Great Ideas in Computational Biology

02-251

Phillip Compeau & Carl Kingsford

What does biology have to do with computers?

- Huge amount of data: too much to analyze by hand, lots of mystery left about how life works.

- Requires clever algorithms to:
  - find interesting patterns
  - store / search / compare
  - visualize vast collections of data
  - predict missing or hard-to-observe features (like protein structure or evolutionary relationships)

- Nearly all molecular biology is now "computational biology": biologists depend on computer scientists every day.

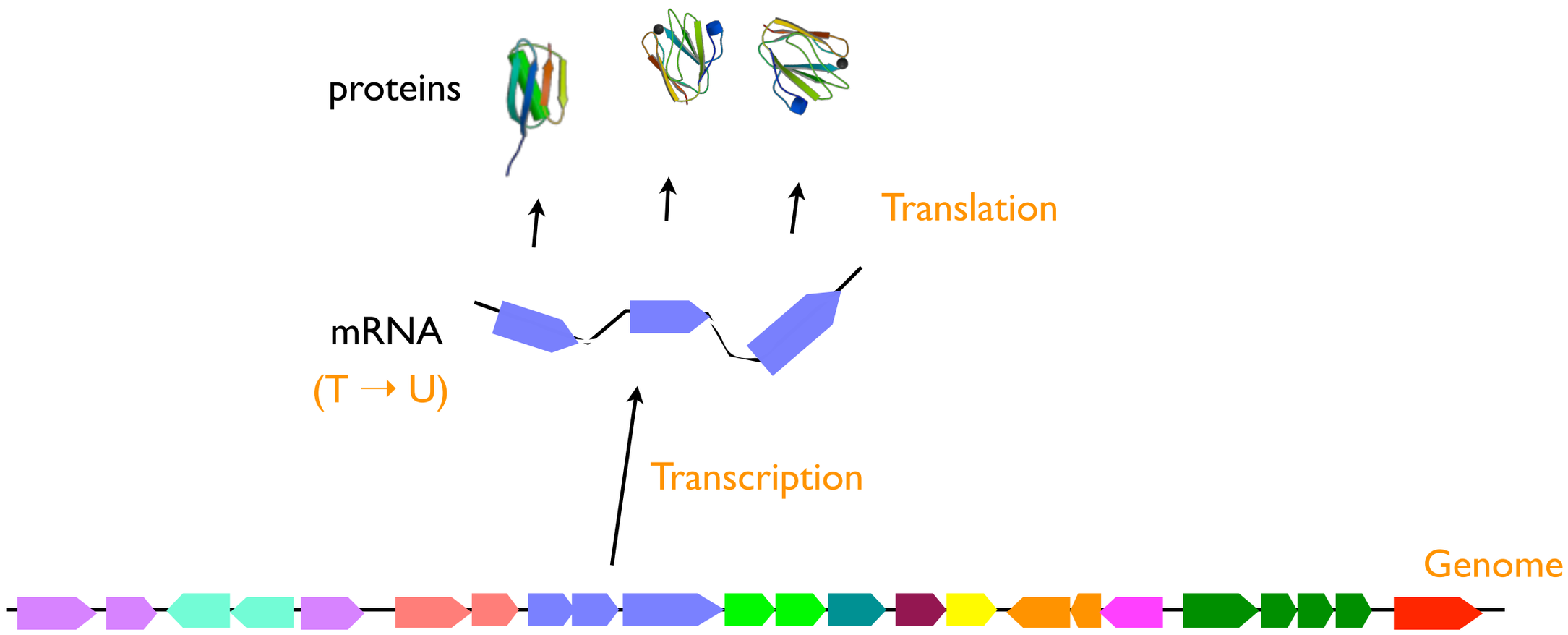
Example Computational Ideas

- Dynamic programming
- String data structures
- Hidden Markov Models
- Machine learning

Example 1: Genomics

- Algorithms for understanding and processing DNA and RNA data
- String algorithms are central

