A THEORY OF GENERALISED POPULATION PROCESSES

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ABSTRACT

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A systematic study of population processes subsuming the Wright-Fisher model in classical population genetics is undertaken. Discrete and continuum methods are developed for the analysis of these generalised processes, which in many respects can exhibit strikingly different dynamics than the canonical model. Genetic features which are stable across the entire class are also identified, and lead to new understandings of the original model.

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List of Notation

$[x]$	Integer part of a real number x.
$P(\cdot)$	The probability of some event.
$\mathbf{P}$	Bold notation denote transition matrices.
$C(X), C^0(X)$	Continuous real-valued functions on a metric space X.
$C^k(X)$	Real-valued functions with k continuous derivatives on X.
$C(S,T)$	Set of continuous functions between metric spaces S and T.
$\overset{d}{=}$	Equality in distribution.
$\mathscr{P}$	Set of polynomials
$\mathcal{D}(A)$	Domain of an operator A.
$P_x(X_t)$	Short-hand for $P(X_t \vert X_0 = x)$.
$E_x(X_t)$	Short-hand for $E(X_t \vert X_0 = x)$.
K_N	The set $\{0, 1/N, 2/N, \ldots, 1\}$.
π_N	The canonical projection $\pi_N : C[0,1] \to C(K_N)$
$\mathcal{M}_1(X)$	The set of Borel probability measures on X.
Ω	A measure-valued function $\Omega : (0,1) \to \mathcal{M}_1(X)$
G_Ω	The Generalised Wright-Fisher operator associated with Ω
G^*	The adjoint of an operator G
$\overline{G}$	The closure of a set or an operator G.

Introduction

The field of population genetics, broadly construed, is concerned with the evolution of heritable traits. Its birth may be traced to the early 20th-century, in a synthesis between two apparently unrelated, and potentially incompatible theories.

Charles Darwin, in *The Origin of Species*, postulated mutation and natural selection as the agent underlying evolution. Moreover, based on his experience as a naturalist, Darwin proposed that variation in organismal traits was continuous, with evolutionary change occurring in incremental, gradual steps. There was a significant objection to this model, however, originating in the so-called "blending" view of inheritance. If phenotypal characteristics were continuous, and offspring tended to mix the characteristics of their parents, then the variance of any trait would rapidly decrease every generation until a population reached complete homogeneity. No variation could then exist for selection to act upon.

In his work on genetical inheritance, Gregor Mendel proposed a "quantal" theory in which inheritance was propagated through discrete units. This theory, rediscovered at the turn of the 20th-century, seemed to contradict the Darwinian gradualist paradigm. Many biologists became adherents of the saltationist view of evolution, wherein change occurred in large mutational jumps. Mendelism, it was said, had destroyed Darwinism.

Significantly, it would require the first serious intrusion of mathematics into the debate to show that these two notions were reconcilable. The intrusion came in the form of the Hardy–Weinberg law, which stands as a turning point in the history of population genetics—not only as the key unifying principle between Mendelism and Darwinism—but also as an example of the clarifying power of mathematics in a discipline hitherto untouched by it. In its simplest form, the theorem states that a Mendelian diploid population having three genotypic frequencies achieves, after a single generation of random mating, stable frequencies which are maintained for all time. Thus, far from contradicting Darwin, Mendel's system in fact supplies the mechanism for inheritance of phenotypic variation needed to complete Darwin's argument.

This foundation rapidly developed, by mid-century, into a mature form of mathematical population genetics, centering around the work of S. Wright, R. Fisher, and J. B. S. Haldane, who formulated a quantitative description of evolutionary processes taking into account both selection and mutational forces, as well as a new, stochastic, effect due to environmental limitations on resources. This Wright–Fisher model considers a population of N reproducing individuals of two genetic types. In each generation, individuals independently produce a large number of gametes (potential offspring) of their own type; the next generation is formed by randomly sampling N gametes from this pool of possible offspring. Total population size remains fixed from generation to generation due to finite carrying capacity: only relative numbers of differing types change. Natural selection is incorporated by favoring fitter individuals in the sampling procedure, and mutation by randomly altering the types of offspring at specified rates. In contemporary language, the fluctuations in the numbers of a given type is a Markov chain $\{X_k, k = 0, 1, \ldots\}$ on state space $\{0, \ldots, N\}$, whose transition matrix takes the form

$$\mathbf{P}_{ij} = \binom{N}{j} (p_i)^j (1 - p_i)^{N-j} \tag{0.0.1}$$

where $p_i = i/N$ in the non-selective, non-mutation case, and a suitably adapted function of i/N when selection and mutation are present.

Among the many interesting questions that can be asked about this model, there are three that stand out: given some initializing state, 1) What is the probability of ultimate survival of a given type? 2) What is the average time for some type to fixate in the population? 3) Does X_k have an equilibrium measure, and what is its form?

While relatively simple to describe, this model turns out to be surprisingly difficult to analyse directly. In principle, of course, the solutions to all these problems are merely the solutions to a system of N linear equations, but the complicated nature of the matrix $\mathbf{P}$ makes the inversion of this system quite intractable for any but minute population sizes N. Moreover, very little qualitative insight could be achieved by a direct numerical inversion.

Instead, in an approach pioneered by M. Kimura [11], and already presaged in the early work of Fisher and Wright, the Markov chain is approximated by a model with continuous variables — its diffusion limit. This approximation, which Kimura called "the partial-differential equation method" becomes increasingly accurate as $N \to \infty$, and involves replacing numbers of individuals with frequencies of types, and discrete-time generations by a continuous time scaling. It was only given a truly rigorous mathematical basis a decade later by Trotter [22] and Feller [6], among others, who showed that the sequence of scaled processes $\frac{1}{N}X^N_{[Nt]}$ converges weakly to a continuous-time Markov process X_t on $[0,1]$, whose generator is

$$Gu(x) = \frac{1}{2}x(1-x)\frac{d^2u}{dx^2} + G_1u(x) \tag{0.0.2}$$

where G_1 is a first-order differential operator encoding selective and mutation effects, and the domain $\mathcal{D}(G)$ described by a Feller boundary condition.

The analogous questions on stopping times and the forms of the asymptotic distribution can now be posed for the limit X_t, which are much easier to answer and understand in some principled way, since all the formidable machinery of the theory of differential and partial differential equations can be invoked. The latter are also easier to solve than the recurrence relations in the discrete setup, in the same way that an integral is usually simpler to evaluate than an infinite sum.

The Wright–Fisher model is founded on a set of assumptions about how organisms reproduce, and the way in which the constraint of finite population size enforces dependencies among individuals. As an example, one important assumption lies in the hypothesis that each individual produces an exceedingly large number of potential offspring. What happens if this assumption is relaxed, for instance, to the statement merely that each individual produces a random (finite) number of offspring? Do general features of the model remain stable? To what extent do the predictions or inferences made using the Wright-Fisher framework depend upon the assumptions?

A significant source of such generalized models was first furnished by C. Cannings in the 1970s. Cannings introduced a very general scheme for evolutionary processes, based only on the probabilistic concept of *exchangeability*—a form of homogeneity deriving from the invariance of the process under a relabeling of individuals. In this process, the conditional distribution of the chain is governed by

$$X_k | X_{k-1} \overset{d}{=} \sum_{i=1}^{X_{k-1}} \nu_i \tag{0.0.3}$$

where ν_i are any positive integer-valued exchangeable variables summing to N. The Wright-Fisher model occurs as the special case when $\nu = (\nu_1, \ldots, \nu_N)$ have a multinomial distribution.

Despite the observation that these processes are, at least conceptually, often more realistic models than the classical theory, and additionally, offer an opportunity of analyzing the sensitivity of predictions over a natural set of models, relatively little work has been done in this area.

One reason for this paucity is a central-limit theorem type dogma: it can be proven that a large class of Cannings processes have precisely the *same* diffusion limit as the Wright–Fisher process. It follows that such processes can be well-approximated by the standard model, with differences arising only in higher-order effects. Secondly, the set of models that cannot be well approximated is difficult to analyse; it was not even understood how to obtain a continuum limit in these cases (necessarily different from the Wright–Fisher diffusion), let alone derive their corresponding evolutionary dynamics. The map between the exchangeable variables ν and the asymptotic process is highly complex and mysterious, aggravated by the fact that the ν_i are often highly negatively dependent random variables.

This dissertation proposes a framework for the study of such generalised population models. While the backward-time, or coalescent theory [21], [18] of these processes has seen a recent flowering, their forward-time analysis has yet to be achieved, particularly in the presence of selection and mutation. This is our principal topic of inquiry, and as far as the author knows, the present thesis records the first systematic exploration of non-Wright-Fisherian aspects of these models.

Chapter I begins with an overview of the relevant Markov chain models for evolution, and the basic definition of the class of systems under study — the Generalized Wright-Fisher (GWF) — two-type processes, a wide-ranging and mathematically compelling class containing the Cannings models. Asymptotic bounds are developed on the distribution of the absorption times and conditional fixation times, and the methods shown how to generalise to higher-dimensional, multi-type Cannings processes. It is next described how to incorporate selection and mutation in a canonical way into GWF processes, and the basic discrete theory of these processes is developed. The chapter concludes with bounds on the absorption times of GWF processes under one-way mutation.

In Chapter II, we introduce and construct some important examples of GWF processes, and show that many of these examples achieve the bounds developed in Chapter I, thereby proving their optimality. Two of these models: the Wright-Fisher Model, and the so-called Λ_1 Cannings model, are identified in some sense as antipodes, and an interesting, biologically realistic, parametric family of power-law models, bridging the two processes is constructed. We end with a discussion of the convexity of the space of GWF processes, and a characterization theorem for the extreme points of this space, which will be needed in succeeding chapters.

Chapter III is devoted to the construction of a continuum theory which generalises the diffusion theory of the Wright-Fisher model. A representation formula for the generator of any continuum limit of a sequence of GWF Markov chains is derived, parameterized by three variables: selection pressure β, mutation rates θ_1, θ_2, and a new object: Ω, a probability measure valued function, which quantifies the type of random drift. The Wright-Fisher model is identified exactly as that process where $\Omega : x \in (0,1) \mapsto \delta_x$, and hence the only continuum process with a local generator and continuous sample paths. We provide a condition for the convergence of a GWF chain to the Wright-Fisher diffusion which generalizes previous characterizations in the literature, and also state conditions under which a GWF chain will converge weakly to a continuum limit. Our theory is used to give an abstract construction of the continuum limit for any convergent Cannings chain. Finally, the continuum limit for each of our example processes is proved and precise formulae for their generators are given.

The generators of a generic GWF continuum limit are integro-differential operators, and the apposite calculations for stopping times and stationary measures usually do not admit closed-form analysis. In Chapter IV, the topological tool of the maximum principle is built up, and we use it to obtain quite precise information concerning solutions. We also pose some interesting extremal problems, such as: which family of drift measures Ω maximizes and minimizes the probability of fixation for a given selection pressure? These extremal problems are solved with the maximum principle, and thus allow bounds to be developed on genetic quantities involving non-zero selection — a case not easily amenable by discrete methods. Finally, we discuss aspects of the stationary distributions for GWF processes, using continuum theory, proving the existence and uniqueness of equilibrium measures for Cannings processes under positive mutation, and develop formulae for the moments of such measures. Since the stationary distribution is, in biological practice, the object of main interest for inferential questions, we devote space to the development of the appropriate parameter estimation framework for GWF processes, and prove theorems regarding the identifiability of mutation parameters. Finally, we extend the validity of the Poisson Random Field approximation theorem, from that of the Wright-Fisher model, to that of any Cannings model. This serves to show that certain classical statistics — the so-called Watterson estimator — is in fact sufficient for the mutation parameter even in this wider generality.

Structurally, this thesis is roughly divided into two parts, based on methodological grounds. In the first two chapters, we restrict ourselves purely to discrete methods, making use only of the very elementary parts of Markov chain and martingale theory. Nonetheless, a surprising amount of information can be obtained. The last two chapters develop continuum methods, and here we employ more advanced mathematics from semigroup theory, functional analysis, differential equations, and the convergence theory of Markov processes. These two methodologies complement one another: only a few of our theorems seem to be easily proved with either method.

The contributions of the present thesis are both mathematical and biological. To the pure mathematician, of greatest interest is perhaps the development of a non-diffusive continuum theory for the approximation of time-homogeneous, bounded, martingale Markov chains which have a given conditional variance vanishing at the boundaries. Diffusion approximation is formally trivial: one finds some natural scaling so that means and covariances converge: these second-order statistics parameterize the diffusion, and the rest is just "rigorizing the obvious" — notwithstanding its technical challenge. In the systems we consider, the higher moments are a vital part of the process and cannot be ignored; the very structure of the continuum limit becomes interesting. Consequently, the resulting class of generators we consider is extremely large, and are found to be parameterized by a measure-valued function Ω; we also demonstrate a kind of converse, and show how approximation by extreme measures allows one in effect to construct weak solutions to backward Kolmogorov equations associated to Ω. There are other things, such as the use of completely elementary methods to construct fairly powerful estimates on the distribution of absorption times, or the employment of maximum principles to obtain quite concrete quantitative estimates, which may pique the interest of the purist. The applied mathematician will find many new results on the forward-time analysis of Cannings processes: these include absorption and fixation time bounds, probability of fixation bounds under selection, as well as a great deal of information on their stationary measures.

This thesis was written mainly for mathematically-trained practitioners, but there seem to be important consequences of our results for biology at large. From the broader purview of science, our work can be considered foundational, in that we have arrived at a deeper understanding of the classical Wright-Fisher model itself, by probing its sensitivity to modifications in its assumptive offspring structure. We can identify the stable features of the Wright-Fisher model (conditional fixation times, for example), and we can also identify properties which are highly model dependent (fixation probabilities of a mutant, as another example). An important new biological idea which has emerged from our general analysis is that there are many different *kinds* of genetic drift, as parameterized by a measure-valued function: the random drift that biologists have hitherto recognized has only been a single manifestation of this more general drift. That the *type* of genetic drift has profound effect on some predictions — and less so on others — is one of the main messages of this work.

What may also be of significant surprise is that the classical model — the Wright-Fisher model — is anything but an “average” or “typical” model. Geometrically, one might naively expect that it lies somewhere in the center of the space of Cannings models, but this is very far from the truth. It is in actuality an extreme point, and operates very near the lower bound for a number of genetic quantities, fixation probability being one of them. One striking consequence is that the model of Wright and Fisher is the drift model most disadvantageous for the perpetuation of new and selectively advantageous mutants. This has inferential ramifications: any inference on selective pressure from data employing the Wright-Fisher framework is an upper bound on its actual value.

Chapter 1

Markov Chain Models of Evolution

After a brief recapitulation of the classical theory of population genetics, this chapter defines generalized two-type processes and explores a number of their basic properties, derived from the discrete Markov chain. We describe the absorbing states of a generalized process, and develop tail bounds on the absorption time, using this to prove almost sure absorption of every path, as well as establishing limits on the mean absorption time. The properties of the chains conditional on fixation are also explored, including the probability of fixation and time to fixation, which are proved to be stable features of any generalized processes. We provide extensions of some of these methods to the higher-dimensional K-type case. The adjunction of selection and mutational forces to the model are then described, and further fundamental aspects of the processes are investigated using purely discrete methods.

1.1 Classical Neutral Models

1.1.1 The Wright-Fisher Model

In the early 1930's, Fisher [7] originally, and Wright [23] subsequently, described a new mathematical model of evolution. Its novelty arose from the incorporation of stochastic effects arising from finite population size, a crucial improvement upon Haldane's preceding deterministic theory of evolution. They considered a fixed population of N asexual reproducing individuals of two types: A and B. In every generation, individuals independently produce a large number of gametes (potential offspring) of type identical to their parent; the collection of gametes is placed into an urn and the next generation is formed by sampling N gametes from the urn. Let X_k denote the number of individuals of type A at time points $k = 0, 1, \ldots$. Then one readily sees that in the large offspring limit, X_k has the structure of a Markov chain on states $\{0, \ldots, N\}$, with the binomial transition matrix

$$\mathbf{P}_{ij} = \binom{N}{j} \left(\frac{i}{N}\right)^{j} \left(1 - \frac{i}{N}\right)^{N-j} \tag{1.1.1}$$

Simple computations show that X_k is a martingale (in correspondence with the specification of selective neutrality), and $\{0, N\}$ the only absorbing states, with absorption occurring almost surely. Wright and Fisher then proceeded to determine the behavior of various important genetic quantities from this description, foremost among them 1) the probability of fixation of a type, and 2) the average time to absorption/fixation of a type, starting at $X_0 = 1$. We shall not repeat these calculations here, because a study of these functionals, in a much more expanded setting, will be conducted.

1.1.2 The Cannings Exchangeable Model

There is another construction of the Wright-Fisher model which leads to an important generalization due to Cannings [2]. We suppose that individuals reproduce independently from an offspring number distribution F. If $\xi_1, \ldots, \xi_N$ are independent random variables each with law F, let

$$\nu = (\nu_1, \ldots, \nu_N) \overset{d}{=} (\xi_1, \ldots, \xi_N) | \sum_{i=1}^{N} \xi_i = N \tag{1.1.2}$$

In other words, ν_i is the random number of offspring contributed to the subsequent generation by individual i, the fixed population size stipulation enforced by the conditioning event $\sum \nu_i = N$. One notes that ν is an exchangeable vector of random variables. Because of this, the conditional variable $X_k | X_{k-1}$ now has the structure:

$$X_k | X_{k-1} \overset{d}{=} \sum_{i=1}^{X_{k-1}} \nu_i \tag{1.1.3}$$

The Wright-Fisher model occurs exactly when F has a Poisson distribution; ν then takes the form of a multinomial distribution with parameters $(N, 1/N, \ldots, 1/N)$. In general, the foregoing model for arbitrary F is called *Karlin's conditional branching process.*

The probabilistic mechanism for ensuring fixed population size in the above may appear artificial: one simply retains those realizations of a standard branching process for which there "happen" only to be N individuals in every generation. In reality, a fixed population size occurs because of the inherent constraint of environmental carrying capacity, or the structure of relationships within a population. Cannings' insight was to take the exchangeable variable ν as fundamental, rather than the independent offspring variables ξ, thus raising the aspect of *homogeneity* to an axiom. In the Cannings' model, the process is fully prescribed by any positive-integer valued exchangeable distribution ν satisfying $\sum \nu_i = N$, with the Markov chain for the evolution of a given type governed then by (1.1.3).

While equation (1.1.3) in principle gives a mapping between the exchangeable variable ν and the associated Markov transition matrix, this mapping is extremely ungainly, depending on partition-theoretic properties of N. The complexity of the map is an enormous obstruction to a forward-time understanding of the Cannings model. The conditioning inherent in Karlin's model also makes a direct analysis difficult: Karlin himself published a few questionable theorems on his model (e.g. the diffusion limit theorems 4 and 5 in [10] are most likely false, see [19] for the correct hypotheses).

Surprisingly little is known about the forward-time behavior of the Markov chain (1.1.3), other than the eigenvalues of its transition matrix $\mathbf{P}_{ij}$, which can be computed exactly from the moments of ν_i. One might naively expect that the eigenvalues of $\mathbf{P}$ — for example, the so-called "eigenvalue gap" between the top and second-largest eigenvalues — would contain information about such quantities as the absorption time, but this is rather misleading: it turns out that the eigenvalue gap is the same for all Cannings models, but we will prove that the absorption time can differ greatly, by even orders of magnitude for different choices of exchangeable variable ν. This is a general problem related to the asymmetry, or lack of self-adjointness, of $\mathbf{P}$. Even in the simple case of the Wright-Fisher model, knowledge of the eigenvalues of $\mathbf{P}$ is insufficient for an understanding of the absorption time: one needs actually to understand the entire spectral decomposition (left and right eigenvectors) of $\mathbf{P}$ — which do not have closed-form expressions [5].

Moments of the Cannings Model

The moments of a Cannings process have a beautiful structural regularity which we will employ in due course. Using the fact that $E\nu_i = 1$, one verifies easily that every Cannings process X_k is a martingale:

$$E[X_{k+1}|X_k] = X_k \tag{1.1.4}$$

Moreover, the second-order statistics depend not on the full distribution ν, but only on the offspring variance $\sigma^2 = Var(\nu_i)$:

$$E[X_{k+1}^2|X_k] = \frac{N\sigma^2}{N-1}X_k(1 - X_k/N) + X_k^2 \tag{1.1.5}$$

One can continue to show that all conditional moments $E[X_{k+1}^m|X_k]$ are m-th order polynomials in X_k. This implies, by taking expectations, that the *unconditional* moments satisfy linear recurrence relations, with inhomogeneities entering in from the solutions of lower-order equations (c.f. Section 1.3.1).

The formulae (1.1.4) and (1.1.5) illustrate the first "stable" properties of generic neutral processes: for populations of a given offspring variance, the conditional first and second order statistics — and by taking expectations, the *unconditional* lower moments too — behaves identically across the entire class of Cannings models. This invariance of the first two moments now leads us to consider an even more general definition.

1.2 Neutral Generalized Processes

Let us first begin with a definition for a two-type generalized population process:

Definition 1.2.1. X_k is a *Pure-Drift*[1] *Generalized Process* with offspring variance σ_N^2 if it is a Markov chain on states $\{0, \ldots, N\}$ for which the conditional moments satisfy

$$E[X_{k+1}|X_k] = X_k \tag{1.2.1}$$

$$E[X_{k+1}^2|X_k] = \frac{N\sigma_N^2}{N-1} X_k(1 - X_k/N) + X_k^2 \tag{1.2.2}$$

or alternatively, and more transparently:

$$E[X_{k+1}|X_k] = X_k \tag{1.2.3}$$

$$Var[X_{k+1}|X_k] = \frac{N\sigma_N^2}{N-1} X_k(1 - X_k/N) \tag{1.2.4}$$

Let $\mathbf{Q}_{ij}$ be the transition matrix underlying X_k. Consistent with Cannings' model, we shall call the distribution accorded to row $\mathbf{Q}_{1,j}$ the *offspring distribution*. The above moment conditions are equivalently restated as:

$$\sum_{j=0}^{N} j\mathbf{Q}_{ij} = i \tag{1.2.5}$$

$$\sum_{j=0}^{N} (j-i)^2 \mathbf{Q}_{ij} = \frac{N\sigma_N^2}{N-1} i \left(1 - \frac{i}{N}\right) \tag{1.2.6}$$

There are many reasons why one chooses a particular definition over another, and not all such reasons lie within the immediate power of words to convey: much depends on the experience of the definer. Viewed in the light of the Cannings' model, the specifications (1.2.1,1.2.2) are the natural manifestation of symmetry assumptions; qualitatively, the mean condition (1.2.1) expresses a basic neutrality, while (1.2.2) is a gross, second-order characterization of the strength of drift as a function of allele frequency. Taken together,

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[1] There are two definitions of the abused term "drift" in the literature, unfortunately at odds with one another: probabilists employ the word for the infinitesimal mean of a diffusion, while biologists use the term to describe the stochastic integral term in an Ito process. We will side with the biologists, and drift will generally denote the random component of a process.

they could be construed as a minimal set of desiderata on any neutral population process: our definition of a GWF process is from this vantage point natural. On the other hand, if one's interest is confined strictly to Cannings' processes, the definition may be considered too general, particularly since equally natural higher-order symmetry hypotheses such as $\mathbf{Q}_{i,j} = \mathbf{Q}_{N-i,N-j}$ are not imposed. Nevertheless, it will turn out the inclusion of asymmetric processes becomes technically important in the derivation of bounds under selection (Section 4.5). Moreover, for many of our results it will be possible to find symmetric, and even Cannings processes which operate near our theoretical limits (which are established over the entire class of asymmetric models).

Now it is a well-known result of diffusion theory (c.f. [17]), that if a Markov chain X_k satisfies $(1.2.1, 1.2.2)$, $\sigma_N^2 \to \sigma^2 < \infty$ and additionally possesses *some* conditional higher moment $E[|X_{k+1}/N - X_k/N|^{2+\delta}|X_k]$ of order $o(1/N)$ uniformly in X_k, then X_k can be well approximated by Kimura's diffusion process for large N, and hence by the Wright-Fisher model itself. Since we take particular interest in exploring GWF and Cannings processes which cannot be approximated by the standard model, we refrain from imposing any constraints on higher-order statistics of the process.

Our principal task will be to determine the conceivable range of behavior for important genetic quantities (absorption times, probabilities of fixation etc.) under the proposed constraints on the first two conditional statistics, but when the higher-order properties of genetic drift are allowed to freely vary.

1.2.1 Examples of Pure-Drift GWF Processes.

It is opportune here to introduce model cases for $\mathbf{Q}_N$, whose behavior in many respects are typical of non-Wright-Fisherian models, and which will be used to illustrate aspects of our theory. Deeper examinations of specific properties of the following processes are conducted in several passes, particularly in Chapters 2, 3 and 4.

Cannings Models.

As remarked above, by a simple computation on its moments, every Cannings model, and in particular the Wright-Fisher model, is a pure-drift GWF process; the last thus already contains a large and biologically germane set of processes.

The Λ_1-Cannings Model.

In a sense the antipode to the Wright-Fisher process, this Cannings process is defined by the transition matrix:

$$\mathbf{Q}_{ij} = \begin{cases} \frac{N-i}{N^2}, & j = 0 \\ 1 - \frac{1}{N}, & j = i \\ \frac{i}{N^2}, & j = N \end{cases} \tag{1.2.7}$$

Mechanistically, individuals produce exactly one offspring each generation, until a random time of average length N generations where a single individual replaces the entire population. The name by which we have designated this model originates in the theory of Λ-coalescents (c.f. [18]), a class of non-standard coalescents parameterized by measures on $[0, 1]$. Our forward-time Λ_1 process corresponds in the retrospective theory to a Λ

measure concentrated at the point 1. While making no claim to accurately depicting any but a few special systems, the Λ_1-Cannings model nonetheless will delimit certain extreme aspects of GWF processes.

Power-law Models.

The divide between Wright-Fisher and Λ_1 models can be partially spanned by a special one-parameter family. We define a pure-drift Markov process whose transition matrix has tails of decay "index" $\alpha > 0$:

$$\mathbf{Q}_{ij} = \begin{cases} \frac{c_i}{1+b_{1,i}|j-i|^\alpha}, & j < i, 0 < i < N \\ \frac{c_i}{1+b_{2,i}|j-i|^\alpha}, & j \geq i, 0 < i < N \\ \delta_{0,j}, & i = 0 \\ \delta_{N,j}, & i = N \end{cases} \tag{1.2.8}$$

where $b_{1,i}, b_{2,i} > 0$ are "slope" parameters and the normalisation constant c_i designed so $\sum_{j=0}^{N} \mathbf{Q}_{ij} = 1$. Three free parameters are introduced to satisfy the normalisation and two GWF constraints. In Chapter 2 we shall explicitly construct these processes, by proving that there exist unique positive $b_{1,i}, b_{2,i}, c_i$ which satisfy the GWF conditions (1.2.1,1.2.2), for each population size N. Since the conditional distribution of the Wright-Fisher model is of Gaussian decay, one may roughly associate it to the limiting case $\alpha = \infty$, though we shall prove (See Theorem 3.11.3 and Theorem 3.11.6) that the standard diffusion approximation holds already for $\alpha \geq 3$. Conversely, the models $0 < \alpha < 3$ are poorly approximated by Kimura's diffusion, and possess a behavior that can be markedly different from the Wright-Fisher model.

Convex aggregates.

A large number of intermediate models can be formed by taking any two GWF processes with transitions $\mathbf{Q}_1$ and $\mathbf{Q}_2$, and taking their convex combination $\mathbf{P} = a\mathbf{Q}_1 + (1-a)\mathbf{Q}_2$, for $0 < a < 1$. It is immediate from the linearity of the GWF conditions (1.2.1, 1.2.2) that $\mathbf{P}$ is also a GWF process.

1.2.2 Empirical Plausibility of Non-Diffusive GWF Processes.

Few works in the literature have been concerned with empirical confirmation of the standard model; of those, for example [1], typically only verification up to second-order statistics of the process has been sought, since the calculation of the full likelihood of the model was not feasible with the technology of the time. Modern computing has allowed us to compute the full likelihood of a number of evolutionary data sets for a cross-section of the models presented above. The results indicate that the power-law models are indeed quite plausible, even those in the non-diffusive range $\alpha < 3$. For details see our forthcoming biological publication [3].

1.3 Basic Properties of Pure-Drift Generalized Processes

We now begin to infer some of the consequences of our definitions (1.2.1), (1.2.2). We will be principally, though not universally, concerned with the realistic case where the offspring variance is convergent: $\lim_{N\to\infty} \sigma_N^2 = \sigma^2 < \infty$.

1.3.1 Unconditional Moments

The conditional moments (1.2.1, 1.2.2) imply, by taking expectations,

$$EX_{k+1} = EX_k \tag{1.3.1}$$

$$EX_{k+1}^2 = \frac{N\sigma_N^2}{N-1} EX_k + \left(1 - \frac{\sigma_N^2}{N-1}\right) EX_k^2 \tag{1.3.2}$$

These recurrences can be easily solved to produce closed-form expressions for the time evolution of the first two statistics of a GWF process:

Proposition 1.3.1. *The unconditional first two moments of a Pure-Drift Generalized Process satisfy:*

$$\begin{aligned} EX_k &= X_0 \qquad (1.3.3) \\ EX_k^2 &= X_0^2 \lambda_N^k + N X_0 (1 - \lambda_N^k) \\ Var\ X_k &= X_0 (N - X_0)(1 - \lambda_N^k) \end{aligned}$$

where $\lambda_N = 1 - \frac{\sigma_N^2}{N-1}$.

We observe that these moments coincide exactly with those of the Wright-Fisher process. As an elementary corollary, *any* function of the first two moments — heterozygosity $EX_k(N - X_k)$, for example, is invariant over the entire set of GWF processes.

1.3.2 Absorption Times

Theorem 1.3.2. *The absorbing states of a Generalized Process are exactly* $\{0, N\}$.

Proof. Immediate from the variance prescription (1.2.4). □

The biological import is clear: in the absence of mutation, if at any time a given type becomes all-pervasive in a population, no further changes in allele frequency can occur.

In what follows, for ease of notation we have often assumed that the offspring variance $\sigma_N^2 = 1 - 1/N$. The general results follow by a simple scaling of the expected times by $1/\sigma_N^2$.

Define the time to absorption, given the starting value X_0 of the population process, by $\tau = \inf\{k : X_k \in \{0, N\}\}$, which may a priori be infinite. The following theorem, a principal result, gives bounds on the distribution of τ.

Theorem 1.3.3. *For a Pure-Drift Generalized Process X_k with $\sigma_N^2 = 1 - 1/N$, we have the estimates:*

$$P(\tau > k) \geq \frac{X_0(N - X_0)\alpha^k(2 - \alpha^k)}{(N - \alpha^k(N - X_0))(N - X_0\alpha^k)} \tag{1.3.4}$$

$$P(\tau > k) \leq \min\left\{1, \frac{X_0(N - X_0)}{N - 1}\alpha^k\right\} \tag{1.3.5}$$

where $\alpha = 1 - \frac{1}{N}$.

Proof. We start with the lower bound, beginning with:

$$P(\tau \leq k) = P(X_k = N \cup X_k = 0) = P(X_k = N) + P(X_k = 0) \tag{1.3.6}$$

The first term can be estimated by the Glivenko-Chebyshev inequality: if Y is a random variable Y of mean zero, and $\lambda > 0$,

$$P(Y \geq \lambda) \leq \frac{EY^2}{EY^2 + \lambda^2} \tag{1.3.7}$$

Putting $Y = X_k - X_0$ and $\lambda = N - X_0$, one determines

$$P(X_k = N) \leq \frac{Var(X_k)}{Var(X_k) + (N - X_0)^2} \tag{1.3.8}$$

From the Cauchy-Schwarz inequality applied to $X_k 1_{X_k > 0}$ the second term of (1.3.6) satisfies:

$$P(X_k = 0) \leq \frac{Var(X_k)}{Var(X_k) + X_0^2} \tag{1.3.9}$$

Combining into (1.3.6), and substituting the moment formulae (1.3.3),

$$P(\tau > k) \geq \frac{X_0^2(N - X_0)^2 - [Var(X_k)]^2}{(X_0^2 + Var(X_k))((N - X_0)^2 + Var(X_k))} \tag{1.3.10}$$

which is algebraically equivalent to (1.3.4).

For the upper bound, an easy consequence of Markov's inequality is the following: if $|Y| \leq K$, $0 \leq \lambda < K$, then

$$P(|Y| \leq \lambda) \leq \frac{K^2 - EY^2}{K^2 - \lambda^2} \tag{1.3.11}$$

Since $Y_k = X_k - N/2$ is bounded by $K = N/2$, and so:

$$P(|X_k - N/2| \leq \lambda) \leq \frac{N^2/4 - E(X_k - N/2)^2}{N^2/4 - \lambda^2} = \frac{-EX_k^2 + N \cdot EX_k}{N^2/4 - \lambda^2} \tag{1.3.12}$$

Inserting $\lambda = N/2 - 1$, and applying the solutions (1.3.3), one obtains the desired outcome:

$$P(\tau > k) = P(|X_k - N/2| \leq N/2 - 1) \leq \frac{X_0(N - X_0)}{N - 1}\alpha^k \tag{1.3.13}$$

□

The preceding theorem indicates that in the discrete process, the tail of the absorption time ultimately ranges from slightly faster than exponential (1.3.4) to exponential decay (1.3.5). We do not make the statement, of course, that as a whole, the absorption time distribution is anywhere near exponential. Indeed, for certain starting values X_0, the upper bound remains trivial for at least $O(N)$ values of k, and this probability mass tends to dominates the mean absorption time, rather than the tail. We should also mention that while it is obvious that one has an exponential holding time for a single state in any time-homogeneous Markov chain, the exit time for a general set is no longer exponential, and may be very long. Thus, the bounds derived above are non-trivial.

Our upper bound implies almost sure absorption of every sample path, no matter the initialization:

Corollary 1.3.4. *For a Pure-Drift GWF Process,* $P(\tau < \infty) = 1$

Proof. Immediate from $\lim_{k\to\infty} P(\tau > k) = 0$. □

Moreover, estimates of all the moments of the absorption time can be derived from Theorem 1.3.3. Of highest interest is naturally the mean time, which is obtained by summing over the estimates (1.3.4), (1.3.5).

Proposition 1.3.5. *Let* X_k *be a Pure-Drift Generalized Process with* $\sigma_N^2 = 1 - 1/N$*, and let* τ *be the associated absorption time. Then:*

$$E(\tau) \geq \frac{X_0 \log(N - X_0) + N \log N - X_0 \log X_0 - N \log(N - X_0)}{-N \log \alpha} \tag{1.3.14}$$

$$E(\tau) \leq 1 + [(-\log c)/\log(\alpha)] + c \cdot \sum_{k=[(-\log c)/\log(\alpha)]+1}^{\infty} \alpha^k \tag{1.3.15}$$

where $c = X_0(N - X_0)/(N - 1) \geq 1$*, and* $\alpha = 1 - \frac{1}{N}$*.*

These bounds inhabit a simpler form if we consider their asymptotic ($N \to \infty$) behavior, at the biologically interesting initializations $X_0 = 1$ (time to absorption of a single mutant), and $X_0 = [xN]$, with x a fixed fraction of the population size N. In these cases, the asymptotic analysis of Theorem 1.3.5 can be worked out, and the upper and lower bounds described in the next two theorems.

