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.
Let the fraction of the population with allele \( A_i \) at locus \( i \) be denoted by \( x_i \).

The population phenotypic mean is then

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

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
  \[
  m_i^- = \sum_{j \neq i} (x_i - \frac{1}{2}) Q - \frac{1}{2} Q = m - Qx_i.
  \]
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

$$p_i = \frac{x_i f(m_i^+)}{x_i f(m_i^+) + (1 - x_i) f(m_i^-)} = \frac{x_i f(m + (1 - x_i) Q)}{x_i f(m + (1 - x_i) Q) + (1 - x_i) f(m - x_i Q)}.$$

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.
- \( \phi(0, t) \) gives the number of loci with allele frequency zero, so the \( A \) allele no longer appears in the population.
- \( \phi(1, t) \) gives the number of loci with allele frequency one, so the \( a \) allele no longer appears in the population.
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 $\phi$,

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

where

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

- Here $\rho$ is rescaled optimal trait mean, $\kappa$ is a rescaled strength of selection and $R(t)$ is the trait mean, 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

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

where

\[ m(t) = \kappa(\rho - R(t)) \]

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

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

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

- The problem is highly nonlinear, as \( m(t) \) 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 $R(t) - \rho = (R(0) - \rho) \exp \int_0^t -\kappa S^2(\tau) \, d\tau$
  - 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 $B_i$

- $B_0 = \left\{ \psi \text{ measurable on } [0, 1] : \langle \psi, \psi \rangle_{B_0}^2 < \infty \right\}$ where

$$\langle \phi, \psi \rangle_{B_0} = \int_0^1 x(1-x) \phi \psi \, dx.$$ 

- $B_1 = \left\{ \psi \in B_0 : \langle \psi, \psi \rangle_{B_1}^2 < \infty \right\}$ where

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

- $B_2 = \left\{ \psi \in B_1 : \langle \psi, \psi \rangle_{B_2}^2 < \infty \right\}$ 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

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

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 $\tilde{\phi}$, $\tilde{R}_0$ and $\tilde{R}_1$ so that $|\tilde{R}(t)| < \gamma$.
- 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 $x(1 - x)\phi \in \overset{\circ}{W}^1_2(0, 1) \hookrightarrow C^{1/2}[0, 1]$ 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

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

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

- 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 $B_2 \hookrightarrow C^{\frac{3}{2}}_{\text{loc}}(0, 1)$.
- $C^\infty[0, 1]$ 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:

- $-\left[ x(1-x)\phi_k \right]'' = \lambda_k \phi_k$,
- 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,

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

where $C_k^{(3/2)}$ are the Gegenbauer polynomials.
We have the embedding $B_1 \hookrightarrow L_2(0, 1)$; in particular there is an absolute constant $K_1 \leq 2\sqrt[4]{10}$ so that

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

for any $f \in B_1$.

To prove this, we use some essentially Fourier series techniques.

Indeed, to begin we write

$$f = \sum_{j=1}^\infty \alpha_j \phi_j(x)$$

with convergence in $B_1$ where

$$\alpha_j = \langle f, \phi_j \rangle_{B_0}.$$
Now
\[ \int_0^1 [x(1-x)f(x)]^2 \, dx = \sum_{j,k} \alpha_j \alpha_k \int_0^1 [x(1-x)\phi_j]x[x(1-x)\phi_k]x \, dx \]
\[ = \sum_k \lambda_k \alpha_k^2 \]
\[ = \sum_k (k+1)(k+2)\alpha_k^2 \]

On the other hand
\[ \|f\|_2^2 = \sum_{j,k} |\alpha_j \alpha_k| \int_0^1 \phi_j \phi_k \, dx \leq 2 \sum_{j,k} |\alpha_j \alpha_{j+k}| \int_0^1 \phi_j \phi_{j+k} \, dx \]
First Limiting Embedding

- Because the $\phi_k$ are known in terms of Gegenbauer polynomials, we can evaluate:

$$\int_0^1 \phi_j \phi_{j+k} \, dx = \begin{cases} 
4 \sqrt{\frac{(j + 1)(j + 2)(j + 3/2)(j + k + 3/2)}{(j + k + 1)(j + k + 2)}} & \text{k even} \\
0 & \text{k odd.}
\end{cases}$$

- Thus

$$\|f\|_{L_2}^2 \leq 8 \sum_{j,k} |\alpha_j \alpha_{j+2k}| \sqrt{\frac{(j + 1)(j + 2)(j + 3/2)(j + 2k + 3/2)}{(j + 2k + 1)(j + 2k + 2)}}$$

- Careful application of Hölder’s inequality on the sums together with the fact

$$\int_0^1 [x(1-x)f(x)]^2 \, dx = \sum_k (k + 1)(k + 2) \alpha_k^2$$

gives us the embedding.
Second Limiting Embedding

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

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

for any $f \in B_2$.

- This is proven in essentially the same fashion.

