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4. Molecular population genetics

Polymorphisms on the amino acid and nucleotide level
are conveniently summarized in the form of a gene tree
4.1 neutral theory of molecular evolution
4.2 RGD-mutation equilibrium
4.3 sequence divergence rates
4.4 rates corrected for multiple hits
4.5 molecular clocks
4.6 synonimous and non-synonimous rates
4.7 gene genealogy and coalescent
4.8 within species mol. polymorphism
4.9 two tests of neutrality
4.10 recombination and polymorhism

4.1 Neutral theory of molecular evolution

most mutations are deleterious and quickly removed
Classical theory of molecular evolution
natural selection is the major evolutionary force
predicts little genetic variation
because positive mutations are quickly fixed
Balance theory of molecular evolution
most polymorphisms due to balanced selection
fails to explain protein electrophoresis results
15-50% of enzyme coding genes are polymorphic
with two or more widespread alleles
Neutral theory by M.Kimura, 1968
most polymorphisms are nearly selectively neutral
RGD is a major evolutionary force

4.2 RGD-mutation equilibrium

Population heterozygosity in a dynamic equlibrium
  non-reversible mutation generates new alleles
  RGD eliminates alleles due to gentic sampling
IBD in the presence of mutation = no mutation
  since MRCA (most recent common ancestor)
Neutral mutation rate μ per gene per generation
  $F_t = (1-\mu)^2(\frac{1}{2N_e} + (1 - \frac{1}{2N_e})F_{t-1})$
  equlibrium solution $\hat{F} = \frac{1}{1+\theta}$, where $\theta = 4N_e\mu$

Infinite-alleles mutation model (IAM)
  each mutation produces a novel allele
Identity by descent = identity by state = homozygosity
  average heterozygosity $\hat{H} = 1 - \hat{F} = \frac{\theta}{1+\theta}$

Effective number of alleles

Number k_e of hypothetical alleles with equal frequencies
  resulting in the same as observed $H = 1 - p_1^2 + \ldots + p_k^2$
  $1 - H = (\frac{1}{k_e})^2 + \ldots + (\frac{1}{k_e})^2 = \frac{1}{k_e}$
  neutral mutation equilibrium $k_e = \theta + 1$ under IAM

Ex 1: mutation rate estimation

Fig 1.8 p21 (2.9 p55) allozyme alleles in Drosophila
  $N_e = 10^6$, $\hat{H} = 0.14$, $\hat{\theta} = \frac{\hat{H}}{1-\hat{H}} = 0.163$
  $k_e = 1.163$, $\hat{\mu} = 4 \cdot 10^{-8}$
IAM underestimates μ if based on electrophoresis H
  usually $\mu = 10^{-4} - 10^{-6}$ mut. per gene per generation

Ewens sampling formula

gives a rough estimate of θ based on the sample size and the observed number of alleles

Average number of IAM alleles in a sample of size n

$$\mathrm{E}(k) = 1 + \frac{\theta}{\theta+1} + \frac{\theta}{\theta+2} + \ldots + \frac{\theta}{\theta+n-1}$$

diminishing return in new alleles when n increases

$\mathrm{E}(k) \approx 1$ for small θ and $\mathrm{E}(k) \approx n$ for large θ

4.3 Sequence divergence rates

Two homologous sequences

sequence length: L amino acids, $l = 3L$ nucleotide sites

d = observed nucleotide differences per site, $0 \leq d \leq 1$

D = observed amino acid diff. per site, $0 \leq D \leq 1$

t = divergence time between the homologuos sequences

Parameter estimation problem: using d, D estimate

nucleotide substitution rate $\lambda = \frac{k}{2t}$

amino acid replacement rate $\Lambda = \frac{K}{2t}$

k, K = actual numbers of differences per site

Multiple hits examples

1) observed A $\to$ C, full history A $\to$ T $\to$ G $\to$ C

2) observed A $\to$ A, full history A $\to$ T $\to$ A

Ex 2: bacterial gene

Coding region of *trpA* in two related bacterial strains

K12 (*E.coli*) and LT2 (*Salmonella typhimurium*)

diverged $t = 80$ MY ago (mammalian radiation)

