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Dynamics in a chemostat with an internal inhibitor and resistance mechanisms

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Abstract. We consider a competition model for three different strains wild, mutant and variant bacteria induced by an inhibitor created by one of the strains. We obtain two steady state regimes and we show that is possible the persistence of the three bacteria in the system.

1. Introduction

The Chemostat models are been used for modelling competition between species, Lenski and Hattingh [1], Hsu, Hubbel and Waltman [2], Hsu, Li and Waltman [3] and Hsu and Waltman [4] have studied competition between species in the presence of an inhibitor, the principal cause of the competition phenomenon.

In the environment, strains still sensitive to the inhibitor may persist [5]. Dominance by the resistant survivor strains, is directly linked to the "strength" of the intrinsic or acquired resistance to the inhibitor being used [6]. In [7], we considered two resistance mechanisms, phenotypic switching and mutation, assuming that cell replication does not occur in the phenotypic variant. Since it is characterized by neither growth nor significant reproduction. We generalized those results with the added assumption of the existence of a fraction of phenotypic variants capable of reproduction and we found the conditions to guarantee the persistence of the three bacteria in the system. These results are not according with Gause's law of competitive exclusion.

For these reason and considering that in nature it is known that micro-organisms produce inhibitors against their rivals [8], producing a selective medium in the same sense as the external inhibitor only "naturally", our problem setup is the following: in a constant environment, where resources are supplied at a constant rate, we introduce mutation into the dynamics of the bacterial population, an internal selective medium and as a consequence of this phenotypic switching, then we consider the competition of all bacterial strains for resources.

Section 2 presents the construction of the model, Section 3 contains the model analysis. In Section 4 we present our numerical results and the conclusions are given in Section 5. In Appendix A we present some special cases; proofs are found in Appendix B.

2. General Model

Let $S(t)$ denote the concentration of nutrient in the environment at time t, $u(t)$ the concentration of wild-type bacteria sensitive to a biocide, $v_0(t)$ denotes a mutated strain concentration and the producer of the biocide whose concentration is denoted by $p(t)$. Wild bacteria may mutate


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in a new mutated strain or undergo phenotypic switching to avoid the action of the biocide; to avoid the use of more variables, we assume the new mutated bacteria as the same $v_0(t)$ and $v_1(t)$ indicates the density of the phenotypic variant at time t. Our model takes the form

$$\begin{aligned} S' &= (S^{(0)} - S)D - \frac{Sm_1}{a_1 + S}\Big(u\phi(p) + v_1\Big) - \frac{Sm_2}{a_2 + S}v_0 \\ u' &= \frac{Sm_1}{a_1 + S}\Big(u\phi(p) + \gamma v_1\Big) - \Big(\mu + D + \alpha\big(1 - \phi(p)\big)\Big)u \\ v_0' &= v_0\left(\frac{Sm_2}{a_2 + S}(1 - \delta) - D\right) + \mu u \\ v_1' &= v_1\left(\frac{Sm_1}{a_1 + S}(1 - \gamma) - D\right) + \alpha\big(1 - \phi(p)\big)u \\ p' &= \delta v_0\frac{Sm_2}{a_2 + S} - \frac{hp}{k + p}v_1 - Dp \end{aligned} \tag{1}$$

where, we consider that nutrient is supplied at a constant rate S^0D and is eliminated either by washout at a rate SD, or by consumption, through a Michaelis-Menten function with constants a_i and m_i, $i = 1, 2$. Strain u is sensitive to the biocide so its rate of consumption is decreased by the inhibitor. This effect is represented by the function $\phi(p)$, the degree of inhibition that the biocide exerts upon strain u, given by $\phi(p) = \exp(-\lambda p)$ [1]. The mutation rate is μ and the phenotypic switch occurs at a rate $\alpha(1 - \phi(p))$; mutation results in the increase of the resistant strain numbers v_0 and the phenotypic switching results in the population growth of the phenotypic variant v_1. The parameter δ represents the portion of the nutrient consumption by v_0 that has been allocated to the production of the biocide, in consequence the growth rate corresponding has been debilitated. We generalize our previous model by assuming that the phenotypic variant reproduces and that a fraction γ regress to the wild stage. Finally, p indicates the concentration of biocide that is lost by washout or by absorption by resistant bacteria v_1.

Let

$$\Omega = \{(S, u, v_0, v_1, p) \mid S \geq 0, u \geq 0, v_0 \geq 0, v_1 \geq 0, p \geq 0\} \tag{2}$$

As in [3], [4], [9], [10], let $\bar{S} = S/S^{(0)}$, $\bar{u} = u/S^{(0)}$, $\bar{v_0} = v_0/S^{(0)}$, $\bar{v_1} = v_1/S^{(0)}$, $\bar{p} = p/S^{(0)}$, $\bar{a_i} = a_i/S^{(0)}$, $\bar{m_i} = m_i/D$, $\bar{\mu} = \mu/D$, $\bar{\alpha} = \alpha/D$, $\bar{\lambda} = \lambda S^{(0)}$, $\bar{t} = Dt$, $\bar{h} = h/D$, $\bar{k} = k/S^{(0)}$. The parameters γ and δ are dimensionless. System (2), becomes (dropping the bars)

$$S' = 1 - S - \frac{Sm_1}{a_1 + S}\Big(u\phi(p) + v_1\Big) - \frac{Sm_2}{a_2 + S}v_0 \tag{3a}$$

