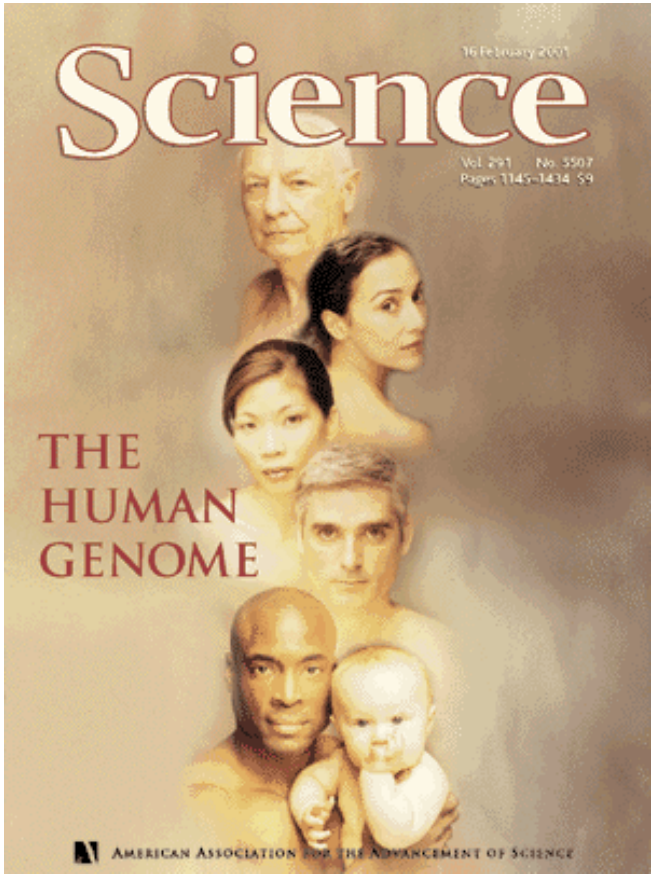
Bioinformatics

- Scientific Computing Lecture, UNICC

Marina Alexandersson

Göteborg, March 25, 2004

The human genome



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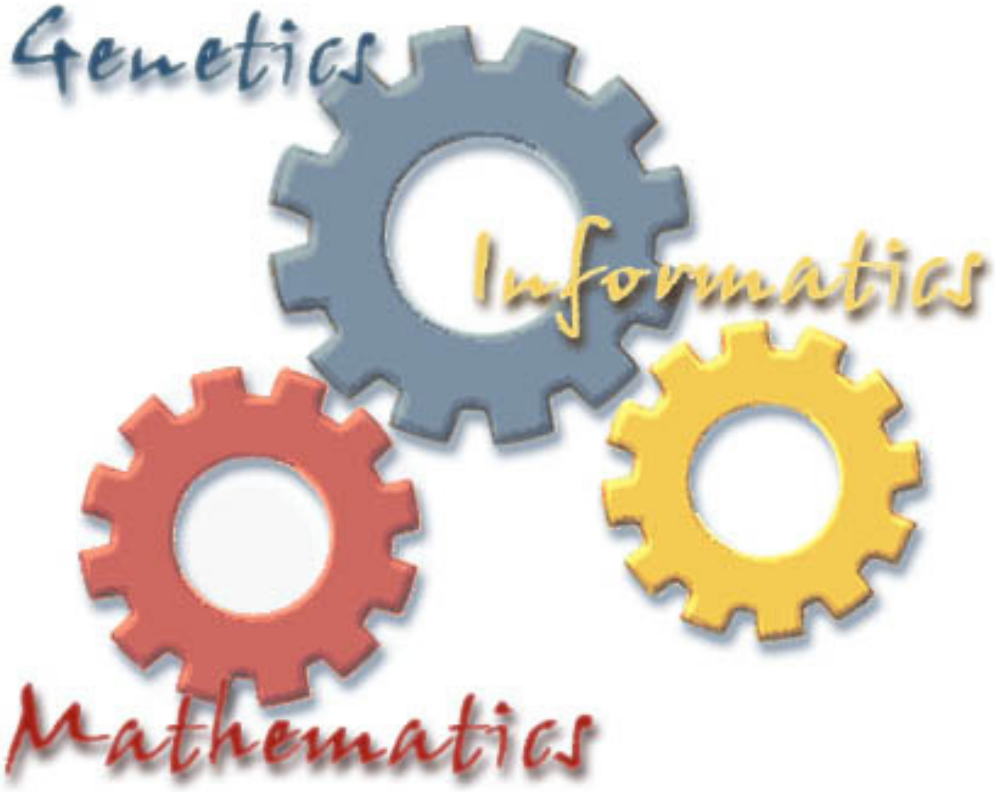
What is bioinformatics?



Where is bioinformatics used?

DNA analysis

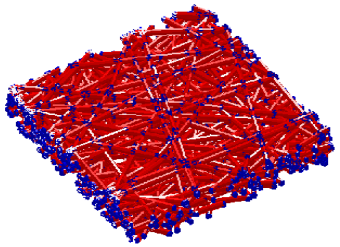
Drug

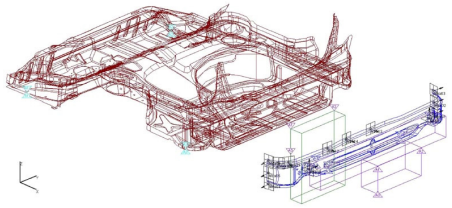
- DNA sequencing
- Sequence analysis
- Genes involved in diseases
- Protein structure and function
- Drug targets
- Lead compound
- Clinical trials

Technologies at the Fraunhofer-Chalmers centre

➢ Computational physics and fatigue

- **materials, mechanics, electromagnetics**
- **fatigue life and load analysis**





➢ Opitmization and quality engineering

- **design, geometry, qulity management**
- **logistics, scheduling, production**

➢ System theoretical methods

- **biostatistics, bioinformatics, systems biology**
- **telecommunciations, signal and image analysis**
- **finance and insurance**

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Bioinformatics

Research, development and application of computational methods and tools to expand the use of biological and medical data, including retrieving, storing, organizing, analyzing and visualizing such data.

- **Sequence analysis** to classify sequence data and identify functional elements
- **Comparative genomics** to detect similarities and differences in related organisms
- **Functional genomics** to infer biological structure and function from primary sequence
- **Proteomics** to identify, characterize and quantify proteins active in certain pathways, tissues, cells or organs
- **Biostatistics and statistical genetics** to analyze disease genotypes and phenotypes, detect environment interactions etc

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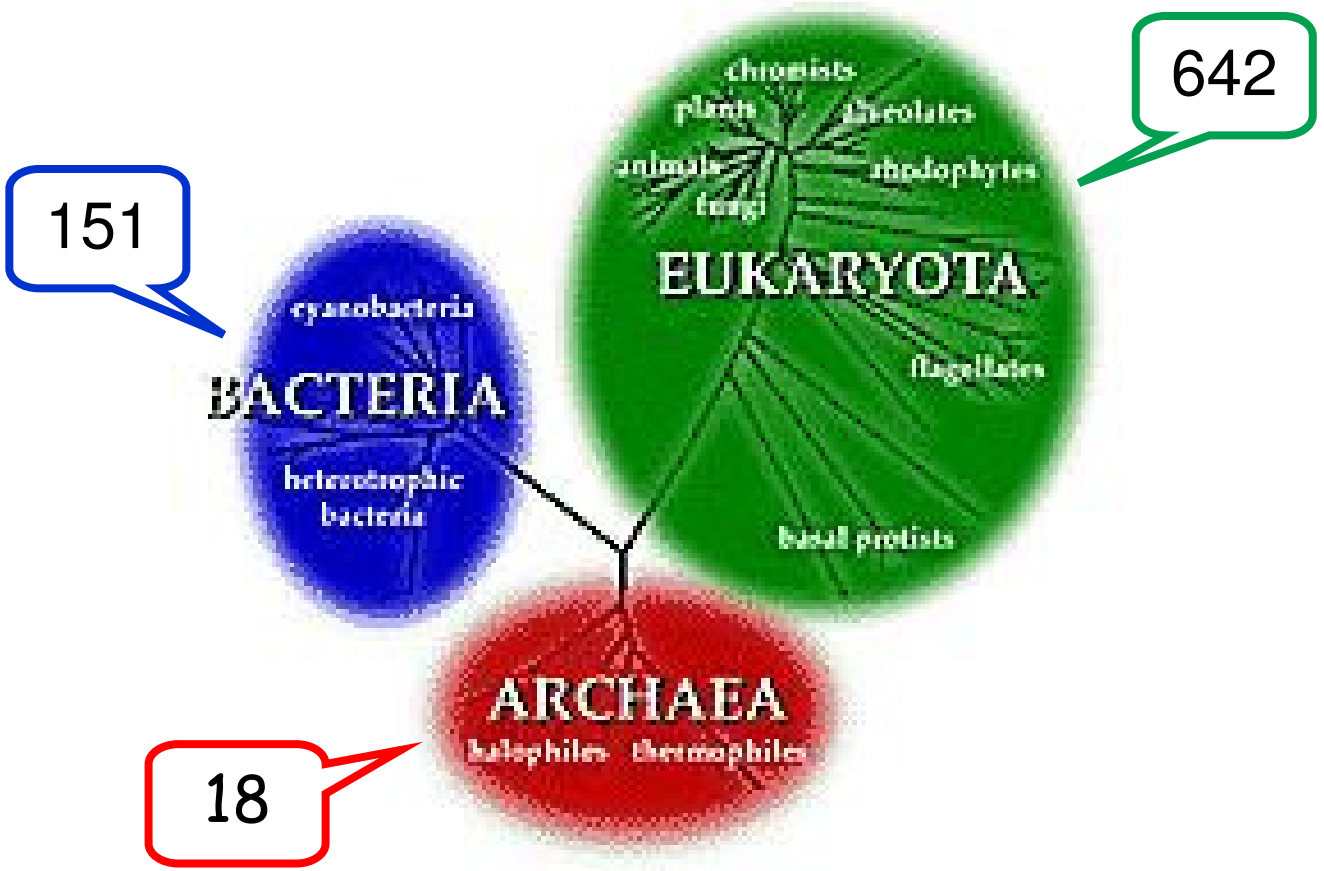
Sequenced genomes



More to come...

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Whole genome analysis - Why?

- Complete gene and protein sets
- Primary sequence of all genes
- Sequence relationships between genes and proteins
- Function of new proteins
- Transcriptional level of all genes
- Understanding methabolic pathways
- Trace disease genes
- ...

Whole genome analysis

- Gene finding
- Sequence comparisons
- Regulatory region identification

Gene finding
- *Generalized HMMs*

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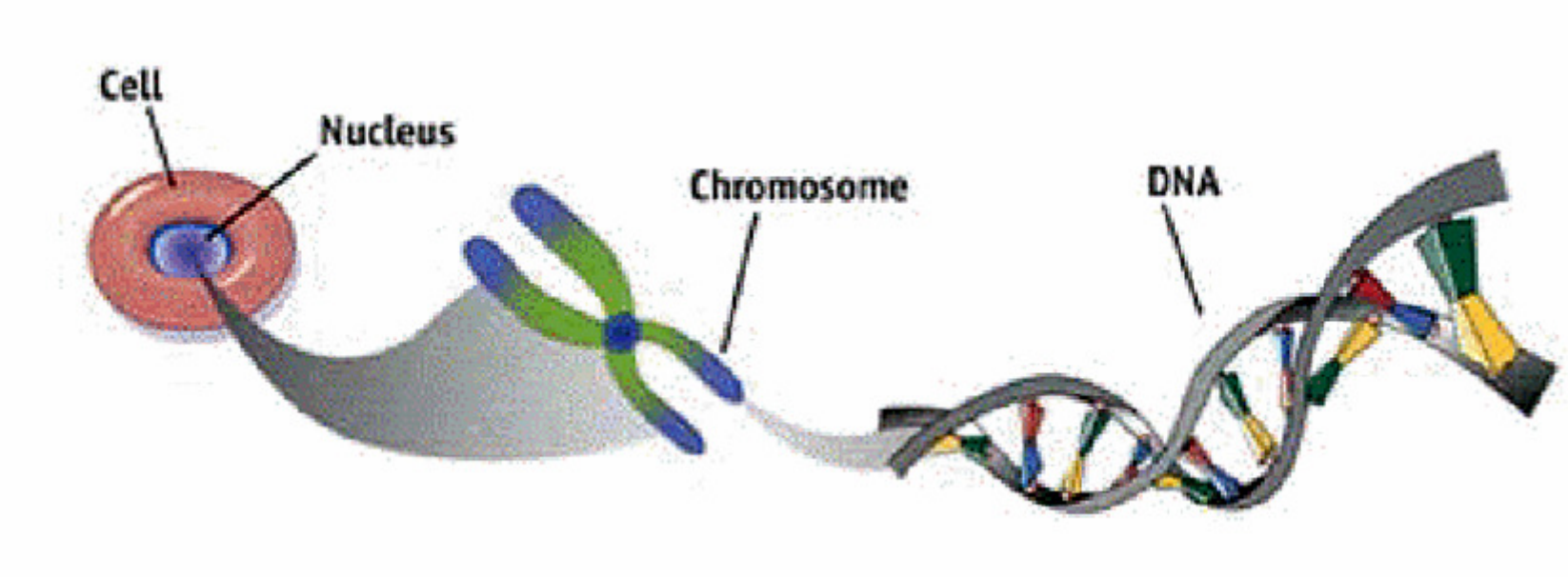
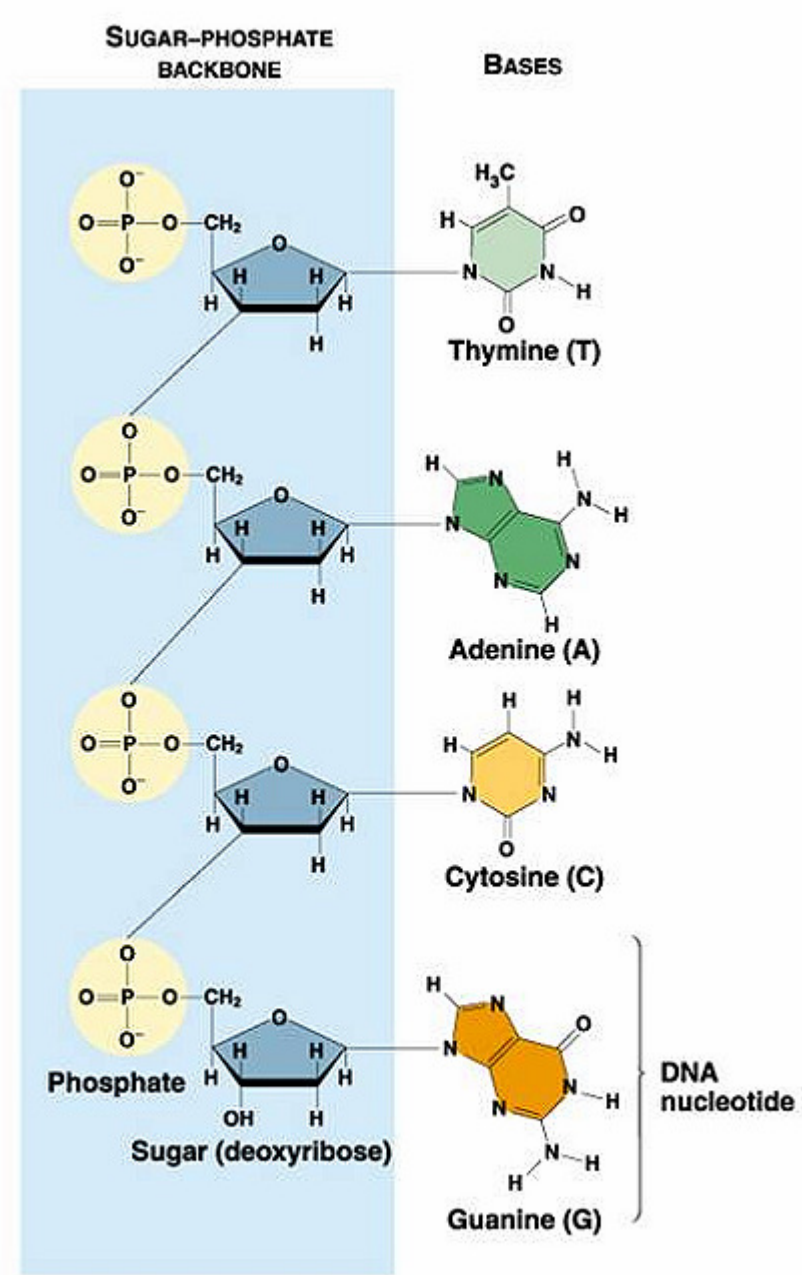
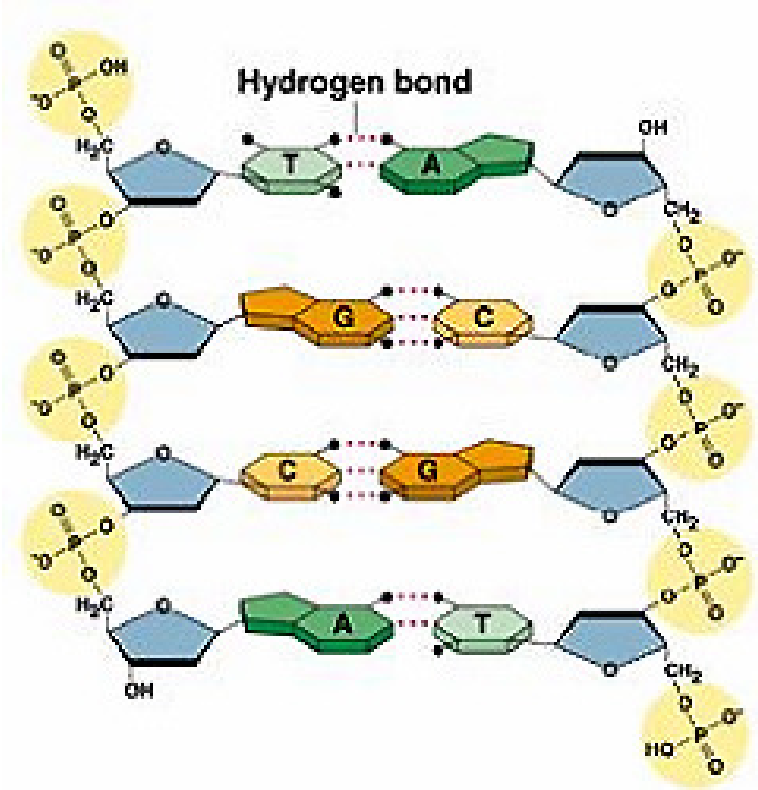
Basic genetics




