An effective management strategy for the control of two lentiviruses in goat breedings

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Abstract

Caprine Arthritis Encephalitis is an endemic disease in goat breedings, caused by viral strains belonging to the Small Ruminant Lentivirus group and characterized by a progressive chronic course. Its clinical signs are not immediately recognizable and can only be detected via costly serological tests. No vaccine is available. Two main strategies for fighting it are in common use. The "test-and-slaughter" approach, that selects infected goats and directly slaughters them, is expensive, time consuming and often leads to endemic low level persistence of the infection. Alternatively, newborns are removed from their mothers to be raised by healthy goats. After weaning they would rejoin their breeds, but then they could still be subject to horizontal conta-

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Highlights

- two competing genotypes of SRLV in goat breeding
- a mathematical model encapsulating the main epidemiological dynamics of an infected breeding
- deriving the replacement rate of the farm as a function of the epidemiological parameters
- stability conditions for equilibria investigated to design effective sanitary measures

gion. In this study a mathematical model that considers the cocirculation of two different SRLV viral genotypes (B and E) is devised and analyzed, based on the key assumption of perfect cross-protection between the two genotypes' infections. Two strategic measures arise from its analysis, that are strongly recommended and whose implementation is encouraged: in the presence of both genotypes, the farmer should not isolate the newborns from their mothers but rather raise them with all the other animals. In the case of genotype-B-only affected farm, serological testing and mother-offspring separation should still be considered the best strategy for CAEV control. These strategies completely reverse the current removal policy and, in due conditions, would lead to disease eradication. These represent very reasonable and cheap measures for the eventual control of the epidemics.

Keywords: Mathematical Model, Caprine Arthritis Encephalitis, Control Strategy

1. Introduction

Small Ruminant Lentivirus (SRLV) represents a very heterogeneous group of RNA viruses, under both genetic and antigenic point of view.

Infected sheep can show dyspnea or neurological signs, which are both eventually fatal. Adult goats generally develop chronic progressive arthri-

tis, while encephalomyelitis is seen in kids. Mastitis and udder deformation occur in both species. Additional economic losses may occur due to marketing and export restrictions, premature culling and/or poor milk production. Economic losses can vary considerably between flocks.

Historically, viral species specific classification was used. Caprine Arthritis Encephalitis Virus (CAEV) and Visna Maedi Virus (VMV) were identified in goats and sheep respectively. Thanks to the molecular biology approach, genome analyses revealed a more complex behavior. To date, four different SRLV genotypes are defined (Shah et al., 2004a): genotype A includes all the VMV-like strains, and genotype B includes all the CAEV-like strains. In both cases, each genotype is able to infect both goats and sheep (Reina et al., 2010). Genotypes C and E seem to be geographically restricted to limited areas, (Gjerset, 2006; Grego et al., 2007).

The main SRLV transmission routes are lactogenic, occurring through the consumption of infected colostrum and/or milk, and horizontal, occurring through direct contact between adult animals. Other routes have been considered as being less important from the epidemiologic perspective and include intrauterine and iatrogenic routes. Both the importance of intrauterine transmission and the fetal infection frequency remain controversial, suggest-

ing that viral and host genetics may be involved (Peterhans et al., 2004; Shah et al., 2004b; Vainas et al., 2006; Minardi da Cruz et al., 2013).

Caprine Arthritis Encephalitis (CAE), firstly reported in 1974 (Cork et al., 1974; Clements et al., 1980), is characterized by a progressive chronic course while clinical signs are not immediately visible. It has been observed that the symptoms usually appear between the ages of 2 and 5 and lead to a decreasing in milk and meat production (Martínez-Navalón et al., 2013). There is currently no effective treatment for this infection and due to a high viral mutation rate, no vaccine is available (Reina et al., 2009). Sanitary measures and animal management are the main tools to control the introduction and the spread of the virus. One of the most used techniques, named "test-and-slaughter", consists in selecting infected goats and directly slaughtering them (Pittavino et al., 2014). In this way the farmer can eradicate the virus but this approach is very time consuming and often not conclusive. A more complex strategy consists in taking the newborns away from their mothers and keeping them in a new breeding area where they are raised avoiding lactogenic transmission. Usually this eradication method needs several years with a strong collaboration among farmers. In several countries (Switzerland and Northeastern Italy) the eradication is focused on the elim-

ination of clinical strains: this strategy can be useful to avoids symptoms, but, in some cases can favor the spread of low pathogenic strains (Cardinaux et al., 2013; Deubelbeiss et al., 2014; Tavella et al., 2018). However, the latter methods is not complete since SRLV genotype CAEV-like B can also be transmitted horizontally through blood or saliva, even from asymptomatic carrier animals.

On the other hand the genotype E is transmitted only through colostrum and it is characterised by the absence of clinical symptoms (Grego et al., 2007). In vitro, genotype E showed peculiar features: it was not able to grow on cells typically used for SRLV isolation (i.e. fibroblast-like cells), but only on monocytes/macrophages cell cultures (Juganaru et al., 2011). It was first discovered in the Roccaverano goat breed in Piedmont (Italy), therefore it is also known as Roccaverano strain. Genome characterization revealed a very large difference between this new genotype and all the other known SRLV strains. Both subtypes belonging to genotype E, E1 in Piedmont and E2 in Sardinia show a mean nucleotide diversity higher than 25% if compared to any other SRLV (Grego et al., 2007). Its genetic divergence is reflected at amino acidic level, and for this reason, it has been hidden from standard serological tests, due to its highly divergent major immunodominant

epitopes. It has been suggested that the Roccaverano goat breed could be resistant to CAEV infection, but this is likely due to the failure of breeders to detect the infection and the absence of symptoms. Several studies have been conducted in order to understand the genotype E pathogenicity (Reina et al., 2011; Crespo et al., 2016). The main aspect about the interaction between genotypes E and B was better clarified by Bertolotti et al. (2013) demonstrating how genotype E can be considered a natural protection against pathogenic strains.

Even if the genotype E infection can be considered as a protective status against SRLV pathogenic strains, and it could be evaluated as a potential vaccine, it is a wild-type virus infection also caused by a different subtype (E2), which was not proven to be asymptomatic but it shares the same in vitro features of pathogenic SRLV strains (Juganaru et al., 2011).

In this article, we propose a mathematical model that encapsulates the main epidemiological dynamics of a breeding affected by SRLV genotypes B and E. The model is formulated in order to study the influence that the circulation of viral strains can have on the replacement rate of the farm, i.e. the fraction of newborns that the farmer must keep in the breeding so to manaint constant the number of animals in the farm. In Section 2, the

model is formulated together with its main assumptions. Then, in Section 3, we consider how strict the sanitary measures have to be in order to prevent the disease from becoming endemic and possibly to eradicate it; to this end, the equilibrium points are obtained and their feasibility is characterized. Finally, the stability conditions for these equilibria are investigated in Section 4 and the important follow-ups of this study for the containment policy are discussed. The Appendix A contains the relevant mathematical details.

2. The Model

We consider a breeding in which both genotypes B and E are present. The genotype B, which is pathogenic, and the genotype E, which does not give any symptom, coexist on the same farm. Denoting by $N(t)$ the total population of the breeding, we partition it into four classes:

- $S(t)$: represents the number of goats which are susceptible to both genotypes of the disease,
- $I_a(t)$: represents the number of the asymptomatic goats infected by genotype B,
- $I_s(t)$: represents the number of the symptomatic goats infected by genotype B,

- $Y(t)$: represents the number of the asymptomatic goats infected by genotype E.

The basic assumptions underlying the dynamics of the breeding follow:

- every goat belonging to class $S(t)$ is equally susceptible to both genotypes,
- genotype B of the lentivirus is transmitted both horizontally and through colostrum,
- the infection by genotype B is characterized by a long period of incubation in which the infected goats do not show any symptom,
- genotype E of the lentvirus is transmitted only through colostrum, since no evidence of horizontal transmission for genotype E has been proven so far,
- the two genoptypes cannot simultaneously infect the same goats.

