CS 598MEB
Computational Cancer Genomics
Lecture 1

Mohammed El-Kebir

January 21, 2020

Course Staff

Instructor:

- Mohammed El-Kebir (melkebir)
- Office hours: Tuesdays, 3:15-4:15pm

Developing combinatorial algorithms for studying all stages of cancer progression.

Course Information

Course website:

- www.el-kebir.net/teaching/cs598MEB

Piazza: (please sign up)

- https://piazza.com/illinois/spring2020/cs598meb

Description:

- This course focuses on **recent algorithmic methods in cancer genomics**, including somatic variant calling, phylogeny inference and identification of driver mutations. Students will study the underlying principles of these methods and the application of these methods to cancer genomics data.

Course Objectives

Learn:

- Learn underlying ideas of common algorithms in cancer genomics.
- Learn to translate a biological problem into a computational problem.
- Learn to read and critique scientific papers.
- Learn to propose and conduct independent research.
- Learn to present key ideas of a paper to other people.
- Learn to ask critical questions.

Not learn:

- Will not learn to run popular cancer genomics packages.
- Will not learn how to program.

Grading

- Class participation (20%)
  - Peer reviews
  - Asking questions
- Paper presentation (30%)
- Course project (50%)
  - Proposal
  - Report/paper
  - Presentation

Tentative Course Schedule

Introductory lectures (Jan 21 to Feb 28)

- Molecular biology and cancer biology
- Fundamental algorithms in computational biology
- Algorithms in computational genomics

Paper presentations (Mar 5 to Mar 29)

- Student presentation of research/survey paper

Course projects (Apr 2 to Apr 30)

- Proposal presentation
- Final presentation + report

Paper Presentation

- Each student will present a paper picked by the student. The goal of the presentation is to facilitate a discussion, focusing on:
  - Presenting the biological problem and corresponding computational problem
  - How did the authors solve the problem?
  - Did they manage to answer the original biological question?
  - How can we improve the results? What are future directions?

- The remaining students are required to write a short peer review
  - Summary
  - Major and minor comments
  - Outlook/future directions

Course Project

- 1-2 students per project
- First write a proposal, which will receive feedback from instructor and fellow students
- Then, conduct research and write a paper
- Pick venue (conference/journal) and use LaTeX style for your paper
- Students will anonymously peer review submitted papers using EasyChair (if time permits)

Lecture Outline

- Primer on Molecular Biology
- Primer on Computational Biology
- Primer on Cancer Biology
- Tumor Phylogeny Inference

Reading

- “Biology for Computer Scientists” by Lawrence Hunter (http://www.el-kebir.net/teaching/CS466/Hunter_BIO_CS.pdf)

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.

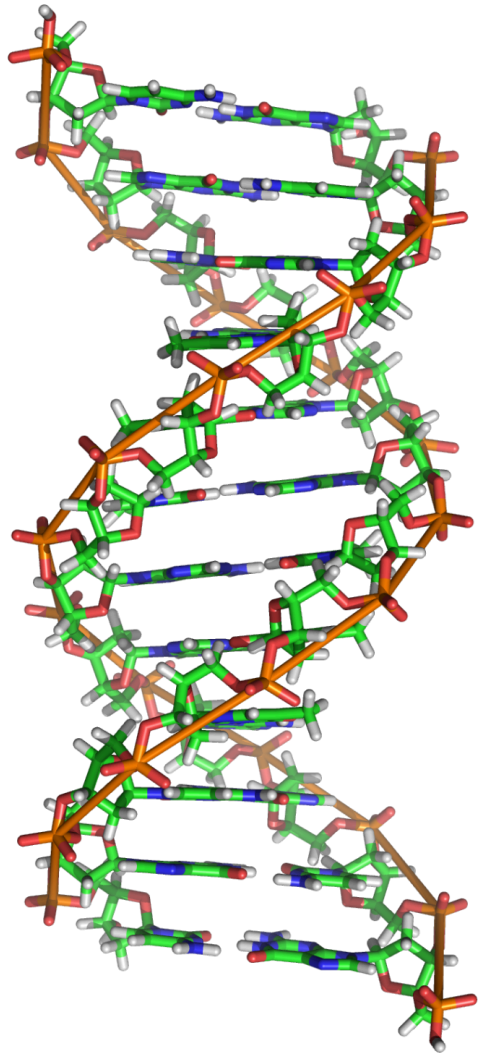
https://www.nature.com/subjects/molecular-biology

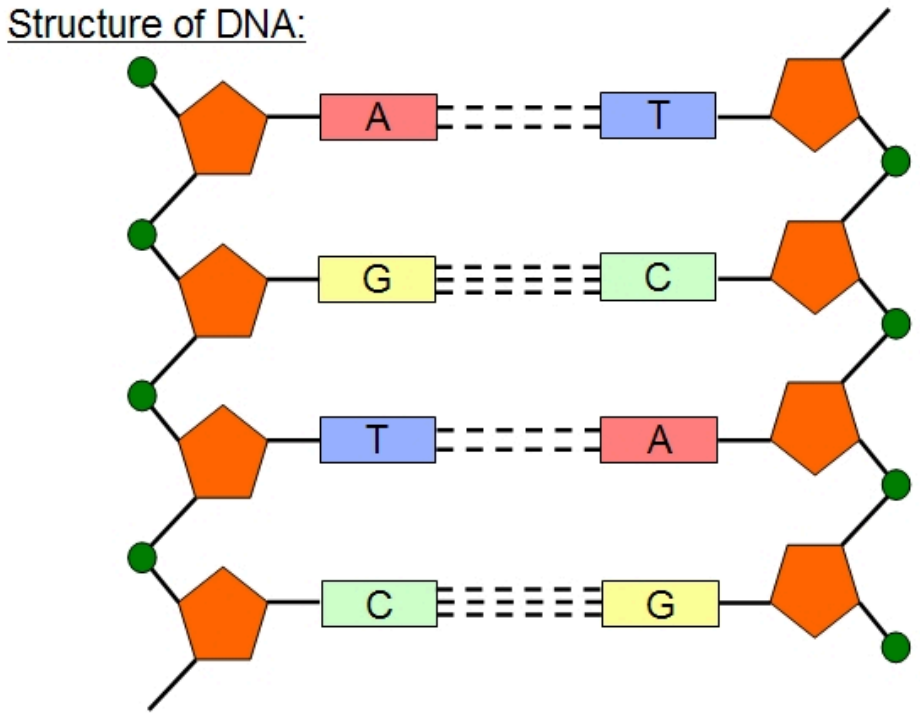
Cellular molecules:

1. DNA
2. RNA
3. Protein

DNA

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





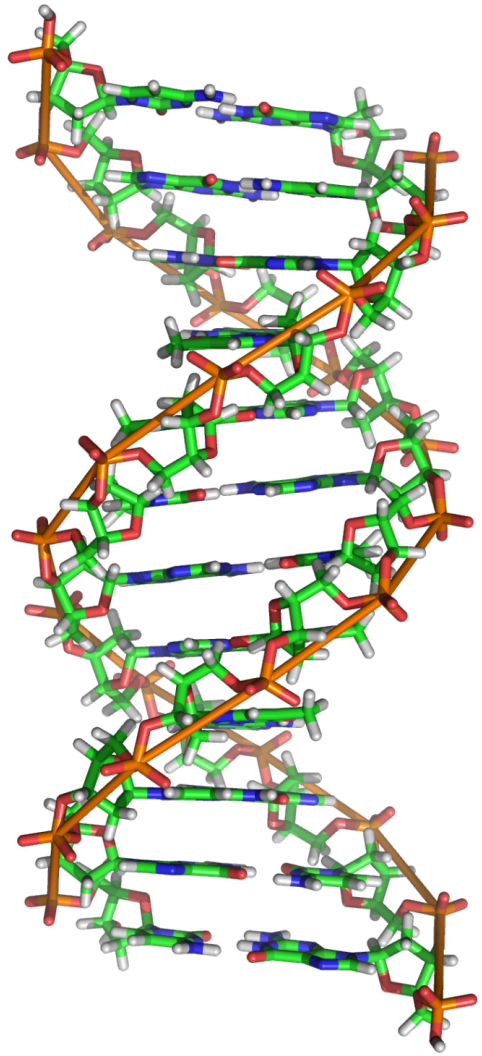
Four nucleotides:

A (adenine)
C (cytosine)
T (thymine)
G (guanine)

A ←→ T, C ←→G Watson-Crick base-pairing

DNA

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



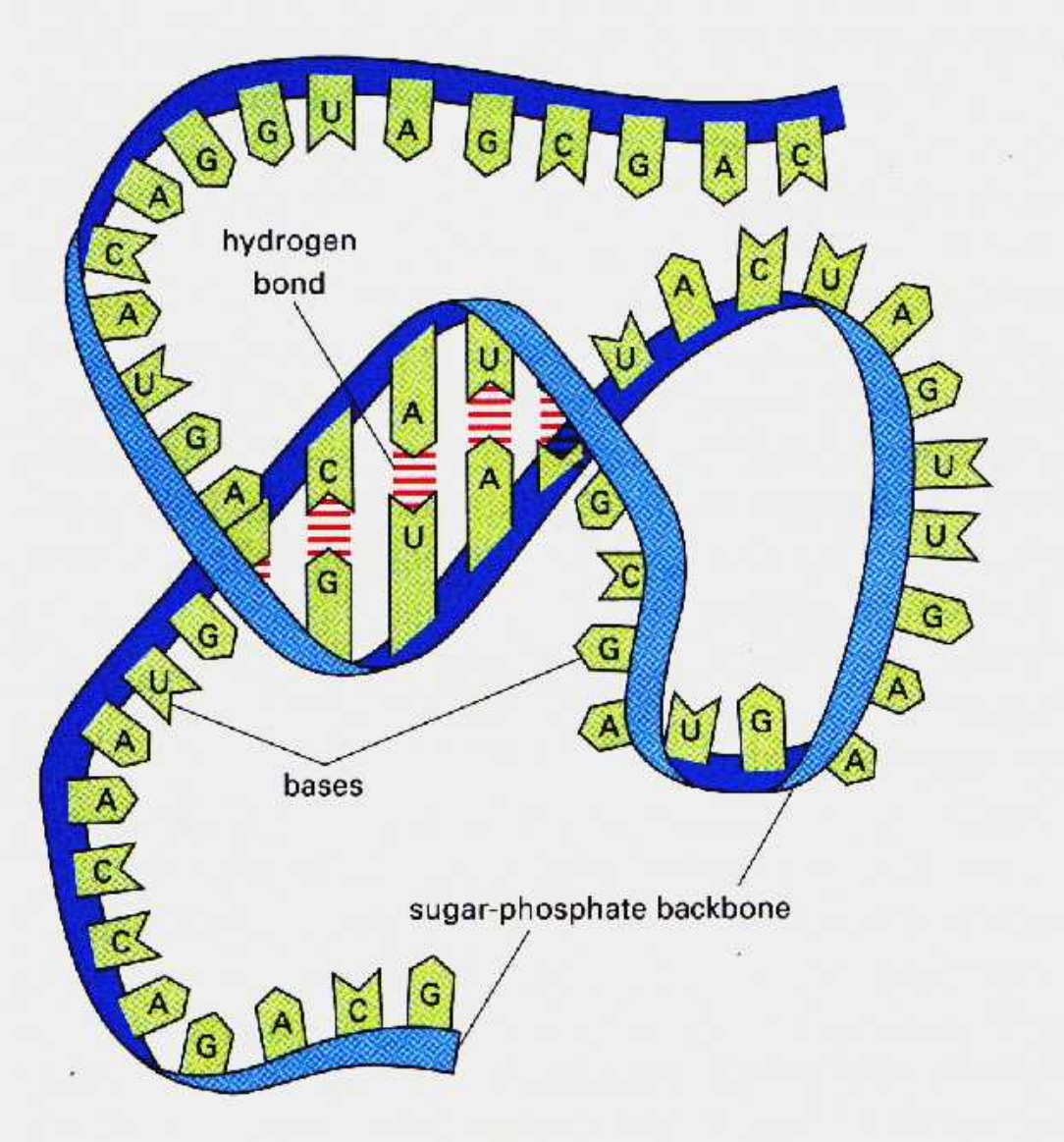
```
5’ …ACGTGACTGAGGACCGTG… 3’
   …|||||||||||||||||||…
3’ …TGCACTGACTCCTGGCAC… 5’
```

