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THE THRESHOLD FOR PERSISTENCE OF PARASITES WITH MULTIPLE INFECTIONS

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Abstract. We analyse a model for macro-parasites in an age-structured host population, with infections of hosts occurring in clumps of parasites. The resulting model is an infinite system of partial differential equations of the first order, with non-local boundary conditions. We establish the condition for the parasite–free equilibrium to be asymptotically stable, in terms of $R_0 < 1$, where R_0 is a quantity that is interpreted as the reproduction number of parasites. To show this, we prove that $s(B - A) < 0$ [> 0] if and only if $\rho(B(A)^{-1}) < 1$ [> 1] where B is a positive operator, and A generates a positive semigroup of negative type. Finally, we discuss how R_0 depends on the parameters of the system, especially on the mean size of infecting clumps.

1. **Introduction.** A basic concept in models for micro-parasites (bacteria, viruses,...) is the basic reproductive number R_0, the expected number of infected hosts produced by a single infected host in a completely susceptible host population [7]: in fact, in most epidemic models, $R_0 > 1$ is a necessary and sufficient condition for the instability of the disease-free equilibrium, and a sufficient condition for the persistence of pathogens.

A similar concept (see, for instance, [24]) has been introduced in several models for macro-parasites (mainly helminths), but it has been difficult to obtain general results, because the basic models for macro-parasites consist of an infinite system of differential equations, whose first root can be traced to Kostizin [15]. Such systems have proved very difficult to analyse (see, however, [10, 17, 18, 22, 23, 20]) and much of the analysis, including the formulation of thresholds for parasite persistence in terms of R_0, has been performed using simplified models consisting of few ordinary differential equations.

Anderson and May [1] introduced in the infinite model by Kostizin the assumption that parasite distributions were, at each time, negative binomial, obtaining simplified models consisting of few ordinary differential equations. The negative binomial distribution has been routinely used to fit empirical data on parasite

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abundance, and is considered an aggregated (or overdispersed) distribution, meaning that, if parasites are distributed among hosts in a negative binomial fashion, most parasites will be aggregated in few hosts. Generally, the negative binomial is parametrized with a positive parameter κ that measures the degree of aggregation κ, that was used as a fixed constant in the model by Anderson and May [1], and in many following applications (see [4, 26] for recent reviews). It has been found that parasite persistence occurs in this model if

$$R_0 := \frac{hK}{c+K} \cdot \frac{1}{\mu+\alpha+\sigma} > 1. \tag{1}$$

It can then be seen that the threshold is independent of the value of the aggregation parameter κ.

While the model by Anderson and May has been extremely influential in understanding the dynamics of host-parasite systems, certainly it is not satisfying on several respects. First of all, the assumption of a negative binomial distribution is inconsistent with the (infinite) system of differential equations where it is inserted; second, the assumption of a fixed k is in contrast with empirical observations [12] of variability of k in space and time; finally, assuming a fixed aggregation index k does not make it possible to understand out of which mechanisms aggregation arises. Thus, progress has been made in several directions, analysing directly the infinite system, or considering other types of low-dimensional approximations [19], or introducing in the model those biological features that may cause parasite aggregation: host heterogeneity and 'clumped' infections have been considered especially relevant in this respect [25].

This paper presents the analysis of the infinite system with the latter feature: 'clumped' infections. By "clumped infections", we mean that a host gets infected with a "parcel" of larvae in the same time. This feature has already been considered in models aimed at characterizing the age-intensity of parasitism among hosts [14], and in dynamic models at the population level [21]. It was found [21] in the analysis of a three-dimensional approximation of the infinite model that (1) is correct only when infections occur only with a single parasite; otherwise, R_0 can be expressed only implicitly, but it can be seen that the value of R_0 decreases as aggregation is increased, in contrast to (1), found with fixed aggregation [1].

It seems therefore interesting understanding how R_0 depends on the level of aggregation in the infinite model, in order to see whether the result of [21] depends on the approximation used. A rigorous treatment of the threshold condition for parasite persistence, written as $R_0 > 1$, has been carried out, using semigroup methods, in [23] (see also [20] for extensions of the idea). The computations performed in [23], while providing the general setting used here, did not yield an explicit expression for the case considered here.

The organization of the paper is as follows. In Section 2 we present the model, set it in abstract form, and, summarizing some results of [22, 23], show (Proposition 2) that the parasite-free-equilibrium is asymptotically stable or unstable, according to whether $s(B+A)$ is negative or positive, where B and A are suitable operators, and s represents the spectral bound [28]. In Section 3, we prove, in an infinite-dimensional setting, a technical lemma on the spectrum of positive operators, well known in finite dimensions [7]: i.e. that $s(B+A) < 0$ $[> 0]$ if and only if $\rho(B(-A)^{-1}) < 1$ $[> 1]$ under suitable assumptions on A and B; such a result is somehow alluded to in the infinite-dimensional definition of R_0 [11], but we could not find in the

literature any explicit statement, or proof. Finally, in Section 4 we compute explictly $R_0 = \rho(B(-A)^{-1})$, and discuss the biological interpretation of the result.

2. **The model, and its abstract setting.** The variables of the model are $p_i(t)$ for $i \geq 0$, the density of hosts which carry i parasites in the host at time t. One can write differential equations for these variables, by taking into account the new infections, the deaths of adult parasites, as well as hosts' births and deaths. The method is explained, for instance, in [23]; the main difference lies in the infection mechanism.

Here, we assume that, as a host is infected, it ingests an infecting "parcel", of which c_l represents the probability that it consists of l larvae, $l \geq 1$; the mean number of larvae in an infecting "packet" is $\gamma = \sum_{l=1}^{\infty} l c_l < +\infty$. Finally, we assume that φ is the rate at which a host ingests an infective parcel.

