Multilocus Evolution II : the successive mutations regime

Last time, we showed that generalizing our serial dilution model to a genome w/ $L>1$ sites leads to a system of coupled stochastic differential equations for each genotype frequency, $f(\vec{g})$, which has the general form:

$$\frac{df(\vec{g},t)}{dt} = \underbrace{\left[X(\vec{g}) - \bar{X}(t)\right] f(\vec{g})}_{\text{natural selection}} + \underbrace{\sum_{\vec{g}'} \left[M_{\vec{g}'\to\vec{g}} f(\vec{g}') - M_{\vec{g}\to\vec{g}'} f(\vec{g})\right]}_{\text{mutation (matrix of rates, } M)}$$

$$+ \underbrace{\rho\left[-f(\vec{g}) + \sum_{\vec{g}_F,\vec{g}_D} T_{\vec{g}_F,\vec{g}_D\to\vec{g}}\, f(\vec{g}_F) f(\vec{g}_D)\right]}_{\text{recombination (tensor of rates, } T_{\vec{g}_F,\vec{g}_D\to\vec{g}})}$$

$$+ \underbrace{\left[\sqrt{\frac{f(\vec{g})}{Ne}}\,\eta(\vec{g},t) - f(\vec{g}) \sum_{\vec{g}'} \sqrt{\frac{f(\vec{g}')}{Ne}}\,\eta(\vec{g}',t)\right]}_{\text{genetic drift}}$$

In contrast to single-locus case ($L=1$), there is no closed form solution of this model — even for simple things like equilibrium distributions or fixation probabilities — for the general multi-locus case, even for L as small as $L=2$!

(similar to multi-particle Schrödinger eq. in Quantum Mechanics)

$\Rightarrow$ instead, the <u>only</u> way we can make progress in understanding the $L>1$ case is by considering behavior in different <u>asymptotic limits</u>. (this is why we spent so much time discussing them earlier in the course... they are our only hope now!)

$\Rightarrow$ the next several lectures will focus on a few different limits where the behavior is reasonably well understood, and when we expect them to apply. (e.g. to data)

$\Rightarrow$ [illegible] a lot is already known, but it is far from a complete picture, and a lot of theoretical work is still being done to understand consequences of this basic model.

Q: Given parameters (knobs), $L, N, X(\vec{g}), M, e, T$,

what are some limits where we might be able to understand behavior of these equations?

(1) Obvious answer: $L=1$. that's cheating! need $L \geq 2$

(but basic idea is a good one... when can we reduce system to something that looks like $L=1$ → then can use what we already know...)

(2) In physics, already primed to take $N \to \infty$ limit since at least then we expect noise to go away...

⇒ is this a good approximation here? for $L=2$ maybe... (@ long times)

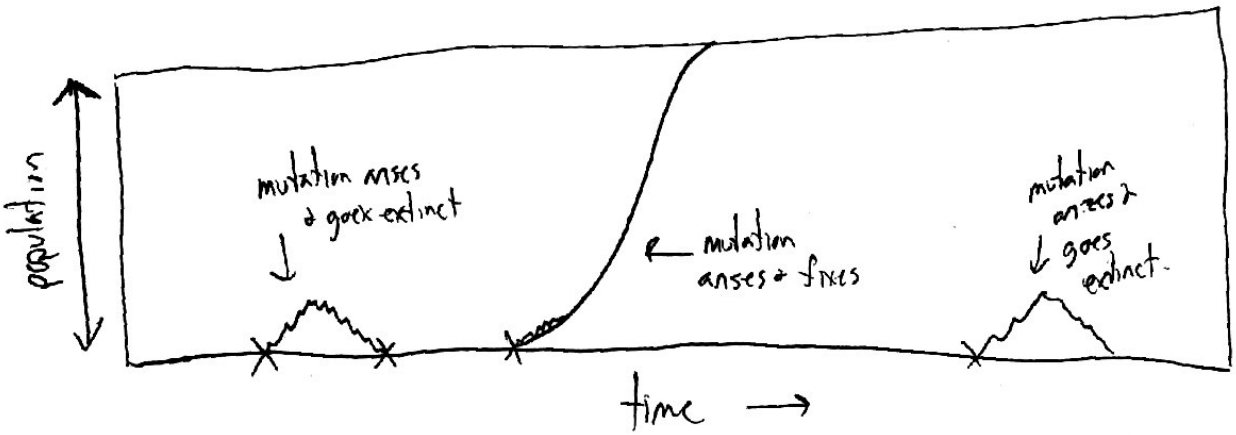
⇒ but for $L \gg 1$ ⇒ 2^L is eventually $\gg N$, even for enormous N, e.g. $L \sim 1000$ (1 gene) - $2^L = 10^{300}$!

