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A Computer Simulation Study Of Adaptive Control Of Theophylline Therapy.

Srinidhi Aragula
University of Alabama at Birmingham

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Aragula, Srinidhi, M.S.B.E.

University of Alabama at Birmingham, 1990

U·M·I
300 N. Zeeb Rd.
Ann Arbor, MI 48106

A COMPUTER SIMULATION STUDY OF ADAPTIVE CONTROL OF THEOPHYLLINE THERAPY

by

SRINIDHI ARAGULA

A THESIS

Submitted in partial fulfillment of the requirements for the degree of Master of Science in the Department of Biomedical Engineering in the Graduate School, The University of Alabama at Birmingham

BIRMINGHAM, ALABAMA

1990

ABSTRACT

In this research project, an adaptive control system was developed to achieve a precise dosage individualization for the bronchodilator theophylline. The system was designed to attain and maintain a serum theophylline concentration of 15 μg/ml. Individual dosage requirements were optimized by estimating and incorporating patient parameters into a model based control law.

The performance of the system was assessed under various sampling schemes and stochastic disturbances in computer simulation studies. The system was validated for three subpopulations of patients, i.e., patients with normal parameters, smokers (high clearance patients), and cirrhotics (low clearance patients). The accuracy of the two parameter estimators (Kalman filter and minimization of the Bayesian objective function) were compared by computing parameter estimation errors.

The sampling scheme of 2, 12, and 30 hours most effectively individualized theophylline requirements. Of the stochastic disturbances considered (besides delays, sampling errors and dosing errors), the assay errors most significantly affected the performance of the system.

For patients with normal parameters, the mean theophylline concentrations of 15.24 +/- 0.92 μg/ml and 15.05 +/- 0.79 μg/ml were achieved by the system employing the recursive Kalman filter and the non-recursive Bayesian parameter estimator, respectively. For smokers and cirrhotics, the mean concentrations of 15.02 +/- 0.63 μg/ml and 15.12 +/- 1.12 μg/ml were achieved, respectively, by the system employing minimization of the Bayesian objective function.

The parameter estimates obtained by minimization of the Bayesian objective function were more accurate than those obtained by the Kalman filter.

DEDICATION

to my mother

ACKNOWLEDGMENTS

I would like to express my deepest and most sincere thanks to Dr. Thomas C. Jannett for his invaluable advice and guidance throughout this research. I am extremely grateful to Dr. Martin J. McCutcheon for his indispensable support and encouragement throughout my graduate education. My special thanks to Drs. Linda C. Lucas and Dale S. Feldman for all their help.

On a separate note, I would like to thank my mother, K. Jayalakshmi, without whom my entire education and career that follows would simply be an impossibility. I also thank other members of my family for their assistance and understanding.

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CHAPTER I

INTRODUCTION

Pharmacokinetics is the study of time course of the uptake, distribution, metabolism, and elimination of a drug from the body. The pharmacokinetics of a drug may be characterized using a compartmental approach that represents the body as a system of compartments and assumes an inter-compartmental transfer and compartmental elimination of the drug. The compartments are not necessarily anatomic or physiologic. In a linear elimination process, the elimination rate of the drug is assumed to be proportional to the amount of the drug in the body. The simplest way to describe the pharmacokinetics of a drug that equilibrates rapidly throughout the body would be to assume the whole body to be a single homogeneous compartment.

The linear one-compartment pharmacokinetics are governed by apparent volume of distribution (V_d) and clearance (Cl). Other pharmacokinetic parameters, such as elimination rate constant and biological half-life, are functions of the volume and the clearance.

The apparent volume of distribution does not refer to a real physiologic volume. Changes in the apparent volume of distribution are sometimes used to explain the variations in

the biological half-life. The clearance is a measure of the efficacy of drug elimination expressed as the volume of plasma cleared of drug per unit time. The biological half life ($t_{1/2}$) is the time required for a 50% decrease in plasma drug concentration. The elimination rate constant (k_e) represents the fraction of drug eliminated per unit time. The relationship between the parameters is given equations (1) and (2).

$$k_e = \frac{(0.693)}{t_{1/2}} \quad (1)$$

$$Cl = (k_e)(V_d) \quad (2)$$

A standard drug-dosing regimen is designed to achieve and maintain a desired response based on the average pharmacokinetic parameter values of a patient population. Patients invariably demonstrate a varying clinical response to the standard dosing regimen. Patients with average parameters usually demonstrate the desired response. Patients with a high clearance may lack response; whereas, patients with a low clearance may develop drug toxicity.

Variations in pharmacokinetic parameters could be secondary to an individual's physiology or to pathological states of the body, such as liver disease, heart disease, and kidney disease. Factors such as diet and other concomitantly administered drugs also could affect the pharmacokinetic parameters. It is not always possible to identify and avoid the factors that cause interpatient variability, and many times the causative factors may not be known. Considering the undesirable responses that could be induced in patients by the

interindividual parameter variation, it becomes imperative that patients with extreme parameters receive individualized therapy, particularly for drugs with a low therapeutic index (ratio of therapeutic effect to toxicity) and sparse response measurements.

Current Drug Infusion Protocols

The current drug infusion protocols attempt dosage individualization based on a patient's clinical condition and response measurements. Initially, a patient is treated with a standard dosing regimen. Response measurements are obtained based upon a predetermined scheme or the patient's clinical condition. Based on the response measurements, proportional changes are usually made in the standard dosing regimen. Individualization is thus attempted by trial-and-error dosage adjustments. Such dosage adjustments may be inappropriate and deleterious, particularly when the response measurements are associated with large errors.

Present Day Computer-Aided Systems

More recently, computer-aided systems have been used to achieve dosage optimization based on individual pharmacokinetics. Utilizing a mathematical model and a parameter estimator, the computer-aided systems tailor the dosage according to an individual's needs. The mathematical model is used to predict the response of a patient to a given drug infusion, and the parameter estimator is used to compute individual parameters.

The dosage individualization achieved by computer-aided systems is not very precise because these systems do not

utilize a specific control strategy to design new infusion regimens. Following parameter estimation, proportional changes are usually made in the standard dosing regimen. Also, the computer-aided systems require time-consuming and cumbersome manual computer entry of the patient's dosage history.

Adaptive Control System

The system discussed in this research project attempts to achieve a more precise dosage individualization, particularly for drugs such as lidocaine [1] and theophylline, whose dosage adjustments are based on infrequent patient response measurements. The serum concentration of these drugs is an accurate indicator of an impending drug toxicity and is therefore used as a response measurement [2].

Following the entry of a patient's response into the computer, the automated system would estimate patient parameters and incorporate them into a mathematical model and a specific control law. Thus, the system would be adapted to the pharmacokinetic characteristics of the patient. The system is therefore termed the "Adaptive Control System."

The adaptive control system consists of a mathematical model, a parameter estimator, a control law, and a feedback control algorithm. The mathematical model is derived from a pharmacokinetic model and has a discrete-time input-output form which is suitable for computer simulation studies. The model is used to predict the response of a patient for a given infusion. The control law is a manipulated mathematical model used to compute infusion rates that can attain and maintain a

desired output in the model. The parameter estimator is used to compute individual parameters by selecting values of the volume and the clearance that minimize the Bayesian objective function (refer to chapter III). The feedback control algorithm regulates the infusion regimen via the control law.

Mode of operation

Initially, each patient is considered to be an average patient of the population; the mathematical model and the control law contain the mean parameter values. The patient is initiated on an infusion regimen designed by the control law to attain and maintain a desired output in the model. As the patient response measurements are obtained and entered into the computer, individual parameters are estimated. The model and the control law are revised with the new parameter estimates.

Because time is required for handling of the blood sample and for the assay procedure, there is a delay between sampling of blood and the actual entry of response measurement into the computer. During the delay, the patient would continue to receive the drug infusion. Hence, at the time of entry of the response into the computer, the actual response of the patient would to be different from the response measurement being entered. Taking the delay into account, the feedback control algorithm designs and implements a new infusion regimen via the control law.

Development of the adaptive control system

The development of an adaptive control system for a specific drug therapy requires formulation of the system

constituents, validation of the system in computer simulation studies, and demonstration of the system's efficacy in clinical trials. In this research project, a mathematical model, a control law, and a feedback control algorithm have been formulated for the bronchodilator theophylline and the system has been validated in computer simulation studies.

CHAPTER II

LITERATURE REVIEW

Theophylline

Theophylline is a potent bronchodilator that has been used for several decades to relieve the symptoms associated with increased airway resistance. Chemically, theophylline is a dimethylated xanthine that is similar in structure to the naturally occurring xanthines, such as caffeine and theobromine found in tea, coffee, chocolate, and cola.

Indications

Theophylline is used in the treatment of acute and chronic bronchial asthma, chronic bronchitis, emphysema, and Cheyne-Stokes respirations. More recently, it has been used to treat apnea and bradycardia associated with prematurity [3], [4]. Theophylline also is used as an adjunct in the treatment of congestive heart failure and acute pulmonary edema [5].

Pharmacology

By acting directly on the bronchial smooth muscles, theophylline relaxes the airway and alleviates the symptoms associated with increased airway resistance [6]. At a cellular level, several mechanisms have been proposed to explain the bronchodilator effect of theophylline and include

inhibition of phosphodiesterase, prostaglandin antagonism, effects on intracellular calcium, and increased binding of cAMP to cAMP-binding proteins [5]. Other pharmacological effects of theophylline include transient diuresis, central nervous system stimulation, cerebral vasoconstriction, increased gastric acid secretion, inhibition of uterine contractions, and increased cardiac biventricular performance [5].

Pharmacodynamics

Efficacy: The bronchodilator action of theophylline begins at a serum concentration of 5 μg/ml and increases proportionally up to a serum concentration of 20 μg/ml. The optimal response is obtained over a serum concentration range of 10-20 μg/ml. Greater improvement in pulmonary function and a shorter duration of intravenous therapy have been demonstrated among patients receiving an infusion producing a mean serum concentration of 19 μg/ml compared to a similar group of patients with a mean concentration of 10 μg/ml [5]. In premature infants, lower serum concentrations in the range of 5-10 μg/ml appear to be effective in controlling apnea and bradycardia. The bronchodilation effect of theophylline diminishes rapidly in a manner that parallels the clearance of theophylline from plasma.

Toxicity: Theophylline therapy is associated with a wide range of adverse effects. Effects of central nervous system stimulation and slight nausea are frequently experienced after a loading dose. Generally, more severe and persistent side effects, such as vomiting, headache, diarrhea, and insomnia,

are associated with serum concentrations exceeding 20 μg/ml [7], [8]. Serum concentrations in excess of 35 μg/ml may result in hyperglycemia, hypotension, cardiac arrythmia, seizures, and death.

Pharmacokinetics

Distribution: After entering the circulation, 40% of theophylline binds to plasma proteins, and the remaining free drug distributes throughout the body water [9]. Theophylline distributes rapidly throughout the body and within one hour following an intravenous injection, the tissue theophylline concentrations equal the serum theophylline concentration. The apparent volume of distribution, in both children and adults, ranges from 300 to 700 ml/kg and averages about 458 +/- 95 ml/kg [10], [11]. In premature newborns and adults with hepatic cirrhosis and uncorrected acidemia, the volume of distribution is slightly larger due to decreased protein binding. In all other circumstances, the apparent volume of distribution remains unaltered [12].

Metabolism and excretion: Theophylline is metabolized by hepatic biotransformation into relatively inactive metabolites (a process involving multiple cytochrome enzymes), which are rapidly excreted by the kidneys. Because the enzymatic metabolism is a capacity limited process, several reports regard the kinetics of theophylline as being nonlinear [13], [14], [15], [16]. However, Tang Liu et al. [14] have demonstrated a unique situation in which the overall clearance of theophylline is, in fact, linear. At high serum concentrations, the metabolic process being relatively slow,

the diuretic effect of theophylline causes rapid excretion of the drug from the kidneys. At low serum concentrations, the renal excretion of the drug is diminished because of the less pronounced diuretic effect, but the relatively rapid metabolic process elevates theophylline elimination [14]. Thus, the metabolic process and the diuretic effect tend to offset each other in maintaining an overall linear clearance of theophylline.

Clearance: The product of volume of distribution and the elimination rate constant accurately reflects theophylline clearance. Otherwise healthy patients have a mean clearance of 0.65 +/- 0.19 ml/min [5]. Several factors, such as age, disease state, smoking, diet, and other concomitantly administered drugs, induce large interpatient clearance variations by changing the rate of hepatic biotransformation of theophylline. Generally, patients with hepatic cirrhosis [17], [18], [19] and congestive heart failure have low clearances [20], and cigarette smokers have significantly higher clearances [10], [21]. Although, the average clearance in children is approximately 40% greater than that reported in adults [22], [23], [24], the slowest clearances have been reported in premature neonates [4]. Conflicting reports have been published regarding the influence of obesity, old age, and sex on theophylline clearance [25], [26], [27], but, sufficient evidence has suggested that subject weight and sex do not significantly alter theophylline clearance. Concomitant therapy with cimetidine may reduce theophylline clearance through enzyme inhibition; whereas, rifampin, phenobarbital,

and phenytoin have been shown to increase theophylline clearance through enzyme induction.

Pharmacokinetic models

Using mathematical and statistical techniques, the serum concentration versus time data of theophylline have been fit to both one- [28] and two-compartment [29] pharmacokinetic models. The governing equation of a one-compartment model is given by

$$\frac{dC}{dt} = (-k_e)(C) + \frac{I}{V_d} \qquad (3)$$

where C (μg/ml) is the compartmental concentration of theophylline, K_e (min^{-1}) is the elimination rate constant, I (mg/hr) is the infusion rate, and V_d (ml/kg) is the apparent volume of distribution.

Theophylline treatment

Theophylline may be administered both orally and parenterally. The intravenous loading dose for aminophylline (79% anhydrous theophylline) is 5-6 mg/kg given over a 15-30 minute period, followed by a continuous infusion of the drug at the rate of 0.3 mg/kg/hr for severely ill patients (e.g., congestive heart failure, liver disease), 0.6 mg/kg/hr for nonsmokers, and 0.9 mg/kg/hr for smokers [30]. Theophylline therapy is monitored by obtaining a serum concentration 1-2 hours after initiation of therapy. The second serum concentration is availed 4 hours later. Subsequent serum concentrations may be obtained if patients develop signs of toxicity.

Present Day Computer Aided Systems

Recently, due to the development of rapid, simple and reliable drug assays on one hand, and the expansion of computer technology on the other, an increasing interest in the application of feedback control methods in clinical pharmacokinetics has resulted in the development of computer-aided systems for optimizing drug therapy. By estimating individual parameters and predicting the future serum concentrations of patients, the computer-aided systems achieve a more precise dosage individualization. Peck et al. [31], [32] were first to develop a microcomputer based dosing program for theophylline [32] utilizing the Bayesian algorithm of Sheiner and Beal [33]. Since then, many applications of this approach have been successfully developed for several drugs, including lidocaine [34], [35], phenytoin [36], and aminoglycosides [37].

The computer-aided systems consist of a mathematical model, a parameter estimator, and a control strategy. The mathematical model is used to predict the response of a patient for a given drug infusion. The parameter estimator utilizes the Bayesian technique (refer to chapter III) and estimates individual parameters.

Mode of operation

Initially, every patient is considered to be an average individual of a patient population and is initiated on a standard infusion regimen. With the availability of response measurements, patient parameters are estimated and incorporated into the model. Based on the parameter estimates, a

new infusion regimen is usually designed by making proportional changes in the standard regimen. Computer simulations based on the revised model, are performed to predict the patient's future serum concentrations for each regimen. The most appropriate infusion regimen is selected to proceed with individualization.

