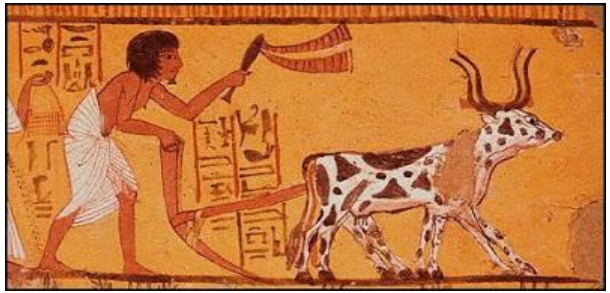
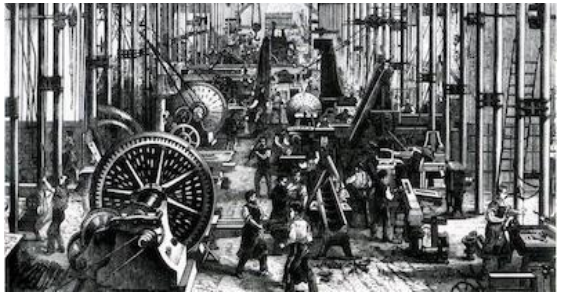
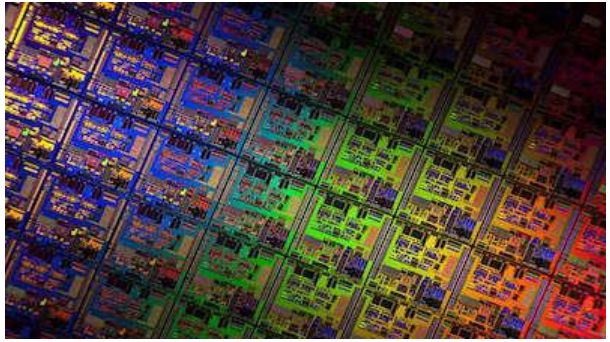
Comp 555 - BioAlgorithms - Spring 2021



Agraian Revolution



Industrial Revolution



Electronics/Digital Revolution

Biotechnology Revolution

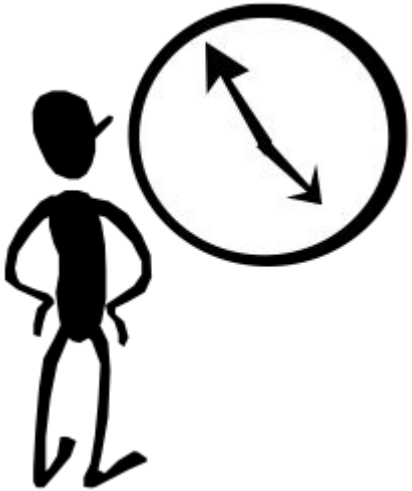
Welcome to the 4th Revolution!

Comp 555's Intended Audience

- Suitable for undergraduate and graduate students
- CS majors who want to learn bioinformatics
- Non CS majors from the statistics, biology, biostatistics, and general sciences who are interested in the algorithms with a focus on problems, and approaches used in bioinformatics.
- BCB/BBSP students

Why?

- **Benefits for Computer Scientists**
  - See CS fundamentals *applied* to real problems
  - What computer scientists can learn from biology
    - Robust, parallel, self-repairing, and energy efficient
- **Benefits for Biologist Multidiciplinary**
  - Help to close the CS-Bio "*language gap*"
  - Appreciate CS as more than just "coding"
  - What is a correct algorithm? An efficient one?
  - Approaches to algorithm "*design*"
- **Growth Potential**
  - Bioinformatics is a very marketable skill
  - Future of both CS and Biology

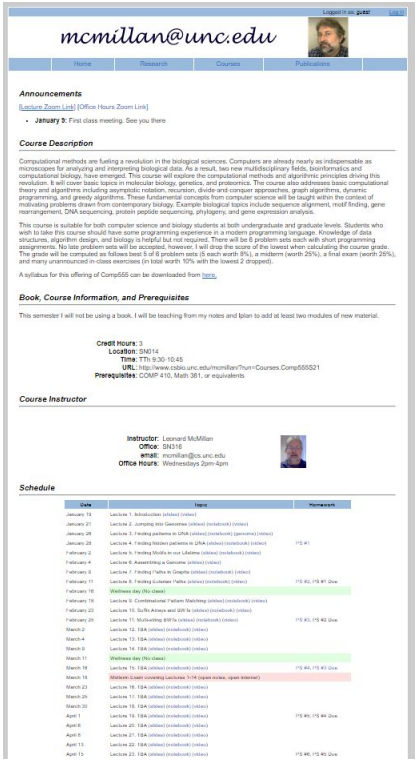


Logistics

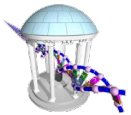
- Course Website:
  https://csbio.unc.edu/mcmillan/index.py?run=Courses.Comp555S21