Under this assumption on the infection process together with constant rates of parasite death σ, of host birth b and death d, plus parasite-induced host death rate α and birth reduction ξ, one obtains the following infinite system of differential equations

$$\begin{cases} \dfrac{d}{dt}p_0(t) = -(\mu + \varphi(t))p_0(t) + \sigma p_1(t) + b\displaystyle\sum_{i=0}^{+\infty} p_i(t)\xi^i \\ \dfrac{d}{dt}p_i(t) = -(\mu + \varphi + i(\alpha+\sigma))p_i(t) + \sigma(i+1)p_{i+1}(t) \\ \qquad\qquad + \varphi \displaystyle\sum_{l=1}^{i} c_l p_{i-l}(t) \qquad i \geq 1. \end{cases} \tag{2}$$

We showed in [23] that including hosts' age in the model (as in [17]) does not really introduce big complications, and indeed makes many expressions more transparent. Thus, we rewrite the model for an age-structured host population, allowing for age-dependent host fertility and mortality, and, in order to have a parasite-free equilibrium, for density-dependent host birth rate.

Thus, the model we consider in the paper is

$$\begin{cases} \dfrac{\partial}{\partial t}p_i(a,t) + \dfrac{\partial}{\partial a}p_i(a,t) = -(\mu(a) + \varphi(t) + i(\alpha+\sigma))p_i(a,t) \\ \qquad\qquad +\sigma(i+1)p_{i+1}(a,t) + \varphi(t)\displaystyle\sum_{l=1}^{i} c_l p_{i-l}(a,t) \qquad i \geq 0 \\ \qquad p_0(0,t) = \psi(N(t))\displaystyle\int_0^{+\infty} \beta(a)\sum_{i=0}^{+\infty} p_i(a,t)\xi^i\, da \\ \qquad p_i(0,t) = 0 \qquad i > 0 \\ \qquad p_i(a,0) = h_i(a) \quad i \geq 0 \end{cases} \tag{3}$$

with the convention $p_{-1}(a,t) \equiv 0$. Here $p_i(a,t)$ for $i \geq 0$ and a in $[0,+\infty)$ denotes the density of hosts of age a harbouring i parasites at time t.

Here $N(t)$ is total population density, and $P(t)$ [to be used below] is total parasite density, given by

$$N(t) = \int_0^{+\infty} \sum_{i=0}^{+\infty} p_i(a,t)\,da \quad \text{and} \quad P(t) = \int_0^{+\infty} \sum_{i=1}^{+\infty} i p_i(a,t)\,da. \tag{4}$$

Moreover, the infection rate $\varphi(t)$, is given, following the time-scale argument of Anderson and May [1] about free-living larvae, by

$$\varphi(t) = \frac{hP(t)}{c + N(t)}. \tag{5}$$

As for demographic parameters, $\mu(a)$ is the natural death rate of hosts while the fertility rate of hosts carrying i parasites is given by $\psi(N(t))\beta(a)\xi^i$, where β is the maximum fertility rate, and ψ is a decreasing function that shapes the density-dependence of fertility.

Following standard assumptions in the theory of age-structured populations [13, 28], we assume that β and μ are nonnegative functions, $\beta \in L^\infty[0,+\infty)$, there exist μ_-, μ_+ such that $0 < \mu_- \le \mu(a) \le \mu_+$ for a.e. $a \in [0,+\infty)$. As for the function ψ, we assume $\psi \in C^1([0,+\infty))$, $\psi(0) = 1$, $\psi'(s) < 0$, $\lim_{s\to+\infty} \psi(s) = 0$.

The behaviour of the purely demographic system ($h_i \equiv 0$ for $i \ge 1$) is well known. Let

$$\pi(a) = \exp\{-\int_0^a \mu(s)\,ds\} \ (\textit{survival function})$$

and

$$\mathcal{R} = \int_0^{+\infty} \beta(a)\pi(a)\,da.$$

It can be easily seen that, if $\mathcal{R} > 1$, there is a stationary solution $\bar{p}$ of (3) given by

$$\begin{cases} \bar{p}_0(a) = \dfrac{K}{\int_0^{+\infty} \pi(u)\,du}\pi(a) \\ \bar{p}_i(a) = 0 \qquad\qquad\qquad\qquad i > 0. \end{cases} \tag{6}$$

This will be called the 'Parasite Free Equilibrium', shortly PFE.

It is well known [13, 28] that $\bar{p}_0$ will be locally asymptotically stable for the purely demographic system if and only if there are no solutions with $\operatorname{Re}\lambda \ge 0$ of

$$\frac{1}{\mathcal{R}}\int_0^\infty \beta(a)\pi(a)e^{-\lambda a}\,da + \frac{\psi'(K)K\mathcal{R}}{\int_0^\infty \pi(a)\,da}\int_0^\infty \pi(a)e^{-\lambda a}\,da = 1.$$

All these conditions on the demographic functions will be implicitly assumed from here onwards.