Advantages and disadvantages

The computer-aided systems achieve a better individualization compared to the current drug-infusion protocols. The Bayesian technique quite accurately estimates pharmacokinetic parameters of the individual patient [38]. However, the present day computer-aided systems have some serious drawbacks. After parameter estimation, usually only proportional changes are made in the standard infusion regimen to design new infusion regimen. The systems do not use a specific control strategy to formulate a new infusion regimen. The burden of interpreting simulation results and choosing a particular regimen lies with the physician or pharmacist. The system also requires time-consuming and cumbersome manual computer entry of infusion rate and patient's dosage history.

CHAPTER III

THE ADAPTIVE CONTROL SYSTEM

The adaptive control system consists of a mathematical model, a parameter estimator, a control law, and a feedback control algorithm. The development of the adaptive control system consists of formulating the system constituents, validating of the system in computer simulation studies, and testing system efficacy in clinical trials. In this research project, the system constituents were formulated and the system was validated in computer simulation studies for the bronchodilator theophylline.

The Constituents of the Adaptive Control System

Mathematical model: The mathematical model is a discrete-time input-output model derived from a pharmacokinetic model [39] via state space transformations. The model is used to predict the response of a patient for a given infusion. The discrete-time input-output form enables computer simulation studies. The model is given by

$$y(t) = -a_1 y(t-1) + b_1 u(t-1) \qquad (4)$$

where $a_1 = -e^{(-Cl/V)\Delta t}$, $b_1 = 1/Cl(1 - e^{(-Cl/V)\Delta t})$, y(t) is the output or the desired patient response, and u(t) is the input or the infusion rate.

b) Parameter estimator: The Bayesian technique for estimating the pharmacokinetic parameters [40], [41] involves the selection of parameter values that minimize the Bayesian objective function given by

$$OBJ_{Bayes}=\sum_{j=1}^{p}\frac{(\ln(P_j)-\ln(\hat{P}_j))^2}{p_j^2}+\sum_{i=1}^{n}\frac{(\ln(C_i))-\ln(\hat{C}_i))^2}{\sigma_i^2} \quad (5)$$

where P_j and $\hat{P}_j$ denote the j=1 to p pharmacokinetic parameters for the population and individual, p_j are the coefficients of variation of the population parameters, σ_i is the coefficient of variation of the measurements, C_i is the concentration predicted for the model using the population pharmacokinetic parameters, and $\hat{C}_i$ is one of n measured concentrations.

The means and the variances of population parameters and the expected and measured drug levels with their respective variabilities are considered in the minimization of the Bayesian objective function. The minimization of the Bayesian objective function may be achieved by the implementation of a Nelder-Mead simplex algorithm [38] or other off-line methods. The minimization technique is associated with cumbersome and time-consuming computations, and the problem of having it run off-line. A Kalman filter (a recursive filter based on the Bayesian technique and developed outside this research project) may be employed to perform on-line parameter estimation.

With each estimation, the Kalman filter gains knowledge about patient parameters and makes reductions in the covariance matrix of the estimator. With successive sampling,

the filter tends to pay less attention to measurements because of the filter's confidence in the previous estimates. Therefore the accuracy of the estimates obtained by the filter does not improve as much as those obtained by the minimization of the Bayesian objective function. To overcome this problem, in this research project, an adhoc modification was made in the covariance matrix of the estimator.

Control law: The control law is a manipulated mathematical model used to calculate an infusion regimen that can attain and maintain a desired response in the model. The control law is given by

$$u(t) = \frac{y_d(t+1) + a_1 y(t)}{b_1} \qquad (6)$$

where u(t) is the infusion rate required for a desired response $y_d(t+1)$.

Feedback control algorithm: If blood is sampled at time t_1, the response is available at time t_2 after a considerable delay because of the time required for assaying and handling the blood sample. After the response is entered, the patient parameters are estimated and incorporated into the model and the control law. A new infusion rate is calculated to proceed with individualization.

Computer Simulation Studies

The computer simulation studies are very effective in the assessment of the performance of an adaptive control system. By utilizing simulation studies, certain design decisions (e.g., sampling times) can be made, the performance of the

system can be tested under stochastic disturbances, and the system can be validated for a population of patients.

CHAPTER IV

COMPUTER SIMULATION

Computer simulations are an effective means to analyze and validate a system. They are fast, and easy to perform, and a large number of patients can be simulated in a short period of time. Prior validation of a system in computer simulation studies reduces the risks involved to patients during the clinical testing of the system. In this research project, computer simulation studies were performed to design blood sampling schemes, to demonstrate the performance of the system under stochastic disturbances, and to validate the adaptive control system for three groups of patients, i.e., patients with normal parameters, smokers (patients with a high clearance), and cirrhotics (patients with a low clearance). To demonstrate interpatient response variation, a population of 500 patients were simulated using an open-loop control. An infusion regimen was designed for a patient with average parameters and was administered to all 500 patients.

Simulation Procedure

To assess and validate the performance of the adaptive control system, Monte Carlo simulations (studies involving randomly generated parameters) were performed for a population of 500 patients. Patients were mimicked by generating the

clearance and volume parameters from scaled and log-normally distributed random numbers. The means and the standard deviations of the parameters for the three groups of patients are presented in Table I. The measurement errors were mimicked by adding log-normally distributed random numbers with a coefficient of variation (CV = standard deviation/mean) of 5% to the response measurements. Delays of 1 hour were incorporated into the simulation studies.

TABLE I

Statistics of the pharmacokinetic parameters for the three subpopulations of patients.

Patient Subpopulations	Clearance(ml/min) Mean	SD	Volume(ml/kg) Mean	SD
Patients with normal parameters	0.65	0.19	458	95
Smokers	1.05	0.32	458	95
Cirrhotics	0.31	0.19	563	80

Initially, the model and the control law contained average parameter values. An infusion regimen was designed using the control law, to attain and maintain a serum theophylline-concentration of 15 μg/ml in the model. Samples were drawn at stipulated times and individual parameters were estimated. The model and the control law were updated with new parameter estimates and a new infusion regimen was calculated to proceed with individualization. Because the control law may at times compute infusion rates higher than the upper limit of 500 mg/hr or negative infusion rates, the infusion regimen was constrained between 0 and 500 mg/hr.

Factors Considered in Simulation Studies

Design factors

Number of samples: The pharmacokinetic parameters can be accurately estimated by obtaining many blood samples. With the availability of quick, accurate, cost-effective bedside assays, many samples could be drawn; however, injudicious sampling of patients may not be beneficial, because the samples may not provide new information. Also, injudicious blood samples would only mean additional expense to the patients and an unnecessary work-load on the nursing staff. Many blood samples may be required to estimate the parameters that are known to vary over time. Intrapatient parameter variation is not frequently encountered during theophylline therapy.

Sampling times: Following the administration of a loading dose, a drug begins to distribute throughout the body. During the distribution phase, the serum concentration of the drug is governed primarily by the volume of distribution. A sample drawn at the end of the distribution phase yields maximum information regarding the volume. The clearance, on the other hand, begins to exert its effect in the transient state and significantly governs the serum concentration during the steady state. A sample drawn in the steady state yields maximum information regarding the clearance.

Considering the aforementioned facts, the following sampling schemes were formulated and tested in simulation studies:

a) 2 and 20 hours;

b) 6 and 20 hours;

c) 10 and 24 hours; and

d) 2, 12, and 30 hours.

For each of the above schemes, a population of 500 patients with normal parameters were simulated employing the Kalman filter for parameter estimation with sampling at the stipulated times. A 5% CV assay error and delays of 1 hour were also included in the simulation studies.

Stochastic disturbances

Assay errors: Both laboratory and bedside assays are available for determining serum theophylline concentrations. High performance liquid chromatography and immunoassay are some of the popular laboratory assay techniques. A rapid immunoassay technique (Seralyzer) and a procedure combining the techniques of immunoassay and thin layer chromatography (Syntex Medical Diagnostics) are available for use by the bedside [42].

Generally, the laboratory assays are more accurate than the bedside assays. The laboratory assays are associated with a 2-5% (CV) error; whereas, the bedside assays are associated with a 5-10% error. The assay errors affect the performance of the system by directly affecting the accuracy of parameter estimation. To demonstrate the effect of assay errors, log-normally distributed errors of 5, 10, and 15% CV were considered in the simulation studies. Monte Carlo simulations were performed for 500 patients with normal parameters employing the Kalman filter for parameter estimation with

sampling at 2, 12, and 30 hours. A delay of 1 hour was included in the studies.

Delays: The delays are a direct consequence of the time required for both the assay procedure and handling the blood sample. The later event particularly could consume more time if a hospital is not equipped with a laboratory facility. Typically, the laboratory assays require more time than the bedside assays. The laboratory assays are associated with 1-4 hour delays, and the bedside assays are associated delays ranging from 15 minutes to an hour. The delays do not affect the accuracy of parameter estimation and, therefore, they should not affect the performance of the system in the steady state. However, due to the delays, patients are required to receive a less specific infusion until response measurements become available. To demonstrate the effect of delays, 30-minutes, 1-hour, and 4-hour delays were considered in the simulation studies. Monte Carlo simulations were performed for 500 patients with normal parameters employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours. A 5% CV assay error was included in the simulation studies.

Sampling error: In a busy hospital setting, a sample scheduled at time t1 may be drawn at time t1 +/- x minutes. Although sampling errors of a few minutes are not uncommon, errors of hours should be a rare occurrance.

The response r1 at time t1 is available at time t2 after a certain delay. Based on the response r2 at time t2, a new infusion regimen is designed. The sampling errors could

result in erroneous predictions of r2 and, thus, affect the specificity of the new infusion regimen designed. To demonstrate the effect of sampling errors, errors of +30 minutes, -30 minutes, +1 hour, and -1 hour were considered in the simulation studies. Monte Carlo simulations were performed for 500 patients with normal parameters employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours. A 5% CV assay error and a 1-hour delay were included in the simulation studies.

Dosing errors: Infusion pumps can deliver fluids only in integer quantities. The infusion rate computed by the control law may be a real number. To take this discrepancy into account, a 1% dosing error was added to the infusion rate. Because the dosing errors would not significantly affect the performance of the system, they were not individually evaluated. Instead, the dosing errors were included in the simulations studies performed to validate the system.

Simulations Performed To Validate The System

The system was validated for the three subpopulations of patients, i.e., patients with normal parameters, smokers, and cirrhotics. From each group, 1000 patients were simulated, employing minimization of the Bayesian objective function for parameter estimation, with sampling at 2, 12, and 30 hours. All stochastic disturbances were considered concurrently in the studies. The assay error varied with a CV of 5%, the dosing error varied with a CV of 1%, and the delays varied between 1-4 hours.

Comments on Parameter Estimation

In order to compare the accuracy of the parameter estimates obtained from the two estimators, another 1000 patients with normal parameters were simulated employing the Kalman filter for parameter estimation. For each sample, the clearance and the volume estimation errors were computed for both the estimators using the formula

$$PE = \log(\hat{P}) - \log(P_i) \qquad (7)$$

where $\hat{P}$ denotes the estimated parameter, and P_i denotes the patient parameter. Prior to sampling, because average parameter values were assumed for each patient, an initial error existed between the average and the patient parameters. The initial errors were also computed using the equation (7), where P denoted the mean parameter values.

The measurement errors were computed using the formula

$$ME = \log(C_m) - \log(C_i) \qquad (8)$$

where C_m denotes the measured concentration and C_i denotes the actual concentration.

CHAPTER V

RESULTS

The performance of the adaptive control system was assessed by inspecting the concentration versus time plots, by examining the mean, the standard deviation (SD), and the coefficient of variation (CV) of concentrations, and by comparing the statistics of the concentrations achieved by the adaptive control versus those achieved by the open-loop control.

Simulation Results for Open-Loop Control

An infusion rate was designed to attain and maintain a serum theophylline concentration of 15 μg/ml in the model. The infusion rate consisted of a loading dose of 500 mg, followed by a maintenance dose of 40 mg/hr for a 70-kg man (Fig. 1). The response of a patient with average pharmacokinetic parameters is illustrated in Fig. 2.

For the Monte Carlo simulations using the open-loop control, plots of concentrations versus time are presented in Figs. 3 and 4. Fig. 3 demonstrates a large clearance variation between patients (inferred by their widely differing 80 hour concentrations); whereas, Fig. 4 demonstrates a wide volume variation (inferred by the range of initial concentrations).

Simulation Results For The Sampling Schemes

A population of 500 patients with normal parameters was simulated employing the Kalman filter for parameter estimation with sampling at the stipulated times. A 5% CV assay error and a delay of 1 hour were included in the simulation studies. The early samples were drawn to estimate the volume, and the late samples to estimate the clearance.

2- and 20-hour samples: The 2-hour sample provided good volume estimates, and the 20-hour sample provided fairly accurate clearance estimates. The concentration versus time of 50 patients in Monte Carlo simulations is illustrated in Fig. 5. A mean concentration of 15.38 +/- 1.3 μg/ml was achieved in 500 patients (Fig. 9).

6- and 20-hour samples: The 6-hour sample could provide neither good volume estimates nor good clearance estimates. The 20-hour sample provided fairly accurate clearance estimates. The concentration versus time of 50 patients in Monte Carlo simulations is presented in Fig. 6. A mean concentration of 15.5 +/- 1.4 μg/ml was achieved in 500 patients (Fig. 10). Fig. 13(a) compares the CV of the concentrations achieved by the sampling schemes of 2 and 20 hours and 6 and 20 hours.

10- and 24-hour samples: The 10-hour sample provided poor estimates of both the volume and the clearance. The 24-hour sample provided fairly accurate clearance estimates. The concentration versus time of 50 patients in Monte Carlo simulations is illustrated in Fig. 7. A mean concentration of 15.45 +/- 1.27 μg/ml was achieved in 500 patients (Fig. 11).

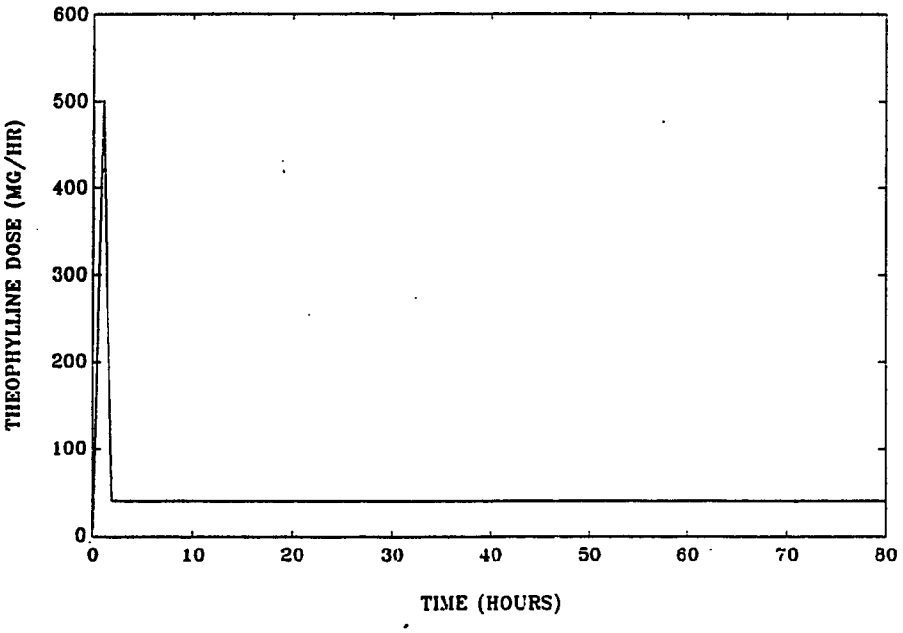

Fig. 1 Infusion regimen calculated by the control law using average parameter values to attain and maintain a concentration of 15 μg/ml.

