Simulation of Adaptive Control of Theophylline Concentrations

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This article describes methods for adaptive control of drug delivery based on sparse measurements. A discussion of model-based open-loop control and Bayesian feedback is presented, and an adaptive control algorithm that combines desirable features of both methods is outlined.

Monte Carlo simulations are used to assess the performance of model-based open-loop control and adaptive control in the representative application of theophylline therapy. The simulation results demonstrate that adaptive control based on sparse measurements may be used to achieve and maintain a target theophylline concentration with a high degree of confidence.

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Determining Dosage Requirements

In the practice of medicine, drugs are administered with a goal of attaining a therapeutic effect without toxicity [1], [2]. For many drugs in which the ratio of therapeutic effect to toxicity (the therapeutic index) is narrow, there is an unacceptably large and unpredictable interindividual variability in the dose-response relationship. Implementation of methods that allow determination of the dosage requirements for a therapeutic response in an individual patient would result in significant improvement in treatment efficacy [3]-[6]. For this reason, automatic control techniques have been applied in drug delivery. There have been many reports describing the use of closed-loop drug delivery in regulating physiological parameters [1], [7], [8]. Closed-loop control is facilitated by the availability of frequent response measurements in "data rich" situations [9].

However, there are many "data poor" applications where interindividual variability in patient response must be overcome by adjusting the infusion rate based on sparse measurements. Because it is an indicator of the likelihood of therapeutic effect or toxicity, the drug serum concentration is used as an intermediate endpoint for adjusting the infusion regimen for many drugs, including antibiotics, antiarrhythmic agents such as lidocaine, the bronchodilator theophylline, and chemotherapeutic agents such as methotrexate. The infusion rate of heparin, which is an anticoagulant, is adjusted in many settings based on the therapeutic response that is measured by a global clotting test such as the activated partial thromboplastin time (APTT) or activated clotting time (ACT).

In this article, the automatic control techniques that dominate applications in "data poor" situations, model-based open-loop control and Bayesian feedback, are briefly reviewed, and a new system for adaptive control based on sparse measurements is described. Adaptive control based on sparse measurements was evaluated in computer simulations for the representative application of theophylline therapy.

Model-Based Open-Loop Control

Computerized systems have been developed to deliver open-loop infusion regimens designed to achieve and maintain a target concentration in the central compartment of a pharmacokinetic model. The target concentration may be raised and lowered as desired by the clinician. A computer-controlled drug infusion pump is used to accurately deliver the complicated infusion regimens that are necessary to achieve a target concentration in a time-optimal manner. The infusion regimens are designed to accommodate infusion rate constraints such as those imposed by the infusion pump, which include a maximum infusion rate and integer pumping rates, and the obvious constraint that drug may be infused but not withdrawn. Since drug effect is more closely correlated with the serum or plasma concentration of a drug than with the drug dose, manipulating the target concentration using model-based open-
Bayesian Feedback

Bayesian feedback is a general approach for modeling individual pharmacokinetics to facilitate dosage adjustment based on sparse measurements of patient response [14], [15]. In Bayesian feedback, the pharmacokinetic parameters of the individual patient are estimated and a revised dosage regimen is developed based on the new parameter estimates [3]. Bayesian estimation allows the parameters of an individual patient to be estimated by taking into account both the expected drug levels and their variability based upon the population pharmacokinetics, and the measured drug levels and the expected variability of the assay. Bayesian estimation is especially useful when the number of measurements is limited. For applications in pharmacokinetics, Bayesian estimation is usually performed by minimizing an appropriate objective function in an off-line analysis of recorded drug dosage and concentration measurement data.

Although Bayesian feedback has been successfully applied in many cases [2], [4], [6], [15], [16], its routine application has been limited by several factors, including a lack of computer hardware and software suitable for implementation [17]. Software has been developed for Bayesian estimation, but the current techniques must be applied off-line and in separate steps to devise a strategy for Bayesian feedback. Much time and effort is required to gather measurement data, record the dosage regimen the patient receives, enter this data into a computer, perform parameter estimation using the software, develop a revised infusion regimen, and determine an appropriate sampling schedule. After it is translated into a form suitable for implementation, the infusion regimen must be described to the clinical personnel who will administer the regimen. However, clinical personnel may not accurately record the dosage history, record the times at which blood samples are drawn, and deliver the specified infusion regimen.

