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Behavioral modulation of the coexistence between *Apis mellifera* and *Varroa destructor*: A defense against colony collapse disorder?

Joyce de Figueiró Santos · Flávio Codeço Coelho · Pierre Alexandre Bliman

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Abstract Colony Collapse Disorder has become a global problem for beekeepers and for the crops which depend on bee polination. Multiple factors are known to increase the risk of colony collapse, and the ectoparasitic mite *Varroa destructor* that parasitize honey bees is among the main threats to colony health. Although this mite is unlikely to, by itself, cause the collapse of hives, it plays an important role as it is a vector for many viral diseases. Such diseases are among the likely causes for Colony Collapse Disorder.

The effects of *V. destructor* infestation are disparate in different parts of the world. Greater morbidity - in the form of colony losses - has been reported in colonies of European honey bees (EHB) in Europe, Asia and North America. However, this mite has been present in Brasil for many years and yet there are no reports of Africanized honey bee (AHB) colonies losses.

Studies carried out in Mexico showed that some resistance behaviors to the mite - especially grooming and hygienic behavior - appear to be different in each subspecies. Could those difference in behaviors explain why the AHB are less susceptible to Colony Collapse Disorder?

In order to answer this question, we propose a mathematical model of the coexistence dynamics of these two species, the bee and the mite, to analyze the role of resistance behaviors in the overall health of the colony, and, as a consequence, its ability to face epidemiological challenges.

Keywords Honeybees · Colony Collapse Disorder · *Varroa destructor* · basic reproduction number

1 Introduction

Since 2007 American beekeepers reported heavier and widespread losses of bee colonies. And this go beyond American borders - many Europeans beekeepers

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complain of the same problem. This mysterious phenomenon was called "Colony Collapse Disorder" (CCD) - the official description of a syndrome in which many bee colonies died in the winter and spring of 2006-2007. Diseases and parasites, in-hive chemicals, agricultural insecticides, genetically modified crops, changed cultural practices and cool brood are pointed as some of the possible causes for CCD (Oldroyd, 2007).

The ectoparasitic mite *Varroa destructor* that parasitize honey bees has become a global problem and is considered as one of the important burdens on bee colonies and a cause for CCD. The Varroa mite is suspected of having caused the collapse of millions of *Apis mellifera* honey bee colonies worldwide. However, the effects caused by *V. destructor* infestation vary in different parts of the world. More intense losses have been reported in European honey bee colonies (EHB) of Europe, Asia and North America (Caldern et al, 2010).

The life cycle of *V. destructor* is tightly linked with the bee's. Immature mites develop together with immature bees, parasitizing them from an early stage. The mite's egg-laying behavior is coupled with the bee's and thus depend on the bee's reproductive cycle. Since worker brood rearing and thus Varroa reproduction occurs all year round in tropical climates, it could be expected that the impact of the parasite would be even worse in tropical regions. But *Varroa destructor* has been present in Brazil for more than 30 years and yet no collapses due to this mite, have been recorded (Carneiro et al, 2007). It is worth noting that the dominant variety of bees in Brazil is the Africanized honey bee (AHB) which since its introduction in 1956, has spread to the entire country (Pinto et al, 2012).

African bees and their hybrids are more resistant to the mite *V. destructor* than European bee subspecies (Medina and Martin, 1999; Pinto et al, 2012). A review by Arechavaleta-Velasco and Guzman-Novoa (2001) in Mexico showed that EHB was twice as attractive to *V. destructor* than AHB. The removal of naturally infested brood, which is termed hygienic behavior, was reported as four times higher in AHB than in EHB, and AHB workers were more efficient in grooming mites from their bodies.

These behaviors are important factors in keeping the mites infestation low in the honey bee colonies.

1.1 Resistance behaviors of the bee against the parasite

Two main resistance behaviors, namely grooming and hygienic behavior (Spivak, 1996), are mechanisms employed by the honey bees to control parasitism in the hive.

The grooming behavior is when a worker bee is able to groom herself with her legs and mandibles to remove the mite and then injure or kill it. (Vandame et al, 2000).

Hygienic behavior is a mechanism through which worker bee broods are uncapped leading to the death of the pupae. This behavior is believed to confer resistance to Varroa infestation since worker bees are more likely to uncap an infested brood, than an uninfested one. It has been demonstrated that the smell of the mite by itself is capable of activating this behavior. (Corra-Marques et al, 1998).

The hygienic behavior serves to combat other illnesses or parasitism to which the brood is susceptible. It is also not a completely accurate mechanism. Correa-Marques and De Jong (1998), report that the majority (53%) of the uncapped cells display no signs of parasitism or other abnormality which would justify the killing of the brood. Thus, in our model we define two parameters for the hygienic behavior: H_g , for the generic hygienic behavior, which may kill uninfested pupae, and h for the success rate in uncapping infested brood cells.

Africanized honey bees have been shown to be more competent in hygienic behavior than European honey bees. Vandame et al (2000) found in Mexico that the EHB are able to remove just 8% of infested brood while AHB removed up 32.5%.

The main goal of this paper is to propose a model capable of describing the dynamics of infestation by *Varroa* sp. in bee colonies taking into consideration bee's resistance mechanisms to mite infestation – grooming and hygienic behavior. In addition, through simulations, we show how the resistance behaviors contribute to the reduction infestation levels and may even lead to the complete elimination of the parasite from the colony.

2 Mathematical model

Previous work by Ratti et al (2012) models the population dynamics of bee and mites together with the acute bee paralysis virus. Here we focus solely on the host-parasite interactions trying to understand the resilience of colonies in Brasil and the role of the more efficient resistance behaviors displayed by AHB to explain the lower infestation rates and incidence of collapses in their colonies.

Vandame et al (2002) discusses the cost-benefit of resistance mechanism of bee against mite. The *grooming* behavior performed by adult bees, includes detecting and eliminating mites from their own body (auto-grooming) or from the body of another bee (allo-grooming). The hygienic behavior occurs when adult bees detect the presence of the mite offspring still in the cells and in order to prevent the mites from spreading in the colony, the worker bees kill the infested brood. Their study compared the results for two subspecies of bees - Africanized and European - to examine whether these two mechanisms could explain the observed low compatibility between Africanized bees and the mite *Varroa destructor*, in Mexico. The results showed that *grooming* and hygienic behavior appears most intense in Africanized bees than in European bees.

The model proposed is shown in the diagram of figure 1, and detailed in the system of differential equations below:

$$\begin{aligned}
 \dot{I} &= \pi \frac{A}{A + A_i} - \delta I - HI \\
 \dot{I}_i &= \pi \frac{A_i}{A + A_i} - \delta I_i - H_i I_i \\
 \dot{A} &= \delta I + g A_i - \mu A \\
 \dot{A}_i &= \delta I_i - g A_i - (\mu + \gamma) A_i
 \end{aligned} \tag{1}$$

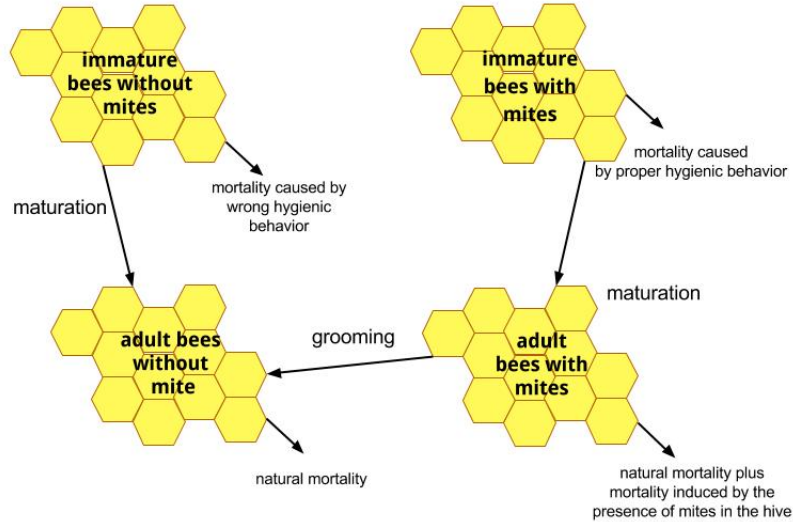


Fig. 1 Diagram to describes the dynamics of the model.

