Global analysis of a model pulsing drug delivery oscillator based on chemomechanical feedback with hysteresis

Bingtuan Li
Institute for Mathematics and Its Applications, University of Minnesota, Minneapolis, Minnesota 55455

Ronald A. Siegel
Departments of Pharmaceutics and Biomedical Engineering, University of Minnesota, Minneapolis, Minnesota 55455

(Received 21 September 1999; accepted for publication 17 May 2000)

A simple model for an autonomous pulsing drug delivery system was previously introduced. This model involves negative feedback action, with hysteresis, of an enzyme on the permeability of a membrane through which substrate, at constant external concentration, must diffuse to reach the enzyme. The qualitative dynamics of this model permit, depending on system parameters and external driving substrate concentration, two separate single steady state, double steady state, and permanently alternating (oscillatory) behaviors. The present contribution is concerned with rigorous proofs regarding the global stability of steady states when permanent alternation is precluded, and the existence and globally asymptotic stability of a limit cycle in the permanently alternating case. Also, we prove that more restrictive but often realistic conditions on the system parameters imply limitations on the number of alternations the system can undergo before reaching steady state. © 2000 American Institute of Physics. [S1054-1500(00)01303-3]

I. INTRODUCTION

Future hormone replacement therapies are expected to mimic the temporal release of hormones, which, in a multitude of cases, has been shown to be periodic and pulsatile in normal individuals. To meet this need a model device based on negative chemomechanical feedback with hysteresis has been constructed. This device consists of a polyelectrolyte gel and an enzyme whose interaction exhibits an oscillatory instability under certain circumstances. In this contribution the mathematical properties of a simplified model of the dynamical behavior of this device are investigated. The model may be described as piecewise linear with hysteresis. Rigorous results are established regarding the global stability of limit sets in this model, including steady states and limit cycles, whose existence depends on the mechanical and chemical properties of the system. These results are related but do not correspond exactly to recent result regarding relay feedback control systems.

Observations of hormonal time series in recent years have revealed that the endogenous release of many hormones occurs as a series of regularly separated pulses.1-4 In certain cases it has been shown that the pulsatile nature of hormone secretion is critical to proper hormone function.5,6 For such hormones replacement therapy requires a close mimicking of the endogenous release pattern, thus motivating the development of novel drug delivery systems that release hormones on a periodic, pulsatile basis.

In previous papers a general scheme for an implantable device that autonomously releases hormones and other drugs in periodic pulses was introduced and analyzed.7-10 The scheme is illustrated in Fig. 1(a). Briefly, the device is a chamber that communicates with the external body fluids through a permselective membrane. The chamber contains the drug or hormone, D, and an enzyme, enz, the substrate, S, of which is present at constant external concentration and can diffuse through the membrane into the chamber. The enzyme converts S into a product, P, which ultimately diffuses out to the body fluids through the membrane. However, high product concentrations are assumed to repress membrane permeation of both substrate and drug, and the characteristic relating membrane permeabilities to product concentration is assumed to exhibit hysteresis, as illustrated in Fig. 1(b). This negative hysteretic feedback was shown, under proper conditions, to be capable of producing periodic, pulsatile behavior.9 It has also been argued, with partial experimental confirmation,10,11 that a system based on glucose oxidase-catalyzed conversion of glucose to a hydrogen ion, coupled with a hydrophobic, weak acid hydrogel membrane, meets the criteria specified by this scheme. In such a system the decrease or increase in hydrogen ion concentration in the chamber acts to mechanically swell or deswell the membrane, altering its permeability. Thus, we say that the negative feedback is chemomechanical in origin.

The behavior of the proposed device depends on the dynamics of substrate and product concentrations inside the chamber and the permeability properties of the membrane. Recently, a simple lumped model of device behavior was considered.9 The model assumes that the chamber and exter-

1054-1500/2000/10(3)/682/9/$17.00 © 2000 American Institute of Physics
provide rigorous proofs in support of the numerical results. In Sec. II the model is described in detail and previous results are summarized. In Sec. III theorems are proved, establishing the global stability of the invariant set, which may be a single steady-state point, a pair of steady-state points, or a limit cycle.

In the case where the system relaxes to a steady state, the theorems of Sec. III provide no means of predicting the number of alternations occurring before convergence. In Sec. IV we show that under a particular auxiliary condition, a maximum of two alternations is possible. Finally, in Sec. V we discuss equivalent systems to which the model applies, compare our results against those obtained for related but not completely isomorphic systems, and speculate on the degree to which the mathematical arguments can be generalized.