  Or just follow the links from
  https://csbio.unc.edu/mcmillan

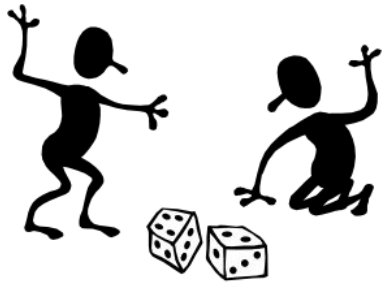
  [Courses|Comp555] (and bookmark it)
- Syllabus is linked on the website
- Look there for annoucements and zoom links.
- Include "COMP555" in subject line of all emails
- Course grading:
  - Many in-class exercises - 10 % (lowest 2 dropped)
  - 2 Problem Sets - 40 % (lowest dropped)
  - Midterm (mid march) - 25 %
  - Final - 25%



Bioinformatics = Biology + Information



- **What is information?**
  - Information: that which resolves uncertainty
  - Computer scientists measure information in “bits”
  - Information = $-\log_2(\text{probability})$
    - A coin is tossed and lands heads. How many bits?
    - A 7 is rolled on a pair of dice. How many bits?
    - A 3 is rolled? How many bits?
  - Information systems need mechanisms for
    - Storing information (memory)
    - Processing information (logic)
    - Transporting information (networks/connectivity)



6 out of 36 possible rolls are "7"s.
Thus, a roll of 7 conveys:

$-\log_2(6/36) = 2.58$ bits

There are only 2 ways
to roll a "3", (1,2) or (2,1)
Thus, a roll of "3" conveys:

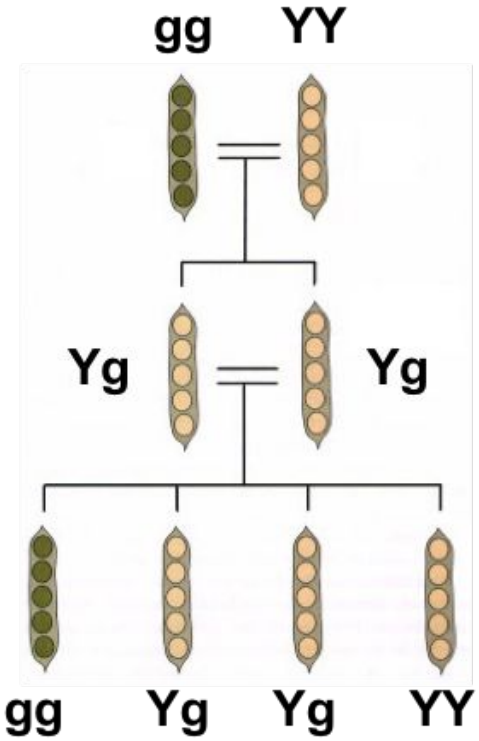
$-\log_2(2/36) = 4.17$ bits

- **Computer science *is* about information**
- **How about biological systems?**
  Are they information systems?

Information in Biological Systems

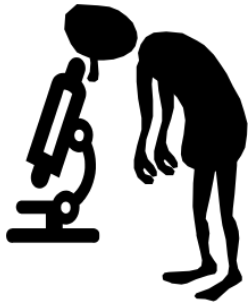
- Information is somehow passed between successive generations of plants and animals
- Distinguishable traits are inherited (phenotypes)
- Latent (recessive) traits can be masked by dominant traits, yet reappear in later generations
- Laws of Heredity
- Basis for Genetics

Gregor Mendel
1822-1884

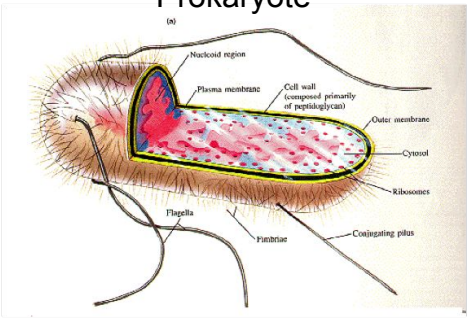


Where is “Biological” Information?

