FUZZY LOGIC MODELING AND INTELLIGENT SLIDING MODE CONTROL TECHNIQUES FOR THE INDIVIDUALIZATION OF THEOPHYLLINE THERAPY TO PEDIATRIC PATIENTS

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FUZZY LOGIC MODELING AND INTELLIGENT SLIDING MODE CONTROL TECHNIQUES FOR THE INDIVIDUALIZATION OF THEOPHYLLINE THERAPY TO PEDIATRIC PATIENTS

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DEDICATION

To My Parents...

TABLE OF CONTENTS

LIST OF FIGURES

CHAPTER I

INTRODUCTION

The clinical effectiveness of many drugs depends upon the accurate control of drug concentration levels in the blood plasma. Unfortunately, several factors make it difficult to target and maintain optimal drug concentration levels. These factors include variability in physiological parameters, drug interactions, and measurement and sample errors. The presence and nature of these variables complicates the application of rational drug therapy.

In this thesis special emphasis is placed on two important aspects of drug administration. These areas are the instruction of pharmacological principles in drug kinetics and the application of modern control techniques to drug dosing.

Purpose of Research

The purpose and final product of this thesis is the creation of a software teaching tool that can be used to illustrate and experiment with issues in the administration of drugs. The software and text of the thesis is specifically oriented to providing information about the kinetics and variability that occur in the administration of the drug theophylline. The development of a simulation tool for experimentation with issues in administration of theophylline is important because theophylline has a limited therapeutic range that requires the accurate maintenance of drug plasma concentrations (between ap-

proximately 10 to 20 μg/ml). Drug levels that are above 20 μg/ml frequently result in toxic side effects and drug levels that are below 10 μg/ml have reduced therapeutic effectiveness.

To accomplish the goals of this thesis, various types of information and modeling techniques have been combined. These techniques include control methods, fuzzy logic, and pharmacological concepts and principles.

Required Information, Techniques, and Methods

Pharmacokinetics

Successful drug therapy requires the consideration of many factors. These factors include the selection of an appropriate form and the design of an optimal schedule for administering the drug. The selection of these factors requires an understanding of the kinetics of drug absorption, distribution, and elimination. Pharmacokinetics is the study of these factors and their relationships.

Fuzzy Logic Modeling Techniques

Fuzzy logic is used to incorporate aspects of human knowledge into the program's software algorithms. Fuzzy logic is based on the mathematical concept of the fuzzy set and was proposed by Lofti A. Zadeh in 1965 [1]. Fuzzy logic provides a convenient way to express the relationships of objects, and facilitates the representation of complex input output relationships. It can be used to model the behavior of complex systems and to incorporate human expertise.

Control Methods

The incorporation of information about the patient with expert rules requires a robust control algorithm. Two types of control algorithms are demonstrated in this thesis. They are Fuzzy Associative Memory Rule Controller (FAM) and Discrete Sliding Mode Control. The FAM based controller is based on rules from medical documentation and practitioner interviews, and the implementation of discrete sliding mode control builds upon the work of Godwin [2].

Thesis Topics and Scope

The first section of the thesis, consisting of chapters 2 and 3, is devoted to the explanation of pharmacological principles and to the development of a mathematical model for theophylline kinetics. Chapter 2 presents important principles of drug pharmacokinetics and chapter 3 develops the model that is used in the software to represent theophylline kinetics.

The second section of the thesis explains how fuzzy sets can be used to model practitioner experience and presents information on the software tool that was developed to accompany this thesis. Chapter 4 provides a review of fuzzy logic modeling and develops a framework for combining patient information and expert rules with modern control techniques. In chapter 5, Information about the software program and features is provided and information about the simulation examples for dose dumping, drug interactions, and capsule release rates is provided. Simulation results for the drug administration controllers that are implemented in the software are shown in chapter 6 and recommendations are made for the future development of these techniques in chapter 7.

CHAPTER II

PHARMACOKINETIC PRINCIPLES

Before developing and presenting the pharmacokinetic model used in this thesis, a review of some of the underlying factors that determine and govern drug pharmacokinetics is needed. To help in this endeavor, the following chapter focuses on presenting the principles and concepts that are necessary for understanding the distribution and movement of drugs in the human body. Figure 2.1 shows the interrelationship that exists between the three most important stages of drug kinetics - the absorption, distribution, and elimination steps.

The absorption step is the process by which a drug enters the blood plasma of the body. Distribution is the transport of drug molecules from the blood region of the body into the surrounding tissues and organs, and elimination is the removal of drug from the body. An important process that affects each of the three steps is the process of transporting drug molecules across tissues and membranes in the body.

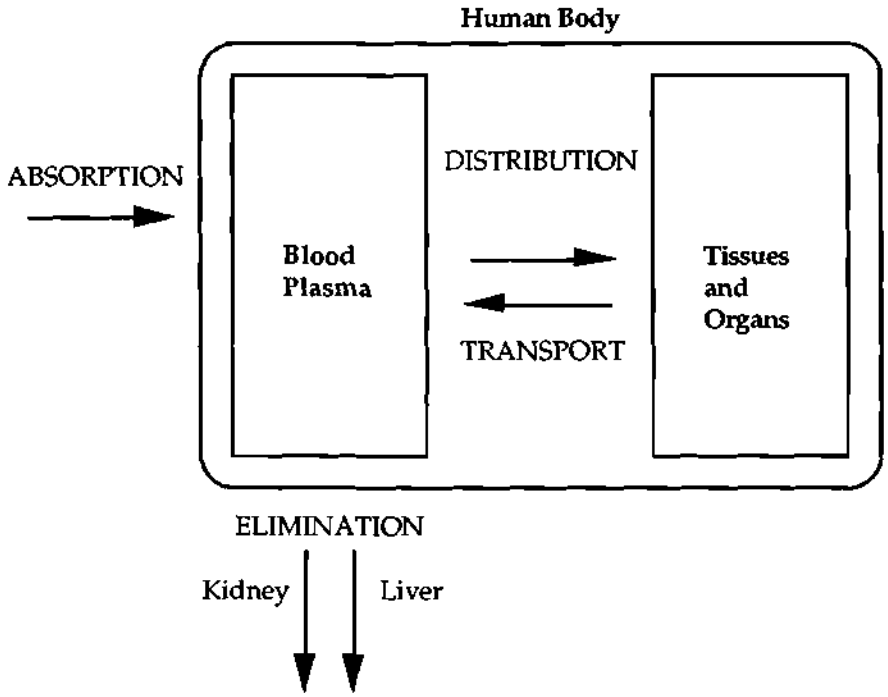

Figure 2.1 Drug Kinetics in the Human Body.

In the following section, factors that affect drug transport are presented. After reviewing these concepts, information about the absorption, distribution, and elimination steps are presented. Although the material in this chapter is applicable to many drugs, special emphasis has be given to theophylline. This information will be used in chapter 3 to develop a mathematical model of theophylline kinetics for use in the computer simulation program.

Drug Transport

Drug transport is the movement of drug molecules throughout organ and tissue membranes and is crucial to the drug absorption, distribution, and elimination phases. Drug transport behavior can be quite complex, because drugs frequently cross several different membranes and spaces [3]. In order to

simplify the modeling process, drug transport will be modeled at the macroscopic level. Modeling at the macroscopic level permits multiple paths to be lumped together so that only the total transport behavior is observed. For those familiar with heat transfer analysis, this technique is similar to the way engineer's combine resistances to obtain heat transfer coefficients. When using lumped modeling techniques, the individuality of each sub-process is lost, but the overall behavior is, hopefully, preserved. This functional simplification holds true as long as the sub-processes are relatively invariant or maintain counterbalancing effects in the presence of other changes to the system.

The pharmacological concepts of drug transport that are important to understanding issues in drug kinetics are permeability, perfusion, saturation, protein binding, passive diffusion, facilitated diffusion, and active transport.

Permeability

Permeability represents the resistance that drug molecules encounter when penetrating the cellular membranes in tissues and organs. Several different factors influence the permeability of cellular tissues to drug molecules. Of these factors, three are frequently mentioned as determinants to permeability. They are lipid solubility, the degree of ionization, and the molecular weight [4]. The importance of these factors on the kinetics of a drug can be illustrated by considering the degree of ionization.

The degree of ionization is defined as the ratio of drug in the ionized and nonionized state. Since drugs are believed to be transferred primarily in their un-ionized form, a drug's degree of ionization can alter drug permeability and affect drug absorption, transport, and elimination [5]. For example, changes in the intestinal pH can affect the permeability of some drugs across intestinal tissues and alter drug absorption. Fortunately, theophylline, which

is a weak acid, has pKa of 9. Using the following relation for weak acids, it can be shown that theophylline is relatively unionized over the range of 1.0 to 8.0 pH typically found in the gastrointestinal tract, and it's permeability due to ionization is, therefore, not likely to be sensitive to changes in pH.

$$pKa = pH + \log\frac{(\text{nonionized acid})}{(\text{ionized acid})} \tag{2.1}$$

Perfusion

Perfusion is a measure of how well blood is circulated or perfused through tissues and organs. It is typically expressed in the units of milliliters of blood per minute per volume of tissue. Values range from 10 for lungs to 0.025 for resting muscle or fat [6]. The rate of transport across membranes can be rate-limited by either perfusion or permeability. As drug permeability decreases, perfusion becomes less significant in determining the transport rate of drugs and membrane permeability becomes the rate-limiting step.

Saturation

Saturation is a system non-linearity that frequently manifests itself as an upper limit to the rate at which physical processes occur. Saturation behavior can be observed in many aspects of drug transport and its manifestation varies from drug to drug. Quite often, saturation effects are linked to drug concentrations. Higher concentrations promote saturation phenomena, while lower concentrations are less likely to cause its effects. An example of absorption phase saturation has been seen in the drugs Riboflavin and Ascorbic Acid [7]. Before saturation, absorption rates steadily increase with larger doses up to a certain point. Beyond this point, larger doses have di-

minishing changes in drug absorption, and eventually drug absorption can become relatively fixed at some maximum value. When this happens, the administration of larger doses in an attempt to increase drug concentration may be futile, because very little additional drug will reach body tissues. One way to reduce this type of saturation phenomenon is to give smaller doses more frequently.

In addition to concentration related saturation, other factors have also been linked to saturation. These factors include drug interactions, intestinal mobility, the presence of food, diseases, and the duration of drug administration. A recent journal article [8] provides an excellent overview of the saturation behavior of several drugs (including theophylline). The specifics of theophylline saturation will be presented in the section on elimination, because saturation phenomena for this drug are primarily seen in the elimination phase.

Protein Binding

Protein binding is a measure of how a drug binds with proteins in the body and can be expressed by the following relationship:

$$\text{Drug} + \text{Protein} \Leftrightarrow \text{Drug-Protein Complex} \tag{2.2}$$

The degree of protein binding is typically expressed by the percentage or fraction unbound and is defined by the following relation:

$$fu = Cu/C \tag{2.3}$$

In the case of theophylline and many other drugs, it is the unbound concentration (Cu) that is usually important. This is because only the unbound drug can diffuse or be transported into tissues and sites of action [9,10]. As a result, protein binding frequently plays an important role in both the distribution and elimination phases of drug kinetics. Because plasma blood samples represent the total concentration of drug (C) and not the unbound concentration, samples are only good predictors of the therapeutically active unbound concentration if protein binding remains relatively stable.

Passive Diffusion

Passive diffusion is the process by which most drugs are transported through membranes in the body [11,12]. In passive diffusion, drug molecules move down a concentration gradient from areas of higher concentration to areas of lower concentration. This process is governed by Fick's equation:

$$\text{Rate of Diffusion} = P \times SA \times (Cu1 - Cu2) \qquad (2.4)$$

Where (P) is the permeability of the membrane , (SA) is the surface area , and (Cu) is the unbound concentration. Since only the unbound drug is available for transport across these membranes, the concentration difference is expressed in terms of the unbound concentration rather than the total concentration. System equilibrium occurs when the difference in the unbound concentrations across the membrane goes to zero. Passive diffusion has the characteristics that each drug molecule diffuses independently of others and that the system cannot be saturated [13].

Facilitated Diffusion

Facilitated diffusion is a form of carrier-mediated transport. This form of transport was developed partially because of the observation that some drugs pass through membranes at higher than expected rates and from the observation that these transport rates become saturated at higher concentrations [14]. These transport observations suggest the existence of carriers which transport drug molecules across membrane surfaces. Like passive diffusion, drug transport occurs in facilitated diffusion from areas of higher concentration to areas of lower concentration, and the equilibrium is reached when the difference in concentrations is zero. The process does not require an expenditure of energy and is not inhibited by metabolic poisons [15]. Facilitated diffusion can exhibit specificity, a preferential transport of certain types of molecular structures, and competitive inhibition. Competitive inhibition is the reduction in drug transport rates that can result when different drugs of similar chemical structure compete for transport carriers across the same membrane.

Active Transport

Active transport is another form of carrier-mediated transport. Unlike facilitated diffusion, active transport is capable of moving drug molecules from areas of lower concentration to areas of higher concentration. As a result of this uphill transport, a release of metabolic energy is needed for active transport, and this process can be inhibited by metabolic poisons such as arsenate and fluoride [16]. Active transport exhibits saturation phenomena, specificity, and competitive inhibition [17].

Phases of Drug Kinetics

Absorption Phase

For our purposes, we will investigate the administration of theophylline through two administration routes. These routes are direct intravenous drug infusion into the blood stream and the oral administration of solid preparations such as capsules. When administering the drug intravenously, the drug is instantly available for transport to secondary tissues from the blood plasma. However, when administering a drug orally, an absorption phase from the gastrointestinal system will occur.

The absorption phase of solid preparations occurs in three distinct steps. These are disintegration, dissolution, and absorption. During the disintegration step, the compressed tablet form is broken into smaller units. In the case of time release capsules, the outer capsule shell dissolves and releases beads of coated drug material. After disintegration, dissolution of the drug particles begins. During this step, the drug material is diffused into the surrounding gastrointestinal fluid where it becomes available for the absorption step. The rate at which dissolution happens is proportional to the surface area of the drug particles and the solubility of the drug. As a result, changes in the pH of the stomach or small intestines will alter the solubility of drug compounds, and may alter the rate of dissolution. Once the drug dissolves into the surrounding fluid, absorption occurs through either passive or active diffusion processes. The predominant mode of absorption for most drugs is reported to be by passive diffusion [18]. In the case of passive diffusion, absorption is characterized by a linear dependency on the administered dose. In contrast, active absorption processes will frequently be linear at low

dosages, but exude saturation phenomena at higher dosages. This saturation phenomena is partially due to the limited availability of drug transport sites. Figure 2.2 below [19] demonstrates the difference between active and passive absorption processes.

