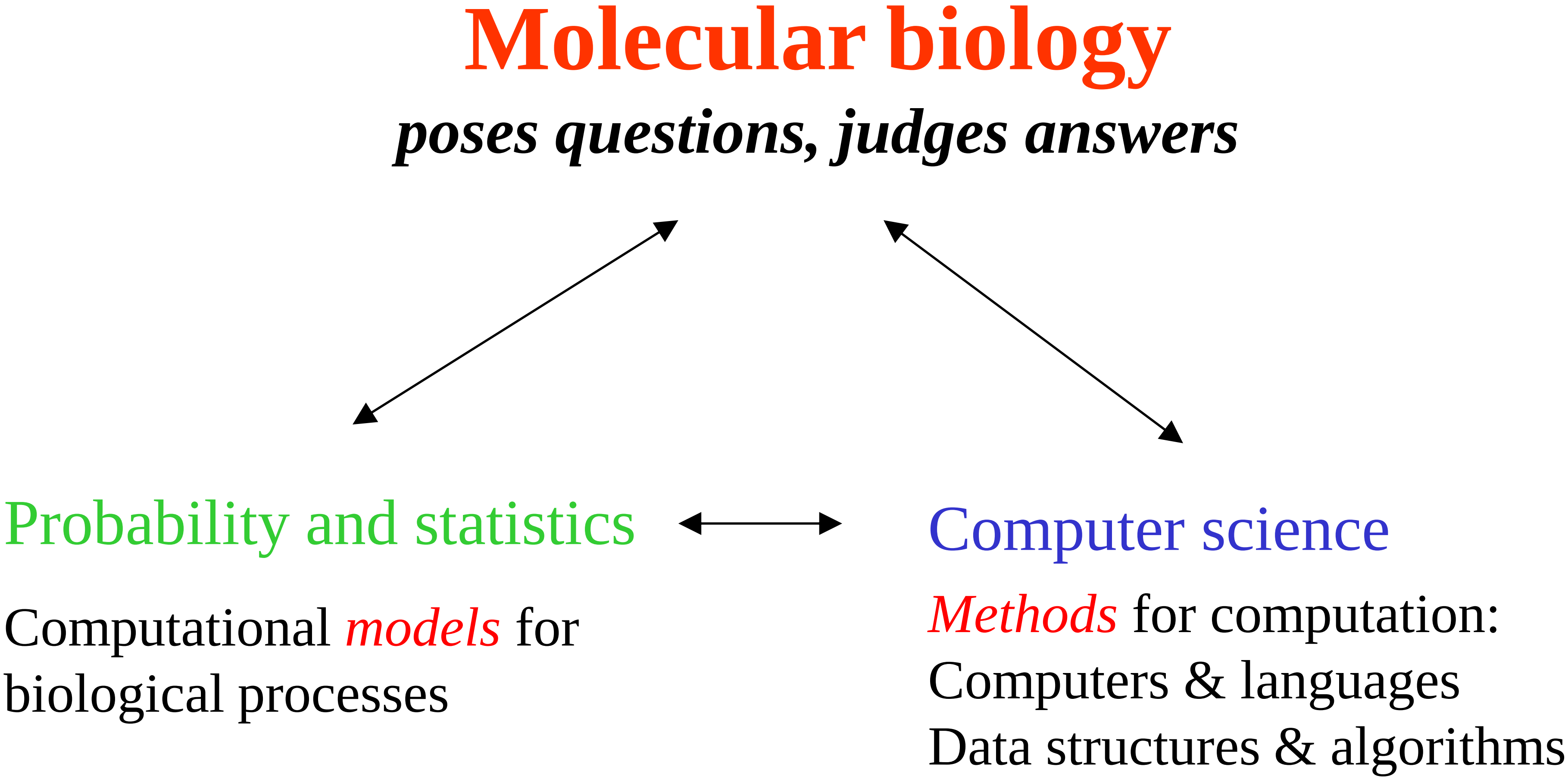
Lecture 1: Overviews

- Computational molecular biology
  - Probabilities in biology
- Interpreting genomes
  - Genome biology
    - Sites
  - Genomicists’ tasks
  - Computational tasks
- This course

Computational Molecular Biology



Molecular biology

poses questions, judges answers

Probability and statistics

Computational *models* for biological processes

Computer science

Methods for computation:

