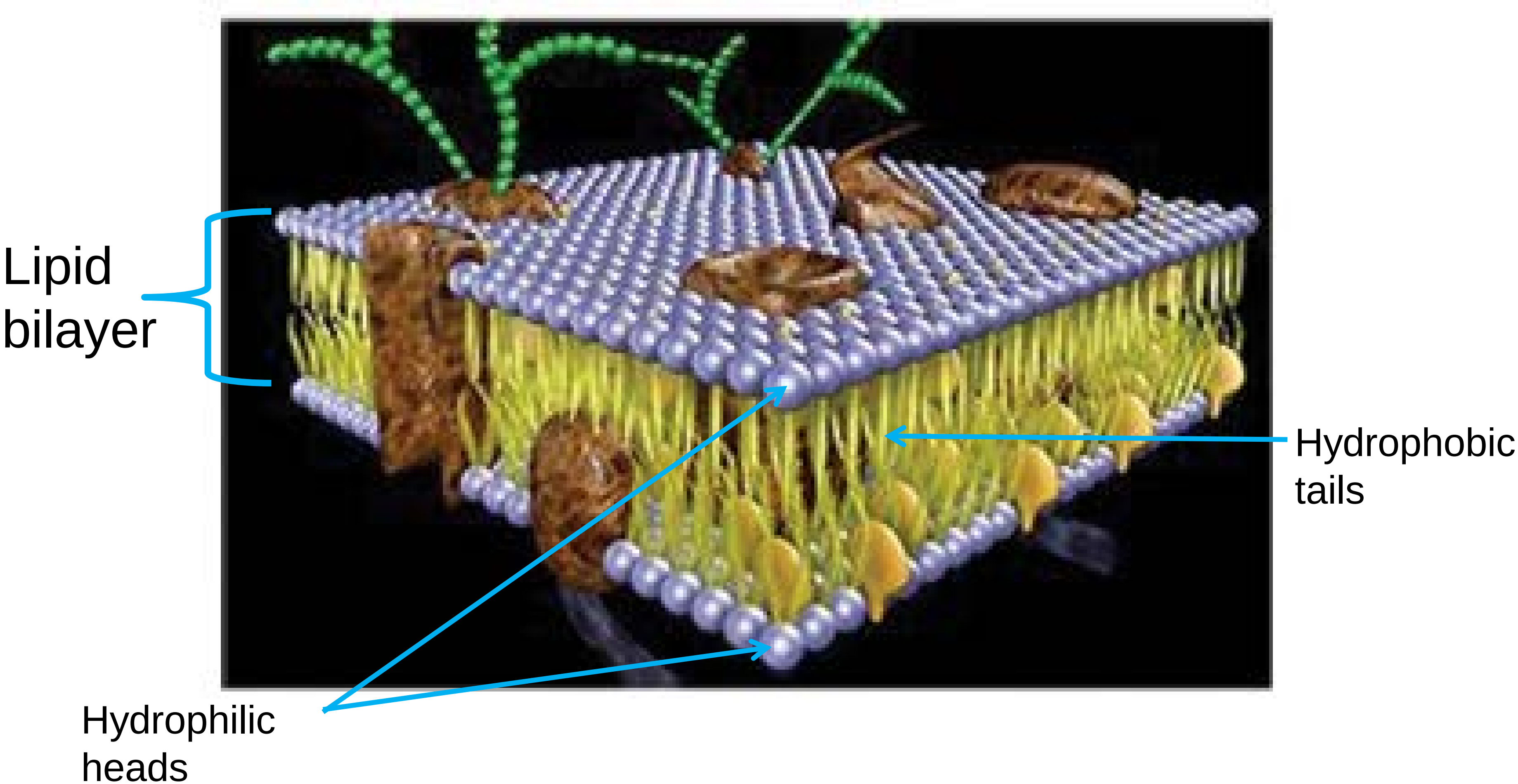


Osteocytes- bone cells

Examining Cell Structure and Related Function

- Key points are the role of proteins, the role of DNA, and cell communication and interaction with materials.
- We will first take a look at the cell wall.
- The wall itself is made of a self assembling phospholipid.
- Phospholipids are also used as a base to create liposomes that are used for drug delivery systems that we will discuss later.
- The cell wall is made of a phospholipid sheet that has ports that regulate nutrients, waste material, communication, and interaction with other cells. So this is how cells, “see”, “communicate”, and “carry out life functions”.
- Proteins are the “key” that opens and closes these ports.
- Man made materials must interact or communicate with the cell.

