ABSTRACT

One area of medicine in which knowledge-based systems may improve day to day patient care is in the design of initial dosing regimens and dosage adjustment of certain drugs whose plasma levels correlate with their toxicity and/or efficacy. Since the general clinician is responsible for the appropriate administration of many of these drugs, a way must be found to enable these clinicians to rapidly determine the appropriate dose or dosage adjustment required to achieve the desired plasma concentration and thus the desired clinical effect. To obtain the best results, a good knowledge of pharmacokinetic principles is required as well as the facility to apply these principles easily and safely. In this study, the intention was to construct a knowledge-based system for the design of drug dosing regimens and to investigate issues relating to the design of such a system which will affect its' utility in general medicine. A multidisciplinary approach to the problem was adopted. A combination of standard pharmacokinetic modelling and artificial intelligence techniques was used to design a system suitable for use by the general physician. The approach was informed by ethnography with the design incorporating features seen as desirable by prospective users and a knowledge base with facts and rules related to the safe and effective use of the system. In addition, a more general method of pharmacokinetic parameter estimation than that employed in most current pharmacokinetic systems was investigated. In the clinical environment, there are a number of sources of error which may invalidate pharmacokinetic calculations. The most important of these being those associated with the incorrect preparation of doses and the recording of incorrect times of dosing and specimen collection. It was observed that current pharmacokinetic systems do not address these sources of error directly. A more general Bayesian approach which might be extended to incorporate these 'external' errors would be appropriate. The method investigated in the report is a Bayesian formulation of the Kalman filter. It was applied to the one and two compartment linear models and to the one compartment nonlinear model. These models being sufficient to cover the majority of drugs of interest in the general hospital setting. Kalman filtering is a general method for handling state-space models which gives optimal estimates of the current state of a dynamic system. It is commonly encountered in the field of control engineering but is also used in the analysis of time series. The method was shown to be adaptable in principle to pharmacokinetic parameter estimation and it is theoretically extendable to incorporate the external sources of error described above. The positive initial results presented in the report form the basis for ongoing research into the possible extension of the system and a formal assessment of user acceptance.

An Expert System as a Clinical Aid in the Administration and Dosage Adjustment of some Commonly Prescribed Therapeutic Drugs and Antibiotics.

by

Kevin John Botsman

A Thesis

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DECLARATION

To the best of my knowledge and belief, the work presented in this thesis is original except as acknowledged in the text. All sources have been cited and no attempt has been made to present the work of others as my own. The work has not been submitted, either in whole or in part, for a degree at this or any other University.

Signature Redacted

Kevin John Botsman

CHAPTER 1

INTRODUCTION

1.1 Background

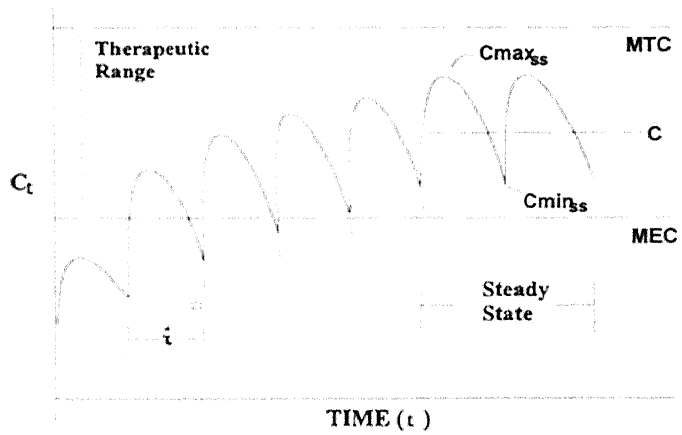
Computers have been used in medicine for a variety of purposes from their earliest days. Perreault and Wiederhold (1990) have identified eight different purposes said to define the basic functions provided by computer systems in medicine. These are: Data acquisition, data analysis, record keeping, communication and integration, surveillance, information storage and retrieval, education and decision support. Knowledge-based systems as decision support tools, are becoming common in many fields of human endeavour. They allow novice practitioners to function at a higher level within a particular area than might otherwise be expected. In medicine, there are a number of areas in which these systems might play an important part in improving the day to day treatment of patients. Unfortunately, for a variety of reasons, there are few, if any, knowledge-based medical systems in routine use [Hannan, 1991].

One area in which knowledge-based systems may improve day to day patient care, is in the design of initial dosing regimens and dosage adjustment of certain drugs whose plasma levels correlate with their toxicity and/or efficacy. To obtain the best results with such drugs, a good knowledge of pharmacokinetic principles is required as well as the facility to apply these principles rapidly and easily. In this study, the intention was to construct a knowledge-based system for the design of drug dosing regimens and to investigate design issues which affect the acceptance or otherwise of these

systems in general medicine.

1.2 The drug dosing problem

For a number of drugs commonly prescribed in the general clinical setting, there is a narrow margin between a therapeutic and toxic dose. In order to maintain adequate therapy and avoid toxicity, the concentration of the drug in the body must be kept above a certain minimum threshold and below the toxic threshold, see figure 1.1. This



MEC = minimum effective concentration.
MTC = minimum toxic concentration.

Figure 1.1 Typical plasma drug concentration-time profile. (multiple identical doses)

is often difficult for the novice practitioner to achieve, since a given dose of a drug

will often result in widely different drug concentrations in different patients even when these patients appear to have similar physical characteristics such as age, weight and gender. [Burton et al., 1985; Goodman Gillman et al., 1985].

Many of the drugs used routinely present no great problems, but the groups of drugs for which difficulties may arise include: the anti-convulsants, the anti-asthmatics, the cardiac glycosides and the aminoglycoside group of antibiotics. There is a significant but manageable number of drugs for which a solution to the problem of predicting the concentration of the drug in the body for a particular dose would contribute to improved patient care.

Since the general clinician is responsible for the appropriate administration of many of these drugs, a way must be found to enable these clinicians to determine rapidly the appropriate dose or dosage adjustment required to achieve the desired plasma concentration and thus the desired clinical effect.

1.3 An approach to the drug dosing problem

There have been a number of attempts to rationalise drug therapy. These attempts have included predictive nomograms and pharmacokinetic models which are described briefly below and discussed further in chapter 2.

Predictive nomograms were amongst the earliest attempts to rationalise drug therapy. They are essentially graphical descriptions of pharmacokinetic equations which are

used to determine appropriate doses based on average population values of the pharmacokinetic parameters. They tend to be inaccurate in that they fail to account for the large interindividual variation in response [Pechere and Dugal, 1979]. They are however simple to apply and are still used, though not very widely.

Computer programs using pharmacokinetic models have had considerable success and are becoming increasingly well regarded [Burton et al., 1985; Erdman et al., 1991; Pryka et al., 1991]. A pharmacokinetic model is a set of equations which contains both drug and patient specific parameters and which may be used to relate the drug plasma concentration at any time in a dosing interval to the dose given. A more complete description of these models is provided in appendix A. To be useful, a way must be found to estimate the patient specific parameters in the appropriate equations and apply them to design an individualised dosing regimen. The estimation is usually done using a few plasma drug levels and the equations applied in a computer program. This is still most often performed only in pharmacology or pharmacy departments and requires considerable expertise to produce reliable results. Few of these programs could be said to have achieved widespread utilisation in the routine clinical setting or be considered suitable for use by the general physician responsible for drug administration.

The proposed approach to the drug administration problem described in 1.2 above, is the development of a knowledge-based computer system which combines pharmacokinetic modelling, symbolic modelling of the patient, and knowledge related to the safe use of these drugs, in a way which meets the specific needs of the

practitioner in the routine clinical setting. This approach is the basis of the work described in detail in later chapters.

1.4 Methodology

An initial investigation was conducted in a representative clinical setting to confirm the desirability of such systems. This investigation took the form of a retrospective study on the efficacy of drug dosing methods currently employed. A prototype system was developed as a vehicle for further system development and the system was placed in operation to promote awareness and to provide a reference for a series of interviews with prospective users of the system. The interviews and observation were used as the basis for changes to the system designed to meet user needs. Interface design issues and problems relating to the mixed nature of the knowledge-base were also addressed and are discussed further later in the report.

In addition, a new approach to pharmacokinetic parameter estimation was investigated and finally incorporated into an advanced prototype system. This method which is based on the Kalman filter, has several advantages over other methods described in the literature and is in line with the design goal of providing a robust simple method requiring minimal input from the user.

A final prototype system was constructed which was designed to be expandable as to the knowledge base. It may serve as the basis for a commercial application.

1.5 Research themes

The purpose of this research was to investigate the design requirements of a computer based drug dosing system which would be suitable for use by the general physician. Initial observations suggested that many, if not all, of the current pharmacokinetic systems may be unsuitable for this purpose and that this may be due to deficiencies in the design process with systems not being designed for users with a limited knowledge of pharmacokinetic principles. In addition, a number of practical difficulties relating to such things as the requirement for accurate timing of specimen collection suggested that a different approach to model parameter estimation might be required. The two major themes of the research presented in this report are the emphasis on design for usability and a new approach to pharmacokinetic parameter estimation, the investigation being carried out in an action research situation within a hospital environment.

1.6 Definitions and summary

According to Bratko 1990, "an expert system is a program that behaves like an expert in some, usually narrow, domain of application." Classically, an expert system can be divided into three components: (1) a knowledge base (2) an inference engine and (3) a user interface. The knowledge-base consists of the knowledge specific to the domain. This knowledge may include various things such as simple facts or as in the drug system mathematical models and rules describing relationships between patient states and dose response. Since knowledge of the domain is integral to the correct

operation of the system, these systems are also called knowledge-based systems. Other terms commonly encountered are 'Advisory system' and 'Decision Support System'. The distinction between these terms is unclear. If there has to be a distinction then it usually has to do with the authority placed in these systems. Expert systems being the most authoritative, followed by knowledge-based systems, followed by advisory systems and decision support systems. All four usually have the capability of explaining their recommendations or decisions, to a greater or lesser extent. For the purposes of this report, these terms will be used interchangeably.

The term 'drug' also needs definition in the context of this report. In its broadest sense, a drug is "any chemical agent that affects living processes"[Goodman Gillman et al.,1985]. In this report, the term drug refers to a subclass of drugs, the therapeutic drugs and in particular, the further subclass of therapeutic drugs which may have toxic effects when dosed inappropriately and for which these toxic effects and/or the efficacy of the treatment may be related to plasma concentration or some other measurable change in body chemistry.

The following chapters contain a review of the relevant literature, the research methods employed and a history of the system's development, a description of the prototype drug system and the pharmacokinetic parameter estimation procedure, a discussion of the results of trials and finally the conclusions drawn from the research.

Refereed publications relating to the work performed are attached to this thesis.

CHAPTER 2

REVIEW OF RELEVANT LITERATURE

This chapter looks at the various systematic methods which have been and are currently being used to provide dosage guidelines for a variety of drugs. It contains a review of some of the literature relevant to the design of pharmacokinetic software and, in addition, it discusses the benefits which may be derived from widespread use of these systems and some of the legal and ethical issues related to this use.

2.1 Drug dosing methods

Drug dosing methods may be classified as either empirical or as based on the science of pharmacokinetics. Empirical drug dosing methods use standard doses or doses based on rules of thumb derived from physician experience. For some classes of drugs, such as certain analgesics and antibiotics, the empirical methods are satisfactory. However, for those drugs where the plasma concentration correlates with clinical response or toxicity, empirical methods are largely inadequate. There is considerable evidence of the generally poor correlation between drug dosing and the ability to achieve a specific serum drug concentration [Sheiner et al., 1979; Burton et al., 1985; Goodman, Gillman et al., 1985; Pryka, Rodvold and Erdman, 1991]. Numerous drug dosing methods have been tried in an attempt to improve this correlation. The latest attempts using pharmacokinetic models and modern adaptive control theory, also venture into the area of artificial intelligence with AI techniques being used to produce dosing guidelines in a way that is acceptable to the general physician.

"Pharmacokinetics deals with the absorption, distribution, biotransformation and excretion of drugs."[Goodman, Gillman et al., 1985]. It is these factors which determine the plasma concentration of a drug and the concentration at the intended site of action. Pharmacokinetic models, which are essentially mathematical descriptions of the time course of plasma drug concentration, have been used successfully for some years to design individualised dosing regimens. *A description of the mathematical basis of these models is given in appendix A.* The earliest methods for individualisation of drug therapy using pharmacokinetic principles, involved the use of predictive nomograms and algorithms [e.g. Chan et al., 1972; Tozer, 1974; Hull and Sarubbi, 1976]. These were notoriously inaccurate [Burton et al., 1985 and 1986; Pancoast 1988], being based on 'average' population values, but still better than empirical methods [Jelliffe, 1983]. Simple computer programs to implement algorithms based on pharmacokinetic principles were also developed at this time [e.g Jelliffe and Jelliffe, 1972], but suffered from similar limitations to those of the predictive nomograms. Jelliffe and Schumitzky (1990) and Buffington, Lampasona and Chandler (1993), have given interesting descriptions of the development history of pharmacokinetic software.

The availability of rapid and inexpensive drug assays made it possible to produce the adaptive pharmacokinetic models which used drug concentration data to adapt the model to an individual patient. These adaptive models were either deterministic or probabilistic in nature. The deterministic pharmacokinetic models [e.g. Sawchuk and Zaske, 1976; Sawchuk, Zaske and Cipolle, 1977] required several serum drug levels within a dosing interval to determine individual pharmacokinetic parameters by means

of simple linear regression analysis. These methods are generally quite accurate but suffer from several limitations in that they use drug levels in a single dosing interval, parameters are recalculated as new data becomes available and high and low data points are assumed known with equal precision. Thus they fail to use what is already known about the individual and are particularly vulnerable to inaccurate data points within a dosing interval [Jelliffe et al., 1991]. Weighted nonlinear regression analysis as used by Jelliffe in 1982 is somewhat more flexible, but generally requires more data points and also discards previous information.

Probabilistic models based on an application of Bayes' theorem were developed at approximately the same time as deterministic models. Bayesian models [e.g. Sheiner et al., 1972 and 1979; Kelman, Whiting and Bryson, 1982] use routine clinical data (age, height, weight, renal function), to provide initial estimates of the patient pharmacokinetic parameters. Then, by applying Bayes theorem and using maximum likelihood estimation, any number of serum drug concentrations may be used to refine the predicted parameters and the dosing regimen. The maximum a posteriori probability (MAP) Bayesian method, described by Sheiner et al. (1979), has the main advantage of being somewhat more flexible in that non uniform dosing schedules and serum levels may be used to refine the initial estimates.

While the Bayesian models have been shown to be accurate and have achieved some commercial success, current implementations do not really account for all the problems encountered in practice. Jelliffe et al in 1993, suggested that what is needed is to implement models in stochastic form, to allow for errors due to factors such as

model misspecification, incorrect preparation of doses and mistiming of administration and collection of blood samples for analysis. Jelliffe and Schumitzky in 1990 had previously described a 'new' method which they called Approximate Optimal Closed-Loop (AOCL) control. In this method, modern adaptive control methods utilising a general nonlinear stochastic system are applied to drug concentration data. The method is said to be superior to current methods in that it is able to actively learn about the system in the process of controlling it. The approach appears to have similar aims to that adopted in the system development which is the subject of this report. The mathematical basis of the approach used in the drugs adviser and some of the implications for further development are discussed in chapters 5 and 6.