- We start with the fact that

$$\int_0^1 x(1-x)[x(1-x)f]_{xx}^2 \, dx = \sum_k (k+1)^2(k+2)^2 \alpha_k^2$$
We also have

$$\left\| \frac{df}{dx} \right\|_{B_0}^2 = \sum_j \left\langle \frac{df}{dx}, \phi_j \right\rangle_{B_0}^2$$

$$= \sum_j \left\langle \sum_k \alpha_k \frac{d\phi_k}{dx}, \phi_j \right\rangle_{B_0}^2$$

$$= \sum_{j,k,\ell} |\alpha_k \alpha_{\ell}| \left\langle \frac{d\phi_k}{dx}, \phi_j \right\rangle_{B_0} \left\langle \frac{d\phi_{\ell}}{dx}, \phi_j \right\rangle_{B_0}$$
Using the fact that the $\phi_k$ are known in terms of Gegenbauer polynomials, we evaluate the integrals, and find

\[ \left\| \frac{df}{dx} \right\|_{B_0}^2 \leq 32 \sum_k \sum_{\ell \geq k} \sum_{j < k} |\alpha_k \alpha_\ell| \]

\[ \sqrt{\frac{(k + 3/2)(\ell + 3/2)}{(k + 1)(k + 2)(\ell + 1)(\ell + 2)}} (j + 1)(j + 2)(j + 3/2). \]

The embedding then follows after another application of Hölder’s inequality.
Energy Estimates for $\phi$

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

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

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

The constants $C$ depend on $\max |\tilde{R}(t)|$. 
Energy Estimates for $\phi$ - Proof sketch

Multiply the equation

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

by $x(1-x)[x(1-x)\phi]_{xx}$ and integrate; then

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

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

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

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

- $\phi \in C_{\text{loc}}((0, 1) \times [0, T));$
- $x^{1-\theta}(1-x)^{1-\theta} \phi(x, t) \in C \left([0, T); C^{1/2-\theta}[0, 1]\right)$ 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 $\nu$

- Recall

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

- Then the energy estimates for $\phi$ allow us to prove

  - $\nu \in L_\infty(0, T; L_2(0, 1))$,
  - $\nu_t \in L_\infty(0, T; L_2(0, 1))$,  
  - $\nu_x \in C^\alpha([0, T]; L_p(0, 1))$, and
  - $\nu \in C^\alpha([0, T]; C^{1 - 1/p}[0, 1])$

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

- In each case, the relevant norm is bounded by $C \| \phi_0 \|_{B_1}$ for $C$ depending on $\max |\tilde{R}(t)|$.

- As a consequence, $\nu(0, t), \nu(1, t) \in C^\beta [0, T)$ for any $0 < \beta < 1/2$. 
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, Proof

- It is easy to see that

\[
\lim_{b \uparrow 1} \lim_{a \downarrow 0} \lim_{\epsilon \downarrow 0} \int_{t_1}^{t_2} \int_{a}^{b} \phi_t^\pm \frac{x(1-x)\phi^\pm}{x(1-x)\phi^\pm + \epsilon} \, dx \, dt = \int_{0}^{1} \phi^\pm(x, t) \, dx \bigg|_{t=t_2} - \int_{0}^{1} \phi^\pm(x, t) \, dx \bigg|_{t=t_1}
\]

\[
\lim_{b \uparrow 1} \lim_{a \downarrow 0} \lim_{\epsilon \downarrow 0} \int_{t_1}^{t_2} \int_{a}^{b} \tilde{m}[x(1-x)\phi^\pm] \frac{x(1-x)\phi^\pm}{x(1-x)\phi^\pm + \epsilon} \, dx \, dt = 0.
\]

- To handle the remaining terms, we first notice that

\[
-\mu(1 - 2x)\phi + \frac{1}{2}[x(1-x)\phi]_x = \frac{1}{2} x^{2\mu} (1 - x)^{2\mu} [x^{1-2\mu} (1 - x)^{1-2\mu} \phi]_x.
\]
Thus

\[
\int_{t_1}^{t_2} \int_{a}^{b} \left\{ -\mu(1-2x)\phi + \frac{1}{2}[x(1-x)\phi]_x \right\} x \frac{\pm x(1-x)\phi^\pm}{x(1-x)\phi^\pm + \epsilon} \, dx \, dt
\]

\[
= -\frac{1}{2} \int_{t_1}^{t_2} \int_{a}^{b} \frac{\epsilon [x(1-x)\phi^\pm]^2}{(x(1-x)\phi^\pm + \epsilon)^2} \, dx \, dt
\]

\[
+ \mu \int_{t_1}^{t_2} \int_{a}^{b} \frac{1-2x}{x(1-x)} \frac{\epsilon [x(1-x)\phi^\pm] [x(1-x)\phi^\pm]_x}{(x(1-x)\phi^\pm + \epsilon)^2} \, dx \, dt
\]

\[
\pm \frac{1}{2} \int_{t_1}^{t_2} x^{2\mu}(1-x)^{2\mu} \left[ x^{1-2\mu}(1-x)^{1-2\mu} \phi \right]_x
\]

\[
\cdot \frac{x(1-x)\phi^\pm}{x(1-x)\phi^\pm + \epsilon} \, dt \bigg|_{x=a}^{x=b}
\]
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

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

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 $\mathcal{F} : \mathcal{U} \rightarrow \mathcal{U}$ 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 and some additional embedding results for the spaces $B_1$ and $B_2$ 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.