0*04	004*	004*	002	002	002	002	004	004	002
GTC	GCA	CCT	ATC	TTC	ATC	TGC	CCG	CCA	AAT
Val	Ala	Pro	Ile	Phe	Ile	Cys	Pro	Pro	Asn
ATC	GCG	CCG	ATC	TTC	ATC	TGC	CCG	CCA	AAT
Ile	Ala	Pro	Ile	Phe	Ile	Cys	Pro	Pro	Asn
N	S	S							

004*	002	002	002*	204*	204	004	002	0*02*	004*
GCC	GAT	GAC	GAC	CTG	CTG	CGC	CAG	ATA	GCC
Ala	Asp	Asp	Asp	Leu	Leu	Arg	Gln	Ile	Ala
GCG	GAT	GAC	GAT	CTT	CTG	CGC	CAG	GTC	GCA
Ala	Asp	Asp	Asp	Leu	Leu	Arg	Gln	Val	Ala
S			S	S				N S	S

Observed differences: 9 nucleotide, 2 amino acid

$l = 60$, $d = 9/60 = 0.15$, $L = 20$, $D = 2/20 = 0.10$

Uncorrected estimates of the rates λ and Λ:

$\tilde{\lambda} = \frac{d}{2t} = 0.94 \cdot 10^{-9}$ substitutions per site per year

$\tilde{\Lambda} = \frac{D}{2t} = 0.63 \cdot 10^{-9}$ replacements per site per year

4.4 Rates corrected for multiple hits

Corrected replacement rate

Poisson process model for one amino acid site

replacement number $X \in \text{Pois}(\Lambda u)$ during time u

no reverse mutations for amino acids (20 letters)

Proportion of differences per site

$D = \frac{1}{L}(1_{\{X_1>0\}} + \ldots + 1_{\{X_L>0\}})$

$\mathrm{E}(D) = 1 - e^{-2t\Lambda}$, $\mathrm{Var}(D) = \frac{1}{L}(1 - e^{-2t\Lambda})e^{-2t\Lambda}$

Method of moments estimate: $D = 1 - e^{-2t\hat{\Lambda}}$ implies

$$\boxed{\text{Corrected replacement rate } \hat{\Lambda} = -\frac{\ln(1-D)}{2t}}$$

Estimated K: $\hat{K} = -\ln(1-D)$, $s_{\hat{K}} = \sqrt{\frac{D}{L(1-D)}}$

saturated $D = 1$ gives $\hat{K} = \infty$

Ex 2: bacterial gene

$\hat{K} = 0.1053$, $s_{\hat{K}} = 0.0745$, $\hat{\Lambda} = 0.66 \cdot 10^{-9}$

Markov Chain models

MC is a stochastic model assuming that

given the current state future is independent of past

Transition rates

	To A	To C	To G	To T
From A	—	r_{AC}	r_{AG}	r_{AT}
From C	r_{CA}	—	r_{CG}	r_{CT}
From G	r_{GA}	r_{GC}	—	r_{GT}
From T	r_{TA}	r_{TC}	r_{TG}	—

Equilibrium base composition

$F = (\pi_{\mathrm{A}}, \pi_{\mathrm{C}}, \pi_{\mathrm{G}}, \pi_{\mathrm{T}})$ with $\pi_{\mathrm{A}} + \pi_{\mathrm{C}} + \pi_{\mathrm{G}} + \pi_{\mathrm{T}} = 1$

