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2. Mutation, migration and selection

2.1 mutation
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Evolutionary forces interfering in HWE
mutation and migration increase genetic variation
selection and RGD decrease genetic variation

2.1 Mutation

One locus two alleles model: A wildtype, a mutant
forward mutation rate μ per generation: $A \to a$
backward mutation rate ν: $a \to A$

Typically μ is about
$10^{-4} - 10^{-6}$ mutations per gene per generation

p_t = population frequency of allele A in generation t

Irreversible mutation

If $\nu = 0$, then pure loss of alleles A each generation
$p_t = p_{t-1}(1-\mu) = p_0(1-\mu)^t \approx p_0 e^{-\mu t}$
Fig 5.1, p. 165: $p_t \to 0$ under mutation pressure

$\Delta p = -p\mu$ incremental frequency $\Delta p = p_t - p_{t-1}$

Half-life of an allele

The number of generations

taking to halve the wildtype allele frequency

$t_{0.5} = \frac{\ln 2}{\mu} = \frac{0.693}{\mu}$ solves equation $p_t = 0.5 \cdot p_0$

If $\mu = 10^{-4}$, the half-life is $t_{0.5} = 6,930$ generations

if $\mu = 10^{-6}$, the half-life is $t_{0.5} = 693,000$ generations

Ex 1: mutation rate estimation

Fig 5.3, p. 167: infection resistance gene in $E.coli$

if the cumulative mutation rate μt is small, then

$p_t \approx p_0(1 - \mu t)$; if moreover $p_0 \approx 1$, then $q_t \approx q_0 + \mu t$

Ex 2: transposon deletion

D. mauritania, a site with transposon *mariner* insertion

spontaneous deletion at rate $\mu = 0.01$: $A \to a$

If, $D_0 = 1$, find t needed to reach $R_t = 0.05$:

assuming random mating $q_t = \sqrt{R_t} = 0.224$

linear approximation $q_t = 0.01 \cdot t$ gives $t = 23$

exact formula $q_t = 1 - (0.99)^t$ gives $t = 26$ generations

Reversible mutation

If $\mu > 0$ and $\nu > 0$, then

the allele A loss and gain interplay:

$p_t = p_{t-1}(1 - \mu) + q_{t-1}\nu = p_{t-1}(1 - \mu - \nu) + \nu$

$$\boxed{\Delta p = -p(\mu + \nu) + \nu}$$

Equlibrium frequency $\hat{p} = \frac{\nu}{\mu+\nu}$ solves $\Delta p = 0$

$p_t = \hat{p} + (p_0 - \hat{p})(1 - \mu - \nu)^t$

Fig 5.4, p. 169

$\mu = 10^{-4}$, $\nu = 10^{-5}$, $\hat{p} = 0.091$

Ex 3: intrachromosomal recombination

Salmonella bacterium:

switching between two forms of flagella

due to an intrachromosomal recombination

switching rates are high: $\mu = 8.6 \cdot 10^{-4}$, $\nu = 4.7 \cdot 10^{-3}$

Observed results for two Salmonella cultures

t	0	30	700
p_t	0	0.16	0.85

t	0	388	700
p_t	1	0.88	0.86

Expected frequencies

1: $p_t = 0.845(1 - (0.994)^t)$, $p_{30} = 0.13$, $p_{700} = 0.83$

2: $p_t = 0.845 + 0.155(0.994)^t$, $p_{388} = 0.86$, $p_{700} = 0.85$

Expected equlibrium frequency $\hat{p} = 0.845$

2.2 Migration

> Immigration rate m into a subpopulation
> = the subpopulation proportion quota for
> new immigrants arriving each generation

If $m = 0.05$, then 5% of the subpopulation individuals have immigrated during the last generation period

One-way migration

Fig 5.14, p. 190: mainland to island migration

mainland frequencies are fixed p^*, q^*

Island frequencies change

$p_t = (1-m)p_{t-1} + mp^*$

$= \{\text{non-imm. with } A\} + \{\text{immigrants with } A\}$

$$\boxed{\Delta p = -pm + mp^*}$$

Convergence to the mainland frequency

$p_t = p^* + (1-m)^t(p_0 - p^*)$ so that $p_t \to p^*$

Ex 4: migration rate estimation

White (Georgia) = mainland, blacks (Georgia) = island

gene	M	S	Fy^a	Jk^a	Js^a	β^s
blacks (W.Africa)	.474	.172	.000	.693	.117	.090
blacks (Georgia)	.484	.157	.045	.743	.123	.043
whites (Georgia)	.507	.279	.422	.536	.002	.000
$\hat{m}$ per generation	.035	-.013	.011	-.028	-.005	.071

