

A boundedness theorem with application to oscillation of autocatalytic chemical reactions

Dieter Erle

Fachbereich Mathematik, Universität Dortmund, D-44221 Dortmund, Germany

Received 5 August 1997; revised 17 August 1998

For a class of dynamical systems of the form $\dot{x} = q(x) - u(x, y)$, $\dot{y} = \varepsilon(v(x, y) - r(y))$, we prove boundedness of all solutions in the positive time direction. We discuss the existence of stable limit cycles for the simplest autocatalytic reaction involving two internal and two external reactants, as well as for a number of other models arising in applications.

1. Introduction

Over a long period of years it has turned out that numerous models in chemistry, biochemistry, biology and population ecology obey a set of differential equations of the following form:

$$\begin{cases} \dot{x} = q(x) - u(x, y), \\ \dot{y} = \varepsilon(v(x, y) - r(y)); \end{cases} \quad (*)$$

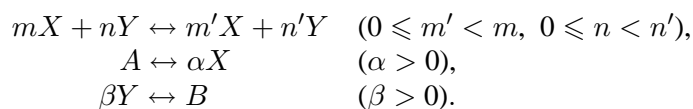
see section 4 for an account of a few examples. In (*), q describes the input and possibly output of one agent, r the output (i.e., removal) and possibly input of a second agent, and u and v describe some mechanism of conversion of the first agent to the second agent (e.g., in an enzyme reaction or a population model). ε is a scaling parameter.

We are interested in boundedness of the solutions, mainly as a prerequisite for applying the Poincaré–Bendixson theorem to obtain periodic solutions. In section 2, we formulate a set of nine conditions of (*) under which we prove forward boundedness of all solutions in the nonnegative quadrant (theorem 2.1). The number of conditions admittedly is appalling; but in most applications (with q , r , u , v rational functions) these are easily checked or even trivially fulfilled. On the other hand, some of the conditions are quite natural in the context of the applications, see the comments in section 2. Above all, our result is flexible enough to handle models originating from areas far apart (cf. section 4).

Boundedness of solutions in positive time direction and the existence of periodic solutions or even limit cycles are the main features one is looking for in studying 2-dimensional models from a qualitative point of view. Systems of the form (*) in

particular occur in describing chemical reactions based on mass action kinetics and can be considered generalizations of the original Lotka–Volterra model. Schnakenberg [16, 17] and Császár et al. [2] provide candidates for limit cycle behavior. Escher [7] detects the coexistence of several limit cycles in quadratic systems. Póta [13] gives a rigorous proof of non-existence of limit cycles for two-component bimolecular systems, a result already stated by Hanusse as well as Tyson and Light. A similar result, also valid in higher dimensions, is achieved by Tóth [21].

Our principal application (cf. remarks 4.1, 4.3 and 4.5 and propositions 4.2 and 4.4) refers to the simplest autocatalytic chemical reaction set involving two internal reactants X, Y whose concentrations vary in time, and two external ones A, B of constant concentrations (cf. [16,17]). The stoichiometric equations are



Under a very weak hypothesis on the reverse rate constants of the second and third equations above, we can prove forward boundedness of all solutions (proposition 4.2). An example from glycolysis (cf. remark 4.3) shows that one cannot do without the hypothesis mentioned. Finally, we show that when $\beta < n$, then there are positive rate constants realizing periodic solutions (proposition 4.4).

This contrasts with the global asymptotic stability of a stationary point and therefore the absence of periodic solutions in the slightly different model, investigated by Hering [9], with reaction steps $A + X \leftrightarrow 2X$, $X + Y \leftrightarrow 2Y$, $Y \leftrightarrow B$. On the other hand, Simon [19] proved the forward boundedness of the solutions and the existence of limit cycles via Hopf bifurcation in a reaction $A + 2X \leftrightarrow 3X$, $X + Y \leftrightarrow 2Y$, $Y \leftrightarrow B$. Moreover, Simon [20] achieved the general result that solutions are forward bounded in systems with a finite number of reaction steps of the form $mX + nY \leftrightarrow m'X + n'Y$. Our example is not a special case of this, because of the reaction steps $A \leftrightarrow \alpha X$, $\beta Y \leftrightarrow B$ ($\alpha, \beta > 0$). These are missing in Simon's system, which would correspond to the case $\alpha = \beta = 0$ and leads to a different system of differential equations (see remark 4.1). Finally, it should be mentioned that Dancsó et al. [3] studied a system that is related to but different from our systems.

We briefly go into studying several of numerous possible applications of theorem 2.1. One is a 2-dimensional model for cyclic AMP signaling by Martiel and Goldbeter [12]. Another one is Rössler's multivibrator system [15]. The interesting feature of these is that they realize cases where u and v are not identical.

The appendix deals with a subtle mathematical problem connected to the Poincaré–Bendixson theorem, which requires nonextendible solutions to be defined in intervals open on the right-hand side. The latter is not necessarily the case in a system where the natural domain of the variables consists of the nonnegative real numbers. Our non-termination lemma (lemma A.1) proposes a simple way out that might be of independent interest.

