# CS 466 Introduction to Bioinformatics Lecture 1

Mohammed El-Kebir August 26, 2020



#### Course Staff

#### **Instructor:**

- Mohammed El-Kebir (melkebir)
- Office hours: Wednesdays, 3:15-4:15pm via Zoom



#### Zoom:

• https://illinois.zoom.us/j/93763998549

Developing combinatorial algorithms to study all stages of cancer progression.

#### TA:

- Sarah Christensen (sac2), office hours: Mondays, 3-4pm via Zoom
- Wesley Wei Qian (weiqian3), office hours: Fridays, 9-10am via Zoom

### Course Organization

#### **Course website:**

www.el-kebir.net/teaching/cs466

#### **Syllabus:**

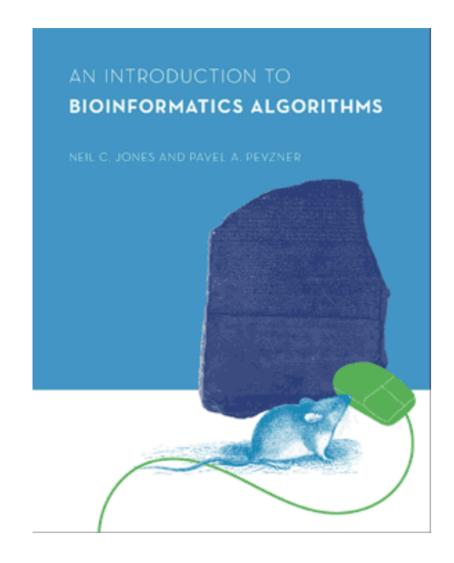
- Prerequisites: CS 225 and its prerequisites
- Textbook

#### **Grading:**

- 5 written/programming assignments
- Midterm
- Final
- Research project

#### Piazza: (please sign up)

https://piazza.com/illinois/fall2020/cs466



### Course Objectives

#### Learn:

- Learn underlying ideas of common algorithms in bioinformatics.
- Learn to translate a biological problem into a computational problem.
- Learn to read scientific papers, propose and conduct independent research.

#### **Not learn:**

- Will not learn to run popular bioinformatics packages.
- Will not learn how to program.

### Homework Assignments

- 5 homework assignments
- Each homework assignment is a combination of written/programming exercises
- LaTeX highly recommended for homework assignments
- Python for programming exercises

#### Late policy:

- Students may request one 3-day extension in the semester for full credit
- Late submission within 3 days 80%

### Primer on Molecular Biology

Molecular Biology is the field of biology that studies the composition, structure and interactions of cellular molecules – such as nucleic acids and proteins – that carry out the biological processes essential for the cell's functions and maintenance.

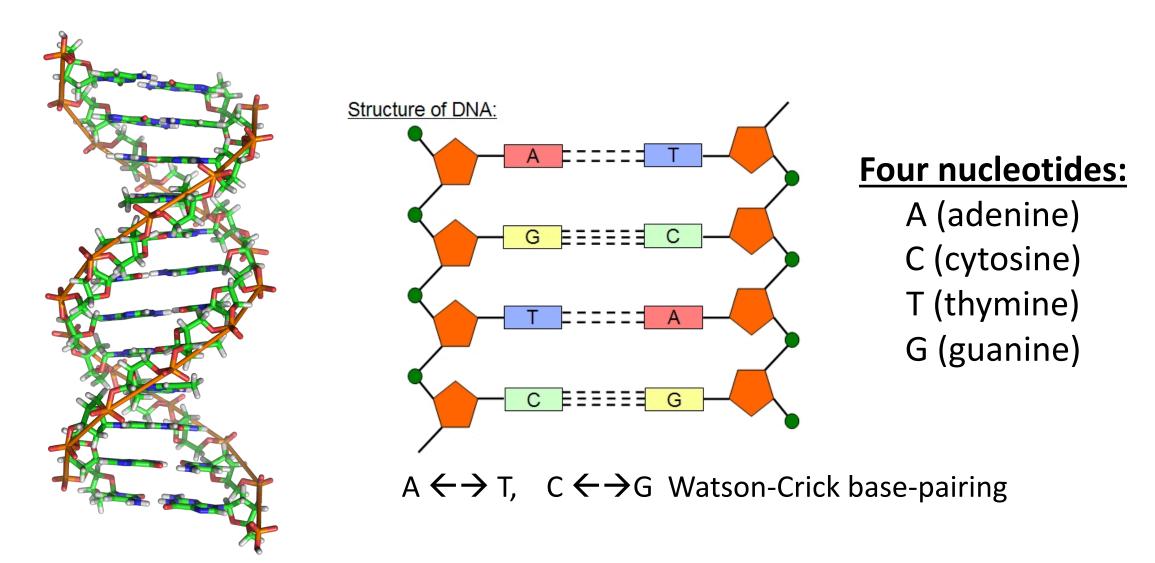
https://www.nature.com/subjects/molecular-biology

#### **Cellular molecules:**

- 1. DNA
- 2. RNA
- 3. Protein

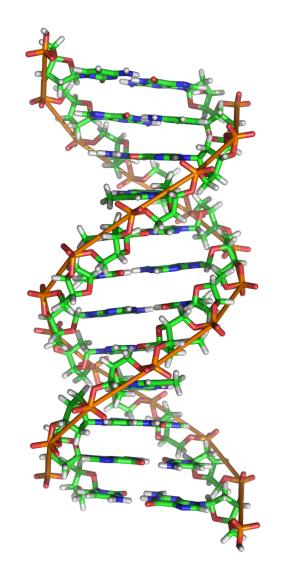
#### DNA

Each strand composed of sequence of covalently bonded nucleotides (bases).



