FoCS Breadth:
Overview of Bioinformatics

Niema Moshiri
UC San Diego SPIS 2019

What is **Bioinformatics**?

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- “Bioinformatics is an interdisciplinary field that develops methods and software tools for understanding biological data” —Wikipedia

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- “The collection, classification, storage, and analysis of biochemical and biological information using computers especially as applied to molecular genetics and genomics” —Webster Dictionary
- “Bioinformatics is conceptualizing biology in terms of macromolecules and then applying ‘informatics’ techniques to understand and organize the information associated with these molecules, on a large-scale” —Nick Luscombe

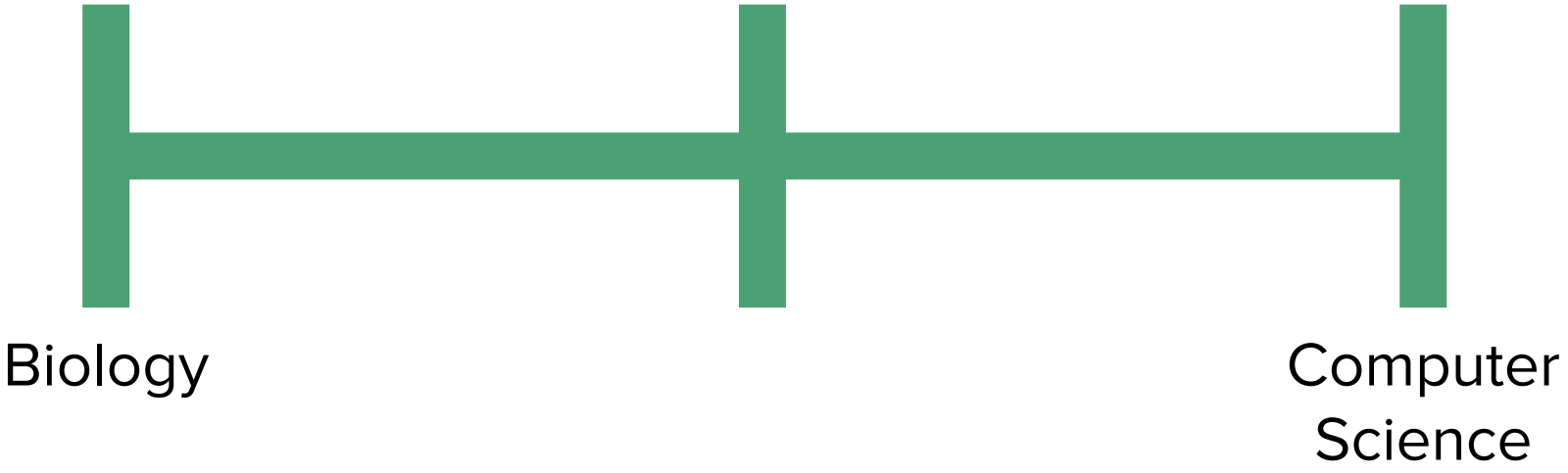
My Definition of Bioinformatics

My Definition of Bioinformatics

Biology

My Definition of Bioinformatics

My Definition of Bioinformatics



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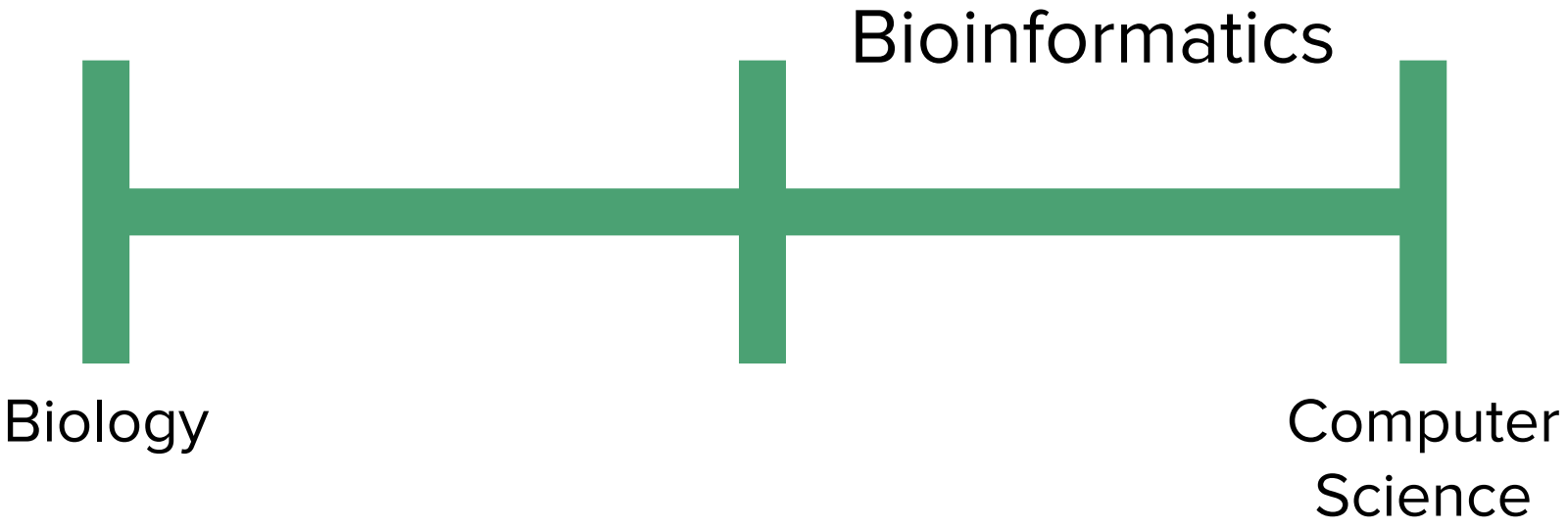

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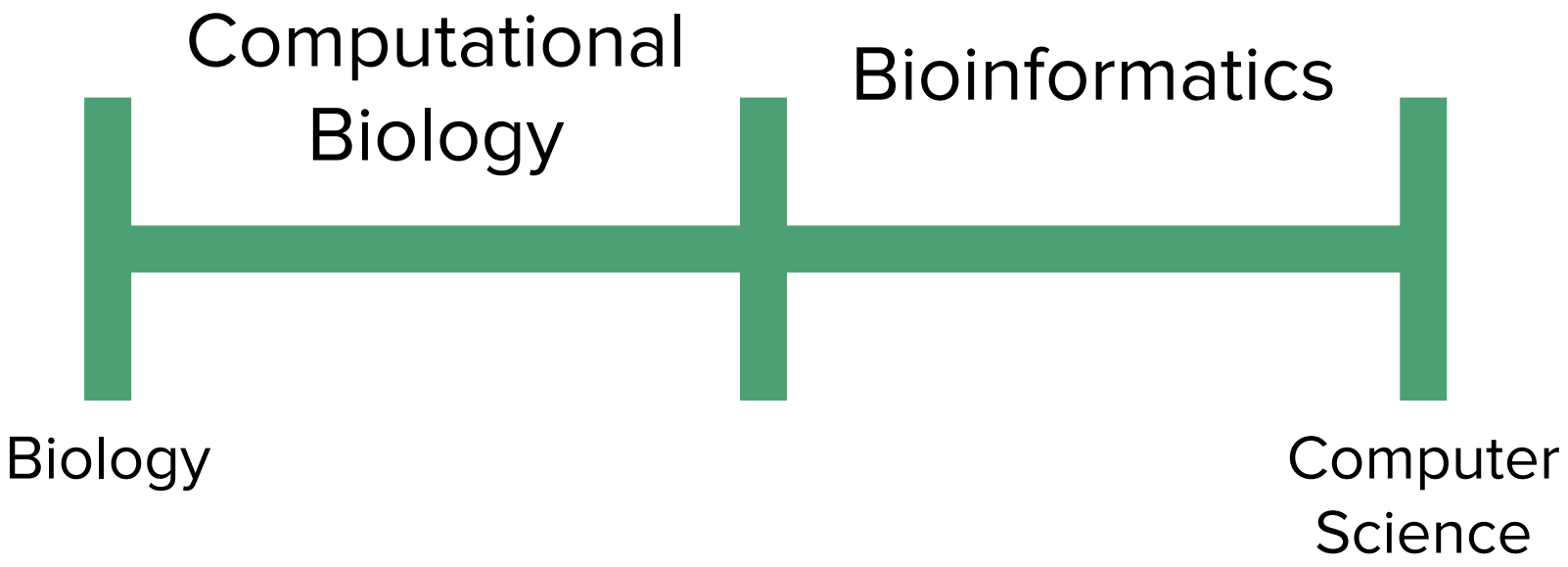

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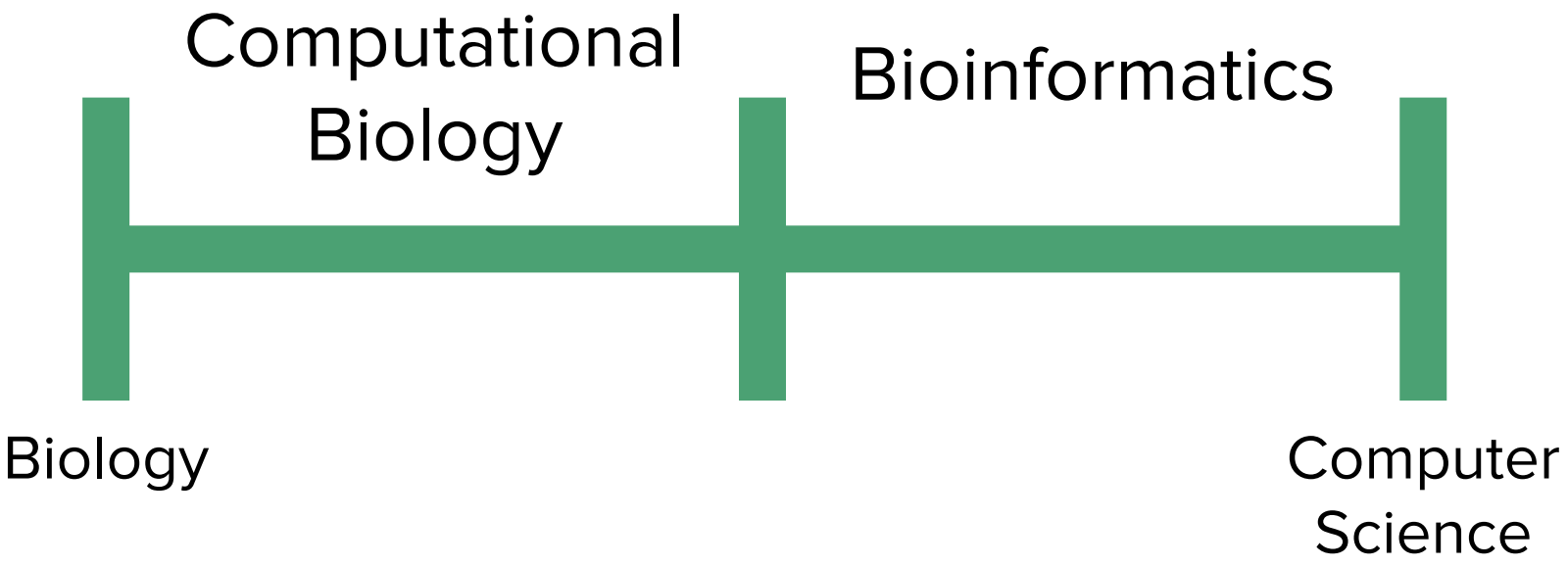
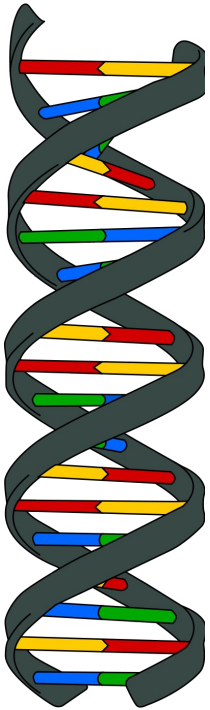


Chemistry? Physics? Statistics?

