Global stability of the multi-strain Kermack-McKendrick epidemic model

Michael T. Meehan\textsuperscript{a}, Daniel G. Cocks\textsuperscript{b}, Emma S. McBryde\textsuperscript{a}

\textsuperscript{a}Australian Institute of Tropical Health and Medicine, James Cook University, Townsville, Australia
\textsuperscript{b}College of Science and Engineering, James Cook University, Townsville, Australia

Abstract

We extend a recent investigation by Meehan et al. (2017)\textsuperscript{1} regarding the global stability properties of the general Kermack-McKendrick model to the multi-strain case. We demonstrate that the basic reproduction number of each strain $R_{0j}$ represents a sharp threshold parameter such that when $R_{0j} \leq 1$ for all $j$ each strain dies out and the infection-free equilibrium is globally asymptotically stable; whereas for $R_{01} \equiv \max_j R_{0j} > 1$ the endemic equilibrium point $\bar{P}_1$, at which only the fittest strain (i.e. strain 1) remains in circulation, becomes globally asymptotically stable.

Keywords: multi-strain global stability Lyapunov competitive exclusion

1. Introduction

Driven by a combination of genetic evolution and primary transmission, we are currently witnessing an explosion in the number of phenotypically distinct lineages of infectious diseases (i.e. strains) circulating in the global population. To simulate the dynamics of several co-circulating pathogen strains, several authors have developed multi-strain extensions of canonical single-strain epidemic models\textsuperscript{2,3,4,5,6,7,8}. Often, these models are constructed by making $n$ copies of the various infectious states considered for a single strain, with the additional constraint that each of the $n$ strains dips from a common susceptible pool. In this case, many authors (e.g.\textsuperscript{2,3,4}) have rediscovered the well-known competitive exclusion principle (first appearing in the ecological literature\textsuperscript{9,10}) which asserts that when several species are competing over a shared resource only one of them can survive indefinitely — namely, the one with the greatest reproductive capacity. Although this result can often be deduced by investigating the asymptotic dynamics of each system, the global stability of the various equilibria has often proven to be more difficult to establish (see for instance\textsuperscript{4}). We also point out, that several notable exceptions, i.e. models that promote strain diversity at equilibrium, have also been found\textsuperscript{11,12,13,14}. Many of the multi-strain models investigated thus far have been of compartmental type for which infected individuals have a fixed infectiousness for the duration of their infectious period (which may or may not follow an exponentially distributed latency period). In this article we extend these approaches by adapting the general Kermack-McKendrick model to the multi-strain context. The model itself is formulated in terms of a system of scalar renewal equations defined in terms of a set general infectivity kernels $A_j(\tau)$: the expected contribution to the force of infection of strain $j$ for an individual with infection age $\tau$. With the exception of a few minor restrictions (e.g. nonnegativity and integrability), the infectivity kernels $A_j(\tau)$ are left as arbitrary functions; in this manner, we develop a general epidemiological model capable of accurately simulating the infection history of many communicable diseases that also encompasses several previous approaches.

Our main result, which follows from a previous investigation into the global dynamics of the single-strain Kermack-McKendrick model, is to establish the necessary and sufficient conditions for the global asymptotic stability of the infection-free and endemic equilibrium points of our multi-strain model. In doing so, we verify that only the strain with the greatest reproduction number can persist indefinitely. To derive this result, we apply the direct Lyapunov method for which we identify appropriate Lyapunov functionals. Importantly, since the general Kermack-McKendrick model incorporates many of the familiar transmission
dynamic models as limiting cases (e.g. the SIR and SEIR models), the analysis and results presented in this article generalize a number of results derived in previous investigations \[8\]. (For applications of the direct Lyapunov method to single-strain epidemic models see e.g. \[15, 16, 17, 18\].)

To begin, in section 2, we describe the multi-strain extension of the general Kermack-McKendrick model and introduce the relevant model parameters. We then calculate the equilibrium states of the system in section 3. Finally, in section 4, we investigate the global stability properties of the system and provide concluding remarks in section 5.

2. Model description

The model we investigate in this article is a multi-strain extension of the general Kermack-McKendrick model outlined in detail in \[1\] (see also \[19\]). In particular, we develop a model with \(n\) distinct, uncoupled pathogen strains which each dip from a common susceptible pool, \(S\). We assume perfect cross-immunity such that, once infected with strain \(j \in \{1, n\}\), individuals are immune to further infection with an alternate strain. Further details beyond the fundamental model ingredients described below can be found in \[1\].