Membrane Structure

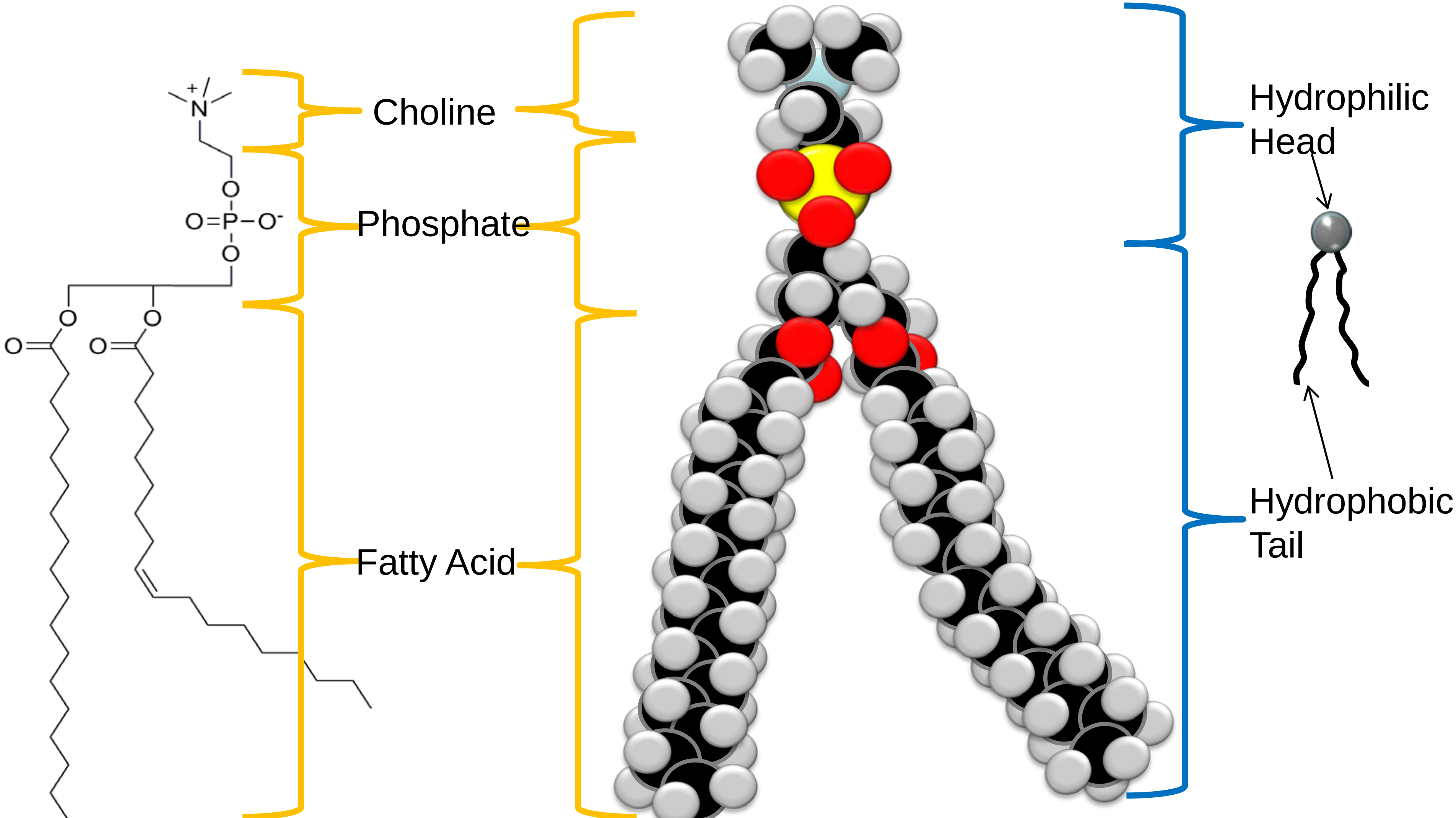


Source: https://www.llnl.gov/str/JanFeb06/Schwegler.html

So what is a Phospholipid?

- Natural **self assembly** unit
- A phospholipid is a molecule related to fat
- The molecule is comprised of:
  - A **hydrophilic** (water loving) phosphate head
  - Two **hydrophobic** (water fearing) fatty acid (hydrocarbon) tails
- When phospholipids are added to water, they self-assemble.
  - The phosphate head points towards the water, keeping the fatty acid tails away from the water, forming a **bilayer**
  - These bilayers act as cell walls.

