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Modeling and Bias-Robust Estimation of the Acoustic Release of Chemotherapeutics from Liposomes

Ali Wadi[1], Mamoun Abdel-Hafez[1], and Ghaleb A. Husseini[2,*]

[1] *Department of Mechanical Engineering, American University of Sharjah, UAE*
[2] *Department of Chemical Engineering, American University of Sharjah, UAE*

This paper models the acoustic drug release of chemotherapeutics from liposomes using a kinetic model that accounts for systematic biases affecting the drug delivery process. An optimal stochastic filter is then proposed to provide robust estimates of the percent drug released. Optimality is guaranteed by accurately identifying the underlying statistical noise characteristics in experimental data. The estimator also quantifies the bias in the release, exhibited by the experimental data. Drug release is experimentally measured as a change in fluorescence upon the application of ultrasound. First, a first-order kinetic model is proposed to model the release, which is aided by a bias term to account for the fact that full release is not achieved under the conditions explored in this study. The noise structure affecting the process dynamics and the measurement process is then identified in terms of the statistical covariance of the measured quantities. The identified covariance magnitudes are then utilized to estimate the dynamics of drug release as well as the bias term. The identified *a priori* knowledge is used to implement an optimal Kalman filter, which was initially tested in a simulation environment. The experimental datasets are then fed into the filter to estimate the state and identify the bias. Experiments span a number of ultrasonic power densities for liposomes. The results suggest that the proposed algorithm, the optimal Kalman filter, performs well in modeling acoustically activated drug release from liposomes.

KEYWORDS: *Chemotherapy, Drug Delivery System, Bias, Kalman Filter, Modeling, Liposomes, Ultrasound.*

INTRODUCTION

The need to alleviate the side effects associated with chemotherapy has pushed the envelope of nanotechnology to develop nanocarrier-based drug delivery systems (DDS) capable of precise and targeted treatment of malignant tumors. Examples of such DDSs include solid lipid nanoparticles, liposomes, niosomes, micelles, archaeosomes, dendrimers and other carrier systems.[1–4] Our DDS makes use of ultrasound (US) as a trigger to release the contents of liposomal nanocarriers. Several reports have demonstrated the mechanism by which ultrasound actuation stimulates the nanocarriers to release their encapsulated agents.[5–12]

The measurement of ultrasound-triggered release of drugs from nanocarriers, similar to other dynamic systems, suffers from noise that affect the experimental results. This noise not only hinders the accurate delivery of chemotherapeutics, but also interferes with the dynamics of the DDS as well as the measurement process. The disturbances affect both the dynamics and measurement models. Dynamic system noises are utilized to account for uncertainties in the mathematical model used to describe the drug delivery process as well as the disturbances inherent to the process itself. Dynamics noise gets propagated along with the state in the mathematical model which helps account for the unmodeled dynamics. On the other hand, measurement noise in a process is utilized to describe disturbances and uncertainty inherent to the measurement apparatus. Accounting for the two types of noises is crucial to accurately estimate the states of any dynamic system. Failure to appropriately consider dynamics and measurements noises breaches the optimality of any estimation algorithm, which translates to inaccurate estimates of the states of the considered dynamic system. Identifying noise statistics associated with a given dynamic system is addressed in literature, and some of the methods that aim to characterize the statistics include Bayesian, Maximum Likelihood, Correlation, and Autocovariance Least-squares techniques.[13,14] Maximum Likelihood estimation is used

*Author to whom correspondence should be addressed.
Email: ghusseini@aus.edu
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here to identify the noise covariance magnitudes affecting the process.[15]

The acoustic release of calcein from liposomes has been studied using mechanistic and probabilistic models.[9–11, 16, 17] Modeling methods range from statistical methods, model dependent methods, and model independent methods.[18] This work models and predicts the behavior of acoustically-activated calcein release from stealth liposomes by proposing a suitable model-dependent kinetic model that best fits experimental release data, performing system identification on the proposed model to find the model parameters that describe the experimental data, and applying a stochastic-based approach to realize a prediction that is a robust to the existence of bias, imperfections, and noise in the drug delivery process.