MN data: $t = 10$, $p_0 = 0.474$, $p_t = 0.484$

$p^* = 0.507$, $(1-m)^{10} = \frac{0.507-0.484}{0.507-0.474}$, $m = 0.035$

Variation in $\hat{m}$ is mostly due to

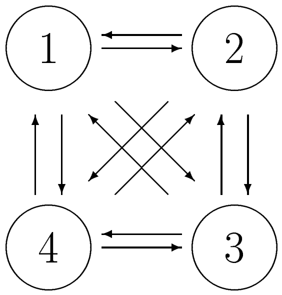
uncertainty of the origin of black Americans and

variablility of gene frequencies across West Africa

Most reliable is Duffy blood groups

since allele Fy^a is absent in W. Africa

Island model of migration



$n = 4$

p_t = allele A frequency
in a certain subpopulation

$\bar{p}$ = allele A frequency
in the metatpopulation
constant over time

The same dynamics as with mainland to island migration

$p_t = (1 - m')p_{t-1} + m'\bar{p}$, where $m' = m \cdot \frac{n}{n-1}$

Gene flow eliminates differences among subpopulations

$p_t = \bar{p} + (1 - m')^t(p_0 - \bar{p})$ so that $p_t \to \bar{p}$

Fig 5.16, p.194

evolution similar to reversible mutation

difference in rates: $m \gg \mu$

2.3 Selection

Haploid selection

Absolute fitnesses W_A, W_a

= offspring numbers for two bacteria strains A and a

Fig 6.1, p. 213: two potential growth rates

Carrying capacity of the habitat is limited

focus on the allele competition within a population

relative fitnesses $w_A : w_a = W_A : W_a$

$\boxed{w_A = 1,\ w_a = 1 - s,\ \text{haploid selection coefficient } s}$

Two potential growth rates

$X_t = X_{t-1} W_A$ number of alleles A in generation t

$Y_t = Y_{t-1} W_a$ number of alleles a in generation t

Allele frequencies

$p_t = \frac{X_t}{X_t + Y_t}$, $q_t = \frac{Y_t}{X_t + Y_t}$ odds ratio $\frac{p_t}{q_t} = \frac{X_t}{Y_t}$

$\frac{p_t}{q_t} = \frac{p_{t-1}}{q_{t-1}}(1-s)^{-1} = \frac{p_0}{q_0}(1-s)^{-t}$

$p_t = \frac{p_0}{p_0 + q_0(1-s)^t}$

$$\boxed{\text{Haploid selection } \Delta p = spq, \text{ if } s \approx 0}$$

Fixation of the favored allele

$p_t \to 1$ if $s > 0$ and $p_t \to 0$ if $s < 0$ as $t \to \infty$

Estimate s using linear regression

$\ln(\frac{p_t}{q_t}) = \ln(\frac{p_0}{q_0}) - t\ln(1-s)$ or

$\ln(\frac{p_t}{q_t}) = \ln(\frac{p_0}{q_0}) + st$, if $s \approx 0$

Ex 5: selection coefficient estimation

Enzyme 6PGD in E.coli:

involved in metabolism of gluconate not ribose

Two alleles $RM43A$ (p) and $RM77C$ (q) code for two allozymes of 6PGD in natural populations

growth medium	p_0	p_{35}	$\ln(\frac{p_{35}}{q_{35}}) - \ln(\frac{p_0}{q_0})$	$\hat{s}$
gluconate	0.455	0.898	2.36	0.065
ribose (control)	0.594	0.587	−0.029	−0.0008

Allele $RM43A$ is better fit to the pure gluconate media

control result is not significant

Diploid selection

genotype	AA	Aa	aa
relative fitness	w_{AA}	w_{Aa}	w_{aa}

Three types of the diploid selection

directional selection:

$w_{AA} > w_{Aa} > w_{aa}$ or $w_{AA} < w_{Aa} < w_{aa}$

overdominance: $w_{Aa} > w_{AA}$ and $w_{Aa} > w_{aa}$

stabilizing selection against homozygotes

underdominance: $w_{Aa} < w_{AA}$ and $w_{Aa} < w_{aa}$

disruptional selection against heterozygotes

Biological components of human fitness

survival to maturity, mating success, and fertility

> Two stage life history model
> adults → random mating → newborns → adults
> fitness is proportional to P(Survival to maturity)

Genotype frequencies

in adults (D, H, R) and newborns (d, h, r)

From newborns to adults survival to maturity

$D : H : R = dw_{AA} : hw_{Aa} : rw_{aa}$

From adults to next generation newborns

random mating $d_{\text{next}} = p^2$, $h_{\text{next}} = 2pq$, $r_{\text{next}} = q^2$