In order to study the stability of the equilibrium $\bar{p}$ of (3), we follow the abstract approach described in [22] using semigroup theory. To perform this, we transform system (3) into the abstract Cauchy problem:

$$\begin{cases} p'(t) = A(p(t) + H(p(t)) + F(p(t)) \\ p(0) = p^0 \end{cases} \tag{7}$$

where A is the generator of a C_0-semigroup on a certain Banach space X, while $F : X \to X$ and $H : X \to F_A$ are locally Lipschitz operators.
Here F_A is the Favard class of A (see [2]). We remember the following general Theorem presented in (see [6] for details):

Theorem A ([22, 6])**.** Assume

($\mathcal{H}_1$) $A : D(A) \subset X \to X$ is the generator of a C_0-semigroup on a Banach space X

($\mathcal{H}_2$) $H : X \to F_A$ and $F : X \to X$ are locally Lipschitz continuous, i.e. for all $R > 0$ there exists $L_R, \quad K_R > 0$ such that

$$||H(p) - H(q)||_{F_A} \leq L_R||p - q||, \quad ||F(p) - F(q)| \leq K_R||p - q||$$

for all $p, q \in X$ such that $||p||, \ ||q|| \leq R$ (more generally, H and F could be defined only on an open set of X).

Then

(a) for each $p^0 \in X$ there exists a unique (local) mild solution of (7) i.e. a continuous function $t \to p(t)$ satisfying the integral equation

$$p(t) = e^{tA}p^0 + A\int_0^t e^{(t-s)A}H(p(s))ds + \int_0^t e^{(t-s)A}F(p(s))ds;$$

(b) If H and F are continuously differentiable and $(p^0 + H(p^0)) \in D(A)$ then $p(t)$ is a classical solution of (7), i.e. $p(t) + H(p(t)) \in D(A)$ for each $t \in [0, t_{max})$, $p(t)$ is differentiable and satisfies the equation (7) for each $0 \leq t < t_{max}$.

(c) The mild solution depend continuously on the initial datum and give rise to a nonlinear semigroup $T(t)$.

To use this "abstract approach" for system (7), we choose for X :

$$X := \left\{ p = (p_i)_{i\in\mathbb{N}} : p_i \in L^1(0, \infty) \ \forall \ i \geq 0, \sum_{i=1}^{+\infty} i \int_0^{+\infty} |p_i(a)|da < \infty \right\}$$

endowed whith the norm:

$$||p|| := \int_0^{+\infty} |p_0(a)|da + \sum_{i=1}^{+\infty} i \int_0^{+\infty} |p_i(a)|da.$$

As the operators A, F and H, we let A be the closure of the (closable) linear operator $\mathcal{A}$ on X defined by:

$$D(\mathcal{A}) = \Big\{ p = (p_i)_{i\in\mathbb{N}} : p_i \in W^{1,1}(0, \infty), p_i(0) = 0 \ \forall i \geq 0, \\ \exists \ N \in \mathbb{N} \text{ s.t. } p_i \equiv 0 \ \forall \ i > N \Big\}$$

$$\mathcal{A}p_i(a) := -p_i'(a) - (\mu(a) + i(\alpha + \sigma))p_i(a) + (i + 1)\sigma p_{i+1}(a) \quad \text{for } i \geq 0$$

F is the non linear operator given by:

$$\begin{aligned} (Fp)_0(a) &= \frac{-h \sum_{i=1}^{+\infty} i \int_0^{+\infty} p_i(s)ds}{c + \sum_{i=0}^{+\infty} \int_0^{+\infty} p_i(s)ds} p_0(a) \\ (Fp)_i(a) &= \frac{-h \sum_{i=1}^{+\infty} i \int_0^{+\infty} p_i(s)ds}{c + \sum_{i=0}^{+\infty} \int_0^{+\infty} p_i(s)ds} \Big(\sum_{j=1}^{i} c_j p_{i-j}(a) - p_i(a) \Big) \ i \geq 1. \end{aligned} \tag{8}$$

F is defined on E where

$$E := \{p \in X : c + \sum_{i=0}^{+\infty} \int_0^{+\infty} p_i(s)ds \neq 0\}.$$

Finally H is

$$\begin{aligned}(Hp)_0(a) &= -\psi\Big(\int_0^{+\infty}\sum_{i=0}^{+\infty}p_i(s)ds\Big)\Big(\int_0^{+\infty}\beta(s)\sum_{i=0}^{+\infty}p_i(s)\xi^i ds\Big)\pi(a)\\ (Hp)_i(a) &\equiv 0 \qquad \text{for } i\geq 1\end{aligned} \tag{9}$$

In order to study the stability of p^*, we will use the linearization principle, proved in [5] for non linear semigroups, and specialized to equations of the type (7) in [23].

Before stating the precise theorem, we recall some standard notations and results about the spectrum of generators of semigroups (see, for instance, [9] or [28]). Let $A : D(A) \subset X \to X$ be the generator of a C_0-semigroup $T(t)$ on a Banach space X, then one can define the quantities:

- $s(A) := \sup\{Re\lambda : \lambda \text{ is an eigenvalue of } A\}$, the *spectral bound of* A.
- $\rho(A) := \sup\{|\lambda| : \lambda \text{ is an eigenvalue of } A\}$, the *spectral radius of* A.
- $\omega_0(A) := \lim_{t\to\infty}\frac{||\log T(t)||}{t}$, the *type or growth bound* of $T(t)$.
- $\omega_1(A) := \lim_{t\to\infty}\frac{||\log \alpha[T(t)]}{t}$, where α is the *measure of noncompactness*

It is well known [28, Prop. 4.13] that $\omega_0(A) = \max(\omega_1(A), s(A)))$.

For an equilibrium p^* of (7), define the linear operator $B_{p^*}p := A(I+H'(p^*))p + F'(p^*)p$. The type of the semigroup generated by B_{p^*} determines the stability of p^*:

Theorem B ([23, Corollary 1])**.** If $\omega_0(B_{p^*}) < 0$, then p^* is exponentially asymptotically stable for (7). If $\omega_0(B_{p^*}) > 0$, $X = X_1 \oplus X_2$ with X_1 finite dimensional, X_i invariant with respect to $e^{tB_{p^*}}$ for $i = 1,\ 2$, and

$$\min\{Re\lambda : \lambda \in \sigma(B_{p^*}|_{X_2})\} > \max\{\omega_0(B_{p^*}|_{X_2}), 0\}$$

then p^* is unstable for (7).

