A Diffusion Model in Population Genetics with Mutation and Dynamic Fitness

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The Problem

- **The question:** What is the behavior of a quantitative polygenic trait under selection, drift, and mutation?
  - Can we determine the long-time behavior of the trait mean?
  - Can we determine the long-time behavior of the total genetic variance?

- Portions of this work are joint with Judith Miller, Georgetown University
The Discrete Model

- Consider a single haploid panmictic population of constant size $N_{\text{pop}}$ with $n_{\text{loci}}$ diallelic loci.
- Suppose that the two alleles at locus $i \in \{1, \ldots, n_{\text{loci}}\}$ are $A_i$ and $a_i$.
- The effect of allele $A_i$ is greater than the effect of allele $a_i$.
- We assume that the difference in phenotype between $A_i$ and $a_i$ is $Q$, and that this is constant across loci.
- We assume strict additivity, so that dominance and epistasis are absent.
The Discrete Model

- Let the fraction of the population with allele $A_i$ at locus $i$ be denoted by $x_i$.
- The population phenotypic mean is then

$$m = \sum_{i=1}^{\text{loci}} \left[ x_i \left( \frac{1}{2} Q \right) + (1 - x_i) \left( -\frac{1}{2} Q \right) \right] = \sum_{i=1}^{\text{loci}} \left( x_i - \frac{1}{2} \right) Q$$

up to a constant.
- We assume that the environment has a most fit phenotype $r_{\text{opt}}$, and that there is a fitness function of the form

$$f(r) = e^{-\kappa (r - r_{\text{opt}})^2}$$

which gives the relative fitness of a phenotype $r$. 
The Discrete Model

- What is the probability $p_i$ that an individual in the next generation will contain allele $A_i$?
  - Clearly, $p_i \propto x_i$.
  - In addition, $p_i$ is proportional to the average fitness of the population that carries $A_i$.

- The average phenotype $m_i^+$ of the population that carries the allele $A_i$ is

$$m_i^+ = \sum_{j \neq i} (x_i - \frac{1}{2}) Q + \frac{1}{2} Q = m + (1 - x_i) Q,$$

- The average phenotype $m_i^-$ of the population that carries the allele $a_i$ is

$$m_i^- = \sum_{j \neq i} (x_i - \frac{1}{2}) Q - \frac{1}{2} Q = m - Qx_i.$$
The Discrete Model

- Assume that alleles at locus $i$ are independent of alleles at locus $j$ (gametic phase equilibrium); then $p_i \propto f(m_i^+)$. 
- Because the population size is fixed at $N_{\text{pop}}$, we then know $(1 - p_i) \propto (1 - x_i)$ and $(1 - p_i) \propto f(m_i^-)$.
- As a consequence

$$p_i = \frac{x_if(m_i^+)}{x_if(m_i^+) + (1 - x_i)f(m_i^-)} = \frac{x_if(m + (1 - x_i)Q)}{x_if(m + (1 - x_i)Q) + (1 - x_i)f(m - x_iQ)}.$$
The Discrete Model

- Let $\phi(x, t)$ be the number of loci with allele frequency $x$ after $t$ generations.
- Then the population phenotypic mean after $t$ generations can be written as

$$m(t) = \sum_x Q(x - \frac{1}{2})\phi(x, t).$$

- We are indexing loci by allele frequency rather than by arbitrary integers.
The Discrete Model

- We scale the variables, and pass to the limits $n_{\text{loci}} \to \infty$, and $N_{\text{pop}} \to \infty$, and as time becomes continuous.
The Continuous Model

- We obtain the partial differential equation for $\phi$,

$$\phi_t = -[x(1-x)m\phi]_x + \frac{1}{2}[x(1-x)\phi]_{xx}$$

where

$$m = \kappa (\rho - R(t));$$

Here $\rho$ is rescaled optimal trait mean, $R(t)$ is a rescaled trait mean, and $\kappa$ is a rescaled strength of selection.
The Continuous Model