Firstly, we introduce the force of infection of each strain \(j\), \(F_j(t)\), which, by definition, is the per-capita rate at which susceptibles are infected with strain \(j\) at time \(t\). It follows then, that the incidence of strain \(j\) at time \(t\), which we denote \(v_j(t)\), is given by

\[
v_j(t) = F_j(t)S(t)
\]

where \(S(t)\) denotes the number of susceptibles. In accordance with our general expectation, we assume that the force of infection depends on the size of each infectious population, such that \(F_j(t)\) can be expressed in terms of a scalar-renewal equation:

\[
F_j(t) = \int_0^\infty A_j(\tau) F_j(t-\tau) S(t-\tau) \, d\tau.
\] (1)

Here, the kernel \(A_j(\tau)\) gives the expected contribution to the force of infection for an individual who has been infected with strain \(j\) for \(\tau\) units of time. Accordingly, if we integrate this contribution over all possible infection ages we find that the basic reproduction number for each strain, \(R_{0j}\), is given by

\[
R_{0j} = S_0 \int_0^\infty A_j(\tau) \, d\tau
\] (2)

where \(S_0\) is the steady-state susceptible population in the absence of infection (see section 3). Next, we assume that individuals are recruited (i.e. born) directly into the susceptible class at a constant rate \(\lambda\) and that all individuals experience a constant per-capita natural death rate, \(\mu\). Therefore, if we combine the demographic influences with the loss of susceptible individuals due to infection, we find that the susceptible population varies according to

\[
\frac{dS(t)}{dt} = \lambda - \mu S(t) - \sum_{j=1}^{n} F_j(t)S(t).
\] (3)

For each infected class \(I_j\), we assume that in addition to the natural mortality rate \(\mu\), infected individuals expire through disease-induced mortality at a strain-specific per-capita rate \(\alpha_j(\tau)\) and recover at a per-capita rate \(\gamma_j(\tau)\). Therefore, the total removal rate from the infected class at infection age \(\tau\) is given by \(\psi_j(\tau) = \mu + \alpha_j(\tau) + \gamma_j(\tau)\). Hence, if we denote the number of individuals infected with strain \(j\) at time \(t\) with infection age \(\tau\) by \(i_j(t, \tau)\) we have

\[
i_j(t, \tau) = e^{-\int_0^\tau \psi_j(s) \, ds} v_j(t-\tau),
\]

\[
= B_j(\tau)v_j(t-\tau),
\] (4)
where \( v_j(t - \tau) \) is the incidence at time \( t - \tau \) and \( B_j(\tau) = e^{-\int_{-\infty}^{\tau} \psi_j(s) \, ds} \) is the probability of surviving to infection age \( \tau \). Naturally we see that \( B_j(0) = 1 \) and \( \lim_{\tau \to \infty} B_j(\tau) = 0 \). Moreover, in this case, \( i_j(t, 0) = v_j(t) \).

Finally, from (4) we can calculate the total infected population of each strain as

\[
I_j(t) = \int_{0}^{\infty} i_j(t, \tau) \, d\tau, \\
= \int_{0}^{\infty} B_j(\tau)v_j(t - \tau) \, d\tau.
\]

(5)

3. Equilibrium points

To determine the equilibrium states of the multi-strain system described in the previous section we first find the fixed points of equations (1) and (3). By inspection, we immediately observe the infection-free equilibrium solution,

\[
P_0^j: F_0^j = 0 \quad \text{for all } j \quad \text{(which by (4) and (5) implies that } I_0^j = 0) \quad \text{and } S_0 = \frac{\lambda}{\mu}.
\]

A superscript is used to label the infection-free equilibrium values (except for \( S_0 \)).

Alternatively, for the case \( \bar{F}_j \neq 0 \) (i.e. at the endemic equilibrium, \( \bar{P}^j \)) we have

\[
\bar{F}_j = \int_{0}^{\infty} A_j(\tau) \, d\tau \bar{S}
\]

which can be rearranged to give the eigenvalue equation:

\[
0 = \left( K - \frac{S_0}{S} E \right) \bar{F}
\]

(6)

where \( \bar{F} = [\bar{F}_1, \bar{F}_2, \ldots ]^\top \), \( E \) is the identity matrix, and \( K \) is the next-generation matrix, defined as

\[
K = S_0 \text{diag} \left( \int_{0}^{\infty} A_j(\tau) \, d\tau \right) = \text{diag} \left( R_{0j} \right).
\]

(7)

From (6) we recognize \( n \) endemic equilibrium solutions which can be associated with each of the \( j \in [1, n] \) pathogen strains. In particular, the quantities \( S_0 / R_{0j} \) represent the eigenvalues of the matrix \( K \) and \( \bar{F}_j \) are the corresponding eigenvectors. Since the matrix \( K \) is diagonal, we can immediately deduce that

\[
\bar{S}_j = \frac{S_0}{R_{0j}}
\]

(8)

and \( \bar{F}_j \propto e_j \), where \( e_j \) is the \( j \)-th canonical basis vector for which the \( j \)-th element is equal to one and the remaining elements are equal to zero. Therefore, at \( P^j \) only strain \( j \) survives.