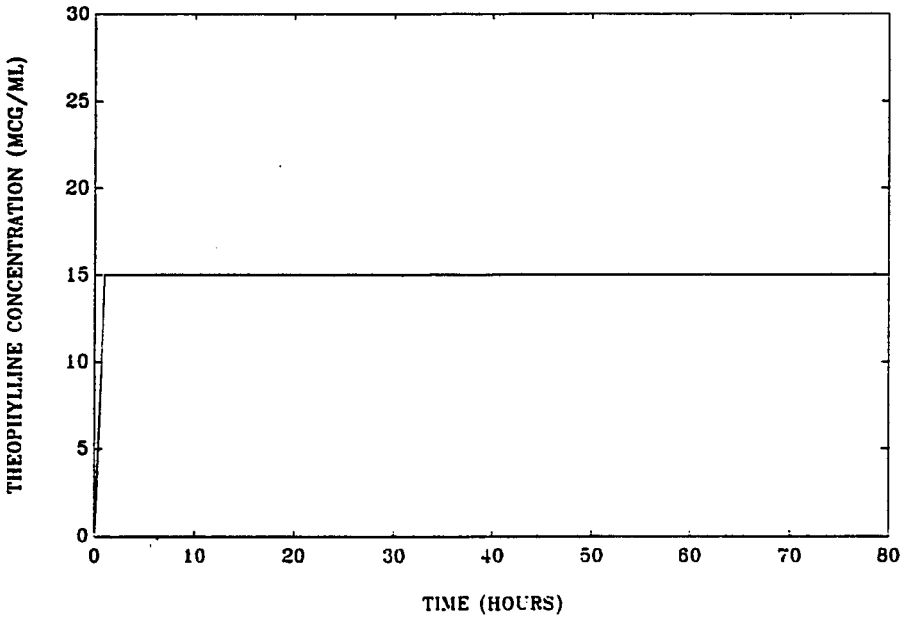

Fig. 2 Concentration achieved in a patient with average pharmacokinetic parameters receiving an infusion regimen calculated to attain and maintain a concentration of 15 μg/ml.

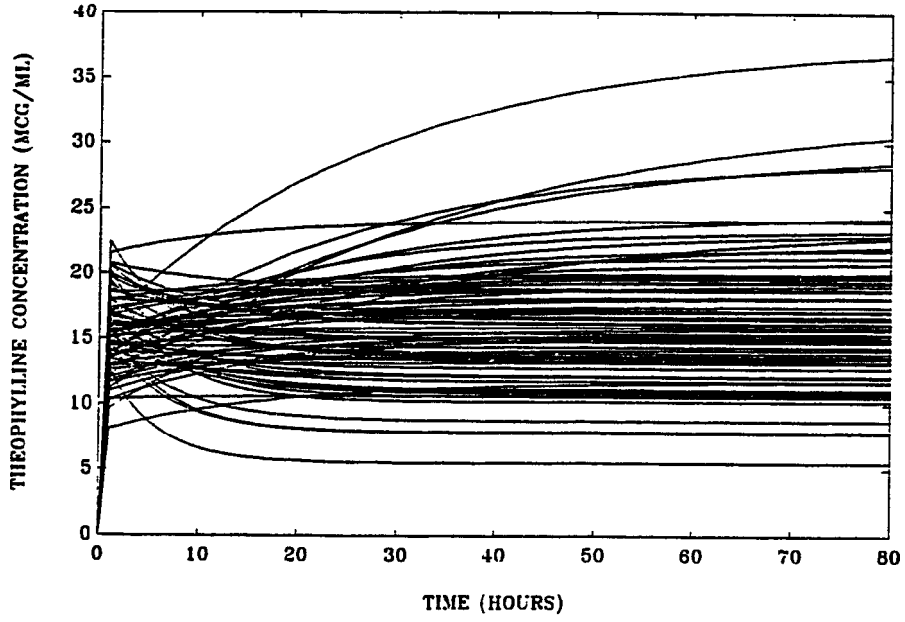

Fig. 3 Concentration vs. time in Monte Carlo simulations of 75 patients with normal parameters using open-loop control.

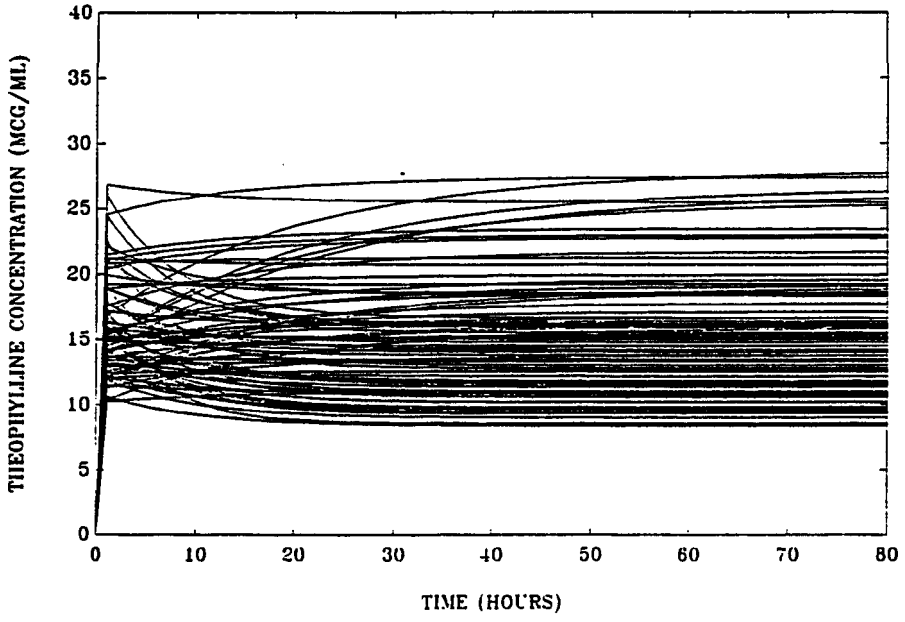

Fig. 4 Concentration vs. time in Monte Carlo simulations of another 75 patients with normal parameters using open-loop control.

2-, 12-, and 30-hour samples: The 2-hour sample provided good volume estimates, the 30-hour sample provided good clearance estimates, and the 12-hour sample reduced the response variation between the 2- and the 30-hour samples. The concentration versus time of 50 patients in Monte Carlo simulations is presented in Fig. 8. A mean concentration of 15.22 +/- 0.9 μg/ml was achieved in 500 patients (Fig. 12). Table II summarizes the statistics of the 80 hour concentrations. Fig. 13(b) compares the CV of the concentrations achieved by the sampling times of 10 and 24 hours and 2, 12, and 30 hours.

TABLE II

Statistics of the 80-hour concentrations achieved in Monte Carlo simulations using open-loop control and adaptive control employing the Kalman filter for parameter estimation with sampling at the stipulated times. (500 patients with normal parameters, 5% (CV) assay error, 1-hour delay).

Sampling Schemes (hours)	Serum concentration(μg/ml) Mean	SD	CV(%)
Open-loop control	15.88	4.56	28.73
2 and 20	15.38	1.30	8.48
6 and 20	15.50	1.40	9.02
10 and 24	15.45	1.27	8.21
2, 12 and 30	15.22	0.90	5.92

Simulation Results for the Stochastic Disturbances

Assay errors: Considering individually the assay errors of 5, 10, and 15% CV, Monte Carlo simulations were performed for 500 patients with normal parameters employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30

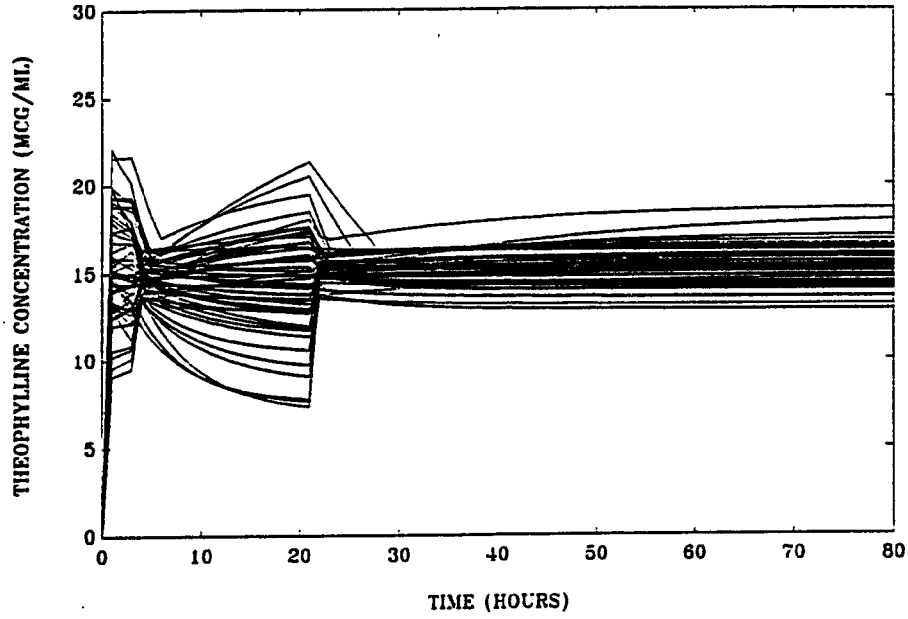

Fig. 5 Concentration vs. time in Monte Carlo simulations achieved by adaptive control employing the Kalman filter for parameter estimation with sampling at 2 and 20 hours. (50 patients with normal parameters, 5% (CV) assay error, 1-hour delay)

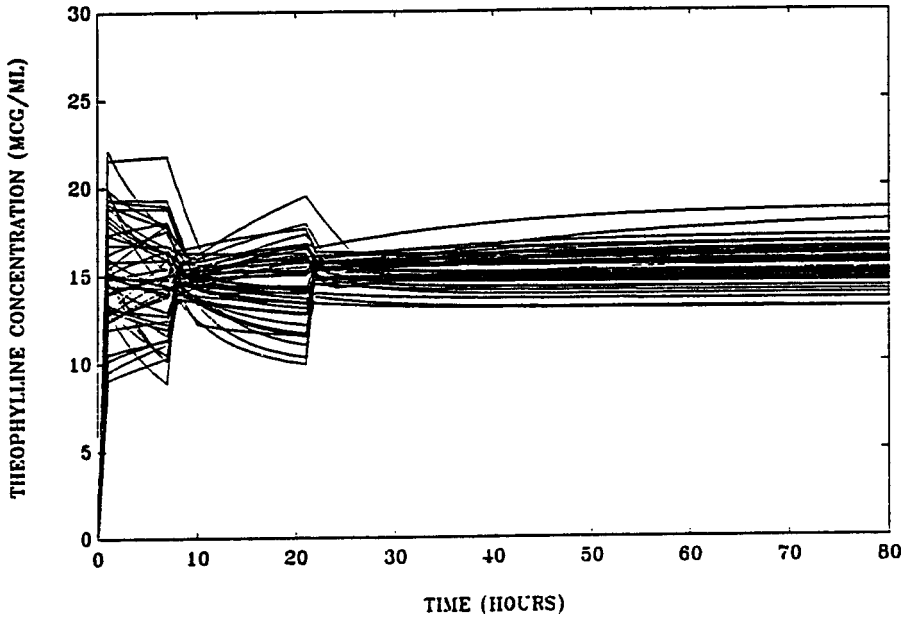

Fig. 6 Concentration vs. time in Monte Carlo simulations achieved by adaptive control employing the Kalman filter for parameter estimation with sampling at 6 and 20 hours. (50 patients with normal parameters, 5% (CV) assay error, 1-hour delay)

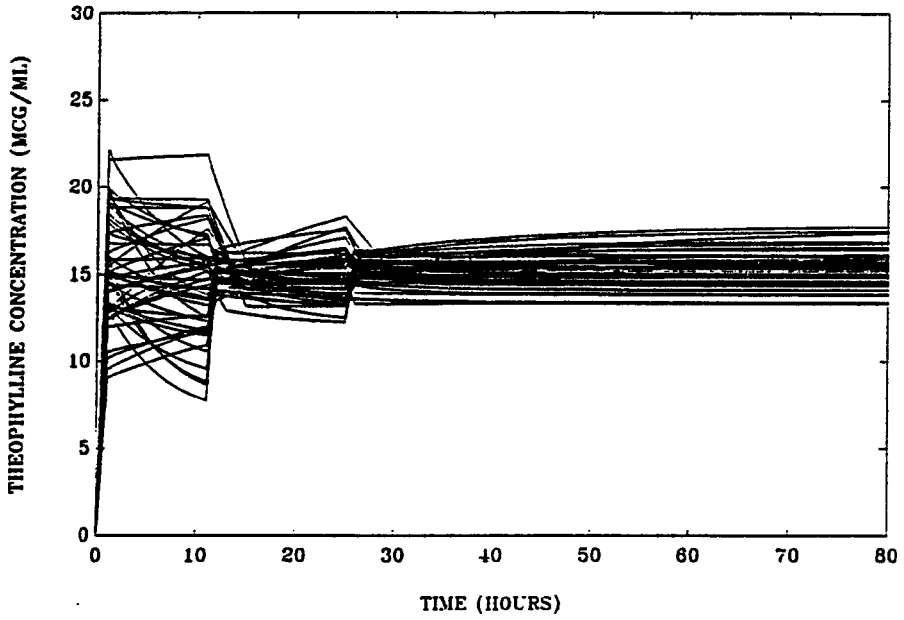

Fig. 7 Concentration vs. time in Monte Carlo simulations achieved by adaptive control employing the Kalman filter for parameter estimation with sampling at 10 and 24 hours. (50 patients with normal parameters, 5% (CV) assay error, 1-hour delay)

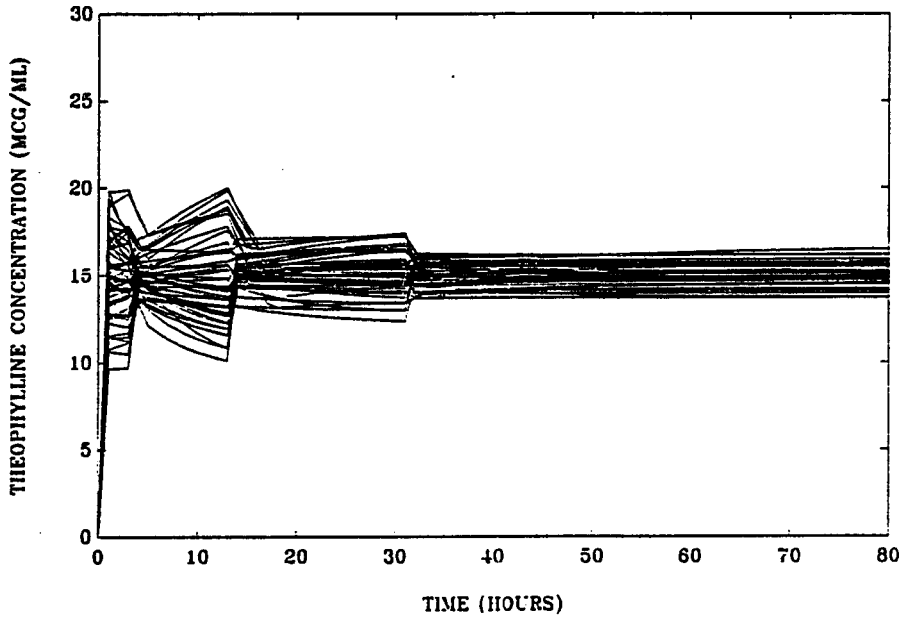

Fig. 8 Concentration vs. time in Monte Carlo simulations achieved by adaptive control employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours. (50 patients with normal parameters, 5% (CV) assay error, 1-hour delay)