Since the number of measurements is limited by the number of blood samples that may be drawn or by the cost of the assay, the sampling schedule should maximize the information obtained from the limited number of measurements that are available. Optimal sampling theory may be used to determine sampling times that provide accurate estimates of pharmacokinetic parameters [18], [19]. However, the influence of model parameters on the concentrations is complex, time varying, and dependent on the infusion regimen. Therefore, the insight offered by the theory is difficult to apply when the goal is to determine sampling times for accurately achieving a target concentration. Determination of sampling times is also complicated by the need to resolve conflicting objectives, such as the necessity of early sampling to facilitate dosage adjustment, and the desirability of delaying sampling until a time that is more optimal for the purpose of obtaining an accurate estimate of a specific parameter [20].

Because of the time required to perform the assay, a delay is introduced between the time a blood sample is drawn and the time at which a measurement is available. When a concentration measurement is available, model parameters are estimated, and the infusion rate must be adjusted based on the new parameter estimates. Ideally, the new infusion regimen would be designed to raise or lower the concentration to the target value, and then maintain the target concentration. However, the measurement gives the concentration at a past time, not the current concentration, which may differ if the system has not remained in the steady state since the time of the measurement. The lack of knowledge of the state of the pharmacokinetic system and the difficulty of designing mathematically complex infusion regimens that achieve a target concentration in a time-optimal manner complicate the design of the infusion regimen. In many cases, these problems are circumvented by simply setting the new infusion rate to the value that would maintain the target concentration in the steady state. This infusion rate is easy to compute using the parameter estimates and eventually produces the target concentration when the system reaches the steady state. However, the target concentration is not achieved in a time-optimal manner, which is detrimental in situations where the drug concentration is toxic or ineffective in a critically ill patient.

Theophylline Therapy

Theophylline is a potent bronchodilator used in the treatment of acute and chronic asthma [21]. The toxic and therapeutic effects of theophylline are related to the concentration of the drug in a patient's blood serum. Serum concentrations between 10 and 20 micrograms per milliliter (mcg/ml) produce a therapeutic effect. The drug is likely to be ineffective at lower concentrations. Symptoms of toxicity may occur at higher concentrations, and severe toxicity may occur at concentrations above 30 mcg/ml. Pharmacokinetic models, which describe the time course of drug uptake, distribution, and elimination, are frequently used to predict the serum concentration resulting from a dose or infusion. Such models are useful for determining dosing strategies or infusion regimens that will achieve and maintain a therapeutic serum concentration.

Pharmacokinetic Model

For an intravenous infusion, theophylline pharmacokinetics are usually described using a one compartment model (Fig. 1) [21]. The time rate of change of the compartmental concentration $C$ is

$$ \frac{dC}{dt} = -k_{10}C + \frac{i}{V_d} $$

(Fig. 1. One compartment pharmacokinetic model for theophylline disposition during intravenous infusion. The concentration $C$ is a function of the infusion rate input $i$ the apparent volume of distribution $V_d$ and the elimination rate constant $k_{10}$.)

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The clearance is defined by

\[ CL = V_d \cdot k_{10} \]

The dose required to move the concentration from an initial value \( C_i \) to a target value \( C_t \) is

\[ D = (C_t - C_i)V_d \]

and the constant infusion rate required to maintain the target concentration in the steady state is

\[ I_t = C_t CL. \]

Means and standard deviations for \( V_d \) and \( CL \) have been determined in population studies [22]. The values for both of these parameters are assumed to vary among patients according to a log-normal distribution. Parameter values for acutely ill nonsmokers are listed in Table I. Since the model includes a single compartment, the compartmental concentration is assumed to reflect the serum concentration. However, the apparent volume of distribution does not correspond to a real physiologic volume. Evidence that drug distribution is not instantaneous has resulted in the practice of infusing loading doses over a period of thirty minutes to one hour to avoid transiently high concentrations that may occur with rapid intravenous administration. Also, it has been recommended that serum concentrations be measured about thirty minutes after a loading dose to allow time for the distribution phase to be completed [21].

