ON WASHOUT IN NONLINEAR COMPARTMENTAL SYSTEMS

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Abstract. Let $x(t)$ be a solution of a compartmental system. If, for some compartment j , $x_j(t) \rightarrow 0$ as $t \rightarrow \infty$, then we say that compartment j washes out. We show that a compartment washes out if it always reaches (along a fixed path) either the environment or another compartment for which there is no return path. Additional criteria, particularly regarding exponential convergence, are also presented. Examples are drawn from tracer kinetics, enzyme reactions, and epidemic models.

1. Introduction. We consider the class of systems of the form,

$$\dot{x}_i = \sum_{\substack{j=1 \\ j \neq i}}^n f_{ij} x_j - \sum_{\substack{k=0 \\ k \neq i}}^n f_{ki} x_i, \quad t \geq 0, \quad x_i(0) = m_i, \quad 1 \leq i \leq n. \quad (1.1)$$

Here $x_i(t) \geq 0$ represents the "mass" in compartment i at time t , $f_{ij}(x_1, x_2, \dots, x_n) \geq 0$ is the (fractional) transfer function from compartment j to compartment $i \neq j$, $f_{0i}(x_1, x_2, \dots, x_n) \geq 0$ is the transfer function from compartment i to the environment, and $m_i \geq 0$ is the initial mass in compartment i .

In the time-invariant linear case, i.e., the case where the f_{ij} are constants, the following result is well known [1-5].

Theorem 1.1. Suppose f_{ij} is constant, $0 \leq i \leq n$, $1 \leq j \leq n$. Then the system washes out, i.e., $x_i(t) \rightarrow 0$ as $t \rightarrow \infty$, $1 \leq i \leq n$, if every compartment reaches the environment, i.e., for each j there is a path from j to 0, $\pi: j = k_0 \rightarrow k_1 \rightarrow \dots \rightarrow k_q = 0$, such that for each transfer along the path, $f_{k_{v+1}k_v} > 0$, $0 \leq v \leq q-1$.

This result was extended to time-dependent linear systems, i.e., systems where the f_{ij} are functions of t alone, by Aronsson and Kellogg [4] and to nonlinear systems by Maeda et al [5]. However, these results impose additional restrictions on the system. For instance, they require in [5] that the transfer function from j to i have the special form $a_{ij}g_j(x_j)$ where a_{ij} is a constant and $g_j(x_j)$ is a function only of the mass x_j in the donor compartment. Moreover, Theorem 1.1 and its extensions [4-5] deal with washout of the entire system and not with the washout of individual compartments.

The purpose of this paper is to show that Theorem 1.1 extends to systems of the form (1.1), without imposing additional conditions. Moreover, we point out that the result can be stated in such a manner that it applies to individual compartments and it can also be stated in the framework of closed as well as open systems. We also develop criteria for exponential washout (Section 4). The results are illustrated in the context of examples drawn from tracer kinetics, enzyme reactions, and epidemic models (Section 5).

2. Preliminaries. It is convenient to set

$$f_{jj} = -\sum_{i=1}^n f_{ij} - f_{0j}, \quad 1 \leq j \leq n. \quad (2.1)$$

Then, $f_{jj} \leq 0$ represents the total outflow from compartment j and the system (1.1) can be expressed in vector form,

$$\dot{x} = F(x)x, \quad f \geq 0, \quad x(0) = m, \quad (2.2)$$

where $x(t), m \in \mathbb{R}^n$ and $F(x)$ is the $n \times n$ matrix of $f_{ij}(x)$, $1 \leq i, j \leq n$.
If

$$f_{0j} = 0, \quad 1 \leq j \leq n,$$

then the system is said to be closed. In this case, the matrix $F(x)$ has the following properties:

- (i) The off-diagonal elements are non-negative.
- (ii) The diagonal elements are non-positive
- (iii) The column sums are zero.

Definition. A matrix having properties (i)-(iii), above, is said to be a

CCM (closed compartmental matrix).

Bellman [6] obtained the following result.

Theorem 2.1 (closed systems). Let $m \geq 0$ (i.e., $m_i \geq 0, 1 \leq i \leq n$) and let

$$\Omega = \{x | x \geq 0, \sum_{i=1}^n x_i = \sum_{i=1}^n m_i\}.$$

Suppose $F(x)$ is a CCM for each x in Ω and suppose that its elements $f_{ij}(x)$ are Lipschitz continuous in Ω . Then the system (2.2) has a unique solution $x(t)$ and, moreover, $x(t)$ lies in Ω for $t \geq 0$.

