

Feller's Contributions to Mathematical Biology

by *Ellen Baake* from Bielefeld
and *Anton Wakolbinger* from Frankfurt am Main

1 Introduction

Feller had a persistent interest in biology. This is documented in numerous examples from mathematical genetics in his monograph [*Feller 1950, *Feller 1966d],¹ and by a couple of influential research papers at the interface of population biology and probability theory. Looking back at these papers in historical perspective is highly rewarding: They are cornerstones of biomathematics; they mirror the development of probability theory of their time; and at least one of them ([Feller 1951d]) had lasting impact on probability theory.

Feller's important papers on the interface to biology are the articles [Feller 1939a], [Feller 1951d], and [Feller 1967c]. The first one addresses general population dynamics, the other two are mainly concerned with models in population genetics. The area of *population dynamics* is concerned with the growth, stabilisation, decay, or extinction of populations. Models of population dynamics describe how the *size* of populations changes over time under given assumptions on birth and death rates of individuals, which may depend on the current population size since individuals interact (e. g. compete) with each other. In contrast, *population genetics* is concerned with the *genetic composition* of populations under the action of various evolutionary processes, such as mutation and selection. Naturally, there is no sharp boundary between the fields, as we will also see in Feller's contributions. Let us now look at them.

2 Feller and population dynamics

In [Feller 1939a], a paper still in German entitled (in English translation) *The foundations of a probabilistic treatment of Volterra's theory of the struggle for life*, Feller

¹The references [Feller 19*nm*] and [*Feller 19*nm*] (the star indicating that the respective paper is not contained in these Selecta) refer to Feller's bibliography, while [*n*] points to the list of references at the end of this essay.

presents a synthesis of two fundamental developments that both started in 1931. On the one hand, Volterra presented his book *Lessons about the mathematical theory of the struggle for life* [28]; on the other hand, Kolmogorov published his seminal paper *On analytical methods in probability theory* [17]. Volterra's book laid the foundations for the *deterministic* description of population dynamics in terms of systems of ordinary differential equations that model birth, death, and interaction of individuals. These models imply that populations are so large that random fluctuations can be neglected, and population sizes are measured in units so large that the size can be considered a continuous quantity. Kolmogorov presented the general and systematic formalism for the description of *stochastic* dynamics in terms of Markov chains in continuous time; in particular, he found the description for the evolution of probability weights and the transport of expectations in terms of differential equations, which we know today under the names of *Kolmogorov forward equations* and *Kolmogorov backward equations*.

In his 1939 paper, Feller ties these two fundamental developments together by applying Kolmogorov's new formalism to some examples of Volterra's population dynamics. We see here the birth of the stochastic description of population dynamics, which today has its firm place in mathematical biology, and is highly developed both in analytical terms and in terms of simulations.

Feller's paper is devoted to the description of single populations (except from a small excursion to predator–prey models in the end) and consists of two large parts. The first establishes the Kolmogorov forward equations (KFE) for the Markov jump processes (namely, birth-and-death processes) that describe finite populations (remarkably, there is no mention of the Kolmogorov backward equations in this paper). The second part discusses a continuum analogue of such processes, a special case of which seems to be the first appearance of what today is called *Feller's branching diffusion*.

It is remarkable to see (and a pleasure to read) that Feller notices some of the crucial relationships between corresponding deterministic and stochastic models in this early paper, which appear as a central theme.

For the sake of clarity, let us make explicit here the two fundamental limits of birth-death processes that are addressed in [Feller 1939a]. Consider a birth-death process $K_N(t)$ with birth rate $n\lambda$ and death rate $n\mu$ when in state n , with N being the initial population size. Then, as the initial population size N tends to ∞ , the sequence of process $(K_N(t)/N)_{t \geq 0}$, $N = 1, 2, \dots$, converges in distribution to the solution of the differential equation

$$(1) \quad \dot{x} = (\lambda - \mu)x, \quad x(0) = 1.$$

This reflects a dynamical version of the Law of Large Numbers (see e. g. [19]). (Notably, due to the linearity, the expectation $M(t) := \mathbb{E}(K_1(t))$ satisfies (1) as well.) A different kind of limit emerges if one assumes that the individual split and death rates λ and μ depend on N and the process is *nearly critical* in the sense that

$$\lambda_N = \beta + \theta_1/N \quad \text{and} \quad \mu_N = \beta + \theta_2/N,$$

with $\theta_1 - \theta_2 =: \alpha$. The Law of Large Numbers then says that the limit of the processes

$(K_N(t)/N)_{t \geq 0}$ is the constant 1. However, on a larger time scale the fluctuations become visible: the sequence of processes $(K_N(Nt)/N)_{t \geq 0}$ converges in distribution to the solution of the *stochastic* differential equation (5.1') stated in paragraph 3.1.1, whose diffusion equation is (4). This is a prototype of a diffusion limit for birth-death processes. In [Feller 1939a], these limiting procedures are not made explicit (but see [Feller 1951d] for a major step in this direction). Feller in 1939 goes rather the other way, in search for stochastic processes that correspond to a given deterministic model. Let us now explain the major lines of his article.

