Working w/ Diffusion limit

That's great for formalism... what can we actually <u>do</u> w/ SDEs/Langevin eqs./ Fokker-Planck eqs?

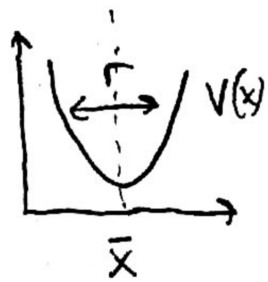
$\Rightarrow$ Gaussian random walk was trivially solvable... other choices for $\mu(x), \sigma^2(x)$ not so easy to integrate

* one classic example from physics (& will arise in many evolution problems as well)

is
$$\frac{dx}{dt} = \underbrace{-r(x-\bar{x})}_{\frac{\partial V}{\partial x}} + \sqrt{D}\,\eta(t)$$

r → restoring force; $\bar{x}$ → equilibrium point; D → diffusion constant ($\propto \frac{1}{kT}$ in physics)

"Brownian particle in quadratic potential"



we'll use this e.g. to illustrate mechanics of SDE manipulation

e.g. say we're interested in dynamics of mean, $\langle x(t) \rangle$

From definition of SDE, $x(t+\delta t) = x(t) - r(x-\bar{x})\delta t + \sqrt{D\delta t}\, Z_t$, where $Z_t \to N(0,1)$

taking averages, we have

$$\langle x(t+\delta t)\rangle = \langle x(t)\rangle - r\langle x(t)\rangle \delta t + r\bar{x}\,\delta t + \overset{\langle Z_t\rangle = 0}{0}$$

$$\Rightarrow \frac{\langle x(t+\delta t)\rangle - \langle x(t)\rangle}{\delta t} = -r\left[\langle x(t)\rangle - \bar{x}\right]$$

$$\Rightarrow \frac{\partial\langle x\rangle}{\partial t} = -r\left[\langle x\rangle - \bar{x}\right] \Rightarrow \langle x(t)\rangle - \bar{x} = \left(\langle x(0)\rangle - \bar{x}\right)e^{-rt}$$

$\Rightarrow \langle x(t)\rangle \to \bar{x}$ ~~at~~ rate r $\boxed{\text{Just like deterministic equation!}}$

* what about <u>spread</u> around this value? e.g. if $\bar{x}=0$, want $\langle x(t)^2\rangle$

Again, from definition: $\langle x(t+\delta t)^2\rangle = \left\langle \left[x(t) - r(x(t))\delta t + \sqrt{D\delta t}\,Z_t\right]^2\right\rangle$

expand to lowest order in δt:

$$\langle x(t+\delta t)^2\rangle = \langle x(t)^2\rangle - 2r\langle x(t)^2\rangle\delta t + \langle D\delta t\,\cancelto{1}{Z_t^2}\rangle + \cancelto{0}{2\langle x(t)\sqrt{D\delta t}\,Z_t\rangle}$$

$$\Rightarrow \frac{\partial\langle x^2\rangle}{\partial t} = \underbrace{-2r\langle x^2\rangle}_{\text{same as deterministic version}} + \underbrace{D}_{\text{new part from stochasticity}}$$

$\Rightarrow \langle x^2\rangle = \dfrac{D}{2r}$ $\boxed{\text{balance between noise \& deterministic restoring force.}}$

can actually get full dist'n @ long times :

E.g. for any SDE of form: $\frac{dx}{dt} = -\frac{dV(x)}{dx} + \sqrt{D}\,\eta(t)$

$\Downarrow$ Fokker-Planck eq: $\frac{dp}{dt} = -\frac{d}{dx}\left[-\frac{dV(x)}{dx}p(x)\right] + \frac{d^2}{dx^2}\left[\frac{p(x)D}{2}\right]$

@ stationarity, $\partial_t p = 0 \Rightarrow \frac{dp}{dx} = -\frac{2}{D}\frac{dV(x)}{dx}\,p(x)$

$\Rightarrow p(x) \propto e^{-\frac{2V(x)}{D}}$ $\boxed{\text{"Boltzmann" distribution}}$ $\xrightarrow[\text{if } \frac{dV}{dx} = r(x-\bar{x})]{}$ $p(x) \propto e^{-\frac{2r(x-\bar{x}_0)^2}{2D}}$ $\boxed{\text{Gaussian dist'n}}$

$\boxed{\text{≈ deterministic dynamics + a little fuzzyness from noise}}$

this is standard physics case... what about evolutionary model?

e.g. $\frac{df}{dt} = sf(1-f) + \sqrt{\frac{f(1-f)}{N}}\,\eta(t)$

($+\mu(1-f)$ for mutation)
($-\nu f$ for back-mutation)

2 key differences:

1. Diffusion const depends on mutant freq.
2. selection term is nonlinear

#2 becomes important if we want to calculate avgs, e.g. $\langle f(t)\rangle$.

