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Global stability for a four dimensional epidemic model

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Abstract. We consider a four compartmental epidemic model which generalizes some tuberculosis models from the literature. We will obtain sufficient conditions for the global stability of the endemic equilibrium by using a generalization of the Poincaré-Bendixson criterion for systems of n ordinary differential equations.

Keywords: Epidemic model, tuberculosis, compound matrices, global stability.

MSC 2000 classification: 34D23; 92D30.

1 Introduction

In the context of tuberculosis (TB) mathematical modelling, [12], in 2005 A. Ssematimba and his coworkers, [26], formulated a mathematical model based on previous work by Z. Feng, C. Castillo-Chavez and coauthors, [11, 13, 14]. In [26] the study focalizes on the size of the area occupied by a population affected by TB in order to eradicate the disease. The results are then applied to the case of Internally Displaced People's Camps (IDPCs) in North Uganda. More recently, C. P. Bhunu and his coworkers, [4], considered a more general tuberculosis model including the exogeneous reinfection and the treatment. The importance to take into account of exogenous reinfection has been stressed in [13]. Indeed, a TB model with reinfection is more realistic and its dynamics is richer. For example, backward bifurcation can occur. The treatment is represented by extra linear terms in the model.

In [4] the problem of finding conditions ensuring the global stability of endemic equilibria is left open.

In [10], a four compartments tuberculosis model has been introduced which can be thought as a generalization of the models considered in [4, 26]. In fact, it incorporates and combines *(i)* the mechanism of the exogeneous reinfection as in [4]; *(ii)* a parameter for the size of the area occupied by the population as in [26]. In [10], the analysis focalizes mainly on bifurcation theory. In particular, sufficient conditions ensuring the occurrence of a backward or a forward bifurcation have been obtained. The application to IDPCs given in [26] has been then revisited.

An important epidemiological issue is to evaluate if the disease may be eradicated or not from the community. This issue may be mathematically attained by performing a stability analysis of peculiar solutions as steady states, or *equilibria*. The so-called *geometric approach* *to global stability* is a powerful tool to obtain sufficient conditions for global stability of endemic equilibria, namely equilibria with all positive components. It is a generalization of the Poincaré-Bendixson criterion for systems of n ordinary differential equations, due to M. Li and J. Muldowney [19, 20, 22]. The majority of applications refer to epidemic models, as SIR, SEIR, SEIS, SEIRS models (see, e.g., [1, 5, 9, 21, 23, 27]) although applications to other population dynamics context may be found, [3, 6].

In a recent analysis on general three dimensional systems, it has been shown that the mathematical structure of SEIR-like systems appears to be particularly suitable for the applications of the method, [7, 8]. Applications to four dimensional systems are still few in the literature, [2, 16].

In [10], some results concerning with the global stability of endemic equilibria - obtained through the geometric approach - have been provided. When dealing with four order differential systems, this procedure becomes analytically quite involved so that in [10] it has been only sketched.

In this paper, we reconsider the model introduced in [10] and perform the global stability analysis through the geometric approach in all the details.

The paper is organized as follows. In Sec. 2 the TB model is introduced and some basic properties are recalled. In Sect. 3, the Li-Muldowney geometric approach is used to study the global stability of the endemic equilibrium. The results are discussed in the concluding section, Sect. 4.

2 The model and its basic properties

In this section we will introduce the four compartmental TB model and summarize the basic properties obtained in [10].

A community affected by tuberculosis is divided into four compartments: susceptibles (S), treated but still susceptibles (T), infectious (I), and exposed (E) (i.e. infected but not infectious). The total population size at time t is:

$$N(t) = S(t) + T(t) + I(t) + E(t). \tag{1}$$

By using the mass action law, the infection rate is:

$$\lambda_i = c_i\, x_i\, I, \qquad i = 1, 2, 3, \tag{2}$$

where $x_1 = S$, $x_2 = T$, $x_3 = E$, c_i is the effective contact rate between the infectious and the individuals of the compartment x_i, i=1,2,3. The dynamics of the disease is described by the following system:

$$\begin{cases} \dot{S} = \Lambda - c_1\, S\, I - \mu S \\ \dot{T} = r_1 E + r_2 I - c_2\, T\, I - \mu T \\ \dot{E} = c_1\, S\, I + c_2\, T\, I - c_3\, E\, I - (\mu + r_1 + k)E \\ \dot{I} = kE - (\mu + r_2 + d)I + c_3\, E\, I, \end{cases} \tag{3}$$

where the upper dot denotes the time derivative, $d\cdot/dt$, and the terms not yet described are: the recruitment rate, Λ; the natural death, μ; the treatment rates for the exposed and infectious individuals, r_1 and r_2; the rate at which the exposed become infectious, k; the disease-induced death rate, d.

The solutions of (3) corresponding to non negative initial values remain non negative for all time. Moreover, $\dot{N} = \Lambda - \mu\, N - d\, I$, so that we can study the model in the region:

$$\mathcal{D} = \left\{ (S, T, E, I) \in \mathbf{R}^4_+ : S + T + E + I \leq \frac{\Lambda}{\mu} \right\}. \tag{4}$$

It can be easily seen that system (3) admits the *disease free* equilibrium

$$P_0 = \left(\frac{\Lambda}{\mu},\, 0,\, 0,\, 0\right), \tag{5}$$

on the boundary of $\mathcal{D}$. If we set

$$R_0 = \frac{kc_1\Lambda}{\mu(\mu + r_1 + k)(\mu + r_2 + d)}, \tag{6}$$

the following stability theorem for P_0 may be proved [10]:

Theorem 1. *The disease free equilibrium P_0 is locally asymptotically stable when $R_0 < 1$, and unstable for $R_0 > 1$.*

Now denote with $P^* = (S^*,\, T^*,\, E^*,\, I^*)$ the generic constant equilibrium with positive components. From (3) it follows:

$$S^* = \frac{\Lambda}{c_1\, I^* + \mu}, \tag{7}$$

$$T^* = \frac{[r_1(\mu + r_2 + d) + r_2 k + r_2 c_3\, I^*]\; I^*}{(c_2\, I^* + \mu)\,(c_3\, I^* + k)}, \tag{8}$$

$$E^* = \frac{(\mu + r_2 + d)\; I^*}{(c_3\, I^* + k)}, \tag{9}$$

and I^* given by the real positive solutions of the following algebraic equation:

$$A\,x^3 + B\,x^2 + C\,x + D = 0, \tag{10}$$

where,

$$\begin{aligned} A &= -(\mu + d)c_1c_2c_3, \\ B &= \frac{c_2c_3\mu\alpha_0\alpha_1}{k} R_0 - c_1\mu\alpha_0\,(c_2 + c_3) - c_2\,(\mu + d)\,(c_1k + c_3\mu)\,, \\ C &= \frac{\mu\alpha_1\alpha_0}{k} R_0\,(c_2k + c_3\mu) - \mu\alpha_0\,[\mu\,(c_2 + c_3) + \alpha_1c_1] - (\mu + d)\,k\mu c_2, \\ D &= \mu^2\alpha_0\alpha_1\,(R_0 - 1)\,, \end{aligned} \tag{11}$$

and $\alpha_0 = \mu + d + r_2$, $\alpha_1 = \mu + r_1 + k$.

The existence of endemic equilibria, according to the values of R_0, is described by the following theorem [10].

Theorem 2. *Let inequality*

$$c_1 < c_2 + c_3\frac{\mu}{k} - c_2k\frac{\mu + d}{\alpha_0\alpha_1} - \mu\frac{c_2 + c_3}{\alpha_1}, \tag{12}$$

holds. Then system (3) admits zero or two endemic equilibria when $R_0 < 1$, whereas it admits a unique endemic equilibrium when $R_0 > 1$.

3 Global stability of the endemic equilibrium

In this section, we will use the geometric approach to study the global stability of the endemic equilibrium [19, 20, 22]. Due to technical difficulties, applications to four dimensional systems are still few in the literature, [2, 16]. Here we follow the approach used in [16] for a SVEIR model of severe acute respiratory syndrome (SARS) epidemic spread.

As far as we know, all the applications available in the literature do not completely report all the involved theoretical cases into details. Here we choose to explicitly report all of them, in order to give an exhaustive framework to those interested in applying the method to similar models.

Consider the autonomous dynamical system:

$$\dot{x} = f(x), \tag{13}$$

where $f : D \to \mathbf{R}^n$, $D \subset \mathbf{R}^n$ open set and simply connected and $f \in C^1(D)$. Let x^* be an equilibrium of (13), i.e. $f(x^*) = 0$. We recall that x^* is said to be *globally stable* in D if it is locally stable and all trajectories in D converge to x^*.

Let $Q(x)$ be a $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function that is C^1 on D and consider

$$A = Q_f Q^{-1} + Q\, M\, Q^{-1},$$

where the matrix Q_f is

$$(q_{ij}(x))_f = (\partial q_{ij}(x)/\partial x)^T \cdot f(x) = \nabla q_{ij} \cdot f(x),$$

and the M is the second additive compound matrix of the Jacobian matrix J. Consider the Lozinskiĭ measure $\overline{\mu}$ of A with respect to a vector norm $||\cdot\ ||$ in $\mathbf{R}^{\binom{n}{2}}$, that is:

$$\overline{\mu}(A) = \lim_{h \to 0^+} \frac{||I + hA||}{h}.$$

We will apply the following [20]:

Theorem 3. [20] *If D_1 is a compact absorbing subset in the interior of D, and there exist $\gamma > 0$ and a Lozinskiĭ measure $\overline{\mu}(A) \le -\gamma$ for all $x \in D_1$, then every omega limit point of system (3) in the interior of D is an equilibrium in D_1.*

Theorem 2 states that $R_0 > 1$ and (12) imply the existence and uniqueness of the endemic equilibrium E. Further, we know that $R_0 > 1$ implies that the disease free equilibrium E_0 is unstable. The instability of E_0, together with $E_0 \in \partial\mathcal{D}$, imply the uniform persistence of the state variables, [15], i.e. there exists a constant $c > 0$ such that:

$$\liminf_{t \to \infty} x_i(t) > c, \quad i = 1, 2, 3, 4.$$

The uniform persistence, together with boundedness of $\mathcal{D}$, is equivalent to the existence of a compact set in the interior of $\mathcal{D}$ which is absorbing for (3), see [17]. Hence Theorem 3 may be applied, with $D = \mathcal{D}$.

Remark 1. As we have shown in [10], model (3) may admit backward bifurcation. As stressed in [1], for cases in which the model exhibits bistability, the compact absorbing set required in Theorem 3 does not exist and an alternative approach must be used. That is, a sequence of surfaces that exists for time $\epsilon > 0$ and minimizes the functional measuring surface area must be considered. The analysis of the global dynamics in the bistability region may be approached as it has been done in [1] for a three dimensional model.

