Feedback Linearization Control and Its Application to MIMO Cancer Immunotherapy

Ting-Li Chien, Chung-Cheng Chen, and Chiou-Jye Huang

***Abstract*—The study proposes a novel feedback linearization and almost disturbance decoupling control of nonlinear multiple-input–multiple-output (MIMO) systems. The goal of cancer immunotherapy is focused on eliciting an immune system response against the tumor. The study investigates a novel feedback linearization control strategy of nonlinear MIMO tumor-immune system. The main contributions of this study are to construct a control strategy such that the resulting closed-loop system is valid for any initial condition with almost disturbance decoupling performance and develop the feedback linearization design for the control of a MIMO cancer model system to improve the cancer load. The performances of drug treatment based on our proposed novel nonlinear geometric feedback control are better than some existing approaches. The numerical results derived by our method imply the tumor load to be reduced to the zero value only after more short days of drug treatment and the recurrence cycle of tumor dynamics not to be existent. All the state variables of the cancer model system can be measured using the Cellometer Auto T4 Cell Counter, programmable research micro-pump and computer with Java program in the clinical study. Electrically automatic apparatus for providing antiretroviral drugs could be constructed based on the quantification of the immune variables.**

***Index Terms*—Almost disturbance decoupling, cancer model, effector cell, feedback linearization approach, tumor cell.**

I. Introduction

CANCER is still a significant cause of death in the human world, yet much is still not known about its dynamics of establishment and destruction. While surgery, radiotherapies, and chemotherapies have played main roles in cancer treatment, it is obvious to see that in many cases they do not represent a true cure. Even when patients go through tumor regression, later relapse will occur. Both preventive measures and more effective treatment strategies are necessary to be addressed. Research along these lines is now being proposed through immunotherapy [18]. Immunotherapy refers to making use of cytokines, usually together with adoptive cellular immunotherapy (ACI). During the process of ACI, T-cells are acquired from cancer patients, then grown and activated in a manner that stimulates them to react to some certain class of antigens. These T-cells are then infused into the patient. The adopted T-cells invade the tumor site and immunologically reject it. Cytokines are inherently protein hormones that mediate both natural and specific immunity. They are created mainly by activated T cells during cellular-mediated immunity. Interleukin-2 (IL-2) is the main cytokine taking keen sense of responsibility for lymphocyte activation, growth, and differentiation. It is created by CD4+ T cells, and in lesser quantities by CD8+ T cells. Clinical trials have shown that IL-2 can enhance activity of CD8+ T cells at different disease stages [25]. ACI injects cultured immune cells that have anticancer reactivity into the tumor host in conjunction with large amounts of IL-2. This can adopt two approaches: 1) lymphokine-activated killer cell (LAK) therapy: These cells are acquired from the *in vitro* culturing with high concentrations of IL-2 of peripheral blood leukocytes removed from patients. The LAKs are then injected back at the cancer site. 2) Tumor infiltrating lymphocyte (TIL) therapy: These cells are acquired from lymphocytes recovered from the patient tumors. They are then incubated with high concentrations of IL-2 *in vitro* and injected back into the patient at the tumor site.

Nowadays, the treatment depends on the medical experience and the patient response to the therapy fundamentally. These problems have limited the wide application in real therapies. All of these drawbacks could be solved if better control strategies are proposed. A great number of researches have attempted to develop mathematical models of untreated or treated tumor growth with varying levels of complexity from the cellular to the macroscopic scale [2]. These models are represented by a set of relatively complex nonlinear differential equations that model the immune system and the long-term interaction with the tumor cell. The nonlinear control method then works for a general nonlinear system and can be applied to find the optimal schedule in a variety of medical treatments. [23] has applied the optimal control theory to find the optimal schedule of injections of an immunotherapeutic agent against cancer. In [10], an optimal control problem is formulated and solved for both the models so as to obtain the chemotherapeutic schedule that minimizes the final tumor size while taking into account the constraints on drug resistance and toxicity. The goal of [27] is to describe the spontaneous regression and the development of cancer system as a prey–predator like system. [9] proposes the phase-space analysis for mathematical models of tumor growth with an immune response and chemotherapy. During the past decade, significant progress has been made in the research of control approaches for nonlinear systems based on the feedback linearization theory [15]. Moreover, feedback linearization approach has been applied successfully to address many real controls [1], [28].

Neural network feedback linearization (NNFBL) was first investigated in [4] and extensively addressed in [5]. [13] obtains the best published result in a cancer chemotherapy problem using NNFBL. NNFBL can be applied to complicated pharmacogenomics systems to find adequate drug dosage regimens [11] and extensively addressed in [12] and [14].

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The aim of [24] is to propose a control strategy of the tumor cells via the optimal control on a fundamental mathematical tumor model. Its result shows that the amount of tumor cells doesn't reach the zero value. Exploring three immunotherapeutic scenarios (CTL therapy, IL-2 therapy, and combined therapy), [3] displays the stability and efficacy of the optimization approach. However, the tumor size cannot be eliminated completely, and the recurrence cycle is about 100 days. On the contrary, based on our proposed approach in this study, the effector cell population can be kept in 1.9×10^4 cells/mL, and the tumor load is reduced to the zero value only after 450 days of drug treatment. Moreover, the recurrence cycle is not existent. We employ feedback linearization control methods to search treatment protocols that are improvements to the standard protocols in use today.

II. Controller Design

We consider the following nonlinear control system with uncertainties and disturbances:

$$\dot{X}(t)=f(X(t))+g(X(t))\,u+\sum_{j=1}^{p}q_j^*\theta_j \tag{2.1a}$$

$$y(t)=h(X(t)) \tag{2.1b}$$

where $X(t)\equiv[x_1(t)x_2(t)\cdots x_n(t)]^T\in\Re^n$ is the state vector, $u\equiv[u_1\ u_2\cdots u_m]^T\in\Re^m$ is the input vector, $y\equiv[y_1\ y_2\cdots y_m]^T\in\Re^m$ is the output vector, $\theta\equiv[\theta_1(t)\ \theta_2(t)\cdots\theta_p(t)]^T$ is a bounded time-varying disturbances vector, and $f\equiv[f_1\ f_2\cdots f_n]^T\in\Re^n$, $g\equiv[g_1\ g_2\cdots g_m]\in\Re^{n\times m}$ and $h\equiv[h_1\ h_2\cdots h_m]^T\in\Re^m$ are smooth vector fields. The nominal system is then defined as follows:

$$\dot{X}(t)=f(X(t))+g(X(t))\,u \tag{2.2a}$$

$$y(t)=h(X(t)). \tag{2.2b}$$

The nominal system of the form (2.2) is assumed to have the vector relative degree $\{r_1,r_2,\cdots,r_m\}$ [15], i.e., the following conditions are satisfied for all $X\in\Re^n$:

(i)

$$L_{g_j}L_f^k h_i(X)=0 \tag{2.3}$$

for all $1\le i\le m$, $1\le j\le m$, $k<r_i-1$, where the operator L is the Lie derivative [15] and $r_1+r_2+\cdots+r_m=r$.

