

# Bioinformatics

## Sequence Analysis: Part III. Pattern Searching and Gene Finding

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Whitehead Institute

# Course Syllabus

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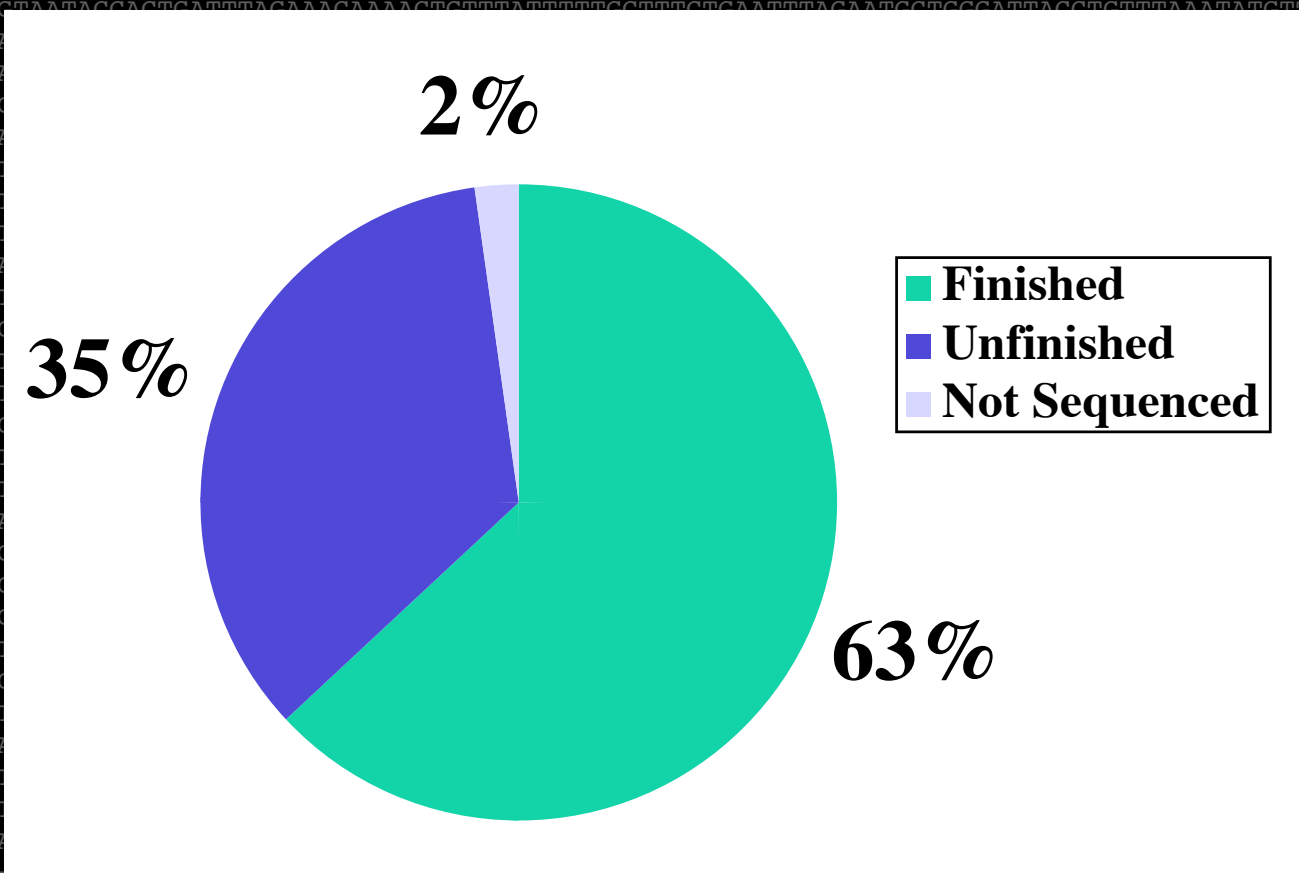
- Jan 7 Sequence Analysis I. Pairwise alignments, database searching including BLAST (FL) [1, 2, 3]
- Jan 14 Sequence Analysis II. Database searching (continued), Pattern searching(FL)[7]
- Jan 21 No Class - Martin Luther King Holiday
- Jan 28 Sequence Analysis III. Hidden Markov models, gene finding algorithms (FL)[8]
- Feb 4 Computational Methods I. Genomic Resources and Unix (GB)
- Feb 11 Computational Methods II. Sequence analysis with Perl. (GB)
- Feb 18 No Class - President's Birthday
- Feb 25 Computational Methods III. Sequence analysis with Perl and BioPerl (GB)
- Mar 4 Proteins I. Multiple sequence alignments, phylogenetic trees (RL) [4, 6]
- Mar 11 Proteins II. Profile searches of databases, revealing protein motifs (RL) [9]
- Mar 18 Proteins III. Structural Genomics: structural comparisons and predictions (RL)
- Mar 25 Microarrays: designing chips, clustering methods (FL)

# Topics to Cover

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- Pattern searching
- Gene Finding algorithms

# Status of Sequencing (12/31/2001)



# Topics to Cover

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- Pattern searching
- Gene Finding algorithms

# Pattern Searching

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RRRRYYYY

# Pattern Searching

---

RRRRYYYY

4 purines followed by 4  
pyrimidines



# Pattern Searching

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RRRRYYYY

4 purines followed by 4  
pyrimidines

TATAA[1,0,0]

# Pattern Searching

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4 purines followed by 4  
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TATAA[1,0,0]

TATAA, allowing 1 mismatch

# Pattern Searching

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RRRRYYYY

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TATAA, allowing 1 mismatch

p1=6...8 GAGA ~p1

# Pattern Searching

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RRRRYYYY

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a hairpin with GAGA as the loop

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p1=6...6 3...8 p1

exact 6 character repeat  
separated by up to 8

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# Pattern Searching

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TATAA[1,0,0]

TATAA, allowing 1 mismatch

p1=6...8 GAGA ~p1

a hairpin with GAGA as the loop

p1=6...6 3...8 p1

exact 6 character repeat separated by up to 8

p1=6...6 3..8 p1[1,1,1]

allow one mismatch, deletion and insertion



# Pattern Searching Programs

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# Pattern Searching Programs

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Patscan

# Pattern Searching Programs

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**Patscan**            `scan_for_matches patfile < inputfile`

# Pattern Searching Programs

---

Patscan            scan\_for\_matches patfile < inputfile

findpatterns

# Pattern Searching Programs

---

**Patscan**            `scan_for_matches patfile < inputfile`

**findpatterns**      `gcg; findpatterns`

# Pattern Searching Programs

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Patscan            scan\_for\_matches patfile < inputfile

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fuzznuc,  
fuzzprot,  
fuzztrans, dreg

