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ONLINE ESTIMATION OF CAPILLARY PERMEABILITY AND CONTRAST AGENT CONCENTRATION IN RAT TUMORS

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Abstract

This paper presents a two-compartment model for the transfer of optical contrast agent, namely indocyanine green (ICG), in the presence of tumors between the plasma and extracellular extravascular space (EES) compartments. An adaptive extended Kalman filter (EKF) has been derived to estimate the quantities that are transferred between the compartments, Moreover, in order to validate the proposed EKF, real data have been utilized and the experimentally obtained ICG concentration data quantitatively analyzed through the estimation of physiological parameters related to capillary permeability and the optical contrast agent concentration in the compartments concurrently. The proposed method produces the estimate of tissue permeability, independent of the initial permeability values, without resorting to computationally expensive nonlinear fitting algorithms. Considering the fact that the change in the tissue permeability occurs usually due to a disease such as cancer, an estimated value of the permeability could be used to extract valuable information about tumor cell behavior patterns.

Keywords: Capillary permeability, Tumor, ICG, Compartment models, Parameter estimation, Extended Kalman filtering.

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1. Introduction

In recent years the use of optical contrast agents and advanced medical imaging techniques to analyze and diagnose tissue abnormalities has become almost a standard procedure [16]. The existence of tumors is one of the main causes of tissue abnormalities, and in [14] it was shown that tumor vessel permeability to macromolecular blood solutes correlates with tumor growth as well as vascular growth. Indocyanine green (ICG) is a blood pool agent that binds to globulin proteins (predominantly albumin) in blood [9], and because of its ability to bind to plasma proteins, it behaves as a macromolecular contrast agent with a low or no vascular permeability. Once injected, ICG rapidly and completely binds to albumin and its macromolecular behavior results in a slow leakage that permits application of a pharmacokinetic model that in return allows for the determination of individual vascular parameters, such as capillary permeability.

Compartmental analysis is a method of bio-mathematical modeling which assumes that a biological system can be divided into a series of homogeneous compartments, where the compartments interact by exchanging material. For compartmental models used in pharmacokinetics, the material concentration varies with time depending on individual pharmacokinetics parameters [2]. If the appropriate parameters are known, then by applying suitable pharmacokinetic equations, the concentration level in a particular compartment may be predicted. Thus, a robust method of identifying and estimating individual parameters is required. The parameter identification problem is a common nonlinear estimation problem. It is the problem of estimating a model parameter that occurs as a coefficient of a dynamic system state variable - either as a dynamic coefficient or as measurement sensitivity. When this estimation problem is solved simultaneously with the state estimation problem (via state vector augmentation), the linear model becomes nonlinear [6]. The extended Kalman filter (EKF) is one of the most popular and intensely investigated estimation technique for nonlinear state estimation. It consists of applying the standard Kalman filter equations to the first-order approximation of the nonlinear model of the last estimate [1].

In [11], an adaptive EKF was developed for the first time to solve the nonlinear estimation problem at the outputs of the compartment models that represented the ingestion and subsequent metabolism of a drug in a given individual. The proposed method was applied to the simulated data and it was shown that, due to its adaptive nature, it successfully estimates both the time invariant and time varying parameters characterizing the transfer rate between the compartments. A study is presented in [5] where the dynamics of optical contrast agents ICG and methylene blue in an adenocarcinoma rat tumor model were investigated. Furthermore some quantitative analysis were carried out on ICG measurements employing an extremely complex nonlinear least-squares fitting algorithm on the solution of the nonlinear equation obtained utilizing the ICG compartmental model. The method employed for the quantitative analysis was not only computationally expensive but also it was sensitive to the choice of initial values of the parameters.

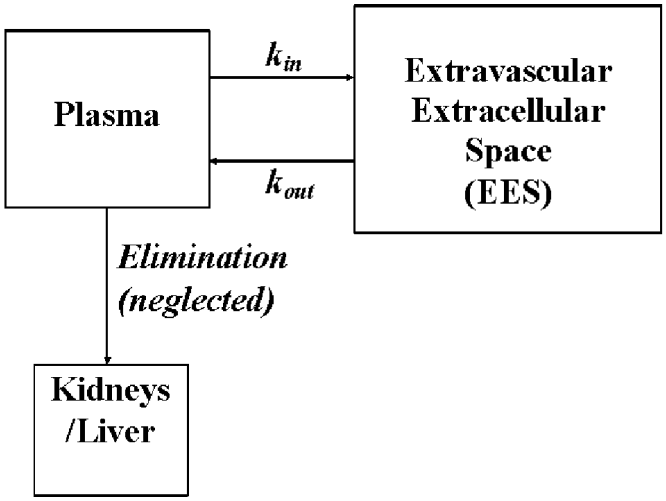
In this study we derive the adaptive EKF for the ICG compartmental model and apply it to some of the experimentally observed data used in [5] in order to demonstrate that the adaptive EKF also works on real data providing online estimation of ICG concentration of the compartments as well as the transcapillary permeability parameters. This paper is organized as follows; the next section outlines the mathematical model and problem statement, while the experimental results are presented in section 3. Finally, some concluding remarks are given.

