ON APPROACH TO EQUILIBRIUM IN NONLINEAR
COMPARTMENTAL SYSTEMS

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1. INTRODUCTION

A closed compartmental system is a set of nonnegative inter-dependent functions,

$$x_1(t), x_2(t), \dots, x_n(t), t \geq 0,$$

such that their sum is constant. The functions can represent populations, masses or concentrations, depending on the particular application. It is convenient to normalize so that

$$x_1(t) + x_2(t) + \dots + x_n(t) = 1,$$

in which case the functions are proportions. It is assumed that the (nonnegative) flow rate from j to i has the form $f_{ij}x_j$. Thus, the rate of change,

$$\dot{x}_i = \sum_{\substack{j=1 \\ j \neq i}}^n f_{ij}x_j - \sum_{\substack{k=1 \\ k \neq i}}^n f_{ki}x_i, \quad 1 \leq i \leq n.$$

The first term is the inflow to i from the other "compartments" and the second term is the outflow from i to the other compartments.

Setting

$$r_{ii} = - \sum_{\substack{k=1 \\ k \neq i}}^n f_{ki}, \quad 1 \leq i \leq n,$$

we obtain the system in vector form,

$$\dot{x} = Fx.$$

In classical compartmental analysis [1]-[4], which deals mainly with tracer and drug studies, each x_i represents the amount of tracer or drug in an organ or a compartment of the human body, hence the term "compartment". Moreover, in classical work, the f_{ij} are treated as constants, however, in more recent work [5]-[12], they are functions,

$$f_{ij}(x), x \in \Omega_n = \{x | x_i \geq 0, 1 \leq i \leq n, \sum_{i=1}^n x_i = 1\}.$$

Let us consider a classical tracer study.

Example 1.1 (liver model). Tracer studies are performed as a diagnostic procedure to identify the particular liver disease that a patient may be suffering from (see [13] and references therein). A radioactive tracer is injected into the patient's blood stream and it circulates through the hepatic system. Since the tracer may be sampled in the blood, urine and feces compartments, a lumped four compartmental model presents itself. It consists of blood (1), liver (2), urine (3) and feces (4) and the paths of flow between compartments are described in the following digraph representation.

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

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

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

$$\dot{x}_3 = f_{31}x_1, \quad \dot{x}_4 = f_{42}x_2.$$

Remark 1.1. In the literature of compartmental analysis, we find open systems as well as closed systems. An open system is a subsystem of a closed system in which one or more absorbing compartments is removed. For instance, in the above example, $\{1,2\}$, $\{1,2,3\}$ and $\{1,2,4\}$ form open subsystems. The removed compartments constitute the environment of the open subsystem.

Let us note that a closed compartmental system may be described formally as a system of differential equations

$$\dot{x}(t) = F(x)x, \quad x(0) = m,$$

where $m \in \Omega_n$ and $F(x)$, $x \in \Omega_n$, has the following properties:

- (i) The off-diagonal elements are nonnegative.
- (ii) The diagonal elements are nonpositive.
- (iii) The column sums are zero.

A matrix having properties (i)-(iii) is said to be closed-compartmental.

Bellman [5] obtained the following result.

Theorem 1.1 (Bellman). Suppose that the fractional transfer functions f_{ij} , are Lipschitz continuous in Ω_n , then the closed compartmental system has a unique global solution $x(t)$, $0 \leq t < \infty$, which lies in Ω_n .

In view of Bellman's Theorem we assume, henceforth, that the fractional transfer functions are Lipschitz continuous in Ω_n .

In this paper, we are concerned with the important question of whether or not

$$x(t) \rightarrow b, \quad t \rightarrow \infty,$$

where b is a constant vector, which, of course, must be an equilibrium point in Ω_n . The question was first raised by Bellman [5] and it has been referred to as Bellman's conjecture [11]. Bellman seemed to have believed that the conjecture is true. As evidence, he pointed out that the conjecture is true for linear systems, in which the fractional transfer coefficients are constants, and it is true for chemical systems of the type which Bellman was attempting to model. Several years later, it was established [1] that the conjecture holds for donor controlled systems, i.e., systems for which $f_{ij}(x) = a_{ij}g_j(x_j)$, and for which $x_j g_j(x_j)$ is increasing. We show here that the conjecture is false in general using relatively simple counter examples. The examples show that compartmental systems allow periodic solutions as well as periodic behavior which does not converge to an equilibrium point.