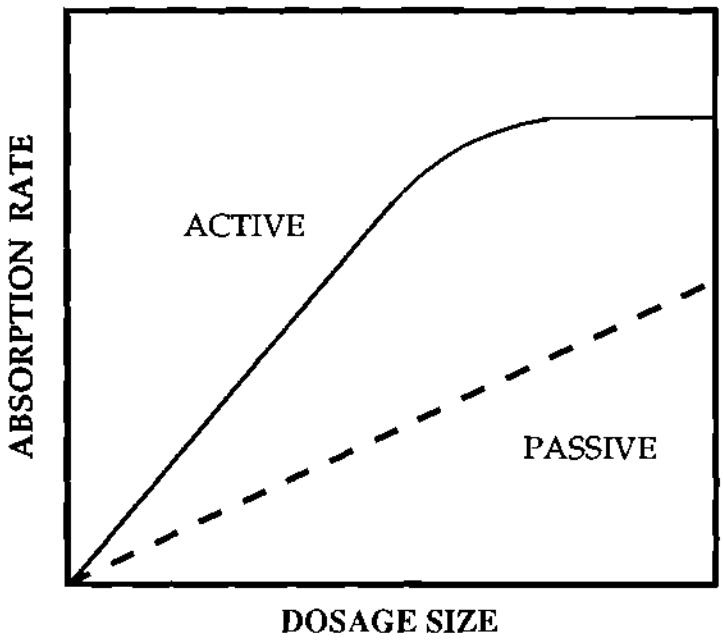

Figure 2.2 Dependency of Absorption Rates on Dosage Size

The rate of each absorption step is dependent on individual drug characteristics and complexity. One drug formulation may have an absorption limited step, in which case, drug transport is relatively insensitive to changes that affect the dissolution or disintegration phases. However, different form of the same drug may be dissolution rate limited. In general, added complexity in the dosage form increases the number of potential rate-limiting steps and increases the risk for incomplete or erratic absorption. From a modeling and controls' standpoint, these phenomena become important, because

individual patient characteristics and drug forms will alter the predictability and controllability of a drug input to the patient body system. Figure 2.3 [20] demonstrates the variation in bioavailability risk as a function of dosage complexity.

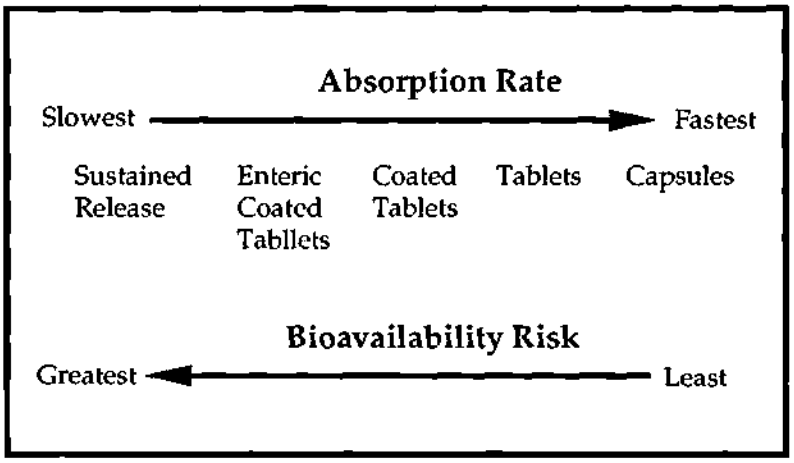

Figure 2.3 Drug Complexity and Bioavailability Risk.

While some absorption does occur in the stomach, the larger surface area, higher blood flow, and lower pH of the small intestine make it the primary site for drug absorption. Changes in gastric emptying (the rate of drug presentation to the small intestine) and changes in intestinal mobility (the amount of time a drug takes to pass through the small intestine) can affect drug absorption rates. The significance of these changes depends on the dosage form and the physiological characteristics of the patient body system.

Absorption of Theophylline

Theophylline is primarily administered intravenously as aminophylline (bioavailability ≈ 90%). This means that if we discount losses in administration devices, such as tubing, that 45 mg out of a 50 mg dose will be available for use by the body. When administering theophylline orally, a multiplicity of forms are available. These preparations vary in frequency of delivery, bioavailability, and have unique release curves as a function of time. Figure 2.4 [21] demonstrates the differences in absorption rates that can be seen with different forms of theophylline tablets. This particular graph compares the absorption rates of coated (slow-release) and uncoated tablets.

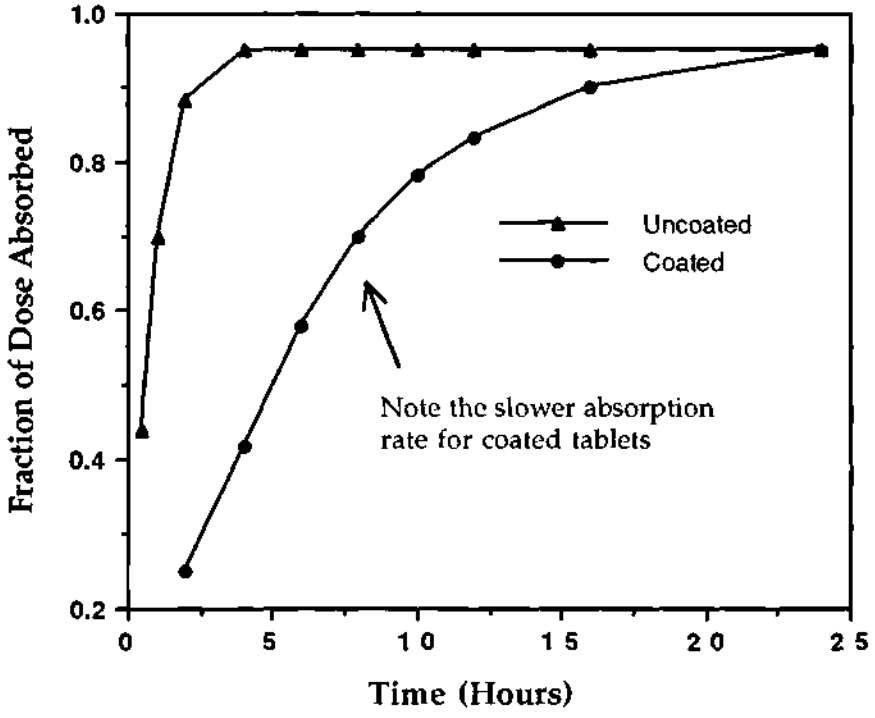

Figure 2.4 Comparison of Release Rates for Coated and Uncoated Theophylline Tablets.

Oral formulations, with their complicated release mechanisms, are prone to complications. One such complication is called dose dumping. This is a phenomenon characterized by the unexpected and sudden release of theophylline. A complete explanation of the dose dumping phenomena is provided in chapter 5 as background information for the simulation example of dose dumping that is available as a teaching example in the software program.

Distribution Phase

After the drug is absorbed or infused into the blood stream, it is available for distribution to other tissues in the body. During distribution, drug molecules are transported throughout the body until an equilibrium exists between the diffusible form of the drug in the tissues and the diffusible form of the drug in the perfusing blood is reached [22]. The determinants of drug distribution are not completely understood. Some factors that are known to affect the distribution process include permeability, perfusion, degree of ionization, and protein binding.

Extent of Distribution. The extent of distribution across membranes and into body tissues is determined by a number of factors and can vary significantly from drug to drug and patient to patient. To compare the differences in distribution, a commonly used concept is the volume of distribution (Vd). This volume is defined by the following relationship:

$$Vd = \frac{\text{Amount of Drug in the body at equilibrium}}{\text{Measured Plasma Drug Concentration}} \qquad (2.5)$$

The volume of distribution is a measure of the apparent volume over which a drug is distributed and is expressed in the units of liters/Kg of body weight. The volume of distribution does not, however, represent the actual physical size of fluid or tissue volumes in the body. The volume of distribution can be understood by considering the two-compartment model presented in [23]:

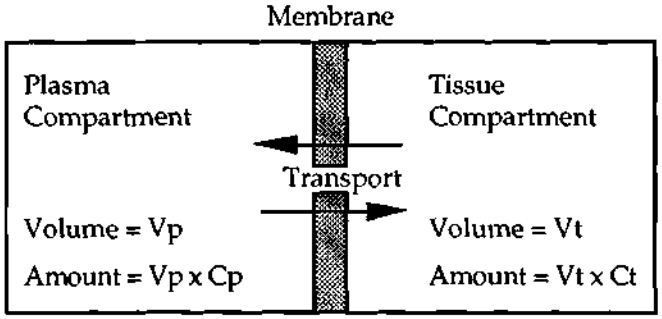

Figure 2.5 2-Compartment Model for Volume of Distribution

Using this model, the total amount of drug in the body is expressed by the following equation:

$$\text{Amount} = Vp \times Cp + Vt \times Ct \tag{2.6}$$

Substituting $A = Vd \; x \; Cp$ for the amount of drug and $Kr = Ct/Cp$ for the ratio of total concentrations into (2.6) yields:

$$Vd = Vp + Vt \times Kr \tag{2.7}$$

Therefore, the volume of distribution is expressed as the sum of the plasma volume (approximately 3 liters in adults) and the total tissue volume multiplied by a ratio of concentrations. Since the body is composed of many tissue volumes, it is more accurate to express the previous relationship as

$$Vd = Vp + \sum_{1}^{i} (Vt_i \times Kr_i) \tag{2.8}$$

From this expression, it is seen that factors which alter tissue volume and/or the concentration ratio will also directly affect the volume of distribution.

Two factors that can alter the extent of distribution are the degree of ionization and protein binding. The importance of ionization can be illustrated by the *pH partition hypothesis* [24]. According to this hypothesis, equilibrium is reached when the un-ionized species of a drug are equal on both sides of the tissue membrane. Increased accumulation of the drug occurs on the side of the membrane that has a pH value which favors the ionized form of the drug. The influence of pH on weak acid drug concentrations is illustrated in the following figure:

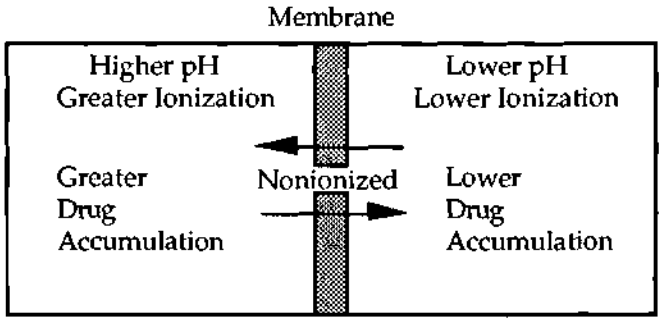

Figure 2.6 The pH Partition Hypothesis for a Weak Acid Drug.

The pH Partition Hypothesis is seen in the drugs salicylate and phenobarbital. Both of these drugs have a restricted access to the central nervous system (CNS). If the blood pH changes and becomes more acidic, the nonionized forms of these drugs will increase and more drug will distribute to the CNS. This transport phenomenon explains why reversing systemic acidemia helps treat toxicity, because a reduction in blood pH will facilitate the exit of these agents from the CNS [25].

The influence of protein binding on the extent of drug distribution is quite significant. Since only unbound drug molecules can cross membranes, protein binding affects the distribution of total drug concentrations in much the same way as ionization. A protein binding model is shown in Figure 2.7.

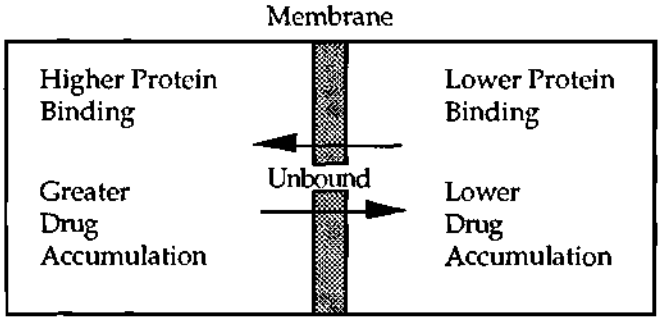

Figure 2.7 Protein Binding Effects on the Extent of Distribution

Here, protein binding causes drugs to preferentially accumulate on the side of the membrane that has greater protein binding (smaller fraction unbound). Equation 2.7 can be re-expressed to account for protein binding effects.

The fraction of unbound drug in the plasma is given by:

$$fu_p = Cu_p/C_p \tag{2.9}$$

Similarly, the fraction of unbound drug in the tissues is given by:

$$fu_t = Cu_t/C_t \tag{2.10}$$

Combining equations 2.7, 2.9, 3.0 for the equilibrium situation (at which the unbound concentrations are equal in both the tissues and plasma) yields:

$$Vd = Vp + Vt \times \frac{fu_p}{fu_t} \tag{2.11}$$

From this relationship, it is seen that the volume of distribution decreases when plasma protein binding increases and/or tissue binding decreases. Although this model sufficiently shows the overall concepts of protein binding, Rowland and Tozer [26] have suggested that a three compartment representation for protein binding is indicated for drugs with high levels of protein binding and small volumes of distribution. This is particularly important for drugs with volumes of distribution that are less than 0.2 liters/Kg. Such drugs include warfarin, ibuprofen, tolmetin, and acetylsalicylic acid. Since theophylline typically has a volume of distribution of about 0.45 liters/Kg and since it is moderately bound, a review of the three compartment model is defered to the reader.

The potential clinical implications and importance of protein binding from a drug administration standpoint can be illustrated by changes that have

been observed in the drugs phenytoin, thiopental, and warfarin [27]. In these drugs, a reduction in protein binding increases the amount of unbound drug. Such changes in protein binding result from a variety of conditions such as burns, pregnancy, renal disease, and cirrhosis [28]. Here, the unbound drug becomes available for elimination and transport across membranes into surrounding tissues. In these particular drugs, it has been found that the amount of free drug in the plasma after the change is almost the same as that before prior to the change [29]. This can present a clinical problem, because the measured drug level, which is based on the total drug, decreases. The danger in this phenomenon is that the new equilibrium total drug concentration could be misinterpreted as being too low. If an increase in drug dosage is prescribed during these conditions, toxicity can result.

Theophylline Distribution Characteristics. The rate of theophylline distribution is very high. Within 30 to 60 minutes of a single bolus dose of theophylline, the body tissues reach a near equilibrium state with the blood concentrations. The rate of distribution is believed to be relatively insensitive to drug interactions, disease states, and saturation effects.

The extent of theophylline distribution can vary significantly from patient to patient. Although the average value for the volume of distribution is 0.45 liters/Kg, values range from about 0.3 to 0.7 liters/Kg [30]. The mean volume of distribution for premature newborns, adults with hepatic cirrhosis, acidemia, and the elderly has been reported to be larger due to reduced plasma protein binding in these patients [31]. The change in protein binding is also believed to be partially responsible for a reduction in the therapeutic range of theophylline in premature newborns [32]. Recall that as protein binding decreases, the level of free and therapeutically active theophylline in-

creases. Based on this observation, increased sensitivity to theophylline is anticipated in patients with other conditions that affect protein binding and may explain why some reports of theophylline-induced seizures in patients with acidosis have occurred at marginally toxic levels [33]. Burn patients and obese patients can also experience large changes in the volume of distribution.

Elimination Phase

Drugs are removed from the body through the process of elimination. There are two basic elimination mechanisms. First, drugs can be eliminated through excretion. In excretion, drug chemicals exit the body through paths such as the air that is exhaled from the lungs or the urine from the kidneys. Drugs can also be removed by the process of metabolism. During metabolism, drug chemicals are changed by biotransformation into new forms called metabolites. Drug metabolism can occur in various places in the body including the skin, kidneys, and liver. Quite often, the therapeutic effects of a drug are caused by the metabolites that result from a drug instead of the drug itself. These types of drugs are called prodrugs.

Elimination takes place in primarily two places, the liver and the kidneys. The liver eliminates drugs through the process of metabolism and the kidneys remove drugs primarily through excretion. Since theophylline is eliminated almost entirely by the liver, greater emphasis will be placed on explaining the elimination processes that occur in this organ.

Clearance is a term used for measuring the effectiveness of an eliminating organ. Clearance can be described in a variety of organ-specific ways. Some examples include hepatic clearance, renal clearance, plasma clearance, and blood clearance.

