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Optimizing the use of ultrasound to deliver chemotherapeutic agents to cancer cells from polymeric micelles

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Abstract

In this study, we present an artificial neural network (ANN) model that attempts to predict the dynamic release of doxorubicin (Dox) from P105 micelles under different ultrasonic power densities at 20kHz. The goal is to utilize the developed ANN model in optimizing the ultrasound application to achieve a target drug release at the tumor site by controlling power density and ultrasound duration via an ANN-based model predictive control. The parameters of the controller are then tuned to achieve good reference signal tracking.

Keywords: NN-MPC; Doxorubicin; P105 micelles; Drug release; Ultrasound stimulation

1. Introduction

Polymers have received ample attention in recent years for their use as drug delivery devices. The drug is usually mixed into a biodegradable polymer matrix allowing for its slow release as it diffuses from the polymer and/or the polymer matrix degrades. The main

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disadvantages of such a system are the complications associated with the surgery needed to implant such a device. To overcome such a problem, drug delivery systems that can be injected into the blood stream are an attractive option [1,2]. These systems include liposomes [3], solid particles [4], polymersomes [5] and polymeric micelles [6,7]. A polymeric drug carrier capable of forming micelles was investigated as a drug delivery carrier to minimize the side effects of conventional chemotherapy. This carrier was capable of retaining hydrophobic drugs and then releasing them by application of ultrasound. We have shown that the DNA damage induced by the drug doxorubicin (Dox) delivered to human leukemia cells (HL-60) from Pluronic P105 micelles, with and without the application of ultrasound, was at an optimum when cells were exposed to ultrasound and micelles containing the anti-neoplastic agent [8]. Using an ultrasonic exposure chamber with real-time fluorescence detection, our group measured acoustically activated drug release from Pluronic P105 micelles under continuous wave (CW) or pulsed ultrasound [9]. The percentage of drug release was highest at 20kHz ultrasound and decreased with increasing ultrasound frequency despite much higher power densities. Later, experiments showed an important role of transient cavitation in drug release [10].

Conventional linear modeling techniques are incapable of capturing the transients of highly nonlinear processes. Black-box modeling algorithms are receiving wide popularity for such situations due to their simplicity and high prediction performance [11]. No prior knowledge of the process mechanism is needed to perform this task. Process engineers need only to gather input–output data from the process under consideration and use them for model training and validation.

Nonlinear modeling techniques can be utilized to predict process dynamics more accurately and can cover wider spectrum of operating conditions. Among these are the neural networks which have the capability of capturing and approximating the behavior of a system under different operating conditions. ANNs have attracted researchers in versatile disciplines to use them for modeling purposes [12–14]. Acoustic release of doxorubicin from unstabilized Pluronic P105 modeling problem was considered in a recent work [15]. This study revealed the great ability of ANNs to model such a complex process. Recently, neural networks are applied as controllers in many industrial applications. They are either directly implemented where the network controller is trained to learn the inverse of the process dynamics, or indirectly by training the neural network to predict future outputs from past and present inputs and outputs. In the former case, the process is modeled with a separate neural network, the controller does not invert the exact process model, and the offset cannot be eliminated. The indirect method is more suitable for control applications. The trained process model is used with a control algorithm to calculate the controller output.

During the past few years, several ANN-based control algorithms have been proposed and some of them were implemented in model predictive control (MPC) [16,17], internal model control (IMC) [18] , dynamic matrix control (DMC) [19] and adaptive control [20].

The application of nonlinear control design techniques for the drug release problem is a demanding research area and needs special attention. In the present study, an ANN dynamic modeling strategy of the drug release process is adopted due to the high nonlinearity and its noisy response of the processes. The validated ANN model is then used to train an ANN-based model predictive controller as previously described [21–27]. The parameters of the controller are later tuned to achieve good reference signal tracking. The application of neural networks based control algorithms such as model predictive algorithm and feedback linearization algorithm is justified by the success of these techniques to control complex nonlinear dynamics chemical and physical processes.

2. Materials

Pluronic® P 105 was provided by BASF Corp. (Mount Olive, NJ). Doxorubicin was obtained from the University of Utah Hospital (Salt Lake City, UT) in a 1:5 mixture with lactose and from Pharmacia & Upjohn Company (Kalamazoo MI), in dosage form; it was dissolved in phosphate buffered saline (PBS) and sterilized by filtration through a 0.2mm filter.