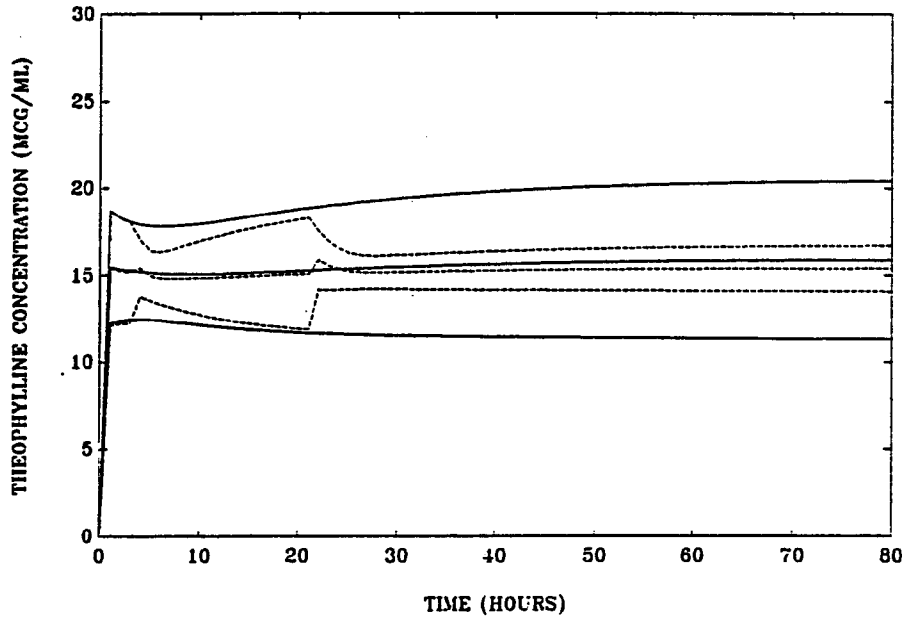

Fig. 9 Mean +/- SD of concentration vs. time in Monte Carlo simulations achieved by open-loop control (solid line) and adaptive control (dashed line) employing the Kalman filter for parameter estimation with sampling at 2 and 20 hours. (500 patients with normal parameters, 5% (CV) assay error, 1-hour delay)

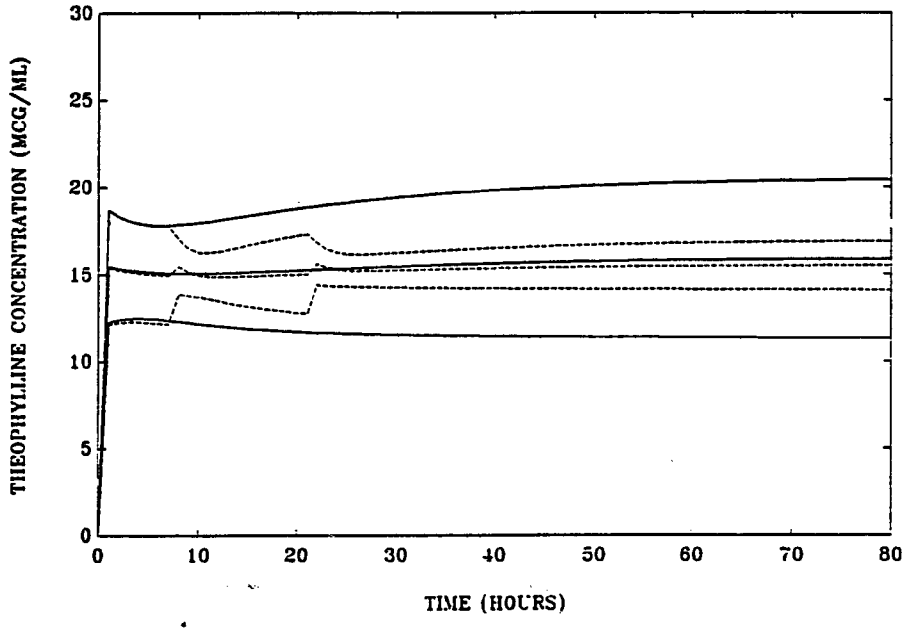

Fig. 10 Mean +/- SD of concentration vs. time in Monte Carlo simulations achieved by open-loop control (solid line) and adaptive control (dashed line) employing the Kalman filter for parameter estimation with sampling at 6 and 20 hours. (500 patients with normal parameters, 5% (CV) assay error, 1-hour delay)

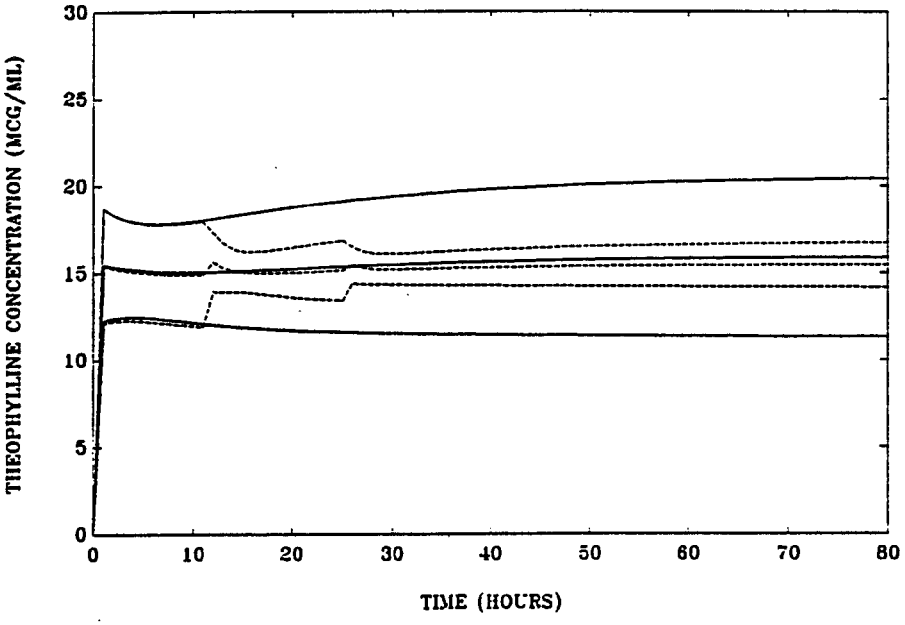

Fig. 11 Mean +/- SD of concentration vs. time in Monte Carlo simulations achieved by open-loop control (solid line) and adaptive control (dashed line) employing the Kalman filter for parameter estimation with sampling at 10 and 24 hours. (500 patients with normal parameters, 5% (CV) assay error, 1-hour delay)

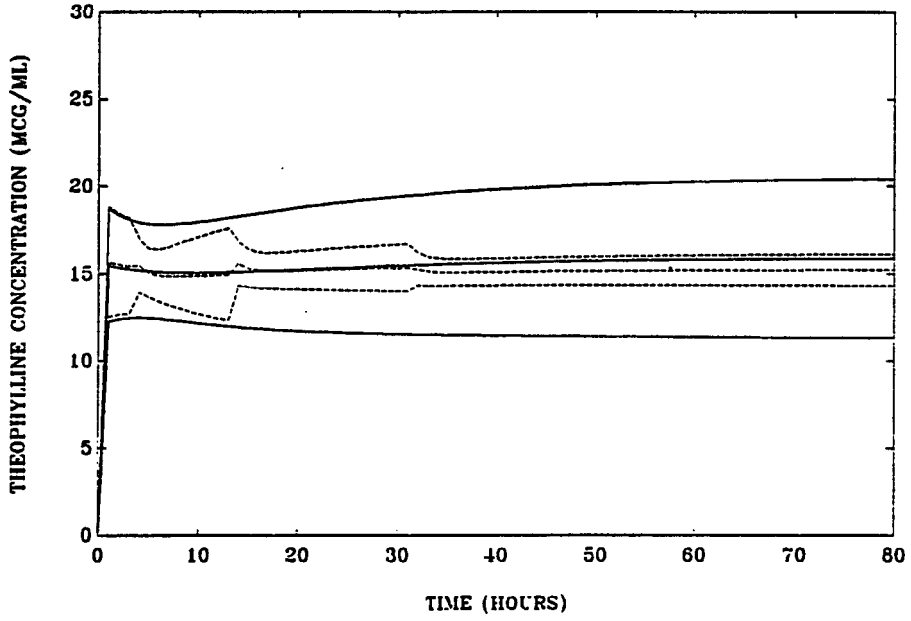

Fig. 12 Mean +/- SD of concentration vs. time in Monte Carlo simulations achieved by open-loop control (solid line) and adaptive control (dashed line) employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours. (500 patients with normal parameters, 5% (CV) assay error, 1-hour delay)

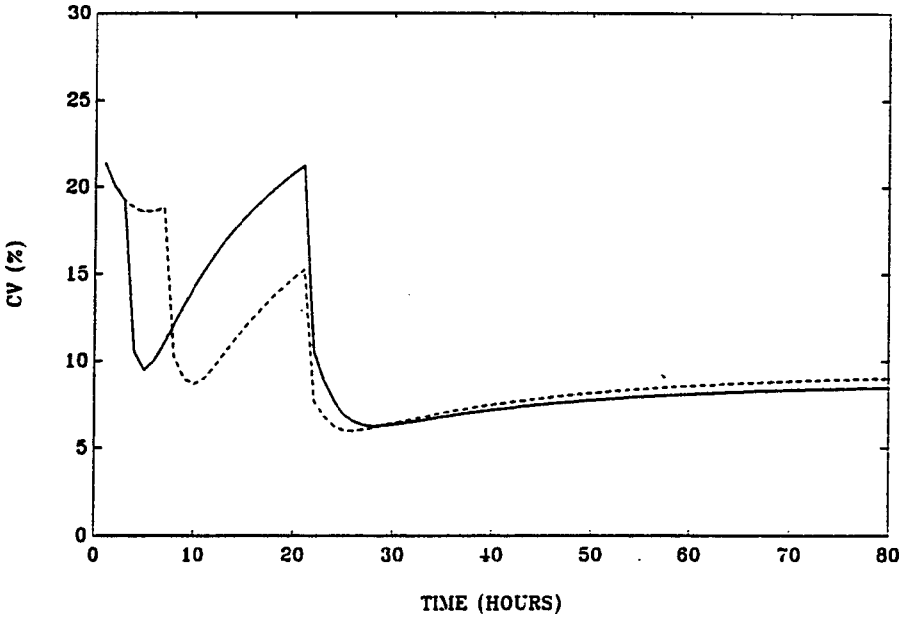

Fig. 13(a) CV (%) of concentration vs. time in Monte Carlo simulations achieved by adaptive control employing the Kalman filter for parameter estimation with sampling at 2 and 20 hours (solid line) and 6 and 20 hours (dashed line). (500 patients with normal parameters, 5% (CV) assay error, 1-hour delay)

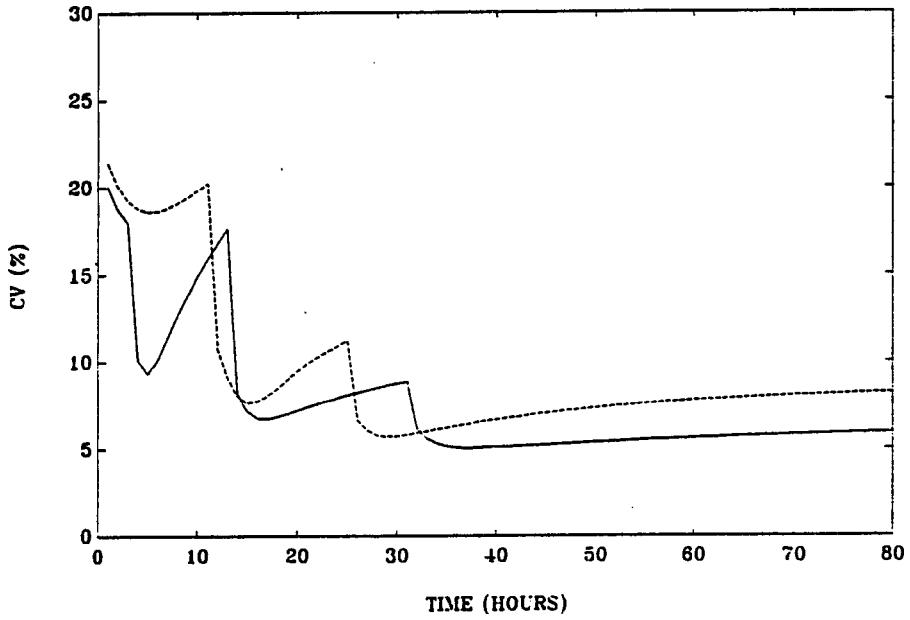

Fig. 13(b) CV (%) of concentration vs. time in Monte Carlo simulations achieved by adaptive control employing the Kalman filter for parameter estimation with sampling at 10 and 24 hours (dashed line) and 2, 12, and 30 hours (solid line). (500 patients with normal parameters, 5% (CV) assay error, 1-hour delay)

hours. A delay of 1 hour was also incorporated into the studies. The mean concentrations of 15.22 +/- 0.9 μg/ml (Fig. 14), 15.25 +/- 1.59 μg/ml (Fig. 15), and 15.25 +/- 2.22 μg/ml (Fig. 16) were achieved in patients for assay errors of 5, 10, and 15%, respectively. Fig. 17 compares the performance of the system for the three assay errors. Table III summarizes the statistics of the 80-hour concentrations.

TABLE III

Statistics of the 80-hour concentrations achieved in Monte Carlo simulations using adaptive control employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours for assay errors of 5, 10, and 15% CV. (500 patients with normal parameters, 1-hour delay)

Assay errors (%CV)	Serum concentration(μg/ml)		
	Mean	SD	CV(%)
5%	15.22	0.90	5.92
10%	15.25	1.59	10.40
15%	15.25	2.22	14.56

Delays: Delays of 30 minutes, 1 hour, and 4 hours were considered individually in Monte Carlo simulations of 500 patients with normal parameters employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours. A 5% CV assay error was incorporated into the studies. The mean concentrations of 15.07 +/- 0.77 μg/ml, 15.22 +/- 0.9 μg/ml, and 15.22 +/- 0.9 μg/ml were achieved in patients for delays of 30 minutes, 1 hour, and 4 hours, respectively. Fig. 18 compares the mean +/- SD of the concentrations achieved for the delays of 1 hour and 4 hours. Table IV summarizes the statistics of the 80-hour concentrations for the delays.