SUGAR–PHOSPHATE BACKBONE
BASES
Thymine (T)
Adenine (A)
Cytosine (C)
Guanine (G)
Phosphate
Sugar (deoxyribose)
DNA nucleotide


Hydrogen bond
T
A
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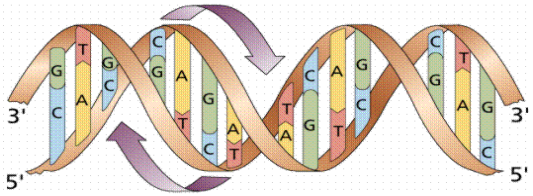
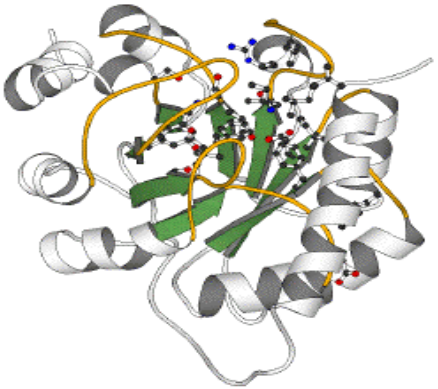
C
C
G
A
T

Gene expression





DNA

transcription

RNA

translation

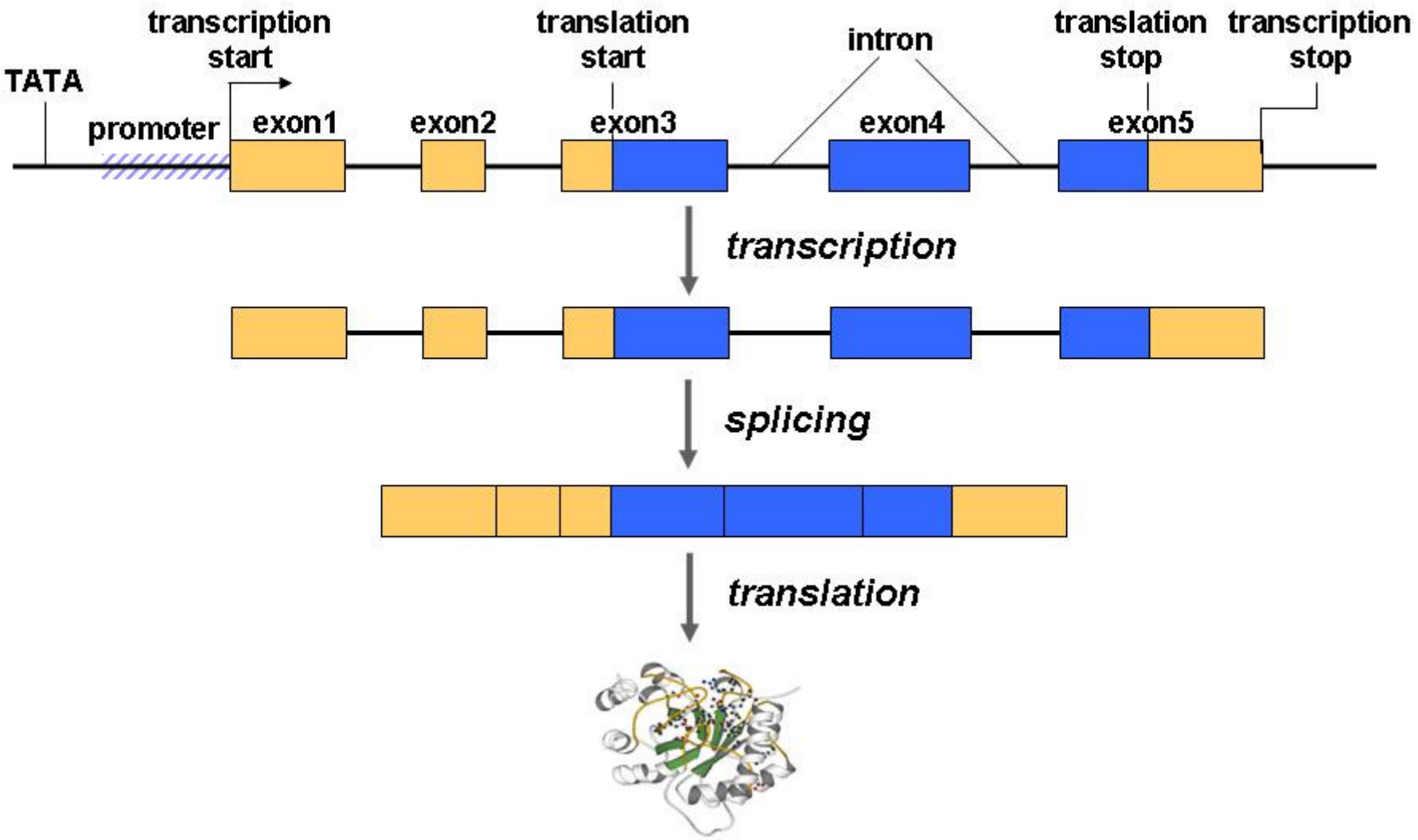
Protein

CCTGAGCCAACTATTGATGAA

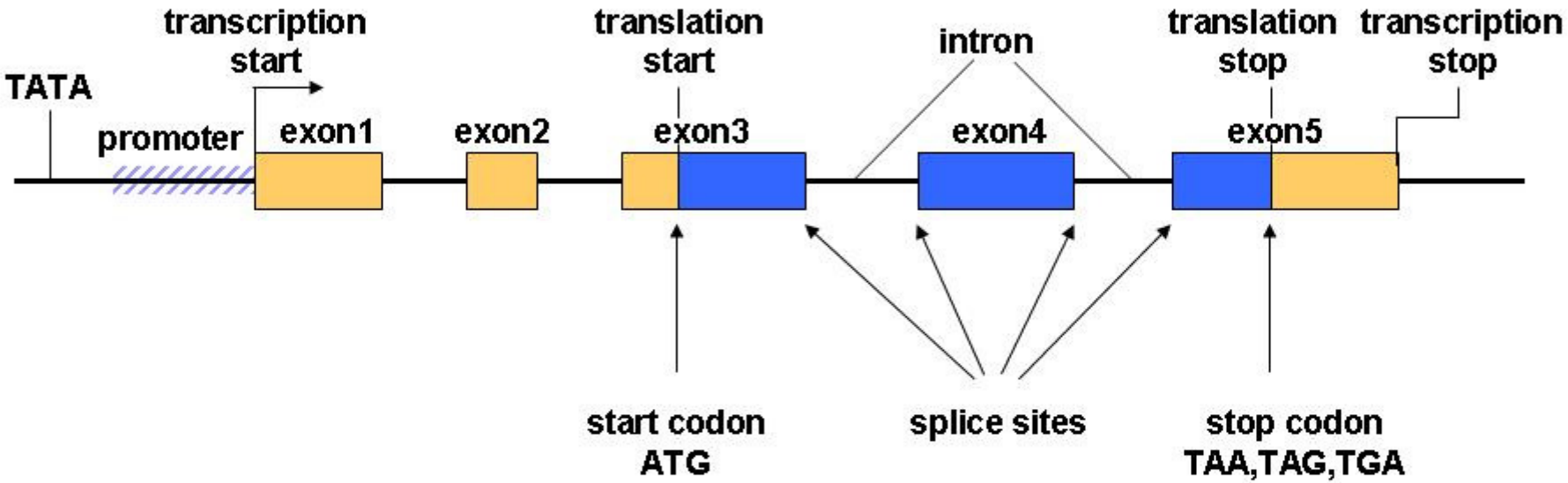
CCUGAGCCAACUAUUGAUGAA

PEPTIDE

Gene structure



Finding genes



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> HSCKIIBE, Human gene for casein kinase II subunit beta (EC 2.7.1.37).
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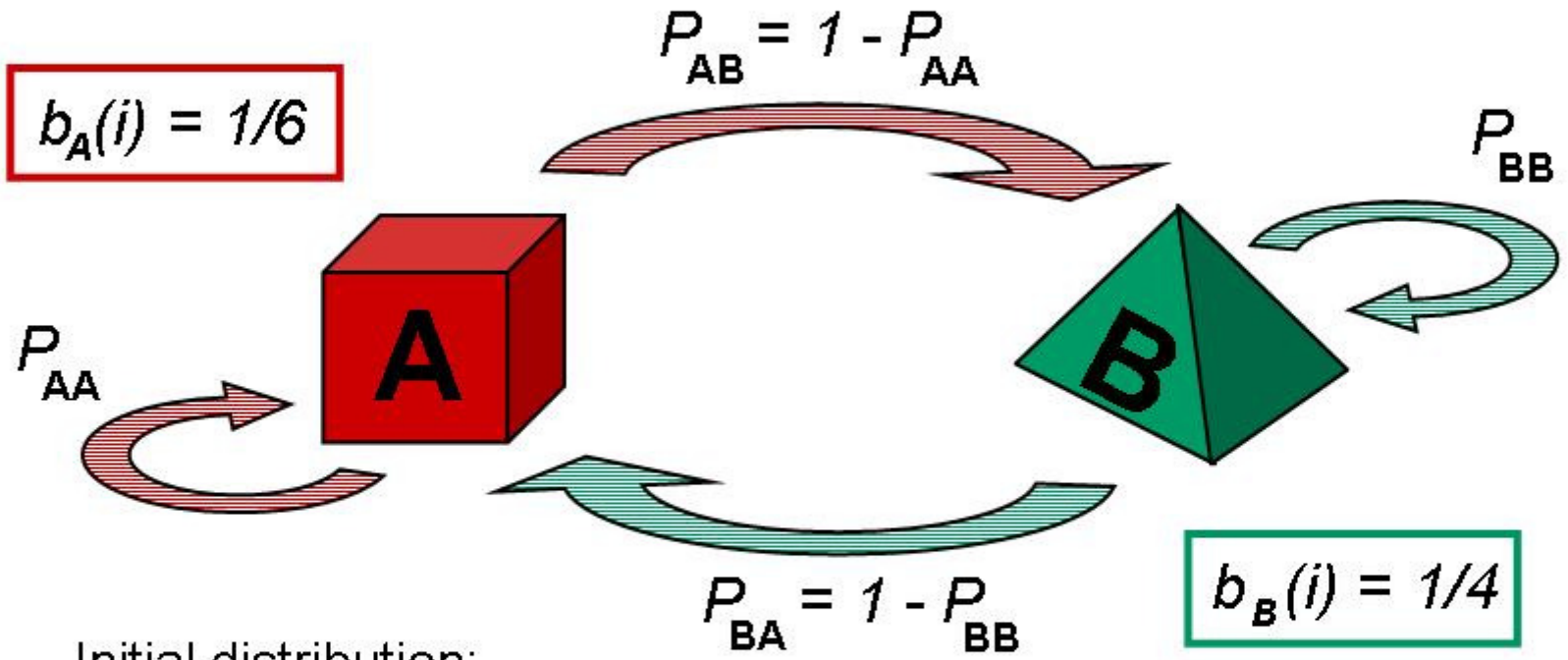
Approaches to gene finding

- Homology searches
  - BLAST, Procrustes
- Ab initio
  - Genscan, Genie, GeneID
- Hybrids
  - GenomeScan, GenieEST, Twinscan, SGP, ROSETTA, CEM, TBLASTX, SLAM