The Kalman filter is a stochastic algorithm that makes use of the information available about the dynamics and measurements of a dynamic system and estimates the states of the dynamic system. The information fed into the algorithm is the mathematical model describing the dynamics of the system as well as the undertaken measurements. A Kalman filter then produces optimal estimates of drug release and identifies systematic errors in the drug delivery system in the form of a bias. The Kalman filter is a minimum-mean-square-error (MMSE) technique which minimizes the expected value of the squared error between the estimate and the true value of release (measured as a percent).[19] The application of a bias identifying drug release state using a stochastic filter, as well as, the identification of the uncertainty structure in the system is a novel effort. It is worth mentioning that we successfully attempted to estimate the chemotherapeutic release of another drug delivery system that uses polymeric micelles (as the drug delivery vehicle) using Kalman filter variants.[13] It is also worth mentioning that this work is targeted at employing the filter to identify the systematic bias present in the DDSs.

In this work, a kinetics model is first proposed to model the release of chemotherapeutics from liposomes and account for systematic errors in the process in the form of biases in the delivery. The noise structure of the dynamics is then identified through a maximum likelihood approach. Consequently, an optimal Kalman filter, which uses the identified *a priori* information, is used to estimate the percent of the drug released and the bias affecting the process. The drug release estimation approach presented here is essential to the design of control systems that make use of the structural information of the model, as well as, the accurate estimates of the filter to deliver chemotherapeutics to patients.[20, 21] The treatment process controller could also make use of the predicted state of percent drug release at times when measurements are not available. This is where the proposed model and high-accuracy percent drug release estimation methods are vital.

METHODS AND MATHEMATICAL MODEL

Experimental Methods

The lipid used to prepare the liposomes was DSPE (1,2-distearoyl-sn-glycero-3-phosphoethanolamine), which was conjugated to polyethylene glycol (PEG) to prolong the circulation time of the nanocarrier-encapsulated model drug, namely calcein. The liposomes were prepared by modifying the lipid with estrone, and adding cholesterol, and 1,2-dipalmitoyl-sn-glycerol-3-phosphocholine (DPPC) which resulted in the synthesis of DSPE-PEG-NH_2. Cyanuric chloride (2,4,6 trichloro-1,3,5 triazine (CC)) was used to conjugate estrone (ES) to DSPE-PEG2000-NH2. ES was reacted with CC in a 1:1 molar ratio, in the presence of trimethylamine (TEA). This type is referred to as DSPE-PEG-ES, hereafter.

Measurement Technique

The percent release of calcin from the liposomes is related to the change in the fluorescence intensity of the environment surrounding the liposomes as they release the model drug. Calcein is a fluorescent molecule with excitation and emission wavelengths of 495 and 515 nm, respectively.[22] It is also loaded at a self-quenching concentration. The application of US releases calcein from the liposomes to the surrounding medium, which relieves the self-quenching of the dye resulting in an observable increase in fluorescence. Equation (1) is used to calculate the percent release of the drug from these nanocarriers.

$$\%\mathrm{Drug}_{\mathrm{Release}} = \frac{F - F_0}{F_{\max} - F_0} \tag{1}$$

where F is the fluorescence intensity of the drug, F_0 is the average baseline fluorescence intensity of the solution under sonication, $F_{\max}$ is the fluorescence intensity of the drug when the entire drug content is released, and the $\%_{\mathrm{Release}} \in [0, 1]$.