2. Formulation of the theorem

Theorem 2.1. In the system of differential equations

$$\begin{cases} \dot{x} = q(x) - u(x, y), \\ \dot{y} = \varepsilon(v(x, y) - r(y)), \end{cases} \quad (*)$$

let ε be a positive constant and let q, r, u, v be functions

$$q, r : [0, \infty[\rightarrow \mathbb{R}, \quad u, v : [0, \infty[\times [0, \infty[\rightarrow \mathbb{R},$$

satisfying a local Lipschitz condition. Moreover, assume that there are a continuous unbounded nondecreasing function $f : [0, \infty[\rightarrow [0, \infty[$ and nonnegative constants a_1, a_2, c_1, c_2, c_3 such that the following nine conditions hold:

- (1) Let $S := \{(x, \bar{y}) \mid 0 \leq \bar{y} \leq f(x)\}$ be the set below the graph of f . Then the function $(x, y) \mapsto u(x, y)$, restricted to S , for each $y \geq 0$ is nondecreasing with respect to x .
- (2) The function $(x, y) \mapsto v(x, y)$, restricted to S , for each $y \geq 0$ is nondecreasing with respect to x .
- (3) For each $y \geq 0$, the inequality $u(0, y) \leq q(0)$ holds.
- (4) $r(0) \leq v(0, 0)$.

Conditions (1) and (2) admit to define

$$w(y) := \lim_{x \rightarrow \infty} u(x, y) \in \mathbb{R} \cup \{\infty\},$$

$$z(y) := \lim_{x \rightarrow \infty} v(x, y) \in \mathbb{R} \cup \{\infty\}.$$

- (5) If $r(0) = z(0)$ then there is $\eta > 0$ such that, for all $x \geq a_1$ and all $y \in [0, \eta]$, $q(x) < u(x, y)$. If $r(0) \neq z(0)$ put $\eta := 0$.
- (6) For all $y \in]0, c_1]$, $z(y) > r(y)$.
- (7) For all $x \geq 0$ and all $y \geq c_2$, $r(y) \geq q(x)$. (This implies that q is bounded above.)
- (8) Let $\tilde{q} := \sup\{q(x) \mid x \geq a_2\}$. Then, for all $y \geq c_1$, $w(y) > \tilde{q}$.
- (9) For all $x \geq 0$ and all $y \geq c_3$, $v(x, y) \leq u(x, y)$.

Then any solution $(x(t), y(t))$ of system (*) is defined and bounded for all $t \geq 0$.

The proof of theorem 2.1 is deferred to section 5.

Comments 2.2. (i) Technically, the nine conditions are used to lock up a given solution starting at (x_0, y_0) in a compact set bounded by line segments. In figure 1 accompanying the proof in section 5, numbers in parentheses attached to a line segment indicate which conditions are responsible for that the solutions cannot pass through this line segment from inside out. In this respect, each condition has its place.

(ii) Rate laws like $u(x, y)$ and $v(x, y)$ typically satisfy some monotonicity condition with respect to the variable x such as condition (1) or (2), respectively. If $u(x, y)$ and $v(x, y)$ are nondecreasing with respect to x on their entire domain, then f may be chosen in an arbitrary way. *Let us agree on an arbitrary f if f is not mentioned explicitly.* As in our main application this monotonicity is only satisfied below the graph of a function f , some intricacy in formulating (1) and (2) is unavoidable.

(iii) Condition (9) says that rate function v does not exceed u above some level of y . Though frequently $u \equiv v$, condition (9) naturally allows for some loss in the process of converting the first to the second agent.

(iv) The constant c_1 occurs in (6) and (8). If $c_1 = 0$ then the interval $]0, c_1]$ is empty and condition (6) is trivially fulfilled.

(v) The following is worth mentioning because it frequently simplifies applications. If $z(y) = \infty$ for all $y > 0$ then (6) is trivially satisfied. Similarly, if $w(y) = \infty$ for all $y \geq c_1$ then (8) holds for trivial reasons.

(vi) As (1)–(9) do not impose any conditions on the constant ε , the theorem is correct even if the data $q, r, u, v, f, a_1, a_2, c_1, c_2, c_3$, and η depend on ε .

3. Applying the Poincaré–Bendixson theorem

In the context of theorem 2.1 we would like to apply the Poincaré–Bendixson theorem to assert the existence of periodic solutions enjoying some sort of stability. The following proposition describes such a situation.

Proposition 3.1. Let q, r, u, v of system (*) be continuously differentiable and suppose they fulfil the conditions of theorem 2.1. Moreover, assume:

- (i) There is a unique stationary point (x_s, y_s) with positive coordinates.
- (ii) The linearization of the vector field has positive determinant and trace at (x_s, y_s) .
- (iii) There is a positively invariant curve emanating from a coordinate axis and keeping positive distance $\geq \delta > 0$ from both axes after some time.

Then the system has an orbitally stable closed orbit. If q, r, u, v are real analytic functions, then an asymptotically orbitally stable closed orbit exists.

Remark 3.2. Mind that apart from the stationary point (x_s, y_s) additional equilibria on the axes are allowed. The positively invariant curve of condition (iii) in most cases will be a positive semi-orbit starting on an axis or the unstable manifold of a hyperbolic saddle point on an axis.