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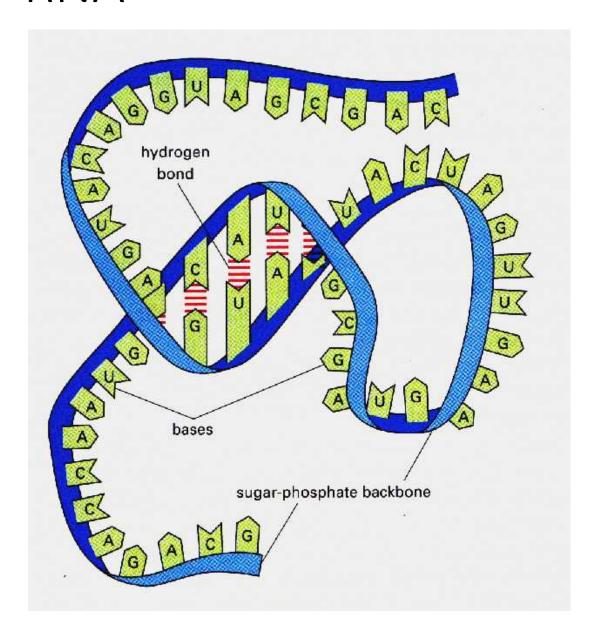


Pair of strings from 4-character alphabet

5' ...ACGTGACTGAGGACCGTG
CGACTGAGACTGACTGGGT
CTAGCTAGACTACGTTTTA
TATATATATATACGTCGTCGT
ACTGATGACTAGATTACAG
TGATTTTAAAAAAAATATT... 3'

Single string from 4-character alphabet

#### RNA



#### Single-stranded

- A (adenine)
- C (cytosine)
- U (uracil)
- G (guanine)
- Can fold into structures due to base complementarity.

$$A \leftarrow \rightarrow U$$
,  $C \leftarrow \rightarrow G$ 

Comes in many flavors:

mRNA, rRNA, tRNA, tmRNA, snRNA, snoRNA, scaRNA, aRNA, asRNA, piwiRNA, etc.

#### Protein

 String of amino acids: 20 letter alphabet

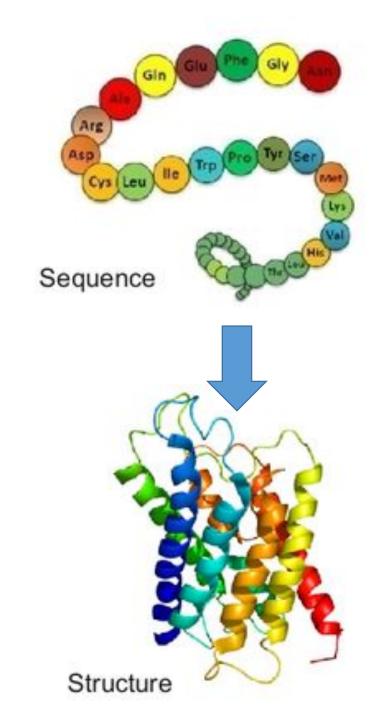
...DTIGDWNSPSFFGIQLVSSVHT
TLWYRENAFPVLGGFSWLSWFNW
HNMGYYYPVYHIGYPMIRCGTHL
VPMQFAFQSIARSFALVHWNAPM
VLKINPHERQDPVFWPCLYYSVD
IRSMHIGYPMIRCYQA...

Amino Acid	3-Letters	1-Letter
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamic acid	Glu	E
Glutamine	Gln	Q G
Glycine	Gly	G
Histidine	His	Н
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

#### Protein

- String of amino acids: 20 letter alphabet
- Folds into 3D structures to perform various functions in cells





### Primer on Molecular Biology

#### Three fundamental molecules:

#### 1. DNA

Information storage.

#### 2. RNA

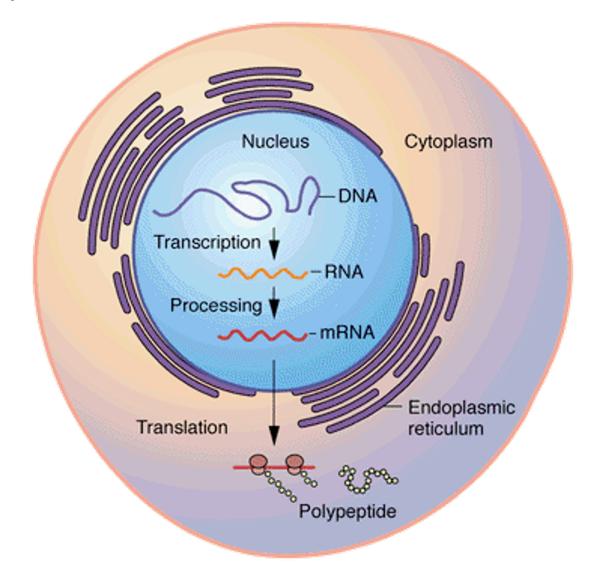
Old view: Mostly a "messenger".

New view: Performs many important

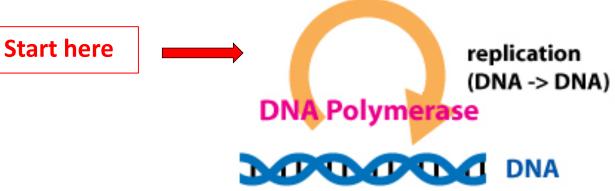
functions.

#### 3. Protein

Perform most cellular functions (biochemistry, signaling, control, etc.)