Under these hypotheses, the following frequency-dependent model represents the breeding epidemiological dynamics in the presence of both genotypes:

$$\begin{aligned}
\frac{\mathrm{d}\,S(t)}{\mathrm{d}\,t} &= \left\{(1-\gamma)+\gamma\left[1-\left(\theta_B\frac{I_a(t)+I_s(t)}{N(t)}+\theta_E\frac{Y(t)}{N(t)}\right)\right]\right\}arN(t) \\
&\quad - mS(t)-\beta S(t)\frac{I_a(t)+I_s(t)}{N(t)}, \\
\frac{\mathrm{d}\,I_a(t)}{\mathrm{d}\,t} &= \theta_B\frac{I_a(t)+I_s(t)}{N(t)}\gamma arN(t)+\beta S(t)\frac{I_a(t)+I_s(t)}{N(t)}-(\delta+m)I_a(t), \\
\frac{\mathrm{d}\,I_s(t)}{\mathrm{d}\,t} &= \delta I_a(t)-\mu I_s(t), \\
\frac{\mathrm{d}\,Y(t)}{\mathrm{d}\,t} &= \theta_E\frac{Y(t)}{N(t)}\gamma arN(t)-mY(t).
\end{aligned} \tag{1}$$

The first equation relates the dynamics of the susceptible class. We denote by $arN(t)$ the number of newborns where r is the reproduction rate, i.e. the relationship between inseminated goats and the number of live newborns, and a the replacement rate of offspring, i.e. the fraction of newborns kept in a farm in order to maintain the population stable in the farm. This parameter maybe different from farm to farm, depending from different farming systems and/or health statuses of the farm. New individuals come into this class because they are either removed from their mothers and raised in an isolated breeding, with probability $1-\gamma$, or are not immediately removed but they contract neither of the two genotypes, with probability

$$\gamma\left[1-\left(\theta_B\frac{I_a(t)+I_s(t)}{N(t)}+\theta_E\frac{Y(t)}{N(t)}\right)\right].$$

We have introduced three parameters: the first one is γ which represents the measures taken by the farmer to avoid the spreading of the disease: it is the probability of not being isolated from infected animals, so that it varies between 0 and 1. The second and the third parameters, θ_B and θ_E, represent the probabilities of the transmission through colostrum of genotypes B and E respectively, assuming there has been a contact between the newborn and the infected mother. Therefore, being

$$\frac{I_a(t) + I_s(t)}{N(t)}, \qquad \frac{Y(t)}{N(t)}$$

respectively the probabilities of having a contact with an individual infected by B or E, we denote by

$$\theta_B \frac{I_a(t) + I_s(t)}{N(t)}$$

the probability of infection through colostrum by genotype B and by

$$\theta_E \frac{Y(t)}{N(t)}$$

the corresponding one by genotype E. Thus, their sum represents the probability of being infected by one of the two genotypes. The second term of the equation represents the natural mortality at rate m while the last term models the horizontal transmission of genotype B, which susceptible individuals can contract both from infected asymptomatic and from infected

symptomatic goats at rate β. This parameter represents the product of the contact rate between susceptible and infected individual by B and the probability of horizontal transmission of the pathogenic genotype.

The second equation describes the dynamics of the infected asymptomatic goats by genotype B. The first term represents the newborns which have not been removed from the breeding, $\gamma arN(t)$, they have taken milk from an infected mother, and they have been infected by B,

$$\theta_B \frac{I_a(t) + I_s(t)}{N(t)} \gamma arN(t).$$

The second term indicates the new goats infected by the virus because of the horizontal transmission while the third term models individuals who leave this class because of either the progression of the infection to symptomatic disease, at rate δ, or the natural mortality.

The third equation represents the dynamics of the infected symptomatic goats. Its first term indicates the new individuals who become part of this class because the disease evolves from asymptomatic to symptomatic. The second term instead describes the mortality rate μ, which indicates natural plus disease-related mortality.

Finally, the last equation models the dynamics of the infected asymptomatic goats by strain E. Its first term represents the newborns which have

not been isolated from infected animals, $\gamma arN(t)$, thus feed from an infected goat, and they have been infected by E,

$$\theta_E \frac{Y(t)}{N(t)} \gamma arN(t).$$

The last term represents the natural mortality.

Simplifying, we can rewrite the system (1):

$$\begin{aligned}
\frac{\mathrm{d}\, S(t)}{dt} &= \left(1 - \gamma\theta_B \frac{I_a(t) + I_s(t)}{N(t)} - \gamma\theta_E \frac{Y(t)}{N(t)}\right) arN(t) - mS(t) \\
&\quad - \beta S(t) \frac{I_a(t) + I_s(t)}{N(t)}, \\
\frac{\mathrm{d}\, I_a(t)}{\mathrm{d}\, t} &= \gamma\theta_B ar(I_a(t) + I_s(t)) + \beta S(t) \frac{I_a(t) + I_s(t)}{N(t)} - (\delta + m) I_a(t), \\
\frac{\mathrm{d}\, I_s(t)}{\mathrm{d}\, t} &= \delta I_a(t) - \mu I_s(t), \\
\frac{\mathrm{d}\, Y(t)}{\mathrm{d}\, t} &= \gamma\theta_E arY(t) - mY(t).
\end{aligned}$$

Observing that $N(t) = S(t) + I_a(t) + I_s(t) + Y(t)$, we can eliminate S from the system and reformulate it by introducing the prevalences:

$$i_a(t) = \frac{I_a(t)}{N(t)}, \qquad i_s(t) = \frac{I_s(t)}{N(t)} \qquad \text{and} \qquad y(t) = \frac{Y(t)}{N(t)},$$

obtaining the reformulated system:

$$\begin{aligned}
\frac{\mathrm{d}\,N(t)}{\mathrm{d}\,t} &= (ar-m)N(t) - (\mu-m)i_s(t)N(t),\\
\frac{\mathrm{d}\,i_a(t)}{\mathrm{d}\,t} &= (\gamma\theta_B - 1)ari_a(t) + \gamma\theta_B ari_s(t) + \beta(i_a(t)+i_s(t))\,[1-(i_a(t)+i_s(t)\\
&\qquad +y(t))] - \delta i_a(t) + (\mu-m)i_a(t)i_s(t),\\
\frac{\mathrm{d}\,i_s(t)}{\mathrm{d}\,t} &= \delta i_a(t) - (ar+\mu-m)i_s(t) + (\mu-m)i_s(t)^2,\\
\frac{\mathrm{d}\,y(t)}{\mathrm{d}\,t} &= (\gamma\theta_E - 1)ary(t) + (\mu-m)i_s(t)y(t).
\end{aligned} \tag{2}$$

Because of the limited resources of the farms, the total population is usually kept at a constant value by the farmer. From now on, we set $N(t) = N$, where N represents the fixed size of the breeding.

From the steady state of the first equation of the system (2) we determine the replacement rate a_{path} of a farm with pathogen circulation that can be then compared to a_{farm}, the replacement rate that the farm would have in absence of pathogen circulation:

$$a_{path} = \frac{m}{r} + \frac{\mu-m}{r}i_s(t) = a_{farm} + \frac{\mu-m}{r}i_s(t) > a_{farm}. \tag{3}$$

In this type of breeding in the presence of both genotypes more offspring must be raised than in the case of a disease-free farm to keep the total number of goats constant. This result is coherent with that found by Collino et al.