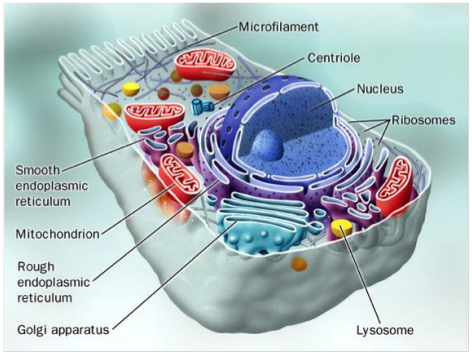
- **Enter the Age of Microbiology**
- **Cells: the smallest structural unit of a living organism capable of functioning independently**
- **Cell composition by weight**
  - 70% water
  - 7% small molecules
    salts, amino acids, nucleotides, lipids (fats, oils, waxes)
  - 23% larger polymers
    proteins, polysaccharides
- **Two cell types**
  - Prokaryotes: bacteria (no nucleus)
  - Eukaryotes: yeast, plants, and animals (with nucleus)



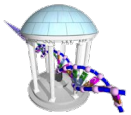
Prokaryote



Eukaryote



Looking for the Source of Heredity

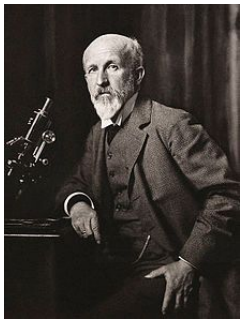


- In 1879 Walther Fleming, a German anatomist, discovered threadlike structures clearly visible during cell division. He called this material chromatin, which was later renamed chromosomes

Fleming

- Zoologists Oskar Hertwig and Hermann Fol first observed the process of fertilization in detail in the early 1880s. In 1881, Edward Zacharias showed that chromosomes contained nucleic acids. In 1884, Hertwig wrote:

  "nucleic acid is the substance that is responsible not only for fertilization but also for the transmission of hereditary characteristics."



Hertwig

Fol

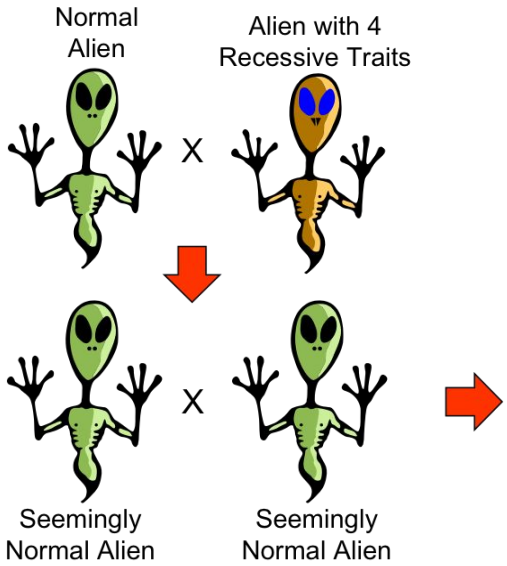
Early 20th Century Genetics

- In 1908, Thomas Hunt Morgan and Alfred H. Sturtevant showed that genes (a new name for inheritable traits) were located on chromosomes. Experimenting with Drosophila (fruit flies) they found sex chromosomes, sex-linked traits, and crossing-over. They were able to associate mutations to specific chromosomal regions, thus mapping gene locations.
- By the 1930's biochemists knew that the nucleic acid present in chromosomes was DeoxyriboNucleic Acid, DNA. They also knew that chromosomes contained proteins in addition to DNA. DNA appeared to be long repetitive chains, and therefore, it seemed unlikely to carry information. Proteins, however, looked more interesting and were generally assumed to contain genetic materials. DNA was considered as just some sort of “glue”.

Morgan

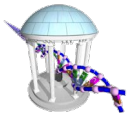
Inferring Genetic Maps

Even without knowing the mechanisms of how heredity information is represented, clever scientists (Morgan) were able to "map" genes…



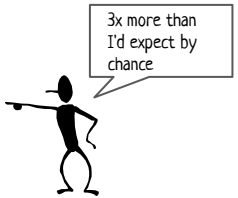
Normal	201	Short-fingered	9
Brown	64	Brown, blue-eyed, & triangle nosed	6
Blue-eyed	58	Triangle-nosed	5
Short fingered & triangle-nosed	54	Short-fingered & Brown	5
Short fingered, triangle-nosed, & brown	21	Brown, short fingered, triangle-nosed, & blue-eyed	4
Short fingered, triangle-nosed, & blue-eyed	20	Short-fingered & blue-eyed	4
Brown & blue-eyed	19	Triangle-nosed & brown	1
Blue-eyed & triangle-nosed	12	Brown, short fingered, & blue-eyed	1

Steps to Infer a Genetic Map

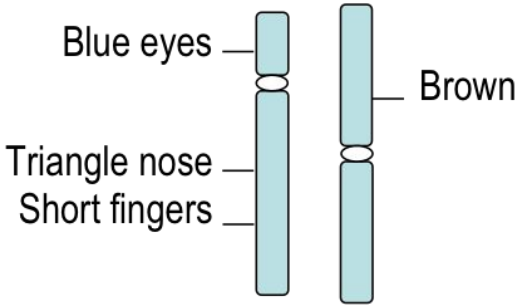


- **Verify Mendelian ratios**
  - Brown (64 + 21 + 19 + 6 + 5 + 4 + 1 + 1) /484 = 0.250
  - Blue-eyes (58 + 20 + 19 + 12 + 6 + 4 + 4 + 1) / 484 = 0.256
  - Triangle-nose (54 + 21 + 20 + 12 + 6 + 5 + 4 + 1) / 484 = 0.254
  - Short-finger (54 + 21 + 20 + 9 + 5 + 4 + 4 + 1) / 484 = 0.244