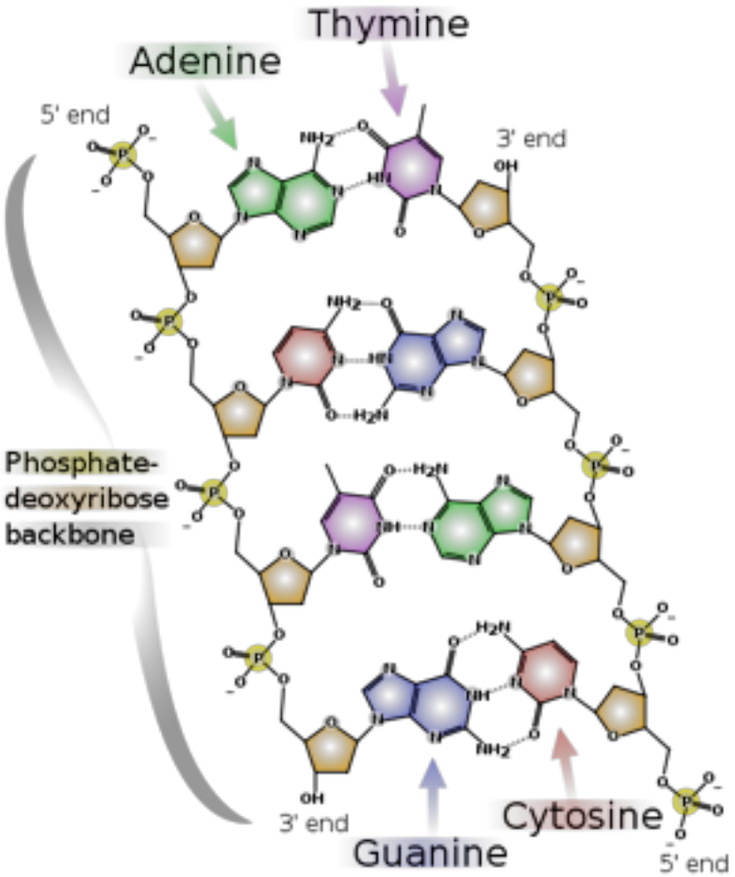
Central Dogma of Biology

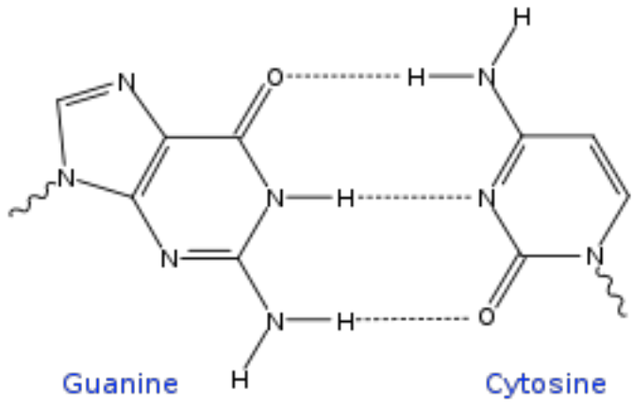


DNA =

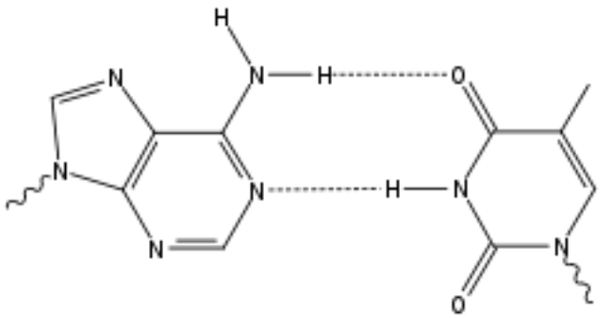
- double-stranded, linear molecule
- each strand is string over {A,C,G,T}
- strands are complements of each other (A ↔ T; C ↔ G)
- substrings encode for genes most of which encode for proteins

DNA


Thymine
Adenine
5' end
3' end
Phosphate-
deoxyribose
backbone
3' end
Guanine
Cytosine
5' end


