A STOCHASTIC APPROACH IN A TWO-COMPARTMENTAL MODEL OF GLUCOSE KINETICS.

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To: My wife Zahra and children Soudh and Mohammad Saggad.

I am deeply grateful for their encouragement and patience throughout this work.

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ABSTRACT

In this research two kinds of stochastic model were studied to describe the decay of a glucose tracer in the blood plasma of a group of female subjects. The group was divided into two subgroups, normal (non-obese) and obese subjects, to study the effect of obesity on the stochastic models. The data were acquired as part of a study at St. Thomas' Hospital, London (Bowes et al., 1996). A known mass of glucose and glucose tracer was injected intravenously in each subject and blood samples were taken at various times. To build a stochastic model of the decay of plasma glucose tracer concentration, a two-compartmental system was considered. Two different stochastic models were discussed.

In model A Soong's approach (Soong, 1971) was applied. The model consists of two differential equations for the concentration of tracer in each compartment. The four parameters of the model were estimated using blood sample data for each subject. The variability in the set of glucose tracer curves was assumed to be due to variability of the parameters and each parameter was assumed to have a quadravariate lognormal frequency distribution. The mean plasma glucose tracer concentration was calculated using a four dimensional integration at times between 0 and 180 minutes.

A comparison was made between the stochastic and deterministic models for the mean concentration of glucose tracer in total group of subjects and in both subgroups. A small difference was found between the two models in the total group of subjects and the two subgroups. Also, the differences between deterministic and stochastic curves in the non-obese group was larger than in the total group of subjects and the obese subgroup. In all groups choosing the deterministic values as the mean concentration of glucose tracer yields a small overestimate error in the mean concentration.

The S. E. of the stochastic and deterministic models for the concentration of the glucose tracer was also calculated together with the S. E. for the original data and for all groups.

There were some large differences between the deterministic and stochastic values particularly for times between 20 minutes to 100 minutes. The differences are quite large in the total group of subjects but small in the non-obese and obese subgroups. The S. E. for the original data are larger than the stochastic models in total and obese subjects and also at large times in non-obese subject. Therefore, using the simple S. E. of the original data at each time point overestimates of the S. E. as predicted by the stochastic model.

For the stochastic model B Limić's approach (Limić, 1989) was used. In this approach the uncertainty in the parameters of the model is incorporated into a compartmental matrix where all elements of the matrix fluctuate randomly under a normal distribution. The mathematical calculation for the mean concentration of glucose tracer is complex. To simplify the model, it was assumed that the fluctuations are the same (ie. non-independent) for all of the elements of the compartmental matrix.

A comparison was made between the deterministic and stochastic models for the mean concentration. It was found that the differences between the deterministic and the stochastic curve for the first compartment were small as in the case of model A. This similarity may be due to the small sample size and/or the dependent random processes for every element of the matrix. Therefore, model B is not recommended since all the elements of the compartmental matrix fluctuate together and this simplification does not represent actual physiological processes which are very likely to have independent fluctuations.

In conclusion, although both methods have a similar mean for the concentration of glucose tracer, the large difference between the S. E. of stochastic and deterministic models is probably due to the small number of measurement or the small sample size. The error should decrease with a greater number of measurements and increasing the sample size. In building the stochastic models this problem does not arise since the data are considered as a distribution, but taking a larger sample should produce a more accurate result.

The above results mean that in building a stochastic model in future studies, we need to consider a larger sample size, a larger number of measurements and restrict the number of the compartments to less than three (model A) to overcome the complexity of the calculation. The compartmental matrix should have elements which fluctuate independently.

Chapter 1

Introduction

1.1: introduction to the thesis

One of the most important activities in clinical medicine, physiology and pharmacology is the screening of subjects into two groups of normal and abnormal subjects. The usual practice is to design a test and use the data for each subject to classify them as normal or abnormal according to appropriate statistical criteria. To follow this approach it is necessary to apply a basic model of the features of the test. Clinicians usually prefer to use very simple test (hence simple models) to classify subjects. For example persons are considered to have frank non-insulin dependent diabetes if the random and fasting blood glucose values are $\geq$ 11.1 and 7.8 mmol/l respectively, and the 2-hour blood glucose following an ingested 75 g glucose load is $\geq$ 11.1 mmol/l (WHO, 1985). This is a relatively coarse classification over a population and a more sophisticated model of the time-varying blood glucose of each subject would allow a more precise classification to be made.

In this study therefore, we will focus on the kinetics of a specific tracer in the body to build a mathematical model of its kinetics . Obviously the model will vary for each subject and we aim to investigate the effects of different subjects on the model. The aim is to develop a stochastic model which can account for the variability of the subjects' different parameters and / or time course in the experiment. Two different stochastic models are studied in this research. The models predict the mean and variance of the decay of a glucose tracer from the blood plasma into the extravascular tissues in a group of female subjects. Also, the subjects are divided into two subgroups according to their weights (obese and non-obese) to study the effects of obesity in the models. Furthermore, the more conventional deterministic model (to be defined later) and the stochastic models will be compared for the various groups of subjects. The objective of this study is to replace the deterministic modelling approach of analysing the tracer

kinetic by a stochastic modelling approach which can account for the observed variability in the subjects.

The definition of mathematical models and application of mathematical modelling in different branches of medicine, especially in metabolic medicine and endocrinology is introduced below. Some useful definitions in model building are also presented. The different types of models, their definitions and applications are introduced in Chapter 2, and stochastic models and their application are described in Chapter 3. In Chapter 4 the design of the experiment, data collection and the software which was used in parameter estimation are introduced. The two stochastic models, their methods of model building and stochastic and deterministic models for the total group of subjects and the subgroup are discussed in Chapters 5 and 6. The deterministic and stochastic models are compared in Chapter 7. The results are discussed in Chapter 8 and concluding remarks are given in Chapter 9.

1.2: Mathematical modelling in clinical medicine

The application of quantitative methods has increased considerably during the past few decades, especially in the field of metabolic medicine and endocrinology. In most of these studies the research trend has been towards the development and application of measurement techniques and the analysis of such experimental data. These improvements have encouraged the replacement of traditional instrument technology and biochemical laboratory methods are replaced with new techniques using tracers and radio-immunoassay.

Application of these methods along with substantial developments in control and system theory have resulted in widespread improvement in the use of mathematical models and their identification and validation. Such techniques have been applied to a wide range of data arising in physiology and medicine, but have been especially significant in endocrinology and metabolism.

The appropriate use of mathematical modelling and identification techniques enable us to describe complex processes, to find ways for improvement of experimental design and allow us to test hypotheses which are related to physiological and biochemical structures. Besides the above applications, it is possible to estimate unknown parameters which are not directly accessible to measurement. Although modelling applications are found in all areas of medical research, they are now increasingly being used in diagnosis and treatment of disease.

A mathematical model is simply a mathematical equation which specifies the relation between one or more independent variable(s) and a dependent (response) variable. When the independent variable(s) changes, the response variable changes according to this equation. If the equation contains only one independent variable, it is described as 'simple'. In the application of mathematical models in medicine we normally deal with simple equations and there is rarely a need to use a complex one. These models normally have only a few unknown parameters to be estimated from the data and these are estimated using a curve-fitting computer program. To build a good model we need to test it against various criteria to obtain a good fit. Using these criteria to test the model, the best model of several candidates can be chosen. After selecting the model we can estimate its unknown parameters. Parameter estimation is the last stage of model building.

To enhance the benefits of modelling in clinical applications, there is clearly a need for improved understanding of the merits and limitations of modelling, identification and validation techniques, and their relevance to the particular physiological system under investigation. This is a large topic and will not be discussed here. Some specific modelling topics used in the thesis are introduced in the following sections.

1.3: Modelling aspects

1.3.1: Background

The application of mathematical modelling has been established in many of the natural and medical sciences for many years. Its origin lies in drug kinetics and continued with widespread application in physiology, pharmacology, biochemistry and related biomedical science (see for example Rescigno and Segre, 1966; and Gibaldi and Perrier, 1975). Most of the practical applications of compartmental theory to these (and other) fields have used deterministic theory, but many recent applications have also attempted to account for a stochastic behaviour in the kinetics. We will introduce these new topics (compartmental, deterministic and stochastic models) later.

Mathematical modelling techniques have been applied to physiological systems, particulary metabolism and endocrinology, by Carson, Cobelli and Finkelstein (1983). They discuss different types of models and the stages of model building in metabolic systems, especially endocrine systems, and describe in detail the aims and purposes of model building. Some useful sections relating to model formulation, identification and validation are given, together with a few case studies.

1.3.2: Some useful definitions

The following definitions are some of the most important terms in compartmental modelling literature and some of them are used in this research.

1.3.3: Compartment or pool

If a substance exists in a biological system in several forms and locations, then all of this substance in a particular form, or in a particular location, is called a compartment or pool. A compartment is an idealised store of some substance in a biological system. Compartments may not occupy an anatomical space in the body. In physiology, plasma

or different substances in plasma such as plasma glucose, lactate and alanine are some examples of compartments. Zinc in bone and thyroxine in the thyroid are two further examples of compartments.

1.3.4: Compartmental system

Two or more interconnected compartments with fluxes of substances between them are described as a compartmental system.

1.3.5: Parameter

A parameter is a specific fixed constant in a mathematical model and in many cases (but usually measurable) may represent an actual physical property of a physiological system. It is neither a dependent variable, an independent variable, or an input. The parameters are usually unknown in a model, and have to be estimated in the model fitting process. We usually attribute a physical meaning to the parameters and can therefore talk of the existence of parameters and their values in the same way as talking of the existence of a compartmental system.

1.4: Different types of models

Various types of models are introduced briefly in the next few sections:

1.4.1: Lumped deterministic models

If the distributed effects in the body have lumped together and treated as a homogeneous entity, we call them lumped deterministic models. In this case the concentration of blood glucose is assumed to be the same in different parts of the blood compartment (Carson et al., 1983).

1.4.2: Linear models

If, in a compartmental system, the outward fluxes of substance are proportional to the mass or concentration of the respective compartments, then the model is called a linear model. Also, in any model there is usually an input rate. These types of models are adequate where (Carson et al., 1983):

(i) The intrinsic dynamics of the system are essentially linear. This type of system is rarely applied in metabolic control systems but may be applicable to the kinetics of individual substances (e.g. unconjugated bilirubin).

(ii) Linearisation has been carried out. If a tracer quantity is applied to a compartmental system, then the dynamical equations which describe the resulting experimental tracer perturbations are linear even though the intrinsic nature of the system may be non-linear. Also, many intrinsic data from the metabolic system can be obtained by applying such a test signal.

1.4.3: Nonlinear models

Research in drug metabolism over the past few years has resulted in the development of many nonlinear models. The objectives, estimation and prediction, of data analysis using nonlinear models are the same as that for linear models. The main difference between linear and nonlinear models is that the computation required for the analysis of the latter is considerably more complex.

1.4.4: Distributed models

As mentioned earlier, in many cases it is possible to represent the metabolic system by a lumped model where the substance is assumed to be distributed homogeneously in the distribution space. Neglecting the effect of blood flow and peripheral circulation on mixing, representation of the metabolic system by a compartmental model is usually

adequate in many cases. In distributed models no such assumption of homogeneity is made. This usually leads to a mathematical formulation in terms of partial differential equations (Carson et al., 1983).

1.4.5: Stochastic models

In many experiments, especially at cellular level, stochastic (random) effects need to be incorporated into the compartmental model, so that a purely deterministic model is likely to be inadequate, since it takes no account of random effects. Probabilistic effects are one of the most important aspect of the modelling of metabolic systems where parameters undergo random temporal fluctuations. This is called a stochastic process and its use in deterministic models and input/output identification experiments can provide a quantitative description of many metabolic systems. This type of model is very important and its application will be discussed in more detail in Chapter 3.

1.4.6: Compartmental models

A compartmental model depends on a compartmental system which consists of a finite number of homogeneous, well-mixed, lumped subsystems. These types of models are relevant in the study of metabolic systems and represent metabolic processes that achieve regulation through the interaction of chemical reaction, storage and transport only and do not involve hormonal control. The compartmental system exchanges material with other compartments and with the environment, so the mass or concentration of substance within each compartment may be described by a first order mass balance differential equation. A compartmental system may be used to model either the kinetics of one, two or more substances. In the first case, compartments occupy different spaces and the inter-compartmental transfer represents the flow of material between compartments. In the second case different compartments may occupy the same space and some of the inter-compartmental transfers represent transformation between substances (Godfrey, 1983). We discuss these types of models in more detail

in Chapter 2.

1.4.7: Time varying models

In time varying models, the rate coefficients (k_{ij} , to be defined later) are functions of time i.e. $k_{ij}=k_{ij}(t)$, but they are not a function of the state variables, x. Therefore, the estimation of the k_{ij} are different from each other over a period of time. In theory, they may be time varying coefficients varying between $-\infty$ and ∞, but, in practice they are non-negative. One of the most important forms of time variation is that in which the rate constants oscillate with time with period T:

$$k_{ij}(t)=k_{ij}(t+T).$$

In the body, many functions vary with a period of approximately 24 hours, and there is a similar periodicity in many ecosystems due to variation in light and temperature.

1.4.8: Time invariant models

In a time invariant model the rate coefficients are constant and independent of time so the k_{ij}s are the same over any epoch.

1.5: Summary

In this chapter the motivation for the work with its aims and objectives was introduced together with the organisation of the thesis. Also, various mathematical models, their applications and background were discussed . Some of the most important terms used in the compartmental modelling literature were defined. In the next chapter some types of compartmental models and their mathematical representation will be discussed. The general solution of a compartmental model with some numerical examples will be also presented together with the so-called non-compartmental approach.

Chapter 2
Compartmental models

2.1: Introduction

Compartmental systems and compartmental models were defined in section 1.4. and 1.5. These systems exchange with each other and with the environment, so that the quantity or concentration of material within each compartment may be described by a first order differential equation. A compartmental system may be used to model either the kinetics of one substance, in which case the compartments occupy different spaces and the inter-compartment transfers represent flow of material from one location to another, or the kinetics of two or more substances (such as a drug and its metabolites) in which case different compartments may occupy the same space and some inter-compartment transfers represent transformation from one substance to another (Godfrey,1983).

2.2: Origins and background

The term compartment was first introduced by Sheppard in 1948. A further significant early paper was that of Sheppard and Householder discussing the mathematical basis for interpreting tracer experiments. The origins of pharmacokinetics can be attributed to Teorell (1937) who used four differential equations representing the transfer of material in the body. O'Neill (1979) introduced compartmental analysis in ecosystem modelling using linear, time-invariant models. This type of model has played an important role in the development of system ecology.

Norwich (1977) thought that all previous work which had been done in studying the kinetics of biological substances (biokinetics) was based on physics and chemistry, and he considered that it was now the time to interrupt the physicochemical development to

introduce the theory of compartment and non-compartment systems. He said that compartments were more mathematical than physical and as such were a simpler approach rather than using physics and chemistry. Perhaps, therefore, it has become necessary for all texts of compartmental analysis to include a description of compartmental approaches to biokinetics, especially as there have been so many papers published in this field.

Jacquez (1985) has described the compartmental system as a most useful tool in analysing physiological and pharmacological data. From an aesthetic viewpoint, the analytic theory of linear compartmental systems is relatively complete. On the other hand, there are many unsolved problems in compartmental modelling, such as the 'inverse problem', system identification and parameter estimation. Finally there are many unsolved problems in non-linear compartmental systems, especially systems with random perturbations of the exchange processes operating between the compartments. Jacquez has divided the main applications of the compartmental system into the following groups:

(i) Development of a model for any particular (biological) system,
(ii) Development of the analytic theory for a given compartmental system,
(iii) Inverse problem.
He has also reviewed some concepts and properties of 'stochastic processes' together with the definitions of probability, density functions and distribution functions and sample and sample moments and Markov sequences.

Cobelli and Saccomani (1995) give some definitions on compartments and compartmental modelling along with some examples on different types of compartments, especially in the body. The concepts of accessible and non-accessible compartments and physical spaces and the meaning of the terms 'well-mixed' and 'homogeneity' are also introduced in their review. Finally, a discussion of the utility of compartments in reducing a complex physiological system into a finite number of compartments was given along with definitions and uniqueness criteria of the

compartmental model for each system. In the field of modelling metabolism and endocrinology, many research papers and text books have appeared since 1948. These works describe the analyses of kinetic data obtained following the administration of radioactively-labelled tracer material and drugs, using compartmental or non-compartmental approaches. The majority of these surveys have focused on limited aspects of the dynamics of metabolic processes, and more general problems have received little attention. A review of compartmental modelling is also discussed in Carson et al., 1983.

2.3: The role of compartmental modelling

The most common description of chemical and quantity transfer processes in biological systems is based on the concept of a compartment which we defined above. The use of compartments for model building is increasing, especially in biomedicine and metabolic processes, and researchers apply it commonly in their work. In using compartmental methods in metabolic processes, experimenters should ask themselves whether the concept of a homogeneous, well-stirred (mixed) 'tank' is appropriate for their particular application. There are also many reviews in this field and for details see for example Carson et al., 1983.

Compartmental models have many applications, for example, in modelling gas exchange in the lungs, where, with modern measuring devices, it is now possible to verify such compartmental models by externally scanning radioactivity content in the lungs.

2.4: Types of compartmental models

Compartmental models may be classified into several types which are presented in the next few sections.

2.4.1: Linear and nonlinear models

Linear systems are the most simple multi-compartmental systems. In these systems the fluxes of drugs or substances leaving a compartment is assumed to be proportional to the mass or concentration of that same compartment.

2.4.2: Open and closed models

If we have irreversible removal from one of the compartments in a system then we call the system an 'open system'. Alternatively, if there is no irreversible removal, the system is a 'closed system'. Figure 2.1 illustrates the general form of an open system, when modelled using multi-compartments.

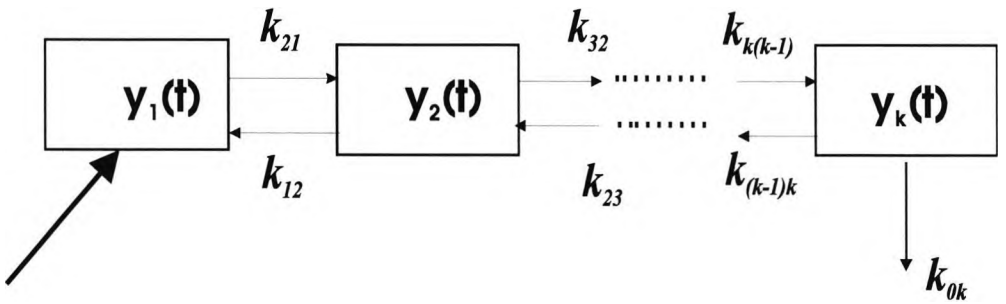


FIGURE 2.1: Open compartmental model.

2.4.3: Time varying models

As stated in section 1.5.7, time varying compartmental models have rate coefficients which are functions of time. The mass balance equation for each compartment is:

$$\frac{dy_i}{dt} = \sum_{j=1\ j\neq i}^{n} (k_{ij}(t)y_j - k_{ji}(t)y_i) - k_{0_i}(t)y_i + u_i(t), \qquad (2.1)$$

where y_i is the quantity of material (mass) in compartment i, and the k_{ij}s are time varying

random transfer rate coefficients. In theory, the k_{ij}s can take any values, but, in practice, they are non-negative.

2.4.4: Time invariant models

As mentioned in section 1.5.8, time invariant compartmental models have fixed transfer rate coefficients, i.e the k_{ij}s are independent of time.

2.5: Some useful definitions

The following sections present some useful definitions which may be applicable in most of the compartmental modelling to follow.

2.5.1: Transfer rate or turnover coefficient

The transfer rate is a non-negative constant that denotes the rate of exchange of drugs between compartments at time t. The k_{ij}s are the transfer rates of drugs from compartment j to i. Since:

$$Transfer\ rate = k = \frac{dQ/dt}{X(mass)} = \frac{(mass/time)}{mass},$$

per unit of volume of compartment, where dQ/dt is the rate of change of mass in any compartment, then the k_{ij}s have dimensions of time $^{-1}$ .The transfer rate which has an index starting with 0 indicates transfer to the system exterior or an irreversible removal.

2.5.2: Clearance rate

The rate of removal of drug from one or two compartments is known as the 'clearance rate' which can be defined as:

$$clearance = \frac{dQ/dt}{c(concentration)} = \frac{(mass/time)}{(mass/volume)} .$$

The dimension of the clearance rate is volume.time^{-1}.

2.5.3: Initial compartment

In a compartmental model, the compartment in which the drug has been introduced at time t=0 is called the 'initial compartment' and is numbered as compartment (1), (Rescigno et al., 1966).

2.5.4: Connected compartment

A system is 'connected' if it is possible to reach all the other compartments from the initial compartment (Rescigno et al., 1966).

2.6: Formulation (mathematical representation) of compartmental models

To develop the mathematical realisation of the compartmental model, we need to write the mass balance equation for each compartment in terms of the flux of substance between compartments. The general form of the equations is as follows:

$$\frac{dQ_i(t)}{dt} = R_{i0} + \sum_{j=1 j\neq i}^{n} R_{ij}(Q_j) - \sum_{j=1 j\neq i}^{n} R_{ij}(Q_i) - R_{0_i}(Q_i). \qquad (2.2)$$

where:

Q_i = quantity of material in compartment i.

R_{ij} = flux of material into compartment i from compartment j, depending on Q_j only.

R_{ji} = flux of material from compartment i to compartment j, depending on Q_i only.

R_{i0} = flux of material into compartment i from the external environment.

R_{0i} = flux of material from compartment i into the external environment.

Obviously, all fluxes are essentially non-negative.

2.7: Matrix representation of compartmental models

To represent the mathematical formulation of the compartmental model, especially in a multi-compartmental system, we have to use matrix representation of compartmental models. For this representation consider Figure 2.1 above. In the Figure $y_i(t)$ is the amount of drug (per unit volume) in compartment i at the time t. Using equation 2.2 we have:

$$dy_1(t)/dt = -k_{21}\ y_1(t) + k_{12} y_2(t) \qquad \textbf{(2.3)}$$

$$dy_2(t)/dt = k_{21} y_1(t) - k_{12}\ y_2(t) - k_{32}\ y_2(t) + k_{23}\ y_3(t) \qquad \textbf{(2.4)}$$

$$\vdots$$

$$dy_k(t)/dt = k_{k(k-1)} y_{k-1}(t) - k_{(k-1)k}\ y_k(t) - k_{0k}\ y_k(t). \qquad \textbf{(2.5)}$$

Therefore:

$$dY(t)/dt = AY(t) \qquad \textbf{(2.6)}$$

where:

$$dY(t)/dt = \begin{pmatrix} dy_1(t)/dt \\ \\ dy_k(t)/dt \end{pmatrix}, \qquad Y(t) = \begin{pmatrix} y_1(t) \\ \\ y_k(t) \end{pmatrix}, \qquad \textbf{(2.7)}$$

and:

$$A = \begin{pmatrix} -k21 & k_{12} & \cdots & 0 \\ k_{12} & -k_{12} - k_{32} & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots \\ 0 & 0 & \cdots & -k_{(k-1)k} - k_{0k} \end{pmatrix} \qquad \textbf{(2.8)}$$

is the matrix of the coefficients (Shah, 1972)

2.8: General solution of the compartmental model

The general solution of a compartmental model is a set of equations which satisfies the mass balance equations. To illustrate the general solution of any compartmental model consider the following two compartment model as shown in Figure 2.2:

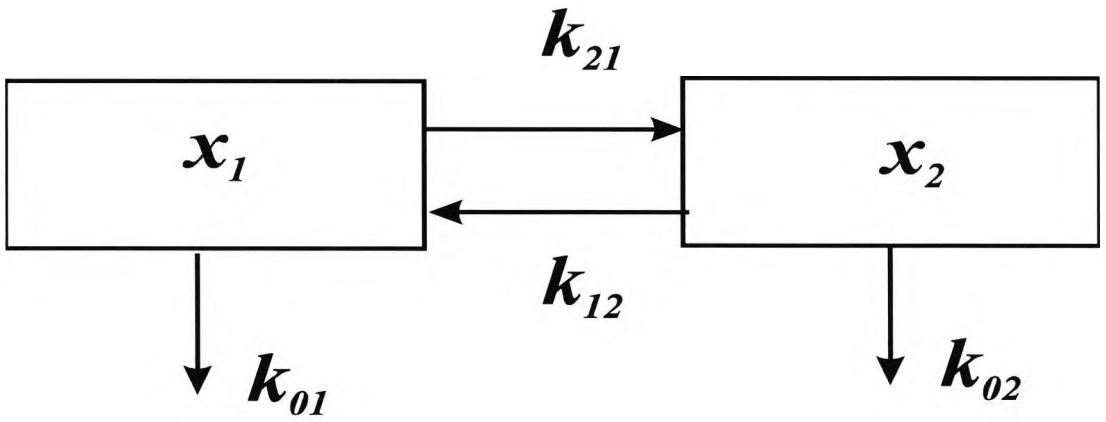


FIGURE 2.2: The general two compartmental model.

To find the general solution of the model we require the following definitions:

1. Let X_{ij} (t), with i , j = 1, 2 , denote the amount of drug that originated in compartment i at time 0 and that is in compartment j at time t.
2. Let k_{ij} , with j=1, 2, i= 0, 1, 2, i≠j denote the constant transfer rate from j to i, where 0 denotes the system exterior.

The following set of linear differential equations describes the deterministic

compartmental model illustrated in Figure 2.2:

$$\begin{aligned} dX_{i1}(t)/dt &= -(k_{01}+k_{21})X_{i1}(t)+k_{12}\ X_{i2}(t) \\ dX_{i2}(t)/dt &= k_{21}X_{i1}(t)-(k_{02}+k_{12})X_{i2}(t). \end{aligned} \tag{2.9}$$

These equations are of the form:

$$\frac{dX(t)}{dt} = -KX(t)+f(t), \tag{2.10}$$

where X(t) is mass, K is the relative rate of elimination (transfer rate) and f(t) is the rate of entry into the compartment.

4. Let

$$X(t) = \begin{pmatrix} X_{11}(t) & X_{12}(t) \\ X_{21}(t) & X_{22}(t) \end{pmatrix} \tag{2.11}$$

denote the matrix of amount.

5. Let

$$K = \begin{pmatrix} -(k_{01}+k_{21}) & k_{21} \\ k_{12} & -(k_{02}+k_{12}) \end{pmatrix} \tag{2.12}$$

be the coefficient matrix.

6. Let

$$\Lambda = \begin{pmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{pmatrix} \tag{2.13}$$

and T= [T_1, T_2] be the matrices of eigenvalues λ_i and corresponding eigenvectors T_i of K. We can then rewrite equation 2.10 in matrix form as:

$$\dot{X}(t) = X(t)K. \tag{2.14}$$

The general matrix solution is

$$X(t) = X(0)\ e^{Kt}, \tag{2.15}$$

which for distinct eigenvalues can be written as

$$X(t) = X(0)Te^{(\Lambda t)}T^{-1}, \tag{2.16}$$

where $e^{\Lambda t}$ is a diagonal matrix with elements $e^{\lambda it}$.

Equation 2.16 implies that solution for $X_{ij}(t)$ is a sum of exponentials.
The above equations can be solved easily in terms of the k_{ij} parameters for two and three compartment models (Matis et al., 1985).

2.9: A numerical example

In Figure 2.3 we have three possible structures for a two-compartmental model. To simplify equation 2.16 we assume a unit initial dose into compartment 1, i.e., $X_{11}(0)=1$. The numerical solutions for $X_{11}(t)$ and $X_{12}(t)$, for each of these models, are given by Rescigno et al (1966) and are shown in Table 2.1.

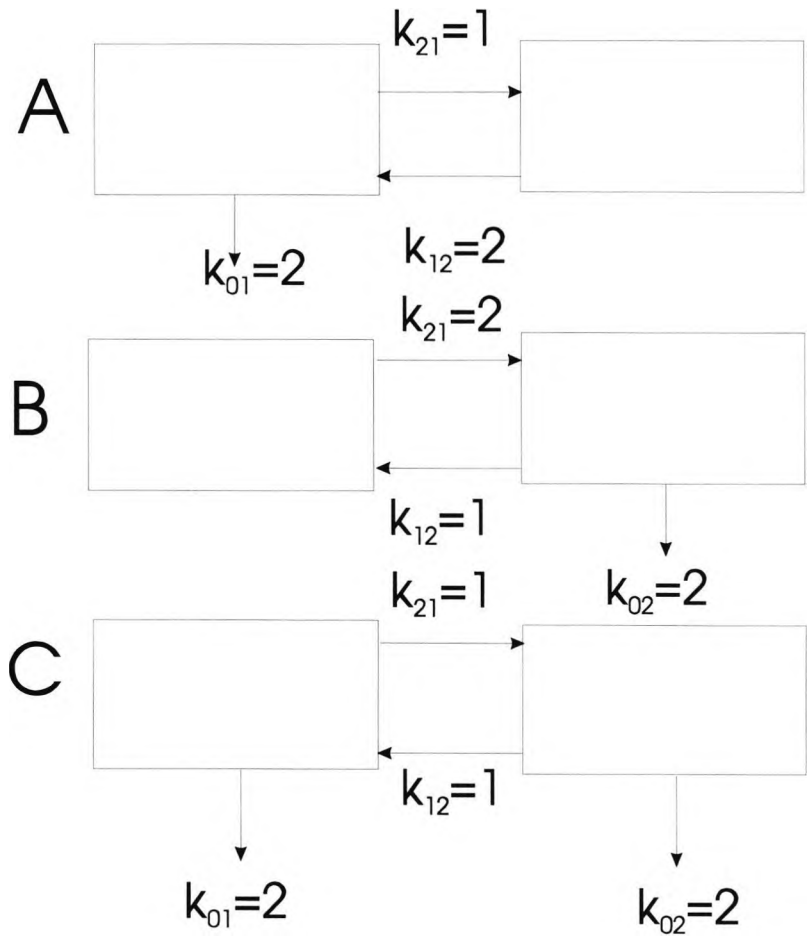


FIGURE 2.3: A specific illustration of three two-compartmental model structures based on different sources of elimination. Elimination from: A, central; B, peripheral; C, both central and peripheral compartments.

The intermediate matrix results are also given in Table 2.1. If we substitute these results into equation 2.16 we obtain the numerical solutions for the three models. Solutions for $X_{21}(t)$ and $X_{22}(t)$ are easy to find from equation 2.16 for any initial amount $X_{22}(0)$, (Godfrey, 1983).

Model A: Central elimination, with $k_{01}=2$, $k_{21}=1$, $k_{12}=2$

$X_{11}(t)=(e^{-t}+2e^{-4t})/3$,$X_{12}(t)=(e^{-t}-e^{-4t})/3$

$$K=\begin{pmatrix}-3 & 1\\ 2 & -2\end{pmatrix} \quad e^{\Lambda t}=\begin{pmatrix}e^{-t} & 0\\ 0 & e^{-4t}\end{pmatrix} \quad T=\begin{pmatrix}1 & 1\\ 2 & -1\end{pmatrix} \quad T^{-1}=\begin{pmatrix}1/3 & 1/3\\ 2/3 & 1/3\end{pmatrix}$$

Model B: Peripheral elimination, with $k_{21}=2$, $k_{02}=2$, $k_{12}=1$

$X_{11}(t)=(2e^{-t}+e^{-4t})/3$,$X_{12}(t)=2(e^{-t}-e^{-4t})/3$

$$K=\begin{pmatrix}-2 & 2\\ 1 & 3\end{pmatrix} \quad e^{\Lambda t}=\begin{pmatrix}e^{-t} & 0\\ 0 & e^{-4t}\end{pmatrix} \quad T=\begin{pmatrix}1 & 1\\ 1/2 & -1\end{pmatrix} \quad T^{-1}=\begin{pmatrix}2/3 & 3/3\\ 1/3 & 1/3\end{pmatrix}$$

Model C: Central and peripheral elimination, with $k_{01}=k_{02}=2$, and $k_{12}=k_{21}=1$

$X_{11}(t)=(e^{-2t}+e^{-4t})/2$,$X_{12}(t)=(e^{-2t}-e^{-4t})/3$

$$K=\begin{pmatrix}-3 & 1\\ 1 & -3\end{pmatrix} \quad e^{\Lambda t}=\begin{pmatrix}e^{-2t} & 0\\ 0 & e^{-4t}\end{pmatrix} \quad T=\begin{pmatrix}1 & 1\\ 1 & -1\end{pmatrix} \quad T^{-1}=\begin{pmatrix}1/2 & 1/2\\ 1/2 & -1/2\end{pmatrix}$$

Table 2.1- Solution for drug distribution over time for selected two-compartment models.

$X_{11}(0)=1$ and λ_1 and λ_2 are eigenvalues satisfying $\det|K-\lambda I|=0$.

2.10: Non-compartmental approaches

Compartmental models, which in many cases are theoretical models, can be used to estimate physical or chemical quantities which are not accessible to measurement. When successfully developed, they are powerful tools in basic physiological studies and clinical investigations. In most cases the compartments have a precise physiological meaning, the constant rate defining transfer of material between compartments involves the aggregation of several complex physiological processes. Sometimes the theoretical knowledge of the system is inadequate; for example, the compartmental structure may not be well defined. In this case, even if a definition is possible, experimental test data

may not be sufficient for identification of the model. To solve this problem, it is necessary to adopt a purely empirical or empirico-theoretical approach, focusing on overall input-output relationships, especially, at the level of the whole organism. This approach is generally called a non-compartmental approach.

In this approach one or two compartments are usually considered, explicitly or implicitly, which are accessible to measurement. The approach enables us to estimate many important physiological quantities (clearance rate, residence time, etc.) without recourse to structural models (Carson et al., 1983).

2.11: The integral equation (convolution) approach

The convolution approach is an important aspects of compartmental modelling. It has not been used in this research but it is given here for completeness.

To determine the amount of a quantity in an accessible compartment, we apply a convolution integral in the non-compartmental approach. In this method we need the rate of appearance in the compartment and the impulse response of the system. These processes are described in the following paragraphs.

In the non-compartmental approach, the well-known convolution integral method of linear system theory is applied (e.g., Finkelstein and Carson, 1985; DiStefano et al., 1976b). There are many applications of this integral, especially in the field of metabolic studies, when the approach involves tracer test methods.

To apply the convolution integral, we need a system which is assumed to have a simple accessible compartment (usually the plasma), containing a quantity of material Q. The impulse response of this system is denoted by h(t). $R_a(t)$ and R_d (t) are the rates of appearance and disappearance of material in the compartment Q, respectively. The mass Q(t) can then be described using the convolution integral

$$Q(t) = \int_0^t R_a(x) h(t-x)\, dx \qquad \textbf{(2.17)}$$

If any two of Q, R_a and h(t) are known, the third unknown quantity can be determined. If the unknown quantity is Q, then the approach simply involves the evaluation of the convolution integral. If the unknown is R_a, it leads the inverse process of deconvolution. In this case, Q and h should be expressed in analytical form, otherwise it requires the use of numerical methods (Carson, et al., 1983).

2.12: Summary

In this chapter the introduction and origin of compartmental models along with its role in model building was introduced. The types of compartmental model were also introduced using some diagrams of possible compartmental systems. Furthermore, some useful definitions were presented which are being used in compartmental modelling. The mathematical representation of compartmental models and also the matrix form of the mathematical representation were also discussed along with the method of obtaining the general solution of the compartmental model. Also, the solution of a compartmental model was discussed using a numerical example. Finally, the non-compartmental approach was discussed in detail at the end of the chapter.

Chapter 3

Stochastic compartmental models

3.1: Introduction

In some applications of deterministic compartmental models, stochasticity (randomness, variability) is incorporated within the model. These applications can be in biological experiments, pharmacokinetics, ecology etc. In this situation it is not useful to analyse the deterministic formulation of compartmental models due to obvious intra- and inter-subject variability and we should use an alternative formulation. There are many papers about linearity and non-linearity of compartmental models, but less about the stochastic nature of the models' parameters (Limić, 1992). Most of the previous modelling theory and virtually all of the previous applications have been based on a deterministic formulation of a compartmental system. Unfortunately, the rigorous and detailed stochastic formulation of such variability is not presented in any recent papers. In this chapter we will introduce and review the stochastic formulation of a compartmental model and its applications.

3.2: Different sources of stochasticity

Besides the diurnal and circadian variations, there are other irregular stochastic sources of variation. In this study we consider stochasticity due to an assumed random nature of the compartmental parameters of models relevant to the kinetics of glucose tracer in metabolic medicine. These variations normally take place over several hours after tracer injection. So measurements should be made over a long period of time in order to observe the fluctuations. Therefore, to determine of the role of the randomness and also for description and classification of the biological system, it is necessary to use a long time period for the stochastic compartmental model (Limić, 1989).

In stochastic compartmental models we have two major sources of stochasticity (Godfrey,

1983)

(i) Stochasticity incorporated into the rate coefficients;

(ii) Stochasticity incorporated into the state variables, with the assumption of deterministic rate coefficients.

For systems with stochastic rate coefficients there are many papers which deal with the variability in response, usually inter-subject, but occasionally intra-subject variability. Matis and Wehrly (1979) have divided the major source of stochasticity into the following classes:

1. The stochasticity associated with individual units or particles. This is further divided into the following sub-classes:

(i) Stochasticity arising from sampling from the random process;

(ii) Stochasticity due to random rate coefficients.

2. The stochasticity associated with replication of the whole experiment. This is further divided into random initial amount and random rate coefficients (time-varying or constant).

If the combination of the above sources of stochasticity is considered, there are many possible types of stochastic models.

The stochasticity in rate coefficients has been the subjects of considerable research within the last two decades. We will define and describe this type of stochasticity in section 3.4, but some recent papers are introduced here briefly. Cobelli and Morato (1978) introduced a biological compartmental model where the rate coefficients were random and possibly varying with time. In the field of pharmacokinetics Soong (1972) presented a compartmental model with random rate coefficients in the study of optimal drug dosage control. Also, the identification of a random compartmental model with random rate coefficients from kinetic data in pharmacokinetics was considered by Soong and Dowdee (1974).

Campello and Cobelli (1978) considered a linear time-invariant biological compartmental model with random rate coefficients. They proposed a procedure for the estimation of the properties of the stochastic rate coefficients of a n-compartmental model from an input-output tracer experiment.

There are also some papers on the estimation of compartmental parameters which is one of the most important tasks in this field. Some of these papers are introduced here briefly. Matis and Hartley (1971) introduced a compartmental system with a discrete population of particles in a steady state. The system is considered to have n compartments and the transition rates are stochastic in nature. The paper is concerned with the estimation of the transition rate parameters and this requires the associated theory of distributions. Landaw and DiStefano (1984) presented a multi-exponential and multi-compartmental model and used a new curve fitting procedure for estimation of the parameters. Allen (1983) introduced a computational technique for the estimation of the parameters in non-linear stochastic compartmental models which was shown to reduce programming effort, facilitate inference about implicit functions of parameters, and allow a more general variance-covariance structure.

The main factors which cause the uncertainties in the rate constant (Soong, 1971) are:

(i) Scatter of experimental kinetic data,
(ii) Environmental effects,
(iii) Variation of patient's parameters over time,
(iv) Effect due to drugs.

There are many factors which cause uncertainties in the rates constant, some of which are:

(i) Individual variability,
(ii) Variation of system parameters with time,
(iii) Interaction with other drugs,

(iv) Variation in volume/area ratio,

(v) Variation in cell membrane dimensions,

(vi) Measurement error,

(vii) Sampling error.

Matis and Tolley (1979) introduced a categorisation for different sources of stochasticity in compartmental models. In their categorisation, they introduced 'probabilistic transfer mechanisms' as a new source of stochasticity which is a general form for the above (ii) division. Also, the 'individual variability' was divided into two different subdivision of intra- and inter-individual variability where in inter-individual for any single experiment the common rate for each unit is a random variable (either time varying or constant). Furthermore, they presented 'random distribution volume' which is exactly the same as (iv) above and fixed in time. Finally, they introduced a new type of stochasticity which can arise from the mixture of the above stochasticity.

3.3: Stochasticity (randomness) in glucose tracer experiments

In glucose tracer experiments a tracer of glucose is injected into the blood and its decay as it diffuses from blood to muscle tissues and cells is measured over a period of time. Normally, a deterministic compartmental model (which assumes fixed compartmental parameters) is used to analyse the data. However, due to the random nature of the parameters, this kind of model is not always appropriate. This is because of the obvious variability in the parameters of the models due to inter-and intra-subject variability. Recent work in this area suggests that the best method to describe the kinetics of substances is to use a stochastic compartmental model which considers the parameters (transfer rate between compartments, losses from compartments and the initial concentration of glucose tracer in blood plasma) as random variables and not fixed constants. This stochasticity (randomness) is assumed to fall into two main categories:

(i) parameters are constant in a specific experiment, but they vary from one experiment to another if we repeat it in the same subject or from one subject to

another,

(ii). the parameters vary randomly with time during the course of a single experiment and they vary from one subject to another but this intra subject variance does not vary with time.

3.4: Stochasticity in transfer rate coefficients

The 'transfer rate coefficient' is a non-negative constant which denotes the rate of exchange between compartments during time. One of the most important types of stochasticity which is incorporated into compartmental systems, is the stochasticity in rate coefficients. In this type of variability, randomness is associated with transfer rate between compartments and also with losses from compartments. Therefore, the transfer rate and, the losses and hence the whole compartmental system have a random nature. This variability is due to variability between subjects when a single experiment is repeated in different subjects, or a single subject takes part in different experiments. In both cases the compartmental parameters have a random nature and therefore random distributions (the parameters are constant in a course of a single experiment). Also, the parameters vary randomly with time during a single experiment and hence between subjects. Thus, the estimation of compartmental parameters leads to different values in different subjects and experiments. This type of variability is considered in this research and will be discussed in more detail in Chapters 5 and 6.

3.5: Stochasticity in initial concentration of glucose tracer

The initial concentration of glucose tracer in compartment 1 is usually produced by an intravenous injection and, due to the above discussion and due to inter- and intra- individual variability, this initial concentration of glucose tracer is considered as a random variable. Therefore, this new source of variability causes an additional degree of randomness in the whole (compartmental) system which must be considered in data analysis. This new type of stochasticity has also been considered in this research because different subjects have

different initial concentrations. Also, the initial concentration of glucose tracer in a single subject varies when different experiments are applied.

3.6: The use of residence time moment in stochastic compartmental models

One recent method in analysing a compartmental model is the use of 'residence time moments', particularly mean and variance residence times. This method can be very useful in modelling and kinetic analysis of a physiological system. There are many papers in this field and some of them will be introduced here. Matis and Wehrly (1985) have introduced a stochastic compartmental model and presented its general solution in matrix form. Then mathematics and statistics were applied to calculate the 'residence time', 'number of visitation' and 'total residence time' of the particles in the (compartmental) system. Kapadia and McInnis (1976) introduced a compartmental system with continuous time-dependent infusions into all compartments and reversible time-independent flow between any two compartments. The first two moments of the distribution of the number of units in the different compartment were also presented, and the method was applied for analysis of the kidney transplant system. Kapur (1980) presented a stochastic compartmental model with continuous infusion, and moments of all orders for the probability distribution of the number of particle in all compartments were discussed.

Besides the above application of statistical moments, there are many applications of moments in pharmacokinetics. Beal (1987) applied the formula of a linear kinetic model in order to introduce some new concepts and role of residence time moments. Yamaoka and Nakagawa (1978) used statistical moments as the parameters which describe the characteristics of the time courses of plasma concentration (area under the curve, mean residence time, and variance of residence time) and of the urinary excretion rate that follows administration of a single dose of drug. Matis, Wehrly and Metzler (1983) presented deterministic and stochastic models for a linear compartmental system with constant coefficients, and they developed expressions for the mean residence time (MRT) and the variance of residence time (VRT) for the stochastic model. The MRT and VRT provide a set of new meaningful response measures for pharmacokinetics analysis and they give added

insight into the system kinetics. Finally, Matis, Wehrly and Gerald (1985) used residence time moments in compartmental analysis. They verified that the formula for time moment formulation has several advantages as follows:

(i) A smaller number of parameters are usually needed to describe a biological system;
(ii) These parameters have a clear physical interpretation;
(iii) Their statistical 'power' to detect certain treatment differences is greater;
(iv) They are computationally simple in many situations.

We shall now introduce, illustrate and show their practical utility following Matis et al, 1985. It is necessary to say that the following definition and methods have not been used in the body of the thesis because they relate to the transition or movement of individual particles in compartmental models. We do not consider individual particles in our models and only glucose tracer is considered. Although these 'residence time moments' have not been used in this research, due to their importance, especially in recent papers they are discussed here for completeness. On the other hand, in section 3.9 there is a numerical example on the applications of the above residence time moments in stochastic compartmental models which clearly show their importance and application in stochastic compartmental models.

3.7: Types of residence time moments

In the next few sections we shall introduce some new types of residence time moments.