(ii) The $m\times m$ matrix

$$A\equiv\begin{bmatrix} L_{g_1}L_f^{r_1-1}h_1(X) & \cdots & L_{g_m}L_f^{r_1-1}h_1(X)\\ L_{g_1}L_f^{r_2-1}h_2(X) & \cdots & L_{g_m}L_f^{r_2-1}h_2(X)\\ \vdots & & \vdots\\ L_{g_1}L_f^{r_m-1}h_m(X) & \cdots & L_{g_m}L_f^{r_m-1}h_m(X)\end{bmatrix} \tag{2.4}$$

is nonsingular. The desired output trajectory y_d^i, $1\le i\le m$ and its first r_i derivatives are all uniformly bounded and

$$\left\|\left[y_d^i,y_d^{i\,(1)},\cdots,y_d^{i\,(r_i)}\right]\right\|\le B_d^i,\quad 1\le i\le m \tag{2.5}$$

where B_d^i is some positive constant. Under the assumption of well-defined vector relative degree, it has been shown [15] that the mapping

$$\phi:\Re^n\to\Re^n \tag{2.6}$$

defined as

$$\begin{aligned}\xi_i&\equiv\left[\xi_1^i\ \xi_2^i\ \cdots\ \xi_{r_i}^i\right]^T\equiv\left[\phi_1^i\ \phi_2^i\ \cdots\ \phi_{r_i}^i\right]^T\\&\equiv\left[L_f^0h_i(X)\ L_f^1h_i(X)\ \cdots\ L_f^{r_i-1}h_i(X)\right]^T\end{aligned} \tag{2.7}$$

$$\phi_k(X(t))\equiv\eta_k(t),\quad k=r+1,r+2,\cdots,n \tag{2.8}$$

and satisfying

$$L_{g_j}\phi_k(X(t))=0,\quad k=r+1,r+2,\cdots,n,\quad 1\le j\le m \tag{2.9}$$

is a diffeomorphism onto image, if

(i) the distribution

$$G\equiv\operatorname{span}\{g_1,g_2,\cdots,g_m\} \tag{2.10}$$

is involutive.

(ii) the vector fields

$$Y_j^k,\quad 1\le j\le m,\quad 1\le k\le r_j \tag{2.11}$$

are complete, where

$$Y_j^k\equiv(-1)^{k-1}ad_{\widetilde{f}}^{k-1}\widetilde{g}_j,\ \ 1\le j\le m,\ \ 1\le k\le r_j \tag{2.12}$$

$$\widetilde{f}(X)\equiv f(X)-g(X)A^{-1}(X)b(X) \tag{2.13}$$

$$b(X)\equiv\left[L_f^{r_1}h_1(x)\ \ L_f^{r_2}h_2(x)\ \ \cdots\ \ L_f^{r_m}h_m(x)\right]^T \tag{2.14}$$

$$\widetilde{g}\equiv[\widetilde{g}_1\ \ \widetilde{g}_2\ \ \cdots\ \ \widetilde{g}_m]\equiv g(X)A^{-1}(X) \tag{2.15}$$

$$ad_f^kg\equiv\left[f\ \ ad_f^{k-1}g\right] \tag{2.16}$$

$$[f\ \ g]\equiv\frac{\partial g}{\partial X}f(X)-\frac{\partial f}{\partial X}g(X). \tag{2.17}$$

For the sake of convenience, define the trajectory error to be

$$e_j^i\equiv\xi_j^i-y_d^{i(j-1)},\ \ i=1,2,\cdots,m,\ \ j=1,2,\cdots,r_i \tag{2.18}$$

$$e^i\equiv\left[e_1^ie_2^i\cdots e_{r_i}^i\right]^T\in\Re^{r_i} \tag{2.19}$$

and the trajectory error to be multiplied with some adjustable positive constant ε

$$\overline{e_j^i}\equiv\varepsilon^{j-1}e_j^i,\ \ i=1,2,\cdots,m,\ \ j=1,2,\cdots,r_i \tag{2.20}$$

$$\overline{e^i}\equiv\left[\overline{e_1^ie_2^i}\cdots\overline{e_{r_i}^i}(t)\right]^T\in\Re^{r_i} \tag{2.21}$$

$$\overline{e}\equiv[\overline{e^1}\ \ \overline{e^2}\ \ \cdots\ \ \overline{e^m}]^T\in\Re^r \tag{2.22}$$

and

$$\xi\equiv[\xi_1\ \ \xi_2\ \ \cdots\ \ \xi_r]^T\in\Re^r, \tag{2.23}$$

$$\eta(t)\equiv[\eta_{r+1}(t)\eta_{r+2}(t)\cdots\eta_n(t)]^T\in\Re^{n-r} \tag{2.24}$$

$$\begin{aligned}q(\xi(t),\eta(t))&\equiv[L_f\phi_{r+1}(t)L_f\phi_{r+2}(t)\cdots L_f\phi_n(t)]^T\\&\equiv[q_{r+1}\ \ q_{r+2}\ \ \cdots\ \ q_n]^T.\end{aligned} \tag{2.25}$$

Define a phase-variable canonical matrix A_c^i to be

$$A_c^i \equiv \begin{bmatrix} 0 & 1 & 0 & \cdots & 0 \\ 0 & 0 & 1 & \cdots & 0 \\ & \vdots & & & \vdots \\ 0 & 0 & 0 & \cdots & 1 \\ -\alpha_1^i & -\alpha_2^i & -\alpha_3^i & \cdots & -\alpha_{r_i}^i \end{bmatrix}_{r_i \times r_i}, \quad 1 \le i \le m \tag{2.26}$$

where $\alpha_1^i, \alpha_2^i, \cdots, \alpha_{r_i}^i$ are any chosen parameters such that A_c^i is Hurwitz and the vector B^i to be

$$B^i \equiv [0 \quad 0 \quad \cdots \quad 0 \quad 1]_{r_i \times 1}^T, \quad 1 \le i \le m. \tag{2.27}$$

Let P^i be the positive definite solution of the following Lyapunov equation:

$$\left(A_c^i\right)^T P^i + P^i A_c^i = -I, \quad 1 \le i \le m \tag{2.28}$$

$$\lambda_{\max}(P^i) \equiv \text{the maximum eigenvalue of } P^i, \quad 1 \le i \le m \tag{2.29}$$

$$\lambda_{\min}(P^i) \equiv \text{the minimum eigenvalue of } P^i, \quad 1 \le i \le m \tag{2.30}$$

$$\lambda_{\max}^* \equiv \min\left\{\lambda_{\max}(P^1), \lambda_{\max}(P^2), \cdots, \lambda_{\max}(P^m)\right\} \tag{2.31}$$

$$\lambda_{\min}^* \equiv \min\left\{\lambda_{\min}(P^1), \lambda_{\min}(P^2), \cdots, \lambda_{\min}(P^m)\right\}. \tag{2.32}$$

Assumption 1: For all $t \ge 0$, $\eta \in \Re^{n-r}$ and $\xi \in \Re^r$, there exists a positive constant M such that the following inequality holds:

$$\|q_{22}(t, \eta, \overline{e}) - q_{22}(t, \eta, 0)\| \le M\left(\|\overline{e}\|\right) \tag{2.33}$$

where $q_{22}(t, \eta, \overline{e}) \equiv q(\xi, \eta)$.