- The trait mean $R(t)$ is given by

$$R(t) = \int_0^1 (x - \frac{1}{2})\phi(x, t) \, dx + R_0(t) + R_1(t)$$

where

$$R'_0(t) = \frac{1}{2} \left[ -\frac{1}{2}[x(1 - x)\phi]_x \right]_{x=0^+}$$

$$R'_1(t) = \frac{1}{2} \left[ -\frac{1}{2}[x(1 - x)\phi]_x \right]_{x=1^-}.$$
Mutation - Hypotheses

- Selection precedes mutation in every generation.
- There is a probability $\mu$ that allele $A_i$ becomes allele $a_i$ or vice-versa for each locus $i$ and for each generation.
The Model with Mutation

Then

$$\phi_t = -[x(1-x) m \phi]_x - [\mu(1-2x) \phi]_x + \frac{1}{2} [x(1-x) \phi]_{xx}$$

where

$$m = \kappa (\rho - R(t))$$

$$R(t) = \int_0^1 (x - \frac{1}{2}) \phi(x, t) \, dx + R_0(t) + R_1(t)$$

$$R'_0(t) = \frac{1}{2} \left[ +\mu \phi - \frac{1}{2} [x(1-x) \phi]_x \right]_{x=0^+}$$

$$R'_1(t) = \frac{1}{2} \left[ -\mu \phi - \frac{1}{2} [x(1-x) \phi]_x \right]_{x=1^-}.$$
Features of the Problem

- The problem is highly nonlinear, as $m$ depends on the solution $\phi$.
- The problem is nonlocal, as some of this dependence is via an integral of the solution $\phi$.
- Though the equation appears to be a non-uniformly parabolic equation, note that it has no boundary conditions.
- The behavior of the solutions at the boundaries are incorporated into the coefficients and the nonlinearity of the problem.
- The mutation term behaves like a leading-order term, not a lower order term.
Main Results

- If the mutation rate $\mu$ is sufficiently small ($\mu < 0.10$ will do) then the problem has a solution.
- The solution is unique and stable under perturbations of the initial data.
- In the case without mutation, we also have:
  - The scaled genetic variance $S^2(t) = \int_0^1 x(1 - x)\phi(x, t) \, dx$ tends weakly to zero as $t \to \infty$.
  - We have $R(t) - \rho = (R(0) - \rho) \exp\left\{ \int_0^t -\kappa S^2(\tau) \, d\tau \right\}$
  - If the initial trait mean is sufficiently close to optimal, then $S^2(t) = O(e^{-ct})$ for some $c > 0$, and
  - $|R(t) - \rho| \geq |R(0) - \rho| \exp[\gamma S^2(0)(e^{-ct} - 1)]$ for some $c, \gamma > 0$, implying that the larger the initial genetic variance, the closer the trait mean can come to the optimum.
Precise Results- The Spaces $B_i$

- $B_0 = \{\psi \text{ measurable on } [0,1] : \langle \psi, \psi \rangle_{B_0}^2 < \infty \}$ where
  
  \[
  \langle \phi, \psi \rangle_{B_0} = \int_0^1 x(1-x)\phi\psi \, dx.
  \]

- $B_1 = \{\psi \in B_0 : \langle \psi, \psi \rangle_{B_1}^2 < \infty \}$ where
  
  \[
  \langle \phi, \psi \rangle_{B_1} = \langle \phi, \psi \rangle_{B_0} + \int_0^1 [x(1-x)\phi]_x [x(1-x)\psi]_x \, dx.
  \]

- $B_2 = \{\psi \in B_1 : \langle \psi, \psi \rangle_{B_2}^2 < \infty \}$ where
  
  \[
  \langle \phi, \psi \rangle_{B_2} = \langle \phi, \psi \rangle_{B_1} + \int_0^1 x(1-x)[x(1-x)\phi]_{xx} \cdot [x(1-x)\psi]_{xx} \, dx.
  \]
Precise Results- Hypotheses

- $\phi_0 \in B_1$
- $\phi_0(x) \geq 0$ for almost every $x$
- $R_0(0)$ and $R_1(0)$ are given.
- $0 \leq \mu < \frac{15}{98} \sqrt{\frac{5}{11}} \approx 0.10319$. 
Precise Results- Existence

- There exists a function

\[ \phi \in C([0, T); B_1) \cap L_2(0, T; B_2) \cap C_{\text{loc}}((0, 1) \times [0, T)) \cap C^\alpha([0, T); L_p(0, 1)) \]

for any \( 1 \leq p < 2 \) and any \( 0 < \alpha < \frac{1}{p} - \frac{1}{2} \).

