

The inverse problem of linear age-structured population dynamics

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Abstract. We consider the problem of determining the individual survival and reproduction functions (or birth and death rates) from data on total population size and cumulative number of births in a linear age-structured population model. We give conditions that guarantee that this inverse problem has a unique solution. The proof uses a variant of the Müntz-Szasz theorem. An age-dependent cell fission model is given special attention.

1. Introduction

Classical deterministic models of population dynamics are formulated in terms of ordinary differential equations for the sizes (e.g. number of individuals per unit area) of the interacting populations. They are based on the tacit assumption that all individuals in the population are equal in the sense that they experience the same risk of dying and have the same probability per unit of time of giving birth. In reality individuals are of course not equal. They may differ in age, size, energy content and other quantities that influence individual development, reproduction and survival. Models of *physiologically structured populations* (Metz and Diekmann 1986) take these differences into account. These models bridge the gap between mechanisms at the individual level and behaviour at the level of the population.

In a typical *direct problem* one prescribes model ingredients that describe mechanisms at the individual level, lifts the model to the population level by straightforward book-keeping, and finally studies phenomena at the population level. In the *inverse problem* the situation is reversed. Using knowledge about behaviour at the population level one wants to deduce the underlying mechanisms at the individual level.

The direct problem of structured populations has been extensively studied for many kinds of models using a variety of mathematical techniques (e.g. pde theory, semigroup theory, renewal theory, branching processes). We mention only the book by Webb (1985) on age-structured populations, the book by Metz and Diekmann (1986) on general physiologically structured populations and the book on branching processes by Jagers (1975). On the other hand, results on the inverse problem seem to be rare (van Straalen 1986).

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In a series of papers Rundell and coworkers (Rundell 1989, 1993; Pilant and Rundell 1991b; Engl *et al.* 1994) have treated certain inverse problems of age-structured population dynamics. In these papers it is assumed that census data in the form of the age distribution of the population are available. However, for many real populations (e.g. bacterial populations) it is difficult if not impossible to measure the age distribution, whereas other quantities at the population level such as the total population size are easily obtained. Pilant and Rundell (1991a) considered in a pde setting the question of determining the initial age-distribution from data on the total population size, when the birth and death rates are known. Berndtsson and Jagers (1979) considered the same question in a branching processes framework.

In this paper we discuss the inverse problem of the simplest structured population model: the linear age-structured model (Sharpe and Lotka 1911, McKendrick 1926). We shall, in fact, use the cumulative formulation (Diekmann *et al.* 1993b, 1998; Gyllenberg *et al.* 1997) of the problem. This not only increases the generality but facilitates the analysis considerably. The specific problem we consider is: Under what conditions does knowledge of the total population size and the cumulative number of births uniquely determine the survival and reproduction functions describing individual behaviour? A typical example we have in mind is a population of cells reproducing by fission. Here the inverse problem is indeed relevant, because the age of a cell cannot usually be measured, whereas the total number of cells is easily observed as is the fraction of dividing cells. If cell death is allowed to occur only as a result of failing mitosis, then knowledge of the total population size is sufficient to determine both the fission rate and the probability of successful mitosis.

2. The model

The classical linear age-structured population model is usually formulated as a hyperbolic pde supplemented by a nonlocal boundary condition (McKendrick 1926):

$$\frac{\partial}{\partial t}n(t, a) + \frac{\partial}{\partial a}n(t, a) = -\mu(a)n(t, a), \quad (2.1)$$

$$n(t, 0) = \int_0^\infty \beta(a)n(t, a)da, \quad (2.2)$$

$$n(0, a) = n_0(a). \quad (2.3)$$

Here the solution $n(t, \cdot)$ is the age-density of the population, $\mu(a)$ is the age-specific per capita death rate and $\beta(a)$ is the age-specific per capita fecundity.

The system (2.1)–(2.3) can be solved by integrating the McKendrick Equation (2.1) along characteristics obtaining an expression for $n(t, a)$ in terms of the initial density $n_0(a)$ and the birth rate $b(t) := n(t, 0)$. Substituting this expression into the birth law (2.2) one

obtains a renewal equation for the birth rate $b(t)$. Once this equation has been solved, the expression for $n(t, a)$ becomes an explicit formula and the problem is solved (see e.g. Gurtin and MacCamy 1974).

We shall, however, proceed along a slightly different line. Following Diekmann *et al.* (1993ab, 1995, 1998, 2001) we formulate the direct problem directly as an integral equation. This has several advantages, one of them being that we do not have to worry about in what sense the constructed solution is a solution of the pde (2.1).

From μ and β we obtain two new functions F and L by defining

$$F(a) = e^{-\int_0^a \mu(\alpha) d\alpha} \quad (2.4)$$

and

$$L(a) = \int_0^a \beta(\alpha) e^{-\int_0^\alpha \mu(\tau) d\tau} d\alpha. \quad (2.5)$$

F is called the *survival function* and L the *reproduction function*. They have the following interpretations:

$F(a)$ is the probability that an individual is still alive at age a .