Theorem 1.3.6. *(Absorption time bounds)*

1. *Started at a fixed fraction x of the population size N, the mean time to absorption $E\tau_N$ (in generations) of a Pure-Drift GWF process satisfies (as $N \to \infty$):*

$$-\frac{N}{\sigma^2}\left(x\log x + (1-x)\log(1-x)\right) \leq E\tau_N \leq \frac{N}{\sigma^2}\log(Nx(1-x)) \tag{1.3.16}$$

2. *Started at $X_0 = 1$, the mean time to absorption $E\tau_N$ satisfies (as $N \to \infty$)*

$$\frac{1}{\sigma^2}\log N \leq E\tau_N \leq \frac{N}{\sigma^2} \tag{1.3.17}$$

Remark: The calculations in Chapter 2 show that these bounds are asymptotically achieved by particular models, and hence the orders (in N) discovered are optimal.

Theorem 1.3.6 provides us our first intimations concerning the sensitivity of the Wright-Fisher model. The absorption time starting at any fixed fraction of the population size — $N/2$, for example, is a rather stable quantity over all generalized models, of order between N and $N\log N$. As one moves towards the boundaries, however, sensitivity increases, and the process started at $X_0 = 1$ or $X_0 = N-1$ can exhibit a significantly wider range of absorption times $O(\log N)$ to $O(N)$. Some intuitive reasons for this result are provided at the end of Chapter 2.

1.4 Auxiliary Exit Times

For a fixed $\lambda < 1$, consider the set of states $A_\lambda = \{x \in \{0 \dots N\}, |x - N/2| \leq \lambda N/2\}$. This is a set excluding a neighborhood of size $(1-\lambda)N$ about the boundaries. Assuming that $X_0 \in A_\lambda$, let us define the first exit time $\tau(\lambda) = \inf\{k : X_k \notin A_\lambda\}$. This is the time taken for one type to first attain a frequency greater than λ within the population. We have:

Theorem 1.4.1. *Let X_k be a Pure-Drift GWF process started at $X_0 = [xN]$. Then the mean exit $E\tau(\lambda)$ has the asymptotic bound ($N \to \infty$):*

$$E\tau(\lambda) \leq \frac{4Nx(1-x)}{\sigma^2(1-\lambda^2)} \tag{1.4.1}$$

Proof. Since $\{X_k \notin A_\lambda\} \subset \{\tau(\lambda) \leq k\}$, $P(\tau > k) \leq P(X_k \in A_\lambda)$. Now one can proceed as in the proof of Theorem 1.3.3, to discover the upper bound

$$P(X_k \in A_\lambda) \leq \frac{-EX_k^2 + NEX_k}{(1-\lambda^2)N^2/4} \tag{1.4.2}$$

Substitution of the moment formulae (1.3.3) and summing over the estimates one has the desired result. □

It is of interest to observe that while it requires only $O(N)$ generations for some type to attain a dominance of frequency λ within a population ($\lambda < 1$), it is conceivable that this time may increase to infinity as $\lambda \uparrow 1$ (as evidenced by the $O(N \log N)$ bound of Theorem (1.3.6). We shall see explicit examples in Chapter 2.

1.4.1 Fixation and Fixation Times

We have seen that almost surely, a generalized population process X_k absorbs into the set $\{0, N\}$. A classical question concerns the probability of *fixation*, i.e. absorption at state N. The martingale property is very strong here, and gives another trivial, but fundamental, stability property of generalized models:

Theorem 1.4.2. *Let* X_k *be a Pure-Drift Generalized process, and* τ *the absorption time (which is finite almost surely). Then*

$$P(X_\tau = N) = \frac{X_0}{N} \tag{1.4.3}$$

Proof. X_k is bounded and hence uniformly integrable, so the optional stopping theorem holds: $X_0 = EX_\tau = N \cdot P(X_\tau = N)$. □

An interesting problem now arises: what is the mean time to fixation conditioned on the event $X_\tau = N$, that is, considering only those sample paths which terminate at the absorbing state N? More precisely, the Markov chain X_k^* *conditioned on ultimate fixation*, defined on the state space $\{1, \ldots, N\}$ has, by Theorem 1.4.2 and Doob's h-transform, the transition matrix:

$$\mathbf{P}^*_{ij} = \mathbf{P}_{ij}\frac{j}{i} \tag{1.4.4}$$

where $\mathbf{P}_{ij}$ is the unconditioned transition. X^* has a single absorbing state at N; let $\tau^* = \inf\{k : X_k^* = N\}$. We find the following exponential tail bounds for τ^*:

Theorem 1.4.3. *The absorption time* τ^* *conditioned on fixation of a pure-drift GWF process with* $\sigma^2 = 1 - 1/N$ *satisfies*

$$\frac{N - X_0}{N - 1}\alpha^k \leq P(\tau^* > k) \leq \min\Big\{1, (N - X_0)\alpha^k\Big\} \tag{1.4.5}$$

where $\alpha = 1 - 1/N$.

Proof. From (1.4.4) we derive the conditional mean relation:

$$\sum_j j\mathbf{P}^*_{ij} = \frac{1}{i}\sum_j j^2\mathbf{P}_{ij} = \frac{1}{i}(i(1 - i/N) + i^2) = 1 + \alpha i \tag{1.4.6}$$

where $\alpha = 1 - 1/N$. It follows by taking expectations that the unconditioned mean of the process satisfies the recurrence

$$EX^*_{k+1} = 1 + \alpha EX^*_k \tag{1.4.7}$$

whose solution is

$$EX^*_k = \frac{1-\alpha^k}{1-\alpha} + \alpha^k X_0 \tag{1.4.8}$$

Applying Markov's inequality on the positive process $X^*_k - 1$, one derives

$$P(\tau^* \leq k) = P(X^*_k = N) \leq \frac{EX^*_k - 1}{N-1} \tag{1.4.9}$$

Finally, after substituting the recurrence solution (1.4.8) and taking complements, find the lower bound

$$P(\tau > k) \geq \alpha^k \frac{N - X_0}{N-1} \tag{1.4.10}$$

To discover an upper bound, apply Markov's inequality on the positive process $N - X^*_k$:

$$P(N - X^*_k \geq 1) \leq N - EX^*_k \tag{1.4.11}$$

so that

$$P(\tau^* > k) = 1 - P(X^*_k > N-1) = P(X^*_k \leq N-1) \leq N - EX^*_k = \alpha^k (N - X_0) \tag{1.4.12}$$

which implies the upper bound of the theorem. □

Again, by summing over these estimates, we derive mean conditional fixation time bounds:

Theorem 1.4.4. *The average absorption time conditioned on fixation* $E\tau^*$ *of a pure-drift GWF process with* $\sigma^2 = 1$ *obeys*

$$\frac{N - X_0}{\alpha} \leq E\tau^* \leq 1 + c + (N - X_0) \sum_{k=c+1}^{\infty} \alpha^k \tag{1.4.13}$$

where $c = [-\log(N - X_0)/\log(\alpha)]$, $\alpha = 1 - 1/N$.

Once more it is germane to discuss the asymptotic order of these quantities when started with a single individual of a given type $X_0 = 1$, as well as the fixed fraction $X_0 = [xN]$.

Theorem 1.4.5. *(Conditional fixation time bounds)*

1. *Started at a fixed fraction* x *of the population size* N*, the mean time to fixation* $E\tau_N^*$ *of a pure-drift GWF process satisfies (as* $N \to \infty$*)*

$$\frac{N}{\sigma^2}(1-x) \leq E\tau_N^* \leq \frac{N}{\sigma^2}\log(N(1-x)) \tag{1.4.14}$$

2. *Started at* $X_0 = 1$*, the mean time to fixation* $E\tau_N^*$ *satisfies (as* $N \to \infty$*)*

$$\frac{N}{\sigma^2} \leq E\tau_N^* \leq \frac{N\log N}{\sigma^2} \tag{1.4.15}$$

The orders in N exhibited by these formulae are tight, with the Wright-Fisher process operating near the lower bound in both cases of initialization, while the Minimal process will meet our upper bounds (see Section 2.3.1) . It is worth commenting that the *conditional* fixation time is significantly more stable even when started near the boundary than for the unconditional absorption time (compare Theorem 1.3.6). Intuitive reasons for this are presented at the end of Chapter 2.

1.5 Generalizations to the K-Allele Case

In this section we briefly show how some of the bounds derived for $K = 2$ types can be generalized to an analysis of the first absorption time for a K-type Cannings process.

1.5.1 The K-types Cannings Model

The mechanism underlying the Cannings model described in Section 1.1.2 describes, without change, the evolution of K types. As usual, suppose $(\nu_1, \ldots, \nu_N)$ is an exchangeable random vector for which $\sum_{i=1}^{N} \nu_i = N$, representing the number of offspring passed into the next generation by individual i. Also assume for simplicity that $Var(\nu_i) = \sigma_N^2 = 1 - 1/N$. Let $X_k = (X_k^{(1)}, \ldots, X_k^{(K-1)})$ be the vector counting numbers of individuals of the first $K-1$ types. Then the Markov chain describing the changes in type frequency has the transition form:

$$X_{k+1}^{(1)} | X_k^{(1)} \overset{d}{=} \sum_{i=1}^{X_k^{(1)}} \nu_i \tag{1.5.1}$$

$$X_{k+1}^{(2)} | X_k^{(2)} \overset{d}{=} \sum_{i=1}^{X_k^{(2)}} \nu_i \tag{1.5.2}$$

$$\vdots \quad = \quad \vdots \tag{1.5.3}$$

Since $E\nu_i = 1$, it is simple to verify that X_k is a martingale. Elementary calculations also show that the second-order statistics of the process are once more parameterized completely by the offspring variance $\sigma^2 = Var(\nu_i)$:

$$Var[X_{k+1}^{(i)} | X_k] = \sigma^2 \frac{N}{N-1} X_k^{(i)} (1 - X_k/N) \tag{1.5.4}$$

$$Cov[X_{k+1}^{(i)}, X_{k+1}^{(j)} | X_k] = -\frac{\sigma^2}{N-1} X_k^{(i)} X_k^{(j)}, \quad i \neq j \tag{1.5.5}$$

Rewriting the second-order conditions, one has

$$E[(X_{k+1}^{(i)})^2 | X_k] = X_k^{(i)} (1 - X_k^{(i)}/N) + (X_k^{(i)})^2 \tag{1.5.6}$$

$$E[X_{k+1}^{(i)} X_{k+1}^{(j)} | X_k] = (1 - 1/N) X_k^{(i)} X_k^{(j)} \tag{1.5.7}$$

Now upon taking expectations in the above, one derives a set of $(K-1)^2$ decoupled difference equations:

$$E(X_{k+1}^{(i)})^2 = EX_k^{(i)} + (1-1/N)E(X_k^{(i)})^2, \quad i = 1, \ldots, K-1 \tag{1.5.8}$$

$$EX_{k+1}^{(i)}X_{k+1}^{(j)} = (1-1/N)EX_k^{(i)}X_k^{(j)}, \quad i \neq j \tag{1.5.9}$$

Solving the recurrences, we have then closed forms for the evolution of the first few statistics of a multi-type Cannings process:

$$Var(X_k^{(i)}) = X_0^{(i)}(N - X_0^{(i)})(1-\alpha^k) \tag{1.5.10}$$

$$Cov(X_k^{(i)}, X_k^{(j)}) = -X_0^{(i)}X_0^{(j)}(1-\alpha^k) \tag{1.5.11}$$

where $\alpha = 1 - 1/N$.

Remark: We do not feel inclined at this moment to introduce a definition of GWF processes in higher dimensions, whose obvious, but incorrect form, would take on (1.5.8), (1.5.9). Subtle constraints inform the relationships between allele frequencies which are not apparent in dimension one. For example, any agglomeration of type variables $X_k^{(i)}$ in the Cannings model is also a martingale.

1.5.2 Bounds on the Time to First Loss

We shall now construct bounds on the time to a loss of an allele, assuming asymptotically finite offspring variance. Let B be the boundary of the simplex $\sum_{i=1}^{K-1} x_i \leq N$, $x_i \in \mathbb{Z}^+$. We seek first to estimate $P(X_k \in B)$. There are K faces to this simplex, the simple boundaries $B_i = \{x_i = 0\}$ and the diagonal boundary $B_K = \{\sum_{i=1}^{K-1} x_i = N\}$. Let

$Y_k = \sum_{i=1}^{K-1} X_k^{(i)}$. Applying the Glivenko-Chebyshev inequality, one finds:

$$P(X_k \in B_K) = P(Y_k = N) \leq \frac{Var(Y_k)}{Var(Y_k) + (N - EY_k)^2} \tag{1.5.12}$$

The Cauchy-Schwarz provides estimates for the other boundaries:

$$P(X_k \in B_i) = P(X_k^{(i)} = 0) \leq \frac{Var(X_k^{(i)})}{Var(X_k^{(i)}) + (EX_k^{(i)})^2} \tag{1.5.13}$$

Hence

$$P(X_k \in B) \leq \frac{Var(Y_k)}{Var(Y_k) + (N - EY_k)^2} + \sum_{i=1}^{K-1} \frac{Var(X_k^{(i)})}{Var(X_k^{(i)}) + (EX_k^{(i)})^2} \tag{1.5.14}$$

and where

$$Var(Y_k) = \sum_{i=1}^{K-1} Var(X_k^{(i)}) + \sum_{i \neq j} Cov(X_k^{(i)}, X_k^{(j)}) \tag{1.5.15}$$

One may also write the estimate more simply, if we introduce the last type $X_k^{(K)}$, as:

$$P(X_k \in B) \leq \sum_{i=1}^{K} \frac{Var(X_k^{(i)})}{Var(X_k^{(i)}) + (EX_k^{(i)})^2} \tag{1.5.16}$$

Note when $K = 2$, we reduce to our one-dimensional procedure.

Inserting the solution (1.5.10) and (1.5.11) to the recurrences into this estimate, one finds

$$P(X_k \in B) \leq \sum_{i=1}^{K} \frac{X_0^{(i)}(N - X_0^{(i)})(1 - \alpha^k)}{X_0^{(i)}(N - X_0^{(i)})(1 - \alpha^k) + (X_0^{(i)})^2} \tag{1.5.17}$$

$$= \sum_{i=1}^{K} \frac{(N - X_0^{(i)})(1 - \alpha^k)}{(N - X_0^{(i)})(1 - \alpha^k) + X_0^{(i)}} \tag{1.5.18}$$

In principle, the above estimate can be used to deduce estimates on the distribution of the first time to loss of an allele. One particularly simple case occurs at the symmetrical initialization $X_0^{(i)} = \frac{1}{K}N$. Define the stopping time $\tau = \inf\{k : X_k \in B\}$, for this equi-frequency initialization. We then have the following theorem.

Theorem 1.5.1. *The time τ to the loss of some allele for a K-type Cannings process with $\sigma_N^2 = 1 - 1/N$ in the equi-frequency initialization satisfies*

$$P(\tau > t) \geq \max\left\{\frac{(1 - K + \frac{1}{K-1}) + (K-1)\alpha^t}{(1 + \frac{1}{K-1}) - \alpha^t}, 0\right\} \tag{1.5.19}$$

Summing over the positive part of this estimate and using an integral approximation, one finds that asymptotically ($N \to \infty$),

$$E\tau \geq N\left[\log\frac{K}{K-1} + (K-2)\log\left(1 - \frac{1}{(K-1)^2}\right)\right] \tag{1.5.20}$$

At $K = 3$ alleles, $E\tau \geq 0.12N$ asymptotically, which can be compared to the equi-frequency Wright-Fisher absorption time $E\tau = 0.8N$. For large K our lower bound is approximately N/K—an intuitively appealing and general finding, consistent with the diffusion results of Littler [14] who established it under the restricted case of the Wright-Fisher process.

1.6 Introducing Mutation and Selection

The forces of selection and mutation are classically [5] introduced into the Wright-Fisher process by biasing the allele frequencies i/N in the urn model (1.1.1). Specifically, if type A has fitness advantage s over type B, and mutation occurs between the two types at rates μ_1, μ_2, then the urn process is altered as follows:

$$\mathbf{P}_{ij} = \binom{N}{j}(x_i^*)^j(1 - x_i^*)^{N-j} \tag{1.6.1}$$

with

$$x_i^* = (1-\mu_1)x_i + (1-x_i)\mu_2 \tag{1.6.2}$$

$$x_i = \frac{i}{N}\left(\frac{1+\frac{s}{2}(1+i/N)}{1+s\frac{i}{N}}\right) \tag{1.6.3}$$

Since GWF processes in general do not possess an urn-like mechanistic interpretation, the preceding procedure does not admit immediate generalization. We can, however, introduce selection and mutation in a natural way, as follows. Let $\mathbf{Q}_N$ be the Markov transition matrix for a pure-drift generalized process on N individuals. We multiply $\mathbf{Q}_N$ with additional transition matrices encoding the requisite effects, say $\mathbf{S}_N$ and $\mathbf{M}_N$. The total model is then defined by the composite transition

$$\mathbf{P}_N = \mathbf{S}_N\mathbf{Q}_N\mathbf{M}_N. \tag{1.6.4}$$

Conceptually, the above sequence partitions events in a generation into three components, in the following order: 1) alteration of the frequency of types based on fitness differences (**S**), 2) A reproduction stage (**Q**), and 3) a mutational stage (**M**).

The mutation matrix **M** can be specified as follows: after reproduction, each individual mutates to the opposing type independently with respective probabilities μ_1, μ_2. If we define $\mathbf{M}_{jk}$ as the probability that, starting with j individuals of type A, one obtains k individuals of type A after mutation, then $\mathbf{M}_{jk}$ is distributed according to a sum of independent binomial random variables X_j and Y_j:

$$P(X_j = r) = \binom{j}{r}(1-\mu_1)^r\mu_1^{j-r}, \quad P(Y_j = r) = \binom{N-j}{r}\mu_2^r(1-\mu_2)^{N-j-r} \tag{1.6.5}$$

$$\mathbf{M}_{jk} = P(X_j + Y_j = k) \tag{1.6.6}$$

Our next calculation shows that, in the absence of selection, our choice of mutation matrix reduces to (1.6.1) when $\mathbf{Q}$ is the pure-drift Wright-Fisher process:

Theorem 1.6.1. *If* $\mathbf{Q}$ *is the pure-drift Wright-Fisher model (1.1.1) and* $\mathbf{M}$ *is defined by (1.6.6), then* $\mathbf{P} = \mathbf{QM}$ *coincides with the classical Wright-Fisher model (1.6.1) under* $s = 0$*.*

Proof. Writing out the matrix multiplication and the convolution of distributions implicit in (1.6.6), one finds:

$$\mathbf{P}_{ik} = \sum_{j=0}^{N} \sum_{l=0}^{j} \binom{N}{j} (i/N)^j (1 - i/N)^{N-j} \binom{j}{l} (1-\mu_1)^l \mu_1^{j-l} \binom{N-j}{k-l} \mu_2^{k-l} (1-\mu_2)^{N-j-(k-l)} \tag{1.6.7}$$

We demonstrate this is binomial. To do this consider the generating function $\phi(z) = \sum_{k \geq 0} \mathbf{P}_{ik} z^k$. Using this with (1.6.7), decomposing $z^k = z^{k-l} z^l$ and summing over k via the binomial theorem, one finds:

$$\phi(z) = \sum_{j=0}^{N} \sum_{l=0}^{j} \binom{N}{j} (i/N)^j (1 - i/N)^{N-j} \binom{j}{l} (1-\mu_1)^l \mu_1^{j-l} (\mu_2 z + 1 - \mu_2)^{N-j} z^l \tag{1.6.8}$$

which re-writes as

$$\phi(z) = \sum_{j=0}^{N} \binom{N}{j} (i/N)^j (1 - i/N)^{N-j} (\mu_2 z + 1 - \mu_2)^{N-j} \sum_{l=0}^{j} \binom{j}{l} \mu_1^{j-l} (z(1-\mu_1))^l \tag{1.6.9}$$

Apply the binomial theorem again, twice:

$$\phi(z) = \sum_{j=0}^{N} \binom{N}{j} (i/N)^j (1 - i/N)^{N-j} (\mu_2 z + 1 - \mu_2)^{N-j} (z(1 - \mu_1) + \mu_1)^j \tag{1.6.10}$$

$$= \sum_{j=0}^{N} \binom{N}{j} (i/N \cdot (z(1 - \mu_1) + \mu_1))^j [(1 - i/N)(\mu_2 z + 1 - \mu 2)]^{N-j} \tag{1.6.11}$$

$$= \left(\frac{i}{N}(z(1 - \mu_1) + \mu_1) + (1 - i/N)(\mu_2 z + 1 - \mu_2) \right)^N \tag{1.6.12}$$

$$= (1 + z((i/N)(1 - \mu_1) + \mu_2(1 - i/N)) - [(i/N)(1 - \mu_1) + \mu_2(1 - i/N)])^N \tag{1.6.13}$$

which is the generating function for the binomial distribution of size N and parameter $(i/N)(1 - \mu_1) + \mu_2(1 - i/N)$, as desired. □

The case of the selection matrix **S** is less clean, and there is no obvious way to introduce it into the discrete model. It is tempting to define **S** as the matrix for which **SPM** agrees with model (1.6.1), but it can be shown (we will omit this proof), that no such stochastic **S** exists. Nonetheless, there do exist matrices for which **SPM** approximates the behavior of the Wright-Fisher model in the limit of large population size. Generically, we can ask that any particular specification of $\mathbf{S}_N$ or $\mathbf{M}_N$ reduces $\mathbf{P}_N$ to Haldane's classical theory of deterministic evolution [8] when the offspring variance $\sigma^2 = 0$, (i. e. $\mathbf{Q}_N = I$), as $N \to \infty$. Mathematically translated, this amounts to the prescription that the transition matrices have generators which converge to the convection terms in Kimura's diffusion:

$$\lim_{N\to\infty} (\mathbf{S}_N - I)u_N = \beta x(1 - x)\frac{du}{dx} \tag{1.6.14}$$

$$\lim_{N\to\infty} (\mathbf{M}_N - I)u_N = \frac{1}{2}(-\theta_1 x + \theta_2(1 - x))\frac{du}{dx} \tag{1.6.15}$$

where the allele of interest has selective advantage $\beta = Ns$, mutation between the two classes occurs at rates $\theta_i = 2N\mu_i$, u is any smooth function, and $u_N(i) = u(i/N)$. When (1.6.14, 1.6.15) are fulfilled, the order in which the matrices are multiplied in (1.6.4) is immaterial, as $N \to \infty$ (See the continuum theory, Section 3.10).

For numerical experiments, we have chosen an $\mathbf{S}$ with the property that its i-th row is a binomial distribution supported on states $\{i, \ldots, N\}$, and probability parameter selected so that its mean agrees with the selected Wright-Fisher model (1.6.1). It is simple with a Taylor expansion to see that this choice satisfies the constraint (1.6.14). When $\mathbf{Q}_N$ is the pure-drift Wright-Fisher model, our numerical experiments show that this choice leads to a model $\mathbf{P}_N$ agreeing extremely well in all respects to (1.6.1), even at very low population sizes N (asymptotically they must agree). It should be emphasized, however, that none of our theoretical results depend upon such specific forms for mutation and selection, but only on the canonical asymptotic forms (1.6.14, 1.6.15).

1.6.1 Stationary Distributions under Selection and Mutation

When two-way non-zero mutation $\mu_1, \mu_2 > 0$ is present, as described in the previous section, it is readily verified that any GWF process must have a transition matrix $\mathbf{P}$ possessing strictly positive entries. The classical Perron-Frobenius theorem then gives the following:

Proposition 1.6.2. *Let* $\mathbf{P}$ *be the transition matrix for a GWF chain with strictly positive two-way mutation rates and arbitrary selection. Then there is a unique stationary distribution* π *for* $\mathbf{P}$*, and* $(\mathbf{P}^*)^k \mathbf{u}_0 \to \pi$ *in norm as* $k \to \infty$ *for any initialization* $\mathbf{u}_0$.

We will use continuum theory (Section 4.6) to develop further properties of the equilibrium.

1.6.2 Evolution of Moments under Selection and Mutation.

Interestingly, the invariance of the unconditional moments over the class of pure-drift GWF processes extends to the case when mutation is present:

Theorem 1.6.3. *For any mutation rates* $\mu_1 \geq 0, \mu_2 \geq 0$*, the first two moments of any GWF process* X_k *coincide, for all time, with a corresponding Wright-Fisher model with the same mutation rates and initial condition.*

Proof. A calculation with the mutation matrix $\mathbf{M}$ shows that even under mutation, EX_k, EX_k^2 satisfy linear difference equations identical to those of the Wright-Fisher model. The theorem then follows from the uniqueness of the solutions to these equations given an initial condition. □

The above stability principle arises from the observation that the functions multiplying the derivative operators in the mutation term (1.6.15) are *linear* functions in allele frequency x. A crucial implication of this is that the evolution of the lower moments in any neutral GWF process is closed, in the sense that moments of order $m \leq 2$ depend only on the moments of order m and lower in previous time generations. In fact, for a very large class of GWF processes, including each of the model examples previously presented, the structure of the moments is closed for all orders m, not merely those less than 2. In this case the moments up to order m will satisfy a finite system of linear recurrences.

No such system is possible once non-zero selection is present, for the quadratic coefficient $x(1-x)$ multiplying the selection operator in (1.6.14) demands that EX_k^m be a function of the $(m+1)$-th moment in the previous generation. In this case, EX_∞ is then a function of *all* the higher moments at finite times; the closed structure breaks, and we lose the invariance property of the preceding theorem. In fact, continuum methods (Chapter 4) will be required for a serious analysis in the case of non-zero selection.

1.6.3 Fundamental Properties of Pure Selection Processes

By *Pure Selection Process* we denote a GWF process with zero mutation rates $\mu_i = 0$. In this case, the transition matrix takes the form $\mathbf{P} = \mathbf{SQ}$. Many of the methods used in the previous sections to obtain information about the evolution of moments are not applicable, due to loss of the martingale and moment structure. The aim of this section is nonetheless to obtain some basic knowledge. Two properties are used repeatedly in the subsequent theorems: strict positivity of the variance of interior states, and the fact that positive selection makes X_k a submartingale ($E[X_k|X_0] \geq X_0$ for every k), a statement simply verified with the choice of selection matrix in Section 1.6.

To begin, recall that two states i, j are *communicating* if $\mathbf{P}_{ij}^k > 0$ for some k, i. e. it is possible to move from i to j in a finite number of steps.

Proposition 1.6.4. *For a GWF process under strictly positive selection, all interior states* $\{1, \ldots, N-1\}$ *communicate with state* N*.*

Proof. Fix an interior state i. Assume that it cannot enter N directly. If row i has variance zero, this can only be if $\mathbf{S}$ moves i to state N or state 0, because the interior rows of $\mathbf{Q}$ have non-zero variance. The former was ruled out by assumption, and the latter cannot occur because $\mathbf{P}$ is a sub-martingale. Therefore row i has strictly positive variance. Since it is a submartingale, i can enter a state strictly larger with positive probability. The argument can be iterated at this larger state, and there can only be a finite number of steps until one reaches a state in direct communication with N. $\square$

Corollary 1.6.5. *Under neutrality (*$\mathbf{P}$ *is both sub- and super-martingale), all interior states are in communication with both* $0, N$.

Lemma 1.6.6. *The absorbing states of the transition* $\mathbf{P}$ *of a Pure Selection Process are precisely* $\{0, N\}$.

Proof. By the stipulations in Section 1.6, states $\{0, N\}$ are still absorbing, and no interior state can be absorbing because of the non-zero variance condition on $\mathbf{Q}$. $\square$

Proposition 1.6.7. *Any stationary distribution* $\mathbf{p}$ *of* $\mathbf{P}$ *must be concentrated on the absorbing states* $\{0, N\}$.

Proof. Write $\mathbf{p} = (p_1, \ldots, p_N)$, let i be an interior state, and k a power of $\mathbf{P}$ for which i can enter N with positive probability: $\mathbf{P}^k_{i,N} > 0$. Denote $\mathbf{R} = \mathbf{P}^k$ as this power, so that $\mathbf{R}_{i,N} > 0$, and consider the invariant equation $\mathbf{R}^*\mathbf{p} = (\mathbf{P}^k)^*\mathbf{p} = (\mathbf{P}^k)^*\mathbf{p} = \mathbf{p}$, the N-th entry of this vector relation is

$$\sum_{j=1}^{N} \mathbf{R}_{j,N} p_j = p_N \tag{1.6.16}$$

Since $\mathbf{R}_{N,N} = 1$, and $\mathbf{R}_{i,N} > 0$, $p_i = 0$. One can now repeat the proof for each interior state i. $\square$

Remark: The use of the communication property in the above demonstration was crucial.

As usual let us define the stopping time $\tau = \inf\{k : X_k \in \{0, N\}\}$, where X_k is the process corresponding to $\mathbf{P}$. The following is a generalization of Corollary 1.3.4.

Theorem 1.6.8. *For a Pure Selection Process,* $P(\tau < \infty) = 1$.

Proof. X_k is a bounded submartingale, so it converges almost surely to a limit X_∞. The distribution $\mathbf{p}$ of X_∞ must be an invariant distribution: $\mathbf{P}^*\mathbf{p} = \mathbf{p}$. By Proposition 1.6.7 $\mathbf{p}$ is concentrated on $\{0, N\}$. Thus $X_k(\omega) \to X_\infty(\omega)$ for all ω in a set T with full measure, and for each $\omega \in T$, $X_k(\omega)$ integer-valued indicates it hits $X_\infty(\omega) \in \{0, N\}$ after a finite time. ☐

Theorem 1.6.9. *Let* X_k *be a Pure Selection Process initialized at* X_0. *Then* $P(X_\tau = N) \geq X_0/N$

Proof. X_k is a bounded submartingale, therefore $j = X_0 \leq EX_\tau = N \cdot P(X_\tau = N)$ by optional stopping. ☐

An obvious corollary summarising the above is the identification

Corollary 1.6.10. *Let* X_k *be a Pure Selection Process. Let* $f : \{0, \ldots, N\} \to \{0, \ldots, N\}$ *be any function such that 0 and* N *are fixed points. Then*

$$P(X_\tau = N) = \frac{Ef(X_\infty)}{N} = \frac{\lim_{k\to\infty} Ef(X_k)}{N} \tag{1.6.17}$$

Proof. The second equality comes from bounded convergence, the first because $Ef(X_\infty) = NP(X_\infty = N)$ and $X_\infty(\omega) = N$ if and only if $X_\tau = N$. ☐

Monotonic Processes

In the continuum theory it will be important to know that $P(X_\tau = N | X_0 = j)$ is an increasing function in j. Biologically, this corresponds to the natural prediction that fixation probability is monotonically increasing in initial allele frequency. Remarkably, this is *not* true for arbitrary choices of GWF process; the counterexamples are complex and will not be discussed here. Our present aim is rather to establish a reasonable class under which such monotonicity does hold.

Definition 1.6.11. A transition matrix $\mathbf{Q}_{ij}$ will be called *monotonic* if the functions $f_i : n \mapsto \sum_{j=n}^{N} \mathbf{Q}_{ij}$ are an increasing family in i.

Each of the example processes considered in detail in Chapter 2 will turn out to possess this monotonicity property. For now, we prove this for the Cannings class:

Lemma 1.6.12. *If* $\mathbf{Q}$ *is the transition matrix for a Cannings process,* $\mathbf{Q}$ *is monotonic.*

Proof. Letting $\nu = (\nu_1, \ldots, \nu_N)$ symbolize the exchangeable vector in the Cannings model, we have that row i and $i+1$ of $\mathbf{Q}$ have the same distribution as the variables $\sum_{j=1}^{i} \nu_j$ and $\sum_{j=1}^{i+1} \nu_j$, and the latter is almost surely larger, and therefore stochastically larger, than the former. $\square$

Lemma 1.6.13. *Let* X *and* Y *be two random variables for which* $P(Y \geq t) \geq P(X \geq t)$ *for all* t*. Then if* f *is an increasing function,* $Ef(Y) \geq Ef(X)$ *whenever the expectations exists.*

Proof. Immediate from integration by parts on the formula for $Ef(Y)$ and $Ef(X)$. $\square$

Remark: The converse to this Lemma is also true, as is readily seen by taking f to be hinge functions.

We can now show that monotonicity is preserved under products.

Theorem 1.6.14. *The product of monotonic transition matrices is monotonic.*

Proof. Let $\mathbf{R}$ and $\mathbf{P}$ be monotonic, and $\mathbf{Q} = \mathbf{RP}$. Then

$$\mathbf{Q}_{ij} = \sum_{k=1}^{N} \mathbf{R}_{ik}\mathbf{P}_{kj} \tag{1.6.18}$$

Consider the associated functions for $\mathbf{Q}$, say f_i and $f_{i'}$, where $i' \geq i$. Then

$$f_i(n) = \sum_{j=n}^{N} \mathbf{Q}_{ij} = \sum_{k=1}^{N} \mathbf{R}_{ik} \left(\sum_{j=n}^{N} \mathbf{P}_{kj} \right) \tag{1.6.19}$$

$$f_{i'}(n) = \sum_{j=n}^{N} \mathbf{Q}_{i'j} = \sum_{k=1}^{N} \mathbf{R}_{i'k} \left(\sum_{j=n}^{N} \mathbf{P}_{kj} \right) \tag{1.6.20}$$

Fix n. By monotonicity, $\sum_{j=n}^{N} \mathbf{P}_{kj}$ is an increasing function in k, and we can think of the sums in (1.6.19) and (1.6.20) as expectations of such a function under the measure associated to rows i and i' of $\mathbf{R}$. Since $i' \geq i$, the monotonicity assumption on R combined with Lemma 1.6.13 tells us $f_{i'}(n) \geq f_i(n)$, as desired. □

One consequence of this product theorem is that as long as the selection matrix $\mathbf{S}$ chosen is monotonic (and it is easily verified that the binomial selection matrix of Section 1.6 has this property), it suffices to check that the drift operator $\mathbf{Q}$ has the desired property to verify for the composite $\mathbf{P}$.

Corollary 1.6.15. *If* $\mathbf{P}$ *is monotonic, so are the* k*-step transition kernels* $\mathbf{P}^k$ *of a generalized population process.*

We finally have the sought-after regularity theorem for monotonic processes:

Theorem 1.6.16. *If the transition matrix* $\mathbf{P}$ *of a pure selection process is monotonic, then* $P(X_\tau = N|X_0 = i) = P(X_\infty = N|X_0 = i)$ *is increasing in* i.

Proof. If $i' \geq i$, then Corollary 1.6.15 along with Lemma 1.6.13 indicate that $E[X_k|X_0 = i'] \geq E[X_k|X_0 = i]$ for all k. Taking limits, since $X_k \to X_\infty$ almost surely as described in the proof of Theorem 1.6.8, and using bounded convergence, we have $E[X_\infty|X_0 = i'] \geq E[X_\infty|X_0 = i]$, and from this follows the second equality as X_∞ concentrates on $\{0, N\}$. The first equality is Corollary 1.6.10. □

1.6.4 GWF Processes under One-Way Mutation

By a *Pure Mutation GWF Process* we mean a GWF process with zero selection, so that $\mathbf{P} = \mathbf{QM}$. If we presume that only one-way mutation occurs from an allele of interest to the other type at rate μ, then absorption at the boundary 0 is assured. Using techniques similar to those employed above, it is again possible to derive bounds on the time to this loss. We will only display the lower bound, since the upper bound, which can also be derived, has a somewhat ungainly form.