A compartmental system which is not closed is said to be open. In all systems (both closed and open) the matrix $F(x)$ has the following properties:

- (i) The off-diagonal elements are nonnegative.
- (ii) The diagonal elements are non-positive.
- (iii) The column sums are non-positive.

Definition. A matrix having properties (i)-(iii), above, is said to be CM(compartmental matrix).

Notice that an open system can be closed by regarding the environment as a additional compartment, i.e., every open system is a subsystem of a closed system. When we apply Theorem 2.1 to the closed system, we immediately obtain the following result.

Theorem 2.2 (open systems). Let $m \geq 0$ and let

$$\Omega_0 = \{x | x \geq 0, \sum_{i=1}^n x_i \leq \sum_{i=1}^n m_i\}.$$

Suppose $F(x)$ is a CM for each x in Ω_0 and suppose its elements $f_{ij}(x)$ are Lipschitz continuous in Ω_0 . Then the system (2.2) has a unique solution $x(t)$ and, moreover, $x(t)$ lies in Ω_0 for $t \geq 0$.

We assume throughout that the function f_{ij} are Lipschitz continuous in the appropriate domain, Ω for closed systems and Ω_0 for open systems.

3. Washout criteria. We begin with open systems.

Theorem 3.1 (open systems). Let $x(t)$ be a solution of the compartmental system (2.2) with $m \geq 0$. Suppose compartment j reaches the environment along a path π for all x in Ω_0 , i.e., there is a path from j to 0:

$$\pi: j = k_0 \rightarrow k_1 \rightarrow \dots \rightarrow k_r = 0,$$

such that for each transfer along the path,

$$f_{k_{v+1}k_v}(x) > 0, \quad x \in \Omega_0. \quad (3.1)$$

Then

$$(i) \quad x_j(t) \rightarrow 0 \quad \text{as } t \rightarrow \infty.$$

$$(ii) \quad \int_0^\infty x_j(t) dt < \infty.$$

Proof. We observe first that statement (ii) implies statement (i). To see this, we first note that since the f_{ij} are continuous functions of x , and since $x(t)$ is restricted to the compact domain Ω_0 , it follows that the $f_{ij}(x(t))$ are bounded functions of t . Consequently,

$$\dot{x}_j(t) = \sum_{k=1}^n f_{jk}(x(t))x_k(t)$$

is also bounded. From this fact, and with the aid of Barbalat's lemma [7], we conclude that (ii) implies (i). Thus, it suffices to prove (ii).

To prove (ii) we argue by induction on the length, q , of the path. For the case $q = 1$, we have $f_{0j}(x) > 0$. Since f_{0j} is continuous on the compact domain Ω_0 , $f_{0j}(x)$ achieves its minimum value, say a , i.e.,

$$f_{0j}(x) \geq a > 0, x \in \Omega_0.$$

Next, we set

$$\sigma(t) = \sum_{i=1}^n x_i(t).$$

$$\text{Then } \dot{\sigma}(t) = \sum_{i=1}^n \dot{x}_i(t) = \sum_{i=1}^n \sum_{k=1}^n f_{ij}(x(t)) x_k(t)$$

$$= \sum_{k=1}^n x_k(t) \sum_{i=1}^n f_{ik}(x(t)) = - \sum_{k=1}^n f_{0k}(x(t)) x_k(t).$$

(We used (2.1) for the last equality.) Thus, $\dot{\sigma}(t) \leq 0$ and

$$-\dot{\sigma}(t) \geq f_{0j}(x(t)) x_j(t) \geq a x_j(t).$$

Integrating from 0 to s , we obtain

$$\int_0^s x_j(t) dt \leq \sigma(0)/a, s > 0.$$

$$\text{Clearly, } \int_0^\infty x_j(t) dt \leq \sigma(0)/a < \infty.$$

We now assume that statement (ii) holds for paths of length $\leq q$ and we consider a path of length $q + 1$. Let i be the precursor of j along the path. Then by the induction hypothesis,

$$J = \int_0^\infty x_i(t) dt < \infty.$$

Moreover, we have the condition

$$f_{ij}(x) \geq c > 0, \quad x \in \Omega_0,$$

where c is the minimum of f_{ij} on Ω_0 . From the equation

$$\dot{x}_i = \sum_{k=1}^n f_{ik} x_k,$$

we obtain

$$\dot{x}_i - f_{ii} x_i = \sum_{k \neq i} f_{ik} x_k \geq f_{ij} x_j \geq c x_j.$$