In the proposed model, I , I_i , A and A_i represent the non-infested immature bees, infested immature bees, non-infested adult worker bees and infested adult worker bees, respectively.

Daily birth rate for bees is denoted by π , δ is the maturation rate, i.e., the inverse of number of days an immature bee requires to turn in adult, this rate is the same for both infested and non-infested immature bees. μ is the mortality rate for adult bees, γ is the mortality rate induced by the presence of mites in the colony bees. The parameters H_i , H e g are the rate of removal of infested pupae via hygienic behavior, the general hygienic rate (affecting uninfested pupae) and grooming rate, respectively.

Table 1 Parameters of the model.

Parameters	Meaning	Value	Unit	Reference
π	Bee daily birth rate	2500	$bees \times day^{-1}$	Pereira et al, 2002
δ	Maturation rate	0.05	day^{-1}	Pereira et al, 2002
H	Generic hygienic behavior	-	day^{-1}	-
H_i	Hygienic behavior towards infested brood	-	day^{-1}	-
g	<i>Grooming</i>	-	day^{-1}	-
μ	Mortality rate	0.04	day^{-1}	(Khoury et al, 2011)
γ	Mite inducing mortality	10^{-7}	day^{-1}	(Ratti et al, 2012)

Choosing parameters

Some of the parameters associated with the bees life cycle, used for the simulations, can be found in the literature, as shown in table 1. For the resistance behavior parameters, very little information is available. Therefore we decided to study the variation of these parameters within ranges which allowed for the system to switch between a mite-free equilibrium to one of coexistence. These ranges also reflected observations described in the literature (Mondragn et al, 2005; Vandame et al, 2002; Arechavaleta-Velasco and Guzman-Novoa, 2001).

Table 2 Varying the parameters

Parameter	Maximum value	Minimum value
g	0.01	0.1
H_i	0.08	0.4
H	0.04	0.2

The three unknown parameters representing resistance behaviors g , H_i , H – grooming, proper hygienic behavior and wrong hygienic behavior – were studied with respect to the existence of a coexistence equilibrium.

3 Results

In order to understand the dynamics of the proposed model of mite infestation of bee colonies, we proceed to analyze it.

3.1 Basic reproduction number of the infested bees

An effective way to look at boundary beyond which coexistence of mites and bees is possible, is to look at the R_0 of infestation. For our model, the basic reproduction number, or R_0 of infested bees, can be thought of as the number of new infestations that one infested bee when introduced into the colony generates on average over the course of its infestation period or while it is not groomed, in an otherwise uninfested population.

Deriving \mathcal{R}_i using the next generation method To calculate the basic reproduction number of infested bees, we will use the next-generation matrix (Van den Driessche and Watmough, 2002), where the whole population is divided into n compartments in which there are $m < n$ infested compartments.

In this method, \mathcal{R}_i is defined as the spectral radius, or the largest eigenvalue, of the next generation matrix.

Let x_i , $i = 1, 2, \dots, m$ be the number or proportion of individuals in the i th compartment. Then

$$\frac{dx_i}{dt} = \mathcal{F}_i(x) - \mathcal{V}_i(x)$$

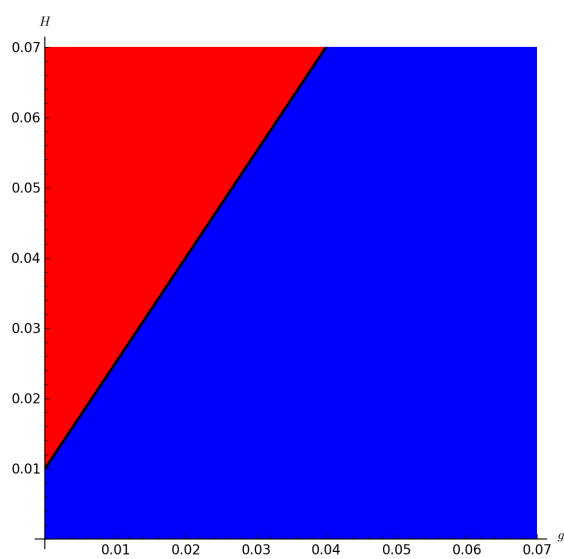


Fig. 2 plot of values of \mathcal{R}_0 for a range of values of g and H . $H_i = 0.01$ and remaining parameters set as described in table 1. The region in red corresponds to $\mathcal{R}_0 > 1$, the black line to $\mathcal{R}_0 = 0$ and the blue region otherwise.

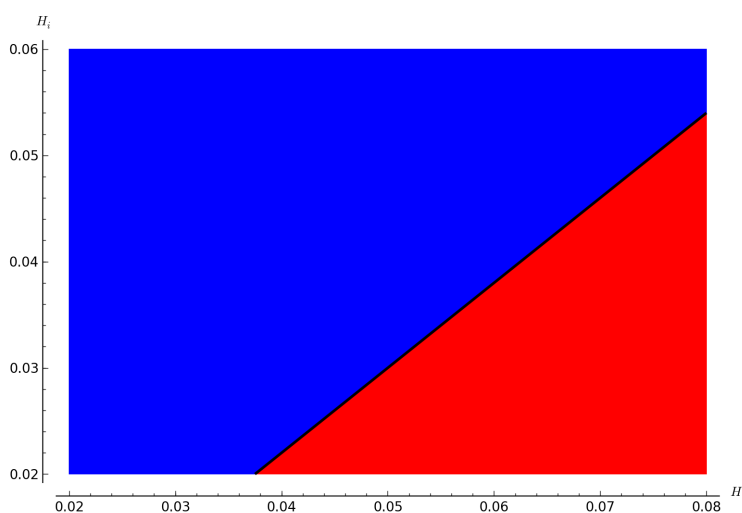


Fig. 3 Values of \mathcal{R}_0 for various combinations of H_i and H . $g = 0.01$ and other parameters as given in table 1. The region in red corresponds to $\mathcal{R}_0 > 1$, the black line to $\mathcal{R}_0 = 0$ and the blue region otherwise. This figure illustrates one of the conditions for coexistence (given other parameters values fixed as in table 1) that H must be larger than H_i .

Where $\mathcal{F}_i(x)$ is the rate of appearance of new infections in compartment i and $\mathcal{V}_i(x) = \mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)$. Where \mathcal{V}_i^- is the rate of transfer of individuals out of the i th compartment and \mathcal{V}_i^+ represents the rate of transfer of individuals into compartment i by all other means.

The next generation matrix is defined by FV^{-1} , where F and V can be formed by the partial derivatives of \mathcal{F}_i and \mathcal{V}_i .

$$F = \left[\frac{\partial \mathcal{F}_i(x_0)}{\partial x_j} \right] \text{ and } V = \left[\frac{\partial \mathcal{V}_i(x_0)}{\partial x_j} \right]$$

where x_0 is the mite free equilibrium.