Substitution rate

$$\lambda = \pi_{\mathrm{A}}(r_{\mathrm{AC}} + r_{\mathrm{AG}} + r_{\mathrm{AT}}) + \pi_{\mathrm{C}}(r_{\mathrm{CA}} + r_{\mathrm{CG}} + r_{\mathrm{CT}})$$
$$+\pi_{\mathrm{G}}(r_{\mathrm{GA}} + r_{\mathrm{GC}} + r_{\mathrm{GT}}) + \pi_{\mathrm{T}}(r_{\mathrm{TA}} + r_{\mathrm{TC}} + r_{\mathrm{TG}})$$

Jukes-Cantor model

JC	A	T	C	G
A	—	α	α	α
T	α	—	α	α
C	α	α	—	α
G	α	α	α	—

$F = (0.25, 0.25, 0.25, 0.25)$

$\lambda = 3\alpha$

JC genetic distance corrected for multiple changes

$\hat{k} = \frac{3}{4}\ln(\frac{3}{3-4d})$, $s_{\hat{k}} = \frac{\sqrt{d(1-d)}}{(1-\frac{4}{3}d)\sqrt{l}}$

$\hat{k} \approx d$ if d is small

$$\boxed{\text{Corrected substitution rate } \hat{\lambda} = \frac{\hat{k}}{2t}}$$

Saturated $d = \frac{3}{4}$ when $\frac{1}{4}$ of sites match by chance

gives $\hat{k} = \infty$

Ex 2: bacterial gene

$\hat{k} = 0.1674$, $s_{\hat{k}} = 0.0576$, $\hat{\lambda} = 1.05 \cdot 10^{-9}$

Kimura two-parameter model

Transitions are more usual than transversions

transversions: purines $\{A,G\} \longleftrightarrow$ pyrimidines $\{T,C\}$

transitions: $A \longleftrightarrow G$ and $T \longleftrightarrow C$

K2P	A	C	G	T
A	—	β	α	β
C	β	—	β	α
G	α	β	—	β
T	β	α	β	—

$F = (0.25, 0.25, 0.25, 0.25)$

$\lambda = \alpha + 2\beta$

K2P genetic distance

$\hat{k} = -\frac{1}{2}\ln(1 - 2P - Q) - \frac{1}{4}\ln(1 - 2Q)$

P = differences per site due to transitions

$Q = p - P$ = differences per site due to transversions

Ex 2: bacterial gene

4 transitions, $P = \frac{4}{60} = 0.0667$

5 transversions, $Q = \frac{5}{60} = 0.0833$

$\hat{k} = 0.1221 + 0.0456 = 0.1677$, $\hat{\lambda} = 1.05 \cdot 10^{-9}$

Ex 3: transition-transversion ratio

α/β ratio for different sequences:
 12S rRNA = 1.75, alpha- and beta-globins = 0.66
 pseudo eta-globins = 2.7, mtDNA = 9.0

4.5 Molecular clocks

Molecular clock hypothesis: average rates of
 molecular evolution λ, Λ are nearly constant over time

Substitution and mutation rates

Substitution rate for neutral mutations

$$\lambda = \#(\text{mutations per gener}) \times (\text{fixation probability})$$
$$= 2N\mu \times \frac{1}{2N} = \mu$$

$$\boxed{\text{Neutral substitutions: } \lambda = \mu \text{ is independent of } N_e}$$

Ex 4: diffusion simulations

Fig 7.1 p319 (8.1 p317): neutral substitutions for different μ
 average fixation time = $4N_e$
 average time between substitutions $\frac{1}{\mu}$

Ex 5: alpha-globin data

Table 7.1 p330 (8.1 p330): differences between alpha-globins
 D above the diagonal, $\hat{K}$ below the diagonal

Molecular clock: data fit a straight line, Fig 7.6 p331 (8.7 p330)
 regression line slope = $2\hat{\Lambda}$, $\hat{\Lambda} = 0.9 \cdot 10^{-9}$
 divergence times based on paleontological data

