Degenerate Diffusions in Population Genetics
In Memory of Gennadi Henkin
MIPT Dolgoprudny

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The work I will describe was done jointly with Rafe Mazzeo and Camelia Pop.

Outline

Population Genetics

Population genetics is the study of how the distribution of variants in a reproducing population evolves over time. There are typically four important effects:

1. The randomness in the number of offspring a given individual, or pair, has in a given generation.
2. Mutation from one type to another type.
3. Differences in "fitness" among the different types.
4. Migration in and out of the given environment.

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Natural Selection

The Darwinian concept of “Natural Selection” is the idea that variants of greater fitness will survive longer and therefore have a larger number of offspring.

As a random process one cannot expect to make exact predictions for the time evolution of a single population, but only for the distribution of types, in an ensemble of populations, given a starting distribution.

Finite populations

The earliest models assumed a fixed population size N, and a finite collection of possible types, $\{1, \ldots, m\}$. The state of the population at each time is described by an m-tuple: $(n_1, \ldots, n_m)$, giving the number of individuals of each type. Here we assume that $n_1 + \cdots + n_m = N$, so the state space consists of the integer points in an $(m-1)$-simplex.

The evolution of the population is then a Markov process specified by the transition probability:

$$\mathrm{Prob}((k_1, \ldots, k_m)|(n_1, \ldots, n_m)).$$

2-Alleles

The simplest haploid case is when there are two types (called alleles) and both types have the same fitness and there is also no mutation. We use A and a to denote the types, and let $X(t)$ be the number of type a at generation $t \in \mathbb{N}$. Since $n_a + n_A = N$, in this case the standard Wright-Fisher model is given by the binomial sampling formula:

$$\text{Prob}(X(t+1) = j | X(t) = i) = \binom{N}{j} \left(\frac{i}{N}\right)^j \left(1 - \frac{i}{N}\right)^{N-j} \quad (1)$$

Mutation and Selection

To incorporate mutation and selection, we change the odds. If a and A have relative fitness $(1+s):1$, and the rate at which $a \to A$ is μ_1 and the rate at which $A \to a$ is μ_2, then we let:

$$p_i = \frac{i(1+s)(1-\mu_1)}{i(1+s)+N-i} + \frac{(N-i)\mu_2}{i(1+s)+N-i}.$$

We alter the transition matrix to

$$\text{Prob}(X(t+1) = j | X(t) = i) = \binom{N}{j} p_i^j (1-p_i)^{N-j} \tag{2}$$

The Infinite Population Limit

The main topic of this talk concerns limits of these sorts of processes as the population N tends to infinity. In the 1d-case, the rescaled processes

$$\frac{1}{N}X^{(N)}([tN]), \tag{3}$$

converge, under suitable hypotheses, to a continuous time stochastic process parametrized by the interval [0, 1]. The backward Kolmogorov operator is the second order differential operator:

$$L^* f(x) = \frac{x(1-x)}{2}\partial_x^2 f + \sigma x(1-x)\partial_x f + m_2(1-x)\partial_x f - m_1 x\partial_x f. \tag{4}$$

Where $\sigma = Ns$, $m_1 = N\mu_1$ and $m_2 = N\mu_2$ are assumed fixed, as $N \to \infty$.

The Infinite Population Limit

In this limit the second order term,

$$\frac{x(1-x)}{2}\partial_x^2 f,$$

is related to the randomness in the number of offspring; whereas mutation and selection become deterministic forces, represented by the vector field,

$$\sigma x(1-x)\partial_x f + m_2(1-x)\partial_x f - m_1 x\partial_x f.$$

There are many different Markov chains that have the same infinite population limit, for example the Moran Model. This limit is largely determined by the first and second moments of the "offspring distribution."

The Classical Higher Dimensional Case

This Markov-chain framework can be used to model populations with a genome of arbitrary length. If there are $M+1$ different types, then the infinite population limit is a Markov process on an M-simplex, Σ_M, where the coordinates give the frequency of each type. We can represent the simplex by

$$\Sigma_M = \{(x_1, \ldots, x_M) : \; 0 \leq x_i \text{ and } \sum_i x_i \leq 1\}. \tag{5}$$

The generator for the infinite population limit is then an operator of the form

$$Lf = \sum_{i,j} x_i(\delta_{ij} - x_j)\partial_{x_i}\partial_{x_j} + V. \tag{6}$$

V is an inward pointing vector field. We let L_{Kim} denote the second order part in (6).

More General Cases

Among other things, these models can also be used to study the interactions of several different evolving populations, with each modeled by a process of this sort. In this case the configuration space is a product of simplices,

$$\Sigma_{M_1} \times \cdots \times \Sigma_{N_P}, \tag{7}$$

where each simplex accounts for the variants in a given population. The interactions between the populations are usually incorporated into the vector field.

Connections to Complex Analysis, I

- Since my work with Gennadi was all in Several Complex Variables:
- While there is no direct connection (that I know of) to several complex variables, the study of these models has much in common, philosophically, with the analysis of the $\bar{\partial}$-Neumann problem.
- Much depends on the geometry of the domains on which the analysis is done, which in the present case are manifolds with corners.
- For example, simplices, or products of simplices fall into this class. An important feature of this class of spaces is that it is closed under Cartesian products (unlike manifolds with boundary).

