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Threshold phenomena for an age-structured epidemic model

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1. Introduction

In the present paper we consider a mathematical model for the spread of infectious diseases in age-structured populations. The model is derived for S-I-R type diseases such as measles, chickenpox, rubella and mumps in a demographically stationary population. That is, the population is composed of three subpopulations; susceptibles (S), infetious (I) and recovered (R). The disease is directly transmitted and a susceptible individual who contracts the disease will become infective but will eventually recover with permanent immunity. It is assumed that the latent period is negligibly short, so all of infected individuals are infectious. Moreover we assume that the existence of diseases does not increase the death rate of the population.

The S-I-R type age-independent epidemic model has already been investigated and its threshold theorem is well known (Hethcote 1974). Let S(t), I(t) and R(t) be the number of respectively the susceptible, infectious and immune population at

time t. The simple age-independent S-I-R model is given by the system of ordinary differential equations

$$S'(t)=\mu N-\beta I(t)S(t)-\mu S(t), \tag{1.1a}$$

$$I'(t)=\beta I(t)S(t)-(\gamma+\mu)I(t), \tag{1.1b}$$

$$R'(t)=\gamma I(t)-\mu R(t), \tag{1.1c}$$

where β is the infection rate, μ the natural death rate, γ the recovery rate and N is the population size. The threshold theorem tells us that there exists a threshold value R_0 such that the disease-free steady state (S=N, I=R=0) is globally stable if $R_0<1$ and there exists only one endemic steady state and it is globally stable if $R_0>1$. Hence the disease can invade into the susceptible population if and only if the threshold value exceeds unity. In epidemiology, the basic reproduction number is defined as the number of secondary cases of infection produced by one primary case in a totally susceptible population. In the context of the simple age-independent S-I-R model, the basic reproduction number is no other than the threshold value R_0 given as

$$R_0=\frac{\beta N}{\gamma+\mu}=(\text{contact rate})\times(\text{population size}) \tag{1.2}$$

$$\times(\text{average infectious period}).$$

The simple model predict that the disease can oscillate about the endemic equilibrium state but that these fluctuations will eventually damp down to the equilibrium level. However, in the real, most reported cases show long-term steady oscillations about an equilibrium level. For example, it is known that the number of cases of incidence of measles has a period of two years (Greenhalgh 1987; Hoppensteadt 1975). This phenomenon suggests

that the real dynamics of S-I-R diseases could be much more complex than predicted by the simple model. It is known that the oscillatory behavior can be explained either by using a stchastic model or by introducing seasonal variation into the contact rate. However another promising way to promote realistic features in the models is to introduce age-structure, since for many directly transmitted diseases, the per capita force or rate of infection tends to vary systematically with age (Anderson 1991). If the age-structured model for S-I-R type epidemics allows time-periodic solutions, it would give an explanation for the oscillation in the recurrence of measles epidemics.

Note 1.1. For S-I-S type model (that is, there is no immune class), it has been proved that periodic oscillations do not occur, even in the age-structured model (Busenberg, et. al 1989).

2. The basic S-I-R type model with age-structure

We subdivide a closed age-structured population into three compartments containing susceptibles, infectives and immunes. We assume that the population is in a demographic stationary state and so the age-density of the population is given by

$$N(a)=B\ell(a), \quad \ell(a):=\exp(-\int_0^a \mu(\sigma)d\sigma),$$

where B is the constant birth rate and $\mu(a)$ is the natural death rate at age a and $\ell(a)$ is the survival rate. Let S(t,a), I(t,a)

and $R(t,a)$ be the age-densities of respectively the susceptible, infected and immune populations at time t, so that

$$N(a)=S(t,a)+I(t,a)+R(t,a).$$

Let $\beta(a,\sigma)\in L^{\infty}_{+}((0,\omega)\times(0,\omega))$ be the age-dependent transmission coefficient, that is, the probability that a susceptible person of age a meets an infectious person of age σ and becomes infected per unit of time. Then the age-structured model for S-I-R type epidemic is described by the system of partial differential equations