Computers & languages

Data structures & algorithms

- Computational methods are ***technology***
- Technology helps ***drive*** science
- … but should not ***displace*** science
  - – not an end in itself
  - – ***novelty*** & ***aesthetics*** should not override ***utility***

Biology involves *probabilities*, at several levels:

- Fundamental laws governing molecular systems
- Mutations (imperfect replication)
- Transmission of DNA from parent to offspring in populations of individuals
- Random aspects of environment

Key Physical Laws Governing Living Organisms

- Individual atoms & molecules:
  - quantum mechanics & quantum electrodynamics
- Systems of interacting molecules:
  - statistical mechanics^{++}, 2d law of thermodynamics

These laws are essentially probabilistic!

“*The true logic of this world is in the calculus of probabilities*” – James Clerk Maxwell

“*I cannot believe that God plays dice with the cosmos*” – Albert Einstein; nonetheless two of his four great 1905 papers dealt with statistical aspects of nature (photoelectric effect & Brownian motion)!

Genome biology overview

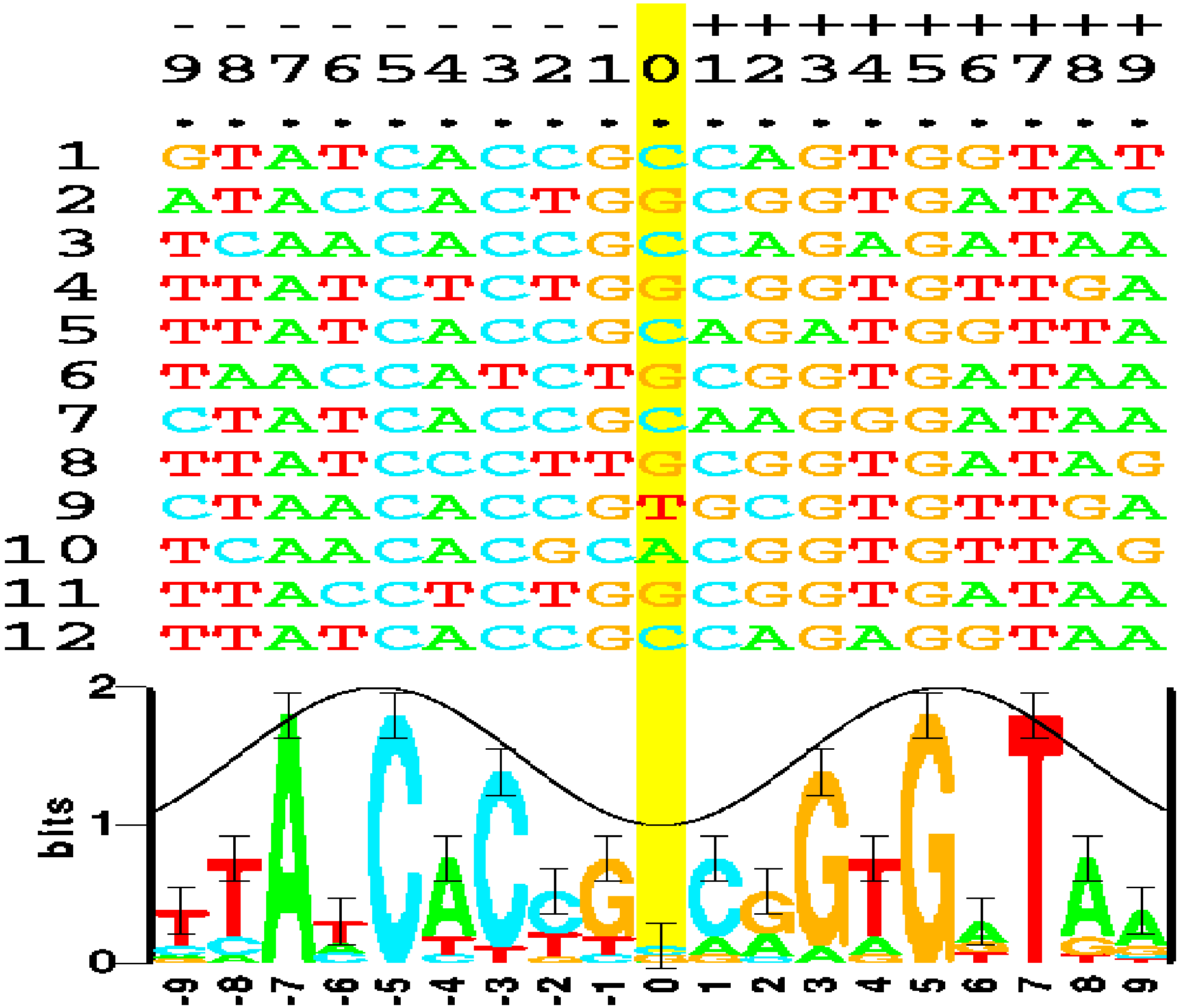
- Genomes undergo two fundamental processes (both involve copying!):
  - Replication
  - Transcription
- Genomic functional information is in the form of *sites:*
  - Short (~2 – ~15 base) sequence segments that bind to an *RNA* or *protein* molecule (the *reader*) to help mediate some function
    - Small size is evolutionarily significant!
  - (there is also information in site *ordering* and *spacing*)