Proof of proposition 3.1. Realize that using theorem 2.1 we know that solutions are defined for all $t \geq 0$. Therefore any orbit has a well-defined positive limit set ($=\omega$ -limit set). An orbit starting on the invariant curve but not on an axis, has a positive

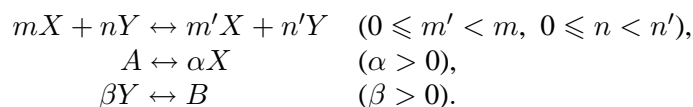
limit set not meeting the axes (because of (iii)) and not containing a stationary point (because of (i) and (ii)), so by the Poincaré–Bendixson theorem it tends to a limit cycle which is the outermost one due to the Jordan curve theorem. An orbit starting close to (x_s, y_s) also tends to a limit cycle (to the innermost one). These two limit cycles bound a closed annulus which is positively invariant. The proposition in [5] states that in this case the annulus contains an orbitally stable closed orbit which can be chosen asymptotically orbitally stable if the vector field is real analytic. \square

4. Autocatalytic reactions and other models

In what follows, all parameters will be assumed to be positive unless a different assumption is explicitly stated. A solution $(x(t), y(t))$ will be called bounded if it is bounded for all $t \geq 0$.

Remark 4.1. By Schnakenberg's study [16] of autocatalytic reactions, candidates for limit cycle behavior abound among systems with two internal reactants. For a result excluding limit cycles, cf. [13]. Theorem 2.1 leads to a proof – not given in [16,17] – that solutions are bounded for many such systems and allows a simply stated result on possible candidates for oscillations.

Assume a chemical system with two internal reactants X, Y and two external reactants A, B and stoichiometric equations



The stoichiometric coefficients m, n', α, β are positive integers, m' and n are non-negative integers. The mass action type kinetic differential equations consist of

$$\begin{cases} \dot{x} = \alpha(k_2 - k_2'x^\alpha) - (m - m')(k_1x^m y^n - k_1'x^{m'} y^{n'}), \\ \dot{y} = (n' - n)(k_1x^m y^n - k_1'x^{m'} y^{n'}) - \beta(k_3y^\beta - k_3'), \end{cases} \quad (\text{S})$$

where x and y are the concentrations of X and Y , respectively, and the constants $k_i > 0$ and $k_i' \geq 0$ describe the forward and reverse rate, respectively, in the i th reaction step above, for $i = 1, 2, 3$.

Proposition 4.2. Assume $k_1, k_2, k_3 > 0$ and $k_1', k_2', k_3' \geq 0$. Assume furthermore: either $n = 0$, or $n > 0$ and $k_3' > 0$, or $n > 0$ and $k_3' = 0$ and $k_2' > 0$. Then system (S) satisfies the hypotheses of theorem 2.1; thus all solutions are bounded for positive time.

Proof. In the notation of system (*), put

$$\begin{aligned} q(x) &:= \alpha(k_2 - k_2'x^\alpha), \\ u(x, y) &= v(x, y) := (m - m')(k_1x^m y^n - k_1'x^{m'} y^{n'}), \end{aligned}$$

$$\varepsilon := \frac{n' - n}{m - m'}, \quad r(y) := \frac{m - m'}{n' - n} \beta (k_3 y^\beta - k'_3).$$

$$\frac{\partial}{\partial x} u(x, y) \geq 0 \Leftrightarrow mk_1 x^{m-m'} \geq m' k'_1 y^{n'-n}.$$

If $m' k'_1 \neq 0$ then (1) and (2) are satisfied with

$$f(x) := \left(\frac{mk_1}{m' k'_1} x^{m-m'} \right)^{1/(n'-n)}.$$

If $m' k'_1 = 0$ then (1) and (2) are satisfied with any f . (3) and (4) are trivial. For $n = 0$, $\infty = z(0) \neq r(0)$. Now assume $n > 0$. Then $z(0) = 0$, so $z(0) \neq r(0)$ if $k'_3 > 0$. If $k'_3 = 0$ then $z(0) = r(0)$; but in this case $k'_2 > 0$ by hypothesis, and there is a_1 such that $q(x) < 0$ for all $x \geq a_1$. Since $n > 0$ implies $u(a_1, 0) = 0$, the inequality $u(a_1, y) > q(a_1)$ holds for all $y \in [0, \eta]$ if $\eta > 0$ is chosen suitably. Then

$$x \geq a_1 \quad \text{and} \quad 0 \leq y \leq \eta \quad \Rightarrow \quad q(x) \leq q(a_1) < u(a_1, y) \leq u(x, y),$$

and (5) is verified in all cases. As $z(y) = w(y) = \infty$ for any $y > 0$, (6) and (8) are true with arbitrary c_1 and a_2 . As $k_3 > 0$, (7) holds and (9) is trivial. \square

Remark 4.3. The assumption in proposition 1 cannot be removed. If $k'_2 = k'_3 = 0$ for positive n then the x -axis is invariant and $k_2 > 0$ leads to an unbounded positive semi-orbit on the x -axis. More seriously, there may be unbounded positive semi-orbits outside the axes, as is shown by the following example: in model II of [18],

$$\begin{aligned} \dot{x} &= 1 - xy^2, \\ \dot{y} &= xy^2 - y, \end{aligned}$$

with reaction steps $X + 2Y \rightarrow 3Y$, $A \rightarrow X$, $Y \rightarrow B$, an easy calculation shows that the graph of $y = 1/(2x)$ is crossed from above for sufficiently great x , so – as $\dot{x} > 0$ there – solutions below this graph are unbounded.

Proposition 4.4. For any set of numbers satisfying $0 \leq m' < m$, $0 < \beta < n < n'$, and $\alpha > 0$, there are constants $k_i > 0$, $k'_i > 0$ ($i = 1, 2, 3$) such that system (S) has an asymptotically orbitally stable closed orbit. The k'_i may be chosen to be arbitrarily close to 0.