- There exist functions \( R_0(t), R_1(t) \in C^\beta[0, T) \) for any \( 0 < \beta < \frac{1}{2} \).

- Define

\[ R(t) = \int_0^1 (x - \frac{1}{2})\phi(x, t) \, dx + R_0(t) + R_1(t). \]

Then \( R \in C^1[0, T) \).
Then

\[ \phi_t = -[x(1 - x) m\phi]_x - [\mu(1 - 2x)\phi]_x + \frac{1}{2} [x(1 - x)\phi]_{xx} \]

as elements of \( L_2(0, T; B_0) \).

Further,

\[ \lim_{t \downarrow 0} \phi(x, t) = \phi_0(x) \]

with the limit taken strongly in \( B_1 \).
Precise Results - Existence

Set

\[ \nu(x, t) = \int_0^t \left\{ -\mu(1 - 2x)\phi(x, s) + \frac{1}{2} [x(1 - x)\phi(x, s)]_x \right\} ds \]

Then \( \nu \in C^\alpha([0, T); C^{1-\frac{1}{p}}[0, 1]) \) for any \( 1 \leq p < 2 \) and any \( 0 < \alpha < \frac{1}{p} - \frac{1}{2} \). Further

\[ R_0(t) = R_0(0) - \frac{1}{4} \nu(0, t), \quad R_1(t) = R_1(0) - \frac{1}{4} \nu(1, t). \]

Notice that, formally differentiating, and substituting for \( \nu \) we find

\[ R'_0(t) = \frac{1}{2} \left[ +\mu\phi - \frac{1}{2} [x(1 - x)\phi]_x \right]_{x=0^+} \]

\[ R'_1(t) = \frac{1}{2} \left[ -\mu\phi - \frac{1}{2} [x(1 - x)\phi]_x \right]_{x=1^-}. \]
Proof Sketch- Existence

- Theory of the spaces $B_0$, $B_1$, and $B_2$.
- Fix and freeze $\tilde{R}(t)$ with $|\tilde{R}(t)| < \gamma$.
- Energy estimates for $\phi$.
- Energy estimates for $\nu$.
- Maximum principle for $\phi$.
- Fixed point argument
The space $B_1$

- If $\phi \in B_1$, then $x(1 - x)\phi \in \dot{W}^1_2(0, 1) \hookrightarrow C^{1/2}[0, 1]$ and

$$|x_1(1 - x_1)\phi(x_1) - x_2(1 - x_2)\phi(x_2)| \leq |x_2 - x_1|^{1/2} \left(\int_0^1 [x(1 - x)\phi(x)]^2 \, dx\right)^{1/2}.$$  

- Proof follows from the fact that for all $\epsilon > 0$, so that $\text{meas}\{x \in (0, k) : |x(1 - x)\phi(x)| \geq \epsilon\} \leq \frac{1}{3} k$ for almost all sufficiently small $k$. 

The space $B_1$ - simple consequences:

- Let $\phi \in B_1$; then

$$\sup_{x \in [0, 1]} x(1 - x)\phi^2(x) \leq 2 \int_0^1 [x(1 - x)\phi]^2 \, dy$$

$$|\phi(x)| \leq 2 \max \left( \frac{1}{\sqrt{x}}, \frac{1}{\sqrt{1 - x}} \right) \| \phi \|_{B_1}.$$ 

- For any $1 \leq p < 2$,

$$B_1 \hookrightarrow L_p$$

and there exists a constant $C = C(p)$ so that if $\phi \in B_1$ then

$$\| \phi \|_{L_p} \leq C \| \phi \|_{B_1}.$$ 

- $C_0^\infty(0, 1)$ is dense in $B_1$. 