$L(a)$ is the expected number of offspring born to an individual before reaching (dead or alive) age a .

We now forget about the rates μ and β and take F and L as the basic ingredients of the population model. This increases the generality, because we can now allow discontinuities in F and L and handle initial populations described by not necessarily absolutely continuous (with respect to Lebesgue measure) measures. It also considerably facilitates the analysis.

The interpretation requires that F and L satisfy certain conditions, which we now formulate.

ASSUMPTION 2.1. *The functions F and L are defined on $(0, \infty)$ and have the following properties:*

- (i) F is nonnegative and nonincreasing.
- (ii) $\lim_{a \downarrow 0} F(a) = 1$.
- (iii) $F(\infty) = \lim_{a \rightarrow \infty} F(a) = 0$.
- (iv) L is nonnegative, nondecreasing, and nonlattice.
- (v) $\lim_{a \downarrow 0} L(a) = 0$.
- (vi) $R_0 = L(\infty) = \lim_{a \rightarrow \infty} L(a) < \infty$.

The assumption in (iv) that L is nonlattice means that L is not a step-function with discontinuities in a subset of an additive subgroup of \mathbf{R} . We thus rule out the possibility that individuals reproduce only upon exactly reaching a prescribed age a_0 (and possibly upon reaching $2a_0, 3a_0, \dots$).

The number R_0 is called the *basic reproduction ratio* and it gives the expected life-time production of offspring of an individual.

The expected number of grand-children produced by an individual before reaching age a is obtained from the convolution

$$L^{(2)}(a) = \int_{[0,a)} L(a - \alpha)L(d\alpha) \quad (2.6)$$

and the expected number of k^{th} generation offspring recursively from

$$L^{(k+1)}(a) = \int_{[0,a)} L(a - \alpha)L^{(k)}(d\alpha). \quad (2.7)$$

By our assumptions the distributional derivative of L is a Borel measure and L itself is a Borel function. Therefore the Stieltjes-convolution in (2.6) makes sense and defines a Borel function the derivative of which is a Borel measure. It follows by induction that the Stieltjes-convolution $L^{(k+1)}$ in (2.7) is also well-defined. By the same token all Stieltjes-convolutions appearing in this paper are well-defined.

The whole *clan* descending from a given individual is obtained by summing up over all generations:

$$R(a) = \sum_{k=1}^{\infty} L^{(k)}(a). \quad (2.8)$$

It follows from our assumptions that the series in (2.8) converges uniformly on compact intervals to an at most exponentially growing function R which is related to L by the renewal equation (resolvent equation)

$$R(a) = L(a) + \int_{[0,a)} L(a - \alpha)R(d\alpha) = L(a) + \int_{[0,a)} R(a - \alpha)L(d\alpha) \quad (2.9)$$

(for a proof, see Feller 1971, p. 182 ff.)

Because R grows at most exponentially we may take the Laplace transform of the renewal equation (2.9) and obtain

$$\widehat{R}(s) = \widehat{L}(s) - s\widehat{R}(s)\widehat{L}(s)$$

or

$$\widehat{R}(s) = \frac{\widehat{L}(s)}{1 + s\widehat{L}(s)}.$$

This together with the nonlattice assumption implies that the asymptotic behaviour of R is given by

$$R(a) = Ce^{ra} + o(e^{ra}), \quad a \rightarrow \infty, \quad (2.10)$$

where r is the unique real root $\lambda = r$ of the Euler-Lotka equation

$$\int_{\mathbf{R}_+} e^{-\lambda a} L(da) = 1. \quad (2.11)$$

The root r is called the *Malthusian parameter* and it is positive if and only if $R_0 > 1$. For details we refer to Feller (1941, 1971).

We denote by $L_a(t)$ the expected number of offspring produced by an a year old individual before reaching age $a + t$. One has

$$L_a(t) = \frac{L(a+t) - L(a)}{F(a)}. \quad (2.12)$$

The corresponding quantity with all generations included is given by the explicit formula

$$Q_a(t) = L_a(t) + \int_{[0,t)} R(t-\tau) L_a(d\tau). \quad (2.13)$$

The population state is a measure m on \mathbf{R}_+ with the interpretation that $m(\omega)$ is the number of individuals having age in the measurable set $\omega \subset \mathbf{R}_+$. Assume that the initial population state is given by the measure m_0 . The solution to the direct problem is now given by the following formula for the population state at time $t > 0$:

$$\begin{aligned} m(t, \omega) = & \int_{\mathbf{R}_+} \frac{F(a+t)}{F(a)} \delta_{a+t}(\omega) m_0(da) \\ & + \int_{\mathbf{R}_+} \int_{[0,t)} \delta_{t-\tau}(\omega) F(t-\tau) Q_a(d\tau) m_0(da) \end{aligned} \quad (2.14)$$

(Diekmann *et al.* 1998; Diekmann 1999). The first term on the right hand side of (2.14) represents all individuals with age in the measurable set ω at time $t > 0$ that were present in the initial population, whereas the latter term represents those that were born after the initial time $t = 0$.