We will also discuss sufficient conditions under which convergence to an equilibrium is assured. In particular, we shall consider the question of when a particular compartment $x_i(t) \rightarrow 0$. In this case, we say that the compartment washes out. Illustrative examples will be drawn from tracer dynamics, chemical systems and from epidemic models.

2. EXAMPLES OF SYSTEMS WHICH DO NOT APPROACH EQUILIBRIUM

Example 2.1 (periodic behavior). We consider the system $\dot{x} = F(x)x$ where

$$F = \begin{bmatrix} -x_2 & 0 & x_1 \\ x_2 & -x_3 & 0 \\ 0 & x_3 & -x_1 \end{bmatrix}.$$

Eliminating x_3 , using the relation $x_1 + x_2 + x_3 = 1$, we obtain the equivalent reduced system:

$$\dot{x}_1 = -x_1(x_1 + 2x_2 - 1). \quad (2.1a)$$

$$\dot{x}_2 = -x_2(1 - 2x_1 - x_2). \quad (2.1b)$$

Setting

$$V = x_1 x_2 (1 - x_1 - x_2),$$

we notice that the above pair of equations have the form

$$\dot{x}_1 = \partial V / \partial x_2, \quad \dot{x}_2 = -\partial V / \partial x_1.$$

We see that along a trajectory $(x_1(t), x_2(t))$,

$$\dot{V} = (\partial V / \partial x_1) \dot{x}_1 + (\partial V / \partial x_2) \dot{x}_2 = 0,$$

i.e., V is constant along the motion. Therefore, $(x_1(t), x_2(t))$ is restricted to the curve

$$\Gamma_0: V(x_1, x_2) = x_1 x_2 (1 - x_1 - x_2) = V_0 = V(x_1(0), x_2(0)).$$

We consider the equations (2.1) on the triangular region

$$\gamma = \{(x_1, x_2) \mid x_1 \geq 0, x_2 \geq 0, x_1 + x_2 \leq 1\},$$

which (by Theorem 1.1) is an invariant set. Since $\Gamma_0 \subset \gamma$ this curve is bounded. Thus, if Γ_0 does not contain equilibrium points then (from the Poincare-Bendixson Theorem [14]) it is a closed orbit and the motion is periodic. Now the equilibrium points of (2.1) are:

$$P_1(0,0), P_2 = (1,0), P_3 = (0,1), P_4 = (1/3, 1/3).$$

At these points

$$V = 0 \text{ (at } P_1, P_2 \text{ or } P_3) \text{ or } V = 1/27 \text{ (at } P_4)$$

Thus, if $P_0 = (x, (0), x_2(0))$ is such that $0 < V < 1/27$ then the solution through P_0 is periodic. It is interesting to note that (2.1) may be transformed into a Hamiltonian system (in which P_4 is located at the origin) and periodicity also follows from Hamiltonian theory [15].

To round out the discussion of this example, we make the following observations.

1. If the initial point P_0 lies in the interior of γ and $P_0 \neq P_4$, then the motion is counterclockwise along Γ_0 . This can be seen by partitioning γ into four regions which are separated by the isoclines:

$$\ell_1: x_1 + 2x_2 - 1 = 0, \ell_2: 1 - 2x_1 - x_2 = 0,$$

2. If the initial point P_0 lies on the boundary of γ and P_0 is not an equilibrium point, then the motion is counterclockwise along the boundary and tending towards the first equilibrium point in its path.

Example 2.2 (aperiodic behavior). We consider the system where

$$F = \begin{bmatrix} -x_2(1-x_4) & 0 & x_1(1-x_4) & x_1 \\ x_2(1-x_4) & -x_3(1-x_4) & 0 & x_2 \\ 0 & x_3(1-x_4) & -x_1(1-x_4) & x_3 \\ 0 & 0 & 0 & -(x_1+x_2+x_3) \end{bmatrix}$$

we make the following observations.

1. Since $x_1 + x_2 + x_3 + x_4 = 1$, the fourth equation of the system may be expressed in the form

$$\dot{x}_4 = -(1-x_4)x_4.$$

2. If $x_4(0) = 1$ then $x_i(0) = 0$, $i = 1, 2, 3$, and the system is in equilibrium. Suppose

$$0 < x_4(0) < 1.$$

Then $x_4(t) = ce^{-t}/[1 + ce^{-t}]$, where $c = x_4(0)/[1-x_4(0)]$. Clearly $x_4(t)$ goes monotonically to zero and the solution is not periodic.