# Pattern Searching Programs

---

Patscan            scan\_for\_matches patfile < inputfile

findpatterns      gcg; findpatterns

fuzznuc,  
fuzzprot,  
fuzztrans, dreg      EMBOSS programs; web and Unix

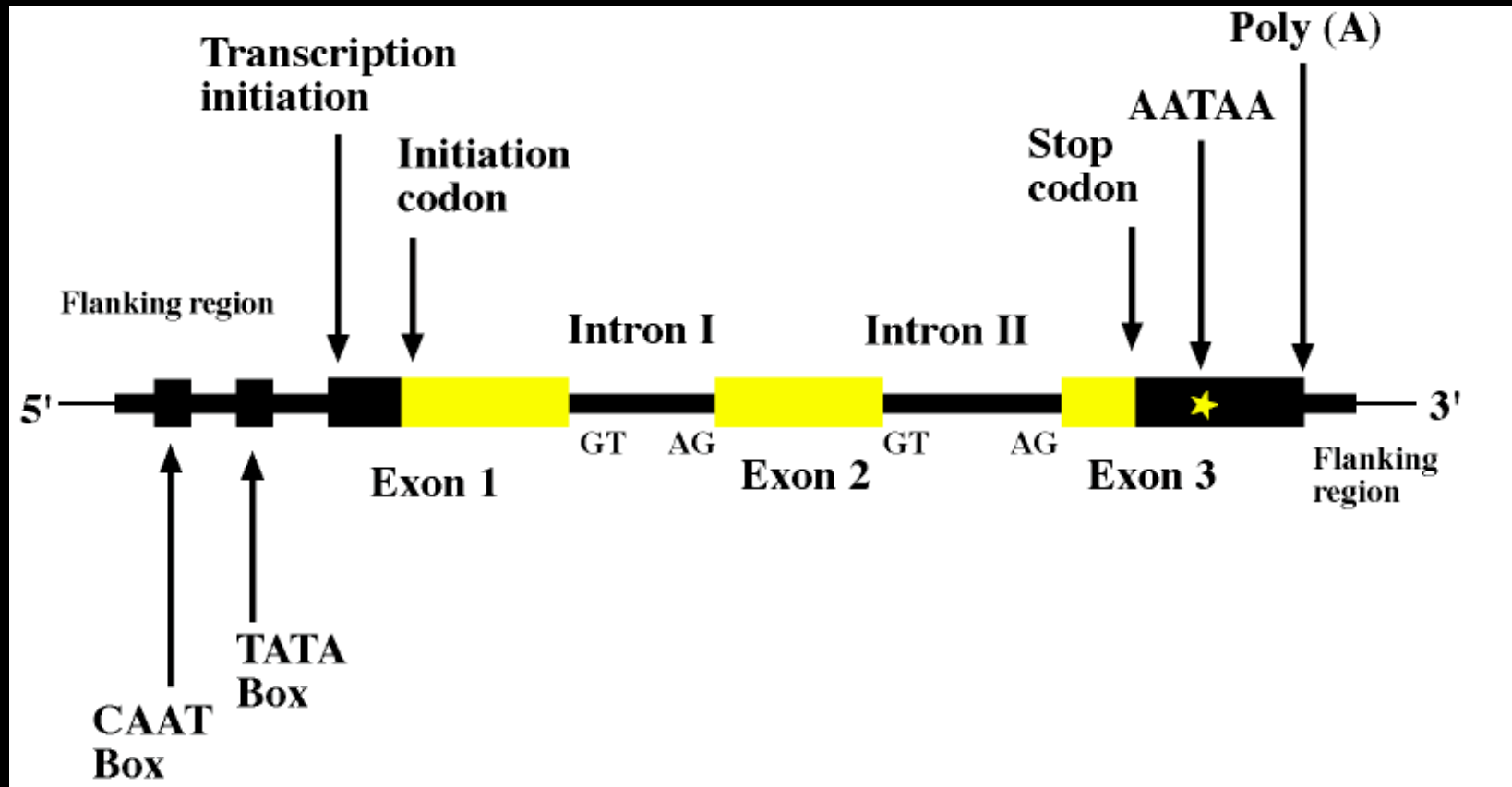
# Topics to Cover

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- Pattern searching
- Gene Finding algorithms



# Problem to Solve



# Types of Signals to Detect

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- Transcriptional
  - TSS
  - TATA box
  - PolyA
- Translational
  - Kozak (CC A/G CCAUGG)
  - Termination codon (UAA, UAG, UGA)
- Splicing
  - Introns - GT.....AG

# Gene Finding Strategies

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# Gene Finding Strategies

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- Content-based methods
  - codon usage, compositional complexity

# Gene Finding Strategies

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- Content-based methods
  - codon usage, compositional complexity
- Site-based methods
  - presence or absence of specific pattern or sequence

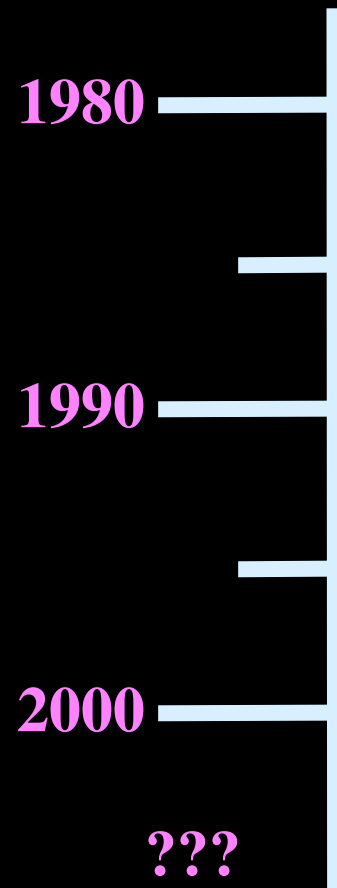
# Gene Finding Strategies

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- Content-based methods
  - codon usage, compositional complexity
- Site-based methods
  - presence or absence of specific pattern or sequence
- Comparative methods
  - determination based on homology

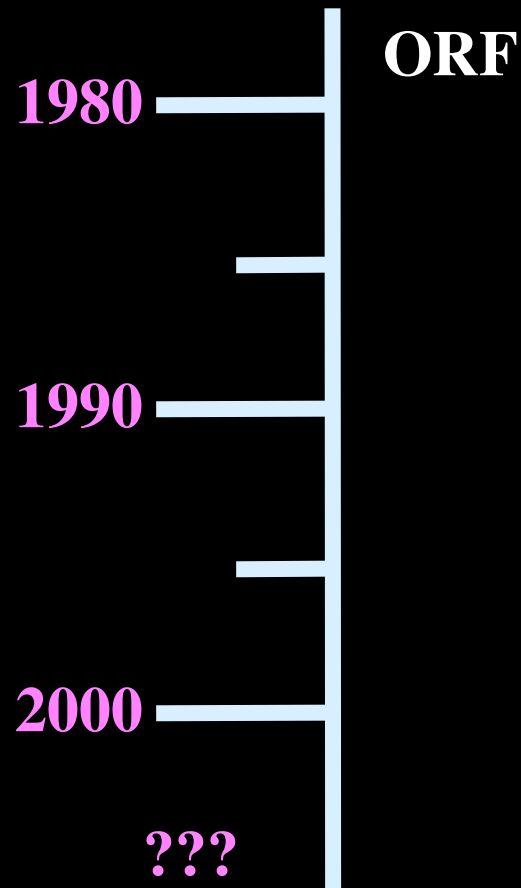
# Evolution of Gene Finding Programs

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# Evolution of Gene Finding Programs