2. The mathematical model and problem statement

In this section we first develop the two-compartment pharmacokinetic model for ICG removal and transfer between the compartments. We then derive the adaptive EKF for this model and apply it for parameter estimation.

2.1. The ICG Compartment Model. As mentioned previously, albumin-bound ICG kinetics demonstrate macromolecular behavior, and its low transcapillary permeability slows diffusion to a system where flow dependant vascular distribution effects are minimal. In [15] it was shown that the existence of tumors increases capillary permeability, allowing albumin-bound ICG molecules to escape from capillaries into the extravascular extracellular space (EES). This makes it possible to come up with a simple model of the concentration dynamics in terms of its distribution between plasma and EES. The two-compartment model illustrated in Figure 1 has been employed in order to investigate this behavior.

Figure 1. Two-compartment pharmacokinetic model of metabolic elimination and transfer of ICG.



The rate of change of ICG concentration in the EES, C_e, is equal to the rate C_p at which ICG is distributed from the plasma to the EES, minus the rate that C_e drains back to the plasma compartment, given by

$$\frac{dC_e(t)}{dt} = k_{in}C_p(t) - k_{out}C_e(t), \tag{2.1}$$

where k_{in} and k_{out} are the rate coefficients related to capillary permeability, representing the leakage into and extraction out of the EES respectively. Modeling the inward and outward capillary permeabilities separately accounts for physiologic causes that affect albumin movement [5].

Similarly, since all compartment models are based on the conservation of mass law, the rate of change C_p of ICG concentration in the plasma is equal to the drainage rate from EES to the plasma minus the leakage rate into the EES minus the metabolic clearance in the kidneys and liver, given by

$$\frac{dC_p(t)}{dt} = -k_{in}C_p(t) + k_{out}C_e(t) - (A_1e^{\alpha_1 t} + A_2e^{\alpha_2 t}), \tag{2.2}$$

where the last term in brackets on the right hand side of equation (2.2) is an approximation for the removal of ICG by metabolic process from the plasma compartment [7, 8], α_1, α_2 are constants that describe the exponential metabolic clearance of ICG, and $A_1 + A_2$ is the initial ICG concentration in the plasma. However, the fact that the long term elimination of ICG from the blood (i.e., plasma) is in the order of hours, [17] suggests that α_1 and α_2 are very small, therefore, considering the short observation time, metabolic clearance of the contrast agent could be ignored. Neglecting the metabolic clearance at the kidneys and liver yields a two-compartment model, where the rate of change is given as

$$\frac{dC_p(t)}{dt} = -k_{in}C_p(t) + k_{out}C_e(t). \tag{2.3}$$

Also, in the pharmacokinetic model presented here, it has been assumed that transcapillary leakage occurs only at the tumor site and that a small perturbation of the global plasma concentration does not affect the bulk removal.

The differential equations given by equations (2.1) and (2.3) will later be used to obtain the state space model for the two-compartment ICG pharmacokinetic model.

2.2. Mathematical model. Let us consider a general discrete-time stochastic system represented by the state and measurement models given by

$$x_{k+1} = \Phi_k x_k + B_k u_k + w_k, \tag{2.4}$$

$$y_k = H_k x_k + v_k, \tag{2.5}$$

where x_k is an $n \times 1$ system vector, y_k is an $m \times 1$ observation vector, Φ_k is an $n \times n$ system matrix, u_k is a $p \times 1$ vector of the input forcing function, B_k is an $n \times p$ matrix, H_k is an $m \times n$ matrix, w_k is an $n \times 1$ vector of zero mean white noise sequence and v_k is an $m \times 1$ measurement error vector assumed to be a zero mean white sequence uncorrelated with the w_k sequence. The matrices $\Phi_k, B_k, H_k, Q_k, R_k$ are assumed known at time k. The covariance matrices w_k and v_k are defined by