Let d be the maximum of $-f_{ii}$ on Ω_0 , then

$$x_j(t) \leq [\dot{x}_i(t) + d x_i(t)]/c.$$

Integrating from 0 to s yields:

$$\int_0^s x_j(t) dt \leq [x_i(s) - x_i(0) + d \int_0^s x_i(t) dt]/c.$$

Since $|x_i(s) - x_i(0)| \leq \sigma(0)$ and $\int_0^s x_i(t) dt \leq J$, it follows that

$$\int_0^\infty x_j(t) dt \leq [\sigma(0) + dJ]/c < \infty.$$

This concludes the induction argument and the proof is complete.

Remark 3.1. Intuitively speaking, the functions $f_{k_{v+1}k_v}$ represent exits along the "escape route" π . Thus, condition (3.1) requires that the exits always be open. In their discussion of time-dependent linear systems, where the exits depend on t and not on x , Aronsson and Kellogg [4] required only that the exits be open "sufficiently wide" for "sufficiently many t "; they could be closed for some t . However, in the nonlinear case, even if the condition fails only on a set of measure zero in Ω_0 then Theorem 3.1 is no longer true (see Ex. 4.3 below).

Remark 3.2. Regarding condition (ii) in Theorem 3.1, if $x_j(t)$ is regarded as the probability that a particle is in compartment j at time t , then $\int_0^\infty x_j(t)dt$ is the mean residence time in compartment j (see [3]). Thus, condition (ii) is another characterization of the washout property.

Remark 3.3. The statement of Theorem 3.1 does not apply to closed systems or even to open systems if compartment j does not reach the environment. However, how we define the environment is a matter of convenience in order to facilitate intuition. If i and j are two compartments and j does not reach i for any x then there is a subsystem containing j which does not contain i , i.e., i is in the environment of the subsystem. In view of this observation, we can restate Theorem 3.1 in a sharper form, which applies to closed as well as open systems, and which does not require compartment j to have a path to the environment. This restatement is Corollary 3.1.

Corollary 3.1. Let $x(t)$ be a solution of the compartmental system (2.1) with $m \geq 0$. Let $\emptyset = \Omega_0$ if the system is open and $\emptyset = \Omega$ if the system is closed.

Suppose i and j are two compartments and compartment j reaches i , another compartment, or the environment, along a path π for all x in $\emptyset$, i.e., there is a sequence from j to i :

$$\pi: j = k_0 \rightarrow k_1 \rightarrow \dots \rightarrow k_q = i,$$

such that for each transfer along the path,

$$f_{k_{v+1}k_v}(x) > 0, x \in \emptyset. \quad (3.2)$$

Suppose further that compartment i does not reach compartment j along a path for any x in $\emptyset$. Then conditions (i) and (ii) of Theorem 3.1 are satisfied for $x_j(t)$.

Returning to open systems, it is clear from Theorem 3.1 that the system washes out, i.e., $x_i(t) \rightarrow 0$ as $t \rightarrow \infty$, $1 \leq i \leq n$, if each compartment has a path to the environment for all x in Ω_0 . Let us consider the special form

$$f_{ij}(x) = a_{ij} f_j(x), \quad 0 \leq i \leq n, \quad 1 \leq j \leq n \quad (3.3)$$

where $f_j(x) \geq 0$ and $A = \{a_{ij}\}$ is a constant CM. This form arises in Ex.'s 4.2 and 4.3 below. In the case of (3.3), the condition for the washout of the system reduces to:

$$(a) \quad f_1(x)f_2(x)\dots f_n(x) > 0 \quad \text{for } x \in \Omega_0.$$

$$(b) \quad \text{For each compartment } j, \text{ there is a sequence } j = k_0 \rightarrow k_1 \rightarrow \dots \rightarrow k_q = 0$$

such that $a_{k_{v+1}k_v} > 0$, i.e., each j reaches the environment in the digraph representation of A .