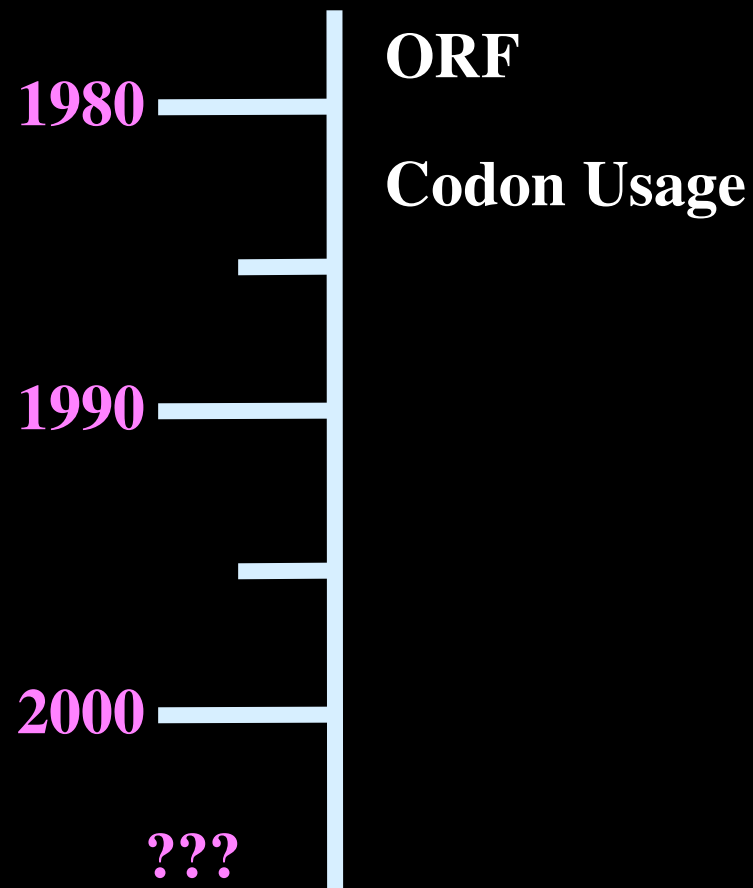
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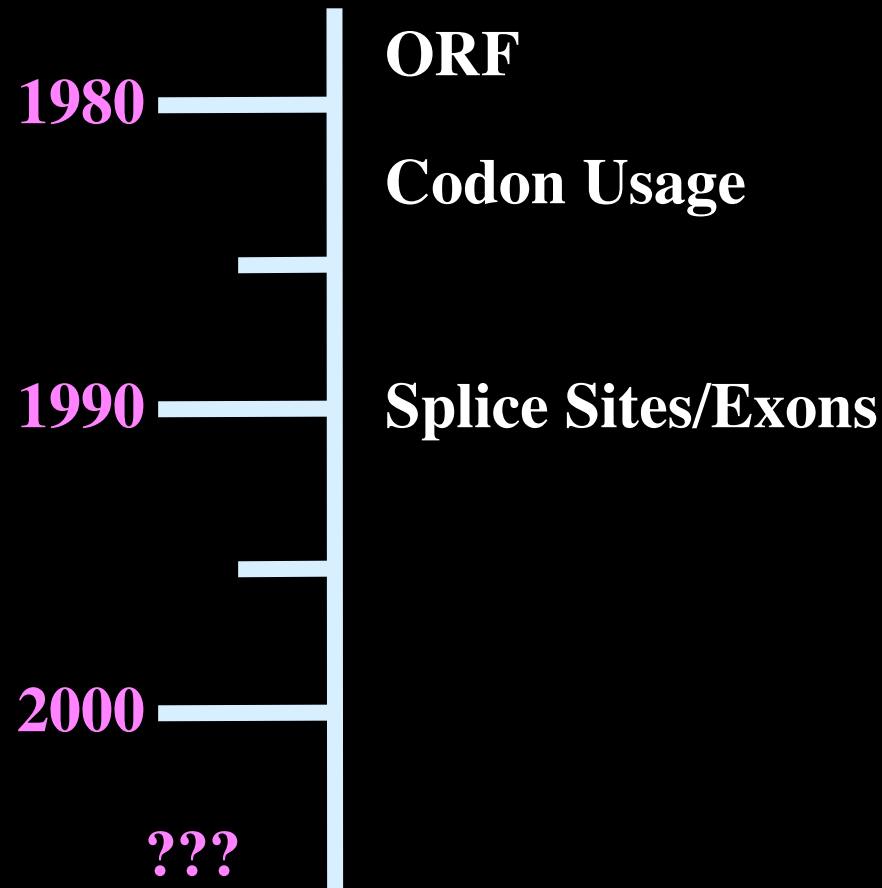
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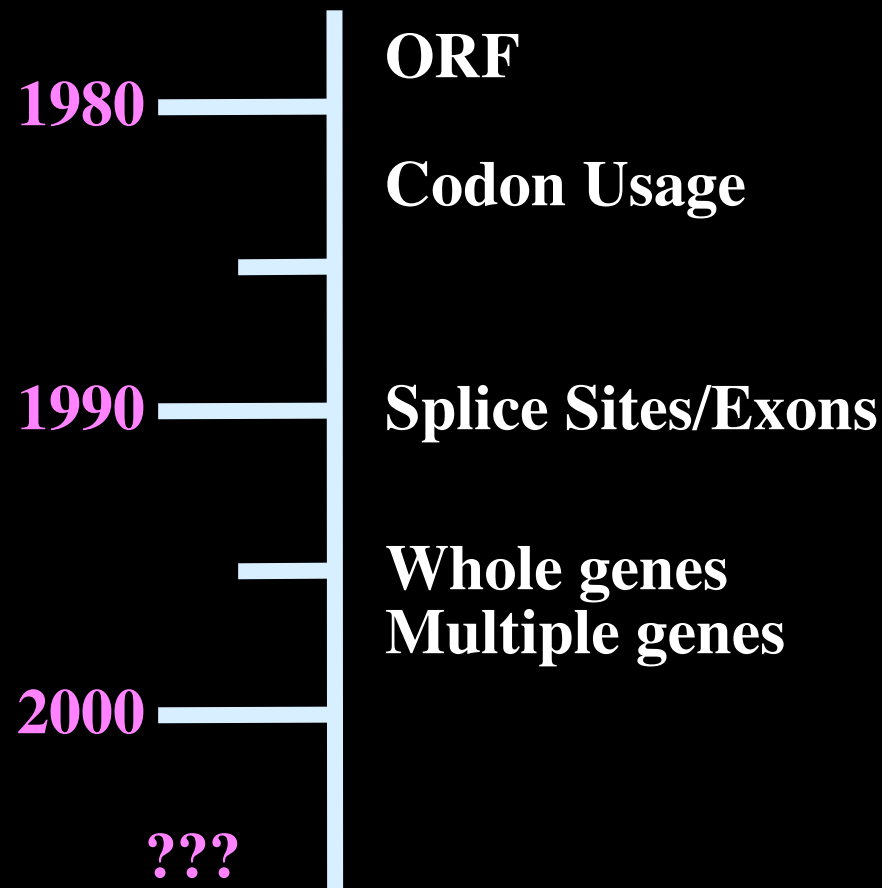
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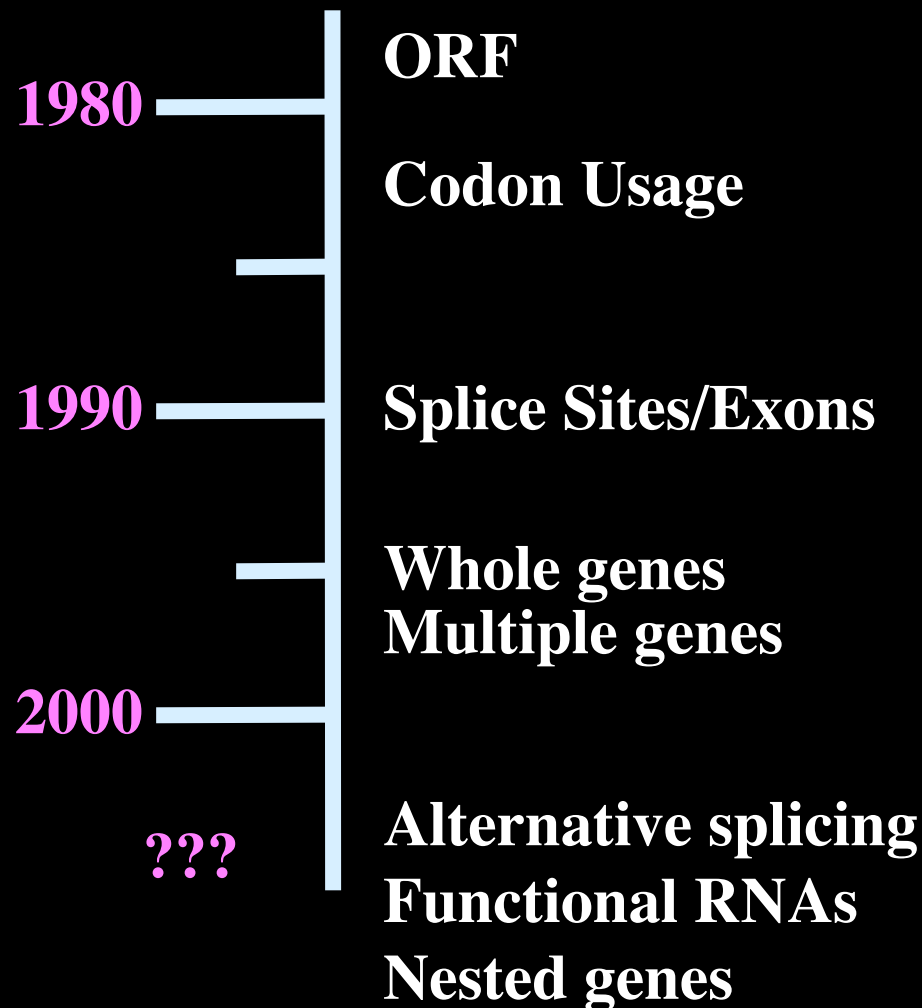
# Evolution of Gene Finding Programs

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# Evolution of Gene Finding Programs

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# RepeatMasker

## RepeatMasker Server

RepeatMasker is a program that screens DNA sequences for low complexity DNA sequences and interspersed repeats. The masked out sequence can be used for BLAST search.

Please refer to: Smit, AFA & Green, P "RepeatMasker" at <http://repeatmasker.genome.washington.edu>

[Home](#) || [Help](#) || [Check Queue](#) || [Your Suggestion](#) || [References](#) || [RepBase Update](#)

run\_repeatmasker

Reset

Enter your sequence ( *sequence in fasta format* )

( OR ) Upload the file

Browse...

DNA Source is from

- Primates
- Primates
- Rodents
- Other Mammals
- Other Vertebrates
- Arabidopsis
- Grasses
- Drosophila

Running options

- Fast (quick search, 3-4 times faster)
- Slow (slow search, 2.5 times slower)

Repeat Options

- Do not mask low\_complexity DNA or simple repeats
- only masks Alus (and 7SLRNA, SVA and LTR5)(only for primate DNA)
- only masks low complex/simple repeats (no interspersed repeats)

Output Options

- Show Alignments
- Mask with X's to distinguish masked regions from Ns already in query
- Produce an annotation table with fixed width columns

[html validate this page](#)