For the sake of stating precisely the investigated problem, define

$$d_{ij} \equiv L_{g_j} L_f^{r_i - 1} h_i(X), \quad 1 \le i \le m, \quad 1 \le j \le m \tag{2.34}$$

$$c_i \equiv L_f^{r_i} h_i(X), \quad 1 \le i \le m \tag{2.35}$$

and

$$\overline{\overline{e^i}} = \alpha_1^i \overline{e_1^i} + \alpha_2^i \overline{e_2^i} + \cdots + \alpha_{r_i}^i \overline{e_{r_i}^i}, \quad 1 \le i \le m \tag{2.36}$$

Theorem 1: Suppose that there exists a continuously differentiable function $V : \Re^{n-r} \to \Re^+$ such that the following three inequalities hold for all $\eta \in \Re^{n-r}$:

(a)

$$\omega_1 \|\eta\|^2 \le V(\eta) \le \omega_2 \|\eta\|^2, \quad \omega_1, \omega_2 > 0 \tag{2.37}$$

(b)

$$\nabla_t V + (\nabla_\eta V)^T q_{22}(t, \eta, 0) \le -2\alpha_x V(\eta), \quad \alpha_x > 0 \tag{2.38}$$

(c)

$$\|\nabla_\eta V\| \le \omega_3 \|\eta\|, \quad \omega_3 > 0 \tag{2.39}$$

then the tracking problem with almost disturbance decoupling is globally solvable by the controller

$$u_{\text{feedback}} = A^{-1}\{-b + v\} \tag{2.40}$$

$$b \equiv \left[L_f^{r_1} h_1 \;\; L_f^{r_2} h_2 \;\; \cdots \;\; L_f^{r_m} h_m\right]^T \tag{2.41}$$

$$v \equiv [v_1 \;\; v_2 \;\; \cdots \;\; v_m]^T \tag{2.42}$$

$$\begin{aligned} v_i \equiv & y_d^{i(r_i)} - \varepsilon^{-r_i} \alpha_1^i \left[L_f^0 h_i(X) - y_d^i\right] \\ & - \varepsilon^{1-r_i} \alpha_2^i \left[L_f^1 h_i(X) - y_d^{i(1)}\right] - \cdots \\ & - \varepsilon^{-1} \alpha_{r_i}^i \left[L_f^{r_i - 1} h_i(X) - y_d^{i(r_i - 1)}\right], \\ & 1 \le i \le m. \end{aligned} \tag{2.43}$$

Moreover, the influence of disturbances on the L_2 norm of the tracking error can be arbitrarily attenuated by increasing the adjustable parameter $NN_2 > 1$, shown in (2.44)–(2.45b) at the bottom of next page, where H is positive definite matrix and $k(\varepsilon) : \Re^+ \to \Re^+$ is any continuous function satisfies

$$\lim_{\varepsilon \to 0} k(\varepsilon) = 0 \text{ and } \lim_{\varepsilon \to 0} \frac{\varepsilon}{k(\varepsilon)} = 0. \tag{2.45c}$$

Proof: Applying the coordinate transformation (2.6) yields

$$\begin{aligned} \dot{\xi}_1^1 &= \frac{\partial h_1}{\partial X} f + \sum_{j=1}^p \frac{\partial h_1}{\partial X} q_j^* \theta_j \\ &= \xi_2^1 + \sum_{j=1}^p \frac{\partial h_1}{\partial X} q_j^* \theta_j \end{aligned} \tag{2.46}$$

$$\vdots$$

$$\begin{aligned} \dot{\xi}_{r_1 - 1}^1 &= \frac{\partial L_f^{r_1 - 2} h_1}{\partial X} f + \sum_{j=1}^p \frac{\partial L_f^{r_1 - 2} h_1}{\partial X} q_j^* \theta_j \\ &= L_f^{r_1 - 1} h_1 + \sum_{j=1}^p \frac{\partial L_f^{r_1 - 2} h_1}{\partial X} q_j^* \theta_j \end{aligned} \tag{2.47}$$

$$\begin{aligned} \dot{\xi}_{r_1}^1 &= c_1 + d_{11} u_1 + \cdots + d_{1m} u_m \\ &\quad + \sum_{j=1}^p \frac{\partial L_f^{r_1 - 1} h_1}{\partial X} q_j^* \theta_j \end{aligned} \tag{2.48}$$

$$\vdots$$

$$\begin{aligned} \dot{\xi}_1^m &= L_f^1 h_m + \sum_{j=1}^p \frac{\partial h_m}{\partial X} q_j^* \theta_j \\ &= \xi_2^m + \sum_{j=1}^p \frac{\partial h_m}{\partial X} q_j^* \theta_j \end{aligned} \tag{2.49}$$

$$\vdots$$

$$\begin{aligned} \dot{\xi}_{r_m - 1}^m &= L_f^{r_m - 1} h_m + \sum_{j=1}^p \frac{\partial L_f^{r_m - 2} h_m}{\partial X} q_j^* \theta_j \\ &= \xi_{r_m}^m + \sum_{j=1}^p \frac{\partial L_f^{r_m - 2} h_m}{\partial X} q_j^* \theta_j \end{aligned} \tag{2.50}$$

$$\begin{aligned} \dot{\xi}_{r_m}^m &= c_m + d_{m1} u_1 + \cdots + d_{mm} u_m \\ &\quad + \sum_{j=1}^p \frac{\partial L_f^{r_m - 1} h_m}{\partial X} q_j^* \theta_j \end{aligned} \tag{2.51}$$

$$\begin{aligned}\dot{\eta}_k(t) &= L_f\phi_k + \sum_{j=1}^{p}\frac{\partial\phi_k}{\partial X}q_j^*\theta_j \\ &= q_k + \sum_{j=1}^{p}\frac{\partial\phi_k}{\partial X}q_j^*\theta_j, \\ k &= r+1, r+2, \cdots, n\end{aligned} \tag{2.52}$$