(2016), where only the strain B was considered. We can also observe that the replacement rate is directly proportional to the B symptomatic infected fraction in the population. The higher the latter, the more newborns need to be kept in the breeding. Substituting the replacement rate a_{path} in the remaining equations, we obtain the final form of the system, with a lower number of equations:

$$\begin{aligned}
\frac{\mathrm{d}\, i_a(t)}{\mathrm{d}\, t} &= -\beta i_a^2(t) + [\gamma\theta_B(\mu - m) - \beta] i_s^2(t) + [\gamma\theta_B(\mu - m) - 2\beta] i_a(t) i_s(t) \\
&\quad - \beta i_a(t) y(t) - \beta i_s(t) y(t) + (\gamma\theta_B m - m + \beta - \delta) i_a(t) \\
&\quad + (\gamma\theta_B m + \beta) i_s(t), \\
\frac{\mathrm{d}\, i_s(t)}{\mathrm{d}\, t} &= \delta i_a(t) - \mu i_s(t), \\
\frac{\mathrm{d}\, y(t)}{\mathrm{d}\, t} &= \gamma\theta_E(\mu - m) i_s(t) y(t) + (\gamma\theta_E - 1) m y(t).
\end{aligned} \tag{4}$$

3. Model analysis

We are now ready for the equilibria analysis. Solving the system (4), we find the following stationary points, namely the disease-free environment O, the genotype-E-free point C and the endemic equilibrium D:

$$O = (0, 0, 0), \tag{5}$$

$$C = (i_a^C, i_s^C, 0) = \left(\frac{\mu[(\mu+\delta)(\gamma\theta_B m + \beta) - \mu(\delta+m)]}{(\mu+\delta)[\beta(\mu+\delta) - \gamma\delta\theta_B(\mu-m)]}, \frac{\delta}{\mu} i_a^C, 0 \right), \quad (6)$$

and

$$D = (i_a^D, i_s^D, y^D) = \left(\frac{(1-\gamma\theta_E)\mu m}{\delta\gamma\theta_E(\mu-m)}, \frac{\delta}{\mu} i_a^D, y^D \right), \quad (7)$$

where

$$y^D = \frac{(\mu+\delta)[\gamma\delta\theta_B m(\mu-m) + \beta\gamma\mu\theta_E(m+\delta) - \beta m(\mu+\delta)]}{\beta\gamma\delta\theta_E(\mu-m)(\mu+\delta)} + \frac{\gamma\delta\mu\theta_E(m-\mu)(m+\delta)}{\beta\gamma\delta\theta_E(\mu-m)(\mu+\delta)}.$$

Since the point C is the same as for the model of genotype B found by Collino et al. (2016), its feasibility conditions are

- if $\frac{\mu(\delta+m)}{\mu+\delta} - \theta_B m \leq \beta < \frac{\mu(\delta+m)}{\mu+\delta}$, the equilibrium C is feasible if and only if the following condition is verified

$$\gamma \geq \frac{\mu(\delta+m)}{\theta_B m(\mu+\delta)} - \frac{\beta}{\theta_B m},$$

- if $\beta \geq \frac{\mu(\delta+m)}{\mu+\delta}$, the equilibrium C is feasible for any value of γ.

We focus now on the equilibrium D. Because its feasibility analysis is quite involved, we defer it to the Appendix and mention here only the main result.

As $1 = s(t) + i_a(t) + i_s(t) + y(t)$, the dynamics of (4) evolves entirely in the standard unit simplex

$$\Sigma = \left\{(i_a^D, i_s^D, y^D) : i_a^D \geq 0, i_s^D \geq 0, y^D \geq 0, i_a^D + i_s^D + y^D \leq 1\right\}$$

with vertices given by the origin and the three unit points on the coordinate axes. Hence the equilibrium D is feasible if and only if each component is not negative and $i_a^D + i_s^D + y^D \leq 1$.

In summary, the feasibility of this equilibrium is guaranteed if

$$\mu\theta_E(m + \delta) - m(\mu + \delta) > 0, \tag{8}$$

and β satisfies (A.4), that is:

$$\beta > \varphi,$$

the equilibrium D is feasible if and only if (A.2) is verified, that is:

$$\gamma \geq \frac{\beta m(\mu + \delta)^2}{\beta\mu\theta_E(m + \delta)(\mu + \delta) + \delta(\mu - m)[\theta_B m(\mu + \delta) - \mu\theta_E(m + \delta)]} \equiv \gamma^+.$$

Equilibrium D represents the coexistence of the two genotypes in the same breeding. As the two strains are transmitted through colostrum, the higher the value of γ is (i.e. the isolation of the newborns from their mothers is worse) the greater the chance of existence of this stationary point will be.

We can try and find an estimate for the values of β that characterize the existence conditions of D. First of all, we need to know if (8) is satisfied.

We take $m = 0.1$, with μ equal to 0.8, 0.9 and 1, since the natural plus disease related mortality is high because if the farmer detects an infected symptomatic goat, he slaughters it immediately. In Figure 1 we plot the surface of equation $z(\theta_E, \delta) = \mu\theta_E(m+\delta) - m(\mu+\delta)$ as function of θ_E and δ. Recall that the latter indicates the rate at which B asymptomatic individuals become symptomatic; it is the reciprocal of the age of the goats when the symptoms appear for the first time. This is estimated to be between 2 and 5 years. Hence $0.2 \leq \delta \leq 0.5$. We consider only the case in which θ_E is larger than 0.5, because it better represents the characteristics of the virus.

From Figure 1, the surfaces are always above the plane $z = 0$, hence in our case (8) is always true.

To find an estimate of the minimum value of β above which the equilibrium D exists, using the ranges for the parameters chosen before, in Figure 2 we represent the surface φ as a function of θ_B and θ_E. From that Figure we can conclude that the higher the value of δ is, i.e. the earlier the symptoms appear, the smaller the range of value of β for which the stationary point can exist.

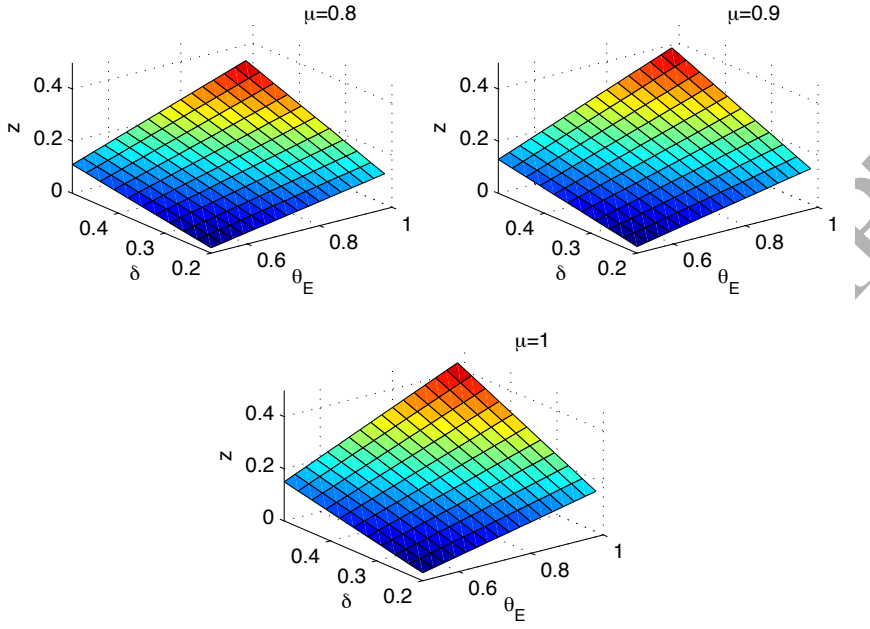

Figure 1: Surface of equation $z(\theta_E, \delta) = \mu\theta_E(m + \delta) - m(\mu + \delta)$ as function of θ_E and δ, for $m = 0.1$ and different values of μ.

4. Discussion and Recommendations

The stability conditions for the first two equilibria (O and C) are derived in the Appendix A, and the general framework is depicted in table 1. Special attention must, however, be paid to the stability of D, as the study of the Jacobian matrix of the system does not allow to either to find the eigenvalues of the matrix, or to use the Routh Hurwitz criterion because the calculations are too complex. This coexistence equilibrium can therefore only be analyzed

numerically.