Notice that solving the direct problem boils down to solving the renewal equation (2.9), that is, to compute the resolvent R through the generation expansion (2.8). Once this has been done, the solution is given by the explicit formula (2.14).

If $F(A) = 0$ for some finite A , then no-one can survive beyond A and the initial measure m_0 must be concentrated on $[0, A]$. Moreover, because dead individuals do not give birth, $L(a)$ must be equal to $L(\infty)$ for ages a larger than A . In fact, we shall make the following assumption.

ASSUMPTION 2.2

- (i) $F(a) = 0 \Rightarrow L(a) = L(\infty)$,
- (ii) $\frac{1}{F} \in L^1(m_0)$.

3. The inverse problem

In many practical situations the population state, that is, the age distribution in our case, cannot be directly observed. When this is the case, it is usually also impossible to experimentally measure the model ingredients L and F . What can be observed is only certain linear functionals of the population state, called *population outputs*. The inverse problem consists of determining F and L (or μ and β) in terms of the outputs.

In this paper we shall be concerned only with two outputs, namely the *total population size*

$$N(t) = \int_{\mathbf{R}_+} m(t, da) \quad (3.1)$$

and the *population birth rate*

$$b(t) = \int_{\mathbf{R}_+} \beta(a)m(t, da). \quad (3.2)$$

Of course, a rate cannot be directly measured; the measured quantity is the *cumulative number* $B(t) = \int_{[0,t)} b(\tau)d\tau$ of births up to time t . The use of B instead of b also has the advantage that B makes sense in cases where the model is formulated in terms of the reproduction function L and not in terms of the per capita birth rate β . One has

$$B(t) = \int_{\mathbf{R}_+} Q_a(t)m_0(da). \quad (3.3)$$

It follows from (2.14) that the total population size $N(t)$ and the cumulative number $B(t)$ of births satisfy the following equations:

$$N(t) = \int_{[0,t)} F(t-\tau)B(d\tau) + \int_{\mathbf{R}_+} \frac{F(a+t)}{F(a)}m_0(da), \quad (3.4)$$

$$B(t) = \int_{[0,t)} L(t-\tau)B(d\tau) + \int_{\mathbf{R}_+} \frac{L(a+t) - L(a)}{F(a)}m_0(da) \quad (3.5)$$

for $t > 0$. We assume that the outputs $N(t)$ and $B(t)$ are produced by admissible ingredients (that is, by functions F and L satisfying Assumptions 2.1 and 2.2) and that they are known on a time-interval of length $T \leq \infty$. We can now give a precise formulation of the inverse problem of linear age-structured population dynamics.

- (IP) Given the measure m_0 and the functions B and N defined on $[0, T)$ ($T \leq \infty$), determine the functions L and F such that the equations (3.4) and (3.5) are satisfied on $[0, T)$.

In particular, we shall be concerned with the question under which conditions the data m_0 , B and N *uniquely* determine the ingredients F and L . On the other hand, we shall not attempt to characterize data that guarantee that F and L are admissible in the sense that they satisfy Assumptions 2.1 and 2.2.

Once F and L have been determined the death rate μ and the fecundity β are obtained from (2.4) and (2.5) as

$$\mu(a) = -\frac{F'(a)}{F(a)}, \quad (3.6)$$

$$\beta(a) = \frac{L'(a)}{F(a)}, \quad (3.7)$$

Observe that by the monotonicity assumptions (i) and (iv) in Assumption 2.1, F and L are indeed differentiable almost everywhere, so the formulas (3.6) and (3.7) make sense.

Before we formulate our results on the inverse problem, we make a few remarks.

REMARK 3.1. A naïve approach to the inverse problem would be to extend F and $b = B'$ as zero to the negative real axis and study the full line convolution equation corresponding to (3.4) with for instance Fourier transform techniques. With this convention N would be defined on the whole real axis and its support $\text{supp } N$ would be $(-\text{ess sup supp } m_0, \infty)$. On the other hand, the measured data contain the values of N on the positive real axis only. The failure of the naïve approach and the difficulty of the inverse problem stem from this fact.