2.1 Markov jump processes for population dynamics

In the first part (Sections 1–4), devoted to the stochastic description of finite populations, Feller explains a variety of birth-and-death processes and sets up the Kolmogorov forward equations for them, i. e. he establishes the system of differential equations that describe how the probability weights for the number of individuals alive at time t evolve over time. He starts with the simple linear death process (where each individual dies at rate λ , independently of all others), proceeds via the corresponding birth process and the linear birth-and-death process and finally arrives at the general birth-and-death process. In an individual-based picture, the latter includes interaction between individuals, so that the birth and/or death rates are no longer linear in the number of individuals. The case of logistic growth, which includes a quadratic competition term, serves as an important example; the case of ‘positive interaction’ (such as symbiosis) is not treated explicitly here. Let us comment on the major insights of this part.

2.1.1 Kolmogorov equations, their solutions, and relationship with deterministic description

Feller notices that for a given net reproduction rate α per individual, by choosing $\lambda - \mu = \alpha$, one obtains a variety of linear birth-death processes whose expectation value $M(t)$ satisfies one and the same ODE (1), whereas for $\alpha > 0$, there is exactly one linear pure birth process ($\lambda = \alpha, \mu = 0$) with this property. Feller states this ambiguity explicitly when discussing *logistic growth*. Its deterministic version is given by the differential equation

$$(2) \quad \dot{m} = m(\lambda - \gamma m) =: f(m),$$

which Feller also calls the *Pearl-Verhulst* equation. Here m is shorthand for $m(t)$, the ‘deterministic version’ of the population size at time t , λ denotes the per capita net reproduction rate in the absence of competition, and γ is the competition parameter. Again, Feller notices that there are many possibilities in terms of birth-death processes that correspond to (2). They are parametrised in his Eq. (27), which describes the process with per capita birth at rate $\omega - \nu n$ and per capita death at rate $\tau - \sigma n$ if there are currently n individuals. Here, we have renamed γ in Feller’s Eq. (27) by ν in order to achieve compatibility with the notation in (2).

Feller starts out by calculating the explicit solution to the KFE of the pure linear death process, that is, the number of individuals alive at time t ; he states this as the result of a recursive construction. With a typo corrected ($e^{\lambda t} - 1$ must be replaced by $1 - e^{-\lambda t}$ in his formula (6)), this same formula says that the number of individuals alive at time t has a binomial distribution with parameters N and $e^{-\lambda t}$ if there are initially N individuals. (Today, after [*Feller 1950], we would conclude this immediately, without solving systems of Kolmogorov forward equations, via the probabilistic argument that there are initially N independent individuals, each of which dies at rate λ and is therefore alive at time t with probability $e^{-\lambda t}$.) Likewise, the solution of the pure linear *birth* process with per capita birth rate λ , which he gives in his Eq. (17), is the negative binomial distribution with parameters N and $e^{-\lambda t}$, which arises as the distribution of the sum of N independent random variables that are geometrically distributed with parameter $e^{-\lambda t}$. Again, this has a nice interpretation as the offspring of N independently reproducing ancestors.

For the general birth process, with arbitrary birth rates p_n , Feller notes that the KFE define a probability distribution if and only if either only finitely many of the p_n are positive, or if $\sum_n 1/p_n$ diverges; this is a standard textbook result today (usually presented in the generalisation to birth-and-death processes). Under the conditions stated, he also gives the explicit solution in passing.

2.1.2 The moments of the stochastic process, and their relationship with the deterministic equation

Feller is particularly interested in the expectation, variance, and other moments of the (random) number of individuals alive at time t . In a trendsetting way, he does not calculate them from the explicit solution of the KFE, even where this is known; he rather uses the KFE to derive *differential equations for the moments*. Let $M(t) = \sum_k k P_k(t) = \mathbb{E}[K(t)]$ be the expected number of individuals at time t . As stated above, Feller observes that, for the linear birth-and-death process, $M(t)$ follows the differential equation for the deterministic population model, and hence the expectation of the stochastic process coincides with the deterministic solution. In contrast, for the logistic model, he finds from the differential equation relating the first and the second moment that

$$(3) \quad \dot{M} < f(M)$$

with f of Eq. (2). From this he argues that M is always less than the solution of the logistic equation. An alternative way to see (3) would be to observe that the KFE gives

$$\frac{d}{dt} \mathbb{E}[K(t)] = \mathbb{E}[g(K(t))]$$

where $g(k) = \sum_n Q(k, n)n$ and

$$\begin{aligned} Q(n, n+1) &= \lambda n, & Q(n, n-1) &= \gamma n^2, \\ Q(n, n) &= -(\lambda n + \gamma n^2), & Q(k, n) &= 0 \text{ otherwise.} \end{aligned}$$

As a matter of fact, it turns out that $g(k) = \lambda k - \gamma k^2$, which is strictly concave, and hence (3) is a consequence of Jensen's inequality. Since Feller does not consider models with positive interaction (such as symbiosis) in this part of the paper, he does not encounter the convex situation.