The plasma clearance (Cl_p) is defined as the ratio of the rate of drug elimination to the total plasma drug concentration [34]:

$$\text{Plasma Clearance} = Cl_p = \text{Rate of Elimination}/C_p \tag{2.12}$$

Another useful measure of elimination is the extraction ratio. The extraction ratio is a measure of the efficiency of drug removal. The extraction ratio is limited to values between 0.0 and 1.0 and is defined by the following equation:

$$E_b = \frac{\text{Rate of Extraction}}{\text{Rate of Presentation}} = \frac{Q_b \cdot (C_{in} - C_{out})}{Q_b \cdot C_{in}} = \frac{(C_{in} - C_{out})}{C_{in}} \tag{2.13}$$

Qb is the flow of blood to the organ and C is the blood concentration. The extraction ratio can be used to express the blood clearance as:

$$\text{Blood Clearance} = Cl_b = Q_b \cdot E_b \tag{2.14}$$

In order to better understand the concept of clearance and extraction ratio, let's consider an example. If an organ, such as the liver, has an extraction ratio of 0.5 and the blood flow to that organ is 1.0 liters/min then the organ completely removes all of the drug from the blood at a rate of 0.5 liters/min. Thus, if we ignore saturation effects and consider a blood concentration of 10 mg/liter, the organ will remove 5 mg of drug/min.

Liver Elimination and Clearance. As mentioned earlier, removal of drug in the liver takes place primarily through metabolism. During metabolism, the administered drug is altered through biotransformation into new chemical species. These new species may be pharmacologically active or inactive. Since theophylline metabolizes into inactive forms, we shall only consider this case.

The function of the liver is pictured in the following figure [35]:

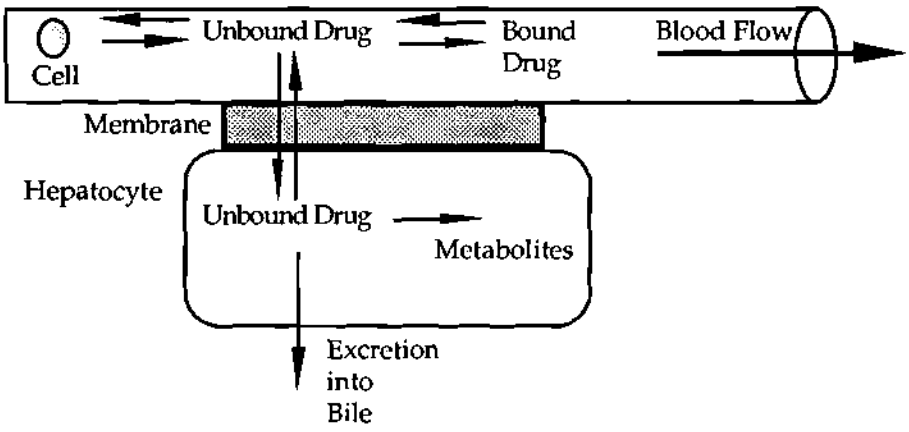

Figure 2.8 Liver Structure and Elimination Processes

A number of different sub-processes are involved in the elimination of drugs from the liver. These processes include various forms of diffusion, chemical reactions, transport mechanisms, etc. As is the case with other biological processes, each individual step is a factor in determining the overall rate at which the process occurs.

Drugs that have a high extraction ratio (> 0.7) are, under normal conditions, insensitive to the rate at which sub-processes occur within the liver. Instead, liver processes occur so rapidly in these drugs, it is the blood flow to

the liver that limits the rate of drug removal [36]. Some examples of drugs with a high extraction ratio include lidocaine, morphine, and nitroglycerin.

For drugs with a low extraction ratio, the rate of elimination is affected by the speed of the sub-processes that occur inside the liver. The rate of elimination for these drugs are affected by such factors as: slow enzymatic reactions, poor diffusion into the hepatic cell, slow diffusion of drug out of the blood cell, slow dissociation of the drug from plasma proteins, poor biliary transport, or a combination of these factors.

Drugs that have a low extraction ratio are sensitive to changes in protein binding. This dependency occurs because only the unbound drug penetrates the membranes of the hepatocyte and is available for elimination. Therefore, the rate of drug elimination in the liver is directly related to the unbound concentration (Cu) of the drug in the plasma. This dependency is expressed by the relation:

$$\text{Rate of Elimination} = Cl_u \cdot C_u \tag{2.15}$$

Note that the clearance value for this expression is also based on the unbound drug concentration.

In addition to protein binding sensitivity, some drugs with a low extraction ratio are also sensitive to changes in enzyme activity. The elimination of these drugs is usually rate-limited by the speed of the enzymatic reactions that biotransform the drug into its various metabolites. Saturation is a characteristic behavior of these drugs. In addition, these drugs can be affected by the administration of other drugs which alter either the availability of enzymes or the rate of the enzyme reactions.

Kidney Elimination and Clearance. The kidneys eliminate drugs through excretion. The rate of drug excretion is defined by three basic parameters. These parameters are the rate of filtration, the rate of secretion, and the rate of reabsorption. The total kidney excretion rate is:

$$\boxed{\text{Rate of Excretion}} = \boxed{\text{Rate of Filtration}} + \boxed{\text{Rate of Secretion}} - \boxed{\text{Rate of Reabsorption}} \tag{2.16}$$

Filtration occurs in the glomerulus of the kidney. Although filtration is always occuring, extraction by this method alone is usually rather low. Only the unbound drug in the plasma (Cu) is filtered by the kidneys. The drug that is bound to macromolecules or blood cells is unable to pass through the glomerular membranes [37]. The rate of filtration is expressed by the following relationship:

$$\text{Rate of Filtration} = \text{GFR} \cdot \text{Cu} \tag{2.17}$$

The GFR is called the glomerular filtration rate and typically averages 120 milliliters/minute in a 70 Kg adult man. A frequently used technique for measuring the effectiveness of an individuals kidney filtration is to test the urine for the presence of creatinine. Creatinine is eliminated through the filtration process.

Secretion is an active transport process which occurs primarily in the proximal tubule of the kidney. Although the kidney secretion process is active, it shows a low degree of specificity to drug structure and is able to pass a variety of different drugs. As with other active processes, drugs that are transported by the same secretion system in the kidney may compete and in-

hibit each other's secretion rate. Kidney secretion, like liver elimination, shows greater dependence on protein binding for drugs with a low extraction ratio. These drugs are typically insensitive to changes in kidney perfusion, and the sum of kidney perfusion and secretion has been found to vary proportionably with changes in the fraction unbound (fu). Drugs that have a high extraction ratio in the kidney are usually insensitive to changes that occur in protein binding. These drugs are typically perfusion rate-limited.

Reabsorption is the third factor which affects the renal elimination of drugs. Reabsorption occurs primarily along the proximal tubule of the kidney. The membranes in the tubule act as a barrier to water soluble substances; therefore, lipophilic substances tend to be highly reabsorbed and polar substances have poor reabsorption [38].

Reabsorption must occur if the renal clearance is less than the clearance from filtration. The rate of drug reabsorption varies from almost complete reabsorption to almost no reabsorption. Reabsorption transport is primarily by passive diffusion, but active transport processes also occur. The reabsorption of drug molecules occurs during the reabsorption of water filtered by the glomerulus of the kidney. Approximately 80 to 98% of the water filtered by the kidneys is reabsorbed [39]. The rate of reabsorption is sensitive to changes in both urine flow and urine pH.

Drugs that are highly reabsorbed are particularly sensitive to changes in urine flow. One such drug is ethyl alcohol. At equilibrium, the concentration of the unbound drug in the urine is almost identical to that in the blood. Therefore, a change in urine flow will also alter clearance. This relationship is expressed as:

$$\text{Renal Clearance} = \text{fu} \cdot \text{Urine Flow} \tag{2.18}$$

Reabsorption can also be affected by the pH of the urine. This sensitivity results because the kidney membranes act as a barrier to ionized substances. As the pH changes, the levels of ionized and non-ionized drug will change, and the reabsorption rate of these chemical species will also increase or decrease.

Theophylline Elimination Characterisitics. The elimination of theophylline takes place primarily in the liver [40,41]. In the liver, theophylline is transformed into relatively inactive metabolites that are excreted in the urine. One of these metabolites is caffeine. Although caffeine formation occurs in all patients, it is most significant in neonates because of its long half-life. The metabolizing process occurs over multiple pathways by both first order and capacity limited processes. The hepatic extraction ratio for theophylline is very low and is only about 10% [42]. Except for neonates, a small percentage of less than 15% of the total dose of theophylline is eliminated in the kidneys in its unchanged form. The renal clearance of theophylline in neonates is significantly higher and approximately 50% of the dose is eliminated from the kidneys unchanged [43]. Consequently, dosage adjustment is not necessary during renal failure (except in neonates).

The renal clearance of theophylline metabolites is much faster than the glomerular filtration rate. As a result, metabolite concentrations are much lower than theophylline drug concentrations. This phenomenon explains why the only active theophylline metabolite, 3-methylxanthine, has no pharmacological effect.

The interpatient variability of theophylline clearance is extremely large and is likely due to variations in the rate of hepatic biotransformation. This suggests that theophylline elimination is rate-limited by the metabolic pro-

cesses which occur in the liver [44]. Clearance values for theophylline have been shown to vary with diseases, drug interactions, age, and diet. Some reports have also indicated some variations due to obesity and gender. These variations can be extremely large (greater than a 100%).

Theophylline elimination also exhibits saturation. This is due to the capacity limitations for some metabolic processes in the liver. Two primary characteristics of theophylline saturation phenomena have been observed. These are a decrease in clearance over time, and a decrease in clearance as dosages are increased. The likelihood of observing theophylline saturation increases at higher dosages.

CHAPTER III

THEOPHYLLINE KINETICS MODEL

A model of the patient body system is needed to simulate the kinetic behavior of drugs in a patient. The following chapter discusses three different modeling approaches for developing pharmacokinetic models and presents the application of the compartmental approach to develop a representation for theophylline kinetics. Although the model presented is specifically oriented to the drug theophylline, it also applicable to other drugs with similar kinetic and transport behavior.

Modeling Approaches

Model Independent Approach

The model independent approach uses sampled data to describe the transient behavior of drug concentrations. In this curve-fitting approach, sampled data is used to determine the coefficients in the exponential series. as a basis for determining representative equations. In linear model independent kinetics, a summation of exponential functions is frequently used to describe the drug kinetics [45]. For example, the following equation is an expression for the concentration after an intravenous bolus dose:

$$\text{Concentration (t)} = \sum_{i=1}^{n} C_i \cdot e^{-\lambda_i t} \qquad (3.1)$$

When using a model independent approach, care must be taken in generalizing the derived equations since errors in the sampled data or unique patient characteristics can skew the results.

Compartmental Approach

The compartmental modeling approach idealizes the body as a set of interconnected homogeneous compartments. For example, a one compartment model lumps all of the body tissues into a single unit. Higher order models, such as two and three compartment models, break the body into more units.

The number of compartments needed to represent the transient response is determined through analysis of the sampled data. Data that displays mono-exponential behavior is modeled as a single compartment, data that displays bi-exponential behavior is modeled by two compartments, etc.

Compartmental models segment tissues and areas of drug distribution into groups that represent the kinetic variability of the body as regions of slow and fast distribution. Although this segmentation is useful, it is still an approximation to the actual physiological system, and compartments rarely represent actual physical volumes.

Model Dependent Approach

In the model dependent approach, kinetic formulas and models are based upon the processes that define the system being modeled. The complexity of the models is dependent upon the kinetics of the drug, the amount of information available, and the level of realism required. One advantage of

model-dependent approaches is the ability to incorporate physical realism into the model.

Theophylline Kinetics Model

The modeling approach adopted for the theophylline kinetics model is a combination of the compartmental and model dependent philosophies. This permits the development of a representation that is similar to the compartmental models presented in texts on pharmacokinetics but also maintains a closer connection to the physical processes than the model independent approach.

Particular emphasis is given in developing the model to recognizing that the distribution, elimination, and therapeutic efficacy of theophylline are dependent on the unbound concentrations of the drug. Many model independent approaches ignore this factor and, as a result, yield transport coefficients that imply active diffusion processes. This conflicts with the observation that most drug transport occurs by passive diffusion. A model that is based on the unbound concentrations removes this confusion and allows us to demonstrate the importance of protein binding on the volume of distribution, rate of elimination, and therapeutic level.

Compartmental Representation

Frequently, theophylline behaves kinetically like a mono-exponential function, and is modeled using one compartment. This single compartment representation is clinically accurate, but hides the presence of other variables, such as protein binding, that are important in drug kinetics. In order to incorporate these effects, a two-compartment model is used.

The two-compartment model that was selected segments the body into a volume for the blood plasma and a volume for the surrounding tissues and organs. This model is shown graphically on the following page in Figure 3.1. Note that the volume in compartment number one is a plasma volume rather than a blood volume, because most drug measurements are taken from plasma and protein binding is typically expressed in terms of the plasma proteins.

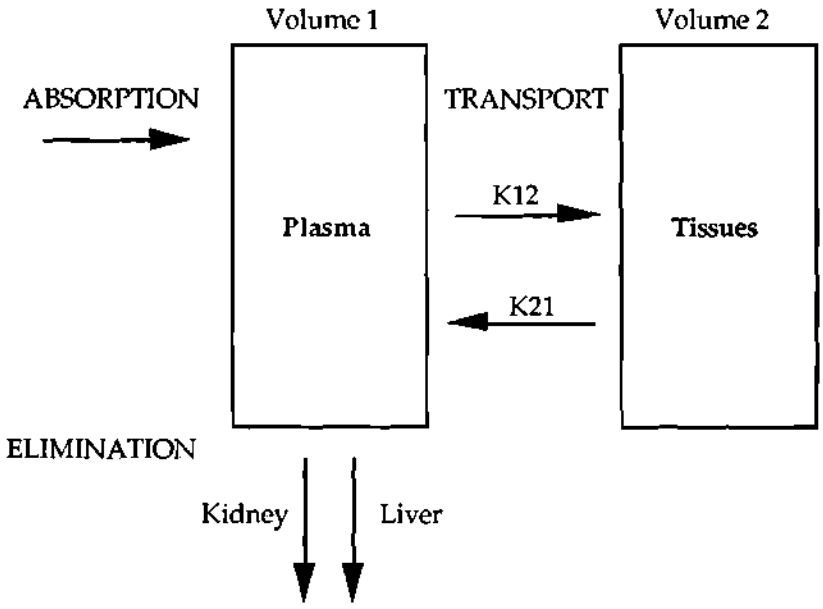

Figure 3.1 Compartmental Model for Theophylline Distribution

In this model, absorption and elimination is confined to the first compartment. This assumption is physiologically consistent since most drugs are absorbed or infused into the blood stream and most drug elimination occurs from the blood stream. Since theophylline is not biotransformed in the sur-

rounding tissues, no elimination or input path is attached to the second compartment.

Drug removal is represented by two elimination routes. One path represents elimination by the kidneys and the other path represents the elimination or biotransformation of theophylline that occurs in the liver. Although most theophylline elimination occurs in the liver, the kidneys also eliminate active drug and are important in drug removal during the early stages of life. Therefore, parameter lumping is not used to combine these two elimination routes, because it removes physical reality from the model.

The diffusion processes that occur between the compartments are represented by two transport paths. The importance of using two paths for theophylline kinetics is marginal due to the apparent reversibility of the transport. However, the consideration of two paths makes it possible to demonstrate the kinetic impact of rate-limited transport and directional preference. For example, this model can be used to demonstrate the kinetic behavior that results when drug molecules develop an increased affinity for tissue proteins.

