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. Problems, and approaches used in bioinformatics.
● BCB/BBSP students
  ○ Starting next year COMP 555 will be co-listed as BCB 555
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 “coding”
  - What is a correct algorithm? An efficient one?

- **Growth Potential**
  - Bioinformatics is a very marketable skill
  - Future of CS and Biology
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)

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

6 out of 36 possible rolls are "7"s. Thus, a roll of 7 conveys:
\[-\log_2(6/36) = 2.58 \text{ bits}\]

There are only 2 ways to roll a "3", (1,2) or (2,1)
Thus, a roll of 2 conveys:
\[-\log_2(2/36) = 4.17 \text{ bits}\]
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)
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.

- 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."
Early 20th 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”.

Morgan
Inferring Genetic Maps

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

Normal Alien  Alien with 4 Recessive Traits

Seemingly Normal Alien  Seemingly Normal Alien

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Frequency</th>
<th>Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>201</td>
<td>Short-fingered</td>
<td>9</td>
</tr>
<tr>
<td>Brown</td>
<td>64</td>
<td>Brown, blue-eyed, &amp; triangle-nosed</td>
<td>6</td>
</tr>
<tr>
<td>Blue-eyed</td>
<td>58</td>
<td>Triangle-nosed</td>
<td>5</td>
</tr>
<tr>
<td>Short fingered &amp; triangle-nosed</td>
<td>54</td>
<td>Short-fingered &amp; Brown</td>
<td>5</td>
</tr>
<tr>
<td>Short fingered, triangle-nosed, &amp; brown</td>
<td>21</td>
<td>Brown, short fingered, triangle-nosed, &amp; blue-eyed</td>
<td>4</td>
</tr>
<tr>
<td>Short fingered, triangle-nosed, &amp; blue-eyed</td>
<td>20</td>
<td>Short-fingered &amp; blue-eyed</td>
<td>4</td>
</tr>
<tr>
<td>Brown &amp; blue-eyed</td>
<td>19</td>
<td>Triangle-nosed &amp; brown</td>
<td>1</td>
</tr>
<tr>
<td>Blue-eyed &amp; triangle-nosed</td>
<td>12</td>
<td>Brown, short fingered, &amp; blue-eyed</td>
<td>1</td>
</tr>
</tbody>
</table>
Steps to Infer a Genetic Map

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

- **Test pairwise linkages**
  (we expect \( \frac{1}{4} \times \frac{1}{4} \times 484 \approx 30 \) 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 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 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!
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 allows it to self replicate (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 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 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.
- 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 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 whereas a hydrophilic amino acid is attracted to water. This influences the shape that proteins fold into.
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 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? 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

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.
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

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