Computational Structural Bioinformatics

ECS129

Instructor: Patrice Koehl

Science, then, and now…

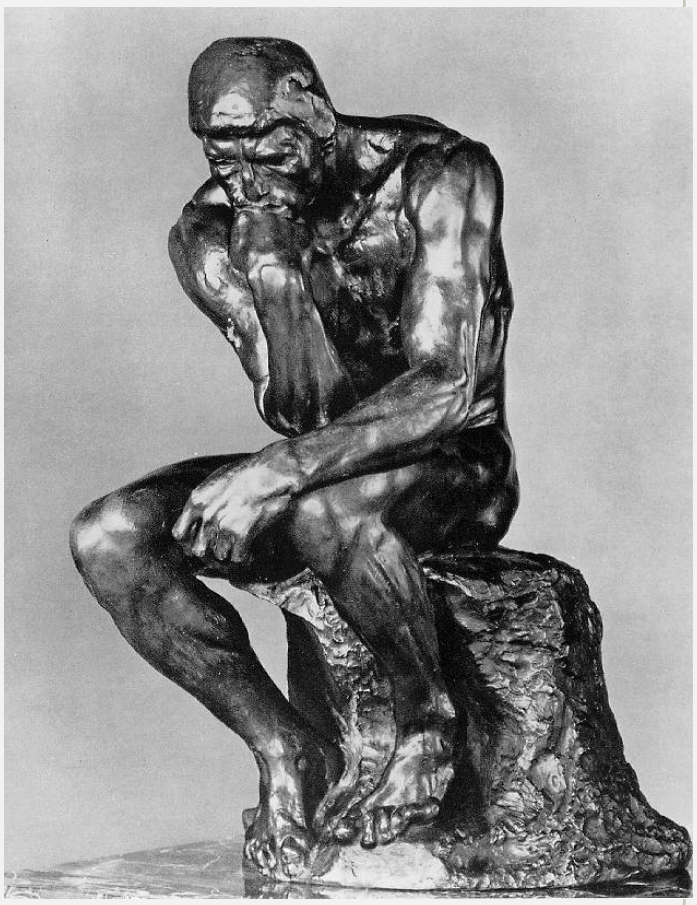
At the beginning, there were thoughts, and observation….

Science, then, and now…

- For a long time, people thought that it would be enough to reason about the existing knowledge to explore everything there is to know.

- One single person could possess all knowledge in her cultural context. (encyclopedia of Diderot and D'Alembert)

- Reasoning, and mostly passive observation were the main techniques in scientific research



Science, then, and now…

"All science is either physics, or stamp collecting"

Rutherford, chemist and physicist, 1876-1937

Science, then and now

- Today's experiment yields massive amounts of data
- From hypothesis-driven to exploratory data analysis:
  - data are used to formulate new hypotheses
  - computers help formulate hypotheses
- No single person, no group has an overview of what is known

Context: Biology

- "Life sciences" have their origins in ancient Greece

  Aristotle wrote influential treatises on zoology, anatomy and botany, that remained influential till the Renaissance

- "Life sciences" have always relied both on observation and discovery

  taxonomy, classifications, theory of evolution,…

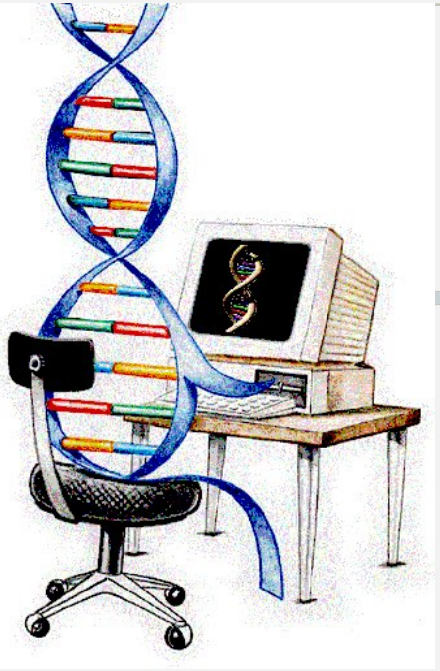
- Biology is changing with the arrival of massive amount of data from the different genomics experiments

What is ‘bioinformatics’?

- The term was originally proposed in 1988 by Dr. Hwa Lim
- The original definition was :

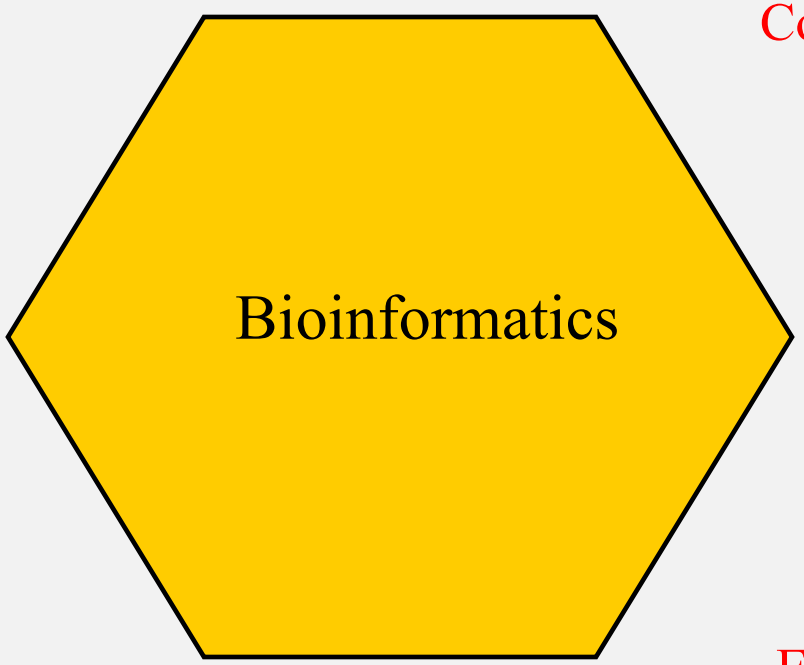
“a collective term for data compilation, organisation, analysis and dissemination”

That means….