II. THE MODEL

Let

\[ S^* = \text{external substrate concentration}, \]
\[ S = \text{substrate concentration in the chamber}, \]
\[ P = \text{product concentration in the chamber}, \]
\[ \kappa_{enz} = \text{the first-order rate constant of enzyme reaction}, \]
\[ A = \text{area of membrane}, \]
\[ V = \text{volume of chamber}, \]
\[ K_{S,H} = \text{membrane permeability to substrate in the } H \text{ state}, \]
\[ K_{S,L} = \text{membrane permeability to substrate in the } L \text{ state}, \]
\[ K_{P,H} = \text{membrane permeability to product in the } H \text{ state}, \]
\[ K_{P,L} = \text{membrane permeability to product in the } L \text{ state}, \]
\[ P_{LH} = \text{product concentration at which the } H \rightarrow L \text{ transition occurs}, \]
\[ P_{LH} = \text{product concentration at which } L \rightarrow H \text{ transition occurs}, \]
\[ t = \text{time}, \]

with all system parameters positive (except possibly \( t \)), \( K_{S,H} > K_{S,L} \) and \( P_{LH} > P_{LH} \). Normalizing all concentrations by \( P_{HL} \), all permeabilities by \( K_{S,H} \), and rates and time by \( K_{S,H} A/V \), we obtain the nondimensional variables

\[ s^* = S/P_{HL}, \quad s = S/P_{HL}, \quad p = P/K_{S,H}, \quad \alpha = K_{S,L}/K_{S,H}, \quad \beta_H = K_{P,H}/K_{S,H}, \quad \beta_L = K_{P,L}/K_{S,H}, \quad \epsilon = P_{LH}/P_{HL}, \quad k = \kappa_{enz}V/(K_{S,H}A) \] and \( \tau = (K_{S,H}A/V)t \). In terms of these variables the dynamic governing equations are the following:

**H State**

\[
\begin{align*}
\frac{ds}{d\tau} &= (s^* - s) - ks, \\
\frac{dp}{d\tau} &= ks - \beta_H p, \quad \text{until } p \uparrow 1;
\end{align*}
\]

**L State**

\[
\begin{align*}
\frac{ds}{d\tau} &= \alpha(s^* - s) - ks, \\
\frac{dp}{d\tau} &= ks - \beta_L p, \quad \text{until } p \downarrow \epsilon;
\end{align*}
\]

with initial conditions \( s(\tau_0) = 0 \) and \( p(\tau_0) \geq 0 \). The membrane may start in the \( H \) state provided \( p(\tau_0) < 1 \) and may start in the \( L \) state if \( p(\tau_0) > \epsilon \).
When in the $H$ state, the system pursues a unique steady state located at the following:

$$ H \text{ steady state: } \bar{s}_H = \frac{s^*}{k+1}; \quad \bar{p}_H = \frac{s^*}{(1+1/k)\beta_H}. $$

(2.3)

If $\bar{p}_H > 1$, or $s^* > (1+1/k)\beta_H$, then the system must switch to the $L$ state before it can reach that stationary point. Correspondingly, in the $L$ state the system pursues a unique steady state at the following:

$$ L \text{ steady state: } \bar{s}_L = \frac{\alpha s^*}{k+\alpha}; \quad \bar{p}_L = \frac{s^*}{(1+1/k)\beta_L}, $$

(2.4)

and the system must revert to the $H$ state when $\bar{p}_L < \epsilon$, or $s^* < (1+1/k)\beta_L\epsilon$. Combining these two observations, we find that when

oscillations: $(1+1/k)\beta_H < s^* < (1+1/k)\beta_L\epsilon$, \quad (2.5)

the system will alternate forever between $H$ and $L$. Notice, however, that this statement does not necessitate convergence to a limit cycle.

In addition, we may assert that when $\bar{p}_H < 1$ and $\bar{p}_L < \epsilon$, the only possible stationary point is ($\bar{s}_H,\bar{p}_H$). When $\bar{p}_H > 1$ and $\bar{p}_L > \epsilon$, the only possible stationary point is ($\bar{s}_L,\bar{p}_L$). When $\bar{p}_H < 1$ and $\bar{p}_L > \epsilon$, either of these points is a potential stationary point, depending on initial conditions. Again these statements by themselves do not guarantee convergence. These three cases can be described in terms of system parameters and external concentration as follows:

single steady state ($H$):

$$ s^* < \min\{(1+1/k)\beta_H, (1+1/k)\beta_L\epsilon\}, \quad (2.6) $$

two steady states:

$$ (1+1/k)\beta_L\epsilon < s^* < (1+1/k)\beta_H. $$

(2.8)

In the following section, we prove that in the first two cases of the previous paragraph the only possible stationary point is a global attractor, and that in the third case the pair of stationary points is globally attracting. Finally, we prove that when Eq. (2.5) holds, a globally stable limit cycle solution exists.