using same approach as above $\left[f(t+\delta t) = f(t) + sf(1-f)\delta t + \sqrt{\frac{f(1-f)\delta t}{N}}\, Z_t \right]$

find: $\frac{d\langle f\rangle}{dt} = s\left[\langle f\rangle - \langle f^2\rangle\right] \Rightarrow$ need $\langle f^2(t)\rangle$ to find $\langle f(t)\rangle$

NOT $= \langle f\rangle^2$

ok... do same thing for $\langle f(t+\delta t)^2 \rangle$:

$$\Rightarrow \text{find} \quad \frac{d\langle f^2 \rangle}{dt} = \underbrace{2s \langle f \cdot f(1-f) \rangle}_{\text{from deterministic part}} + \underbrace{\frac{f(1-f)}{N}}_{\text{from 2 stochastic terms}}$$

$\Rightarrow$ depends on $\langle f^3 \rangle$ in addition to $\langle f^2 \rangle$ and $\langle f \rangle$

$\Rightarrow$ and so on for higher moments. known as "moment hell"
(general consequence of nonlinearity)

since nonlinearity caused by selection, one sol'n is to only look @ evolution problems w/o selection [i.e., $s=0$ or "neutral theory"]
$\Rightarrow$ much of classical pop. gen focuses on this limit.
we will revisit later when we talk about multi site genomes

what about <u>stationary distribution</u>?

also trickier in evolution setting. e.g. one way mutation ($WT \xrightarrow{\mu} mut$)
$f=1$ is absorbing state, so
$f \to 1$ @ long times (boring)

If turn on back-mutations ($WT \underset{\nu}{\overset{\mu}{\rightleftarrows}} mut$) then no absorbing state.

In this case, can show that $p(f) \propto f^{-1}(1-f)^{-1} e^{-2N\Lambda(f)}$

is solution to Fokker-Planck equation (when $\partial_t \rho = 0$)

if we choose $\Lambda(f)$ such that

$$\frac{\partial f}{\partial t} = f(1-f)\left[-\frac{\partial \Lambda(f)}{\partial f}\right] + \sqrt{\frac{f(1-f)}{N}}\,\eta(t)$$

$\Rightarrow$ to see this, just plug in and check:

$$\frac{1}{2N}\frac{\partial^2}{\partial f^2}\left[f(1-f)p(x)\right] = \frac{1}{2N}\frac{\partial}{\partial f}\left[\frac{\partial}{\partial f}\left[Ce^{-2N\Lambda(f)}\right]\right]$$

$$= -\frac{\partial}{\partial f}\left[\frac{\partial \Lambda}{\partial f}\, Ce^{-2N\Lambda(f)}\right]$$

$$= +\frac{\partial}{\partial f}\left[f(1-f)\left[-\frac{\partial \Lambda}{\partial f}\right]p(f)\right] \quad \checkmark$$

in this case, note that (deterministically)

$$\frac{d\Lambda}{dt} = \frac{\partial \Lambda}{\partial f}\frac{\partial f}{\partial t} = -f(1-f)\left(\frac{\partial f}{\partial t}\right)^2 \leq 0$$

So dynamics act to minimize $\Lambda(f)$ [just like "energy"] thus, since $p(f) \propto f^{-1}(1-f)^{-1} e^{-2N\Lambda(f)}$

$\Lambda(f)$ is analogy of "energy" for this SDE w/
N is analogy of "1/temp" non-constant diffusion eq.

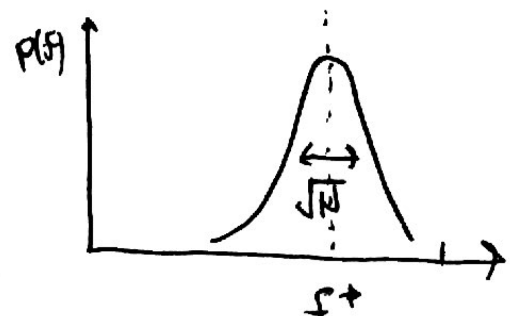
in this particular case, $-\dfrac{\partial\Lambda}{\partial f} = s + \dfrac{\mu}{f} - \dfrac{\nu}{1-f}$

so $\Lambda(f) = sf + \mu \log f + \nu \log(1-f)$

and $\boxed{p(f) \propto f^{N\mu - 1}(1-f)^{N\nu - 1} e^{2Nsf}}$ "mutation-selection-drift" balance (Wright 1930's)

What does dist'n look like? Strongly depends on $N\mu, N\nu$!