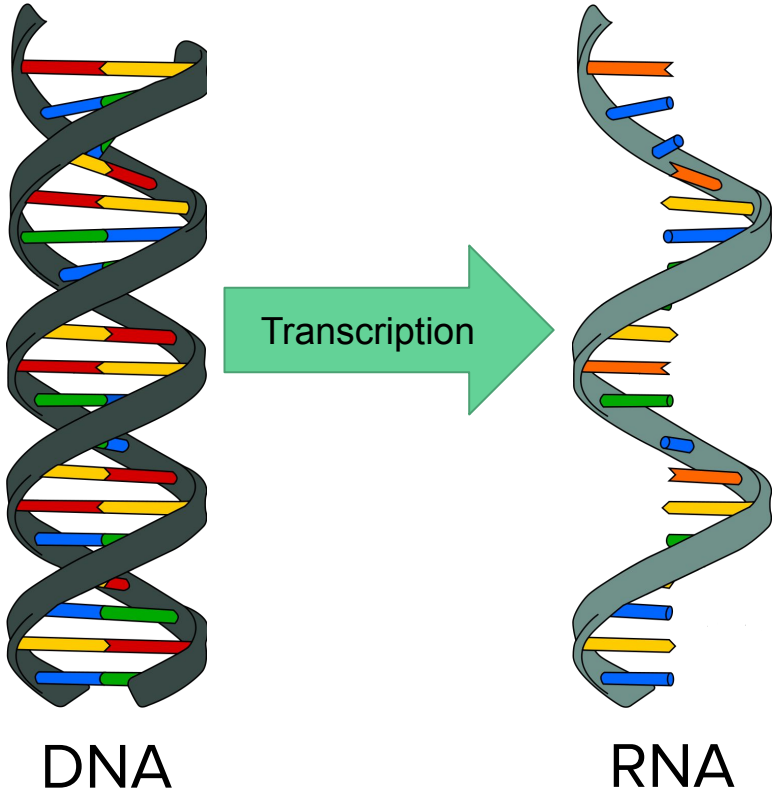
The Central Dogma

The Central Dogma of Biology



DNA

The Central Dogma of Biology



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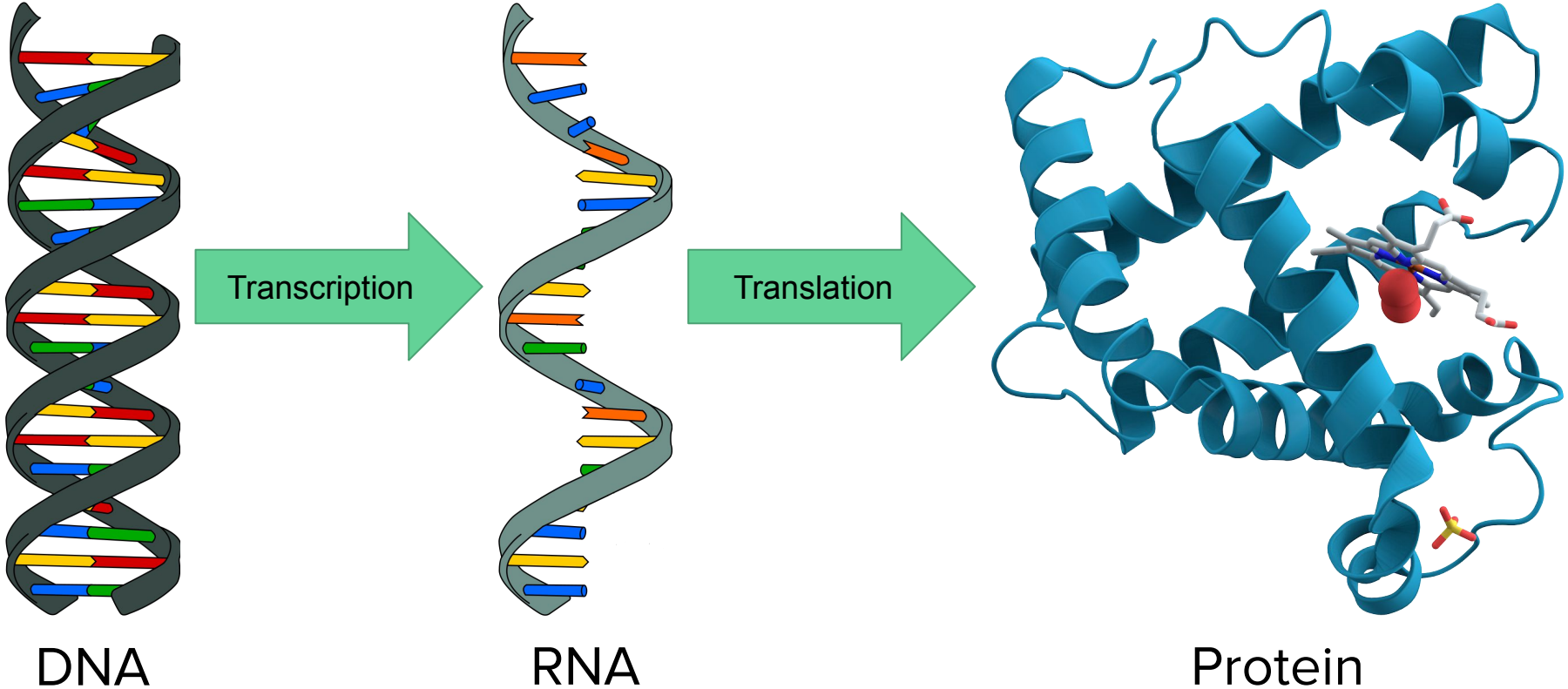

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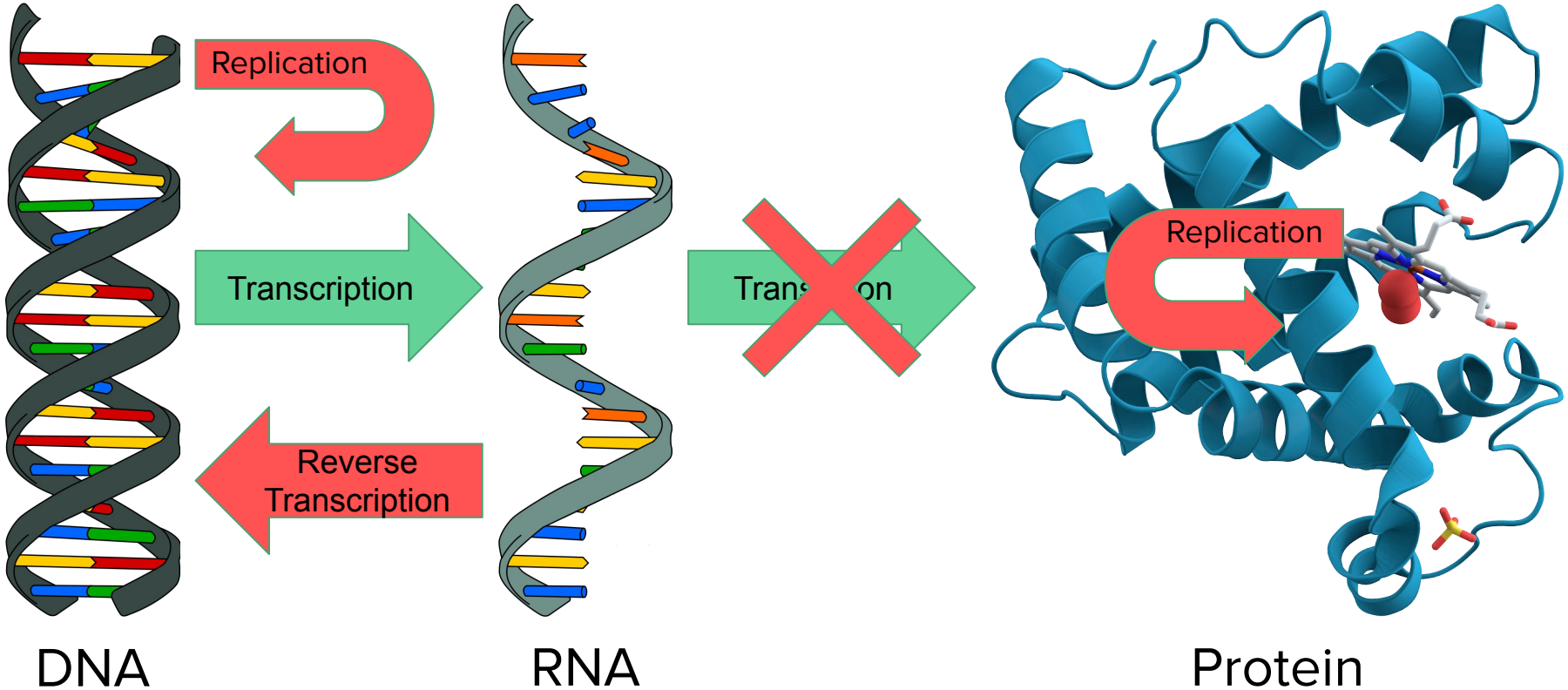

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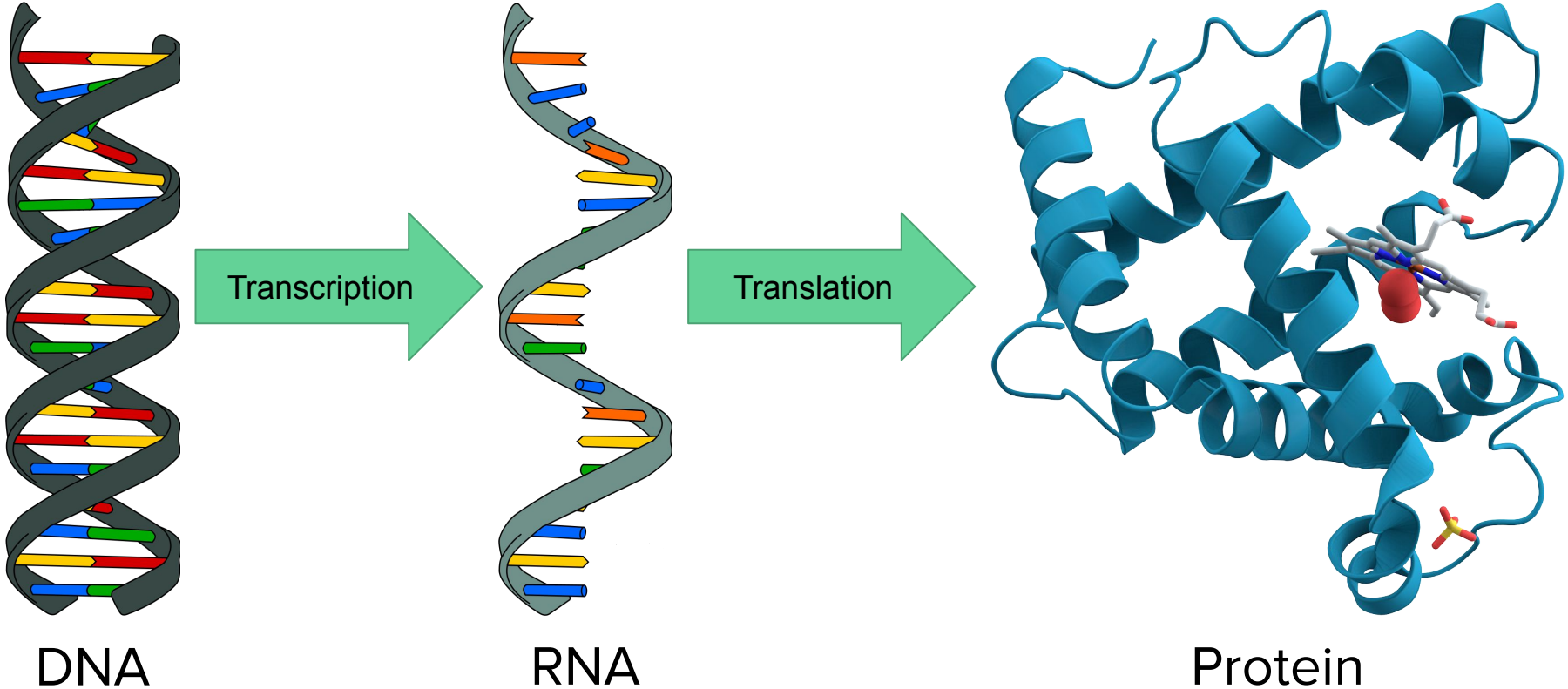
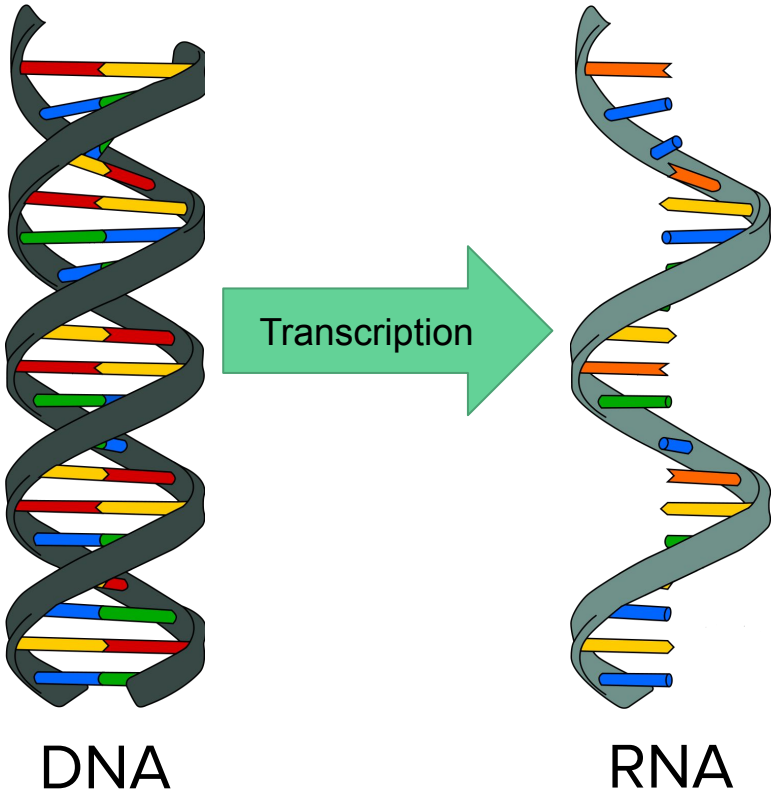


Transcription

Transcription

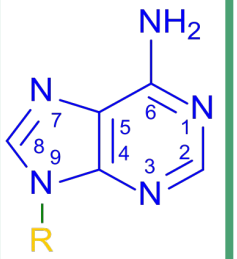
- DNA is **transcribed** to RNA



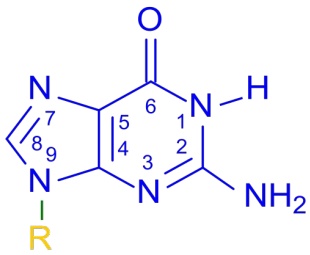
Transcription

- DNA is transcribed to RNA
  - DNA alphabet is {A, C, G, T}

Purines

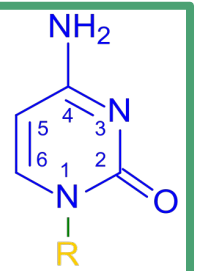


Adenine

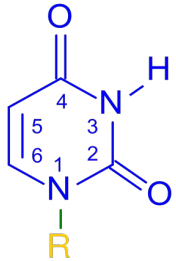


Guanine

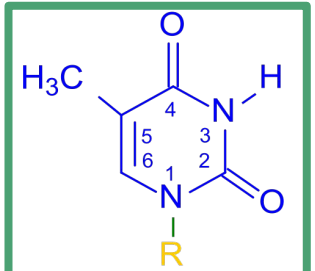
Pyrimidines



Cytosine



Uracil



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  - RNA alphabet is {A, C, G, **U**}

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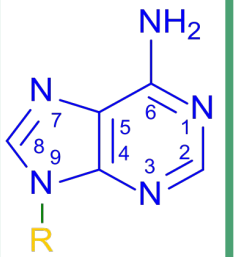

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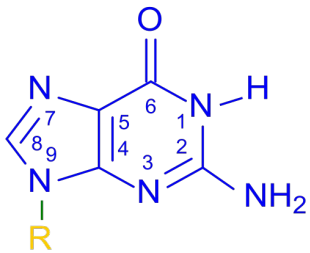

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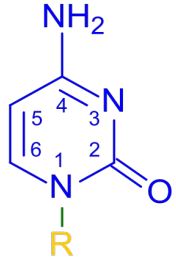

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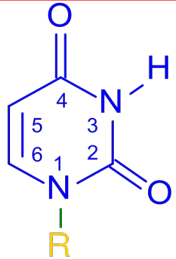

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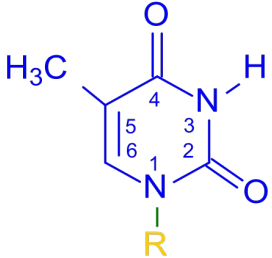

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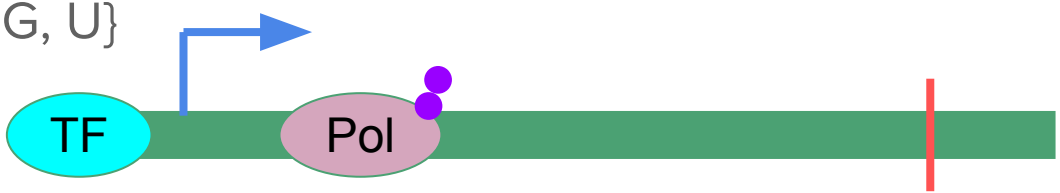

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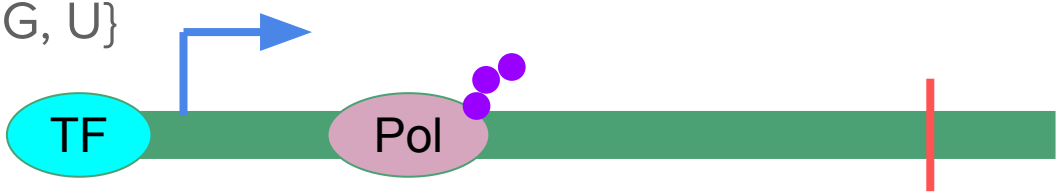

