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Global analysis of a model of plasmid-bearing, plasmid-free competition in a chemostat with inhibitions

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Abstract. A model of competition between plasmid-bearing and plasmid-free organisms in a chemostat was proposed in a paper of Stephanopoulis and Lapidus. The model was in the form of a system of nonlinear ordinary differential equations. Such models were relevant to commercial production by genetically altered organisms in continuous culture. The analysis there was local. The rigorous global analysis was done in a paper of Hsu, Waltman and Wolkowicz in the case of the uninhibited specific growth rates. This paper provides a mathematically rigorous analysis of the global asymptotic behavior of the governing equations in the cases of combinations of inhibited and uninhibited specific growth rates.

Key words: Chemostat – Competition – Plasmid-bearing – Qualitative analysis

1 Introduction

Genetically altered organisms are frequently used to produce foreign products. The alteration is accomplished by the introduction of a recombinant DNA into the cell in the form of a plasmid. The load imposed by production can result in the genetically altered (the plasmid-bearing) organism being a less able competitor than the plasmid-free (or "wild type") organism. Unfortunately, the plasmid can be lost in the reproductive process. Since commercial production can take place on a scale of many generations, it is possible for the plasmid-free organism to take over the culture. In pharmaceuticals, changes in the plasmid could cause changes in the amino acid sequence of a protein product or changes in the background from which it must be purified. It is vital to produce a uniform product if it is a drug intended

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for human use. Since commercial production of products manufactured by genetically altered organisms is a reality, understanding the competition between the plasmid-bearing organisms and plasmid-free organsims in a mathematically rigorous fashion seems important.

The chemostat is a common model of waste-treatment and a model for commerical production of the fermentation process. It is important in ecology because the parameters are readily measurable, and thus, the mathematical results are readily testable. The following model of competition between plasmid-bearing and plasmid-free organisms in a chemostat based on the mass balance of the organisms was proposed by Ryder and Dibiasio [RD]

$$\begin{aligned} \dot{S} &= (S^{(0)} - S)D - \sigma_1(S)x_1 - \sigma_2(S)x_2 , \\ \dot{x}_1 &= x_1(f_1(S)(1-q) - D) , \\ \dot{x}_2 &= x_2(f_2(S) - D) + qx_1 f_1(S) , \\ S(0) &= S_0 \geqq 0, \quad x_i(0) > 0, \quad i = 1,2 . \end{aligned} \tag{1.1}$$

$S(t)$ is the nutrient concentration at time t, $x_1(t)$ is the concentration of plasmid-bearing organisms at time t, $x_2(t)$ is the concentration of plasmid-free organisms at time t. The consumption rates and the specific growth rates of plasmid-bearing and plasmid-free organisms are σ_1, σ_2, f_1 and f_2, respectively. The probability that a plasmid is lost in reproduction is represented by q, and hence

$$0 < q < 1 .$$

The operation parameters are $S^{(0)}$, the input concentration of the nutrient and D, the washout rate of the chemostat.

Assuming that $\sigma_1(S) = \sigma_2(S)$, Ryder and Dibiasio [RD] presented a local stability analysis of the rest points for very general growth kinetics. Based on this analysis they suggest an operational strategy involving feedback control to enhance plasmid stability in the systems.

Instead assuming that $\sigma_1(S) = \sigma_2(S)$, Stephanopoulis and Lapidus [SL] studied the following case:

$$\sigma_i(S) = \frac{f_i(S)}{\gamma} \quad \text{for } i = 1, 2 ,$$

where γ is the yield constant (assumed to be the same for both populations). They used very clever index theory arguments to determine the steady portraits based on the shape mutual disposition of the specific growth rate curves. They did an exhaustive analysis for the two most common growth models, the Monod model (also referred to as Michaelis-Menten kinetics or Holling type II) for uninhibited growth

$$\frac{\mu_{\max} S}{K_s + S}$$

and the Andrews model for inhibited growth

$$\frac{\mu_{\max} S}{K_s + S + S^2/K_1} .$$

Their analysis was local. In the paper of Hsu, Waltman and Wolkowicz [HWW], the authors provide a rigorous global analysis for the case that the specific growth rates $f_1(S)$, $f_2(S)$ are both monotone, i.e., uninhibited.

In this paper we deal with general response functions that are uninhibited and inhibited within the range of interest. The response function $f(S)$ is called uninhibited, if it satisfies the following conditions:

i) $f(S)$ is continuously differentiable;
ii) $f(0) = 0$;
iii) $f(S) > 0$ for all $0 < S \leqq S^{(0)}$;

iv) $f'(S) > 0$ for all $0 < S \leqq S^{(0)}$.

On the other hand, the response function $f(S)$ is called inhibited, if it satisfies the following conditions:

i) $f(S)$ is continuously differentiable;
ii) $f(0) = 0$;
iii) $f(S) > 0$ for all $0 < S \leqq S^{(0)}$;
iv) there exists ρ $(0 < \rho < S^{(0)})$ such that $f'(S) > 0$ for all $0 < S < \rho$; $f'(S) < 0$ for all $\rho < S < S^{(0)}$.

By measuring concentrations of nutrient in units of $S^{(0)}$, time in units of $1/D$, x_i in units of $1/\gamma S^{(0)}$ and each f_i in units of $1/D$, the number of parameters can be reduced and the equations (1.1) becomes

$$\begin{aligned} \dot{S} &= 1 - S - x_1 f_1(S) - x_2 f_2(S) , \\ \dot{x}_1 &= x_1(f_1(S)(1-q) - 1) , \\ \dot{x}_2 &= x_2(f_2(S) - 1) + q x_1 f_1(S) , \\ S(0) &= S_0 \geqq 0, \quad x_i(0) > 0, \quad i = 1,2 . \end{aligned} \tag{1.2}$$

The operating parameters have been scaled out, or, from another point of view, such parameters as $\mu_{\max}$, K_s and K_I are measured relative to the operating environments. (The parameters have changed their biological meaning.) This is mathematically convenient although to be useful, the results must be returned to biologically meaningful units.

Remark 1.1. It is easy to show $\limsup_{t\to\infty} S(t) \leqq 1$. So the response function $f_i(S)$, $i = 1, 2$ in (1.2) is a uninhibited function or an inhibited function depending on $\rho > S^{(0)}$ or $\rho < S^{(0)}$ respectively where $S^{(0)}$ is equal to 1.

2 Preliminaries

Let $\Sigma(t) = 1 - S(t) - x_1(t) - x_2(t)$. The system (1.2) may be written

$$\begin{aligned} \dot{\Sigma} &= -\Sigma\,, \\ \dot{S} &= 1 - S - x_1 f_1(S) - (1 - \Sigma - S - x_1) f_1(S)\,, \\ \dot{x}_1 &= x_1(f_1(S)(1-q) - 1)\,. \end{aligned} \tag{2.1}$$

Clearly $\lim_{t\to\infty}\Sigma(t) = 0$ and so the omega limit set of solution of (1.2) is contained in the set

$$\Lambda = \{(S, x_1, x_2) | S \geqq 0, x_1 \geqq 0, x_2 \geqq 0, \Sigma = 0\}\,.$$

The limiting system, obtained by restricting the initial conditions to the set Λ is

$$\begin{aligned} \dot{S} &= (1 - S)(1 - f_2(S)) - x_1(f_1(S) - f_2(S))\,, \\ \dot{x}_1 &= x_1(f_1(S)(1-q) - 1)\,. \end{aligned} \tag{2.2}$$

These equations, of course, are restricted to the region

$$\Omega = \{(S, x_1) | S \geqq 0, x_1 \geqq 0, S + x_1 \leqq 1\}\,.$$

The boundary of Ω satisfies the following properties:

i) $(S + x_1)(t_0) = 1$, for some $t_0 \geqq 0$, then $\dot{S} + \dot{x}_1 = -qx_1 f_1(S) < 0$ $(Sx_1 \neq 0)$;
ii) $S(t_0) = 0$ for some $t_0 \geqq 0$ then $\dot{S} > 0$;
iii) $x_1(t_0) = 0$ for some $t_0 \geqq 0$ then $x_1(t) = 0$ and $0 \leqq S(t) \leqq 1$ as $t \geqq t_0$.

Therefore, Ω is a positively invariant region.

We use the following notation for the relevant rest points of system (1.2). We say that a rest point of (1.2) does not exist if any one of its components is negative. Since $\lim_{t\to\infty}\Sigma(t) = 0$, any rest point $E = (\bar{S}, \bar{x}_1, \bar{x}_2)$ of (1.2) must satisfy

$$1 - \bar{S} - \bar{x}_1 - \bar{x}_2 = 0\,.$$

The washout rest point is denoted $E_1^3 = (1, 0, 0)$. There are two possible plasmid-free rest points, denoted $E_2^3 = (\lambda_2, 0, 1 - \lambda_2)$, $E_3^3 = (\mu_2, 0, 1 - \mu_2)$ where λ_2 and μ_2 solve the equation $f_2(S) = 1$. (If both exist, let λ_2 be the smaller one.) The mixed culture rest points are denoted $E_{c_1}^3 = (\lambda_1, x_{11}, x_{12})$, $E_{c_2}^3 = (\mu_1, x_{21}, x_{22})$, where λ_1 and μ_1 solve the equation $f_1(S) = 1/(1-q)$ (if both exist, let λ_1 be the smaller one) and

$$x_{11} = \frac{(1 - \lambda_1)(1 - f_2(\lambda_1))}{f_1(\lambda_1) - f_2(\lambda_1)}\,,$$

$$x_{12} = (1 - \lambda_1 - x_{11})\,,$$

$$x_{21} = \frac{(1-\mu_1)(1-f_2(\mu_1))}{f_1(\mu_1) - f_2(\mu_1)},$$

$$x_{22} = (1 - \mu_1 - x_{21}) \,. \tag{2.3}$$

It can easily be seen that no rest point can exist where there are plasmid-bearing but no plasmid-free organisms. The corresponding rest points of (2.2) are simply the projections on $(S - x_1)$ space and are denoted: $E_1 = (1,0)$, $E_2 = (\lambda_2, 0)$, $E_3 = (\mu_2, 0)$, $E_{c_1} = (\lambda_1, x_{11})$, $E_{c_2} = (\mu_1, x_{21})$.

We assume that these do not exist if either component is negative or if the sum of the compounds exceeds 1, since then it would be outside Ω. (This would force the x_2 component in the corresponding rest point in (1.2) to be negative.)

In this paper we analyze the following three types with different response functions:

Type A: f_1 is inhibited, f_2 is uninhibited;
Type B: f_1 is uninhibited, f_2 is inhibited;
Type C: f_1, f_2 are both inhibited.

(*Note*: We will write x instead of x_1 in (2.2) to avoid unnecessary subscripting.)

The case that f_1 and f_2 are both uninhibited was analyzed in the paper [HWW]. In the Sect. 3, we shall give the mathematical analysis and the biological interpretations of Type A species. The mathematical analysis and the biological interpretations of Type B species and Type C species are given in the Sect. 4 and Sect. 5 respectively. There will be a biological discussion for the model (1.2) in the Sect. 6. At the end of this paper, we have Appendices A, B, C, D, and E which contain the figures for references.

3 Analysis of Type A species

3.1. If we consider the analysis of Type A on Ω, there are nine subcases. The reader can refer to the Table 3.1.

From the list in the Table 3.1, we can easily solve the rest point in each case. The set of rest points are shown in the Table 3.2 for each case.

The variational matrix J of (2.2) takes the form

$$J = \begin{bmatrix} -(1-f_2(S)) - (1-S)f_2'(S) - x(f_1'(S) - f_2'(S)), & -(f_1(S) - f_2(S)) \\ x f_1'(S)(1-q), \; f_1(S)(1-q) - 1 & \end{bmatrix}.$$

It is easy to compute the eigenvalues of the variational matrix J at the associated rest points. The Table 3.3 shows the local stability property for each case of Type A.