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Connections to Complex Analysis, II

- Another significant point of contact is that there is degeneration in the order of the operator normal to the boundary. In SCV this is a result of the choice of the $\bar{\partial}$-Neumann boundary condition. For population genetics it is inherent in the principal symbol of the operator itself.
- Because of this degeneracy in the principal symbol, lower terms can play a very significant role in the analytic structure of the associated kernel functions, e.g. the resolvent kernel and the heat kernel. In SCV this comes to the fore in the analysis of operators like $\Box_b$.

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Feller's work

Operators of the general type,

$$L^* f(x) = \frac{x(1-x)}{2}\partial_x^2 f + b(x)\partial_x, \tag{8}$$

were studied in two seminal papers of Feller from 1951 and 1952. He classified the types of boundary conditions (and side conditions) one could specify that define Feller semigroups on $C^0([0,1])$. The techniques he used were quite special to 1-dimension, and he did not address questions of higher regularity.

Mazzeo and I recently studied the regularity question, and Chen and Stroock analyzed the asymptotics of the heat kernel, for the 1d-case (in 2010!).

Other Applications

From the time of Kimura and his collaborators (in the 50s to 70s) the process generated by this operator and its higher dimensional generalizations have been extensively used as a computational tool in the study problems in population genetics.

Notwithstanding its centrality, very little mathematical analysis had been done on these models.

Outline

Distinguishing Features

These models have several key features:

1. The simplex is not a manifold with boundary, but rather a manifold with corners. Very little analysis has been done on such singular spaces.
2. The second order part of L degenerates along the boundary in a very specific way. In a corner of codimension n the operator is modeled by

$$L_{\boldsymbol{b},m} = \sum_{i=1}^{n} [x_i \partial_{x_i}^2 + b_i \partial_{x_i}] + \Delta_{\mathbb{R}^m}, \tag{9}$$

where $b_i \geq 0$. Here $m + n = N$ is the dimension of the manifold with corners.
3. The first order vanishing of the coefficients of the normal second order terms place this operator outside what had been analyzed. It is quite important as it allows paths of the process to reach the boundary in finite time.

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Prior Results on the Kimura Diffusion

Operators of the type appearing on the previous slide have been used in population genetics since the 1950s. The basic existence result for solutions to the heat equation $\partial_t u - L_{\text{Kim}} u = 0$ follows from the fact that L_{Kim} preserves polynomials of degree d. Karlin and Kimura showed that there is a polynomial basis of eigenfunctions. The existence of the C^0-semigroup then follows from the maximum principle.

S. Ethier used the Trotter product formula to show that $L_{\text{Kim}} + V$ also generates such a semigroup if V is inward pointing. Very little was known about the regularity properties of solutions. Notice that *no boundary condition* has been specified; a point we will return to later.

Prior Results on the Analysis of Degenerate Diffusions

After the work of Feller, in the early 1950s, the next well known attempt to analyze degenerate operators of this general sort is a paper of Kohn and Nirenberg in the early 1960s. In the past decade various people have considered variants of the Kimura operator, on either simplices, manifolds with boundary or products of intervals. Among them, Gutiérrez, Cerrai and Clément, Bass and Perkins, et al., H. Koch, Hamilton and Daskalopoulos, and Feehan and Pop. The latter researchers were actually more interested in the Heston operator, an operator arising in Mathematical Finance, of the form $L_{\text{Hes}}u = x(\partial_x^2 u + \partial_y^2 u) + Vu$.

My early work is closest to that of Bass and Perkins, and Hamilton and Daskalopoulos, in that we work with anisotropic Hölder spaces.

Manifolds with Corners

We have somewhat generalized the problem from that appearing in Population Genetics. The first step is to consider spaces that generalize the simplex, which are called "manifolds with corners." An N-dimensional manifold with corners is a topological space, P, so that every point p has a coordinate chart modeled on:

$$[0,1)^n \times (-1,1)^m \text{ with } p \leftrightarrow (0,\ldots,0), \text{ and } N = n+m. \quad (10)$$

We denote these local coordinates by $(x_1,\ldots,x_n; y_1,\ldots,y_m)$. The boundary stratum containing p is locally defined by the equations

$$\{x_1 = \cdots = x_n = 0\}. \quad (11)$$

This class of spaces is closed under products.

Boundary Components

If $n = 0$, then p is an interior point; if $n = 1$, then p lies on a hypersurface boundary component. If $n > 1$, then p lies on a boundary component of codimension n. The key property is that: **A boundary component of codimension n arises as the intersection of n hypersurface boundary components.**

A regular convex polyhedron in $\mathbb{R}^N$ is an example of a manifold with corners of dimension N, but it should be noted that manifolds with corners can also have very complicated topology.

The key point is that no more that N boundary hypersurfaces can meet.

Generalized Kimura Operators, I

We consider operators that take the following form in the $(x; y)$-coordinates:

$$L = \sum_{i=1}^{n} a_{ii}(x, y) x_i \partial_{x_i}^2 + \sum_{i,j=1}^{n} a_{ij}(x, y) x_i x_j \partial_{x_i} \partial_{x_j} + \sum_{i=1}^{n} \sum_{l=1}^{N-n} c_{il}(x, y) x_i \partial_{x_i} \partial_{y_l} + \sum_{l,m=1}^{N-n} c_{lm}(x, y) \partial_{y_l} \partial_{y_m} + V, \quad (12)$$

where L is strictly elliptic at interior points, and the coefficients satisfy

$$a_{ii}(0, y) > 0, \quad \sum_{l,m=1}^{N-k} c_{lm}(0, y) \xi_l \xi_m \geq C|\xi|^2, \quad (13)$$

for a $C > 0$, and $V(x, y) x_i \geq 0$, where $x_i = 0$.