- Using information technology to help solve biological problems by designing novel algorithms and methods of analyses *(computational biology)*
- It also serves to establish innovative software and create new or maintain existing databases of information, allowing open access to the records held within them *(bioinformatics)*

Bioinformatics is interdisciplinary



Biomedicine

Mathematics
Statistics
Computer Science

Molecular
Biology
Structural
Biology

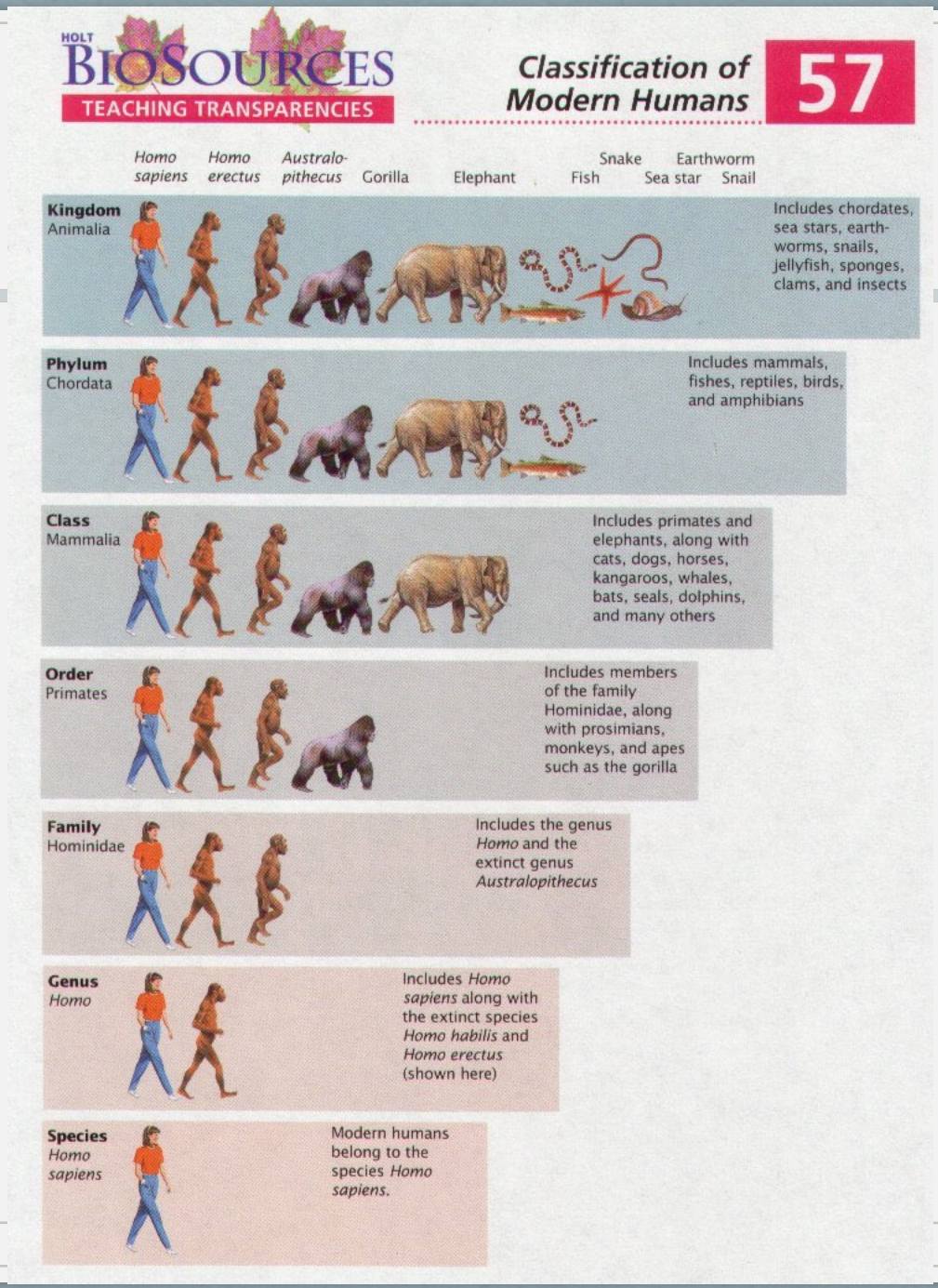
Biophysics

Ethical,
legal and
social implications

Evolution

What data?

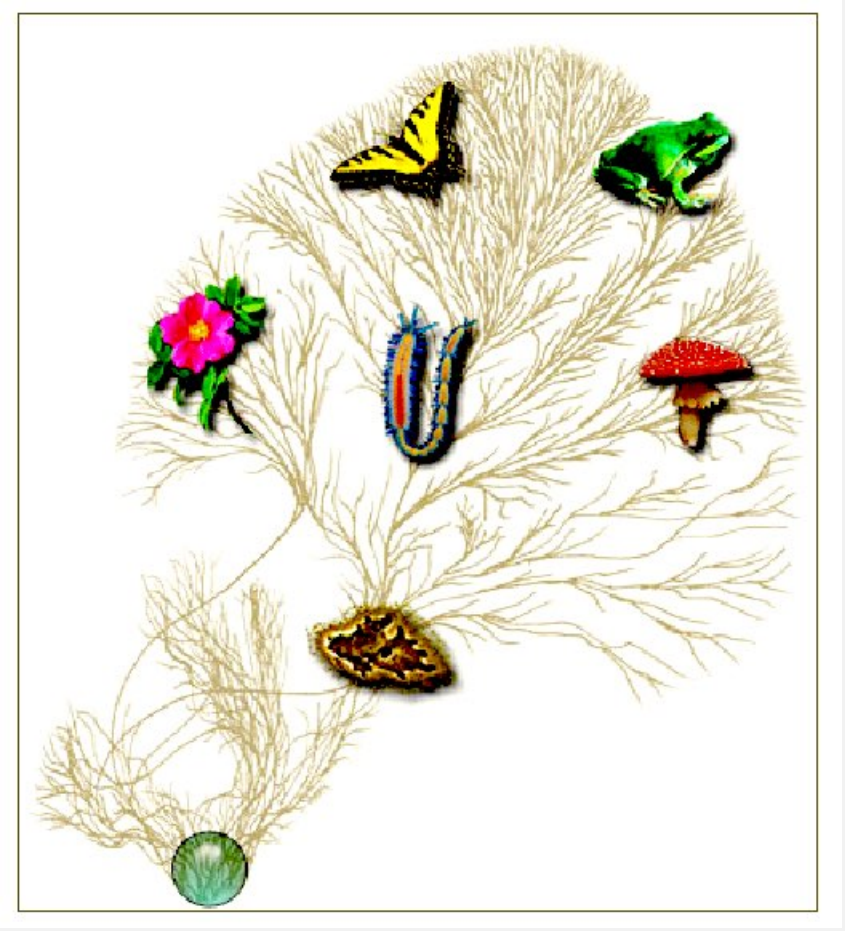
Biologists have been classifying data on plants and animals since the Greeks