Table 3.1

A_1	$f_1(\rho_1) < \frac{1}{1-q}$, $f_2(1) < 1$
A_2	$f_1(\rho_1) < \frac{1}{1-q}$, $f_2(1) > 1$
A_3	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) > \frac{1}{1-q}$, $f_2(1) < 1$
A_4	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) > \frac{1}{1-q}$, $f_2(1) > 1, 0 < \lambda_1 < \lambda_2 < 1$
A_5	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) > \frac{1}{1-q}$, $f_2(1) > 1, 0 < \lambda_2 < \lambda_1 < 1$
A_6	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) < \frac{1}{1-q}$, $f_2(1) < 1$
A_7	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) < \frac{1}{1-q}$, $f_2(1) > 1, 0 < \lambda_1 < \lambda_2 < \mu_1 < 1$
A_8	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) < \frac{1}{1-q}$, $f_2(1) > 1, 0 < \lambda_2 < \lambda_1 < 1$
A_9	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) < \frac{1}{1-q}$, $f_2(1) > 1, 0 < \mu_1 < \lambda_2 < 1$

ρ_1 is the maximum point of f_1, λ_1 and μ_1 solve $f_1(S) = 1/(1-q)$ and λ_2 solves $f_2(S) = 1$.

Remark 3.1. In Table 3.3, for the rest points E_1 and E_2, stable and unstable means stable node and unstable node respectively. However for the interior rest point E_{c_1}, stable (unstable) means stable node (unstable node) or stable focus (unstable focus) depending on the parameter q or D. Similarly for the Table 4.3 and Table 5.3 in Sect. 4 and Sect. 5, "stable" and "unstable" have the same interpretations for boundary rest points E_1, E_2, E_3 and interior rest point E_{c_1}.

Based on the local stability analysis in the Table 3.3, the main results are stated in the following theorems.

Theorem 3.1 i) *For the case A_1, E_1 is a global attractor of Ω.* ii) *For each of the cases A_2, A_5, A_8, E_2 is a global attractor of Ω. (See Figs. A_1, A_2, A_5, A_8 in Appendix A.)*

Theorem 3.2 *For each of the cases A_3, A_4, A_7, E_{c_1} is a global attractor in the interior of Ω. (See Figs. A_3, A_4, A_7 in Appendix A.)*

Table 3.2

Case	The rest points set
A_1	E_1
A_2	E_1, E_2
A_3	E_1, E_{c_1}
A_4	E_1, E_2, E_{c_1}
A_5	E_1, E_2
A_6	E_1, E_{c_1}, E_{c_2}
A_7	E_1, E_2, E_{c_1}
A_8	E_1, E_2
A_9	E_1, E_2, E_{c_1}, E_{c_2}

Table 3.3

	E_1	E_2	E_{c_1}	E_{c_2}
A_1	$s_\star$	$\star$	$\star$	$\star$
A_2	sa	$s_\star$	$\star$	$\star$
A_3	sa	$\star$	$s_{\star\star}$	$\star$
A_4	$u_\star$	sa	$s_{\star\star}$	$\star$
A_5	$u_\star$	$s_\star$	$\star$	$\star$
A_6	$s_\star$	$\star$	$s_{\star\star}$	sa
A_7	sa	sa	$s_{\star\star}$	$\star$
A_8	sa	$s_\star$	$\star$	$\star$
A_9	sa	$s_\star$	$s_{\star\star}$	sa

s: stable; u: unstable; sa: saddle; $\star$: the absence of the rest point; $_\star$: node; $_{\star\star}$: node or focus

Theorem 3.3 i) *For the case A_6, the stable manifold Γ of E_{c_2} separates the region Ω into two regions Ω_1 and Ω_2 where Ω_1, Ω_2 are attracted by E_{c_1}, E_1 respectively.* ii) *For the case A_9, the stable manifold Γ of E_{c_2} separates the region Ω into two regions Ω_1, Ω_2 where Ω_1, Ω_2 are attracted by E_{c_1}, E_2 respectively.* (*See Figs. A_6, A_9 in Appendix A.*)

Proof of Theorem 3.1. Since there is no interior rest point in Ω for each case of A_1, A_2, A_5, A_8, it follows that for each of these cases no limit cycle exists. Thus the global stability of E_1 and E_2 for the case A_1 and the cases A_2, A_5, A_8, respectively follows directly from the Pioncarè-Bendixson Theorem and the local asymptotic stability of E_1 and E_2. Q.E.D.

Two lemmas will be given before we prove Theorem 3.2.

Lemma 3.4 *For each of the cases* A_3, A_4, A_7, *there exist* v_1, v_2, *such that*

$$\Omega' \equiv \Omega \cap \{(S,x) \mid 0 < v_1 < S < v_2 \leqq 1\}$$

is a positive invariant set. On the region Ω', *we have that* $f_1(S) > 1 > f_2(S)$. *The trajectory will enter* Ω' *eventually.*

Proof. Let v_1 satisfies $f_1(v_1) = 1$. Since $f_1(\lambda_1) = 1/(1-q) > 1$, it follows that $0 < v_1 < \lambda_1$. Let v_2 be λ_2 if $f_2(1) > 1$ or $v_2 = 1$ if $f_2(S) < 1$ for $0 < S < 1$. We note that in cases A_3, A_4, A_7, $\lambda_1 < \lambda_2$ if λ_2 exist. Hence $f_2(\lambda_1) < 1$. Let

$$\Omega' \equiv \Omega \cap \{(S,x) \mid 0 < v_1 < S < v_2 \leqq 1\} .$$

From (2.2) we have for $(S,x) \in \Omega'$

$$\begin{aligned} \left.\frac{dS}{dt}\right|_{S=v_1} &= (1-v_1)(1-f_2(v_1)) - x(f_1(v_1) - f_2(v_1)) \\ &= (1-f_2(v_1))(1-v_1-x) \\ &> 0 , \end{aligned}$$

$$\left.\frac{dS}{dt}\right|_{S=v_2} = (1-v_2)(1-f_2(v_2)) - x(f_1(v_2) - f_2(v_2)) .$$

If $v_2 = \lambda_2$ then from $f_1(v_2) > 1/1-q > 1$, it follows that

$$\left.\frac{dS}{dt}\right|_{S=v_2} = -x(f_1(v_2) - 1) < 0 .$$

It is easy to verify that Ω' is a positively invariant region and from Poincarè-Bendixson Theorem the trajectory will enter Ω' in finite time (see Figs. A_3, A_4, A_7 in Appendix A). Since $f_1(v_1) = 1$ and $f_2(v_2) \leqslant 1$, it follows that

$$f_1(S) > 1 > f_2(S) \quad \text{in } \Omega' . \tag{3.1}$$

Q.E.D.

Lemma 3.5 *Let* $a > b > 1 > c > d > 0$. *Then* $(1-c)/(a-c) < (1-d)/(b-d)$.

Proof. Let $h(x)$, $g(x)$ be strictly increasing differentiable functions defined on $[0,1]$ satisfying

$$h(0) = d, \qquad h(1) = c, \qquad g(0) = b, \qquad g(1) = a$$

and

$$f(x) = \frac{1 - h(x)}{g(x) - h(x)} .$$

Then

$$\begin{aligned} f'(x) &= \frac{(g-h)(-h') - (1-h)(g'-h')}{(g-h)^2} \\ &= \frac{h'(1-g) + (h-1)g'}{(g-h)^2} \\ &< 0 . \end{aligned}$$

Hence

$$f(1) < f(0)$$

or

$$\frac{1-c}{a-c} < \frac{1-d}{b-d} .$$

Q.E.D.

Proof of Theorem 3.2. We construct a Lyapunov function

$$V(S,x) = \int_{\lambda_1}^{S} \frac{f_1(\eta)(1-q) - 1}{f_1(\eta) - f_2(\eta)}\, d\eta + \int_{x_1^*}^{x} \frac{\eta - x_1^*}{\eta}\, d\eta \quad \text{on } \Omega' , \tag{3.2}$$

where $x_1^* = x_{11}$ in (2.3), then

$$\dot{V} = (f_1(S)(1-q) - 1)\left(\frac{(1-S)(1-f_2(S))}{f_1(S) - f_2(S)} - x_1^*\right) . \tag{3.3}$$

There are two possible cases, namely,

i) $\nu_1 < \nu_2 < \rho_1$;
ii) $\nu_1 < \rho_1 < \nu_2$.

Let $(\nu_1, \nu_2) = (\nu_1, \lambda_1) \cup [\lambda_1, \nu_2)$. Let

$$\phi(S) = \frac{(1-S)(1-f_2(S))}{f_1(S) - f_2(S)} - x_1^* . \tag{3.4}$$

Then $\phi(\lambda_1) = 0$. From (3.3), if we are able to show that

$$\phi(S) > 0 \quad \text{on } (\nu_1, \lambda_1) \tag{3.5}$$

and

$$\phi(S) < 0 \quad \text{on } (\lambda_1, \nu_2) \tag{3.6}$$

then $\dot{V} \leqq 0$. By LaSalle's Invariance Principle [H], we complete the proof of Theorem 3.2. If $\nu_1 < \nu_2 < \rho_1$, then

$$f_1'(S) > 0, \quad \text{for } \nu_1 < S < \nu_2 . \tag{3.7}$$

Since

$$\phi'(S) = \frac{(f_1(S) - f_2(S))(f_2(S) - 1) + (f_1(S) - f_2(S))(1 - S)(-f_2'(S))}{(f_1(S) - f_2(S))^2}$$

$$- \frac{(1 - S)(1 - f_2(S))(f_1'(S) - f_2'(S))}{(f_1(S) - f_2(S))^2}$$

$$= \frac{(f_1(S) - f_2(S))(f_2(S) - 1) + (1 - f_2(S))(1 - S)(-f_1'(S))}{(f_1(S) - f_2(S))^2}$$

$$- \frac{(1 - S)(f_1(S) - 1)(f_2'(S))}{(f_1(S) - f_2(S))^2}$$

From (3.1), (3.7) $\phi'(S) < 0$, for all $v_1 < S < v_2$. Hence (3.5) and (3.6) hold.

If $v_1 < \rho_1 < v_2$, then from the fact $\lambda_1 < \rho_1$, we write

$$(v_1, v_2) = (v_1, \lambda_1] \cup [\lambda_1, \rho_1) \cup [\rho_1, v_2) .$$

Since $f_1'(S) > 0$ on (v_1, ρ_1), we have $\phi'(S) < 0$ on (v_1, ρ_1). Obviously (3.5) hold. In order to establish (3.6), it suffices to show that $\phi(S) < 0$ for $\rho_1 < S < v_2$. From (3.3) it suffices to show

$$\frac{(1 - S)(1 - f_2(S))}{f_1(S) - f_2(S)} < \frac{(1 - \lambda_1)(1 - f_2(\lambda_1))}{f_1(\lambda_1) - f_2(\lambda_1)} \quad \text{for } \rho_1 < S < v_2 .$$

Since $1 - \lambda_1 > 1 - S$ for $\rho_1 < S < v_2$, it suffices to show that

$$\frac{(1 - f_2(\lambda_1))}{f_1(\lambda_1) - f_2(\lambda_1)} > \frac{(1 - f_2(S))}{f_1(S) - f_2(S)}, \quad \text{for } \rho_1 < S < v_2 .$$

Let $d = f_2(\lambda_1)$, $c = f_2(S)$, $b = f_1(\lambda_1)$, and $a = f_1(S)$, since $\lambda_1 < \rho_1 < S < v_2$, it follows that

$$f_2(v_2) = 1 > c = f_2(S) > f_2(\lambda_1) = d$$

and

$$a = f_1(S) > \frac{1}{1 - q} = f_1(\lambda_1) = b > 1 .$$

From Lemma 3.5, we have

$$\frac{(1 - S)(1 - f_2(S))}{f_1(S) - f_2(S)} < \frac{(1 - \lambda_1)(1 - f_2(\lambda_1))}{f_1(\lambda_1) - f_2(\lambda_1)} .$$

Thus we complete the proof of Theorem 3.2. Q.E.D.