The space $B_2$

- Let $\phi \in B_2$; then

$$\int_0^1 x(1-x)\phi^2 \, dx \leq 2 \int_0^1 x(1-x)[x(1-x)\phi]_{xx}^2 \, dx,$$

$$\int_0^1 [x(1-x)\phi]_x^2 \leq 8 \int_0^1 x(1-x)[x(1-x)\phi]_{xx}^2 \, dx.$$

- We have the embedding $B_2 \hookrightarrow C^3_{\text{loc}}(0,1)$.
- $C^\infty[0,1]$ is dense in $B_2$.
- Proofs follow by using the Green's function for $\psi'' = 0$, $\psi(0) = \psi(1) = 0$ and the representation

$$\phi(x) = \frac{1}{x(1-x)} \int_0^1 G(x,y) [y(1-y)\phi]_{yy} \, dy.$$
There exists a sequence of eigenvalues $\lambda_k$ and eigenfunctions $\phi_k \in B_2$ so that:

- $-[x(1-x)\phi_k]'' = \lambda_k \phi_k$,
- The set $\{\phi_k\}_{k=1}^{\infty}$ is an orthonormal basis for $B_0$, and
- The set $\{\phi_k\}_{k=1}^{\infty}$ forms a basis for $B_1$.

In fact,

$$\lambda_k = (k+1)(k+2)$$

$$\phi_k(x) = \sqrt{\frac{8(k+3/2)}{(k+1)(k+2)}} C_{(3/2)}^k (2x-1)$$

where $C_{(3/2)}^k$ are the Gegenbauer polynomials.
Limiting Embeddings

- The space $B_1 \hookrightarrow L_2(0,1)$; in particular there is an absolute constant $K_1 \leq 2\sqrt[4]{10}$ so that

$$\|f\|_{L_2(0,1)} \leq K_1 \left( \int_0^1 [x(1-x)f(x)]^2_x \, dx \right)^{1/2}$$

for any $f \in B_1$.

- There is an absolute constant $K_2 \leq \frac{49}{15} \sqrt{\frac{11}{5}}$ so that

$$\left\| \frac{df}{dx} \right\|_{B_0} \leq K_2 \left( \int_0^1 x(1-x)[x(1-x)f]_{xx}^2 \, dx \right)^{1/2}$$

for any $f \in B_2$. 
Energy Estimates for $\phi$

- Freeze the choice of $\tilde{R}(t)$.
- We have the energy estimates

$$\sup_{0 \leq t < T} \int_0^1 x(1-x)\phi^2 \, dx + \int_0^T \int_0^1 [x(1-x)\phi]_x^2 \, dx \, dt \leq C \|\phi_0\|_{B_0}^2$$

$$\sup_{0 \leq t < T} \int_0^1 [x(1-x)\phi]_x^2 \, dx + \int_0^T \int_0^1 x(1-x)[x(1-x)\phi]_{xx} \, dx \, dt \leq C \|\phi_0\|_{B_1}^2$$

The constants $C$ depend on $\max |\tilde{R}(t)|$. 
Multiply the equation by \([x(1-x)\phi]_{xx}\); then

\[
\frac{1}{2} \frac{d}{dt} \int_0^1 [x(1-x)\phi]^2 dx + \frac{1}{2} \int_0^1 x(1-x) [x(1-x)\phi]^2_{xx} dx
\]

\[
\leq \|\tilde{m}\|_{\infty} \left( \int_0^1 [x(1-x)\phi]^2 dx \right)^{\frac{1}{2}} \left( \int_0^1 x(1-x) [x(1-x)\phi]^2_{xx} dx \right)^{\frac{1}{2}}
\]

\[
+ \mu \left[ 2 \left( \int_0^1 x(1-x)\phi^2 dx \right)^{\frac{1}{2}} + \left( \int_0^1 x(1-x) \left( \frac{\partial \phi}{\partial x} \right)^2 dx \right)^{\frac{1}{2}} \right]
\]

\[
\cdot \left( \int_0^1 x(1-x)[x(1-x)\phi]^2_{xx} dx \right)^{\frac{1}{2}}
\]
Energy Estimates for $\phi$

