Predicting the Release of Chemotherapeutics From the Core of Polymeric Micelles Using Ultrasound

Mamoun Abdel-Hafez, *Member, IEEE*, and Ghaleb A. Husseini*, *Member, IEEE*

***Abstract*—In this paper, the estimation of acoustic drug release from micelles is addressed. The release is measured as a decrease in fluorescence once ultrasound is applied. Initially, a Kalman filter is used to fuse the drug encapsulation (calculated as 100% − release %) dynamics and measurements. Since the measurements' noise statistics are not known *a priori*, the encapsulation estimate is not optimal. Therefore, an approach is proposed to adaptively estimate the drug release given the statistical properties of the measurements. In this approach, a number of measurement covariance magnitudes are hypothesized. A Kalman filter is used to obtain the estimate of the acoustic release given each hypothesized measurement noise covariance. Simultaneously, the probabilities of these measurement covariance hypotheses are sequentially computed as the measurements and the predicted release estimates are obtained. Finally, the optimal release estimate is obtained by probabilistically adding the estimates from the hypothesized Kalman filter estimates. The proposed algorithms are first tested using a simulation environment. Subsequently, experimental results are shown to validate their performance. The experiments conducted cover various ultrasonic power densities for both non-targeted and targeted micelles.**

***Index Terms*—Chemotherapy, drug release, Kalman filter, modeling, pluronic® micelles, ultrasound.**

I. Introduction

NANOTECHNOLOGY has enabled engineers and scientists to make great strides in the biomedical and bioengineering fields including in the areas of drug and gene delivery. In fact, Ueno *et al.* have described several new breakthroughs of nanotechnology in nanobioscience and a multitude of their applications [1]. Some innovative biomedical techniques for drug delivery include the transdermal drug delivery using an electrode-reservoir device devised and discussed by Pliquett and Weaver, and the use of microneedles elaborated on by Davis *et al.* [2], [3]. Of particular interest to our research group is the use of nanocarriers (i.e., micelles and liposomes) to deliver high concentrations of chemotherapeutic agents to malignant tumors and then trigger their release using ultrasound [4]. This manner of drug delivery reduces the undesired side effects associated with conventional chemotherapy since the agent is allowed to have minimal interaction with healthy cells while the bulk of its effect is directed towards the diseased tissue.

Micelles are colloidal particles with a size that ranges between 10 and 1000 nm [5]. Drug entrapment inside biodegradable micelles has many advantages that includes prolonging the drug's circulation period in the body, protecting the drug from inactivation in bodily fluids, decreasing drug systemic toxicity and biodegradability, while increasing tissue uptake into tumors via the enhanced retention and permeation (EPR) effect [6], [7].

Our research employs acoustic waves as a means of inducing drug release from micelles [8]. Ultrasound was shown to prompt drug release from polymeric micelles and to enhance the intracellular uptake of both the released and encapsulated drug through a process called sonoporation. Sonoporation is the formation of pores in the cell membranes of tissue exposed to US, which induces the temporary permeabilization of cells, allowing for the drugs to be taken into the cell cytosol [9]. The ultrasonic intensity that is applied on the specific part of the body causes the cavitation of microbubbles, thus inducing shockwaves and microjets, which in turn can cause these microbubbles to explode, a process known as collapse cavitation [10]. When the bubbles explode, the micelles are sheared opened, thus allowing the drug to diffuse out of the carrier. Rodamporn *et al.* experimentally determined the efficiency of such processes to reach 70% [11]. Siu *et al.* discussed an innovative method of achieving this endeavor using miniature ultrasound transducers [12]. Moreover, this process could be further aided by the therapy imaging probe system (TIPS) designed and discussed in Seip *et al.* [13].

We have reported earlier the release of Dox from P105 micelles and have examined its kinetics mechanistically and probabilistically [14]–[16]. In this paper, we use a Kalman filter to predict the dynamic behavior of this triggered drug delivery system [17]. The Kalman filter is a mechanistic approach used to fuse the dynamics and the measurements of the system. In this dynamic system, the knowledge of the dynamic model of the percent drug encapsulation is used along with the system's measurement to obtain an optimal estimate of the percent drug encapsulation. The Kalman filter is an optimal estimator that minimizes the expected value of the square error between the estimate and the true value of the percent encapsulation (a minimum mean square error estimator).

