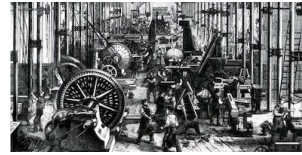


# Comp 555 – BioAlgorithms – Spring 2018

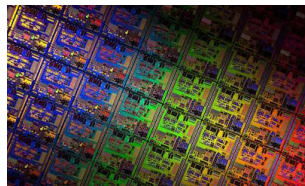
Welcome to the 4<sup>th</sup> revolution!



Agrarian Revolution



Industrial Revolution



Electronics/Digital  
Revolution



Biotechnology Revolution

**Lecture 1: Course Preliminaries & Information in Biological Systems**

# Comp 555 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 and approaches used in bioinformatics.
- BCB/BBSP students



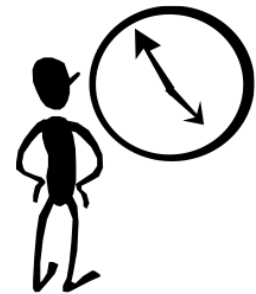
# Why?

- **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**
  - Help to close the CS-Bio “language” gap
  - Appreciate CS as more than “coding”
  - What is a correct algorithm? An efficient one?
- **Growth Potential**
  - Bioinformatics is a very marketable skill
  - Future of CS and Biology



# Course Logistics

- Course website:  
<http://csbio.unc.edu/mcmillan/?run=Courses.Comp555S18> (<http://csbio.unc.edu/mcmillan/?run=Courses.Comp555S18>)  
Look here first for
  - News, hints, and helpful resources
  - Revisions, solutions, and corrections to problem sets
- Office Hours: Tuesdays 2pm-4pm
- Grading
  - 5 – Problem sets (worth 10% each)
  - Midterm Exam (worth 20%)
  - Final Exam (worth 30%)
- Problem Sets
  - Roughly one every three weeks
  - Will include a short program to write



# Bioinformatics = Biology + Information

- What is information?
  - Information: that which resolves uncertainty
  - We measure information in bits
  - Information =  $-\log_2(\text{probability})$ 
    - The coin I tossed landed heads.  
How many bits?
    - You rolled a 7 on a pair of dice.  
How many bits?  
You roll a 3?
  - Concrete systems need mechanisms for
    - Reliably storing information (memory)
    - Reliably processing information (logic)
    - Reliably transporting information (connectivity)
  - The focus of computer science is information
- How about biological systems?

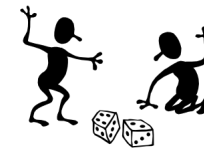
6 ways out of 36 to roll a 7.

Thus, 7 conveys

$$-\log(6/36) = 2.58 \text{ bits.}$$

Likewise, a roll of 3 conveys

$$-\log(2/36) = 4.17 \text{ bits}$$



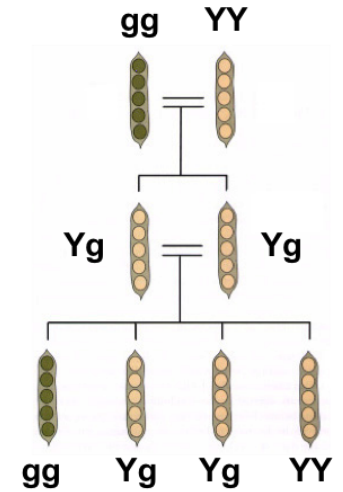
# There Must Be Information!

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

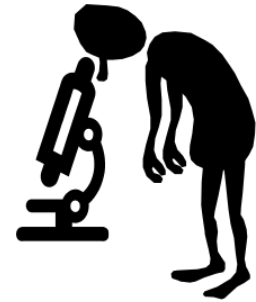


Gregor Mendel  
1822-1884



# Where is the 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 types
  - Prokaryotes: bacteria (no nucleus)
  - Eukaryotes: yeast, plants, and animals (with nucleus)

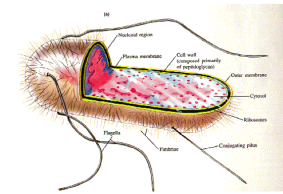


# Looking for the Source of Heredity

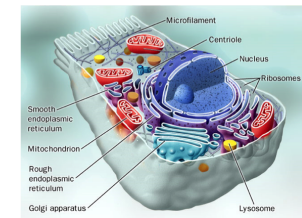
- In 1879 Walther Fleming, a German anatomist, discovered threadlike structures clearly visible during cell division. He called this material *chromatin*, which was later called *chromosomes*
- Zoologists Oskar Hertwig and Herman Fol first observed the process of fertilization in detail in the early 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."*