It is well known ([1]-[3], [5]) that the second condition is equivalent to

$$(b') \quad \det A \neq 0.$$

Therefore, the following result is true.

Theorem 3.2 (open systems). Suppose $\dot{x} = F(x)x$ is a compartmental system such that the fractional transfer functions have the form (3.3). The system washes out if conditions (a) and (b'), above, are satisfied.

Theorem 3.2 does not require that f_j be a function of x_j only ($1 \leq j \leq n$); in this regard, it is an extension of Theorem 2 in [5].

4. Exponential washout. A system is said to washout exponentially if there are positive constants α and λ such that

$$|x_i(t)| \leq \alpha e^{-\lambda t}, \quad 1 \leq i \leq n.$$

Results dealing with exponential washout typically involve the diagonal dominance property for matrices. A matrix A is said to be column diagonally dominant if

$$|a_{jj}| > \sum_{\substack{i=1 \\ i \neq j}}^n |a_{ij}|, \quad 1 \leq j \leq n,$$

and A is row diagonally dominant if

$$|a_{ii}| > \sum_{\substack{j=1 \\ j \neq i}}^n |a_{ij}|, \quad 1 \leq i \leq n.$$

Ladde [8,9] showed that a compartmental system washes out exponentially if it is (or it can be transformed into) a system for which the transfer matrix is diagonally dominant with respect to either columns or rows Sanberg [10] considered more general compartmental systems (than (2.2)). He showed that exponential washout occurs if the Jacobian matrix G is column diagonally dominant and compartmental (i.e., $g_{ij} \geq 0$, $i \neq j$, $\sum_{i=1}^n g_{ij} < 0$, $1 \leq j \leq n$). The following is a generalization of Sandberg's result which does not require

the nonnegativity of the off-diagonal elements.

Theorem 4.1. Suppose that γ is a compact, convex, invariant set in $\mathbb{R}^n$ for an autonomous system, $\dot{x}(t) = f(x(t))$. Suppose further that the elements of the Jacobian matrix, $G = \partial f / \partial x$, are continuous in γ and that G has the following properties:

- (i) The off-diagonal elements of G are negative.
- (ii) G is column diagonally dominant.

Then there exists one and only one equilibrium point b in γ and moreover, every solution $x(t)$ in γ satisfies

$$\|x(t) - b\|_1 \leq \|x(0) - b\|_1 e^{-\lambda t}, \quad t \geq 0,$$

where $\|\cdot\|_1$ denotes the ℓ_1 norm, i.e., $\|x\|_1 = \sum_{j=1}^n |x_j|$, and λ is a positive constant. In particular, if $0 \in \gamma$, $f(0) = 0$, then $b = 0$ and the system washes out exponentially.

Proof. Let $x(t)$ and $y(t)$ be any two solutions in γ and let

$$w(t) = x(t) - y(t).$$

Then

$$\dot{w}(t) = A(t)w(t),$$

where

$$A(t) = \int_0^1 G(sy(t) + (1-s)x(t)) ds.$$

Now, conditions (i) and (ii) may be expressed as

$$g_{0j}(x) = -g_{jj}(x) - \sum_{i \neq j} |g_{ij}(x)| > 0, \quad x \in \gamma, \quad 1 \leq j \leq n.$$

Since these functions are continuous in γ and γ is compact,

$$g_{0j}(x) \geq \lambda > 0, \quad x \in \gamma, \quad 1 \leq j \leq n,$$

where λ is a positive constant. Now $A(t)$ inherits this property from $G(x)$. More precisely, let

$$a_{0j}(t) = -a_{jj}(t) - \sum_{i \neq j} |a_{ij}(t)|.$$

Clearly,

$$a_{0j}(t) \geq \int_0^1 g_{0j}(sy(t) + (1-s)x(t))ds \geq \int_0^1 \lambda ds = \lambda.$$

Next, we compute the Dini derivative,

$$\begin{aligned} D^+ \|w(t)\|_1 &= \lim_{h \rightarrow 0^+} \sup [\|w(t+h)\|_1 - \|w(t)\|_1] / h \\ &= \lim_{h \rightarrow 0^+} \sup [\|w(t) + hA(t)w(t)\|_1 - \|w(t)\|_1] / h. \end{aligned}$$