The problem was tackled in two different approaches. The first was to estimate the systems noise properties using statistical approaches [18]–[21]. In the other approach, the unknown

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M. Abdel-Hafez is with the Department of Mechanical Engineering, American University of Sharjah, Sharjah, United Arab Emirates (e-mail: mabdelhafez@aus.edu).

*G. A. Husseini is with the Department of Chemical Engineering, American University of Sharjah, Sharjah, United Arab Emirates (e-mail: ghusseini@aus.edu).

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systems' error statistics were assumed as a system's, or measurement, fault [22], [23]. In the latter assumption, a possible fault bank is hypothesized and probabilistic algorithms are used to determine the correct fault hypothesis [23].

In this paper, the percent drug release of the triggered drug delivery system was estimated. Initially, a Kalman filter, with *a priori* assumptions of the statistical covariance of the measurement noise, was used to estimate the drug release. However, since the drug release measurement is characterized with highly uncertain, and possibly changing, measurement noise statistics, a multiple-model Kalman filter is used to estimate the drug release. Practical uncertainty in the system parameters including ultrasound frequency, amplitude, time, pulse time, distance from target, is the reasons why the proposed multiple model estimator is used. Therefore, a bank of possible measurement noise covariance magnitudes was hypothesized. A number of Kalman filters were simultaneously used to estimate the drug release each under the assumption of a certain measurement noise covariance. The *a priori* estimate of drug release along with the measurements was used to obtain the probability of each measurement noise covariance. The optimal estimate of drug release was finally calculated as the probabilistic sum of the estimates obtained from the bank of Kalman filters. The intrinsic advantage of the proposed approach is the determination of the probabilistic belief measure for the various implemented Kalman filters [19]. This leads to an enhancement in the optimality of the drug release estimator [18]. As the proposed Kalman filter adaptively estimates the statistics of the measurement noise, there is no need to retune the filter if the measurement conditions change.

The proposed Kalman-filter based percent drug release estimation method is essential to design a model-predictive controller for cancer treatment. A high-accuracy estimate of the percent drug release is needed to enhance the optimality of the controller. Additionally, to control the treatment process, the predicted state of percent drug release is needed at times when measurements are not available. This is where the proposed high-accuracy percent drug release estimation method is vital.

II. Materials and Methods

A. Drug Encapsulation in Pluronic® Targeted and Non-Targeted Micelles

Define Stock solutions of Pluronic® P105 (gift from BASF, Mount Olive, NJ, USA) were prepared by dissolving the polymer in a PBS (phosphate buffered saline) solution to a final concentration of 10% wt. Doxorubicin Hydrochloride-Dox (Pharmacia & Upjohn Company Kalamazoo, MI, USA) in dosage form (1:5, Dox: lactose) was dissolved into the P105 solutions at room temperature to produce a final Dox concentration of 4.5 μg/ml in 5% wt. Pluronic®. The drug was encapsulated inside non-targeted Pluronic P105 micelles and folate-targeted Pluronic P105 micelles [17]. As a control, the same drug concentration was also prepared in PBS.

B. Measuring the Acoustic Release From Micelles

To quantify the release, a custom chamber was built to measure the change in fluorescence and hence the Dox release in the presence and absence of ultrasound (Fig. 1) [17]. The beam of an argon ion laser (Ion Laser Technology, Model 5500 A) 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 (used to monitor the laser power) and the other portion of the beam was directed into a fiber optic bundle. The drug concentration was quantified by measuring fluorescence emissions at 535 nm produced by an excitation wavelength of 488 nm as shown in Fig. 1 and reported earlier [10].