3. Let $\dot{x}_i = f_i(x_1, x_2, x_3)$, $i = 1, 2, 3$, be the system obtained by eliminating x_4 . The equilibrium points of this system are:

$$P_1 = (0, 0, 0), P_2 = (1, 0, 0), P_3 = (0, 1, 0), P_4 = (0, 0, 1), P_5 = (1/3, 1/3, 1/3).$$

4. Let

$$W = x_1 x_2 x_3 (x_1 + x_2 + x_3)^3.$$

It can be seen by direct computation that W is invariant along the motion (i.e., $\dot{W} = 0$). At an equilibrium point,

$$W = 0 \text{ (at } P_1, i = 1, 2, 3, 4) \text{ or } W = 1/27 \text{ (at } P_5)$$

Thus, if $W = W_0$ at an initial point P_0 and $W_0 \neq 0$ or $W_0 \neq 1/27$, then the trajectory through P_0 can not approach an equilibrium point.

Moreover, if $0 < x_4(0) < 1$, then (as we have already observed) the motion is aperiodic.

Remark 2.1. Counter examples can not be constructed for closed systems with only two compartments. It is not difficult to show in such cases that $x_i(t)$, $i = 1, 2$, goes monotonically to a limit.

Remark 2.2. A counter example is presented in [11] (p. 38) to show that Bellman's conjecture is false. However, this example is not in the class specified by Bellman, i.e., it does not have the form $\dot{x} = F(x)x$ with f_{ij} Lipschitz continuous.

Remark 2.3. Ex. 2.1 resembles equations arising in chemical reactions. In fact, consider the hypothetical reaction which is described schematically by

If $k_i = 1$, $i = 1, 2, 3$, then the rate equations are precisely those of Example 2.1.

3. GLOBAL EXPONENTIAL CONVERGENCE

In view of the counter examples presented in the previous section, we see that further conditions are required to obtain convergence to an equilibrium point. Such criteria may be found in [8]-[12] but the theory is still rather limited. In this section we will contribute further results, which apply more generally to systems (not necessarily

compartmental) that have an invariant set which is compact and convex.

In the case of n -compartmental systems (closed or open),

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

is such an invariant set. Moreover, for closed systems, the reduced system obtained by eliminating one of the variables by the conservation law, $\sum_{i=1}^n x_i = 1$, has γ_{n-1} as an invariant set. The results in this section are based on methods by Ladde [6]-[7], who applied differential inequality arguments to obtain stability results.

Theorem 3.1. Suppose that γ is a compact, convex, invariant set in $\mathbb{R}^n$ for an autonomous system,

$$\dot{x}(t) = f(x).$$

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 diagonally dominant with respect to rows.

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.

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

$$g_{i0}(x) \equiv -g_{i1}(x) - \sum_{j \neq i} |g_{ij}(x)| > 0, \quad x \in \gamma, \quad 1 \leq i \leq n.$$

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

$$g_{i0}(x) \geq \lambda > 0, \quad x \in \gamma, \quad 1 \leq i \leq n,$$

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

$$a_{i0}(t) \equiv -a_{i1}(t) - \sum_{j \neq i} |a_{ij}(t)|.$$

Clearly,

$$a_{10}(t) \geq \int_0^1 g_{10}(sy(t) + (1-s)x(t)) ds \geq \int_0^1 \lambda ds = \lambda.$$

Next, we compute the Dini derivative,

$$\begin{aligned} D^+ \|w(t)\|_{\infty} &= \limsup_{h \rightarrow 0^+} [\|w(t+h)\|_{\infty} - \|w(t)\|_{\infty}] / h \\ &= \limsup_{h \rightarrow 0^+} [\|w(t) + h A(t)w(t)\|_{\infty} - \|w(t)\|_{\infty}] / h. \end{aligned}$$

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

$$\begin{aligned} \|w(t) + hA(t)w(t)\|_{\infty} &\leq \max_{1 \leq i \leq n} [(1 + ha_{11}(t)) |w_1(t)| + h \sum_{j \neq 1} |a_{1j}(t)| |w_j(t)|] \\ &\leq [1 - h \min_{1 \leq i \leq n} g_{10}(x)] \|w(t)\|_{\infty} \\ &\leq [1 - h\lambda] \|w(t)\|_{\infty}. \end{aligned}$$

Thus, $D^+ \|w(t)\|_{\infty} \leq -\lambda \|w(t)\|_{\infty}$.