$$\begin{aligned} E\left(w_k w_k'\right) &= Q_k \delta_{kl}, \\ E\left(v_k v_k'\right) &= R_k \delta_{kl}, \\ E\left(w_k v_k'\right) &= 0, \end{aligned}$$

where δ_{kl} is the Kronecker delta function. The optimum Kalman filter update equations are

$$\begin{aligned} \hat{x}_{k|k-1} &= \Phi_{k-1}\hat{x}_{k-1} + B_{k-1}u_{k-1}, \\ \hat{x}_k &= \hat{x}_{k|k-1} + K_k[y_k - H_k\hat{x}_{k|k-1}], \\ P_{k|k-1} &= \Phi_{k-1}P_{k-1}\Phi_{k-1}' + Q_{k-1}, \\ P_k &= (I - K_k H_k)P_{k|k-1}, \end{aligned} \tag{2.6}$$

where K_k, the optimum Kalman gain, is given by

$$K_k = P_{k|k-1}H_k'(H_k P_{k|k-1}H_k' + R_k)^{-1}, \tag{2.7}$$

In the above equations $\hat{x}_{k|k-1}$ is the *a priori* and $\hat{x}_k$ is the *a posteriori* estimate of x_k. Also, $P_{k|k-1}$ and P_k are the covariance of the *a priori* and *a posteriori* estimates, respectively [4]. In [10] a scalar, namely a forgetting factor, was proposed for the standard Kalman filtering that was introduced in the error covariance equation to limit the memory of the recursive least square,

$$P_{k|k-1} = \alpha(\Phi_{k-1}P_{k-1}\Phi_{k-1}' + Q_{k-1}). \tag{2.8}$$

This modification adds an adaptive nature to the standard filter which provides robustness to the filter when time varying parameters are to be estimated. For $\alpha = 1$ the

resulting filter is the same as the standard Kalman filter, whereas for $\alpha > 1$ the filter has an adaptive nature via exponential data weighting. The idea behind using a forgetting factor is to artificially emphasize the effect of current data by exponentially weighting the observations. In the next section this modification will be expanded to the EKF to yield an adaptive extended Kalman filter.

2.3. EKF as the Permeability Parameter Estimator. The state space model of the metabolic removal and transfer of ICG between compartments has been obtained in the following way. Let $x_k = \begin{bmatrix} x_{1,k} & x_{2,k} \end{bmatrix}^T$ be the state vector containing the states to be estimated at time k, where the states are defined as $x_{1,k} = C_p$ and $x_{2,k} = C_e$. Then, using the differential equations (2.1) and (2.3) and also applying a simple forward Euler approximation (integration), the state space model of the two-compartment model is obtained in the form

$$x_{k+1} = \begin{bmatrix} x_{1,k+1} \\ x_{2,k+1} \end{bmatrix} = \begin{bmatrix} 1 - k_{\text{in}}\Delta_t & k_{\text{out}}\Delta_t \\ k_{\text{in}}\Delta_t & 1 - k_{\text{out}}\Delta_t \end{bmatrix} \begin{bmatrix} x_{1,k} \\ x_{2,k} \end{bmatrix}, \tag{2.9}$$

$$y(k) = \begin{bmatrix} 0 & 1 \end{bmatrix} x_k, \tag{2.10}$$

where k_{in} and k_{out} are the rate coefficients related to capillary permeability to be estimated, known to satisfy the inequality $k_{\text{in}} > k_{\text{out}}$ by [8], and Δ_t is the integration time interval subdivider. While this constitutes a good model to estimate the states, it does not account for the unknown parameters k_{in} and k_{out}. Therefore, this model has to be extended to include these parameters in the estimation process. For this purpose, let $\Phi_k(\theta)$ be a known vector that is a function of the unknown vector $\theta = \begin{bmatrix} k_{\text{in}} & k_{\text{out}} \end{bmatrix}^T$. Here, θ is treated as a random variable and the objective is to identify θ. Also, we assume that the random variable θ evolves according to,

$$\theta_{k+1} = \theta_k + \zeta_k, \tag{2.11}$$

where ζ_k is any zero-mean white noise sequence uncorrelated with v_k and with pre-assigned positive definite variances $\text{Var}(\zeta_k) = S_k$. In applications, S_k may be chosen as $S_k = S > 0$ for all k. The system given by equations (2.9) and (2.10), together with the assumption given in equation (2.11) and the assumption that the input forcing function satisfies $u_k = 0$, can be re-formulated as the nonlinear model:

$$\begin{bmatrix} x_{k+1} \\ \theta_{k+1} \end{bmatrix} = \begin{bmatrix} \Phi_k(\theta_k)x_k \\ \theta_k \end{bmatrix} + \begin{bmatrix} w_k \\ \zeta_k \end{bmatrix}, \tag{2.12}$$

$$y_k = \begin{bmatrix} H_k & 0 \end{bmatrix} \begin{bmatrix} x_k \\ \theta_k \end{bmatrix} + v_k. \tag{2.13}$$

The EKF procedure (see the Appendix) can be applied to estimate the state vector, which contains the parameter vector θ_k as one of its components. That is, θ_k, the vector of rate coefficients related to the permeabilities, is estimated optimally in an adaptive way. This procedure is called adaptive system identification in [1]. The extended Kalman filtering process can then be applied to adaptively estimate the states and parameters.

Let us define the initial state and the corresponding covariance as

$$\begin{aligned} \begin{bmatrix} \hat{x}_0 \\ \widehat{\theta}_0 \end{bmatrix} &= \begin{bmatrix} E(x_0) \\ E(\theta_0) \end{bmatrix}, \\ P_0 &= \begin{bmatrix} \text{Cov}(x_0) & 0 \\ 0 & S_0 \end{bmatrix}. \end{aligned} \tag{2.14}$$

Then the state prediction and predicted covariance, in the adaptive form, are given as follows for $k = 1, 2, \ldots,$

$$\begin{bmatrix} \hat{x}_{k|k-1} \\ \widehat{\theta}_{k|k-1} \end{bmatrix} = \begin{bmatrix} \Phi_{k-1}(\widehat{\theta}_{k-1})\hat{x}_{k-1} \\ \widehat{\theta}_{k-1} \end{bmatrix},$$

$$P_{k|k-1} = \alpha \begin{bmatrix} \Phi_{k-1}(\widehat{\theta}_{k-1}) \dfrac{d}{d\theta}(\Phi_{k-1}(\widehat{\theta}_{k-1}))\hat{x}_{k-1} & \\ 0 & I \end{bmatrix} \times P_{k-1} \begin{bmatrix} \Phi_{k-1}(\widehat{\theta}_{k-1}) & \dfrac{d}{d\theta}(\Phi_{k-1}(\widehat{\theta}_{k-1}))\hat{x}_{k-1} \\ 0 & I \end{bmatrix}^T + \alpha \begin{bmatrix} Q_{k-1} & 0 \\ 0 & S_{k-1} \end{bmatrix}.$$

The estimated state and the associated covariance are now given by

$$\begin{aligned} \begin{bmatrix} \hat{x}_k \\ \widehat{\theta}_k \end{bmatrix} &= \begin{bmatrix} \hat{x}_{k|k-1} \\ \widehat{\theta}_{k|k-1} \end{bmatrix} + K_k\{y_k - [H_k \hat{x}_{k|k-1}]\}, \\ P_k &= \Big(I - K_k \begin{bmatrix} H_k & 0 \end{bmatrix}\Big) P_{k|k-1}, \end{aligned} \tag{2.15}$$

where K_k is the Kalman gain defined as

$$K_k = P_{k|k-1} \begin{bmatrix} H_k & 0 \end{bmatrix}' \Big(\begin{bmatrix} H_k & 0 \end{bmatrix} P_{k|k-1} \begin{bmatrix} H_k & 0 \end{bmatrix}' + R_k \Big)^{-1}.$$

This concludes the derivation of the adaptive extended Kalman filter with forgetting factor α that is used to discount old measurements.

3. Experimental results and discussion

The derived compartment model has been tested using some experimental data that were kindly provided to us. Details of the experimental setup, and how the data were collected can be found in [5]. Since this work deals with the collected date, here only a very brief discussion regarding the experiments is given in order to put more emphasis on the mathematical representation, along with parameter estimation. In the experiments, bolus injections of the optical contrast agent ICG were administered to the rat through the tail vein. The measurements were collected by placing the probe normal to the tumor surface and probing the whole tissue including plasma. After injection, ICG rapidly and completely binds to albumin, after which the kinetics of ICG are governed by the temporal dynamics of albumin in and between the vascular compartment and the EES. Healthy tissues would not let albumin bound ICG leak from the plasma into the EES [13]. However, under diseased conditions such as the tumors cause, the capillary permeability of ICG-albumin can increase to a higher level, allowing it to move into the EES [15]. This fact makes it possible to examine cancerous tissues through the use of a contrast agent, ICG in this case, and the mathematical model derived in the previous section helps us quantitatively analyze the changes that occur in and outside the compartments.