Proof of Theorem 3.3. It is easy to see that E_1 and E_2 attracts each point of Ω_2 in the case A_6 and the case A_9 respectively (see the Figs. A_6, A_9 in

Appendix A). From Poincarè-Bendixson Theorem, the trajectory with intial conditions in Ω_1, it will enter the region $S \leqq \mu_1$ in finite time. For the cases A_6, A_9 we have $\nu_2 = \lambda_2 > \mu_1$ and $\nu_2 = 1 > \mu_1$ respectively. Then the trajectory will stay in the region $\Omega' = \{(S, x) \mid \nu_1 < S < \mu_1 < \nu_2\}$. As we did in Theorem 3.2, we construct the Liapunov function V in (3.2) with $\dot{V} \leqq 0$ in $\Omega' \cap \Omega_1$. If there exists a periodic orbit in Ω_1, then the periodic orbit $\{(S^*(t), x^*(t))\}_{0 \leqq t \leqq T}$ lies in the region $\Omega' \cap \Omega_1$. Then

$$0 = \int_0^T \frac{dV}{dt}(S^*(t), x^*(t))dt = \int_0^T \dot{V} d t < 0 .$$

This is a contradiction. Hence no periodic solution in Ω_1. Hence E_{c_1} attracts each point in Ω_1. Q.E.D.

3.2 In Theorem 1.5 of [T] states that for an asymptotically quasi-autonomous system if there is no chain of equilibria in the limit equation, then the ω-limit set of a bounded trajectory of the asymptotically autonomous system will consists of an equilibrium or a periodic orbit. From this theorem and the above analysis, the global results for Type A species in the equations (1.2) follows. In order to give biological interpretations in this section and also in Sect. 4 and Sect. 5, for the uninhibited growth function $f_i(S)$, we restrict our attentions to the Monod model

$$f_i(S) = \frac{m_i S}{a_i + S} \tag{3.8}$$

where m_i is the maximal specific growth rate and a_i is the Michaelis-Menten constant. For the inhibited growth function $f_i(S)$, we restrict our attentions to the Andrews model

$$f_i(S) = \frac{m_i S}{a_i + S + K_i S^2} \tag{3.9}$$

where the parameter K_i measure the inhibition effect. It is easy to verify that the function $f_i(S)$ in (3.8) is strictly monotone and the function $f_i(S)$ in (3.9) attains the unique maximum $m_i/(1 + 2\sqrt{a_i K_i})$ at $S = \rho_i = \sqrt{a_i/K_i}$. Hence when the inhibition constant K_i is large, ρ_i and $f_i(\rho_i)$ become small. Under the scaling which reduce the equations (1.1) to the equation (1.2), the "new" parameters m_i, a_i, K_i, S, x_i are the "old" m_i/D, $a_i/S^{(0)}$, $K_i S^{(0)}$, $S/S^{(0)}$, $x_i/\gamma S^{(0)}$ respectively, where $S^{(0)}$, D are input concentration of the substrate and the dilution rate respectively. For the biological interpretation of the results of Type A species, we state in terms of the original parameters and $f_1(S) = m_1 S/(a_1 + S + K_1 S^2)$ and $f_2(S) = m_2 S/(a_2 + S)$.

The rest points in terms of the original parameters are:

$$\mathscr{E}_1 = (S^{(0)}, 0, 0),$$

$$\mathscr{E}_2 = (\lambda_2, 0, \gamma(S^{(0)} - \lambda_2)) \quad \text{where } f_2(\lambda_2) = D ,$$

$$\mathscr{E}_{c_1} = \left(\lambda_1, \frac{\gamma(S^{(0)} - \lambda_1)(D - f_2(\lambda_1))}{f_1(\lambda_1) - f_2(\lambda_1)}, \frac{\gamma(S^{(0)} - \lambda_1)(f_1(\lambda_1) - D)}{f_1(\lambda_1) - f_2(\lambda_1)}\right),$$

$$\mathscr{E}_{c_2} = \left(\mu_1, \frac{\gamma(S^{(0)} - \mu_1)(D - f_2(\mu_1))}{f_1(\mu_1) - f_2(\mu_1)}, \frac{\gamma(S^{(0)} - \mu_1)(f_1(\mu_1) - D)}{f_1(\mu_1) - f_2(\mu_1)}\right)$$

where λ_1, μ_1 solve $f_1(S)(1 - q) = D$ and $\lambda_1 < \mu_1$. The rescaling of Table 3.1 is shown in Table 3.4.

Remark 3.2. In the followings, we recall some results from [HHW] and [BW]. Consider the one species chemostat equation

$$\begin{aligned} \dot{S} &= (S^{(0)} - S)D - f(S)x , \\ \dot{x} &= (f(S) - D)x , \\ S(0) &\geqq 0, \quad x(0) > 0, \quad i = 1,2 . \end{aligned} \tag{3.10}$$

If the functional response $f(S)$ is of Michaelis-Menten type, i.e., $f(S) = mS/(a + S)$, then the authors of [HHW] proved the followings:

(i) If $f(S^{(0)}) \leqq D$, then $\lim_{t\to\infty} x(t) = 0$ and $\lim_{t\to\infty} S(t) = S^{(0)}$. In this case, the input concentration $S^{(0)}$ is too small or the dilution rate D is too large for the species to survive.

Table 3.4

Case	Criteria for existence of rest points	Rest points
A_1	$f_1(\rho_1)(1 - q) < D,\ f_2(S^{(0)}) < D$	$\mathscr{E}_1$
A_2	$f_1(\rho_1)(1 - q) < D,\ f_2(S^{(0)}) > D$	$\mathscr{E}_1, \mathscr{E}_2$
A_3	$f_1(\rho_1)(1 - q) > D,\ f_1(S^{(0)})(1 - q) > D,\ f_2(S^{(0)}) < D$	$\mathscr{E}_1, \mathscr{E}_{c_1}$
A_4	$f_1(\rho_1)(1 - q) > D,\ f_1(S^{(0)})(1 - q) > D,\ f_2(S^{(0)}) > D,$ $0 < \lambda_1 < \lambda_2 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_{c_1}$
A_5	$f_1(\rho_1)(1 - q) > D,\ f_1(S^{(0)})(1 - q) > D,\ f_2(S^{(0)}) > D,$ $0 < \lambda_2 < \lambda_1 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2$
A_6	$f_1(\rho_1)(1 - q) > D,\ f_1(S^{(0)})(1 - q) < D,\ f_2(S^{(0)}) < D$	$\mathscr{E}_1, \mathscr{E}_{c_1}, \mathscr{E}_{c_2}$
A_7	$f_1(\rho_1)(1 - q) > D,\ f_1(S^{(0)})(1 - q) < D,\ f_2(S^{(0)}) > D,$ $0 < \lambda_1 < \lambda_2 < \mu_1 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_{c_1}$
A_8	$f_1(\rho_1)(1 - q) > D,\ f_1(S^{(0)})(1 - q) < D,\ f_2(S^{(0)}) > D,$ $0 < \lambda_2 < \lambda_1 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2$
A_9	$f_1(\rho_1)(1 - q) > D,\ f_1(S^{(0)})(1 - q) < D,\ f_2(S^{(0)}) > D,$ $0 < \mu_1 < \lambda_2 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_{c_1}, \mathscr{E}_{c_2}$

(ii) If $f(S^{(0)}) > D$, i.e., the break-even concentration $\lambda = a/(m/D - 1) < S^{(0)}$, then $\lim_{t\to\infty} x(t) = x^* = S^{(0)} - \lambda$ and $\lim_{t\to\infty} x(t) = \lambda$. In this case the species survives due to the larger $S^{(0)}$ and smaller D.

If the functional response $f(S)$ is inhibited and is of Andrews type, i.e., $f(S) = mS/(a + S + KS^2)$, then the authors of [BW] proved the followings:

(i) If $D \geqq \max_{0 \leqq S \leqq S^{(0)}} f(S) = f(\rho) = m/(1 + 2\sqrt{aK})$ then $\lim_{t\to\infty} x(t) = 0$ and $\lim_{t\to\infty} S(t) = S^{(0)}$. In this case, the highly inhibited growth of the species or the large dilution rate causes the extinction of the species.

(ii) If $f(S^{(0)}) \leqq D < f(\rho)$ then we have three rest points $E_0 = (S^{(0)}, 0)$, $E_1 = (\lambda, x_1^*)$, $E_2 = (\mu, x_2^*)$ where $0 < \lambda < \mu < S^{(0)}$ satisfy $f(\lambda) = f(\mu) = D$, $\lambda + x_1^* = \mu + x_2^* = S^{(0)}$. Furthermore (μ, x_2^*) is a saddle point with one-dimensional manifold Γ separating the first quadrant of the S–x plane into two regions Ω_1 and Ω_2. The asymptotically stable rest points (λ, x_1^*), $(S^{(0)}, 0)$ attracts each points of Ω_1, Ω_2 respectively. In this case, the species either goes to extinction or survives depending on the initial populations.

(iii) If $f(S^{(0)}) > D$, then $\lim_{t\to\infty} x(t) = x^*$ and $\lim_{t\to\infty} S(t) = \lambda$ where $f(\lambda) = D$ and $\lambda + x^* = S^{(0)}$. In this case the species survives and goes to a steady state.

Next we consider the chemostat equation with two species:

$$\begin{aligned} \dot S &= (S^{(0)} - S)D - f_1(S)x_1 - f_2(S)x_2 \\ \dot x_1 &= (f_1(S) - D)x_1 , \\ \dot x_2 &= (f_2(S) - D)x_2 , \\ S(0) &\geqq 0, \quad x_1(0) > 0, \quad x_2(0) > 0, \quad i = 1,2 . \end{aligned} \tag{3.11}$$

where the functional response $f_i(S)$, $i = 1, 2$ is either uninhibited or inhibited. For each $i = 1, 2$ let λ_i, μ_i be the break-even concentrations of i-th species, i.e., λ_i, μ_i satisfy $f_i(\lambda_i) = f_i(\mu_i) = D$, $\lambda_i < \mu_i$ in the case of inhibited functional response and setting $\mu_i = +\infty$ when $f_i(S)$ is uninhibited.

In the following we state the results in [BW] which will be used in the biological interpretations for the Type A, B, C species.

Theorem 3.6 [BW]. *Let* $Q = (\lambda_1, \mu_1) \cup (\lambda_2, \mu_2)$ *and* $\lambda_1 < \lambda_2 < S^{(0)}$ *and* Λ *denote the set of left endpoints of components of* Q *together with* $S^{(0)}$, *if* $S^{(0)}$ *is not in the set* Q. *With the exception of a set of initial conditions of Lebesque measure zero, all solutions of* (3.11) *satisfy*

$$\lim_{t\to\infty} S(t) = \gamma, \quad \gamma \in \Lambda$$

with the corresponding asymptotic behavior

$$lim_{t\to\infty} x_i(t) = S^{(0)} - \lambda_i, \qquad \lim_{t\to\infty} x_j(t) = 0 ,$$

where $j \neq i$ *if* $\gamma = \lambda_i$ *and* $\lim_{t\to\infty} x_j(t) = 0, j = 1, 2$ *if* $\gamma = S^{(0)}$. *Furthermore if* Q *is connected, then* $\lim_{t\to\infty} x_2(t) = 0$. *If, in addition,* $S^{(0)} \in Q$ *then* $(\lambda_1, S^{(0)} - \lambda_1, 0)$ *is globally asymptotically stable for* (3.11).

Now we are in a position to give the biological interpretations for each case A_i: $A_1 \sim A_2$: Species 1 (plasmid-bearing species) cannot survive alone due to the large dilution rate D or highly inhibited growth. In the case A_1, the input concentration $S^{(0)}$ is too small or D is too large to support the survival of the species 2 (plasmid-free species) alone. Hence both species go to extinction. In the case A_2, species 2 is able to survive alone under $S^{(0)}$ and D. Hence species 1 goes to extinction and species 2 eventually takes over the culture.

