A&QT-R 2004 (THETA 14)

2004 IEEE-TTTC - International Conference on Automation, Quality and Testing, Robotics

May 13 – 15, 2004, Cluj-Napoca, Romania

NEURAL NETWORKS FEEDBACK LINEARIZATION FOR CANCER CHEMOTHERAPY CONTROL

A. G. Floareş

Artificial Intelligence Department,
Oncology Institute, Cluj-Napoca, Str. Republicii No 34-36, Romania
Email: alexandru-floares@xnet.ro

Abstract. This study addresses an important cancer chemotherapy problem: the design of drug dosage regimens capable of minimizing the tumor burden at the end of treatment, and of balancing the benefits against the toxic side effects. This constrained control problem is approached by neural networks adaptive control methods. The NARMA-L2 version of feedback-linearization neural network is used to control a patient model. The patient model has a pharmacokinetic component and a pharmacodynamic one based on the Gompertzian model of tumor growth. Simulation results produced excellent control policies of drug scheduling in cancer chemotherapy, superior to those published in literature.

Keywords: Control, Neural Networks, Feedback Linearization, Drug Dosage Regimens, Cancer Chemotherapy

1. INTRODUCTION

An important problem in cancer chemotherapy is to design such drug dosage regimens as at the end of treatment the tumor burden to be minimized. A proper dosage regimen has to balance the benefits of the treatment against the often serious toxic side effects. At present, treatments are developed trough empirical clinical trials. This led to a large number of patients being treated in sub-optimal ways.

This control problem was approached using conventional methods and, less frequently, artificial intelligence methods. Martin [1] used non-linear programming techniques. The results were improved by Bojkov et al. (quoted in [2]), who used an intuitive approach coupled with direct search procedure. Direct search procedure combined with random numbers and contraction search region techniques was used by Luus et al. (quoted in [2]). Tan et al. [2] applied distributed evolutionary computing methods. The aim of this paper was to introduce an adaptive neural networks (NN) control approach [3], [4], based on feedback linearization, for optimizing chemotherapy regimens.

2. MATERIALS AND METHODS

The objective of chemotherapy protocols is to minimize the tumor burden after a fixed period of treatment. More precisely, it means a reduction from an initial tumor size of about 10^{10} cells to the lowest possible size given the treatment constraints.

2.1 Constraints:
The constraints are:

- *Toxicity constraints*: 1. the highest plasma concentration of the drug, $Cmax \leq 50$, 2. the cumulative drug dosage over the treatment period – $AUC \leq 2.1 \times 10^3$, and 3. the damage caused to various tissues.
- *Drug resistance constraints*: The probability of drug resistant cells emergence increases with the mutation rate and tumor size. For this reason, the tumor size is forced to reduce by at least 50% at the end of every 3 weeks.

All cytotoxic drugs used in cancer chemotherapy have narrow therapeutic indices. This means that the dose levels at which these drugs significantly affect a tumor are close to those levels at which unacceptable toxic side effects result. This is the main motivation for using advanced control methods in drug dosage regimens design.

We adopted the standard treatment schedule: new cycles begin on days 21 or 28 after the first dose. The dose-response curve is usually *sigmoidal* in shape, with a threshold, a lag phase, a step linear phase, and a plateau phase.

An important concept is *dose intensity* - the amount of drug delivered per unit of time, expressed as milligrams per square meter per week, regardless of the schedule [5]. This gives treatment delays equal weight with dose reductions. Scheduling influences outcome mostly by affecting toxicity. This allows higher doses to be administered over the same time frame.

2.2 Mathematical Model of Tumor Growth

Typically a tumor will grow very rapidly with the growth rate proportional to the tumor size. However, as tumors increase, the growth rate decreases as tumor size increases. In order to reflect this, differential equation models have been proposed. It is customary to assume that tumor volume and number of tumor cells are proportional and so the model which follows describes $dN(t)/dt$, where $N(t)$ represents the number of tumor cells at time t. Three models have been widely used in the study of tumor growth: exponential, logistic and Gompertz growth.

The *Gompertz* differential equation used in this study is the most widely accepted tumor growth model [5]. We incorporated the effect of chemotherapy by adding a kill term to the differential equation. It is assumed that: 1) the drug will cause a decline in tumor cell population jointly proportional to its concentration and the population size at any given time and 2) there is a threshold drug concentration level β below which no tumor cells are killed. This led to the *pharmacodynamic* (PD) component of the patient model:

$$\frac{dN}{dt} = N\left(\lambda \ln\left(\frac{\theta}{N}\right) - k\left(C-\beta\right)H\left(C-\beta\right)\right) \qquad (1)$$

where N is the number of tumor cells, λ is a positive constant, θ is the largest possible size of the tumor, and H is the Heaviside unit function:

$$H(C-\beta)=\begin{cases}1 \text{ if } C \geq \beta \\ 0 \text{ if } C \leq \beta\end{cases}$$

The *pharmacokinetics* (PK) of the drug is modeled by a differential equation based on delivery and elimination rate, proportional with concentration C:

$$\frac{dC}{dt}=u-\gamma C \qquad (2)$$

where γ = 0.27 (per day) is a constant of proportionality. The half-life of the drug is $\ln(2)/\gamma$.

