Bioinformatics 1

Distances and models. Synonymous and non-synonymous substitutions. Basics of the neutral theory.

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office hours - see the web site

http://www.bioinformatics.uni-muenster.de/teaching/courses-2011/bioinf1/index.hbi

Computer Lab B, Schlossplatz 2b

- Alignment and BLAST [November 14]
- Gene prediction [November 21]
- Phylogenetic inference [November 28]

Registration http://www.bioinformatics.unimuenster.de/cgi-bin/teaching/coursereg.cgi

DNA damage

Copying errors

MUTATIONS: heritable changes to the genome, essential for evolution.

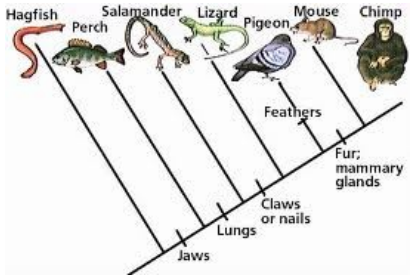
LARGE SCALE → SMALL SCALE

Chromosomal rearrangements

Point mutations

POLYMORPHISMS

?



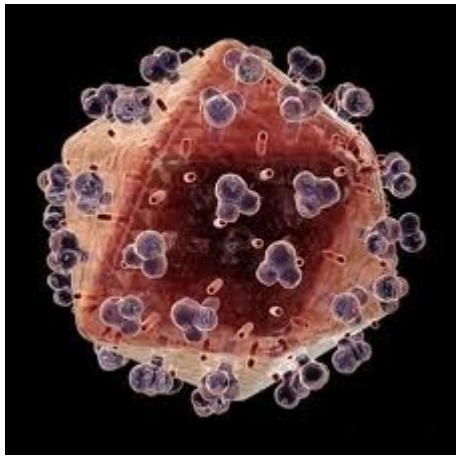
SUBSTITUTIONS

Selection on

De novo mutations vs. Standard genetic variation

Selection on

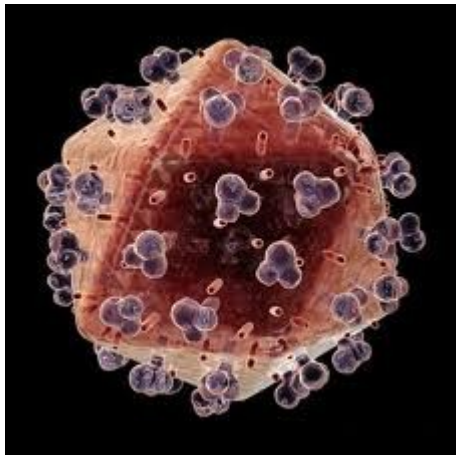
De novo mutations vs. Standard genetic variation



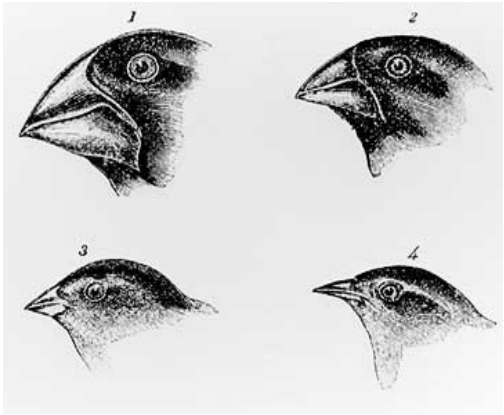
HIV virus evolution

Selection on

De novo mutations vs. Standard genetic variation



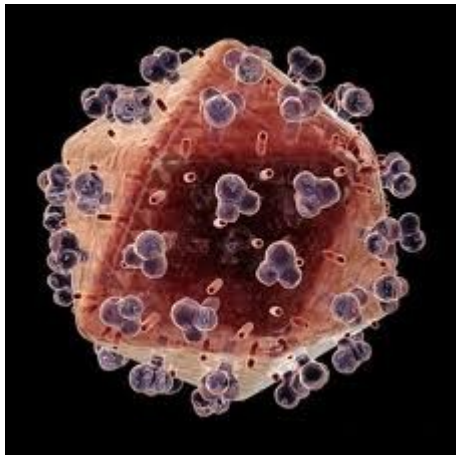
HIV virus evolution



Darwin's finches

Selection on

De novo mutations vs. Standard genetic variation



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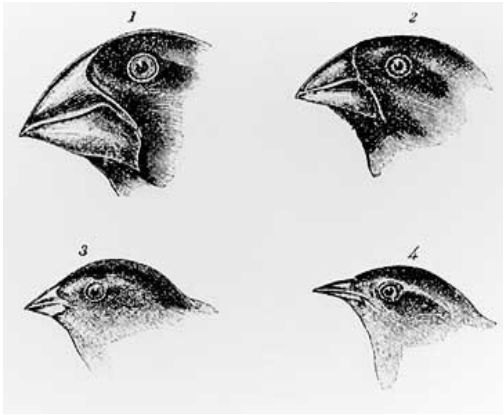
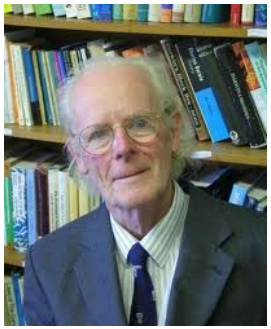
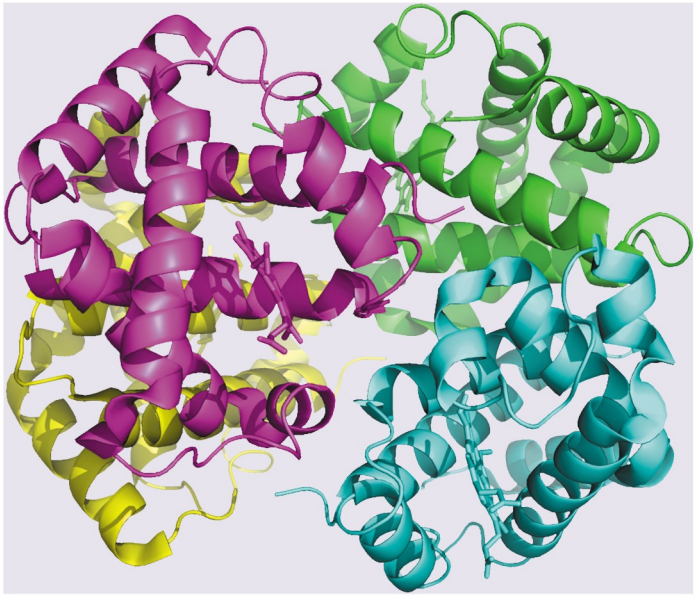