Since

$$c_i(\xi(t),\eta(t)) \equiv L_f^{r_i}h_i(X(t)), \quad 1 \le i \le m \tag{2.53}$$

$$\begin{aligned}d_{ij} &\equiv L_{g_j}L_f^{r_i-1}h_i(X) \\ &1 \le i \le m, \quad 1 \le j \le m\end{aligned} \tag{2.54}$$

$$q_k(\xi(t),\eta(t)) = L_f\phi_k(X), \quad k = r+1, r+2, \cdots, n \tag{2.55}$$

the dynamic equations of system (2.1) in the new coordinates are as follows:

$$\begin{aligned}\dot{\xi}_i^1(t) &= \xi_{i+1}^1(t) + \sum_{j=1}^{p}\frac{\partial}{\partial X}L_f^{i-1}h_1q_j^*\theta_j \\ &i = 1, 2, \cdots, r_1 - 1\end{aligned} \tag{2.56}$$

$$\begin{aligned}\dot{\xi}_{r_1}^1(t) &= c_1(\xi(t),\eta(t)) + d_{11}(\xi(t),\eta(t))u_1 + \cdots \\ &+ d_{1m}(\xi(t),\eta(t))u_m \\ &+ \sum_{j=1}^{p}\frac{\partial}{\partial X}L_f^{r_1-1}h_1q_j^*\theta_j\end{aligned} \tag{2.57}$$

$$\vdots$$

$$\begin{aligned}\dot{\xi}_i^m(t) &= \xi_{i+1}^m(t) + \sum_{j=1}^{p}\frac{\partial}{\partial X}L_f^{i-1}h_mq_j^*\theta_j \\ &i = 1, 2, \cdots, r_m - 1\end{aligned} \tag{2.58}$$

$$\begin{aligned}\dot{\xi}_{r_m}^m(t) &= c_m(\xi(t),\eta(t)) + d_{m1}(\xi(t),\eta(t))u_1 + \cdots \\ &+ d_{mm}(\xi(t),\eta(t))u_m \\ &+ \sum_{j=1}^{p}\frac{\partial}{\partial X}L_f^{r_m-1}h_mq_j^*\theta_j\end{aligned} \tag{2.59}$$

$$\begin{aligned}\dot{\eta}_k(t) &= q_k(\xi(t),\eta(t)) + \sum_{j=1}^{p}\frac{\partial}{\partial X}\phi_k(X)q_j^*\theta_j \\ &k = r+1, \cdots, n\end{aligned} \tag{2.60}$$

$$y(t) = \xi_1^i(t), \quad 1 \le i \le m. \tag{2.61}$$

According to (2.18), (2.43), (2.53), and (2.54), the tracking controller can be rewritten as

$$u_{\text{feedback}} = A^{-1}[-b + v]. \tag{2.62}$$

Substituting (2.62) into (2.57) and (2.59), the dynamic equations of system (2.1) can be shown as follows:

$$\begin{aligned}\dot{\xi}_i &= \begin{bmatrix}0 & 1 & 0 & \cdots & 0\\ 0 & 0 & 1 & 0 & \cdots & 0\\ & \vdots & & & & \vdots\\ 0 & 0 & 0 & \cdots & 1\\ 0 & 0 & 0 & \cdots & 0\end{bmatrix}\xi_i + B^iv_i \\ &+ \begin{bmatrix}\sum_{j=1}^{p}\frac{\partial}{\partial X}h_iq_j^*\theta_j & \sum_{j=1}^{p}\frac{\partial}{\partial X}L_f^1h_iq_j^*\theta_j & \cdots \\ \sum_{j=1}^{p}\frac{\partial}{\partial X}L_f^{r_i-1}h_iq_j^*\theta_j\end{bmatrix}^T\end{aligned} \tag{2.63}$$

$$\dot{\eta}(t) = q(\xi(t),\eta(t)) + \phi_\eta\theta \tag{2.64}$$

$$\begin{aligned}H(\varepsilon) &\equiv \begin{bmatrix}H_{11} & H_{12}\\ H_{12} & H_{22}\end{bmatrix} \\ &\equiv \begin{bmatrix}2\alpha_x - \frac{3\omega_3^2}{\omega_1}\|\phi_\eta\|^2 & -\frac{1}{\sqrt{k(\varepsilon)}}\left[\frac{\omega_3M}{\sqrt{2\omega_1\lambda_{\min}^*}}\right] \\ -\frac{1}{\sqrt{k(\varepsilon)}}\left[\frac{\omega_3M}{\sqrt{2\omega_1\lambda_{\min}^*}}\right] & \frac{1}{\varepsilon\lambda_{\max}^*} - \frac{6k(\varepsilon)\|\phi_\xi^1\|^2\|P^1\|^2}{\varepsilon^2\lambda_{\min}(P^1)} - \cdots - \frac{6k(\varepsilon)\|\phi_\xi^m\|^2\|P^m\|^2}{\varepsilon^2\lambda_{\min}(P^m)}\end{bmatrix}\end{aligned} \tag{2.44}$$

$$\alpha_s(\varepsilon) \equiv \frac{H_{11} + H_{22} - \left[(H_{11} - H_{22})^2 + 4H_{12}^2\right]^{\frac{1}{2}}}{4}$$

$$N \equiv 2\alpha_s(\varepsilon), \; N_1 \equiv \frac{m+1}{12}\left(\sup_{t_0\le\tau\le t}\|\theta(\tau)\|\right)^2$$

$$N_2 \equiv \min\left\{\omega_1, \frac{k(\varepsilon)}{2}\lambda_{\min}^*\right\} \tag{2.45a}$$

$$\phi_\xi^i(\varepsilon) \equiv \begin{bmatrix}\varepsilon\frac{\partial}{\partial X}h_iq_1^* & \cdots & \varepsilon\frac{\partial}{\partial X}h_iq_p^* \\ \vdots & & \vdots \\ \varepsilon^{r_i}\frac{\partial}{\partial X}L_f^{r_i-1}h_iq_1^* & \cdots & \varepsilon^{r_i}\frac{\partial}{\partial X}L_f^{r_i-1}h_iq_p^*\end{bmatrix}$$

$$\phi_\eta(\varepsilon) \equiv \begin{bmatrix}\frac{\partial}{\partial X}\phi_{r+1}q_1^* & \cdots & \frac{\partial}{\partial X}\phi_{r+1}q_p^* \\ \vdots & & \vdots \\ \frac{\partial}{\partial X}\phi_nq_1^* & \cdots & \frac{\partial}{\partial X}\phi_nq_p^*\end{bmatrix} \tag{2.45b}$$

$$\begin{aligned} y_i &= [1\ 0\ \cdots\ 0\ 0]_{1\times r_i}\left[\xi_1^i(t)\ \xi_2^i(t)\ \cdots\ \xi_{r_i-1}^i(t)\ \xi_{r_i}^i(t)\right]^T \\ &= \xi_1^i(t), \quad 1 \le i \le m. \end{aligned} \tag{2.65}$$