From figures A.5 and A.6, we can observe that for small values of β, the three compartments are equal to zero, so the farm is free from the virus and the origin (i.e. the disease-free environment) is the only stable equilibrium. We can also note that this does not depend on the value of γ, except for a small range of values of β. In fact we have seen that in this case the behaviour of the farmer can help to keep the breeding free from the disease.

When β increases, also the equilibrium values of the three populations of infected individuals increase. For small values of γ, i.e. the isolation of newborns from their mothers is efficient, the population which represents E asymptomatic goats vanishes while the B-infected populations grow, especially the B asymptomatic one. However for large values of γ, i.e. the isolation of newborns from their mothers is less effective, the population of E asymptomatic goats grows quickly, while the B infected individuals decrease.

These mathematical results are coherent with reality. Indeed if the farmer separates newborns from parents, thus γ is small, only the genotype B, transmitted both through colostrum and horizontally, can be transmitted while strain E, which is transmitted only through colostrum, soon disappears. Moreover, if the farmer does not adopt any effective strategy, that is γ is

large, both genotypes could exist.

For these simulations we have considered the initial conditions equal to $(0.3, 0.1, 0.3)$ but we can obtain a similar result describing the steady states of the populations starting from the point $(0.1, 0.05, 0.8)$. Thus this model is robust enough. It essentially represents the situation observed in the Roccaverano farms, where the genotype B is not present even in the absence of disease containment measures by the farmers. This is possible because the dynamics of the breeding follows the behaviour shown in the Figures.

We can conclude that strain E takes over genotype B. It therefore acts as a kind of natural vaccine against the disease, as supported in the in-vivo experiments in Bertolotti et al. (2013). In fact if the parameter γ exceeds a certain threshold, the equilibrium D becomes feasible and asymptotically stable arising via a transcritical bifurcation, see condition (A.12). The results of this study are summarized in Table 1. Observe that only one of the three equilibria can be attained as they are all mutually exclusive. The threshold values of γ namely γ^+ and

$$M \equiv \frac{\mu(\delta + m)}{\theta_B m(\mu + \delta)} - \frac{\beta}{\theta_B m}.$$

characterize the system outcome and ultimately the epidemics behavior in the farm.

This study shows the fact that mathematical models help in both qualitatively and quantitatively substantiating the intuition of other scientists. Note that the current control strategy would try to achieve the disease-free equilibrium, see Figures A.5 and A.6, but this is quite difficult because the farmer can certainly directly influence the parameter γ, which represents the newborns removal rate, but he can hardly affect the horizontal transmission rate β. Or better, he can try to reduce it, but to keep it close to zero would mean to isolate each goat in the farm, which is quite an impossible task to achieve. Instead of pursuing this goal, Figures A.5 and A.6 suggest to try to look for low values of the genotype B-infected goats. These are indeed found for large values of both γ and β, namely in the far left corner of the pictures. In these corners instead the genotype E population has a peak. But the latter is not a problem for the farmer, as these genotype E-affected goats do not show clinical symptoms.

These considerations prompt the actual findings of this investigation. Ultimately they indicate that two scenarios can be highlighted and enhanced. First of all, in the presence of both genotypes and when the only control measure is the mother-newborn separation, i.e. no serological testing is performed, a complete reversal of the current raising policy should be performed.

Indeed, the farmer should not isolate the newborns from their mothers but rather let them be raised with all the other animals in the farm and favor instead their high mixing. Secondly, in case of an only-genotype B-affected farm, since it is not feasible to introduce in it goats that are affected by the genotype E, serological testing and mother-offspring separation should be still considered the best strategy for CAEV control. In view of the fact that serological testing is costly and time consuming, and the "test and slaughter" policy is not totally effective, these indications represent very reasonable and cheap measures and are therefore highly recommended to be implemented in the goats breedings for the eventual control and eradication of the epidemics.

Condition	O	C	D	Bifurcation
$\gamma < M$	Stable	Infeasible	Infeasible	
$\gamma = M$				Transcritical
$M < \gamma < \gamma^+$	Unstable	Stable	Infeasible	
$\gamma = \gamma^+$				Transcritical
$\gamma > \gamma^+$	Unstable	Unstable	Stable	

Table 1: Equilibria of the system (4) for a breeding affected by two strains.

Appendix A. Appendix

Feasibility of D

Recall that the dynamics of (4) evolves entirely in the standard unit simplex Σ with vertices given by the origin and the three unit points on the coordinate axes and that for its feasibility we need all its components nonnegative.

We start studying under what conditions, i_a^D and i_s^D are non-negative. In view of the following relationship found in the populations of equilibrium D,

$$i_s^D = \frac{\delta}{\mu} i_a^D,$$

we analyze only i_a^D because the two parameters δ and μ are positive. We can immediately observe that i_a^D is always positive. In fact both the numerator and the denominator are nonnegative because, for the first one, $0 < \gamma < 1$ and $0 < \theta_E < 1$, while for the second one, $\mu > m$.

We concentrate now on y^D. Note that its denominator is always positive, also in this case because $\mu > m$, so the fraction will be non-negative if and only if the numerator is non-negative. For

$$\beta > \frac{\delta(\mu-m)[\mu\theta_E(m+\delta)-\theta_B m(\mu+\delta)]}{\mu\theta_E(m+\delta)(\mu+\delta)} \equiv \widehat{H}, \tag{A.1}$$

the numerator of y^D will be non-negative under the condition:

$$\gamma \geq \frac{\beta m(\mu+\delta)^2}{\beta\mu\theta_E(m+\delta)(\mu+\delta)+\delta(\mu-m)[\theta_B m(\mu+\delta)-\mu\theta_E(m+\delta)]} \equiv \gamma^+, \tag{A.2}$$

otherwise, if the condition (A.1) is not true, it will be non-negative under the condition:

$$\gamma \leq \gamma^+. \tag{A.3}$$

But the latter is impossible. In fact for γ^+, the numerator is positive and the denominator is negative because (A.1) is not satisfied. So the fraction, i.e. γ^+, is negative, but γ cannot be negative in view of the assumption $0 \leq \gamma \leq 1$. We thus conclude that $y^D \geq 0$ only if both (A.1) and (A.2) hold.

We need however to verify whether the fraction, i.e. $\widehat{H}$, in (A.1) is negative, in which case this condition would not be necessary. The numerator is positive for

$$\mu\theta_E(m+\delta) - \theta_B m(\mu+\delta) > 0,$$

so that

- if $\mu\theta_E(m+\delta) - \theta_B m(\mu+\delta) > 0$ and β satisfies (A.1), then $y^D \geq 0$ if condition (A.2) holds;

- if $\mu\theta_E(m+\delta) - \theta_B m(\mu+\delta) < 0$, $y^D \geq 0$ under condition (A.2), for any value of β.

As far as (A.2) is concerned, we know that $\gamma^+ \geq 0$, but we do not know if γ^+ is smaller than one. Only in this case γ could verify it. Thus we need to impose $\gamma^+ < 1$. We obtain that if

$$\mu\theta_E(m+\delta) - m(\mu+\delta) > 0,$$

(A.2) is satisfied under the condition

$$\beta > \frac{\delta(\mu-m)[\mu\theta_E(m+\delta) - \theta_B m(\mu+\delta)]}{(\mu+\delta)[\mu\theta_E(m+\delta) - m(\mu+\delta)]} \equiv \varphi, \tag{A.4}$$

otherwise, if

$$\mu\theta_E(m+\delta) - m(\mu+\delta) < 0,$$

(A.2) is satisfied under the condition

$$\beta < \varphi. \tag{A.5}$$

Observe that:

$$\mu\theta_E(m+\delta) - m(\mu+\delta) < \mu\theta_E(m+\delta) - \theta_B m(\mu+\delta), \tag{A.6}$$

because $0 < \theta_B < 1$. So φ in (A.4) is positive and the condition has to be satisfied.