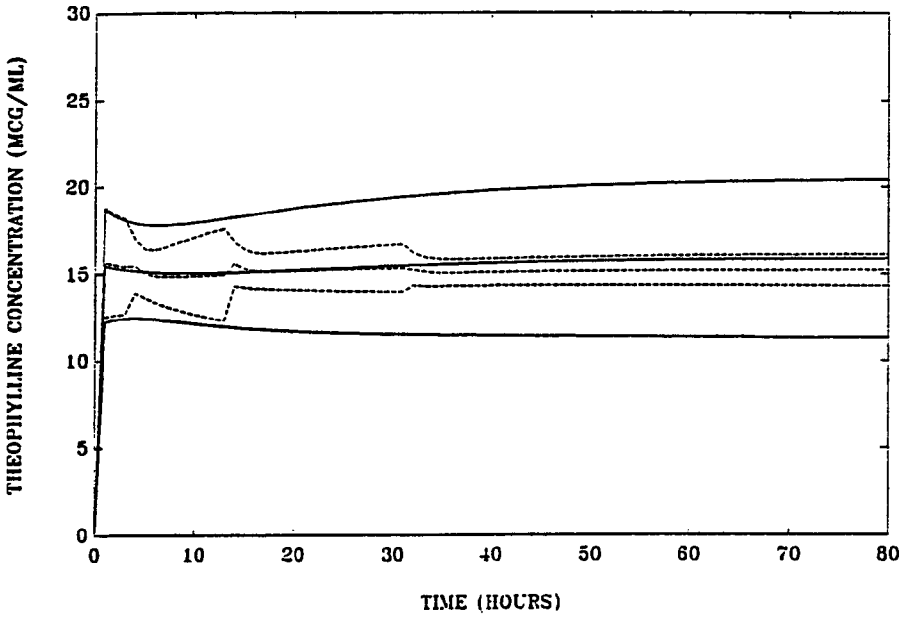

Fig. 14 Mean +/- SD of concentration vs. time data in Monte Carlo simulations achieved by open-loop control (solid line) and adaptive control (dashed line) employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours for 5% (CV) assay error. (500 patients with normal parameters, 1-hour delay)

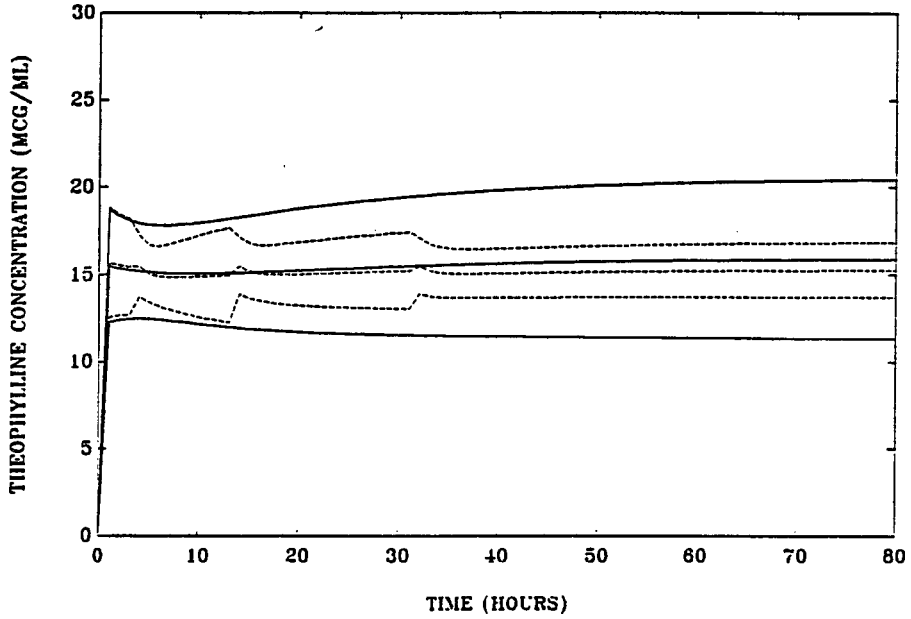

Fig. 15 Mean +/- SD of concentration vs time data in Monte Carlo simulations achieved by open-loop control (solid line) and adaptive control (dashed line) employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours for 10% (CV) assay error. (500 patients with normal parameters, 1-hour delay)

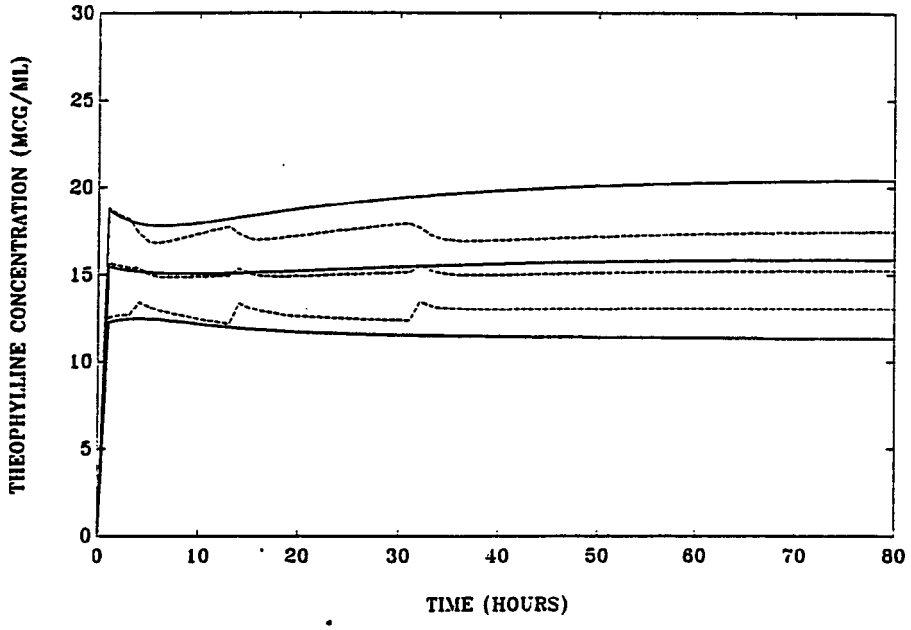

Fig. 16 Mean +/- SD of concentration vs. time data in Monte Carlo simulations achieved by open-loop control (solid line) and adaptive control (dashed line) employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours for 15% (CV) assay error. (500 patients with normal parameters, 1-hour delay)

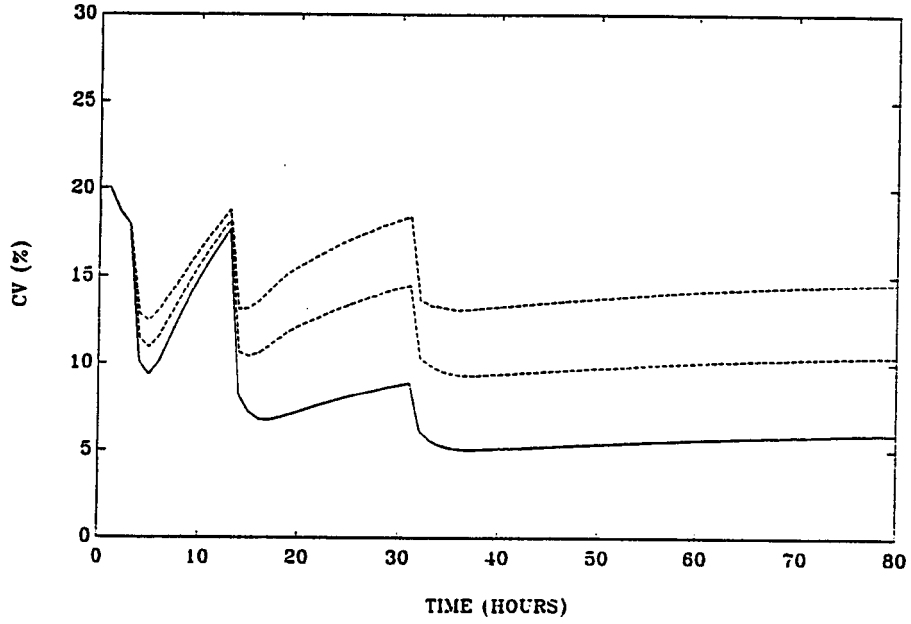

Fig. 17 CV (%) of concentration vs. time data in Monte Carlo simulations achieved by adaptive control employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours for assay errors of 5% (solid line), 10% (lower dashed line) and 15% (upper dashed line) CV. (500 patients with normal parameters, 1-hour delay)

TABLE IV

Statistics of the 80-hour concentrations achieved in Monte Carlo simulations using adaptive control employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours for delays of 30 minutes, 1 hour, and 4 hours. (500 patients with normal parameters, 5% (CV) assay error).

Assay delays	Serum concentration(μg/ml)		
	Mean	SD	CV(%)
30 minutes	15.07	0.77	5.14
1 hour	15.22	0.90	5.92
4 hours	15.23	0.90	5.92

Sampling errors: Sampling errors of +30 and -30 minutes and +1 and -1 hour were considered in Monte Carlo simulations of 500 patients with normal parameters employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours. A 5% CV assay error and a delay of 1 hour were also included in the simulation studies. Figs. 19(a) and (b) illustrate the CV of the concentrations achieved for sampling errors of +1 and -1 hour respectively. Table V lists

TABLE V

Statistics of the 80-hour concentrations achieved in Monte Carlo simulations using adaptive control employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours for sampling errors of 30 minutes and 1 hour. (500 patients with normal parameters, 5% (CV) assay error, 1-hour delay).

Sampling errors	Serum concentration(μg/ml)		
	Mean	SD	CV(%)
+30 minutes	15.07	0.76	5.13
-30 minutes	15.07	0.77	5.15
+1 hour	15.21	0.87	5.86
-1 hour	15.24	0.91	5.96

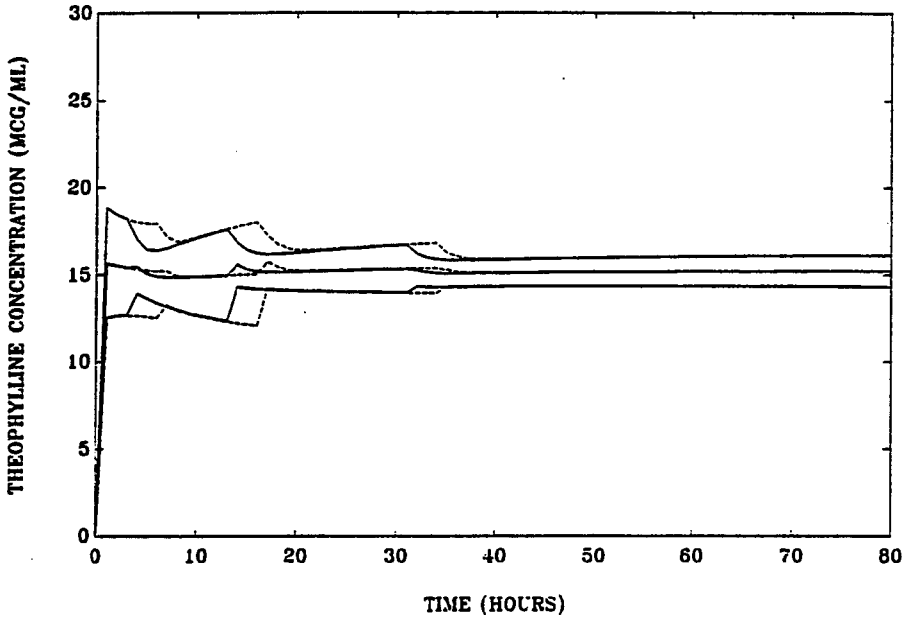

Fig. 18 Mean +/- SD of concentration vs. time in Monte Carlo simulations achieved by adaptive control employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours for delays of 1 hour (solid line) and 4 hours (dashed line). (500 patients with normal parameters, 5% (CV) assay error)

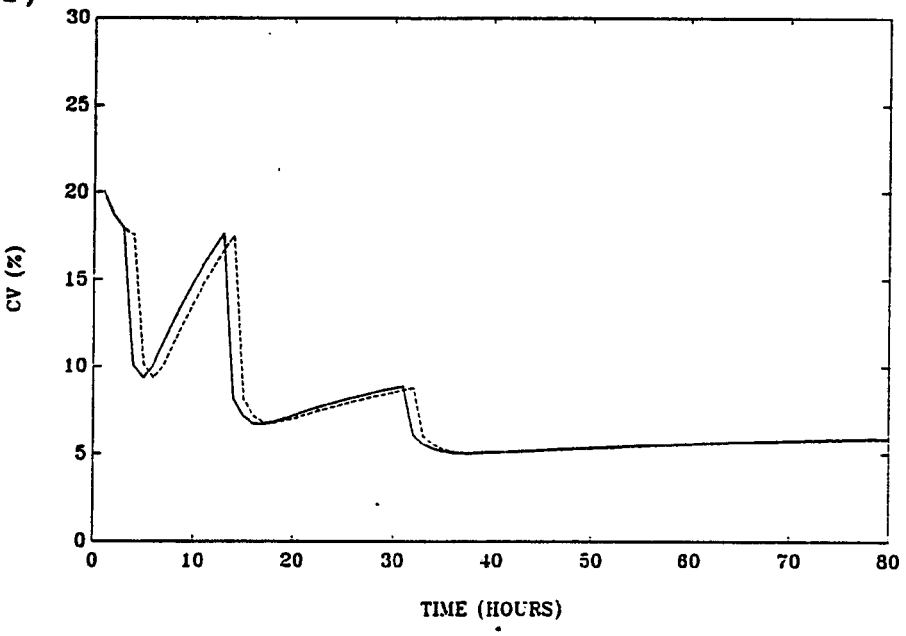

Fig. 19(a) CV (%) of concentration vs. time in Monte Carlo simulations achieved by adaptive control employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours in Monte Carlo simulations performed with (dashed line) and without (solid line) +1 hour sampling time error. (500 patients with normal parameters, 5% (CV) assay error, 1-hour delay)

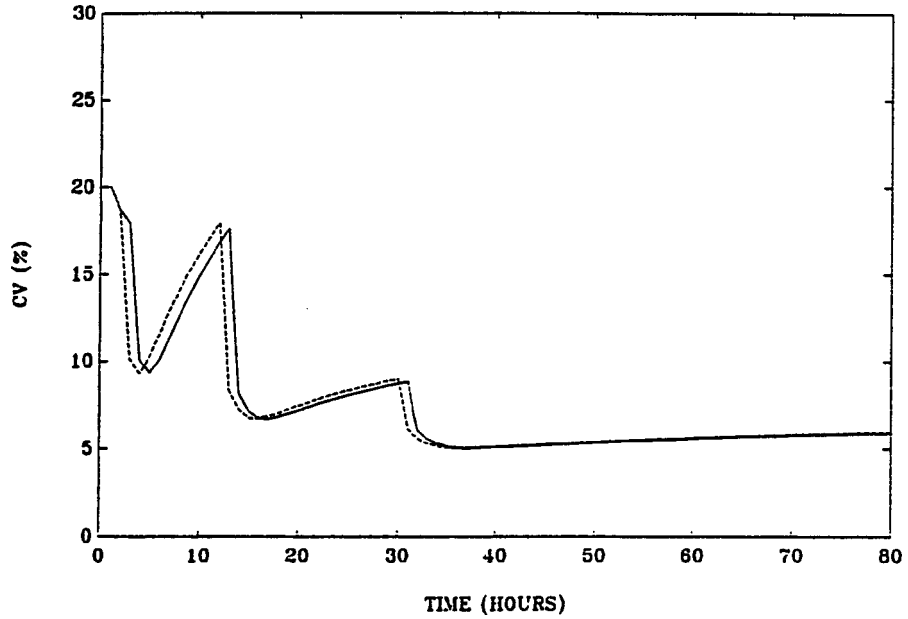

Fig. 19(b) CV (%) of concentration vs. time in Monte Carlo simulations achieved by adaptive control employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours in Monte Carlo simulations performed with (dashed line) and without (solid line) -1 hour sampling time error. (500 patients with normal parameters, 5% (CV) assay error, 1-hour delay)

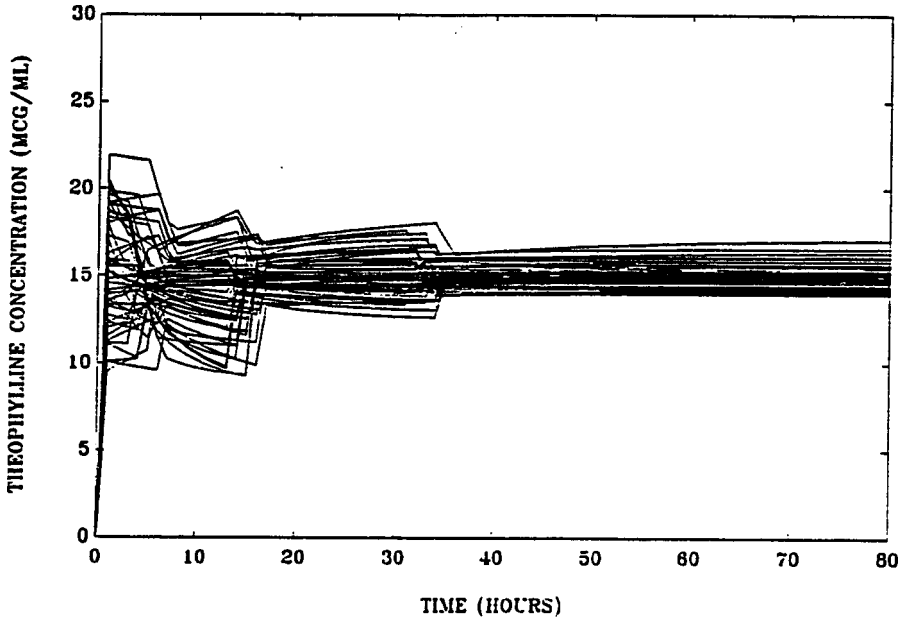

Fig. 20 Concentration vs. time in Monte Carlo simulations achieved by adaptive control employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours. (50 patients with normal parameters, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing error)

the mean, the standard deviation, and the coefficient of variation of the 80-hour concentrations.