# RepeatMasker

## Repeat sequence:

SW score	perc div.	perc del.	perc ins.	query sequence	position in query begin end (left)	matching repeat repeat	repeat class/family	position in repeat begin end (left)	repeat ID
2117	3.9	0.0	1.2	myseq	7 263 (8487)	+ AluY	SINE/Alu	58 311 (0)	1
7658	20.9	6.8	5.7	myseq	2193 2517 (6233)	C LlMDa	LINE/L1	(1460) 5080 4760	2
2516	4.9	2.0	0.0	myseq	2518 2822 (5928)	+ AluY	SINE/Alu	1 311 (0)	3
7658	20.9	6.8	5.7	myseq	2823 4135 (4615)	C LlMDa	LINE/L1	(1780) 4760 3462	2
5685	6.2	0.8	0.0	myseq	4136 4864 (3886)	+ LlPA10	LINE/L1	5417 6151 (17)	4
7658	20.9	6.8	5.7	myseq	4865 5181 (3569)	C LlMDa	LINE/L1	(3078) 3462 3150	2
2130	11.2	3.0	0.7	myseq	5182 5303 (3447)	+ AluSq	SINE/Alu	1 119 (194)	5
351	0.0	0.0	0.0	myseq	5304 5342 (3408)	+ (TAAA)n	Simple_repeat	2 40 (0)	6
2130	11.2	3.0	0.7	myseq	5343 5514 (3236)	+ AluSq	SINE/Alu	119 302 (11)	5
2593	6.6	2.8	0.0	myseq	5525 5886 (2864)	+ LlPA13	LINE/L1	5792 6163 (0)	7
7658	20.9	6.8	5.7	myseq	5887 6390 (2360)	C LlMDa	LINE/L1	(3398) 3142 2645	2
2092	9.6	1.0	3.6	myseq	6391 6693 (2057)	C AluSc	SINE/Alu	(13) 296 2	9
7658	20.9	6.8	5.7	myseq	6694 8738 (12)	C LlMDa	LINE/L1	(3895) 2645 491	2

# RepeatMasker

## Summary:

Total length: 8750 bp

GC level: 35.61%

Bases masked: 6803 bp (77.75%)

	number of elements*	length occupied	percentage of sequence
SINES:	4	1159 bp	13.25 %
ALUs	4	1159 bp	13.25 %
MIRs	0	0 bp	0.00 %
LINEs:	3	5605 bp	64.06 %
LINE1	3	5605 bp	64.06 %
LINE2	0	0 bp	0.00 %
L3/CR1	0	0 bp	0.00 %
LTR elements:	0	0 bp	0.00 %
MaLRs	0	0 bp	0.00 %
ERVL	0	0 bp	0.00 %
ERV_classI	0	0 bp	0.00 %
ERV_classII	0	0 bp	0.00 %
DNA elements:	0	0 bp	0.00 %
MER1_type	0	0 bp	0.00 %
MER2_type	0	0 bp	0.00 %
Unclassified:	0	0 bp	0.00 %
Total interspersed repeats:		6764 bp	77.30 %
Small RNA:	0	0 bp	0.00 %
Satellites:	0	0 bp	0.00 %
Simple repeats:	1	39 bp	0.45 %
Low complexity:	0	0 bp	0.00 %

# Coding Measures

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- Look at frequencies of codons (e.g. redundancy of genetic code; Leucine = UUA, UUG, CUU, CUC, CUA, CUG)

- 6-tuple or hexamer approach

ACCTCG TACTCG GCCCTC  
Thr Ser Tyr Ser Ala Leu



# Fifth Order Markov Models

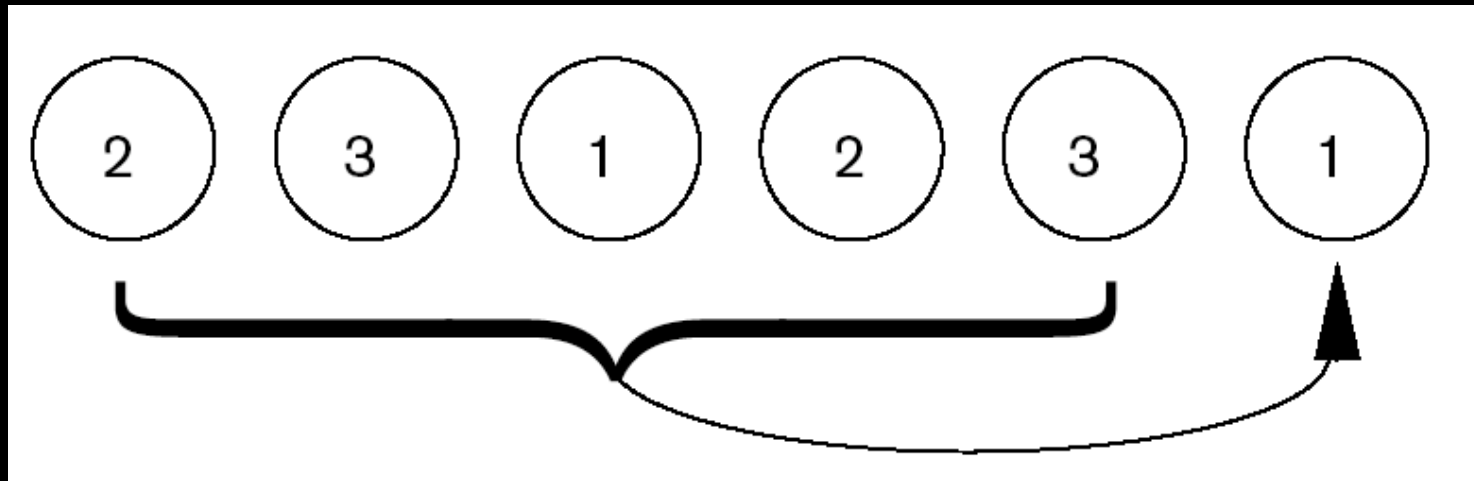
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Periodic fifth order Markov model. Circles represent consecutive DNA bases, numbers indicate codon position, and the arrows indicate that the next base is generated conditionally on the previous five and on the codon position.

Burge and Karlin, *Current Opinions in Structural Biology* 1998, 8:346-354.

# Fifth Order Markov Models

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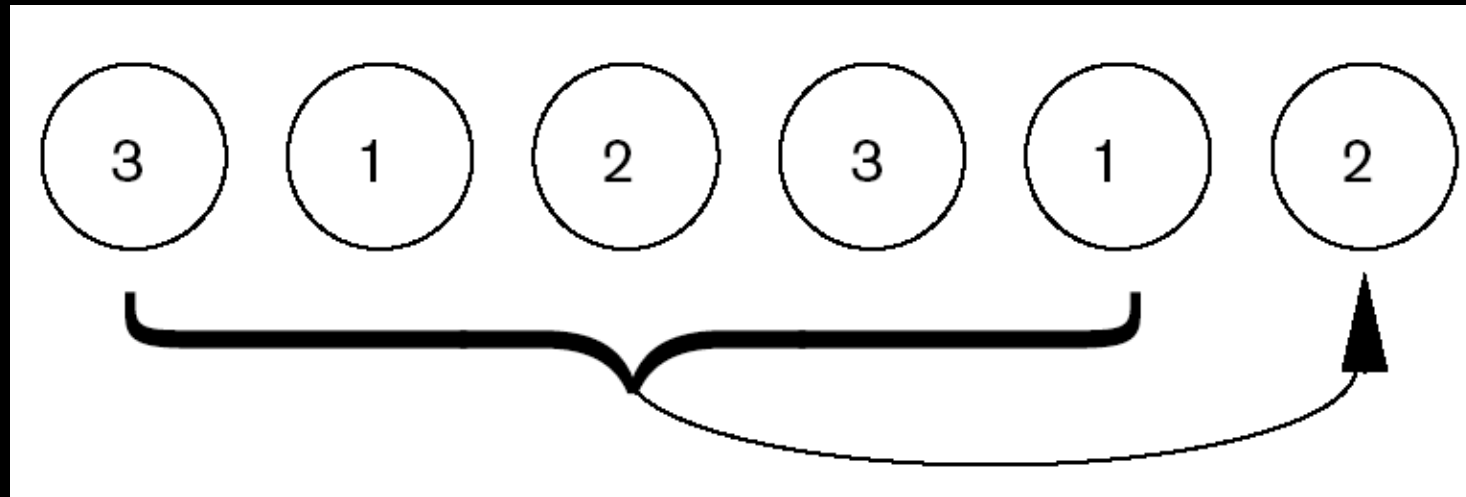


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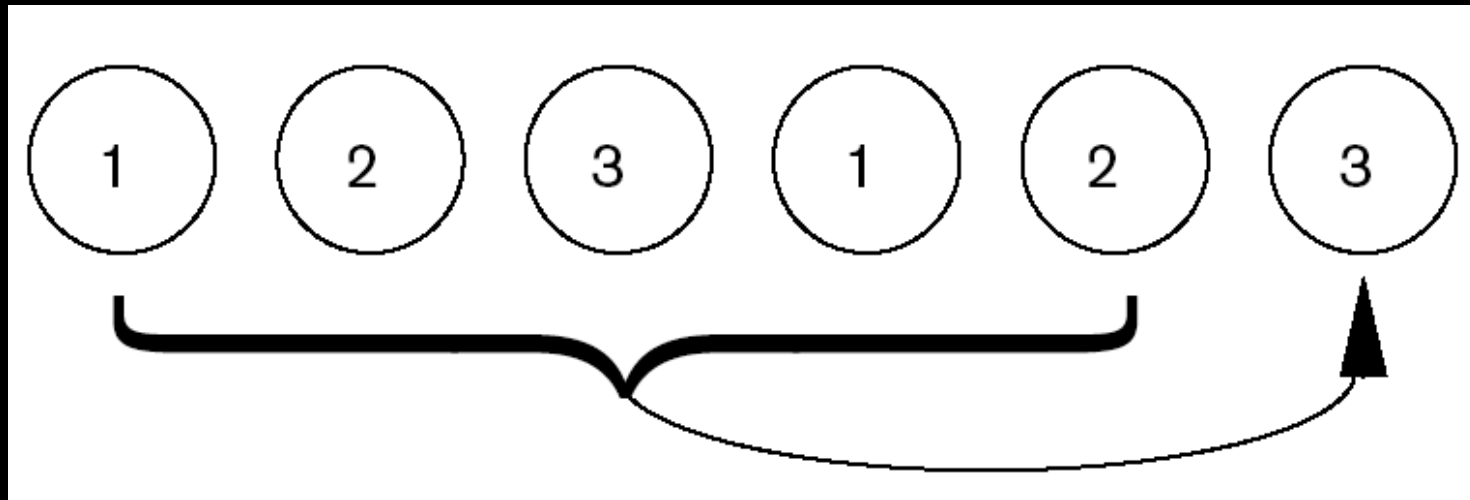