(a) if $N\mu, N\nu \gg 1$, then $p(f)$ is strongly peaked around some characteristic frequency $f^* \in (0,1)$ minimum of $\Lambda(f)$



$\Rightarrow \dfrac{\partial\Lambda}{\partial f} = 0 \Rightarrow s + \dfrac{\mu}{f} - \dfrac{\nu}{1-f} = 0$

note: same as deterministic solution to $\dfrac{\partial f}{\partial t} = 0$.

$\Rightarrow$ "deterministic mutation-selection balance"

(or just mutation balance if $s=0$)

full distribution is expansion around f^*: → 0 by def. of f^* (7)

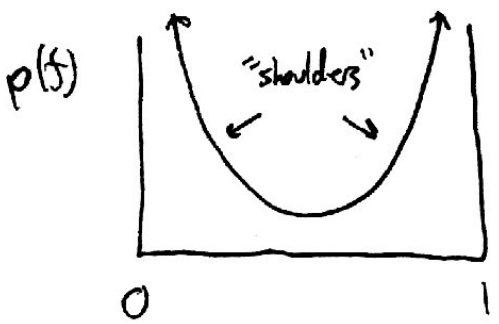
$$p(f) \propto\approx f^{*^{-1}}(1-f^*)^{-1}\exp\left[-2N\Lambda(f^*) + \cancel{2N\frac{d\Lambda(f^*)}{df}}(f-f^*)\right.$$

$$\left.-\frac{2N}{2}\frac{\partial^2\Lambda(f^*)}{\partial f^2}(f-f^*)\right]$$

$\Rightarrow$ Gaussian w/ variance $\propto \frac{1}{\sqrt{N}}$.

So $N\mu, N\nu \gg 1$ limit is standard situation of mostly deterministic, w/ some spread produced by noise.

(b) Howerever, if $N\mu, N\nu < 1$, dist'n takes on "U-shaped" form:



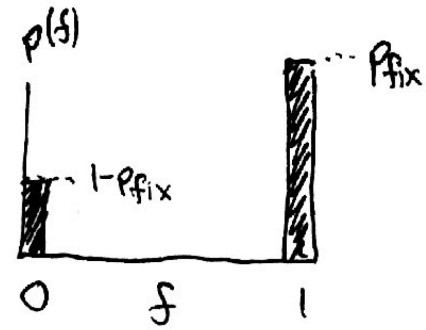
where "height" of shoulders (roughly speaking) differ by factor of e^{2Nsf}

$\Rightarrow$ definitely not deterministic + (a little noise.)
even if N itself is big!

what's going on here under the hood? what are "shoulders"?
how long does it take to reach this stationary state?
is it ever relevant in practice? (e.g. data?)

can gain a little more insight into these Qs by considering final stationary dist'n scenario:

no mutation: $$\frac{df}{dt} = sf(1-f) + \sqrt{\frac{f(1-f)}{N}}\,\eta(t)$$



$\Rightarrow$ in this case, 0 and 1 are *both* absorbing states, so $p(f)$ will be mixture: w/ weight $p_{fix} \equiv \Pr(f=1)$ that depends on initial freq f_0 $\Rightarrow$ fundamentally out-of-equilibrium question (though posed in terms of eq. measurement)

$\Rightarrow$ recall when $s=0$ used trick that $\langle f(t)\rangle = \text{const}$ to show $p_{fix}(f_0) = f_0$
How does natural selection change this?

Unfortunately, Fokker-Planck eq doesn't work well for discrete dist'n (what does $\frac{dp}{df}$ mean?). But generating function is still useful:

$$H(z,t) \equiv \langle e^{-zf(t)} \rangle \equiv \int e^{-zf} p(f,t)\, df$$

using same approach as we did for other moments, $\langle f(t)\rangle$, $\langle f(t)^2\rangle$, can work out equation of motion for $H(z,t)$:

$$H(z,t+\delta t) \equiv \left\langle e^{-zf(t+\delta t)} \right\rangle = \left\langle e^{-z\left[f(t) + sf(1-f)\delta t + \sqrt{\frac{f(1-f)\delta t}{N}}\,Z_t\right]} \right\rangle$$

= talyor expand through $\mathcal{O}(\delta t)$ and avg over Z_t

$$= \underbrace{\left\langle e^{-zf(t)} \right\rangle}_{H(z,t)} + \left\langle e^{-zf}\left[-z\underbrace{sf(1-f)}_{\text{deterministic part}} + \underbrace{\frac{z^2}{2N}f(1-f)}_{\text{2 stochastic terms avg'd}}\right]\delta t \right\rangle$$

$$\Rightarrow \quad \frac{H(z,t+\delta t) - H(z,t)}{\delta t} = \left\langle -\left[sz - \frac{z^2}{2N}\right]\underbrace{f(1-f)e^{-zf}}_{\left[-\frac{\partial}{\partial z} + \frac{\partial^2}{\partial z^2}\right]e^{-zf}} \right\rangle$$

$$\Rightarrow \quad \frac{\partial H}{\partial t} = \left[sz - \frac{z^2}{2N}\right]\left[\frac{\partial H}{\partial z} - \frac{\partial^2 H}{\partial z^2}\right]$$