Combining (2.18), (2.20), (2.21), (2.26), and (2.43), it can be easily verified that (2.63)–(2.65) can be transformed into the following form:

$$\dot{\eta}(t) = q(\xi(t), \eta(t)) + \phi_\eta \theta := q_{22}(t, \eta(t), \overline{e}) + \phi_\eta \theta \tag{2.66a}$$

$$\varepsilon \dot{\overline{e^i}}(t) = A_c^i \overline{e^i} + \phi_\xi^i \theta, \quad 1 \le i \le m \tag{2.66b}$$

$$y_i(t) = \xi_1^i(t), \quad 1 \le i \le m. \tag{2.67}$$

We consider $L(\overline{e}, \eta)$ defined by a weighted sum of $V(\eta)$ and $W(\overline{e})$

$$\begin{aligned} L(\overline{e}, \eta) &:= V(\eta) + k(\varepsilon) W(\overline{e}) \\ &:= V(\eta) + k(\varepsilon)\left(W^1(\overline{e^1}) + \cdots + W^m(\overline{e^m})\right) \end{aligned} \tag{2.68}$$

where

$$W(\overline{e}) := W^1(\overline{e^1}) + \cdots + W^m(\overline{e^m}) \tag{2.69}$$

as a composite Lyapunov function of the subsystems (2.66a) and (2.66b) [20], where $W(\overline{e^i})$ satisfies

$$W^i(\overline{e^i}) := \frac{1}{2} \overline{e^i}^T P^i \overline{e^i} \tag{2.70}$$

In view of (2.18), (2.33), (2.37), (2.38), and (2.39), the derivative of L along the trajectories of (2.66a) and (2.66b) is given by

$$\begin{aligned} \dot{L} &= \left[\nabla_t V + (\nabla_\eta V)^T \dot{\eta}\right] \\ &\quad + \frac{k}{2}\left[(\dot{\overline{e^1}})^T P^1 \overline{e^1} + (\overline{e^1})^T P^1 (\dot{\overline{e^1}}) + \cdots \right. \\ &\qquad \left. + (\dot{\overline{e^m}})^T P^m \overline{e^m} + (\overline{e^m})^T P^m (\dot{\overline{e^m}})\right] \\ &\le -\left(2\alpha_x - \frac{3\omega_3^2}{\omega_1}\|\phi_\eta\|^2\right)(\sqrt{V})^2 \\ &\quad + 2\left(\frac{\omega_3 M}{\sqrt{2\omega_1 k \lambda_{\min}^*}}\right)\sqrt{V}\sqrt{kW} \\ &\quad - \left(\frac{1}{\varepsilon \lambda_{\max}^*} - \frac{3k\left\|\phi_\xi^1\right\|^2 \|P^1\|^2}{\frac{1}{2}\varepsilon^2 \lambda_{\min}(P^1)} - \cdots \right. \\ &\qquad \left. - \frac{3k\left\|\phi_\xi^m\right\|^2 \|P^m\|^2}{\frac{1}{2}\varepsilon^2 \lambda_{\min}(P^m)}\right)(\sqrt{kW})^2 + \frac{m+1}{12}\|\theta\|^2 \\ &= -\begin{bmatrix}\sqrt{V} & \sqrt{kW}\end{bmatrix} H \begin{bmatrix}\sqrt{V} \\ \sqrt{kW}\end{bmatrix} + \frac{m+1}{12}\|\theta\|^2 \end{aligned} \tag{2.71}$$

i.e.,

$$\dot{L} \le -\lambda_{\min}(H) L + \frac{m+1}{12}\|\theta\|^2 \tag{2.72}$$

where $\lambda_{\min}(H)$ denotes the minimum eigenvalue of the matrix H. Utilizing the fact that $\lambda_{\min}(H) = 2\alpha_s$, we obtain

$$\begin{aligned} \dot{L} &\le -2\alpha_s\left(\omega_1\|\eta\|^2 + \frac{k}{2}\lambda_{\min}^*\|\overline{e}\|^2\right) + \frac{m+1}{12}\|\theta\|^2 \\ &\le -NN_2\left(\|\eta\|^2 + \|\overline{e}\|^2\right) + \frac{m+1}{12}\|\theta\|^2. \end{aligned} \tag{2.73}$$

Define

$$\overline{e} \equiv [\overline{e^1}\ \overline{e^2}\ \cdots\ \overline{e^m}]^T \equiv \left[\overline{e_1^1}\ \overline{e_{\text{rem}}^1}\right]^T, \quad \overline{e_{\text{rem}}^1} \in \Re^{r-1}. \tag{2.74}$$

Hence

$$\dot{L} \le -NN_2\left(\|\eta\|^2 + \left\|\overline{e_1^1}\right\|^2 + \left\|\overline{e_{rem}^1}\right\|^2\right) + \frac{m+1}{12}\|\theta\|^2. \tag{2.75}$$

Utilizing (2.75) easily yields

$$\int_{t_0}^{t} \left(y_1(\tau) - y_d^1(\tau)\right)^2 d\tau \le \frac{L(t_0)}{NN_2} + \frac{m+1}{12NN_2}\int_{t_0}^{t}\|\theta(\tau)\|^2 d\tau. \tag{2.76}$$

Similarly, it is easy to prove that

$$\begin{aligned} &\int_{t_0}^{t} \left(y_i(\tau) - y_d^i(\tau)\right)^2 d\tau \\ &\quad \le \frac{L(t_0)}{NN_2} + \frac{m+1}{12NN_2}\int_{t_0}^{t}\|\theta(\tau)\|^2 d\tau, \quad 2 \le i \le m. \end{aligned} \tag{2.77}$$

From (2.73), we get

$$\dot{L} \le -NN_2\left(\|y_{\text{total}}\|^2\right) + \frac{m+1}{12}\|\theta\|^2 \tag{2.78a}$$

where

$$\|y_{\text{total}}\|^2 \equiv \|\overline{e}\|^2 + \|\eta\|^2. \tag{2.78b}$$

By virtue of [17, Theorem 5.2], (2.78a) implies the input-to-state stability for the closed-loop system. Furthermore, it is easy to see that

$$\Delta_{\min}\left(\|\overline{e}\|^2 + \|\eta\|^2\right) \le L \le \Delta_{\max}\left(\|\overline{e}\|^2 + \|\eta\|^2\right) \tag{2.79}$$

i.e.,

$$\Delta_{\min}\left(\|y_{\text{total}}\|^2\right) \le L \le \Delta_{\max}\left(\|y_{\text{total}}\|^2\right) \tag{2.80}$$

where $\Delta_{\min} \equiv \min\{\omega_1, (k/2)\lambda_{\min}^*\}$ and $\Delta_{\max} \equiv \max\{\omega_2, (k/2)\lambda_{\max}^*\}$. From (2.73) and (2.80), we get

$$\dot{L} \le -\frac{NN_2}{\Delta_{\max}} L + \frac{m+1}{12}\left(\sup_{t_0 \le \tau \le t}\|\theta(\tau)\|\right)^2. \tag{2.81}$$