Comparing $\widehat{H}$ and φ, we note that:

$$\frac{\delta(\mu-m)[\mu\theta_E(m+\delta)-\theta_B m(\mu+\delta)]}{\mu\theta_E(m+\delta)(\mu+\delta)} < \frac{\delta(\mu-m)[\mu\theta_E(m+\delta)-\theta_B m(\mu+\delta)]}{(\mu+\delta)[\mu\theta_E(m+\delta)-m(\mu+\delta)]},$$

since:

$$\frac{1}{\mu\theta_E(m+\delta)} < \frac{1}{\mu\theta_E(m+\delta)-m(\mu+\delta)},$$

It follows that if $\mu\theta_E(m+\delta) - m(\mu+\delta) > 0$ and β satisfies (A.4), $y^D \geq 0$ under the condition (A.2).

Now we consider (A.5): φ must be positive, because β is. We need to assess where the numerator of φ is negative, i.e. $\mu\theta_E(m+\delta)-\theta_B m(\mu+\delta) < 0$. As $\mu\theta_E(m+\delta) - m(\mu+\delta) < \mu\theta_E(m+\delta) - \theta_B m(\mu+\delta)$, we have that $y^D \geq 0$ under the condition (A.2) if $\mu\theta_E(m+\delta)-\theta_B m(\mu+\delta) < 0$ and β satisfies (A.5).

Finally, let us consider which values of γ satisfy the constraint $i_a^D + i_s^D + y^D \leq 1$. This explicitly becomes

$$\frac{1}{\beta\gamma\delta\theta_E(\mu-m)(\mu+\delta)}[\beta m(1-\gamma\theta_E)(\mu+\delta)^2 + \gamma\delta\theta_B m(\mu-m)(\mu+\delta)$$
$$+\beta\gamma\mu\theta_E(m+\delta)(\mu+\delta) - \beta m(\mu+\delta)^2 + \gamma\delta\mu\theta_E(m-\mu)(m+\delta)] \leq 1.$$

The denominator is positive, so we must have:

$$\gamma[\delta\theta_B m(\mu-m)(\mu+\delta) + \beta\mu\theta_E(m+\delta)(\mu+\delta) - \beta\theta_E m(\mu+\delta)^2$$
$$-\delta\mu\theta_E(\mu-m)(m+\delta) - \beta\delta\theta_E(\mu-m)(\mu+\delta)] \leq 0.$$

This inequality is true if and only if:

$$\beta\theta_E(\mu+\delta)[\mu(m+\delta)-m(\mu+\delta)-\delta(\mu-m)]$$
$$\leq \delta(\mu-m)[\mu\theta_E(m+\delta)-\theta_B m(\mu+\delta)].$$

But $\mu(m+\delta)-m(\mu+\delta)-\delta(\mu-m) = \mu m+\delta\mu-\mu m-\delta m-\delta\mu+\delta m = 0$. Hence the inequality will be true if and only if the right hand side is non-negative, i.e. if $\mu\theta_E(m+\delta)-\theta_B m(\mu+\delta) > 0$.

Thus we conclude that sufficient conditions for the feasibility of the equilibrium D are given by (8), (A.4) and (A.2).

Preliminaries for the stability of the equilibria

We analyze now the local stability of the equilibria, starting with some common preliminaries. The Jacobian of the system (4) is

$$J = \begin{pmatrix} J_{11} & J_{12} & -\beta(i_a+i_s) \\ \delta & -\mu & 0 \\ 0 & \gamma\theta_E(\mu-m)y & J_{33} \end{pmatrix},$$

where

$$\begin{aligned} J_{11} &= -2\beta i_a + (\gamma\theta_B(\mu-m)-2\beta)i_s - \beta y + \gamma\theta_B m - m + \beta - \delta, \\ J_{12} &= (\gamma\theta_B(\mu-m)-2\beta)i_a + 2(\gamma\theta_B(\mu-m)-\beta)i_s - \beta y + \gamma\theta_B m + \beta, \\ J_{33} &= \gamma\theta_E(\mu-m)i_s + (\gamma\theta_E - 1)m. \end{aligned}$$

We are now ready to study the local behaviour of each stationary point.

Stability of O

The Jacobian evaluated at $O = (0, 0, 0)$ has one eigenvalue that factors out, $(\gamma\theta_E - 1)m < 0$, which does not influence stability as $0 < \gamma, \theta_E < 1$. The Routh Hurwitz conditions give the stability for the virus-free equilibrium:

$$\beta \leq \frac{\mu(\delta + m)}{\mu + \delta} - \theta_B m, \qquad \text{(A.7)}$$

$$\frac{\mu(\delta + m)}{\mu + \delta} - \theta_B m < \beta < \frac{\mu(\delta + m)}{\mu + \delta}, \quad \gamma < \frac{\mu(m + \delta)}{\theta_B m(\mu + \delta)} - \frac{\beta}{\theta_B m}.$$

Stability of C

Now we consider the second equilibrium, $C = (i_a^C, i_s^C, 0)$.

Again, immediately one eigenvalue is: $\gamma\theta_E(\mu - m)i_s^C + (\gamma\theta_E - 1)m$, while the other two come from the submatrix which coincides with the matrix for the local stability of C for a breeding only in the presence of the genotype B of the virus, Collino et al. (2016). Specifically,

$$-\mathrm{tr}(J_{|C}) > 0, \qquad \det(J_{|C}) > 0.$$

The latter yields the feasibility condition of C:

$$\gamma > \frac{\mu(\delta + m)}{\theta_B m(\mu + \delta)} - \frac{\beta}{\theta_B m}, \qquad \text{(A.8)}$$

The first condition of the Routh Hurwitz criterion, $-\mathrm{tr}(J_{|C}) = -J_{11}^{C} + \mu > 0$, Collino et al. (2016), is satisfied if

$$\beta > \frac{\delta(\mu - m)[\mu(\mu + \delta) + \delta(m + \delta)]}{m(\mu + \delta)^2} \equiv \widehat{K}, \tag{A.9}$$

because it gives:

$$\gamma > \frac{-\beta(\mu + \delta)[\beta(\mu + \delta) + \mu(\mu - m) + \delta(\delta + m)]}{\theta_B \{\beta m(\mu + \delta)^2 + \delta(m - \mu)[\mu(\mu + \delta) + \delta(m + \delta)]\}} \equiv \psi, \tag{A.10}$$

which holds since $0 < \gamma < 1$ and the denominator is positive in view of (A.9). Otherwise, if (A.9) is not true, the condition on the trace is satified for:

$$\gamma < \psi. \tag{A.11}$$

To these conditions for the negativity of the two eigenvalues of the submatrix, we need to add the negativity of the first one:

$$\gamma\theta_E(\mu - m)\frac{\delta[(\mu + \delta)(\gamma\theta_B m + \beta) - \mu(\delta + m)]}{(\mu + \delta)[\beta(\mu + \delta) - \gamma\delta\theta_B(\mu - m)]} + (\gamma\theta_E - 1)m < 0.$$

Exploiting the feasibility conditions for C, implying that the denominator of i_a^C is positive, we obtain that if (A.1) is verified, the eigenvalue will be negative under the condition:

$$\gamma < \frac{\beta m(\mu + \delta)^2}{\beta\mu\theta_E(\mu + \delta)(m + \delta) + \delta(\mu - m)[\theta_B m(\mu + \delta) - \mu\theta_E(\delta + m)]} \equiv \gamma^+, \tag{A.12}$$

otherwise if the condition (A.1) is not true, it will be negative unconditionally, since it requires $\gamma > \gamma^+$, which is always satisfied, because the denominator of γ^+ is negative, while $0 \leq \gamma \leq 1$. Comparing (A.12) and (A.2), at $\gamma = \gamma^+$ a transcritical bifurcation arises, for which the coexistence equilibrium D emerges from the genotype-E-free point C when the newborns removal rate γ crosses from below the critical value γ^+.