In our model, $m = 2$ and the infested compartments are:

$$\begin{aligned} \frac{dI_i}{dt} &= \pi \frac{Ai}{A + Ai} - \delta I_i - HI_i \\ \frac{dAi}{dt} &= \delta I_i - gAi - (\mu + \gamma)Ai \end{aligned} \quad (2)$$

Now we write the matrices F and V , substituting the mite-free equilibrium values, $A^* = \frac{\delta\pi}{\mu(\delta+H)}$ and $A_i^* = 0$.

$$F = \begin{bmatrix} 0 & \frac{\mu(\delta+H)}{\delta} \\ 0 & 0 \end{bmatrix}$$

$$V = \begin{bmatrix} \delta + H_i & 0 \\ -\delta & g + \gamma + \mu \end{bmatrix}$$

Let the next-generation matrix G be the matrix product FV^{-1} . Then

$$G = \begin{bmatrix} \frac{\mu(\delta+H)}{(\delta+H_i)(g+\gamma+\mu)} & \frac{\mu(\delta+H)}{\delta(g+\gamma+\mu)} \\ 0 & 0 \end{bmatrix}$$

Now we can find the basic reproduction number, R_0 , which is the largest eigenvalue of the matrix G .

$$R_0 = \frac{\mu(\delta+H)}{(\delta+H_i)(g+\gamma+\mu)} \quad (3)$$

Figures 2, 3 and 4 shows the boundary between mite-free (blue region, $\mathcal{R}_0 < 1$) and coexistence equilibria (red region, $\mathcal{R}_0 > 1$).

3.2 Well-Posed and Boundedness

For sake of simplicity, we denote

$$\alpha \doteq \delta + H, \quad \alpha_i \doteq \delta + H_i, \quad \mu_i \doteq \mu + \gamma \quad (4)$$

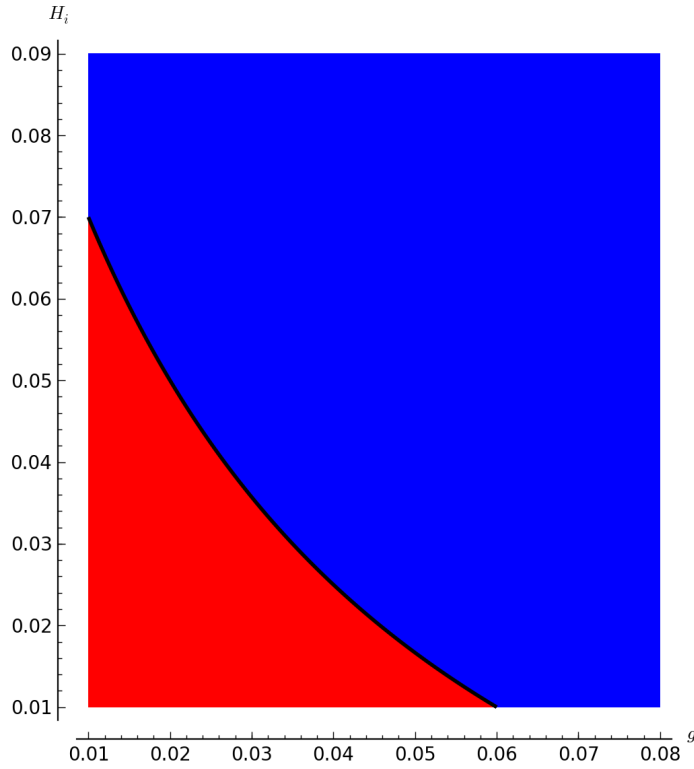


Fig. 4 Implicit plot for \mathcal{R}_0 letting g and H_i vary. Using the values for parameters π , δ , μ and γ from table 1 The red region represent $\mathcal{R}_0 > 1$ which means that for these combination of g and H_i the mite will stay in the colony. On the other hand, the blue region represents $\mathcal{R}_0 < 1$ which means that for these these combination of g and H_i the mites will be eliminated.

in such a way that the system under study rewrites

$$\dot{I} = \pi \frac{A}{A + A_i} - \alpha I \quad (5a)$$

$$\dot{A} = \delta I - \mu A + g A_i \quad (5b)$$

$$\dot{I}_i = \pi \frac{A_i}{A + A_i} - \alpha_i I_i \quad (5c)$$

$$\dot{A}_i = \delta I_i - (\mu_i + g) A_i \quad (5d)$$

We assume that all the coefficients involved are positive, that is:

$$\pi, \delta, \mu > 0, \quad \alpha, \alpha_i > \delta, \quad \mu_i > \mu. \quad (6)$$

The previous system of equations is written

$$\dot{X} = f(X), \quad X = (I, A, I_i, A_i) \quad (7)$$

The right-hand side of (7) is not properly defined in the points where $A + A_i = 0$. However, the following result demonstrates that this has no consequence on the

solutions, as the latter stays away from this part of the subspace. For subsequent use, we denote \mathcal{D} the subset of those elements $X = (I, A, I_i, A_i) \in \mathbb{R}_+^4$ such that $A + A_i \neq 0$.

Theorem 1 (Well-posedness and boundedness). *If $X_0 \in \mathcal{D}$, then there exists a unique solution of (7) defined on $[0, +\infty)$ such that $X(0) = X_0$. Moreover, for any $t > 0$, $X(t) \in \mathcal{D}$, and*

$$\frac{\pi}{\alpha_{\max}} \leq \liminf_{t \rightarrow +\infty} (I(t) + I_i(t)) \leq \limsup_{t \rightarrow +\infty} (I(t) + I_i(t)) \leq \frac{\pi}{\alpha_{\min}} \quad (8a)$$

$$\frac{\delta\pi}{\mu_i\alpha_{\max}} \leq \liminf_{t \rightarrow +\infty} (A(t) + A_i(t)) \leq \limsup_{t \rightarrow +\infty} (A(t) + A_i(t)) \leq \frac{\delta\pi}{\mu\alpha_{\min}} \quad (8b)$$

where by definition $\alpha_{\min} \doteq \min\{\alpha; \alpha_i\}$, $\alpha_{\max} \doteq \max\{\alpha; \alpha_i\}$. Also,

$$\frac{1}{(\alpha - \alpha_{\min})\mu + \alpha g} \frac{\pi g \mu \alpha_{\min}}{\mu_i \alpha_{\max}} \leq \liminf_{t \rightarrow +\infty} I(t), \quad \frac{1}{(\alpha - \alpha_{\min})\mu + \alpha g} \frac{\delta\pi g \alpha}{\mu_i \alpha_{\max}} \leq \liminf_{t \rightarrow +\infty} A(t) \quad (9)$$

and

$$(I_i(0), A_i(0)) \neq (0, 0) \Rightarrow \forall t \geq 0, I_i(t) > 0, A_i(t) > 0 \quad (10)$$

Define \mathcal{D}' as the largest set included in \mathcal{D} and fulfilling the inequalities of Theorem 1, that is:

$$\mathcal{D}' \doteq \left\{ (I, A, I_i, A_i) \in \mathbb{R}_+^4 : \frac{\pi g \mu \alpha_{\min}}{\mu_i \alpha_{\max}} \leq I, \frac{\delta\pi g \alpha}{\mu_i \alpha_{\max}} \leq A, \frac{\pi}{\alpha_{\max}} \leq I + I_i \leq \frac{\pi}{\alpha_{\min}}, \frac{\delta\pi}{\mu_i \alpha_{\max}} \leq A + A_i \leq \frac{\delta\pi}{\mu \alpha_{\min}} \right\}. \quad (11)$$

Theorem 1 shows that the compact set \mathcal{D}' is positively invariant and attracts all the trajectories. Therefore, in order to study the asymptotics of system (5), it is sufficient to consider the trajectories of (5) that are in \mathcal{D}' .