Pair of strings from 4 character alphabet

```
5’ …ACGTGACTGAGGACCGTG
   CGACTGAGACTGACTGGGT
   CTAGCTAGACTACGTTTTA
   TATATATATACGTCGTCGT
   ACTGATGACTAGATTACAG
   TGATTTTAAAAAAATATT… 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 ←→ U, C ←→G
- Comes in many flavors:

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

Protein

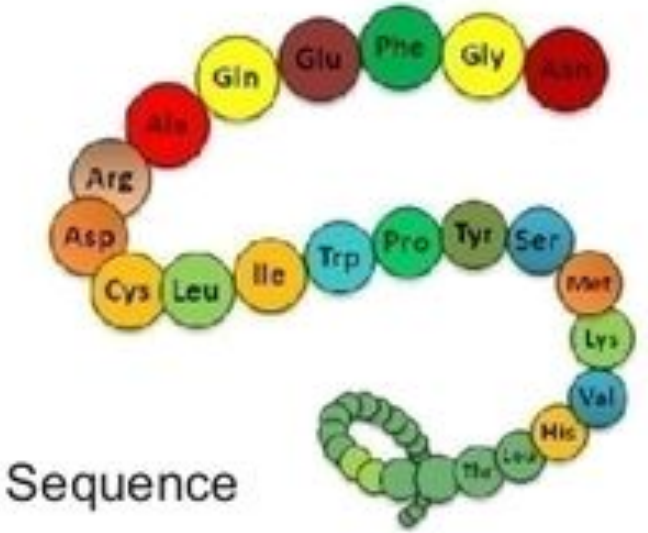
- String of amino acids: 20 letter alphabet

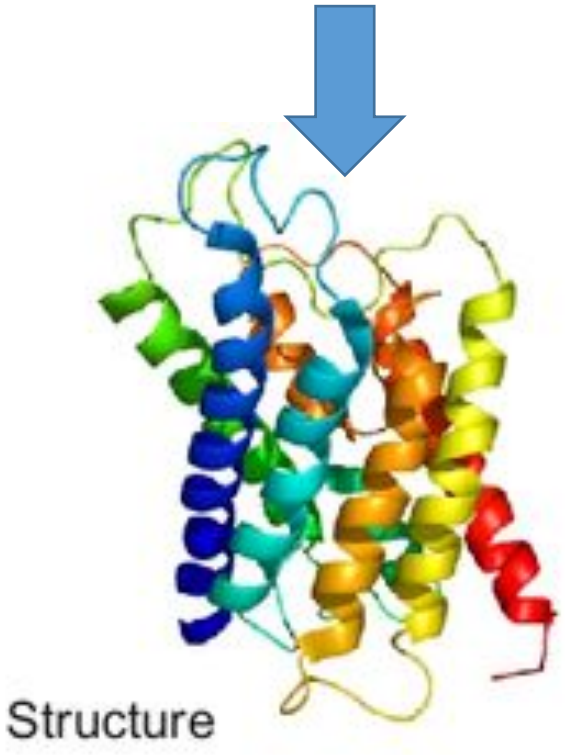
…DTIGDWNSPSFFGIQLVSSVHT
TLWYRENAFPVLGGFSWLSWFNW
HNMGYYYPVYHIGYPMIRCGTHL
VPMQFAFQSIARSFALVHWNAPM
VLKINPHERQDPVFWPCLYYSVD
IRSMHIGYPMIRCYQA…

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
Glycine	Gly	G
Histidine	His	H
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





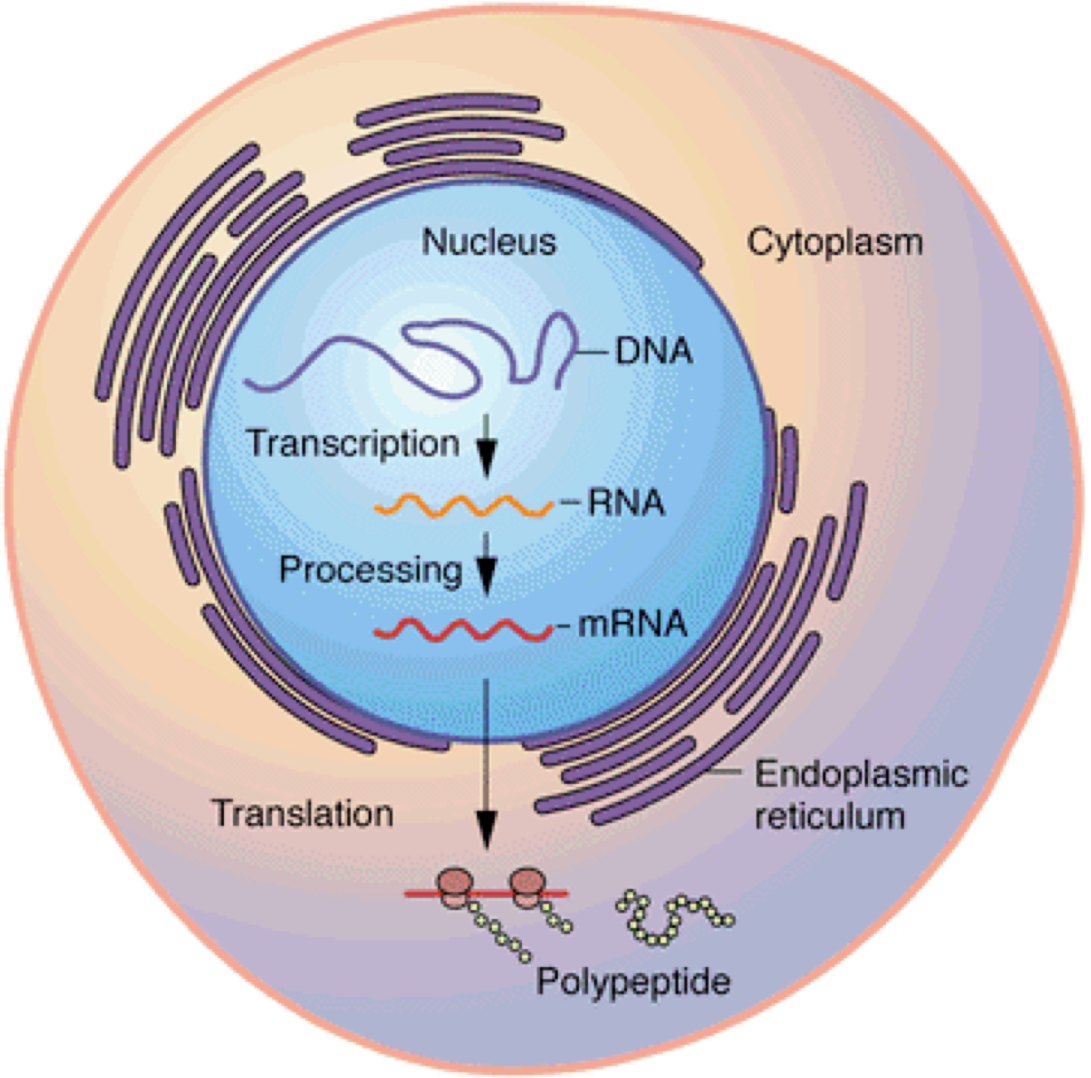
Primer on Molecular Biology

Three fundamental molecules:

1. **DNA**
   Information storage.

2. **RNA**
   Old view: Mostly a “messenger”.
   New view: Performs many important functions.

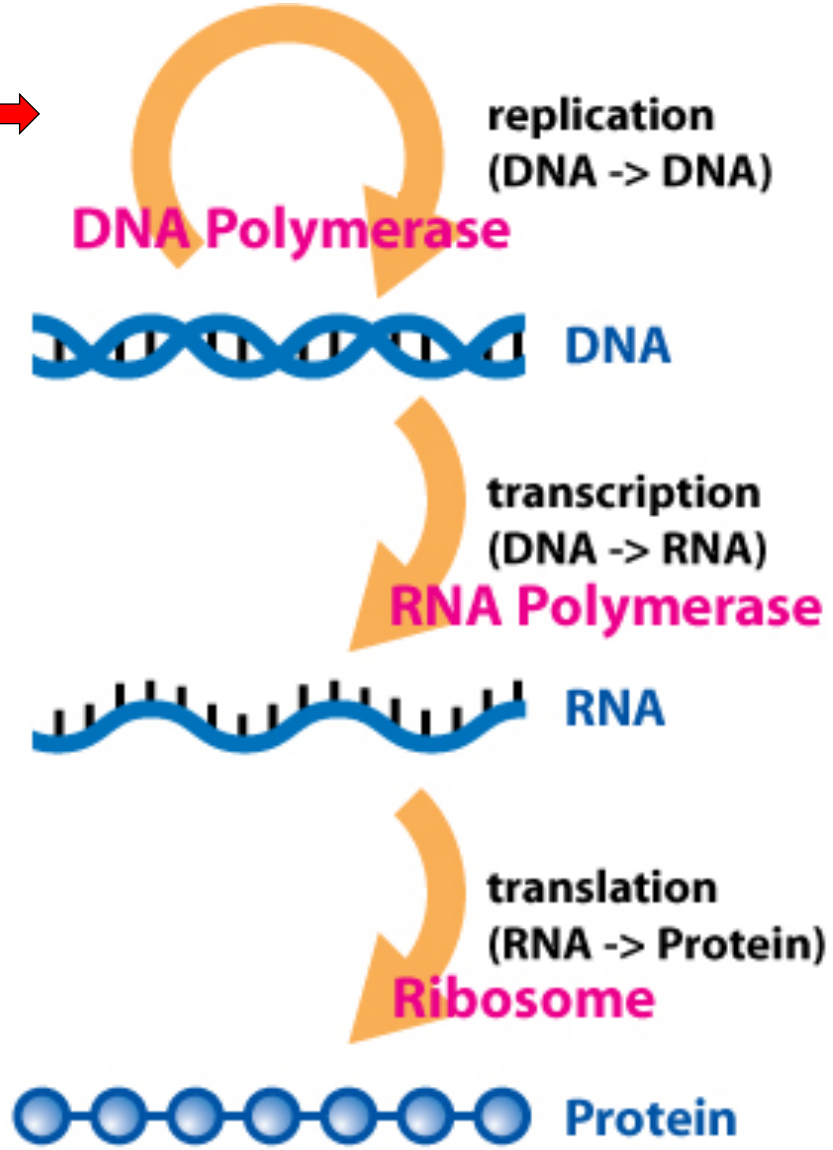
3. **Protein**
   Perform most cellular functions (biochemistry, signaling, control, etc.)



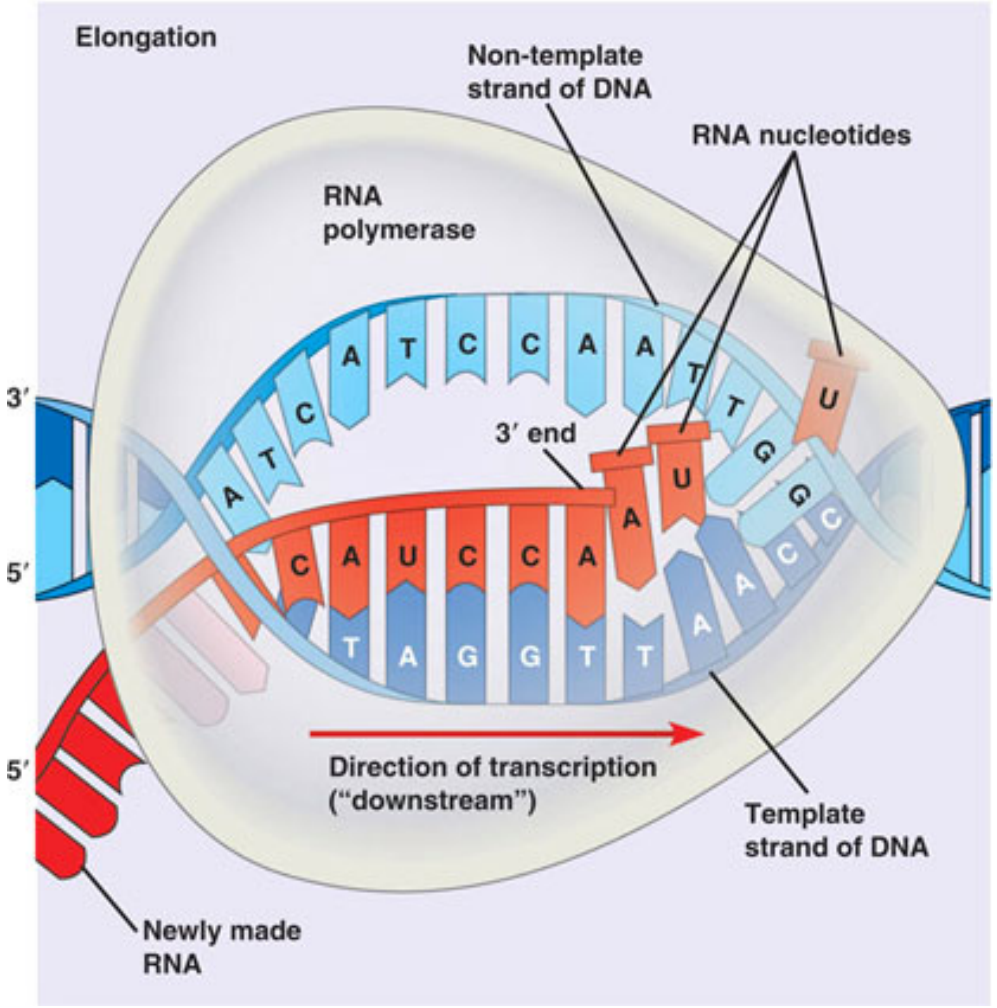
Central Dogma of Molecular Biology

DNA → RNA → Protein:
The process by which cells "read" the genome

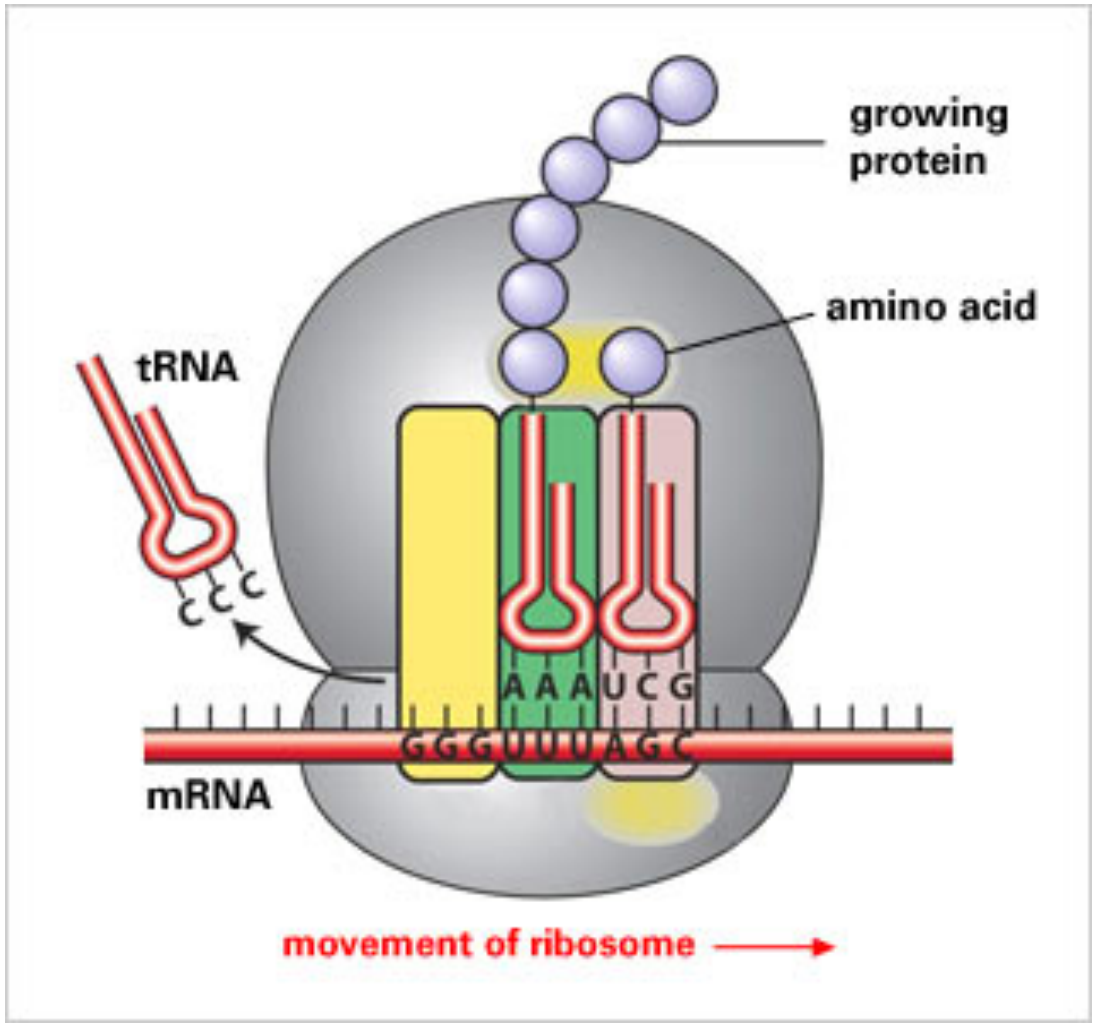
First proposed by Francis Crick in 1956.



Transcription and Translation

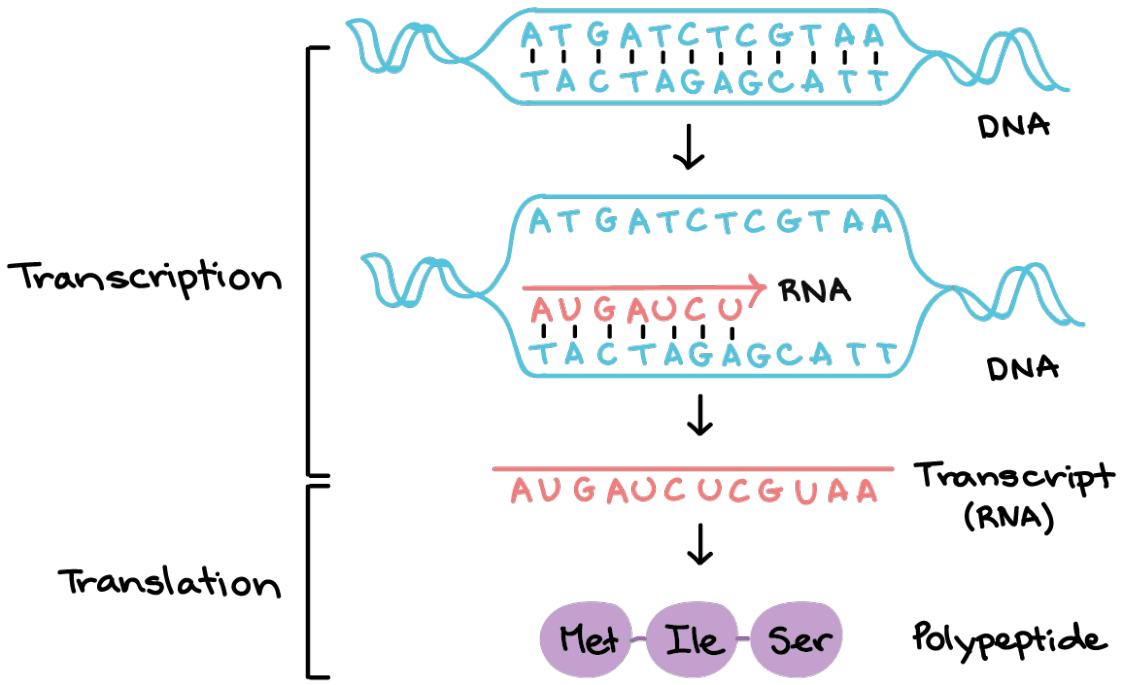


http://dna-rna.net/wp-content/uploads/2011/08/rna-transcription2.jpg

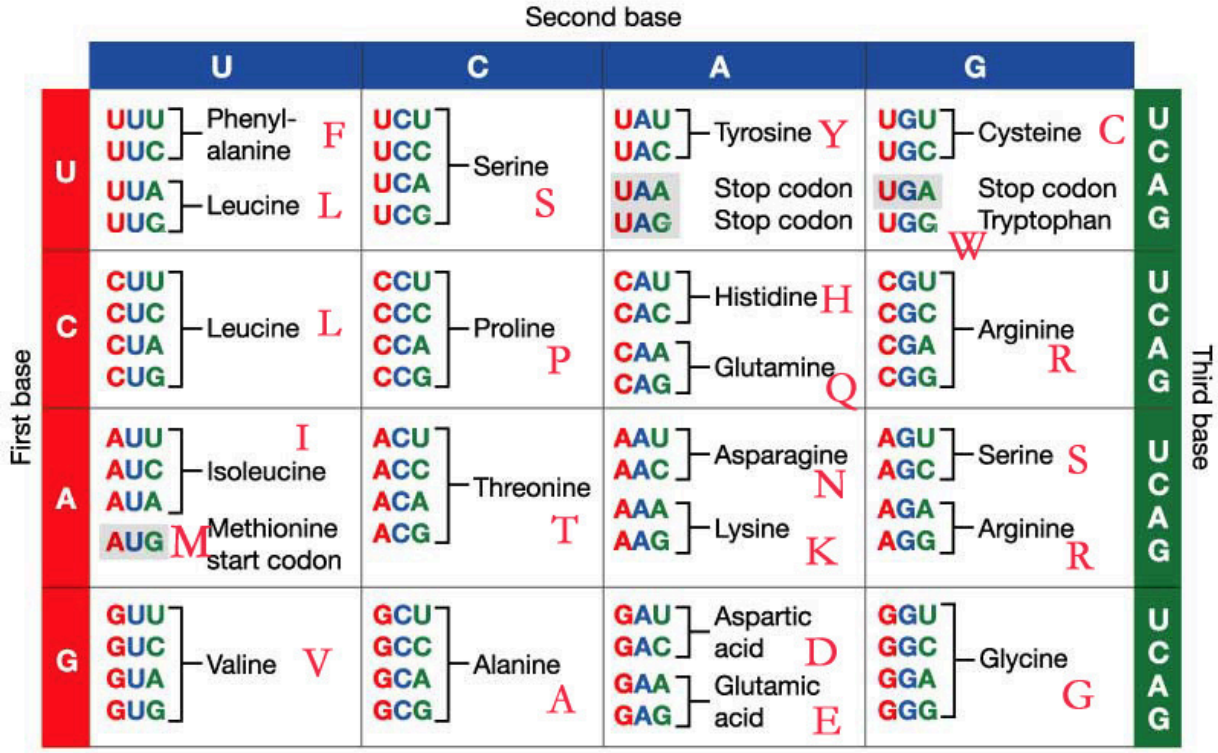


http://www.frontiers-in-genetics.org/en/pictures/translation_1.jpg

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

Lecture Outline

- Primer on Molecular Biology
- Primer on Computational Biology
- Primer on Cancer Biology
- Tumor Phylogeny Inference

Reading

- “Biology for Computer Scientists” by Lawrence Hunter (http://www.el-kebir.net/teaching/CS466/Hunter_BIO_CS.pdf)

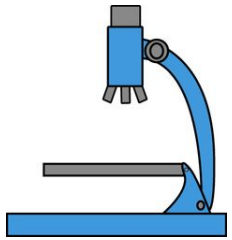
What is Computational Biology/Bioinformatics?

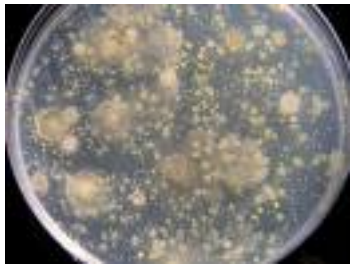
Computational biology and **bioinformatics** is an interdisciplinary field that develops and applies **computational methods** to analyze large collections of biological data, such as genetic sequences, cell populations or protein samples, to make new predictions or **discover new biology**.

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

Technology and Bioinformatics are Transforming Biology

Until late 20th Century





Hypothesis Generation and Validation

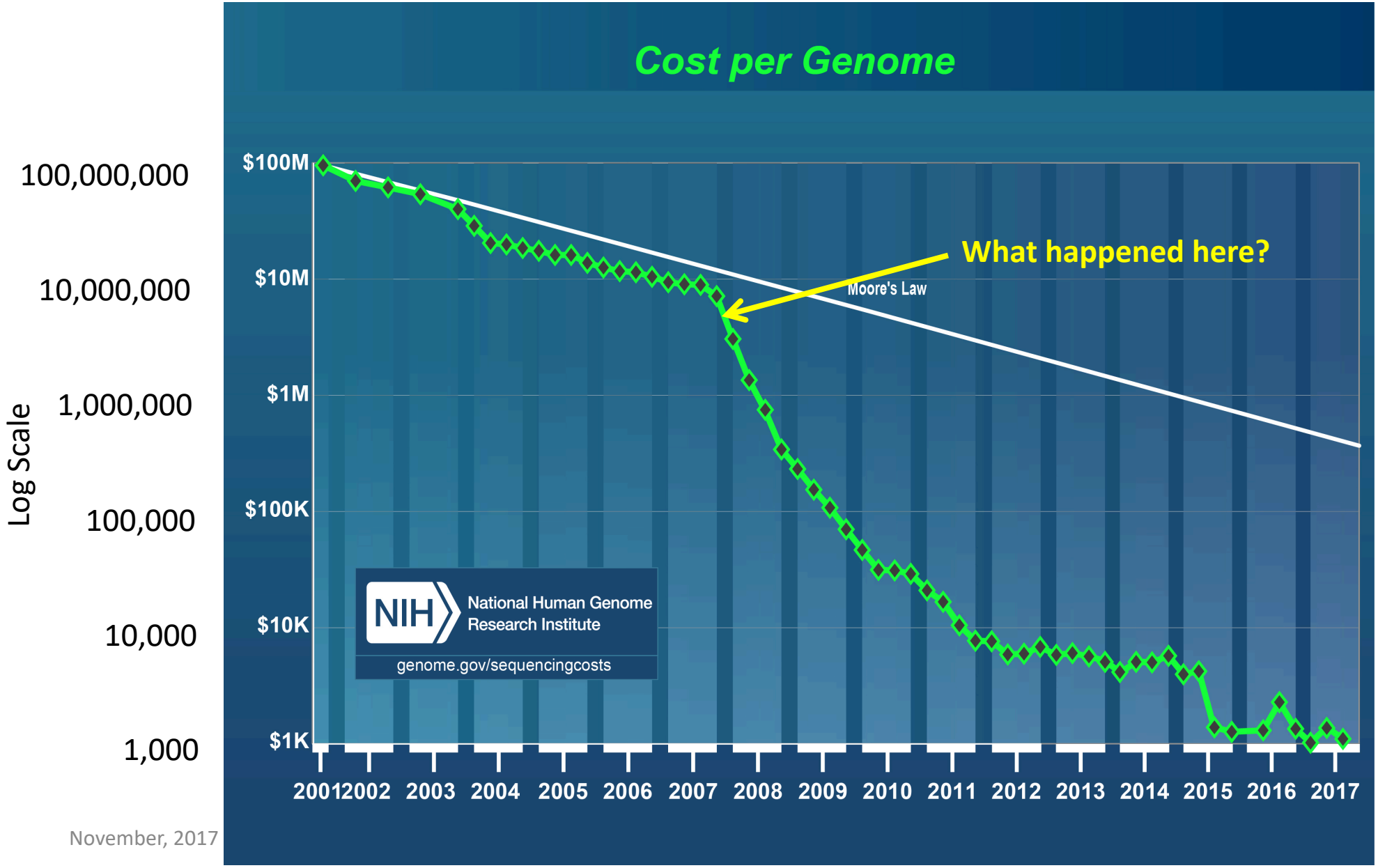
21th Century and Beyond

Algorithms

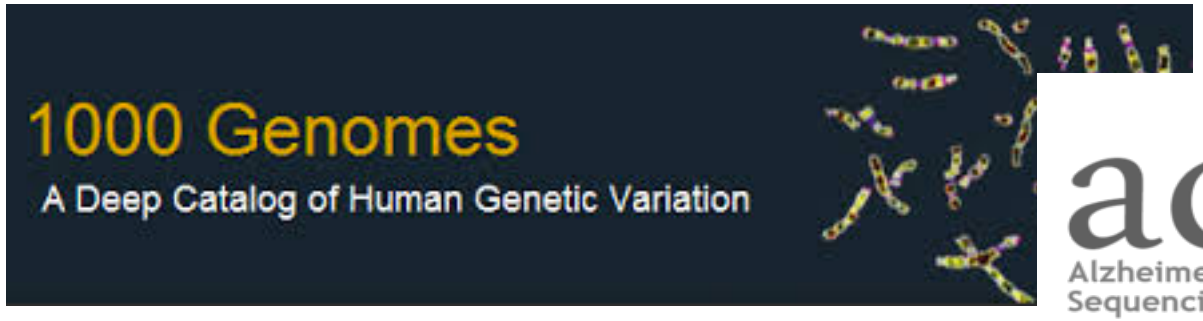
Hypothesis Generation and Validation

High throughput technologies