Ex 6: beta-globin data
Primates, $L = 146$, fosil evidence for 6 paires of species

t MY (x_i)	85	60	42	40	30	15
# differences	25.5	24.0	6.25	6.0	2.5	1.0
D	0.175	0.164	0.043	0.041	0.017	0.007
$\hat{K}$ (y_i)	0.192	0.180	0.044	0.042	0.018	0.007

Least squares estimate of the slope $b = 0.00315$
$\hat{\Lambda} = \frac{b}{2} = 1.58 \cdot 10^{-9}$ replacements per site per year
Coefficient of determination
$r^2 = 86\%$ of variation in Y is explained by X

Variation in clock rates
Different substitution rates
for different genes and different taxonomic groups
Episodic clock: substitution is a Poisson process with
randomly changing rate (variance larger than mean)

Ex 7: viral clocks
Fig 7.9 p335 (8.9 p334): NS gene of influenza virus
$l = 890$, $\lambda = 1.9 \cdot 10^{-3}$ subst. per site per year
pol gene of HIV: $\lambda = 0.5 \cdot 10^{-3}$ per site per year
divergence time between HIV1 and HIV2 is 200 years

Ex 8: clock retardation
Fig 7.10 p336 (8.10 p335):
slow-down of substitutions in certain gene genalogies

Generation-time effect

Neutral evolution theory prediction:
species with shorter generation times evolve faster
strong effect observed for syn. subst. in mammals

Fig 7.7 p332 (8.8 p332): weak effect for amino-acid replacements
evolutionary rate for proteins is nearly constant across
species if time is measured in years, not generations

Explanation by negative selection: Λ decreases with N
N is inversely proportional to generation time

4.6 Synonimous and non-synonimous rates

Genetic code is redundant Table 7.2 p341 (8.2 p339)
three types of sites: 0 = non-degenerate site
2 = two-fold site and 4 = four-fold site

$$\boxed{\text{At a two-fold site } \tfrac{1}{3} \text{ of substitutions are synonimous}}$$

Effective numbers of sites
$l_s = l_4 + \frac{1}{3} \cdot l_2$ and $l_n = l_0 + \frac{2}{3} \cdot l_2$
total length $l = l_0 + l_2 + l_4 = l_s + l_n$

Fig 7.12 p342 (8.12 p341) and Fig 7.13 p343 (8.13 p342)
different substitution rates $\lambda_s = \frac{d_s}{2t}$ and $\lambda_n = \frac{d_n}{2t}$
$d_s = \frac{\text{synonimous changes}}{l_s}$ and $d_n = \frac{\text{nonsynonimous changes}}{l_n}$

Usually $\lambda_s > \lambda_n$ because of deleterious mutations
Fig 7.14 p345 (8.14 p343): mammalian nuclear DNA rates

$$\boxed{\text{Neutrality: } \lambda_s = \lambda_n, \text{ positive selection: } \lambda_s < \lambda_n}$$

Genome averages

Wide variety of unconstrained substitution rates λ_s

plant chloroplast DNA	$1{\cdot}10^{-9}$
mammalian nuclear DNA	$3.5{\cdot}10^{-9}$
plant nuclear DNA	$5{\cdot}10^{-9}$
E.coli and Salmonella enterica bacteria	$5{\cdot}10^{-9}$
Drosophila nuclear DNA	$1.5{\cdot}10^{-8}$
mammalian mitochondrial DNA	$5.7{\cdot}10^{-8}$
HIV-1	$6.6{\cdot}10^{-3}$
Influenza A virus	$1.3{\cdot}10^{-2}$

Ex 2: bacterial gene

Observed differences per site

$d_s = \frac{7}{10+12/3} = 0.5$, $d_n = \frac{2}{38+12\cdot 2/3} = 0.04$

uncorrected estimates $\tilde{\lambda}_s = 3.1 \cdot 10^{-9}$, $\tilde{\lambda}_n = 0.3 \cdot 10^{-9}$

Positive selection evidence

in a study of 3595 groups of homologous sequences only

17 groups with λ_n/λ_s significantly larger than 1

many of these are sex-related genes (favor speciation)