3.3 Equilibria

Theorem 2 (Equilibria and asymptotic behavior). *Define*

$$\beta \doteq \frac{\mu}{\alpha_i} - \frac{\mu_i + g}{\alpha} \quad (12)$$

• If $\beta \leq 0$, then there exists a unique equilibrium point of system (7) in \mathcal{D}' , that corresponds to a mite-free situation. It is globally asymptotically stable, and given by

$$X_{MF} = \frac{\pi}{\alpha} \begin{pmatrix} 1 \\ \frac{\delta}{\mu} \\ 0 \\ 0 \end{pmatrix}. \quad (13)$$

- If on the contrary $\beta > \frac{1}{\alpha_i}$, then there exists two equilibrium points in \mathcal{D}' , namely X_{MF} and a coexistence equilibrium defined by

$$X_{CO} = \frac{\delta \pi g}{\alpha_i(\mu_i + g)} \frac{\alpha \mu - \alpha_i(\mu_i + g)}{\alpha(\mu + g) - \alpha_i(\mu_i + g)} \begin{pmatrix} \frac{1}{\delta} \frac{\alpha_i(\mu_i + g)}{\alpha \mu - \alpha_i(\mu_i + g)} \\ \frac{\alpha}{\alpha \mu - \alpha_i(\mu_i + g)} \\ \frac{\mu_i + g}{\delta g} \\ \frac{1}{g} \end{pmatrix}. \quad (14)$$

Moreover, for all initial conditions in \mathcal{D}' except in a zero measure set, the trajectories tend towards X_{CO} .

Recall that $\mathcal{R}_0 = \frac{\alpha \mu}{\alpha_i(\mu_i + g)}$, in such a way that

$$\beta > 0 \Leftrightarrow \mathcal{R}_0 > 1. \quad (15)$$

Theorem 3. *Being $\mathcal{R}_0 = 1$ a bifurcation point by definition, leading the system through a transcritical bifurcation as it gets larger than 1, $\beta = 0$ is also a bifurcation point. Thus, to the right of the point $\beta = 0$ we must find two equilibria, one mite-free (unstable) and another of coexistence which is stable.*

Proof. When $\beta = 0$,

$$\begin{aligned} \frac{\mu}{\alpha_i} &= \frac{\mu_i + g}{\alpha} \\ \frac{\alpha \mu}{\alpha_i(\mu_i + g)} &= 1 \\ \mathcal{R}_0 &= 1 \end{aligned} \quad (16)$$

from 16, we can find a value for α which we will use as a bifurcation parameter: $\alpha = \frac{\alpha_i(\mu_i + g)}{\mu} \approx 0.125$, after substituting the parameter values.

If we solve numerically the system from 5, we confirm the existence of two equilibria when α crosses the bifurcation value of 0.125. The instability and stability of the mite-free and coexistence equilibria, respectively is shown in the simulation of figure 6. \square

Figures 6 and 7 show simulations representing the coexistence and mite-free equilibria, respectively.

4 Discussion and Conclusions

Coexistence of bees and Varroa mites in nature is an undeniable fact. However, this coexistence is fraught with dangers for the bees, since Varroa mites can be vectors of lethal viral diseases. These deleterious effects for the health of the individual workers and the whole colony, has led to the evolution of resistance behaviors such as the higienic behaviour and grooming.

Those behaviors are not entirely without cost to the bees, exarcebated higienic behavior – when both H and H_i are intensified – can exert a substantial toll on the fitness of the queen. So it is safe to say that this parasitic relationship has evolved within a vary narrow range of parameters. Even if the mite-free equilibrium is advantageous to the colony, maintaining it may be too expensive to the bees.

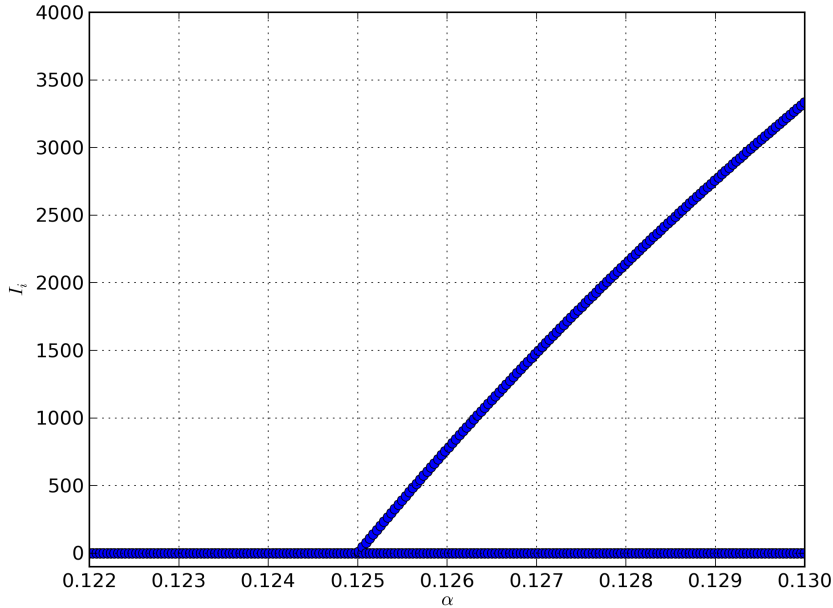


Fig. 5 Bifurcation diagram showing the transcritical bifurcation with bifurcation point corresponding to $\alpha \approx 0.125$ ($\beta = 0$, $\mathcal{R}_0 = 1$). Blue dots correspond to the equilibrium values of I_i

[we need some discussion regarding the conditions for stability of X_{MF} , or the invasibility of the colony by mites]

On the other hand, in the absence of viral diseases, mite parasitism seem to be fairly harmless. If we look at the expression for the R_0 of infestation (3), we can see that the mite-induced bee mortality, γ , (not by viral diseases), must be kept low or risk destabilizing the co-existence equilibrium.

Africanized Honey bees, having evolved more effective resistance behaviors, are more resistant to CCD by their ability to keep infestation levels lower than those of their european counterparts (Moretto et al, 1991, 1993). Unfortunately, the lack of more detailed experiments measuring the rates of grooming and higienic behaviors in both groups (EHB and AHB), it is hard to position them accurately in the parameter space of the model presented.

Finally, we hope that the model presented here along with its demonstrated dynamical properties will serve as a solid foundation for the development of other models including viral dynamics and other aspects of bee colony health.