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# Fifth Order Markov Models

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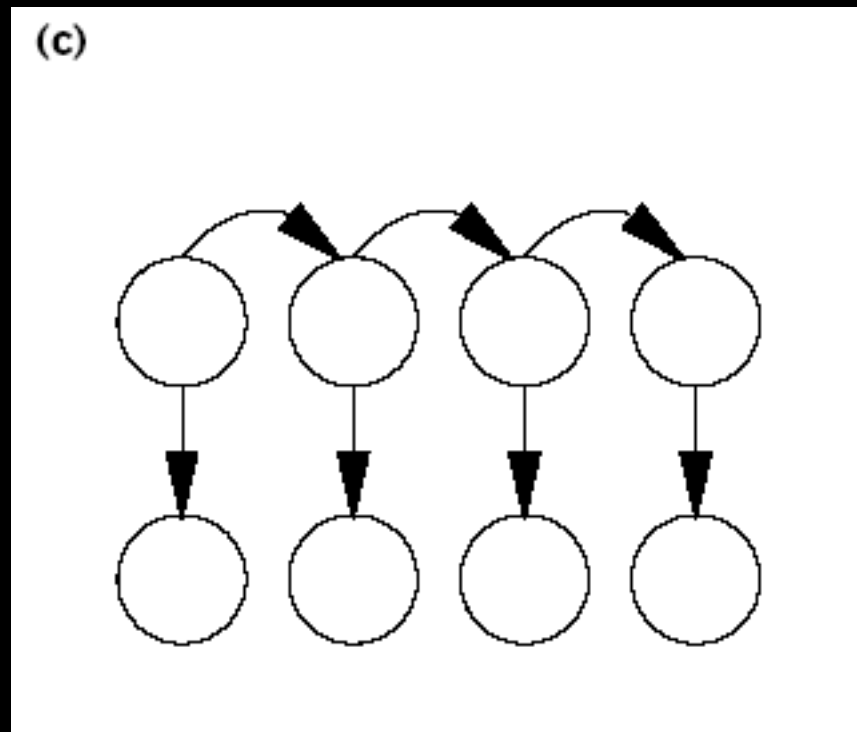


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# Hidden Markov Models

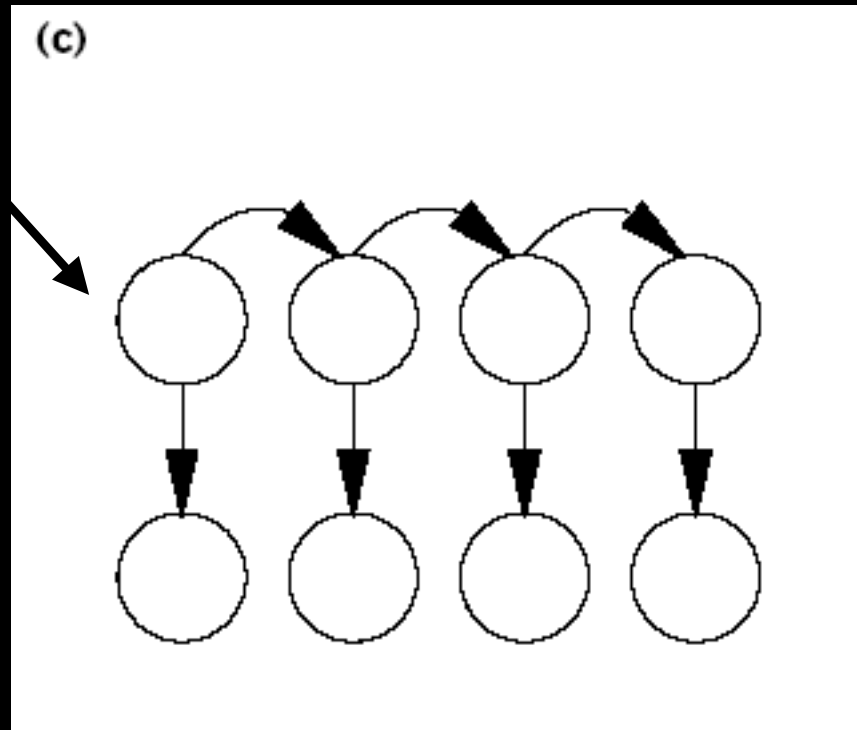
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# Hidden Markov Models

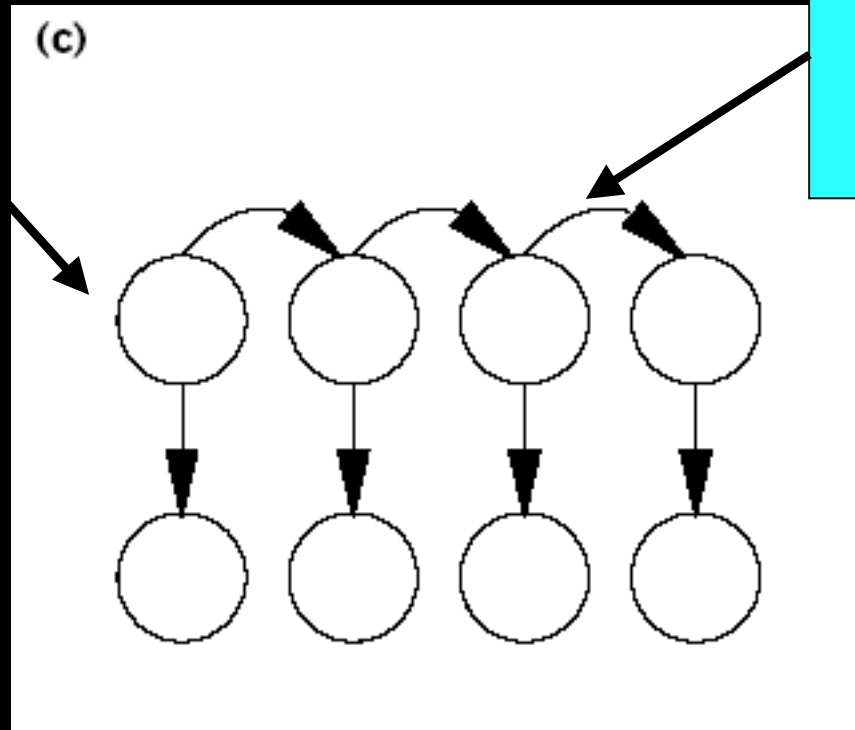
unobserved or  
“hidden” states (e.g.  
coding or noncoding)



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# Hidden Markov Models

unobserved or  
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states generated  
according to a first  
order Markov chain

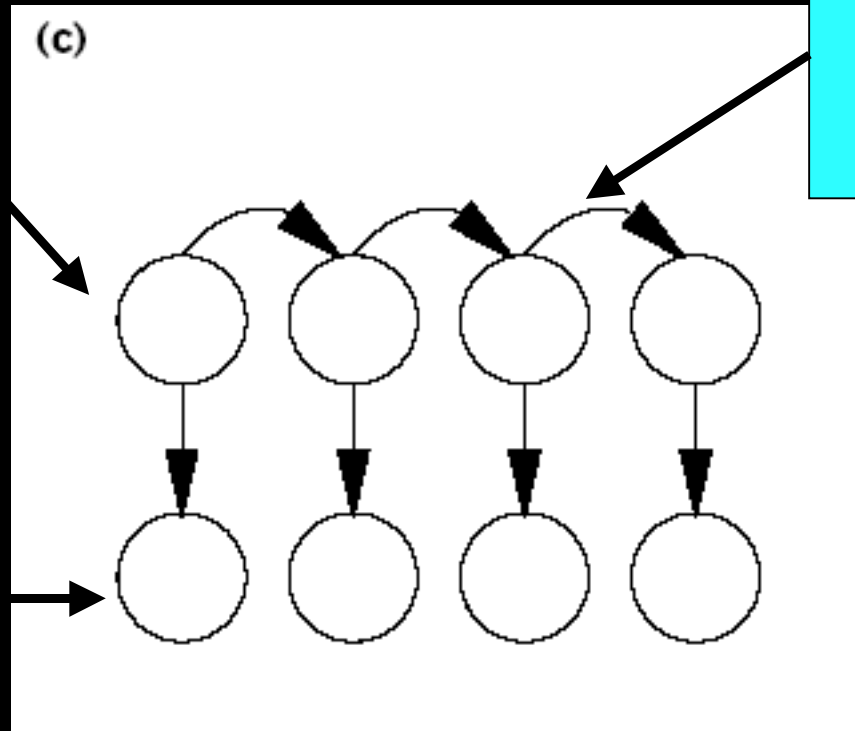
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# Hidden Markov Models