$$(\partial_t+\partial_a)S(t,a)=-\lambda(t,a)S(t,a)-\mu(a)S(t,a), \tag{2.1a}$$

$$(\partial_t+\partial_a)I(t,a)=\lambda(t,a)S(t,a)-(\mu(a)+\gamma)I(t,a), \tag{2.1b}$$

$$(\partial_t+\partial_a)R(t,a)=\gamma I(t,a)-\mu(a)R(t,a), \tag{2.1c}$$

$$S(t,0)=B,\ I(t,0)=R(t,0)=0, \tag{2.1d}$$

$$\lambda(t,a)=\int_0^{\omega}\beta(a,\sigma)I(\sigma,t)d\sigma, \tag{2.1e}$$

where $\lambda(t,a)$ is the force of infection and ω is the life span of the population.

Existence and uniqueness of solutions for the system (2.1) can be shown by using semigroup method (Inaba 1990: Webb 1985) or by inducing the integral equation for $I(t,a)$ (Gripenberg 1983). Moreover the solution is positive with respect to the positive initial data.

3. The invasion problem

First let us consider the situation that very small infectious population invade into a totally susceptible population. In this initial phase of epidemic, the growth of infecteds is described by the following linearized equation

$$(\partial_t+\partial_a)I(t,a)=N(a)\int_0^\omega \beta(a,\sigma)I(t,\sigma)d\sigma-(\mu(a)+\gamma)I(t,a), \qquad (3.1)$$

$$I(t,0)=0, \quad I(0,a)=I_0(a),$$

since we can ignore the fact that the density of susceptibles decreases due to the infection process. Let $\hat{I}(a,\tau)$, $\tau\in C$ be the Laplace transform of $I(t,a)$

$$\hat{I}(a,\tau):=\int_0^\infty e^{-\tau t}I(t,a)dt. \qquad (3.2)$$

It is easily seen that using a priori estimate for $I(t,a)$, the integral (3.2) exists for τ with large real part. From (3.1), we have

$$\partial_a\hat{I}(a,\tau)=I_0(a)-(\mu(a)+\gamma+\tau)\hat{I}(a,\tau)+N(a)\int_0^\omega \beta(a,\sigma)\hat{I}(\sigma,\tau)d\sigma. \qquad (3.3)$$

It is not difficut to write down the expression as

$$\hat{I}(a,\tau)=\int_0^a e^{-(\tau+\gamma)(a-\sigma)}\frac{\ell(a)}{\ell(\sigma)}[I_0(\sigma)+N(\sigma)\int_0^\omega \beta(\sigma,\eta)\hat{I}(\eta,\tau)d\eta]d\sigma. \qquad (3.4)$$

From (3.4), it follows that

$$\int_0^\omega \beta(a,\sigma)\hat{I}(\sigma,\tau)d\sigma=(I-T_\tau)^{-1}\int_0^\omega \beta(*,\sigma)\int_0^\sigma e^{-(\tau+\gamma)(\sigma-\eta)}\frac{\ell(\sigma)}{\ell(\eta)}I_0(\eta)d\eta d\sigma, \qquad (3.5)$$

where the linear operator T_τ is defined by

$$(T_\tau\psi)(a):=\int_0^\omega \Phi_\tau(a,\eta)\psi(\eta)d\eta, \quad \Phi_\tau(a,\eta):=\int_\eta^\omega \beta(a,\sigma)N(\sigma)e^{-(\gamma+\tau)(\sigma-\eta)}d\sigma. \qquad (3.6)$$

Let $\Sigma:=\{\tau \in C:\ I-T_\tau$ is not invertible$\}$. In the following we assume that T_τ is a compact operator from $L^1(0,\omega)$ to $L^1(0,\omega)$. Then it follows that $\Sigma=\{\tau \in C:\ 1 \in P_\sigma(T_\tau)\}$ ($P_\sigma(A)$ denotes the point spectrum of operator A) and the function $\tau \to (I-T_\tau)^{-1}$ is meromorphic in the complex domain. Hence Σ is a discrete set whose element are poles of $(I-T_\tau)^{-1}$ of finite order. Since $I-T_\tau$ is invertible for τ with large real part, there exists a number σ such that the inverse Laplace transform is possible

$$I(t,a)=\frac{1}{2\pi i}\int_{\sigma-i\infty}^{\sigma+i\infty} e^{\tau t}\hat{I}(a,\tau)d\tau. \tag{3.7}$$

Therefore we know that the behavior of $I(t,a)$ can be determined by the method of residues.