Two broad classes of sites:

1. Sites acting ***at the DNA level*** (usually via *protein* readers) to help carry out or regulate a fundamental process

   - Replication
     - Replication origins, centromeres, telomeres (each usually having *multiple* sites)
   - Transcription
     - Promoters, enhancers, suppressors (each usually having *multiple* sites, with readers being *transcription factors*)

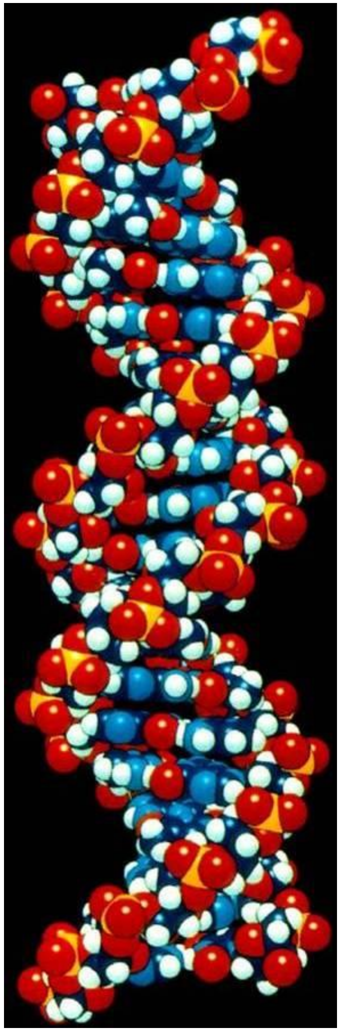
From http://www-lmmb.ncifcrf.gov/~toms/sequencelogo.html