- **Test pairwise linkages**
  (we expect 1/4 × 1/4 × 484 ≈ 30 if independent)
  - Short-finger & triangle-nose 54 + 21 + 20 + 4 = 99
  - Triangle nose & brown 21 + 6 + 4 + 1 = 32
  - Short-finger & brown 21 + 5 + 4 + 1 = 31
  - Blue-eyes & triangle-nose 20 + 12 + 6 + 4 = 42
  - Short-finger & blue-eyes 20 + 4 + 4 + 1 = 29
  - Brown & blue-eyes 19 + 6 + 4 + 1 = 30

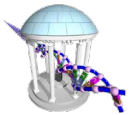


- **Indicates**
  - Short-fingers & triangle-nose are closely linked
  - Blue-eyes & triangle-nose are probably linked
  - Short-finger & blue-eyes appear independent, thus the triangle nose gene should lie between them
  - Brown gene is likely to be on another chromosome

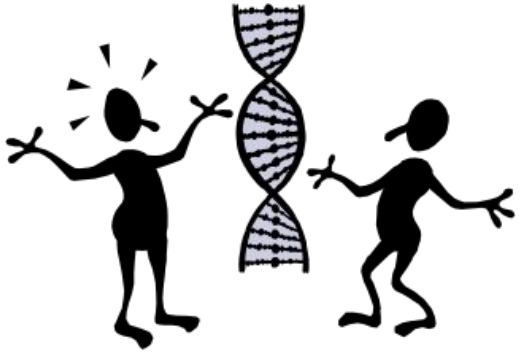


Morgan came up with even more clever techniques that were able to precisely locate the relative positions of genes on chromosomes. Even today chromosomal gene positions are measured in units of centiMorgans

DNA's Central Role



- In 1944, Oswald Avery showed that one of those “nucleic acids”, DNA, not proteins, carries hereditary information.
- In the late 1940’s and early 50’s Linus Pauling and associates develop methods for simultaneously determining the structure and chemical make-up of crystallized proteins and other large molecules.
- In 1952, James Watson and Francis Crick, are able to determine the structure and chemical makeup of DNA, using X-ray crystallography data collected by Rosalind Franklin and Maurice Wilkins.

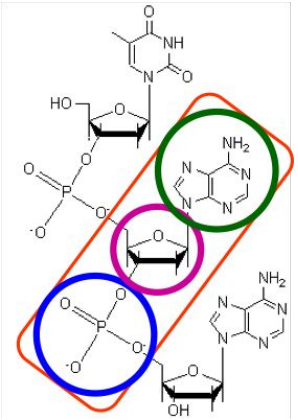


Beginning of Molecular Biology!

More on DNA

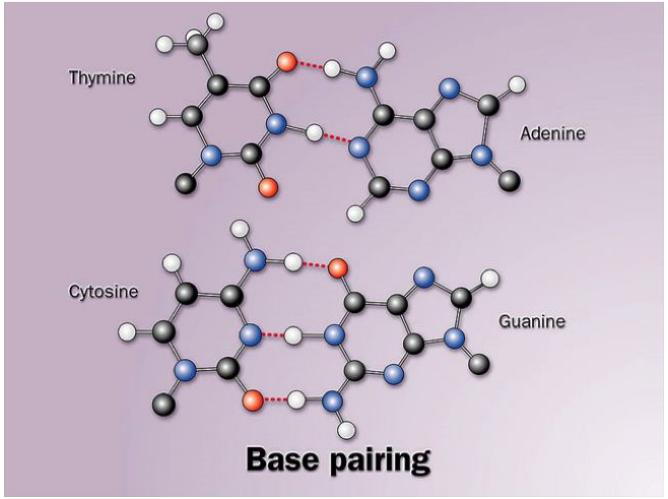
- The *information* stored in DNA organizes inanimate molecules into living organisms and orchestrates their lifelong function
- A long “complementary” chain of nucleotides

- Each nucleotide has 3 components
  - A ***phosphate*** group
  - A ***ribose sugar***
  - One of four ***nitrogenous bases***
- The information resides in the sequence of bases



DNA Components

- DNA is used by all living organisms
- Differences in nitrogenous bases code sequences that distinguish
  - Plants from animals
  - Species
  - Individuals
- A complete DNA sequence for an organism is called its “genome”
- Code sequences are composed of 4 bases (Adenine, Cytosine, Guanine, Thymine)
- Each base binds with another specific base (Thymine with Adenine and Cytosine with Guanine)