⇒ always will be some genotypes that will be unoccupied, and mutations into these genotypes will be strongly influenced by noise... so large N doesn't help here.

(3) Successive mutations regime

what if mutation rates are so low that only 0, or 1 mutations are present in population @ any given time.

↳ i.e., mutation occurs and then either fixes or goes extinct before next mutation occurs.



then @ any given time, only 2 genotypes present in population:

"current wildtype", $\vec{g}_0 = (1,0,1,1,0,0,0)$ → site ℓ.

single mutation away from WT e.g. @ site ℓ. $\vec{g}_m = (1,0,1,1,0,\underline{1},0)$

what can recombination do?

no change!

$\vec{g}_0 = (1,0,1,1,0,0,0)$ → creates and/or $\vec{g}_m$

$\vec{g}_m = (1,0,1,|0,1,0)$ (or vice versa)

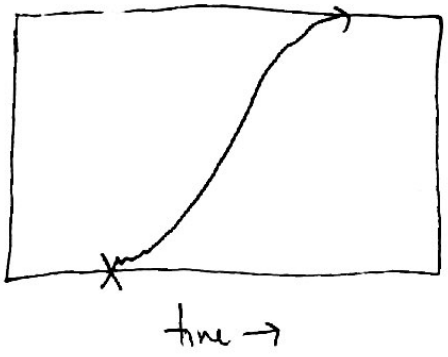
⇒ recombination drops out.

then right after a mutation occurs, we're left w/ something that looks like a single locus model

$$\text{w/ } s \equiv X(\vec{g}_m) - X(\vec{g}_0)$$

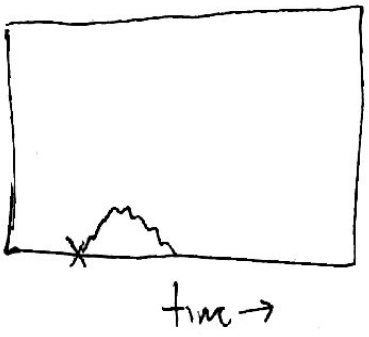
$\Rightarrow$ in this case, we know exactly what happens:

(i) w/ probability $p_{fix}(s) = \frac{2s}{1-e^{-2N_e s}}$, the mutation takes over ("sweeps")



and $\vec{g}_0 \rightarrow \vec{g}_m$; process repeats.

(ii) otherwise, mutation goes extinct and $\vec{g}_0$ stays put.



to account for all the [redacted] ways that this mutation could have occurred, [redacted] let's assume for simplicity that $\mu_\ell = \nu_\ell$ [redacted] (forward & back mutations occur @ same rate)

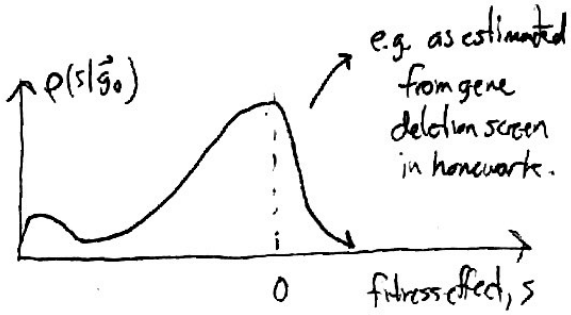
$\Rightarrow$ total mutation rate for all genotypes is $U \equiv \sum_{\ell=1}^{L} \mu_\ell$

the fitness effect of each mutation is given by

$$s_\ell = X\left(\vec{g}_0 + \begin{matrix}\text{mutation} \\ @\ \text{site} \\ \ell\end{matrix}\right) - X(\vec{g}_0)$$

and entire collection $\{(\nu_\ell, s_\ell)\}_{\ell=1}^{L}$ is sometimes summarized as a distribution of fitness effects (DFE)

$$\rho(s|\vec{g}_0) \equiv \frac{1}{U}\sum_{\ell=1}^{L} \nu_\ell \delta(s - s_\ell)$$



↑ technically, depends on current wildtype

↳ probability of drawing a mutation w/ effect, s.