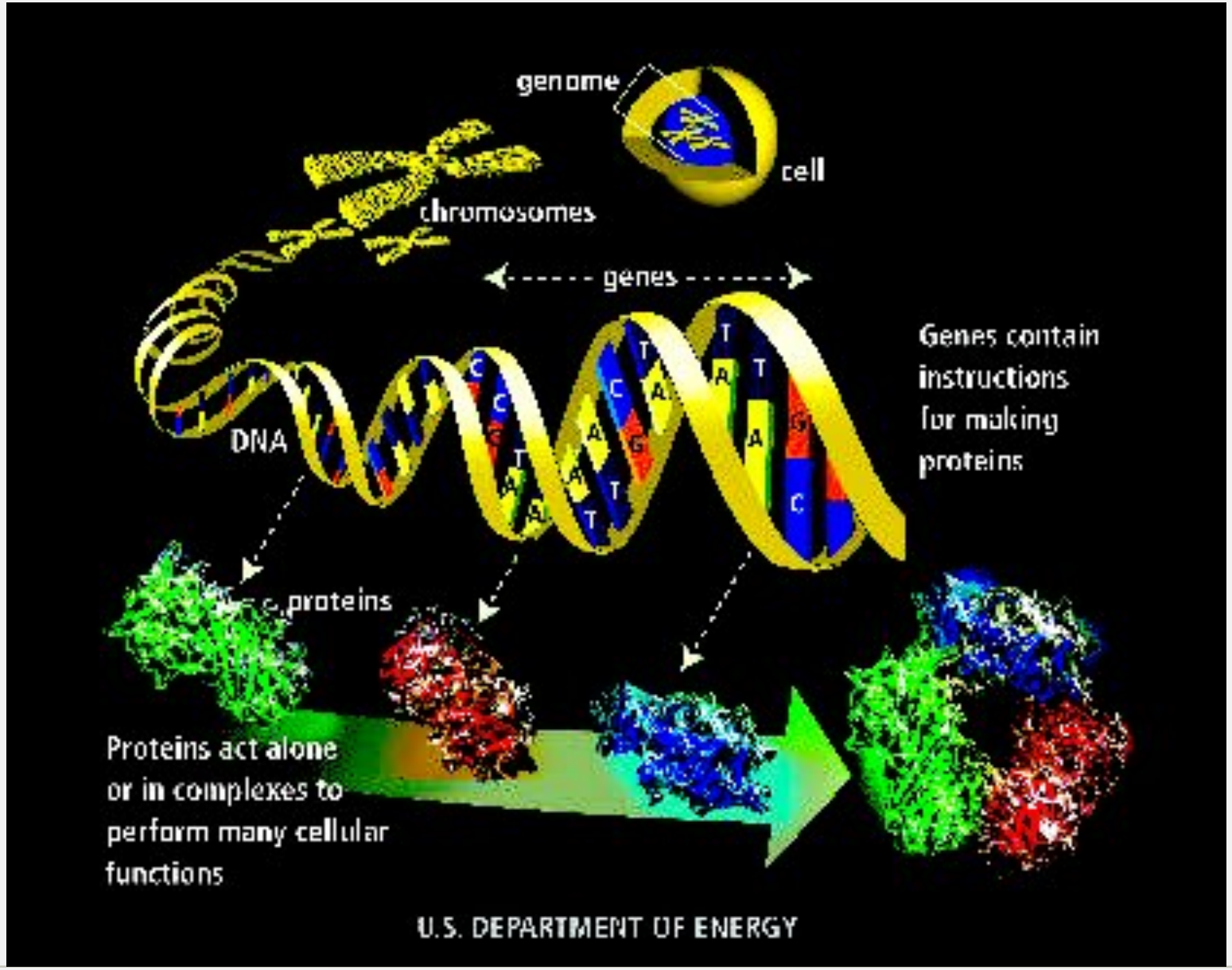
The Tree of Life

"The affinities of all beings of the same class have sometimes been represented by a great tree… As buds give rise by growth to fresh buds, and these if vigorous, branch out and overtop on all sides many a feebler branch, so by generation I believe it has been with the great Tree of Life, which fills with its dead and broken branches the crust of the earth, and covers the surface with its ever branching and beautiful ramifications."

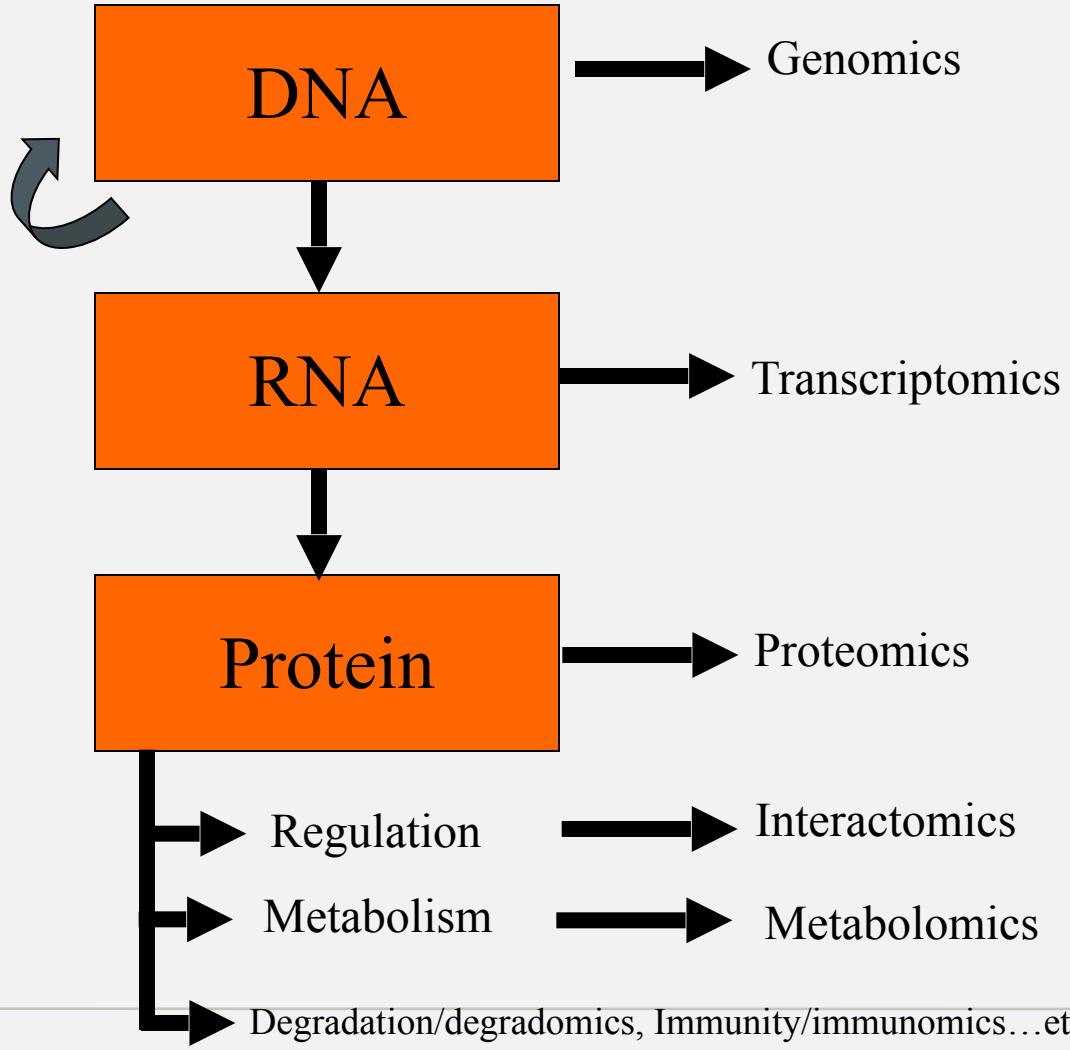
Charles Darwin, 1859



http://tolweb.org


genome
cell
chromosomes
genes
DNA
Genes contain instructions for making proteins
proteins
Proteins act alone or in complexes to perform many cellular functions
U.S. DEPARTMENT OF ENERGY

