

MCB 41

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Office hours:

Fridays 1:00-2:30 (13:00-14:30)

21 Koshland

or

By appointment

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Class reading: Chapter 11, page 148-151 (enhancers)

Sequencing Genomes

Why???

Curiosity

Evolution

Speciation

Model systems

Diseases

Relationships

Sequencing Genomes

How much DNA is there in a Genome?

Prokaryote: 1×10^6 - 10×10^6 bp

Yeast: 12×10^6 bp

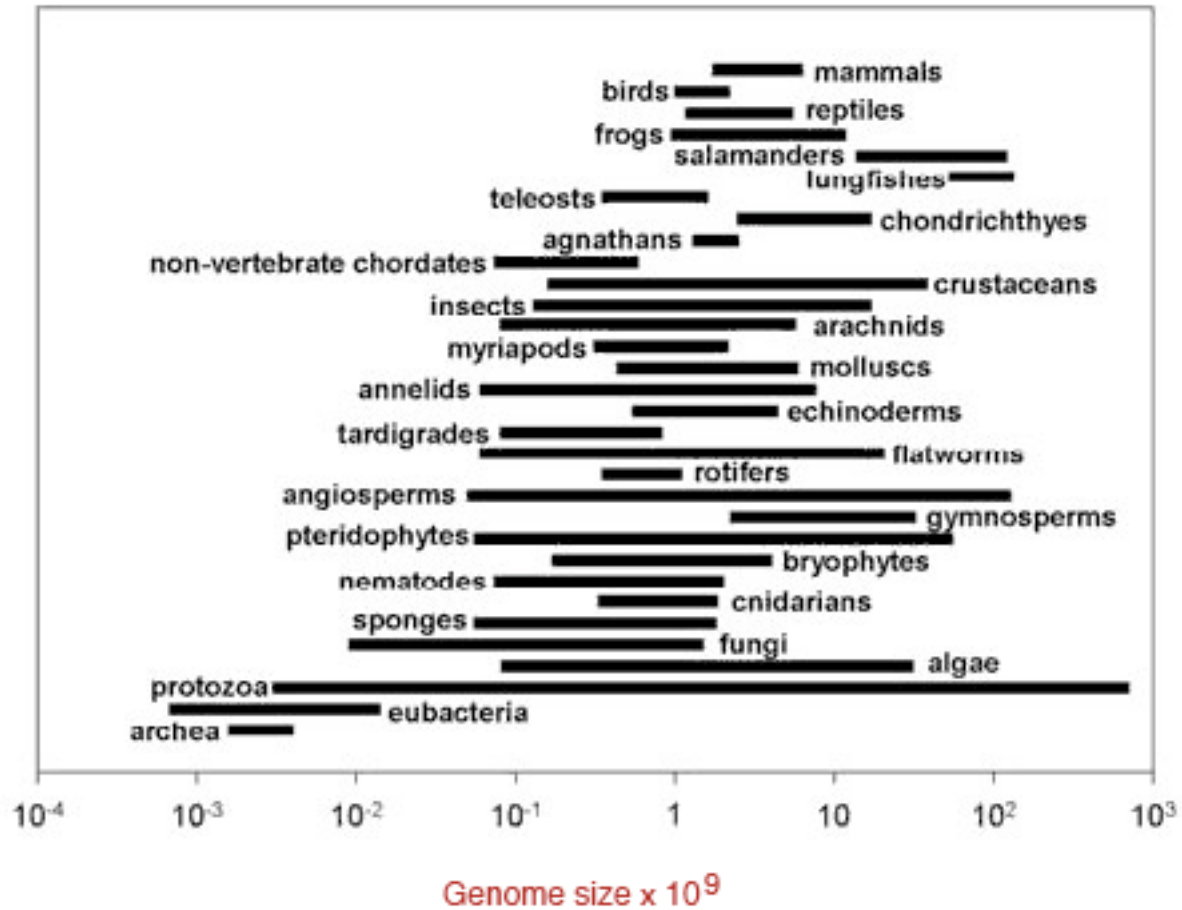
Fish: 0.4×10^9 - 3×10^9 bp

Mammals: 1.5×10^9 - 8×10^9 bp

Bible 3.5×10^6 letters

Milky Way Galaxy 10^{11} stars

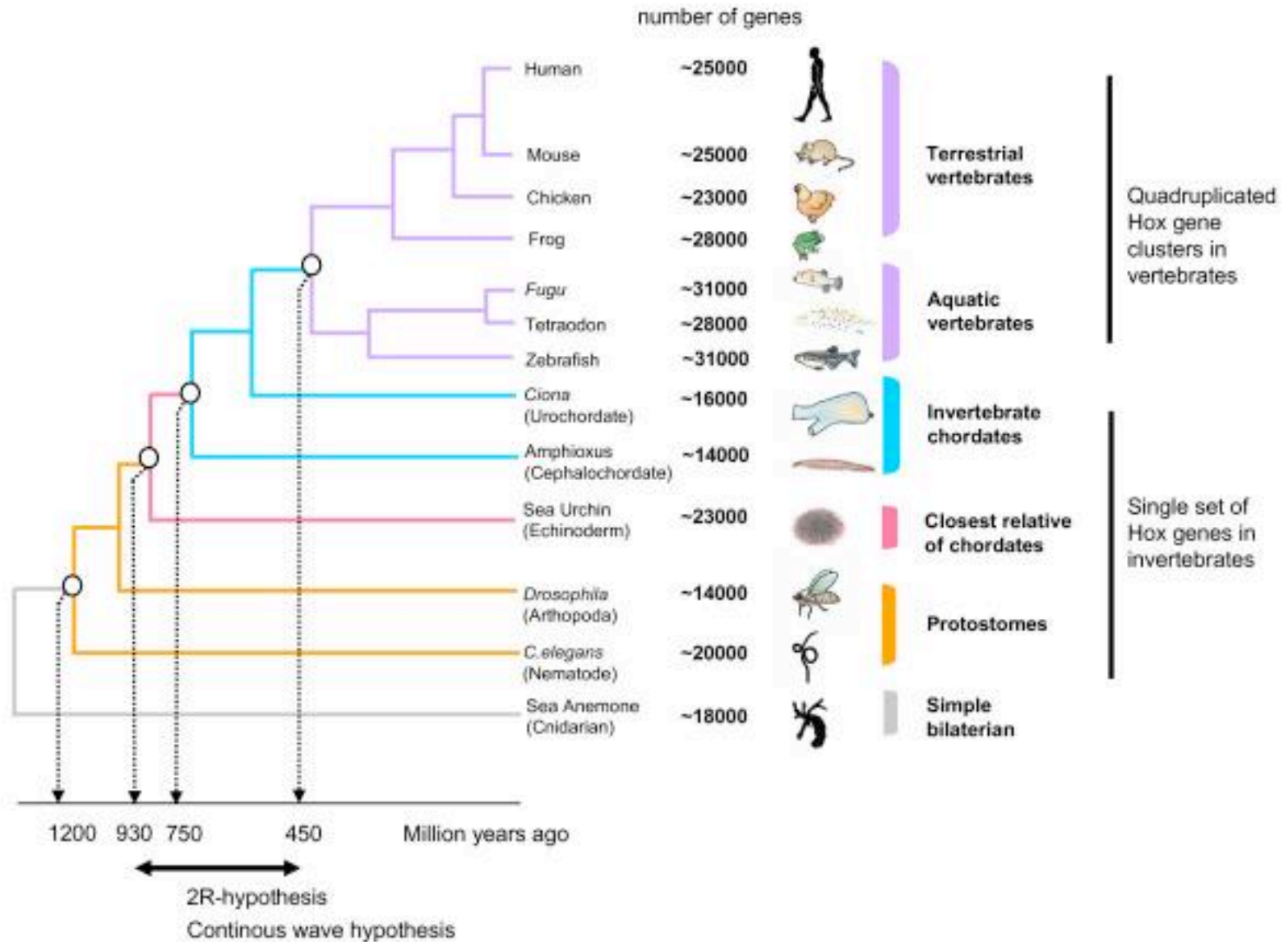
How much DNA is there in a Genome?