Generalized Kimura Geometry

The principal symbol of a generalized Kimura operator defines a metric, ds^2_{WF}, on P. This metric is incomplete, but there are nonetheless unique shortest geodesics joining points sufficiently close to the boundary; we let $\rho_{\mathrm{WF}}(p,q)$ denote the distance function defined by this metric.

Near to a boundary point of codimension n this metric is equivalent to

$$d\sigma^2_{\mathrm{WF}} = \sum_{i=1}^{n} \frac{dx_i^2}{x_i} + \sum_{j=1}^{m} dy_j^2, \tag{14}$$

and

$$\rho_{\mathrm{WF}}((x;y),(x';y')) \sim \sum_{i=1}^{n} |\sqrt{x_i} - \sqrt{x_i'}| + |y - y'|. \tag{15}$$

Generalized Kimura Operators, II

These conditions are easily seen to be coordinate invariant. We call this class of operators *generalized Kimura operators*.

Theorem (Normal Form Theorem)

Adapted Coordinates (x, y), *can be introduced in a neighborhood of any boundary point so that the coefficients* $\{a_{ii}(x, y)\}$ *are all equal* 1.

This is simply a matter of using the Fermi coordinates defined using ds^2_{WF}. As noted, this metric is incomplete, but geodesics foliate a neighborhood of every boundary point, whatever the codimension.
This class of operators includes all examples that have arisen in Population Genetics.

Weights

In local coordinates $(x; y)$ the vector field takes the form

$$V = \sum_{i=1}^{n} b_i(x; y)\partial_{x_i} + \sum_{j=1}^{m} d_j(x; y)\partial_{y_j}. \tag{16}$$

It is not difficult to show that, in adapted coordinates, the value of the coefficient

$$\beta_i = b_i(x; y) \restriction_{x_i=0} \tag{17}$$

is invariantly defined as function on the maximal hypersurface boundary component containing $\{x_i = 0\}$. We call these functions the *weights* of the operator L. We assume that the weights are non-negative. The analytic properties of the resolvent and heat kernels are quite different near the loci where weights vanish.

The Problems we Study

To begin, we consider the inhomogeneous parabolic problem:

$$\begin{cases} \partial_t u - Lu = g \text{ on } (0, T) \times P \text{ where} \\ u(0, p) = f(p) \end{cases} \tag{18}$$

as well as the elliptic problem:

$$(\lambda - L)w = f \text{ for } \lambda \in \mathbb{C}, \tag{19}$$

and establish existence, uniqueness and regularity for data, f, g in certain an-isotropic Hölder spaces.

Boundary Conditions, I

Thus far we have not said anything about boundary conditions, which seems a bit odd for a PDE on a space with such a complicated boundary. The 1d-model operator, $x\partial_x^2 + b\partial_x$ has two indicial roots 0 and $1 - b$; Feller singled out the two natural boundary conditions corresponding to these roots:

$$\lim_{x\to 0^+} x^b \partial_x f(x) = 0 \text{ and } \lim_{x\to 0^+} [\partial_x x f(x) - (2-b)f] = 0 \text{ if } b < 2; \tag{20}$$

the first excludes x^{1-b} whereas the second excludes $x^0 = 1$.

Boundary Conditions, II

For the backward Kolmogorov operator we work with the analogue of the first condition $\lim_{x\to 0^+} x^b\partial_x f(x) = 0$, but it's more natural to simply impose the regularity conditions that $\partial_x f(x)$ has a continuous extensions to 0, and

$$\lim_{x\to 0^+} x\partial_x^2 f(x) = 0. \tag{21}$$

In the sequel we call this, and its generalizations the *regular* solution.

Regular Solutions

In the higher dimensional cases we seek regular solutions to the parabolic and elliptic problems, where now we require that the derivatives $\{\partial_{x_i} f(x, y), \partial_{y_l} f(x, y), \partial_{y_l}\partial_{y_m} f(x, y)\}$ extend continuously to the boundary, and the scaled derivatives

$$x_i \partial_{x_i}^2 f(x, y), x_i x_j \partial_{x_i}\partial_{x_j} f(x, y), x_i \partial_{x_i}\partial_{y_l} f(x, y), \tag{22}$$

extend continuously to vanish on the boundary, where-ever the coefficients vanish. Again these are coordinate invariant conditions. We denote this space by $\mathscr{D}_{\mathrm{WF}}(P)$.

Solutions to the heat equation that satisfy these conditions (for $t > 0$) are called regular solutions.

The Domain of the Regular Operator

If $\mathscr{D}(L) \subset \mathscr{C}^2(P)$ denotes the domain of the regular operator, then a remarkable fact about the regular operator is that data in $\mathscr{C}^{2k}(P)$ is automatically in $\mathscr{D}(L^k)$, which is very peculiar for an operator on an incomplete manifold with boundary, but is familiar from the theory of the Chebyshev operator on $[-1, 1]$:

$$(1 - x^2)\partial_x^2 - x\partial_x,$$

which is a generalized Kimura diffusion.

The Maximum Principle

The basic uniqueness results follow from:

Theorem

Let P be a compact manifold with corners and L a generalized Kimura operator on P. If $u \in \mathscr{C}^1((0,T) \times P) \cap \mathscr{C}^0([0,T] \times P)$ and $u(t,\cdot) \in \mathscr{D}_{\mathrm{WF}}(P)$ for $t > 0$ and u satisfies

$$\partial_t u - Lu \leq 0, \tag{23}$$

then

$$\sup_{[0,T]\times P} u(t,p) = \sup_P u(0,p). \tag{24}$$

So for a regular solution one can specify initial data, but not values on $\partial P \times [0,\infty)$.