Proof. We want to apply proposition 3.1. First, suppose all k'_i are zero. There is a single equilibrium (x_s, y_s) with $x_s, y_s > 0$, namely

$$\begin{aligned} x_s &= \left(\frac{1}{k_1} \left(\frac{\alpha k_2}{m - m'} \right)^{1-n/\beta} \left(\frac{\beta k_3}{n' - n} \right)^{n/\beta} \right)^{1/m}, \\ y_s &= \left(\frac{(n' - n) \alpha k_2}{(m - m') \beta k_3} \right)^{1/\beta}. \end{aligned}$$

The determinant of the linearization of the vector field at this point is computed to be

$$(m - m')m\beta^2 k_1 k_3 x_s^{m-1} y_s^{n+\beta-1} > 0.$$

This means that the two sets, given by $\dot{x} = 0$ and $\dot{y} = 0$, in a neighborhood of (x_s, y_s) are smooth curves intersecting transversally at (x_s, y_s) and nowhere else. Therefore, by continuity and by the proposition in [10, chapter 16, section 1], for $k'_i > 0$ sufficiently small, the sets $\dot{x} = 0$ and $\dot{y} = 0$ still have a unique intersection point with positive coordinates and the linearization there has a positive determinant. Moreover, for $k'_i > 0$, there are no equilibria on the axes, and solutions leave the axes transversally ($x = 0 \Rightarrow \dot{x} > 0$, $y = 0 \Rightarrow \dot{y} > 0$). This takes care of assumption (iii) of proposition 3.1, see remark 3.2. Thus we can apply proposition 3.1, provided the linearization at the unique equilibrium has a positive trace. Again for $k'_i = 0$, this trace can be calculated to be

$$\begin{aligned} & (n' - n)nk_1 x_s^m y_s^{n-1} - (m - m')mk_1 x_s^{m-1} y_s^n - \beta^2 k_3 y_s^{\beta-1} \\ & = k_3 y_s^{\beta-1} ((n - \beta)\beta - K k_1^{1/m} k_2^{(m+n-\beta)/(m\beta)} k_3^{-(m+n)/(m\beta)}), \end{aligned}$$

with a positive constant K independent of the k_i . As $n > \beta$, this is clearly positive for an appropriate choice of the k_i ($i = 1, 2, 3$). By continuity, for all $k'_i > 0$ sufficiently small, the trace will be positive at the unique equilibrium. This completes the proof of proposition 4.4. \square

Remark 4.5. For $n \leq \beta$, the above trace is negative for arbitrary $k_i > 0$ if all k'_i vanish. It stays negative after introduction of sufficiently small $k'_i > 0$.

Martiel and Goldbeter propose a reduction of their model for cyclic AMP signaling to a 2-variable system [12, (7), p. 817] of the form

$$\begin{cases} \dot{x} = -x(f_1(y) + f_2(y)) + f_2(y), \\ \dot{y} = s\Phi(x, y) - ky, \end{cases} \tag{MG}$$

where

$$\begin{aligned} f_1(y) &= (k_1 + k_2 y)/(1 + y), & f_2(y) &= (k_1 L_1 + k_2 L_2 c y)/(1 + c y), \\ \Phi(x, y) &= \frac{\alpha(\lambda\theta + ex^2 y^2/(1 + y)^2)}{1 + \alpha\theta + (1 + \alpha)ex^2 y^2/(1 + y)^2}. \end{aligned}$$

Proposition 4.6. If $1 + \alpha\theta \geq (1 + \alpha)\lambda\theta$ then system (MG) satisfies the hypotheses of theorem 2.1 and all solutions are bounded for positive time.

Remark 4.7. In particular, each of $\max\{\lambda, \theta\} \leq 1$, $\lambda\theta \leq (1 + \alpha)^{-1}$ is sufficient. In practice, this is fulfilled because λ and θ are small constants in the model. The numerical studies of [12] give biochemically relevant values for the constants allowing application of proposition 3.1 and realizing asymptotically orbitally stable limit cycles.

Proof of proposition 4.6. This is a case where the functions u and v of (*) do not coincide. Put

$$\begin{aligned} q(x) &:= q = \frac{\alpha}{1 + \alpha} + \max\{k_1 L_1, k_2 L_2\} \quad (\text{constant}), \\ u(x, y) &:= x(f_1(y) + f_2(y)) - f_2(y) + q, \\ \varepsilon &:= s, \quad v(x, y) := \Phi(x, y), \quad r(y) := ky/s. \end{aligned}$$

Conditions (1), (3) and (4) are trivial, (2) holds because $1 + \alpha\theta \geq (1 + \alpha)\lambda\theta$ implies $\partial v/\partial x \geq 0$. $z(0) = \alpha\lambda\theta/(1 + \alpha\theta) > r(0) = 0$ whence (5) follows. As $w(y) \equiv \infty$, (6) and (8) are fulfilled with $c_1 = 0$ and any a_2 . (Concerning (6), cf. comments 2.2(iv).) For (7), choose $c_2 \geq qs/k$. Furthermore, $\Phi \leq \alpha/(1 + \alpha)$ and $f_2 \leq \max\{k_1 L_1, k_2 L_2\}$; therefore, $\Phi + f_2 \leq q \leq x(f_1 + f_2) + q$ and $v \leq u$, such that (9) holds with $c_3 = 0$. \square

For Rössler's multivibrator system

$$\begin{cases} \dot{x} = k_1 x - k_2 xy/(x + K) - k_3 x^2 + k_4, \\ \dot{y} = k_5 x - k_6 y \end{cases} \quad (\text{R})$$

(cf. [15]), the following holds.

