# Central dogma of molecular biology

- Information is stored in DNA
- Genome is processed into messenger RNA molecules (transcription)
- RNA molecules are processed to form proteins (translation)

# Open reading frames

- Generally defined as regions in genes between a start (ATG) and stop (eg. TGA) codon.
- Size is a multiple of 3
- Six possibilties given any DNA sequence
  - 0 offset, + strand; 1 offset, + strand, 2 offset, + strand
  - 0 offset, - strand; 1 offset, - strand, 2 offset, - strand

# Long ORFs

- At random, we'd expect a stop codon every 64 nucleotides.
- Many bacteria genes are much longer than this.
- These can be used to train a statistical model.

# IMM

- Interpolated Markov Models (IMMs) overcome the training problem by generating models of variable order.
- Bias is put towards higher models if and only if there is enough training data.
- Achieved via a linear combination of probabilities based on varied lengths.

# Simple linear interpolation

$$P_{\text{IMM}}(x_i \mid x_{i-n},\ldots,x_{i-1}) = \lambda_0 P(x_i) + \lambda_1 P(x_i \mid x_{i-1}) + \ldots + \lambda_n P(x_i \mid x_{i-n},\ldots,x_{i-1})$$

- where $\sum_i \lambda_i = 1$

# GLIMMER

- Addressed the fundamental training problem of markov models
- As mentioned before, we want the highest order model possible
- However, a $k^{th}$ order model requires $4^{k+1}$ probabilities to be estimated
  - Impractical for small genomes

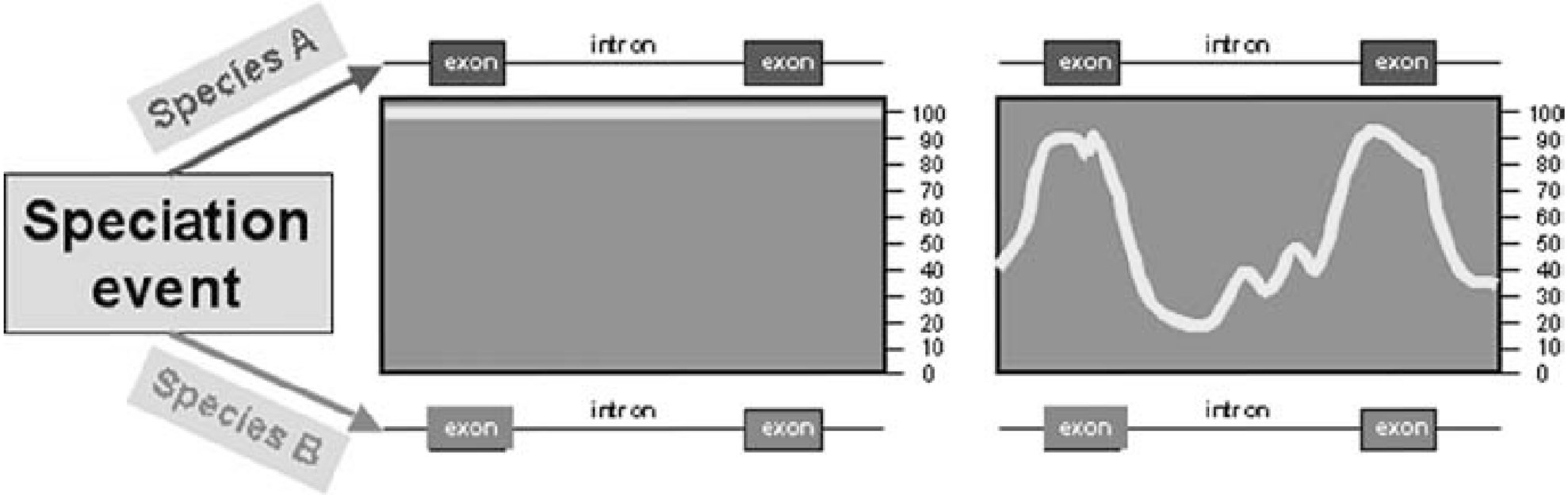
**Table 1.** Comparison of the IMM model used in GLIMMER to a 5th-order Markov model

| Model | Genes found | Genes missed | Additional genes |
|---|---|---|---|
| GLIMMER IMM | 1680 (97.8% | 37 | 209 |
| 5th-Order Markov | 1574 (91.7%) | 143 | 104 |

The first column indicates how many of the 1717 annotated genes in *H.influenzae* were found by each algorithm. The 'additional genes' column shows how many extra genes, not included in the 1717 annotated entries, were called genes by each method.