$A_3 \sim A_5$: In these cases, species 1 is able to survive alone. In the case A_3, species 2 cannot survive alone. However a fraction of species 1 is converted into species 2, the coexistence of both species follows. In the case A_4, species 2 is also able to survive alone. The break-even concentration λ_1 of species 1 is smaller than λ_2, the break-even concentration of species 2. Then species 2 is an inferior competitor. Hence both species coexist due to the conversion of a fraction of species 1 into species 2. In the case A_5, species 1 has larger break-even concentration. Then species 1 is an inferior competitor. This causes the extinction of species 1.

$A_6 \sim A_9$: In these cases, species 1 either goes to extinction or survives in the absence of species 2. In the case A_6, species 2 cannot survive alone. Hence either both species are washed out or both coexists. The outcomes depend on the initial populations. In the cases A_7, A_8, A_9, species 2 is able to survive alone. In the case A_7, the break-even concentration λ_2 of species 2 lies between those λ_1, μ_1 of species 1. From Theorem 3.6, species 1 is a better competitor. Hence both species coexists. In the case A_8, species 2 has smaller break-even concentration. From Theorem 3.6, species 2 is a better competitor and hence species 1 goes to extinction. In the case A_9, in the absence of conversion of species 1 into species 2, either species 1 or species 2 survive (see Theorem 3.6). Hence either species 1 goes to extinction or they coexist depending on the initial populations.

In order to see how the species 1 (the plasmid-bearing species) survives as the dilution rate D is gradually decreased, we consider the following case, namely, $f_2(S) > f_1(S)(1-q)$ for all $0 < S < \tilde{S}$, $f_2(S) < f_1(S)(1-q)$ for all $\tilde{S} < S < S^{(0)}$ where $0 < \tilde{S} < \rho_1$ for demonstration. Fig. E_1 in Appendix E is the bifurcation diagram of the dilution rate D with respect to the plasmid-bearing population in the steady state for this case. In a similar manner it is easy to see that effect of varying the input concentration $S^{(0)}$.

4 Analysis of Type B species

4.1 For the analysis of Type B on Ω, there are ten subcases. The reader can refer to the Table 4.1.

The set of rest points are shown in Table 4.2 for each case of Type B.

Table 4.1

B_1	$f_1(1) < \frac{1}{1-q}$, $f_2(\rho_2) < 1$
B_2	$f_1(1) < \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) > 1$
B_3	$f_1(1) < \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) < 1$
B_4	$f_1(1) > \frac{1}{1-q}$, $f_2(\rho_2) < 1$, $0 < \lambda_1 < \rho_2 < 1$
B_5	$f_1(1) > \frac{1}{1-q}$, $f_2(\rho_2) < 1$, $0 < \rho_2 < \lambda_1 < 1$
B_6	$f_1(1) > \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) > 1$, $0 < \lambda_1 < \lambda_2 < 1$
B_7	$f_1(1) > \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) > 1$, $0 < \lambda_2 < \lambda_1 < 1$
B_8	$f_1(1) > \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) < 1$, $0 < \lambda_1 < \lambda_2 < 1$
B_9	$f_1(1) > \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) < 1$, $0 < \lambda_2 < \lambda_1 < \mu_2 < 1$
B_{10}	$f_1(1) > \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) < 1$, $0 < \mu_2 < \lambda_1 < 1$

ρ_2 denotes the maximal point of f_2, λ_1 solves $f_1(S) = 1/(1-q)$, and λ_2, μ_2 solves $f_2(S) = 1$.

It is a routine computation to evaluate the eigenvalues of the variational matrix J at the associated rest points. The following Table 4.3 gives the local stability properties for each case of Type B.

Since the analysis for the cases of Type B on Ω is similar to that of Type A on Ω, we only state the results in the following. In the meantime, the reader can refer to the phase portrait of each case in Appendix B.

B_1: Obviously E_1 is globally asymptotically stable.
B_2: Obviously E_2 is globally asymptotically stable.
B_3: The stable manifold Γ of E_3 separates the region Ω into two regions Ω_1, Ω_2. Obviously E_2, E_1 have the domain of attraction Ω_1, Ω_2 respectively.
B_4: This case and B_5, B_{10} are the most interesting cases of Type B in mathematical sense. Here we only state the results. The further details will be described later.

Table 4.2

Case	The rest points set
B_1	E_1
B_2	E_1, E_2
B_3	E_1, E_2, E_3
B_4	E_1, E_{c_1}
B_5	E_1, E_{c_1}
B_6	E_1, E_2, E_{c_1}
B_7	E_1, E_2
B_8	E_1, E_2, E_3, E_{c_1}
B_9	E_1, E_2, E_3
B_{10}	E_1, E_2, E_3, E_{c_1}

Table 4.3

	E_1	E_2	E_3	E_{c_1}
B_1	$s_\star$	$\star$	$\star$	$\star$
B_2	sa	$s_\star$	$\star$	$\star$
B_3	sa	$s_\star$	sa	$\star$
B_4	$s_\star$	$\star$	$\star$	$s_{\star\star}$
B_5	sa	$\star$	$\star$	$s_{\star\star}$ or $u_{\star\star}$
B_6	$u_\star$	sa	$\star$	$s_{\star\star}$
B_7	$u_\star$	$s_\star$	$\star$	$\star$
B_8	sa	sa	$u_\star$	$s_{\star\star}$
B_9	sa	$s_\star$	$u_\star$	$\star$
B_{10}	sa	$s_\star$	sa	$s_{\star\star}$ or $u_{\star\star}$

s: stable; *u*: unstable; *sa*: saddle; $\star$: the absence of the rest point; $\star$: node; $\star\star$: node or focus

i) If $f_2(\lambda_1) < f_2(1)$, E_{c_1} is globally asymptotically stable.

ii) If $f_2(\lambda_1) > f_2(1)$, we are not able to prove the global stability of E_{c_1}.

B_5: E_{c_1} may be stable or unstable. As some parameters vary, there is a Hopf bifurcation for E_{c_1}.

B_6: As we did in Theorem 3.2, the trajectory will enter the region Ω'. We construct a Lyapunov function V on Ω' and show that E_{c_1} is globally asymptotically stable in the interior of Ω.

B_7: Since E_{c_1} does not exist, obviously E_2 is globally asymptotically stable.

B_8: Similar to the proof of Theorem 3.2, we can construct a Lyapunov fuction V on the invariant region Ω' and show that E_{c_1} is globally asymptotically stable in the interior of Ω.

B_9: Since no interior rest point exists, it is obvious that E_2 is globally asymptotically stable in the interior of Ω.

B_{10}: The stable manifold Γ of E_3 separates the region Ω into two regions Ω_1 and Ω_2. In Ω_1, each point is attracted by E_2. In Ω_2, as parameters vary, there is a Hopf bifurcation for E_{c_1} as in the case B_5.

Now we state some results for the cases B_4 and B_5. Let $a(S) = (1 - S)(1 - f_2(S))$ and $b(S) = f_1(S) - f_2(S)$, then the equations (2.2) becomes

$$\begin{cases} \dfrac{dS}{dt} = a(S) - xb(S) \ , \\ \dfrac{dx}{dt} = x(f_1(S)(1 - q) - 1) \ . \end{cases} \tag{4.1}$$

The interior rest point of (4.1) is (λ_1, x_1^*), where

$$f_1(\lambda_1) = \frac{1}{1-q},$$

$$x_1^* = \frac{(1-\lambda_1)(1-f_2(\lambda_1))}{f_1(\lambda_1) - f_2(\lambda_1)}. \tag{4.2}$$

For the cases B_4 and B_5, $E_{c_1} = (\lambda_1, x_1^*)$ exists because

$$x_1^* = (1-\lambda_1)\frac{1-f_2(\lambda_1)}{f_1(\lambda_1) - f_2(\lambda_1)} < 1 - \lambda_1.$$

The variational matrix at E_{c_1} is

$$\begin{bmatrix} a'(\lambda_1) - x_1^* b'(\lambda_1), & -b(\lambda_1) \\ x_1^*(1-q) f_1'(\lambda_1), & 0 \end{bmatrix}.$$

Since $-b(\lambda_1)x_1^*(1-q)f_1'(\lambda_1) < 0$, so the eigenvalues of the variational matrix have negative real parts if and only if

$$a'(\lambda_1) - x_1^* b'(\lambda_1) < 0$$

or

$$a'(\lambda_1) - \frac{a(\lambda_1)}{b(\lambda_1)} b'(\lambda_1) < 0$$

or

$$b(\lambda_1)\left(\frac{a(S)}{b(S)}\right)'\Bigg|_{S=\lambda_1} < 0.$$

Hence $E_{c_1} = (\lambda_1, x_1^*)$ is locally asymptotically stable if and only if the isocline $x = h(S) = a(S)/b(S)$ has negative slope at $S = \lambda_1$ and E_{c_1} is unstable if and only if

$$h'(\lambda_1) > 0.$$

Hence in order to understand the stability property of E_{c_1}, it suffices to know the shape of the isocline $x = h(S)$. Since

$$h(S) = \frac{(1-S)(1-f_2(S))}{f_1(S) - f_2(S)},$$

it follows that

$$h'(S) = \frac{f_2(S) - 1}{f_1(S) - f_2(S)} + \frac{1-S}{(f_1(S) - f_2(S))^2} \cdot [f_1'(S)(f_2(S) - 1) + f_2'(S)(1 - f_1(S))] \tag{4.3}$$

i) For the case B_4, the assumption $\lambda_1 < \rho_2$ implies $h'(\lambda_1) < 0$, i.e, E_{c_1} is locally asymptotically stable.

ii) For the case B_5, the assumption is $\lambda_1 > \rho_2$. If we fix $f_1(S)$ for $S \geqslant 0$ and $f_2(S)$ for $S \leqq \rho_2$. Let the function $f_2(S)$ change rapidly for some interval $(\tilde{\rho}_2, \tilde{\rho}_2 + c)$, then from (4.3), $h'(S) > 0$ for $\tilde{\rho}_2 < S < \tilde{\rho}_2 + c$ $(\tilde{\rho}_2 \geqq \rho_2)$. Then from (4.2) there is an interval $(q_{\min}, q_{\max})$ such that if $q \in (q_{\min}, q_{\max})$ then $h'(\lambda_1) > 0$. Hence it is possible to find parameters such that E_{c_1} is unstable and hence there exists a periodic solution for (2.2). Another way to explain the existence of periodic solutions, we may consider the important special case

$$f_2(S) = \frac{m_2 S}{a_2 + S + KS^2} .$$

Since

$$f_2'(S) = \frac{m_2(a_2 - KS^2)}{(a_2 + S + KS^2)^2} ,$$

$f_2(S)$ attains its maximum at $\rho_2 = (a_2/K)^{1/2}$. Assume $f_2(\rho_2) = 1$ then

$$(m_2 - 1)\left(\frac{a_2}{K}\right)^{1/2} = 2a_2$$

or

$$K = K^* = \frac{(m_2 - 1)^2}{4a_2} .$$

Assume $0 < \rho_2 < 1$ or $m_2 - 1 > 2a_2$. When $K = K^*$, from (4.3) the shape of the isocline $x = h(S, K^*)$ is like the Fig. D_1 in Appendix D.

Obviously for K near K^*, there exist an interval on which $h'(S, K) > 0$. Thus we may vary the parameter q such that λ_1 as a function of q satisfies that $h'(\lambda_1, K)$ is greater than zero. Hence the instability of E_{c_1} is possible. The Figs. D_2 and D_3 in Appendix D illustrate the existence of a stable limit cycle. Fig. D_2 gives the time course, while Fig. D_3 shows the limit cycle in the three-dimensional phase space. The result suggests that the plasmid-bearing organisms and the plasmid-free organisms may coexist in the form of oscillations.