In the mathematical model, the initial ICG concentration in the plasma has been taken as $C_p(0) = 1$. Also it was assumed that some leakage of ICG into the EES had occurred, and the ICG concentration in the EES at $t = 0$ has been taken as $C_e(0) = 0.1$. Since the extended Kalman estimator we have derived for this application estimates the states and parameters concurrently, initial values of k_{in} and k_{out} also have to be defined. However, the selected initial values for the permeability parameters are not of great importance, as a well constructed mathematical model will quickly converge. The state vector x, that is assumed to evolve according to equation (2.4), is defined as $x_k = \begin{bmatrix} x_1 & x_2 & p_1 & p_2 \end{bmatrix}^T$,

where x_1 and x_2 are the states at the output of the plasma and the EES compartments, respectively, whereas p_1 and p_2 are the rate coefficients, i.e., k_{in} and k_{out}, respectively, related to the capillary permeability to be estimated. Since the experiment through which the measurements were collected assumed no input, the control input u_k given in equation (2.4) has been taken as zero¶, also since the change in the capillary permeability could be considered time invariant during the short course of observation, the forgetting factor α has been chosen to be 1, resulting in the Standard Extended Kalman filter. However, by simply setting $\alpha > 1$, the estimator derived here could be used to estimate parameters that change as a function of time as well [11].

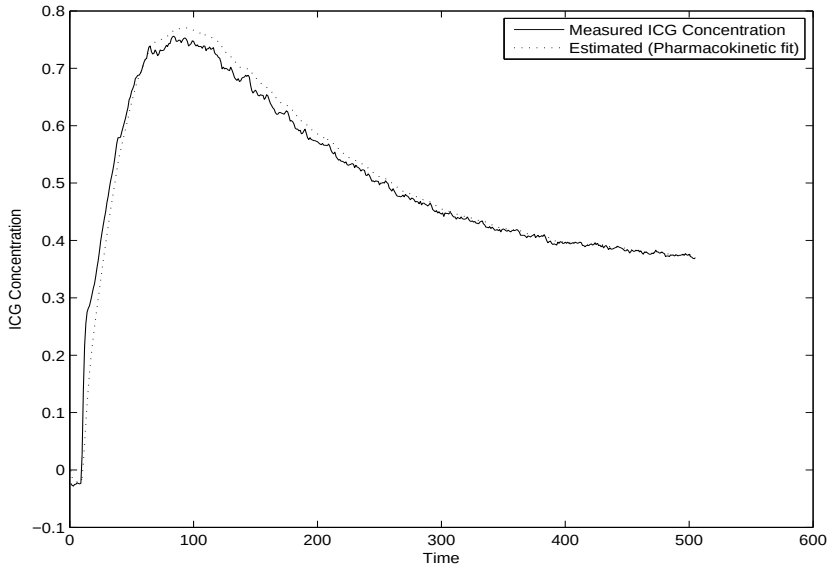
Initial values of the states and parameters have been taken as

$$x(0) = \begin{bmatrix} 1 & 0.1 & 0.02 & 0.01 \end{bmatrix}^T.$$

The standard deviation of the process noise has been determined by examining the measured data, and chosen as 0.149, while the measurement noise standard deviation has been set at 0.075. Standard deviations of the parameters p_1 and p_2, that are embedded in the innovation covariance matrix S, are 0.005 and 0.001 respectively.

The mathematical model assumes that there is no information about the rate coefficients related to the capillary permeability, and produces estimations of them at each scan. As reported in previous studies such as [3] and [12], and confirmed by simulations in [11], the EKF is rather sensitive to its initialization, and to the selection of appropriate values of the arbitrary matrices, measurement covariance R and the process noise covariance Q. Hence, the careful selection of the matrices R and Q is essential, as these matrices play a central role in improving the convergence of the EKF. In [3] some criteria were presented on the appropriate selection of these matrices. The rough values used in the design of the EKF in this study have been reached by taking the suggestions made in [3], and optimized through trial and error.