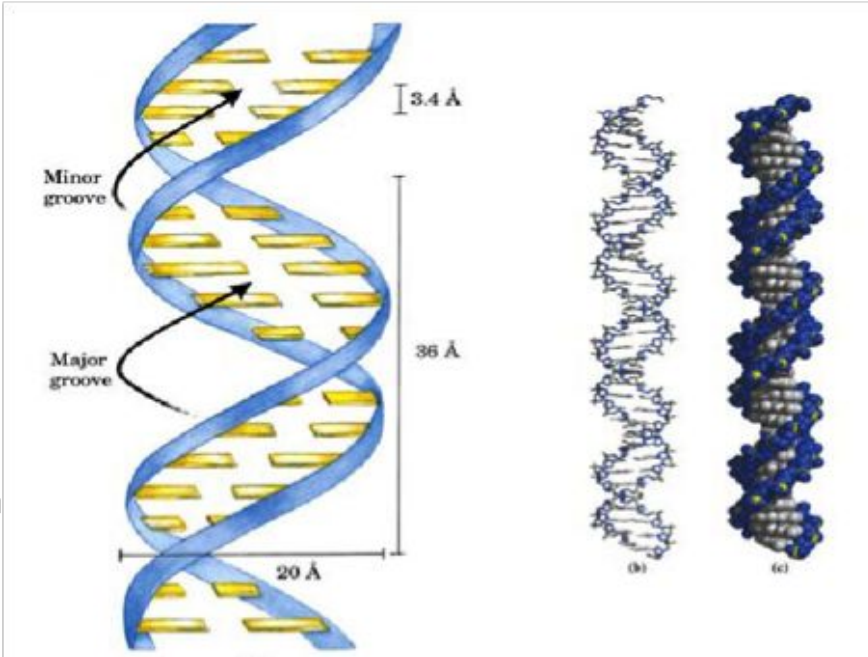


- A DNA molecule is comprised of primary sequence and a redundant "complementary" copy that aids self replication (each acts like a template for the other sequence)

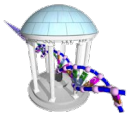
DNA Schematic

- Many more details are required to give a complete picture of DNA
  - Complementary strands are antiparallel and, thus, oriented
  - Not a simple twist, but has a major and minor grooves which are recognized by interacting with proteins
- Rather than keep track of all the details we will often consider DNA as a string of nucleotides

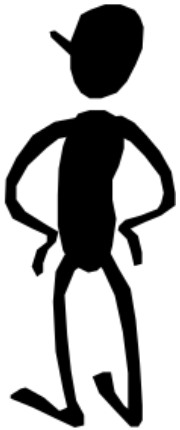
  `5'...ACGGATAGCATGGA...3'`
- By convention DNA sequences are always ordered in the 5’-to-3’ direction. Not coincidentally, this is also the order in which they are synthesized using an important class of molecules call polymerases.



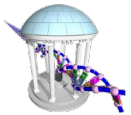
Biological Computing Machines



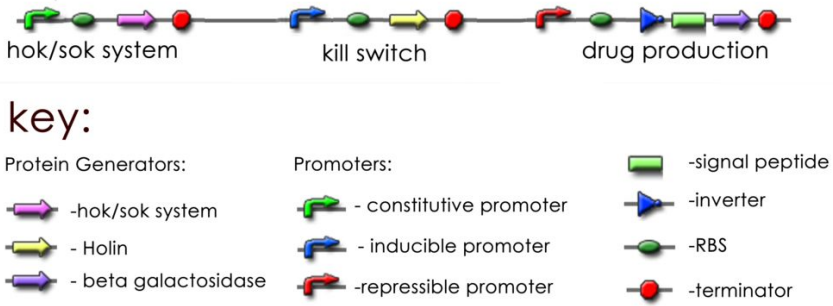
- **DNA is an “Operating System” with “programs”**
  - Collect raw materials and covert chemicals to energy
  - Perform specialized functions (neurons, muscle, retinal cones)
  - Protect and repair itself
  - Replicate itself, or duplicate an entire organism
- **How are these “programs” encoded?**
- **What biological machinery “executes” this program?**
- **How is the program’s execution sequenced?**