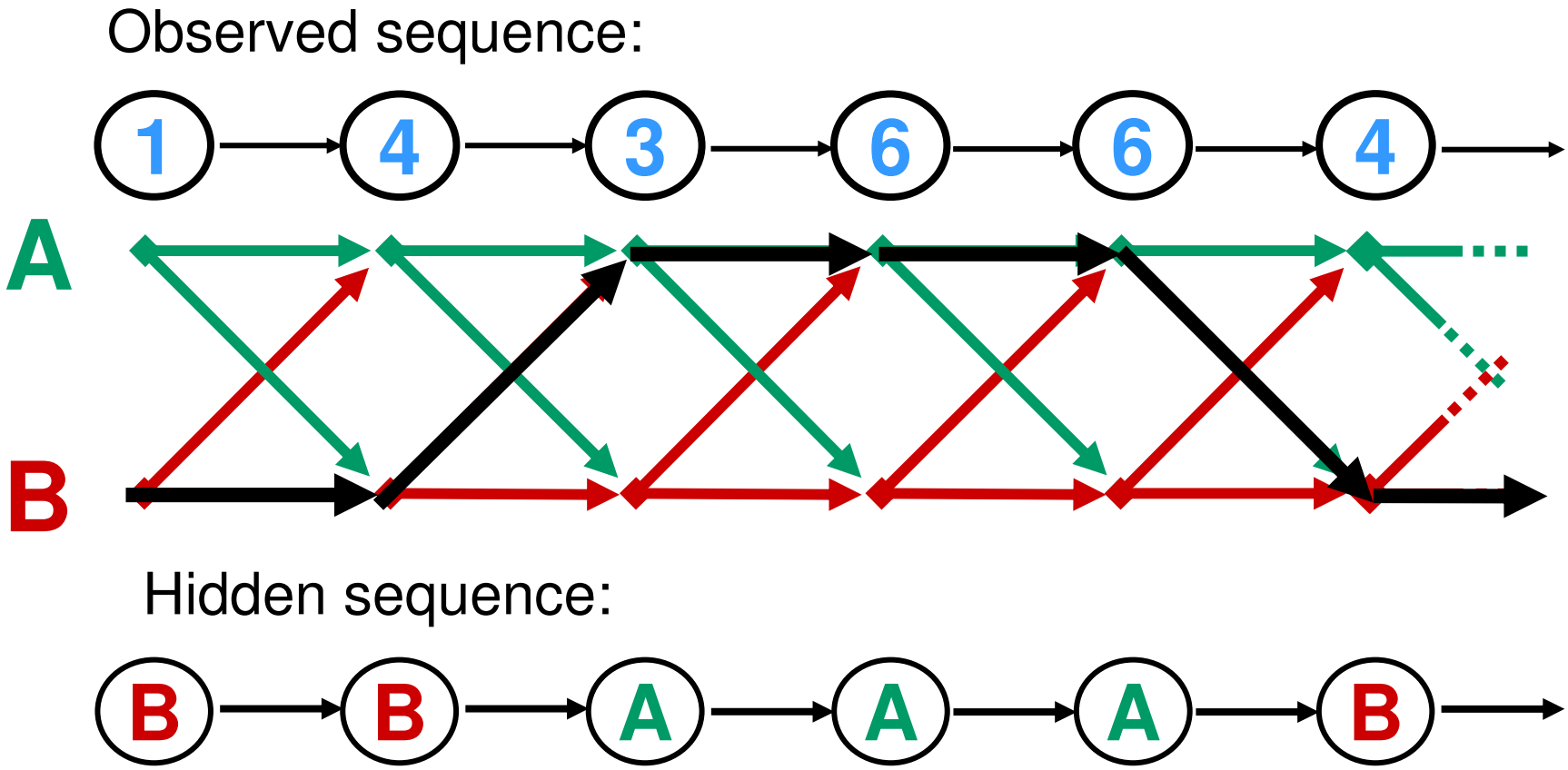
A simple Hidden Markov Model (HMM)



Initial distribution:

$\pi = (\pi_A, \pi_B)$

A lattice view



Two fundamental problems

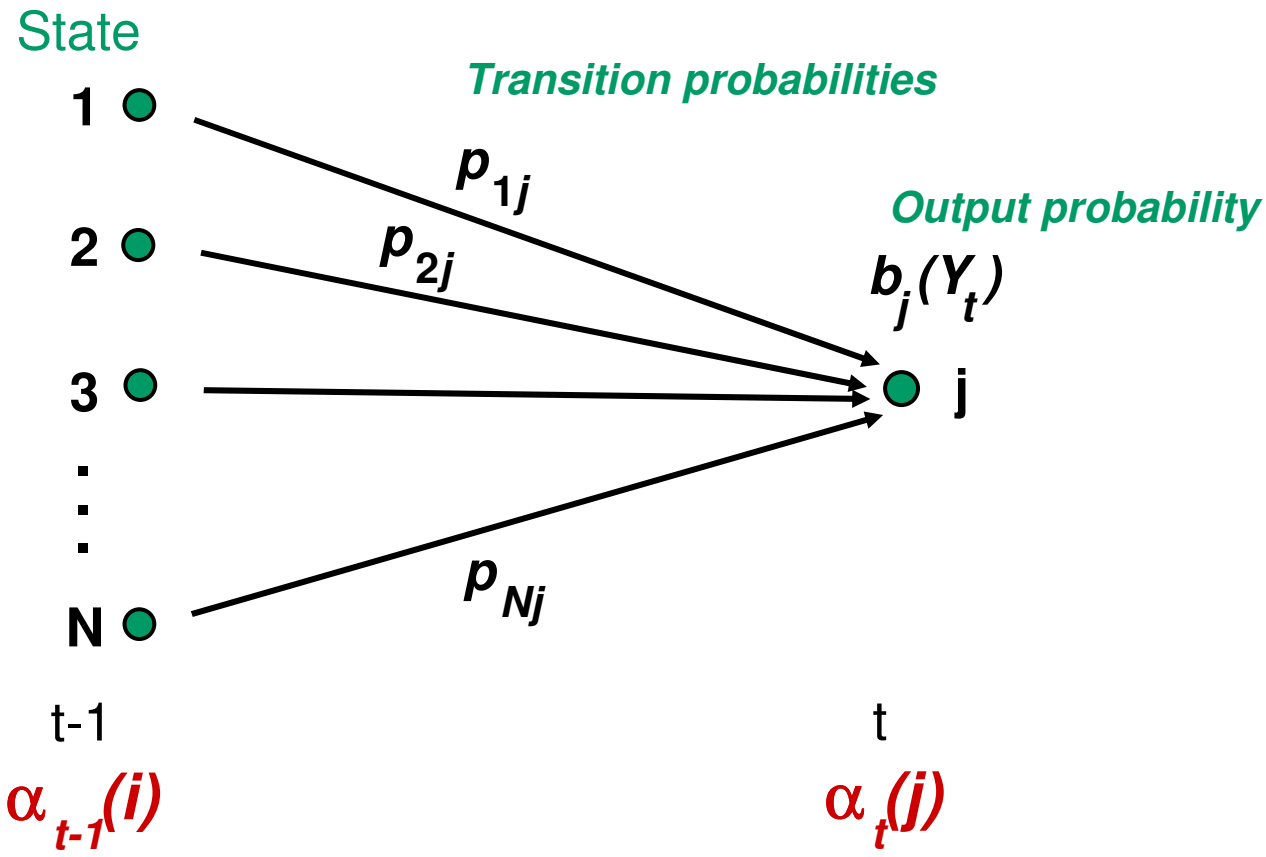
- The probability of the observed data given the model.

  The forward algorithm

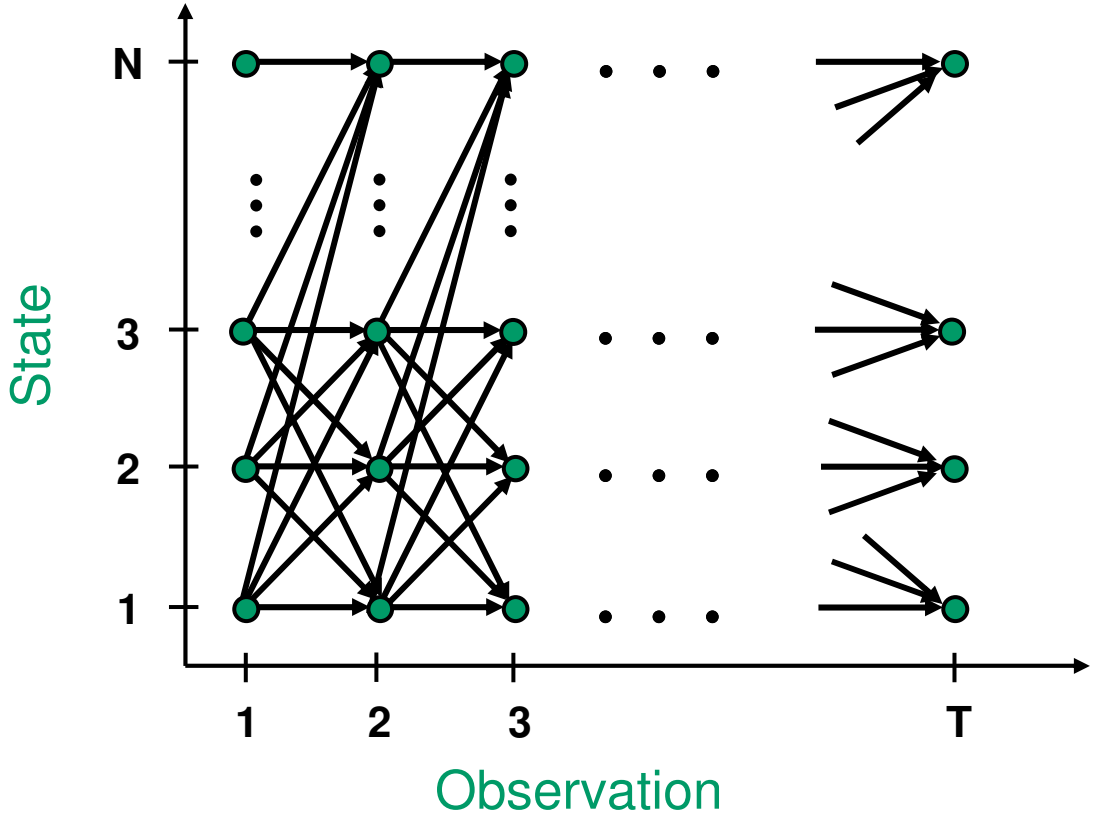
- The best hidden state sequence given the data.