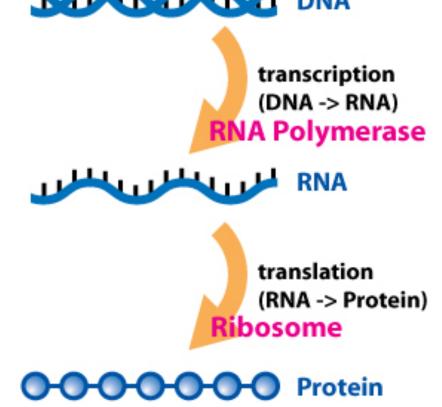
### Central Dogma of Molecular Biology



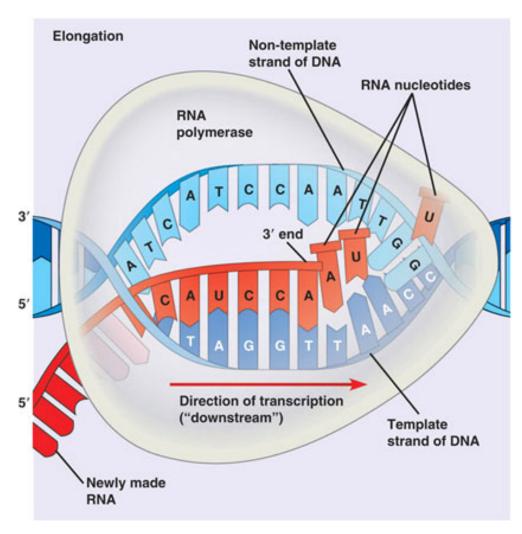
#### DNA $\rightarrow$ RNA $\rightarrow$ Protein:

The process by which cells "read" the genome

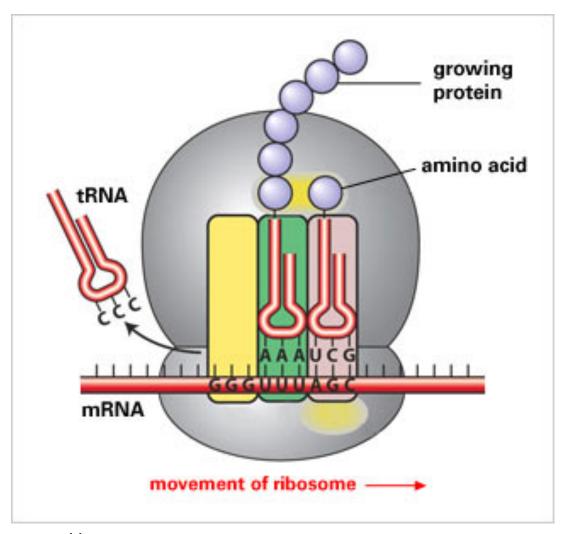
First proposed by Francis Crick in 1956.



### Transcription and Translation

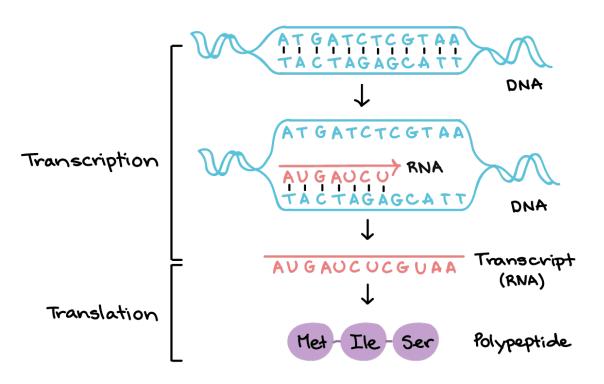


http://dna-rna.net/wp-content/uploads/2011/08/rna-transcription2.jpg

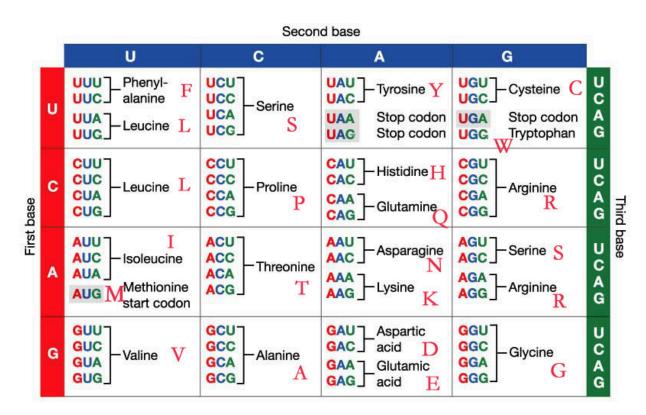


http://www.frontiers-ingenetics.org/en/pictures/translation\_1.jpg

### Transcription and Translation



https://www.khanacademy.org/science/biology/gene-expression-central-dogma/transcription-of-dna-into-rna/a/overview-of-transcription



http://bioinfo.bisr.res.in/project/crat/pictures/codon.jpg

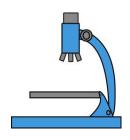
### What is Computational Biology/Bioinformatics?

Computational biology and bioinformatics is an interdisciplinary field that develops and applies computational methods to analyze large collections of biological data, such as genetic sequences, cell populations or protein samples, to make new predictions or discover new biology.