2.2 Diffusion equations for population dynamics

The second part of the paper (Sections 5–8 and 10) is devoted to the diffusion limit of stochastic population dynamics. We cannot resist to quote Feller's thoughts from the beginning of Section 5, formulated in an almost literary German, about the *substantially more lithesome probabilistic treatment, in which the population size is no longer assumed as integer-valued*, and where he alludes to similarities to the Brownian motion:

Wir wenden uns nun der anderen von der in der Einleitung erwähnten wahrscheinlichkeitstheoretischen Behandlungsweisen des Wachstumsproblems zu, welche wesentlich geschmeidiger ist, und bei der die Grösse der Population nicht mehr ganzzahlig vorausgesetzt wird. Den Mechanismus des Vorgangs kann man sich hier ähnlich wie bei der Brownschen Molekularbewegung vorstellen. Der Zustand der betrachteten Population, d. h. ihre gesamte Lebensenergie ist einer dauernden Veränderung unterworfen [...]

Starting from the transition density, Feller calculates the infinitesimal drift $a(x)$ and the infinitesimal variance $b(x)$ (provided they exist). With remarkable intuition, and a clear view of the branching property, he states that, in the case of a stochastically independent reproduction of the individuals, $a(x)$ and $b(x)$ must be proportional to x . Again, let us quote in German:

Nimmt man beispielsweise an, dass die Grösse der Population keinen Einfluss hat auf die durchschnittliche Vermehrungsgeschwindigkeit der Einzelindividuen, d. h. dass diese untereinander stochastisch unabhängig sind [...], so müssen $a(x)$ und $b(x)$ offenbar proportional zu x sein [...]

This gives rise to his equation (38), which reads as

$$(4) \quad \frac{\partial w(t,x)}{\partial t} = \beta \frac{\partial^2(xw(t,x))}{\partial x^2} - \alpha \frac{\partial(xw(t,x))}{\partial x}.$$

Here $w(t, \cdot)$ is the density of population size at time t , and α and β are positive constants. This seems to be the first appearance of what became famous as *Feller's branching diffusion*. We will come back to this in Section 3.1.

It is interesting to note that the diffusion process in this second part of the paper is *not derived* from the birth-death jump processes which Feller has presented in the first part; maybe, at this early stage, the subtle rescaling required for this limit was not yet at his fingertips. A decade later, however, he had these techniques; see Section 3.1 on *Diffusion processes in genetics*. In 1939, Feller does allude to the birth-death

processes, but the connection is not yet clear. For example, he tells us that the α in (4) corresponds to the λ encountered in the pure birth process. This is correct for the expected growth rate, but as a matter of fact a pure birth process cannot have the diffusion limit (4), since the paths of the former can only increase in time, whereas the paths of the latter have fluctuations in both directions.

This issue reappears when Feller discusses the extinction probability of the diffusion process. He notes the important fact that this quantity increases with β , since it is tied to the fluctuations of the process, and at the same time emphasises as a sort of paradox that, even for a positive net growth $\alpha > 0$, the diffusion process may die out with positive probability, while the population described by the deterministic differential equation (1), as well as a pure birth process, cannot die out. (This paradox is resolved when one has in mind the different rescalings that lead to (1) and (4).)

Following these considerations of the linear birth-and-death process, Feller includes dependence between individuals in Sections 8 and 10. He presents two specific examples. The first is his Equation (51), which is the diffusion version of his Equation (7) and known today as *Feller's branching diffusion with logistic growth* [20, 23]. The second is the (two-dimensional) diffusion describing a two-species model with predator-prey interactions, which now is also called *Lotka-Volterra process*, see Eq. (1.2) in [3]. As with the jump processes in the first part of his paper, Feller is concerned with the moments of the diffusion processes and writes down a general recursion for the k th moments M_k . In the two-species model, the interaction is positive (from the point of view of the predator), so we finally encounter the convex case, in which the expectation is greater than the solution of the corresponding ODE.

In Section 9, Feller makes some final remarks concerning the deterministic limit of both the birth-death jump processes and the branching diffusion. These are brief, heuristic calculations, which hint at the convergence of the stochastic models to Volterra's population models in the limit of infinite population size. Today, powerful laws of large numbers are available for large classes of such processes [8, Chap. 11]. They go far beyond the simple linear case alluded to in (1); rather, they include quite general forms of density dependence. This leads us to the present state of population dynamics.

2.3 Afterthoughts

Today, 75 years after [Feller 1939a], stochastic population dynamics constitute a vibrant area of research, so wide that it is impossible to give an overview in a short paragraph. Suffice it to say that major questions raised by Feller continue to be ardent research themes. Above all, this is true of interactions within and between populations. Even simple models for the competition of two populations, whose deterministic limit can be tackled as an easy exercise, turn into hard problems when considered probabilistically. Specifically, diffusion models with interaction have become objects of intense research, see, e.g., [6, 27] and references therein.

In the context of this commentary, it is particularly noteworthy that a class of models known under the name of *adaptive dynamics* brings together ecological aspects (on a short time scale) and genetical aspects (on a longer time scale) and thus builds

a bridge between population dynamics and population genetics. A nice overview of this topic and many others may be found in the monograph by Haccou, Jagers, and Vatutin [12]. Let us now turn to Feller's contributions to population genetics.