Central Dogma and the "omics"
Integrative Systems Biology



Genes (1)

- Genes are the basic units of heredity
- A gene is a sequence of bases that carries the information required for constructing a particular protein (gene “encode” the protein)
- The human genome comprises ~ 20,000 genes

Organism	Estimated size	Estimated gene #	Number of chromosome
Homo sapiens (human)	2900 million bases	~20,000	46
Rattus norvegicus (rat)	2,750 million bases	~30,000	42
Mus musculus (mouse)	2500 million bases	~30,000	40
Oryza sativa L. (rice)	450 million bases	~40,000	12
Drosophila melanogaster (fruit fly)	180 million bases	13,600	8
Arabidopsis thaliana (plant)	125 million bases	25,500	5
Caenorhabditis Elegans (roundworm)	97 million bases	19,100	6
Saccharomyces cerevisiae (yeast)	12 million bases	6300	16
Escherichia coli (bacteria)	4.7 million bases	3200	1
H. Influenzae (bacteria)	1.8 million bases	1700	1

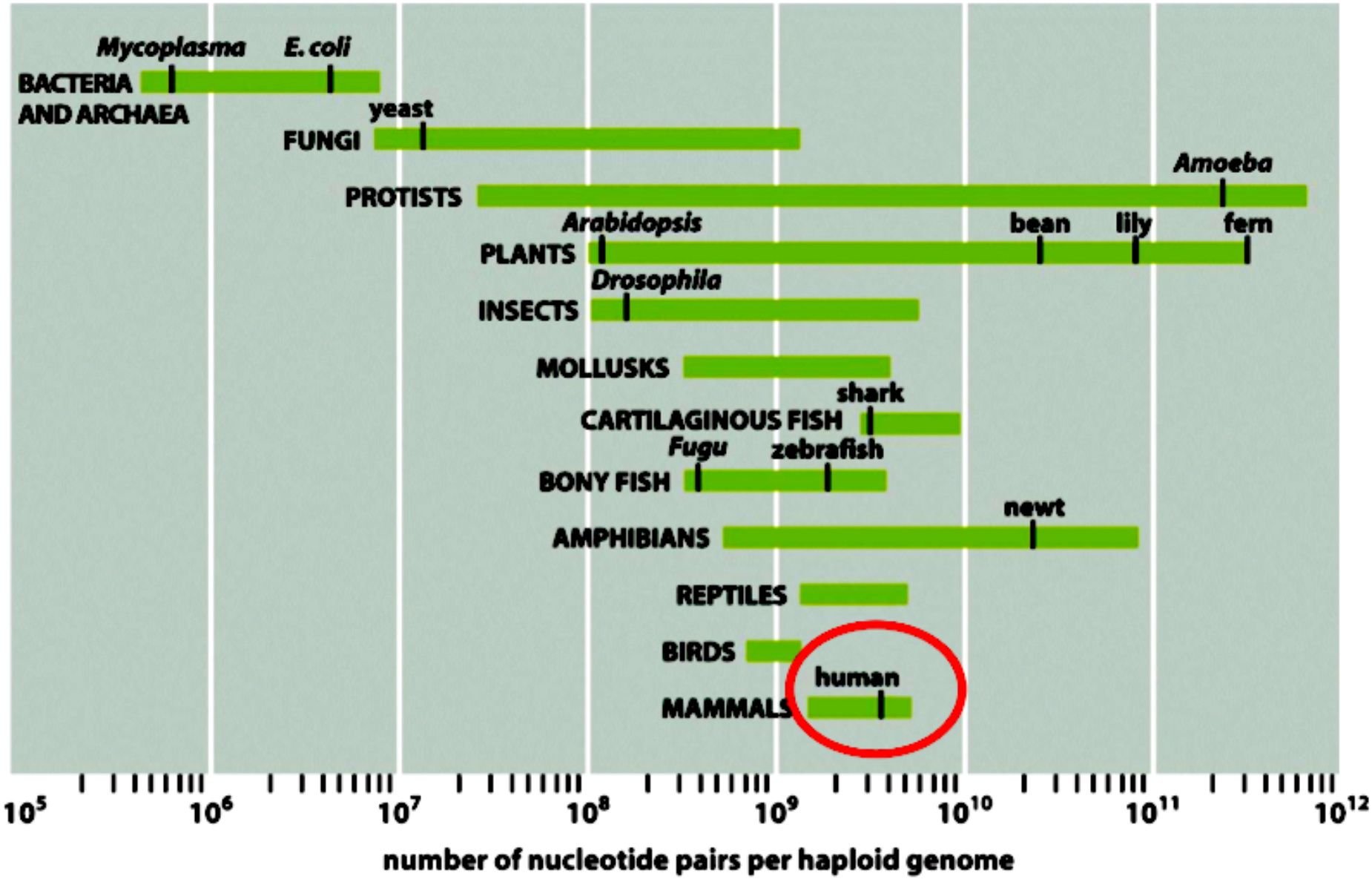
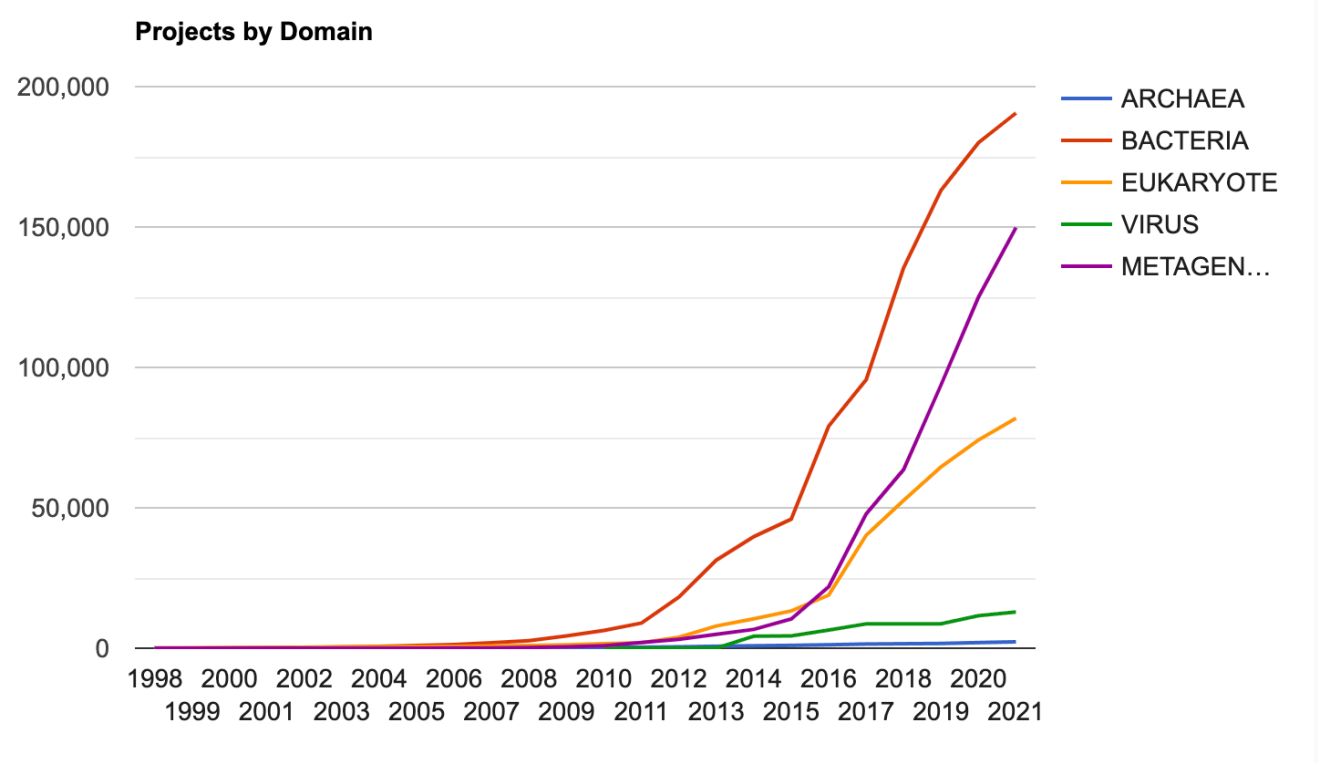