Guanine
Cytosine

G C


Adenine
Thymine

A T

Genome of the Cow

a sequence of 2.86 billion letters

enough letters to fill a million pages of a typical book.

```
TATGGAGCCAGGTGCCTGGGGCAACAAGACTGTGGTCACTGAATTCATCCTTCTTGGTCTAACAGAGAACATAG
AACTGCAATCCATCCTTTTTGCCATCTTCCTCTTTGCCTATGTGATCACAGTCGGGGGCAACTTGAGTATCCTG
GCCGCCATCTTTGTGGAGCCCAAACTCCACACCCCCATGTACTACTTCCTGGGGAACCTTTCTCTGCTGGACAT
TGGGTGCATCACTGTCACCATTCCTCCCATGCTGGCCTGTCTCCTGACCCACCAATGCCGGGTTCCCTATGCAG
CCTGCATCTCACAGCTCTTCTTTTTCCACCTCCTGGCTGGAGTGGACTGTCACCTCCTGACAGCCATGGCCTAC
GACCGCTACCTGGCCATTTGCCAGCCCCTCACCTATAGCATCCGCATGAGCCGTGACGTCCAGGGAGCCCTGGT
GGCCGTCTGCTGCTCCATCTCCTTCATCAATGCTCTGACCCACACAGTGGCTGTGTCTGTGCTGGACTTCTGCG
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GACAAGGACAAGGGCATTGGCATCCTCAACACTGTCATCAGCCCCATGCTGAACCCACTCATCTACAGCCTCCG
GAACCCTGATGTGCAGGGCGCCCTGAAGAGGTTGCTGACAGGGAAGCGGCCCCCGGAGTG ...
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   1 atactataaa tccacctctc attttattca cttcatacat gctattacac actctgtgcc
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```