3 Feller and population genetics

As already laid out in Section 1, important processes in population genetics are those that describe the evolution of type frequencies, or in other words, of proportions of subpopulation sizes within a total population, whose size may vary as well. In this context, we may think of the individuals as *genes*, where each gene is of a certain type, say a or A .

The foundations of mathematical population genetics were laid starting in the 1920s by Fisher, Wright, and Haldane. Their work mirrors the genetics of their time, today known as *classical genetics*. It had to rely on the phenotypic appearance of individuals (colour of flower, surface structure of peas, body weight, milk yield . . .). The molecular basis of genetics was still unknown, so genes had to be treated as abstract entities. When *molecular genetics* entered the labs in the 1960s, population genetics changed dramatically, with Kimura as a leading figure, see Section 3.2.1. The next (and, from a 2015 perspective, the last) big leap took place in 1982, when Kingman introduced the genealogical perspective via the *coalescent process*. Comprehensive overviews of population genetics theory are given in the textbooks by Ewens [9] and Durrett [5]; for coalescent theory in particular, we further recommend Berestycki [2] (from a mathematical point of view) and Wakeley [29] (from a more biological perspective).

With his contributions to population genetics, Feller thus was in the midst of an important line of development. We will comment on two of these articles. The first, *Diffusion processes in genetics* [Feller 1951d], is a landmark contribution towards stochastic modelling and analysis via diffusion processes, and, as a matter of fact, reaches far beyond population genetics as such. The second, *On fitness and the cost of natural selection* [Feller 1967c], uses deterministic modelling (and is therefore similar in spirit to the 'Volterra equations').

3.1 Diffusion processes in genetics

Feller's article *Diffusion processes in genetics* [Feller 1951d] appeared in the Proceedings of the 2nd Berkeley Symposium on Mathematical Statistics and Probability, which took place in 1950. The central role of [Feller 1951d] is nicely put into perspective by the following quote from Thomas Nagylaki's review [24] on Gustave Malécot and the transition from classical to modern population genetics:

Mathematical research in diffusion theory influenced population genetics only gradually. As described in more detail below, Wright was unaware of Kolmogorov's (1931) pioneering paper, and Wright, Malécot, and Kimura were all apparently unacquainted with Khintchine's (1933)

book. [...] Thus, the mutually beneficial cross-fertilization between diffusion theory and population genetics did not start until Feller published his seminal 1951 paper.

In the introduction of that paper, Feller sets the stage by writing:

Relatively small populations require discrete models, but for large populations it is possible to apply a continuous approximation, and this leads to processes of the diffusion type.

Two diffusion processes are in the focus of the paper. One is what is nowadays called *Feller's branching diffusion*, the other is the so-called *Wright-Fisher diffusion*. Feller describes them by their *diffusion equations* (5.1) and (7.1), which are the Kolmogorov forward equations (or Fokker-Planck equations) for the densities, here called $u(t, x)$, cf. Section 2.2. Feller writes on pp. 228–229:

It is known that an essential part of Wright's theory is mathematically equivalent to assuming a certain diffusion equation for the *gene frequency* (that is, the proportion of a -genes).

In a footnote on the same page, Feller gives hints to the roots of this knowledge in the work of Kolmogorov, Fisher, Wright, and Malécot.

3.1.1 A foresight: Feller's diffusions as solutions of stochastic differential equations

Nowadays we do not hesitate to write the process described by Feller's equations (5.1) and (7.1) as solutions of stochastic differential equations in the sense of Itô:

$$(5.1') \quad dZ_t = \sqrt{2\beta Z_t} dW_t + \alpha Z_t dt,$$

$$(7.1') \quad dY_t = \sqrt{2\beta Y_t(1-Y_t)} dW_t + (\gamma_2(1-Y_t) - \gamma_1 Y_t) dt,$$

where W is a standard Brownian motion. Feller legitimately resisted writing the processes in this form. In [Feller 1952c], which grew out of Feller's invited lecture at the International Congress of Mathematicians in the year 1950, he writes about Itô's Stochastic Analysis:

This approach has the advantage that it permits a direct study of the properties of the path functions, such as their continuity, etc. In principle, we have here a possibility of proving the existence theorems for the partial differential equations [...] directly from the properties of the path functions. However, the method is for the time being restricted to the infinite interval and the conditions on [the diffusion and drift coefficients] a and b are such as to guarantee the uniqueness of the solution. So far, therefore, we cannot obtain any new information concerning the 'pathological' cases.

3.1.2 An emerging theme: What happens at the boundary?

Indeed, the state spaces of (5.1) and (7.1) are not the ‘infinite interval’ $(-\infty, \infty)$ but $[0, \infty)$ and $[0, 1]$, and it took 20 years until T. Yamada and S. Watanabe proved that the coefficients in the above stated SDEs are good enough to guarantee strong uniqueness of the solution, see [32] and also [31]. A coupling argument from Stochastic Analysis then guarantees that the solution of (7.1') converges in law to the unique equilibrium distribution whose density is the unique invariant probability density of (7.1), which is the Beta(γ_2/β , γ_1/β)-density. Thus, although for $\gamma_1 < \beta$ the random path Y hits 0 with probability one (and similarly for $\gamma_2 < \beta$ it hits 1 with probability one), these visits to the boundary do not lead (as conjectured by Feller on p. 239) to a non-vanishing *accumulation of the masses concentrated at $x = 0$ and $x = 1$ which is maintained in the steady state*, in other words, the coefficient μ in his equation (7.3) is in fact equal to 1.