3. Drug encapsulation in Pluronic® unstabilized/stabilized micelles

Stock solutions of Pluronic® (BASF, Mount Olive, NJ) were prepared by dissolving P105 in a PBS solution to a final concentration of 10 wt%. Dox was dissolved into the P105 solutions at room temperature to produce a final Dox concentration of 10mg/ml in 10% wt Pluronic®. The same drug concentration was also prepared in phosphate buffered saline (PBS) [9].

3.1. Experimental setup

A chamber was built to measure the change of fluorescence upon application of ultrasound. The apparatus employed an argon ion laser (Ion Laser Technology, Model 5500 A) mounted on an optical bench. The laser beam was directed to a beam splitter attenuator (metal film neutral density attenuator). The intensity of the split portion of the beam was measured by a photodetector and was used to monitor the laser power. Photodetector measurements were digitized for storage in a computer.

The drug concentration was quantified by measuring the fluorescence emissions produced by an excitation wavelength of 488nm. A fiber optic probe (100 bundled multinode fibers, approximately 40cm in length) was used to collect fluorescence emissions. The emitted light was directed through a multinode dielectric band and filter (Omega Optical Model 535DF35, Brattleboro, VT) to a silicon detector (Model EGSG). The filter was used to cut off any emissions with a wavelength below 535nm. The detector signal was digitized with an A/D converter (National Instruments, Austin, TX) and sent to a Macintosh computer (Apple Computers, Cupertino, CA) for storage and processing. The temperature of the ultrasonic exposure chamber was maintained at 371C using a thermostated bath.

The chamber described above was used to measure the kinetics of acoustically activated drug release (DOX) from P105 micelles. The drug exhibited a large decrease in fluorescence when

transferred from the hydrophobic core of the micelle to the surrounding aqueous solution. Therefore, the release was manifested by a decrease in fluorescence intensity.

The power density was measured using a hydrophone (Bruel and Kjaer model 8103, Decatur, GA), which sent a voltage signal to an oscilloscope. The power density was determined by measuring the peak-to-peak voltage of the signal appearing on the oscilloscope. The power density was reported by the manufacturer to be directly proportional to the square of the output voltage recorded on the oscilloscope. For example, the power density at 70kHz was calculated using the following formula:

$$Power = 16.6\frac{mW}{cm^2V^2}x(Vpp)^2 \qquad (1)$$

In Eq. (1), V_{PP} is the peak-to-peak voltage measured by the oscilloscope. To quantify the amount of drug released, the decrease in fluorescence after the drug was released from micelles was assumed to be directly proportional to the amount of the drug released relative to a known baseline. For instance, the fluorescence from the drug in PBS was measured in the absence of Pluronic to simulate 100% release into an aqueous solution. The percentage release was calculated using Eq. (2)

$$\%release = \frac{I_{p105}-I}{I_{P105}-I_{PBS}} \qquad (2)$$

In Eq. (2), I is the instantaneous fluorescence intensity, I_{PBS} refers to the fluorescence intensity recorded when the drug was introduced in a solution of PBS which corresponds to 100% release or no encapsulation, while I_{P105} refers to the intensity recorded when the drug was encapsulated in Pluronic P105 which corresponds to 0% release or 100% encapsulation.

The experimental procedure proceeded as follows. First, the fluorescence intensity of the drug in PBS was measured both with and without ultrasound exposure, and no difference in fluorescence was observed. This value was used for I_{PBS}. Then, without changes in the