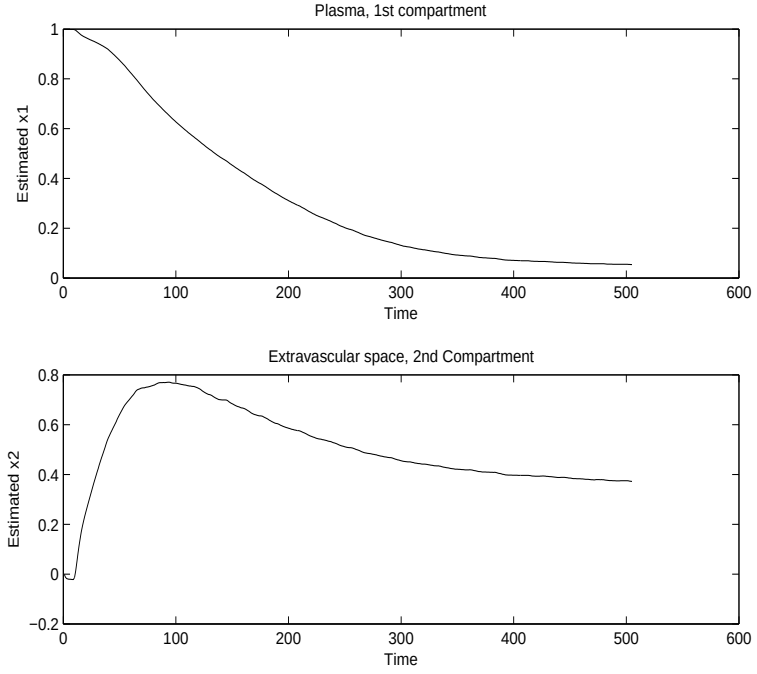
Figure 2. The observed ICG concentration and its pharmacokinetic fit obtained using EKF



¶For a non-zero control input i.e., $u_k \neq 0$, the system is a non-closed system and the solution to such systems with known control inputs is also available [8].

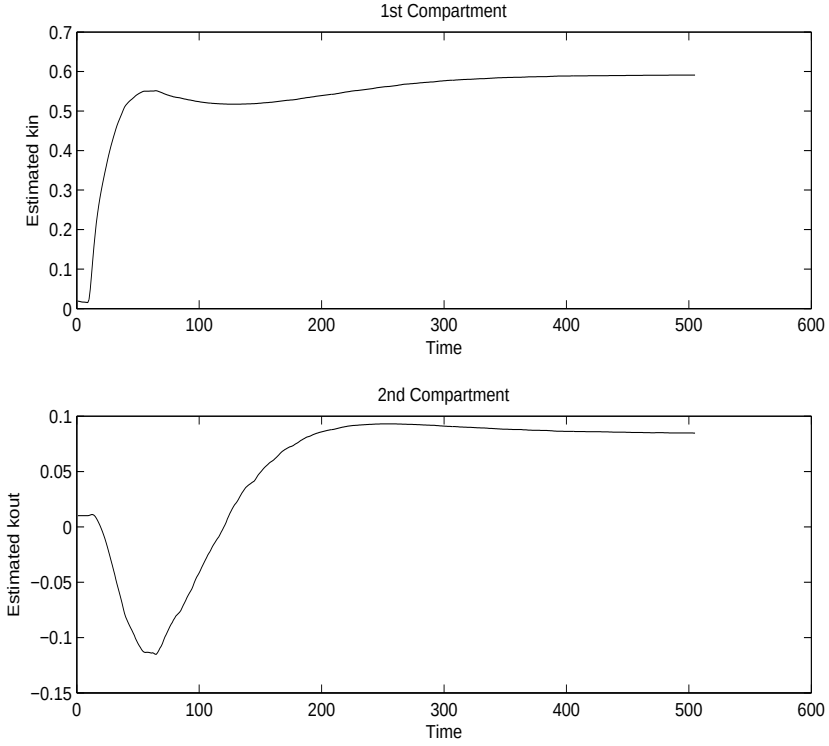
In the experiment, the ICG concentration in the lump space, i.e. EES and plasma, was monitored for 500 seconds. Figure 2 depicts the observed ICG concentration and the pharmacokinetic fit obtained through the use of EKF. It is clearly seen that the derived mathematical model provides a rather good fit to the observations, which indicates the correctness of the model. Figure 3 presents the estimated ICG concentrations at outputs of the compartments. The top figure shows the change of the ICG in the plasma compartment, C_p. Please note that the estimation of this compartmental output would not be possible by utilizing other mathematical models, such as presented in [5], and this is one of the novel outcomes that our proposed method offers. Monitoring the estimated change in the plasma compartment could provide additional information regarding the tumor that might help in deciding the treatment procedure for the tumor. It can be easily verified that the change in both plasma and EES compartments is consistent with the solution of the differential equations (2.1) and (2.3). Moreover, the estimated change is also consistent with the physiological facts, as can be seen from the estimated C_p, the contrast agent injected in vivo quickly escapes into the EES until the osmotic balance has been established, after which the transfer rate between the compartments settles.