A Deluge of Data



A Deluge of Data



adsp
Alzheimer's Disease Sequencing Project

1000 Plant Genomes

T1K Fish-T1K
Transcriptomes of 1000 Fishes

Autism Genome 10K

GENOME 10K

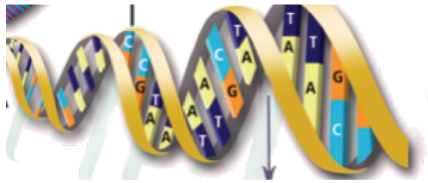
International Cancer Genome Consortium

HMP
NIH HUMAN MICROBIOME PROJECT

NIH THE CANCER GENOME ATLAS
National Cancer Institute
National Human Genome Research Institute

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!



Genome
Millions -billions nucleotides

Next-generation DNA sequencing

… CATTCAGTAG …
… AGCCATTAG …
… GGTAGTTAG …
… GGTAAACTAG …
… TATAATTAG …
… CGTACCTAG …

10-100's million noisy ***reads***
Reads: 30-1000 nucleotides

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	Worst Jobs
1. Actuary	200. Newspaper reporter
2. Audiologist	199. Lumberjack
3. Mathematician	198. Enlisted Military Personnel
4. Statistician	197. Cook
5. Biomedical Engineer	196. Broadcaster
6. Data Scientist	195. Photojournalist
7. Dental Hygienist	194. Corrections Officer
8. Software Engineer	193. Taxi Driver
9. Occupational Therapist	192. Firefighter
10. Computer Systems Analyst	191. Mail Carrier

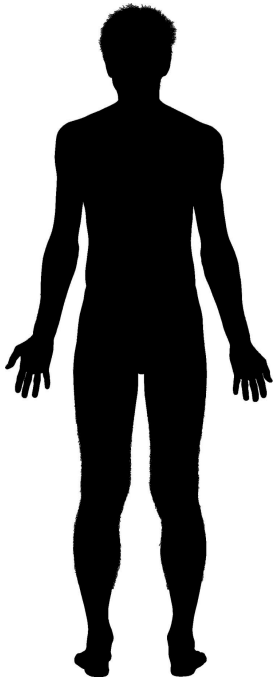
http://www.careercast.com/jobs-rated/jobs-rated-report-2015-ranking-top-200-jobs

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

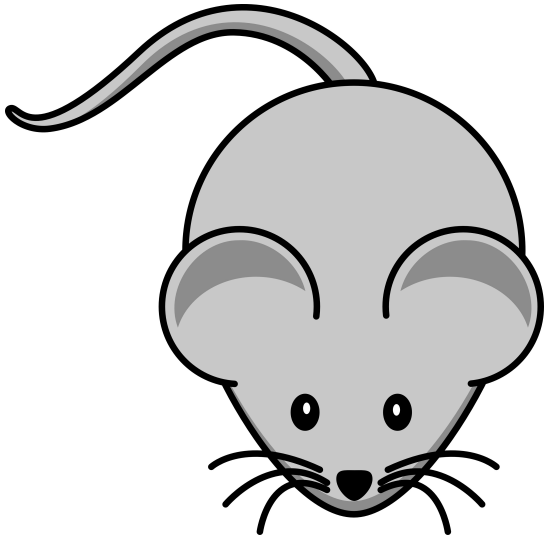
"I can't be as confident about computer science as I can about biology. Biology easily has 500 years of exciting problems to work on. It's at that level."

Computational Biology: Sequence Alignment

Question: How do we compare two genes/genomes?



vs.



Human Genome:

…ACTCGACTGAGAGGATTTCGAGCATGA…

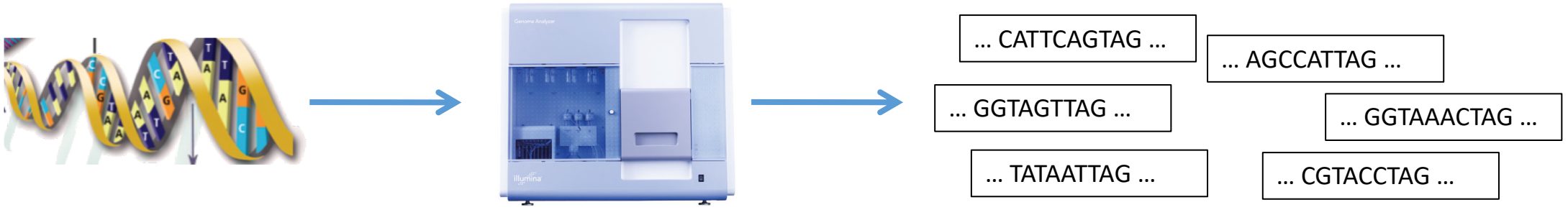
≈3.2 x 10^9 bp

Mouse Genome:

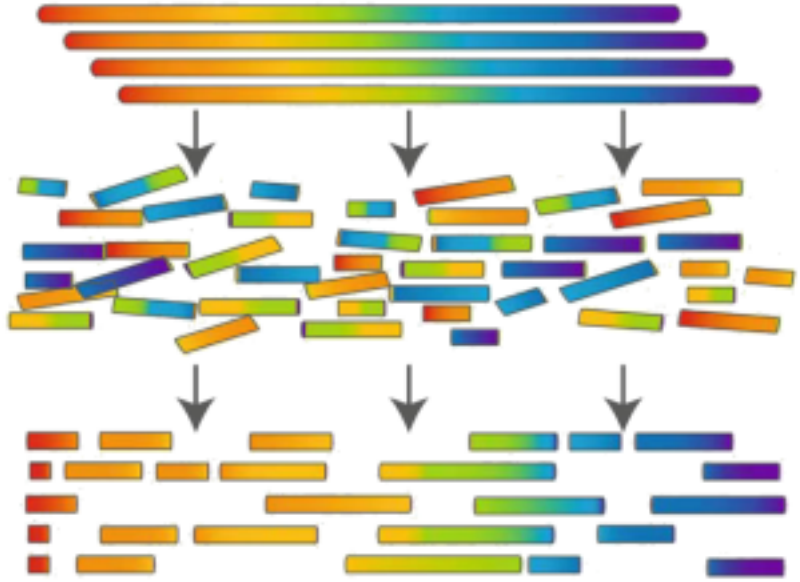
…ACTCAACTGAGATTCGAGCTTCAATGA…

≈2.8 x 10^9 bp

Computational Biology: Genome Assembly

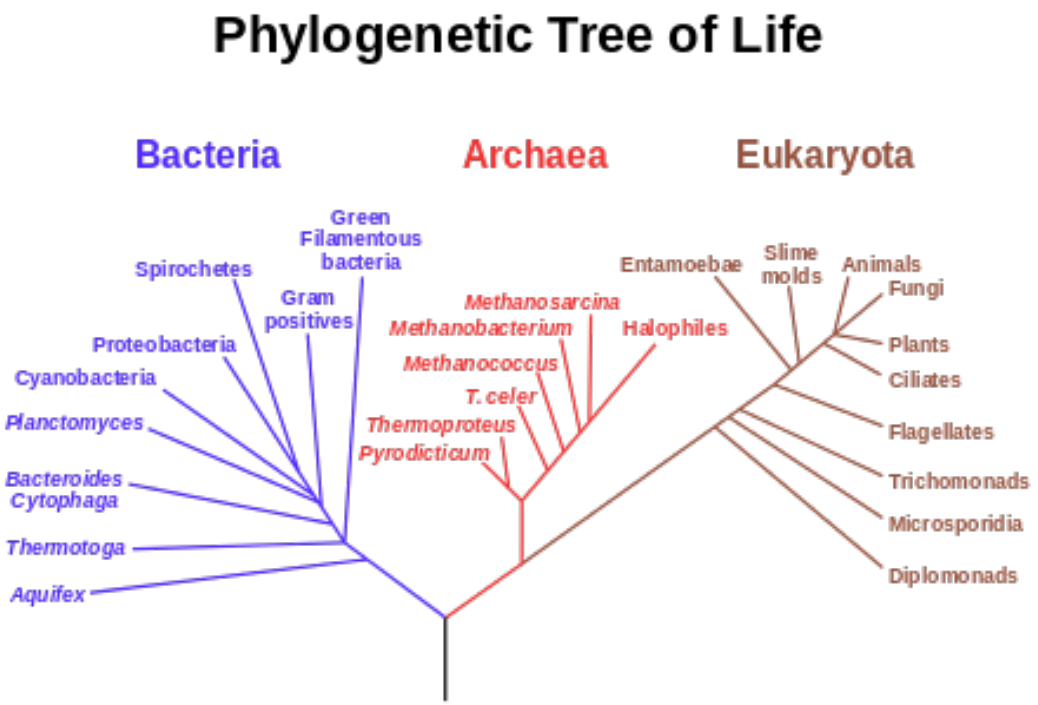


Question: How do we put all the pieces back together?



ATGTTCCGATTAGGAAACCTATCTGTAACTGTTTCATTCAGTAAAAGGAGGAAATATAA

Computational Biology: Phylogenetics

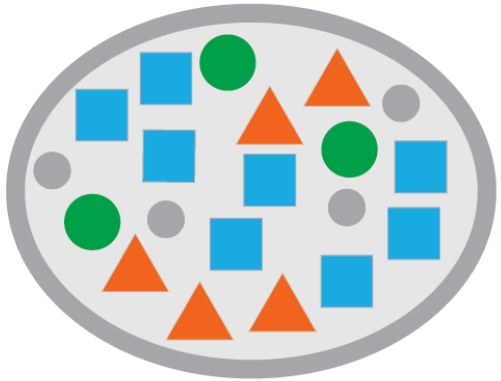


https://en.wikipedia.org/wiki/Phylogenetic_tree

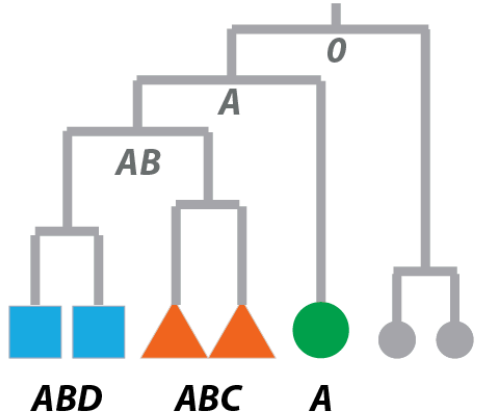
Question: Can we reconstruct the evolutionary history of different species?

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

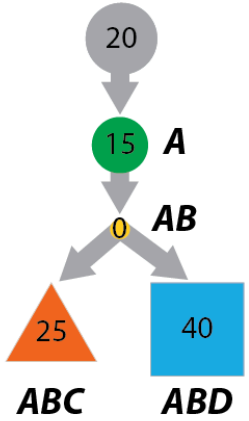
Poly-clonal tumor at sampling



Classical phylogenetic tree

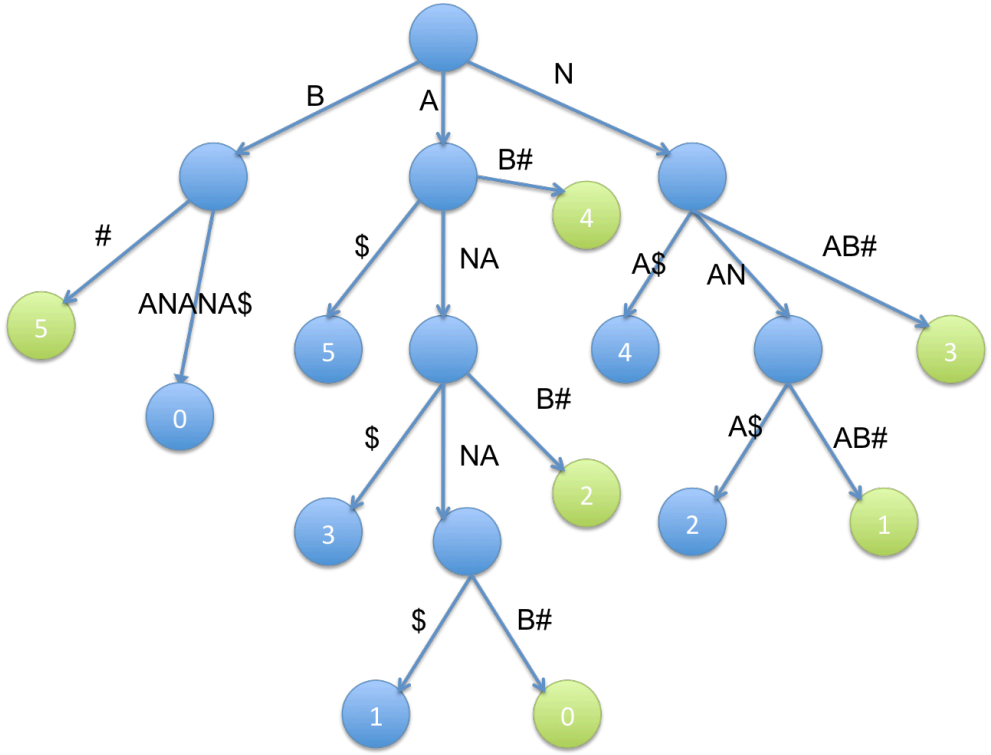


Clonal evolution tree



https://scientificbsides.wordpress.com/2014/06/09/inferring-tumour-evolution-2-comparison-to-classical-phylogenetics/

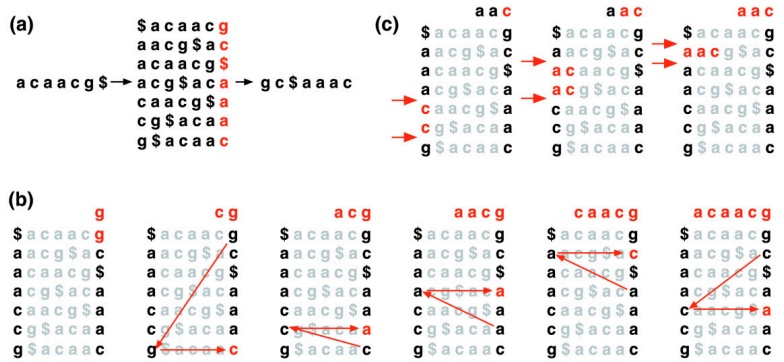
Computational Biology: Pattern Matching