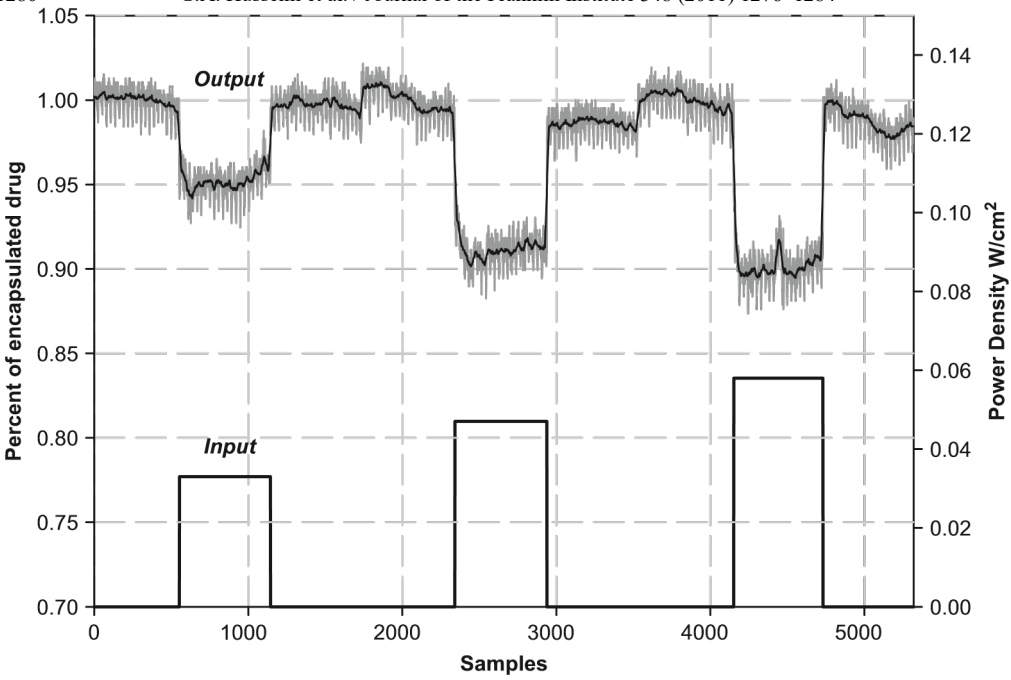


Fig. 1. Raw (grey line) and smoothed (black line) experimentally generated fluorescence data and the corresponding power density signals.

experimental set-up, the PBS solution was carefully removed and replaced with the drug solution of the same concentration in Pluronic micelles.

Fig. 1 shows the 5374 collected experimental data points. The observation that the three pulses produced a nonlinear response in fluorescence quenching indicates a nonlinear behavior for the drug release process. The three acoustic power density pulses of sizes 0.033, 0.048 and 0.058W/cm^2 resulted in the new fluorescence steady-state values of 0.9542, 0.9123 and 0.9057, respectively. It is clear that the second and third pulses achieved steady states that are not comparable in size to that of the excitations introduced. The amount of released drug calculated from Eq. (2) created by the three pulses are not proportional to the magnitudes of the acoustic power. This nonlinearity triggers the need to use a control technique that is capable of handling such process complexities efficiently. Another interesting aspect of Fig. 1 is the fact that the fluorescence level recovers to its original level after the ultrasound is turned off. This suggests that the drug is going back inside the core of the micelles and, therefore, will only interact with tissue where ultrasound is focused (the tumor) and not downstream of the focal volume.

4. Modeling and controller design results

A nonlinear model based control strategy is used to provide good reference tracking with the least number of controller moves for complex processes such as the drug release process. The input (power densities used in the experiments) and output (percent encapsulated doxorubicin) data were first smoothed to reduce noise associated with the experiments and prepare for ANN training. A moving average smoothing strategy was used with a sampling proportion of 0.01 (Fig. 1) which revealed the drug release nonlinearity, especially within the periods of pulse dampening where unusual response jumps occur.

A feedforward ANN with output feedback was constructed with one hidden layer. For more information on the general structure of this network please refer to our previous publication [15].

The Matlab software implementation of the Levenberg–Marquardt backpropagation optimization algorithm (LMBP) was used for this purpose. This algorithm converges to optimum solution with the least optimization steps. The 53,741 input/output pairs were then divided into three subsets with the ratio of 2:1:1 (training, validation and testing, respectively).

A total of 427 epochs (training steps) were used to achieve a prediction error of 2.1710^{7}, 3.7010^{7} and 2.210^{6} for the three respective subsets within a search time of 104s. With this performance the trained ANN can predict process dynamics accurately. Fig. 2 shows the simulation of the trained ANN for the three subsets as well as the original data. The ANN predictions are very close to the actual drug release data.

After modeling the drug release process dynamics by tracking the percent of encapsulated drug, the generated trained ANN was implemented in the NN-MPC controller. The controller structure of the model is based on feedforward neural networks given by Liu et al. (1998) [28].