For fixed $h > 0$ and h sufficiently small,

$$\begin{aligned} \|w(t) + hA(t)w(t)\|_1 &= \sum_{i=1}^n [|w_i(t) + ha_{ii}(t)w_i(t) + h \sum_{j=1}^n a_{ij}(t)w_j(t)|] \\ &\leq \sum_{i=1}^n [(1+ha_{ii}(t))|w_i(t)| + h \sum_{j \neq i} |a_{ij}(t)||w_j(t)|] \\ &= \|w(t)\|_1 + h \sum_{i=1}^n \sum_{j=1}^n d_{ij}(t)|w_j(t)|, \end{aligned}$$

where $d_{ij}(t) = |a_{ij}(t)|$ for $j \neq i$ and $d_{ii}(t) = a_{ii}(t)$.

Interchanging orders of summation,

$$\begin{aligned} \|w(t) + hA(t)w(t)\|_1 - \|w(t)\|_1 &\leq h \sum_{j=1}^n |w_j(t)| \sum_{i=1}^n d_{ij}(t) \\ &\leq -h\lambda \|w(t)\|_1, \quad \text{since } -\sum_{i=1}^n d_{ij}(t) = a_{0j}(t) \geq \lambda. \end{aligned}$$

Consequently, $D^+ \|w(t)\|_1 \leq -\lambda \|w(t)\|_1$ and it follows [11](p.15) that $\|w(t)\|_1 \leq \|w(0)\|_1 e^{-\lambda t}$ or

$$\|x(t) - y(t)\|_1 \leq \|x(0) - y(0)\|_1 e^{-\lambda t}$$

for any pair of solutions, $x(t)$ and $y(t)$.

Finally, we recall [12] (p.49) that a compact, convex, invariant set in R^n must contain at least one equilibrium point b , which, by virtue of the above inequality, must be unique. Setting $y = b$ yields the desired result.

In a similar manner, we obtain the following companion result.

Theorem 4.2. Suppose that γ is a compact, convex, invariant set in R^n for an autonomous system, $\dot{x}(t) = f(x(t))$. Suppose further that the elements of the Jacobian matrix, $G = \partial f / \partial x$, are continuous in γ and G has the following properties:

- (i) The off-diagonal elements of G are negative.
- (ii) G is row diagonally dominant.

Then there exists one and only one equilibrium point b in γ and, moreover, every solution $x(t)$ in γ satisfies

$$\|x(t) - b\|_\infty \leq \|x(0) - b\|_\infty e^{-\lambda t}, \quad t \geq 0,$$

where $\|\cdot\|_\infty$ denotes the ℓ_∞ norm, i.e.,

$$\|x\|_\infty = \max\{|x_i|, 1 \leq i \leq n\},$$

and λ is a positive constant. In particular, if $0 \in \gamma$, $f(0) = 0$, then $b = 0$ and the system washes out exponentially.

The above results can apply to open compartmental systems of the form

(2.2). In this case $\gamma = \Omega_0$ is a convex, compact, invariant set, $0 \in \gamma$, and $f_i(x) = \sum_{j=1}^n f_{ij}(x)x_j$ has the property that $f_i(0) = 0$, $1 \leq i \leq n$.

However, the diagonally dominant conditions on the Jacobian matrix are not typically satisfied in practice.

An alternate approach to establishing exponential washout, which applies to practical problems of interest (see, e.g., Ex. 5.2) can be utilized in cases when the nonlinear terms in $F(x)x$ are quadratic or of higher order. More specifically, suppose

$$\dot{x} = Ax + \phi(x), \quad (4.1)$$

where

$$\|\phi(x)\|/\|x\| \rightarrow 0 \text{ as } x \rightarrow 0 \text{ } (x \in \Omega_0), \quad (4.2)$$

where $\|\cdot\|$ is a norm on $\mathbb{R}^n$ and A is a constant compartmental matrix with $\det A \neq 0$ (equivalently, every compartment has a path in A to the environment). The idea is as follows. Suppose it can be shown (say by Theorem 3.1) that the system washes out. Then for t large, the equations approximate the linear system $\dot{x} = Ax$. It is well known that such linear systems wash out exponentially. The formal argument is given below.

Theorem 4.3 (open systems). Suppose that the compartmental system has the form (4.1)-(4.2) where $\det A \neq 0$ and suppose that the system washes out. Then the system washes out exponentially.