According to [24], the Lozinskiĭ measure in Theorem 3 can be evaluated as:

$$\overline{\mu}(A) = \inf \left\{ \overline{k} : D_+ ||\mathbf{z}|| \le \overline{k} ||\mathbf{z}||, \text{ for all solutions of } \mathbf{z}' = \mathrm{A}\mathbf{z} \right\},$$

where D_+ is the right-hand derivative. When $R_0 > 1$ the endemic equilibrium is locally stable. Hence, in order to apply Theorem 3 and get the global asymptotic stability, it is necessary to find a norm $||\cdot||$ such that $\overline{\mu}(A) < 0$ for all x in the interior of $\mathcal{D}$.

We begin by recalling that, for a general 4×4 matrix,

$$\begin{pmatrix} a_{11} & a_{12} & a_{13} & a_{14} \\ a_{21} & a_{22} & a_{23} & a_{24} \\ a_{31} & a_{32} & a_{33} & a_{34} \\ a_{41} & a_{42} & a_{43} & a_{44} \end{pmatrix},$$

the second additive compound matrix is given by:

$$\begin{pmatrix} a_{11}+a_{22} & a_{23} & a_{24} & -a_{13} & -a_{14} & 0 \\ a_{32} & a_{11}+a_{33} & a_{34} & a_{12} & 0 & -a_{14} \\ a_{42} & a_{43} & a_{11}+a_{44} & 0 & a_{12} & a_{13} \\ -a_{31} & a_{21} & 0 & a_{22}+a_{33} & a_{34} & -a_{24} \\ -a_{41} & 0 & a_{21} & a_{43} & a_{22}+a_{44} & a_{23} \\ 0 & -a_{41} & a_{31} & -a_{42} & a_{32} & a_{33}+a_{44} \end{pmatrix}.$$

Hence, the second additive compound matrix of J is given by:

$$M = \begin{pmatrix} M_{11} & M_{12} & M_{13} & 0 & M_{15} & 0 \\ M_{21} & M_{22} & M_{23} & 0 & 0 & M_{26} \\ 0 & M_{32} & M_{33} & 0 & 0 & 0 \\ M_{41} & 0 & 0 & M_{44} & M_{45} & M_{46} \\ 0 & 0 & 0 & M_{54} & M_{55} & M_{56} \\ 0 & 0 & M_{63} & 0 & M_{65} & M_{66} \end{pmatrix},$$

where,

$$\begin{array}{l} M_{11} = -c_1 I - c_2 I - 2\mu; \quad M_{21} = c_2 I; \quad M_{41} = -c_1 I; \quad M_{12} = r_1; \\ M_{22} = -c_1 I - c_3 I - 2\mu - r_1 - k; \quad M_{32} = k + c_3 I; \quad M_{13} = r_2 - c_2 T; \\ M_{33} = -c_1 I + c_3 E - 2\mu - r_2 - d; \quad M_{63} = c_1 I; \quad M_{44} = -c_2 I - c_3 I - 2\mu - r_1 - k; \\ M_{54} = k + c_3 I; \quad M_{15} = c_1 S; \quad M_{45} = c_1 S + c_2 T - c_3 E; \quad M_{23} = c_1 S + c_2 T - c_3 E; \\ M_{55} = -c_2 I + c_3 E - 2\mu - r_2 - d; \quad M_{65} = c_2 I; \quad M_{26} = c_1 S; \\ M_{46} = -r_2 + c_2 T; \quad M_{56} = r_1; \quad M_{66} = -c_3 I + c_3 E - 2\mu - r_1 - k - r_2 - d. \end{array}$$

Consider now the matrix:

$$Q = \begin{pmatrix} 1/E & 0 & 0 & 0 & 0 & 0 \\ 0 & 1/E & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1/E & 0 & 0 \\ 0 & 0 & 1/I & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1/I & 0 \\ 0 & 0 & 0 & 0 & 0 & 1/I \end{pmatrix} \tag{14}$$

Then we get the matrix $A = Q_f Q^{-1} + QMQ^{-1}$, where Q_f is the derivative of Q in the direction of the vector field f. More precisely, we have:

$$Q_f Q^{-1} = -diag(\dot{E}/E,\, \dot{E}/E,\, \dot{E}/E,\, \dot{I}/I,\, \dot{I}/I,\, \dot{I}/I)$$

$$QMQ^{-1} = \begin{pmatrix} M_{11} & M_{12} & 0 & M_{13}\frac{I}{E} & M_{15}\frac{I}{E} & 0 \\ M_{21} & M_{22} & 0 & M_{23}\frac{I}{E} & 0 & M_{26}\frac{I}{E} \\ M_{41} & 0 & M_{44} & 0 & M_{45}\frac{I}{E} & M_{46}\frac{I}{E} \\ 0 & M_{32}\frac{E}{I} & 0 & M_{33} & 0 & 0 \\ 0 & 0 & M_{54}\frac{E}{I} & 0 & M_{55} & M_{56} \\ 0 & 0 & 0 & M_{63} & M_{65} & M_{66} \end{pmatrix}$$