Low-frequency ultrasound actuation was used to release the drug from the liposomes, which was achieved through the use of a 20-kHz piezoelectric ultrasonic transducer. In our research experiments, a 3-mm probe connected to a VCX 750 actuator (Vibra cells, Sonics and Material) is used to trigger drug release.[23, 24] The probe is tapered and produces 20-kHz ultrasonic waves. The probe tip is water-resistant and is inserted into the solution immediately before sonication. The solution is placed in a cuvette with a 1 cm × 1 cm opening, allowing the probe to vibrate freely which ensures maximum energy transfer into the liposomal solution. For more information, please refer to Ref. [25].

Modeling Drug Release

Literature presents a multitude of dynamic models to describe the kinetic release of model drugs/dye/drugs from nanocarriers. Examples of these models include zero- and first-order release models, the Higuchi model,

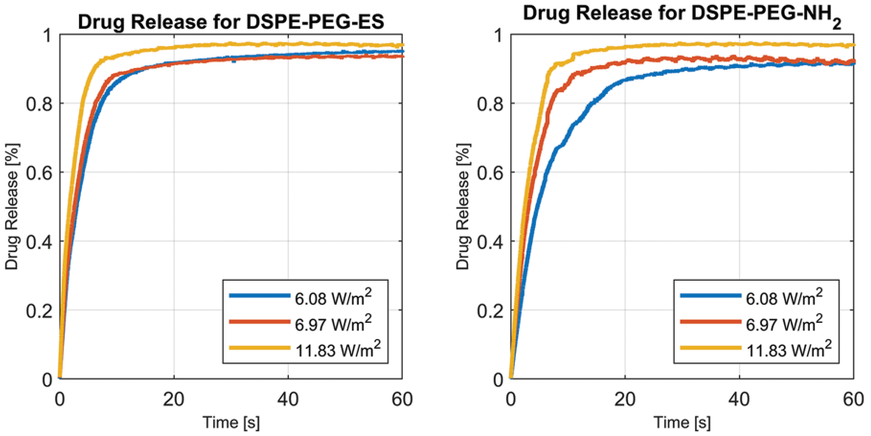

Figure 1. **Drug release for the liposome types.**

the Korsmeyer-Peppas model, or other models that rely on chemical or physical attributes of the release process.[26, 27]

After examining our experimental data and fitting it against the zero-order, the first-order, the Higuchi model, and the Korsmeyer-Peppas model,[28] we conclude that the first-order model is the most suitable at modeling the exponential behavior of US-assisted drug release from liposomes. A steady state value corresponding to 100% release is attained for every test upon the addition of a surfactant (Triton X) that dissolves the liposomal structure releasing all its contents. A first-order release kinetics model is proposed.

$$\dot{R}|_{US} = -k_r R \tag{2}$$

where R is the state of drug release, and k_r is the release constant that governs the dynamics of the model.

It is, however, observed that the drug release steady state value does not correspond to the 100% release of the drug due to experimental errors that could relate to the batch prepared, the way the release was triggered, or the incomplete destruction of the nanocarriers. Therefore, a bias term is added to the first-order model. This way, the steady-state value of the drug release is more representative of a realistic setting. This decision is inspired by the fact that the drug release in the proposed model will have a steady state value of $R_\infty = b/k_r$.

$$\dot{R}|_{US} = -k_r R + b \tag{3}$$

where b is the bias.

The mathematical model is expressed as shown in Eq. (2), where R is the amount of drug released, b is the bias term accounting for the sub-full release of the drug, k_r is the release rate constant of the drug. Experiments were conducted with different ultrasonic power densities for the two types of liposomes, ES and NH_2. Figure 1 presents the data collected for various ultrasonic power densities.

The experimental constants, k_r and b are shown in Table I alongside the standard deviation corresponding to a 95% confidence interval. The variance of the constants representing the dynamic behavior of the drug delivery system appears to be very small in magnitude.