For the sign of the eigenvalue J_{33}^C, we have the following situations:

- if $\mu\theta_E(\delta + m) - \theta_B m(\mu + \delta) > 0$, there are two possibilities:
  - if (A.1) holds, the eigenvalue is negative under the condition (A.12),
  - if (A.1) does not hold, the eigenvalue is negative for any γ,
- if $\mu\theta_E(\delta + m) - \theta_B m(\mu + \delta) < 0$, the eigenvalue will be negative under the condition (A.12) for every value of β.

The feasibility of D tells when condition (A.12) must be imposed, because if it is larger than one it will always be verified, in view of the bounds for γ:

- if $\mu\theta_E(\delta + m) - m(\mu + \delta) > 0$, if (A.4) is true, the condition (A.12) has to be verified, otherwise if (A.4) is not true, it is always satisfied,
- if $\mu\theta_E(\delta + m) - m(\mu + \delta) < 0$, if (A.5) is true, the condition (A.12) has to be verified, otherwise if (A.5) is not true, it is always satisfied.

But (A.6) is verified, i.e:

$$\mu\theta_E(m+\delta) - m(\mu+\delta) < \mu\theta_E(m+\delta) - \theta_B m(\mu+\delta),$$

thus if $\mu\theta_E(\delta+m) - m(\mu+\delta) > 0$, as we have observed that the expression of (A.1) is smaller than the expression of (A.4), we can say that the sign of the eigenvalue J_{33}^C is negative in the following cases:

- $\beta < \widehat{H}$, for every value of γ,
- $\widehat{H} < \beta < \varphi$, for any γ because the condition (A.12) is always verified,
- $\beta > \varphi$, if γ satisfies (A.12).

If $\mu\theta_E(\delta+m) - m(\mu+\delta) < 0$, we need $\mu\theta_E(\delta+m) - \theta_B m(\mu+\delta) < 0$ for (A.5) to hold. Thus in such case the sign of the eigenvalue J_{33}^C is negative for:

- $\beta < \varphi$, if γ satisfies (A.12),
- $\beta > \varphi$, for any γ because the condition (A.12) is always verified.

Combining these last results with those found earlier, (A.9)-(A.11), several cases arise. Some can be excluded in the following way.

The characteristics of the virus prevent the inequality $\mu\theta_E(\delta + m) - \theta_B m(\mu + \delta) < 0$ to hold. Indeed taking $m = 0.1$ and $\mu = 0.9$ and representing the surface $z = \mu\theta_E(\delta + m) - \theta_B m(\mu + \delta)$ as function of θ_B and θ_E, for the values of δ equals to 0.2, 0.3, 0.4 and 0.5, with $0.5 \leq \theta_B \leq 1$ and $0.5 \leq \theta_E \leq 1$, better representing the features of the disease, the surface is always above the plane $z = 0$, Figure A.3.

We study only β in comparison with $\widehat{H}$ but do not consider the relation of this parameter with φ, to simplify the analysis. We focus in particular on condition (A.12), possibly leading to a transcritical bifurcation, but this depending only on the mutual values of β and $\widehat{H}$.

If $\beta < \widehat{K}$, we need (A.11). We then find that $\widehat{H} < \widehat{K}$ because it reduces to $\mu\theta_E m(\mu + \delta)(\delta + m) < \mu^2\theta_E(m + \delta)(\mu + \delta)$, true in view of $m < \mu$.

Now we are ready to analyze the six possibilities that can occur which depend on the positions that $\widehat{H}$ and $\widehat{K}$ with respect to the values characterizing the feasibility of C.

For a strain B-affected breeding, we have, Collino et al. (2016)

$$\widehat{K} \geq \frac{\mu(\delta + m)}{\mu + \delta}.$$

We now compare $\widehat{H}$ with the relevant quantities appearing in the feasibility

	$\widehat{H} < \widehat{K} < \mu\frac{\delta+m}{\mu+\delta} - \theta_B m < \mu\frac{\delta+m}{\mu+\delta}$	
condition	C feasibility	C stability
$\frac{\mu(\delta+m)}{\mu+\delta} - \theta_B m \leq \beta < \frac{\mu(\delta+m)}{\mu+\delta}$	(A.8)	(A.12)
$\beta \geq \frac{\mu(\delta+m)}{\mu+\delta}$	—	(A.12)

Table A.2: Case 1 for equilibrium C of model (4).

	$\widehat{H} < \mu\frac{\delta+m}{\mu+\delta} - \theta_B m < \widehat{K} < \mu\frac{\delta+m}{\mu+\delta}$	
condition	C feasibility	C stability
$\frac{\mu(\delta+m)}{\mu+\delta} - \theta_B m \leq \beta < \widehat{K}$	(A.8)	(A.11), (A.12)
$\widehat{K} < \beta < \frac{\mu(\delta+m)}{\mu+\delta}$	(A.8)	(A.12)
$\beta \geq \frac{\mu(\delta+m)}{\mu+\delta}$	—	(A.12)

Table A.3: Case 2 for equilibrium C of model (4).

of C, i.e. we study the surface

$$z = \frac{\mu(\delta+m)}{\mu+\delta} - \theta_B m - \widehat{H}$$

as function of $\theta_B \in [0.5, 1]$ and $\theta_E \in [0.5, 1]$, for $m = 0.1$, $\mu = 0.9$ and several values of δ. From Figure A.4, the surface lies always above the plane $z = 0$, so that

$$\widehat{H} < \frac{\mu(\delta+m)}{\mu+\delta} - \theta_B m.$$

	$\mu\frac{\delta+m}{\mu+\delta} - \theta_B m < \widehat{H} < \widehat{K} < \mu\frac{\delta+m}{\mu+\delta}$	
condition	C feasibility	C stability
$\frac{\mu(\delta+m)}{\mu+\delta} - \theta_B m \leq \beta < \widehat{H}$	(A.8)	(A.11)
$\widehat{H} < \beta < \widehat{K}$	(A.8)	(A.11), (A.12)
$\widehat{K} < \beta < \frac{\mu(\delta+m)}{\mu+\delta}$	(A.8)	(A.12)
$\beta \geq \frac{\mu(\delta+m)}{\mu+\delta}$	—	(A.12)

Table A.4: Case 3 for equilibrium C of model (4).

	$\widehat{H} < \mu\frac{\delta+m}{\mu+\delta} - \theta_B m < \mu\frac{\delta+m}{\mu+\delta} < \widehat{K}$	
condition	C feasibility	C stability
$\frac{\mu(\delta+m)}{\mu+\delta} - \theta_B m \leq \beta < \frac{\mu(\delta+m)}{\mu+\delta}$	(A.8)	(A.11), (A.12)
$\frac{\mu(\delta+m)}{\mu+\delta} \leq \beta < \widehat{K}$	—	(A.11), (A.12)
$\beta > \widehat{K}$	—	(A.12)

Table A.5: Case 4 for equilibrium C of model (4).

Thus we are in the above Case 4.

Stability of D

Now we consider the equilibrium of coexistence, $D = (i_a^D, i_s^D, y^D)$. The study of the Jacobian matrix of the system does not allow either to find the

	$\mu\frac{\delta+m}{\mu+\delta} - \theta_B m < \widehat{H} < \mu\frac{\delta+m}{\mu+\delta} < \widehat{K}$	
condition	C feasibility	C stability
$\frac{\mu(\delta+m)}{\mu+\delta} - \theta_B m \leq \beta < \widehat{H}$	(A.8)	(A.11)
$\widehat{H} < \beta < \frac{\mu(\delta+m)}{\mu+\delta}$	—	(A.11), (A.12)
$\frac{\mu(\delta+m)}{\mu+\delta} < \beta < \widehat{K}$	—	(A.12)
$\beta > \widehat{K}$	—	(A.12)

Table A.6: Case 5 for equilibrium C of model (4).