Under appropriate conditions, we can expect that Σ has a real dominant singuler point τ_0 such that $\tau_0 \in R\ \Sigma$, $\tau_0>\sup\{Re\tau:\ \tau \in \Sigma-\{\tau_0\}\}$. In fact, on the real axis, T_τ is a positive operator and its spectral radius $r(T_\tau)$ is decreasing for real τ. From Krein-Rutman's theorem, $r(T_\tau)$ is an eigenvalue if T_τ is compact positive and $r(T_\tau)\neq 0$. Hence real roots of the equation $r(T_\tau)=1$ are elements of Σ. Then if $r(T_\tau)$ is strictly decreasing from $+\infty$ to zero, there exists only one real root τ_0 for the equation $r(T_\tau)=1$. Making use of its special form of the operator T_τ and of positive operator theory, it is possible to show that τ_0 is

the dominant root. Though we ommit the proof, the following assumption is sufficient to justify our rough argument (Inaba 1990):

Assumption 3.1. (1) $\lim_{h\to 0}\int_0^\omega |\beta(a+h,\varsigma)-\beta(a,\varsigma)|da=0$ uniformly for ς where $\beta=0$ for a, $\varsigma\in(-\infty,0)\cup(0,\omega)$,

(2) There exists a nonnegative function $\beta_0(\varsigma)$ such that $\beta(a,\varsigma)\geq\beta_0(\varsigma)$ for all (a,ς) and β_0 is positive near to $\varsigma=\omega$.

Note that the condition (1) implies that T_τ is compact for all $\tau\in C$. Moreover it follows from the condition (2) that for real τ, there exists a strictly positive functional F_τ and a quasi-interior point e with respect to natural cone L^1_+ such that $T_\tau\psi\geq<F_\tau,\psi>e$, $\lim_{\tau\to-\infty}<F_\tau,e>=+\infty$. Hence we know that T_τ, $\tau\in R$ is a nonsupporting operator in the sense of Sawashima (1964) and the spectral radius $r(T_\tau)$ is strictly decreasing from $+\infty$ to zero.

The dominant root τ_0 determines the local stability of the disease-free steady state of the population, since τ_0 is the growth rate of the principal part of I(t,a). From monotonicity of $r(T_\tau)$, we obtain that $\tau_0>0$ if $r(T_0)>1$; $\tau_0=0$ if $r(T_0)=1$; $\tau_0<0$ if $r(T_0)<1$. Then we have the threshold criterion: the disease can invade if $r(T_0)>1$, whereas it cannot if $r(T_0)<1$. Then $r(T_0)$ can be interpreted as the basic reproduction number R_0 (Diekmann, et. al 1990).

Note. 3.2. From (3.6), it follows that $r(T_0)=Br(S)$ where the operator S is given by

$$(S\psi)(a):=\int_0^\omega \Phi(a,\eta)\psi(\eta)d\eta, \quad \Phi(a,\eta):=\int_\eta^\omega \beta(a,\sigma)\ell(\sigma)e^{-\gamma(\sigma-\eta)}\,d\sigma, \tag{3.8}$$

that is independent of the population size. Since $r(T_0)=1$ if and only if $B=r(S)^{-1}$, we know that there exists a critical size N_0 of the totally susceptible population such that the disease can invade if the population size exceeds N_0, otherwise the disease will be eradicated. That is, N_0 is given by

$$N_0=r(S)^{-1}\int_0^\omega \ell(a)da. \tag{3.9}$$

Note 3.3. Let K be the total cone of a Banach space and let K^* be the dual cone. A positive linear operator T is called <u>nonsupporting</u> iff for every pair $\psi \in K-\{0\}$, $F\in K^*-\{0\}$, there exists a positive integer $p=p(\psi,F)$ such that $\langle F,T^n\psi\rangle>>0$ for all $n\geq p$. If a nonsupporting compact operator T has positive spectral radius, the Perron-Frobenius type theorem holds (Sawashima 1964; Marek 1970):