### III. Global Analysis

The system in the $H$ or $L$ state is linear. The solution in each state can be easily calculated. In the $H$ state the solution for the system takes the form

$$ s(\tau) = \bar{s}_H + e^{-(k+1)(\tau-\tau_0)}(s(\tau_0) - \bar{s}_H), $$

$$ p(\tau) = \bar{p}_H + e^{-(k+1)(\tau-\tau_0)}(p(\tau_0) - \bar{p}_H) $$

$$ + \frac{k}{k+1-\beta_H} \left[e^{-\beta_H(\tau-\tau_0)} - e^{-(k+1)(\tau-\tau_0)}\right] \times (s(\tau_0) - \bar{s}_H). $$

(3.1)

where $s(\tau_0)$ and $p(\tau_0)$ are starting concentrations with $0 \leq p(\tau_0) < 1$. In the $L$ state the solution for the system takes the form

$$ s(\tau) = \bar{s}_L + e^{-(k+1)(\tau-\tau_0)}(s(\tau_0) - \bar{s}_L), $$

$$ p(\tau) = \bar{p}_L + e^{-(k+1)(\tau-\tau_0)}(p(\tau_0) - \bar{p}_L) $$

$$ + \frac{k}{k+\alpha-\beta_L} \left[e^{-\beta_L(\tau-\tau_0)} - e^{-(k+1)(\tau-\tau_0)}\right] \times (s(\tau_0) - \bar{s}_L), $$

(3.2)

where $p(\tau_0) \geq \epsilon$. In (3.1) and (3.2), $\tau_0$ is the starting time in the state. All terms in (3.1) and (3.2) are bounded and we shall make use of the fact that for $\tau > \tau_0$,

$$ 0 < \frac{k}{k+1-\beta_H} \left[e^{-\beta_H(\tau-\tau_0)} - e^{-(k+1)(\tau-\tau_0)}\right] \leq \frac{k}{k+1-\beta_H}, $$

(3.3)

The following observation plays an important role in the global analysis of the system:

**Lemma 1:** The compact set $D=[\bar{s}_L, \bar{s}_H]$ is invariant with respect to $s$, and is a global attractor for $s$ in the $H$ and $L$ states. Further, if $s(\tau_0)$ lies outside $D$, then $s(\tau)$ approaches $D$ monotonically.

**Proof:** It is clear that solutions for the system are always positive for $\tau > \tau_0$. Note that $k>0$, $0 < \alpha < 1$, and $\bar{s}_L < \bar{s}_H$. The $s$ equation in the $H$ state (2.1) can be rewritten as

$$ \frac{ds}{d\tau} = -(k+1)(s-%\bar{s}_H), $$

and the $s$ equation in the $L$ state (2.2) can be rewritten as

$$ \frac{ds}{d\tau} = -(k+\alpha)(s-%\bar{s}_L). $$

(3.4)

Combining these two equations, we have at all times (and for either membrane state)

$$ \frac{ds}{d\tau} > -(k+\alpha)(s-%\bar{s}_L), \text{ for } s%\bar{s}_L, $$

$$ \frac{ds}{d\tau} < -(k+1)(s-%\bar{s}_H), \text{ for } s%\bar{s}_H. $$

(3.5)

Examination of these inequalities reveals that all trajectories of the system originating outside $D$ approach $D$ monotonically and exponentially. Equation (3.5) also indicates that no solution of the system can cross the two boundaries $s = \bar{s}_H$ and $s = \bar{s}_L$ from the interior of $D$, and therefore $D$ is invariant. This completes the proof.

The first main result of this section is that limit sets containing steady-state points are global attractors.

**Theorem 1:**

1. If Eq. (2.6) holds, then every solution of the system approaches the $H$ steady state.
2. If Eq. (2.7) holds, then every solution of the system approaches the $L$ steady state.
(3) If Eq. (2.8) holds, then every solution of the system approaches either the $H$ steady state or $L$ steady state, depending on the initial condition.

Proof: By Lemma 1, we need only consider solutions in the interval

$$D_\delta = [\bar{s}_L - \delta, \bar{s}_H + \delta]$$

for sufficiently small positive $\delta$. $D_\delta$ is closed, invariant with respect to $s$, and contains $D$ as a subset.

It is clear from (3.1) that if a solution remains in the $H$ (or $L$) state, then it approaches the $H$ (or $L$) steady state.

Consider (i). In view of $\bar{p}_L < \epsilon$, there is no solution for the system that can stay in the $L$ state forever. If a solution enters $D_\delta$ within the $L$ state then it must hit the line $p = \epsilon$ at some time, say $\tau_0$, with $\bar{s}_L - \delta \leq s(\tau_0) \leq \bar{s}_H + \delta$. Note that $s(\tau_0) - \bar{s}_H \leq \delta$ and $p(\tau_0) = \epsilon$. It follows from $\epsilon < \bar{p}_H$, (3.1), and (3.3) that for $\tau > \tau_0$,

$$p(\tau) \leq \bar{p}_H + \delta + \frac{k}{k + 1 - \beta_H} \left[ e^{-\beta_H(\tau - \tau_0)} - e^{-(k-1)(\tau - \tau_0)} \right].$$

This indicates that for $\tau > \tau_0$,

$$p(\tau) \leq \bar{p}_H + \delta + \frac{k}{k + 1 - \beta_H} < 1,$$

if $\delta$ is small enough. Therefore the solution will remain in the $H$ state for $\tau > \tau_0$ and approach the $H$ steady state.

The proof of (ii) is completely symmetrical to that of (i). The proof for (iii) follows by noting that if $\bar{p}_H < 1$ and $\bar{p}_L > \epsilon$, then a sufficiently small $\delta$ can be chosen such that either the system will remain in one state forever upon entering $D_\delta$, or a single permanent transition to the other state will occur. The proof is completed.

