CSE 427
Computational Biology

Gene Prediction

A statistical interlude: Fair or biased?

H H H H T H H T T H

More likely fair or biased?

H H H H T H H T T H

More likely H0 or H1?

H H H H T H H T T H

- H0: .5 – .5
- H1: .9 – .1

Quantify likelihood: H_0 vs H_1

H H H H T H H T T H

H0: .5 – .5 .5^10
H1: .9 – .1 .9^7 * .1^3

Likelihood ratio: (.5^10)/(.9^7 * .1^3) = .4898
(I.e., odds favor "biased" by about 2:1)

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Gene Finding: Motivation

Sequence data flooding into Genbank

What does it mean?

- protein genes, RNA genes, mitochondria, chloroplast, regulation, replication, structure, repeats, transposons, unknown stuff, …

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Protein Coding Nuclear DNA

Focus of this lecture

Goal: Automated annotation of new sequence data

State of the Art:

- In Eukaryotes:
  - predictions ~ 60% similar to real proteins
  - ~80% if database similarity used
- Prokaryotes
  - better, but still imperfect
- lab verification still needed, still expensive

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Biological Basics

Central Dogma:

DNA —transcription→ RNA —translation→ Protein

Codons: 3 bases code one amino acid

- Start codon
- Stop codons
- 3', 5' Untranslated Regions (UTR's)

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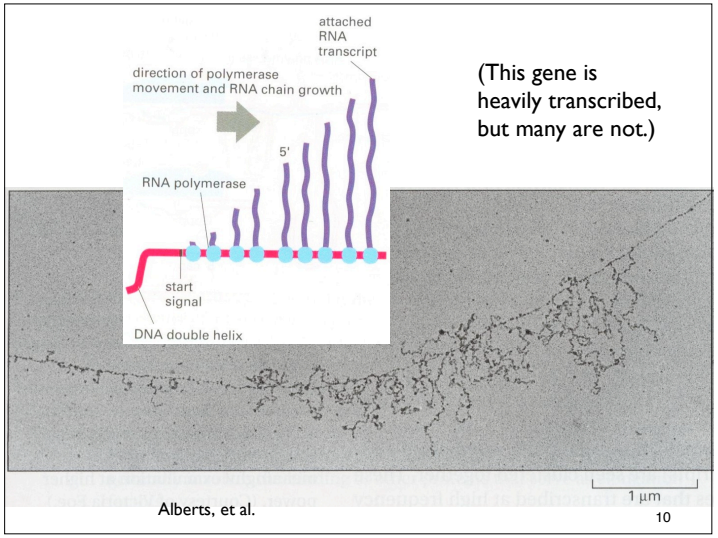


(This gene is heavily transcribed, but many are not.)

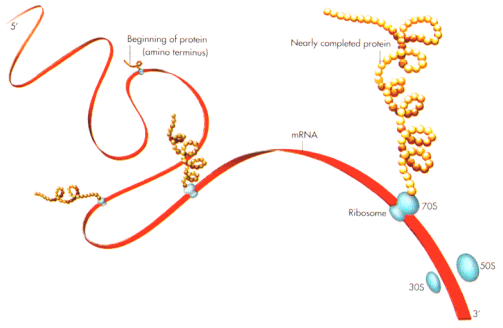
Alberts, et al.

Codons & The Genetic Code

First Base	Second Base U	Second Base C	Second Base A	Second Base G	Third Base
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	Stop	Stop	A
	Leu	Ser	Stop	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met/Start	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

