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_{pop} with n_{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

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

  up to a constant.
- We assume that the environment has a most fit phenotype r_{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

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

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

$$m_i^- = \sum_{j \neq i} \left(x_i - \tfrac{1}{2} \right) Q - \tfrac{1}{2} Q = m - Q x_i.$$

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_{pop}, we then know $(1 - p_i) \propto (1 - x_i)$ and $(1 - p_i) \propto f(m_i^-)$.
- As a consequence

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

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

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

  - We are indexing loci by allele fequency 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 ϕ,

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

  where

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

- Here ρ is rescaled optimal trait mean, κ 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 μ that allele A_i becomes allele a_i or vice-versa for each locus i and for each generation.

The Model with Mutation

- Then

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

where

$$\begin{aligned}
m(t) &= \kappa(\rho - R(t)) \\
R(t) &= \int_0^1 (x - \tfrac{1}{2})\phi(x,t)\,dx + R_0(t) + R_1(t) \\
R_0'(t) &= \frac{1}{2}\left[+\mu\phi - \frac{1}{2}[x(1-x)\phi]_x\right]_{x=0^+} \\
R_1'(t) &= \frac{1}{2}\left[-\mu\phi - \frac{1}{2}[x(1-x)\phi]_x\right]_{x=1^-}.
\end{aligned}$$

Features of the Problem

- The problem is highly nonlinear, as $m(t)$ depends on the solution ϕ.
- The problem is nonlocal, as some of this dependence is via an integral of the solution ϕ.
- 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 μ 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 sufficently close to optimal, then $S^2(t) = O(e^{-ct})$ for some $c > 0$, and
  - $|R(t) - \rho| \geqslant |R(0) - \rho| \exp[\gamma S^2(0)(e^{-ct} - 1)]$ for some $c, \gamma > 0$, implying that the larger the intitial 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

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

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 $1 \leqslant p < 2$ 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

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

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

Precise Results- Existence

- 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

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

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

$$R_0(t) = R_0(0) - \tfrac{1}{4}v(0,t), \qquad R_1(t) = R_1(0) - \tfrac{1}{4}v(1,t).$$

- Notice that, formally differentiating, and substituting for v 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 ϕ.
- Energy estimates for ν.
- Maximum principle for ϕ.
- Fixed point argument

The space B_1

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

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

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

The space B_1- simple consequences:

- Let $\phi \in B_1$; then

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

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

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

$$B_1 \hookrightarrow L_p$$

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

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

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

The space B_2

- Let $\phi \in B_2$; then

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

- 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 $\phi(x) = \frac{1}{x(1-x)}\int_0^1 G(x,y)[y(1-y)\phi]_{yy}\,dy$.

Eigenvalues

There exists a sequence of eigenvalues λ_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,

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

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

where $C_k^{(3/2)}$ are the Gegenbauer polynomials.

First Limiting Embedding

- We have the embedding $B_1 \hookrightarrow L_2(0,1)$; in particular there is an absolute constant $K_1 \leqslant 2\sqrt[4]{10}$ so that

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

  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

$$\alpha_j = \langle f, \phi_j \rangle_{B_0} .$$

First Limiting Embedding

- Now

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

- On the other hand

$$\|f\|_{L_2}^2 = \sum_{j,k} |\alpha_j \alpha_k| \int_0^1 \phi_j \phi_k \, dx \leqslant 2 \sum_{j,k} |\alpha_j \alpha_{j+k}| \int_0^1 \phi_j \phi_{j+k} \, dx$$

First Limiting Embedding

- Because the ϕ_k are known in terms of Gegenbauer polynomials, we can evaluate:

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

- Thus

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

- Careful application of Hölder's inequality on the sums together with the fact $\int_0^1 [x(1-x)f(x)]_x^2\, dx = \sum_k (k+1)(k+2)\alpha_k^2$ gives us the embedding.

Second Limiting Embedding

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

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

  for any $f \in B_2$.
- This is proven in essentially the same fashion.
- We start with the fact that

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

Second Limiting Embedding

- We also have

$$\begin{aligned}\left\|\frac{df}{dx}\right\|_{B_0}^2 &= \sum_j \left\langle \frac{df}{dx}, \phi_j \right\rangle_{B_0}^2 \\ &= \sum_j \left\langle \sum_k \alpha_k \frac{d\phi_k}{dx}, \phi_j \right\rangle_{B_0}^2 \\ &= \sum_{j,k,\ell} |\alpha_k \alpha_\ell| \left\langle \frac{d\phi_k}{dx}, \phi_j \right\rangle_{B_0} \left\langle \frac{d\phi_\ell}{dx}, \phi_j \right\rangle_{B_0}\end{aligned}$$

Second Limiting Embedding

- Using the fact that the ϕ_k are known in terms of Gegenbauer polynomials, we evaluate the integrals, and find

$$\left\| \frac{df}{dx} \right\|_{B_0}^2 \leqslant 32 \sum_k \sum_{\ell \geqslant k} \sum_{j<k} |\alpha_k \alpha_\ell| \sqrt{\frac{(k+3/2)(\ell+3/2)}{(k+1)(k+2)(\ell+1)(\ell+2)}(j+1)(j+2)(j+3/2)}.$$

- The embedding then follows after another application of Hölder's inequality.