Proposition 4.8. In (R), let $k_1, k_2, k_4, K \geq 0$ and $k_3, k_5, k_6 > 0$. Then the hypotheses of theorem 2.1 are satisfied and all solutions are bounded for positive time.

Proof. Introduce two additional positive constants ε and c subject to $\varepsilon c \geq k_5$. Put

$$\begin{aligned} q(x) &:= k_4 + k_1 x - k_3 x^2 + cx, \\ u(x, y) &:= k_2 xy/(x + K) + cx, \\ v(x, y) &:= k_5 x/\varepsilon, \quad r(y) := k_6 y/\varepsilon. \end{aligned}$$

Then $w(y) \equiv \infty$, $z(y) \equiv \infty$, and q is bounded above. Conditions (1)–(8) are verified by simple calculations (by a choice of $c_1 = 0$). The inequality $v(x, y) \leq u(x, y)$ in (9) holds for all (x, y) because $k_5/\varepsilon \leq c$. \square

Remark 4.9. An example of stable oscillations due to proposition 3.1 in (R) is given by $k_2 = k_3 = k_4 = K = 1$, $k_1 = 5$, $k_5 = 3$, $k_6 = 0.3$, and (1, 10) as the unique stationary point.

Remark 4.10. It is striking how many models investigated in the literature are of the form (*). The famous Brusselator [14] can be put into this form. The class of systems for enzyme reactions studied in [6] is a special case of (*). So are the models of [1] which require the rate function r to have positive derivative everywhere, a condition obsolete in applying theorem 2.1. Finally, Gause-type predator–prey models can be studied via theorem 2.1; many of our conditions (1)–(9) result from natural hypotheses imposed in [8,11].

Remark 4.11. An interesting special case of the latter is Ding’s system [4]

$$\begin{cases} \dot{x} = cx(1 - x/K) - x^n y/(a + x^n), \\ \dot{y} = \mu x^n y/(a + x^n) - dy, \end{cases} \tag{D}$$

who imposed $n = 1$ or 2 .

A simple computation shows that, for any $n \geq 1$ and for any positive choice of the parameters, system (D) satisfies the hypotheses of theorem 2.1. Moreover, if

$$\left(1 - \frac{1}{n}\right)\mu < d < \mu$$

and

$$K > \left(1 + \frac{\mu}{nd - (n - 1)\mu}\right)^n \sqrt[n]{\frac{ad}{\mu - d}},$$

then there is an asymptotically orbitally stable limit cycle by proposition 3.1. Here we encounter a situation where the nonnegative axes are invariant and contain stationary points. The unstable manifold of $(K, 0)$ serves as the positively invariant curve in condition (iii) of proposition 3.1. Choosing

$$\mu = 2n, \quad d = 2n - 1, \quad a = \frac{K^n}{(2n - 1)4^n},$$

c and K arbitrary, leads to numerical values realizing propositions 2.1 and 3.1.

5. Proof of theorem 2.1

For the vector field of system (*), the notation (\dot{x}, \dot{y}) will be used throughout. Given a solution, the positive semi-orbit stays in a compact set K to be constructed. In figure 1, numbers in parentheses attached to a line segment bounding K indicate the conditions accounting for that the solution does not leave K via this line segment. Note, however, it is not claimed that the set K is necessarily positively invariant.

By condition (3),

$$\dot{x}(0, y) = q(0) - u(0, y) \geq 0 \quad \text{for all } y \geq 0.$$

By (2) and (4),

$$\dot{y}(x, 0) = \varepsilon(v(x, 0) - r(0)) \geq \varepsilon(v(0, 0) - r(0)) \geq 0 \quad \text{for all } x \geq 0.$$

(Note that $[0, \infty[\times \{0\} \subset S$.) So, by the non-termination lemma below, all solutions are defined on maximal intervals half-open on the right, and no solution terminates at a boundary point of the positive quadrant in the plane.

Let (x_0, y_0) be an arbitrary initial point. First, assume $r(0) = z(0)$. It is no restriction to assume $a_1 \geq x_0$. By (5), for any $x \geq a_1$, on the vertical line segment with end points $(x, 0)$ and (x, η) , the inequality $\dot{x} < 0$ holds, and orbits pass through