The tuning parameters for this controller are: the prediction horizon (N_2), the control horizon (N_u), the control weighting factor (l) and the search parameter (a). The prediction and control horizons were set at their best values of 10 and 5, respectively. These values showed moderate aggressiveness and good stability of the controller response. The effect of

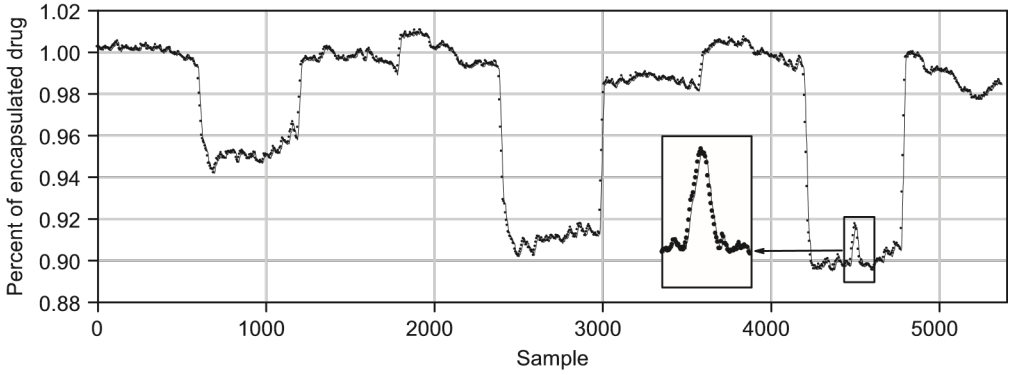


Fig. 2. Simulated ANN predictions and experimental data.

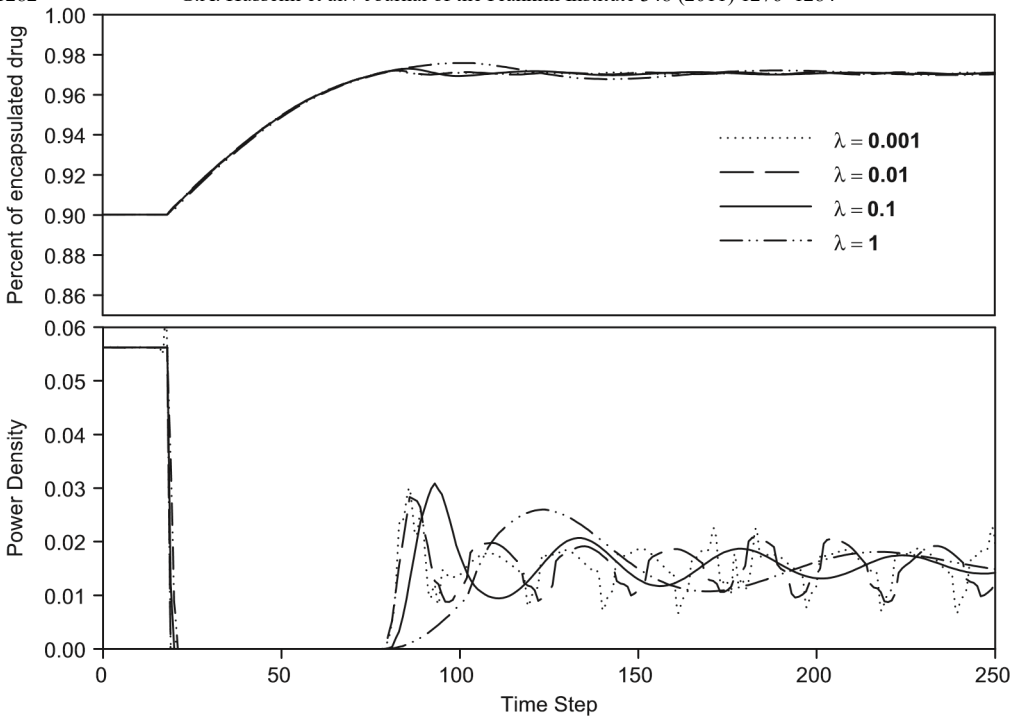
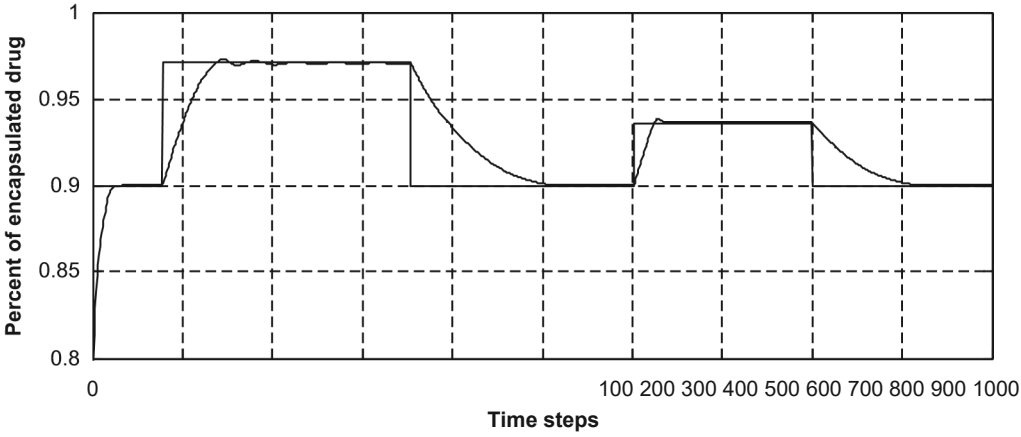