The second main result of this section is that when no reachable steady state exists, the system is globally attracted to a limit cycle.

Theorem 2: If (2.5) holds, then the system switches back and forth between the $H$ and $L$ states forever, and there is a limit cycle solution that is the attractor for all $(s, p)$ trajectories.

Proof: For a given point $s_0 \in D$, consider the solution of Eq. (2.1) ($H$ state) with initial condition $(s, p) = (s_0, \epsilon)$. This solution will hit the line $p = 1$ at a point, say $s_1 = h(s_0)$. Next, consider the solution of Eq. (2.2) ($L$ state) with initial condition $(s, p) = (s_1, 1)$. This solution will hit the line $p = \epsilon$ at some point, say $s_2 = l(s_1)$. Forming the composition $q(s) = l(h(s))$ (Poincaré return map) and recalling that $D$ is invariant for the system, we have $s_2 = q(s_0) \in D$. The graphical depiction of $q$ is in Fig. 2. Clearly, $q$ is a continuous function from $D$ to itself. By Brouwer’s fixed point theorem, there exists $s_0 \in D$ such that $q(s_0) = s_0$. Therefore a limit cycle solution exists.

Next, we show that for all $s \in D$,

$$|q'(s)| \leq r < 1.$$  \hfill (3.5)

for some $r > 0$. Equation (3.5) clearly indicates that the Poincaré return map $q$ is globally contracting, and the global stability of the limit cycle solution follows immediately.

It suffices to show the same statement as Eq. (3.5) is true for $h$ and $l$. Here we only show that (3.5) is true for $h$. The proof for $l$ is similar and is omitted.

In the $H$ state, in view of Eq. (3.1), we have

$$k + 1 - \beta_H = \frac{k + 1 - \beta_H}{k} \left(1 - \bar{p}_H + h(s) - \bar{s}_H\right)$$

$$= \left(k + 1 - \beta_H \frac{h(s) - \bar{s}_H}{s - \bar{s}_H}\right) \frac{b_{H/(k+1)}}{\bar{p}_H},$$

(3.6)

where $s \in D$. Let

$$x = s - \bar{s}_H$$

and $f(x) = h(x + \bar{s}_H) - \bar{s}_H$.  \hfill (3.7)

Evidently, $x \equiv 0$ and $f(x) \equiv 0$ for all $s \in D$. Now let

$$H_1 = \frac{k + 1 - \beta_H}{k} (1 - \bar{p}_H)$$

and

$$H_2 = \frac{k + 1 - \beta_H}{k} (e - \bar{p}_H).$$

These definitions render Eq. (3.6) into the simpler form,

$$f(x) + H_1 = \left(x - H_1 \left(\frac{f(x)}{x}\right)^{\beta_{H/(k+1)}}\right).$$

(3.8)

FIG. 2. An illustration of functions $h$ and $l$ in the phase plane. The function $h$ maps the line $(s, \epsilon)$ into the line $(s, 1)$ via $H$-state trajectories that move toward the $H$ steady-state point $(\bar{s}_H, \bar{p}_H)$ but cannot reach that point because of the state transition to $L$ upon reaching $p = 1$. The function $l$ maps the line $(s, 1)$ into the line $(s, \epsilon)$ via $L$-state trajectories that move toward the $L$ steady-state point $(\bar{s}_L, \bar{p}_L)$ but cannot reach that point because of the state transition to $H$ upon reaching $p = \epsilon$. The composition of these two functions, $q(s) = h(l(s))$, therefore maps the line $(s, \epsilon)$ into itself.
Let $F_H = [\bar{x}_L - \bar{x}_H, 0]$. Then $s \in D$ if and only if $x \in F_H$.

By the attraction of the $H$ steady state, $0 < f(x)/x < 1$ for $x \in F_H \setminus \{0\}$. Also, $f(x) \to 0$ as $x \to 0$, and from (3.8) it follows that

$$\lim_{x \to 0} f(x) = \left(\frac{H_1}{H_\varepsilon}\right)^{(k+1)/\beta_H} < 1. \tag{3.9}$$

Therefore by the continuity of $f(x)$ we can state that there is a positive constant $r_H < 1$ such that, for all $x \in F$,

$$0 < \frac{f(x)}{x} < r_H, \tag{3.10}$$

where the value of $f(x)/x$ at $x=0$ is defined to be $(H_1/H_\varepsilon)^{(k+1)/\beta_H}$.