Questions like these may have been one source of motivation for Feller to initiate his groundbreaking studies on the boundary classification of diffusion processes, see his footnote on p. 234, where he speaks of *boundary conditions of an altogether new type*, and the one on p. 229 *added in proof*, where he announces that *a systematic theory, including the new boundary condition, is to appear in the Annals of Math*. Feller's *classification of boundaries* is reviewed and commented in Section 2 of Masatoshi Fukushima's essay in these selecta.

3.1.3 The diffusion approximation of the Wright–Fisher chain and beyond

As already indicated, another important aspect that is taken up in Feller's paper is that of the *diffusion approximation*, i. e. the convergence of a sequence of (properly scaled) discrete processes to the solution of (5.1) and (7.1), respectively. In the former case the underlying discrete process is a Galton–Watson process, in the latter it is the Wright–Fisher Markov chain. The transition probabilities of the Wright–Fisher chain are given by (3.2), (3.4) and (3.5). The *diffusive mass-time-scaling* is given by (8.5): a unit of time consists of N generations, and a unit of mass consists of N (or here $2N$) individuals, with N being the total population size. The scaling (8.4) of the individual mutation probabilities α_1, α_2 is that of *weak mutation*, which leads in the scaling limit to the *infinitesimal mean displacement $a(x)$* and the *infinitesimal variance $2b(x)$* , see (8.6) and (8.7). In the context of (7.1), the *drift coefficient $a(x)$* is due to the effect of mutation, and the *diffusion coefficient $b(x)$* describes the strength of the fluctuations that come from the random reproduction. (In order to be consistent with (7.1), β_i should be replaced by γ_i in (8.4), (8.6) and (8.9)). The ‘convergence of generators’ which emerges from (8.6) and (8.7) can be lifted to the convergence of the corresponding semigroups, see e. g. the chapter on *Genetic Models* in the monograph [8] by Ethier and Kurtz.

The convergence theorems in [8] comply with Feller's programmatic proposal: *It should be proved that our passage to the limit actually leads from (8.2) to (8.6)*, i. e. from the probability weights of the Wright–Fisher chain to the probability densities the Wright–Fisher diffusion. To achieve this, Feller proposed an expansion into eigenfunctions (in particular he found the eigenvalues of the Wright–Fisher transition

semigroup) and checked part of the convergence in Section 8 and Appendix I. Such a representation is not required in the systematic approach presented in [8]. Still, the approach via eigenfunctions is interesting in its own right, and has been extensively used in Mathematical Biology.

At the beginning of Section 9 (entitled *Other possibilities*) Feller writes :

The described passage to the limit which leads to Wright's diffusion equation (7.1) is different from the familiar similar processes in physical diffusion theory where the ratio $\Delta x/\Delta t$ tends to infinity rather than to a constant. It rests entirely on the assumption (8.4) [of weak mutation]. We shall now see that *any modification of this assumption leads to a non-singular diffusion equation of the familiar type (to normal distributions)*.

Indeed, for the scaling (9.1), (9.2) $\alpha_i = \gamma_i \varepsilon$, $i = 1, 2$, $N\varepsilon \rightarrow \infty$, which corresponds to *strong mutation*, Feller states a law of large numbers, i. e. a convergence of the type frequencies to the equilibrium point $\left(\frac{\gamma_2}{\gamma_1 + \gamma_2}, \frac{\gamma_1}{\gamma_1 + \gamma_2}\right)$, and argues that the (properly scaled) process of fluctuations around this equilibrium point converges to a process whose probability density satisfies the diffusion equation (9.10) (and thus is an Ornstein-Uhlenbeck process).

3.1.4 The diffusion approximation of Galton–Watson processes

The diffusion equation (5.1) appeared already in [Feller 1939a], see Eq. (4) in Section 2.2. However, as we have seen there, certain issues concerning the (scaling) limits of Galton–Watson processes had remained unrevealed in [Feller 1939a]. Towards 1950, Feller was ready to attack this. As to the diffusion approximation of a sequence of ‘nearly critical’ Galton–Watson processes by (5.1), Feller gives a proof in Appendix II. His idea is to take the iterates f_n of the offspring generating function (which are known to describe the generating functions of the subsequent generation sizes) to their scaling limit. This limit turns out to satisfy the PDE (12.9) (which, in turn, corresponds to (5.1)). Feller writes:

We effect this passage to the limit formally: it is not difficult to justify these steps, since the necessary regularity properties of the generating functions $f_n(x)$ were established by Harris [13].

Again, from today's perspective, an alternative way is provided by the convergence of generators, see [8]. In the very last lines of his Appendix II, Feller remains a bit sketchy when he writes that

the boundary condition $u(t, 0)$ follows from the fact that in the branching process the probability mass flowing out into the origin tends to zero.