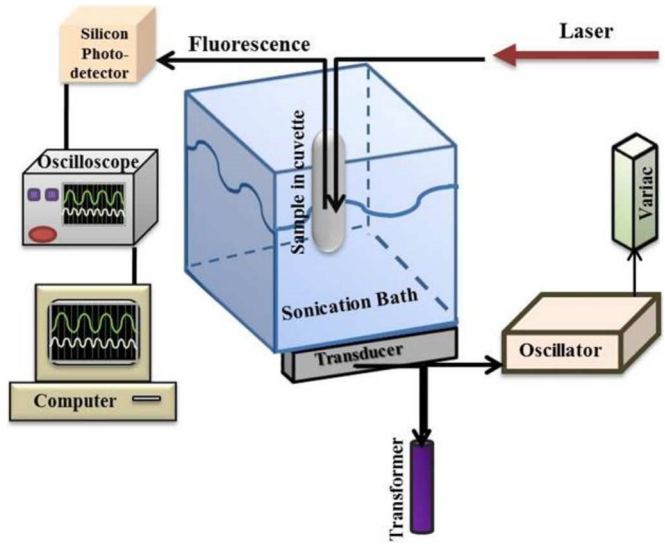

Fig. 1. Schematic of the ultrasound exposure chamber with fluorescence detection used to measure the release of doxorubicin.

C. Mechanistic Dynamic Model

In this study, we used the model previously formulated by Husseini *et al.* [16]. The model proposes that Dox is released from micelles at a constant rate while the ultrasound is on, and the simultaneous rate of re-encapsulation is first-order with respect to the concentration of the free drug. This model is based on the theory that ultrasound may create inertial cavitation events that result in the destruction of micelles at a constant rate, and that this rate does not depend on the micelle concentration. The destroyed micelles release the drug, but the free Dox molecules are taken up by micelles at a rate proportional to the free drug concentration. The drug can either be re-encapsulated into micelles that were not destroyed, or into newly-formed micelles.

Mathematically, the model can be represented as in (1), where E is the amount of drug encapsulated, F is the amount of free drug, T is total amount of the drug in solution (4.5 μg/ml), k_r is the zero-order release rate constant, and k_e is the first order re-encapsulation rate constant.

$$\left.\frac{dE}{dt}\right|_{US} = -k_r + k_e F = -k_r + k_e(T - E) \tag{1}$$

D. Data Fitting

The raw fluorescence data were noisy, and since the pulsing of the ultrasound was done manually, the exact on/off times do not coincide for all experiments. For each power density, several experimental runs were conducted, and then the regions were divided according to where release and re-encapsulation occurred. The curves of release versus time were plotted and were subsequently overlapped over the horizontal and vertical axes. Details on the how the release and re-encapsulation kinetic constants of this system can be found elsewhere [16].

III. Encapsulation Estimation

A. Kalman Filter Design

A Kalman filter was used to obtain an estimate of the drug encapsulation percent. The encapsulation percent is calculated by subtracting the release percent from 100% encapsulation (or unity), as in

$$E(t) = 100\% \text{ encapsulated drug} - \%\,\text{Release}(t). \tag{2}$$

The Kalman filter is an optimal algorithm for fusing the dynamics and measurements of the system. Starting with the dynamic model of the system that is given in (2), the model is first discretized given the measurement frequency of 50 Hz as in (3), with as the sampling time, taken as 0.2 seconds, as dynamics noise, assumed as a Gaussian white noise and

$$E(k) = e^{-ke\Delta e}E(k-1) + B_d + \omega(k). \tag{3}$$

The measurement was modeled as in (4), where is the measurement noise assumed as a Gaussian white noise.

$$y(k) = E(k) + \upsilon(k) \tag{4}$$

Starting with the initial encapsulation boundary conditions using

$$\begin{aligned} E[E(0)|y(0)] &= \hat{E}(0) \\ \text{cov}[E(0)|y(0)] &= P(0), \end{aligned} \tag{5}$$

and, with the process and measurement noise sequences assumed to have zero mean and covariance given by

$$\begin{aligned} \text{cov}[\omega(k))] &= Q \\ \text{cov}[\upsilon(k))] &= R. \end{aligned} \tag{6}$$