## Prokaryote



## Eukaryote





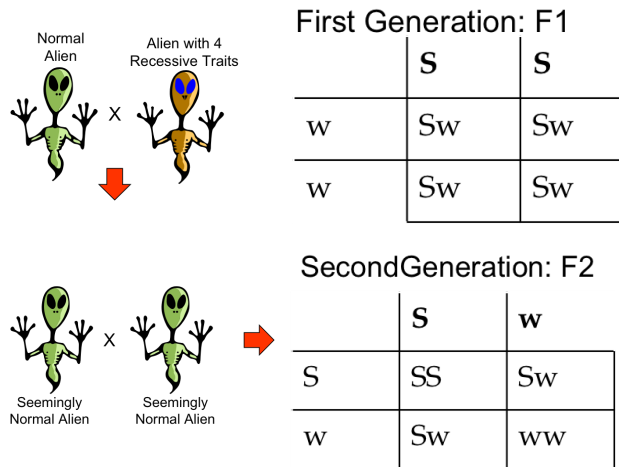
# Early 20<sup>th</sup> Century Genetics

- In 1908, Thomas Hunt Morgan and Alfred H. Sturtevant showed that genes 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.



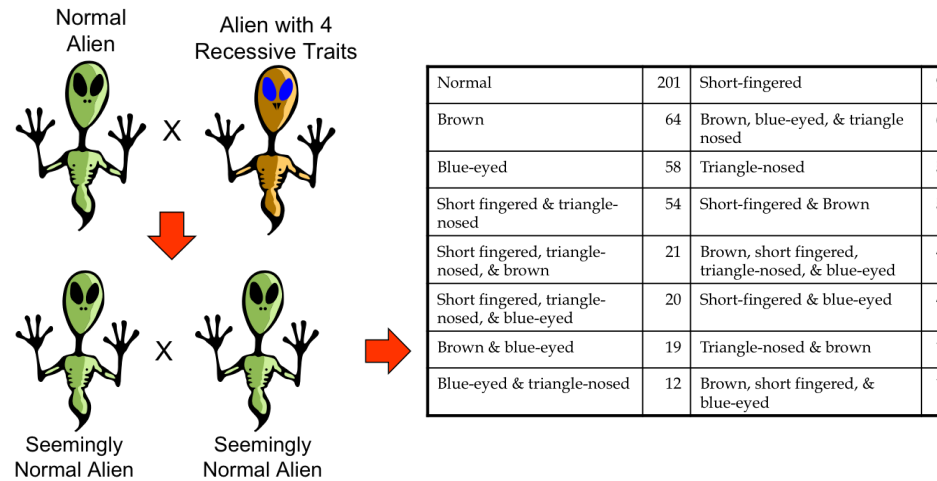
# Inferring Genetic Maps

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



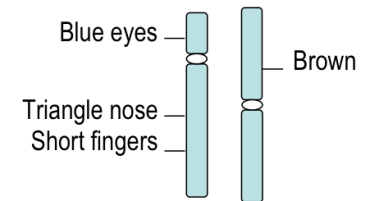
# Inferring Genetic Maps


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# Steps to Infer a Genetic Map

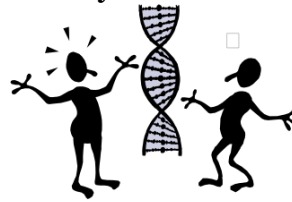
- Verify Mendelian ratios
  - Brown  $(64 + 21 + 19 + 6 + 5 + 4 + 1 + 1) / 484 = 0.250$
  - Blue-eyes  $(58 + 20 + 19 + 12 + 6 + 4 + 4 + 1) / 484 = 0.256$
  - Triangle-nose  $(54 + 21 + 20 + 12 + 6 + 5 + 4 + 1) / 484 = 0.254$
  - Short-finger  $(54 + 21 + 20 + 9 + 5 + 4 + 4 + 1) / 484 = 0.244$
- Test for pairwise linkages (we'd expect  $1/4 \times 1/4 \times 484 \approx 30$  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 DNA, not proteins, carries hereditary information.
- In the late 1940's and early 50's Linus Pauling and associates develop modeling methods for simultaneously determining structure and chemical make-up of 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.



