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Influence of diffusion on the stability of equilibria in a reaction–diffusion system modeling cholera dynamic

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Abstract A reaction–diffusion system modeling cholera epidemic in a non-homogeneously mixed population is introduced. The interaction between population and toxigenic *Vibrio cholerae* concentration in contaminated water has been taken into account. The existence of biologically meaningful equilibria is investigated together with their linear and nonlinear stability. Using the data collected during the Haiti cholera epidemic, a numerical simulation is performed.

Keywords Stability · Epidemic models · Reaction–diffusion systems · Lyapunov direct method · Cholera

Mathematics Subject Classification 92D30 · 34D23 · 35B35

1 Introduction

Cholera is an acute intestinal infection caused by the bacterium *Vibrio cholerae*. The mechanism of transmission occurs, principally, via ingestion of contaminated food or water and, secondarily but more rarely, via direct human-to-human contacts (Sanches et al. 2011). In the developed world, seafood (in particular consuming contaminated oysters and shellfish) is the usual cause, while in the developing world it is more

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often water. Generally, the incubation period lasts from less than one day to five days. Symptoms are watery diarrhea and vomiting that can quickly lead to severe dehydration and death if treatment is not promptly given. Without treatment the case-fatality rate for severe cholera is about 50 % (Sack et al. 2004). Only 1–30 % of *V. cholerae* infections develop into severe cholera cases (Sack and Cadoz 1999). People with lowered immunity (for example people with AIDS or malnourished children) are more likely to experience a severe case if they become infected.

Cholera is endemic in many parts of the world such as Asia, India, Africa and Latin America. It affects 3–5 million people and causes 100,000–130,000 deaths a year as of 2010 (Tian and Wang 2011). The primary therapy consists in re-hydrating infected people in order to replace contaminated water in the organism and correct electrolyte imbalance. However, prevention strategy is strongly recommended by the World Health Organization (WHO). It provides water purification, sterilization of all materials that come in contact with cholera patients, improvements in sanitation systems and in personal hygiene. These measurements minimize human contact with contaminated water and consequently spread of the epidemic. Till now, the preventive care consists in active immunization by mean of vaccines. Injectable vaccines are given by two intramuscular or subcutaneous inoculations. Protection lasts not more than 6 months and it is not complete. Because of the high side effects, this kind of care is actually deterred. Oral vaccines are available by two preparations. The first (*Orochol*) can be given to people being more than 2 years old. Efficiency is for 60–90 %, it starts after seven days and can last up to 2 years (boosters have to be given every 6 months). The second preparation (*Cholerix*) is given in two doses far-between 2 weeks. Efficiency is in 65 %.

In order to study infectious diseases transmission, the mathematical models play a central role. In fact, although they represent only an approximation of the problem (they consider only some variables that are involved in the phenomenon), they allow to obtain estimation about the spread of epidemics. In this way it is possible to predict the asymptotic behaviour of infection and, consequentially, to take some actions to control epidemics. When a population is not infected by a disease, all the individuals are regarded as susceptibles. On introducing a few number of infected in the community, in order to know if the epidemic will die out or if it will blow up, it would be useful to study the stability of the so called *disease-free* equilibrium. If the disease-free equilibrium is stable, then epidemic will decay. In general, the problem to determine if *endemic equilibria* (i.e. equilibria with positive components) exist, arises. When endemic equilibria exist, their stability analysis allows to state if epidemic will persist. Mathematical models for infectious diseases have been widely studied in literature (see, for example, Buonomo and Lacitignola 2008, 2010; Buonomo and Rionero 2010; Capasso 1978, 1993; Capasso and Maddalena 1981; Capasso and Paveri-Fontana 1979; Chinviriyasit and Chinviriyasit 2010; Kermack and McKendrick 1927; Mulone et al. 2007; Shuai and Van Den Driessche 2012; Tian et al. 2010).

Many of them are devoted to study cholera outbreak in different parts of the world. In particular Capasso and Paveri-Fontana (1979) studied the cholera epidemic in Bari (Italy) in 1973 by introducing a system modeling the evolution of infected people in the community and the dynamics of the aquatic population of pathogenic bacteria. In fact, cholera diffusion is strictly linked to the interactions between individuals in

community and bacteria in contaminated water. Successively, Capasso and Maddalena (1981), in order to let the model be more realistic, assumed that the bacteria diffuse randomly in the habitat. Hence they analyzed a model consisting in two nonlinear parabolic equations under boundary conditions of the third type. Many studies (see, for example, Colwell and Huq 1994) found that toxigenic *V. cholerae* can survive in some aquatic environments for months to years. This suggests to believe that the aquatic environment may be a reservoir of toxigenic *V. cholerae* in endemic regions. Codeco (2001) analyzed the role of aquatic reservoir in promoting cholera outbreak by introducing an ODE model that includes the dynamics of the susceptible population. Three possible scenario, when cholera comes into a new place, have been analyzed: no outbreak (cholera-free); an outbreak followed by few waves (epidemic pattern); an outbreak followed by subsequent outbreaks that can assume a seasonal pattern (endemic pattern). Tian and Wang (2011) introduced a fourth equation in order to study the evolution of removed individuals.

In this paper, we generalize the above mentioned models on taking into account of non-homogeneously mixed toxigenic *V. cholerae* reservoir in contaminated water and on dividing the total population in three disjointed and not homogeneously mixed in the environment classes (susceptibles–infected–removed) in order to study—among other things—the role of diffusivity of each population on the model dynamics. In particular, the PDE model is introduced in Sect. 2. Equilibria analysis is performed in the subsequent Sect. 3. It is shown that the model always admits the disease-free equilibrium while it admits a unique endemic equilibrium if and only if the parameter R_0 defined by (7) is greater than 1. The stability analysis of the equilibria is performed in Sects. 4, 5, and 6. In particular, after having introduced some preliminaries to the stability analysis of the equilibria (Sect. 4), by mean of the Routh–Hurwitz conditions, necessary and sufficient conditions guaranteeing the linear stability of the equilibria are obtained in Sect. 5. By using a peculiar Liapunov functional, directly linked to the principal invariants of the linear system, in Sect. 6 it has been shown that these conditions are also necessary and sufficient to guarantee the nonlinear stability. Hence the coincidence between linear and nonlinear stability thresholds is obtained. A numerical comparison of the obtained results with a real case is furnished in Sect. 7. In this section, experimental data of cholera outbreak in Haiti (period: October 2010–January 2014) are compared with model previsions showing that mathematical model predicts very well the epidemic behaviour. The paper ends with a discussion on the obtained results (Sect. 8).

2 Mathematical model

Let $\Omega \subset \mathbb{R}^3$ be a smooth convex domain in which cholera is diffusing. Let us suppose that the population is divided in three disjointed classes: S, the susceptibles; I, the infected; R the removed and let us denote by B the concentration of toxigenic *V. cholerae* in water (cells/ml). The physics of the problem leads to suppose that S, I, R, B are positive, smooth functions. Further, we suppose that these functions depend on time as well as on space. The reaction–diffusion equations which, as far as we know, appear to be new in the existing literature and govern cholera disease, are

Table 1 Description of the constants appearing in (1)

Symbols	Description	Units
N_0	Total population size at time $t = 0$	Person
γ_i	Diffusion coefficients (i = 1, 2, 3, 4)	t^{-1} m^2
μ	Birth/death rate	t^{-1}
σ	Recovery rate	t^{-1}
μ_B	Loss rate of bacteria	t^{-1}
π_B	Growth rate of bacteria	t^{-1}
$e = \frac{p}{W}$	Contribution of each infected person to the population of *V. cholerae*	Cells/ml t^{-1} $person^{-1}$
p	Rate at which bacterias are produced by an infected individual	Cells t^{-1} $person^{-1}$
W	Volume of contaminated water in infected individual	ml
β	Contact rate with contaminated water	t^{-1}

$$\begin{cases} \frac{\partial S}{\partial t} = \mu(N_0 - S) + \gamma_1 \Delta S - \beta\lambda(B)S, \\ \frac{\partial I}{\partial t} = \beta\lambda(B)S - (\sigma + \mu)I + \gamma_2 \Delta I, \\ \frac{\partial B}{\partial t} = eI - (\mu_B - \pi_B)B + \gamma_3 \Delta B, \\ \frac{\partial R}{\partial t} = \sigma I - \mu R + \gamma_4 \Delta R. \end{cases} \tag{1}$$

In comparison with existing models in literature, the additional diffusion terms $\gamma_1 \Delta S$, $\gamma_2 \Delta I$, $\gamma_3 \Delta B$, $\gamma_4 \Delta R$ have been introduced in order to take into account of the possibility of each constituent to move in the environment. In (1)

$$\lambda(B) = \frac{B}{K_B + B},$$

is the probability to catch cholera (Sengupta et al. 1998), being K_B (cells/ml) the constant indicating the half saturation rate and it is linked to the concentration of *V. cholerae* in water that yields 50 % chance of catching cholera. The constants appearing in (1) are positive and have been specified in Table 1. Further, according to Codeco (2001), Islam et al. (1994), and Zhou and Cui (2010), it is supposed that $\mu_B > \pi_B$.