In fact, for the solution Z of (5.1') (with $Z_0 = 1$, say), the probability mass flowing out into the origin is non-zero at any fixed time t , and the density of Z_t does not vanish near the origin. Again, the desire to obtain clarity on questions like these may have been a motivation for Feller's then upcoming research on the boundary behaviour of one-dimensional diffusions.

3.1.5 From two-type to continuum-type generalisations of Feller's branching diffusion

In the introduction, Feller points out that *serious difficulties arise if one wishes to construct population models with interactions among the individuals, and that the situation grows worse if the population consists of different types of individuals*. He then writes:

In fact, the bivariate branching process leads to such difficulties that apparently not one single truly bivariate case has been treated in the literature. In the theory of evolution this difficulty is overcome by the assumption of a constant population size [...] In Section 10 the assumptions of constant population size is dropped and a truly bivariate model is constructed which takes into account selective advantages in a more flexible way. [...] The same limiting process which leads [...] to the diffusion equation of Wright's theory can be applied to our new bivariate model and leads to a diffusion equation in two dimensions.

These *two-dimensional Markov processes with branching property* have been taken up and analysed in a broader context in 1969 in the paper [31] which carries that title. Already before, Watanabe had published his seminal paper [30] which established Feller's branching diffusions with a continuum of types. This together with the pioneering work of Don Dawson gave rise to a class of processes that were later called Dawson–Watanabe superprocesses ([6, 4]). A good part of Perkins' Saint Flour Lecture Notes (part 2 of [4]) is devoted to superprocesses with interactions, and thus is fully on the line of Feller's program to construct population models with different types of individuals and with interactions among the individuals.

3.1.6 The inner life of Feller's branching diffusion: excursions and continuum trees

This is a good place to mention another fascinating development which is connected with Feller's branching diffusions and is associated with the names of Daniel Ray and Frank Knight (the latter was Feller's doctoral student and Ed Perkins' PhD advisor).

Thanks to the branching property (and the thereby implied infinite divisibility), the random path Z of a Feller branching diffusion is a Poissonian sum of countably many 'Feller excursions' ζ . In fact, each of them has an 'internal life' in the sense that ζ_t is the size at time t of a continuum population originating from one single ancestor. The genealogical tree of this population can be described by a Brownian excursion η reaching level t , which can be imagined as the 'exploration path' of a continuum random tree whose mass alive at level t is ζ_t . The second Ray–Knight theorem says that ζ_t can be represented as the local time spent by η at level t . In a discrete setting of Galton–Watson processes, this is anticipated in Harris' work [11] with its section on *walks and trees*. The correspondence between a Feller excursion ζ and an Itô excursion η is depicted on the first page of [25], framed by pictures of Feller and Itô, who met in person at Princeton in 1954. See [25] for more

explanations, and references to groundbreaking developments that dealt with the genealogical structure behind Feller's branching diffusion, such as Aldous' *Continuum Random Tree* (which plays in the world of random trees a similar role to that of Brownian motion in the classical invariance principle) and Le Gall's *Random Snake*, which provides a representation of the Dawson–Watanabe super-Brownian motion as a continuum-tree-indexed Markov motion.

For more on excursions and excursion point processes in relation with Feller's work, see Section 3.1 of the contribution of M. Fukushima.

3.1.7 Frequencies in multivariate continuum branching: conditioning and time change

Another interesting question which Feller addresses at the end of his introduction concerns the relative frequencies in a bivariate model of branching diffusions. Feller writes:

[...] it is to be observed that *in no truly bivariate case does the gene frequency satisfy a diffusion equation* (Sections 6 and 10). In fact, if the population size is not constant, then the gene frequency is not a random variable of a Markov process. Thus, conceptually at least, the assumption of a constant population size plays a larger role than would appear on the surface.

Indeed, as it turns out (and Feller may have been well aware of this), one way of passing from (5.1) to (7.1), say with $\alpha = \gamma_1 = \gamma_2 = 0$, is to consider two independent Feller branching diffusions (solutions of (5.1')) $Z^{(1)}$ and $Z^{(2)}$, conditioned to $Z^{(1)} + Z^{(2)} = 1$. Of course, this must be given a precise meaning, and this has been done in a much more general context in the papers by Etheridge and March [7] and Perkins [26]. The title of Perkins' paper is programmatic: A Dawson–Watanabe superprocess conditioned to have constant mass one is a Fleming–Viot process (which is the continuum-type, and thus measure-valued, generalisation of the Wright–Fisher diffusion). In the context of (5.1) to (7.1) this means that under the conditioning $Z^{(1)} + Z^{(2)} = 1$ the process $Y := Z^{(1)}$ is a Wright–Fisher diffusion. On the level of genealogies, the conditioning to a constant total mass takes the continuum random forest that underlies (5.1') into Kingman's coalescent.

A second way to get from (5.1') to (7.1') (again for $\alpha = \gamma_1 = \gamma_2 = 0$) is to consider the relative frequency $Y := \frac{Z^{(1)}}{Z^{(1)} + Z^{(2)}}$ after a time change $ds = dt / (Z^{(1)} + Z^{(2)})$. In this way, the relative frequencies again become Markovian and, by an easy application of Itô's formula, turn out to solve (7.1').