$$u' = \frac{Sm_1}{a_1 + S}\Big(u\phi(p) + \gamma v_1\Big) - \Big(\mu + 1 + \alpha\big(1 - \phi(p)\big)\Big)u \tag{3b}$$

$$v_0' = v_0\left(\frac{Sm_2}{a_2 + S}(1 - \delta) - 1\right) + \mu u \tag{3c}$$

$$v_1' = v_1\left(\frac{Sm_1}{a_1 + S}(1 - \gamma) - 1\right) + \alpha\big(1 - \phi(p)\big)u \tag{3d}$$

$$p' = \delta v_0\frac{Sm_2}{a_2 + S} - \frac{hp}{k + p}v_1 - p \tag{3e}$$

3. Analysis.

For (3) we observe that

$$S' + u' + v_0' + v_1' + p' = 1 - (S + u + v_0 + v_1 + p) - \frac{hp}{k+p}v_1 \leq 1 - S - u - v_0 - v_1 - p$$

implying

$$S(t) + u(t) + v_0(t) + v_1(t) + p(t) \leq 1 + c\ \exp(-t). \tag{4}$$

Thus, the bacteria population is bounded. Moreover, at any omega limit point $S + u + v_0 + v_1 + p \leq 1$, that is, the right hand side of (3) is bounded.

In Appendix A we analyze the special cases for γ, that is, the case when phenotypic strain is able to have total replication ($\gamma = 0$) and the case when there is not replication ($\gamma = 1$).

We claim that $E_0 = (1, 0, 0, 0, 0) \in \Omega$, the bacteria-free equilibrium point is globally asymptotically stable as it will be proven shortly. Following [4], [10], using (3c) and (3d) we obtain the break-even parameters for v_0 and v_1 respectively:

$$\frac{\lambda_2 m_2}{a_2 + \lambda_2} = \frac{1}{1-\delta}, \qquad \frac{\lambda_1 m_1}{a_1 + \lambda_1} = \frac{1}{1-\gamma}. \tag{5}$$

There is another equilibrium point given by $E_1 = \Big(\lambda_2, 0, (1-\lambda_2)(1-\delta), 0, \delta(1-\lambda_2)\Big)$, E_1 exists only if $0 < \lambda_2 < 1$. By calculating the variational matrix of (3) and substituting into E_0 and E_1 we obtain

Lemma 1.

- The equilibrium E_0 is locally asymptotically stable if $1 < \min\{\lambda_2, \lambda_1\}$ and $\dfrac{m_1}{a_1+1} < 1 + \mu$.

- The equilibrium E_1 is locally asymptotically stable if it exists ($0 < \lambda_2 < 1$), and if

$$0 < \frac{\lambda_2 m_1}{a_1 + \lambda_2} < \min\left\{\chi_1, \frac{\mu + 2 + \alpha(1-\hat{\phi})}{\hat{\phi} + 1 - \gamma}\right\} \qquad \text{or} \qquad \chi_2 < \frac{\lambda_2 m_1}{a_1 + \lambda_2} < \frac{\mu + 2 + \alpha(1-\hat{\phi})}{\hat{\phi} + 1 - \gamma},$$

where χ_1 and χ_2 are the positive real roots of

$$\chi^2 \hat{\phi}(1-\gamma) - \chi\left(\left[\mu + 1 + \alpha(1-\hat{\phi})\right](1-\gamma) + \hat{\phi} + \alpha(1-\hat{\phi})\right) + \left[\mu + 1 + \alpha(1-\hat{\phi})\right] = 0$$

with $\hat{\phi} = \exp(-\lambda\delta(1-\lambda_2))$.

The proof is a straight-forward computation (see Appendix B).

From Lemma 1 we see that competitive exclusion may take place. In order to prove the existence of a non trivial interior equilibrium point (one where all coordinates are positive), we consider equation (3e) and we assume that S, v_1 and v_0 are biologically feasible then we get that p is a root of

$$G(x) = x^2(a_2 + S) + x[k(a_2 + S) + hv_1(a_2 + S) - \delta v_0 S m_2] - \delta v_0 S m_2 k \tag{6}$$

and we can note that independently of the sign on the linear coefficient, we just have a positive solution (see Figure 1).

In particular, for some fixed values for S, v_0 and v_1 we obtain a unique positive value (see Figure 2)