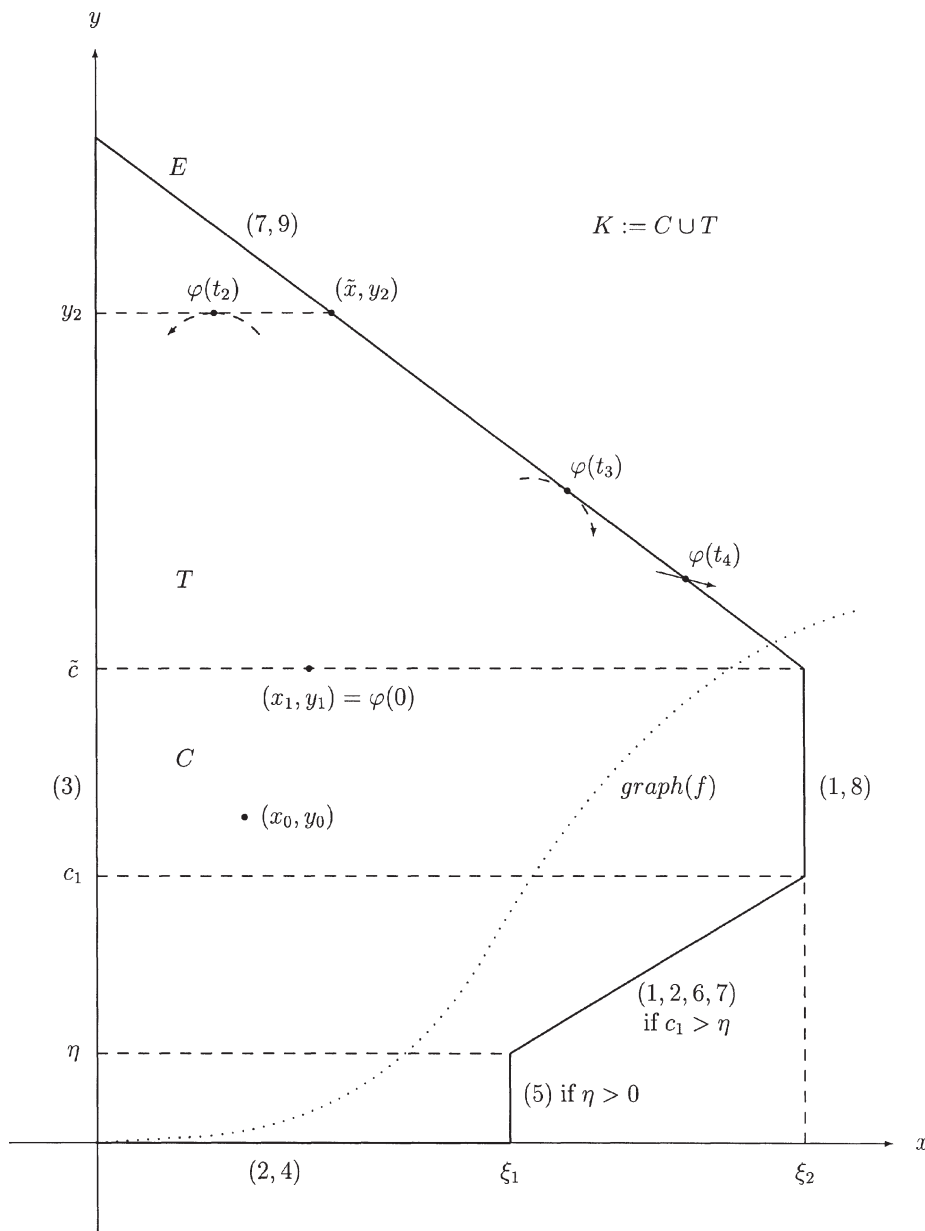


Figure 1.

this line segment from right to left. If $r(0) \neq z(0)$ then (4) and (2) imply $r(0) < z(0)$ and η is zero. In any case, by decreasing η and increasing a_1 if necessary, it may be assumed that $\eta \leq c_1$ and $[a_1, \infty[\times [0, \eta] \subset S$.

By (6), $z(y) > r(y)$ for all $y \in [\eta, c_1]$. (This interval is possibly degenerate.) Therefore, given $\tilde{y} \in [\eta, c_1]$, there is $x \geq 0$ such that $(x, y) \in S$ and $v(x, y) > r(y)$

for all y in a neighborhood of \tilde{y} . Compactness of $[\eta, c_1]$ and condition (2) yield $b_1 \geq 0$ such that $v(b_1, y) > r(y)$ for any $y \in [\eta, c_1]$. Without loss of generality, $b_1 \geq \max\{x_0, a_1, a_2\}$ and $[b_1, \infty[\times [0, c_1] \subset S$. The number

$$p := \min\{v(b_1, y) - r(y) \mid \eta \leq y \leq c_1\}$$

is positive. Let $q_{\text{sup}} := \sup\{q(x) \mid x \geq 0\}$ (finite by (7)). Then on the set

$$\{(x, y) \mid x \geq b_1 \text{ and } \eta \leq y \leq c_1\} \subset S,$$

the vector field by (1) satisfies

$$\dot{x}(x, y) = q(x) - u(x, y) \leq q_{\text{sup}} - u(b_1, y) \leq M,$$

for a suitable positive real number M , and

$$\dot{y}(x, y) = \varepsilon(v(x, y) - r(y)) \geq \varepsilon p > 0;$$

hence $\dot{x}/\dot{y} \leq M/(\varepsilon p)$, and orbits pass through any line segment of slope $\varepsilon p/(2M)$ in this set from below.

Let $\tilde{c} > \max\{y_0, c_1, c_2, c_3\}$. By compactness of $[c_1, \tilde{c}]$ and an argument already used above, (8) and (1) imply: there is $b_2 \geq b_1$ such that $[b_2, \infty[\times [0, \tilde{c}] \subset S$ and $u(b_2, y) > \tilde{q}$ for all $y \in [c_1, \tilde{c}]$. Thus, if $x \geq b_2$ and $y \in [c_1, \tilde{c}]$ then

$$\dot{x}(x, y) = q(x) - u(x, y) \leq \tilde{q} - u(b_2, y) < 0,$$

and orbits pass through the vertical line segment with end points (x, c_1) and (x, \tilde{c}) from right to left.

Define C to be the compact set bounded by a closed polygonal curve joining the ordered vertices $(0, 0), (\xi_1, 0), (\xi_1, \eta), (\xi_2, c_1), (\xi_2, \tilde{c}), (0, \tilde{c}), (0, 0)$, where $\xi_1 \geq b_1$ and $\xi_2 \geq b_2$, subject to the condition that the line through (ξ_1, η) and (ξ_2, c_1) has slope $\varepsilon p/(2M)$, except when $\eta = c_1$; in the latter case, choose $\xi_1 = \xi_2$. Then the positive semi-orbit of any point in C (e.g., (x_0, y_0)) can leave C only via the top horizontal edge.