A Hopf Maximum Principle

With a cleanness hypothesis on the vector field, one can prove a very nice Hopf boundary maximum principle for solutions with considerably less regularity.

Lemma

Let P be a compact, connected manifold with corners, and L a generalized Kimura diffusion operator that meets ∂P cleanly. Suppose that $w \in \mathscr{D}^2_{\mathrm{WF}}$ is a subsolution of L, $Lw \geq 0$, in a neighborhood, U, of a point $p_0 \in \partial P$ which lies in the interior of a boundary component $\Sigma \in \partial P^{\pitchfork}(L)$. If w attains a local maximum at p_0, then w is constant on U.

L meets ∂P cleanly means that $L\rho_j \equiv 0$ or is strictly positive on each boundary face, $H_j = \{\rho_j = 0\}$; $j = 1, \ldots, M$. $\partial P^{\pitchfork}(L)$ are the boundary components $\Sigma = H_{i_1} \cap \cdots \cap H_{i_k}$, such that L is transverse to each of the faces $\{H_{i_j} : j = 1, \ldots, k\}$.

Analyzing PDEs

To analyze a PDE one generally requires three things:

1. A normal form theorem for the operator (we already gave it).
2. Model problems that can be solved more or less explicitly.
3. A functional analytic framework in which to do the needed perturbation theory to treat the "non-constant coefficient" case.

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Model Operators

For the model spaces we use $\mathbb{R}_+^n \times \mathbb{R}^m$ and for operators, $L_{\boldsymbol{b},m}$, where

$$L_{\boldsymbol{b},m} = \sum_{i=1}^{n} [x_i \partial_{x_i}^2 + b_i \partial_{x_i}] + \Delta_{\mathbb{R}^m}. \tag{25}$$

We have established existence, uniqueness, and very precise regularity results using explicit formulæ for the solutions to the parabolic problems. We did our initial work in Hölder spaces specially adapted to the geometry of these operators, i.e. by the metric defined the principal symbol.

Hölder Spaces, I

Using this metric we define the basic Hölder spaces as the subspace of $\dot{\mathscr{C}}^0(\mathbb{R}_+^n \times \mathbb{R}^m)$ for which the semi-norm

$$[f]_{WF,0,\gamma} = \sup_{(x,y)\neq(\tilde{x},\tilde{y})} \frac{|f(x,y) - f(\tilde{x},\tilde{y})|}{\rho_{WF}((x,y),(\tilde{x},\tilde{y}))^{\gamma}} \tag{26}$$

is finite. Here $0 < \gamma < 1$. We denote this space by $\mathscr{C}_{WF}^{0,\gamma}(\mathbb{R}_+^n \times \mathbb{R}^m)$. There are also higher order versions of these spaces $\mathscr{C}_{WF}^{k,\gamma}(\mathbb{R}_+^n \times \mathbb{R}^m)$, as well as "heat space" analogues, $\mathscr{C}_{WF}^{k,\gamma}([0,\infty] \times \mathbb{R}_+^n \times \mathbb{R}^m)$. In the heat spaces one time derivative is approximately equal in order to two spatial derivatives. The basic seminorm is

$$[g]_{WF,0,\gamma} = \sup_{(x,y,t_1)\neq(\tilde{x},\tilde{y},t_2)} \frac{|g(x,y,t_1) - g(\tilde{x},\tilde{y},t_2)|}{[\sqrt{|t_2 - t_1|} + \rho_{WF}((x,y),(\tilde{x},\tilde{y}))]^{\gamma}}. \tag{27}$$

Two Scales of Spaces

Following Daskalopoulos and Hamilton, and Koch we actually need to define two scales of spaces. The space $\mathscr{C}^{0,2+\gamma}_{\mathrm{WF}}(\mathbb{R}^n_+ \times \mathbb{R}^m)$ is defined by requiring that $f \in \dot{\mathscr{C}}^1(\mathbb{R}^n_+ \times \mathbb{R}^m)$ such that the following semi-norm is finite:

$$[f]_{\mathrm{WF},0,2+\gamma} = [\nabla f]_{\mathrm{WF},0,\gamma} + \sum_{i,j} \left[\sqrt{x_i x_j}\partial_{x_i}\partial_{x_j} f\right]_{\mathrm{WF},0,\gamma} + \sum_{i,l} \left[\sqrt{x_i}\partial_{x_i}\partial_{y_l} f\right]_{\mathrm{WF},0,\gamma} + \sum_{l,m} \left[\partial_{y_l}\partial_{y_m} f\right]_{\mathrm{WF},0,\gamma}. \tag{28}$$

It is easy to see that

$$L_{\boldsymbol{b},m} : \mathscr{C}^{0,2+\gamma}_{\mathrm{WF}}(\mathbb{R}^n_+ \times \mathbb{R}^m) \longrightarrow \mathscr{C}^{0,\gamma}_{\mathrm{WF}}(\mathbb{R}^n_+ \times \mathbb{R}^m). \tag{29}$$

The key to the analysis is to show, e.g., that $(L_{\boldsymbol{b},m} - \mu)^{-1}$ maps $\mathscr{C}^{0,\gamma}_{\mathrm{WF}}$ to $\mathscr{C}^{0,2+\gamma}_{\mathrm{WF}}$.