5 Appendix – Proofs of the theorems

Proof of Theorem 1. • Clearly, the right-hand side of the system of equations is globally Lipschitz on any subset of \mathcal{D} where $A + A_i$ is bounded away from zero. The

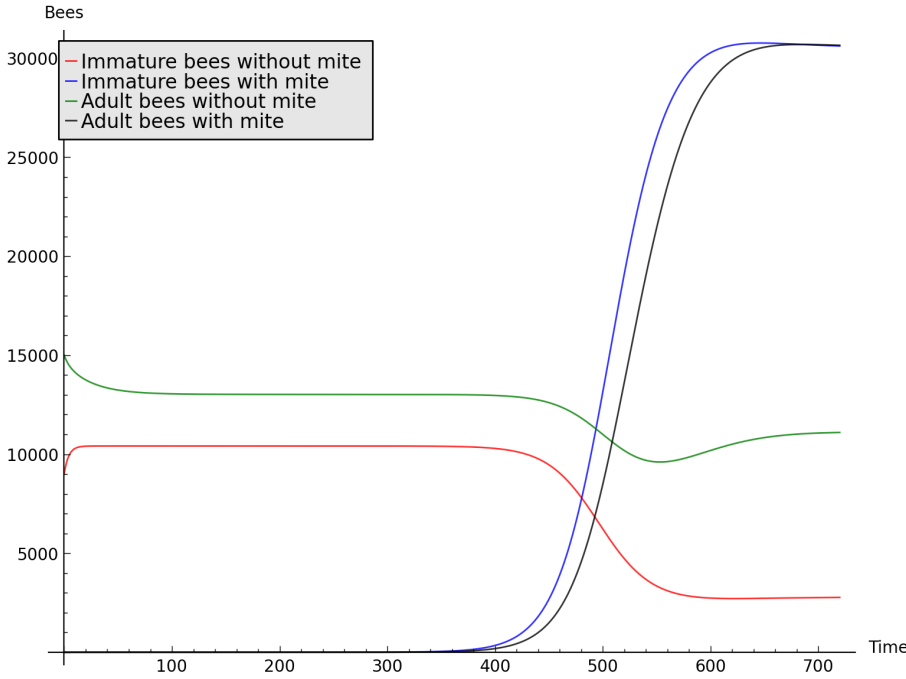


Fig. 6 Simulation showing the infestation of a colony, by a single infested adult bee, with parameters giving $R_0 \approx 1.33$. Initial conditions: $I = 5000$, $I_i = 0$, $A = 20000$, $A_i = 0$ and parameters $g = 0.01$, $H_i = 0.1$, $\mu = 0.04$, $\delta = 0.05$, $\gamma = 10^{-7}$ and $H = 0.19$. On time $t = 100$, a single infested adult bee is introduced into the colony. For this simulation, $\beta = 0.375$ and $\mathcal{R}_0 \approx 3.199$

existence and uniqueness of the solution of system (5) is then obtained for each trajectory staying at finite distance of this boundary. We will show that the two formulas provided in the statement are valid for each trajectory departing initially from a point where $A + A_i \neq 0$. As a consequence, the fact that all trajectories are defined on infinite horizon will ensue.

- Summing up the first two equations in (5) yields, for any point inside \mathcal{D} :

$$\dot{I} + \dot{I}_i = \pi - \alpha I - \alpha_i I_i \geq \pi - \alpha_{\max}(I + I_i). \quad (17)$$

Integrating this differential inequality between any two points $X(0) = X_0$ and $X(t)$ of a trajectory for which $X(\tau) \in \mathcal{D}$, $\tau \in [0; t]$, one gets

$$I(t) + I_i(t) \geq \frac{\pi}{\alpha_{\max}} \left(1 - e^{-\alpha_{\max} t}\right) + (I(0) + I_i(0))e^{-\alpha_{\max} t}, \quad (18)$$

where the right-hand side is in any case positive for any $t > 0$.

Similarly, one has

$$\dot{I} + \dot{I}_i \leq \pi - \alpha_{\min}(I + I_i), \quad (19)$$

and therefore

$$I(t) + I_i(t) \leq \frac{\pi}{\alpha_{\min}} \left(1 - e^{-\alpha_{\min} t}\right) + (I(0) + I_i(0))e^{-\alpha_{\min} t}. \quad (20)$$

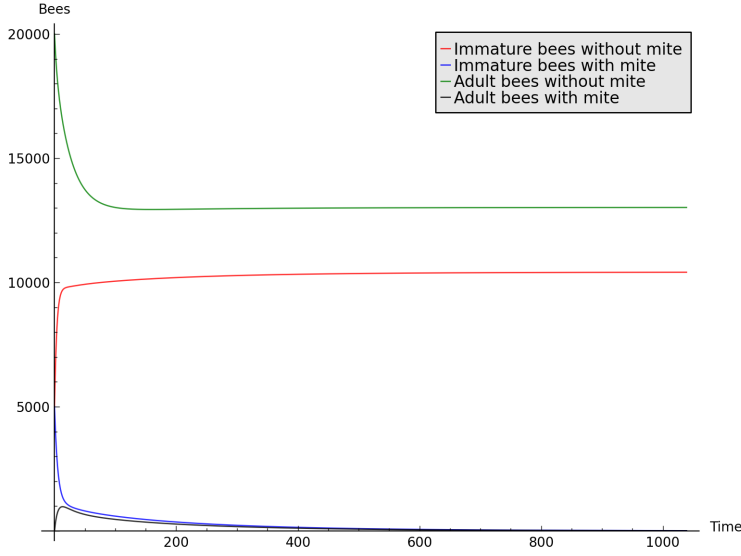


Fig. 7 Simulation showing the elimination of the mites from a colony, by a single infested adult bee, when $R_0 < 1$. Initial conditions: $I = 5000$, $I_i = 5000$, $A = 20000$, $A_i = 1$ and parameters $g = 0.01$, $H_i = 0.1$, $\mu = 0.05$, $\delta = 0.05$, $\gamma = 10^{-7}$ and $H = 0.19$.

This proves in particular that the inequalities in (8a) hold for any portion of trajectory remaining inside \mathcal{D} .

We now consider the evolution of A, A_i . Similarly to what was done for I, I_i , one has

$$\dot{A} + \dot{A}_i = \delta(I + I_i) - \mu A - \mu_i A_i \geq \delta(I + I_i) - \mu_i(A + A_i) \quad (21)$$

Therefore,

$$A(t) + A_i(t) \geq (A(0) + A_i(0))e^{-\mu_i t} + \delta \int_0^t (I(\tau) + I_i(\tau))e^{-\mu_i(t-\tau)} d\tau. \quad (22)$$

Integrating the lower bound of $I + I_i$ extracted from (18) yields the conclusion that any solution departing from \mathcal{D} indeed remains in \mathcal{D} as long as it is defined. On the other hand, we saw previously that trajectories remaining in \mathcal{D} could be extended on the whole semi-axis $[0, +\infty)$. Therefore, any trajectory departing from a point in \mathcal{D} can be extended to $[0, +\infty)$, and remains in \mathcal{D} for any $t > 0$. In particular, (8a) holds for any trajectory departing inside \mathcal{D} .

Let us now achieve the proof by bounding $A + A_i$ from above. One has

$$\dot{A} + \dot{A}_i \leq \delta(I + I_i) - \mu(A + A_i) \quad (23)$$

and thus

$$A(t) + A_i(t) \leq (A(0) + A_i(0))e^{-\mu t} + \delta \int_0^t (I(\tau) + I_i(\tau))e^{-\mu(t-\tau)} d\tau. \quad (24)$$

Using (20) then permits to achieve the proof of (8b), and finally the proof of (8).