Table I. **Release constants for the conducted experiments.**

Exp	Liposome type	Power density (W/cm^2)	$k_r \pm 1.96\sigma$	$b \pm 1.96\sigma$
1	PEG-ES	6.08	$0.259 \pm 6.0 \times 10^{-4}$	$0.242 \pm 6.5 \times 10^{-4}$
2		6.97	$0.305 \pm 6.0 \times 10^{-4}$	$0.283 \pm 6.5 \times 10^{-4}$
3		11.83	$0.426 \pm 8.5 \times 10^{-4}$	$0.412 \pm 9.5 \times 10^{-4}$
4	NH_2	6.08	$0.159 \pm 3.0 \times 10^{-4}$	$0.144 \pm 2.5 \times 10^{-4}$
5		6.97	$0.257 \pm 4.5 \times 10^{-4}$	$0.238 \pm 3.5 \times 10^{-4}$
6		11.83	$0.306 \pm 6.5 \times 10^{-4}$	$0.297 \pm 6.0 \times 10^{-4}$

Data Acquisition

The release was observed during the "on" pulse of ultrasound. A significantly noisy response was observed due to fluorescence detection and ultrasound application. A number of experiments were carried out at different ultrasonic power densities. The true biases, b, that affect the dynamics of release are identified through the postprocessing of the data to compare against the algorithm estimate.

UNCERTAINTY IDENTIFICATION AND DRUG RELEASE ESTIMATION

Identification of the Uncertainty Structure

The system dynamics noise as well as the measurements noise are the two sources of uncertainty disturbing the process dynamics and the measurement apparatus, respectively. This uncertainty structure is modeled as zero-mean additive Gaussian white noise sequences. Identifying the

uncertainty structure entails finding the process and measurement noise covariance magnitudes. Knowledge of the covariance magnitudes is vital to the optimal estimation of the percent drug encapsulation. Figure 1 shows the noisy behavior, especially towards the end of the response where the drug has almost been fully delivered.

To apply the estimation algorithm and to identify the uncertainties affecting the release, the model is discretized at a sampling frequency of 100 Hz. The discretized linear model is written in state space form, and is comprised of a dynamic and a measurement equations form as shown in Eqs. (4) and (5). R_K is the amount of drug released at time step k, b_K is the bias at time step k, Δt is the sampling time period equal to 0.01 s, and w_k and v_{k+1} are the dynamics and measurement noises at times t_k and t_{k+1}. The state vector $x_k = [R_k \;\; b_k]^T$

$$\begin{bmatrix} R_{k+1} \\ b_{k+1} \end{bmatrix} = \begin{bmatrix} 1-\Delta t k_r & \Delta t \\ 0 & 1 \end{bmatrix} \begin{bmatrix} R_k \\ b_k \end{bmatrix} + \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \begin{bmatrix} w_{1k} \\ w_{2k} \end{bmatrix} = A\; x_k + B\; W_k \tag{4}$$

$$z_{k+1} = [1 \quad 0] \begin{bmatrix} R_{k+1} \\ b_{k+1} \end{bmatrix} + v_{k+1} = C x_k + v_{k+1} \tag{5}$$

The dynamic equation in (4) is stable as $1 - \Delta t k_r < 1$. Also, the system represented in Eqs. (4) and (5) is observable as the observability Gramian is full rank. It is necessary to write the measurement equation in terms of the state of drug release at time 0 as shown in Eq. (6).

As a consequence of the stability of the dynamics in (3), $\forall k > \tau$ time steps, $|A^\tau| < \delta$ for $\delta > 0$ being a small magnitude threshold that is designed to be less than 1×10^{-5}. δ should be small in magnitude such that subsequent time steps are dominated by the noises in the system. Choosing δ properly translates to the independence of the measurements after τ time of the initial state.

$$\begin{bmatrix} z_0 \\ z_1 \\ \vdots \\ z_N \end{bmatrix} = \begin{bmatrix} C \\ CA^1 \\ \vdots \\ CA^N \end{bmatrix} (x_0) + \begin{bmatrix} v_1 \\ v_2 \\ \vdots \\ v_{N+1} \end{bmatrix} + \begin{bmatrix} 0 & 0 & \dots & 0 \\ C & 0 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ CA^{N-1} & CA^{N-2} & \dots & C \end{bmatrix} \begin{bmatrix} w_0 \\ w_1 \\ \vdots \\ w_N \end{bmatrix} \tag{6}$$