The propagations tageoftheKalmanfilterisperformedasin (7),where $\bar{E}(k) = E(k|k-1)$ isthepropagatedestimateofthe encapsulation.

$$\bar{E}(k) = e^{-k_e\Delta t}\hat{E}(k-1) + B_d \tag{7}$$

The covariance of this propagated estimate is given as

$$P(k|k-1) = \bar{P}(k) = \exp^{-2k_e\Delta t}\hat{P}(k) + Q, \tag{8}$$

with the *a priori* measurement evaluated as

$$E[y(k)|k-1) = \bar{y}(k) = \bar{E}(k). \tag{9}$$

The innovation is defined as

$$\tilde{y}(k) = y(k) - \bar{y}(k), \tag{10}$$

for which, the innovation covariance is defined as

$$S(k) = \bar{P}(k) + R. \tag{11}$$

The innovation covariance is used to obtain the updated estimate of the encapsulation as in (12), where is the Kalman gain calculated as .

$$\hat{E}(k) = \bar{E}(k) + W(k)\tilde{y}(k) \tag{12}$$

The covariance of the updated estimate of the encapsulation percent, $P(k|k) = P(k)$, is given as

$$P(k) = \bar{P}(k) - W(k)S(k)W^T(k). \tag{13}$$

The process noise covariance matrix can be found by expanding the term in (3) as

$$B_d = \bar{B}_d + \frac{\partial B_d}{\partial k_e}\Delta k_e + \frac{\partial B_d}{\partial k_r}\Delta k_r \tag{14}$$

But, with given as

$$k_r = Ae^{-\frac{PDa}{PD}}, \tag{15}$$

the term is expanded as

$$k_r = \bar{k}_r + \frac{\partial k_r}{\partial A}\Delta A + \frac{\partial k_r}{\partial PDa}\Delta PDa + \frac{\partial k_r}{\partial PD}\Delta PD.$$

Therefore, the covariance of the process noise can be represented as in (18), where $E[\Delta k_r^2]$ is calculated as in (17).

$$\begin{aligned} E\left[\Delta k_r^2\right] &= \left(\frac{\partial k_r}{\partial A}\right)^2 E[\Delta A^2] + \left(\frac{\partial k_r}{\partial PDa}\right)^2 E[\Delta PDa^2] \\ &\quad + \left(\frac{\partial k_r}{\partial PD}\right)^2 E[\Delta PD^2] \end{aligned} \tag{16}$$

$$\begin{aligned} Q = E[(B_d - \bar{B}_d)^2] &= \left(\frac{\partial B_d}{\partial k_e}\right)^2 E\left[\Delta k_e^2\right] \\ &\quad + \left(\frac{\partial B_d}{\partial k_r}\right)^2 E\left[\Delta k_r^2\right] \end{aligned} \tag{17}$$

ment noise covariance matrix, R. The filter is optimal only if

(18)

The Kalman filter assumes the knowledge of the measure-

the chosen measurement covariance matrix is representative of the actual measurement noise statistics. Due to the high noise in the encapsulation measurement structure, it is hard to characterize the measurement noise statistics accurately. Therefore, a multiple model Kalman filter approach is proposed to enhance the optimality of the filter by probabilistically determining the covariance of the measurement noise.

B. A Multiple Model Approach

In this approach, a number of hypotheses, $h = 1, 2, \ldots n$, are assumed for the covariance of the measurement noise. The probability density of the measurement in (7) given a certain hypothesis h, is given in (19), where S_h is the covariance of the innovation given the measurement noise.

$$f_h(y(k)) = \frac{1}{\sqrt{2\pi S_h}} \exp\left\{-\frac{1}{2}\tilde{y}^T S_h^{-1} \tilde{y}\right\} \tag{19}$$

But the probability of the hypothesis H_h given all the measurements up to time k needs to be calculated to check whether this measurement statistical hypothesis is valid or not. The probability that this hypothesis is correct is designated as

$$F_h(k) = P(H_h | y(0), y(1), \ldots y(k)). \tag{20}$$

This probability is expanded using the Bayes' rule as

$$P_h(k) = \frac{P(H_h, y(k) | y(0), y(1), \ldots y(k-1))}{P(y(k) | y(0), y(1), \ldots y(k-1))}. \tag{21}$$

Equation (21) can be rewritten utilizing Bayes' rule as in (22). The denominator of (22) can be expanded, utilizing the total probability theorem, as in (23).