For the case B_4, we have partial result for the global asymptotic stability of E_{c_1}. Let

$$f_2(\lambda_1) < f_2(1) . \tag{4.4}$$

First we shall show that under the assumption (4.4) the isocline $x = h(S)$ satisfies

$$(S - \lambda_1)(h(S) - x_1^*) < 0 \quad \text{for } 0 < S < 1 \ (S \neq \lambda_1) . \tag{4.5}$$

From the assumption $\lambda_1 < \rho_2$ and (4.3), it follows that $h'(S) < 0$ for $0 < S < \lambda_1$. To show (4.5), it suffices to show that $h(S) < h(\lambda_1)$ for $\lambda_1 < S < 1$ or equivalently

$$\frac{(1 - S)(1 - f_2(S))}{f_1(S) - f_2(S)} < \frac{(1 - \lambda_1)(1 - f_2(\lambda_1))}{f_1(\lambda_1) - f_2(\lambda_1)} \quad \text{for all } \lambda_1 < S < 1 .$$

Since $1 - S < 1 - \lambda_1$ for $\lambda_1 < S < 1$, it suffices to show that

$$\frac{(1 - f_2(S))}{f_1(S) - f_2(S)} < \frac{(1 - f_2(\lambda_1))}{f_1(\lambda_1) - f_2(\lambda_1)} \tag{4.6}$$

for all $\lambda_1 < S < 1$. Let $a = f_1(S)$, $b = f_1(\lambda_1) = 1/(1 - q)$, $c = f_2(S)$ and $d = f_2(\lambda_1)$ where $\lambda_1 < S < 1$ $(f_2(1) > f_2(\lambda_1))$, then $a > b > 1$, $1 > c > d$ and (4.6) follows directly from Lemma 3.5. Hence under the assumption (4.4), we obtain the global stability of E_{c_1}.

4.2 As we did in Sect. 3, we can apply Theorem 1.5 of [T] to obtain the global results of Type B for the equation (1.2). In the following, we give the biological interpretations for Type B species. Here $f_1(S) = m_1 S/(a_1 + S)$ and $f_2(S) = m_2 S/(a_2 + S + K_2 S^2)$. The rest points in terms of the original parameters are:

$$\mathscr{E}_1 = (S^{(0)}, 0, 0)\,,$$

$$\mathscr{E}_2 = (\lambda_2, 0, \gamma(S^{(0)} - \lambda_2))\,,$$

$$\mathscr{E}_3 = (\mu_2, 0, \gamma(S^{(0)} - \mu_2))\,,$$

$$\mathscr{E}_{c_1} = \left(\lambda_1, \frac{\gamma(S^{(0)} - \lambda_1)(D - f_2(\lambda_1))}{f_1(\lambda_1) - f_2(\lambda_1)}, \frac{\gamma(S^{(0)} - \lambda_1)(f_1(\lambda_1) - D)}{f_1(\lambda_1) - f_2(\lambda_1)}\right)$$

where $f_1(\lambda_1)(1 - q) = D$ and $f_2(\lambda_2) = f_2(\mu_2) = D$, $\lambda_2 < \mu_2 < S^{(0)}$. The rescaling of Table 4.1 is as follows.

In the following, we give the biological interpretations for each case B_i.

$B_1 \sim B_3$: In these cases, species 1 (plasmid-bearing species) cannot survive alone due to the large dilution rate D or small input concentration $S^{(0)}$. In the case B_1, species 2 (plasmid-free species) also cannot survive alone. Hence both species go to extinction. In the case B_2, species 2 is able to survive alone. Hence species 1 goes to extinction and species 2 takes over the culture. In the case B_3, in the absence of species 1, species 2 either survive or goes to extinction depending on the initial population. Hence either both species will be washed out or only species 2 survives depending on initial populaions.

$B_4 \sim B_5$: In these cases, species 1 is able to survive alone and species 2 cannot survive alone. Then both species coexist in the steady state for the case B_4 and may coexist in the form of oscillations for the case B_5.

$B_6 \sim B_7$: In these cases, both species are able to survive alone. In the case B_6, species 1 has smaller break-even concentration λ_1, hence both species coexist. In the case B_7, species 1 has larger break-even concentration and it is an inferior competitor. Due to the conversion of species 1 into species 2, species 1 goes to extinction and species 2 survives.

Table 4.4

Case	Criteria for existence of rest points	Rest points
B_1	$f_1(S^{(0)})(1-q) < D,\ f_2(\rho_2) < D$	$\mathscr{E}_1$
B_2	$f_1(S^{(0)})(1-q) < D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) > D$	$\mathscr{E}_1, \mathscr{E}_2$
B_3	$f_1(S^{(0)})(1-q) < D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) < D$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_3$
B_4	$f_1(S^{(0)})(1-q) > D,\ f_2(\rho_2) < D,\ 0 < \lambda_1 < \rho_2 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_{c_1}$
B_5	$f_1(S^{(0)})(1-q) > D,\ f_2(\rho_2) < D,\ 0 < \rho_2 < \lambda_1 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_{c_1}$
B_6	$f_1(S^{(0)})(1-q) > D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) > D,$ $0 < \lambda_1 < \lambda_2 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_{c1}$
B_7	$f_1(S^{(0)})(1-q) > D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) > D,$ $0 < \lambda_2 < \lambda_1 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2$
B_8	$f_1(S^{(0)})(1-q) > D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) < D,$ $0 < \lambda_1 < \lambda_2 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_3, \mathscr{E}_{c_1}$
B_9	$f_1(S^{(0)})(1-q) > D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) < D,$ $0 < \lambda_2 < \lambda_1 < \mu_2 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_3$
B_{10}	$f_1(S^{(0)})(1-q) > D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) < D,$ $0 < \mu_2 < \lambda_1 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_3, \mathscr{E}_{c_1}$

$B_8 \sim B_{10}$: In these cases, species 1 is able to survive alone and species 2, in the absence of species 1, either goes to extinction or survives depending on the initial population. In the case B_8, species 1 has smallest break-even concentration λ_1 and it should be a better competitor. Hence both species coexist. In the case B_9, λ_1 lies between two break-even concentration λ_2, μ_2 of species 2. From Theorem 3.6, species 2 is a better competitor. Hence species 2 survives and species 1 goes to extinct. It is interesting that our analysis shows species 2 survives in the steady state. In the case B_{10}, from Theorem 3.6, it follows that either species 1 or species 2 survives in the absence of conversion of species 1 into species 2. Hence either both species coexist or species 1 goes to extinction and species 2 survives depending on initial populations.

In order to see how the species 1 (the plasmid-bearing species) survives as the dilution rate D is gradually decreased, we consider the following case, namely, $f_1(S)(1-q) < f_2(S)$ for all $0 < S < \tilde{S}$ and $f_1(S)(1-q) > f_2(S)$ for all $\tilde{S} < S < S^{(0)}$ where $\rho_2 < \tilde{S} < S^{(0)}$ and $f_1(S^{(0)})(1-q) < f_2(\rho_2)$ for demonstration. Figure E_2 in Appendix E is the bifurcation diagram of the dilution rate D with respect to the plasmid-bearing population in the steady state for this case. In a similar manner it is easy to see that effect of varying the input concentration $S^{(0)}$.

5 Analysis of Type C species

5.1 In Type C, if we consider the analysis on Ω then there are twenty one subcases which are shown in the following.

Table 5.1

C_1	$f_1(\rho_1) < \frac{1}{1-q}$, $f_2(\rho_2) < 1$
C_2	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) > \frac{1}{1-q}$, $f_2(\rho_2) < 1$, $0 < \lambda_1 < \rho_2 < 1$
C_3	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) > \frac{1}{1-q}$, $f_2(\rho_2) < 1$, $0 < \rho_2 < \lambda_1 < 1$
C_4	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) < \frac{1}{1-q}$, $f_2(\rho_2) < 1$, $0 < \lambda_1 < \rho_2 < 1$
C_5	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) < \frac{1}{1-q}$, $f_2(\rho_2) < 1$, $0 < \rho_2 < \lambda_1 < 1$
C_6	$f_1(\rho_1) < \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) > 1$
C_7	$f_1(\rho_1) < \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) < 1$
C_8	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) > \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) > 1$, $0 < \lambda_1 < \lambda_2 < 1$
C_9	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) > \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) > 1$, $0 < \lambda_1 < \lambda_2 < 1$
C_{10}	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) < \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) > 1$, $0 < \lambda_2 < \lambda_1 < 1$
C_{11}	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) < \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) > 1$, $0 < \lambda_1 < \lambda_2 < \mu_1 < 1$
C_{12}	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) < \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) > 1$, $0 < \lambda_1 < \mu_1 < \lambda_2 < 1$
C_{13}	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) > \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) < 1$, $0 < \lambda_1 < \lambda_2 < 1$
C_{14}	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) > \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) < 1$, $0 < \lambda_2 < \lambda_1 < \mu_2 < 1$

Table 5.1 (continued)

C_{15}	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) > \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) < 1$, $0 < \mu_2 < \lambda_1 < 1$
C_{16}	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) < \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) < 1$, $0 < \lambda_1 < \mu_1 < \lambda_2 < \mu_2 < 1$
C_{17}	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) < \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) < 1$, $0 < \lambda_1 < \lambda_2 < \mu_1 < \mu_2 < 1$
C_{18}	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) < \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) < 1$, $0 < \lambda_2 < \lambda_1 < \mu_1 < \mu_2 < 1$
C_{19}	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) < \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) < 1$, $0 < \lambda_1 < \lambda_2 < \mu_2 < \mu_1 < 1$
C_{20}	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) < \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) < 1$, $0 < \lambda_2 < \lambda_1 < \mu_2 < \mu_1 < 1$
C_{21}	$f_1(\rho_1) > \frac{1}{1-q}$, $f_1(1) < \frac{1}{1-q}$, $f_2(\rho_2) > 1$, $f_2(1) < 1$, $0 < \lambda_2 < \mu_2 < \lambda_1 < \mu_1 < 1$

ρ_1, ρ_2 denote the maximal point of f_1, f_2 respectively, λ_1, μ_1 solve $f_1(S) = 1/(1-q)$, and λ_2, μ_2 solve $f_2(S) = 1$.

The rest points set and the local analysis correspondence to each case are shown in the Tables 5.2 and 5.3.

Since the analysis for Type C on Ω is similar to that for Type A and Type B on Ω, we only state the results in the following. (See the figures in Appendix C.)

C_1: Obviously E_1 is globally asymptotically stable.

C_2: E_{c_1} is locally asymptotically stable. As in the case B_4, we have

i) If $f_2(1) > f_2(\lambda_1)$, then E_{c_1} is globally asymptotically stable;

ii) $f_2(1) \leqq f_2(\lambda_1)$, the global result is unknown.

C_3: Similar to the case B_5, E_{c_1} may be stable or unstable.

C_4: E_{c_2} is a saddle point with one dimensional stable manifold Γ separating the region Ω into two regions Ω_1 and Ω_2. E_1 is locally asymptotically stable and attracts each point in Ω_2. As in the case A_3, it can be shown that if $\mu_1 < \rho_2$, then E_{c_1} attracts each point in the interior of Ω_1. When $f_2(\lambda_1) > f_2(\mu_1)$, we conjecture that E_{c_1} attracts each point in Ω_1.

C_5: E_{c_1} may be stable or unstable. Hence Hopf bifurcation may occur as the parameters vary.