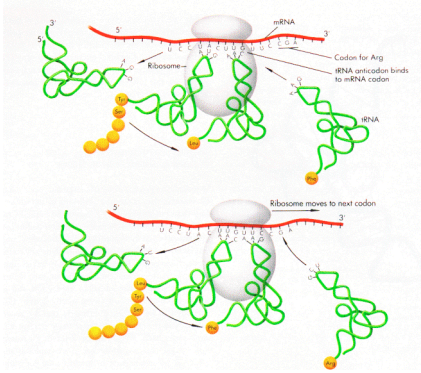
Ala : Alanine
Arg : Arginine
Asn : Asparagine
Asp : Aspartic acid
Cys : Cysteine
Gln : Glutamine
Glu : Glutamic acid
Gly : Glycine
His : Histidine
Ile : Isoleucine
Leu : Leucine
Lys : Lysine
Met : Methionine
Phe : Phenylalanine
Pro : Proline
Ser : Serine
Thr : Threonine
Trp : Tryptophane
Tyr : Tyrosine
Val : Valine

Translation: mRNA → Protein



Watson, Gilman, Witkowski, & Zoller, 1992

Ribosomes



Watson, Gilman, Witkowski, & Zoller, 1992

Idea #1: Find Long ORF's

Reading frame: which of the 3 possible sequences of triples does the ribosome read?

Open Reading Frame: No stop codons

In random DNA

- average ORF = 64/3 = 21 triplets
- 300bp ORF once per 36kbp per strand

But average protein ~ 1000bp

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A Simple ORF finder

start at left end

scan triplet-by-non-overlapping triplet for AUG

then continue scan for STOP

repeat until right end

repeat all starting at offset 1

repeat all starting at offset 2

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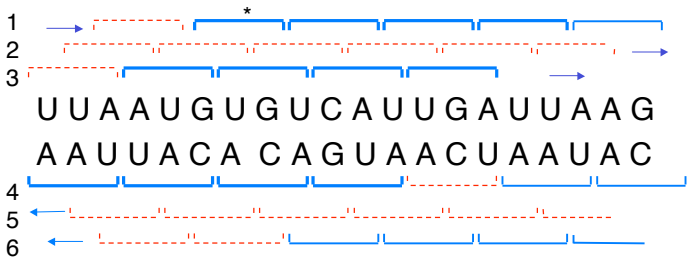
Scanning for ORFs



* In bacteria, GUG is sometimes a start codon…

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Idea #2: Codon Frequency

In random DNA

- Leucine : Alanine : Tryptophan = 6 : 4 : 1

But in real protein, ratios ~ 6.9 : 6.5 : 1

So, coding DNA is not random

Even more: synonym usage is biased (in a species dependant way)

- examples known with 90% AT 3rd base
  - Why? E.g. efficiency, histone, enhancer, splice interactions

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Recognizing Codon Bias

Assume

- Codon usage i.i.d.; abc with freq. f(abc)
- $a_1a_2a_3a_4\ldots a_{3n+2}$ is coding, unknown frame

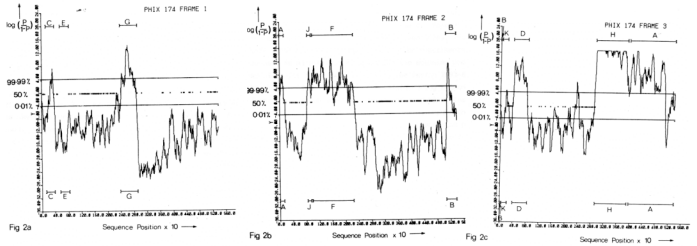
Calculate

- $p_1 = f(a_1a_2a_3)f(a_4a_5a_6)\ldots f(a_{3n-2}a_{3n-1}a_{3n})$
- $p_2 = f(a_2a_3a_4)f(a_5a_6a_7)\ldots f(a_{3n-1}a_{3n}\,a_{3n+1})$
- $p_3 = f(a_3a_4a_5)f(a_6a_7a_8)\ldots f(a_{3n}\,a_{3n+1}a_{3n+2})$
- $P_i = p_i / (p_1+p_1+p_3)$

More generally: k-th order Markov model

- k=5 or 6 is typical (next lecture)

Codon Usage in Φx174



Staden & McLachlan, NAR 10, 1 1982, 141-156