Absorption and Infusion Kinetics

The absorption and infusion kinetics of the system are not directly represented in the model. Instead, the drug input into the system is represented by an infusion or absorption path into the system. This input path has units that are expressed as:

$$\text{Infusion Path Units} = \text{Mass of Drug/Unit Time} \tag{3.2}$$

The actual input rate to the system is dependent upon the dosage form, the method of delivery, and other variables. These absorption rate kinetics are

handled in a separate system representation that passes the drug input rate as a parameter to the the theophylline kinetics model. This is a modular approach which facilitates modeling different drug administration methods.

Transport Kinetics

Transportation between the two compartments is represented by two transport routes. These routes consist of a path from the plasma compartment to the surrounding tissues and a return path from the tissues to the plasma compartment. The transport across these paths is modeled as a facilitated diffusion process. The rate of diffusion is based upon the difference in the unbound concentrations:

$$\text{Rate of Diffusion} = (Cu_1 - Cu_2) \cdot K \tag{3.3}$$

Elimination Kinetics

Drug elimination is represented here as occurring in two organs - the liver and the kidney. The actual elimination of theophylline from these organs is assumed to be dependent on the unbound concentrations of the drug. This is a logical modeling conclusion, since the extraction ratio for theophylline is very low (see Chapter 2).

The rate of elimination from the liver is given by:

$$\text{Liver Elimination} = Cu_1 \cdot K_l \tag{3.4}$$

The rate of elimination from the kidney is represented as:

$$\text{Kidney Elimination} = Cu_1 \cdot K_k \tag{3.5}$$

Typical units for the unbound concentration (Cu) and the elimination proportionality value (K) are mg/liter and liters/hour or μg/ml and ml/min respectively. Since the transport is a function of the unbound concentrations, the proportionality values are actually the unbound clearance. Care must be taken to avoid confusing this with the total clearance which is based on the total concentration.

Saturation of the elimination paths which can occur at high drug concentrations and is represented by a separate computer algorithm. This algorithm is based on the Michaelis-Menton equation and expresses the rate of drug elimination in terms of the total drug concentration (C), the maximum elimination rate (V_{max}), the half maximal elimination rate (Km), and the rate of total clearance (CL). In this equation, the rate of elimination is represented as occurring from two paths, one saturable and one first-order. The expression is:

$$\text{Rate of Elimination} = V_{max} \times C/(Km + C) + CL \times C \tag{3.6}$$

At low concentrations relative to Km, the elimination rate is approximately first order, and at higher concentrations the elimination rate behaves nonlinearly and approaches a new rate of:

$$\text{Rate of Elimination} = Km + CL \times C \tag{3.7}$$

In the saturation algorithm, equation 5.1 is re-expressed in terms of the total clearance as:

$$\text{Total Clearance} = V_{max}/(Km + C) + \text{First Order Clearance} \qquad (3.8)$$

During saturation kinetics, the algorithm computes the value of elimination from equation 5.3 and modifies the current values of K_k and K_l in the theophylline kinetics model.

Kinetic Model Derivation

A total mass balance relation for the system that is given by:

$$\dot{m}1 = \dot{u}1 + \dot{m}_{21} - \dot{m}_{12} - \dot{m}_L - \dot{m}_K \qquad (3.9)$$

$$\dot{m}2 = \dot{m}_{12} - \dot{m}_{21} \qquad (3.10)$$

The terms for $\dot{m}$ are the mass flow (mg/h) of drug into and out of the two compartments. The u1 term is the drug input to the system. To be useful for simulation and control, these expressions must be expressed in terms of drug concentrations. Recall that the unbound concentrations in the compartments can be expressed as $Cu = C \; x \; fu$.

Because drug transport phenomena is based on the unbound drug concentrations, the following relations result:

$$\dot{m}1 = \dot{u}1 + (C2 \cdot fu2 - C1 \cdot fu1) \cdot K21 - (C1 \cdot fu1 - C2 \cdot fu2) \cdot K12 - (C1 \cdot fu1) \cdot K_L - (C1 \cdot fu1) \cdot K_K \quad (3.11)$$

$$\dot{m}2 = (C1 \cdot fu1 - C2 \cdot fu2) \cdot K12 - (C2 \cdot fu2 - C1 \cdot fu1) \cdot K21 \quad (3.12)$$

In equations 3.8 and 3.9, the concentration (C) is the total plasma drug concentration. When the time variance in the volumes of distribution is small:

$$\dot{m} = \frac{\dot{C}}{V} \quad (3.13)$$

Using (3.10) to rewrite (3.8) and (3.9) yields:

$$\dot{C}1 = \frac{\dot{u}1}{V1} + (C2 \cdot fu2 - C1 \cdot fu1) \cdot \frac{K21}{V1} - (C1 \cdot fu1 - C2 \cdot fu2) \cdot \frac{K12}{V1} - (C1 \cdot fu1) \cdot \frac{K_L}{V1} - (C1 \cdot fu1) \cdot \frac{K_K}{V1} \quad (3.14)$$

$$\dot{C}2 = (C1 \cdot fu1 - C2 \cdot fu2) \cdot \frac{K12}{V2} - (C2 \cdot fu2 - C1 \cdot fu1) \cdot \frac{K21}{V2} \quad (3.15)$$

Equations 3.11 and 3.12 are the two coupled, linear, ordinary differential equations used to represent the kinetic behavior of theophylline. The state-space representation for these equations can be developed by introducing the following new expressions for the rate of transport between compartments and for the rate of drug elimination.

The rate of transport is expressed as:

$$\overline{K} = (K12 + K21) \tag{3.16}$$

The value for the combined transport rate is dependent on the relative concentrations in the two compartments. This concentration dependance is expressed as:

$$\begin{array}{l} K = K12 \quad (C1>C2) \\ K = K21 \quad (C2>C1) \end{array} \tag{3.17}$$

Equation 3.14 is necessary for modeling the directional nature of the transport between the two compartments. The combined expression for the rate of drug elimination is:

$$Kel = (K_L + K_K) \tag{3.18}$$

After simplifying Equations (3.11) and (3.12), the following state-space representation is obtained:

$$\begin{bmatrix} \dot{C1} \\ \dot{C2} \end{bmatrix} = \begin{bmatrix} -\frac{fu1}{V1}(\overline{K}+Kel) & \frac{fu2}{V1}(\overline{K}) \\ \frac{fu1}{V2}(\overline{K}) & -\frac{fu2}{V2}(\overline{K}) \end{bmatrix} \begin{bmatrix} C1 \\ C2 \end{bmatrix} + \begin{bmatrix} \frac{1}{V1} \\ 0 \end{bmatrix} [\dot{U1}] \tag{3.19}$$

The methods used to solve these differential equations within the software program are briefly discussed in chapter 5.

CHAPTER IV

FUZZY LOGIC MODELING AND INTELLIGENT CONTROL

This chapter discusses fuzzy logic and intelligent control. Particular emphasis is given to explaining the structure of fuzzy associative memory controllers (FAM). After some introductory material, two control algorithms which incorporate information about the patient with intelligence rules are developed. The first algorithm is a FAM controller and the second algorithm is a combination of discrete sliding mode control with fuzzy logic rules for sampling rate and error detection.

Fuzzy Logic Modeling

Fuzzy logic modeling is based on the concept of the fuzzy set. It was initially developed by Lofti Zadeh in 1965 [46]. Fuzzy logic expresses truth as a matter of degree. To illustrate this concept, Figure 4.1 shows a fuzzy set representation of the control action that could be used to apply medium brake pressure in an automobile. In this figure, the membership function relates numerical values of the control variable to the concept of medium brake pressure. This particular membership function classifies a medium brake pressure as having a value of 5. Other values of the control effort are considered to be medium to a degree that is determined by the membership function. This ability to associate numerical values to qualitative control concepts,

such as medium brake pressure, simplifies the representation of control rules that are based on human linguistics and knowledge.

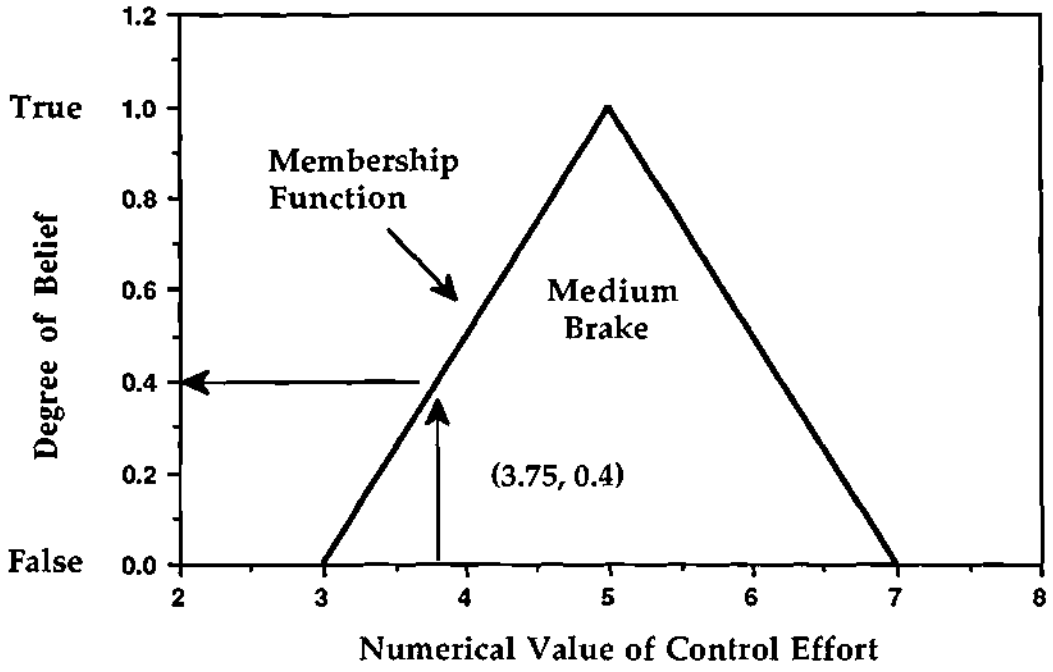

Figure 4.1 Fuzzy Set Representation for Applying Medium Brake Pressure

Fuzzy logic models and FAM controllers associate information and knowledge through the use of rules that are expressed in the form of "IF-THEN" relationships. Although this feature is shared by conventional rule-base structures, fuzzy logic rules apply in multiple situations with differing degrees of output response. This increased range of application greatly reduces the total number of rules required.

Consider the following "IF-THEN" rule:

IF *Control Error* is **Small Negative**
AND *Velocity* is **Large Positive**
THEN *Brakes* **Medium**.

In a normal "IF-THEN" rule, the application of the rule is usually a boolean function of the input variables (The rule is active or inactive). When fuzzy sets are used within this framework, the rule functions when the variable for control error and the variable for velocity are either completely or partially matched. The resulting output for the application of the brakes in the automobile is a function of the degree to which the conditions for the variables are matched.

When expressing a fuzzy logic variable, the set of all possible values for the variable (universe of discourse) is represented by several overlapping fuzzy sets. Returning to the example for automobile brakes, the library of fuzzy sets for the variable control error is shown in Figure 4.2. Here, the variable is represented by seven different fuzzy sets. These sets are named large negative (LN), medium negative (MN), small negative (SN), zero (ZE), small positive (SP), medium positive (MP), and large positive (LP). In developing these membership functions, a rule of thumb is to require the adjacent fuzzy-set values overlap approximately 25 percent [47]. Adopting this rule, values for the variable control error are members of at least one of the fuzzy sets and, in some regions, are members of two fuzzy sets. This dual membership is one of the conditions that causes fuzzy control rules to activate in parallel. If a value for one of the control variables has membership in two or more fuzzy sets, multiple rules will be activated by the single numerical value of the control variable. The activation of control rules in parallel is important because

it reduces discontinuities that would otherwise exist in switching from one rule to another. The application of multiple rules also increases the robustness of the fuzzy rule-base, because errors in a single rule are less likely to corrupt the overall output behavior.

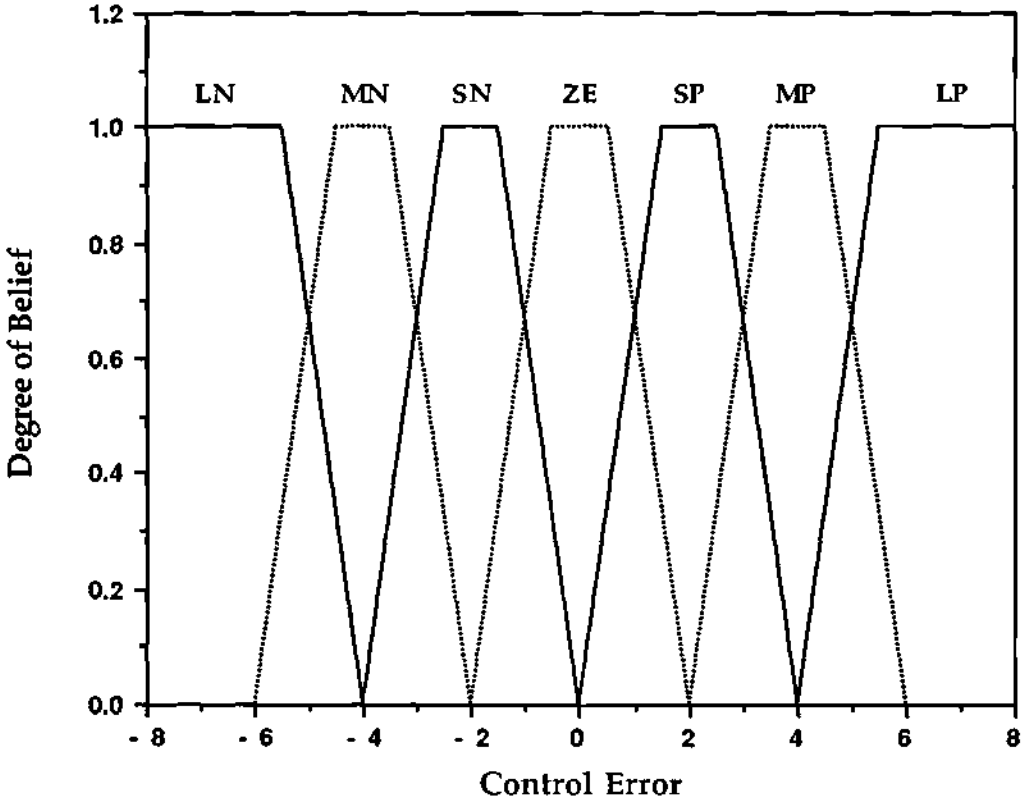

Figure 4.2 Fuzzy Set Representation for the Values of Control Error

The determination of a fuzzy control effort from the IF-THEN rule is a multi-step process that requires the manipulation of fuzzy sets. First, the degrees of membership for the values of *control error* and *velocity* to the fuzzy sets **negative small** and **positive large** must be determined. After determining the degree of membership, its value is used to scale the output fuzzy set **medium** that is used for brake control. In rules that have the AND conjunc-

tion, the smallest degree of belief is used to scale the output fuzzy set. This reflects the fact that the variable with the smallest level of agreement should be the limiting factor in determining the control effort. Likewise, rules with the OR conjunction use the highest degree of belief to scale the output fuzzy set.

A fuzzy control system activates multiple rules simultaneously to determine the output variable. Each of the scaled fuzzy sets that were calculated from the degree of memberships are added together. The output variable that results is a new fuzzy set that is a superimposed combination of the fuzzy set outputs from each of the individual control rules. The resulting fuzzy set appears similar to the representation shown in Figure 4.3.