And by Bayes' rule, (23) is written as in (24), at the bottom of the page.

But, with

$$P(H_h | y(0), y(1), \ldots y(k-1)) = F_h(k-1), \tag{25}$$

and, since the measurement noise is assumed independent and identically distributed,

$$\begin{aligned} P(y(k) | H_h, y(0), y(1), \ldots y(k-1)) &= P(y(k) | H_h) \\ &= f_h(y(k)). \end{aligned} \tag{26}$$

The probability of hypothesis H_h givenallmeasurementsup totime k canbeexpressedfrom(26)as

$$F_h(k) = \frac{F_h(k-1) f_h(y(k))}{\sum_{h=1}^{n} F_h(k-1) f_h(y(k))} \tag{27}$$

Therefore,inthisapproach, n Kalmanfilterswillbeoperating in parallel. Each of these Kalman filters will be assuming a certain hypothesis associated with an assumed measurement

$E_h(k)$ $P_h(k)$

noise covariance to obtain an estimate of the encapsulation and its associated covariance, and , respectively. Equation (27) will be used to calculate the probability of each hypothesis. The encapsulation is finally estimated by probabilistically summing the estimates of the various Kalman filters as

$$\hat{E}_{\text{optimal}}(k) = \sum_{h=1}^{n} F_h(k) \hat{E}_h(k), \tag{28}$$

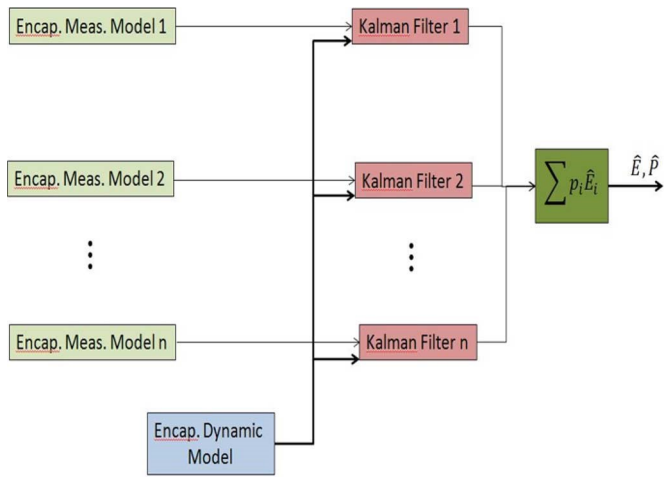

Fig. 2. Multiple-model adaptive filter structure for estimating encapsulation.

with an associated covariance that is given as

$$P_{\text{optimal}}(k) = \sum_{h=1}^{n} F_h(k) P_h(k). \tag{29}$$

The proposed approach is summarized in Fig. 2.

IV. Results

A. Simulation Results

Initially, a simulation environment was built to test the proposed approaches. In this environment, the encapsulation dynamics and measurement were simulated by (3) and (4). Subsequently, the proposed Kalman filter and the adaptive Kalman filter approaches were used to estimate the encapsulation. Since the true encapsulation is known, the performance of the proposed methods can be verified. The results of the simulation are shown in Fig. 3.

Fig. 3 shows the encapsulation percent estimates using a Kalman filter and an adaptive Kalman filter. The figure shows both the estimated and the true encapsulation. It can be seen that the adaptive Kalman filter produces a higher accuracy estimate than the Kalman filter. This is because the Kalman filter assumes a certain value of the measurement noise, which may not be correct. In comparison, the adaptive Kalman filter hypothesizes a number of values for the measurement noise covariance and probabilistically determines the encapsulation percent estimate that matches the statistical properties of the measurements.