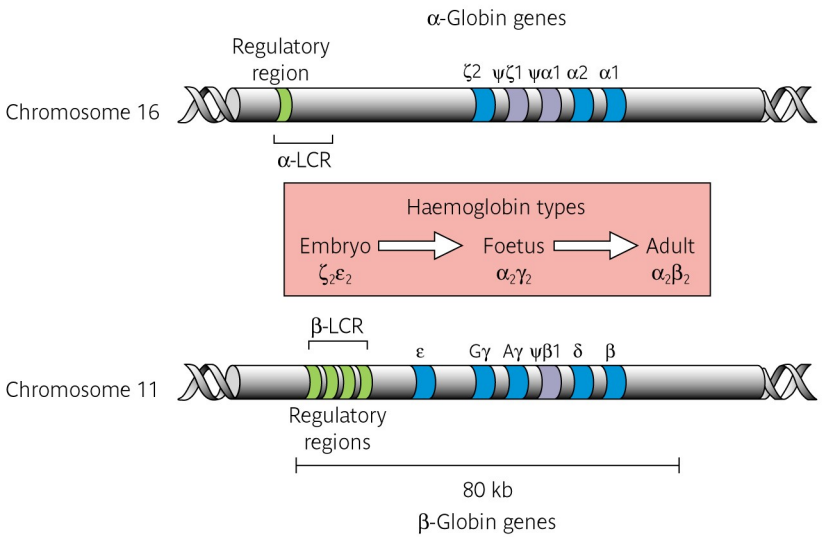
Darwin's finches

The effect of the environment

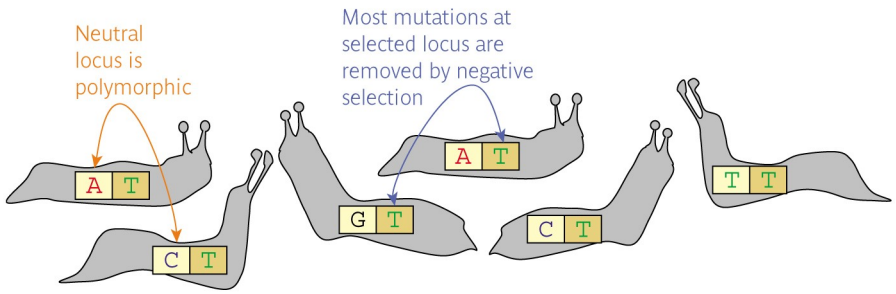


Genetic background of a mutation

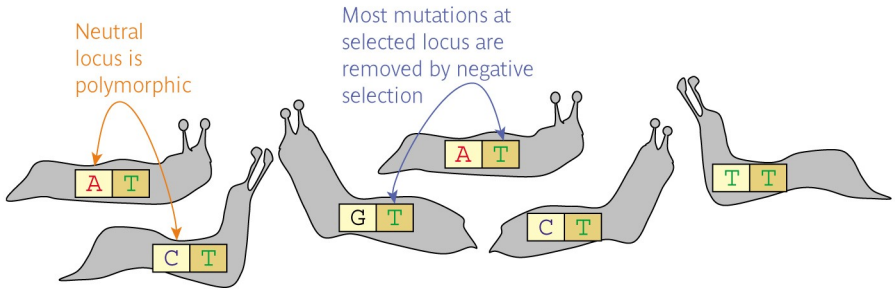




Linkage


Neutral locus is polymorphic
Most mutations at selected locus are removed by negative selection
A T
C T
G T
A T
C T
T T