**Intravenous Theophylline Infusion**

Theophylline is administered by intravenous infusion to provide rapid relief of acute asthmatic symptoms. The infusion regimen usually consists of a loading dose followed by a continuous infusion. The loading dose and rate of continuous infusion are calculated based on the average values of the pharmacokinetic parameters in the patient population. The loading dose is calculated to achieve the desired concentration for the volume of distribution. The clearance is used to determine the rate of continuous infusion required to maintain a desired concentration in the steady state. The ranges of the parameters may be considered in limiting the loading dose or infusion rate to decrease the likelihood of achieving toxic concentrations in patients with extreme values of pharmacokinetic parameters.

Since there is a wide variability in the pharmacokinetic parameters between patients, the dosage should be adjusted for an individual patient based on measurements of the serum concentration [21]. Thirty minutes to one hour after the loading dose, the serum concentration is measured to determine if additional loading doses are necessary, or if the measured concentration exceeds the desired value. After the continuous infusion is begun, the serum concentration will rise or fall if the patient’s clearance is significantly different from the value used to compute the continuous infusion rate.

A second serum concentration measurement obtained six to eight hours into the infusion may be used as the basis for infusion rate adjustment to compensate for the difference between the patient’s clearance and the assumed value for which the continuous infusion rate is designed. A third measurement may be obtained at twenty-four hours into the infusion to determine if an additional infusion rate adjustment is required. In patients with congestive heart failure or pneumonia, the clearance is initially lower than the value for normal patients, and may increase over time as theophylline therapy is continued [22]. Additional measurements may be obtained every twenty-four hours to allow the infusion rate to be adjusted to compensate for any clearance changes that may occur. However, as outlined in the discussion of Bayesian feedback, determining the appropriate infusion rate adjustment is complicated by the delay between sampling and availability of the measurement, the system not being in the steady state, and the difficulty of computing mathematically-complex infusion regimens.

**Adaptive Control**

Model-based control and Bayesian estimation are coupled in the adaptive control system employed in the simulation of theophylline therapy. The infusion regimen is computed to achieve and maintain a target concentration in a pharmacokinetic model. The model parameters are initially set to the best estimates available given the prior information about the patient. When a measurement of the patient response is available, a Bayesian method is used to estimate the parameters of the individual patient, and the model parameters are adapted to the new parameter estimates for the patient. The infusion rate is then automatically adjusted as required to move the concentration to the target level.

In an implementation of the adaptive control system, the infusion regimen would be automatically delivered by means of a computer-controlled infusion pump or syringe pump, depending on the clinical setting. Bayesian estimation and adaptive control would be performed automatically when a measurement of the concentration was entered into the adaptive control system.

**Control Law**

A discrete-time model of the pharmacokinetic system (1) is

\[ y(t) = -cy(t - 1) + bu(t - 1) \]  \hspace{1cm} (2)

where \( y \) is the compartmental concentration, \( u \) is the drug infusion rate, and

\[ a = -e^{-CL/V_d} \]  \hspace{1cm} (2)

\[ b = \frac{1}{CL} \left( 1 - e^{-CL/V_d} \right) \]

where \( h \) is the discrete time interval.

For the model (2), the infusion rate that is required to achieve a target concentration \( y_t \) is given by the control law

\[ u(t) = \frac{y(t) + cy(t - 1)}{b} \]  \hspace{1cm} (3)

Since the infusion rate is constrained by several factors, including limitations of the infusion pump and the fact that negative infusion rates are not possible, a constrained infusion rate \( u_c \) is delivered to the patient instead of the computed rate \( u \). Values of \( y \) used in the control law are predicted using the model (2) for the infusion rate that is actually delivered to the patient, \( u_c \).

If the concentration is to be raised, the action of the control law is to infuse drug rapidly until the model-based prediction of the concentration is at the target level, and then begin a continuous infusion at a rate that would maintain the target concentration for the model. If the concentration is to be lowered, then the action of the control law, with the
constraint that negative infusion rates are not allowed, is to set the infusion rate to zero until the predicted concentration falls to the target, and then begin a continuous infusion at a rate that would maintain the target concentration for the model.