Theorem 1.6.17. *(Time to Loss for One-Way Mutation). Suppose one-way mutation from a type occurs at rate* $\theta = 2N\mu$ *in a pure mutation GWF process, then*

1. *Started at a fixed fraction* x *of the population size, the mean time to loss* $E\tau_N$ *of the type satisfies (as* $N \to \infty$*)*

$$E\tau_N \geq \frac{xN \log\left(\frac{x(\sigma^2+\theta/2)}{\sigma^2}\right)}{(\theta/2 + \sigma^2)\left(x - \frac{\sigma^2}{\sigma^2+\theta/2}\right)} \tag{1.6.21}$$

2. Started at $X_0 = 1$, the mean time to loss $E\tau_N$ satisfies (as $N \to \infty$)

$$E\tau_N \geq \frac{\log(\frac{\sigma^2}{\sigma^2+\theta/2}N)}{\sigma^2} \tag{1.6.22}$$

Proof. Let $A \to B$ with probability $\mu > 0$. An easy computation with the mutation matrix of (1.6.6) shows:

$$E(X_{k+1}|X_k) = X_k(1-\mu) \tag{1.6.23}$$

$$E(X_{k+1}^2|X_k) = cX_k + \left(1 - \frac{\sigma^2}{N-1}\right)(1-\mu)^2 X_k^2 \tag{1.6.24}$$

where $c = \mu + N\sigma^2/(N-1) \cdot (1-2\mu)$.

Taking the expectation of both sides, the lower moments satisfy the following recurrences:

$$EX_{k+1} = vEX_k \tag{1.6.25}$$

$$EX_{k+1}^2 = cEX_k + v^2\left(1 - \frac{\sigma_N^2}{N-1}\right)EX_k^2 \tag{1.6.26}$$

where $v = 1 - \mu$. Solving the recurrences produces

$$EX_k = v^k X_0 \tag{1.6.27}$$

$$EX_k^2 = c\frac{v^{k-1}X_0}{1-v\lambda_N}(1-(v\lambda_N)^k) + (v^2\lambda_N)^k X_0^2 \tag{1.6.28}$$

with $\lambda_N = 1 - \frac{\sigma_N^2}{N-1}$.

Using the Cauchy-Schwarz inequality, one discovers:

$$P(X_k = 0) \leq \frac{EX_k^2 - (EX_k)^2}{EX_k^2} \tag{1.6.29}$$

Thus if τ is the time to absorption at 0,

$$P(\tau > k) \geq \frac{(EX_k)^2}{EX_k^2} = \frac{v^k X_0}{C(1-(v\lambda_N)^k) + X_0(v\lambda_N)^k} \tag{1.6.30}$$

where $C = \frac{cv^{-1}}{1-v\lambda_N}$. The previous equation has the lower bound:

$$\int_0^\infty \frac{X_0(v\lambda_N)^x}{C(1-(v\lambda_N)^x)+(v\lambda_N)^x X_0}\,dx = \frac{X_0(\log(X_0/C))}{-[\log(v\lambda_N)](X_0-C)} \tag{1.6.31}$$

For large N, this bound reads

$$E\tau \geq \frac{NX_0\log(X0/(kN))}{(\theta/2+\sigma^2)(X_0-kN)} \tag{1.6.32}$$

where $k = \frac{\sigma^2}{\theta/2+\sigma^2}$. This in turn reduces to, in the special cases $X_0 = 1, X_0 = [xN]$:

$$E\tau \geq \frac{\log(kN)}{\sigma^2} \tag{1.6.33}$$

$$E\tau \geq \frac{xN\log(x/k)}{(\theta/2+\sigma^2)(x-k)} \tag{1.6.34}$$

$\square$

For comparison, and akin to the situation with absorption times, Kimura's classical value of $E\tau_N = \int_{1/N}^1 y^{-1}(1-y)^{\theta-1}\,dy \sim 2\log N$ for time to loss of a new mutant under $\sigma^2 = 1$ is near the lower bound (1.6.22). On the other hand, it can be shown that the Λ_1-Cannings model has an analogous time to loss of the significantly larger order $O(N)$ generations (see Section 2.2).

Chapter 2

Classes and Examples of Neutral Models

Section 1.2.1 gave a brief introduction to a number of models of interest, both mathematical and biological. In this chapter we now formally take up their construction, analyzing their specific properties with the aid of only discrete methods. One of the goals is to demonstrate that the bounds on neutral absorption and fixation times derived in the previous chapter are asymptotically tight. Finally, we make a preparatory study of the convex structure of the space of discrete GWF processes, which will be an important ingredient in our continuum theory. In each case, we have given the specification for the (asymptotically) unit offspring variance $\sigma^2 = 1$ model.

2.1 The Wright-Fisher Model

We have already introduced this classical process as the GWF model with transition $\mathbf{Q}_{ij} = \binom{N}{j}\left(\frac{i}{N}\right)^j\left(1-\frac{i}{N}\right)^{N-j}$. Our present task is merely to record known results concerning its neutral absorption and fixation times. We have the well-known proposition, from [5]:

Proposition 2.1.1. *(Kimura)*

1. *Started at a fixed fraction x of the population size N, the mean time to absorption $E\tau_N$ (in generations) of the Pure-Drift Wright-Fisher process satisfies*

$$E\tau_N \sim -2N\left(x\log x + (1-x)\log(1-x)\right) \tag{2.1.1}$$

2. *Started at $X_0 = 1$, the mean time to absorption $E\tau_N$ satisfies (as $N \to \infty$)*

$$E\tau_N \sim 2\log N \tag{2.1.2}$$

3. *Started at a fixed fraction x, the conditional fixation time $E\tau_N^*$ satisfies*

$$E\tau_N^* \sim -2N\frac{(1-x)\log(1-x)}{x} \tag{2.1.3}$$

4. *Started at $X_0 = 1$, the conditional fixation time satisfies*

$$E\tau_N^* \sim 2N \tag{2.1.4}$$

We note that these values are of the same asymptotic order in N as the lower bounds recorded in our Theorems 1.3.6 and 1.4.5, and indeed, are only a factor of at most two larger, depending on the initializing state.

2.2 The Λ_1-Cannings Model

Cannings processes are defined by the prescription of an exchangeable positive integer-valued random vector $(\nu_1, \ldots, \nu_N)$ satisfying the fixed population constraint $\sum_{i=1}^{N} \nu_i = N$. An equivalent specification is to give a measure on the sample space of partitions of N. We define the Λ_1-model as that Cannings model specified by the measure $\mu(P_1) = 1 - 1/N$, and $\mu(P_2) = 1/N$, where P_i are the partitions $P_1 = 1 + \cdots + 1$, $P_2 = N + 0 + \cdots + 0$. The resulting transition matrix for the allele frequencies has the form:

$$\mathbf{Q}_{ij} = \begin{cases} \frac{N-i}{N^2}, & j = 0 \\ 1 - \frac{1}{N}, & j = i \\ \frac{i}{N^2}, & j = N \end{cases} \tag{2.2.1}$$

Mechanistically, individuals produce exactly one offspring each generation, until a random time of average length N generations where a single individual replaces the entire population. This observation is formally set out in the following obvious proposition.

Proposition 2.2.1. *The expected absorption time $E\tau_N$ and expected conditional fixation time $E\tau_N$ for the pure-drift Λ_1-Cannings Process are each N generations, for any initialization $X_0 \notin \{0, N\}$.*

The preceding establishes the exact optimality of the upper bound in Theorem 1.3.6(b).

2.3 The Minimal and Maximal Processes.

There are two extreme processes, which, while not possessing much biological relevance, nonetheless will play a crucial technical role in our continuum theory. In particular they will be seen to delimit two extreme boundaries within the space of GWF processes.

The conditional increments in the Wright-Fisher process are binomial distributions, indicating that jumps to states at distance d decay roughly exponentially in d. In looking for processes with markedly differing behavior, it is reasonable, then, to attempt to maximize the mass assigned to the tails (and thus indirectly the incremental higher moments), subject to the GWF constraints. Define two cost functions: $J_{-}^{(i)}(\mathbf{P}_{ij}) = \mathbf{P}_{i,0}$, and $J_{+}^{(i)}(\mathbf{P}_{ij}) = \mathbf{P}_{i,N}$, which favor skewness to the extreme ends. The maximization of $J_{-}^{(i)}$ and $J_{+}^{(i)}$, for each row i, subject to the linear GWF constraints (1.2.5, 1.2.6) is a problem in linear programming. Application of the simplex method yields the following transition matrices, which we turn the Minimal and Maximal transitions respectively. Their nomenclature will become clearer in Chapter 4.

Minimal Process

Define $\mathbf{Q}^{-}$ as the transition matrix:

$$\begin{pmatrix} 1 & 0 & 0 & \cdots & & & & 0 \\ x_1^{(1)} & x_2^{(1)} & x_3^{(1)} & 0 & \cdots & & & 0 \\ x_1^{(2)} & 0 & x_2^{(2)} & x_3^{(2)} & 0 & \cdots & & 0 \\ \vdots & & & & & & & \\ 0 & \cdots & & & & & 0 & 1 \end{pmatrix} \tag{2.3.1}$$

whose entries are

$$x_1^{(i)} = \frac{N-i}{N(i+1)}, \qquad x_2^{(i)} = \frac{i}{N}, \qquad x_3^{(i)} = \frac{N-i}{N} - \frac{N-i}{N(i+1)} \tag{2.3.2}$$

The above stochastic matrix maximizes the cost function $J_-^{(i)}$ subject to the GWF conditions for every $0 \leq i \leq N$.

Maximal Process

Define $\mathbf{Q}^+$ as the transition matrix:

$$\begin{pmatrix} 1 & 0 & 0 & \cdots & 0 & 0 \\ x_1^{(1)} & x_2^{(1)} & 0 & \cdots & 0 & x_3^{(1)} \\ 0 & x_1^{(2)} & x_2^{(2)} & 0 & \cdots & x_3^{(2)} \\ 0 & 0 & x_1^{(3)} & \cdots & & \\ \vdots & & & & & \\ 0 & \cdots & & & 0 & 1 \end{pmatrix} \tag{2.3.3}$$

with entries

$$x_1^{(i)} = \frac{i}{N} - \frac{i}{N(N-i+1)}, \qquad x_2^{(i)} = 1 - \frac{i}{N}, \qquad x_3^{(i)} = \frac{i}{N(N-i+1)} \tag{2.3.4}$$

The above stochastic matrix maximizes the cost function $J_+^{(i)}$ subject to the GWF conditions for every $0 \leq i \leq N$.

2.3.1 Expected Absorption Times of Extreme Processes

We shall compute the expected absorption and fixation times of the above extreme processes. This is tenable, due to the special structure and sparseness of the transition matrix.

Theorem 2.3.1. *(Absorption/Fixation Times for Extreme Processes)*

1. *Started at a fixed fraction x of the population size, the mean time to absorption $E\tau_N$ for the Maximal Process satisfies (as $N \to \infty$):*

$$(1-x)N\log N \leq E\tau \leq N\log N \tag{2.3.5}$$

2. *Started in state i, the conditional time to fixation $E\tau_N^*$ for the Minimal Process is asymptotically*

$$E\tau^* \sim N\log(N-i) \tag{2.3.6}$$

Proof. We consider the maximal process because the analagous results for the minimal process can be obtained by reflection. The upper bound of the theorem is simply that recorded from Theorem 1.3.6. Suppose we begin in state $0 < i < N$. The process monotonically decreases until either a jump to state N occurs, or until 0 is reached. Let t_j be the expected time spent in state j, with $X_0 = i$, conditioned on the event the process reaches level j. We have $E_i\tau = \sum_{j=1}^{i} t_j \cdot P_j$, where P_j is the probability that the process reaches state j. If in state j, the probability of maintaining the state for

n consecutive generations is $(1 - j/N)^n$. It follows $t_j = N/j$, and calculating P_j via conditional probabilities produces

$$E_i\tau = \frac{N}{i} + N\sum_{j=1}^{i-1}\frac{1}{j}\prod_{k=j+1}^{i}(1 - \frac{1}{N-k}) \tag{2.3.7}$$

The equation can be clarified by examination of the hitting time to zero conditioned that X_n fixates at zero. Here, the probability that the process in state j maintains such a state for n generations is $[(1 - j/N)/(1 - j/(N(N - j + 1)))]^n$. Consequently,

$$E_i[\tau|X_\infty = 0] = \sum_{j=1}^{i}\sum_{n=0}^{\infty}\left(\frac{1 - j/N}{1 - j/N(N - j + 1))}\right)^n \tag{2.3.8}$$

$$= \sum_{j=1}^{i}\frac{N+1}{j} \sim (N+1)\log i \tag{2.3.9}$$

Given that

$$E_i[\tau] = E_i[\tau|X_\infty = 0]\cdot(1 - \frac{i}{N}) + E_i[\tau|X_\infty = N]\cdot\frac{i}{N} \tag{2.3.10}$$

this proves the first part of the theorem. The second part follows from (2.3.8) and reflection of the maximal process. □

We make the observation that these results have the same asymptotic orders and even meet the upper bounds in Theorems 1.3.6, 1.4.5.

2.4 Power-Law Models.

The preceding models are technically useful in obtaining an intuition about the very large space of possible generalization population models, but are perhaps somewhat inadequate from the perspective of biology in offering viable alternatives to the Wright-Fisher process. If the conditional distributions of the Wright-Fisher model are the discrete analogues of the

Gaussian distribution, a natural class of alternatives to consider are those with conditional distributions with power-law decay of index α.

2.4.1 Construction of the Models

Define the transition $\mathbf{Q}$ matrix:

$$\mathbf{Q}_{ij} = \begin{cases} \frac{c_i}{1+b_{1,i}|j-i|^\alpha}, & j < i, 0 < i < N \\ \frac{c_i}{1+b_{2,i}|j-i|^\alpha}, & j \geq i, 0 < i < N \\ \delta_{0,j}, & i = 0 \\ \delta_{N,j}, & i = N \end{cases} \tag{2.4.1}$$

We hope for slope parameters $b_{1,i}, b_{2,i} > 0$, and a normalisation c_i making $\mathbf{Q}$ stochastic and satisfying the GWF conditions (1.2.5, 1.2.6). This is borne out in the next theorem, which proves the existence and uniqueness of solutions to the associated nonlinear equations.

Theorem 2.4.1. *For each $0 < \alpha \leq 3$, there exist unique positive $b_{1,i} > 0, b_{2,i} > 0, c_i > 0$ satisfying the GWF conditions (1.2.5,1.2.6), for all population sizes $N \geq 12$.*

Proof. **Existence:** Fix a row $i \geq 1$, and write for ease of notation b_1, b_2 in place of $b_{1,i}, b_{2,i}$. From symmetry ($b_{1,i} = b_{2,N-i}$), we need only prove the result for rows $i \leq N/2$. The normalization c_i must have the value

$$c_i = \left(\sum_{j=0}^{i-1} \frac{1}{1+b_1|j-i|^\alpha} + \sum_{j=i}^{N} \frac{1}{1+b_2|j-i|^\alpha} \right)^{-1} \tag{2.4.2}$$

The mean $m(b_1, b_2)$, and second moment $s(b_1, b_2)$ of the resulting probability distribution take the forms:

$$m(b_1, b_2) = \frac{\sum_{j=1}^{i-1} \frac{j}{1+b_1|j-i|^\alpha} + \sum_{j=i}^{N} \frac{j}{1+b_2|j-i|^\alpha}}{\sum_{j=0}^{i-1} \frac{1}{1+b_1|j-i|^\alpha} + \sum_{j=i}^{N} \frac{1}{1+b_2|j-i|^\alpha}} \tag{2.4.3}$$

$$s(b_1,b_2) = \frac{\sum_{j=1}^{i-1} \frac{j^2}{1+b_1|j-i|^\alpha} + \sum_{j=i}^{N} \frac{j^2}{1+b_2|j-i|^\alpha}}{\sum_{j=0}^{i-1} \frac{1}{1+b_1|j-i|^\alpha} + \sum_{j=i}^{N} \frac{1}{1+b_2|j-i|^\alpha}} \tag{2.4.4}$$

A direct computation, or a simple probabilistic argument shows that $\frac{\partial m}{\partial b_2}, \frac{\partial s}{\partial b_2} < 0$, and $\frac{\partial m}{\partial b_1}, \frac{\partial s}{\partial b_1} > 0$, for all $b_1, b_2 \geq 0$. Fix now any $b_1 \geq 0$, and let $f(b_2) = m(b_1, b_2)$. We have $f(b_1) \geq i$, and

$$f(\infty) = \frac{\sum_{j=1}^{i-1} \frac{j}{1+b_1|j-i|^\alpha} + i}{\sum_{j=0}^{i-1} \frac{1}{1+b_1|j-i|^\alpha} + 1} < i \tag{2.4.5}$$

The previous inequality can be verified by multiplication of both sides by the denominator and simplifying to the obvious inequality

$$0 < \frac{i}{1+b_1 i^\alpha} + \sum_{j=1}^{i-1} \frac{i-j}{1+b_1|j-i|^\alpha} \tag{2.4.6}$$

It follows that for each value of b_1, there exists a unique value of $b_2 \geq b_1$ for which $m(b_1, b_2) = i$. Combined with the implicit function theorem, this gives us a differentiable curve $b_2 = \gamma_m(b_1)$, defined for all $b_1 \geq 0$, such that $m(b_1, \gamma_m(b_1)) = i$. Some further facts about $\gamma_m(b_1)$ come from the previous observations: it lies above the line $b_2 = b_1$, and is strictly increasing, since $-\frac{\partial m}{\partial b_1} / \frac{\partial m}{\partial b_2} > 0$.

A similar analysis can be performed on the second moment function s. Fix $b_1 \geq 0$, and let $g(b_2) = s(b_1, b_2)$, a strictly decreasing function. One checks that

$$g(\infty) = \frac{\sum_{j=1}^{i-1} \frac{j^2}{1+b_1|j-i|^\alpha} + i^2}{\sum_{j=0}^{i-1} \frac{1}{1+b_1|j-i|^\alpha} + 1} < i(1-i/N) + i^2 \tag{2.4.7}$$

the inequality being verified once again by reduction to a simple inequality, this time,

$$0 < i(1-i/N) \left(\sum_{j=0}^{i-1} \frac{1}{1+b_1|j-i|^\alpha} + 1 \right) + \frac{i^2}{1+b_1 i^\alpha} + \sum_{j=1}^{i-1} \frac{i^2-j^2}{1+b_1|j-i|^\alpha} \tag{2.4.8}$$

Also,

$$g(0)=\frac{\sum_{j=1}^{i-1}\frac{j^2}{1+b_1|j-i|^\alpha}+\sum_{j=i}^{N}j^2}{\sum_{j=0}^{i-1}\frac{1}{1+b_1|j-i|^\alpha}+N-i+1}\geq\frac{\sum_{j=i}^{N}j^2}{N+1}\geq i(1-i/N)+i^2 \tag{2.4.9}$$

for all $i\leq N/2$. The final inequality can be verified by checking only at $i=N/2$ or $i=(N-1)/2$, depending on whether N is odd or even, since the left-hand side is minimized, and the right-hand side is maximized at that value.

We now have a differentiable, strictly increasing curve $b_2=\gamma_s(b_1)$, defined for $b_1\geq 0$, for which $s(b_1,b_2)=i(1-i/N)+i^2$ if and only if (b_1,b_2) is on the graph of the curve γ_s. The intersection points of γ_m and γ_s (if any exist), then produce all the pairs (b_1,b_2) in the positive quadrant which realise the GWF conditions. Let us establish the existence of at least one intersection point. First we demonstrate that $\gamma_s(0)>\gamma_m(0)$. We again consider a row $1\leq i\leq N/2$. Let $b_1=0$. To ease the notation, it will to suffice to prove that $\gamma_s(0)\geq\gamma_m(0)$ when the γ_s curve is a constant i^2+i second moment, as opposed to constant $i^2+i(1-i/N)$ curve. By multiplying by the denominators in (2.4.3) and (2.4.4), it is an easy matter of algebra to show that the mean condition is satisfied iff b_2 solves

$$\sum_{k=1}^{N-i}\frac{k}{1+b_2k^\alpha}=\frac{1}{2}(i^2+i) \tag{2.4.10}$$

and satisfies the (modified) second moment condition iff

$$\sum_{k=1}^{N-i}\frac{k^2-i}{1+b_2k^\alpha}=\frac{2}{3}i^3+\frac{3}{2}i^2+\frac{5}{6}i-2i\sum_{k=1}^{N-i}\frac{k}{1+b_2k^\alpha} \tag{2.4.11}$$

We shall now show that if b_2 is chosen so that the mean condition is satisfied, then the left-hand side of (2.4.11) is larger or equal than its right-hand side, indicating $\gamma_s(0)$ must be greater than or equal to that value of b_2 (because the LHS at $b_2=\infty$ is 0, and the RHS at $b_2=\infty$ is positive).

When b_2 is chosen such that (2.4.10) is satisfied, the RHS of (2.4.11) becomes $\frac{-1}{3}i^3 + \frac{1}{2}i^2 + \frac{5}{6}i$, which is negative for all $i \geq 3$. The smallest value that the LHS of (2.4.11) can attain is:

$$\sum_{k=1}^{N-i} \frac{k^2 - i}{1 + b_2 k^\alpha} \geq \sum_{k=1}^{[\sqrt{i}]} (k^2 - i) = \frac{1}{3}[\sqrt{i}]^3 + \frac{1}{2}[\sqrt{i}]^2 + \frac{1}{6}[\sqrt{i}] - i[\sqrt{i}] \tag{2.4.12}$$

which is easily verified to be larger or equal to $\frac{-1}{3}i^3 + \frac{1}{2}i^2 + \frac{5}{6}i$ as long as $i \geq 3$. Finally, consider the cases $i = 1, 2$, which require a slight variation on this argument. First, it is easy to verify by factorization that

$$\sum_{k=1}^{9} \frac{k^2 - 1 - k}{1 + b_2 k^3} > 0 \tag{2.4.13}$$

for all $b_2 \geq 0$. Since only the first term of that sum is negative, we deduce

$$\sum_{k=1}^{N-1} \frac{k^2 - 1 - k}{1 + b_2 k^\alpha} > 0 \tag{2.4.14}$$

for all $0 < \alpha \leq 3$, and $N \geq 10$.

Now let $i = 1$, and b_2 solve (2.4.10). The RHS of both (2.4.10) and (2.4.11) are now 1, and we can estimate the LHS of (2.4.11) with (2.4.14)

$$\sum_{k=1}^{N-1} \frac{k^2 - 1}{1 + b_2 k^\alpha} > \sum_{k=1}^{N-1} \frac{k}{1 + b_2 k^\alpha} = 1 = \text{RHS of (2.4.11)} \tag{2.4.15}$$

which proves the case $i = 1$ under the proviso $N \geq 10$.

Finally, let $i = 2$. This time, we use

$$\sum_{k=1}^{10} \frac{k^2 - 2 - k/3}{1 + b_2 k^3} > 0 \tag{2.4.16}$$

and hence

$$\sum_{k=1}^{N-2} \frac{k^2 - 2 - \frac{1}{3}k}{1 + b_2 k^\alpha} > 0 \tag{2.4.17}$$

for all $b_2 \geq 0$, $N \geq 12$ and $0 < \alpha \leq 3$. If b_2 solves (2.4.10), the RHS of (2.4.11) is 3, and the RHS of (2.4.11) is 1, thus:

$$\text{LHS of (2.4.11)} = \sum_{k=1}^{N-2} \frac{k^2-2}{1+b_2k^\alpha} > \frac{1}{3}\sum_{k=1}^{n-2} \frac{k}{1+b_2k^\alpha} = 1 = \text{RHS of (2.4.11)} \tag{2.4.18}$$

We have thus proved $\gamma_s(0) > \gamma_m(0)$ for every row, as long as $N \geq 12$. To complete our proof of existence, we shall show that $\lim_{b_1\to\infty} \gamma_s(b_1) = \text{const}$. First recall γ_s is increasing; we need only show it is bounded. Let $K = i(1-i/N) + i^2$. Rearranging the equation $s = K$ in (2.4.4) shows that (b_1, b_2) satisfies

$$\sum_{j=i}^{N} \frac{j^2-K}{1+b_2|j-i|^\alpha} = \sum_{j=0}^{i-1} \frac{K-j^2}{1+b_1|j-i|^\alpha} \tag{2.4.19}$$

We had proven that for each positive b_1, there exists a unique $b_2 > 0$ satisfying the above. In the left-hand side of (2.4.19), the first term is negative, and the remaining terms are positive:

$$\sum_{j=i}^{N} \frac{j^2-K}{1+b_2|j-i|^\alpha} = -i(1-i/N) + \sum_{j=i+1}^{N} \frac{j^2-K}{1+b_2|j-i|^\alpha} \tag{2.4.20}$$

At $b_2 = 0$, the RHS of the above expression is positive (exercise in algebra), and as $b_2 \to \infty$, strictly negative, already implying the curve γ_s is bounded, since the RHS of (2.4.19) is always positive. Additionally, there exists a finite value of b_2 for which

$$-i(1-i/N) + \sum_{j=i+1}^{N} \frac{j^2-K}{1+b_2|j-i|^\alpha} = 0, \tag{2.4.21}$$

and this constant is the asymptotic value of γ_s. This fact, combined with the previously-noted property that $\gamma_m(b_1)$ lies above the line $b_2 = b_1$, gives the existence of an intersection point.

Uniqueness:

Because the constant mean curve γ_m is strictly increasing, the variance function restricted to γ_m is strictly decreasing in b_1 (this intuitively obvious statement can be verified simply with an elementary probabilistic argument). Hence γ_m intersects γ_s at exactly one point. $\square$

Remark: The actual proof goes beyond the statement of the theorem, to establish the existence of appropriate parameters for all $\alpha > 0$ and all $N \geq 12$, for rows $3 \leq i \leq N-2$. In our continuum theory (Chapter 3), it will be useful to be in possession of power-law processes for parameters $\alpha > 3$. Since continuum limits ignore rows a fixed distance from the boundaries, we will simply assign arbitrary probability distributions to the first two rows when $\alpha > 3$ for the required extension.

2.4.2 An Algorithm for Computation of the Parameters

Our proof suggests an iterative algorithm that can be used to compute the parameters b_1, b_2, given N and a row i — an algorithm necessary for simulations. Observe that $\gamma_s \geq \gamma_m$ for all b_1 smaller than the intersection point, and both curves strictly increase. Thus given a point on γ_m lying before the intersection, its second component can be increased until the point lies on γ_s; similarly the first component of a point (lying before intersection) residing on γ_s can be increased until γ_m is hit. Initializing at $(0,0)$ and then alternately finding these hitting points via a bisection algorithm on equations (2.4.3), (2.4.4), one obtains a sequence of points converging to the desired intersection.

2.4.3 Absorption times of Power-law models

Having introduced the power-law models, we proceed to study their neutral absorption times near a boundary for these models, still restricting ourselves to discrete methods. These times will turn out to be considerably longer than the absorption time for the Wright-Fisher model. The general problem of exit times where the initializing frequency occurs at fixed frequencies of N — and hence away from the boundary — can be attacked with the methods of Chapter 4.

Absorption Time near the Boundary of the Cauchy Model

We will call the case $\alpha = 2$ the *Cauchy* model. As usual, let $E_j \tau_N$, $j = 0 \dots N$ be the expected absorption time for the Cauchy process X_k of population size N, started at $X_0 = j$. Let $\mathbf{P}_{ij}$ be the Markov transition matrix for X_k. Of vital importance is the consideration of the *holding time in state 1*, $\tau^* = \inf\{k : X_k \neq 1, X_0 = 1\} - 1$.

First, a very simple Lemma:

Lemma 2.4.2. $E_1 \tau = E\tau^* + \sum_{j=2}^{N-1} \frac{\mathbf{P}_{1j}}{1-\mathbf{P}_{11}} \cdot E_j \tau$

In words, this lemma simply states that the mean absorption time is the mean time spent in the initial state 1, plus the average time to absorption starting at any of the states 2 through $N-1$, weighted by the conditional probabilities of actually jumping to that state upon exit of state 1.

Proof. Let τ^{**} be the random time to fixation after the state 1 exit; so that $(\tau | X_0 = 1) =$

$\tau^* + \tau^{**}$. Let A_j be the event that $X_{\tau^*+1} = j$. Then $\{A_j\}$ partitions the sample space, so

$$P(\tau^{**} = a) = \sum_{j=0}^{n} P(\tau^{**} = a | A_j) P(A_j) \tag{2.4.22}$$

Multiplying both sides by a and summing,

$$\sum_{a=0}^{\infty} aP(\tau^{**} = a) = \sum_{j=0}^{n} \sum_{a=0}^{\infty} aP(\tau^{**} = a | A_j) P(A_j) \tag{2.4.23}$$

$$E\tau^{**} = \sum_{j=0}^{n} E[\tau^{**} | A_j] P(A_j) \tag{2.4.24}$$

From the Markov property, $E[\tau^{**}|A_j] = E_j\tau$, and noting that $P(A_1) = 0$, $P(A_j) = \frac{\mathbf{P}_{1j}}{1-\mathbf{P}_{11}}$ for $j \neq 1$, and $E_0\tau = E_N\tau = 0$, the result follows. □

We will use Lemma 2.4.2 to estimate lower and upper bounds for $E[\tau | X_0 = 1]$, by computing the expected holding time $E\tau^*$, and finding upper bounds on the second summand. Let us now estimate more definitely the probabilities $\mathbf{P}_{1j}$.

Lemma 2.4.3. *In the Cauchy model, one has the estimates*

$$c = \mathbf{P}_{11} = 1 - \frac{\log N}{N} + o(N^{-1}\log N) \tag{2.4.25}$$

$$\mathbf{P}_{10} \sim \frac{\log N}{N} \tag{2.4.26}$$

Proof. Recall that the first row of the transition matrix for the Cauchy model is of form:

$$\mathbf{P}_{1j} = \begin{cases} \frac{c}{1+b_1^{(N)}}, & j = 0 \\ \frac{c}{1+b_2^{(N)}(j-1)^2}, & j \geq 1 \end{cases} \tag{2.4.27}$$

with c a normalization, and $b_1^{(N)}, b_2^{(N)} > 0$ chosen to match the first two GWF statistics. We aim to obtain the asymptotics for $b_1^{(N)}$ and $b_2^{(N)}$. Writing out the Wright-Fisher constraints on mean and variance, one finds the following two equations must be satisfied (we shall suppress the superscript N for ease of notation):

$$\frac{1}{1+b_1} = \sum_{m=0}^{N-1} \frac{m}{1+b_2 m^2} \tag{2.4.28}$$

$$\sum_{m=1}^{N-1} \frac{m^2 + \frac{m}{N} - 1 + \frac{1}{N}}{1+b_2 m^2} = 1 - \frac{1}{N} \tag{2.4.29}$$

Equation (2.4.29) immediately implies $b_2^{(N)} \sim N$. Equation (2.4.28) allows us to eliminate b_1 and write all probabilities in terms of b_2 alone, from which one deduces the statements:

$$c = \mathbf{P}_{11} = \frac{1}{1 + \sum_{m=1}^{N-1} \frac{1}{1+b_2 m^2} + \sum_{m=1}^{N-1} \frac{m}{1+b_2 m^2}} = 1 - \frac{\log N}{N} + o(N^{-1} \log N) \tag{2.4.30}$$

$$\mathbf{P}_{10} = c \cdot \sum_{m=0}^{N-1} \frac{m}{1+b_2 m^2} \sim \frac{\log N}{N} \tag{2.4.31}$$

□

Now we can prove the following asymptotic for the absorption time of the Cauchy model:

Theorem 2.4.4. *In the Cauchy process started at* $X_0 = 1$, *the expected absorption time* $E_1 \tau_N$ *satisfies (as* $N \to \infty$*):*

$$\frac{N}{\log N} \le E\tau_1 \le C \frac{N}{\log N} \tag{2.4.32}$$

where $C = 1 + \sum_{j=2}^{\infty} \frac{1+\log j}{(j-1)^2} \approx 4.44$

Proof. **Asymptotic Lower Bound**

Since $P(\tau^* \ge k) = \mathbf{P}_{11}^k$, by Lemma 2.4.3,

$$E\tau^* = \sum_{k \ge 0} \mathbf{P}_{11}^k = 1/(1 - \mathbf{P}_{11}) \sim \frac{N}{\log N} \tag{2.4.33}$$

And hence from Lemma 2.4.2,

$$E_1\tau \geq \frac{N}{\log N} \qquad (N \to \infty) \tag{2.4.34}$$

Asymptotic Upper Bound

Next we shall make use of our previously derived upper bounds on the expected fixation time $E_j\tau$ for any GWF process. From the upper bound in Theorem 1.3.5, one deduces the asymptotic inequality:

$$E_j\tau \leq N \log\left(\frac{j(N-j)}{N}\right) + j(N-j)\left(1 - \frac{1}{N}\right)^{N\log\left(\frac{j(N-j)}{N}\right)} \tag{2.4.35}$$

Therefore, the second term of Lemma 2.4.2 has the asymptotic upper bound ($N \to \infty$):

$$\sum_{j=2}^{N-1} \frac{\mathbf{P}_{1j}}{1-\mathbf{P}_{11}} E_j\tau \leq \frac{N}{\log N} \sum_{j=2}^{N-1} \frac{E_j\tau}{1+N(j-1)^2} \tag{2.4.36}$$

$$\leq \frac{1}{\log N} \sum_{j=2}^{N-1} \frac{E_j\tau}{(j-1)^2} \tag{2.4.37}$$

$$\leq \frac{N}{\log N} \sum_{j=2}^{\infty} \frac{1+\log j}{(j-1)^2} \tag{2.4.38}$$

from which we finally conclude the statement, via Lemma 2.4.2.

□

Absorption Time Near the Boundary of Power-law Modelss, $2 < \alpha < 3$

We observed in the last section that, started at a single individual $X_0 = 1$, it required on average $O((\log N)/N)$ generation for absorption to occur in the Cauchy ($\alpha = 2$) model —

not nearly as long as the $O(N)$ length for that of the Λ_1-model, but significantly longer than the $O(\log N)$ generations of the Wright-Fisher model.

If the Wright-Fisher model is to be identified roughly as that α process associated to $\alpha = \infty$, one expects the above absorption time to decrease with increasing α. Our next theorem is suggestive of this fact, and can be proved by identical methods to those in the previous section.

Theorem 2.4.5. *The expected absorption time* $E_1\tau$ *for the power-law models started at* $X_0 = 1$ *satisfies* ($N \to \infty$):

$$E\tau_1 \geq C_\alpha N^{3-\alpha} \tag{2.4.39}$$

for all $2 < \alpha < 3$.

We remark that these absorption times are still of considerably larger orders than that of the Wright-Fisher process; interestingly, the lower bound becomes trivial at $\alpha = 3$. This is no coincidence: with continuum theory we shall prove that at $\alpha = 3$, the Kimura diffusion limit holds, and hence the processes for $\alpha \geq 3$ can already be well approximated by the Wright-Fisher system.

2.5 Discussion of GWF Absorption and Fixation Times

Having, in the last two chapters, proved a number of theorems mostly regarding aspects of fixation and absorption in pure-drift GWF processes, we will pause here to give some qualitative comments on our theory so far.

One of the original motivations in introducing a theory of generalised population processes was to determine which aspects of the Wright-Fisher model were robust to changes to its offspring mechanism (as encoded, in Cannings models for example, in the exchangeable variable ν). In the case of pure-drift processes, a number of quantities remain unchanged to such perturbations — those, for instance, which are functions solely of the lower-order symmetry properties, including fixation probabilities and the first two unconditional moments. These stabilities carry over even under non-zero mutation, where a special linear dependence on allele frequency preserves the closed structure of moments. For functionals not exactly preserved over all pure-drift processes our study indicates that sensitivity is highly dependent on the initial starting frequency of the process. For example, the stability of absorption times increases as the initial frequency increases in distance to an absorbing state(s). On the other hand, enormous deviations will be seen to result when selection is introduced, regardless of initial distance to absorption, as evidenced by variations in fixation probabilities over several orders of magnitude (Chapter 4).