3.7.1: Mean and variance of transit times

Let R_i, with i=1, 2,...,n, denote the random retention time (also called transit time) during the current visit of a particle in compartment i prior to its next transfer out of compartment i (to any other compartment or the exterior) . We use mean and variance of random retention time later (Matis et al., 1985).

3.7.2: Mean and variance of number of visits

Let V_{ij}, with i, j=1, 2,..., n, denote the random number of visitations that a particle originating in compartment i, say at t=0, will make to compartment j prior to its departure from the system. We denote the mean and variance of random number of visitation with τ'_{ij}, and γ'_{ij} respectively. We will also discuss these later (Matis et al., 1985).

3.7.3: Mean and variance of residence times

Mean and variance of residence times (MRT and VRT) denote the total residence times that a particle originating in compartment i will accumulate in compartment j during its various visits. So, the residence time is the sum of the random number of visitations. Thus, if we denote the random number of visitations by V_{ij} (i, j= 1,2,...,n), and the total residence time by S_{ij} (i,j=1,2,...,n), we have (Matis et al., 1985):

$$S_{ij} = \sum_{i,\,j} V_{ij} \ .$$

3.7.4: Mean and variance of system residence times

Mean and variance of the system residence time are defined by the total residence time that a particle originating in compartment i will accumulate in the system prior to its departure. So, if we illustrate the system residence time by $S_{i.}$ we have (Matis et al., 1985):

$$S_{i.} = \sum_{j} S_{ij.} \ .$$

3.8: Residence time moment of non-compartmental models

Recently, a new method of finding statistical moments has become widely used in pharmacokinetic data analysis. This method, called the non-compartmental approach, is used to calculate the moments from concentration time curves. Also, this approach has many applications in other sciences, particularly in chemical engineering. Since the theory

is 'non-compartmental' we have the following

(i). These statistical moments methods do not require the assumption of a specific compartmental model;

(ii). There is (now) very much less interest in characterising the pharmacokinetics of a drug in terms of model-dependent constants.

This new approach is very useful where is has been correctly applied, otherwise, it has led to considerable confusion in its implementation. Consider Figure 2.3; if a particle is introduced into compartment 1, and it can leave the system via compartment 1, then the non-compartmental approach may be very useful in finding certain moments. From the three models of Figure 2.3 only model (A) satisfies the necessary assumption for the use of a non-compartmental approach.

The basic non-compartmental result relating to residence time are:

$$(i)\ Area\ Under\ Curve = AUC = \int_0^\infty X_{11}(t)\ dt$$

$$(ii)\ MRT = \int_0^\infty t X_{11}(t)\, dt / AUC$$

$$(iii)\ VRT = \int_0^\infty (t - MRT)^2 X_{11}(t)\, dt / AUC.$$

also , it is possible to develop other measures, such as:

$$(iv)\ \tau_{11} = AUC / X_{11}(0),$$

where $X_{11}(0)$ is the amount of substance that originated in the first compartment and is still in the same compartment at time t=0 and τ_{11} is the mean residence time. Note that all of these results are calculated directly from $X_{11}(t)$, which is often interpreted as the drug level in the plasma and hence is usually observable. So, we can estimate all of these by numerical integration of $X_{11}(t)$ and we do not need any specific compartmental structure. Also, in estimating these moments we do not require to estimate the k_{ij} rate coefficients, although estimation of k_{ij} was necessary in the previous method. It is important to use this approach correctly, for otherwise serious errors in estimation of the moments may occur (Matis et al., 1985).

3.9: A numerical example

Let R_i, V_{ij}, S_{ij}, and S_i denote respectively the random transit time, random number of visitations, total residence time and system total residence time.

(i) Let τ_{ij} and γ_{ij} denote the mean and variance of the residence times S_{ij} ;

(ii) Let τ'_{ij} and γ'_{ij} denote the mean and variance of the number of visitations V_{ij} ;

(iii) Let τ_i and γ_i denote the mean and variance of the total system residence times S_i ;

(iv) Let $\tau=(\tau_{ij})$, $\tau'=(\tau'_{ij})$, $\gamma=(\gamma_{ij})$ and $\gamma'=(\gamma'_{ij})$ be matrices of the means and variances.

The following result are easy to prove (Matis et al., 1985):

(i) $\tau=-K^{-1}$,

where K is the relative rate of elimination from the compartment;

(ii) $\gamma=2\tau\tau_D-\tau_{(2)}$,

where τ_D is the diagonal matrix$(\tau_{11},\tau_{22},...)$ and $\tau_{(2)}$ is the matrix of squared elements of τ;

(iii) $\tau'=(i-K')^{-1}$,

where K' is the normalised K matrix, and thus $\acute{K}_{ii}=0$ and $\acute{K}_{ij}=-K_{ij}/K_{ii}$ for $i\neq j$, and i is the identity matrix;

(iv) $\gamma'=2\tau'\tau'_D-\tau'_{(2)}$ where τ'_D and $\tau'_{(2)}$ are defined like above (Matis et al., 1985)

(v) $\text{cov}[S_{ij}, S_{ik}]=\tau_{ij}\,\tau_{jk}+\tau_{ik}\tau_{kj}-\tau_{ij}\,\tau_{ik}$.

Now consider Figure 2.3 in Chapter Two. Table 3.1 contains the results when the previous formulae based on the compartmental approach are implemented for the three models given previously.

For model (A) we have:

$E(R_1)$ = expected transition time in compartment 1=1/3.

$E(R_2)$ = expected transition time in compartment 2=1/2.

The mean and variance of visitations of the particle which is introduced to compartment 1 is:

τ'_{11} = 3/2 which is the mean number visits to compartment 1;

τ'_{12} = ½ which is the mean number visits to compartment 2.

The expected residence times of a particle are:

τ_{11} = ½ in compartment 1;

τ_{12} = 1/4 in compartment 2.

The total expected residence time, i.e. the mean residence time of the system, is the sum of the residence times in the individual compartments. So for the present particle one has:

$$\text{MRT} = \tau_1 = \tau_{11}+\tau_{12} = 3/4.$$

The VRT is the sum of the individual variances in the two compartments plus twice the covariance. From (v) above we can calculate the covariance between S_{11} and S_{12}, which is

1/8. So for the present particle we have:

$$VRT = \gamma_{1.} = \gamma_{11} + \gamma_{12} + 2\text{cov}\,[s_{11}, s_{12}] = 13/16.$$

It is possible to calculate many other moments that are useful for describing the kinetics of particles in model (A). For example, a particle initially in compartment 2 has an MRT of $\tau_{2.} = 5/4$ and a VRT of $\gamma_{2.} = 17/16$. Also, a particle originating in 1 is expected to visit a compartment $\tau'_{1.} = 2$ times on average.

These moments and other higher order moments, e.g. for skewness, kurtosis, and cross-moments, are useful in developing monitoring tests for the basic assumptions, e.g. of constant rates. Such tests are under current investigation.

The particle kinetics of models, B and C are similar to model A and are presented in Table 3.1. To summarise, we present only two moments of great interest in the subsequent development, namely, for model B one has:

$$MRT = \tau_{1.} = 5/4 \quad \text{and} \quad VRT = \gamma_{1.} = 17/16$$

and for model C one has:

$$MRT = \tau_{1.} = \tfrac{1}{2} \quad \text{and} \quad VRT = \gamma_{1.} = 1/4.$$

Model (A): Elimination from central compartment, with $k_{01} = 2$, $k_{21} = 1$, $k_{12} = 2$

$E(R_1) = 1/3$ $\quad$ $E(R_2) = ½$

$$K = \begin{pmatrix} -3 & 1 \\ 2 & -2 \end{pmatrix} \quad \tau = \begin{pmatrix} 1/2 & 1/4 \\ 1/2 & 3/4 \end{pmatrix} \quad \gamma = \begin{pmatrix} 1/4 & 5/16 \\ 1/4 & 9/16 \end{pmatrix}$$

$$\acute{K} = \begin{pmatrix} 0 & 1/3 \\ 1 & 0 \end{pmatrix} \quad t = \begin{pmatrix} 3/2 & 1/2 \\ 3/2 & 3/2 \end{pmatrix} \quad \acute{\gamma} = \begin{pmatrix} 9/4 & 5/4 \\ 9/4 & 9/4 \end{pmatrix}$$

Model (B): Elimination from peripheral compartment, with $k_{21} = 2$, $k_{02} = 2$, $k_{12} = 1$

$E(R_1) = 1/2$ $\quad$ $E(R_2) = 1/3$

$$K = \begin{pmatrix} -2 & 2 \\ 1 & -3 \end{pmatrix} \quad \tau = \begin{pmatrix} 3/4 & 1/2 \\ 1/4 & 1/2 \end{pmatrix} \quad \gamma = \begin{pmatrix} 9/16 & 1/4 \\ 5/16 & 1/4 \end{pmatrix}$$

$$\acute{K} = \begin{pmatrix} 0 & 1 \\ 1/3 & 0 \end{pmatrix} \quad t = \begin{pmatrix} 3/2 & 1/2 \\ 1/4 & 3/3 \end{pmatrix} \quad \acute{\gamma} = \begin{pmatrix} 9/4 & 9/4 \\ 5/4 & 9/4 \end{pmatrix}$$

Model (C): Elimination from central and peripheral compartments with $k_{01} = k_{02} = 2$ and $k_{12} = k_{21} = 1$

$E(R_1) = 1/3$ $\quad$ $E(R_2) = 1/3$

$$K = \begin{pmatrix} -3 & 1 \\ 1 & -3 \end{pmatrix} \quad \tau = \begin{pmatrix} 3/8 & 1/8 \\ 1/8 & 3/8 \end{pmatrix} \quad \gamma = \begin{pmatrix} 9/64 & 5/64 \\ 5/64 & 9/64 \end{pmatrix}$$

$$\acute{K} = \begin{pmatrix} 0 & 1/3 \\ 1/3 & 0 \end{pmatrix} \quad t = \begin{pmatrix} 9/8 & 3/8 \\ 3/8 & 9/8 \end{pmatrix} \quad \acute{\gamma} = \begin{pmatrix} 81/64 & 45/64 \\ 45/64 & 81/64 \end{pmatrix}$$

Table 3.1: Solution for statistical moments based on a compartmental approach for selected two compartment models.

To calculate the residence time moments in the non-compartmental approach, suppose for model A of Figure 2.3 Chapter 2 we have $X_{11}(t) = (e^{-t}+2e^{-4t})/3$ and we are going to calculate the above moments. From equations, (i) to (iii) Section 3.8 we have:

AUC = ½ , MRT = 3/4 , and VRT = 13/16.

Since $X_{11}(0)=1$ from (iv) in section 3.8 we have $\tau_{11}=1/2$. As can be seen, all of these results agree with the earlier results for the compartmental approach.

As mentioned earlier, the assumption cannot be satisfied in models B and C, so improper use of equations (i) to (iv), in Section 3.8, with this method yields incorrect results. To illustrate this point, we apply the above equations in model B. We have:

AUC=3/4, MRT=11/12 , VRT=137/144 and $\tau_{11}=3/4$.

It is easy to see that MRT and VRT do not agree with the compartmental results and they are incorrect. Similarly for model C, we can find:

AUC=3/8, MRT=5/12, VRT=29/144 and $\tau_{11}=3/8$.

Also, we see here a difference between the MRTs and VRTs result in the two methods (see Section 3.8), so the non-compartmental results for MRT and VRT are incorrect (Matis et al., 1985)

3.10: Population modelling in pharmacokinetics

In this section population modelling in pharmacokinetics and its usefulness in pharmacokinetics studies is briefly introduced. Normally, this topic is applied in professional studies in pharmacology and pharmacokinetics, but due to its explicit application in this study, especially in Chapters 5 and 6, it is discussed here for completeness.

Pharmacokinetics (PK) is the study of various biological processes affecting a drug: dissolution, absorption, distribution, metabolism and elimination. Population pharmacokinetics (PPK) is the study of the variability in plasma drug concentration between

subjects when standard dosages are administered (Aarons, 1993). Population models were developed to analyse processes that can be described normally by parametric models using measurements obtained in a sample of subjects. These measurements are often analysed using linear or non-linear regression. The individual data are usually sparse and noisy in comparison with traditional pharmacokinetic studies.

The traditional PK analysis involves the study of individual PK parameters. The population modelling method considers the time-concentration data pooled from more than one subject to estimate the PK parameters in a target population.

There are some statistical methods which assume that the inter-subject variabilities of parameters are random variables. Covariates, such as demographic data (age, body weight etc.), or the disease stage are not controlled in the study but are, nevertheless, considered. These variables are the best tools for analysing the source of inter-subject variability in the PPK approach. The covariates are usually easy to measure and may be related to absorption, distribution or elimination processes of drug. The goal is to find a relationship between some of the PK parameters and some of the covariates to estimate the residual variability in order to identify meaningful covariates. These covariates are used as additional prior information in dosage optimization or used to find high risk subgroups.

To analyse PK data that are pooled over all sampled individuals, a non-linear mixed effect regression model is often used. These models (mixed effect models) contain variance components for both random (for example, measurement error) and fixed effects (for example, gender). The fixed effects relate PK parameters to covariates (uncontrolled factors) and normally account for the large inter-subject PK variability. The inter-subject random effects (type one) quantify the residual unexplained variability and an additional random effect (type two) quantifies intra-subject and measurement variability. There are many papers in this area and a brief summary of some of them is given below.

Beal and Sheiner (1982) developed a method for analysing the data arising from a population PK study. They considered the variabilities between the PK / PD parameters

across the subjects, which are related to the variabilities between the factors such as age, gender etc. They applied different models and statistical analysis (maximum likelihood, least squares approach etc.) and introduced a new approach to fit the models to the above data to estimate the PK parameters. All the above models and approaches, and their advantages and disadvantages in facilitating the accurate parameter estimation, were compared. They also introduced so-called two-stage method for considering the variability of the model parameters (in a single subject or in the population) and estimation of the parameters.

Aarons (1993) applied an estimation-maximization (EM) algorithm to analyse the data from a non-linear mixed-effect model. In this approach the fixed parameters were determined by the maximum likelihood method using a simplex minimization program (NAG routine E04CCF, NAG Workstation Library (1989)), and the random effects were estimated by the EM algorithm. The application of a simple linear model and population PK were also described together with the use of posterior parameter estimates for investigation of covariate relationship (Racine-Poon, et al., 1990) . A comparison of the EM algorithm and other minimization algorithms was made and their advantages were discussed. Yue et al. (1994) reviewed the methodology and applications of population PK together with obtaining measurements from sampled individuals after administration of the drug. The method of building a non-linear regression PK model using the data together with the definition of PK parameters was also presented. The traditional and more recent methods to design experiments were also discussed with the description of a traditional 'standard two-stage method' used to analyse the data. In this method, the individuals' parameters are obtained using non-linear regression in stage I. At stage II, a central value and a measure of variability is obtained for each parameter from the empirical distribution of the stage I parameter estimates. The method of considering the variability between and within subjects and a brief discussion of non-linear mixed effect regression models were also described. Finally, a brief bibliography on linear mixed effects models, non-linear models and the application of PK / pharmacodynamics (PD)were presented. Mentré et al. (1994) described the application of PK to measure the inter-subject variability. The parametric and non-parametric approaches to investigate effect of covariates on gentamicine

data were compared. The advantages and limitations of each approach regarding handling of covariates are illustrated and compared using the same data.

Vozeh et al. (1996) and colleagues used the non-linear mixed effect model program, NONMEM, to analyse variability in the PK data. They also divided the different stages of study and considered four different phases. Phase 1 described the administration of drug to groups of subjects under well-defined and controlled experimental conditions and taking blood samples from all subjects. Phase 2 defined whether a compound had the expected clinical effect and also defined the possible clinical dose range in the subjects. In phases 2b and 3 the design strategy for the clinical trial was considered using data collected in the previous phases. In late phase 3 and phase 4, clinical trials were performed to assess the tolerability of a drug that had been shown to be effective. Finally, the design of population studies, practical considerations, software for the population approach were reviewed in detail with many references. Mandema et al. (1992) applied NONMEM to find the relationship between patients' PK and PD parameters, and other specific covariates. They used a three stage strategy. In the first stage, the patient's PK/ PD parameters were used as empirical Bayes estimates, based on a prior NONMEM fit using no covariates. In the second stage, the PK/ PD parameters were regressed on the covariates using a generalized additive model. In the final step, NONMEM was used to optimize and finalize the population model. To test the effectiveness of the above approach, four real data sets were used and it was found that the generalized additive model for the estimated parameters is the best initial guess for NONMEM. It was also shown that the approach successfully selects the most important covariates and their functional representation. Finally, it was shown that this numerical approach is fast and the number of necessary NONMEM runs is reduced, so less time is required to derive a population model.

Power (1993) divided pharmacokinetic studies into 3 different categories as follows:

(i) Population based investigations;

(ii) Individual based compartmental;

(iii) Individual based non-compartmental research projects.

The methods of study in all categories were discussed in detail using relevant mathematical formalisms. There is also an overview about basic statistical considerations underlying any experimental design. The history of population PK, the traditional and recent approaches in PK and the statistical analysis to consider the variability between subjects were also discussed together with the definition of random and fixed effects. The application of NONMEM software in data analysis was also briefly introduced. Finally, suitable statistical analysis for individual-based PK was described together with some statistical tests. Best et al. (1995) described a Bayesian approach to population PK analysis which used a technique known as Gibbs sampling to simulate values for each model parameters. This method was demonstrated via an application to gentamicine population in neonates. For the population PK estimation NONMEM software was used. Dursano (1991) applied an optimal sampling approach which determines the most information-rich sampling schedule to allow robust parameters estimate to be determined from minimal number of sampling in a spacecraft environment. NONMEM software was used to allow the patients' data sets to contribute to the population parameter estimates. The determination of the influence of microgravity environment on drug distribution and elimination was also discussed using some examples. These examples showed the validity of these techniques and their usefulness.

There are many population PK software packages which are used in population PK/ PD studies. Some of the more well-known packages are introduced below.

(1). NONMEM (Non-linear Mixed Effect Modelling based on work by Beal and Sheiner (1982)): This is a widely used and well-supported program for PK / PD population analysis. It is an approach where the population is taken as the unit of analysis, allowing generation of estimates of PK parameter values in a single step. Fragmentary data from different subjects can contribute to the estimation of parameter values. The program also partitions the observed variance into that attributable to the PK model as well as the difference between subjects (inter-subject variance) and within-subject (intra-subject variance / residual error) (Drusano, 1991). NONMEM uses a first-order Taylor series expansion to produce a linear random- effect model. Estimation of the population parameters is achieved

through maximization of the associated likelihood objective function. NONMEM also estimates the first two moments of the population distribution of PK parameters of interest. While these estimates fully specify the probability density function of parameters when the underlying distribution is normal or lognormal, they provide incomplete information in situations where the density is non-symmetric (Best et al., 1995). Some of the applications of NONMEM were introduced in the above literature review.

(2). ADAPT II: This is a software package which is used for PK studies. It has two main programs ID (parameter estimation) and SIM (simulation). In this section we will discuss the SIM program very briefly as more details are given in Chapter 4. SIM has 4 options which the third (population simulation) and fourth (population simulation with output noise) of which the options are related to population modelling. In the population simulation option, SIM performs a specific number of simulations of the model, with values of the model parameters (say α) randomly selected from a normal and lognormal distribution. Also, α can be partitioned into a normal or lognormal component, α_1, and a component α_2 which comes from an independent uniform distribution. In population simulation with output noise option, the program allows for a population simulation with output error. The output of the program in the above cases (both options) is a table containing the mean, SD and minimum and maximum values for each output at each observation time. A summary of parameters is also provided with the same statistical analysis. Furthermore, there are plots displayed at each observation time containing the average output with SD bars. A continuous curve is displayed for each model output, that is obtained using the population mean parameters values.

(3). POPKAN: This is a population PK modelling and analysis PC software tool. It offers clinical and PK researchers a menu driven application tool for population modelling and analysis. The software also supports the analysis of the most important kinetics and dynamic models. It provides extensive tools for model and outlier diagnostics and offer prediction features. It also presents the summaries and results in graphical and numerical forms.

(4). P-PHARM: This is a population PK / PD data modelling computer program designed for fitting a general nonlinear regression model to the data. The data for analysis are collected from preclinical studies, especially the administration of a drug to different individuals and obtaining the output measurements in different biological fluids. To build a model using the above data, one needs to account for both unexplained inter-subject effects (random effects) along with the measurement covariate effects (fixed effects). P-PHARM has been designed to allow the user to define such mixed effect modelling. The approach is useful when only a few measurements are available for each individual sampled within population. The software uses a two-stage procedure and / or an EM- type algorithm (for sparse data). This is an iterative process suitable for computing the maximum likelihood in complex problems. The software supplies a multi-dimensional search (stepwise multiple regression) option to identify the possible optimal linear relationship between the model parameters and the available covariates. P-PHARM also has a procedure to validate the PK model and the estimation population parameters together with a procedure to identify the outlier subjects and / or measurements.

Some of the methodology used above is relevant to the work that is discussed in Chapters 5-6. However, most of the methodology is more appropriate to advanced pharmacokinetic studies. To study the pharmacokinetic response obtained from a subject after the administration of a drug the output was obtained at different time points and in different subjects. To find the parameter estimates, a model is fitted to the response to predict the concentration of drug at times other than observation times and potentially more than one site (and with drug dosage other than the administrated dosage in more complicated pharmacokinetic studies). In this thesis two double-compartment models for the concentration of drug in blood plasma are proposed and the method of model building is discussed in detail in Chapter 5 and 6.

3.11: Summary and discussion

In this chapter stochastic compartmental models were introduced and some different sources of stochasticity, especially stochasticity in the rate coefficients and in the initial

concentration of glucose tracer, were also discussed. The stochastic model in tracer experiments was also introduced in detail. The definition, application and types of residence moments for the particles which are being introduced to the system were also introduced. The method of calculation of residence time moments was discussed using a numerical example. Furthermore, the method of calculation of residence time moments in the non-compartmental approach was also introduced and it was shown that this approach is useful for calculation of residence time moments of a particle. Finally, the population modelling in pharmacokinetics and its usefulness in pharmacokinetics studies is briefly introduced and a brief review of the literature and a description of some software packages is given.

Chapter 4

Method and data analysis

4.1:Introduction

The data were obtained from a sample of seventeen women from St. Thomas' Hospital in London (Bowes et al., 1996). All the women were in their post-partum periods and some of them had gestational diabetes mellitus (GDM) during pregnancy. To study the effect of obesity, the sample was divided into two groups of obese and normal subjects; each group also contains normal and GDM subjects. The subject whose mass is at least 30% more than her ideal body mass (Diem, et al., 1971), which is a function of height and age, is considered as an obese subject. Table 4.1 gives details of the sample. As can be seen there is a large difference between the two groups of subjects. Using the t-test, a significant difference was found between the mass of the two groups and ($p<0.0033$), but there was no significant differences between ages and heights of the groups.

An intravenous glucose tolerance test (IVGTT) (Nattras, 1986) was administered to each subject. A bolus of glucose and glucose tracer (20 mg/kg body mass) was injected into an arm vein of over one minute and blood samples were drawn from the contralateral vein at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160 and 180 minutes after injection. Table C_1 in Appendix C shows the glucose tracer concentration in the blood plasma of subjects at each sample time after injection. Figure 4.1 shows the mean blood plasma glucose tracer concentration for the obese and non-obese groups. The curves for the total group of subjects have been omitted for clarity.

No	GDM Status	Obese (Y/N)	Age yr	Height cm	Body Weight kg
1	GDM	Y	35	159	79.8
2	GDM	N	34	169	69.3
3	GDM	N	38	154	54.6
4	GDM	N	34	161	72.3
5	normal	N	29	163	69.3
6	normal	Y	39	160	77.9
7	normal	Y	20	164	98.5
8	normal	Y	30	167	109.8
9	normal	Y	27	177	101.4
10	normal	N	25	161	64.6
11	normal	N	38	175	78.1
12	normal	Y	30	148	68.0
13	normal	N	30	157	61.0
14	GDM	N	32	156	67.5
15	normal	Y	33	157	86.5
16	normal	Y	30	151	80.0
17	normal	N	31	169	63.6

Table 4.1: The distribution of women according to age, height and weight.

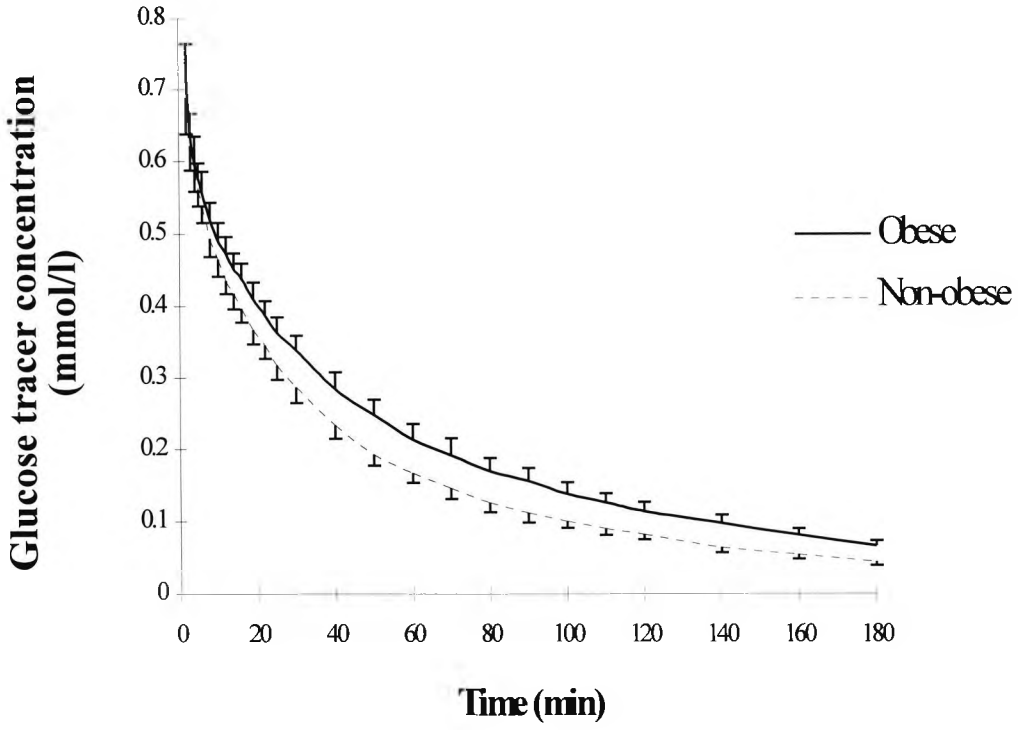


Figure 4.1: Mean blood plasma glucose tracer concentration for obese and non-obese groups.

4.2: Gas chromatograph-mass spectrometer (GCMS)

Each blood sample was analysed at St. Thomas' Hospital using a GCMS. To obtain the mass spectrum of a single compound, a mixture of compounds is separated in the gas chromatograph into single components before entering the mass spectrometer. The gas chromatograph is widely used to separate mixtures in the gas or vapour phase and was first coupled to the mass spectrometer in the 1960s.

The GCMS is the most widely used instrument for quantitative mass spectrometry analysis. The GC provides an on line separation step, concentraining the analytes into defined peaks for sequential admission to the mass spectrometer (Markey, 1981). The Selected Ion Monitoring GCMS in which the mass spectrometer monitors a small number of selected Ions, represents the major use of stable isotopes (Haskins, 1982).

4.3. Estimation of unknown data

The data for some of the above time points were not available. The unknown glucose tracer concentration was estimated at these points to obtain the data at all the time points. To estimate the missing values, the parameters of a simple double exponential model were estimated in each subject using the original data and the ADAPT program ID (D'Argenio et al., 1992) (see below). These model parameters were then inserted into the model and the ADAPT program SIM was used to estimate the missing values at the relevant time points. A double exponential model was considered to be appropriate in view of the two compartmental nature of the curves. The procedures of parameters estimation will be discussed later. Table C_2 in Appendix C shows the original data and the estimated data.

4.4:ADAPT Software . simulation (SIM) and parameter estimation (ID) program

One of the more powerful tools in parameter estimation and simulation, especially in compartmental modelling and pharmacokinetics, is the ADAPT software. There are two main tasks in this software which are introduced here.

(i). Parameter estimation (ID)

In this program, the mass balance (differential) equations or the analytic solution of the model are entered into the program along with the number of parameters to be estimated. In the next stage the program requires some further details such as the number of rate and bolus inputs, dose events and the number of outputs together with observation information (time units and measured values for each output). There are four parameter estimation options one of which is the weighted least squares (WLS). The WLS was used with the weights set equal to the inverse of the variance of the measurement error at each time point. In this case, the above variance is approximated as a linear function of the observed glucose data. To define this function, the program requires two points on this standard deviation-observation line. The final stage of the program is the selection of the initial estimations of the parameters. The different options of parameter estimation and the output of (ID) will

be discussed in Chapter 5.

(ii). Simulation (SIM)

The simulation program requires that the number of rate and bolus inputs and the number of dose events together with the mass balance equations or the analytical solution of the model be specified. For simulation there are four options

(i) Individual simulation;

(ii) Individual simulation with output noise;

(iii) Population simulation;

(iv) Population simulation with output noise.

In our case we chose the first option. For the next stage the program requires the number of outputs and observations together with the observation information (time) and the values for indicated parameters. The output of the SIM program are the estimated values for each selected time and the fitted curves.

4.5: Summary

In this chapter the details of the subjects were discussed. There are 17 females in the sample, 8 obese and 9 non-obese. The obese subjects are those who have at least 30% more mass than their ideal body mass. To build the stochastic model for the subjects, a bolus of glucose and glucose tracer was injected intravenously and blood samples were obtained over a period of 3 hours for all the patients. The tracer content of the blood sample was determined by GCMS. To focus the data analysis on some fixed times, 26 time points which have the largest frequencies were chosen and missing data were estimated using the ADAPT program ID and SIM. Finally, some details of ADAPT software and its applications in simulation, parameter estimation etc. were described.

Chapter 5

Stochastic compartmental model A

5.1: Review of Soong's approach

In 1971 Soong (Soong, 1971) presented a stochastic two-compartmental model in which the stochasticity was incorporated into the transfer fluxes, k_{ij}, between the compartments (see Figure 5.1). He assumed that the compartmental parameters are constant during a particular experiment but vary from one experiment to another if repeated in the same subject and from one subject to another.

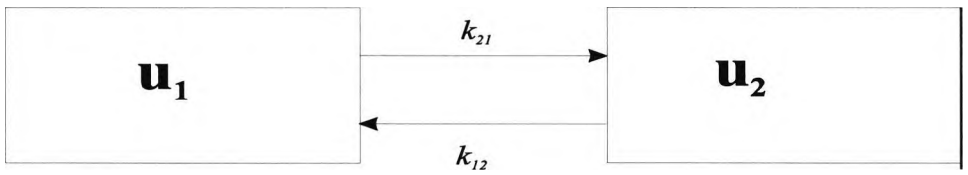


Figure 5.1: Two compartmental stochastic model (Soong,1971)

According to his assumptions the two parameters k_{21} and k_{12} are assumed to have known statistical distributions. To build a stochastic model for the above compartmental model, he started by writing the mass balance equations as follows:

$$\frac{dU(t)}{dt} = \begin{vmatrix} \frac{dU_1(t)}{dt} \\ \frac{dU_2(t)}{dt} \end{vmatrix} = \begin{pmatrix} -k_{21} & k_{12} \\ k_{21} & -k_{12} \end{pmatrix} \begin{pmatrix} U_1(t) \\ U_2(t) \end{pmatrix}, \qquad (5.1)$$

where U(t) is a 2 by 1 matrix of $U_1(t)$ and U_2 (t) and U_1 (t) and U_2 (t) are the concentration of substances in the first and second compartment. In the above equation the initial condition is:

$$U_0(0) = \begin{pmatrix} C_1 \\ C_2 \end{pmatrix} . \qquad (5.2)$$

where C_1 and C_2 are the concentrations of glucose in the first and second compartment respectively at the time of t=0.

It is easy to show that the solution for the above equations is given by:

$$U(t) = \frac{1}{k_{12}+k_{21}} \begin{pmatrix} k_{12}+k_{21}e^{-(k_{21}+k_{12})t} & k_{12}(1-e^{-(k_{21}+k_{12})t}) \\ k_{21}(1-e^{-(k_{21}+k_{12})t} & k_{21}+k_{12}e^{-(k_{21}+k_{12})t} \end{pmatrix} . U_0 . \qquad (5.3)$$

where C_1 and C_2 are defined above.

Soong assumed (for simplicity) that Prob(C_1=1, C_2 =0) =1 and k_{12} and k_{21} have a truncated bivariate normal distribution and also k_{21} and k_{12} have normal distributions with the means of 1 and 0.5 and the variances of 0.1 and 0.04 respectively, i.e. k_{21}~N(1, 0.1) and k_{12}~N(.5,0.04). Therefore, by substituting equation 5.2 into 5.3 and considering C_1=1 C_2=0 we can write:

$$U_1(t) = \frac{(k_{12}+k_{21}e^{-(k_{12}+k_{21})t})}{(k_{21}+k_{12})} . \qquad (5.4)$$

Hence we can find the probability distribution function (PDF) of $U_1(t)$ using the cumulative distribution function method. The cumulative distribution function of a random variable x, denoted by F_X (.), is defined to be that function with its domain on the real line in the interval [0,1] which satisfies:

$$F_X(x) = P[X \leq x] = P[\{\omega : X(\omega) \leq x\}]$$

for every real number x (Mood et al., 1974). Therefore, for building the cumulative distribution function of U_1 (t) we have (v is a arbitrary variable):

$$prob\ (U_1(t) \le v \mid C_1 = 1, C_2 = 0) = prob(k_{12} + k_{21} e^{-(k_{21}+k_{12})t} \le (k_{21}+k_{12}) \quad \textbf{(5.5)}$$

and after some manipulation (see Appendix D) we obtain the density function of $U_1(t)$ in the form:

$$f_{u_1}(v\ ;\ C_1=1,\ C_2=0) = \int_x^{\infty} \frac{s}{(1-e^{-st})}\, \phi_0[\frac{s(1-v)}{1-e^{-st}}, s - \frac{s(1-v)}{1-e^{-st}}]ds, \quad \textbf{(5.6)}$$

where x=logv/t and Φ_0 is the joint density function of k_{12} and k_{21} given by:

$$\Phi_0(k_{12}, k_{21}) = \frac{1}{2\pi\sqrt{(1-\rho^2)}\sigma_1\sigma_2} e^{-\frac{1}{2(1-\rho^2)}[\frac{(k_{12}-\mu_1)^2}{\sigma_1^2} - 2\frac{\rho(k_{12}-\mu_1)(k_{21}-\mu_2)}{\sigma_1\sigma_2} + \frac{(k_{21}-\mu_2)^2}{\sigma_2^2}]}. \quad \textbf{(5.7)}$$

Also, μ_1, μ_2, σ_1 and σ_2 are the means and standard deviations of k_{12} and k_{21} respectively and ρ is the coefficient of correlation. We need a truncated joint normal distribution similar to Φ_0 such that its integration over the range $(0, \infty)$ is 1.00 and that it predicts the sample values $\bar{k}_{12}$, $\bar{k}_{21}$, s_{k12}, s_{k21} and r. We define a PDF as

$$\Phi'_0(k_{12}, k_{21}) = \frac{1}{2\pi\sqrt{(1-\rho^2)}\sigma_1\sigma_2 k} e^{-\frac{1}{2(1-\rho^2)}[\frac{(k_{12}-\mu_1)^2}{\sigma_1^2} - 2\frac{\rho(k_{12}-\mu_1)(k_{21}-\mu_2)}{\sigma_1\sigma_2} + \frac{(k_{21}-\mu_2)^2}{\sigma_2^2}]}. \quad \textbf{(5.8)}$$

such that the following six equations (for six unknown) are satisfied.

$$\int_0^\infty \int_0^\infty k_{12} \Phi'_0 dk_{12} dk_{21} = \bar{k}_{12}$$

$$\int_0^\infty \int_0^\infty k_{21} \Phi'_0 dk_{12} dk_{21} = \bar{k}_{21}$$

$$\int_0^\infty \int_0^\infty (k_{12} - \bar{k}_{12})^2 \Phi'_0 dk_{12} dk_{21} = s^2_{k_{12}}$$

$$\int_0^\infty \int_0^\infty (k_{21} - \bar{k}_{21})^2 \Phi'_0 dk_{12} dk_{21} = s^2_{k_{21}} \qquad \textbf{(5.9)}$$

$$\int_0^\infty \int_0^\infty (k_{21} - \bar{k}_{21})(k_{12} - \bar{k}_{12}) \Phi'_0 dk_{12} dk_{21} = r s_{k_{21}} s_{k_{12}}$$

$$\int_0^\infty \int_0^\infty \Phi'_0 \, dk_{12} dk_{21} = 1$$

where $\bar{k}_{12}$ and $\bar{k}_{21}$ are the sample means of k_{12} and k_{21} respectively, s^2_{k12} and s^2_{k21} are the sample variances, s_{k12}, s_{k21} are the standard deviations of k_{12} and k_{21} and r is the estimate of ρ, the correlation coefficient. However, the solution of these non-linear equations is relatively difficult and by using $\bar{k}_{12}$, $\bar{k}_{21}$, s_{k12}, s_{k21} and r in place of μ_1, μ_2, σ_1, σ_2 and ρ it was found that k = 0.999. Hence a good approximation is to define Φ'_0 as above and avoid having to solve the above 6 non-linear equations.

Presumably this is the approach taken by Soong in using the truncated distribution, although he did not mention it in his paper. To build the stochastic model, we have to calculate the expectation of U_1 (t) which is given by

$$E(U_1(t)) = \int_0^\infty U_1(t) \, f_{u_1}(t) \, du_1. \qquad \textbf{(5.10)}$$

For a deterministic model it is sufficient to insert the following values in the density function of $U_1(t)$, where $f(k_{12})$ and $f(k_{21})$ are PDF of k_{12} and k_{21} respectively:

$$E(k_{12}) = \int k_{12} f(k_{12})\, dk_{12} \qquad E(k_{21}) = \int k_{21} f(k_{21}) dk_{21}. \qquad \textbf{(5.11)}$$

Figure 5.2 shows the stochastic curve for the above model when $\rho=0$ together with the deterministic curve.

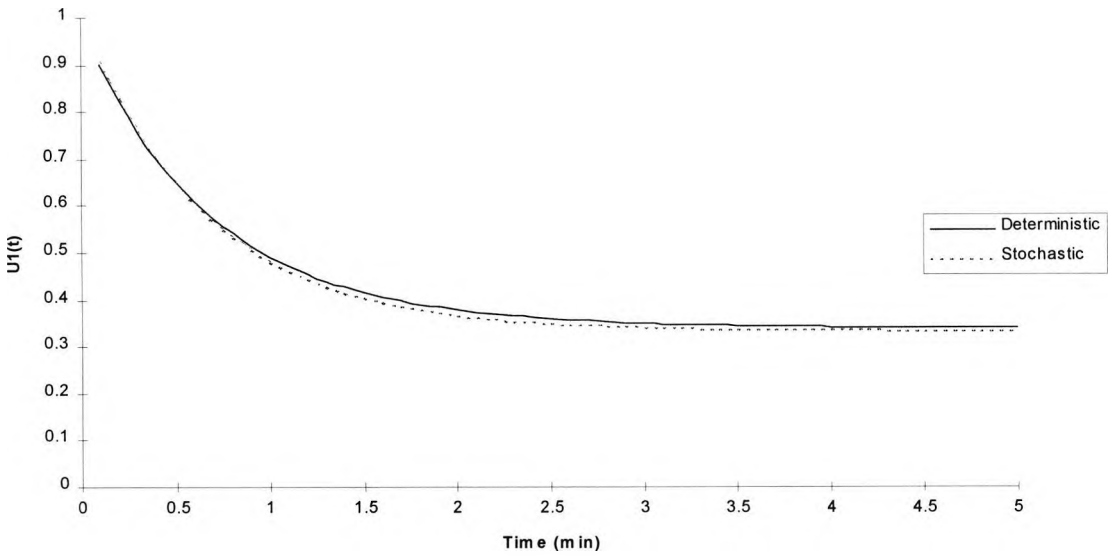


Figure 5.2: Stochastic and deterministic curves for the mean of u_1 (t) when $\rho=0$.

5.2: Data analysis

The following model (Figure 5.3) was considered.

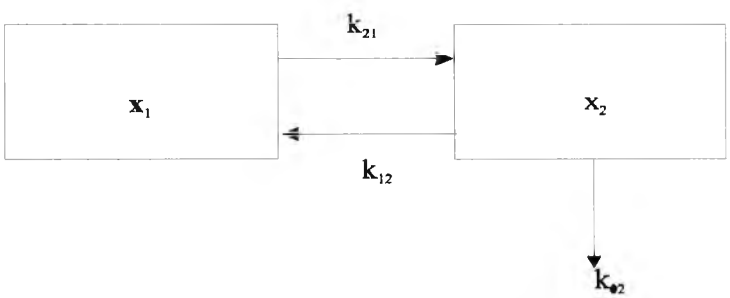


Figure 5.3: Two-compartmental stochastic model with a loss from the second (extravascular) compartment.

The glucose concentration in blood plasma decays as it is consumed mostly by the muscles. Eventually the glucose concentration falls to the basal value . Also, it has a loss from the second compartment and the initial concentration of glucose tracer at the first compartment was taken to be a random variable in different individuals ($X_1(0)=c_1$). The variables x_1 and x_2 are the concentrations in the first (blood plasma) and second (extravascular tissue) compartments respectively. The mass balance equations (Carson et al., 1983) are as follows:

$$\frac{dX_1(t)}{dt} = -k_{21}X_1(t) + k_{12}X_2(t), \tag{5.12}$$

$$\frac{dX_2(t)}{dt} = k_{21}X_1(t) - (k_{12} + k_{02})X_2(t). \tag{5.13}$$

It can be shown that the model output is given by

$$X_1 = A_1 e^{\lambda_1 t} + A_2 e^{\lambda_2 t} \tag{5.14}$$

where:

$$\lambda_1 = -(1/2)[(k_{21} + k_{12} + k_{02}) - \sqrt{(k_{21} + k_{12} + k_{02})^2 - 4k_{21}k_{02}}], \tag{5.15}$$

$$\lambda_2 = -(1/2)[(k_{21} + k_{12} + k_{02}) + \sqrt{(k_{21} + k_{12} + k_{02})^2 - 4k_{21}k_{02}}] \tag{5.16}$$

$$A_1 = \frac{(\lambda_1 + k_{12} + k_{02})X_1(0)}{\lambda_1 - \lambda_2}, \tag{5.17}$$

and

$$A_2 = -\frac{(k_{12} + k_{02} + \lambda_2) X_1(0)}{\lambda_1 - \lambda_2}. \qquad \textbf{(5.18)}$$

5.2.1: Curve fitting

There are four unknown parameters in the model (Equation 5.14) and these are estimated using the ADAPT package (D'Argenio and Schumitzky, 1992) . The package offers a choice of several minimisation functions such as weighted least square (WLS), maximum likelihood (ML), generalised least square (GLS) and maximum a posteriori probability (Bayesian). Following other workers the WLS function was chosen since we need to give different weights to the measurements according to their variances. This requires the minimisation of

$$o_{wls} = \sum_{i=1}^{l} \sum_{j=1}^{m} w_{ij}(z_i(t_j) - y_i(\alpha, t_j))^2, \qquad \textbf{(5.19)}$$

where the α are the parameters to be estimated;

w_{ij}s are the weights;

l is the number of the outputs (which in our case is one);

m is the number of the data points;

$z_i(t_j)$ are the measured data at the time of t_j and

$y_i(\alpha, t_j)$ are computed (estimated) data at the time of t_j.

The weights are set equal to the inverse of the variance of the measurement error ($w'_{ij}=1/\sigma_{ij}$) at each time point. Since the error is proportional to the variance, using this weighting enables us to give less weight to measurements with high error and high weight to those who have less error. In this case σ_{ij} is approximated as a linear function of the observed glucose data i.e. $\sigma_{ij}=a\, z_i(t_j)+b$, where $z_i(t_j)$ are the measured data at the time of t_j. To define this function, we have to enter two points on this standard deviation-observation line.

In the output of the parameter estimation program, in the section with (weighting information) headings, there are two points which specify the above regression line. These are two points with arbitrary measurement ($z_i(t_j)$) which we enter as a low measurement for glucose and its standard deviation (1, 0.0236) and also a high measurement for the above values (10, 0.236). The program calculates the above regression line using these points. Furthermore, there is a matrix at the bottom of the first page of the output which shows the correlation between the estimated parameters. Therefore, the correlation between k_{12} and k_{21} is equal to 0.91 and so on.

Figures 5.4 and 5.5 show the typical output of ADAPT (for subject 1) . The complete output of ADAPT together with the program for all samples is given in Appendix A.