This assumption allows Eq. (6) to be rewritten as in Eq. (7). The vector of measurements occurring after time step τ is seen on the L.H.S. of Eq. (7). It is observed that the vector of measurements is exclusively a function of the dynamics and measurement noise sequences, as seen on the R.H.S. of Eq. (7).

$$Y = \begin{bmatrix} z_\tau \\ z_{\tau+1} \\ \vdots \\ z_{N+\tau-1} \end{bmatrix} \approx \begin{bmatrix} v_\tau \\ v_{\tau+1} \\ \vdots \\ v_{N+\tau} \end{bmatrix} + \Theta * \begin{bmatrix} w_0 \\ w_1 \\ \vdots \\ w_{N+\tau-1} \end{bmatrix} \tag{7}$$

where the details pertaining to the formulation of the matrix Θ from the dynamics and measurement models are available in our previous publication.[13]

As a consequence of the noise sequences being normally distributed, Y is a multivariate Gaussian vector described as $Y \sim N(0, P)$ with covariance matrix P given by (8):

$$P = \Theta \begin{bmatrix} Q_w & & \\ & \ddots & \\ & & Q_w \end{bmatrix} \Theta^T + \begin{bmatrix} R_v & & \\ & \ddots & \\ & & R_v \end{bmatrix} \tag{8}$$

where Q_w and R_v are the covariance matrices for the dynamics and measurement noises, respectively, and Θ^T is the transpose of Θ.

One can formulate a maximum likelihood estimation (MLE) problem by exploiting the maximum likelihood equation of the multivariate normal distribution, which describes how Y is distributed, as shown in Eq. (9):

$$\min_{Q_w - R_v} |\ln(|P|) + Y' * P^{-1} * Y| \tag{9}$$

where the Cholesky decomposition was used to evaluate the determinant as the matrix P is sparse and straight evaluation of the determinant leads to numerical divergence.

Therefore, the process and measurement covariance magnitudes that minimize the MLE cost function in Eq. (9) represent the true statistics of the process and measurement noise sequences, denoted as Q_{MLE}, R_{MLE}, respectively. The estimate of the percent drug release as well as the bias is described next.

Release and Bias State Estimation

The released was calculated using Eq. (1). The identified process uncertainty structure from Eq. (9) allows for the optimal estimate of the released drug amount as well as the correct bias present in the process to be estimated using a Kalman filter approach. The approach is summarized in Figure 2.

Starting with the initial conditions of the expected value of encapsulation given the measurement and its covariance; the *a priori* estimate of the state is realized through propagating (in time) the previous estimate of the drug release state through the dynamic model, and the *a priori* state covariance is also realized through propagating the

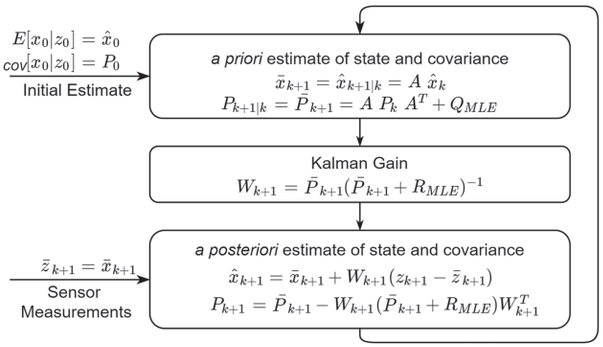

Figure 2. **Kalman filter algorithm diagram.**

previous covariance estimate through the model. The optimal gain is then computed to obtain the optimal *a posteriori* release state and covariance estimates from the Kalman filter. As discussed earlier, the drug release estimate from our algorithm is the optimal one, and the identified noise statistics are representative of the real data.