Only 1 of the 37 genes missed by GLIMMER was found by the 5th order model

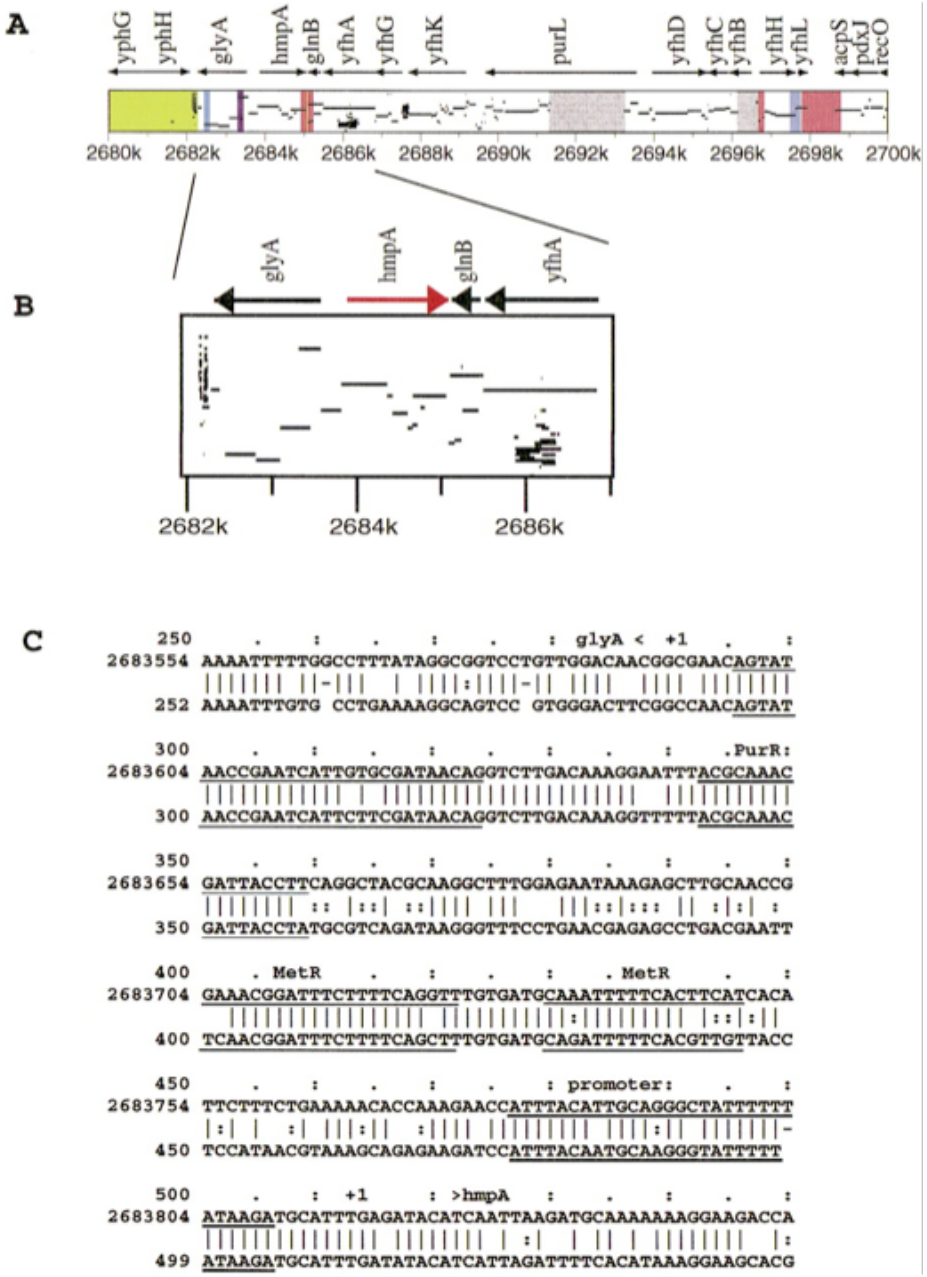
On the other hand, it found 107 more true genes




From: Miller et al. Annu. Rev. Genom. Human. Genet. 2004.5:15-56.

# Pipmaker

- http://www.bx.psu.edu/miller_lab/
- Visualization of BLASTZ alignments
- Although pips are compact and informative, they do not show alignment information for the second sequence.
  - Dotplots are used to see relevant differences


A
yphG
yphH
glyA
hmpA
glnB
yfhA
yfhG
yfhK
purL
yfhD
yfhC
yfhB
yfhH
yfhL
acpS
pdxJ
recO
2680k
2682k
2684k
2686k
2688k
2690k
2692k
2694k
2696k
2698k
2700k
B
glyA
hmpA
glnB
yfhA
2682k
2684k
2686k
C
250 . : . : . : glyA < +1 . :
2683554 AAAATTTTTGGCCTTTATAGGCGGTCCTGTTGGACAACGGCGAACAGTAT
252 AAAATTTGTG CCTGAAAAGGCAGTCC GTGGGACTTCGGCCAACAGTAT
300 . : . : . : . : .PurR:
2683604 AACCGAATCATTGTGCGATAACAGGTCTTGACAAAGGAATTTACGCAAAC
300 AACCGAATCATTCTTCGATAACAGGTCTTGACAAAGGTTTTTACGCAAAC
350 . : . : . : . : . :
2683654 GATTACCTTCAGGCTACGCAAGGCTTTGGAGAATAAAGAGCTTGCAACCG
350 GATTACCTATGCGTCAGATAAGGGTTTCCTGAACGAGAGCCTGACGAATT
400 . MetR . : . : . MetR . :
2683704 GAAACGGATTTCTTTTCAGGTTTGTGATGCAAATTTTTCACTTCATCACA
400 TCAACGGATTTCTTTTCAGCTTTGTGATGCAGATTTTTCACGTTGTTACC
450 . : . : . : promoter: . :
2683754 TTCTTTCTGAAAAACACCAAAGAACCATTTACATTGCAGGGCTATTTTTT
450 TCCATAACGTAAAGCAGAGAAGATCCATTTACAATGCAAGGGTATTTTT
500 . : +1 : >hmpA : . : . :
2683804 ATAAGATGCATTTGAGATACATCAATTAAGATGCAAAAAAAGGAAGACCA
499 ATAAGATGCATTTGATATACATCATTAGATTTTCACATAAAGGAAGCACG