Simulation Results for System Validation

A population of 1000 patients belonging to each group was simulated with sampling at 2, 12, and 30 hours while incorporating into the studies a 5% CV assay error, a 1% CV dosing error, and 1-4 hour delays. Initially, patients with normal parameters were simulated employing the Kalman filter for parameter estimation. The concentration versus time of 50 patients is presented in Fig. 20. The system achieved a mean concentration of 15.24 +/- 0.92 μg/ml (Fig. 24).

Subsequently, patients from each group were simulated employing minimization of the Bayesian objective function for parameter estimation. The concentrations versus time of 50 patients with normal parameters, smokers, and cirrhotics are presented in Figs. 21, 22, and 23, respectively. The mean concentrations of 15.05 +/- 0.79 μg/ml (Fig. 25), 15.02 +/- 0.63 μg/ml (Fig. 26), and 15.12 +/- 1.12 μg/ml (Fig. 27) were

TABLE VI

Statistics of the 80-hour concentrations achieved in Monte Carlo simulations using adaptive control employing both Kalman filter and the minimization of Bayesian objective function in separate studies with sampling at 2, 12, and 30 hours. (1000 patients with normal parameters, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing errors).

Parameter estimators	Serum concentration(μg/ml)		
	Mean	SD	CV(%)
KF	15.24	0.92	6.02
BOF	15.05	0.79	5.24

achieved in patients with normal parameters, smokers, and cirrhotics, respectively. Table VI and Fig. 28 present the statistics of concentration achieved by the Kalman filter and minimization of the Bayesian objective function. Table VII summarizes the statistics of the 80-hour concentrations achieved in the three subpopulations of patients.

TABLE VII

Statistics of the 80-hour concentrations achieved in Monte Carlo simulations using adaptive control employing the minimization of Bayesian objective function for parameter estimation with sampling at 2, 12, and 30 hours. (1000 patients, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing errors).

Sub-populations	Serum concentration(μg/ml)		
	Mean	SD	CV(%)
Patients with normal parameters	15.05	0.79	5.24
Smokers	15.02	0.63	4.16
cirrhotics	15.12	1.22	8.08

Results of Parameter Estimation

The histogram of the natural log of initial volume error is presented in Figs. 29(a). The histograms of the natural log of the volume estimation errors for the Kalman filter and minimization of the Bayesian objective function are presented in Figs. 29(b-d) and 30(b-d), respectively. The histogram of the natural log of initial clearance error is presented in Fig. 31(a). The histograms of the natural log of the clearance estimation errors for the Kalman filter and minimization of the Bayesian objective function are presented in Figs. 31(b-d) and 32(b-d), respectively.

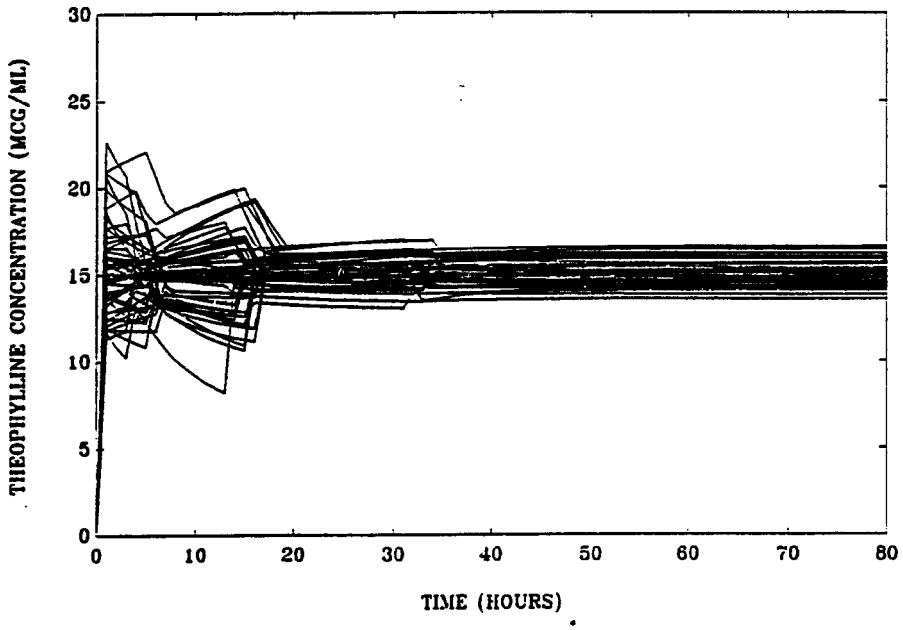

Fig. 21 Concentration vs. time in Monte Carlo simulations achieved by adaptive control employing minimization of the Bayesian objective function for parameter estimation with sampling at 2, 12, and 30 hours. (50 patients with normal parameters, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing error)

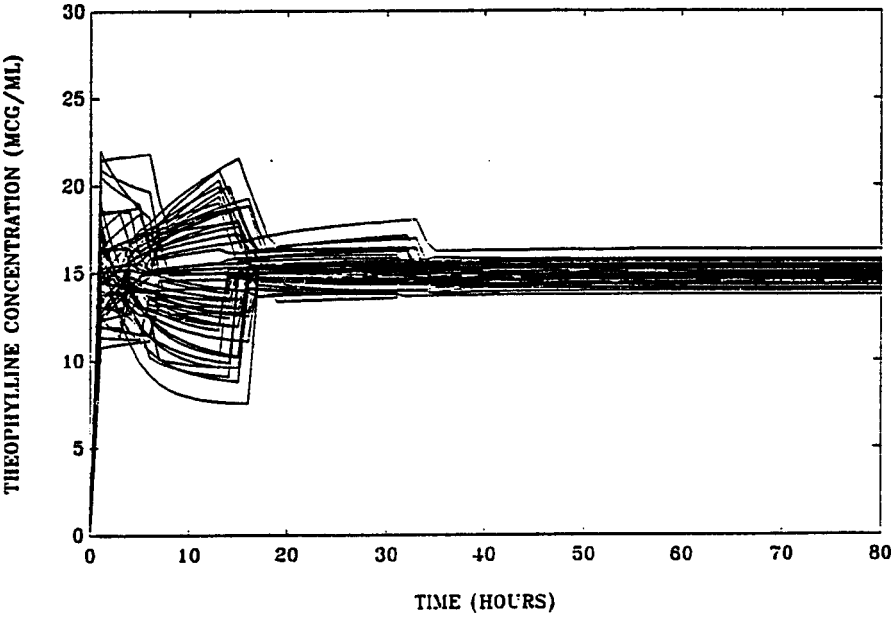

Fig. 22 Concentration vs. time in Monte Carlo simulations achieved by adaptive control employing minimization of the Bayesian objective function for parameter estimation with sampling at 2, 12, and 30 hours. (50 smokers, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing error)

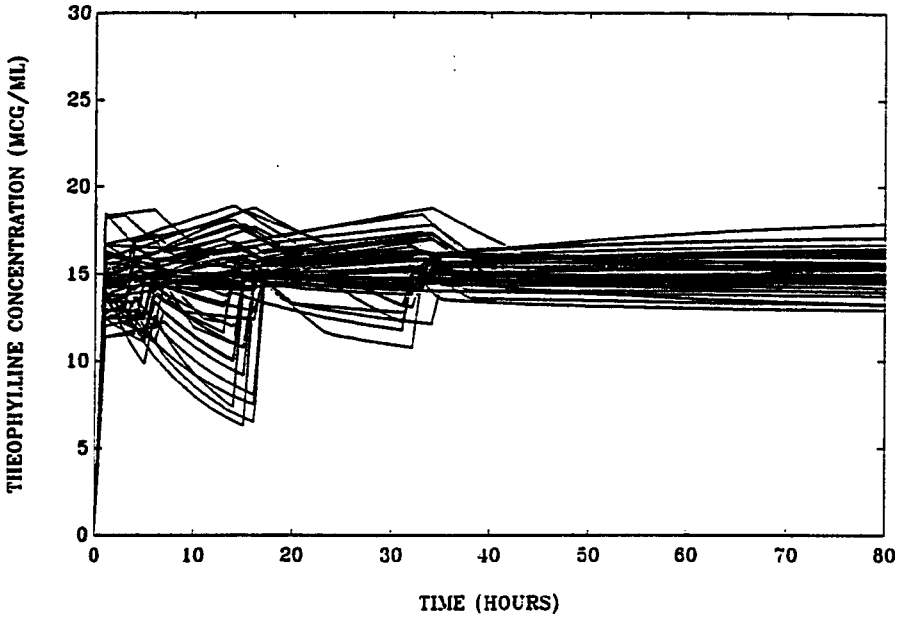

Fig. 23 Concentration vs. time in Monte Carlo simulations achieved by adaptive control employing minimization of the Bayesian objective function for parameter estimation with sampling at 2, 12, and 30 hours. (50 cirrhotics, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing error)

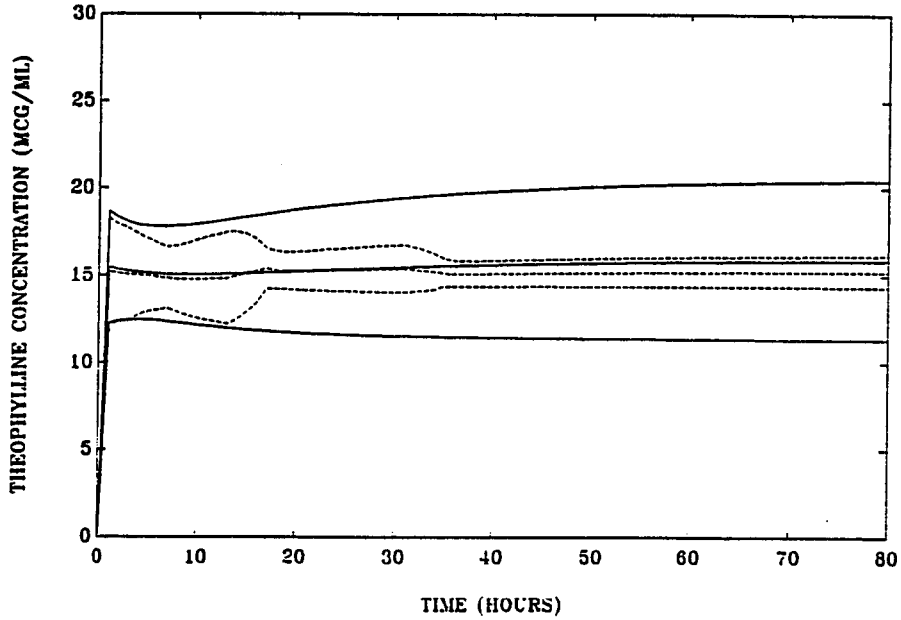

Fig. 24 Mean +/- SD of concentration vs. time in Monte Carlo simulations achieved by open-loop control (solid line) and adaptive control (dashed line) employing the Kalman filter for parameter estimation with sampling at 2, 12, and 30 hours. (1000 patients with normal parameters, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing error)

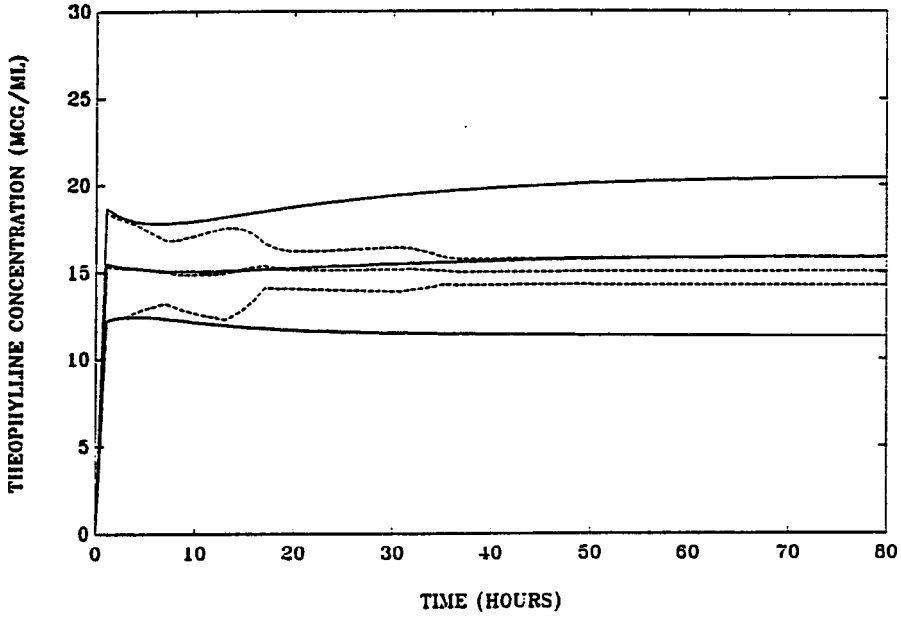

Fig. 25 Mean +/- SD of concentration vs. time in Monte Carlo simulations achieved by open-loop control (solid line) and adaptive control (dashed line) employing minimization of the Bayesian objective function for parameter estimation with sampling at 2, 12, and 30 hours. (1000 patients with normal parameters, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing error)