Phospholipid Structure



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The Nucleus

- Nuclear envelope is also formed from **self assembled** bilayer of phospholipid like the external cell wall.
- The most prominent organelle in an animal cell.
- The nucleus houses deoxyribonucleic acid (DNA), which is responsible for protein synthesis in the cell.
- The nuclear envelope protects the DNA.
- The DNA is like a “hard drive”, and it contains all the “programs” the body needs to carry out life functions.

The Nuclear Envelope

- The entire nucleus is separated from the cytoplasm (the rest of the cell) by a **nuclear envelope**
  - A double membrane, lipid bilayers, separated by a space of 20 to 30 nm
  - The envelope is perforated by pores that are about 100nm in diameter, these regulate the transport of macromolecules and particles.
  - **Naturally for the nanotechnologist these size parameters determine material interaction, material process tool set, and characterization tools.**
  - The nucleus houses DNA, that is packaged as chromosomes during cell division.

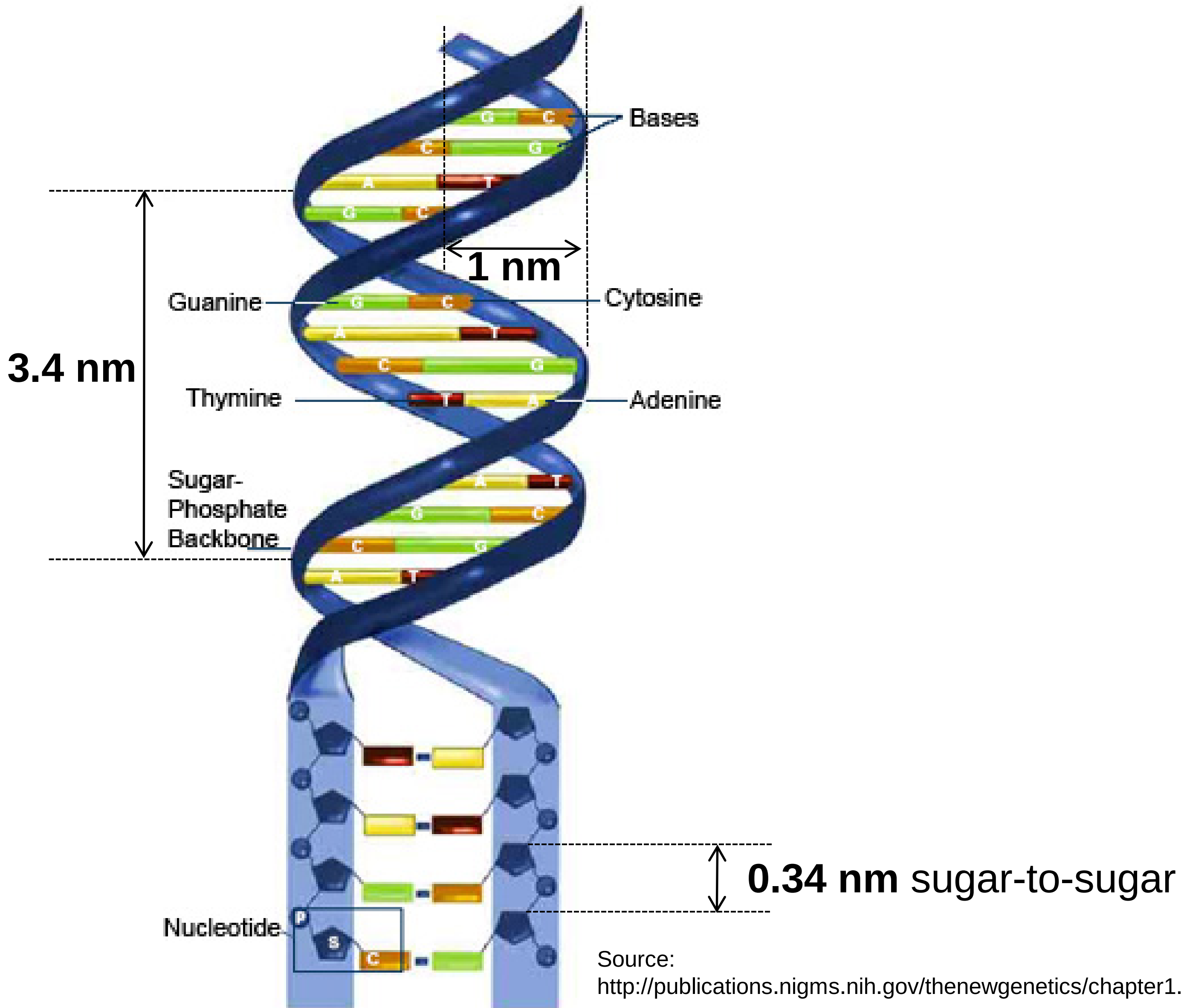
DNA and Proteins

- Why do we care about DNA and proteins?
- DNA is an excellent example of controlled self assembly.
  - DNA is transcribed into RNA, which is translated into proteins
  - DNA is the “software/template”, proteins carry out life functions
- We will review DNA first, then see how DNA is used to create proteins later in the presentation.

Deoxyribonucleic Acid (DNA)

- Chemically, DNA consists of a series of **nucleotides**
  - The building block of nucleic acids, made up of a five carbon sugar, deoxyribose, covalently bonded to a nitrogenous base, base pairs, and a phosphate group.
  - The phosphate of one nucleotide is bonded to the sugar of the next nucleotide in line, resulting in a sugar-phosphate “backbone” from which the bases project
  - Co·don, A set of three consecutive nucleotides in a strand of DNA or RNA that provides the genetic information to code for a specific amino acid that will be incorporated into a protein chain or serve as a termination signal.