RESULTS

Uncertainty Identification

The proposed MLE method was applied to the experiments shown in Table I to identify the statistics of the measurement and process noise sequences. A numerical solver in the MATLAB environment was used to identify the global minimizing solution to the MLE problem. The constraints imposed on the solver are: (1) the solution should be positive and (2) a lower limit of 1×10^{-5} is set for the covariance magnitudes. A sample contour plot for the cost function is shown in Figure 3, where the diagonal elements of the covariance matrix Q are the same allowing for the generation of a two-dimensional representation of the cost function. For experiments $1 \rightarrow 6$, the obtained

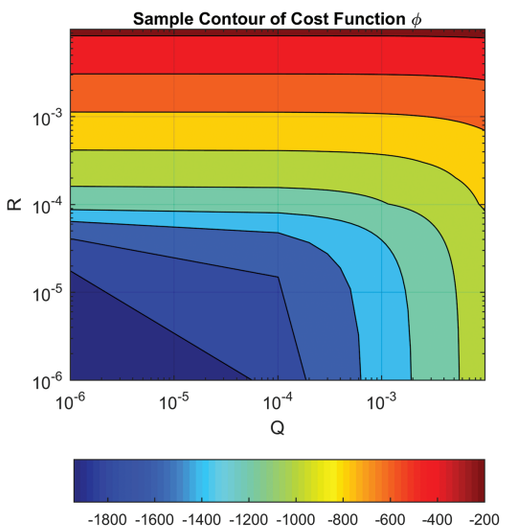

Figure 3. **Contour plot of cost function ϕ.**

Table II. **MLE identified dynamics and measurement NOISE covariance values for experiments $1 \rightarrow 6$.**

Exp #	Dynamics noise covariance (Q_{MLE})	Measurement noise covariance (R_{MLE})
$1 \rightarrow 6$	$\begin{bmatrix} 1.00 & 0 \\ 0 & 1.00 \end{bmatrix} \times 10^{-5}$	1.00×10^{-5}

MLE solution to the cost function happens to be at the lower limit. The solution to the optimization problem is presented in Table II.

Simulation Results

The algorithm was first implemented in a simulation environment. Equations (3) and (4) were used to simulate the dynamic as well as the measurement process of our system. A Kalman filter was used to estimate the drug release percent and the release bias affecting the drug delivery system. The true state, which was simulated, is known in this case, and hence the performance validation is possible. Figure 4 presents the estimation results on an experimental run. The exaggerated noise magnitudes used here were $w = 4.5 \times 10^{-3}$, and $v = 4.5 \times 10^{-3}$.

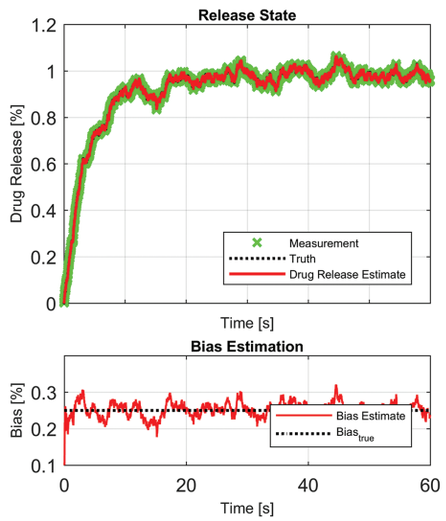

Figure 4. **Simulated environment drug release and bias estimation.**

Table III. **Estimation mean square error in simulated environments for all experimental conditions.**

Experiment	M.S.E.
Exp 1	1.673×10^{-5}
Exp 2	1.594×10^{-5}
Exp 3	1.657×10^{-5}
Exp 4	1.645×10^{-5}
Exp 5	1.615×10^{-5}
Exp 6	1.649×10^{-5}