Taking the derivative of $f(x)$ with respect to $x$ implicitly in Eq. (3.8), one obtains

$$f'(x) = \left(1 - \frac{\beta_H}{k+1} \frac{x}{x} \right) \frac{f(x)}{x} \beta_H^{(k+1)/\beta_H}, \tag{3.11}$$

Rearranging Eq. (3.8),

$$\frac{f(x)}{x} \beta_H^{(k+1)/\beta_H} = f(x) + H_1 \frac{x}{x} + H_\varepsilon \tag{3.12}$$

If $x = -H_\varepsilon$, then by Eq. (3.8), $f(x) = -H_1$. In this case, we still define $[f(x) + H_1]/(x + H_\varepsilon)$ to be $(f(x)/x)\beta_H/(k+1)$. Equation (3.11) then can be rewritten as

$$f'(x) = \left(1 - \frac{\beta_H}{k+1} \frac{x}{x} \right) \frac{f(x)}{x} \beta_H^{(k+1)/\beta_H},$$

or

$$f'(x) = \frac{H_\varepsilon}{x} + \frac{k+1}{\beta_H} \frac{f(x)}{x} \beta_H^{(k+1)/\beta_H}, \tag{3.12}$$

This derivative vanishes at $x_0 = H_\varepsilon/\left(\frac{k+1}{\beta_H} - 1\right)$. \tag{3.13}

The point $x_0$ divides $F_H$ into two intervals as follows:

$I_1 = \{x: x > x_0, x \in F_H\}$

and

$I_2 = \{x: x < x_0, x \in F_H\}$.

The intervals $I_1$ and $I_2$ represent two different qualitative behaviors of trajectories, as illustrated in Fig. 3. For $x$ originating in $I_1$, trajectories are increasing in $p$, whereas trajectories originating in $I_2$ are biphasic. Moreover, $f(x)$ is monotonically increasing for $x \in I_1$, but is monotonically decreasing for $x \in I_2$. These distinctive behaviors require us to treat them separately in the following demonstration.

Case 1: $x \in I_1$. Rearranging (3.8),

$$1 + \frac{H_\varepsilon}{x} \frac{f(x)}{x} \beta_H^{(k+1)/\beta_H} < 1,$$

for $x \in I_1 \setminus \{0\}$.

We first assume $k+1 > \beta_H$. It follows that $H_\varepsilon < H_1 < 0$. Note that $1 + H_\varepsilon/x > 0$, $1 + H_1/f(x) > 0$, and $x \geq x_0$ in Eq. (3.13) leads to the inequality

$$1 + \frac{H_\varepsilon}{x} \frac{k+1}{\beta_H} > 0. \tag{3.15}$$

By Eqs. (3.10) and (3.14),

$$1 + \frac{H_\varepsilon}{x} \frac{k+1}{\beta_H} > 0. \tag{3.16}$$

Therefore

$$0 \leq \frac{H_\varepsilon}{x} \frac{k+1}{\beta_H} < 1,$$

for $x \in I_1 \setminus \{0\}$. On the other hand, Eqs. (3.9) and (3.12) show that $\lim_{x \to 0} f'(x)$ exists and

$$\lim_{x \to 0} f'(x) = \left(\frac{H_1}{H_\varepsilon}\right)^{(k+1)/\beta_H} < 1. \tag{3.17}$$

Therefore $0 \leq f'(x) < 1$ for all $x \in I_1$. By continuity of $f'(x)$, there is a positive constant $d_1 < 1$ such that for all $x \in I_1$,

$$0 \leq f'(x) < d_1. \tag{3.18}$$

where $f'(0)$ is defined to be $(H_1/H_\varepsilon)^{(k+1)/\beta_H}$.

Now suppose $k+1 < \beta_H$. Then $0 < H_1 < H_\varepsilon$ and

$$1 + \frac{H_\varepsilon}{x} \frac{k+1}{\beta_H} \leq 0, \tag{3.19}$$

for $x \in I_1$. By Eqs. (3.10) and (3.14)

$$1 + \frac{H_\varepsilon}{x} \frac{f(x)}{x} \beta_H^{(k+1)/\beta_H} > 1. \tag{3.20}$$
If $1 + H_e/x > 0$, then from Eq. (3.20) we have $1 + H_e/x > 1 + H_1/f(x) > 0$. It then follows from Eq. (3.19) that

$$1 + \frac{H_1}{f(x)} - \frac{k+1}{\beta_H} < 0. \quad (3.21)$$

If $1 + H_e/x < 0$, then from Eq. (3.20), $1 + H_1/f(x) < 0$. In this case, Eq. (3.21) is automatically true. If $1 + H_e/x = 0$, then from Eq. (3.8), $1 + H_1/f(x) = 0$, and thus (3.21) holds. Therefore Eq. (3.21) is true for $x \in I_1$ in all cases. Simple calculations show that

$$0 \leq \frac{1 + \frac{H_e}{x} - \frac{k+1}{\beta_H}}{1 + \frac{H_1}{f(x)}} < 1 \quad (3.22)$$

which is equivalent to

$$1 + \frac{H_e}{x} - \frac{k+1}{\beta_H} > 1 \quad (3.23)$$

In view of Eq. (3.20), Eq. (3.22) is true, and it follows from Eqs. (3.12), (3.20), (3.22), and (3.10) that

$$0 \leq f'(x) < \frac{f(x)}{x} < r_H < 1.$$  

Therefore in case (i) there is a positive constant $r_1 < 1$ such that $0 \leq f'(x) < r_1$ for $x \in I_1$.