Figure 1-37 Molecular Biology of the Cell 5/e (© Garland Science 2008)

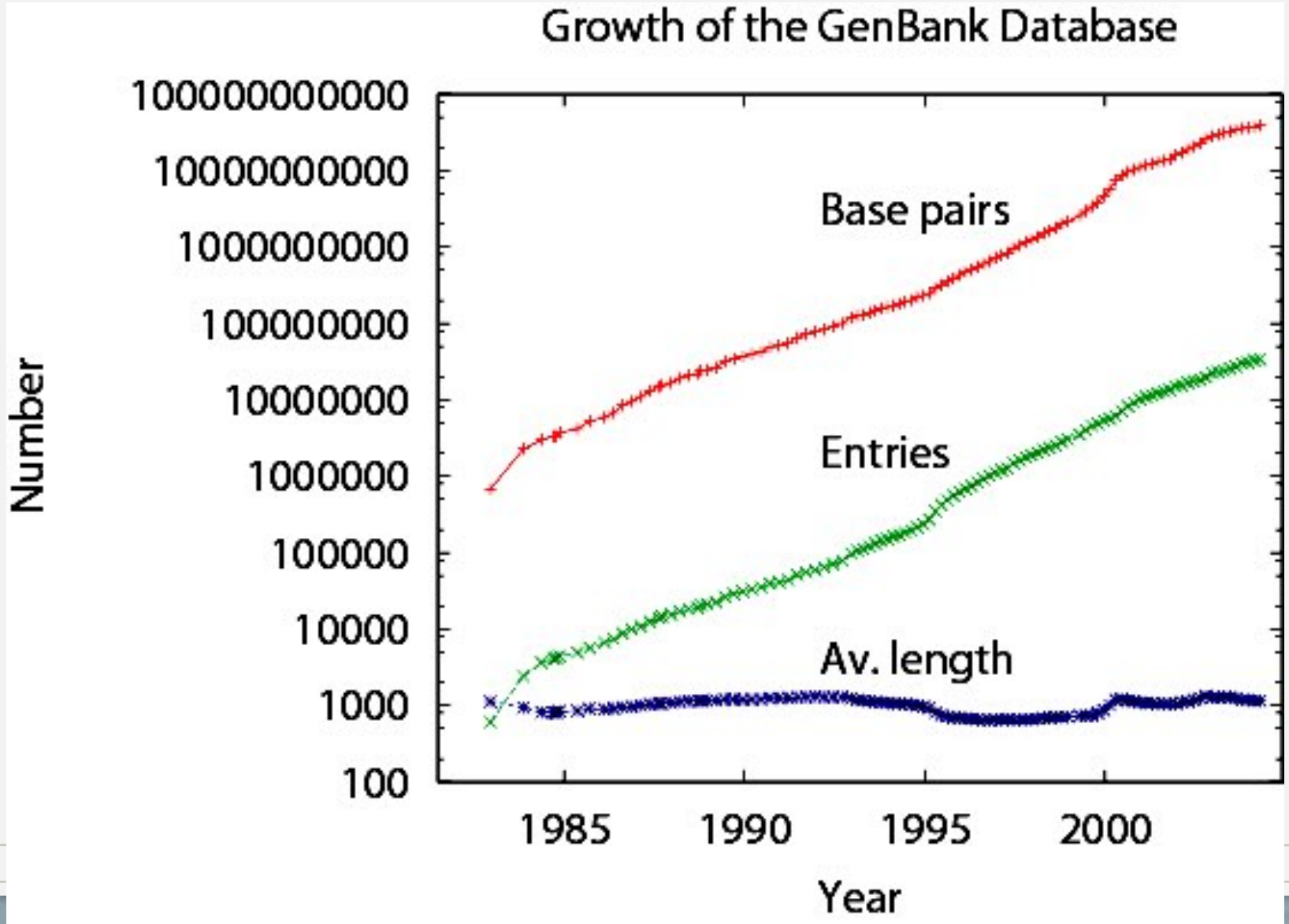
The genomics projects

Studies	49,867
Biosamples	147,318
Sequencing Projects	436,918
Analysis Projects	328,692
Organisms	418,931

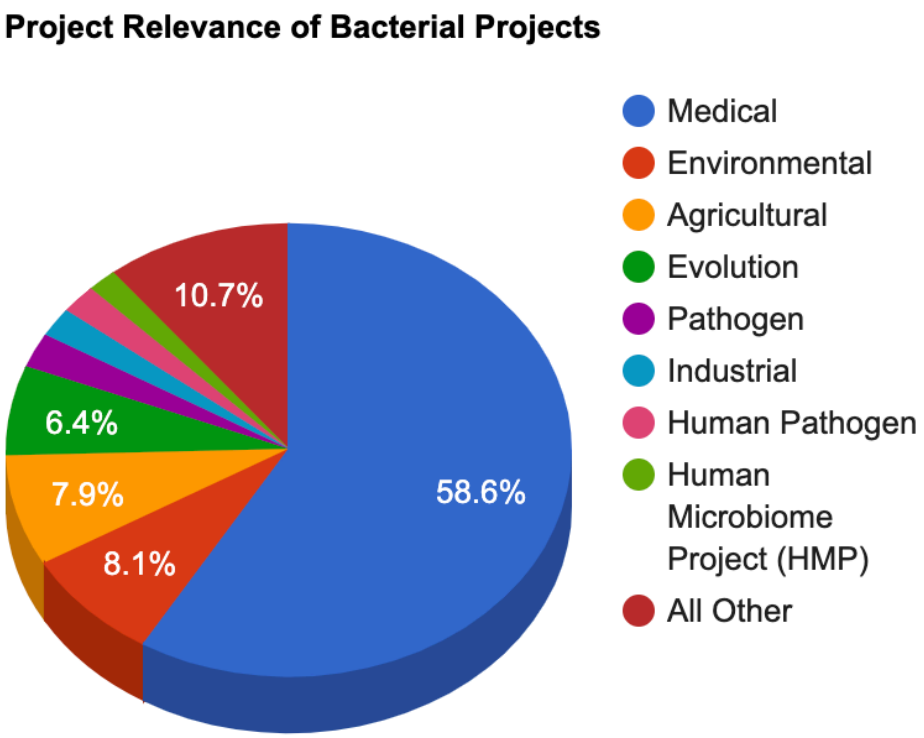


http://www.genomesonline.org (GOLD)