Hence, taking into account that,

$$\frac{\dot{E}}{E} = c_1\, S\, \frac{I}{E} + c_2\, T\, \frac{I}{E} - c_3\, I - (\mu + r_1 + k),$$

$$\frac{\dot{I}}{I} = k\frac{E}{I} - (\mu + r_2 + d) + c_3\, E,$$

we obtain:

$$A = \begin{pmatrix} A_{11} & A_{12} & 0 & A_{14} & A_{15} & 0 \\ A_{21} & A_{22} & 0 & A_{24} & 0 & A_{26} \\ A_{31} & 0 & A_{33} & 0 & A_{35} & A_{36} \\ 0 & A_{42} & 0 & A_{44} & 0 & 0 \\ 0 & 0 & A_{53} & 0 & A_{55} & A_{56} \\ 0 & 0 & 0 & A_{64} & A_{65} & A_{66} \end{pmatrix}$$

where,

$$\begin{aligned}
&A_{11} = -c_1\, S\, \tfrac{I}{E} - c_2\, T\, \tfrac{I}{E} + (c_3 - c_1 - c_2)I + r_1 + k - \mu; \\
&A_{21} = c_2 I; \quad A_{31} = -c_1 I; \quad A_{31} = -c_1 I, \quad A_{12} = r_1; \\
&A_{22} = -c_1\, S\, \tfrac{I}{E} - c_2\, T\, \tfrac{I}{E} - c_1 I - \mu; \quad A_{42} = k\tfrac{E}{I} + c_3 E; \\
&A_{33} = -c_1\, S\, \tfrac{I}{E} - c_2\, T\, \tfrac{I}{E} - c_2 I - \mu; \quad A_{53} = k\tfrac{E}{I} + c_3 E; \quad A_{14} = (r_2 - c_2 T)\tfrac{I}{E}; \\
&A_{24} = (c_1 S + c_2 T)\tfrac{I}{E} - c_3 I; \quad A_{44} = -k\tfrac{E}{I} - c_1 I - \mu; \quad A_{64} = c_1 I; \quad A_{15} = (c_1 S)\tfrac{I}{E}; \\
&A_{35} = (c_1 S + c_2 T)\tfrac{I}{E} - c_3 I; \quad A_{55} = -k\tfrac{E}{I} - c_2 I - \mu; \quad A_{65} = c_2 I; \quad A_{26} = (c_1 S)\tfrac{I}{E}; \\
&A_{36} = (-r_2 + c_2 T)\tfrac{I}{E}; \quad A_{56} = r_1; \\
&A_{66} = -k\tfrac{E}{I} - c_3 I - \mu - r_1 - k.
\end{aligned}$$

As in [16], we consider the following norm on $\mathbf{R}^6$:

$$\|\mathbf{z}\| = \max\{U_1,\, U_2\}\,, \tag{15}$$

where $\mathbf{z} \in \mathbf{R}^6$, with components z_i, $i = 1, \ldots, 6$, and

$$U_1(z_1, z_2, z_2) = \begin{cases} \max\{|z_1|,\, |z_2| + |z_3|\} & \text{if} \quad \mathrm{sgn}(z_1) = \mathrm{sgn}(z_2) = \mathrm{sgn}(z_3) \\ \max\{|z_2|,\, |z_1| + |z_3|\} & \text{if} \quad \mathrm{sgn}(z_1) = \mathrm{sgn}(z_2) = -\mathrm{sgn}(z_3) \\ \max\{|z_1|,\, |z_2|,\, |z_3|\} & \text{if} \quad \mathrm{sgn}(z_1) = -\mathrm{sgn}(z_2) = \mathrm{sgn}(z_3) \\ \max\{|z_1| + |z_3|,\, |z_2| + |z_3|\} & \text{if} \quad -\mathrm{sgn}(z_1) = \mathrm{sgn}(z_2) = \mathrm{sgn}(z_3) \end{cases}$$

$$U_2(z_4, z_5, z_6) = \begin{cases} |z_4| + |z_5| + |z_6| & \text{if} \quad \mathrm{sgn}(z_4) = \mathrm{sgn}(z_5) = \mathrm{sgn}(z_6) \\ \max\{|z_4| + |z_5|,\, |z_4| + |z_6|\} & \text{if} \quad \mathrm{sgn}(z_4) = \mathrm{sgn}(z_5) = -\mathrm{sgn}(z_6) \\ \max\{|z_5|,\, |z_4| + |z_6|\} & \text{if} \quad \mathrm{sgn}(z_4) = -\mathrm{sgn}(z_5) = \mathrm{sgn}(z_6) \\ \max\{|z_4| + |z_6|,\, |z_5| + |z_6|\} & \text{if} \quad -\mathrm{sgn}(z_4) = \mathrm{sgn}(z_5) = \mathrm{sgn}(z_6) \end{cases}$$

In the next, we will use the following inequalities:

$$|z_2| < U_1, \quad |z_3| < U_1, \quad |z_2 + z_3| < U_1,$$

and

$$|z_i|,\ |z_i + z_j|,\ |z_4 + z_5 + z_6| \le U_2(z); \qquad i = 4, 5, 6;\ i \ne j.$$

Moreover, we assume that:

$$c_1 > c_2 > c_3. \tag{16}$$

These inequalities will be used to get the estimates on $D_+||\mathbf{z}||$. However, some more restrictive conditions will be adopted in the statement of the global stability theorem later (inequalities (49))

<u>Case 1</u>: $U_1 > U_2$, $\quad z_1, z_2, z_3 > 0$, and $\quad |z_1| > |z_2| + |z_3|$. Then:

$$\|\mathbf{z}\| = |z_1|, \tag{17}$$

so that

$$\begin{aligned}
D_+\,\|\mathbf{z}\| \quad &= z_1' \\
&= A_{11}z_1 + A_{12}z_2 + A_{14}z_4 + A_{15}z_5 \\
&\le \left[-c_1\, S\, \tfrac{I}{E} - c_2\, T\, \tfrac{I}{E} + (c_3 - c_1 - c_2)I + r_1 + k - \mu\right]\, |z_1| + \\
&\quad + r_1\, |z_2| + \left[(r_2 + c_2 T)\tfrac{I}{E}\right] |z_4| + (c_1 S)\tfrac{I}{E}\, |z_5|.
\end{aligned}$$