• Let us now prove (9). One deduces from (5a) and (5b) and the bounds established earlier the differential inequalities

$$\dot{I} \geq \frac{\pi}{\limsup(A + A_i)} A - \alpha I \geq \frac{\mu\alpha_{\min}}{\delta} A - \alpha I, \quad (25a)$$

$$\dot{A} \geq \delta I - \mu A + g(\liminf(A + A_i) - A) \geq \delta I - (\mu + g)A + \frac{\delta\pi g}{\mu_i\alpha_{\max}} \quad (25b)$$

The auxiliary linear time-invariant system

$$\frac{d}{dt} \begin{pmatrix} I' \\ A' \end{pmatrix} = \begin{pmatrix} -\alpha & \frac{\mu\alpha_{\min}}{\delta} \\ \delta & -(\mu + g) \end{pmatrix} \begin{pmatrix} I' \\ A' \end{pmatrix} + \begin{pmatrix} 0 \\ \frac{\delta\pi g}{\mu_i\alpha_{\max}} \end{pmatrix} \quad (26)$$

is monotone, as the state matrix involved is a Metzler matrix (?). Moreover, it is asymptotically stable, as the associated characteristic polynomial is equal to

$$\left| \begin{matrix} s + \alpha & -\frac{\mu\alpha_{\min}}{\delta} \\ -\delta & s + \mu + g \end{matrix} \right| = s^2 + (\alpha + \mu + g)s + \alpha(\mu + g) - \mu\alpha_{\min}, \quad (27)$$

and thus Hurwitz because $\alpha(\mu + g) - \mu\alpha_{\min} = (\alpha - \alpha_{\min})\mu + \alpha g > 0$. Therefore, all trajectories of (26) tend towards the unique equilibrium:

$$\begin{aligned} \lim_{t \rightarrow +\infty} \begin{pmatrix} I'(t) \\ A'(t) \end{pmatrix} &= - \begin{pmatrix} -\alpha & \frac{\mu\alpha_{\min}}{\delta} \\ \delta & -(\mu + g) \end{pmatrix}^{-1} \begin{pmatrix} 0 \\ \frac{\delta\pi g}{\mu_i\alpha_{\max}} \end{pmatrix} \\ &= \frac{1}{(\alpha - \alpha_{\min})\mu + \alpha g} \begin{pmatrix} \mu + g & \frac{\mu\alpha_{\min}}{\delta} \\ \delta & \alpha \end{pmatrix} \begin{pmatrix} 0 \\ \frac{\delta\pi g}{\mu_i\alpha_{\max}} \end{pmatrix} \\ &= \frac{1}{(\alpha - \alpha_{\min})\mu + \alpha g} \begin{pmatrix} \frac{\pi g \mu \alpha_{\min}}{\mu_i \alpha_{\max}} \\ \frac{\delta \pi g \alpha}{\mu_i \alpha_{\max}} \end{pmatrix}. \end{aligned} \quad (28)$$

Invoking Kamke's Theorem, see e.g. (Coppel, 1965, Theorem 10, p. 29), one deduces from (25) and the monotony of (26) the following comparison result, that holds for all trajectories of (32):

$$\liminf_{t \rightarrow +\infty} \begin{pmatrix} I(t) \\ A(t) \end{pmatrix} \geq \frac{1}{(\alpha - \alpha_{\min})\mu + \alpha g} \begin{pmatrix} \frac{\pi g \mu \alpha_{\min}}{\mu_i \alpha_{\max}} \\ \frac{\delta \pi g \alpha}{\mu_i \alpha_{\max}} \end{pmatrix}. \quad (29)$$

This gives (9).

• One finally proves (10). Using (8b), identity (5c) implies

$$\dot{I}_i \geq \frac{\pi}{\limsup(A + A_i)} A_i - \alpha_i I_i \geq \frac{\mu\alpha_{\min}}{\delta} A_i - \alpha_i I_i \quad (30)$$

Joining this with (5d) and using Kamke's result as before, one deduces that both I_i and A_i have positive values when at least one of their two initial values are positive. This achieves the proof of Theorem 1. \square

Proof of Theorem 2. The proof is organized as follows.

1. We first write system (5) under the form of an I/O system, namely

$$\dot{I} = \pi \frac{A}{A + A_i} - \alpha I \quad (31a)$$

$$\dot{A} = \delta I - \mu A + u \quad (31b)$$

$$\dot{I}_i = \pi \frac{A_i}{A + A_i} - \alpha_i I_i \quad (31c)$$

$$\dot{A}_i = \delta I_i - (\mu_i + g) A_i \quad (31d)$$

$$y = g A_i \quad (31e)$$

where u , resp. y , is the input, resp. the output, closed by the unitary feedback

$$u = y . \quad (31f)$$

For subsequent use of the theory of monotone systems, one determines, for any (nonnegative) constant value of u , the equilibrium values of (I, A, I_i, A_i) for equation (31a)-(31d), and the corresponding values of y as given by (31e).

2. The equilibrium points of system (5) are then exactly (and easily) obtained by solving the fixed point problem $u = y$ among the solutions of the previous problem.

unique equilibrium points when $\beta \leq 0$, and there exist exactly two equilibrium points when $\beta > 0$. points.

3. One then shows that the I/O system $u \mapsto y$ defined by (31a)-(31e) is anti-monotone with respect to certain order relation, and the study of the stability of these equilibria shows that it admits single-valued I/S and I/O characteristics, as in (?).

4. Using this properties, the stability of the equilibria of the system obtained by closing the loop (31a)-(31e) by (31f) is then established using arguments similar to Angeli and Sontag (2003).

1. For fixed $u > 0$, the equilibrium equations of the I/O system (31) are given by

$$\pi \frac{A}{A + A_i} - \alpha I = 0 \quad (32a)$$

$$\delta I - \mu A + u = 0 \quad (32b)$$

$$\pi \frac{A_i}{A + A_i} - \alpha_i I_i = 0 \quad (32c)$$

$$\delta I_i - (\mu_i + g) A_i = 0 \quad (32d)$$

$$y = g A_i \quad (32e)$$

Summing up the first and third identities gives

$$\pi = \alpha I + \alpha_i I_i , \quad (33)$$

and thus necessarily:

$$\exists \lambda \in [0; 1], \quad I = \lambda \frac{\pi}{\alpha}, \quad I_i = (1 - \lambda) \frac{\pi}{\alpha_i} . \quad (34)$$

• The case $\lambda = 0$ yields $I = 0$, and then $A = 0$ by (32a), and therefore u has to be zero from (32b). Also, $I_i = \frac{\pi}{\alpha_i}$, $A_i = \frac{\delta \pi}{\alpha_i (\mu_i + g)}$ by (32d), and then

$y = gA_i = \frac{g\delta\pi}{\alpha_i(\mu_i+g)}$. in (11) and should be discarded. obtained point is located outside \mathcal{D} and has to be discarded; or

• The case $\lambda = 1$ yields $I_i = 0$, and then $A_i = 0$ by (32d) or (32c), and $y = 0$. There remains the two following conditions:

$$\pi = \alpha I, \quad \delta I = \mu A - u \quad (35)$$

which yield

$$I = \frac{\pi}{\alpha}, \quad A = \frac{\delta\pi}{\alpha\mu} + \frac{u}{\mu} \quad (36)$$

unconditionally.