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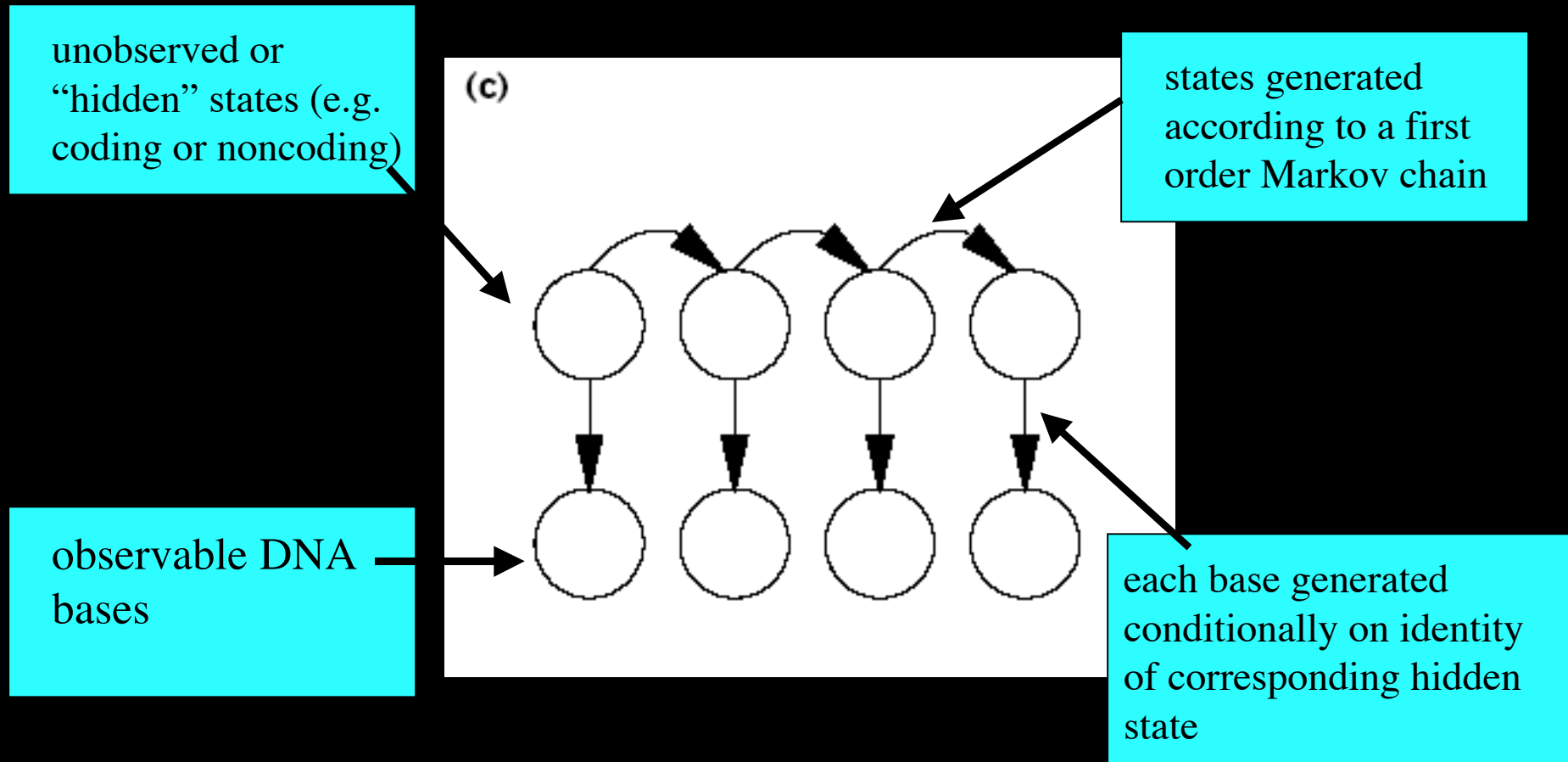
observable DNA  
bases



Burge and Karlin, *Current Opinions in Structural Biology* 1998, 8:346-354.



# Hidden Markov Models



Burge and Karlin, *Current Opinions in Structural Biology* 1998, 8:346-354.

# GENSCAN

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Burge and Karlin, *JMB*:268:78-94, 1997

# GENSCAN

---

- MM - prob for a given nuc to occur at position  $p$  depends on nuc occupying previous  $k$  positions

Burge and Karlin, JMB:268:78-94, 1997

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- Generalized Hidden Markov Model (GHMM)

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- Generalized Hidden Markov Model (GHMM)
- Optimize module performing signal recognition

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- Generalized Hidden Markov Model (GHMM)
- Optimize module performing signal recognition
- Incorporates influence of C+G content

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- Generalized Hidden Markov Model (GHMM)
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- Incorporates influence of C+G content
- Considers gene models on both strands

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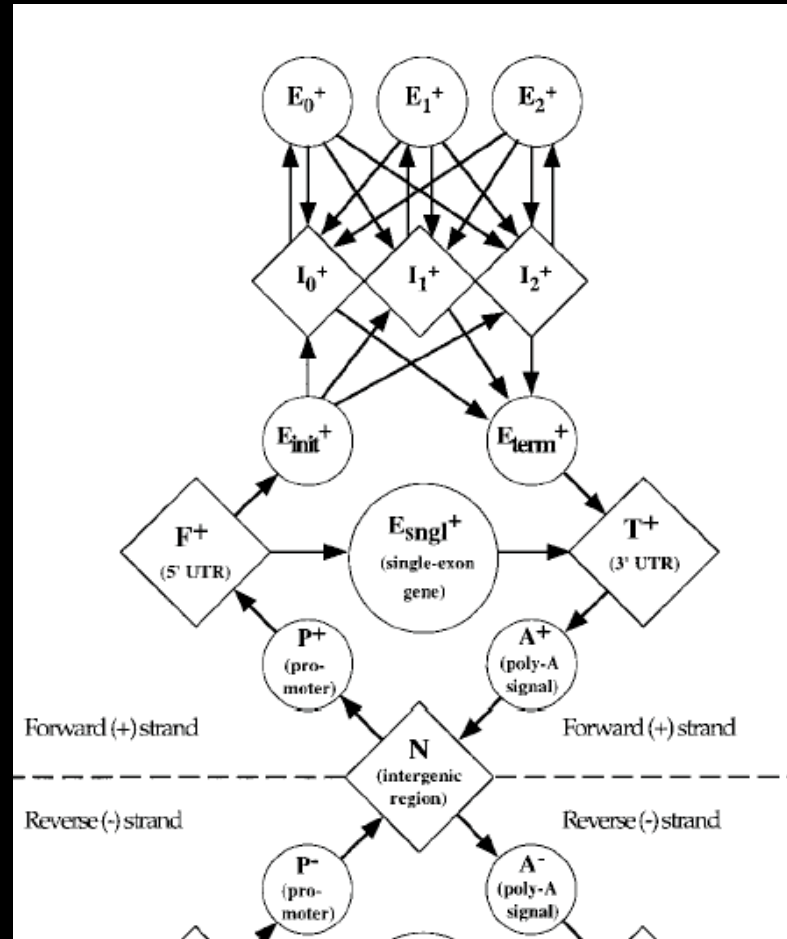
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- MM - prob for a given nuc to occur at position  $p$  depends on nuc occupying previous  $k$  positions
- Generalized Hidden Markov Model (GHMM)
- Optimize module performing signal recognition
- Incorporates influence of C+G content
- Considers gene models on both strands
- Can identify multiple genes

Burge and Karlin, *JMB*:268:78-94, 1997



# GENSCAN



Burge and Karlin,  
JMB:268:78-94, 1997

# Gene Finding Programs

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# Gene Finding Programs

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- FGENES - Sanger Center, UK

# Gene Finding Programs

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- FGENES - Sanger Center, UK
- GeneMark HMM - Georgia Tech

# Gene Finding Programs

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- FGENES - Sanger Center, UK
- GeneMark HMM - Georgia Tech
- Genie - UCSC

# Gene Finding Programs

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- FGENES - Sanger Center, UK
- GeneMark HMM - Georgia Tech
- Genie - UCSC
- Genscan - Stanford and MIT