Although the fuzzy output is useful, most control action requires a single numerical value. To obtain a single value from the fuzzy set, a process called defuzzification is used. Here, the technique of defuzzification that is used is the centroid method. In this method, the output value corresponds to the center of gravity for the output fuzzy sets.

When defining a fuzzy logic rule-base, a significant amount of effort must be devoted to defining the fuzzy sets and selecting the membership functions that are used within the rule-base structure. A variety of different techniques for developing fuzzy sets have been used over the years. At present, there is no standardized approach. The technique that is used to develop the algorithms in this thesis is based on the judgement of experienced personnel. This is useful because practitioner rules for drug dosing are often based on intuition. The fuzzy sets, rules, and membership functions that are developed using this approach represent a subjective view of the problem based upon past experience.

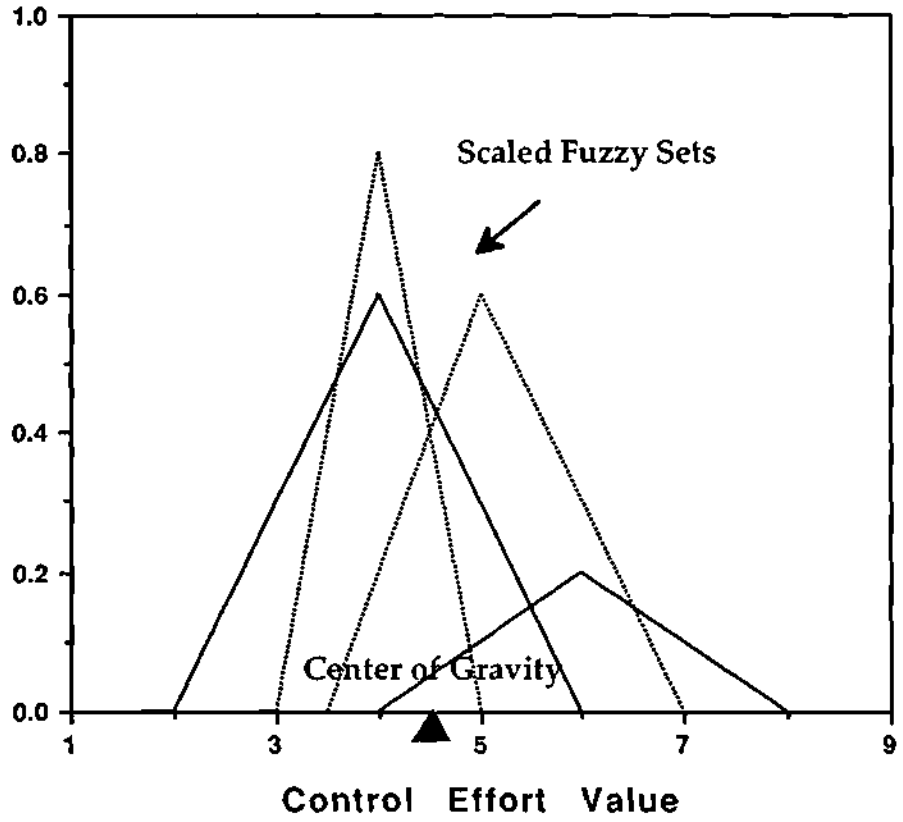

Figure 4.3 Fuzzy Set Representation for the Values of Control Error

Intelligence-Based Control Algorithms

The following chapter introduces the application of intelligence-based control for drug administration. The purpose for developing these algorithms is to illustrate their ability to increase control performance at slow sampling rates (several hours) by using information about the patient. Improvements are achieved by using additional information such as knowledge about the patient and drug kinetics to supplement standard feedback data. One of the purposes for using this additional information is to modify

the controller response to the type of patient being treated and to reduce the effects of sampling errors.

The controllers adjust their control characteristics based on several different types of data. The data considered here includes the style of therapy, the presence of interacting drugs or diseases, and the past performance of the controller. Specific data, such as the exact kinetic parameters, are not required by the algorithms. This important because exact information about the patient parameters is difficult to obtain.

The initial infusion rate is determined by from population information. After a delay of 3 times the half-life, the controllers actively adjust the drug concentrations. This initial infusion approach is adopted to create a faster control response and to reduce the number of samples during the first hours of drug administration.

Two different knowledge-based algorithms are presented. The first uses fuzzy logic and FAM control techniques exclusively. The second implements a combination of discrete sliding mode control and fuzzy logic. Simulation results for the controllers are presented in chapter 6.

FAM Controller

The FAM controller uses fuzzy logic rules to adjust the infusion and sampling rates of the administered drug. This controller is similar to the knowledge-based controller that was described by Linkens and Mahfouf [48] for muscle relaxant anaesthesia. A block diagram representation for this controller is provided below in Figure 4.4. The left side of the diagram shows the input variables into the modules of the controller. The right side shows the control action and the affect of the scaling factor and maximum infusion rate variables.

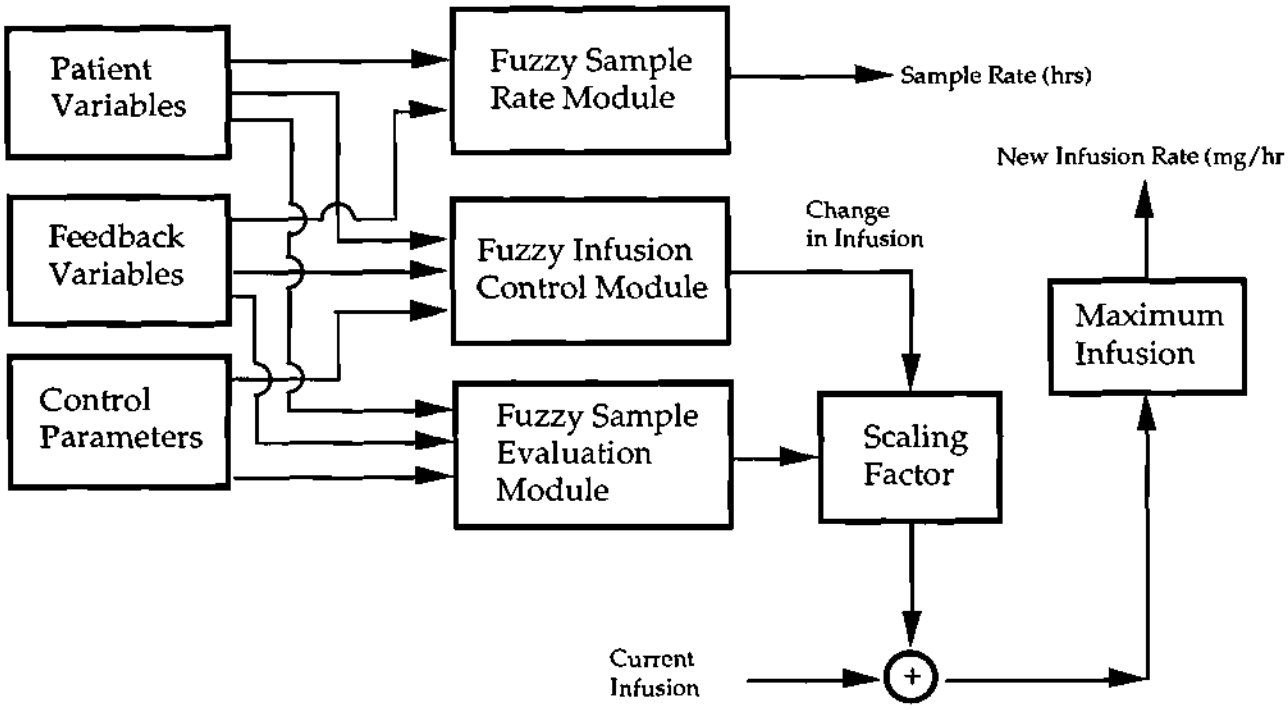

Figure 4.4 Block Diagram Representation of the FAM Controller

The controller is composed of three primary algorithms. The control module uses feedback information and other data to make alterations in the drug infusion rate. The sample rate module uses data to modify the sampling rate of the controller, and the sample evaluation module uses information about past errors to help detect possible sensor errors.

Control Variables. Several different types of variables are used by the FAM controller to determine its output. These variables can be categorized into three groups - feedback variables, patient information variables, and control parameter variables.

Feedback variables are used by the controller to calculate adjustments to the infusion rate and to detect sensor errors. These variables include the concentration error, the proximity to the recommended infusion, the maximum infusion rate, and the kinetic scaling factor.

The concentration error variable is the difference between the desired and the actual concentrations. The proximity to the recommended infusion is based on the difference between the current infusion rate and the recommended infusion rate which is calculated from population averages. The maximum infusion rate variable is in units of (mg/hr) and is used as a limit on the control output. The kinetic scaling factor is based on the relative clearance of the system and is defined as:

$$\text{Kinetic Scaling Factor} = \frac{\text{Est. Clearance}}{\text{Reference Clearance}} \tag{4.1}$$

The estimated clearance in (4.1) is based on the age, weight, and population base of the patient; the reference clearance is the value that was used in developing the control algorithm.

The scaling factor helps to maintain similar control convergence for different patients. A variable for the change in concentration error is not used because of the slow sampling rates that are used (2 to 3 times the half-life of the system).

The patient information parameters affect the sampling and evaluation of plasma concentrations. The variables are boolean and indicate the

presence of liver disease and the concurrent administration of either cimetidine or erythromycin.

The control parameter variables affect the control performance characteristics. These parameters are the sample data memory and the style of therapy. The sample data memory can be one of three values - long, medium, or short. A higher value for the memory variable increases the weighting (w) on the absolute value of the concentration error and affects the following equation (the forgetfulness formula):

$$\text{Average Error} = \frac{|CE3| \cdot (w) + |CE2| \cdot (w+0.25) + |CE1|}{(1.25 + 2w)} \qquad (4.2)$$

The variable for the style of therapy modifies the control action of the fuzzy logic rule-base. The variable can assume values that are between 0 and 10 and is used to adjust the behavior of the controller. Values for the variable correspond to conservative (0), moderate (5), or aggressive treatment styles (10). Depending on value of the variable, the controller will implement more or less aggressive control actions. Here, a value of 3, will implement a style of therapy that is a combination of the conservative and moderate treatment styles.

Infusion Control Algorithm - Structure and Principals. The control action of the FAM controller is determined by a group of IF-THEN rules. Two modules of control rules determine the overall control system strategy. The first group is used to modifying the infusion rate. The second group is used to adjust the sample rate.

The general philosophy behind the control rules for modifying the infusion rate is to increase the amount of drug infusion if the drug concentrations are to low. The proximity to the recommended infusion rate and the style of therapy are used as references for choosing the size of the dosage change. The variable for the maximum infusion rate prevents the controller from infusing levels of drug that are higher than those set by the operator of the controller. The rules for this part of the algorithm are structured in the following fashion:

IF *Control Error* is **Positive Medium**
AND *Recommended Proximity* is **Close**
AND *Therapy Style* is **Conservative**
THEN *Change in Infusion* is **Positive Small**

The module for sample rate adjustments uses information such as the concentration error and presence of disease states. To adjust the sampling rate In conditions of large concentration error or drug interactions, smaller sampling times are used. When the system is near the desired concentration and is not likely to be susceptible to changes from drug interactions and other factors, a longer sampling time is used. The rules for this part of the controller are structured in the following format:

IF *Control Error* is **Zero**
AND *Drug Interaction* is **Low**
THEN *Sample Rate* is **Slow**

The module for sample evaluation uses the value of the current concentration error, the average concentration error from (4.2), and the presence of diseases or drug interactions to evaluate the current sampled data. In conditions of large concentration error, the module compares the current sample to prior samples. If the previous samples were near the desired concentration and interactions are unlikely, the module will reduce changes in the infusion by adjusting the scaling factor. A second sample is taken within 4 hours to validate or nullify the effects of the previous sample. The rules for this part of the controller are structured in the following format:

IF *New Concentration Error* is **Negative Big**
AND Average *Concentration Error* is **Low**
AND *Drug Interaction* is **Low**
THEN *Scale* is **Low**

Fuzzy Logic and Discrete Sliding Mode Control

The second controller uses fuzzy logic rules to adjust the infusion and sampling rates of the administered drug and to evaluate the sampled data. The actual administration rates are determined by using discrete sliding mode control [49]. The parameter bounds for the sliding mode controller are automatically selected based on population information for the patient groups that have been modeled in the system. The fuzzy modules for this controller are similar to those used with the FAM controller. A block diagram representation for this controller is provided below in Figure 4.5.

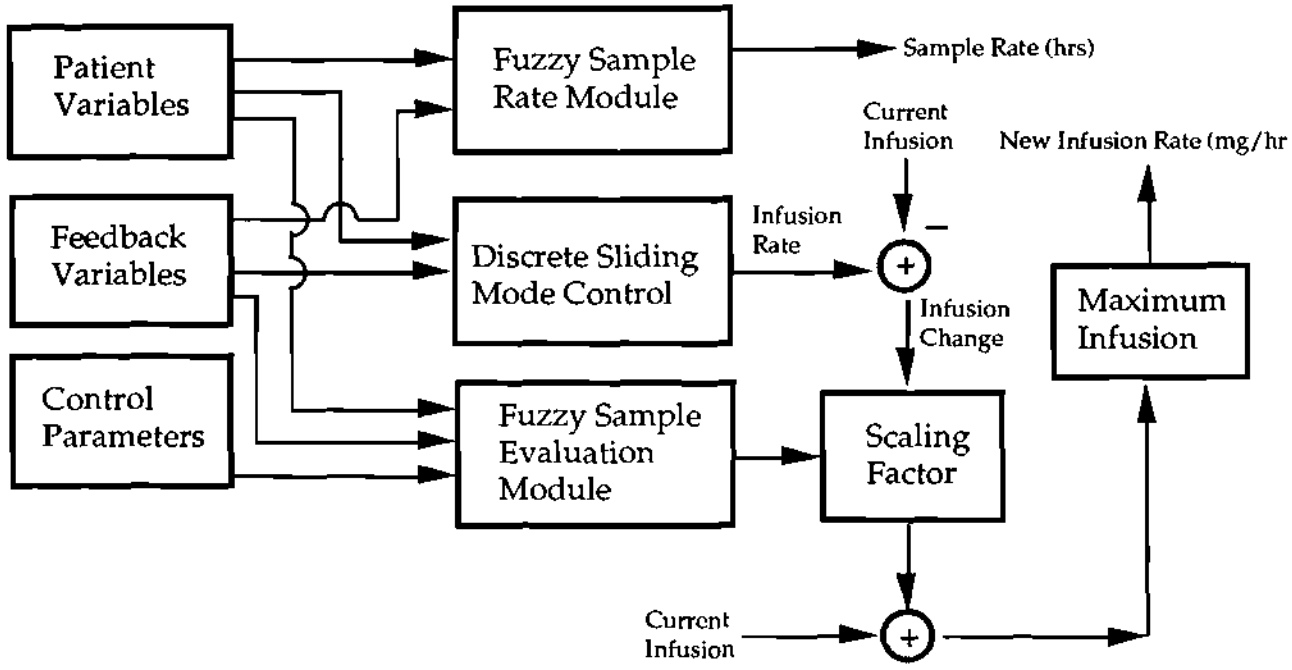

Figure 4.5 Block Diagram for the Discrete Sliding Mode Controller

CHAPTER V

SOFTWARE INFORMATION

The software that accompanies this thesis functions as a teaching tool for pharmacokinetics and serves as a platform for experimenting with control algorithms for drug administration. The software has three primary modes of operation. These modes are used for simulating drug kinetics, for teaching aspects of drug administration, and for investigating the performance of control algorithms. In this chapter, information is provided to familiarize the user with the general features of the software and to briefly explain some of the program algorithms.