To determine the normalization factors for the eigenvectors \( \bar{F}_j \) we substitute the solution \( \bar{F}_j = C_j e_j \) and (8) into (3) to get

\[
\bar{F}_j = \mu \left( R_{0j} - 1 \right).
\]

(9)

Importantly, we see from (9) that each of the endemic equilibrium points, \( \bar{P}^j \), only exist in the positive orthant \( \mathbb{R}_{>0}^{n+1} \) when \( R_{0j} > 1 \); for the limiting case \( R_{0j} = 1 \), \( \bar{P}^j \) and \( P^0 \) coincide.

4. Global stability analysis

We now establish the stability properties of the equilibrium solutions of the system (3) and (5). Note, however, that because the analysis below closely follows that presented in [1], we omit some of the detailed working and simply provide the necessary steps required to establish our argument.
4.1. Infection-free equilibrium

**Theorem 1.** The infection-free equilibrium point $P^0$ is globally asymptotically stable in the nonnegative orthant $\mathbb{R}_{\geq 0}^{2n+1}$ if $R_{0j} \leq 1$ for all $j$. However, if $R_{0j} > 1$ for any $j$, solutions of (3)-(5) starting sufficiently close to $P^0$ in $\mathbb{R}_{\geq 0}^{2n+1}$ move away from $P^0$, except those starting on the invariant $S$-axis which approach $P^0$ along this axis.

**Proof.** To verify theorem 1, consider the multi-strain extension of the Lyapunov functional given in [1]:

$$U = U_1 + U_2$$

where

$$U_1 = S - S_0 \log S \quad \text{and} \quad U_2 = \sum_{j=1}^{n} \int_{0}^{\infty} \eta_j(\tau)v_j(t - \tau) d\tau$$

and

$$\eta_j(\tau) = S_0 \int_{\tau}^{\infty} A_j(s) ds.$$  \hspace{1cm} (10)

In particular we have

$$\eta_j(0) = R_{0j} \quad \text{and} \quad \eta'_j(\tau) = -S_0 A_j(\tau)$$ \hspace{1cm} (11)

where $'$ denotes differentiation with respect to $\tau$. Moreover, $\lim_{\tau \to \infty} \eta_j(\tau) = 0$.

Importantly, the functional $U(t)$ is positive and continuous, and has a global minimum in $\mathbb{R}_{\geq 0}^{2n+1}$ at the infection-free equilibrium point $P^0$.

Calculating the time derivative of (10) along the system trajectories yields (see [1] for further details)

$$\frac{dU}{dt} = -\mu S \left(1 - \frac{S_0}{S}\right)^2 - \sum_{j=1}^{n} (1 - R_{0j}) F_j S,$$

$$\leq 0. \hspace{1cm} (12)$$

The derivative $\dot{U} = 0$ if and only if $S = S_0$ and either (a) $R_{0j} = 1$ or (b) $F_j = 0$ for all $j$. Therefore, the largest invariant subset in $\mathbb{R}_{\geq 0}^{2n+1}$ for which $\dot{U} = 0$ is the singleton $\{P^0\}$. Hence, by LaSalle’s extension of Lyapunov’s global asymptotic stability theorem, the infection-free equilibrium point $P^0$ is globally asymptotically stable in $\mathbb{R}_{\geq 0}^{2n+1}$ if $R_{0j} \leq 1$ for all $j$.

Moreover, if $R_{0j} > 1$ for any $j$, the derivative $\dot{U} > 0$ for $S$ sufficiently close to $S_0$, provided $F_j > 0$. Therefore, solutions starting sufficiently close to the infection-free equilibrium point $P^0$ leave a neighbourhood of $P^0$, except those starting along the invariant $S$-axis. Since $\dot{U} \leq 0$ for solutions starting along the invariant $S$-axis these solutions approach $P^0$ along this axis.