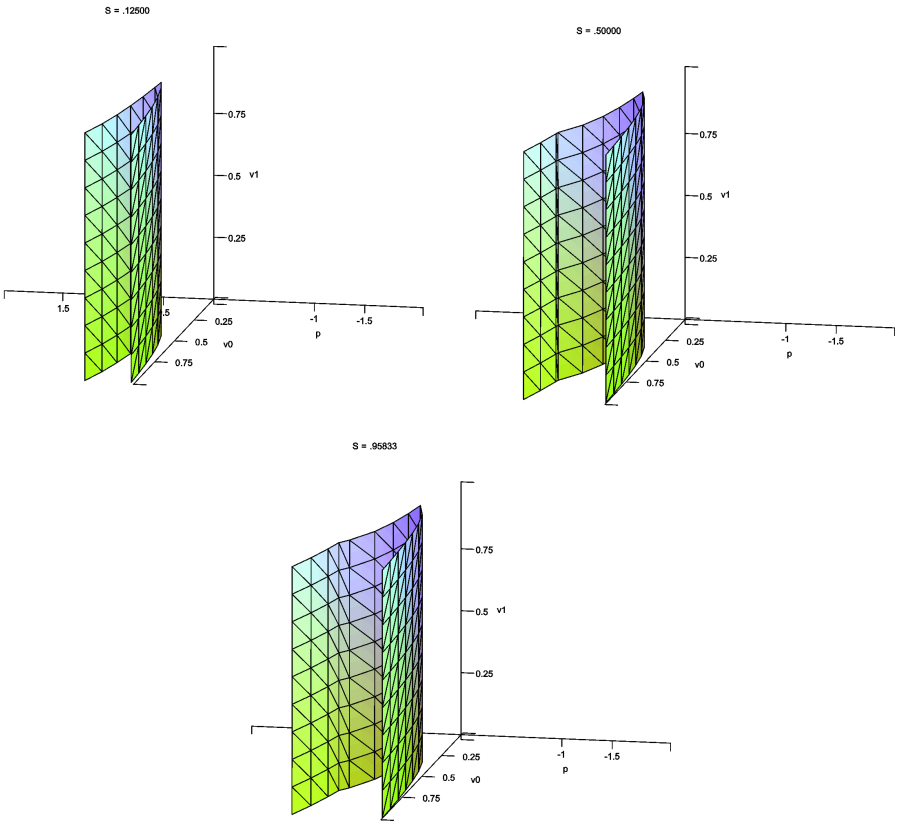


Figure 1. Graphic of the polynomial $G(p)$ given Equation (6). We show the behavior considering the axes p, $v0$ and v_1 and different values for S. We note that independently of the value of $S \in (0, 1)$, the graphic of $G(x)$ is on the positive side of p.

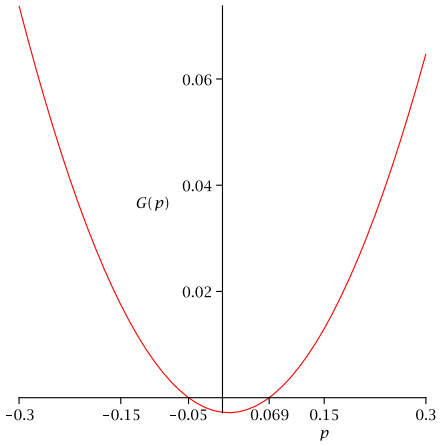


Figure 2. Graphic of the polynomial $G(p)$ considering $S = 0.7, v0 = 0.075$ and $v_1 = 0.07$ we observe that the only one positive root for $G(p)$ is given by $p = 0.069$. Replacing these values in (3) we get $u = 0.087$;then we obtain a non trivial equilibrium point.

3.1. Global stability

Our model has two equilibrium points E_0 and E_1, and depending on the biological feasibility of S, v_1 and v_0, a third non-trivial one E_c. When E_c does not exist and $\lambda_2 > 1$ (that is, E_1 does not exist), then the unique equilibrium point is E_0 and in consequence, if $\lambda_1 > 1$ and $\dfrac{m_1}{a_1+1} < \mu+1$, E_0 is globally stable.

Theorem 1. If $0 < \lambda_2 < 1$, E_c does not exist, the break-even parameter for $\gamma = 0$ that is $\frac{m_1\hat{\lambda}_1}{a_1+\hat{\lambda}_1} = 1$ is such that either of the following two conditions hold

(i) $\hat{\lambda}_1 > 1$

(ii) $\lambda_2 < \hat{\lambda}_1 < 1$

where λ_2 is defined as in (5), and either of the following hold

(iii) $0 < \delta m_1 m_2 < m_2 - m_1 \qquad and \qquad a_2 \leq a_1$

(iv) $\dfrac{m_2}{a_2} < \dfrac{m_1}{a_1}$

then the equilibrium point $E_1 = (\lambda_2, 0, (1-\lambda_2)(1-\delta), 0, \delta(1-\lambda_2))$ is globally asymptotically stable.

Conditions (i) and (ii) require the nutrient concentration of the phenotypic strain to be at equilibrium ($\hat{\lambda}_1$). For the interpretation of (iii) and (iv) let $f_1 = \frac{Sm_1}{a_1+S}$ be the phenotypic variant consumption function and $f_2 = \frac{Sm_2}{a_2+S}$ be the one for the mutant strain. Then, (iii) implies $f_2 > f_1$; in case (iv) the behavior of f_1 and f_2 depends upon if $m_1 > m_2$ or $m_1 < m_2$. Now, we will prove the theorem.

Proof. Consider the Lyapunov function

$$V(S,u,v_0,v_1,p) = \int_{\lambda_2}^{S} \frac{\eta-\lambda_2}{\eta}d\eta + c_1(u+v_1) + c_2\int_{(1-\lambda_2)(1-\delta)}^{v_0} \frac{\eta-(1-\lambda_2)(1-\delta)}{\eta}d\eta$$

where $c_1, c_2 > 0$ are to be determined. We see that $V(E_1) = 0$ and $V(S,u,v_0,v_1,p) \in C^1(\Re^5_+, \Re)$. Moreover, $V(S,u,v_0,v_1,p) > 0$ for all $(S,u,v_0,v_1,p) \in \Delta \setminus E_1$ where

$$\begin{aligned}\Delta &= \Omega - \{(S,0,0,0,0)\} \\ &= \{(S,u,v_0,v_1,p) | S \geq 0, u \geq 0, v_0 \geq 0, v_1 \geq 0, p \geq 0\} - \{(S,0,0,0,0)\}.\end{aligned}$$

Observe that

- for $S > \lambda_2$ we have $\frac{\eta-\lambda_2}{\eta} > 0$, then the first integral in V is positive.
- for $S < \lambda_2$ we have $\frac{\eta-\lambda_2}{\eta} < 0$, then the first integral in V is positive.