TABLE I EXPERIMENTAL CONDITIONS FOR CONDUCTED TESTS

B. Experimental Results

In this section, experimental encapsulation estimation results are shown. The experiments were conducted for non-targeted and targeted micellar release. The experiments were also repeated under varying ultrasonic power density. Table I summarizes the experimental conditions of the conducted tests.

$$F_h(k) = \frac{P(y(k)|H_h, y(0), y(1), \ldots y(k-1))P(H_h|y(0), y(1), \ldots y(k-1))}{P(y(k)|y(0), y(1), \ldots y(k-1))} \tag{22}$$

$$P(y(k)|y(0), y(1), \ldots y(k-1)) = \sum_{h=1}^{n} P(y(k), H_h|y(0), y(1), \ldots y(k-1)) \tag{23}$$

$$P(y(k)|y(0), y(1), \ldots y(k-1)) = \sum_{h=1}^{n} P(y(k)|H_h, y(0), y(1), \ldots y(k-1))P(H_h|y(0), y(1), \ldots y(k-1)) \tag{24}$$

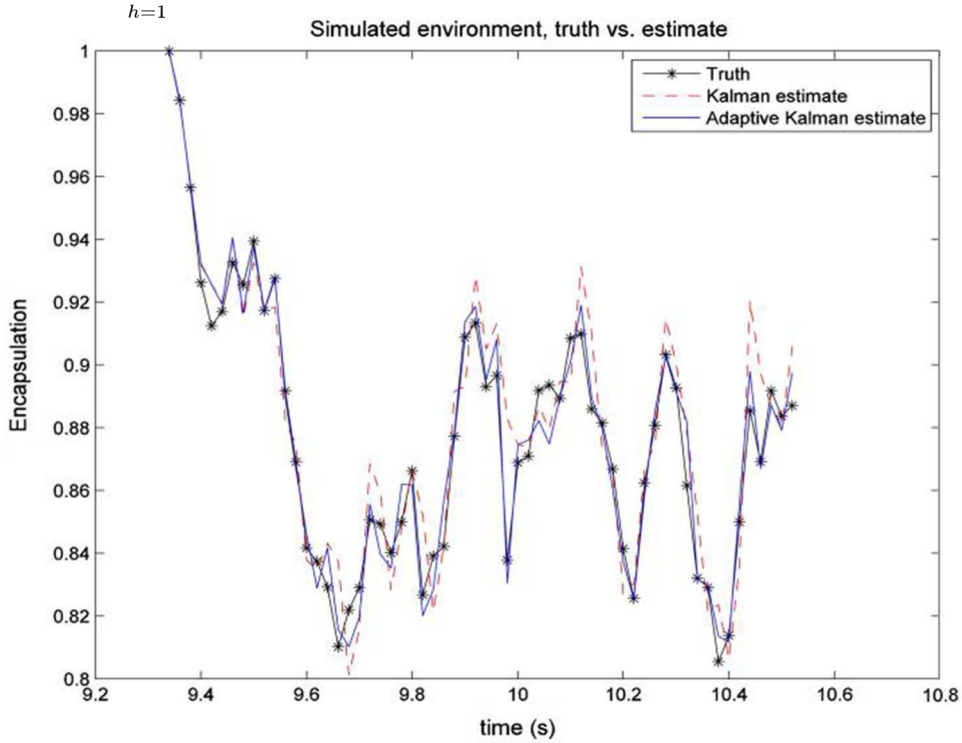

Fig. 3. Estimate of encapsulation using a Kalman filter vs. an adaptive Kalman filter, simulation environment.