2.2 Drug dosing systems

Table 2 gives a necessarily incomplete list of available drug dosing systems. The list focuses on clinical systems commercially available. It is necessarily incomplete as this is an active area of applied research with a number of systems being developed which have achieved a largely local following [Reidenberg, 1993, Buffington et al., 1993]. The commercial systems themselves are continuously being upgraded as trends change, the option of Bayesian parameter updating being a good example. Most of the commercial development has occurred in the last five to six years, mainly in the USA, although European development is proceeding apace. There are also a number of pharmacokinetic systems appearing in the literature, such as NONMEM, PC-NONLIN, MKMODEL, which have been developed as modelling programs and are not designed

SYSTEM	PARAMETER UPDATING	ORIGIN	STATUS
USC*PACK programs	Bayesian / Non Bayesian	USA	Commercial Time Share
Abbottbase PK System.	Bayesian / Non Bayesian.	USA	Commercial
SIMKIN Pharmacokinetic	Bayesian / Non Bayesian	USA	Commercial
KINETIDEX	Bayesian / Non Bayesian	USA	Commercial
DRUGCALC	Non Bayesian	USA	Commercial
MSMEDS Pharmacy info.	Non Bayesian	USA	Commercial included in large Pharm. system
MW/Pharm	Bayesian / Non Bayesian	Holland	Commercial
APIS	Bayesian	France	Commercial
OPT	Bayesian	UK	unknown
PEDA	Bayesian	Japan	research prototype.
MULTI(2)	Bayesian	Japan	Commercial

Table 2.1 Various Clinical Pharmacokinetics Systems, their country of origin and current status, where known.

primarily as clinical tools [Buffington et al., 1993], these also have not been included in the table, as this report is concerned with developing a system for clinical use. The remainder of this section discusses interesting aspects of some of the systems in the table and others.

A number of early pharmacokinetic programs were based on the traditional method of parameter estimation which uses simple linear least squares regression as described by Sawchuk and Zaske in 1976. This is the prototypical method based on the pharmacokinetic model. Much of the earlier work was done on the aminoglycoside antibiotics and is still relevant today. The method has been applied to various therapeutic drugs with suitable modification of the model and it is often used in 'in house' systems such as that produced by Kaka and Buchanan in 1983. These systems have been largely superseded by programs employing nonlinear least squares regression or Bayesian analysis.

The USC*PACK of programs [Jelliffe, 1982], generated considerable interest in pharmacokinetic programs. They were originally designed to operate on mainframe computer systems but were later adapted to the PC. These programs have been modified over time to include Bayesian parameter estimation and are the most widely used pharmacokinetic programs in the United States with some 650 installed systems in the US and internationally [Buffington et al., 1993]. The Abbottbase PK system [Moller, 1992] is the next most widely used system in the US and elsewhere and has been installed at several sites in Australia. New versions have been produced and although expensive to purchase, it may be supplied free of charge to sites using

Abbott products. These programs are usually found in pharmacy or clinical pharmacology departments and require considerable expertise to produce good results.

The KINETIDEX program listed in table 2.1, is part of a suite of programs to support clinical decision making. It is produced by Micromedex corporation [Micromedex, Inc. Denver USA, 1974 - 1993] and supports the largest number of drugs of any of these systems. Along with SIMKIN, it has the interesting feature of providing for selection of clinical factors which the program will use to adjust initial pharmacokinetic parameters. This approach has been extended by Lenert et al. (1992) in their design of a prototype system which they call the Aminoglycoside Therapy Manager (ATM). The ATM uses a combination of Bayesian pharmacokinetic modelling and symbolic modelling of the patient to produce dosing and therapeutic monitoring strategies. The symbolic model of the patient is generated from clinical data provided by the user in response to questions from the system. A similar approach has been adopted in the Drugs Adviser. It is important in systems designed to be used by those with limited expertise in pharmacokinetics.

Pharmacokinetic software may also serve as a useful teaching tool [MacFadyen et al., 1993] and some systems have been designed with this in mind. The APIS system [Iliades et al., 1992] was designed to assist clinicians in optimizing drug therapy, but also includes simulation facilities which allows the user to investigate the appropriate model for a particular drug. This obviously requires a reasonable knowledge of pharmacokinetics and may in fact be used to illustrate pharmacokinetic principles. APIS has been used successfully in this teaching role at the University of Marseille

for some time.

Another of the more recent systems applying the Bayesian method is PEDA [Higuchi et al., 1987]. Using appropriate pharmacokinetic models this systems has been extended to include a variety of therapeutic drugs. It has been successful, mainly in the research setting, and is said to have similar accuracy to the deterministic pharmacokinetic methods. Interestingly, practicality in clinical use was one of the design criteria for PEDA . This was an attempt to improve on perceived weaknesses in this area of the Bayesian MULTI [Yamaoka et al., 1985] and raises the general question of system design.

Finally, this section would not be complete without some mention of one of the best known antibiotic dosage advisory systems, MYCIN [Bennett and Scott, 1980; Buchanan and Shortliffe, 1984]. This system uses a built in knowledge base about infectious diseases and susceptibility to antibiotics, together with patient specific data to customise dosages. The patient pharmacokinetic parameters are estimated from patient data such as renal status, height and weight. These are then used to graph the probable time course of drug levels for a given dosage regimen using a basic pharmacokinetic model. It thus precedes the adaptive models and has not been included in table 2.1. It does, however have several interesting features, the most striking of these being the capability of explaining program recommendations in response to simple questions from the user. The questions of explanation and practicality in clinical use lead to consideration of more general design issues in the next section.

2.3 Design issues

Medical artificial intelligence has begun to move from the research laboratory into clinical settings [Shortliffe, 1987; Spackman and Connelly, 1987; Wiener et al., 1989]. With this move, there has been a growing emphasis on logistics and design so that medical personnel would be encouraged to use the systems and come to regard them as helpful rather than a hindrance or threat. There seems to be an inherent resistance by physicians to the use of computers in clinical practice , often mentioned or at least alluded to in the literature [Shortliffe, 1986 and 1987]. However, at least one study suggests that physicians believe that assistance from computer based advisory systems will ultimately be of benefit to medical practice [Teach and Shortliffe, 1981] and a recent survey of medical students at one Australian medical school concluded that "the perceived importance of computing in medicine was high among all students and there was enthusiasm for the development and inclusion of a course on medical computing in the undergraduate curriculum" [Kidd et al., 1993].

It does seem clear that in order for medical advisory systems to fulfil their promise, a greater emphasis must be placed on those aspects of system design related to usability. The main design issues which any developer has to confront are those relating to the design of the interface, the provision of appropriate explanation facilities, the ability of the system to handle uncertainty and system validation. Some current ideas on these issues are discussed below.

2.3.1 The user interface

One important factor that can influence physicians to accept or reject a system is the quality of the user interface [Shortliffe, 1987; Buffington et al., 1993]. Many programs have been written with the ability to produce accurate results, but few have gained widespread acceptance. This is clearly due to the fact that the production of results is only part of the requirements for success. Shortliffe (1987) has called these other requirements 'Human Factor Issues' and further subdivides them into Logistical, Mechanical and Psychological. Logistical issues cover such things as physical access to the system, the requirement to re-enter patient information each time the system is used and the time it takes to start the system. Mechanical issues involve the mode of interaction with the system. The interaction may be via keyboards, mouse devices, touch screens, voice interfaces or some other means. Psychological issues relate to the way in which the user interacts with the system. For instance, the content and appearance of what is shown on the screen will affect the way the user feels about the system and whether or not it will be used. Bankowitz et al., (1989) have concluded that "they must incorporate man machine interfaces suitable for use by physicians and be as convenient as making a phone call to a colleague". Most current systems either fail to address these issues at all or use outdated interface designs.

Shneiderman (1987) provides useful guidelines for designing the interface. The interface must be designed to meet the needs of the users and to suit their level of expertise. There are a number of different types of interface. These include, menu systems, command language interfaces and natural language interfaces. Natural

language interfaces are difficult to construct and may be too slow for practical use although voice command systems may make them more acceptable. A similar objection applies to command interfaces where instructions have to be typed into the system using some kind of command language. The WIMP (Windows, Icons, Menus and Pointers) interface is a generalised type of menu system which has become standard in modern software. The WIMP interface design is flexible and easy for inexperienced users to learn. Furthermore, WIMP interfaces tend to have the same 'look and feel' which makes for consistent screen formats within and across applications. Linear sequences of menus are also a simple and effective way to guide a user through a complex task [Shneiderman, 1987; Chignell and Waterworth, 1991]. Of the different types currently available, the WIMP interface seems the most suitable for medical decision support software.

2.3.2 Explanation

One of the more important elements relating to the human factor issues in medical advisory systems, is the ability of the system to explain the basis of the advice given with justifications as required. The problem of providing appropriate explanation is one which occurs in all expert system applications and what constitutes appropriate explanation is both domain and user dependent. Explanation and interface design are closely linked. The design of the interface will affect the way in which the explanation is presented and its acceptability.

Chandrasekaren, Tanner and Josephson (1989), in an introductory review of work in

this area, decomposed the explanation problem into three top-level components. These components are distinguished by:

1. How the problem solver represents its activity and retrieves relevant portions appropriately in response to queries from the user.
2. How a user's goals, expertise etc. are used to shape the output so that the explanation is appropriate to the particular user.
3. How appropriately and effectively the interface displays information to the user.

They also contend that the first component above is central to the main task and itself has three components. These explanations of problem solving are:

1. Explaining why certain decisions were made or were not made.
2. Explaining the elements of the knowledge base itself.
3. Explaining the problem-solving strategy.

These different types of explanation provide a useful classification of one aspect at least of the explanation problem.

For explaining problem solving, Chandrasekaren et al.(1989), outline a theory of problem solving types and describe a representation of deep models of a domain. Their idea is that there are "generic tasks in knowledge-based problem solving" and that by using these generic tasks as a framework for system design they will be able to produce explanations which are closer to the conceptual level of the user. The approach was implemented in a mission planning assistant (MPA) prototype.

Medical systems have provided some of the best known practical applications of

explanation. In MYCIN, [Bennett and Scott, 1980], the basic explanation facility used to justify the systems' recommendations came from responses to the classical How and Why questions. Should the user ask the system Why a particular question was asked, the response is provided as a list of rules which the system is trying to prove and if the user asks the system How a conclusion was reached then the system lists all the rules invoked in the proof. Thus, while adequately addressing the type 1 explanation described above, MYCIN was unable to explain the strategies it was using in solving a particular problem or justify its rules (explanation types 2 and 3 above). In NEOMYCIN, [Clancey, 1983], the explanation facility was extended to include additional diagnostic operators which represented the diagnostic strategies employed and which could be used to explain these problem solving strategies to the user. Thus NEOMYCIN addressed the type 2 problem above but was still unable to explain the elements in the knowledge base. In the XPLAIN system ("explainable expert systems"), Swartout (1983) described the use of an explicit recording of the design process to build systems which are able to use general domain knowledge. Two main types of knowledge, factual and problem solving methods were recognized. By means of appropriate mappings, explanations at different levels are provided. The XPLAIN system uses a "domain model" and a representation of problem solving strategies called "domain principles", which may be used to justify the system's rules and its behaviour.

Model-based expert systems utilise a different paradigm from that of classical expert systems [Widman and Loparo, 1989]. Classical expert systems use production rules and frame-based knowledge representations while model-based systems contain

symbolic models of the domain which are descriptions of the structure of the domain and the principles which control its behaviour. These structural descriptions and domain principles are often referred to as "deep" knowledge as compared to the "shallow" knowledge contained in the classical systems. Models may be characterized in many different ways. Most often, the classification is by means of the application area they are being used to describe. In model-based expert systems, the models are most often described as symbolic models which contain objects, relationships between objects and object attributes. This is somewhat vague as many terms appear to have multiple meanings in the literature and there is considerable overlap between model types [Rothenberg, 1989]. Potentially, model based systems are able to provide more detailed explanations than the classical rule based systems but generally require considerable investment in interface design to extract maximum benefit [Kunz, Stelzner, Williams, 1989; Miller and Larson 1992]. Teach and Shortliffe (1981) noted that one of the requirements for clinical systems is that they exhibit common sense. In a prototype system modelling the water balance mechanism of the kidney, Kuipers (1989) describes a qualitative model based system which is said to exhibit a "type of common sense" in that it is able, by means of suitable constraints generated by a method referred to as "abstraction by time scale", to distinguish clinically undesirable courses of action which may however have produced a solution.

The issue of transparency is closely related to the issue of appropriate explanation. Knowledge based systems should be transparent [Smith J.D., 1991]. That is, the users and experts, should be able to verify the knowledge being used, whether it be tables, equations, diagnostic profiles of a disease, or some other. The reasoning being applied

to a particular case should also be transparent to the user. Thus the use of a graphical concentration time profile in pharmacokinetic systems which provides a rapid visual check on the likely validity of the recommendations and, indeed, why these recommendations were produced. Transparency thus requires that the knowledge being used must be accessible to the user, verifiable by the expert and capable of being updated as required.

Much of the work on explanation presented above has remained largely theoretical. There is no standard way of providing appropriate explanations and several methods are commonly used including simple text justification, graphical representations where appropriate and response to the standard How and Why questions as used in MYCIN. Text justification with 'reference to higher authority' is widely used in the medical domain. For example, ANABEL, a system for the interpretation of arterial blood gases, [Zarkadakis et al., 1989], uses a 'semantic trace', natural language text which explains the system's reasoning and justifies the interpretation. The KINETIDEX drug dosing system provides literature references, access to the pharmacokinetic equations and a plot of the predicted concentration-time data as justification for its calculations and recommendations. Whatever the method used, it seems that some sort of justification for the recommendations is mandatory if a system is to be widely used by physicians.

2.3.3 Learning and uncertainty

A further issue in the design of clinical decision support system is the problem of

dealing with uncertainty. Uncertainty occurs when the knowledge-base is incomplete, when data which is not completely known is used or when stochastic relationships between propositions exist. In these situations, classical probability theory is often inappropriate or simply cannot be used and other methods are applied [Spiegelhalter, 1986].

A number of alternatives to classical probability theory have been proposed. These include: Certainty theory as used in MYCIN, the Dempster-Schafer theory of evidence and fuzzy logic. Castillo and Alvarez (1991) provide a useful introduction to these theories. Certainty factors combine measures of belief and unbelief in a given hypothesis due to some known information or evidence. The hypothesis may be the presence of some disease state and the evidence, the presence or lack of some symptom. The certainty factors may then be propagated according to consistent laws derived from the original definition. The Dempster-Schafer theory of evidence uses two measures of uncertainty, a belief function and plausibility and fuzzy logic uses another measure of probability called possibility.

Unfortunately, the use of these alternatives to probability theory carries its own risks. Most seem to agree that, where appropriate, probabilistic techniques should be used. The aim of expert systems in medicine and other areas, is to propagate human knowledge not human errors. In hybrid systems such as some pharmacokinetic systems, more than one method may be used. Classical probability theory (Bayesian) may be used to estimate pharmacokinetic parameters and predict the time course of plasma drug concentration. Confidence intervals may be derived and deviations from

expected values may provide evidence of poor timing of sample collection or possible changes in the patients' state. However, if the system includes advice on appropriate drug levels, then other uncertainty measures may need to be used.

In areas where knowledge is incomplete or incomplete data is provided to the system, it would be desirable for expert systems to learn from past experience. There are a multitude of ways in which computer systems may learn from experience or data. Some of the methods used in various systems include linear discriminant analysis, neural network techniques, nearest neighbour techniques and decision tree methods. There are a number of useful texts discussing these various techniques [e.g. Castillo and Alvarez, 1991; Weiss and Kulikowski, 1990]. Interest in the use of Neural networks in medical systems appears to be increasing [Sharpe et al., 1993] and their application in pharmacokinetics is being explored [e.g. Veng-Pedersen and Modi, 1993; Hussain et al. 1993]. Pharmacokinetic systems using statistical techniques to estimate an individual patients' pharmacokinetic parameters from data supplied by the user may also be said to learn. There has been considerable effort to improve population parameter estimates of pharmacokinetic parameters from data gathered directly from patients receiving drugs of interest [e.g. Sheiner, 1984 and 1992], but no examples of pharmacokinetic systems incorporating this type of learning could be found. The relatively new AOCL control methods discussed above indicate that the ability for a system to learn is considered as a possible solution for some of the problems related to everyday use of pharmacokinetic systems.

2.3.4 Evaluation

For expert systems, there does not seem to be any generally recognised definition of what 'evaluation' means. Hollnagel (1989) considers expert system evaluation to comprise assessment of three different aspects of the system. The first is the systems reliability, the second its validity and the third its usability. These terms are defined as follows: Reliability involves software engineering and knowledge-base verification, in the sense that given the same input, the same output is always produced. Validity refers to whether the system produces the results it should and usability refers to the ease with which the user can apply the system to the problem it is designed to solve. Others use slightly different definitions and categories [e.g Liebowitz, 1986]. However, it seems clear that evaluation must be considered throughout the design process and that issues such as transparency, sensitivity and interface design need to be considered from the beginning.