Applying the same procedure to the second integral and given that $c_1, c_2 > 0$ we have $V(S,u,v_0,v_1,p) > 0$. The derivative of V is

$$\begin{aligned}\dot{V} &= \frac{S-\lambda_2}{S}\dot{S} + c_1(\dot{u}+\dot{v_1}) + c_2\Big(\frac{v_0-(1-\lambda_2)(1-\delta)}{v_0}\Big)\dot{v_0} \\ &= A(S) + B(S,p)u + C(S)v_1 + D(S)v_0 - c_2\mu(1-\lambda_2)(1-\delta)\frac{u}{v_0} \\ &< A(S) + B(S,p)u + C(S)v_1 + D(S)v_0 \qquad (7)\end{aligned}$$

where

$$\begin{aligned} A(S) &= \frac{(S-\lambda_2)(1-S)}{S} - c_2(1-\lambda_2)(1-\delta)\left[\frac{Sm_2}{a_2+S}(1-\delta)-1\right] \\ B(S,p) &= \frac{m_1\phi(p)}{a_1+S}\left[S(c_1-1)+\lambda_2\right] - c_1 - \mu(c_1-c_2) \\ C(S) &= \frac{-(S-\lambda_2)m_1}{a_1+S} + c_1\left(\frac{Sm_1}{a_1+S}-1\right) \\ D(S) &= \frac{-(S-\lambda_2)m_2}{a_2+S} + c_2\left(\frac{Sm_2}{a_2+S}(1-\delta)-1\right) \end{aligned}$$

From $A(S)$ define

$$T(S) = \frac{(S-\lambda_2)(1-S)}{S(1-\lambda_2)(1-\delta)\left(\frac{Sm_2}{a_2+S}(1-\delta)-1\right)};$$

then $T(S) > 0$ for all $S \in (0,1) \setminus \lambda_2$, $T(1) = 0$, and therefore

$$\lim_{S\to 0^+} T(S) = +\infty \qquad \lim_{S\to\lambda_2} T(S) = \lim_{S\to\lambda_2} \frac{\frac{\lambda_2 - S^2}{S^2}}{(1-\lambda_2)\left(\frac{a_2 m_2 (1-\delta)^2}{(a_2+S)^2}\right)} = \frac{m_2\lambda_2}{a_2}.$$

So, defining $c_2 = \frac{m_2\lambda_2}{a_2}$ we obtain $A(S) < 0$. Moreover, by replacing this value into $D(S)$ we get $D(S) = 0$. Now, $B(S,p)$ depends on c_1 and c_2 and thus we need to consider the cases $c_1 = c_2$ and $c_1 \neq c_2$.

- For the case $c_1 = c_2$, we obtain

  $$C(S) = -\frac{\lambda_2}{a_2(a_1+S)}\left[(m_2 - m_1 - \delta m_1 m_2)S + (a_1 m_2 - a_2 m_1)\right]$$

  and

  $$B(S,p) = C(S)\phi(p) + \tfrac{m_2\lambda_2}{a_2}\big(\phi(p)-1\big).$$

  By assumption (iii) the expression within brackets in $C(S)$ is positive for all $S \in (0,1)$. Therefore, $C(S)$ and $B(S,p)$ are negative, and thus we have $\dot{V} \leq 0$ for all $(S,u,v_0,v_1,p) \in \Delta$.

- For the case $c_1 \neq c_2$, from $C(S)$ define

  $$T_1(S) = \frac{(S-\lambda_2)\dfrac{m_1}{a_1+S}}{\dfrac{Sm_1}{a_1+S}-1}.$$

  Then

  $$T_1'(S) = \frac{-m_1(m_1-1)\left(\hat{\lambda}_1 - \lambda_2\right)}{\Big[S(m_1-1)-a_1\Big]^2};$$

observe that, independently of conditions (i) or (ii), $T_1(S)$ is a decreasing function of S that satisfies $T_1(0) > 0$, $T_1(\lambda_2) = 0$ and

$$\lim_{S\to\hat{\lambda}_1^+} T_1(S) = +\infty \qquad \lim_{S\to\hat{\lambda}_1^-} T_1(S) = -\infty$$

Then, for case (i), we choose $c_1 = T_1(0) > 0$. Since $T_1(S)$ is decreasing $T(0) \geq T_1(S)$ for all $S \in (0,1)$ and, because the denominator of $T_1(S)$ is negative in $(0,1)$ ($\hat{\lambda}_1 > 1$ in this case), $C(S) < 0$ for all $S \in (0,1)$.
For case (ii), note that given $T_1(S)$, there exists $c_1 > 0$ such that

$$\max_{(0,\hat{\lambda}_1)} T_1(S) \leq c_1 \leq \min_{(\hat{\lambda}_1,1)} T_1(S).$$

If c_1 does not exist, then there exists $\tau > 0$ such that the equation $T_1(S) = \tau$ has at least two different roots η_1, η_2 satisfying $0 < \eta_1 < \lambda_2 < \hat{\lambda}_1 < \eta_2 < 1$ (these roots are not in $(\lambda_2, \hat{\lambda}_1)$ since $T_1(S) < 0$); however this is a contradiction. For the critical values of $T_1(S)$ we can calculate the relation

$$T_1(0) = \frac{\lambda_2 m_1}{a_1} \leq c_1 \leq (1-\lambda_2)\frac{m_1\hat{\lambda}_1}{a_1(1-\hat{\lambda}_1)} = T_1(1) \tag{8}$$

so, if c_1 satisfies (8) then $C(S) < 0$.