--- C. WLS Estimation Summary---

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 44

Number of function calls: 199

Estimator criterion value: 150.996

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.991	150.996	.108340E-01

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K21	.1000	.7267E-01	9.349	[.5858E-01, .8676E-01]
K12	.1000	.6485E-01	9.842	[.5161E-01, .7809E-01]
K02	.1000	.2350E-01	3.180	[.2195E-01, .2505E-01]
IC(1)	.5000	.8638	2.640	[.8165 , .9111]
IC(2)	.0000	Fixed		

	K21	K12	K02	IC(1)
K21	1.00			
K12	.91	1.00		
K02	-.13	.27	1.00	
IC(1)	.92	.72	-.37	1.00

FIGURE 5.4: Typical output of the parameters estimation program ID in ADAPT along with the values of estimated parameters and their CVs, R^2, SS and WLS (for subject 1).

... D. Estimated Model Prediction and Data Summary ---

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	2.000	.7800	.7540	.2605E-01	2951.
2	3.000	.7600	.7092	.5083E-01	3108.
3	4.000	.6700	.6699	.6627E-04	4000.
4	5.000	.6000	.6355	-.3547E-01	4987.
5	6.000	.5800	.6051	-.2514E-01	5337.
6	8.000	.5500	.5546	-.4648E-02	5935.
7	10.00	.4900	.5148	-.2482E-01	7478.
8	12.00	.4700	.4830	-.1296E-01	8128.
9	14.00	.4600	.4570	.2952E-02	8485.
10	16.00	.4400	.4356	.4396E-02	9274.
11	19.00	.4400	.4095	.3053E-01	9274.
12	22.00	.4200	.3884	.3163E-01	.1018E+05
13	25.00	.4000	.3706	.2938E-01	.1122E+05
14	30.00	.3700	.3458	.2422E-01	.1312E+05
15	40.00	.3300	.3056	.2440E-01	.1649E+05
16	50.00	.2700	.2720	-.1983E-02	.2463E+05
17	60.00	.2400	.2425	-.2496E-02	.3117E+05
18	70.00	.2000	.2163	-.1630E-01	.4489E+05
19	80.00	.1800	.1930	-.1296E-01	.5542E+05
20	90.00	.1600	.1721	-.1214E-01	.7014E+05
21	100.0	.1400	.1536	-.1357E-01	.9161E+05
22	113.0	.1300	.1324	-.2390E-02	.1062E+06
23	120.0	.1200	.1222	-.2223E-02	.1247E+06
24	140.0	.1000	.9727E-01	.2727E-02	.1795E+06
25	160.0	.8000E-01	.7742E-01	.2584E-02	.2805E+06
26	180.0	.7000E-01	.6161E-01	.8386E-02	.3664E+06

FIGURE 5.5: Typical output of the parameter estimation program ID in ADAPT along with the original data, estimated data, residuals and the weight (for subject 1).

A summary of the estimated parameters along with the values of the parameters' CVs (coefficient of variation) in each unit and the CV for the curve fitting are given in Table 5.1. Since the values of the coefficient of determination (R^2), (Draper & Smith, 1966) were almost the same in all the parameter estimations (between 0.966 and 0.997) they were not presented in the table. Furthermore, the parameters' CVs calculation and the method for calculation of the CV for the curve fitting are given as follows.

A) The CV of the parameters:

The asymptotic covariance matrix of the estimated parameters is given by

$$c\hat{o}v(\hat{\alpha}) = (P^T W P)^{-1}(P^T W R W P)(P^T W P)^{-1} \qquad \textbf{(5.20)}$$

where the superscripts T and -1 denotes, respectively, the matrix transpose and the matrix inverse, P is the m.l × p (the number of the system parameter) Jacobean matrix obtained from

$$P = \frac{\partial y(\hat{\alpha})}{\partial \alpha},\ y = (y_1(t_1)\ y_2(t_2)...y_l(t_m))^T \qquad \textbf{(5.21)}$$

$y_i(t_j)$s are the i th output at the time t_j, and W is the m.l × m.l matrix of weights used in equation 5.19,

$$W = diag[w_{11} w_{12}...w_{lm}]. \qquad \textbf{(5.22)}$$

For a weighted least squares (WLS), the m.l× m.l matrix R contains estimates of the error variance for each output:

$$R = diag[\sigma_1^2...\sigma_1^2\sigma_2^2...\sigma_l^2]. \qquad \textbf{(5.23)}$$

where

$$\sigma_i^2 = \frac{1}{df_i} \sum_{j=1}^{m} w_{ij}(z_i(t_j) - y_i(\hat{\alpha}, t_j))^2, \qquad \textbf{(5.24)}$$

and df_i are the number of degrees of freedom given by

$$df_i = m_i - (p/l),\ i = 1,\ldots,l. \qquad \textbf{(5.25)}$$

In this last equation the number of degrees of freedom for the i^{th} output, m_i is the number of non-missing, non-zero weight observation for the i^{th} output. Using the above procedure it is possible to estimate the coefficients of variation of the parameter estimates.

B) The CV for curve fitting:

The CV for curve fitting is a criterion for evaluation of the curve fitting. It is calculated from

$$CV(\%) = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(y_{comp_i} - y_{obs_i})^2} \times \frac{100}{\mu_{yobs_i}} \qquad \textbf{(5.26)}$$

where $\mu_{yobsi} = 1/n\Sigma y_{obsi}$.

The term inside the square root is the variance of residuals (using a zero sample mean). This is not the only definition of CV and also this definition is not analogous to that of the CV for a series of repeated measurements of a single sample that has been divided in to alquots but it is convenient to use.

A small CV means that the variance of the residuals per unit mean ordinate (μ_{yobsi})is small so we have a good fit. Thus the larger ordinate for a given variance the smaller the CV.

Subjects No	k_{21} min^{-1}		k_{12} min^{-1}		k_{02} min^{-1}		c_1 min^{-1}		CV
1	0.072670	(09)	0.064850	(10)	0.023500	(03)	0.86	(3)	5.7
2	0.059040	(22)	0.105300	(23)	0.036540	(06)	0.59	(4)	2.6
3	0.054770	(03)	0.012350	(05)	0.015110	(03)	0.73	(1)	10
4	0.017190	(06)	0.005538	(38)	0.015730	(24)	0.55	(1)	11
5	0.050700	(02)	0.008911	(05)	0.009436	(04)	0.79	(1)	8.4
6	0.023920	(04)	0.007911	(17)	0.014620	(10)	0.61	(1)	7.3
7	0.025150	(08)	0.015560	(20)	0.018000	(09)	0.63	(2)	6.6
8	0.036930	(05)	0.018930	(09)	0.013300	(05)	0.62	(1)	6.7
9	0.038290	(03)	0.010920	(07)	0.010750	(05)	0.67	(1)	6.9
10	0.045030	(04)	0.017160	(08)	0.017330	(03)	0.76	(1)	6.9
11	0.044600	(03)	0.012250	(07)	0.013490	(04)	0.73	(1)	5.2
12	0.044730	(03)	0.013420	(07)	0.014390	(04)	0.76	(1)	10
13	0.035460	(05)	0.015130	(15)	0.026590	(05)	0.78	(2)	8.6
14	0.037250	(04)	0.014270	(08)	0.012820	(05)	0.8	(1)	9.1
15	0.017370	(07)	0.005103	(35)	0.011740	(27)	0.55	(2)	9.1
16	0.042110	(12)	0.054520	(17)	0.025170	(05)	0.89	(2)	9.4
17	0.030420	(04)	0.010080	(12)	0.014750	(07)	0.5	(1)	3.9
mean	0.039743		0.023071		0.017251		0.69		
SD	0.0147		0.026740		0.006950		0.116		

Table 5.1: Distribution of k_{21}, k_{12}, k_{02} and c_1 together with the values of CV of the fitted curves. The numbers in the brackets show the CVs of the parameters which are rounded to nearest integers.

5.3: Finding the quadravariate normal distribution of the parameters

To develop a stochastic model first we need the probability distribution function (PDF) of the parameters(k_{12}, k_{21}, k_{02} , $c_1=X_1(0)$) where c_1 is the initial condition in the first compartment. We cannot use a quadravariate normal distribution for the above parameters, since some of them (especially k_{12}) have a large standard deviations (in comparison with their means), so the probability of accepting negative values in the parameters is large. It is impossible for the parameters to have negative values since all of them are positive fluxes or concentration. Therefore, we have to choose another method. We could have considered a quadravariate truncated (at zero) normal distribution. For this PDF, we require to find 15 unknown parameters of the model (4 means, 4 variances, 6 covariances and a scale factor) so we require 15 non-linear equations similar to equation 5.9. The numerical solution for these 15 non-linear equations is likely to be difficult, and it was decided to use a method which avoids negative parameter values. The most obvious method is to use a lognormal transformation. Fortunately, it was found that the parameters are well fitted by lognormal distributions.

We start with some details of quadravariate normal distribution and the lognormal distribution will be discussed later. Consider the following PDF which is normal distribution (Mardia et al., 1979 & Soong,1971):

$$f(k_{12},\ k_{21},\ k_{02},\ c_1) = \frac{1}{(2\pi)^2|\Lambda|^{1/2}} e^{-1/2(X-m)^T \Lambda^{-1}(X-m)}, \qquad \textbf{(5.27)}$$

where $X^T = (k_{21}, k_{12}, k_{02}, c_1)$ with mean values $m^T = [m_1, m_2, m_3, m_4]$ and $\Lambda=[\mu_{ij}]$ is the 4 by 4 covariance matrix of X where:

$$\mu_{ij}(t) = E\{[X_i-m_i][X_j-m_j]\}.$$

The superscripts T and -1 denote, respectively, the matrix transpose and the matrix inverse. From Table 5.1 we have $E(m_1) = 0.0397429$, $E(m_2)=0.0230707$, $E(m_3) = 0.0172509$ and $E(m_4) = 0.6947764$. Also from the same Table we have $s_1= 0.0147446$, $s_2= 0.0267480$, $s_3= 0.0069506$ and $s_4= 0.1156524$ which are the standard deviations of

the variables.

Since f in equation 5.27 is a PDF, for the above multivariate distribution the following multiple integral should be identically equal to 1.00:

$$\int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty} f(k_{21},\ k_{12},\ k_{02},\ c_1)dk_{21}\ dk_{12}dk_{02}dc_1. \qquad \textbf{(5.28)}$$

It was decided to confirm this result numerically as a check on the Fortran program and the values of the variance-covariance matrix. The variance-covariance matrix , Λ, was calculated using MATLAB (Matlab, Users guide, 1992) and is given by equation 5.29. The diagonal elements (Λ_{11}, Λ_{22}, Λ_{33} and Λ_{44}) are the variances of k_{21} ,k_{12} , k_{02} and c_1 respectively. The other elements of Λ (Λ_{ij} , $i \neq j$) are the covariance of the above variables (k_{21} , k_{12} , k_{02} and c_1) where

$COV[X, Y] = E[(X-\mu_x)(Y-\mu_y)]$.

$$\Lambda = \begin{pmatrix} .000217403 & .000246372 & .000040627 & .001046521 \\ .000246372 & .000715458 & .000159395 & .000624259 \\ .000040627 & .000159395 & .000048310 & .000120083 \\ .001046521 & .000624259 & .000120083 & .013375473 \end{pmatrix}. \qquad \textbf{(5.29)}$$

The above normal distribution can be more easily manipulated by transforming it to standardized variables as follows:

Suppose $x_1=k_{21}$, $x_2=k_{12}$, $x_3=k_{02}$ and $x_4=c_1$. Consider the following transformation:

$$\begin{aligned} y_1 &= \frac{x_1-\mu_{x_1}}{S_{x_1}} \\ y_2 &= \frac{x_2-\mu_{x_2}}{S_{x_2}} \\ y_3 &= \frac{x_3-\mu_{x_3}}{S_{x_3}} \\ y_4 &= \frac{x_4-\mu_{x_4}}{S_{x_4}}, \end{aligned} \qquad \textbf{(5.30)}$$

where μ_{x1} to μ_{x4} are the means and s_{x1} to s_{x4} are the standard deviation of the above four variables respectively. If we apply the above trasformation, the new variables become standard normal with zero means and unit variances. Also, the elements of Λ which is a symmetric positive definite matrix (Chatfield and Collins, 1980) changes as follows:

$$cov(y_i, y_j) = \frac{\Lambda_{ij}}{\sigma_i \sigma_j} , \qquad \textbf{(5.31)}$$

where σ_i and σ_j are the standard deviations of y_i and y_j respectively. Therefore the new variance-covariance matrix is as follows:

$$\Sigma = \begin{pmatrix} 1.000000000 & 0.624691919 & 0.396424239 & 0.613705696 \\ 0.624691919 & 1.000000000 & 0.857358907 & 0.201798677 \\ 0.396424239 & 0.857358907 & 1.000000000 & 0.149385125 \\ 0.613705696 & 0.201796877 & 0.149385125 & 1.00000000 \end{pmatrix} . \qquad \textbf{(5.32)}$$

The above matrix shows the correlation coefficients of variables. We can test for significance of the relationship between the variables using

$$r.\sqrt{\frac{n-2}{1-r^2}} \qquad \textbf{(5.33)}$$

where r is the sample correlation coefficient and n is the sample size (Altman, 1991). Under the null hypothesis that there is no relation between the different variables ($\rho = 0$) it can be shown that 5.33 has a t distribution with n-2 degree of freedom. Using 5.33 and the above correlation coefficients (matrix 5.32) r_{12}, r_{14} and r_{23} are significant ($\alpha = 0.05$). From a physiological point of view we expect there to be a good correlation between flux rate coefficient of glucose tracer leaving the blood (k_{21}) compartment and the initial concentration of glucose tracer (c_1). The significant correlation 0.61 suggests

that the above interpretation is correct. Also, we expect weaker correlations between the initial concentration and the two exit fluxes rate (k_{12} and k_{02}) coefficients in the more remote second compartment and 0.20 and 0.149 which are not significant confirms this. Furthermore, there should be a good correlation between k_{02} and k_{12} and r = 0.857 which is significant again suggests the above interpretation is also correct, so the correlation matrix confirms all of these meaning.

The inverse of the correlation matrix 5.32 is

$$\Sigma^{-1} = \begin{pmatrix} -3.325437958 & -3.115515164 & 1.599475955 & -1.651071294 \\ -3.115515164 & 6.774240213 & -4.760536599 & 1.256130043 \\ 1.599475955 & -4.760536599 & 4.552130122 & -0.700958043 \\ -1.651071294 & 1.256130043 & -0.700958043 & 1.864499182 \end{pmatrix} \quad \textbf{(5.34)}$$

Also, $(\det(\Sigma))^{-0.5} = 0.27614700$.

It is easy to show that the quadravariate normal distribution (5.27) transforms to:

$$f(y_1,y_2,y_3,y_4) = \frac{1}{(2\pi)^2|\Sigma|^{1/2}} e^{-\frac{1}{2}(y^T\Sigma^{-1}y)} = \frac{1}{(4\pi)^2.0.27614700} e^{-\frac{1}{2}(y^T\Sigma^{-1}y)} \quad \textbf{(5.35)}$$

Equation 5.28 with f given by equation 5.35 was integrated using the NAG library program D01FCF (see section 5.5) and it was found to be equal to 1.0000.

5.4: Building a quadravariate lognormal distribution for the calculation of the concentration of glucose tracer in blood plasma

As was mentioned in 5.3, some of the variables have a large standard deviation in comparison with the means, so the contribution to the expectation value of such negative values is likely to be a significant proportion. On the other hand, all the variables (fluxes and concentration) are essentially positive and cannot accept negative values.

Therefore, it is not feasible to fit a normal distribution to the data where the proportion of negative values is no longer small. To overcome the problem, a quadravariate lognormal distribution was used to calculate the stochastic model for the concentration of glucose tracer in blood plasma. The details of the lognormal distribution are described below.

Consider the normal distribution in equation 5.35. We take the log of the parameters in Table 5.1 as shown in Table 5.1A. Figure 5.6 shows the distribution of the data in lognormal scale.

The new lognormal variables have the following means and standard deviations respectively:
μ_{k21}=-3.296389365, μ_{k12}= -4.163966483, μ_{k02}=-4.123128262 and μ_{c1}= -0.377619552. Also s_{k21}= 0.402603383, s_{k12}=0.823363712, s_{k02}= 0.352277693 and s_{c1}= 0.170572963. The new variance-covariance matrix for the lognormal variables was also computed in MATLAB and is given below using equations 5.30.

$$s = \begin{pmatrix} 1.000000000 & 0.698110349 & 0.308200326 & 0.657913612 \\ 0.698110349 & 1.000000000 & 0.783588032 & 0.413387621 \\ 0.308200326 & 0.783588032 & 1.000000000 & 0.155465819 \\ 0.657913612 & 0.413387621 & 0.155465819 & 1.000000000 \end{pmatrix} \quad \textbf{(5.36)}$$

The inverse of s is as follows:

$$s^{-1} = \begin{pmatrix} 3.678329603 & -3.376487907 & 1.712741391 & -1.290497553 \\ -3.376487907 & 6.445315526 & -4.038580729 & 0.184884962 \\ 1.712741391 & -4.038580729 & 3.640336002 & -0.023284412 \\ -1.290497553 & 0.184884962 & -0.023284413 & 1.77622668 \end{pmatrix} \quad \textbf{(5.37)}$$

Subject Number	k_{21}	k_{12}	k_{02}	c_1
1	-2.62182663	-2.735678368	-3.750754857	-0.146414018
2	-2.829540098	-2.250941859	-3.309347728	-0.527802247
3	-2.904612680	-4.394099215	-4.192398502	-0.316218730
4	-4.063427459	-5.196121854	-4.152185561	-0.599839003
5	-2.981829368	-4.720468810	-4.663223117	-0.239272933
6	-3.733040349	-4.839501082	-4.224681063	-0.501700715
7	-3.682897382	-4.160484364	-4.017383521	-0.460449416
8	-3.298731050	-3.967007313	-4.319991243	-0.475458479
9	-3.262566513	-4.517159308	-4.532849524	-0.395415772
10	-3.100426344	-4.065174184	-4.055316175	-0.273647683
11	-3.110021419	-4.402229341	-4.305806608	-0.321445702
12	-3.107110861	-4.311009147	-4.241221758	-0.269187489
13	-3.339349978	-4.191075751	-3.627220073	-0.249230886
14	-3.290103334	-4.249595847	-4.356748827	-0.223643676
15	-4.053010698	-5.277926676	-4.444753464	-0.602940912
16	-3.167470036	-2.909187672	-3.682102469	-0.119910296
17	-3.492654992	-4.597202016	-4.216512196	-0.696954418
Mean	-3.296389365	-4.163966483	-4.123128262	-0.377619552
SD	0.402603383	0.823363712	0.352277693	0.170572963

Table 5.1A: Distribution of k_{21}, k_{12}, k_{02} and c_1 in logarithmic scale.

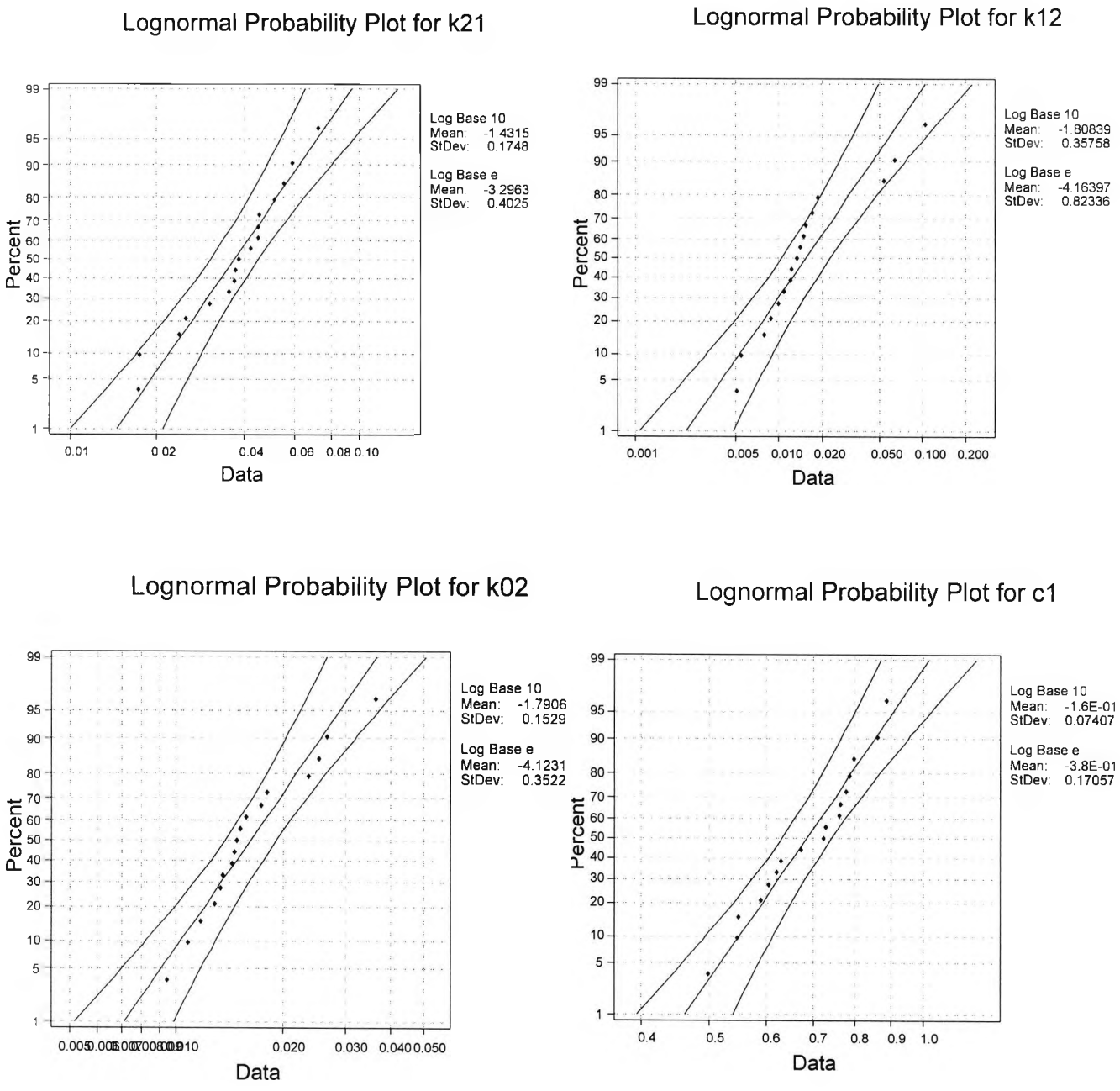


Figure 5.6: Distribution of k_{21}, k_{12}, k_{02} and c_1 in lognormal scale.

Also $(\det(s))^{-0.5} = 0.28158229$.

Therefore the PDF of the lognormal distribution is:

$$f(y_1,y_2,y_3,y_4)=\frac{1}{(2\pi)^2|s|^{1/2}}e^{-1/2(y^T S^{-1}y)}=\frac{1}{(2\pi)^2.0.281582295}e^{-1/2(y^T s^{-1}y)} \quad \textbf{(5.38)}$$

where y is the lognormal standard variable with zero means and unit variances.

To calculate the stochastic model for the concentration of glucose tracer in blood plasma, we need to calculate the following integration after standardizing X_1.

$$E(X_1)=\int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty}X_1\, f(y_1,\, y_2,\, y_3,\, y_4)dy_1\, dy_2\, dy_3\, dy_4, \quad \textbf{(5.39)}$$

where X_1 is the concentration of glucose tracer in the first compartment and f is the quadravariate lognormal distribution of k_{21} , k_{12} , k_{02} and c_1. To standardize X_1 we need to use equations 5.30 for x_1, x_2, x_3 and x_4 as follows:

$$\begin{aligned} x_1&=y_1.s_{x_1}+\mu_{x_1}\\ x_2&=y_2.s_{x_2}+\mu_{x_2}\\ x_3&=y_3.s_{x_3}+\mu_{x_3}\\ x_4&=y_4.s_{x_4}+\mu_{x_4}. \end{aligned} \quad \textbf{(5.40)}$$

where μs and σs are the mean and standard deviation of lognormal variables and should not be confused with the notation of section 5.3.

For every individual (subject) there is a unique X_1 which is different from others, so by definition the average of these X_1s or $E(X_1)$ is the stochastic response for the concentration in the first compartment. The stochastic model will be described in more detail later.

5.5: Calculation of the multivariate integrals

The above numerical integration is complex (it is not possible to calculate it analytically) and an advanced numerical integration program was used. After some

experimentation with MATHCAD and MATHEMATICA, which were found to be too slow, it was decided to apply the NAG (Numerical Algorithms Group) Workstation Library. The library contains many advanced programs for mathematical and statistical calculations. The program D01FCF was used to calculate the integration. D01FCF attempts to evaluate a multi-dimensional integration (up to 15 dimensions), with constant and finite limits, to a specified relative accuracy by using an adaptive subdivision strategy. The lower and upper limits of the integration is set to be Φ^{-1} (Tolerance/10^4) where Φ^{-1} is the inverse univariate normal distribution function, n is the dimension of the integral which is four in our case (Numerical Algorithms Group). Therefore with tolerance 0.0001 the lower and upper limits are set to be -3.32915 and 3.32915.

5.6: Calculation of the stochastic model for the mean concentration of glucose tracer in blood plasma in total subjects

The following is a short summary of the integrations:

1. The upper and lower limits of the integration are set to be -3.32915 and 3.32915 (see section 5.5).
2. The minimum number of integrand evaluations was chosen to be 160000.
3. The tolerance of the integration was Tol=0.0001.
4. The program calculated the result for any time between 0 and 180 minutes.

The programs are given in Appendix B.

5.6.1: The results for the total group:

After the above procedures were carried out the results of the integral was obtained at each time point between 0 to 180 (min). Table C_3 in Appendix C shows the results of the above integrals at each time points (for simplicity only even times are given).

5.6.2: Deterministic model:

To obtain the deterministic model for the concentration of glucose tracer in blood plasma, we proceed as follows:

In the distribution of $X_1(t)$, equation 5.14, we replace the parameters by their expectations (i.e. mean values) :

$$E(k_{21}) = \mu_{k_{21}} = \int k_{21}\, f(k_{21})\, dk_{21}, \tag{5.41}$$

$$E(k_{12}) = \mu_{k_{12}} = \int k_{12}\, f(k_{12}) dk_{12}, \tag{5.42}$$

$$E(k_{02}) = \mu_{k_{02}} = \int k_{02}\, f(k_{02})\, dk_{02}\ , \tag{5.43}$$

and

$$E(c_1) = \mu_{c_1} = \int c_1\, f(c_1)\, dc_1, \tag{5.44}$$

where $f(k_{21})$, $f(k_{12})$, $f(k_{02})$ and $f(c_1)$ are the probability distribution functions of k_{21}, k_{12}, k_{02} and c_1 respectively. Now $\hat{\mu}_{k21}=0.0397429$, $\hat{\mu}_{k12}=0.0230707$, $\hat{\mu}_{k02}=0.0172509$ and $\hat{\mu}_{c1}=0.6947764$, thus after substituting the above value in X_1 we obtain the deterministic model at any time t as:

$$X_1(t) = 0.349e^{-.01t} + 0.346e^{-.07t}. \tag{5.45}$$

5.6.3: Comparison between deterministic and stochastic curves

Table C_3 shows the deterministic and stochastic values for the concentration of glucose

tracer in blood plasma at times between 0 and 180 (minutes) and for the total group of subjects. The deterministic values are calculated using the deterministic equation 5.45. The table is given in Appendix C.

Figure 5.7 shows the deterministic and stochastic curves together with the original data. It can be seen that the deterministic values are greater than the stochastic value for about t >20 minutes. Although the difference between the two curves is small, the data are closer to the stochastic curves, and the stochastic curve fits the data better than the deterministic curve . Also, the CV for curve fitting (see equation 5.26) was calculated as 16.95 % indicates a reasonable fit to the data. Figure 5.7 shows that it is less appropriate to use the deterministic values (that is the mean concentration of glucose tracer in blood plasma) as these are overestimation of the average values. If we consider the stochastic curve to be a more realistic estimate of the actual metabolic processes in the body then these differences show clearly that the deterministic model is likely to be a less satisfactory in general, although it is very much easier approximation to calculate.

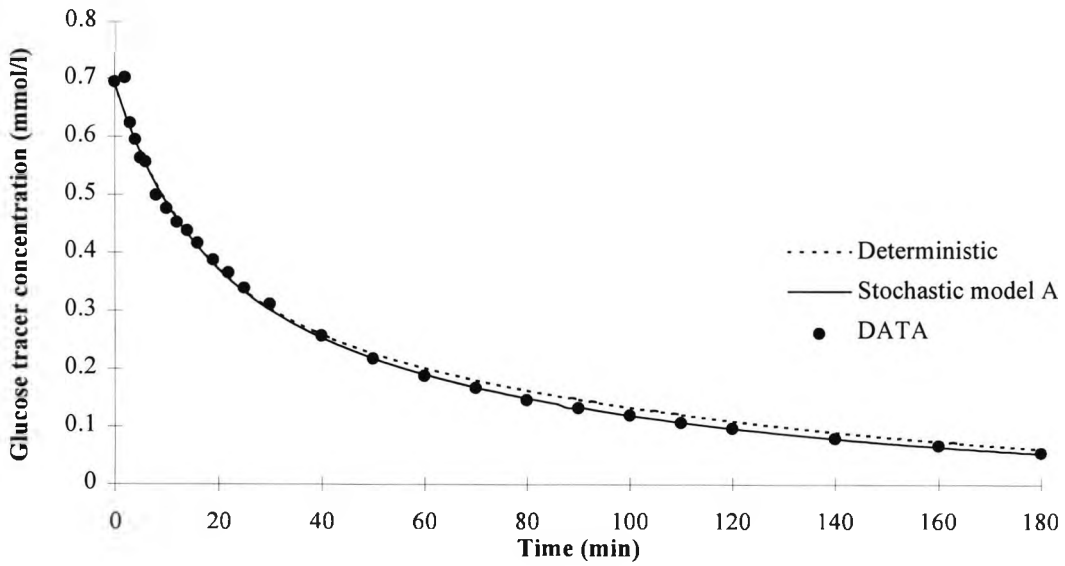


Figure 5.7: Stochastic and deterministic curves for the glucose tracer concentration in blood plasma following an intravenous glucose tolerance test (IVGTT) in total group of subjects.

5.6.4: Estimation of the parameters of the stochastic model

The parameters were estimated using the ADAPT (D'Argenio *et al.*, 1992) program. A single and double exponential models were fitted to the above stochastic curves in turn and the output of the ADAPT, especially R^2, showed that the best fit was achieved with the double exponential model as follows

$$f(X,t) = Ae^{-Bt} + Ce^{-Ct} \qquad \textbf{(5.46)}$$

For parameter estimation, 46 points from the stochastic model were considered so every four points were selected (i.e. 0, 4, 8,...). According to the above inputs, the output was obtained which has a high coefficient of variation (Draper & Smith, 1966) or R^2. The correlation coefficient is a non-negative coefficient which is always less than or equal to one. When R^2 is near to one there is a good fit to the curve, otherwise not. If R^2= 0.85 it means that 85% of the total variation in the value of f(x, t) ,or any response variable, is presented by the fitted curves (plane). From the ADAPT (D'Argenio *et al.*, 1992) manual the formula of correlation coefficient is given by

$$R_i^2 = \frac{\sum_{j=1}^{m} (y_i(\alpha,t_j) - \bar{y}_i(\alpha))(z_i(t_j) - \bar{z}_i)}{\sum_{j=1}^{m} (y_i(\alpha,t_j) - \bar{y}_i(\alpha))^2 \sum_{j=1}^{m} (z_i(t_j) - \bar{z}_i)^2} \qquad i = 1,\ldots, l$$

In our case we have R^2 =1. 0 so we have a very good fit.

The estimation of the parameters, their CVs and confidence intervals along with the R^2, the weighted sum of squares (WSS) and the sum of squares (SS) are given in Appendix A. Furthermore, the data at every time point (0, 4, 8,...) and the model estimation at the same times are also introduced with the residuals and the weights. Finally, the model along with the data are presented. The formula for the stochastic model is as follows

$$f(x,\ t) = 0.3495\ e^{-0.06005t} + 0.3308\ e^{-0.01023t}\ . \qquad (5.47)$$

5.6.5: Calculation of the stochastic values for the S. E. of the concentration of glucose tracer in blood plasma in the total group of subjects

In this section, the S. E. of glucose tracer concentration in blood plasma is calculated for different times from 0 to 180 minutes. For calculation of the S. E. for the stochastic model, the same program with the same upper and lower limits and the same number of integrand evaluation were applied but the value of tolerance was changed to 0.00001 due to the much smaller values of S. E. at each time points. The variance was evaluated from $E[(x(t)-\mu)^2]$ where $\mu=E(x)$, and substituted in equation 5.39 and the integral calculated at different time values. The program and the result are given in Appendix B. Figure 5.8 shows the S. E. of the stochastic and deterministic models of the concentration of glucose tracer in blood plasma together with the same values obtained from the S.E. of the original data at each time point. For calculation of the S. E. of the deterministic model, the predicted values for every minute and for each subject were used. The S.E. of the original data are shown again in Table 6.1. The S. E. of the stochastic models falls rapidly at first then decays to 0.0005 mmol/l at 180 minutes. The stochastic curve fits the S. E. of the original data quite well at small time points ($t < 20$) and large time points ($t > 100$), but between 20 to 100 minutes the values are above the stochastic curve. On the other hand, the deterministic curve has quite a good fit to the S. E. of the original data for all the time points. If we consider the stochastic model to be a more realistic model then simply taking the S.E. of the deterministic and the original data at each time point appears to introduce a bias towards a higher predicted S.E. values in the region 20-100 minutes. Obviously, taking the simple average and variance of the data of all the subjects at each fixed time point is inappropriate as the time course for each subject is different.

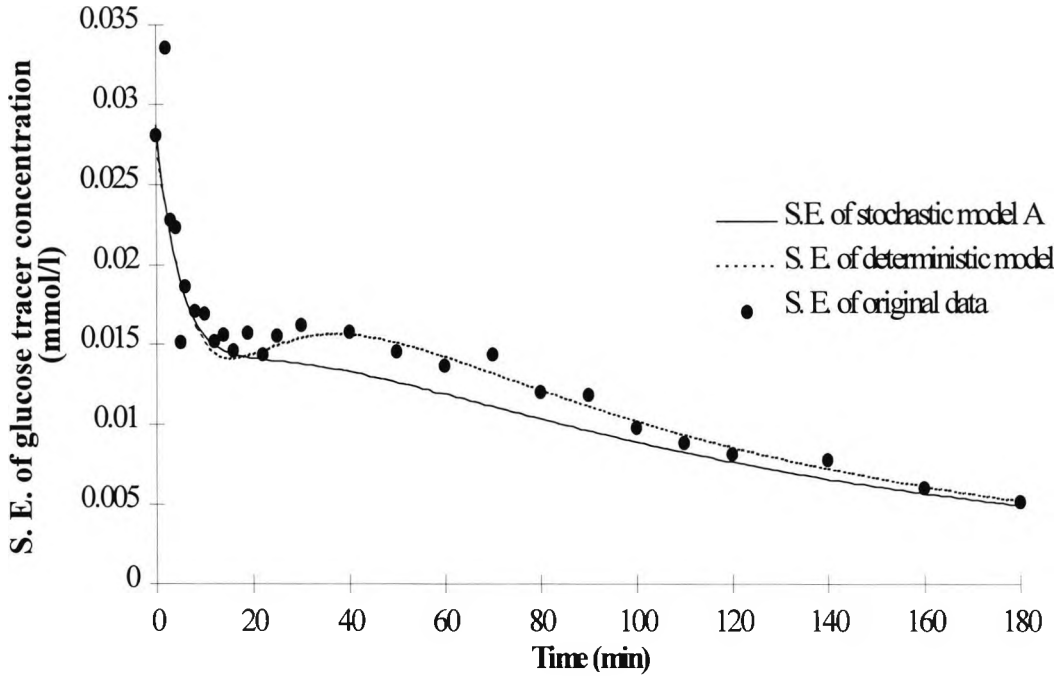


FIGURE 5.8: The S. E. of the stochastic and deterministic models and the original data for the concentration of glucose tracer in blood plasma following an IVGTT in total group of subjects.

5.7: Division of the sample into two subgroups

It was mentioned in Chapter 4 that the sample was divided into the two subgroups:

1. Obese normal and obese GDM (gestational diabetes mellitus)
2. Normal and GDM.

There are eight women in the first group and nine women in the second group. The aim of the division is to compare the deterministic and stochastic models in the two groups. Before starting the comparison, it is useful to compare the two groups according to some of their personal features.

5.7.1: Comparison according to estimated transfer rate

To see if there is any difference between the estimated transfer rates (k_{21} , k_{12} , k_{02} and c_1) in the two groups, the t-test was used and no significant difference was found

between the above transfer rates in the two groups. Therefore differences in body weight (see Chapter 4) do not affect to the values of estimated transfer rates.

5.8: Calculation of the stochastic model for the mean concentration of glucose tracer in blood plasma in non-obese subjects

To obtain the stochastic model for the non-obese subjects, we followed the same method of model building as in the total subject group with a few changes. The following points show the similarities and differences between model building in total subjects and obese group:

A) SIMILARITIES:

1. We used equation 5.39, so we applied the quadravariate lognormal distribution for integration to build the stochastic model for the non-obese group;
2. We applied the same program (D01FCF) for the integration;
3. The upper and lower limits are the same as the integral for the total subjects;
4. We applied the same tolerance and number of integrand evaluation.

The program and the result will be given in Appendix B. Also, the stochastic and deterministic values are shown together in Table C_4 in Appendix C.

B) DIFFERENCES:

1. The values of mean for the four variables k_{21}, k_{12} , k_{02} and c_1 changed.
2. The variance covariance matrix, which is a function of the mean, also changed according to the change of the number of the variables (in the total group there are 17 subjects so 17 values for the variables, but in the non-obese group there are only 9 subjects so 9 values for the variables) . Therefore, its inverse and determinant are also changed.

Figure 5.9 shows the resulting deterministic and stochastic curves together with the original data for non-obese subjects. As can be seen, there are larger differences between the two curves than in the total group of subjects. The stochastic curve fits the non-obese data better than in the case of the total group of subjects.

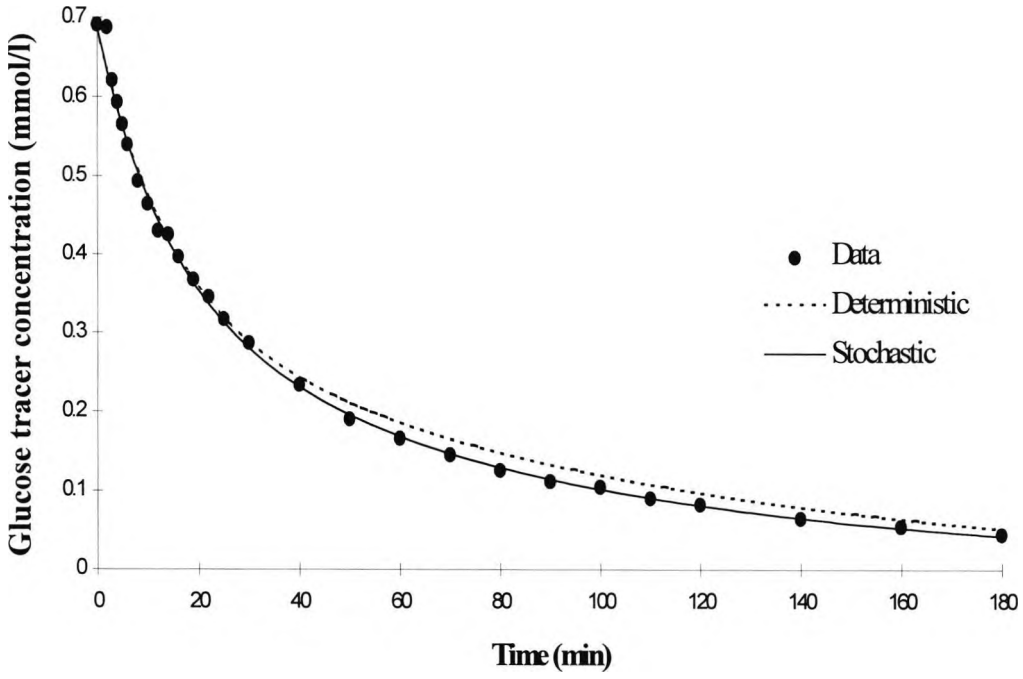


Figure 5.9: Stochastic and deterministic curves for the concentration of glucose tracer in blood plasma following an IVGTT in non-obese subjects.

5.8.1: Parameter estimation for the stochastic model of non-obese subjects

To estimate the parameter for the non-obese subjects, the same procedure for the total subjects was used. In this case the ADAPT software was applied again to estimate the parameters of a double exponential model as the stochastic model for non-obese subjects. The output of the program is given in Appendix A. The formula for the stochastic model is as follows:

$$f_{non-obese}(x,t) = 0.3744\, e^{-0.05955t} + 0.3024 e^{-0.01098t} \qquad \textbf{(5.48)}$$

5.8.2: Calculation of the stochastic values for the S. E. of the concentration of glucose tracer in blood plasma in non-obese subjects

For the calculation of the stochastic values for the S. E. of the concentration of glucose tracer in blood plasma for non-obese subjects, the following steps were followed:

1. We used the same program that was used for the calculation of the S. E. of concentration of glucose tracer in blood plasma in total subjects. The only change was in the values of the mean, variance, matrix of variance-covariance and its inverse and determinant according to the new values for the variables.

2. The upper and lower limits, the number of integrand evaluations and the tolerance were the same as the program for calculation of the S. E. for the total group.

3. The program calculated the stochastic values for the variance of the concentration of glucose tracer in blood plasma from 0 to 180 minutes and the values of S. E. were obtained using these calculated values.

The program and its result is given in Appendix B.

Figure 5.10 shows the S.E. of the stochastic and deterministic models for the concentration of glucose tracer in blood plasma together with the S. E. of the original glucose tracer concentration data at each time point. As can be seen the S.E. of the original data for times greater than 20 minutes are an overestimate when compared to the S. E. of the stochastic model, whilst the deterministic model of course fits the S. E. of the original data quite well for all times, especially for times greater than 40 minutes.

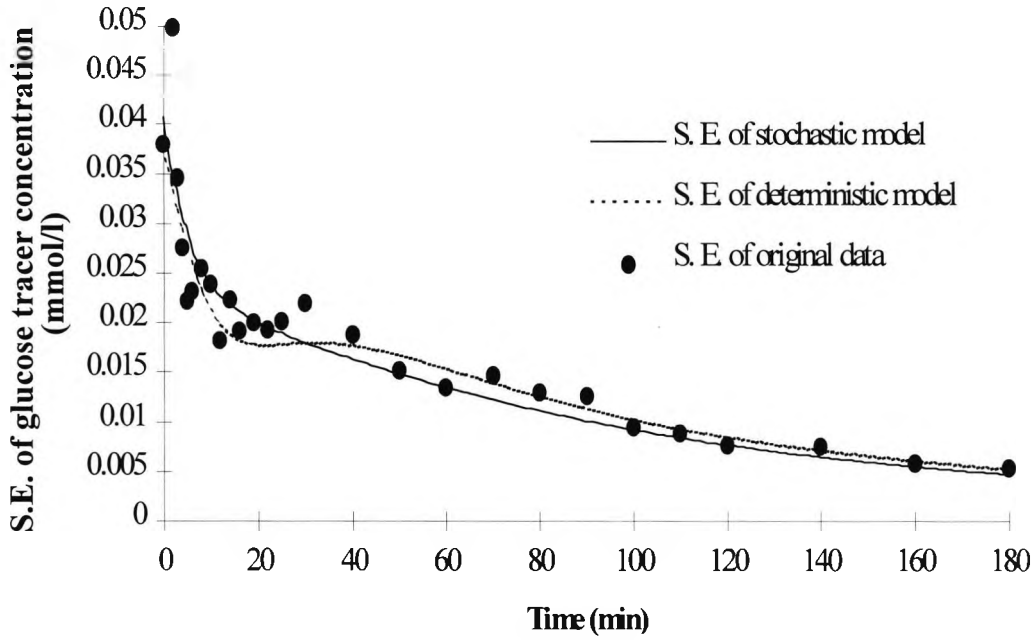


FIGURE 5.10: The S. E. of the stochastic and deterministic models and the original data for the concentration of glucose tracer in blood plasma following an IVGTT in non-obese subjects.

5.9: Calculation of the stochastic model for the mean concentration of glucose tracer in blood plasma in obese subjects

The model building procedures for the above subjects are exactly the same as for the non-obese subjects, i.e. using the same equation for the integration, the same program, tolerance and limits. Also, the values of the mean for the four variables (k_{21} , k_{12} , k_{02}, c_1) along with the variance-covariance matrix were changed due to the change of the above variables. Therefore, the inverse and determinant of the matrix changed. The program and the results are given in Appendix B. Also, the stochastic and deterministic values are shown together in Table C_4 in Appendix C. Figure 5.11 shows the results of the stochastic and deterministic model for the obese subjects. The values of the deterministic curve is still larger than the stochastic curve and the stochastic curve has a better fit to the data. The two curves are very close as in the case of the total group.