How to Sequence a Genome

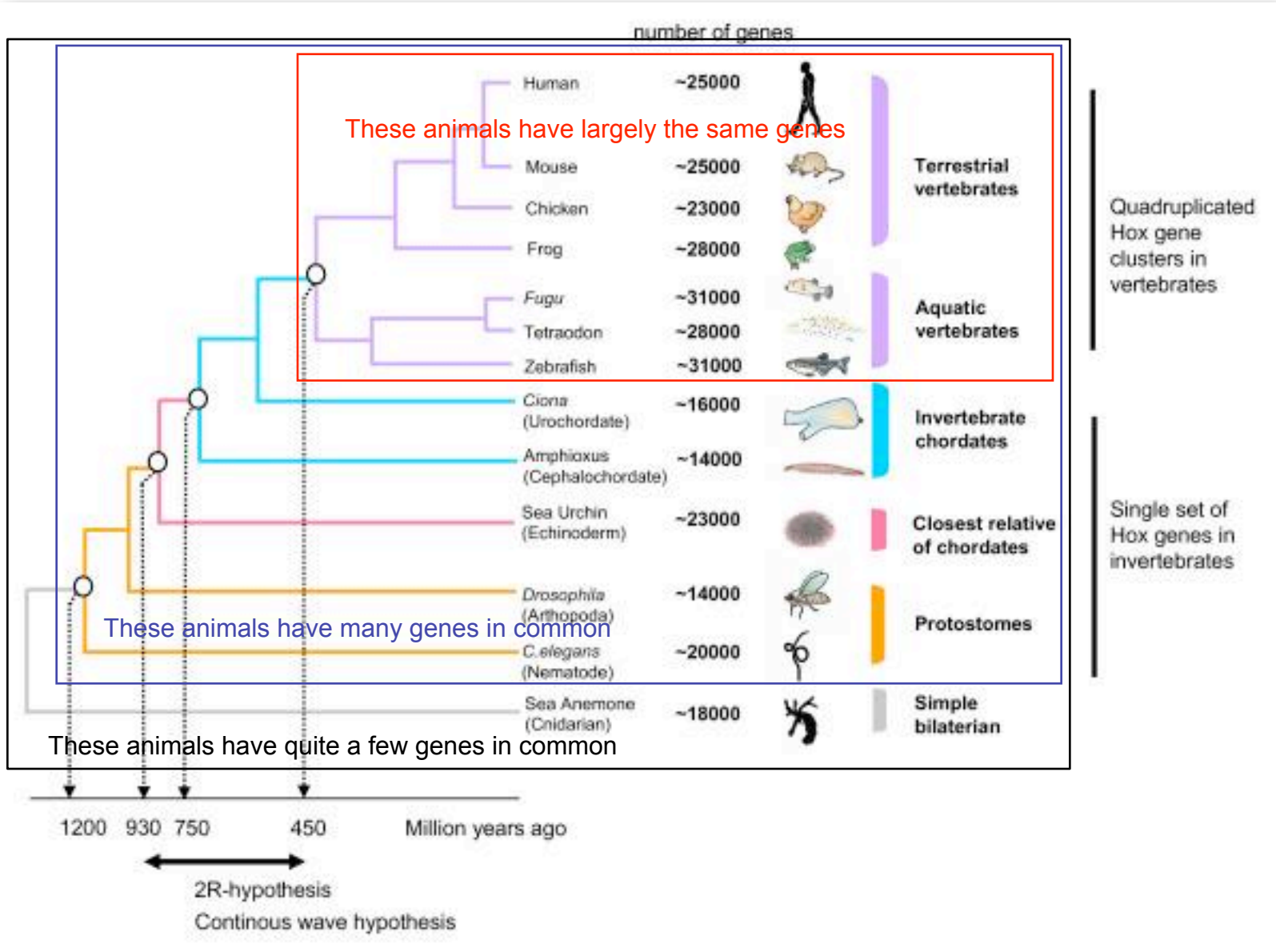
- 1/ DNA: get your organism and extract DNA
- 2/ Cut into small fragments and (sub)clone
- 3/ Sequence each subclone
- 4/ Assemble
- 5/ Compare with other sequences