Experiment #		Power Density (W/cm^2)	k_e
1	Non-Folated Micelles	3.54	27.38
2		5.09	26.41
3		5.43	31.86
4		5.91	23.16
5	Folated Micelles	3.54	21.20
6		5.09	23.89
7		5.43	10.07
8		5.91	21.18

Initially, the Kalman filter approach and the adaptive Kalman filter approach were used to estimate the encapsulation percent (which is equal to 1- release percent) for a non-targeted micelle with the release being achieved using 5.91 W/cm2 of 70-kHz ultrasound. This is experiment 4 in Table I. The results of the two proposed approaches are shown in Fig. 4. It can be seen that the adaptive Kalman filter achieves a better estimate of the drug encapsulation percent which is more in agreement with the measured experimental data. This is attributed to the higher ac-

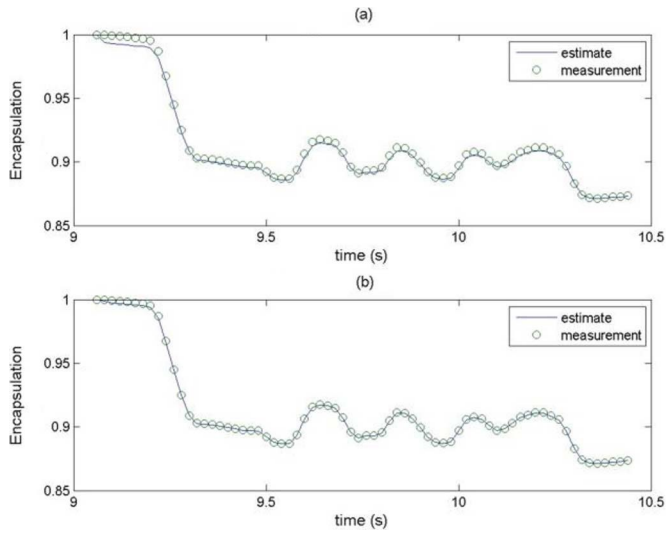

Fig.4. PD = 5.91 W/cm², usingnon-targetedmicelles:(a)usingaKalmanfilter;(b)usingan Estimate of encapsulation for an experimental test with adaptive Kalman filter.

curacy estimate produced by probabilistically fusing the results of the hypothesized Kalman filters' encapsulation estimates.

The performance of the adaptive Kalman filter was further checked by estimating the encapsulation percent of the drug in non-targeted experiments for ultrasonic power density of 3.54, 5.09, and 5.43 W/cm2 and targeted experiments for ultrasonic power densities of 3.54, 5.09, 5.43, and 5.91 W/cm2. Similar to the performance shown in Fig. 4(b), the adaptive Kalman filter achieved high accuracy estimates that are in agreement with the measured experimental encapsulation. The figures demonstrating the performance of the proposed estimation approach in these experiments are not shown for brevity.

V. Discussion and Conclusion

This paper estimates the release of drugs from targeted and non-targeted micelles, using an adaptive Kalman filter method. Release reaches steady state at approximately 15%, where equilibrium, between the chemotherapy drug encapsulated inside the micelles and that in the surrounding solution, is achieved. But, why is release observed as evidenced by a decrease in fluorescence (i.e., a decrease in percent encapsulation)? Polymeric micelles (in our case Pluronic® P105 micelles, whether targeted or non-targeted) may be sufficiently close to an oscillating bubble that the local stresses disrupt the micelle. These microbubbles are present in the micellar media and their oscillation in an acoustic field is termed cavitation.

The term cavitation can be defined as the formation of gas-bubbles within a liquid by an ultrasonic wave. Generally speaking cavitation can be divided into two types: stable and transient cavitation. Cavitation occurs due to an ultrasound-induced gradient that is found in the medium. The first occurs when the change in the bubble's size oscillation is almost stable. During stable cavitation, two more phenomena occur: microstreaming, and acoustic pressure. Once the resonance frequency of the microbubble is equal to that of the ultrasound frequency, the microbubble collapses. This collapse phenomenon is termed transient cavitation and it occurs when the change in the bubble's size becomes great and eventually leads to the burst of the bubble. When comparing stable and transient cavitation, it has been inferred that stable cavitation does not generate the same violent behavior as that generated by transient cavitation events. Upon collapse of the microbubble, shockwaves generating high stresses shear the micelle opened and hence the drug diffuses out of nanocarrier's core, thus releasing its contents.