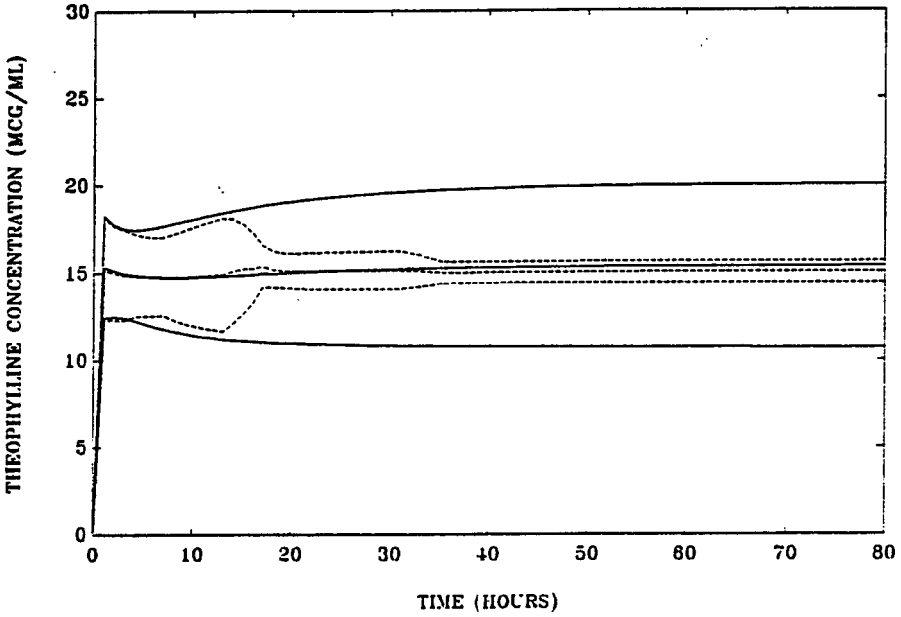

Fig. 26 Mean +/- SD of concentration vs. time in Monte Carlo simulations achieved by open-loop control (solid line) and adaptive control (dashed line) employing minimization of the Bayesian objective function for parameter estimation with sampling at 2, 12, and 30 hours. (1000 smokers, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing error)

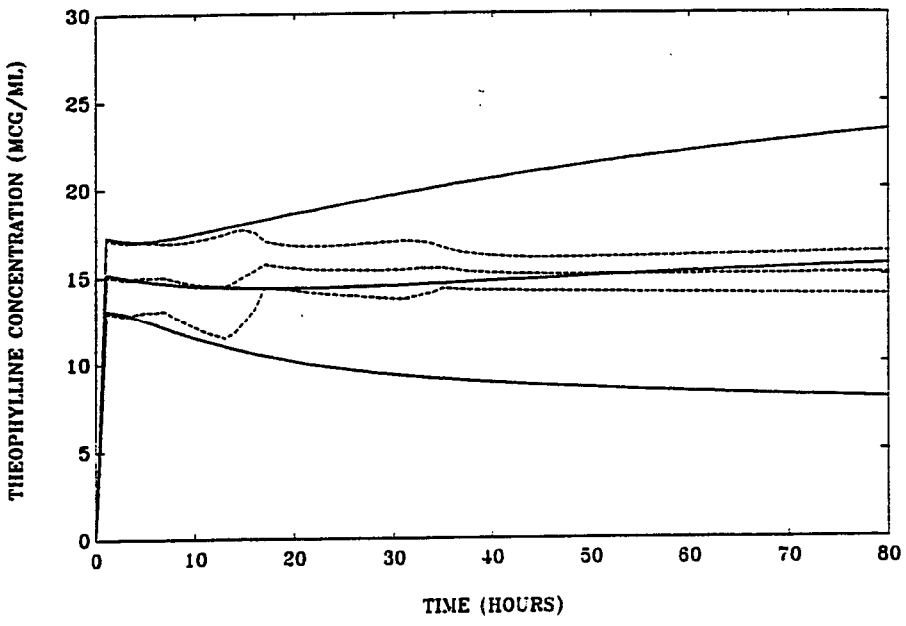

Fig. 27 Mean +/- SD of concentration vs. time in Monte Carlo simulations achieved by open-loop control (solid line) and adaptive control (dashed line) employing minimization of the Bayesian objective function for parameter estimation with sampling at 2, 12, and 30 hours. (1000 cirrhotics, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing error)

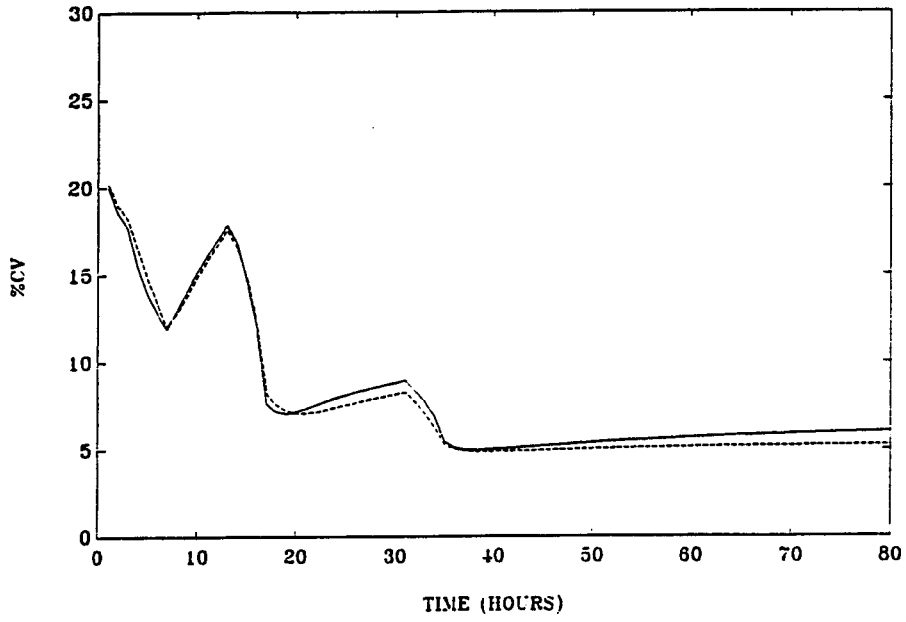

Fig. 28 CV (%) of concentration vs. time in Monte Carlo simulations achieved by adaptive control employing the Kalman filter (solid line) and minimization of the Bayesian objective function (dashed line) for parameter estimation with sampling at 2, 12, and 30 hours. (1000 patients with normal parameters, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing error)

Table VIII

The standard deviation of the initial volume errors (%) and the volume estimation errors (%) associated with 2-, 12-, and 30-hour samples for parameter estimation using the Kalman filter and minimization of the Bayesian objective function. (1000 patients with normal parameters, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing error)

sampling time	σ_v (KF)	σ_v (BOF)
Initial	20.79	20.53
2 hours	7.54	6.89
12 hours	6.81	5.84
30 hours	6.69	5.50

Tables VIII and IX list the standard deviations of the estimation errors of volume and clearance, respectively, for both the Kalman filter and minimization of the Bayesian objective function.

Table IX

The standard deviation of the initial clearance errors (%) and the clearance estimation errors (%) associated with 2-, 12, and 30-hour samples for parameter estimation using the Kalman filter and minimization of the Bayesian objective function. (1000 patients with normal parameters, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing error)

sampling time	σ_{cl} (KF)	σ_{cl} (BOF)
Initial	29.34	29.85
2 hours	28.93	29.03
12 hours	10.75	9.59
30 hours	6.01	5.06

The histogram of the measurement errors (CV 4.95%) is presented in Fig. 33.

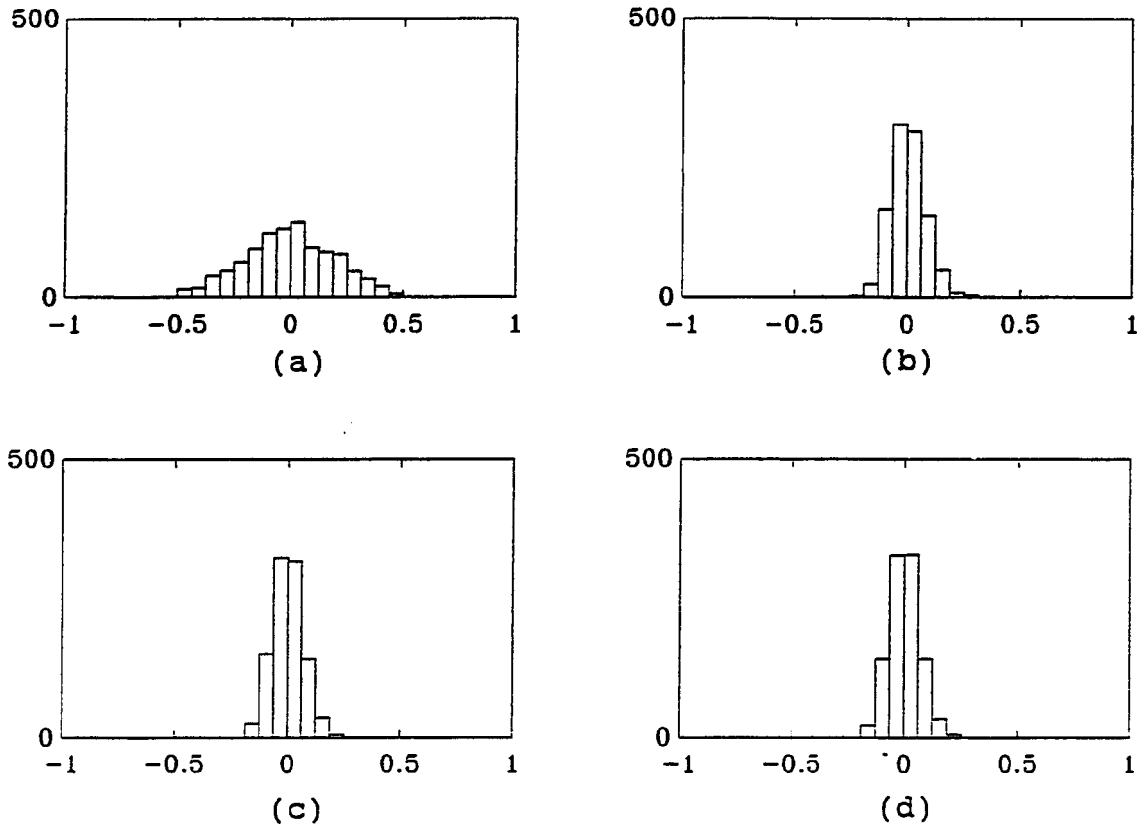

Fig. 29(a) Histogram of the initial volume errors (%) for 1000 patients with normal parameters.

(b-d) Histogram of the volume estimation errors (%) associated with 2-, 12-, and 30-hour samples for parameter estimation using the Kalman filter. (1000 patients with normal parameters, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing error)

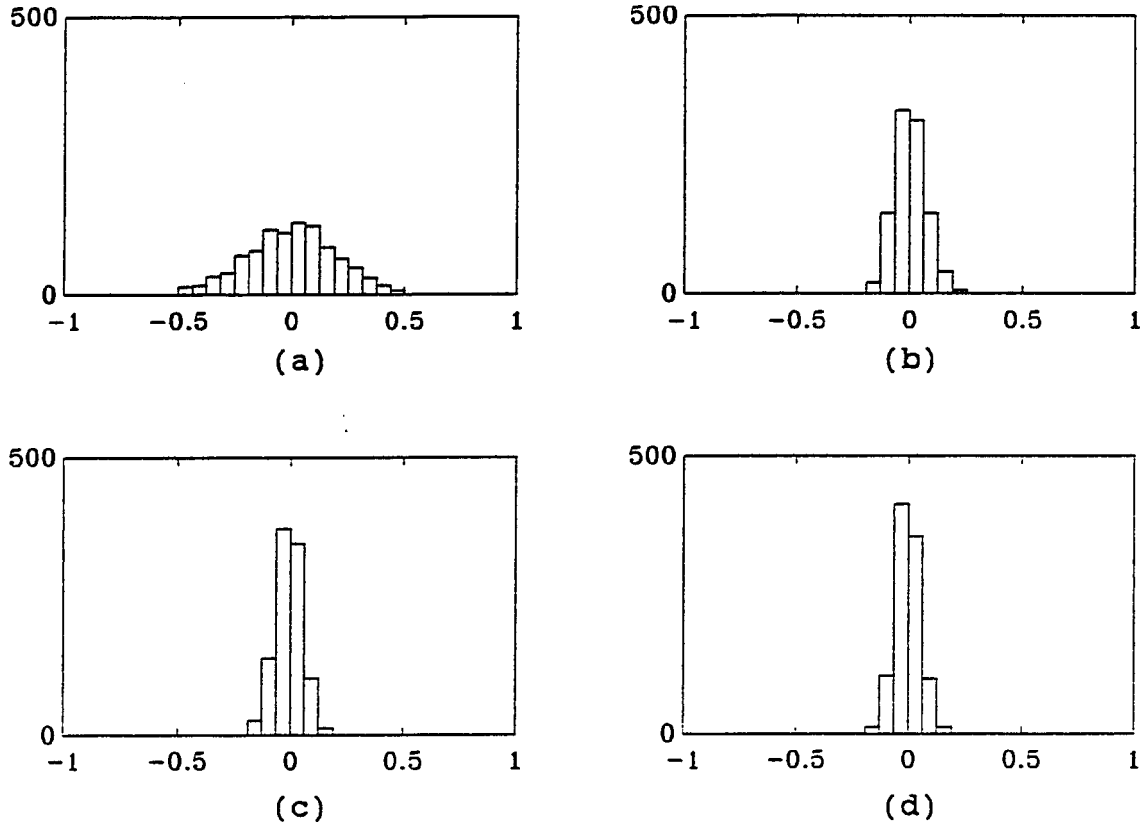

Fig. 30(a) Histogram of the initial volume errors (%) for 1000 patients with normal parameters.

(b-d) Histogram of the volume estimation errors (%) associated with 2-, 12-, and 30-hour samples for parameter estimation using minimization of the Bayesian objective function. (1000 patients with normal parameters, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing error)

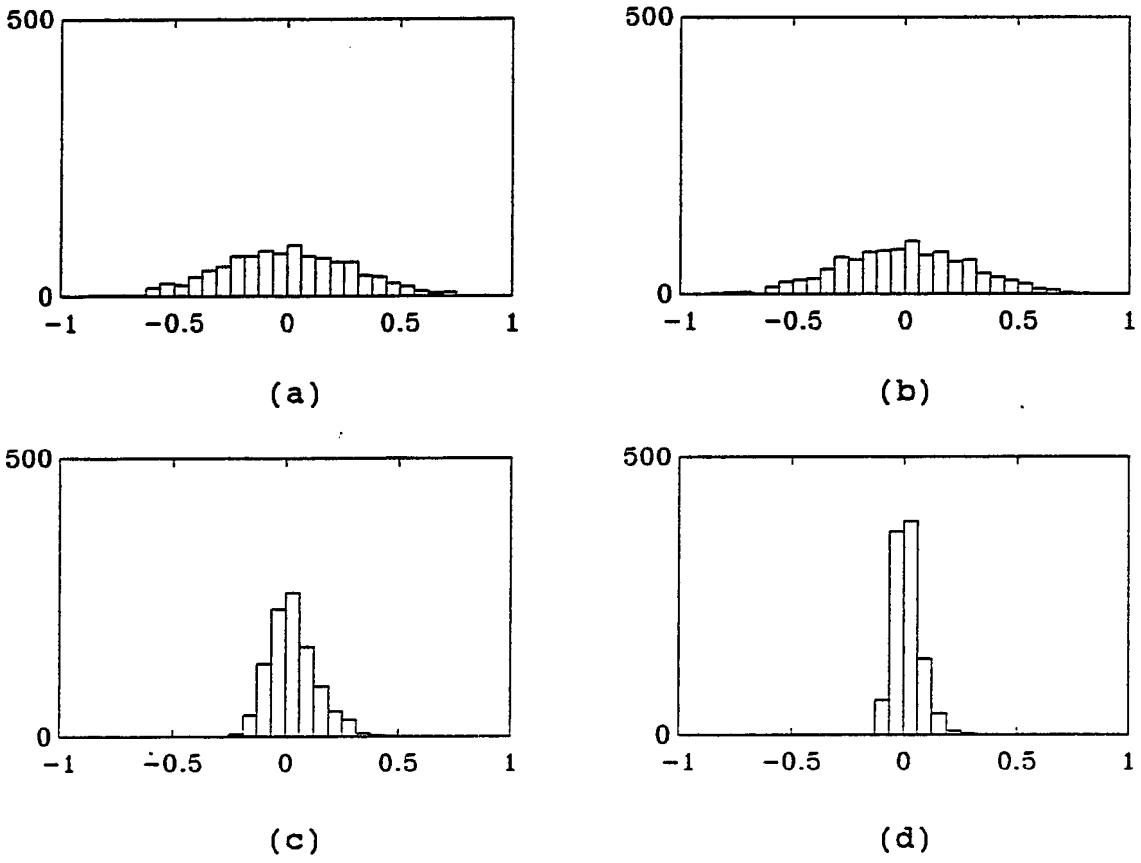

Fig. 31(a) Histogram of the initial clearance errors (%) for 1000 patients with normal parameters.