Linkage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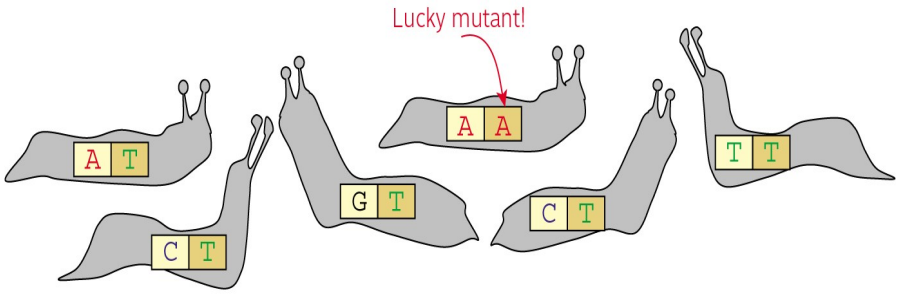
Lucky mutant!
A T
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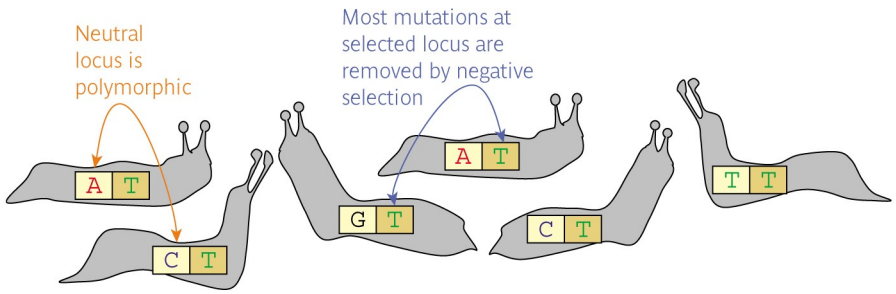
Linkage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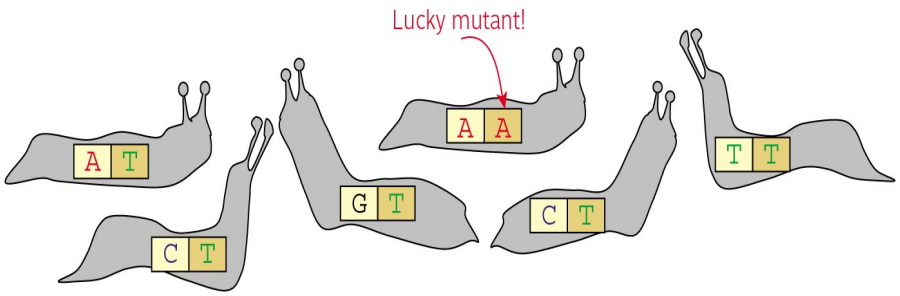
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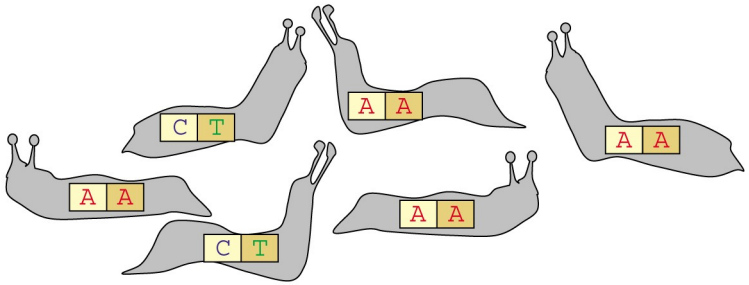
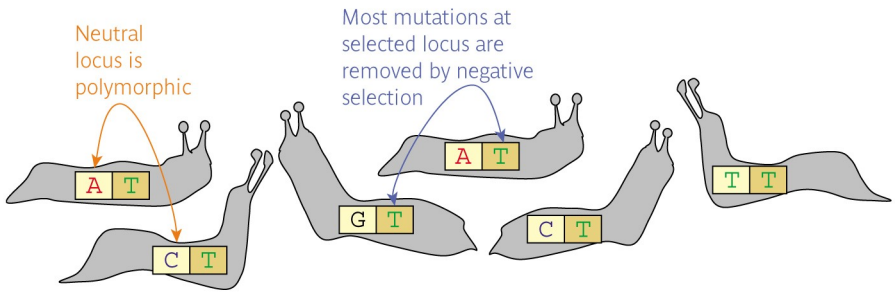