- $\phi \in C_{\text{loc}}((0, 1) \times [0, T));$
- $x^{1-\theta}(1-x)^{1-\theta}\phi(x, t) \in C\left([0, T); C^{\frac{1}{2}-\theta}[0, 1]\right)$ for any \(0 \leq \theta < \frac{1}{2};\)
- $\sup_{0 \leq t < T} |\phi(x, t)| \leq C \max\left(\frac{1}{\sqrt{x}}, \frac{1}{\sqrt{1-x}}\right) \|\phi_0\|_{B_1}$
- $\sup_{0 \leq t < T} \|\phi(\cdot, t)\|_{L^p(0, 1)} \leq C_p \|\phi_0\|_{B_1}$ for \(1 \leq p \leq 2.\)
- $\phi \in C^{1/2}([0, T); B_0)$
- $\phi \in C^\alpha([0, T); L^p(0, 1))$ for any \(1 \leq p < 2\) and any \(0 < \alpha < \frac{1}{p} - \frac{1}{2}\)
- $\phi_t \in L^2(0, T; B_0);$
Energy Estimates for $\nu$

- $\nu \in L^\infty(0, T; L^2(0, 1))$ and $\nu_t \in L^\infty(0, T; L^2(0, 1))$
- For any $1 \leq p \leq 2$
  \[
  \sup_{0 \leq t < T} \left\| \frac{\partial \nu}{\partial x} (\cdot, t) \right\|_{L^p(0,1)} \leq C \left\| \phi_0 \right\|_{B^1}
  \]

  while for any $0 < \alpha < \frac{1}{p} - \frac{1}{2}$ we have

  \[
  \frac{\partial \nu}{\partial x} \in C^\alpha ([0, T); L^p(0, 1)) \text{ and }
  \left\| \frac{\partial \nu}{\partial x} (\cdot, t_2) - \frac{\partial \nu}{\partial x} (\cdot, t_1) \right\|_{L^p(0,1)} \leq C |t_2 - t_1 |^\alpha \left\| \phi_0 \right\|_{B^1}
  \]

- For any $1 \leq p < 2$ and for any $0 < \alpha < \frac{1}{p} - \frac{1}{2}$

  \[
  \nu \in C^\alpha ([0, T); C^{1-1/p}[0, 1])
  \]
Maximum Principle

- Maximim Principle: For any $0 \leq t_1 \leq t_2 < T$

\[
\int_0^1 \phi^\pm(x, t_2) \, dx \leq \int_0^1 \phi^\pm(x, t_1) \, dx
\]

- The proof follows by using

\[
\frac{x(1-x)\phi^\pm}{x(1-x)\phi^\pm + \epsilon}
\]

as a test function on the interval $[a, b]$, then letting $\epsilon \downarrow 0$, $a \downarrow 0$ and $b \uparrow 1$. 
Maximum Principle: Consequences

- \( R \in C^1[0, T) \) and

\[
|R(t)| \leq |R(0)| + \| \phi_0 \|_{L_1} \left[ \frac{1}{2} \mu t + \int_0^t \kappa |\rho - \tilde{R}(t)| \, ds \right]
\]

- This follows from the identity

\[
R(t_2) - R(t_1) = \int_{t_1}^{t_2} \int_0^1 \left[ \tilde{m}x(1-x) + \mu(x - \frac{1}{2}) \right] \phi \, dx \, dt
\]

which follows from the use of \( x - \frac{1}{2} \) as a test function.
Let \( \mathcal{U} = C([0, T); L_1(0, 1)) \times C[0, T) \times C[0, T) \) and consider the function \( \mathcal{F} : \mathcal{U} \to \mathcal{U} \) defined by

\[
\mathcal{F}(\tilde{\phi}, \tilde{R}_0, \tilde{R}_1) = (\phi, R_0, R_1)
\]

where \( \phi \) is the solution of the problem with frozen coefficients with corresponding values of \( R_0, R_1 \). Our energy estimates show that \( \mathcal{F} \) is continuous and compact.

The maximum principle shows that the set \( \{ (\phi, R_0, R_1) \in \mathcal{U} : (\phi, R_0, R_1) = \sigma \mathcal{F}(\phi, R_0, R_1) \text{ for some } 0 \leq \sigma \leq 1 \} \) is bounded in \( \mathcal{U} \).

Existence follows from Schaefer’s Fixed Point Theorem.