In some immunoglobulin genes

$\lambda_n/\lambda_s > 1$ in certain regions

overdominant selection for antibody diversity

4.7 Gene genealogy and coalescent

Gene genealogy =

tree formed by sequences of alleles from a single species

Ex 9: Adh gene in D.melanogaster

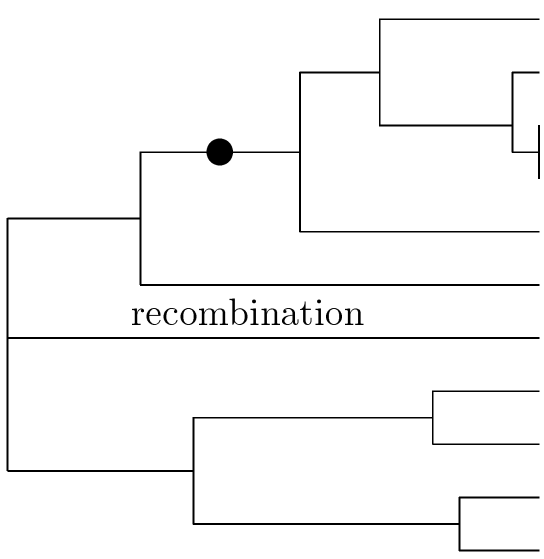
A parsimony tree for eleven *Adh* alleles in *D.melanogaster*

sampled from different geographical regions

two allozymes Fast and Slow - higher diversity of the S allele

clearly makes it appear to be older

Branch lengths are proportional to nucleotide
differences estimated by parsimony algorithm



Coalescent

a simple stochastic model of a gene genealogy
for n chromosomes sampled from a large population

Coalescent models evolution backward in time

diffusion approximation: evolution forward in time
backward simulations more effective in view of RGD

Coalescent is based on WFM with neutral mutations

reproduction and mutation processes are independent

$$\boxed{\text{A unit of coalescent time} = 2N \text{ generations in WFM}}$$

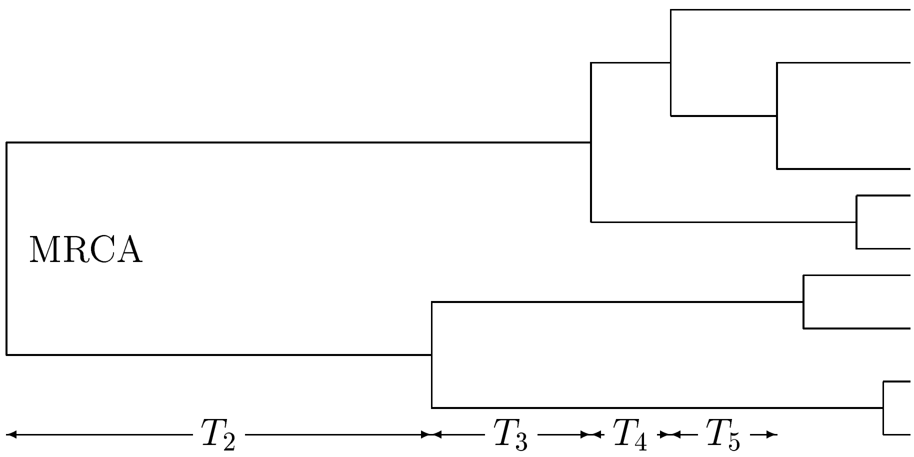
Topology of the coalescent tree

any out of $\binom{n}{2}$ pairs of ancestral lines join first

Coalescent branch lengths: $T_2 \in \mathrm{Exp}(1)$, $T_n \in \mathrm{Exp}\binom{n}{2}$

$\mathrm{E}(T_n) = \frac{2}{n(n-1)}$ more branches - sooner the next merger

$\sigma(T_n) = \frac{2}{n(n-1)}$ huge uncertainty in the tree evolution



Scaled time to the most recent common ancestor

$T_{\text{MRCA}} = T_2 + T_3 + \ldots + T_n$ sum of independent r.v.