https://www.nature.com/subjects/computational-biology-and-bioinformatics

### Technology and Bioinformatics are Transforming Biology

Until late 20<sup>th</sup> Century





Hypothesis Generation and Validation

21th Century and Beyond

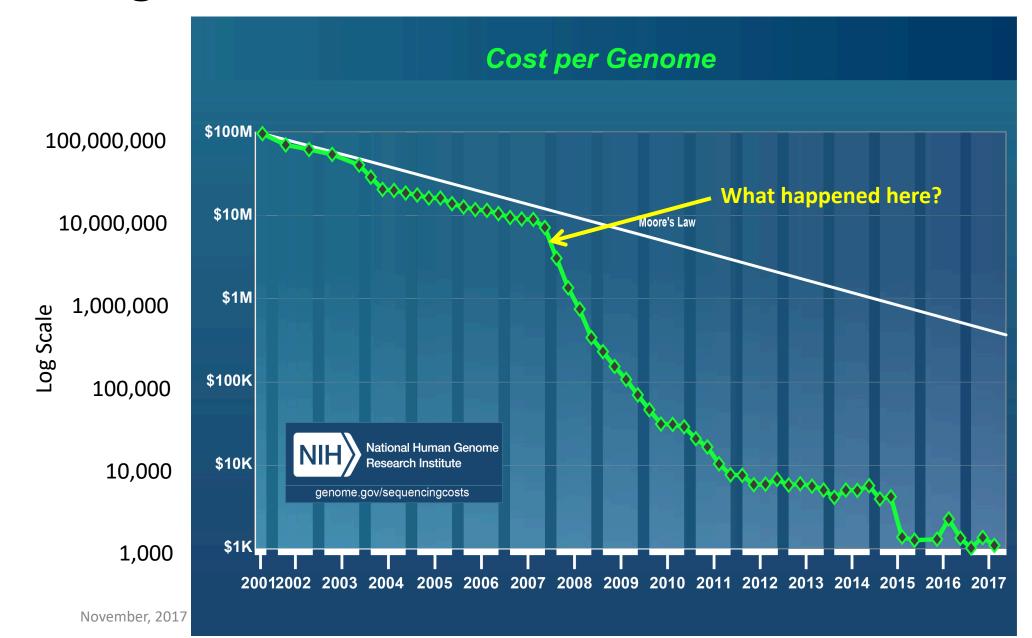


Algorithms

Hypothesis Generation and Validation

High throughput technologies

### A Deluge of Data



### A Deluge of Data



1000 Plant Genomes



Fish-T1K

Transcriptomes of 1000 Fishes







GENOME 10K



International Cancer Genome Consortium



NIH HUMAN MICROBIOME PROJECT



#### THE CANCER GENOME ATLAS

National Cancer Institute
National Human Genome Research Institute

### A Deluge of Data

Biologists propose to sequence the DNA of all life on

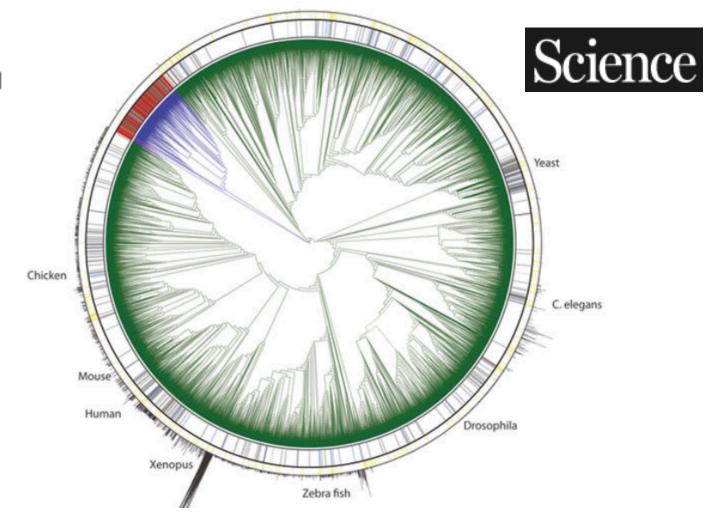
Earth

By Elizabeth Pennisi | Feb. 24, 2017, 1:15 PM

#### Outer ring color scheme:

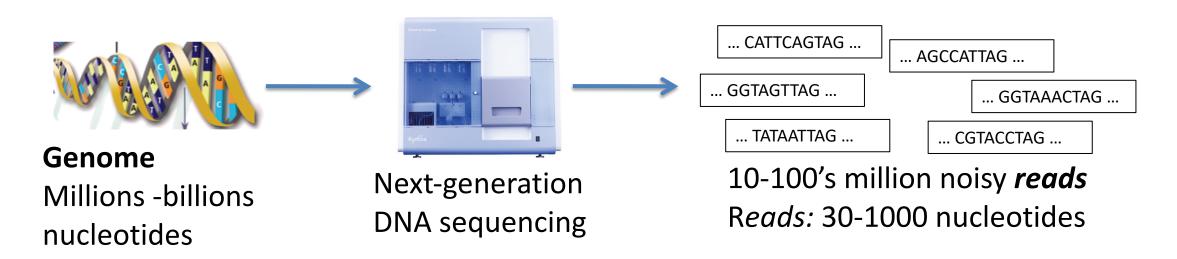
Red: Completed genome

Light Blue: Low resolution genome



#### Question: What does it mean that we can sequence a genome?

## No technology exists that can sequence a complete (human) genome from end to end!



Making sense of this data absolutely requires the use and development of algorithms!

### Why Study Computational Biology?

#### Interdisciplinary

Biology

**Computer Science** 

**Mathematics** 

**Statistics** 

= FUN!



Why choose just 1?

#### **Best Jobs**

- 1. Actuary
- 2. Audiologist
- 3. Mathematician
- 4. Statistician
- 5. Biomedical Engineer
- 6. Data Scientist
- 7. Dental Hygienist
- 8. Software Engineer
- 9. Occupational Therapist
- 10. Computer Systems Analyst

#### **Worst Jobs**

- 200. Newspaper reporter
- 199. Lumberjack
- 198. Enlisted Military
- Personnel
- 197. Cook
- 196. Broadcaster
- 195. Photojournalist
- 194. Corrections Officer
- 193. Taxi Driver
- 192. Firefighter
- 191. Mail Carrier

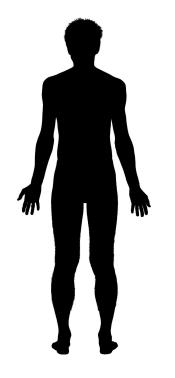


**Donald Knuth**Professor emeritus of Computer Science at Stanford University
Turing Award winner
"father of the analysis of algorithms."

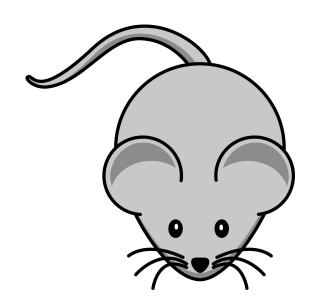
"I can't be as confident about computer science as I can about biology. Biology easily has 500 years of exciting problems to work on. It's at that level."

### Course Topic #1: Sequence Alignment

#### **Question**: How do we compare two genes/genomes?



VS.