Gene Databases



Project Relevance of Bacterial Genome Projects



Genes (2)

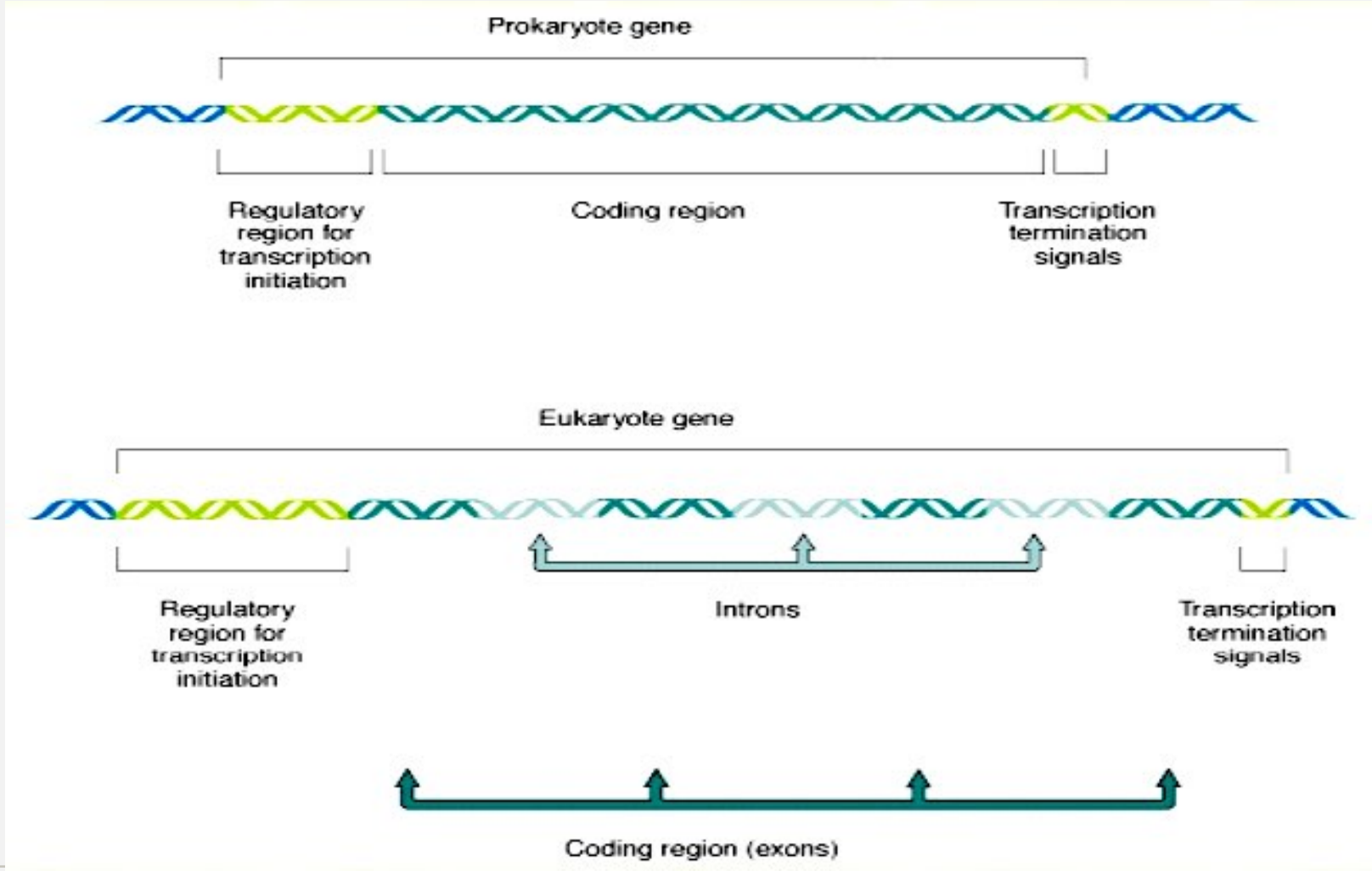
- The ~20,000 genes of the human genome encode > 100,000 polypeptides
- Not all of the DNA in a genome encodes protein

  microbes: 90% coding gene

  human: 3% coding gene

- About ½ of the non-coding DNA in humans is highly conserved (functionally important)

