Outline of paper

- Introduction:
  - developmental systems drift
  - justification of passage to the infinitesimal model
- Model:
  - heuristics and pictures from simulation below
  - justification of passage to the infinitesimal model
  - comparison to simulation: shape of the distribution; recombination load
- Conclusion
  - limiting distribution: general sizes and how it depends on selection and segregation variance
  - recombionation load
  - speed of approach to optimum (?)
  - influence of dimensionality

General picture We want to describe the dynamics of a population that is evolving under stabilizing selection around not a single point but a manifold of optimal phenotypes, using the infinitesimal model. We think the right picture is that as the population size N grows, the dynamics of the measure become deterministic, which flow quickly to within $1/N$ of the manifold, and then we can follow only the mean as it diffuses as an OU-like process near the manifold, with drift and diffusion terms depending on the (deterministic) shape of the stable population measure around that point.

Deterministic flow Let X be a population of size N, recorded as the empirical distribution on phenotypes

$$X = \frac{1}{N}\sum_{i=1}^{N} \delta_{x_i}.$$

This evolves as a Moran process under the infinitesimal model with death rates depending on state x. Concretely, an individual whose phenotype is x dies at rate $1 + \mu(x)$ and is replaced by a new individual of phenotype

$$\frac{y+z}{2} + \xi,$$

where y and z are independent draws from X and ξ is an independent $N(0, \eta^2)$. Let $\nu(X)$ denote the distribution of $\frac{y+z}{2} + \xi$. This has generator

$$\begin{aligned}
\mathcal{L}\Phi(X) &= \int\int\int\int \left(\Phi(X + \frac{1}{N}\delta_{(y+z)/2+\xi} - \frac{1}{N}\delta_x) - \Phi(X)\right)(1+\mu(x))X(dx)X(dy)X(dz)e^{-(\xi/\eta)^2/2}d\xi \\
&= \int\int \left(\Phi(X + \frac{1}{N}\delta_u - \frac{1}{N}\delta_x) - \Phi(X)\right)(1+\mu(x))X(dx)\nu(X)(du).
\end{aligned}$$

For a test function ϕ, setting $\Phi(X) = \langle \phi, X\rangle$ we get the first moment

$$\begin{aligned}
\mathcal{L}\langle \phi, X\rangle &= \frac{1}{N}\int\int\int\int \left(\phi\left(\frac{y+z}{2} + \xi\right) - \phi(x)\right)(1+\mu(x))X(dx)X(dy)X(dz)e^{-(\xi/\eta)^2/2}d\xi \\
&= \frac{1}{N}\langle \phi, \nu(X)\rangle\langle 1+\mu, X\rangle - \frac{1}{N}\langle \phi, (1+\mu)X\rangle.
\end{aligned}$$

Note that $\langle \phi, \partial_{\nu(X)} X \rangle = \langle \phi, \nu(X) \rangle$, so that this is a first derivative in the direction of $\langle 1+\mu, X\rangle \nu(X) - (1+\mu)X$.

More generally, if $\Phi(X) = \prod_i \langle \phi_i, X \rangle$ then

$$\mathcal{L}\Phi(X) = \frac{1}{N} \sum_i \left(\langle 1+\mu, X \rangle \langle \phi_i, \nu(X) \rangle - \langle \phi_i, (1+\mu)X \rangle \right) \prod_{j \neq i} \langle \phi_j, X \rangle + O(1/N^2).$$

This implies that after rescaling time by N and suitible other caveats, the limiting process is a deterministic flow in the direction of $\nu(X)\langle 1+\mu, X\rangle - (1+\mu)X$.

Stable measures If Z is a fixed point of this flow, then $\nu(Z)\langle 1+\mu, Z\rangle = (1+\mu)Z$. We assume that $\mu(x) = 0$ on a nice smooth "optimal" manifold, and that it increases with distance to the manifold. With $\eta = 0$, any fixed point is either a point mass, or possibly uniform on the optimal manifold if it is linear. We think an argument for this is obtained SOMETHING LIKE THE FOLLOWING: if Z is a fixed point and ϕ is a test function that is convex and increasing with distance from the optimal manifold, then $\langle \phi, \nu(Z) \rangle < \langle \phi, Z \rangle < \langle \phi, (1+\mu)Z \rangle / \langle 1+\mu, Z \rangle$, since averaging contracts Z while reweighting by $1+\mu$ expands Z.

If η is not zero, then we hope that for each point z on the optimal manifold, there exists a unique measure $Z(z)$ with mean z that is a fixed point of the flow.