Fig. 3. Effect of control weighting factor on the performance of the NN-MPC.

control weighting factor value on the performance of the NN-MPC for a drug release step (0.9–0.96) is shown in Fig. 3. Choosing a high value (l=1) causes oscillations in the predicted drug release while selecting a small value (l=0.001) results in oscillatory power density input. Hence a value of (l=0.1) was selected which gave very good tracking with low oscillatory behavior.

The search parameter a is used to control the optimization speed and performance and determines when the search process stops. The optimization algorithm used in this work



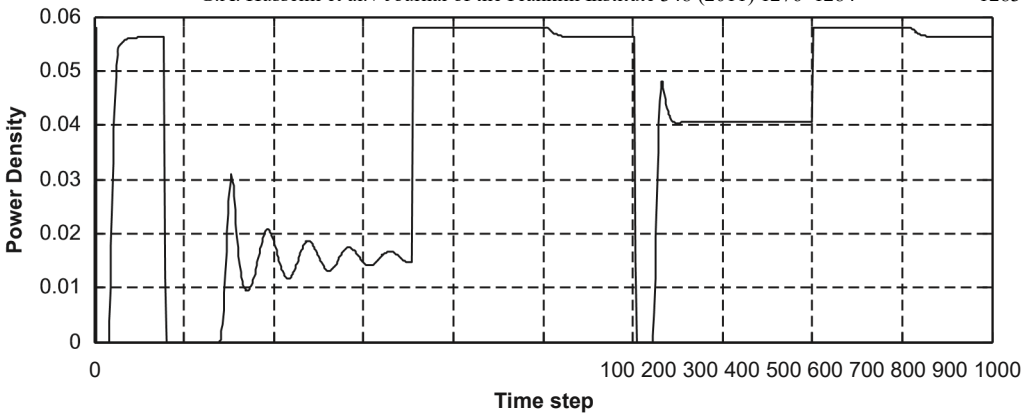


Fig. 4. NN-MPC setpoint tracking performance and the corresponding controller moves.

utilizes this scale factor to minimize the performance training function along the search direction. In this work a was set to a value of 0.001.

To test the final design of the NN-MPC controller, a series of random set-points in the drug release setpoint were introduced in the process control loop and the controller performance was recorded. Fig. 4 shows the resulting profile of the process as well as the corresponding controller moves. In terms of controller moves the NN-MPC configuration produced smooth and non-aggressive changes in the power density. The controller output was bounded within the allowable limits of power density used experimentally at 20kHz. The figure indicates that the controller was able to follow the reference signals excitations within a reasonable response time.

5. Conclusions

NN-MPC was shown to be an effective tool to model, optimize, and control the release of doxorubicin from P105 micelles under different ultrasonic power densities at 20kHz. The feed-foreword neural network was able to capture accurately the drug release dynamic data. Tuning of MPC-NN controller was performed to achieve satisfactory reference signal tracking in terms of smoothness and response speed.

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