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MONOTONICITY PROPERTIES OF THE MICHAELIS-MENTEN REACTIONS OF ENZYME KINETICS

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ABSTRACT. The Michaelis-Menten reactions of enzyme kinetics can be written $E + S \rightleftarrows ES \rightarrow P + E$ (E is the enzyme). Assuming mass-action kinetics, the concentrations are governed by a system of ordinary differential equations. An investigation is made of the signs of the derivatives of the concentrations with respect to each initial concentration. Although the system does not give rise to an order preserving flow with respect to an orthant, many of the derivatives with respect to an initial concentration are of one sign.

1. Introduction. The Michaelis-Menten reactions of enzyme kinetics can be written

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \overset{k_2}{\rightarrow} P + E,$$

where E, S, ES, and P are the enzyme, substrate, complex, and product, respectively. Denoting the concentrations of E, S, ES, and P by x, y, z, w, respectively, the law of mass-action gives the system of differential equations

$$\begin{aligned} \dot{x} &= -k_1 xy + (k_{-1} + k_2) z \\ \dot{y} &= -k_1 xy + k_{-1} z \\ \dot{z} &= k_1 xy - (k_{-1} + k_2) z \\ \dot{w} &= k_2 z \end{aligned}, \tag{1.1}$$

where a dot indicates the time derivative and k_1, k_{-1}, and k_2 are positive constants (the rate constants). For background, see [**5**] and [**3**].

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We denote the initial concentrations

$$x(0) = \xi, \quad y(0) = \eta, \quad z(0) = \zeta, \quad w(0) = \nu; \tag{1.2}$$

they are required to satisfy

$$\xi \geq 0,\ \eta \geq 0,\ \zeta \geq 0,\ \nu \geq 0,\ \xi + \zeta > 0,\ \eta + \zeta > 0. \tag{1.3}$$

The last two inequalities of (1.3) are to insure that we are working with nontrivial (i.e., nonequilibrium) solutions of (1.1). Biochemists take $\zeta = 0$, $\xi > 0$, $\eta > 0$.

Since the system (1.1) is smooth, any partial derivative of a concentration with respect to an initial concentration exists and is smooth (in fact, analytic) in its dependence on t, ξ, η, ζ, and ν. We shall investigate the signs of these partial derivatives. Table 1 summarizes most of our results.

TABLE 1. Behavior of concentrations with respect to changes in initial concentrations.

	x	y	z	w
ξ	$+$	$-$	$*$	$+$
η	$-$	$+$	$+$	$+$
ζ	$+$	$*$	$*$	$+$
ν	0	0	0	$+$

Each entry indicates the sign of a partial derivative of a concentration (column heading) with respect to an initial concentration (row heading), for $t > 0$. A $+$ or $-$ indicates a positive or negative partial derivative, a 0 indicates a zero partial derivative, and a $*$ indicates that the partial derivative changes sign as a function of t. The $+, -$ and 0 entries give monotonicity properties of the corresponding concentration profiles (concentration versus time). For example, from $\partial y/\partial \xi < 0$ it follows that the y concentration profiles decrease as ξ is increased (see Figure 1).

In the case of a $*$ entry, we will prove that any two concentration profiles, with two different initial concentrations intersect. This is illustrated in Figure 2 for the z concentration profiles with respect to changes in ξ. (Note: the entries for $\partial y/\partial \zeta$ and $\partial z/\partial \zeta$ were incorrectly stated in [**6**]).