Using (iv) and (8) and taking the value found for c_2, that is $c_2 = \dfrac{m_2\lambda_2}{a_2}$ we get $c_2 < c_1$ and, therefore,

$$B(S,p) = C(S)\phi(p) + c_1\big(\phi(p) - 1\big) + \mu(c_2 - c_1) < 0.$$

We have shown that $\dot{V} \leq 0$ for all $(S, u, v_0, v_1, p) \in \Delta$. We now seek the maximum invariant region in the set $\{(S, u, v_0, v_1, p) \mid \dot{V} = 0\}$. Since $A(S), B(S,p), C(S) \leq 0$, $D(S) = 0$ and $\dot{V}$ is given by (7), it must be the case when $A(S) = 0$. Then S is a root of

$$(S - \lambda_2)^2\big(S\lambda_2 + a_2\big) = 0;$$

therefore $S = \lambda_2$. Moreover, $B(\lambda_2, p) < 0$ (since $\lambda_2 < \hat{\lambda}_1$) so, $u = 0$. The constant values $S = \lambda_2$, $u = 0$ forces in (3) that $v_1 = 0$, $v_0 = (1-\lambda_2)(1-\delta)$ and $p = \delta(1-\delta)$. The only invariant set in this region is the rest point E_1. By LaSalle invariance principle [13] we conclude that E_1 is globally asymptotically stable. □

Numerical simulation of (3) shows the stability of the equilibrium point given by $E_1 = (\lambda_2, 0, (1-\lambda_2)(1-\lambda), 0, \delta(1-\lambda_2))$ considering the parameters $a_1 = 0.08$, $a_2 = 0.4$, $m_1 = 1.1$, $m_2 = 2.1$, $\alpha = 1$, $\gamma = 0.5$, $\mu = 0.07$, $\lambda = 0.1$, $h = 0.001$ and $k = 0.05$. (**Theorem 1**).

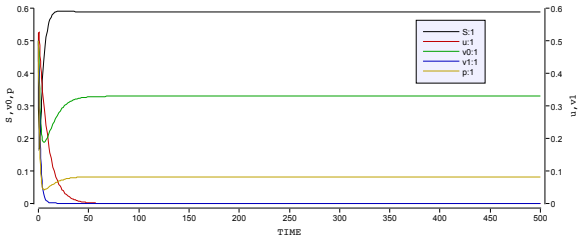


Figure 3. In this case we use $\delta = 0.2$. Figure shows the values of S, u, v_0, v_1 and p corresponding to the equilibrium point E_1.

Next figures show the stability for different values of δ in each case.

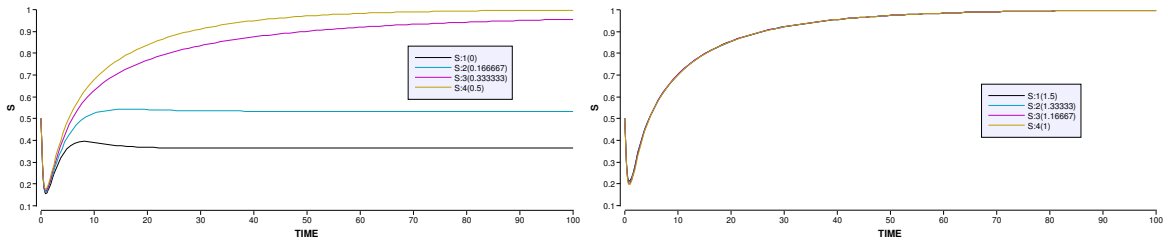


Figure 4. Stability of S . We observe that the most remarkable changes in the equilibrium value of S occurs when $\delta \in (0, 0.5)$ (figure at left), after these values S does not have significant changes in its stability value (figure at right).

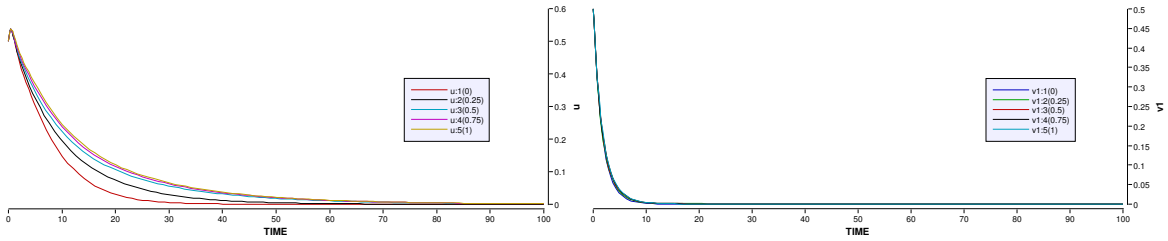


Figure 5. Stability of u and v_1. We note that the stability value for u is highly sensitive to changes in δ; for $\delta \in (0, 0.5)$ u tends to zero faster than for $\delta \in (0.5, 1)$. This behavior does not occur for v_1 that regardless on the value of δ tends to zero at the same rate.