Using $|z_4| < U_2 < |z_1|$, $|z_5| < U_2 < |z_1|$, $|z_2| < |z_1|$, and (17), it follows:

$$D_+ \|\mathbf{z}\| \quad \leq \left[2r_1 + k - \mu + (c_3 - c_1 - c_2)I + r_2 \tfrac{I}{E}\right] \|\mathbf{z}\| \,. \tag{18}$$

<u>Case 2</u>: $U_1 > U_2$, $z_1, z_2, z_3 > 0$, and $|z_1| < |z_2| + |z_3|$. Then:

$$\|\mathbf{z}\| = |z_2| + |z_3|, \tag{19}$$

so that

$$\begin{aligned} D_+ \|\mathbf{z}\| \quad &= z_2' + z_3' \\ &\leq (c_2 - c_1)I\,|z_1| + \left[-c_1\, S\, \tfrac{I}{E} - c_2\, T\, \tfrac{I}{E} - c_1 I - \mu\right] |z_2| + \\ &\ \ + \left[-c_1\, S\, \tfrac{I}{E} - c_2\, T\, \tfrac{I}{E} - c_2 I - \mu\right] |z_3| + \\ &\ \ + \left[c_1\, S\, \tfrac{I}{E} + c_2\, T\, \tfrac{I}{E}\right] |z_4 + z_5 + z_6| + c_3 I\, |z_4 + z_5| + r_2 \tfrac{I}{E}\, |z_6|. \end{aligned}$$

Using now $|z_4 + z_5 + z_6| < U_2 < |z_2| + |z_3|$, $|z_4 + z_5| < U_2 < |z_2| + |z_3|$, $|z_6| < U_2 < |z_2| + |z_3|$, and taking into account of (16) and (19), one has:

$$D_+ \|\mathbf{z}\| \quad \leq \left[-\mu + r_2 \tfrac{I}{E}\right] \|\mathbf{z}\| \,. \tag{20}$$

<u>Case 3</u>: $U_1 > U_2$, $z_1 < 0$, $z_2, z_3 > 0$, and $|z_1| > |z_2|$. Then:

$$\|\mathbf{z}\| = |z_1| + |z_3|, \tag{21}$$

so that

$$\begin{aligned} D_+ \|\mathbf{z}\| \quad &= -z_1' + z_3' \\ &\leq \left[-c_1\, S\, \tfrac{I}{E} - c_2\, T\, \tfrac{I}{E} + (c_3 - c_2)I + r_1 + k - \mu\right] |z_1| - r_1 |z_2| + \\ &\ \ + \left[-c_1\, S\, \tfrac{I}{E} - c_2\, T\, \tfrac{I}{E} - c_2 I - \mu\right] |z_3| + c_2\, T\, \tfrac{I}{E}\, |z_4 + z_5 + z_6| + \\ &\ \ + r_2 \tfrac{I}{E}\, |z_4 + z_6| + c_3 I\, |z_5|. \end{aligned}$$

Using $|z_4 + z_5 + z_6| < U_2 < |z_1| + |z_3|$, $|z_4 + z_6| < U_2 < |z_1| + |z_3|$, $|z_5| < U_2 < |z_1| + |z_3|$, and $-r_1|z_2| \leq r_1|z_2| < r_1|z_1|$ and taking into account of (21), it follows:

$$D_+ \|\mathbf{z}\| \quad \leq \left[k + 2r_1 - \mu + (2c_3 - c_2)\, I + r_2 \tfrac{I}{E}\right] \|\mathbf{z}\| \,. \tag{22}$$

<u>Case 4</u>: $U_1 > U_2$, $z_1 < 0$, $z_2, z_3 > 0$, and $|z_1| < |z_2|$. Then:

$$\|\mathbf{z}\| = |z_2| + |z_3|, \tag{23}$$

so that

$$\begin{aligned} D_+ \|\mathbf{z}\| \quad &= z_2' + z_3' \\ &\leq (c_1 - c_2)I\,|z_1| + \left[-c_1\, S\, \tfrac{I}{E} - c_2\, T\, \tfrac{I}{E} - c_1 I - \mu\right] |z_2| + \\ &\ \ + \left[-c_1\, S\, \tfrac{I}{E} - c_2\, T\, \tfrac{I}{E} - c_2 I - \mu\right] |z_3| + \\ &\ \ + \left[c_1\, S\, \tfrac{I}{E} + c_2\, T\, \tfrac{I}{E}\right] |z_4 + z_5 + z_6| + c_3 I\, |z_4 + z_5| + r_2 \tfrac{I}{E}\, |z_6|. \end{aligned}$$

Using $|z_4 + z_5 + z_6| < U_2 < |z_2| + |z_3|$, $|z_4 + z_5| < U_2 < |z_2| + |z_3|$, $|z_6| < U_2 < |z_2| + |z_3|$, and in view of $|z_1| < |z_2|$, (16), (23), it follows:

$$D_+ \|\mathbf{z}\| \quad \leq \left[(c_3 - c_2)I - \mu + r_2 \tfrac{I}{E}\right] \|\mathbf{z}\| \,. \tag{24}$$

<u>Case 5</u>: $U_1 > U_2$, $z_1, z_2 > 0$, $z_3 < 0$, and $|z_2| > |z_1| + |z_3|$. Then:

$$\|\mathbf{z}\| = |z_2|, \tag{25}$$

so that

$$\begin{aligned} D_+\,\|\mathbf{z}\| &= z_2' \\ &\le c_2 I\,|z_1| + \left[-c_1\,S\,\tfrac{I}{E} - c_2\,T\,\tfrac{I}{E} - c_1 I - \mu\right]\,|z_2| + \\ &\quad + \left[c_1\,S\,\tfrac{I}{E}\right]\,|z_4 + z_6| + \left[c_2\,T\,\tfrac{I}{E} + c_3 I\right]\,|z_4|. \end{aligned}$$