Define T the compact triangular surface with vertices $(0, \tilde{c}), (\xi_2, \tilde{c})$ and a third vertex on the y -axis such that one edge, denoted E , has slope -2ε . Let $K := C \cup T$. As will be seen, a positive semi-orbit of a point in C cannot leave K . This is due to the limitations on the directions of the vector field in T , namely:

Let (x, y) with $y \geq \tilde{c}$.

Case I: $u(x, y) > q(x)$. Then $\dot{x}(x, y) < 0$. Moreover,

(a) $\dot{y}(x, y) \leq 0$, or

(b) $\dot{y}(x, y) > 0$, in which case the following holds at (x, y) :

$$v > r \quad (\text{as } \dot{y} > 0) \quad \text{and} \quad r \geq q \quad (\text{because of (7)})$$

$$\Rightarrow 0 < v - r \leq u - q \quad (\text{because of (9)})$$

$$\Rightarrow 0 < \dot{y}/(-\dot{x}) \leq \varepsilon;$$

hence $0 > \dot{y}/\dot{x} \geq -\varepsilon > -2\varepsilon$.

Case 2: $u(x, y) = q(x)$. Then at (x, y) , $\dot{x} = 0$ and $\dot{y} = \varepsilon(v - r) \leq \varepsilon(u - q) = 0$ (by (7) and (9)). The vector field is stationary or points vertically down at (x, y) .

Case 3: $u(x, y) < q(x)$. Then at (x, y) , $\dot{x} > 0$ and $\dot{y} = \varepsilon(v - r) \leq \varepsilon(u - q) < 0$ (by (7) and (9)).

Suppose a solution $\varphi(t) = (x(t), y(t))$, with initial point $(x_1, y_1) \in C$ at $t = 0$, leaves K . The last point in C (before it leaves K) has y -coordinate \tilde{c} ; so, one may assume that (x_1, y_1) is this last point and $y_1 = \tilde{c}$. Let φ leave K for the first time at $t = t_4$. Then $(x_4, y_4) := \varphi(t_4) \in E$. As E has slope -2ε , cases 1 and 2 above are ruled out at (x_4, y_4) . Thus, at (x_4, y_4) , $\dot{x} > 0$ and $\dot{y} < 0$ according to case 3, and $y(t) > y_4$ for some $t < t_4$. Let $y|_{[0, t_4]}$ take on its last maximum y_2 at $t = t_2$, and let $(x_3, y_3) := \varphi(t_3)$ be the first point on E with $t_2 \leq t_3 \leq t_4$. Then $\dot{y}(t_2) = 0$ and $\dot{x}(t_2) \neq 0$, so $\dot{x}(t_2) < 0$ (case 1), and $\varphi(t_2)$ is in the interior of T . Therefore, $t_2 < t_3$. Moreover, $y_2 > y_3$. Let J be the closed Jordan curve consisting of $\varphi([t_2, t_3])$ and the two line segments joining the point $(\tilde{x}, y_2) \in E$ with $\varphi(t_2)$ and $\varphi(t_3)$. J is contained in T .

As $\varphi([0, t_2]) \subset T$, as the line segment from $\varphi(t_2)$ to (\tilde{x}, y_2) is not completely contained in $\varphi([0, t_2])$, and, as $y(t) \leq y_2$ for all $t \in [0, t_2]$, there is some $t \in [0, t_2]$ such that $\varphi(t)$ is contained in the interior region of J . Therefore, all of $\varphi([0, t_2])$ is contained in that region, which is a subset of the interior of T . But $\varphi(0) = (x_1, y_1) = (x_1, \tilde{c})$ is not in $\text{int}(T)$; a contradiction.

This shows that $\varphi(t)$ stays in K for all $t \geq 0$ for which it is defined. As K is compact, $\varphi(t)$ is defined for all $t \geq 0$. This completes the proof of theorem 2.1. \square

Appendix

Lemma A.1 (non-termination lemma). Let $P^n \subset \mathbb{R}^n$ be the nonnegative orthant $P^n = [0, \infty[^n$, $V \subset P^n$ a subset open in P^n , $G: V \rightarrow \mathbb{R}^n$ a vector field satisfying a local Lipschitz condition and the following hypothesis:

$$\text{If } k \in \{1, \dots, n\} \text{ and } x \in V \text{ such that } x_k = 0 \text{ then } G_k(x) \geq 0.$$

(The index k indicates the k th component.) Then the differential system

$$\dot{y} = G(y)$$

has a solution semi-flow $\Psi: W \rightarrow V$ on an open subset W of $[0, \infty[\times V$.

This means, if $y_0 \in V$ then the initial value problem $\dot{y} = G(y)$, $y(0) = y_0$, has a unique solution on a half-open interval $[0, \tau[$ that cannot be extended on the right-hand side. In particular, following a nonextendible solution in positive direction does not terminate at some point of the boundary of P^n .

Remark A.2. The proof below consists of two steps: extension of the vector field to an open set in \mathbb{R}^n and proof of a “non-exit lemma” (not explicitly stated) saying that solutions of the extended system do not leave P^n in positive time direction.