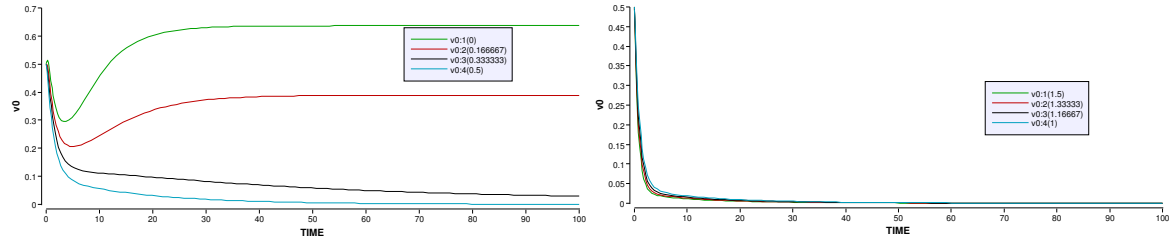


Figure 6. Stability of v_0. We can see that changes in δ are inversely proportional to the stability value of v_0, this is because when δ tends to 1, the strain v_0 will increase due to mutation of u (see equation (3c)) which tends to zero.

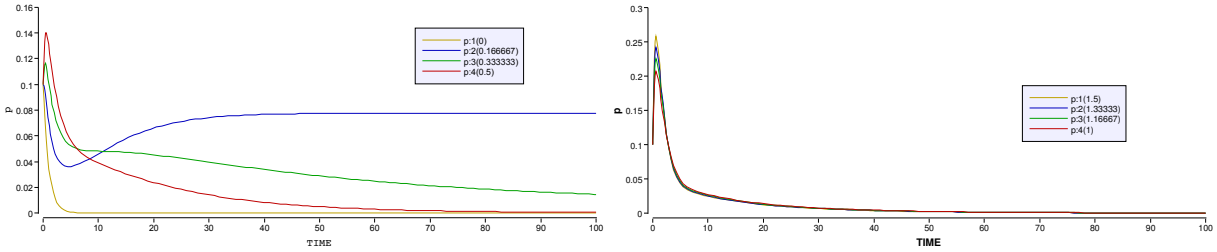


Figure 7. Stability of p. Different from S, we observe that if $\delta \in (0, 0.5)$ then p has an equilibrium value different from zero, however, if $\delta \in (0.5, 1)$ then the equilibrium value for p tends to zero .

Finally, considering the same values as before for γ, k, h and μ, and $m_1 = 1.4, m_2 = 2.1, a_1 = 0.2, a_2 = 0.1, \lambda = 0.8, \delta = 0.5$ and $\alpha - 5.5$ we observe a non trivial equilibrium point (figure 6)

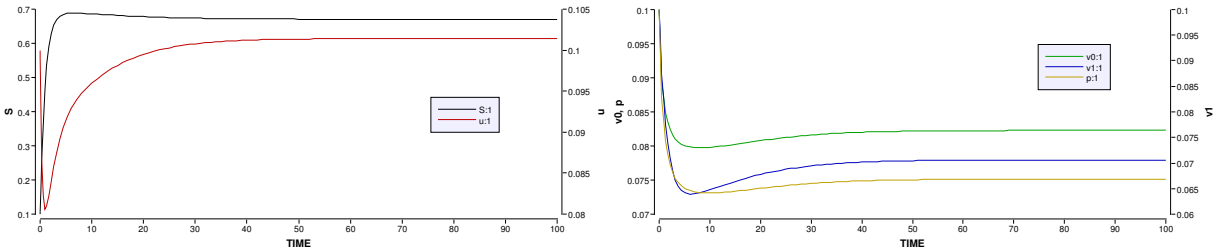


Figure 8. Numerical simulation of the non trivial equilibrium point. We note that equilibrium value of u is bigger than equilibrium values of v_0 and v_1, it means that the cost on the inhibitor production is bigger than the inhibition on u growth.

4. Discusion and conclusion

Competition models in a chemostat in the presence of an inhibitor can serve as a model system for ecological processes. For example, we can think the resistant organism as a detoxifying agent in the environment. From the standpoint of competition, the question is whether the detoxifying organisms survive in the environment [10].

In contrast to the models studied in [2], [3], [4], [10], we consider three strains in competition under the effects of an internal inhibitor; one of the strains is a wild strain on which two different

mechanisms of resistance, mutation and phenotypic switching are acting. We have proven that both resistant types may coexist together with the wild type: there is no competitive exclusion. This result is not general since it depends on parameter values (in fact, in our last simulation we observe that the cost on the inhibitor production is bigger than its inhibition on u growth but we can not proof this in general). With an appropriate selection of them, competitive exclusion can be obtained and, as before, the mutant strain is the one that survives in the environment.

Appendix A

A.1 Special case $\gamma = 0$.

This special case of (3) considers that phenotypic strain is able to have replication as a whole and, as a consequence, we obtain the wash out of the wild strain.

When we consider in (3) the special case $\gamma = 0$ we get the model:

$$S' = 1 - S - \frac{Sm_1}{a_1 + S}\Big(u\phi(p) + v_1\Big) - \frac{Sm_2}{a_2 + S}v_0 \tag{A.1a}$$

$$u' = \frac{Sm_1}{a_1 + S}u\phi(p) - \Big(\mu + 1 + \alpha\big(1 - \phi(p)\big)\Big)u \tag{A.1b}$$

$$v_0' = v_0\left(\frac{Sm_2}{a_2 + S}(1 - \delta) - 1\right) + \mu u \tag{A.1c}$$

$$v_1' = v_1\left(\frac{Sm_1}{a_1 + S} - 1\right) + \alpha\big(1 - \phi(p)\big)u \tag{A.1d}$$

$$p' = \delta v_0\frac{Sm_2}{a_2 + S} - \frac{hp}{k + p}v_1 - p \tag{A.1e}$$

About this model we get an important result:

Theorem 2. There is no non-trivial equilibrium point with all coordinates different to zero for the system (A.1).