$\Rightarrow$ mutations w/ fitness effect s are produced as a Poisson process @ rate $NU\rho(s|\vec{g})$. If each one is successful w/ probability $p_{fix}(s)$, then occurrence of successful* mutations is Poisson process w/ total rate

$$R \equiv \int NU\rho(s|\vec{g}_0)\, p_{fix}(s)\, ds.$$

(*technically, "mutations destined to be successful")

the time until the next successful mutation is born is

$$T_{est} \sim \text{Exponential}\left(\frac{1}{R}\right)$$

$\Rightarrow$ when a successful mutation occurs, the probability it was site ℓ is given by

$$p_\ell = \frac{N\mu_\ell P_{fix}(s_\ell)}{R} = \frac{\mu_\ell P_{fix}(s_\ell)}{\sum_\ell \mu_\ell P_{fix}(s_\ell)}$$

$\Rightarrow$ alternatively, probability it has fitness effect $s \pm ds$ is

$$\rho_{fix}(s) \propto P_{fix}(s)\rho(s)$$

$\Rightarrow$ so we randomly select a site to fix, take $\vec{g}_0 \to \vec{g}_M$, and repeat!

when is this a good approximation?

$\Rightarrow$ need $T_{est} \sim \frac{1}{R} \gg T_{fix} \sim \begin{cases} N & \text{if } |s| \ll \frac{1}{N} \\ \frac{1}{s}\log(Ns) & \text{if } |s| \gg \frac{1}{N} \end{cases}$

thus, we see that T_{fix} is bounded from above by N

$\Rightarrow$ if we have $\frac{1}{R} \gg N \gtrsim T_{fix}$, or $\boxed{\int NU N p_{fix}(s) \rho(s) ds \ll 1}$

$\Rightarrow$ then successive mutations picture will apply.

$\Rightarrow$ known as "weak mutation limit" (better "rare mutation limit")
Since we can always find a U low enough that the WM condition applies. How low? Different behavior depending on s's that dominate $p_{fix}(s)\rho(s)$ integral.

(i) if $p_{fix}(s)\rho(s)$ dominated by neutral mutations ($s \approx 0$)

then $\int NU N p_{fix}(s)\rho(s) ds \approx NU_0$ (where U_0 is neutral mutation rate, typically $\Theta(U)$.)

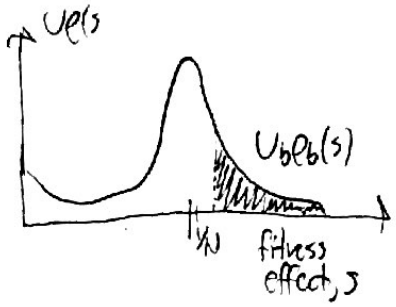
$\Rightarrow$ weak mutation limit when $NU_0 \ll 1$.

(ii) if $p_{fix}(s)\rho(s)$ dominated by $s \gg \frac{1}{N}$, then

$\int NU N p_{fix}(s)\rho(s) ds \approx$ [illegible] $\int 2NU_b N s \rho_b(s) ds$

where $U_b \rho_b(s)$ is the strongly beneficial portion of the original DFE ($U_b \ll U$)

where $p_{fix}(s) \approx 2s$.