In order to apply Theorem B to the equilibrium $\bar{p}$ of (3), we need first to linearize H and F. We can easily establish the following:

Lemma 2.1. *Let $c_i \geq 0,\ i \geq 1$ and $\sum_{i=1}^{+\infty} c_i = 1$. The Frèchet derivative of F and H in $\bar{p}$ are given by:*

$$\begin{aligned}\Big[F'(\bar{p})u\Big]_0(a) &= -\frac{h}{c+K}\frac{\pi(a)}{\int_0^{+\infty}\pi(u)du}\sum_{i=1}^{+\infty} i\int_0^{+\infty}u_i(s)ds\\ \Big[F'(\bar{p})u\Big]_i(a) &= \frac{c_i h}{c+K}\frac{\pi(a)}{\int_0^{+\infty}\pi(u)du}\sum_{i=1}^{+\infty} i\int_0^{+\infty}u_i(s)ds,\ i\geq 1\\ \Big[H'(\bar{p})u\Big]_0(a) &= -\Big(\frac{\psi'(K)K\mathcal{R}}{\int_0^{+\infty}\pi(u)du}\sum_{i=0}^{+\infty}\int_0^{+\infty}u_i(s)ds\\ &\qquad + \frac{1}{\mathcal{R}}\int_0^{+\infty}\beta(s)\sum_{i=1}^{+\infty} iu_i(s)\xi^i ds\Big)\pi(a)\\ \Big[H'(\bar{p})u\Big]_i(a) &= 0,\ i\geq 1.\end{aligned}$$

Note that these operators differ from those obtained in [23] only in the components $\big[F'(\bar{p})u\big]_i$, $i \geq 1$. Indeed, if $c_1 = 1$ and $c_i = 0$ for $i > 1$ (infections with a single parasite), we recover exactly the results in [23].

Because of the structure of $H'(\bar{p})$ (all components beyond the 0-th are 0), the following proposition is useful to determine the type of the semigroup generated by $B(\bar{p})$:

Theorem C ([23, Theorem 3])**.** Let A_0 and B_1 be the generators of C_0-semigroups on the Banach spaces Y_0 and Y_1 respectively. Let $H_i \in \mathcal{L}(Y_i, F_{A_0})$ for $i = 0, 1$ and $B_{10} \in \mathcal{L}(Y_1, Y_0)$.Then:

(i) The operator $\tilde{B}$ defined by:

$$\tilde{B}\begin{pmatrix} q_0 \\ q_1 \end{pmatrix} = \begin{pmatrix} A_0(q_0 + H_0 q_0 & +H_1 q_1) + B_{10} q_1 \\ & B_1 q_1 \end{pmatrix}$$

is the generator of a C_0-semigroup on $Y = Y_0 \oplus Y_1$;

(ii) If, letting I_0 be the identity in Y_0,

$$(I_0 + H_0) \quad \text{is invertible on } Y_0,$$

then

$$\omega_0(B_1) < 0 \quad \text{and} \quad \omega_0(A_0(I_0 + H_0)) < 0 \Longleftrightarrow \omega_0(\tilde{B}) < 0$$

We now show that Theorem C can be applied to $\tilde{B} := B_{\bar{p}}$.
Set

$$\bar{X}_1 = \{\bar{q}_1 = (q_i)_{i\geq 1} : q_i \in L^1(0, +\infty), \sum_{i=1}^{+\infty} \int_0^{+\infty} i|q_i(a)|da < \infty\}$$

$$X_0 = X_1 = L^1(0, +\infty) \quad \text{and} \quad X = X_0 \oplus \bar{X}_1$$

The operator $\tilde{B}$ can be represented as

$$\tilde{B}\begin{pmatrix} q_0 \\ \bar{q}_1 \end{pmatrix} = \begin{pmatrix} A_0(q_0 + H_0 q_0 & +H_1 \bar{q}_1) + B_{10} \bar{q}_1 \\ & \bar{B}_1 \bar{q}_1 \end{pmatrix}$$

where

$$\begin{aligned}
A_0 &: D(A_0) = \{q_0 \in X_0 : q_0 \in W^{1,1}(o, \infty), q_0(0) = 0\} \to X_0 \\
A_0 q_0(a) &= -q_0'(a) - \mu(a) q_0(a), \\
B_{10} &: \bar{X}_1 \to X_0 \\
B_{10}\bar{q}_1(a) &= \frac{-h \sum_{i=1}^{+\infty} i \int_0^{+\infty} q_i(s)ds}{c + K} p_0^*(a) + \sigma q_1(a); \\
H_0 &: X_0 \to F_{A_0}, \\
H_0 q_0(a) &= -\Big(\frac{\psi'(K) K \mathcal{R}}{\int_0^{+\infty} \pi(u)du} \int_0^{+\infty} q_0(s)ds + \frac{1}{\mathcal{R}} \int_0^{+\infty} \beta(s) q_0(s) ds\Big)\pi(a); \\
H_1 &: X_1 \to F_{A_0} \\
H_1 \bar{q}_1(a) &= -\Big(\frac{\psi'(K) K \mathcal{R}}{\int_0^{+\infty} \pi(u)du} \sum_{i=1}^{+\infty} \int_0^{+\infty} q_i(s)ds + \frac{1}{\mathcal{R}} \int_0^{+\infty} \beta(s) \sum_{i=1}^{+\infty} q_i(s)\xi^i ds\Big)\pi(a).
\end{aligned}$$