REMARK 3.2. Because the age distribution cannot in general be measured, the initial population state m_0 is in many applications unknown. It would therefore be desirable to determine not only the ingredients F and L , but also the initial age distribution m_0 from the outputs N and B . But this can never be achieved. To see this, assume that $N(t)$ and $B(t)$ are given twice differentiable functions defined for $t \in \mathbf{R}_+$ and that

$$F(a) = 0, \quad a \geq 1. \quad (3.8)$$

Assume in addition that

$$\frac{m_0(da)}{F(a)} = c \, da \quad (3.9)$$

for some positive constant $c \neq b(0)$. Inserting (3.8) and (3.9) into (3.4) and differentiating, one obtains the Volterra equation

$$(c - b(0)) F(t) = -N'(t) + \int_0^t b'(t - \tau) F(\tau) d\tau, \quad 0 \leq t \leq 1. \quad (3.10)$$

Obviously different values of c give rise to different functions F and consequently equation (3.4) can be satisfied for (infinitely) many different choices of (F, m_0) .

REMARK 3.3. The solution R of the renewal equation (2.9) grows (or declines) asymptotically exponentially according to (2.10). It now follows from (3.3) that

$$B(t) = Ce^{rt} + o(e^{rt}), \quad a \rightarrow \infty \quad (3.11)$$

and hence by (3.4) that

$$N(t) = Ce^{rt} + o(e^{rt}), \quad a \rightarrow \infty. \quad (3.12)$$

Hence, if the output $N(t)$ or $B(t)$ can be measured, then the Malthusian parameter r is automatically known. The Malthusian parameter is therefore considered as part of the inverse problem data.

Next we give a simple example, which shows that $N(t)$ and $B(t)$ need not determine the survival function $L(a)$ uniquely.

EXAMPLE 3.4. Assume that $b(t)$ and $N(t)$ grow not only asymptotically, but *exactly* exponentially, that is, assume that

$$B(t) = \frac{b_0}{r}(e^{rt} - 1), \quad (3.13)$$

$$N(t) = N_0 e^{rt}, \quad (3.14)$$

and that m_0 is absolutely continuous with distributional derivative n_0 . Substituting (3.13) and (3.14) into (3.4), multiplying both sides with e^{-rt} and letting $t \rightarrow \infty$, one finds that

$$N_0 = b_0 \int_0^\infty e^{-ra} F(a) da. \quad (3.15)$$

Equation (3.4) is now an equation with F as the only unknown, and it is satisfied by

$$F(a) = \frac{1}{b_0} e^{ra} n_0(a), \quad a \geq 0. \quad (3.16)$$

With N , B and F given by (3.13), (3.14), (3.15) and (3.16) one easily checks that equation (3.5) holds for any function L satisfying

$$\int_{[0, \infty)} e^{-ra} L(da) = 1. \quad (3.17)$$

We thus conclude that the outputs (3.13) and (3.14) do *not* determine the model ingredients uniquely. Note that (3.17) is the same as the Euler–Lotka equation (2.11), but now the Malthusian parameter $\lambda = r$ is given and the survival function L has to be found.

The situation described in Example 3.4 occurs when the initial population is at demographic equilibrium. The (normalized) age-distribution remains the same for all times and it is intuitively clear that the model ingredients cannot be determined from such stable data.

One can easily check that uniqueness fails also in the case where N and b are finite linear combinations of $e^{\lambda_k t}$. The situation changes drastically when the linear combination becomes infinite. Our main theorem (Theorem 4.2) says that the inverse problem has a unique solution whenever the exponential functions $e^{\lambda_k t}$ are complete in the continuous functions.

Another situation in which it is clear that no unique solution to the inverse problem can be found is when all individuals in the initial population are passed their reproductive age. Mathematically this means that the the initial measure m_0 is concentrated on an interval (A, ∞) on which $L(a) = L(\infty)$ and that $B(t) = 0$ for all $t \geq 0$. The equation (3.5) then reduces to the identity $0 = 0$ and nothing can be said about L . Clearly one cannot deduce any information about $F(a)$ for $a \in [0, A]$ because no individual will ever have age in that interval.

4. Results

As shown by Example 3.4, the inverse problem does not possess a unique solution if the population is initially at demographic equilibrium. In order to prove uniqueness we therefore have to introduce extra conditions. This can be done by making restrictions either on the initial age-distribution m_0 or on the outputs $N(t)$ and $b(t)$.

If the initial measure is concentrated at the origin, then the system (3.4) and (3.5) reduces to the following system of renewal equations:

$$N(t) = \int_{[0,t)} F(t - \tau)B(d\tau) + F(t) \quad \text{for } t > 0, \quad (4.1)$$

$$B(t) = \int_{[0,t)} L(t - \tau)B(d\tau) + L(t) \quad \text{for } t > 0. \quad (4.2)$$

This system can easily be solved using Laplace transform techniques as soon as the functions B and N grow at most exponentially. Because the solution of the direct problem satisfies the asymptotical exponential growth conditions (3.11) and (3.12) it is natural to assume that the inverse problem data satisfy them, too. We thus arrive at our first positive result on the inverse problem.