Suffix Trees

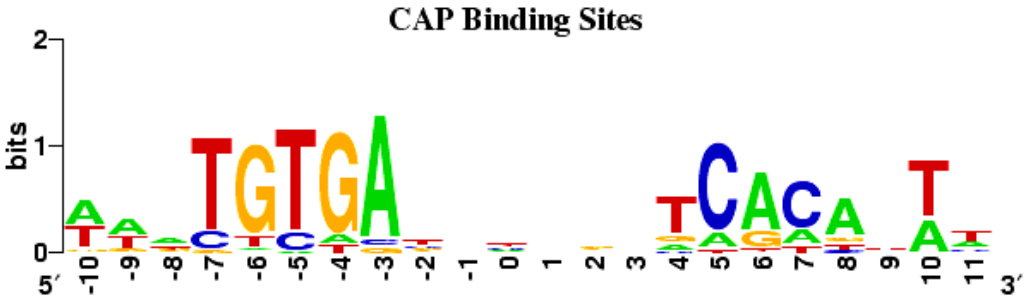
Question: How do we start to make sense of all these sequences?

Burrows Wheeler Transform



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

Motif Finding



Computational Biology is Computer Science

1. Sequence alignment
   'How do we compare two genes/genomes?'
   Dynamic programming: edit distance

2. Genome assembly
   'How do we put all the pieces back together?'
   Graphs: de Bruijn graph, Eulerian and Hamiltonian paths

3. Phylogenetics
   'What is the evolutionary history of different sequences?'
   Trees and distances: distance matrices, neighbor joining, hierarchical clustering, Sankoff/Fitch algorithms, perfect phylogeny and compatibility

4. Pattern matching
   'How do we start to make sense out of all these sequences?'
   Suffix trees/arrays. Burrows-Wheeler transform, Hidden Markov Models (HMMs)

Pet Peeve: Problem != Algorithm

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

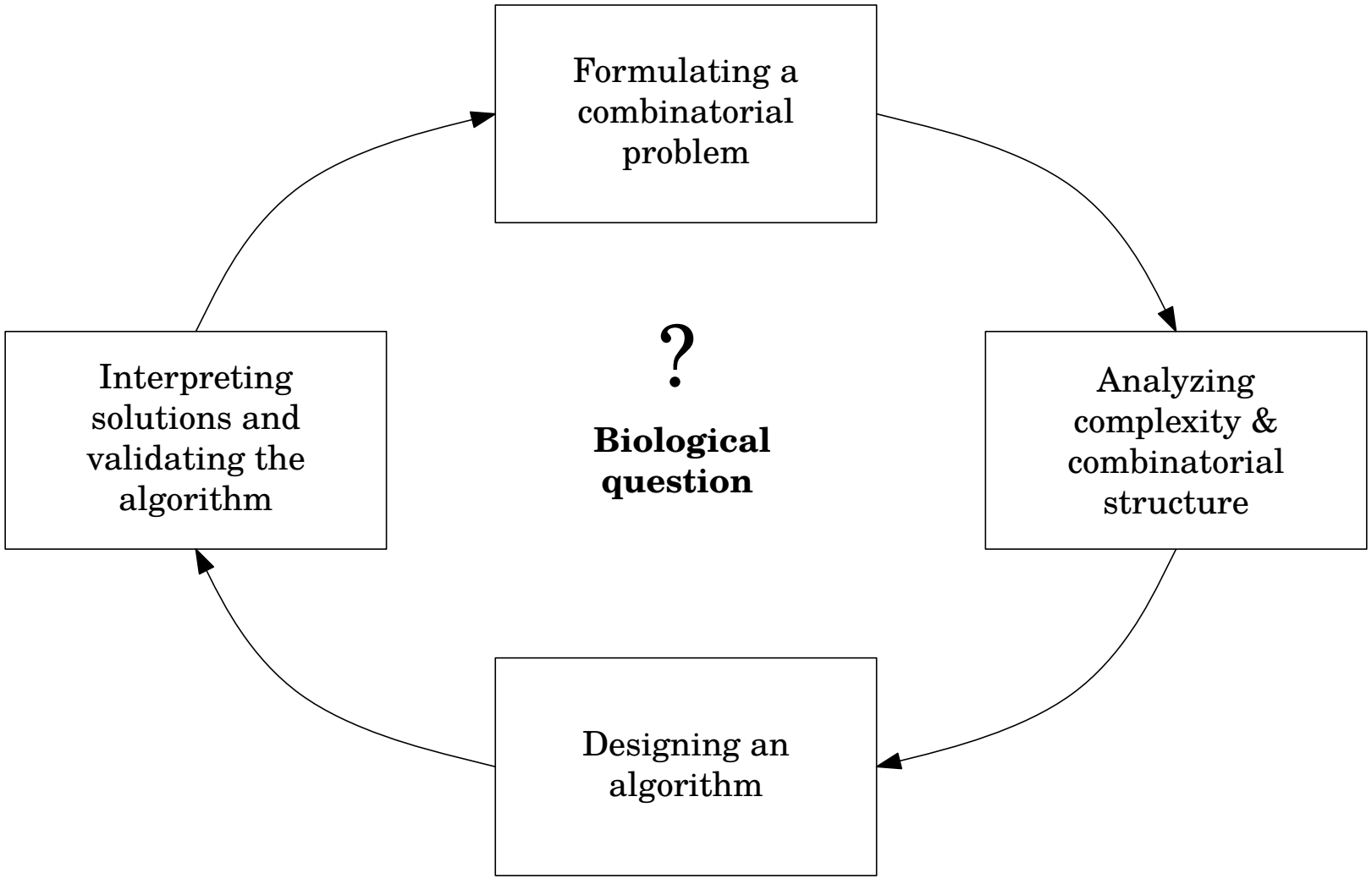
- Decision problem:
  - Is $\Pi(X) = \emptyset$?
- Optimization problem:
  - Find $y^* \in \Pi(X)$ s.t. $f(y^*)$ is optimum.
- Counting problem:
  - Compute $|\Pi(X)|$.
- Sampling problem:
  - Sample uniformly from $\Pi(X)$.
- Enumeration problem:
  - Enumerate all solutions in $\Pi(X)$

Algorithms:

Set of instructions for solving problem.

- Exact
- Heuristic

Key Challenge in Computational Biology



Translating a biological problem into a computational biology

Lecture Outline

- Primer on Molecular Biology
- Primer on Computational Biology
- Primer on Cancer Biology
- Tumor Phylogeny Inference

Reading

- “Biology for Computer Scientists” by Lawrence Hunter (http://www.el-kebir.net/teaching/CS466/Hunter_BIO_CS.pdf)

Cancer Statistics: Incidence and Mortality

The Burden of Cancer in the United States

- In 2018, an estimated 1,735,350 new cases of cancer will be diagnosed in the United States and 609,640 people will die from the disease.
- The number of new cases of cancer (cancer incidence) is 439.2 per 100,000 men and women per year (based on 2011–2015 cases).
- The number of cancer deaths (cancer mortality) is 163.5 per 100,000 men and women per year (based on 2011–2015 deaths).
- Approximately 38.4% of men and women will be diagnosed with cancer at some point during their lifetimes (based on 2013–2015 data).

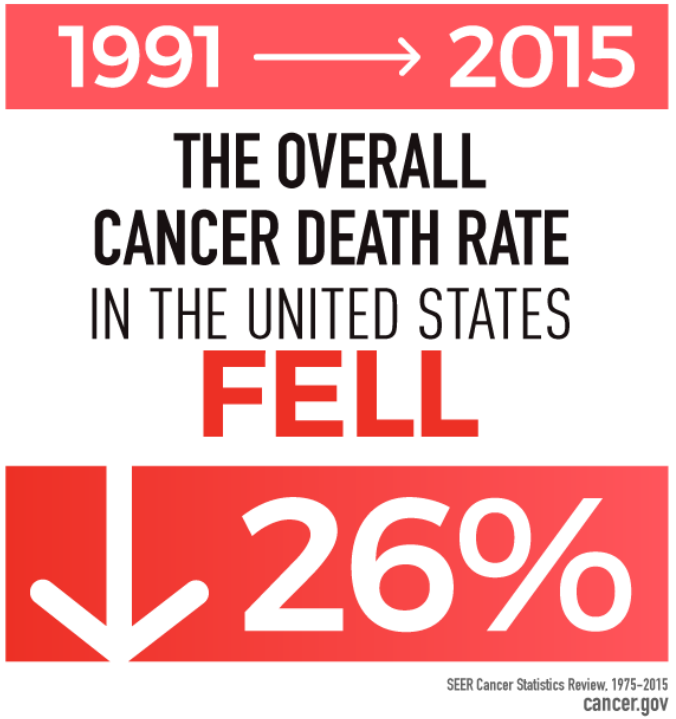
  Source: Surveillance, Epidemiology, and End Results (SEER) Program

Cancer Statistics: Incidence and Mortality

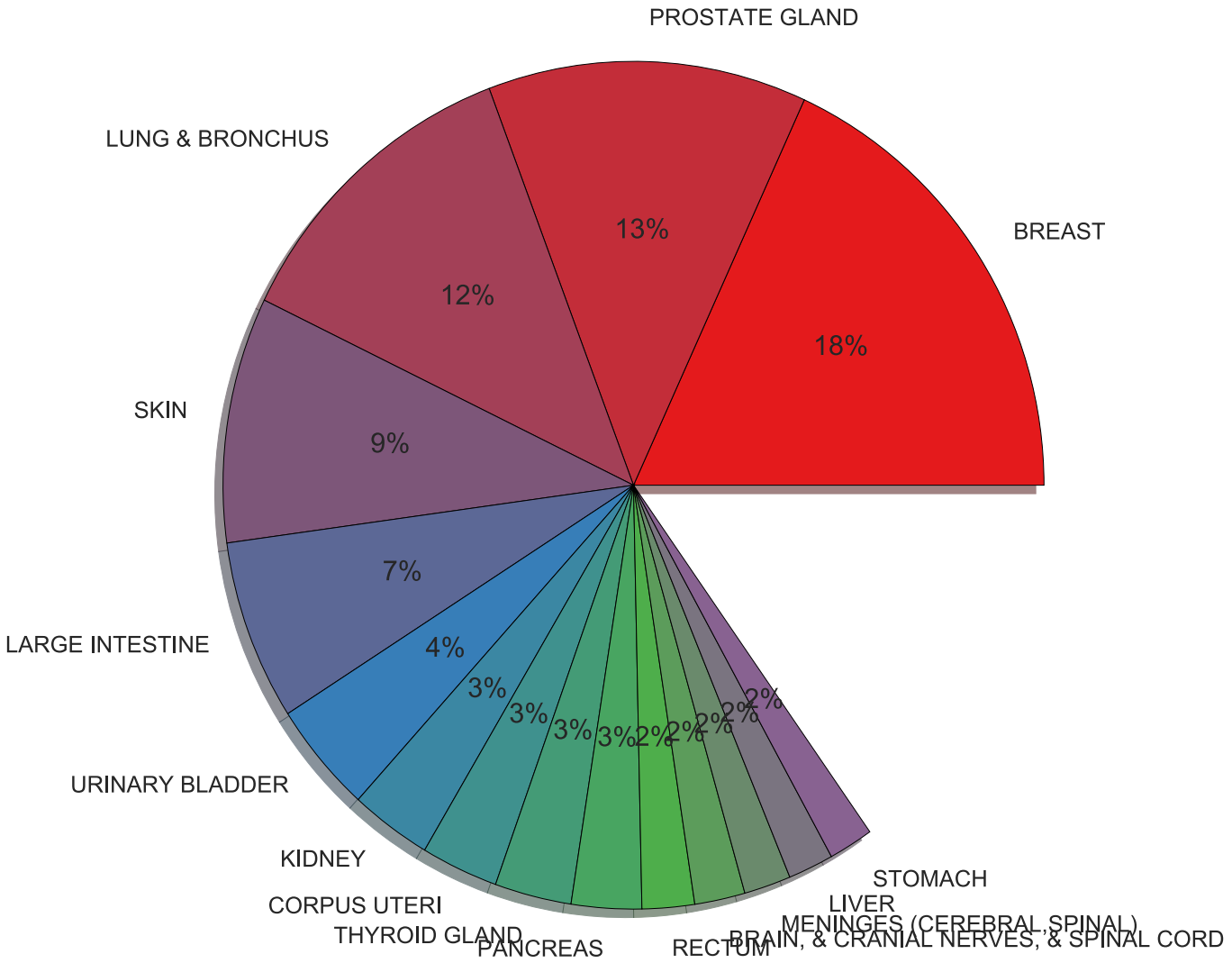
The Burden of Cancer in the United States

- In 2018, an estimated 1,735,350 new cases of cancer will be diagnosed in the United States and 609,640 people will die from the disease.