Genes are the Programs

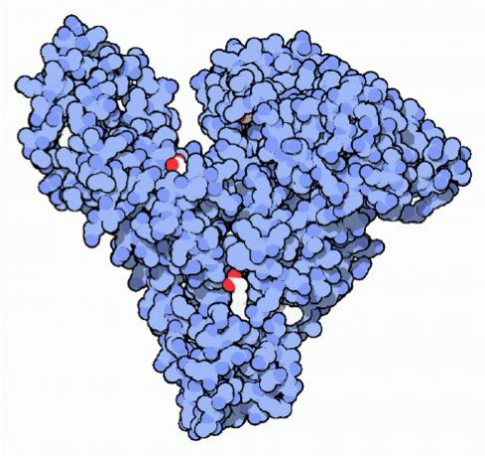


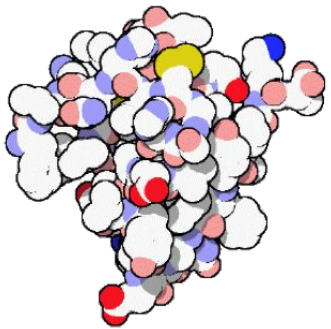
- Specific subsequences of DNA bases determine specific functions (programs) of a cell, these subsequences are called “genes”
- Genes are distributed throughout a genome
- Not all DNA sequence sections contain genes
- Genes might not be entirely contiguous within the DNA sequence
- Genes can be either active or inactive
- Genes provide instructions for assembling proteins, which are the machinery of life
- How are these instructions encoded?
- What is the output of these programs?



What are Proteins?

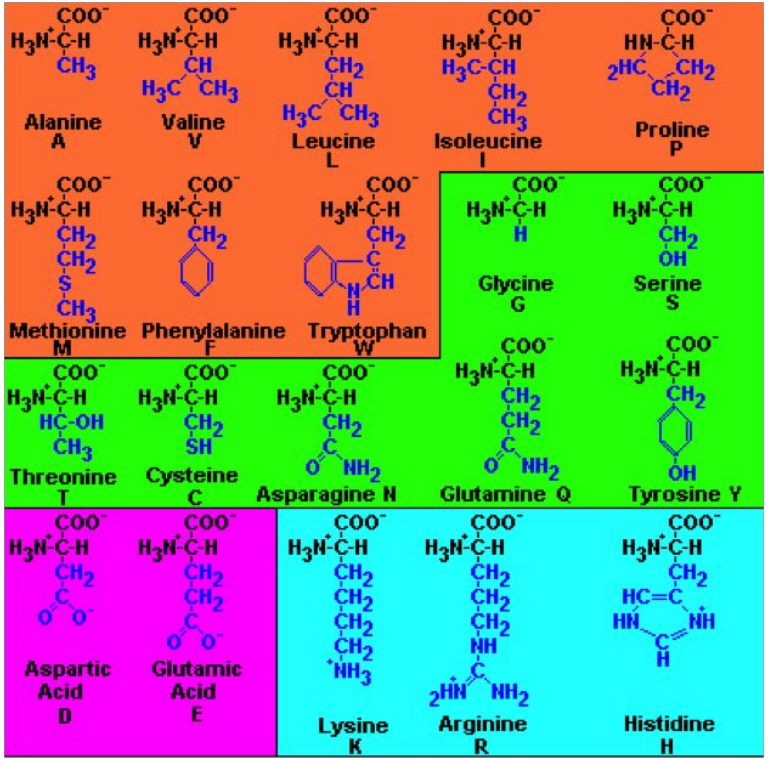
- Proteins are incredibly diverse and composed of another type of sequence (amino acid peptides)
- Some are building materials, like collagen which provides structural support and rigidity
- Some make other things happen-- like enzymes (pepsin) which act as catalysts that hasten critical reactions without taking part in them
- Some proteins deliver cargo, i.e. transport small molecules and minerals to where they are needed within an organism (hemoglobin)
- Some are used for signaling and intercellular communication (insulin)
- Others absorb photons to enable vision (rhodopsin)
- Proteins are assembled from simple molecules, called amino acids.





Amino Acids

- 20 main ingredients of proteins
- Varying side chain is shown in dark blue
- Orange indicates non-polar and Hydrophobic, the remainder are polar or hydrophilic
- Magenta indicates acidic
- Cyan indicates a base



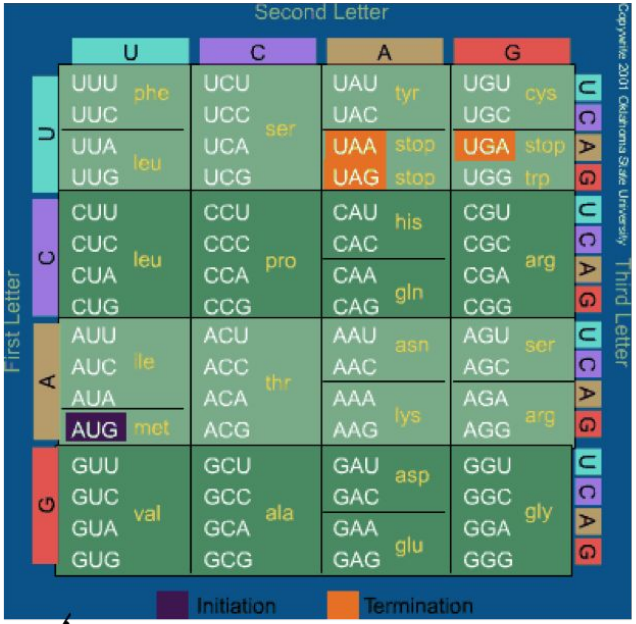
A hydrophobic amino acid avoids water wherreas a hydrophillic amino acid is attached to water. This influeces the shapes that proteins fold into.