$\bar{B}_1$ is the closure of

$$B_1 : D(B_1) \to \bar{X}_1, \quad B_1 = B + A_1$$

with

$$\begin{aligned} A_1 &: D(A_1) \to \bar{X}_1 \\ D(A_1) &= \Big\{ \bar{q}_1 \in \bar{X}_1 : q_i \in W^{1,1}(0,+\infty), q_i(0) = 0 \ \forall\ i \geq 1, \\ &\qquad\qquad \exists\ N \in \mathbb{N} \text{ s.t. } p_i \equiv 0 \ \forall\ i > N \Big\} \\ A_1 q_i(a) &= -q_i'(a) + (\mu(a) + i(\alpha+\sigma) q_i(a) + \sigma(i+1) q_{i+1}, \quad i \geq 1 \end{aligned} \tag{10}$$

and

$$\begin{aligned} B &: \bar{X}_1 \to \bar{X}_1 \\ B\bar{q}_1(a) &= b\varphi(\bar{q}_1), \text{ with } b(\in X_1) = (c_1, c_2, \dots)\pi(a), \\ \varphi(\bar{q}) &= \frac{hK}{(c+K)L} \sum_{i=1}^{\infty} i \int_0^{+\infty} q_i(s) ds. \end{aligned} \tag{11}$$

Proposition 1. *The closure $\overline{A}_1$ of A_1 generates a C_0-semigroup on $\bar{X}_1$, with $\omega_0(\overline{A}_1) < 0$. The closure of B_1 generates a C_0-semigroup on $\bar{X}_1$.*

Proof. To see that $\overline{A}_1$ generates a C_0-semigroup on $\bar{X}_1$ with $\omega_0(\overline{A}_1) < 0$, one can follow the proof given for the operator A in [22].

Since B is bounded, the classical result on bounded perturbations can be applied and $\overline{B}_1 = \overline{A}_1 + B$ generates a C_0-semigroup. □

Proposition D ([23, Prop. 5 and 6])**.** $I_0 + H_0$ has a bounded inverse on X_0, and $\omega_0(A_0(I_0 + H_0)) < 0$.

Summarizing the results of this Section, we have the following

Proposition 2. *The equilibrium $\bar{p}$ of (3) is asymptotically stable [unstable] if $\omega_0(\overline{A}_1 + B) < [>]\ 0$, with A_1 and B defined in (10) and (11).*

3. $s(B + A) < 0 \iff \rho(B(-A)^{-1}) < 1$**.** It is well known that, in most epidemic models, stability [or instability[of the disease–free equilibrium holds if $R_0 < 1$ [> 1], where R_0 represents the average number of infectious produced by a single infected over its infectious period. Diekmann and Heesterbeek [7] have given a general definition of R_0 in terms of the spectral radius of a positive operator. In [8] they show, in a finite dimensional context, the equivalence between $R_0 < 1$ and the stability of the disease–free equilibrium, by proving the following

Proposition E. Let B a nonnegative irreducible matrix, and D an invertible matrix with nonnegative inverse. Then

$$s(B - D) < 0 \iff \rho(BD^{-1}) < 1.$$

In most applications, the variables indicate different infectious stages, D describes the transitions between stages (in many cases, D is a diagonal matrix whose entries are the exit rates from the infective classes) and B represents the infection process.

In this Section, we give an extension of Proposition E to the infinite-dimensional case that can be applied to Proposition 2. Heesterbeek [11] gives a definition of R_0 in an infinite-dimensional case, but we could not find in the literature any explicit statement, or proof, of a result analogous to Proposition E in infinite dimensions.

Our proof is completely analogous to that in [8], but, first, we need the following

Lemma 3.1. *Let C be an linear compact positive operator on Banach space X, with total positive cone X^+ (i.e., its linear hull is dense in X). If C has a spectral radius $\rho > 0$, then ρ is a pole of the risolvent of maximal order on the spectral circle, with an eigenvector in X^+.*

Proof. See [27, Appendix 2.4, Corollary]. □

Our result is the following

Proposition 3. *Let A and K be operators on a Banach space X with total positive cone X^+. Let:*

H1) *A is the generator of a positive strongly continuos semigroup with $\omega_0(A) < 0$. Hence there exists $(-A)^{-1}$ and $(-A)^{-1} = \int_0^{+\infty} e^{tA}dt \geq 0$ (see [9] , Cap. VI, Lemma 1.9 for details).*

H2) *K is a linear compact positive operator.*

Then the following are equivalent:

(a) $s(A + K) < 0$

(b) $\rho(K(-A)^{-1}) < 1$

Proof. $(a) \Longrightarrow (b)$ Since K is compact $\omega_1(A + K) = \omega_1(A)$[28, Proposition 4.14]. Therefore from (1) $\omega_1(A + K) = \omega_1(A) \leq \omega_0(A) < 0$ and from this and (a)

$$\omega_0(A + K) = \max(s(A + K), \omega_1(A + K)) < 0 \tag{12}$$

Since $A+K$ generates a strongly positive semigroup, Lemma VI.1.9 of [9] can be applied to the semigroup generated by $A+K$ and we have from (12) $[-(A+K)]^{-1} \geq 0$. From $H1)$ and $H2)$ it follows that the operator $K(-A)^{-1}$ is compact and positive, therefore $\rho(K(-A)^{-1}) \in \sigma(K(-A)^{-1})$ [3, Prop. A 3.12].