These phenomena have a unified explanation, which we now delineate via a thought-experiment on the probabilistic behavior induced by rows of the drift matrix. The center row of $\mathbf{Q}_N$ for the Wright-Fisher process is a discrete symmetric distribution about $N/2$, approximately Gaussian. Consider a deformation of this distribution, with the object of maintaining its mean, or even its symmetry. Two directions of deformation arise: probability mass may be moved to the tails of the distribution, or further concentrated about the mean. The additional constraint of a fixed variance, however, implies that for any mass moved to the extremes, a compensating mass must be concentrated near its center; similar injunctions hold in the reverse direction. Our two GWF moment prescriptions (1.2.5, 1.2.6) then imply a range of distributions, some with heavier tails than the Wright-Fisher model, but correspondingly more strongly peaked about their mean, or conversely, possessing tails of greater decay, and smaller central peaks. These two directions of deformation are associated with increases and decreases, respectively, of the higher (centered) moments of the distribution.

One of these directions is fruitless, if models with significantly divergent dynamics from the Wright-Fisher process are sought, for *reductions* in the size of the higher moments only improves the applicability of a diffusion approximation. Hence non-standard behavior only occurs for deformations which broaden the tails, along with the concomitant concentration of mass about a distribution's mean. Figure 1 illustrates the principles described above through plots of the center row of $\mathbf{Q}_N$ associated to our model GWF processes: in each case, the distributions are more strongly peaked and have heavier tails than the Wright-Fisher counterpart. Similar ideas clearly hold for any of the rows.

One consequence of a strongly-peaked transition distribution is that the *holding time* of states is lengthened. Indeed, the holding time ranges from $O(1)$ in the Wright-Fisher model to $O(N)$ in the Λ_1 model. This enormous variation is what principally accounts for the great sensitivity of mean absorption times when initialized near absorbing states, since such times are dominated by the holding period in the initial state. Conversely, when started away from absorbing states, initial holding times contribute only a small fraction to overall absorption times, the latter then more dictated by global conditions imposed by the lower moments: thus their improved stability. This also explains the robustness of conditional fixation times of new mutants in Theorem 1.4.5, despite an initialization near

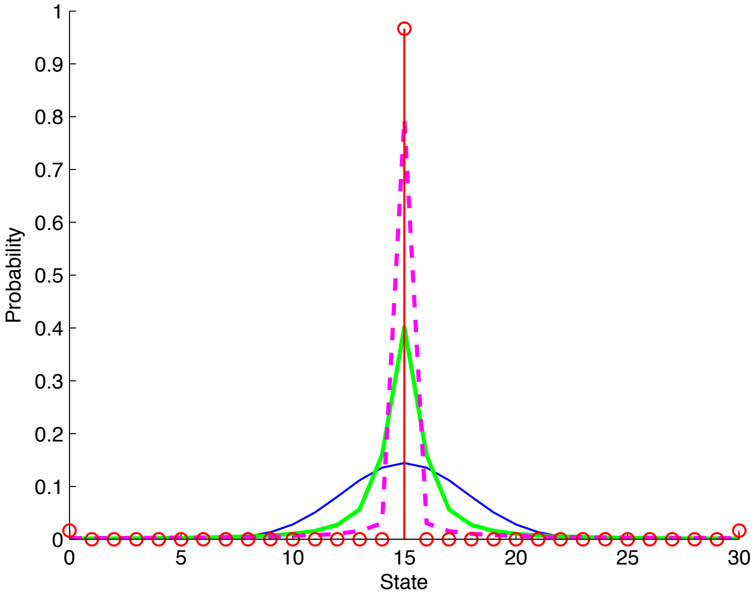

Figure 2.1: Center transition distributions of $\mathbf{Q}_N$, $N = 30$. Solid: Wright-Fisher, Bold: $\alpha = 2$, Dashed: $\alpha = 1$, circle-stem: Λ_1.

the boundary: conditioning effectively removes the absorbing state at 0, and once more the initial holding period contributes negligibly to the overall fixation time.

2.6 The Convex Space of GWF Processes.

Let $\mathbf{P}_1$ and $\mathbf{P}_2$ be any two GWF transition matrices for a fixed population size N and of some offspring variance σ_N^2. Because the GWF conditions are linear constraints, their convex combination $\mathbf{P} = a\mathbf{P}_1 + (1-a)\mathbf{P}_2$, $0 < a < 1$, defines another GWF process of the same offspring variance. Hence the set of all GWF processes is a convex set. Moreover, it is obvious that this set is compact in the standard topology for finite-dimensional matrices. The Krein-Milman theorem then states that there must be extreme points, and that the space of all GWF processes is the convex hull of these points. Our present aim is to characterise these extreme points. The study will also prove useful later, since these aptly named extreme points will also turn out to be extremal with respect to a number of important biological quantities.

Let $\mathbf{p} = (p_0, \ldots, p_N)$ be a probability mass function on the states, i.e. a non-negative vector summing to 1. It is clear that the space of probability mass functions with a prescribed mean i and second moment s_i also form a compact convex set K, and that a GWF transition matrix is extremal if and only if each of its rows is extremal in K.

Theorem 2.6.1. *Let* $\mathbf{p} = (p_0, \ldots, p_N)$ *be a probability mass function* $\mathbf{p}$ *with a given mean* i *and second moment* s_i*. Let* $n = \#\{j : p_j \neq 0\}$.

(a) If $n \geq 4$*, then* $\mathbf{p}$ *is not extreme in* K.

(b) If $n \leq 3$*, then* $\mathbf{p}$ *is extreme in* K.

Proof. For (a), define the linear (Vandermonde) transformation on the strictly positive pmf values $p_{k_1}, \dots, p_{k_n}$ with indices $k_1, \dots, k_n$.

$$f(p_{k_1}, p_{k_2}, \dots, p_{k_n}) = (\sum_j p_{k_j}, \sum_j k_j p_{k_j}, \sum_i k_j^2 p_{k_j}) \tag{2.6.1}$$

We have $f(\mathbf{p}) = (1, i, s_i)$. Say $n \geq 4$; then as $f(p_{k_1}, p_{k_2}, p_{k_3}, 0, 0, \dots)$ is invertible, the implicit function theorem gives the existence of a second pmf defined on supp $\mathbf{p}$, $\mathbf{p}' \neq \mathbf{p}$ (continuity allows for positivity) such that $f(\mathbf{p}') = (1, i, s_i)$. Define $\mathbf{p}'' = \frac{\mathbf{p} - a\mathbf{p}'}{1-a}$ which is positive for small a as well as satisfying $f(\mathbf{p}'') = (1, i, s_i)$. Then $\mathbf{p} = a\mathbf{p}' + (1-a)\mathbf{p}''$ is a non-trivial convex decomposition.

To (b), note that the convex decomposants must have support a subset of supp $\mathbf{p}$. For $n \leq 3$, f is injective, and so only a trivial decomposition is possible.

□

Let us now turn to the existence of extreme three-point pmfs. Certainly the support of such measures cannot be arbitrary.

Theorem 2.6.2. *Let $i_1 < i_2 < i_3$ be indices in $\{0, \dots, N\}$, with corresponding pmf (possibly zero) weights $(p_1, p_2, 1 - p_1 - p_2)$. Then there exists a unique mass function on (i_1, i_2, i_3) which has Wright-Fisher mean i and variance v_i, if and only if the conditions*

(a) $i_1 \leq i \leq i_3$

(b) $d_3 d_1 \geq v_i \geq d_2 \max(d_3, d_1)$

are satisfied, where $d_1 = |i - i_1|, d_2 = |i - i_2|, d_3 = |i - i_3|$. Under these circumstances, the pmf is extreme and p_1, p_2 are the unique solution to

$$\begin{pmatrix} i_1 - i_3 & i_2 - i_3 \\ i_1^2 - i_3^2 & i_2^2 - i_3^2 \end{pmatrix} \begin{pmatrix} p_1 \\ p_2 \end{pmatrix} = \begin{pmatrix} i - i_3 \\ i(1 - i/N) + i^2 - i_3^2 \end{pmatrix} \tag{2.6.2}$$

Proof. Matrix equation (2.6.2) records the mean and variance conditions; the 2×2 matrix is always invertible when $i_1 \neq i_2 \neq i_3$; we simply find the algebraic conditions ensuring $p_1, p_2 \geq 0$, and $p_1 + p_2 \leq 1$. Criterion (a) is obviously necessary, since the sought-after mean must lie between i_1 and i_3. Assuming this, it is elementary algebra to show from (2.6.2) that the three conditions reduce to $(i_3 - i)(i - i_1) \geq v_i$, $v_i \geq (i_3 - i)(i - i_2)$, and $v_i \geq (i - i_1)(i_2 - i)$, which is equivalent to (b). Extremity of the pmf comes from Theorem 2.6.1b. □

Theorem 2.6.2 gives a fairly explicit characterisation of all extreme GWF processes in terms of extremal probability distributions supported on at most three points. It is immediate from this that the Minimal, Maximal, and Λ_1-processes introduced earlier are in fact extreme points in this space. We shall study these extreme processes at greater length with the aid of continuum theory in the next chapter, and also make use of Theorem 2.6.2 in the proof of our continuum representation Theorem 3.5.1.

Chapter 3

Continuum Theory

In this chapter we introduce a theory of continuum limits, which generalises the diffusion equation approach traditionally used to explore population genetic models. This theory becomes critical since it turns out that the continuous-time limits of GWF processes do not generally possess continuous sample paths, and hence cannot be approximated by diffusive processes. We derive the general representation theorem for the generators of GWF processes, discuss the approximation of Markov chains by such processes, and calculate the continuum limits for a number of the discrete models previously introduced.

3.1 Preliminary Ideas

In previous sections, we introduced a number of models for evolution, all having the structure of a Markov chain $X_k^{(N)}$ on states $\{0, \ldots, N\}$ with transition matrix $\mathbf{P}_{ij}^{(N)}$. When no mutation was present, $\{0, N\}$ were absorbing states, and the quantities of scientific interest were the expected absorption time $E_j \tau$ started at initial number j, and the probabilities of fixation at N. Under the influence of mutation, the germane questions were expected time to loss of an allele, or the form of the stationary distribution μ.

The classical theory of Markov chains provides answers to these questions in the form of solutions of systems of linear equations, specifically of the following type:

$$(\mathbf{P}^{(N)} - \mathbf{I})u_N = g \tag{3.1.1}$$

$$(\mathbf{P}^{(N)} - \mathbf{I})^* \mu_N = 0 \tag{3.1.2}$$

When $g = 0$, the solution u to (3.1.1) solves the fixation probability problem (subject to appropriate boundary conditions); when $g = -1$, u solves the absorption time problem; finally, (3.1.2) is the equation satisfied by the stationary distribution π.

While there are certain classes of transition matrices (e.g. so-called continuant chains), for which the exact computations to (3.1.1, 3.1.2) are possible, the solution to these equations generally becomes rapidly untenable for large N. Even if one can solve the associated problems numerically, very little qualitative insight is afforded into the nature of the solutions.

An alternative approach is the following. We consider scaling the Markov chains by some natural parameter — population size N, for example, and hope that the scaled processes converge to limiting, continuous-time Markov processes. Under many circumstances, the respective discrete solutions u_N converge to functions u which satisfy the continuous counterparts of (3.1.1,3.1.2), i. e. $Gu = g$ and $G^*\mu = 0$, where G is the generator of the limiting process. The solutions to the continuum problem are typically easier to study, since they involve, in the diffusion case, the analysis of second-order differential and partial differential equations — a classical and well-mined field. Qualitative insight is achieved because the continuum limit is very much a first-order approximation to the dynamics of a discrete system: chains differing only in second-order effects have the same continuum limit. The act of taking a continuum limit thereby collapses the number of models to a simpler and, in many ways, more elegant space.

The seminal work in continuum approximation for the classical Wright-Fisher model was pioneered by Kimura [11], and later put on a rigorous basis by Trotter and Feller. There, it was shown that when X_k is the pure-drift Wright-Fisher model, then $\frac{1}{N}X_{[Nt]}$ converges to a continuous-time process X_t with generator $Gu = \frac{1}{2}x(1-x)u''(x)$, and domain described by a local boundary condition, à la Feller's classification.

In our consideration of Cannings, and, more generally, GWF processes, we will find that the limiting generator G is very rarely a second-order differential operator. There will exist a class of GWF processes which do converge to the standard Kimura diffusion, but the continuum space will also contain many other interesting limits, with radically different properties. The apposite questions in our theory will be: what form does the limit G take? Can one rigorously prove the convergence (in some sense) of the discrete model to the continuum? What characterisations can one prove about those processes that do converge to the standard diffusion population genetic model? Can one solve or obtain qualitative understanding of the solutions to the resulting continuum equations (which may be non-differential)? We propose to answer these questions in the remainder of this chapter and the next.

3.2 The GWF Operator

We will begin our study by analyzing the operator, which we call *the pure drift GWF operator* $G : D \subset C[0,1] \to [0,1]^{\mathbb{R}}$, given by

$$Gu(x) = \sigma^2 x(1-x) \int_0^1 \frac{u(y) - u(x) - u'(x)(y-x)}{(y-x)^2} d\Omega_x(y) \tag{3.2.1}$$

for a family of (Borel) probability measures $\{\Omega_x,\ 0 < x < 1\}$ supported on $[0,1]$. Its importance will become apparent as the chapter progresses. We will sometimes use the notation G_Ω to emphasize the dependence of the operator on the family of measures Ω. Also, in the sequel we will use $\mathcal{M}_1([0,1])$, or more simply $\mathcal{M}_1$ to denote the space of Borel probability measures on $[0,1]$.

3.2.1 Domain and Range

Since G can be an unbounded operator, $D = \mathcal{D}(G)$ can in general only be a dense subset of the continuous functions. What should its domain include? This depends greatly on the Markov chains for which G will be a putative limiting generator. A clue is taken from the Wright-Fisher generator, wherein $D \supset C^2[0,1]$. In many of our examples (for instance, in the Cannings construction to come later), the polynomials $\mathscr{P}$ on $[0,1]$ will also play a role, since many of our physical models have important structural regularities involving polynomials. Indeed, for the purposes of construction of generators, $\mathscr{P}$ will serve as the simplest choice for a core. In any case, in what follows below, we make the assumption that D contains at least $\mathscr{P}$, and in many settings also $C^2[0,1]$. In each case we will indicate if the theorem holds true if the domain of G is known only to contain the polynomials, or the respective modification of the theorem under that scenario.

The specification of G only on C^2 or $\mathscr{P}$ will be insufficient to make G the generator of a C^0-semigroup. In such circumstances we will take the closure of G (which must be proven to exist) — in other words, the smallest closed set in the graph topology containing $\{(u, Gu), u \in \mathcal{D}(G)\}$.

For notational purposes we write

$$h_u(x,y) = \frac{u(y) - u(x) - u'(x)(y-x)}{(y-x)^2} \tag{3.2.2}$$

It follows from Taylor's theorem that h_u is continuous on $[0,1] \times [0,1]$ whenever $u \in C^2[0,1]$, with the obvious definition of h_u at the removable singularity $x = y$. The following lemma is now useful.

Lemma 3.2.1. *For any fixed* $0 < x^* < 1$, *and given* $f \in C^2[0,1]$ *(or* $\mathscr{P}$*), there exists a* $u \in C^2[0,1]$ *(respectively* $\mathscr{P}$*) such that* $h_u(x^*, y) = f(y)$ *for* $y \in [0,1]$.

Proof. It is easy to check that $u(y) = f(y)(y - x^*)^2$ fits the bill. ☐

Further topological restrictions on the family of measures Ω_x must be made, if G is to map into the continuous functions: specifically, the measure-valued function $\Omega : (0,1) \to \mathcal{M}_1$ must satisfy a continuity condition. This is addressed in the following proposition.

Proposition 3.2.2. *Let* $G : C^2[0,1] \to (0,1)^{\mathbb{R}}$ *be defined above, for some Borel probability measure valued function* $\Omega : (0,1) \to \mathcal{M}_1$. *Then* $Im(G) \subset C(0,1)$ *if and only if* Ω *is sequentially weak-$*$ continuous: for any* $x \in (0,1)$ *and* $x_n \to x$, *one has, for any* $f \in C[0,1]$,

$$\lim_{n\to\infty} \int_0^1 f d\Omega_{x_n} = \int_0^1 f d\Omega_x \tag{3.2.3}$$

Proof. For necessity, assume the continuity condition is not satisfied: then there exists a point x^* and a sequence $x_n \to x^*$, and a continuous function f, which can in fact be taken to be C^2, so that $|\int_0^1 f d\Omega_{x_n} - \int_0^1 f d\Omega_x| > \epsilon$, for all n. Select u as in Lemma 3.2.1, so that $h_u(x^*, y) = f(y)$. Because of uniform continuity of h_u, the functions $h_u(x_n, y)$ viewed as functions of y, converge uniformly to $h_u(x^*, y)$; from this, it is easy to see Gu must be discontinuous at the point x^*. For the sufficiency, let $x_n \to x$, then

$$\left| \int_0^1 h_u(x_n, y) d\Omega_{x_n} - \int_0^1 h_u(x, y) d\Omega_x \right| \leq \tag{3.2.4}$$

$$\left| \int_0^1 h_u(x_n, y) d\Omega_{x_n} - \int_0^1 h_u(x, y) d\Omega_{x_n} \right| + \left| \int_0^1 h_u(x, y) d\Omega_{x_n} - h_u(x, y) d\Omega_x \right| \tag{3.2.5}$$

The first term is small from continuity of h_u; the second term is small from continuity of Ω. □

Remark: The above proposition remains true if G is only defined on $\mathscr{P}$ instead of C^2.

In the sequel we shall assume Ω satisfies the continuity condition. Observe that by applying Taylor's theorem, $G : C^2[0,1] \to C(0,1)$ satisfies $|Gu(x)| \leq \frac{\sigma^2}{2} x(1-x) \|u''\|_\infty$. Therefore we can assign the value 0 to Gu at the endpoints, and we learn then G must map C^2 into continuous functions vanishing at the boundaries.

Here is a very simple thing: let Φ be the map taking $\Omega \mapsto (G_\Omega : C^2[0,1] \to C[0,1])$. Then

Lemma 3.2.3. Φ *is injective.*

Proof. Let Ω^1 and Ω^2 be different families, and say $\Omega^1_x \neq \Omega^2_x$ at x. Then there is a C^2

function f distinguishing them: $\int_0^1 f(y)d\Omega_x^1(y) \neq \int_0^1 f(y)d\Omega_x^2(y)$. Now select a $u \in C^2$ so that $h_u(x,y) = f(y)$ as in Lemma 3.2.1, and then $G_{\Omega^1}u(x) \neq G_{\Omega^2}u(x)$. $\square$

Remark: Lemma 3.2.3 also remains true if $D(G_\Omega) = \mathscr{P}$, instead of C^2.

3.2.2 Topology of GWF Operators

Let $\mathcal{M}_1([0,1])$ denote the set of probability Borel measures on the unit interval. The usual weak-$*$ topology put on $\mathcal{M}_1$ is the weakest topology which makes all the linear functionals $l_f(\mu) = \int_0^1 f d\mu, f \in C[0,1]$ continuous. While in general weak-$*$ topologies are not metrizable, when restricted to bounded sets they sometimes are, and $\mathcal{M}_1$ is precisely one of those cases: its topology can be induced by the so-called Levy-Prokhorov metric. Let us quickly review some of the salient facts.

If (S,d) is a metric space, we shall denote by $\mathcal{M}_1(S)$ the set of Borel measures on S. For any closed set F, define its ϵ-neighborhood by $F_\epsilon = \{x \in S : d(x,F) < \epsilon\}$. Then the Prokhorov distance between the measures μ, ν is:

$$\rho(\mu,\nu) = \inf\{\epsilon > 0, \mu(F) \leq \nu(F_\epsilon) + \epsilon, \text{ for all } F \text{ closed}\} \tag{3.2.6}$$

For notation, we let $\overline{C}(S)$ denote the bounded and continuous functions on a S. The important properties of the Prokhorov metric are summarised in the following, highly useful, theorem:

Theorem 3.2.4. *(Prokhorov). Let (S,d) be a complete, separable metric space. Then:*

1. *$\int f d\mu_N \to \int f d\mu$ for all uniformly continuous $f \in \overline{C}(S)$ if and only if $\rho(\mu_N,\mu) \to 0$.*

2. *$\mathcal{M}_1(S)$ is complete and separable under the Prokhorov metric.*

3. *(Characterization of compacta).* $\mathcal{M} \subset \mathcal{M}_1(S)$ *is relatively compact if and only if* $\mathcal{M}$ *is a tight family, i.e. for every* $\epsilon > 0$ *there exists a compact subset* K *such that* $\inf_{\mu \in \mathcal{M}} \mu(K) \geq 1 - \epsilon$.

This theorem has relevance in our situation, for our state-space $S = [0,1]$ is compact, and thus all families of measures on S are tight. It follows from Prokhorov's theorem that $(\mathcal{M}_1([0,1]), \rho)$ is a compact metric space, and in particular, any family of measures from $\mathcal{M}_1([0,1])$ has a weakly convergent subsequence to some other probability measure — a fact which will be used often in the sequel. The theorem also gives an alternative way to describe the topological weak-$*$ constraint of Proposition 3.2.2 on $\{\Omega_x\}$: it is equivalent to say that it is simply any continuous function $\Omega : (0,1) \to (\mathcal{M}_1([0,1]), \rho)$.

Finally, let $C((0,1), \mathcal{M}_1([0,1])$ be the set of all weak-$*$ continuous families of Borel probability measures. We can topologize this set with the usual compact-open topology, metrised by $d(\Omega^1, \Omega^2) = \sup_{x \in (0,1)} \rho(\Omega^1_x, \Omega^2_x)$; this gives a notion of closeness to the different GWF operators. Note, however, the resulting metric space is not compact, nor even complete.

3.3 Semigroups

We would like to associate G with a C^0-semigroup of bounded operators $T_t : C^0 \to C^0$. This entails that G be so defined as to satisfy the Hille-Yosida conditions [13]. If T_t is contractive ($\|T_t\| \leq 1$), positivity preserving ($T_t f \geq 0$ whenever $f \geq 0$) and conservative ($G1 = 0$), then it is called a *Feller* semigroup. A major theorem of Markov processes is that to every Feller semigroup, there corresponds a strong Markov process (aptly named a

Feller process) on the space of cadlag paths [12]. We shall now quickly review the relevant ideas from semigroup theory.

Definition 3.3.1. A linear operator $A : D \to C[0,1]$ is said to satisfy the *maximum principle* if for every $f \in D$ and $x_0 \in [0,1]$ satisfying $f(x_0) = \sup_{x\in[0,1]} f(x)$, it follows $Af(x_0) \leq 0$.

Important consequences of the maximum principle are the dissipativity of the linear operator A, which allows one to prove the Yosida resolvent estimate, and positivity of the resolvent. It is simple to see that our GWF operator (3.2.1) satisfies the maximum principle on $C^2[0,1]$ (or any subset).

Lemma 3.3.2. *The operator G defined by (3.2.1) on $\mathcal{D} = C^2[0,1]$ satisfies the maximum principle.*

Proof. Let $f \in C^2$, and x_0 be a maximum, i.e. $f(x_0) = \sup f(x)$. If x_0 is at the boundary, then we have previously shown that $Gf(x_0) = 0$. If x_0 is an interior point, $f'(x_0) = 0$, and $f(z) \leq f(x_0)$ for all z, immediately implying $Gf(x_0) \leq 0$. $\square$

The important theorem which permits an operator G to induce a Feller semigroup is the following:

Theorem 3.3.3. *(Hille-Yosida Theorem c.f. [12]) Let $G : D \to C[0,1]$ be a linear operator defined on a domain D dense in C^0, satisfying the maximum principle, $G1 = 0$, and $Im(\lambda - G)$ dense in $C[0,1]$ for some $\lambda > 0$. Then G is closable, and its closure $\bar{G}$ generates a Feller semigroup.*

Given any closed linear operator $G : \mathcal{D}(G) \to C[0,1]$, a subset $\mathcal{C} \subset \mathcal{D}(G)$ of functions is called a *core* for G if $\overline{\{(f, Gf), f \in \mathcal{C}\}} = \{(f, Gf), f \in \mathcal{D}(G)\}$, where the closure of the set is defined with respect to the topology induced by of the graph norm $\|(f, Gf)\| = \|f\| + \|Gf\|$.

Abstractly, with the GWF operator G defined in C^2 (or $\mathscr{P}$), all the conditions of the Hille-Yosida Theorem are fulfilled, with the possible exception of the range condition $\overline{Im(\lambda - G)} = C[0,1]$, which depends on the particular form of the family of measures Ω. In the constructions to come at the end of this chapter, we will perform an explicit check of this density. Should the range condition be satisfied, C^2 (respectively $\mathscr{P}$) then becomes a core for $\overline{G}$.

Suppose we start with a pre-generator G as defined by the GWF operator on C^2 or $\mathscr{P}$, and we are able to verify the density condition on $\lambda - G$ for a chosen family Ω. Because $\lambda - \bar{G}$ must then biject onto $C[0,1]$, there is only one closed extension $\tilde{G}$ of G for which $\lambda - \tilde{G}$ is still injective, namely $\tilde{G} = \overline{G}$. From this we get the following uniqueness principle:

Proposition 3.3.4. *(Uniqueness of semigroup). If Ω is a sequentially weak-$*$ continuous family of measures, G_Ω the associated GWF operator with domain containing C^2 (respectively $\mathscr{P}$), and $G_\Omega C^2$ (respectively $G_\Omega \mathscr{P}$) is dense in $C[0,1]$, then there is exactly one Feller semigroup with a generator $\tilde{G}$ extending G_Ω.*

In other words, the specification of an appropriate family of measures $\{\Omega_x\}$ and that the domain of the generator include enough functions such that $(\lambda - G)D$ is dense in $C[0,1]$ suffices to uniquely prescribe the semigroup.

In the theory of diffusion processes, the infinitesimal first and second-order parameters (and hence the formal symbol of the generator) suffice to only characterize the behavior of a random process on the interior of its state-space. To fully prescribe the random process, boundary knowledge must be appended, and this information is encoded in the domain of the generator. Similar considerations would generally attend for the formal symbol G_Ω; but if we suppose that C^2, or the polynomials, form a core for G_Ω, then this boundary behavior is fixed, as the next proposition shows.

Proposition 3.3.5. *Let X_t be a Feller process on $[0,1]$ with generator $\tilde{G}$ which extends $G_\Omega : C^2 \to C^0$, and where C^2 is a core for G. Then $\{0,1\}$ are absorbing states of X_t.*

Proof. Since $G_\Omega u$ vanishes at the endpoints for all $u \in C^2$, this extends to its closure, and $\tilde{G}$ annihilates every function in its domain at $\{0,1\}$. That these are absorbing points now follows from Dynkin's characterization on absorbing states (x is an absorbing state if and only if for every $u \in \mathcal{D}(\tilde{G})$ one has $\tilde{G}u(x) = 0$, see [4]). □

Remark: The above clearly holds with $\mathscr{P}$ replacing C^2.

3.4 Markov Chains, their Limits, and Approximation of Semigroups

Let $\mathbf{P}_{ij}^{(N)}$ be a sequence of Markov chains on the states $\{0,\ldots,N\}$ associated to the random processes $X_k^{(N)}$. We shall define the *continuum limit* for this sequence as the limiting process when time and state are scaled by N:

$$X(t) = \lim_{N\to\infty} \frac{1}{N} X_{[Nt]}^{(N)} \tag{3.4.1}$$

whenever the above limit X exists as a Feller process. The type of convergence we will desire will be made precise in the course of this chapter, and amounts to convergence in the strong operator topology with respect to the generators, and weak convergence of measures on the function space of cadlag paths.

The situation can also be looked at analytically, in terms of the corresponding semigroups. If X_t is a putative limiting Feller process, then $T_t f(x) = E[f(X(t))|X_0 = x]$ defines a C^0-semigroup T_t. Let $G : \mathcal{D}(G) \to C[0,1]$ be its generator. Then it is one of the first results of semigroup theory that the semigroup $u(x,t) = T_t f(x)$ solves the parabolic equation

$$\frac{\partial u}{\partial t} = Gu \tag{3.4.2}$$

with initial data $u(x,0) = f(x)$. Moreover, if G satisfies appropriate maximum principles (often the case when G is associated to a random process), the solution is unique up to a specification on the parabolic boundary.

The sequences of Markov chains $\mathbf{P}^{(N)}$ can be thought of as defining approximating semigroups to the solution of the parabolic equation (3.4.2). Indeed, we can embed $\mathbf{P}^{(N)}$ into the space of bounded operators from $C[0,1]$ to itself as follows: first for $x = i/N$, $i = 0, \ldots, N$, define

$$\tilde{P}_N f(x) = \sum_{j=0}^{N} \mathbf{P}_{ij}^{(N)} f(j/N) \tag{3.4.3}$$

and then linearly interpolate the values of $\tilde{P}_N f(x)$ to define $\tilde{P}_N f(x)$ for all $x \in [0,1]$. It is easy to check that $\tilde{P}_N$ is a bounded operator on $C[0,1]$.

If discrete approximations are defined recursively as $u_{k+1} = \tilde{P}_N u_k$, with $u_0 = f$, one intuitively expects the sequence u_k to approximate the actual solution of (3.4.2), as long as the following "consistency" condition is satisfied:

$$\lim_{N\to\infty} \|(N(\tilde{P}_N - I) - G)u\| = 0 \tag{3.4.4}$$

for a sufficiently large set of u in the domain of G. These hopes are borne out in the Markov approximation theorem of Trotter and Skorohod (c.f. [12]), a theorem already presaged in analytic form by the so-called Lax equivalence theorem [13]. It will be our main tool for establishing and justifying the use of continuum limits to analyse properties of the discrete system. Before stating it in a form most congenial for our purposes, we remind the reader that $D_E(A)$ is the space of cadlag functions on a state space A having values in a metric space E.

Theorem 3.4.1. *(Trotter-Skorohod-Lax Approximation Theorem) Let X_t be a Feller process on state-space $[0,1]$ with generator G and a core $\mathcal{C} \subset C[0,1]$. Let T_t be the associated semigroup to G. Let Z_k^N be a time-homogeneous Markov chain on state-space $\{0, 1/N, \ldots, 1\}$ associated to a transition matrix $\mathbf{P}_{ij}^{(N)}$, and define the extended process $X^{(N)}$ with sample paths in cadlag space $D_{[0,1]}[0,\infty)$ by $X^{(N)}(t) = Z_{[Nt]}^{(N)}$. Also let $\tilde{P}_N$ be the bounded operators defined above in (3.4.3) associated to the Markov chain transition matrices $\mathbf{P}_{ij}^{(N)}$. Then if for each $u \in \mathcal{C}$, we have*

$$\lim_{N\to\infty} \|(N(\tilde{P}_N - I) - G)u\| = 0, \tag{3.4.5}$$

then the approximations $u_k = \tilde{P}_N^k f$ tend to $T_t f$ as k/N tends to t, for all $f \in C[0,1]$. Even more, if $X^{(N)}(0)$ converges weakly to $X(0)$, then $X^{(N)}$ converges weakly to X in $D_{[0,1]}[0,\infty)$, i.e. for every function $f : D_{[0,1]}[0,\infty) \to \mathbb{R}$ continuous in the Skorohod topology, $Ef(X^{(N)}) \to Ef(X)$. In particular, the finite-dimensional distributions of $X^{(N)}$ converge to those of X.

Remark: In the above theorem, one must *begin* with an operator G that *is already known* to be the generator for a semigroup or Markov process (for instance, by checking the Hille-Yosida conditions), before one attempts to verify the convergence of the chains. It is tempting to wish to *deduce* that G is a generator of a semigroup, on the basis of such convergence. While this does not appear generally possible, we will give an example where such a conclusion can be made, in the construction of Cannings generators (see Section 3.9). Additional comments on this issue appear in that section.

The following lemma will make some of our calculations less burdensome:

Lemma 3.4.2. *The convergence in (3.4.5) is equivalent to uniform convergence only on the sampling sets* $K_N = \{0, 1/N, 2/N, \ldots, 1\}$*:*

$$\lim_{N\to\infty} \sup_{x\in K_N} |(N(\tilde{P}_N - I) - G)u(x)| = 0 \tag{3.4.6}$$

Its proof is simple and will be omitted.

As a complement and converse which is slightly stronger than Theorem 3.4.1 above, the following proposition in the theory of approximating semigroups will be useful to us, quoted here from [12] and recast for our purposes into the language of Markov chains.

Theorem 3.4.3. *Let* T_t *be a strongly continuous contraction semigroup on* $C[0,1]$ *with generator* A*, and let* $\mathcal{C}$ *be a core for* A*. Let* $\mathbf{P}^{(N)}$ *be a Markov transition matrix,* $\mathbf{A}_N = N(\mathbf{P}^{(N)} - I)$*, and* $\pi_N : C[0,1] \to C(K_N)$ *the canonical projection onto the samples* $K_N = \{0, 1/N, \ldots, 1\}$*. Then the following are equivalent:*

1. *For each* $f \in C[0,1]$*,* $T > 0$*,* $\sup_{0\le t\le T} \|P_N^{[tN]}\pi_N f - \pi_N T_t f\| \to 0$

2. *For each* $f \in \mathcal{C}$*, there exists* $f_N \in C(K_N)$ *such that* $\|f_N - \pi_N f\| \to 0$ *and* $\|\mathbf{A}_N f_N - \pi_N A f\| \to 0$.

The implication (2) implies (1) in the preceding will be the direction employed in justifying our continuum limits.

We have been using the term continuum limit somewhat loosely up to this point. We now make the formal definition.

Definition 3.4.4. Let $X_k^{(N)}$ be a sequence of pure-drift GWF processes normalised to the state space $\{0, 1/N, \ldots, 1\}$. We will say that the Feller process X_t is a *continuum limit* for $\{X^{(N)}\}$ if the generator G of X_t satisfies

$$\|(N(\mathbf{P}^{(N)} - I)\pi_N u) - \pi_N G u\| \to 0 \tag{3.4.7}$$

for every $u \in \mathcal{D}(G)$, and π_N is the projection in Theorem 3.4.3.

Remark: It is clear that (3.4.7) need only be verified on a core of G.

3.5 A Representation Theorem

In this section we shall prove a representation theorem for the continuum limits of pure-drift GWF processes, which demonstrates that the generator for any limiting GWF model must take on the form of the GWF operator (3.2.1).

As a reminder, we say that a Markov chain with transition matrix $\mathbf{P}_{ij}^{(N)}$ on states

$\{0, \ldots, N\}$ is GWF if its first two moments have the form

$$\sum_{j=0}^{N} j P_{ij}^{(N)} = i \tag{3.5.1}$$

$$\sum_{j=0}^{N} (j-i)^2 P_{ij}^{(N)} = \sigma_N^2 i(1 - i/N) \tag{3.5.2}$$

with $\sigma_N^2 \to \sigma^2 < \infty$. Our motivating question is this: can anything be said about the form of G, if the convergence (3.4.5) takes place?

To fix notation, and also to introduce an important transformation, let S be the set of all probability measures μ with positive variance on $[0,1]$. For notational purposes, we let $\rho : S \to \mathcal{M}_1([0,1])$ be the transformation:

$$(\rho(\mu))(A) = \int_A \frac{(y-m)^2}{v} d\mu(y) \tag{3.5.3}$$

where m and v are respectively the mean and variance of μ. Also, we let ζ be the map taking measures of positive variance on $\{0, \ldots, N\}$ to measures on the sampling sets $K_N \subset [0,1]$ by simple scaling of the state by N. Finally define

$$\Gamma = \rho \circ \zeta \tag{3.5.4}$$

The following is our principal structure theorem.