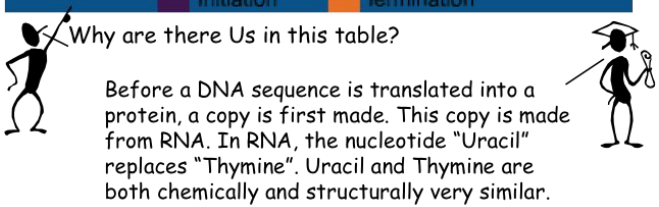
Encoding Protein Assembly

- Each DNA base can be one of 4 values (G,C,A,T)
- Proteins are polymer chains of amino acids ranging in length from tens to millions
- There are 20 amino acids
- How do you encode variable length chains of 20 amino acids using only 4 bases?
- Do you need other codings?
- Clearly, we can't encode 20 different amino acids using only one base. How many encodings are possible using a pair of bases? How many with three?

Codons

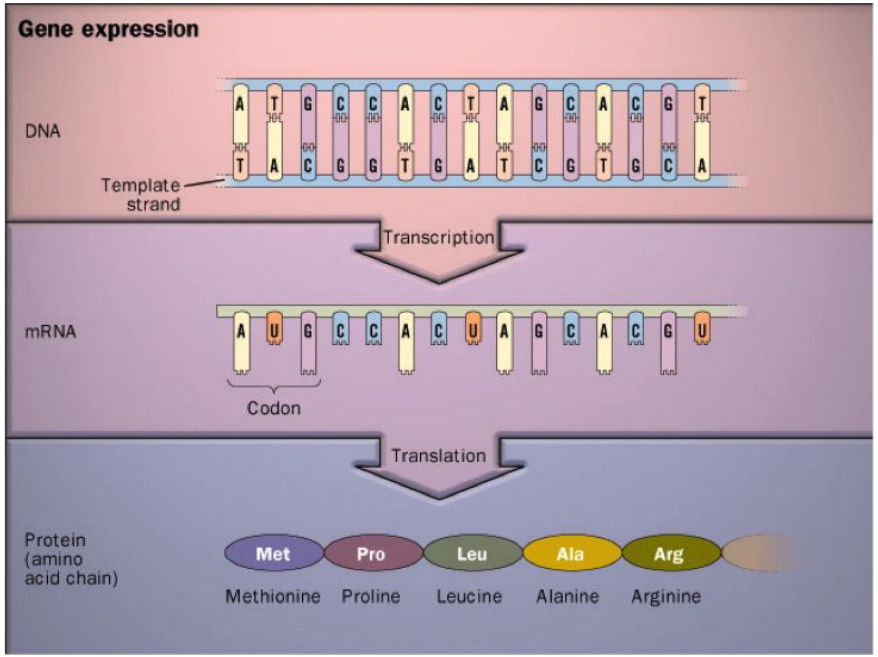
- Triplets of nucleotide bases determine the amino acid sequence of a protein
- All genes begin with a particular code, AUG, for the amino acid Methonine
- Three codes are used to indicate STOP, and thus end the transcription process for the gene
- Most amino acids have redundant encodings



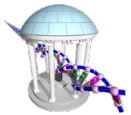


From Genes to Proteins

The central dogma of molecular biology is that information encoded by the bases of DNA are transcribed by RNA and then converted (translated) into proteins.

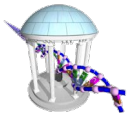


Is the Code Perfect?



- Proteins are generally unaffected by small variations in their code sequence, particularly changes to a small number of bases (error-correction)
- Minor variations in genes, called alleles, are responsible for many individual variations (blood-type, hair color, etc.)
- Errors in *translation* (the substitution for one amino acid for the one encoded by the gene), occur at roughly 0.1% of all residues. This means that a single large protein will have at least one incorrect amino acid somewhere! Many of these will still function, in part because the substituted residue will often be adequate. Still, is a bit curious that this level of error is acceptable.
- In eukaryotes (humans, plants) gene sequences are not contiguous. They are broken into codon carrying segments called ***exons*** separated by seemingly meaningless base sequences called introns

How Big is a Genome?