Two relations combined

$D_{\text{next}} = p^2 \frac{w_{AA}}{\bar{w}}$, $H_{\text{next}} = 2pq \frac{w_{Aa}}{\bar{w}}$, $R_{\text{next}} = q^2 \frac{w_{aa}}{\bar{w}}$

Average fitness $\bar{w} = p^2 w_{AA} + 2pq w_{Aa} + q^2 w_{aa}$

is close to one if selection is weak

$$\boxed{\Delta p = \frac{pq}{\bar{w}}(p(w_{AA} - w_{Aa}) + q(w_{Aa} - w_{aa}))}$$

2.4 Directional diploid selection

Directional selection favoring allele A

$w_{AA} = 1$, $w_{Aa} = 1 - hs$, $w_{aa} = 1 - s$

diploid selection coefficient $s > 0$

Degree of dominance or heterozygous effect h

$h = 0$: harmful allele a is recessive in fitness

$h = 1$: harmful allele a is dominant in fitness

$0 < h < 1$: incomplete dominance

$h = 0.5$: additive selection

$$\boxed{\Delta p = spq(ph + q(1 - h)), \text{ if } s \approx 0}$$

Allele fixation dynamics

Directional selection eventually fixes the favored allele

Fig. 6.3, p. 225: three different curves of allele fixation

$h = 0$, $\Delta p = spq^2$ $\quad\boxed{\ln(\frac{p_t}{q_t}) + \frac{1}{q_t} = \ln(\frac{p_0}{q_0}) + \frac{1}{q_0} + st}$

$h = 0.5$, $\Delta p = \frac{s}{2}pq$ $\quad\boxed{\ln(\frac{p_t}{q_t}) = \ln(\frac{p_0}{q_0}) + \frac{st}{2}}$

$h = 1$, $\Delta p = sp^2q$ $\quad\boxed{\ln(\frac{p_t}{q_t}) - \frac{1}{p_t} = \ln(\frac{p_0}{q_0}) - \frac{1}{p_0} + st}$

Rare diseases: natural selection eliminates

dominant diseases more effectively than recessive ones

Additive selection is similar to haploid selection
with haploid selection coefficient $\frac{s}{2}$

Ex 6: industrial melanism

melanic allele A, wildtype allele a

Fig 3.4, p. 86: if no lichens, then A is a favored dominant

melanic moth frequency: 1% in 1848, 95% in 1898

1 generation = 1 year

Selection coefficient estimation

$p_0^2 + 2p_0q_0 \approx 0.01$, $p_0 \approx 0.005$ $\qquad \ln(\frac{p_0}{q_0}) + \frac{1}{q_0} \approx -4.29$

$1 - q_{50}^2 \approx 0.95$, $p_{50} \approx 0.776$ $\qquad \ln(\frac{p_{50}}{q_{50}}) + \frac{1}{q_{50}} \approx 5.72$

Solve equation

$5.72 = -4.29 + 50s$ to find $s = 0.20$

Ex 7: pesticide resistance

US in 1940's 7% crops lost to insects

new environment: use of chemical pesticides

US in 1985 13% crops lost to insects

natural selection: 400 pest species evolved resistance

If p_0 and p_t are small, then

$h = 0$: $\ln(p_t) + 1 = \ln(p_0) + 1 + st$ and $t = \frac{1}{s}\ln(\frac{p_t}{p_0})$

$h = 0.5$: $\ln(p_t) = \ln(p_0) + \frac{st}{2}$ and $t = \frac{2}{s}\ln(\frac{p_t}{p_0})$

$s = 0.5$	$p_t/p_0 = 10^2$	$p_t/p_0 = 10^4$	$p_t/p_0 = 10^7$
$h = 0$	$t = 9.2$	$t = 18.4$	$t = 32$
$h = 0.5$	$t = 18.4$	$t = 36.8$	$t = 64$

2.5 Overdominance

Overdominance favors heterozygotes

$w_{Aa} = 1$, $w_{AA} = 1 - s_1$, $w_{aa} = 1 - s_2$

$\Delta p = \frac{pq}{\bar{w}}(qs_2 - ps_1)$, $\bar{w} = 1 - p^2 s_1 - q^2 s_2$

$$\boxed{\text{Equlibrium frequencies } \hat{p} = \frac{s_2}{s_1+s_2},\ \hat{q} = \frac{s_1}{s_1+s_2}}$$