Example Genomic Sequence

⇐ Giant Panda (*Ailuropoda melanoleuca*) mitochondrion sequence [Peng et al, Gene 397:76-83 (2007)]

Obviously, computers are needed to understand what this means.

- Where are the genes encoded in this sequence?
- What causes each gene to be turned on or off?
- How does the genome produce observed traits?

Researchers at many institutions are putting together the genomes of many animals.

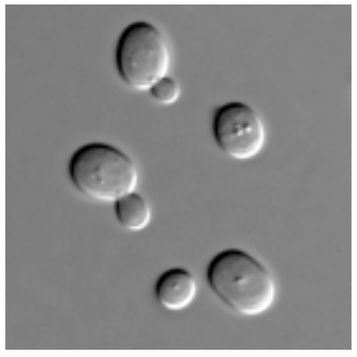
Help understand how to make animals and plants more hardy, resistant to disease, and understand their biology.

New technologies and larger genomes require new algorithms.

Other Sequenced Genomes

Arabidopsis thailiana

Callithrix jacchus
(marmoset)

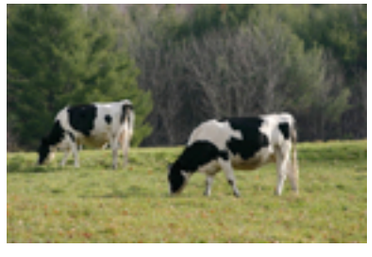


Saccharomyces cerevisiae
(baker's yeast)

Canis lupus familiaris
(dog)

Apis mellifera
(honey bee)

Drosophila melanogaster
(fruit fly)



Bos torus
(cow)

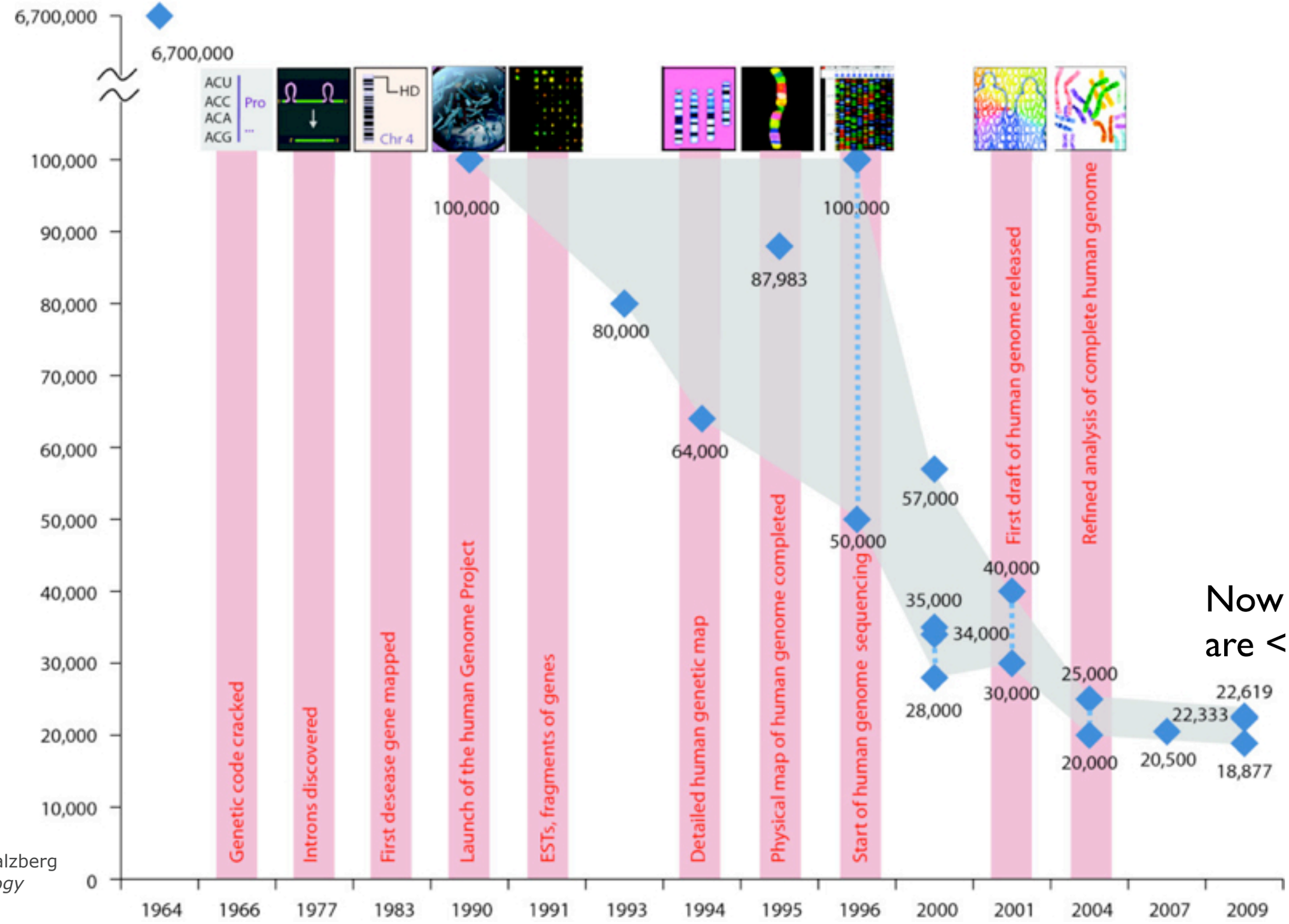
Equus caballus
(horse)

and many more...

Sequenced Eukaryotic Chromosomes