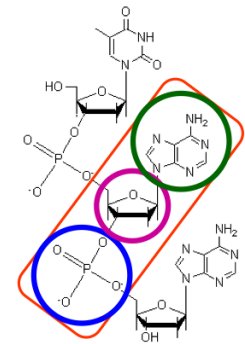
Beginning of Molecular Biology!

# Details of DNA

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

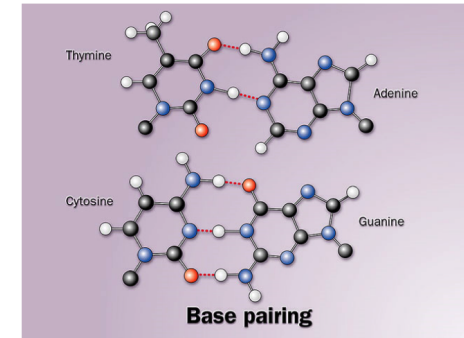


- Each nucleotide has 3 components
  - A phosphate group
  - A ribose sugar
  - One of four nitrogenous bases
- The information resides in the sequence of bases



# DNA Components

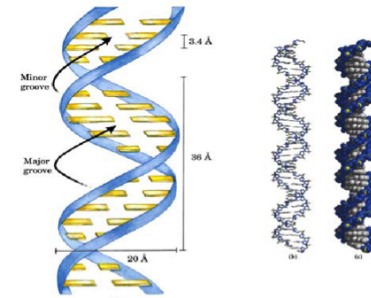
- The same DNA encodes all living organisms
- Different code sequences distinguish
  - Plants from animals
  - Species
  - Individuals
- A complete DNA sequence for an organism is called its *genome*
- Code sequences are composed of 4 bases (Adenine, Cytosine, Guanine, Thymine)
- Each base binds with another specific base (Thymine with Adenine and Cytosine with Guanine)
- A DNA molecule is comprised of primary sequence and a redundant "complementary" copy that allows it to self replicate (each acts like a template for the other sequence)



# Schematic DNA

- 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'

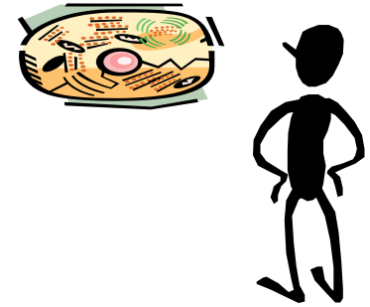


By convention DNA sequences are always ordered in the 5'-to-3' direction. Not coincidentally, this is also the order in which they can be synthesized using an important class of molecules call polymerases, which we will discuss in more detail in the next lecture.



# Biological Computing Machines

- DNA is an “Operating System” with “programs”
  - Collect raw materials and convert 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?

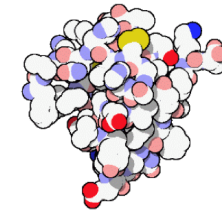
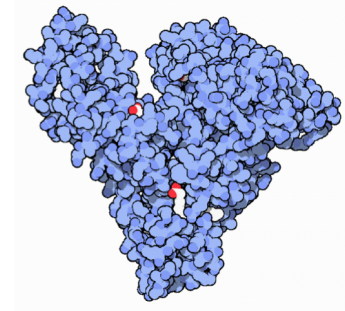


# Genes are the Programs

- Specific subsequences of DNA bases determine specific functions (programs) of a cell, these subsequences have commandeered the name “gene”
- 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?

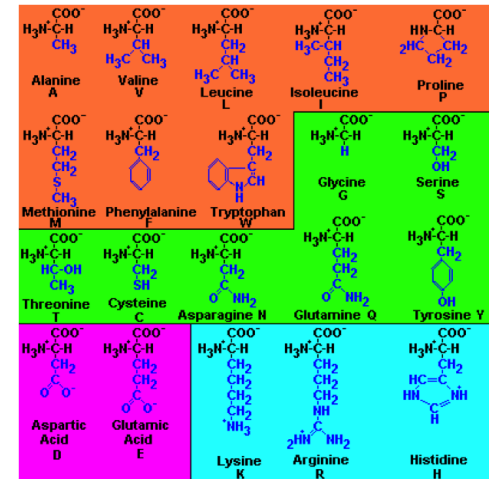
# What are Proteins

- Proteins are incredibly diverse
  - Structural proteins (collagen) provide structural support and rigidity
  - Enzymes act as biological catalysts (pepsin) that hasten critical reactions without taking part in them
  - Proteins transport small molecules and minerals to where they are needed within an organism (hemoglobin)
  - Used for signaling and intercellular communication (insulin)
  - Absorb photons to enable vision (rhodopsin)
- Proteins are assembled from simple molecules, called amino acids.