Evaluation and validation of clinical decision support systems is a particular area of concern since their application is often in areas of critical care. A number of approaches have been proposed for knowledge-base verification [e.g. Perkins et al., 1989] but, as for advisory systems in general, there are no well accepted general techniques for overall evaluation of clinical software. Buffington et al. (1993) reviewed various pharmacokinetic systems commercially available in the USA and provided guidelines for choosing appropriate software. Witbeck and Brooks (1983) have provided guidelines for evaluation of software for clinical decision making which may be adapted to pharmacokinetic systems. Several features are seen as highly

desirable. Full descriptions of the mathematical models used should be provided and the validity of these models thoroughly tested both retrospectively and where possible prospectively. For novice users, the system should provide the correct model to be used for each drug. It should be made clear that 100% accuracy and reliability is not achievable and the user should be made aware of the limitations of the system at each session, particularly those factors such as age and disease state of the patient which are likely to affect the results of calculations. The users must also be made aware that theirs is the final responsibility and that the use of such a system is no substitute for sound clinical judgement.

2.4 Benefits and cost-effectiveness

Therapeutic drug monitoring (TDM) which provides the basis for the development of pharmacokinetic software has been well established in clinical practice as a means of improving patient care, but its benefits are by no means universally accepted [e.g. McCormack and Jewesson, 1992; Cantú et al., 1993]. There is also evidence that TDM is being misused, with some studies showing 40 percent or more drug assay results either ignored or misapplied in dosage adjustment [Travers, 1987]. Not all drugs are suitable candidates for TDM and the timing and number of specimens collected are important considerations in the interpretation of drug levels [Bochner and Tonkin, 1993]. Appropriately designed pharmacokinetic software may be beneficial by reducing the incidence of misuse of TDM and providing a rational basis for individualisation of drug therapy. In a prospective audit of an aminoglycoside consultation service, Li et al. (1992), concluded that the introduction of the service

"had a positive impact on the effective use of aminoglycosides". There was a significant reduction in toxicity and a significant reduction in the number of uninterpretable assays performed. In addition, there was a reduced, but not statistically significant, number of aminoglycoside courses judged clinically inappropriate.

The accuracy of well designed pharmacokinetic software in predicting serum drug concentrations and designing effective dosing regimens is well known [Burton et al., 1985]. The cost-effectiveness of these systems is less easy to demonstrate [Vozeh et al., 1987]. Burton et al. (1991) performed a controlled trial of the cost benefit of computerized aminoglycoside administration and demonstrated a significant improvement in response rates in the test group with a concomitant reduction in the length of stay in hospital. On the basis of this reduced length of stay, it was concluded that a potential cost saving of $1311 per patient was achievable. There are few such studies in the literature and more are needed to firmly establish and quantify the cost-effectiveness of pharmacokinetic systems.

There are not many examples in the literature of medical support systems undergoing clinical evaluation. If any medical decision support system is to gain general acceptance, then it must undergo extensive evaluation in a clinical setting. For pharmacokinetic systems to gain widespread acceptance, the end result of such evaluations will have to be that there are clear benefits to be gained in the areas of patient care and/or efficiency which generally equates to dollars. Drug dosage systems have been in development for almost 20 years and while TDM has become well established in clinical medicine, the tools for correct interpretation of assay results are

less well accepted. Systems such as that proposed in this report, focussing on usability, may go some way towards correcting this deficiency.

2.5 Legal and ethical issues

The legal principle which governs the use of pharmacokinetic software is still unclear. Up to the present, there has been no litigation surrounding the use of these systems but this does not guarantee that a manufacturer or user will not be held liable for some perceived harm caused by one of these systems at some time in the future [Schwartz and Fink, 1989]. The pivotal concern seems to be whether or not such a situation will be viewed under negligence law or product liability law [Miller et al., 1985]. Negligence law means that a product must meet reasonable standards of safety. Product liability law on the other hand requires that a product must not cause harm. Since clinicians are subject to negligence law, it seems unreasonable to apply higher standards to decision support systems and the present view is that negligence law would apply. The United States Food and Drug Administration at present has no plans to regulate systems in which the physicians judgement can override the system's recommendations [Young, 1987]. The eventual determination of which legal principle applies, will have important implications for the acceptance of decision support tools by physicians.

The inverse question to that of the liability of the manufacturer or user was proposed by Shortliffe in 1987. Is a physician who does not use a program liable if the programs advice might have prevented an adverse outcome? Shortliffe considers the

answer would be that she would if the use of such a system had become the standard of care in the community.

Another interesting question that often appears is who should use such systems? The major concern seems to be that the user may not be trained to operate the system safely [Miller et al., 1985]. Some feel that only those with a thorough understanding of pharmacokinetics should use pharmacokinetic based systems [e.g. Buffington et al 1993]. This seems to ignore the potential for improving the general clinicians performance in this area by means of the experience gained while using these systems and ignores the fact that the general clinician is ultimately the one responsible for the safe and effective use of the drug. In addition, several 'in house' systems such as that described by Vozeh et al. (1984 and 1985) are used successfully by clinicians. Provided the system has been thoroughly tested and appropriately designed, there seems no reason why it should not be used by the general physician.

2.6 Summary

This chapter reviewed various drug dosing methods which have been used and aspects of system design related to producing a drug dosage advisory system for general use.

Pharmacokinetic systems are currently commercially available and are used successfully at a number of sites. The Bayesian, adaptive control systems appear to produce the best results and appear to be more suitable for use in the clinical environment than systems using deterministic pharmacokinetic parameter estimation

methods. There are few, if any, systems which have been designed for use by the general physician.

A number of issues relating to systems for general use were also discussed. These included: design of the user interface, types of explanation, validation and evaluation and legal and ethical issues. These issues have been addressed in various clinical advisory systems but do not appear to have been adequately addressed for pharmacokinetic systems.

Use of pharmacokinetic systems also appears to have benefits in terms of cost savings and improved patient care.

CHAPTER 3

SYSTEM DESCRIPTION

This chapter describes the structure and purpose of the prototype Drug Dosage Adviser. It includes a description of the contents of the mixed knowledge base and describes aspects of the program structure designed to allow for ease of maintenance and expandability.

3.1 Purpose

The Drug Dosage Adviser is designed to produce dosing recommendations for some commonly prescribed therapeutic drugs and antibiotics. It uses plasma drug levels to derive an individualised pharmacokinetic model of the patient which may then be used to modify the amount of drug being given to produce the desired drug levels. In addition, it uses clinical knowledge, in the form of facts and rules, to suggest appropriate drug levels for the individual patient and to provide additional information related to safe use of the drug. As explained in the introduction, this is not a trivial problem in medicine and it has attracted considerable research efforts. The unique aspects of the Dosage Adviser in this area are its design for usability and a new approach to individual pharmacokinetic parameter estimation. The system produces an initial dosing recommendation by applying the appropriate pharmacokinetic model using population based estimates of the pharmacokinetic parameters rather than individual values. These population estimates are then updated or individualised, as plasma levels become available. The antibiotic drugs gentamicin and vancomycin and

the anticoagulant drug, heparin, were chosen for the initial implementation of the system as they are used extensively in the general clinical setting and may be modelled by the one compartment, two compartment and non linear models, respectively. These models are sufficient to cover the majority of drugs of interest.

3.2 System overview

The operation of the system was designed to be largely intuitive. The system operates in the Windows environment, [Microsoft Windows version 3.1, Microsoft Corporation, Washington, USA 1991], which provides a standard user interface with a consistent look and feel and which is familiar to most potential users. Within this environment, the operation of the system was kept simple with few choices of action required at each stage in a consultation. This supports the requirements of simplicity and ease of operation expressed by potential users. The system is menu driven with extensive use made of popup dialogue windows and single choice menus. The necessity for typing was avoided as much as possible although a small amount of alphanumeric data entry for drug levels, times of sample collection and patient demographics is required.

The system was constructed in Edinburgh standard Prolog. LPA Prolog, [LPA 386-PROLOG version 2.600, Logic Programming Associates Ltd, London, England, 1994], is the particular vehicle. All dialogue windows and popup menus were written using the available Prolog GUI (graphical user interface) predicates. The code for pharmacokinetic parameter updating is written directly in ANSI C and loaded as a DLL (dynamic link library) for access by Prolog.

The general architecture employed [Smith J. D. 1991] is described in figure 3.1. This is an idealised view and the distinction between the navigation program and the inference program in this implementation, is not as sharp as it appears in the figure. However, the outline was followed as closely as possible to allow for ease of maintenance, particularly when expanding the system to handle additional drugs.

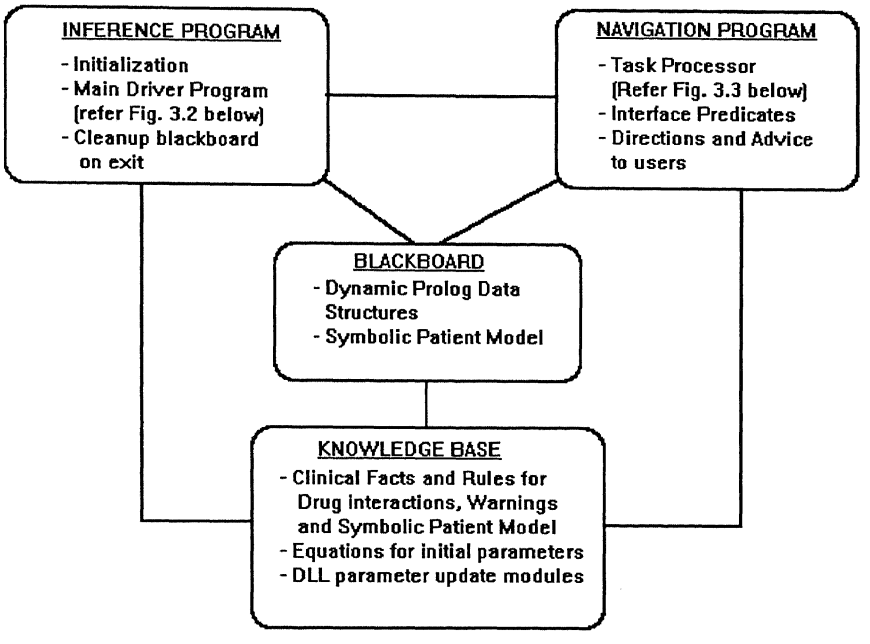


Figure 3.1 Architecture of the Drug Dosing System. A Blackboard Structure

The results of a consultation and patient demographics may be stored or retrieved from the hard or floppy disk. A graphics function is available to enable the user to plot past or forecast drug concentration data and there is a help function which includes an introduction to the system with a description of basic system operation. Data validation and consistency checks are applied where appropriate in the interface predicates. There are additional consistency checks applied to drug concentration data

entered by the user. These checks which may be used to provide warnings about suspected errors in collection or timing of samples are described in greater detail in chapters 4 and 5.

Further discussion of the individual system components is presented in the sections which follow.

3.3 Navigation and inference

The inference program or main driver program uses a 'failure driven loop' to process a group of Prolog predicates which together are capable of deriving everything which needs to be derived from the knowledge base. Figure 3.2 describes the code structure used (for the non specialist reader of figure 3.2, unfamiliar with Prolog, a word starting with an uppercase letter is a variable and variables get their values from the user or from other Prolog predicates. For example, the Prolog predicate "choosedrug(Drugstatus,Drug)", obtains the current value of "Drug" and "Drugstatus" by direct input from the user or from a global data structure called the blackboard, see 3.4 below). At the start of a consultation, the user must choose from a main menu which of several main tasks is to be performed. Depending on this choice, a particular group of Prolog predicates are called sequentially. They determine the initial system state. This state is communicated to the navigation program via the blackboard which further interacts with the user to refine the state and generate a solution. The main driver program also handles initialisation of the system and cleanup on exit.

```
solve:-
        repeat,
        data_cleanup,

        select_task(Task),

        ( Task == calculate_a_dosing_regimen,

                get_consult_status(Patstatus,Drugstatus),
                choosedrug(Drugstatus,Drug),
                obtain_patient_data(Patstatus,Patient),
                start_or_adjust_dose(Start_or_update),
                route_of_administration(Drug,AdmRoute),
                task_list(Drug,Task,Start_or_update,AdmRoute,Tasklst),
                process_tasks(Tasklst),
                fail
% OR
        ; Task == predict_levels,

                get_consult_status(Patstatus,Drugstatus),
                choosedrug(Drugstatus,Drug),
                obtain_patient_data(Patstatus,Patient),
                get_parameter_status(Drug,Drugstatus,Paramstatus),
                    route_of_administration(Drug,AdmRoute),
                task_list(Drug,Task,Paramstatus,AdmRoute,Tasklst),
                process_tasks(Tasklst),
                 fail
% OR
        ; Task == plot,

                plot_conc_profile,
                fail
% OR
        ; Task == quit),

                cleanup.
```

Figure 3.2 Structure of the main driver program for the Drug Dosage Adviser.

There are certain operations common to each main task. These include obtaining patient information, choosing the drug and determining whether an initial dosing regimen or an adjustment to a current dosing regimen is required. The solutions to these intermediate goals determine the initial state of the system. The navigation program obtains this initial state from the blackboard and uses this and other information obtained from the user to refine further the state on the way to a solution. Interaction with the user is by means of popup dialogues containing single choice menus or edit fields for text and/or numeric data.

The navigation program is a modification of an idea presented by Coulston, Smith and Tilley in 1992 and is described in figure 3.3. It consists of a task processor which operates on a list of tasks to determine a solution. Individual tasks are Prolog predicates which calculate intermediate results or provide for interaction with the user to refine the system state. The task list processed is uniquely determined by the initial system state. Intermediate results produced by the navigation program and stored on the blackboard may be used by other tasks in the list to generate the final solution.

After the navigation program has completed its tasks and displayed a solution, control is returned to the inference program which searches for major adverse drug interactions and suggests appropriate monitoring strategies, depending on the system state. When the main task is complete, logical failure returns control to the main menu from which further inference can proceed or the consultation can be halted.

The navigation program must be sensitive to the users requirements and thus contains

most of the interface code. The main driver program also needs to interact with the user initially so that it also contains appropriate blocks of code for this purpose. The user interface is thus provided by the navigation program and certain elements within the inference program. The inference program must also perform problem solving using the different types of knowledge available. It generates intermediate results

```
/* TASK PROCESSOR */

process_tasks([ ]).

process_tasks([Task | Rest_of_tasks]):-
        call(Task),
process_tasks(Rest_of_tasks).

/* TASK LISTS */

task_list(`Gentamicin`,calculate_a_dosing_regimen,start,ivr,
        [advise_requirements(gentamicin,start,ivr),
         renal_function,
        initial_parameter_estimates(gentamicin,start,ivr),
        calc_dosing_regimens(gentamicin,start,ivr),
         report_recommendations(gentamicin,start,ivr),
        report_warnings(gentamicin,start,ivr)] ).
```

Figure 3.3 Navigation program - A task processor and a list of tasks.

which may be used by other tasks within the navigation program or by the main driver program. This structure is characteristic of blackboard systems and serves to differentiate them from the 'classical' expert system which has a more rigid structure

of separate inference engine, knowledge base and user interface. Ease of maintenance and perspicuity are not compromised however due to the structure of the navigation program and the main driver program. An individual task within a navigation list for a given system state, may be modified or have its order changed quickly and simply. The inference program itself is less than 50 lines of code and so straightforward to maintain.

3.4 The blackboard

The program must keep track of the consultation, noting intermediate results which may have to be changed or results of actual problem solving such as initial pharmacokinetic parameter estimates or later updated parameter estimates. This is done on the blackboard [Nii 1989; Schwartz and Sterling 1992]. Intermediate results may be asserted as simple Prolog facts or rules.