Estimates for the # of Human Genes

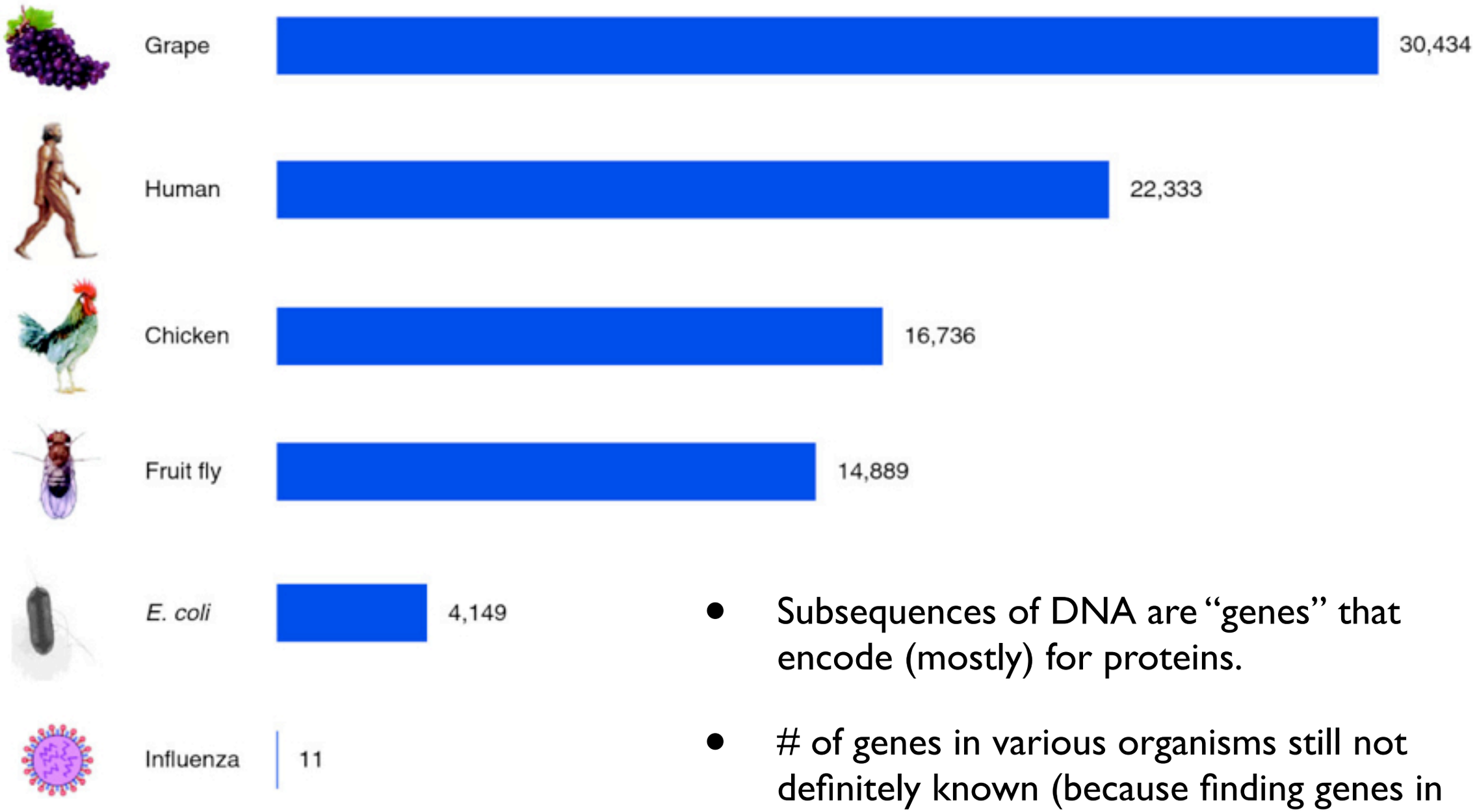
Before human genome sequence was available, many
(but not all) estimates for # of genes were high (> 80,000).



Now estimates are < 23,000.

Pertea and Salzberg
Genome Biology
2010 **11**:206

of Genes in Various Organisms



Pertea and Salzberg
Genome Biology 2010
11:206

- Subsequences of DNA are "genes" that encode (mostly) for proteins.
- # of genes in various organisms still not definitely known (because finding genes in the sequence is a hard problem that we will talk about).
- But there are reasonably good estimates.

Example 2: Phylogenetics

- Algorithms for modeling how organisms evolved
- Algorithms on trees are central

Influenza Virus

(Toda et al., 2006)

Rapidly evolving (it's genome is mutating):

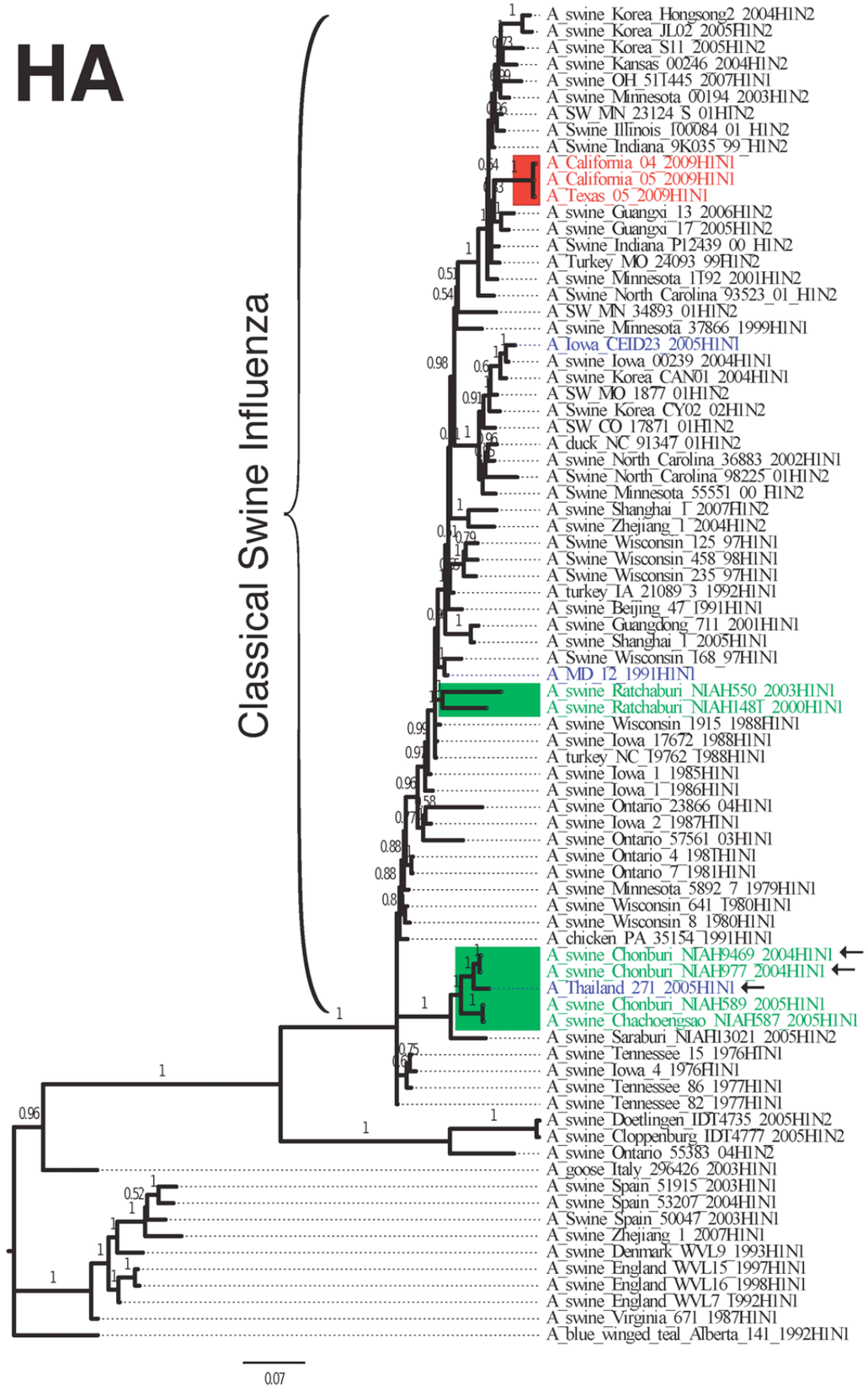
that's why you have to get a different flu shot every year

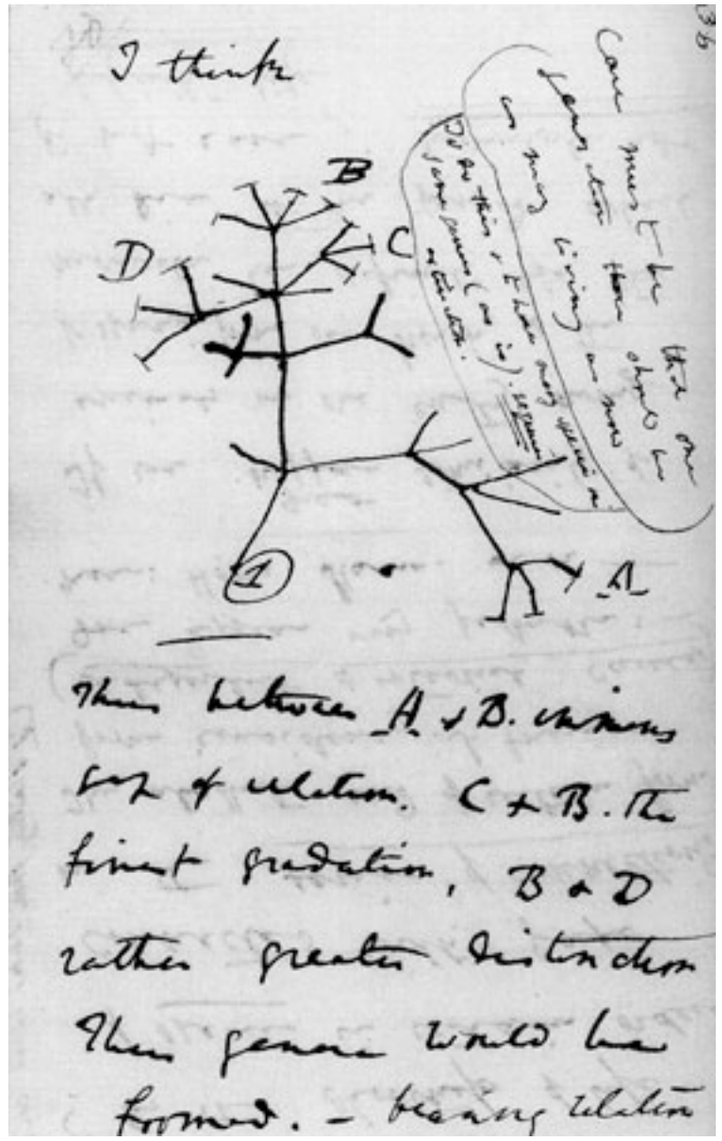
3 strains must be selected each year to include in the vaccine.

So, the evolution of the virus is must be predicted.