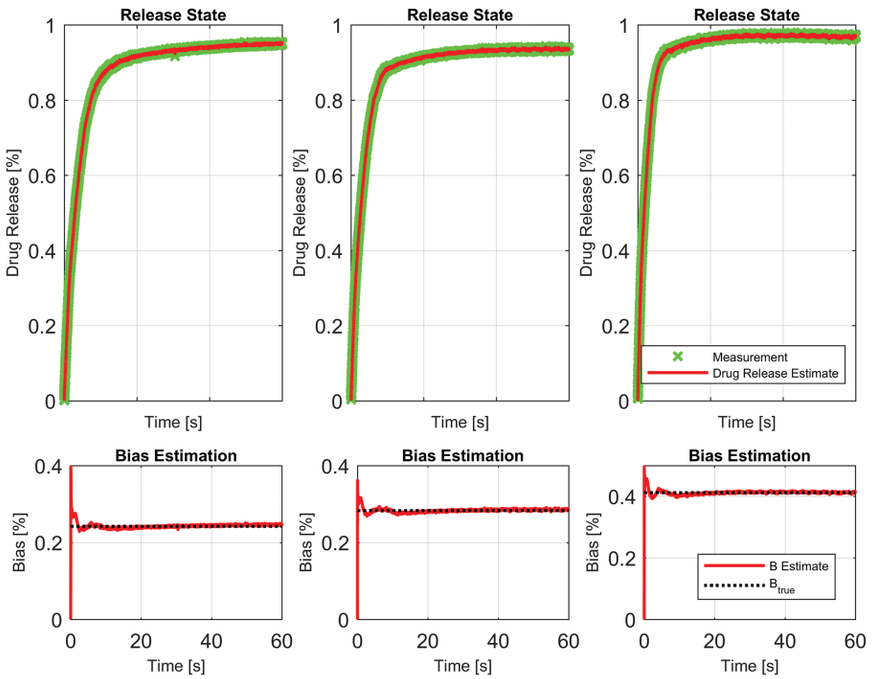

Figure 5. **Drug release and bias estimation results for DSPE-PEG-ES. The ultrasonic power densities used for the experiments are 6.08, 6.97, and 11.83 W/m^2 (from left to right).**

The exaggerated injected noise sequences, while somewhat unrealistic, serve to test proof the algorithm and validate performance. Figure 4 shows that the measurement is around the vicinity of the true noisy state, the drug release estimate is close to the truth state, and the bias was quickly identified. The variation in the bias is due to the very high magnitude of the noise affecting the process in the simulated environment.