Case 2: $x \in I_2$. In this case $f'(x) \leq 0$. As illustrated in Fig. 3, a trajectory starting on $R; \rho = \infty$ will first decrease in $p$, pass through a minimum, and then increase and cross $R$ at a point to the right of $x_0$, eventually hitting the line $p = 1$.

We construct a function $u$ from $I_2$ to $I_1$, given by

$$u(x) = \frac{u(x) + H_e}{\beta_H^{(k+1)}} \quad (3.24)$$

$u(x)$ represents the point where the trajectory, starting at a point $x \in I_2$ and $p = \infty$, hits the line $p = 1$ again after the initial decrease. See Fig. 3 for a graphical depiction of $u$. Clearly, $u(x < 0).$ Since trajectories cannot cross, $u(x)$ is a decreasing function. It follows that $u'(x) \leq 0$ if $u'$ exists. Note that $u(x_0) = x_0$, and $u(x) \to x_0$ as $x \to x_0$, or

$$\lim_{x \to x_0} \frac{u(x)}{x} = 1. \quad (3.25)$$

Taking the derivative of $u(x)$ with respect to $x$ implicitly in (3.23), one obtains

$$u'(x) = \frac{1 + \frac{H_e}{x} - \frac{k+1}{\beta_H}}{1 + \frac{H_e}{u(x)} \frac{k+1}{\beta_H}} u(x) \beta_H^{(k+1)} \quad (3.26)$$

or

$$u'(x) = \frac{1 + \frac{H_e}{x} - \frac{k+1}{\beta_H}}{1 + \frac{H_e}{u(x)} \frac{k+1}{\beta_H}} u(x) \beta_H^{(k+1)} \quad (3.27)$$

We now calculate the value of $u'(x_0)$. Using (3.24) and (3.26), we have

$$\lim_{x \to x_0} u'(x) = \lim_{x \to x_0} \frac{H_e + \left(1 - \frac{k + 1}{\beta_H}\right) u(x)}{u(x) \beta_H^{(k+1)}} x \quad (3.28)$$

Note that $H_e + \left(1 - \frac{k + 1}{\beta_H}\right) x_0 = H_e + \left(1 - \frac{k + 1}{\beta_H}\right) u(x_0) = 0$. Then

$$H_e + \left(1 - \frac{k + 1}{\beta_H}\right) \frac{x}{u(x)} = \frac{u(x)}{u(x_0)} \quad (3.29)$$

From this, Eq. (3.28) and L'Hopital's rule,

$$\lim_{x \to x_0} u'(x) = \lim_{x \to x_0} \frac{u(x)}{u(x_0)} \quad (3.30)$$
It follows that \( u'(x_0) = 1/u'(x_0) \), and thus \( u'(x_0) = -1 \).

One can calculate that

\[
\frac{u''(x)}{u(x)} = \frac{1 - \frac{k+1}{\beta_H} \left( 1 - \frac{1}{(1 - \frac{k+1}{\beta_H}) u(x) + H_e} \right) \left[ 1 - \frac{1}{(1 - \frac{k+1}{\beta_H}) u(x) + H_e} (u'(x))^2 \right] \beta_H/(k+1)}{(1 - \frac{k+1}{\beta_H}) u(x) + H_e}.
\]

Note that the second term in Eq. (3.28) is always nonpositive. From the definition of \( H_e \) and noting that \( u(x_0) > 0 \), it follows that

\[
1 - \frac{k+1}{\beta_H} > 0, \quad \text{when} \quad 1 - \frac{k+1}{\beta_H} \neq 0.
\]

Therefore the first term in Eq. (3.28) is negative if \( u'(x) \leq -1 \) [note that \( x/u(x) > 1 \) for \( x \in I_2 \setminus x_0 \)], and we obtain the following condition:

\[
u''(x) < 0, \quad \text{if} \quad u'(x) \leq -1, \quad \text{for} \quad x \in I_2 \setminus x_0.
\]

We are now ready to show that \( 1 < u'(x) \leq 0 \) for \( x \in I_2 \setminus x_0 \). If at a point, say \( x_i \) with \( x_i < x_0, u'(x_i) \leq -1 \), then it follows from Eq. (3.29) that \( u'(x) \) is decreasing for \( x \in (x_i, x_0) \). Accordingly, \( u'(x) < -1 \) for \( x \in (x_i, x_0) \). This contradicts \( u'(x_0) = -1 \). Therefore \( -1 \leq u'(x) \leq 0 \) for \( x \in I_2 \).

For \( x \in I_2 \), the function \( f(x) \) can be written as a composition of \( f \) and \( u \), i.e.,

\[
f(x) = f(u(x)).
\]

Note that \( u(x) \in I_1 \). Also note that

\[
f'(x) = f'(u(x)) u'(x).
\]

From case (i) and the fact that \( -1 \leq u'(x) \leq 0 \), we have \( -r_1 < f'(x) \leq 0 \) for \( x \in I_2 \) (\( r_1 \) is given above and \( 0 < r_1 < 1 \)). Therefore, for \( x \in F_H \), \( |f'(x)| < r_1 \), which is equivalent to \( |h'(s)| < r_1 \) for \( s \in D \). The proof is complete.