THEOREM 4.1. *Assume that $B(t)$ and $N(t)$ are defined on $[0, \infty)$ and satisfy (3.11) and (3.12), respectively. Assume moreover that $m_0 = \delta_0$, the Dirac measure concentrated*

at the origin. Then the functions $N(t)$ and $B(t)$ uniquely determine $F(a)$ and $L(a)$ as the inverse Laplace transforms of

$$\widehat{F}(s) = \frac{\widehat{N}(s)}{1 + s\widehat{B}(s)} \quad (4.3)$$

and

$$\widehat{L}(s) = \frac{\widehat{B}(s)}{1 + s\widehat{B}(s)}, \quad (4.4)$$

respectively.

Observe that when the initial population is a Dirac measure it cannot be at demographic equilibrium and therefore the possibility of exact exponential growth is ruled out.

To motivate the next theorem we return for a while to the direct problem, where F and L are given. Denote the latter term on the right hand side of (3.5) by $H(t)$. Then the Laplace transform of b is given by

$$\widehat{b}(s) = \frac{s\widehat{H}(s)}{1 - s\widehat{L}(s)} \quad (4.5)$$

Assume that the maximum life-time is finite, say 1. Then the support of F , $\text{supp } F = [0, 1]$ and $L(a) = L(1)$ for all $a \geq 1$ by Assumption 2.2. It follows that $s\widehat{H}(s)$ and $s\widehat{L}(s)$ are entire functions and hence that \widehat{b} is meromorphic in the whole plane. The zeros of $1 - s\widehat{L}(s)$ (the poles of \widehat{b}) are the roots of the Euler-Lotka equation (2.11). An easy application of Hadamard's factorization theorem (Titchmarsh 1939, p. 250) shows that the Euler-Lotka equation has infinitely many complex roots λ_k (for details, see Gyllenberg 1985). If $\widehat{b}(s)$ admits an expansion

$$\widehat{b}(s) = \sum \frac{b_k}{s - \lambda_k} \quad (4.6)$$

with $\sum |b_k| < \infty$, then, as proven by Feller (1941), the solution of (3.5) (or rather its derivative b) is representable as the series

$$b(t) = \sum b_k e^{\lambda_k t}, \quad (4.7)$$

where the series converges absolutely for all $t \geq 0$. The coefficients b_k are complex. Because b is positive the characteristic roots λ_k appear as pairs of complex conjugates. We have assumed that all roots are simple. The result above is easily generalized to the case of multiple roots (Feller 1941). Note, however, that due to positivity, the unique real root $\lambda_0 = r$ is necessarily simple and has real part larger than the real parts of all other roots.

The discussion above suggests that we consider inverse problem data $b(t)$ and $N(t)$ that admit series expansions of the type (4.7) on an interval $[0, T)$. This is indeed a large and

nonrestrictive class of functions; for instance, it is obviously dense in $C(I)$ for every compact interval $I \subset [0, T)$. In the main result of this paper (Theorem 4.2) we show that the inverse problem has a unique solution if and only if the subspace spanned by the functions $e^{\lambda_k t}$ occurring in the expansion of $b(t)$ is still dense in $C(I)$. In the Appendix we prove a variant of the Müntz-Szasz theorem, which gives a criterion for when the span of $\{e^{\lambda_k t}\}_{k=0}^{\infty}$ is dense in terms of the complex numbers λ_k .

The support of a distribution f is denoted by $\text{supp } f$ and the convex hull of a set E by $\text{ch } E$.

THEOREM 4.2. *Let $\text{supp } m_0 \subset [0, 1]$ and assume that m_0 does not have an atom at 1. Let $b(t)$ and $N(t)$ be defined on $[0, 1 + \varepsilon)$ and representable as series*

$$b(t) = \sum b_k e^{\lambda_k t} \quad (4.8)$$

and

$$N(t) = \sum N_k e^{\mu_k t} \quad (4.9)$$

which converge absolutely for $t \in [0, 1 + \varepsilon)$, where $\varepsilon > 0$. Then Equation (3.4) has a solution F with $\text{supp } F = [0, 1]$ if and only if

$$\lambda_k = \mu_k \quad \text{for all } k, \quad (4.10)$$

and

$$N_k = b_k \int_0^1 e^{-\lambda_k a} F(a) da \quad \text{for all } k. \quad (4.11)$$

If this is the case, then the function $b(t)$ can be real-analytically continued to $(-1, 1 + \varepsilon)$. Moreover, the solution F of (3.4) is unique and given by

$$F(a) = \frac{n_0(a)}{b(-a)}, \quad (4.12)$$

where n_0 is the distributional derivative of m_0 . Moreover, every function L for which

$$\int_{[0,1]} e^{-\lambda_k a} L(da) = 1 \quad \text{for all } k \quad (4.13)$$

satisfies equation (3.5). There is a unique such L if and only if

$$\sum \left(1 - \left| \frac{\lambda_k + 2\pi i}{\lambda_k - 2\pi i} \right| \right) = \infty. \quad (4.14)$$

Proof. Inserting the series (4.8) and (4.9) into Equation (3.4) one obtains

$$\sum N_k e^{\mu_k t} = \sum b_k e^{\lambda_k t} \int_0^1 e^{-\lambda_k a} F(a) da \quad (4.15)$$

for $t \in [1, 1 + \varepsilon)$. This immediately implies (4.10) and (4.11).