Hölder Spaces, II

We also define the higher regularity spaces $\mathscr{C}_{\mathrm{WF}}^{k,2+\gamma}(\mathbb{R}_+^n \times \mathbb{R}^m)$, for $k \in \mathbb{N}$. Using the adapted coordinates introduced above we can transfer these spaces to a manifold with corners, obtaining the Banach spaces $\mathscr{C}_{\mathrm{WF}}^{k,\gamma}(P)$, $\mathscr{C}_{\mathrm{WF}}^{k,2+\gamma}(P)$, for $0 < \gamma < 1$, and $k \in \mathbb{N}_0$. Finally these spaces are augmented with "heat-space" analogues $\mathscr{C}_{\mathrm{WF}}^{k,\gamma}([0,T] \times P)$, $\mathscr{C}_{\mathrm{WF}}^{k,2+\gamma}([0,T] \times P)$.

Overall Strategy

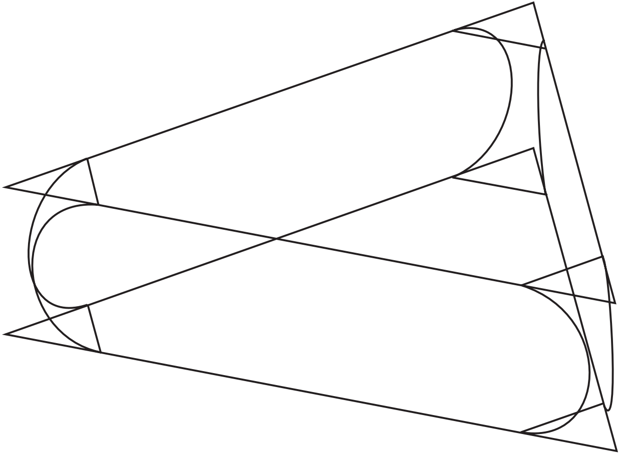
These spaces provide a suitable framework for the needed perturbative arguments. The next step is prove estimates for solutions of the model problems in these Banach spaces.

Because the heat kernel is a product of 1-dimensional kernels, estimates can be proved using the *one-variable-at-a-time method*: Everything is reduced to estimates on the 1-dimensional kernels.

The final argument uses as induction over the maximum codimension of a boundary component, which requires a generalization of the tubular neighborhood theorem.

Doubling Picture

An example of the doubling construction is shown below. It reduces the maximum codimension by 1.



Basic Existence Theorem

The basic existence theorem we prove in the general case is the following:

Theorem

Let P be a compact manifold with corners, and L a generalized Kimura operator defined on P. For $k \in \mathbb{N}_0$, $0 < \gamma < 1$, and $\eta \in \{0, 2\}$, if $f \in \mathscr{C}^{k,\eta+\gamma}_{\mathrm{WF}}(P)$ then the initial value problem

$$\partial_t v - Lv = 0 \text{ with } v(0, p) = f(p) \tag{30}$$

has a unique solution

$$v \in \mathscr{C}^{k,\eta+\gamma}_{\mathrm{WF}}([0, \infty) \times P) \cap \mathscr{C}^{\infty}((0, \infty) \times P),$$

which extends analytically to $\operatorname{Re} t > 0$.

We have an analogous result for the inhomogeneous problem.

The Resolvent

In the elliptic case we have

Theorem

Let P be a compact manifold with corners, and L a generalized Kimura operator defined on P. For $k \in \mathbf{N}_0$, $0 < \gamma < 1$ the spectrum, E, of L acting on $\mathscr{C}^{k,2+\gamma}_{\mathrm{WF}}(P) \subset \mathscr{C}^{k,\gamma}_{\mathrm{WF}}(P)$ is independent of (k, γ). It is a discrete subset lying in the left half plane in a conic neighborhood of $(-\infty, 0]$. The eigenfunctions belong to $\mathscr{C}^{\infty}(P)$.

The are several things to note: 1. These domains are not dense in $\mathscr{C}^{k,\gamma}_{\mathrm{WF}}(P)$. 2. The eigenfunctions may not have a dense span, as these operators are not, in any obvious sense, self adjoint.

Some Consequences, I

The results above require the data to be Hölder continuous, but the applications to Population Genetics and finance require a semi-group defined on $\mathscr{C}^0(P)$.

Using the density of these Hölder spaces in $\mathscr{C}^0(P)$, the Lumer-Phillips theorem easily implies the existence of a positivity preserving c_0-semigroup with generator the graph closure of L acting on $\mathscr{C}^3(P)$.

Some Consequences, II

However, higher order regularity for $t > 0$ with initial data in $\mathscr{C}^0(P)$, is *not* immediately obvious.

The perturbation arguments involve integrations down to $t = 0$. If the data is not in a Hölder space, then it is not clear that these integrals are finite. This is because the parametrix for the heat kernel that we construct is very crude.

Some Consequences, III

A standard construction of Phillips applies to show that the forward Kolmogorov operator L^t, the adjoint of L, generates a semigroup on a (non-dense) subspace of $[\mathscr{C}^0(P)]'$, Borel measures on P.

In Population Genetics, this is the generator of the limiting Markov process. Analytically it is much more complicated than the case described above, as the implied boundary condition selects for the irregular solution. Indeed, if the weights vanish on strata of the boundary, then the domain of L^t contains elements that are measures supported on positive codimensional strata of the boundary. Such elements also arise in the null-space.

Outline

Estimates for data in $\mathscr{C}^0$

The reason that we could not show that solutions to $\partial_t v - Lv = 0$ with $v(p, 0) = f(p) \in \mathscr{C}^0(P)$, are smooth when $t > 0$ was that our parametrix for the heat kernel is very crude. This is largely dictated by the complexity of boundary of P, and the fact that the indicial roots of the operator (essentially the weights) vary along the boundary. It prevents applying the perturbative arguments for data in $\mathscr{C}^0$.