(can also get from Laplace transform of Fokker-Planck eq.)

still hard to solve... but for one particular value of z, very easy

E.g. let $z^* = 2Ns$. then

$$\frac{\partial H(z^*,t)}{\partial t} = \cancelto{0}{\left[s(2Ns) - \frac{(2Ns)^2}{2N}\right]}\left[\frac{\partial H}{\partial z} - \frac{\partial^2 H}{\partial z^2}\right] = 0$$

and hence $H(z^*,t) = \text{const} = H(z^*, t=0) = e^{-zf_0}$

(z^* is known as a characteristic curve - will see more later)

* this is really cool - allows us to connect initial condition w/ property of dist'n @ long times.

as in neutral case, @ $t \to \infty$: $f \to 0$ w/ prob $1 - p_{fix}$, $f \to 1$ w/ prob p_{fix}

so $$H(z^*, t=\infty) = \underbrace{e^{-z^*\cdot 0}\cdot(1-p_{fix}) + e^{-z^*\cdot 1}\cdot p_{fix}}_{\text{defintion of } H(z) \text{ @ } t=\infty} \underset{\text{characteristic curve.}}{=} \underbrace{e^{-zf^*}}_{\text{definition of } H(z) \text{ @ } t=0}$$

$\Rightarrow$ solve for $p_{fix}(f_0)$ $\Rightarrow$ $$\boxed{p_{fix}(f_0) = \frac{1-e^{-2Nsf_0}}{1-e^{-2Ns}}}$$ "fixation probability" (Kimura 1950's)

Fixation prob is battle between selection & genetic drift.

(a) if $Ns \ll 1 \Rightarrow p_{fix}(f_0) = f_0$ as before. (drift wins)

(b) if $Ns \gg 1$

$$p_{fix}(f_0) \approx \begin{cases} 1 & \text{if } f_0 \gg \frac{1}{2Ns};\ s>0 \longrightarrow \text{"selection wins"} \\ 2Nsf_0 & \text{if } f_0 \ll \frac{1}{2Ns};\ s>0 \longrightarrow \text{outcome uncertain...} \\ e^{-2N|s|(1-f_0)} & \text{if } s<0; \longrightarrow \approx 0 \text{ "selection wins"} \end{cases}$$

e.g. if $f_0 = \frac{1}{N}$ (e.g. new mutation) $\Rightarrow$ $\boxed{P_{fix}(s) = 2s \text{ "Haldane's formula" (Haldane 1920's)}}$

if $s = 0.01$ $\Rightarrow$ only 2% chance that mutation takes over pop'n
(pretty beneficial) $\Rightarrow$ 98% of these mutations are lost to genetic drift.

$\Rightarrow$ but same mutant mixed @ 50-50 will always take over!

even in $N \to \infty$ limit.

what's going on here?

$\Rightarrow$ @ least naively, if $N \to \infty$, we expect to be able to drop noise term in $\frac{\partial f}{\partial t} = sf(1-f) + \sqrt{\frac{f(1-f)}{N}}\,\eta(t)$, where $\sqrt{\frac{f(1-f)}{N}} \to 0$

(i.e. plug in $N = \infty$).

$\Rightarrow$ but we can't! (otherwise mutations should always take over)

How can we understand this?

Fixation probability contains clue: $P_{fix} \approx 1$ for $f_0 \gg \frac{1}{2Ns}$.

even when f_0 itself $\ll 50\%$.

$\Rightarrow$ outcome only uncertain when f_0 gets close to $\frac{1}{2Ns}$ ($\ll 1$ when $Ns \gg 1$)

this suggests that we can gain a complete picture of weird behavior by focusing on $f \ll 1$ limit, and once $f(t) \gg \frac{1}{2Ns}$ (but still $\ll 1$), "patching" back on to deterministic limit, $\frac{\partial f}{\partial t} = sf(1-f)$.

$\Rightarrow$ this can be done rigorously using an approach known as "asymptotic matching". for our purposes, will get gist of what's going on using "patching" analogy.

$\Rightarrow$ when $f \ll 1 \Rightarrow \frac{\partial f}{\partial t} = sf + \sqrt{\frac{f}{N}}\,\eta(t)$ (+ μ if 1-way mutation)

known as "linear branching process"

$\Rightarrow$ turns out that this is now simple enough to get complete picture of dynamics as well as stationary quantities like $p(f)$, $P_{fix}(f_0)$.

$\Rightarrow$ this gives lots of intuition for what's going on in evolutionary problems (+ good to extend to more complicated scenarios) (+ data w/ time-dependence)

$\Rightarrow$ will take a deeper dive into these dynamics now.