Using $|z_4 + z_6| < U_2 < |z_2|$, $|z_4| < U_2 < |z_2|$ together with $|z_1| < |z_2|$ and (25), it follows:

$$D_+\,\|\mathbf{z}\| \quad \le \left[(c_2 + c_3 - c_1)I - \mu\right]\,\|\mathbf{z}\|\,. \tag{26}$$

Case 6: $U_1 > U_2$, $\quad z_1, z_2 > 0$, $z_3 < 0$, and $\quad |z_2| < |z_1| + |z_3|$. Then:

$$\|\mathbf{z}\| = |z_1| + |z_3|, \tag{27}$$

so that

$$\begin{aligned} D_+\,\|\mathbf{z}\| &= z_1' - z_3' \\ &\le \left[-c_1\,S\,\tfrac{I}{E} - c_2\,T\,\tfrac{I}{E} + (c_3 - c_2)I + r_1 + k - \mu\right]|z_1| + r_1|z_2| + \\ &\quad + \left[-c_1\,S\,\tfrac{I}{E} - c_2\,T\,\tfrac{I}{E} - c_2 I - \mu\right]|z_3| + c_2\,T\,\tfrac{I}{E}\,|z_4 + z_5 + z_6| + \\ &\quad + r_2\,\tfrac{I}{E}\,|z_4 + z_6| + c_3 I\,|z_5|. \end{aligned}$$

Using $|z_4 + z_5 + z_6| < U_2 < |z_1| + |z_3|$, $\;|z_4 + z_6| < U_2 < |z_1| + |z_3|$, $\;|z_5| < U_2 < |z_1| + |z_3|$, $r_1|z_2| < r_1(|z_1| + |z_3|)$ and taking into account of (27), it follows:

$$D_+\,\|\mathbf{z}\| \quad \le \left[k + 2r_1 - \mu + (2c_3 - c_2)\,I + r_2\,\tfrac{I}{E}\right]\;\|\mathbf{z}\|\,. \tag{28}$$

Case 7: $U_1 > U_2$, $\quad z_1, z_3 > 0$, $z_2 < 0$, and $\quad |z_1| > \max\{|z_2|, |z_3|\}$. Then:

$$\|\mathbf{z}\| = |z_1|, \tag{29}$$

so that

$$\begin{aligned} D_+\,\|\mathbf{z}\| &= z_1' \\ &\le \left[-c_1\,S\,\tfrac{I}{E} - c_2\,T\,\tfrac{I}{E} + (c_3 - c_1 - c_2)I + r_1 + k - \mu\right]|z_1| + r_1|z_2| + \\ &\quad + \left[(r_2 + c_2 T)\tfrac{I}{E}\right]|z_4| + \left(c_1\,S\,\tfrac{I}{E}\right)|z_5|. \end{aligned}$$

Using $|z_4| < U_2 < |z_1|$, $|z_5| < U_2 < |z_1|$ and $r_1|z_2| < r_1|z_1|$, it follows:

$$D_+\,\|\mathbf{z}\| \quad \le \left[k + 2r_1 - \mu + (c_3 - c_1 - c_2)\,I + r_2\,\tfrac{I}{E}\right]\;\|\mathbf{z}\|\,. \tag{30}$$

Case 8: $U_1 > U_2$, $z_1, z_3 > 0$, $z_2 < 0$, and $|z_2| > \max\{|z_1|, |z_3|\}$. Then:

$$\|\mathbf{z}\| = |z_2|, \tag{31}$$

so that

$$\begin{aligned} D_+\,\|\mathbf{z}\| &= -z_2' \\ &\le c_2 I\,|z_1| + \left[-c_1\,S\,\tfrac{I}{E} - c_2\,T\,\tfrac{I}{E} - c_1 I - \mu\right]\,|z_2| + \\ &\quad + \left[c_1\,S\,\tfrac{I}{E}\right]\,|z_4 + z_6| + \left[c_2\,T\,\tfrac{I}{E} + c_3 I\right]\,|z_4|. \end{aligned}$$

Using $|z_4 + z_6| < U_2 < |z_2|$, $|z_4| < U_2 < |z_2|$ and in view of $|z_1| < |z_2|$, (31), one has:

$$D_+\,\|\mathbf{z}\| \quad \le \left[(c_2 + c_3 - c_1)I - \mu\right]\,\|\mathbf{z}\|\,. \tag{32}$$

Case 9: $U_1 > U_2$, $\quad z_1, z_3 > 0$, $z_2 < 0$, and $\quad |z_3| > \max\{|z_1|, |z_2|\}$. Then:

$$\|\mathbf{z}\| = |z_3|, \tag{33}$$

so that

$$\begin{aligned} D_+\,\|\mathbf{z}\| &= z_3' \\ &\le -c_1 I\,|z_1| + \left[-c_1\,S\,\tfrac{I}{E} - c_2\,T\,\tfrac{I}{E} - c_2 I - \mu\right]\,|z_3| + \\ &\quad + c_2\,T\,\tfrac{I}{E}|z_5 + z_6| + \left(c_1\,S\,\tfrac{I}{E} + c_3 I\right)|z_5| + r_2\,\tfrac{I}{E}|z_6|. \end{aligned}$$