C T
A A
A A
A A
C T
A A

Linkage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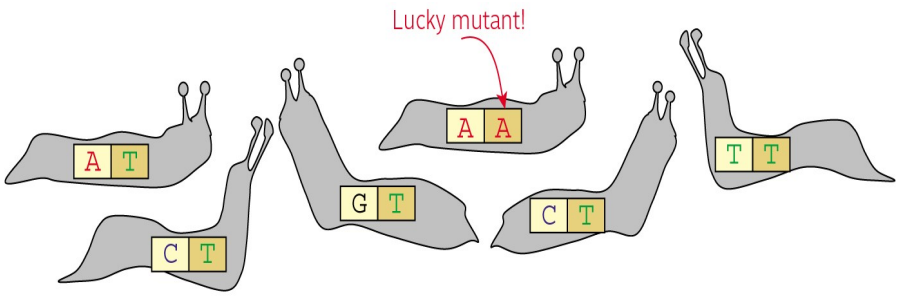
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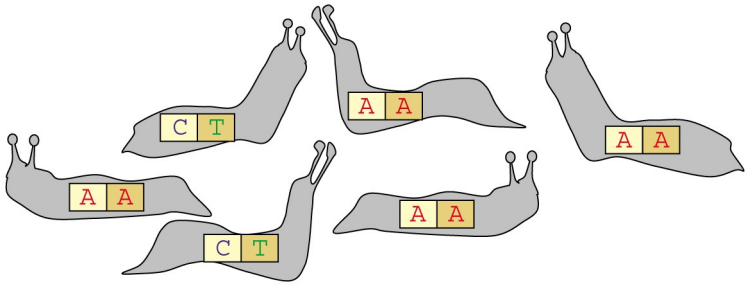
C T
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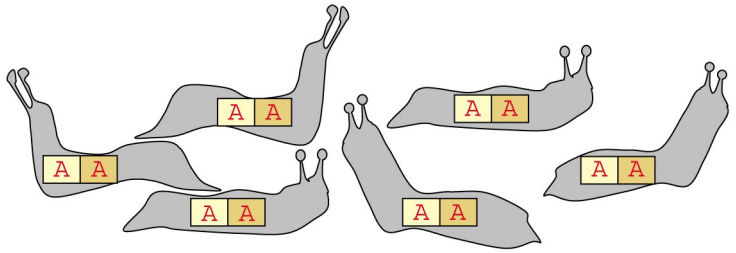
A A
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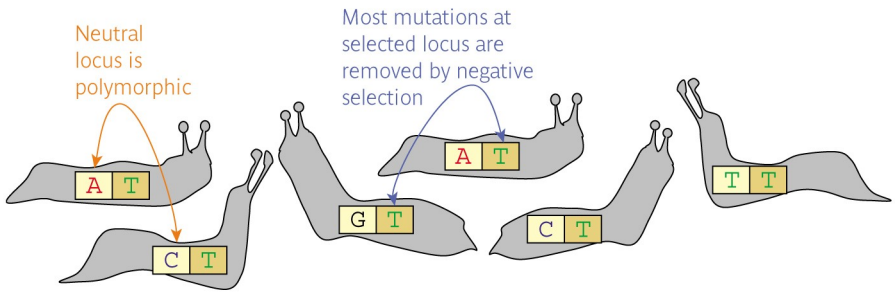
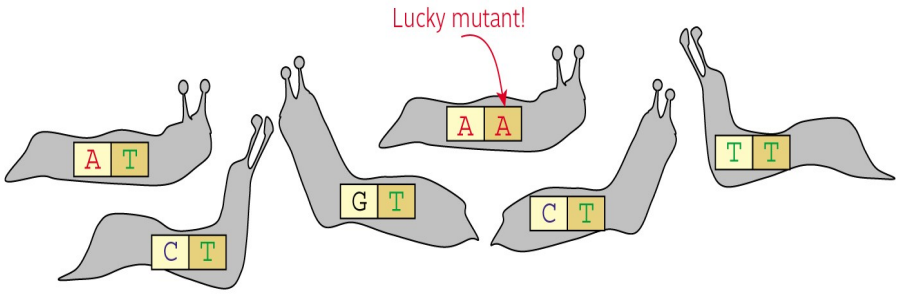
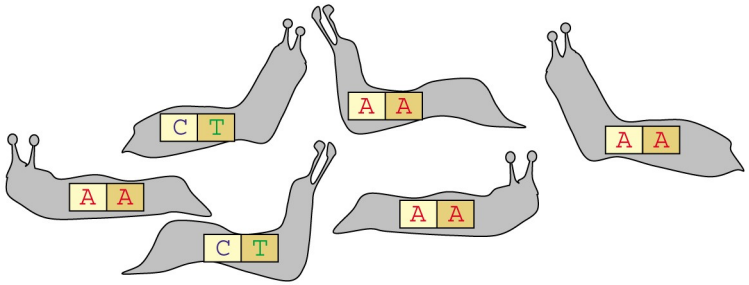
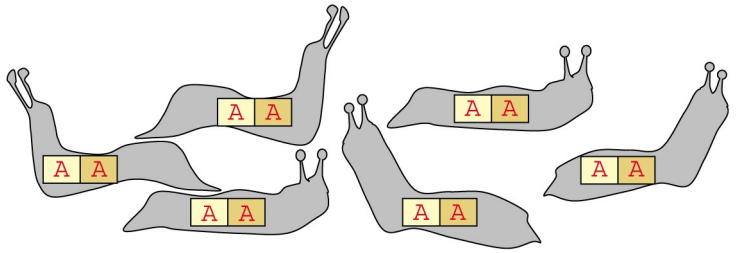
Linkage