$\text{E}(T_{\text{MRCA}}) = 2(1 - \frac{1}{n})$

If $n = 2$, then $T_{\text{MRCA}} = T_2$, $\text{E}(T_2) = 1$, $\text{Var}(T_2) = 1$

$$\boxed{\text{If } n \text{ is large, then } \text{E}(T_{\text{MRCA}}) \approx 2,\ \text{Var}(T_{\text{MRCA}}) \approx 1.16}$$

Fixation time of a new neutral mutation

is approximately $T_{\text{MRCA}} \times 2N$ with $n = 2N$

the average fixation time $\approx 4N$

Total branch length in the gene tree

$J_n = 2T_2 + 3T_3 + \ldots + nT_n$ sum of independent r.v.

$$\boxed{\begin{array}{ll} \text{E}(J_n) = 2a_1 & a_1 = 1 + \frac{1}{2} + \ldots + \frac{1}{n-1} \\ \text{Var}(J_n) = 4a_2 & a_2 = 1 + \frac{1}{4} + \ldots + (\frac{1}{n-1})^2 \end{array}}$$

Total length L_n of the external branches

$\text{E}(L_n) = 2$ is independent of n

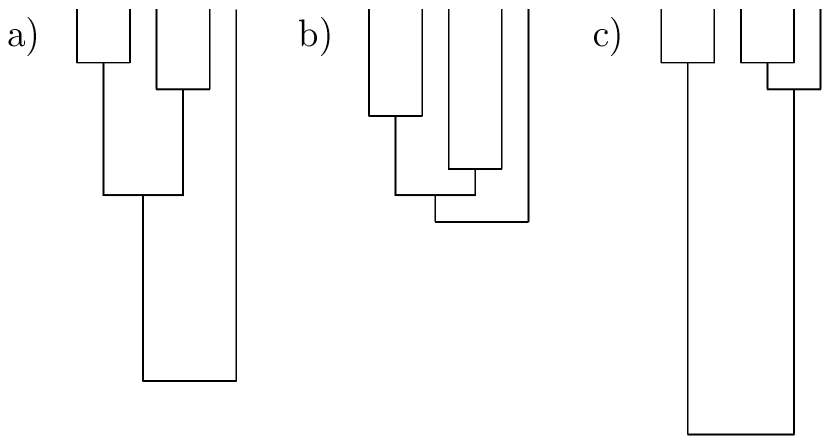
Hypothesis testing using trees

Tree shapes explained by the coalescent theory

a) Theoretical coalescent tree: constant population size, neutral mutations (no selection), no recombination

b) Star-like tree
growing population size, bottleneck (all loci) or positive selection, recent fixation (single locus)

c) Longer branches near the root: pop. subdivision (all loci) or balancing selection (single locus)



4.8 Within species molecular polymorphism

Two measures of molecular polymorphism

nucleotide polymorphism $S = \frac{\#(\text{ss})}{l}$, segregating sites

nucleotide diversity $\pi = \frac{\#(\text{pmm})}{\binom{n}{2}\cdot l}$, pairwise mismatches

Alternative way of computing π: $\pi = \frac{n}{n-1}\bar{h}$

average heterozygosity $\bar{h} = \frac{h_1+\ldots+h_l}{l}$

one site heterozygosity $h_i = 1 - \hat{p}_{iA}^2 - \hat{p}_{iC}^2 - \hat{p}_{iG}^2 - \hat{p}_{iT}^2$