Proof. It is well known [13] that a nonsingular compartmental matrix A is stable, i.e., all of its eigenvalues have negative real parts. Moreover,

there is a unique negative eigenvalue, called the leading eigenvalue, $-\lambda$, such that every other eigenvalue has real part less than $-\lambda$. It follows that

$$\|e^{tA}\| \leq c e^{-\lambda t}, \quad t \geq 0,$$

where c is a positive constant. Let ϵ be any quantity such that

$$0 < \epsilon < \lambda$$

In view of (4.2), and since $x(t) \rightarrow 0$ as $t \rightarrow \infty$, there is a t_0 sufficiently large so that

$$\|x(t)\| \leq \epsilon/c, \quad \|\phi(x(t))\| \leq \epsilon\|x(t)\|, \quad t \geq t_0.$$

Now for $t \geq t_0$, (4.1) can be written in the form,

$$x(t) = e^{(t-t_0)A} x(t_0) + \int_{t_0}^t e^{(t-s)A} \phi(x(s)) ds.$$

$$\text{Thus, } \|x(t)\| \leq c e^{-\lambda(t-t_0)} \|x(t_0)\| + \int_{t_0}^t e^{-\lambda(t-s)} \|\phi(x(s))\| ds$$

$$\leq \epsilon e^{-\lambda(t-t_0)} + \epsilon \int_{t_0}^t e^{-\lambda(t-s)} \|x(s)\| ds.$$

Multiplying by $e^{\lambda(t-t_0)}$, and setting

$$m(t) = \|x(t)\| e^{\lambda(t-t_0)}, \quad \text{we obtain}$$

$$m(t) \leq \epsilon + \epsilon \int_{t_0}^t m(s) ds$$

It follows from Gronwall's inequality (e.g., see [11], p. 37) that

$$m(t) \leq \epsilon e^{\epsilon(t-t_0)}, \quad t \geq t_0.$$

Thus, $\|x(t)\| \leq \varepsilon e^{-v(t-t_0)}$, $t \geq t_0$, where $v = \lambda - \varepsilon > 0$, and the proof is complete.

5. Examples. We begin with an example from tracer kinetics.

Example 5.1 (tracer kinetics). Tracer studies are performed as a diagnostic procedure to identify various types of liver diseases (see [14], [3] and references therein). A radioactive tracer (e.g., rose bengal transport) is injected into the blood and it circulates through the hepatic system. The tracer may be sampled from the blood, urine and feces compartments. A four compartmental system consisting of blood (1), liver (2), urine (3) and feces (4) is described by the following digraph.

Let $x_i(t)$ be the proportion of tracer in compartment i at time t , then the rate equations for the closed system are:

$$\dot{x}_1 = -(f_{21} + f_{31})x_1 + f_{12}x_2.$$

$$\dot{x}_2 = f_{21}x_1 - (f_{12} + f_{42})x_2.$$

$$\dot{x}_3 = f_{31}x_1.$$

$$\dot{x}_4 = f_{42}x_2.$$

From the physiology we expect compartments 1 and 2 to washout so that the tracer is ultimately excreted into the urine and feces compartments. The condition which is provided by Corollary 3.1 to give this result is: either $f_{31}(x)f_{42}(x) > 0$ or $f_{31}(x)f_{12}(x) > 0$ or $f_{42}(x)f_{21}(x) > 0$ for all $x \geq 0$ such that $x_1 + x_2 + x_3 + x_4 = 1$. Similarly, $x_1(t) \rightarrow 0$ as $t \rightarrow \infty$

if either $f_{31}(x) > 0$ or if $f_{42}(x)f_{21}(x) > 0$ and $x_2(t) \rightarrow 0$ as $t \rightarrow \infty$
 if either $f_{42}(x) > 0$ or if $f_{31}(x)f_{12}(x) > 0$.

In regards to Remark 3.3, we notice that compartments 1 and 2 form a subsystem in which 3 and 4 play the role of the environment.

Example 5.2 (enzyme kinetics). We consider the process by which a substrate reacts reversibly with an enzyme to form a complex that subsequently breaks down to form free enzyme plus one or more products. The reactions are represented schematically by

where E , S , C , and P denote enzyme, substrate, complex, and product respectively and the arrows indicate the possible directions of the reactions.