Because the sum in (4.9) converges absolutely for $t \geq 0$ we get from (4.11) that

$$\sum |b_k| \int_0^1 e^{-\operatorname{Re}\lambda_k a} F(a) da < \infty. \quad (4.16)$$

Since $F(a)$ is nonincreasing, it follows that

$$\sum |b_k| \int_0^t e^{-\operatorname{Re}\lambda_k a} da < \infty \quad (4.17)$$

for all $t \in (0, 1)$ and hence that

$$\sum |b_k| \frac{1}{\operatorname{Re}\lambda_k} (e^{-\operatorname{Re}\lambda_k t} - 1) < \infty \quad (4.18)$$

for all $t \in (0, 1)$. But this implies that $\sum b_k e^{\lambda_k t}$ converges absolutely for $t \in (-1, 0)$, and hence that $b(t)$ can be real-analytically continued to the interval $(-1, 0)$.

Substituting (4.10) and (4.11) back into Equation (3.5) one gets

$$\begin{aligned} \sum b_k e^{\lambda_k t} \int_0^1 e^{-\lambda_k a} F(a) da &= \sum b_k e^{\lambda_k t} \int_0^t e^{-\lambda_k a} F(a) da \\ &+ \int_0^1 \frac{n_0(a)}{F(a)} F(a+t) da \end{aligned} \quad (4.19)$$

for all $t \geq 0$, where n_0 is the distributional derivative of m_0 . Equation (4.19) can be rewritten as

$$\int_0^1 \left(\sum b_k e^{-\lambda_k a} - \frac{n_0(a)}{F(a)} \right) F(a+t) da = 0, \quad t \geq 0. \quad (4.20)$$

More precisely, (4.20) should be written as

$$\operatorname{supp} F * g_- \subset \mathbf{R}_- \quad (4.21)$$

where g is the restriction (in the distributional sense) of

$$\left(\sum b_k e^{-\lambda_k a} - \frac{n_0(a)}{F(a)} \right)$$

to the compact set $[0, 1]$ and defined to be zero outside that interval, and $g_-(a) = g(-a)$. Obviously

$$\operatorname{ch} \operatorname{supp} g_- \subset [-1, 0] \quad (4.22)$$

By (4.21) and the theorem of supports (Titchmarsh 1926, Hörmander 1983, p. 107) we have

$$\operatorname{ch} \operatorname{supp} g_- + \operatorname{ch} \operatorname{supp} F = \operatorname{ch} \operatorname{supp} F * g_- \subset \mathbf{R}_-. \quad (4.23)$$

Since $\text{supp } F = [0, 1]$, it follows from (4.22) and (4.23) that $\text{ch supp } g_-$ is either the empty set or the set $\{-1\}$. The latter alternative is ruled out by the assumption that m_0 does not have an atom at 1. Therefore $\text{ch supp } g = \emptyset$. (4.12) now follows immediately.

Substituting the expression (4.12) for $\frac{n_0(a)}{F(a)}$ and the series (4.8) for $b(t)$ into (3.4) one finds that every L satisfying (4.13) is a solution. The uniqueness assertion now follows from Corollary A.2 in the Appendix. \square

Condition (4.14) is certainly not satisfied if the series is a finite sum, that is, if the expansions of b and N have only a finite number of terms. In particular, uniqueness fails in the case of exact exponential growth. Our elementary counter example given in Example 3.4 is thus seen to be a special case of our main result.

The solution semigroup of the direct problem has eigenvalues $e^{\lambda_k t}$ with corresponding eigenfunctions $e^{-\lambda_k a} F(a)$, where λ_k are roots of the Euler-Lotka equation. Asymptotically the dynamics happen on the one-dimensional space spanned by the eigenfunction $e^{-r a} F(a)$ corresponding to the dominant eigenvalue independently of the initial age-distribution. Theorem 4.2 says that if the initial age-distribution lies in a subspace spanned by a finite number of eigenfunctions, then the inverse problem does not have a unique solution.

Because b is analytic and F a function, it follows from (4.12) that n_0 is also a function, in other words, the initial measure m_0 is absolutely continuous. We point out that this smoothness of m_0 is part of the conclusions and not of the assumptions of Theorem 4.2.

We now specialize the model to the case of a population of cells reproducing by fission. When a cell splits into two daughter cells the mother cell disappears. Cell death is modelled by assuming that mitosis is successful with probability $p \in (0, 1]$. Consequently no daughter cells are produced with probability $1 - p$. Death during the intermitotic phase of the cell cycle is neglected. This means that

$$L(a) = 2p(1 - F(a)), \quad (4.24)$$

or, equivalently,

$$F(a) = 1 - \frac{1}{2p} L(a), \quad (4.25)$$

and that we thus can take as model ingredients the reproduction function L and the probability p of successful mitosis. It turns out that for this model knowledge of $N(t)$ alone suffices to determine the model ingredients: $B(t)$ is not needed.