If $\rho(K(-A)^{-1}) = 0$ (b) is true. Therefore assume $\rho(K(-A)^{-1}) > 0$; by virtue of Lemma 3.1 there exists a positive eigenvector φ that corresponds to $\rho(K(-A)^{-1})$. From $K(-A)^{-1}\varphi = \rho(K(-A)^{-1})\varphi$ it follows

$$(K(-A)^{-1} - I)\varphi = (\rho(K(-A)^{-1}) - 1)\varphi;$$

letting $\psi = (-A)^{-1}\varphi$, this identity becomes

$$K\psi + A\psi = (\rho(K(-A)^{-1}) - 1)\varphi. \tag{13}$$

Applying $[-(A + K)]^{-1}$ to this identity, we have

$$-\psi = (-A - K)^{-1}(\rho(K(-A)^{-1}) - 1)\varphi.$$

Since $-\psi \leq 0$ it follows that $\rho(K(-A)^{-1}) - 1 \leq 0$, that is

$$\rho(K(-A)^{-1}) \leq 1.$$

If $\rho(K(-A)^{-1}) = 1$, (13) becomes $K\psi + A\psi = 0$ which contradicts (a). This concludes the proof of (b).

$(b) \Longrightarrow (a)$ We show at first that $s(K(-A)^{-1} - I) \leq \rho(K(-A)^{-1}) - 1$. To prove this, let λ be an eigenvalue of $K(-A)^{-1} - I$, that corresponds to the eigenvector v, then $K(-A)^{-1}v - v = \lambda v$, therefore $K(-A)^{-1}v = (\lambda + 1)v$ and $|\lambda + 1| \leq \rho(K(-A)^{-1})$; from this it easily follows that $\operatorname{Re}\lambda \leq \rho(K(-A)^{-1}) - 1$ and therefore $s(K(-A)^{-1} - I) \leq \rho(K(-A)^{-1}) - 1$.

From $H1)$ and (2) $K(-A)^{-1}$ is linear positive and continuous, therefore it generates a strongly positive continuous semigroups and $0 \in \rho(K(-A)^{-1} - I)$; then

Lemma 1.9, Cap.VI of [9] can be applied to $K(-A)^{-1}$ and since $s(K(-A)^{-1}-I)<0$ we get $[-(K(-A)^{-1}-I)]^{-1}\geq 0$. Therefore, since $(-A)^{-1}\geq 0$

$$[(-K(-A)^{-1}+I)(-A)]^{-1}=(-A)^{-1}[-(K(-A)^{-1}-I)]^{-1}\geq 0$$

and

$$[(-K(-A)^{-1}+I)(-A)]^{-1}=(-K-A)^{-1}\geq 0.$$

Then Lemma VI.1.9 of [9] can be applied to $A+K$ and we conclude that $s(A+K)<0$. □

4. **The threshold for the stability of the parasite–free equilibrium.** By Proposition 2, we know that $\bar{p}$ is asymptotically stable if $\omega(B+\overline{A}_1)<0$. From the previous Section, we have

Proposition 4. $s(B+\overline{A}_1)<0 \Longleftrightarrow \rho(B(-\overline{A}_1)^{-1})<1$.

Proof. By virtue of Proposition 1 $\overline{A}_1$ verifies $H1)$ of Proposition 3; B is a linear compact (with one-dimensional range) positive operator, satisfying $H2)$ of Proposition 3. Moreover L^1_+ is a total cone in L^1. Therefore the thesis follows from Proposition 3. □

Theorem 4.1. *The equilibrium $\bar{p}$ of (3) is asymptotically stable if $R_0<1$ and unstable if $R_0>1$ where*

$$\begin{aligned} R_0 &= \rho(B(-\overline{A}_1)^{-1}) \\ &= \frac{hK}{(c+K)L}\int_0^{+\infty} e^{(-\alpha+\sigma)a}G'\Big(\frac{\sigma}{\alpha+\sigma}+\frac{\alpha}{\alpha+\sigma}e^{(-\alpha+\sigma)a}\Big)da\int_0^{+\infty}\pi(a+s)ds. \end{aligned} \tag{14}$$

and $G(z):=\sum_{i=1}^{+\infty}c_iz^i$.

Proof. By Proposition 4, $s(B+\overline{A}_1)<0\Longleftrightarrow\rho(B(-\overline{A}_1)^{-1})<1$. Moreover, $\omega_1(\overline{A}_1+B)=\omega_1(A_1)$ since B is compact [28], Prop. 4.14) and $\omega_1(\overline{A}_1)<0$ (Proposition 1); therefore $\omega_0(B_1)<0$ if and only if $\rho(B(-\overline{A}_1)^{-1})<1$.

We now show that $\rho(B(-\overline{A}_1)^{-1})$ is given by the expression (14).

In fact, let ρ be an eigenvalue and q an eigenvector of $B(-A_1)^{-1}$, that is

$$B(-A_1)^{-1}q=\rho q \tag{15}$$

By the definition (11) of B we have $B(-\overline{A}_1)^{-1}q=b\varphi((-\overline{A}_1)^{-1}q)$. Then in (15) we can set $q=b$ so that necessarily $\rho=\varphi((-\overline{A}_1)^1b)$. This means that $\rho(B(-\overline{A}_1)^{-1})=\varphi(p)$ with $p:=(-A_1)^{-1}b$.