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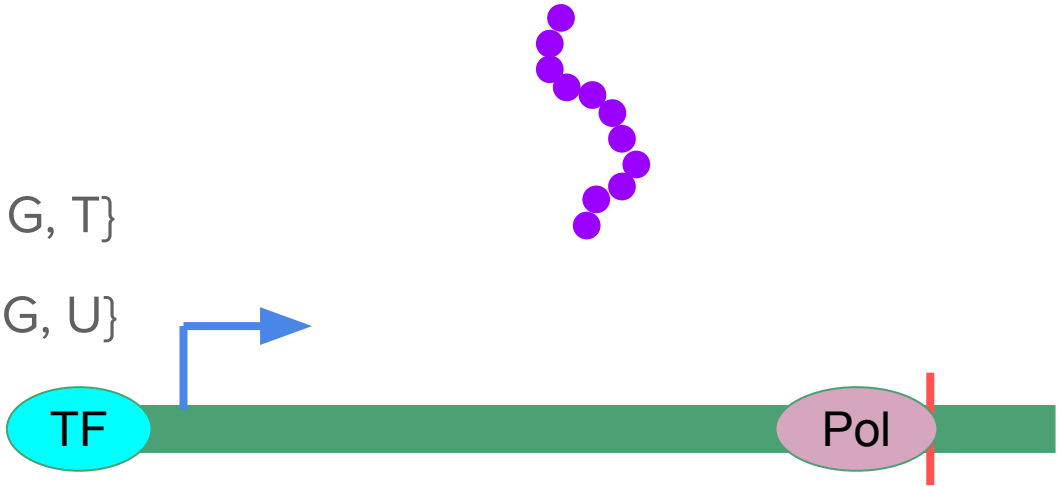

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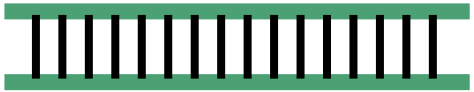

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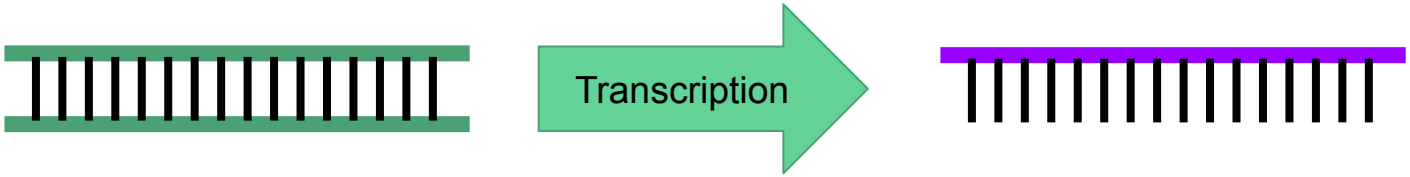

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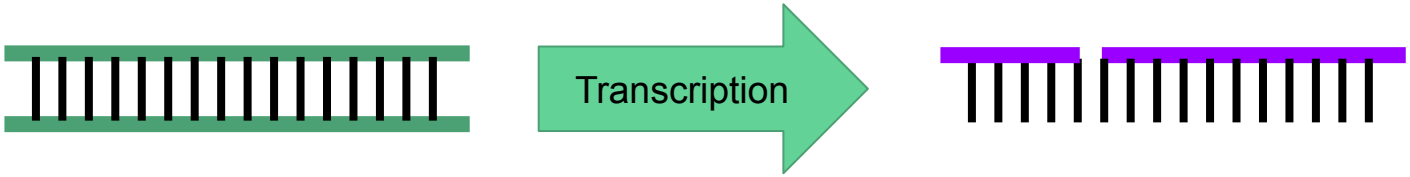

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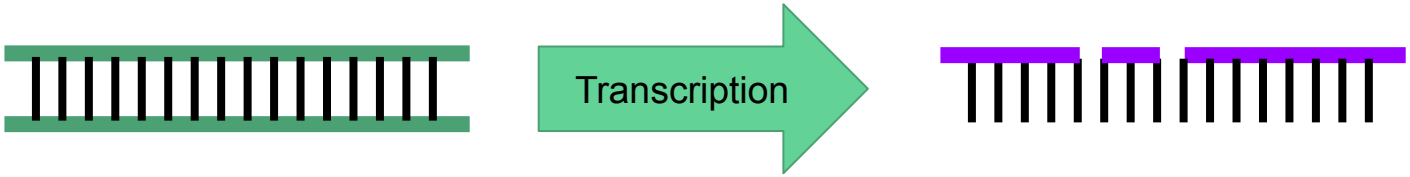

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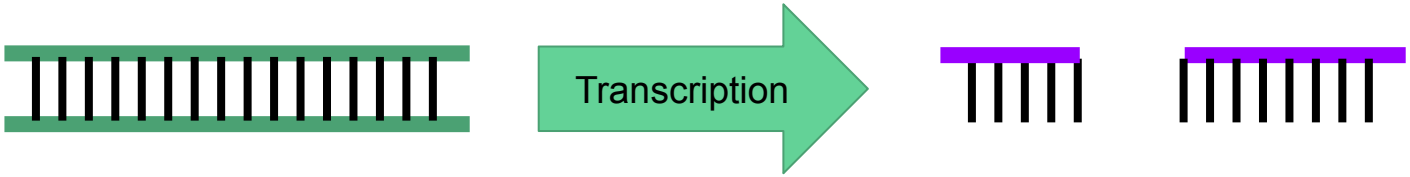

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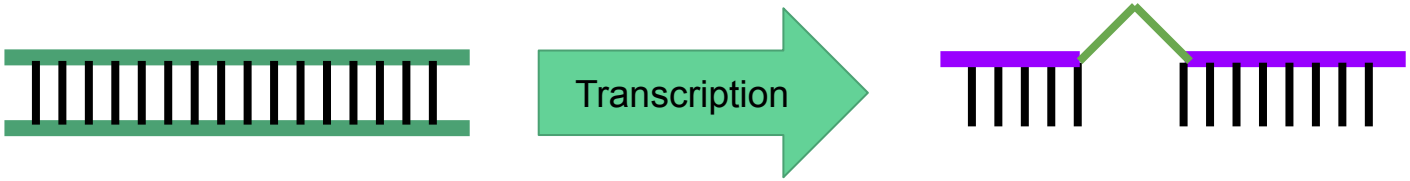

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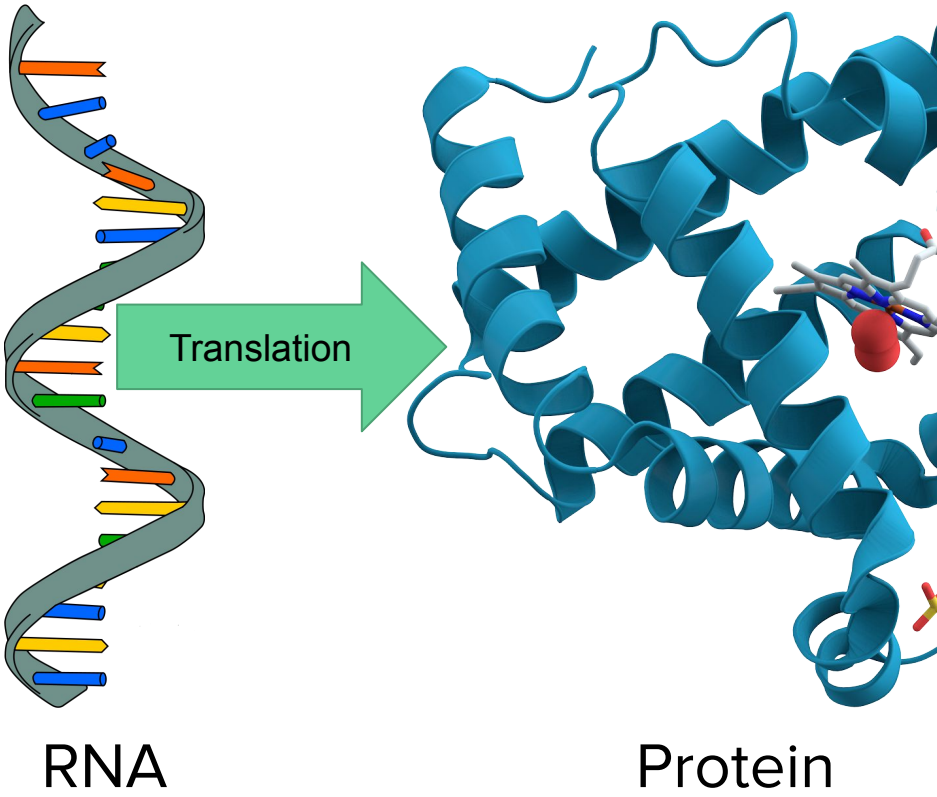
Translation

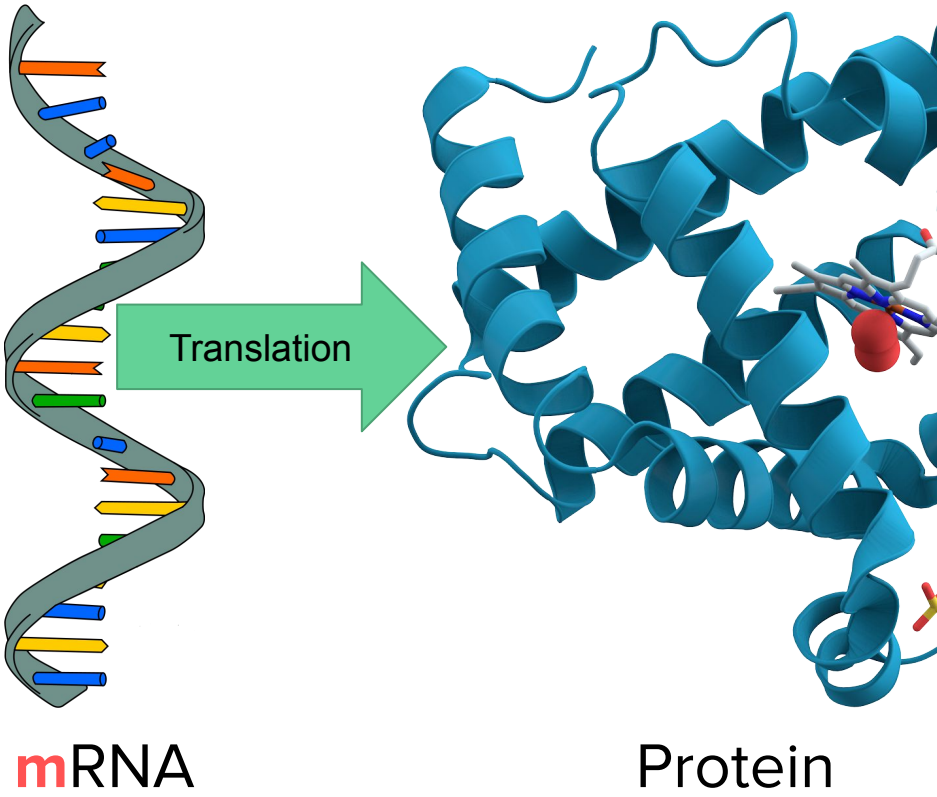
Translation

- RNA is **translated** to Protein



Translation

- mRNA is **translated** to Protein
  - “Messenger” RNA



Translation

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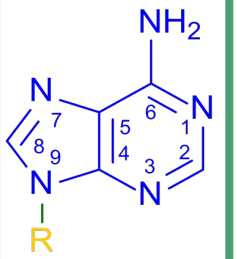

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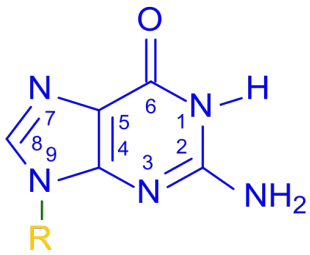

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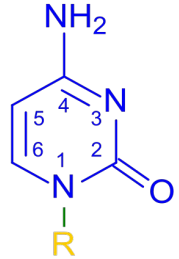

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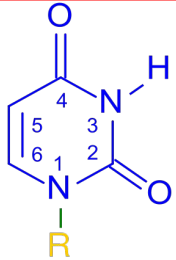

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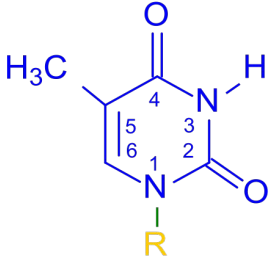
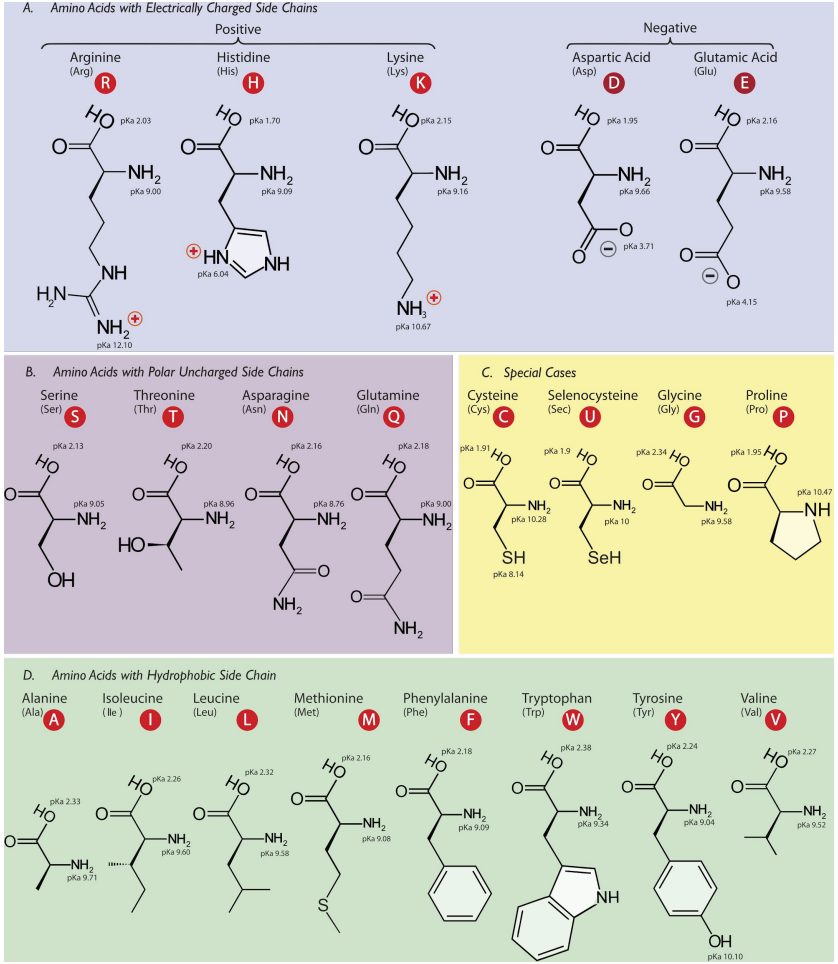


