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A Stability Property of Nonlinear Systems with Inputs Having Slowly Varying Average and Its Application to HIV Problem

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Abstract— **In this paper, a stability property is proved for a class of three-time-scale systems, which is induced by a time-varying input that is highly oscillatory but, on average, is slowly-varying. We show a practical stability for such systems in the sense that if the ratios of time-scales are sufficiently large, the systems still remain close to the point that is an equilibrium of the average of the input. As an application, a drug dose control problem for the AIDS treatment is considered. The main result asserts that the long-term planning of drug dose is still effective under the short-term variation of drug effect in a body.**

I. Introduction

In the early 1990s, Kelemen [1], Lawrence and Rugh [2], and Khalil and Kokotović [3] have presented a stability property of nonlinear systems with slowly varying inputs, which can now be found in a graduate textbook such as [4]. The goal of this paper is to extend the result of [1–3] in the sense that the same stability property is established under inputs having slowly varying 'average.' In other words, we consider an input that may not be slowly varying itself, but whose average is slowly varying.

To be concrete, let us consider a dynamical system given by

$$\dot{x} = f(x, u), \tag{1}$$

where $f(\cdot,\cdot)$ is continuously differentiable, $x \in \mathbb{R}^n$, $u \in \Gamma \subset \mathbb{R}^m$ in which Γ is a connected compact set. Suppose that, for each *frozen* (i.e., constant) input $u \in \Gamma$, there exists a corresponding equilibrium $x^*(u)$ such that $f(x^*(u), u) = 0$. Suppose also that, for any two (constant) inputs u_1 and u_2 contained in Γ, we want to drive the state $x(t)$, which is initially located in a neighborhood of $x^*(u_1)$, into a neighborhood of $x^*(u_2)$. This problem has been dealt with in [1–3], where it is proved that, if there exists a curve $\mathcal{U}$ in Γ that connects two points u_1 and u_2 and, for each fixed $\bar{u}$ on the curve $\mathcal{U}$, the corresponding equilibrium $x^*(\bar{u})$ is locally exponentially[1] stable, then, by changing $u(t)$ sufficiently slowly from u_1 to u_2 along the curve $\mathcal{U}$, the state $x(t)$ that is close to the point $x^*(u_1)$ can be driven into a small neighborhood of $x^*(u_2)$. In this paper, it is asserted that, for the same result, slowly varying $u(t)$ is not necessary but it is sufficient that the average of $u(t)$ is slowly varying along the curve $\mathcal{U}$ if the oscillation of $u(t)$ is sufficiently fast.

In practice, there are several occasions where the slowly-varying-average-input assumption is more suitable than the slowly-varying-input assumption. A classical example of the slowly-varying-average-input is the PWM (pulse-width modulation) control whose net effect is the average of instantaneous control inputs. Another example is the drug dose control for a patient (that will be presented in Section III). In fact, the drug effect in the body reaches its maximum immediately after a patient takes the medicine and then is going down until the patient takes another next time. However, since it is too complicated to consider the instantaneous variation of the drug effect, a long-term planning of drug dose schedule does not usually take it into account assuming that the net effect of the drug will be the average of instantaneous drug effect. In this paper, we will demonstrate an application of the proposed analysis into a treatment of HIV[2] infected patient in Section III after presenting our main result in Section II.

II. Main Result

To effectively describe the system under consideration, we suppose that the system is given by

$$\dot{x}(t) = f(x(t), u_a(t), u_f(\frac{1}{\epsilon}t)), \quad u_a \in \mathbb{R}^m,\ u_f \in \mathbb{R}^l, \tag{2}$$

where $f(\cdot,\cdot,\cdot)$ is continuously differentiable, $u_a(\cdot)$ is locally Lipschitz, and $u_f(\cdot)$ is a uniformly bounded measurable function. The small positive parameter ϵ (to be specified) indicates that the function u_f varies fastly. In fact, we are going to rely on three-time scale behavior of the system by specifying ϵ sufficiently small so that u_f oscillates sufficiently fast and by specifying the upper bound of the derivative of u_a (i.e., $\|\frac{du_a}{dt}\| \le \kappa$ almost everywhere[3] with κ sufficiently small) so that u_a varies sufficiently slowly, relatively to the behavior of the system state $x(t)$.

Let $B_r(x)$ ($\bar{B}_r(x)$) denote the open (closed) ball centered at x with the radius $r > 0$.