THEOREM 4.3. *Assume F , L and p are related according to (4.24) and that at either of the following conditions holds:*

- (i) $m_0 = \delta_0$;
- (ii) $\text{supp } F = [0, 1]$, $\text{supp } m_0 \subset [0, 1]$ and m_0 does not have an atom at 1, N is representable as a series $N(t) = \sum N_k e^{\lambda_k t}$.

If $R_0 > 1$, then m_0 and $N(t)$ uniquely determine $L(a)$ and p .

Proof. Since $R_0 > 1$ one has $p > 1/2$. It therefore follows from (3.4), (3.5) and (4.24) that

$$B(dt) = \frac{2p}{2p-1} N(dt). \quad (4.26)$$

Substituting (4.26) into (3.4) one obtains

$$N(t) = \frac{2p}{2p-1} \int_{[0,t)} F(t-\tau) N(d\tau) + \int_{[0,\infty)} \frac{F(a+t)}{F(a)} m_0(da). \quad (4.27)$$

Depending on which of the conditions (i) or (ii) is satisfied either Theorem 4.1, or 4.2 shows that equation (4.27) has a unique solution F_p . It is immediately seen from the form of equation (4.27) that

$$K(a) = \frac{2p}{2p-1} F_p(a) \quad (4.28)$$

is independent of p . Substituting (4.28) and (4.24) into the Euler–Lotka equation (2.11) with $\lambda = r$, one obtains

$$1 = -(2p-1) \int_{[0,\infty)} e^{-ra} K(da). \quad (4.29)$$

Because, as pointed out in Remark 3.3, the Malthusian parameter r is part of the data (it is determined by N), p is uniquely solved from (4.29). This completes the proof. \square

A. Appendix: A variant of the Müntz-Szasz theorem

THEOREM A.1. *Let $I = [0, 2\pi]$, let λ_k be a sequence of complex numbers with $\text{Im}\lambda_k > 0$ and let X be the subspace of $C(I)$ spanned by $\{e^{i\lambda_k t} : k \in \mathbf{N}\}$. Then X is dense in $C(I)$ if and only if*

$$\sum_{k=1}^{\infty} \left(1 - \left|\frac{\lambda_k - 1}{\lambda_k + 1}\right|\right) = \infty. \quad (\text{A.1})$$

Proof. If X is not dense in $C(I)$, then there exists by the Hahn-Banach theorem and the Riesz representation theorem a complex Borel measure $m \neq 0$ such that

$$\int_I e^{i\lambda_k t} m(dt) = 0 \quad \text{for all } k. \quad (\text{A.2})$$

Hence the claim follows if we can show that (A.2) implies $m = 0$. By the Fourier inversion theorem it is sufficient to show that

$$f(z) := \int_I e^{izt} m(dt)$$

vanishes identically if $f(\lambda_k) = 0$ for all k .

f is clearly entire and bounded in the upper half plane because

$$|f(z)| \leq \int_I |e^{-\operatorname{Im}z}| |m|(dt) \leq C, \quad \operatorname{Im}z > 0,$$

for some constant C . Define

$$g(z) := f\left(\frac{i-z}{i+z}\right).$$

Then $g \in H^\infty(D)$, where D is the unit disc. By (A.2) $f(\lambda_k) = 0$ and hence

$$g\left(i\left(\frac{1-\lambda_k}{1+\lambda_k}\right)\right) = 0 \quad \text{for all } k.$$

The claim now follows from the corollary to Theorem 15.23 of (Rudin 1974). \square

COROLLARY A.2. *Let m be a complex Borel measure supported on $[0, 1]$ such that the Laplace transform*

$$\int_{[0,1]} e^{-zt} m(dt) \tag{A.3}$$

vanishes at $z = \lambda_k$, $k = 1, 2, \dots$, where $\operatorname{Re}\lambda_k < 0$. Then $m = 0$ if and only if

$$\sum_{k=1}^{\infty} \left(1 - \left|\frac{\lambda_k + 2\pi i}{\lambda_k - 2\pi i}\right|\right) = \infty. \tag{A.4}$$