$\Rightarrow$ in this case, weak mutation limit applies when

$$N U_b \bar{N s_b} \ll 1 \Rightarrow N U_b \ll 1/\bar{N s_b} \quad (\bar{s_b} \equiv \int s \rho_b(s) ds)$$

(very small)

$\Rightarrow$ this condition is maybe too stringent, since $T_{fix} \sim N$ only for neutral mutations. The mutations that dominate R have $T_{fix} \sim \frac{1}{\bar{s_b}} \log(N \bar{s_b}) \ll N$. If we only care about these, then the successive mutations picture applies when

$$\frac{1}{\bar{s_b}} \log(N \bar{s_b}) \ll \frac{1}{2 N U_b \bar{s_b}} \Rightarrow \boxed{N U_b \ll 1/\log(N \bar{s_b}) \lesssim 1}$$

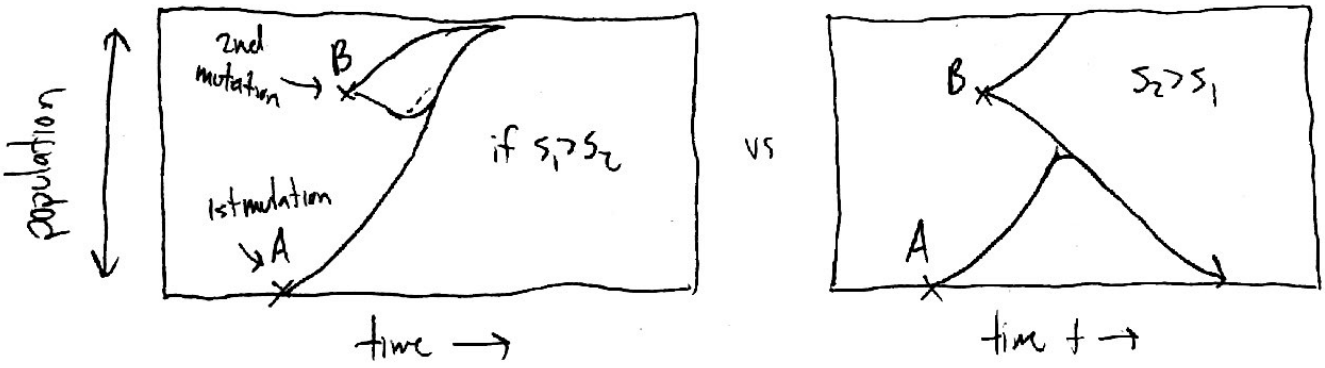
$\Rightarrow$ this is known as the strong-selection weak-mutation (SSWM) regime, because only strongly beneficial mutations have a chance of fixing.

What does this condition look like for some real parameter values?

$\Rightarrow$ $U_b s_b(s)$ is hardest to constrain; from Problem 4 last week, you estimated $U_b \sim 5\times10^{-6}$, $s_b \sim 2e^{-02}$ just from L.O.F. mutations (probably a lower bound on U_b...)

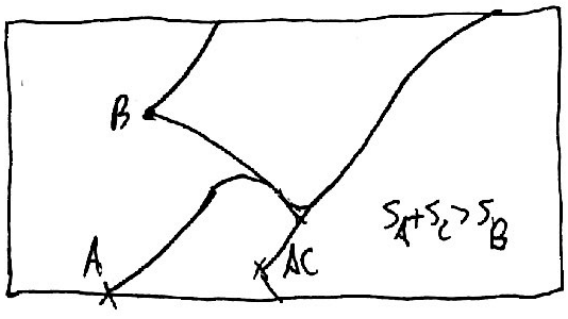
$\Rightarrow$ if $N = 10^5$, then $2NU_b \log(N\bar{s}_b) \approx 3$, so already outside region of validity.

$\Rightarrow$ what does behavior look like instead?



$\Rightarrow$ either way, a successful mutation has been wasted. known as "clonal interference".

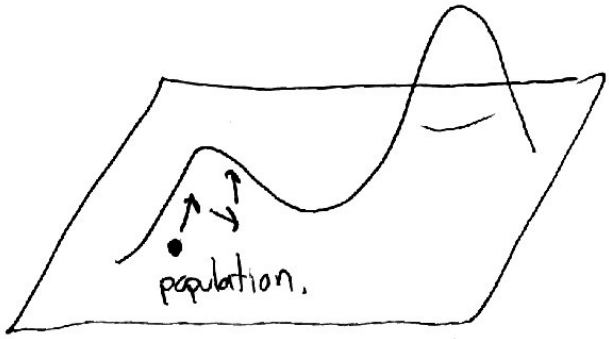
can get arbitrarily complicated when more mutations involved:



However, for small enough N, the SSWM limit will apply.