Evolutionary Trees

HA





http://www.amnh.org/exhibitions/darwin/idea/treelg.php

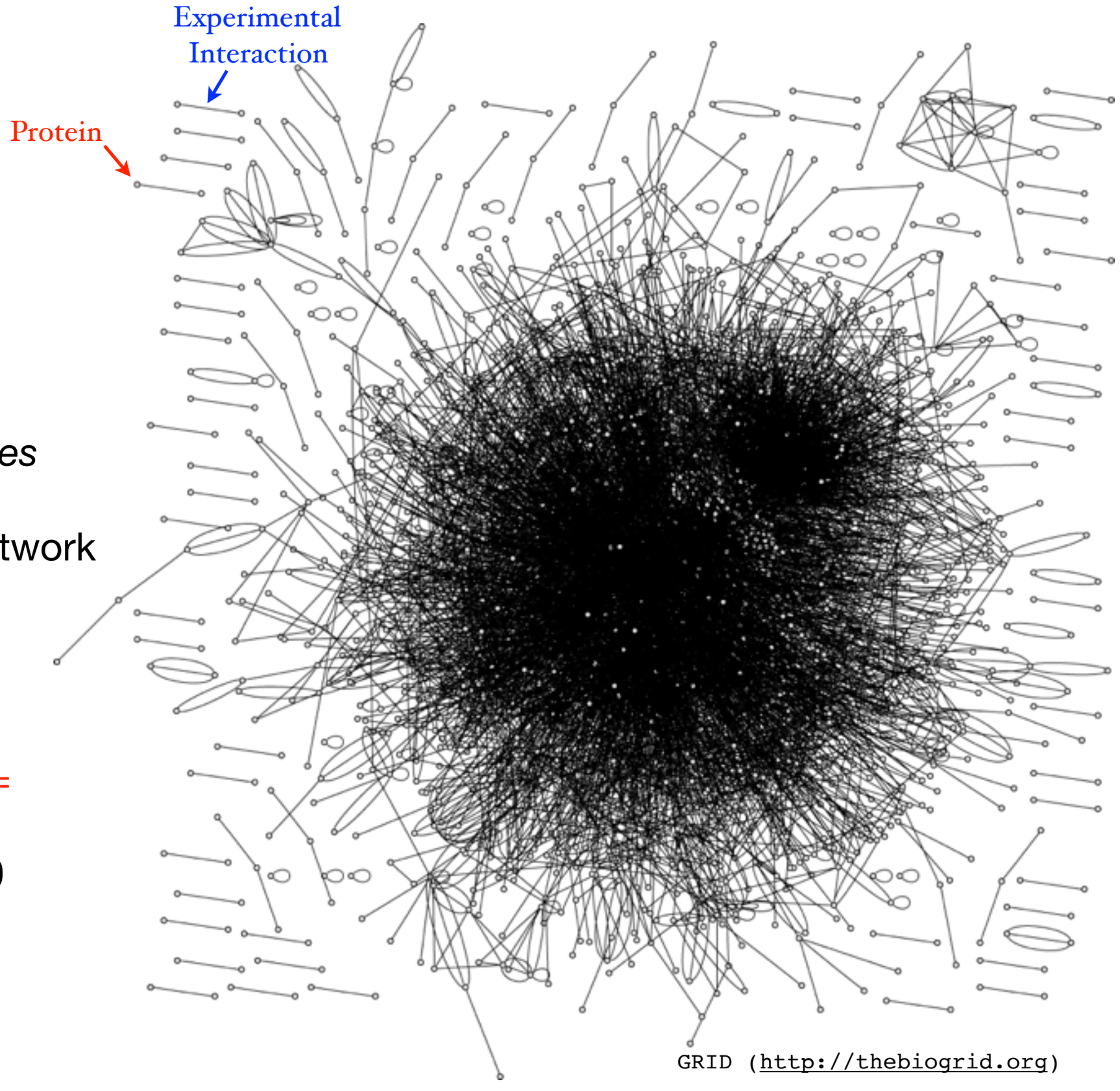
Example 3: Network Biology

- Algorithms for modeling how cellular components work together
- Graph algorithms are central

Yeast (aka *Saccharomyces cerevisiae)* interaction network

8,742 edges

3113 nodes (= proteins) (out of ~6,000 genes)



Network Questions

- Can we find groups of molecules that work together to perform a function?

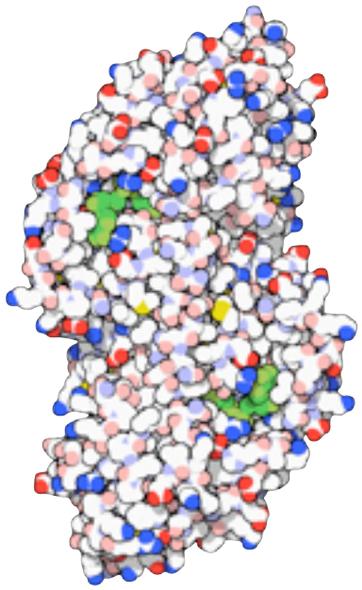
- Can we use interactions between proteins to predict what a protein does?

- Can we determine the how such a complex system evolved?

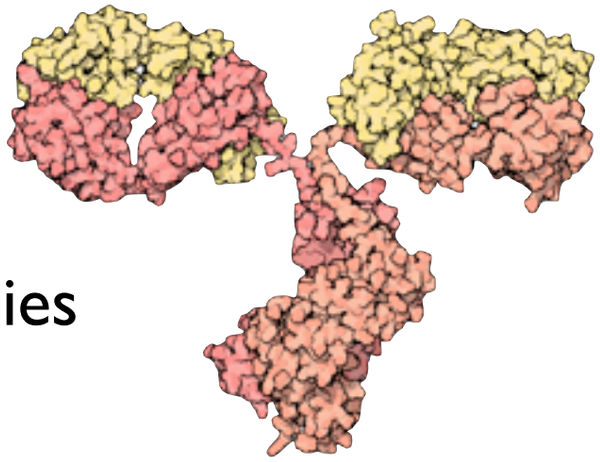
Example 4: Protein Structure

- Predicting the 3D structure of proteins
- Optimization algorithms are central

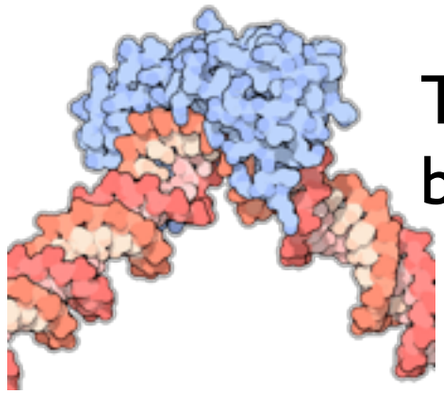
Examples of Proteins



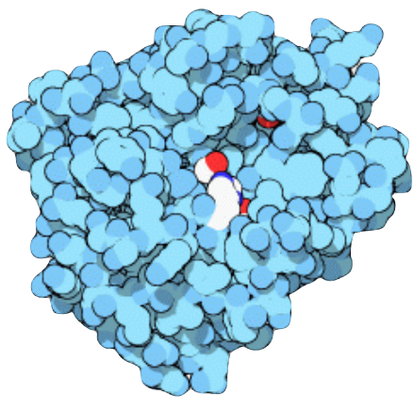
Alcohol dehydrogenase



Antibodies



TATA DNA binding protein



Trypsin: breaks down other proteins

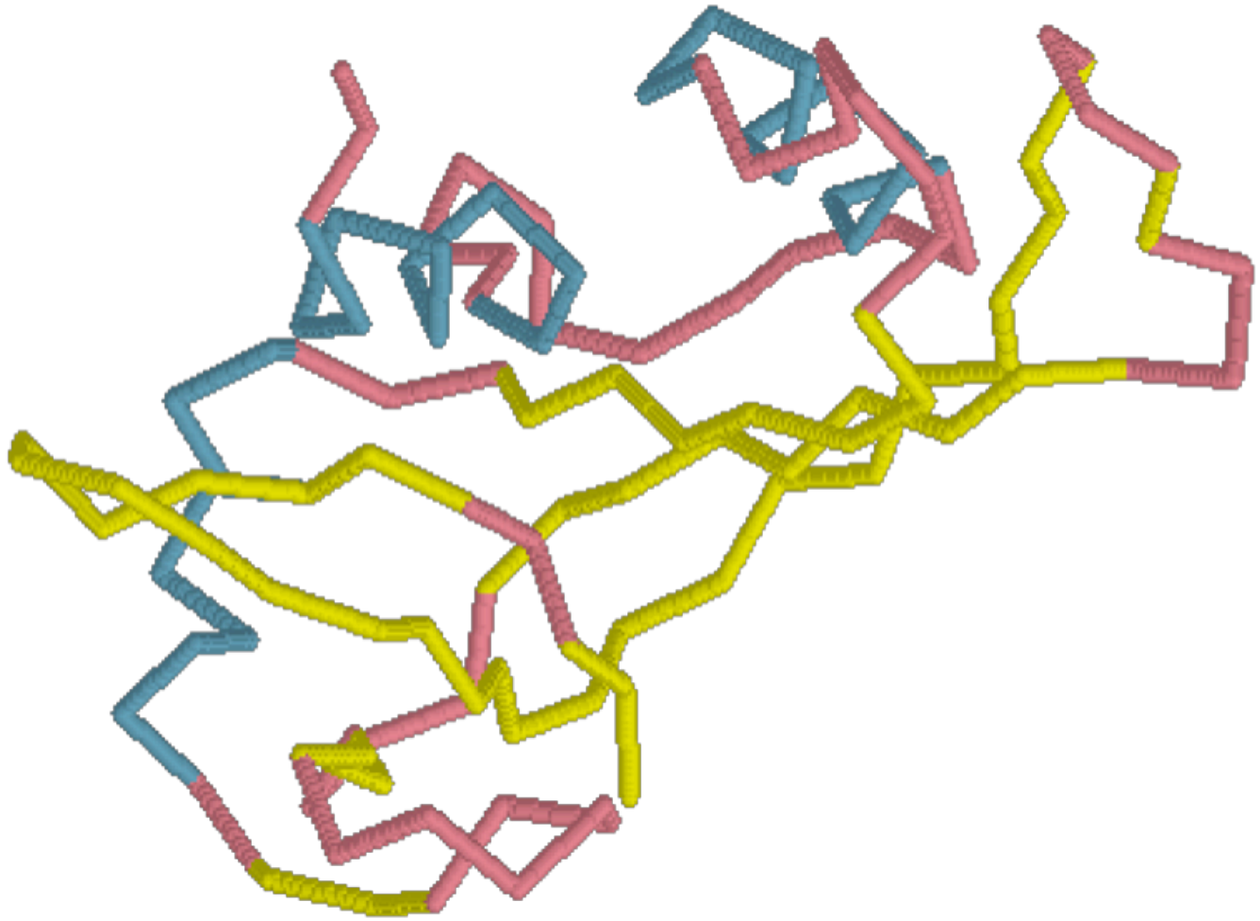