The cytotoxic effect is a function of the concentration and *exposure* to the drug. This effect is included by adding the last differential equation:

$$\frac{d(AUC)}{dt}=C \qquad (3)$$

The *performance index* to be minimized is the tumor size at the end of the treatment period expressed as $y = \ln(N/\theta)$ with $y(0) = \ln(100) = 4.6052$. The control optimization is subject to *constraints* on the drug administration and state variables - drug concentration and cumulative drug effect. In order to reduce the likelihood of the emergence of drug resistant cells, the tumor size is forced to reduce by at least 50% every 3 weeks. The parameters of cancer chemotherapy model are: λ (per day) = 9.9 x 10^{-4}, k (per day, per D) = 8.4 x 10^{-3}, β (D) = 10, γ (per day) = 0.27, $\theta = 10^{12}$, and $\theta = 10^{12}$.

2.3 Neural Networks Control for Chemotherapy Optimization

The steps involved in developing a NN for control are system identification and control design [3]. The first infers a NN model of the PKPD model to be controlled, from a set of data resulted from model simulations. The input has to be persistently exciting, its values should be such that the output does not saturate; it should span the entire operating range of the system, and contains enough dynamics to adequately characterize the response of the system. The sampling time must be chosen in accordance with the fastest dynamic of the system. A random input $u(k)$, with the highest value close to the maximal acceptable dose of the drug and a minimal value of zero, is injected into the system at random intervals of time ranging from the duration of an infusion (3 hours) to the greatest dose-to-dose interval (21 days).

The next step is to select a *model structure*. For our particular choice of neurocontroller, feedback linearization, the model structure will have the following form:

$$\begin{aligned} y(k+d) = {} & f\left[y(k), y(k-1), ..., y(k-n+1), u(k-1), ..., u(k-n+1)\right] \\ & + g\left[y(k), y(k-1), ..., y(k-n+1), u(k-1), ..., u(k-n+1)\right] \cdot u(k) \end{aligned} \qquad (4)$$

where f and g are two nonlinear functions and the next controller input $u(k)$ is *not* contained in the nonlinearity. For identification two NNs have to be trained to approximate the nonlinear functions f and g. We wanted the system output to follow a *reference trajectory* meeting with the constraints. We chose a sigmoid reference trajectory because biological systems usually respond in such a fashion to inputs.

After the model structure was selected, the next choice that has to be made is the *model order*. At the end, the following specifications, identical for both NN, were used:

- the number of hidden layers was one,
- the number of neurons in the hidden layer was three,
- the activation functions were tangent hyperbolic for the neurons in the hidden layer and linear in the output layer,
- the training algorithm was Levenberg-Marquandt,
- the model order - number of past output, $n = 3$, number of past input, $n = 3$, and the time lag, $d = 1$,
- the sampling time was 0.01,
- the total number of samples was 8400, and
- the number of training epochs was 1000.

When NNs have been trained, the next step is to evaluate them. The most common method of validation is to investigate the prediction errors by cross-validation on a test set. Control performances depend crucially on the quality of identification. This was very good, with a mean square error (MSE) of the order 10^{-5}.

Based on the identified model, the next step is to develop a *neural controller*. Given the rigorous and elegant theoretical foundations of *feedback linearization*, a version of this type of controller has been used - NARMA-L2 [6]. The general idea of the input-output linearization technique is to linearize the input-output characteristics of a nonlinear system via an appropriate nonlinear feedback control law, by canceling the nonlinearities. To apply the exact input-output feedback linearization theory, affine models are necessary. The term affine means that the input must appear linearly in the state space description of the model. The choice of this neurocontroller is also motivated by the fact that *all* pharmacokinetics models are affine. Using the NARMA-L2 model the following controller is obtained:

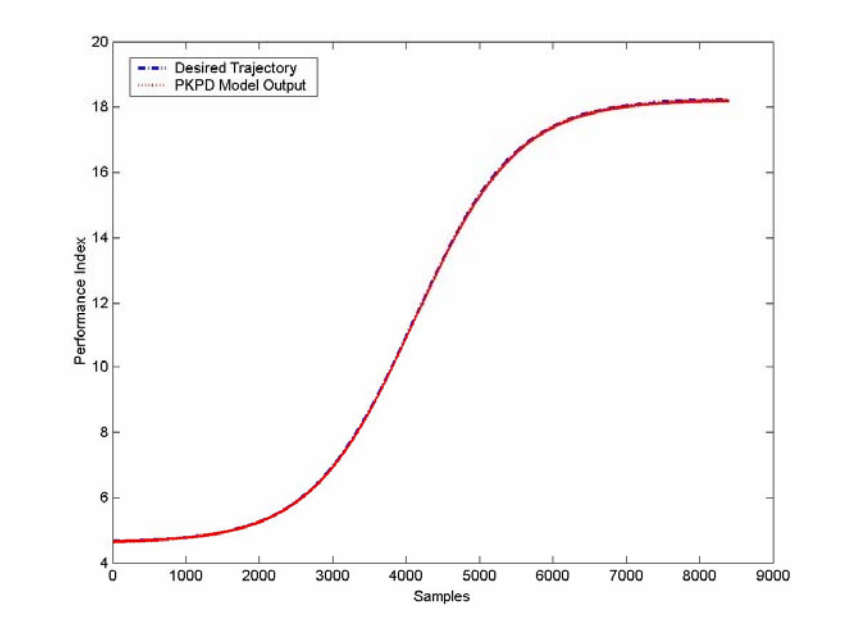

Fig. 1 NARMA-L2 controller constraining, via input, the PKPD model output to follow the desired trajectory

$$u(k+1)=\frac{y_r(k+d)-f\left[y(k),...,y(k-n+1),u(k),...,u(k-n+1)\right]}{g\left[y(k),...,y(k-n+1),u(k),...,u(k-n+1)\right]} \qquad (5)$$

The fact that *g* is never equal to zero induces a globally valid feedback linearizing control law, i.e. which is valid everywhere in the space of admissible inputs and outputs. This is not the same as the Jacobian linearization around an equilibrium point. The latter one is only a linear approximation of the process at a particular operation point.

3. RESULTS AND DISCUSSION

The versatility and effectiveness of the adaptive NN control in chemotherapy optimization is illustrated by considering the most accepted model of tumor growth - Gompertz model, the NARMA-L2 controller version of feedback linearization, and a therapeutic goal. The last one is attained with high precision and the toxicity and drug resistance constraints are all met. These are incorporated in a sigmoid reference trajectory to reflect the typical response to the inputs of biological systems. Besides having a sound theoretical foundation, feedback linearization has lower memory and computation time requirements than other NN and genetic algorithms based controllers. More than this, *all* pharmacokinetics models, regardless of the route of administration, number of compartments and doses, satisfy the conditions of applicability of feedback linearization. Due to its modular construction the proposed system is very *flexible*. The PKPD model and/or the therapeutic goals can be changed to adequately describe different clinical situations; the NN control will learn to model and control this new situation. The NARMA-L2 controller performance (see Fig. 1), expressed as percentage differences as compared to the best-known in the literature, is better with 4.1% (see [3] and [4]). Usually, the designers of dosage regimens do not take into account the important concept of dose intensity. Often the obtained optimal dosage regimens have very unrealistic times of administration, inter-dose intervals, dose sizes, and no clinical relevance. To overcome this major impediment, we did not consider directly the input computed by the NN as the optimal drug schedule. The *optimal dose intensity* can be derived from the optimal computed input. Optimal dose intensity allows simple calculation of *clinically applicable* optimal dosage regimen. These results are generalized to the most representative classes of pharmacological models in [7] (results not shown).

5. CONCLUSION

This paper presented the optimal control drug scheduling of cancer chemotherapy using adaptive NN control methods based on feedback linearization. It has been shown that this approach is simple and capable of solving complex cancer chemotherapy problems in a realistic manner. Simulation results produced excellent control policies of drug scheduling in cancer chemotherapy, better than the solutions published in literature.

6. REFERENCES

[1] R. B. Martin, (1992), ”Optimal control drug scheduling of cancer chemotherapy”, *Automatica*, vol. 28, pp. 1113-1123.
[2] K. C. Tan, E. F. Khor, J. Cai, C. M. Heng, and T. H. Lee, (2002), ”Automating the drug scheduling of cancer chemotherapy via evolutionary computation”, *Art. Intel. Med.*, vol. 25, pp. 169-185.
[3] A. G. Floares, (2003), “Adaptive Neural Networks Control of Drug Dosage Regimens in Cancer Chemotherapy”, *Proceedings of the International Joint Conference on Neural Networks*, Portland, OR, pp. 154-159, (invited paper).
[4] A. G. Floares, (2003), “Adaptive Neural Networks for Optimal Control of Drug Dosage Regimens in Cancer Chemotherapy”, Proceedings *of the1st MEDINF2003 International Conference on Medical Information & Engineering,* Craiova, pp. 20-24.
[5] V. T. DeVita Jr., S. Hellman, S. A. Rosenberg, *CANCER. Principles and Practice of Oncology*, 6th Ed, Philadelphia: JB Lippincott, 2001.
[6] M. T. Hagan, and H. B. Demuth, (1999), ”Neural Networks for Control”, *Proceedings of the 1999 American Control Conference*, San Diego, CA, pp. 1642-1656.
[7] A. G. Floares, (2004) Adaptive feedback linearization neurocontrol applied to the most representative classes of pharmacological models (invited paper to the *International Joint Conference on Neural Networks*, Budapest.