⇒ in this case, we have a well-defined limit for thinking about evolution on a long genome:

⇒ the population is represented by a single point in genotype space, and it undergoes a biased random walk to higher fitness values, as dictated by the DFE

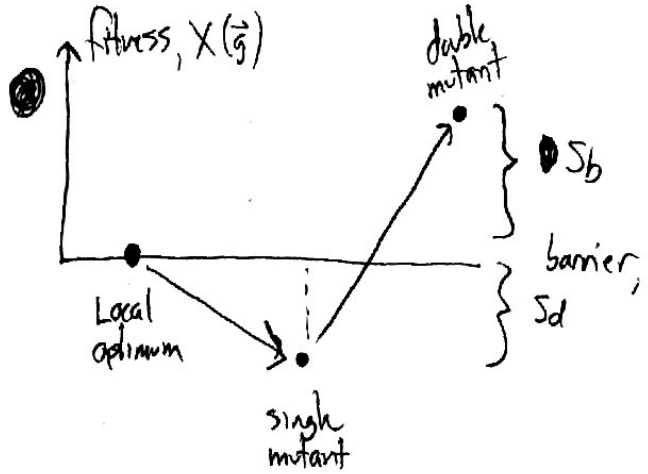


⇒ this is the classic picture of evolution as hill-climbing that many of us have in our heads. Here we see it emerges only in a very simple limit when we ignore the complexities of what's going on w/in a population.

⇒ in this hill-climbing picture, all of the interesting behavior boils down to epistasis: how long will the population wander before it gets trapped in a local fitness peak. how many peaks are there? ("ruggedness")

of course, when the population *does* reach a local optimum, the SSWM limit will not apply in its original sense, because $U_b e_b(s) = 0$!

To escape, population must cross a "fitness valley":



$\Rightarrow$ How fast does this happen?

$\Rightarrow$ when $Ns_d \gg 1$, very low rate of fixing deleterious intermediate

($N p_{fix} \sim N s_d e^{-Ns_d}$)

$\Rightarrow$ however, each deleterious mutation has *some chance* of producing successful mutation before it dies off.

$\Rightarrow$ can model this w/ 2-locus branching process

(since all interesting behavior will happen when $f_1, f_2 \ll 1$)

$$\frac{df_1}{dt} = -s_d f_1 - \mu_{1\to 2} f_1 + \sqrt{\frac{f_1}{N}}\eta_1(t) \qquad f_1(0) = \frac{1}{N},\ f_2(0) = 0$$

$$\frac{df_2}{dt} = s_b f_2 + \mu_{1\to 2} f_1 + \sqrt{\frac{f_2}{N}}\eta_2(t)$$

↳ what happens @ long times?

this is similar to our single locus B.P. model, except that now f_2 is coupled to random input νf_1.

$\Rightarrow$ as before, can solve by turning to generating function, this time for 2 variables: $H(z_1, z_2, t) = \left\langle e^{-z_1 f_1(t) - z_2 f_2(t)} \right\rangle$

$\Rightarrow$ @ time $t=0$: $H(z_1, z_2, 0) = e^{-z_1 \frac{1}{N}} \approx 1 - \frac{1}{N} z_1$

$\Rightarrow$ @ long times, $H(z_1, z_2, t) \to e^{-0} \cdot P_{ext} + e^{-\infty} \cdot (1 - P_{ext})$

↳ beneficial mutant takes off.

$\Rightarrow$ using same SDE manipulations as before, can show that generating function satisfies PDE: (excercise for reader)

$$\frac{\partial H}{\partial t} = \left[-s_1 z_1 + N_2 z_2 - \frac{z_1^2}{2N} \right] \frac{\partial H}{\partial z_1} + \left[s_2 z_2 - \frac{z_2^2}{2N} \right] \frac{\partial H}{\partial z_2}$$

$\Rightarrow$ can solve completely w/ method of characteristics (excercise)

but can also look for z_1^*, z_2^* s.t. $\frac{\partial H}{\partial t} = 0$.