The diffusion coefficients γ_i, $(i = 1, 2, 3, 4)$ in model (1) are strictly linked to the possibility of population to move in the environment. Generally γ_i, $(i = 1, 2, 3, 4)$ are such that $\gamma_i \neq \gamma_j$, $(i \neq j)$ and depend on the poor hygiene state, on the country in which the disease is developed.

When no population flux across the boundary $\partial\Omega$ is admissible, the following homogeneous Neumann boundary conditions have to be added to (1)

$$\nabla S \cdot \mathbf{n} = 0, \ \nabla I \cdot \mathbf{n} = 0, \ \nabla B \cdot \mathbf{n} = 0, \ \nabla R \cdot \mathbf{n} = 0 \quad \text{on } \partial\Omega \times \mathbb{R}^+, \tag{2}$$

being $\mathbf{n}$ the unit outward normal on $\partial\Omega$. Let us define

$$N(t) = \frac{1}{|\Omega|} \int_\Omega [S(\mathbf{x}, t) + I(\mathbf{x}, t) + R(\mathbf{x}, t)] \, d\Omega,$$

the population size at time t ($|\Omega|$ is the measure of Ω). Hence

$$N_0 = \frac{1}{|\Omega|}\int_\Omega [S(\mathbf{x},0) + I(\mathbf{x},0) + R(\mathbf{x},0)]\, d\Omega.$$

By adding $(1)_1$, $(1)_2$, $(1)_4$ and integrating over Ω, one has

$$\begin{aligned}\frac{d}{dt}\int_\Omega (S+I+R)\, d\Omega &= \mu N_0\,|\Omega| - \mu\int_\Omega (S+I+R)\, d\Omega \\ &+ \gamma_1\int_\Omega \Delta S\, d\Omega + \gamma_2\int_\Omega \Delta I\, d\Omega + \gamma_4\int_\Omega \Delta R\, d\Omega. \end{aligned} \tag{3}$$

In view of the boundary conditions (2), the divergence theorem leads to

$$\int_\Omega \Delta\varphi\, d\Omega = \int_\Omega \nabla\cdot\nabla\varphi\, d\Omega = \int_{\partial\Omega} \nabla\varphi\cdot\mathbf{n}\, d\Sigma = 0, \quad \forall\varphi\in\{S, I, R\}$$

and hence (3) becomes

$$\frac{d}{dt}N(t) + \mu N(t) = \mu N_0. \tag{4}$$

Integrating (4), one easily obtains

$$N(t) = N_0, \qquad \forall t \geq 0, \tag{5}$$

i.e. the total population size in Ω is constant for all time.

Remark 1 We remark that, in view of (5), it turns out that $\forall\varphi\in\{S, I, R\}$

$$\int_\Omega \varphi(\mathbf{x},t)\, d\Omega \leq N_0|\Omega|.$$

Hence $\varphi(\mathbf{x},t)$ is bounded by N_0 a.e. in Ω, i.e.

$$\|\varphi\|_\infty \leq N_0, \qquad \forall\varphi\in\{S, I, R\}. \tag{6}$$

In the sequel we shall assume that:

(i) $\Omega\subset\mathbb{R}^3$ is a smooth domain having the internal cone property;
(ii) $\varphi\in W^{1,2}(\Omega)\cap W^{1,2}(\partial\Omega)$, $\forall\varphi\in\{S, I, R, B\}$, where $W^{1,2}(A)$ is the Sobolev space $H^1(A) = \{f\in L^2(A)/Df\in L^2(A)\}$.

3 Biologically meaningful equilibria

A fundamental role in disease-diffusion is played by the *basic reproduction number*, denoted usually as R_0, which is linked to the ability of disease to invade a population and it is defined as "the expected number of secondary cases produced by a typical infected individual during its entire period of infectiousness in a completely susceptible

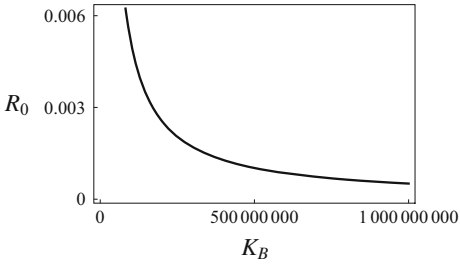

Fig. 1 Reproduction number in the case $N_0 = 10{,}000,\ \beta = 1,\ e = 10,\ \sigma = 0.2,\ \mu = 0.0001,\ \mu_B - \pi_B = 0.33$

population" (Diekmann et al. 1990). The basic reproduction number, for model (1), has been estimated by Codeco (2001), Tian and Wang (2011) in the case of $S,\ I,\ R,\ B$ depending only on time. It is given by

$$R_0 = \frac{N_0 \beta e}{K_B(\mu_B - \pi_B)(\sigma + \mu)}. \tag{7}$$

Hence, as one is expected, R_0 grows up with β and e, i.e. with the contact rate with contaminated water and contamination of aquatic environment of each infected person. R_0 behaviour with respect to K_B is showed in Fig. 1.

The biologically meaningful equilibria of (1) are the non-negative solutions $(\bar{S},\ \bar{I},\ \bar{B},\ \bar{R})$ of the system

$$\begin{cases} \mu(N_0 - S) - \beta \dfrac{BS}{K_B + B} = 0, \\ \beta \dfrac{BS}{K_B + B} - (\sigma + \mu) I = 0, \\ eI - (\mu_B - \pi_B) B = 0, \\ \sigma I - \mu R = 0. \end{cases} \tag{8}$$

It is easy to remark that (8):

(i) always admits the *disease-free equilibrium* $(S_1, I_1, B_1, R_1) = (N_0, 0, 0, 0)$ which—from biological point of view—means that all individuals are susceptibles and no infection arises;
(ii) if and only if $R_0 > 1$, admits a unique *endemic equilibrium* (i.e. a solution with positive components)

$$\begin{cases} S_2 = \dfrac{K_B(\sigma + \mu)(\mu_B - \pi_B)(\beta + \mu R_0)}{\beta e(\beta + \mu)}, \\ I_2 = \dfrac{\mu K_B(\mu_B - \pi_B)}{e(\beta + \mu)}(R_0 - 1), \\ B_2 = \dfrac{\mu K_B}{\beta + \mu}(R_0 - 1), \\ R_2 = \dfrac{\sigma K_B(\mu_B - \pi_B)}{e(\beta + \mu)}(R_0 - 1). \end{cases} \tag{9}$$

Let us denote by $T > 0$ an arbitrary fixed time and by $\Omega_T = \Omega \times (0, T]$ the parabolic cylinder, Ω_T being the parabolic interior of $\bar{\Omega} \times [0, T]$ (i.e. Ω_T includes the top $\Omega \times \{t = T\}$). Therefore, the parabolic boundary of Ω_T, $\Gamma_T = \bar{\Omega}_T - \Omega_T$, includes the bottom and vertical sides of $\Omega \times [0, T]$, but not the top. The following theorem holds.

Theorem 1 *Let $B \in C_1^2(\Omega_T) \cap C(\bar{\Omega}_T)$. Then B is bounded according to*

$$B \leq M = \max \left\{ \frac{eN_0}{\mu_B - \pi_B}, \max_{\bar{\Omega}} B(\mathbf{x}, 0), \bar{B} \right\}. \tag{10}$$

Proof The proof can be obtained by following the same procedure used by Capone (2008). For the sake of completeness, the proof of this theorem is given in the appendix.