C_6: Obviously E_2 is globally asymptotically stable.
C_7: E_3 is a saddle point. As in the case B_3, E_2 attracts each point in Ω_1, and E_1 attracts each point in Ω_2.
C_8: Obviously E_2 is globally asymptotically stable.
C_9: As we did in Theorem 3.2, the trajectory will enter the region Ω'. We construct a Lyapunov function V on Ω' and show that E_{c_1} is globally asymptotically stable in the interior of Ω.
C_{10}: Obviously E_2 is globally asymptotically stable.
C_{11}: Similar to the proof of Theorem 3.2, we can construct a Lyapunov function V on the invariant region Ω' to show that E_{c_1} is globally asymptotically stable in the interior of Ω.
C_{12}: E_{c_2} is a saddle point with one dimensional stable manifold Γ. As in the case A_9, E_{c_1} attracts each points in the interior of Ω_1, E_2 attracts each point in Ω_2.
C_{13}: As in the case B_8, E_{c_1} is globally asymptotically stable.
C_{14}: Since the interior rest point does not exist, as in the case B_9, E_2 is globally asymptotically stable.
C_{15}: E_{c_1} exists. As in the case B_{10}, E_2 is locally asymptotically stable and E_3 is a saddle point with one dimensional stable manifold Γ which separates the region Ω into two regions Ω_1, Ω_2. E_2 attracts each point in Ω_1 while E_{c_1} may be stable or unstable as the parameters vary.
C_{16}: The interior rest points E_{c_1}, E_{c_2} exist. E_{c_2} and E_3 are saddle points, E_1, E_2, E_{c_1} are locally asymptotically stable. The stable manifolds of E_3, E_{c_2} separate the region Ω into three regions Ω_1, Ω_2 and Ω_3. E_1 attracts each point in Ω_3, E_2 attracts each point in Ω_2 and E_{c_1} attracts each point in the interior of Ω_1.
C_{17}: E_{c_1} exists, but E_{c_2} does not exist. The stable manifold Γ of E_3 separates the region Ω into two regions Ω_1, Ω_2. E_{c_1} attracts each point in the interior of Ω_1 and E_1 attracts each point in Ω_2.
C_{18}: E_3 is a saddle point with one dimensional stable manifold Γ which separates the region Ω into two regions Ω_1, Ω_2. E_1 attracts each point in Ω_2 and E_2 attracts each point in Ω_1.
C_{19}: E_{c_1} and E_{c_2} exist. E_{c_2} is connected to E_3. E_{c_1} attracts each point in the interior of Ω_1. E_1 is an attractor for Ω_2.
C_{20}: E_{c_1} does not exist. E_{c_2} is chained to E_3. E_1 attracts each point in Ω_2 and E_2 attracts each point in Ω_1.
C_{21}: E_3, E_{c_2} are saddle points with one dimensional stable manifold Γ_1, Γ_2 respectively. Γ_1, Γ_2 separate Ω into three regions Ω_1, Ω_2, and Ω_3. E_2 attracts the points in Ω_1. E_1 is the global attractor of Ω_2. The rest point E_{c_1} is stable or unstable as parameters vary.

5.2 Use Theorem 5 of [T] again to get the similar global results of Type C on the equation (1.2) as above. The reader can try to modify the description of the results of Type C on Ω for oneself. For the biological interpretation of the results of Type C species, we state in terms of the original parameters and $f_1(S) = m_1 S/(a_1 + S + K_1 S^2)$ and $f_2(S) = m_2 S/(a_2 + S + K_2 S^2)$. The rest

Table 5.2

Case	The rest points set	Case	The rest points set
C_1	E_1	C_{12}	$E_1, E_2, E_{c_1}, E_{c_2}$
C_2	E_1, E_{c_1}	C_{13}	E_1, E_2, E_3, E_{c_1}
C_3	E_1, E_{c_1}	C_{14}	E_1, E_2, E_3
C_4	E_1, E_{c_1}, E_{c_2}	C_{15}	E_1, E_2, E_3, E_{c_1}
C_5	E_1, E_{c_1}, E_{c_2}	C_{16}	$E_1, E_2, E_3, E_{c_1}, E_{c_2}$
C_6	E_1, E_2	C_{17}	E_1, E_2, E_3, E_{c_1}
C_7	E_1, E_2, E_3	C_{18}	E_1, E_2, E_3
C_8	E_1, E_2	C_{19}	$E_1, E_2, E_3, E_{c_1}, E_{c_2}$
C_9	E_1, E_2, E_{c_1}	C_{20}	E_1, E_2, E_3, E_{c_2}
C_{10}	E_1, E_2	C_{21}	$E_1, E_2, E_3, E_{c_1}, E_{c_2}$
C_{11}	E_1, E_2, E_{c_1}		

points in terms of the original parameters are:

$$\mathscr{E}_1 = (S^{(0)}, 0, 0) ,$$

$$\mathscr{E}_2 = (\lambda_2, 0, \gamma(S^{(0)} - \lambda_2)) ,$$

$$\mathscr{E}_3 = (\mu_2, 0, \gamma(S^{(0)} - \mu_2)) ,$$

$$\mathscr{E}_{c_1} = \left(\lambda_1, \frac{\gamma(S^{(0)} - \lambda_1)(D - f_2(\lambda_1))}{f_1(\lambda_1) - f_2(\lambda_1)}, \frac{\gamma(S^{(0)} - \lambda_1)(f_1(\lambda_1) - D)}{f_1(\lambda_1) - f_2(\lambda_1)}\right) ,$$

$$\mathscr{E}_{c_2} = \left(\mu_1, \frac{\gamma(S^{(0)} - \mu_1)(D - f_2(\mu_1))}{f_1(\mu_1) - f_2(\mu_1)}, \frac{\gamma(S^{(0)} - \mu_1)(f_1(\mu_1) - D)}{f_1(\mu_1) - f_2(\mu_1)}\right)$$

where $f_1(\lambda_1)(1 - q) = f_1(\mu_1)(1 - q) = D$, $\lambda_1 < \mu_1 < S^{(0)}$ and $f_2(\lambda_2) = f_2(\mu_2) = D$, $\lambda_2 < \mu_2 < S^{(0)}$. The rescaling of Table 5.1 is as follows.

In the following, we give the biological interpretations for each case C_i.

C_1, C_6, C_7: In these cases, species 1 (plasmid-bearing species) cannot survive alone. In the case C_1, species 2 (plasmid-free species) also cannot survive alone. Hence both species go to extinction. In the case C_6, species 2 is able to

Table 5.3

	E_1	E_2	E_3	E_{c_1}	E_{c_2}
C_1	$s_{\star}$	★	★	★	★
C_2	sa	★	★	$s_{\star\star}$	★
C_3	sa	★	★	$s_{\star\star}$ or $u_{\star\star}$	★
C_4	$s_{\star}$	★	★	$s_{\star\star}$	sa
C_5	$s_{\star}$	★	★	$s_{\star\star}$ or $u_{\star\star}$	sa
C_6	sa	$s_{\star}$	★	★	★
C_7	$s_{\star}$	$s_{\star}$	sa	★	★
C_8	$u_{\star}$	$s_{\star}$	★	★	★
C_9	$u_{\star}$	sa	★	$s_{\star\star}$	★
C_{10}	sa	$s_{\star}$	★	★	★
C_{11}	sa	sa	★	$s_{\star\star}$	★
C_{12}	sa	$s_{\star}$	★	$s_{\star\star}$	sa
C_{13}	sa	sa	$u_{\star}$	$s_{\star\star}$	★
C_{14}	sa	$s_{\star}$	$u_{\star}$	★	★
C_{15}	sa	$s_{\star}$	sa	$s_{\star\star}$ or $u_{\star\star}$	★
C_{16}	$s_{\star}$	$s\star$	sa	$s_{\star\star}$	sa
C_{17}	$s_{\star}$	sa	sa	$s_{\star\star}$	★
C_{18}	$s_{\star}$	$s_{\star}$	sa	★	★
C_{19}	$s_{\star}$	sa	$u_{\star}$	$s_{\star\star}$	sa
C_{20}	$s_{\star}$	$s_{\star}$	$u_{\star}$	★	sa
C_{21}	$s_{\star}$	$s_{\star}$	sa	$s_{\star\star}$ or $u_{\star\star}$	sa

s: stable; u: unstable; sa: saddle; ★: the absence of the rest point; $_{\star}$: node; $_{\star\star}$: node or focus

survive alone. Hence species 1 goes to extinction and species 2 survives. In the case C_7, species 2 either goes to extinction or survives in the absence of species 1 depending on the initial population. Hence as expected either both species go to extinction or species 2 takes over the culture depending on the initial populations.

Table 5.4

Case	Criteria for existence of rest points	Rest points
C_1	$f_1(\rho_1)(1-q) < D,\ f_2(\rho_2) < D$	$\mathscr{E}_1$
C_2	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) > D,\ f_2(\rho_2) < D, 0 < \lambda_1 < \rho_2 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_{c_1}$
C_3	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) > D,\ f_2(\rho_2) < D, 0 < \rho_2 < \lambda_1 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_{c_1}$
C_4	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) < D,\ f_2(\rho_2) < D, 0 < \lambda_1 < \rho_2 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_{c_1}, \mathscr{E}_{c_2}$
C_5	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) < D,\ f_2(\rho_2) < D, 0 < \rho_2 < \lambda_1 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_{c_1}, \mathscr{E}_{c_2}$
C_6	$f_1(\rho_1)(1-q) < D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) > D$	$\mathscr{E}_1, \mathscr{E}_2$
C_7	$f_1(\rho_1)(1-q) < D, f_2(\rho_2) > D,\ f_2(S^{(0)}) < D,$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_3$
C_8	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) > D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) > D, 0 < \lambda_2 < \lambda_1 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2$
C_9	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) > D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) > D, 0 < \lambda_1 < \lambda_2 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_{c_1}$
C_{10}	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) < D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) > D, 0 < \lambda_2 < \lambda_1 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2$
C_{11}	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) < D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) > D, 0 < \lambda_1 < \lambda_2 < \mu_1 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_{c_1}$
C_{12}	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) < D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) > D, 0 < \lambda_1 < \mu_1 < \lambda_2 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_{c_1}, \mathscr{E}_{c_2}$
C_{13}	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) > D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) < D, 0 < \lambda_1 < \lambda_2 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_3, \mathscr{E}_{c_1}$
C_{14}	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) > D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) < D, 0 < \lambda_2 < \lambda_1 < \mu_2 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_3$
C_{15}	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) > D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) < D, 0 < \mu_2 < \lambda_1 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_3, \mathscr{E}_{c_1}$
C_{16}	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) < D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) < D, 0 < \lambda_1 < \mu_1 < \lambda_2 < \mu_2 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_3, \mathscr{E}_{c_1}, \mathscr{E}_{c_2}$
C_{17}	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) < D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) < D, 0 < \lambda_1 < \lambda_2 < \mu_1 < \mu_2 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_3, \mathscr{E}_{c_1}$
C_{18}	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) < D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) < D, 0 < \lambda_2 < \lambda_1 < \mu_1 < \mu_2 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_3$
C_{19}	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) < D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) < D, 0 < \lambda_1 < \lambda_2 < \mu_2 < \mu_1 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_3, \mathscr{E}_{c_1}, \mathscr{E}_{c_2}$
C_{20}	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) < D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) < D, 0 < \lambda_2 < \lambda_1 < \mu_2 < \mu_1 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_3, \mathscr{E}_{c_2}$
C_{21}	$f_1(\rho_1)(1-q) > D,\ f_1(S^{(0)})(1-q) < D,\ f_2(\rho_2) > D,\ f_2(S^{(0)}) < D, 0 < \lambda_2 < \mu_2 < \lambda_1 < \mu_1 < S^{(0)}$	$\mathscr{E}_1, \mathscr{E}_2, \mathscr{E}_3, \mathscr{E}_{c_1}, \mathscr{E}_{c_2}$

$C_2 \sim C_5$: In these cases species 2 cannot survive alone. In the cases C_2 and C_3, the species 1 is able to survive alone. Hence both species coexist. In the case C_4 and C_5, species 1 either goes to extinction or survives depending on the initial population. Hence either both species are washed out or both coexist depending on the initial populations.