Figure 3. Estimated compartment outputs



Estimated rate coefficients related to the capillary permeability in the presence of tumor cells are given in Figure 4. As expected, k_{in} reflects capillary permeability to ICG-albumin, exchange surface area, tissue density and driving forces (transmural pressure difference and concentration difference) from the plasma to the EES. In parallel, k_{out} has the same meaning, but from the EES to the plasma. As can be seen in Figure 4, for steady state, the ratio $k_{\text{out}}/k_{\text{in}}$ suggests that ICG-albumin leaks into the EES much more quickly than it returns to the plasma, which conforms both to the mathematical model and to physiological expectations.

Figure 4. Estimated capillary permeabilities



When compared to the nonlinear least-squares Levenberg-Marquart fitting algorithm employed in [5] to estimate the change in ICG concentration in the compartments, and the rate coefficients related to the capillary permeability, the EKF method proposed in this paper has following advantages;

- The extended Kalman estimator is a much simpler approach that does not require extensive evaluation of complex equations.
- Not just the steady state values of the parameters but all changes both in the ICG concentration and capillary permeability could be investigated very sensitively throughout the observations.
- Since it has been shown that tumor vessel permeability to macromolecular blood solutes correlates with tumor growth [14], comparison of estimated permeability change before and after a particular treatment would yield important information regarding the effectiveness of the treatment.
- The model presented here provides the rates of change for both the states and parameters, independent of the initial values of the states and parameters in question.
- Estimation of the outputs of both compartments is possible even when the measurement from a particular compartment is not available.
- If the number of cells in the plasma is known, then the number of extracellular cells could be determined with an appropriately constructed EKF, which means the number of cells transferred to the other compartment can be estimated online. This is very important for prognosis of tumor pathologies.

4. Conclusions

In this study we have introduced a two-compartment pharmacokinetic model representing the metabolic elimination and transfer of ICG between compartments in rat tumors, and presented a method for the quantitative analysis of experimentally obtained ICG concentration data. The proposed method provides online estimation of both the concentration changes at the output of the compartments, namely the plasma and EES, and the capillary permeabilities that govern the transfer. The EKF compares very favorably with complex nonlinear fitting algorithms, and produces extra information that cannot be obtained with other methods. This would be useful in the analysis of tumor cell behavior patterns in cancerous tissues.

Appendix

A state-space description of a system which is not necessarily linear will be called a *nonlinear model* of the system. Consider a nonlinear model of the form

(A.1) $x_{k+1} = f_k(x_k, u_k) + w_k,$

(A.2) $y_k = g_k(x_k) + v_k.$

where f_k and g_k are vector-valued functions, w_k and v_k are uncorrelated, zero-mean white noise sequences, with covariance matrices Q_k and R_k, respectively. The adaptive extended Kalman filter algorithm is as follows:

$$\hat{x}_0 = (x_0),$$
$$P_0 = \mathrm{Var}\,(x_0).$$

For $k = 1, 2, \ldots,$

(A.3) $$P_{k|k-1} = \alpha\Big(\Big[\frac{\partial f_{k-1}}{\partial x_{k-1}}(\hat{x}_{k-1})\Big] P_{k-1}\Big[\frac{\partial f_{k-1}}{\partial x_{k-1}}(\hat{x}_{k-1})\Big]' + Q_{k-1}\Big),$$

(A.4) $$\hat{x}_{k|k-1} = f_{k-1}(\hat{x}_{k-1}),$$

(A.5) $$K_k = P_{k|k-1}\Big[\frac{\partial g_k}{\partial x_k}(\hat{x}_{k|k-1})\Big]'\Big[\Big[\frac{\partial g_k}{\partial x_k}(\hat{x}_{k|k-1})\Big] P_{k|k-1}\Big[\frac{\partial g_k}{\partial x_k}(\hat{x}_{k|k-1})\Big]' + R_k\Big]^{-1},$$

(A.6) $$P_k = \Big[I - K_k\Big[\frac{\partial g_k}{\partial x_k}(\hat{x}_{k|k-1})\Big]\Big] P_{k|k-1},$$

(A.7) $$\hat{x}_{k|k} = \hat{x}_{k|k-1} + K_k[y_k - g_k(\hat{x}_{k|k-1})].$$

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References

[1] Anderson, B. D. O. and Moore, J. B. *Optimal Filtering* (Prentice Hall, 1979).