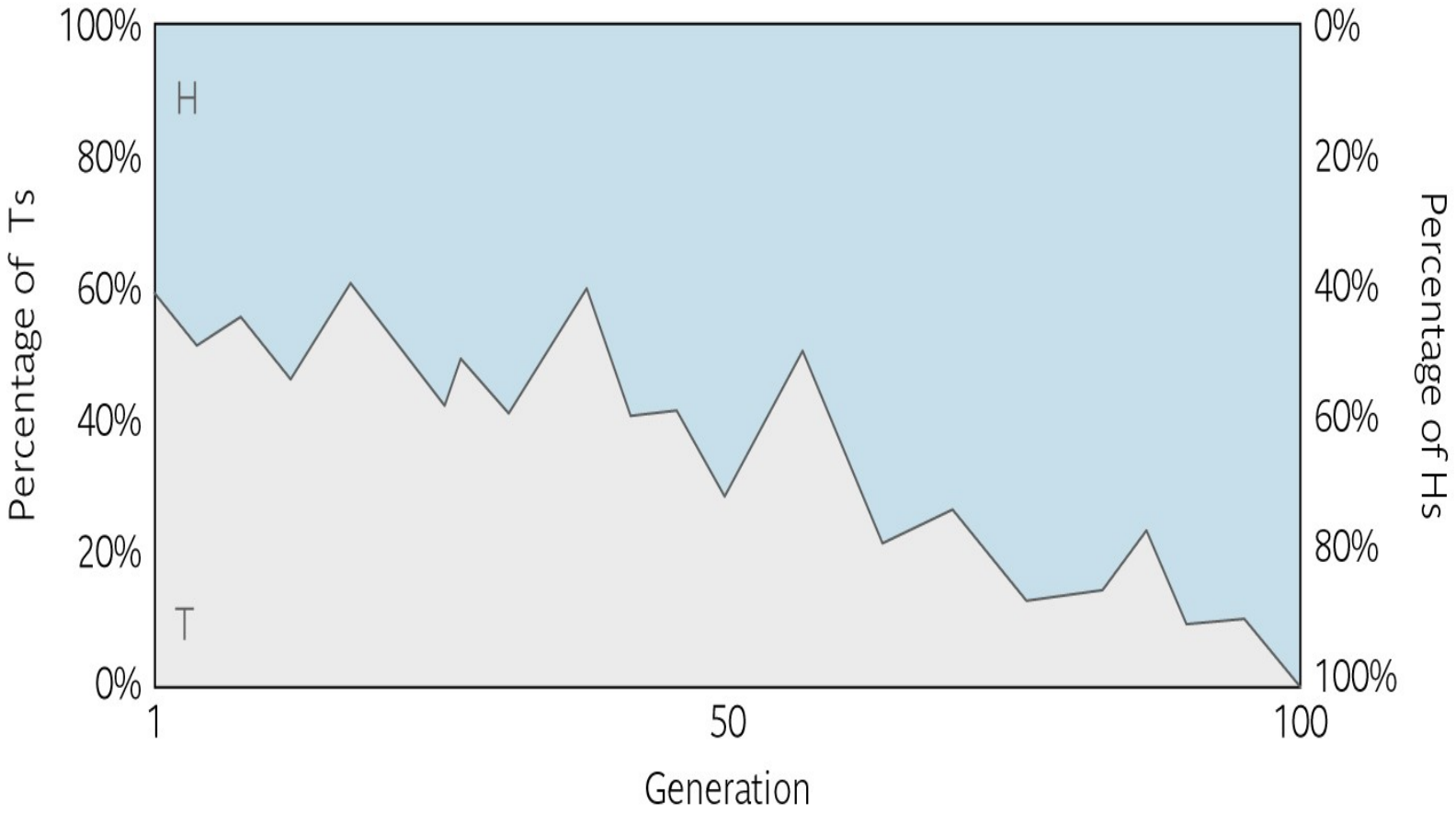






Hitchhiking

Fixation without selection: Drift



Neutral theory

Genetic drift is the main force changing allele frequencies.

M. Kimura

Distinguishing between different types of selection

NEGATIVE SELECTION: Conservation of sequences

Homo sapiens	GRSRDGGLRFGEME
Rattus norvegicus	GRSRDGGLRFGEME
Drosophila melanogaster	GRARDGGLRFGEME
Neurospora crassa	GRARDGGLRFGEME
Oryza sativa	GRKYGGGIRFGEME
Escherichia coli	GKAQFGGQRFGEME

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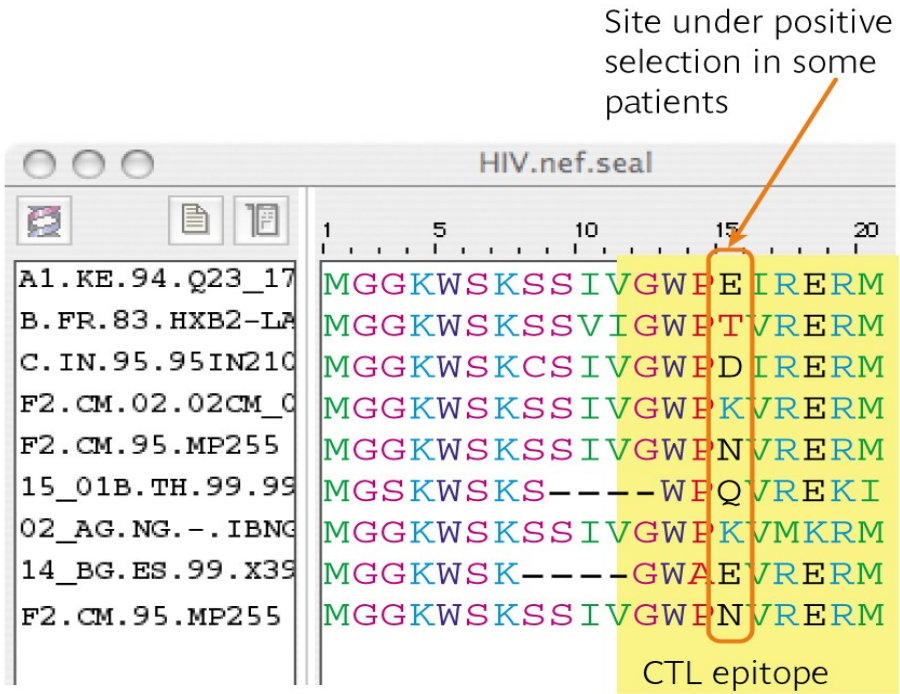
Escherichia coli	GKAQFGGQRFGEME

Homo sapiens	GGTAGATCTCGTGATGGTGGCCTGCGTTTTGGAGAAATGGAA
Rattus norvegicus	GGCAGATCGCGTGATGGTGGCCTGCGCTTTGGAGAAATGGAG
Drosophila melanogaster	GGTCGTGCTCGTGATGGTGGCTTGCGTTTCGGTGAGATGGAG
Neurospora crassa	GGTCGTGCCAGAGACGGTGGTCTCCGTTTCGGTGAAATGGAA
Oryza sativa	GGAAGGAAATACGGTGGAGGGATTCGGTTCGGTGAGATGGAG
Escherichia coli	GGTAAGGCACAGTTCGGTGGTCAGCGTTTCGGGGAGATGGAA