Proof of lemma A.1. Define $\rho: \mathbb{R}^n \rightarrow P^n$ by

$$\rho_k(x_1, \dots, x_n) := \begin{cases} x_k & \text{if } x_k \geq 0, \\ 0 & \text{if } x_k < 0, \end{cases}$$

for $k = 1, \dots, n$. The vector field ρ is the identity on P^n . Let $U := V \cup \rho^{-1}(V \cap \text{bd}(P^n))$, $F: U \rightarrow \mathbb{R}^n$, $F := G \circ \rho$, where $\text{bd} = \text{boundary}$. The vector field F is defined on the open set U in \mathbb{R}^n , satisfies a local Lipschitz condition and coincides with G on V .

Solutions of $\dot{y} = F(y)$ are solutions of $\dot{y} = G(y)$ as long as they stay in V . Let Φ be the solution semi-flow of $\dot{y} = F(y)$ on U , and let $z \in V \cap \text{bd}(P^n)$. It is sufficient to show that $\Phi(t, z) \in P^n$ for all $t > 0$ for which $\Phi(t, z)$ is defined. Assume $\Phi(t_1, z) \notin P^n$ for some $t_1 > 0$. Then $\Phi_k(t_1, z) < 0$ for some k , and there is $t_0 \in [0, t_1[$ such that $\Phi_k(t_0, z) = 0$ and $\Phi_k(t, z) < 0$ for all $t \in]t_0, t_1]$,

$$\Phi_k(t_1, z) = \Phi_k(t_0, z) + \int_{t_0}^{t_1} \frac{\partial}{\partial t} \Phi_k(t, z) dt = \int_{t_0}^{t_1} G_k \circ \rho(\Phi(t, z)) dt,$$

$$t \in]t_0, t_1] \Rightarrow \rho_k \circ \Phi(t, z) = 0 \Rightarrow G_k \circ \rho(\Phi(t, z)) \geq 0.$$

Hence, $\Phi_k(t_1, z) \geq 0$, a contradiction. Therefore, $\Phi(t, z) \in P^n$ for $t > 0$ if defined. \square

Acknowledgements

The author would like to thank the referees for their helpful advice.

References

- [1] F. Battelli and C. Lazzari, Boundedness and stable oscillations in two-dimensional enzyme reduced systems, *Math. Biosci.* 82 (1986) 1–17.
- [2] A. Császár, L. Jicsinszky and T. Turányi, Generation of model reactions leading to limit cycle behavior, *React. Kinet. Catal. Lett.* 18 (1981) 65–71.
- [3] A. Dancsó, H. Farkas, M. Farkas and G. Szabó, Investigations into a class of generalized two-dimensional Lotka–Volterra schemes, *Acta Appl. Math.* 23 (1991) 103–127.
- [4] S.H. Ding, Global structure of a kind of predator–prey system, *Appl. Math. Mech.* 9 (1988) 999–1003.
- [5] D. Erle, Stable closed orbits in plane autonomous dynamical systems, *J. Reine Angew. Math.* 305 (1979) 136–139.
- [6] D. Erle, K.H. Mayer and T. Plesser, The existence of stable limit cycles for enzyme catalyzed reactions with positive feedback, *Math. Biosci.* 44 (1979) 191–208.
- [7] C. Escher, Bifurcation and coexistence of several limit cycles in models of open two-variable quadratic mass-action systems, *Chem. Phys.* 63 (1981) 337–348.
- [8] H.I. Freedman, *Deterministic Mathematical Models in Population Ecology* (Dekker, New York, 1980).
- [9] R.H. Hering, Oscillations in Lotka–Volterra systems of chemical reactions, *J. Math. Chem.* 5 (1990) 197–202.
- [10] M. Hirsch and S. Smale, *Differential Equations, Dynamical Systems, and Linear Algebra* (Academic Press, New York, 1974).

- [11] Y. Kuang and H.I. Freedman, Uniqueness of limit cycles in Gause-type models of predator–prey systems, *Math. Biosci.* 88 (1988) 67–84.
- [12] J.-L. Martiel and A. Goldbeter, A model based on receptor desensitization for cyclic AMP signaling in *Dictyostelium* cells, *Biophys. J.* 52 (1987) 807–828.
- [13] G. Póta, Two-component bimolecular systems cannot have limit cycles: A complete proof, *J. Chem. Phys.* 78 (1983) 1621–1622.
- [14] I. Prigogine and R. Lefever, Symmetry breaking instabilities in dissipative systems. II, *J. Chem. Phys.* 48 (1968) 1695–1700.
- [15] O.E. Rössler, A principle for chemical multivibration. Letter to the Editor, *J. Theor. Biol.* 36 (1972) 413–417.
- [16] J. Schnakenberg, Simple chemical reaction systems with limit cycle behavior, *J. Theor. Biol.* 81 (1979) 389–400.
- [17] J. Schnakenberg, *Thermodynamic Network Analysis of Biological Systems*, 2nd correct. updated ed. (Springer, Berlin, 1981).
- [18] E.E. Sel'kov, Self-oscillations in glycolysis. 1. A simple kinetic model, *Eur. J. Biochem.* 4 (1968) 79–86.
- [19] P.L. Simon, The reversible LVA model, *J. Math. Chem.* 9 (1992) 307–322.
- [20] P.L. Simon, Globally attracting domains in two-dimensional reversible chemical dynamical systems, *Ann. Univ. Sci. Budapest. Sect. Comput.* 15 (1995) 179–200.
- [21] J. Tóth, Bendixson-type theorems with applications, *Z. Angew. Math. Mech.* 67 (1987) 31–35.