**Human Genome:** 

...ACTCGACTGAGAGGATTTCGAGCATGA...

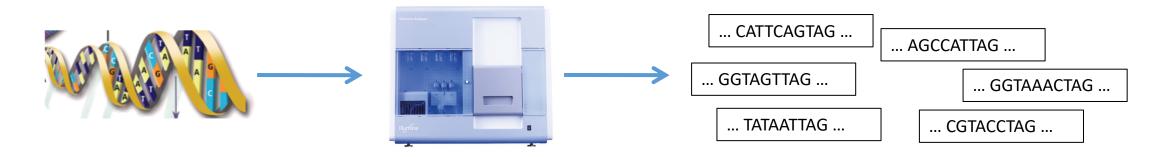
 $\approx 3.2 \times 10^9 \text{ bp}$ 

Mouse Genome:

...ACTCAACTGAGATTCGAGCTTCAATGA...

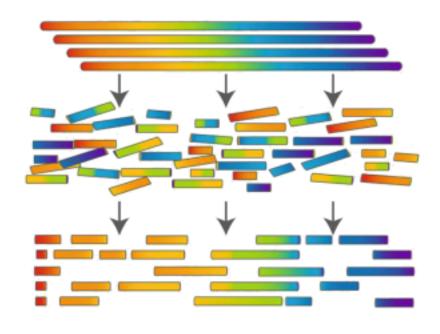
 $\approx 2.8 \times 10^9 \text{ bp}$ 

### Course Topic #2: Genome Assembly



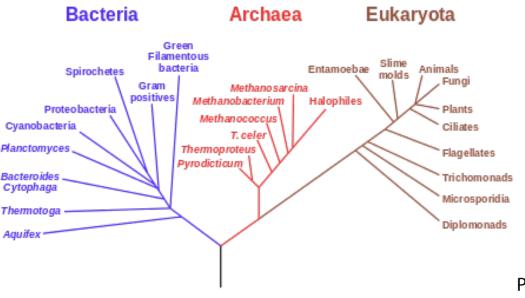
#### Question: How do we put all the pieces back together?





### Course Topic #3: Phylogenetics

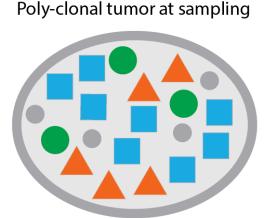
#### Phylogenetic Tree of Life

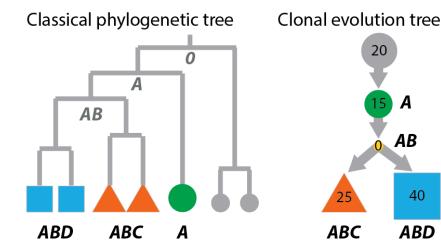


Question: Can we reconstruct the evolutionary history of different species?

https://en.wikipedia.org/wiki/Phylogenetic tree

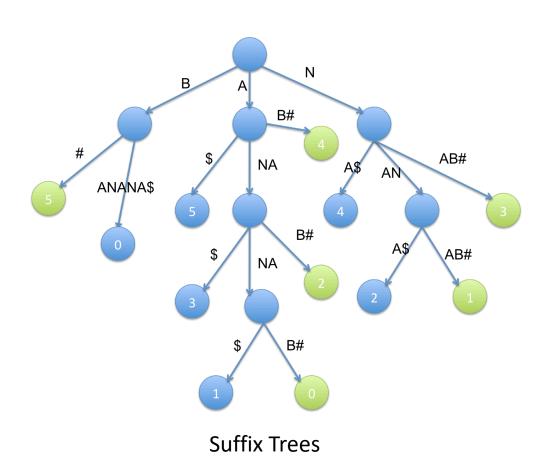
Question: Can we recover how a tumor has evolved overtime?





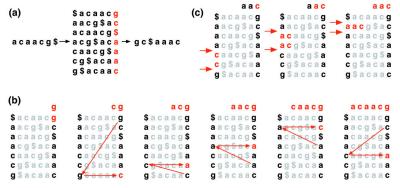
ABD

### Course Topic #4: Pattern Matching



**Question:** How do we start to make sense of all these sequences?

#### **Burrows Wheeler Transform**



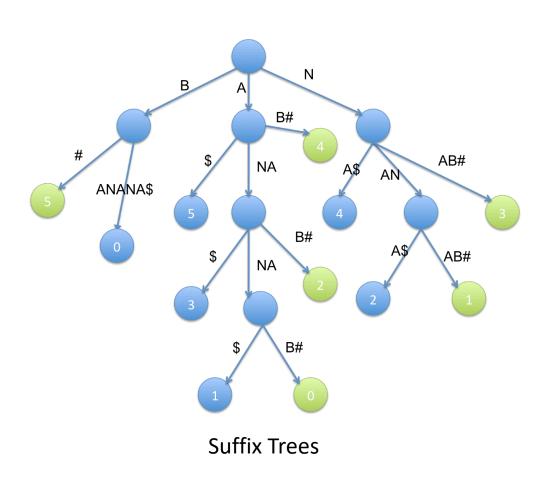
http://www.genomebiology.com/2009/10/3/R25/figure/F1?highres=y

#### CAP Binding Sites

Motif Finding

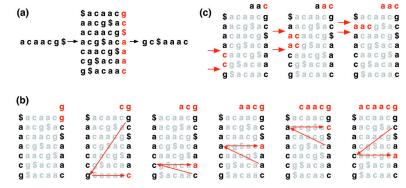


### Course Topic #4: Pattern Matching



**Question:** How do we start to make sense of all these sequences?





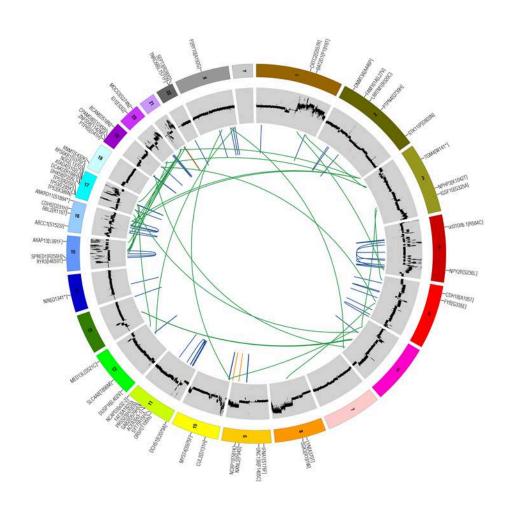
http://www.genomebiology.com/2009/10/3/R25/figure/F1?highres=y