Thymine

Translation

- mRNA is translated to Protein
  - “Messenger” RNA
  - RNA alphabet is {A, C, G, U}
  - Protein alphabet is 20 letters



Translation

- mRNA is translated to Protein
  - “Messenger” RNA
  - RNA alphabet is {A, C, G, U}
  - Protein alphabet is 20 letters
  - Each triplet (“codon”) of RNA maps to a specific amino acid

first letter	second letter: U	C	A	G	third letter
U	UUU, UUC Phe UUA, UUG Leu	UCU, UCC, UCA, UCG Ser	UAU, UAC Tyr UAA stop UAG stop	UGU, UGC Cys UGA stop UGG Trp	U C A G
C	CUU, CUC, CUA, CUG Leu	CCU, CCC, CCA, CCG Pro	CAU, CAC His CAA, CAG Gln	CGU, CGC, CGA, CGG Arg	U C A G
A	AUU, AUC, AUA Ile AUG Met	ACU, ACC, ACA, ACG Thr	AAU, AAC Asn AAA, AAG Lys	AGU, AGC Ser AGA, AGG Arg	U C A G
G	GUU, GUC, GUA, GUG Val	GCU, GCC, GCA, GCG Ala	GAU, GAC Asp GAA, GAG Glu	GGU, GGC, GGA, GGG Gly	U C A G

Translation: Mechanism

- Translation starts at an early-on AUG (not necessarily the first)

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- Starting with AUG, each codon is “translated” to a specific amino acid

Translation: Mechanism

- Translation starts at an early-on AUG (not necessarily the first)
- Starting with AUG, each codon is “translated” to a specific amino acid
- Translation continues codon-by-codon until a STOP codon is reached

Translation: Summary

RNA: GAGCUGAUGGCUACUACACAUAUUGCCAGUUGAUGGGUU

Protein:

Translation: Summary

```
    RNA: GAGCUGAUGGCUACUACACAUAUUGCCAGUUGAUGGGUU
Protein: M
```

Translation: Summary

RNA: GAGCUGAUGGCUACUACACAUAUUGCCAGUUGAUGGGUU

Protein: MA

Translation: Summary

RNA: GAGCUGAUGGCU**ACU**ACACAUAUUGCCAGUUGAUGGGUU

Protein: MA**T**

Translation: Summary

RNA: GAGCUGAUGGCUACU**ACA**CAUAUUGCCAGUUGAUGGGUU

Protein: MAT**T**

Translation: Summary

RNA: GAGCUGAUGGCUACUACA**CAU**AUUGCCAGUUGAUGGGUU

Protein: MATT**H**

Translation: Summary

RNA: GAGCUGAUGGCUACUACACAU**AUU**GCCAGUUGAUGGGUU

Protein: MATTH**I**

Translation: Summary

```
    RNA: GAGCUGAUGGCUACUACACAUAUUGCCAGUUGAUGGGUU
Protein: MATTHIA
```

Translation: Summary

```
    RNA: GAGCUGAUGGCUACUACACAUAUUGCCAGUUGAUGGGUU
Protein: MATTHIAS
```

Translation: Summary

RNA: GAGCUGAUGGCUACUACACAUAUUGCCAGU**UGA**UGGGUU

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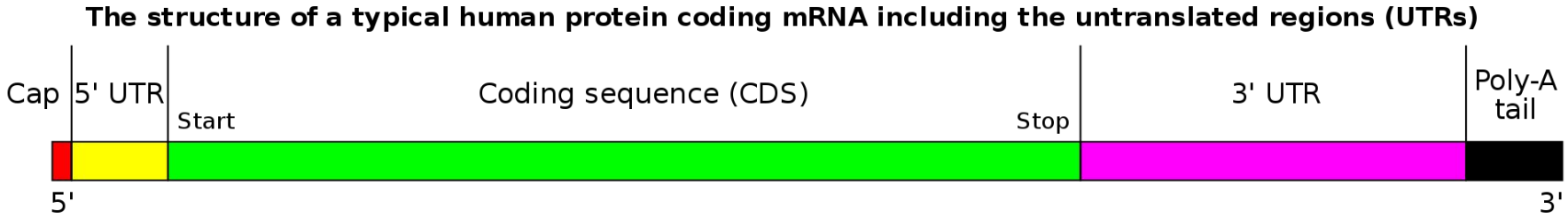
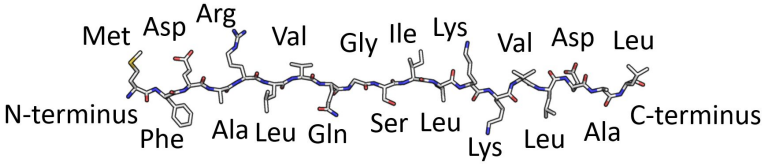


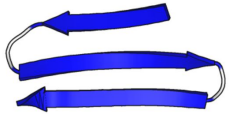
Protein Structure

- A protein's function is largely based on its structure

Primary



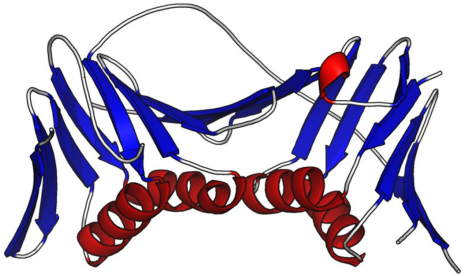
Secondary



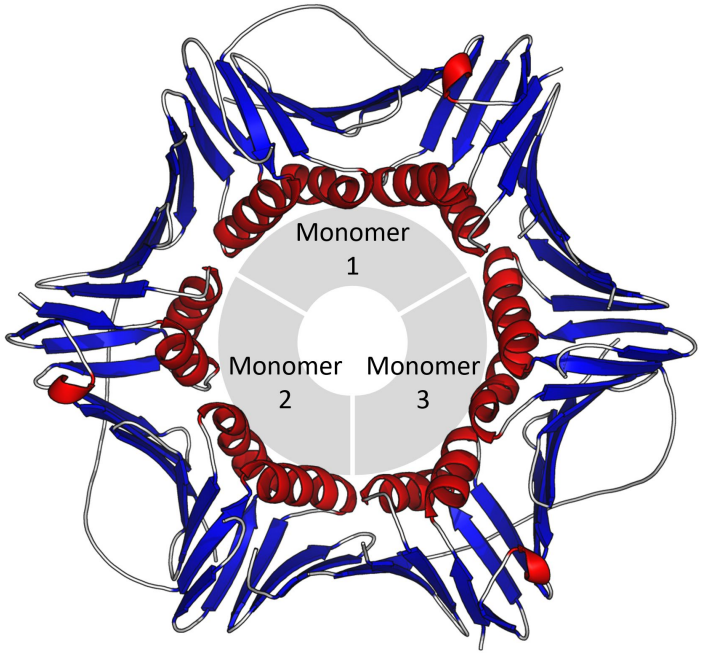
β-Sheet (3 strands)

α-helix

Tertiary



Quaternary



The Central Dogma: Summary

DNA: GAGCTGATGGCTACTACACATATTGCCAGTTGATGGGTT

Transcription

RNA: GAGCUGAUGGCUACUACACAUAUUGCCAGUUGAUGGGUU

Translation

Protein: MATTHIAS

Natural Selection

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- There is always natural variance (both “genotypic” and “phenotypic”) in a population of a given species

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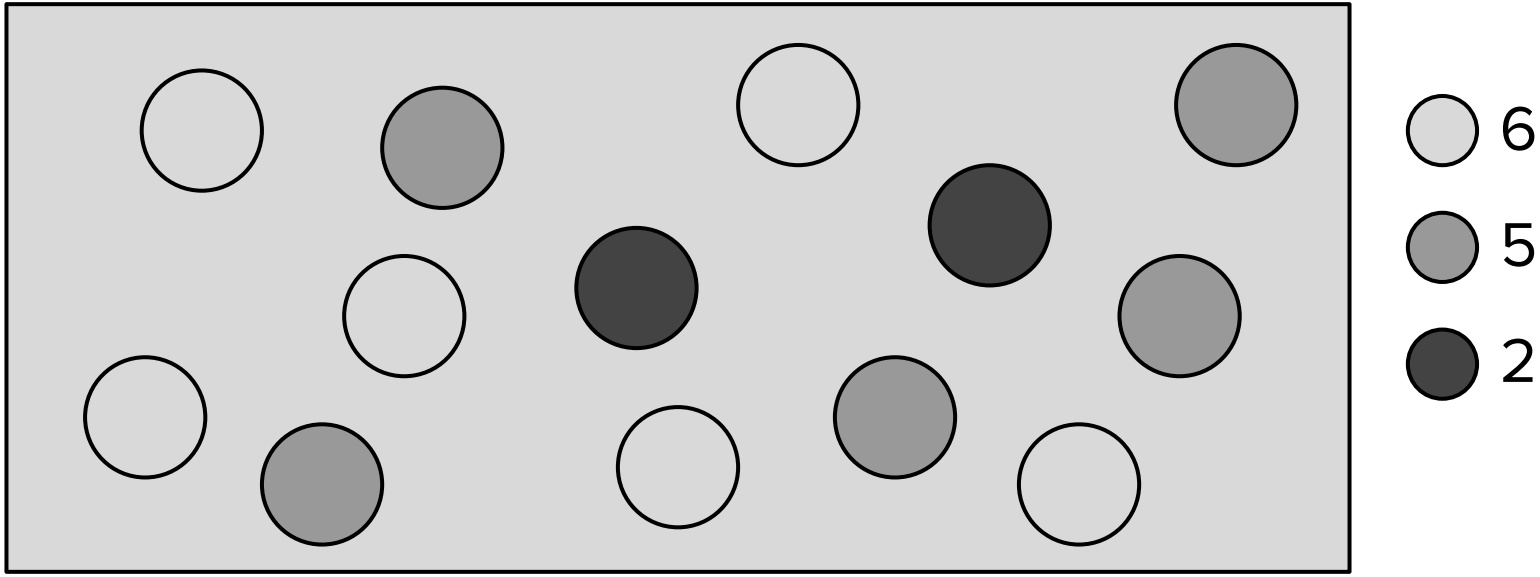
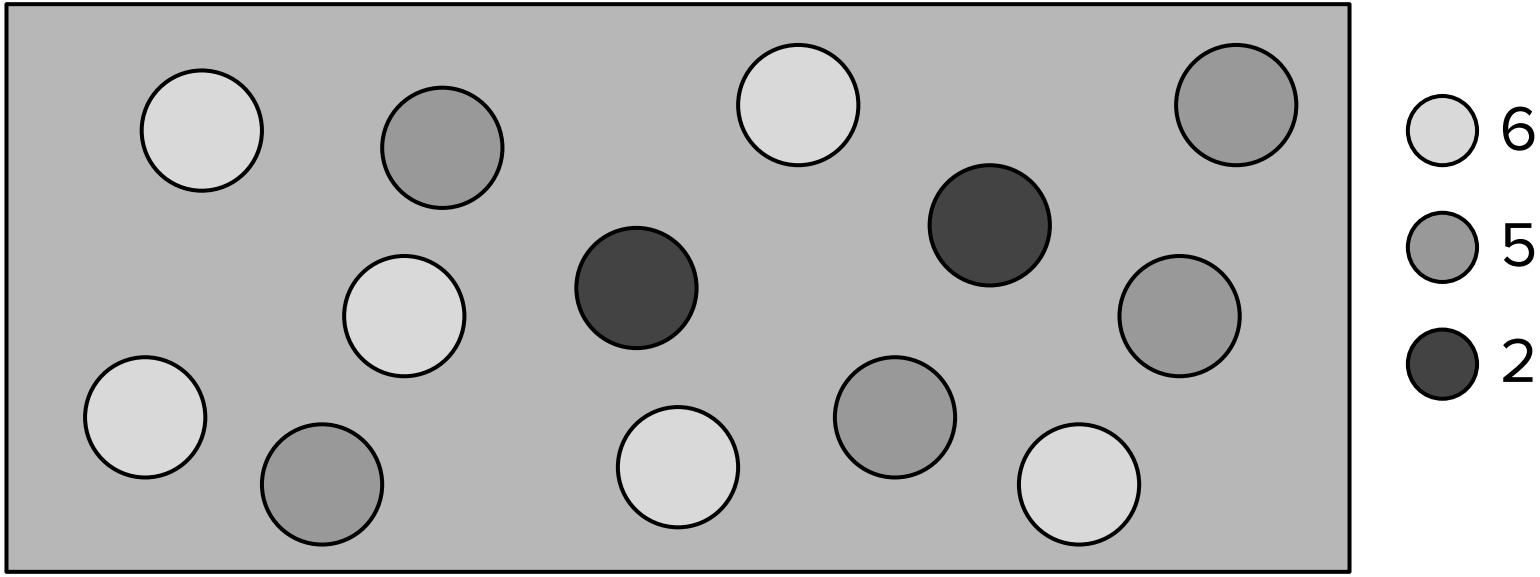
  - Traits that are “heritable” pass down to its offspring
  - Individuals without this trait are less likely to reproduce
  - In the next generation, a larger portion of the population will have the trait