Distinguishing between different types of selection

POSITIVE SELECTION: Rapid substitution

E.g., HIV CTL Epitopes



How can we quantify?

```
#Human     V-LSPADKTN VKAAWGKVGA HAGEYGAEAL ERMFLSFPTT KTYFPHF-DL SHGSAQVKGH
#Horse     ....A..... .....S...G .......... .....G.... .......... ........A.
#Cow       ....A...G. .........G ..A....... .......... .......... ..........
#Kangaroo  ....A...GH ...I.....G .....A..G. ..T.H..... .......... ......IQA.
#Newt      MK..AE..H. ..TT.DHIKG .EEAL..... F...T.L.A. R....AK... .E..SFLHS.
#Carp      S...DK..AA ..I..A.ISP K.DDI..... G..LTVY.Q. ....A.WA.. .P..GP..-.

#Human     GKKVA-DALT NAVAHVDDMP NALSALSDLH AHKLRVDPVN FKLLSHCLLV TLAAHLPAEF
#Horse     .......G.. L..G.L..L. G...D..N.. .......... .........S ...V...ND.
#Cow       .A....A... K..E.L..L. G...E..... .......... ......S... ...S...SD.
#Kangaroo  ...I.....G Q..E.I..L. GT..K..... .......... .......... .F....GDA.
#Newt      ....M.G..S .....I..ID A..CK...K. .QD.M...A. .PK.A.NI.. VMGI..K.HL
#Carp      ....IMG.VG D..SKI..LV GG.AS..E.. .S......A. ..I.ANHIV. GIMFY..GD.

#Human     TPAVHASLDK FLASVSTVLT SKYR
#Horse     .......... ..S....... ....
#Cow       .......... ...N...... ....
#Kangaroo  ..E....... ...A...... ....
#Newt      .YP..C.V.. ..DV.GH... ....
#Carp      P.E..M.V.. .FQNLALA.S E...
```

Statistical measures of evolutionary distance between amino acid sequences

```
#Human     V-LSPADKTN VKAAWGKVGA HAGEYGAEAL ERMFLSFPTT KTYFPHF-DL SHGSAQVKGH
#Horse     ....A..... .....S...G .......... .....G.... .......... .........A.
#Cow       ....A...G. .........G ..A....... .......... .......... ..........
#Kangaroo  ....A...GH ...I.....G .....A..G. ..T.H..... .......... ......IQA.
#Newt      MK..AE..H. ..TT.DHIKG .EEAL..... F...T.L.A. R....AK... .E..SFLHS.
#Carp      S...DK..AA ..I..A.ISP K.DDI..... G..LTVY.Q. ....A.WA.. .P..GP..-.
```