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- FGENES - Sanger Center, UK
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- Genie - UCSC
- Genscan - Stanford and MIT
- HMMgene - CBS, Denmark

# Gene Finding Programs

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- GeneMark HMM - Georgia Tech
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- Genscan - Stanford and MIT
- HMMgene - CBS, Denmark
- Morgan - John Hopkins



# Gene Finding Programs

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- FGENES - Sanger Center, UK
- GeneMark HMM - Georgia Tech
- Genie - UCSC
- Genscan - Stanford and MIT
- HMMgene - CBS, Denmark
- Morgan - John Hopkins
- MZEF - Cold Spring Harbor

# HMR195 Test Set

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*Rogic, Mackworth and Ouellette, Genome Research 11:817-832, 2001*

# HMR195 Test Set

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- 103 human, 82 mouse, 10 rat sequences

*Rogic, Mackworth and Ouellette, Genome Research 11:817-832, 2001*

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- 103 human, 82 mouse, 10 rat sequences
- Sequence new since August, 1997

*Rogic, Mackworth and Ouellette, Genome Research 11:817-832, 2001*

# HMR195 Test Set

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- Sequence new since August, 1997
- Genomic sequences containing exactly one gene

*Rogic, Mackworth and Ouellette, Genome Research 11:817-832, 2001*

# HMR195 Test Set

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- 103 human, 82 mouse, 10 rat sequences
- Sequence new since August, 1997
- Genomic sequences containing exactly one gene
- No mRNA sequences, pseudogenes or alternatively spliced genes

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# HMR195 Test Set

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- 103 human, 82 mouse, 10 rat sequences
- Sequence new since August, 1997
- Genomic sequences containing exactly one gene
- No mRNA sequences, pseudogenes or alternatively spliced genes
- The mean length of sequences is 7,096 bp

*Rogic, Mackworth and Ouellette, Genome Research 11:817-832, 2001*

# HMR195 Test Set (con't)

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*Rogic, Mackworth and Ouellette, Genome Research 11:817-832, 2001*



# HMR195 Test Set (con't)

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- 43 single-exon genes; 152 multi-exon genes

*Rogic, Mackworth and Ouellette, Genome Research 11:817-832, 2001*

# HMR195 Test Set (con't)

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- 43 single-exon genes; 152 multi-exon genes
- Average number of exons per gene is 4.86

*Rogic, Mackworth and Ouellette, Genome Research 11:817-832, 2001*

# HMR195 Test Set (con't)

---

- 43 single-exon genes; 152 multi-exon genes
- Average number of exons per gene is 4.86
- Mean exon length = 208 bp,  
mean intron length = 678 bp,  
mean coding length per gene = 1,015 bp  
(~330 aa)

*Rogic, Mackworth and Ouellette, Genome Research 11:817-832, 2001*

# HMR195 Test Set (con't)

---

- 43 single-exon genes; 152 multi-exon genes
- Average number of exons per gene is 4.86
- Mean exon length = 208 bp,  
mean intron length = 678 bp,  
mean coding length per gene = 1,015 bp  
(~330 aa)
- Coding sequence 14%, intronic sequence 46% and intergenic DNA 40%.

*Rogic, Mackworth and Ouellette, Genome Research 11:817-832, 2001*

# Definitions

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- **Sensitivity:** the proportion of true sites (e.g., exons or donor splice sites) which are correctly predicted =  $TP / (TP + FN)$
- **Specificity:** the proportion of predicted sites which are correct =  $TP / (TP + FP)$

# Results of Program Comparisons

**Table 2.** Accuracy versus Signal Type

Programs	Signal type			
	start codon (195)	acceptor site (753)	donor site (753)	stop codon (195)
FGENES	0.67 (0.63)	0.80 (0.77)	0.85 (0.82)	0.75 (0.72)
GeneMark.hmm	0.46 (0.60)	0.81 (0.75)	0.82 (0.78)	0.57 (0.64)
Genie	0.56 (0.57)	0.77 (0.82)	0.78 (0.83)	0.72 (0.73)
Genscan	0.61 (0.78)	0.87 (0.80)	0.90 (0.84)	0.76 (0.86)
HMMgene	0.75 (0.78)	0.81 (0.85)	0.83 (0.87)	0.78 (0.81)
Morgan	0.43 (0.43)	0.66 (0.57)	0.65 (0.56)	0.39 (0.39)
MZEF	—	0.59 (0.65)	0.66 (0.73)	—

For each program, the proportion of actual signals identified correctly (the upper number) and the proportion of predicted signals that are correct (the lower number) are averaged over all signals belonging to a particular type. The number in parenthesis in the header of each column represents the number of signals of each type in the HMR195 dataset.

*Rogic, Mackworth and  
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# Results of Program Comparisons

- Genscan and HMMgene had reliable scores for exons

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MZEF	—	0.59 (0.65)	0.66 (0.73)	—

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Ouellette, Genome Research  
11:817-832, 2001*

# Results of Program Comparisons

- Genscan and HMMgene had reliable scores for exons
- Nucleotide  $S_n = .95$  for Genscan and  $.93$  for HMMgene.

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HMMgene	0.75 (0.78)	0.81 (0.85)	0.83 (0.87)	0.78 (0.81)
Morgan	0.43 (0.43)	0.66 (0.57)	0.65 (0.56)	0.39 (0.39)
MZEF	—	0.59 (0.65)	0.66 (0.73)	—

For each program, the proportion of actual signals identified correctly (the upper number) and the proportion of predicted signals that are correct (the lower number) are averaged over all signals belonging to a particular type. The number in parenthesis in the header of each column represents the number of signals of each type in the HMR195 dataset.

*Rogic, Mackworth and  
Ouellette, Genome Research  
11:817-832, 2001*



# Results of Program Comparisons

- Genscan and HMMgene had reliable scores for exons
- Nucleotide Sn = .95 for Genscan and .93 for HMMgene.
- Sp = .90 and .93, respectively

**Table 2.** Accuracy versus Signal Type

Programs	Signal type			
	start codon (195)	acceptor site (753)	donor site (753)	stop codon (195)
FGENES	0.67 (0.63)	0.80 (0.77)	0.85 (0.82)	0.75 (0.72)
GeneMark.hmm	0.46 (0.60)	0.81 (0.75)	0.82 (0.78)	0.57 (0.64)
Genie	0.56 (0.57)	0.77 (0.82)	0.78 (0.83)	0.72 (0.73)
Genscan	0.61 (0.78)	0.87 (0.80)	0.90 (0.84)	0.76 (0.86)
HMMgene	0.75 (0.78)	0.81 (0.85)	0.83 (0.87)	0.78 (0.81)
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# Results of Program Comparisons

- Genscan and HMMgene had reliable scores for exons
- Nucleotide Sn = .95 for Genscan and .93 for HMMgene.
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- Accuracy dependent on G+C content

*Rogic, Mackworth and Ouellette, Genome Research 11:817-832, 2001*

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# GenomeScan

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Yeh, Lim, and Burge, *Genome Research* 11:803-816, 2001.

# GenomeScan

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- Combines exon-intron and splice signal models with similarity to known proteins

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- Used to identify genes in human draft sequence
- Uses GENSCAN and BLASTX

Yeh, Lim, and Burge, *Genome Research* 11:803-816, 2001.