$C_8 \sim C_{12}$: In these cases, species 2 is able to survive alone. In the cases C_8 and C_9, species 1 is also able to survive alone. However in the case C_8, species 1 has larger break-even concentration λ_1. It follows that species 1 is an inferior competitor and species 2 takes over the culture eventually. In the case C_9, species 1 has smaller break-even concentration and hence both species coexist. In the cases C_{10}, C_{11}, C_{12}, species 1 either goes to extinction or survives in the absence of species 2. In the case C_{10}, species 1 has larger break-even concentration. It follows that species 2 survives and species 1 goes to extinction. In the case C_{11}, since $\lambda_1 < \lambda_2 < \mu_1$, from Theorem 3.6, species 1 is a better competitor. Hence both species coexist. In the case C_{12}, since $\lambda_1 < \mu_1 < \lambda_2$, from Theorem 3.6, in the absence of conversion of species 1 into species 2, either species 1 or species 2 survives. Hence either both species coexist or species 2 takes over the culture eventually depending on the initial populations.

$C_{13} \sim C_{15}$: In these cases, species 1 is able to survive alone, and species 2 either survives or goes to extinction in the absence of species 1. In the case C_{13}, since $\lambda_1 < \lambda_2 < \mu_2 < \mu_1 = \infty$, from Theorem 3.6, species is a better competitor. Hence both species coexist. In the case C_{14}, since $\lambda_2 < \lambda_1 < \mu_2$, from Theorem 3.6, species 2 is a better competitor. As we did in case B_9, the species 2 survives and the species 1 goes to extinction. In the case C_{15}, as we did in case B_{10}, either both species coexist or only species 2 survives.

$C_{16} \sim C_{21}$: In these cases, both species either survives or goes to extinction in the absence of the other species. In the cases C_{17}, C_{19}, from Theorem 3.6, species 1 is a better competitor. Hence either both species go to extinction or both coexist. In the case C_{18}, C_{20}, from Theorem 3.6, species 2 is a better competitor. Hence either species 2 go to extinction or only species 2 survives. In the case C_{16}, C_{21}, as we did in the case C_{12}, either both species coexist or both species go to extinction or only species 2 survives.

In order to see how the species 1 (the plasmid-bearing species) survives as the dilution rate D is gradually decreased, we consider the following cases:

1. $f_1(S)(1-q) < f_2(S)$ for $S < \tilde{S}$ and $f_1(S)(1-q) > f_2(S)$ for $S^{(0)} > S > \tilde{S}$, where $\rho_2 > \tilde{S} > \rho_1$ and $f_1(S^{(0)})(1-q) < f_2(\tilde{S}) < f_2(\rho_2) < f_1(\rho_1)(1-q)$.

2. $f_1(S)(1-q) > f_2(S)$ for $S < \tilde{S}_1$, $f_1(S)(1-q) < f_2(S)$ for $\tilde{S}_1 < S < \tilde{S}_2$ and $f_1(S)(1-q) > f_2(S)$ for $S^{(0)} > S > \tilde{S}_2$ where $\rho_1 < \tilde{S}_1 < \rho_2 < \tilde{S}_2$ and $f_1(\rho_1)(1-q) < f_2(\rho_2)$ for demonstration.

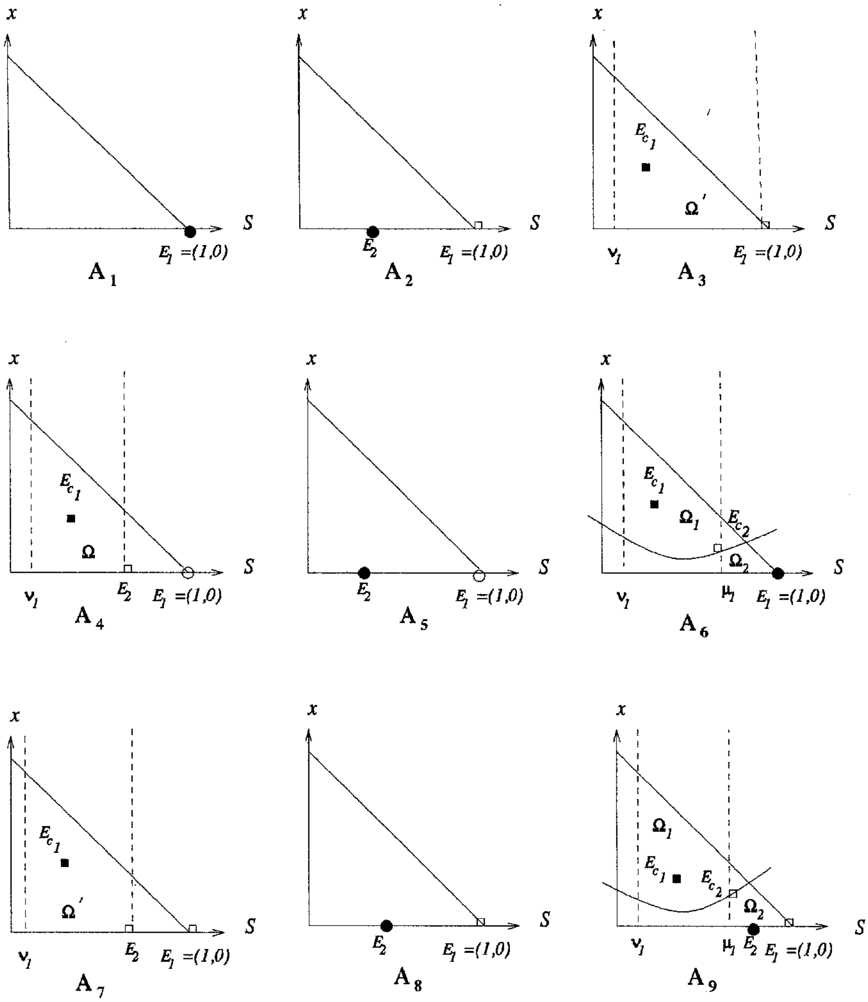
Figs. E_3, E_4 in Appendix E are the bifurcation diagrams of the dilution rate D with respect to the plasmid-bearing population in the steady state for these cases. In a similar manner it is easy to see that effect of varying the input concentration $S^{(0)}$.

6 Discussion

In this paper we give a global analysis of the asymptotic behavior of the model studied by Stephanopoulis and Lapius [SL], assuming uninhibited or inhibited growth for both plasmid-bearing and plasmid-free populations. In [HWW] the authors gave a complete analysis for the case of uninhibited growth rates. The foregoing sections gave a global analysis for the Type A species (plasmid-bearing species is inhibited and plasmid-free species is uninhibited), Type B species (plasmid-bearing species is uninhibited and plasmid-free species is inhibited) and Type C species (both of plasmid-bearing and plasmid-free species are inhibited). Although it is not very realistic to have the Type A and the Type B species in practice, we follow the same line as the authors of [SL] and [RD] did, to do the analysis for the sake of completeness. In reality, both of the plasmid-bearing and plasmid-free species have the same type of growth response functions for the substrate. Hence the results of Type C species in this paper and those in [HWW] are important in application.

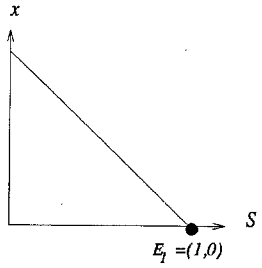
Our results demostrate the existence of multiple states as Macken, Levin and Waldstätter did for the bacteria-plasmid systems [MLW]. Our analysis also shows that the possibility of coexistence in the form of oscillations in the cases of B_5, B_{10}, C_{15}, C_{21}. There are a number of models for plasmid loss referenced in [SL]. There is also a nice paper of Simonsen [S], surveying a number of experiments and giving an estimate q as $10^{-3} - 10^{-5}$ HR^{-1}. The interested reader may consult it for further biological considerations.

Appendices A to E

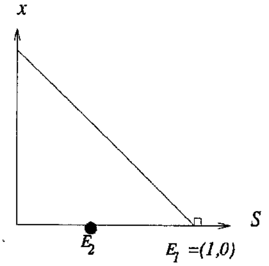


Appendix A: ● stable node ■ stable node or stable focus

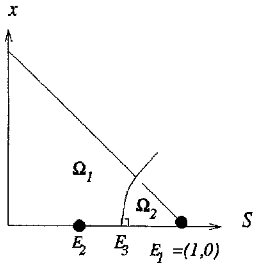
○ unstable node □ saddle



B 1



B2



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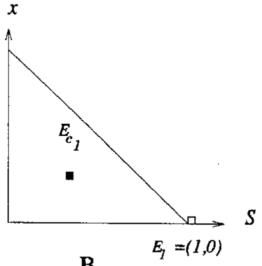

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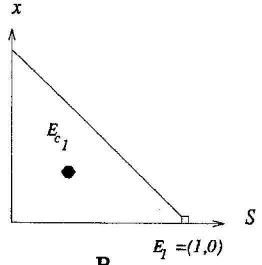

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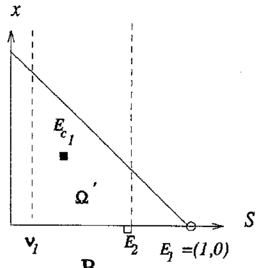

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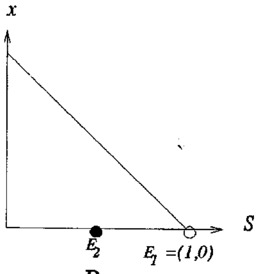

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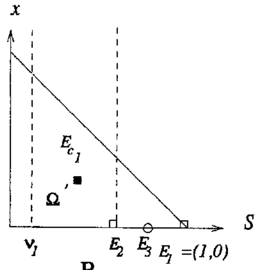
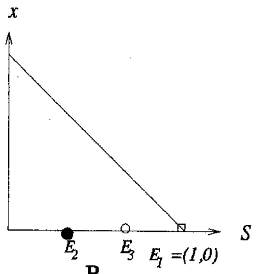
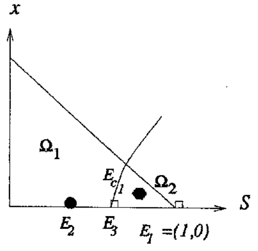


B 8



B 9



B10

Appendix B: ● stable node ■ stable node or stable focus □ saddle

○ unstable node ⬢ stable or unstable node (focus)