Gene Processing

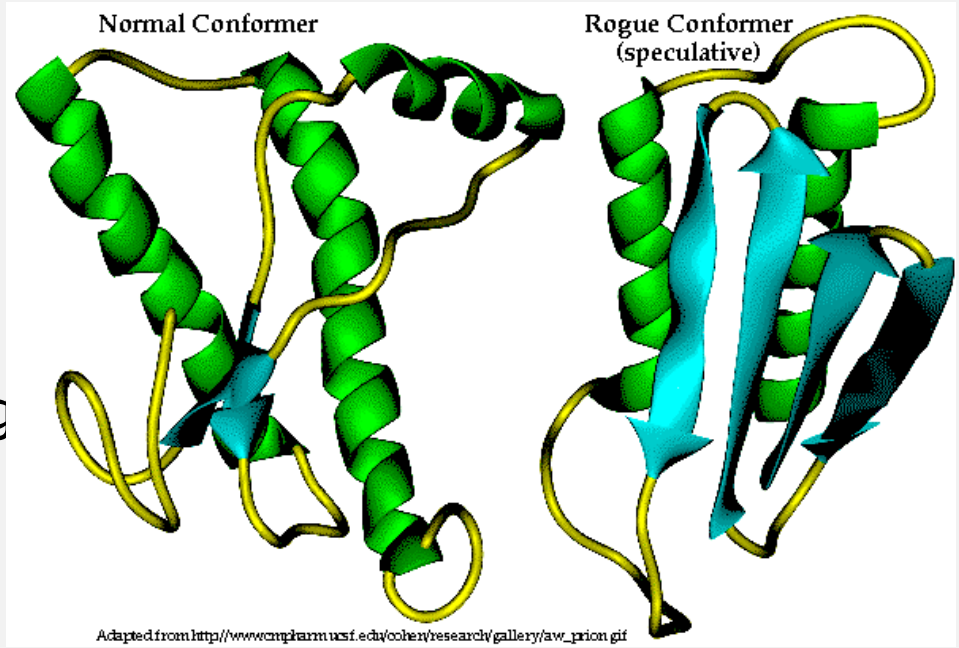


Proteins: The Molecules of Life

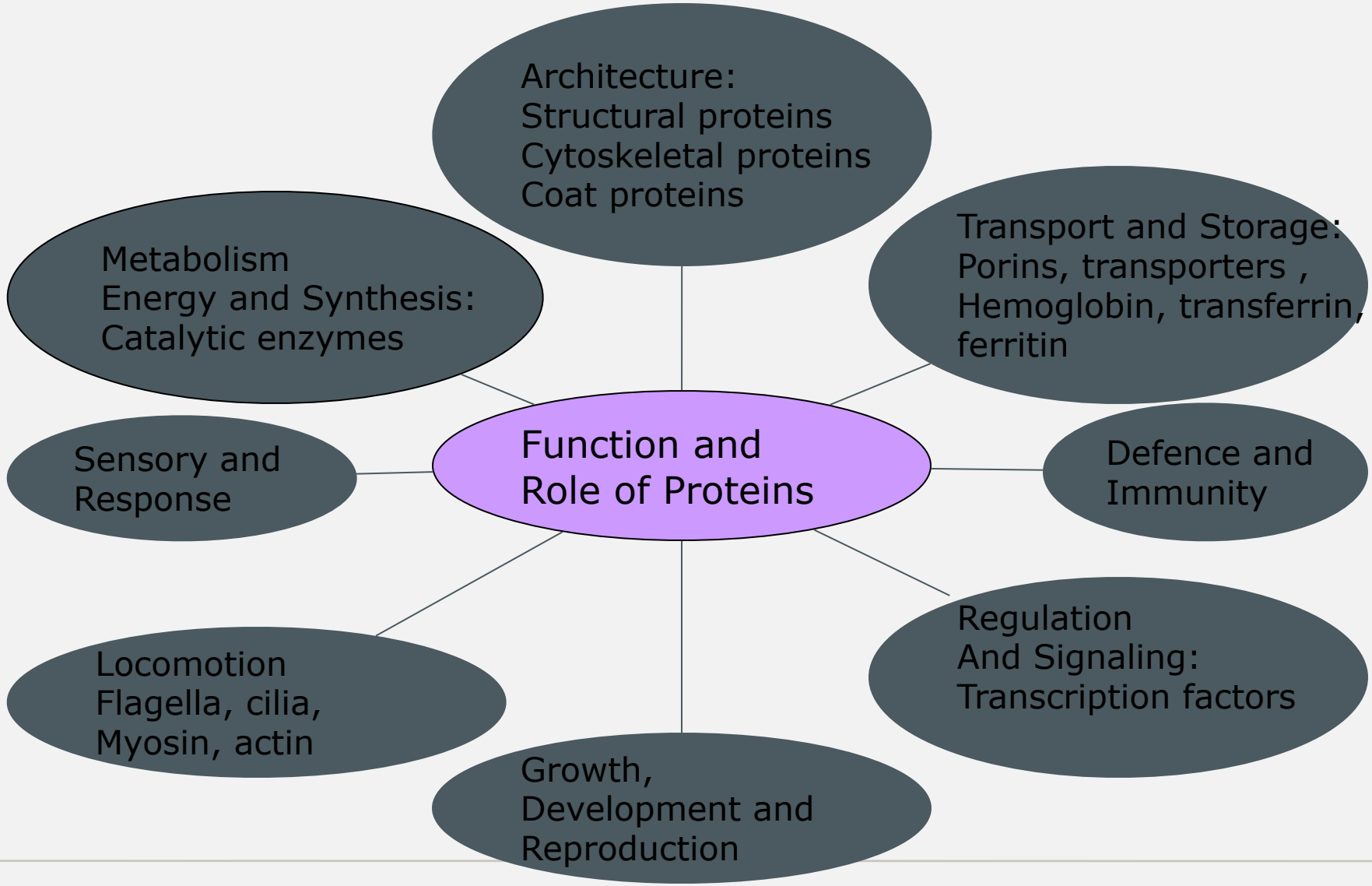
-Ubiquitous molecules that are involved in all
  cellular functions

-Communication agents between cells

-Failure of a protein (missing inactive, …)
 can lead to serious health problems
 (prions, …)



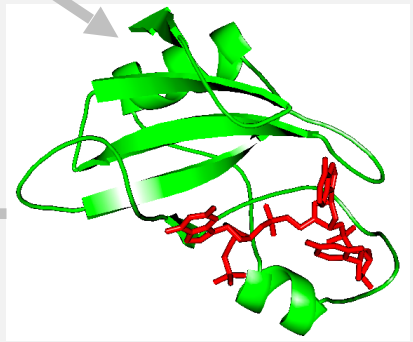
Why Proteins?