The concept of time change is central also in the work of John Lamperti. Lamperti's work can be seen as a direct continuation and extension of Feller's ideas, introducing and analysing the continuum mass limits of Galton–Watson processes also for heavy-tailed offspring distributions [21]. His article [22], which was communicated by H. P. McKean, another former PhD student of Feller, introduced what is now

called Lamperti's transform, a time change which establishes the link between Lévy processes and continuous state branching processes.

To conclude: Feller's paper *Diffusion processes in genetics* is a remarkable contribution at the interface of probability theory and population biology, with enduring stimulations in either direction. It takes a central place in the development of mathematical population genetics, and has triggered substantial new directions in the modern theory of stochastic processes.

3.2 The cost of natural selection

Feller's article *On fitness and the cost of natural selection* [Feller 1967c] appeared in *Genetical Research Cambridge*, a renowned biology journal. The introduction contains the disclaimer

This paper is written by a mathematician, and accordingly no new biological models or hypotheses are advanced.

It may be added that the mathematics is fairly elementary as well, and the strength of the article is the concise conceptual thinking by which Feller dissects the logics of an argument that enormously influenced the genetic thinking of that time, and finds a fundamental weak point in it.

3.2.1 The 1960s and the neutral theory of population genetics

As hinted at already, the 1960s were turbulent times for genetics – and for population genetics in particular. Until then, the variation between individuals could only be observed at the phenotypical level, and much of this was easily explained by selection: Stronger beaks crack harder nuts; webbing eases swimming; fat pads protect against the cold. Then, in the 1960s, the first observations of *variation at the molecular level* became available – not yet via sequencing, but via so-called restriction length polymorphisms (RFLP) of DNA or via gel electrophoresis of proteins. The resolution of these methods is lower than that of sequencing but, nevertheless, the variation was so much larger than expected on phenotypic grounds that researchers were shocked – and were puzzled about the question: *Can this all be explained by selection?*

These considerations were strongly influenced by the concept of the *genetic load*, coined by Haldane [10]; in particular the concept of the *substitutional load*. This is the number of *selective deaths*, that is, the number of individuals 'killed' by selection in the process of substituting one type by a fitter one. Put differently, the substitutional load (or *cost of natural selection*) is the number of excess individuals that must be produced in a population under selection. In 1968, Kimura [15] concluded that, if a large fraction of the observed variability is selective, the load is forbidding. This led to one of the most influential and conflict-prone hypotheses of evolutionary theory, namely, to the so-called *neutral theory*, which claims that the overwhelming proportion of the observed molecular variation is selectively neutral, that is, most mutations do not change fitness.

In what follows, we look more closely into the concept of the substitutional load, and into Feller's criticism of it. We restrict ourselves to the case of haploid populations (i.e., carrying only one copy of the genetic information) that reproduce asexually (Sections 1–5 in Feller's paper). In Sections 6–9, he tackles additional complications that emerge in diploid individuals (with two copies of every gene), but the conceptual issues are more transparent in the haploid case.

3.2.2 Absolute and relative frequencies in population genetics

Feller considers a population of individuals that consists of our two types A and a , large enough to justify deterministic treatment. He assumes discrete generations where every A -individual leaves an average of μ offspring for the next generation, whereas every a -individual produces an average of $\mu' = \mu(1 - k)$ descendants where $0 < k < 1$. The quantities μ and μ' are known as (absolute) fitnesses in population genetics. Each of the two subpopulations then grows (or decays) geometrically,

$$(5) \quad N_n = \mu N_{n-1}, \quad N'_n = \mu(1 - k)N'_{n-1},$$

so $N_n = N_0\mu^n$ and $N'_n = N'_0(\mu(1 - k))^n$, where N_n and N'_n denote the size of the A - and a -subpopulations, respectively.

Now population genetics is traditionally more concerned with relative frequencies of types than with absolute ones; the main reason is that relative frequencies are easier to measure. One therefore considers

$$p_n := \frac{N_n}{N_n + N'_n}, \quad q_n := \frac{N'_n}{N_n + N'_n}.$$

Clearly, under (5),

$$(6) \quad q_n = \frac{q_0(1 - k)^n}{p_0 + q_0(1 - k)^n},$$

which is Feller's Eq. (3.5). Obviously, the powers of μ cancel out, which is a strength and a weakness at the same time: On the one hand, this means that knowledge only of the ratio of the fitness values is required to predict the behaviour of the population. Actually, (6) holds more generally than the simple derivation may suggest: It continues to hold if (5) is replaced by

$$(7) \quad N_n = \mu N_{n-1}f(N_n + N'_n), \quad N'_n = \mu(1 - k)N'_{n-1}f(N_n + N'_n).$$

Here f is a function that depends on the total population size only and acts on both types in the same way. In typical ecological models, one uses a monotonically decreasing function f with $f(0) = 1$ in order to describe how population size decreases the per capita offspring size due to competition. In particular, for suitable choices of f , both the population size and the relative frequencies will, in the long run, approach stationary values.