  The Viterbi algorithm

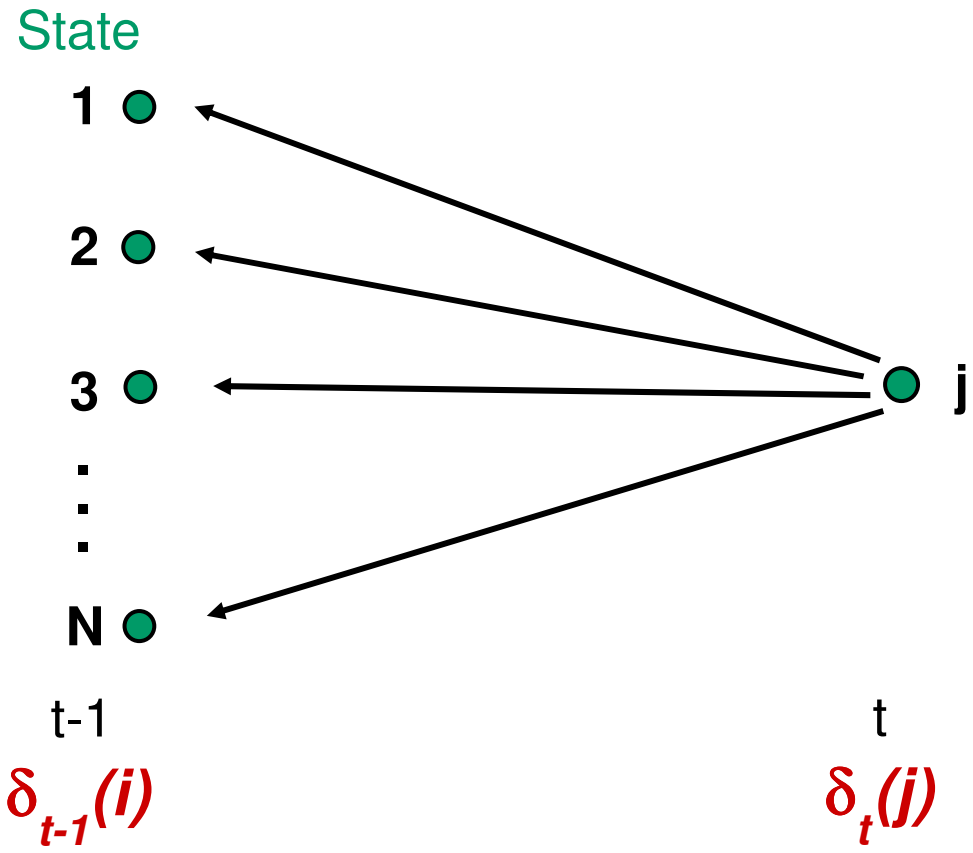
The forward algorithm - α



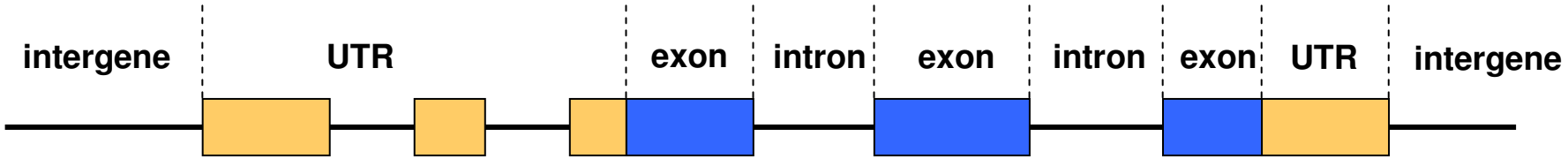
The forward algorithm



The Viterbi algorithm - δ



HMMs for gene finding



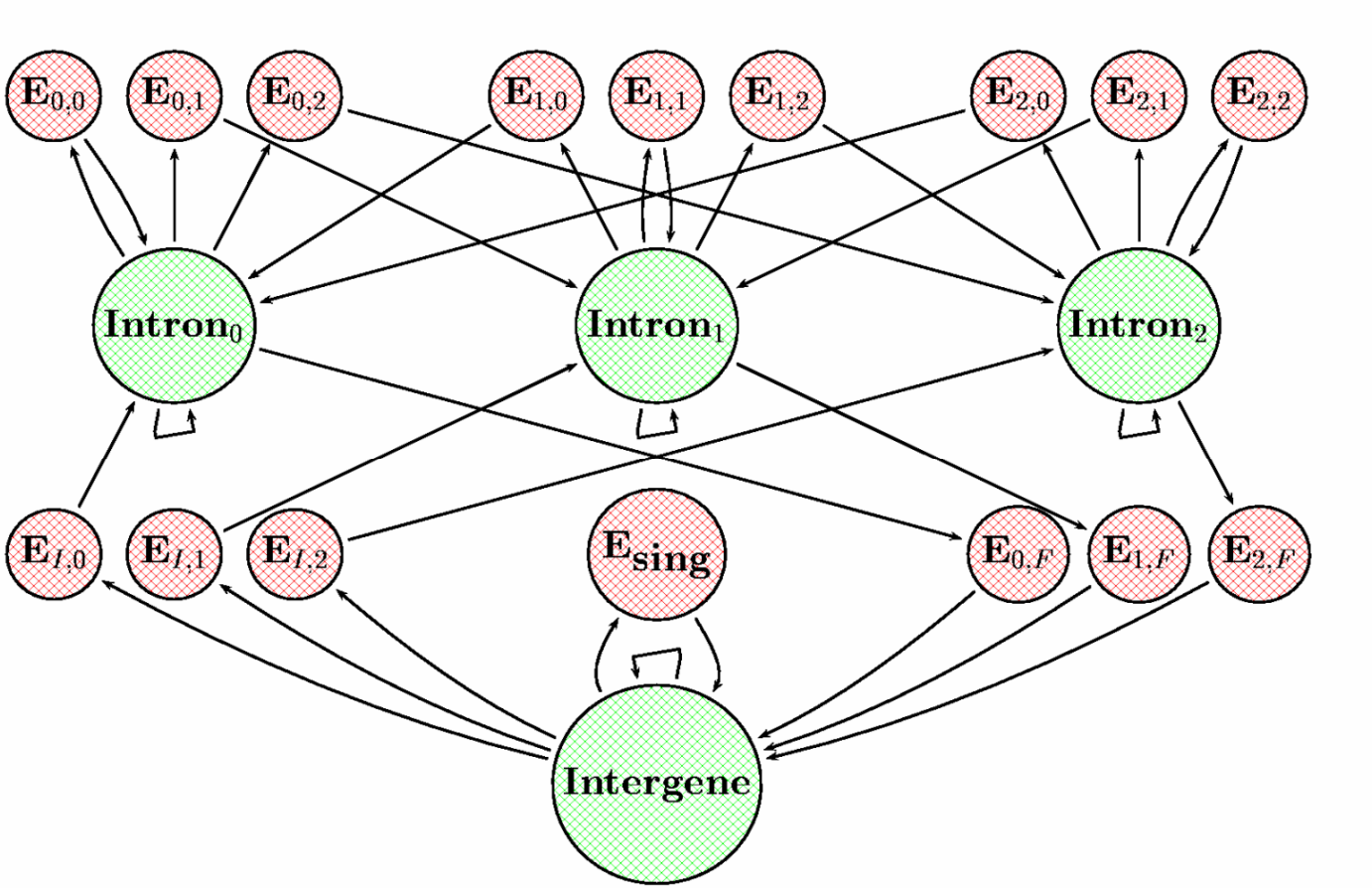
Observed:

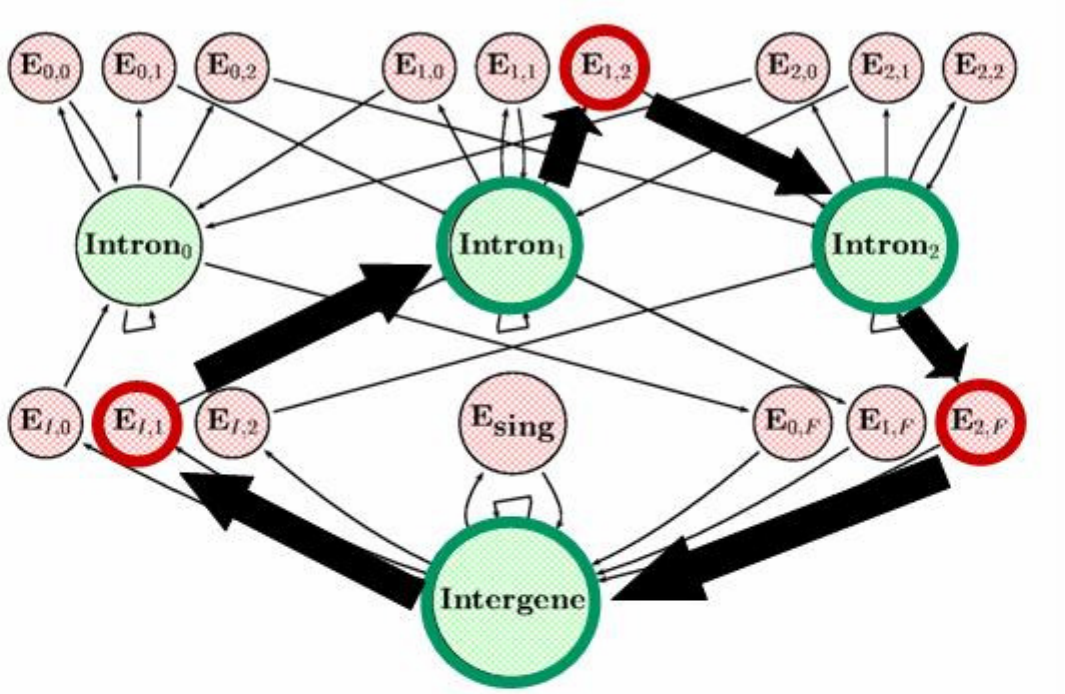
CTTGATGCTGGCACGTTCTGCTTCATCGGAGACAAATTACGGCTTTCCGGAGCA

Hidden:

CTTGATGCTGGCACGTTCTGCTTCATCGGAGACAAATTACGGCTTTCCGGAGCA

Generalized HMM





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Sequence alignment

- Pair HMMs

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Sequence alignment

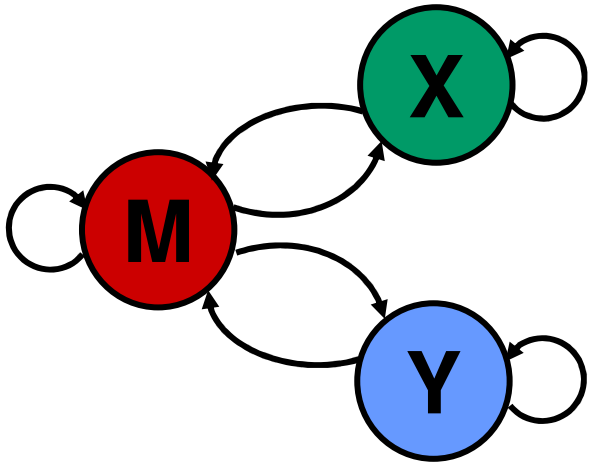
```
 50     .    :    .    :    .    :    .    :    .    :
247 GGTGAGGTCGAGGACCCTGCA  CGGAGCTGTATGGAGGGCA   AGAGC
    |:   ||  ||||:  |||| --:||  ||| |::|   |||---||||
368 GAGTCGGGGGAGGGGGCTGCTGTTGGCTCTGGACAGCTTGCATTGAGAGG

100     .    :    .    :    .    :    .    :    .    :
292 TTC          CTACAGAAAAGTCCCAGCAAGGAGCCACACTTCACTG
    |||----------|| |   |::| |: ||||::|:||:-||  ||:| |
418 TTCTGGCTACGCTCTCCCTTAGGGACTGAGCAGAGGGCT CAGGTCGCGG

150     .    :    .    :    .    :    .    :    .    :
332               ATGTCGAGGGGAAGACATCATTCGGGATGTCAGTG
    ---------------|||||||||||||||||||:||||||||||||
467 TGGGAGATGAGGCCAATGTCGAGGGGAAGACATCATTTGGGATGTCAGTG

200     .    :    .    :    .    :    .    :    .    :
367 TTCAACCTCAGCAATGCCATCATGGGCAGCGGCATCCTGGGACTCGCCTA
    |||||:||||||||:||||||||||||||:|| ||:||||||:||||||||
517 TTCAATCTCAGCAACGCCATCATGGGCAGTGGAATTCTGGGGCTCGCCTA
```

Pair HMMs for alignment



M = (mis)match
X = insert seq1
Y = insert seq2

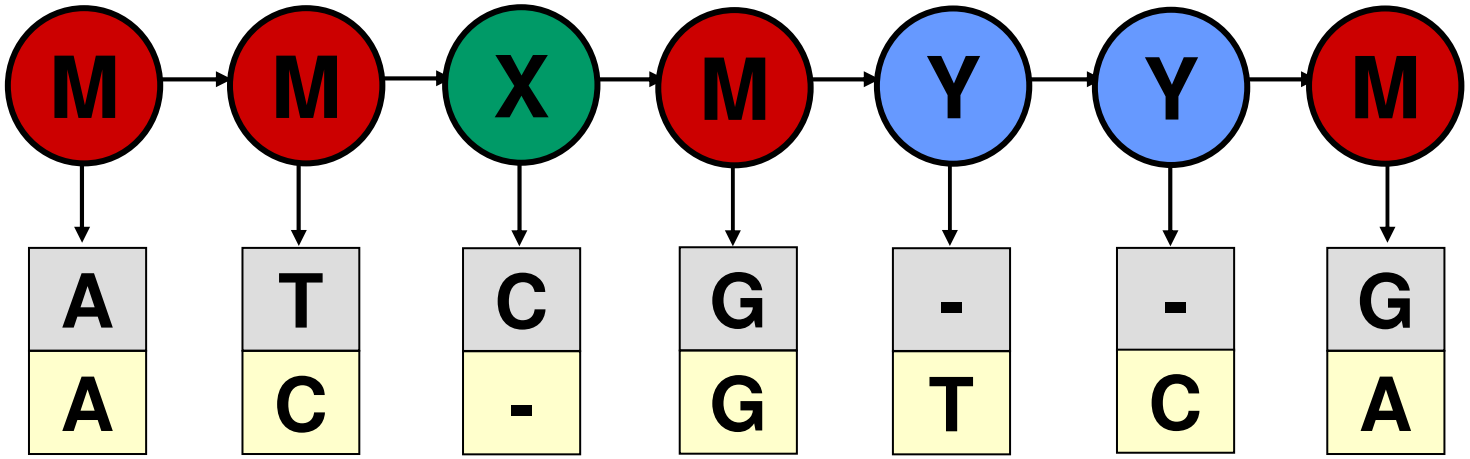
Output sequence:

ATCG- - G
AC- GTCA

Observed sequences:

ATCGG
ACGTCA

Pair HMMs



Output sequence:

ATCG- - G

AC- GTCA

Observed sequences:

ATCGG

ACGTCA

Comparative gene finding

- Generalized Pair HMMs

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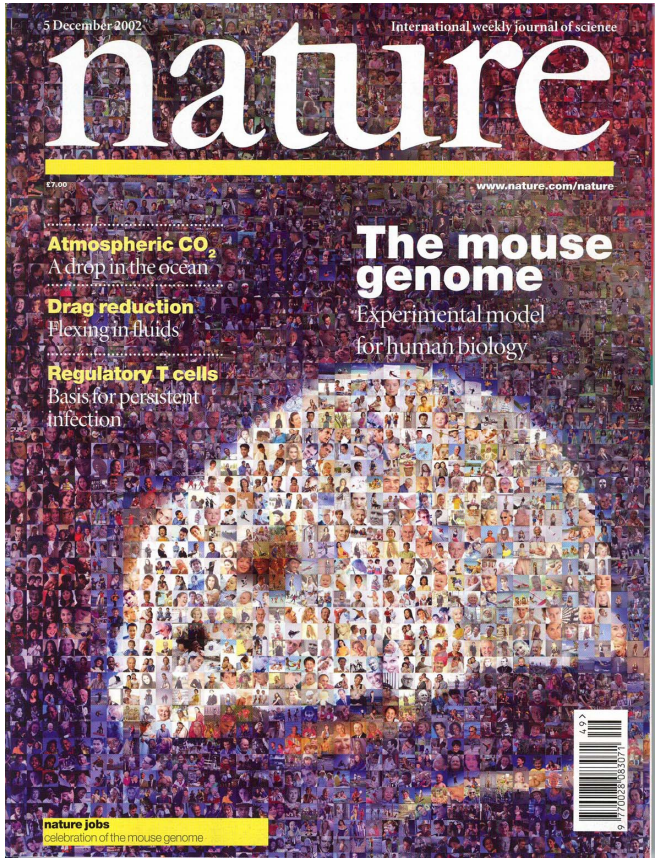
Comparing human and mouse



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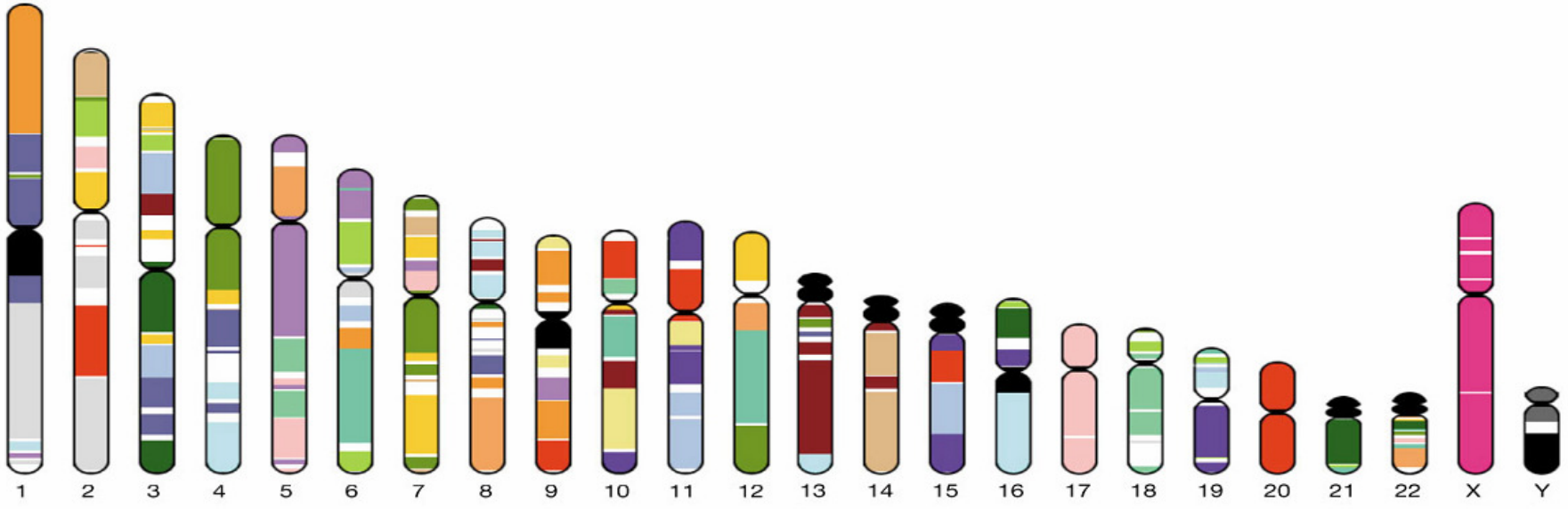
Why mouse?