(1) r(T) is a point spectrum and is a simple pole of the resolvent,

(2) The eigenspsce corresponding to r(T) is one-dimensional and the corresponding eigenvector is a quasi-interior point and is a unique eigenvector in the cone K,

(3) The eigenspace of the dual operator T^* corresponding to $r(T)$ is also one-dimensional and is spanned by a strictly positive functional,

(4) If S and T are nonsupporting and compact with $r(T)\neq 0$, then $S\leq T$, $S\neq T$ imply that $r(S)<r(T)$.

Note 3.4. From (2.1b) and (3.1), it is easy to see that the solution $I(t,a)$ of the linearized equation (3.1) is bigger than the the solution $I(t,a)$ of the nonlinear system (2.1). Therefore, the local stability condition $r(T_0)<1$ implies the global stability of the disease-free steady state of the original system (2.1).

4. Existence of steady states

Let $S(a)$, $I(a)$ be the steady state solution for the system (2.1). Then we obtain the expressions

$$S(a)=N(a)\exp(-\int_0^a \lambda(\sigma)d\sigma), \tag{4.1a}$$

$$I(a)=N(a)\int_0^a e^{-\gamma(a-\sigma)}\lambda(\sigma)\exp(-\int_0^\sigma \lambda(\eta)d\eta)d\sigma, \tag{4.1b}$$

where $\lambda(a)$ is the force of infection at the steady state

$$\lambda(a)=\int_0^\omega \beta(a,\sigma)I(\sigma)d\sigma. \tag{4.2}$$

Substituting (4.1) into (4.2) and integrating by parts, we have an equation for λ

$$\lambda(a)=\int_0^{\omega}\Phi_0(a,\sigma)\lambda(\sigma)\exp(-\int_0^{\sigma}\lambda(\eta)d\eta)d\sigma, \qquad (4.3)$$

Let us define a nonlinear positive operator Φ in $L^1(0,\omega)$ by

$$\Phi(\psi)(a):=\int_0^{\omega}\Phi_0(a,\sigma)\psi(\sigma)\exp(-\int_0^{\sigma}\psi(\eta)d\eta)d\sigma, \quad \psi\in L^1. \qquad (4.4)$$

Then the solutions of (4.3) correspond to nonnegative fixed points of the operator Φ. Observe that T_0 is the majorant of Φ, $T_0\psi-\Phi(\psi)\in L^1_+-\{0\}$ for $\psi\in L^1_+-\{0\}$ and the Frechet derivative of Φ at $\psi=0$ is given by T_0. Then we can prove the following:

Proposition 4.1. Suppose that assumption 3.1. holds. Then there is no endemic steady state if $r(T_0)\leq 1$, whereas there exists at least one endemic steady state if $r(T_0)>1$.

(proof) If there exists a $\psi\in L^1_+-\{0\}$ being a fixed point of Φ, then $\psi=\Phi(\psi)\leq T_0\psi$. Let F be the adjoint eigenvector of T_0 corresponding to $r(T_0)$. Taking duality pairing, we have $\langle F,T_0\psi-\psi\rangle=(r(T_0)-1)\langle F,\psi\rangle>>0$ since $T_0\psi-\psi$ is nonzero positive and F is strictly positive. Thus $r(T_0)>1$ if there exists an endemic steady state. This is the proof of the first part of our proposition. Next suppose that $r(T_0)>1$. First it is observed that the nonlinear operator Φ is also compact. Define the subset Ω by $\Omega:=\{\psi\in L^1_+ : \|\psi\|\leq M\}$ where