Genes are very old
 More “complexity” does not require more genes



Blue Ridge Mountains
Oldest Mountains in the USA, 10^9 years old

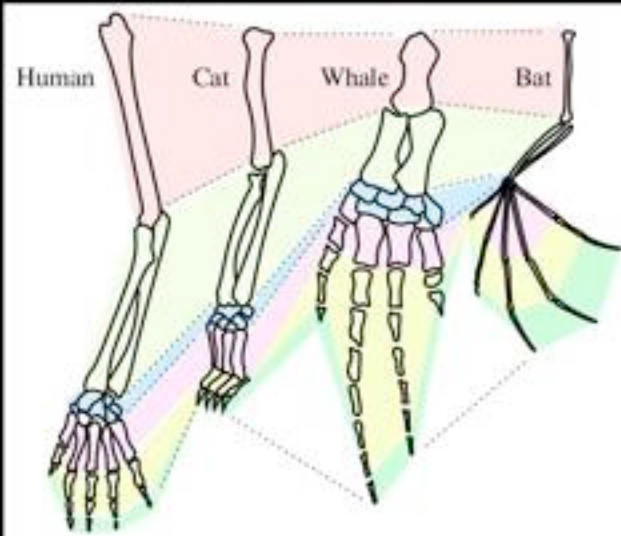
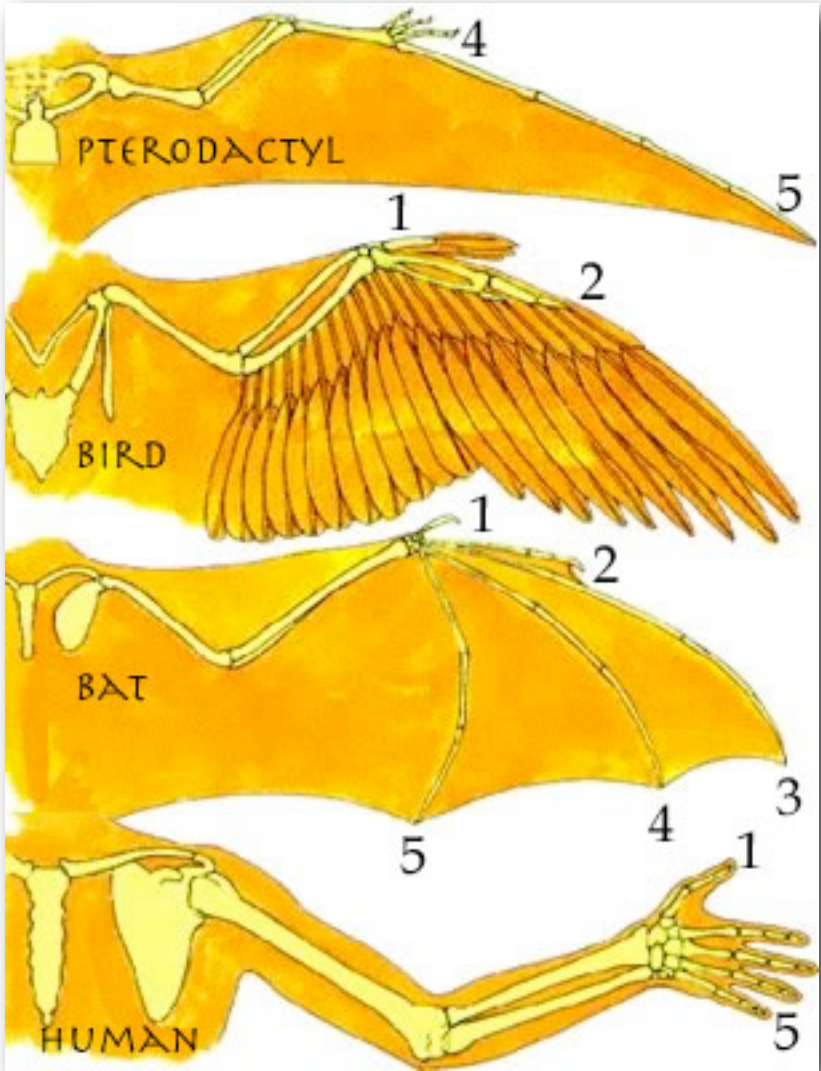