Natural Selection: Example



Generation 0

Natural Selection: Example



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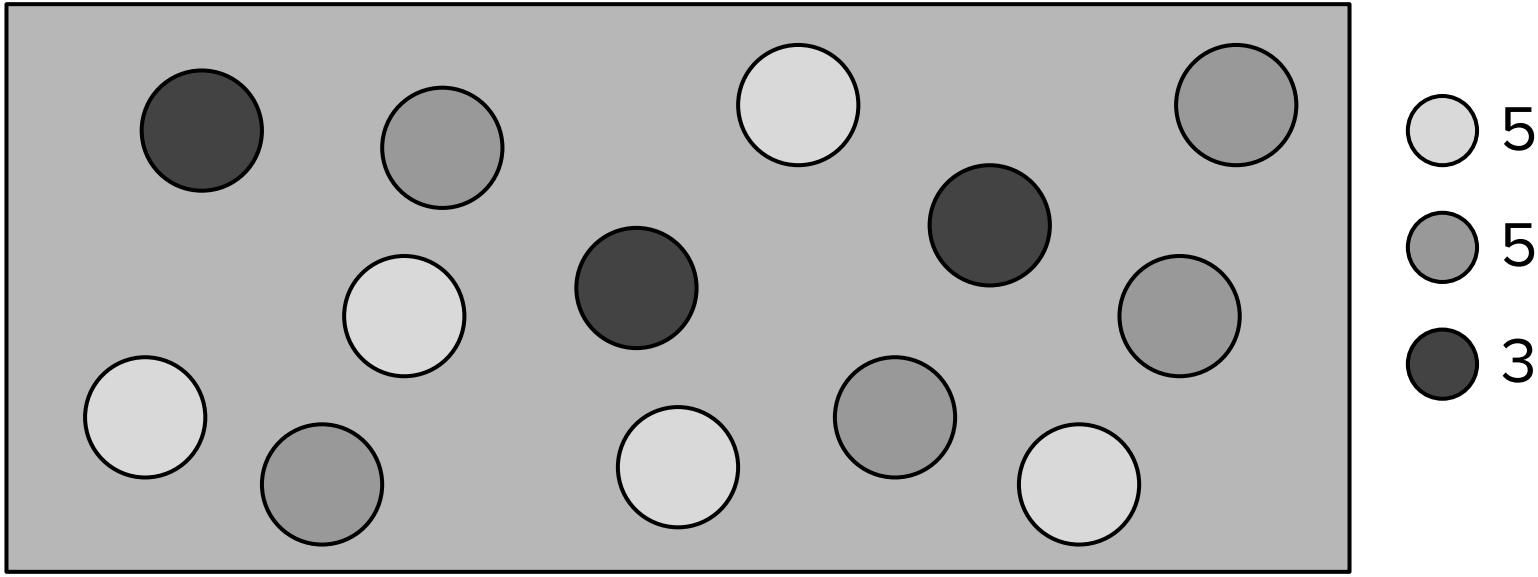
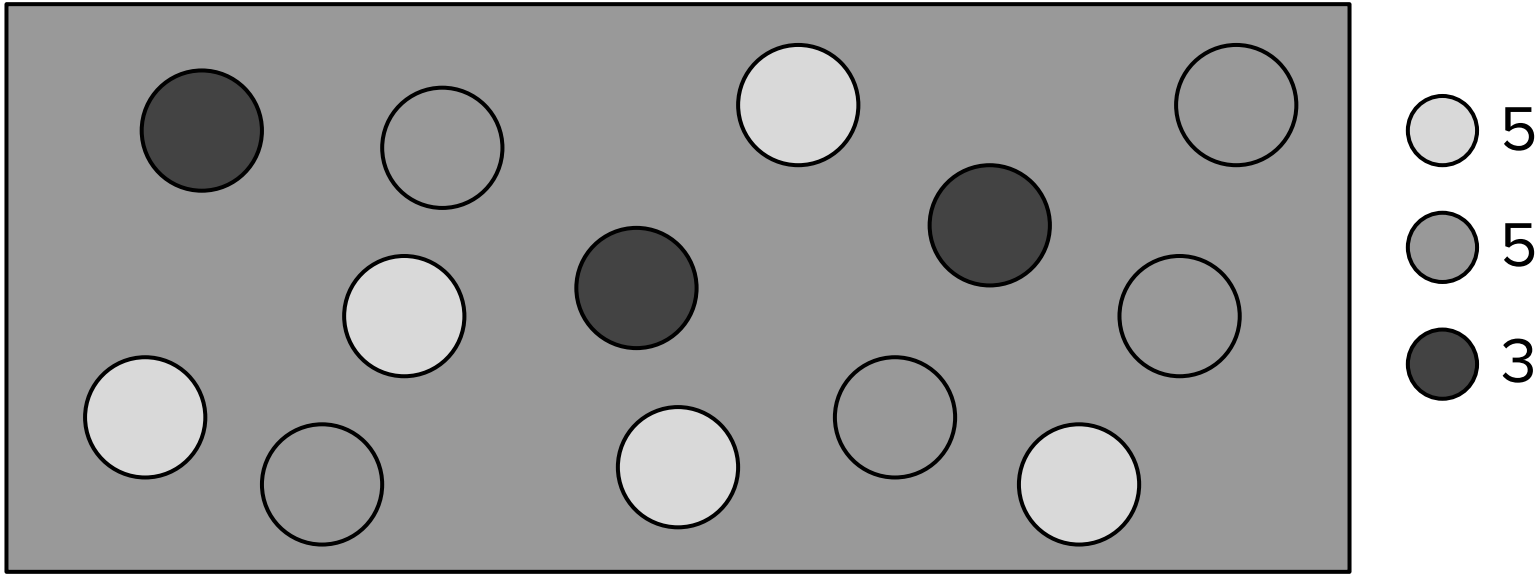
Natural Selection: Example



Generation 1

Natural Selection: Example



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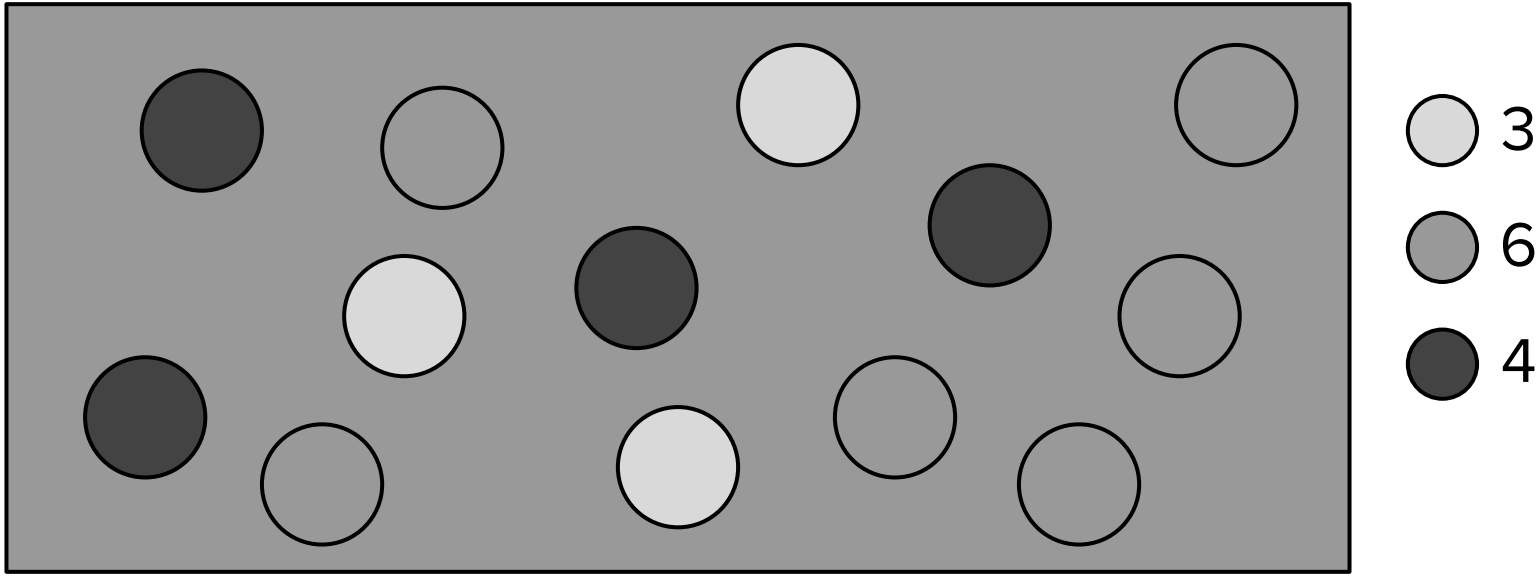
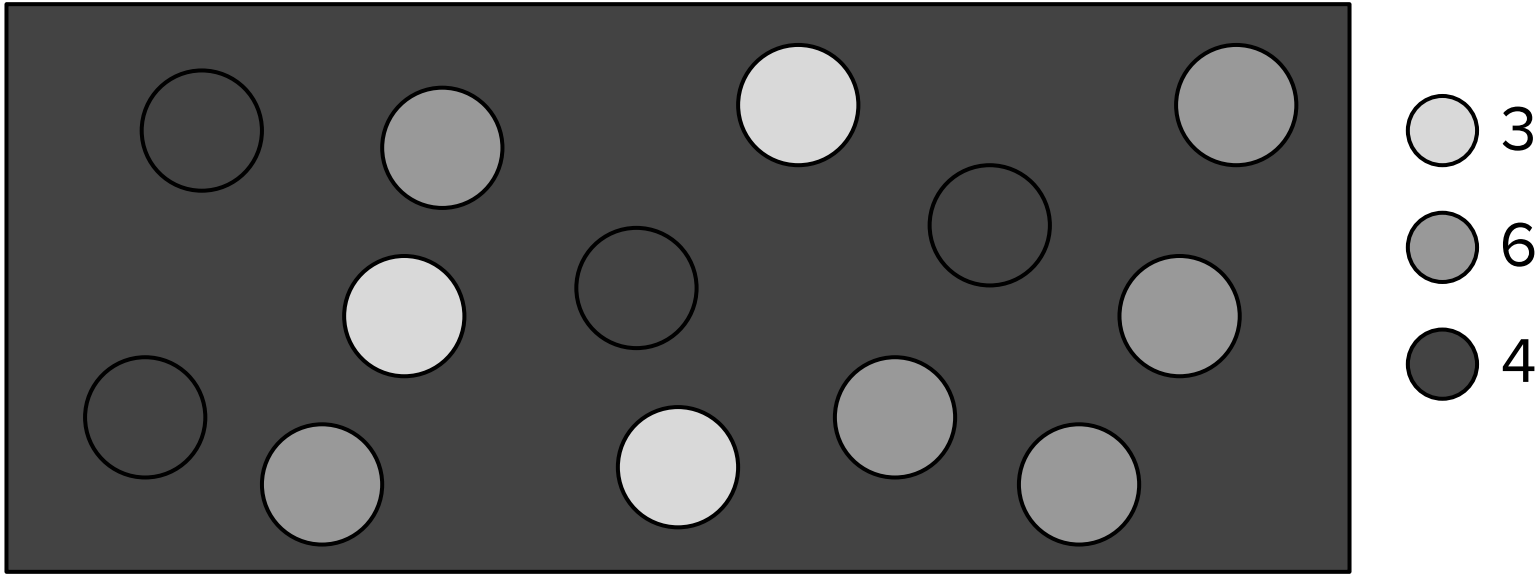


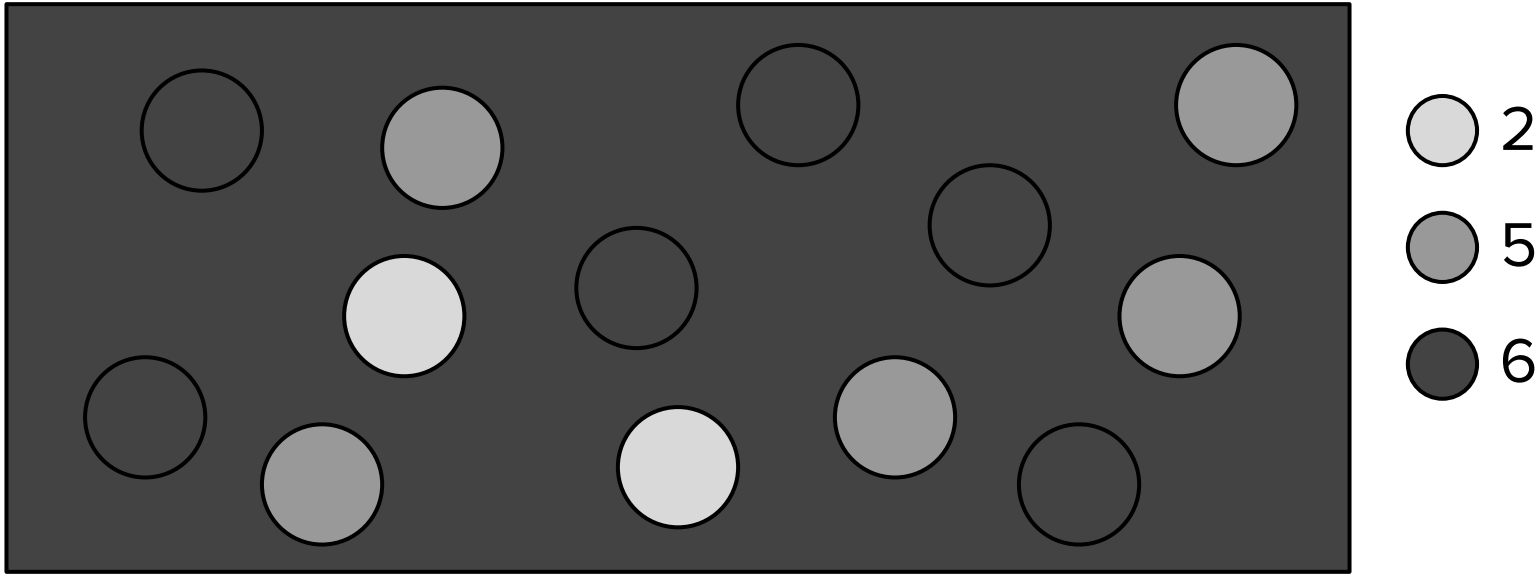
Generation 2

Natural Selection: Example



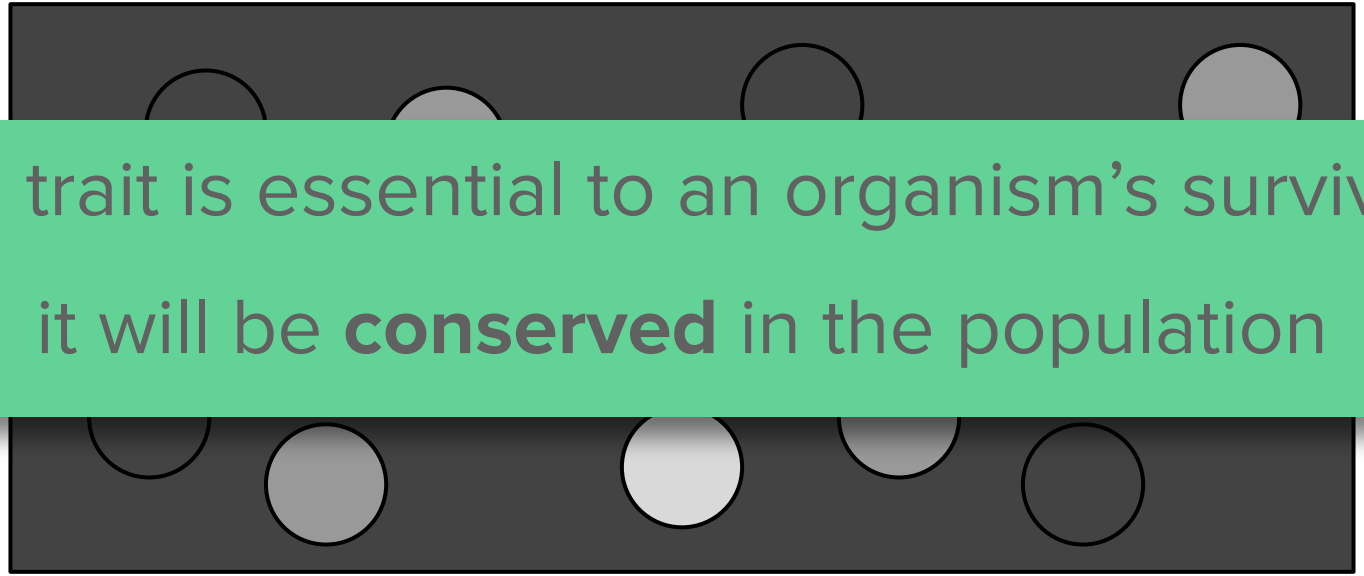
Generation 2

Natural Selection: Example



Generation 3

Natural Selection: Example



If a trait is essential to an organism's survival,

it will be **conserved** in the population

Generation 3

Sequence Alignment

Pairwise Sequence Alignment

- General Idea: If I have two strings *s* and *t*, if I were to stick gaps in either string, could I make them line up better?