Software Development

The current version of the software was developed using the C programming language and is designed to run on Macintosh color computers. The Macintosh computer was chosen because of its graphics capabilities and ease of use. Because the software implements special features of the Macintosh, the program code is not directly portable to other machines running ANSI C. However, the program algorithms which are used for control, simulation, parameter variation, and other features are transferable.

Screen Layout

The graphical layout for the program is shown in Figure 5.1. As shown here, the program screen displays a two compartment model (item#1) in which the first compartment represents the plasma volume and the second compartment represents the tissue volume. The numerical displays (item#2) give the current parameter values for the transport coefficients, infusion rate, volumes of distribution, and elimination rate. The arrow keys that are located to the right and left of the parameter value display boxes are for changing the current parameter values up or down. It should be noted that the liver and kidney values are expressed in terms of the unbound concentrations (see Chapter 3). The upper right corner of the program screen has a selectable, 3 parameter graphics display (item #3) which plots parameter value as a function of the time. The buttons located below the graphics display, run, pause, and reset the computer program. A clock (item #4) indicates the current time of the simulation in days and hours. Beneath the graphics display, a small outlined region is reserved for displaying text about the patient or for explaining concepts when the program is in the teaching mode. Arrow keys located to the right and left of the box are for stepping through the text and example simulations. The lower right portion of the screen has controls for adjusting the protein binding (item #5) in the two compartments and is expressed in terms of the percent of unbound drug.

Software Menus

Program features are selected through the use of pull down menus. A total of four main menus are implemented in the software. These are the system setup, simulation mode, study mode, and control mode menus. (see Figure 5.1) Listed inside of each pull down menu is a list of options. These op-

tions reference a dialog window that is used for inputing information into the program. When the user selects a menu item, the referenced window appears on the computer screen and is available for use. A brief description of the four main menus follows.

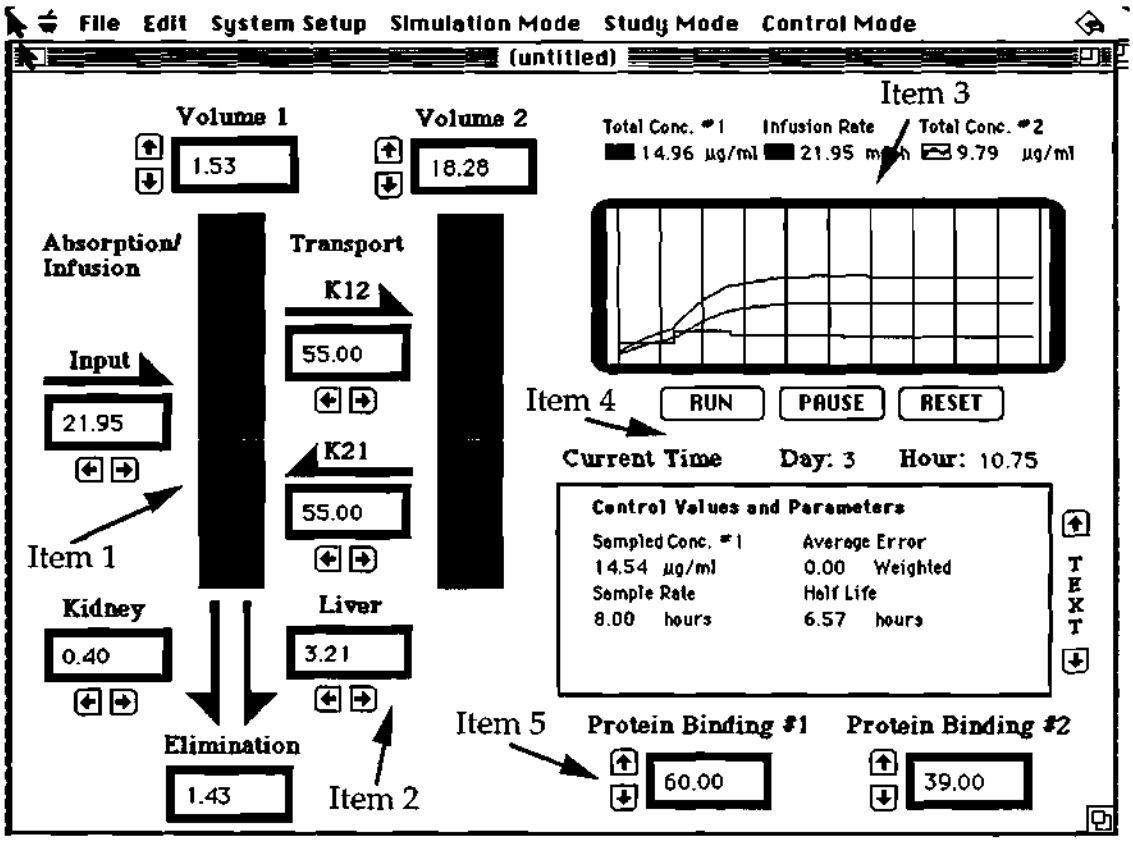

Figure 5.1 Software Screen Layout and Graphics Display

System Setup Menu

The system setup menu allows the user to select parameters that affect software plotting, graphing, operation mode, and data storage features. The purpose of this menu is to allow the user to customize the software for illustrating selected topics. For example, the submenu compartment level refer-

ences a dialog window that allows the user to modify the compartmental display. The user can select to display the drug levels in terms of either the unbound or total drug concentrations. This flexibility can be used to display the effects of protein binding on total drug concentration or for demonstrating that the drug distribution model is at equilibrium when the unbound concentrations are identical.

Simulation Mode Menu

The simulation mode menu has five submenus that affect the behavior of the program when it is operating in the simulation mode. These options allow the user to alter initial conditions, change the reference data, adjust infusion or absorption rates, select the method of delivery, and add saturation kinetics. The purpose of this menu is to permit the user to simulate and study the effects of various changes in the pharmacokinetic model developed in chapter 3.

Four different methods of drug administration are available to the user in the simulation mode of the software. These are bolus dose infusion, rapid release capsules, slow release capsules, and continuous infusion. The biovailability for the capsules is assumed to be 95% and the biovailability for the continuous infusion is assumed to be 100%.

Study Mode Menu

The study mode menu allows the user to select a topic in pharmacokinetics and receive instruction and a short demonstration on the concept chosen. The topics available for instruction include drug interactions, dose dumping, and capsule release rates.

Dose Dumping Tutorial. Dose Dumping is a phenomenon characterized by the unexpected and sudden release of theophylline from oral capsules. It is usually observed with the use of slow release formulations and quite frequently is associated with taking the tablet with food. The following figure [50] demonstrates the effects of dose dumping.

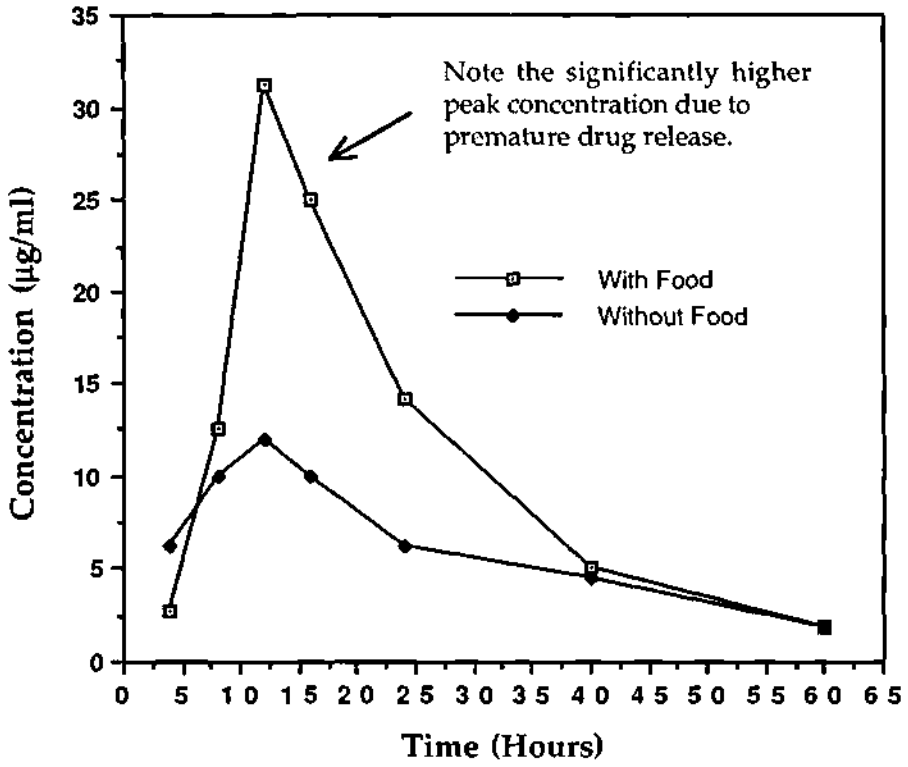

Figure 2.4 Theophylline Dose Dumping of a Slow Release Product.

Drug Interaction Tutorial. The drug interaction example illustrates the effect of a concurrently administered drug on theophylline clearance and steady state drug concentrations. A drug interaction occurs if the pharmacokinetics or pharmacodynamics of one drug is altered by the concurrent administration of a second drug. The noticeable effects of a drug interaction are frequently delayed for hours or days after starting the concurrent administra-

tion. The concurrently administered drug used in this lesson causes a reduction in theophylline clearance and increases the steady-state concentrations.

Release Rate Tutorial. When choosing a form of theophylline administration, it is important to consider the characteristics of the patient that is being treated. In this lesson, the properties of slow and fast release capsules are compared. The simulations show that the age and characteristics of the patient affect the selection of administration forms. Patients that have high clearances and shorter half-lives will have larger fluctuations with the fast release product. As a result, slower release products are shown to yield more desirable concentration responses in these patients.

Control Mode Menu

The control mode menu is designed to allow the user to adjust parameters necessary to experiment with drug infusion control techniques. Menus permit the user to select and set options on each of the three control techniques presented. The user can change sampling rates, adjust patient parameters, and modify control performance criteria. Patient input information and parameter variation options are also available. These allow the experimenter to create a realistic patient and add uncertainty and error to the system as a way to evaluate controller performance.

Software Algorithms

The software implements a number of features through specialized algorithms. These algorithms include program code for altering patient parameters, for determining drug concentrations from reference models, and

for controlling drug levels. Information and a brief explanation about some of these algorithms is given in the following paragraphs.

Reference Model Algorithm

The reference model algorithm for the patient body system is based upon the equations that were derived in Chapter 3. These differential equations express the kinetic behavior of drugs in a patient and are time variant.

To solve the model equations, two approaches were compared. These were a fourth order Runge-Kutta algorithm and a time-invarient exact solution that was determined using Laplace transform techniques. The stepsize for the Runge-Kutta algorithm was adaptively controlled in order to maintain an accuracy of 1.0e-6.

Two methods of parameter selection were tried for the time-invarient solution. The first method used the current parameter value during the integration. The second used the average of the current and previous value during the integration (midpoint method). In the simulation, the period of integration for the time-invarient case was 15 minutes (relative simulation time). This effectively discretizes parameter changes into several small steps, because most parameter changes occur slowly in the body over a period of several hours.

Three time variations in the level of drug clearance, one linear and two nonlinear, were considered. The Runge-Kutta algorithm with error control was stable and accurate, but used more time to calculate the next concentration. In contrast, the exact solution was nearly twice as fast as the Runge-Kutta solution, but sacrificed accuracy. Using the Runge-Kutta solutions as a reference, the two time-invarient solutions were compared. The average percentage difference for the algorithm using the current parameter value dur-

ing integration was 0.1677%. The percent difference for the algorithm using average parameter values was 0.0055% and is 30 times more accurate than the current value algorithm

Because of its speed and accuracy, the time-invarient method with average parameter values is implemented in the software. This algorithm uses a static variable structure to maintain information about previous parameter values. During simulation, new parameter values are averaged with old ones and substituted into the equations for determining the concentration.

Control Algorithms

Three different control algorithms are used by the software. They are a discrete sliding mode control, fuzzy logic control, and a control algorithm which combines fuzzy logic with discrete sliding mode control.

Discrete Sliding Mode Control. The sliding mode control algorithm is an implementation of the work by Godwin. [51] The algorithm uses bounding of the parameters and achieves control stability in the presence of uncertainty. The selection of the parameter bounds is a function of information about the patient. Two options exist for parameter selection. These are automatic and manual mode. In the manual mode, control parameters are selected by the software user. In the automatic mode, population information regarding typical values is used to set the parameter bounds.

Fuzzy Logic Control. The fuzzy logic control algorithm is based upon a a set of fuzzy logic rules for basic system control. The rule base uses rules of the following form:

IF Concentration is Slightly High
AND Change in Concentration is Positive
AND Change in Concentration is Small
THEN Reduction in Infusion is Medium.

Fuzzy Logic Decision Rules and Discrete Sliding Mode Control. The final control algorithm combines discrete sliding mode control with fuzzy logic decision rules. The fuzzy logic rules in this algorithm use a basic level of clinical judgement to evaluate sampled data feedback and make determinations about the infusion rate. In general, the rules are oriented to try and make the overall application stability of the discrete sliding mode control algorithm higher. The discrete sliding mode control algorithm is used to make recommendations on the next infusion rate because of its stability and ability to function in the presence of parameter uncertainty.

Patient Parameter Algorithms

The parameters for the patient can be varied in several different ways. The purpose of this variation is to add uncertainty and time changes which approximate those that occur in real patients. By doing this, it is possible to create realistic situations that test control effectiveness. The types of variations and uncertainty that are available to the user include sampling error, steady state parameter error, parametric variation, and saturation kinetics. The block diagram representation of these variations is shown below in Figure 5.2.

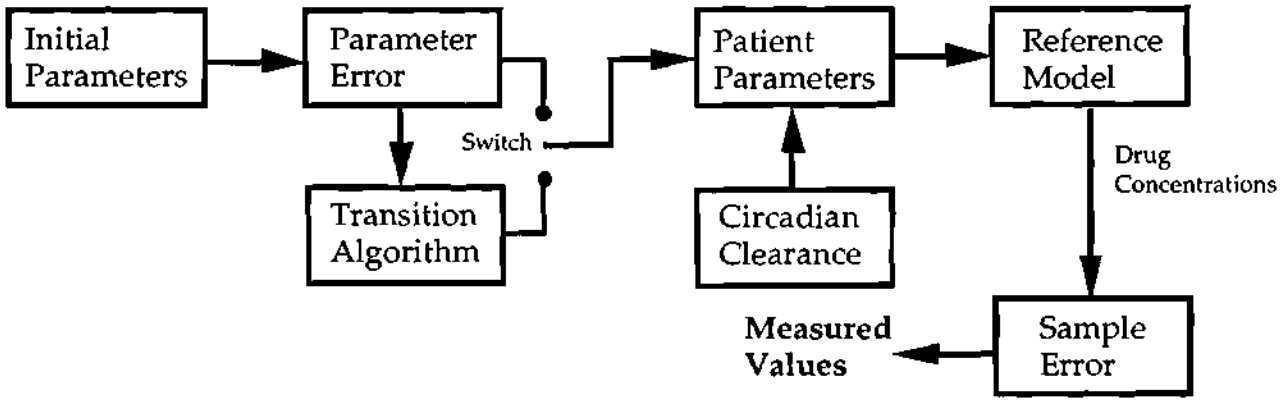

Figure 5.2 Block Diagram Representation of Patient Parameter Algorithms

Sampling Error. The algorithm for sampling error uses an algorithm from [52] to generate sampling errors. The normal distributions that are used have a mean of zero and a standard deviation that is specified by the user. Two independent distributions are implemented. The first simulates the sample errors which occur in the sampling process, and the second simulates the uncertainty that is a result of laboratory assay. In addition, a third random number generator is used to approximate the affects of a defective sensor.