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[1]Local exponential stability is easily relaxed to local asymptotic stability in [3] once the region of attraction of each $x^*(\bar{u})$ does not vanish along the curve $\mathcal{U}$. The latter property has been coined as 'NvBA (Non-vanishing Basin of Attraction) stability' and a verification method of it is proposed in [5].

[2]Human Immunodeficiency Virus, which is known to cause AIDS (Acquired Immune Deficiency Syndrome).

[3]By the Rademacher's theorem, a locally Lipschitz function has its derivative almost everywhere.

Assumption 1: For the uniformly bounded measurable function $u_f(\cdot)$, there is a non-empty open set $S \subset \mathbb{R}^n \times \mathbb{R}^m$ on which the function $f(x, u_a, u_f(\cdot))$ has the *general average*; that is, for each $(x, u_a) \in S$, there exists the limit

$$f_{av}(x, u_a) := \lim_{T\to\infty} \frac{1}{T} \int_t^{t+T} f(x, u_a, u_f(s))ds, \quad {}^\forall t \geq 0.$$

Moreover, for each compact set $D \subset S$, there is a strictly decreasing continuous function $\sigma_D : [0, \infty) \to [0, \infty)$ such that $\sigma_D(T) \to 0$ as $T \to \infty$, satisfying

$$\left\| \frac{1}{T} \int_t^{t+T} f(x, u_a, u_f(s))ds - f_{av}(x, u_a) \right\| \leq \sigma_D(T)$$

for all $(x, u_a) \in D$ and $t, T \geq 0$. ◊

Remark 1: It is well-known that if $u_f(\cdot)$ is a periodic function with a period T, then the function f_{av} becomes the natural average (i.e., $f_{av}(x, u_a) = (1/T) \int_0^T f(x, u_a, u_f(s))ds$) well-defined on $S = \mathbb{R}^n \times \mathbb{R}^m$, and the convergence function $\sigma_D(T)$ is given as the form of $k/(1+T)$ where $k > 0$ depending on the set D. ◊

Remark 2: A system having an input $u(t)$ whose average is slowly varying can be seen as

$$\dot{x}(t) = f(x(t), u(t)) = f(x(t), u_a(t) + u_f(\frac{1}{\epsilon}t))$$

where $u_a(t)$ is slowly varying and the function $u_f(\cdot)$ has zero average in a certain sense. In this way, this system is cast into (2). ◊

Now we formally assume the stability property of the averaged system with *frozen* input u_a as follows.

Assumption 2: For the function $u_a(\cdot)$, the range Γ of $u_a(\cdot)$ (i.e., $u_a : [0, \infty) \to \Gamma \subset \mathbb{R}^m$) is compact, and the averaged system

$$\dot{x} = f_{av}(x, u_a) \tag{3}$$

has an isolated equilibrium $x^*(u_a)$ for each constant input $u_a \in \Gamma$ such that $x^*(\cdot)$ is continuous and $(x^*(u_a), u_a) \in S$. Moreover, each equilibrium $x^*(u_a)$ is locally asymptotically stable with the property that the region of attraction of each $x^*(u_a)$ for $u_a \in \Gamma$ contains an open ball of radius $r > 0$, centered at $x^*(u_a)$, where r is independent of u_a. Specifically it is assumed that there exist a C^1 function $V : \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}$ and a positive number r such that, for all $u_a \in \Gamma$ and all $x \in \bar{B}_r(x^*(u_a))$, it holds that $(x, u_a) \in S$ and

$$\alpha_1(\|x - x^*(u_a)\|) \leq V(x, u_a) \leq \alpha_2(\|x - x^*(u_a)\|), \tag{4}$$

$$\frac{\partial V}{\partial x} f_{av}(x, u_a) \leq -\alpha_3(\|x - x^*(u_a)\|), \tag{5}$$

where $\alpha_i(\cdot)$, $i = 1, 2, 3$, are class-$\mathcal{K}$ functions. ◊

Remark 3: In this assumption, it should be also noted that the region of attraction for each $x^*(u_a)$ does not vanish as u_a varies on Γ. For example, the equilibrium $x^*(u_a) = u_a$ of the system $\dot{x} = -x(x^2 - u_a^2)$ is locally asymptotically stable for each $u_a \in \Gamma = [0, 1]$, but it does not have such $r > 0$ of the assumption. One sufficient condition for ruling out this defect is the local exponential stability of $x^*(u_a)$ for each $u_a \in \Gamma$. Refer to [4, Lem. 9.8], or for more discussion, to [5]. ◊