Any measure Z that is a fixed point has the property that (the average of two independent draws plus segregation noise) is equal in distribution to (a $1+\mu$-weighted draw). Concretely, with A, B, and C independent draws from Z,

$$\mathbb{E}\left[f\left(\frac{A+B}{2} + \xi \right) \right] = \frac{\mathbb{E}\left[f(C)(1+\mu(C)) \right]}{\mathbb{E}[1+\mu(C)]}.$$

Let

$$m_k = \mathbb{E}[A^k] = \langle x^k, X \rangle,$$

and note that since $\mathbb{E}[\xi^w] = \eta^w (w-1)!!$ for even w,

$$\langle x^k, \nu(X) \rangle = \sum_{u+v+w=k} \binom{k}{u, v, w} 2^{w-k} m_u m_v \eta^w (w-1)!!.$$

We can calculate some things about this measure for the case that $\mu(x) = ax^2$ (or generally, if this is a Taylor expansion). Then

$$\frac{\mathbb{E}\left[C^k (1+\mu(C)) \right]}{\mathbb{E}[1+\mu(C)]} = \frac{m_k + a m_{k+2}}{1 + a m_2}.$$

This gives us an equation for m_{k+2} in terms of lower-order terms. With $k = 2$ and assuming that Z is symmetric,

$$\frac{m_2}{2} + \eta^2 = \frac{m_2 + a m_4}{1 + a m_2},$$

and so

$$m_4 = m_2 \left(\eta^2 + \frac{1}{2} m_2 \right) + \frac{1}{a} \left(\eta^2 - \frac{1}{2} m_2 \right).$$

We believe that as $a \to 0$ this does not blow up, implying that $m_2 = 2\eta^2 + O(a)$, and that in fact approaches Gaussian, for which $m_4 = 3m_2^2$, and so $\eta^2 - m_2/2 = a\eta^2 + O(a^2)$, and hence

$$\begin{aligned} m_2 &= 2\eta^2 (1 - a\eta^2) + O(a^2) \\ m_4 &= 4\eta^4 + O(a). \end{aligned}$$

If we take $1 + \mu(x) = e^{ax^2}$, then there is a Gaussian solution, as is common in quant gen. (Write this down in arbitrary dimensions!)

Fitness and load Note that since reproduction is unweighted, fitness is proportional to lifetime, so the fitness function is $1/(1+\mu(x))$. Since replacement occurs at rate $\langle 1+\mu, X\rangle$, the mean number of offspring per individual of type x in population X is $\langle 1+\mu, X\rangle/(1+\mu(x))$.

Take $\mu(x) = ax^2$. The mean fitness in the population is then

$$\begin{aligned}\langle 1/(1+\mu), X\rangle &= \langle 1 - ax^2 + a^2x^4, X\rangle + O(a^3) \\ &= 1 - am_2 + a^2 m_4 + O(a^3) \\ &= 1 - 2a\eta^2 + 6a^2\eta^4 + O(a^3),\end{aligned}$$

and the mean fitness of *offspring* is

$$\begin{aligned}\langle 1/(1+\mu), \nu(X)\rangle &= \langle 1 - ax^2 + a^2x^4, \nu(X)\rangle + O(a^3) \\ &= 1 - a\left(\frac{m_2}{2} + \eta^2\right) + a^2\left(2m_4 + 6m_2^2 + 12m_2\eta^2 + 3\eta^4\right) + O(a^3) \\ &= 1 - a\left(2\eta^2 - a\eta^4\right) + a^2\left(8\eta^4 + 24\eta^4 + 24\eta^4 + 3\eta^4\right) + O(a^3) \\ &= 1 - 2a\eta^2 + 60a^2\eta^4 + O(a^3).\end{aligned}$$

This implies that the difference in mean fitness between parents and offspring (maybe this is called recombination load?) is

Diffusion of the mean Since we work with a Moran model, the mean evolves simply by jumping at rate $\langle 1+\mu, X\rangle$, and at each jump, adding w/N and subtracting $\tilde{x}/N$, where w is drawn from $\nu(X)$ and $\tilde{x}$ is drawn from $(1+\mu)X/\langle 1+\mu, X\rangle$. This implies that if the mean is currently $\bar{X}$ and the population distribution is X, then with $\phi_{id}(x) = x$, if

$$m(X) = N\left(\langle \phi_{id}, \nu(X)\rangle\langle 1+\mu, X\rangle - \langle \phi_{id}, (1+\mu)X\rangle\right)$$

is of order 1, then the $\bar{X}$ run on a time scale of N^2 should behave as a diffusion with drift $m(X)$ and variance equal to the variance of w plus the variance of $\tilde{x}$, which is

$$\frac{1}{2}\int (x-\bar{X})^2 X(dx) + \eta^2 + \frac{\int x^2(1+\mu(x))X(dx) - \left(\int x(1+\mu(x))X(dx)\right)^2}{\langle 1+\mu, X\rangle}.$$

Joint process By writing the joint dynamics of the mean and the measure realtive to the mean, we hope to show that the picture above makes sense, that in the limit we can take the measure as deterministic given the mean.

Weak selection It may be nice to consider weak selection, in which case perhaps the limiting measures are all Gaussian.