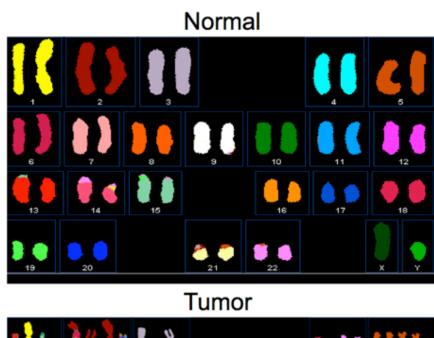


Motif Finding



### Course Topic #5: Cancer Genomics







**Question:** How can we analyze available data to determine what drives tumor growth and how to treat or prevent it?

### Course Topics

- 1. Sequence alignment 'How do we compare two genes/genomes?'
- 2. Genome assembly 'How do we put all the pieces back together?'
- 3. Phylogenetics 'What is the evolutionary history of different sequences?'
- 4. Pattern matching 'How do we start to make sense out of all these sequences?'
- 5. Cancer genomics 'How do we identify what drives tumor growth and how to treat/prevent it?'

### Course Topics

- 1. Sequence alignment Dynamic programming: edit distance
- 2. Genome assembly Graphs: de Bruijn graph, Eulerian and Hamiltonian paths
- 3. Phylogenetics
  Trees and distances: distance matrices, neighbor joining, hierarchical clustering. Phylogenies: Sankoff/Fitch algorithms, perfect phylogeny and compatibility
- 4. Pattern matching Suffix trees/arrays. Burrows-Wheeler transform, Hidden Markov Models (HMMs)
- 5. Cancer genomics Cancer phylogenies: Integer linear optimization and graph algorithms

### Problem != Algorithm

#### **Problem** $\Pi$ with instance X and solution set $\Pi(X)$ :

- Decision problem:
  - Is  $\Pi(X) = \emptyset$ ?
- Optimization problem:
  - Find  $y^* \in \Pi(X)$  s.t.  $f(y^*)$  is optimum.
- Counting problem:
  - Compute  $|\Pi(X)|$ .
- Sampling problem:
  - Sample uniformly from  $\Pi(X)$ .
- Enumeration problem:
  - Enumerate all solutions in  $\Pi(X)$

#### Algorithms:

Set of instructions for solving problem.

- Exact
- Heuristic

### The Change Problem

• Suppose we have three coins:



• What is the minimum number of coins needed to make change for *M* cents?

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**Change Problem:** Given amount  $M \in \mathbb{N} \setminus \{0\}$  and coins  $\mathbf{c} = (c_1, \dots, c_n) \in \mathbb{N}^n$  s.t.  $c_n = 1$  and  $c_i \geq c_{i+1}$  for all  $i \in [n-1] = \{1, \dots, n-1\}$ , find  $\mathbf{d} = (d_1, \dots, d_n) \in \mathbb{N}^n$  s.t. (i)  $M = \sum_{i=1}^n c_i d_i$  and (ii)  $\sum_{i=1}^n d_i$  is minimum

### Idea #1: Choose largest coin possible

GreedyChange( $M, c_1, ..., c_n$ )

- 1. for  $i \leftarrow 1$  to n
- 2.  $d_i \leftarrow \lfloor M/c_i \rfloor$
- 3.  $M \leftarrow M d_i c_i$

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Is this a good algorithm? Two properties of a good algorithm:

# Idea #1: Choose largest coin possible

GreedyChange( $M, c_1, ..., c_n$ )

- 1. for  $i \leftarrow 1$  to n
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- 3.  $M \leftarrow M d_i c_i$

Is this a good algorithm? Two properties of a good algorithm:

**Correctness:** gives the correct output for any input.

- Works for c = (5, 3, 1) and M = 8.
- But what about c = (5, 4, 1) and M = 8?

**Efficient:** running time of the algorithm does not increase too rapidly with input size.

## Idea #2: When in doubt, apply brute force...

**Change Problem:** Given amount  $M \in \mathbb{N} \setminus \{0\}$  and coins  $\mathbf{c} = (c_1, \dots, c_n) \in \mathbb{N}^n$  s.t.  $c_n = 1$  and  $c_i \ge c_{i+1}$  for all  $i \in [n-1] = \{1, \dots, n-1\}$ , find  $\mathbf{d} = (d_1, \dots, d_n) \in \mathbb{N}^n$  s.t. (i)  $M = \sum_{i=1}^n c_i d_i$  and (ii)  $\sum_{i=1}^n d_i$  is minimum

Correct? yes
Efficient? no

- Check all possible solutions:
  - 11 = 5 + 5 + 1
  - 11 = 5 + 4 + 1 + 1
  - 11 = 5 + 1 + 1 + 1 + 1 + 1 + 1
  - 11 = 4 + 4 + 1 + 1 + 1

• ...