Human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X
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Mouse


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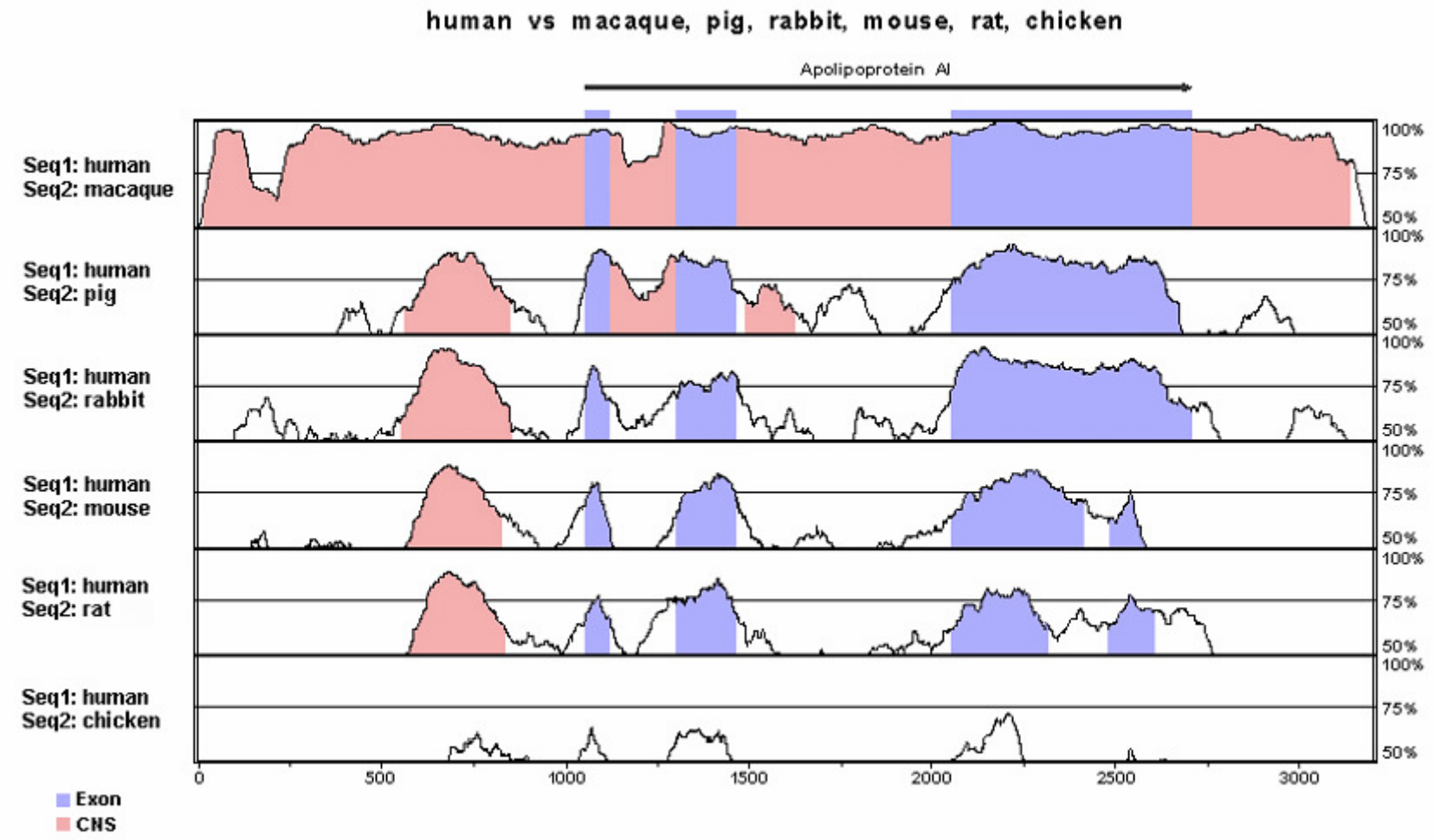
X
Y



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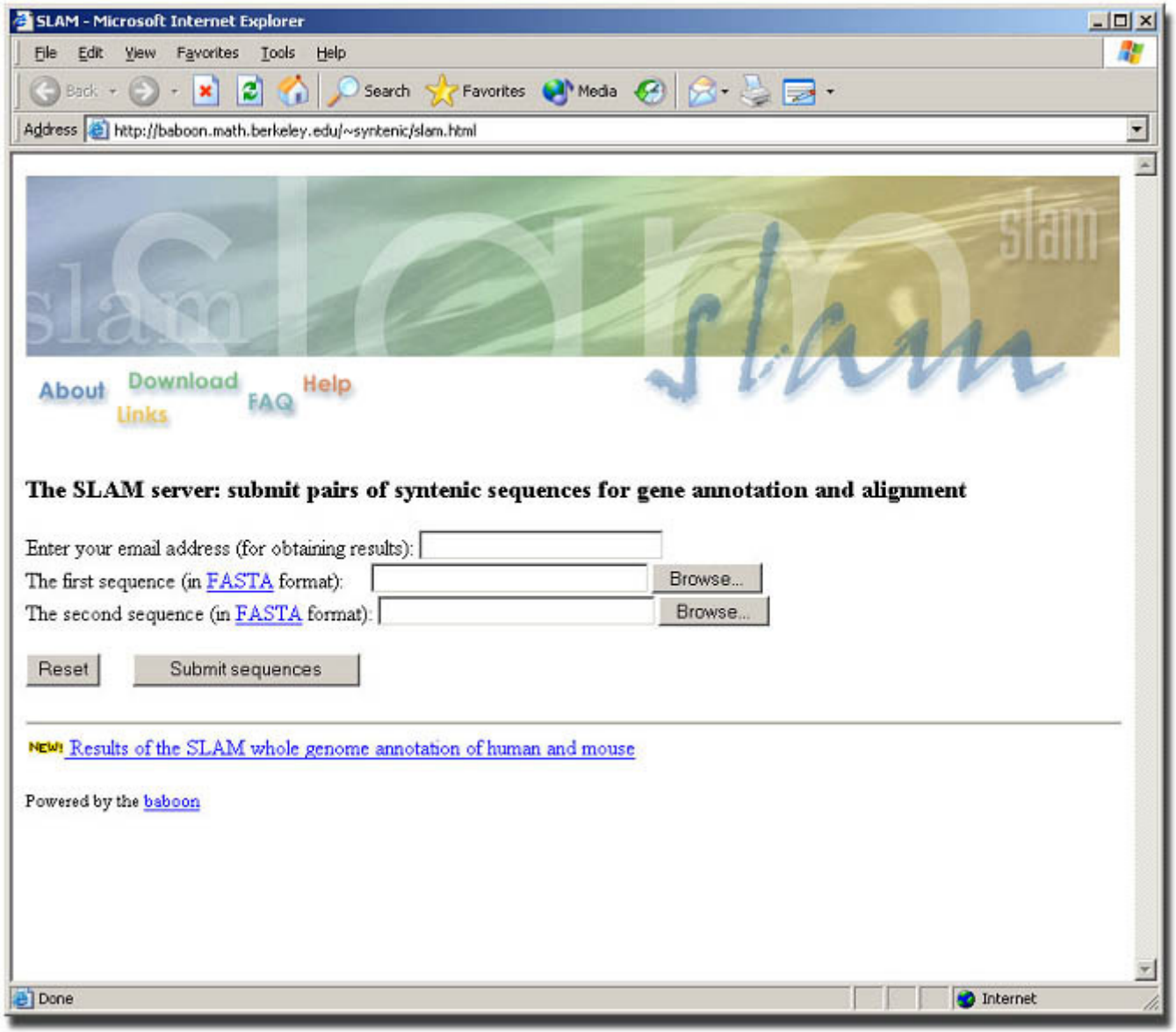
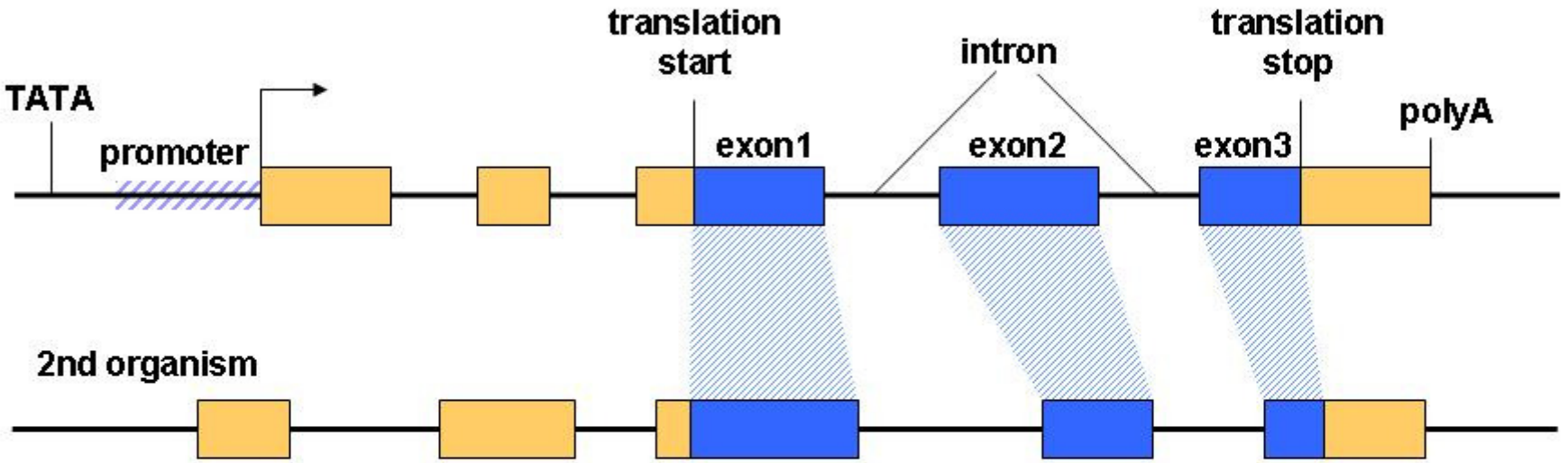
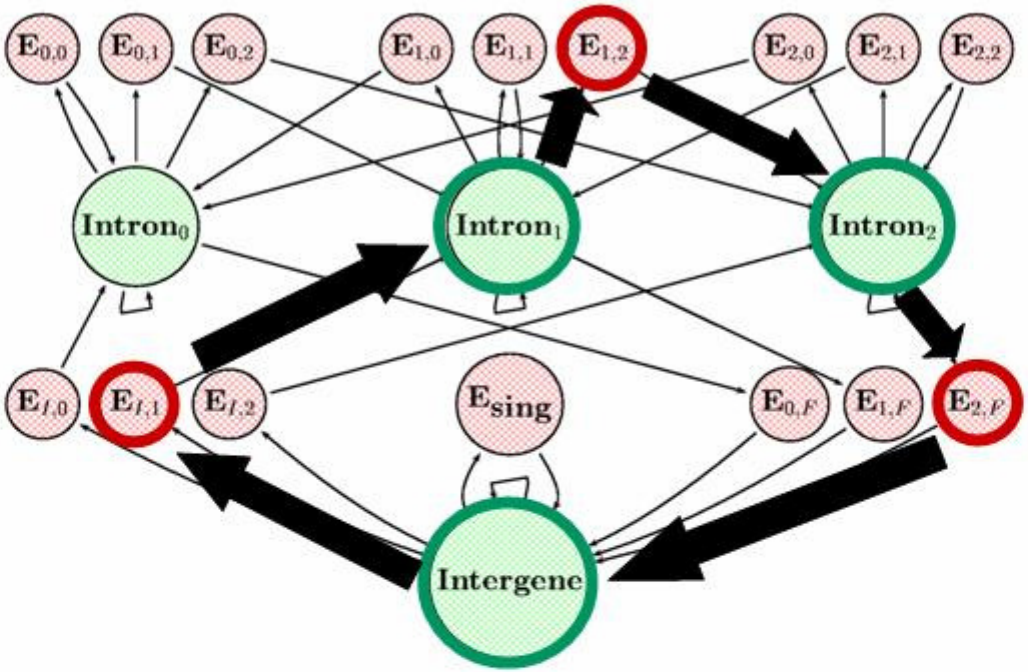
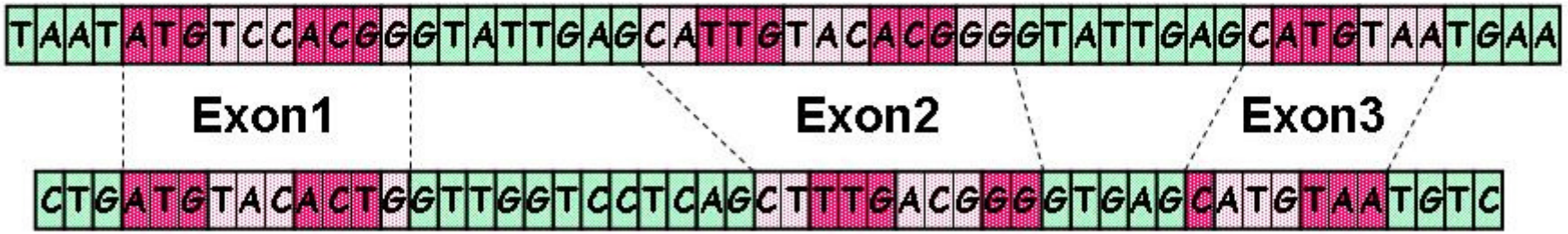


http://bio.math.berkeley.edu/slam/

Comparative gene finding in SLAM







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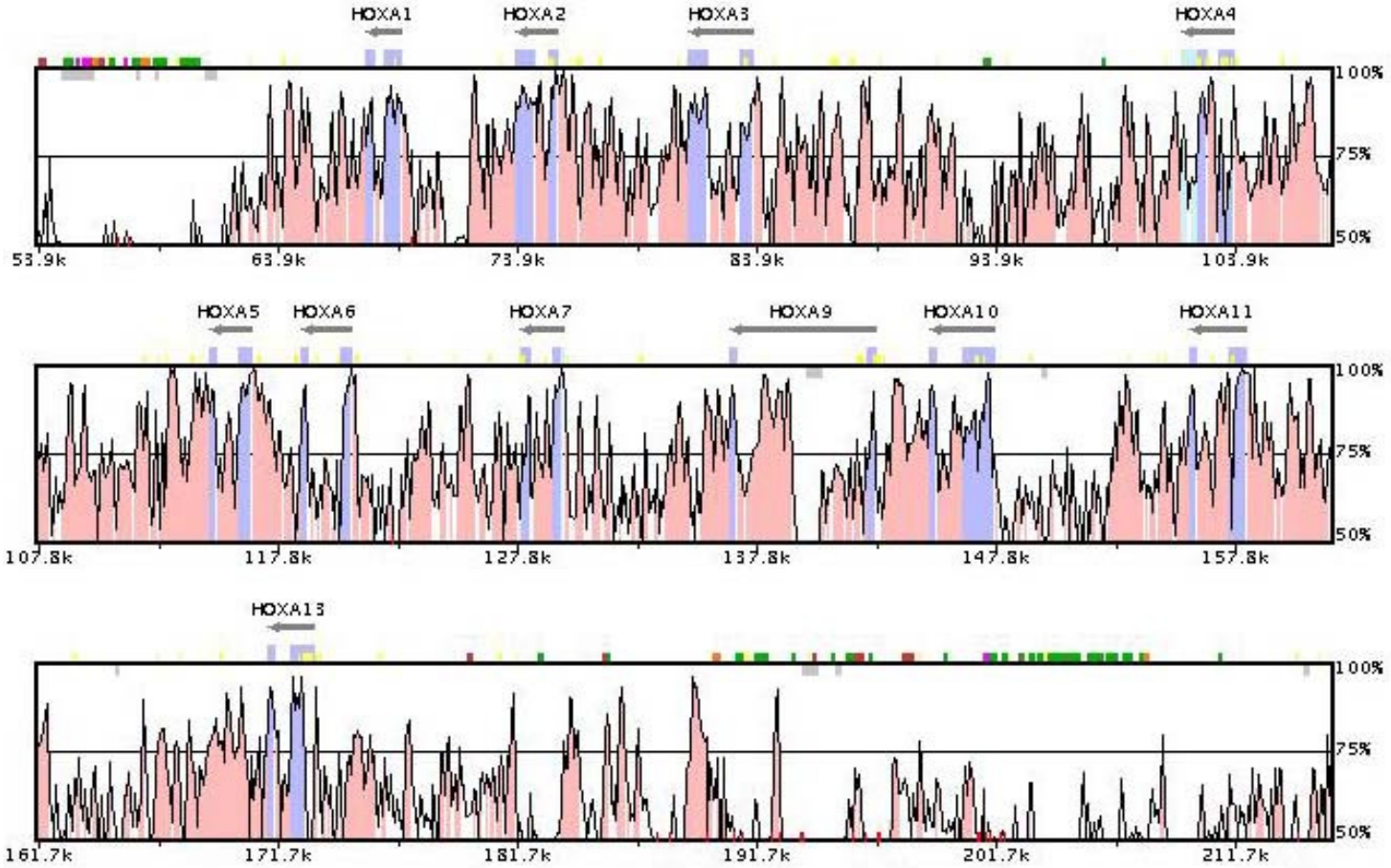
The Rosetta set