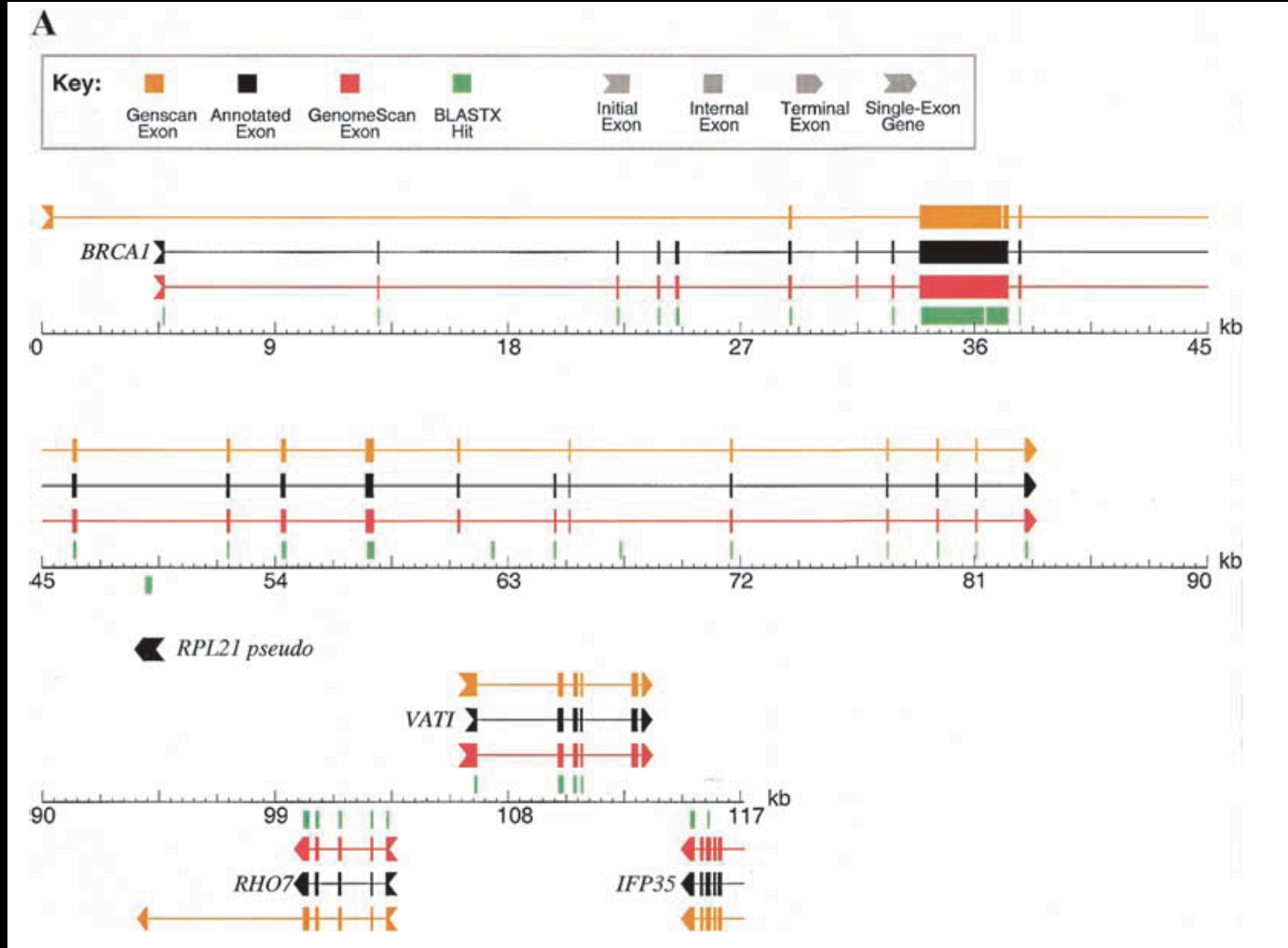
# GenomeScan

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- Combines exon-intron and splice signal models with similarity to known proteins
- Used to identify genes in human draft sequence
- Uses GENSCAN and BLASTX
- Procrustes and Genewise similar but can only predict one gene per genomic sequence

Yeh, Lim, and Burge, *Genome Research* 11:803-816, 2001.

# GenomeScan

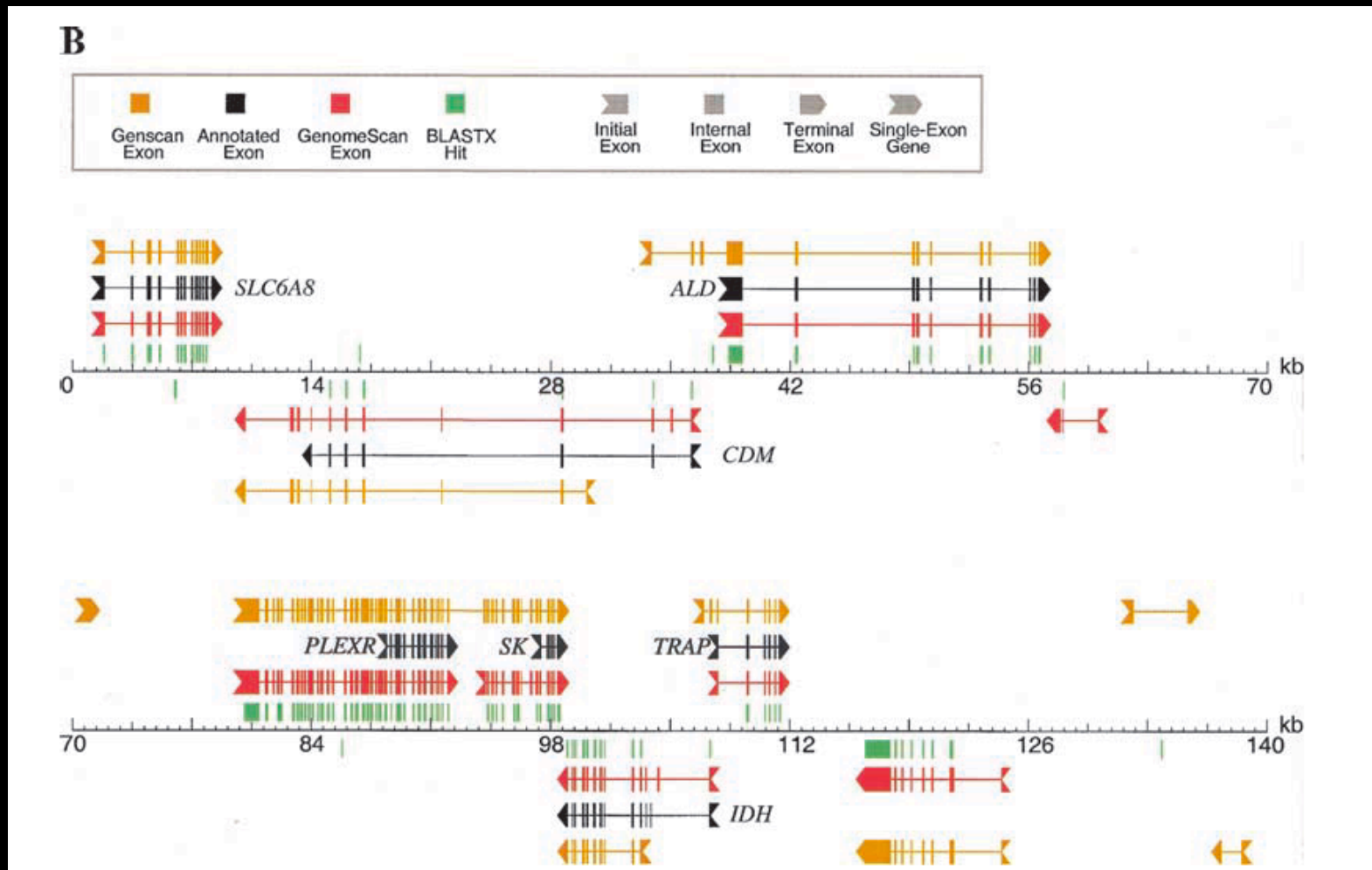


Yeh, Lim, and Burge, *Genome Research* 11:803-816, 2001.

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# GenomeScan



Yeh, Lim, and Burge, *Genome Research* 11:803-816, 2001.

# GenomeScan

**Table 4.** Summary of GenomeScan-predicted Genes and Partial Genes in the Human Genome

Similarity category	Type of predicted gene						
	Complete genes (>2 exons)			Partial genes		All genes (partial + complete)	
	No. of genes	No. of exons/gene	No. of aa/gene	No. of genes	No. of exons/gene	No. of genes	% of all predicted genes
Known (cDNA)	5698	9.6	496	8901	4.9	16040	41.5
Protein + EST	4502	8.8	510	6537	5.5	12546	32.5
Proteins only	2767	5.2	303	4600	3.1	10061	26.0
All	12967	8.4	460	20038	4.7	38647	100.0

Genes were predicted in the September 2000 GoldenPath human genome sequence as described in Methods. Predicted coding sequences (CDS) were first compared to cDNAs in the RefSeq cDNA database (September 2000) using BLASTN; those which had a hit at least 100 bp long with at least 98% identity are listed as "known". The remaining predicted coding sequences were searched against dbEST (September 2000 release) using BLASTN; those which had a hit at least 100 bp long with at least 97% identity are listed as "Protein + EST". All other predicted genes are categorized as "Protein only" because all GenomeScan-predicted genes have at least modest similarity to a known protein. Statistics are listed separately for predicted partial genes and predicted complete genes with at least three exons; the category "all genes" includes these two groups as well as predicted 1- and 2-exon genes.

Yeh, Lim, and Burge, *Genome Research* 11:803-816, 2001.

# Other Approaches

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- Use microarrays to identify expressed genes based on the coexpression of sets of adjacent exons as predicted by GENSCAN (Shoemaker, et al, Nature 409:922-927, 2001)

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- Use microarrays to identify expressed genes based on the coexpression of sets of adjacent exons as predicted by GENSCAN (Shoemaker, et al, Nature 409:922-927, 2001)
- RT-PCR with radio-labeled primers targeted to pairs of adjacent predicted exons, followed by sequencing of the amplified product (Burge et al, in preparation)

# Future Challenges

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- Alternative Splicing
- Gene products functioning at RNA level
- Nested genes
- 5' end of genes
- Other unusual characteristics

# Coming attractions

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# Coming attractions

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- Next section on Computational Methods



# Coming attractions

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- Next section on Computational Methods
- Unix accounts

# Coming attractions

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- Course Projects