It follows [16] (p.15) that $\|w(t)\|_{\infty} \leq \|w(0)\|_{\infty} e^{-\lambda t}$ or

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

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

Finally, we recall ([14] (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 3.2. Suppose that γ is a compact, convex, invariant set in $\mathbb{R}^n$ for an autonomous system, $\dot{x}(t) = f(x)$. 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 diagonally dominant with respect to columns.

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.

Example 3.1 (enzyme kinetics). Enzyme kinetics are described in [17].

As a prototype example, we consider the reaction,

in which an enzyme (E) reacts with a substrate (S) to form a complex (C) which then results in a product (P). The rate equations for this reaction are:

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

To obtain a compartmental formulation we eliminate one of the variables

using the identity $e(t) - s(t) = e(0) - s(0)$. Let $x_1 = e$ if $s(0) \geq e(0)$ and $x_1 = s$ if $e(0) \geq s(0)$ (either choice if $s(0) = e(0)$). We also set $x_2 = c$, $x_3 = p$ and $\alpha = |e(0) - s(0)|$. We then obtain the closed compartmental system,

$$\dot{x}(t) = \begin{bmatrix} -k_{+1}(x_1 + \alpha) & k_{-1} & 0 \\ k_{+1}(x_1 + \alpha) & -(k_{-1} + k_{+2}) & k_{-2} \\ 0 & k_{+2} & -k_{-2} \end{bmatrix}$$

We use normalized units so that $x_1(0) + x_2(0) + x_3(0) = 1$ and it follows from the conservation law (Theorem 1.1) that $x_1(t) + x_2(t) + x_3(t) = 1$. Using this relation, we reduce the system further by eliminating x_2 to obtain:

$$\dot{x}_1 = -k_{+1}(x_1 + \alpha)x_1 + k_{-1}(1 - x_1 - x_3).$$

$$\dot{x}_3 = k_{+1}(1 - x_1 - x_3) - k_{-2}x_3.$$

Recall that $\gamma_2 = \{(x_1, x_3) \mid x_1 \geq 0, x_3 \geq 0, x_1 + x_3 \leq 1\}$ is an invariant set. Computing the Jacobian,

$$G = \begin{bmatrix} -k_{+1}(2x_1 + \alpha) - k_{-1} & -k_{-1} \\ -k_{+2} & -(k_{+2} + k_{-2}) \end{bmatrix},$$

we see that the hypothesis of Theorem 3.1 is satisfied provided

$$\lambda = \min\{k_{+1}\alpha, k_{-2}\} > 0.$$

In this case, the equilibrium equations $-k_{+1}(x_1 + \alpha)x_1 + k_{-1}(1 - x_1 - x_3) = 0$, $k_{+1}(1 - x_1 - x_3) - k_{-2}x_3 = 0$ have a unique solution in γ_2 , (b_1, b_3) , and

$$\max\{|x_1(t) - b_1|, |x_3(t) - b_3|\} \leq \max\{|x_1(0) - b_1|, |x_3(0) - b_3|\} e^{-\lambda t}.$$

4. WASHOUT

We now turn from consideration of the entire system to individual compartments. If a particular compartment $x_j(t) \rightarrow 0$ as $t \rightarrow \infty$ then we say that compartment j washes out. Intuitively, we might expect a compartment to wash out if the particles can flow out of the compartment and then become trapped so that they can not return to the compartment. This intuitive reasoning is formalized in Theorem 4.1.

Theorem 4.1. Suppose that compartment j reaches another compartment, say i , along a path π for all π in Ω_n , i.e., there is a sequence from j to i :

$$\pi: j = k_0 \rightarrow k_1 \rightarrow \dots \rightarrow k_q = i, \quad (4.1)$$

such that for each transfer along the path,

$$f_{k_{2+1}k_2}(x) > 0, \quad x \in \Omega_n. \quad (4.2)$$

Suppose further that there is no return path from $i \rightarrow j$, i.e., for any path $i = m_0 \rightarrow m_1 \rightarrow \dots \rightarrow m_s = j$ and for any $x \in \Omega_n$, there is at least one m_v such that $f_{m_{v+1}m_v}(x) = 0$. Then:

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

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

Proof. We observe first that statement (ii) implies statement (i). To

see this we first note that since the $f_{ij}(x)$ are continuous functions of x and since $x(t)$ is restricted to the compact set Ω_n , it follows that the $f_{ij}(x(t))$ are bounded functions of t . Consequently, the functions $\dot{x}_p(t) = \sum_{q=1}^n f_{pq}(x(t))x_q(t)$ are also bounded. From this fact, and with the aid of Barbalat's lemma [18], we conclude that (ii) implies (i). Thus, it suffices to prove (ii).