- The number of new cases of cancer (cancer incidence) is 439.2 per 100,000 men and women per year (based on 2011–2015 cases).
- The number of cancer deaths (cancer mortality) is 163.5 per 100,000 men and women per year (based on 2011–2015 deaths).
- Approximately 38.4% of men and women will be diagnosed with cancer at some point during their lifetimes (based on 2013–2015 data).

  Source: Surveillance, Epidemiology, and End Results (SEER) Program



Cancer Statistics: Primary Tumor Location



90% of cancer patients die of **metastasis** [Gupta, G. P. & Massagué, Cell, 2006]

Hallmarks of Cancer

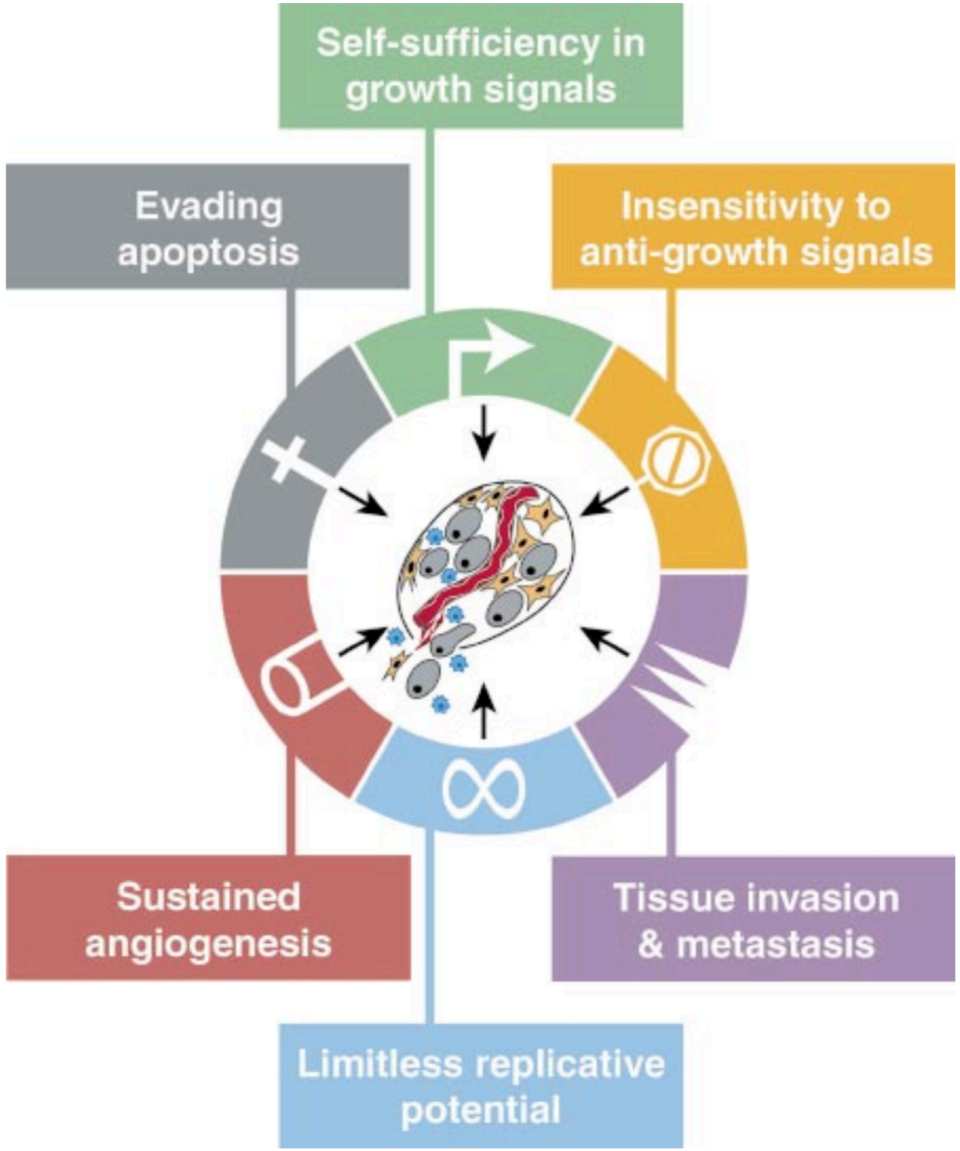
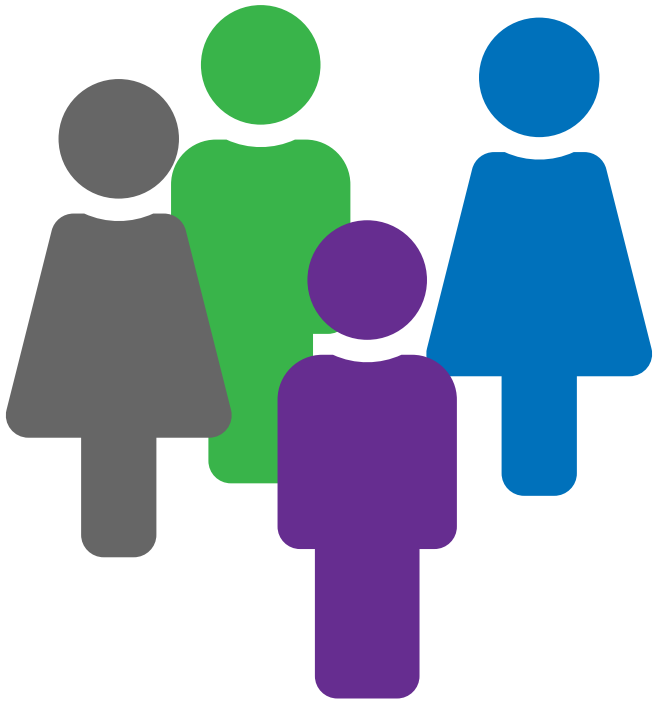


Figure 1. Acquired Capabilities of Cancer

We suggest that most if not all cancers have acquired the same set of functional capabilities during their development, albeit through various mechanistic strategies.

Hallmarks of Cancer



Inter-tumor heterogeneity:
Every tumor is different!

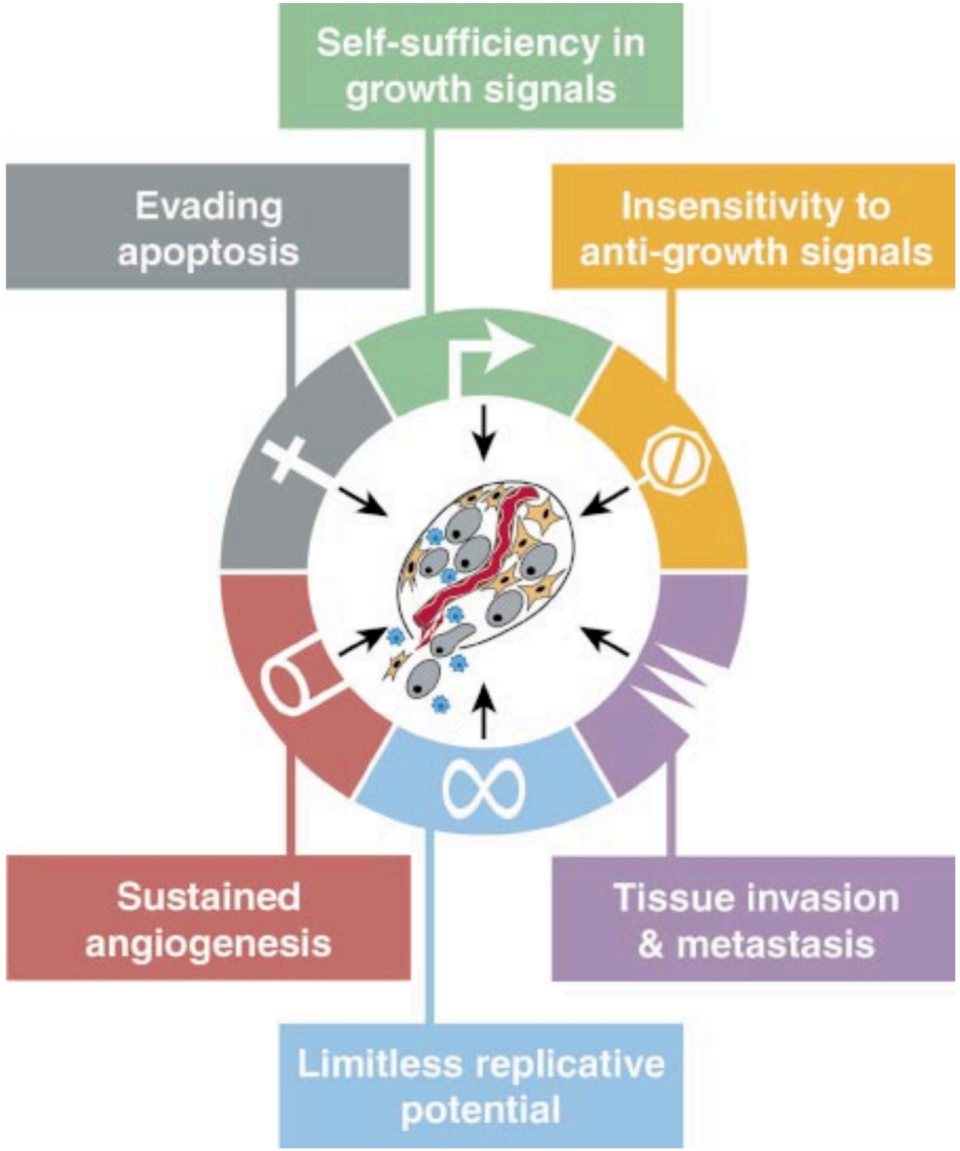


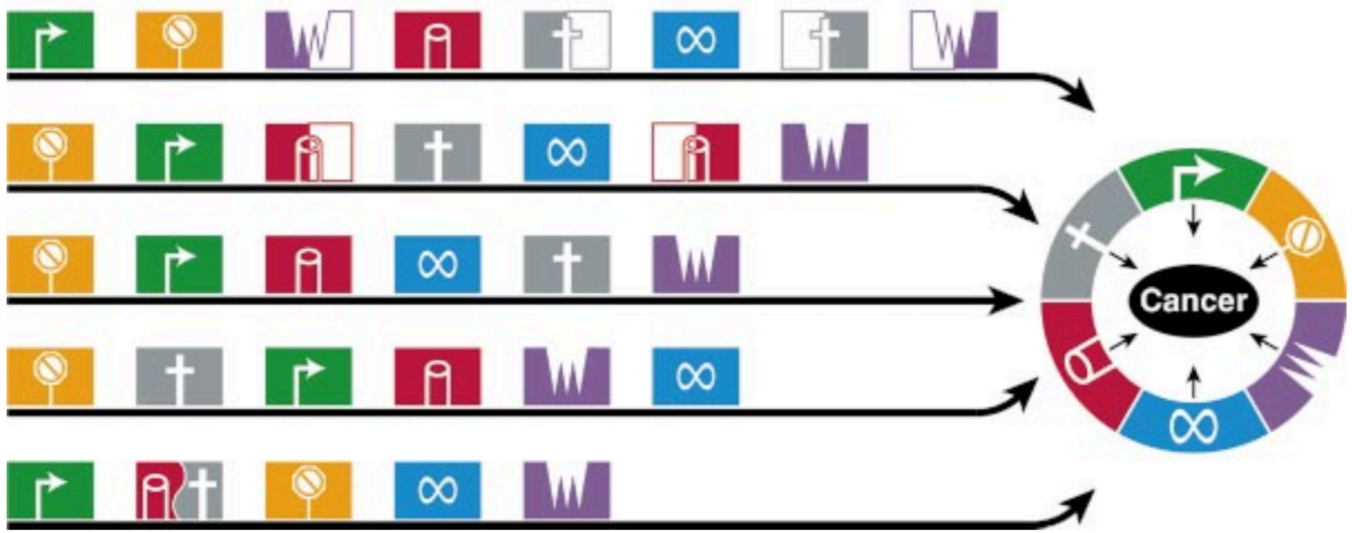
Figure 1. Acquired Capabilities of Cancer

We suggest that most if not all cancers have acquired the same set of functional capabilities during their development, albeit through various mechanistic strategies.

A

Component	Acquired Capability	Example of Mechanism
	Self-sufficiency in growth signals	Activate H-Ras oncogene
	Insensitivity to anti-growth signals	Lose retinoblastoma suppressor
	Evading apoptosis	Produce IGF survival factors
	Limitless replicative potential	Turn on telomerase
	Sustained angiogenesis	Produce VEGF inducer
	Tissue invasion & metastasis	Inactivate E-cadherin

B



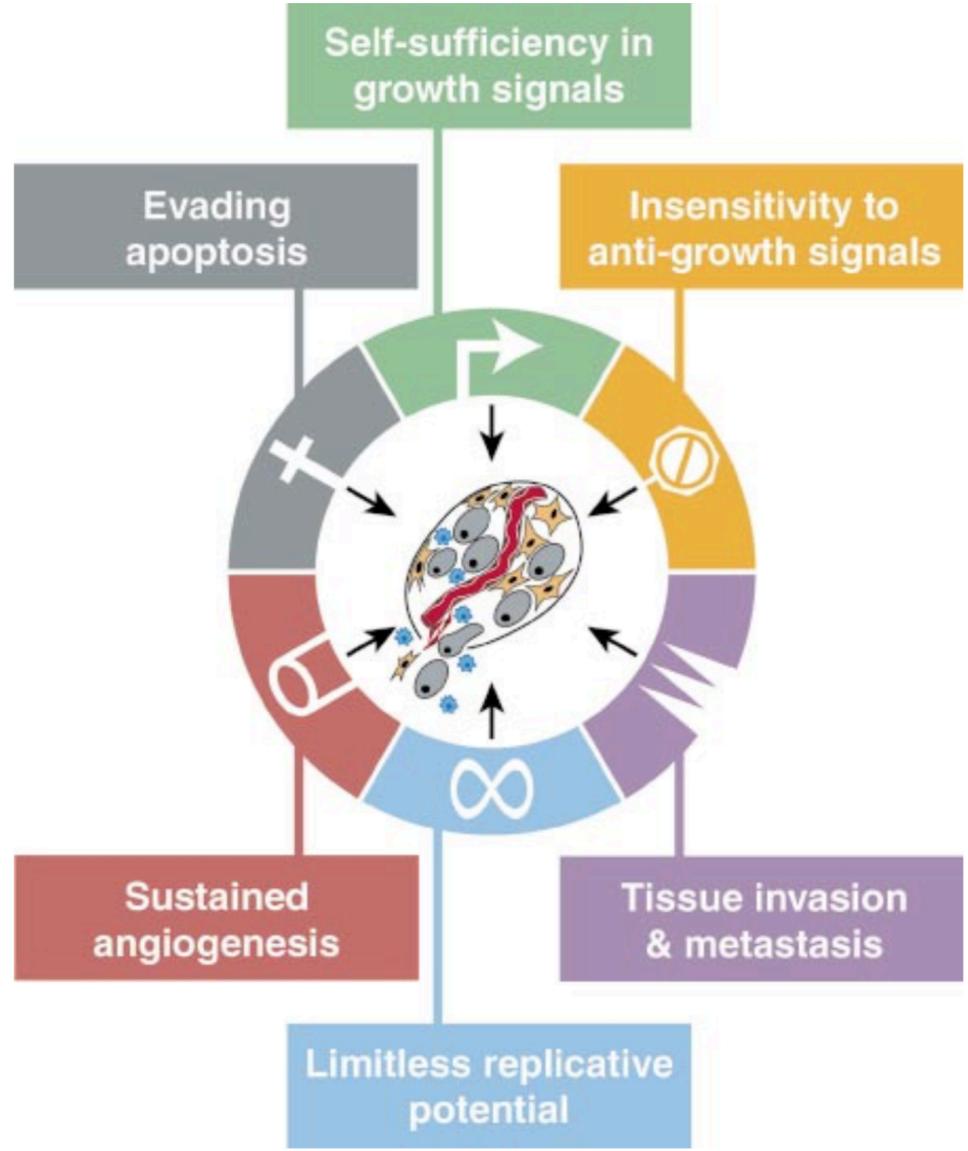
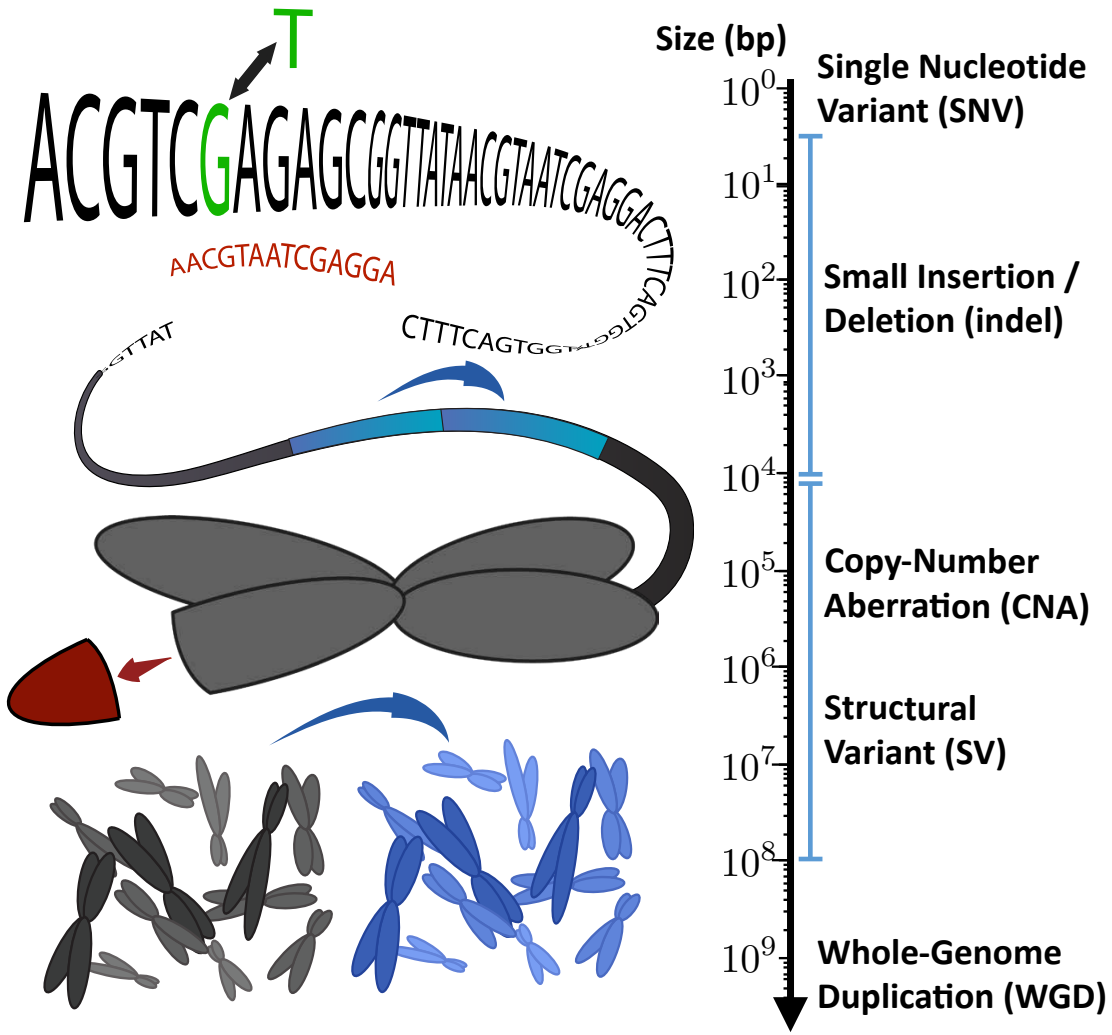


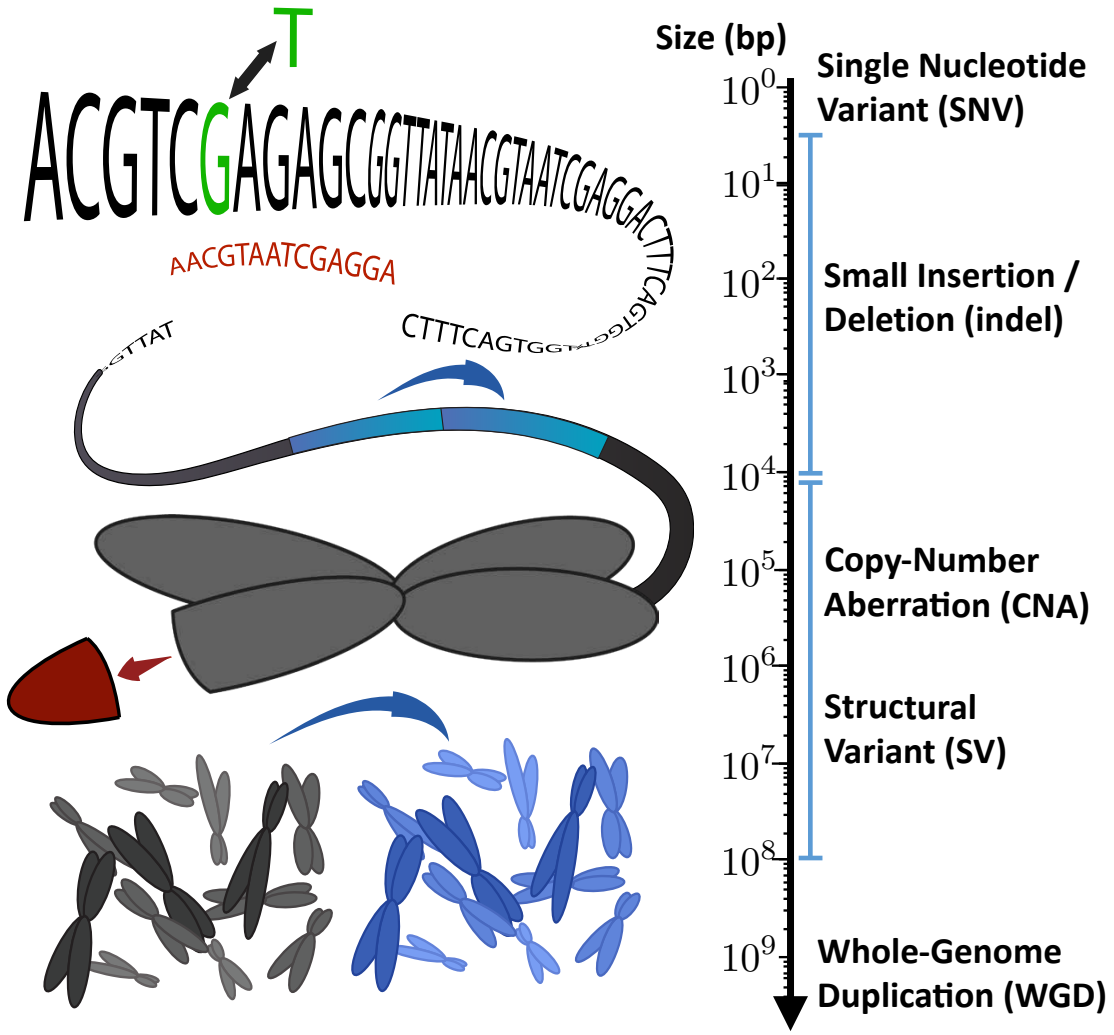
Figure 1. Acquired Capabilities of Cancer

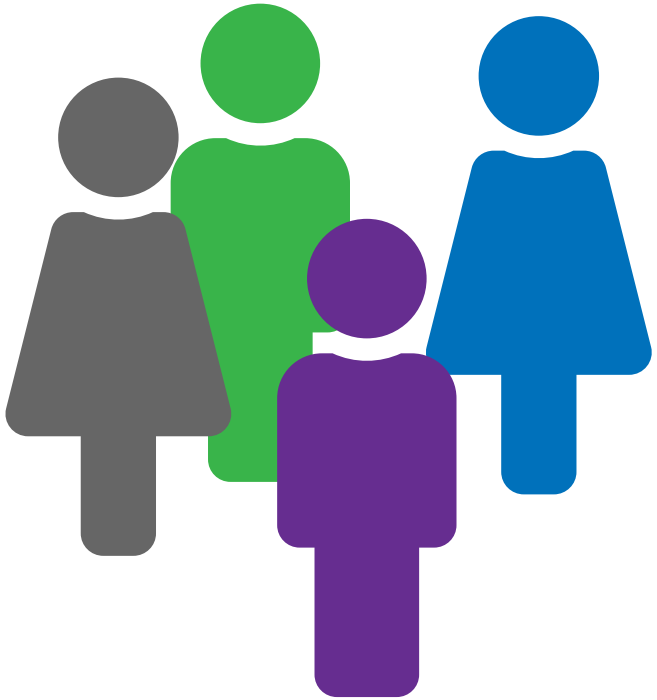
We suggest that most if not all cancers have acquired the same set of functional capabilities during their development, albeit through various mechanistic strategies.

Cancer is Caused by Somatic Mutations



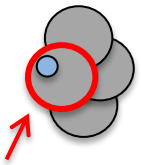
Cancer is Caused by Somatic Mutations





Question: Why is there inter-tumor heterogeneity?

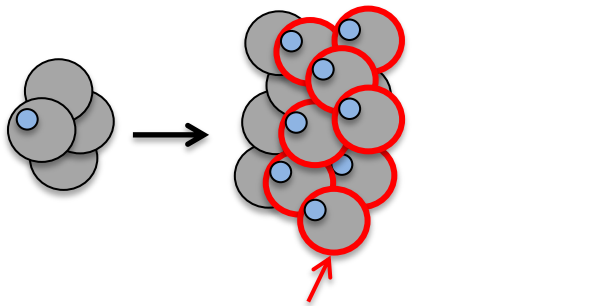
Tumorigenesis: Cell Mutation

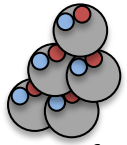


Founder
tumor cell
with somatic mutation:
(e.g. BRAF V600E)

Tumorigenesis: Cell Mutation, Division

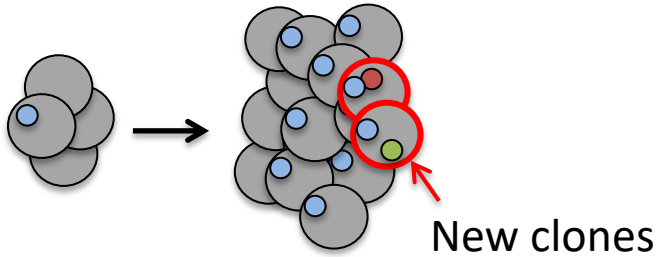
Clonal Evolution Theory of Cancer
[Nowell, 1976]

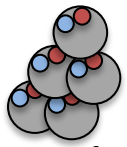


Clone  is a group  of cells
with the same mutations {  ,  }

Tumorigenesis: Cell Mutation, Division