Theorem 1: Consider the system (2) under Assumptions 1 and 2. Given a positive number ρ, there exist positive numbers ϵ^*, κ and δ such that, if $u_a(\cdot)$ is locally Lipschitz and

$$\left\| \frac{du_a}{dt}(t) \right\| \leq \kappa, \qquad \text{almost everywhere,} \tag{6}$$

so that the input $u_a(t)$ varies sufficiently slowly, and $0 < \epsilon < \epsilon^*$ so that the input $u_f(\frac{1}{\epsilon}t)$ varies sufficiently fastly, then the state $x(t)$ initiated in a neighborhood of $x^*(u_a(0))$ such that $\|x(0) - x^*(u_a(0))\| \leq \delta$ stays in a neighborhood of $x^*(u_a(t))$, that is,

$$\|x(t) - x^*(u_a(t))\| \leq \rho, \qquad {}^\forall t \geq 0.$$

◊

Proof: First of all, let us define a compact set (in $\mathbb{R}^n \times \mathbb{R}^m$) of our interest as

$$D := \left\{ (y, u_a) \in \mathbb{R}^n \times \Gamma : y \in \bar{B}_r(x^*(u_a)) \right\}.$$

For each $(y, u_a) \in D$, let

$$f_p(y, u_a, u_f) := f(y, u_a, u_f) - f_{av}(y, u_a).$$

Note that, with this construction,

$$\frac{1}{T} \left\| \int_t^{t+T} f_p(y, u_a, u_f(s))ds \right\| \leq \sigma_D(T), \quad {}^\forall t, T \geq 0.$$

Now define

$$w(y, u_a, \tau, \epsilon) := \int_0^\tau f_p(y, u_a, u_f(s)) \exp[-\epsilon(\tau - s)]ds.$$

Then, it can be shown (like in [4, p. 416]) that there exists a class $\mathcal{K}$ function α such that

$$\epsilon \|w(y, u_a, \tau, \epsilon)\| \leq \alpha(\epsilon), \tag{7}$$

$$\epsilon \left\| \frac{\partial w}{\partial y}(y, u_a, \tau, \epsilon) \right\| \leq \alpha(\epsilon), \tag{8}$$

$$\epsilon \left\| \frac{\partial w}{\partial u_a}(y, u_a, \tau, \epsilon) \right\| \leq \alpha(\epsilon), \tag{9}$$

for all $(y, u_a, \tau, \epsilon) \in D \times [0, \infty) \times [0, \infty)$.

By way of w, a (time-varying) C^1 coordinate change between x and y is constructed as

$$x = y + \epsilon w(y, u_a, t/\epsilon, \epsilon). \tag{10}$$

In fact, there exists an $\epsilon_1 > 0$ such that, for each $(u_a, t, \epsilon) \in \Gamma \times [0, \infty) \times [0, \epsilon_1]$, the map (10) is C^1 and bijective for all $y \in \bar{B}_r(x^*(u_a))$. According to [8, Thm. 1], this is verified by showing that the Jacobian of the map (with respect to y) is nonsingular and that the ratio of each leading principal minor of the Jacobian is strictly positive on $\bar{B}_r(x^*(u_a))$.

Indeed, because the Jacobian of (10) is $I + \epsilon\frac{\partial w}{\partial y}$ (and the leading principal minors are in the order[4] of $1 + O(\alpha(\epsilon))$), both conditions are satisfied with ϵ small enough by (8).

Now, differentiating both sides of the equation (10) with respect to time, we have the following relation

$$\begin{aligned}\dot{x}(t) = \dot{y}(t) &+ \epsilon\frac{\partial w}{\partial y}(y(t), u_a(t), t/\epsilon, \epsilon)\dot{y}(t)\\ &+ \epsilon\frac{\partial w}{\partial u_a}(y(t), u_a(t), t/\epsilon, \epsilon)\dot{u}_a(t)\\ &+ \epsilon\frac{\partial w}{\partial \tau}(y(t), u_a(t), t/\epsilon, \epsilon)\frac{1}{\epsilon}.\end{aligned}$$