Proof. Define the measure m_1 on $[0, 2\pi]$ by

$$\langle m_1, f \rangle = \int_{[0,1]} f\left(\frac{t}{2\pi}\right) m(dt)$$

and apply the previous theorem. \square

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REFERENCES

- [1] BERNDTSSON, B. and JAGERS, P., *Exponential growth of a branching process usually implies stable age distribution*. J. Appl. Prob. 16 (1979), 651–656.
- [2] DIEKMANN, O., *Modeling and analysing physiologically structured populations*, In Mathematics inspired by biology, V. Capasso and O. Diekmann (Eds.), Springer-Verlag, Berlin; Centro Internazionale Matematico Estivo (C.I.M.E.), Florence, 1999, 1–37.
- [3] DIEKMANN, O., GYLLENBERG, M. and THIEME, H. R., *Perturbing semigroups by solving Stieltjes renewal equations*. Differential and Integral Equations 6 (1993a), 155–181.
- [4] DIEKMANN, O., GYLLENBERG, M., METZ, J. A. J. and THIEME, H. R., The “cumulative” formulation of (physiologically) structured population models, In “Evolution Equations, Control Theory and Biomathematics”, (Ph. Clément and G. Lumer, Eds.), 1993b, 145–154, Marcel Dekker, New York.
- [5] DIEKMANN, O., GYLLENBERG, M. and THIEME, H. R., *Perturbing evolutionary systems by step responses and cumulative outputs*. Differential and Integral Equations 8 (1995), 1205–1244.
- [6] DIEKMANN, O., GYLLENBERG, M., METZ, J. A. J. and THIEME, H. R., *On the formulation and analysis of general deterministic structured population models. I. Linear theory*. Journal of Mathematical Biology 36 (1998), 349–388.
- [7] DIEKMANN, O., GYLLENBERG, M., HUANG, H., KIRKILIONIS, M., METZ, J. A. J. and THIEME, H. R., *On the formulation and analysis of general deterministic structured population models. II. Nonlinear theory*. Journal of Mathematical Biology, 43 (2001), 157–189.
- [8] ENGL, H. W., RUNDELL, W. and SCHERZER, O., *A regularization scheme for an inverse problem in age-structured populations*. J. Math. Anal. Appl. 182 (1994), 658–679.
- [9] FELLER, W., *On the integral equation of renewal theory*, Ann. Math. Statist. 12 (1941), 243–267.
- [10] FELLER, W., *An introduction to probability theory and its applications* vol. II, Second Edition, Wiley, New York, 1971.
- [11] GURTIN, M. E. and MACCAMY, R. C., *Non-linear age-dependent population dynamics*, Arch. Rat. Mech. Anal. 54 (1974), 281–300.
- [12] GYLLENBERG, M., *The age structure of populations of cells reproducing by asymmetric division*, In Mathematics in Biology and Medicine, V. Capasso, E. Grosso, and S. L. Paveri-Fontana (Eds.), Springer, Berlin, 1985, 320–327.
- [13] GYLLENBERG, M., HANSKI, I. and HASTINGS, A., *Structured metapopulation models*. In: “Metapopulation biology: ecology, genetics and evolution” (I.A. Hanski and M.E. Gilpin, Eds.) 1997, 93–122, Academic Press, San Diego.
- [14] HÖRMANDER, L., *The analysis of linear partial differential operators I*, Springer, Berlin, 1983.
- [15] JAGERS, P., *Branching Processes with Biological Applications*, Wiley, London, 1975.
- [16] MCKENDRICK, A. G., *Applications of Mathematics to Medical Problems*, Proc. Edinb. Math. Soc. 44 (1926), 98–130.
- [17] METZ, J. A. J. and DIEKMANN, O., *The Dynamics of Physiologically Structured Populations*, Springer, Berlin.
- [18] PILANT, M. AND RUNDELL, W., *Determining the initial age distribution for an age structured population*, Math. Population Stud. 3 (1991a), 3–20.
- [19] PILANT, M. and RUNDELL, W., *Determining a coefficient in a first-order hyperbolic equation*, SIAM J. Appl. Math. 51 (1991b), 294–506.
- [20] RUDIN, W., *Real and Complex Analysis*. Second Edition. McGraw-Hill, New York, 1974.
- [21] RUNDELL, W., *Determining the birth function for an age structured population*. Math. Population Stud. 1 (1989), 377–395, 397.
- [22] RUNDELL, W., *Determining the death rate for an age-structured population from census data*. SIAM J. Appl. Math. 53 (1993), 1731–1746.
- [23] SHARPE, F. R. and LOTKA, A. J., *A problem in age-distribution*, Philosophical Magazine 21 (1911), 435–438.
- [24] VAN STRAALLEN, N. M., *The “inverse problem” in demographic analysis of stage-structured populations*, In The Dynamics of Physiologically Structured Populations, J.A.J. Metz and O. Diekmann (Eds.) 1986, 393–408, Springer, Berlin.

- [25] TITCHMARSH, E. C., *The zeros of certain integral functions*. Proc. London Math. Soc. 25 (1926), 283–302.
- [26] TITCHMARSH, E. C., *The Theory of Functions*. Second Edition. Oxford University Press, Glasgow, 1939.
- [27] WEBB, G. F., *Nonlinear Age-Dependent Population Dynamics*, Marcel Dekker, New York, 1985.

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