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AGTACGTACGT
ACGTACGTAAT

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```
A-GTACGTACGT
ACGTACGTAA-T
```

Pairwise Sequence Alignment

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```
A-GTACGTACGT
ACGTACGTAA-T
```

Pairwise Sequence Alignment

- General Idea: If I have two strings *s* and *t*, if I were to stick gaps in either string, could I make them line up better?

- Biological Motivation: Align an important gene in human and its "ortholog" (equivalent) in mouse to see which parts are conserved

Pairwise Sequence Alignment: Scoring Function

Given an **alignment**, a **gap penalty** $\boldsymbol{\sigma}$, and a **scoring matrix** $\boldsymbol{M}$, let the **score** of the alignment be defined as the **sum** of the scores of each position of the alignment, where a position is scored $\boldsymbol{\sigma}$ if either sequence has a **gap**, else $\boldsymbol{M(c,c')}$ where c is the symbol at the position in one sequence and c' is the symbol at the position in the other sequence

Pairwise Sequence Alignment: Scoring Function

```
A-GTACGTACGT
ACGTACGTAA-T
```

Score: 0

	A	C	G	T
A	+1	-1	-1	-1
C	-1	+1	-1	-1
G	-1	-1	+1	-1
T	-1	-1	-1	+1

$\sigma = -1$

Pairwise Sequence Alignment: Scoring Function

```
A-GTACGTACGT
ACGTACGTAA-T
```

Score: 1

	A	C	G	T
A	+1	-1	-1	-1
C	-1	+1	-1	-1
G	-1	-1	+1	-1
T	-1	-1	-1	+1

$\sigma = -1$

Pairwise Sequence Alignment: Scoring Function

```
A-GTACGTACGT
ACGTACGTAA-T
```

Score: 0

	A	C	G	T
A	+1	-1	-1	-1
C	-1	+1	-1	-1
G	-1	-1	+1	-1
T	-1	-1	-1	+1

$\sigma = -1$

Pairwise Sequence Alignment: Scoring Function

```
A-GTACGTACGT
ACGTACGTAA-T
```

Score: 1

	A	C	G	T
A	+1	-1	-1	-1
C	-1	+1	-1	-1
G	-1	-1	+1	-1
T	-1	-1	-1	+1

$\sigma = -1$

Pairwise Sequence Alignment: Scoring Function

```
A-GTACGTACGT
ACGTACGTAA-T
```

Score: 2

	A	C	G	T
A	+1	-1	-1	-1
C	-1	+1	-1	-1
G	-1	-1	+1	-1
T	-1	-1	-1	+1

$\sigma = -1$

Pairwise Sequence Alignment: Scoring Function

```
A-GTACGTACGT
ACGTACGTAA-T
```

Score: 3

	A	C	G	T
A	+1	-1	-1	-1
C	-1	+1	-1	-1
G	-1	-1	+1	-1
T	-1	-1	-1	+1

$\sigma = -1$

Pairwise Sequence Alignment: Scoring Function

```
A-GTACGTACGT
ACGTACGTAA-T
```

Score: 4

	A	C	G	T
A	+1	-1	-1	-1
C	-1	+1	-1	-1
G	-1	-1	+1	-1
T	-1	-1	-1	+1

$\sigma = -1$

Pairwise Sequence Alignment: Scoring Function

```
A-GTACGTACGT
ACGTACGTAA-T
```

Score: 5

	A	C	G	T
A	+1	-1	-1	-1
C	-1	+1	-1	-1
G	-1	-1	+1	-1
T	-1	-1	-1	+1

$\sigma = -1$

Pairwise Sequence Alignment: Scoring Function

```
A-GTACGTACGT
ACGTACGTAA-T
```

Score: 6

	A	C	G	T
A	+1	-1	-1	-1
C	-1	+1	-1	-1
G	-1	-1	+1	-1
T	-1	-1	-1	+1

$\sigma = -1$

Pairwise Sequence Alignment: Scoring Function

```
A-GTACGTACGT
ACGTACGTAA-T
```

Score: 7

	A	C	G	T
A	+1	-1	-1	-1
C	-1	+1	-1	-1
G	-1	-1	+1	-1
T	-1	-1	-1	+1

$\sigma = -1$

Pairwise Sequence Alignment: Scoring Function

```
A-GTACGTACGT
ACGTACGTAA-T
```

Score: 6

	A	C	G	T
A	+1	-1	-1	-1
C	-1	+1	-1	-1
G	-1	-1	+1	-1
T	-1	-1	-1	+1

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A-GTACGTACGT
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	A	C	G	T
A	+1	-1	-1	-1
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T	-1	-1	-1	+1

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ACGTACGTAA-T
```

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	A	C	G	T
A	+1	-1	-1	-1
C	-1	+1	-1	-1
G	-1	-1	+1	-1
T	-1	-1	-1	+1

$\sigma = -1$

Pairwise Sequence Alignment: Scoring Function

A-GTACGTACGT

We want to **maximize** this scoring function

Score: 6

	A	C	G	T
A	+1	-1	-1	-1
G	-1	-1	+1	-1
T	-1	-1	-1	+1

$\sigma = -1$

The Global Alignment Problem

Given two strings ***s*** and ***t***, a gap penalty ***σ***, and a scoring matrix ***M***, return a **maximum-scoring** alignment of *s* and *t*

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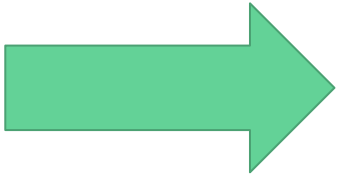

```
A-GTACGTACGT
ACGTACGTAA-T
```

The Local Alignment Problem

Given two strings ***s*** and ***t***, a gap penalty ***σ***, and a scoring matrix ***M***,
return a **maximum-scoring** alignment of
a *substring* of *s* and a *substring* of *t*

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AGTACGTACGT
ACGTACGTAAT

GTACGTA
GTACGTA

The Multiple Sequence Alignment Problem

Given **multiple strings**, a gap penalty $\boldsymbol{\sigma}$, and a scoring matrix $\boldsymbol{M}$, return a **maximum-scoring** alignment of the strings

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Given **multiple strings**, a gap penalty ***σ***, and a scoring matrix ***M***, return a **maximum-scoring** alignment of the strings

```
Q5E940_BOVIN -----------MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADNVGSKQMQQIRMSLRGK-AVVLMGKNTMMRKAIRGHLENN--PALE
  RLA0_HUMAN -----------MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADNVGSKQMQQIRMSLRGK-AVVLMGKNTMMRKAIRGHLENN--PALE
  RLA0_MOUSE -----------MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADNVGSKQMQQIRMSLRGK-AVVLMGKNTMMRKAIRGHLENN--PALE
    RLA0_RAT -----------MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADNVGSKQMQQIRMSLRGK-AVVLMGKNTMMRKAIRGHLENN--PALE
  RLA0_CHICK -----------MPREDRATWKSNYFMKIIQLLDDYPKCFVVGADNVGSKQMQQIRMSLRGK-AVVLMGKNTMMRKAIRGHLENN--PALE
  RLA0_RANSY -----------MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADNVGSKQMQQIRMSLRGK-AVVLMGKNTMMRKAIRGHLENN--SALE
Q7ZUG3_BRARE -----------MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADNVGSKQMQTIRLSLRGK-AVVLMGKNTMMRKAIRGHLENN--PALE
  RLA0_ICTPU -----------MPREDRATWKSNYFLKIIQLLNDYPKCFIVGADNVGSKQMQTIRLSLRGK-AIVLMGKNTMMRKAIRGHLENN--PALE
  RLA0_DROME -----------MVRENKAAWKAQYFIKVVELFDEFPKCFIVGADNVGSKQMQNIRTSLRGL-AVVLMGKNTMMRKAIRGHLENN--PQLE
  RLA0_DICDI -----------MSGAG-SKRKKLFIEKATKLFTTYDKMIVAEADFVGSSQLQKIRKSIRGI-GAVLMGKKTMIRKVIRDLADSK--PELD
Q54LP0_DICDI -----------MSGAG-SKRKNVFIEKATKLFTTYDKMIVAEADFVGSSQLQKIRKSIRGI-GAVLMGKKTMIRKVIRDLADSK--PELD
  RLA0_PLAF8 -----------MAKLSKQQKKQMYIEKLSSLIQQYSKILIVHVDNVGSNQMASVRKSLRGK-ATILMGKNTRIRTALKKNLQAV--PQIE
  RLA0_SULAC -----MIGLAVTTTKKIAKWKVDEVAELTEKLKTHKTIIIANIEGFPADKLHEIRKKLRGK-ADIKVTKNNLFNIALKNAG-----YDTK
  RLA0_SULTO ----MRIMAVITQERKIAKWKIEEVKELEQKLREYHTIIIANIEGFPADKLHDIRKKMRGM-AEIKVTKNTLFGIAAKNAG-----LDVS
  RLA0_SULSO ----MKRLALALKQRKVASWKLEEVKELTELIKNSNTILIGNLEGFPADKLHEIRKKLRGK-ATIKVTKNTLFKIAAKNAG-----IDIE
  RLA0_AERPE MSVVSLVGQMYKREKPIPEWKTLMLRELEELFSKHRVVLFADLTGTPTFVVQRVRKKLWKK-YPMMVAKKRIILRAMKAAGLE---LDDN
  RLA0_PYRAE -MMLAIGKRRYVRTRQYPARKVKIVSEATELLQKYPYVFLFDLHGLSSRILHEYRYRLRRY-GVIKIIKPTLFKIAFTKVYGG---IPAE
  RLA0_METAC ------MAEERHHTEHIPQWKKDEIENIKELIQSHKVFGMVGIEGILATKMQKIRRDLKDV-AVLKVSRNTLTERALNQLG-----ETIP
  RLA0_METMA ------MAEERHHTEHIPQWKKDEIENIKELIQSHKVFGMVRIEGILATKIQKIRRDLKDV-AVLKVSRNTLTERALNQLG-----ESIP
```

Variant Calling

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ACATACGTACGT
ACGTACGTACGT
ACGTACGTACGT
ACATACGTTCGT
ACGTACGTACGT
ACGTACGTACGT
ACATACGTACGT
ACGTACGTACGT
ACGTACGTTCGT

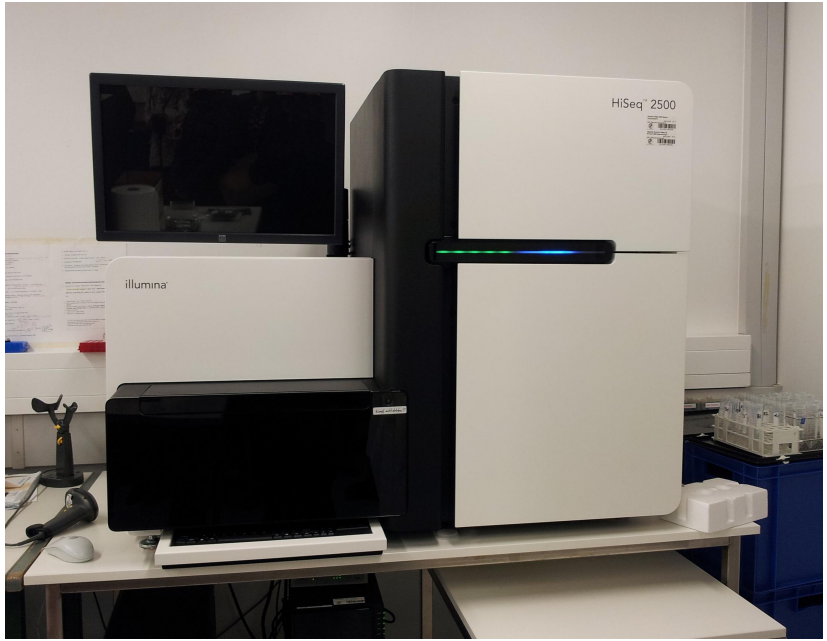
Variant Calling

- Any two humans have genomes that are roughly 99.9% identical
- Single Nucleotide Variants (SNVs)
- Structural Variants (SVs)

ACAGCAGCAGCAGTT
ACAGCAGTT
ACAGTT
ACAGCAGCAGTT

SNV Calling: General Approach

- Sequence the DNA of the individual



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          ACTTACGT
             GTACGTAC
        TACGTACG
           CTTACGTA
     CGTACTTA
REF: ...ACGTACGTACGTACGTACGTACGT...
```