The Protein Cycle

Structure

Function



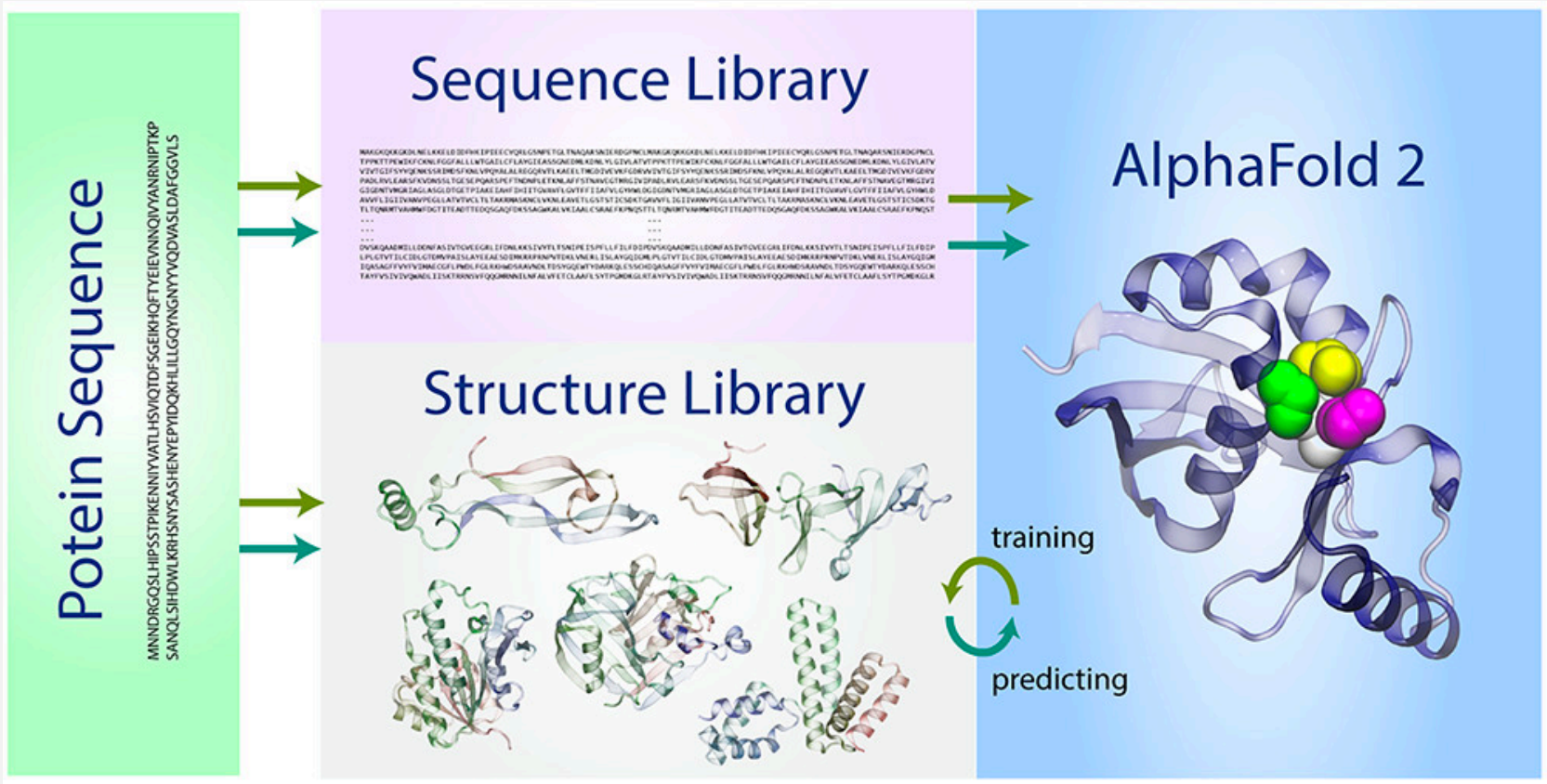
ligand

Sequence

```
KKAVINGEQIRSISDLHQTLKK
WELALPEYYGENLDALWDCLTG
VEYPLVLEWRQFEQSKQLTENG
AESVLQVFREAKAEGCDITI
```

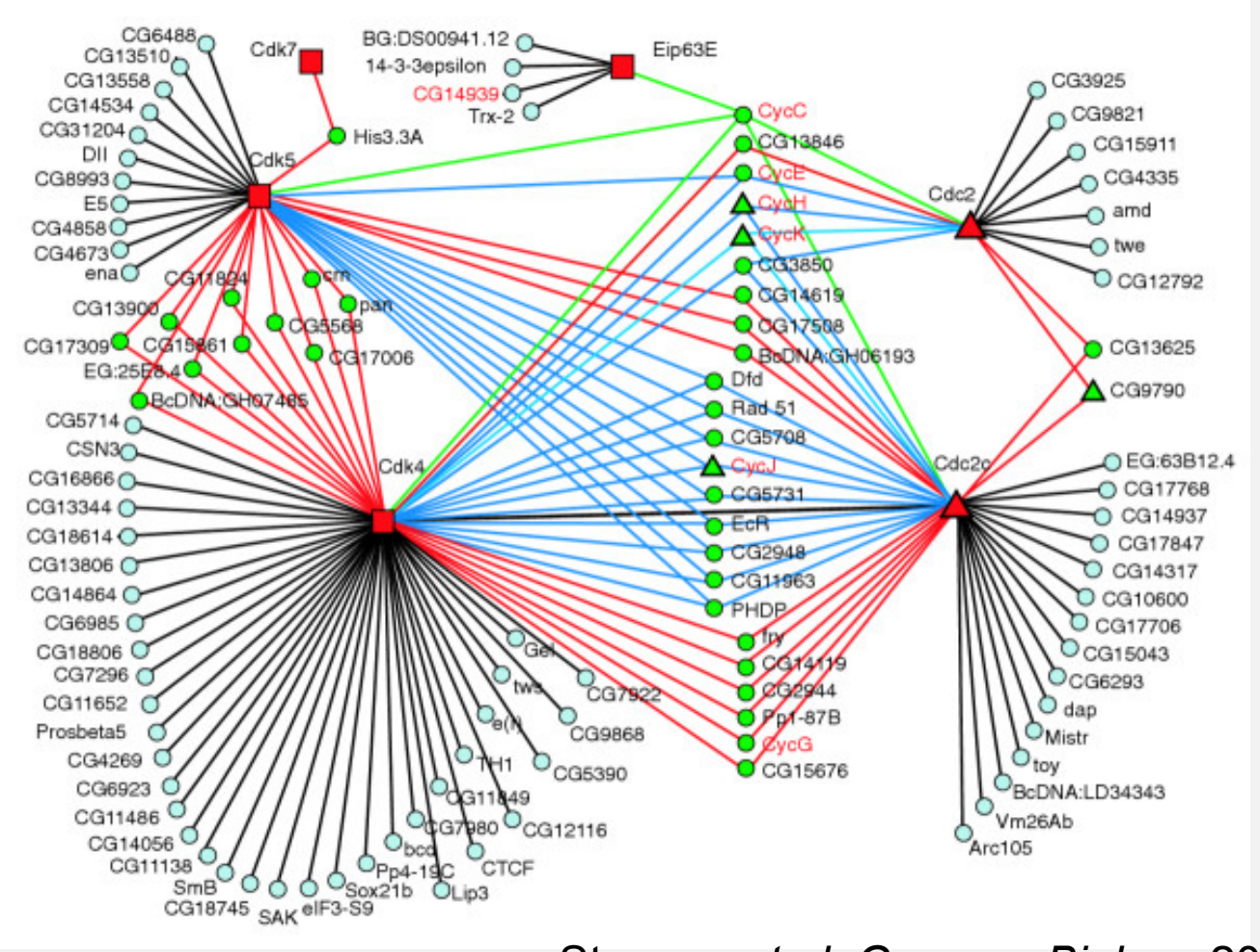
Evolution

AlphaFold2: AI for Biology



Interactomics

Which proteins (biomolecules) interact with which proteins (biomolecules)?



Stanyon *et al. Genome Biology* 2004 **5**:R96

Is there a danger, in molecular biology, that the accumulation of data will get so far ahead of its assimilation into a conceptual framework that the data will eventually prove an encumbrance ?

John Maddox, 1988

Top ten challenges for bioinformatics

1) Precise models of where and when transcription will occur in a genome (initiation and termination) ability to predict where and when transcription will occur in genome
2) Precise, predictive models of alternative RNA splicing: ability to predict the splicing pattern of any primary transcript in any tissue
3) Precise models of signal transduction pathways; ability to predict cellular responses to external stimuli
4) Determining protein:DNA, protein:RNA, protein:protein recognition codes
5) Accurate ab-initio protein structure prediction

Top ten challenges for bioinformatics

6) Rational design of small molecule inhibitors of proteins

7) Mechanistic understanding of protein evolution: understanding exactly how new protein functions evolve

8) Mechanistic understanding of speciation: molecular details of how speciation occurs

9) Development of effective gene ontologies: systematic ways to describe gene and protein function

10) Education: development of bioinformatics curricula

Source: Birney (EBI), Burge (MIT), Fickett (Glaxo)

Rough Outline of the Course

1) Overview of DNA, RNA and proteins
2) Sequence analysis
3) Structure analysis
4) Structure prediction
5) Molecular interactions
6) Drug design
7) Simulations
8) Available resources in bioinformatics