# Amino Acids

- 20 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 whereas a hydrophilic amino acid is attracted to water. This influences the shape that proteins fold into.



# Encoding Protein Assembly

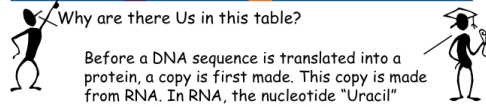
- Each DNA base can be one of 4 values (G,C,A,T)
- Proteins are polymer chains of amino acids ranging in length from tens to millions
- There are 20 amino acids
- How do you encode variable length chains of 20 amino acids using only 4 bases?
- Do you need other codings?

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

		Second Letter			
		U	C	A	G
U	U	UUU phe	UCU ser	UAU tyr	UGU cys
	U	UUC phe	UCC ser	UAC tyr	UGC cys
	U	UUA leu	UCA ser	UAA stop	UGA stop
	U	UUG leu	UCG ser	UAG stop	UGG trp
C	U	CUU leu	CCU pro	CAU his	CGU arg
	C	CUC leu	CCC pro	CAC his	CGC arg
	A	CUA leu	CCA pro	CAA his	CGA arg
	G	CUG leu	CCG pro	CAG his	CGG arg
A	U	AUU ile	ACU thr	AAU asn	AGU ser
	U	AUC ile	ACC thr	AAC asn	AGC ser
	A	AUA ile	ACA thr	AAA lys	AGA arg
	G	AUG met	ACG thr	AAG lys	AGG arg
G	U	GUU val	GCU ala	GAU asp	GGU gly
	U	GUC val	GCC ala	GAC asp	GGC gly
	A	GUA val	GCA ala	GAA asp	GGA gly
	G	GUG val	GCG ala	GAG asp	GGG gly

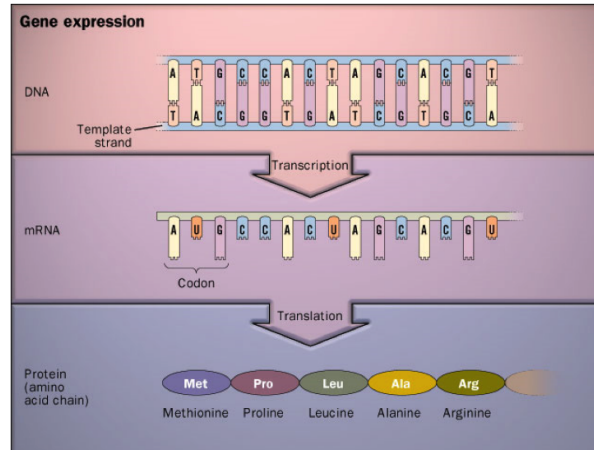


Why are there Us in this table?

Before a DNA sequence is translated into a protein, a copy is first made. This copy is made from RNA. In RNA, the nucleotide "Uracil" replaces "Thymine". Uracil and Thymine are both chemically and structurally very similar.

# 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 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
- Minor variations in genes, called *alleles*, are responsible for 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.

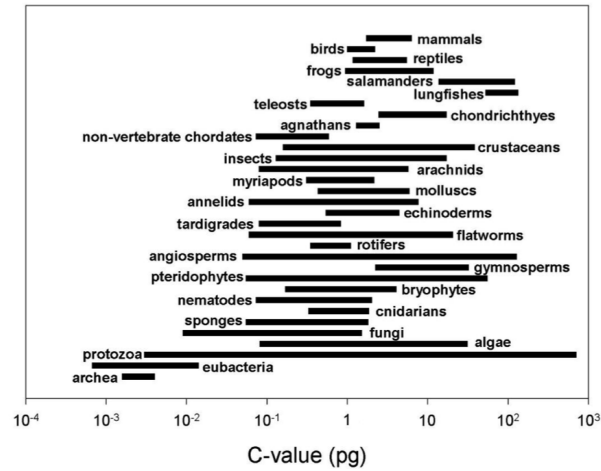
# Is Bigger Better?

- The genome size of a species is 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



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 (stains 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 unrepliated 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

- Examining DNA sequences
- Looking for Patterns
- Data-driven hypotheses
- DNA Replication