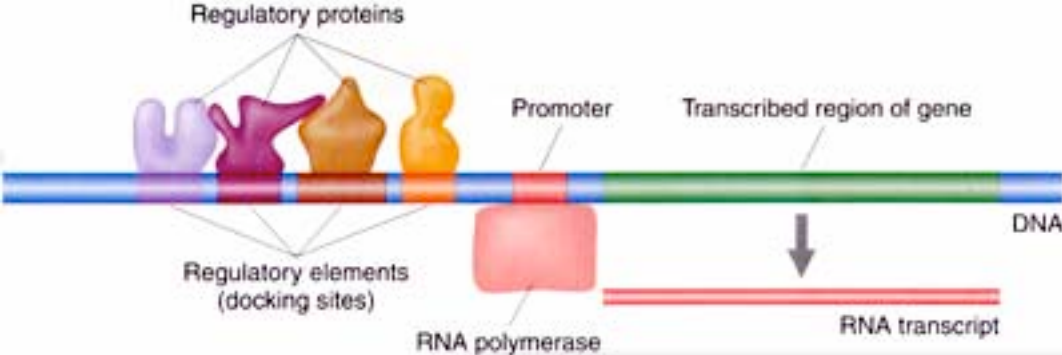
If animals are made from the same gene products, what makes a mouse different from a frog or a bird?



Differences are Relative



The limb bones of different mammals are clearly equivalent. We can "morph" one into another just by changing the sizes and proportions. Genetic mutations altering the gene-control proteins, the diffusible molecules, and the patterns of expression of the limb-development genes, are sufficient to make these changes in living things. One mutation occurs at a time, and the internal control mechanisms of embryo development integrate the body parts to form a working whole.