Collagen: forms tendons, bones, etc.

Examples of "Molecules of the Month" from the Protein Data Bank
http://www.rcsb.org/pdb/

Predicting Structure

Given: ATGAAGATGATAGATGGGGCCCGACAG…

Determine:



Course Mechanics

- **Homework** (30%): mix of “theory” and programming assignments
  - Theory assignments submitted via Gradescope
  - Programming assignments submitted via Stepik and autograded.
  - You can use any programming language.
  - NO LATE ASSIGNMENTS ACCEPTED

- **Exams** (40%): 2 in-class midterms (10% each) + final (20%)
  - Midterm 1: Thursday, February 14
  - Midterm 2: Tuesday, April 2
  - Final: TBD by the university (do not schedule flights until this is posted)

Course Mechanics, cont.

- **Project** (20%): more details later in the semester
  - Will involve applying ideas we've learned to some real data
  - Write-up + in-class presentation

- **Participation** (10%):
  - Attendance of lectures is required
  - You are allowed 3 missed classes
  - New material will be introduced in recitations.
  - **NO UNAPPROVED USE OF ELECTRONICS IN CLASS**

- **Mini-Lectures:**
  - Two lectures will be on-your-own watching of a computational biology lecture from a menu we will provide.
  - You will write a summary of these lectures in lieu of attending the two lectures before the midterms.

Academic Honesty

- You may discuss programming assignments with classmates

- **However, you must not share or show or see the code of your classmates. You must write your own code entirely.**

- You may never use, look at, study, or copy any answers from previous semesters of this course or from the internet.

- All class work should be done independently unless explicitly indicated on the assignment handout.

Prerequisites

- You should be comfortable programming
- We generally don't assume any biological background – we'll introduce the relevant biology as it is needed
- Mathematics: we assume elementary math & logical thinking & some familiarity with probability
  - We'll review probability facts as needed
  - Assume you are familiar with big-O notation

Questions?