	$\mu\frac{\delta+m}{\mu+\delta} - \theta_B m < \mu\frac{\delta+m}{\mu+\delta} < \widehat{H} < \widehat{K}$	
condition	C feasibility	C stability
$\frac{\mu(\delta+m)}{\mu+\delta} - \theta_B m \leq \beta < \frac{\mu(\delta+m)}{\mu+\delta}$	(A.8)	(A.11)
$\frac{\mu(\delta+m)}{\mu+\delta} < \beta < \widehat{H}$	—	(A.11)
$\widehat{H} < \beta < \widehat{K}$	—	(A.11), (A.12)
$\beta > \widehat{K}$	—	(A.12)

Table A.7: Case 6 for equilibrium C of model (4).

eigenvalues of the matrix, or to use the Routh Hurwitz criterion because the calculations are too complex. This coexistence equilibrium can therefore only be analyzed numerically.

In figures A.5 and A.6 we represent the trend of the three populations, $i_a(t)$, $i_s(t)$ and $y(t)$ with respect to the variations of β and γ, for $m = 0.1$, $\mu = 0.9$, θ_B and θ_E both equal to 0.8 and two different values of δ.

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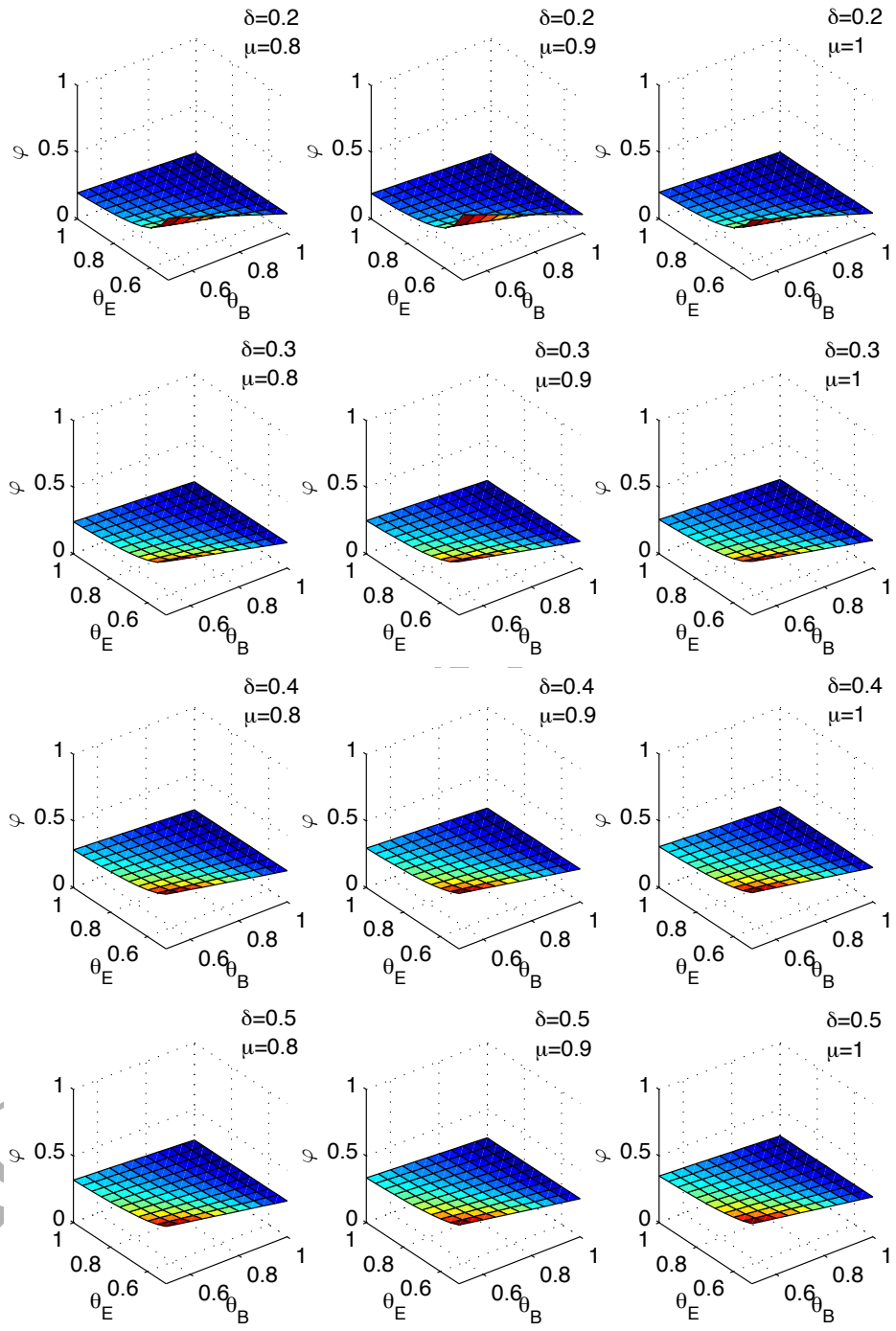

Figure 2: Estimate of the quantity φ as a function of θ_B and θ_E for $m = 0.1$ and different values of δ and μ.

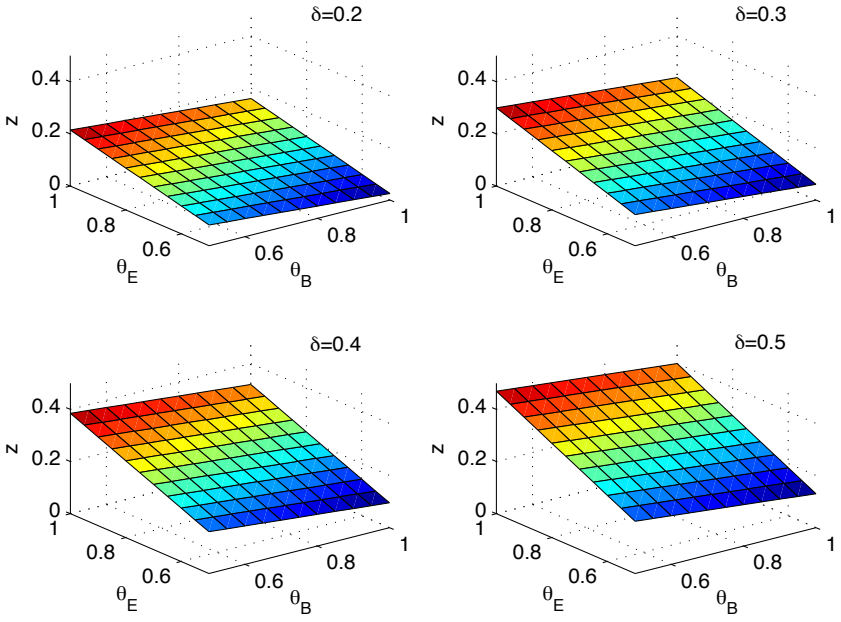

Figure A.3: Surface of equation $z = \mu\theta_E(\delta + m) - m(\mu + \delta) = 0$ as function of θ_B and θ_E for $m = 0.1$, $\mu = 0.9$ and different values of δ.