Use $|z_5+z_6|<U_2<|z_3|$, $|z_5|<U_2<|z_3|$, $|z_6|<U_2<|z_3|$, and in view of $-c_1I\,|z_1|<0$, (16), (33), it follows:

$$D_+\,\|\mathbf{z}\| \quad \le \left[(c_3-c_2)I-\mu+r_2\tfrac{I}{E}\right]\,\|\mathbf{z}\|\,. \tag{34}$$

Case 10: $U_1<U_2$, $z_4,z_5,z_6>0$. Then:

$$\|\mathbf{z}\| = |z_4|+|z_5|+|z_6|, \tag{35}$$

so that

$$\begin{aligned} D_+\,\|\mathbf{z}\| \quad &= z_4'+z_5'+z_6' \\ &\le \left(k\tfrac{E}{I}+c_3E\right)|z_2+z_3| + \left(-k\tfrac{E}{I}-\mu\right)(|z_4|+|z_5|)+ \\ &+\left(-k\tfrac{E}{I}-\mu-k-c_3I\right)|z_6|. \end{aligned}$$

Using $|z_2+z_3|<U_1<|z_4|+|z_5|+|z_6|$, along with $-(c_3I+k)|z_6|<0$ and (35), it follows:

$$D_+\,\|\mathbf{z}\| \quad \le (c_3E-\mu)\,\|\mathbf{z}\|\,. \tag{36}$$

Case 11: $U_1<U_2$, $z_4,z_5>0$, $z_6<0$, and $|z_5|>|z_6|$. Then:

$$\|\mathbf{z}\| = |z_4|+|z_5|, \tag{37}$$

so that

$$\begin{aligned} D_+\,\|\mathbf{z}\| \quad &= z_4'+z_5' \\ &\le \left(k\tfrac{E}{I}+c_3E\right)|z_2+z_3| + \left(-k\tfrac{E}{I}-\mu\right)(|z_4|+|z_5|)+ \\ &-c_1I|z_4|-c_2I|z_5|+r_1|z_6|. \end{aligned}$$

Using $|z_2+z_3|<U_1<|z_4|+|z_5|$, $|z_6|<|z_5|+|z_4|$, and in view of $-c_1I|z_4|<0$, $-c_2I|z_5|<0$ and (37), one has:

$$D_+\,\|\mathbf{z}\| \quad \le (c_3E+r_1-\mu)\,\|\mathbf{z}\|\,. \tag{38}$$

Case 12: $U_1<U_2$, $z_4,z_5>0$, $z_6<0$, and $|z_5|<|z_6|$. Then:

$$\|\mathbf{z}\| = |z_4|+|z_6|, \tag{39}$$

so that

$$\begin{aligned} D_+\,\|\mathbf{z}\| \quad &= z_4'-z_6' \\ &\le \left(k\tfrac{E}{I}+c_3E\right)|z_2| - \left(k\tfrac{E}{I}+\mu\right)(|z_4|+|z_6|)-2c_1I|z_4|-c_2I\,|z_5|+ \\ &-(r_1+k+c_3I)\,|z_6|. \end{aligned}$$

By using $|z_2|<U_1<|z_4|+|z_6|$ and from (39), it follows:

$$D_+\,\|\mathbf{z}\| \quad \le (c_3E-\mu)\,\|\mathbf{z}\|\,. \tag{40}$$

Case 13: $U_1<U_2$, $z_4,z_6>0$, $z_5<0$, and $|z_5|>|z_4|+|z_6|$. Then:

$$\|\mathbf{z}\| = |z_5|, \tag{41}$$

so that

$$\begin{aligned} D_+\,\|\mathbf{z}\| \quad &= -z_5' \\ &\le \left(k\tfrac{E}{I}+c_3E\right)|z_3| - \left(k\tfrac{E}{I}+c_2I+\mu\right)|z_5|-r_1|z_6|. \end{aligned}$$

By using $|z_3|<U_1<|z_5|$ and from (41), it follows:

$$D_+\,\|\mathbf{z}\| \quad \le (c_3E-\mu)\,\|\mathbf{z}\|\,. \tag{42}$$

Case 14: $U_1<U_2$, $z_4,z_6>0$, $z_5<0$, and $|z_5|<|z_4|+|z_6|$. Then:

$$\|\mathbf{z}\| = |z_4|+|z_6|, \tag{43}$$

so that

$$\begin{aligned} D_+\|\mathbf{z}\| &= z_4' + z_6' \\ &\le \left(k\tfrac{E}{I} + c_3E\right)|z_2| - \left(k\tfrac{E}{I} + \mu\right)(|z_4| + |z_6|) + \\ &-c_2I\,|z_5| - (r_1 + k + c_3I)\,|z_6|. \end{aligned}$$

By using $|z_2| < U_1 < |z_4| + |z_6|$ and from (43), it follows:

$$D_+\|\mathbf{z}\| \quad \le (c_3E - \mu)\ \|\mathbf{z}\|\,. \tag{44}$$

Case 15: $U_1 < U_2$, $\quad z_5, z_6 > 0$, $z_4 < 0$, and $\quad |z_5| < |z_4|$. Then:

$$\|\mathbf{z}\| = |z_4| + |z_6|, \tag{45}$$

so that

$$\begin{aligned} D_+\|\mathbf{z}\| &= -z_4' + z_6' \\ &\le \left(k\tfrac{E}{I} + c_3E\right)|z_2| - \left(k\tfrac{E}{I} + \mu\right)(|z_4| + |z_6|) + \\ &+c_2I\,|z_5| - 2c_1I\,|z_4| - (r_1 + k + c_3I)\,|z_6|. \end{aligned}$$