Local	SN	SP	AC
Genscan	0.96	0.91	0.93
Twinscan	0.96	0.94	0.94
SGP-1	0.94	0.96	0.94
SLAM	0.95	0.98	0.96

Global	SN	SP	AC
Genscan	0.87	0.87	0.84
Twinscan	0.89	0.92	0.89
SGP-2	0.88	0.94	0.89
SLAM	0.87	0.96	0.90

A problem: HoxA human-mouse



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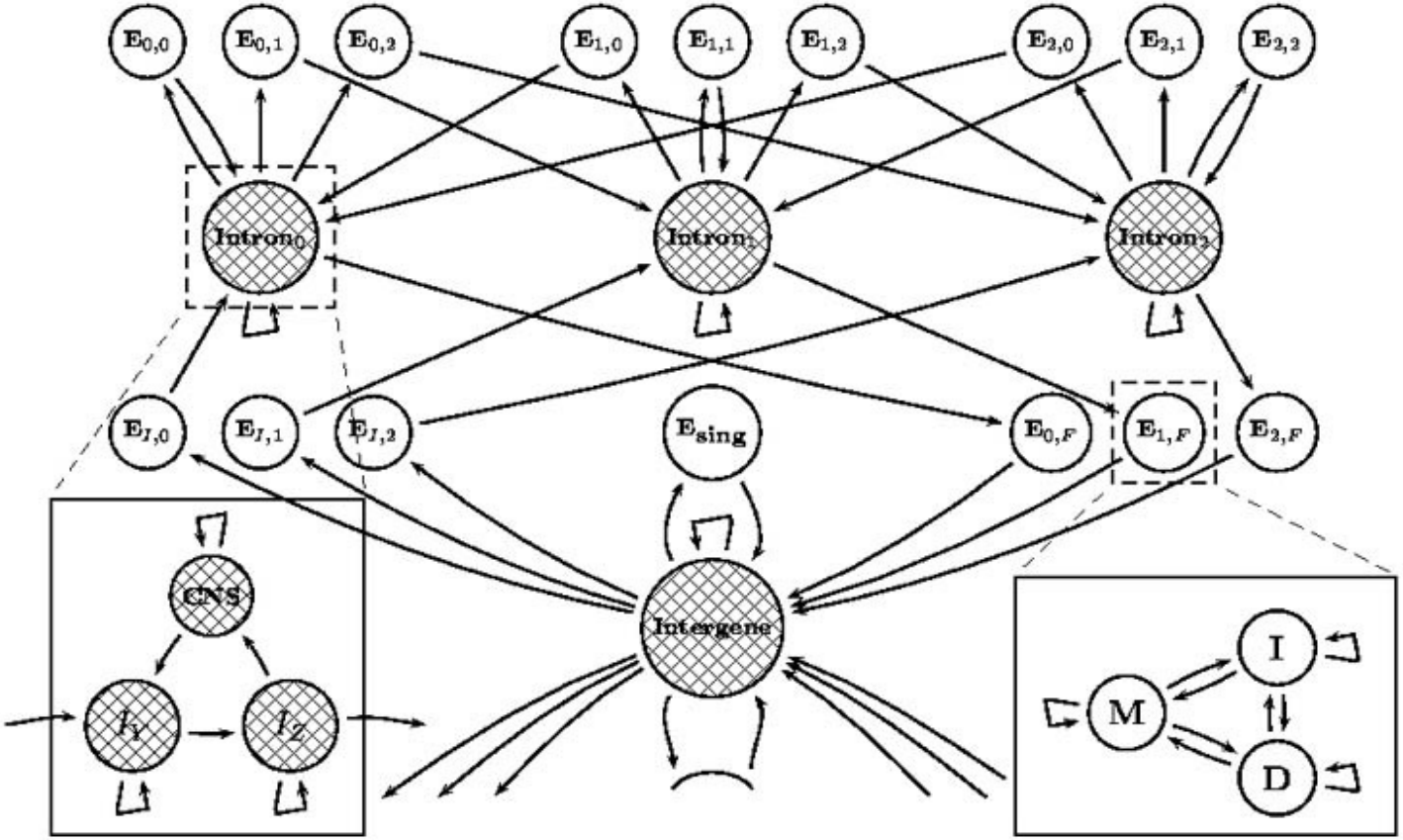
The SLAM model



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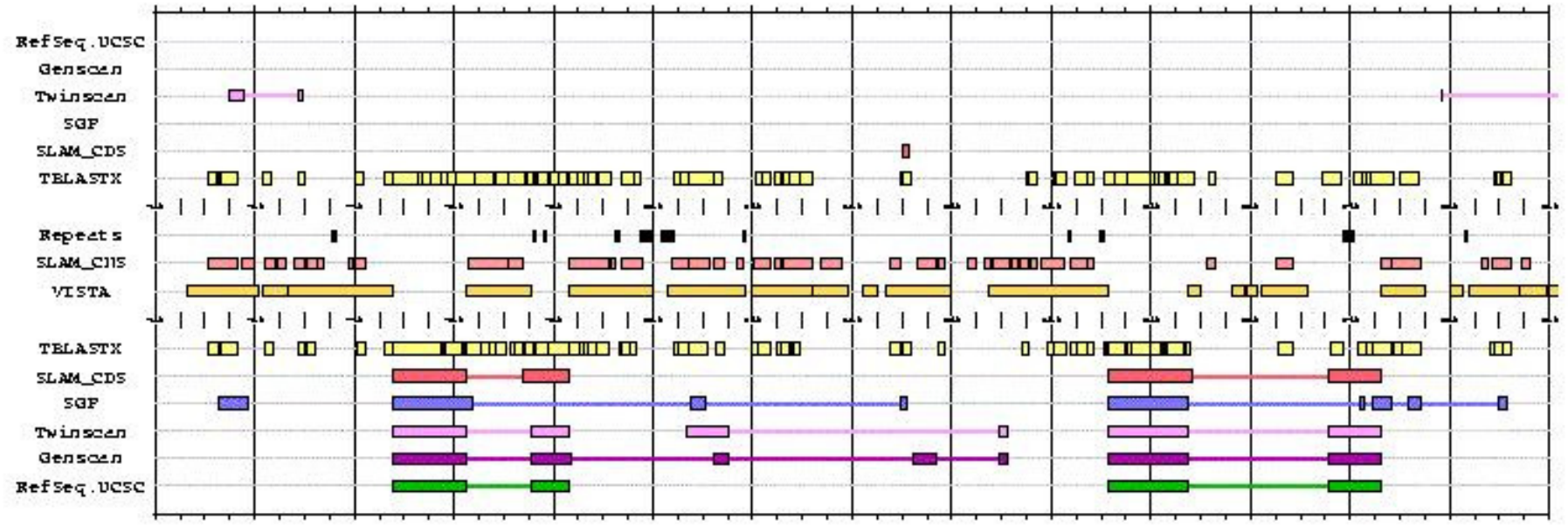
Example: HoxA2 and HoxA3



VISTA TBLASTX SLAM Twinscan

RefSeq SLAM CNS SGP-2 Genscan

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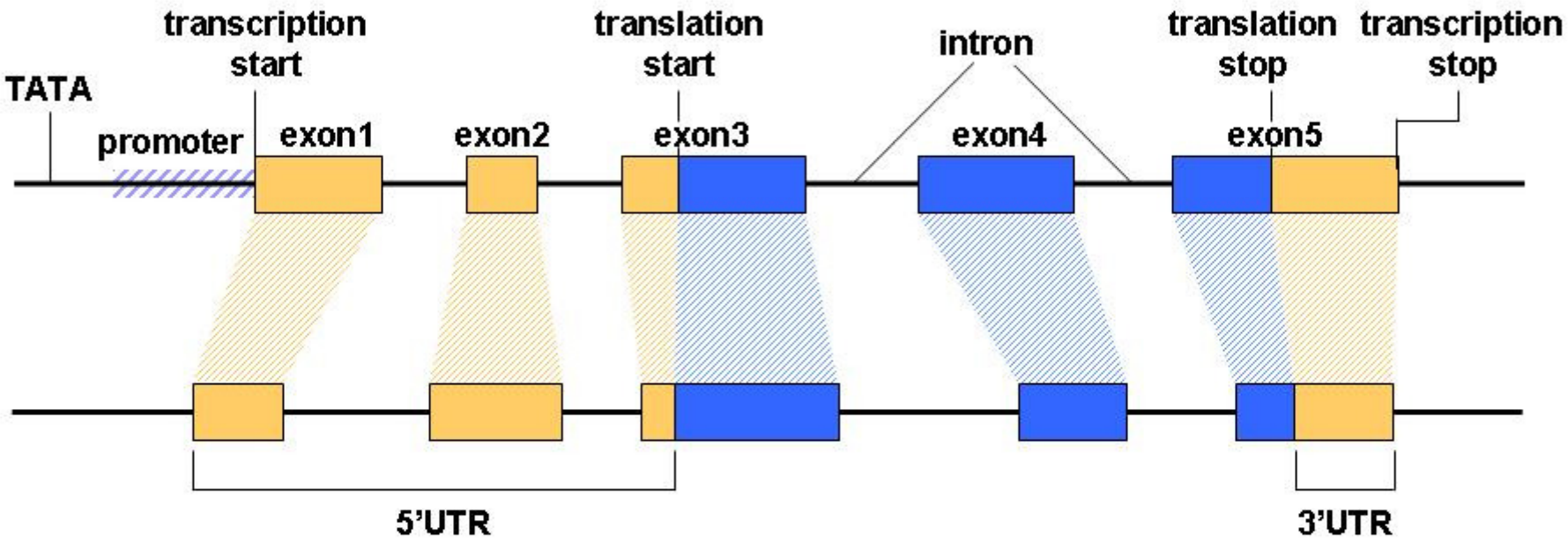
Comparative UTR prediction



Reducing computational complexity

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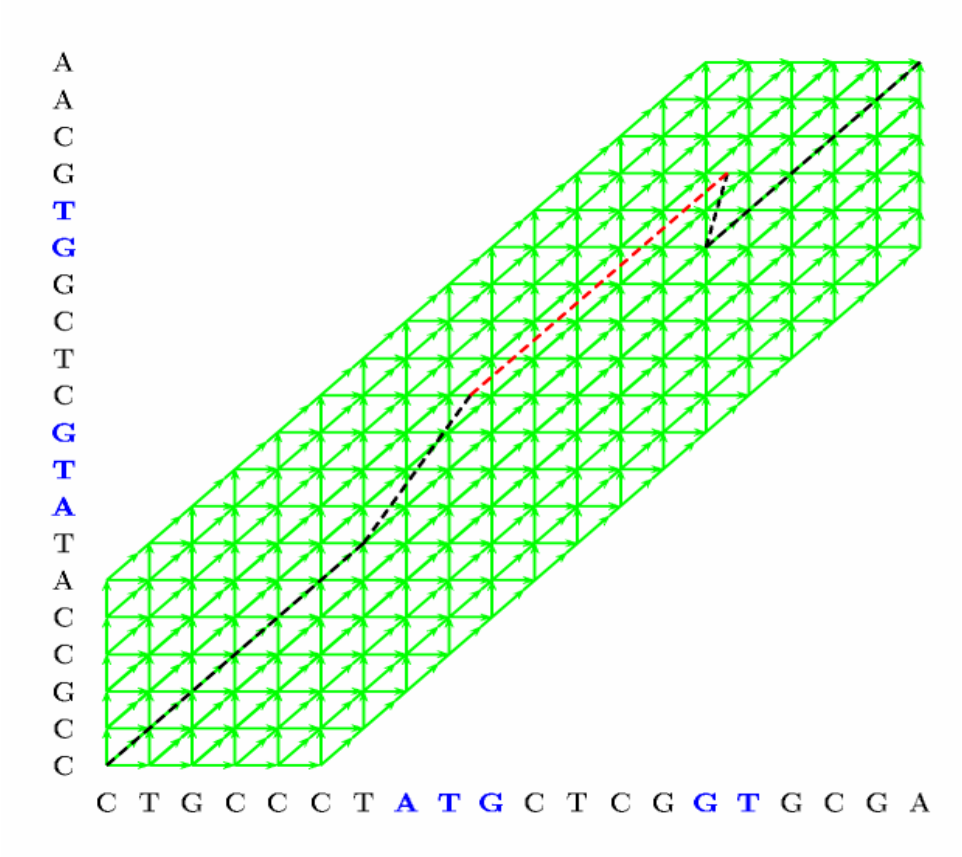
Computational complexity