4 Preliminaries to the stability of equilibria

Let be $(\bar{S}, \bar{I}, \bar{B}, \bar{R})$ a biologically meaningful equilibrium of (1). We recall that, if $R_0 < 1$, then the only admissible equilibrium is the disease-free while, if $R_0 > 1$, another equilibrium exists, the endemic one. On setting

$$X_1 = S - \bar{S}, \quad X_2 = I - \bar{I}, \quad X_3 = B - \bar{B}, \quad X_4 = R - \bar{R}, \tag{11}$$

model (1) becomes

$$\begin{cases} \frac{\partial X_1}{\partial t} = \mu(N_0 - X_1 - \bar{S}) + \gamma_1 \Delta X_1 - \beta f(X_1, X_3), \\ \frac{\partial X_2}{\partial t} = \beta f(X_1, X_3) - (\sigma + \mu)(X_2 + \bar{I}) + \gamma_2 \Delta X_2, \\ \frac{\partial X_3}{\partial t} = e(X_2 + \bar{I}) - (\mu_B - \pi_B)(X_3 + \bar{B}) + \gamma_3 \Delta X_3, \\ \frac{\partial X_4}{\partial t} = \sigma(X_2 + \bar{I}) - \mu(X_4 + \bar{R}) + \gamma_4 \Delta X_4, \end{cases} \tag{12}$$

where

$$f(X_1, X_3) = \frac{(X_1 + \bar{S})(X_3 + \bar{B})}{K_B + X_3 + \bar{B}},$$

under the boundary conditions

$$\nabla X_i \cdot \mathbf{n} = 0 \quad \text{on} \quad \partial\Omega \times \mathbb{R}^+ \qquad i = 1, 2, 3, 4. \tag{13}$$

Remark 2 Let us remark that, in order to preserve the uniqueness of the solution for the perturbation system (12) under the boundary conditions (13), it is necessary to require that

$$\int_\Omega X_1 \, d\Omega = \int_\Omega X_2 \, d\Omega = \int_\Omega X_3 \, d\Omega = \int_\Omega X_4 \, d\Omega = 0.$$

Denoting by $W^*(\Omega)$ the functional space defined by

$$W^*(\Omega) = \left\{ \varphi \in W^{1,2}(\Omega) \cap W^{1,2}(\partial\Omega) : \frac{d\varphi}{d\mathbf{n}} = 0 \text{ on } \partial\Omega \times \mathbb{R}^+, \int_\Omega \varphi \, d\Omega = 0 \right\},$$

our aim is to study the stability of $(\bar{S}, \bar{I}, \bar{B}, \bar{R})$ with respect to the perturbations $(X_1, X_2, X_3, X_4) \in [W^*(\Omega)]^3$.

Remark 3 We remark that the infimum

$$\bar{\alpha}(\Omega) = \inf_{\varphi \in W^*(\Omega)} \frac{\|\nabla\varphi\|^2}{\|\varphi\|^2} \tag{14}$$

exists and is a real positive number (Cantrell and Cosner 2003; Smoller 1967).

In view of the Mac–Laurin expansion

$$f(X_1, X_3) = \frac{\bar{S}\bar{B}}{K_B + \bar{B}} + \frac{\bar{B}}{K_B + \bar{B}} X_1 + \frac{K_B \bar{S}}{(K_B + \bar{B})^2} X_3 - F(X_1, X_3),$$

with

$$F(X_1, X_3) = \frac{K_B X_3}{(K_B + \theta_1 X_3 + \bar{B})^2} \left[\frac{(\theta_1 X_1 + \bar{S}) X_3}{(K_B + \theta_1 X_3 + \bar{B})} - X_1 \right],$$

$(0 < \theta_1 < 1)$. On adding and subtracting the term $\bar{\alpha}\gamma_i X_i$ to Eq. $(12)_i$, $(i = 1, 2, 3, 4)$ introducing the scalings μ_i $(i = 1, 2, 3, 4)$ (μ_i are positive constants to be chosen suitably later) and setting

$$\begin{cases} X_i = \mu_i U_i, \qquad \mathbf{U} = (U_1, U_2, U_3, U_4)^T, \\ \bar{F} = \beta F(\mu_1 U_1, \mu_3 U_3) = \dfrac{\beta K_B \mu_3 U_3}{(K_B + \theta_1 \mu_3 U_3 + \bar{B})^2} \left[\dfrac{(\theta_1 \mu_1 U_1 + \bar{S}) \mu_3 U_3}{K_B + \theta_1 \mu_3 U_3 + \bar{B}} - \mu_1 U_1 \right] \\ \tilde{F}_1 = \frac{1}{\mu_1} \bar{F} + \gamma_1 (\Delta U_1 + \bar{\alpha} U_1), \ \ \tilde{F}_2 = -\frac{1}{\mu_2} \bar{F} + \gamma_2 (\Delta U_2 + \bar{\alpha} U_2), \\ \tilde{F}_3 = \gamma_3 (\Delta U_3 + \bar{\alpha} U_3), \ \ \tilde{F}_4 = \gamma_4 (\Delta U_4 + \bar{\alpha} U_4), \ \ \tilde{\mathbf{F}} = (\tilde{F}_1, \tilde{F}_2, \tilde{F}_3, \tilde{F}_4)^T, \end{cases} \tag{15}$$

(12) reduces to

$$\frac{\partial \mathbf{U}}{\partial t} = \tilde{L}\mathbf{U} + \tilde{\mathbf{F}}, \tag{16}$$

where $\tilde{L}$ is the Jacobian matrix

$$\tilde{L} = \begin{pmatrix} b_{11} & 0 & b_{13} & 0 \\ b_{21} & b_{22} & b_{23} & 0 \\ 0 & b_{32} & b_{33} & 0 \\ 0 & b_{42} & 0 & b_{44} \end{pmatrix}$$

with

$$\begin{cases} b_{11} = -\left(\mu + \frac{\beta \bar{B}}{K_B + \bar{B}} + \bar{\alpha}\gamma_1\right) (<0),\ b_{13} = -\frac{\mu_3 \beta K_B \bar{S}}{\mu_1 (K_B + \bar{B})^2} (<0), \\ b_{21} = \frac{\mu_1 \beta \bar{B}}{\mu_2 (K_B + \bar{B})} (\geq 0),\ b_{22} = -(\sigma + \mu + \bar{\alpha}\gamma_2)(<0), \\ b_{23} = \frac{\mu_3 \beta K_B \bar{S}}{\mu_2 (K_B + \bar{B})^2} (>0), \quad b_{32} = \frac{\mu_2}{\mu_3} e (>0), \\ b_{33} = -(\mu_B - \pi_B + \bar{\alpha}\gamma_3)(<0),\ b_{42} = \frac{\mu_2}{\mu_4}\sigma (>0),\ b_{44} = -\mu - \bar{\alpha}\gamma_4 (<0), \end{cases} \tag{17}$$

The boundary conditions (13) become

$$\nabla U_i \cdot \mathbf{n} = 0, \quad \text{on} \quad \partial\Omega \times \mathbb{R}^+, \quad i = 1, 2, 3, 4. \tag{18}$$

Hence the problem to find conditions guaranteeing the stability of $(\bar{S},\ \bar{I},\ \bar{B},\ \bar{R})$ is reduced to determine conditions guaranteeing the stability of the null solution of (16)–(18).

5 Linear stability analysis of biologically meaningful equilibria

The null solution of (16) is linearly stable if and only if all the eigenvalues of $\tilde{L}$ have negative real parts. The characteristic equation of $\tilde{L}$ is given by

$$(b_{44} - \lambda)(\lambda^3 - \mathtt{I}_1\lambda^2 + \mathtt{I}_2\lambda - \mathtt{I}_3) = 0, \tag{19}$$

where $\mathtt{I}_i,\ (i = 1, 2, 3)$ are the principal invariants of the matrix

$$\tilde{L}_1 = \begin{pmatrix} b_{11} & 0 & b_{13} \\ b_{21} & b_{22} & b_{23} \\ 0 & b_{32} & b_{33} \end{pmatrix}$$

and are given by

$$\begin{cases} \mathtt{I}_1 = \text{trace}\tilde{L}_1 = b_{11} + b_{22} + b_{33} = \lambda_1 + \lambda_2 + \lambda_3, \\ \mathtt{I}_2 = \begin{vmatrix} b_{11} & 0 \\ b_{21} & b_{22} \end{vmatrix} + \begin{vmatrix} b_{11} & b_{13} \\ 0 & b_{33} \end{vmatrix} + \begin{vmatrix} b_{22} & b_{23} \\ b_{32} & b_{33} \end{vmatrix} \\ \quad = b_{11}(b_{22} + b_{33}) + b_{22}b_{33} - b_{23}b_{32} = \lambda_1(\lambda_2 + \lambda_3) + \lambda_2\lambda_3, \\ \mathtt{I}_3 = \det\tilde{L}_1 = b_{11}(b_{22}b_{33} - b_{23}b_{32}) + b_{13}b_{21}b_{32} = \lambda_1\lambda_2\lambda_3. \end{cases}$$

Accounting for (19), the eigenvalues of $\tilde{L}$ are given by $\lambda_i,\ (i = 1, 2, 3)$ and

$$\lambda_4 = b_{44},$$

where, in view of $(17)_9$, $\lambda_4 = b_{44} < 0$. Passing now to the equation

$$\lambda^3 - \mathtt{I}_1\lambda^2 + \mathtt{I}_2\lambda - \mathtt{I}_3 = 0, \tag{20}$$

as it is well known, the necessary and sufficient conditions guaranteeing that all the roots of (20) have negative real part, are the Routh–Hurwitz conditions (Merkin 1997):

$$\mathtt{I}_1 < 0, \quad \mathtt{I}_3 < 0, \quad \mathtt{I}_1\mathtt{I}_2 - \mathtt{I}_3 < 0. \tag{21}$$