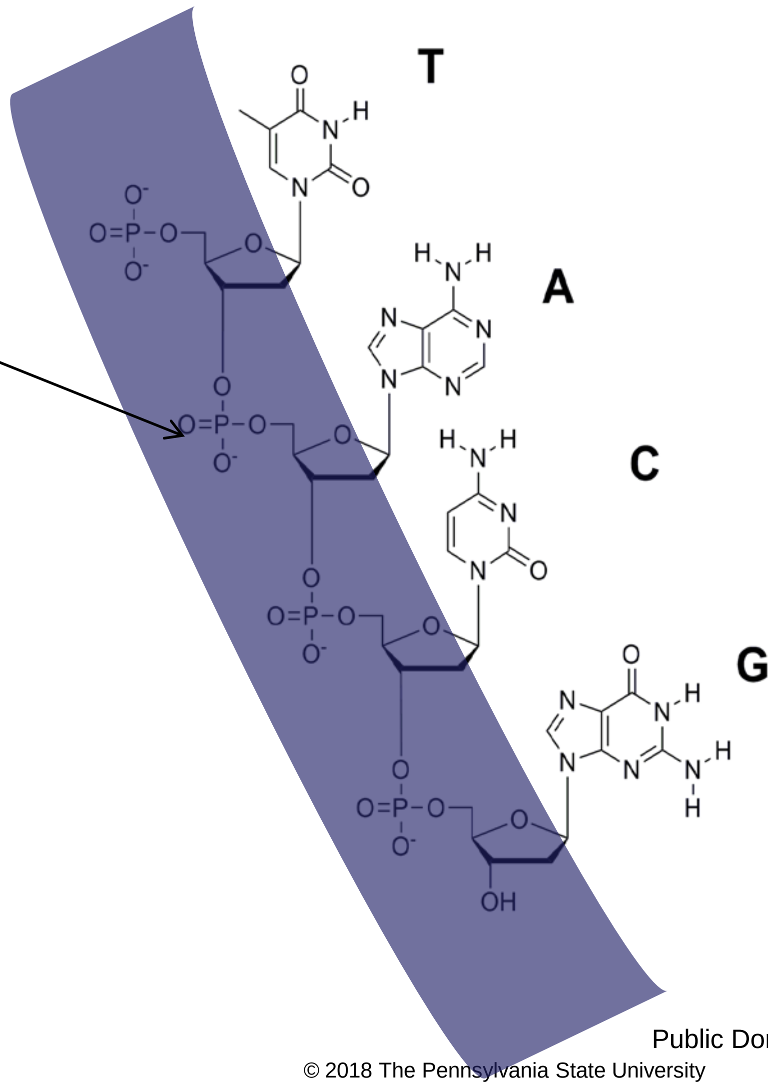
DNA Structure



Source:
http://publications.nigms.nih.gov/thenewgenetics/chapter1.html

Deoxyribonucleic Acid (DNA), Single Strand

Sugar-phosphate backbone



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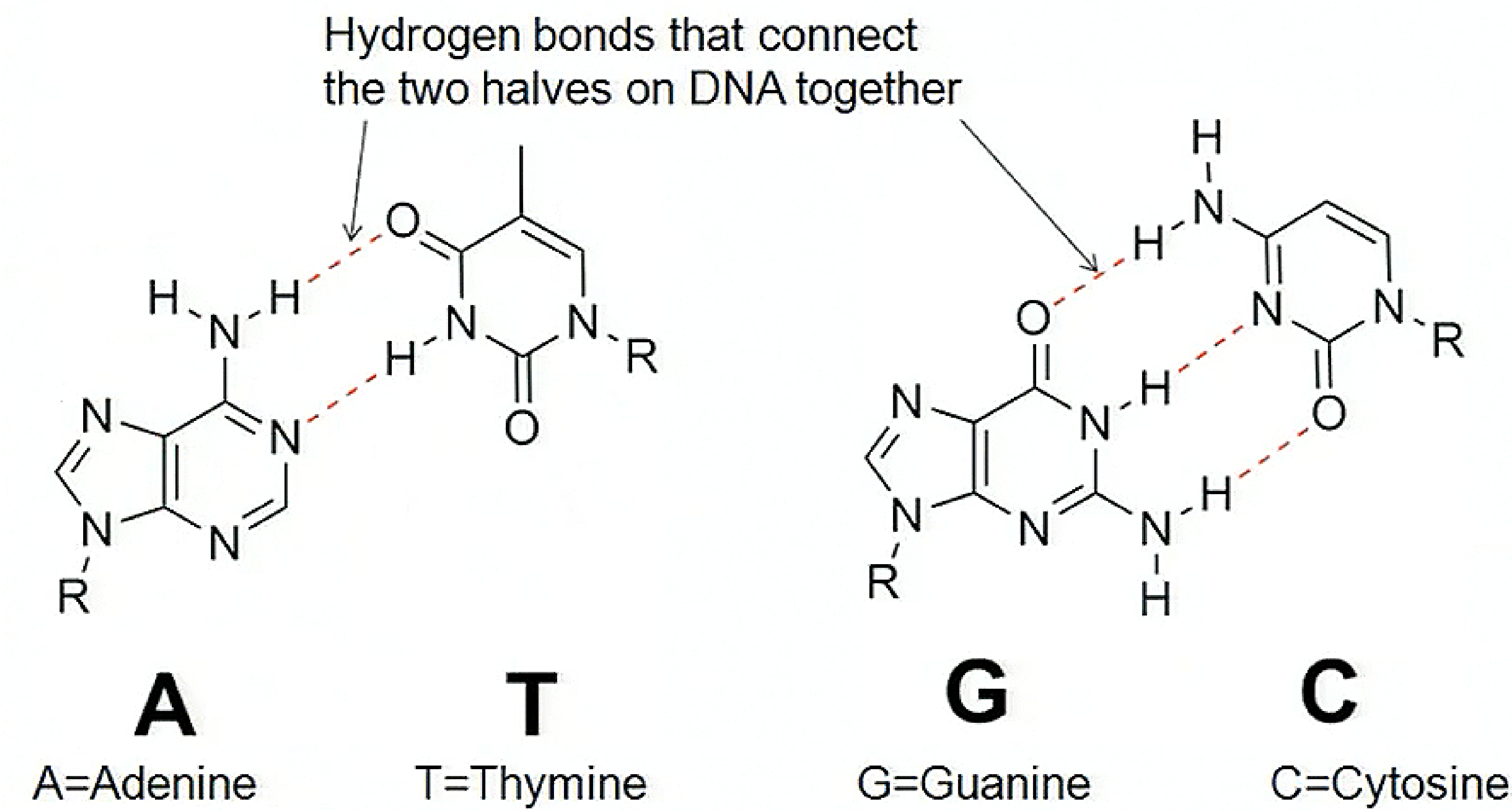
Assembly Rules of DNA

- Purines bond to pyrimidines and vice versa via hydrogen bonding
  - **never to each other**
- Bonding **always** occurs in the following convention
  - **A-T**
  - **C-G**
  - This allows ½ of the DNA chain to be replicated
- Human DNA contains about 6 billion base pairs.
- Nature uses three base pairs to define a specific amino acid, and these amino acids are coupled together to form functional proteins.