The downside of thinking in terms of relative fitnesses is that one loses sight of the absolute population sizes. The latter may lead to absurd conclusions, in particular in cases where one or both subpopulations go extinct. This leads us to Feller's criticism of the genetic load.

3.2.3 The substitutional load and Feller's criticism

Feller now recalls Haldane's definition of the genetic load: In generation n , the mixed population has a loss of $d_n := kq_n$ offspring relative to a population consisting of A individuals only, where d_n must be measured in units of the total population size of generation n . Over M generations, Haldane takes $D := \sum_{n=0}^M d_n$ as the total genetic load. Calculating this with reasonable parameters and as $M \rightarrow \infty$, he arrives at a representative value of 30 for the cost of substitution of one gene by a fitter one.

Haldane's definition of D makes sense only if population size remains constant over time, or if changes in population size are so small that they can safely be neglected. Haldane does not make this explicit; Feller has an eye on both possibilities.

Feller first considers the case that the population size is not constant; rather, N_n and N'_n behave as in (5). Since $\mu = 1$ and $k < 1$ is assumed, this means that $N_n \equiv N_0$ and $N'_n \rightarrow 0$ as $n \rightarrow \infty$, so the total population size decreases from $N_n + N'_n$ to N_0 . On an absolute scale, the loss of individuals due to selection is $N'_n - N'_{n+1} = kN'_n$ in generation n , and altogether

$$(N'_0 - N'_1) + (N'_1 - N'_2) + \dots = N'_0,$$

in agreement with the decrease of the total population size from $N_0 + N'_0$ to N_0 . In contrast, Haldane's D , which neglects the size change, can give much larger values; in particular, it can be larger than the number of a individuals ever born. Obviously, this understanding of the load produces severe artifacts.

Feller then discusses how Haldane's argument may be 'rescued'. One possibility is to keep population size constant by immigration from a reservoir population, in exactly the same proportions as in the current population under consideration. Then, Haldane's D gives the correct answer (but it must be kept in mind that the cost of selection is then borne by the reservoir population). The second possibility is to assume an ecological model rather than geometric growth. Feller speaks of μ depending on population size; maybe as in our Eq. (7), where μ is replaced by $\mu f(N_n + N'_n)$. But more general models are also possible; for example, each type may be affected by competition in a different way. The genetic load would then be identified with the decrease in the stationary population size due to the reduced reproduction rate of one type. But now there is a wealth of possible models, and the genetic load would depend on the details. Specifying these is a task Feller assigns to the biologists.

3.2.4 Feller's criticism in the general context

With remarkable insight, Feller dissects a conceptual problem of his time: Load arguments can be inconsistent if they blindly rely on relative frequencies. His fellow researchers in biology do, however, not seem to have taken too much notice of his criticism. After all, as already mentioned in Section 3.2.1, a year after Feller's paper (and without citing it), Kimura did put forward his neutral theory of molecular evolution, to a large extent on the basis of load arguments [15]. More precisely, Kimura used an extension of Haldane's argument. He assumed a sequence of numerous genetic loci (rather than Haldane's and Feller's single locus), each of which can be of

a favourable or a less favourable type, with fitness assumed as *multiplicative across loci*. As a consequence, there is a multitude of possible genotypes; fitness differences between individuals can become enormous; and the load (if calculated in Haldane's manner) can become astronomical (Kimura and Ohta [16] give a value of $D = 10^{78}$). Here the misconception lies in the assumption of multiplicativity over loci, which is completely unrealistic, but was hardly questioned at that time. For the details, see the insightful presentation in [9, Chapter 2.11].

Let us return to the original question that load arguments were supposed to answer: Can all the variation observed at the molecular level be explained by selection? Indeed, today, a large fraction of the molecular variation is considered selectively neutral or nearly so, although single mutations with spectacular selective effects are well known. But this insight is no longer built on load arguments – rather, the assumption of neutrality has proved extremely successful in describing patterns of genetic variation.

Last but not least, it should be noted that there is a lot of truth in Feller's general warning not to neglect population size in population genetics. Indeed, load arguments are not the only artifacts of this kind. Another example is the famous phenomenon of *Muller's ratchet*, which describes the *ad infinitum* accumulation of deleterious mutations due to stochastic effects in finite populations of constant size. If described in terms of an ecologically more realistic (and conceptually more correct) model with variable population size, the accumulation does not continue forever. Rather, when fitness has declined below a threshold value, the population experiences a *mutational meltdown*, which ultimately leads to extinction (see [1] for a review).

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All citations of the form [Feller 19nn], resp., [*Feller 19nn] (if the respective paper is not included in these Selecta) point to Feller's bibliography, pp. xxv–xxxiv.

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Prof. Ellen Baake
 Universität Bielefeld
 Technische Fakultät
 Postfach 10 01 31
 33501 Bielefeld, Germany
 ebaake@techfak.uni-bielefeld.de

Prof. Anton Wakolbinger
Goethe-Universität Frankfurt
Institut für Mathematik
Robert-Mayer-Straße 10
60325 Frankfurt am Main, Germany
wakolbinger@math.uni-frankfurt.de



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