(b-d) Histogram of the clearance estimation errors (%) associated with 2-, 12-, and 30-hour samples for parameter estimation using the Kalman filter. (1000 patients with normal parameters, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing error)

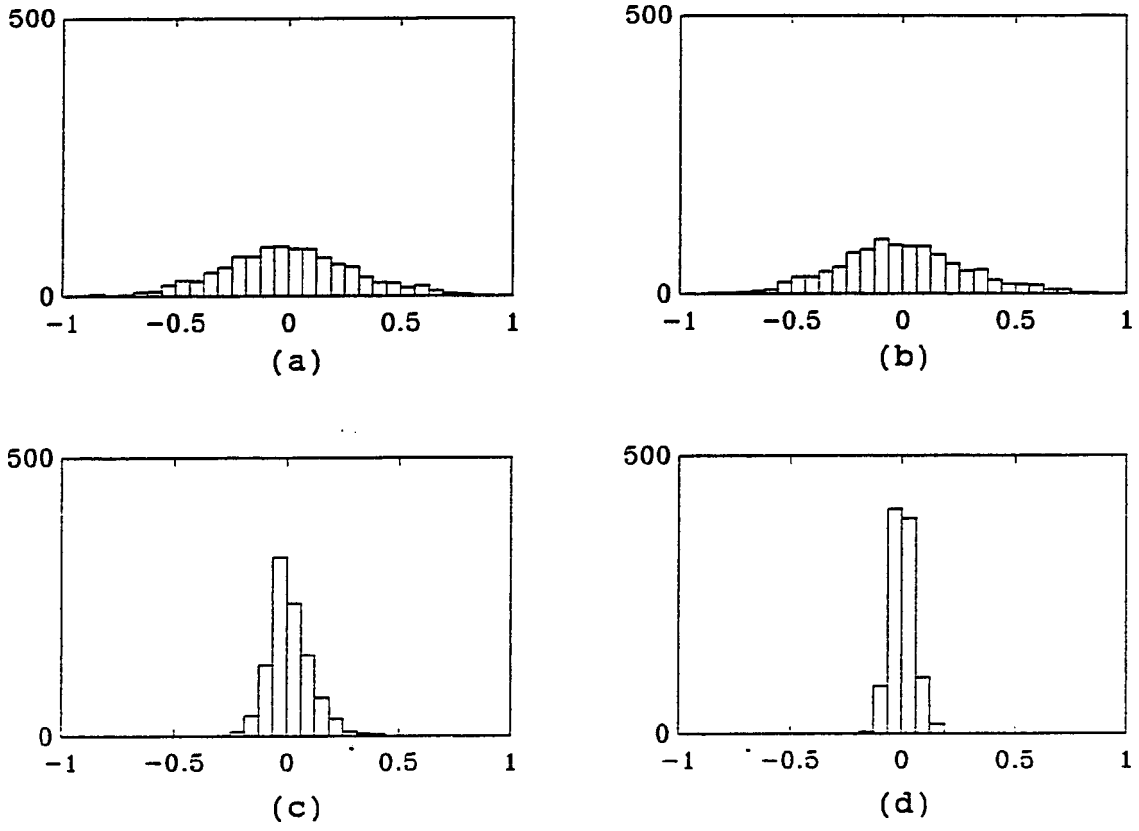

Fig. 32(a) Histogram of the initial clearance errors (%) for 1000 patients with normal parameters.

(b-d) Histogram of the clearance estimation errors (%) associated with 2-, 12-, and 30-hour samples for parameter estimation using minimization of the Bayesian objective function. (1000 patients with normal parameters, 5% (CV) assay error, 1-4 hour delays, 1% (CV) dosing error)

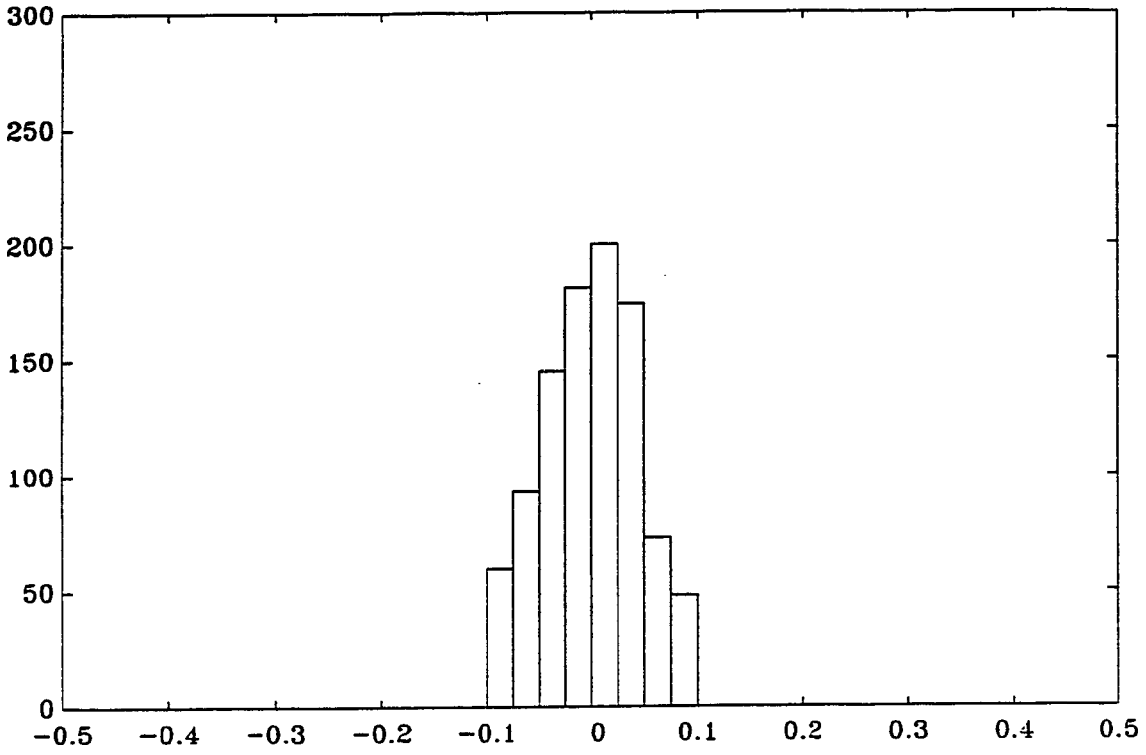

Fig. 33 Histogram of the measurement errors (CV 4.95%) incorporated in the Monte Carlo simulations.

CHAPTER VI

DISCUSSION

The results obtained from the Monte Carlo simulation studies of the adaptive control of theophylline therapy were encouraging. The system performed as expected under the influence of the sampling schemes and the stochastic disturbances.

System Performance for the Sampling Schemes

Because the serum concentration of a drug is governed primarily by the volume during the initial stages and by the clearance during the later stages of therapy, the early samples were expected to provide good volume estimates and the late samples to provide good clearance estimates.

2- and 20-hour samples: As expected, the 2 hour sample provided good volume estimates and poor clearance estimates. The 2-hour sample helped to reduce the response variation early during therapy. The influence of the volume is limited to early phases of therapy, therefore, the responses of the patients are seen to diverge (Fig. 5). The 20-hour sample provided better clearance estimates and reduced the response variation at 80 hours. Considerable interpatient response variation persisted between 2 and 20 hours.

6- and 20-hour samples: The 6- and 20-hour scheme was designed to reduce the response variations between the samples. The scheme was expected to provide better clearance estimates at 20 hours by gaining information at 6 hours. The 6-hour sample did not provide accurate estimates of either parameter. However, it reduced the response variation early during therapy (compare Figs. 9 and 10). The 20-hour sample did not provide very accurate clearance estimates and, therefore, the performance of the system (at 80 hours) did not differ significantly between the sampling schemes of 2 and 20 hours and 6 and 20 hours (Fig. 13(a)).

10- and 24-hour samples: The 10-hour sample provided poor volume estimates and improved clearance estimates compared to the estimates obtained from the 6-hour sample. The 24-hour sample fairly accurately estimated the clearance (Fig. 7). As expected, the performance of the system at 80 hours was significantly improved. However, the main drawback of the scheme was that it did not attempt individualization until 10 hours after the initiation of therapy and, therefore, resulted in large response variations early during therapy (Fig. 11).

2-, 12-, and 30-hour samples: Because the schemes employing 2 samples failed to reduced the response variation either during the initial stages or the later stages of therapy, the scheme with 3 samples was devised. As expected, the 2-hour sample provided good volume estimates and reduced the response variation early during therapy. The 30-hour sample estimated clearance fairly accurately and improved the

performance of the system significantly at 80 hours (Fig. 13(b)). The 12-hour sample reduced the response variation between the 2- and the 30-hour samples (Fig. 8).

System Performance Under Stochastic Disturbances

Assay errors: As expected, the assay errors were significantly detrimental to the performance of the system. The assay errors directly affected the accuracy of the parameter estimation. Accordingly, the parameter estimates obtained from the studies incorporating the 5% assay error were more accurate than those obtained from studies incorporating the 10 and 15% assay errors (compare Figs. 14, 15 and 16). The statistics of the 80-hour concentrations were higher for the assay errors of 10 and 15% when compared to those achieved for the 5% assay error (Fig. 17 and Table III).

Delays: As expected, the delays did not affect parameter estimation; therefore, the performance of the system at 80 hours did not differ for the 30-minute, the 1 hour, and the 4-hour delays (Table IV). However, with longer delays, the interpatient response variations persisted for longer durations during the post-sampling periods (Fig. 18).

Sampling errors: Theophylline has a long half-life, therefore, the serum concentration of the drug (for a given dose) does not change rapidly over a short period of time. Therefore, the prediction errors introduced by the sampling errors were negligible. Hence, the sampling errors did not significantly affect the performance of the system (Fig. 19(a and b) and Table V).

System Validation

The simulation results obtained for the Kalman filter were satisfactory. The system achieved a mean concentration of 15.24 +/- 0.92 μg/ml (Fig. 24), with a CV of 6.02% in the steady state. The interpatient response variation was reduced throughout the therapy (Fig. 20). The Kalman filter is a recursive filter; therefore, the parameter estimates were not quite as accurate as those obtained by minimization of the Bayesian objective function and, thus, the performance of the system employing the Kalman filter was not as good as that achieved by the system employing the minimization of the Bayesian objective function (Fig. 28 and Table VII).

The simulation results obtained for the minimization of the Bayesian objective function were very satisfactory. The interpatient response variation was reduced throughout the therapy (Fig. 21). The system achieved the mean concentrations of 15.05 +/- 0.79 μg/ml (Fig. 25), 15.02 +/- 0.63 μg/ml (Fig. 26), and 15.12 +/- 1.12 μg/ml (Fig. 27) in patients with normal parameters, smokers, and cirrhotics, respectively. The smokers, because of their high clearance, attained the steady-state concentrations faster. Maximum clearance information provided by this group led to an accurate clearance estimation and a precise dosage individualization (Fig. 22). The cirrhotics, because of their low clearance, required longer period of time to reach steady state. Insufficient clearance information provided by this group of patients resulted in a poor clearance estimation and an inadequate dosage individualization. The performance of

the system might be improved for the cirrhotics either by postponing the 10- and the 30-hour samples or availing an additional sample at 45 hours.

Comments on Parameter Estimation

To compare the accuracy of the parameter estimates obtained by the Kalman filter versus those obtained by the minimization technique, the parameter estimates of 1000 patients with normal parameters were used to compute the parameter estimation errors. The minimization of the Bayesian objection function is an iterative process and takes into account the previous measurements and estimates while estimating parameters. The Kalman filter, on the other hand, is a recursive filter, and it takes into account only the last measurement and the last parameter estimates while estimating the parameters. Hence, the parameter estimates obtained from minimization of the Bayesian objective function were more accurate than those obtained from the Kalman filter.

The volume was accurately estimated by both the estimators from the 2-hour sample (Figs. 29 and 30, and Table VIII). The accuracy of the volume estimates obtained by both the Kalman filter and minimization of the Bayesian function improved slightly with successive sampling.

The clearance was estimated poorly by both the estimators from the 2-hour sample. The accuracy of clearance estimation improved for both the estimators with successive sampling; although in the case of Kalman filter, this was more due an ad hoc modification made in the covariance matrix of the estimator. As expected, the clearance estimates obtained from

the minimization technique were more accurate than those obtained from the Kalman filter (Figs. 31 and 32 and Table IX).

CHAPTER VII

CONCLUSION

In this research project, the performance of the adaptive control system was assessed in computer simulation studies. Various sampling schemes were designed and tested, the influence of the stochastic disturbances was evaluated, and the system was validated for the three groups of patients simulated. The accuracy of the parameter estimates obtained from the two estimators was compared.

The schemes employing 2 samples failed to reduce the interpatient response variations either earlier or later during therapy. The 2-, 12-, and 30-hour scheme most effectively individualized theophylline requirements and reduced the interpatient response variation throughout therapy. Of the stochastic disturbances considered, the assay errors profoundly affected the performance of the system by directly affecting the accuracy of parameter estimation. The effect of the delays, the sampling errors, and the dosing errors seemed negligible at 80 hours.

The system was validated for the three subpopulations of patients. The performance of the system for the cirrhotics may be improved by redesigning the 2-, 12-, and 30-hour sampling scheme or by availing another sample later during therapy.

The parameter estimates obtained by the minimization of Bayesian objective function were slightly more accurate than those obtained from the Kalman filter.

Further Studies

In this research project, a mathematical model, a model based control law, and a feedback control algorithm were formulated for the bronchodilator theophylline. The adaptive control system was validated in computer simulation studies. As a final stage in the development of the system, future studies could be directed towards testing the system's efficacy in clinical trials.

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GRADUATE SCHOOL
UNIVERSITY OF ALABAMA AT BIRMINGHAM
THESIS APPROVAL FORM

Name of Candidate Srinidhi Aragula

Major Subject Biomedical Engineering

Title of Thesis "A Computer Simulation Study of Adaptive Control of Theophylline Therapy"

Thesis Committee:

Martin J. McCutcheon, Chairman — Martin J McCutcheon

Thomas C. Jannett, III, Co-Chair — Thomas C. Jannett

Linda C. Lucas — Linda C. Lucas

Dale S. Feldman — Dale Feldman

Director of Graduate Program — Martin J McCutcheon

Dean, UAB Graduate School — Richard Bond

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