Ex 10: Rh3 gene of D.simulans

$n = 5$ aligned sequences of length $l = 500$

16 segregating sites, $S = \frac{16}{500} = 0.032$

One non-synonimous polymorphism at site 142

find what is odd about 142

132	**142**	162	192	198	201	207	240	246	351	354	372	375	405	417	483
T	C	T	A	C	C	T	C	C	T	C	G	G	T	T	A
T	C	C	T	A	C	C	T	C	C	T	G	G	T	T	T
C	T	C	C	C	C	C	T	C	T	T	T	G	C	T	A
C	T	C	C	C	C	C	T	T	C	T	G	A	C	T	T
C	T	C	C	C	T	C	T	T	T	T	G	G	C	C	A

$$\pi = \frac{79}{5000} = 0.0158$$
$$\bar{h} = \frac{6.32}{500} = 0.0126, \text{ same } \pi = \frac{5}{4} \cdot 0.0126 = 0.0158$$

configuration	(5,0)	(4,1)	(3,2)	(3,1,1)	tot
number of sites	484	9	6	1	500
number of pmm/site	0	4	6	7	
total number of pmm	0	36	36	7	79
h_i	0	0.32	0.48	0.56	
sum of h_i	0	2.88	2.88	0.56	6.32

Infinite-sites model

ISM is a narrower version of IAM assuming that

new mutations occur at sites not previously mutated

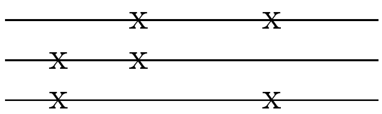
Number of mutations in the gene tree since MRCA

= number of alleles in IAM

= number of segregating sites in ISM

3 alleles possible under IAM

but impossible under ISM



If ISM holds, then tree reconstruction is easier

Neutral mutation rate estimation

Consider n aligned sequences of length l assuming ISM

number of segregating sites $l \cdot S \in \mathrm{Bin}(2Nl \cdot J_n, \mu)$

J_n = total branch length in the coalescent

μ = mutation rate per nucleotide site per generation

Two unbiased estimates of θ

$\hat{\theta} = S/a_1$ with $\mathrm{E}(\hat{\theta}) = \theta$ and π with $\mathrm{E}(\pi) = \theta$

$\hat{\theta}$ is consistent, π is inconsistent

$\mathrm{Var}(\hat{\theta}) = \frac{\theta}{la_1} + \frac{a_2\theta^2}{a_1^2}$

$\mathrm{Var}(\pi) = \frac{b_1}{l}\theta + b_2\theta^2$, $b_1 = \frac{n+1}{3(n-1)}$, $b_2 = \frac{2(n^2+n+3)}{9n(n-1)}$

Stochastic variance component

$\lim_{n\to\infty} \mathrm{Var}(\pi) = \frac{\theta}{3l} + \frac{2}{9}\theta^2$

due to sequence dependence by common ancestry

Clustering effect of alleles

coalescent is dominated by T_2, two major clusters

positive covariation of pmm due to few major clusters

new sequences add little information

Ex 11: human effective population size

mtDNA data: 21 humans of diverse origin

868 nucleotide sites with $\pi = 0.0018$

no recombination, high mutation rate

Haploid maternal inheritance implies that

under neutrality π is close to $\theta = 2N_f\mu = N_e\mu$

N_f = effective population size for females

Mammalian mtDNA mutation rate

$5{\cdot}10^{-9}$ to $10{\cdot}10^{-9}$ nucl. subst. per site per year

$\mu = 10^{-7}$ to $2{\cdot}10^{-7}$ subst. per site per generation

human $N_e = \frac{\theta}{\mu} = 9,000$ to 18,000

Fig 10.20 p560 (8.24 p364): star shaped tree, mitochondrial Eve

lived between 180,000 and 360,000 years ago in Africa

4.9 Two tests of neutrality

H_0: observed polymorphism is due to selective neutrality
of mutations and not due to natural selection

McDonald-Kreitman test

Chi-square test of homogeneity comparing two pairs of
numbers of (synonimous, non-synonimous) differences