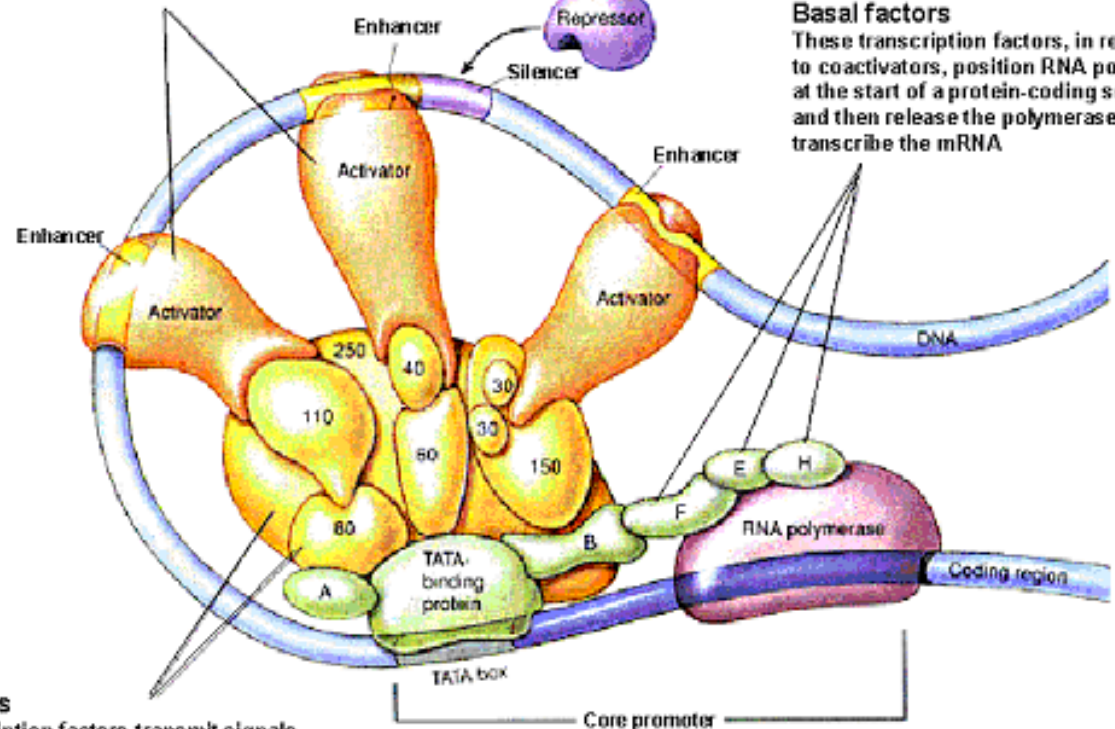
There is more to a gene than the protein coding sequences

Activators

The regulatory proteins bind to DNA at distant sites known as enhancers. When DNA folds so that the enhancer is brought into proximity with the transcription complex, the activator proteins interact with the complex to increase the rate of transcription.

Repressors

These regulatory proteins bind to "silencer sites" on the DNA preventing the binding of activator to nearby enhancers and so slowing transcription.



Basal factors

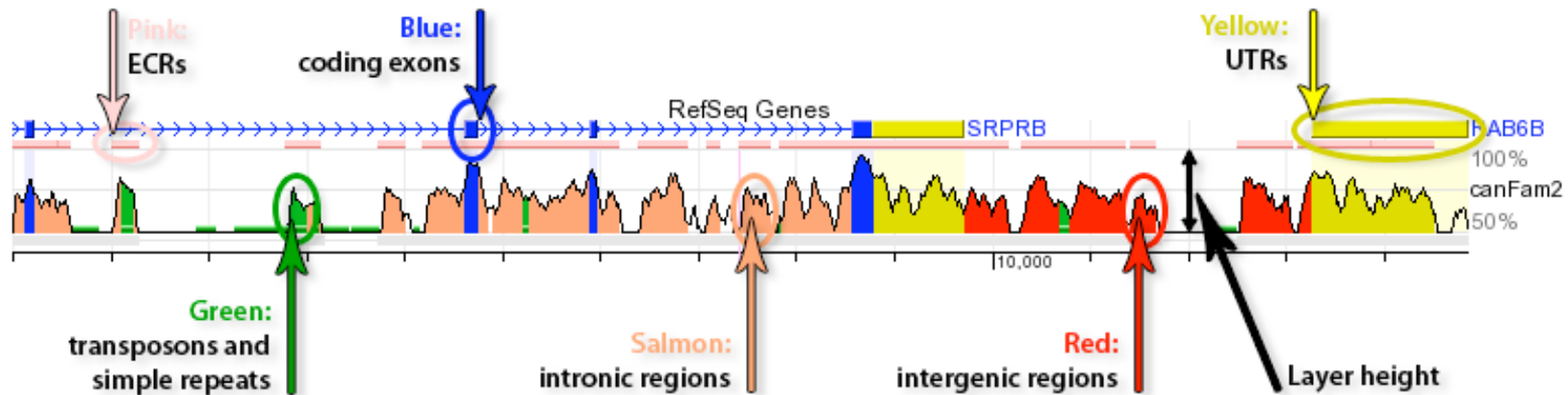
These transcription factors, in response to coactivators, position RNA polymerase at the start of a protein-coding sequence, and then release the polymerase to transcribe the mRNA.

Coactivators

These transcription factors transmit signals from activator proteins to the basal factors.

How do you recognize these non-coding regulatory sequences (enhancers)?