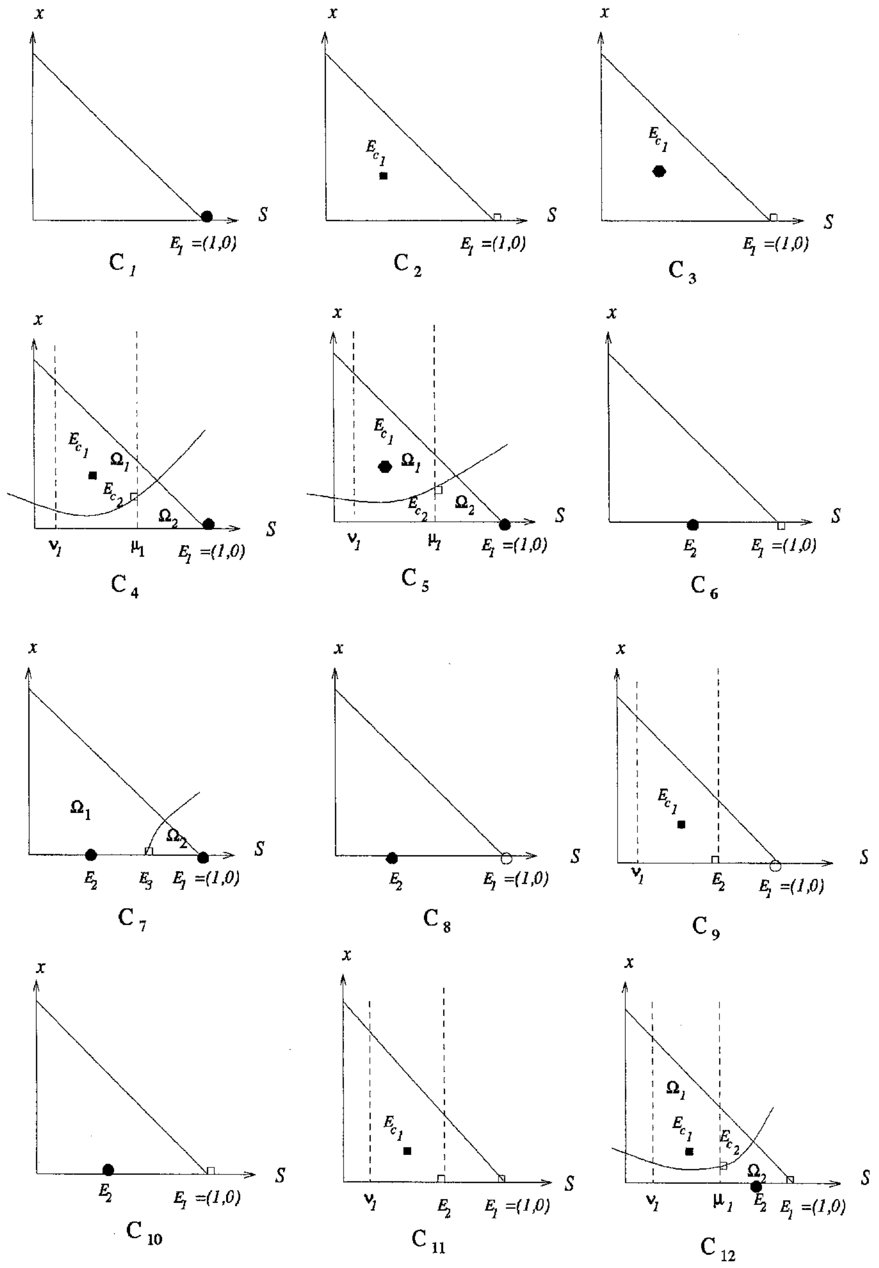


Fig. C_1 (continued)

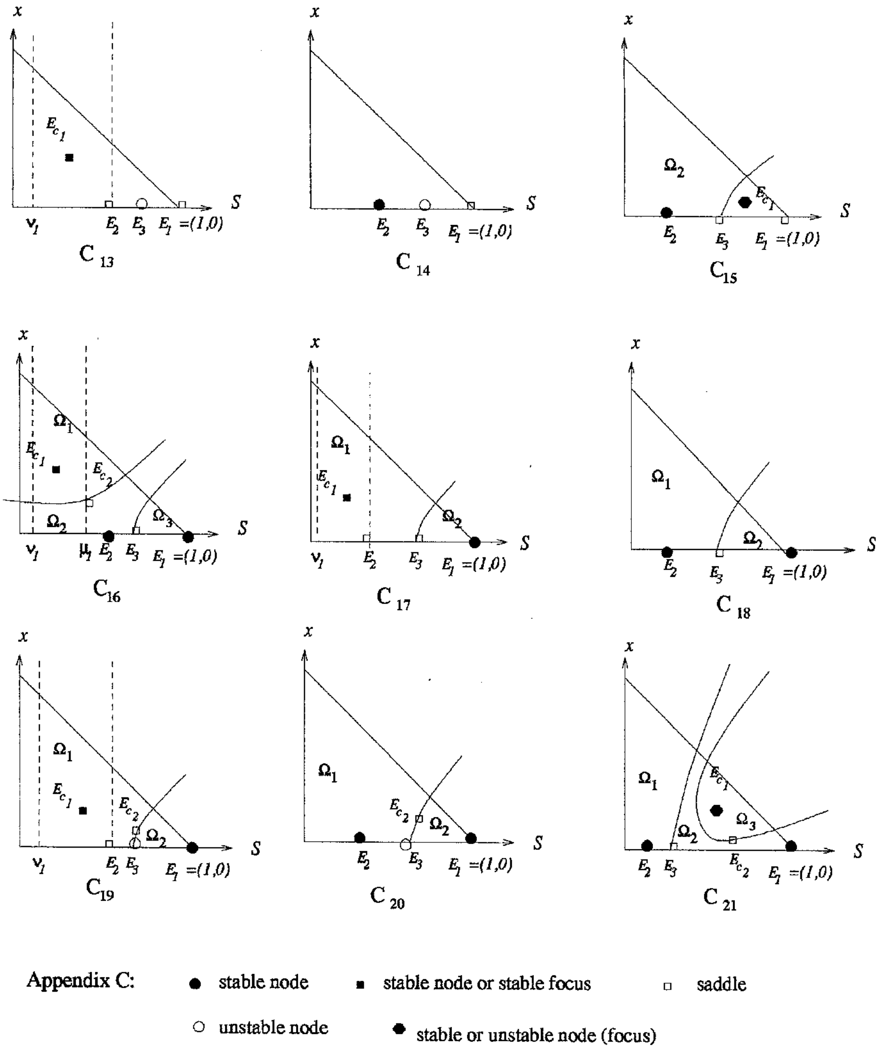
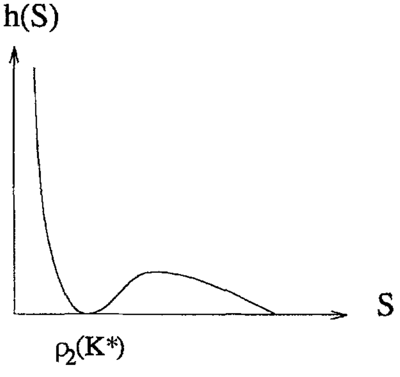
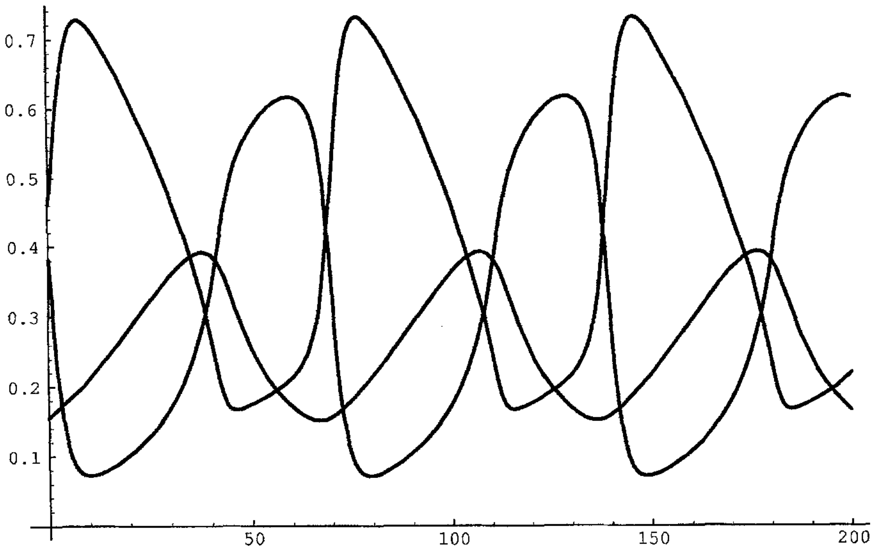

x
S
ν_1
E_{c_1}
E_2 E_3 $E_1=(1,0)$
C 13
C 14
Ω_2
C15
Ω_1
Ω_2
Ω_3
E_{c_2}
μ_1
C16
C 17
C 18
C19
C 20
C 21
Appendix C:
● stable node
▪ stable node or stable focus
□ saddle
○ unstable node
⬢ stable or unstable node (focus)

Fig. C_2

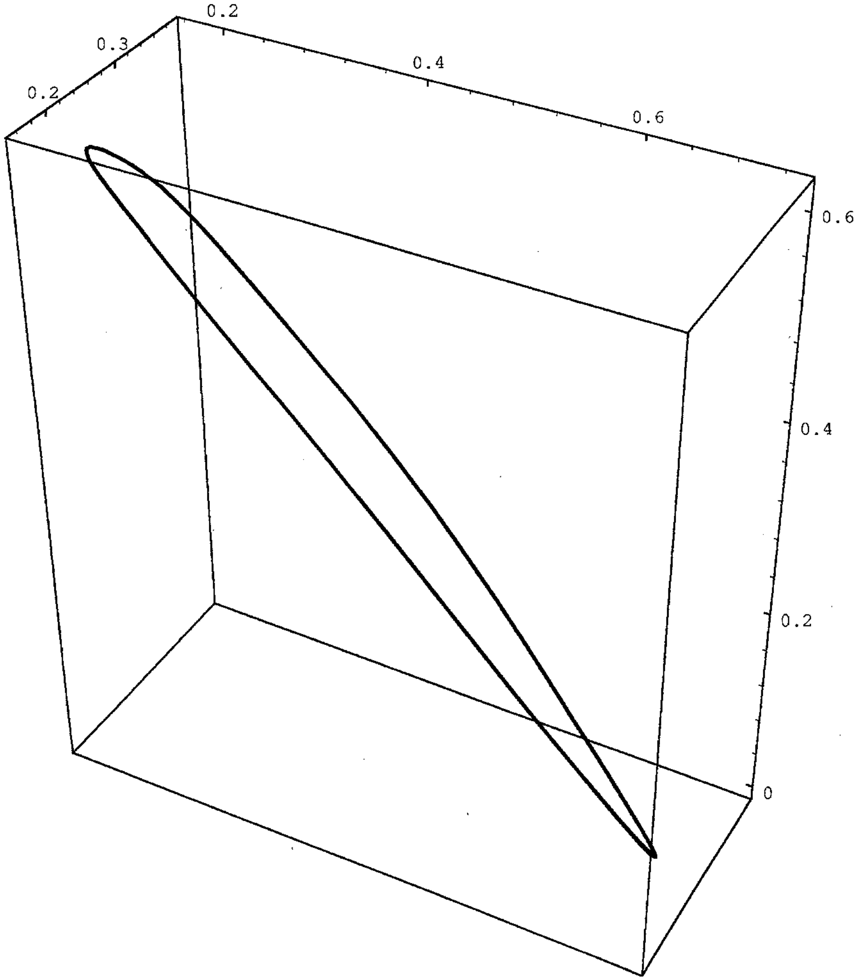


D_1

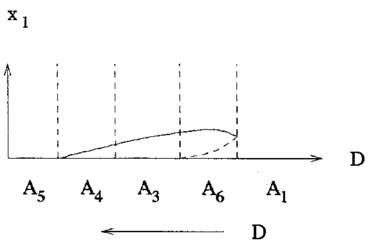
Appendix D_1



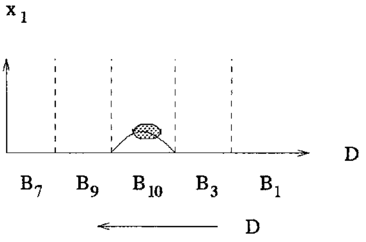
Appendix D_2. Plot of 200 timesteps in the case of oscillatory coexistence. The reponse functions $f_1(S)$ is $1.22S/0.02 + S$ and $f_2(S)$ is $4.8S/0.4 + S + 10.0S^2$, $q = 0.13$



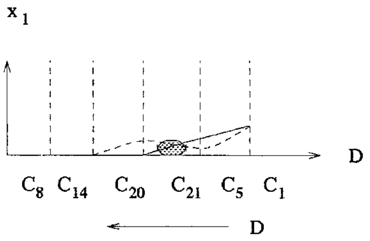
Appendix D_3. Plot in R^3 of the limit cycle given in D_2



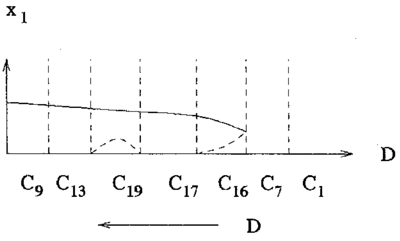
E_1



E_2



E_3



E_4

Appendix E:

⁄	The bifurcation curve of x_1 of E_{c_1}
- - -	The bifurcation curve of x_1 of E_{c_2}
▨	The possible area of oscillation

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