Next, we observe that all compartments which reach j (for some x in Ω_n) form an open subsystem,

$$\dot{x}_k(t) = \sum_{m \in S} f_{km}(x)x_m, \quad k \in S,$$

which includes j but not i . Let

$$\sigma(t) = \sum_{k \in S} x_k(t).$$

$$\begin{aligned} \text{Then } \dot{\sigma}(t) &= \sum_{k \in S} \dot{x}_k(t) = \sum_{k \in S} \sum_{m \in S} f_{km}(x(t))x_m(t) \\ &= -\sum_{m \in S} f_{0m}(x(t))x_m(t), \end{aligned}$$

where

$$f_{0m}(x) = -\sum_{k \in S} f_{km}(x) = \sum_{p \notin S} f_{pm}(x) \geq 0, \quad m \in S.$$

Thus, $\dot{\sigma}(t) \leq 0$ and hence $\sigma(t) \leq \sigma(0)$.

To obtain statement (ii), we argue by induction on the length q of the path in (4.1). Suppose first that $q = 1$. Then $f_{ij}(x) > 0$, $x \in \Omega_n$. Since Ω_n is compact,

$$f_{ij}(x) \geq a > 0, \quad x \in \Omega_n,$$

where a is the minimum of f_{ij} on Ω_n . Thus,

$$f_{0j}(x) \geq f_{ij}(x) \geq a, \quad x \in \Omega_n.$$

Consequently, $-\dot{\sigma}(t) = \sum_{m \in S} f_{0m}(x(t))x_m(t) \geq a x_j(t)$. Clearly,

$$\int_0^\infty x_j(t) dt \leq \sigma(0)/a < \infty.$$

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

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

Moreover, we have

$$f_{pj}(x) \geq c > 0, \quad x \in \Omega_n,$$

where c is the minimum of f_{pj} on Ω_n . From the equation

$$\dot{x}_p = \sum_{k=1}^n f_{pk} x_k, \quad \text{we obtain}$$

$$\dot{x}_p - f_{pp} x_p = \sum_{k \neq p} f_{pk} x_k \geq f_{pj} x_j \geq c x_j.$$

Let d be the maximum of $-f_{pp}$ on Ω_n , then

$$x_j(t) \leq [\dot{x}_p(t) + dx_p(t)]/c,$$

which yields

$$\int_0^\infty x_j(t) dt \leq [1 + dJ]/c < \infty.$$

This concludes the induction argument and the proof is complete.

Example 4.1 (liver model). We continue from Example 1.1. Applying Theorem 4.1 to the liver compartment, it washes out if it reaches the feces: $f_{42}(x) > 0$, $x \in \Omega_4$, or if it reaches the urine: $f_{31}(x)f_{12}(x) > 0$, $x \in \Omega_4$. Similarly, $x_1(t) \rightarrow 0$ if either $f_{31}(x) > 0$, $x \in \Omega_4$, or if $f_{42}(x)f_{21}(x) > 0$, $x \in \Omega_4$.

Example 4.2 (epidemic kinetics). We consider the classical S-I-R model for the spread of a disease [19]. Let x_1 , x_2 and x_3 denote the proportion of susceptibles, infectives and removed individuals, respectively. Then

$$\dot{x}_1 = -\alpha x_1 x_2, \quad \dot{x}_2 = \alpha x_1 x_2 - \gamma x_2, \quad \dot{x}_3 = \gamma x_2,$$

where α and γ are positive constants. The system is closed compartmental. It is well known that $x_2(t) \rightarrow 0$ and this fact is also immediate from Theorem 4.1 since $f_{32} = \gamma > 0$ and 3 does not reach 2. There is also a path from 1 to 3, $f_{32}f_{21} = \alpha x_2 \gamma$, except when $x_2 = 0$, and 3 does not reach 1. In spite of the fact that the hypothesis of Theorem 4.1 (in regard to compartment 1) is violated only when $x_2 = 0$, it is well known that 1 does not wash out (except when $x_1(0) = 0$). Thus, strict inequality in (4.2) is essential.

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