We need only to compute $\varphi(p)$. By definition, $b=-\overline{A}_1p$, i.e.

$$b+\overline{A}_1p=0. \tag{16}$$

Using $b_i=c_i\pi(a)$ for $i\geq 1$, (16) becomes,

$$\begin{cases} -p_i'(a)-(\mu(a)+i(\alpha+\sigma))p_i(a)+\sigma(i+1)p_{i+1}(a)+c_i\pi(a)=0 \\ p_i(0)=0 \end{cases} \tag{17}$$

If we set $q_i:=\dfrac{p_i(a)}{\pi(a)}$, the first of (17) become

$$q_i'(a)=-i(\alpha+\sigma))q_i(a)+\sigma(i+1)q_{i+1}(a)+c_i \quad \text{for} \quad i\geq 1 \tag{18}$$

Multiplying (18) by z^i and summing from 0 to $+\infty$ (for $i = 0$, we can set $c_0 = 0$ so that $q_0' = \sigma q_1$) we get:

$$\sum_{i=0}^{+\infty} q_i'(a)z^i = -\sum_{i=0}^{+\infty} i(\alpha+\sigma))q_i(a)z^i + \sum_{i=0}^{+\infty} \sigma(i+1)q_{i+1}(a)z^i + \sum_{i=0}^{+\infty} c_i z^i \tag{19}$$

Setting

$$Q(a,z) := \sum_{i=0}^{+\infty} q_i(a)z^i$$

(19) can be written as

$$\begin{cases} Q_a(a,z) = (\sigma - (\alpha+\sigma)z)Q_z(a,z) + G(z) \\ Q(0,z) = 0 \end{cases} \tag{20}$$

We can then obtain

$$\begin{aligned} \varphi(p) &= \frac{hK}{(c+K)L}\int_0^{+\infty}\sum_{i=1}^{+\infty} ip_i(a)da = \frac{hK}{(c+K)L}\int_0^{+\infty}\pi(a)\sum_{i=1}^{+\infty} iq_i(a)da \\ &= \frac{hK}{(c+K)L}\int_0^{+\infty}\pi(a)Q_z(a,1)da. \end{aligned} \tag{21}$$

The solution of (20) is

$$Q(a,z) = \int_0^a G\left(e^{-(\alpha+\sigma)(a-s)}z + \frac{\sigma}{\alpha+\sigma}(1-e^{-(\alpha+\sigma)(a-s)})\right)ds. \tag{22}$$

Substituting (22) in (21), we obtain

$$\begin{aligned} \varphi(p) = \frac{hK}{(c+K)L}\int_0^{+\infty}\pi(a)da\int_0^a e^{-(\alpha+\sigma)(a-s)} \\ \times G'\left(e^{-(\alpha+\sigma)(a-s)} + \frac{\sigma}{\alpha+\sigma}(1-e^{-(\alpha+\sigma)(a-s)})\right)ds \end{aligned}$$

which, interchanging the order of integration and changing variables, can be written as

$$\begin{aligned} R_0 = \varphi(p) = \frac{hK}{(c+K)L}\int_0^{+\infty}\int_0^{+\infty}\pi(s+\tau)e^{-(\alpha+\sigma)\tau} \\ \times G'\left(\frac{\sigma}{\alpha+\sigma} + \frac{\alpha}{\alpha+\sigma}e^{-(\alpha+\sigma)\tau}\right)d\tau\, ds. \end{aligned} \tag{23}$$

Finally, with further changes of the order of integration and of variables, one arrives at showing that $\varphi(p)$ and hence $\rho(B(-\overline{A}_1)^{-1})$ is given by the expression in (14). □

In order to give a biological interpretation of the quantity R_0 defined in the previous Theorem, it is convenient to think in terms of the average number of infectious 'parcels' produced, in a population at the infection–free equilibrium, by one average infectious 'parcel' in absence of further infections.

By definition, at time $\tau = 0$, the 'parcel' will consist of i parasites with probability c_i; then, it will be subject to a death-and-extinction process $Z(\tau)$, due to parasite deaths (at rate σ) and host deaths (at rate $\mu(a)+\alpha j$), if host's age is a and number of parasites is j). Assume that the initial host's age (at time $\tau = 0$) is a. Then

$p_i(\tau)$ (the probability that the host is alive and carries i parasites at time τ) satisfy the following system of equations:

$$\begin{cases} p_i'(\tau) = -(\mu(a+\tau) + i(\alpha+\sigma))p_i(\tau) + \sigma(i+1)p_{i+1}(\tau) \\ p_i(0) = c_i \end{cases} \tag{24}$$

Analogously to above, considering the variables $q_i(\tau) := \dfrac{p_i(\tau)\pi(a)}{\pi(a+\tau)}$ and

$$Q(\tau, z) := \sum_{i=0}^{+\infty} q_i(\tau) z^i,$$

we find that Q satisfies

$$\begin{cases} Q_\tau(\tau, z) + ((\alpha+\sigma)z - \sigma)Q_z(\tau, z) = 0 \\ Q(0, z) = G(z). \end{cases} \tag{25}$$

The solution of (25) is

$$Q(\tau, z) = G\left(e^{-(\alpha+\sigma)\tau} z + \frac{\sigma}{\alpha+\sigma}(1 - e^{-(\alpha+\sigma)\tau})\right). \tag{26}$$

Furthermore, the average number of parasites surviving (together with the host) at time τ is

$$\begin{aligned} \mathbb{E}(Z(\tau)) &= \sum_{i=1}^{\infty} i p_i(\tau) = \frac{\pi(a+\tau)}{\pi(a)} \sum_{i=1}^{\infty} i q_i(\tau) = \frac{\pi(a+\tau)}{\pi(a)} Q_z(\tau, 1) \\ &= \frac{\pi(a+\tau)}{\pi(a)} G'\left(\frac{\sigma}{\alpha+\sigma} + \frac{\alpha}{\alpha+\sigma} e^{-(\alpha+\sigma)\tau}\right) e^{-(\alpha+\sigma)\tau} \end{aligned} \tag{27}$$

Since the rate at which each parasite produces new successful infectious 'parcels' is (when the population density is K) $\dfrac{hK}{c+K}$, the average number of new successful parcels produced over all times $\tau > 0$ is

$$\begin{aligned} R(a) &= \frac{hK}{c+K} \int_0^\infty \mathbb{E}(Z(\tau))\, d\tau \\ &= \frac{hK}{c+K} \int_0^\infty \frac{\pi(a+\tau)}{\pi(a)} G'\left(\frac{\sigma}{\alpha+\sigma} + \frac{\alpha}{\alpha+\sigma} e^{-(\alpha+\sigma)\tau}\right) e^{-(\alpha+\sigma)\tau}\, d\tau. \end{aligned} \tag{28}$$

We made explicit the dependence of the previous computations on the initial host's age a.