In accordance with the law of mass action, the rate equations are assumed to be the following [15]:

$$\begin{aligned}\dot{s} &= -k_{+1}es + k_{-1}c, \\ \dot{e} &= -k_{+1}es + (k_{-1} + k_{-2})c, \\ \dot{c} &= k_{+1}es - (k_{-1} + k_{+2})c, \\ \dot{p} &= k_{+2}c,\end{aligned}$$

where the lower case letters denote the concentrations of the reactants. The rate constants $k_{\pm 1}$ are positive constants representing association (+) and dissociation (-). Initially, it is assumed that we start with enzyme and substrate only, i.e.,

$$(s, e, c, p) = (s_0, e_0, 0, 0) \text{ at } t = 0.$$

We wish to show that the following statements are true:

- (i) The substrate decreases (monotonically) to zero.
- (ii) The enzyme decreases at first, reaches a minimum value, and then it increases to its initial value, e_0 .
- (iii) The complex increases at first, reaches a maximum value, and then it decreases to zero.
- (iv) The product increases to s_0 .

To verify these statements let us reduce the system to compartmental form. We observe first that the total enzyme is always conserved, existing either as free enzyme or as part of the complex. Mathematically, we observe, by adding the second and the third equations we obtain $d/dt(e+s) = 0$, and therefore,

$$e + c = e_0.$$

We use this relation to eliminate e from the rate equations and obtain the closed compartmental system:

$$\begin{aligned}\dot{s} &= -k_{+1}e_0s + (k_{+1}s + k_{-1})c, \\ \dot{c} &= k_{+1}e_0s - (k_{+1}s + k_{-1} + k_{+2})c, \\ \dot{p} &= k_{+2}c.\end{aligned}$$

Since compartments S and C both reach P , which is an absorbing compartment, it follows from Corollary 3.1 that

$$s \rightarrow 0, c \rightarrow 0 \text{ as } t \rightarrow \infty.$$

Moreover, because the system is closed, we have the conservation law,

$$s + c + p = s_0.$$

which expresses the fact that the total substrate can exist either as free substrate, as part of the complex, or as part of the product. In view of this relation,

$$p \rightarrow s_0 \text{ as } t \rightarrow \infty$$

and, because the product is an absorbing compartment, the convergence is (monotonically) increasing.

To show that s is decreasing, we first reduce the system further by eliminating c through the conservation law. We obtain

$$\dot{s} = f_1(s, p), \quad \dot{p} = f_2(s, p),$$

where

$$f_1 = -k_{+1}e_0s + (k_{+1}s + k_{-1})(s_0 - s - p),$$

$$f_2 = k_{+2}(s_0 - s - p).$$

Next, we set

$$u_1 = -\dot{s}, \quad u_2 = \dot{p}.$$

Then $\dot{u}_1 = -\ddot{s} = -(\partial f_1 / \partial s)\dot{s} - (\partial f_1 / \partial p)\dot{p} = (\partial f_1 / \partial s)u_1 - (\partial f_1 / \partial p)u_2 = -[k_{+1}(2s + e_0) + k_{-1}]u_1 + [k_{+1}s + k_{-1}]u_2$. Similarly, we obtain $\dot{u}_2$ and the pair of equations can be written in the vector form

$$\dot{u} = Gu,$$

where

$$G = \begin{bmatrix} -[k_{+1}(2s + e_0) + k_{-1}] & [k_{+1}s + k_{-1}] \\ k_{+2} & -k_{+2} \end{bmatrix}.$$

We can regard this equation as a linear, time-dependent system for u , and because the off-diagonal elements of G are nonnegative, it follows from the quasimonotonicity theory [16] that u is always nonnegative if it is so initially. Now, at $t = 0$, $u_1 = -\dot{s} = k_{+1}e_0s_0 > 0$ and $u_2 = \dot{p} = 0$. Thus, $(-\dot{s}, \dot{p})$ is nonnegative and consequently s is decreasing. There remains to verify statements (ii) and (iii) which, in view of the relation $e + c = e_0$, are equivalent. To verify (iii) we need to show that once c reaches a relative maximum it must decrease after that point. We again employ the quasimonotonicity theory. This time we set

$$v_1 = -\dot{s}, \quad v_2 = -\dot{c},$$

and we obtain

$$\dot{v} = \begin{bmatrix} -k_{+1}(e_0 - c) & k_{+1}s + k_{-1} \\ k_{+1}(e_0 - c) & -(k_{+1}s + k_{-1} + k_{+2}) \end{bmatrix} v.$$

Since the off-diagonal elements of the matrix are nonnegative, we know that once v becomes nonnegative it must remain nonnegative for all later times. Let t_0 be the first instant at which $\dot{c} = 0$. We have already shown that s is decreasing and hence $\dot{s} \leq 0$ at t_0 . Consequently, $\dot{c} \leq 0$ for $t \geq t_0$ and statement (iii) follows.