1. fixed differences between species
2. within species polymorphic sites

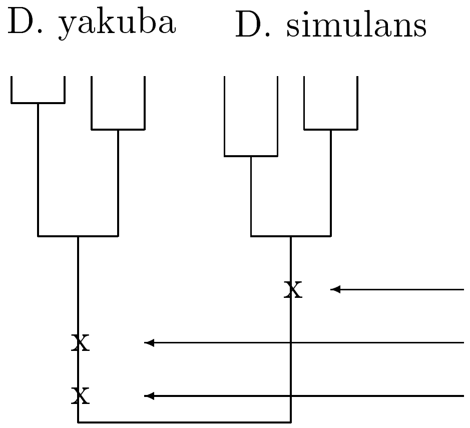
Reject the null hypothesis of neutrality
if two distributions are significantly different

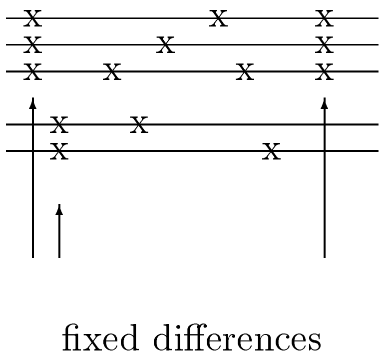
Ex 12: G6PD gene in Drosophila

12 alleles in *D.yakuba* and 6 alleles in *D.simulans*

differences	between species	within species	total
synonymous	17(20.3)	29(25.7)	46
nonsynonymous	6(2.7)	0(3.3)	6
total	23	29	52

Excess of nonsynonimous fixed differences
positive selection of advadtageous nonsyn. mutations
$X^2 = 8.6$, df $= 1$, $\sqrt{8.6} = 2.93$, $P = 0.0034$, reject H_0





Tajima test

tests neutrality using polymorphisms in one species

compares two estimates of θ: $\hat{\theta} = S/a_1$ and π

S and π react differently on presence of selection

S examines the number of polymorphic sites

π assesses the site frequences p_A, p_G, p_T, p_C

Very unequal p_A, p_G, p_T, p_C imply smaller π
almost equal p_A, p_G, p_T, p_C imply larger π

Ex 13: configuration and nucletide diversity

$n = 12$, $l = 1$, number of pairs of sequences $\binom{12}{2} = 66$

config	(10,1,1,0)	(9,1,1,1)	(6,3,2,1)	(4,3,3,2)	(3,3,3,3)
#(pmm)	21	30	48	53	54
π	0.318	0.455	0.727	0.803	0.818

Tajima test statistic

Under hypothesis of neutrality $\mathrm{Var}(\pi - \frac{S}{a_1}) = \frac{c_1\theta}{l} + c_2\theta^2$

where $c_1 = b_1 - \frac{1}{a_1}$, $c_2 = b_2 - \frac{n+2}{a_1 n} + \frac{a_2}{a_1^2}$

$$\boxed{D = \frac{\pi - S/a_1}{\sqrt{e_1 S + e_2 S(S-1/l)}}, \text{ where } e_1 = \frac{c_1}{a_1},\ e_2 = \frac{c_2}{a_1^2 + a_2}}$$

Null distribution of Tajima's D is tabulated by simulation

might be approximated by a Beta distribution

Significant $D > 0$ means almost equal p_A, p_G, p_T, p_C:

either balancing selection (overdominance) or

diversifying selection when rare alleles are favored

Significant $D < 0$ means very unequal p_A, p_G, p_T, p_C:

either selection against rare alleles or

recent bottleneck implying reduced genetic variation

4.10 Recombination and polymorphism

Fig 4.15 p184 (5.9 p182):
evolutionary benefit of recombination

Fig 9.5 p476 (5.10 p183):
low recombination rate $\rightarrow$ low polymorphism

Hitchhiking effect
advantageous mutation results in reduced
number of segregating sites in tightly linked region

Background selection
reduced diversity at a neutral locus
tightly surrounded by many loci of harmful mutations