4.2. Endemic equilibrium

To begin, without loss of generality, we label the strain with the maximum reproduction number number strain 1, such that

$$R_{01} \equiv \max_j R_{0j}. \hspace{1cm} (13)$$

Additionally, in this section we adopt the shorthand notation that an overbar refers to the value of a state variable at the endemic equilibrium point $\bar{P}^1$ such that, for example, $\bar{S} \equiv \bar{S}^1$, $\bar{F} \equiv \bar{F}^1$ and $\bar{v} \equiv \bar{v}^1$.

**Theorem 2.** If $R_{01} > 1$ the endemic equilibrium point $\bar{P}^1$ is globally asymptotically stable in $\mathbb{R}_{>0}^{2n+1}$ (i.e. away from the invariant $S$-axis).
Proof. Firstly, we introduce a multi-strain extension of the Lyapunov functional given in [1]:

$$W = W_1 + W_2 + W_3$$ (14)

where

$$W_1 = S - \bar{S} \log S,$$

$$W_2 = \sum_{j=1}^{n} \int_{0}^{\infty} \chi_j(\tau) v_j(t - \tau) d\tau,$$

$$W_3 = -\bar{v} \int_{0}^{\infty} \chi_1(\tau) \log v_1(t - \tau) d\tau$$

with

$$\chi_j(\tau) = \bar{S} \int_{\tau}^{\infty} A_j(s) ds.$$ (13)

In particular, we have

$$\chi_j(0) = \frac{R_{0j}}{R_{01}}$$ and $$\chi_j'(\tau) = -\bar{S} A_j(\tau)$$

so that $$\chi_1(0) = 1$$ and $$\lim_{\tau \to \infty} \chi_j(\tau) = 0.$$ (14)

The functional $$W$$ is positive and continuous, and has a global minimum in $$\mathbb{R}^{2n+1}_{>0}$$ at the endemic equilibrium point $$\bar{P}_1.$$

Taking the time derivative of $$W_1$$ and $$W_2$$ and substituting in the definition of $$\chi(\tau)$$ gives (see [1] for details)

$$\frac{dW_1}{dt} = -\mu S \left( 1 - \frac{\bar{S}}{S} \right)^2 + \bar{F} \bar{S} \left( 1 - \frac{\bar{S}}{S} \right) - \sum_{j=1}^{n} F_j(S - S),$$ (15)

$$\frac{dW_2}{dt} = \sum_{j=1}^{n} F_j \left( \frac{R_{0j}}{R_{01}} S - S \right).$$ (16)

Lastly, to calculate $$\dot{W}_3,$$ we integrate by parts and substitute in the definition of $$\chi(\tau)$$ to get

$$\frac{dW_3}{dt} = -\bar{v} \int_{0}^{\infty} \chi_1(\tau) \frac{d \log v_1(t - \tau)}{d\tau} d\tau,$$

$$= -\bar{v} \left[ \log v_1(t) - \bar{S} \int_{0}^{\infty} A_1(\tau) \log v_1(t - \tau) d\tau \right].$$ (17)

Repeating the steps undertaken in [1], we can bound the expression in the square brackets from below using Jensen’s inequality:\footnote{For a concave function $$\varphi(\cdot),$$ and probability distribution $$h(t),$$ the following inequality holds:
$$\varphi \left( \int_{0}^{\infty} h(t) f(t) dt \right) \geq \int_{0}^{\infty} h(t) \varphi(f(t)) dt.$$}

$$\log v_1(t) - \bar{S} \int_{0}^{\infty} A_1(\tau) \log v_1(t - \tau) d\tau \geq \log v_1(t) - \log \left( \bar{S} \int_{0}^{\infty} A_1(\tau) v_1(t - \tau) d\tau \right),$$

$$= \log(F_1 S) - \log(F_1 \bar{S}),$$

$$= \log \left( \frac{S}{\bar{S}} \right),$$

$$\geq 1 - \frac{\bar{S}}{S}.$$ (18)

1For a concave function $$\varphi(\cdot),$$ and probability distribution $$h(t),$$ the following inequality holds:
$$\varphi \left( \int_{0}^{\infty} h(t) f(t) dt \right) \geq \int_{0}^{\infty} h(t) \varphi(f(t)) dt.$$ (5)
where in the last line we have also used $\log x \ge 1 - \frac{1}{x}$.
Substituting this result back into (17) we then have
\[
\frac{dW_3}{dt} \le -F\bar{S} \left( 1 - \frac{\bar{S}}{S} \right). \tag{19}
\]
Finally, combining (15), (16) and (19) yields
\[
\frac{dW}{dt} \le -\mu S \left( 1 - \frac{\bar{S}}{S} \right)^2 - \sum_{j=1}^{n} \left( 1 - \frac{R_{0j}}{R_{01}} \right) F_j S, \\
\le 0. \tag{20}
\]
From equation (20) we see that the largest invariant subset in $\mathbb{R}^{2n+1}_{>0}$ for which $\dot{W} = 0$ is the endemic equilibrium point $\bar{P}^1$. Hence, by LaSalle’s extension of Lyapunov’s asymptotic stability theorem, the endemic equilibrium point $\bar{P}^1$ is globally asymptotically stable.