Self Assembly Rule



Codon Table for Amino Acids

Second base of codon

First base of codon	U		C		A		G		Third base of codon
U	UUU	Phenylalanine phe	UCU	Serine ser	UAU	Tyrosine tyr	UGU	Cysteine cys	U
	UUC		UCC		UAC		UGC		C
	UUA	Leucine leu	UCA		UAA	STOP codon	UGA	STOP codon	A
	UUG		UCG		UAG		UGG	Tryptonphan trp	G
C	CUU	Leucine leu	CCU	Proline pro	CAU	Histidine his	CGU	Arginine arg	U
	CUC		CCC		CAC		CGC		C
	CUA		CCA		CAA	Glutamine gln	CGA		A
	CUG		CCG		CAG		CGG		G
A	AUU	Isoleucine ile	ACU	Threonine thr	AAU	Asparagine asn	AGU	Serine ser	U
	AUC		ACC		AAC		AGC		C
	AUA		ACA		AAA	Lysine lys	AGA	Arginine arg	A
	AUG	Methionine met (start codon)	ACG		AAG		AGG		G
G	GUU	Valine val	GCU	Alanine ala	GAU	Aspartic acid asp	GGU	Glycine gly	U
	GUC		GCC		GAC		GGC		C
	GUA		GCA		GAA	Glutamic acid glu	GGA		A
	GUG		GCG		GAG		GGG		G

Codons, to Polypeptides, to Proteins

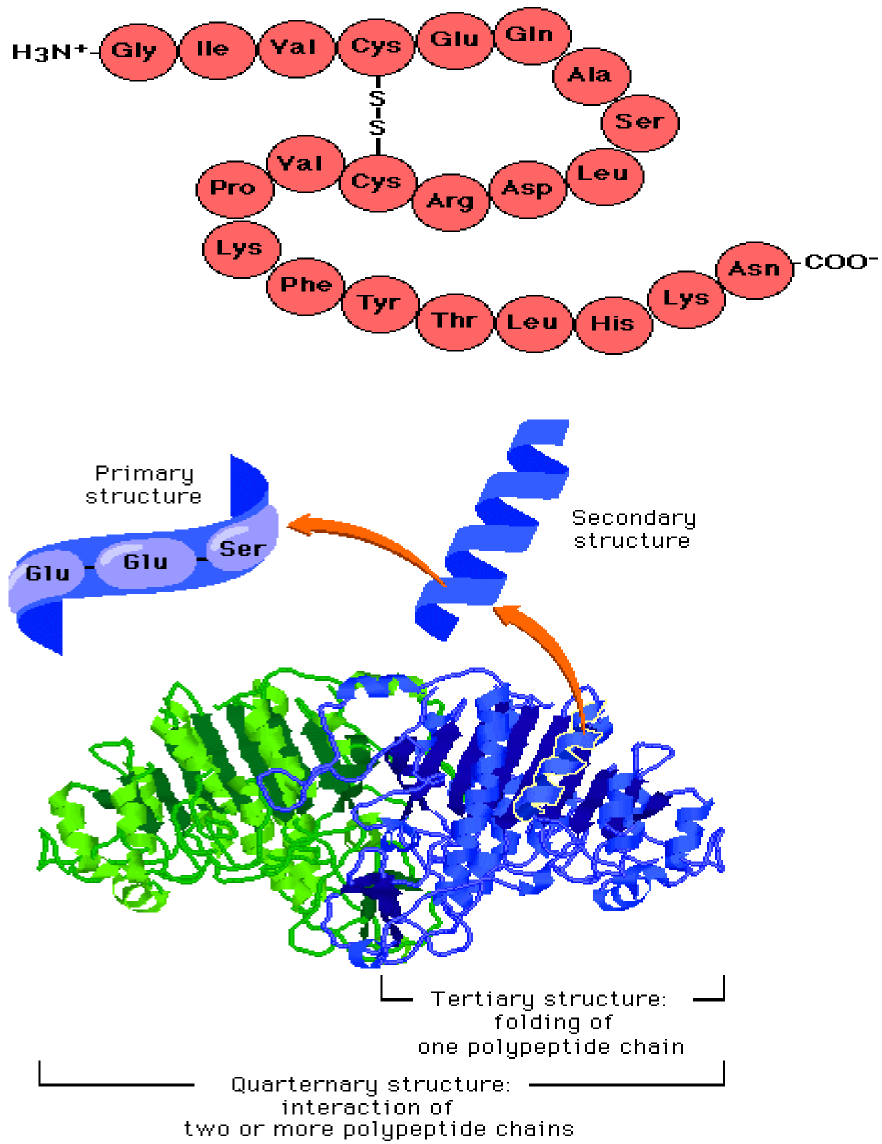
Codons encode the information for specific amino acids