Steady State Parameter Error. The algorithm for steady state parameter error allows the user to selectively offset the patient parameters from the population norms. This allows the software user to test the controller sensitivity to values that are higher or lower than expected. Two parameters, clearance and total volume, can be varied. These particular parameters were

selected because they represent the areas of greatest parameter variability and uncertainty in theophylline patients.

Parameter Variation. In addition to steady state error, additional uncertainty can be added in the form of time variations to the patient parameters. These variations include circadian clearance, and transitions between sick and normal patient parameter values.

The algorithm for circadian clearance is used to add a cyclical variation in the clearance values and is expressed by the following relationship:

$$\text{Clearance} = Cl \times (1+(Var\%/100) \times \sin(2\pi/P) \times \text{time})) \qquad (5.1)$$

The user inputs the percentage of variation (Var%) and the period of the variation (P) to create a desirable parameter variation.

The Transition algorithm is a parameter variation algorithm that alters patient parameters between two extremes of physical conditions, sick and normal. The algorithm linearly adjusts patient parameters between each of the two extremes, and two types of variations can be chosen. The user can select to have the patient transition from normal to sick or from sick to normal. The user inputs the delay time before starting the time over which the transition should occur. The final values of the parameters are determined by the steady-state parameter error algorithm which was described earlier.

CHAPTER VI

CONTROL SIMULATIONS

Simulations on the control techniques that were explained and developed in chapter 4 are presented in the following chapter. The simulations were performed in order to evaluate the effectiveness of each controller. The performance of the controller is a function of its ability to maintain the proper drug concentration levels while parameter variations and sampling error are occurring in the system.

Three different control algorithms are compared. They are discrete sliding mode control, fuzzy logic control, and intelligent sliding mode control (a combination of patient information and fuzzy rules with sliding mode control). The model variation, sampling error, and other simulation options that are used for testing the control algorithms are components of the software program and are selected through the use of menus such as the one shown in Figure 6.1.

In the first simulation, the effects of sampling error are considered. Figure 6.2 shows the affect of sampling errors on the control response of the discrete sliding mode controller. Here, sensor errors cause a serious alteration in the drug infusion rate and control performance. This alteration in control performance is indicated by the large fluctuation in the plasma drug concentration levels.

Figure 6.3 displays the simulation results for the intelligent sliding mode controller. In this controller, a fuzzy logic routine is used to evaluate the sampled data. The application of this evaluation algorithm reduces the sensitivity to sample errors.

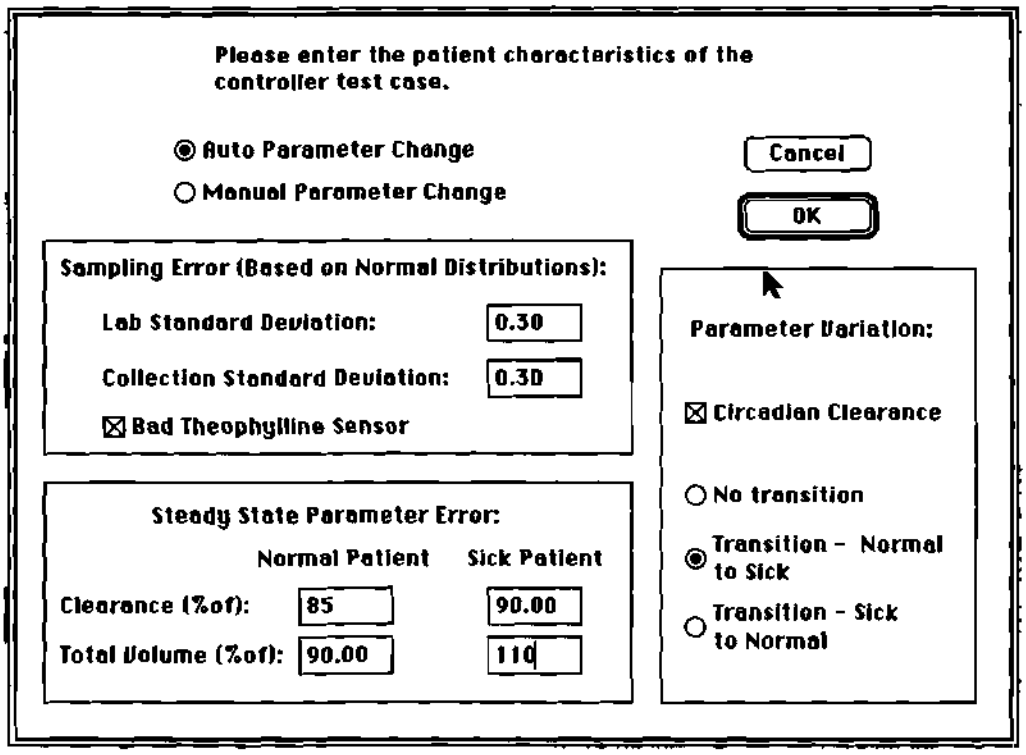

Figure 6.1 The Computer Software Menu for Model Variation.

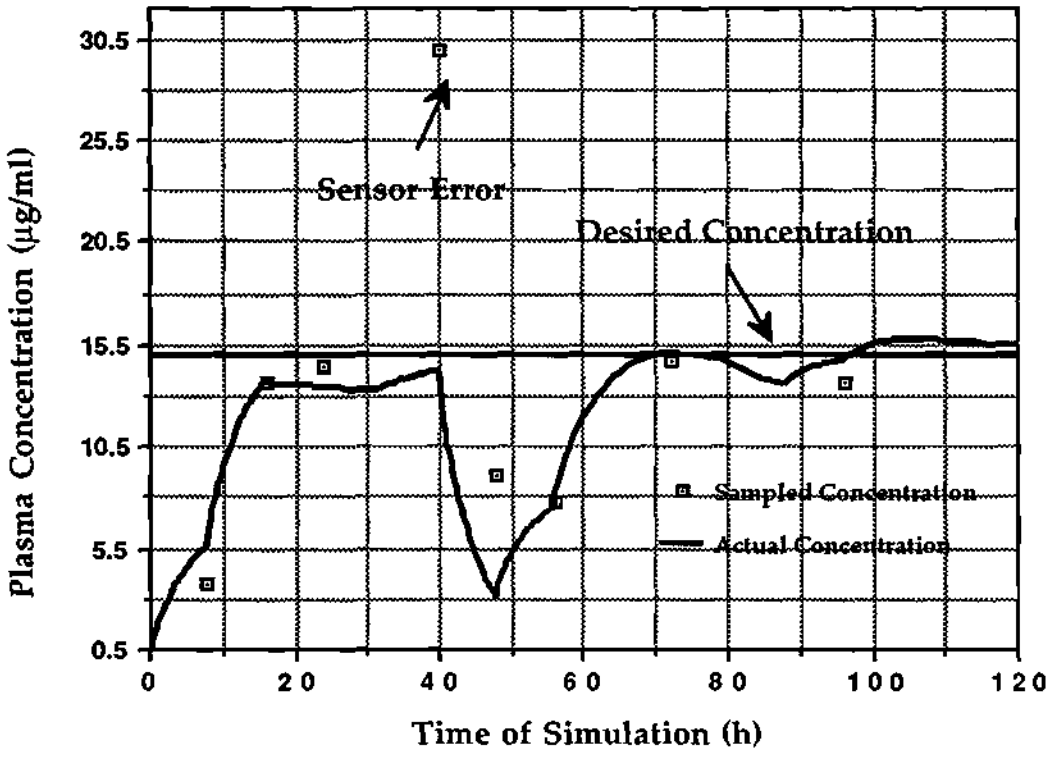

Figure 6.2 Controller Response without a Sample Evaluation Algorithm

Figure 6.4 demonstrates the degradation in controller performance that occurs as a result of selecting the control variables (parameter bounds, rise time, etc.) for the discrete sliding mode control algorithm incorrectly. In this example, the controller performance is reduced and the response is very slow This controller fails to achieve the desired drug concentrations prior to the end of the time of simulation.

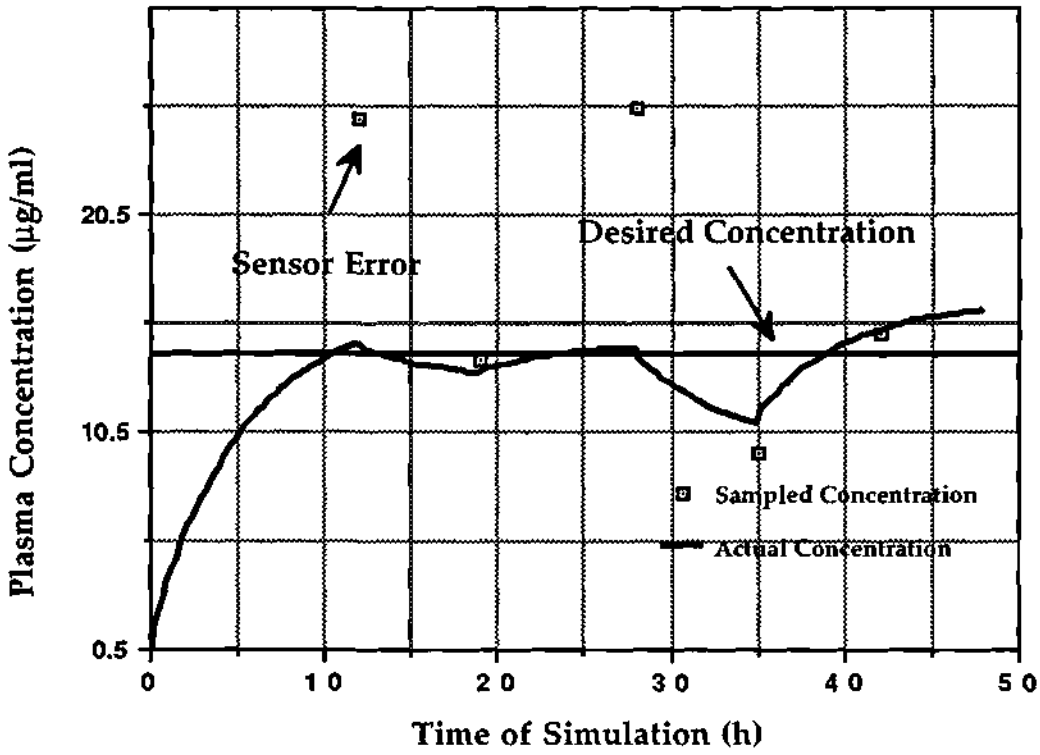

Figure 6.3 Controller Response with a Sample Evaluation Algorithm

In contrast, Figure 6.5, shows the performance of the same control algorithm after information about the patients age, weight, and condition have been used to determine the control parameters. The result is an improvement in the rate of convergence to the desired drug concentration. This improvement illustrates the importance of patient information to optimal control performance.

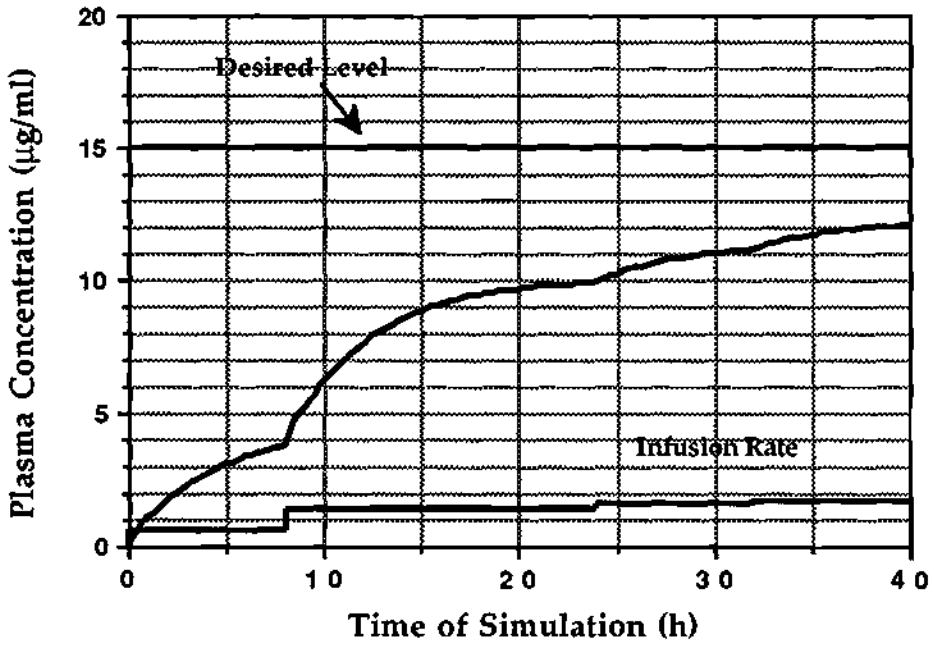

Figure 6.4 Control Performance without Proper Parameter Selection

Figure 6.6 is a plot of the control response and infusion rate changes that occur when the fuzzy logic controller is used with an algorithm to automatically adjust the sample rates. Here, the controller uses a smaller sampling rate during the initial stages of drug treatment. After the first few hours, the controller increases the delay between samples. The capability to dynamically adjust sample rates is important because drug samples are expensive and labor intensive to perform.

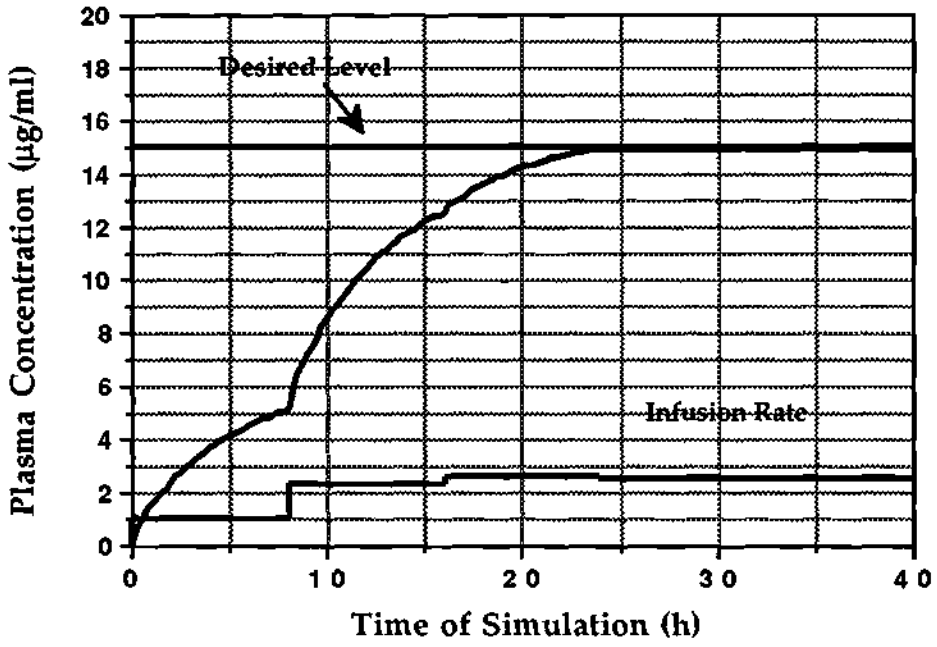

Figure 6.5 Control Performance with Proper Parameter Selection

The next group of figures are from simulations in which the controllers are used to administer theophylline to a simulated patient case. The test is based on the pharmacokinetic parameters of a pediatric patient that is 8 years old and has a weight of 25 Kg. The patient is assumed to be concurrently taking erythromycin (an interacting drug). The desired steady-state plasma concentration for the patient is 15 µg/ml.