Proof. Considering $u \neq 0$ in (A.1b) and due to $1 > \phi(p) > 0$ and doing some algebra with (A.1d), we get the expression:

$$\Big(\mu + (\alpha + 1)(1 - \phi(p))\Big)v_1 + \alpha(1 - \phi(p))\phi(p)u = 0$$

which does not make biological sense if u and v_1 are both positive. Therefore, there is no non-trivial equilibrium point with all bacteria strain present.

Moreover, we obtain the equilibrium points

$$E_0 = (1, 0, 0, 0, 0) \text{ and } E_1 = \Big(\lambda_2, 0, (1 - \lambda_2)(1 - \delta), 0, \delta(1 - \lambda_2)\Big),$$

where λ_2 is the solution of $\dfrac{\lambda_2 m_2}{a_2 + \lambda_2}(1 - \delta) = 1$. □

A.2 Special case $\gamma = 1$.

This special case of (3) considers that there is not phenotypic strain replication.

When we consider in (3) the special case $\gamma = 1$ we get the model:

$$\begin{aligned} S' &= 1 - S - \frac{Sm_1}{a_1+S}\Big(u\phi(p) + v_1\Big) - \frac{Sm_2}{a_2+S}v_0 \\ u' &= \frac{Sm_1}{a_1+S}\Big(u\phi(p) + v_1\Big) - \Big(\mu + 1 + \alpha\big(1-\phi(p)\big)\Big)u \\ v_0' &= v_0\left(\frac{Sm_2}{a_2+S}(1-\delta) - 1\right) + \mu u \\ v_1' &= -v_1 + \alpha\big(1-\phi(p)\big)u \\ p' &= \delta v_0 \frac{Sm_2}{a_2+S} - \frac{hp}{k+p}v_1 - p \end{aligned} \tag{A.2}$$

Before the important result for this model we observe that due to $S + u + v_0 + v_1 + p < 1$, we can approximate

$$\phi(p) = 1 - \lambda p + \frac{(\lambda p)^2}{2!} - \frac{(\lambda p)^3}{3!} + \cdots \approx 1 - \lambda p$$

then, replacing in (A.2) we get

$$S' = 1 - S - \frac{Sm_1}{a_1+S}\Big(u(1-\lambda p) + v_1\Big) - \frac{Sm_2}{a_2+S}v_0 \tag{A.3a}$$

$$u' = \frac{Sm_1}{a_1+S}\Big(u(1-\lambda p) + v_1\Big) - \Big(\mu + 1 + \alpha\lambda p\Big)u \tag{A.3b}$$

$$v_0' = v_0\left(\frac{Sm_2}{a_2+S}(1-\delta) - 1\right) + \mu u \tag{A.3c}$$

$$v_1' = -v_1 + \alpha\lambda p u \tag{A.3d}$$

$$p' = \delta v_0 \frac{Sm_2}{a_2+S} - \frac{hp}{k+p}v_1 - p \tag{A.3e}$$

Theorem 3. If $\lambda_1^* < \lambda_2$ where λ_1^* and λ_2 are the solutions of

$$\frac{\lambda_1^* m_1}{a_1+\lambda_1^*} = \frac{\mu + 1 + \alpha\lambda p_*}{1 + \lambda p_*(\alpha - 1)} \text{ and } \frac{\lambda_2 m_2}{a_2+\lambda_2} = \frac{1}{1-\delta}$$

and p_* is a positive root of

$$P_3\ Z^3 + P_2\ Z^2 + P_1\ Z + (1-\lambda_1^*)\delta F\mu k = 0 \tag{A.4}$$

with

$$P_3 = \alpha\lambda[F(1-\delta) - 1]$$

$$P_2 = (1-\lambda_1^*)[F(1-\delta)-1]h\alpha\lambda + (\mu + 1 + k\alpha\lambda)[F(1-\delta)-1] - F\mu$$

$$P_1 = (1-\lambda_1^*)\delta F\mu + k(1+\mu)[F(1-\delta)-1] - kF\mu$$

and

$$F = \frac{\lambda_1^* m_2}{a_2+\lambda_1^*} \tag{A.5}$$

then, there is non-trivial equilibrium point $E_2 = (\lambda_1^*, u_*, v_{0_*}, v_{1_*}, p_*)$ with all coordinates different to zero for the system (A.3) .

Proof. From the cerocline for (A.3d) we get $v_1 = \alpha\lambda p u$ then, replacing in (A.3b) and considering $u \neq 0$ we get the expression:

$$\frac{Sm_1}{a_1 + S} = \frac{\mu + 1 + \alpha\lambda p}{1 + \lambda p(\alpha - 1)}$$

We observe that if $p = p_*$, then the solution of last equation is $S = \lambda_1^*$. Assuming this, and replacing in (A.3a), (A.3c) and (A.3e) we obtain:

$$\begin{aligned} u_* &= -\frac{(F(1-\delta)-1)(1-\lambda_1^*)}{\mu F - B} \\ v_{0_*} &= \frac{\mu(1-\lambda_1^*)}{\mu F - B} \\ p_* & \end{aligned}$$

where p_* satisfy (A.4), F is given by (A.5), and B is given by

$$B = \big(F(1-\delta) - 1\big)(\mu + 1 + \alpha\lambda p\big)$$

Now, from hypothesis, $\lambda_1^* < \lambda_2$ then $F(1-\delta) - 1 < 0$ and in consequence coefficients P_3 and P_2 in (A.4) are negatives, and due to $B < 0$, we obtain $\mu F - B > 0$. Therefore, u_*, v_{0_*} and $v_1 = \alpha\big(1 - \phi(p)\big)$ are positive, moreover by Descartes' Rule of Signs, polinomial (A.4) has a positive real root that is, exists non trivial equilibrium point for (A.3). □