Theorem 3.5.1. *(Representation of Continuum Limits). Let* $\tilde{P}_N$ *be the sequence of bounded operators on* $C[0,1]$ *associated to a sequence of Pure-Drift GWF Markov chains* $\mathbf{P}_{ij}^{(N)}$ *as described in Section 3.4, and suppose there is a linear operator* $G : D \to C[0,1]$, *with* $C^2[0,1] \subset D$ *(respectively* $\mathscr{P} \subset D$*), for which*

$$\lim_{N\to\infty} \|(N(\tilde{P}_N - I) - G)u\| = 0 \tag{3.5.5}$$

for each $u \in C^2$ *(respectively* $\in \mathscr{P}$*). Then there exists a continuous function* $\Omega : (0,1) \to \mathcal{M}_1([0,1])$ *from the interval to Borel probability measures topologized with the Prokhorov metric, such that*

$$Gu(x) = \sigma^2 x(1-x) \int_0^1 \frac{u(y) - u(x) - u'(x)(y-x)}{(y-x)^2} d\Omega_x(y) \tag{3.5.6}$$

for all $u \in C^2[0,1]$ *(respectively* $\mathscr{P}$*).*

Proof. We will prove it for $D \supset C^2[0,1]$; the proof for when D only contains the polynomials $\mathscr{P}$ goes through similarly. The convergence condition (3.5.5) implies, in particular, that given any fixed $0 < x < 1$, and $u \in C^2$, $\lim_N N(\tilde{P}_N - I)u([xN]/N)$ exists, and has value $Gu(x)$. Let $F_{N,i}$, with support in K_N be the atomic measure associated with the i-th row of the transition $\mathbf{P}^N_{ij}$. We can rewrite $N(\tilde{P}_N - I)$ as:

$$N(\tilde{P}_N - I)u([xN]/N) = N \int_0^1 u(y) dF_{N,[Nx]}(y) - Nu([xN]/N) \tag{3.5.7}$$

$$= N \int_0^1 (u(y) - u([xN]/N)) dF_{N,[xN]}(y) \tag{3.5.8}$$

$$= N \int_0^1 (u(y) - u([xN]/N) - u'([xN]/N)(y - [xN]/N)) dF_{N,[xN]}(y) \tag{3.5.9}$$

$$= \sigma_N^2 \frac{[xN]}{N} \left(1 - \frac{[xN]}{N}\right) \int_0^1 \frac{u(y) - u([xN]/N) - u'([xN]/N)(y - [xN]/N)}{(y - [xN]/N)^2} dF^*_{N,[xN]}(y) \tag{3.5.10}$$

$$= \sigma_N^2 \frac{[xN]}{N} \left(1 - \frac{[xN]}{N}\right) \int_0^1 h_u([xN]/N, y) dF^*_{N,[xN]}(y) \tag{3.5.11}$$

where $F^*_{i,N} = \Gamma(F_{i,N})$ is the measure defined by (when $i \neq 0, N$):

$$dF^*_{N,i}(y) = \frac{N(y - i/N)^2}{\sigma_N^2 (i/N)(1 - i/N)} dF_{N,i}(y) \tag{3.5.12}$$

and for $i \in \{0, N\}$, $F^*_{N,i}$ can be an arbitrary measure. Equation (3.5.9) follows because of the mean condition (3.5.1) on GWF processes. Fix $0 < x < 1$. Because of the variance condition of GWF processes, the sequence of measures $\{F^*_{N,[Nx]}\}$ are Borel probability measures. We claim that this sequence has a weak limit. Indeed, if not, we can select two subsequences $\{F^*_{N_k,[N_k x]}\}$, $\{F^*_{N_j,[N_j x]}\}$ which converge to different measures Ω^1_x and Ω^2_x. Let f be a C^2 function which distinguishes them: $\int_0^1 f(y)d\Omega^1_x(y) \neq \int_0^1 f(y)d\Omega^2_x(y)$, and select a $u \in C^2$ as in Lemma 3.2.1 such that $h_u(x,y) = f(y)$. Then along the two subsequences, we have the different limits

$$\int_0^1 h_u([xN_k]/N_k, y)dF^*_{N_k,[N_k x]}(y) \to \int_0^1 h_u(x,y)d\Omega^1_x(y) = \int_0^1 f(y)d\Omega^1_x(y) \qquad (3.5.13)$$

$$\int_0^1 h_u([xN_j]/N_j, y)dF^*_{N_j,[N_j x]}(y) \to \int_0^1 h_u(x,y)d\Omega^2_x(y) = \int_0^1 f(y)d\Omega^2_x(y) \qquad (3.5.14)$$

which contradicts the existence of the limit $\int_0^1 h_u([xN]/N, y)dF^*_{N,[Nx]}(y)$.

So we have proved, for each $x \in (0,1)$, that $F^*_{N,[Nx]}$ converges to a measure Ω_x. This measure must be a probability measure, because of tightness of the sequence F^*_N. Finally, taking the limit of (3.5.10), we see that

$$\begin{aligned} Gu(x) &= \lim_{N\to\infty} N(P_N - I)u([xN]/N) && (3.5.15)\\ &= \lim_{N\to\infty} \sigma^2_N \frac{[xN]}{N}\left(1 - \frac{[xN]}{N}\right)\int_0^1 h_u([xN]/N, y)dF^*_{N,[xN]}(y) && (3.5.16)\\ &= \sigma^2 x(1-x)\int_0^1 h_u(x,y)d\Omega_x(y) && (3.5.17)\end{aligned}$$

The continuity of Ω has already been observed from Theorem 3.2.2 and our remarks following Theorem 3.2.4. □

3.6 Convergence of GWF Markov Chains

The actual criterion for convergence in (3.4.4) is posed in terms of generators. In our applications it will be helpful to reformulate this convergence in simpler terms, using the corresponding measure-valued function Ω. This easy-to-verify condition comes in the form of a type of "uniform convergence in distribution" — posed in terms of a weighted uniform convergence of the moments.

Theorem 3.6.1. *(Condition for convergence of GWF processes). Let* $\mathbf{P}_{ij}^{(N)}$ *be a sequence of GWF Markov chains,* $\tilde{P}_N$ *the associated bounded linear operators, and let* $F^*_{N,i}$ *be the measures*

$$F^*_{N,i}(\cdot) = \Gamma(\mathbf{P}_{i,\cdot}^{(N)}) \tag{3.6.1}$$

with Γ *as defined by* (3.5.4, 3.5.3)*. Let* $\Omega \in C([0,1], \mathcal{M}_1([0,1]))$*. If for each* $k = 1, 2, \ldots,$

$$\lim_{N\to\infty} \sup_{0\le i\le N} \frac{i}{N}\left(1-\frac{i}{N}\right)\left|\int_0^1 y^k dF^*_{N,i}(y) - \int_0^1 y^k d\Omega_{i/N}(y)\right| = 0, \tag{3.6.2}$$

Then one has convergence of the generators: for each $u \in C^2$*,*

$$\lim_{N\to\infty} \|N(\tilde{P}_N - I)u - G_\Omega u\| = 0 \tag{3.6.3}$$

Proof. As in the proof of Theorem 3.5.1, we can write

$$\begin{aligned} &N(\tilde{P}_N - I)u(i/N) - G_\Omega u(i/N) \\ &\qquad = \sigma^2 \frac{i}{N}(1-i/N)\left(\int_0^1 h_u(i/N,y)dF^*_{N,i}(y) - \int_0^1 h_u(i/N,y)d\Omega_{i/N}(y)\right) \end{aligned} \tag{3.6.4}$$

Now note that if $r(x,y)$ is any bivariate polynomial: $r(x,y) = \sum_{j=0}^K q_j(x)y^j$, the assumptions of our theorem easily implies

$$\sup_{i=0,\ldots,N}\left|\sigma^2\frac{i}{N}(1-i/N)\left(\int_0^1 r(i/N,y)dF^*_{N,i}(y) - \int_0^1 r(i/N,y)d\Omega_{i/N}(y)\right)\right| \to 0 \tag{3.6.5}$$

If $u \in C^2$, $h_u \in C([0,1]^2)$, so approximate h_u by $r(x,y)$ to within ϵ uniformly; then the usual argument adduces from (3.6.4) that

$$\sup_i \left| N(\tilde{P}_N - I)u(i/N) - G_\Omega u(i/N) \right| \tag{3.6.6}$$

$$= \sup_i \left| \sigma^2 \frac{i}{N}(1 - i/N) \left(\int_0^1 h_u(i/N, y) dF^*_{N,i}(y) - \int_0^1 h_u(i/N, y) d\Omega_{i/N}(y) \right) \right| \to 0 \tag{3.6.7}$$

This implies the theorem, from Lemma 3.4.2. □

3.7 Converse to the Representation Theorem

The representation Theorem 3.5.1 showed that if the semigroups corresponding to the discrete Markov chain converged to that of a limiting semigroup, then the generator for that semigroup had to satisfy the particular form of a GWF operator, assuming that $C^2[0,1]$ or $\mathscr{P}$ was contained in the domain of that generator. We can ask the converse question: Given a GWF operator, is there a sequence of GWF chains converging to it? To answer this, we will make use of our study on the convex space of GWF chains (Section 2.6).

3.7.1 Approximation of Ω by Extreme Measures

We shall construct a sequence of GWF chains which converge to a given G_Ω in the sense of Theorems 3.5.1 and 3.6.1. This result will require several stages of approximation.

First let us consider a sequence of measures Q_N, with the trait that Q_N is a Dirac mass at the point j_N/N, $j_N \in \{0, \ldots, N\}$. We will show how Q_N can be approximated by $\Gamma(\mu)$, where Γ is as usual defined by (3.5.4, 3.5.3), and μ is an extreme GWF measure of a pre-specified mean i and variance $v_i = \sigma^2 i(1 - i/N)$.

It will be enough to restrict ourselves to the case $[\sigma\sqrt{N}] \leq i \leq N - [\sigma\sqrt{N}]$. Note that the variance is always bounded by $\sigma^2 N/4$. Now given a Q_N of the type above, always place $i_2 = i$, so that $d_2 = 0$ and the lower-bound condition on existence in Theorem 2.6.2 is always satisfied. Our scheme divides into two cases. Case 1: $|j_n - i| \leq [\sigma N^{3/4}]$. In this case put $i_1 = i - [\sigma\sqrt{N}]$, and $i_3 = i + [\sigma\sqrt{N}]$, and since $d_1 d_3 = ([\sigma\sqrt{N}])^2 > \sigma^2 N/4$, Theorem 2.6.2 gives us the existence of an extreme GWF measure μ_N supported on i_1, i_2, i_3. For case 2, we assume that $|j_N - i| > [\sigma N^{3/4}]$, and $j_N > i$. Put $i_2 = i$ again, $i_3 = j_N$, and $i_1 = i - [\sigma\sqrt{N}]$. Then $d_1 d_3 \geq v_i$ once more, and we obtain here again the existence of an extreme measure μ_N. In the last case 3: $j_N < i$, and $|j_N - i| > [\sigma N^{3/4}]$. Put $i_2 = i$, $i_1 = j_N$, and $i_3 = i + [\sigma\sqrt{N}]$, and apply Theorem (2.6.2) to find the extreme measure. For each Q_N then, and a pre-specified index i, we have constructed a sequence of extreme GWF measures μ_N, each concentrated on 3 points, according to the scheme above. Let us calculate the distributional error between Q_N and $F_N^* = \Gamma(\mu_N)$.

Lemma 3.7.1. *Let $f \in C^1$. Under the scheme set forth above,*

$$\left| \int_0^1 f(y) dQ_N(y) - \int_0^1 f(y) dF_N^* \right| \leq \frac{\max\{4\sigma, 1\} \|f'\|}{N^{1/4}} \tag{3.7.1}$$

Of prime important is that the RHS goes to zero and is *independent* of the indices i and j_N.

Proof. One needs to check the statement in each of the three cases of the scheme set forth. The measure F_N^* is always concentrated on at most two points, whose values are:

$$F_{i,j_N}^*(i_1/N) = r_1 = \frac{i - i_1}{i_3 - i_1} \tag{3.7.2}$$

$$F_{i,j_N}^*(i_3/N) = r_2 = \frac{i_3 - i}{i_3 - i_1} \tag{3.7.3}$$

where $r_1 + r_2 = 1$. In case 1,

$$\left|\int_0^1 f(y)dQ_N(y) - \int_0^1 f(y)dF_N^*\right| = |f(i_1/N)r_1 + f(i_3/N)r_2 - f(j_N/N)| \tag{3.7.4}$$

$$\leq |f(i_1/N) - f(j_N/N)| + |f(i_3/N) - f(j_N/N)| \tag{3.7.5}$$

Since $|i_1 - j_N| \leq \sigma\sqrt{N} + \sigma N^{3/4}$, and $|i_3 - j_N| \leq \sigma\sqrt{N} + \sigma N^{3/4}$, the result follows. In case 2,

$$\left|\int_0^1 f(y)dQ_N(y) - \int_0^1 f(y)dF_N^*\right| = |f(i_1/N)r_1 + f(j_N/N)r_2 - f(j_N/N)| \tag{3.7.6}$$

$$= |f(i_1/N) - f(j_N/N)|\, r_1 \tag{3.7.7}$$

Note $r_1 \leq \frac{\sigma\sqrt{N}}{\sigma N^{3/4}} = N^{-1/4}$. Hence the result. Case three is handled similarly.

□

We can take now convex combinations of the extreme points above to generalise to the case where Q_N is any discrete measure.

Lemma 3.7.2. *Let $f \in C^1$. Fix $[\sqrt{N}] \leq i \leq N - [\sqrt{N}]$, and let R_i be the set of probability mass functions on $\{0, \ldots, N\}$ with mean i and variance $\sigma^2 i(1 - i/N)$. Given a sequence of discrete measures Q_N each supported on K_N, there exists a sequence of GWF measures $\mu_N \in R_i$ such that*

$$\left|\int_0^1 f(y)dQ_N(y) - \int_0^1 f(y)dF_N^*(y)\right| \leq \frac{\max\{4\sigma, 1\}\|f'\|}{N^{1/4}} \tag{3.7.8}$$

where $F^* = \Gamma(\mu_N)$.

Proof. Write $Q_N = \sum_{j=0}^N a_j \delta_{j/N}$. For each j, find the extreme μ_N^j as in the scheme above, and then put $\mu_N = \sum_{j=0}^N a_j \mu_N^j$. Finally, observe that Γ preserves/respects convex combinations, and apply Lemma 3.7.1 to each term. □

Finally, we require a lemma on the approximation of any measure by an atomic one. Let Q_N be any Borel measure on $[0, 1]$, and let F_N denote its distribution function. We denote $\tilde{F}_N$ its quantization: constant on the semi-open interval $[j/N, (j + 1)/N)$, for $j = 0, \ldots, N - 1$, and $\tilde{F}_N(j/N) = F_N(j/N)$, $j = 0, \ldots, N$. We let μ_N be the atomic measure constructed from $\tilde{F}_N$, it has support on K_N. Then

Lemma 3.7.3. *If $f \in C^1$,*

$$\left| \int_0^1 f(y) dQ_N(y) - \int_0^1 f(y) d\mu_N(y) \right| \leq \frac{\|f'\|}{N} \tag{3.7.9}$$

Proof. Integration by parts shows $\int_0^1 f dG = f(1) - \int_0^1 G(y) f'(y) dy$, where G is the distribution function of measure dG. Thus we can write:

$$\left| \int_0^1 f(y) dQ_N(y) - \int_0^1 f(y) d\mu_N(y) \right| = \left| \int_0^1 f'(y) F_N(y) dy - \int_0^1 f'(y) \tilde{F}_N(y) dy \right| \tag{3.7.10}$$

$$\leq \|f'\| \int_0^1 |F_N(y) - \tilde{F}_N(y)| dy \leq \frac{\|f'\|}{N} \tag{3.7.11}$$

□

We can now prove the following converse to the representation theorem.

Theorem 3.7.4. *Let Ω be any continuous function from $(0, 1) \to \mathcal{M}_1([0, 1])$, and $G_\Omega : C^2 \to C[0, 1]$ the associated GWF operator defined by (3.2.1). Then there exists a sequence of GWF Markov chain $\mathbf{P}_{ij}^{(N)}$, with associated operators $\tilde{P}_N$, such that $\lim_{N\to\infty} \|N(\tilde{P}_N - I)u - G_\Omega u\| = 0$ for every $u \in C^2$.*

Proof. We only need to verify the convergence condition of Theorem 3.6.1 for our discrete chains. To construct the approximating sequence, let $\mathbf{P}_{ij}^{(N)}$ have arbitrary GWF measures for rows near the boundary $i \leq [\sqrt{N}]$ and $i \geq N - [\sqrt{N}]$; these rows go automatically to zero (as long as they have the right mean i and variance v_i) because of the variance weights in Theorem 3.6.1. For each N, consider the measures $\{\Omega_{i/N}\}$, $[\sqrt{N}] \le i \le N - \sqrt{N}$. For each row i, now, approximate $\Omega_{i/N}$ first by an atomic measure Q_N on K_N as in Lemma 3.7.3, then use Lemma 3.7.2 to find the GWF measures μ_N^i with mean i and variance $\sigma^2 i(1-i/N)$ whose transform under Γ approximates Q_N. The estimates in the lemmas above are independent of the row means i, and so by triangle inequality one discovers:

$$\sup_{i\in K_N} \frac{i}{N}(1-i/N)\left|\int_0^1 f(y)d\Gamma(\mu_N^i) - \int_0^1 f(y)d\Omega_{i/N}\right| \le \|f'\|\left(\frac{1}{N} + \frac{\max\{4\sigma, 1\}}{N^{1/4}}\right) + \frac{2\|f\|}{\sqrt{N}} \tag{3.7.12}$$

for every $f \in C^1$ (the last $\sqrt{N}$ term is the maximum possible contribution from the boundaries), which approaches zero as desired. □

Theorems 3.5.1 and 3.7.4 taken together give a representation formula for the generator of the continuum limits of GWF chains. Any sequence of convergent chains in the sense of 3.4.4 has a continuum limit of type (3.2.1); moreover the limiting measure Ω can be computed from (3.5.12). Conversely, for any operator of type (3.2.1) there is a sequence of GWF chains converging to it. Applications of our representation formula will appear in Chapter 4.

3.7.2 The Kimura Diffusion Limit

The standard Wright-Fisher diffusion limit can be defined as that Markov process with generator $\tilde{G}$, which is the closure of $Gu(x) = \frac{1}{2}\sigma^2 x(1-x)u''(x)$ where $\mathcal{D}(G) = C^2[0,1]$. From Lemma 3.2.3, $G_\Omega = G$ on C^2 if and only if Ω is the family of Dirac measures $\Omega_x(y) = \delta_x(y)$. Thus a Corollary of Theorem 3.6.1 is

Corollary 3.7.5. *Let* $\mathbf{P}_{ij}^{(N)}$ *be the transition matrices for a sequence of GWF Markov chains* $X_k^{(N)}$*. Let* $F^*_{N,i}$ *be the measures*

$$F^*_{N,i}(\cdot) = \Gamma(P^{(N)}_{i,\cdot}) \tag{3.7.13}$$

where Γ *is defined by* (3.5.4, 3.5.3)*. If for each continuous function* $f \in C[0,1]$,

$$\lim_{N\to\infty} \sup_{0\le i\le N} \frac{i}{N}\left(1-\frac{i}{N}\right)\left|\int_0^1 f(y)dF^*_{N,i} - f(i/N)\right| = 0 \tag{3.7.14}$$

Then $\frac{X^{(N)}_{[Nt]}}{N}$ *converges weakly to the Kimura diffusion* $X(t)$*.*

Proof. Condition (3.7.14) clearly implies the moment hypothesis of Theorem 3.6.1 with $\Omega_x(y) = \delta_x(y)$: it is equivalent to it by a standard Weierstrass approximation argument. The conclusion of Theorem 3.6.1 demonstrates the weak convergence. ☐

The previous corollary gives a non-trivial condition — essentially necessary and sufficient — for the convergence of a GWF chain to the Kimura diffusion, and is more discriminating than the $(2+\delta)$-moment condition of Norman [17].

Continuity of Sample Paths

Let X_t be a Feller process on $[0,1]$ with generator G which is the continuum limit of a sequence of pure-drift GWF chains. When does X_t have continuous sample paths — in other words, is a diffusive process? D. Ray has given the following characterization:

Theorem 3.7.6. *(D. Ray).* X_t *has continuous sample paths almost surely if and only if* G *is of* local character*: given* $f \in \mathcal{D}(G)$*, if* f *vanishes identically in a neighborhood of* x^**, then* $Gf(x^*) = 0$*.*

We can apply the foregoing to show that the Kimura diffusion is the only GWF continuum process with continuous sample paths.

Theorem 3.7.7. *Let X_t be a GWF continuum process with generator G_Ω, for some Ω. Then X_t has continuous sample paths almost surely only if X_t is the Kimura diffusion.*

Proof. If X_t is the Kimura diffusion, $\Omega_x(y) = \delta_x(y)$, leading to $G_\Omega u(x) = \frac{\sigma^2}{2} x(1-x)u''(x)$, which is clearly of local character. On the other hand, suppose $\Omega : (0,1) \to \mathcal{M}_1([0,1])$ is any other family of measures: then there exists a point $0 < x^* < 1$ and an open set A excluding a neighborhood of x^* such that $\Omega_{x^*}(A) > 0$. Construct a non-negative C^2 function f on $[0,1]$ such that f vanishes in a neighborhood of x^*, and strictly positive on A. Define the function $u(y) = f(y)(y - x^*)^2$ as in Lemma 3.2.1; thus u vanishes in a neighborhood of x^*. But from Lemma 3.2.1,

$$G_\Omega u(x^*) = \sigma^2 x^*(1 - x^*) \int_0^1 f(y) d\Omega_{x^*}(y) > 0 \tag{3.7.15}$$

and so G_Ω is not of local character. □

3.8 Continuum Limits and the Generator Problem

The machinery developed so far gives us a recipe for the computation and justified use of a continuum limit to approximate any discrete GWF Markov chain. It consists of the following steps:

1. Given $\mathbf{P}_{ij}^{(N)}$, the transition matrices for the sequence of GWF chain $X_k^{(N)}$, form the measures:

$$F_{N,i}^*(\cdot) = \Gamma(\mathbf{P}_{i,\cdot}^{(N)}) \tag{3.8.1}$$

where Γ is given by (3.5.4, 3.5.3).

2. Compute a putative limiting family of measures, Ω_x, defined by the weak limit

$$\Omega_x = w. \lim_{N \to \infty} F^*_{N,[xN]} \tag{3.8.2}$$

3. Check that the resulting GWF operator G_Ω defined on C^2 or $\mathscr{P}$ by (3.2.1) possesses an appropriate closed extension, i. e. is actually the generator for a continuous-time Markov process (see the Generator Problem below)

4. Verify that the convergence condition of Theorem 3.6.1 holds to rigorously justify the approximation.

3.8.1 The Generator Problem

Given an operator $G : \mathcal{D}(G) \to C[0,1]$ with $\mathcal{D}(G)$ dense in $C[0,1]$, an important problem is to determine whether G possesses an extension $\tilde{G}$ which is the generator for a C^0-semigroup. As already previously discussed, according to the semigroup theory, this would then imply existence of a solution to the backward equation

$$\frac{\partial u}{\partial t} = \tilde{G}u, \quad u(x,0) = f(x) \tag{3.8.3}$$

as well as the existence of a time-homogeneous Markov process with cadlag paths with generator $\tilde{G}$.

Since GWF operators satisfy the maximum principle, the main task of solving the generator problem consists in verifying the third Hille-Yosida condition: that for some $\lambda > 0$, there is a set of functions $\mathcal{C}$ in the domain of G for which $(\lambda - G)\mathcal{C}$ is dense in $C[0,1]$. In each of the applications and continuum limits we consider in the next chapter, this verification will be simple, due to the structure of the generator. But can any general argument be made?

We have shown that, for every GWF operator defined on C^2 into the continuous functions, there exists a sequence of Markov chains whose discrete generators converge to it. It is tempting on this basis to conclude that the limiting GWF operator then indeed possesses a requisite extension which makes it the generator for a C^0 semigroup. For this it would be natural to employ the approximating semigroups $\tilde{P}_N$ (with $G_N = N(\tilde{P}_N - I)$), and verify the density condition by a limiting argument. This argument can succeed if the limiting G_Ω is a bounded operator (which, unfortunately, is not the interesting case, since the semigroup $\exp(tG)$, defined by functional calculus already gives an independent solution to the generator problem), but fails in general when G is unbounded, because the C_0 limit of functions in the domain of G generally fails to fall back in the domain of G. For its success, one would require additional control on the approximating semigroups: at least some information about the regularity of the limits of classes of functions under the operation of G_N.

If we cannot expect this deduction to be possible at present, there are nevertheless forebodings that the conclusion may yet be true. For example, one can show, using results from functional analysis, that our converse Theorem 3.7.4 already implies the existence of a weak solution to (3.8.3). An ongoing project of ours is to determine whether our theorem, with sufficient additional control over the approximating bounded operators $\tilde{P}_N$, can be used to prove the existence of a strong classical solution. One would expect this to be true, for example, when Ω has sufficient smoothness properties.

Despite the generic obstacles outlined above, there do exist classes of regular GWF chains which, due to their special properties, allow the above plan to work with no further restrictions. We study these in the "abstract" Cannings construction of Section 3.9. For now, and as a preparation for the sequel, we note that if G_Ω satisfies the special constraint of mapping polynomials to polynomials of a certain degree, than it is simple to solve the generator problem.

Theorem 3.8.1. *Let a continuous* Ω *be prescribed, and suppose that* $G_\Omega x^m$ *is a polynomial of degree at most* m*, for every* $m = 0, 1, 2, \ldots$. *Then* G_Ω *has a closure* $\overline{G_\Omega}$ *which generates a* C_0 *semi-group, and* $\mathscr{P}$ *is a core for* $\overline{G_\Omega}$.

Proof. As discussed above, we need only check the Hille-Yosida density condition. As $G_\Omega x^m$ is a polynomial, let $A = \{a_m : m = 0, 1, 2, \ldots\}$ be the sequence of coefficients multiplying the leading term in this series of polynomials, and let $\lambda > 0$ be any number not in A. It then follows $(\lambda - G_\Omega)x^m$ is a polynomial of degree m; by taking linear combinations it follows $(\lambda - G_\Omega)\mathscr{P}$ is dense in $C[0, 1]$, and so the closure $\overline{G_\Omega}$ generates a C_0 semi-group, and $\mathscr{P}$ is a core for this generator. $\square$

The hypotheses of the preceding theorem seem special, but in fact it will suffice for many of our most important examples and applications. We use it next to establish the existence of continuum limits for Cannings processes.

3.9 An Abstract Construction of Continuum Cannings Processes

The discrete Cannings processes have a very special property, which is a consequence of exchangeability. We recall that these were processes whose transitions are defined by

$$X_k | X_{k-1} \overset{d}{=} \sum_{i=1}^{X_{k-1}} \nu_i \tag{3.9.1}$$

where $(\nu_1, \ldots, \nu_N)$ is a positive exchangeable vector summing to N. By induction, it is trivial to prove that the conditional moments are polynomials, in the following way:

$$E[X_{k+1,N}^m | X_{k,N}] = p_{N,m}(X_{k,N}) \tag{3.9.2}$$

where $p_{N,m}$ is a polynomial whose coefficients depend on the power m and chain size N. Even more importantly, deg $p_{N,m} = m$, and hence depends on m only, *not* N.

This special property can be generalised to the following class, which we will call Polynomial-moment GWF (PGWF) processes:

Definition 3.9.1. A Markov chain on states $\{0, \ldots, N\}$ will be called a PGWF process if its first two conditional moments satisfy the GWF conditions, and the higher moments satisfy (3.9.2), where deg $p_{N,m} \leq m$, and is a function of m only.

We prove the existence of a continuum limit for any sequence of "convergent" PGWF chains, with the theory delineated previously. The success of solving the generator problem for the limiting G_Ω hinges upon the fact the uniform limit of polynomials *of a given degree or lower* is itself a polynomial. Therefore, regularity of the limit is assured.

Theorem 3.9.2. *Let* $\mathbf{P}^{(N)}$ *be the transition matrix of a GWFP chain,* $\pi_N : C[0,1] \to K_N$ *the canonical projection and suppose that for every* $u \in \mathscr{P}$, $N(\mathbf{P}^{(N)} - I)\pi_N u$ *is uniformly Cauchy sequence. Then there exists a continuous measure-valued function* Ω *and associated operator* $G_\Omega : \mathscr{P} \to C[0,1]$, *such that* $\overline{G_\Omega}$ *is the generator for a* C_0-*semigroup* T_t*; the polynomials* $\mathscr{P}$ *are a core for* $\overline{G_\Omega}$, *and we have convergence of the approximating semigroups to* T_t*: for each* $f \in C[0,1]$,

$$\|P_N^{[tN]}\pi_N f - \pi_N T_t f\| \to 0, \quad \forall t \geq 0. \tag{3.9.3}$$

The limiting generator has the property that $\overline{G_\Omega}x^m$ *is a polynomial of degree at most* m.

Proof. If $u \in \mathscr{P}$, $f = \lim_N N(\mathbf{P}^{(N)} - I)\pi_N u$ exists as a continuous function; define $G : \mathscr{P} \to C[0,1]$ by $Gu = f$. In fact, because $\mathbf{P}^{(N)}$ is a GWFP chain, the sequence is a uniform limit of polynomials of bounded degree whenever u is a polynomial, and hence G maps polynomials of degree m to polynomials of degree at most m. It is trivially verified that G is linear. Now use Theorem 3.5.1 to see that $G = G_\Omega$ for some continuous family of measures Ω_x. The density condition in the Hille-Yosida Theorem is valid by Theorem 3.8.1. Convergence of the semigroups follows from Theorem 3.4.3. $\square$

The preceding theorem establishes the existence of a continuum limit for all convergence Cannings processes, and shows that the generator must be of the form of a GWF operator for some G_Ω. The particular family of measures Ω was constructed abstractly, as a weak limit. On the surface, it appears that our construction gives very little quantitative information as to the nature of the process, but it turns out we will be able to prove, with the modest aid of qualitative methods, quite interesting properties of such features as probability of fixation and the evolution of moments. Our representation thus has decided advantages over the infinite-series representation of the generator established by Moehle for Cannings processes in [16].

3.10 Incorporating Selection and Mutation

The representation of Theorem 3.5.1 holds only for pure-drift GWF processes, since its proof heavily depends upon the martingale property. But it is easy to deduce the correct representation for processes in the presence of selection and mutation. Recall in Section 1.6 that we had defined, given any pure-drift transition $\mathbf{Q}_N$, the corresponding full model of evolution by the composite $\mathbf{P}_N = \mathbf{S}_N\mathbf{Q}_N\mathbf{M}_N$, where $\mathbf{S}_N, \mathbf{M}_N$ were selection and mutation matrices satisfying conditions:

$$\lim_{N\to\infty} \|(\mathbf{S}_N - I)\pi_N u - \pi_N(\beta x(1-x)u'(x))\| = 0 \tag{3.10.1}$$

$$\lim_{N\to\infty} \|(\mathbf{M}_N - I)\pi_N u - \pi_N(\frac{1}{2}(-\theta_1 x + \theta_2(1-x))u'(x))\| = 0 \tag{3.10.2}$$

for every $u \in C^2[0,1]$, and where π_N is the projection onto the sampling points $\{0, 1/N, \ldots, 1\}$, as usual. In particular, it is easy to prove using a Taylor expansion that the specific selection and mutation matrices introduced in Section 1.6 satisfy the above two considerations.

Theorem 3.10.1. *Let $\mathbf{Q}_{ij}^{(N)}$ be a sequence of pure-drift GWF processes which have a continuum limit associated with operator $G_\Omega : C^2[0,1] \to C[0,1]$. Define the composite sequence of processes $\mathbf{P}^{(N)} = \mathbf{S}^{(N)}\mathbf{Q}^{(N)}\mathbf{M}^{(N)}$. Then $\mathbf{P}^{(N)}$ has a continuum limit associ-*

ated with the operator $\hat{G} : C^2[0,1] \to C[0,1]$ *given by:*

$$\hat{G}u(x) = \beta x(1-x)u'(x) + \frac{1}{2}(-\theta_1 x + \theta_2(1-x))u'(x)) + G_\Omega u(x) \tag{3.10.3}$$

and $\|(\mathbf{P}^{(N)} - I)\pi_N u - \pi_N \hat{G}u\| \to 0$.

Proof. From the algebraic identity

$$N(\mathbf{S}^{(N)}\mathbf{Q}^{(N)}\mathbf{M}^{(N)} - I) = N(\mathbf{S}^{(N)} - I) + N\mathbf{S}^{(N)}(\mathbf{Q}^{(N)} - I) + N\mathbf{S}^{(N)}\mathbf{Q}^{(N)}(\mathbf{M}^{(N)} - I) \tag{3.10.4}$$

we deduce that

$$\|N(\mathbf{P}^{(N)} - I)\pi_N u - \pi_N \hat{G}u\| \leq \|N(\mathbf{S}^{(N)} - I)\pi_N u - \pi_N(\beta x(1-x)u'(x))\| \tag{3.10.5}$$

$$+ \|N\mathbf{S}^{(N)}(\mathbf{Q}^{(N)} - I)\pi_N u - \pi_N G_\Omega u\| \tag{3.10.6}$$

$$+ \|N\mathbf{S}^{(N)}\mathbf{Q}^{(N)}(\mathbf{M}^{(N)} - I) - \pi_N(\frac{1}{2}(-\theta_1 x + \theta_2(1-x))u'(x))\| \tag{3.10.7}$$

which goes to zero from (3.10.1, 3.10.2), the hypotheses on the pure-drift process $\mathbf{Q}^N$ and the observation that $\|\mathbf{R}^{(N)}\pi_N u - \pi_N u\| \to 0$ for each of $\mathbf{R} = \mathbf{S}, \mathbf{Q}, \mathbf{M}$. □

Remark: The preceding proof also shows that as long as the selection and mutation matrices satisfy (3.10.1) and (3.10.2), the order in which they are composed in $\mathbf{P}^{(N)} = \mathbf{S}^{(N)}\mathbf{Q}^{(N)}\mathbf{M}^{(N)}$ is immaterial in the continuum limit.

3.10.1 The Generator Problem for $\hat{G}$

We now define the complete GWF operator $\hat{G}_{\Omega,\beta,\theta_1,\theta_2}$ incorporating all the forces of drift, selection, and mutation as the linear map $\hat{G} : C^2[0,1] \to C[0,1]$

$$\hat{G}_{\Omega,\beta,\theta_1,\theta_2}u(x) = \beta x(1-x)u'(x) + \frac{1}{2}(-\theta_1 x + \theta_2(1-x))u'(x)) + G_\Omega u(x) \tag{3.10.8}$$

Does $\hat{G}$ have an extension which makes it the generator of a continuous-time Markov process? We again must verify the Hille-Yosida conditions. It is obvious that $\hat{G}$ is conservative: $G1 = 0$. Also,

Lemma 3.10.2. *For $\beta \in \mathbb{R}$ and $\theta_1, \theta_2 \geq 0$, $\hat{G}_{\Omega,\beta,\theta_1,\theta_2}$ satisfies the maximum principle.*

Proof. If x_0 is an interior maximum, $u'(x_0) = 0$ and it is obvious as in Lemma 3.3.2 that $\hat{G}u(x_0) \leq 0$. If $x_0 = 0$, then $u'(0) \leq 0$, and since $\theta_2 \geq 0$ we again have $\hat{G}u(0) \leq 0$. If $x_0 = 1$, then $u'(1) \geq 0$, and the result follows again because $\theta_1 \geq 0$. $\square$

The most difficult hypothesis to check is, as usual, the range condition. For a pure mutation process it is trivial for polynomial generators:

Theorem 3.10.3. *Let a continuous Ω be prescribed, and suppose $G_\Omega x^m$ is a polynomial of degree at most m, for every $m = 0, 1, \ldots$. Then for every $\theta_1, \theta_2 \geq 0, \beta = 0$, $\hat{G}_{\Omega,\beta,\theta_1,\theta_2}$ has a closure $\overline{\hat{G}}$ that generates a C_0 semi-group, and $\mathscr{P}$ is a core for this extension. In consequence $\overline{\hat{G}}$ is the generator for a time-homogeneous Markov process with cadlag paths.*

Proof. It remains only to verify the density condition. If $\beta = 0$, then $(\lambda - \hat{G}x^m)$ is a polynomial of degree m whenever λ is not chosen from the set of coefficients multiplying the leading term in the series of polynomials $\hat{G}x^m$. Thus $(\lambda - G_\Omega)\mathscr{P}$ is dense in $C[0, 1]$ by taking linear combinations. $\square$

When β is not zero, $\hat{G}x^m$ is still a polynomial, but of degree $m+1$, and so the function $g(x) = x$ is not in $\hat{G}\mathscr{P}$: the triangulization argument above fails. Nevertheless, it is likely that the conclusion still holds.