Fig 6.4, p.229: equilibrium frequency $\hat{p}$ maximizes $\bar{w}$

if $p = \hat{p}$, then $\frac{d\bar{w}}{dp} = 2\hat{q}s_2 - 2\hat{p}s_1 = 0$, $\bar{w}_{\max} = 1 - \frac{s_1 s_2}{s_1+s_2}$

$$\boxed{\text{Segregational load } L = 1 - \bar{w}_{\max} = \frac{s_1 s_2}{s_1+s_2}}$$

Due to gene segregation $\bar{w}$ is always less than theoretical maximal genotype fitness $w_{Aa} = 1$

Equlibrium genotype frequencies

$D = \frac{1-s_1}{\bar{w}} \cdot \hat{p}^2$, $H = \frac{2}{\bar{w}} \cdot \hat{p}\hat{q}$, $R = \frac{1-s_2}{\bar{w}} \cdot \hat{q}^2$

excess of heterozygotes $F = 1 - \frac{1}{\bar{w}} = -\frac{s_1 s_2}{s_1+s_2-s_1 s_2}$

Ex 8: sickle-cell anemia

Fig 6.5, p. 231: regions in Africa with incidences of malaria and sickle-cell anemia

Gene coding for β chain of hemoglobin

A = normal allele, S = anemia allele

Relative fitnesses in Africa regions with malaria

$w_{AS} = 1$, $w_{AA} = 0.9$ (malaria), $w_{SS} = 0.2$ (anemia)

Selection coefficients and equilibrium frequencies

$s_1 = 0.1$, $s_2 = 0.8$, $\hat{p} = \frac{8}{9} = 0.89$, $\hat{q} = \frac{1}{9} = 0.11$

$\hat{q} = 0.11$ is close to the average q across West Africa
considerable variation in q among local populations

Ex 9: multiple alleles selection

West Africa: S is prevalent, it is found a rare allele C

genotype	AA	AS	SS	AC	SC	CC
premalarial environment	1.0	1.0	0.2	1.0	0.7	1.0
malarial environment w	0.9	1.0	0.2	0.9	0.7	1.3

Historical stable equilibrium $A : S = 8 : 1$, $\bar{w} = 0.911$
genotype ratio for new allele $AC : SC : CC = 8 : 1 : 0$
marginal $w_C = 0.9 \cdot \frac{8}{9} + 0.7 \cdot \frac{1}{9} = 0.878$ less than $\bar{w}$
Fig 6.11, p. 252: fixation of C starts from $p_C = 0.073$

Ex 10: rat control in WWII

Warfarin environment: a blood anticoagulant
two alleles $S =$ normal, $R =$ resistant to warfarin
Relative fitnesses in two environments
no warfarin: $w_{SS} = 1$, $w_{SR} = 0.77$, $w_{RR} = 0.46$
warfarin: $w_{SS} = 0.68$, $w_{SR} = 1$, $w_{RR} = 0.37$
Equlibrium warfarin frequency $\hat{q} = \frac{0.32}{0.32+0.63} = 0.34$
after stopping with warfarin how many generations
it takes to go from $q_0 = \hat{q}$ down to $q_t = 0.01$?
Additive selection case
$1 : 0.77 : 0.46 \approx 1 : 0.75 : 0.50$ implying $s = h = 0.5$
$\ln(\frac{0.99}{0.01}) = \ln(\frac{0.66}{0.34}) + \frac{t}{4}$, $t = 16$ generations

2.6 Other types of selection

Underdominance

Heterozygote inferiority: $w_{AA} > w_{Aa}$ and $w_{aa} > w_{Aa}$

$w_{Aa} = 1$, $w_{AA} = 1 + s_1$, $w_{aa} = 1 + s_2$

$$\boxed{\Delta p = \frac{pq}{\bar{w}}(ps_1 - qs_2),\ \bar{w} = 1 + p^2 s_1 + q^2 s_2}$$

Fig 6.7, p. 235: three equilibria

two locally stable equilibria $\hat{p} = 0$, $\hat{p} = 1$

one unstable equilibrium $\hat{p} = \frac{s_2}{s_1 + s_2}$

Ex 11: disruptive selection

North American lacewings (insects): green or brown

two extreme colors provide camouflage in two different niches, but intermediate color offers no protection