By using $|z_2| < U_1 < |z_4| + |z_6|$, and $|z_5| < |z_4|$, taking into account of (16) and from (45), it follows:

$$D_+\|\mathbf{z}\| \quad \le (c_3E - \mu)\ \|\mathbf{z}\|\,. \tag{46}$$

Case 16: $U_1 < U_2$, $\quad z_5, z_6 > 0$, $z_4 < 0$, and $\quad |z_5| > |z_4|$. Then:

$$\|\mathbf{z}\| = |z_5| + |z_6|, \tag{47}$$

so that

$$\begin{aligned} D_+\|\mathbf{z}\| &= z_5' + z_6' \\ &\le \left(k\tfrac{E}{I} + c_3E\right)|z_3| - c_1I\,|z_4| + \\ &- \left(k\tfrac{E}{I} + \mu\right)(|z_5| + |z_6|) - (c_3I + k)\,|z_6|. \end{aligned}$$

By using $|z_3| < U_1 < |z_5| + |z_6|$ and from (47), one has:

$$D_+\|\mathbf{z}\| \quad \le (c_3E - \mu)\ \|\mathbf{z}\|\,. \tag{48}$$

Now let us assume that:

$$c_1 > c_2 + c_3, \qquad c_2 > 2c_3. \tag{49}$$

Such inequalities are stronger than (16) and implies that the linear coefficient of I in the sixteen estimates of $D_+||\mathbf{z}||$ above, are negative. In this way, the inequalities (18), (20), (22), (24), (26), (28), (30), (32), (34), (36), (38), (40), (42), (44), (46), (48) may be combined to get the following:

$$D_+\|\mathbf{z}\| \quad \le \max\left\{-\mu + r_1 + c_3E,\ -\mu + 2r_1 + k + r_2\tfrac{I}{E}\right\}\|\mathbf{z}\|\,. \tag{50}$$

We can summarize the results obtained above with the following sufficient conditions for the global asymptotic stability of the endemic equilibrium:

Theorem 4. *For $R_0 > 1$, system (3) admits an unique endemic equilibrium which is globally asymptotically stable in the interior of $\mathcal{D}$, provided that inequalities (12) and (49) are satisfied, and that:*

$$\max\left\{-\mu + r_1 + c_3\sup_{t\in(0,\infty)} E,\ -\mu + 2r_1 + k + r_2\sup_{t\in(0,\infty)}\frac{I}{E}\right\} < -\nu \tag{51}$$

for some positive constant ν.

4 Discussion

This paper deals with a specific aspect of a tuberculosis model: the global asymptotic stability of the endemic equilibrium. Biologically speaking, this analysis gives the conditions, written in terms of the parameters of the system, under which the TB cannot be eliminated from the community. From a mathematical point of view, it represents a quite difficult task because of the high dimensionality of the system. Here, we have applied the method of Li and Muldowney, say the geometric approach to global stability for n dimensional systems.

Following the strategy of costructing a suitable norm on $\mathbf{R}^6$, described into details in [25] and developed in [16] for a SVEIR model of SARS epidemic spread, we have obtained the sufficient conditions for the global stability of the endemic equilibrium contained in Theorem 4.

In view of (51) it sufficies to set:

$$\mu > \max\left\{ r_1 + c_3 \sup_{t\in(0,\infty)} E,\ 2r_1 + k + r_2 \sup_{t\in(0,\infty)} \frac{I}{E} \right\}. \tag{52}$$

Some of the sufficient conditions required by Theorem 4, precisely (49) and (51), or equivalently (52), arise from the application of the method and numerical simulations suggest that they are not necessary.

We can also show that some of the required inequalities are somewhat counterintuitive. In fact, let us consider the case of no reinfection, i.e. let us set $c_3 = 0$, and assume further that $r_2 = 0$, that is only the latentely infected are treated (through chemoprophylaxis, case 2 in [4]). Then, the assumption $R_0 > 1$ becomes:

$$k > \frac{\mu(\mu + r_1)(\mu + d)}{c_1\Lambda - \mu(\mu + d)}; \tag{53}$$

further, inequalities (49) reduce to $c_1 > c_2$ and (52) implies $\mu > k$. This last suggests that the global stability of the endemic state is supported by a small rate of progression to active TB, which is in contrast with (53). A similar result is obtained also in [16] and well represents the drawbacks of the geometric stability method, when it is applied to system with complex structure.

However, we stress that the sufficient conditions for global stability we found here might in principle be improved. In fact, the geometric approach to stability is based on two crucial choices: the entries of the matrix Q and the vector norm in $\mathbf{R}^{\binom{n}{2}}$. In our case, (14) and (15).

It can be seen, [22], that the stability condition stated in Theorem 3 is ensured by taking the Lyapunov function $V(x,z) = \|Q(x)z\|$ on the $n + \binom{n}{2}$ - dimensional system given by (13) and the second compound equation:

$$\dot{z} = J^{[2]}(x)z. \tag{54}$$

In fact, $\dot{V}$ negative definite is equivalent to condition $\overline{\mu}(A) \leq -\gamma$ in Theorem 3, [22].

As finding Lyapunov functions is a matter of experience, thus the best choice for the matrix and the vector norm can not be determined through a general way. Obviously, different choices of the matrix Q and of the vector norm may lead, in principle, to better sufficient conditions than the ones we found here, in the sense that the restrictions on the parameters may be weakened.

Finally, we stress that the dynamics of model (3) may be very rich, including backward bifurcation and bistability. Such issues have been investigated in details in [10], where this model has been applied to the case study considered in [26].

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