In cases where the initial substrate is much larger than the initial enzyme ($e_0/s_0 \sim 10^{-3}$ is not uncommon) then the maximum of c , which is called the quasi-steady-state value, is approximated by the Michaelis-Menten theory [15]

$$c_{\max} \sim k_{+1}e_0s_0/[k_{+1}s_0 + k_{-1} + k_{+2}]$$

and during the initial phase of the reaction,

$$c \sim c_{\max} [1 - e^{-t/\tau}],$$

where $\tau = (k_{+1}s_0 + k_{-1} + k_{+2})^{-1}$ is the approximate mean time to reach quasi-steady state.

In spite of the fact that a quasi-steady state value is reached in the initial phase, the substrate and complex compartments wash out exponentially. This can be seen by expressing the first two equations in the form

$$\begin{bmatrix} \dot{s} \\ \dot{c} \end{bmatrix} = \begin{bmatrix} -k_{+1}e_0 & k_{-1} \\ k_{+1}e_0 & -(k_{-1}+k_{+2}) \end{bmatrix} \begin{bmatrix} s \\ c \end{bmatrix} + \begin{bmatrix} k_{+1}s_0 \\ -k_{+1}s_0 \end{bmatrix}$$

and applying Theorem 4.3.

By neglecting the quadratic terms we can estimate the mean washout time, ω , i.e., the mean time required for substrate to be converted into product. From [3], $\omega = t_{11} + t_{21}$, where $-T$ is the inverse of the matrix comprising the linear part, i.e.,

$$\omega = (k_{+1}e_0 + k_{-1} + k_{+2}) / (k_{+1}k_{+2}e_0).$$

The fraction of the washout time required to reach quasi-steady state is approximately

$$\tau/\omega = k_{+1}k_{+2}e_0 / \{[k_{+1}e_0 + k_{-1} + k_{+2}][k_{+1}s_0 + k_{-1} + k_{+2}]\}.$$

Example 5.3 (epidemic kinetics). We consider the following classical model for the spread of a disease. Suppose x_1, x_2 and x_3 denote the number of susceptibles, infectives and removed individuals, respectively, in an epidemic. Then Kermack-McKendric equations are [17], [18]:

$$\dot{x}_1 = -\alpha x_1 x_2.$$

$$\dot{x}_2 = \alpha x_1 x_2 - \gamma x_2.$$

$$\dot{x}_3 = \gamma x_2.$$

Here α and γ are positive rate constants. It is well known (see [17] or [18]) that $x_2(t) \rightarrow 0$ as $t \rightarrow \infty$ and $x_2(t)$ goes monotonically to a limit which is not zero unless $x_1(0) = 0$.

The equations may be expressed in closed compartmental form, $\dot{x} = F(x)x$, where

$$F = \begin{bmatrix} -\alpha x_2 & 0 & 0 \\ \alpha x_2 & -\gamma & 0 \\ 0 & \gamma & 0 \end{bmatrix}.$$

Note that: compartment 3 does not reach compartments 1 or 2 for any $x \geq 0$, compartment 2 reaches compartment 3 for all $x \geq 0$, and compartment 1 reaches compartment 3 for all $x \geq 0$ except when $x_2 = 0$. Corollary 3.1 can be applied to show $x_2(t) \rightarrow 0$ as $t \rightarrow \infty$ but it does not apply to compartment 1, and in fact, compartment 1 does not washout when $x_1(0) > 0$. The example is interesting in regard to Remark 3.1.

Let us recall that a time-invariant system, $\dot{x} = Ax$, washes out if $\det A \neq 0$. It is interesting to note that in this example, compartments 1 and 2 form a (nonlinear) open system, $\dot{x} = A(x)x$, with compartment 3 as the environment, and $\det A(x(t)) \neq 0$, $t \geq 0$, when $x_2(0) > 0$, but the system does not wash out when $x_1(0) > 0$.

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