• Let us now look for possible values of λ in $(0; 1)$. From (34) and (32a)-(32c), one deduces

$$\frac{A}{A_i} = \frac{\alpha I}{\alpha_i I_i} = \frac{\lambda}{1-\lambda}. \quad (37)$$

Using (34) on the one hand and summing the two identities (32b)-(32d) on the other hand, yields

$$\delta(I + I_i) = \delta\pi \left(\frac{\lambda}{\alpha} + \frac{1-\lambda}{\alpha_i} \right) = \mu A + (\mu_i + g)A_i - u = A \left(\mu + (\mu_i + g) \frac{1-\lambda}{\lambda} \right) - u. \quad (38)$$

This permits to express A as a function of λ , namely:

$$A = \frac{\lambda}{\lambda\mu + (1-\lambda)(\mu_i + g)} \left[\delta\pi \left(\frac{\lambda}{\alpha} + \frac{1-\lambda}{\alpha_i} \right) + u \right]. \quad (39)$$

Using this formula together with (34), (32d) and (37) now allows to find an equation involving only the unknown λ , namely:

$$\begin{aligned} \delta I_i &= \frac{\delta\pi}{\alpha_i}(1-\lambda) = (\mu_i + g)A_i = (\mu_i + g) \frac{A_i}{A} A \\ &= (\mu_i + g) \frac{1-\lambda}{\lambda} \frac{\lambda}{\lambda\mu + (1-\lambda)(\mu_i + g)} \left[\delta\pi \left(\frac{\lambda}{\alpha} + \frac{1-\lambda}{\alpha_i} \right) + u \right]. \end{aligned} \quad (40)$$

Simplifying (as $\lambda \neq 0, 1$) gives:

$$\frac{\delta\pi}{\alpha_i} = \frac{\mu_i + g}{\lambda\mu + (1-\lambda)(\mu_i + g)} \left[\delta\pi \left(\frac{\lambda}{\alpha} + \frac{1-\lambda}{\alpha_i} \right) + u \right]. \quad (41)$$

The previous condition is clearly affine in λ . It writes

$$(\lambda\mu + (1-\lambda)(\mu_i + g)) \frac{\delta\pi}{\alpha_i} = (\mu_i + g) \left(\delta\pi \left(\frac{\lambda}{\alpha} + \frac{1-\lambda}{\alpha_i} \right) + u \right) \quad (42)$$

which, after developing and simplifying, can be expressed as:

$$\lambda\mu \frac{\delta\pi}{\alpha_i} = (\mu_i + g) \left(\delta\pi \frac{\lambda}{\alpha} + u \right) \quad (43)$$

and finally

$$(\mu_i + g)u = \delta\pi \left(\frac{\mu}{\alpha_i} - \frac{\mu_i + g}{\alpha} \right) \lambda = \delta\pi\beta\lambda. \quad (44)$$

For $u \geq 0$, this equation admits a solution in $(0; 1)$ if and only if

$$\beta > 0 \quad \text{and} \quad u < u^* \doteq \frac{\delta\pi\beta}{\mu_i + g}, \quad (45)$$

and the latter is given as

$$\lambda = \frac{\mu_i + g}{\delta\pi\beta} u. \quad (46)$$

The state and output values may then be expressed explicitly as functions of u . In particular, one has

$$y(u) = gA_i = \frac{\delta g}{\mu_i + g} I_i = \frac{\delta\pi g}{\alpha_i(\mu_i + g)} (1 - \lambda) = \frac{\delta\pi g}{\alpha_i(\mu_i + g)} \left(1 - \frac{\mu_i + g}{\delta\pi\beta} u \right). \quad (47)$$

• (32) admits exactly one solution in \mathcal{D}' for any $u \geq 0$; admits a supplementary solution in \mathcal{D}' for any $u \in [0; u^*)$. The following tables summarize the number of solutions of (32) for all nonnegative values of u .

Values of $u \geq 0$	Number of distinct solutions of (32)
$u = 0$	2
$0 < u$	1

Fig. 8 $\mathcal{R}_0 \leq 1$ (i.e. $\beta \leq 0$).

Values of $u \geq 0$	Number of distinct solutions of (32)
$u = 0$	3
$0 < u < u^*$	2
$u^* \leq u$	1

Fig. 9 $\mathcal{R}_0 > 1$ (i.e. $\beta > 0$).

2. The equilibrium points of system (5) are exactly those points for which $u = y(u)$ for some nonnegative scalar u , where $y(u)$ is one of the output values corresponding to u previously computed. We now examine in more details the solutions of this equation.

• For the value $\lambda = 0$ in the previous computations, one should have $u = 0$, due to (46); but on the other hand $y > 0$ for $u = 0$, due to (47). Therefore this point does not correspond to an equilibrium point of system (32).

• The value $\lambda = 1$ yields a unique equilibrium point. Indeed, $y = 0$, so u should be zero too, and the unique solution is given by

$$I = \frac{\pi}{\alpha}, \quad A = \frac{\delta\pi}{\alpha\mu}, \quad I_i = 0, \quad A_i = 0, \quad y = 0. \quad (48)$$

This corresponds to the equilibrium denoted X_{MF} in the statement.

• Let us consider now the case of $\lambda \in (0; 1)$. For this case to be considered, it is necessary that $\beta > 0$, that is $\mathcal{R}_0 > 1$. The value of u should be such that (see (47))

$$y = \frac{\delta\pi g}{\alpha_i(\mu_i + g)} - \frac{g}{\alpha_i\beta} u = u, \quad (49)$$

that is

$$\left(1 + \frac{g}{\alpha_i \beta}\right) u = \frac{\delta \pi g}{\alpha_i (\mu_i + g)}, \quad (50)$$

or again

$$u = \frac{\delta \pi \beta g}{(\alpha_i \beta + g)(\mu_i + g)} = \frac{\delta \pi g}{\alpha_i (\mu_i + g)} \frac{\alpha \mu - \alpha_i (\mu_i + g)}{\alpha (\mu + g) - \alpha_i (\mu_i + g)}, \quad (51)$$

after replacing β by its value defined in (12). The corresponding value of

$$\lambda = \frac{\mu_i + g}{\delta \pi \beta} u = \frac{g}{\alpha_i \beta + g}, \quad (52)$$

given by (46), is clearly contained in $(0; 1)$ when $\beta > 0$. Therefore, when $\beta > 0$, there also exists a second equilibrium. The latter is given by:

$$I = \lambda \frac{\pi}{\alpha} = \frac{\mu_i + g}{\alpha \delta \beta} u = \frac{1}{\delta} \frac{\alpha_i (\mu_i + g)}{\alpha \mu - \alpha_i (\mu_i + g)} u, \quad A_i = \frac{u}{g}, \quad (53a)$$

$$I_i = \frac{\mu_i + g}{\delta} A_i = \frac{\mu_i + g}{\delta g} u \quad (53b)$$

$$A = \frac{1}{\mu} (\delta I + u) = \frac{1}{\mu} \left(\frac{\alpha_i (\mu_i + g)}{\alpha \mu - \alpha_i (\mu_i + g)} + 1 \right) u = \frac{\alpha}{\alpha \mu - \alpha_i (\mu_i + g)} u, \quad (53c)$$

and corresponds to X_{CO} defined in the statement.

diagonal that comes from the loop closing.

3. Let \mathcal{K} be the cone in \mathbb{R}_+^4 defined as the product of orthants $\mathbb{R}_+ \times \mathbb{R}_+ \times \mathbb{R}_- \times \mathbb{R}_-$. We endow the state space with this order. In other words, for any $X = (I, A, I_i, A_i)$ and $X' = (I', A', I'_i, A'_i)$ in \mathbb{R}_+^4 , $X \leq_{\mathcal{K}} X'$ means:

$$I \leq I', A \leq A', I_i \geq I'_i, A_i \geq A'_i. \quad (54)$$

With this structure, one may verify that the system (31a)-(31e) has the following monotonicity properties (Hirsch, 1988; Smith, 2008)

- For any function $u \in \mathcal{U} \doteq \{u : [0; +\infty) \rightarrow \mathbb{R}, \text{ locally integrable and taking on positive values almost everywhere}\}$, for any $X_0, X'_0 \in \mathbb{R}_+^4$,

$$X_0 \leq_{\mathcal{K}} X'_0 \quad \Rightarrow \quad \forall t \geq 0, X(t; X_0, u) \leq_{\mathcal{K}} X(t; X'_0, u) \quad (55)$$

where by definition $X(t; X_0, u)$ denotes the value at time t of the point in the trajectory departing at time 0 from X_0 and subject to input u .