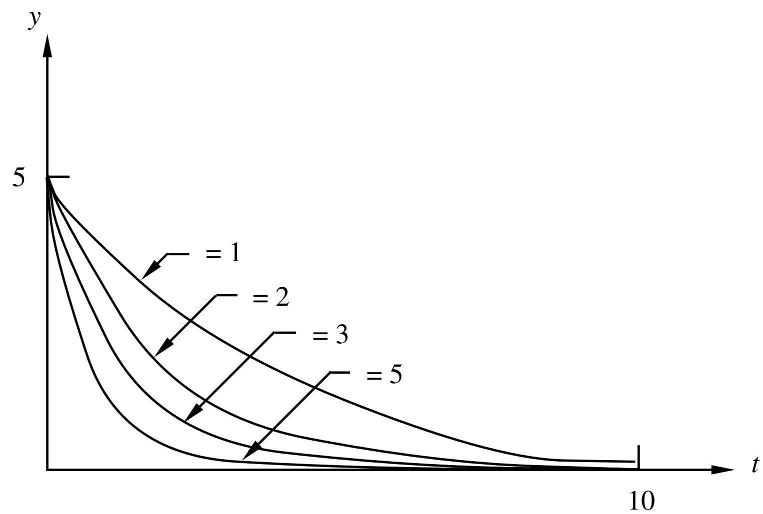

FIGURE 1. Four y-concentration profiles with $\xi = 1, 2, 3, 5, \eta = 5, \zeta = .5$, and $k_1 = k_{-1} = k_2 = 1$.

These results are related to the theory of monotone flows. For background, see [**4**] and [**7**]. When a system of differential equations $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}), \mathbf{x}(0) = \boldsymbol{\xi}$ generates an order preserving flow with respect to an orthant (OPF), each partial derivative with respect to an initial value, $\partial x_i/\partial \xi_j$, is nonnegative or nonpositive, as a function of time. Necessary and sufficient conditions for a system of differential equations to generate an OPF are given in [**7**]. These conditions depend on the signs of the off-diagonal elements of the Jacobian matrix of $\mathbf{f}$. The first three equations of (1.1) (denoted (1.1a,b,c)) have corresponding Jacobian matrix

$$\begin{pmatrix} \cdot & -k_1 x & k_{-1} + k_2 \\ -k_1 x & \cdot & k_{-1} \\ k_{-1} + k_2 & k_{-1} & \cdot \end{pmatrix}.$$

Since, for $x \neq 0$, there are an odd number of negative entries above the diagonal, by [**7**, p. 102] (1.1a,b,c) does not give rise to an OPF. It follows that the full system (1.1) cannot generate an OPF.

The paper is organized as follows. In Section 2 we discuss the long time behavior of solutions to (1.1) based on a preliminary transforma-

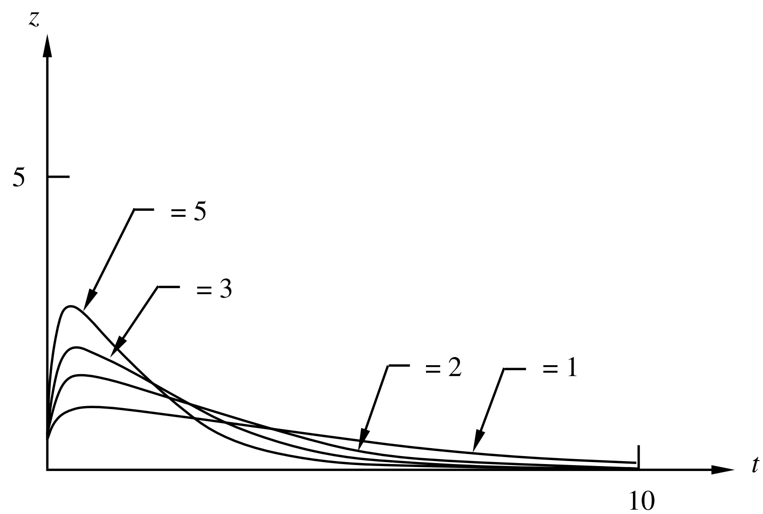

FIGURE 2. Four z-concentration profiles with $\xi = 1, 2, 3, 5, \eta = 5, \zeta = .5$, and $k_1 = k_{-1} = k_2 = 1$.

tion to a two-dimensional system. Section 3 has the nonmonotonicity results corresponding to the $*$ entries in Table 1. Section 4 contains the monotonicity results corresponding to the rest of Table 1. In Section 5 we make some final remarks.

We will use an informal method of presentation of our results, indicating main results by boldface numbers. Individual equations in a system of equations will be referred to by adding a letter (a,b,c, etc.) to the equation number.

2. Long time behavior. In this section we examine the long time behavior of solutions to (1.1). First, we reduce considerations to a two-variable problem.