Obviously (21) require necessarily that $\mathtt{I}_2 > 0$. If one of (21) is reversed, then there exists at least one eigenvalue of $\tilde{L}$ with positive real part and hence the null solution of (16) is linearly unstable. Denoting by $\mathtt{I}^*$, A^* the principal invariants of the matrix $\begin{pmatrix} b_{22} & b_{23} \\ b_{32} & b_{33} \end{pmatrix}$, i.e.

$$\mathtt{I}^* = b_{22} + b_{33}, \quad A^* = b_{22}b_{33} - b_{23}b_{32},$$

it follows that

$$\begin{cases} \mathtt{I}_1 = b_{11} + \mathtt{I}^*, \quad \mathtt{I}_2 = b_{11}\mathtt{I}^* + A^*, \ \mathtt{I}_3 = b_{11}A^* + b_{13}b_{21}b_{32}, \\ \mathtt{I}_1\mathtt{I}_2 - \mathtt{I}_3 = (b_{11} + \mathtt{I}^*)b_{11}\mathtt{I}^* + A^*\mathtt{I}^* - b_{13}b_{21}b_{32}. \end{cases} \tag{22}$$

On setting

$$A_1^* = -\frac{b_{13}b_{21}b_{32}}{b_{11}} \ (\leq 0), \qquad A_2^* = \frac{b_{13}b_{21}b_{32} - b_{11}\mathtt{I}^*(b_{11} + \mathtt{I}^*)}{\mathtt{I}^*}, \tag{23}$$

the following lemma holds.

Lemma 1 *The Routh–Hurwitz conditions are verified if and only if*

$$A^* > \max\left\{A_1^*, A_2^*\right\}. \tag{24}$$

Proof In view of (22), (21) are equivalent to

$$\begin{cases} b_{11} + \mathtt{I}^* < 0, \quad b_{11}A^* + b_{13}b_{21}b_{32} < 0, \\ (b_{11} + \mathtt{I}^*)b_{11}\mathtt{I}^* + A^*\mathtt{I}^* - b_{13}b_{21}b_{32} < 0. \end{cases} \tag{25}$$

From (17), since $I^* < 0$, it easily follows that $(25)_1$ is always satisfied while $(25)_2$–$(25)_3$ are verified if and only if (24) holds.

On setting

$$R_0^* = 1 + \frac{\bar{\alpha}[\gamma_2(\mu_B - \pi_B) + \gamma_3(\sigma + \mu) + \bar{\alpha}\gamma_2\gamma_3]}{(\sigma + \mu)(\mu_B - \pi_B)}, \tag{26}$$

from Lemma 1, the following two theorems hold. □

Theorem 2 *The disease-free equilibrium is linearly stable if and only if*

$$R_0 < R_0^*. \tag{27}$$

Proof The proof is performed in the appendix.

Theorem 3 *When the endemic equilibrium exists, it is always linearly stable.*

Proof The proof is performed in the appendix.

6 Nonlinear stability analysis of biologically meaningful equilibria

In epidemic disease models, the nonlinear analysis of the biologically meaningful equilibria has to be investigated in order to take into account of the contribution of nonlinear terms. Many papers find that the conditions ensuring the linear stability of equilibria are only sufficient to guarantee the nonlinear stability. Hence, the problem to find if there exists coincidence between linear and nonlinear stability thresholds, arises. In this section we will prove that, for the biologically meaningful equilibria of (1), there is coincidence between linear and nonlinear stability thresholds. To this end, let us introduce the Rionero–Lyapunov functional (see Rionero 2011a, b for more details)

$$W = W_1 + W_2, \tag{28}$$

with

$$W_1 = \frac{1}{2}\|U_1\|^2 + V, \qquad W_2 = \frac{1}{2}\|U_4\|^2 \tag{29}$$

and

$$V = \frac{1}{2}\left[A^*(\|U_2\|^2 + \|U_3\|^2) + \|b_{22}U_3 - b_{32}U_2\|^2 + \|b_{23}U_3 - b_{33}U_2\|^2\right]. \tag{30}$$

Remark 4 Let us remark that if $(\bar{S}, \bar{I}, \bar{B}, \bar{R}) = (S_2, I_2, B_2, R_2)$ then $A^* > 0$ and V, W are positive definite. If $(\bar{S}, \bar{I}, \bar{B}, \bar{R}) = (N_0, 0, 0, 0)$ then (27) is equivalent to require that $A^* > 0$ and hence to guarantee that V and W are positive definite.

The time derivative of W_1 along the solutions of (16) is

$$\dot{W}_1 = b_{11}\|U_1\|^2 + I^*A^*(\|U_2\|^2 + \|U_3\|^2) + \Phi^* + \Phi, \tag{31}$$

where

$$\begin{cases} A_1 = A^* + b_{32}^2 + b_{33}^2, \;\; A_2 = A^* + b_{22}^2 + b_{23}^2, \;\; A_3 = b_{22}b_{32} + b_{23}b_{33}, \\ \Phi^* = A_1 b_{21}\langle U_1, U_2\rangle + (-A_3 b_{21} + b_{13})\,\langle U_1, U_3\rangle, \\ \Phi = \gamma_1\langle U_1, \Delta U_1 + \bar{\alpha}U_1\rangle + \Phi_1 + \Phi_2, \\ \Phi_1 = \langle A_1U_2 - A_3U_3, \gamma_2(\Delta U_2 + \bar{\alpha}U_2)\rangle + \langle A_2U_3 - A_3U_2, \gamma_3(\Delta U_3 + \bar{\alpha}U_3)\rangle \\ \Phi_2 = \frac{1}{\mu_1}\langle U_1, \bar{F}\rangle + \frac{1}{\mu_2}\langle A_1U_2, \bar{F}\rangle - \frac{1}{\mu_2}\langle A_3U_3, \bar{F}\rangle \end{cases} \tag{32}$$

and $\bar{F}$ given by $(15)_3$. On setting

$$\begin{cases} c_1 = \dfrac{\beta N_0}{K_B^2}, \ c_2 = \dfrac{\beta}{K_B}, \ c_3 = \dfrac{A_1 \beta N_0}{K_B^2}, \\ c_4 = \dfrac{A_1 \beta}{K_B}, \ c_5 = \dfrac{|A_3| \beta N_0}{K_B^2}, \ c_6 = \frac{|A_3| \beta}{K_B} \end{cases}$$

and

$$\bar{c} = \max \left\{ \frac{c_1 M}{\mu_1}, \frac{c_2 N_0}{\mu_1}, \frac{c_3 M}{\mu_2}, \frac{c_4 N_0}{\mu_2}, \frac{2c_5 M}{\mu_2}, \frac{2c_6 N_0}{\mu_2} \right\},$$

where M is given by (10), the following lemma holds.

Lemma 2 *Let the conditions ensuring the linear stability of the equilibria hold. Then:*

(i)

$$\Phi_1 \leq 0; \tag{33}$$

(ii)

$$\Phi^* \leq \frac{1}{2} \left[|b_{11}| \|U_1\|^2 + |I^* A^*| (\|U_2\|^2 + \|U_3\|^2) \right]; \tag{34}$$

(iii)

$$\Phi_2 < \mu_3 \bar{c} (\|U_1\|^2 + \|U_2\|^2 + \|U_3\|^2). \tag{35}$$

Proof The proof is performed in the appendix.

Remark 5 We remark that, denoting by

$$p = \frac{A^*}{2}, \quad q = \frac{A^*}{2} + b_{22}^2 + b_{23}^2 + b_{32}^2 + b_{33}^2, \tag{36}$$

it follows that

$$p(\|U_2\|^2 + \|U_3\|^2) \leq V \leq q(\|U_2\|^2 + \|U_3\|^2). \tag{37}$$

The following lemmas hold.

Lemma 3 *Let the conditions ensuring the linear stability hold, then*

$$\dot{W}_1 < -h W_1, \qquad h = const. \tag{38}$$

Proof By virtue of (14), (32)–(33), (35), one has that

$$\Phi \leq \Phi_2 < \mu_3 \bar{c}(\|U_1\|^2 + \|U_2\|^2 + \|U_3\|^2).$$

Hence, from (31), in view of (34), it follows that

$$\begin{aligned}\dot{W}_1 < &-\tfrac{1}{2}\left[|b_{11}|\|U_1\|^2 + |I^*A^*|(\|U_2\|^2 + \|U_3\|^2)\right] \\ &+\mu_3\bar{c}(\|U_1\|^2 + \|U_2\|^2 + \|U_3\|^2).\end{aligned}$$

Moreover, by virtue of (37), it turns out that

$$\dot{W}_1 < -\frac{1}{2}\left[|b_{11}|\|U_1\|^2 + \frac{|I^*A^*|}{q}V\right] + \mu_3\bar{c}\left(\|U_1\|^2 + \frac{1}{p}V\right),$$

i.e.

$$\dot{W}_1 < -(\delta_1 - \mu_3\delta_2)W_1, \tag{39}$$

with

$$\delta_1 = \min\left(|b_{11}|, \frac{|I^*A^*|}{2q}\right), \qquad \delta_2 = \bar{c}\left(2 + \frac{1}{p}\right) \tag{40}$$

and the thesis follows on setting $h = \delta_1 - \mu_3\delta_2$.