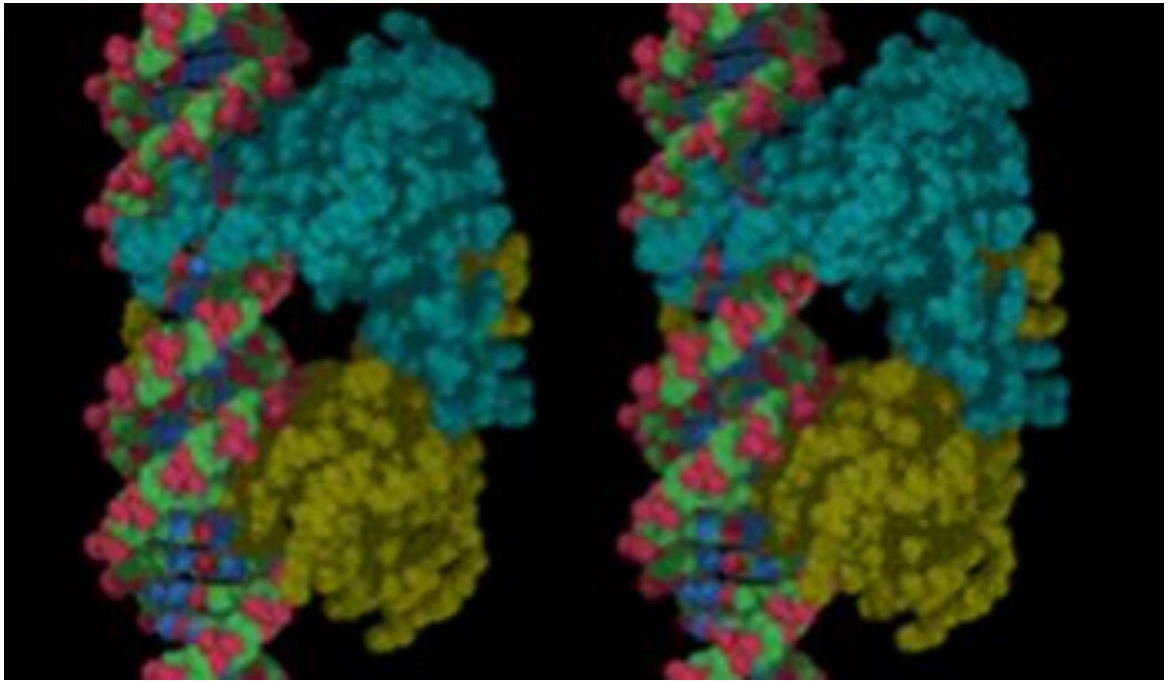


```
     ---------+++++++++
     9876543210123456789
     ...................
 1   GTATCACCGCCAGTGGTAT
 2   ATACCACTGGCGGTGATAC
 3   TCAACACCGCCAGAGATAA
 4   TTATCTCTGGCGGTGTTGA
 5   TTATCACCGCAGATGGTTA
 6   TAACCATCTGCGGTGATAA
 7   CTATCACCGCAAGGGATAA
 8   TTATCCCTTGCGGTGATAG
 9   CTAACACCGTGCGTGTTGA
10   TCAACACGCACGGTGTTAG
11   TTACCTCTGGCGGTGATAA
12   TTATCACCGCCAGAGGTAA
```

12 Lambda cI and cro binding sites

Fig. 1. Some aligned sequences and their sequence logo. At the top of the figure are listed the 12 DNA sequences from the P_L and P_R control regions in bacteriophage lambda. These are bound by both the cI and cro proteins [16]. Each even numbered sequence is the complement of the preceding odd numbered sequence. The sequence logo, described in detail in the text, is at the bottom of the figure. The cosine wave is positioned to indicate that a minor groove faces the center of each symmetrical protein. Data which support this assignment are given in reference [17].



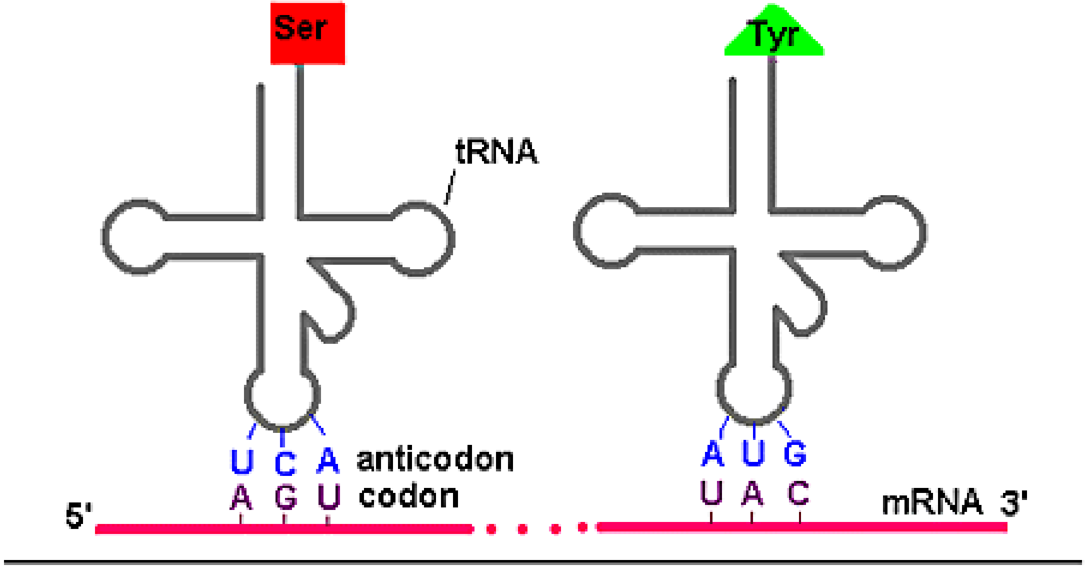


from http://gibk26.bse.kyutech.ac.jp

from http://www.dna-dna.net/

2. Sites acting ***within a transcript*** (often via RNA readers) to help carry out the transcript's function

- in *protein coding* transcripts:
  - Translation start sites, codons (reader = charged tRNA), splice sites, microRNA binding sites, polyadenylation sites, …
- in *functional RNA* transcripts:
  - Stem structures (the transcript reads itself!), …