Comparing (1.1a) and (1.1c), we have $\dot{z} = -\dot{x}$, from which follows

$$x = \xi + \zeta - z. \tag{2.1}$$

Also, by adding (1.1b), (1.1c), and (1.1d), we have $\dot{y} + \dot{z} + \dot{w} = 0$, from which follows

$$w = \eta + \zeta + \nu - y - z. \tag{2.2}$$

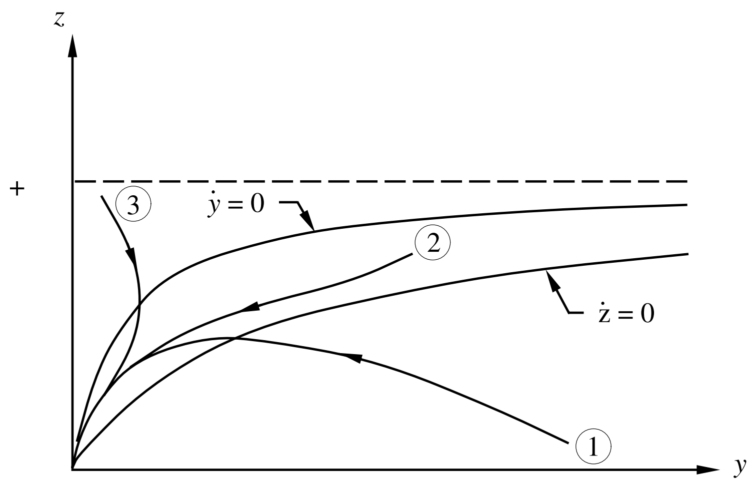

FIGURE 3. The three types of trajectories of the yz-system.

We can now (using (2.1)) obtain a system of two equations which determine y and z, the yz-system

$$\begin{aligned} \dot{y} &= -k_1(\xi+\zeta-z)y + k_{-1}z \\ \dot{z} &= k_1(\xi+\zeta-z)y - (k_{-1}+k_2)z. \end{aligned} \tag{2.3}$$

When we determine the behavior of y and z, the behavior of x and w can be obtained from (2.1) and (2.2).

The first quadrant in the yz-plane is divided into three regions by the curves

$$z = \frac{k_1(\xi+\zeta)y}{k_{-1}+k_1y} \text{ and } z = \frac{k_1(\xi+\zeta)y}{k_{-1}+k_2+k_1y},$$

where $\dot{y}=0$ and $\dot{z}=0$, respectively. Starting at (η,ζ), a trajectory can take one of three forms (see Figure 3). Each trajectory ends up between the two curves and must tend to $(0,0)$ as $t\to\infty$. Thus, $y(t)>0$ and $0<z(t)<\xi+\zeta$, for $t>0$, and $\lim_{t\to\infty} y(t) = \lim_{t\to\infty} z(t) = 0$.

We can say more. Because any solution to (2.3) approaches the equilibrium point (0,0), it must behave asymptotically like a solution to the linearized system (linearized about (0,0))

$$\begin{aligned} \dot{\bar{y}} &= -k_1(\xi+\zeta)\bar{y} + k_{-1}\bar{z} \\ \dot{\bar{z}} &= k_1(\xi+\zeta)\bar{y} - (k_{-1}+k_2)\bar{z}. \end{aligned} \tag{2.4}$$

We find that the coefficient matrix of (2.4) has two real eigenvalues $\lambda_2 < \lambda_1 < 0$,

$$\lambda_1, \lambda_2 = \frac{-(a+b+c) \pm \sqrt{(a+b+c)^2 - 4bc}}{2}, \tag{2.5a,b}$$

with $a = k_{-1}, b = k_2$, and $c = k_1(\xi+\zeta)$. Two independent solutions of (2.4) are

$$\boldsymbol{\phi}_1(t) = e^{\lambda_1 t}\begin{pmatrix} a \\ \lambda_1 + c \end{pmatrix} \text{ and } \boldsymbol{\phi}_2(t) = e^{\lambda_2 t}\begin{pmatrix} a \\ \lambda_2 + c \end{pmatrix}. \tag{2.6}$$