$\Rightarrow$ from above: $z_1^* = N p_{fix}$ ← probability of generating successful double mutant before going extinct.

system of quadratic equations:

$$s_b z_2^* - \frac{z_2^{*2}}{2N} = 0$$

$$-s_d z_1^* + 0/N z_2^* - \frac{z_1^{*2}}{2N} = 0$$

$\Rightarrow$ note: same trick works for arbitrary # of types coupled together!

$\Rightarrow$ in this case, can easily reduce to 1 quadratic:

$$z_1^{*2} + 2N s_d z_1^* - 2N s_b N/N = 0$$

$$\Rightarrow P_{fix} \approx \begin{cases} \frac{N}{s_d} \cdot 2s_b & \frac{s_b N}{s_d^2} \ll 1 \\ \sqrt{2\mu s_b} & \text{if } \frac{s_b N}{s_d^2} \gg 1 \end{cases}$$

$\Rightarrow$ how can we understand this result?

$\Rightarrow$ for each double mutant produced, probability of establishment is $\sim s_b$.

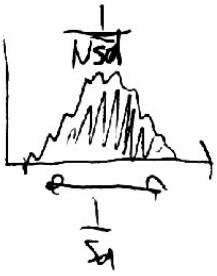
probability of producing double mutant before going extinct is

$$P_{fix} \approx \left\langle 1 - e^{-\int_0^\infty N\mu f_1(t) \cdot s_b \cdot dt} \right\rangle_{f_1(t)}$$

← i.e., depends on integral of random function.

we saw before that $f_1(t)$ can survive for as long as $\sim 1/s_d$ generations and grow to size $\sim$ ~~$1/Ns_d$~~ w/ probability s_d.

$\Rightarrow$ when this happens, $\int f_1(t)dt \sim \frac{1}{Ns_d} \cdot \frac{1}{s_d}$



height ($f_{1,max}$) width (dt)

$\Rightarrow \int_0^\infty N\mu f_1 \cdot s_b dt \approx \frac{Ns_b}{s_d^2}$ $\Rightarrow$ if $\ll 1$, then can taylor expand exponential, and obtain:

$$p_{fix} \approx \left\langle 1 - e^{-\int_0^\infty N\mu f_1(t) s_b dt} \right\rangle \approx \left\langle \int_0^\infty N\mu f_1(t) \cdot s_b dt \right\rangle$$

$$= \int_0^\infty N\mu s_b \langle f_1(t) \rangle dt \approx \frac{N}{s_d} s_b \quad \checkmark.$$

$\langle f_1(t) \rangle \to \frac{1}{N} e^{-s_d t}$

$\Rightarrow$ on the other hand, if $\frac{Ns_b}{s_d^2} \gg 1$, then by time $f_1(t)$ reaches ~~$\sim 1/Ns_d$~~, it is already very likely to have produced several successful double mutants. Instead, probability is dominated

by lineages that just barely make it to $\int N\mu f_1(t) s_1 dt \sim 1$
& have a high probability of producing successful double mutants.

$\Rightarrow$ recall that for $f_1 \ll \frac{1}{Ns_d}$, lineage is essentially neutral:

w/ prob $1/T$ it will survive for $\sim T$ generations & reach size $\sim T/N$. $\Rightarrow$ $\int_0^\infty f_1(t)dt \sim \frac{T^2}{N}$ w/ prob $1/T$.

$\Rightarrow$ $\int_0^\infty N\mu f_1(t) s_b dt \approx N\mu \frac{T^2}{N} s_b \sim 1$ when $T \sim \frac{1}{\sqrt{\mu s_b}}$.

$\Rightarrow$ $P_{est} \sim (1-e^{-1})\frac{1}{T} \approx \sqrt{\mu s_b}$ ✓.

$\Rightarrow$ total rate of valley crossing (summing over many downhill mutations)

is then $N\mu_{0\to1} P_{fix} \sim \begin{cases} \frac{N\mu_{0\to1}\mu_{1\to2} s_b}{s_d} & \text{if } \frac{\mu_{1\to2} s_b}{s_d^2} \ll 1 \\ N\mu_{0\to1}\sqrt{\mu_{1\to2} s_b} & \text{else} \end{cases}$ → happens when s_b is large!