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ACTTACGT
   GTACGTAC
TACGTACG
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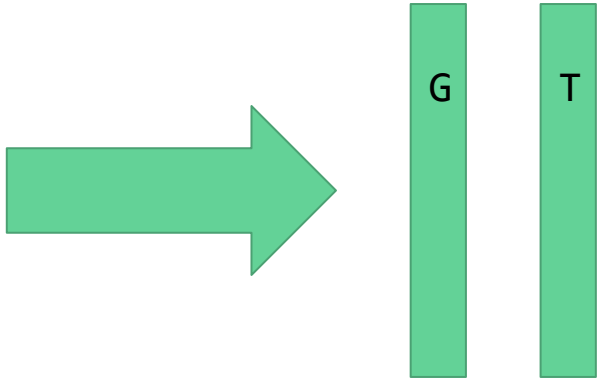
CGTACTTA
REF: ...ACGTACGTACGTACGTACGTACGT...
```

50% G

50% T



SNV Calling: Challenges

- Some regions of the genome are difficult to sequence

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- Some regions of the genome are difficult to sequence
- Sequencing technologies have sequencing error

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- Sequencing technologies have sampling error

Population Genetics

- Once we’ve called SNVs and SVs in enough people, what can we do?

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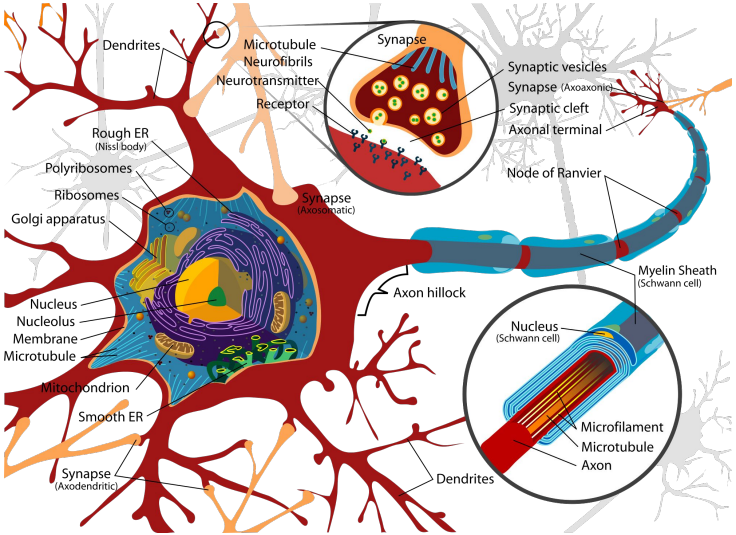
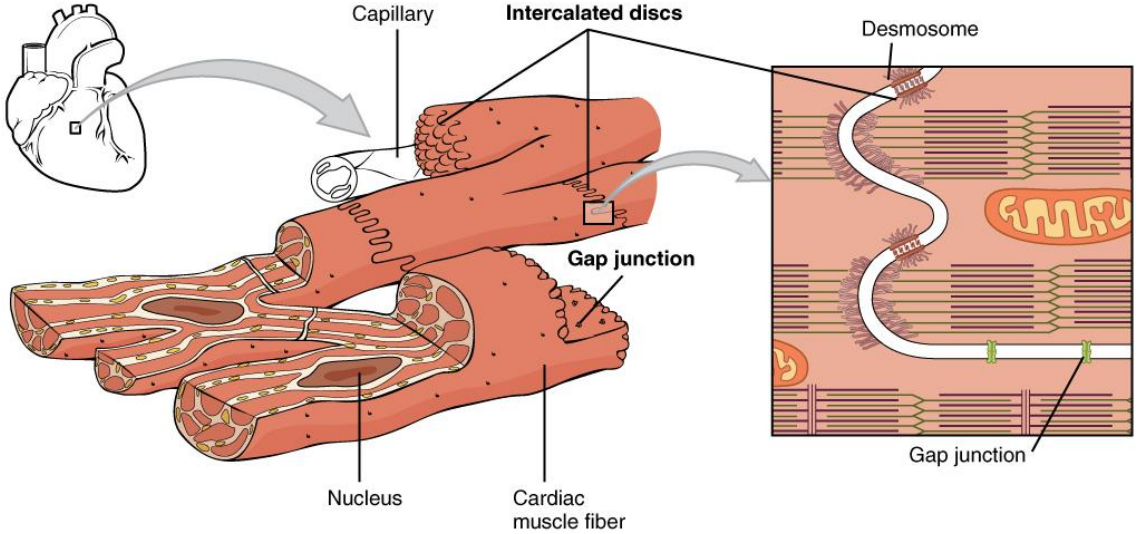
Differential Expression Analysis

Differential Expression Analysis: RNA-Seq

- All cells in the body have (roughly) identical genomes





Differential Expression Analysis: RNA-Seq

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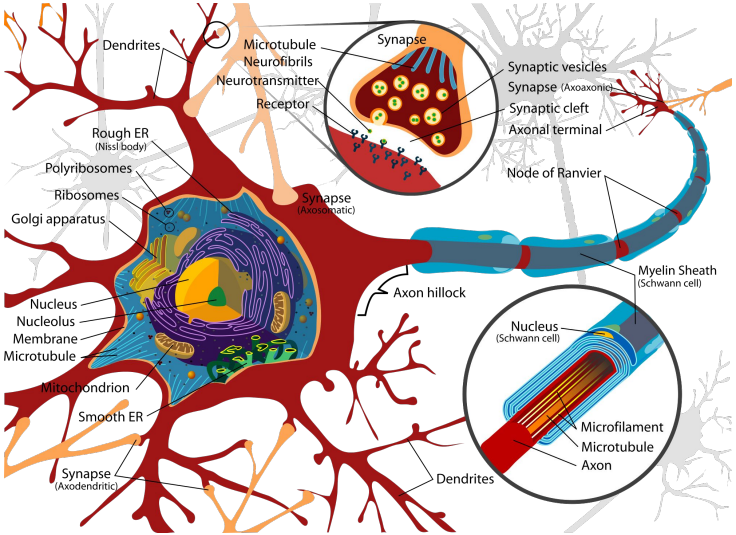
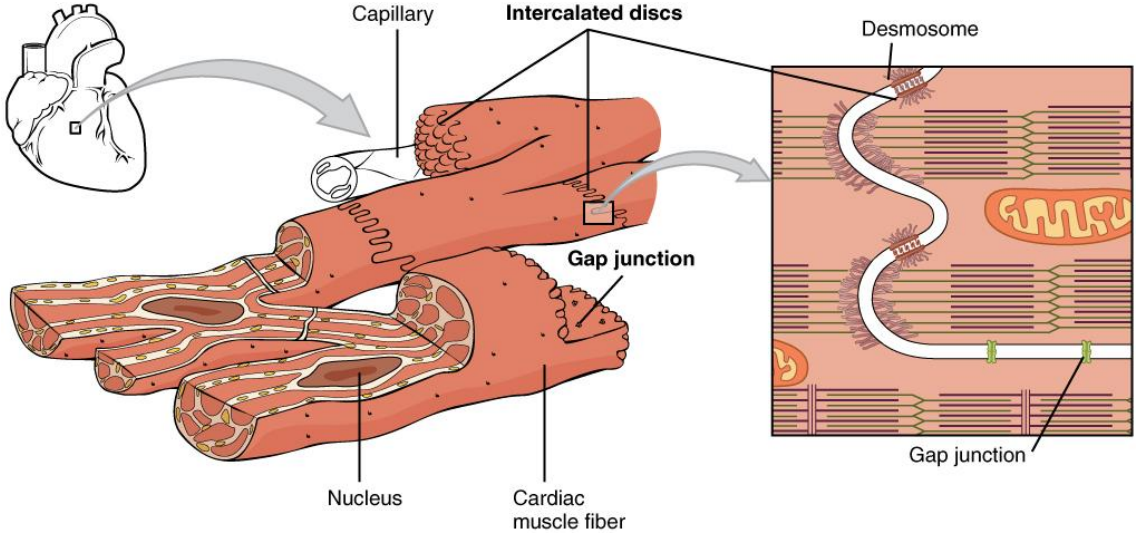
  - Differences in how they look/function are caused by “differential expression” of genes





Differential Expression Analysis: RNA-Seq

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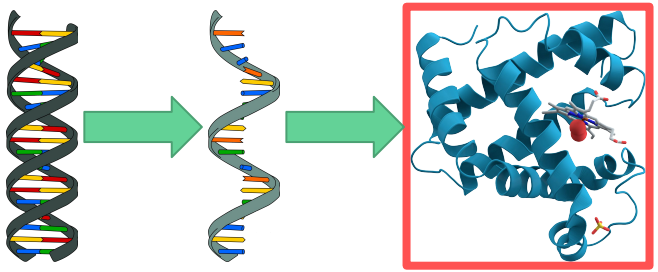
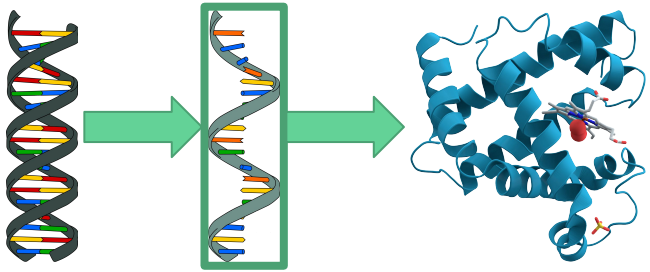
  - We want to measure protein levels, but we can’t in high-throughput



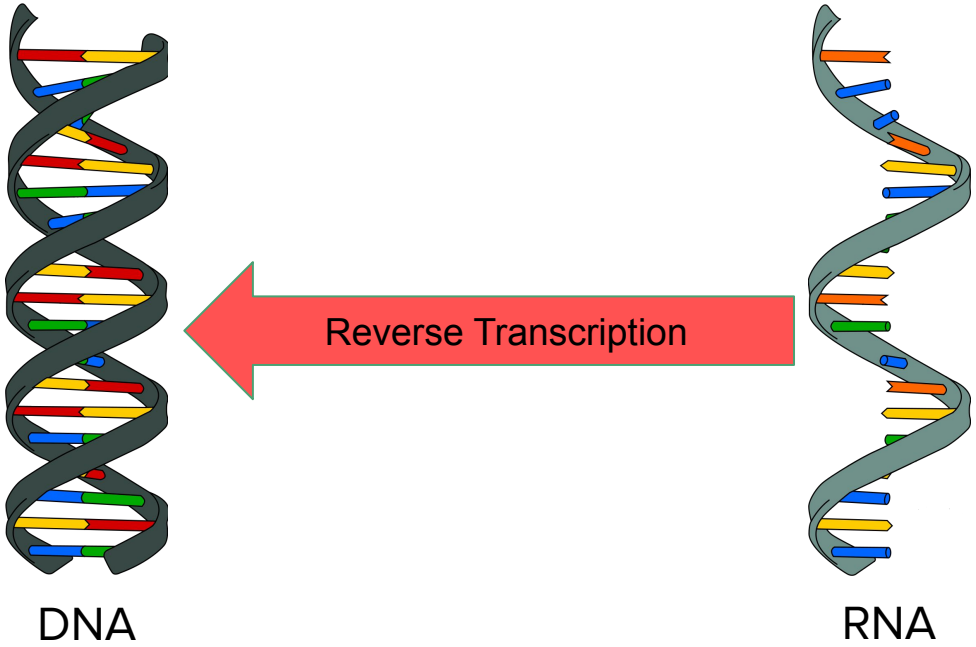
Differential Expression Analysis: RNA-Seq

- All cells in the body have (roughly) identical genomes
  - Differences in how they look/function are caused by “differential expression” of genes
- <u>Biological Question</u>: Given two different samples, what genes are differentially expressed across them?
  - We want to measure protein levels, but we can’t in high-throughput
  - Instead, we measure RNA levels



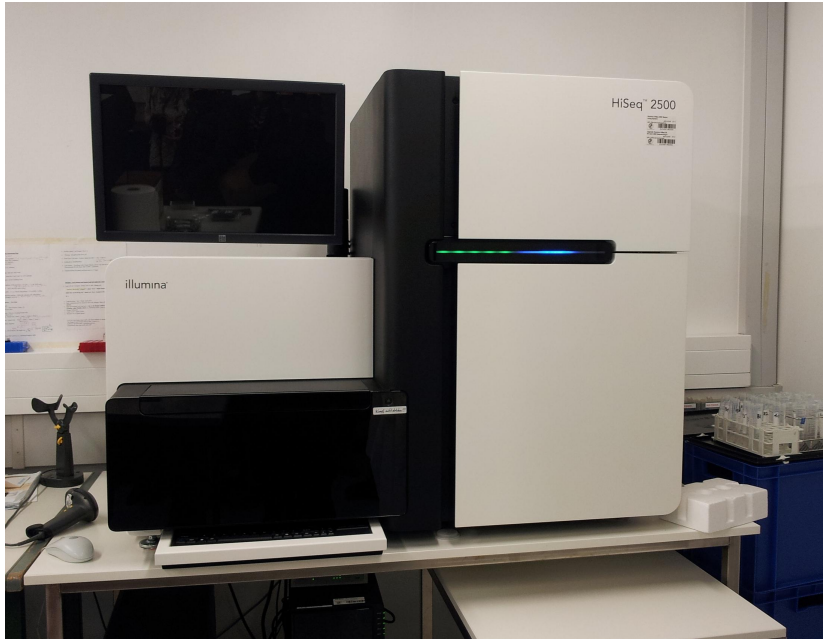
SNV Calling: General Approach

- Reverse Transcribe RNA to DNA



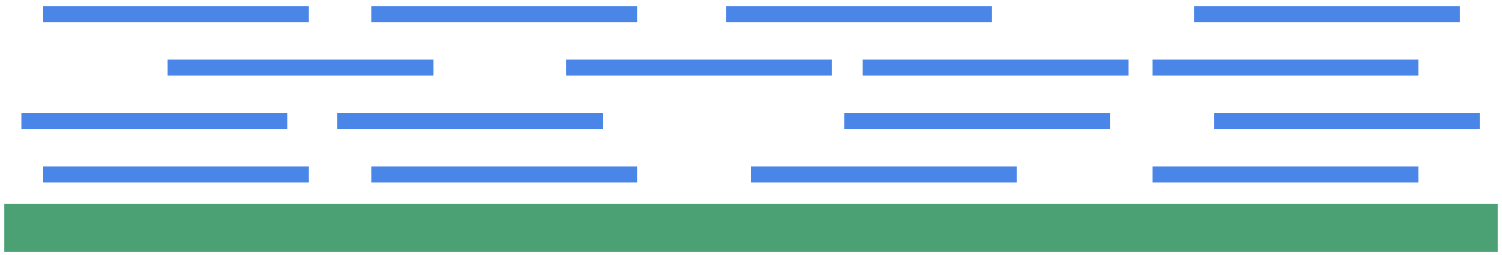
SNV Calling: General Approach

- Reverse Transcribe RNA to DNA
- Sequence the resulting DNA



SNV Calling: General Approach

- Reverse Transcribe RNA to DNA
- Sequence the resulting DNA
- Align the reads to the reference genome



SNV Calling: General Approach

Gene	Sample 1 Count	Sample 2 Count
A	###	###
B	###	###
C	###	###

- Reverse Transcribe RNA to DNA
- Sequence the resulting DNA
- Align the reads to the reference genome