The above equation is rearranged as follows:

$$\begin{aligned}&\left[I + \epsilon\frac{\partial w}{\partial y}(y(t), u_a(t), t/\epsilon, \epsilon)\right]\dot{y}(t)\\ &= \dot{x}(t) - \epsilon\frac{\partial w}{\partial u_a}(y(t), u_a(t), t/\epsilon, \epsilon)\dot{u}_a(t)\\ &\quad - \frac{\partial w}{\partial \tau}(y(t), u_a(t), t/\epsilon, \epsilon)\\ &= f(x(t), u_a(t), u_f(t/\epsilon)) - \epsilon\frac{\partial w}{\partial u_a}(y(t), u_a(t), t/\epsilon, \epsilon)\dot{u}_a(t)\\ &\quad - f_p(y(t), u_a(t), u_f(t/\epsilon)) + \epsilon w(y(t), u_a(t), t/\epsilon, \epsilon)\\ &= f_{av}(y(t), u_a(t)) - \epsilon\frac{\partial w}{\partial u_a}(y(t), u_a(t), t/\epsilon, \epsilon)\dot{u}_a(t)\\ &\quad + f(x(t), u_a(t), u_f(t/\epsilon)) - f(y(t), u_a(t), u_f(t/\epsilon))\\ &\quad + \epsilon w(y(t), u_a(t), t/\epsilon, \epsilon)\\ &= f_{av}(y, u_a) + p_0(y, u_a, t, \epsilon)\dot{u}_a + p_1(y, u_a, u_f, t, \epsilon)\end{aligned}$$

where

$$\begin{aligned}p_0(y, u_a, t, \epsilon) &= -\epsilon\frac{\partial w}{\partial u_a}(y, u_a, t/\epsilon, \epsilon)\\ p_1(y, u_a, u_f, t, \epsilon) &= [f(y + \epsilon w, u_a, u_f) - f(y, u_a, u_f)]\\ &\quad + \epsilon w(y, u_a, t/\epsilon, \epsilon)\\ &= \bar{f}(y, u_a, u_f, \epsilon w)\epsilon w + \epsilon w(y, u_a, t/\epsilon, \epsilon)\end{aligned}$$

in which, $\bar{f}$ is a matrix of continuous functions whose existence follows from the continuous differentiability of f. Then, from (7) and (9), it holds that

$$\|p_0(y, u_a, t, \epsilon)\| \le \alpha(\epsilon) \tag{11}$$

$$\|p_1(y, u_a, u_f(t/\epsilon), t, \epsilon)\| \le (c_f + 1)\alpha(\epsilon) \tag{12}$$

for all $(y, u_a) \in D$, $t \in [0, \infty)$ and $\epsilon \in [0, \epsilon_1]$, where

$$c_f = \sup_{(y,u_a)\in D,\, 0\le\tau,\, 0\le\epsilon w\le\alpha(\epsilon_1)} \|\bar{f}(y, u_a, u_f(\tau), \epsilon w)\|$$

($c_f < \infty$ since $\bar{f}$ is continuous and $u_f(\cdot)$ is uniformly bounded).

Remark 4: The uniform bound of $u_f(\cdot)$ is used only for obtaining the finite c_f. Therefore, the boundedness of $u_f(\cdot)$ can be relaxed if the above c_f is finite regardless of u_f; e.g., the case when the system is affine with respect to the input u_f and the input vector field is constant so that $\bar{f}$ does not depend on u_f. ◊

The time derivative of V of Assumption 2 along the system in y-coordinates is given by

$$\begin{aligned}\dot{V}(y, u_a) &= \frac{\partial V}{\partial y}\dot{y}(t) + \frac{\partial V}{\partial u_a}\dot{u}_a(t)\\ &= \frac{\partial V}{\partial y}\left[I + \epsilon\frac{\partial w}{\partial y}\right]^{-1}(f_{av} + p_0\dot{u}_a + p_1) + \frac{\partial V}{\partial u_a}\dot{u}_a\\ &= \frac{\partial V}{\partial y}f_{av} + \frac{\partial V}{\partial y}\left(\left[I + \epsilon\frac{\partial w}{\partial y}\right]^{-1} - I\right)f_{av}\\ &\quad + \frac{\partial V}{\partial y}\left[I + \epsilon\frac{\partial w}{\partial y}\right]^{-1}(p_0\dot{u}_a + p_1) + \frac{\partial V}{\partial u_a}\dot{u}_a.\end{aligned}$$