Hence

$$L(t) \le L(t_0)e^{-\frac{NN_2}{\Delta_{\max}}(t-t_0)} + \frac{\Delta_{\max}(m+1)}{12NN_2}\left(\sup_{t_0\le\tau\le t}\|\theta(\tau)\|\right)^2, \quad t \ge t_0 \tag{2.82}$$

which implies

$$|y_1(t) - y_d^1(t)| \le \sqrt{\frac{2L(t_0)}{k\lambda^*_{\min}}}e^{-\frac{NN_2}{2\Delta_{\max}}(t-t_0)} + \sqrt{\frac{\Delta_{\max}(m+1)}{6k\lambda^*_{\min}NN_2}}\left(\sup_{t_0\le\tau\le t}\|\theta(\tau)\|\right). \tag{2.83}$$

Similarly, it is easy to prove that

$$|y_i(t) - y_d^i(t)| \le \sqrt{\frac{2L(t_0)}{k\lambda^*_{\min}}}e^{-\frac{NN_2}{2\Delta_{\max}}(t-t_0)} + \sqrt{\frac{\Delta_{\max}(m+1)}{6k\lambda^*_{\min}NN_2}}\left(\sup_{t_0\le\tau\le t}\|\theta(\tau)\|\right), \quad 2 \le i \le m. \tag{2.84}$$

Equations (2.77) and (2.84) conclude that the tracking problem with almost disturbance decoupling is globally solved [21].

According to the previous theorem and discussion, an efficient algorithm for deriving the almost disturbance decoupling control is proposed as follows:

Step 1) Calculate the vector relative degree $r_1, r_2, \cdots, r_m$ of the given system.

Step 2) Choose the diffeomorphism ϕ such that the assumption 1 is satisfied.

Step 3) Adjust some parameters $\alpha_1^i, \alpha_2^i, \cdots, \alpha_{r_i}^i$ such that the matrices A_c^i are Hurwitz and calculate the positive definite matrices P^i of the Lyapunov equations (2.28) by some software package, such as MATLAB.

Step 4) Based on the famous Lyapunov approach, design a Lyapunov function to solve the conditions (2.37)–(2.39).

Step 5) Appropriately tune the parameters k, ε such that $NN_2 > 1$ and go to the next step. Otherwise, we go to the step 3 and repeat the overall designing procedures.

Step 6) According to the (2.40), the desired feedback linearization control law u can be constructed such that the uniform ultimate bounded stability is guaranteed. That is, the system dynamics enter a neighborhood of zero state and remain within it thereafter.

III. Control Strategy of Cancer Immunotherapy

To begin a model of cancer-immune dynamics, we first investigate some existing models. [19] constructs a model with ordinary differential equation for effector cells and cancer cells. They exploit the fact that the model has stable spirals, but the Dulac–Bendixson rule shows there are no stable closed orbits. [8] again considers ordinary differential equation for the populations of immune and cancer cells. Its result shows that survival increases if the immune system is excited. [22] proposes a model of adoptive cellular immunotherapy based on result by [26]. The model incorporates stochastical effects on the effector–cancer interactions. However, this model does not consider sensitivity and bifurcation. Finally, there is a complicated model given by [7] with 10 differential equations coupled with five algebraic equations investigating most of the players in the cancer-immune dynamics. They are able to show both cancer regression and uncontrolled cancer growth. Our goal is to apply the best ideas in these systems, but to keep the model as simple as possible while combining the most significant concepts of cancer-immune dynamics together with the structure of immunity Interleukin-2 dynamics. Therefore, we define three populations. These include: $x_t(t)$, the concentration of activated immune-system cells (commonly called *effector* cells) such as cytotoxic T-cells, macrophages, and natural killer cells that are cytotoxic to the cancer cells; $y_t(t)$, the concentration of cancer cells; and $z_t(t)$, the concentration of IL-2 in the single cancer-site compartment. Our model describing the interaction between the effector cells, cancer cells, and the cytokine (IL-2) is [18]

$$\frac{dx_t}{dt} = cy_t - \mu_2 x_t + \frac{p_1 x_t z_t}{g_1 + z_t} + u_1(t) \tag{3.1a}$$

$$\frac{dy_t}{dt} = r_2(1 - by_t)y_t - \frac{a x_t y_t}{g_2 + y_t} \tag{3.1b}$$

$$\frac{dz_t}{dt} = \frac{p_2 x_t y_t}{g_3 + y_t} - \mu_3 z_t + u_2 \tag{3.1c}$$

where x_t denotes the concentration of immune cells or effector cells, $y_t(t)$ denotes the concentration of cancer cells and $z_t(t)$ denotes the concentration of IL-2 in the single tumor-site compartment. The system parameters used in the cancer model are $c = 0.035$, $p_1 = 0.1245$ days^{-1}, $g_2 = 10^5$, $a = 1$, $\mu_3 = 10$ days^{-1}, $g_3 = 10^3$, $\mu_2 = 0.03$ days^{-1}, $g_1 = 2 \times 10^7$, $r_2 = 0.18$, $b = 10^{-9}$, $p_2 = 5$ days^{-1}. These parameters have been used in [18], and the model terms are described as follows. Equation (3.1a) describes the rate of change for the effector-cell population. Effector cells are stimulated to grow based on term1 and term 3. Term 1 is a recruitment source due to the direct presence of the tumor, where the parameter c models the antigenicity of the tumor. Antigenicity can be viewed as a measure of how different the tumor is from "self." Term 3 is a proliferation term whereby effector cells are stimulated by IL-2 that is created by effector cells in both an autocrine and paracrine manner. This term is of Michaelis–Menten form to indicate the saturated effects of the immune response, where p_1 is the maximal growing rate of effectors cells without TGF-β, which is able to induce the cancer evolution, and g_1 is the mean saturation constant of the effector cells without TGF-β. Term 2 is the natural death of the effector calls at μ_2 rate. Lastly, u_1 is a treatment term that represents an external source of effector cells such as LAK or TIL cells. Equation (3.1b) includes a logistic term in order to model the decay rate of tumor cells. This can be described by a linear growth term or as a type of limiting-growth such as logistic or Gompertz and b is the pharmacological product's weight. The loss of tumor cells is represented by an immune-effector cell interaction at rate a, and g_2 is the mean saturation constant of the tumor growing. This rate constant, a represents the strength of the immune response and is modeled by Michaelis–Menten kinetics [16] to indicate the limited immune response for the tumor. Equation (3.1c) gives the rate of change for the concentration of IL-2, where p_2 is the maximal growing rate of tumor

cells and g_3 indicates a response bound while the tumor cells are stimulated with cytokines. This reproduces the tumor cells, stimulating the interaction with the effectors cells to produce IL-2. Its source is the effector cells that are stimulated by interaction with the tumor and also has Michaelis–Menten kinetics to account for the self-limiting production of IL-2. The next term (μ_3) represents degraded rate of IL-2. Finally, u_2 is a treatment term that represents an external input of effector cells such as LAK or TIL cells.