<http://ecrbrowser.dcode.org/>



Parameters: Graph length similarity height system
[change] smooth 100 70 55 relative

chr7:155285000-15529349

UCSC

[GENOME ALIGNMENT](#): Align your sequence to a genome

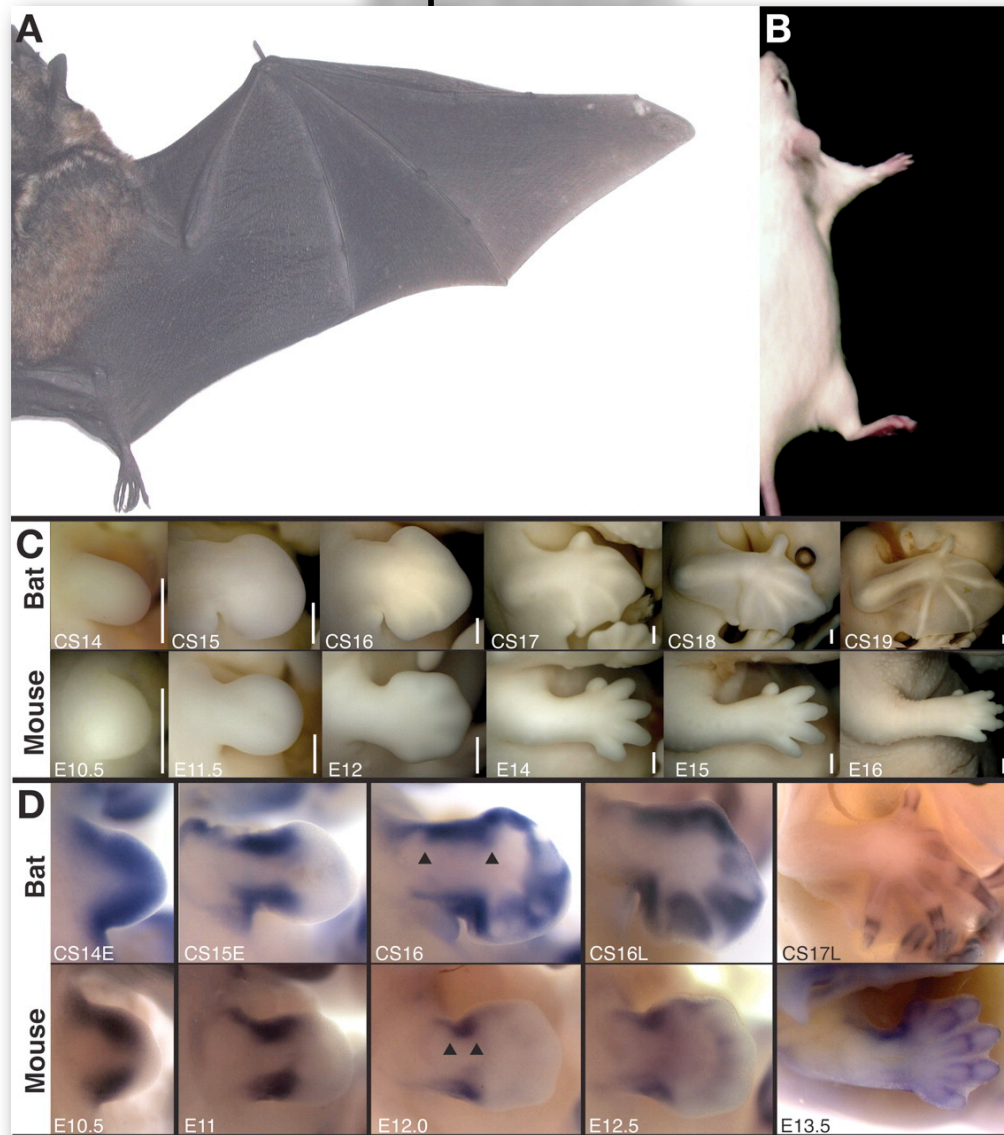


Flip move: Left Right zoom in: 1.5x 3x 10x zoom out: 1.5x 3x 10x

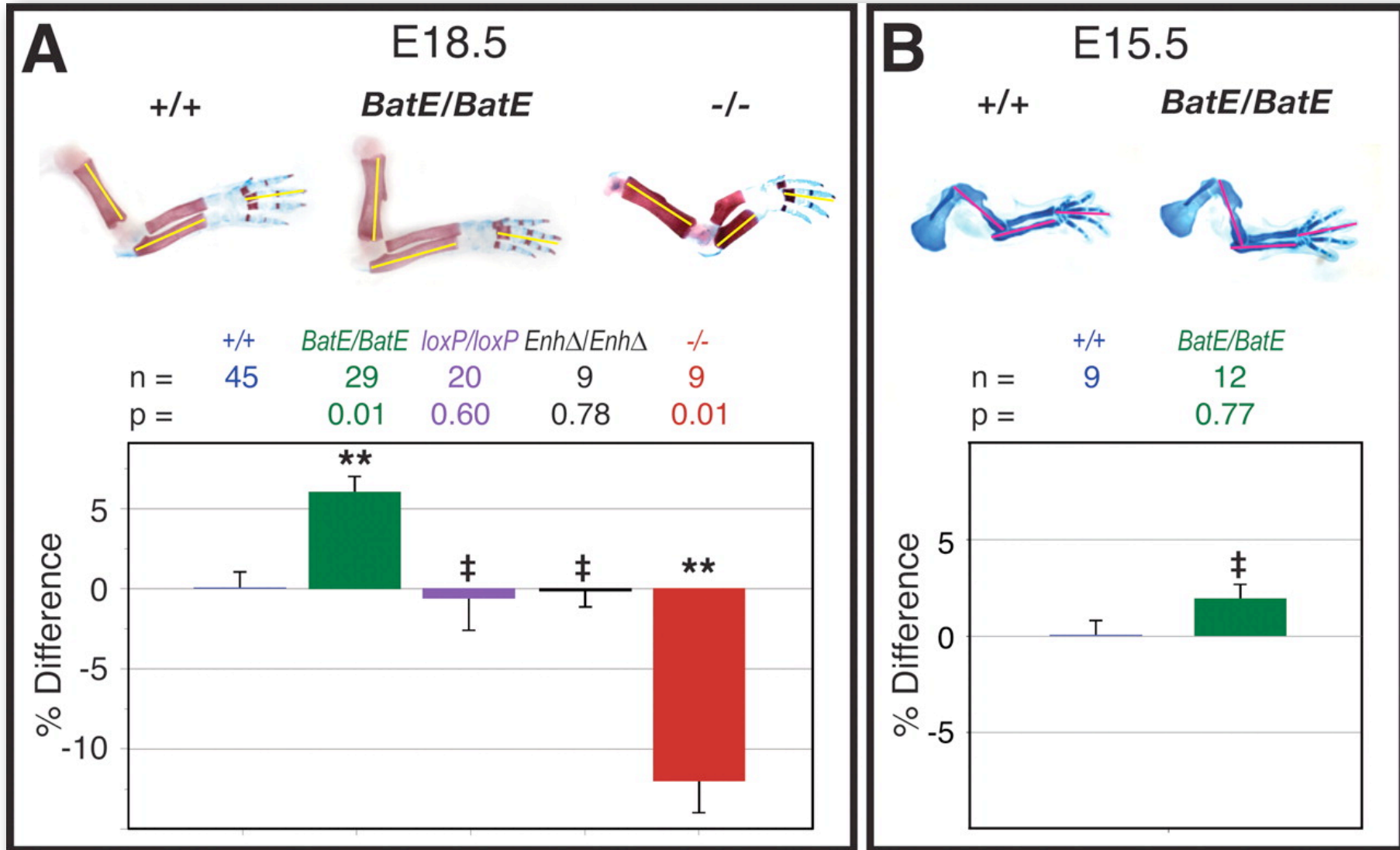
- Overall genomes look a lot alike