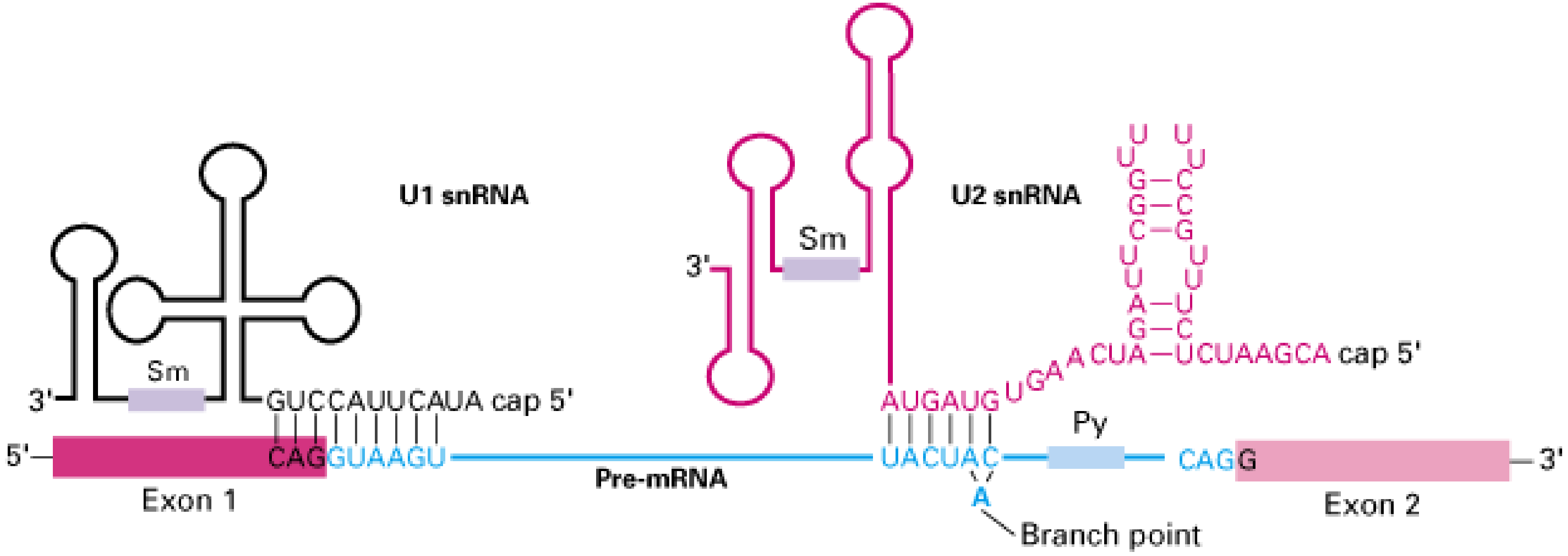
2nd base in codon

1st base in codon

3rd base in codon

	U	C	A	G	
U	Phe Phe Leu Leu	Ser Ser Ser Ser	Tyr Tyr STOP STOP	Cys Cys STOP Trp	U C A G
C	Leu Leu Leu Leu	Pro Pro Pro Pro	His His Gln Gln	Arg Arg Arg Arg	U C A G
A	Ile Ile Ile Met	Thr Thr Thr Thr	Asn Asn Lys Lys	Ser Ser Arg Arg	U C A G
G	Val Val Val Val	Ala Ala Ala Ala	Asp Asp Glu Glu	Gly Gly Gly Gly	U C A G

The Genetic Code



from **http://departments.oxy.edu/biology/Stillman/bi221/111300/processing_of_hnrnas.htm**