The goal of the control inputs of antiretroviral drugs $u_1(t)$ and $u_2(t)$ is to keep the system around the equilibrium point where the tumor load has a zero value. The controlled model can be written in the general form

$$\dot{x}(t) = f(x) + g_1(x)u_1(t) + g_2(x)u_2(t) \tag{3.2a}$$
$$y_1(t) = h_1(x) = x_2(t) \tag{3.2b}$$
$$y_2(t) = h_2(x) = x_3(t) \tag{3.2c}$$

where $x = [x_t\ y_t\ z_t]^T$, $f(x) = [-\mu_2 x_1 + cx_2 + (p_1 x_1 x_3/(g_1 + x_3))\ \ r_2 x_2 - br_2 x_2^2 - (ax_1 x_2/(g_2 + x_2))\ \ (p_2 x_1 x_2/(g_3 + x_2)) - \mu_3 x_3]^T$, $g_1(x) = [1\ 0\ 0]^T$, and $g_2(x) = [0\ 0\ 1]^T$. Now we will show how to explicitly construct a controller that reduces the tumor load to be the zero value and attenuates the disturbance's effect on the output terminal to an arbitrary degree of accuracy. Let's arbitrarily choose $\alpha_1^1 = 1$, $\alpha_2^1 = 10$, and $\alpha_1^2 = 10$ such that $A_c^1 = \begin{bmatrix} 0 & 1 \\ -10 & -10 \end{bmatrix}$, $A_c^2 = -10$, $P^1 = \begin{bmatrix} 1.05 & 0.05 \\ 0.05 & 0.055 \end{bmatrix}$, $P^2 = 0.05$. According to (2.97), the desired control strategy can be expressed as in the set of equations at the bottom of the page. It can be verified that the relative conditions of Theorem 1 are satisfied with $\varepsilon = 0.1$, $\|P^1\| = \|P^2\| = 1.0525$, $\lambda_{\max}(P^1) = 1.0525$, $\lambda_{\max}(P^2) = 0.05$, $\lambda_{\min}(P^1) = 0.0525$, $\lambda_{\min}(P^2) = 0.05$, $B^1 = B^2 = [0\ 1]^T$ and $k = 0.316$. Consequently, it follows from Theorem 1 that the controller (3.3) will steer the output tracking error $y_1 - y_d^1 = x_2 - 0 = x_2$ of the closed-loop system, starting from any initial value, to be asymptotically attenuated to the zero value(i.e. the concentration of cancer cells approaches to the zero value).

The simulation of introducing the treatment is shown in Fig. 3.1 with the initial conditions: $x_t(0) = 1$, $y_t(0) = 1$, $z_t(0) = 1$. The effector cells increases and are held in acceptable level when control chemotherapy is used. The action of chemotherapy begins to appear and reduces the tumor cells to the zero value. It is obvious to see that the amount of tumor cells drops to the zero value after only 450 days based on the utilization of our proposed control treatment and recurrence cycle is not existent. On the other hand, the simulations of [24] and [6] show that the amount of tumor cells doesn't reach the zero value. [3] applies the optimal control theory to the tumor immune system. The related simulations indicate that the multitherapy with CTL & IL-2 is the optimal solution in controlling the tumor growth. However, the tumor size cannot be eliminated completely and the recurrence cycle is about 100 days. In [27], the optimal control theory is applied to the tumor immume system. The simulations indicate that the therapy is the most successful in controlling the tumor growth. However, the tumor cells cannot be eliminated completely and reach the stabilizing value after 450 days.

It is worthy to note that our proposed nonlinear feedback linearization control needs the quantification of all the state variables for cancer system. All the state variables including the concentrations of effector cells, cancer cells and IL-2 will be measured in the clinic. We will begin clinical study of the feedback linearization controller (3.3) of antiretroviral drugs based on the utilization of Cellometer Auto T4 Cell Counter (http://www.nexcelom.com/Products/Vision/index.html), Harvard PHD 2000 programmable research pump (http://www.18show.cn/show/145792/Product_5450168.html), and computer with Java program shown in Fig. 3.2. Electrically automatic apparatus for providing antiretroviral drugs could be constructed based on the quantification of the state variables. The desired feedback linearization control algorithm will be programmed in Java language chosen for its multiplatform portability and prototyping. The Java program will be divided

$$\begin{aligned}
u_{fe} &\equiv A^{-1}\{-b + v\} \\
v &\equiv \begin{bmatrix} v_1 \\ v_2 \end{bmatrix} \\
&= \begin{bmatrix} -10\varepsilon^{-2}x_2 - 10\varepsilon^{-1}\left(0.18x_2 - 0.18\times 10^{-9}x_2^2 - \frac{x_1x_2}{x_2+10^5}\right) \\ -10\varepsilon^{-1}x_3 \end{bmatrix} \\
A &= \begin{bmatrix} \frac{-x_2}{x_2+10^5} & 0 \\ 0 & 1 \end{bmatrix},\ b \equiv \begin{bmatrix} b_1 \\ b_2 \end{bmatrix},\ b_2 = \frac{5x_1x_2}{x_2+10^3} - 10x_3 \\
b_1 &= \left(\frac{-x_2}{x_2+10^5}\right)\left(-0.03x_1 + 5\times 10^{-5}x_2 + \frac{0.1245x_1x_3}{x_3+2\times 10^7}\right) \\
&\quad + \left(0.18 - 0.36\times 10^{-9}x_2 - \frac{x_1(x_2+10^5) - x_1x_2}{(x_2+10^5)^2}\right) \\
&\quad \times \left(0.18x_2 - 0.18\times 10^{-9}x_2^2 - \frac{x_1x_2}{x_2+10^5}\right)
\end{aligned}$$