[2] Botsman, K., Tickle, K. and Smith, J. D. *A Bayesian formulation of the Kalman filter applied to the estimation of individual pharmacokinetic parameters*, Comput. Biomed. Res. **30**, 83–93, 1997.

[3] Boutayeb, M. and Aubry, D. *A strong tracking extended Kalman observer for nonlinear discrete time systems*, IEEE Trans. Automatic Control. **44**, 1550–1556, 1999.

[4] Bryson, A. E. and Ho, Y. C. *Optimization, Estimation and Control* (Ginn and Company, 1969).

[5] Cuccia, D. J., Bevilacqua F., Durkin, A. J., Merritt S., Tromberg, B. J., Gulsen, G., Yu, H., Wang, J. and Nalcioglu O. *In vivo quantification of optical contrast agent dynamics in rat tumors by use of diffuse optical spectroscopy with magnetic resonance imaging coregistration*, Appl. Opt. **42**, 2940–2950, 2003.

[6] Greval, M. S. and Andrews, A. P. *Kalman Filtering Teory and Practice* (Prentice Hall, 1984).
[7] Gurfinkel, M., Thompson, A. B., Ralston, W., Troy, T. L., Moore, A. L., Moore, T. A., Gust, J. D., Tatman, D., Reynolds, J. S., Muggenburg, B., Nikula, K., Pandey, R., Mayer, R. H., Hawrysz, D. J. and Sevick-Muraca, E. M. *Pharmacokinetics of ICG and HPPH-car for the detection of normal and tumor tissue using flourescence, near-infrared reflectance imaging: A case study*, Photochem. and Photobiol. **72**, 94–102, 2000.
[8] McClamroch, N. H. *State Models of Dynamic Systems* (Springer-Verlag, 1980).
[9] Ntziachristos, V., Yodh, A. G., Schnall, M. and Chance, B. *Concurrent MRI and diffuse optical tomography of breast after indocyanine green enhancement*, Proc. Natl. Acad. Sci. USA **97**, 2767–2772, 2000.
[10] Ozbek, L. and Aliev, F. *Comments on adaptive fading Kalman filter with an application*, Automatica **34**, 1663–1664, 1998.
[11] Ozbek, L. and Efe, M. *An adaptive extended Kalman filter with application to compartment models*, Commun. Stat. Simul. Comput. **33**, 145–158, 2004.
[12] Reif K. and Unbehauen, R. *The extended Kalman filter as an exponential observer for nonlinear systems*, IEEE Trans. Signal Processing. **47**, 2324–2328, 1999.
[13] Springett, R., Sakata, Y. and Delpy, D. T. *Precise measurement of cerebral blood flow in newborn piglets from the bolus passage of indocyanine green*, Phys. Med. Biol. **46**, 2209–2225, 2001.
[14] Su, M.Y., Jao, J. C. and Nalcioglu, O. *Measurement of vascular volume fraction and blood-tissue permeability constants with a pharacokinetic model: studies in rat muscle tumors with dynamic Gd-DTPA enhanced MRI*, Magn. Reson. Med. **32**, 714–724, 1994.
[15] Su, M. Y., Wang, Z., Carpenter, P. M., Lao, X., Muhler, A. and Nalcioglu, O. *Characterization of N-ethyl-N-nitrosourea induced malignant and benign breast tumors in rats by using three MR contrast agents* J. Magn. Reson. Imag. **9**, 177–186, 1999.
[16] Tofts, P. S. *Modeling tracer kinetics in dynamic Gd-DTPA MR imaging*, J. Magn. Reson. Imag. **7**, 91–101, 1997.
[17] Yates, M. S., Bowmer, C. J. and Emmerson, J. *The plasma clearance of indocyanine green in rats with acute renal failure: effect of dose and route of administration*, Biochem. Pharmacol. **32**, 3109–3114, 1983.