Polypeptides are chains of amino acids

Proteins are made up of one or more polypeptide molecules

Protein shape gives functionality

We will review protein synthesis later in the presentation



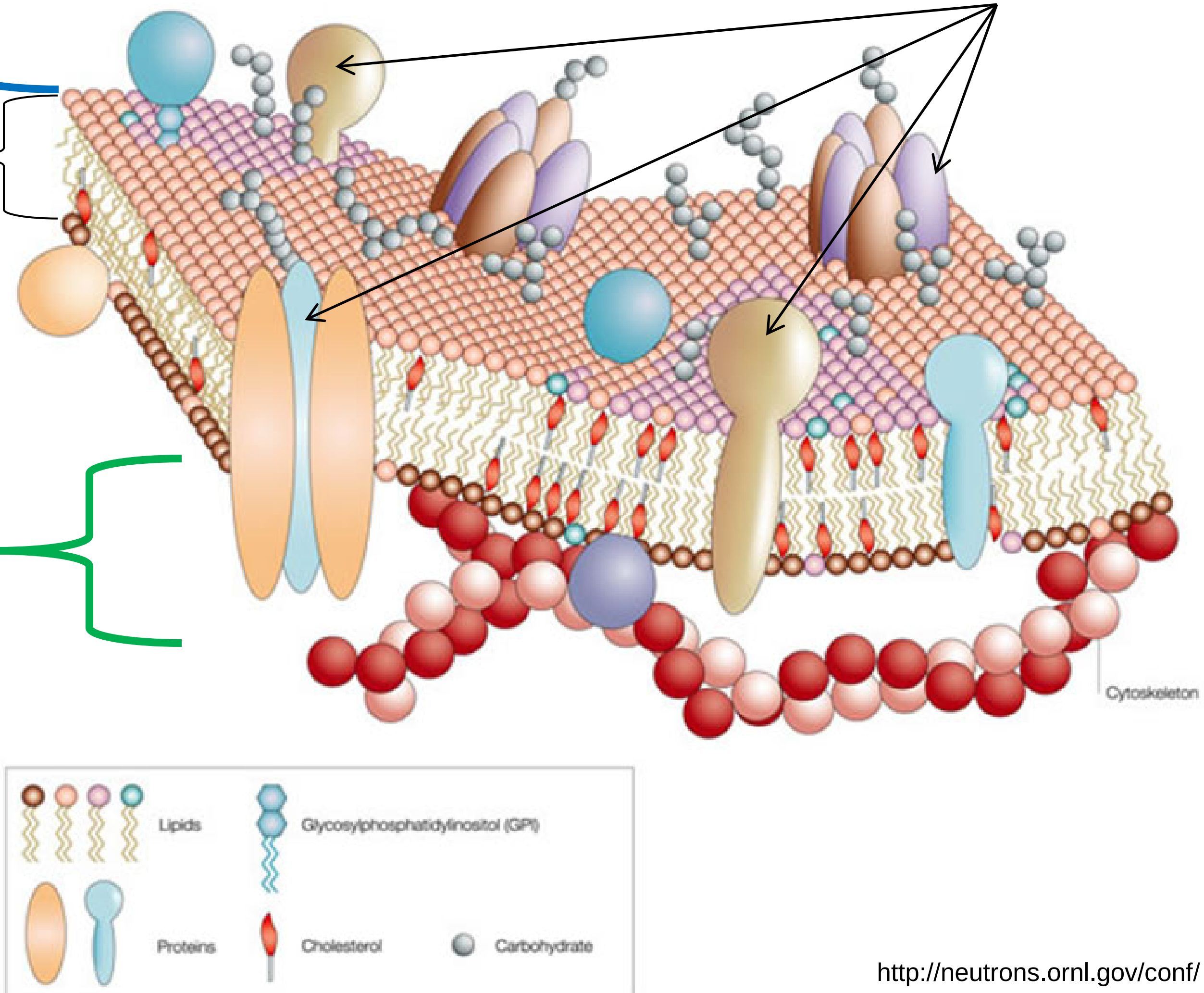
Membrane Structure/Protein Keys

Extracellular environment

Lipid Bilayer:
Excellent example of how “nature” does self assembly

Intercellular region (cytoplasm)