Since (0,0) is a stable node, by [**2**; Chapter VIII, Theorem 3.5, part (ii), p. 218], any solution to (2.3) must satisfy

(2.7)
$$\begin{pmatrix} y \\ z \end{pmatrix} = c_1 e^{\lambda_1 t}\begin{pmatrix} a + o(1) \\ \lambda_1 + c + o(1) \end{pmatrix} \text{ or } \begin{pmatrix} y \\ z \end{pmatrix} = c_2 e^{\lambda_2 t}\begin{pmatrix} a + o(1) \\ \lambda_2 + c + o(1) \end{pmatrix}$$

as $t \to \infty$, where c_1 and c_2 are constants. To see which possibility holds, note that

$$\lambda_1 + c > 0 \text{ and } \lambda_2 + c < 0. \tag{2.8}$$

These inequalities follow from the simple inequality

$$\sqrt{(a+b+c)^2 - 4bc} > |a+b-c| \tag{2.9}$$

for positive a, b and c (which is proved by squaring both sides). Now, since y and z are positive for all time, they must satisfy the first possibility in (2.7), i.e.,

$$\begin{pmatrix} y \\ z \end{pmatrix} = c_1 e^{\lambda_1 t}\begin{pmatrix} a + o(1) \\ \lambda_1 + c + o(1) \end{pmatrix} \tag{\textbf{2.10}}$$

as $t \to \infty$, with $c_1 > 0$. Of course, the positive constant c_1 depends on the specific solution.

3. Nonmonotonicity results. In this section we prove two sorts of nonmonotonicity results for each $*$ entry in Table 1: (a) intersection of concentration profiles and (b) change in the sign of the partial derivative of the concentration with respect to the initial concentration. We shall use the terminology that a statement is *true initially* if it is true for $0 < t < t_1$, some t_1, and *true eventually* if it is true for $t > t_2$, some t_2.

3a. *Intersection of concentration profiles.* Consider the z component of two solutions to (1.1)–(1.3) with different ξ values, $z(t) = z(t;\xi)$ and $\bar{z}(t) = z(t;\bar{\xi})$, where $\xi < \bar{\xi}$, and all other initial conditions are the same. We first show that

$$z(t) < \bar{z}(t) \quad \text{initially.} \tag{3.1}$$

The partial derivative with respect to ξ will be denoted by a prime. Differentiating $z(0) = \zeta$ and $\dot{z}(0) = k_1\xi\eta - (k_{-1} + k_2)\zeta$, we have

$$z'(0) = 0, \quad \dot{z}'(0) = k_1\eta. \tag{3.2}$$

Differentiating (1.1c) with respect to t and ξ, and evaluating at $t = 0$, gives

$$\ddot{z}'(0) = k_1 k_{-1}\xi \quad \text{if } \eta = 0. \tag{3.3}$$

Equations (3.2) and (3.3) show that either $\dot{\bar{z}}(0) > \dot{z}(0)$ or $\dot{\bar{z}}(0) = \dot{z}(0)$ and $\ddot{\bar{z}}(0) > \ddot{z}(0)$ (using the assumption that not both ξ or η are zero). This implies (**3.1**).

We next show that

$$\bar{z}(t) < z(t) \quad \text{eventually.} \tag{3.4}$$

By (**2.10**), we have

$$\begin{aligned} z(t) &= c_1 e^{\lambda_1 t}[\lambda_1 + c + o(1)] \\ \bar{z}(t) &= \bar{c}_1 e^{\bar{\lambda}_1 t}[\bar{\lambda}_1 + \bar{c} + o(1)] \end{aligned} \tag{3.5}$$

as $t \to \infty$, where c_1 and $\bar{c}_1$ are positive constants. Differentiating (2.5a) with respect to ξ gives

$$\frac{2\lambda_1'}{k_1} = -1 + \frac{a - b + c}{\sqrt{(a+b+c)^2 - 4bc}}, \tag{3.6}$$

and inequality (2.9) implies that

$$\lambda_1' < 0. \tag{3.7}$$

From (3.7) we have $\bar{\lambda}_1 < \lambda_1$. The conclusion (**3.4**) now follows from (3.5).