ExhaustiveChange( $M, c_1, ..., c_n$ )

- 1. for  $(d_1,\ldots,d_n)\in\{0,\ldots,\lfloor M/c_1\rfloor\}\times\ldots\times\{0,\ldots,\lfloor M/c_n\rfloor\}$
- **2.** if  $\sum_{i=1}^{n} c_i d_i = M$ 
  - **8.** return  $(d_1,\ldots,d_n)$



Value	1	2	3	4	5	6	7	8	9	10	11
Min # coins	?	?	?	?	?	?	?	?	?	?	?
-3											

### **Optimal substructure:**

Optimal solution is obtained from optimal solutions of subproblems



Value	1	2	3	4	5	6	7	8	9	10	11
Min # coins	?	?	?	?	?	?	?	?	?	?	?
							×	5	-3		

- This example can be expressed using a recurrence relation
- Let minNumCoins(M) be the minimum number of coins to make change for M cents

$$\min \text{NumCoins}(M) = \min \begin{cases} \min \text{NumCoins}(M-1) + 1, \\ \min \text{NumCoins}(M-3) + 1, \\ \min \text{NumCoins}(M-5) + 1. \end{cases}$$

```
Change Problem: Given amount M \in \mathbb{N} \setminus \{0\} and coins \mathbf{c} = (c_1, ..., c_n) \in \mathbb{N}^n s.t. c_n = 1 and c_i \ge c_{i+1} for all i \in [n-1] = \{1, ..., n-1\}, find \mathbf{d} = (d_1, ..., d_n) \in \mathbb{N}^n s.t. (i) M = \sum_{i=1}^n c_i d_i and (ii) \sum_{i=1}^n d_i is minimum
```

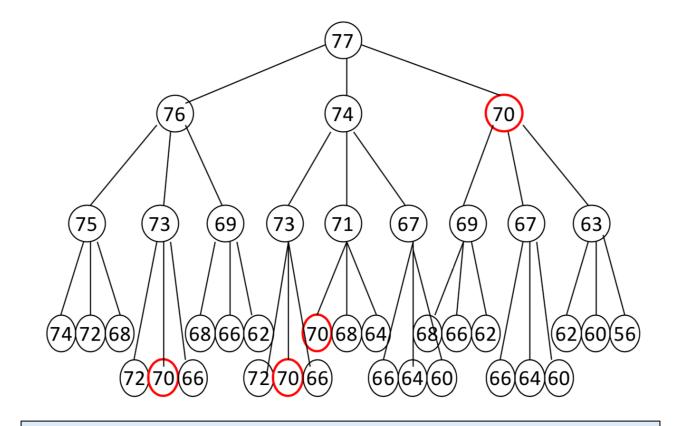
```
\min \text{NumCoins}(M) = \min \begin{cases} \min \text{NumCoins}(M - c_1) + 1, \\ \min \text{NumCoins}(M - c_2) + 1, \\ \dots \\ \min \text{NumCoins}(M - c_n) + 1. \end{cases}
```

Given coins  $\mathbf{c} = (1, 3, 7)$  and amount M = 77, find  $\mathbf{d} = (d_1, ..., d_n) \in \mathbb{N}^n$  such that: (i)  $M = \sum_{i=1}^n c_i d_i$  and (ii)  $\sum_{i=1}^n d_i$  is minimum.

```
\min \text{NumCoins}(77-1)+1,
\min \text{NumCoins}(77) = \min \langle \min \text{NumCoins}(77-3) + 1,
                                \min \text{NumCoins}(77-7) + 1,
                                 minNumCoins(76 - 1) + 1,
\min \text{NumCoins}(76) = \min \langle \min \text{NumCoins}(76 - 3) + 1,
                                \min \text{NumCoins}(76-7)+1
 \min \text{NumCoins}(7) = 1
 \min \text{NumCoins}(3) = 1
 \min \text{NumCoins}(1) = 1
```

RecursiveChange( $M, c_1, ..., c_n$ )

- **1.** if M = 0
- **2.** return 0
- 3. bestNumCoins  $\leftarrow \infty$
- **4.** for  $i \leftarrow 1$  to n
- 5. if  $M \ge c_i$
- 6. numCoins  $\leftarrow$ RecursiveChange $(M - c_i, c_1, ..., c_n)$
- 7. if numCoins + 1 < bestNumCoins
- 8. bestNumCoins  $\leftarrow$  numCoins + 1
- 9. return bestNumCoins

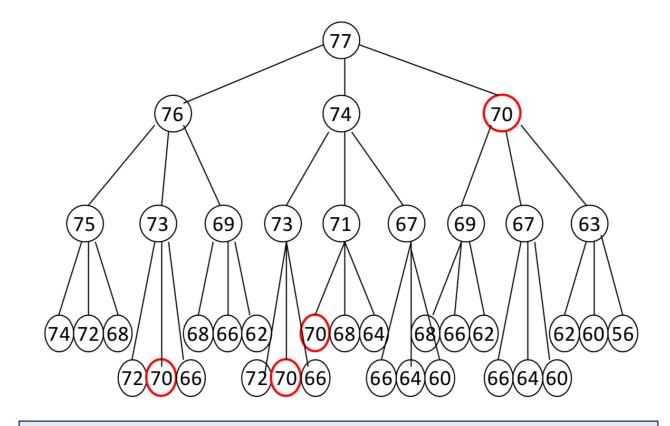


#### **Correct but inefficient:**

Same subproblem is solved many times!

RecursiveChange( $M, c_1, ..., c_n$ )

- **1.** if M = 0
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- 3. bestNumCoins  $\leftarrow \infty$
- **4.** for  $i \leftarrow 1$  to n
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- 7. if numCoins + 1 < bestNumCoins
- 8. bestNumCoins  $\leftarrow$  numCoins + 1
- 9. return bestNumCoins



#### **Correct but inefficient:**

Same subproblem is solved many times!