The estimation of drug release from micelles using ultrasound was addressed in this paper. First, a Kalman filter was proposed to obtain an optimal estimate. However, since the Kalman estimator is optimal only under correct assumptions of dynamics and measurement noise statistical properties, the optimality of the filter cannot be guaranteed. This is because the statistics of the measurement noise is not known *a priori*. Therefore, a multiple-model adaptive Kalman filter structure was proposed to obtain an accurate estimate of drug encapsulation. In this structure, a number of Kalman filters were used to estimate drug encapsulation, but each under a certain hypothesis of measurement noise covariance. The probability of each hypothesized measurement noise covariance was sequentially computed as the measurements were obtained and given the encapsulation predicted estimate. The final estimate of the drug encapsulation was obtained by probabilistically summing all the estimates of the Kalman filters. Simulation results were first used to verify the accuracy of the presented algorithms. Afterwards, the experimental results obtained in release experiments were used to validate the accuracy of the proposed Kalman filter structure. The modeling technique in this paper has the capability of tracing the percentage of drug release with high accuracy. Additionally, the proposed adaptive estimation algorithm does not require retuning in case of a change, or degradation, in the measurement quality. The probabilistic belief measure, which is calculated for the various implemented Kalman filters, is the intrinsic characteristic to enhance the optimality of drug release estimation.

The proposed adaptive Kalman filter for predicting the percent drug release is essential for model predictive control of cancer treatment processes. Obtaining a high-accuracy estimate of percent drug release is essential for the optimality of the model predictive controller. Additionally, to control the drug release at a certain percentage, the controller needs the predicted estimate of percent drug release at times when the measurement of the system is unavailable.

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Mamoun F. Abdel-Hafez received his B.S. degree in mechanical engineering from Jordan University of Science and Technology, Irbid, Jordan, in 1997, his M.Sc. degree in mechanical engineering from the University of Wisconsin, Milwaukee, WI, USA, in 1999, and his Ph.D. degree in mechanical engineering from the University of California, Los Angeles, CA, USA (UCLA) in 2003. He is an Associate Professor in the Department of Mechanical Engineering at the American University of Sharjah, Sharjah, United Arab Emirates. Dr. Abdel-Hafez served as a Postdoctoral Research Associate in the Department of Mechanical and Aerospace Engineering at UCLA from June 2003 to December 2003, where he was involved in a research project on fault-tolerant autonomous multiple aircraft landing. His research interests are in stochastic estimation, control systems, sensor fusion, fault detection, algorithms and applications of GPS/INS systems, and dynamic analysis and synthesis of vehicle systems.

Ghaleb A. Husseini received the Ph.D. degree in chemical engineering (biomedical engineering emphasis) from Brigham Young University, Provo, UT, USA, in 2001 and joined the American University of Sharjah, Sharjah, United Arab Emirates (AUS) as an Assistant Professor in the Chemical Engineering Department in January 2004. He was promoted to Associate Professor and Professor in 2008 and 2013, respectively. Two years ago, Dr. Husseini took a sabbatical leave which enabled him to travel to Ecole Polytechnique Fédérale de Lausanne (EPFL), and work in Dr. Jeffrey Hubbell's laboratory.

He works in the area of ultrasound activated drug delivery. His research involves sequestering chemotherapeutic agents in liposomes, micelles, and other nanoparticles. The contents of this drug delivery system can then be released using ultrasound (US). This way the drug has minimal interactions with the healthy cells in the host body, and it can carry out its therapeutic effect at the sonicated cancerous region only and reduce the undesirable side effects associated with chemotherapy. He has recently established a Drug Delivery laboratory at AUS using an internal grant.

Dr. Husseini has published 73 journal articles (in addition to 1 book chapter and 1 patent) and 40 conference papers/abstracts. In addition, he was a Theme Editor for a special issue in *Advanced Drug Delivery Reviews* and is currently serving on the Editorial Board of the *International Review of Applied Sciences and Engineering* (IRASE). He has been elected into the Distinguished Lecturer Program-**IEEE-EMBS** (January 2014–December 2015).