The same type of reasoning also produces the following results. Let $\zeta < \bar{\zeta}$; then,

$$y(t;\zeta) < y(t;\bar{\zeta}) \text{ initially, and } y(t,\bar{\zeta}) < y(t;\zeta) \text{ eventually.} \tag{\textbf{3.8}}$$

The same statement (**3.8**) holds with y replaced by z.

3b. *Sign changes of derivatives with respect to initial concentrations.* Again, the partial derivative with respect to ξ will be denoted by a prime. Equations (3.2) and (3.3) show that

$$z' > 0 \quad \text{initially.} \tag{\textbf{3.9}}$$

We next prove

$$z' < 0 \quad \text{eventually.} \tag{\textbf{3.10}}$$

Differentiating (2.3) with respect to ξ gives

(3.11)
$$\begin{pmatrix} y' \\ z' \end{pmatrix}^{\cdot} 3 = \begin{pmatrix} -k_1(\xi+\zeta-z) & k_1 y + k_{-1} \\ k_1(\xi+\zeta-z) & -k_1 y - (k_{-1}+k_2) \end{pmatrix} \begin{pmatrix} y' \\ z' \end{pmatrix} + \begin{pmatrix} -k_1 y \\ k_1 y \end{pmatrix}.$$

We know y and z approach zero exponentially, hence (3.11) can be considered to be a perturbed linear system, $\dot{\mathbf{x}} = (A + P(t))\mathbf{x} + \mathbf{b}(t)$, with constant matrix A,

$$A = \begin{pmatrix} -k_1(\xi+\zeta) & k_{-1} \\ k_1(\xi+\zeta) & -(k_{-1}+k_2) \end{pmatrix}.$$

This is the same matrix as that for the linearized system (2.4). Note that $\lim_{t\to\infty} P(t) = 0$ and $\lim_{t\to\infty} \mathbf{b}(t) = 0$. The eigenvalues of A are negative, so that, by the method of proof of Theorem 3.1 of Chapter 13 [**1**, pp. 327–328], we have

$$\textbf{(3.12)} \qquad \lim_{t\to\infty} y' = 0, \quad \lim_{t\to\infty} z' = 0.$$

In view of the precise behavior of y and z given by (**2.10**), we can write (3.11) as

$$(3.13) \qquad \begin{pmatrix} y' \\ z' \end{pmatrix}^{\cdot} = A \begin{pmatrix} y' \\ z' \end{pmatrix} + \mathbf{d},$$

with

$$\mathbf{d} = k_1 \begin{pmatrix} -y(1+o(1)) \\ y(1+o(1)) \end{pmatrix} = c_3 e^{\lambda_1 t} \begin{pmatrix} -1+o(1) \\ 1+o(1) \end{pmatrix}$$

as $t \to \infty$ and c_3 a positive constant. We now solve (3.13) for (y', z') by the variation of parameters method. A fundamental matrix for (2.4) is given by $X(t) = (\boldsymbol{\phi}_1(t)\ \boldsymbol{\phi}_2(t))$, with $\boldsymbol{\phi}_1(t)$ and $\boldsymbol{\phi}_2(t)$ defined in (2.6). Since $y'(0) = z'(0) = 0$, we have

$$(3.14) \qquad \begin{pmatrix} y' \\ z' \end{pmatrix} = X(t) \int_0^t X^{-1}(s)\mathbf{d}(s)\, ds.$$

A calculation using the asymptotic formulas $\int_0^t (1+o(1))\, ds = t(1+o(1))$ and $\int_0^t e^{ks}(1+o(1))\, ds = (e^{kt}/k)(1+o(1))$, $k > 0$, as $t \to \infty$, then gives

$$\textbf{(3.15)} \qquad z' = \frac{c_3(\lambda_1 + c)}{a(\lambda_1 - \lambda_2)}(a + c + \lambda_2) t e^{\lambda_1 t}(1 + o(1))$$

as $t \to \infty$. Since $a + c + \lambda_2 < 0$ (by inequality (2.9)) and the other terms are positive, (**3.10**) now follows from (**3.15**).