Appendix B

Proof. **of lemma 1** The Jacobian matrix of the system is, for a general point $E = (S, u, v_0, v_1, p)$ in Ω, is given by:

$$A = \begin{pmatrix} -A_{11} & -\frac{Sm_1}{a_1+S}\phi(p) & -\frac{Sm_2}{a_2+S} & -\frac{Sm_1}{a_1+S} & -\frac{Sm_1}{a_1+S}u\phi'(p) \\ A_{21} & A_{22} & 0 & \frac{Sm_1}{a_1+S}\gamma & \Big(\frac{Sm_1}{a_1+S} + \alpha\Big)u\phi'(p) \\ A_{31} & \mu & A_{33} & 0 & 0 \\ A_{41} & \alpha(1-\phi(p)) & 0 & A_{44} & -\alpha u\phi'(p) \\ \frac{a_2 m_2}{(a_2+S)^2}\delta v_0 & 0 & \frac{Sm_2}{a_2+S}\delta & \frac{-hp}{k+p} & -A_{55} \end{pmatrix}$$

Where

$$\begin{aligned}
A_{11} &= 1+\frac{a_1m_1}{(a_1+S)^2}\Big(u\phi(p)+v_1\Big)+\frac{a_2m_2}{(a_2+S)^2}v_0\\
A_{21} &= \frac{a_1m_1}{(a_1+S)^2}\Big(u\phi(p)+\gamma v_1\Big)\\
A_{22} &= \frac{Sm_1}{a_1+S}\phi(p)-\Big[\mu+1+\alpha\Big(1-\phi(p)\Big)\Big]\\
A_{31} &= \frac{a_2m_2}{(a_2+S)^2}(1-\delta)v_0\\
A_{33} &= \frac{Sm_2}{a_2+S}(1-\delta)-1\\
A_{41} &= \frac{a_1m_1}{(a_1+S)^2}(1-\gamma)v_1\\
A_{44} &= \frac{Sm_1}{a_1+S}(1-\gamma)-1\\
A_{55} &= 1+\frac{kh}{(k+p)^2}v_1
\end{aligned}$$

Replacing E_0 we obtain the characteristic polynomial in x:

$$\Big(1+x\Big)^2\ \left(\frac{m_2}{a_2+1}(1-\delta)-1-x\right)\ \left(\frac{m_1}{a_1+1}-1-\mu-x\right)\ \left(\frac{m_1}{a_1+1}(1-\gamma)-1-x\right)=0$$

So, E_0 is locally asymptotically stable if and only if

$$1<min\left\{\lambda_1,\lambda_2\right\}\quad\text{and}\quad\frac{m_1}{a_1+1}<\mu+1$$

On the other hand, replacing E_1 into the Jacobian matrix, we obtain the characteristic polynomial:

$$(x+1)^2\left(x+\frac{a_2(1-\lambda_2)}{\lambda_2(a_2+\lambda_2)}\right)(x^2+Ax+B)=0$$

where

$$\begin{aligned}
A &= 2+\mu+\alpha\left(1-\hat{\phi}\right)-\chi\left(1-\gamma+\hat{\phi}\right)\\
B &= \chi^2\hat{\phi}(1-\gamma)-\chi\left(\Big[\mu+1+\alpha(1-\hat{\phi})\Big](1-\gamma)+\hat{\phi}+\alpha(1-\hat{\phi})\right)+\Big[\mu+1+\alpha(1-\hat{\phi})\Big]\\
\chi &= \frac{\lambda_2m_1}{a_1+\lambda_2}\\
\hat{\phi} &= \exp(-\lambda\delta(1-\lambda_2))
\end{aligned}$$

So, E_1 will be locally stable if the roots of x^2+Ax+B have negative real part, that is $A>0$ and $B>0$. From expression for A we get $A>0$ if and only if

$$\chi<\frac{\mu+2+\alpha(1-\hat{\phi})}{\hat{\phi}+1-\gamma}. \tag{A.6}$$

Now, we observe that B is a quadratic polynomial for χ whose determinant is given by

$$\begin{aligned}\mathcal{D} &= \left(\left[\mu+1+\alpha(1-\hat{\phi})\right](1-\gamma)-\hat{\phi}\right)^2+2\hat{\phi}\gamma\alpha(1-\hat{\phi})+\left(\gamma\alpha(1-\hat{\phi})\right)^2 \\ &+ 2\gamma\alpha(1-\hat{\phi})\left[\mu+1+\alpha(1-\hat{\phi})\right](1-\gamma)\end{aligned}$$

then B has two positive real roots (χ_1 and χ_2) and in consequence will be positive if and only if

$$0<\chi<\chi_1 \qquad \text{or} \qquad \chi>\chi_2. \tag{A.7}$$

Therefore, from (A.6) and (A.7), E_1 will be locally stable if and only if

$$0<\chi<\min\left\{\chi_1,\frac{\mu+2+\alpha(1-\hat{\phi})}{\hat{\phi}+1-\gamma}\right\} \qquad \text{or} \qquad \chi_2<\chi<\frac{\mu+2+\alpha(1-\hat{\phi})}{\hat{\phi}+1-\gamma}.$$

□

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