The generator problem can also be tackled by perturbation methods: for instance, if the order of G_Ω is larger than one, then the selection term can be viewed as a perturbation, and the generator problem for $\hat{G}$ is effectively reduced to the generator problem for the pure-drift operator G_Ω. A similar situation holds if G_Ω can be dominated by the selection and mutation operators — which will sometimes be the case in a few of our important examples. In that scenario, the following perturbation theorem, due to Hille-Phillips will be vital:

Theorem 3.10.4. *(Hille-Phillips Perturbation Theorem [9]) If A is the generator of a C_0 contraction semigroup, and B is a bounded operator on C_0, then $A + B$ with domain $\mathcal{D}(A)$ generates a C_0 semigroup.*

3.11 Continuum Limits of Example Processes

In this section we will give concrete calculations of the continuum limits of a number of our pure-drift example processes, in each case deriving the limiting generator. We shall follow the recipe given in Section 3.8.

3.11.1 Wright-Fisher Model

Since this is the classical model, we only review it from the perspective of our continuum theory. One finds that

$$dF^*_{N,i}(y) = \frac{(y-i)^2}{i(1-i/N)} \binom{N}{y} \left(\frac{i}{N}\right)^y \left(1 - \frac{i}{N}\right)^{N-y} \tag{3.11.1}$$

If we fix $0 < x < 1$, let $i = [xN]$ and take $N \to \infty$, it is easy to show that, due to the lightness of the tails,

$$\lim_{N\to\infty} dF^*_{N,[xN]}(y) = \delta_x(y) \tag{3.11.2}$$

Thus we deduce that $\Omega_x(y) = \delta_x(y)$, in which case $G_\Omega = \frac{1}{2}x(1-x)u''(x)$, which is a polynomial operator of the type described in Theorem 3.8.1, and thus possesses a requisite extension which makes it the generator for a continuous-time Markov process. The question of convergence of the chain to G_Ω is easy and classical, requiring only a uniform Taylor expansion to third order [22].

3.11.2 Λ_1-Cannings Model

By using the definition of the transition matrix (2.2.1) one easily computes that for $0 < x < 1$,

$$d\Omega_x(y) = \lim_{N\to\infty} dF^*_{N,[xN]}(y) = x\delta_0(y) + (1-x)\delta_1(y) \tag{3.11.3}$$

and thus that

$$G_\Omega u(x) = (1-x)u(0) - u(x) + xu(1) \tag{3.11.4}$$

G_Ω on C^2 is a polynomial operator satisfying the hypotheses of Theorem 3.8.1, and hence has closure generating a C_0 contractive semigroup. The convergence condition (3.6.1) of Theorem 3.6.1 is trivial to verify.

3.11.3 Minimal and Maximal Processes

A straightforward calculation with the matrices (2.3.1) and (2.3.3) show that in this case,

$$d\Omega_x(y)^- = \lim_{N\to\infty} dF^*_{N,[xN],-}(y) = \delta_0(y) \tag{3.11.5}$$

$$d\Omega_x(y)^+ = \lim_{N\to\infty} dF^*_{N,[xN],+}(y) = \delta_1(y) \tag{3.11.6}$$

where Ω^-, Ω^+ are the families of measures associated with the minimal and maximal continuum limits, respectively. Thus the minimal and maximal GWF operators have the form:

$$G_-u(x) = \frac{1-x}{x}(u(0) - u(x) + xu'(x)) \tag{3.11.7}$$

$$G_+u(x) = \frac{x}{1-x}(u(1) - u(x) - (1-x)u'(x)) \tag{3.11.8}$$

These two GWF operators are of polynomial type, and so have closures which generate C_0 semigroups. The convergence condition of Theorem 3.6.1 is once again easy to verify.

3.11.4 Power-law Models

We now come to a significantly more elaborate and realistic set of processes: the α-power-law processes. The derivation of their continuum limit is far more involved. Theorem 2.4.1 proved the existence of their transition matrices for every $0 < \alpha \leq 3$, but as remarked at the end of that section, the proof actually gave a construction for all $\alpha > 0$, for rows $3 \leq i \leq N-2$. Since continuum limits are unaffected by rows that are a fixed distance from the boundaries, we define power-law processes for all α by placing arbitrary transition measures in the states $i = 1, 2, N-2, N-1$.

Parameter limits

We shall first need to compute $\lim_N dF^*_{N,[xN]}(y)$, which entails detailed knowledge of the asymptotics of the parameters $b^{(N)}_{1,i}, b^{(N)}_{2,i}$. The theorem below produces this, and also intimates the presence of a phase change at the critical value $\alpha = 2$.

Theorem 3.11.1. *Fix* $0 < x < 1$*. In the power-law process with* $0 < \alpha < 3$*, the sequence of parameters* $(b^{(N)}_{1,[xN]}, b^{(N)}_{2,[xN]})$ *have the asymptotic forms:*

$$(b^{(N)}_{1,[xN]}, b^{(N)}_{2,[xN]}) \sim (d_\alpha(x), d_\alpha(x)) N^{\frac{2-\alpha}{1-1/\alpha}}, \qquad 2 \leq \alpha < 3 \tag{3.11.9}$$

$$(b^{(N)}_{1,[xN]}, b^{(N)}_{2,[xN]}) \sim (d^{(1)}_\alpha(x), d^{(2)}_\alpha(x)) N^{2-\alpha}, \qquad 0 \leq \alpha < 2 \tag{3.11.10}$$

where $d_\alpha(x), d^{(1)}_\alpha(x), d^{(2)}_\alpha(x)$ *are non-zero finite values for each* x *and* α*.*

Remark: Observe that the exponent in the asymptotics of N changes continuously but non-smoothly at $\alpha = 2$.

Proof. Fix $0 < x \leq 1$, and let $i = [xN]$. Let $b^{(N)}_{1,[xN]}, b^{(N)}_{2,[xN]}$, be the unique values simultaneously satisfying (2.4.3), (2.4.4), $N \geq 12$ as in Theorem 2.4.1. First let us demonstrate the parameter sequence lies in a bounded set. By re-indexing, we can rewrite (2.4.3), (2.4.4) equivalently as the two constraints:

$$\sum_{m=0}^{[Nx]} \frac{m}{1+b_{1,[xN]}^{(N_k)} m^\alpha} = \sum_{m=0}^{N-[Nx]} \frac{m}{1+b_{2,[xN]}^{(N_k)} m^\alpha} \tag{3.11.11}$$

$$\frac{1}{N}\sum_{m=1}^{[Nx]} \frac{m^2}{1+b_{1,[xN]}^{(N)} m^\alpha} + \frac{1}{N}\sum_{m=1}^{n-[Nx]} \frac{m^2}{1+b_{2,[xN]}^{(N)} m^\alpha} \tag{3.11.12}$$

$$= \frac{[Nx](1-[Nx]/n)}{N}\left(\sum_{m=1}^{[Nx]} \frac{1}{1+b_{1,[xN]}^{(N)} m^\alpha} + \sum_{m=1}^{n-[Nx]} \frac{1}{1+b_{2,[xN]}^{(N)} m^\alpha} + 1\right)$$

Let us define $k(\alpha) = 2-\alpha$, or $k(\alpha) = \frac{2-\alpha}{1-1/\alpha}$ depending on whether $0 < \alpha < 2$ or $2 \le \alpha < 3$. Write $b_{1,[xN]} = d_{1,[xN]}N^{k(\alpha)}$, and $b_{2,[xN]} = d_{2,[xN]}N^{k(\alpha)}$. First claim: the d_i lie in a bounded set. First assume $2 < \alpha \le 3$. For instance, say we have subsequences $d_1 \to \infty$, and $d_2 \to const$. Using the Euler-Maclaurin formula to discover the asymptotics of the sums on either side of (3.11.11), both sides are asymptotic to

$$\frac{1}{d_i^{2/\alpha} N^{\frac{4-2\alpha}{\alpha-1}}} \int_0^\infty \frac{u}{1+u^\alpha} du \tag{3.11.13}$$

But this is a contradiction, since by after multiplying by $N^{\frac{4-2\alpha}{\alpha-1}}$, one side tends to zero and the other will be larger than a positive constant. The other case $\alpha \le 2$ is handled similarly, by finding a contradiction in the rates of either side of (3.11.11). We have learned that if one component d_i diverges, the other also diverges. From the variance equation (3.11.12), now take a subequence of d_i both tending to infinity. In case $2 \le \alpha < 3$, an integral asymptotic evaluation of both sides shows that the LHS of (3.11.12) is $\sim C_1 d_i^{-1} N^{\frac{\alpha-2}{\alpha-1}}$, while the RHS is equivalent to $C_2 d_i^{-1/\alpha} N^{\frac{\alpha-2}{\alpha-1}}$: this again is a contradiction, since $d_i \to \infty$. If $\alpha < 2$, from the variance equation, LHS is less than $\frac{1}{N_k d_{1,x}^{(N)} N^{2-\alpha}} \sum_{m=1}^{N_k x} m^{2-\alpha} +$similar $\le \frac{1}{d_{1,x}^{(N)}} O(1) \to 0$. But the RHS is always larger than $Nx(1-x) > 0$ — contradiction again. We have now proved that for all $0 < \alpha < 3$, d_i are bounded away from infinity.

The d's are also bounded away from zero. Again we split into cases. Suppose that $2 \geq \alpha$. Say d_1 goes to zero. Passing to subsequence, say however, $d^{(N)}N^2$ converges to a c. Bound the LHS of variance equation (3.11.12):

$$LHS > \frac{1}{N}\sum_{m=1}^{Nx}\frac{m^2}{1+d_1N^2} = \frac{1}{const}O(N^2) \tag{3.11.14}$$

But the RHS is at most $O(N)$. We learn that $d^{(N)}N^2$ is unbounded. So pass to a subsequence so $d^{(N)}N^2$ diverging to infinity. Multiply the variance equation on both sides by $d^{(N)}$. The LHS is now (replacing m^α by N^α):

$$\frac{1}{N}\sum_{m=1}^{N}\frac{d^{(N)}m^2}{1+d^{(N)}N^{2-\alpha}m^\alpha} > \frac{d^{(N)}}{N(1+d^{(N)}N^2)}(N^3/3+O(N^2)) \to 1/3 \tag{3.11.15}$$

However, the RHS will converge to zero. Indeed

$$RHS = K\sum_{m=1}^{N}\frac{d^{(N)}}{1+d^{(N)}N^{2-\alpha}m^\alpha} + o(1) < K\sum_{m=1}^{N}\frac{d^{(N)}}{1+d^{(N)}m^{2-\alpha}m^\alpha} = K\sum_{m=1}^{n}\frac{d^{(N)}}{1+d^{(N)}m^2} \tag{3.11.16}$$

This latter goes to zero by integral approximation:

$$\sum_{m=1}^{N}\frac{d^{(N)}}{1+d^{(N)}m^2} < d^{(N)}\int_0^N\frac{d^{(N)}x}{1+d^{(N)}x^2} < \sqrt{d^{(N)}}\int_0^\infty\frac{d^{(N)}u}{1+u^2} \to 0 \tag{3.11.17}$$

This argument was for each respective component on both sides; now we can combine the argument on both terms (the respective LHS majorizes the RHS term + 1/2). That covers the case $0 < \alpha < 2$. By similar calculations, it is not more difficult to demonstrate that (d_1, d_2) are bounded away from zero when $2 \leq \alpha < 3$ — we leave the details to the reader.

The above confirms that the asymptotic rates for the parameters b_i stated in the theorem are correct, since (d_1, d_2) lie in a bounded set. Now take convergence subsequences of the sequence, to the limits $(d_1(x), d_2(x))$, necessarily positive. By using the

Euler-Maclaurin formula on (3.11.11, 3.11.12), we can derive a pair of equations which the limits must satisfy. Taking $N_k \to \infty$ in (3.11.11), the limiting version of (3.11.11) states that

$$d_2(x) = \left(\frac{1-x}{x}\right)^{2-\alpha} d_1(x), \qquad 0 < \alpha < 2 \tag{3.11.18}$$

$$d_2(x) = d_1(x), \qquad 2 \leq \alpha < 3 \tag{3.11.19}$$

On the other hand, taking the limit of (3.11.12) adduces

$$\frac{x^{3-\alpha}}{(3-\alpha)d_1(x)} + \frac{(1-x)^{3-\alpha}}{(3-\alpha)d_2(x)} = x(1-x), \qquad 0 < \alpha < 2 \tag{3.11.20}$$

$$\frac{x}{d_1(x)} + \frac{1-x}{d_2(x)} = x(1-x)\left(1 + \sum_{m=1}^{\infty} \frac{1}{1+d_1(x)m^2} + \sum_{m=1}^{\infty} \frac{1}{1+d_2(x)m^2}\right), \quad \alpha = 2 \tag{3.11.21}$$

$$\frac{x^{3-\alpha}}{(3-\alpha)d_1(x)} + \frac{(1-x)^{3-\alpha}}{(3-\alpha)d_2(x)} = \left(\frac{1}{d_1^{1/\alpha}(x)} + \frac{1}{d_2^{1/\alpha}(x)}\right) x(1-x) \int_0^{\infty} \frac{1}{1+u^{\alpha}}, \quad 2 < \alpha < 3 \tag{3.11.22}$$

Now we are nearly done, because for each α, the pairs of equations satisfied by $d_1(x), d_2(x)$ characterize d uniquely. If $\alpha \neq 2$, this is obvious, because d_1, d_2 can be solved in closed form. For $\alpha = 2$, we observe that constraint (3.11.21), in conjunction with $d_1 = d_2$, may be rewritten as the transcendental equation

$$\pi x(1-x)\sqrt{d(x)} \coth\left(\frac{\pi}{\sqrt{d(x)}}\right) = 1 \tag{3.11.23}$$

We already have proved, for each $0 < x < 1$, that there exists a $d(x) > 0$ solving the above equation (it was the limit of some convergent subsequence of the d's); this $d(x)$ is unique because it is readily verified that $u \coth(\pi/u)$ is a strictly increasing function for $u > 0$.

To sum up, we have shown that every convergence subsequence of $(d_{1,[Nx]}, d_{2,[Nx]})$ converges to the same limits $(d_1(x), d_2(x))$ given as the unique solution to the pairs of equations above; it follows that the sequence $(d_{1,[Nx]}, d_{2,[Nx]})$ itself is convergent to $d_1(x), d_2(x)$, and the asymptotic representations of the theorem follow. □

By using the previous theorem, and the specific limiting forms involved in the proof of that theorem in conjunction with the quantization Lemma 3.7.3, one can now calculate the weak limits

Theorem 3.11.2. *In the power-law processes* $0 < \alpha < 3$*, one has*

$$d\Omega_x^{(\alpha)}(y) = w.\lim_{N\to\infty} dF^*_{N,[xN]}(y) = \begin{cases} \frac{(3-\alpha)\,dy}{x^{2-\alpha}|y-x|^{\alpha-2}}, & y < x \\ \frac{(3-\alpha)\,dy}{(1-x)^{2-\alpha}|y-x|^{\alpha-2}}, & y \geq x \end{cases} \qquad 0 < \alpha < 2 \tag{3.11.24}$$

$$= \frac{(3-\alpha)\,dy}{(x^{3-\alpha} + (1-x)^{3-\alpha})|y-x|^{\alpha-2}}, \qquad 2 \leq \alpha < 3 \tag{3.11.25}$$

It is remarkable to observe that as $\alpha \uparrow 3$, $d\Omega_x^{(\alpha)}$ approaches the delta measure at x, $d\Omega_x = \delta_x$ — indicating the diffusion limit occurs at $\alpha \geq 3$. Indeed, in a manner similar to what has been presented above, the asymptotics for the power-law processes three and larger can be easily worked out, obtaining:

Theorem 3.11.3. *In the power-law processes* $\alpha \geq 3$*, one has*

$$d\Omega_x^{(\alpha)}(y) = w.\lim_{N\to\infty} dF^*_{N,[xN]}(y) = \delta_x(y) \tag{3.11.26}$$

The preceding theorems reveal then two phase changes: at the location $\alpha = 2$, where the asymptotics for the parameters b_1, b_2 change in a non-smooth way, and at $\alpha = 3$, where the Kimura diffusion becomes applicable. Since the case $\alpha > 3$ is classical, we now propose to study the regime $0 < \alpha \leq 2$; unfortunately the techniques which follow cannot be easily applied to $2 < \alpha < 3$. In some sense that interval remains mysterious to us.

Let us denote by G_α the pure-drift GWF operator associated to $\Omega^{(\alpha)}$ as revealed in Theorem 3.11.2. We shall first derive an alternative representation for the α operators, valid on a slightly larger domain than $C^2[0,1]$.

Theorem 3.11.4. *Let $\mathcal{D}$ be the functions $u \in C[0,1]$ for which u'' exists (but is not necessarily bounded) on $(0,1)$ and $|u'| \in L^1[0,1]$ is integrable. Fix $0 < \alpha < 2$, and $\alpha \neq 1$. Then the following expressions are well-defined for $x \in (0,1)$ and equivalent:*

1. $G_\alpha u(x) = x(1-x) \int_0^1 \frac{u(z)-u(x)-(z-x)u'(x)}{(z-x)^2} d\Omega_x^{(\alpha)}(z)$

2. $G_\alpha u(x) = \frac{3-\alpha}{\alpha-1}\left[u(x) - xu(1) - (1-x)u(0)\right] - \frac{x(1-x)}{x^{2-\alpha}} \int_0^x \frac{(x-z)^{1-\alpha}}{\alpha-1} u'(z)\, dz$
$+ \frac{x(1-x)}{(1-x)^{2-\alpha}} \int_x^1 \frac{(z-x)^{1-\alpha}}{\alpha-1} u'(z)\, dz$

Moreover, G_α maps $\mathcal{D}$ to functions continuous on (0,1).

Proof. Fix $0 < x < 1$; the integrand in (1) is continuous and so the integral is well-defined. Moreover, if N_{x_0} is a neighborhood of x_0 bounded away from 0 and 1, the function $g(x,z) = \frac{u(z)-u(x)-(z-x)u'(x)}{(z-x)^2} f(x,z)$ is (uniformly) continuous on $\overline{N_{x_0}} \times [0,1]$, hence $\int_0^1 g(x,z)\, dz$ is continuous on $(0,1)$. To show the equivalence of the expressions, split (1) into two parts and integrate each by parts. The first piece V_1 has form

$$V_1 = \frac{x(1-x)}{3-\alpha}\int_0^{x-\epsilon}\frac{u(z)-u(x)-(z-x)u'(x)}{(z-x)^2}d\Omega_x^{(\alpha)}(z) \tag{3.11.27}$$

$$= \frac{x(1-x)}{x^{2-\alpha}}\int_0^{x-\epsilon}(u(z)-u(x)-(z-x)u'(x))\frac{1}{(x-z)^\alpha}\,dz \tag{3.11.28}$$

$$= \frac{x(1-x)}{x^{2-\alpha}}\Big[(u(z)-u(x)-(z-x)u'(x))(\frac{1}{\alpha-1}(x-z)^{1-\alpha}|_{z=0}^{z=x-\epsilon}) \tag{3.11.29}$$

$$-\int_0^{x-\epsilon}\frac{(x-z)^{1-\alpha}}{\alpha-1}(u'(z)-u'(x))\,dz\Big]$$

$$= \frac{x(1-x)}{x^{2-\alpha}}\left[(u(x-\epsilon)-u(x)+\epsilon u'(x))\frac{\epsilon^{1-\alpha}}{\alpha-1}-(u(0)-u(x)+xu'(x))\frac{x^{1-\alpha}}{\alpha-1}-I\right] \tag{3.11.30}$$

where I is the integral term in (3.11.29). The second piece V_2 is worked out as:

$$V_2 = \frac{x(1-x)}{3-\alpha}\int_{x+\epsilon}^{1}\frac{u(z)-u(x)-(z-x)u'(x)}{(z-x)^2}d\Omega_x^{(\alpha)}(z) \tag{3.11.31}$$

$$= \frac{x(1-x)}{(1-x)^{2-\alpha}}\int_{x+\epsilon}^{1}(u(z)-u(x)-(z-x)u'(x))\frac{1}{(z-x)^\alpha}\,dz \tag{3.11.32}$$

$$= \frac{x(1-x)}{(1-x)^{2-\alpha}}\Big[(u(z)-u(x)-(z-x)u'(x))(\frac{-1}{\alpha-1}(z-x)^{1-\alpha}|_{z=x+\epsilon}^{z=1}) \tag{3.11.33}$$

$$+\int_{x+\epsilon}^{1}\frac{(z-x)^{1-\alpha}}{\alpha-1}(u'(z)-u'(x))\,dz\Big]$$

$$= \frac{x(1-x)}{(1-x)^{2-\alpha}}\Big[(u(1)-u(x)-(1-x)u'(x))\frac{-1}{\alpha-1}(1-x)^{1-\alpha} \tag{3.11.34}$$

$$-(u(x+\epsilon)-u(x)+\epsilon u'(x))\frac{-1}{\alpha-1}\epsilon^{1-\alpha}+I_2\Big]$$

with I_2 is the integral in (3.11.34).

As u is locally Lipschitz, all terms with ϵ vanish as $\epsilon \to 0$, and we find that:

$$V_1 = \frac{x(1-x)}{x^{2-\alpha}}\left[(-u(0)+u(x)-xu'(x))\frac{x^{1-\alpha}}{\alpha-1}-I\right] \tag{3.11.35}$$

and the second part:

$$V_2 = \frac{x(1-x)}{(1-x)^{2-\alpha}}\left[(u(1)-u(x)-(1-x)u'(x))(\frac{-1}{\alpha-1})(1-x)^{1-\alpha}+I_2\right] \tag{3.11.36}$$

Adding these:

$$V_1 + V_2 = \frac{1}{\alpha - 1}\left[u(x) - xu(1) - (1-x)u(0)\right] - \frac{x(1-x)}{x^{2-\alpha}} I + \frac{x(1-x)}{(1-x)^{2-\alpha}} I_2 \qquad (3.11.37)$$

What remains after the cancelations is the desired form (2). ☐

With this representation we can now show G_α does generate a C_0 semigroup.

Theorem 3.11.5. *The GWF operator* $G_\alpha : C^2 \to C^0$, *for* $0 < \alpha \leq 2$, $\alpha \neq 1$ *is a polynomial operator, and hence has a closure generating a* C^0 *contraction semigroup.*

Proof. Using the classical Abel integral identity and a fortuitous cancellation in the signs of the two integrals, it is simple to calculate that $G_\alpha x^m$ is a polynomial of degree m, and hence by Theorem 3.8.1 has an extension which generates a C^0-semigroup. ☐

The continuum limit calculation of Theorem 3.11.1 is a pointwise calculation: weak convergence of the measure valued function is established for each fixed state x. We now strengthen this convergence to a uniform convergence across x, in the sense of Theorem 3.6.1.

Theorem 3.11.6. *For each* $0 < \alpha \leq 2$, $\alpha \neq 1$, *let* $Y_t^{(\alpha)}$ *be the Feller process associated with the generator* $\overline{G_\Omega^{(\alpha)}}$. *If* $X_k^{(\alpha)}$ *are the Markov chains associated to the discrete power-law processes, then the scaled processes* $\{\frac{1}{N}X_{[Nt]}\}$ *converge weakly to* $Y^{(\alpha)}$. *If* $\alpha \geq 3$, *the processes* $\{\frac{1}{N}X_{[Nt]}\}$ *converge weakly to the standard Kimura diffusion.*

Proof. We must verify the uniform convergence condition of Theorem 3.6.1. For brevity the proof will be given in full only for $\alpha = 2$; similar asymptotics refining those in the proof of Theorem 3.11.1 establish for the range under consideration.

Because of the symmetry of the transition matrix, it suffices to prove uniform convergence on $1 \le i \le N/2$. Our strategy is to divide the indices into two regimes $i < N^{3/4}$, and $N^{3/4} < i < N/2$, establishing uniformity on each regime separately. We do this because, roughly speaking, a different behavior occurs depending on whether i is small or large. The choice of $N^{3/4}$ is convenient for this splitting. It is obvious that for indices $i < N^{3/4}$, that the convergence hypothesis of Theorem 3.6.1 occurs trivially because each term *separately* converges to zero.

To suppress notational redundancy the shorthand $\mathcal{I} = \{i : N^{3/4} \le i \le N/2\}$ is adopted.

Lemma 3.11.7. *The set* $\{(b^{(N)}_{1,i}, b^{(N)}_{2,i} : i \in \mathcal{I}, N \in \mathbb{Z}^+\}$ *is bounded away from zero.*

Proof. Recall the "variance" equation derived from the Wright-Fisher conditions:

$$\frac{1}{N}\sum_{m=1}^{i}\frac{m^2}{1+b^{(N)}_{1,i}m^2} + \frac{1}{N}\sum_{m=1}^{N-i}\frac{m^2}{1+b^{(N)}_{2,i}m^2} = \frac{i}{N}(1-i/N)\Big(1+\sum_{m=1}^{i}\frac{1}{1+b^{(N)}_{1,i}m^2} \tag{3.11.38}$$

$$+\sum_{m=1}^{N-i}\frac{1}{1+b^{(N)}_{2,i}m^2}\Big) \tag{3.11.39}$$

Now suppose that $b^{N_k}_{1,i_{N_k}}$ is a subsequence converging to zero. First, if $b^{N_k}_{1,i_{N_k}} \cdot N_k^2$ is bounded, then the LHS of the above equation is at least $C \cdot (i^3_{N_k}/N_k)$, while the RHS is at most $C_2 N_k$. But this is impossible since $i_{N_k} \ge {N_k}^{3/4}$ implies the LHS is larger than $C(N_k^{5/4})$. It follows that $b^{(N)}_{1,i}$ cannot decay too quickly, WLOG pass to a subsequence converging to zero for which $b^{(N)}_{1,i}N^2 \to \infty$. Since $b^{(N)}_{2,i} \ge b^{(N)}_{1,i}$ on the set indicated, $b^{(N)}_{2,i}N^2 \to \infty$. Then the Euler-Maclaurin development of the LHS shows that it is at least $C\frac{i}{N}\frac{1}{b^{(N)}_{1,i}}$, whereas the RHS, after a similar development, is bounded by $C_2\frac{i}{N}\frac{1}{\sqrt{b^{(N)}_{1,i}}}$ — contradiction. Thus $\{b^{(N)}_{1,i}\}$ is bounded away from zero, as is $\{b^{(N)}_{2,i}\}$. □

Asymptotically, the ratio $b_{2,i}/b_{1,i}$ is determined by the first-order WF condition, while the absolute sizes of $b_{1,i}, b_{2,i}$ are controlled by the variance restraint.

Lemma 3.11.8. *On the set $\mathcal{I}$,*

$$\frac{b_{2,i}^{(N)}}{b_{1,i}^{(N)}} = \frac{\log(N-i)}{\log i}\left(1 + O\left(\frac{1}{i\log i}\right)\right) \tag{3.11.40}$$

Proof. Recall the first-order WF condition, which may be written as:

$$\sum_{m=0}^{i} \frac{m}{1+b_{1,i}^{(N)}m^2} = \sum_{m=0}^{N-i} \frac{m}{1+b_{2,i}^{(N)}m^2} \tag{3.11.41}$$

The LHS is $\sum_{m=1}^{i} \frac{1}{b_{1,i}^{(N)}m} + O(1/((b_{1,i}^{(N)})^2m^3))$, which is

$$\sum_{m=1}^{i} \frac{1}{b_{1,i}^{(N)}m} + O(1/((b_{1,i}^{(N)})^2m^3)) = \frac{1}{b_{1,i}^{(N)}}(\log i + O(1/i)) + O(1/((b_{1,i}^{(N)})^2i^2)) \tag{3.11.42}$$

$$= \frac{1}{b_{1,i}^{(N)}}[\log i + O(1/i)] \tag{3.11.43}$$

where we have used Lemma 3.11.7 in the last line. By an identical development, the RHS of (3.11.41) is $\frac{1}{b_{2,i}^{(N)}}[\log(N-i) + O(1/(N-i))] = \frac{1}{b_{2,i}^{(N)}}[\log(N-i) + O(1/i)]$, because $N/2 \geq i$. Equating these two expressions and solving for $b_{2,i}/b_{1,i}$ we obtain the desired estimate. □

From Lemma 3.11.8 it is clear that

Corollary 3.11.9. *The ratios $\frac{b_{1,i}^{(N)}}{b_{2,i}^{(N)}}$ and $\frac{b_{2,i}^{(N)}}{b_{1,i}^{(N)}}$ are bounded away from 0 and ∞ on $\mathcal{I}$.*

It will be useful to give a name to the quantity appearing in the LHS of (3.11.38). We make the definition

$$\gamma_{i,N} \equiv \left[\frac{1}{N}\sum_{m=1}^{i} \frac{m^2}{1+b_{1,i}^{(N)}m^2} + \frac{1}{N}\sum_{m=1}^{N-i} \frac{m^2}{1+b_{2,i}^{(N)}m^2}\right]^{-1} \tag{3.11.44}$$

In the point-wise analysis for i a fixed proportion of N, this $\gamma_{i,N}$ converges to $b_1(x) = b_2(x)$. This is no longer true for the range of indices $i \in \mathcal{I}$, but nonetheless the quantities $\frac{\gamma_{i,N} - b_{1,i}^{(N)}}{b_{1,i}^{(N)}}$ and $\frac{\gamma_{i,N} - b_{2,i}^{(N)}}{b_{2,i}^{(N)}}$ will be small, with the appropriate weights.

Lemma 3.11.10. $\frac{\gamma_{i,N}}{b_{1,i}^{(N)}} = \left[\frac{i}{N} + \frac{N-i}{N}\frac{b_{1,i}^{(N)}}{b_{2,i}^{(N)}}\right]^{-1} + O\left(\frac{1}{iN}\right)$.

Proof.

$$\begin{aligned}
\gamma_{i,N}/b_{1,i}^{(N)} &= \left[\frac{1}{N}\sum_{m=1}^{i}\frac{b_{1,i}^{(N)}m^2}{1+b_{1,i}^{(N)}m^2} + \frac{1}{N}\sum_{m=1}^{N-i}\frac{b_{1,i}^{(N)}m^2}{1+b_{2,i}^{(N)}m^2}\right]^{-1} && (3.11.45)\\
&= \left[\frac{1}{N}\sum_{m=1}^{i} 1 + O\left(\frac{1}{b_{1,i}m^2}\right) + \frac{1}{N}\sum_{m=1}^{N-i}\frac{b_{1,i}^{(N)}}{b_{2,i}^{(N)}} + O\left(\frac{b_{1,i}^{(N)}}{(b_{2,i}^{(N)})^2 m^2}\right)\right]^{-1} && (3.11.46)\\
&= \left[\frac{i}{N} + \frac{1}{b_{1,i}^{(N)}}O(1/(Ni)) + \frac{N-i}{N}\frac{b_{1,i}^{(N)}}{b_{2,i}^{(N)}} + \frac{1}{N}\frac{b_{1,i}^{(N)}}{(b_{2,i}^{(N)})^2}O\left(\frac{1}{N-i}\right)\right] && (3.11.47)\\
&= \left[\frac{i}{N} + \frac{N-i}{N}\frac{b_{1,i}^{(N)}}{b_{2,i}^{(N)}} + O\left(\frac{1}{iN}\right)\right]^{-1} && (3.11.48)\\
&= \left[\frac{i}{N} + \frac{N-i}{N}\frac{b_{1,i}^{(N)}}{b_{2,i}^{(N)}}\right]^{-1} + O\left(\frac{1}{iN}\right) && (3.11.49)
\end{aligned}$$

The penultimate inequality makes use of $i \in \mathcal{I}$ and $b_{2,i} \geq b_{1,i}$, the last because the second term in the brackets is bounded away from zero, from Corollary 3.11.9. □

Combining Lemma 3.11.8, 3.11.10 and Corollary 3.11.9, we find

Lemma 3.11.11. $\frac{\gamma_{i,N}}{b_{1,i}^{(N)}} = \left(\frac{i}{N} + \frac{N-i}{N}\frac{\log i}{\log(N-i)}\right)^{-1} + O\left(\frac{1}{i\log i}\right)$.

We can now establish the key uniform estimate:

Proposition 3.11.12.

$$\sup_{i\in\mathcal{I}} \frac{i}{N}\left|\frac{\gamma_{i,N}}{b_{1,i}^{(N)}} - 1\right| \leq \frac{C}{\log N} \tag{3.11.50}$$

Proof. We use Lemma 3.11.4. The error term in that lemma is obviously dominated by the estimate in the present proposition. One has, after some algebra

$$\frac{i}{N}\left|\left(\frac{i}{N}+\frac{N-i}{N}\frac{\log i}{\log(N-i)}\right)^{-1}-1\right| = \frac{i}{N}\left(\frac{(N-i)\log(N/i-1)}{i\log(N-i)+(N-i)\log i}\right) \tag{3.11.51}$$

$$\leq \frac{i\log(N/i-1)}{i\log(N-i)+(N-i)\log i} \tag{3.11.52}$$

$$= \frac{i\log(N/i-1)}{N\log i + i\log(N/i-1)} \tag{3.11.53}$$

$$= \frac{1}{1+\log i\cdot\frac{N/i}{\log(N/i-1)}} \tag{3.11.54}$$

Finally there exists $K > 0$ such that $\frac{N/i}{\log(N/i-1)} > K$ for $i \in \mathcal{I}$, and now the proposition follows since $i \geq N^{3/4}$. □

In identical manner, one proves the other required inequality:

Proposition 3.11.13.

$$\sup_{i\in\mathcal{I}}\frac{i}{N}\left|\frac{\gamma_{i,N}}{b_{2,i}^{(N)}}-1\right| \leq \frac{C'}{\log N} \tag{3.11.55}$$

We are now sufficiently prepared to prove

$$\lim_{n\to\infty}\sup_{i\in\mathcal{I}}\frac{i}{N}(1-i/N)\int_0^1\left|dF^*_{N,i}(y)-\mu_N\right|\,dy = 0. \tag{3.11.56}$$

where μ_N is the discrete uniform distribution given equal weight to the sampling points $\{0, 1/N, \ldots, 1\}$. This may be rewritten as:

$$\lim_{n\to\infty}\sup_{i\in\mathcal{I}}\frac{i}{N}(1-i/N)\frac{1}{N}\sum_{j=0}^{i}\left|\frac{(j-i)^2[\gamma_{i,N}-b_{1,i}^{(N)}]-1}{1+b_{1,i}^{(N)}(j-i)^2}\right| \tag{3.11.57}$$

$$+\frac{1}{N}\sum_{j=i+1}^{N}\frac{(j-i)^2[\gamma_{i,N}-b_{2,i}^{(N)}]-1}{1+b_{2,i}^{(N)}(j-i)^2} = 0 \tag{3.11.58}$$

Each term can be separated into two parts; for instance the first term is

$$\frac{i}{N}\left(1-\frac{i}{N}\right)\left|\frac{1}{N}\sum_{j=0}^{i}\frac{(j-i)^2[\gamma_{i,N}-b_{1,i}^{(N)}]}{1+b_{1,i}^{(N)}(j-i)^2}+\frac{1}{N}\sum_{j=0}^{i}\frac{-1}{1+b_{1,i}^{(N)}(j-i)^2}\right| \tag{3.11.59}$$

The first term of the above is smaller than $\frac{i}{N}\left(1-\frac{i}{N}\right)\frac{1}{N}\sum_{j=0}^{i}\left|\frac{\gamma_{i,N}}{b_{1,i}}-1\right|$, which by Proposition 3.11.12 approaches zero uniformly. The second sum in (3.11.59) is a convergent series because of Lemma 3.11.7, and thus is bounded by $K/N \to 0$. A repeat of this argument with the application of Proposition 3.11.13 proves the second term of 3.11.57 uniformly approaches zero. Thus (3.11.56) is true. This, in conjunction with the quantization Lemma 3.7.3 and Theorem 3.6.1, finishes the proof.