The same type of reasoning shows

$$\textbf{(3.16)} \quad \frac{\partial y}{\partial \zeta} \quad \text{and} \quad \frac{\partial z}{\partial \zeta} \quad \text{are initially positive and eventually negative.}$$

There is another way to prove that $\partial z/\partial \zeta = z'$ changes sign. By adding equations (2.3a) and (2.3b), we obtain

$$\dot{y} + \dot{z} = -k_2 z.$$

Differentiating with respect to ξ and integrating from 0 to t yields

$$y' + z' = -k_2 \int_0^t z'\, ds.$$

Applying (**3.12**) in taking a limit as $t \to \infty$, it follows that

$$\textbf{(3.17)} \qquad \int_0^\infty z'\, ds = 0,$$

which shows that z' cannot have one sign.

4. Monotonicity properties. The monotonicity properties with respect to ξ, η, ζ, and ν will be proved in subsections (4a)–(4d). We again use the terminology that a statement is *true initially* if it holds for some interval, $0 < t < t_1$. A prime will denote a derivative with respect to ξ, η, ζ, or ν in each of the corresponding subsections.

4a. *Monotonicity with respect to* ξ. Let

$$x' = \frac{\partial x}{\partial \xi}, \quad y' = \frac{\partial y}{\partial \xi}, \quad z' = \frac{\partial z}{\partial \xi}, \quad w' = \frac{\partial w}{\partial \xi}.$$

First we show that

(4.1) x' and w' are initially positive, y' is initially negative.

This follows from

$$(4.2) \qquad x'(0) = 1$$

$$(4.3) \qquad y'(0) = 0, \quad \dot{y}'(0) = -k_1\eta, \quad \ddot{y}'(0) = -k_1k_{-1}\zeta \quad \text{if } \eta = 0$$

(4.4)
$$w'(0) = 0, \quad \dot{w}'(0) = 0, \quad \ddot{w}'(0) = k_2k_1\eta, \quad \dddot{w}'(0) = k_2k_1k_{-1}\zeta \quad \text{if } \eta = 0,$$

since η and ζ are not both zero. The equations (4.2)–(4.4) are obtained from differentiating the differential equations (1.1) and the initial conditions (1.2).

It is convenient to introduce the xy-system ((1.1a,b), making use of (2.1)),

$$\begin{aligned} \dot{x} &= -k_1 xy + (k_{-1} + k_2)(\xi + \zeta - x) \\ \dot{y} &= -k_1 xy + k_{-1}(\xi + \zeta - x). \end{aligned} \tag{4.5}$$

Subtracting (4.5b) from (4.5a) gives us

$$\dot{x} - \dot{y} = k_2(\xi + \zeta - x).$$

By differentiating with respect to ξ and rearranging, we see that

$$\dot{x}' + k_2 x' = k_2 + \dot{y}',$$

and, solving for x', we get

$$x' = e^{-k_2 t}\left(1 + \int_0^t e^{k_2 s}(k_2 + \dot{y}')\, ds\right).$$

Integrating by parts yields

$$x' = 1 + y' - k_2 e^{-k_2 t} \int_0^t e^{k_2 s} y'\, ds. \tag{4.6}$$

We now show that

$$y' < 0, \quad \text{for } t > 0. \tag{4.7}$$

Differentiating (4.5b) gives

$$\dot{y}' = -k_1(x'y + xy') + k_{-1}(1 - x'). \tag{4.8}$$

Suppose $y'(t) = 0$ at some positive t; let τ be the first such time. We have $y'(t) < 0$ for $0 < t < \tau$, and $y'(\tau) = 0$, hence $\dot{y}'(\tau) \geq 0$. On the other hand, by (4.6), $x'(\tau) > 1$, so that, by (4.8), $\dot{y}'(\tau) = -k_1 x'(\tau) y(\tau) + k_{-1}(1 - x'(\tau)) < 0$, a contradiction.