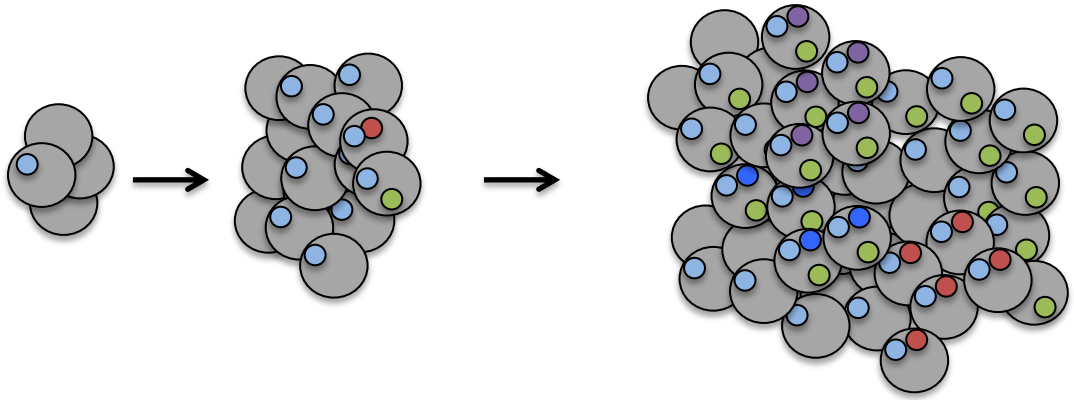
Clonal Evolution Theory of Cancer
[Nowell, 1976]



Clone  is a group  of cells
with the same mutations {●, ●}

Tumorigenesis: Cell Mutation, Division

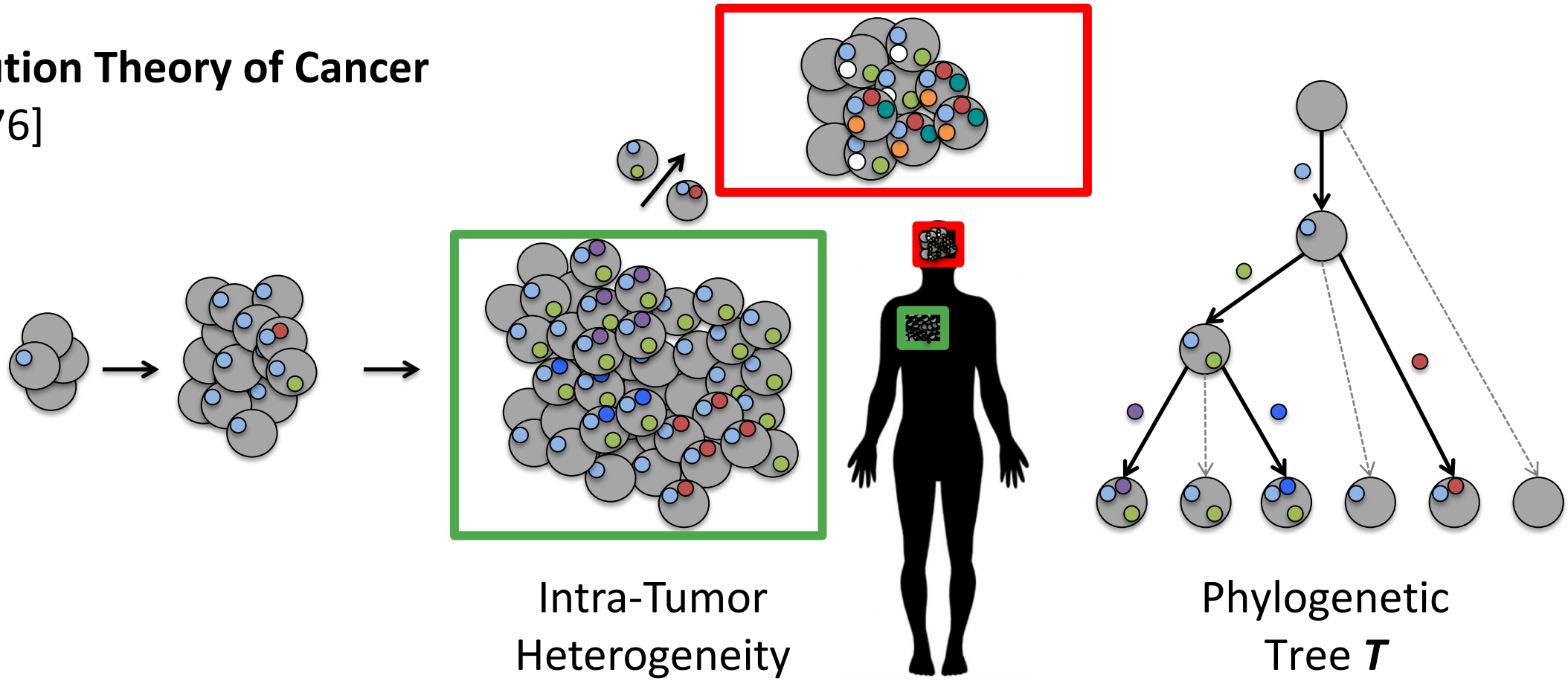
Clonal Evolution Theory of Cancer
[Nowell, 1976]



Intra-Tumor
Heterogeneity

Tumorigenesis: Cell Mutation, Division & Migration

Clonal Evolution Theory of Cancer
[Nowell, 1976]



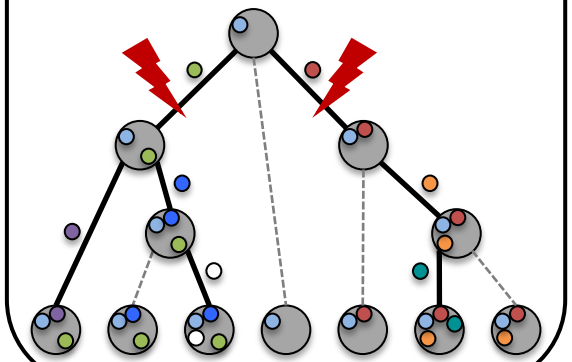
Intra-Tumor Heterogeneity

Phylogenetic Tree ***T***

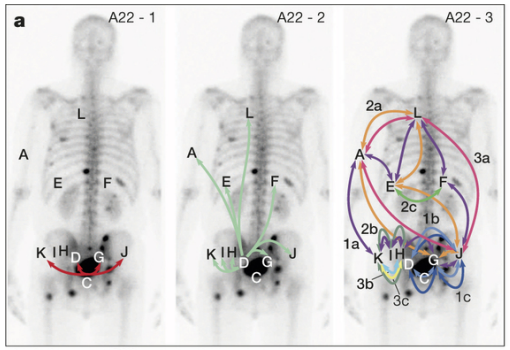
Question: Why are tumor phylogenies important?

Phylogenies are Key to Understanding Cancer

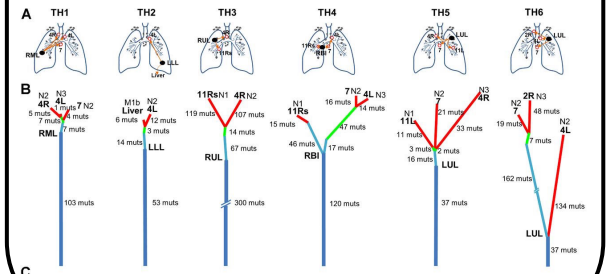
Identify targets for treatment



Understand metastatic development

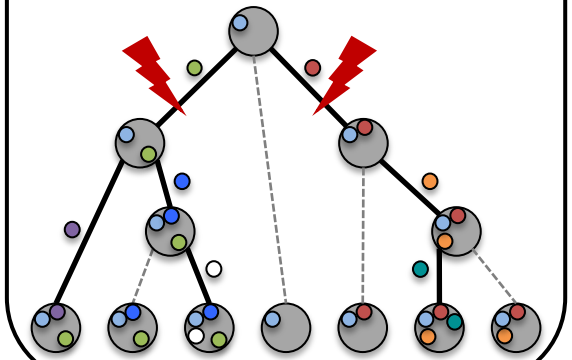


Recognize common patterns of tumor evolution across patients

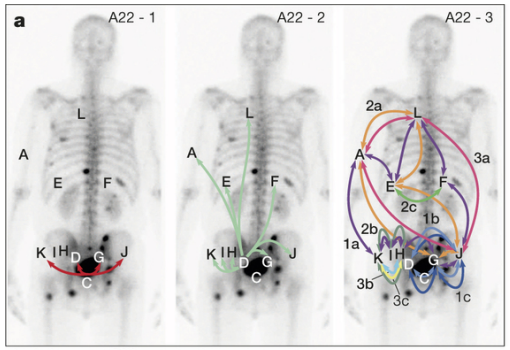


Phylogenies are Key to Understanding Cancer

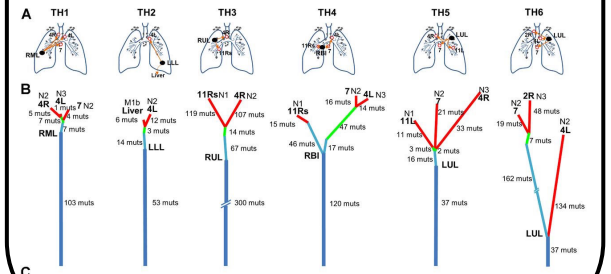
Identify targets for treatment



Understand metastatic development



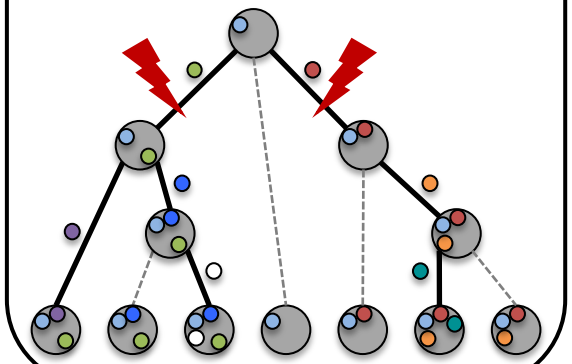
Recognize common patterns of tumor evolution across patients



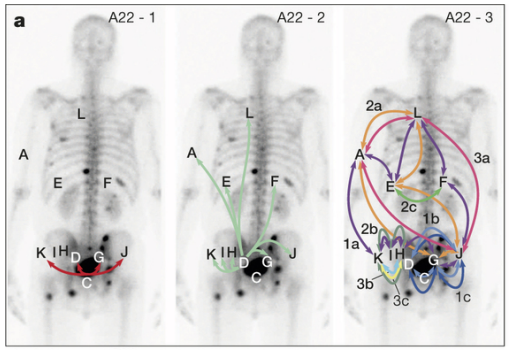
These downstream analyses **critically rely** on accurate tumor phylogeny inference

Phylogenies are Key to Understanding Cancer

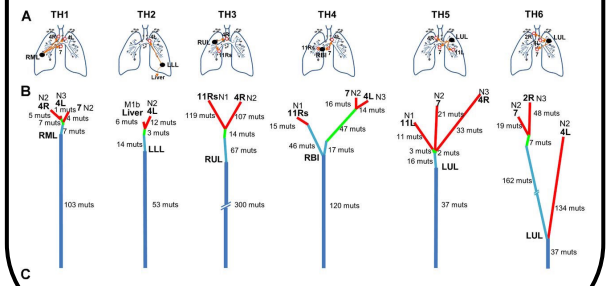
Identify targets for treatment



Understand metastatic development



Recognize common patterns of tumor evolution across patients



These downstream analyses **critically rely** on accurate tumor phylogeny inference

Key challenge in phylogenetics:
Accurate phylogeny inference from data at present time

Lecture Outline

- Primer on Molecular Biology
- Primer on Computational Biology
- Primer on Cancer Biology
- Tumor Phylogeny Inference

Reading

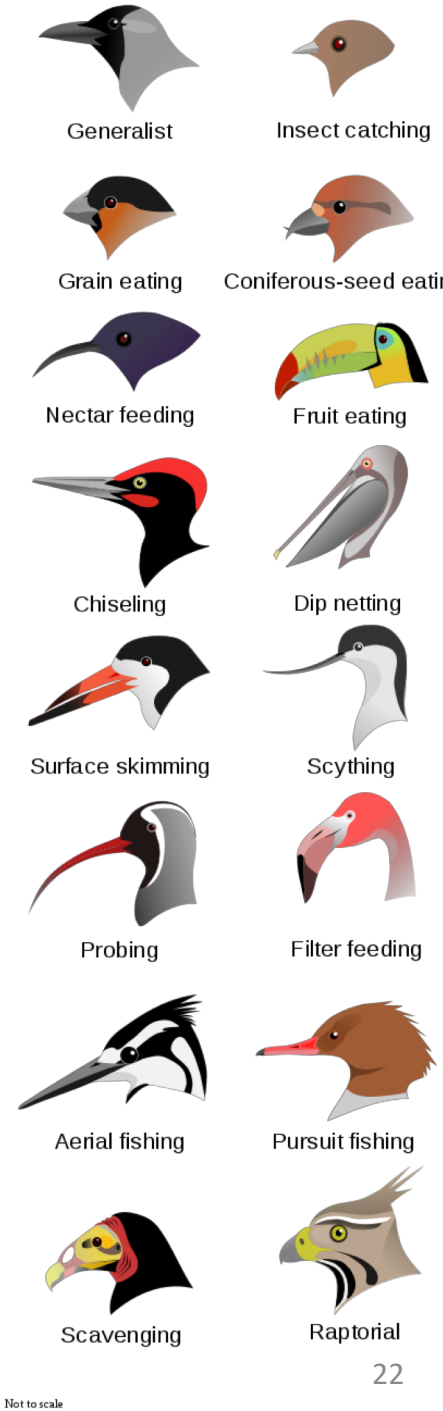
- “Biology for Computer Scientists” by Lawrence Hunter (http://www.el-kebir.net/teaching/CS466/Hunter_BIO_CS.pdf)

Character-Based Tree Reconstruction

- Characters may be morphological features
  - Shape of beak {generalist, insect catching, ...}
  - Number of legs {2,3,4, ..}
  - Hibernation {yes, no}

- Character may be nucleotides/amino acids
  - {A, T, C, G}
  - 20 amino acids

- Values of a character are called states
  - We assume discrete states

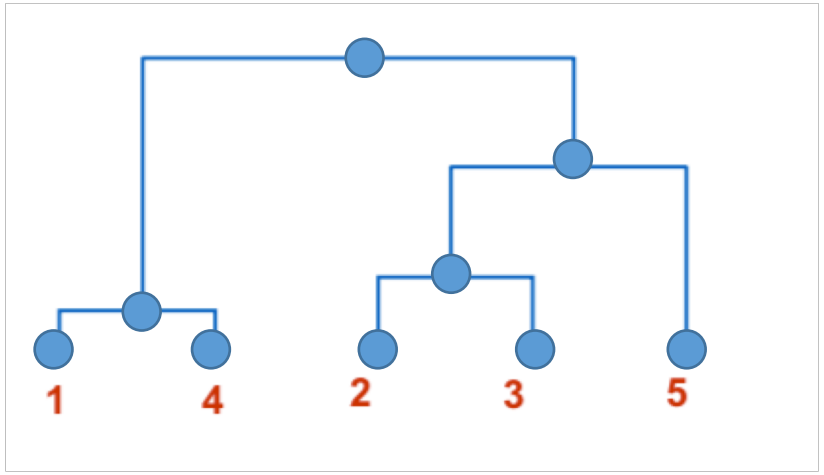


Character-Based Phylogeny Reconstruction

Input characters → Output optimal tree

Question: What is optimal?

Want: Optimization criterion



Character-Based Phylogeny Reconstruction

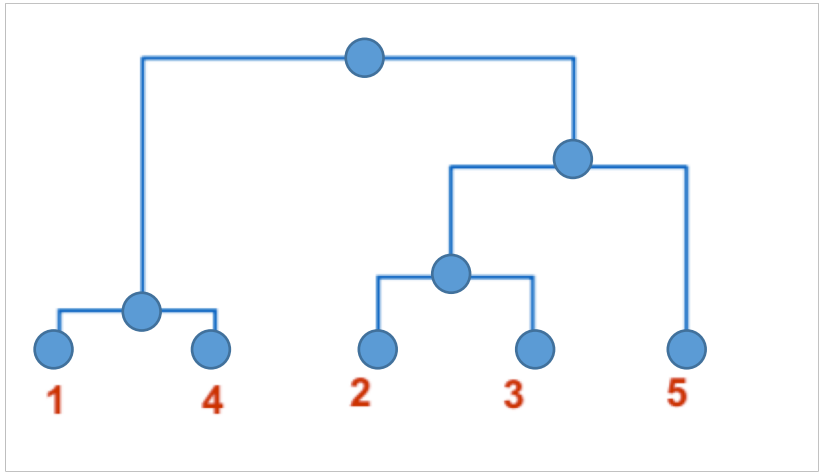
Input characters → Output optimal tree

Question: What is optimal?

Want: Optimization criterion