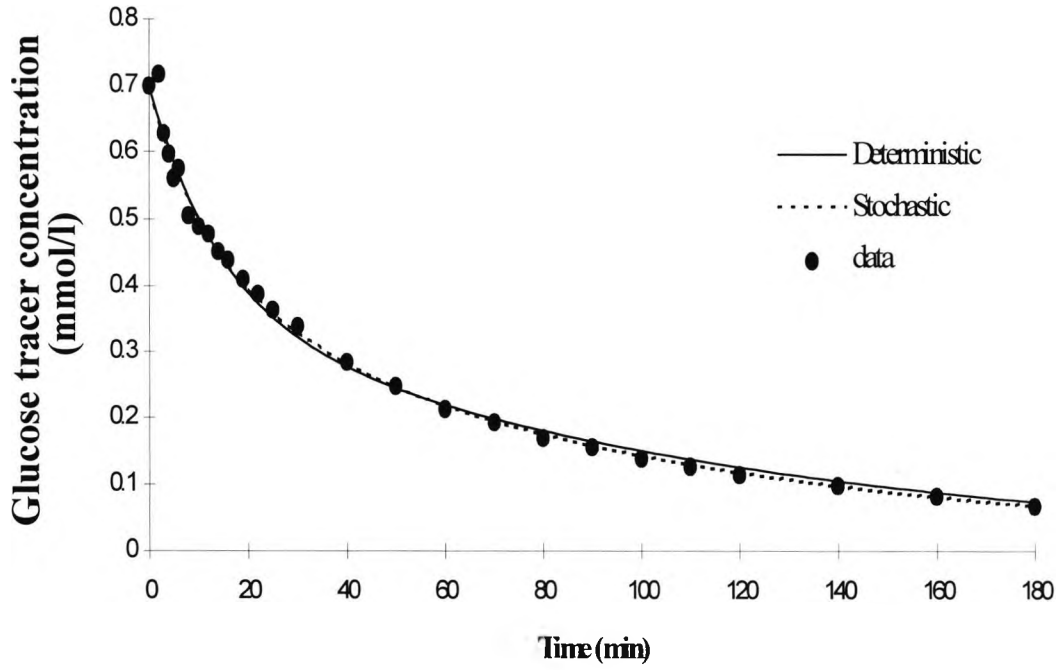


Figure 5.11: Stochastic and deterministic curves for the concentration of glucose tracer in blood plasma following an IVGTT in obese subjects.

5.9.1: Parameter estimation for the stochastic model of obese subjects

For the parameter estimation of the obese subjects again a best fit (double exponential model) was selected. The ADAPT software with 46 data (time=0, 4, 8,...) was used to estimate the four parameters of the model. The stochastic model for obese subjects was well fitted to the data (R^2 =1) and is given by

$$f_{obese}(X,\ t) = 0.3149\ e^{-0.0611t} + 0.3691\ e^{-0.009625t}. \qquad \textbf{(5.49)}$$

The software output along with the data, their estimation, the residuals, SS and WSS are presented in Appendix A.

5.9.2: Calculation of the stochastic values for the S. E. of the concentration of glucose tracer in blood plasma in obese subjects

The calculation of the S. E. of the stochastic model of the concentration of glucose tracer

in blood plasma for obese group of subjects was done in a similar way to the case of the non-obese group of subjects. The program and the results are given in Appendix B. Figure 5.12 shows the S. E. of the stochastic and deterministic models of the concentration of glucose tracer in blood plasma in obese subjects together with the S. E. of the original glucose tracer concentration data. As can be seen there is a large difference between the S. E. of the stochastic model and both deterministic model and the original data, especially at times between 20 minutes to 100 minutes. The S. E. of the deterministic model fits the original data quite well as to be expected. This shows that the S. E. of the deterministic and the original data are biassed even though the mean values of the stochastic model and both the deterministic and the original data are very close at each time point (see Figure 5.11).

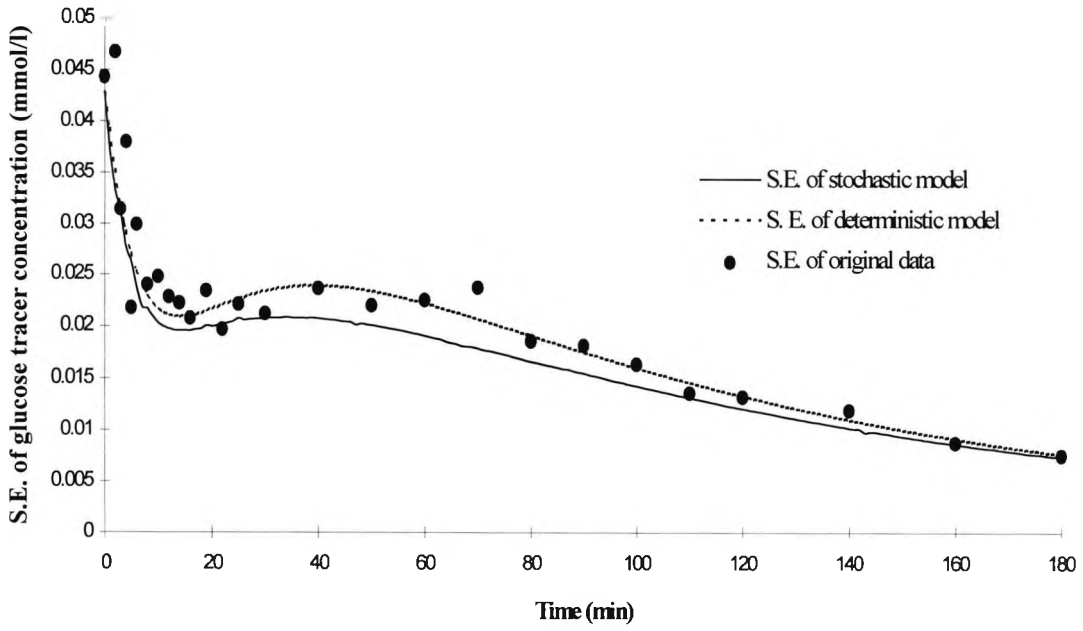


Figure 5.12: The S. E. of the stochastic and deterministic models and the original data for the concentration of glucose tracer in blood plasma following an IVGTT in obese group of subjects.

5..10: Discussion and Summary

In this Chapter a two-compartmental model of glucose kinetics was considered. The first compartment is blood (plasma) and the second compartment is extravascular tissue. A bolus of glucose was injected intravenously and blood samples was collected at various times ranging from 2 to 180 minutes after the injection.

The concentration of glucose tracer in blood (plasma) was collected using a mass balance (differential) equation for the system which is a function of four variables (k_{21}, k_{12}, k_{02} and c_1= the initial concentration of glucose tracer in the first compartment) and time.

To build a stochastic model for the concentration of glucose tracer in blood plasma, at first the parameters of the above function were estimated (weighted least square error) using the output for all the subjects. Then the mean of glucose tracer concentration in blood (plasma), say X_1 , was calculated using a four dimensional integration. It is assumed that the parameters of X_1, k_{21}, k_{12}, k_{02} and c_1, have a quadravariate log-normal distribution.

For calculation of the above huge integration, $E(X_1)$, the NAG software library was used and the results were obtained at every minute , t=0,1, 2, 3,...,180, so the stochastic model which is a double exponential curve was built.

The parameters of the above stochastic model were then estimated. Also, the stochastic models for obese and non-obese subjects were built using the same procedures and their parameters were estimated.

There are differences between the mean concentration of glucose tracer in the stochastic and deterministic curves. These differences are smaller in the total group of subjects than in the non-obese group. In all groups choosing the deterministic values as the mean

concentration of glucose tracer in blood plasma yields small overestimate in the mean concentration values of the glucose tracer. Also, the stochastic model for the mean concentration of glucose tracer gives a better fit to the data. Furthermore, it seems that choosing a large sample size yields a stochastic curve which more closely approaches the deterministic curve. Finally, the model A approach does not seem an appropriate approach when the number of the compartments is greater than two, due to complexity of the integration. We will discuss this result further in Chapter 8 where some new aspects of the stochastic models will be introduced.

The S. E. of the stochastic and deterministic models and of the original data glucose tracer concentration in blood plasma were also calculated using a similar program for the ordinary definition of variance and the values were compared.

As it can be seen, although the stochastic and deterministic models for the mean concentration of glucose tracer for the total, obese and non-obese subjects are almost the same, there are quite large differences in the S. E. of the stochastic model and the original data in all groups. These differences are small in total group of subjects and quite large in the non-obese and obese subgroups. In all groups the S.E. of the original data are larger than that of the stochastic model and this suggests that simply taking the S. E. of the original data at each time point introduces an overestimate of the S. E. at these times.

Chapter 6

Stochastic compartmental model B

6.1: Introduction

In Chapter 5, a stochastic model (model A) was presented. In this stochastic modelling approach, the compartmental parameters (k_{21}, k_{12}, k_{02}, $c_1 = x_1(0)$) are not fixed and it is assumed that they vary in different subjects and also in the same subject if we repeat the experiment on the same subject.

In this chapter we introduce another type of stochastic model, which is a population model, for the concentration of glucose tracer in blood plasma. It is still assumed that the compartmental parameters vary randomly and also from one subject to another but in addition, since we have several measurements at every time point, we will assume that measurements at a fixed time have a special frequency distribution, taken to be normal in our case. Furthermore, all of the elements of the compartmental matrix fluctuate according to this random process. There are some properties and restrictions on this random process which will be defined later.

When the elements of the compartmental matrix fluctuate, all of the compartmental parameters which describe the flux of glucose tracer from the first compartment (blood plasma) to the second compartment (extravascular tissue) fluctuate. These fluctuations of the compartmental parameters cause an uncertainty in the compartmental system. Thus the deterministic method introduced in the previous chapter is unable to represent the real variations of the system, especially the decay of glucose tracer in the second compartment. In 1989 Limić proposed a new stochastic model for concentration of glucose tracer in both compartments. The stochasticity in Limić's model involves a random process and its

statistical moments. We will describe this random process and the details of the modelling method in the next section .

6.2: Limić's model

Limić considered a n-compartmental model each containing some amount of a given substance. The mass balance equation for the set of compartments is

$$\frac{dC(t)}{dt} + A(t)c(t) = q(t) = 0 \qquad C(t_0) = C_0 \ , \tag{6.1}$$

where $A(t)=\{a_{ij}(t)\}$ is the compartmental matrix and C is the vector of the amounts of substance in each compartment. It is assumed that all $a_{ij}(t)$ fluctuate as well as the input and the initial state undergo random fluctuations. Thus all the a_{ij} (t)s have their own random fluctuations relating to a random process and also the input and the initial state have fluctuations, not necessarily the same as the $a_{ij}(t)$s fluctuations. The following is a condensed account of Limić 's analysis:

1 The parameters $a_{ij}(t)$ are assumed to have a constant mean value of $d_{ij}=E(a_{ij}(t))$ and their fluctuations are of the form

$f_{ij}(t)=d_{ij}\,\Phi_{ij}(t)$

where $\Phi_{ij}(t)$ i, j=1, 2, ..., n are random processes. Therefore,

$A(t)=D+F(t)$

where $D=\{d_{ij}\}$ and $F=\{f_{ij}(t)\}$.

2 The $\Phi_{ij}(t)$s are assumed to have truncated (at zero) normal distributions and the same statistical moments, so we have:

$$\mu_n(t_1,t_2,\ldots,t_n)=E(\phi(t_1)\ \phi(t_2)\ldots\phi(t_n)). \tag{6.2}$$

3 The $\Phi_{ij}(t)$s have a small probability of accepting negative values, but if we suppose that their standard deviations are small enough, such probabilities are also small. Therefore the assumptions are taken as reasonable.

Suppose that

$$b(t)=e^{Dt}C(t), \tag{6.3}$$

then:

$$\frac{db(t)}{d}(t)+S(t)b(t)=P(t), \tag{6.4}$$

where

$$S(t)=e^{Dt}F(t)e^{-Dt}, \qquad P(t)=e^{Dt}q(t)=0. \tag{6.5}$$

The solution of equation 6.4 with the initial condition $b(t_0)=b_0$ and vanishing input, can be represented by the following series:

$$b(t)=\sum_{j=0}^{\infty}u_j(t), \qquad u_0(t)=b_0\ , \tag{6.6}$$

where

$$u_j(t)=(-1)^j\int_{t_0}^{t}dt_1\int_{t_0}^{t_1}dt_2\ldots\int_{t_0}^{t_{n-1}}dt_jS(t_1)S(t_2)\ldots S(t_j)b_0\ . \tag{6.7}$$

It can be shown that

$$\frac{d}{dt}[E(C(t))]+(D-\sigma^2D^2)E[C(t)]+h(t)D^2[EC(t)]=0, \qquad E[C(t_0)]=C_0, \tag{6.8}$$

where

$$\sigma^2 = \lim_{t\to\infty} \int_0^t \mu_2(t,\ s)\ ds, \tag{6.9}$$

$$h(t) = \sigma^2 - \int_0^t \mu_2(t,\ s) ds, \tag{6.10}$$

and

$$\mu_2(t,\ s) = E(\phi(t)\ \phi(s)). \tag{6.11}$$

6.3: Evaluation of Limić's model

The structure of the random process is actually more limited than Limić intended (Dr R Gerrard , personal communication, 1994). This can be seen as follows:

From equation 6.2 for $\Phi_{i1\,j1}$ (t) and $\Phi_{i2\,j2}$ (t) we have

$$E\ [\Phi_{i_1 j_1}(t_1)\Phi_{i_2 j_2}(t_2)] = E\ [\Phi_{i_1 j_1}]^2(t_1) = E\ [\Phi_{i_2 j_2}]^2(t_2) = \mu_2(t_1,\ t_2). \tag{6.12}$$

Therefore

$$E[\Phi_{i_1 j_1}(t_1) - \Phi_{i_2 j_2}(t_2)]^2 = 0. \tag{6.13}$$

So

$$\Phi_{i_1 j_1}(t_1) = \Phi_{i_2 j_2}(t_2) \tag{6.14}$$

for all t_1 and t_2. We have the same for all subscripts of i and j, so all the Φs are equal and each parameter does not vary independently. Since all the Φs are equal we call them Φ(t)

and thus A(t) may be written as equation 6.15.

$$A(t)=(1+\Phi(t))\,D. \tag{6.15}$$

The effect of this constraint on the model will be discussed later.

We then have

$$\mu_2(t,\ s)=E(\Phi(t)\Phi(s)). \tag{6.16}$$

Also, for $\mu_2(t,s)$ in equation 6.9 and 6.10, the limits of the integrations must be restricted since they could be infinite unless certain assumptions are made. With zero input we have:

$$\frac{d}{dt}\ C(t)=-(1+\Phi(t))DC(t), \tag{6.17}$$

where

$$C(t)=e^{-\int_{t_0}^{t}(1+\Phi(s))ds\ D}\ C_0. \tag{6.18}$$

With the assumption of normality for $\Phi(t)$, the variable

$$\int_{t_0}^{t}(1+\Phi(s))\ ds \tag{6.19}$$

is normal and its mean and variance are respectively given by ($t-t_0$) and

$$\tau_t^2=\int_{t_0}^{t}\int_{t_0}^{t}\mu_2(u,v)dudv \tag{6.20}$$

If we calculate the expectation of C(t) in equation 6.18 and substitute the mean and variance of 6.19 as mentioned above, then we obtain

$$E(C(t))=e^{\frac{1}{2}D^2\tau_t^2-D(t-t_0)}\ C_0. \tag{6.21}$$

Therefore

$$\frac{d}{dt}E(C(t)) = (-D + D^2 \int_{t_0}^{t} \mu_2(t,v)dv)\ E(C(t)). \qquad \textbf{(6.22)}$$

The above equation is the mean of the solutions of 6.1 where D=E(A) and A is the compartmental matrix. Equation 6.22 (which was introduced by Limić) is the same as equation 6.8. Also it was shown earlier that Limić's solution is correct but for a far more restricted stochastic model than the author intended. According to the result given by 6.14 each parameter (fluxes of substances between compartments) fluctuates randomly in a pattern which is the same for all the other parameters. So, knowing the fluctuation pattern of one parameter determines us to predict the fluctuations of the other parameters. On the other hand, one of the most important properties of a stochastic compartmental model is that each parameter may fluctuate differently from the others. However, building a stochastic model with this property is extremely complex. Hence, despite its limitations, we choose Limić's stochastic model as the first attempt to show the difference between stochastic and deterministic models.

6.4: Data analysis

To develop model B, it is necessary to calculate the mean of glucose tracer (say $\bar{G}(t)$) by averaging glucose tracer measurements of a group of subjects at each time point. This averaging is necessary because we need to build a model for the mean of the glucose tracer at every time point to use in our future stochastic model. We calculate the arithmetic mean of glucose tracer, $\bar{G}(t_j)$, at each time point t_j (26 time points) over all the subjects (N=17) from

$$\bar{G}(t_j) = \frac{1}{17} \sum_{i=1}^{17} g_i(t_i). \qquad \textbf{(6.23)}$$

The means and the S.E of blood glucose tracer are given in Table 6.1 at every time point and Figure 6.1 shows the average curve.

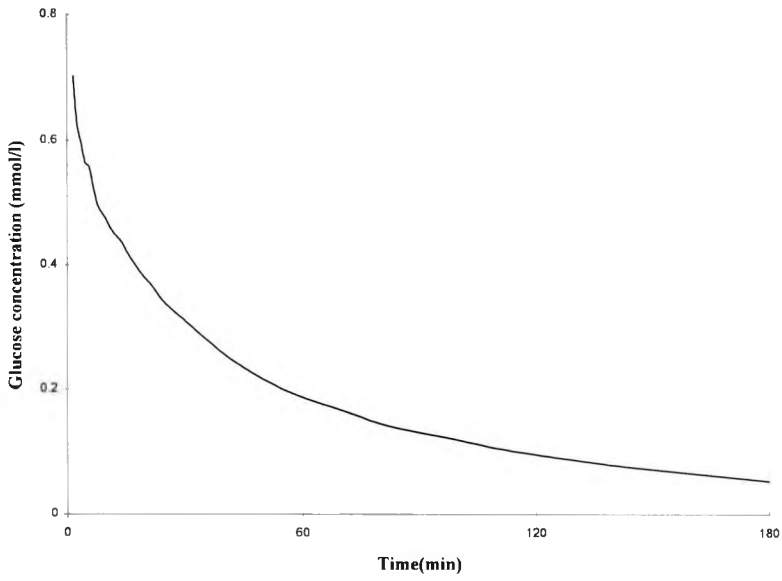


FIGURE 6.1: Blood plasma glucose tracer concentration averaged over the total group of subjects.

Time (min)	Mean (mmol/l)	S.E. (mmol/l)	Time (min)	Mean (mmol/l)	S.E. (mmol/l)
2	0.702	0.033	30	0.311	0.016
3	0.624	0.022	40	0.257	0.016
4	0.595	0.022	50	0.217	0.014
5	0.563	0.015	60	0.188	0.014
6	0.556	0.019	70	0.167	0.014
8	0.499	0.017	80	0.146	0.012
10	0.476	0.017	90	0.132	0.012
12	0.452	0.015	100	0.120	0.010
14	0.438	0.015	110	0.107	0.008
16	0.416	0.014	120	0.097	0.008
19	0.387	0.016	140	0.080	0.008
22	0.365	0.014	160	0.067	0.006
25	0.338	0.015	180	0.055	0.005

Table 6.1: Mean and S.E. (of the mean) of glucose tracer.

6.5: Parameter estimation of the mean model

A model for the mean of the glucose tracer at different time points is required in the calculation of the statistical moments of the random process. The data in Table 6.1 shows that an exponential model has the best fit to the data. We assume different exponential models (single, double and more than double exponential) and finally a double exponential model which had the best fit was obtained as follows:

$$Y_1(t) = A\ e^{-Bt} + C\ e^{-Dt}. \qquad \textbf{(6.24)}$$

To estimate the unknown parameters A, B, C and D, the ADAPT program ID and the data in Table 6.1 was used. Due to the initial mixing transient following injection, the data at

times t=2, 3, 4 and 5 minutes were not included. The ADAPT output is given in Appendix A and a short summary of the results follows.

The program estimates the parameters using initial values which are defined by the user. For parameter estimation, the weighted least square (WLS) method was used in the development of model B above. For the WLS method the program require two points (upper and lower) of the regression line of the S.E. of the data set and these points are introduced in the section of the output with 'weighting information' heading. A 95% confidence interval for the estimated parameters along with the values of CVs are also given in the ADAPT output. Furthermore, there is a section in the ADAPT output with the title of 'estimated model prediction and data summary' which gives the original data at each time point along with the corresponding model prediction, the residual and weight.

The result for the mean was found to be:

$$\mu(t) = 0.3438\ e^{-0.04577t} + 0.2907\ e^{-0.009245t}. \qquad \textbf{(6.25)}$$

6.6: The model for the S.E. of glucose tracer and estimation of the parameters

As was mentioned above, to calculate the statistical moment of the random process we also need a model for the S.E. of the glucose tracer which was obtained from the output data (Table C_2 in Appendix C). Table 6.1 shows the values for S.E. at each time point. The data suggests that a simple linear model will suffice.

A regression line was fitted (Microsoft Excel, Version 5.0, 1994) to the S.E. of glucose tracer, $\mu(t)$, as follows:

$$\sigma(t) = -0.000069t + 0.017206. \qquad \textbf{(6.26)}$$

As in the model of the glucose tracer mean, we exclude the data at the times=2, 3, 4 and 5 minutes due to mixing transients after tracer injection. The value of R^2 was about 0.94 showing that a linear model is a good one. Figure 6.2 shows the regression line of the S.E. (glucose tracer) vs time in the total group of subjects.

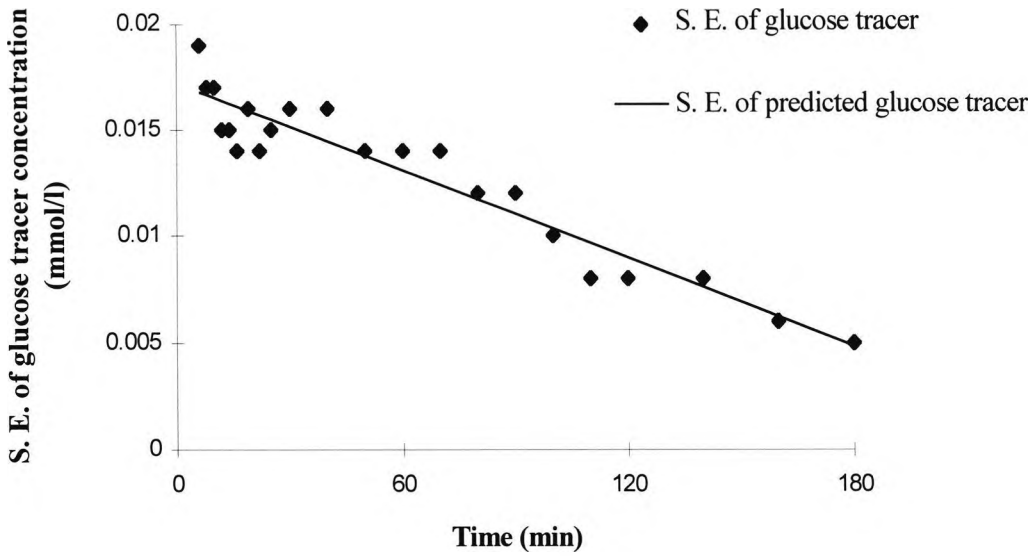


Figure 6.2: The regression line of the S. E. of blood glucose tracer vs time in the total group of subjects.

6.7: Calculation of the statistical moments of the random process

Equation 6.11 is used to compute the statistical moments, μ_2 (t, s), of the random process in a two compartmental model and we will require the above models for the mean and S.E. of the glucose tracer.

Since $\Phi(t)$ and $\Phi(s)$ are random processes with truncated normal (at zero) distributions, their probability density functions are given by

$$\phi(X,\ t)=\frac{1}{\sqrt{2\pi}\sigma(t)}e^{\frac{-(x-\mu(t))^2}{2\sigma(t)^2}},$$
$$\phi(Y,\ s)=\frac{1}{\sqrt{2\pi}\sigma(s)}e^{\frac{-(y-\mu(s))^2}{2\sigma(s)^2}}. \qquad \textbf{(6.27)}$$

Equation 6.11 gives

$$\mu_2(t,\ s)=E(\phi(t)\ \phi(s))=\int_0^\infty\int_0^\infty X(t)Y(s)\ f(X(t),Y(s))\ dxdy, \qquad \textbf{(6.28)}$$

where f(X(t),Y(s)) is the bivariate normal distribution given by

$$f(X(t),Y(s))=$$
$$\frac{1}{2\pi\sigma(s)\sigma(t)\sqrt{1-\rho^2}}e^{-\frac{1}{2(1-\rho^2)}\left[\frac{(X-\mu(t))^2}{\sigma(t)^2}-2\rho\frac{(X-\mu(t))(Y-\mu(s))}{\sigma(t)\sigma(s)}+\frac{(y-\mu(s))^2}{\sigma(s)}\right]} \qquad \textbf{(6.29)}$$

where $\mu(t)$, $\mu(s)$, $\sigma(t)$ and $\sigma(s)$ are given by equations 6.25 and 6.26 and ρ is the population coefficient of correlation between X and Y. This was estimated as r, the sample coefficient correlation. So $\hat{\rho}$= r.

The integrals in equation 6.28 were evaluated using the NAG library program D01FCF for two dimensions. The program is given in Appendix B.

In equation 6.29 when s = t then we have $\hat{\rho}$ = r = 1, and a singularity appears in its integrand. To avoid the singularity, the ordinary formula for the expectation of the product of two variables (Mood et al., 1974) was used, as shown below:

$$R=\frac{\left(E(XY)-E(X)E(Y)\right)}{\left(\sigma_{\bar{X}}\ \sigma_{\bar{Y}}\right)}=1, \qquad \textbf{(6.30)}$$

where $\sigma_{\bar{x}}$ and $\sigma_{\bar{y}}$ are the standard errors of the means. Thus

$$E(XY) = E(X)E(Y) + \sigma_{\bar{X}}\ \sigma_{\bar{Y}}\ . \qquad \textbf{(6.31)}$$

Furthermore, for the calculation of the statistical moments of the random processes, when s=0 we need the correlation coefficients of the glucose tracer mass in blood plasma especially at time zero. These correlations can be used as the estimated values of ρ in equation 6.29. There is no data at time zero and values of the glucose tracer mass in blood plasma (X_1 (0)=c_1) were estimated from able 5.1. It is now possible to calculate the statistical moments of the random processes.

Table 6.2 shows the result of the integration for different time points (t,s) when
t, s= 0, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160 and 180. Also, we have:
$\mu_2(i, j) = \mu_2(j, i)$ for any i, j.

t	s (min)									
(min)	0	6	8	10	12	14	16	19	22	25
0	0.403									
6	0.022	0.288								
8	0.323	0.273	0.259							
10	0.306	0.000	0.000	0.233						
12	0.291	0.000	0.000	0.000	0.211					
14	0.007	0.219	0.227	0.000	0.065	0.191				
16	0.263	0.061	0.211	0.200	0.135	0.017	0.173			
19	0.246	0.194	0.197	0.187	0.174	0.000	0.000	0.151		
22	0.054	0.195	0.185	0.175	0.167	0.132	0.000	0.000	0.132	
25	0.169	0.182	0.172	0.163	0.156	0.149	0.055	0.000	0.000	0.116
30	0.195	0.159	0.156	0.148	0.141	0.018	0.128	0.022	0.084	0.000
40	0.162	0.137	0.130	0.123	0.118	0.112	0.102	0.079	0.023	0.086
50	0.137	0.116	0.111	0.105	0.099	0.095	0.091	0.085	0.078	0.002
60	0.120	0.101	0.096	0.091	0.087	0.083	0.078	0.071	0.063	0.063
70	0.105	0.089	0.084	0.080	0.076	0.069	0.066	0.053	0.049	0.042
80	0.094	0.079	0.075	0.071	0.068	0.065	0.038	0.057	0.013	0.050
90	0.084	0.070	0.067	0.063	0.061	0.058	0.055	0.049	0.048	0.001
100	0.075	0.063	0.060	0.057	0.055	0.052	0.050	0.045	0.040	0.040
110	0.064	0.058	0.054	0.052	0.046	0.046	0.045	0.042	0.037	0.014
120	0.061	0.052	0.049	0.047	0.045	0.043	0.041	0.038	0.035	0.023
140	0.051	0.043	0.041	0.039	0.037	0.034	0.032	0.030	0.029	0.027
160	0.042	0.036	0.034	0.032	0.031	0.029	0.028	0.024	0.024	0.000
180	0.034	0.030	0.028	0.027	0.025	0.024	0.023	0.021	0.020	0.014

Table 6.2: Distribution of the statistical moment, μ_2 (t, s).

t	s (min)									
(min)	30	40	50	60	70	80	90	100	110	120
30	0.095									
40	0.079	0.066								
50	0.066	0.056	0.048							
60	0.034	0.044	0.000	0.036						
70	0.050	0.043	0.034	0.000	0.028					
80	0.045	0.036	0.030	0.011	0.023	0.022				
90	0.041	0.032	0.029	0.021	0.000	0.000	0.018			
100	0.000	0.030	0.026	0.022	0.000	0.000	0.000	0.014		
110	0.031	0.028	0.000	0.008	0.000	0.016	0.000	0.000	0.012	
120	0.009	0.000	0.021	0.014	0.001	0.000	0.012	0.000	0.000	0.009
140	0.024	0.021	0.017	0.006	0.000	0.000	0.000	0.000	0.000	0.000
160	0.020	0.017	0.015	0.013	0.010	0.010	0.001	0.000	0.007	0.000
180	0.016	0.014	0.012	0.004	0.005	0.000	0.000	0.000	0.000	0.000

Table 6.2: Continued.

t	s (min)		
(min)	140	160	180
140	0.006		
160	0.000	0.004	
180	0.000	0.000	0.003

Table 6.2: Continued.

6.8: Numerical integration of the statistical moment of the random process

Before we can solve equation 6.8 of model B, we need the values of σ^2 and h(t) as defined in equations 6.9 and 6.10. Since the largest value of t in our data is 180, this was inserted in the upper limit of the integral in equation 6.9. Therefore, the following integral calculated:

$$\sigma^2 = \int_0^{180} \mu_2(180,\ s)\ ds. \qquad \textbf{(6.32)}$$

The integrand is tabulated at points given in Table 6.2 and program D01GAF from the NAG library, which is suitable for tabulated integrands, was used, with the result $\sigma^2 = 1.1715$. The program is given in Appendix B.

To calculate h(t) in equation 6.10, the second part of the right side of the equation was calculated using D01GAF (when the number of points were less than four , the integration was calculated manually). When $0 < t < 6$, a regression analysis with the times t=0, 6, 8 and 10 was used to estimate the unknown values of h(t). Obviously $h(0)=\sigma^2$ from equation 6.10. h(t) is tabulated at the original time points in Table 6.3.

Time (min)	h(t)	Time (min)	h(t)
0	1.1715	30	-1.3433
2	0.7349	40	-1.3511
3	0.5625	50	-2.1115
4	0.3902	60	-1.8100
5	0.2178	70	-1.9668
6	0.2405	80	-1.5743
8	-1.1485	90	-1.4537
10	-0.0818	100	-1.0461
12	1.0319	110	-0.9249
14	1.1847	120	-0.5765
16	0.5945	140	-0.4685
19	-1.5815	160	-0.5434
22	-1.5048	180	0.0000
25	-1.6382		

Table 6.3: Distribution of h(t).

6.9: Calculation of model B

In equation 6.8 we define $\bar{C}(t) = E(C(t))$ where C is the column vector $[C_1(t), C_2(t)]$. Then equation 6.8 may be rewritten

$$\frac{d}{dt}\begin{pmatrix}\bar{C}_1(t)\\ \bar{C}_2(t)\end{pmatrix} + (D - \sigma^2 D^2 + h(t)D^2)\begin{pmatrix}\bar{C}_1(t)\\ \bar{C}_2(t)\end{pmatrix} = 0 \qquad \begin{pmatrix}\bar{c}_1(t_0)\\ \bar{c}_2(t_0)\end{pmatrix} = \begin{pmatrix}\bar{C}_{10}\\ \bar{C}_{20}\end{pmatrix}, \qquad \textbf{(6.33)}$$

where the matrix D is given by

$$E(A)=D=\begin{pmatrix} \bar{k}_{21} & -\bar{k}_{12} \\ -\bar{k}_{21} & (\bar{k}_{12}+\bar{k}_{02}) \end{pmatrix} = \begin{pmatrix} 0.0397429 & -0.0230707 \\ -0.0397429 & 0.0403216 \end{pmatrix}, \tag{6.34}$$

where we have substituted for $\bar{k}_{ij}$ (the mean of k_{ij}) from Table 5.1. Also

$$D^2 = \begin{pmatrix} 0.00249639 & -0.00184714 \\ -0.00318199 & 0.00254272 \end{pmatrix}, \tag{6.35}$$

$$\sigma^2 D^2 = \begin{pmatrix} 0.00292452 & -0.00216392 \\ -0.00372770 & 0.00297880 \end{pmatrix},$$

and thus

$$D-\sigma^2 D^2 = \begin{pmatrix} 0.03681837 & -0.020906775 \\ -0.03601519 & 0.03734279 \end{pmatrix}. \tag{6.36}$$

Therefore from equation 6.33 we have:

$$\frac{d\bar{C}_1(t)}{dt} + (0.03681837 + 0.00249639.h(t)).\bar{C}_1(t) + (-0.02090677 - 0.00184714.h(t)).\bar{C}_2(t) = 0, \qquad \bar{C}_1(t_0) = C_{01}, \tag{6.37}$$

and

$$\frac{d\bar{C}_2(t)}{dt} + (-0.03601519 - 0.00318199.h(t)).\bar{C}_1(t) + (0.03734279 + 0.00254272.h(t)).\bar{C}_2(t) = 0, \qquad \bar{C}_2(t_0) = C_{02}, \tag{6.38}$$

where h(t) was tabulated in Table 6.3.

The solutions for equations 6.37 and 6.38 are the model B for the mean of the glucose tracer concentration in blood plasma and the concentration of glucose tracer in extra-vascular tissue respectively.

6.10: Calculation of the stochastic models for the amounts of glucose tracer in blood plasma and extravascular tissue

To calculate the concentration of glucose tracer in blood plasma,Y(1), and extravascular tissue,Y(2), program D02BBF from the NAG library was used. The program is given in Appendix B. This program integrates a set of first order differential equations by the method of Hall and Watt (Hall and Watt, 1976). Since the values of h(t) are known at discrete time points given in Table 6.3, a subroutine was added to the above program to linearly interpolate h(t) for times between each tabulated time point. The program output is given in Appendix B. Figure 6.3 shows the stochastic and deterministic curves for the concentration of glucose tracer in blood plasma.

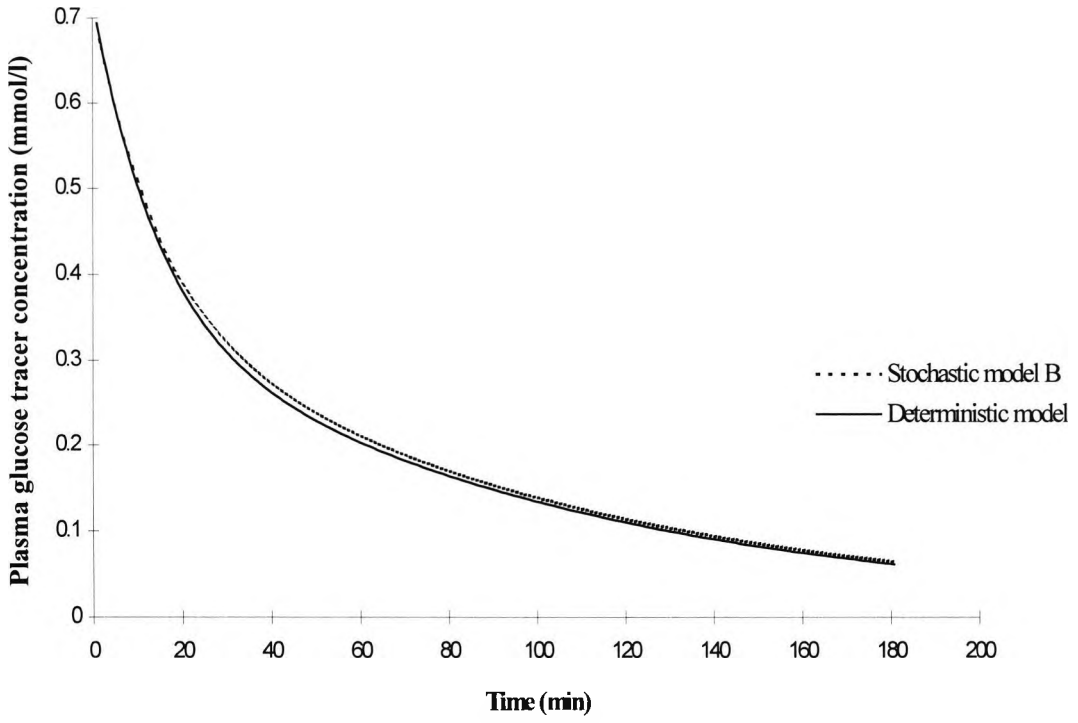


Figure 6.3: Stochastic and deterministic curves for the concentration of glucose tracer in blood plasma.

6.11: Summary and discussion

In this chapter a brief summary of model B approach for model building is presented. We are dealing with a matrix form of mass balance equations for a 2-compartmental system. Also, there is a random process where all the elements of the compartmental matrix fluctuate according to the above distribution. Despite the nature of the random process, there are two possible patterns of fluctuations as follows:

a) The elements have the same frequencies of fluctuation at the same time points, although they may have different amplitudes.

b) The elements have different frequencies of fluctuation and possibly different amplitudes.

In both cases the elements can have another fluctuation superimposed on the primary fluctuation which may have different variances for each element and at each time point. In this approach, which is perhaps the simplest case, it is assumed that all the elements of the compartmental matrix have the same frequency of fluctuation. In the more complex cases all the above elements would fluctuate independently and this is one of the defects of model B. However, solution of such a system would be considerably more complex.

Each element of the compartmental matrix is the sum of the fluctuation and the expectation of the elements of the matrix. The solution of the 2-compartmental matrix was also calculated using the above mass balance equations which are a function of the compartmental matrix and the moments of the random process (for a two compartmental model only the second moments were considered).

To build model B, the average and variance of the concentration of glucose tracer in blood plasma for all the subjects (17 subjects) at every time point (26 time points) was calculated and two models were built using the above means and variance. The model for variance is a linear model where its two parameters were estimated using regression analysis. The model for the mean of the glucose tracer in blood plasma at every time point was a double

exponential model and its four parameters were estimated.

In the next stage we dealt with a new distribution. According to the model B method, all the data at a specific time point are assumed to have a normal distribution, so there are 26 normal distributions each with 17 data points. To calculate the statistical moments of the random process, the expectation of the product of the distributions was used. Therefore, for all of the distributions the above expectation was calculated using a suitable double integration program from the NAG library. For equal times, the values of the coefficient correlation are unity and there is a singularity in the denominator of the integrand of the integration. This was avoided by applying the ordinary formulation for the expectation of the multiplication of two variables.

All the unknown functions of the solution of the differential equations were calculated and were inserted into the solution. Then the solution of the above differential equations (for the two compartmental system) was integrated numerically. The values of the concentration of glucose tracer were interpolated between the discrete time points. Finally, the stochastic model for concentration of glucose tracer in blood plasma and was obtained using the above program.

The shape of stochastic and deterministic curves for blood plasma are almost identical. Their only difference is in the values of glucose tracer in blood plasma between 10 and 60 minutes. From Figure 6.3, the stochastic values for concentration of glucose tracer in blood plasma for times less than 10 minutes are identical and at greater times the stochastic values are greater than the corresponding deterministic values. This difference increases from about 10 minutes up to almost 30 minutes and then starts decreasing to almost 60 minutes. Although the stochastic values for the concentration of glucose tracer in blood plasma are greater than the corresponding deterministic values at times greater than 60 minutes, they are almost the same elsewhere. Also, it is possible to apply the model B approach for more than two compartments and it is a much simpler method than that of model A. On the other hand, in the model B approach we can obtain the stochastic model for concentration of substances in all of the compartments at the same time, but in model A to calculate the

concentration of the substances in any compartment, we need to solve its concentration equation. One of the greatest defects of the model B approach, however, is the similarity of the fluctuations in all the elements of compartmental matrix. A random process where all the points have the same fluctuations is unrealistic in a physiological sense. We expect that the physiological parameters of the body will fluctuate in a normal population. However the calculation of concentration in such a system is too complex. As was mentioned above, we consider this simple case as a first attempt before introducing the more complex case where all the points have a different fluctuation.

Chapter 7

A comparison between stochastic and deterministic models

7.1: Introduction

There are several differences between the stochastic and deterministic models, especially in model building and the predicted shape of the curves in the total, obese and non-obese groups of subjects. These aspects are discussed below.

7.2: Differences in model building

In the next few sections there are short discussions on the methods of building deterministic and stochastic models and their advantages and disadvantages are compared.

7.2.1: Deterministic models

The method of building a deterministic model was discussed in the previous chapters and we will discuss it again here briefly. As was mentioned, we build up mass balance differential equations according to the present compartmental system, its fluxes, its losses and its output. Then the solution of the differential equations is calculated and the parameters of the fitted curve are estimated. Normally we are interested in the solution of concentration or mass in the compartment from which samples are taken, but it is, of course, possible to calculate the solution in any compartment within the compartmental system.

The above parameters are estimated using the output data for each individual and the

mean is found for each parameter over the group of individuals. If the mean of each parameter is inserted into the compartmental system, then there is a unique solution for the differential equations. This unique solution is called the deterministic model for that compartmental system.

It should be mentioned that, if the number of individuals is large enough, say about 30, (Bland, 1995), then blood sample data will have a normal distribution. In this case, to calculate the mean of the parameters (to insert into the solution) we use the following equation:

$$E(X_i) = \int_{-\infty}^{+\infty} X_i \, f(X_i) \, dX_i \,, \qquad \textbf{(7.1)}$$

where X_i is the concentration of substances in i^{th} compartment and $f(X_i)$ is the PDF of X_i which is a normal distribution.

However, when the number of individuals is less than 30 we need to find the distribution of each variable (and hence the distribution of X_i which is a function of the variables) and then use equation 7.1. If it is difficult finding the distribution of the variables and there is no other information about their distributions then the ordinary mean of each parameter can be inserted into the solution of the compartmental system (equation 5. 3) to build the deterministic model. However, a small error will be made which should be considered in any future work.

7.2.2: Stochastic models A and B

In stochastic model building, we allow the parameters to fluctuate. Since we develop two stochastic models we discuss them individually.

Model A

We applied all the different stages of the deterministic model building like writing the mass balance equations, calculation of the concentration of glucose tracer in blood plasma and estimation of the parameters of the model from blood samples data. If we estimate the unknown parameters using the data for each individual, we obtain k values for each variable (k is the number of individuals). There are two methods for building the stochastic model as follows:

A) Method of multivariate distribution

In this method, after estimation of k values for each variable, we find the multivariate distribution for all the variables. To build up the stochastic model, suppose we have n different parameters, $p_1, p_2,...,p_n$, with a multivariate distribution $f(X_1, X_2,..., X_n)$. Also, let the following function be the solution (concentration of substances in i^{th} compartment) of the compartmental system:

$$X_i(t) = g(X_1, X_2,..., X_n, t) \qquad \textbf{(7.2)}$$

Therefore, the stochastic model can be built using model A approach as follows

$$E(X_i) = \int ... \int g(X_1, X_2,..., X_n, t)\, f(X_1, X_2,..., X_n)\, dX_1 dX_2 ... dX_n \ . \qquad \textbf{(7.3)}$$

Advantages and disadvantages of the method

There are some advantages and disadvantages in applying the model A approach as follows:

Advantages

1. If $k \geq 30$, then $f(X_1, X_2, ..., X_n)$ has a multivariate normal distribution with a known PDF. Therefore it is possible to integrate 7.3 especially when n is small (say n=2).