The fact that the indicial roots of P vary renders the usage of geometric microlocal analytic techniques problematic, even for the case of a manifold with boundary.

Methods for Estimates with Data in $\mathscr{C}^0$

Recently, working with Camelia Pop, we have overcome the difficulties that come from low regularity initial data. To do that requires a very different sort of technology. In fact we found two different approaches to this problem.

Camelia used our global existence and regularity theory, along with a localization technique of Krylov and Safanov, to prove local Hölder regularity, for $t > 0$, of solutions to the homogeneous Cauchy problem with initial data in $\mathscr{C}^0$. She proved this in essentially the general case, however it does not lead to heat kernel estimates.

Mazzeo and I found another approach using Dirichlet Forms in the context of "metric-measure" spaces, that gives these local regularity results, but also gives pointwise bounds for the heat kernel. This approach requires the assumption that the "weights" are strictly positive.

Dirichlet Forms, I

To analyze the case of positive weights we use Dirichlet forms, a la K.T. Sturm, to prove Harnack inequalities. Using these techniques we obtain local estimates, so it suffices to work on the model space $S_{n,m} = \mathbb{R}_+^n \times \mathbb{R}^n$. For u, v in an appropriate space of functions, defined on an open set B, $\mathscr{D}_B(Q)$, we define the quadratic form

$$Q_B(u, v) = \int_B \langle A(x; y)\nabla u(x; y), \nabla v(x; y)\rangle d\mu_{\boldsymbol{b}}(x; y), \tag{31}$$

where

$$d\mu_{\boldsymbol{b}}(x; y) = x_1^{b_1(x;y)-1} \cdots x_n^{b_n(x;y)-1} dxdy. \tag{32}$$

The matrix $A(x; y)$ is determined by the principal symbol of L.

Dirichlet Forms, II

Following Sturm, the *intrinsic* metric is that defined by the symbol of the operator; it is equal to ds^2_{WF}. The measure is defined by the weights:

$$d\mu_{\boldsymbol{b}} = x_1^{b_1(x,y)-1} \cdots x_n^{b_n(x,y)-1} dx dy. \tag{33}$$

To show that this is a " doubling measure" we need to assume that the $\{b_i(x, y)\}$ are continuous functions, which are bounded from below by a positive constant. For simplicity we take them to be constant outside a compact neighborhood of $(0, 0)$.

By gluing together these locally defined measures we can define a measure $d\mu_L$ globally on P. There are many possible extensions, which are equivalent along the boundary.

Dirichlet Forms, III

We use $d\mu_{\boldsymbol{b}}$ to define the Hilbert space $\mathscr{H} = L^2(B)$. Integrating by parts we get a second order operator

$$Q(u, v) = (L_Q u, v)_{\mathscr{H}}. \tag{34}$$

A function $u \in \mathscr{D}(Q)$ belongs to $\mathscr{D}(L_Q)$ if this identity holds for all $v \in \mathscr{D}_B(Q)$. This defines the "natural boundary condition," which the regular solution always satisfies.

Singular Tangent Perturbations

In general the operator L_Q defined by the Dirichlet form does not agree with the original Kimura diffusion L. Instead the difference $L - L_Q = V_X$ is a vector field, formally tangent to ∂P. If the weights are non-constant, then the coefficients of V_X are slightly singular

$$V_X = \sum_{i,j} \alpha_{ij}(x;y) \log x_j x_i \partial_{x_i} + \sum_{j,l} \beta_{j,l}(x;y) \log x_j \partial_{y_l} + \widetilde{V}, \quad (35)$$

where $\widetilde{V}$ is a smooth vector field tangent to ∂P.

By working with a non-symmetric Dirichlet form we can incorporate these terms as well:

$$Q^X(u,v) = \int_B [\langle A(x;y)\nabla u(x;y), \nabla v(x;y)\rangle + \langle A(x;y)\nabla u(x;y), X(x;y)v(x;y)\rangle] d\mu_{\boldsymbol{b}}(x;y) \quad (36)$$

Controlling the Singular Tangent Perturbations

To control the singular perturbation we prove:

Lemma (1)

Assume that $\boldsymbol{b} = (b_1, \dots, b_n)$ are positive differentiable functions of $(\boldsymbol{x}; \boldsymbol{y})$, with $0 < \beta_0 < b_j$, constant outside a compact set. Let q be a measurable function on $S_{n,m}$ that satisfies $|q(x;y)| \leq M\left[\chi_B(x;y)\sum_{j=1}^{l}|\log x_i|^k + 1\right]$, for some $k \in \mathbb{N}$, B a bounded set, and $M > 0$. Given $\eta > 0$ there is a $0 < \delta < \frac{1}{2}$, so that if $\operatorname{supp}\chi \subset [0,\delta]^n \times (-1,1)^m$, *then there is a C_η so that*

$$\int\limits_{S_{n,m}} \chi^2(x;y)|q(x;y)|u^2(x;y)d\mu_{\boldsymbol{b}} \leq \eta \int\limits_{S_{n,m}} \langle A\nabla u, \nabla u\rangle \chi^2 d\mu_{\boldsymbol{b}} + C_\eta \int\limits_{S_{n,m}} [\langle A\nabla\chi, \nabla\chi\rangle + \chi^2]u^2 d\mu_{\boldsymbol{b}}, \quad (37)$$

Scale Free L^2-Poincaré Inequality

We can prove that there is a constant C so that, for $B = B_r(p)$ a ball or radius r, if $u \in \mathscr{D}_B(Q)$, then we have the Scale Free L^2-Poincaré Inequality inequality:

$$\int\limits_{B_r(p)} |u - u_B|^2 d\mu_{\boldsymbol{b}} \leq Cr^2 Q(u, u), \tag{38}$$

where

$$u_B = \frac{1}{\mu_{\boldsymbol{b}}(B_r(p))} \int\limits_{B_r(p)} u(x, y) d\mu_{\boldsymbol{b}}(x, y). \tag{39}$$

Using results of K.T. Sturm one can show that this implies that non-negative local solutions of $\partial_t u - L_Q u = 0$ satisfy a Harnack inequality, which in turn implies that, even weak solutions with L^2-initial data, satisfy Hölder estimates for $t > 0$.