Protein receptors for cell communication



http://neutrons.ornl.gov/conf/dsm2008/registration.shtml

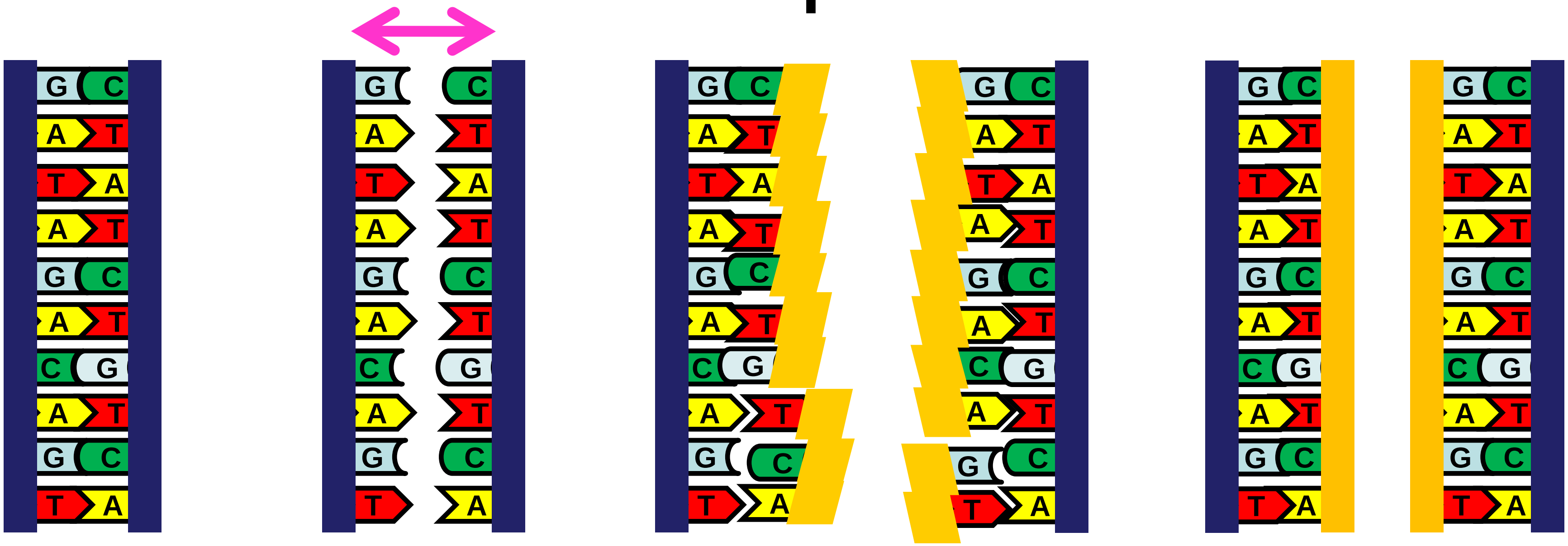
DNA Structure

- **Double Helix**
  - ***Scale***
  - The native form of DNA
  - Consists of two adjacent strands, held together by hydrogen bonds between base pairs and wound into a spiral shape
  - The double helix is 2 nm in diameter
  - The base pairs are 0.34 nm apart
  - There are ten pairs per turn of the helix

DNA Assembly Overview

- Example of controlled self assembly.
- During cell division, DNA is “split” between the old and new cell.
- Before replication, the parent cell contains two complimentary strands of DNA.
- The parent cell’s two strands are separated.
- Each “old” strand serves as a template that controls the synthesis of “new” complimentary strands.
- Each DNA molecule consists of one “old” strand and one “new” strand resulting in two identical copies.
- Later in this presentation we will look at nanotechnology that inhibits DNA replication as a means to destroy cancer tumors (Doxil).

DNA Replication



1) Before DNA is replicated it two complete strands

2) The enzyme helicase splits the two strands of DNA apart

3) The two original strands of DNA serve as templates for the self-assembly of two new complement strands of DNA starting with the nucleotides

4) After the nucleotides are aligned they connect to one another to form the sugar phosphate backbone, and are now two complete DNA chains