(Jonathon Stillman, Grace Fisher-Adams)

Sites: some key properties

- Sites typically
  - *Recur:* multiple sites within a genome, with possibly varying sequences, may be recognized by the same reader
    - Sequence variation may be represented by a *motif* or *sequence logo*
  - *Cluster:* several sites, with the same or different readers, may act collectively to carry out some function
    - Positional constraints within clusters vary in stringency
    - A *gene* is a cluster of sites involved in ***expressing*** a particular transcript

- Average site density (i.e. the fraction of the genome that is functional) may be quite small!
  - < 10% of human genome; remaining > 90% mostly transposon relics, ‘dead’ genes & processed pseudogenes
  - strength of selection for ‘genome efficiency’ depends on
    - Population size
    - Reproductive life span
    - Genome size

- Whether or not a site is active in a given cell may depend on
  - reader status (local concentration, whether modified, etc)
    - Also interaction partners of the reader
  - chromatin & methylation status
  - whether nearby (or overlapping) sites are bound by their readers

Genomicists' tasks

- Find the ***genome sequence***

- Find the ***transcripts***

- Find the ***sites*** ...

- … and their ***functions*** …

Finding the genome sequence

- Get *reads* (short, overlapping, error-prone pieces of the sequence)
- *Assemble* : identify read overlaps, infer underlying sequence
- Main challenge:
  - (Near-)duplicate sequences

Finding transcripts (“RNASeq”)

- Get *reads* from cDNA copies of the processed (spliced + edited) transcripts
- *Assemble* to infer transcript sequence
- *Align* to genome sequence
- Main challenges:
  - Expression bandwidth
  - Transcripts may be processed in more than one way (isoforms)
  - A transcript may be non-functional!