Blackboard system is a generic term which covers different types of systems with a variety of program structures. The basic characteristics of a blackboard system are: First, the knowledge base can be separated into different modules each containing a particular knowledge representation and which may or may not have its own inference program. Second, the different knowledge modules produce changes to the blackboard, a global data structure, which leads incrementally to a solution.

The drug system was constructed as a type of blackboard system. The final solution is generated serially in a manner controlled by the navigation and inference programs.

Some of the advantages of the general blackboard architecture are lost by using the serial approach, but it is a practical method which retains the advantages of the blackboard model in handling different styles of knowledge representation while acknowledging the limitations of current computer architecture [Nii, 1989].

3.5 The knowledge base

The knowledge base has three main components. First, it contains the appropriate pharmacokinetic equations and rules for determining initial estimates of pharmacokinetic parameters to be applied to the different classes of drugs. Second, it contains the facts and rules which are applied to construct a symbolic model of a patient which may then be used to suggest an appropriate dosing regimen and third, it contains facts gleaned from the literature which are used as the basis for advice on possible drug interactions and patient states which may require a modification of the dosing regimen. Knowledge based systems which use mathematical models are widely termed model based. However, this is not strictly accurate since any knowledge base is a model [Clancey, 1993; Gaines, 1993].

The pharmacokinetic equations which form the basis of the models used in the system fall into three categories.

1) the one compartment linear model with administration of multiple doses at regularly spaced intervals.

2) the two compartment linear model with elimination from the central compartment only and with administration of multiple doses at regularly spaced intervals.

3) the one compartment nonlinear model with elimination obeying Michaelis-Menten kinetics and with administration by continuous constant rate infusion.

These equations are sufficient to adequately model the behaviour of the current drugs of interest. They are an integral part of the DLLs used for parameter updating and they are stored in individual prolog predicates used to forecast drug concentrations and to design dosing regimens. The models are described more fully in appendix A and Chapter 5.

The clinical knowledge is in the form of facts and rules. The knowledge base for determining adverse drug interactions contains Prolog facts derived directly from the medical literature. Target values for drug levels are determined by applying clinical rules. A type of symbolic model, similar to that described by Lenert and Lurie (1992), is constructed to describe a particular patient and stored in a frame representation. This model may then be used to determine an appropriate target plasma level for the drug of interest by application of appropriate production rules. For example, the rule in figure 3.4 is fired if the patient is being treated for severe sepsis, is not immunocompromised and has normal renal function. The target peak plasma level of gentamicin is suggested to be 8.5 mg/L.

The rules and frames were constructed using 'flex' a near-standard expert system toolkit supported by LPA [LPA flex, an expert system toolkit, version 1.2, Logic Programming Associates, London, 1990]. Each of the different knowledge representations are stored in separate program modules. This makes addition, deletion or modification a straightforward process.

```
rule gp10
if renal_status is normal
and immune_status is normal
and infection_site is blood
then target_peak is 8.5 .
```

Figure 3.4 A rule to determine a target serum gentamicin concentration; renal_status, immune_status, and infection_site are slot values of the frame representation of the patient.

3.6 Summary

The system described above incorporates all those features considered desirable, based on experience with earlier prototypes and interview data acquired from prospective users. The system is an advanced prototype which has been designed to be readily expandable with regard to the knowledge base. It has the major characteristics of a blackboard application as compared with the classical expert system structure, with different types of knowledge stored in separate knowledge modules. It operates in the Windows environment and was constructed using standard Edinburgh Prolog. Development history and research methods are to be discussed in the chapters which follow.

CHAPTER 4

RESEARCH

In this chapter the research methods and their rationale are described and results presented.

4.1 Assessment of current dosing methods

As described previously in this report, there is considerable evidence in the literature of the poor correlation between the amount of a drug given and the plasma levels achieved in a particular patient. In the case of certain classes of drugs, this may result in therapeutic failures or serious toxicity. In order to confirm these general observations at the research site (Mackay Base Hospital), it was decided to conduct a short retrospective study on one of the drugs of interest, gentamicin, which would provide an indication of whether a drug dosage system might be useful in this hospital. The study was conducted in early 1992 and based on data obtained before the prototype drug adviser was made available for use. The results were published in the Australian Journal of Medical Science in 1993 [Botsman,1993]. A copy of this paper may be found in the attachments to this report.

In the study, the medical records of 107 patients were reviewed and dose response data abstracted and assessed. The main conclusions may be summarised as follows. First, the dosing methods employed did not often achieve the serum levels generally considered necessary for effective therapy. Approximately 50% of the serum levels

achieved initially were classified as sub-therapeutic, potentially toxic or both. Second, there was an equally low success rate for dose/interval adjustment based on the initial serum levels. Approximately 29% remained sub-therapeutic and 38% remained potentially toxic. Third, low mean peak levels (< 5mg/L) suggested caution in dosing habits. There was a general reluctance to increase doses markedly, even when such increases were clearly indicated.

While the results of the study allowed for no conclusions to be drawn regarding the clinical efficacy of the treatment, they nevertheless supported the general observations on the difficulty of achieving desired drug plasma levels by means of empirical techniques and confirmed the relevance of these observations to the research site.

4.2 Design for usability

A recurrent theme in this research is the development of a drug dosage advisory system suitable for use by the general physician in a wide range of clinical settings. In order to gain information on the requirements of such a system and to increase awareness, a series of interviews was conducted with medical staff likely to use the system.

The approach was informed by ethnography [Fetterman, 1989] and used semi-structured interviews as a particular technique [Welch, 1983]. The interviews were conducted from December 1991 to April 1992. There were eight interviews in all and the medical officers interviewed included those with as little as twelve months

experience as resident medical officers to principal house officers with over ten years experience. They were selected based on their assignments at the time i.e. those working in the medical and surgical wards where they were most likely to use the proposed system. A copy of the questions used as the basis for the interviews and a summary of the responses are provided in appendix B and further discussion may be found in copies of papers attached to this report. Some of the more important and interesting points arising from these interviews are presented in the following paragraphs.

The prospective user group had a 'typical' profile:

(a) Variable computer literacy (low to average).

(b) Scanty knowledge of pharmacokinetics.

(c) Generally busy.

This basic profile served to provided a philosophical framework for development of the prototype drug dosage adviser.

Additional findings of interest may be illustrated by the following extracts. Contrary to expectations, there appeared to be a greater recognition of the potential value of the system by those with more rather than less medical experience. There was very little curiosity about the mechanics of the system. Also, surprisingly, accessibility and ease of operation were given a higher priority than accuracy. Most were of the opinion that any system was likely to be more accurate than the methods currently employed.

From the interview process, the following design priorities emerged.

1) Simplicity.

2) Accuracy.

3) Flexibility / Practicality.

4) Robustness.

These design priorities involve issues relating to the human computer interface as well as those relating to more fundamental program structure. The steps taken to address these priorities are discussed in the next section on system development.

4.3 Prototype development

The current prototype was developed in three main stages. Stage one involved the development of an initial system for the aminoglycoside antibiotic gentamicin. It was constructed using turbo-Prolog version 2.0. The initial prototype was developed in response to a suggestion from a consulting physician at the Mackay hospital. This system used a pharmacokinetic model to predict gentamicin concentrations at steady state. The calculations were primarily deterministic in nature and based on the early work of Sawchuk and Zaske in 1976. The system was demonstrated at a physicians' conference in Mackay at the end of 1990. In response to a questionnaire, appendix B, all who saw the system at the conference indicated that they would use such a system and they would like to see it extended to other drugs. An initial literature search was conducted to determine the state of the art in computer aided dosage adjustment. There were few such systems available and none that could be said to be in general use. The few commercial systems available, such as the Abbott PKS system [Abbott GmbH Diagnostica, Wiesbaden, Germany], seemed to be directed primarily towards

pharmacists and pharmacologists rather than the general clinician. The approach adopted in this research appeared to be unique and the initial evidence was that a suitably designed system could find a niche in the area of clinical decision support.

Initial testing of the underlying model was performed as described in 4.5 below. It was decided that, with suitable modification, this original prototype could serve as the basis for an exemplary system which would be used as a test vehicle for further system development.

Stage two involved system redesign in order to produce an exemplary system which would also serve as a vehicle for further research. The basic calculations for initial parameter estimation and updating were unchanged. The system redesign was conducted concurrently with the interviews described in 4.2 above and a number of modifications were made based on the design priorities which emerged from these interviews. These modifications were as follows.

Operation of the system was simplified by reducing the number of keystrokes required to operate the system from seven to four. The number of choices for the user at each stage were also reduced.

Improvements in flexibility and practicality were achieved by blending the solutions and data requirements with the normal protocols used in the hospital. Most gentamicin dosing (> 90%, unpublished study) at the Mackay hospital is by intravenous infusion at regularly spaced intervals. The efficacy of the dosing regimen is then assessed by

collecting specimens for assay just before the next dose (trough level) and 30 minutes after a 30 minute infusion (peak level). These specimens are usually collected after 3-4 doses have been given. Thus the system needed to be able to calculate a starting regimen and to recommend an appropriate dosage adjustment, if required, based on a peak and trough level only. A starting regimen was calculated using the appropriate equations and starting estimates of the individuals' pharmacokinetic parameters derived from equations gleaned from the literature [Kaka and Buchanan, 1983] which relate physical characteristics such as age, weight and sex to these parameters. Dosage adjustment based on plasma levels requires updated estimates of the individuals' pharmacokinetic parameters. The usual deterministic method uses 2 or 3 levels within a dosing interval. Since most levels are collected after 3-4 doses have been given, parameter estimation and dosage adjustment was achieved by assuming that the trough level remains approximately constant (i.e. approx. steady state) and the calculations were then based on these 2 levels and the trough level from the previous dose only. Practicality of the solutions was achieved by having the doses rounded to the nearest 10 mg and dosing intervals being adjusted to 6, 8, 12, 16 or 24 hours. This was to allow for ease of administration. Robustness was achieved by modular design and extensive testing.

Accuracy was given a surprisingly low priority by the prospective users interviewed but was retained as a design priority for ethical reasons. The uncertainty in the calculations is difficult to quantify for the deterministic methods. Approximate confidence intervals may be determined statistically, but other effects such as poor timing in the collection of specimens or unrecorded variations in the infusion rate are

impossible to quantify. For this reason, it was decided initially that the reporting of confidence intervals was likely to be of limited benefit and that a better approach would be to apply consistency checks to the data entered and provide warnings when large changes occur in the parameter estimates. The approach was extended in the advanced prototype to include confidence intervals as a test for possible errors as described in chapter 5.

Stage three was the development of an advanced prototype using adaptive Bayesian parameter updating and incorporating a representative group of drugs. These drugs, gentamicin, vancomycin and heparin, were chosen for two reasons. First, they are used extensively in the hospital and second the pharmacokinetic models required include the one compartment, two compartment and nonlinear models. These are sufficient to cover the majority of drugs in routine clinical use for which pharmacokinetic modelling is appropriate. This advanced prototype was described in chapter 3.

4.4 Pharmacokinetic parameter updating

To recapitulate briefly on section 2.1 of chapter 2, there are two 'classical' techniques for updating initial estimates of pharmacokinetic parameters from plasma drug levels. These are deterministic methods and probabilistic methods. The deterministic methods use either simple linear regression techniques, as described by Sawchuk and Zaske in 1976, to directly estimate the parameters from several drug plasma levels within a dosing interval, or nonlinear regression as used by Jelliffe in 1982, to estimate the parameters from drug plasma levels in one or more dosing intervals. The probabilistic

methods, as described by Sheiner et al. in 1972 and 1979, use Bayesian techniques, to update initial population estimates of the parameters from a few drug plasma levels, also in one or more dosing intervals. Of the two, the Bayesian methods are more flexible and thus more suitable for use in the general clinical setting when there are usually only a few plasma drug levels available. A simple method of implementing the Bayesian algorithm was sought. Kalman filtering is a particular Bayesian technique for forecasting the elements of a time series and determining the variances of these estimates. The advantages of the technique include recursive calculations, rapid convergence and the capacity to follow changes in the parameters when these parameters do not remain constant. The procedure is readily programmed and the recursive calculations are uncomplicated, involving only simple matrix algebra. This scheme for parameter estimation is in line with the design objectives of simplicity and flexibility. As few references to the application of this particular technique to the problem of pharmacokinetic parameter estimation have been found in the literature, a separate chapter (chapter 5) in this report gives a more complete discussion of the application.

4.5 Test results

4.5.1 Retrospective testing of deterministic parameter updating

A short retrospective study was conducted to 'prove' the model and to assess the possible usefulness of the initial prototype. A sample of ten patients who were receiving gentamicin and who had their doses adjusted empirically, was chosen

arbitrarily and dose response data were abstracted from their medical records. The program was used to calculate individual pharmacokinetic parameters which were then used to predict steady state peak and trough levels for each patient following dosage adjustment. These predicted levels were compared with actual measured values. The results are summarised in table 4.1.

Patient	Predicted Steady state Concentration (mg/L)		Measured Steady State Concentration (mg/L)	
	Peak	Trough	Peak	Trough
A	7.2	3.2	8.4	4.5
B	6.9	0.2	4.7	1.1
C	6.7	0.1	5.5	1.0
D	4.2	0.1	4.5	0.6
E	6.5	1.5	--	2.2
F	8.6	0.1	7.8	0.3
G	2.0	0.1	4.5	1.3
H	6.1	0.3	7.1	2.1
I	8.0	1.7	9.8	3.5
J	5.4	0.4	7.4	0.8

Table 4.1 Comparison between predicted and measured gentamicin levels, at steady state, for patients used in the trial. (The non adaptive model).

This initial study indicated that the program would be useful for establishing

regimens for gentamicin dosing. For example, for patient A in the table, a dangerously high trough level would have been predicted and a suitable modification made. Similarly, for patient D, the low peak level, which may have allowed a 'breakthrough' bacteraemia, could have been avoided. In the case of patient I, the failure of the program to predict the high trough level was unexplained but felt to be probably due to inaccurate initial data. This is a common problem in the practical application of these systems.

This initial testing was followed by more extensive testing over a period of several months while the program was further developed and thoroughly debugged. This completed the first phase of testing.

4.5.2 Simulation studies

The second phase of testing involved validation of the Kalman filter algorithm for pharmacokinetic parameter updating. Simulation studies were performed on the three drugs included in the Bayesian prototype. These drugs, gentamicin, vancomycin and heparin, being modelled by the one compartment, two compartment and nonlinear models respectively.

The simulations were performed as follows: Simulated concentration data for each of the drugs was produced, at arbitrary times within a dosing interval, using the appropriate pharmacokinetic equations and pharmacokinetic parameters perturbed from 'average' values by an arbitrary amount. The simulated data were used as input to the

parameter estimation modules which had the 'average' values as initial parameter estimates. The %Error, defined as - %Error = [(Simulated Yt - Expected Yt) / Simulated Yt] x 100, where Yt is the measured output, was determined after each parameter update.

The results of a typical simulation run for the antibiotic gentamicin, described by the one compartment model, are shown in table 4.2.

Sequence of Observations	Simulated Concentration	Expected Concentration	%Error
1	12.2	6.2	+49.2
2	3.7	4.2	-13.5
3	10.6	9.9	+6.6
4	5.0	5.3	-6.0
5	9.1	8.9	+2.2
6	4.3	4.5	-4.7

Starting Parameter estimates: V_d = 16.8 L; k_e = 0.27 hrs-1.
Parameters used to simulate data: V_d = 12.0 L; k_e = 0.15 hrs-1.
Parameter estimates after Observation 3: V_d = 13.0 L; k_e = 0.14 hrs-1.

Where: V_d is the volume of distribution in the central compartment and k_e is the elimination rate constant for elimination from the central compartment.

Table 4.2 Predictive performance over time of the one compartment Kalman filter, using simulated data for the antibiotic gentamicin.