Next, we show

$$x' > 0, \quad \text{for } t \geq 0. \tag{4.9}$$

Differentiating (4.5a) gives

$$\dot{x}' = -k_1(x'y + xy') + (k_{-1} + k_2)(1 - x') \tag{4.10}$$

Suppose that $x'(t) = 0$ at some positive t; let τ be the first such time. We have $x'(t) > 0$ for $0 < t < \tau$ and $x'(\tau) = 0$, hence $\dot{x}'(\tau) \leq 0$. However, by (4.10), $\dot{x}'(\tau) = -k_1 x(\tau)y'(\tau) + (k_{-1} + k_2) > 0$ (using (**4.7**)), a contradiction.

Finally, we show that

$$w' > 0, \quad \text{for } t > 0. \tag{\textbf{4.11}}$$

By (1.1d) and (2.2),

$$\dot{w} = k_2(\eta + \zeta + \nu - y - w). \tag{4.12}$$

Differentiating gives

$$\dot{w}' = -k_2(y' + w'). \tag{4.13}$$

Suppose $w'(t) = 0$ at some positive t. Denoting the first such time τ, we have $w'(t) > 0$ for $0 < t < \tau$ and $w'(\tau) = 0$, hence $\dot{w}'(\tau) \leq 0$. However, by (4.13), $\dot{w}'(\tau) = -k_2 y'(\tau) > 0$ (using (**4.7**)), a contradiction.

4b. *Monotonicity with respect to* η. Let

$$x' = \frac{\partial x}{\partial \eta}, \quad y' = \frac{\partial y}{\partial \eta}, \quad z' = \frac{\partial z}{\partial \eta}, \quad w' = \frac{\partial w}{\partial \eta}.$$

First, we show that

$$x' < 0,\ y' > 0,\ z' > 0,\ w' > 0 \quad \text{initially.} \tag{4.14}$$

This follows from

$$x'(0) = 0,\ \dot{x}'(0) = -k_1\xi,\ \ddot{x}'(0) = -k_1(k_{-1} + k_2)\zeta \quad \text{if } \xi = 0 \tag{4.15}$$

$$y'(0) = 1 \tag{4.16}$$

$$z'(0) = 0, \quad \dot{z}'(0) = k_1\xi, \quad \ddot{z}'(0) = k_1(k_{-1} + k_2)\zeta \quad \text{if } \xi = 0 \tag{4.17}$$

and
(4.18)
$w'(0) = 0,\ \dot{w}'(0) = 0,\ \ddot{w}'(0) = k_2 k_1 \xi,\ \dddot{w}'(0) = k_2 k_1 (k_{-1}+k_2)\zeta$ if $\xi = 0$.

Now, differentiating the xy-system (4.5) with respect to η results in

$$\begin{aligned} \dot{x}' &= -k_1(x'y + xy') - (k_{-1} + k_2)x' \\ \dot{y}' &= -k_1(x'y + xy') - k_{-1}x'. \end{aligned} \tag{4.19}$$

We show that

$$x' < 0 \quad \text{and} \quad y' > 0 \qquad \text{for} \quad t > 0. \tag{4.20}$$

Since these statements are true initially, if one of these statements fails, there must be a smallest positive time τ at which this occurs. There are then three possibilities: (1) $x'(\tau) = 0, y'(\tau) > 0$; (2) $x'(\tau) < 0, y'(\tau) = 0$; and (3) $x'(\tau) = y'(\tau) = 0$. Under case (1), $\dot{x}'(\tau) \geq 0$; but, by (4.19a), $\dot{x}'(\tau) = -k_1 x(\tau) y'(\tau) < 0$, a contradiction. Under case (2), $\dot{y}'(\tau) \leq 0$; but, by (4.19b), $\dot{y}'(\tau) = -k_1 x'(\tau) y(\tau) - k_{-1} x'(\tau) > 0$, a contradiction. Under case (3), by uniqueness of solutions to (4.19), $x' \equiv 0$ and $y' \equiv 0$, also a contradiction.

Next, we show

$$z' > 0 \quad \text{and} \quad w' > 0 \qquad \text{for} \quad t > 0. \tag{4.21}$$

By (2.1), $z' = -x'$, so that $z' > 0$. Integrating (1.1d), $w = \nu + k_2 \int_0^t z\, ds$, hence $w' = k_2 \int_0^t z'\, ds > 0$, for $t > 0$.