Question: How to optimize this criterion?

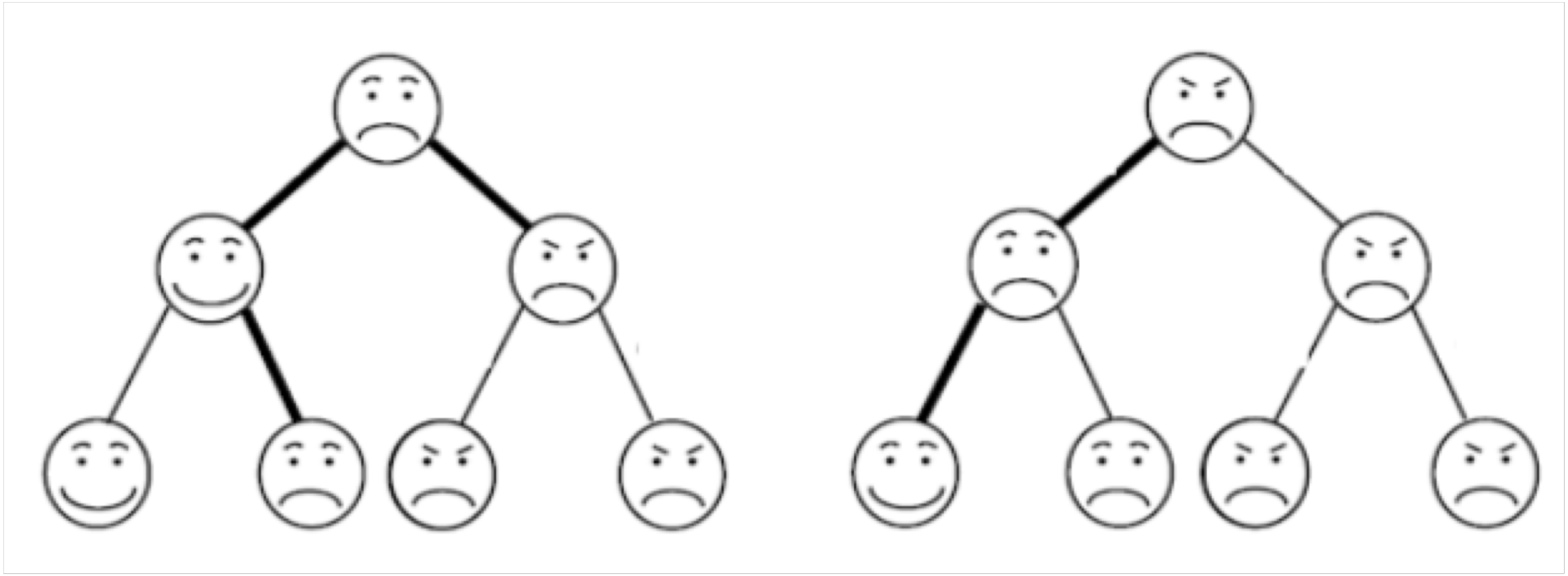
Want: Algorithm



Character-Based Phylogeny Reconstruction: Input

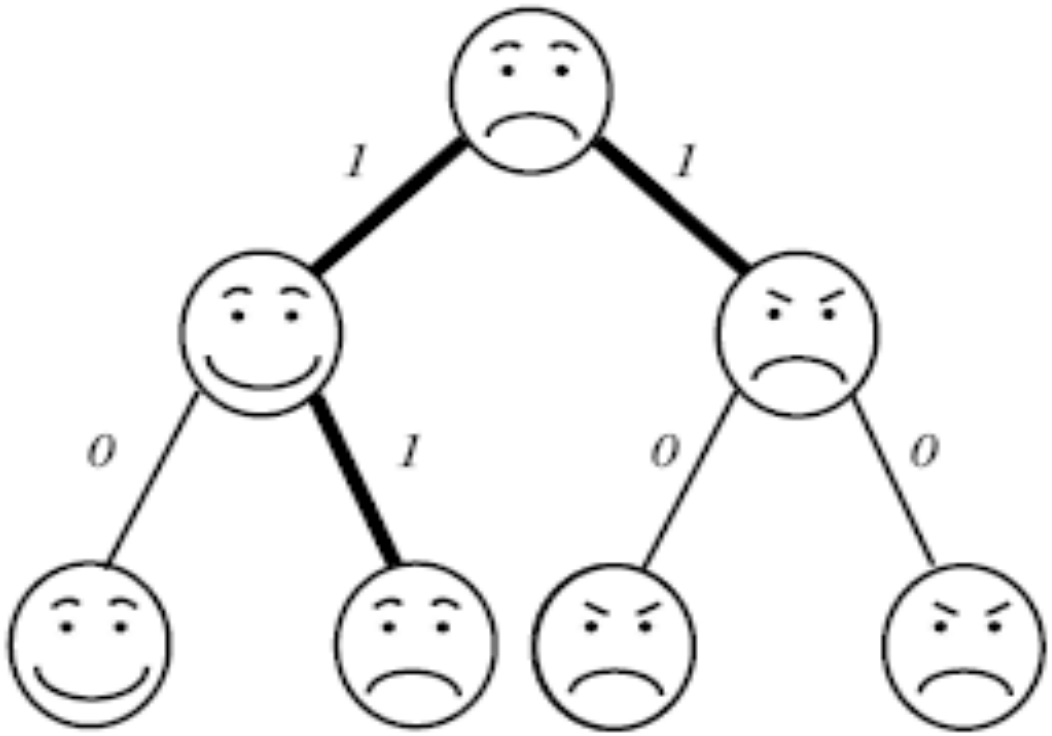
Characters / states	State 1	State 2
Mouth	Smile	Frown
Eyebrows	Normal	Pointed

Character-Based Phylogeny Reconstruction: Criterion

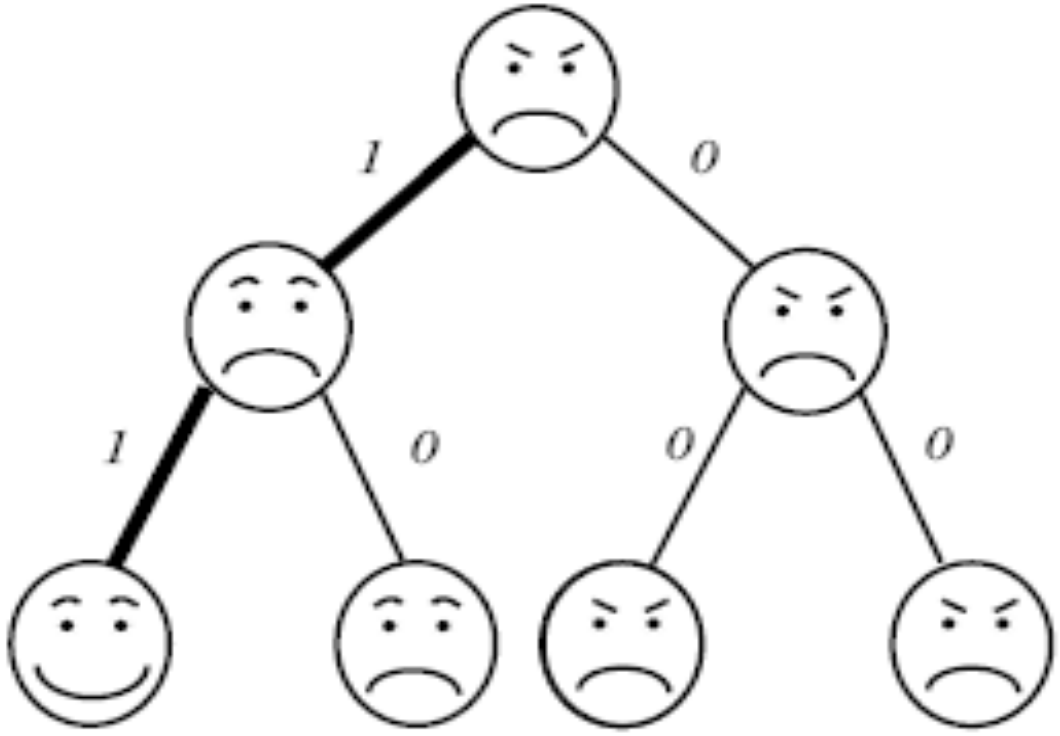


Question: Which tree is better?

Character-Based Phylogeny Reconstruction: Criterion



(a) *Parsimony Score=3*

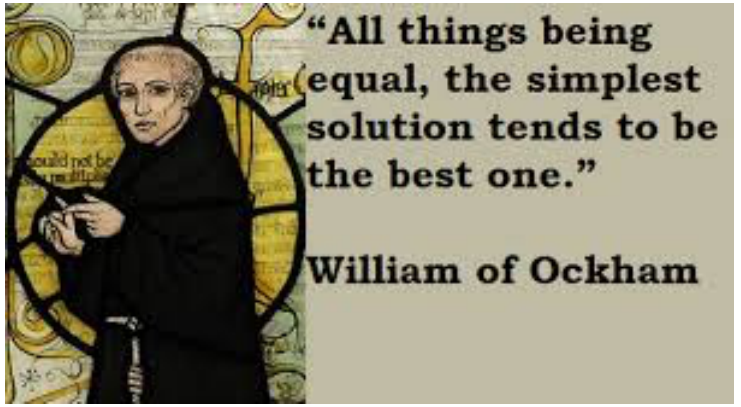


(b) *Parsimony Score=2*

Parsimony: minimize number of changes on edges of tree

Why Parsimony?

- Ockham's razor: "simplest" explanation for data
- Assumes that observed character differences resulted from the fewest possible mutations
- Seeks tree with the lowest **parsimony score**, i.e. the sum of all (costs of) mutations in the tree.



A Small and a Large Problem

Small Maximum Parsimony Phylogeny Problem:

Given $m \times n$ matrix $A = [a_{i,j}]$ and tree T with m leaves, find assignment of character states to each internal vertex of T with minimum parsimony score.

Large Maximum Parsimony Phylogeny Problem:

Given $m \times n$ matrix $A = [a_{i,j}]$, find a tree T with m leaves labeled according to A and an assignment of character states to each internal vertex of T with minimum parsimony score.

A Small and a Large Problem

Small Maximum Parsimony Phylogeny Problem:

Given $m \times n$ matrix $A = [a_{i,j}]$ and tree T with m leaves, find assignment of character states to each internal vertex of T with minimum parsimony score.

Large Maximum Parsimony Phylogeny Problem:

Given $m \times n$ matrix $A = [a_{i,j}]$, find a tree T with m leaves labeled according to A and an assignment of character states to each internal vertex of T with minimum parsimony score.

Question: Are both problems easy (i.e. in P)?

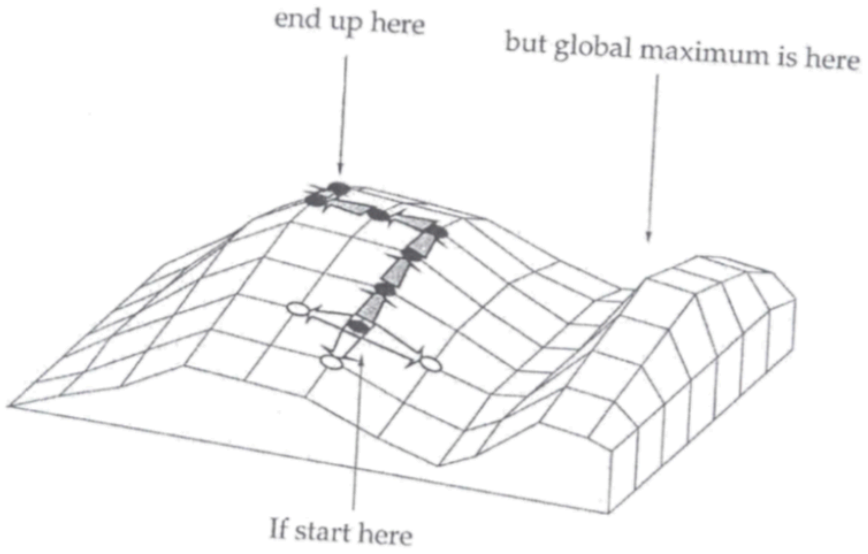
Large Maximum Parsimony Phylogeny

- This problem is NP-hard
- Heuristics using local search (tree moves)

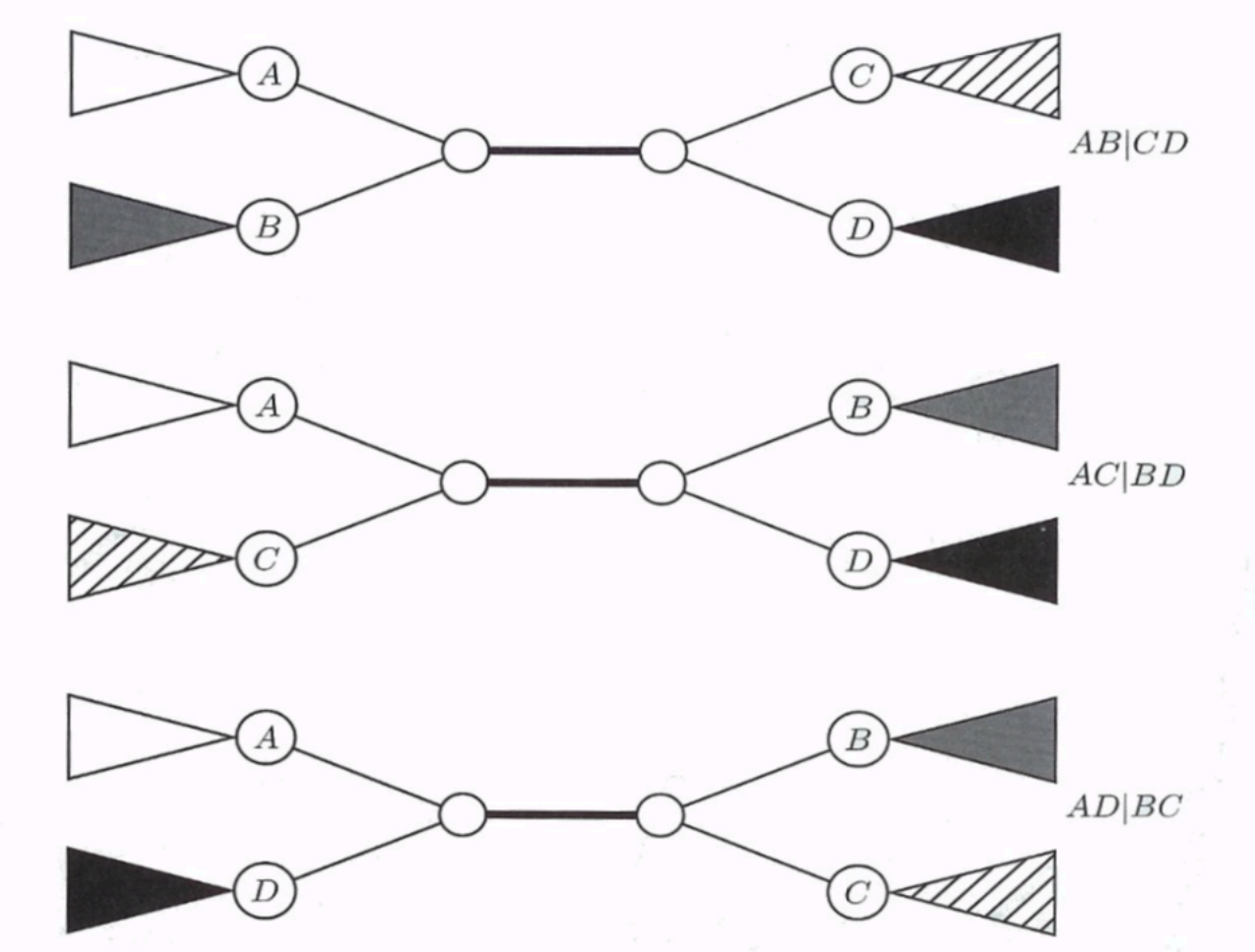
1. Start with an arbitrary tree *T.*
2. Check "neighbors" of *T*.
3. Move to a neighbor if it provides the best improvement in parsimony/likelihood score.

Caveats:

Could be stuck in **local** optimum, and not achieve global optimum



Example: Nearest-Neighbor Interchange (NNI)

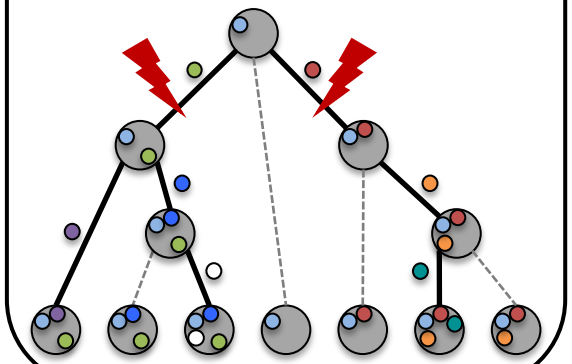


Rearrange four subtrees defined by one internal edge

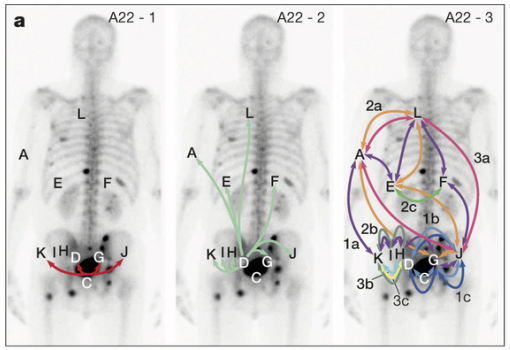
Figure: Jones and Pevzner

Phylogenies are Key to Understanding Cancer

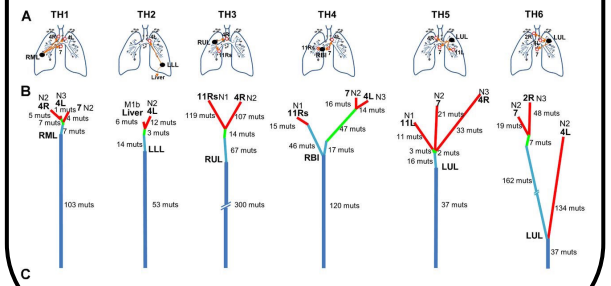
Identify targets for treatment



Understand metastatic development



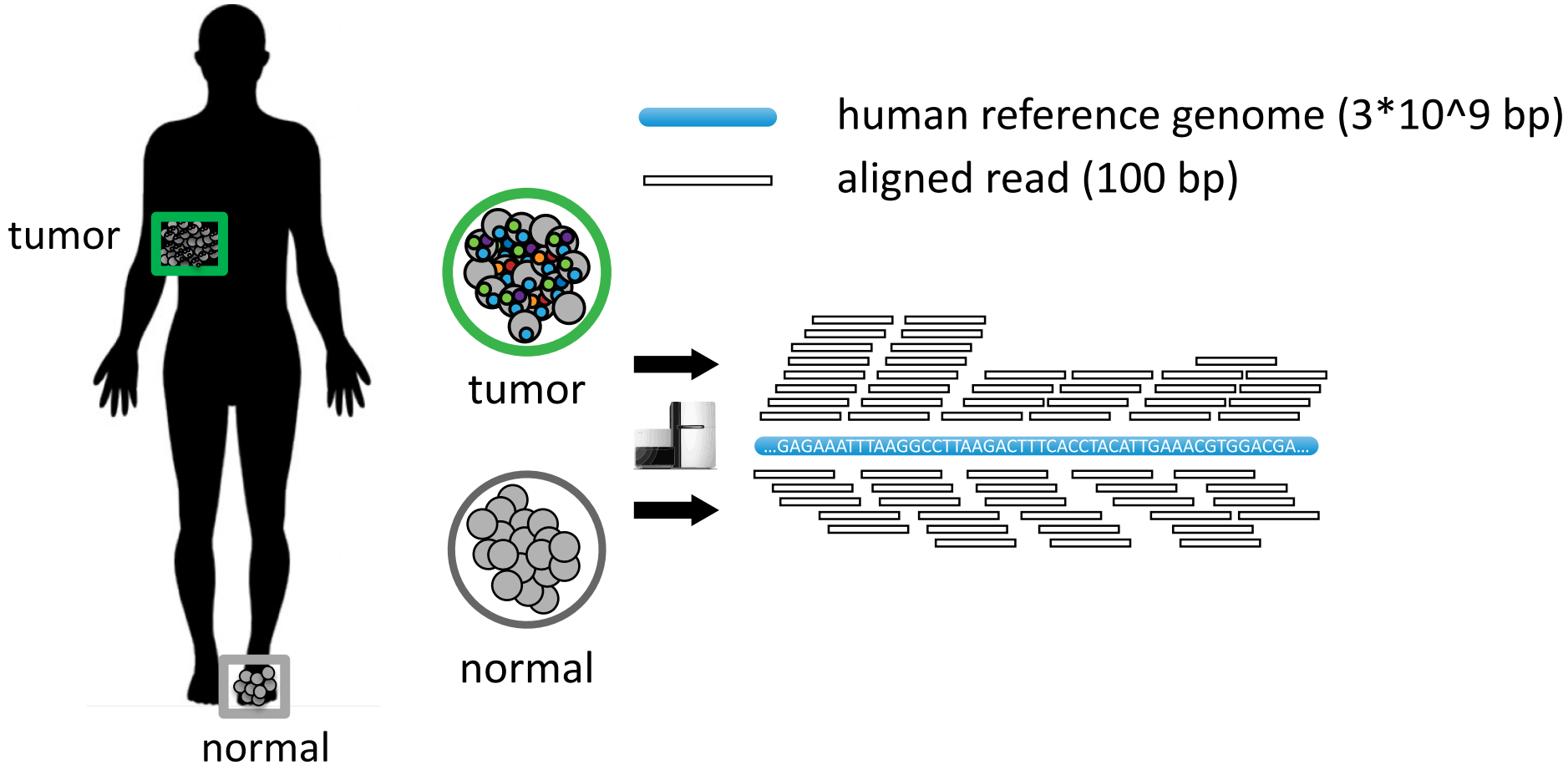