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SNV Calling: General Approach

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SNV Calling: General Approach

Gene	Sample 1 FPKM	Sample 2 FPKM	Log-2 Ratio	*p*
A	###	###	###	###
B	###	###	###	###
C	###	###	###	###

- Reverse Transcribe RNA to DNA
- Sequence the resulting DNA
- Align the reads to the reference genome
- Count the number of reads that mapped to each gene
- Normalize by gene length and by sequencing depth
- Perform differential expression statistical tests for each gene

Genome Assembly

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- What is the genome sequence of a given organism?

...ATACAGTGGAACACCATCTG...

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          GGAACA
                CACCAT
                   CCATCT
...ATACAGTGGAACACCATCTG...
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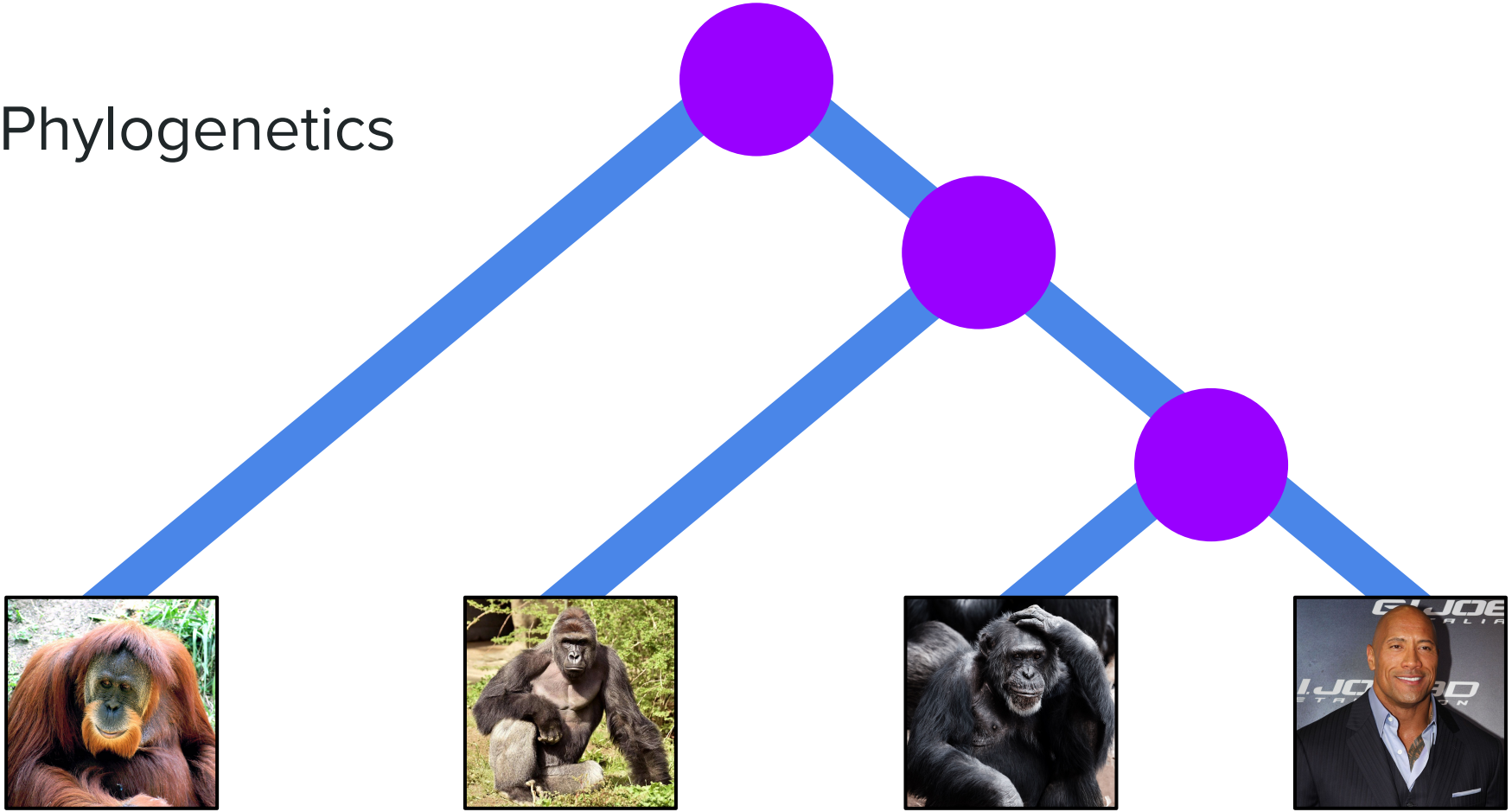
Genome Assembly

- What is the genome sequence of a given organism?
- We are able to sequence small fragments of an organism's genome
- How do we tie these small fragments together into a single string?

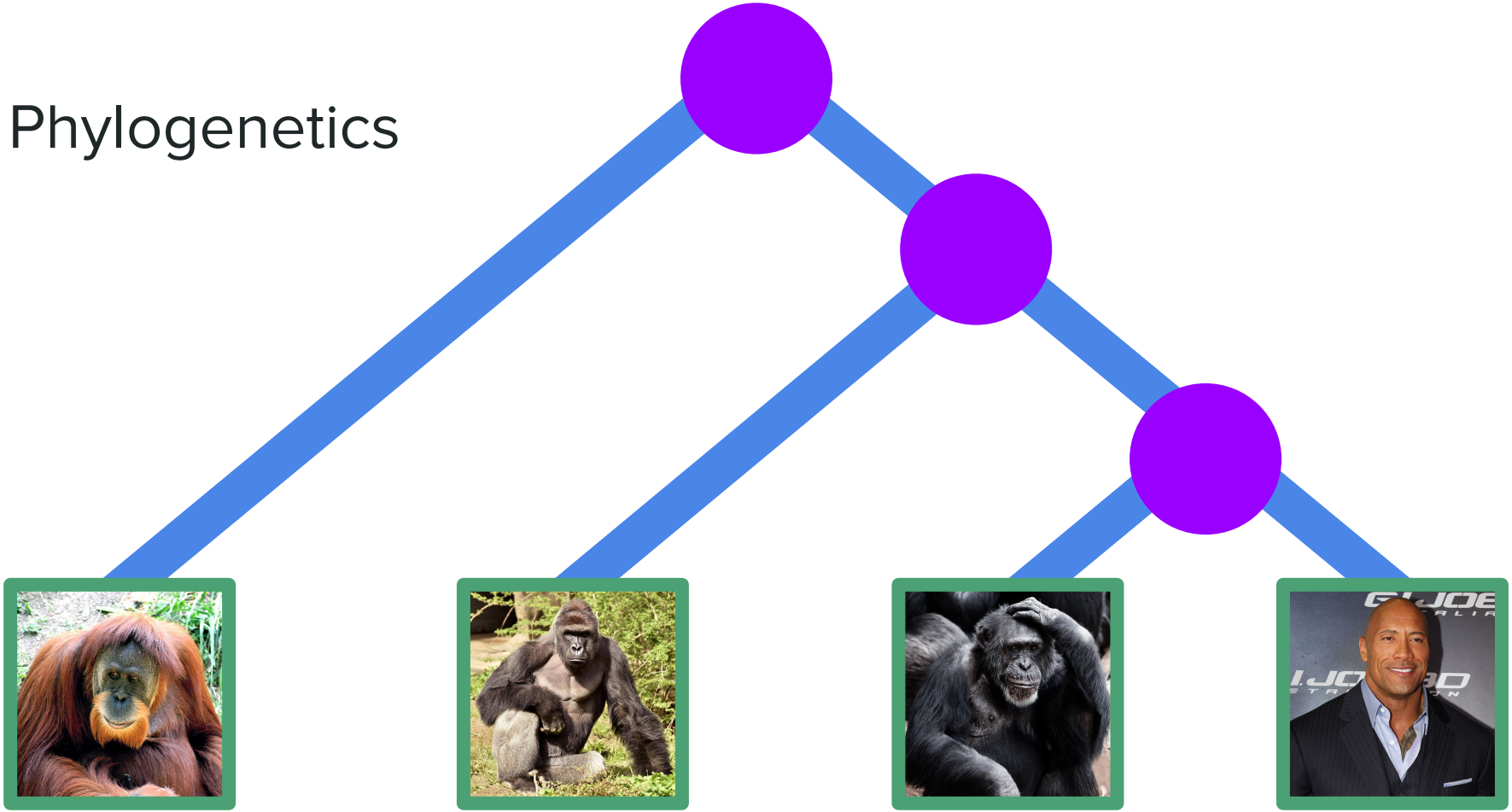
- <u>Computational Problem</u>: Given a list of strings *reads*, find the shortest superstring of *reads*

Phylogenetics

Phylogenetics

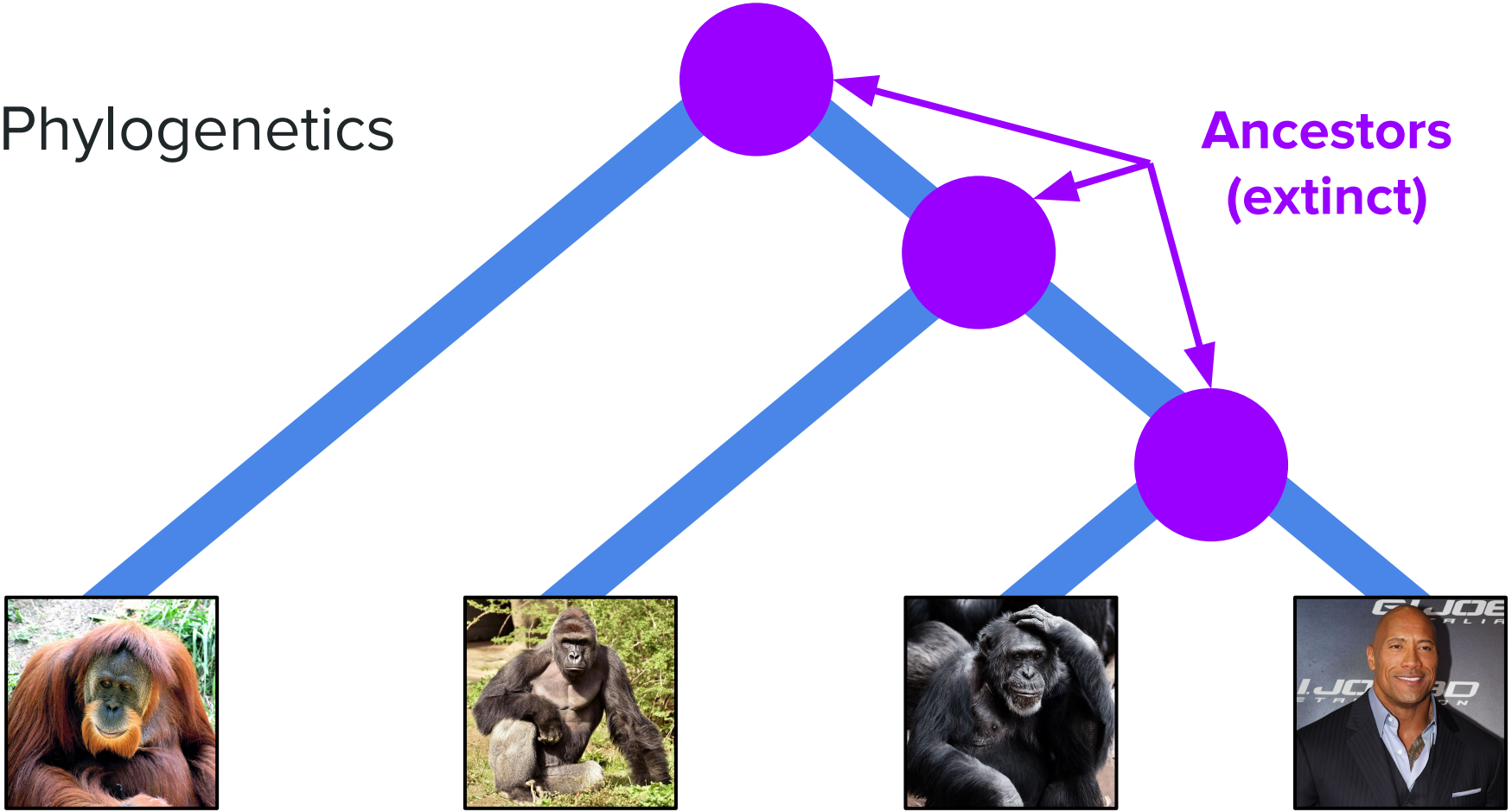


Phylogenetics

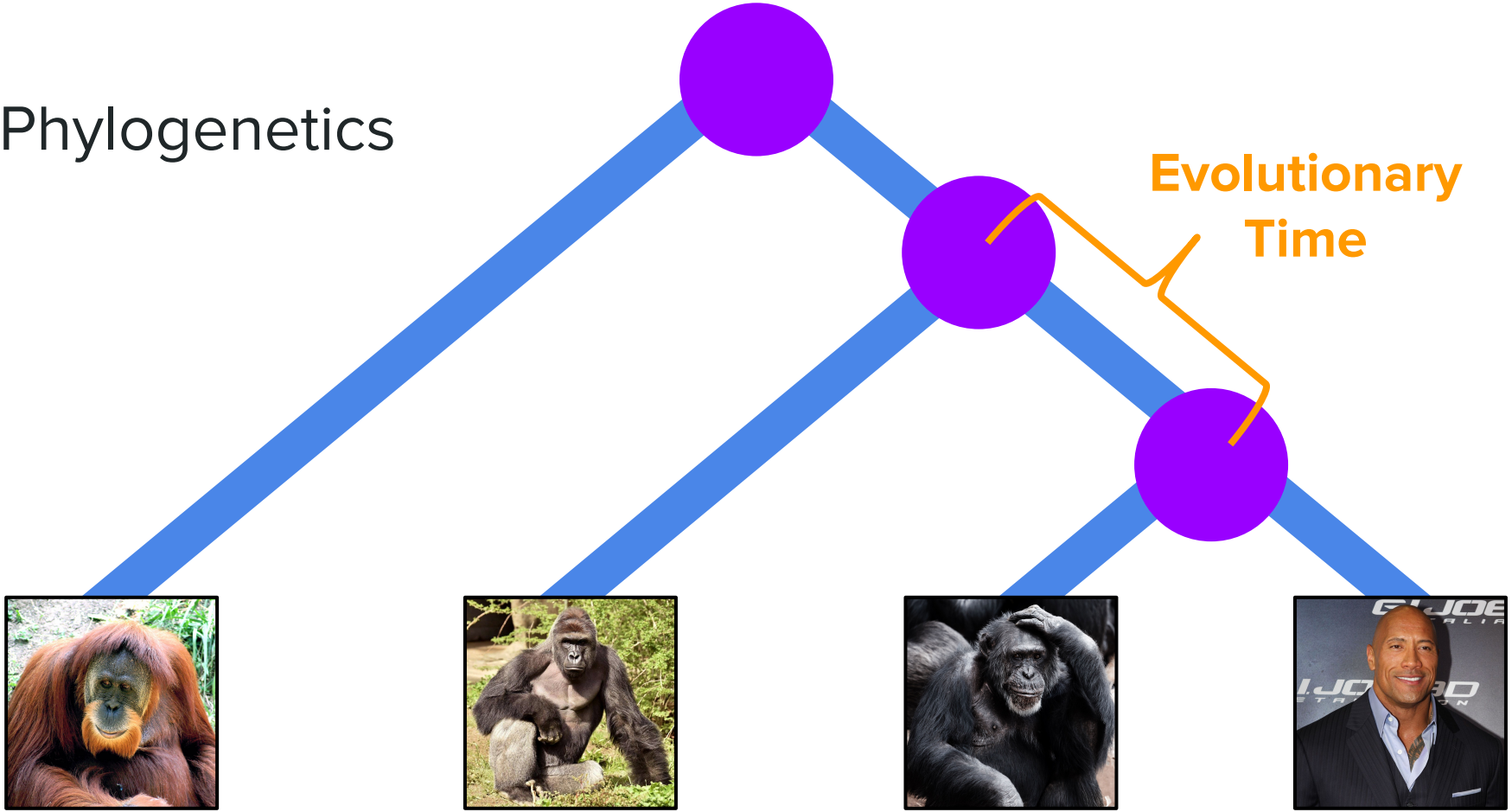


Present-Day Species

Phylogenetics



Phylogenetics



Models of Evolution

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  - Are some sequences more likely to be observed (e.g. fitness)?

Phylogenetic Inference

- Can we somehow reconstruct the evolutionary history of species based solely on their sequences?

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Phylogenetic Inference

- Can we somehow reconstruct the evolutionary history of species based solely on their sequences?
  - Raw Sequences ➔ Multiple Sequence Alignment ➔ Tree
- <u>Maximum Likelihood</u>: Given a **multiple sequence alignment** and a **model** of (sequence evolution), find the tree that maximizes the "likelihood function" (i.e., probability of observing the alignment given the tree)

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- We started with some basic molecular biology review
- We then introduced multiple important biological problems and discussed their bioinformatics computational problem formulation
- Bioinformatics = BIG data!
  - We need efficient algorithms
  - **We need optimized implementations of these algorithms**