Elimination of all sites with indels from the computations

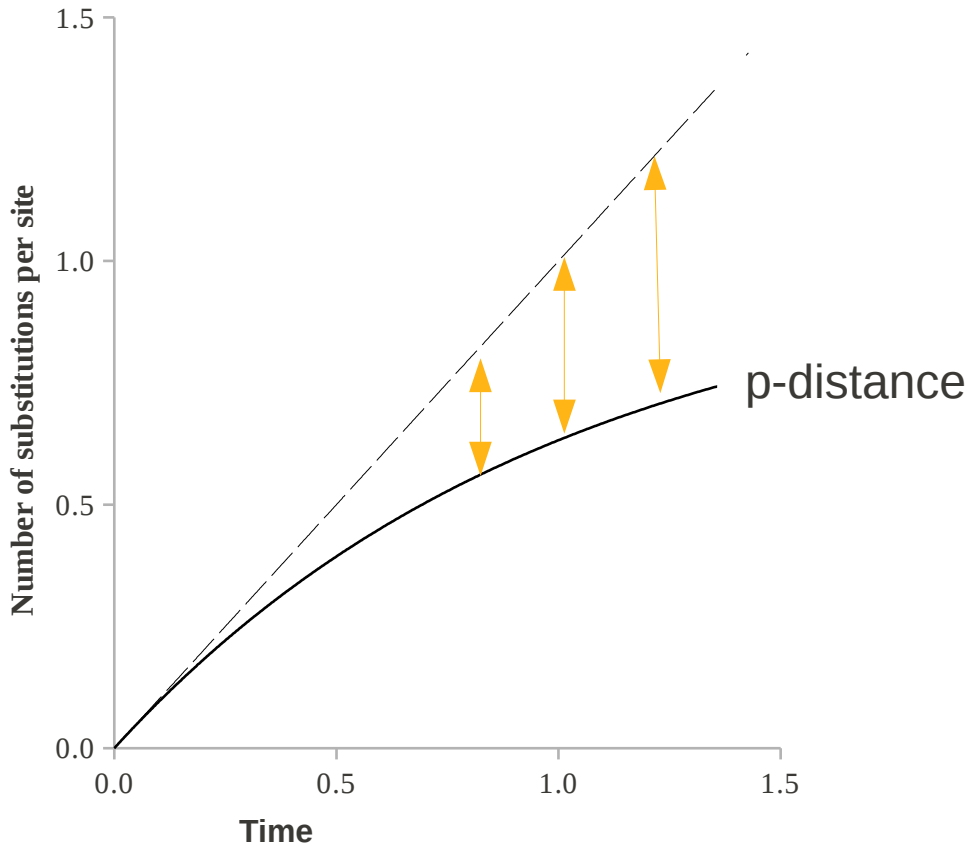
$$P = n_d / n$$

$$P = n_d / 140$$

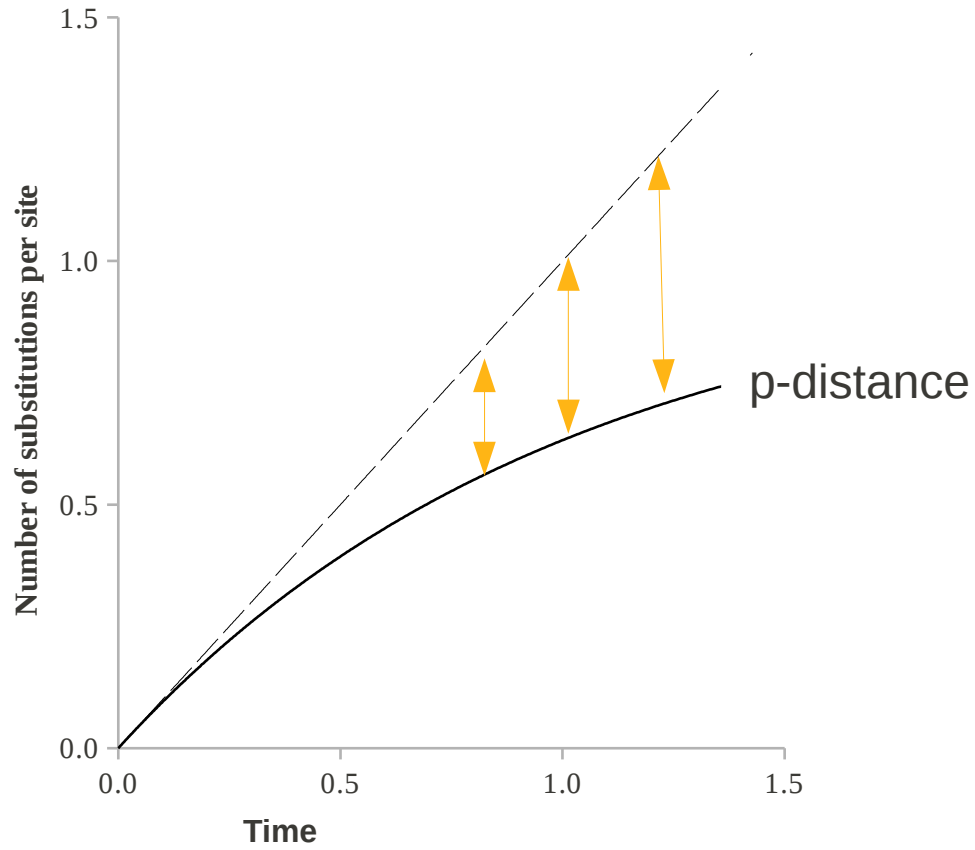
	Human	Horse	Cow	Kangaroo	Newt	Carp
Human		17	17	26	61	68
Horse	0.121		17	29	66	67
Cow	0.121	0.121		25	63	65
Kangaroo	0.186	0.207	0.179		66	71
Newt	0.436	0.471	0.450	0.471		74
Carp	0.486	0.479	0.464	0.507	0.529	

Easy, and clean!

Is the p-distance a well defined distance?



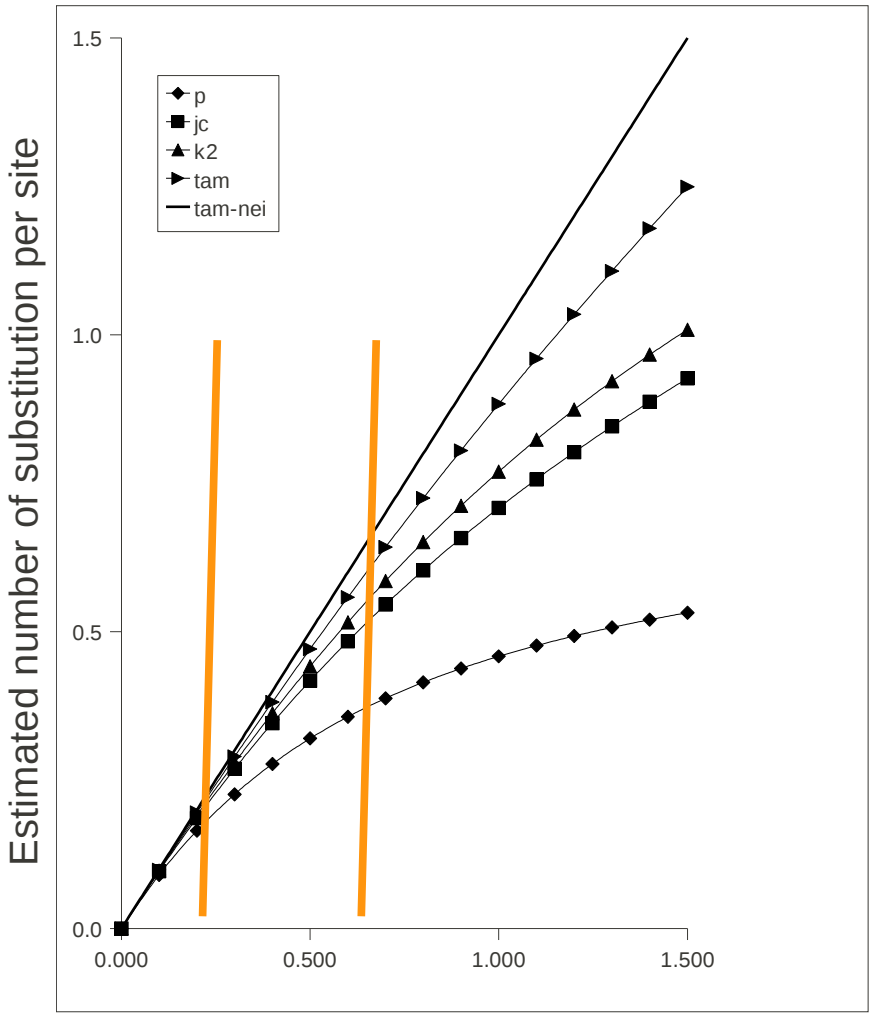
Is the p-distance a well defined distance?