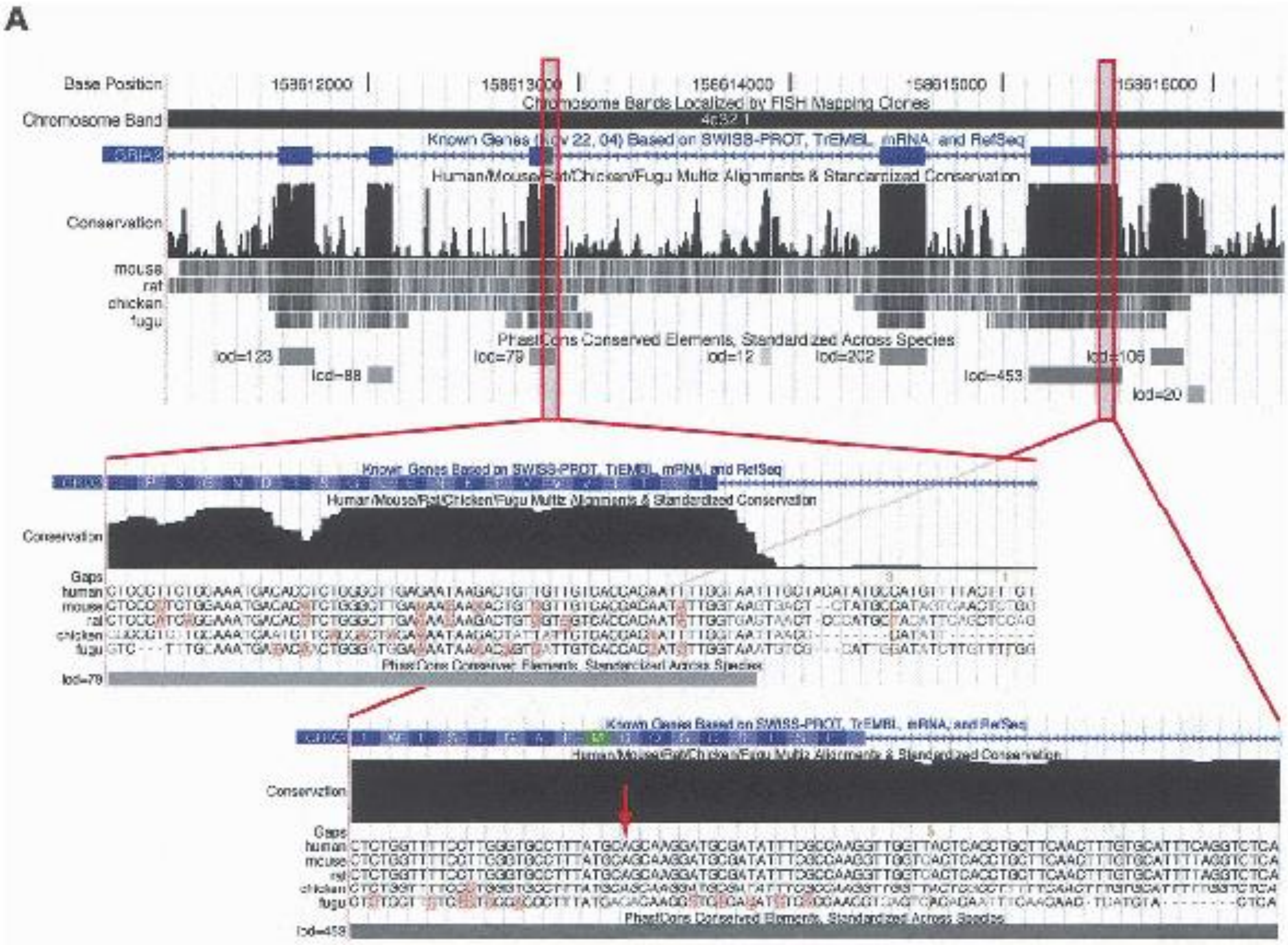
Finding sites

- Direct detection of binding events (e.g. ChIPSeq)
  - ***but*** binding may be non-functional!
- Computational search for clusters of recurring motifs
  - ***but*** motifs occur frequently by chance, in any large genome!
- Both methods are error-prone, and may not illuminate ***function.*** So we also …

Compare genomes of …

- a lab organism & a singly mutated variant with an altered phenotype
  - the mutation must then alter (or create!) a site
    - or alter site spacing
  - and the phenotypic change illuminates its function
  - but remember that cells with identical genomes can sometimes have different phenotypes!
    - Tissues in multicellular organisms
- members of a natural population
  - Usually *multiple* genomic and phenotypic differences
  - find correlations (of *recurring* differences) to identify sites that affect a particular phenotype.

- different species
  - *Many* differences
  - ***atypically similar* (= “conserved”)** regions likely represent site clusters in which mutations have been selected against (“purifying selection”)
    - and likely have similar functions in the two species
  - But many sites may have been *lost*, and *created*, in each lineage



from Siepel A. *et al.* (2005). Evolutionarily conserved elements in vertebrate, insect, worm, and yeast genomes. *Genome Res.* 15:1034-50.

Some major computational tasks

- Comparing & aligning sequences
  - Reads to reads
    - assembly
  - Reads to genomes
    - variant detection
  - Transcripts to genomes
  - Genomes (or portions thereof) to genomes

Appropriate alignment method depends on how similar the sequences are!

- Developing probability models of
  - Genome sequences (sites, and “background”)
  - Sequence evolution
  - Other types of ‘linear’ data associated to the genome (e.g. read depth)

and using them to find genomic features.

This course

- The focus is ***sequence-based*** CMB
  - i.e. methods (& models) for obtaining & analyzing the information encoded in the genome
- We emphasize the underlying ***biology***
- ***Simple / interpretable*** computational models are favored
- ***Proofs*** are often only intuitive sketches, omitting details

Main topics

- ***Suffix arrays*** (& hash tables) for finding exact matches
- ***Background sequence models***
- ***Site models,*** weight matrices & sequence logos
- Highest weight paths on weighted directed acyclic graphs: ***dynamic programming algorithm***
- Finding non-background-like regions ("HMMs lite")
- Edit graphs & ***gapped-alignment algorithms***
- ***Hidden Markov models*** and applications
  - Parsing genomes (into sites & non-sites)
  - Finding conserved regions
- Simple molecular evolution models

We do ***not*** cover:

- Motif-finding methods
- Sequence evolution models (in depth)
- Statistical genetics
- Deep neural nets & other complex machine-learning models
- ‘Non-linear’ (non-sequence based) computational biology, such as:
  - Most proteomics, metabolic & signalling pathways, models for interacting molecules …

(See Genome 541, & courses in CSE, Stat, Biostat)