Lemma 4 *Let*

$$0 < \varepsilon < \frac{\mu_4}{\sigma\mu_3}(\mu + \gamma_4\bar{\alpha}), \qquad k = 2\left(\mu + \gamma_4\bar{\alpha} - \sigma\varepsilon\frac{\mu_3}{\mu_4}\right) > 0, \tag{41}$$

then

$$\dot{W}_2 \leq -kW_2 + \sigma\frac{\mu_3}{\varepsilon\mu_4}\|U_3\|^2. \tag{42}$$

Proof Multiplying $(16)_4$ for U_4 and integrating over Ω, it follows that

$$\frac{1}{2}\frac{d}{dt}\|U_4\|^2 \leq \sigma\frac{\mu_3}{\mu_4}\int_\Omega U_3U_4\,d\Omega - \mu\|U_4\|^2 + \gamma_4\int_\Omega U_4\Delta U_4\,d\Omega. \tag{43}$$

On applying the divergence theorem, Holder and Cauchy inequalities, by virtue of (14) and $(18)_4$, it turns out that

$$\frac{1}{2}\frac{d}{dt}\|U_4\|^2 \leq \left(-\mu - \gamma_4\bar{\alpha} + \sigma\varepsilon\frac{\mu_3}{\mu_4}\right)\|U_4\|^2 + \sigma\frac{\mu_3}{\varepsilon\mu_4}\|U_3\|^2, \ \varepsilon = \text{ const} > 0. \tag{44}$$

Hence, by virtue of (41), (42) immediately follows.

The following theorem holds.

Theorem 4 *The biologically meaningful equilibria of* (1) *are nonlinearly, asymptotically stable with respect to the $W-$norm if and only if they are linearly stable.*

Proof Necessity follows by remarking that, if one of the Routh–Hurwitz conditions is reversed, then there is linear instability. Passing to prove sufficiency, since, by virtue of (37)

$$\|U_3\|^2 \leq \|U_2\|^2 + \|U_3\|^2 \leq \frac{V}{p},$$

from (42) one obtains that

$$\dot{W}_2 \leq -kW_2 + \frac{m}{\mu_4} W_1, \qquad m = \frac{\sigma \mu_3}{\varepsilon p}.$$

From (28), in view of (39), if

$$\mu_3 < \frac{\delta_1}{\delta_2}, \tag{45}$$

it follows that

$$\dot{W} \leq -\left(h - \frac{m}{\mu_4}\right) W_1 - kW_2, \quad \text{with } h = \delta_1 - \mu_3 \delta_2 = \text{const} > 0. \tag{46}$$

On choosing

$$\mu_4 > \frac{m}{h},$$

from (46) one obtains

$$\dot{W} \leq -\delta W, \qquad \delta = \min\left\{h - \frac{m}{\mu_4}, k\right\} = \text{const.} > 0. \tag{47}$$

Remark 6 From Theorem 4 it follows that:

(1) when $R_0 < 1$ the disease-free equilibrium is linearly and nonlinearly, asymptotically stable;
(2) when $1 < R_0 < R_0^*$ both the disease-free and the endemic equilibria are linearly and nonlinearly stable;
(3) when $R_0 > R_0^*$ the disease-free equilibrium is unstable while the endemic equilibrium is nonlinearly, asymptotically stable.

Remark 7 We remark that:

(i) in the absence of diffusion, $R_0 = R_0^* = 1$ is a bifurcation parameter for the disease-free equilibrium. In this case, when R_0 is slightly greater than 1, then the disease-free equilibrium loses its stability and a globally stable endemic equilibrium (not existing for $R_0 < 1$) arises;

(ii) in presence of diffusion, $R_0 = R_0^*$ is a bifurcation parameter for the disease-free equilibrium. When $1 < R_0 < R_0^*$ there is coexistence of disease-free and endemic equilibria which are both stable. In a neighborhood of R_0^* the following scenario is verified:
   – for $R_0 < R_0^*$, a stable disease-free equilibrium coexists with a stable endemic equilibrium (bistability);
   – for $R_0 > R_0^*$, the disease-free equilibrium becomes unstable while the endemic equilibrium remains stable.

Bistability analysis in disease-models has been widely studied in literature (see, for example, Buonomo and Lacitignola (2008), Dushoff et al. (1998), Wang (2006) and the references therein). When bistability occurs, the disease-free and the endemic equilibrium are both stable at the same time. From a biological point of view, this means that it is not sufficient to reduce R_0 below R_0^* in order to eradicate the disease. In fact, it is necessary to reduce R_0 below 1 in order to eliminate the endemic equilibrium.

7 A numerical application to Cholera in Haiti

Cholera outbreak in Haiti has been ongoing since October 2010, 10 months after a powerful earthquake which devastated the nation's capital and southern towns. It caused 8531 deaths at January, 4, 2014 and 696922 cumulative cholera cases (data source available at "PAHO's Interactive Report of Cholera Outbreak http://new.paho.org/hq/images/atlas_ihr/cholerahispaniola/atlas.html"). Cases continue to be reported but in smaller numbers than earlier in the outbreak. In Fig. 2, the new cholera cases in the first 72 weeks are showed.

Figure 2 shows that cholera epidemics in Haiti reached its peak after 9 weeks, when the number of new infected people was 26,249. After the initial outbreak, epidemic reached other two peaks: the first one after 34 weeks (number of new cholera cases $\simeq$14,898); the second one after 51 weeks (number of new cholera cases $\simeq$6,563). Then, the epidemic decays to the endemic equilibrium.

In this section, we want to furnish numerical simulations of the obtained results applied to Haiti Cholera outbreak during the period October 10, 2010–March 3, 2012. For the sake of simplicity, we refer to a uni-dimensional domain $x \in [0, 1]$. The values of N_0, μ, σ, have been evaluated on taking into account of recorded data during the epidemic. The estimation of e, μ_B, π_B is given by Codeco (2001), while

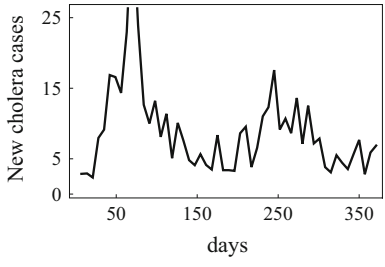

Fig. 2 New cholera cases ($\times 10^3$) in the period October 10, 2010–March 3, 2012

Table 2 Estimated parameters during cholera outbreak in Ouest Department in Haiti (October 10, 2010–March 3, 2012)

Symbol	Value
N_0	3,700 (person)
μ	0.014 (day^{-1})
σ	1.0678 (day^{-1})
e	10 (cell/ml day^{-1} person^{-1})
K_B	10^5 (cells/ml)
μ_B	1.06 day^{-1}
π_B	0.73 day^{-1}

K_B is evaluated by Codeco (2001), Sanches et al. (2011). These parameters have been reported in Table 2.

When cholera invades a population, control strategies are inclined to reduce the contact rate with contaminated water (β) by distributing, for example, pure water bottles and by improving personal hygiene state. In the following simulations, we analyze three possible cases: $\beta = 0.8$, $\beta = 1$, $\beta = 1.2$.

(1) $\beta = 0.8$. In this case $R_0 \simeq 0.827463$. Since $R_0 < 1$ there exists only the disease-free equilibrium $E_0 = (3{,}700, 0, 0, 0)$. In order to show, numerically, the stability of E_0, let us associate to (1) the initial conditions

$$
\begin{aligned}
S(\mathbf{x}, 0) &= \begin{cases} 3{,}200\pi \cos(\pi x) & \text{if } 0 \le x \le 1/2 \\ 0 & \text{otherwise} \end{cases} \\
I(\mathbf{x}, 0) &= \begin{cases} 100\pi \cos(\pi x) & \text{if } 0 \le x \le 1/2 \\ 0 & \text{otherwise} \end{cases} \\
B(\mathbf{x}, 0) &= \begin{cases} 10\pi \cos(\pi x) & \text{if } 0 \le x \le 1/2 \\ 0 & \text{otherwise} \end{cases} \\
R(\mathbf{x}, 0) &= \begin{cases} 400\pi \cos(\pi x) & \text{if } 0 \le x \le 1/2 \\ 0 & \text{otherwise} \end{cases}
\end{aligned} \tag{48}
$$

Figure 3 shows trajectories when

$$\gamma_1 = 0.8, \quad \gamma_2 = 0.1, \quad \gamma_3 = 0.01, \quad \gamma_4 = 0.5. \tag{49}$$

(2) $\beta = 1$. In this case $R_0 \simeq 1.03433$. Since $R_0 > 1$, in addition to the disease-free equilibrium E_0, there exists also the endemic one given by $E_1 = (3{,}578.9,\ 1.56408,\ 47.3964,\ 119.54)$. In order to evaluate R_0^*, one has to determine the positive constants $\bar{\alpha}$, γ_i ($i = 1, 2, 3, 4$). The constant $\bar{\alpha}$ appearing in (14) depends on the domain Ω and it has been estimated by Payne and Weinberger (1960) to be

$$\bar{\alpha}(\Omega) \ge \frac{\pi^2}{D^2},$$

where D is the diameter of the convex domain Ω. Different values of R_0^* for different values of $\bar{\alpha}$, γ_2, γ_3, are collected in Table 3.