$$M:=\sup_{0\le\sigma\le\omega}\int_0^{\omega}\Phi_0(a,\sigma)da.$$

Then it follows that $\Phi(L^1_+)\subset\Omega$. Moreover if we define an operator Φ_r by $\Phi_r(\psi)=\Phi(\psi)$ if $\|\psi\|\ge r$, $\Phi_r(\psi)=\Phi(\psi)+(r-\|\psi\|)\psi_0$ if $\|\psi\|\le r$ where ψ_0 is the positive eigenvector of T_0 corresponding to $r(T_0)$. Then Φ_r is compact and the set $\Omega_r:=\{\psi\in L^1_+ : \|\psi\|\le M+r\|\psi_0\|\}$ is invariant under Φ_r. Since Ω_r is bounded, convex and closed in L^1, Φ_r has a fixed point $\psi_r\in\Omega_r$ (Schauder's principle). According to Krasnoselskii (1964, Theorem 4.11), using the fact that $r(T_0)=r(\partial\Phi[0])>1$ and T_0 does not have eigenvector in L^1_+ corresponding to the eigenvalue one, we can prove that if r is sufficiently small, the norm of the fixed point ψ_r is greater than r. That is, Φ has a positive fixed point.

The next important problem is whether the non-trivial fixed point of Φ is unique or not. For this purpose, we introduce a class of concave operators:

Definition 4.2. (Krasnoselskii 1964) Let K be a cone in a real Banach space E and $\le$ be the partial ordering defined by K. A positive operator T: K → K is called <u>concave</u> if there exists a $\psi_0\in$ K-{0} that satisfies the following: (1) for any $\psi\in$ K-{0} there exist $\alpha=\alpha(\psi)>0$ and $\beta=\beta(\psi)>0$ such that $\alpha\psi_0\le T\psi\le\beta\psi_0$; (2) $T(t\psi)\ge tT(\psi)$

for $0\le t\le 1$ and for every $\psi\in K$ such that $\alpha(\psi)\psi_0 \le\psi\le\beta(\psi)\psi_0$ $(\alpha(\psi)>0,$ $\beta(\psi)>0)$.

Lemma 4.3. Suppose that the operator $T: K \to K$ is monotone and concave. If for any $\psi\in K$ satisfying $\alpha_1\psi_0\le\psi\le\beta_1\psi_0$ $(\alpha_1=\alpha_1(\psi)>0,$ $\beta_1=\beta_1(\psi)>0)$ and any $0<t<1$, there exists $\eta=\eta(\psi,t)>0$ such that

$$T(t\psi)\ge tT(\psi)+\eta\psi_0, \tag{4.5}$$

then the operator T has at most one positive fixed point.

(proof) Suppose that $\psi_1\in K-\{0\}$ and $\psi_2\in K-\{0\}$ are two positive fixed points of T. From the concavity of T, we can choose positive constants $\alpha_1=\alpha_1(\psi_1)>0$ and $\beta_2=\beta_2(\psi_2)>0$ such that

$$\psi_1=T\psi_1\ge\alpha_1\psi_0=\alpha_1\beta_2^{-1}\beta_2\psi_0\ge\alpha_1\beta_2^{-1}T\psi_2=\alpha_1\beta_2^{-1}\psi_2.$$

If we define $k:=\sup\{\mu:\psi_1\ge\mu\psi_2\}$, then it follows from the above inequality that $k>0$. If we assume that $0<k<1$, then there exists $\eta=\eta(\psi_2,k)>0$ such that

$$\psi_1=T\psi_1\ge T(k\psi_2)\ge kT(\psi_2)+\eta\psi_0\ge k\psi_2+\eta\beta_2^{-1}T(\psi_2)=(k+\eta\beta_2^{-1})\psi_2,$$

which contradicts the definition of k. Hence we have $k\ge 1$ and $\psi_1\ge\psi_2$. In the same way, we can prove $\psi_2\ge\psi_1$. Thus $\psi_1=\psi_2$.

Proposition 4.4. Suppose that for all $(a,\sigma)\in[0,\omega]\times[0,\omega]$, the inequality

$$\beta(a,\sigma)\lambda(\sigma)-\gamma\int_\sigma^\omega\beta(a,\xi)\lambda(\xi)e^{-\gamma(\xi-\sigma)}\,d\xi\ge 0, \tag{4.6}$$

holds. If $r(T_0)>1$, Φ has only one positive fixed point; that is, the endemic steady state is unique.