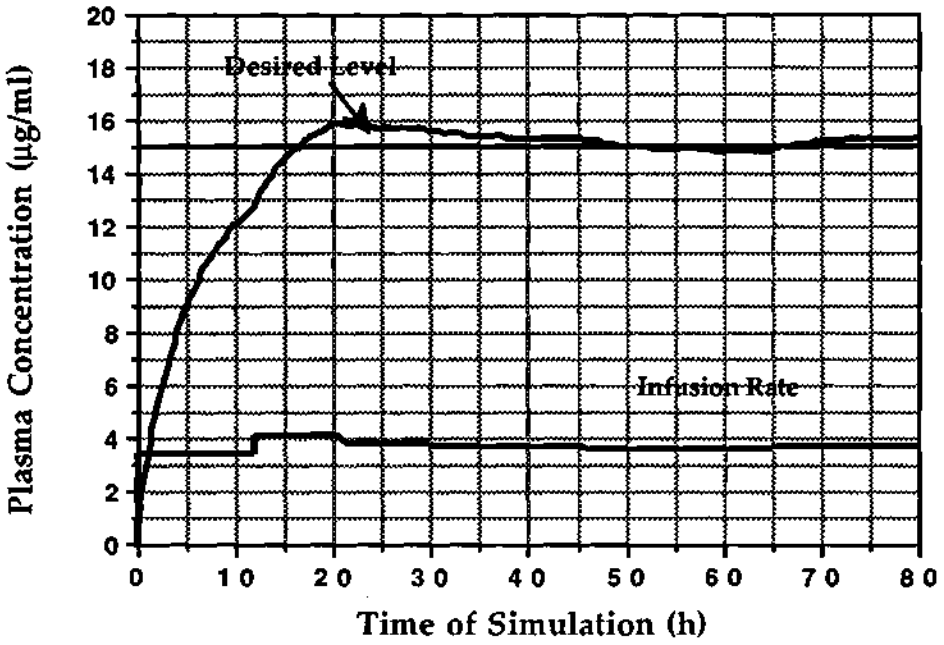

Figure 6.6 Sample Rate Adjustment in the Fuzzy Logic Controller

Errors in the laboratory measurement of theophylline concentrations in the laboratory are assumed to have a standard deviation of 0.3. The collection standard deviation is assumed to be 0.8. The theophylline sensor is selected to be detective (yields frequent and large sample errors). The steady state parameter errors are set to be at 90% of the sick and normal patient values respectively. Circadian variation in the clearance is set to occur at a period of 28 hours with a percentage variation of +- 20%. The transition between the normal and sick patient parameters is set to be delayed by 30 hours after the initiation of drug therapy and occurs over a time period of 12 hours (similar to an actual drug interaction).

The performance results of the discrete sliding mode controller with a fixed sampling rate of 6 hours are shown below in Figure 6.7.

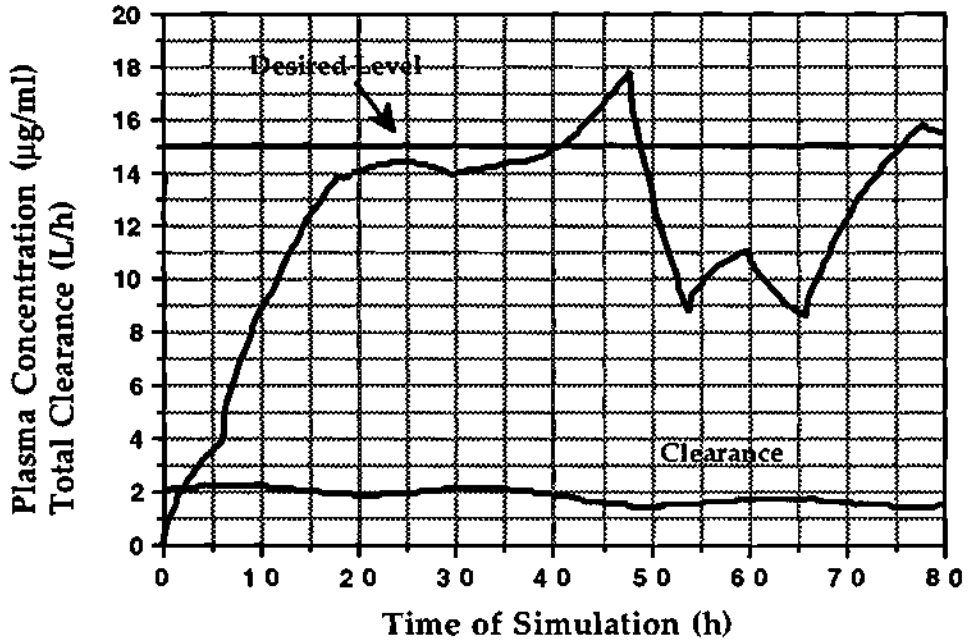

Figure 6.7 Discrete Sliding Controller (Sample Rate = 6 hours)

The large decrease in concentrations for the discrete sliding mode controller is the result of errors from bad sample points. The next three figures are simulations for the fuzzy logic controller response to the test case. Figure 6.8 is a simulation for the control response that occurs when the fuzzy logic controller is set to administer drug dosing conservatively.

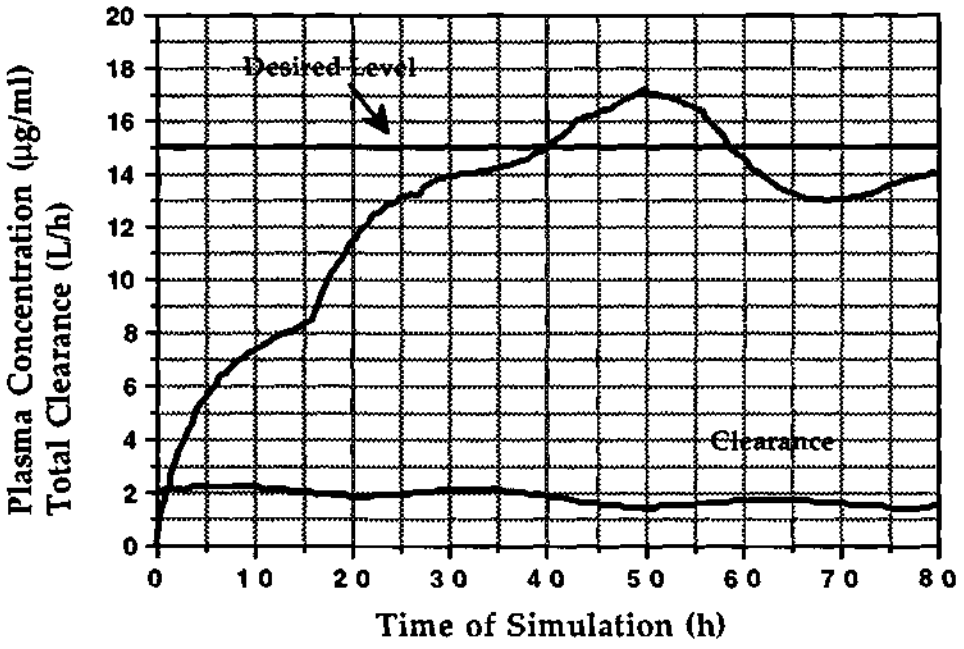

Figure 6.8 Fuzzy Logic Controller (Conservative Treatment Style)

The response time for the fuzzy logic controller is slower while operating with this style of therapy; however, the likelihood of patient toxicity is also reduced.

Figure 6.9 shows the simulation results for the controller while functioning with a moderate style of drug treatment, and Figure 6.10 corresponds to an aggressive style of drug treatment. These figures show that the more aggressive styles of drug treatment increase the peak drug concentration levels.

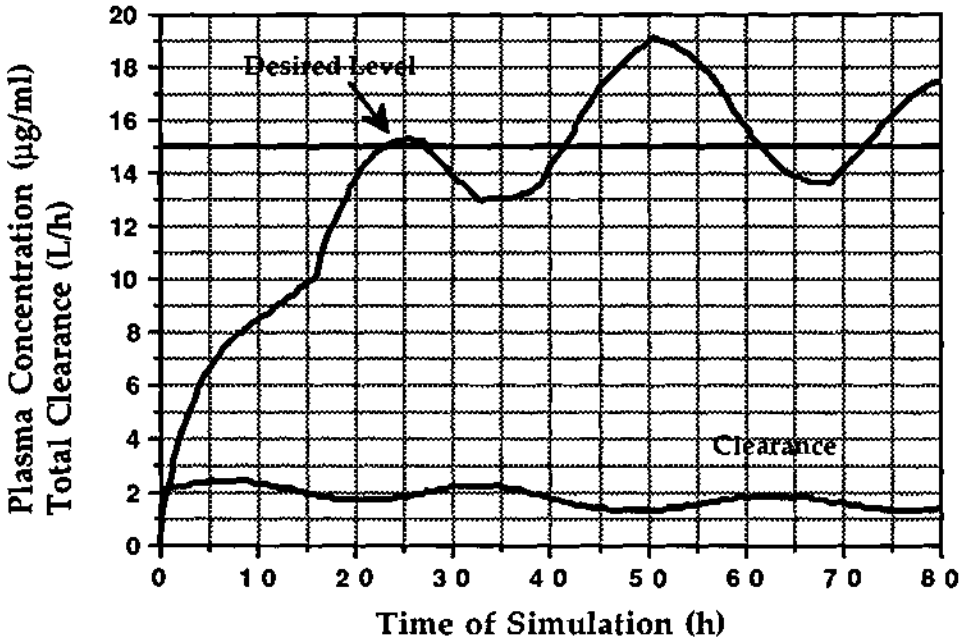

Figure 6.9 Fuzzy Logic Controller (Moderate Treatment Style)

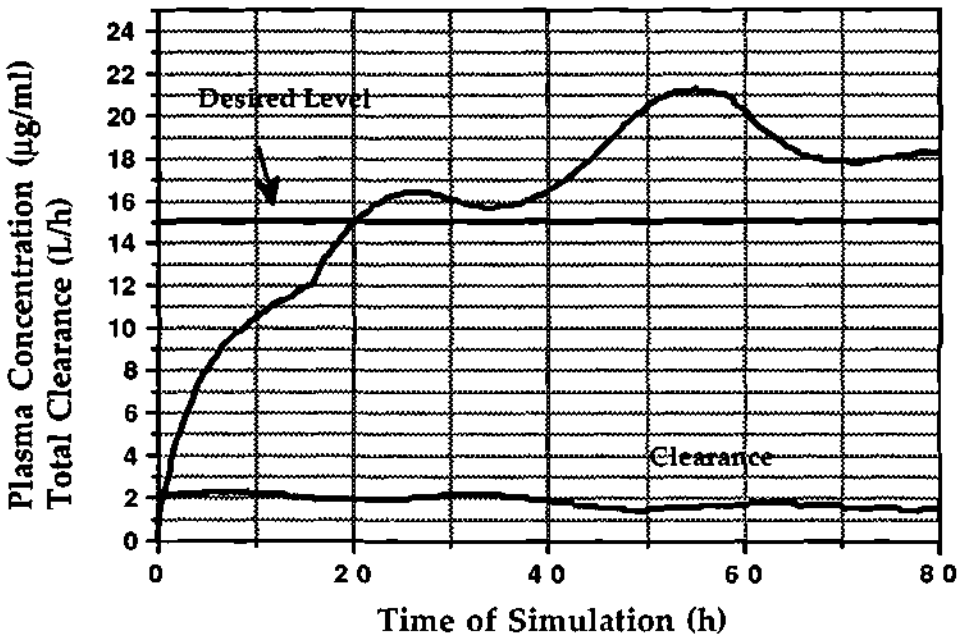

Figure 6.10 Fuzzy Logic Controller (Aggressive Treatment Style)

Figure 6.11 on the following page shows the simulation results for the intelligent discrete sliding mode controller. This controller achieves the desired concentration rapidly and maintains reasonable peak concentration values that are below 20 µg/ml.

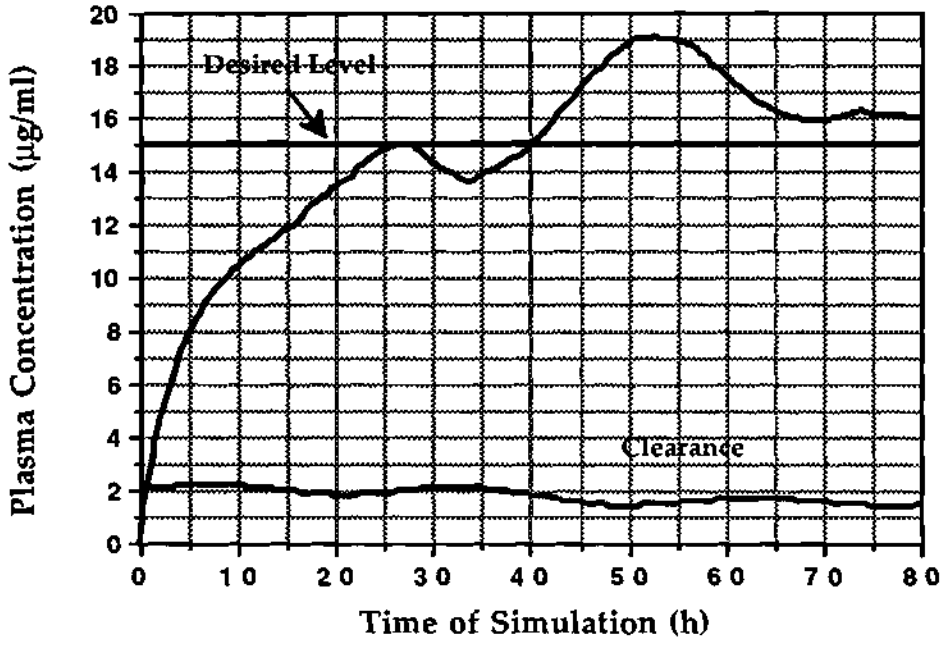

Figure 6.11 Intelligent Discrete Sliding Mode Controller

CHAPTER VII

CONCLUSION AND RECOMMENDATIONS

This thesis has focused on the development of a computer software teaching tool for theophylline kinetics and on the use of modern control techniques for drug administration. Special emphasis was given to developing an accurate model representation of theophylline kinetics. This model is based on the transport of the unbound portion of the drug and acknowledges that it is the unbound drug that is therapeutically important.

The simulation results from the drug administration controllers have demonstrated the importance of information such as disease states and drug interactions on improving the accuracy of drug administration techniques. The application of fuzzy logic has been shown to yield improved controller response, particularly in the case of large sensor errors which undermine traditional techniques.

Although the controllers that were developed implement some knowledge about the patient, considerably more information should be incorporated into future algorithms. For example, information about the severity of illness and temporal (time) relationships could also prove to be useful in improving controller response.

ENDNOTES

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