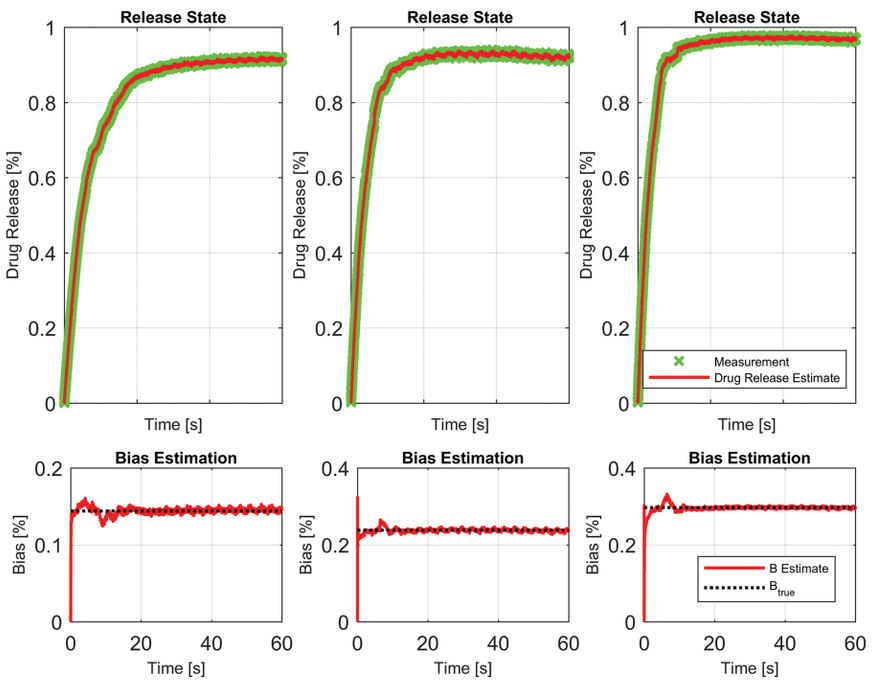

Figure 6. **Drug release and bias estimation results for DSPE-PEG-NH$_2$. The ultrasonic power densities used for the experiments are 6.08, 6.97, and 11.83 W/m^2 (from left to right).**

Table IV. Estimation mean square error of experimental measurements.

Experiment	M.S.E.
Exp 1	5.876×10^{-6}
Exp 2	5.175×10^{-6}
Exp 3	6.904×10^{-6}
Exp 4	6.608×10^{-6}
Exp 5	8.156×10^{-6}
Exp 6	6.827×10^{-6}

To present a qualitative analysis in a simulated setting, a measure of the performance of the filter in the form of the mean square error of the estimate with respect to the available true state of drug release follows. For the sake of brevity, we do not present simulation responses other than those of Figure 4, which utilize the identified constants of experiment 1 (Table I). Also, Table III presents the mean square error for all the simulated experimental conditions. The filter proves successful at both estimating the drug release as well as identifying the bias affecting the process. The numbers show the consistency of the optimal Kalman filter at estimating both the drug release and the systematic error affecting the delivery system, which is attributed to the fact that the correct statistical information for both the dynamics and measurement noises is available initially in the optimal filter. It is of interest to note that the differences between the experiments lie solely in the difference in the release constant and the bias and having the correct information to initialize the Kalman filter ensures its proper function and improves the accuracy of our runs.

Experimental Results

After validating the performance of the method in the simulation environment, the algorithm was applied to the experimental data obtained at different ultrasonic power densities for both types of liposomes, given in Table I. Figures 5 and 6 present the drug release and bias estimation results for the experimental conditions investigated. The bias true state was identified through post-processing of the data to check the validity of the Kalman estimate. The optimum Kalman filter exhibits very good tracking performance of the measurements. It also enables the accurate identification of the bias affecting the drug delivery system early on through the response thus allowing for precise delivery of chemotherapeutics to the patient.

Table IV summarizes the performance of the filter operating under all the experimental conditions available. The Kalman filter, then, gives a small mean square error of the release estimates.

DISCUSSION AND CONCLUSION

The accurate prediction of the systematic error in the form of biases affecting the release of chemotherapeutics from liposome carriers is vital in modeling and predicting the behavior of the drug delivery process. This work models the acoustic release of calcein from liposomes using a first-order kinetics model that is augmented with a bias term which accounts for errors in the drug delivery process. Numerical fitting of experimental data sets allowed the identification of the kinetic release constants and the true bias terms. The statistics of the noise sequences affecting the dynamics and measurement of the chemotherapeutic drug delivery system were also identified using a maximum likelihood approach. Subsequently, a resulting optimal stochastic filter, the Kalman filter, enabled the estimation of the drug release and the bias error.

The proposed algorithm was first tested in a simulation setting. To validate the performance of the estimators, experiments were conducted, where the drug release was measured, and the true bias was identified through post-processing. The true drug release state is unknown, but the bias term is known through the performed numerical modeling and fitting. The optimal filter proved successful at capturing the correct bias term in all experiments, and it tracked the measurements well. The algorithm proved capable of identifying the bias term early in the response while still filtering the recorded measurement. By improving the prediction in the modeling of drug delivery systems, we inch closer to fully understand the physical and chemical mechanisms that govern acoustic drug release from liposomes.

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