Parameter Estimator

When a new measurement is available, estimates of the volume of distribution and clearance are revised by minimizing the Bayesian objective function

\[ J_{\text{Bayes}} = \sum_{j=1}^{m} \frac{(\ln(\theta_j) - \ln(\hat{\theta}_j))^2}{\sigma_j^2} + \sum_{i=1}^{n} \frac{(\ln(y_i) - \ln(C_i))^2}{\sigma_i^2}. \]  

In (4), \( \theta_j \) and \( \hat{\theta}_j \) represent one of the \( m \) pharmacokinetic parameters for the patient population and an individual patient, respectively. One of \( n \) concentrations predicted by the population pharmacokinetic model and measured from an individual patient are represented by \( y_i \) and \( C_i \), respectively. The variances of the natural logarithms of one of the \( m \) population pharmacokinetic parameters and one of the \( n \) concentration measurements are \( \sigma_j^2 \) and \( \sigma_i^2 \), respectively. When the parameters are treated as uncorrelated independent random variables, the objective function is expressed as in (4). The Bayesian objective function that accommodates correlated parameters is more complex [4]. The Bayesian objective function (4) may also be modified to allow the discrepancy between the model prediction and the measurements to be partially attributed to time-varying pharmacokinetic parameters [16].

Simulation Study

Monte Carlo simulations were used to assess the performance of adaptive control of theophylline therapy over the expected range of pharmacokinetic parameters in the patient population and over the expected range of measurement errors. For the simulation, the parameter values shown in Table I were used to generate random values of \( V_d \) and \( CL \) for a log-normal distribution. Random measurement errors, which represent the errors in the theophylline concentration measurement introduced by the laboratory assay, were generated from a log-normal distribution with a coefficient of variation \( \sigma \) of 5%. The discrete-time interval for computing predicted concentrations and infusion rates was 30 min. Each simulation was designed to represent an 80 h theophylline infusion. The maximum infusion rate was limited to 500 mg/h. Open-loop control was simulated by having each patient receive the infusion regimen that would achieve and maintain a target concentration of 15 mcg/ml in a pharmacokinetic model with population parameters.

Adaptive control was simulated for samples drawn at 1, 8, and 24 h. The times at which the measurements were available for adaptive control were randomly selected, according to a uniform distribution, to be 30, 60, 90 or 120 min after sampling. Two strategies for manipulating the target concentration were selected for simulation of adaptive control of theophylline therapy. In the first strategy, the target concentration was 15 mcg/ml, which is the center of the therapeutic range. In the second strategy, the target concentration was initially set to 10 mcg/ml and was later increased to 15 mcg/ml. For the second strategy, the target concentration was increased after adaptation based on the first measurement. The second strategy reflects a more conservative approach to theophylline therapy, since it reduces the number of patients in which a potentially toxic concentration is likely to result from the loading dose [21].

Simulation Results

Figs. 2, 3, and 4 show the means and one standard deviation bounds for the theophylline concentration achieved in simulations of open-loop and adaptive control in 500 patients. Figs. 3 and 4 also show the maximum (upper trace) and minimum (lower trace) concentrations achieved in the simulations of adaptive control in 500 patients. Figs. 2, 3, and 4 show the results for the first 50 hours of the 80 h simulations.

With open-loop control, there is a significant number of patients for which the theophylline concentration is outside the therapeutic range of 10 to 20 mcg/ml. The wide variability in achieved concentrations demonstrates the need for infusion rate adjustment based on the concentrations measured in an individual patient. With adaptive control based on samples obtained at 1, 8, and 24 h, the variability in achieved concentrations is greatly reduced.

Optimal sampling theory suggests that for the accurate estimation of a parameter, a sample should be obtained at a time when the influence of the parameter on the measured variable is at a maximum [19]. Since the influence of the volume of distribution on the concentration is near its maximum at the one hour sampling time, an estimate of the patient’s volume of distribution based on the one-hour sample would be expected to be accurate. The most accurate clearance estimate would be obtained from a sample drawn after the pharmacokinetic system has reached steady state, when the concentration depends solely on the clearance [20]. The 8 h sample allows the infusion regimen to be adjusted for improved control, even though the sampling time is not optimal for estimation of the clearance. The 24 h sample provides a more accurate

![Figure 2](image-url)  

**Figure 2.** Simulation of open-loop control for a target theophylline concentration of 15 mcg/ml. Curves show mean and one standard deviation bounds for the concentrations achieved in the simulation for 500 patients.
clearance estimate that allows for precise control of the concentration in the steady state.