'Average' population values were calculated for a hypothetical patient with the following characteristics: Age 40 years; Sex Male; Weight 70 kg; Stable serum creatinine 0.08 mmol/L. Using the approximate relationships between these characteristics and the pharmacokinetic parameters of volume of distribution (V_d) and elimination rate constant (k_e) [Kaka and Buchanan, 1983; Cockcroft and Gault, 1976], the parameters were calculated to be: V_d = 16.8, k_e = 0.27 hrs-1. The initial concentration prior to the first dose ($Y_0(1)$) was assumed to be zero. These parameter values were used to start the updating procedure. Observation data were generated by using parameter values of V_d = 12 L, k_e = 0.15 hrs-1.

As can be seen from the table, useful results may be obtained with as few as two or three concentration results even when initial parameter estimates are quite poor. For further discussion see chapter 5.

For the two compartment model, simulated data were produced for the antibiotic vancomycin and the predictive performance of the model determined as for the one compartment model above. The results of a simulation are shown in table 4.3.

For vancomycin, initial parameter estimates were determined using data produced by Hurst et al., (1990). These parameters were perturbed from the population values by arbitrary amounts and the perturbed values used as the actual parameters representing an individual patient. The excellent predictive performance shown in table 4.3, while typical, is dependent on appropriate timing of serum concentration measurements. Initial observations must be taken in both the alpha and beta phases

Sequence of Observations	Simulated Concentration	Expected Concentration	%Error
1	33.3	17.8	+46.5
2	12.4	9.0	+27.4
3	22.8	22.9	-2.6
4	11.5	11.8	-2.6
5	13.5	13.6	-0.7
6	20.2	20.1	+0.5

Initial macroparameter estimates: A = 31.4, B = 16.4, alpha = 2.4, beta = 0.10.
Macroparameters used to simulate data: A = 15.9, B = 15.7,
alpha = 3.0, beta = 0.08.
Final macroparameter estimates: A = 16.8, B = 15.6,
alpha = 3.3, beta = 0.08.

where: A, B, alpha, beta are macroconstants which are functions of the microconstants (see Appendix A).

Table 4.3. Predictive performance over time of the two compartment Kalman filter, using simulated data for the antibiotic vancomycin.

or the predictive performance at the low or high end suffers. Further explanation and discussion may be found in chapter 5.

The nonlinear model was tested using simulated data for the anticoagulant heparin. Predictive performance was again assessed as described above and the results of a simulation are shown in table 4.4. The activated partial thromboplastin time (APTT), rather than the heparin concentration, is the measurable output (chapter 5).

Sequence of Observations	Simulated APTT	Expected APTT	%Error
1	39.7	54.7	-37.8
2	44.3	45.8	-3.3
3	50.7	52.2	-3.0
4	60.4	61.9	-2.5
5	76.3	77.4	-1.4
6	172.6	169.8	+1.9

Initial parameters: M = 2.0, V_m = 2500, K_m = 0.45.
Parameters used to simulate data: M = 1.6, V_m = 3500, K_m = 0.35.
Final parameter estimates: M = 1.8, V_m = 3538, K_m = 0.40.

Where: M is the heparin sensitivity factor. V_m is the maximal rate of elimination. K_m is the concentration at which elimination is half maximal.

Table 4.4. Predictive performance over time of the nonlinear one compartment Kalman filter, using simulated APTT response data for the anticoagulant heparin.

Initial parameters for heparin were based on the work of Mungall, Raskob et al., (1989), Mungall and Floyd (1989) and Kershaw et al. (1994). As demonstrated in table 4.4, useful results may be obtained with as few as one or two APTT results. Further explanation and discussion may again be found in chapter 5.

4.5.3 Usability

The gentamicin prototype system included code for determining system usage by recording the date of a consultation and the starting and finishing times. This was designed to gain an indication of both the acceptance of the system by prospective users and its' usability. The data were obtained over a full year in 1992 and the number of monthly consultations are plotted in figure 4.1 below.

The shortest consultation time was approximately 1.5 minutes and the longest approximately 40 minutes, the average being approximately 6 minutes. The total number of consultations represents approximately 10% of the gentamicin monitoring requests for the same period. Lowest usage occurred at the beginning, the end and the middle of the year.

The average consultation time of 6 minutes appeared to be well tolerated by medical staff. It should be noted that the system was installed at only three sites in the hospital and this was not considered adequate to judge system acceptance. However, the 10% usage rate may be regarded as quite high as not all serum levels indicate that dosage adjustment is required and serum levels are often requested following dosage

adjustment to monitor the effect of the change. In addition, inappropriate ordering of serum levels is not uncommon. The fluctuation in usage of the system may be due to changes in medical staff. New medical officers appear each year and rotation through different areas occurs mid-year. Additional evidence that this might be the case was the observation that a small amount of 'in-house advertising' caused usage to increase in the period immediately following.

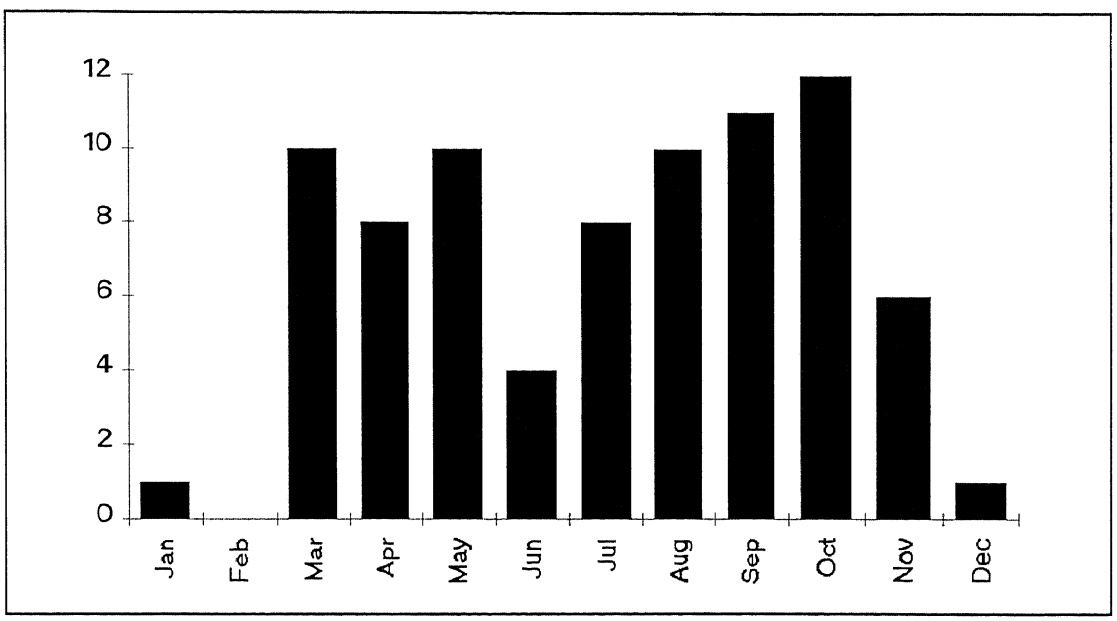


Figure 4.1 Gentamicin prototype usage for the year 1992.

Obviously, the data presented above is insufficient to draw any major conclusions regarding the design for usability. However, the indications for the prototype were considered positive. A final assessment requires the installation of the system at additional sites throughout the hospital and a more structured assessment protocol. This will be possible in the future as a network system comes on line.

4.6 Summary

The research was conducted in several stages. Initial research indicated that a drug dosage advisory system might be accepted by the general physician and be clinically useful. A basic prototype was produced to act as a vehicle for further research and assessment of current dosing practices was undertaken at the research site. Interviews were conducted to determine the major design requirements for the system and research into a new method of pharmacokinetic parameter updating which was felt to have advantages over current methods was conducted. Simulation studies to prove the parameter updating procedure were conducted and typical results are presented. A final prototype incorporating the design requirements and the parameter updating method based on the Kalman filter was produced. The prototype incorporates three drugs which require the use of pharmacokinetic models which are sufficient to cover most drugs commonly used and for which pharmacokinetic modelling is appropriate. The full system is extensible and awaits clinical trials.

CHAPTER 5

A NEW APPROACH TO THE ESTIMATION OF INDIVIDUAL PHARMACOKINETIC PARAMETERS.

This chapter, describes the mathematical basis of the method of pharmacokinetic parameter estimation used in the drugs adviser. In addition, the application to particular drugs is discussed and methods used for data validation are described.

5.1 General considerations

For compartmental models used in pharmacokinetics, the drug concentration varies with time depending on individual pharmacokinetic parameters, the mode of administration and the dose given. If the appropriate parameters are known, then, by applying suitable pharmacokinetic equations, the drug level in a particular compartment may be predicted for a given dose and mode of administration at any time during the dosing regimen. Thus the drug concentration may be considered as a continuous time series. Due to interindividual variation in parameter values, a robust method of estimating individual parameters is required to enable accurate forecasting of drug concentrations.

Bayesian forecasting is a general approach to forecasting the elements of a time series and may include such methods as exponential smoothing, regression and filtering. Filtering is a process by which recent observations on a time series are used to revise estimates of the parameters which in turn determines the forecast values. In particular,

Kalman filtering is a recursive procedure for updating the parameter estimates and the standard error of the estimation based on the most recent observation. Advantages of the technique include: (1) the calculations are recursive (2) it converges quickly when the model is constant and (3) it can follow the movement of a system should the model parameters not remain constant. It is this technique which has been applied to the problem of estimation of individual pharmacokinetic parameters.

5.2 The model

The General Univariate Dynamic Linear Model in state-space representation, as developed by West and Harrison (1989) is given by the following system of equations:

$$\begin{aligned}
\text{System equation:} \quad & Y_t = \boldsymbol{F}_t\boldsymbol{\theta}_t + \nu_t \qquad \nu_t \sim N[0, V_t] \\
\text{Observation equation:} \quad & \boldsymbol{\theta}_t = \boldsymbol{G}_t\boldsymbol{\theta}_{t-1} + \boldsymbol{\omega}_t \qquad \boldsymbol{\omega}_t \sim N[0, \boldsymbol{W}_t] \\
\text{Initial prior:} \quad & (\boldsymbol{\theta}_0 \mid D_0) \sim N[\boldsymbol{m}_0, \boldsymbol{C}_0]
\end{aligned}$$

Where:

- Y_t is the observed value of the series at time t.
- $\mathbf{F}_t$ is an nx1 matrix relating the observation Y_t to the parameter vector $\boldsymbol{\theta}_t$.
- $\boldsymbol{\theta}_t$ is the parameter vector, of size 1xn.
- $\mathbf{G}_t$ is the evolution transfer matrix which for some models is the identity matrix.
- ν_t, ω_t are the errors assumed to be independent and normally distributed.
- D_0 is the initial information set.

By means of standard normal theory or by application of Baye's theorem, the updating and forecasting equations are given by West and Harrison (1989) as:

(a) Posterior distribution for $\boldsymbol{\theta}_{t-1}$:

$$(\boldsymbol{\theta}_{t-1} \mid D_{t-1}) \sim N[\boldsymbol{m}_{t-1}, \boldsymbol{C}_{t-1})$$

for some mean $\mathbf{m}_{t-1}$ and variance $\mathbf{C}_{t-1}$. Prior information D_{t-1}.

(b) Prior distribution for $\boldsymbol{\theta}_t$:

$$(\boldsymbol{\theta}_t \mid D_{t-1}) \sim N[\boldsymbol{m}_{t-1}, \boldsymbol{R}_t]$$

where

$$\boldsymbol{R}_t = \boldsymbol{C}_{t-1} + \boldsymbol{W}_t$$

(c) One-step forecast:

$$(Y_t \mid D_{t-1}) \sim N[f_t, Q_t]$$

where

$$f_t = \boldsymbol{F}_t \boldsymbol{m}_{t-1} \quad \text{and} \quad Q_t = \boldsymbol{F}^T{}_t \boldsymbol{R}_t \boldsymbol{F}_t + V_t$$

(d) Posterior distribution for $\boldsymbol{\theta}_t$:

$$(\boldsymbol{\theta}_t \mid D_t) \sim N[\boldsymbol{m}_t, \boldsymbol{C}_t)$$

with

$$\boldsymbol{m}_t = \boldsymbol{m}_{t-1} + \boldsymbol{A}_t e_t \quad \text{and} \quad \boldsymbol{C}_t = \frac{\boldsymbol{R}_t \boldsymbol{V}_t}{Q_t}$$

and where

$$\boldsymbol{A}_t = \frac{\boldsymbol{F}_t \boldsymbol{R}_t}{Q_t} \quad \text{and} \quad e_t = Y_t - f_t$$

Hence the Kalman filter can be seen as a method of recursively updating parameter estimates and their variances, based on new observations as they become available. There is no requirement that the intervals between observations be constant.

The recursive updating equations are:

$$\boldsymbol{m}_t = \boldsymbol{m}_{t-1} + \boldsymbol{A}_t e_t$$
$$\boldsymbol{C}_t = \boldsymbol{R}_t - \boldsymbol{A}_t \boldsymbol{A}^{\boldsymbol{T}}{}_t Q_t$$

where

$$Q_t = \boldsymbol{F}^{\boldsymbol{T}}{}_t \boldsymbol{R}_t \boldsymbol{F}_t + V_t$$
$$\boldsymbol{A}_t = \text{Kalman gain} = \frac{\boldsymbol{R}_t \boldsymbol{F}_t}{Q_t}$$

5.3 Applying the model

The elements of the model equations may be related to drug concentration data as follows:

- Y_t is the observed drug concentration at time t.

- $\mathbf{F}_t$ represents the appropriate pharmacokinetic equation.

- $\boldsymbol{\theta}_t$, the pharmacokinetic parameters.

- $\mathbf{G}_t$ is the evolution transfer matrix for the parameters.

- ν_t, ω_t are the errors.

For drug concentration data, the pharmacokinetic parameters remain constant, in the short term at least, and the evolution matrix is thus the identity matrix and the evolution of the parameters through time is constant. The nonlinearity of the function F_t will be addressed below.

Since the function F is nonlinear, it must first be linearised before the Kalman filter is applied. The simplest method is by means of a Taylor series approximation about the expected value of the vector random variable $\boldsymbol{\theta}$. Expanding the function F about the prior value of $\boldsymbol{\theta} = \boldsymbol{\theta}'$, and assuming the linear terms dominate, we obtain

$$F_t(\boldsymbol{\theta}_t) = F_t(\boldsymbol{\theta}'_t) + \mathbf{F}'_t(\boldsymbol{\theta}_t - \boldsymbol{\theta}'_t) + \text{quadratic and higher order terms}$$

where $\mathbf{F}'$ is the vector derivative of F evaluated at the prior value of $\theta = \theta'$.

The system equation may then be written as

$$Y_t = f_t + \mathbf{F}'_t(\boldsymbol{\theta}_t - \boldsymbol{\theta}'_t) + \upsilon_t$$

$$= (f_t - \mathbf{F}'_t\boldsymbol{\theta}'_t) + \mathbf{F}'_t\boldsymbol{\theta}_t + \upsilon_t$$

where

$$f_t = F_t\boldsymbol{\theta}_t.$$

and the standard updating equations continue to apply.

In the practical application, the expected observation is obtained by substitution into the appropriate pharmacokinetic equation, using the best parameter estimates so far. The more commonly required pharmacokinetic equations are given in appendix A. Note that as long as the mode of administration is known for a particular dosing interval, then the function F is defined and the technique may be applied.

In order to initialise the calculations, starting estimates of the pharmacokinetic parameters and their standard deviations are required. These may be obtained directly from published data or estimated from other sources. The better the initial estimates, the faster the convergence and the more useful the revised estimate.

The remainder of this section deals with the application of the method to the pharmacokinetic models used in the drugs adviser. These are the one and two compartment models with administration by constant rate infusion at regularly spaced intervals, and the nonlinear model with administration by continuous constant rate infusion. They represent the most common methods of administration used for the drugs included in the prototype. The extension to other modes of administration would require that additional pharmacokinetic equations be added to the knowledge base. However, the basic method remains the same.

5.3.1 The one compartment model

For a drug administered by constant rate intravenous infusion at regularly spaced intervals, the equation representing the time course of drug concentration in the one compartment model (appendix A) is given by:

$$Y_t = Y_0 \cdot e^{-k_e t} + \frac{D}{T \cdot V_d \cdot k_e} \cdot (1 - e^{-k_e T}) \cdot e^{-k_e (t-T)} \quad \ldots (1)$$

where

Y_t is the concentration at any time t in a dosing interval.