- The Jacobian matrix of the I/O system is

$$\begin{pmatrix} -\alpha & \pi \frac{A_i}{(A+A_i)^2} & 0 & -\pi \frac{A}{(A+A_i)^2} \\ \delta & -\mu & 0 & 0 \\ 0 & -\pi \frac{A_i}{(A+A_i)^2} & -\alpha_i & \pi \frac{A}{(A+A_i)^2} \\ 0 & 0 & \delta & -(\mu_i + g) \end{pmatrix}, \quad (56)$$

which is irreducible when $A \neq 0$ and $A_i \neq 0$. The system is therefore strongly monotone in $\mathcal{D}' \setminus \{X : A_i = 0\}$ (notice that \mathcal{D}' does not contain points for which $A = 0$), and also on the invariant subset $\mathcal{D}' \cap \{X : I_i = 0, A_i = 0\}$.

- The input-to-state map is monotone, that is: for any inputs $u, u' \in \mathcal{U}$, for any $X_0 \in \mathbb{R}_+^4$,

$$u(t) \leq u'(t) \text{ a.e.} \Rightarrow \forall t \geq 0, X(t; X_0, u) \leq_{\mathcal{K}} X(t; X_0', u). \quad (57)$$

- The state-to-output map is anti-monotone, that is: for any $X, X' \in \mathbb{R}_+^4$,

$$X \leq_{\mathcal{K}} X' \Rightarrow \forall t \geq 0, gA_i \geq gA'_i \quad (58)$$

monotone (due to the irreducibility of the Jacobian matrix) for any constant value of u .

- In order to construct I/S and I/O characteristics for system (32), we now examine the stability of the equilibria of system (32) for any fixed value of $u \in \mathbb{R}_+$. As shown by Theorem 1, all trajectories are precompact.

- When $\beta \leq 0$, it has been previously established that for any $u \in \mathbb{R}$ there exists at most one equilibrium in \mathcal{D}' to the I/O system (32). The strong monotonicity property of this system depicted above then implies that this equilibrium is globally attractive (Hirsch, 1988, Theorem 10.3). Therefore, system (32) possesses I/S and I/O characteristics. As for any value of u , this equilibrium corresponds to zero output, the I/O characteristics is zero. Applying (? , Theorem XXX), one gets that the closed-loop system equilibrium X_{MF} is an almost globally attracting equilibrium for system (5).

- Let us now consider the case where $\beta > 0$. We first show that the equilibrium point with $I_i = 0, A_i = 0$ and (35) is locally unstable. Notice that this point is located on a branch of solution parametrized by u and departing from X_{MF} for $u = 0$. The Jacobian matrix (56) taken at this point is

$$\begin{pmatrix} -\alpha & 0 & 0 & -\frac{\mu\alpha\pi}{\delta\pi+\alpha u} \\ \delta & -\mu & 0 & 0 \\ 0 & 0 & -\alpha_i & \frac{\mu\alpha\pi}{\delta\pi+\alpha u} \\ 0 & 0 & \delta & -(\mu_i + g) \end{pmatrix}. \quad (59)$$

This matrix is block triangular, with diagonal blocks

$$\begin{pmatrix} -\alpha & 0 \\ \delta & -\mu \end{pmatrix} \quad \text{and} \quad \begin{pmatrix} -\alpha_i & \frac{\mu\alpha\pi}{\delta\pi+\alpha u} \\ \delta & -(\mu_i + g) \end{pmatrix}. \quad (60)$$

The first of them is clearly Hurwitz, while the second, whose characteristic polynomial is

$$\begin{aligned} s^2 + (\alpha_i + \mu_i + g)s + \alpha_i(\mu_i + g) - \frac{\mu\alpha\delta\pi}{\delta\pi + \alpha u} &= s^2 + (\alpha_i + \mu_i + g)s - \alpha\alpha_i(\beta - u(\mu_i + g)) \\ &= s^2 + (\alpha_i + \mu_i + g)s - \alpha\alpha_i(\mu_i + g)(u^* - u) \end{aligned} \quad (61)$$

(where u^* is defined in (45)) is not Hurwitz when $\beta > 0$ and $0 \leq u \leq u^*$, and has a positive root for $0 < u < u^*$. Therefore, the corresponding equilibrium of the I/O system (31) is unstable for these values of u .

The other solution, given as a function of u by (53), is located on a branch of solution parametrized by u and departing from X_{CO} for $u = 0$. As the other solution is unstable for $0 < u < u^*$, one can deduce from Hirsch (1988, Theorem 10.3) that these solutions are locally asymptotically stable.

• One may now associate to any $u \in [0; u^*]$ the corresponding unique locally asymptotically stable equilibrium point, and the corresponding output value, defining therefore respectively an I/S characteristic k_X and an I/O characteristic k for system (31).

For any scalar $u \in [0; u^*]$, for almost any $X_0 \in \mathcal{D}'$, one has

$$\lim_{t \rightarrow +\infty} X(t; X_0, u) = k_X(u), \quad \lim_{t \rightarrow +\infty} y(t; X_0, u) = k(u), \quad (62)$$

and, from the monotony properties, for any scalar-valued continuous function u , for almost any $X_0 \in \mathcal{D}'$:

$$k \left(\limsup_{t \rightarrow +\infty} u(t) \right) \leq \liminf_{t \rightarrow +\infty} y(t; X_0, u) \leq \limsup_{t \rightarrow +\infty} y(t; X_0, u) \leq k \left(\liminf_{t \rightarrow +\infty} u(t) \right). \quad (63)$$

Using the fact that k is anti-monotone and that $u = y$ for the closed-loop system, one deduces, as e.g. in Gouzé (1988) that, for the solutions of the latter,

$$k^{2l} \left(\liminf_{t \rightarrow +\infty} y(t; X_0, u) \right) \leq \liminf_{t \rightarrow +\infty} y(t; X_0, u) \leq \limsup_{t \rightarrow +\infty} y(t; X_0, u) \leq k^{2l} \left(\limsup_{t \rightarrow +\infty} y(t; X_0, u) \right). \quad (64)$$

Here $k(u)$, defined by (47), is a linear decreasing map. When its slope is smaller than 1, then the sequences in the left and right of (64) tend towards the fixed point that corresponds to the output value at $X = X_{CO}$, see (51).

This slope value, see (47), is equal to

$$\frac{\delta\pi g}{\alpha_i(\mu_i + g)} \frac{\mu_i + g}{\delta\pi\beta} = \frac{1}{\alpha_i\beta}, \quad (65)$$

and it thus smaller than 1 if and only if $\beta > \frac{1}{\alpha_i}$, which is an hypothesis of the statement.

Under these assumptions, one then obtains that the \liminf and \limsup in (64) are equal, and thus that y , and thus u , possesses limit for $t \rightarrow +\infty$. Moreover, the state itself converges towards the equilibrium X_{CO} when $t \rightarrow +\infty$ for almost every initial conditions $X(0)$. This achieves the proof of Theorem 2. \square

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