5. Conclusions

In this article we investigated the global stability properties of the multi-strain Kermack-McKendrick model. We found that when the basic reproduction number $R_{0j} \le 1$ for all strains $j$ the infection-free equilibrium $P^0$ is unique in $\mathbb{R}^{2n+1}_{>0}$ and is globally asymptotically stable. We also discovered a set of $n$ endemic equilibrium solutions, $\{\bar{P}^j\}$, at which only strain $j$ survives with a positive infected population, à la competitive exclusion. Moreover, we found that $\bar{P}^j$ only exists in the positive orthant if $R_{0j} > 1$. Our main result, which was derived using the direct Lyapunov method, was to show that of this set, $\bar{P}^1$ — at which the fittest strain, defined by $R_{01} = \max_j R_{0j}$, survives indefinitely — is globally asymptotically stable when it exists.

References

[1] M. T. Meehan, D. G. Cocks, E. S. McBryde, Global stability of a general, scalar-renewal epidemic model, arXiv:1707.03489.
[2] R. M. Anderson, R. May, Coevolution of hosts and parasites, Parasitology 85 (02) (1982) 411–426.
[3] K. Beck, Coevolution: Mathematical analysis of host-parasite interactions, J. Math. Biol. 19 (1) (1984) 63–77.
[4] H. J. Bremermann, H. R. Thieme, A competitive exclusion principle for pathogen virulence, J. Math. Biol. 27 (2) (1989) 179–190.
[5] V. Andreasen, A. Pugliese, Pathogen coexistence induced by density-dependent host mortality, J. Theor. Biol. 177 (2) (1995) 159–166.
[6] M. Lipsitch, E. R. Moxon, Virulence and transmissibility of pathogens: what is the relationship?, Trends Microbiol. 5 (1) (1997) 31 – 37.
[7] S. A. Ackleh, J. L. Allen, Competitive exclusion and coexistence for pathogens in an epidemic model with variable population size, J. Math. Biol. 47 (2) (2003) 153–168.
[8] D. Bichara, A. Iggidr, G. Sallet, Global analysis of multi-strains SIS, SIR and MSIR epidemic models, J. Appl. Math. and Comput. 44 (1) (2013) 273–292.
[9] V. Volterra, Variations and fluctuations of the number of individuals in animal species living together, J. Cons. Int. Explor. Mer 3 (1) (1928) 3–51.
[10] S. A. Levin, Community equilibria and stability, and an extension of the competitive exclusion principle, Am. Nat. (1970) 413–423.
[11] R. M. May, M. A. Nowak, Superinfection, metapopulation dynamics, and the evolution of diversity, J. Theor. Biol. 170 (1) (1994) 95 – 114.
[12] M. Lipsitch, S. Siler, M. A. Nowak, The evolution of virulence in pathogens with vertical and horizontal transmission, Evolution (1996) 1729–1741.
[13] M. Martcheva, A non-autonomous multi-strain SIS epidemic model, J. Biol. Dynam. 3 (2-3) (2009) 235–251.
[14] M. Meehan, D. Cocks, J. Trauer, E. McBryde, Coupled, multi-strain epidemic models of mutating pathogens, arXiv:1611.04204.
[15] A. Korobeinikov, G. Wake, Lyapunov functions and global stability for SIR, SIRS, and SIS epidemiological models, Appl. Math. Lett. 15 (8) (2002) 955 – 960.
[16] M. Y. Li, J. S. Muldowney, Global stability for the SEIR model in epidemiology, Math. Biosci. 125 (2) (1995) 155–164.
[17] M. Fan, M. Y. Li, K. Wang, Global stability of an SEIS epidemic model with recruitment and a varying total population size, Math. Biosci. 170 (2) (2001) 199–208.
[18] C. C. McCluskey, Complete global stability for an SIR epidemic model with delay: distributed or discrete, Nonlinear Anal.: Real 11 (1) (2010) 55–59.
[19] W. O. Kermack, A. G. McKendrick, A contribution to the mathematical theory of epidemics, in: P. Roy. Soc. Lond. A Math., Vol. 115, 1927, pp. 700–721.