From L_Q to L

As noted above, in the cases of principle interest (different mutation rates between different types), the coefficients of the tangent vector field part of L_Q are slightly singular: they include $\log x_i$ terms. We really want to analyze solutions to $\partial_t u - Lu = 0$. Using Lemma 1, we can adapt Moser's original argument to show that the non-negative, weak, local solutions of the original equation also satisfy a Harnack inequality, and so are also Hölder continuous for positive times.

Local Estimates, Heat Kernel Estimate, Higher Norms

Combining these results we get Harnack inequalities for local solutions to Kimura diffusion equations, which in turn imply Hölder estimates for positive times, and pointwise upper and lower bounds on the heat kernels. Once we have Hölder estimates, then we can use our earlier results to obtain higher norm estimates as well. In particular we learn that the operator L, defined as the $\mathscr{C}^0(P)$-graph closure of its action on $\mathscr{C}^3(P)$ has a compact resolvent, with spectrum in a conic neighborhood of $(-\infty, 0]$.

Regularity for Kimura Diffusions on $\mathscr{C}^0(P)$

Theorem

Let P be a compact manifold with corners and L is a generalized Kimura diffusion operator defined on P with positive weights. If $\overline{L}$ is the $\mathscr{C}^0$-graph closure of L acting on $\mathscr{C}^3(P)$, then for μ with $\operatorname{Re}\mu > 0$, the resolvent operator $(\mu - \overline{L})^{-1}$ is bounded from $\mathscr{C}^0(P)$ to $\mathscr{C}^{0,\gamma}_{\mathrm{WF}}(P)$, and is therefore a compact operator.

For initial data in $\mathscr{C}^0(P)$, the regular solution to the initial value problem $\partial_t u - Lu = 0$ lies in $u \in \mathscr{C}^\infty(P \times (0,\infty))$, and has an analytic extension to the half-plane $\{t : \operatorname{Re} t > 0\}$.

The spectrum, $\sigma_{\mathscr{C}^0}(\overline{L})$, lies in a conic neighborhood of $(-\infty, 0]$.

The spectrum and eigenfunctions of $\overline{L}$ are the same as for the closure of the operator on $L^2(P)$. Because this operator is not self-adjoint, we do not know if the span of the eigenvectors is dense.

Outline

The Heat Kernel

As noted above, the kernel function for the semigroup e^{tL} takes the form $p_t(\xi, \eta) d\mu_L(\eta)$. The kernel function satisfies the equations

$$\begin{aligned} (\partial_t - L_\xi) p_t(\xi, \eta) &= 0 \text{ and} \\ (\partial_t + L^t_\eta) p_t(\xi, \eta) &= 0, \end{aligned} \tag{40}$$

and the operator it defines converges to the identity as $t \to 0^+$. Here L^t_η is the adjoint w.r.t. $d\mu_L$. If the weights are non-constant then L^t_η includes a tangent vector field with log-singularities.

We give a "Gaussian" estimate for the heat kernel in terms of the intrinsic distance $\rho_{\mathrm{WF}}(\xi, \eta)$ defined by the principal symbol of L.

Estimates for the Heat Kernel

We can prove the following result:

Theorem

Assume that P is a compact manifold with corners and L is a generalized Kimura diffusion defined on P with positive weights. If we represent the kernel of the operator e^{tL} as $p_t(\xi,\eta)d\mu_L(\eta)$, then there are positive constants C_0, C_1, C_2 so that, for all $t > 0$ and pairs $\xi, \eta \in P$ we have

$$p_t(\xi,\eta) \leq \frac{C_0 \exp\left(-\frac{\rho^2_{\mathrm{WF}}(\xi,\eta)}{C_2 t}\right)}{\sqrt{\mu_L(B^i_{\sqrt{t}}(\xi))\mu_L(B^i_{\sqrt{t}}(\eta))}} \times \left(1 + \frac{\rho_{\mathrm{WF}}(\xi,\eta)}{\sqrt{t}}\right)^D \cdot \exp(C_1 t). \tag{41}$$

For each $\eta \in P$, the function $(\xi, t) \mapsto p_t(\xi,\eta)$ belongs to $\mathscr{C}^\infty(P \times (0,\infty))$.

Estimates for the Heat Kernel with Constant Weights

The previous result can be refined somewhat, if all the weights are positive and constant. In this case we can show that the kernel function

$$p_t(\xi,\eta)\in\mathcal{C}^\infty(P\times P\times(0,\infty)), \tag{42}$$

so that the singularities of the heat kernel are precisely those defined by the measure, $d\mu_L$, which has the form

$$d\mu_L(\eta)=w(\eta)\prod_{j=1}^{M}\rho_j(\eta)^{b_j-1}dV_P. \tag{43}$$

Here the $\{\rho_j\}$ are defining functions for the boundary hypersurfaces, $w\in\mathcal{C}^\infty(P)$ and dV_P is a smooth, non-degenerate measure on P. The kernel p_t also satisfies a lower bound similar to the upper bound in (41).