Model	Time	Space
HMM	N^2T	NT
PHMM	N^2TU	NTU
GHMM	D^2N^2T	NT
GPHMM	D^4N^2TU	NTU

N = no. states T = length seq1

D = max duration U = length seq2

Approximate alignment



Reduces

TU*-factor to *hT

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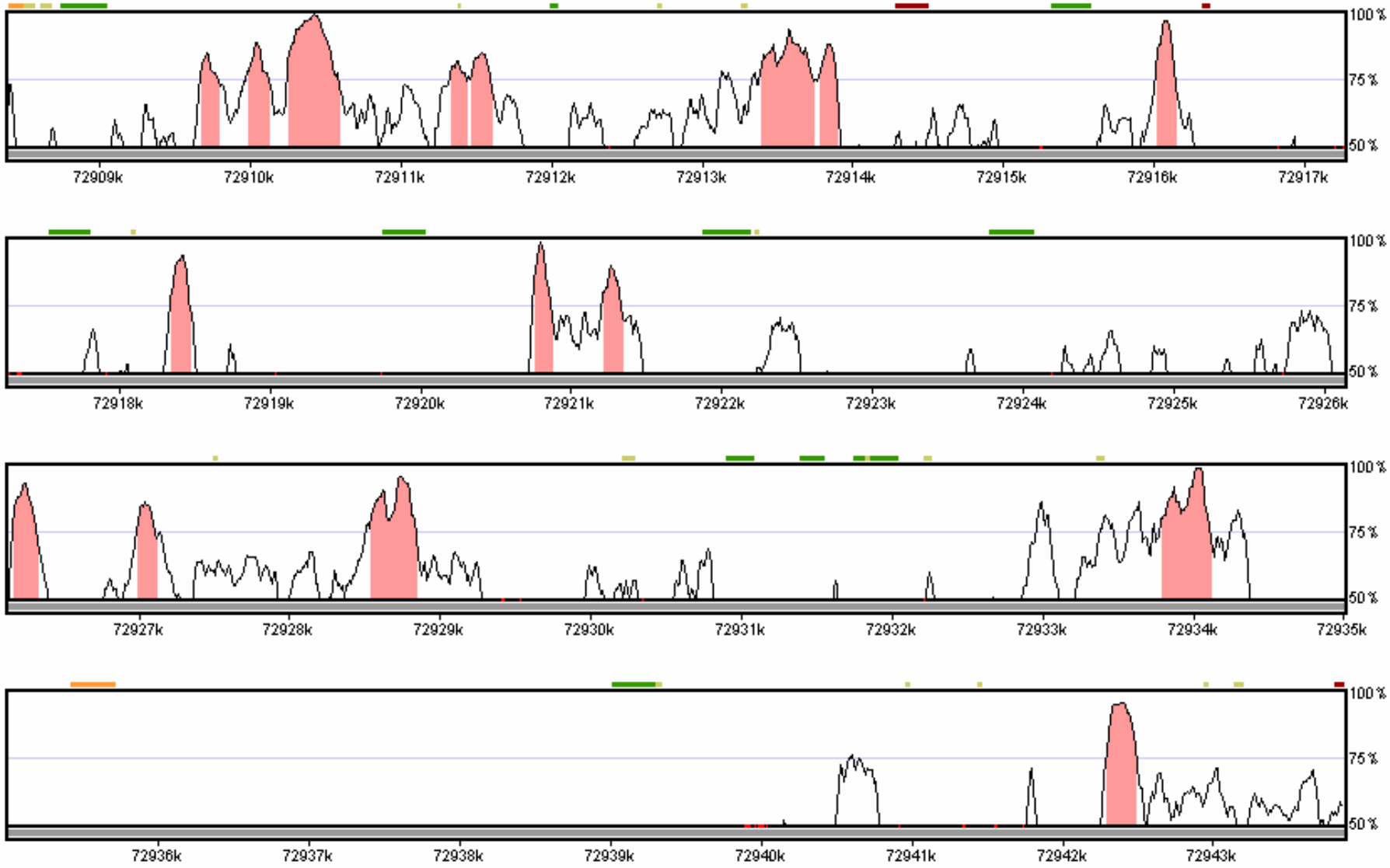
100 %
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50 %
72909k
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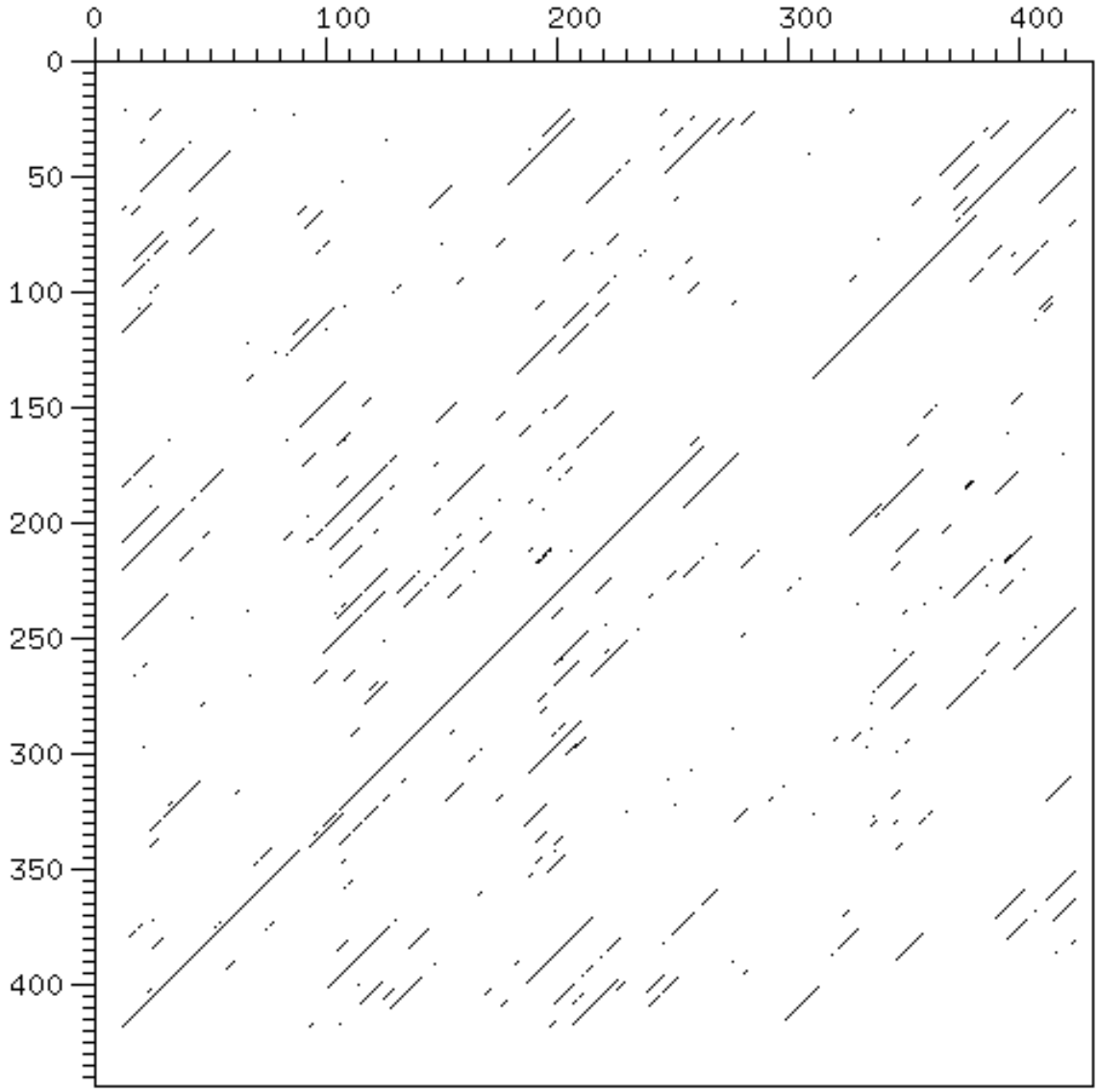
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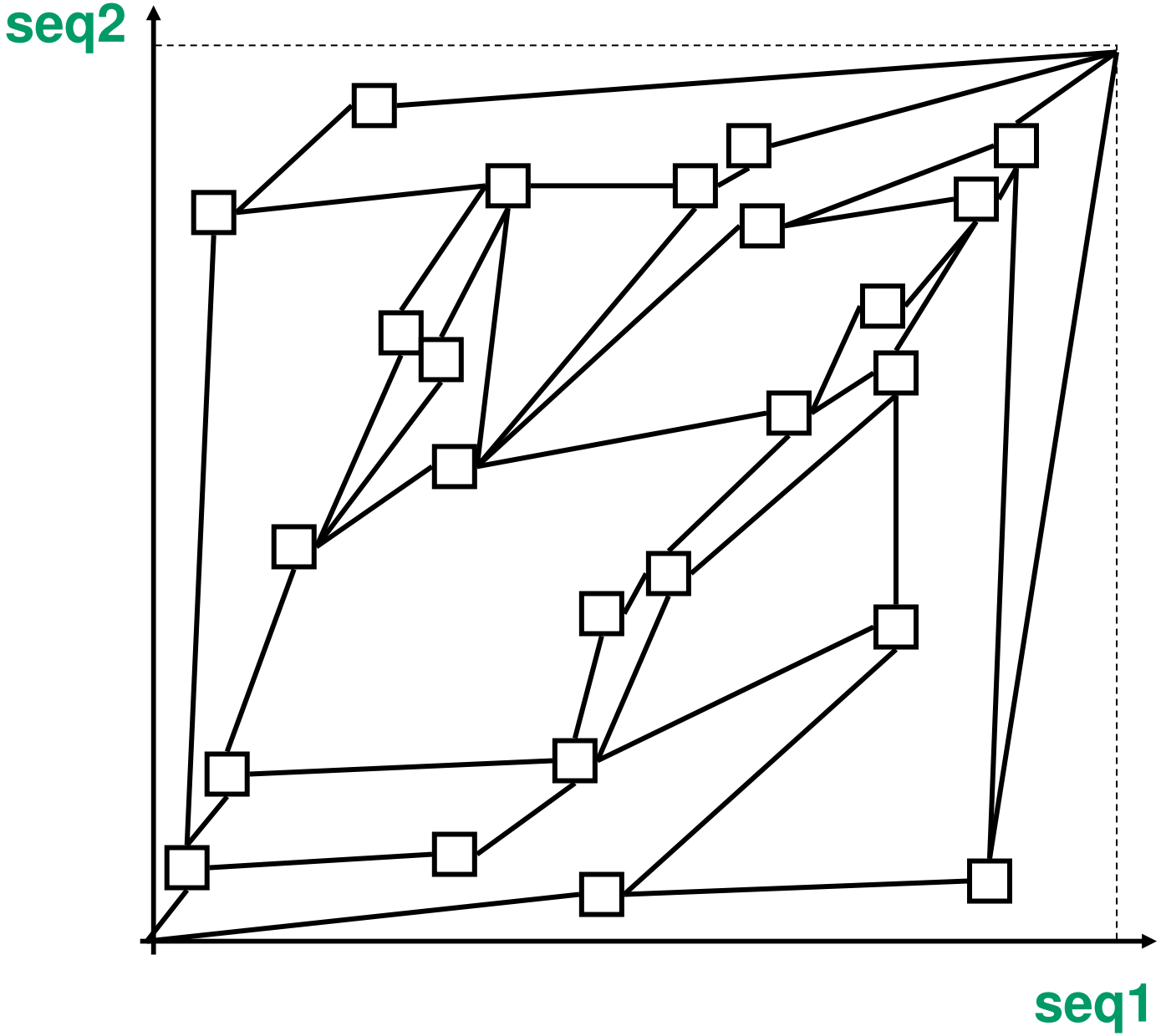
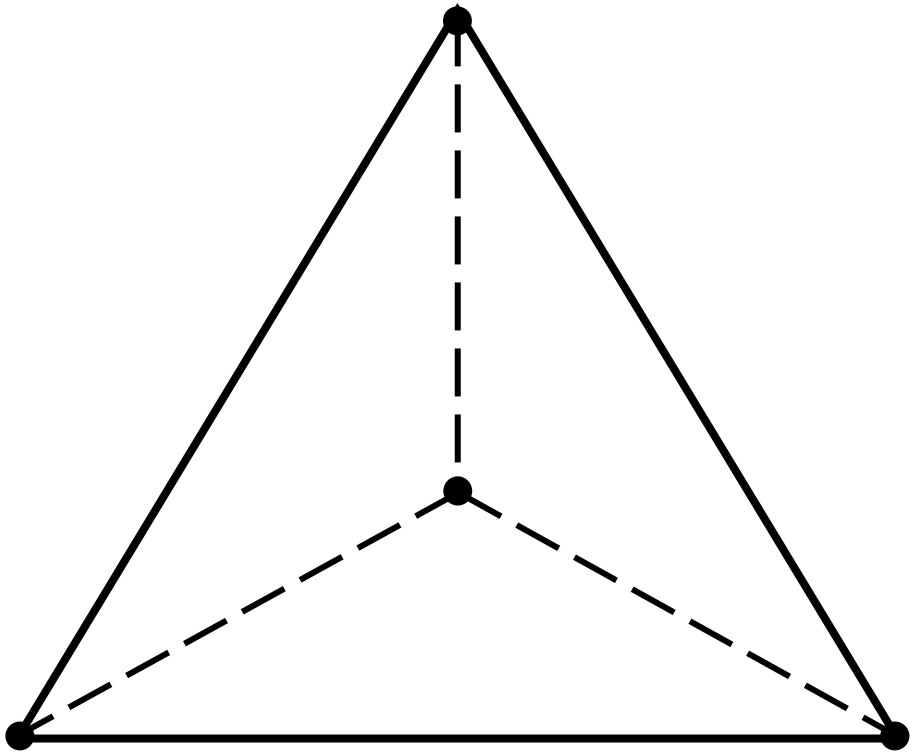
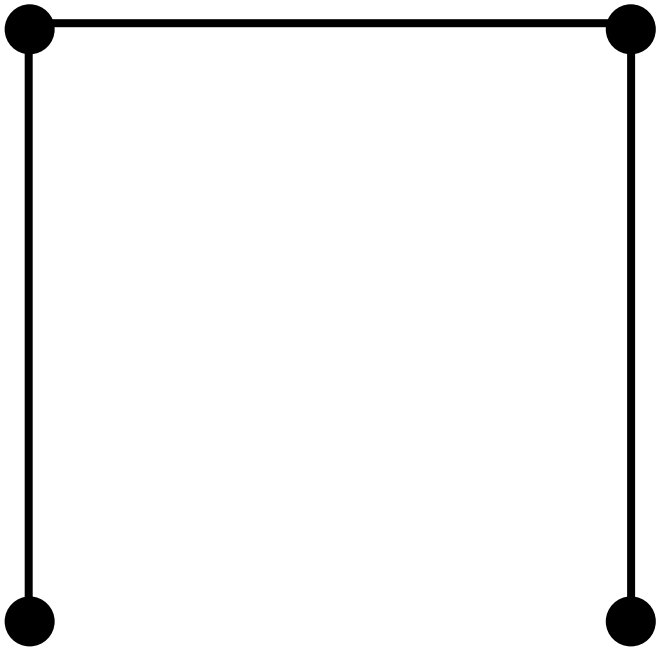