Gradual underestimation of the real distance

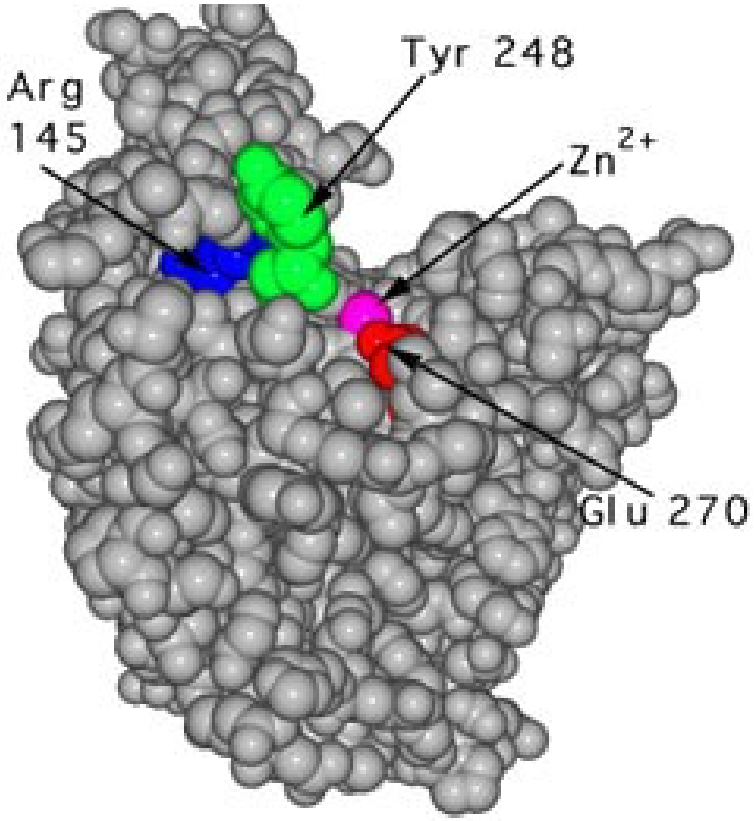
WHY?

Models


1.5
1.0
0.5
0.0
0.000
0.500
1.000
1.500
p
jc
k2
tam
tam-nei
Estimated number of substitution per site
Expected number of substitution per site

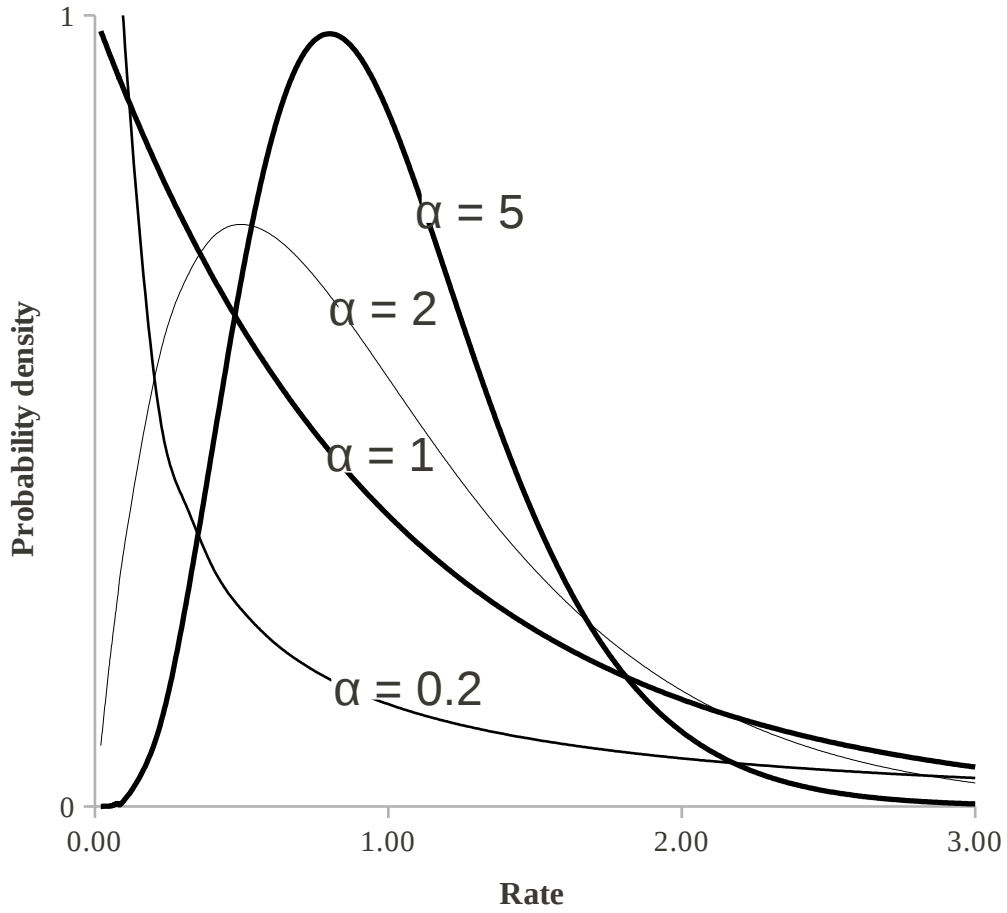
How do we deal with functional heterogeneity between sites?

Functional-structural constraints



What is the rate of amino acid substitution in different regions?

Gamma distribution (Uzzell and Corbin 1971)



Heterogeneity between sites: a well understood case

Synonymous and non-synonymous sites

1st	2nd: U	2nd: C	2nd: A	2nd: G	3rd
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	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

Neutral substitution rate is determined by mutation rate

Statistical measures of rate of Syn NonSyn substitutions

Approximation:

$1^{st} + 2^{nd}$ vs. 3^{rd} codon positions

Count number of Syn and NonSyn sites!

Exact calculation based on the genetic code

D_s = # Syn Subst / # Syn sites

D_n = # NonSyn Subst / # NonSyn sites

What do we expect?

Synonymous substitution to be more frequent than Nonsynonymous substitutions

Rate of Synonymous substitutions to be more similar between genes than the rate of Nonsynonymous substitutions

Dn/Ds measure of positive selection

Sliding window approach to detect local signal of positive selection