2. There are many numerical integration programs to calculate the above integral.

Disadvantages

There are some disadvantages in applying the multivariate distribution method. One of the most important disadvantages is the determination of the multivariate distribution of the parameters, especially when there are more than two variables. In multivariate analysis the calculation of the above distribution is too complex, especially when the parameters do not have normal distributions. Another disadvantage of the method is the complex mathematical procedure to build the model, especially when we have more than two parameters. This will restrict the application of the method to a complex and mathematical and statistical problem which may not be interesting in medical research. Also, there are some numerical disadvantages for the method as follows:

1. If k<30 we need to find the PDF of the variables which is difficult, especially when the number of parameter, n>2.
2. If n>2 then it is preferable that the parameters should have a normal distribution, for otherwise it is too complex to determine their multivariate distribution.
3. When the number of the variables are equal or greater than two, it is not possible to calculate the above integration manually.

B) Method of Probability Density Function

In this method, at first we try to calculate the PDF of the in X_i (t) in equation 7.2 (the concentration or mass of glucose tracer in i^{th} compartment) using the distribution method as follows:

$$Prob(X_i(t)<v) = Prob(g(X_1,X_2,...,X_n,t)<v) , \quad \textbf{(7.4)}$$

where v is a arbitrary variable. Suppose after using the above method we obtain the PDF of X_i(t) as

$$f_{x_i}(t) = h(y_1, y_2, \ldots, y_n, t) \ , \qquad (7.5)$$

then it is easy to build the stochastic model as

$$\boldsymbol{E}\,(X_i(t)) = \int_{-\infty}^{+\infty} X_i(t)\, f_{x_i}(t) dX_i \ . \qquad (7.6)$$

The calculation of the expectation for the concentration or the mass of the compartment is relatively difficult on a PC, especially when there are three or more variables in the integral. This is one of the most serious disadvantages of this method.

Model B

In model B we use Limić's approach to build a stochastic model. In this model we consider a n-compartmental model with the mass of C and the mass balance equations given by

$$\frac{d}{dt}C(t) + A(t)C(t) = q(t) \ , \qquad (7.7)$$

where A(t) and q(t) were defined in Chapter 6. All the elements of A(t) have a fluctuation according to a random generator (process), say Φ_{ij} (t). Thus for every a_{ij} (t) we have:

$$f_{ij}(t) = d_{ij}\ \Phi_{ij}(t) \ . \qquad (7.8)$$

where f_{ij} (t) and d_{ij} were defined in Chapter 6. We find the solution of 7.7 considering the fluctuations in equation 7.8 and its properties.

7.3: Summary of the differences in model building

The most important difference between a deterministic and a stochastic model is in the application of probabilistic effects. In situations where the compartmental parameters

vary in different subjects and times, stochastic models are the best models to use. In stochastic models we apply probabilistic effects where all the elements of the compartmental matrix can fluctuate. In the special case that was applied in this research, all the points have the same fluctuations, so having the fluctuation at one of the points enables us to estimate the fluctuation for all the other points. In the more general case where all the elements of the compartmental matrix fluctuate independently building a stochastic model is likely to be too complex.

7.4: Differences in the shapes of the models

Besides the differences in model building, there are some differences in the shape of the curves in deterministic and stochastic models for mean and S.E. of concentration of glucose tracer. In this section the differences are shown in detail using the stochastic curves which were obtained by the model A and B approaches.

7.4.1: Differences in deterministic models for the mean concentration of glucose tracer

There are only small differences in the deterministic model for the total, obese and non-obese groups. So dividing the subjects into two subgroups does not produce a large difference in the shape of the deterministic models. In the deterministic curves shown in Figure 7.1, the obese subjects have the largest values for the mean concentration of glucose tracer, and the non-obese subjects have the smallest at various time points between 0 to 180 minutes. The curve for the total group lies between these two as would be expected for a deterministic approach where the effects of averaging should be apparent.

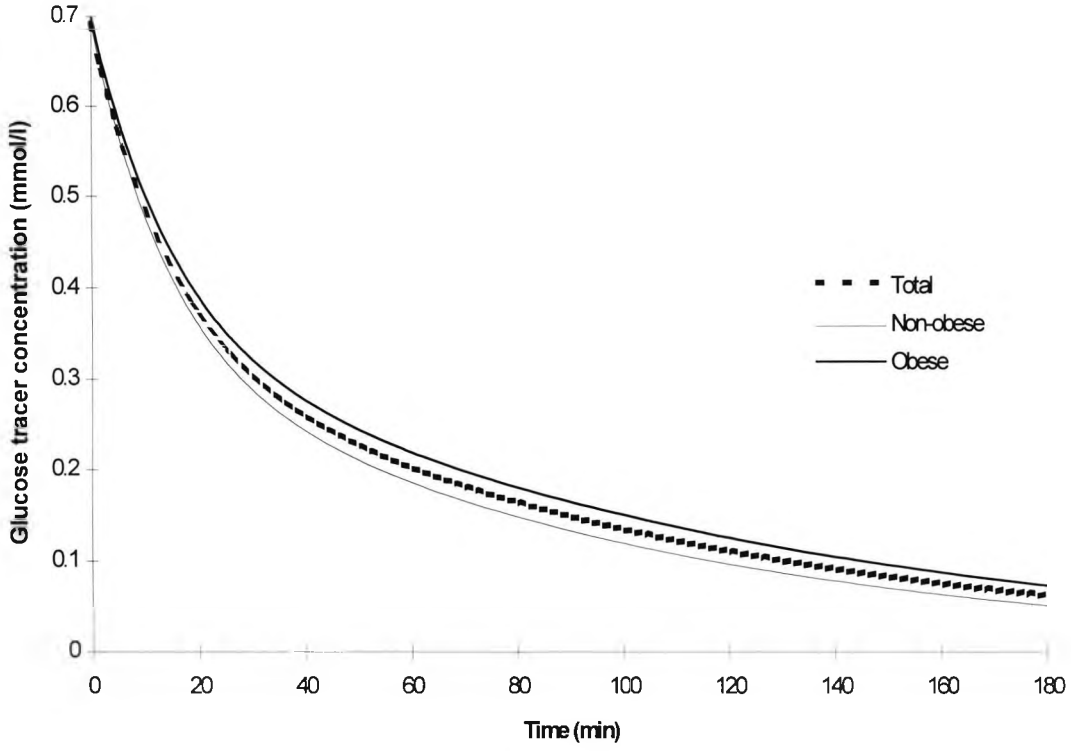


Figure 7.1: Deterministic curves for the mean concentration of glucose tracer in blood plasma in total, obese and non-obese subjects following an IVGTT.

7.4.2: Differences in stochastic models for the mean concentration of glucose tracer

There are only small differences in the stochastic model in model A for the total, obese and non-obese groups. Therefore, dividing subjects into two subgroups does not produce a large difference in their stochastic values of the concentration of glucose tracer.

The stochastic model curve for the obese subjects has the largest values at all times. The stochastic models for total and non-obese subjects have the next smaller values respectively for the same times which are in the same ordering of the deterministic curves for these groups. Therefore, due to the similarity in the shapes of the stochastic curves for the three groups (all have a double exponential curve) if we shift down the stochastic curve for the obese subjects, we obtain the stochastic curve for total and non-obese subjects respectively. Also, the differences between the stochastic model values at small times is less than the differences for large times. Figure 7.2 shows the

stochastic curves for the three groups.

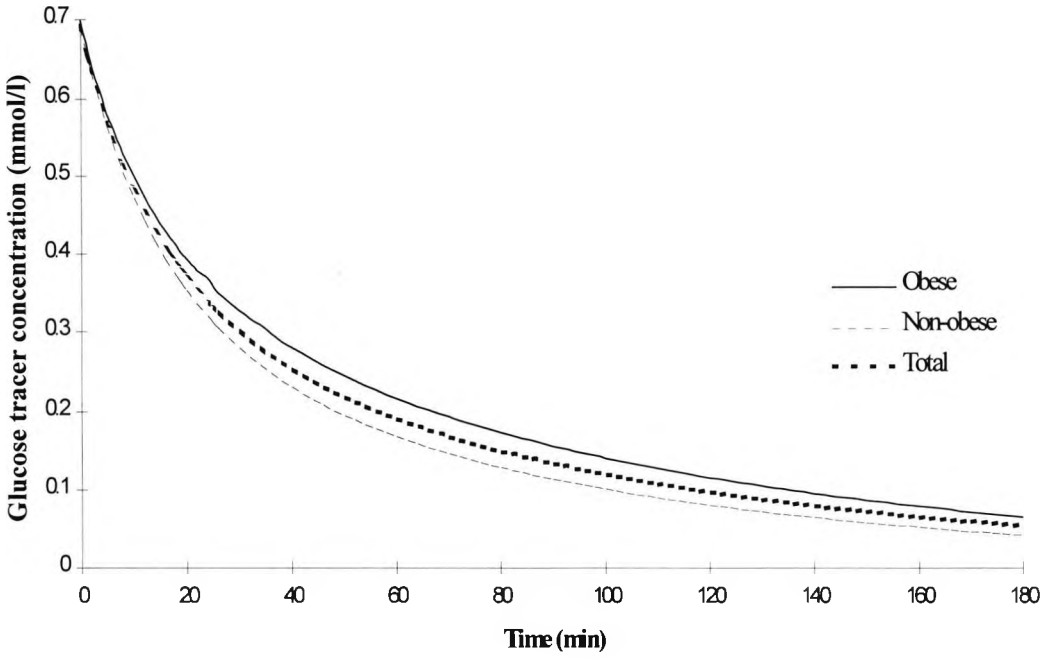


Figure 7.2: Stochastic curves for glucose tracer concentration in blood plasma in total, obese and non-obese subjects following an IVGTT.

Since the model B approach was applied only to the total group of subjects, we do not have any curves to compare. The only difference between the shape of the stochastic model A and B in the total group of subjects is in the location of the curves. The stochastic curve for the total subjects lies slightly above the deterministic curve in model B, but slightly below it in model A, with a similar shape to the deterministic curve. This is due to the different stochastic modelling approaches.

7.4.3: The comparison of deterministic and stochastic models for the mean concentration of glucose tracer

Table C_4 in Appendix C shows the stochastic values and the differences between deterministic and stochastic models in the obese, non-obese and total group of subjects, using the model A approach.

As was mentioned earlier, the difference between the stochastic and deterministic curves for the mean concentration of glucose tracer and for all groups is very small. To compare the above differences in all groups, the difference between the two curves was calculated at every time point and their mean was also calculated.

The standard deviations of the above differences at any time point show that the obese group has the largest variability and the total group has the smallest (the standard deviation of the differences for obese, non-obese and total subjects are 0.0051, 0.0049 and 0.0041 mmol/l respectively), but the standard deviation of all stochastic values (total model A, total model B, obese and non-obese) are exactly the same correct to two decimal places.

Also, comparing the median (the element which is at the middle of the distribution, i.e. the element which is at 90 minutes) of the distribution of the differences in the three groups shows that the largest one is in the non-obese group (0.0132 mmol/l) and the smallest one is in the obese group (0.0069 mmol/l).

In model B the difference between the deterministic and stochastic curves and for the total group is also very small . There are some new aspects between the differences between the stochastic and deterministic curves (in total group of subjects) in model A and model B approaches as follows:

1. In model B, the stochastic curve lies above the deterministic curve for all time points except t=0, but in model A the stochastic curve lies below the deterministic curve.

2. The difference between the stochastic and deterministic curves at different times in the model B approach is less then the same differences in model A, and we find that the mean of the differences in model B is 0.0053 whereas the same mean for model A is 0.0088.

3. The variability of the differences between the stochastic and deterministic curves in model B is less than the same variability in model A (the standard deviation of the differences in model B is 0.0032 whereas the corresponding standard deviation for model A is 0.0041.

7.4.4: The comparison between the stochastic and deterministic values for the S. E. of glucose concentration

The comparison between the deterministic and stochastic values for the S. E. of the concentration of glucose tracer in blood plasma (model A approach) shows a small difference in the total group of subjects and a large difference in the non-obese and obese group of subjects, especially in the later group. In the total group of subjects the deterministic values are close to the stochastic values especially at large times (> 100 minutes) and small times (< 20 minutes). In the non-obese and obese groups the data are not as close to the stochastic values, but the deterministic values in non-obese subjects are closer to the stochastic values (especially at small time points) in comparison with obese subjects. In all cases, the stochastic values are a poor fit to the deterministic values in the middle of the time range and the deterministic values at small and large times are closer to the stochastic values. It seems likely that by increasing the sample size the stochastic curve will approach the deterministic values.

7.5: Summary and discussion

In this chapter a comparison between the models is considered as follows:

(i). Differences in model building

The methods and procedures of building the deterministic and stochastic models (Model A and B approaches) were presented in this chapter. For the model A approach, two methods were introduced and their differences and similarities and advantages and

disadvantages were also discussed. The difference between the two curves is small although the two approaches are very different. In the model A approach, the stochastic model was built using 'multivariate distribution' or 'PDF' methods and the advantages and disadvantages of both methods were presented. In the model B approach, the ordinary mass balance differential equations were used for model building.

(ii). Differences in the shape of the models

The differences between the shapes of the deterministic and stochastic curves in model A for the total, obese and non-obese groups were presented using some figures to clarify the above differences. As can be seen the three corresponding stochastic and deterministic curves are almost the same. It was found that the stochastic model for the obese group had the larger values.

In the stochastic model B the deterministic and the stochastic curves (for the total subjects) are also the same, but there is only a small difference between the stochastic model A and B.

Chapter 8

Discussion

8.1: Introduction

The study of the kinetics of drugs in the body has been one of the most important research activities in the past few decades, with applications in pharmacology and other related disciplines such as biochemistry, physiology and metabolic medicine.

Usually a known mass of tracer is injected intravenously, subcutaneously or ingested orally. In the present research a glucose tracer was injected intravenously. The concentration of the tracer in blood plasma is measured at several time points after injection. This tracer species is sufficiently different from the endogenous species to enable it to be distinguished. The concentration of the plasma glucose tracer decreases monotonically with time as it is consumed mostly by the muscles.

In this research we studied two different stochastic models to describe the decay of the plasma glucose tracer in a group of female subjects. The subjects were divided into two subgroups, non-obese and obese subjects, to study the effects of obesity on the stochastic models. A known mass of glucose and glucose tracer (proportional to body mass) was injected intravenously and blood samples were taken at various times over a period of 3 hours after the injection. To build a stochastic model and compare it with a deterministic one, a two-compartmental system was considered. The compartments are the effective blood plasma and the effective extravascular tissue spaces.

The above data were used to build a model for the kinetics and decay of glucose tracer in these two compartments. Normally a deterministic model would be used to analyse the data without considering the obvious inter-subject and intra-subject variability. The

deterministic model was presented in Chapter 5 and is the solution of a differential equation which describes the flow of glucose tracer between the compartments. A new method for obtaining mass (concentration) of glucose in blood plasma was presented. A brief summary of this type of model will be given later.

8.2: Why a stochastic model instead of a deterministic model?

As mentioned above, the deterministic model is a theoretical solution for the mass balance differential equations. In this kind of model, the probabilistic (stochastic) effects are not taken into account, and it is assumed that there are no probabilistic effects or random variability in the differential equations.

In this study it is assumed that the compartmental parameters describing the flow of glucose tracer from the blood to the cells vary randomly. It is obvious that output data will vary for each subject in a particular experiment (inter-subject variability) and from one experiment to another if it is repeated in the same subject (intra-subject variability). This variability is assumed to be due to a variability in the transfer rates between compartments. Thus all the transfer rates are assumed to be random variables having special distributions. Also, it is assumed that the initial concentration of glucose tracer in blood plasma is a random variable. This variability produces an uncertainty in the whole compartmental system which the deterministic model is not able to deal with. Since the solution of the compartmental model is a function of the above variables, so the solution is not the same in different subjects at any fixed time point.

If the parameters of the above model are estimated using the output data and are inserted into the equations of the compartmental system, we obtain different curves for different sets of parameters. In this case we have many different models which also differ from the deterministic model which has already been obtained (the number of the curves is obviously equal to the number of subjects). The use of the deterministic approach in a compartmental system, which is evidently stochastic may cause a large error in the resulting parameters . Furthermore, there is another type of variability which has not yet

been mentioned so far. This is the variation of the parameters with time during the course of a single experiment and also their variation from one subject to another (the intra-subject variance is assumed to be constant over the group of subjects). This type of variation will be discussed later. Finally, the aim of this study is to replace the deterministic modelling approach of analysing the glucose tracer kinetics by a stochastic modelling approach which can account for the observed variability in subjects.

8.3: Types of stochastic modelling

We applied two different stochastic approaches according to two different types of variability, as follows:

(i). The parameters of the compartmental system are constant during a particular experiment, but vary from one experiment to another if repeated in the same subject and from one subject to another:

For this type of variation, the Model A modelling approach was applied. The concentration of glucose tracer in blood plasma was computed as a function of four variables. The four unknown parameters are the two fluxes of glucose tracer between the compartments, the loss from second compartment and the initial concentration of glucose tracer in blood plasma. A set of two mass balance differential equations was proposed and its parameters were estimated using blood sample data for each subject. It is assumed that the above four variables have a quadravariate normal distribution. Thus to build a stochastic model, the expectation of the concentration of glucose tracer in blood plasma was used together with the probability distribution function of the parameters. The expectation value of the resulting glucose tracer concentration in blood plasma is the primary variable of interest. This is a four dimensional integration because of the assumed quadravariate normal distribution of the parameters. The calculation of the integration was one of the most complex tasks in this study. The details of the results will be presented later.

(ii). The parameters vary with time during the course of a single experiment and also from one subject to another (with fixed intra-subject variance):

In this type of variability, the stochastic Model B approach was applied. The concentration of glucose tracer in blood plasma at each time point in all the subjects is assumed to have a special distribution. At every time point the glucose tracer concentration is assumed to have a normal distribution which varies over time. Also, it is assumed that there is a bivariate normal distribution between any pair of values of the concentration of glucose tracer at respective blood sampling times. The resulting uncertainty is incorporated into a compartmental matrix where all the elements of the matrix fluctuate randomly. The random process is assumed to have a truncated normal distribution and its statistical moments are assumed to be identical, i.e. for example μ_2 (t, s) is a function of t and s only. It is assumed that all the elements of the compartmental matrix have identical fluctuations. The differential equations are functions of the compartmental matrix and the second moment of the random process and were integrated numerically using the NAG FORTRAN Library. The Model B approach was presented in Chapter 6 and only a brief discussion of the results will be given.

8.4: Discussion on Model A and Model B approaches

There are some important differences between the two stochastic models and also in their applications.

In Model A we had to deal with a complex integration to construct the mean concentration of glucose tracer in the sampled compartment model and there were many problems such as finding the distribution of the variables and also using standard multivariate lognormal distribution to prevent negative parameter values. The integration was computed from time 0 to 180 minutes using the NAG FORTRAN Library to obtain the stochastic model. A comparison between the deterministic and stochastic curves for the mean concentration of glucose tracer in total, obese and non-

obese groups shows small differences between the models. The differences are smaller at small and large times but larger at the middle time points (between 20 to 100 minutes) and the largest difference is for the non-obese group. Therefore, if the deterministic values are used as the actual values then a small error will be made. Furthermore, the mean difference between the deterministic and stochastic curves at all time points is significant in the obese and non-obese group of subjects.

In the model A approach we also calculated the S. E. for the concentration of glucose tracer in blood plasma and for all groups. As was mentioned in Chapter 5, the S.E. of deterministic model is near to the S. E. of stochastic values in the total group of subjects. The S.E. of the stochastic values are a poor fit to the S.E. of the deterministic values in both obese and non-obese subjects, but the difference between the S. E. of stochastic and deterministic values in the non-obese group are closer than the same values in the obese subgroup.

The Model A method is likely to be too complex for a compartmental system with three or more compartments since the integrand where there are more than four variables will be very complex. Therefore, the Model A approach is appropriate when there are only a few stochastic transfer or elimination rates.

In the Model B approach, although there are also some complex equations, the approach is in a matrix form which is more manageable. Using NAG Library software to integrate the differential equations enabled us to compute the solutions for every compartment at every time point. The possibility of calculating the concentration of any substance in a n-compartmental system ($n>2$) and for every compartment is one of the most important advantages of Model B over Model A.

It is interesting to note that in Model B the location of the stochastic curve lies above the stochastic curve, but in model A and for all groups the stochastic curves are below the deterministic curves. Also, in the Model B approach we deal with a random process which is assumed to be the same for all the elements of the compartmental matrix. This

is rather abnormal and is not likely to be useful for building a stochastic model in general. Therefore, Model B approach will be useful only if there are different random processes present at every point. Furthermore, it is possible that the similarity between the stochastic and deterministic models may be due to the particular random process chosen, or to the number of the compartments , although no direct evidence was found to confirm this.

8.5: Future implications

The results of this research should encourage those working in the same field to continue to explore the above modelling approaches. As was mentioned, some of the results seem to vary according to new constraints and conditions (number of the compartments, sample and using different random processes for each parameter). In this section we will discuss these conditions and new results which are different from the previous cases will be given. We consider these conditions separately in the two types of models.

8.5.1: Model A approach

The differences between the stochastic and the deterministic curves for the total subjects and the subgroups were discussed above. There are no large differences between the stochastic and deterministic curves for all groups. Furthermore, the changes in the stochastic curves are not known if we change the sample (member, size, method of the sampling,...) , especially if the experiment is repeated in the same subjects. Therefore, the stochastic curves may probably change if the sample changes, so it is possible to have larger or smaller differences between the stochastic and deterministic curves according to different samples. Also, it is obvious that if we choose a large enough sample (say more than 30) then it is possible to assume that the distribution of all parameters is normal, otherwise we will be facing an complex problem in finding the distribution of the parameters. The method of sampling is one of the most important parts of the work. A poorly chosen sample may produce bias in the result. Choosing samples according to standard sampling rules can help researchers to get more

reasonable results. Therefore, working with a compartmental system with a large enough sample size can possibly overcome the above problem.

The next important thing which may affect the stochastic curve is the number of compartments. When the number of compartments is two, we have two fluxes between compartments, a loss and the initial concentration of glucose tracer in blood plasma, that is, four unknown parameters. If we increase the number of the compartments to three and suppose there are two fluxes between compartments and only one loss then there are six parameters. If we have an extra loss or output, the parameters will be doubled in comparison with a two-compartmental model. The calculation of glucose concentration in this case is very complex and will involve a six, seven or even eight dimensional integration, all of which are likely to be difficult to evaluate. Therefore, we need to try a system with fewer parameters and the results need to be compared with the compartmental system.

8.5.2: Model B approach

In this approach the deterministic and stochastic curves are almost the same at most time points, which is the same as the Model A approach. This difference is smaller than the model A approach, especially at small time points. There are some possible reasons for this situation which are given below:

1) Same fluctuation at every point:

As was mentioned earlier, all the elements of the compartmental matrix have a particular fluctuation which is assumed to be the same for all parameters. In fact, in general the parameters are more likely to have independent fluctuations, for otherwise they are unlikely to represent actual physiological processes. This can be one of the most important reasons for the similarity of the stochastic and deterministic curves and this needs to be considered in any future work. The kinetics of glucose will probably have independent fluctuations in its parameters and constraining them to have the same

fluctuations may not generate a useful and convincing result.

2) Sample size:

We are still uncertain about the role of the sample size in this part of the research. A large enough sample size and collecting the sample according to the statistical rules (sampling techniques) can help researchers to be sure about the final results. A large sample of 30 or more using the sampling techniques generally accepted by statisticians may probably change the results.

3) The number of compartments:

There is no information about the role of the number of the compartments in the final results. If the number of the compartments increases to three or more and the shape of the curves are still similar, then the result is probably independent of the number of the compartments.

This requires a new study of the n-compartmental model with a larger sample size and also employing independent random processes to investigate the shape of the deterministic and stochastic curves.

Chapter 9

Conclusions

9.1: Introduction

The methods of model building were discussed in Chapters 5 and 6. A comparison between models, discussion about the main findings and suggestions for research work in the same field in the future were given in Chapters 7 and 8. In this chapter final remarks about the two methods of model building are made.

9.2: Model A and Model B approaches in stochastic model building

Model A approach

The model A approach is a special type of model where the stochasticity is incorporated into the compartmental parameters (transfer rates, elimination rates). In this approach the mean concentration of glucose tracer in blood plasma is computed from a set of differential equations. The solution is a function of some unknown parameters which are estimated using the output data for each subject. Therefore, there are some estimated parameters (four in our study) where every parameter has several values equal in number to the sample size (N=17). Each set of estimated parameters has its own distribution and the four parameters overall are assumed to have a quadravariate lognormal distribution. The estimated parameters in every subject predict N different curves for the tracer concentration. This variability is assumed to be due to the variability of the above four estimated parameters which causes an uncertainty in the solution. The expectation of the solution is the mean stochastic model when the above four parameters are considered as a quadravariate lognormal distribution.

For model building, the expectation of concentration of glucose tracer in blood plasma

was calculated as the average of all the output curves for each subject. The details of the method was discussed in Chapter 5, but we summarise some of the most important conclusions here.

Looking at the values of mean concentration of glucose tracer in the blood plasma in all groups, there are small differences between the stochastic and deterministic curves for the mean concentration of glucose tracer. These differences are very small at small times and small at intermediate times (between 20 to 100 minutes). The stochastic and deterministic curves for the mean concentration of glucose tracer in blood plasma for the obese subjects have the largest values . The stochastic and deterministic curves for the total group of subjects lie between the two corresponding curves of the subgroups as to be expected. The small differences between the curves are perhaps due to the small sample size or the small number of compartments and this needs to be further investigated with a large enough sample size and a multi-compartmental system.

Although the differences between the stochastic and deterministic values are not large, it is still necessary to choose a stochastic model to predict the values for the mean concentration of glucose tracer in blood plasma because the stochasticity between individuals' parameters are considered in stochastic model building. If the deterministic values are used as the real values, there will be an error which, although not large for the data studied, may be large in general.

The next important point is the nature of the Model A approach. For a two compartmental model the Model A approach is suitable and efficient, but the approach becomes very complex when the numbers of the compartments ($n > 2$) and hence the number of the parameters increases.

There are large differences between the stochastic and deterministic models for the S. E. of glucose tracer, especially between 20 minutes to 100 minutes. This difference is the largest in the total group of subjects and the smallest in the non-obese subjects.

Model B approach

The Model B approach is a method of model building where it is assumed that the values of concentration of glucose tracer in blood plasma at each time point are normally distributed. Also, a bivariate normal distribution is assumed to exist between the concentration of glucose tracer at every pair of time points t_1 and t_2.

In this method of stochastic model building the mass balance equations are written first. These are a function of the concentration of glucose tracer in blood plasma and also a function of the compartmental matrix. The stochasticities are incorporated with the compartmental matrix, so that every element of the compartmental matrix fluctuates randomly according to a random process. It is assumed that each element of the compartmental matrix is the sum of the above random process and the expectation of the matrix elements. The solution of the above mass balance equations is a function of the compartmental matrix and the second statistical moments of the random process. The calculation of the solution (discussed in Chapter 6) is very complex.

If we look at the shape of the mean concentration predicted by Model B, the difference between it and the deterministic curve is still small as in the case of model A. The possible reasons about the similarities of the deterministic and stochastic curves in the Model B approach are summarized as follows:

1. Small sample size;
2. Common random process at each true point;
3. A combination of both of the above.

The above features should be checked using a large enough sample size and also with a random process which is different at each time point.

Another important point in the Model B approach is its possible application for more than two compartments. Since the mass balance equations are in matrix form the

solution is also in matrix form. This should enable us to generalise the two compartmental system to a n-compartmental system and at the same time obtain the concentration solution for every compartment. As was mentioned above the Model A approach is not suitable for more than two compartments and especially when there are many transfer/elimination rates in a multi-compartmental system. Therefore, for the multi-compartmental system, the Model B approach is the best choice. If the stochastic model in the above two-compartmental system is independent of the sample size or random processes, then the approach is obviously inefficient since the difference between the stochastic and deterministic models is small.

The Model B approach was not applied for more than two compartments and there is no information about the shape of the stochastic model. Therefore, using the approach for more than two compartments, with a large enough sample size and a different random process may yield a new stochastic model which will be probably different from the deterministic model and also from Model A concentration curve.

9.3: Suggestions for screening and future work

In this section there are some suggestions and recommendations for screening procedures arising from the results of this study which clinicians may consider following up. Consider the difference in the mean and S. E. between the stochastic and deterministic curves of the obese and normal groups. We can generalise this approach in classifying two different groups, normal and abnormal, regardless of the nature of the abnormality.

It is usual to divide a group of subjects into two groups, normal and abnormal, using some agreed criterion of abnormality. The data produced by a clinical test on each subject is then analysed using some plausible deterministic model. The resulting sets of individual parameters of each group are then compared using a suitable statistical test (an unpaired t-test if the parameter distributions of each group are found to be normal). If the difference between the two sets is found to be significant then this model and the

associated criterion will become a method of screening an individual according to some agreed level of probability of being in the abnormal group.

Obviously, this process depends on what criterion is used to subdivide the subjects in the first place. The method of subdivision, based on a particular kinetic response to some challenge, is often not at all precise or is too simplistic, given the complexity of the response and its day-to-day and subject-to-subject variability. For example, subjects are screened for non-insulin dependent diabetes by administering an oral glucose challenge and estimating the slope of the resulting plasma glucose curve between two arbitrary times when plotted on log-linear graph paper. Consider now the situation where a plausible stochastic model is used instead. The distributions of the set of individuals' model parameters of each group will be used to build a reference stochastic model for each group. If these two stochastic models are also significantly different from each other and also from the associated deterministic models then we can screen any new subjects more easily. When screening an unknown subject, the set of subject's parameters will be compared with the reference parameters of the two stochastic models as well as those of the deterministic models. In view of the potentially large difference between the S. E. of the stochastic and deterministic models as compared to the difference between their means (as found in Chapter 5) , it is very likely that a significant proportion of subjects will be diagnosed as abnormal by the stochastic model but not by the deterministic model, or vice versa. If the two stochastic models are not significantly different from each other and hence are not different from the above deterministic models (suppose in each group the deterministic and stochastic models are similar) then for screening of an unknown subjects, we need to compare the confidence intervals for the mean stochastic models in both groups. The confidence intervals can be large when the S. E. is large or a large error ($\alpha > 0.05$) for confidence interval is chosen. When screening a new subject, its mean will be compared with both stochastic models. If the mean curve for the new subject is between the upper and lower limits of the confidence intervals of the mean for the stochastic model for any groups, then it can be screened using the associated stochastic model. If there is an intersection between the confidence intervals, the differences between the parameters of the new subjects and

the stochastic model can be used as a method for the screening in this special case. The above method is very likely to choose a significant proportion of subjects as abnormal using the stochastic models but not by the deterministic models, or vice versa. With the passage of time the true proportion of abnormals will become apparent and it should possible to compare the sensitivities and specificities of the two screening approaches.

Thus, the most important extension of this research would be to study candidate methods of subdivision into normal and abnormal group based on the statistical properties of the individual parameter sets and the associated stochastic models, and to move away from a purely deterministic modelling approach in which the effects of intra-subject and inter-subject variability are not properly accounted for. Perhaps this may become a new development in the methods of screening patients in the remaining years of the 20th century.

Appendix A

The output of ADAPT

I. The following is a Fortran program (in ADAPT) to estimate the parameters of the fitted curve for each subjects.

```
C*****************************************************************
C                              ADAPT II
C                              Release  3
C*****************************************************************
C                                 MODEL                          *
C                                                                *
C          This file contains the Fortran subroutines listed below in  *
C          which the user must enter the relevant equations and constants.  *
C          Consult the user's manual for details concerning the format for  *
C          entered equations and definition of symbols.          *
C                                                                *
C    1. DiffEq- System differential equations.                   *
C    2. Amat  - System state matrix.                             *
C    3. Output- System output equations.                         *
C    4. Symbol- Parameter symbols and model constants.           *
C    5. Varmod- Error variance model equations.                  *
C    6. Prior - Parameter mean and covariance values             *
*****************************************************************
      Subroutine DIFFEQ(T,X,XP)
      Implicit None

      Include '\adapt\globals.inc'
      Include '\adapt\model.inc'
```

```
      Real*8 T,X(MaxNDE),XP(MaxNDE)

C-------------------------------------------------------------------------------------------
C 1.  Enter Differential Equations Below  {e.g.  XP(1) = -P(1)*X(1) }                    C
C-------------------------------------------------------------------------------------------
C
     XP(1)=-p(1)*X(1)+P(2)*X(2)
     XP(2)=P(1)*X(1)-(P(2)+P(3))*X(2)
C-------------------------------------------------------------------------------------------
C
C-------------------------------------------------------------------------------------------
C
C
      Return
      End
C#########################################################################
      Subroutine AMAT(A)
      Implicit None
      Include '\adapt\globals.inc'
      Include '\adapt\model.inc'

      Integer I,J
      Real*8 A(MaxNDE,MaxNDE)

      DO I=1,Ndeqs
        Do J=1,Ndeqs
          A(I,J)=0.0D0
        End Do
      End Do
C-------------------------------------------------------------------------------------------C
2. Enter non zero elements of state matrix  {e.g.  A(1,1) = -P(1) }
```

```
C-------------------------------------------------------------------------------------------C

C-------------------------------------------------------------------------------------------C-
C-------------------------------------------------------------------------------------------C
C
      Return
      End

C#########################################################################C

      Subroutine OUTPUT(Y,T,X)
      Implicit None

      Include '\adapt\globals.inc'
      Include '\adapt\model.inc'

      Real*8 Y(MaxNOE),T,X(MaxNDE)

C-------------------------------------------------------------------------------------------C
C     3.  Enter Output Equations Below   {e.g.  Y(1) = X(1)/P(2) }                          C
C-------------------------------------------------------------------------------------------C
      Y(1) =X(1)

C-------------------------------------------------------------------------------------------C
C-------------------------------------------------------------------------------------------C
C
      Return
      End

C#########################################################################C
      Subroutine SYMBOL
```

```
      Implicit None
      Include '\adapt\globals.inc'
      Include '\adapt\model.inc'
      Integer Ieqsol
      character*60 descr
      common /eqsol/ Ieqsol
      common /descr/  Descr
C-----------------------------------------------------------------------------C
C         4.  Enter as Indicated                                              C
C-----------------------------------------------------------------------------C

    NDEqs   = 2    ! Enter # of Diff. Eqs.
    NSParam = 3    ! Enter # of System Parameters.
    NVparam = 0    ! Enter # of Variance Parameters.
    Ieqsol  = 1    ! Model type: 1 - DIFFEQ, 2 - AMAT, 3 - OUTPUT only.
    Descr   = ' Insert Model File description  '
C-----------------------------------------------------------------------------C
C-----------------------------------------------------------------------------C
C
C-----------------------------------------------------------------------------C
C         4.  Enter Symbol for Each System Parameter (eg. Psym(1)='Kel')      C
C-----------------------------------------------------------------------------C
      PSYM(1)='K21'
      PSYM(2)='K12'
      PSYM(3)='K02'

C-----------------------------------------------------------------------------C
C-----------------------------------------------------------------------------C
```

```
C-------------------------------------------------------------------------------------------C
C          4. Enter Symbol for Each Variance Parameter {eg: PVsym(1)='Sigma'}     C
C-------------------------------------------------------------------------------------------C

C-------------------------------------------------------------------------------------------C
C-------------------------------------------------------------------------------------------C
C
      Return
      End
C#########################################################################C

      Subroutine VARMOD(V,T,X,Y)
      Implicit None

      Include '\adapt\globals.inc'
      Include '\adapt\model.inc'

      Real*8 V(MaxNOE),T,X(MaxNDE),Y(MaxNOE)
C-------------------------------------------------------------------------------------------C
C          5.   Enter Variance Model Equations Below                                    C
C        {e.g. V(1) = PV(1)**2 * Y(1)**PV(2) }                                          C
 C-------------------------------------------------------------------------------------------C

C-------------------------------------------------------------------------------------------C
C-------------------------------------------------------------------------------------------C
C
      Return
      End
C#########################################################################C
      Subroutine Prior(Pmean,Pcov)
      Implicit None
```

```
      Include '\adapt\globals.inc'
      Include '\adapt\model.inc'
      Integer I,J
      Real*8 Pmean(MaxNSP+MaxNDE)
      Real*8 Pcov(MaxNSP+MaxNDE, MaxNSP+MaxNDE)
       Do I=1,NSparam
            Pmean(I) = 0.0D0
            Do J=1,NSparam
                 Pcov(J,I) = 0.0D0
            End Do
       End Do


C-------------------------------------------------------------------------------------------C
C        6.   Enter Nonzero Elements of Prior Mean Vector                                  C
C       {  e.g. Pmean(2) = 10.0    }                                                       C
C-------------------------------------------------------------------------------------------C

C-------------------------------------------------------------------------------------------C
C-------------------------------------------------------------------------------------------C

C-------------------------------------------------------------------------------------------C
C      6. Enter Nonzero Elements of Covariance Matrix (Lower Triang.)                      C
C       {  e.g. Pcov(2,1) = 0.25    }                                                      C
C-------------------------------------------------------------------------------------------C

C-------------------------------------------------------------------------------------------C
C-------------------------------------------------------------------------------------------C
      Return
      End
```

II. The following outputs show the estimated parameters, the original and model estimated data in different time points together with curve fitting in the all subjects.

--- C. WLS Estimation Summary (subject 1)

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 44

Number of function calls: 199

Estimator criterion value: 150.996

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.991	150.996	.108340E-01

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K21	.1000	.7267E-01	9.349	[.5858E-01, .8676E-01]
K12	.1000	.6485E-01	9.842	[.5161E-01, .7809E-01]
K02	.1000	.2350E-01	3.180	[.2195E-01, .2505E-01]
IC(1)	.5000	.8638	2.640	[.8165 , .9111]
IC(2)	.0000	Fixed		

--- D. Estimated Model Prediction and Data Summary (Subject 1)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	2.000	.7800	.7540	.2605E-01	2951.
2	3.000	.7600	.7092	.5083E-01	3108.
3	4.000	.6700	.6699	.6627E-04	4000.
4	5.000	.6000	.6355	-.3547E-01	4987.
5	6.000	.5800	.6051	-.2514E-01	5337.
6	8.000	.5500	.5546	-.4648E-02	5935.
7	10.00	.4900	.5148	-.2482E-01	7478.
8	12.00	.4700	.4830	-.1296E-01	8128.
9	14.00	.4600	.4570	.2952E-02	8485.
10	16.00	.4400	.4356	.4396E-02	9274.
11	19.00	.4400	.4095	.3053E-01	9274.
12	22.00	.4200	.3884	.3163E-01	.1018E+05
13	25.00	.4000	.3706	.2938E-01	.1122E+05
14	30.00	.3700	.3458	.2422E-01	.1312E+05
15	40.00	.3300	.3056	.2440E-01	.1649E+05
16	50.00	.2700	.2720	-.1983E-02	.2463E+05
17	60.00	.2400	.2425	-.2496E-02	.3117E+05
18	70.00	.2000	.2163	-.1630E-01	.4489E+05
19	80.00	.1800	.1930	-.1296E-01	.5542E+05
20	90.00	.1600	.1721	-.1214E-01	.7014E+05
21	100.0	.1400	.1536	-.1357E-01	.9161E+05
22	113.0	.1300	.1324	-.2390E-02	.1062E+06
23	120.0	.1200	.1222	-.2223E-02	.1247E+06
24	140.0	.1000	.9727E-01	.2727E-02	.1795E+06
25	160.0	.8000E-01	.7742E-01	.2584E-02	.2805E+06
26	180.0	.7000E-01	.6161E-01	.8386E-02	.3664E+06

--- C. WLS Estimation Summary (Subject 2)

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 75

Number of function calls: 248

Estimator criterion value: 48.4865

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.997	48.4865	.150810E-02

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K12	.7000E-01	.5904E-01	21.95	[.3209E-01, .8599E-01]
K21	.6000E-01	.1053	22.91	[.5514E-01, .1555]
K02	.2000E-01	.3654E-01	6.286	[.3176E-01, .4132E-01]
IC(1)	.8600	.5899	3.634	[.5453 , .6345]
IC(2)	.0000	Fixed		

--- D. Estimated Model Prediction and Data Summary (Subject 2)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	2.000	.5400	.5304	.9575E-02	6157.
2	3.000	.5000	.5070	-.6991E-02	7182.
3	4.000	.4800	.4868	-.6833E-02	7793.
4	5.000	.4900	.4694	.2061E-01	7478.
5	6.000	.4400	.4542	-.1421E-01	9274.
6	8.000	.4200	.4292	-.9155E-02	.1018E+05
7	10.00	.4100	.4093	.6560E-03	.1068E+05
8	12.00	.4000	.3932	.6818E-02	.1122E+05
9	14.00	.3900	.3796	.1042E-01	.1180E+05
10	16.00	.3600	.3678	-.7775E-02	.1385E+05
11	19.00	.3600	.3524	.7615E-02	.1385E+05
12	22.00	.3400	.3388	.1169E-02	.1553E+05
13	25.00	.3300	.3265	.3520E-02	.1649E+05
14	30.00	.3100	.3076	.2353E-02	.1868E+05
15	40.00	.2800	.2741	.5850E-02	.2290E+05
16	50.00	.2500	.2446	.5406E-02	.2873E+05
17	60.00	.2100	.2183	-.8270E-02	.4071E+05
18	70.00	.2000	.1948	.5215E-02	.4489E+05
19	80.00	.1700	.1738	-.3828E-02	.6213E+05
20	100.0	.1400	.1384	.1565E-02	.9161E+05
21	110.0	.1200	.1235	-.3540E-02	.1247E+06
22	120.0	.1000	.1102	-.1025E-01	.1795E+06
23	140.0	.9000E-01	.8780E-01	.2198E-02	.2217E+06
24	160.0	.7000E-01	.6992E-01	.7519E-04	.3664E+06
25	180.0	.6000E-01	.5569E-01	.4311E-02	.4987E+06

--- C. WLS Estimation Summary (Subject 3)

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 57

Number of function calls: 209

Estimator criterion value: 441.619

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.984	441.619	.203961E-01

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K12	.6000E-01	.5477E-01	2.694	[.5171E-01, .5782E-01]
K21	.1000	.1235E-01	5.056	[.1105E-01, .1364E-01]
K02	.2000E-01	.1511E-01	2.602	[.1430E-01, .1593E-01]
IC(1)	.6000	.7289	1.397	[.7078 , .7501]
IC(2)	.0000	Fixed		

--- D. Estimated Model Prediction and Data Summary (Subject 3)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	2.000	.7700	.6542	.1158	3028.
2	3.000	.6000	.6204	-.2044E-01	4987.
3	4.000	.6100	.5888	.2117E-01	4825.
4	5.000	.6000	.5592	.4075E-01	4987.
5	6.000	.5000	.5316	-.3156E-01	7182.
6	8.000	.4500	.4813	-.3135E-01	8866.
7	10.00	.4200	.4373	-.1728E-01	.1018E+05
8	12.00	.3800	.3986	-.1857E-01	.1243E+05
9	14.00	.3500	.3645	-.1450E-01	.1466E+05
10	16.00	.3300	.3345	-.4494E-02	.1649E+05
11	19.00	.2800	.2960	-.1596E-01	.2290E+05
12	22.00	.2800	.2639	.1611E-01	.2290E+05
13	25.00	.2500	.2371	.1291E-01	.2873E+05
14	30.00	.2200	.2016	.1843E-01	.3710E+05
15	40.00	.1600	.1538	.6218E-02	.7014E+05
16	50.00	.1300	.1242	.5836E-02	.1062E+06
17	60.00	.1100	.1042	.5809E-02	.1484E+06
18	70.00	.8000E-01	.8958E-01	-.9575E-02	.2805E+06
19	80.00	.7000E-01	.7813E-01	-.8133E-02	.3664E+06
20	90.00	.6000E-01	.6873E-01	-.8727E-02	.4987E+06
21	100.0	.7000E-01	.6074E-01	.9258E-02	.3664E+06
22	110.0	.6000E-01	.5383E-01	.6171E-02	.4987E+06
23	120.0	.5000E-01	.4778E-01	.2225E-02	.7182E+06
24	140.0	.4000E-01	.3771E-01	.2286E-02	.1122E+07
25	160.0	.4000E-01	.2981E-01	.1019E-01	.1122E+07
26	180.0	.2000E-01	.2356E-01	-.3564E-02	.4489E+07

--- C. WLS Estimation Summary (Subject 4)

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 62

Number of function calls: 241

Estimator criterion value: 326.477

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.955	326.477	.330798E-01

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K12	.5000E-01	.1719E-01	6.249	[.1496E-01, .1941E-01]
K21	.1000E-01	.5538E-02	37.67	[.1212E-02, .9865E-02]
K02	.2000E-01	.1573E-01	23.90	[.7931E-02, .2353E-01]
IC(1)	.7300	.5489	1.192	[.5354 , .5625]