If the target concentration is 15 mcg/ml in the early phases of either open-loop or adaptive control, a potentially toxic concentration may result in patients having a volume of distribution that is significantly less than the average value for which the early infusion regimen is designed (Figs. 2 and 3). With the second adaptive control strategy, the estimate of the volume of distribution based on the first sample allows the target concentration to be increased safely from 10 to 15 mcg/ml. The maximum concentration achieved during the simulation does not exceed 25 mcg/ml in any patient (Fig. 4). After 10 h, the concentration does not fall below 10 mcg/ml in any patient.

![Fig. 3. Simulation of adaptive control for a target theophylline concentration of 15 mcg/ml. Adaptive control was based on measurements from blood samples drawn at 1, 8, and 24 h. Curves show mean and one standard deviation bounds, and maximum (upper trace) and minimum (lower trace) values for the concentrations achieved in the simulation for 500 patients.](image)

Previous simulation studies of adaptive control of theophylline therapy utilized the simple strategy of adjusting the maintenance infusion rate with a goal of achieving the target concentration in the steady state [5, 20]. With this suboptimal strategy, the concentration approaches the steady-state value according to the response of the first-order pharmacokinetic system to a step change in the infusion rate. For a patient with average pharmacokinetic model parameters, the time constant is 13 h. Therefore, with the suboptimal strategy, the change in the concentration does not reach 90% of its final value until about 30 h (2.3 τ) after the change in the infusion rate. The simulations reported in this paper employ a control law (3) that achieves and maintains a target concentration in a time-optimal manner (Figs. 3 and 4).

An implementation of the adaptive control system described in this article would provide an integrated environment for real-time application of Bayesian feedback that would require less time and effort to use than is needed for clinical personnel to plan, monitor, and implement a patient’s therapy using current techniques. The computerized adaptive control system would allow the target concentration to be adjusted with a high degree of confidence that the resulting concentration is close to the target. The system would provide improved performance by precisely delivering an infusion regimen to achieve the target concentration in a time-optimal manner. Automatic administration of the infusion regimen using a computer-controlled infusion pump would ensure accurate delivery and recording of the infusion regimen, would eliminate setting infusion rates by manual adjustment of an infusion pump, and would eliminate the need for manual recording of the infusion regimen. In a simulation study of computer-assisted dosage adjustment, the use of a “smart pump” for accurate administration and recording of the dosage contributed more to precise control of drug concentrations than the combination of the accuracy of dose preparation, the accuracy of the serum level assay, and the accuracy of the knowledge of the time at which serum levels were drawn [23].

After a blood sample is drawn and the measurement of the theophylline concentration is determined, the measurement and the time at which the sample was obtained would be entered into the adaptive control system. Parameter estimation and adaptive control would automatically be performed. The new infusion regimen would be delivered automatically using the computer-controlled infusion pump. The infusion regimen would be recorded by the control computer. Therefore, with the adaptive control system described in this article, the infusion regimen would be adjusted sooner after a measurement is available than is possible using the current techniques of Bayesian feedback. The capability for immediate adjustment of the infusion rate, and achieving the target concentration in a time-optimal manner, is important in situations where the measured drug concentration is at a toxic level or is below the effective level. Rapid infusion rate adjustment is particularly advantageous when fast assays are available for measuring theophylline concentrations.

**Prospective Applications and Future Work**

Adaptive control based on sparse measurements has the potential to be applied in other areas for which Bayesian feedback has been utilized, including the delivery of antibiotics, antiarrhythmic agents, and chemotherapeutic agents. Another potential application is the administration of heparin to provide anticoagulation during extracorporeal blood circulation and in other situations. It has been suggested that if a rapid intraoperative assay for alfentanil were developed, it could be coupled with computer-controlled infusion pumps in a system for Bayesian feedback that could improve the popularity and accuracy of intravenous anesthesia during long procedures [24, 25].
When only sparse measurements of patient response are available, there may be a high degree of uncertainty in the model parameter estimates. The ability to forecast the resulting level of uncertainty in the response would allow the physician to make better decisions regarding therapy and to make better interpretation of concurrent indicators of the patient’s clinical status. The times at which the samples are obtained drastically affect the performance of the system in achieving and maintaining a target concentration. The sampling strategies that are currently used in Bayesian feedback are often so simple that they do not take full advantage of the limited number of available measurements. The development of forecasting algorithms and algorithms for determining the sampling times that result in improved control system performance are topics for future research.

References


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