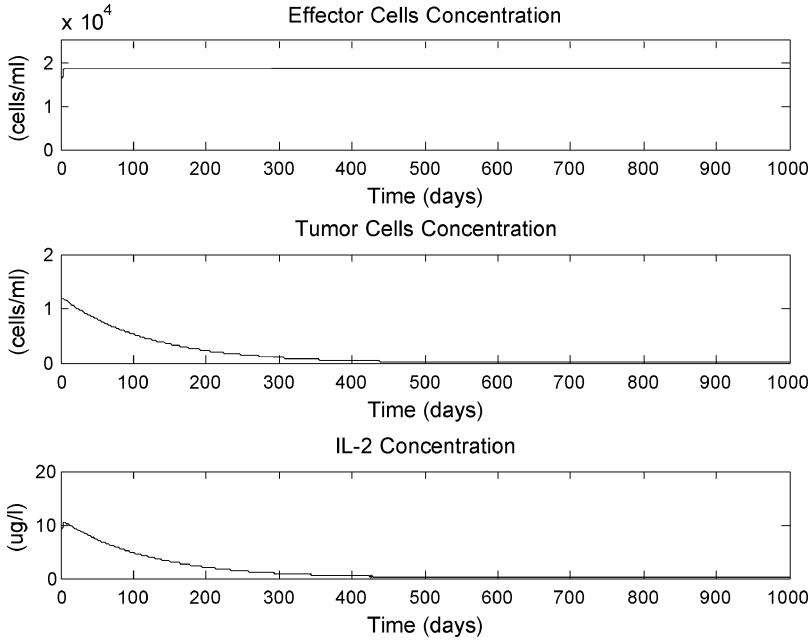

Fig. 3.1. The concentrations of effector cells, the tumor cells, and IL-2 with control.

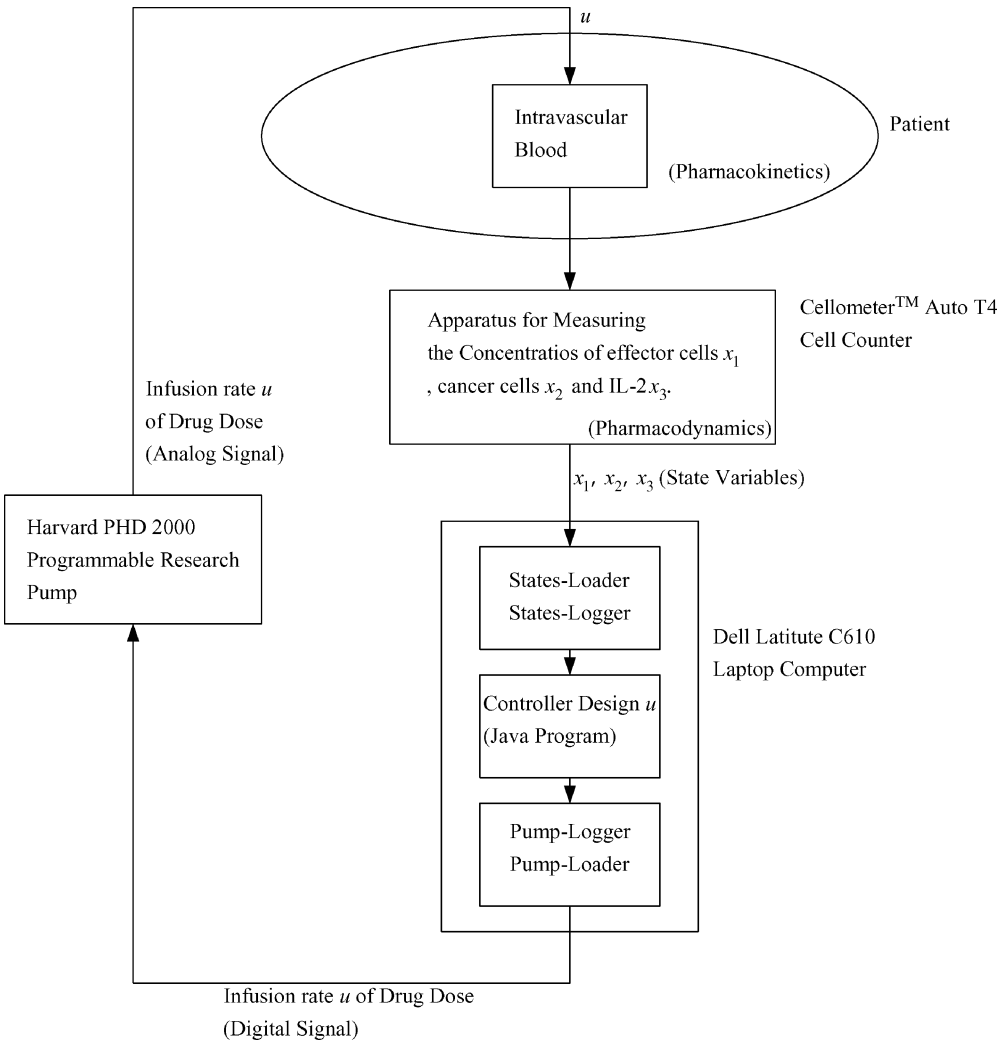

Fig. 3.2. Clinical study of the feedback linearization controller (3.3) of antiretroviral drugs.

into five blocks, which include states-loader, states-logger, controller, pump-logger, and pump-loader. States-loader and states-logger handle the communication between Cellometer Auto T4 Cell Counter and computer, while pump-logger and pump-loader control the micro-pump device. The dose input (3.3) is calculated by the controller block and communicated to the infusion micro-pump using a 9600 baud rate, eight data bits, two stop bits, and zero parity with the utilization of a universal serial bus port connector. Finally, the pump-loader opens the communication port to the micro-pump and constructs the communication protocol, while pump-logger transfers the dose input $u(t)$ to the micro-pump.

IV. Conclusion

In this paper, we propose a novel control strategy such that the resulting closed-loop system is valid for any initial condition with almost disturbance decoupling performance and develop the feedback linearization design for the control of a MIMO cancer model system to improve the cancer load. The discussion and practical application of feedback linearization of nonlinear control systems by parameterized coordinate transformation have been presented. A practical treatment of MIMO cancer model demonstrated the applicability of the proposed feedback linearization approach and the composite Lyapunov approach. Simulation results exploited the fact that the proposed methodology is successfully applied to feedback linearization problem and achieves the desired tracking and almost disturbance decoupling performances of the MIMO tumor-immune system. In comparison with some existing approaches, the performances of drug treatment based on our proposed novel nonlinear geometric feedback control approach are better than some existent approaches, i.e., the effector cell population can be kept in 1.9×10^4 cells/ml and the tumor load is reduced only after more short days of drug treatment. All the state variables of cancer model system can be measured using the Cellometer Auto T4 Cell Counter, programmable research micro-pump and computer with Java program in the clinical study. Finally, we believe that the novel methodology can be used for solving many control problems in biomedical areas in future.

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