--- D. Estimated Model Prediction and Data Summary (Subject 4)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	2.000	.4800	.5305	-.5048E-01	7793.
2	3.000	.5700	.5216	.4844E-01	5526.
3	4.000	.5400	.5128	.2715E-01	6157.
4	5.000	.5200	.5043	.1568E-01	6640.
5	6.000	.5900	.4960	.9401E-01	5158.
6	8.000	.4200	.4799	-.5986E-01	.1018E+05
7	10.00	.4100	.4644	-.5442E-01	1068E+05
8	12.00	.4000	.4496	-.4965E-01	.1122E+05
9	14.00	.4800	.4355	.4450E-01	7793.
10	16.00	.4500	.4219	.2806E-01	8866.
11	19.00	.4200	.4027	.1734E-01	.1018E+05
12	22.00	.4200	.3846	.3545E-01	.1018E+05
13	25.00	.4300	.3675	.6247E-01	9710.
14	30.00	.3500	.3414	.8621E-02	.1466E+05
15	40.00	.2900	.2962	-.6212E-02	.2135E+05
16	50.00	.2500	.2588	-.8833E-02	.2873E+05
17	60.00	.2100	.2276	-.1759E-01	.4071E+05
18	70.00	.2100	.2012	.8776E-02	.4071E+05
19	80.00	.1600	.1788	-.1877E-01	.7014E+05
20	90.00	.1700	.1595	.1052E-01	.6213E+05
21	100.0	.1400	.1428	-.2780E-02	.9161E+05
22	110.0	.1300	.1282	.1787E-02	.1062E+06
23	120.0	.1200	.1154	.4575E-02	.1247E+06
24	140.0	.1000	.9412E-01	.5882E-02	.1795E+06
25	160.0	.8000E-01	.7721E-01	.2793E-02	.2805E+06
26	180.0	.6000E-01	.6360E-01	-.3597E-02	.4987E+06

--- C. WLS Estimation Summary (Subject 5)

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 58

Number of function calls: 257

Estimator criterion value: 222.565

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.988	222.565	.154319E-01

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K12	.1700E-01	.5070E-01	2.209	[.4838E-01, .5302E-01]
K21	.5500E-02	.8911E-02	4.722	[.8038E-02, .9784E-02]
K02	.1500E-01	.9436E-02	3.953	[.8663E-02, .1021E-01]
IC(1)	.5500	.7872	1.216	[.7673 , .8070]
IC(2)	.0000	Fixed		

--- D. Estimated Model Prediction and Data Summary (Subject 5)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	2.000	.7300	.7119	.1809E-01	3369.
2	3.000	.6300	.6775	-.4751E-01	4524.
3	4.000	.6100	.6451	-.3510E-01	4825.
4	5.000	.5800	.6145	-.3455E-01	5337.
5	6.000	.5500	.5857	-.3575E-01	5935.
6	8.000	.5800	.5330	.4699E-01	5337.
7	10.00	.5400	.4861	.5388E-01	6157.
8	12.00	.4700	.4444	.2559E-01	8128.
9	14.00	.4400	.4073	.3272E-01	9274.
10	16.00	.4100	.3742	.3578E-01	.1068E+05
11	19.00	.3400	.3312	.8763E-02	.1553E+05
12	22.00	.2900	.2950	-.5008E-02	.2135E+05
13	25.00	.2700	.2644	.5591E-02	.2463E+05
14	30.00	.2000	.2235	-.2346E-01	.4489E+05
15	40.00	.1600	.1681	-.8135E-02	.7014E+05
16	50.00	.1400	.1346	.5388E-02	.9161E+05
17	60.00	.1100	.1132	-.3173E-02	.1484E+06
18	70.00	.1000	.9853E-01	.1470E-02	.1795E+06
19	80.00	.8000E-01	.8780E-01	-.7798E-02	.2805E+06
20	90.00	.8000E-01	.7940E-01	.6042E-03	.2805E+06
21	100.0	.8000E-01	.7245E-01	.7549E-02	.2805E+06
22	110.0	.7000E-01	.6648E-01	.3524E-02	.3664E+06
23	120.0	.7000E-01	.6119E-01	.8807E-02	.3664E+06
24	140.0	.5000E-01	.5211E-01	-.2112E-02	.7182E+06
25	160.0	.4000E-01	.4451E-01	-.4507E-02	.1122E+07
26	180.0	.4000E-01	.3805E-01	.1951E-02	.1122E+07

--- C. WLS Estimation Summary (Subject 6)

model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 70

Number of function calls: 251

Estimator criterion value: 176.322

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.979	176.322	.200695E-01

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K12	.5000E-01	.2392E-01	4.404	[.2174E-01, .2610E-01]
K21	.9000E-02	.7911E-02	17.06	[.5118E-02, .1070E-01]
K02	.9000E-02	.1462E-01	10.44	[.1146E-01, .1777E-01]
IC(1)	.7900	.6055	1.101	[.5917 , .6193]

--- D. Estimated Model Prediction and Data Summary (Subject 6)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	1.000	.6300	.5913	.3873E-01	4524.
2	2.000	.6800	.5775	.1025	3883.
3	3.000	.5200	.5641	-.4407E-01	6640.
4	4.000	.5000	.5511	-.5110E-01	7182.
5	5.000	.5100	.5385	-.2854E-01	6903.
6	6.000	.5300	.5264	.3644E-02	6392.
7	8.000	.4900	.5031	-.1310E-01	7478.
8	10.00	.4700	.4812	-.1123E-01	8128.
9	12.00	.4700	.4607	.9334E-02	8128.
10	14.00	.4600	.4413	.1869E-01	8485.
11	16.00	.4400	.4231	.1692E-01	9274.
12	19.00	.4000	.3977	.2318E-02	.1122E+05
13	22.00	.3800	.3744	.5577E-02	.1243E+05
14	25.00	.3600	.3531	.6911E-02	.1385E+05
15	30.00	.3500	.3213	.2869E-01	.1466E+05
16	40.00	.2700	.2694	.6276E-03	.2463E+05
17	50.00	.2200	.2292	-.9218E-02	.3710E+05
18	60.00	.1800	.1976	-.1759E-01	.5542E+05
19	70.00	.1700	.1722	-.2205E-02	.6213E+05
20	80.00	.1500	.1514	-.1449E-02	.7980E+05
21	90.00	.1500	.1342	.1582E-01	.7980E+05
22	100.0	.1200	.1196	.4123E-03	.1247E+06
23	110.0	.1100	.1071	.2919E-02	.1484E+06
24	120.0	.9000E-01	.9624E-01	-.6236E-02	.2217E+06
25	140.0	.8000E-01	.7835E-01	.1653E-02	.2805E+06
26	160.0	.7000E-01	.6423E-01	.5773E-02	.3664E+06
27	180.0	.5000E-01	.5287E-01	-.2867E-02	.7182E+0

--- C. WLS Estimation Summary (Subject 7)

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 54

Number of function calls: 211

Estimator criterion value: 184.841

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.986	184.841	.975899E-02

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K12	.2300E-01	.2515E-01	8.284	[.2074E-01, .2957E-01]
K21	.8000E-02	.1556E-01	20.34	[.8854E-02, .2227E-01]
K02	.1500E-01	.1800E-01	8.595	[.1472E-01, .2129E-01]
IC(1)	.6055	.6310	1.569	[.6100 , .6520]
IC(2)	.0000	Fixed		

--- D. Estimated Model Prediction and Data Summary (Subject 7)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	2.000	.5900	.6005	-.1052E-01	5158.
2	3.000	.6200	.5862	.3383E-01	4671.
3	4.000	.5600	.5724	-.1238E-01	5725.
4	5.000	.5400	.5591	-.1913E-01	6157.
5	6.000	.6000	.5464	.5362E-01	4987.
6	10.00	.5000	.5001	-.5026E-04	7182.
7	12.00	.4600	.4794	-.1939E-01	8485.
8	14.00	.4600	.4602	-.1910E-03	8485.
9	16.00	.4300	.4423	-.1234E-01	9710.
10	22.00	.3900	.3957	-.5692E-02	.1180E+05
11	50.00	.2700	.2624	.7646E-02	.2463E+05
12	60.00	.2300	.2331	-.3098E-02	.3394E+05
13	71.00	.2700	.2067	.6332E-01	.2463E+05
14	80.00	.1800	.1883	-.8292E-02	.5542E+05
15	90.00	.1600	.1704	-.1042E-01	.7014E+05
16	100.0	.1500	.1547	-.4673E-02	.7980E+05
17	110.0	.1300	.1406	-.1064E-01	.1062E+06
18	140.0	.1100	.1064	.3635E-02	.1484E+06
19	160.0	.1000	.8850E-01	.1150E-01	.1795E+06
20	180.0	.7000E-01	.7368E-01	-.3682E-02	.3664E+06

--- C. WLS Estimation Summary (Subject 8)

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 63

Number of function calls: 203

Estimator criterion value: 109.467

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.986	109.467	.113058E-01

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K12	.2500E-01	.3693E-01	4.917	[.3318E-01, .4069E-01]
K21	.1500E-01	.1893E-01	8.730	[.1551E-01, .2235E-01]
K02	.1800E-01	.1330E-01	4.945	[.1194E-01, .1467E-01]
IC(1)	.6310	.6216	1.468	[.6028 , .6405]
IC(2)	.0000	Fixed		

--- D. Estimated Model Prediction and Data Summary (Subject 8)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	2.000	.6400	.5782	.6181E-01	4383.
2	3.000	.6200	.5582	.6180E-01	4671.
3	4.000	.5400	.5393	.7140E-03	6157.
4	5.000	.5200	.5214	-.1379E-02	6640.
5	6.000	.5000	.5044	-.4422E-02	7182.
6	7.000	.4700	.4884	-.1836E-01	8128.
7	8.000	.4400	.4731	-.3314E-01	9274.
8	10.00	.4200	.4450	-.2502E-01	.1018E+05
9	12.00	.4100	.4197	-.9725E-02	.1068E+05
10	14.00	.3800	.3969	-.1693E-01	.1243E+05
11	16.00	.3700	.3763	-.6343E-02	.1312E+05
12	19.00	.3400	.3491	-.9089E-02	.1553E+05
13	22.00	.3300	.3256	.4448E-02	.1649E+05
14	25.00	.3200	.3051	.1488E-01	.1753E+05
15	30.00	.2900	.2767	.1333E-01	.2135E+05
16	40.00	.2500	.2347	.1525E-01	.2873E+05
17	50.00	.2200	.2055	.1454E-01	.3710E+05
18	60.00	.1900	.1835	.6460E-02	.4974E+05
19	70.00	.1600	.1661	-.6080E-02	.7014E+05
20	80.00	.1500	.1515	-.1469E-02	.7980E+05
21	90.00	.1400	.1388	.1197E-02	.9161E+05
22	100.0	.1200	.1276	-.7557E-02	.1247E+06
23	110.0	.1100	.1174	-.7419E-02	.1484E+06
24	120.0	.1100	.1082	.1805E-02	.1484E+06
25	140.0	.9000E-01	.9200E-01	-.2004E-02	.2217E+06
26	160.0	.8000E-01	.7830E-01	.1696E-02	.2805E+06
27	180.0	.7000E-01	.6666E-01	.3336E-02	.3664E+06

--- C. WLS Estimation Summary (Subject 9)

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 37

Number of function calls: 162

Estimator criterion value: 98.3367

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.989	98.3367	.119945E-01

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K12	.3700E-01	.3829E-01	3.031	[.3589E-01, .4069E-01]
K21	.1900E-01	.1092E-01	6.957	[.9349E-02, .1249E-01]
K02	.1300E-01	.1075E-01	5.080	[.9625E-02, .1189E-01]
IC(1)	.6216	.6734	1.145	[.6574 , .6893]
IC(2)	.0000	Fixed		

- D. Estimated Model Prediction and Data Summary (Subject 9)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	1.000	.7200	.6482	.7179E-01	3463.
2	2.000	.6500	.6243	.2574E-01	4250.
3	3.000	.5800	.6015	-.2145E-01	5337.
4	4.000	.5400	.5797	-.3973E-01	6157.
5	5.000	.5500	.5590	-.9042E-02	5935.
6	6.000	.5300	.5393	-.9334E-02	6392.
7	8.000	.4600	.5027	-.4267E-01	8485.
8	10.00	.4800	.4694	.1064E-01	7793.
9	12.00	.4600	.4391	.2091E-01	8485.
10	14.00	.4100	.4116	-.1562E-02	.1068E+05
11	16.00	.4100	.3865	.2350E-01	.1068E+05
12	19.00	.3500	.3530	-.3035E-02	.1466E+05
13	22.00	.3400	.3239	.1612E-01	.1553E+05
14	25.00	.3000	.2984	.1573E-02	.1995E+05
15	30.00	.2800	.2628	.1716E-01	.2290E+05
16	40.00	.1900	.2108	- .2079E-01	.4974E+05
17	50.00	.1800	.1757	.4287E-02	.5542E+05
18	60.00	.1500	.1510	-.1029E-02	.7980E+05
19	70.00	.1300	.1328	- .2816E-02	.1062E+06
20	80.00	.1200	.1187	.1282E-02	.1247E+06
21	90.00	.1100	.1073	.2687E-02	.1484E+06
22	100.0	.1000	.9774E-01	.2260E-02	.1795E+06
23	110.0	.9000E-01	.8947E-01	.5331E-03	.2217E+06
24	120.0	.8000E-01	.8216E-01	-.2164E-02	.2805E+06
25	140.0	.7000E-01	.6969E-01	.3092E-03	.3664E+06
26	160.0	.6000E-01	.5933E-01	.6662E-03	.4987E+06
27	180.0	.5000E-01	.5060E-01	-.5951E-03	.7182E+06

--- C. WLS Estimation Summary (Subject 10)

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 45

Number of function calls: 184

Estimator criterion value: 84.5219

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.990	84.5219	.121146E-01

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K12	.3800E-01	.4503E-01	3.961	[.4133E-01, .4873E-01]
K21	.1100E-01	.1716E-01	7.580	[.1446E-01, .1985E-01]
K02	.1100E-01	.1733E-01	3.463	[.1608E-01, .1857E-01]
IC(1)	.6734	.7606	1.475	[.7373 , .7838]
IC(2)	.0000	Fixed		

-- D. Estimated Model Prediction and Data Summary (Subject 10)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	2.000	.7900	.6961	.9386E-01	2877.
2	3.000	.6700	.6668	.3215E-02	4000.
3	4.000	.6500	.6392	.1082E-01	4250.
4	5.000	.5800	.6132	-.3320E-01	5337.
5	6.000	.5600	.5887	-.2875E-01	5725.
6	8.000	.5200	.5440	-.2403E-01	6640.
7	10.00	.5000	.5043	-.4323E-02	7182.
8	12.00	.4700	.4690	.1002E-02	8128.
9	14.00	.4400	.4375	.2486E-02	9274.
10	16.00	.4100	.4094	.6038E-03	.1068E+05
11	19.00	.3800	.3726	.7355E-02	.1243E+05
12	22.00	.3500	.3414	.8636E-02	.1466E+05
13	25.00	.3100	.3146	-.4591E-02	.1868E+05
14	30.00	.2700	.2779	-.7907E-02	.2463E+05
15	40.00	.2400	.2252	.1477E-01	.3117E+05
16	50.00	.1900	.1894	.5997E-03	.4974E+05
17	60.00	.1700	.1631	.6906E-02	.6213E+05
18	70.00	.1400	.1425	-.2494E-02	.9161E+05
19	80.00	.1300	.1256	.4428E-02	.1062E+06
20	90.00	.1000	.1112	-.1122E-01	.1795E+06
21	100.0	.1000	.9879E-01	.1214E-02	.1795E+06
22	110.0	.9000E-01	.8789E-01	.2109E-02	.2217E+06
23	120.0	.8000E-01	.7827E-01	.1729E-02	.2805E+06
24	140.0	.6000E-01	.6216E-01	-.2161E-02	.4987E+06
25	160.0	.5000E-01	.4940E-01	.5963E-03	.7182E+06
26	180.0	.4000E-01	.3927E-01	.7259E-03	.1122E+07

--- C. WLS Estimation Summary (Subject 11)

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 62

Number of function calls: 229

Estimator criterion value: 126.003

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.995	126.003	.599103E-02

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K12	.4500E-01	.4460E-01	3.145	[.4169E-01, .4751E-01]
K21	.1700E-01	.1225E-01	6.532	[.1059E-01, .1391E-01]
K02	.1700E-01	.1349E-01	3.844	[.1242E-01, .1457E-01]
IC(1)	.7606	.7251	1.358	[.7047 , .7455]
IC(2)	.0000	Fixed		

--- D. Estimated Model Prediction and Data Summary (Subject 11)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	2.000	.7100	.6639	.4607E-01	3562.
2	3.000	.6700	.6359	.3414E-01	4000.
3	4.000	.6200	.6093	.1067E-01	4671.
4	5.000	.5800	.5842	-.4239E-02	5337.
5	6.000	.5600	.5605	-.5171E-03	5725.
6	8.000	.5000	.5169	-.1686E-01	7182.
7	10.00	.4600	. 4778	-.1777E-01	8485.
8	12.00	.4300	.4427	-.1273E-01	9710.
9	14.00	.3800	.4113	-.3130E-01	.1243E+05
10	16.00	.3700	.3831	-.1308E-01	.1312E+05
11	19.00	.3500	.3460	.4032E-02	.1466E+05
12	22.00	.3300	.3142	.1577E-01	.1649E+05
13	25.00	.2900	.2870	.2998E-02	.2135E+05
14	30.00	.2600	.2497	.1029E-01	.2656E+05
15	40.00	.2000	.1969	.3148E-02	.4489E+05
16	50.00	.1600	.1622	-.2229E-02	.7014E+05
17	60.00	.1400	.1381	.1880E-02	.9161E+05
18	70.00	.1300	.1203	9748E-02	.1062E+06
19	80.00	.1100	.1062	.3761E-02	.1484E+06
20	90.00	.9000E-01	.9474E-01	-.4737E-02	.2217E+06
21	100.0	.9000E-01	.8497E-01	.5028E-02	.2217E+06
22	110.0	.7000E-01	.7649E-01	-.6486E-02	.3664E+06
23	120.0	.7000E-01	.6900E-01	.1002E-02	.3664E+06
24	140.0	.5000E-01	.5634E-01	-.6345E-02	.7182E+06
25	160.0	.5000E-01	.4611E-01	.3892E-02	.7182E+06
26	180.0	.4000E-01	.3776E-01	.2240E-02	.1122E+07

--- C. WLS Estimation Summary (Subject 12)

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 40

Number of function calls: 151

Estimator criterion value: 155.016

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.981	155.016	.266770E-01

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K12	.4500E-01	.4473E-01	3.332	[.4164E-01, .4782E-01]
K21	.1200E-01	.1342E-01	6.688	[.1156E-01, .1528E-01]
K02	.1300E-01	.1439E-01	3.623	[.1331E-01, .1547E-01]
IC(1)	.7251	.7640	1.391	[.7419 , .7860]
IC(2)	.0000	Fixed		

-- D. Estimated Model Prediction and Data Summary (Subject 12)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	2.000	.8300	.6995	.1305	2606.
2	3.000	.7300	.6699	.6011E-01	3369.
3	4.000	.6300	.6420	-.1197E-01	4524.
4	5.000	.5700	.6156	-.4561E-01	5526.
5	6.000	.5400	.5907	-.5071E-01	6157.
6	8.000	.5300	.5450	-.1495E-01	6392.
7	10.00	.5000	.5041	-.4072E-02	7182.
8	12.00	.4600	.4675	-.7503E-02	8485.
9	14.00	.4300	.4348	-.4753E-02	9710.
10	18.00	.3800	.3790	.9914E-03	.1243E+05
11	19.00	.3700	.3668	.3163E-02	.1312E+05
12	22.00	.3400	.3339	.6076E-02	.1553E+05
13	25.00	.3000	.3057	-.5706E-02	.1995E+05
14	30.00	.2800	.2671	.1292E-01	.2290E+05
15	40.00	.2300	.2122	.1778E-01	.3394E+05
16	50.00	.1800	.1760	.4001E-02	.5542E+05
17	60.00	.1400	.1505	-.1045E-01	.9161E+05
18	70.00	.1300	.1312	-.1233E-02	.1062E+06
19	80.00	.1100	.1160	-.5954E-02	.1484E+06
20	93.00	.1100	.9986E-01	.1014E-01	.1484E+06
21	100.0	.9000E-01	.9244E-01	-.2441E-02	.2217E+06
22	110.0	.9000E-01	.8299E-01	.7014E-02	.2217E+06
23	120.0	.7000E-01	.7463E-01	-.4631E-02	.3664E+06
24	140.0	.6000E-01	.6053E-01	-.5273E-03	.4987E+06
25	160.0	.5000E-01	.4917E-01	.8315E-03	.7182E+06
26	180.0	.4000E-01	.3996E-01	.3533E-04	.1122E+07

--- C. WLS Estimation Summary (Subject 13)

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 45

Number of function calls: 201

Estimator criterion value: 170.275

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.986	170.275	.225610E-01

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K12	.4500E-01	.3546E-01	5.238	[.3161E-01, .3931E-01]
K21	.1300E-01	.1513E-01	14.68	[.1052E-01, .1974E-01]
K02	.1400E-01	.2659E-01	5.196	[.2373E-01, .2946E-01]
IC(1)	.7640	.7794	1.508	[.7550 , .8038]
IC(2)	.0000	Fixed		

--- D. Estimated Model Prediction and Data Summary (Subject 13)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	2.000	.8100	.7268	.8318E-01	2737.
2	3.000	.7700	.7024	.6757E-01	3028.
3	4.000	.6800	.6792	.7839E-03	3883.
4	5.000	.6500	.6571	-.7111E-02	4250.
5	6.000	.6300	.6361	-.6052E-02	4524.
6	8.000	.5900	.5968	-.6838E-02	5158.
7	10.00	.5400	.5611	-.2115E-01	6157.
8	12.00	.4400	.5286	-.8860E-01	9274.
9	14.00	.5100	.4989	.1113E-01	6903.
10	16.00	.4600	.4716	-.1164E-01	8485.
11	21.50	.4000	.4077	-.7664E-02	.1122E+05
12	23.50	.3900	.3877	.2268E-02	.1180E+05
13	29.00	.3700	.3402	.2980E-01	.1312E+05
14	30.00	.3600	.3325	.2746E-01	.1385E+05
15	40.00	.2900	.2687	.2127E-01	.2135E+05
16	50.50	.2300	.2197	.1031E-01	.3394E+05
17	60.00	.1900	.1855	.4464E-02	.4974E+05
18	70.00	.1500	.1567	-.6716E-02	.7980E+05
19	80.00	.1300	.1332	-.3179E-02	.1062E+06
20	90.00	.1100	.1136	-.3618E-02	.1484E+06
21	100.0	.1000	.9717E-01	.2830E-02	.1795E+06
22	110.0	.8000E-01	.8323E-01	-.3233E-02	.2805E+06
23	120.0	.7000E-01	.7136E-01	-.1365E-02	.3664E+06
24	140.0	.5000E-01	.5255E-01	-.2550E-02	.7182E+06
25	160.0	.4000E-01	.3874E-01	.1265E-02	.1122E+07
26	180.0	.3000E-01	.2856E-01	.1436E-02	.1995E+07

--- C. WLS Estimation Summary (Subject 14)

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 42

Number of function calls: 176

Estimator criterion value: 163.504

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.980	163.504	.277426E-01

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K12	.3500E-01	.3725E-01	4.063	[.3410E-01, .4040E-01]
K21	.1500E-01	.1427E-01	8.351	[.1179E-01, .1675E-01]
K02	.2660E-01	.1282E-01	5.096	[.1146E-01, .1418E-01]
IC(1)	.7800	.7996	1.388	[.7765 , .8227]

.... D. Estimated Model Prediction and Data Summary (Subject 14)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	2.000	.8800	.7430	.1370	2319.
2	3.000	.7300	.7168	.1323E-01	3369.
3	4.000	.6900	.6919	-.1866E-02	3771.
4	5.000	.6400	.6682	-.2820E-01	4383.
5	6.000	.6000	.6457	-.4569E-01	4987.
6	8.000	.5700	.6039	-.3394E-01	5526.
7	10.00	.5500	.5661	-.1614E-01	5935.
8	12.00	.5300	.5319	-.1899E-02	6392.
9	14.00	.5100	.5008	.9164E-02	6903.
10	16.00	.4700	.4726	-.2625E-02	8128.
11	19.00	.4500	.4350	.1498E-01	8866.
12	22.00	.4200	.4023	.1767E-01	.1018E+05
13	25.00	.3500	.3738	-.2380E-01	.1466E+05
14	30.00	.3800	.3339	.4613E-01	.1243E+05
15	40.00	.2900	.2750	.1501E-01	.2135E+05
16	50.00	.2100	.2344	-.2440E-01	.4071E+05
17	70.00	.1800	.1821	-.2135E-02	.5542E+05
18	80.00	.1800	.1638	.1619E-01	.5542E+05
19	90.00	.1500	.1484	.1569E-02	.7980E+05
20	100.0	.1400	.1351	.4858E-02	.9161E+05
21	110.0	.1200	.1234	-.3418E-02	.1247E+06
22	120.0	.1100	.1129	-.2928E-02	.1484E+06
23	140.0	.9000E-01	.9484E-01	-.4845E-02	.2217E+06
24	160.0	.8000E-01	.7982E-01	.1843E-03	.2805E+06
25	180.0	.7000E-01	.6722E-01	.2779E-02	.3664E+06

--- C. WLS Estimation Summary (Subject 15)

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 110

Number of function calls: 431

Estimator criterion value: 137.081

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.970	137.081	.159240E-01

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K12	.3700E-01	.1737E-01	6.576	[.1497E-01, .1977E-01]
K21	.1400E-01	.5103E-02	35.02	[.1349E-02, .8857E-02]
K02	.1200E-01	.1174E-01	26.82	[.5126E-02, .1836E-01]
IC(1)	.8000	.5472	1.542	[.5295 , .5649]
IC(2)	.0000	Fixed		

--- D. Estimated Model Prediction and Data Summary (Subject 15)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	2.000	.6000	.5286	.7140E-01	4987.
2	6.000	.5500	.4938	.5618E-01	5935.
3	8.000	.4200	.4776	-.5755E-01	.1018E+05
4	10.00	.4100	.4620	-.5198E-01	.1068E+05
5	12.00	.4600	.4471	.1292E-01	8485.
6	14.00	.4200	.4328	- .1281E-01	.1018E+05
7	16.00	.4400	.4191	.2086E-01	9274.
8	19.00	.4100	.3997	.1029E-01	.1068E+05
9	22.00	.4000	.3815	.1853E-01	.1122E+05
10	25.00	.3600	.3644	-.4353E-02	.1385E+05
11	30.00	.3300	.3381	-.8079E-02	.1649E+05
12	40.00	.2900	.2929	-.2885E-02	.2135E+05
13	50.00	.2700	.2557	.1426E-01	.2463E+05
14	60.00	.2300	.2249	.5057E-02	.3394E+05
15	70.00	.2000	.1992	.8071E-03	.4489E+05
16	80.00	.1800	.1775	.2531E-02	.5542E+05
17	90.00	.1500	.1590	-.8980E-02	.7980E+05
18	100.0	.1400	.1431	-.3107E-02	.9161E+05
19	112.0	.1300	.1268	.3162E-02	.1062E+06
20	120.0	.1200	.1174	.2625E-02	.1247E+06
21	160.0	.8000E-01	.8176E-01	-.1764E-02	.2805E+06
22	180.0	.7000E-01	.6902E-01	.9764E-03	.3664E+06

--- C. WLS Estimation Summary (Subject 16)

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 90

Number of function calls: 361

Estimator criterion value: 157.671

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.966	157.671	.477340E-01

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K12	.1700E-01	.4211E-01	12.44	[.3125E-01, .5297E-01]
K21	.5000E-02	.5452E-01	16.68	[.3566E-01, .7338E-01]
K02	.1170E-01	.2517E-01	5.071	[.2252E-01, .2781E-01]
IC(1)	.5470	.8870	2.282	[.8450 , .9290]
IC(2)	.0000	Fixed		

--- D. Estimated Model Prediction and Data Summary (Subject 16)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	2.000	.9700	.8190	.1510	1908.
2	3.000	.6700	.7895	-.1195	4000.
3	4.000	.8200	.7626	.5737E-01	2670.
4	5.000	.6900	.7381	-.4807E-01	3771.
5	6.000	.7700	.7156	.5442E-01	3028.
6	8.000	.6900	.6760	.1399E-01	3771.
7	10.00	.6400	.6425	-.2456E-02	4383.
8	12.00	.6300	.6137	.1626E-01	4524.
9	14.00	.5900	.5889	.1077E-02	5158.
10	16.00	.5700	.5673	.2744E-02	5526.
11	19.00	.5500	.5394	.1062E-01	5935.
12	22.00	.5000	.5157	-.1574E-01	7182.
13	25.00	.4900	.4952	-.5211E-02	7478.
14	30.00	.4600	.4659	-.5889E-02	8485.
15	40.00	.4100	.4183	-.8300E-02	.1068E+05
16	50.00	.3700	.3788	-.8813E-02	.1312E+05
17	60.00	.3400	.3441	-.4122E-02	.1553E+05
18	70.00	.3400	.3130	.2704E-01	.1553E+05
19	80.00	.2800	.2847	-.4727E-02	.2290E+05
20	90.00	.2700	.2591	.1092E-01	.2463E+05
21	100.0	.2400	.2358	.4244E-02	.3117E+05
22	110.0	.2100	.2145	-.4536E-02	.4071E+05
23	120.0	.1900	.1952	-.5227E-02	.4974E+05
24	140.0	.1700	.1617	.8333E-02	.6213E+05
25	160.0	.1300	.1339	-.3876E-02	.1062E+06
26	180.0	.1100	.1109	-.8626E-03	.1484E+06

--- C. WLS Estimation Summary (Subject 17)

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 61

Number of function calls: 250

Estimator criterion value: 96.0671

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.996	96.0671	.212993E-02

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
K12	.4200E-01	.3042E-01	4.066	[.2786E-01, .3299E-01]
K21	.5450E-01	.1008E-01	11.67	[.7640E-02, .1252E-01]
K02	.2500E-01	.1475E-01	6.666	[.1271E-01, .1679E-01]
IC(1)	.8870	.4981	1.283	[.4848 , .5113]
IC(2)	.0000	Fixed		

--- D. Estimated Model Prediction and Data Summary (Subject 17)

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	2.000	.4800	.4690	.1104E-01	7793.
2	3.000	.4500	.4553	-.5262E-02	8866.
3	4.000	.4600	.4421	.1790E-01	8485.
4	5.000	.4500	.4295	.2055E-01	8866.
5	6.000	.4300	.4173	.1270E-01	9710.
6	8.000	.3900	.3944	-.4378E-02	.1180E+05
7	10.00	.3500	.3732	-.2319E-01	.1466E+05
8	12.00	.3500	.3536	-.3579E-02	.1466E+05
9	14.00	.3300	.3354	-.5422E-02	.1649E+05
10	16.00	.3100	.3186	-.8594E-02	.1868E+05
11	19.00	.2900	.2956	-.5607E-02	.2135E+05
12	23.00	.2700	.2687	.1344E-02	.2463E+05
13	25.00	.2500	.2566	-.6574E-02	.2873E+05
14	30.00	.2300	.2298	.1522E-03	.3394E+05
15	40.00	.1900	.1882	.1800E-02	.4974E+05
16	50.00	.1600	.1578	.2233E-02	.7014E+05
17	60.00	.1500	.1348	.1517E-01	.7980E+05
18	70.00	.1200	.1170	.2996E-02	.1247E+06
19	80.00	.1000	.1027	-.2724E-02	.1795E+06
20	90.00	.9000E-01	.9098E-01	-.9772E-03	.2217E+06
21	100.0	.8000E-01	.8109E-01	-.1092E-02	.2805E+06
22	110.0	.7000E-01	.7262E-01	-.2617E-02	.3664E+06
23	120.0	.7000E-01	.6525E-01	.4754E-02	.3664E+06
24	140.0	.5000E-01	.5301E-01	-.3013E-02	.7182E+06
25	160.0	.4000E-01	.4329E-01	-.3285E-02	.1122E+07
26	180.0	.4000E-01	.3543E-01	.4570E-02	.1122E+07

III. The following output are the parameter estimation and the original and model estimated data in stochastic model for the concentration of glucose tracer in blood plasma in total subjects.

--- C. WLS Estimation Summary---

Data file name: a:fin.dat

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 80

Number of function calls: 318

Estimator criterion value: 3.07989

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	1.00	3.07989	.265534E-03

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
A	.1000	.3495	3.202	[.3271 , .3718]
B	.1000	.6005E-01	5.285	[.5370E-01, .6639E-01]
C	.1000	.3308	2.182	[.3163 , .3452]
D	.1000	.1023E-01	1.564	[.9909E-02, .1055E-01]

	A	B	C	D
A	1.00			
B	.15	1.00		
C	-.29	.82	1.00	
D	-.31	.76	.98	1.00

--- D. Estimated Model Prediction and Data Summary ---

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	.0000	.6932	.6802	.1298E-01	3736.
2	4.000	.5929	.5923	.5523E-03	5108.
3	8.000	.5167	.5209	-.4235E-02	6725.
4	12.00	.4575	.4626	-.5062E-02	8578.
5	16.00	.4102	.4145	-.4334E-02	.1067E+05
6	20.00	.3717	.3747	-.3027E-02	.1300E+05
7	24.00	.3399	.3415	-.1566E-02	.1554E+05
8	28.00	.3131	.3134	-.3329E-03	.1832E+05
9	32.00	.2901	.2896	.5138E-03	.2133E+05
10	36.00	.2703	.2691	.1196E-02	.2457E+05
11	40.00	.2529	.2513	.1563E-02	.2807E+05
12	44.00	.2375	.2358	.1727E-02	.3183E+05
13	48.00	.2238	.2220	.1796E-02	.3585E+05
14	52.00	.2113	.2097	.1591E-02	.4021E+05
15	56.00	.2001	.1986	.1468E-02	.4484E+05
16	60.00	.1898	.1886	.1231E-02	.4984E+05
17	64.00	.1804	.1794	.1043E-02	.5517E+05
18	68.00	.1716	.1709	.7324E-03	.6097E+05
19	72.00	.1635	.1630	.5043E-03	.6716E+05
20	76.00	.1559	.1557	.2425E-03	.7387E+05
21	80.00	.1488	.1488	.1489E-04	.8109E+05
22	84.00	.1422	.1423	-.1231E-03	.8879E+05
23	88.00	.1360	.1362	-.2263E-03	.9707E+05
24	92.00	.1301	.1305	-.3574E-03	.1061E+06
25	96.00	.1245	.1250	-.4853E-03	.1158E+06
26	100.0	.1192	.1198	-.5843E-03	.1264E+06

27	104.0	.1142	.1148	-.6324E-03	.1377E+06
28	108.0	.1095	.1101	-.6110E-03	.1497E+06
29	112.0	.1050	.1056	-.6039E-03	.1629E+06
30	116.0	.1007	.1013	-.5973E-03	.1771E+06
31	120.0	.9660E-01	.9718E-01	-.5789E-03	.1924E+06
32	124.0	.9270E-01	.9324E-01	-.5379E-03	.2089E+06
33	128.0	.8900E-01	.8946E-01	-.4644E-03	.2267E+06
34	132.0	.8540E-01	.8585E-01	-.4498E-03	.2462E+06
35	136.0	.8200E-01	.8239E-01	-.3860E-03	.2670E+06
36	140.0	.7880E-01	.7907E-01	-.2658E-03	.2892E+06
37	144.0	.7570E-01	.7588E-01	-.1824E-03	.3133E+06
38	148.0	.7270E-01	.7283E-01	-.1295E-03	.3397E+06
39	152.0	.6990E-01	.6990E-01	-.1222E-05	.3675E+06
40	156.0	.6710E-01	.6709E-01	.7834E-05	.3988E+06
41	160.0	.6450E-01	.6440E-01	.1029E-03	.4316E+06
42	164.0	.6200E-01	.6181E-01	.1887E-03	.4671E+06
43	168.0	.5960E-01	.5933E-01	.2701E-03	.5055E+06
44	172.0	.5730E-01	.5695E-01	.3512E-03	.5468E+06
45	176.0	.5510E-01	.5466E-01	.4364E-03	.5914E+06
46	180.0	.5300E-01	.5247E-01	.5295E-03	.6392E+06

IV. The following output are the parameter estimation and the original and model estimated data in stochastic model for the concentration of glucose tracer in blood plasma in nonobese subjects.

--- C. WLS Estimation Summary---

Data file name: c:\rod\fin.dat

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 148

Number of function calls: 572

Estimator criterion value: 3.47977

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	1.00	3.47977	.271216E-03

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
A	.1000	.3744	2.890	[.3527 , .3960]
B	.1000	.5955E-01	4.644	[.5402E-01, .6508E-01]
C	.1000	.3024	2.285	[.2886 , .3163]
D	.1000	.1098E-01	1.513	[.1065E-01, .1131E-01]

	A	B	C	D
A	1.00			
B	.16	1.00		
C	-.27	.82	1.00	
D	-.29	.77	.98	1.00

--- D. Estimated Model Prediction and Data Summary ---

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	.0000	.6902	.6768	.1340E-01	3769.
2	4.000	.5856	.5845	.1144E-02	5236.
3	8.000	.5058	.5095	-.3691E-02	7018.
4	12.00	.4433	.4483	-.5014E-02	9137.
5	16.00	.3938	.3981	-.4293E-02	.1158E+05
6	20.00	.3534	.3566	-.3192E-02	.1438E+05
7	24.00	.3202	.3220	-.1846E-02	.1751E+05
8	28.00	.2924	.2931	-.6590E-03	.2100E+05
9	32.00	.2688	.2685	.2707E-03	.2485E+05
10	36.00	.2484	.2476	.8158E-03	.2910E+05
11	40.00	.2308	.2295	.1267E-02	.3371E+05
12	44.00	.2153	.2138	.1470E-02	.3873E+05
13	48.00	.2016	.2000	.1561E-02	.4418E+05
14	52.00	.1893	.1878	.1483E-02	.5010E+05
15	56.00	.1783	.1769	.1411E-02	.5648E+05
16	60.00	.1686	.1670	.1563E-02	.6316E+05
17	64.00	.1591	.1581	.1015E-02	.7093E+05
18	68.00	.1507	.1499	.8052E-03	.7906E+05
19	72.00	.1429	.1424	.5472E-03	.8792E+05
20	76.00	.1357	.1354	.3315E-03	.9750E+05
21	80.00	.1290	.1289	.1315E-03	.1079E+06
22	84.00	.1227	.1228	-.9278E-04	.1193E+06
23	88.00	.1169	.1171	-.1925E-03	.1314E+06
24	92.00	.1114	.1117	-.3272E-03	.1447E+06
25	96.00	.1063	.1067	-.3635E-03	.1589E+06
26	100.0	.1014	.1019	-.4733E-03	.1746E+06
27	104.0	.9680E-01	.9733E-01	-.5330E-03	.1916E+06
28	108.0	.9250E-01	.9302E-01	-.5224E-03	.2098E+06

29	112.0	.8830E-01	.8892E-01	-.6245E-03	.2303E+06
30	116.0	.8440E-01	.8502E-01	-.6242E-03	.2521E+06
31	120.0	.8080E-01	.8131E-01	-.5084E-03	.2750E+06
32	124.0	.7730E-01	.7777E-01	-.4657E-03	.3005E+06
33	128.0	.7390E-01	.7439E-01	-.4857E-03	.3288E+06
34	132.0	.7090E-01	.7116E-01	-.2592E-03	.3572E+06
35	136.0	.6770E-01	.6808E-01	-.3780E-03	.3917E+06
36	140.0	.6490E-01	.6513E-01	-.2342E-03	.4263E+06
37	144.0	.6210E-01	.6232E-01	-.2210E-03	.4656E+06
38	148.0	.5950E-01	.5963E-01	-.1318E-03	.5072E+06
39	152.0	.5700E-01	.5706E-01	-.6073E-04	.5526E+06
40	156.0	.5460E-01	.5460E-01	-.2074E-05	.6023E+06
41	160.0	.5230E-01	.5225E-01	.4939E-04	.6564E+06
42	164.0	.5020E-01	.5000E-01	.1986E-03	.7125E+06
43	168.0	.4810E-01	.4785E-01	.2502E-03	.7760E+06
44	172.0	.4610E-01	.4579E-01	.3086E-03	.8448E+06
45	176.0	.4420E-01	.4382E-01	.3780E-03	.9190E+06
46	180.0	.4240E-01	.4194E-01	.4623E-03	.9987E+06

V. The following output are the parameter estimation and the original and model estimated data in stochastic model for the concentration of glucose tracer in blood plasma in obese subjects.

--- C. WLS Estimation Summary---

Data file name: a:finobs.dat

Model file description: Insert Model File description

Weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 135

Number of function calls: 519

Estimator criterion value: 4.37465

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	1.00	4.37465	.363254E-03

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
A	.1000	.3149	3.708	[.2915 , .3383]
B	.1000	.6110E-01	6.293	[.5341E-01, .6879E-01]
C	.1000	.3691	2.063	[.3539 , .3844]
D	.1000	.9625E-02	1.590	[.9319E-02, .9931E-02]

	A	B	C	D
A	1.00			
B	.13	1.00		
C	-.32	.81	1.00	
D	-.33	.75	.97	1.00

--- D. Estimated Model Prediction and Data Summary ---

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	.0000	.6988	.6840	.1477E-01	3677.
2	4.000	.6004	.6018	-.1405E-02	4981.
3	8.000	.5295	.5349	-.5416E-02	6404.
4	12.00	.4741	.4801	-.6028E-02	7988.
5	16.00	.4299	.4349	-.5009E-02	9715.
6	20.00	.3939	.3973	-.3371E-02	.1157E+05
7	24.00	.3679	.3657	.2246E-02	.1327E+05
8	28.00	.3384	.3388	-.4336E-03	.1568E+05
9	32.00	.3163	.3158	.4529E-03	.1795E+05
10	36.00	.2973	.2959	.1362E-02	.2031E+05
11	40.00	.2801	.2785	.1588E-02	.2288E+05
12	44.00	.2650	.2631	.1902E-02	.2557E+05
13	48.00	.2513	.2493	.1972E-02	.2843E+05
14	52.00	.2387	.2369	.1790E-02	.3151E+05
15	56.00	.2271	.2256	.1489E-02	.3481E+05
16	60.00	.2165	.2152	.1251E-02	.3831E+05
17	64.00	.2067	.2057	.1022E-02	.4202E+05
18	68.00	.1975	.1968	.7197E-03	.4603E+05
19	72.00	.1890	.1885	.5361E-03	.5026E+05
20	76.00	.1810	.1807	.3466E-03	.5480E+05
21	80.00	.1734	.1733	.1119E-03	.5971E+05
22	84.00	.1662	.1663	-.1186E-03	.6500E+05
23	88.00	.1595	.1597	-.2044E-03	.7058E+05
24	92.00	.1531	.1534	-.3122E-03	.7660E+05
25	96.00	.1470	.1474	-.4142E-03	.8309E+05
26	100.0	.1412	.1417	-.4869E-03	.9005E+05

27	104.0	.1357	.1362	-.5106E-03	.9750E+05
28	108.0	.1305	.1310	-.4682E-03	.1054E+06
29	112.0	.1226	.1259	-.3395E-02	.1195E+06
30	116.0	.1206	.1211	-.5284E-03	.1234E+06
31	120.0	.1160	.1165	-.5066E-03	.1334E+06
32	124.0	.1116	.1121	-.4696E-03	.1442E+06
33	128.0	.1075	.1078	-.3081E-03	.1554E+06
34	132.0	.1035	.1037	-.2139E-03	.1676E+06
35	136.0	.9960E-01	.9978E-01	-.1792E-03	.1810E+06
36	140.0	.9590E-01	.9600E-01	-.9691E-04	.1952E+06
37	144.0	.9220E-01	.9236E-01	-.1605E-03	.2112E+06
38	148.0	.8880E-01	.8886E-01	-.6378E-04	.2277E+06
39	152.0	.8540E-01	.8550E-01	-.1010E-03	.2462E+06
40	156.0	.8220E-01	.8227E-01	-.6661E-04	.2657E+06
41	160.0	.7930E-01	.7916E-01	.1445E-03	.2855E+06
42	164.0	.7640E-01	.7616E-01	.2372E-03	.3076E+06
43	168.0	.7350E-01	.7328E-01	.2161E-03	.3324E+06
44	172.0	.7100E-01	.7051E-01	.4858E-03	.3562E+06
45	176.0	.6840E-01	.6785E-01	.5505E-03	.3838E+06
46	180.0	.6590E-01	.6529E-01	.6142E-03	.4134E+06

VI. The following output are the parameter estimation and the original and model estimated data in mean model for the concentration of glucose tracer in blood plasma for total subjects. This model was used for calculation of the statistical moments for the random processes (Chapter 6).