□

Chapter 4

Applications of Continuum Theory

In the preceding chapter we derived a representation formula for the generator of any continuum limit of GWF chains, and calculated these explicitly for our example processes. Since the operators are no longer differential, but rather integro-differential, and indeed may be of fractional order, the functional calculations $Gf = g$ associated to stopping time problems are quite difficult to solve explicitly, except in very simple cases.

In the present chapter, we develop the maximum principle for GWF operators, and show how this technique can be applied to obtain both qualitative insight and in some cases precise quantitative information concerning the solutions of the associated operator equations — those connected with fixation probabilities and the evolution of moments of the processes, for instance. We pose an interesting extremal problem and solve it with the aid of our continuum representation. Next we discuss aspects of the stationary distribution of continuum limits, proving their uniqueness and existence for the Cannings class. The statistical theory of GWF equilibrium measures is taken up, and a generalised Poisson Random Field approximation proven for the sampled frequency spectrum.

4.0.5 Extreme Processes in the Continuum Limit

The space of measure-valued functions $C([0,1],\mathcal{M}_1([0,1]))$ is convex, and because the map $\Phi : \Omega \mapsto G_\Omega$ respects this property, the space of GWF operators is also convex. With the topology induced from the metric d defined in Section 3.2.2 , the space is not compact: we cannot apply the Krein-Milman theorem. Nonetheless, there are extreme points, and it is of interest to discover them. Quickly, the functions of type $d\Omega_x(y) = \delta_{f(x)}(y)$ come under examination, where $f : [0,1] \to [0,1]$, and indeed, it is readily seen that such families are weak-$*$ continuous if and only if f is continuous, which then induce extreme GWF operators. It also appears likely that these are the only extreme processes, though the proof of that statement would take us too far afield.

On this basis, we see that of our example processes, the minimal, maximal and Kimura diffusion processes are extreme points. That this property holds for the minimal and maximal processes comes as no surprise: they were extreme in the discrete space. But that the Wright-Fisher model is asymptotically extreme, even in this very large space, is an interesting insight, which is gleaned only from our continuum representation formula, since the Wright-Fisher process is very far from extreme in the space of discrete GWF chains.

A generic function defined on a convex set rarely achieves its maximum or minimum at the extreme points. This is true generically; but it is also true that some of the most biologically interesting functionals *will* in fact achieve their maximum or minimum at certain extreme points. It is to this that we now turn to.

4.1 The Generalized Wright-Fisher Operator with Selection

One of the principal advantages of the continuum representation is the ability to study GWF processes under the influence of non-zero selection. To begin, we develop some important maximum principles associated with the GWF operator. We shall write:

$$G_{\beta,\Omega}u(x) = \beta x(1-x)u'(x) + x(1-x)\int_0^1 \frac{u(y)-u(x)-u'(x)(y-x)}{(y-x)^2}d\Omega_x(y) \qquad (4.1.1)$$

defined on at least $C^2[0,1]$, and parameterized by selection pressure β, and a continuous family of measures Ω_x. Subscripts will be omitted whenever typographical compression is warranted.

Some of the succeeding results pertain to the case of positive selection $\beta \geq 0$; if G is associated to a symmetric process ($d\Omega_x(y) = d\Omega_{1-x}(1-y)$), the necessary results for negative selection $\beta < 0$ can be obtained simply by reflection. In the analysis in Section 4.4 of the parabolic equation we make no restriction on symmetry or the range of the selection coefficient.

4.2 Maximum Principles

The maximum principle for G is a limiting form for the discrete positive maximum principle associated to $\mathbf{P}-I$, where $\mathbf{P}$ is a Markov transition matrix. It is a simple consequence of the fact that the rows of $\mathbf{P}$ are probability distributions. We have already touched upon the principle in Section 3.3, we now refine that discussion and prove a number of such principles. In the following, some laxness in the domain of G will be inevitable, since we will not wish to restrict ourselves to defining G only on its domain as a putative generator, but possibly on its extension as the characteristic operator of a Markov process (so that, for example, the absorption time problem is soluble). In every case, nonetheless, we assume that $u \in C[0,1] \cap C^1(0,1)$.

Lemma 4.2.1. *(Basic Maximum Property) If x_0 is an interior global maximum of u, $G_{\beta,\Omega}u(x_0) \leq 0$.*

Proof. If x_0 is an interior global maximum, $u'(x_0) = 0$, and $u(y) - u(x_0) \leq 0$ for all y. $\square$

Lemma 4.2.2. *(Proto-Maximum Principle) Suppose $G_{\beta,\Omega}u(x) > 0$ for all $x \in (0,1)$. Then any global maximum of u occurs only at the boundaries $x = 0, 1$.*

Proof. Immediate from Lemma 4.2.1. $\square$

The strict inequality in the preceding lemma will not be sufficient to prove any of our desired results. So we refine this to a true (weak) maximum principle for the inequality $Gu \geq 0$, which explicitly uses $\beta \geq 0$ (or at least $\beta > -1/2$).

Theorem 4.2.3. *(Maximum Principle) Let $\beta \geq 0$, and suppose u satisfies $G_{\beta,\Omega}u(x) \geq 0$ on $x \in (0,1)$. Then $\max_{x\in[0,1]} u(x) = \max\{u(0), u(1)\}$.*

Proof. Say $u(c) = \max_{x \in [0,1]} u(x) = M$, c is an interior point. We will prove $u(1) = M$. For if $u(1) < M$, define the function $z(x) = x^2 - c^2$. A simple computation shows (as $d\Omega_x$ are probability measures),

$$Gz(x) = x(1-x)(1+\beta 2x) > 0 \tag{4.2.1}$$

Now look at $w(x) = u(x) + \epsilon z(x)$, $\epsilon > 0$. We have the strict inequality $Gw(x) > 0$ throughout the open interval, and $w(0) < M$, $w(c) = M$, and $w(1) = u(1) + \epsilon z(1) < M$ for sufficiently small ϵ. This constructed w would then have an interior global maximum, contradicting Lemma 4.2.2. □

By applying the maximum principle to $-u(x)$, we obtain the minimum principle.

Theorem 4.2.4. *(Minimum Principle) Let* $\beta \geq 0$*. If* $G_{\beta,\Omega} u \leq 0$ *throughout* $(0,1)$*, then* $\min_{x \in [0,1]} u(x) = \min\{u(0), u(1)\}$.

A basic corollary of these properties, which is used repeatedly in the sequel is

Corollary 4.2.5. *If* $Gu = 0$ *on* $(0,1)$ *and* $u(0) = u(1)$*, then* $u \equiv$ *const.*

Proof. Immediate from maximum and minimum principles. □

Remark: While it is unnecessary for the succeeding results, it can be asked whether a strong, Hopf-like maximum principle is available — i.e $Gu \geq 0$ and u has a global interior maximum implies u is a constant. This is a possibility less likely than for the case of local operators (where it is generally true). Indeed, we see below that the non-local nature of G does not generally gainsay the existence of local maxima/minima.

4.3 Comparison and Uniqueness Principles

We can use the preceding maximum principles to obtain some basic results on the properties of solutions to typical genetics problems. Later, it will be important to study the Dirichlet problem $Gu = 0$, which is related to asymptotic probability of fixation (see Theorem 4.5.5). It is convenient here to establish a uniqueness principle.

Probability of Fixation Problem (PFP): Solve $Gu = 0$, subject to $u(0) = a, u(1) = b$.

We shall see below that a solution to this problem may not exist (for instance, in some power-law processes, for sufficiently large selective pressure and $a \neq b$). But if the solution exists, it must be unique:

Proposition 4.3.1. *The solution to **PFP** is unique in the space of continuous functions it exists.*

Proof. If u_1 and u_2 are two solutions, then $h = u_1 - u_2$ satisfies $Gh = 0$ with conditions $h(0) = 0, h(1) = 0$; now the maximum principle implies $h \equiv 0$. □

Proposition 4.3.2. *For $a \leq b$, if a continuous solution u to **PFP** exists then it satisfies $a \leq u \leq b$. In particular, for the selection problem $a = 0, b = 1$, u can be interpreted as a probability.*

Proof. Immediate from max/min principles. □

We can also ascertain the dimension of the null space of G:

Proposition 4.3.3. *G annihilates constant functions. The null space of G, has either dimension 1 or 2.*

Proof. That G annihilates constants is obvious. Let D be the domain of functions continuous up to the boundary. Suppose that $f \in D$ is non-constant and annihilated by G. We can assume $f(0) = 0$. Now $f(1)$ cannot be zero, or else $f \equiv 0$ by the maximum principle. Let h be any other function in D annihilated by G. Consider the function $k(x) = h(x) - h(0) - [h(1) - h(0)]f(x)/f(1)$. Note $k(x)$ is annihilated by G, and $k(0) = 0, k(1) = 0$. Therefore k is identically zero, and $h(x)$ is a linear combination of a constant and $f(x)$. $\square$

One can reformulate this as an alternative characterization of the existence of a solution to the two-point problem:

Proposition 4.3.4. *There is a solution to $Gu = 0$ satisfying $u(0) = a \neq b = u(1)$ if and only if dim ker $G = 2$, where the domain is restricted to functions continuous up to the boundary.*

Proof. If G has null-space of dimension 1, then only constant functions satisfy $Gu = 0$, and so there is no solution if $a \neq b$. On the other hand, suppose dim ker $G = 2$, and let f be a non-constant function annihilated by G. Then the maximum principle tells us $f(0) \neq f(1)$, and so the equations $c_1 + c_2 f(0) = a$, $c_1 + c_2 f(1) = b$ can be solved for c_1, c_2. $\square$

4.3.1 Selective Monotonicity

In this section we fix a measure-valued drift Ω, and compare two GWF operators with possibly different selective pressures. We have the following intuitive property, evidence of the submartingale nature of pure-selection processes.

Theorem 4.3.5. *If u solves $G_\beta u = 0$, with $u(0) = 0, u(1) = 1$, then $u(x) \geq x$ if $\beta > 0$, and $u(x) \leq x$ if $\beta < 0$.*

Proof. Suppose $\beta > 0$. Define $h(x) = u(x) - x$. Note that the function $f(x) = x$ is annihilated by the pure drift part of the operator, so

$$G_\beta h = G_\beta u - \beta x(1-x) = -\beta x(1-x) \tag{4.3.1}$$

and $h(0) = 0, h(1) = 0$. If h is strictly negative somewhere, it has a global interior minimum somewhere, and so there is a x_0 for which $Gh(x_0) \geq 0$, which would contradict the above equation. Same proof for $\beta < 0$. $\square$

One would also like to prove the more general monotonicity property that probabilities of fixation are always increasing functions of β. This can be established under the assumption that at least one of the fixation curves is an increasing function of initial allele frequency (recall that this was not always true: but see Section 1.6.3 for the derivation of a large class of processes for which this holds).

Theorem 4.3.6. *Let $\beta_1 \geq \beta_2 \geq 0$, and $G_{\beta_1} u_1 = 0$, $G_{\beta_2} u_2 = 0$, and the boundary conditions $u(0) = 0$, $u(1) = 1$. Further suppose that u_2 is increasing. Then $u_1 \geq u_2$.*

Proof. This time if $h = u_1 - u_2$, one discovers $G_{\beta_1} h = G_{\beta_1} u_1 - \beta_1 x(1-x)u_2'(x) + \beta_2 x(1-

$x)u_2'(x) = (-\beta_1 + \beta_2)x(1-x)u_2'(x)$, which is ≤ 0. Since $h(0) = 0, h(1) = 0$, h cannot be strictly negative, by the minimum principle. $\square$

4.4 The Parabolic Equation

We shall now study the Kolmogorov backward operator connected to G:

$$L_{\beta,\Omega}u(x,t) = G_{\beta,\Omega}u(x,t) - \partial_t u(x,t) \tag{4.4.1}$$

When associated to a generator G for a time-homogeneous Markov process X_t, a function $u(x,t)$ in the null space of L satisfying $u(x,0) = f(x)$ gives the value of the probabilistic quantity $E[f(X_t)|X_0 = x]$.

We can also establish weak maximum principles for L, this time valid for all selection parameters β. As a setup, we look at functions $u(x,t)$ in the rectangle $R = \{(x,t) \in [0,1] \times [0,T]\}$, and label three of the respective sides $S_1 = [0,1] \times 0$, $S_2 = 0 \times [0,T]$, $S_3 = 1 \times [0,T]$.

Theorem 4.4.1. *(Parabolic maximum principle). Let* u *be continuous on* R*, and suppose* $Lu \geq 0$ *throughout the interior of* R*. Then*

$$\max_R u = \max_{S_1 \cup S_2 \cup S_3} u \tag{4.4.2}$$

Proof. First we prove the statement for a function satisfying the more stringent $Lu > 0$ throughout R. In this case, if u has an interior global maximum at (x_0, t_0), $\partial_t u(x_0, t_0) = 0$, and because $Gu(x_0, t_0) \leq 0$ from the 1-D maximum principle, we obtain a contradiction. If the global maximum occurs at (x_0, T), one still has $Gu(x_0, t_0) \leq 0$ which implies

$\partial_t u(x_0, t_0) < 0$, contradicting the maximality of (x_0, t_0). The conclusion then follows whenever $Lu > 0$.

Now suppose only $Lu \geq 0$ throughout R. Setting $u_\epsilon = u - \epsilon t$, we have $Lu_\epsilon > 0$ for all $\epsilon > 0$. Thus

$$\max_R u_\epsilon = \max_{S_1 \cup S_2 \cup S_3} u_\epsilon \tag{4.4.3}$$

and the statement follows by taking $\epsilon \downarrow 0$. □

The corresponding minimum principle is arrived at by using the preceding on $-u$:

Theorem 4.4.2. *(Parabolic minimum principle). Let u be continuous on R, and $Lu \leq 0$ throughout the interior of R. Then*

$$\min_R u = \min_{S_1 \cup S_2 \cup S_3} u \tag{4.4.4}$$

4.5 Aspects of Fixation Probabilities and Asymptotic Moments under Selection

We discussed in Section 1.6.2 the difficulty of using discrete methods to analyze GWF processes once non-zero selection is introduced. By virtue of the martingale property, pure-drift GWF processes all have identical probabilities of fixation. Once non-zero selection is introduced, this no longer holds, and a large and interesting spectrum of possibilities arises. The lower moments no longer satisfy systems of linear recurrence relations, and so even basic questions such as the evolution of the mean of a process were unapproachable. In this, our continuum theory has provided one important advantage over the discrete methods: it has allowed us to elegantly obtain optimal bounds for these quantities over the class of GWF processes, as a function of initial allele frequency.

4.5.1 Absorption Time

If $X_k^{(N)}$ is a pure-selection discrete GWF process, we defined a stopping time $\tau = \inf\{k : X_k \in \{0, N\}\}$, and proved that $P(\tau < \infty) = 1$ (Theorem 1.6.8). If $X_k^{(N)}$ converges to a continuum limit X_t, one can define an analagous stopping time $\tau = \inf\{t, X_t \in \{0, 1\}\}$. Unfortunately, in the continuum limit, it is *not* true that $P(\tau < \infty) = 1$; this is foretold already in the strictly super-linear growth in expected absorption time ($O(N \log N)$) for certain processes such as the minimal and maximal processes. Nevertheless, X_t has one important regularity property, which gets around this difficulty: it is a bounded submartingale if the selection pressure $\beta \geq 0$, and it is a supermartingale if $\beta \leq 0$. To see this, assume $\beta \geq 0$, and note that from the Markov property, we only need check that $E[X_t|X_0] \geq X_0$ for all X_0 and all t, and this holds because the analagous equation holds in the discrete models. The verification is complete by taking $N \to \infty$ and using weak convergence of the marginal distributions.

Bounded submartingales have limits: $X_t \to X_\infty$ almost surely. With this we can now define the stopping time $\tau = \inf\{t : X_t \in \{0, 1\}\}$ for a continuum process, with the understanding it may be infinite; X_τ is well-defined. And in keeping with the terminology of the discrete processes, we shall call $P(X_\tau = 1|X_0 = x)$ the fixation probability of a pure-selection continuum process, again with the recognition that such fixation may, with non-zero probability, take an infinite amount of time. What follows is the continuum version of Theorem 1.6.10.

Theorem 4.5.1. *Let X_t be the continuum limit of a sequence of GWF chains. If τ is the absorption time of X defined above, then for any $f \in C[0,1]$ and $f(0) = 0, f(1) = 1$, we have*

$$P(X_\tau = 1|X_0 = x) = E(f(X_\infty)|X_0 = x) = \lim_{t\to\infty} E[f(X_t)|X_0 = x] \tag{4.5.1}$$

Proof. We assume $\beta \geq 0$, a similar proof holds for β the opposite sign. The second equality is merely dominated convergence. For the first, note that X_∞ must be concentrated on $\{0,1\}$. To see this, let μ be the distribution of X_∞; it must be a stationary distribution so if G is the generator of X_t, $\int_0^1 Gu\, d\mu = 0$ for every $u \in \mathcal{D}(G)$ (see the characterization of stationary distribution in Theorem 4.6.1). For a pure selection GWF process, if $u(x) = x^2$, then $Gu = x(1-x) + 2\beta x^2(1-x)$ which is strictly positive on the interior of $[0,1]$ and vanishing at its boundaries. We deduce that μ can only be concentrated on $\{0,1\}$, and hence also for X_∞. The first equality now holds because if $\tau = \infty$, it is a tautology, and if $\tau < \infty$, $X_\infty = 1$ if and only if $X_\tau = 1$. $\square$

How is $P_x(X_\tau = 1)$ connected to $\lim_{N\to\infty} P_{[xN]}(X^{(N)}_{\tau_N} = N)$? It is quite likely they are always the same, though in fact it cannot be deduced from the uniform convergence of the semigroup over only bounded time intervals as implied by Theorem 3.4.3 (a uniform convergence over all time would be the most forceful hypothesis for the result to be true). We shall let this matter rest for the present. What remains is that indeed, just as was the case in discrete time, $\lim_{t\to\infty} E_x X_t$ is a surrogate computation that may be used in place of $P_x(X_\tau = 1)$.

We now intend to derive, with the tool of the maximum principle, effective bounds for the continuum fixation probability. Even more, the problem of finding the processes attaining these bounds can be solved. Specifically, we pose the following infinite-dimensional *extremal problem.*

Extremal Problem: Let $\pi(x) = P_x(X_\tau = 1)$ be the probability of fixation of a continuum pure-selection GWF process started at initial frequency x. For a fixed selection pressure $\beta = Ns$, what GWF drift measures Ω maximize and minimize $\pi(x)$ for all x?

This is interesting from a biological point of view, because it relates to processes which are maximal and minimal selection amplifiers. A priori, it appears doubtful that a solution could exist, demanding as it would that a single process, at once, *for all initializing frequencies*, proves to be the extremizer. And indeed, no solution can exist over certain classes of processes — for example, the set of Cannings processes, since for any two such models with respective fixation probabilities π_1 and π_2, if $\pi_1(x_0) \geq \pi_2(x_0)$ at a point x_0, symmetry demands $\pi_1(1-x_0) \leq \pi_2(1-x_0)$. Yet remarkably, a solution does exist over the space of GWF processes. We devote the remainder of this section to solving the above extremal problem.

4.5.2 Maximal and Minimal GWF Processes and the Evolution of Means

We have previously distinguished two special processes: a minimal process X_t^- associated to the family of measures $d\Omega_x(y) = \delta_0(y)$, and a maximal process X_t^+ corresponding to $d\Omega_x(y) = \delta_1(y)$. Referring to Section 3.11.3 for the form of their pure-drift generators, we can form the operators $G_\pm u : C^2 \to C^0$ with the addition of selection:

$$G_- u(x) = \beta x(1-x)u'(x) + (1-x)u'(x) + \frac{1-x}{x}(u(0) - u(x)) \tag{4.5.2}$$

$$G_+ u(x) = \beta x(1-x)u'(x) - xu'(x) + \frac{x}{1-x}(u(1) - u(x)) \tag{4.5.3}$$

Since these operators are first-order, it is simple to show that $\lambda u - G_\pm u = f$ can be solved for enough smooth functions f, and thereby $G_\pm$ satisfy the Hille-Yosida conditions and have unique extensions $\tilde{G}_\pm$ which are the generators for the minimal and maximal pure selection Feller process $X^{\beta,\pm}$.

Let us consider the evolution of the means $m_-(x,t)$ and $m_+(x,t)$ of these two processes. They are solutions to the backward equation $L^\pm_\beta u = 0$, subject to the initializing prescription $u(x,0) = x$. Using the method of characteristics, one can derive the following solutions, which are readily checked to satisfy $L^\pm_\beta m_\pm = 0$ and the condition $m_\pm(x,0) = x$.

$$m_-(x,t) = \frac{(1+\beta)x}{1 + \beta x + \beta(1-x)e^{-(1+\beta)t}} \tag{4.5.4}$$

$$m_+(x,t) = \frac{x(1 - \beta e^{-(1-\beta)t})}{1 - \beta + \beta x(1 - e^{-(1-\beta)t})} \tag{4.5.5}$$

These solutions are valid for *all* real β, with $\beta = -1$ for m_- and $\beta = 1$ for m_+ taken as the appropriate limits. It is immediate via the parabolic maximum and minimum principles of the previous section that they are the unique continuous solutions on the strip $[0,1] \times [0,\infty)$ satisfying the initial condition $m(x,0) = x$ and the boundary conditions $m(0,t) = 0, m(1,t) = 1$. As in the argument of Proposition 3.3.5, $\tilde{G}u$ vanishes at $\{0,1\}$ for every u in its domain, and thus the boundaries are absorbing states of $X^\pm$, hence $E[X^\pm_t | X^\pm_0 = x]$ is constant for all time whenever $x \in \{0,1\}$; this proves that indeed

$E[X_t^{\pm}|X_0^{\pm} = x] = m_{\pm}(x,t)$.

Some hint of the properties of these extreme processes become apparent in the time evolution of the mean: they are extreme selection amplifiers/supressors, in different directions: the minimal process reaches a singularity at $\beta = -1$, wherein the asymptotic mean $m_{\pm}(\infty)$ is zero for all interior starting frequencies x, while the maximal processes has a singularity at $\beta = 1$, for which the asymptotic mean is 1, independently of the initializing frequency. Nonetheless, the means are strictly positive and sub-unital at any *finite* time t, no matter the size of selection — a superb balance.

We now proceed to the principal result: that the functions $m_{\pm}$ optimally bound the solutions to the evolution of means over *all* generalized Wright-Fisher processes.

Theorem 4.5.2. *Let $u(x,t)$ be a continuous solution on $[0,1] \times [0,\infty)$ to $L_{\beta,\Omega}u = 0$, satisfying the boundary conditions $u(x,0) = x$, and $u(0,t) = 0, u(1,t) = 1$ for all time. Then*

$$m_-(x,t) \leq u(x,t) \leq m_+(x,t), \qquad \forall (x,t) \in [0,1] \times [0,\infty) \tag{4.5.6}$$

Proof. Fix a rectangle $R = [0,1] \times [0,T]$. For the lower bound, one need only to prove $L_\Omega m_- \geq 0$ throughout the interior of R; for then $L(u - m_-) \leq 0$ and the parabolic minimum principle tells us $u - m_- \geq 0$ due to the zero boundary conditions of $u - m_-$. So let us try: inserting the expression for m_- into the formula for L, one needs to verify, after some algebra:

$$1 - (1 + \beta e^{-(1+\beta)t}) \int_0^1 \frac{d\Omega_x(y)}{1 + \beta y + \beta e^{-(1+\beta)t} - \beta y e^{-(1+\beta)t}} \geq 0, \qquad \beta \geq 0 \tag{4.5.7}$$

$$1 - (1 + \beta e^{-(1+\beta)t}) \int_0^1 \frac{d\Omega_x(y)}{1 + \beta y + \beta e^{-(1+\beta)t} - \beta y e^{-(1+\beta)t}} \leq 0, \qquad \beta \leq 0 \tag{4.5.8}$$

By dividing into the cases $\beta \geq 0, -1 \leq \beta \leq 0, \beta \leq -1$, the two inequalities

$$\frac{1+\beta e^{-(1+\beta)t}}{1+\beta e^{-(1+\beta)t}+\beta y(1-e^{-(1+\beta)t})} \leq 1, \qquad \beta \geq 0 \tag{4.5.9}$$

$$\frac{1+\beta e^{-(1+\beta)t}}{1+\beta e^{-(1+\beta)t}+\beta y(1-e^{-(1+\beta)t})} \geq 1, \qquad \beta \leq 0 \tag{4.5.10}$$

can be readily checked on R. From this follow the equations (4.5.7), (4.5.8) since $d\Omega_x$ is a probability measure for each $0 < x < 1$. One proves the upper bound in similar fashion, via the maximum principle and verifying $L_\Omega m_+ \leq 0$. $\square$

The preceding theorem is significantly stronger than that sought by the extremal problem, since it shows that the minimal and maximal processes have respectively the smallest and largest means amongst all GWF processes, for *all* time. By letting time tend to infinity, we can calculate the fixation probabilities of the extreme processes as:

$$p_-(x) = \lim_{t\to\infty} m_-(x,t) = \begin{cases} \frac{(1+\beta)x}{1+\beta x}, & \beta > -1 \\ \\ 1 - 1_{[0,1)}(x), & \beta \leq -1 \end{cases} \tag{4.5.11}$$

$$p_+(x) = \lim_{t\to\infty} m_+(x,t) = \begin{cases} \frac{x}{1-\beta(1-x)}, & \beta < 1 \\ \\ 1_{(0,1]}(x), & \beta \geq 1 \end{cases} \tag{4.5.12}$$

The probabilistic version of the foregoing analytic result is

Corollary 4.5.3. *Let X_t be the continuum limit of a sequence of pure-selection GWF chains. Let τ be the absorption time of X_t as defined above. Then*

$$m_-(x,t) \leq E[X_t|X_0 = x] \leq m_+(x,t), \quad (x,t) \in [0,1] \times [0,\infty) \tag{4.5.13}$$

$$p_-(x) \leq P(X_\tau = 1|X_0 = x) \leq p_+(x), \quad 0 \leq x \leq 1 \tag{4.5.14}$$

Proof. Because X_t must have absorbing boundaries, $u(x,t) = E[X_t|X_0 = x]$ satisfies all the hypotheses of Theorem 4.5.2, and so the first part follows. For the second, take $t \to \infty$ and apply Theorem 4.5.1. $\square$

The second part of the above theorem effectively solves the extremal problem posed above: it demonstrates that the minimal and maximal processes have respectively the minimum ad maximum probabilities of fixation for a given selection pressure, uniformly across all initializing frequencies x.

The first part of Theorem 4.5.3 can now be related back to the discrete GWF processes in the following theorem, which provide optimal asymptotic bounds for the mean of a pure-selection GWF process, from the weak convergence of the discrete models:

Theorem 4.5.4. *Let $X_k^{(N)}$ be a sequence of discrete pure-selection GWF chains with continuum limit X_t. Then For any fixed $t > 0$, and initial frequency $0 \leq x \leq 1$,*

$$m_-(t,x) \leq \lim_{N\to\infty} E(X_{[tN]}|X_0 = [xN]) \leq m_+(t,x) \tag{4.5.15}$$

4.5.3 Probability of Fixation for Example Processes

We will now use our continuum theory to obtain more precise results for fixation probabilities of our non-standard example processes, results which cannot be approached with discrete methods.

In the preceding section, the evolution of the mean of the minimal and maximal process was employed to obtain universal bounds on the asymptotic probability of fixation of a sequence of converging discrete GWF processes. Instead of the mean function $f(x) = x$, we could have employed any other reasonably continuous function fixing the boundaries, because of the identification in Theorem 4.5.1. This fact allows us to prove the following highly pertinent theorem:

Theorem 4.5.5. *Suppose* X_t *is the continuum limit of a sequence of pure selection GWF chains, whose generator is* G*. Suppose that* $f_1, f_2 \in \mathcal{D}(G)$*,* f_1, f_2 *have* $\{0,1\}$ *as fixed points and* $Gf_1 \geq 0, Gf_2 \leq 0$*. Let* τ *be the absorption time of* X_t*. Then for all* $0 \leq x \leq 1$*,*

$$f_1(x) \leq P(X_\tau | X_0 = x) \leq f_2(x) \tag{4.5.16}$$

In particular, if $Gf = 0$*,* $f(x)$ *is the probability of fixation started at frequency* x*.*

Proof. We prove the lower bound; the upper bound is established in the same way. We know that $u(x,t) = E_x f_1(X_t)$ solves the backward equation $Lu = Gu - \partial u_t = 0$, with initial condition $u(x,0) = f_1(x)$. Define $v(x,t) = f_1(x)$ for all time, then $L(v-u) \geq 0$; since $v - u$ vanishes on the parabolic boundary, the parabolic maximum principle gives $v \leq u$ on $(x,t) \in [0,1] \times [0,\infty)$. Take $t \to \infty$, and we obtain $v(x) \leq E_x f_1(X_\infty)$. The proof is finished by applying Theorem 4.5.1, which identifies $E_x f_1(X_\infty)$ with the probability of fixation. □

We now apply this to several of our example models.

Wright-Fisher Model

This model is classical, and so the probability of fixation is known. We list it here for comparison with our other models:

Theorem 4.5.6. *(Ethier-Kimura) If* X_t *is the Kimura diffusion model with selection* *pressure β, and τ its absorption time, then*

$$P_x(X_\tau = 1) = \frac{1 - e^{-2\beta x}}{1 - e^{-2\beta}}, \tag{4.5.17}$$

Probability of Fixation for Extreme Processes

We have already proved the theorem which follows, but we state it here formally and use the method of proof outlined above, which does not require us to compute the entire trajectory of the mean.

Theorem 4.5.7. *Let $X_t^\pm$ be the continuum maximal and minimal processes undergoing selection pressure β, and $\tau^\pm$ the respective absorption times. Then:*

$$P(X_{\tau^-}^- = 1) = p_-(x) = \frac{(1+\beta)x}{1+\beta x}, \quad \beta > -1 \tag{4.5.18}$$

$$P(X_{\tau^+}^+ = 1) = p_+(x) = \frac{x}{1-\beta(1-x)}, \quad \beta < 1 \tag{4.5.19}$$

Proof. The functions p_-, p_+ are in C^2, and so clearly are in the domain of the generators $G_\pm$ given by the formulae (4.5.2), (4.5.3). It is then easily checked that $G_\pm p_\pm = 0$ and all the hypotheses of Theorem 4.5.5 are satisfied. $\square$

Attention should be drawn to a very striking effect revealed in the above theorem. In the Maximal process, $p_+(x) \to 1$ as $\beta \uparrow 1$, and thus *probability one fixation* occurs in this model for a *finite* limiting value of β . To compare, (4.5.17) indicates that the probability of fixation for the Wright-Fisher model is always strictly less than one, for all $\beta < \infty$. The Maximal process may thus be viewed as a very strong *selection amplifier* for $\beta > 0$ and as a suppressor of negative selection for $\beta < 0$.

Λ_1-Cannings Model with Selection

Let $X_k^{(N)}$ be a sequence of Λ_1-Cannings models with selection. We consider the GWF operator $G : C^2 \to C[0,1]$ defined by

$$Gu(x) = \beta x(1-x)u'(x) + (1-x)u(0) - u(x) + xu(1) \tag{4.5.20}$$

Let G_S be the semigroup associated with only the selection portion of the operator $G_S u(x) = \beta x(1-x)u'(x)$. By Feller's boundary classification, G_S generates a C^0 contraction semigroup whose domain consists of functions continuously differentiable on the open interval $(0,1)$ (but not necessarily bounded), and for which $\lim_{x\downarrow 0} G_S u(x) = \lim_{x\uparrow 1} G_S u(x) = 0$. Since the neutral part of G is a bounded operator, by the Hille-Phillips perturbation Theorem 3.10.4, G generates a C^0 semigroup with domain equal to that of G_S.

Now we investigate solutions of $Gu(x) = 0$, subject to $u(0) = 0$, $u(1) = 1$. Since it is merely a first-order differential equation, this is easy, and its unique solution is

$$u(x) = \frac{1}{\beta}\left(\frac{x}{1-x}\right)^{1/\beta} \int_x^1 y^{-1/\beta}(1-y)^{1/\beta-1}\,dy \tag{4.5.21}$$

The function u is clearly in the domain of G, and thus we have, by Theorem 4.5.5,

Theorem 4.5.8. *Let X_t be the continuum Λ_1 Cannings model with selection pressure β, and τ the absorption time. Then*

$$P(X_\tau = 1) = \frac{1}{\beta}\left(\frac{x}{1-x}\right)^{1/\beta} \int_x^1 y^{-1/\beta}(1-y)^{1/\beta-1}\,dy \tag{4.5.22}$$

It is interesting to note that $u'(0)$ can be significantly larger than the corresponding quantity in the Wright-Fisher model (in fact it diverges for β large), which names this model a relative selection amplifier, for small initializing frequencies. But unlike the Maximal process, no finite value of β can obtain almost sure fixation.

Fixation Probabilities for Power-law Models with Selection, $0 < \alpha < 1$

We saw that the Maximal process possessed the astonishing property of almost sure fixation of paths whenever $\beta > \beta^*$, where β^* was a finite selective pressure (there $\beta^* = 1$). It turns out that the much less pathological power-law processes also possess this property for a certain range of α, but to see this will require an analysis of much greater difficulty. To begin, recall that the pure-drift generator for $\alpha < 2$ took on the form of Theorem 3.11.4:

$$G_\alpha u(x) = \frac{1}{\alpha - 1}\left[u(x) - xu(1) - (1-x)u(0)\right] - \frac{x(1-x)}{x^{2-\alpha}} \int_0^x \frac{(x-z)^{1-\alpha}}{\alpha - 1} u'(z)\, dz \tag{4.5.23}$$

$$+ \frac{x(1-x)}{(1-x)^{2-\alpha}} \int_x^1 \frac{(z-x)^{1-\alpha}}{\alpha - 1} u'(z)\, dz \tag{4.5.24}$$

When $0 < \alpha < 1$, an even more useful alternative form is available:

Proposition 4.5.9. *For parameters* $0 < \alpha < 1$*, one has the equivalent formula for* $u \in C^1[0,1]$*:*

$$G_\alpha u(x) = \frac{3-\alpha}{1-\alpha}\Big(- u(x) + (1-\alpha)x^{\alpha-1}(1-x) \int_0^x (x-z)^{-\alpha} u(z)\, dz \tag{4.5.25}$$

$$+ (1-\alpha)x(1-x)^{\alpha-1} \int_x^1 (z-x)^{-\alpha} u(z)\, dz \Big) \tag{4.5.26}$$

Proof. Simply integrate by parts, as in the proof of Theorem 3.11.4. □

We can use the above form to see that G_α can be defined as a bounded operator on all of C^0. As in the discussion of the Λ_1 model, the Hille-Phillips perturbation theorem shows that that $G_{\beta,\alpha}u = \beta x(1-x)u'(x) + G_\alpha u$ defined on $\mathcal{D}(G_S)$ is the generator for a C^0 semigroup, and $\mathcal{D}(G_S)$ contains functions u continuously differentiable on the interior of the interval with $G_S u$ vanishing at the endpoints.