We need now to consider an average infection. In a stationary population, the probability density of hosts' age is $\dfrac{\pi(a)}{L}$. Hence, a natural definition for the reproductive number is

$$R_0 = \int_0^\infty \frac{\pi(a)}{L} R(a)\, da.$$

Substituting (28) in this expression, we obtain exactly expression (23) for R_0.

Finally, we consider the special case, already studied through 3-dimensional approximations, where no parameters are age-dependent and the distribution of infectious 'parcels' follows a (truncated) Poisson.

Corollary 1. *Let $\mu(a) \equiv \mu$ for each $a \in [0, +\infty)$, and $c_i = \dfrac{\lambda^i e^{-\lambda}}{i!(1-e^{-\lambda})}$ for $i \geq 1$. Then*

$$R_0 = \frac{hK}{c+K}\frac{\lambda e^{-\lambda}}{1-e^{-\lambda}}\frac{1}{\alpha+\sigma}e^{\frac{\lambda\sigma}{\alpha+\sigma}}\int_0^1 t^{\frac{\mu}{\alpha+\sigma}}e^{\frac{\lambda\alpha t}{\alpha+\sigma}}\,dt. \tag{29}$$

Proof. By Proposition 4.1

$$R_0 = \frac{hK}{(c+K)L}\int_0^{+\infty} e^{-(\alpha+\sigma)a}G'\Big(\frac{\sigma}{\alpha+\sigma}+\frac{\alpha}{\alpha+\sigma}e^{(-\alpha+\sigma)a}\Big)da\int_0^{+\infty}\pi(a+s)ds.$$

Since $\mu(a) = \mu$, we have $\pi(a+s) = e^{-\mu(a+s)}$ and $L = \int_0^{+\infty}\pi(s)\,ds = \frac{1}{\mu}$. Moreover

$$G(z) = \sum_{i=1}^{+\infty}\frac{z^i\lambda^i e^{-\lambda}}{i!(1-e^{-\lambda})} = \frac{e^{-\lambda}(e^{\lambda z}-1)}{1-e^{-\lambda}} \text{ so that } G'(z) = \frac{\lambda e^{-\lambda}}{1-e^{-\lambda}}e^{\lambda z}.$$

Therefore we have

$$R_0 = \frac{hK}{c+K}\frac{\lambda e^{-\lambda}}{1-e^{-\lambda}}\int_0^{+\infty} e^{-(\alpha+\sigma+\mu)a}e^{\lambda(\frac{\sigma}{\alpha+\sigma}+\frac{\alpha}{\alpha+\sigma}e^{-(\alpha+\sigma)a})}\,da$$

that, with a change of variables, reduces to the form (29). □

Remark 1. Note that in the 3-dimensional approximation of the same model [21], it was obtained

$$R_0 = \frac{hK}{c+K}\frac{\lambda}{1-e^{-\lambda}}\frac{1}{\mu+\sigma+\alpha+\eta_K}$$

where η_K solves the second degree equation

$$\eta(\sigma+\alpha+\eta+\frac{hK}{c+K}) - \alpha\lambda\frac{hK}{c+K} = 0.$$

It is then apparent that this approximation does not yield the correct threshold parameter (29).

In order to interpret (29), it is first of all worth noting that $\dfrac{\lambda}{1-e^{-\lambda}}$ is the average number of parasites per clump, so that, when λ goes to 0, we recover the model with single infections. Consistently, it is easy to see that, setting $\lambda = 0$ in (29), we obtain the expression (1). Hence, in order to properly understand the effect of clumps, it is convenient to set $h' = h\dfrac{\lambda}{1-e^{-\lambda}}$, so that rate of parasite production becomes independent of λ and we write

$$R_0 = \frac{h'K}{c+K}\frac{1}{\alpha+\sigma}\int_0^1 t^{\frac{\mu}{\alpha+\sigma}}e^{-\frac{\lambda\alpha(1-t)}{\alpha+\sigma}}\,dt. \tag{30}$$

One easily sees that the expression (30); hence, infections in clumps have a negative effect on the reproduction number R_0. If parasite aggregation were caused by 'clumped' infections, increasing aggregation would reduce the reproduction number, and so the persistence, of parasites, in contrast with the conclusions obtained in the 2–dimensional approximation [1].

Finally, since (30) is anyway a complex expression, some approximations may be useful. Here in particular, we consider the cases of α close to 0 (little mortality induced by parasites) and λ close to 0 (small clumps).

For the first case, one easily obtains

$$R_0 = \frac{h'K}{c+K}\frac{1}{\mu+\sigma}\left(1-\alpha(\frac{1}{\mu+\sigma}+\frac{\lambda}{\mu+2\sigma})+O(\alpha^2)\right). \tag{31}$$

The other approximation yields

$$R_0 = \frac{h'K}{c+K}\frac{1}{\mu+\alpha+\sigma}\left(1 - \frac{\alpha\lambda}{\mu+2(\alpha+\sigma)} + O(\lambda^2)\right). \tag{32}$$

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