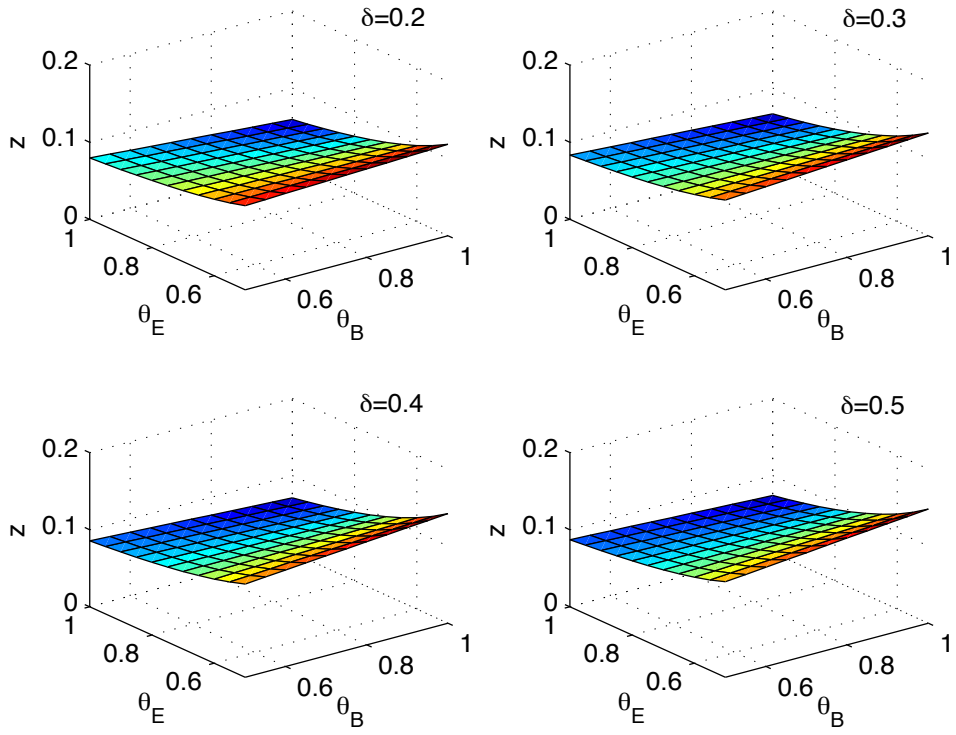

Figure A.4: Surface of equation $z = \dfrac{\mu(\delta + m)}{\mu + \delta} - \theta_B m - \widehat{H}$ as function of θ_B and θ_E, for $m = 0.1$, $\mu = 0.9$ and several values of δ.

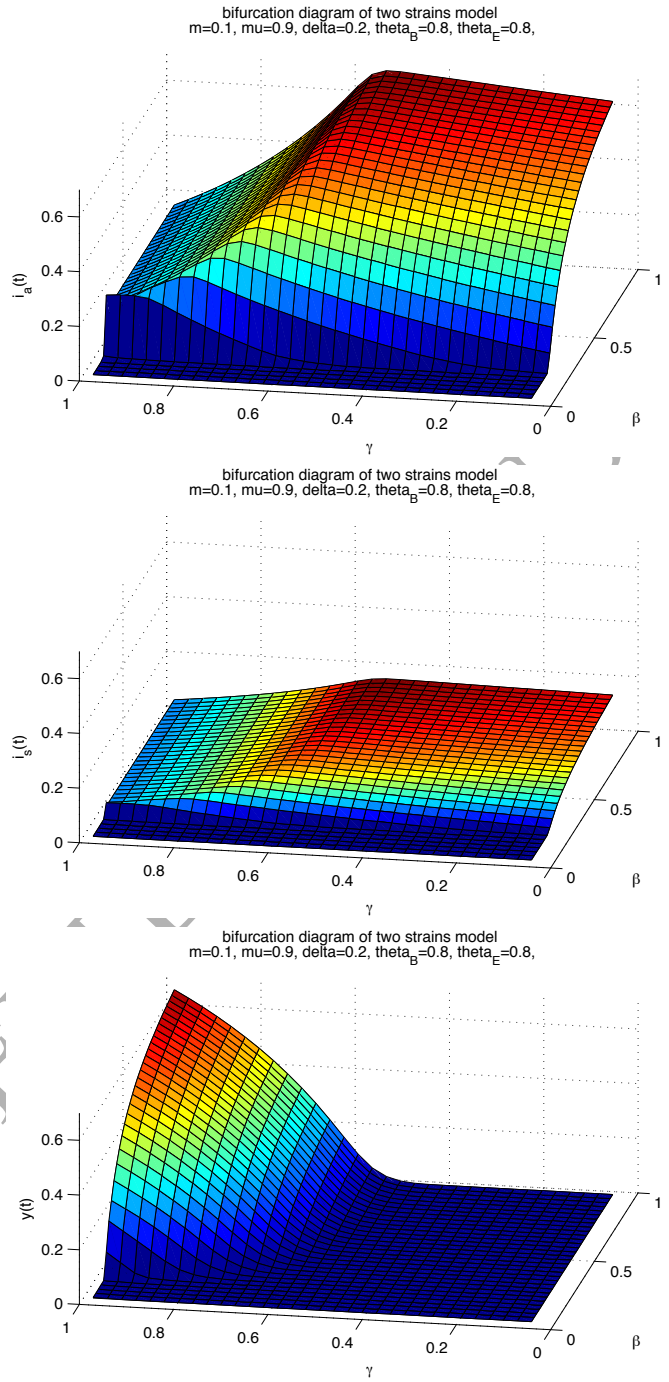

Figure A.5: Trend of the three populations, $i_a(t)$, $i_s(t)$ and $y(t)$ as functions of β and γ, for $\delta = 0.2$.

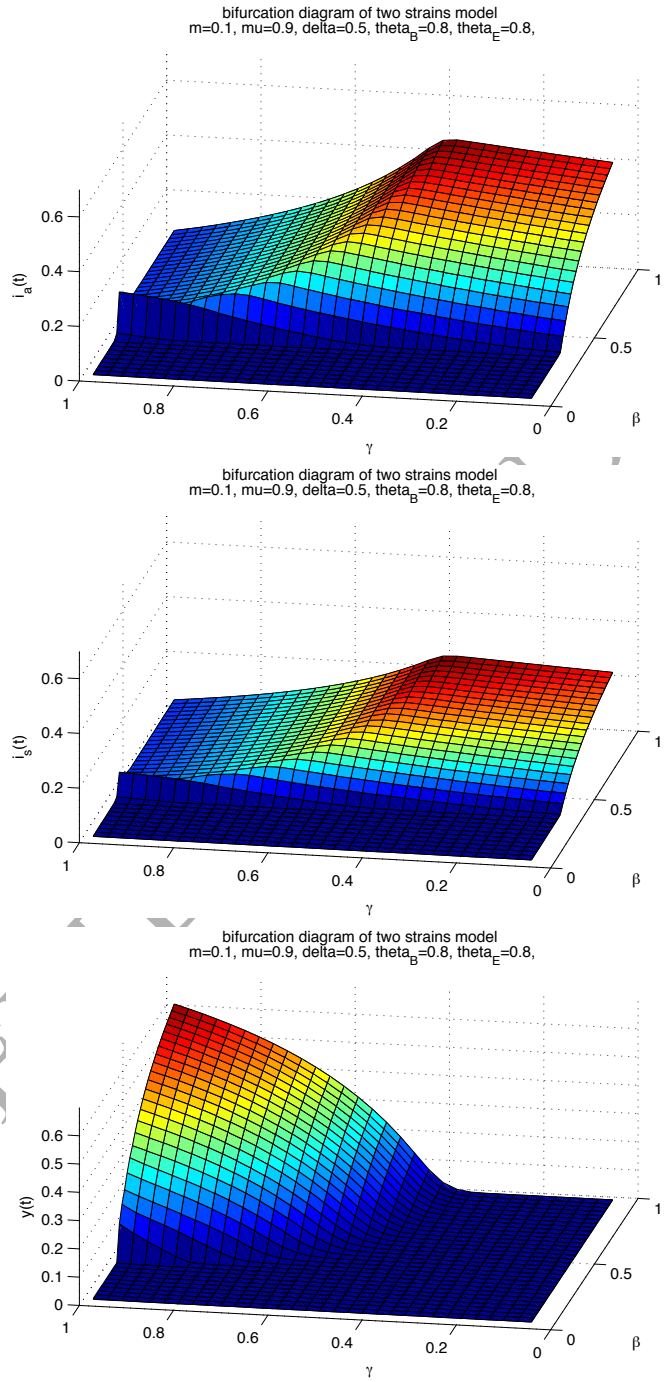

Figure A.6: Trend of the three populations, $i_a(t)$, $i_s(t)$ and $y(t)$ as functions of β and γ, for $\delta = 0.5$.