This type of selection maintains population diversity

it might even cause one species to evolve into two

Frequency-dependent selection

Genotype fitness decreases with its frequency

$w_{AA} = 1 - c \cdot p^2$, $w_{Aa} = 1 - 2c \cdot p \cdot q$, $w_{aa} = 1 - c \cdot q^2$

c is a positive constant of proportionality

$$\boxed{\Delta p = \frac{c}{\bar{w}} pq(q - p)(p^2 - pq + q^2)}$$

Stable equilibrium $\hat{p} = \hat{q} = 0.5$

despite heterozygote inferiority in the equilibrium state

$w_{AA} = w_{aa} = 1 - \frac{c}{4}$, $w_{Aa} = 1 - \frac{c}{2}$

2.7 Mutation-selection balance

Directional selection favoring allele A

increases p $\Delta p = spq[ph + q(1-h)]$

Irreversible harmful recurrent mutation of rate μ

decreases p $\Delta p = -p\mu$

Combined effect $\Delta p = spq[ph + q(1-h)] - p\mu$

$$\boxed{\text{Equilibrium equation:} \quad pqh + q^2(1-h) = \tfrac{\mu}{s}}$$

Equlibrium frequencies of the harmful allele

$$\boxed{\hat{q} = \sqrt{\tfrac{\mu}{s}}, \text{ if } h = 0} \qquad \boxed{\hat{q} = \tfrac{\mu}{hs}, \text{ if } 0 < h \leq 1,\ p \approx 1}$$

Typically $\mu = 10^{-5}$ to 10^{-6} while $s = 10^{-1}$ to 10^{-2}

$h = 1$ (dominant disease): $\hat{q} = 10^{-3}$ to 10^{-5}

$h = 0$ (recessive disease): $\hat{q} = 3 \cdot 10^{-2}$ to $3 \cdot 10^{-3}$

Fig 6.8, p. 238: let $\mu = 5 \cdot 10^{-6}$ and $s = 1$

$\hat{q} = \sqrt{\mu} = 0.0022$ if $h = 0$ compare with

$\hat{q} = \frac{\mu}{h} = 0.0002$ if $h = 0.025$

Ex 12: Huntington disease

Severe inherited dominant disorder: degeneration of the neuromuscular system after age 35

Michigan sample frequency $\hat{q} = 5 \cdot 10^{-5}$

$w_{AA} = 1$, $w_{Aa} = 0.81$ due to late onset, $w_{aa} = 0$

Estimation of mutation rates in humans

$\hat{\mu} = \hat{q}hs \approx 10^{-5}$ mutations per gene per generation

Ex 13: cystic fibrosis

Two possible explanations of the polymorphism $\hat{q} = 0.02$

mutation-selection balance $w_{AA} = w_{Aa} = 1$, $w_{aa} = 0$

overdominance $w_{AA} < w_{Aa} = 1$, $w_{aa} = 0$

Mutation-selection balance $s = 1$, $h = 0$

$\mu = \hat{q}^2 = 0.0004$ unrealistically high mutation rate

Overdominance $\hat{q} = \frac{s_1}{1+s_1}$, $s_1 = 0.02$

heterozygotes are resistant against typhoid fever

2% advantage in heterozygous fitness

Mutation load

Mutation load = reduction in average fitness

caused by recurrent harmful mutation

$$\boxed{\text{Mutation load } L = 1 - \bar{w} \text{ for } 0 \leq h \leq 1,\ s > 0}$$

Haldane-Muller principle

1. if $h = 0$, then $L = \mu$ is independent of s
2. if $h > 0$, then $L = 2\mu$ is independent of s and h

The effect of deleterious mutation on the mean population fitness depends only on mutation rate and not on severity of mutations

Milder mutations are present at higher frequency whereas more severe mutations have lower frequency

Segregation distortion

Non-Mendelian segregation

heterozygotes Aa produce a skewed ratio $k : (1-k)$ of A-gametes and a-gametes

Segregation distortion without selection

leads to fixation of allele A if $k > 0.5$

Assuming random mating

$p_t = p_{t-1}^2 + k2p_{t-1}q_{t-1}$, $q_t = q_{t-1}^2 + (1-k)2p_{t-1}q_{t-1}$

$\Delta p = pq(2k-1)$ like add. selection with $\frac{s}{2} = 2k-1$

Ex 14: segregation distortion chromosome

SD chromosome in $D.melanogaster$

$A =$ SD chromosome, $a =$ wildtype chromosome

segregation ratio $= 0.75 : 0.25$

Selection against SD chromosome

AA is lethal, $w_{AA} = 0$, $w_{Aa} = w_{aa} = 1$

Combined effect of segregation distortion and selection

$p_t = 1.5p_{t-1}q_{t-1}\frac{1}{\bar{w}}$

$q_t = q_{t-1}^2\frac{1}{\bar{w}} + 0.5p_{t-1}q_{t-1}\frac{1}{\bar{w}}$

$\bar{w} = 2pq + q^2 = q(1+p)$

Incremental and equilibrium frequencies

$\Delta p = \frac{p(0.5-p)}{1+p}$ and $\hat{p} = 0.5$