--- C. WLS Estimation Summary---

weighting Information

Option for Y(1): 2 with (1.000 ,.2360E-01) and (10.00 ,.2360)

Convergence achieved

Number of iterations: 52

Number of function calls: 191

Estimator criterion value: 4.92188

Output	R-squared	Weighted Sum of Squares	Sum of Squares
Y(1)	.999	4.92188	.599067E-03

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
A	.3000	.3438	4.113	[.3140 , .3735]
B	.1000E-01	.4577E-01	8.846	[.3726E-01, .5428E-01]
C	.3000	.2907	5.740	[.2556 , .3257]
D	.1000E-01	.9245E-02	4.200	[.8430E-02, .1006E-01]

	A	B	C	D
A	1.00			
B	-.24	1.00		
C	-.60	.90	1.00	
D	-.63	.84	.98	1.00

--- D. Estimated Model Prediction and Data Summary ---

Y(1)

Obs.Num.	Time	Data	Model Est.	Residual	Weight
1	6.000	.5560	.5362	.1981E-01	5808.
2	8.000	.4990	.5083	-.9303E-02	7211.
3	10.00	.4760	.4825	-.6507E-02	7924.
4	12.00	.4520	.4586	-.6626E-02	8788.
5	14.00	.4380	.4365	.1502E-02	9359.
6	16.00	.4160	.4160	.2404E-04	.1038E+05
7	19.00	.3870	.3879	- .9135E-03	.1199E+05
8	22.00	.3650	.3628	.2241E-02	.1348E+05
9	25.00	.3390	.3402	-.1159E-02	.1562E+05
10	30.00	.3110	.3073	.3655E-02	.1856E+05
11	40.00	.2570	.2559	.1087E-02	.2718E+05
12	50.00	.2170	.2179	-.9434E-03	.3813E+05
13	60.00	.1880	.1890	-.9720E-03	.5080E+05

14	70.00	.1680	.1661	.1869E-02	.6361E+05
15	80.00	.1460	.1476	-.1566E-02	.8423E+05
16	90.00	.1320	.1321	-.7141E-04	.1030E+06
17	100.0	.1200	.1188	.1150E-02	.1247E+06
18	110.0	.1070	.1074	-.3678E-03	.1568E+06
19	120.0	.9700E-01	.9726E-01	-.2622E-03	.1908E+06
20	140.0	.7980E-01	.8023E-01	-.4327E-03	.2819E+06
21	160.0	.6700E-01	.6644E-01	.5563E-03	.4000E+06
22	180.0	.5500E-01	.5513E-01	-.1290E-03	.5935E+06

Appendix B

The NAG library programs and output

I. The following is the program which was used to calculate the integrations for the mean concentration of glucose tracer in blood plasma in total subjects (section 5.6).

```
*    Program D01FCF
*    NAG Mark 14 Revised. 1989.
*    .. Parameters ..
     INTEGER          NDIM, MAXPTS, LENWRK
     PARAMETER        (NDIM=4,MAXPTS=40000*NDIM,LENWRK=(NDIM+2)
    +                 *(1+MAXPTS/(2**NDIM+2*NDIM*NDIM+2*NDIM+1)))
     INTEGER          NIN, NOUT
     PARAMETER        (NIN=5,NOUT=6)
*    .. Local Scalars ..
     DOUBLE PRECISION ACC, EPS, FINVAL
     INTEGER          IFAIL, MINPTS,II
*    .. Local Arrays ..
                      DOUBLE PRECISION A(NDIM), B(NDIM),
WRKSTR(LENWRK),A1(NDIM,NDIM),
    + TT(180),PI1,PI,SDET, MU(NDIM), T, SIGMA(NDIM), FAC,
    + INFP, INFM
*    .. External Functions ..
     DOUBLE PRECISION FUNCTN
     EXTERNAL         FUNCTN
*    .. External Subroutines ..
     EXTERNAL         D01FCF
     COMMON A1, MU, SIGMA, T, FAC
*    .. Executable Statements ..
     WRITE (NOUT,*) 'D01FCF Example Program Results'
```

```
      INFP=3.32915D0
      INFM=-3.32915D0
      PI=3.141592653579D0
      PI1=(2.0D0*PI)**(-2)
      SDET=0.281582295285140D0
      FAC=PI1/SDET
      MU(1)=-3.2963893649113120D0
      MU(2)=-4.163966483092740D0
      MU(3)=-4.123128262102940D0
      MU(4)=-0.377619552052800D0
      SIGMA(1)=0.40260338296610D0
      SIGMA(2)=0.823363712571080D0
      SIGMA(3)=0.352277693854120D0
      SIGMA(4)=0.170572963140060D0
      DO 4 i=1,NDIM
    4 B(i)=INFP
      DO 5 i=1,NDIM
    5 A(i)=INFM
*
      A1(1,1)=3.678329602866370D0
      A1(1,2)=-3.376487907477970D0
      A1(1,3)=1.712741391306840D0
      A1(1,4)=-1.290497553369580D0
      A1(2,1)=A1(1,2)
      A1(2,2)=6.445315525926440D0
      A1(2,3)=-4.038580729185090D0
      A1(2,4)=0.184884962273850D0
      A1(3,1)=A1(1,3)
      A1(3,2)=A1(2,3)
      A1(3,3)=3.640336002419940D0
      A1(3,4)=-0.023284412621930D0
```

```
      A1(4,1)=A1(1,4)
      A1(4,2)=A1(2,4)
      A1(4,3)=A1(3,4)
      A1(4,4)=1.776226681738680D0
      DO 3 II=1,181,2
      T=DFLOAT(II-1)
      EPS=0.0001D0
      MINPTS=0
      IFAIL=1
      CALL D01FCF(NDIM,A,B,MINPTS,MAXPTS,FUNCTN,EPS,ACC,LENWRK,
     + WRKSTR, FINVAL,IFAIL)
*
      TT(II)=FINVAL
      IF (IFAIL.EQ.0.OR.IFAIL.EQ.2) THEN
      WRITE (NOUT,99996) T,TT(II)
      ELSE
        WRITE (NOUT,99999) 'IFAIL =', IFAIL
        WRITE (NOUT,*)
      END IF
    3 CONTINUE
*
99999 FORMAT (1X,A,I5)
99996 FORMAT (F3.0,2X,F8.4)
*
      END

      DOUBLE PRECISION FUNCTION FUNCTN(NDIM,Z)
*     .. Scalar Arguments ..
      INTEGER     NDIM
*     .. Array Arguments ..
      DOUBLE PRECISION Z(NDIM),X(4), Y(4), X1, SUM, A1(4,4),
```

```
     +      A,B,P,Q, LAMDA1, LAMDA2, MU(4),SIGMA(4),T, FAC
      COMMON A1, MU, SIGMA, T, FAC
*     .. Intrinsic Functions ..
      INTRINSIC   DEXP, DSQRT
*     .. Executable Statements ..
      DO 2 I=1,NDIM
    2 Y(I)=Z(I)*SIGMA(I)+MU(I)
      DO 3 I=1,NDIM
    3 X(I)=DEXP(Y(I))
      P=X(1)+X(2)+X(3)
      Q=DSQRT(P*P-4.0D0*X(1)*X(3))
      LAMDA1=0.5D0*(P-Q)
      LAMDA2=0.5D0*(P+Q)
      A=0.5D0+0.5D0*(-X(1)+X(2)+X(3))/Q
      B=1.0D0-A
      X1=(A*DEXP(-LAMDA1*T)+B*DEXP(-LAMDA2*T))*X(4)
      SUM=0.0D0
      DO 1 I=1,NDIM
      DO 1 J=1,NDIM
    1 SUM=SUM+Z(I)*Z(J)*A1(I,J)
      FUNCTN=FAC*X1*DEXP(-0.5D0*SUM)
      RETURN
      END
```

II. The following is the program for the calculation of the S. E. of the concentration of glucose tracer in blood plasma in total subjects (section 5.6.5).

```
*    Program D01FCF
*    NAG Mark 14 Revised. 1989.
*    .. Parameters ..
     INTEGER          NDIM, MAXPTS, LENWRK
     PARAMETER        (NDIM=4,MAXPTS=40000*NDIM,LENWRK=(NDIM+2)
    +                 *(1+MAXPTS/(2**NDIM+2*NDIM*NDIM+2*NDIM+1)))
     INTEGER          NIN, NOUT
     PARAMETER        (NIN=5,NOUT=6)
*    .. Local Scalars ..
     DOUBLE PRECISION ACC, EPS, FINVAL
     INTEGER          IFAIL, MINPTS,II
     DIMENSION  AX1(91)
*    .. Local Arrays ..
                      DOUBLE PRECISION A(NDIM), B(NDIM),
WRKSTR(LENWRK),A1(NDIM,NDIM),
    + TT(180),PI1,PI,SDET, MU(NDIM), T, SIGMA(NDIM), FAC, INFP, INFM,
    + AX1 ,TX1
*    .. External Functions ..
     DOUBLE PRECISION FUNCTN
     EXTERNAL         FUNCTN
*    .. External Subroutines ..
     EXTERNAL         D01FCF
     COMMON A1, MU, SIGMA, T, FAC , TX1
*    .. Executable Statements ..
     WRITE (NOUT,*) 'D01FCF Example Program Results'
     INFP=3.32915D0
     INFM=-3.32915D0
     PI=3.141592653579D0
```

```
      PI1=(2.0D0*PI)**(-2)
      SDET=0.281582295285140D0
      FAC=PI1/SDET
      MU(1)=-3.2963893649113120D0
      MU(2)=-4.163966483092740D0
      MU(3)=-4.123128262102940D0
      MU(4)=-0.377619552052800D0
      SIGMA(1)=0.40260338296610D0
      SIGMA(2)=0.823363712571080D0
      SIGMA(3)=0.352277693854120D0
      SIGMA(4)=0.170572963140060D0
      DO 4 I=1,NDIM
    4 B(I)=INFP
      DO 5 I=1,NDIM
    5 A(I)=INFM
*
      A1(1,1)=3.678329602866370D0
      A1(1,2)=-3.376487907477970D0
      A1(1,3)=1.712741391306840D0
      A1(1,4)=-1.290497553369580D0
      A1(2,1)=A1(1,2)
      A1(2,2)=6.445315525926440D0
      A1(2,3)=-4.038580729185090D0
      A1(2,4)=0.184884962273850D0
      A1(3,1)=A1(1,3)
      A1(3,2)=A1(2,3)
      A1(3,3)=3.640336002419940D0
      A1(3,4)=-0.023284412621930D0
      A1(4,1)=A1(1,4)
      A1(4,2)=A1(2,4)
      A1(4,3)=A1(3,4)
```

```
      A1(4,4)=1.776226681738680D0
      READ (*,*) (AX1(I),I=1,91)
      DO 3 II=1,181,2
      TX1=AX1((II+1)/2)
      T=DFLOAT(II-1)
      EPS=0.0001D0
      MINPTS=0
      IFAIL=1

 CALL D01FCF(NDIM,A,B,MINPTS,MAXPTS,FUNCTN,EPS,ACC,LENWRK,
+  WRKSTR, FINVAL,IFAIL)
*
      TT(II)=FINVAL
      IF (IFAIL.EQ.0.OR.IFAIL.EQ.2) THEN
      WRITE (NOUT,99996) T,TT(II),(II+1)/2, TX1
      ELSE
        WRITE (NOUT,99999) 'IFAIL =', IFAIL
        WRITE (NOUT,*)
      END IF
    3 CONTINUE
*
99999 FORMAT (1X,A,I5)
99996 FORMAT  (F8.2,2x,F8.6,I3.1,F6.4)
*
      END

      DOUBLE PRECISION FUNCTION FUNCTN(NDIM,Z)
*     .. Scalar Arguments ..
      INTEGER     NDIM
*     .. Array Arguments ..
      DOUBLE PRECISION Z(NDIM),X(4), Y(4), X1, SUM, A1(4,4),
```

```
     +      A,B,P,Q, LAMDA1, LAMDA2, MU(4),SIGMA(4),T, FAC, TX1
      COMMON A1, MU, SIGMA, T, FAC ,TX1
*     .. Intrinsic Functions ..
      INTRINSIC   DEXP, DSQRT
*     .. Executable Statements ..
      DO 2 I=1,NDIM
    2 Y(I)=Z(I)*SIGMA(I)+MU(I)
      DO 3 I=1,NDIM
    3 X(I)=DEXP(Y(I))
      P=X(1)+X(2)+X(3)
      Q=DSQRT(P*P-4.0D0*X(1)*X(3))
      LAMDA1=0.5D0*(P-Q)
      LAMDA2=0.5D0*(P+Q)
      A=0.5D0+0.5D0*(-X(1)+X(2)+X(3))/Q
      B=1.0D0-A
      X1=(A*DEXP(-LAMDA1*T)+B*DEXP(-LAMDA2*T))*X(4)
      SUM=0.0D0
      DO 1 I=1,NDIM
      DO 1 J=1,NDIM
    1 SUM=SUM+Z(I)*Z(J)*A1(I,J)
      FUNCTN=FAC*((X1-TX1)**2)*DEXP(-0.5D0*SUM)
      RETURN
      END
```

III. The following shows the output of the above program (II) for the even time points.

T	TT(II)	(II+1)/2	TX1
0.00	.013999	1	.6932
2.00	.009444	2	.6394
4.00	.006895	3	.5929
6.00	.005440	4	.5522
8.00	.004598	5	.5167
10.00	.004104	6	.4853
12.00	.003812	7	.4575
14.00	.003634	8	.4325
16.00	.003527	9	.4102
18.00	.003455	10	.3900
20.00	.003407	11	.3717
22.00	.003370	12	.3551
24.00	.003326	13	.3399
26.00	.003304	14	.3259
28.00	.003269	15	.3131
30.00	.003234	16	.3012
32.00	.003193	17	.2901
34.00	.003151	18	.2799
36.00	.003104	19	.2703
38.00	.003056	20	.2613
40.00	.003004	21	.2529
42.00	.002950	22	.2450
44.00	.002894	23	.2375
46.00	.002836	24	.2305
48.00	.002777	25	.2238
50.00	.002715	26	.2174
52.00	.002655	27	.2113
54.00	.002593	28	.2056
56.00	.002530	29	.2001

58.00	.002433	30	.1949
60.00	.002407	31	.1898
62.00	.002342	32	.1850
64.00	.002282	33	.1804
66.00	.002220	34	.1759
68.00	.002160	35	.1716
70.00	.002103	36	.1675
72.00	.002043	37	.1635
74.00	.001985	38	.1596
76.00	.001928	39	.1559
78.00	.001877	40	.1523
80.00	.001818	41	.1488
82.00	.001765	42	.1454
84.00	.001712	43	.1422
86.00	.001662	44	.1390
88.00	.001612	45	.1360
90.00	.001564	46	.1330
92.00	.001518	47	.1301
94.00	.001473	48	.1273
96.00	.001429	49	.1245
98.00	.001386	50	.1218
100.00	.001345	51	.1192
102.00	.001304	52	.1167
104.00	.001264	53	.1142
106.00	.001226	54	.1118
108.00	.001189	55	.1095
110.00	.001153	56	.1072
112.00	.001118	57	.1050
114.00	.001084	58	.1028
116.00	.001052	59	.1007
118.00	.001020	60	.0986

120.00	.000990	61	.0966
122.00	.000960	62	.0946
124.00	.000931	63	.0927
126.00	.000903	64	.0908
128.00	.000873	65	.0890
130.00	.000851	66	.0872
132.00	.000824	67	.0854
134.00	.000800	68	.0837
136.00	.000776	69	.0820
138.00	.000755	70	.0804
140.00	.000731	71	.0788
142.00	.000710	72	.0772
144.00	.000690	73	.0757
146.00	.000669	74	.0742
148.00	.000649	75	.0727
150.00	.000630	76	.0713
152.00	.000612	77	.0699
154.00	.000594	78	.0685
156.00	.000577	79	.0671
158.00	.000560	80	.0658
160.00	.000544	81	.0645
162.00	.000528	82	.0633
164.00	.000513	83	.0620
166.00	.000498	84	.0608
168.00	.000484	85	.0596
170.00	.000471	86	.0585
172.00	.000457	87	.0573
174.00	.000444	88	.0562
176.00	.000432	89	.0551
178.00	.000420	90	.0541
180.00	.000408	91	.0530

IV. The following shows the program for the calculation of the mean concentration of glucose tracer in blood plasma in non-obese subjects (section 5.8).

```
*    Program D01FCF  3/10/96
*    NAG Mark 14 Revised. 1989.
*    .. Parameters ..
     INTEGER          NDIM, MAXPTS, LENWRK
     PARAMETER        (NDIM=4,MAXPTS=20000*NDIM,LENWRK=(NDIM+2)
    +                 *(1+MAXPTS/(2**NDIM+2*NDIM*NDIM+2*NDIM+1)))
     INTEGER          NIN, NOUT
     PARAMETER        (NIN=5,NOUT=6)
*    .. Local Scalars ..
     DOUBLE PRECISION ACC, EPS, FINVAL
     INTEGER          IFAIL, MINPTS,II
*    .. Local Arrays ..
                      DOUBLE PRECISION A(NDIM), B(NDIM),
WRKSTR(LENWRK),A1(NDIM,NDIM),
    + TT(180),PI1,PI,SDET, MU(NDIM), T, SIGMA(NDIM), FAC,
    + INFP, INFM
*    .. External Functions ..
     DOUBLE PRECISION FUNCTN
     EXTERNAL         FUNCTN
*    .. External Subroutines ..
     EXTERNAL         D01FCF
     COMMON A1, MU, SIGMA, T, FAC
*    .. Executable Statements ..
     WRITE (NOUT,*) 'D01FCF Example Program Results'
     INFP=3.32915D0
     INFM=-INFP
     PI=3.141592653579D0
     PI1=(2.0D0*PI)**(-2)
```

```
      SDET=0.28566290943791950D0
      FAC=PI1/SDET
      MU(1)=-3.2346628529019120D0
      MU(2)=-4.2296565424736860D0
      MU(3)=-4.0976398657231830D0
      MU(4)=-0.38311725362959460D0
      SIGMA(1)=0.37715729787689840D0
      SIGMA(2)=0.8147941929577250D0
      SIGMA(3)=0.4032571906708360D0
      SIGMA(4)=0.17702640335519240D0
      DO 4 I=1,NDIM
    4  B(I)=INFP
      DO 5 I=1,NDIM
    5  A(I)=INFM
    *
      A1(1,1)=4.4447873714862840D0
      A1(1,2)=-4.9026164383340780D0
      A1(1,3)=2.7552011527496260D0
      A1(1,4)=-1.6350184796303270D0
      A1(2,1)=A1(1,2)
      A1(2,2)=8.0009214275151810D0
      A1(2,3)=-5.1334443396841550D0
      A1(2,4)=1.3688849071546260D0
      A1(3,1)=A1(1,3)
      A1(3,2)=A1(2,3)
      A1(3,3)=4.462544944432160D0
      A1(3,4)=-0.40348717985764560D0
      A1(4,1)=A1(1,4)
      A1(4,2)=A1(2,4)
      A1(4,3)=A1(3,4)
      A1(4,4)=1.7373850488447230D0
```

```
      DO 3 II=1,181,2
      T=DFLOAT(II-1)
      EPS=0.0001D0
      MINPTS=0
      IFAIL=1
      CALL D01FCF(NDIM,A,B,MINPTS,MAXPTS,FUNCTN,EPS,ACC,LENWRK,
     + WRKSTR, FINVAL,IFAIL)
*
      TT(II)=FINVAL
      IF (IFAIL.EQ.0.OR.IFAIL.EQ.2) THEN
      WRITE (NOUT,99996) T, TT(II)
      ELSE
        WRITE (NOUT,99999) 'IFAIL =', IFAIL
        WRITE (NOUT,*)
      END IF
    3 CONTINUE
*
99999 FORMAT (1X,A,I5)
99996 FORMAT (F6.0,2X, F6.4)
*
      END

      DOUBLE PRECISION FUNCTION FUNCTN(NDIM,Z)
*     .. Scalar Arguments ..
      INTEGER    NDIM
*     .. Array Arguments ..
      DOUBLE PRECISION Z(NDIM),X(4), Y(4), X1, SUM, A1(4,4),
     +     A,B,P,Q, LAMDA1, LAMDA2, MU(4),SIGMA(4),T, FAC
      COMMON A1, MU, SIGMA, T, FAC
*     .. Intrinsic Functions ..
      INTRINSIC   DEXP, DSQRT
```

```
*     .. Executable Statements ..
      DO 2 I=1,NDIM
    2 Y(I)=Z(I)*SIGMA(I)+MU(I)
      DO 3 I=1,NDIM
    3 X(I)=DEXP(Y(I))
      P=X(1)+X(2)+X(3)
      Q=DSQRT(P*P-4.0D0*X(1)*X(3))
      LAMDA1=0.5D0*(P-Q)
      LAMDA2=0.5D0*(P+Q)
      A=0.5D0+0.5D0*(-X(1)+X(2)+X(3))/Q
      B=1.0D0-A
      X1=(A*DEXP(-LAMDA1*T)+B*DEXP(-LAMDA2*T))*X(4)
      SUM=0.0D0
      DO 1 I=1,NDIM
      DO 1 J=1,NDIM
    1 SUM=SUM+Z(I)*Z(J)*A1(I,J)
      FUNCTN=FAC*X1*DEXP(-0.5D0*SUM)
      RETURN
      END
```

V. The following shows the output of the above program (IV) for the even time points.

D01FCF Example Program Results

0.0 .6902
2.0 .6342
4.0 .5856
6.0 .5431
8.0 .5058
10.0 .4728
12.0 .4433
14.0 .4172
16.0 .3938
18.0 .3726
20.0 .3534
22.0 .3361
24.0 .3202
26.0 .3058
28.0 .2924
30.0 .2798
32.0 .2688
34.0 .2583
36.0 .2484
38.0 .2392
40.0 .2308
42.0 .2228
44.0 .2153
46.0 .2083
48.0 .2016
50.0 .1953
52.0 .1893

54.0	.1837
56.0	.1783
58.0	.1732
60.0	.1686
62.0	.1636
64.0	.1591
66.0	.1548
68.0	.1507
70.0	.1467
72.0	.1429
74.0	.1392
76.0	.1357
78.0	.1323
80.0	.1290
82.0	.1258
84.0	.1227
86.0	.1198
88.0	.1169
90.0	.1141
92.0	.1114
94.0	.1088
96.0	.1063
98.0	.1038
100.0	.1014
102.0	.0991
104.0	.0968
106.0	.0946
108.0	.0925
110.0	.0904
112.0	.0883
114.0	.0864

116.0 .0844

118.0 .0826

120.0 .0808

122.0 .0790

124.0 .0773

126.0 .0756

128.0 .0739

130.0 .0723

132.0 .0709

134.0 .0692

136.0 .0677

138.0 .0663

140.0 .0649

142.0 .0635

144.0 .0621

146.0 .0608

148.0 .0595

150.0 .0582

152.0 .0570

154.0 .0558

156.0 .0546

158.0 .0535

160.0 .0523

162.0 .0513

164.0 .0502

166.0 .0491

168.0 .0481

170.0 .0471

172.0 .0461

174.0 .0452

176.0 .0442

178.0 .0433

180.0 .0424

182.0 .0415

VI. The following is the program for the calculation of the S. E. of the concentration of glucose tracer in blood plasma in non-obese subjects (section 5.8.2).

```
*    Program D01FCF 3/10/96
*    NAG Mark 14 Revised. 1989.
*    .. Parameters ..
     INTEGER          NDIM, MAXPTS, LENWRK
     PARAMETER        (NDIM=4,MAXPTS=40000*NDIM,LENWRK=(NDIM+2)
    +                 *(1+MAXPTS/(2**NDIM+2*NDIM*NDIM+2*NDIM+1)))
     INTEGER          NIN, NOUT
     PARAMETER        (NIN=5,NOUT=6)
*    .. Local Scalars ..
     DOUBLE PRECISION ACC, EPS, FINVAL
     INTEGER          IFAIL, MINPTS,II
     DIMENSION AX1(91)
*    .. Local Arrays ..
                      DOUBLE PRECISION A(NDIM), B(NDIM),
WRKSTR(LENWRK),A1(NDIM,NDIM),
    + TT(180),PI1,PI,SDET, MU(NDIM), T, SIGMA(NDIM), FAC,
    + INFP, INFM, AX1,TX1
*    .. External Functions ..
     DOUBLE PRECISION FUNCTN
     EXTERNAL         FUNCTN
*    .. External Subroutines ..
     EXTERNAL         D01FCF
     COMMON A1, MU, SIGMA, T, FAC ,TX1
*    .. Executable Statements ..
     WRITE (NOUT,*) 'D01FCF Example Program Results'
     INFP=3.32915D0
     INFM=-INFP
     PI=3.141592653579D0
```

```
      PI1=(2.0D0*PI)**(-2)
      SDET=0.28566290943791950D0
      FAC=PI1/SDET
      MU(1)=-3.2346628529019120D0
      MU(2)=-4.2296565424736860D0
      MU(3)=-4.0976398657231830D0
      MU(4)=-0.38311725362959460D0
      SIGMA(1)=0.37715729787689840D0
      SIGMA(2)=0.8147941929577250D0
      SIGMA(3)=0.4032571906708360D0
      SIGMA(4)=0.17702640335519240D0
      DO 4 I=1,NDIM
    4 B(I)=INFP
      DO 5 I=1,NDIM
    5 A(I)=INFM
    *
      A1(1,1)=4.4447873714862840D0
      A1(1,2)=-4.9026164383340780D0
      A1(1,3)=2.7552011527496260D0
      A1(1,4)=-1.6350184796303270D0
      A1(2,1)=A1(1,2)
      A1(2,2)=8.0009214275151810D0
      A1(2,3)=-5.1334443396841550D0
      A1(2,4)=1.3688849071546260D0
      A1(3,1)=A1(1,3)
      A1(3,2)=A1(2,3)
      A1(3,3)=4.462544944432160D0
      A1(3,4)=-0.40348717985764560D0
      A1(4,1)=A1(1,4)
      A1(4,2)=A1(2,4)
      A1(4,3)=A1(3,4)
```

```
      A1(4,4)=1.7373850488447230D0
      READ (*,*) (AX1(I),I=1,91)
      DO 3 II=1,181,2
      TX1=AX1((II+1)/2)
      T=DFLOAT(II-1)
      EPS=0.00001D0
      MINPTS=0
      IFAIL=1
 CALL D01FCF(NDIM,A,B,MINPTS,MAXPTS,FUNCTN,EPS,ACC,LENWRK,
+  WRKSTR, FINVAL,IFAIL)
*
      TT(II)=FINVAL
      IF (IFAIL.EQ.0.OR.IFAIL.EQ.2) THEN
      WRITE (NOUT,99996) T,TT(II),(II+1)/2,TX1
      ELSE
        WRITE (NOUT,99999) 'IFAIL =', IFAIL
        WRITE (NOUT,*)
      END IF
    3 CONTINUE
*
99999 FORMAT (1X,A,I5)
99996 FORMAT (F8.2,2X,F6.6,I3.1,F6.4)
*
      END

      DOUBLE PRECISION FUNCTION FUNCTN(NDIM,Z)
*     .. Scalar Arguments ..
      INTEGER     NDIM
*     .. Array Arguments ..
      DOUBLE PRECISION Z(NDIM),X(4), Y(4), X1, SUM, A1(4,4),
     +      A,B,P,Q, LAMDA1, LAMDA2, MU(4),SIGMA(4),T, FAC ,TX1
```

```
      COMMON A1, MU, SIGMA, T, FAC ,TX1
*     .. Intrinsic Functions ..
      INTRINSIC   DEXP, DSQRT
*     .. Executable Statements ..
      DO 2 I=1,NDIM
    2 Y(I)=Z(I)*SIGMA(I)+MU(I)
      DO 3 I=1,NDIM
    3 X(I)=DEXP(Y(I))
      P=X(1)+X(2)+X(3)
      Q=DSQRT(P*P-4.0D0*X(1)*X(3))
      LAMDA1=0.5D0*(P-Q)
      LAMDA2=0.5D0*(P+Q)
      A=0.5D0+0.5D0*(-X(1)+X(2)+X(3))/Q
      B=1.0D0-A
      X1=(A*DEXP(-LAMDA1*T)+B*DEXP(-LAMDA2*T))*X(4)
      SUM=0.0D0
      DO 1 I=1,NDIM
      DO 1 J=1,NDIM
    1 SUM=SUM+Z(I)*Z(J)*A1(I,J)
      FUNCTN=FAC*((X1-TX1)**2)*DEXP(-0.5D0*SUM)
      RETURN
      END
```

VII. The following shows the output of the above program (VI) for even time points.

D01FCF Example Program Results

T	Variance	(II+1)/2	data
0.00	0.014989	1	0.6902
2.00	0.010768	2	0.6342
4.00	0.008349	3	0.5856
6.00	0.006809	4	0.5431
8.00	0.005808	5	0.5058
10.00	0.005139	6	0.4728
12.00	0.004657	7	0.4433
14.00	0.004297	8	0.4172
16.00	0.00402	9	0.3938
18.00	0.003792	10	0.3726
20.00	0.0036	11	0.3534
22.00	0.003437	12	0.3361
24.00	0.003284	13	0.3202
26.00	0.003145	14	0.3058
28.00	0.003016	15	0.2924
30.00	0.002899	16	0.2798
32.00	0.002787	17	0.2688
34.00	0.00268	18	0.2583
36.00	0.00258	19	0.2484
38.00	0.002489	20	0.2392
40.00	0.002395	21	0.2308
42.00	0.002303	22	0.2228
44.00	0.002218	23	0.2153
46.00	0.002136	24	0.2083
48.00	0.002054	25	0.2016
50.00	0.001979	26	0.1953
52.00	0.001905	27	0.1893

54.00	0.001836	28	0.1837
56.00	0.001767	29	0.1783
58.00	0.001701	30	0.1732
60.00	0.001637	31	0.1686
62.00	0.001576	32	0.1636
64.00	0.001516	33	0.1591
66.00	0.001459	34	0.1548
68.00	0.001405	35	0.1507
70.00	0.001352	36	0.1467
72.00	0.001303	37	0.1429
74.00	0.001254	38	0.1392
76.00	0.001206	39	0.1357
78.00	0.001160	40	0.1323
80.00	0.001117	41	0.1290
82.00	0.001075	42	0.1258
84.00	0.001033	43	0.1227
86.00	0.000995	44	0.1198
88.00	0.000958	45	0.1169
90.00	0.000923	46	0.1141
92.00	0.000888	47	0.1114
94.00	0.000855	48	0.1088
96.00	0.000824	49	0.1063
98.00	0.000793	50	0.1038
100.00	0 .000764	51	0.1014
102.00	0.000736	52	0.0991
104.00	0.000709	53	0.0968
106.00	0.000684	54	0.0946
108.00	0.000659	55	0.0925
110.00	0.000635	56	0.0904
112.00	0.000612	57	0.0883
114.00	0.000591	58	0.0864

116.00	0.000568	59	0.0844
118.00	0.000550	60	0.0826
120.00	0.000530	61	0.0808
122.00	0.000512	62	0.0790
124.00	0.000495	63	0.0773
126.00	0.000477	64	0.0756
128.00	0.000461	65	0.0739
130.00	0.000445	66	0.0723
132.00	0.000430	67	0.0709
134.00	0.000415	68	0.0692
136.00	0.000402	69	0.0677
138.00	0.000387	70	0.0663
140.00	0.000374	71	0.0649
142.00	0.000363	72	0.0635
144.00	0.000351	73	0.0621
146.00	0.000339	74	0.0608
148.00	0.000328	75	0.0595
150.00	0.000318	76	0.0582
152.00	0.000308	77	0.0570
154.00	0.000299	78	0.0558
156.00	0.000289	79	0.0546
158.00	0.000279	80	0.0535
160.00	0.000271	81	0.0523
162.00	0.000262	82	0.0513
164.00	0.000254	83	0.0502
166.00	0.000246	84	0.0491
168.00	0.000238	85	0.0481
170.00	0.000231	86	0.0471
172.00	0.000224	87	0.0461
174.00	0.000218	88	0.0452
176.00	0.000211	89	0.0442

178.00	0.000205	90	0.0433
180.00	0.000198	91	0.0424

VIII. The following is the program for the calculation of the mean concentration of glucose tracer in blood plasma in obese subgroup (section 5.9).

```
*    Program D01FCF  3/10/96
*    NAG Mark 14 Revised. 1989.
*    .. Parameters ..
     INTEGER          NDIM, MAXPTS, LENWRK
     PARAMETER        (NDIM=4,MAXPTS=20000*NDIM,LENWRK=(NDIM+2)
    +                 *(1+MAXPTS/(2**NDIM+2*NDIM*NDIM+2*NDIM+1)))
     INTEGER          NIN, NOUT
     PARAMETER        (NIN=5,NOUT=6)
*    .. Local Scalars ..
     DOUBLE PRECISION ACC, EPS, FINVAL
     INTEGER          IFAIL, MINPTS,II
*    .. Local Arrays ..
                      DOUBLE PRECISION A(NDIM), B(NDIM),
WRKSTR(LENWRK),A1(NDIM,NDIM),
    + TT(180),PI1,PI,SDET, MU(NDIM), T, SIGMA(NDIM), FAC,
    + INFP, INFM
*    .. External Functions ..
     DOUBLE PRECISION FUNCTN
     EXTERNAL         FUNCTN
*    .. External Subroutines ..
     EXTERNAL         D01FCF
     COMMON A1, MU, SIGMA, T, FAC
*    .. Executable Statements ..
     WRITE (NOUT,*) 'D01FCF Example Program Results'
     INFP=3.32915D0
     INFM=-INFP
     PI=3.141592653579D0
     PI1=(2.0D0*PI)**(-2)
```

```
      SDET= 0.072237851335872560D0

      FAC=PI1/SDET
      MU(1)=-3.365831690921886D0
      MU(2)=-4.089744242 8510250D0
      MU(3)=-4.151717237941370D0
      MU(4)=-0.37143463777891040D0
      SIGMA(1)=0.44442279920618740D0
      SIGMA(2)=0.8825961170156720D0
     SIGMA(3)=0.30987033651105220D0
      SIGMA(4)=0.1749438050064110D0
      DO 4 I=1,NDIM
4     B(I)=INFP
      DO 5 I=1,NDIM
5     A(I)=INFM
*
      A1(1,1)=10.656851970040990d0
      A1(1,2)=-9.80235845777752D0
      A1(1,3)=8.037064262954582 0D0
      A1(1,4)=-6.6944719145092830D0
      A1(2,1)=A1(1,2)
      A1(2,2)= 16.407386247151220D0
      A1(2,3)=-10.716551712837650D0
      A1(2,4)=2.1745082771824880D0
      A1(3,1)=A1(1,3)
      A1(3,2)=A1(2,3)
      A1(3,3)=9.9891282998062720D0
      A1(3,4)=-5.1246137976021630D0
      A1(4,1)=A1(1,4)
      A1(4,2)=A1(2,4)
      A1(4,3)=A1(3,4)
```

```
      A1(4,4)=8.7849713201665160D0
      DO 3 II=1,1
      T=DFLOAT(II-1)
      EPS=0.0001D0
      MINPTS=0
      IFAIL=1
      CALL D01FCF(NDIM,A,B,MINPTS,MAXPTS,FUNCTN,EPS,ACC,LENWRK,
     + WRKSTR, FINVAL,IFAIL)
*
      TT(II)=FINVAL
      IF (IFAIL.EQ.0.OR.IFAIL.EQ.2) THEN
      WRITE (NOUT,99996) T, TT(II)
      ELSE
        WRITE (NOUT,99999) 'IFAIL =', IFAIL
        WRITE (NOUT,*)
      END IF
    3 CONTINUE
*
99999 FORMAT (1X,A,I5)
99996 FORMAT (F3.1,2X,F6.4)
*
      END
      DOUBLE PRECISION FUNCTION FUNCTN(NDIM,Z)
*     .. Scalar Arguments ..
      INTEGER     NDIM
*     .. Array Arguments ..
      DOUBLE PRECISION Z(NDIM),X(4), Y(4), X1, SUM, A1(4,4),
     +      A,B,P,Q, LAMDA1, LAMDA2, MU(4),SIGMA(4),T, FAC
      COMMON A1, MU, SIGMA, T, FAC
*     .. Intrinsic Functions ..
      INTRINSIC   DEXP, DSQRT
```

```
*     .. Executable Statements ..
      DO 2 I=1,NDIM
    2 Y(I)=Z(I)*SIGMA(I)+MU(I)
      DO 3 I=1,NDIM
    3 X(I)=DEXP(Y(I))
      P=X(1)+X(2)+X(3)
      Q=DSQRT(P*P-4.0D0*X(1)*X(3))
      LAMDA1=0.5D0*(P-Q)
      LAMDA2=0.5D0*(P+Q)
      A=0.5D0+0.5D0*(-X(1)+X(2)+X(3))/Q
      B=1.0D0-A
      X1=(A*DEXP(-LAMDA1*T)+B*DEXP(-LAMDA2*T))*X(4)
      SUM=0.0D0
      DO 1 I=1,NDIM
      DO 1 J=1,NDIM
    1 SUM=SUM+Z(I)*Z(J)*A1(I,J)
      FUNCTN=FAC*X1*DEXP(-0.5D0*SUM)
      RETURN
      END
```

IX. The following shows the output of the above program (VIII) for even time points.

D01FCF Example Program Results

Time	Mean
0.0	.6988
2.0	.6459
4.0	.6004
6.0	.5626
8.0	.5295
10.0	.5001
12.0	.4741
14.0	.4508
16.0	.4299
18.0	.4110
20.0	.3939
22.0	.3783
24.0	.3679
26.0	.3500
28.0	.3384
30.0	.3270
32.0	.3163
34.0	.3086
36.0	.2973
38.0	.2882
40.0	.2801
42.0	.2723
44.0	.2650
46.0	.2580
48.0	.2513
50.0	.2449
52.0	.2387

54.0 .2327

56.0 .2271

58.0 .2217

60.0 .2165

62.0 .2115

64.0 .2067

66.0 .2020

68.0 .1975

70.0 .1932

72.0 .1890

74.0 .1849

76.0 .1810

78.0 .1771

80.0 .1734

82.0 .1698

84.0 .1662

86.0 .1628

88.0 .1595

90.0 .1563

92.0 .1531

94.0 .1500

96.0 .1470

98.0 .1441

100.0 .1412

102.0 .1384

104.0 .1357

106.0 .1330

108.0 .1305

110.0 .1279

112.0 .1255

114.0 .1230

116.0 .1206

118.0 .1182

120.0 .1160

122.00 .1138

124.00 .1116

126.00 .1095

128.00 .1075

130.00 .1055

132.00 .1035

134.00 .1015

136.00 .0996

138.00 .0977

140.00 .0959

142.00 .0940

144.00 .0922

146.00 .0905

148.00 .0888

150.00 .0870

152.00 .0854

154.00 .0838

156.00 .0822

158.00 .0807

160.00 .0793

162.00 .0779

164.00 .0764

166.00 .0748

168.00 .0735

170.00 .0721

172.00 .0710

174.00 .0697

176.00 .0684

178.00 .0671

180.00 .0659

X. The following shows the program for the calculation of the S.E. of concentration of glucose tracer in blood plasma in obese sub-group (section 5.9.2).

```
*    Program D01FCF  3/10/96
*    NAG Mark 14 Revised. 1989.
*    .. Parameters ..
     INTEGER          NDIM, MAXPTS, LENWRK
     PARAMETER        (NDIM=4,MAXPTS=40000*NDIM,LENWRK=(NDIM+2)
    +                 *(1+MAXPTS/(2**NDIM+2*NDIM*NDIM+2*NDIM+1)))
     INTEGER          NIN, NOUT
     PARAMETER        (NIN=5,NOUT=6)
*    .. Local Scalars ..
     DOUBLE PRECISION ACC, EPS, FINVAL
     INTEGER          IFAIL, MINPTS,II
     DIMENSION AX1(91)
*    .. Local Arrays ..
                      DOUBLE PRECISION A(NDIM), B(NDIM),
WRKSTR(LENWRK),A1(NDIM,NDIM),
    + TT(180),PI1,PI,SDET, MU(NDIM), T, SIGMA(NDIM), FAC,
    + INFP, INFM,AX1,TX1
*    .. External Functions ..
     DOUBLE PRECISION FUNCTN
     EXTERNAL         FUNCTN
*    .. External Subroutines ..
     EXTERNAL         D01FCF
     COMMON A1, MU, SIGMA, T, FAC ,TX1
*    .. Executable Statements ..
     WRITE (NOUT,*) 'D01FCF Example Program Results'
     INFP=3.32915D0
     INFM=-INFP
     PI=3.141592653579D0
```

```
      PI1=(2.0D0*PI)**(-2)
      SDET= 0.072237851335872560D0

      FAC=PI1/SDET
      MU(1)=-3.365831690921886D0
      MU(2)=-4.089744241851025OD0
      MU(3)=-4.151717237941370D0
      MU(4)=-0.37143463777891040D0
      SIGMA(1)=0.44442279920618740D0
      SIGMA(2)=0.8825961170156720D0
      SIGMA(3)=0.30987033651105220D0
      SIGMA(4)=0.1749438050064110D0
      DO 4 I=1,NDIM
4     B(I)=INFP
      DO 5 I=1,NDIM
5     A(I)=INFM
*
      A1(1,1)=10.656851970040990d0
      A1(1,2)=-9.80235845777752D0
      A1(1,3)=8.0370642629545820D0
      A1(1,4)=-6.6944719145092830D0
      A1(2,1)=A1(1,2)
      A1(2,2)= 16.407386247151220D0
      A1(2,3)=-10.716551712837650D0
      A1(2,4)=2.1745082771824880D0
      A1(3,1)=A1(1,3)
      A1(3,2)=A1(2,3)
      A1(3,3)=9.9891282998062720D0
      A1(3,4)=-5.1246137976021630D0
      A1(4,1)=A1(1,4)
      A1(4,2)=A1(2,4)
```

```
      A1(4,3)=A1(3,4)
      A1(4,4)=8.7849713201665160D0
      READ (*,*) (AX1(I), I=1,91)
      DO 3 II=1,181,2
      TX1=AX1((II+1)/2)
      T=DFLOAT(II-1)
      EPS=0.00001D0
      MINPTS=0
      IFAIL=1
      CALL D01FCF(NDIM,A,B,MINPTS,MAXPTS,FUNCTN,EPS,ACC,LENWRK,
     + WRKSTR, FINVAL,IFAIL)
*
      TT(II)=FINVAL
      IF (IFAIL.EQ.0.OR.IFAIL.EQ.2) THEN
      WRITE (NOUT,99996) T, TT(II), (II+1)/2,TX1
      ELSE
        WRITE (NOUT,99999) 'IFAIL =', IFAIL
        WRITE (NOUT,*)
      END IF
    3 CONTINUE
*
99999 FORMAT (1X,A,I5)
99996 FORMAT (F8.2,2X,F8.6,I3.1,F6.4)
*
      END

      DOUBLE PRECISION FUNCTION FUNCTN(NDIM,Z)
*     .. Scalar Arguments ..
      INTEGER     NDIM
*     .. Array Arguments ..
      DOUBLE PRECISION Z(NDIM),X(4), Y(4), X1, SUM, A1(4,4),
```

```
     +      A,B,P,Q, LAMDA1, LAMDA2, MU(4),SIGMA(4),T, FAC,TX1
      COMMON A1, MU, SIGMA, T, FAC ,TX1
     *    .. Intrinsic Functions ..
      INTRINSIC   DEXP, DSQRT
     *    .. Executable Statements ..
      DO 2 I=1,NDIM
    2 Y(I)=Z(I)*SIGMA(I)+MU(I)
      DO 3 I=1,NDIM
    3 X(I)=DEXP(Y(I))
      P=X(1)+X(2)+X(3)
      Q=DSQRT(P*P-4.0D0*X(1)*X(3))
      LAMDA1=0.5D0*(P-Q)
      LAMDA2=0.5D0*(P+Q)
      A=0.5D0+0.5D0*(-X(1)+X(2)+X(3))/Q
      B=1.0D0-A
      X1=(A*DEXP(-LAMDA1*T)+B*DEXP(-LAMDA2*T))*X(4)
      SUM=0.0D0
      DO 1 I=1,NDIM
      DO 1 J=1,NDIM
    1 SUM=SUM+Z(I)*Z(J)*A1(I,J)
      FUNCTN=FAC*((X1-TX1)**2)*DEXP(-0.5D0*SUM)
      RETURN
      END
```

XI. The following shows the output for the above (X) program for even time points.

D01FCF Example Program Results

Time	Variance	(II+1)/2	data
0.00	.014743	1	.6988
2.00	.008860	2	.6459
4.00	.006123	3	.6004
6.00	.004551	4	.5626
8.00	.003774	5	.5295
10.00	.003304	6	.5001
12.00	.003120	7	.4741
14.00	.003062	8	.4508
16.00	.003058	9	.4299
18.00	.003116	10	.4110
20.00	.003191	11	.3939
22.00	.003261	12	.3783
24.00	.003338	13	.3679
26.00	.003388	14	.3500
28.00	.003416	15	.3384
30.00	.003445	16	.3270
32.00	.003461	17	.3163
34.00	.003484	18	.3086
36.00	.003463	19	.2973
38.00	.003452	20	.2882
40.00	.003436	21	.2801
42.00	.003401	22	.2723
44.00	.003363	23	.2650
46.00	.003326	24	.2580
48.00	.003279	25	.2513
50.00	.003231	26	.2449
52.00	.003171	27	.2387