IV. NUMBER OF ALTERNATIONS

Although Theorem 1 establishes the global stability of the single or double steady states determined by the criteria specified in Eqs. (2.6)–(2.8), it says nothing about whether the system undergoes alternations between the \( H \) and \( L \) states before converging. Generally the number of alternations will depend on the initial conditions and system parameters. However, we have determined one auxiliary condition in which the number of alternations is restricted to two or less.

Theorem 3: Let

\[
\beta_L < \frac{\beta_H}{\epsilon}.
\]

(i) If Eq. (2.6) holds, then the pattern of the switching state takes one of the three possible forms: \( H \to L \), or \( H \to L \to H \), depending on the initial condition.

(ii) If Eq. (2.7) holds, then the pattern of the switching state takes one of the three possible forms: \( L \to H \), or \( L \to H \to L \), depending on the initial condition.

(iii) If Eq. (2.8) holds, then the pattern of the switching state takes one of the six possible forms: \( H \to L \), \( H \to L \to H \), \( L \to H \), \( L \to H \), or \( L \to H \), depending on the initial condition.

Proof: Observe that in the \( H \) state \( dp/dt < 0 \) if \( p = 1 \) and \( s < \beta_H/k \), and in the \( L \) state \( dp/dt > 0 \) if \( p = 1 \) and \( s > \beta_L/k \). This clearly shows that if the system is in the \( H \) (or \( L \)) state, \( p < 1 \) (or \( p > 1 \)) and \( s < \beta_H/k \) (or \( s > \beta_L/k \)), then it will remain in the \( H \) (or \( L \)) state. In other words, if the system is in the \( H \) (or \( L \)) state and \( p < 1 \) (or \( p > 1 \)), it can switch to the \( L \) (or \( H \)) state when \( s > \beta_H/k \) (or \( s < \beta_L/k \)).

Consider (i). It follows from Eq. (2.6) that \( \beta_H/k > \bar{s}_H \) and \( \beta_L/k < \bar{s}_L \). In this case, if the system switches from the \( L \) state to the \( H \) state at a point \( s_0 \) where \( p = 1 \), then \( s_0 > \beta_L/k \). On the other hand, by Eq. (4.1), \( \beta_L/k < s_0 \). It follows that after switching to the \( H \) state at \( s_0 \), the system must remain in the \( H \) state, and approaches the \( H \) steady state. This proves (i).

The proof for (ii) is completely symmetrical to that of (i), and we omit the details.

Consider (iii). It follows from Eq. (2.8) that \( \beta_H/k > \bar{s}_H \) and \( \beta_L/k < \bar{s}_L \). In this case, if the system switches from the \( L \) state to the \( H \) state at a point \( s_0 \) where \( p = 1 \), then \( s_0 < \beta_L/k \). A similar argument indicates that after switching to the \( H \) state at \( s_0 \), the system remains in the \( H \) state, and approaches the \( H \) steady state. By symmetry, if the system switches from the \( H \) state to the \( L \) state at a point \( s_1 \) where \( p = 1 \), then \( s_1 > \beta_H/k \), and it will remain in the \( L \) state, and approaches the \( L \) steady state. This proves (iii).

V. DISCUSSION

Our purpose in this work was to provide rigorous proofs regarding behaviors of an idealized negative feedback system with hysteresis. The system is meant to model a periodically pulsating drug delivery device. In a previous discussion of this device scheme, an even simpler model in which the enzyme reaction is assumed to be instantaneous was considered. The substrate dynamics are eliminated in the simpler model and the description of product dynamics amounts to a first-order linear differential equation with hysteretically switching coefficients. The global stability characteristics of steady states or limit cycles are then trivial to prove, since a switch occurs at only one possible value of product concentration, and thereafter only a single product concentration trajectory is possible. The introduction of substrate dynamics into the present model leads to much more complex proofs, as evidenced above.

Nevertheless, the model considered here is relatively simple, and some of the proof techniques rely on the availability of tractable solutions of the piecewise linear differential equations. Properties of these solutions are incorporated
into the overall strategy of first identifying an attractor that is compact in substrate concentration, and then demonstrating convergence of all trajectories originating in the attractor to the appropriate limit sets (steady-state points or limit cycles). In particular, convergence in the limit cycle case was demonstrated by constructing an everywhere contracting Poincaré return map for the switching subsets of the attractor. Other more complicated models may fit into this proof strategy, either by finding explicit solutions or by using known properties of the model equations. For example, the introduction of saturation in the enzyme reaction or of nonconstant permeabilities that nevertheless can be classified into two nonoverlapping "states," the transitions between which exhibit hysteresis, may not affect the final conclusions, although the details of the proofs may differ.

The most severe approximation imposed in this work is that transitions between membrane states are considered to be instantaneous. Relaxing this assumption may lead to more complex, perhaps distributed, dynamics relating to transport and phase transitions in polymer gel membranes and to greater complications in establishing global stability than would be expected for some of the generalizations described in the last paragraph.