Since $[I + \epsilon(\partial w)/(\partial y)]^{-1} = I - \epsilon(\partial w)/(\partial y) + \cdots$, it is seen that, for $\epsilon < \alpha^{-1}(1)$,

$$\left\|\left[I + \epsilon\frac{\partial w}{\partial y}\right]^{-1}\right\| \le \frac{1}{1 - \alpha(\epsilon)},$$

$$\left\|\left[I + \epsilon\frac{\partial w}{\partial y}\right]^{-1} - I\right\| \le \frac{\alpha(\epsilon)}{1 - \alpha(\epsilon)}.$$

Also, let

$$\begin{aligned}c_v &= \max_{(y,u_a)\in D}\left\|\frac{\partial V}{\partial y}(y, u_a)\right\|\\ c_w &= \max_{(y,u_a)\in D}\left\|\frac{\partial V}{\partial u_a}(y, u_a)\right\|\\ c_a &= \max_{(y,u_a)\in D}\|f_{av}(y, u_a)\|.\end{aligned}$$

Then, we obtain, from Assumption 2, (11) and (12),

$$\begin{aligned}\dot{V}(y(t), u_a(t)) \le &-\alpha_3(\|y(t) - x^*(u_a(t))\|)\\ &+ c_v\frac{\alpha(\epsilon)}{1 - \alpha(\epsilon)}c_a + c_v\frac{1}{1 - \alpha(\epsilon)}\alpha(\epsilon)\|\dot{u}_a(t)\|\\ &+ c_v\frac{1}{1 - \alpha(\epsilon)}(c_f + 1)\alpha(\epsilon) + c_w\|\dot{u}_a(t)\|\end{aligned}$$

on D, almost everywhere in t.

Now, without loss of generality, suppose that the given number $\rho \le r$. Take a pair of positive numbers (ϵ_2, κ) such that

$$\frac{\alpha(\epsilon_2)}{1 - \alpha(\epsilon_2)}c_v(c_a + \kappa + c_f + 1) + c_w\kappa \le (\alpha_3 \circ \alpha_2^{-1} \circ \alpha_1)(\frac{\rho}{2}).$$

Then,

$$\dot{V} \le -\alpha_3(\alpha_2^{-1}(V)) + (\alpha_3 \circ \alpha_2^{-1} \circ \alpha_1)(\frac{\rho}{2}),$$

which implies that, if $V(y(0), u_a(0)) \le \alpha_1(\rho/2)$, then $V(y(t), u_a(t)) \le \alpha_1(\rho/2)$ for all $t \ge 0$. Therefore, letting $\delta = (\alpha_2^{-1} \circ \alpha_1)(\frac{\rho}{2})$, we have

$$\|y(t) - x^*(u_a(t))\| \le \frac{\rho}{2},$$

[4]The order of magnitude notation $\mathcal{O}$ is used as follows: $\delta_1(\epsilon) = \mathcal{O}(\delta_2(\epsilon))$ if there exist $k > 0$ and $c > 0$ such that $|\delta_1(\epsilon)| \le k|\delta_2(\epsilon)|$, $^\forall|\epsilon| < c$.

for all $t \geq 0$ if $\|y(0) - x^*(u_a(0))\| \leq \delta$ and $\epsilon < \min\{\epsilon_1, \epsilon_2, \alpha^{-1}(1)\}$.

So far, the analysis has been done in y-coordinates, that is, we have found a bound for initial conditions, and upper bounds for $\|\dot{u}_a\|$ and ϵ so that the state $y(t)$ remains in $\bar{B}_{\frac{\rho}{2}}(x^*(u_a(t)))$ for all $t \geq 0$.

Now it is left to verify the claim of the theorem in x-coordinates. From (10), $x(0) = y(0)$. Thus, if $\|x(0) - x^*(u_a(0))\| \leq \delta$, then $\|y(t) - x^*(u_a(t))\| \leq \frac{\rho}{2}$ and $(y(t), u_a(t)) \in D$ for all $t \geq 0$, which implies that

$$\begin{aligned}\|x(t) - x^*(u_a(t))\| &\leq \|x(t) - y(t)\| + \|y(t) - x^*(u_a)\| \\ &\leq \|\epsilon w(y(t), u_a(t), t/\epsilon, \epsilon)\| + \frac{\rho}{2} \\ &\leq \alpha(\epsilon) + \frac{\rho}{2}.\end{aligned}$$

Therefore, we finally set

$$\epsilon^* = \min\{\epsilon_1, \epsilon_2, \alpha^{-1}(1), \alpha^{-1}(\frac{\rho}{2})\},$$

and we have

$$\|x(t) - x^*(u_a(t))\| \leq \rho,$$

for all $t \geq 0$.