Recognize common patterns of tumor evolution across patients



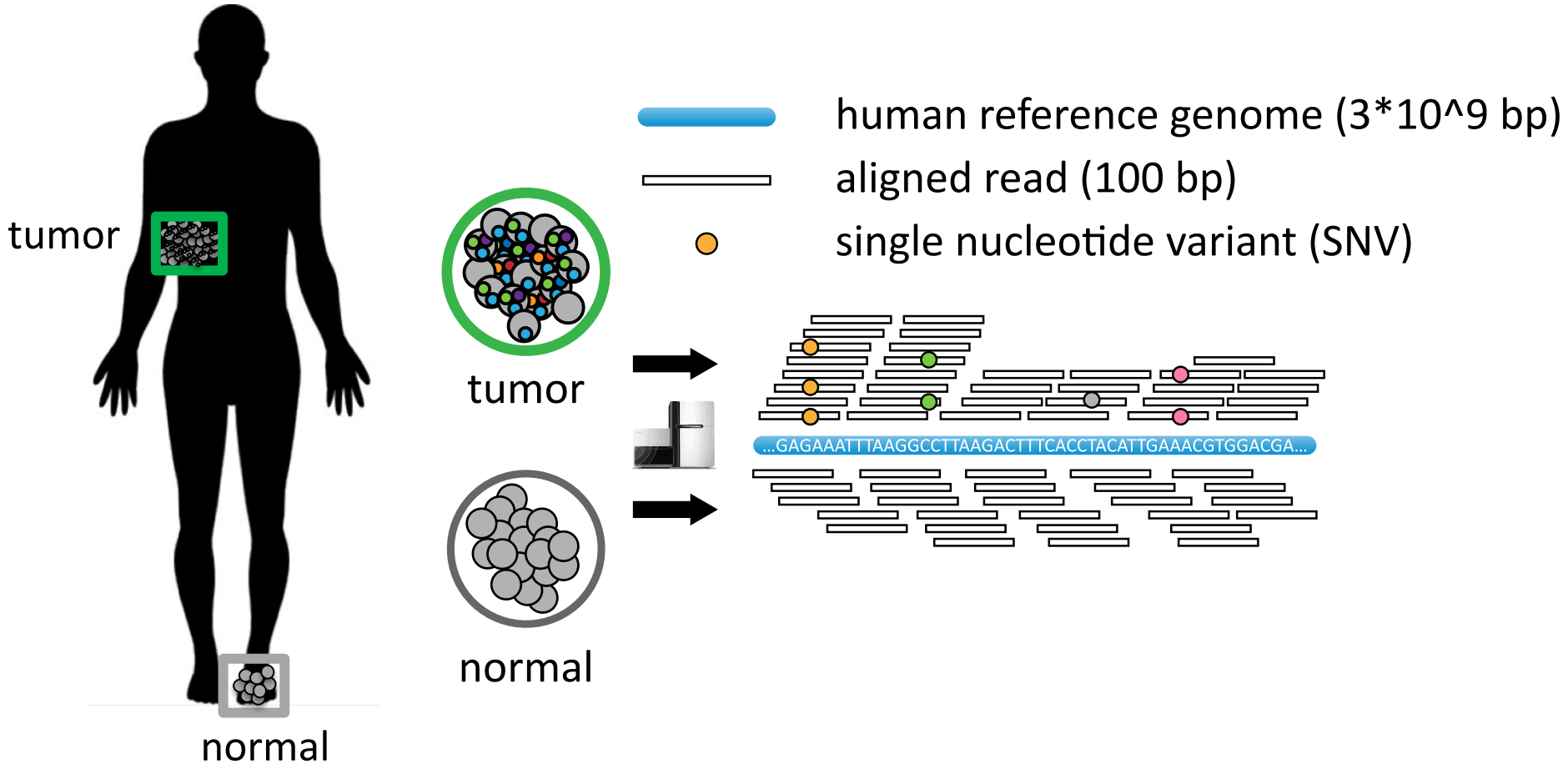
These downstream analyses **critically rely** on accurate tumor phylogeny inference

Key challenge in phylogenetics:
Accurate phylogeny inference from data at present time

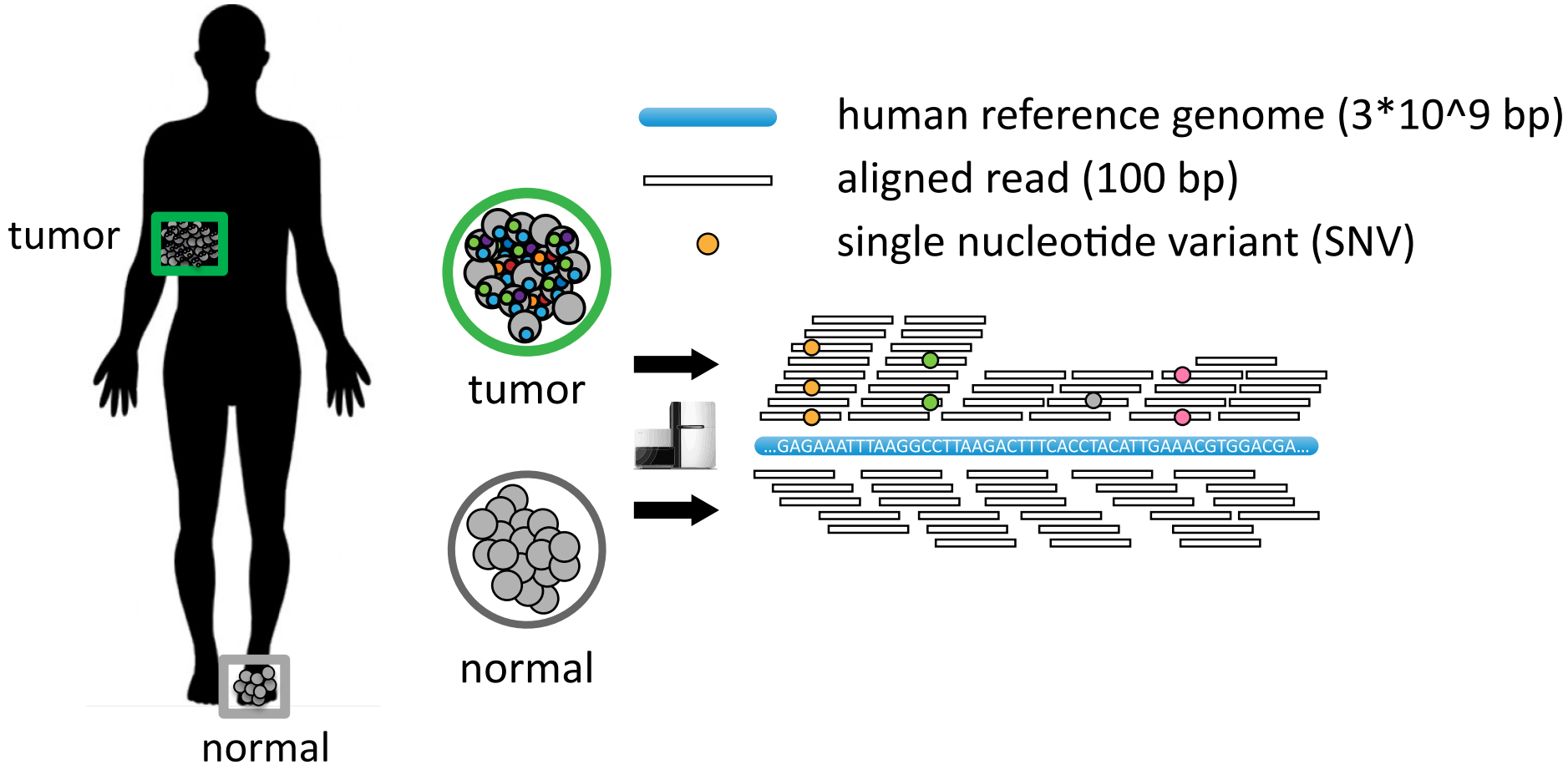
Additional Challenge in Cancer Phylogenetics



Additional Challenge in Cancer Phylogenetics



Additional Challenge in Cancer Phylogenetics

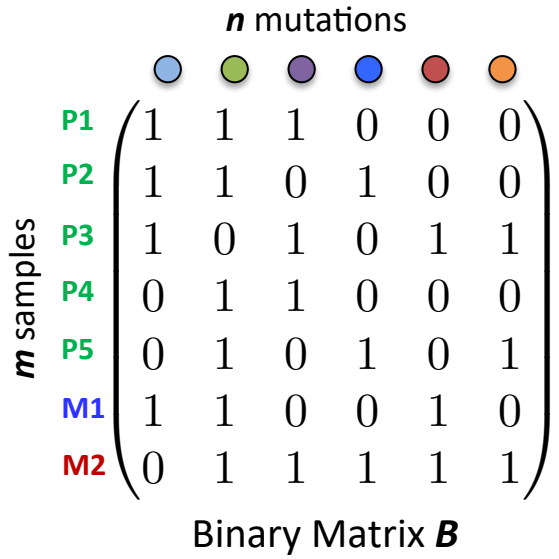


Additional challenge in cancer phylogenetics:
Phylogeny inference from **mixed bulk samples** at present time

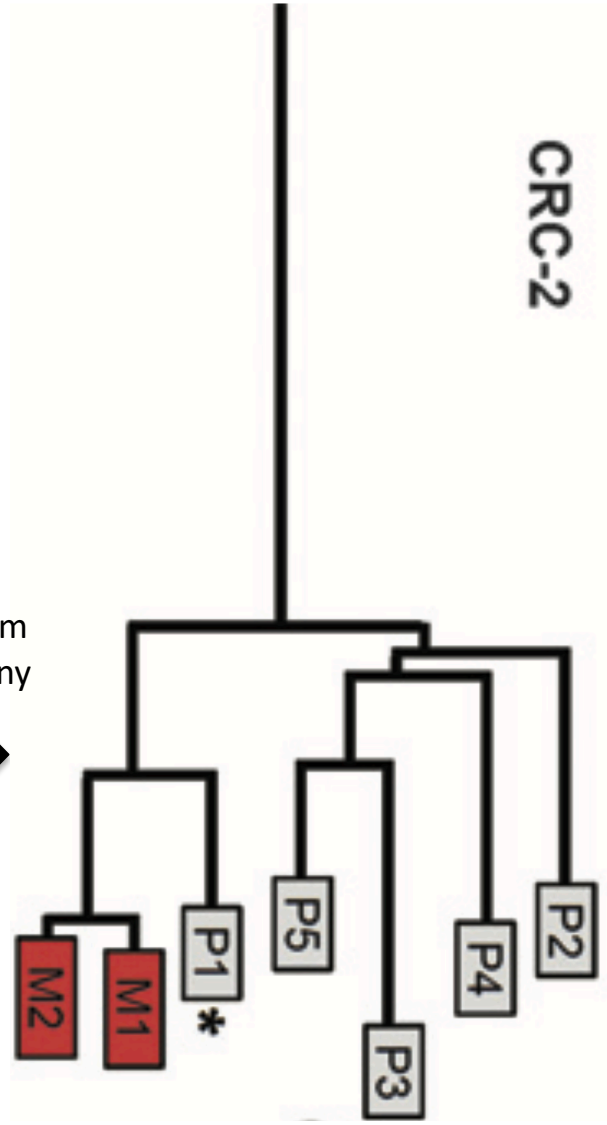
Tumor Phylogeny Inference

Metastatic Colorectal Cancer (Patient CRC2)
[Kim et al., *Clin Cancer Res* 21(19), 2015]:

- 5 primary samples (P1-P5)
- 2 metastases (M1-M2)
- 412 single-nucleotide variants (SNVs)



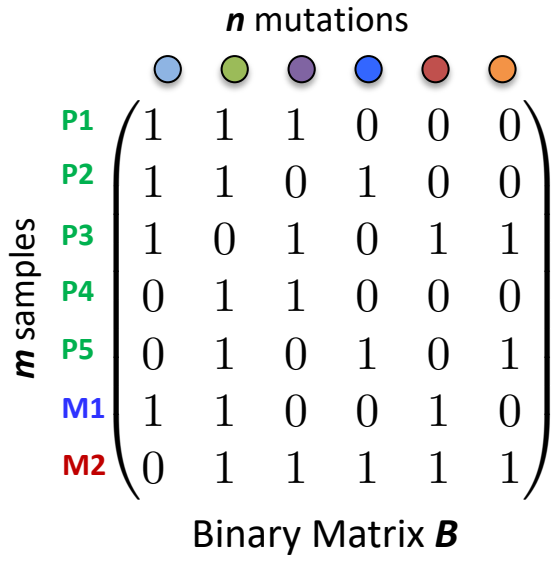
Maximum Parsimony



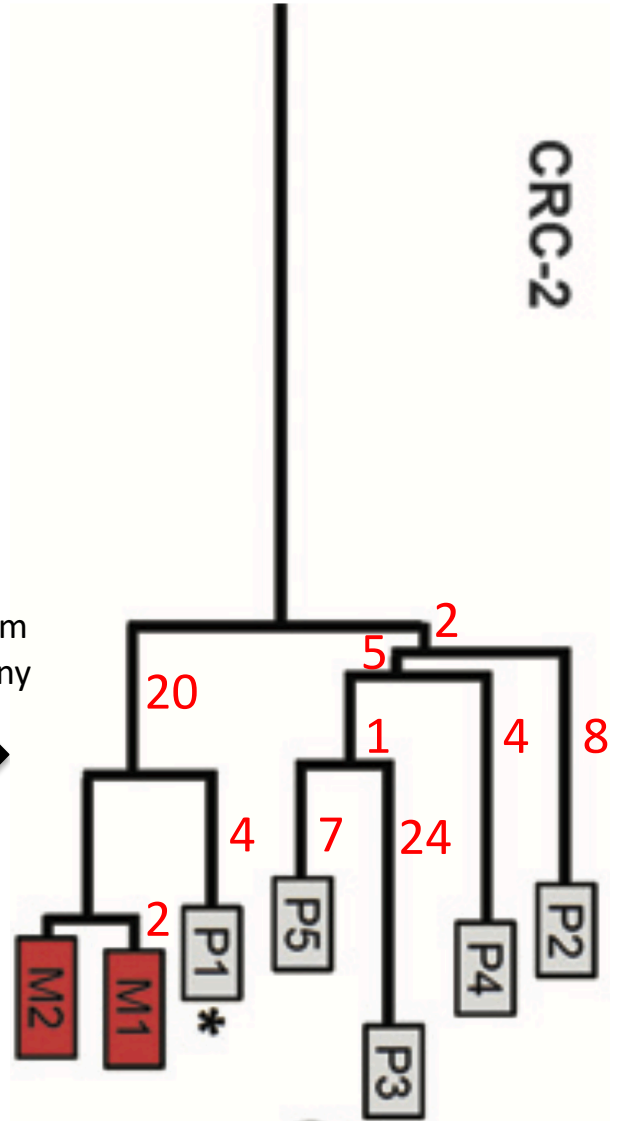
Tumor Phylogeny Inference

Metastatic Colorectal Cancer (Patient CRC2)
[Kim et al., *Clin Cancer Res* 21(19), 2015]:

- 5 primary samples (P1-P5)
- 2 metastases (M1-M2)
- 412 single-nucleotide variants (SNVs)
- 41 mutate more than once (**homoplasy**)



Maximum Parsimony



Heuristic for Tumor Phylogeny Inference

Metastatic Colorectal Cancer (Patient CRC2)
[Kim et al., *Clin Cancer Res* 21(19), 2015]:

- 5 primary samples (P1-P5)
- 2 metastases (M1-M2)
- 412 single-nucleotide variants (SNVs)
- 41 mutate more than once (**homoplasy**)

n mutations

m samples

P1	0.80	0.62	0.53	0.03	0.01	0.02
P2	0.45	0.34	0.04	0.43	0.02	0.02
P3	0.66	0.04	0.89	0.02	0.15	0.30
P4	0.04	0.72	0.54	0.01	0.01	0.00
P5	0.02	0.67	0.03	0.06	0.03	0.11
M1	0.74	0.43	0.01	0.02	0.14	0.00
M2	0.01	0.54	0.15	0.25	0.32	0.38

Frequency Matrix ***F***

Discretize

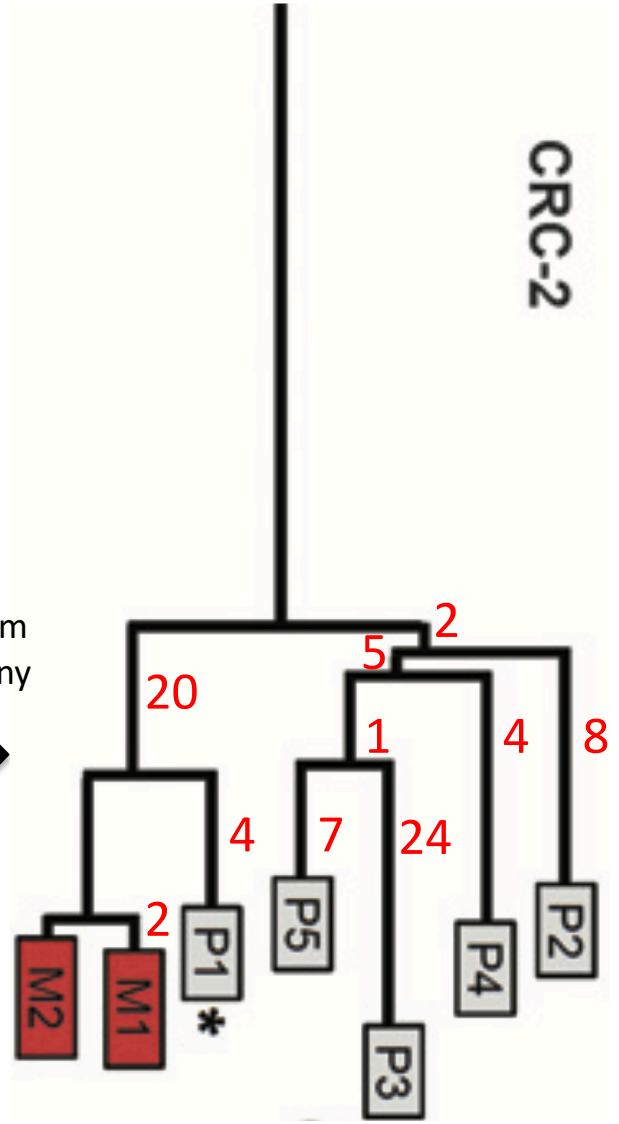
n mutations

m samples

P1	1	1	1	0	0	0
P2	1	1	0	1	0	0
P3	1	0	1	0	1	1
P4	0	1	1	0	0	0
P5	0	1	0	1	0	1
M1	1	1	0	0	1	0
M2	0	1	1	1	1	1

Binary Matrix ***B***

Maximum Parsimony



Resulting sample tree is **not** representative of the division/mutation history or the migration history

Summary

- DNA, RNA and proteins are sequences
  - Central dogma of molecular biology: DNA -> RNA -> protein
- Problem != algorithm
- Key challenge in computational biology is translating a biological problem into a computational problem
- Cancer is a genetic disease caused by somatic mutations
- Inter-tumor heterogeneity and intra-tumor heterogeneity:
  - *Not only is every tumor different, but so is every tumor cell…*
- Reading:
  - “Biology for Computer Scientists” by Lawrence Hunter (http://www.el-kebir.net/teaching/CS466/Hunter_BIO_CS.pdf)