54.00	.003103	28	.2327
56.00	.003045	29	.2271
58.00	.002973	30	.2217
60.00	.002905	31	.2165
62.00	.002835	32	.2115
64.00	.002742	33	.2067
66.00	.002673	34	.2020
68.00	.002610	35	.1975
70.00	.002550	36	.1932
72.00	.002487	37	.1890
74.00	.002423	38	.1849
76.00	.002352	39	.1810
78.00	.002270	40	.1771
80.00	.002204	41	.1734
82.00	.002142	42	.1698
84.00	.002087	43	.1662
86.00	.002028	44	.1628
88.00	.001964	45	.1595
90.00	.001909	46	.1563
92.00	.001848	47	.1531
94.00	.001792	48	.1500
96.00	.001730	49	.1470
98.00	.001672	50	.1441
100.00	.001619	51	.1412
102.00	.001569	52	.1384
104.00	.001519	53	.1357
106.00	.001469	54	.1330
108.00	.001418	55	.1305
110.00	.001373	56	.1279
112.00	.001330	57	.1255
114.00	.001285	58	.1230

116.00	.001243	59	.1206
118.00	.001201	60	.1182
120.00	.001162	61	.1160
122.00	.001126	62	.1138
124.00	.001088	63	.1116
126.00	.001053	64	.1095
128.00	.001018	65	.1075
130.00	.000984	66	.1055
132.00	.000951	67	.1035
134.00	.000919	68	.1015
136.00	.000887	69	.0996
138.00	.000857	70	.0977
140.00	.000830	71	.0959
142.00	.000802	72	.0940
144.00	.000776	73	.0922
146.00	.000757	74	.0905
148.00	.000730	75	.0888
150.00	.000701	76	.0870
152.00	.000678	77	.0854
154.00	.000655	78	.0838
156.00	.000634	79	.0822
158.00	.000613	80	.0807
160.00	.000595	81	.0793
162.00	.000575	82	.0779
164.00	.000556	83	.0764
166.00	.000538	84	.0748
168.00	.000522	85	.0735
170.00	.000506	86	.0721
172.00	.000488	87	.0710
174.00	.000472	88	.0697
176.00	.000461	89	.0684

178.00	.000446	90	.0671
180.00	.000432	91	.0659

XII. The following program is for the calculation of a two dimensional definite integration of the statistical moments of the random process. (section 6.7).

```
*    D01FCF Example Program Text
*    Mark 14 Revised.  NAG Copyright 1989.
*    .. Parameters ..
     INTEGER          NDIM, MAXPTS, LENWRK
     PARAMETER        (NDIM=2,MAXPTS=1000*NDIM,LENWRK=(NDIM+2)
    +                 *(1+MAXPTS/(2**NDIM+2*NDIM*NDIM+2*NDIM+1)))
     INTEGER          NOUT
     PARAMETER        (NOUT=6)
*    .. Local Scalars ..
     DOUBLE PRECISION ACC, EPS, FINVAL
     INTEGER          IFAIL, MINPTS
*    .. Local Arrays ..
     DOUBLE PRECISION A(NDIM),B(NDIM),WRKSTR(LENWRK)
*    .. External Functions ..
     DOUBLE PRECISION FUNCTN
     EXTERNAL         FUNCTN
*    .. External Subroutines ..
     EXTERNAL         D01FCF
*    .. Executable Statements ..
     WRITE (NOUT,*) 'D01FCF Example Program Results'

       A(1)=0.0D0
       B(1)=3.0D0
       A(2)=0.0d0
       B(2)=3.0d0

     EPS = 0.0001D0
     MINPTS = 0
```

```
      IFAIL =1
      CALL
     D01FCF(NDIM,A,B,MINPTS,MAXPTS,FUNCTN,EPS,ACC,LENWRK,WRKSTR,
     +           FINVAL,IFAIL)
     *
      WRITE (NOUT,*)
      IF (IFAIL.NE.0) THEN
        WRITE (NOUT,99999) 'IFAIL =', IFAIL
        WRITE (NOUT,*)
      END IF
      IF (IFAIL.EQ.0 .OR. IFAIL.GE.2) THEN
       WRITE (NOUT,99998) 'Requested accuracy = ', EPS
        WRITE (NOUT,99997) 'Estimated value    = ', FINVAL
        WRITE (NOUT,99998) 'Estimated accuracy = ', ACC
      END IF


     99999 FORMAT (1X,A,I5)
     99998 FORMAT (1X,A,D12.2)
     99997 FORMAT (1X,A,F22.20)
      END

      DOUBLE PRECISION FUNCTION FUNCTN(NDIM,Z)
     *  .. Scalar Arguments ..
      INTEGER                  NDIM
     *  .. Array Arguments ..
      DOUBLE PRECISION  Z(NDIM),t,s,r,PI,A,B,C,D,M1,M2,SIG1,SIG2
     *  .. Intrinsic Functions ..
      INTRINSIC                DEXP,DSQRT

     *  .. Executable Statements ..
```

```
T=100.0d0
S=70.d0
r=0.988738d0
PI=3.141592654D0
SIG1=-.000069*T+.017206
SIG2=-.000069*S+.017206
M1=.3438*DEXP(-.04577*T)+0.2907*DEXP(-0.009245*T)
M2=.3438*DEXP(-.04577*S)+0.2907*DEXP(-0.009245*S)
A=1/(2*PI*SIG1*SIG2*DSQRT(1-R**2))
B=(Z(1)-M1)/SIG1
C=(Z(2)-M2)/SIG2
D=1/(2*(1-R**2))
FUNCTN =A*Z(1)*Z(2)*DEXP(-D*(B**2-2*R*B*C+C**2))
RETURN
END
```

XIII. The following is a program for a discrete integration for calculation of h(t) and σ^2 (section 6.8).

```
*    D01GAF Example Program Text
*    Mark 14 Revised.  NAG Copyright 1989.
*    .. Parameters ..
     INTEGER          NMAX
     PARAMETER        (NMAX=25)
     INTEGER          NIN, NOUT
     PARAMETER        (NIN=5,NOUT=6)
*    .. Local Scalars ..
     DOUBLE PRECISION ANS, ERROR
     INTEGER          I, IFAIL, N
*    .. Local Arrays ..
     DOUBLE PRECISION X(NMAX), Y(NMAX)
*    .. External Subroutines ..
     EXTERNAL         D01GAF
*    .. Executable Statements ..
     WRITE (NOUT,*) 'D01GAF Example Program Results'
*    Skip heading in data file
     READ (NIN,*)
     READ (NIN,*) N
     WRITE (NOUT,*)
     IF (N.LE.NMAX) THEN
       READ (NIN,*) (X(I),Y(I),I=1,N)
       IFAIL = 0
*
       CALL D01GAF(X,Y,N,ANS,ERROR,IFAIL)
*
       IF (IFAIL.EQ.0) THEN
         WRITE (NOUT,99999) 'Integral = ', ANS, +  '    Estimated error = ', ERROR
```

```
      ELSE IF (IFAIL.EQ.1) THEN
        WRITE (NOUT,*) 'Less than 4 points supplied'
      ELSE IF (IFAIL.EQ.2) THEN
        WRITE (NOUT,*)
     +    'Points not in increasing or decreasing order'
      ELSE IF (IFAIL.EQ.3) THEN
        WRITE (NOUT,*) 'Points not all distinct'
      END IF
    ELSE
      WRITE (NOUT,*) 'More than NMAX data points'
    END IF
    STOP
*
99999 FORMAT (1X,A,F7.4,A,F7.4)
    END
```

XIV. This program integrates a set of first order differential equations by the method of Hall and Watt to calculate the concentration of glucose tracer in blood plasma and extravascular tissues (section 6.10).

```
*    D02BBF Example Program Text
*    Mark 14 Revised.  NAG Copyright 1989.
*    .. Parameters ..
     INTEGER          NOUT
     PARAMETER        (NOUT=6)
     INTEGER          N
     PARAMETER        (N=2)
*    .. Scalars in Common ..
     DOUBLE PRECISION H, XEND,TIME(27),G1(27)
     INTEGER          I
*    .. Local Scalars ..
     DOUBLE PRECISION TOL, X
     INTEGER          IFAIL, IR,J
*    .. Local Arrays ..
     DOUBLE PRECISION W(N,7), Y(N)
*    .. External Functions ..
     DOUBLE PRECISION X01AAF
     EXTERNAL         X01AAF
*    .. External Subroutines ..
     EXTERNAL         D02BBF, FCN, OUT,INTPOL
*    .. Intrinsic Functions ..
     INTRINSIC        DBLE
*    .. Common blocks ..
     COMMON           XEND, H, I,TIME,G1
*    .. Executable Statements ..
      TIME(1)=0.0D0
      TIME(2)=2.0D0
```

```
TIME(3)=3.0D0
TIME(4)=4.0D0
TIME(5)=5.0D0
TIME(6)=6.0D0
TIME(7)=8.0D0
TIME(8)=10.0D0
TIME(9)=12.0D0
TIME(10)=14.0D0
TIME(11)=16.0D0
TIME(12)=19.0D0
TIME(13)=22.0d0
TIME(14)=25.0D0
TIME(15)=30.0D0
TIME(16)=40.0D0
TIME(17)=50.0D0
TIME(18)=60.0D0
TIME(19)=70.0D0
TIME(20)=80.0D0
TIME(21)=90.0D0
TIME(22)=100.0D0
TIME(23)=110.0D0
TIME(24)=120.0D0
TIME(25)=140.0D0
TIME(26)=160.0D0
TIME(27)=180.0D0
G1(1)=1.1715D0
G1(2)=0.7349D0
G1(3)=0.5625D0
G1(4)=0.3902D0
G1(5)=0.2178D0
G1(6)=.2405D0
```

```
G1(7)=-1.1485D0
G1(8)=-0.0818D0
G1(9)=1.0319D0
G1(10)=1.1847D0
G1(11)=0.5945D0
G1(12)=-1.5815D0
G1(13)=-1.5048D0
G1(14)=-1.6382D0
G1(15)=-1.3433D0
G1(16)=-1.3511D0
G1(17)=-2.1115D0
G1(18)=-1.81D0
G1(19)=-1.9668D0
G1(20)=-1.5743D0
G1(21)=-1.4537D0
G1(22)=-1.0461D0
G1(23)=-0.9249D0
G1(24)=-0.5765D0
G1(25)=-0.4685D0
G1(26)=-0.5434D0
G1(27)=0.0D0
WRITE (NOUT,*) 'D02BBF Example Program Results'
IR = 0
XEND = 180.0D0
DO 20 J = 4,4
  TOL = 10.0D0**(-J)
  WRITE (NOUT,*)
  WRITE (NOUT,99999) 'Calculation with TOL =', TOL
  WRITE (NOUT,*) '    T        Y(1)        Y(2)'
  X =0.0D0
  Y(1) =0.694756D0
```

```
      Y(2) =0.0D0
      I =179
      H = (XEND-X)/DBLE(I+1)
      IFAIL =0
    CALL D02BBF(X,XEND,N,Y,TOL,IR,FCN,OUT,W,IFAIL)
*
      IF (TOL.LT.0.0D0) WRITE (NOUT,*) ' Range too short for TOL'
  20 CONTINUE
    STOP
*
99999 FORMAT (1X,A,D8.1)
    END
*
    SUBROUTINE FCN(X,Y,F)
*    .. Parameters ..
    INTEGER       N
    PARAMETER     (N=2)
*    .. Scalar Arguments ..
    DOUBLE PRECISION X,TIME(27),G1(27),G
*    .. Array Arguments ..
    DOUBLE PRECISION F(N), Y(N)
    COMMON TIME,G1
*    .. Executable Statements ..
    CALL INTPOL (G,X)
    F(1)=-(0.0368183736986+0.0024963946*G)*Y(1)+(0.02090677+
   + 0.00184714*G)*Y(2)
    F(2)=(0.03601519236893+0.0031819954*G)*Y(1)-(0.03734279+
   + 0.00254272*G)*Y(2)
    RETURN
    END
*
```

```
      SUBROUTINE OUT(X,Y)
*     .. Parameters ..
      INTEGER       NOUT
      PARAMETER     (NOUT=6)
      INTEGER       N
      PARAMETER     (N=2)
*     .. Scalar Arguments ..
      DOUBLE PRECISION X
*     .. Array Arguments ..
      DOUBLE PRECISION Y(N)
*     .. Scalars in Common ..
      DOUBLE PRECISION H, XEND,TIME(27),G1(27)
      INTEGER       I
*     .. Local Scalars ..
      INTEGER       J
*     .. Intrinsic Functions ..
      INTRINSIC     DBLE
*     .. Common blocks ..
      COMMON        XEND, H, I,TIME,G1
*     .. Executable Statements ..
      WRITE (NOUT,99999) X, (Y(J),J=1,2)
      X = XEND - DBLE(I)*H
      I = I - 1
      RETURN
*
99999 FORMAT (1X,F7.2,2F13.5)
      END
*
      SUBROUTINE INTPOL(G,T)
      DOUBLE PRECISION TIME(27),G1(27),T,G,GG1,GG2,T1,T2
      COMMON XEND,H,I,TIME,G1
```

```
      DO 1 I=1,26
      T1=TIME(I)
      T2=TIME(I+1)
      GG1=G1(I)
      GG2=G1(I+1)
      IF(T.GT.T1.AND.T.LT.T2) THEN
      G=(T-T1)*(GG2-GG1)/(T2-T1)+GG1
      GO TO 2
      END IF
1     CONTINUE
2     RETURN
      END
```

XV. The following is the result of the above set of first order differential equations for the calculation of glucose tracer in blood plasma and extravascular tissues. For simplicity only even times were considered (section 6.10).

D02BBF Example Program Results

T	Y(1)	Y(2)
0	0.69476	0.0000
2	0.64352	0.05015
3	0.62058	0.07183
4	0.59919	0.09156
5	0.57921	0.10952
6	0.5604	0.12601
8	0.5271	0.15361
10	0.49759	0.17655
12	0.4691	0.19827
14	0.44257	0.2176
16	0.41912	0.23319
18	0.39911	0.24466
19	0.39036	0.24892
20	0.38217	0.25253
22	0.36675	0.2587
24	0.35244	0.26365
25	0.34574	0.26564
26	0.33928	0.26736
28	0.32702	0.27012
30	0.31554	0.27208
32	0.30482	0.27328
34	0.29484	0.27375
36	0.28552	0.27357
38	0.27678	0.27287

40	0.26859	0.27168
42	0.26089	0.27007
44	0.25365	0.26809
46	0.24683	0.26577
48	0.2404	0.26318
50	0.23431	0.26037
52	0.22851	0.25737
54	0.22295	0.25425
56	0.21762	0.25102
58	0.2125	0.24769
60	0.20758	0.24429
62	0.20284	0.24083
64	0.19829	0.23731
66	0.1939	0.23375
68	0.18967	0.23016
70	0.18559	0.22655
72	0.18164	0.22294
74	0.1778	0.21933
76	0.17408	0.21573
78	0.17047	0.21215
80	0.16695	0.20858
82	0.16353	0.20503
84	0.16019	0.20152
86	0.15694	0.19803
88	0.15377	0.19457
90	0.1507	0.19115
92	0.1477	0.18777
94	0.14477	0.18442
96	0.14191	0.18112
98	0.13912	0.17786
100	0.13639	0.17464

102	0.13372	0.17146
104	0.1311	0.16833
106	0.12854	0.16525
108	0.12604	0.16221
110	0.12359	0.15922
112	0.12119	0.15627
114	0.11885	0.15337
116	0.11656	0.15052
118	0.11431	0.14772
120	0.11211	0.14496
122	0.10996	0.14225
124	0.10784	0.13958
126	0.10577	0.13696
128	0.10375	0.13439
130	0.10176	0.13186
132	0.0998	0.12938
134	0.09789	0.12694
136	0.09602	0.12454
138	0.09418	0.12219
140	0.09238	0.11988
142	0.09062	0.11761
144	0.08889	0.11539
146	0.08719	0.1132
148	0.08553	0.11106
150	0.0839	0.10895
152	0.0823	0.10689
154	0.08073	0.10486
156	0.0792	0.10288
158	0.07769	0.10093
160	0.07621	0.09901
162	0.07476	0.09714

164	0.07334	0.0953
166	0.07194	0.09349
168	0.07057	0.09172
170	0.06923	0.08998
172	0.06792	0.08827
174	0.06663	0.0866
176	0.06536	0.08495
178	0.06412	0.08334
180	0.0629	0.08176

Stop - Program terminated.

Appendix C: Tables of the data and results

Time	Subject								
(min)	1	2	3	4	5	6	7	8	9
2	0.78	0.54	0.77	0.48	0.73	0.68	0.59	0.64	0.65
3	0.76	0.50	0.60	0.57	0.63	0.52	0.62	0.62	0.58
4	0.67	0.48	0.61	0.54	0.61	0.50	0.56	0.54	0.54
5	0.60	0.49	0.60	0.52	0.58	0.51	0.54	0.52	0.55
6	0.58	0.44	0.50	0.59	0.55	0.53	0.60	0.50	0.53
8	0.55	0.42	0.45	0.42	0.58	0.49	*	0.44	0.46
10	0.49	0.41	0.42	0.41	0.54	0.47	0.50	0.42	0.48
12	0.47	0.40	0.38	0.40	0.47	0.47	0.46	0.41	0.46
14	0.46	0.39	0.35	0.48	0.44	0.46	0.46	0.38	0.41
16	0.44	0.36	0.33	0.45	0.41	0.44	0.43	0.37	0.41
19	0.44	0.36	0.28	0.42	0.34	0.40	*	0.34	0.35
22	0.42	0.34	0.28	0.42	0.29	0.38	0.39	0.33	0.34
25	0.40	0.33	0.25	0.43	0.27	0.36	*	0.32	0.30
30	0.37	0.31	0.22	0.35	0.20	0.35	*	0.29	0.28
40	0.33	0.28	0.16	0.29	0.16	0.27	*	0.25	0.19
50	0.27	0.25	0.13	0.25	0.14	0.22	0.27	0.22	0.18
60	0.24	0.21	0.11	0.21	0.11	0.18	0.23	0.19	0.15
70	0.20	0.20	0.08	0.21	0.10	0.17	*	0.16	0.13
80	0.18	0.17	0.07	0.16	0.08	0.15	0.18	0.15	0.12
90	0.16	*	0.06	0.17	0.08	0.15	0.16	0.14	0.11
100	0.14	0.14	0.07	0.14	0.08	0.12	0.15	0.12	0.10
110	0.13	0.12	0.06	0.13	0.07	0.11	0.13	0.11	0.09
120	0.12	0.10	0.05	0.12	0.07	0.09	*	0.11	0.08
140	0.10	0.09	0.04	0.10	0.05	0.08	0.11	0.09	0.07
160	0.08	0.07	0.04	0.08	0.04	0.07	0.10	0.08	0.06
180	0.07	0.06	0.02	0.06	0.04	0.05	0.07	0.07	0.05

Table C_1 : Distribution of blood glucose tracer (mmol/l) following an IVGTT. The symbol * demonstrates missing data.

Time	Subject							
(min)	10	11	12	13	14	15	16	17
2	0.79	0.71	0.83	0.81	0.88	0.60	0.97	0.48
3	0.67	0.67	0.73	0.77	0.73	*	0.67	0.45
4	0.65	0.62	0.63	0.68	0.69	*	0.82	0.46
5	0.58	0.58	0.57	0.65	0.64	*	0.69	0.45
6	0.56	0.56	0.54	0.63	0.60	0.55	0.77	0.43
8	0.52	0.50	0.53	0.59	0.57	0.42	0.69	0.39
10	0.50	0.46	0.50	0.54	0.55	0.41	0.64	0.35
12	0.47	0.43	0.46	0.44	0.53	0.46	0.63	0.35
14	0.44	0.38	0.43	0.51	0.51	0.42	0.59	0.33
16	0.41	0.37	*	0.46	0.47	0.44	0.57	0.31
19	0.38	0.35	0.37	*	0.45	0.41	0.55	0.29
22	0.35	0.33	0.34	*	0.42	0.40	0.50	*
25	0.31	0.29	0.30	*	0.35	0.36	0.49	0.25
30	0.27	0.26	0.28	0.36	0.38	0.33	0.46	0.23
40	0.24	0.20	0.23	0.29	0.29	0.29	0.41	0.19
50	0.19	0.16	0.18	*	0.21	0.27	0.37	0.16
60	0.17	0.14	0.14	0.19	*	0.23	0.34	0.15
70	0.14	0.13	0.13	0.15	0.18	0.20	0.34	0.12
80	0.13	0.11	0.11	0.13	0.18	0.18	0.28	0.10
90	0.10	0.09	*	0.11	0.15	0.15	0.27	0.09
100	0.10	0.09	0.09	0.10	0.14	0.14	0.24	0.08
110	0.09	0.07	0.09	0.08	0.12	*	0.21	0.07
120	0.08	0.07	0.07	0.07	0.11	0.12	0.19	0.07
140	0.06	0.05	0.06	0.05	0.09	*	0.17	0.05
160	0.05	0.05	0.05	0.04	0.08	0.08	0.13	0.04
180	0.04	0.04	0.04	0.03	0.07	0.07	0.11	0.04

Table C_1 : Continued.

Subject	Time (min)								
No	2	3	4	5	6	8	10	12	14
1	0.78	0.76	0.67	0.60	0.58	0.55	0.49	0.47	0.46
2	0.54	0.50	0.48	0.49	0.44	0.42	0.41	0.40	0.39
3	0.77	0.60	0.61	0.60	0.50	0.45	0.42	0.38	0.35
4	0.48	0.57	0.54	0.52	0.59	0.42	0.41	0.40	0.48
5	0.73	0.63	0.61	0.58	0.55	0.58	0.54	0.47	0.44
6	0.68	0.52	0.50	0.51	0.53	0.49	0.47	0.47	0.46
7	0.59	0.62	0.56	0.54	0.60	0.52	0.50	0.46	0.46
8	0.64	0.62	0.54	0.52	0.50	0.44	0.42	0.41	0.38
9	0.65	0.58	0.54	0.55	0.53	0.46	0.48	0.46	0.41
10	0.79	0.67	0.65	0.58	0.56	0.52	0.50	0.47	0.44
11	0.71	0.67	0.62	0.58	0.56	0.50	0.46	0.43	0.38
12	0.83	0.73	0.63	0.57	0.54	0.53	0.50	0.46	0.43
13	0.81	0.77	0.68	0.65	0.63	0.59	0.54	0.44	0.51
14	0.88	0.73	0.69	0.64	0.60	0.57	0.55	0.53	0.51
15	0.60	0.52	0.51	0.50	0.55	0.42	0.41	0.46	0.42
16	0.97	0.67	0.82	0.69	0.77	0.69	0.64	0.63	0.59
17	0.48	0.45	0.46	0.45	0.43	0.39	0.35	0.35	0.33
μ	0.70	0.62	0.59	0.53	0.56	0.50	0.48	0.45	0.44

Table C_2 : Distribution of glucose tracer concentration in blood plasma following an IVGTT.

Subject	Time (min)								
No	16	19	22	25	30	40	50	60	70
1	0.44	0.44	0.42	0.40	0.37	0.33	0.27	0.24	0.20
2	0.36	0.36	0.34	0.33	0.31	0.28	0.25	0.21	0.20
3	0.33	0.28	0.28	0.25	0.22	0.16	0.13	0.11	0.08
4	0.45	0.42	0.42	0.43	0.35	0.29	0.25	0.21	0.21
5	0.41	0.34	0.29	0.27	0.20	0.16	0.14	0.11	0.10
6	0.44	0.40	0.38	0.36	0.35	0.27	0.22	0.18	0.17
7	0.43	0.42	0.39	0.38	0.35	0.30	0.27	0.23	0.21
8	0.37	0.34	0.33	0.32	0.29	0.25	0.22	0.19	0.16
9	0.41	0.35	0.34	0.30	0.28	0.19	0.18	0.15	0.13
10	0.41	0.38	0.35	0.31	0.27	0.24	0.19	0.17	0.14
11	0.37	0.35	0.33	0.29	0.26	0.20	0.16	0.14	0.13
12	0.40	0.37	0.34	0.30	0.28	0.23	0.18	0.14	0.13
13	0.46	0.43	0.40	0.37	0.36	0.29	0.22	0.19	0.15
14	0.47	0.45	0.42	0.35	0.38	0.29	0.21	0.20	0.18
15	0.44	0.41	0.40	0.36	0.33	0.29	0.27	0.23	0.20
16	0.57	0.55	0.50	0.49	0.46	0.41	0.37	0.34	0.34
17	0.31	0.29	0.27	0.25	0.23	0.19	0.16	0.15	0.12
μ	0.42	0.39	0.36	0.34	0.31	0.25	0.22	0.19	0.17

Table C_2 : Continued.

Subject	Time (min)							
No	80	90	100	110	120	140	160	180
1	0.18	0.16	0.14	0.14	0.12	0.10	0.08	0.07
2	0.17	0.16	0.14	0.12	0.10	0.09	0.07	0.06
3	0.07	0.06	0.07	0.06	0.05	0.04	0.04	0.02
4	0.16	0.17	0.14	0.13	0.12	0.10	0.08	0.06
5	0.08	0.08	0.08	0.07	0.07	0.05	0.04	0.04
6	0.15	0.15	0.12	0.11	0.09	0.08	0.07	0.05
7	0.18	0.16	0.15	0.13	0.13	0.11	0.10	0.07
8	0.15	0.14	0.12	0.11	0.11	0.09	0.08	0.07
9	0.12	0.11	0.10	0.09	0.08	0.07	0.06	0.05
10	0.13	0.10	0.10	0.09	0.08	0.06	0.05	0.04
11	0.11	0.09	0.09	0.07	0.07	0.05	0.05	0.04
12	0.11	0.10	0.09	0.09	0.07	0.06	0.05	0.04
13	0.13	0.11	0.10	0.08	0.07	0.05	0.04	0.03
14	0.18	0.15	0.14	0.12	0.11	0.09	0.08	0.07
15	0.18	0.15	0.14	0.13	0.12	0.10	0.08	0.07
16	0.28	0.27	0.24	0.21	0.19	0.17	0.13	0.11
17	0.10	0.09	0.08	0.07	0.07	0.05	0.04	0.04
μ	0.14	0.13	0.12	0.11	0.10	0.08	0.07	0.05

Table C_2 : Continued.

Time Min	Det mmol/l	Stoch mmol/	Time Min	Det mmol/l	Stoch mmol/l	Time Min	Det mmol/l	Stoch mmol/l
0	0.6948	0.6932	62	0.196	0.185	124	0.1047	0.0927
2	0.6429	0.6394	64	0.1917	0.1804	126	0.1027	0.0908
4	0.597	0.5929	66	0.1876	0.1759	128	0.1007	0.089
6	0.5564	0.5522	68	0.1836	0.1716	130	0.0988	0.0872
8	0.5204	0.5167	70	0.1797	0.1675	132	0.0969	0.0854
10	0.4884	0.4853	72	0.176	0.1635	134	0.095	0.0837
12	0.46	0.4575	74	0.1723	0.1596	136	0.0931	0.082
14	0.4345	0.4325	76	0.1688	0.1559	138	0.0913	0.0804
16	0.4117	0.4102	78	0.1654	0.1523	140	0.0896	0.0788
18	0.3913	0.39	80	0.162	0.1488	142	0.0878	0.0772
20	0.3729	0.3717	82	0.1587	0.1454	144	0.0861	0.0757
22	0.3563	0.3551	84	0.1555	0.1422	146	0.0845	0.0742
24	0.3412	0.3399	86	0.1524	0.139	148	0.0828	0.0727
26	0.3275	0.3259	88	0.1494	0.132	150	0.0812	0.0713
28	0.315	0.3131	90	0.1464	0.133	152	0.0797	0.0699
30	0.3035	0.3012	92	0.1435	0.1301	154	0.0781	0.0685
32	0.293	0.2901	94	0.1407	0.1273	156	0.0766	0.0671
34	0.2833	0.2799	96	0.1379	0.1245	158	0.0751	0.0658
36	0.2743	0.2703	98	0.1352	0.1218	160	0.0737	0.0645
38	0.2659	0.2613	100	0.1326	0.1192	162	0.0723	0.0633
40	0.2581	0.2529	102	0.13	0.1167	164	0.0709	0.062
42	0.2508	0.245	104	0.1274	0.1142	166	0.0695	0.0608
44	0.244	0.2375	106	0.125	0.1118	168	0.0682	0.0608
46	0.244	0.2305	108	0.1225	0.1095	170	0.0668	0.0585
48	0.2314	0.2238	110	0.1201	0.1072	172	0.0656	0.0573
50	0.2256	0.2174	112	0.1178	0.105	174	0.0643	0.0562
52	0.2201	0.2113	114	0.1155	0.1028	176	0.063	0.0551
54	0.2149	0.2056	116	0.1133	0.1007	178	0.0618	0.0541
56	0.2099	0.2001	118	0.1111	0.0986	180	0.0606	0.053
58	0.205	0.1949	120	0.1089	0.0966			
60	0.2004	0.1898	122	0.1068	0.0946			

Table C_3: The stochastic (Stoch) and deterministic (Det) values for the mean concentration of glucose tracer in blood plasma at times between 0 and 180 minutes (total subjects).

Time (min)	S1	S2	D1	D2	Time (min)	S1	S2	D1	D2
0	0.6902	0.6988	0.6909	0.6992	92	0.1114	0.1531	0.1295	0.1607
4	0.5856	0.6004	0.5893	0.6058	96	0.1063	0.147	0.1241	0.1549
8	0.5058	0.5295	0.5101	0.5322	100	0.1014	0.1412	0.119	0.1494
12	0.4433	0.4741	0.4478	0.4739	104	0.0968	0.1357	0.114	0.144
16	0.3938	0.4299	0.3984	0.4271	108	0.0925	0.1305	0.1093	0.1389
20	0.3534	0.3939	0.3587	0.3893	112	0.0883	0.1255	0.1048	0.134
24	0.3202	0.3679	0.3265	0.3583	116	0.0844	0.1206	0.1005	0.1292
28	0.2924	0.3384	0.2999	0.3325	120	0.0808	0.116	0.0963	0.1247
32	0.2688	0.3163	0.2777	0.3109	124	0.0773	0.1116	0.0924	0.1203
36	0.2484	0.2973	0.2589	0.2923	128	0.0739	0.1075	0.0886	0.116
40	0.2308	0.2801	0.2427	0.2763	132	0.0709	0.1055	0.0814	0.1119
44	0.2153	0.265	0.2285	0.2622	136	0.0677	0.0996	0.0781	0.108
48	0.2016	0.2513	0.216	0.2497	140	0.0649	0.0959	0.0749	0.1042
52	0.1893	0.2387	0.2047	0.2497	144	0.0621	0.0922	0.0718	0.1005
56	0.1783	0.2271	0.1946	0.2281	148	0.0595	0.0888	0.0718	0.0969
60	0.1686	0.2165	0.1852	0.2186	152	0.057	0.0854	0.0689	0.0935
64	0.1591	0.2067	0.1766	0.2098	156	0.0546	0.0822	0.066	0.0902
68	0.1507	0.1975	0.1686	0.2016	160	0.0523	0.0793	0.0633	0.087
72	0.1429	0.189	0.1686	0.1939	164	0.0502	0.0764	0.0607	0.084
76	0.1357	0.181	0.1541	0.1866	168	0.0481	0.0735	0.0582	0.081
80	0.129	0.1734	0.1475	0.1796	172	0.0461	0.071	0.0558	0.0782
84	0.1227	0.1662	0.1412	0.173	176	0.0442	0.0684	0.0536	0.0754
88	0.1169	0.1595	0.1352	0.1667	180	0.0424	0.0659	0.0514	0.0728

Table C_4: The stochastic values in non-obese (S1) and obese (S2) subjects along with the deterministic values in non-obese (D1) and obese (D2) subjects for the concentration of glucose tracer in blood plasma at times between time 0 to 180 minutes.

N.B. The units for S1, S2, D1 and D2 are mmo/l.

APPENDIX D:The calculation of the PDF for the concentration of the first compartment in Soong's two-compartmental model .

The following is the calculation of the PDF of the concentration in the first compartment in a two- compartmental model which stochasticity was incorporated into the transfer rates of k_{12} and k_{21} between compartments. The author would like to acknowledge to Dr. Tom Hennessy for his co-operation in finding the results.

We can write from equations 5.3 and 5.4:

$$U_1(t) = \frac{k_{12} + k_{21} e^{-(k_{12}+k_{21})t}}{k_{12}+k_{21}} \qquad (1)$$

We require $E(U_1(t))$ when k_{21} , k_{12} have a truncated bivariate normal distribution of Φ_0 (k_{12}, k_{21}) where

$$\Phi_0(k_{12}, k_{21}) = \frac{1}{2\pi\sqrt{(1-\rho^2)}\sigma_1\sigma_2} e^{-\frac{1}{2(1-\rho^2)}\left[\frac{(k_{12}-\mu_1)^2}{\sigma_1} - \frac{2\rho(k_{12}-\mu_1)(k_{21}-\mu_2)}{\sigma_1\sigma_2} + \frac{(k_{21}-\mu_2)^2}{\sigma_2}\right]} \qquad (2)$$

To find the distribution function for $U_1(t)$, $F_{U1}(t)$, we write:

$$F_{U_1}(u_1 \le \nu) = P\left(\frac{k_{12} + k_{21}e^{(k_{12}+k_{21})t}}{k_{12}+k_{21}} \le \nu\right). \quad (3)$$

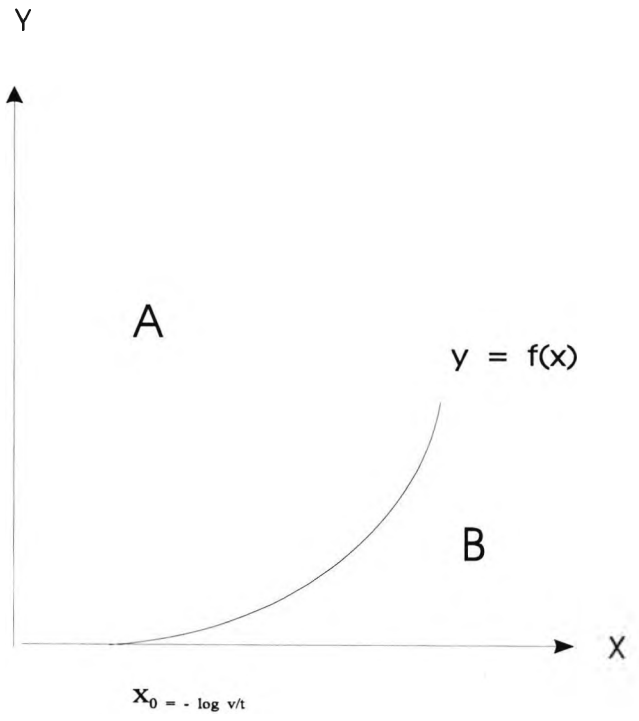
Let $k_{21} = x$ and $k_{12} = y$ for convenience, so:

$$F_{U_1}(u_1 \le \nu) = P(y + xe^{-(x+y)t} \le \nu(x+y)). \quad (4)$$

Let ν = constant>0 and suppose we plot the following curve for the fixed ν and t

$$y + xe^{-(x+y)t} = \nu(x+y) \quad (5)$$

i.e. $y = f(x)$, $f(x_0)=0$, and therefore $x_0 = -1/t \log\nu$.



Consider the following regions:

Region A: $y+x.e^{-(x+y)t} \ge \nu(x+y)$ Region B: $y+x.e^{-(x+y)t} \le \nu(x+y)$

Therefore

$$F_{u_1}(u_1 \le \nu) = prob(region\ \ B) = \int_{x_0}^{\infty} \int_{0}^{y_1 = f(x)} \phi_0(x,y)\, dy\, dx. \tag{6}$$

We require $\partial F_{u1} / \partial \nu$, but this is difficult to obtain because the limits of the integrand are functions of ν. By transforming to new variables it should be possible to change the limits, so that the function can be more easily differentiated. The following transformation of the variables is the obvious one to choose:

$$\begin{aligned} x + y &= s & x &= \frac{s(1-\nu)}{1-e^{-st}} \\ \frac{y + x e^{-(x+y)t}}{x+y} &= \nu & y &= s - \frac{s(1-\nu)}{1-e^{-st}} \end{aligned} \tag{7}$$

Then

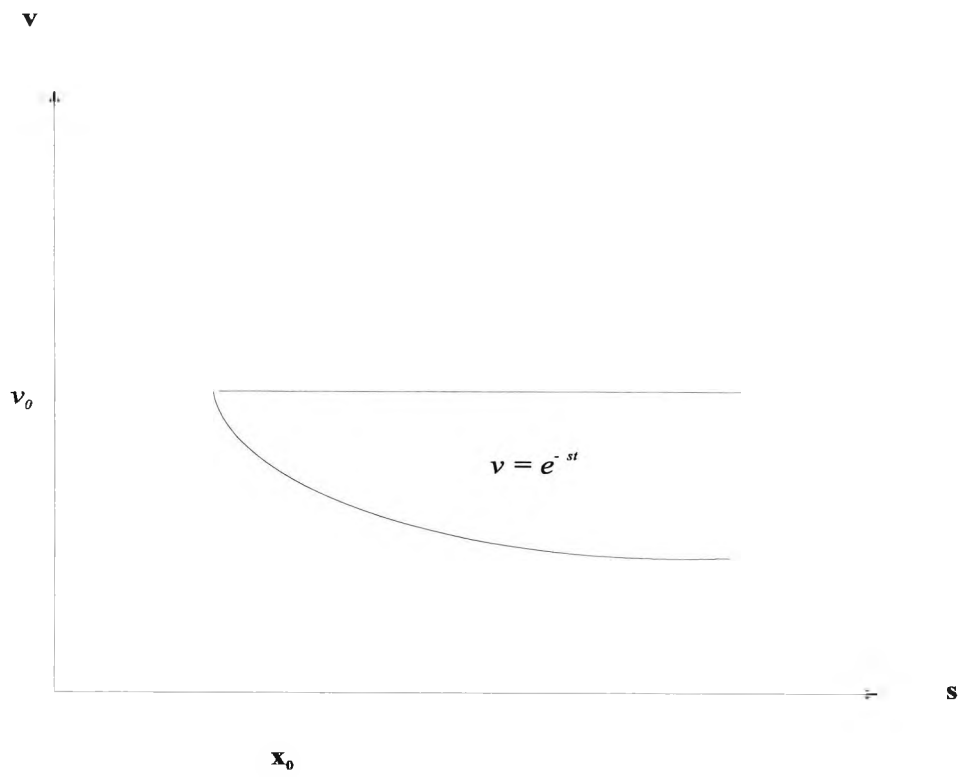
$$F_{U_1}(u_1) = \int_A^B \int_C^D |J| \Phi_0 \left[\frac{s(1-\nu)}{1-e^{-st}}, s - \frac{s(1-\nu)}{1-e^{-st}} \right] ds\, d\nu \tag{8}$$

where J is the Jacobean matrix is given by

$$J = \begin{vmatrix} \frac{\partial x}{\partial s} & \frac{\partial y}{\partial s} \\ \frac{\partial x}{\partial \nu} & \frac{\partial y}{\partial \nu} \end{vmatrix} = \frac{s}{1-e^{-st}}. \tag{9}$$

To calculate the limits of integrals, we consider the following curve:

The original area is mapped onto the area shown on the s,ν plane. The axis y = 0 maps to



$s = x$, $\nu = e^{-xt}$ or $\nu = e^{-st}$, i.e. the lowers limit is $s=-1/t \log\nu$. The boundary $y=f(x)$ maps onto $\nu=\nu_0$ =constant where $x_0= -1/t \log\nu_0$. Therefore the limits of ν are $[0,\nu_0]$ andwe have:

$$F_{U_1}(\nu_0)=\int_{\nu=0}^{\nu=\nu_0}[\int_{(-1/t)\log\nu}^{\infty}\frac{s}{1-e^{-st}}\Phi_0[\frac{s(1-\nu)}{1-e^{-st}},\ s-\frac{s(1-\nu)}{1-e^{-st}}]ds]d\nu \qquad \textbf{(10)}$$

The inner integral, $h(\nu)$, is not a function of ν_0 so differentiation is easy. To differentiate $F_{U1}(\nu_0)$ we have:

$$\frac{\partial F_{U_1}}{\partial \nu_0}=\frac{\partial}{\partial \nu_0}(\int_{\nu=0}^{\nu=\nu_0} h(\nu)d\nu)=h(\nu_0)=\int_{(-1/t)\log\nu_0}^{\infty}\frac{s}{1-e^{-st}}\Phi_0(\frac{s(1-\nu)}{1-e^{-st}},\ s-\frac{s(1-\nu)}{1-e^{-st}})ds \qquad \textbf{(11)}$$

which is the probability density function of $U_1(t)$.

SYMBOLS AND ABBREVIATIONS

The following is a list of symbols and abbreviations that were used in the thesis. Symbols were defined in the text but since some of them are repeated in following sections they are summarised here.

A. Symbol

1. Roman

Cov(x,y)	The covariance of variables x and y.
$D=\{d_{ij}\}$	The matrix D with elements of d_{ij}
E(X)	The expectation of variable X.
$F_X(x)$	Cumulative distribution function for X.
$\bar{G}$	The mean of G.
$k_{0i}(t)$	The flux of substance from compartment i to the outside of the system.
$k_{ij}(t)$, $R_{ij}(t)$	The flux of substance from the compartment j to the compartment i.
R^2	The coefficient of determination.
$R_d(t)$	Rate of disappearance of material from the compartment.
$R_a(t)$	Rate of appearance of material in the compartment
R_i	Random retention time.
r	The coefficient of correlation in the sample.
S_{ij}	The total residence time.
S_i	The system total residence time.
S^2_X, S^2_Y	The sample variance for the variables of X and Y.

V_{ij}	Random number of visitation that a particle originating in compartment i will make to j prior to its departure from the system
W_{ij}	The weights in the WLS method.
$X_i(0)$	Concentration of substance in the first compartment.
x_{ij}	The element in the i^{th} row and j^{th} of matrix x.
X^T	The transpose of matrix X .
X^{-1}	The inverse of matrix X.
$\|X\|$	The determinant of the matrix X.
$X \sim N(\mu,\sigma^2)$	X has a normal distribution with mean and variance of μ and σ^2
$y_i(a, t_j)$	Computed data at the time of t_j.
$Z_i(t_j)$	The measured data at the time of t_j.

2. Greek

μ_2 (t,s)	The statistical moment of the random process.
ρ	The coefficient of correlation in the population.
$\hat{\rho}$	The estimated coefficient of correlation.
σ_{ij}	The variance of the measurement error for i^{th} outputs at the time of t_j.
σ^2	The population variance.
μ	The population mean.
τ	The matrix of the mean of the total residence time.
$\tau_{(2)}$	The matrix of squared elements of τ.
τ_D	Diagonal matrix.
τ'	The matrix of the mean of the random number of visitation of a particle originating in compartment i will make to j prior to its departure from the system.
τ_{ij}	The mean of the residence time that a particle originating in compartment i will accumulate in compartment j during its number of visit.
γ	The matrix of the variance of the total residence time.
$\gamma'=[\gamma'_{ij}]$	The matrix of the variance of the random number of visitation of a particle originating in compartment i will make to j prior to its departure from the system.
γ_{ij}	The variance of the residence time that a particle originating in compartment i will accumulate in compartment j during its number of visit.

$\tau_{i.}$ The mean of the system residence time that a particle originating in compartment i will accumulate in the system prior to its departure from the system.

$\gamma_{i.}$ The variance of the system residence time that a particle originating in compartment i will accumulate in the system prior to its departure from the system.

τ'_{ij} The mean of the random number of visitation of a particle originating in compartment i will make to j prior to its departure from the system.

γ'_{ij} The variance of the random number of visitation of a particle originating in compartment i will make to j prior to its departure from the system

Λ Variance-covariance matrix of compartmental parameters.

Φ_0 (x, y) Joint distribution function of x and y.

B. Abbreviations

BSA Body surface area

CV Coefficient of variation

Df Degrees of freedom

ID Parameter estimation program in ADAPT

IVGTT Intraveneous glucose tolerance test

GCMS Gas chromatography mass spectrometer

GDM	Gestational diabetes mellitus
GLS	Generalised least squares
MAP	Maximum a posteriori probability
ML	Maximum likelihood
MRT	Mean of the total residence time of a particle in a compartmental system
PDF	Probability distribution function
SIM	Simulation program in ADAPT
SS	Sum of squares of residuals
VRT	Variance of the total residence time of a particle in a compartmental system
WLS	Weighted least squares of residuals
WSS	Weighted sum of squares of residuals

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