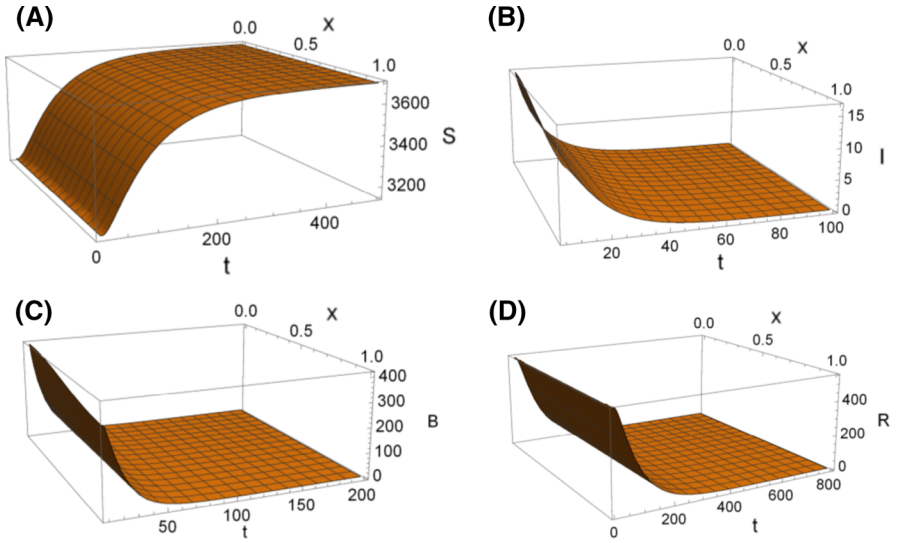

Fig. 3 S, I, B, R trajectories under the initial conditions (48) in the case (49)

Table 3 Stability thresholds R_0^* for different values of $\bar{\alpha}$, γ_2, γ_3

$\bar{\alpha}$	γ_2	γ_3	R_0^*
1	0.002	0.02	1.06256
π	0.2	0.02	1.88039
0.5	1.5	0.50	2.97361
1	0.5	1.5	8.10332
$\pi/2$	0.9	0.8	11.0784
$\pi/2$	1.2	1.8	26.2056

In the case $\Omega = [0, 1]$ one has that $\bar{\alpha} = \pi^2$ (cfr. Flavin and Rionero 1996). On assuming (49), $R_0^* \simeq 2.48186$ and hence $1 < R_0 < R_0^*$. Trajectories revert to one of the steady states depending on the initial data. Figure 4 shows trajectories when initial data are

$$
\begin{aligned}
S(\mathbf{x}, 0) &= \begin{cases} 0.8\cos(\pi x) & \text{if } 0 \le x \le 1/2 \\ 3{,}500 & \text{otherwise} \end{cases} \\
I(\mathbf{x}, 0) &= \begin{cases} 3{,}699.2 & \text{if } 0 \le x \le 1/2 \\ -0.1\cos(\pi x) & \text{otherwise} \end{cases} \\
B(\mathbf{x}, 0) &= \begin{cases} 0.01\cos(\pi x) & \text{if } 0 \le x \le 1/2 \\ 0 & \text{otherwise} \end{cases} \\
R(\mathbf{x}, 0) &= \begin{cases} 0.5\cos(\pi x) & \text{if } 0 \le x \le 1/2 \\ 198 & \text{otherwise} \end{cases}
\end{aligned} \tag{50}
$$

while Fig. 5 shows trajectories under initial data $S(x, 0) = 3{,}500$, $(48)_2$, $(48)_3$, $R(x, 0) = 100$. A bifurcation diagram is showed in Fig. 6.

(3) $\beta = 1.2$. In this case $R_0 \simeq 1.24119$. Assuming

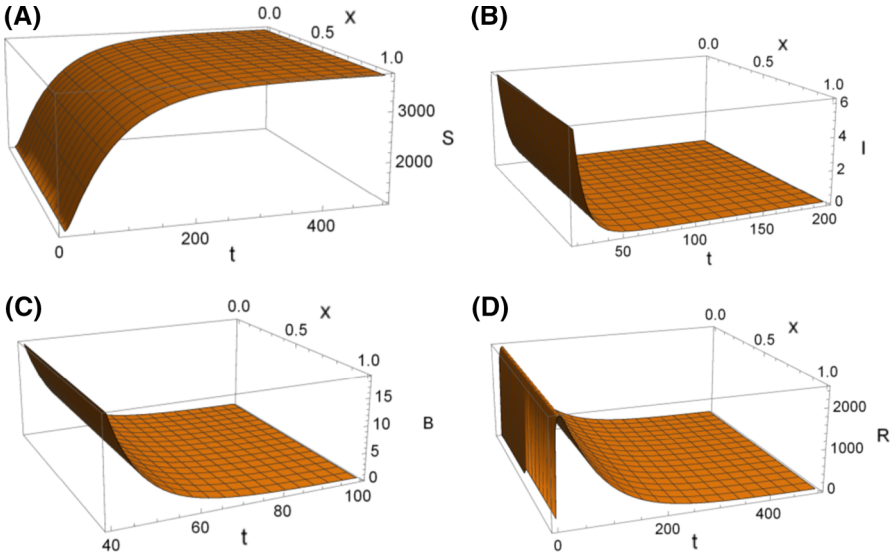

Fig. 4 S, I, B, R trajectories under the initial conditions (50) in the case (49)

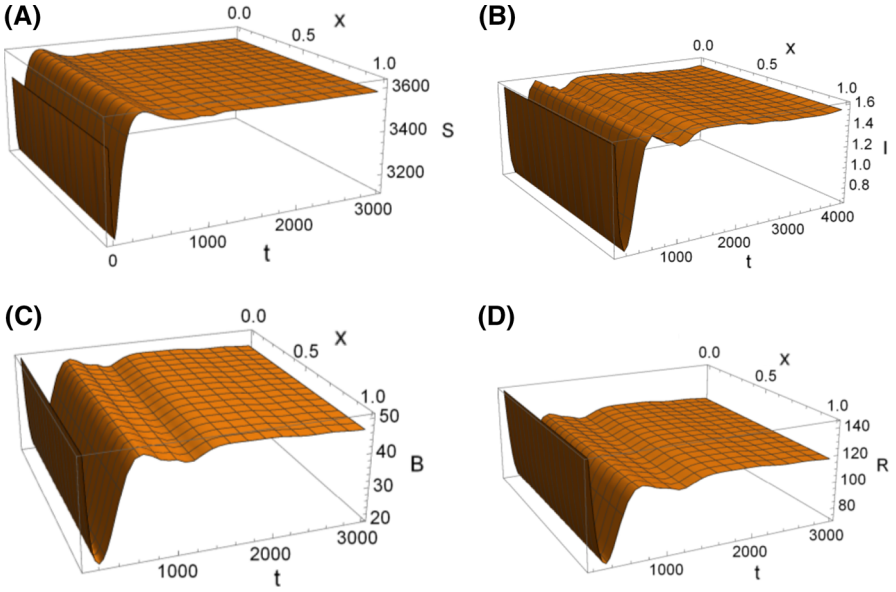

Fig. 5 S, I, B, R trajectories under the initial conditions $S(x,0) = 3{,}500$, $(48)_2$, $(48)_3$ $R(x,0) = 100$ in the case (49)

$$\gamma_1 = 0.8, \quad \gamma_2 = 0.003, \quad \gamma_3 = 0.002, \quad \gamma_4 = 0.5, \tag{51}$$

it follows that $R_0^* \simeq 1.08876$. Hence $R_0 > R_0^*$, E_0 is unstable while $E_1 = (2989.29,\ 9.17889,\ 278.148,\ 701.53)$ is stable (Fig. 7).