- Sequence information is much more valuable when compared with other species
- Sequences conserved over many many years are likely to be important
- The devil is in the details: relevant differences are harder to find than conserved sequences

Functional tests are cumbersome and costly, but really interesting!

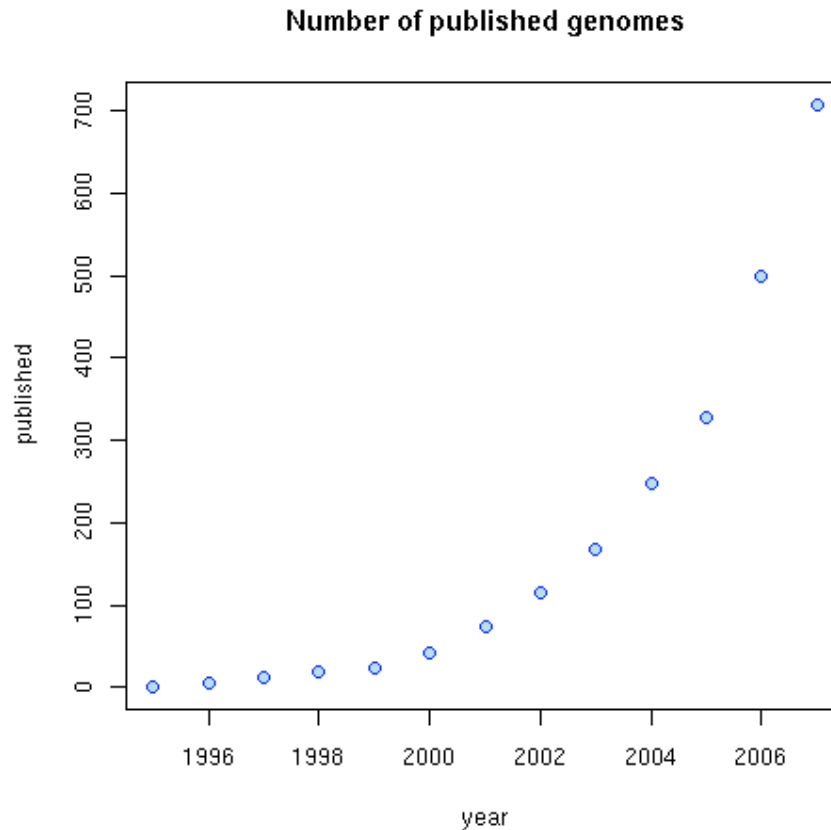
Comparison of bat and mouse forelimb morphogenesis and *Prx1* expression