Y_0 is the concentration at the start of a dosing interval.

k_e is the elimination rate constant.

T is the infusion period.

V_d is the volume of distribution.

D is the dose given.

This model was applied to the aminoglycoside antibiotic, gentamicin. The pharmacokinetic parameters of interest are the volume of distribution and the elimination rate constant. It was also decided to treat the initial concentration as an additional parameter. This allows for uncertain prior dosing history and for deviation of the parameters used to estimate the initial concentration from the 'true' values. The parameters are constrained to 'reasonable' values, see 5.4 below, and the effect of these constraints is mitigated by rerunning the filter until the deviation from the expected value is within a predetermined arbitrary limit, usually less than 1%.

Simulation has shown the Kalman filter applied to the one compartment model to be well behaved. Initial testing (Chapter 4) suggests that clinically useful results are obtainable from the sparse data usually available in the clinical setting.

5.3.2 The two compartment model

For the two compartment model with elimination from the central compartment only, the concentration in the central compartment at any time t in a dosing interval is given by the following equation.

$$(Y_t)_n = \sum_{i=0}^{n} \left[A_i \cdot e^{-\alpha \cdot t} + B_i \cdot e^{-\beta \cdot t} \right] \quad \ldots (2)$$

where

$(Y_t)_n$ is the concentration in the central compartment at time t following the n th dose. A_i , B_i , α , β are the macroparameters to be estimated. These being related to the microparameters as described in appendix A.

The model was applied to the antibiotic vancomycin which is frequently used to treat a number of resistant micro-organisms in the hospital setting, particularly methicillin resistant staphylococcus aureus, the so called 'golden staph'. The parameters of interest are the macroparameters A_i , B_i , α and β. For the estimation of these parameters, a slightly different approach was adopted to that used for the one compartment model described above. The concentration at any time t in the dosing interval may be considered as a combination of the effect of two separate processes described by the two exponential terms in equation 2. The forecast and observed concentrations may then be decomposed into two components proportional to the expected contribution from each of these exponential processes. The total concentration in the central compartment is thus the aggregate of two processes which in classical terms could be

said to correspond, at least approximately, to the alpha and beta phases referred to in standard texts on pharmacokinetics. This decomposition avoids problems associated with the nature of the concentration-time curve which allows for multiple 'fits' on single data points.

The strategy then is to apply the Kalman filter to each of the constituent processes in turn using the decomposed observed and expected concentrations and corresponding variance terms. This ensures that the process dominant at a particular time in the interval is adjusted appropriately. This strategy is described in West and Harrison (1989) and it is noted that providing the proportions are stable and well defined, the strategy can perform well even though the proportions are themselves forecasts.

5.3.3 Nonlinear model

The time course of drug concentration in a one compartment model for a drug obeying nonlinear kinetics and administered by constant rate continuous infusion may be described by the following equation (Appendix A).

$$\frac{dY_t}{dt} = R - \frac{(V_m \cdot Y_t)}{(K_m + Y_t)} \qquad \ldots (3)$$

where:

Y_t = the drug concentration at time t.

V_m = maximal rate of drug elimination.

K_m = the drug concentration at which the rate of elimination is half maximal.

R = constant infusion rate.

At steady state, the equation may be written as:

$$Y_{ss} = \frac{R \cdot K_m}{(V_m - R)} \qquad \ldots (4)$$

where Y_{ss} is the concentration at steady state and K_m, V_m, R are as before.

The steady state model was applied to the anticoagulant drug heparin which has a short apparent half-life and which is normally administered by constant rate intravenous infusion following a bolus dose to rapidly achieve therapeutic levels. However, the concentration of heparin in the plasma is rarely measured. Instead, the anticoagulant effect of heparin is measured in vitro by means of a laboratory test called the activated partial thromboplastin time (APTT). The APTT may be related to the concentration of heparin by means of the following [Mungall et al., 1989]:

$$APTT = APTT_0 \cdot e^{M \cdot Y_t} \qquad \ldots (5)$$

where:

$APTT_0$ = the baseline APTT, prior to therapy.

APTT = the observed APTT.

Y_t = the concentration of heparin at time t.

M = a 'sensitivity factor'.

By taking the natural logarithm of equation 5 and substituting into equation 4, an expression for lnAPTT, equation 6 below, may be obtained.

$$\ln APTT = \ln APTT_0 + \frac{M \cdot R \cdot K_m}{(V_m - R)} \quad \ldots (6)$$

The desired pharmacokinetic goal is an APTT within the recommended therapeutic range. The appropriate therapeutic range depends on the condition being treated. For example, following myocardial infarction, the recommended therapeutic range is 1.5 to 2.5 times the baseline APTT [Hirsh et al., 1992]. The parameters of interest are M, K_m and V_m and these are estimated for the individual by applying the Kalman filter method directly as in 5.3.1 above. Simulation studies have shown the filter to be well behaved for this model and if suitable constraints are applied, problems of erratic behaviour due to poor initial parameter estimates are avoided.

The strategy which the drugs adviser follows for heparin may be summarised as follows:

(1) If required, calculate an initial bolus dose and infusion rate based on the patient's weight.

(2) Determine the desired therapeutic APTT based on the patients condition or as direct input from the user.

(3) Predict APTT at steady state (after approximately 6 hours of therapy) using known infusion rate, baseline APTT and population based estimates of M, V_m and K_m.

(4) Obtain measured APTT from user.

(5) If the measured APTT is within the recommended therapeutic range then report as such. Otherwise, update the estimates of M, K_m and V_m using Kalman filter method for each observed APTT and recalculate the infusion rate to bring the APTT within the therapeutic range.

The strategy described above was adopted as it follows the normal protocols used in the hospital and was thus more likely to be generally accepted. However, it might be possible to calculate an improved initial infusion rate based on the initial population estimates of the pharmacokinetic parameters. This has not yet been tested.

5.4 Data validation and constraints

Three approaches to data validation were taken in the drugs adviser. The first uses 'standard' checks on data as it is entered by the user, the second is a probability based check on the data entered and the third uses rule based reasoning on the output. Questionable or obviously incorrect data generates appropriate messages displayed as text in a separate window in the centre of the screen.

The 'standard' approach used to validate data as it is entered by the user involves the usual software techniques which provide for real time checks on the raw data. These checks include allowing only numerical entry where this is required and checking that numerical entry such as dosing times and doses given are within possible or probable ranges. For 'unlikely' data, the drugs adviser uses a 'three times and it must be right' check. For example, if a grossly abnormal weight is entered, the user is prompted to

check the entry twice before it is accepted. It is not possible to detect all errors using this method but many problems are avoided initially by paying careful attention to this aspect of initial data entry at the risk of some minor annoyance to the user.

The second probability based approach uses one of the characteristics of the Kalman filter. Following each update, the observation and parameter variances are also updated. By applying standard probability theory, it is possible to determine confidence limits for the expected value of future observations. If an observation falls outside some arbitrarily chosen confidence limits, 99% for the drugs adviser, it may indicate that there is an error in the data provided. This method is only applied after two or more observations have been made and obviously, it will not pinpoint where the error lies. Nevertheless, experience appears to indicate that it is a useful pointer to gross errors commonly encountered in practice, such as those associated with misrecording the time and amount of doses given and the time of sample collection. A similar approach to changes in individual pharmacokinetic parameters might provide useful indications of a change in the patient's physical state. This has not been tested and the approach has not been implemented in the drugs adviser.

The third approach uses some simple rules to test the output from the system. For example, if an unusually high dose of gentamicin seems to be required to achieve the target drug levels, a warning is generated. The warning contains the reason why it is being displayed and other relevant information. This information may include possible errors which may have occurred, disease states which may invalidate the analysis or alternative therapies which might be considered. This approach was designed to avoid

clinically dangerous situations which may arise from inappropriate use of the drugs adviser.

The three main approaches to data validation discussed above are complemented by the provision of a graphical plot of the past and forecast drug concentrations where such a plot is appropriate. It was not, for example, considered appropriate for heparin as in this case, it is not the concentration which is being observed and a plot of the forecast APTT at steady state is unlikely to provide useful information. For those cases where it is appropriate, the graphical plot provides a rapid visual check of the likely overall validity of the outcome of a consultation.

Range constraints were applied to the pharmacokinetic parameters to be estimated in each of the models in 5.3 above. The constraints are necessary to avoid initial erratic behaviour of the filter when the prior parameter estimates are poor. The initial behaviour is of particular importance in the data poor environment commonly encountered in practice. The general approach used to determine appropriate constraints was as follows:

(1) All pharmacokinetic parameters are constrained to be positive real numbers.

(2)Where parameters may be considered to have some physical analogue, they are constrained to realistic values, for example, the volume of distribution (V_d) in the one compartment model.

(3) If known relationships exist between parameters, these are maintained. For example, in the two compartment model $\alpha >> \beta$.

The effect of applying constraints is that a poor fit may occur initially. The 'goodness of fit' is determined by producing a revised forecast of the observed concentration using the constrained parameters. If the observed and expected concentrations differ by a predetermined arbitrary amount, the filter is rerun until either the parameters are no longer constrained or the fit is within the predetermined limits. Variance updating is performed after the 'goodness of fit' criteria are met. This heuristic approach to the problem has not been subjected to rigorous statistical analysis but it seems reasonable to consider the method as equivalent to the type of feed-back intervention commonly employed in Bayesian forecasting [West and Harrison, 1989].

5.5 Notes on the method

(a) Kalman filtering is a general method for handling state-space models which gives optimal estimates of the current state of a dynamic system [Chatfield, 1989]. The original work on the filter was published by Kalman in 1960 and Kalman and Bucy in 1961. The method is commonly encountered in the field of control engineering but is of equal use in the area of time series analysis. West and Harrison (1989) have described a Bayesian forecasting method based on a model called the 'dynamic linear model' which is closely related to the general class of state-space models. A Bayesian formulation of the Kalman filter is used to update the state vector whenever a new observation becomes available. It is this method which has been adapted to the problem of estimating individual pharmacokinetic parameters.

(b) The error terms ν_t and ω_t in the model are assumed to be mutually independent and normally distributed. Clearly, the independence assumptions are not always valid. For the two compartment model described in appendix A, the macroparameters are highly correlated. However, in practice, this correlation appears to have little effect. This is consistent with the view expressed by West and Harrison (1989) that the independence assumptions are not central to the model as it is always possible to rephrase the model to satisfy these assumptions.

(c) In the analysis described in 5.2 above, the updating and forecast equations were based on the assumed normality as well as the independence of the observational and evolutionary error terms. Again, West and Harrison (1989) have pointed out that the updating and forecasting methods may continue to be applied when the normality assumptions are dropped and the distributions are unspecified apart from their first and second moments. This has important implications for possible extensions of the model. A short discussion of some of these possibilities is included in the next chapter.

(d) The use of constraints and the heuristic employing the 'goodness of fit' criteria discussed above, might appear to place too much emphasis on the most recent observation. In practice, however, the filter is usually only rerun for the first one or two observations. After this the usual single updating recurrences are sufficient. It is for this reason that the probability method for data validation is only applied after two or more observations have been fitted.

(e) No formal comparison with other Bayesian methods of pharmacokinetic parameter estimation has, as yet, been attempted. Nevertheless, some general comparisons with the maximum a posteriori (MAP) method of Sheiner et al., (1979) may be made. The MAP method has been adapted to several commercial products and is the prototypical Bayesian method used in pharmacokinetic systems. The two methods are similar in their approach but differ in some important respects. The implementation of the MAP method which is most often used is essentially a Bayesian adaptation of the standard nonlinear weighted least squares algorithm with the weights set to the relative precisions ($1/\sigma^2$) of each of the parameters and observations [e.g. Sheiner and Beal, 1982]. The weights are commonly estimated in an ad hoc fashion. An efficient method of calculating the least squares parameter estimates is required.

The Bayesian formulation of the Kalman filter is a more general and flexible approach to parameter estimation than weighted nonlinear least squares. Model variances are updated when a new observation is made and the method can incorporate variance learning for unknown observational variance. It also allows in a natural way for changing model parameters. In addition, the method may be extended to include nonlinear and non-normal models and the recursive calculations are readily programmed [West and Harrison, 1989]. It may be noted that, under certain circumstances, principally the assumptions of normality and constant variance, the recurrence relations for updating the prior distributions developed in 5.2 above, are equivalent to the non-Bayesian Kalman filter equations. These in turn have been shown to be equivalent to recursive least squares [Chatfield, 1989].

5.6 Summary

A general method of Bayesian forecasting employing a model known as the dynamic linear model has been adapted to the problem of estimating individual pharmacokinetic parameters. It has been applied to three different pharmacokinetic models which together are sufficient to cover the majority of drugs of interest in the general clinical setting. The Bayesian forecasting method incorporates an efficient Kalman filter algorithm for updating pharmacokinetic parameter estimates when further observations are made. The Kalman filter method is a more general and flexible method than other Bayesian methods currently used.

CHAPTER 6

FURTHER SYSTEM DEVELOPMENT

The subject of this report is the development of an advanced prototype drug dosage advisory system which uses pharmacokinetic principles and other knowledge to aid the general physician in the administration and dosage adjustment of some commonly prescribed therapeutic drugs. During the course of the research, a number of possible avenues for further system development have presented themselves. In this chapter, some of these avenues are discussed as well as additional work required to field a fully functional system.

6.1 Additional work required

The current prototype contains three pharmacokinetic models and additional knowledge for three drugs of interest. Some commercial systems contain up to twenty different pharmacokinetic models and cater for up to 50 different drugs. It is not always clear that all drugs included are suitable candidates for the type of system envisaged in this report. However, the knowledge base should be expanded to include some additional drugs and pharmacokinetic models. The additional drugs would include, other aminoglycosides, the common antiepileptics, the cardiac glycosides, other anticoagulants, lithium and theophylline. The additional models would include the equations for the appropriate modes of administration for each drug. The current prototype has been designed with this in mind. Modular construction has been used extensively to enable rapid expansion of the knowledge base.

The Kalman filter method for pharmacokinetic parameter updating requires further testing, both retrospective and prospective. The initial testing presented in this report has demonstrated the feasibility of the method but its' robustness in the clinical environment has yet to be proved conclusively. It would be of interest to test the method against the other methods that are currently used. As noted in chapter 5, Kalman filtering appears to have some advantages over current methods and there are recent references to similar applications in the literature.

One of the major themes of the research was design for usability. While consultation with prospective users was an integral part of the design process, additional work to test user acceptance is required. The question of who should use such systems is still open and it is a question which is unlikely to be easily answered. Clearly extensive field trials in a clinical environment will be necessary before user acceptance may be adequately judged and the question of whether adequately designed systems may be used by the general physician can be at least partly answered.

6.2 Possible extensions to the system

It is well known that significant errors in the estimation of individual pharmacokinetic parameters may be due to 'external' sources such as incorrect preparation of doses and errors in recording when doses were given and when samples were taken. Jelliffe, Schumitzky et al. (1993) have suggested that what is needed is to implement models in stochastic form with a parameter in the dynamic equations to account for these 'external' errors. The Bayesian forecasting method described in chapter 5 may well be

adapted in this way. Little work has been done in this area as yet. The NONMEM population program discussed in chapter 2, is said to have been modified to account for these sources of error but at present, no clinical systems appear to be available.

There is a belief in some quarters that pharmacokinetic systems are largely irrelevant in a hospital setting due to the errors in drug administration described above. It might well be useful to build sensitivity analysis into the system and include it in the presentation of results. There has been considerable work on determining optimal sampling times [e.g. Drusano et al., 1988; D'Argenio, 1981 and 1990] but less on determining the effect of inaccuracies in administration. It would be a relatively straightforward process to determine the effect on the observed drug levels of errors in the timing of future doses given or specimens collected. This might be of value in alleviating the concerns. However, these ideas and their presentation have not yet been tested with users.