#### **Solutions:**

- Remember previously computed values: memoization
  - Bottom up computation: dynamic programming

Fill in table "bottom up": from smallest to largest.

$$\mathbf{c} = (5), 3, 1)$$

Value	1	2	3	4	5	6	7	8	9	10	11
Min # coins	1		1		1						

$$\min \text{NumCoins}(M) = \min \begin{cases} \min \text{NumCoins}(M-1)+1, \\ \min \text{NumCoins}(M-3)+1, \\ \min \text{NumCoins}(M-5)+1. \end{cases}$$

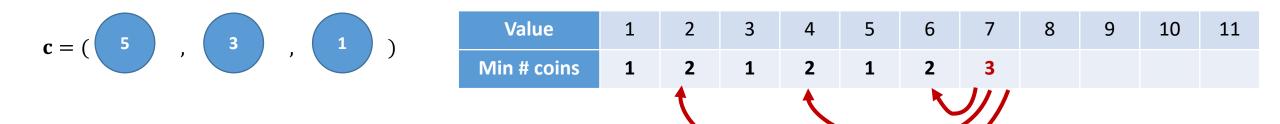
Only one coin is needed to make change for the values 1, 3 and 5

Fill in table "bottom up": from smallest to largest.

$$\min \text{NumCoins}(M) = \min \begin{cases} \min \text{NumCoins}(M-1) + 1, \\ \min \text{NumCoins}(M-3) + 1, \\ \min \text{NumCoins}(M-5) + 1. \end{cases}$$

Two coins are needed to make change for the values 2, 4 and 6

Fill in table "bottom up": from smallest to largest.



$$\min \text{NumCoins}(M) = \min \begin{cases} \min \text{NumCoins}(M-1) + 1, \\ \min \text{NumCoins}(M-3) + 1, \\ \min \text{NumCoins}(M-5) + 1. \end{cases}$$

Three coins are needed to make change for the value 7

Fill in table "bottom up": from smallest to largest.



$$\min \text{NumCoins}(M) = \min \begin{cases} \min \text{NumCoins}(M-1) + 1, \\ \min \text{NumCoins}(M-3) + 1, \\ \min \text{NumCoins}(M-5) + 1. \end{cases}$$

**Optimal substructure:** Optimal solution obtained from optimal subsolutions

11

Fill in table "bottom up": from smallest to largest.

Value	1	2	3	4	5	6	7	8	9	10	11
Min # coins	1	2	1	2	1	2	3	2	3	2	3

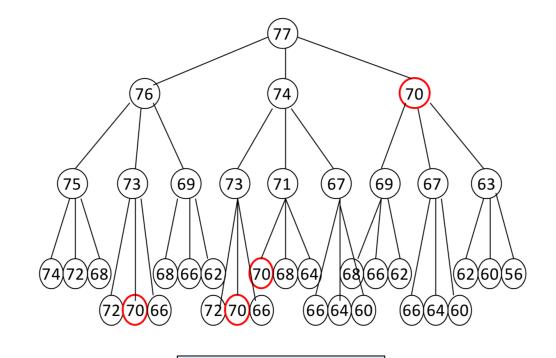
$$\min \text{NumCoins}(M) = \min \begin{cases} \min \text{NumCoins}(M-1) + 1, \\ \min \text{NumCoins}(M-3) + 1, \\ \min \text{NumCoins}(M-5) + 1. \end{cases}$$

**Optimal substructure:** Optimal solution obtained from optimal subsolutions

**Change Problem:** Given amount  $M \in \mathbb{N} \setminus \{0\}$  and coins  $\mathbf{c} = (c_1, ..., c_n) \in \mathbb{N}^n$  s.t.  $c_n = 1$  and  $c_i \ge c_{i+1}$  for all  $i \in [n-1] = \{1, ..., n-1\}$ , find  $\mathbf{d} = (d_1, ..., d_n) \in \mathbb{N}^n$  s.t. (i)  $M = \sum_{i=1}^n c_i d_i$  and (ii)  $\sum_{i=1}^n d_i$  is minimum

```
DPChange(M, c_1, ..., c_n)
```

- 1. for  $m \leftarrow 1$  to M
- **2.** minNumCoins[m]  $\leftarrow \infty$
- 3. for  $i \leftarrow 1$  to n
- **4.** minNumCoins[ $c_i$ ]  $\leftarrow$  1
- 5. for  $m \leftarrow 1$  to M
- 6. for  $i \leftarrow 1$  to n
- 7. if  $m > c_i$
- 8.  $\min \text{NumCoins}[m] \leftarrow \min(1 + \min \text{NumCoins}[m c_i], \min \text{NumCoins}[m])$
- **9.** return minNumCoins[M]



Correct? yes Efficient? yes

## Different algorithm techniques

**Change Problem:** Given amount  $M \in \mathbb{N} \setminus \{0\}$  and coins  $\mathbf{c} = (c_1, ..., c_n) \in \mathbb{N}^n$  s.t.  $c_n = 1$  and  $c_i \ge c_{i+1}$  for all  $i \in [n-1] = \{1, ..., n-1\}$ , find  $\mathbf{d} = (d_1, ..., d_n) \in \mathbb{N}^n$  s.t. (i)  $M = \sum_{i=1}^n c_i d_i$  and (ii)  $\sum_{i=1}^n d_i$  is minimum

Technique	Correct?	Efficient?
Greedy algorithm [GreedyChange]	no	yes
Exhaustive enumeration [ExhaustiveChange]	yes	no
Recursive algorithm [RecursiveChange]	yes	no
Dynamic programming [DPChange]	yes	yes

## Summary

- DNA, RNA and proteins are sequences
  - Central dogma of molecular biology: DNA -> RNA -> protein
- Problem != algorithm
- Different algorithm techniques
  - Greedy
  - Exhaustive search/brute force
  - Recursive algorithm
  - Dynamic programming algorithm
- Reading:
  - "Biology for Computer Scientists" by Lawrence Hunter (http://www.el-kebir.net/teaching/CS466/Hunter\_BIO\_CS.pdf)
  - Jones and Pevzner: Chapters 2.1, 2.3, 2.4, 6.2

### Sources

- CS 362 by Layla Oesper (Carleton College)
- CS 1810 by Ben Raphael (Brown/Princeton University)
- An Introduction to Bioinformatics Algorithms book (Jones and Pevzner)