■

III. An Example: Control of HIV Infection

In this section, we analyze the consequence of the fluctuation of drug effect for the treatment of AIDS. The following dynamic system (taken from [9]) is a model for the HIV infection:

$$\begin{aligned}\dot{x}(t) &= \lambda - dx(t) - (1 - \eta^* u(t))\beta y(t)x(t) \\ \dot{y}(t) &= (1 - \eta^* u(t))\beta y(t)x(t) - ay(t) - pz(t)y(t) \\ \dot{w}(t) &= cx(t)y(t)w(t) - cqy(t)w(t) - bw(t) \\ \dot{z}(t) &= cqy(t)w(t) - hz(t),\end{aligned} \tag{13}$$

where the state variable represents the population of indivisual immunocytes[5]: uninfected CD4 T-helper cell (x), infected CD4 T-helper cell (y), memory CTL precursor (w), and memory CTL effector (z), to be precise; and $u(t)$ represents the drug dosage whose value is between 0 and 1. All the other parameters such as λ, d, and so on are positive constants. For the details, refer to [9] or [7].

Based on the model, a possible treatment of AIDS has been proposed in [9], which can be translated into a control problem; that is, drive any initial state located in $\mathbb{R}_{>0} \times \mathbb{R}_{>0} \times \mathbb{R}_{>0} \times \mathbb{R}_{>0}$ into a neighborhood of (x^*, y^*, w^*, z^*) where

$$x^* = \frac{[c(\lambda + dq) - b\beta] + \sqrt{[c(\lambda + dq) - b\beta]^2 - 4c^2\lambda qd}}{2cd},$$

$$y^* = \frac{b}{c(x^* - q)}, \quad w^* = \frac{hz^*}{cqy^*}, \quad z^* = \frac{\beta x^* - a}{p}.$$

[5]An immunocyte is a cell of the lymphoid series which can react with antigen to produce antibody or to become active in cell-mediated immunity or delayed hypersensitivity reactions; called also immunologically competent cell.

(In fact, this is one of four equilibria of the model with $u = 0$ and is the so-called 'non-progressor' whose clinical meaning is that the patient has HIV but his/her immune system can still work. See, again, [9] or [7].) This control problem has been solved in [7] by the simple law—apply maximum dose of drug ($u = 1$) for a while and then reduce the dose sufficiently slowly until the dose becomes zero ($u = 0$). See Fig. 3(a) and its simulation result in Fig. 1.

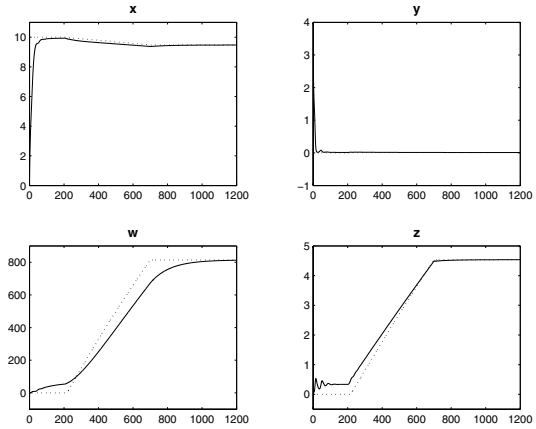


Fig. 1. Simulation result of slowly varying input of Fig. 3(a) for 1,200 days with $\lambda = 1$, $d = 0.1$, $\beta = 0.5$, $a = 0.2$, $p = 1$, $c = 0.1$, $q = 0.5$, $b = 0.01$, $h = 0.1$, $\eta^* = 0.9958$ and with the initial condition $x(0) = 0.53$, $y(0) = 3.59$, $w(0) = 0.036$, $z(0) = 0.064$. The target point (x^*, y^*, w^*, z^*) is $(9.47, 0.0111, 814, 4.54)$ and indicated by dotted lines. These are taken from [9].