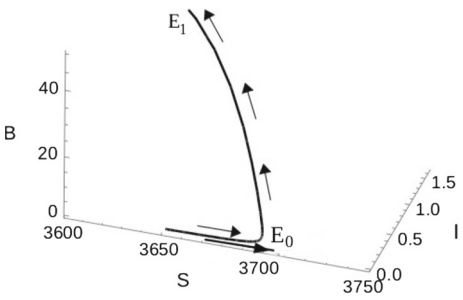

Fig. 6 Bifurcation diagram in the case (49)

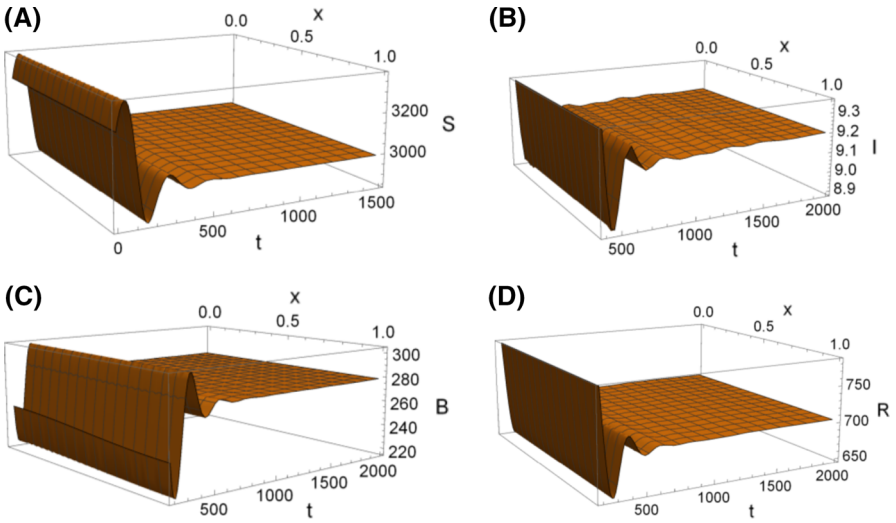

Fig. 7 S, I, B, R trajectories under the initial conditions (48) in the case (51)

8 Discussion

The paper deals with the longtime behaviour of the solutions of the reaction–diffusion system (1) modeling spread of cholera in a smooth three-dimensional domain. In particular

- the set of critical points and the (expected) existence of endemic equilibria have been investigated;
- the necessary and sufficient conditions guaranteeing the linear stability of the biologically meaningful equilibria have been obtained;
- via a peculiar Lyapunov function the coincidence between the linear and nonlinear asymptotic stability thresholds is shown.

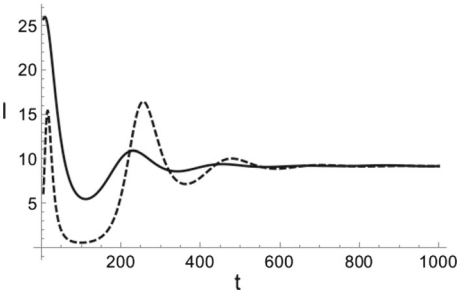

Fig. 8 *Dashed line* infected asymptotic behaviour at $x = 0.5$ with $\gamma_1 = 0.005$, $\gamma_2 = 0.0008$, $\gamma_3 = 0.0006$, $\gamma_4 = 0.0003$ under (48). *Continuous line* infected asymptotic behaviour at $x = 0.5$ in the case (49) under (48)

We remark that:

(i) in the absence of diffusion ($\gamma_i = 0$, $i = 1, 2, 3, 4$) the disease-free equilibrium is globally nonlinearly stable (Codeco 2001) if

$$R_0 < 1. \tag{52}$$

Comparing (27) with (52), it follows that the diffusion produces a stabilizing effect on the disease-free equilibrium. This means that, when diffusion is allowed in the model, cholera epidemic blows up later than in the absence of diffusion, as one is expected;

(ii) in presence of diffusion, the endemic equilibrium is always nonlinearly asymptotically stable when $R_0 > R_0^*$. This result holds in the absence of diffusion too (Tian and Wang 2011). Since the diffusion coefficients are present in δ in (47), we can conclude that the exponential decay of $\dot{W}$ is faster in presence of diffusion. This means that solutions of perturbed system tend more quickly to zero and, from a biological point of view, (S, I, R, B) reverts more quickly to the endemic equilibrium (Fig. 8).

Acknowledgments This paper has been performed under the auspices of the G.N.F.M. of I.N.d.A.M. The Referees' competence and comments are gratefully acknowledged.

Appendix

Proof of Theorem 1

Let us set $\max_{\bar{\Omega}_T} B = B(\mathbf{x}_1, t_1)$. We have to distinguish two cases.

(1) If $(\mathbf{x}_1, t_1)$ belongs to the interior of Ω_T, then $(1)_3$ and $\|I\|_\infty \leq N_0$ imply that

$$\left[\frac{\partial B}{\partial t} - eN_0 + (\mu_B - \pi_B)B - \gamma_3 \Delta B\right]_{(\mathbf{x}_1, t_1)} < 0. \tag{53}$$

Since

$$\left[\frac{\partial B}{\partial t}\right]_{(\mathbf{x}_1, t_1)} = 0, \qquad [\Delta B]_{(\mathbf{x}_1, t_1)} < 0,$$

then (53) can hold if and only if

$$-eN_0 + (\mu_B - \pi_B)B(\mathbf{x}_1, t_1) < 0$$

and hence if and only if $B(\mathbf{x}_1, t_1) < \frac{eN_0}{\mu_B - \pi_B}$.

(2) If $(\mathbf{x}_1, t_1) \in \Gamma_T$, in view of the regularity of the domain Ω, since Ω verifies in any point $\mathbf{x}_0 \in \partial\Omega$ the interior ball condition, there exists an open ball $B^* \subset \Omega$ with $\mathbf{x}_0 \in \partial B^*$. If $B(\mathbf{x}_1, t_1) > \frac{eN_0}{\mu_B - \pi_B}$, on choosing the radius of B^* sufficiently small, it follows that

$$\gamma_3 \Delta B - \frac{\partial B}{\partial t} > 0, \quad \text{in } B^*$$

and by virtue of Hopf's Lemma (Protter and Weinberger 1967), one obtains that

$$\left(\frac{dB}{d\mathbf{n}}\right)_{(\mathbf{x}_1, t_1)} > 0.$$

Since $\frac{dB}{d\mathbf{n}} = 0$ on $\partial\Omega \times \mathbb{R}^+$, (10) follows.

8.1 Proof of Theorem 2

Substituting $(\bar{S},\ \bar{I},\ \bar{B},\ \bar{R}) = (N_0, 0, 0, 0)$ in (17), one has that

$$\begin{cases} b_{11} = -(\mu + \bar{\alpha}\gamma_1), \quad b_{13} = -\frac{\mu_3 \beta N_0}{\mu_1 K_B}, \quad b_{21} = 0, \\ b_{22} = -(\sigma + \mu + \bar{\alpha}\gamma_2), \quad b_{23} = \frac{\mu_3 \beta N_0}{\mu_2 K_B}, \\ b_{32} = \frac{\mu_2}{\mu_3} e, \quad b_{33} = -(\mu_B - \pi_B + \bar{\alpha}\gamma_3). \end{cases} \tag{54}$$

Hence

$$\begin{aligned} A^* &= (\sigma + \mu + \bar{\alpha}\gamma_2)(\mu_B - \pi_B + \bar{\alpha}\gamma_3) - \frac{\beta N_0 e}{K_B} \\ &= (\sigma + \mu)(\mu_B - \pi_B)\left[1 - R_0 + \frac{\bar{\alpha}[\gamma_2(\mu_B - \pi_B) + \gamma_3(\sigma + \mu) + \bar{\alpha}\gamma_2\gamma_3]}{(\sigma + \mu)(\mu_B - \pi_B)}\right] \\ &= (\sigma + \mu)(\mu_B - \pi_B)(R_0^* - R_0) \end{aligned} \tag{55}$$

and

$$A_1^* = 0, \quad A_2^* = -b_{11}(b_{11} + \mathtt{I}^*) < 0. \tag{56}$$

In view of (56), it follows that

$$\max\{A_1^*, A_2^*\} = 0.$$

Hence (24) is verified if and only if

$$A^* > 0, \tag{57}$$

i.e., by virtue of (55), if and only if (27) holds.