Now we study solutions to

$$G_{\beta,\alpha}u = 0, \qquad u(0) = 0, u(1) = 1 \tag{4.5.27}$$

or equivalently, after a simple scaling:

$$Lu = kx(1-x)u' - u(x) + (1-\alpha)x^{\alpha-1}(1-x)\int_0^x (x-z)^{-\alpha}u(z)\,dz \tag{4.5.28}$$

$$+ (1-\alpha)x(1-x)^{\alpha-1}\int_x^1 (z-x)^{-\alpha}u(z)\,dz = 0 \tag{4.5.29}$$

with $k = \beta\frac{1-\alpha}{3-\alpha}$.

The complicated nature of the integro-differential equation which is involved with L makes it unlikely that any closed-form solution exists; nevertheless we can obtain significant understanding of the properties of its solutions as a function of the selective pressure by applying the maximum principle, which L satisfies.

It is important to first analyze the auxiliary operator defined by

$$L_0 u = kxu' - u + (1-\alpha)x^{\alpha-1}\int_0^x \frac{u(z)}{(x-z)^\alpha}\,dz \tag{4.5.30}$$

As $x \downarrow 0$, all the terms have homogeneous order. This suggests inserting expressions of the form x^p: and indeed L_0 has a large number of eigenfunctions of that form. By considering $u(x) = x^p$, and applying the change of variables $t = z/x$, one finds

$$L_0 x^p = kpx^p - x^p + (1-\alpha)x^p\int_0^1 \frac{t^p}{(1-t)^\alpha}\,dt \tag{4.5.31}$$

One therefore sees that $u(x) = x^p$ for $p > -1$ is an eigenvector of L_0 associated to the eigenvalue $\lambda_p = kp - 1 + (1-\alpha)B(p+1, 1-\alpha)$, with $B(\cdot,\cdot)$ the Beta-function.

Since we expect the operator L_0 to mimic that of L near $x = 0$, we examine the critical points in the spectrum. Define

$$S(p) = \beta\frac{1-\alpha}{3-\alpha}p - 1 + (1-\alpha)\int_0^1 t^p(1-t)^{-\alpha}\,dt \tag{4.5.32}$$

for values $p > -1$, $0 < \alpha < 1$, $\beta > 0$. As $p \downarrow -1$, the integral term diverges, and $S(-1) = \infty$. When $p \to \infty$, the first term becomes large, so $S(\infty) = -\infty$. We also have $S(0) = 0$. The derivative is

$$S'(p) = \beta\frac{1-\alpha}{3-\alpha} + (1-\alpha)\int_0^1 t^p \log t(1-t)^{-\alpha}dt \tag{4.5.33}$$

The integral term is strictly monotonic in p, so $S'(p)$ is strictly monotonic increasing, with $S'(-1) = -\infty$ and $S'(\infty) = \beta\frac{1-\alpha}{3-\alpha} > 0$, so there is a unique value where $S'(p^*) = 0$. We conclude that S has at most one other root p_r besides $p = 0$, and the shape of the graph of S is convex. Examining the equation $S'(p^*) = 0$, one sees that the two terms are of opposite sign. If β is small, p^* must be very large, and if β is large, p^* decreases. Indeed, it is clear that as $\beta \to \infty$, $p^* \downarrow -1$, which implies that the other root p_r tends to -1 as $\beta \to \infty$. We also have the other statement, if $\beta \downarrow 0$, $p^* \to \infty$, and so the other root $p_r \to \infty$ as well.

It then follows from monotonicity that there is a single value of β for which one has $p_r = 0$ exactly; and from all of the foregoing this occurs exactly when $p^* = p_r = 0$. Thus the double-root manifests when $S'(0) = 0$, or

$$\beta\frac{1-\alpha}{3-\alpha} + (1-\alpha)\int_0^1 \log t(1-t)^{-\alpha}dt = 0 \tag{4.5.34}$$

or equivalently

$$\beta^* = -(3-\alpha)\int_0^1 (1-t)^{-\alpha}\log t\,dt \tag{4.5.35}$$

It will also be useful to identify the selective value when first $p_r = 1$. Solving the equation $S(1) = 0$ gives

$$\beta^{**} = \frac{3-\alpha}{2-\alpha} \tag{4.5.36}$$

The preceding analysis is summarised in

Theorem 4.5.10. *Let $S_\beta(p)$ be defined by (4.5.32). Then there is a unique non-trivial root $p(\beta)$ to $S_\beta(p) = 0$; $p(\beta)$ is monotonically decreasing, and descends from infinity to 1 as β increases from 0 to β^{**}, and descends to zero as β further increases to β^*, where β^* and β^{**} are given by (4.5.35)and (4.5.36).*

Next, note that the operator L can be written as

$$Lu = L_0u - x(L_0u + u) + (1-\alpha)x(1-x)^{\alpha-1}\int_x^1 (z-x)^{-\alpha}u(z)dz \tag{4.5.37}$$

Theorem 4.5.11. *Let p be the non-trivial root of $kp - 1 + (1-\alpha)B(p+1, 1-\alpha) = 0$, where $k = \beta\frac{1-\alpha}{3-\alpha}$. Setting $u(x) = x^p$, one has $Lu \geq 0$.*

Proof. For any $\rho > 0$, setting $u(x) = x^\rho$ gives

$$Lx^\rho = \lambda_\rho x^\rho(1-x) - x^{\rho+1} + (1-\alpha)x(1-x)^{\alpha-1}\int_x^1 (z-x)^{-\alpha}z^\rho dz \tag{4.5.38}$$

In particular, choose $\rho = p$ such that $\lambda_p = 0$, then

$$Lx^\rho = -x^{p+1} + (1-\alpha)x(1-x)^{\alpha-1}\int_x^1 (z-x)^{-\alpha}z^p dz \tag{4.5.39}$$

The above is clearly larger than zero everywhere, by using the simple bound $z \geq x$ in the integral. □

Our next theorem gives an upper bound.

Theorem 4.5.12. *Let p be the non-trivial root of $kp - 1 + (1-\alpha)Beta(p+1, 1-\alpha) = 0$, with $k = \beta\frac{1-\alpha}{3-\alpha}$. Then there exists a $\rho < p$ and a $C > 1$ such that $u(x) = Cx^\rho + (1-C)x$ satisfies $Lu(x) \leq 0$.*

Proof. We consider the function $u(x) = Cx^\rho + (1-C)x$, which satisfies the desired boundary conditions. Since the neutral part of L annihilates linear functions,

$$L(Cx^\rho + (1-C)x) = C[\lambda_\rho x^\rho(1-x) - x^{\rho+1} + (1-\alpha)x(1-x)^{\alpha-1}\int_x^1 (z-x)^{-\alpha}z^\rho dz] \\ + (1-C)kx(1-x) \tag{4.5.40}$$

We wish to make the above expression negative. Now consider ρ in the range $0 < \rho < p^*$, where p^* makes $\lambda_{p^*} = 0$. For these values, $\lambda_\rho < 0$. The first term is negative then: let us not worry about it. By bounding the integral term by x, we are led to consider

$$C[-x^{\rho+1} + x] + (1-C)kx(1-x) \tag{4.5.41}$$

This formula vanishes at the endpoints. Its derivative is

$$C[-(\rho+1)x^\rho + 1] + (1-C)k(1-2x) \tag{4.5.42}$$

Fixing an x_1 near zero, we see that for all sufficiently large $C > C_0$ and $\rho < \rho_0$ near to zero, the derivative is strictly negative, uniformly for all $x < x_1$. Thus the above expression is negative on $[0, x_1]$. If we fix an x_2 near to 1, then for large $C > C_1$ and all $\rho < \rho_1$ the derivative is positive on $[x_2, 1]$, and hence again the function is negative there. It remains to be seen it is negative on $[x_1, x_2]$. But this is clear from the original expression (4.5.41), as $-x^{\rho+1} + x$ converges uniformly to zero on $[x_1, x_2]$ as $\rho \downarrow 0$, and by making C very large the value becomes negative. This establishes the result. □

Since the functions involved in Theorems 4.5.11 and 4.5.12 are in the domain of $\mathcal{D}(G_S) = \mathcal{D}(G_\alpha)$, and satisfy the $\{0,1\}$ fixed point condition, we can apply Theorem 4.5.5 to obtain

Theorem 4.5.13. *Let $X_t^{(\alpha)}$ be the continuum α-process undergoing selection pressure β, and τ_α its absorption time, $0 < \alpha < 1$. Let ρ be the positive root of the equation $\beta \frac{1-\alpha}{3-\alpha}\rho - 1 + (1-\alpha)B(\rho+1, 1-\alpha) = 0$, with selective pressure $0 < \beta < \beta^*$, where β^* is given by (4.5.35). Then there exist constants $C > 0, 0 < r < \rho$, such that*

$$x^\rho \leq P(X_{\tau^\alpha}^{(\alpha)} = 1 | X_0^{(\alpha)} = x) \leq Cx^r + (1-C)x \tag{4.5.43}$$

Theorem 4.5.13 reveals the *precise* selective pressure which ensures almost sure fixation, for every positive initializing frequency. The lower bound indicates this singularity must occur, at the very least for the finite value $\beta = \beta^*$. On the other hand, the upper bound indicates that the probability of fixation curve is strictly sub-unital in a neighborhood of zero whenever $\beta < \beta^*$. Therefore $\beta^* = -(3-\alpha)\int_0^1 (1-t)^{-\alpha} \log t \, dt$ is indeed the critical value of selection upon which almost sure fixation turns.

Equation (4.5.35) was derived under the assumption that $0 < \alpha < 1$, but the formula on the right-hand side has an analytic extension to α in the range $0 < \alpha < 2$. It appears likely this formula correctly predicts the critical value of β under which almost-sure fixation occurs in the power-law models, even in the range $1 < \alpha < 2$.

Further Comments on Fixation Probabilities

The preceding results are rich in insights into what is and is not possible in the space of generalized processes, and the location of the Wright-Fisher process itself within the generalized class.

The extreme values indicated in (4.5.18,4.5.19) are those that are achieved by the maximal and minimal processes, but we have seen that the power-law processes, $0 < \alpha < 1$ exhibit much the same characteristics. Namely, in each case, there exists a finite value of selection pressure β^* leading to almost sure fixation of all paths, regardless of initial frequency. In the Maximal process, this occurred at $\beta^* = 1$, in the power-law processes, this value starts at $\beta^* = 3$ for $\alpha = 0$, and increases as α increases. Our solution to the extremal problem also proved a sort of converse: namely that if $\beta < 1$, then almost sure fixation is impossible in *any* model.

We can also observe that as $\beta \to \infty$, $p_-(x) \to 1$, and hence every process fixates almost surely in the limit of $\beta \to \infty$: this has the interpretation that no ultimate GWF selection-suppressors exist.

More heuristically, we can use Theorem 4.5.3 to obtain a rough estimate of probabilities of fixation of single mutants by inserting the initializing "frequency" $x = 1/N$. This gives:

$$s \leq P(\text{fixation}|X_0 = 1/N) \leq 1 \tag{4.5.44}$$

It is instructive to compare these bounds to the actual achievements of the Wright-Fisher process. There:

$$P_{\text{WF}}(\text{fixation}|X_0 = 1/N) = 2s, \qquad s > 0 \tag{4.5.45}$$

In population biology, s is quite small, and hence the Wright-Fisher model is seen to lie very near the absolute lower bound across all GWF processes. This is commensurate with the intuitive belief that the Wright-Fisher process has the "strongest drift" out of all processes, and is in fact a very strong selection depressor. To contrast, the Λ_1-Cannings model has a much larger fixation probability for new mutants.

4.6 Aspects of the Stationary Distribution

In this section we consider the continuum limits of pure-mutation processes where both mutation rates are strictly positive, and analyze aspects of the resulting stationary distributions.

Let $X_k^{(N)}$ be a sequence of GWF chains with mutation parameters $\theta_1, \theta_2 > 0$, and arbitrary selection, as defined in Section 1.6. According to Theorem 1.6.2, there exists a unique stationary distribution μ_N for $X^{(N)}$. If $X^{(N)}$ has continuum limit X_t, one might suppose that μ_N would converge in distribution to a stationary measure μ of X_t. This need not be true in the most general case, but we will work towards a proof of the statement for a certain class of GWF processes.

To begin, the following standard characterization of stationary distributions is very useful:

Theorem 4.6.1. *(c.f. [12]). The probability measure μ is a stationary distribution for the process associated to a C^0 semigroup T_t with generator G if and only if either of the following equivalent conditions is satisfied:*

1. $\int T_t f d\mu = \int f d\mu, \quad f \in C^0, t \geq 0$

2. $\int G f d\mu = 0, \quad f \in \mathcal{D}(G)$

Let us first tackle the question of the existence of stationary distributions for the continuum limit.

Theorem 4.6.2. *Suppose $X_k^{(N)}$ is a sequence of GWF chains with strictly positive mutation parameters $\theta_1, \theta_2 > 0$, and arbitrary selection. Further suppose that $X^{(N)}$ has a continuum limit X. Then there exists a stationary measure μ for X.*

Proof. Let μ_N be the sequence of stationary measures for $X^{(N)}/N$, associated to the transition matrices $\mathbf{P}^{(N)}$, by Theorem 1.6.2. The sequence of μ_N are tight, and let μ be any weak limit point, so that $\mu_{N_k} \to \mu$. Then for each continuous f:

$$\begin{aligned}
\int_0^1 T_t f d\mu &= \lim_{N_k \to \infty} \int_0^1 T_t f d\mu_{N_k} && (4.6.1)\\
&= \lim_{N_k \to \infty} \int_0^1 \mathbf{P}^{[N_k t]}(\pi_{N_k} f) d\mu_{N_k} && (4.6.2)\\
&= \lim_{N_k \to \infty} \int_0^1 \pi_{N_k}(f) d\mu_{N_k} && (4.6.3)\\
&= \int_0^1 f d\mu && (4.6.4)
\end{aligned}$$

where the second line follows from the definition of convergence to the continuum limit. Hence μ is a stationary distribution for X from Theorem 4.6.1. □

We have learnt that the continuum limit always has a stationary distribution. When is it unique? Our study of this question is restricted to the special case of Cannings processes.

Theorem 4.6.3. *Let $X^{(N)}$ be a sequence of convergent Cannings chains normalised to the unit interval, with a continuum limit X, generated by G. Then $Gx^n = \sum_{j=0}^{n} -a_{jn} x^j$, where $a_{n,n} > 0$, for all $n \geq 2$.*

Proof. The reader is referred to the proof of Theorem 3.9.2 for the basic setup. We have the strong limit $Gu = \lim_{N\to\infty} N(\mathbf{P}^{(N)} - I)\pi_N u$. If $u(x) = x^j$, it is easily verified that

$$(\mathbf{P}^{(N)}\pi_N u)(i) = (i^{[j]}/N^j)E(y_1 \cdots y_j) + \text{terms in } (i/N)^{j-1}, (i/N)^{j-2} \tag{4.6.5}$$

where $i^{[j]} = i(i-1)\cdots(i-j+1)$, and $y_j = \nu_j/N$ are the normalised exchangeable variables. Note that $E(y_1 \cdots y_j) < 1$: specifically $E(y_1 \cdots y_j) = 1 - c/N + O(N^2)$, where $c > 0$, so we can deduce that $\lim_{N\to\infty} N(\mathbf{P}^{(N)} - I)\pi_N u = p(x)$, where $p(x)$ is a polynomial of degree j and the coefficient in front of the highest power is strictly negative. □

The Cannings processes are not the only process to satisfy this constraint — in fact every single one of our example polynomial generators has this property. For them, we can obtain the following theorem on the stationary distribution, which is stated for Cannings processes, but obviously generalises to any process satisfying the conclusion of the foregoing Theorem.

Theorem 4.6.4. *Let X be a Cannings continuum limit with mutation rates $\theta_1, \theta_2 > 0$, and zero selection. Then X has a unique stationary distribution μ, and denoting the j-th moments of μ by $m_1, m_2, \ldots, m_j$, they have the form*

$$m_1(\theta_1, \theta_2) = \frac{\theta_2}{\theta_1 + \theta_2} \tag{4.6.6}$$

$$m_2(\theta_1, \theta_2) = \frac{(1 + \theta_2)\theta_2}{(1 + \theta_1 + \theta_2)(\theta_1 + \theta_2)} \tag{4.6.7}$$

$$\vdots \tag{4.6.8}$$

$$m_k(\theta_1, \theta_2) = \frac{\sum_{j=0}^{k-1} b_{jk} m_j(\theta_1, \theta_2)}{c_k + k(\theta_1 + \theta_2)} \tag{4.6.9}$$

where $c_k > 0$ for all $k \geq 3$, and b_{jk} are some constants, and $m_0 = 1$.

Proof. Write $Gu(x) = \frac{1}{2}(-\theta_1 x + \theta_2(1-x))u'(x) + G_\Omega u(x)$, where G_Ω is the pure-drift part of the generator. We have that $Gx = 0$, $Gx^2 = x(1-x)$, and more generally that Gx^k is a polynomial with negative leading coefficient for $k \geq 2$. Then the relation

$$\int_0^1 \left[\frac{1}{2}(-\theta_1 x + \theta_2(1-x))kx^{k-1} + Gx^k\right] d\mu = 0 \tag{4.6.10}$$

holds for every $m \geq 1$. If $Gx^k = \sum_{j=0}^{k} -a_{j,k}x^j$, collecting terms, one derives:

$$-(a_{k,k} + \frac{1}{2}(\theta_1 + \theta_2))m_k + \frac{k}{2}\theta_2 m_{k-1} - \sum_{j=0}^{k-1} a_{j,k-1}m_j = 0 \tag{4.6.11}$$

which is a recursive equation that can be solved for m_k whenever $k \geq 2$, since $\theta_1, \theta_2 > 0$ and $a_{k,k} \geq 0$ for all k and equal to zero only when for $k = 1$. Since all the moments of μ are uniquely specified by this recurrence relation, and since a bounded random variable is uniquely determined from knowledge of its moments, μ is unique. □

Finally, we terminate this section by proving a convergence theorem for the stationary distributions.

Theorem 4.6.5. *Let $X^{(N)}$ be Cannings chains with continuum limit X, with fixed mutation rates θ_1, θ_2, and zero selection. Let μ_N be the unique stationary distribution for each $X^{(N)}$, and let μ be the unique stationary distribution for X. Then μ_N converges weakly to μ.*

Proof. The μ_N are relatively compact; the proof of Theorem 4.6.2 shows that any weak limit point of μ_N is a stationary distribution of X, but this limit point is uniquely characterized by Theorem 4.6.4, and so every weakly convergent subsequence of μ_N converges to μ. □

4.7 Statistical Properties of the Stationary Distribution

4.7.1 Inference and Identifiability from Equilibrium

In our theory of GWF processes, each continuum population model was parameterized by three objects: 1) a measure-valued function Ω on $[0,1]$ (random drift), 2) a selection pressure β, and 3) mutation rates θ_1, θ_2. Biologists have long used Kimura's model, in the special case $\Omega_x = \delta_x$, to infer from physical data the values of selection and mutation rates. Typically the field biologist does not have access to a collection of sample paths from the process; rather, only samples from population frequencies ostensibly assumed to be at equilibrium are accessible. These samples come in the form of population frequencies collected from sites in the genome, all assumed to be evolving under independent Wright-Fisher processes undergoing the same selection, mutation rates and drift patterns. From this coarse-grained histogram of the stationary distribution, inference of $\beta, \theta_1, \theta_2$ can be performed in the standard (e.g. maximum-likelihood) manner.

In the GWF framework, the introduction of a general drift variable Ω raises a number of interesting and complex questions, since the stationary distribution μ now depends on an infinite-dimensional parameter. Perhaps the most basic question is identifiability: what aspects of the process can be inferred from the stationary distribution of a GWF process alone?

The first illusion to be shattered is this: Ω cannot be identified from the equilibrium in general. For a counterexample, consider the continuum Λ_1-process with mutation parameters $\theta_1 = \theta_2 = \theta$.

Proposition 4.7.1. *The stationary distribution μ for the Λ_1-process undergoing symmet-*

ric mutation has density

$$\frac{d\mu}{dx} = \frac{1}{\theta}|1-2x|^{\frac{1-\theta}{\theta}} \tag{4.7.1}$$

Proof. The generator for the process is $Gu = \frac{1}{2}\theta(1-2x)u'(x) + (1-x)u(0) - u(x) + xu(1)$, and $C^2[0,1]$ is a core for G. Noting that the density $d\mu/dx$ satisfies the equation $-d/dx(\frac{\theta}{2}(1-2x)d\mu/dx) - d\mu/dx = 0$ and integrating by parts, it can be readily verified that $\int_0^1 Gu\, d\mu = 0$ for every $u \in C^2$. Thus μ is the stationary distribution for the process, by the uniqueness of Theorem 4.6.4. □

For comparison, the Kimura diffusion possesses a Dirichlet-type equilibrium measure:

$$\frac{d\mu_{WF}}{dx} = \frac{\Gamma(2\theta)}{(\Gamma(\theta))^2}x^{\theta-1}(1-x)^{\theta-1} \tag{4.7.2}$$

We observe that at $\theta = 1$, both measures (4.7.1) and (4.7.2) coincide at the uniform distribution — this despite the enormous difference between their drift measures Ω! Hence the map from Ω to the stationary distribution is not injective, and therefore Ω is not identifiable.

This has disappointing consequences for the biologist: Ω captures information concerning stochastic aspects of offspring production, and it is perhaps surprising that there are situations in which even markedly contrasting offspring distributions cannot be distinguished in equilibrium (they can, of course, be distinguished from sample path data).

If we cannot hope to identify Ω from the stationary measure, is it nonetheless possible to estimate θ_1, θ_2 from equilibrium? This is a semiparametric problem: one regards the infinite-dimensional parameter Ω as a nuisance object. Remarkably, and with a quite simple proof, this turns out to be well-posed.

Theorem 4.7.2. *(Identifiability of mutation parameters) Let* $(\theta_1^1, \theta_2^1, \Omega^1)$ *and* $(\theta_1^2, \theta_2^2, \Omega^2)$ *be given parameters for two continuum Cannings processes, and let* μ^1, μ^2 *be the unique stationary measures for* G^1 *and* G^2*. If* $(\theta_1^1, \theta_2^1) \neq (\theta_1^2, \theta_2^2)$*, then* $\mu_1 \neq \mu_2$*, irrespective of* Ω^1 *and* Ω^2*.*

Proof. According to Theorem 4.6.4, independently of Ω^i, the first two moments of the stationary distributions μ_1, μ_2 are given by

$$m_1(\theta_1, \theta_2) = \frac{\theta_2}{\theta_1 + \theta_2} \tag{4.7.3}$$

$$m_2(\theta_1, \theta_2) = \frac{(1 + \theta_2)\theta_2}{(1 + \theta_1 + \theta_2)(\theta_1 + \theta_2)} \tag{4.7.4}$$

and it is straightforward to verify that the map $(\theta_1, \theta_2) \mapsto (m_1, m_2)$ is injective whenever $\theta_1, \theta_2 > 0$. □

Remark: The above remains true for all GWF processes admitting unique stationary measures, not merely those of Cannings type. Theorem 4.7.2 actually suggests a consistent estimator for (θ_1, θ_2), namely the inverse map $(m_1, m_2) \mapsto (\theta_1, \theta_2)$ of the first two sample moments.

4.7.2 The Sampled Frequency Spectrum

In practice, biologists do not actually have access to samples from the continuum stationary distribution, but rather only a coarsened version of it. This histogram is called the "sampled frequency spectrum" and we now describe one version of it.

We have a population of very large size N, modeled as a continuum pure mutation Cannings process X_t which records the fraction of individuals of a particular type A at time t. We assume symmetric mutation rates $\theta = \theta_1 = \theta_2$. Let μ_θ be the stationary distribution for this process. Suppose we sample n individuals from the population at equilibrium, assuming $n \ll N$, and let Y be the number of individuals in the sample of type A. Then

$$p_j = P(Y = j) = \int_0^1 \binom{n}{j} x^j (1-x)^{n-j} \, d\mu_\theta(x), \quad 0 \leq j \leq n \tag{4.7.5}$$

Observe that this probability function incorporates explicitly higher moments of heterozygosity related to the stationary distribution. Now presume that there exist L "sites" along the genome for which the above population process occurs, identically and independently, and with associated random variables $Y_1, \ldots, Y_L$ representing the number of individuals at site i with a particular binary choice of allele. The distribution for Y has the form

$$P(Y_1 = y_1, \ldots, Y_L = y_L) = \prod_{i=1}^{L} \int_0^1 \binom{n}{y_i} x^{y_i} (1-x)^{n-y_i} \, d\mu_\theta(x) \tag{4.7.6}$$

An associated vector of random variables, derived from Y_i, may be defined as

$$Z_k = \sum_{i=1}^{L} 1_{Y_i = k}, \quad k = 0, \ldots, n \tag{4.7.7}$$

The variables Z_k record the number of sites with precisely k (out of n) individuals of a given type, and hence represents a sampled version of the stationary distribution μ. Since $\sum_{k=0}^{n} Z_k = L$, the probability function for $(Z_0, \ldots, Z_n)$ is defined on a discrete simplex. It is easy to see that the Z_k have the form of the multinomial distribution with parameters $(L, p_0, \ldots, p_n)$. The vector $(Z_0, \ldots, Z_n)$ is called the *sampled frequency spectrum*, the sites

$Z_1, \ldots, Z_{n-1}$ are called the *segregating sites*, since they represent sites where there is an observed diversity in type; Z_0, Z_n are called *monomorphic* sites for equally clear reasons.

4.7.3 The Finite Sites Poisson Random Field Model

There is a limiting approximation for the segregating site variables $Z_1, \ldots, Z_{n-1}$ known, as the *Poisson Random Field*, or PRF model. It is the model derived in the limit of infinite sites $L \to \infty$, and under the assumption that the "global mutation rate" $\Theta = L\theta$ converges, as given by the following classic result (c.f. [20]):

Theorem 4.7.3. *(PRF Approximation). Assume that a Wright-Fisher process occurs at each of the sites, and hence* μ *is the equilibrium measure given by (4.7.2). If* $L\theta \to \Theta < \infty$*, as* $L \to \infty$*, then the segregating site variables* $(Z_1, \ldots, Z_{n-1})$ *converge to a sequence of independent Poisson random variables with means* $\frac{\Theta}{2}\frac{n}{j(n-j)}$ *for* $j = 1, \ldots, n-1$*.*

We now will present a large generalization of the preceding theorem, which shows that the PRF model holds with significantly wider scope. It makes use of the structure of the moments of the stationary distribution as found in Theorem 4.6.4. First we require a preliminary lemma.

Lemma 4.7.4. *Let* μ_θ *be the stationary distribution of a Cannings process undergoing symmetric mutation* θ*. Then there exist constants* $c_j \geq 0$*, for* $1 \leq j \leq n-1$*,*

$$p_j(\theta) = \int_0^1 \binom{n}{j} x^j (1-x)^{n-j} \, d\mu_\theta(x) = c_j\theta + o(\theta), \quad \theta \downarrow 0 \tag{4.7.8}$$

Proof. The lemma is equivalent to saying $p_j(0) = 0$ and p_j has a derivative at $\theta = 0$. First observe from Theorem 4.6.4 that under $\theta_1 = \theta_2$, all the moments $m_k(\theta)$ of the stationary distribution are differentiable in θ for all $\theta \geq 0$, and hence $p_j(\theta)$ is differentiable everywhere. Applying the moment formulae of Theorem 4.6.4, we learn that

$$|p_j(\theta)| \leq \binom{n}{j} \int_0^1 x(1-x)\, d\mu_\theta(x) = \binom{n}{j} \frac{2\theta}{1+2\theta} \tag{4.7.9}$$

hence $p_j(\theta) \to 0$ as $\theta \downarrow 0$. □

Now we can prove a general PRF representation theorem.

Theorem 4.7.5. *(General PRF Approximation). Assume that a continuum Cannings process occurs at each of the sites, and* μ_θ *is its respective equilibrium measure. If* $L \cdot \theta \to \Theta < \infty$ *as* $L \to \infty$*, then the segregating site variables* $(Z_1, \ldots, Z_{n-1})$ *converge to a sequence of independent Poisson random variables with means* $c_j\Theta$*, where the* c_j *are given by*

$$c_j = \lim_{\theta \downarrow 0} \frac{1}{\theta} \int_0^1 \binom{n}{j} x^j (1-x)^{n-j}\, d\mu_\theta(x) \tag{4.7.10}$$

Proof. All we need to do is apply the well-known Poisson approximation to the multinomial distribution: many such theorems exist in the literature. One which more than suffices for our purposes is a result due to McDonald (c.f. [15]), stated here simply for our application:

Theorem 4.7.6. *(Poisson-Multinomial Approximation). If* $(Z_0, \ldots, Z_n)$ *is multinomial with parameters* $(L, p_0, \ldots, p_n)$*, and* $(V_1, \ldots, V_{n-1})$ *are independent Poissons with means* Lp_j*, then*

$$\|(Z_1, \ldots, Z_{n-1}) - (V_1, \ldots, V_{n-1})\| \leq 2L \left(\sum_{j=1}^{n-1} p_j \right)^2 \tag{4.7.11}$$

where $\|\cdot\|$ *is the total variation norm of measures.*

The PRF approximation is now obvious, since $p_j(\theta) = O(\theta) = O(1/L)$ by Lemma 4.7.4 and therefore the right-hand side of 4.7.11 goes to zero as $L \to \infty$. Since $(V_1, \ldots, V_{n-1})$ are converging to a sequence of independent Poisson distributions with finite means $c_j\Theta$, where c_j are as in Lemma 4.7.4, so must $(Z_1, \ldots, Z_{n-1})$. $\square$

Theorem 4.7.5 shows that in the limit of a large number of sites, the sampled frequency spectrum still converges to that of a Poisson Random Field. Note, however, that the means of the Poisson variables are in general $c_j = \lim_{L\to\infty} Lp_j$, which depend upon the heterozygotic moments of the stationary distribution, and in general do *not* coincide with those of the Wright-Fisher distribution.

The PRF model releases some interesting insights which are enshrouded in the finite site system. As an example, in the Wright-Fisher PRF, one learns that the number of segregating sites, i.e. the statistic $T(\Theta) = \sum_{i=1}^{n-1} Z_i$—is sufficient for Θ, a statistic which vastly compresses the data. This follows simply from Neyman's factorization criterion applied to the sequence of independent Poisson distributions Z_i. Our extended PRF Theorem 4.7.5 demonstrates this fact remains true even in the generality of Cannings models.

Concluding Remarks

Our research originated in the aim of trying to understand the classical and biologically ubiquitous Wright-Fisher model at a deeper level, and with the goal of generalising its analysis to a larger class of processes which, in many cases, are biologically more sensible. To this end, the set of Generalised Wright Fisher (GWF) processes was introduced, containing as special cases many of the previously known Wright-Fisher generalisations: these include S. Karlin's conditional branching process, the Schweinsberg sampling model, and the Cannings processes. A canonical way of incorporating selective and mutational forces into the processes was discovered, and their basic discrete theory studied, using techniques from Markov and martingale theory. Bounds on the distribution of the absorption times of the models were obtained, in particular optimal estimates of the mean absorption and conditional fixation times. These results showed that in the neutral models, the exit time of a set S lies within a narrow range when the processes are initialised in the interior of S, but can range over practically large orders when initialised near the boundary of S.

In order to study the finer aspects of generalised processes, a continuum approximation theory of the Markov chains was developed to replace the traditional diffusion theory approach — the latter found inadequate due to the importance of higher-order moments in the limiting processes, and the observation that all GWF processes coincide in their first two conditional moments. A representation theorem for the generators $G_{\Omega,\beta,\theta}$ of the continuum limits was derived, parameterized by a Levy-like kernel $\Omega_x(y)$, which has the interpretation of describing a generalised conception of biological random drift, and selection and mutation parameters $\beta, \theta_1, \theta_2$. We also provided a converse to the representation formula, which showed that for any parameters β, $\theta_i \geq 0$ and continuous Ω, there exists a sequence of GWF chains converging in a strong-operator sense to the $G_{\Omega,\beta,\theta}$; this result in effect gives a weak solution to the generator problem associated to $G_{\Omega,\beta,\theta}$. More discriminating convergence conditions than those announced in the literature were derived, under the assumption that the continuum process is the standard Wright-Fisher diffusion; this diffusion was also characterized as the only continuum process with continuous sample paths.

For the purposes of illustrating our theory and offering interesting, biologically pertinent models, a number of GWF processes with non-Wright-Fisherian features were constructed, most notably the power-law α-processes, $\alpha > 0$. By a study of the asymptotics of these processes, their limiting continuum generators were calculated, and it was shown that the continuum limit was Kimura diffusive if and only if $\alpha \geq 3$. That the corresponding α-operators admitted closures inducing Feller semigroups and processes was deduced using the Hille-Yosida theory; we were also able to establish the existence of continuum limits for converging Cannings processes in the same way, by applying the polynomial structure of the moments of these models.

Further, we studied the maximum principles appropriate for GWF operators and the parabolic backward operator; these were rallied to solve a number of important genetic problems, including the extremal problem of finding the GWF processes with the maximal and minimal fixation probabilities under a given fixed selection pressure β. In doing so we succeeded in deriving universal bounds on the evolution of means of pure-selection processes. Maximum principles were also invoked to study properties of the harmonic functions connected to the α-generators; there we proved the startling result that for each index α between 0 and 1, there existed a *finite* selection pressure β^* which ensured the absorption of almost every sample path at only *one* of the boundaries. This contrasts strongly with the classical model, where $\beta^* = \pm\infty$.

Finally, the stationary distributions of pure-mutation GWF processes were considered: we were able to prove existence and uniqueness of a stationary measure for all Cannings processes, and gave formulae for the structure of the moments of this measure. This information was applied to prove a generalised Poisson Random Field approximation theorem for the sampled frequency spectrum of any Cannings model. We also explored the question of which features of GWF processes could be identified from knowledge of its stationary distribution alone: the mutation parameters θ_i proved to be identifiable, but unfortunately for the field scientist, not the drift Ω.

The technique and analysis in this thesis has been mostly mathematical, but the questions it presumes to shed light on include scientific ones; and so it does not appear supererogatory at this point to allude to some interesting biological implications.

Perhaps most surprising is that, far from being an average model, the classical Wright-Fisher model is an extreme process, even when viewed in the enormous space of GWF processes. This extremity can be summarised in the doctrine that it is the model with the "strongest drift"; the tenet has exact manifestations in a number of forms. First, it is mathematically an extreme point of the convex space of continuum models. Second, its generator, as a second-order differential operator, dominates all other GWF operators, which have orders less than two at every interior point of the state space. Related to this fact, the Wright-Fisher diffusion is the only process with continuous sample paths: all other processes possess discontinuities. Finally, the classical model proves to be the minimizer or near minimizer for a number of genetic functionals: expected absorption times started at low frequencies, and fixation probability among them. The strength of Wright-Fisherian drift indeed makes it the model most *disadvantageous* for the propagation and fixation of new mutants of superior fitness. This makes the well-known observation in evolutionary biology — that the rates of substitution of new mutants in populations appears constant, even over many diverse lineages and over many eras — even more remarkable, owing to the fact that non-Wright-Fisherian processes possess significantly greater ability, relative to the classical model, to discriminate small selective pressures from the neutral case. Our work then only lends even greater support to the sobering substance of Kimura's Neutral Theory: that the majority of mutations which have fixed in evolutionary history have done so not by any real inherent superiority of trait, but rather by pure chance.

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