The particular form of the model described in chapter 5, with the evolution matrix G equal to the identity matrix, might not always be best. The state-space representation is most often used to model a dynamic system where the parameters, although not directly observable, are known to change in a predictable way with time. This often occurs in medicine where different disease states will affect pharmacokinetic and pharmacodynamic responses. For example, a patient with changing renal function will show a more or less predictable change in the elimination rate constant of drugs such as gentamicin that are eliminated primarily by the renal route. This may be modelled by means of an appropriate evolution term in the system equation. Other effects might

be handled similarly.

Various methods have been suggested to enhance the performance of the basic Kalman filter updating equations. In the data poor environment encountered in pharmacokinetic applications, these methods may exhibit certain advantages over the basic method described in chapter 5. One such method described by Shumway (1988) is based on the expectation-maximisation (EM) algorithm of Dempster et al. (1977). This method uses the output from backward and forward Kalman filter recursions to perform multivariate normal maximum likelihood estimation. It is a recursive procedure which may better handle nonlinear systems such as those encountered in pharmacokinetics, although this would need to be demonstrated. An adaptation of the method has been proposed by Schumitzky (1991) for the estimation of prior distributions in population pharmacokinetic studies.

6.3 Summary

In this chapter, possible directions for further research and some of the additional work required to produce a fully functional system were presented. In particular the problem of the errors due to incorrect dosage preparation and the recording of when doses were given and specimens collected was raised and a possible direction for investigation indicated. These errors are arguably the most important problems encountered in the practical implementation of dosage advisory systems in the clinical environment.

CHAPTER 7

CONCLUSIONS

The research presented in this report was focussed around two themes. The first is the design of a drug dosage advisory system based on pharmacokinetic modelling which is suitable for use by the general physician. The second is the investigation of a pharmacokinetic parameter updating procedure which might be extended to allow for the major sources of error encountered in the practical use of such systems.

The results of the research suggest that there is a requirement for the type of system which is the subject of this research and that suitably designed systems would be used. In addition, the general Bayesian forecasting procedure using the Kalman filter algorithm has been shown to be adaptable to pharmacokinetic systems and the indications are that further research may prove its applicability for dealing with sources of error apart from those due to interindividual variability in pharmacokinetic parameters. It also seems clear that in order for pharmacokinetic systems to be used safely in the general clinical setting, they must incorporate other forms of knowledge than pharmacokinetic models, as in the system in this report.

In the early development phase, the majority of the effort was expended on the design of the user interface (estimated > 60%). In this author's opinion the importance of the interface is difficult to overstate. Systems that are difficult to use will not be used, especially in an environment where empirical methods are widely accepted. Simple changes such as reducing the number of keystrokes required to operate the system

have a marked effect on user acceptance. The design was user focussed. It was felt that it is better to make the system compatible with the user requirements than to attempt to change traditional work practices markedly. Simplicity of design and ease of use of pharmacokinetic systems, at the possible expense of some accuracy, has been criticised [Buffington et al., 1993]. It is difficult for this author to have much sympathy with this view. A cursory examination of the relevant literature shows that pharmacokinetic systems are still most often used in large institutions and then only by those who would appear to have the least requirement for such a system, that is trained pharmacists and pharmacologists. This author contends that the full benefits of pharmacokinetic systems will not be realised until appropriately designed systems are used routinely by the general physician. This view is supported by observations made by prospective users in the interviews conducted as part of this research. It was a widely held view that provided the system met reasonable standards of accuracy, it certainly could not be any worse than the empirical methods often employed. An appropriately designed system available to all medical staff, perhaps restricted to certain classes of drugs, would appear to have advantages with regard to patient safety and efficacy of treatment. There also appears to be cost benefits [Burton et al., 1991]. Perhaps the provision of such systems should be seen as being complementary to the services provided by hospital pharmacies and departments of pharmacology, where these services are available.

Interface design and the provision of appropriate explanation are intimately related. In the earliest phases of design, the provision of appropriate explanation was not given as much attention as was probably warranted. This was due to the fact that the

provision of an explanation facility was given a low priority by prospective users. It was later concluded that the traditional explanations of How and Why were not in fact what the users wanted. There was little interest in the actual mechanics of the system. Most medical practitioners are aware of general pharmacokinetic principles. They are not complete novices and do not need to be told Why a serum creatinine level is required for dosage calculations concerning drugs excreted by the kidneys. Nor did they seem particularly interested in the mathematical models employed in these calculations. They were however intensely interested in such things as possible drug interactions and contraindications for use of a particular drug. Thus the explanation provided by the advanced prototype deviates from the traditional in that it provides certain types of explanation without being asked by the user and in other circumstances allows the user to request when and how much explanation is required. The latter was implemented in the final prototype by means of a hierarchical menu structure similar to most windows help functions and the former by natural language warnings of major drug interactions and simple explanations of data requirements and possible sources of error presented in windows in the middle of the screen. This latter form of explanation was also considered to be necessary for safe operation of the system by non expert users.

Next to system design and clinical accuracy, availability was seen as the most important factor affecting system acceptance. It was impossible to formally test this effect due to the low local availability of suitable hardware. However, the impression was gained that this might not be as important as previously thought. The location effect would appear to be dependent on how often the system is likely to be used, how

useful it is perceived to be and a general awareness of its availability. It was not unusual for casualty or other ward staff to use the system located in pathology which is located a considerable distance from the ward areas. From the interview data presented in chapter 4 and appendix B, it was noted that the general physician had only a scanty knowledge of pharmacokinetics. Suitably designed and widely available systems might thus have an educational role as well as the primary one of advising on drug dosing.

While no definite conclusions can be drawn about the suitability of the design for use by the general physician, the preliminary results presented in the body of this report are encouraging. Appropriate explanation and careful attention to the physical aspects of operation are seen as essential components of a successful implementation. It would have been useful to conduct formal trials of the system with a number of different prospective users, but this was not considered feasible in the particular development environment. Rotation of staff and the generally hectic work pace made it almost impossible to gather and retain a representative group. Nevertheless considerable interest was generated and many informal suggestions on possible system enhancements were received. Further assessment of the design awaits more extensive trials with prospective users. This will become possible following further testing and the availability of the system on the hospital network.

In the clinical environment, there are a number of sources of error which may invalidate pharmacokinetic calculations. Arguably, the most important of these are those associated with the incorrect preparation of doses and the recording of incorrect

times of dosing and specimen collection. It was observed that current pharmacokinetic systems do not address these sources of error directly and it was decided to investigate the applicability of a more general Bayesian approach which might be extended to incorporate these 'external' errors. The particular approach adopted in this implementation was based extensively on the method described by West and Harrison in 1989. This general Bayesian forecasting approach, incorporating the Kalman filter algorithm, was shown to be applicable in principle to the problem of estimating pharmacokinetic parameters in an individual patient. The positive initial results presented in this report form the basis for ongoing research into the possible extension of the system to incorporate the 'external' sources of error discussed above. It is currently envisaged that the model will be extended to include additional terms which account for these errors and that estimation of these effects will enable users of the system to more readily distinguish errors in dosing and sampling from those due to interindividual variation in pharmacokinetic response. This may, in fact, be too narrow an approach to the problem and the particular form of the Kalman filter algorithm presented in this report may not be the best for this purpose, but, at the least, it serves as an initial direction for further research.

A number of avenues for further research were presented in the previous chapter. The obvious next step is to conduct extensive testing of the parameter updating procedure to demonstrate its robustness and accuracy followed by clinical trials to gauge acceptance of the system and its clinical benefits. These are in hand.

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APPENDIX A

PHARMACOKINETIC MODELS

This appendix contains a short summary of basic pharmacokinetic principles as applied in the drugs adviser. Most of the material presented may be found in any standard text on basic pharmacokinetics such as that by Wagner (1975). It is included as an aid to understanding the mathematical basis of the calculations performed by the program and is not intended as a comprehensive review of the science of pharmacokinetics.

(a) Compartmental models

Pharmacokinetics is a scientific discipline whose basic purpose is to study the time course of drug and drug metabolite concentrations and/or effects in biological fluids and tissues. Clinical pharmacokinetics uses mathematical models as an aid in the provision of safe and effective drug therapy for an individual patient. The most common form of model used is the compartmental model in which the body is considered to consist of one or more compartments into which the drug passes and is distributed uniformly. The disposition of the drug between compartments may involve linear or nonlinear kinetics. Kinetic linearity may be defined as direct proportionality of rate of change of drug amount to the amount of drug present. In general, the compartments do not have direct physiological anologues but are average 'states' of nonhomogeneous systems. The actual models are the equations but the graphical

representations shown in figure A.1 and A.2 are used for clarity.

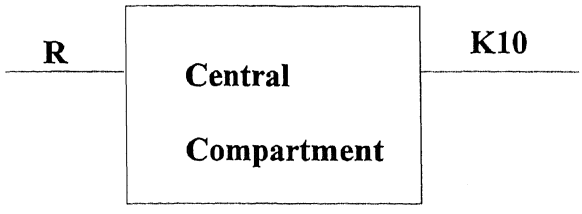

Figure A.1 The one compartment model.

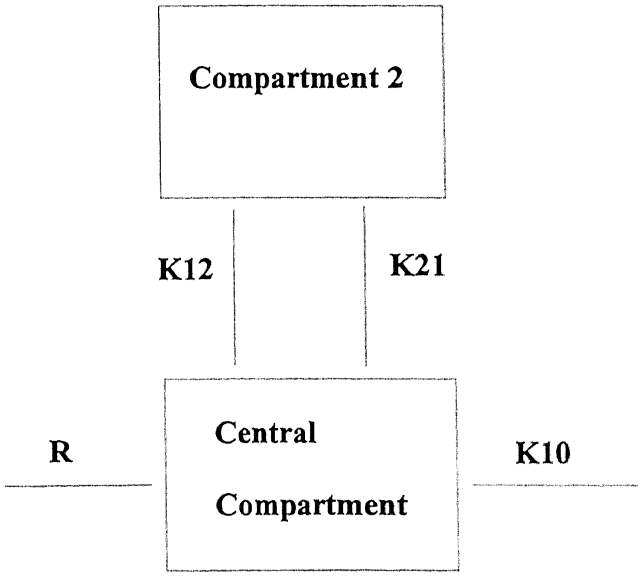

Figure A.2 The two compartment model.

(b) Linear compartmental models

Linear pharmacokinetic models are derived by making a number of assumptions about the way a drug is absorbed, distributed and eliminated from the human body. The major assumptions are: (1) the body consists of one or more separate uniform compartments (2) the drug is distributed uniformly within each compartment (3) elimination, absorption and distribution obeys first order kinetics and (4) distribution between compartments occurs rapidly compared to elimination or absorption. Many of the drugs in routine use may be described adequately by the one or two compartment linear models described graphically above.

The basic equation describing the amount of drug in the central compartment for the one compartment linear model when the drug is administered by constant rate intravenous infusion, is as follows:

$$\frac{dX}{dt} = R - k_{10}.X \qquad \ldots (1)$$

where

X is the amount of drug in the central compartment.

k_{10} (or k_e) is referred to as the elimination rate constant.

R is the constant rate of infusion of the drug into the central compartment.

Similarly, the amount of drug in the body for the two compartment model is given by the following system of equations:

$$\frac{dX}{dt} = R - k_{10}.X - k_{12}.X + k_{21}.Y \quad \ldots (2)$$

$$\frac{dY}{dt} = k_{12}.X - k_{21}.Y \quad \ldots (3)$$

where:

k_{10} (or k_e) is referred to as the elimination rate constant and k_{12}, k_{21} are rate (proportionality) constants describing the transfer of drug between compartments 1 (central) and 2.

R is the constant rate of infusion of the drug into the central compartment.

X and Y are the amounts of drug present in compartments 1 and 2 respectively at time t in a dosing interval.

Equations 2 and 3 may be solved to give the following equation for the concentration of the drug in the central compartment at any time in a dosing interval after the infusion ceases.

$$(C_t)_n = \sum_{i=0}^{n} [\, A_i . e^{-\alpha . t} + B_i . e^{-\beta . t} \,] \quad \ldots (4)$$

where

$(C_t)_n$ is the concentration in the central compartment at time t following the n th dose.

A_i, B_i, α, β are the macroparameters to be estimated.

and

$$\alpha = \frac{1}{2}[k_{10} + k_{12} + k_{21}] + \sqrt{(k_{10} + k_{12} + k_{21})^2 - 4k_{21}k_{10}}$$

$$\beta = \frac{1}{2}[k_{10}+k_{12}+k_{21}] - \sqrt{(k_{10}+k_{12}+k_{21})^2 - 4k_{21}k_{10}}$$

$$A_i = \frac{D(k_{21}-\alpha)(1-e^{\alpha T_i})}{V\alpha(\alpha-\beta)} e^{\alpha t_i}$$

$$B_i = \frac{D(\beta-k_{21})(1-e^{\beta T_i})}{V\beta(\alpha-\beta)} e^{\beta t_i}$$

where D is the dose given, V is the volume of distribution in the central compartment and k_{10} , k_{12} , k_{21} are as before.

For an n compartment model, sets of equations similar to 2 and 3 above, may be integrated to produce solutions of the form.

$$C_t = \sum_{i=0}^{n} A_i . e^{-\alpha_i . t} \qquad \ldots (5)$$

where:

C_t is the concentration is the concentration in the central compartment at time t in a dosing interval.

A_i are coefficients which are functions of the rate constants describing the transfer between compartments.

α_i are exponential coefficients which are also functions of the transfer rate constants and n corresponds to the number of compartments (usually).

In general, equation 5 is in fact two different sets of equations. One set describing the drug concentration in the central compartment during the course of the infusion and the other set applies after the infusion ceases. Similar sets of equations may be generated to describe the drug concentration in the peripheral compartments.

The equations presented above are for drugs administered by constant rate infusion into the central compartment and which are also eliminated from this compartment only. In theory, the drug could be administered into any compartment or more than one compartment simultaneously and also eliminated from one or more compartments. Similarly, different methods of drug administration are possible. Some models deal with these possibilities but in the practical circumstances commonly encountered in the hospital setting, the equations described above are the usual forms applicable with some modifications made for different modes of administration as described in (d) below.

(c) Nonlinear compartmental models

The most common causes of nonlinear pharmacokinetics are: (1) the existence of Michaelis-Menten or other nonlinear elimination kinetics (2) the presence of high doses which leads to saturable tissue binding or (3) high doses leading to nonlinear plasma-protein binding. The most commonly encountered cause in the drugs of interest is that of Michaelis-Menten elimination kinetics, exhibited by drugs such as phenytoin or heparin. For the one compartment model, the equation governing the amount of drug in the central compartment during constant rate infusion, is given by:

$$\frac{dC_t}{dt} = R - \frac{(V_m \cdot C_t)}{(K_m + C_t)} \qquad \ldots (6)$$

where

C_t is the concentration of the drug in the central compartment at time t.

R is the constant rate of infusion of the drug into the central compartment.

V_m is the maximal rate of drug elimination.

K_m is the drug concentration at which the rate of elimination is half maximal.

This equation may be solved explicitly [Beal, 1983] but this is quite 'messy' and often not necessary. Many drugs obeying nonlinear kinetics are administered orally over extended periods of time and thus steady state conditions apply and $dC/dt = 0$. In other cases, the drug is administered by constant rate continuous infusion over short periods of time and steady state is reached quickly. In either case the equation is simplified considerably and the explicit solution is not required for dosage adjustment calculations. Of course, there are methods for handling non steady-state calculations [e.g. Scheyer and Mattson, 1991] and these may be employed if warranted.

Extension to models with two or more compartments is also possible and the equations are similar to 2 and 3 above with one or more terms replaced by a term of the form of the right side of equation 6. Similar arguments to those used for linear kinetic models as regards administration and elimination also apply.

(d) Drug administration and elimination

A drug may be administered by a number of different routes. These include the oral, intramuscular, subcutaneous, intradermal, intra-pleural, intra-peritoneal and intravenous routes. The route of administration affects the rate at which a drug is absorbed, the amount of drug reaching a particular compartment and thus the form of the

appropriate pharmacokinetic equation. Other input factors include the form of the dosage e.g solid tablet forms, rectal dosage forms, liquid dosage forms. These factors affect the amount of the dose reaching a particular compartment.