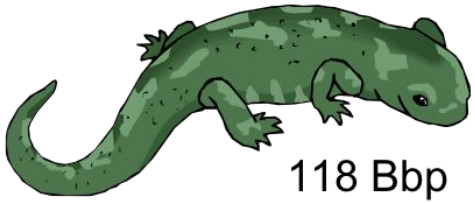


- The human genome is roughly 3 billion bases
- A typical gene is roughly 3000 bases
- The largest known human gene (dystrophin) has 2.4 million bases
- The estimated number of human genes is roughly 30K
- The genome is nearly identical for every human (99.9%)
- Human DNA is 98% identical to chimpanzee DNA.
- The functions are unknown for more than 50% of discovered genes.
- Genes appear to be concentrated in random areas along the genome, with vast expanses of noncoding DNA between.

Is Bigger Better? More Advanced?

- The genome size of a species is relatively constant
- Large variations can occur across species lines
- Not strictly correlated with organism complexity
- Genome lengths can vary as much as 100 fold between similar species
- Length and variability are more of an indications of a phylum's susceptibility to mutation

670 Bbp



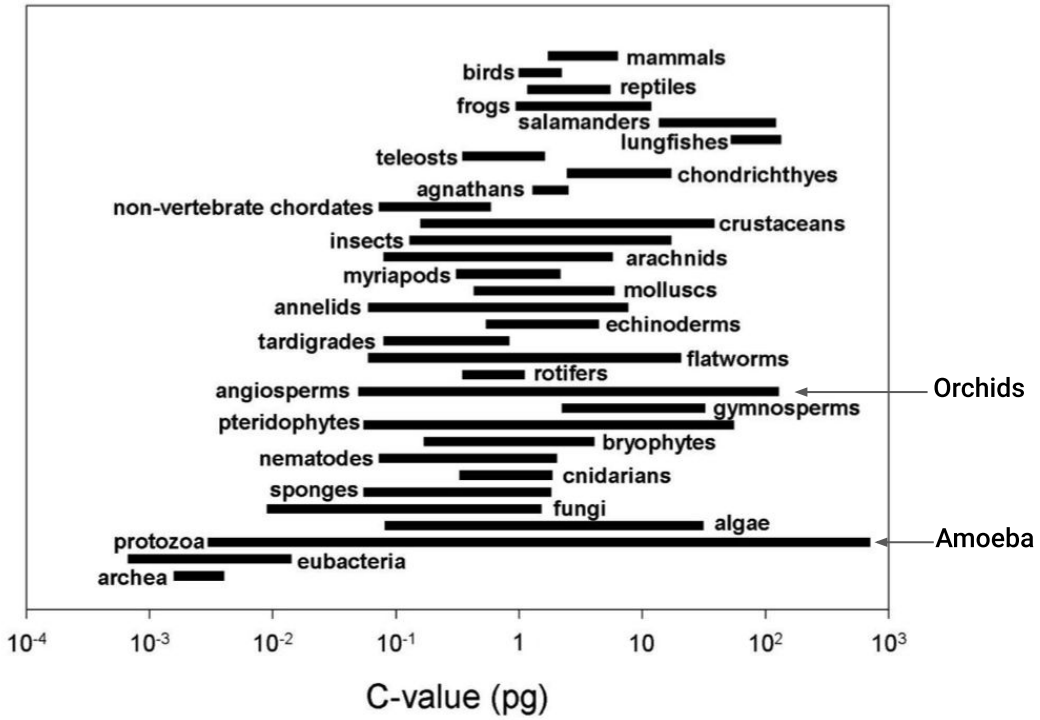
118 Bbp

13 Bbp

168 x

Amoeba (Amoeba dubia) ~ 670 Bbp
Salamander (120.60pg, Necturus lewisi, Gulf coast waterdog) ~118 Bbase pairs
Frog (13.40pg, Ceratophrys ornata (8n), Ornate horned frog) ~13 Bbase pairs
Marbled Lung fish (130pg) ~ 130 Bbp
Orchids (angiosperms) have the the largest variation within a species
(strains that can interbreed and generate fertile progeny) with a range that varies at least 168-fold.

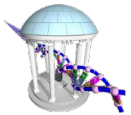
Genome Variation



Length and variability are more of an indications of a phylum's susceptibility to mutations than its complexity

(C-value = the Amount of DNA in an unreplicated gametic nucleus. It is measures in pico Grams, and 1pg = 978M base pairs.)

Summary



- Information resolves uncertainty
- Heredity provides evidence that information is passed on by biological systems
- Biological information is stored as DNA
- Genes are segments of DNA sequence that encode assembly instructions for proteins
- The central dogma of molecular biology is that DNA sequences are transcribed by RNA polymerases into mRNAs that are then translated by ribosomes into proteins.
- A genome's length is not a good indicator of its information content

Next Time

- Examine DNA sequences
- Look for Patterns
- Data-driven hypotheses