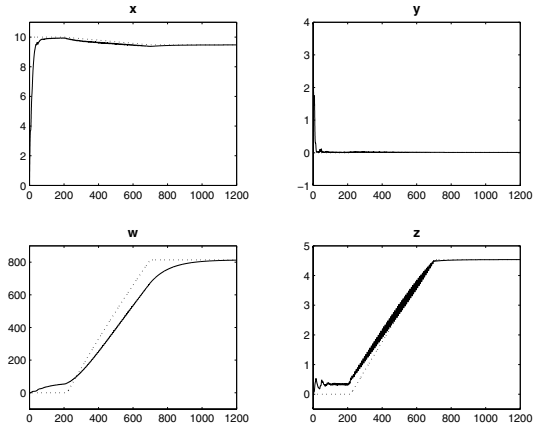
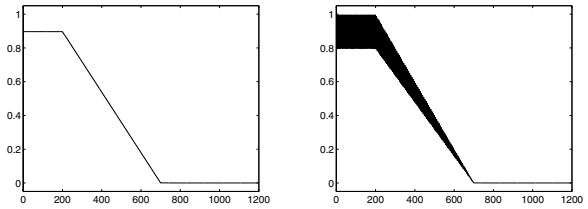


Fig. 2. Simulation result of slowly-varying-average input of Fig. 3(b) with the same parameters and the same initial condition.

Unfortunately, this scheme (i.e., slow reduction of dose) did not consider the drug delivery mechanism. Although the scheme says that sufficient slow variation of dose (e.g., in Fig. 3(a), it takes about 500 days from 1 to 0) guarantees driving into a neighborhood of the target equilibrium, the real drug effect in cells changes relatively rapidly because it goes high immediately after the medicine is injected and it diminishes gradually until the next medicine. This brings



(a) Drug dosage reduces slowly.

(b) The average of drug dosage reduces slowly.

Fig. 3. Plot of drug dose input. (a) Slowly varying input (slow reduction of drug dose) proposed in [7]. For a fair comparison of Figs. 1 and 2, the dose of initial phase until 200 days is not 1 but 0.9 that is the average of the fluctuated drug effect (14). (b) Fastly varying input having slowly varying average. Oscillation of $u(t)$ presumes that a patient takes the drug approximately every 8 days.

about a fast (compared to the long-term reduction of the drug dose) fluctuation of dose effect, which violates the key assumption of [7]. However, Theorem 1 justifies the slow reduction scheme by saying that if the *average* of instantaneous drug effect is slowly varying then the slow reduction scheme of [7] is still valid.

To see this, we first assume that the real drug effect is modeled by

$$u(t) = u_a(t)(1 + u_f(t)), \tag{14}$$

where $u_a(t)$ is the function used in Fig. 3(a), and $u_f(t)$ represents the fluctuation of drug effect. For example, we simply use a function $u_f(t) = \frac{1}{9}\sin(\frac{\pi}{4}t)$ whose average is zero, assuming that a patient takes medicine every eight days. In fact, the input u_f need not be periodic considering the fact that a patient may take medicine somewhat irregularly, and even in this case Theorem 1 can still be applied once the function u_f satisfies the general averaging condition of Assumption 1.

With the input (14), the system (13) satisfies Assumption 1 with $S = \mathbb{R}^5$ and $\sigma_D(T) = \frac{k}{T+1}$, $k > 0$ (see Remark 1). In addition, because the averaged system is the system (13) with the input u replaced by u_a, the result of [7] guarantees Assumption 2, where the necessary property of Assumption 2 (i.e., non-vanishing basin of attraction discussed in Remark 3) has been formally proved with a Lyapunov function V.

Fig. 2 shows a simulation result for 1,200 days under the input of (14) (Fig. 3(b)). In the figure, the dashed line illustrates the curve of the equilibria obtained by (13) with $u = u_a(t)$ (considered as a frozen parameter) and it can be seen that the solution trajectory still tracks the dashed line approximately.

IV. Conclusion

The problem of driving the state along the curve of asymptotically stable equilibria obtained by each frozen input was solved in the literature using a sufficiently slowly varying input. In this paper, we have shown that, for the same result, the input itself need not be slowly-varying and it is enough to have a slowly-varying-average input. Furthermore, the result has been used to show that a long-term planning of drug dose for AIDS treatment can be validated still under a short-term variation of real drug effect once the fluctuation of drug effect is sufficiently fast yielding the slowly varying average.

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