Although this work was motivated by the chemomechanically based drug delivery system device in Fig. 1, it should be noted that other realizations are possible. For example, an equivalent electrical circuit diagram is shown in Fig. 4. The diagram shows two RC networks with dependent sources and conductances. The circuit on the left corresponds to substrate dynamics. The conductances $G_s$ and $G_e$, correspond, respectively, to the membrane area x permeability to substrate ($AK_s$), and the enzyme rate constant, $k_{enz}$, and the capacitance $C$ corresponds to the chamber volume ($V$). The voltages $V_0$ and $v_1$ correspond to the external and internal substrate concentrations ($S^e$) and ($S$), respectively. The current $i_p$ represents the rate of conversion of substrate to product. The circuit on the right represents product dynamics. Here $C$ is defined as before and $G_p$ represents the area x permeability of the membrane to product ($AK_p$). This circuit is fed by the product generation "current," $i_p$, and the voltage $v_2$ corresponds to product concentration ($P$). To complete the analogy, the conductances $G_s$ and $G_e$ depend on $v_2$ in a piecewise, hysteretic manner. This can be arranged in an electronic system using relays or bistable hysteretic switching networks. In a similar manner, one could devise mechanical or hydraulic systems with appropriate elements that would exhibit the same behavior.

The mathematical model of the device discussed here is partially related to models of automatic control systems involving relay feedback. In these models, a fixed linear dynamical system, usually characterized by a set of linear ordinary differential equations (ODEs), is driven by telegraph wavelike inputs that switch between two constant levels when the system output reaches specified values. A number of results have been published in which sufficient conditions for the existence, local stability, or global stability of limit cycle oscillations are identified. In most cases the results are based on Poincaré return maps between the two switching surfaces associated with the hysteretic relay. Local stability is usually established by calculating the eigenvalues of a Jacobian matrix associated with the Poincaré map. These switching surfaces and Jacobians are related in turn to matrices that represent the ODEs.

Results regarding the global stability of limit cycles in relay feedback systems have been established only recently and are restricted to the "symmetric" case in which the control inputs are either positive or negative with equal magnitude and in which the switching surfaces represent vector subspaces of the state space associated with the ODEs. Goncalves et al. derived criteria based on Lyapunov functions for the Poincaré maps, which can be constructed by a numerical search procedure based on certain "linear matrix inequalities." Varigonda and Georgiou derived a procedure for bounding the derivatives and establishing the contractive nature of the Poincaré map over a compact attractor, a strategy that is similar to that pursued in this work. Their results apply to whole classes of linear dynamical systems, whereas our results were derived by exploiting the properties of a particular set of linear ODEs. Varigonda and Georgiou point out, however, that their procedure is difficult to apply when the dimensionality of the dynamical system (i.e., the number of ODEs) exceeds two.

In the models described in the previous paragraph the steady-state point switches back and forth with hysteresis, but the linear dynamical system remains constant. The present model is more complicated insofar as both the steady state and the dynamics change at a switching point. Moreover, our model and proofs do not possess or rely on the "symmetry" properties used in the studies of global stability in relay feedback control. The techniques introduced to study relay feedback control systems might, however, be extendable to cover the present model, and this may permit proofs that do not rely on explicit solutions, as were used in this paper. The latter point is currently under study.

While the present system is intrinsically more nonlinear than the relay feedback systems, at least one aspect of the

---

FIG. 4. Equivalent electrical circuit diagram of the system illustrated in Fig. 1. Definitions of circuit variables and correspondences to chemomechanical system variables are given in the text.
proofs is simplified due to the structure of the particular system studied here. For the general systems studied in Refs. 23–25, the continuity (and hence differentiability) of the Poincaré maps can be compromised when the dynamics permit trajectories that ‘‘graze’’ switching sets tangentially at various points and do not cross them at those points. This scenario is impossible in the present system, however, as the (s,p) trajectories are monotonically increasing in p as they approach the switching set p=1 in the H state, and are monotonically decreasing in p as they approach p=ε in the L state. Thus continuity of the Poincaré maps is assured.

ACKNOWLEDGMENTS

This research was supported by an Institute for Mathematics and its Applications Postdoctoral Fellowship with funds provided by the National Science Foundation (NSF), and by NSF Grant No. CHE-9996223. We would like to thank Professor George R. Sell for fruitful discussions, and Mr. Subbarao Varigonda for introducing us to the relay feedback control literature.

13When k + a = β_H, p(t) = β_H + e^(−β_L(t−τ_0))(p(τ_0)−β_H) + k(τ−τ_0) × e^(-k+1s(t−τ_0))s(τ_0)−s_0 replaces the p(t) equation in (3.1). When k + α = β_L, p(t) = β_L + e^(−β_L(t−τ_0))(p(τ_0)−β_L) + k(τ−τ_0)e^(-k+1s(t−τ_0)) × s(τ_0)−s_0 replaces the p(t) equation in (3.2). Proofs for these special cases are simple (but technically tedious) extensions of the logic applied below, and therefore are not included.
14As noted in Ref. 13, we only consider the case in which (k+1)/β_H≠1.