(proof) From Proposition 4.1 and Lemma 4.3, it is sufficient to show that Φ is a monotonic concave operator satisfying the condition (4.5). Observe that

$$\Phi(\psi)(a)=\int_0^\omega \Phi_0(a,\sigma)(-\frac{d}{d\sigma})\exp(-\int_0^\sigma \psi(\eta)d\eta)d\sigma$$

$$=\Phi(a,0)-\int_0^\omega [\beta(a,\sigma)N(\sigma)-\gamma\Phi_0(a,\sigma)]\exp(-\int_0^\sigma \psi(\eta)d\eta)d\sigma.$$

Then the operator Φ is monotonic under the inequality (4.6). Next it is easily observed that

$$\alpha_1(\psi)\psi_0\leq\Phi(\psi)\leq\alpha_2(\psi)\psi_0,$$

where $\psi_0=1$ and

$$\alpha_1(\psi):=\int_0^\omega f(\sigma)\psi(\sigma)\exp(-\int_0^\sigma \psi(\eta)d\eta)d\sigma,$$

$$\alpha_2(\psi):=\int_0^\omega g(\sigma)\psi(\sigma)\exp(-\int_0^\sigma \psi(\eta)d\eta)d\sigma,$$

where $f(\sigma)$, $g(\sigma)$ are defined by

$$f(\sigma):=\int_\sigma^\omega \beta_0(\xi)N(\xi)e^{-\gamma(\xi-\sigma)}d\xi,\quad g(\sigma):=\sup|\beta|\int_\sigma^\omega N(\xi)e^{-\gamma(\xi-\sigma)}d\xi.$$

Thus it follows that α_1, α_2 are strictly positive functionals. Further, if we define

$$\eta(\psi,t):=t\int_0^\omega f(\sigma)\psi(\sigma)\exp(-\int_0^\sigma \psi(\eta)d\eta)[\exp((1-t)\int_0^\sigma \psi(\eta)d\eta)-1]d\sigma,$$

then it is easily seen that Φ satisfies $\Phi(t\Psi)\geq t\Phi(\Psi)+\eta$. Thus Φ is a concave operator satisfying (4.5) with $\Psi_0=1$. This completes the proof.

Note 4.5. The inequality (4.6) holds if $\beta(a,\sigma)$is independent of the age of infectives σ. Further, no matter whether the inequality (4.6) holds, if $\beta(a,\sigma)$ can be factorized as $\beta_1(a)\beta_2(\sigma)$ (the proportionate mixing assumption), there always exists a unique endemic steady state under the condition $r(T_0)>1$.

5. Discussion

Although we have not so far argued about the stability of the endemic steady states, the local stability of the endemic steady states can be analysed by solving the eigenvalue problem associated with the linearized equation around the endemic steady state (the principle of linearized stability). Inaba (1990) proved that if the force of infection λ at an endemic equilibrium satisfies the inequality

$$\exp(-\int_0^\omega \lambda(\sigma)d\sigma)\geq\gamma\int_0^\omega e^{-\gamma(\omega-\sigma)}\exp(-\int_0^\sigma \lambda(\eta)d\eta)d\sigma, \qquad (5.1)$$

then the endemic equilibrium is locally asymptotically stable. In particuler, it follows that the rate of infection at the equilibrium is sufficiently small, the endemic equilibrium is locally stable. But it is still an open problem to obtain more general characterization for the local stability. For example,

we can guess that the uniqueness of the endemic equilibrium implies its stability. Further, we have not yet known conditions under which the endemic steady state is globally stable.

Thieme (1991) shows that the endemic equilibrium can be unstable at certain parameter values, if the rate of a susceptible individual to be infected is independent of its age but, as for the age of the infective individual, is highly concentrated in a specific age class. Nevertheless the existence of periodic solutions in case that the endemic equilibrium is unstable is still an unsettled problem. We can also ask whether more complicated behavior than periodic oscillation can be generated by a deterministic age-structured S-I-R model.

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