Forelimb length of Prx1 mutants

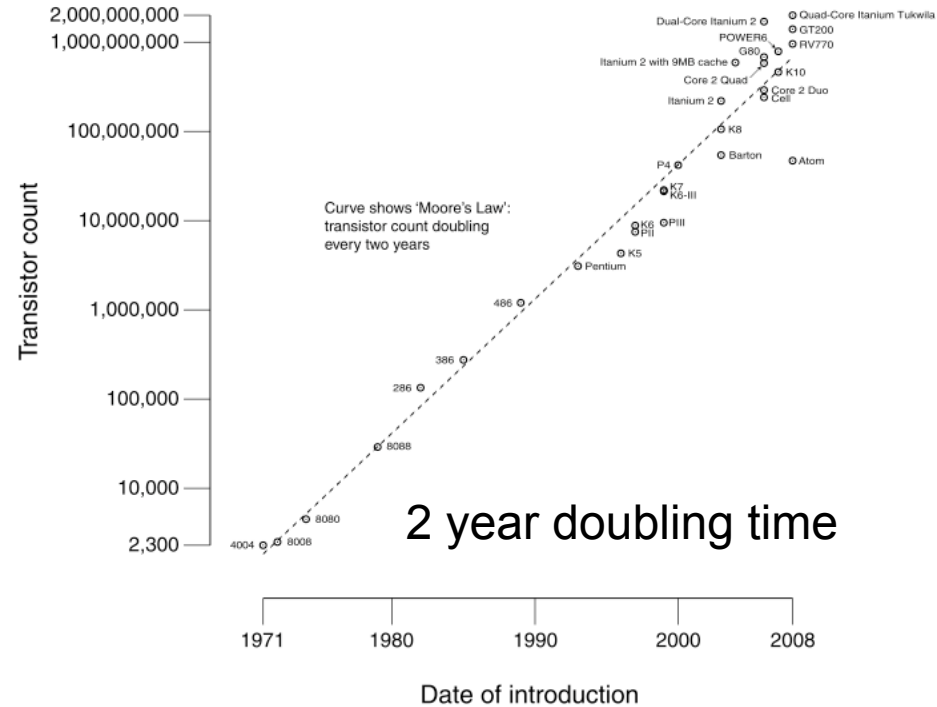
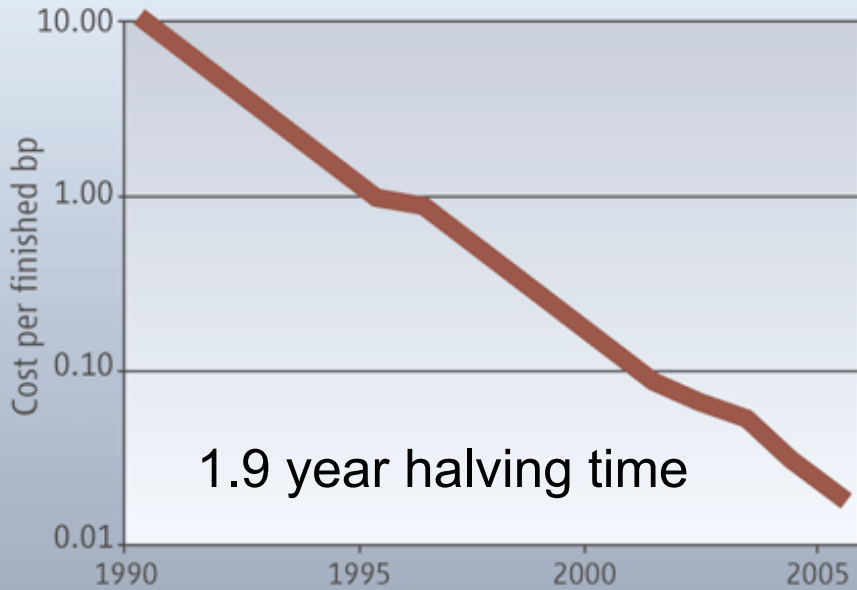


How about sequencing your favorite organism?



1.5 year doubling time

Decrease in the Cost of Finished DNA Sequencing



Currently: [Knome](#) offers a $\$10^5$ personal sequence ($\$10^{-5}$ /base, 4 month halving time)

A \$1000 ($\10^{-7} /base) genome 2 years away????

All of you will know your complete genome sequence if you so desire, and are willing to dish out <\$1000

- Ancestry
- Diseases / Life expectancy
- Partner matching
- Personality traits
- Personalized Medicine

Who might be interested in your DNA sequence?

- Your Health Insurance
- Your Life Insurance
- Your Mortgage Bank
- Your Employer
- The Police
- The CIA
- The Federal Government
- The US Olympic Committee
- Your Family (is your father really your father?)

Still want to sequence your genome?

Who will own the data?