Elimination of the drug occurs when it is metabolised or excreted or both. Drug metabolites may also have a pharmacological effect but this is ignored for the purposes of this report. The elimination rate constant occurring in the pharmacokinetic equations may thus be considered as the sum of the rate constants of all the different elimination processes occurring.

As illustration, assuming a one compartment model with first order elimination, the equations describing the concentration of the drug at any time t in a dosing interval for different modes of administration are:

(i) Intravenous bolus administration:

$$C_t = C_0 \cdot e^{-k_{10} \cdot t} + \frac{D}{V} \cdot e^{-k_{10} \cdot t}$$

(ii) Intravenous infusion:

$$C_t = C_0 \cdot e^{-k_{10} \cdot t} + \frac{D}{V \cdot T \cdot k_{10}} \cdot \left(1 - e^{-k_{10} \cdot T}\right) \cdot e^{-k_{10} \cdot (t - T)}$$

(iii) Intramuscular injection:

$$C_t = C_0 \cdot e^{-k_{10} \cdot t} + \frac{D \cdot k_m}{V \cdot (k_m - k_{10})} \cdot \left(e^{-k_{10} \cdot t} + e^{-k_m \cdot t}\right)$$

(iv) Oral:

$$C_t = C_0 \cdot e^{-k_{10} \cdot t} + \frac{F_a \cdot D \cdot k_a}{V \cdot (k_a - k_{10})} \cdot (e^{-k_{10} \cdot t} + e^{-k_a \cdot t})$$

where:

k_{10} is the first order elimination rate constant.

k_m is the first order intramuscular absorption rate constant.

k_a is the first order oral absorption rate constant.

F_a is the bioavailability.

T is the infusion period.

C_0 is the drug concentration before the dose is given.

D is the dose given.

V is the volume of distribution.

C_t is the concentration at time t in a dosing interval.

When multiple doses of a drug are given (the usual case), the equations may be applied iteratively to determine the concentration at any time in a particular dosing interval or multiple dosing forms of the equations may be used. The multiple dosing forms assume linear kinetics and multiple doses given at regularly spaced intervals. These forms, incorporating the sum of a geometric series, are often applicable in the clinical setting. The multiple dosing form of a drug administered by intravenous injection at regularly spaced intervals and using the one compartment model, is given by equation 7 below.

$$C_t = \frac{D}{V} \cdot \left[\frac{(1 - e^{-n \cdot k_e \cdot \tau})}{(1 - e^{-k_e \cdot \tau})} \right] \cdot e^{-k_e \cdot t} \qquad \ldots (7)$$

where:

C_t is the concentration at any time t in a dosing interval, D is the dose given each τ hours, k_e is the elimination rate constant, V is the volume of distribution and n is the number of doses given.

APPENDIX B

QUESTIONNAIRES USED IN THE RESEARCH AND SUMMARIES OF RESPONSES

This appendix provides copies of the questionnaires used in the research and summaries of the responses received. These were used as the basis for design changes to the prototype Drug Dosage Adviser so as to better reflect the needs of the prospective users.

A basic prototype system was first demonstrated at the North Queensland physicians conference held in Mackay at the end of 1990. The participants were all specialist physicians from a variety of institutions both public and private. Individuals were shown the system in operation and then encouraged to operate the system themselves. A questionnaire was also provided for the participants to record their impressions of the system. The questionnaire is reproduced in figure B.1 and a summary of the responses in table B.1.

Following initial research and prototype modification, a series of interviews with medical staff likely to use the system were conducted at the end of 1991 and the beginning of 1992. The interviewees were selected arbitrarily from those working in wards where it was decided that the system would most likely be used, that is the medical and surgical wards. The interviewees had different levels of expertise and experience and provided a good cross section of the medical staff within the hospital. There were eight interviews in all, the eight interviewees representing approximately

20% of the hospital medical staff. The interviews were semi-structured. The questions asked are reproduced in figure B.2 and a summary of the responses is provided below each question. Responses were recorded in longhand at the time of the interviews and fair copies transcribed shortly after. The summaries represent as closely as possible the replies received without significant exclusions. Exact quotes are given in double quotation marks and the short responses recorded and reproduced in the figure, paraphrase the actual responses as closely as possible.

QUESTIONNAIRE - GENTAMICIN PROGRAM

Please tick the appropriate response.

[1] Do you own or have ready access to a personal computer ? yes[ ] no[ ]

[2] Do you use a personal computer professionally on a regular basis ? yes[ ] no[ ]

[3] Have you seen another program similar to that on display ? yes[ ] no[ ]

[4] Would you use such a program as a clinical aid ? yes[ ] no[ ]

[5] If you would use such a program, would you prefer

(a) - to use it yourself [ ]
(b) - have someone else use it for you [ ]
(c) - no preference [ ]

[6] Should a program such as that on display, be used in:

(a) - physicians office [ ]
(b) - hospital ward [ ]
(c) - Pathology lab. [ ]
(d) - all of the above [ ]

[7] Do you think a similar program would be useful for:

(a) - other aminoglycosides [ ]
(b) - antiepileptics [ ]
(c) - aminophylline [ ]
(d) - cardiac glycosides [ ]
(e) - all of the above [ ]
(f) - none of the above [ ]

[8] When entering data into such a system, would you prefer:

(a) - all data entry on the one screen (report format) [ ]
(b) - prompts for each item on separate screens(as here) [ ]
(c) - no preference [ ]
(d) - don't understand the question [ ]

[9] Is a colour display

(a) - essential [ ]
(b) - desirable [ ]
(c) - undesirable [ ]
(d) - irrelevant [ ]
(e) - no opinion [ ]

[10] Any other comments ?

Figure B.1 Gentamicin questionnaire.

Ques.	Responses							
	yes	no	(a)	(b)	(c)	(d)	(e)	(f)
1	4	2						
2	0	6						
3	2	4						
4	6	0						
5			1	3	2			
6			0	1	2	3		
7			1	1	0	0	4	0
8			2	2	1	1		
9			0	1	1	4	0	
10	2 suggested Heparin be added / 1of these suggested Cyclosporin be added as well / 2 said they liked it / 2 had no further comments.							

Table B.1 Summary of responses to gentamicin questionnaire.

Interview Questions and Responses

General.

Question 1.
Interviewee demographics - Name , Age, Sex, Current position, Previous experience.

Interviewee	age	sex	experience	current position
A	28	M	5 years	Principal House Officer
B	33	M	10 years	Principal house Officer
C	31	M	8 years	Principal House Officer
D	29	M	3 years	Junior House Officer
E	26	F	1.5 years	Resident Medical Officer
F	23	M	< 1 year	Resident Medical Officer
G	35	M	11 years	Principal House Officer
H	25	F	2 years	Junior House Officer

Figure B.2 Interview questions and summaries of responses.
(Continued over)

Question 2.
Please explain your professional duties. How Busy are you ?

Interviewee	duties
A	Ward management, Patient assessment & care, Admissions, minor operations, relevant special procedures, coordinate paramedical services. Busy -long hours.
B	Management of patient care, review admissions, minor operations, specialist procedures. Very Busy
C	Supervise and manage patient treatment in ICU, CCU and Medical wards. Short staffed, Busy
D	Patient management under supervision of PHO and consultants; long hours
E	Check admissions, patient management, discharge summaries. Busy
F	Assess patients and treatment, Responsible to registrar, Quite busy.
G	Assess patients for Theatre, Minor operations, Supervise post op treatment. Busy.
H	Assess and manage patients, minor procedures. Busy, long hours.

Figure B.2 Interview questions and summaries of responses.
(Continued over)

Computers and Medical computing.

Question 3.
What experience with computers you do you have ? Professional ? Personal ?

Interviewee	Professional	Personal
A	"not much really" , Word processing, Ward terminals at RBH for lab results.	Fairly knowledgeable. Father wrote accounting software." Some programming myself."
B	"virtually nil"	Own a PC for word processing and games.
C	"not much" some MEDLINE searches.	"zero"
D	MEDLINE searches.	Own a PC but don't use it much.
E	Some experience with Hospital computers in England for ordering procedures and getting results and Drug cards.	none
F	Ward terminals at RBH for results etc. Zero otherwise.	"not a lot".
G	Use MEDLINE and CDROM databases	none
H	"not much"	none

Question 4.
Do you own a personal computer ?

A	B	C	D	E	F	G	H
yes	yes	no	yes	no	no	no	no

Figure B.2 Interview questions and summaries of responses.
(Continued over)

Question 5.
Do you use a computer regularly - professionally or otherwise ?

A	B	C	D	E	F	G	H
no	no	some	yes(Pro)	no	yes(Pro)	no	no

Question 6.
What do you understand by the terms -
Medical informatics ? Medical / clinical advisory systems ? Expert system ?

Interviewee	Medical Informatics	Advisory systems	Expert systems
A	"heard the term but not sure exactly what it is"	"MEDLINE? not sure"	"nothing really"
B	nothing	nothing	nothing
C	"never heard of it"	"the gentamicin program?" not sure.	not sure
D	nothing	"advice from a computer?"	"not much; A very good system?"
E	nothing	nothing	nothing
F	nothing	"MEDLINE type system?"	nothing
G	nothing	nothing	nothing
H	nothing	nothing	nothing

Figure B.2 Interview questions and summaries of responses.
(Continued over)

Question 7.
Do you see a place for computers in medicine ? Where ?
(prompt - diagnostics, databases, medical records)

Interviewee	computers in medicine
A	Yes. Medical records eventually. Laboratory results and programs like MEDLINE
B	Yes. Predominantly in medical records and for ordering tests and interpreting results. "Drug dosing of course"
C	Yes. Information retrieval and storage. Advice on clinical decisions; Printing reports etc.
D	Yes. Summary of medical records. Maybe for access to information.
E	Yes. "can type reasonably well"
F	Yes. "useful for access to information in abroad sense"
G	Yes. Access to databases. Help in diagnosis, eventually "is that an expert system?" " Not medical records while I can't type"
H	Yes. Medical records maybe. Lab. results.

Question 8.
Would you use a medical advisory system ?
(following explanation where required)

A	B	C	D	E	F	G	H
Some, maybe.	yes, if it works.	yes	Possibl yif conv-enient	Maybe. Check it first.	Yes	Yes, if easy to use.	Yes

Figure B.2 Interview questions and summaries of responses.
(Continued over)

Question 9.
What knowledge of pharmacokinetics do you have ? How much do you use it ?

Interviewee	Knowledge of pharmacokinetics / use
A	Quite knowledgeable. Rely a lot on advice from consultants, reference texts. / Use it quite a lot.
B	Not much knowledge. / "don't seem to need it much."
C	Remember a bit from med. school. Usually rely on experience / use knowledge occasionally.
D	"not a lot". Remember a bit from pharmacology at med. school / don't use it much.
E	Remember most of what was taught in pharmacology at Uni. / use it regularly.
F	Basic university knowledge / used "a couple of times maybe"
G	Quite extensive, studied anaesthetics. / use it regularly
H	Remember some from Uni. / not much use.

Figure B.2 Interview questions and summaries of responses.
(Continued over)

Question 10.
What do you understand by the terms -
Half-life of a drug ? Elimination rate constant ? Volume of distribution of a drug?
Pharmacokinetic model ?

	Understanding (yes, not at all, vague)			
Interviewee	Half-life	Rate constant	Volume Distrib.	Model
A	yes	vague	yes	vague
B	yes	vague	vague	not at all
C	yes	yes	yes	yes
D	yes	vague	vague	vague
E	yes	not at all	not at all	not at all
F	yes	vague	yes	vague
G	yes	yes	yes	yes
H	yes	not at all	vague	not at all

Figure B.2 Interview questions and summaries of responses.
(Continued over)

Question 11.
How would you normally choose a drug dosing regimen ? for Gentamicin ?

Interviewee	general	gentamicin
A	"guesstimate" based on renal and hepatic function, recommended dosages in reference texts. Experience.	"guesstimate" based on creatinine if available.
B	Based on renal and hepatic function. Experience. Reference texts.	Same
C	Use MIMS and other references.	Experience and renal function. Check drug levels.
D	Reference texts. Experience.	Same.
E	Use MIMS and other references	Standard start doses. "guesstimates"
F	Use MIMS and other references.	Use consultants' nomogram or "standard doses if patient seems 'normal' ".
G	Experience and using renal function, hepatic function, age weight , sex adjustments. Reference texts where necessary.	Similar to that used for other drugs.
H	Standard doses from MIMS and other references.	Standard doses.

Figure B.2 Interview questions and summaries of responses.
(Continued over)

Question 12.
Do you see any value in using a computer to calculate dosing regimens ?

Interviewee	response - comments
A	Yes. Avoids toxicity. Better levels earlier.
B	Yes. More accurate. "Takes some guessing out of it"
C	Yes. If convenient could eliminate need for extra tests. "couldn't be worse than the methods being used"
D	Yes. If convenient and on wards.
E	Maybe. Should be fairly good.
F	Yes. "Could be handy". "need access there and then".
G	Yes. "But would need to be very accessible and easy to use."
H	Yes. If easy to use.

Figure B.2 Interview questions and summaries of responses.
(Continued over)

Question 13.
What would you expect in such a system ?
(prompt - accuracy, reliability, availability,explanation)

Interviewee	Features
A	"easy to use". Fast. Like more interpretation including drug interactions. Must have ready access. Needs to be reasonably accurate. "Don't need the equations and things.."
B	User friendly. As simple as possible to use. Should be accurate. Might need some help.
C	Convenient to get at. Easy to use. "know what the creatinine is for"
D	User friendly. Good results. Fast "and not too many questions asked."
E	Must be simple to use. Should give good results.
F	Not too complicated to use. Should have other information such as interaction with other drugs.
G	Simple to use. Fast. Other knowledge such as drug interactions. Access to patient database for other drugs used. Not much explanation necessary.
H	Simple to use. Convenient. Should know what information you need to enter into program.

Question 14.
Would you prefer such a system to be operated by you or someone else e.g. Lab, pharmacy?

A	B	C	D	E	F	G	H
By me.	By me.	Prefer Lab. say	By me	Someone else.	By me.	By me	By me.

Figure B.2 Interview questions and summaries of responses.
(Continued over)

Question 15.
Would you prefer a choice of options or a single 'best' solution from such a system?

A	B	C	D	E	F	G	H
Single best or small number of choices	Single best.	A choice	A small number of choices	A choice	A choice	Single best.	A choice.

Question 16.
Have you seen the gentamicin program ? Have you used it ?
Your Impressions of the program ?

Interviewee	use	impressions
A	Have seen it. Used it.	Program is good. Happy with results. Use it as a guide mainly.
B	Have seen it. Used it.	A good idea.
C	Have seen it. Used it.	Good.
D	Haven't used it. Heard about it.	Sounds good.
E	Haven't used it. Heard a bit about it.	---
F	Have seen it. Used it.	Program looks good. Seems to work.
G	Have seen it. "Haven't really used it."	Good potential.
H	Haven't seen it.	---

Figure B.2 Interview questions and summaries of responses.
(Continued over)

Question 17.
Would you like to see the gentamicin program extended to include other drugs ?
Which drugs ?

Interviewee	extension?	other drugs
A	Yes	Other antibiotics, Vancomycin
B	Yes	Digoxin, antiepileptics.
C	Yes	Vancomycin, Digoxin, dilantin
D	Maybe	other aminoglycosides.
E	Yes	Digoxin, tegretol, maybe others.
F	Yes	Other antibiotics, other toxic drugs.
G	Yes	Warfarin, Heparin, antiepileptics.
H	Yes	Other antibiotics, digoxin.

Figure B.2 Interview questions and summaries of responses.
(Continued over)

Question 18.
Any general comments ?

Interviewee	comments
A	Program is good. Aware that it has limitations.
B	Program is a good idea. never seen a program like that before. Good if MO's had access 24 hours a day.
C	Good idea. Not enough staff aware of it.
D	Haven't used it.
E	Should use it.
F	Program looks good. "Be more helpful if we had computers on the wards"
G	Good.
H	no.

Figure B.2 Interview questions and summaries of responses.