4c. *Monotonicity with respect to* ζ. Let a prime denote the partial derivative with respect to ζ. First, we show

$$x' > 0 \quad \text{and} \quad w' > 0 \qquad \text{initially.} \tag{4.22}$$

This follows from

$$x'(0) = 0, \quad \dot{x}'(0) = k_{-1} + k_2 \tag{4.23}$$

and

$$w'(0) = 0, \quad \dot{w}'(0) = k_2 \tag{4.24}$$

(using $z'(0) = 1$).

Next we show that

$$\textbf{(4.25)} \qquad x' \text{ and } y' \text{ cannot both be } \geq 1.$$

To prove this, we argue by contradiction. If, for some time, both x' and y' are ≥ 1, then, since $x'(0) = y'(0) = 0$, there is a smallest positive time τ in the set $\{t : x'(t) \geq 1, y'(t) \geq 1\}$. At $t = \tau$, $x'(\tau) \geq 1$ and $y'(\tau) \geq 1$. Now, differentiating the xy-system (4.5) with respect to ζ yields

$$\begin{aligned} \dot{x}' &= -k_1(x'y + xy') + (k_{-1} + k_2)(1 - x') \\ \dot{y}' &= -k_1(x'y + xy') + k_{-1}(1 - x'). \end{aligned} \tag{4.26}$$

From (4.26), $\dot{x}'(\tau) < 0$ and $\dot{y}'(\tau) < 0$, hence $x' > 1$ and $y' > 1$ in an interval $\sigma < t < \tau$, contradicting the definition of τ.

We can now establish

$$\textbf{(4.27)} \qquad w' > 0 \quad \text{for} \ \ t > 0.$$

By (1.1d) and (2.2),

$$\dot{w}' = k_2(1 - y' - w'). \tag{4.28}$$

Suppose $w'(t) = 0$ at some positive t. Denoting the smallest such time τ, then $\dot{w}'(\tau) \leq 0$. By (4.28), $\dot{w}'(\tau) = k_2(1 - y'(\tau))$, so that $y'(\tau) \geq 1$. Also, by (2.1) and (2.2),

$$x' = w' + y', \tag{4.29}$$

giving $x'(\tau) = y'(\tau) \geq 1$, which contradicts (**4.25**).

Next we show

$$\textbf{(4.30)} \qquad x' > 0 \quad \text{for} \ \ t > 0.$$

Suppose $x'(t) = 0$ at some positive time t. Denote the first such time τ; then $\dot{x}'(\tau) \leq 0$. By (4.26a) and (4.29),

$$\begin{aligned} \dot{x}'(\tau) &= -k_1 x(\tau) y'(\tau) + k_{-1} + k_2 \\ &= k_1 x(\tau) w'(\tau) + k_{-1} + k_2 > 0 \end{aligned}$$

(using (**4.27**)), a contradiction.

From (**4.25**), it also follows that

$$y' < 1 \quad \text{for} \ \ t \geq 0. \tag{4.31}$$

Noting that $y' = x' - w' < x'$ (by (4.29) and (**4.27**)), if $x' \leq 1$, then $y' < 1$, and if $x' > 1$, then $y' < 1$ by (**4.25**).

4d. *Monotonicity with respect to* ν. Let a prime denote the partial derivative with respect to ν. Since equations (1a,b,c) do not involve w it is clear that $x' = y' = z' = 0$. Integrating (1d), $w = \nu + k_2 \int_0^t z\, ds$. Hence, $w' = 1$. We have shown

$$x' \equiv 0, \qquad y' \equiv 0, \qquad z' \equiv 0, \qquad w' \equiv 1. \tag{4.32}$$

5. Final remarks. We have given a complete discussion of monotonicity and nonmonotonicity results for solutions to (1.1)–(1.3). These results are obtained for a system which does not generate a monotone flow with respect to an orthant. For other results of this sort, see [**6**].

In view of this work, there is some hope that a general theory providing partial monotonicity results can be developed.

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