The Heat Kernel with Vanishing Weights

The heat kernel was studied by Shimakura, among others, in the classical case of the simplex, Σ_n, where the weights are constant. If the weights all vanish on a stratum of $\partial\Sigma_n$, then the operator L is "tangent" to this stratum.

Shimakura showed that each stratum, S, where the weights are all zero contributes a term to the heat kernel of the form

$$p_t^S(\xi,\eta)d\mu_{L,S}(\eta), \tag{44}$$

where $d\mu_{L,S}(\eta)$ is a measure supported on S.

From Shimakura's results it is quite clear that estimates like those that hold when the weights are positive cannot hold when weights vanish on hypersurface boundary components. These results have recently been generalized to the "clean case" by C. Pop and myself.

Outline

The Terminal Boundary

In certain special cases we can describe the null-space of L and L^t quite precisely. We say that L meet ∂P cleanly if the vector field V is either uniformly transverse, or tangent to each hypersurface boundary of P.

In this case we define the *terminal boundary* of P, relative to L, $\partial P_{\text{ter}}(L)$, to be connected components of the stratification of ∂P to which L is tangent, which are themselves closed manifolds, or such that L is everywhere transverse to the boundary of the component. If L is everywhere transverse to ∂P, then P itself is the only terminal boundary component.

The Null-space of L^t

It turns out to be somewhat easier to describe the null-space of the adjoint. As L acts on $\mathscr{C}^0(P)$, its adjoint acts naturally on a subspace of the Borel measures on P. Because $\mathscr{C}^0(P)$ is not reflexive, this subspace is typically not dense.

Theorem

Suppose that L meets ∂P cleanly. To each element of $\Sigma \in \partial P_{\text{ter}}(L)$ there is an element of the null-space of L^t represented by a non-negative measure supported on Σ.

The Null-space of L

We can also show that the null-space of the adjoint of L acting on the Hölder spaces $\mathscr{C}^{0,\gamma}_{\mathrm{WF}}(P)$ agrees with the null-space of L^t. Since L is Fredholm of index 0, this implies that the null-space of L acting on $\mathscr{C}^{0,\gamma}_{\mathrm{WF}}(P)$ has dimension equal to $n_0 = |\partial P_{\mathrm{ter}}(L)|$. This space is spanned by a collection of non-negative, smooth functions, $\{w_1, , \dots, w_{n_0}\}$.

Finally, using Pop's regularity results, it follows that this null-space also agrees with that of graph closure of L acting on $\mathscr{C}^0(P)$.

Long-time Asymptotics

For the operators acting on the Hölder spaces and $\mathscr{C}^0(P)$ we can establish the existence of a spectral gap

$$\max\{\operatorname{Re} z : z \in \operatorname{spec}(L) \setminus \{0\}\} = \eta < 0. \tag{45}$$

If the initial data for the parabolic equation is $f \in \mathscr{C}^0(P)$, then we have the asymptotic behavior:

$$v(p,t) = \sum_{j=1}^{n_0} \ell_j(f) w_j + O(e^{\eta t}). \tag{46}$$

Here $\{\ell_j\}$ are non-negative functionals defined by elements of the null-space of L^t.

Outline

The Martingale Problem, I

Connected to the operator L is a stochastic differential equation on P and a martingale problem. In joint work with Camelia Pop, we have established the existence of a unique weak solution to the SDE on the non-compact model spaces, $S_{m,n}$, which in turn leads to a unique solution to the martingale problem in the manifold with corners context.

The SDE is rather complicated to analyze because it has only Holder 1/2 coefficients. In light of this we found it easier to piece together the solutions of the martingale problem to solve it on a manifold with corners.

The Martingale Problem, II

Let P be a manifold with corners, and L a generalized Kimura diffusion operator on P. Let $\mathscr{X} = \mathscr{C}^0([0,\infty); P)$ be the paths on P, and $\mathscr{B}_t$ the usual filtration by the Borel subsets, $\mathscr{B}$, of $\mathscr{C}^0([0,t]; P)$. For each $p \in P$, there is a unique probability measure $\mathbb{Q}^p$ on $(\mathscr{X}, \mathscr{B})$, such that $\mathbb{Q}^p(\omega(0) = p) = 1$, and for all $\varphi \in \mathscr{C}^\infty([0,\infty) \times P)$,

$$M_t^\varphi = \varphi(t,\omega(t)) - \varphi(0,\omega(0)) - \int_0^t [\varphi_t(s,\omega(s)) + L\varphi(s,\omega(s))]ds \tag{47}$$

is a martingale with respect to the appropriate filtration.

The family of probability measures $\{\mathbb{Q}^p : p \in P\}$ on the filtered space $(P, \mathscr{B}, \{\mathscr{B}_t\}_{t\geq 0})$ satisfies the strong Markov property.

Using these results we get a Feynmann-Kac representation for solutions to the Kimura diffusion equation

$$\begin{aligned} \partial_t u - Lu &= 0 \text{ on } (0,\infty)\times P \\ u(0,p) &= f(p). \end{aligned} \tag{48}$$

It is

$$u(t,p) = \mathbb{E}_{\mathbb{Q}^p}[f(\omega(t))]. \tag{49}$$

This representation allows us to use PDE methods to study many properties of these processes.

Thanks!

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