seq2
seq1

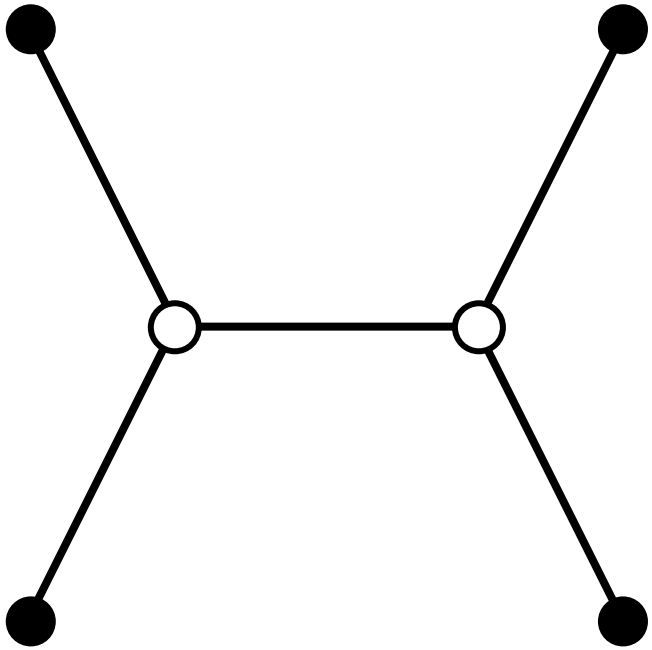
Steiner trees



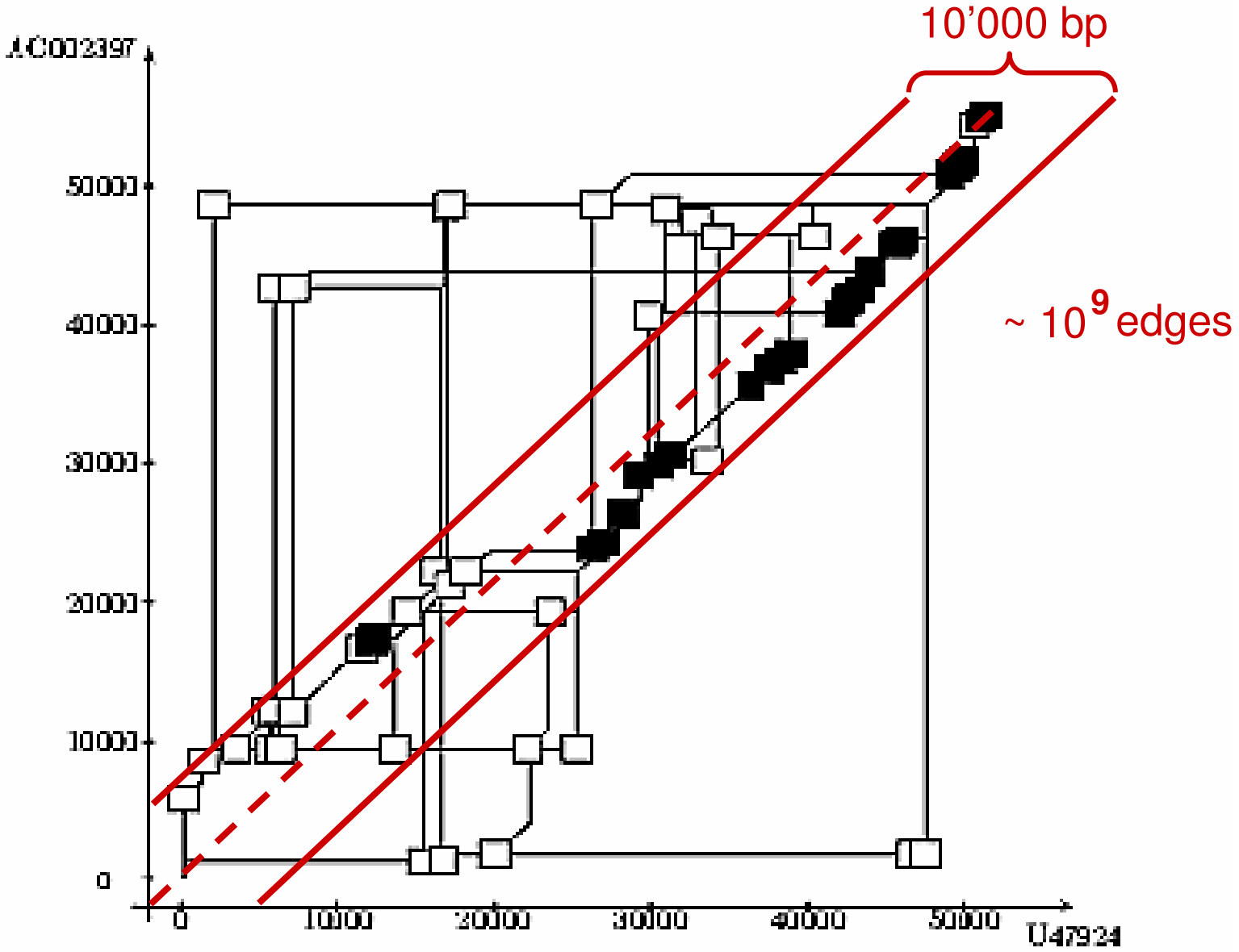
Steiner trees



Minimum spanning tree



Steiner tree



2-approximation in $O(n^3)$

Regulatory regions

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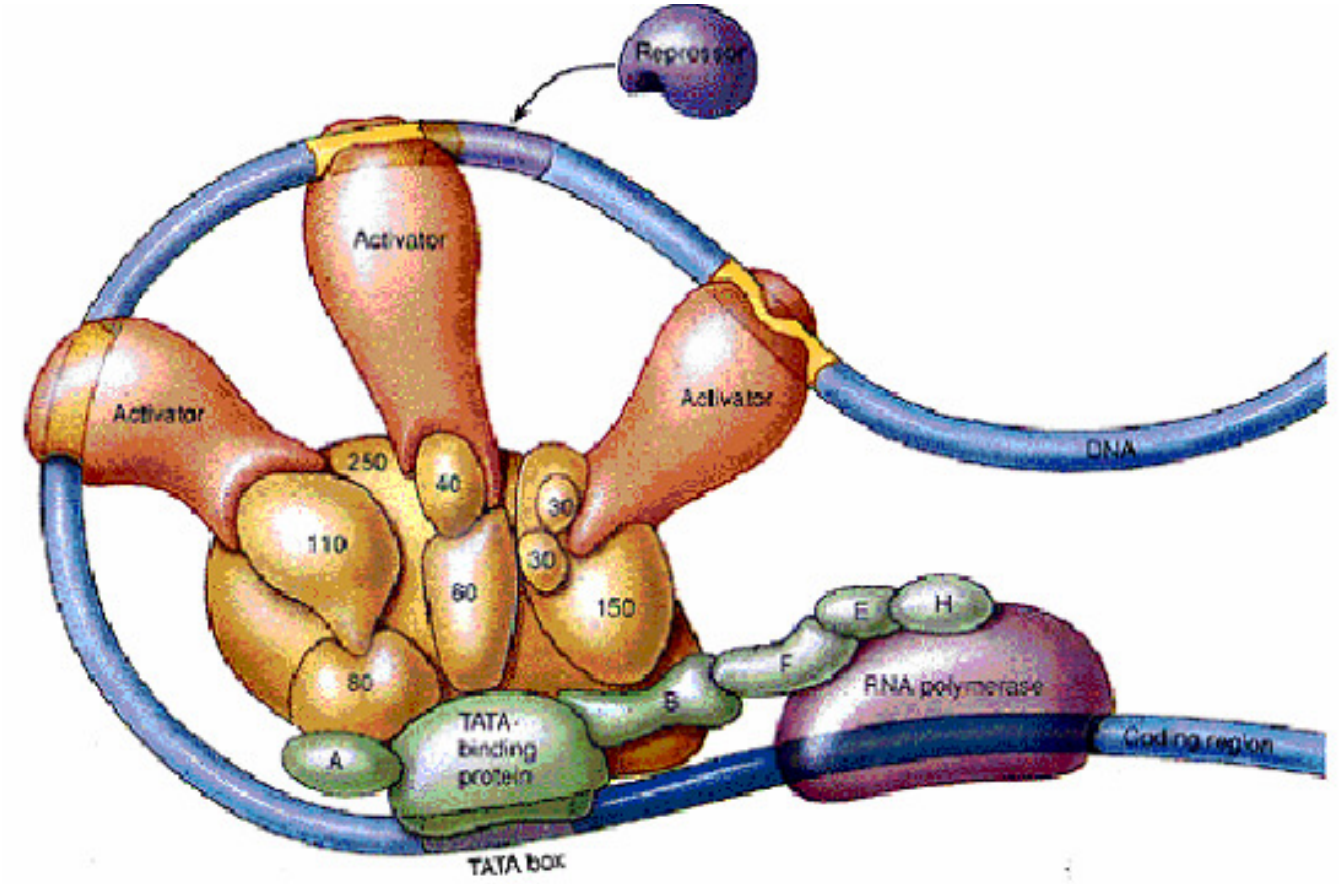
Regulatory complex



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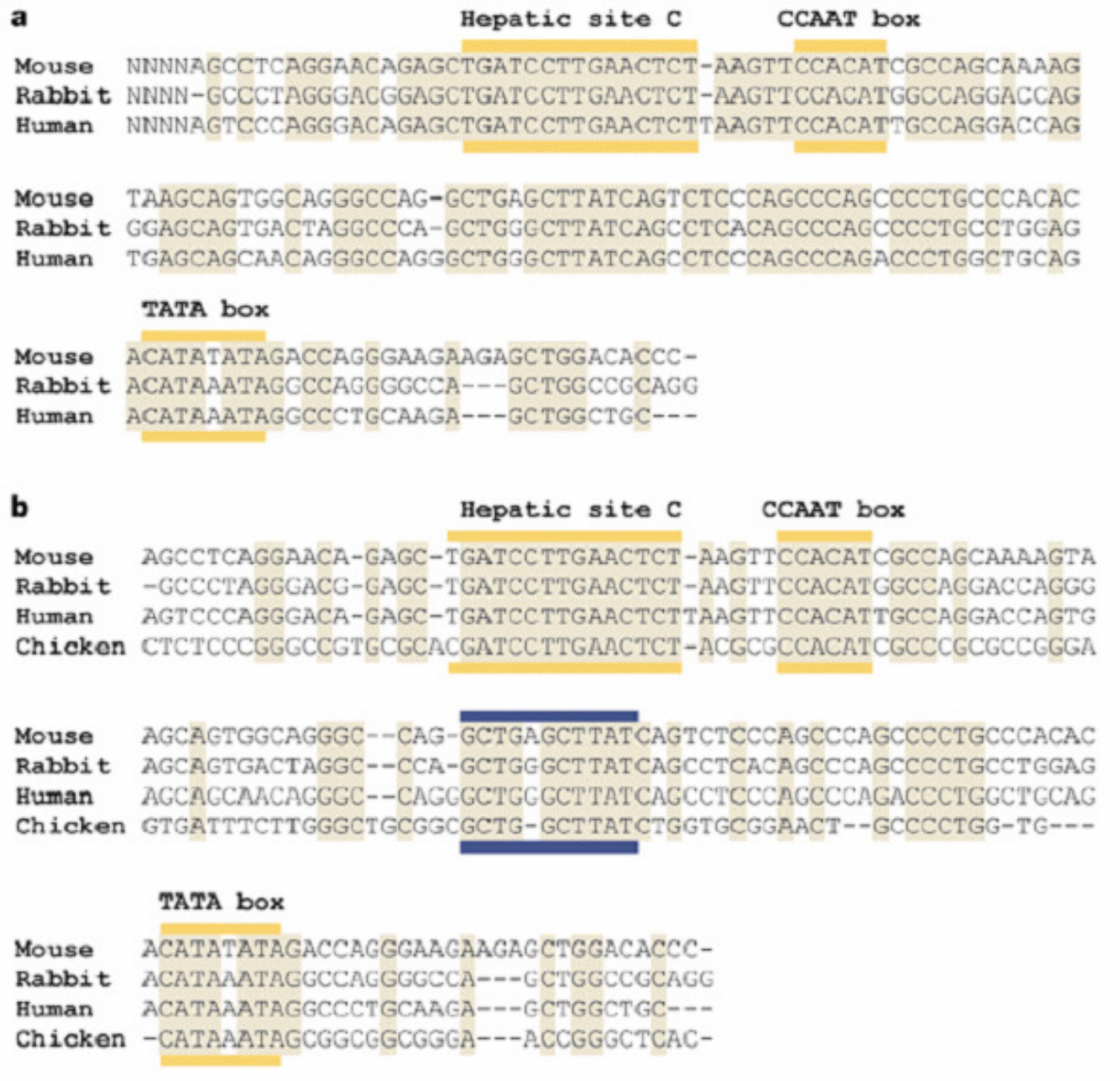
a
Hepatic site C
CCAAT box
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Rabbit NNNN-GCCCTAGGGACGGAGCTGATCCTTGAACTCT-AAGTTCCACATGGCCAGGACCAG
Human NNNNAGTCCCAGGGACAGAGCTGATCCTTGAACTCTTAAGTTCCACATTGCCAGGACCAG
Mouse TAAGCAGTGGCAGGGCCAG-GCTGAGCTTATCAGTCTCCCAGCCCAGCCCCTGCCCACAC
Rabbit GGAGCAGTGACTAGGCCCA-GCTGGGCTTATCAGCCTCACAGCCCAGCCCCTGCCTGGAG
Human TGAGCAGCAACAGGGCCAGGGCTGGGCTTATCAGCCTCCCAGCCCAGACCCTGGCTGCAG
TATA box
Mouse ACATATATAGACCAGGGAAGAAGAGCTGGACACCC-
Rabbit ACATAAATAGGCCAGGGGCCA---GCTGGCCGCAGG
Human ACATAAATAGGCCCTGCAAGA---GCTGGCTGC---
b
Hepatic site C
CCAAT box
Mouse AGCCTCAGGAACA-GAGC-TGATCCTTGAACTCT-AAGTTCCACATCGCCAGCAAAAGTA
Rabbit -GCCCTAGGGACG-GAGC-TGATCCTTGAACTCT-AAGTTCCACATGGCCAGGACCAGGG
Human AGTCCCAGGGACA-GAGC-TGATCCTTGAACTCTTAAGTTCCACATTGCCAGGACCAGTG
Chicken CTCTCCCGGGCCGTGCGCACGATCCTTGAACTCT-ACGCGCCACATCGCCCGCGCCGGGA
Mouse AGCAGTGGCAGGGC--CAG-GCTGAGCTTATCAGTCTCCCAGCCCAGCCCCTGCCCACAC
Rabbit AGCAGTGACTAGGC--CCA-GCTGGGCTTATCAGCCTCACAGCCCAGCCCCTGCCTGGAG
Human AGCAGCAACAGGGC--CAGGGCTGGGCTTATCAGCCTCCCAGCCCAGACCCTGGCTGCAG
Chicken GTGATTTCTTGGGCTGCGGCGCTG-GCTTATCTGGTGCGGAACT--GCCCCTGG-TG---
TATA box
Mouse ACATATATAGACCAGGGAAGAAGAGCTGGACACCC-
Rabbit ACATAAATAGGCCAGGGGCCA---GCTGGCCGCAGG
Human ACATAAATAGGCCCTGCAAGA---GCTGGCTGC---
Chicken -CATAAATAGCGGCGGCGGGA---ACCGGGCTCAC-

How many genes do we have???

27’462

Acknowledgements

- Lior Pachter, UC Berkeley
- Simon Cawley, Affymetrix

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