8.2 Proof of Theorem 3

Substituting $(\bar{S},\ \bar{I},\ \bar{B},\ \bar{R}) = (S_2,\ I_2,\ B_2,\ R_2)$ in (17), one has that

$$\begin{cases} b_{11} = -\dfrac{\mu(\beta+\mu)R_0 + \bar{\alpha}\gamma_1(\beta+\mu R_0)}{\beta+\mu R_0}, \\ b_{13} = -\dfrac{\mu_3(\sigma+\mu)(\mu_B-\pi_B)(\beta+\mu)}{\mu_1 e(\beta+\mu R_0)}, \\ b_{21} = \dfrac{\mu_1\beta\mu(R_0-1)}{\mu_2(\beta+\mu R_0)}, \quad b_{22} = -(\sigma+\mu+\bar{\alpha}\gamma_2), \\ b_{23} = -\dfrac{\mu_1}{\mu_2}b_{13}, \quad b_{32} = \dfrac{\mu_2}{\mu_3}e, \quad b_{33} = -(\mu_B-\pi_B+\bar{\alpha}\gamma_3). \end{cases} \tag{58}$$

Hence

$$\begin{aligned} A^* &= (\sigma+\mu+\bar{\alpha}\gamma_2)(\mu_B-\pi_B+\bar{\alpha}\gamma_3) - \frac{(\sigma+\mu)(\mu_B-\pi_B)(\beta+\mu)}{\beta+\mu R_0} \\ &= \frac{\mu(\sigma+\mu)(\mu_B-\pi_B)(R_0-1)}{\beta+\mu R_0} + \bar{\alpha}\left[\gamma_2(\mu_B-\pi_B) + \gamma_3(\sigma+\mu) + \bar{\alpha}\gamma_2\gamma_3\right], \end{aligned} \tag{59}$$

and

$$\begin{cases} A_1^* = -\dfrac{\beta\mu(\beta+\mu)(\sigma+\mu)(\mu_B-\pi_B)(R_0-1)}{(\beta+\mu R_0)[\mu R_0(\beta+\mu)+\bar{\alpha}\gamma_1(\beta+\mu R_0)]}, \\ A_2^* = -\dfrac{K_1R_0^2 + K_2R_0 + K_3}{(\beta+\mu R_0)^2[\sigma+\mu+\mu_B-\pi_B+\bar{\alpha}(\gamma_2+\gamma_3)]} (<0), \end{cases} \tag{60}$$

where $K_i,\ (i=1,2,3)$ are positive constants given by

$$\begin{aligned} K_1 = \mu^2(\sigma+\mu+\mu_B-\pi_B+\bar{\alpha}(\gamma_2+\gamma_3))\,\{&\bar{\alpha}\gamma_1[\sigma+\mu+\mu_B-\pi_B \\ &+\bar{\alpha}(\gamma_1+\gamma_2+\gamma_3)] + (\beta+\mu)\,[\beta+\mu+\sigma+\mu+\mu_B-\pi_B \\ &+\ \bar{\alpha}(\gamma_1+\gamma_2+\gamma_3)+\bar{\alpha}\gamma_1]\}, \end{aligned}$$

$$\begin{aligned} K_2 = \beta\mu\,\{&\left[\sigma+\mu+\mu_B-\pi_B+\bar{\alpha}(\gamma_2+\gamma_3)\right]\left[\bar{\alpha}(\beta+\mu)(\gamma_1+\gamma_2+\gamma_3)\right. \\ &\left.+\bar{\alpha}\gamma_1(\beta+\mu)+2\bar{\alpha}\gamma_1(\sigma+\mu+\mu_B-\pi_B+\bar{\alpha}(\gamma_1+\gamma_2+\gamma_3))\right] \\ &+(\beta+\mu)(\mu_B-\pi_B)^2+(\beta+\mu)(\sigma+\mu+\mu_B-\pi_B)[\sigma+\mu+\bar{\alpha}(\gamma_2+\gamma_3)]\Big\} \end{aligned}$$

and

$$K_3 = \beta^2\bar{\alpha}\gamma_1[\sigma+\mu+\mu_B-\pi_B+\bar{\alpha}(\gamma_2+\gamma_3)][\sigma+\mu+\mu_B-\pi_B+\bar{\alpha}(\gamma_1+\gamma_2+\gamma_3)] \\ +\beta\mu(\mu_B-\pi_B)(\sigma+\mu)(\beta+\mu).$$

Since $(S_2,\ I_2,\ B_2,\ R_2)$ exists if and only if $R_0 > 1$, then, from (59) and $(60)_1$, it turns out that

$$A^* > 0, \quad A_1^* < 0. \tag{61}$$

In view of $(60)_2$ and (61), it follows that (24) is always satisfied.

8.3 Proof of Lemma 2

By virtue of Remark 4, the linear stability of the biologically meaningful equilibria guarantees that $A^* > 0$. Hence, the proof of (i) can be obtained on following the same procedure by Rionero (2011a, b), Capone et al. (2013, 2014). As concerns (ii), for the disease-free equilibrium, since $b_{21} = 0$, one has that

$$\Phi^* = b_{13}\langle U_1, U_3\rangle \le \frac{\mu_3^3\beta^2N_0^2}{2\mu_1^2K_B^2|I^*A^*|}\|U_1\|^2 + \frac{1}{2}|I^*A^*|(\|U_2\|^2+\|U_3\|^2).$$

On choosing

$$\frac{\mu_3^2}{\mu_1^2} = \frac{|b_{11}I^*A^*|K_B^2}{\beta^2N_0^2}, \tag{62}$$

(ii) is obtained. For the endemic equilibrium, since $b_{21} > 0$ and $b_{13} < 0$, on choosing

$$\frac{\mu_1^2}{\mu_2\mu_3} = -\frac{(\sigma+\mu)(\mu_B-\pi_B)(\beta+\mu)}{A_3e\beta\mu(R_0-1)} > 0, \tag{63}$$

it follows that $b_{13} - A_3b_{21} = 0$ and

$$\Phi^* = \frac{\mu_1\beta\mu(R_0-1)A_1}{\mu_2(\beta+\mu R_0)}\langle U_1, U_2\rangle \le \frac{\mu_1^2\beta^2\mu^2(R_0-1)^2A_1^2}{2|I^*A^*|\mu_2^2(\beta+\mu R_0)^2}\|U_1\|^2 + \frac{1}{2}|I^*A^*|\|U_2\|^2.$$

Hence, on taking

$$\frac{\mu_1^2}{\mu_2^2} = \frac{|b_{11}I^*A^*|(\beta+\mu R_0)^2}{\beta^2\mu^2(R_0-1)^2A_1^2}, \tag{64}$$

(34) is proved.

As concerns (iii), by virtue of (6), (11), $(15)_1$, the following inequalities hold a.e. in Ω

$$\theta_1\mu_1 U_1 + \bar{S} = \theta_1 X_1 + \bar{S} = \theta_1(S - \bar{S}) + \bar{S} = \theta_1 S + (1-\theta_1)\bar{S} \leq N_0$$

and

$$K_B + \theta_1\mu_3 U_3 + \bar{B} = K_B + \theta_1 B + (1-\theta_1)\bar{B} > K_B.$$

Hence, from $(32)_7$, it turns out that

$$\begin{aligned}\Phi_2 \; < \mu_3 \Bigg[& c_1 \frac{\mu_3}{\mu_1} \int_\Omega |U_1| U_3^2 \, d\Omega + c_2 \int_\Omega U_1^2 |U_3| \, d\Omega \\ & + c_3 \frac{\mu_3}{\mu_2} \int_\Omega |U_2| U_3^2 \, d\Omega + c_4 \frac{\mu_1}{\mu_2} \int_\Omega |U_1 U_2 U_3| \, d\Omega \\ & + c_5 \frac{\mu_3}{\mu_2} \int_\Omega |U_3|^3 \, d\Omega + c_6 \frac{\mu_1}{\mu_2} \int_\Omega |U_1| U_3^2 \, d\Omega \Bigg].\end{aligned}$$

From (6), (10) and $(15)_1$ one obtains

$$\|U_i\|_\infty = \frac{1}{\mu_i}\|X_i\|_\infty \leq \frac{2N_0}{\mu_i}, \quad i = 1, 2$$

and

$$\|U_3\|_\infty = \frac{1}{\mu_3}\|X_3\|_\infty = \frac{1}{\mu_3}\|B - \bar{B}\|_\infty \leq \frac{2M}{\mu_3}.$$

Hence

$$\begin{aligned}\Phi_2 < \mu_3 \Bigg[& \frac{2c_1 M}{\mu_1} \int_\Omega |U_1||U_3| d\Omega + \frac{2c_2 N_0}{\mu_1} \int_\Omega |U_1||U_3| d\Omega + \frac{2c_3 M}{\mu_2} \int_\Omega |U_2||U_3| d\Omega \\ & + \frac{2c_4 N_0}{\mu_2} \int_\Omega |U_2||U_3| d\Omega + \frac{2c_5 M}{\mu_2} \int_\Omega U_3^2 d\Omega + \frac{2c_6 N_0}{\mu_2} \int_\Omega U_3^2 d\Omega \Bigg].\end{aligned}$$

On applying the Cauchy–Schwarz, (35) is obtained.

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