Energy Estimates for ϕ

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

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

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

The constants C depend on $\max |\tilde{R}(t)|$.

Energy Estimates for ϕ- Proof sketch

Multiply the equation

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

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

$$\begin{aligned}
&\frac{1}{2}\frac{d}{dt}\int_0^1 [x(1-x)\phi]_x^2 dx + \frac{1}{2}\int_0^1 x(1-x)[x(1-x)\phi]_{xx}^2 dx \\
&\quad \leqslant \|\tilde{m}\|_\infty \left(\int_0^1 [x(1-x)\phi]_x^2 dx\right)^{\frac{1}{2}} \left(\int_0^1 x(1-x)[x(1-x)\phi]_{xx}^2 dx\right)^{\frac{1}{2}} \\
&\qquad + \mu \left[2\left(\int_0^1 x(1-x)\phi^2 dx\right)^{\frac{1}{2}} + \left(\int_0^1 x(1-x)\left(\frac{\partial\phi}{\partial x}\right)^2 dx\right)^{\frac{1}{2}}\right] \\
&\qquad\quad \cdot \left(\int_0^1 x(1-x)[x(1-x)\phi]_{xx}^2 dx\right)^{\frac{1}{2}}
\end{aligned}$$

Energy Estimates for ϕ

- $\phi \in C_{\text{loc}}((0,1) \times [0,T))$;
- $x^{1-\theta}(1-x)^{1-\theta}\phi(x,t) \in C\left([0,T); C^{\frac{1}{2}-\theta}[0,1]\right)$ for any $0 \leqslant \theta < \frac{1}{2}$;
- $\sup\limits_{0 \leqslant t < T} |\phi(x,t)| \leqslant C \max\left(\frac{1}{\sqrt{x}}, \frac{1}{\sqrt{1-x}}\right) \|\phi_0\|_{B_1}$
- $\sup\limits_{0 \leqslant t < T} \|\phi(\cdot,t)\|_{L_p(0,1)} \leqslant C_p \|\phi_0\|_{B_1}$ for $1 \leqslant p \leqslant 2$.
- $\phi \in C^{1/2}([0,T); B_0)$
- $\phi \in C^{\alpha}([0,T); L_p(0,1))$ for any $1 \leqslant p < 2$ and any $0 < \alpha < \frac{1}{p} - \frac{1}{2}$
- $\phi_t \in L_2(0,T; B_0)$;

Energy Estimates for v

- Recall

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

- Then the energy estimates for ϕ allow us to prove
  - $v \in L_\infty(0,T;L_2(0,1))$,
  - $v_t \in L_\infty(0,T;L_2(0,1))$,
  - $v_x \in C^\alpha([0,T);L_p(0,1))$, and
  - $v \in C^\alpha([0,T);C^{1-1/p}[0,1])$

  for any $1 \leqslant p \leqslant 2$ 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, $v(0,t), v(1,t) \in C^\beta[0,T)$ for any $0 < \beta < 1/2$.

Maximum Principle

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

$$\int_0^1 \phi^{\pm}(x, t_2)\, dx \leqslant \int_0^1 \phi^{\pm}(x, t_1)\, dx$$

- 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

$$\lim_{b\uparrow 1}\lim_{a\downarrow 0}\lim_{\epsilon\downarrow 0}\int_{t_1}^{t_2}\int_a^b \phi_t^{\pm}\frac{x(1-x)\phi^{\pm}}{x(1-x)\phi^{\pm}+\epsilon}\,dx\,dt = \int_0^1 \phi^{\pm}(x,t)\,dx\Big|_{t=t_1}^{t=t_2}$$

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

- To handle the remaining terms, we first notice that

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

Maximum Principle, Proof

- Thus

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

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

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

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

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

Maximum Principle: Consequences

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

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

- This follows from the identity

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

which follows from the use of $x - \frac{1}{2}$ as a test function.

Fixed Point Argument

- Let $\mathcal{U} = C([0,T); L_1(0,1)) \times C[0.T) \times C[0,T)$ and consider the function $\mathfrak{F} : \mathcal{U} \to \mathcal{U}$ defined by

$$\mathfrak{F}(\tilde{\phi}, \tilde{R}_0, \tilde{R}_1) = (\phi, R_0, R_1)$$

  where ϕ 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 $\mathfrak{F}$ is continuous and compact
- The maximum principle shows that the set $\{(\phi, R_0, R_1) \in \mathcal{U} : (\phi, R_0, R_1) = \sigma\mathfrak{F}(\phi, R_0, R_1)$ for some $0 \leqslant \sigma \leqslant 1$ is bounded in $\mathcal{U}$.
- Existence follows from Schaefer's Fixed Point Theorem.